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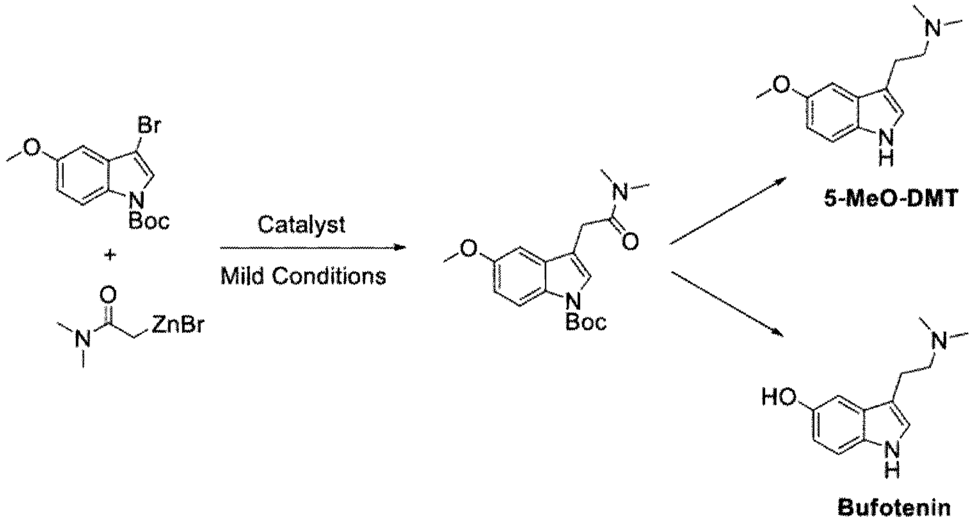
(54) **Title:** CATALYTIC TRYPTAMINE PROCESSES AND PRECURSORS

FIGURE 1



(57) **Abstract:** The present disclosure relates to the use of tryptamine precursor compounds and zinc amide enolate compounds for the preparation of tryptamines. The disclosure also relates to the use of catalysts and catalytic processes for the preparation of tryptamines using the zinc amide enolate compounds and the tryptamine precursor compounds.

[Continued on next page]

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CATALYTIC TRYPTAMINE PROCESSES AND PRECURSORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/184,538 filed May 5, 2021, the contents of which are incorporated herein by reference in its entirety.

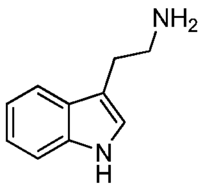
FIELD OF THE DISCLOSURE

The present disclosure relates to the use of zinc amide enolate compounds for the preparation of tryptamines. The disclosure also relates to the use of catalysts and catalytic processes for the preparation of tryptamines using the zinc amide enolate compounds and tryptamine precursor compounds.

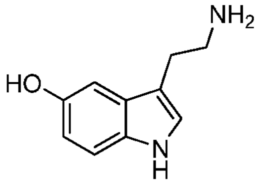
BACKGROUND OF THE DISCLOSURE

Tryptamines are serotonin analogues, which can be described as derivatives of the indolamine metabolite of the amino acid tryptophan. Tryptamine itself (2-(3-indolyl)ethylamine) activates 5-HT4 receptors and regulates gastrointestinal mobility in humans (J.A. Jenkins et al. *Nutrients* **2016**, *8*, 56).

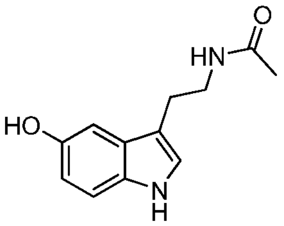
The molecular structure of substituted tryptamines contains an indole ring connected to an amino group by an ethyl linker. The indole core, ethyl linker and amino group can be further modified with other substituents.



Tryptamine



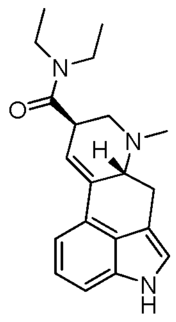
Serotonin



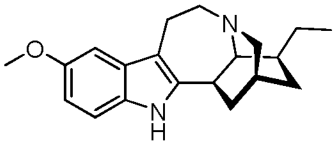
Melatonin

The neurotransmitter serotonin (5-hydrotryptamine or 5-HT) and the sleep regulating hormone melatonin are well-known examples of substituted tryptamines (S. Young, *J. Psychiatry Neurosci.* **2007**, *32*, 394-399; R. Jockers et al. *Br. J. Pharmacol.* **2016**, *173*, 2702-2725).

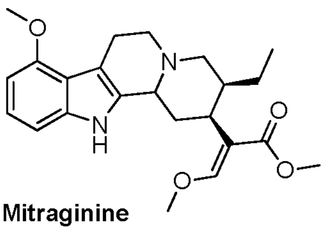
The tryptamine core is present in more complex compounds such as LSD, ibogaine, mitragynine, yohimbine, cipargamin, methysergide and flovatriptan.



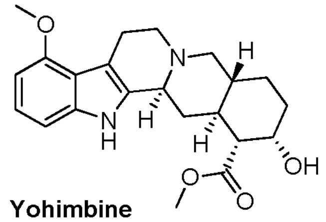
LSD



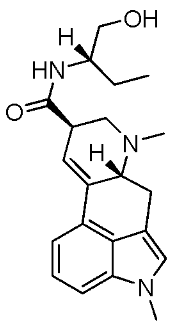
Ibogaine



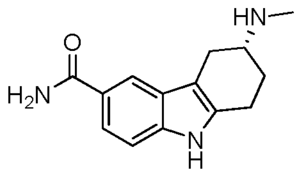
Mitraginine



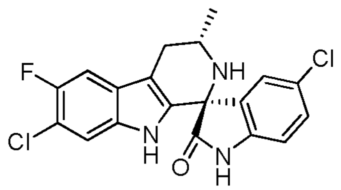
Yohimbine



Methysergide



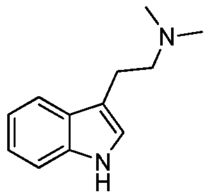
Flovatriptan



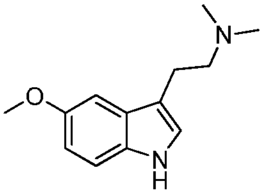
Cipargamin

Tryptamine alkaloids are found in fungi, plants and animals. Some of these constitute traditional sources of medicines in various cultures or for neurological and psychotropic uses. These include N,N-dimethyltryptamine (DMT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), bufotenin, psilocin and psilocybin (D.J. McKenna et al. *J. Ethnopharmacol.* **1984**, *10*, 195-223; J.J.H. Rucker et al. *Neuropharmacology*, **2018**, *142*, 200). Psilocybin is structurally related to other phosphorylated tryptamine natural products including norbaeocystin, baeocystin, and aeruginascin (J. Fricke et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 12352-12355). On ingestion, psilocybin rapidly hydrolyses to psilocin, which is the pharmaceutically active ingredient (R.J. Dinis-Olivera *Drug Metab. Rev.* **2017**, *49*, 84)

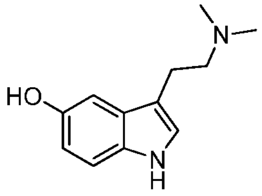
Natural and synthetic sources of these compounds and their analogues are used as psychedelic drugs. However, they also have medicinal therapeutic uses, and several are being investigated for treating psychiatric illnesses and disorders, opioid use disorders, alcohol use disorders, sleep deprivation, anxiety disorders, major depressive disorders, and cancer-related psychiatric distress (A.C. Krugel and J. Sporn, *WO 2021168082*; J.P. Roiser and G. Rees *Curr. Biol.* **2012**, *22*, 231; D.E. Nichols et al. *Clin. Pharmacol. Ther.* **2017**, *101*, 209).



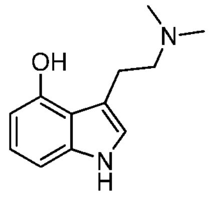
DMT



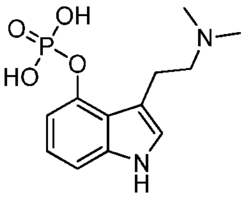
5-MeO-DMT



Bufotenin



Psilocin



Psilocybin

In addition to their therapeutic properties, there are increasing worldwide uses of tryptamines as recreational drugs (R. Haroz and M.I. Greenberg, *Med. Clin. N. America* **2005**, *89*, 1259-1276). The therapeutic uses and potential for abuse warrant the need for more rigorous research. Currently there is a demand for high purity compounds for investigational and therapeutic studies.

Tryptamines can be obtained from biological sources, biocatalytic processes and synthetic methods. Psilocin, psilocybin, DMT, 5-MeO-DMT and bufotenin can all be extracted from psychedelic mushrooms and plant sources. However, such supplies rely on agricultural practices, which can be difficult and inconsistent. The yields are typically low (1-2% of biomass) and some compounds, such as psilocybin decomposes easily (D. Hoffmeister et al. *Chem. Eur. J.* **2019**, *25*, 897-903).

Biosynthetic production methods are currently being developed. These typically use enzymes extracted from mushroom, plant, or animal sources. There are several reports of advances using genetically modified yeasts and microbes, along with efforts to optimize and improve production yields using generational genetic optimization techniques (A.M. Adams et al. *Metabolic Engineering* **2019**, *56*, 111-119).

Synthetic methods have been developed for several substituted tryptamines. DMT, psilocin and 5-MeO-DMT can be prepared from the reaction of the respective indole with oxalyl chloride, followed by reaction with dimethylamine and reduction of the carbonyl functionalities with lithium aluminum hydride (M.E. Speeter and W.C. Anthony *J. Am. Chem. Soc.* **1954**, *76*, 6208-6210). Phosphorylation of psilocin is used to prepare psilocybin. Bufotenin can be derived from 5-O-benzyl-DMT by catalytic hydrogenolysis.

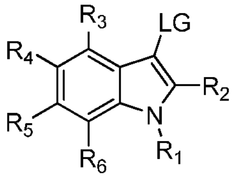
As research advances, there is a desire for simple and economical means for the preparation of substituted tryptamines, including compound libraries, stable isotope labelled compounds and radioisotope labelled compounds. Advanced clinical studies and commercial launches of successful drug candidates will require cost-effective, environmentally friendly and scalable manufacturing processes.

SUMMARY OF THE DISCLOSURE

The present disclosure, in some aspects, describes a new approach to the synthesis of tryptamines that focuses on the use of commercially available and stable precursors that can be transformed into the desired tryptamine products and their phosphorylated derivatives.

In various aspects, the invention relates to the use of zinc amide enolates and tryptamine precursors for the preparation of tryptamines and their derivatives using catalysts and catalytic processes. The zinc amide enolates and tryptamine precursors can be prepared and purified prior to transformation to the desired products. The indole precursors are air-stable and shelf-stable compounds that can be stored, transported and converted into the desired products on demand.

Accordingly, in some embodiments, the present invention relates to precursor compounds of Formula (I):



(I)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R_c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

LG represents any suitable leaving group, such as a halide group, sulphonate, or any other anionic leaving group;

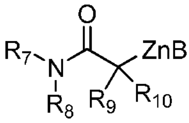
R_2 to R_6 represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In a general way, the compounds of Formula (I) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (I) is achiral.

In another embodiment of the disclosure, the compound of Formula (I) is chiral.

In another embodiment, the present disclosure relates to zinc amide enolates of Formula (II):



(II)

wherein,

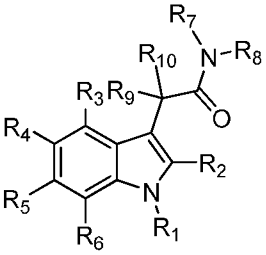
R_7 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_7 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In a general way, the compounds of Formula (II) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (II) is achiral.

In another embodiment of the disclosure, the compound of Formula (II) is chiral.

In another embodiment, the present disclosure relates to the preparation of compounds of Formula (III):



(III)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

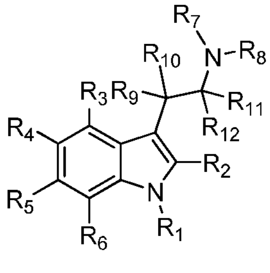
R_2 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In a general way, the compounds of Formula (III) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (III) is achiral.

In another embodiment of the disclosure, the compound of Formula (III) is chiral.

In yet another embodiment, the present invention relates to the preparation of tryptamine compounds of Formula (IV):



(IV)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

R_2 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups;

and R_{11} to R_{12} represent hydrogen or deuterium.

In a general way, the compounds of Formula (IV) can be prepared and isolated prior to use.

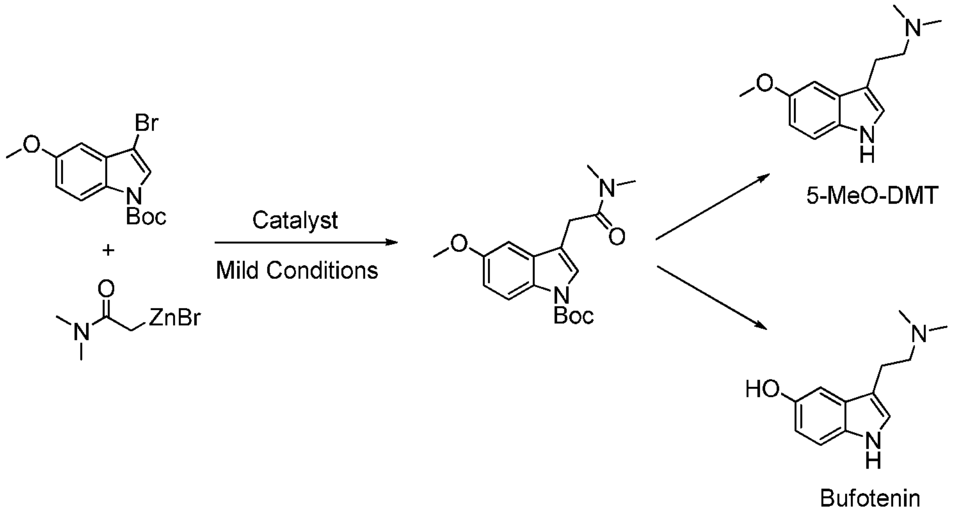
In another embodiment of the disclosure, the compound of Formula (IV) is achiral.

In another embodiment of the disclosure, the compound of Formula (IV) is chiral.

In another embodiment, one or more of the carbon-12 atoms in the molecule are replaced with carbon-13.

In various embodiments of the disclosure, the transformations to which the compounds of the invention can be applied include but are not limited to catalytic and non-catalytic carbon-carbon bond forming Negishi reactions. Such carbon-carbon bond forming reactions include the use of compounds of the present disclosure to prepare tryptamine compounds.

Scheme 1 illustrates the preparation of tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate, 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine (5-MeO-DMT) and 3-(2-(dimethylamino)ethyl)-1H-indol-5-ol (bufotenin), according to the processes of this invention. This is shown as Figure 1.



Scheme 1

The present disclosure also includes compositions, methods of producing the compounds and compositions comprising the compounds of the invention, kits comprising any one or more of the components of the foregoing, optionally with instructions to make or use same and uses of any of the foregoing.

Other features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the disclosure are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The disclosure will be described in greater detail with reference to the following drawings, which are meant to be illustrative by certain embodiments of the invention and are not meant to limit the scope of the invention:

Figure 1 shows the scheme for the catalytic preparation of 5-MeO-DMT and bufotenin;

Figure 2 shows the X-ray crystal structure of tert-butyl 5-acetoxy-3-bromo-1H-indole-1-carboxylate;

Figure 3 shows the X-ray crystal structure of tert-butyl 3-bromo-5-methoxy-1H-indole-1-carboxylate;

Figure 4 shows the X-ray crystal structure of tert-butyl 3-(2-(diisopropylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate;

Figure 5 shows the X-ray crystal structure of 2-(1H-indol-3-yl)-N,N-diisopropylacetamide;

Figure 6 shows the X-ray crystal structure of 2-(1H-indol-3-yl)-N,N-dimethylbutanamide;

Figure 7 shows the X-ray crystal structure of 4-(2-(1H-indol-3-yl)ethyl)morpholine;

Figure 8 shows the ^{1}H NMR spectrum of tert-butyl 3-(2-(dimethylamino)-2-oxoethyl)-1H-indole-1-carboxylate;

Figure 9 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylacetamide;

Figure 10 shows the ^{1}H NMR spectrum of tert-butyl 3-(1-(dimethylamino)-1-oxopropan-2-yl)-1H-indole-1-carboxylate;

Figure 11 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylpropanamide;

Figure 12 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylbutanamide;

Figure 13 shows the ^{1}H NMR spectrum of 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylacetamide;

Figure 14 shows the ^{1}H NMR spectrum of 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylacetamide;

Figure 15 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-diisopropylacetamide;

Figure 16 shows the ^{1}H NMR spectrum of N,N-diisopropyl-2-(5-methoxy-1H-indol-3-yl)acetamide;

Figure 17 shows the ^{1}H NMR spectrum of tert-butyl 3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate;

Figure 18 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-1-morpholinoethanone;

Figure 19 shows the ^{1}H NMR spectrum of 4-(2-(1H-indol-3-yl)ethyl)morpholine;

Figure 20 shows the ^{1}H NMR spectrum of tert-butyl 5-methoxy-3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate;

Figure 21 shows the ^{1}H NMR spectrum of 2-(5-methoxy-1H-indol-3-yl)-1-morpholinoethanone;

Figure 22 shows the ^{1}H NMR spectrum of 4-(2-(5-methoxy-1H-indol-3-yl)ethyl)morpholine.

DETAILED DESCRIPTION OF THE DISCLOSURE

(I) DEFINITIONS

The term "(C_1-C_p)-alkyl" as used herein means straight and/or branched chain, saturated alkyl radicals containing one or more carbon atoms and includes (depending on the identity of "p") methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, 2,2-dimethylbutyl, n-pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, n-hexyl and the like.

The term "(C_2-C_p)-alkenyl" as used herein means straight and/or branched chain, unsaturated alkyl radicals containing two or more carbon atoms and one to three double bonds, and includes (depending on the identity of "p") vinyl, allyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, 2-methylbut-1-enyl, 2-methylpent-1-enyl, 4-methylpent-1-enyl, 4-methylpent-2-enyl, 2-methylpent-2-enyl, 4-methylpenta-1,3-dienyl, hexen-1-yl and the like.

The term "(C_2-C_p)-alkynyl" as used herein means straight and/or branched chain, unsaturated alkyl radicals containing two or more carbon atoms and one to three triple bonds, and includes (depending on the identity of "p") ethynyl, propynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, 3-methylbut-1-enyl, 3-methylpent-1-ynyl, 4-methylpent-1-ynyl, 4-methylpent-2-ynyl, penta-1,3-di-ynyl, hexyn-1-yl and the like.

The term “(C_1-C_p)-alkoxy” as used herein means straight and/or branched chain alkoxy group containing one or more carbon atoms and includes (depending on the identity of “p”) methoxy, ethoxy, propyloxy, isopropyloxy, t-butoxy, heptoxy, and the like.

The term “(C_3-C_p)-cycloalkyl” as used herein means a monocyclic, bicyclic or tricyclic saturated carbocylic group containing three or more carbon atoms and includes (depending on the identity of “p”) cyclopropyl, cyclobutyl, cyclopentyl, cyclodecyl and the like.

The term “(C_6-C_p)-aryl” as used herein means a monocyclic, bicyclic or tricyclic aromatic ring system containing at least one aromatic ring and 6 or more carbon atoms (and depending on the identity of “p”) and includes phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like.

The term “(C_5-C_p)-heteroaryl” as used herein means a monocyclic, bicyclic or tricyclic ring system containing one or two aromatic rings and 5 or more atoms of which, unless otherwise specified, one, two, three, four or five are heteromoieties independently selected from N, NH, N(alkyl), O and S and depending on the value of “p” includes thienyl, furyl, pyrrolyl, pyrididyl, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl and the like.

The term “halo” or “halogen” as used herein means chloro, fluoro, bromo or iodo.

The term "fluoro-substituted" as used herein means that at least one, including all, of the hydrogens on the referenced group is replaced with fluorine.

The suffix “ene” added on to any of the above groups means that the group is divalent, i.e. inserted between two other groups.

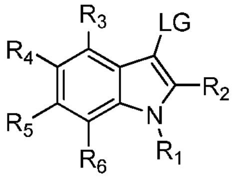
The term “ring system” as used herein refers to a carbon-containing ring system, that includes monocycles, fused bicyclic and polycyclic rings, bridged rings and metalocenes. Where specified, the carbons in the rings may be substituted or replaced with heteroatoms.

The term “leaving group” as used herein refers to a group capable of being displaced from a compound when the compound undergoes reaction with a nucleophile.

In understanding the scope of the present disclosure, the term "comprising" and its derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms, "including", "having" and their derivatives. For instance, “including” also encompasses “including but not limited to”. Finally, terms of degree such as "substantially", "about" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least ±5% of the modified term if this deviation would not negate the meaning of the word it modifies.

(II) COMPOUNDS OF THE DISCLOSURE

The present disclosure relates to precursors compounds of Formula (I):



(I)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

LG represents any suitable leaving group, such as a halide group, sulphonate, or any other anionic leaving group; and

R_2 to R_6 represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In a general way, the compounds of Formula (I) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (I) is achiral.

In another embodiment of the disclosure, the compound of Formula (I) is chiral.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{20})$-alkyl, -(C=O)-O-$(C_1\text{-}C_{20})$-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, or $(C_6\text{-}C_{20})$-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl, $(C_5\text{-}C_{10})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{10})$-alkyl, -(C=O)-O-$(C_1\text{-}C_{10})$-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, or $(C_6\text{-}C_{10})$-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of

R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, -(C=O)-O-(C_1-C_6)-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, or (C_6)-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, phenyl, or -C(=O)-(C_1-C_6)-alkyl, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 is a nitrogen protecting group such as a phosphinyl group, a phosphoryl group, a sulfenyl group, a sulfonyl group, or a silyl group (such as TMS, TIPS, TBDMS).

In one embodiment, LG represents any suitable leaving group, such as a halide group, sulphonate, or any other anionic leaving group. In one embodiment, LG is chloro, bromo or iodo. In another embodiment, LG is mesylate, triflate or tosylate.

In one embodiment, R_2 to R_6 represent hydrogen, deuterium, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

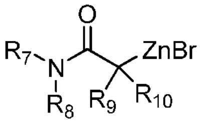
In one embodiment, R_2 to R_6 represent hydrogen, deuterium, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_6 represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_6 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_6 represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, or (C_5-C_6)-heteroaryl.

The present disclosure also relates to a tryptamine precursors of Formula (I), wherein one or more of the carbon-12 atoms are replaced with carbon-13.

The present disclosure also relates to zinc amide enolates of Formula (II):


(II)

wherein,

R_7 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted 5-10-membered carboyclic or heterocyclic ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_7 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In one embodiment, R_7 to R_{10} represent hydrogen, deuterium, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl, $\text{-C(=O)-}(C_1\text{-}C_{20})$-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_7 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_7 to R_{10} represent hydrogen, deuterium, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl, $(C_5\text{-}C_{10})$-heteroaryl, $\text{-C(=O)-}(C_1\text{-}C_{10})$-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_7 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_7 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_7 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_7 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, or (C_5-C_6)-heteroaryl.

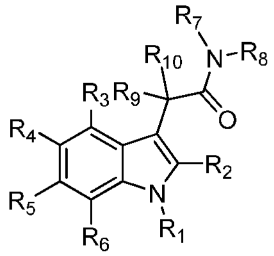
In one embodiment, R_7 and R_8 are joined together, along with the nitrogen atom to which they are attached, to form a 5-8-membered carbocyclic or heterocyclic ring. In one embodiment, the 5-8-membered ring is optionally substituted with halogen, oxo (C=O), OH, optionally substituted phenyl or (C_1-C_6)-alkyl

In a general way, the compounds of Formula (II) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (II) is achiral.

In another embodiment of the disclosure, the compound of Formula (II) is chiral.

The present disclosure also relates to compounds of Formula (III):


(III)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

R_2 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl, $-C(=O)\text{-}(C_1\text{-}C_{20})$-alkyl, $-(C=O)\text{-}O\text{-}(C_1\text{-}C_{20})$-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, or $(C_6\text{-}C_{20})$-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl, $(C_5\text{-}C_{10})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{10})$-alkyl, -(C=O)-O-$(C_1\text{-}C_{10})$-alkyl, OR^c, or $NR^c{}_2$, each of which are optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, or $(C_6\text{-}C_{10})$-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_3\text{-}C_7)$-cycloalkyl, (C_6)-aryl, $(C_5\text{-}C_6)$-heteroaryl, -C(=O)-$(C_1\text{-}C_6)$-alkyl, -(C=O)-O-$(C_1\text{-}C_6)$-alkyl, OR^c, or $NR^c{}_2$, each of which are optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_3\text{-}C_7)$-cycloalkyl, or (C_6)-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_3\text{-}C_7)$-cycloalkyl, phenyl, or -C(=O)-$(C_1\text{-}C_6)$-alkyl, each of which are optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}$

C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to $R_{\backslash 10}$ is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

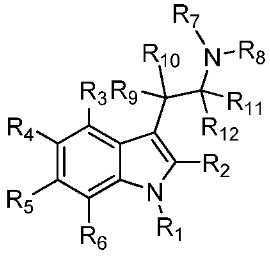
In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, or (C_5-C_6)-heteroaryl.

In a general way, the compounds of Formula (III) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (III) is achiral.

In another embodiment of the disclosure, the compound of Formula (III) is chiral.

In yet another embodiment, the present disclosure relates to compounds of Formula (IV):



(IV)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

R_2 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups; and

R_{11} to R_{12} represent hydrogen or deuterium.

In one embodiment, R_1 represents hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl,

-C(=O)-(C_1-C_{20})-alkyl, -(C=O)-O-(C_1-C_{20})-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, or (C_6-C_{20})-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 represents hydrogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, -(C=O)-O-(C_1-C_{10})-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, or (C_6-C_{10})-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, -(C=O)-O-(C_1-C_6)-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, or (C_6)-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, phenyl, or -C(=O)-(C_1-C_6)-alkyl, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to $R_{\backslash 10}$ is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, or (C_5-C_6)-heteroaryl.

