(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 May 2016 (06.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/069949 A1

(51) International Patent Classification:
A61K 31/4545 (2006.01) *C07D 471/04* (2006.01)

(21) International Application Number:
PCT/US2015/058157

(22) International Filing Date:
29 October 2015 (29.10.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/069,874 29 October 2014 (29.10.2014) US

(71) Applicant: **VIRGINIA TECH INTELLECTUAL PROPERTIES, INC.** [US/US]; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US).

(72) Inventors: **CARLIER, Paul, R.**; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US). **CASSERA, Maria, Belen**; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US). **MERINO, Emilio, Fernando**; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US). **YAO, Zhong-Ke**; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US). **GHAVAMI, Maryam**; 2200 Kraft Drive, Suite 1050, Blacksburg, VA 24060 (US).

(74) Agents: **MILLER, Carin, R.** et al.; Thomas | Horstemeyer LLP, 400 Interstate North Parkway, SE, Suite 1500, Atlanta, GA 30339 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: COMPOSITIONS AND FORMULATIONS OF METHYLERTHRITOL PHOSPHATE PATHWAY INHIBITORS AND USES THEREOF

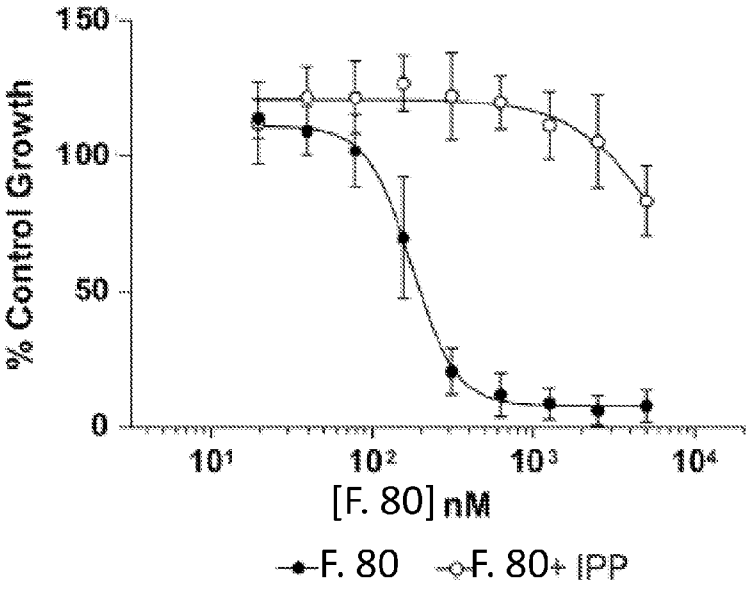


FIG. 6B

(57) Abstract: Described herein are compounds and formulations thereof that can inhibit the methylerythritol phosphate pathway (MEP). Also described herein are methods of making and uses of the compounds and formulations thereof described herein.

WO 2016/069949 A1

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

COMPOSITIONS AND FORMULATIONS OF METHYLERTHRITOL PHOSPHATE PATHWAY INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 62/069,874 filed on October 29, 2014, having the title "Novel Methylerthritol Phosphate Pathway Inhibitors", the entirety of which is incorporated herein by reference.

STATEMENT REGARDING FEDERALY SPONSORED RESEARCH OR DEVELOPMENT

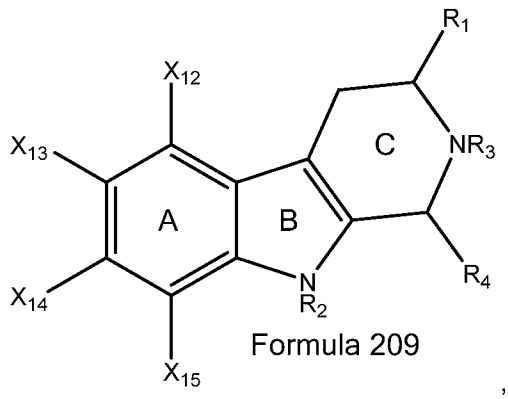
This invention was made with government support under grant numbers AI082581 and AI108819 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

With over 200 million cases worldwide and accounting for about one-half million deaths, primarily in children under the age of 5 and pregnant women, malaria remains a serious global health threat. Although therapeutics for malaria infection exist, the causative protozoan parasites are becoming resistant to many of the current front-line therapies. As such, there exists an immediate need for improved treatments and preventatives for malaria.