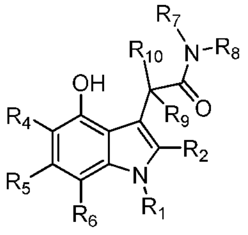
In a general way, the compounds of Formula (IV) can be prepared and isolated prior to use.

In another embodiment of the disclosure, the compound of Formula (IV) is achiral.

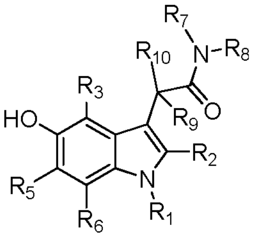
In another embodiment of the disclosure, the compound of Formula (IV) is chiral.

In another embodiment, one or more of the carbon-12 atoms in the molecule are replaced with carbon-13.

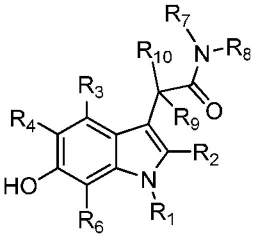
In another embodiment, the present disclosure relates to compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII):



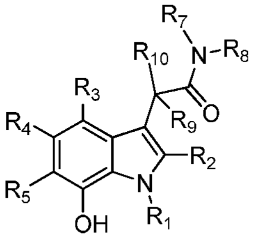
(V)



(VI)



(VII)



(VIII)

wherein,

R_1 represents hydrogen, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or an acyl group, possibly substituted, or a carbamate group, possibly substituted, or an OR^c group or an NR^c_2 group, possibly substituted, in which R^c is a hydrogen atom or a cyclic, linear or branched alkyl, aryl or alkenyl group;

R_2 to R_{10} represent hydrogen, deuterium, a linear or branched alkyl group of any length, possibly substituted, or an alkenyl group of any length, possibly substituted, or an alkynyl group, possibly substituted, or a cycloalkyl group, possibly substituted, or an aryl group, possibly substituted, or an heteroaryl group, possibly substituted, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, or an acyl group, possibly substituted, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups.

In one embodiment, R_1 represents hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, -(C=O)-O-(C_1-C_{20})-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, or (C_6-C_{20})-aryl.

In one embodiment, R_1 represents hydrogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, -(C=O)-O-(C_1-C_{10})-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, or (C_6-C_{10})-aryl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, -(C=O)-O-(C_1-C_6)-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, or (C_6)-aryl.

In one embodiment, R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, phenyl, or -C(=O)-(C_1-C_6)-alkyl, each of which are optionally substituted with halogen, OH, or (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

In one embodiment, R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, or (C_5-C_6)-heteroaryl

In a general way, the compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII) can be prepared and isolated prior to use.

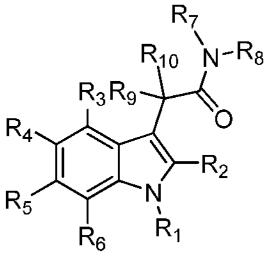
In another embodiment of the disclosure, the compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII) are achiral.

In another embodiment of the disclosure, the compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII) are chiral.

In another embodiment, one or more of the carbon-12 atoms in the molecule are replaced with carbon-13.

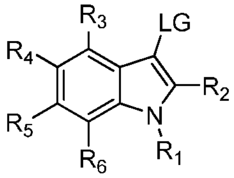
(III) PROCESSES OF THE DISCLOSURE

The present disclosure also relates to processes for the preparation of compounds of Formula (III):



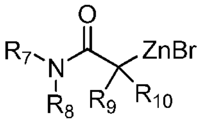
(III)

by contacting a compound of Formula (I):



(I)

with a compound of Formula (II):



(II)

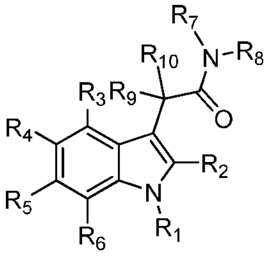
in the presence of a suitable catalyst,

wherein the variables R_1-R_{10} and LG are as defined above.

In some aspects, the transformation of a compound of Formula (I) and Formula (II) to a compound of Formula (III) requires a suitable catalyst. Suitable catalysts include but are not limited to transition metal salts and complexes, such as compounds of palladium, nickel, iron, ruthenium, cobalt, rhodium, iridium and copper.

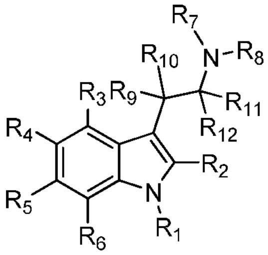
In some aspects, the catalysts are chiral and can facilitate asymmetric carbon-carbon bond forming reactions.

The disclosure also relates to processes for the catalytic and non-catalytic conversion of compounds of Formula (III):



(III)

to compounds of Formula (IV):



(IV),

\wherein the variables R_1-R_{12} and LG are as defined above.

Carbon-carbon bond forming reactions for the preparation of compounds of Formula (III) include but are not limited to catalytic and non-catalytic Negishi reactions.

Reactions for the preparation of compounds of Formula (IV) include but are not limited to catalytic and non-catalytic reduction and hydrogenation reactions. Suitable reducing agents include borohydrides, borodeuterides, aluminohydrides, aluminodeuterides, silanes, boranes, hydrogen gas and deuterium gas.

In some embodiments of the disclosure, the catalytic system characterizing the process of the instant invention may comprise a base. In some embodiments, said base can be any conventional base. In some embodiments, non-limiting examples include: organic non-coordinating bases such as DBU, an alkaline or alkaline-earth metal carbonate, a carboxylate salt such as sodium or potassium acetate, or an alcoholate or hydroxide salt. Preferred bases are the alcoholate or hydroxide salts selected from the group consisting of the compounds of formula $(RO)_2M'$ and ROM'', wherein M' is an alkaline-earth metal, M'' is an alkaline metal and R stands for hydrogen or a linear or branched alkyl group.

The catalyst can be added to the reaction medium in a large range of concentrations. As non-limiting examples, one can cite as catalyst concentration values ranging from 0.001 % to 50 %, relative to the amount of substrate, thus representing respectively a substrate/catalyst (S/cat) ratio of 100,000 to 2. Preferably, the complex concentration will be comprised between 0.01 % and 10 %, i.e. a S/cat ratio of 10,000 to 10 respectively. In some preferred embodiments, there will be used concentrations in the range of 0.1 to 5 %, corresponding to a S/cat ratio of 1000 to 20 respectively.

If required, useful quantities of base, added to the reaction mixture, may be comprised in a relatively large range. In some embodiments, non-limiting examples include: ranges between 1 to 100 molar equivalents relative to the substrate. However, it should be noted that it is also possible to add a small amount of base (e.g. base/substrate = 1 to 3) to achieve high yields.

In the processes of this disclosure, the catalytic reaction can be carried out in the presence or absence of a solvent. When a solvent is required or used for practical reasons, then any solvent currently used in catalytic reactions can be used for the purposes of the invention. Non-limiting examples include aromatic solvents such as benzene, toluene or xylene, hydrocarbon solvents such as hexane or cyclohexane, ethers such as tetrahydrofuran, or yet primary or secondary alcohols, or water, or mixtures thereof. A person skilled in the art is well able to select the solvent most convenient in each case to optimize the catalytic reaction.

The temperature at which the catalytic reaction can be carried out is comprised between -30 °C and 200 °C, more preferably in the range of between 0 °C and 100 °C. Of course, a person skilled in the art is also able to select the preferred temperature.

Standard catalytic conditions, as used herein, typically implies the mixture of the substrate with the catalyst with or without a base, possibly in the presence of a solvent, and then treating such a mixture with the desired reactant at a chosen temperature in air or under an inert atmosphere of nitrogen or argon gas. Varying the reaction conditions, including for example, catalyst, temperature, solvent and reagent, to optimize the yield of the desired product would be well within the abilities of a person skilled in the art.

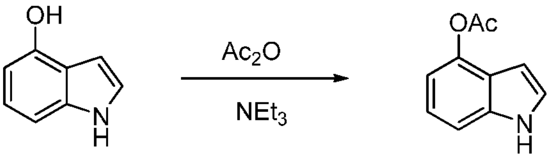
The present disclosure is described in the following Examples, which are set forth to aid in the understanding of the invention, and should not be construed to limit in any way the scope of the invention as defined in the claims which follow thereafter.

EXAMPLES

The disclosure will now be described in further details by way of the following examples, wherein the temperatures are indicated in degrees centigrade and the abbreviations have the usual meaning in the art.

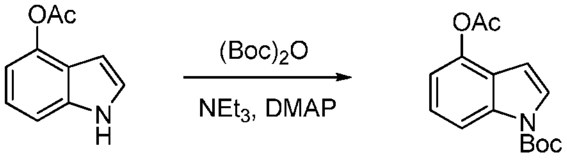
All the procedures described hereafter have been carried out under an inert atmosphere unless stated otherwise. All preparations and manipulations under air-free conditions were carried out under N_2 or Ar atmospheres with the use of standard Schlenk, vacuum line and glove box techniques in dry, oxygen-free solvents. Deuterated solvents were degassed and dried over activated molecular sieves. NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F and 162 MHz for ^{31}P). All ^{31}P chemical shifts were measured relative to 85% H3PO4 as an external reference. ^{1}H and ^{13}C chemical shifts were measured relative to partially deuterated solvent peaks but are reported relative to tetramethylsilane.

Example 1. Preparation of 1H-indol-4-yl acetate



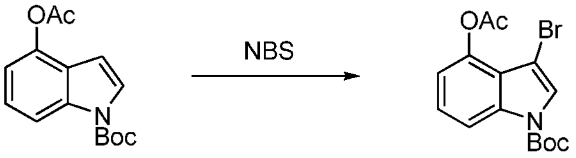
Acetic anhydride (3.27 g, 32 mmol) was added slowly to a mixture of 4-hydroxyindole (3.88 g, 29 mmol) and triethylamine (4.4 g, 44 mmol) in dichloromethane (50 ml) at room temperature. The reaction was stirred for 3 hours, then water (30 ml) added. The phases were separated, and the aqueous layer was extracted with dichloromethane (2 x 15 ml). The combined organic layer was washed with water (50 ml), then brine (20 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue eluted through a silica gel pad using hexanes/ethyl acetate (2:1) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a white crystalline solid. Yield = 4.75 g.

Example 2. Preparation of tert-Butyl 4-acetoxy-1H-indole-1-carboxylate



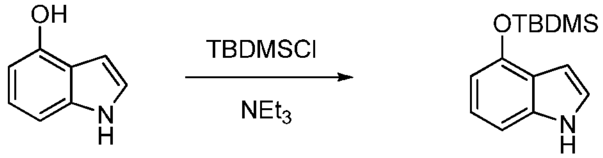
A solution of $(Boc)_2O$ (1.3 g, 6.0 mmol) in dichloromethane (5 ml) was added to a mixture of 1H-indol-4-yl acetate (1.33 g, 5.7 mmol), triethylamine (1.15 g, 11.4 mmol), DMAP (2 mg) in dichloromethane (10 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated NaHCO3 solution (20 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using ethyl acetate/hexanes (1:3) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a colourless oil. Yield = 1.48 g.

Example 3. Preparation of tert-Butyl 4-acetoxy-3-bromo-1H-indole-1-carboxylate



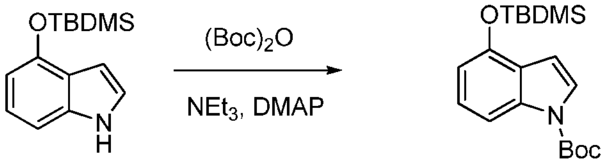
NBS (3.06 g, 17.2 mmol) was added to a mixture of tert-butyl 4-acetoxy-1H-indole-1-carboxylate (4.5 g, 16.4 mmol) and NH_4Cl (5 mg) in dichloromethane (100 ml) and the reaction stirred overnight at room temperature. Water (50 ml) was added, and the phases separated. The combined organic portion was washed with brine (20 ml), then water (20 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using EA/CH_2Cl_2/hexanes (1:2:10) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 6.0 g.

Example 4. Preparation of 4-(tert-butyldimethylsilyloxy)-1H-indole



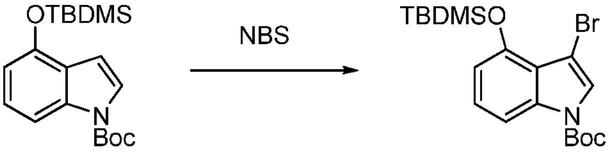
Triethylamine (2.28 g, 22.5 mmol) was added to a solution of 4-hydroxyindole (2.0 g, 15.0 mmol) in dichloromethane (10 ml), followed by TBDMSCl (2.26 g, 15.0 mmol) and the mixture was stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and hexanes/ether (5:2, 20 ml) was added. The mixture was stirred for 30 minutes, then filtered through a pad of silica gel. The filtrate was evaporated to dryness to give the product as an off-white solid. Yield = 3.68 g.

Example 5. Preparation of tert-butyl 4-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate



Triethylamine (3.04 g, 30 mmol) was added to a solution of 4-(tert-butyldimethylsilyloxy)-1H-indole (3.1 g, 12.5 mmol) in dichloromethane (20 ml) and di-tert-butyl decarbonate (3.27 g, 15 mmol) added, followed by DMAP (0.08 g, 0.65 mmol). The mixture was stirred for 24 hours with venting of the evolved gas through a bubbler. The reaction was evaporated to dryness and the residue was eluted through a pad of silica gel using hexanes/ether (7:1). The filtrate was evaporated to dryness to give the product as a colourless oil. Yield = 4.29 g.

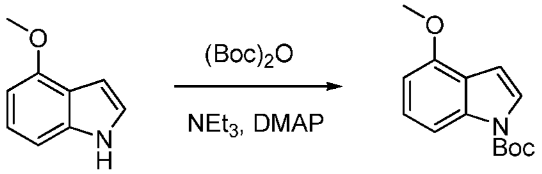
Example 6. Preparation of tert-butyl 3-bromo-4-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate



NBS (0.282 g, 1.58 mmol) was added to a mixture of tert-butyl 4-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate (0.5 g, 1.44 mmol) in dichloromethane (10 ml) and the reaction stirred overnight at room temperature.

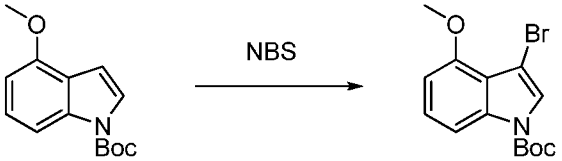
It was quenched with saturated NaHCO3 solution (10 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic portion was washed water (10 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using CH_2Cl_2/hexanes (1:3) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a colourless oil. Yield = 0.42 g.

Example 7. Preparation of tert-butyl 4-methoxy-1H-indole-1-carboxylate



Triethylamine (2.75 g, 27.2 mmol) was added to a solution of 4-methoxyindole (2.0 g, 13.6 mmol) in dichloromethane (20 ml) and di-tert-butyl decarbonate (3.0 g, 13.7 mmol) added, followed by DMAP (0.07 g, 0.54 mmol). The mixture was stirred for 16 hours with venting of the evolved gas through a bubbler. The reaction was evaporated to dryness and the residue was eluted through a pad of silica gel using hexanes/ethylacetate. The filtrate was evaporated to dryness to give the product as a colourless oil. Yield = 3.17 g.

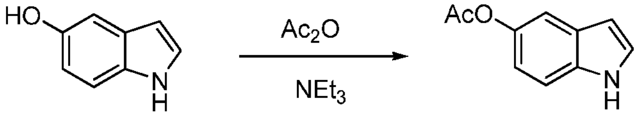
Example 8. Preparation of tert-butyl 3-bromo-4-methoxy-1H-indole-1-carboxylate



NBS (9.0 g, 50.6 mmol) was added to a mixture of tert-butyl 4-methoxy-1H-indole-1-carboxylate (11.5 g, 46.5 mmol) and NH_4Cl (20 mg) in dichloromethane (200 ml), THF (10 ml) and DMF (4 drops) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (100 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml) and the combined organic portion was washed with brine (50 ml), then water (50 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using

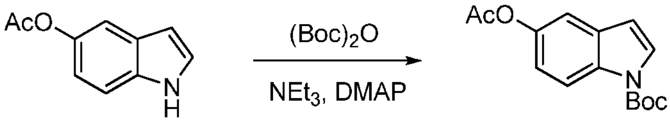
CH_2Cl_2/hexanes (31) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 11.2 g.

Example 9. Preparation of 1H-indol-5-yl acetate



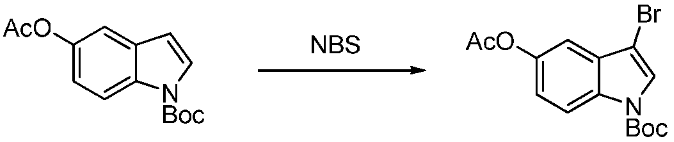
Acetic anhydride (4.4 g, 43 mmol) was added slowly to a mixture of 5-hydroxyindole (5.2 g, 39 mmol) and triethylamine (5.9 g, 58 mmol) in dichloromethane (50 ml) at room temperature. The reaction was stirred for 3 hours, then water (30 ml) added. The phases were separated, and the aqueous layer was extracted with dichloromethane (2 x 15 ml). The combined organic layer was washed with water (100 ml), then brine (20 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue eluted through a silica gel pad using hexanes/ethyl acetate (2:1) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a white crystalline solid. Yield = 6.75 g.

Example 10. Preparation of tert-Butyl 5-acetoxy-1H-indole-1-carboxylate



A solution of $(Boc)_2O$ (9.25 g, 42 mmol) in dichloromethane (20 ml) was added to a mixture of 1H-indol-5-yl acetate (6.75 g, 38 mmol), triethylamine (7.78 g, 77 mmol), DMAP (5 mg) in dichloromethane (70 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (50 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using ethyl acetate/hexanes (1:3) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a pale-yellow oil. Yield = 10.63 g.

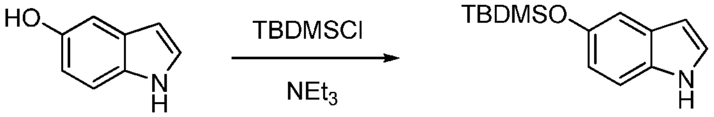
Example 11. Preparation of tert-Butyl 5-acetoxy-3-bromo-1H-indole-1-carboxylate



NBS (6.83 g, 38.4 mmol) was added to a mixture of tert-butyl 5-acetoxy-1H-indole-1-carboxylate (10.0 g, 36.3 mmol) and NH_4Cl (0.2 g) in dichloromethane (100 ml) and the reaction stirred overnight at room temperature. Water (40 ml) was added, and the phases separated. The combined organic portion was washed with brine (30 ml), then water (20 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using EA/CH_2Cl_2/hexanes (1:2:10) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 10.29 g.

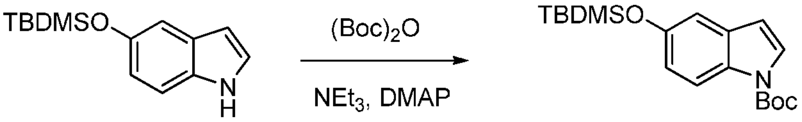
Figure 2 shows the X-ray crystal structure of tert-Butyl 5-acetoxy-3-bromo-1H-indole-1-carboxylate.

Example 12. Preparation of 5-(tert-butyldimethylsilyloxy)-1H-indole



Triethylamine (2.28 g, 22.5 mmol) was added to a solution of 5-hydroxyindole (2.0 g, 15.0 mmol) in dichloromethane (10 ml), followed by TBDMSCl (2.26 g, 15.0 mmol) and the mixture was stirred at room temperature for 20 hours. The solvent was removed under reduced pressure and hexanes/ether (5:2, 20 ml) was added. The mixture was stirred for 30 minutes, then filtered through a pad of silica gel. The filtrate was evaporated to dryness to give the product as an off-white solid. Yield = 4.2 g.

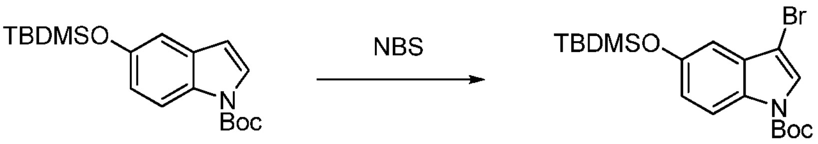
Example 13. Preparation of tert-butyl 5-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate



Triethylamine (3.04 g, 30 mmol) was added to a solution of 5-(tert-butyldimethylsilyloxy)-1H-indole (3.1 g, 12.5 mmol) in dichloromethane (20 ml) and di-tert-butyl decarbonate (3.27 g, 15 mmol) added, followed by DMAP (0.08

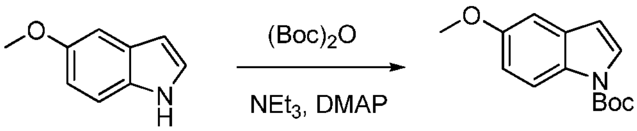
g, 0.65 mmol). The mixture was stirred for 24 hours with venting of the evolved gas through a bubbler. The reaction was evaporated to dryness and the residue was eluted through a pad of silica gel using hexanes/ether (7:1). The filtrate was evaporated to dryness to give the product as a colourless oil. Yield = 4.1 g.

Example 14. Preparation of tert-butyl 3-bromo-5-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate



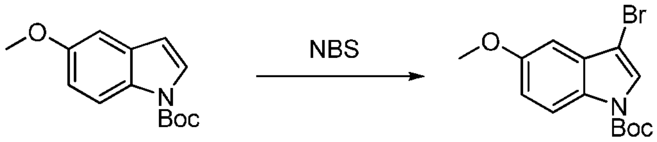
NBS (0.282 g, 1.58 mmol) was added to a mixture of tert-butyl 5-(tert-butyldimethylsilyloxy)-1H-indole-1-carboxylate (0.5 g, 1.44 mmol) in dichloromethane (10 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (10 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic portion was washed water (10 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using CH_2Cl_2/hexanes (1:3) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a colourless oil. Yield = 0.38 g.

Example 15. Preparation of tert-butyl 5-methoxy-1H-indole-1-carboxylate



A solution of $(Boc)_2O$ (15.0 g, 68.6 mmol) in dichloromethane (20 ml) was added to a mixture of 5-methoxy-1H-indole 10.0 g, 68 mmol), triethylamine (13.7 g, 136 mmol), DMAP (80 mg) in dichloromethane (100 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (60 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using CH_2Cl_2/hexanes (1:1) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a white crystalline solid. Yield = 16.7 g.

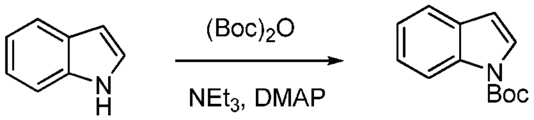
Example 16. Preparation of tert-butyl 3-bromo-5-methoxy-1H-indole-1-carboxylate



NBS (9.0 g, 50.6 mmol) was added to a mixture of tert-butyl 5-methoxy-1H-indole-1-carboxylate (11.5 g, 46.5 mmol) and NH_4Cl (20 mg) in dichloromethane (200 ml), THF (10 ml) and DMF (4 drops) and the reaction stirred for one hour at room temperature. It was quenched with saturated $NaHCO_3$ solution (100 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml) and the combined organic portion was washed with brine (50 ml), then water (50 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using CH_2Cl_2/hexanes (31) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 13.7 g.

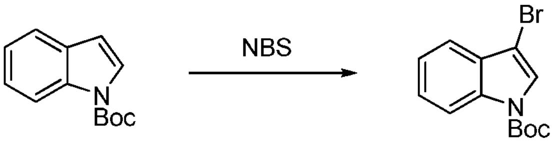
Figure 3 shows the X-ray crystal structure of tert-butyl 3-bromo-5-methoxy-1H-indole-1-carboxylate.

Example 17. Preparation of tert-butyl 1H-indole-1-carboxylate



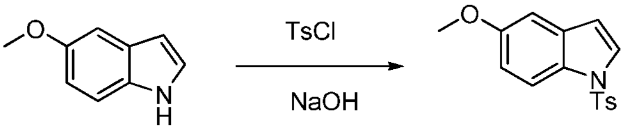
A solution of $(Boc)_2O$ (13.94 g, 64 mmol) in dichloromethane (20 ml) was added to a mixture of indole (6.8 g, 58 mmol), triethylamine (11.7 g, 116 mmol), DMAP (5 mg) in dichloromethane (70 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (50 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using ethyl acetate/hexanes (1:3) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a pale-yellow oil. Yield = 12.6 g.

Example 18. Preparation of tert-butyl 3-bromo-1H-indole-1-carboxylate



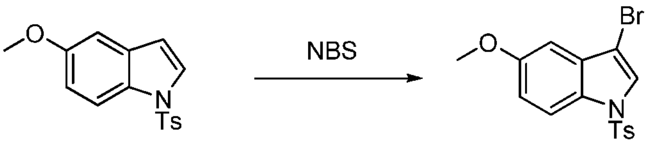
NBS (10.36 g, 58 mmol) was added to a mixture of tert-butyl 1H-indole-1-carboxylate (12.05 g, 55.4 mmol) and NH_4Cl (30 mg) in dichloromethane (150 ml) and the reaction stirred overnight at room temperature. Water (40 ml) was added, and the phases separated. The combined organic portion was washed with brine (30 ml), then water (20 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using EA/CH_2Cl_2/hexanes (1:2:10) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 16.2 g.

Example 19. Preparation of 5-methoxy-1-tosyl-1H-indole



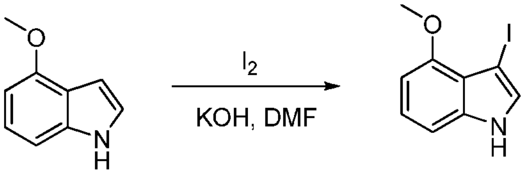
A solution of TsCl (2.6 g, 13.6 mmol) in toluene (20 ml) was added dropwise to a mixture of 5-methoxyindole (2.0 g, 13.6 mmol), 50% NaOH solution (14 ml) and TBAF (0.355 g, 1.36 mmol) with vigorous stirring at room temperature. Stirring was continued for another 3 hours after the addition was completed. The reaction was quenched with saturated $NaHCO_3$ solution (20 ml) and the phases separated. The aqueous layer was extracted with toluene (2 x 10 ml). The combined organic portion was washed with water and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using ethyl acetate as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a white solid. Yield = 4.1 g.

Example 20. Preparation of 3-bromo-5-methoxy-1-tosyl-1H-indole



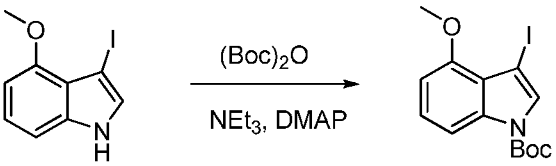
A solution of NBS (0.30 g, 1.7 mmol) in dichloromethane (5 ml) was added dropwise to a mixture of 5-methoxy-1-tosyl-1H-indole (0.50 g, 1.66 mmol) in dichloromethane (30 ml) at 0 °C. The reaction was stirred overnight at room temperature. Water (40 ml) was added, and the phases separated. The combined organic portion was washed with brine (30 ml), then water (20 ml), then dried over $MgSO_4$ and filtered. The solvent was removed, and the residue was eluted through a silica gel pad using EA/CH_2Cl_2/hexanes (1:2:10) as eluent. The solvent was removed, and the residue dried under vacuum to give the product as a white crystalline solid. Yield = 0.61 g.

Example 21. Preparation of 3-iodo-4-methoxy-1H-indole



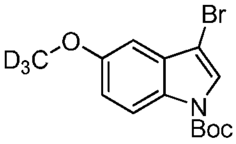
A solution of iodine (2.57 g, 10.1 mmol) in DMF (15 ml) was added dropwise to a mixture of 4-methoxyindole (1.5 g, 10.2 mmol) in DMF (15 ml) and KOH (1.66 g, 25 mmol) at room temperature. The mixture was stirred for 50 minutes, then the reaction mixture poured into ice-water (200 ml) containing 1% NH_4OH and 0.2% sodium sulphite. The precipitate was filtered, washed with ice-water and dried under vacuum. The product was obtained as a brown solid. Yield = 2.55 g.

Example 22. Preparation of tert-butyl 3-Iodo-4-methoxy-1H-indole-1-carboxylate



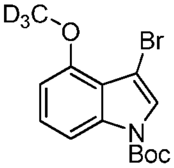
A solution of $(Boc)_2O$ (2.24 g, 10.3 mmol) in dichloromethane (10 ml) was added to a mixture of 3-iodo-4-methoxy-1H-indole (2.55 g, 9.3 mmol), triethylamine (1.9 g, 18.6 mmol), DMAP (11 mg) in dichloromethane (30 ml) and the reaction stirred overnight at room temperature. It was quenched with saturated $NaHCO_3$ solution (20 ml) and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml). The combined organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed, and the residue eluted through a silica gel pad using CH_2Cl_2/hexanes (1:2) as eluent. The solvent was removed, and the residue was dried under vacuum to give the product as a grey crystalline solid, that darkens over time. It was stored in the dark. Yield = 3.4 g.

Example 23. Preparation of tert-butyl 3-bromo-5-(methoxy-d_3)-1H-indole-1-carboxylate



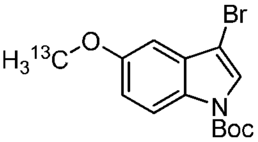
This was prepared from 5-(methoxy-d_3)-1H-indole using the procedures described in Examples 15 and 16.

Example 24. Preparation of tert-butyl 3-bromo-4-(methoxy-d_3)-1H-indole-1-carboxylate



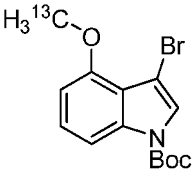
This was prepared using 4-(methoxy-d_3)-1H-indole and the procedures described in Examples 7 and 8.

Example 25. Preparation of tert-butyl 3-bromo-5-(methoxy-^{13}C)-1H-indole-1-carboxylate



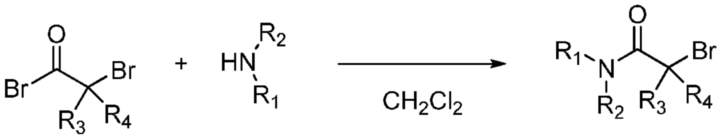
This was prepared from 5-(methoxy-^{13}C)-1H-indole using the procedures described in Examples 15 and 16.

Example 26. Preparation of tert-butyl 3-bromo-4-(methoxy-^{13}C)-1H-indole-1-carboxylate



This was prepared from 4-(methoxy-^{13}C)-1H-indole using the procedures described in Examples 15 and 16.

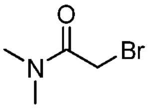
Example 27. General procedure for the preparation of α-bromo amides



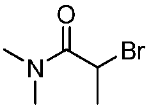
A solution of the amine (99.1 mmol) in dichloromethane (100 ml) was added to a solution of 2-bromoacetyl bromide (49.5 mmol) in dichloromethane (50 ml) at -16 °C over 30 minutes and the reaction mixture stirred for another 30 minutes after the addition was completed. It was allowed to warm to room temperature and stirred for another one hour. Water (50 ml) was added, and the phases separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml). The combined organic portion was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under vacuum to yield the product.

This procedure was used for the preparation of the α-bromo amides below.

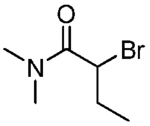
Example 27(i). 2-Bromo-N,N-dimethylacetamide



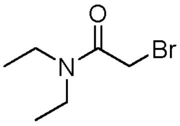
Example 27(ii). 2-Bromo-N,N-dimethylpropanamide



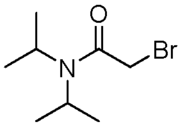
Example 27(iii). 2-Bromo-N,N-dimethylbutanamide



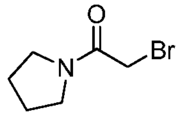
Example 27(iv). 2-Bromo-N,N-diethylacetamide



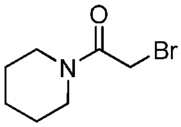
Example 27(v). 2-Bromo-N,N-diisopropylacetamide



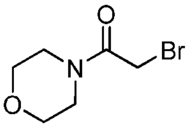
Example 27(vi). 2-Bromo-1-(pyrrolidin-1-yl)ethanone



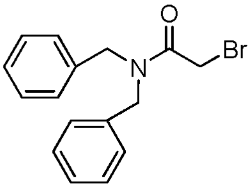
Example 27(vii). 2-Bromo-1-(piperidin-1-yl)ethanone



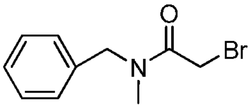
Example 27(viii). 2-Bromo-1-morpholinoethanone



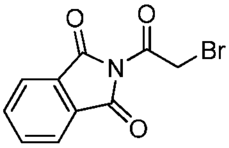
Example 27(ix). N,N-Dibenzyl-2-bromoacetamide



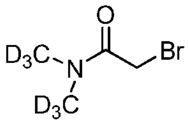
Example 27(x). N-Benzyl-2-bromo-N-methylacetamide



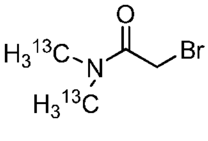
Example 27(xi). 2-(2-Bromoacetyl)isoindoline-1,3-dione



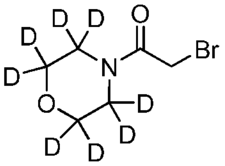
Example 27(xii). 2-Bromo-N,N-bis(methyl-d_3)acetamide



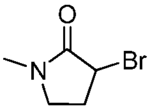
Example 27(xiii). 2-Bromo-N,N-di(methyl-^{13}C)acetamide



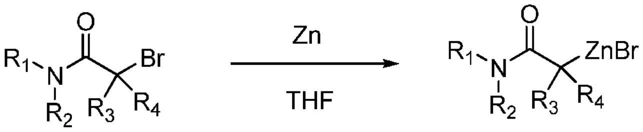
Example 27(xiv). 2-Bromo-1-(morpholino-d$_8$)ethan-1-one



3-Bromo-1-methylpyrrolidin-2-one was obtained from commercial sources.



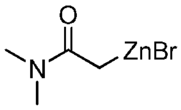
Example 28. General procedure for the preparation of zinc amide enolates



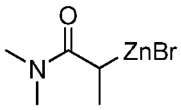
Zinc granules (0.90 g, 13.76 mmol) were dried under vacuum while heating in a Schlenk flask, then refilled with argon. The flask was cooled to room temperature and a pinch of iodine was added while the flask was still warm. The a-bromo amide (12.53 mmol) was degassed with argon and dry THF (22 ml) added. The amide solution was added dropwise to the zinc at 0 °C with vigorous stirring. The mixture was allowed to warm to room temperature after the addition was completed and the stirring continued until all the amide reacted. The zinc amide enolates were used as a suspension in THF.

This procedure was used for the preparation of the zinc amide enolates below.

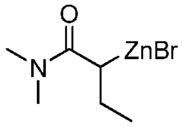
Example 28(i). (2-(Dimethylamino)-2-oxoethyl)zinc(II) bromide



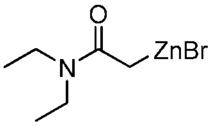
Example 28(ii). (1-(Dimethylamino)-1-oxopropan-2-yl)zinc(II) bromide



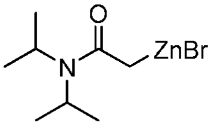
Example 28(iii). (1-(Dimethylamino)-1-oxobutan-2-yl)zinc(II) bromide



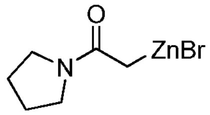
Example 28(iv). (2-(Diethylamino)-2-oxoethyl)zinc(II) bromide



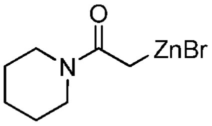
Example 28(v). (2-(Diisopropylamino)-2-oxoethyl)zinc(II) bromide



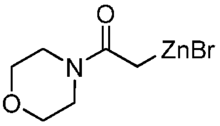
Example 28(vi). (2-Oxo-2-(pyrrolidin-1-yl)ethyl)zinc(II) bromide



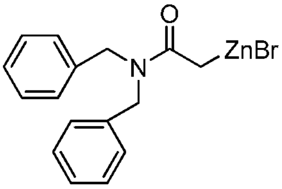
Example 28(vii). (2-Oxo-2-(piperidin-1-yl)ethyl)zinc(II) bromide



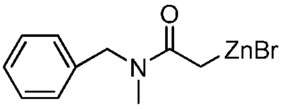
Example 28(viii). (2-Morpholino-2-oxoethyl)zinc(II) bromide



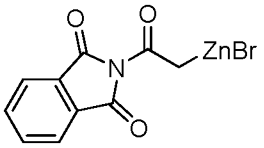
Example 28(ix). (2-(Dibenzylamino)-2-oxoethyl)zinc(II) bromide



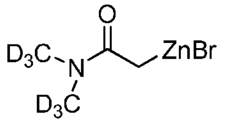
Example 28(x). (2-(Benzyl(methyl)amino)-2-oxoethyl)zinc(II) bromide



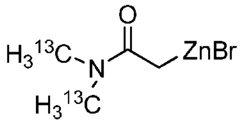
Example 28(xi). (2-(1,3-Dioxoisoindolin-2-yl)-2-oxoethyl)zinc(II) bromide



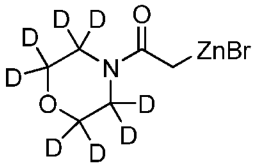
Example 28(xii). (2-bis(methyl-d$_3$)amino)-2-oxoethyl)zinc(II) bromide



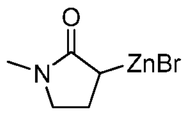
Example 28(xiii). (2-(di(methyl-^{13}C)amino)-2-oxoethyl)zinc(II) bromide



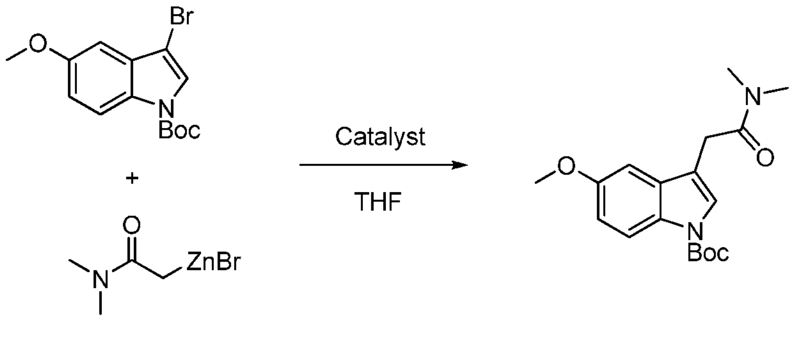
Example 28(xiv). (2-(Morpholino-d$_8$)-2-oxoethyl)zinc(II) bromide



Example 28(xv). (1-Methyl-2-oxopyrrolidin-3-yl)zinc(II) bromide



Example 29. Catalyst screening for the Negishi coupling of tert-butyl 3-bromo-5-methoxy-1H-indole-1-carboxylate and (2-(dimethylamino)-2-oxoethyl)zinc(II) bromide

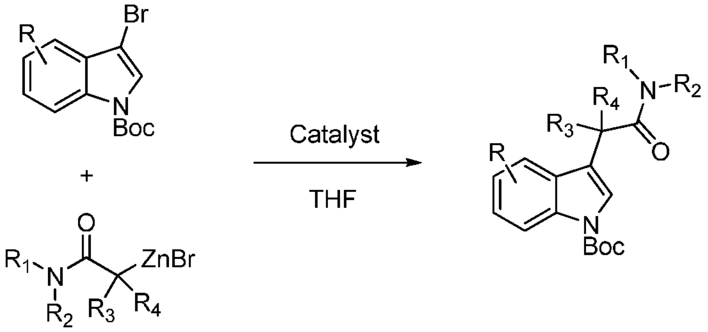


A THF suspension of (2-(dimethylamino)-2-oxoethyl)zinc(II) bromide (1.0 ml, 0.5 mmol) was added to a mixture of tert-butyl 3-bromo-5-methoxy-1H-indole-1-carboxylate (100 mg, 0.3 mmol) and the catalyst (0.015 mmol) in a Schlenk flask under argon. The mixture was stirred at the required temperature under argon and the reaction progress monitored by TLC and ^{1}H NMR. The results for the various catalyst investigated are summarized in Table 1.

Table 1. Catalysts used in Example 29.

Example	Catalyst	Temp./ºC	Time/hour	Conv./%
i	$PdCl_2$(dppf)	65	20	< 5
ii	$PdCl_2$(dppe)	65	20	0
iii	$NiCl_2$(dppf)	65	20	0
iv	$NiCl_2$(dppe)	65	20	0
vi	$PdCl_2(PPh_3)_2$	65	20	0
vii	$PdCl_2$(Xantphos)	65	20	< 5
viii	(Xantphos)PdG2	65	20	< 5
ix	XPhosPdG1	65	20	10
x	RuPhosPdG1	65	20	10
xi	SPhosPdG1	65	20	10
xii	tBuXPhosPdG1	65	20	100
xiii	tBuXPhosPdG1	35	20	25
xiv	tBuXPhosPdG1	50	20	50
xv	tBuXPhosPdG1	65	5	75
xvi	tBuXPhosPdG1	65	16	100
xvii	QPhos/$Pd(dba)_2$	65	20	< 5
xviii	$PtBu_3$PdG2	65	20	< 5
xix	PCy_3PdG2	65	20	< 5
xx	BrettPhosPdG1	65	20	10
xxi	PEPPSI-IPr	65	20	0
xxii	PEPPSI-SIPr	65	20	0

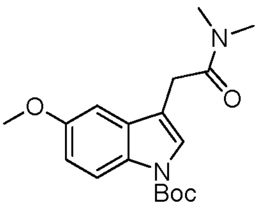
Example 30. General procedure for the Negishi coupling of 3-halo-indoles and zinc amide enolates



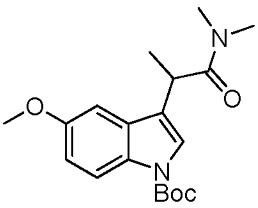
A suspension of the zinc amide enolate (2.5 mmol) was added to a mixture of the 3-halo-indole (1.5 mmol) and the catalyst tBuXPhosPdG1 (50 mg, 0.073 mmol) in a Schlenk flask under argon. The mixture was stirred at 65 °C under argon for 16 hours. it was cooled to room temperature and the solvent removed under reduced pressure. Water (10 ml) and ether (10 ml) were added with stirring and the phases separated. The ether layer was dried over $MgSO_4$, then filtered and the solvent removed under reduced pressure. The residue was eluted through a silica gel pad. The eluent was evaporated to yield the crude product, which was purified by silica gel chromatography.

This procedure was used for the preparation of the products below.

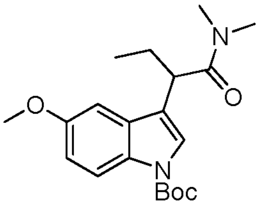
Example 30(i). tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



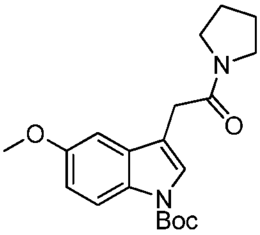
Example 30(ii). tert-Butyl 3-(1-(dimethylamino)-1-oxopropan-2-yl)-5-methoxy-1H-indole-1-carboxylate



Example 30(iii). tert-Butyl 3-(1-(dimethylamino)-1-oxobutan-2-yl)-5-methoxy-1H-indole-1-carboxylate



Example 30(iv). tert-Butyl 5-methoxy-3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate



Example 30(v). tert-Butyl 5-methoxy-3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate

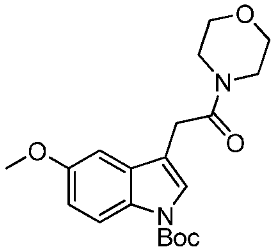
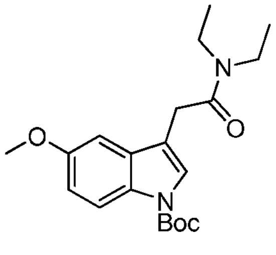


Figure 20 shows the ^{1}H NMR spectrum of tert-Butyl 5-methoxy-3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate.

Example 30(vi). tert-Butyl 3-(2-(diethylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



Example 30(vii). tert-Butyl 3-(2-(diisopropylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate

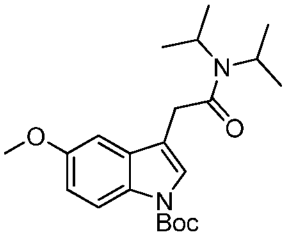
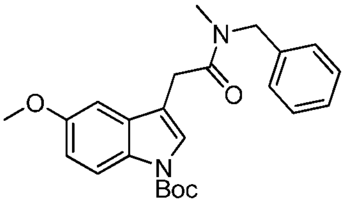
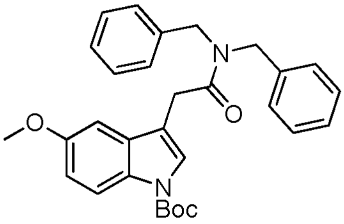


Figure 4 shows the X-ray crystal structure of tert-Butyl 3-(2-(diisopropylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate.

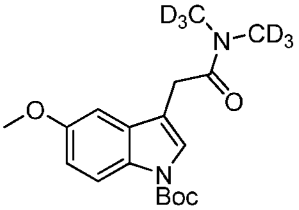
Example 30(viii). tert-Butyl 3-(2-(benzyl(methyl)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



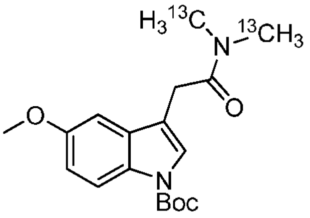
Example 30(ix). tert-Butyl 3-(2-(dibenzylamino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



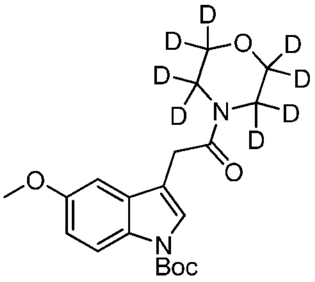
Example 30(x). tert-Butyl 3-(2-(bis(methyl-d$_3$)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



Example 30(xi). tert-Butyl 3-(2-(di(methyl-^{13}C)amino)-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate



Example 30(xii). tert-Butyl 5-methoxy-3-(2-(morpholino-d8)-2-oxoethyl)-1H-indole-1-carboxylate



Example 30(xiii). tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-1H-indole-1-carboxylate

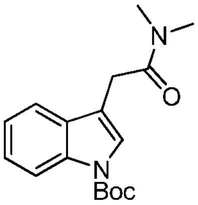


Figure 8 shows the ^{1}H NMR spectrum of tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-1H-indole-1-carboxylate.

Example 30(xiv). tert-Butyl 3-(1-(dimethylamino)-1-oxopropan-2-yl)-1H-indole-1-carboxylate

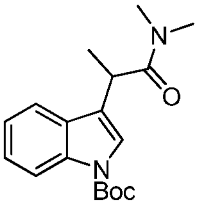
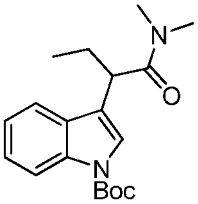
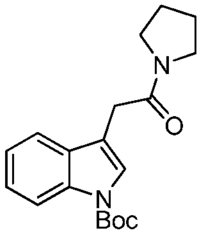


Figure 10 shows the ^{1}H NMR spectrum of tert-Butyl 3-(1-(dimethylamino)-1-oxopropan-2-yl)-1H-indole-1-carboxylate.

Example 30(xv). tert-Butyl 3-(1-(dimethylamino)-1-oxobutan-2-yl)-1H-indole-1-carboxylate



Example 30(xvi). tert-Butyl 3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate



Example 30(xvii). tert-Butyl 3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate

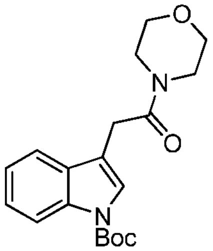
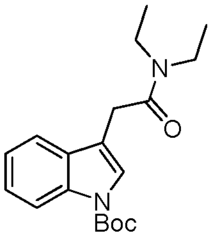
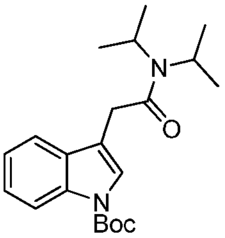


Figure 17 shows the ^{1}H NMR spectrum of tert-Butyl 3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate.