SUMMARY

Provided herein are compositions and pharmaceutical formulations thereof where the composition can have a structure according to Formula 209:



Formula 209

,

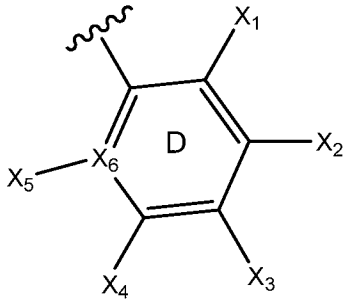
where R_1 can be H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 can be H or a C_1-C_6 alkyl,

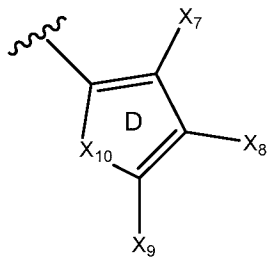
where R_3 can be H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} can each be independently selected from the group of: H and a halogen,

where R_4 can have a structure according to Formula 210 or 211



Formula 210



Formula 211

,

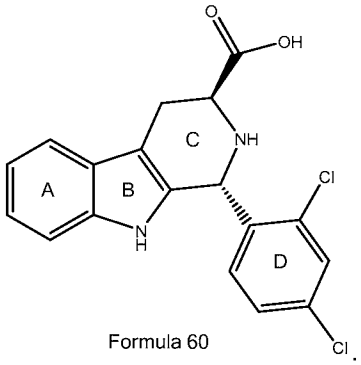
where X_1-X_5 can each be independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen,

where X_6 can be C or N,

where X_{10} can be selected from the group of O, S, and NX_{11}, where X_{11} can be selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} can be a halogen and

where X_7-X_9 can each be independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen.

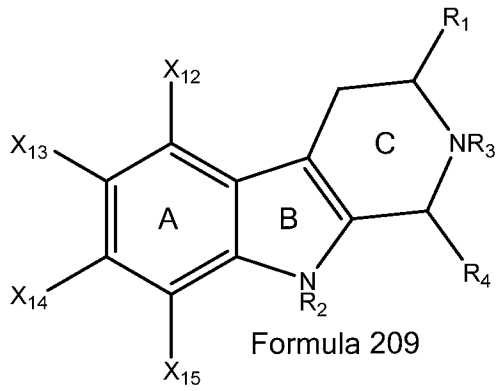
In some embodiments, the compound does not have a structure according to Formula 60



Formula 60

The composition can have (1*R*,3*S*) configuration. The compound can have an R_4 of Formula 210. The halogens specifed in composition can be each independently selected from F, Cl, Br, and I. In some embodiments, X_1 and X_3 are each can each be a halogen. The halogen can be independently selected from F, Cl, Br, and I. In other embodiments, X_1 and X_3 can each be independently selected from a halogen and a C_1-C_6 alkyl. The halogen can be independently selected from F, Cl, Br, and I and the C_1-C_6 alkyl is a methyl. In some embodiments, R_1 can be COOH or $CONHCH_3$. The compositions can, in some embodiments, inhibit an enzyme of the methylerythritol phosphate pathway. The compositions can, in some embodiments, be toxic to to an organism of the genus *Plasmodium*. In some embodiments, the toxicity at 5 μM of compound is completely eliminated by supplementation with an amount of isopentenyl diphosphate (IPP). In further embodiments, the toxicity at 5 μM of compsition is completely eliminated by supplementation with an amount of IPP. In some embodiments, the composition can be according to Formula 70, 74, 75, 80, 90, 126, 127, 128, 129, 131, 133, 138, or 140. In some embodiments, the composition can be according to Formula 74, 80, 90, 126, 127, 128, 129, 133, 138, or 140. In some embodiments, the composition can have an IC_{50} for growth inhibition of the organisim of about 880 nM or less. In some embodiments, the composition can have an IC_{50} for growth inhibition of the organisim of about 650 nM or less. The pharmaceutial formulations thereof can include a pharmaceutically acceptable carrier.