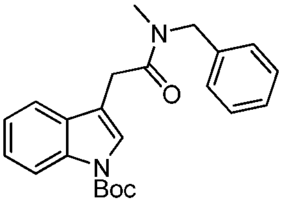
Example 30(xviii). tert-Butyl 3-(2-(diethylamino)-2-oxoethyl)-1H-indole-1-carboxylate



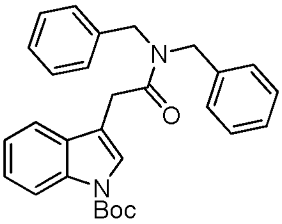
Example 30(xix). tert-Butyl 3-(2-(diisopropylamino)-2-oxoethyl)-1H-indole-1-carboxylate



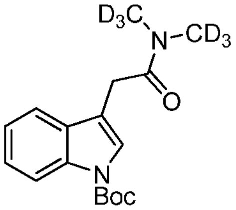
Example 30(xx). tert-Butyl 3-(2-(benzyl(methyl)amino)-2-oxoethyl)-1H-indole-1-carboxylate



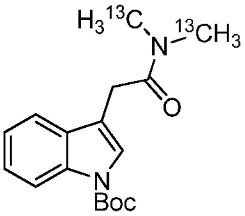
Example 30(xxi). tert-Butyl 3-(2-(dibenzylamino)-2-oxoethyl)-1H-indole-1-carboxylate



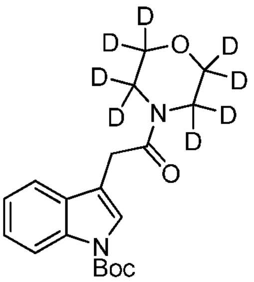
Example 30(xxii). tert-Butyl 3-(2-(bis(methyl-d_3)amino)-2-oxoethyl)-1H-indole-1-carboxylate



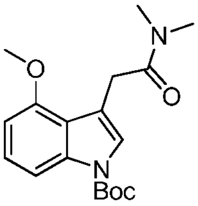
Example 30(xxiii). tert-Butyl 3-(2-(di(methyl-^{13}C)amino)-2-oxoethyl)-1H-indole-1-carboxylate



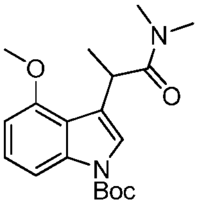
Example 30(xxiv). tert-Butyl 3-(2-(morpholino-d_8)-2-oxoethyl)-1H-indole-1-carboxylate



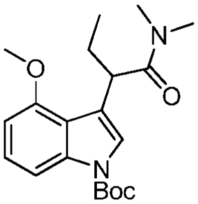
Example 30(xxv). tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



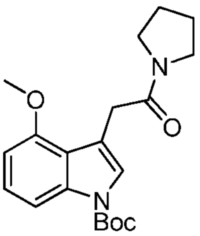
Example 30(xxvi). tert-Butyl 3-(1-(dimethylamino)-1-oxopropan-2-yl)-4-methoxy-1H-indole-1-carboxylate



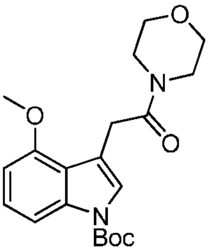
Example 30(xxvii). tert-Butyl 3-(1-(dimethylamino)-1-oxobutan-2-yl)-4-methoxy-1H-indole-1-carboxylate



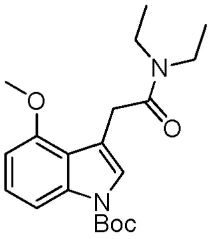
Example 30(xxviii). tert-Butyl 4-methoxy-3-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate



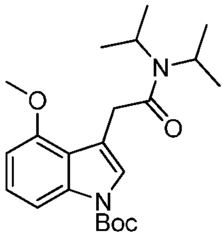
Example 30(xxix). tert-Butyl 4-methoxy-3-(2-morpholino-2-oxoethyl)-1H-indole-1-carboxylate



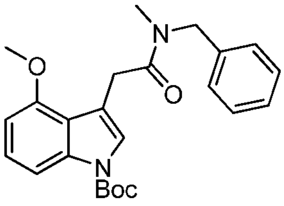
Example 30(xxx). tert-Butyl 3-(2-(diethylamino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



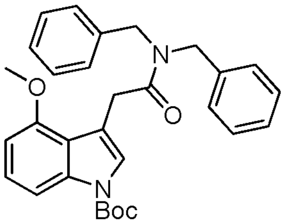
Example 30(xxxi). tert-Butyl 3-(2-(diisopropylamino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



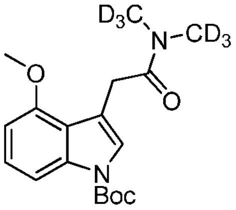
Example 30(xxxii). tert-Butyl 3-(2-(benzyl(methyl)amino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



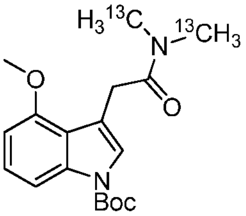
Example 30(xxxiii). tert-Butyl 3-(2-(dibenzylamino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



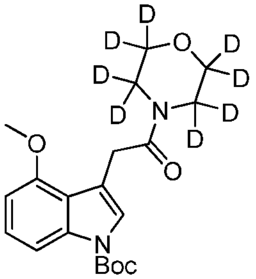
Example 30(xxxiv). tert-Butyl 3-(2-(bis(methyl-d3)amino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



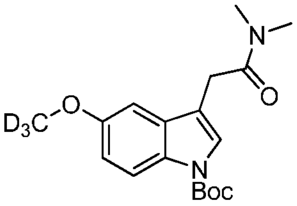
Example 30(xxxv). tert-Butyl 3-(2-(di(methyl-^{13}C)amino)-2-oxoethyl)-4-methoxy-1H-indole-1-carboxylate



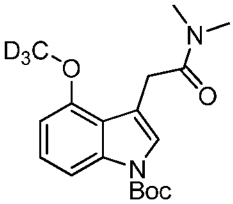
Example 30(xxxvi). tert-Butyl 4-methoxy-3-(2-(morpholino-d_8)-2-oxoethyl)-1H-indole-1-carboxylate



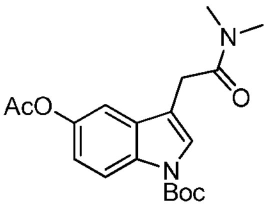
Example 30(xxxvii). tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-5-(methoxy-d_3)-1H-indole-1-carboxylate



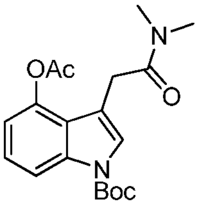
Example 30(xxxviii). tert-Butyl 3-(2-(dimethylamino)-2-oxoethyl)-4-(methoxy-d_3)-1H-indole-1-carboxylate



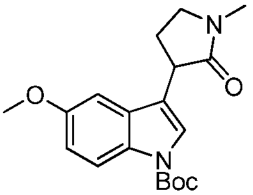
Example 30(xxxix). tert-Butyl 5-acetoxy-3-(2-(dimethylamino)-2-oxoethyl)-1H-indole-1-carboxylate



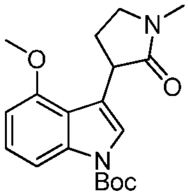
Example 30(xxxx). tert-Butyl 4-acetoxy-3-(2-(dimethylamino)-2-oxoethyl)-1H-indole-1-carboxylate



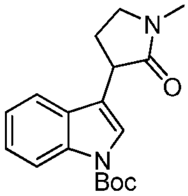
Example 30(xxxxi). tert-Butyl 5-methoxy-3-(1-methyl-2-oxopyrrolidin-3-yl)-1H-indole-1-carboxylate



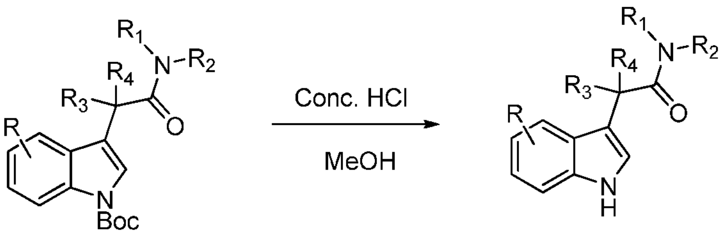
Example 30(xxxxii). tert-Butyl 4-methoxy-3-(1-methyl-2-oxopyrrolidin-3-yl)-1H-indole-1-carboxylate



Example 30(xxxxiii). tert-Butyl 3-(1-methyl-2-oxopyrrolidin-3-yl)-1H-indole-1-carboxylate



Example 31. General procedure for the preparation of 2-(1H-indol-3-yl) acetamides



A mixture of Conc. HCl (1.0 ml) and methanol (2 ml) was added to the tert-butyl 3-(2-amino-2-oxoethyl)-1H-indole-1-carboxylate (50 mg) and the mixture stirred for 12-24 hours at room temperature until the reaction was completed (TLC). The mixture was evaporated under reduced pressure and sodium carbonate solution added to the residue. The mixture was stirred for 10 minutes, then dichloromethane added, and the phases separated. The organic layer was dried over $MgSO_4$, then filtered and the solvent removed under reduced pressure. The residue was eluted through a silica gel pad. The eluent was evaporated to yield the crude product, which was purified by silica gel chromatography.

This procedure was used for the preparation of the products below.

Example 31(i). 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethylacetamide

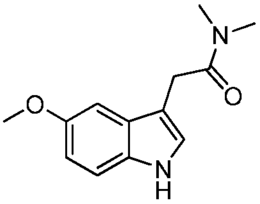
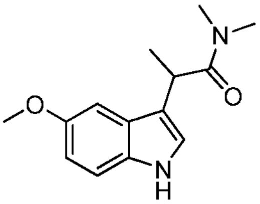
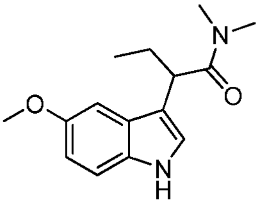


Figure 13 shows the ^{1}H NMR spectrum of 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethylacetamide.

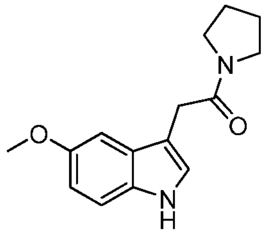
Example 31(ii). 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethylpropanamide



Example 31(iii). 2-(5-Methoxy-1H-indol-3-yl)-N,N-dimethylbutanamide



Example 31(iv). 2-(5-Methoxy-1H-indol-3-yl)-1-(pyrrolidin-1-yl)ethanone



Example 31(v). 2-(5-Methoxy-1H-indol-3-yl)-1-morpholinoethanone

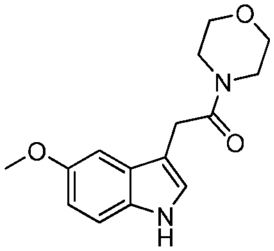
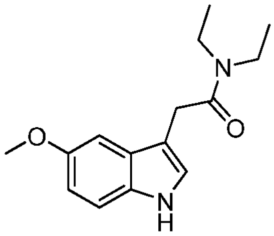


Figure 21 shows the ^{1}H NMR spectrum of 2-(5-Methoxy-1H-indol-3-yl)-1-morpholinoethanone.

Example 31(vi). N,N-diethyl-2-(5-methoxy-1H-indol-3-yl)acetamide



Example 31(vii). N,N-Diisopropyl-2-(5-methoxy-1H-indol-3-yl)acetamide

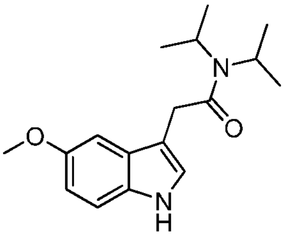
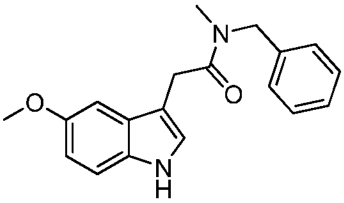
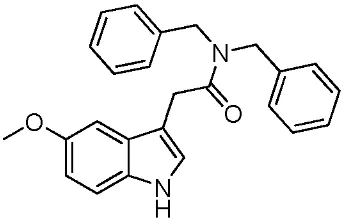


Figure 16 shows the ^{1}H NMR spectrum of N,N-Diisopropyl-2-(5-methoxy-1H-indol-3-yl)acetamide.

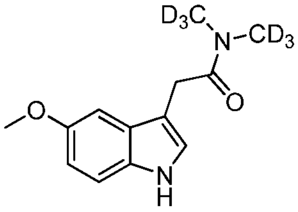
Example 31(viii). N-Benzyl-2-(5-methoxy-1H-indol-3-yl)-N-methylacetamide



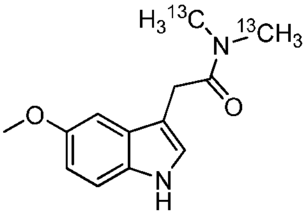
Example 31(ix). N,N-dibenzyl-2-(5-methoxy-1H-indol-3-yl)acetamide



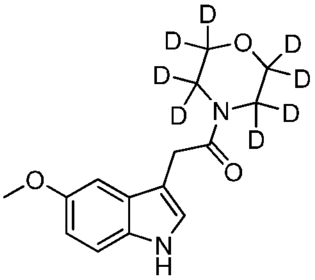
Example 31(x). 2-(5-Methoxy-1H-indol-3-yl)-N,N-bis(dimethyl-d_3)acetamide



Example 31(xi). 2-(5-Methoxy-1H-indol-3-yl)-N,N-di(methyl-^{13}C)acetamide



Example 31(xii). 2-(5-Methoxy-1H-indol-3-yl)-1-(morpholino-d_8)ethanone



Example 31(xiii). 2-(1H-indol-3-yl)-N,N-dimethylacetamide

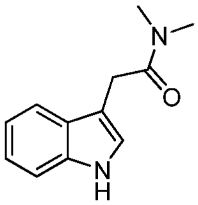


Figure 9 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylacetamide.

Example 31(xiv). 2-(1H-indol-3-yl)-N,N-dimethylpropanamide

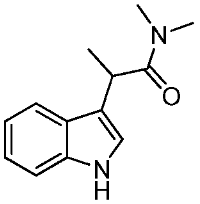


Figure 11 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylpropanamide.

Example 31(xv). 2-(1H-indol-3-yl)-N,N-dimethylbutanamide

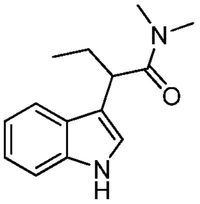
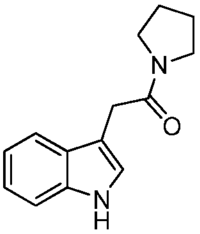


Figure 6 shows the X-ray crystal structure of 2-(1H-indol-3-yl)-N,N-dimethylbutanamide.

Figure 12 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-dimethylbutanamide.

Example 31(xvi). 2-(1H-indol-3-yl)-1-(pyrrolidin-1-yl)ethanone



Example 31(xvii). 2-(1H-indol-3-yl)-1-morpholinoethanone

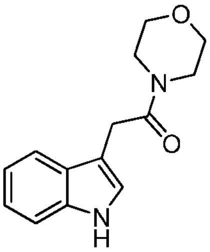
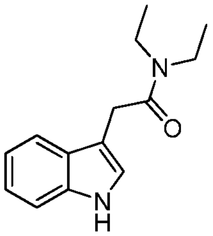


Figure 18 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-1-morpholinoethanone.

Example 31(xviii). N,N-diethyl-2-(1H-indol-3-yl)acetamide



Example 31(xix). 2-(1H-indol-3-yl)-N,N-diisopropylacetamide

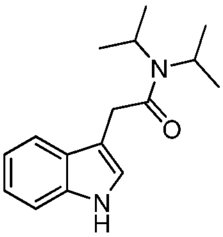
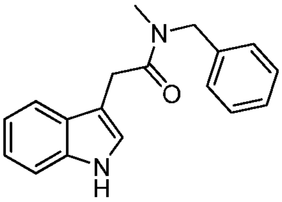


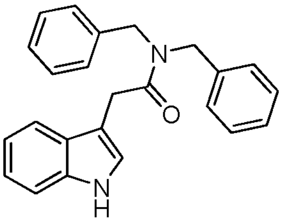
Figure 5 shows the X-ray crystal structure of 2-(1H-indol-3-yl)-N,N-diisopropylacetamide.

Figure 15 shows the ^{1}H NMR spectrum of 2-(1H-indol-3-yl)-N,N-diisopropylacetamide.

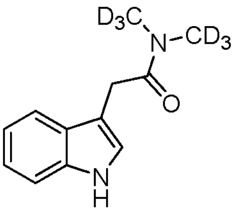
Example 31(xx). N-benzyl-2-(1H-indol-3-yl)-N-methylacetamide



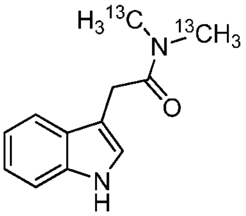
Example 31(xxi). N,N-dibenzyl-2-(1H-indol-3-yl)acetamide



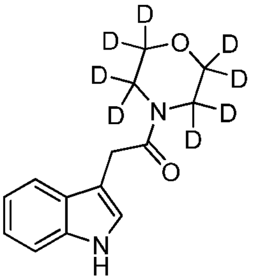
Example 31(xxii). 2-(1H-indol-3-yl)-N,N-bis(methyl-d$_3$)acetamide



Example 31(xxiii). 2-(1H-indol-3-yl)-N,N-di(methyl-^{13}C)acetamide



Example 31(xxiv). 2-(1H-indol-3-yl)-1-(morpholino-d_8)ethanone



Example 31(xxv). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylacetamide

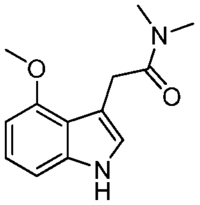
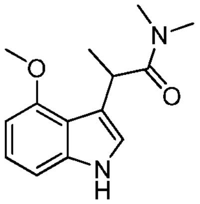
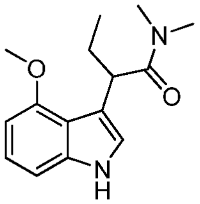


Figure 14 shows the ^{1}H NMR spectrum of 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylacetamide.

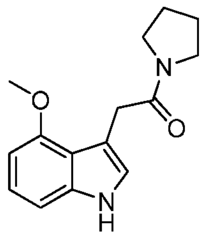
Example 31(xxvi). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylpropanamide



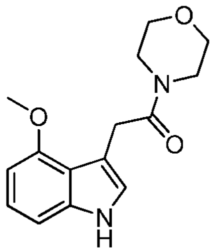
Example 31(xxvii). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylbutanamide



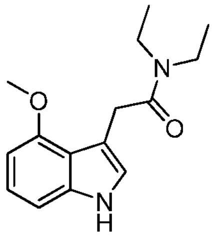
Example 31(xxviii). 2-(4-methoxy-1H-indol-3-yl)-1-(pyrrolidin-1-yl)ethanone



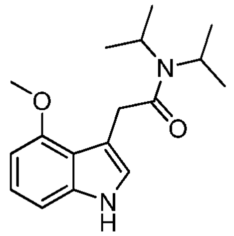
Example 31(xxix). 2-(4-methoxy-1H-indol-3-yl)-1-morpholinoethanone



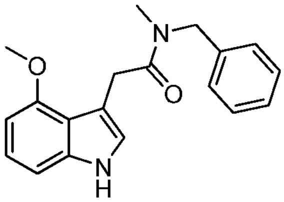
Example 31(xxx). N,N-diethyl-2-(4-methoxy-1H-indol-3-yl)acetamide



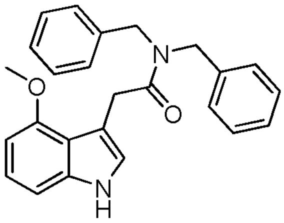
Example 31(xxxi). N,N-diisopropyl-2-(4-methoxy-1H-indol-3-yl)acetamide



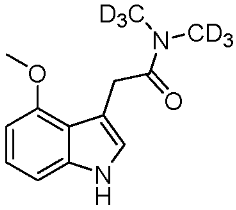
Example 31(xxxii). N-benzyl-2-(4-methoxy-1H-indol-3-yl)-N-methylacetamide



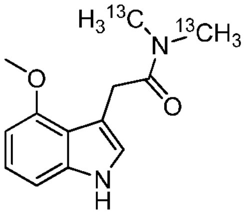
Example 31(xxxiii). N,N-dibenzyl-2-(4-methoxy-1H-indol-3-yl)acetamide



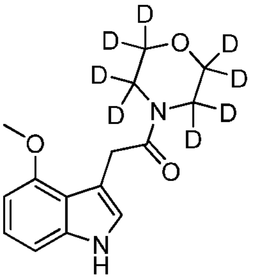
Example 31(xxxiv). 2-(4-methoxy-1H-indol-3-yl)-N,N-bis(methyl-d$_3$)acetamide



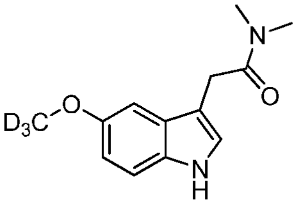
Example 31(xxxv). 2-(4-methoxy-1H-indol-3-yl)-N,N-di(methyl-^{13}C)acetamide



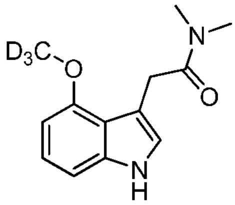
Example 31(xxxvi). 2-(4-methoxy-1H-indol-3-yl)-1-(morpholino-d$_8$)ethanone



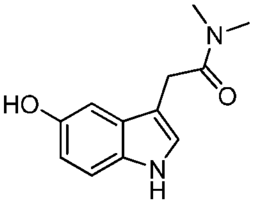
Example 31(xxxvii). 2-(5-(Methoxy-d$_3$)-1H-indol-3-yl)-N,N-dimethylacetamide



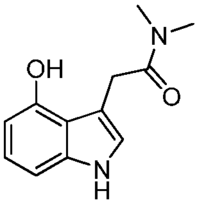
Example 31(xxxviii). 2-(4-(Methoxy-d_3)-1H-indol-3-yl)-N,N-dimethylacetamide



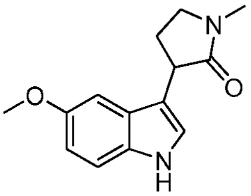
Example 31(xxxix). 2-(5-hydroxy-1H-indol-3-yl)-N,N-dimethylacetamide



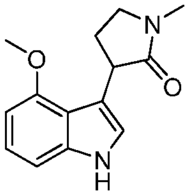
Example 31(xxxx). 2-(4-hydroxy-1H-indol-3-yl)-N,N-dimethylacetamide



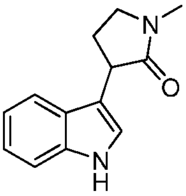
Example 31(xxxxi). 3-(5-methoxy-1H-indol-3-yl)-1-methylpyrrolidin-2-one



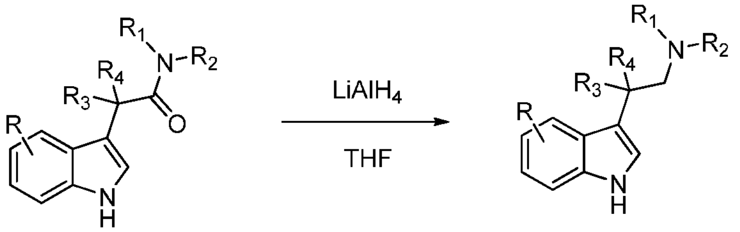
Example 31(xxxxii). 3-(4-methoxy-1H-indol-3-yl)-1-methylpyrrolidin-2-one



Example 31(xxxxiii). 3-(1H-indol-3-yl)-1-methylpyrrolidin-2-one



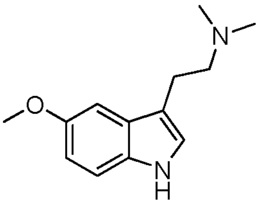
Example 32. General procedure for the preparation of 2-(1H-indol-3-yl ethanamines



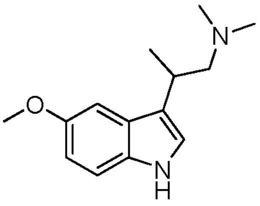
Lithium aluminium hydride solution (1.0 ml of a 1.0 M solution in THF) was added to the 2-(1H-indol-3-yl) acetamide (50 mg) in a Schlenk flask under argon and the mixture stirred for one hour. The solvent was removed, and ether (2 ml) added. Water (2 ml) was added dropwise at 0 °C and the resulting suspension stirred for 30 minutes. The phases were separated, and the ether layer was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product.

This procedure was used for the preparation of the products below.

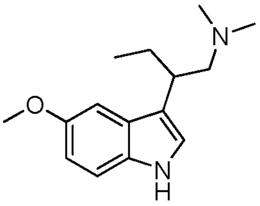
Example 32(i). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine



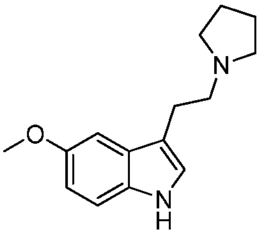
Example 32(ii). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylpropan-1-amine



Example 32(iii). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylbutan-1-amine



Example 32(iv). 5-methoxy-3-(2-(pyrrolidin-1-yl)ethyl)-1H-indole



Example 32(v). 4-(2-(5-methoxy-1H-indol-3-yl)ethyl)morpholine

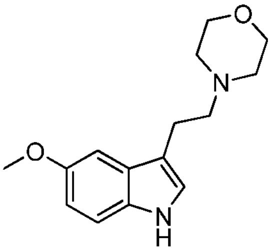
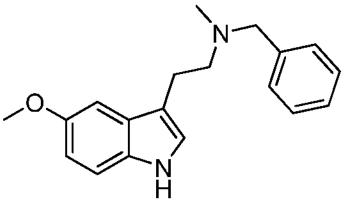
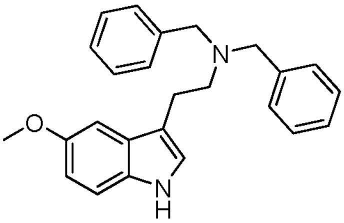


Figure 22 shows the ^{1}H NMR spectrum of 4-(2-(5-methoxy-1H-indol-3-yl)ethyl)morpholine.

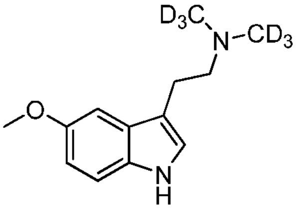
Example 32(vi). N-benzyl-2-(5-methoxy-1H-indol-3-yl)-N-methylethanamine



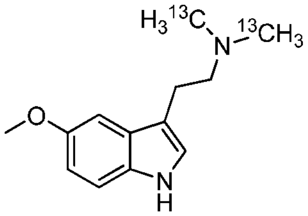
Example 32(vii). N,N-dibenzyl-2-(5-methoxy-1H-indol-3-yl)ethanamine



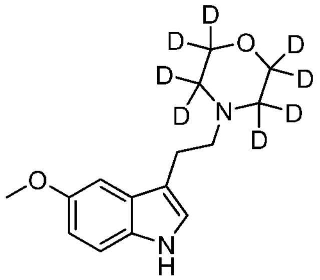
Example 32(viii). 2-(5-methoxy-1H-indol-3-yl)-N,N-bis(methyl-d$_3$)ethanamine



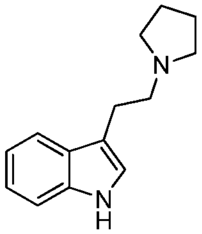
Example 32(ix). 2-(5-methoxy-1H-indol-3-yl)-N,N-di(methyl-^{13}C)ethanamine



Example 32(x). 4-(2-(5-methoxy-1H-indol-3-yl)ethyl)morpholine-d$_8$



Example 32(xi). 3-(2-(pyrrolidin-1-yl)ethyl)-1H-indole



Example 32(xii). 4-(2-(1H-indol-3-yl)ethyl)morpholine

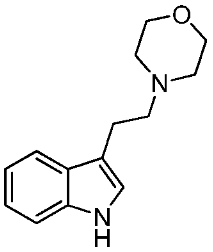
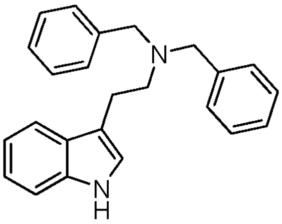


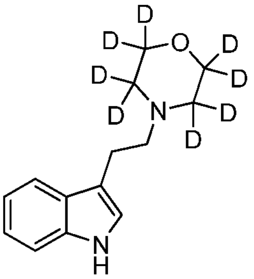
Figure 7 shows the X-ray crystal structure of 4-(2-(1H-indol-3-yl)ethyl)morpholine.

Figure 19 shows the ^{1}H NMR spectrum of 4-(2-(1H-indol-3-yl)ethyl)morpholine.

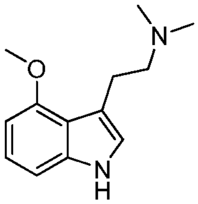
Example 32(xiii). N,N-dibenzyl-2-(1H-indol-3-yl)ethanamine



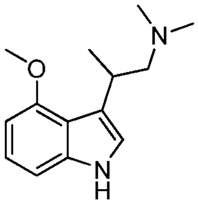
Example 32(xiv). 4-(2-(1H-indol-3-yl)ethyl)morpholine-d8



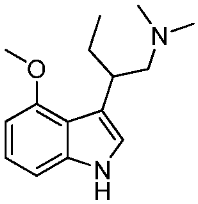
Example 32(xv). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine



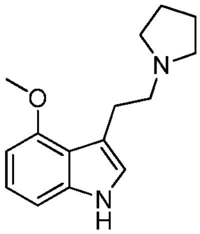
Example 32(xvi). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylpropan-1-amine



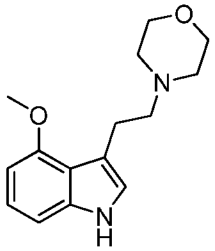
Example 32(xvii). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylbutan-1-amine



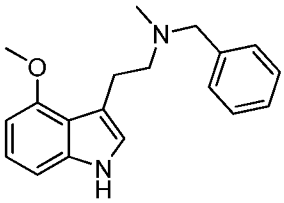
Example 32(xviii). 4-methoxy-3-(2-(pyrrolidin-1-yl)ethyl)-1H-indole



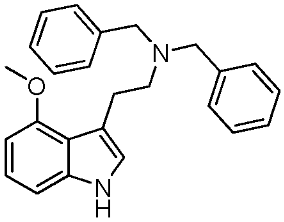
Example 32(xix). 4-(2-(4-methoxy-1H-indol-3-yl)ethyl)morpholine



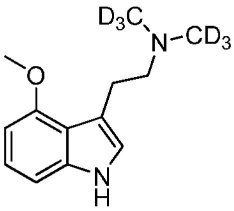
Example 32(xx). N-benzyl-2-(4-methoxy-1H-indol-3-yl)-N-methylethanamine



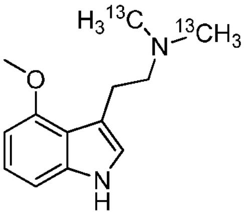
Example 32(xxi). N,N-dibenzyl-2-(4-methoxy-1H-indol-3-yl)ethanamine



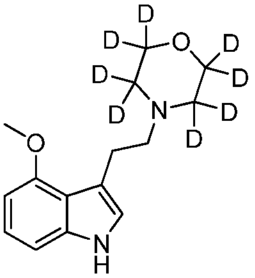
Example 32(xxii). 2-(4-methoxy-1H-indol-3-yl)-N,N-bis(methyl-d_3)ethanamine



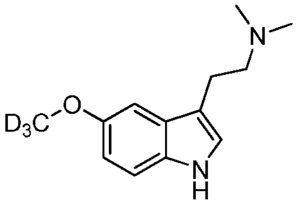
Example 32(xxiii). 2-(4-methoxy-1H-indol-3-yl)-N,N-di(methyl-^{13}C)ethan-1-amine



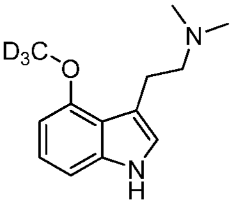
Example 32(xxiv). 4-(2-(4-methoxy-1H-indol-3-yl)ethyl)morpholine-d$_8$



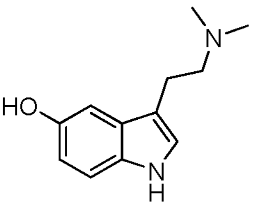
Example 32(xxv). 2-(5-(methoxy-d$_3$)-1H-indol-3-yl)-N,N-dimethylethan-1-amine



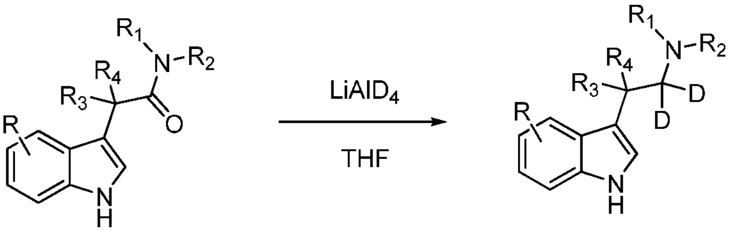
Example 32(xxvi). 2-(4-(methoxy-d$_3$)-1H-indol-3-yl)-N,N-dimethylethan-1-amine



Example 32(xxvii). 3-(2-(dimethylamino)ethyl)-1H-indol-5-ol



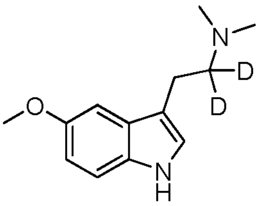
Example 33. General procedure for the LiAlD$_4$ reduction of 2-(1H-indol-3-yl) acetamides



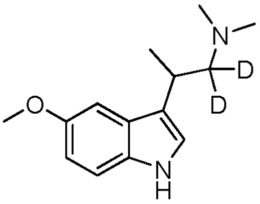
Lithium aluminium deuteride solution (1.0 ml of a 1.0 M solution in THF) was added to the 2-(1H-indol-3-yl) acetamide (50 mg) in a Schlenk flask under argon and the mixture stirred for one hour. The solvent was removed, and ether (2 ml) added. Water (2 ml) was added dropwise at 0 °C and the resulting suspension stirred for 30 minutes. The phases were separated, and the ether layer was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product.

This procedure was used for the preparation of the products below.

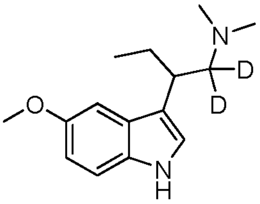
Example 33(i). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethan-1-amine-1,1-d$_2$



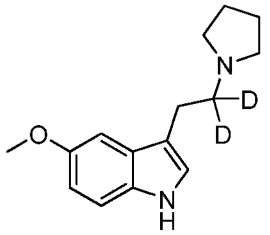
Example 33(ii). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylpropan-1-amine-1,1-d$_2$



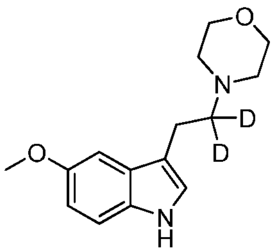
Example 33(iii). 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylbutan-1-amine-1,1-d$_2$



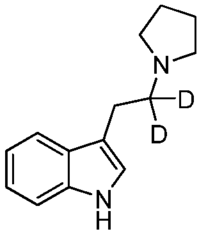
Example 33(iv). 5-methoxy-3-(2-(pyrrolidin-1-yl)ethyl-2,2-d$_2$)-1H-indole



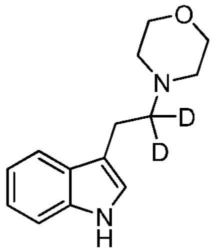
Example 33(v). 4-(2-(5-methoxy-1H-indol-3-yl)ethyl-1,1-d$_2$)morpholine



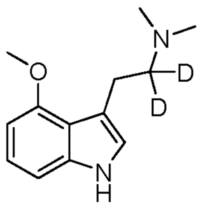
Example 33(vi). 3-(2-(pyrrolidin-1-yl)ethyl-2,2-d$_2$)-1H-indole



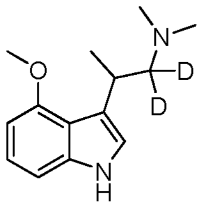
Example 33(vii). 4-(2-(1H-indol-3-yl)ethyl-1,1-d$_2$)morpholine



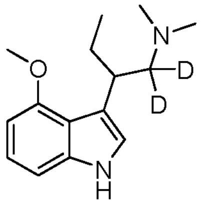
Example 33(viii). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylethan-1-amine-1,1-d$_2$



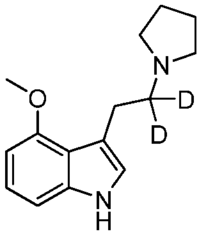
Example 33(ix). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylpropan-1-amine-1,1-d$_2$



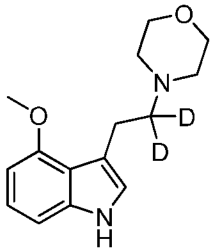
Example 33(x). 2-(4-methoxy-1H-indol-3-yl)-N,N-dimethylbutan-1-amine-1,1-d$_2$



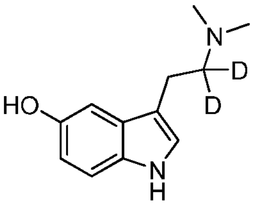
Example 33(xi). 4-methoxy-3-(2-(pyrrolidin-1-yl)ethyl-2,2-d$_2$)-1H-indole



Example 33(xii). 4-(2-(4-methoxy-1H-indol-3-yl)ethyl-1,1-d$_2$)morpholine



Example 33(xiii). 3-(2-(dimethylamino)ethyl-2,2-d$_2$)-1H-indol-5-ol

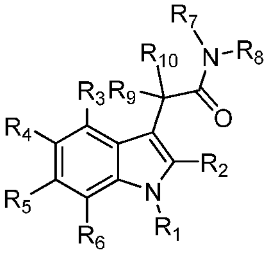


While the foregoing disclsoure has been described in some detail for purposes of clarity and understanding, it will be appreciated by one skilled in the art, from a reading of the disclosure that various changes in form and detail can be made without departing from the true scope of the disclosure in the appended claims.

All publications, patents, and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

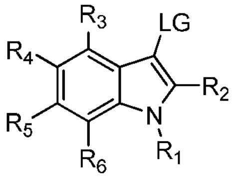
WHAT IS CLAIMED IS:

1. A process for the preparation of compounds of Formula (III):



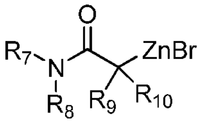
(III),

comprising contacting a compound of Formula (I):



(I),

with a compound of Formula (II):



(II)

in the presence of a catalyst,

wherein,

R_1 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, -(C=O)-O-(C_1-C_{20})-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, or (C_6-C_{20})-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl;

R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_3-C_{20})-cycloalkyl, (C_6-C_{20})-aryl, (C_5-C_{20})-heteroaryl, -C(=O)-(C_1-C_{20})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and $(C_1\text{-}C_6)$-alkyl;

LG represents any suitable leaving group.

2. The process according to claim 1, wherein one or more of the carbon-12 atoms in a compound of Formula (III) are replaced with carbon-13.

3. The process according to any one of claims 1 to 2, wherein the compound of Formula (III) is achiral.

4. The process according to any one of claims 1 to 3, wherein the compound of Formula (III) is chiral.

5. The process according to any one of claims 1 to 4, wherein the catalyst comprises transition metal salts and complexes.

6. The process according to claim 5, wherein the transition metal salts and complexes comprises palladium, nickel, iron, ruthenium, cobalt, rhodium, iridium or copper.

7. The process according to any one of Claims 1 to 6, wherein R_1 represents hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, $(C_6\text{-}C_{10})$-aryl, $(C_5\text{-}C_{10})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{10})$-alkyl, -(C=O)-O-$(C_1\text{-}C_{10})$-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_2\text{-}C_{10})$-alkynyl, $(C_3\text{-}C_{10})$-cycloalkyl, or $(C_6\text{-}C_{10})$-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl.

8. The process according to claim 7, wherein R_1 represents hydrogen, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_3\text{-}C_7)$-cycloalkyl, (C_6)-aryl, $(C_5\text{-}C_6)$-heteroaryl, -C(=O)-$(C_1\text{-}C_6)$-alkyl, -(C=O)-O-$(C_1\text{-}C_6)$-alkyl, OR^c, or NR^c_2, each of

which are optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and wherein R^c is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, or (C_6)-aryl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

9. The process according to claim 8, wherein R_1 represents hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, phenyl, or -C(=O)-(C_1-C_6)-alkyl, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_1 is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which, where possible, is optionally substituted with one or more groups selected from halo, OH, optionally substituted phenyl or (C_1-C_6)-alkyl.

10. The process according to any one of claims 1 to 9, wherein R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_2-C_{10})-alkynyl, (C_3-C_{10})-cycloalkyl, (C_6-C_{10})-aryl, (C_5-C_{10})-heteroaryl, -C(=O)-(C_1-C_{10})-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

11. The process according to claim 10, wherein R_2 to R_{10} represent hydrogen, deuterium, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_7)-cycloalkyl, (C_6)-aryl, (C_5-C_6)-heteroaryl, -C(=O)-(C_1-C_6)-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or (C_1-C_6)-alkyl, and

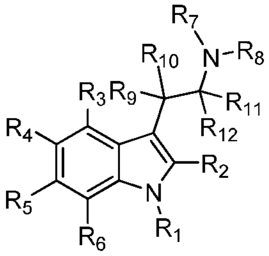
one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and $(C_1\text{-}C_6)$-alkyl.

12. The process according to claim 11, wherein R_2 to R_{10} represent hydrogen, deuterium, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_3\text{-}C_7)$-cycloalkyl, (C_6)-aryl, or $(C_5\text{-}C_6)$-heteroaryl.

13. The process according to any one of claims 1 to 12, wherein LG is an anionic leaving group.

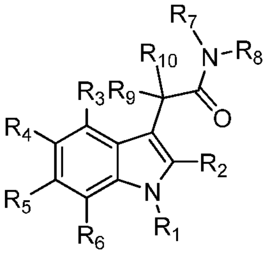
14. The process according to claim 13, wherein LG is a halide group, or a sulphonate.

15. A process for the preparation of compounds of Formula (IV):



(IV)

by contacting a compound of Formula (III),



(III),

with a hydrogen or deuterium source optionally in the presence of a catalyst wherein,

R_1 to R_{10} are as defined in any one of claims 1 to 12; and

R_{11} to R_{12} represent hydrogen or deuterium;

16. A process according to Claim 15, wherein the compound of Formula (IV) is achiral.

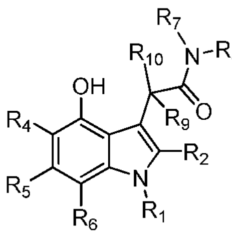
17. A process according to Claim 15, wherein the compound of Formula (IV) is chiral.

18. A process according to Claim 15; wherein one or more of the carbon-12 atoms in a compound of Formula (IV) are replaced with carbon-13.

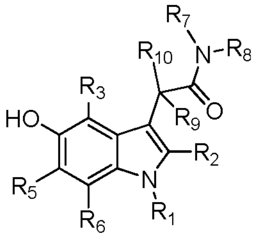
19. A process according to Claim 15; for the preparation of a compound of Formula (IV) by contacting a compound of Formula (III) with a hydrogen or deuterium source in the absence of a catalyst.

20. A process according to Claim 15; wherein the hydrogen or deuterium source is a borohydride, a borodeuteride, an aluminohydride, an aluminodeuteride, a silane, a borane, hydrogen gas or deuterium gas.

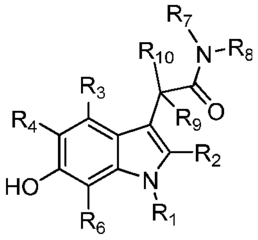
21. A Compound of Formula (V), Formula (VI), Formula (VII) or Formula (VIII):



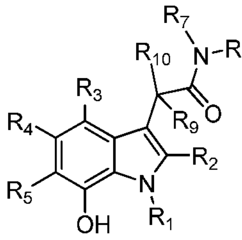
(V)



(VI)



(VII)



(VIII)

wherein,

R_1 represents hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{20})$-alkyl, -(C=O)-O-$(C_1\text{-}C_{20})$-alkyl, OR^c, or NR^c_2, each of which are optionally substituted with halogen, OH, optionally substituted phenyl or $(C_1\text{-}C_6)$-alkyl, and wherein R^c is hydrogen, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, or $(C_6\text{-}C_{20})$-aryl;

R_2 to R_{10} represent hydrogen, deuterium, $(C_1\text{-}C_{20})$-alkyl, $(C_2\text{-}C_{20})$-alkenyl, $(C_2\text{-}C_{20})$-alkynyl, $(C_3\text{-}C_{20})$-cycloalkyl, $(C_6\text{-}C_{20})$-aryl, $(C_5\text{-}C_{20})$-heteroaryl, -C(=O)-$(C_1\text{-}C_{20})$-alkyl, or two adjacent or geminal groups are bonded together to form an optionally substituted ring, each of which is optionally substituted with halogen, OH, or $(C_1\text{-}C_6)$-alkyl, and one or more of the carbon atoms in the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or acyl groups of R_2 to R_{10} is optionally replaced with a heteroatom selected from the group consisting of O, S, N, P and Si, which is optionally substituted with one or more groups selected from halogen, OH, and (C_1-C_6)-alkyl.

22. Compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII), according to Claim 21, wherein R_1 represents a nitrogen protecting group.

23. Compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII), according to Claim 21, wherein one or more of the carbon-12 atoms in the molecule are replaced with carbon-13.

24. Compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII), according to Claim 21, which are achiral.

25. Compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII), according to Claim 21, which are chiral.

26. Use of Compounds of Formula (V), Formula (VI), Formula (VII) and Formula (VIII) for pharmaceutical applications.

FIGURE 1

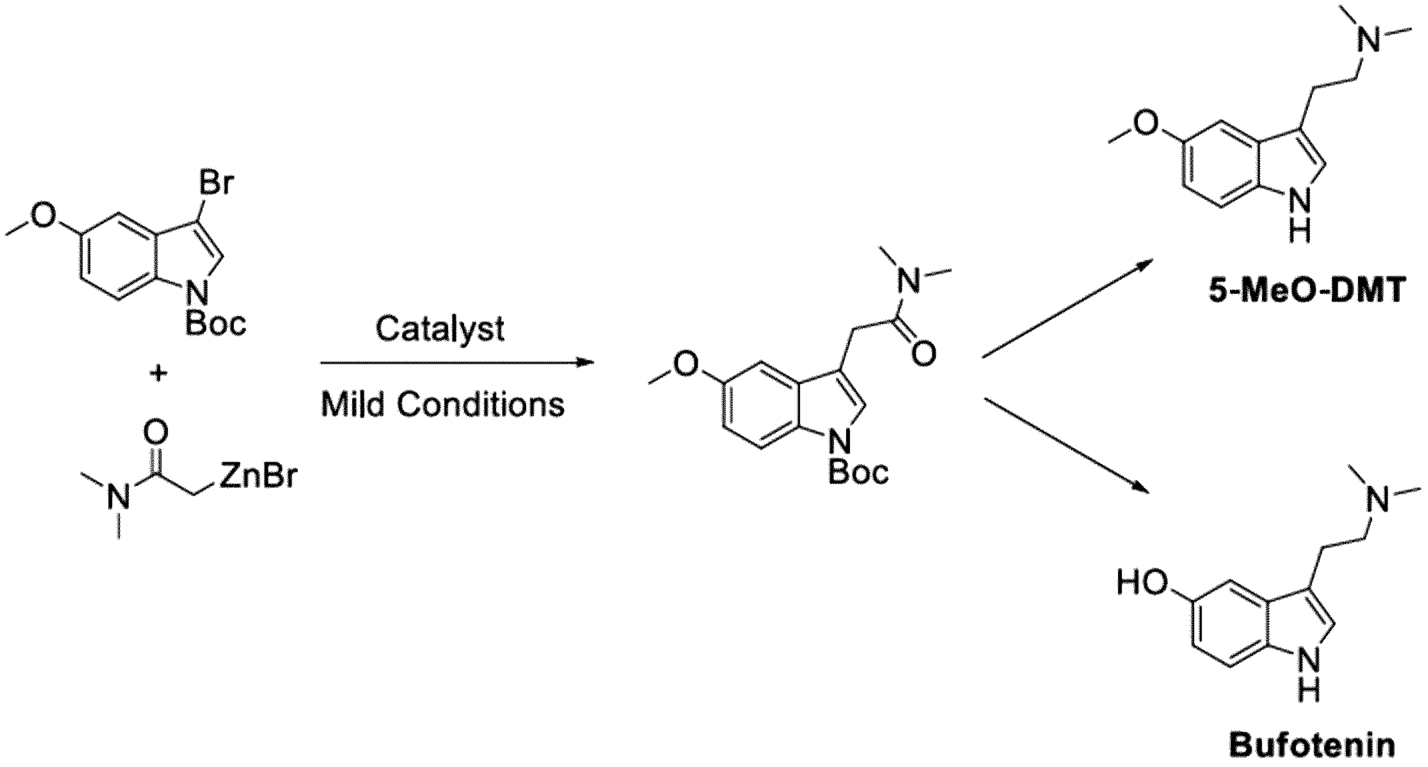

Br
N
Boc
+
O
N
ZnBr
Catalyst
Mild Conditions
N
O
N
Boc
N
N
H
5-MeO-DMT
N
HO
N
H
Bufotenin