Also provided herein are methods of administering a composition or pharmaceutical formulation thereof to a subject in need thereof where the composition can have a structure according to Formula 209:



Formula 209

,

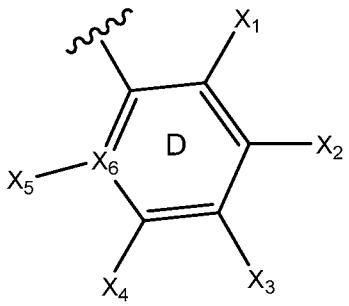
where R_1 can be H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 can be H or a C_1-C_6 alkyl,

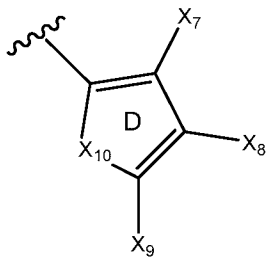
where R_3 can be H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} can each be independently selected from the group of: H and a halogen,

where R_4 can have a structure according to Formula 210 or 211



Formula 210



Formula 211

,

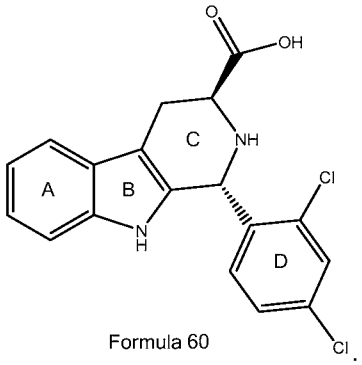
where X_1-X_5 can each be independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen,

where X_6 can be C or N,

where X_{10} can be selected from the group of O, S, and NX_{11}, where X_{11} can be selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} can be a halogen, and

where X_7-X_9 can each be independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen.

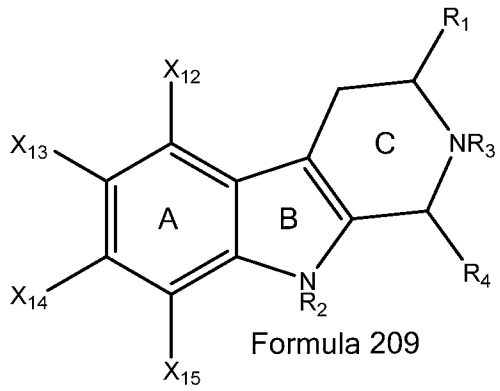
In some embodiments, the compound does not have a structure according to Formula 60



Formula 60

The pharmaceutial formulations thereof can include a pharmaceutically acceptable carrier. The subject can be infected with or can be suspected of being infected with a methylerythritol phosphate (MEP) pathway obligate organism. The composition or pharmaceutical formulation can be administered prophylactically to prevent infection by a methylerythritol phosphate (MEP) pathway obligate organism. The organisim can be a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebsiella, Acinetobacter, Pseudomonas,* or *Neisseria*. The organisim can be *P. falciparum*, *P. malariae, P. ovale, P. vivax* or *P. knowlesi*. The organisim can be *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, or N. gonorrhoeae*. The composition or pharmaceutical formulation can be administered orally, intramuscularly, intravenously, topically or subcutaneously.