FIGURE 2

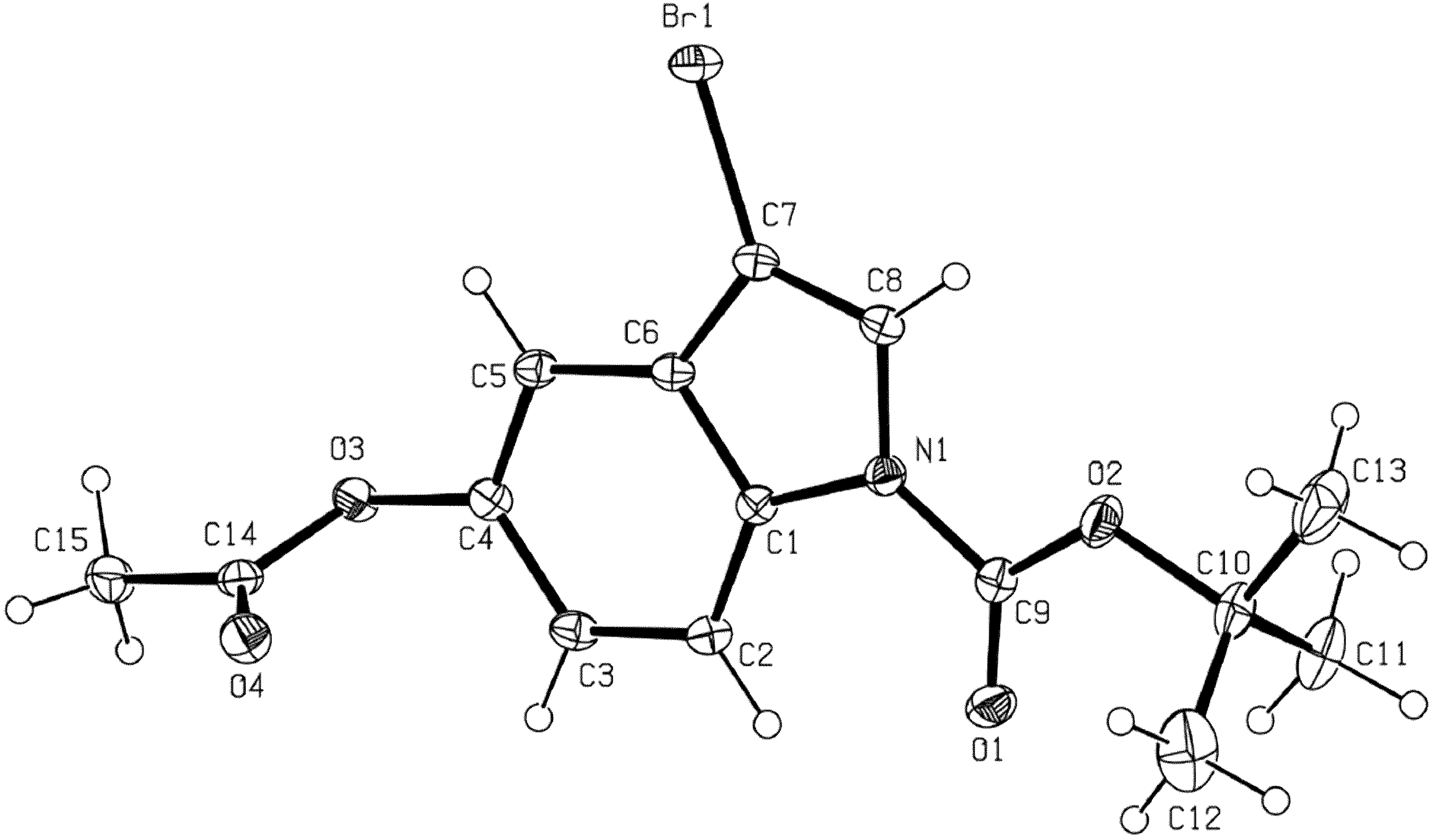


FIGURE 3

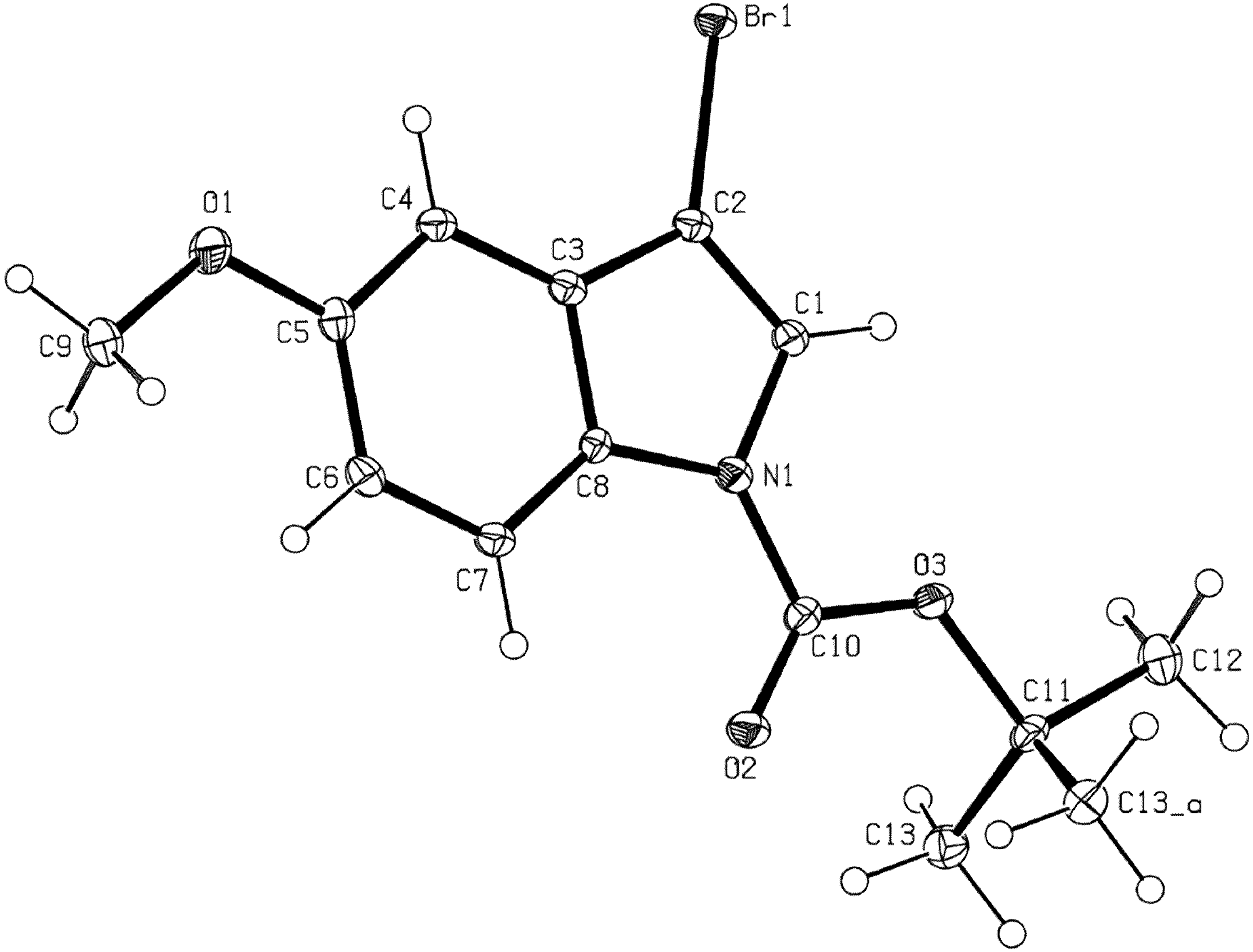


FIGURE 4

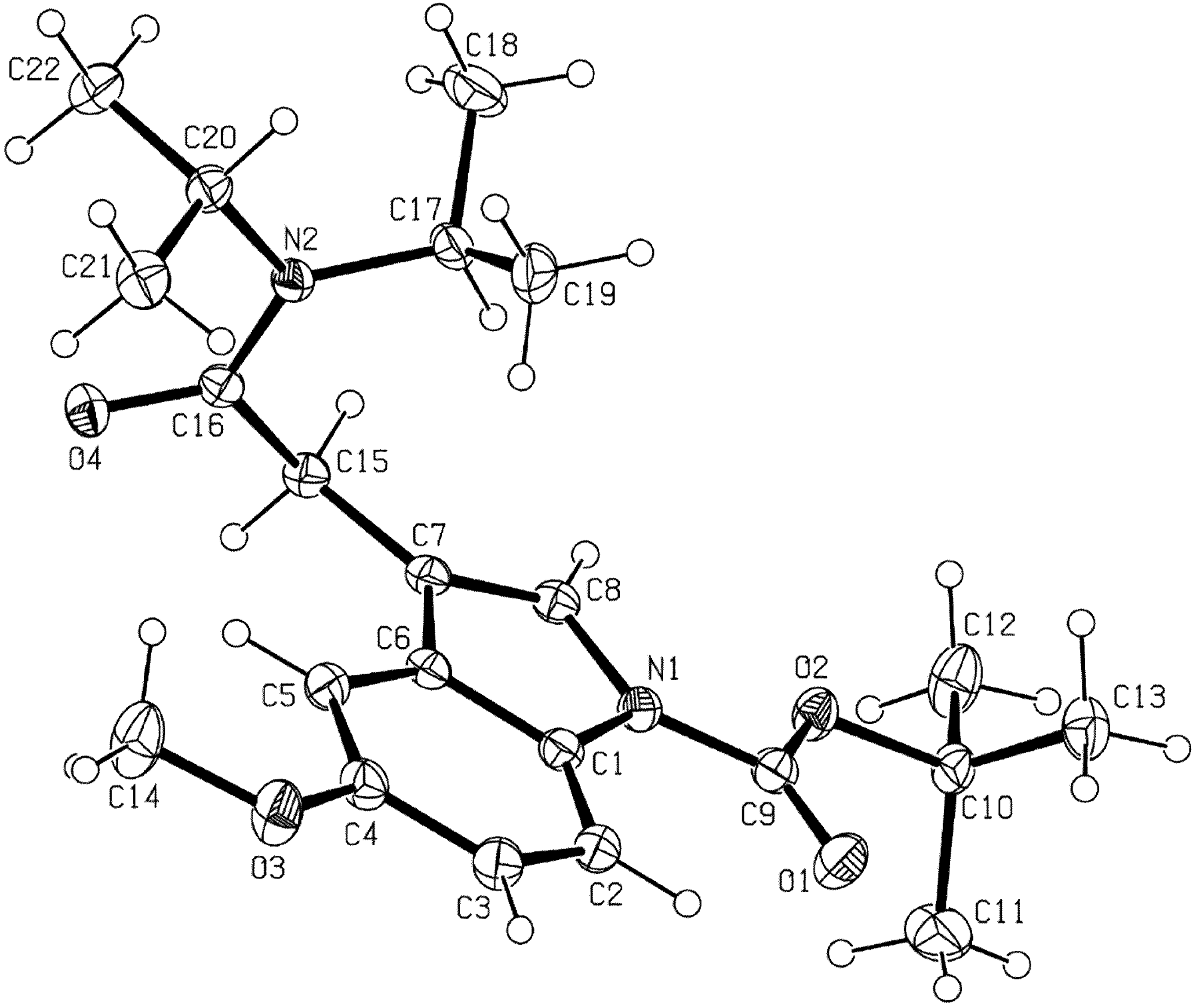

C22
C18
C20
C17
N2
C21
C19
O4
C16
C15
C7
C8
C12
C6
N1
O2
C13
C5
C1
C10
C14
C9
O3
C4
C3
C2
O1
C11

FIGURE 5

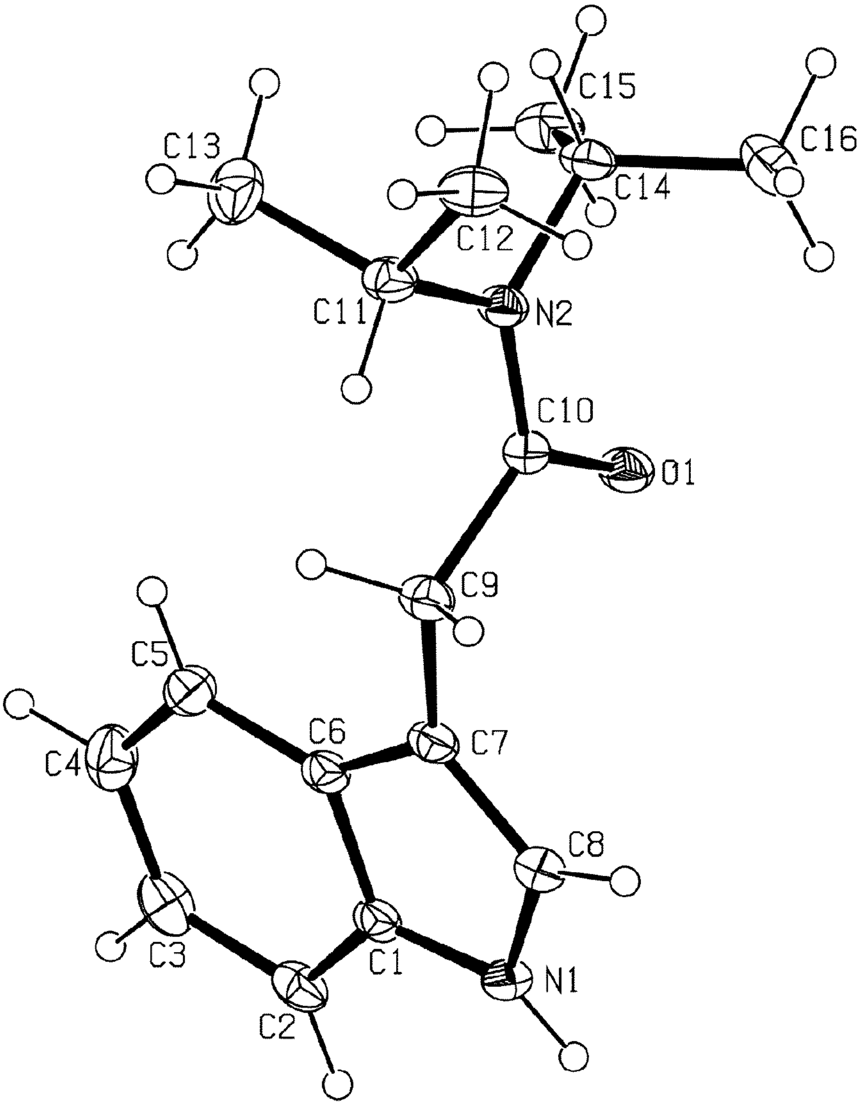


FIGURE 6

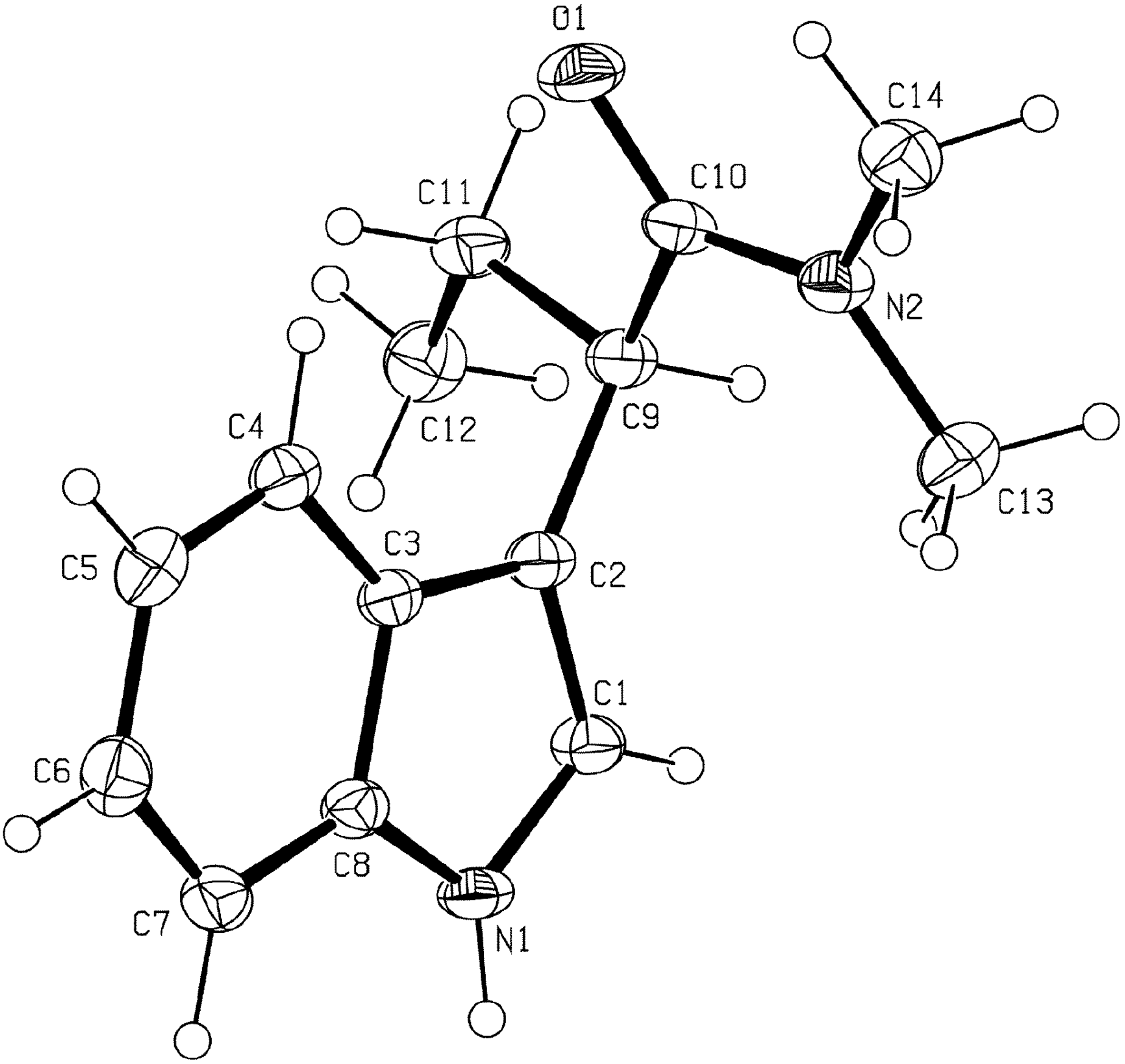


FIGURE 7

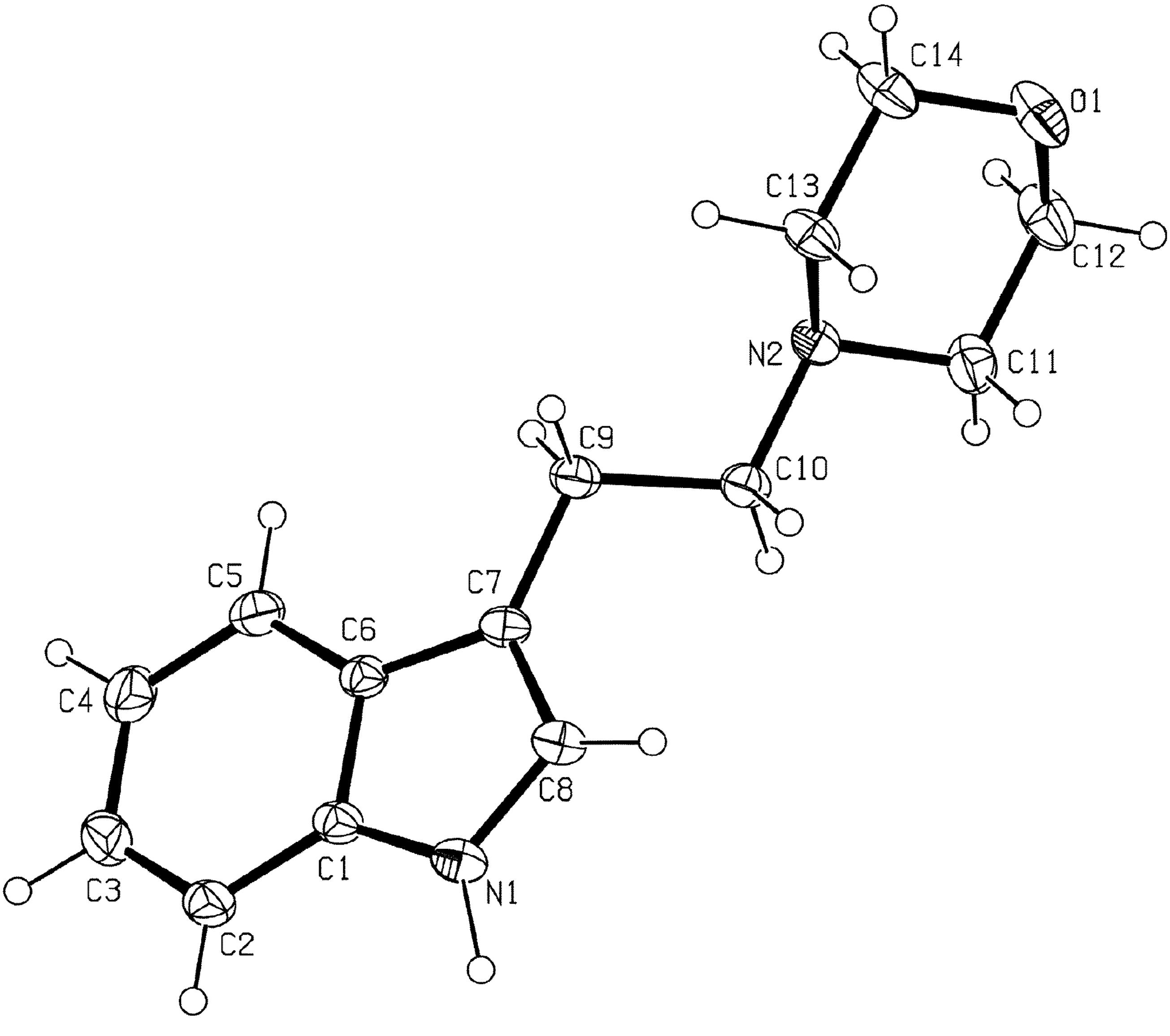


FIGURE 8

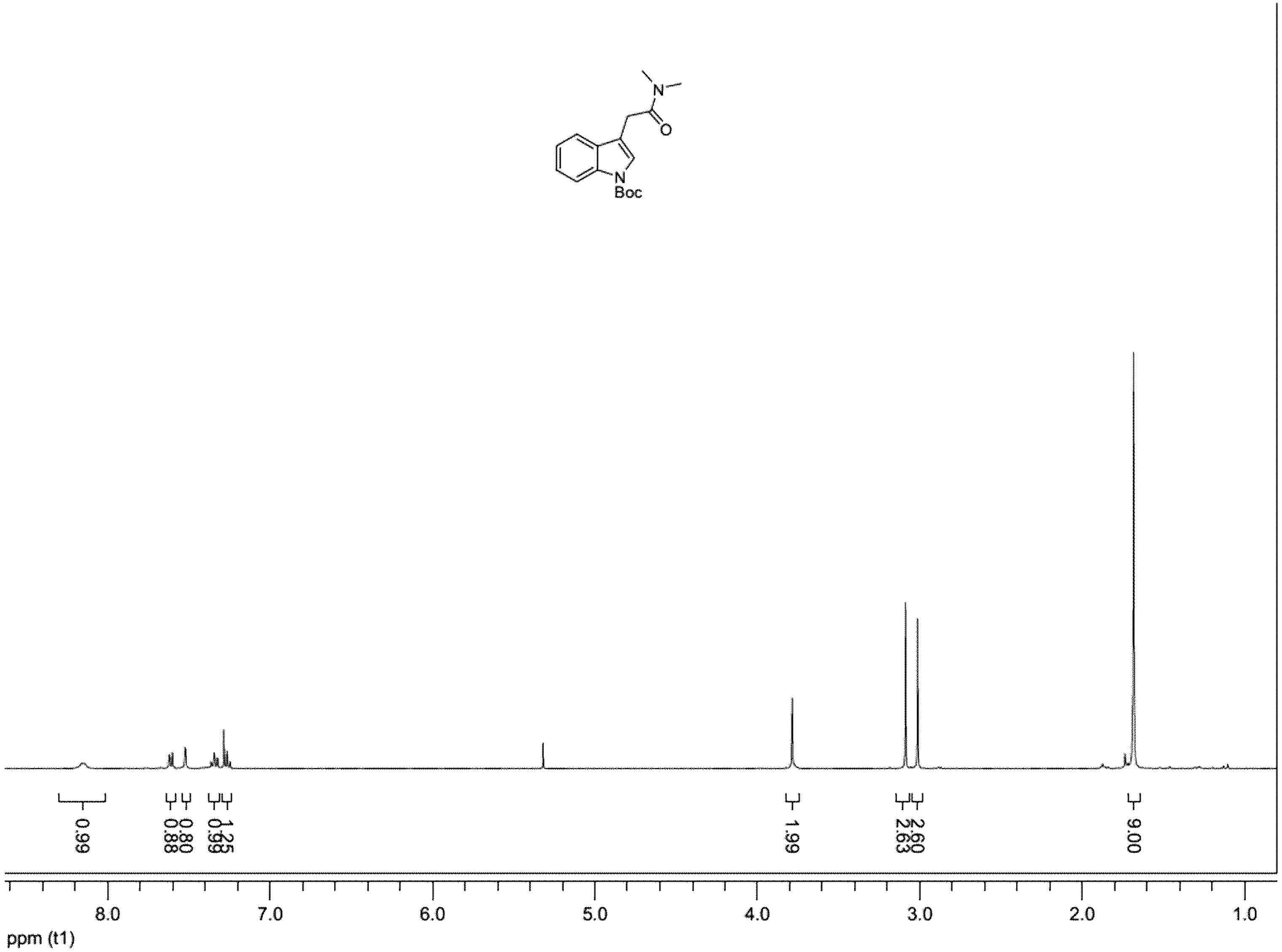

N
O
N
Boc
0.99
0.88
0.80
0.99
1.25
1.99
2.63
2.60
9.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

FIGURE 9

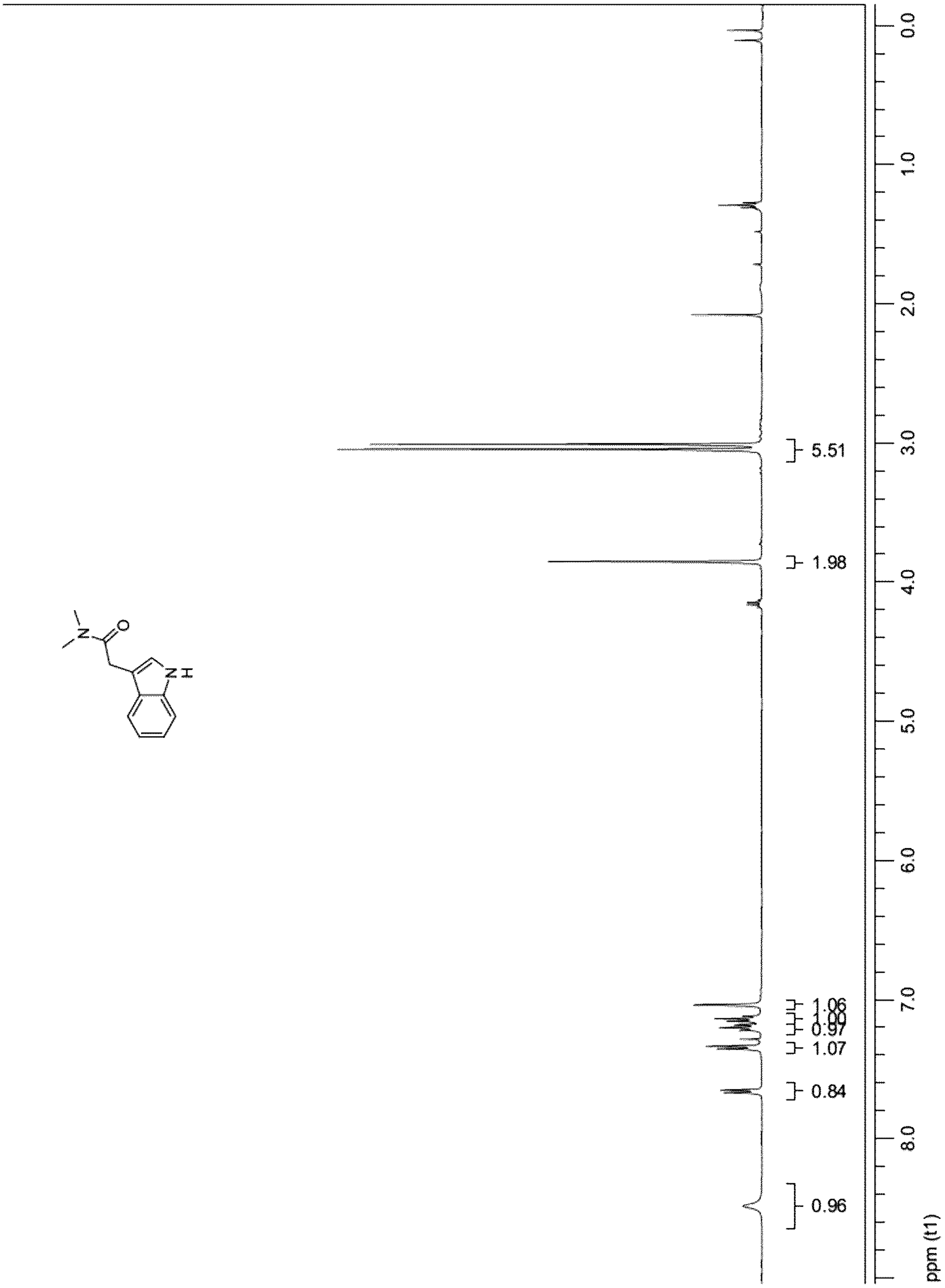

O
N
NH
5.51
1.98
1.06
1.00
0.97
1.07
0.84
0.96
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

FIGURE 10

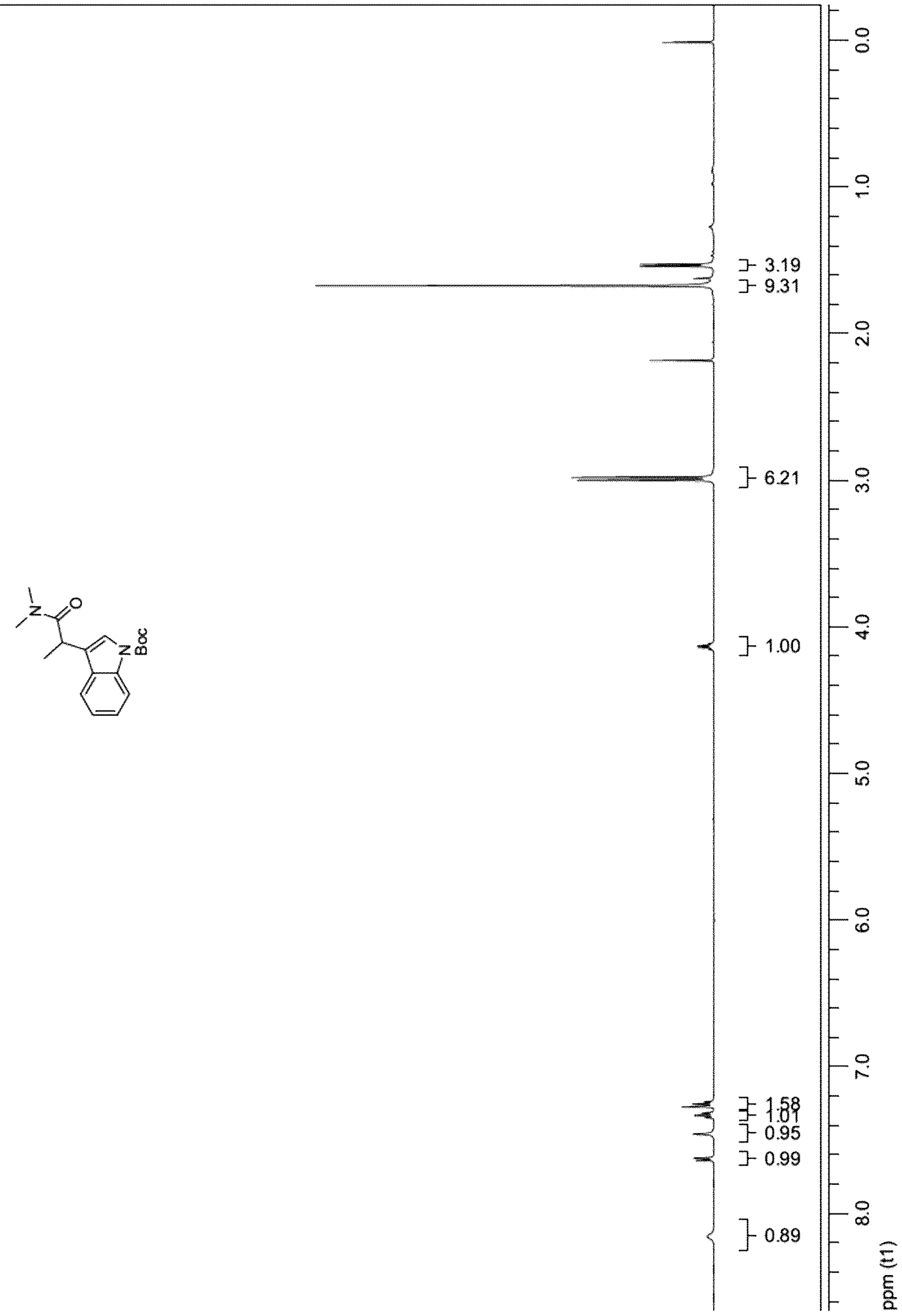

O
N
N
Boc
3.19
9.31
6.21
1.00
1.58
1.01
0.95
0.99
0.89
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

FIGURE 11

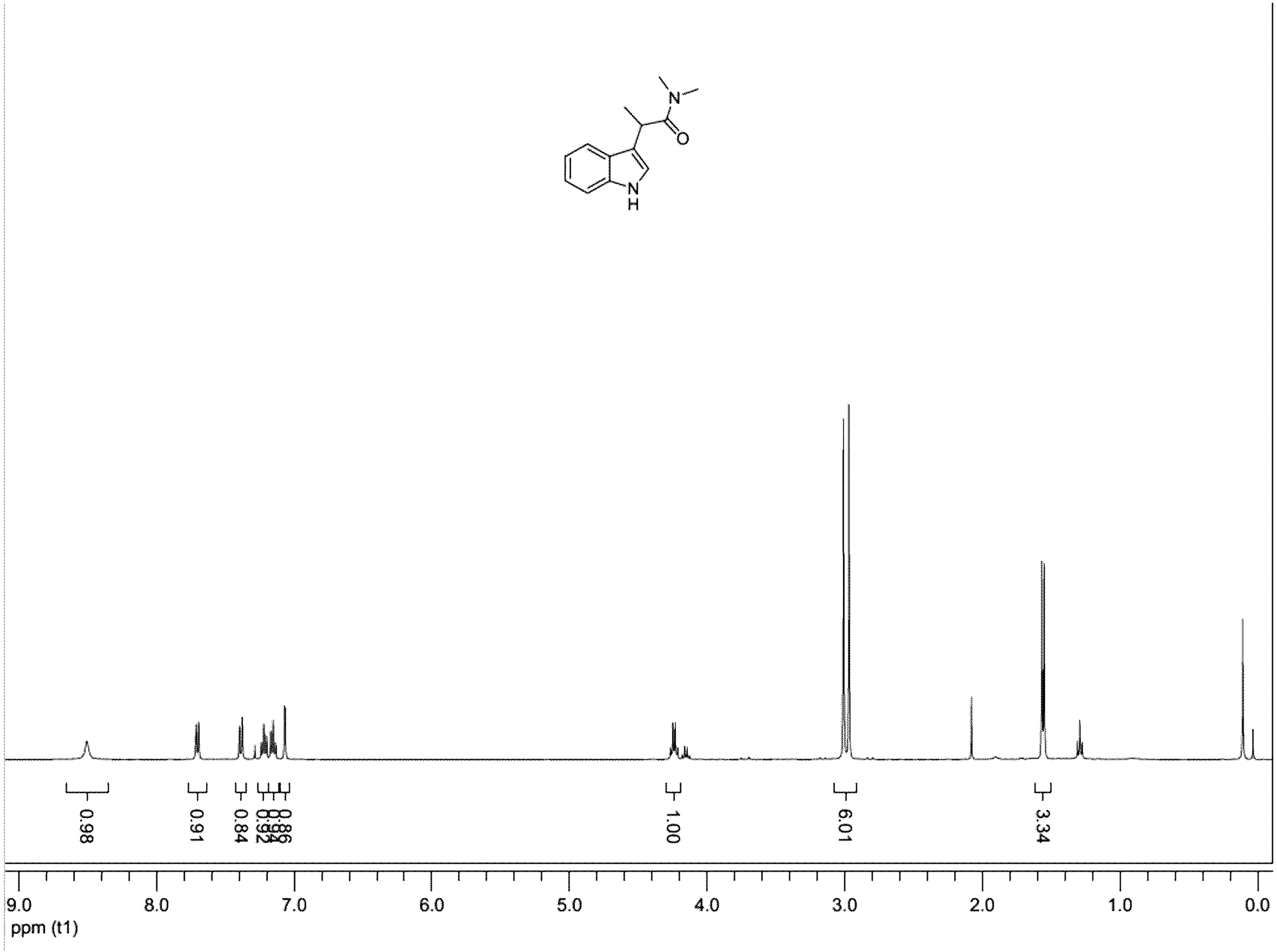

N
O
N
H
0.98
0.91
0.84
0.92
0.94
0.86
1.00
6.01
3.34
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

FIGURE 12

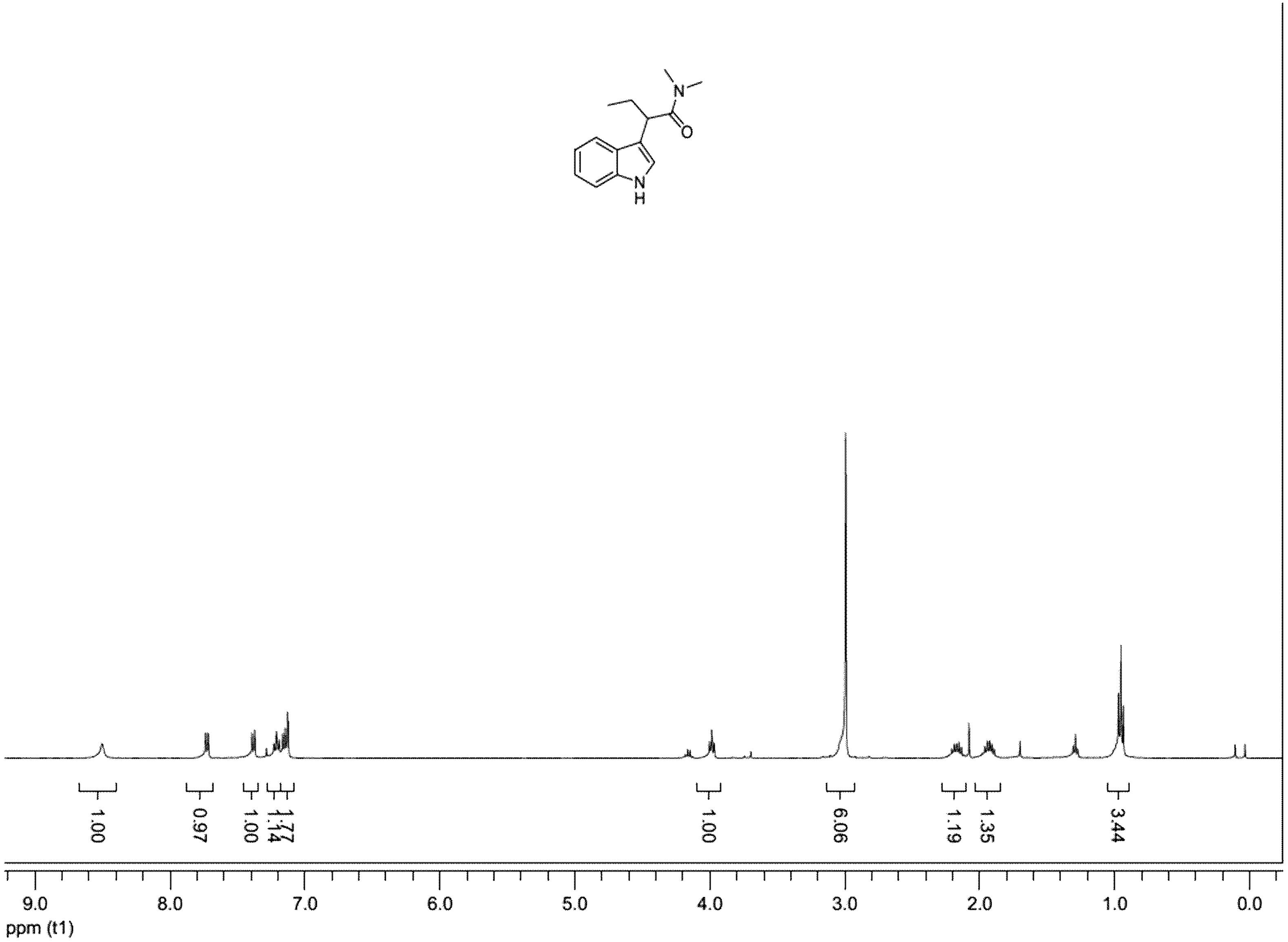

N
O
N
H
1.00
0.97
1.00
1.14
1.77
1.00
6.06
1.19
1.35
3.44
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

FIGURE 13

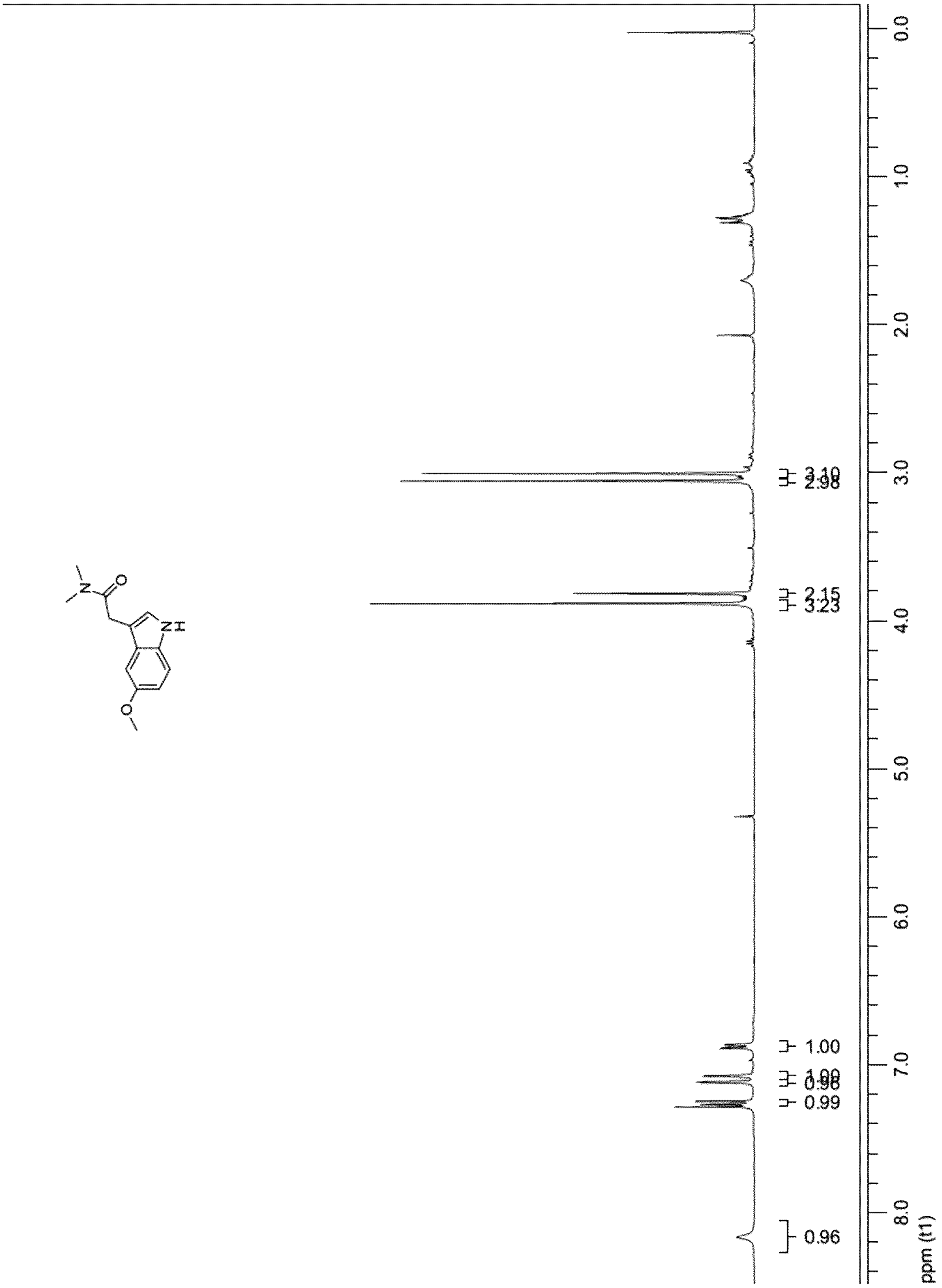

O
N
NH
O
3.10
2.98
2.15
3.23
1.00
1.00
0.98
0.99
0.96
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

FIGURE 14

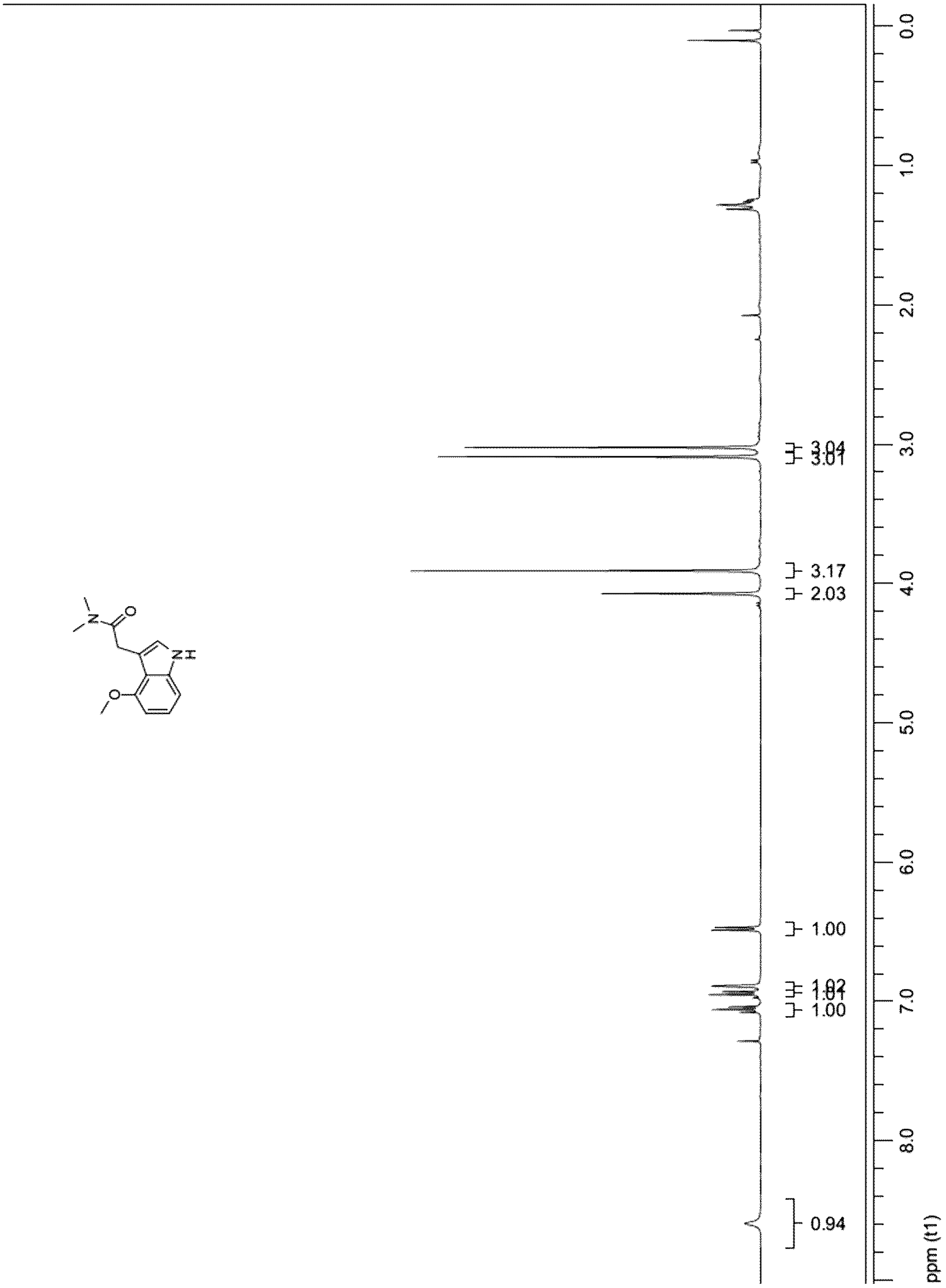

O
N
NH
O
3.04
3.01
3.17
2.03
1.00
1.02
1.01
1.00
0.94
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

FIGURE 15

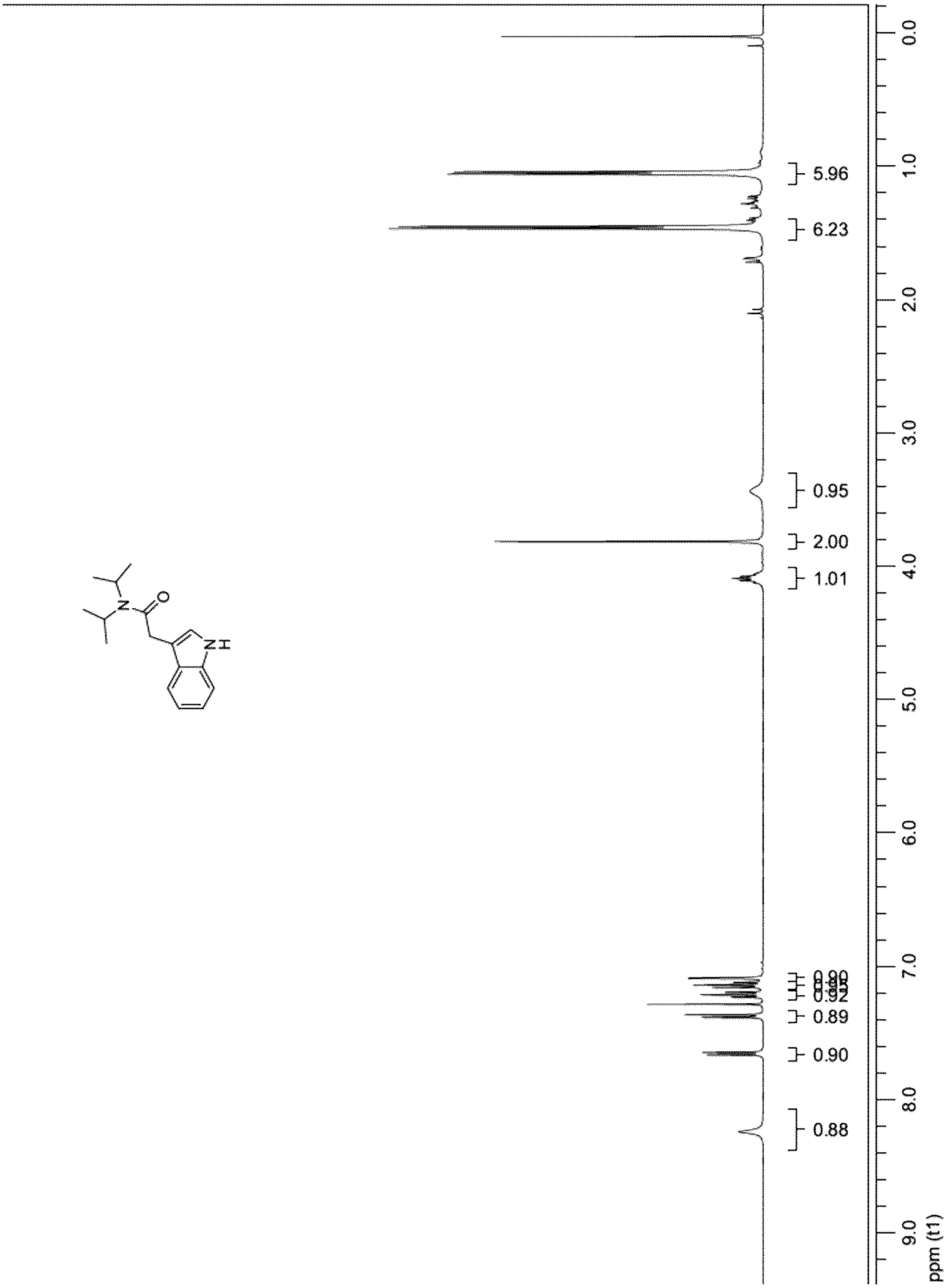

5.96
6.23
0.95
2.00
1.01
0.90
0.92
0.89
0.90
0.88
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
O
N
NH

FIGURE 16

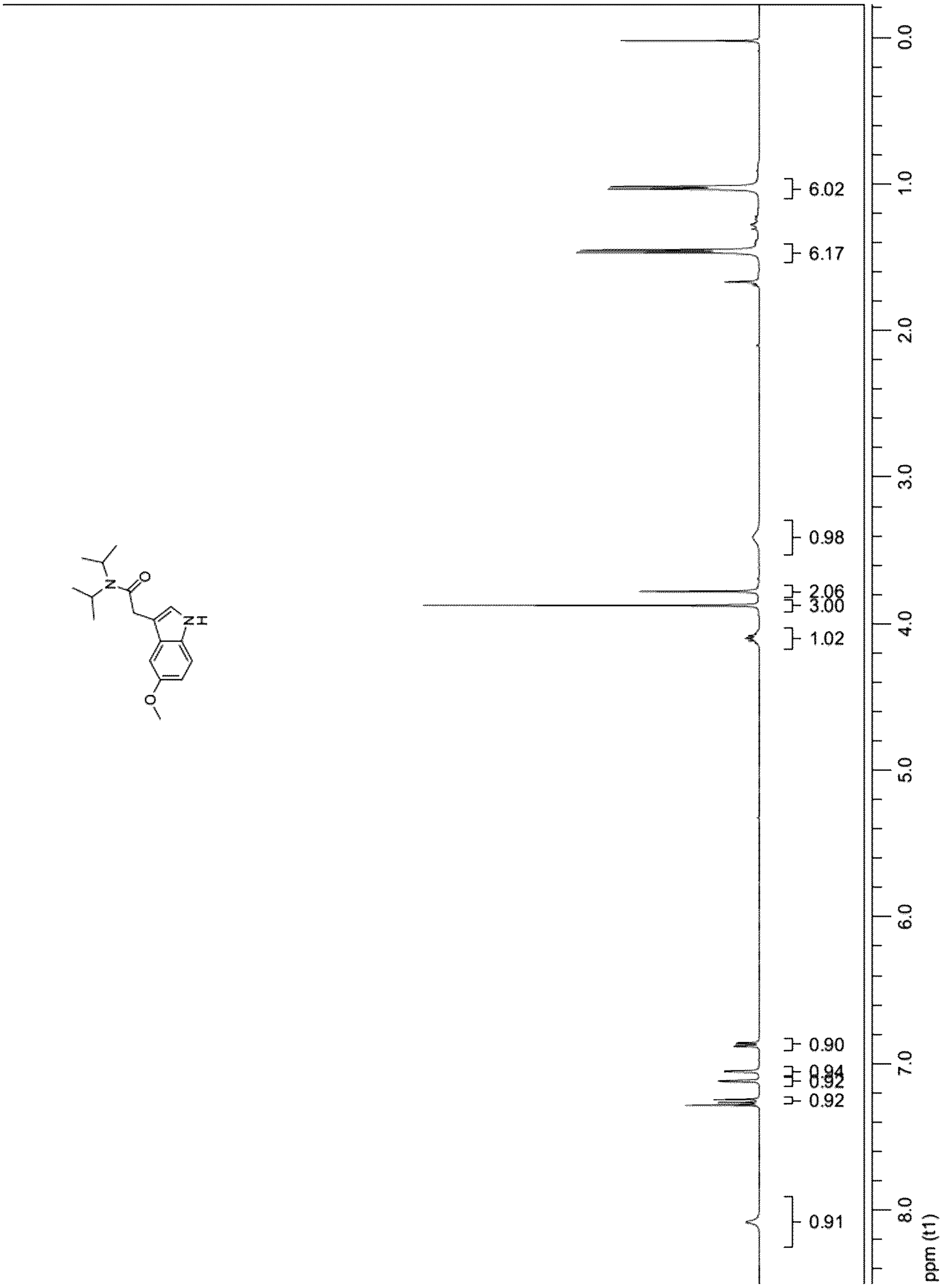

6.02
6.17
0.98
2.06
3.00
1.02
0.90
0.94
0.92
0.92
0.91
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
O
N
NH