Also provided herein are methods of contacting an organism with an amount of a composition or pharmaceutical formulation thereof where the composition can have a structure according to Formula 209:



Formula 209

,

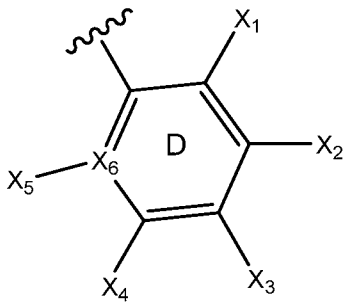
where R_1 can be H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 can be H or a C_1-C_6 alkyl,

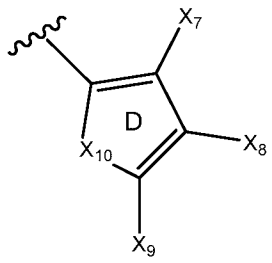
where R_3 can be H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} can each be independently selected from the group of: H and a halogen,

where R_4 can have a structure according to Formula 210 or 211



Formula 210



Formula 211

,

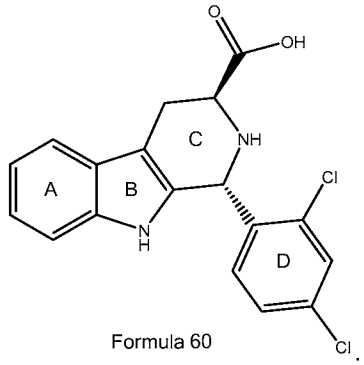
where X_1-X_5 can each be independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen,

where X_6 can be C or N,

where X_{10} can be selected from the group of O, S, and NX_{11}, where X_{11} can be selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} can be a halogen,

where X_7-X_9 can each be independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen.

In some embodiments, the compound does not have a structure according to Formula 60



Formula 60

The organisim can be a methylerythritol phosphate (MEP) pathway obligate organism. The organsim can use the methylerythritol phosphate (MEP) pathway to synthesize isopentenyl diphosphate (IPP). The organism can be a plant. The organism can be a protazoan. The organsim can be a bacterium.

Also provided herein are methods of administering a composition according to Formula 60 or a pharmaceutical formulation comprising a composition according to Formula 60 to a subject in need thereof, where the subject in need thereof can be infected with or can be suspected of being infected with a methylerythritol phosphate (MEP) pathway obligate organism.

Also provided herein are methods of prophylactically adminstering.a composition according to Formula 60 or a pharmaceutical formulation comprising a composition according to Formula 60 to a subject in need thereof to prevent infection by a methylerythritol phosphate (MEP) pathway obligate organism.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure will be readily appreciated upon review of the detailed description of its various embodiments, described below, when taken in conjunction with the accompanying drawings.

Fig. 1 shows a cartoon demonstrating nisotropic displacement ellipsoid drawings (50%) of X-ray structure of Formula 80, confirming (1*R*, 3*S*)-absolute configuration.

Fig. 2 shows a table demonstrating *P. falciparum* growth inhibitory activity and effect of isopentenyl diphosphate (IPP) supplementation of MMV08138 stereoisomers and D-ring variants.

Fig. 3 shows a table demonstrating the synthesis and isolated yields for various embodiments of the compositions described herein.

Fig. 4 shows a table demonstrating the effect of C3-substitution on the *P. falciparum* growth inhibitory activity of a compound according to Formula 60 and some D-ring variants.

Fig. 5 shows embodiments of a synthesis scheme for C3 variants of Formula 60. The reagents and conditions were (i) 2,4-dichlorobenzaldehyde, 4 Å molecular sieves, CH_2Cl_2, 24h. (ii) Requisite amine or hydrazine, 25°C or 50°C, 24 h.

Figs. 6A and 6B show graphs demonstrating the effects of compounds according to Formula 60 (Fig. 6A) and Formula 80 (Fig. 6B) on *P. falciparum* Dd2 strain growth in the absence and presence of 200 μ< IPP (72h incubation). Data represent the average and standard error of five independent experiments.

Fig. 7 shows a table demonstrating *in vitro* ADME Toxicity of compounds according to Formulas 60 and 80.

Fig. 8 shows a graph demonstrating pharmokinetics of a compound according to Formula 60 in the Mouse via oral (PO) (40 mg/kg) or intravenous (IV) (10 mg/kg) administration.

Fig. 9 shows a graph demonstrating surviability of E. coli in the presence of various compositions described herein.

DETAILED DESCRIPTION

Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that

stated range, is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided could be different from the actual publication dates that may need to be independently confirmed.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order that is logically possible.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of molecular biology, microbiology, nanotechnology, organic chemistry, chemistry biochemistry, botany and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

Definitions

As used herein, "about," "approximately," and the like, when used in connection with a numerical variable, generally refers to the value of the variable and to all values of the

variable that are within the experimental error (e.g., within the 95% confidence interval for the mean) or within .+-.10% of the indicated value, whichever is greater.

As used herein, “control” is an alternative subject or sample used in an experiment for comparison purposes and included to minimize or distinguish the effect of variables other than an independent variable. A “control” can be positive or negative.

As used herein, “pharmaceutical formulation” refers to the combination of an active agent, compound, or ingredient with a pharmaceutically acceptable carrier or excipient, making the composition suitable for diagnostic, therapeutic, or preventive use in vitro, in vivo, or ex vivo.

As used herein, “pharmaceutically acceptable carrier or excipient” refers to a carrier or excipient that is useful in preparing a pharmaceutical formulation that is generally safe, non-toxic, and is neither biologically or otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable carrier or excipient” as used in the specification and claims includes both one and more than one such carrier or excipient.

As used herein, “pharmaceutically acceptable salt” refers to any acid or base addition salt whose counter-ions are non-toxic to the subject to which they are administered in pharmaceutical doses of the salts.

As used interchangeably herein, "subject," "individual," or "patient," refers to a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, murines, simians, humans, farm animals, sport animals, and pets. The term “pet” includes a dog, cat, guinea pig, mouse, rat, rabbit, ferret, and the like. The term farm animal includes a horse, sheep, goat, chicken, pig, cow, donkey, llama, alpaca, turkey, and the like.

As used herein, “therapeutic” refers to treating or curing a disease or condition.

As used herein, “preventative” refers to hindering or stopping a disease or condition before it occurs or while the disease or condition is still in the sub-clinical phase.

As used herein, “active agent” or “active ingredient” refers to a component or components of a composition to which the whole or part of the effect of the composition is attributed.

As used herein, “dose,” “unit dose,” or “dosage” refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the nanoparticle composition or formulation calculated to produce the desired response or responses in association with its administration.

As used herein, “antibody” refers to a protein produced by B cells that is used by the immune system to identify and neutralize foreign compounds, which are also known as antigens. Antibodies are glycoproteins belonging to the immunoglobulin superfamily. Antibodies, recognize and bind to specific epitopes on an antigen.

As used herein, “aptamer” refers to single-stranded DNA or RNA molecules that can bind to pre-selected targets including proteins with high affinity and specificity. Their specificity and characteristics are not directly determined by their primary sequence, but instead by their tertiary structure.

As used herein “immunomodulator,” refers to an agent, such as a therapeutic agent, which is capable of modulating or regulating one or more immune function or response.

As used herein, “deoxyribonucleic acid (DNA)” and “ribonucleic acid (RNA)” generally refer to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. RNA may be in the form of a tRNA (transfer RNA), snRNA (small nuclear RNA), rRNA (ribosomal RNA), mRNA (messenger RNA), anti-sense RNA, RNAi (RNA interference construct), siRNA (short interfering RNA), or ribozymes.

Anti-infectives include, but are not limited to, antibiotics, antibacterials, antifungals, antivirals, and antiproatozoals.