FIGURE 17

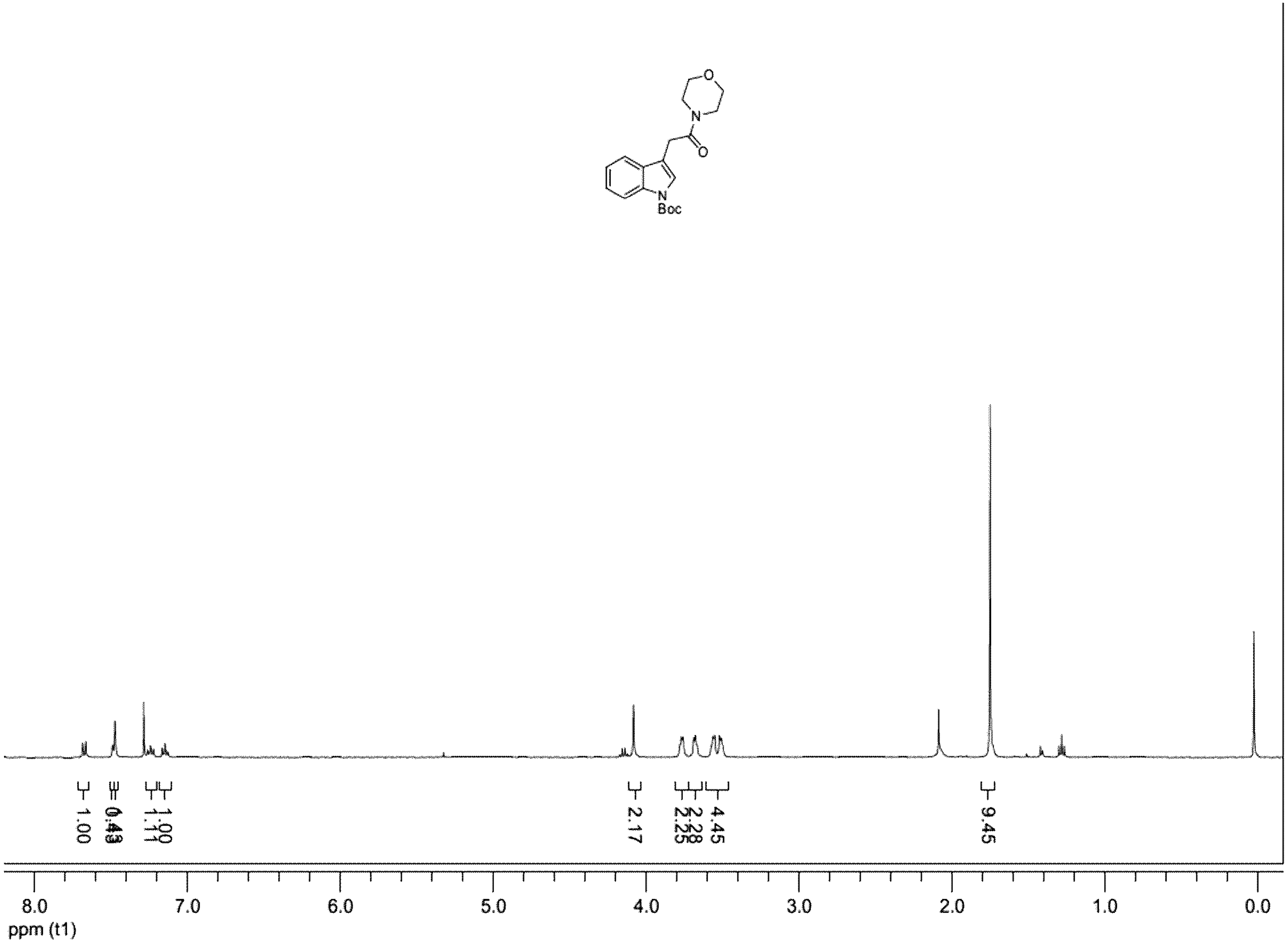

O
N
O
N
Boc
1.00
0.43
1.43
1.11
1.00
2.17
2.25
2.28
4.45
9.45
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

FIGURE 18

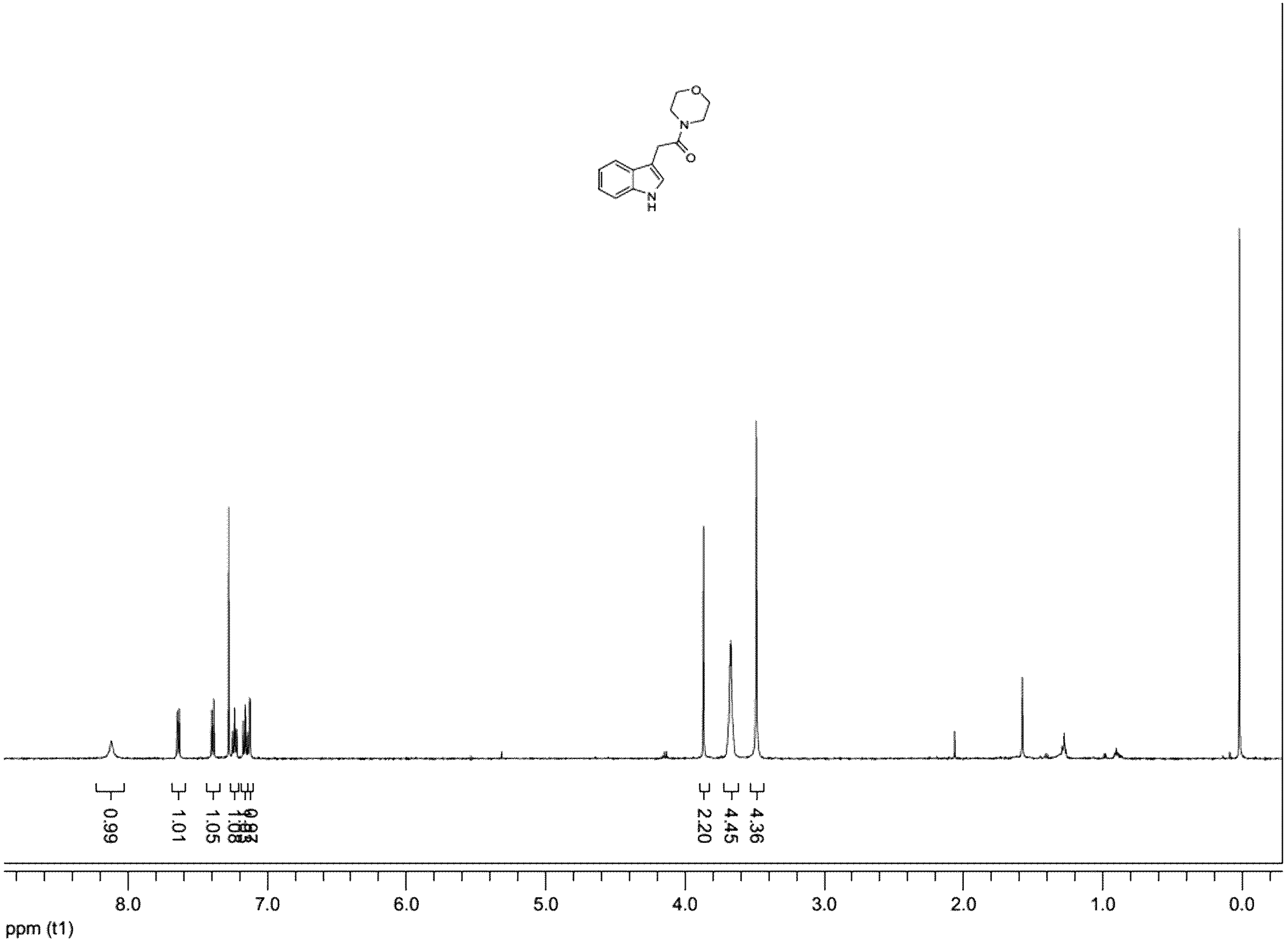


FIGURE 19

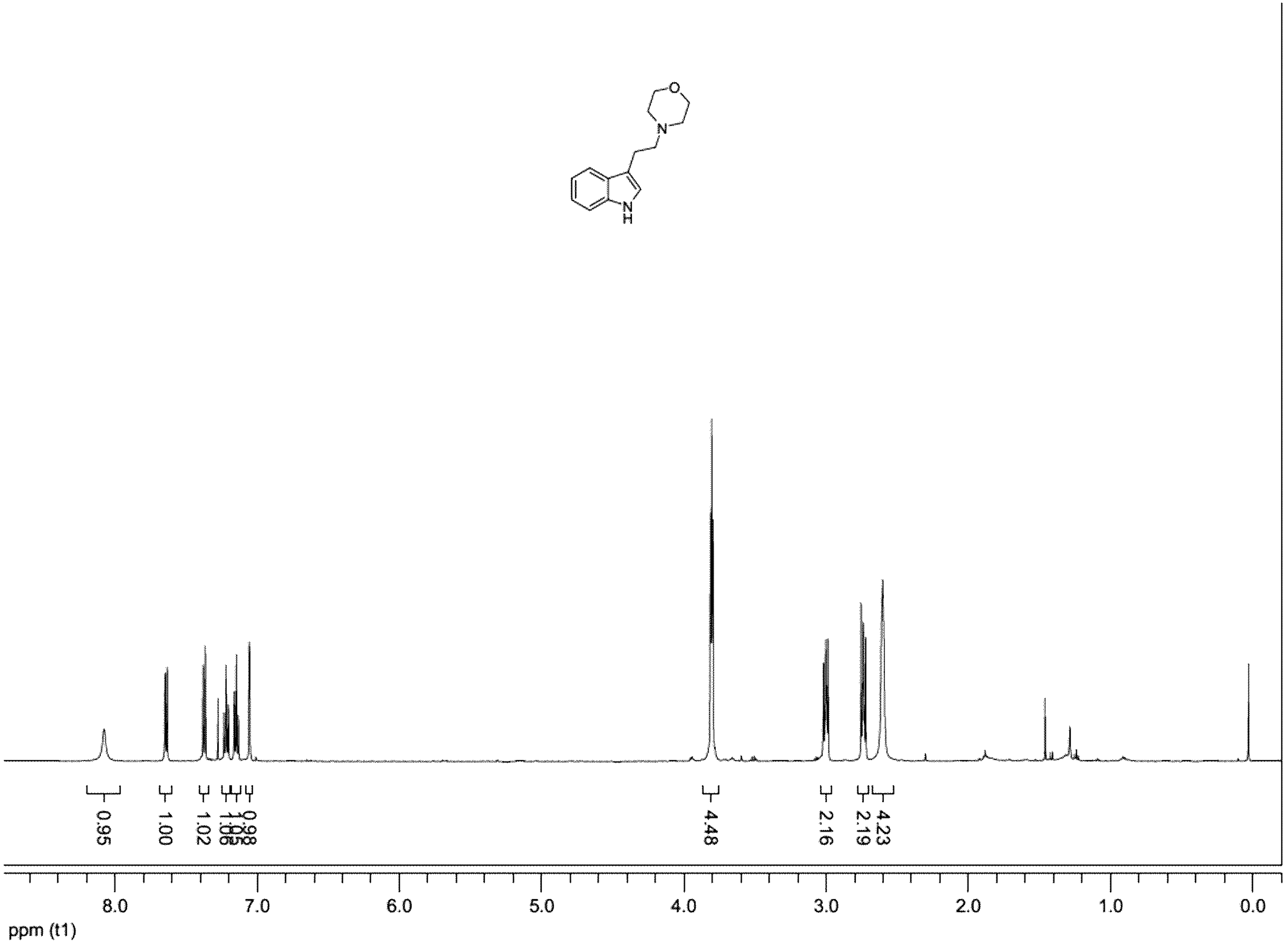

N
O
N
H
0.95
1.00
1.02
1.06
1.05
0.98
4.48
2.16
2.19
4.23
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

FIGURE 20

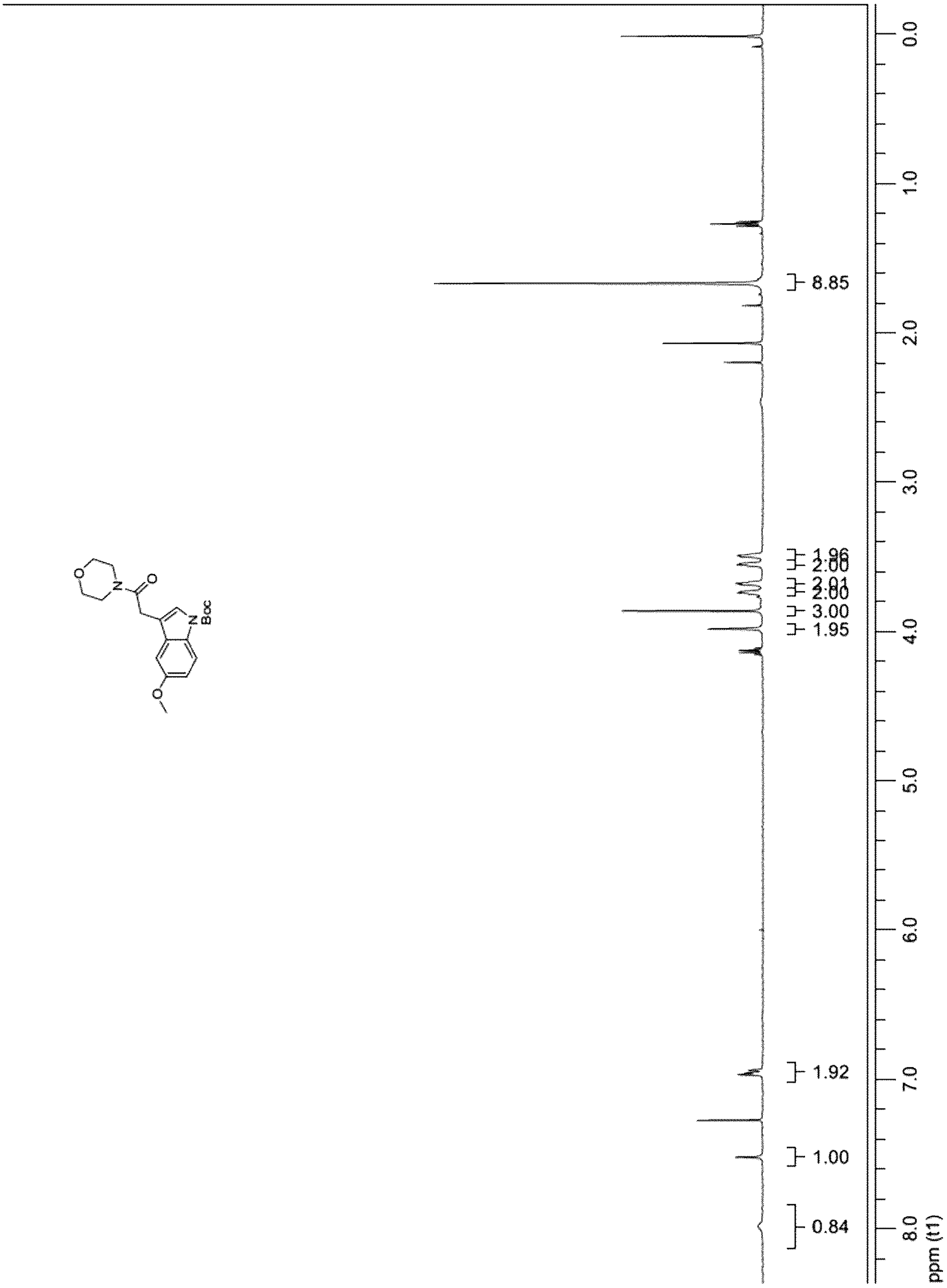

O
N
O
N
Boc
O
8.85
1.96
2.00
2.01
2.00
3.00
1.95
1.92
1.00
0.84
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

FIGURE 21

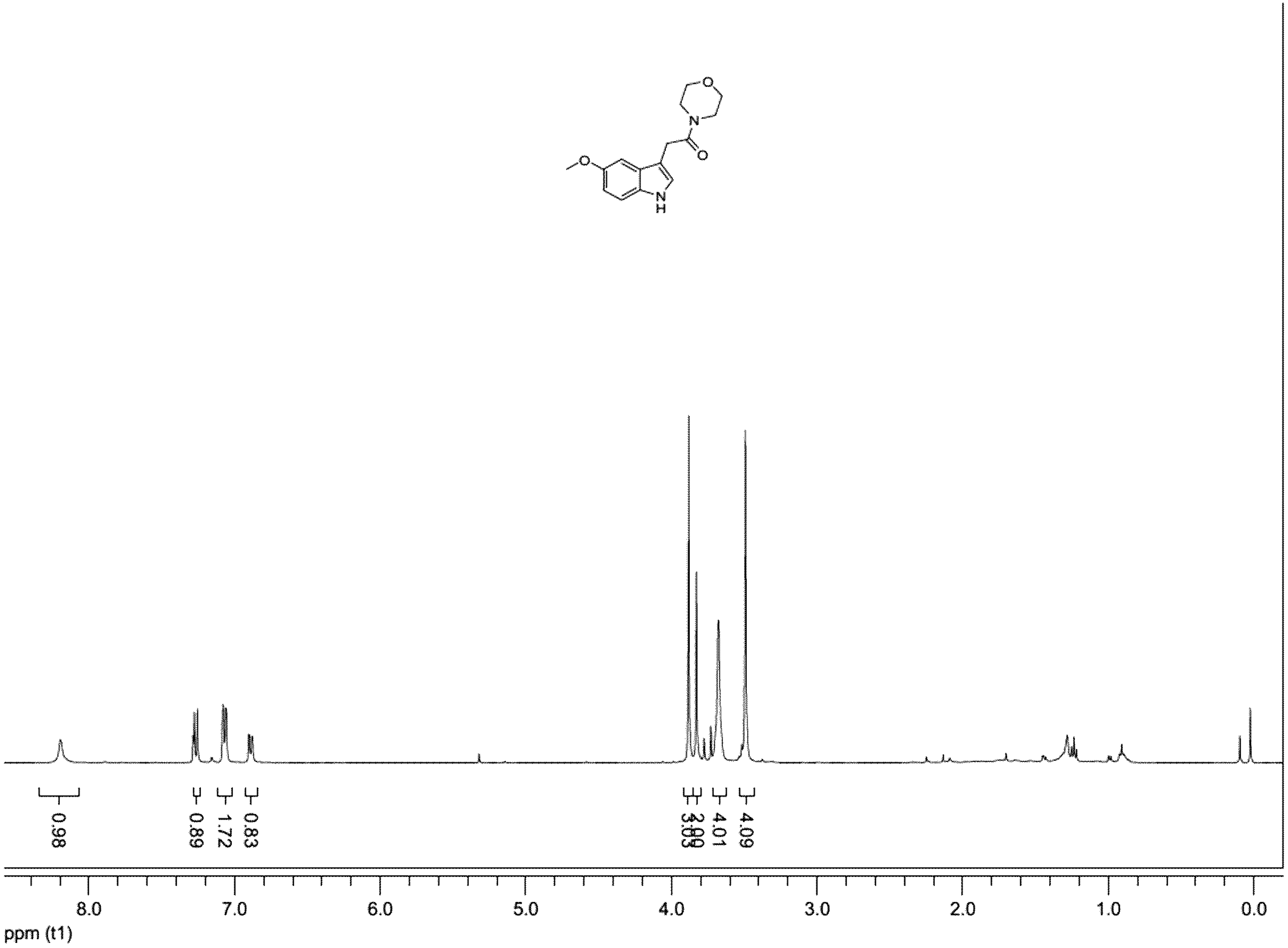
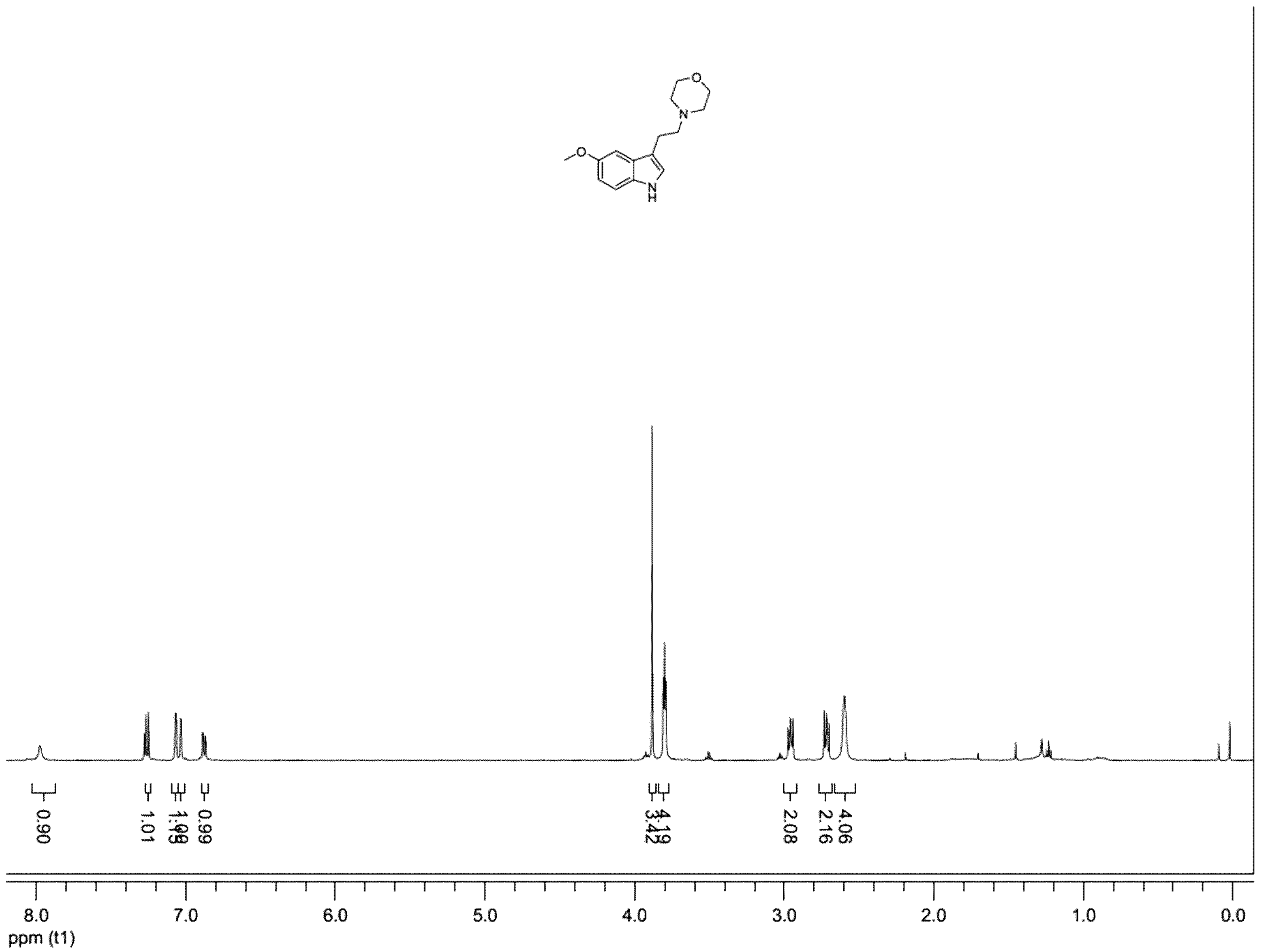

0.98
0.89
1.72
0.83
3.03
2.00
4.01
4.09
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
O
N
O
O
N
H

FIGURE 22


O
N
O
H
0.90
1.01
1.08
1.13
0.99
3.42
4.19
2.08
2.16
4.06
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 209/18*** (2006.01) , ***A61K 31/404*** (2006.01) , ***A61K 31/405*** (2006.01) , ***C07D 403/04*** (2006.01)

CPC: **C07D 209/18** (2020.01) , A61K 31/404 (2020.01) , A61K 31/405 (2020.01) , C07D 403/04 (2020.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Keywords and structures used across the whole IPC.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: CaPlus, Registry, CASReact, Questel Orbit, Scopus, The Canadian Patent Database.

Keywords: Trytamine, Negishi, Zinc enol, indole, hydroxyindole cross-coupling

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2020/245133 A1 (RANDS et al.) 10 December 2020 (10-12-2020) *See Scheme 2, page 17 and examples*	15-20
X	CAS 5933-27-7 Entered in STN: 16 November 1984 (16-11-1984)	21, 23 and 24

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
“A” document defining the general state of the art which is not considered to be of particular relevance
“D” document cited by the applicant in the international application
“E” earlier application or patent but published on or after the international filing date
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
“O” document referring to an oral disclosure, use, exhibition or other means
“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“&” document member of the same patent family

Date of the actual completion of the international search 03 June 2022 (03-06-2022)	Date of mailing of the international search report 15 July 2022 (15-07-2022)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Julie Brousseau

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	CAS16606-62-5 Entered in STN: 16 November 1984 (16-11-1984)	21, 23 and 24
X	ZHOU et al., "*Facile Synthesis of Unsymmetrical N-Aryl-2,2-di(1H-indol-3-yl)Acetamide Derivatives*". Chemical Research in Chinese Universities, 23 November 2016 (23-11-2016), Vol. 32, pp. 959-966, *See page 965, table 2, entries 6 and 15*	21, 23, 25 and 26
X	WO2011/060330 A1 (STOCK et al.) 19 May 2011 (19-05-2011) *See page 88, example 10*	21, 23, 25 and 26
X	WO2011/047156 A1 (BLAGG et al.) 21 April 2011 (21-04-2011) *See page 20, compound 10*	21, 23, 24 and 26
X	CA2751536 A1 (HACHIRO et al.) 12 August 2010 (12-08-2010) *See page 53, line 3*	21, 23, 24 and 26
X	EICHENBERGER et al., "*Decomposition of N-Hydroxylated Compounds During Atmospheric Pressure Chemical Ionization*". Journal of Mass Spectrometry, 26 November 2006 (26-11-2006), Vol. 45, pp. 190-197, *See page 195, compounds 5-9*	21, 23 and 24
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X	EICHENBERGER et al., "*Structure Elucidation of Polyamine Toxins in the Venom of the Spider Larinioides folium*". Chimia, 27 April 2007 (27-04-2007), Vol. 61, pp. 161-164, *See entire document*	21 and 23-26
X	PINTORE et al., "*3D QSAR Study of Human PLA2 Inhibitors. A Modeling Approach to Select New and Specific Anti-Inflammatory Drugs*". Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 6 January 2006 (06-01-2006), Vol. 5, pp. 175-187, *See page 178, table 1, compounds 1-8, 10 and 11*	21-24 and 26
X	WO96/40097 A1 (MUELLER et al.) 19 December 1996 (19-12-1996) *See page 38, compound 13*	21, 23, 24 and 26
X	MENCIU ER AL., "*New N-(Pyridin-4-yl)-(Indol-3-yl)Acetamides and Propanamides as Antiallergic Agents*". Journal of Medicinal Chemistry, 29 January 1999 (29-01-1999), Vol. 42, pp. 638-648, *See page 639, scheme 1, compound 84*	21-24 and 26

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO95/22524 A1 (BITONTI et al.) 24 August 1995 (24-08-1995) *See examples 29-33, 142, 147, 153, 160, 163 and 182*	21-24 and 26
X	KOVACS et al., "*Synthetic Analogues of Naturally Occurring Spider Toxins*". Helvetica Chimica Acta, 2 October 1992 (02-10-1992), Vol. 75, pp. 1909-1924. *See page 1910, compounds 21, 28, 37 and 39*	21, 23, 25 and 26
A	WO2001/001973 A1 (GALATSIS et al.) 3 January 2014 (03-01-2014) *See examples 1, 2, 4, 7-10 and 198 and Methods B (page 76), C (Page 77) and E (page 79)*	1-14

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