As used herein, “derivative” refers to any compound having the same or a similar core structure to the compound but having at least one structural difference, including substituting, deleting, and/or adding one or more atoms or functional groups. The term “derivative” does not mean that the derivative is synthesized from the parent compound either as a starting material or intermediate, although this may be the case. The term “derivative” can include prodrugs, or metabolites of the parent compound. Derivatives include compounds in which free amino groups in the parent compound have been derivatized to form amine hydrochlorides, p-toluene sulfoamides, benzoxycarboamides, t-butyloxycarboamides, thiourethane-type derivatives, trifluoroacetylamides, chloroacetylamides, or formamides. Derivatives include compounds in which carboxyl groups in the parent compound have been derivatized to form methyl and ethyl esters, or other types of esters or hydrazides. Derivatives include compounds in which hydroxyl groups in the parent compound have been derivatized to form O-acyl or O-alkyl derivatives. Derivatives include compounds in which a hydrogen bond donating group in the parent compound is replaced with another hydrogen bond donating group such as OH, NH, or SH. Derivatives include replacing a hydrogen bond acceptor group in the parent compound with

another hydrogen bond acceptor group such as esters, ethers, ketones, carbonates, tertiary amines, imine, thiones, sulfones, tertiary amides, and sulfides. “Derivatives” also includes extensions of the replacement of the cyclopentane ring with saturated or unsaturated cyclohexane or other more complex, *e.g.,* nitrogen-containing rings, and extensions of these rings with side various groups.

As used herein, “administering” refers to an administration that is oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation, or via an implanted reservoir. The term “parenteral” includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional, and intracranial injections or infusion techniques.

As used herein, "suitable substituent" means a chemically and pharmaceutically acceptable group, i.e., a moiety that does not significantly interfere with the preparation of or negate the efficacy of the inventive compounds. Such suitable substituents may be routinely chosen by those skilled in the art. Suitable substituents include but are not limited to the following: a halo, C1-C6 alkyl, C2-C6 alkenyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C2-C6 alkynyl, C3-C8 cycloalkenyl, (C3-C8 cycloalkyl)C1-C6 alkyl, (C3-C8 cycloalkyl)C2-C6 alkenyl, (C3-C8 cycloalkyl) C1-C6 alkoxy, C3-C7 heterocycloalkyl, (C3-C7 heterocycloalkyl)C1-C6 alkyl, (C3-C7 heterocycloalkyl)C2-C6 alkenyl, (C3-C7 heterocycloalkyl)C1-C6 alkoxyl, hydroxy, carboxy, oxo, sulfanyl, C1-C6 alkylsulfanyl, aryl, heteroaryl, aryloxy, heteroaryloxy, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, nitro, cyano, amino, C1-C6 alkylamino, di-(C1-C6 alkyl)amino, carbamoyl, (C1-C6 alkyl)carbonyl, (C1-C6 alkoxy)carbonyl, (C1-C6 alkyl)aminocarbonyl, di-(C1-C6 alkyl)aminocarbonyl, arylcarbonyl, aryloxycarbonyl, (C1-C6 alkyl)sulfonyl, and arylsulfonyl. The groups listed above as suitable substituents are as defined hereinafter except that a suitable substituent may not be further optionally substituted.

As used herein, “optically substituted” indicates that a group may be unsubstituted or substituted with one or more substituents as defined herein.

The term "alkyl" refers to the radical of saturated aliphatic groups (i.e., an alkane with one hydrogen atom removed), including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups.

In some embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chains, and C_3-C_{30} for branched chains). In other embodiments, a straight chain or branched chain alkyl contains 20 or fewer, 15 or fewer, or 10 or fewer carbon atoms in its backbone. Likewise, in some embodiments cycloalkyls have 3-10 carbon atoms in their ring structure. In some of these embodiments, the cycloalkyl have 5, 6, or 7 carbons in the ring structure.

The term "alkyl" (or "lower alkyl") as used herein is intended to include both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having one or more substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents include, but are not limited to, halogen, hydroxyl, carbonyl (such as a carboxyl, alkoxycarbonyl, formyl, or an acyl), thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), alkoxyl, phosphoryl, phosphate, phosphonate, phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, sulfhydryl, alkylthio, sulfate, sulfonate, sulfamoyl, sulfonamido, sulfonyl, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include halogen, hydroxy, nitro, thiols, amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Cycloalkyls can be substituted in the same manner.

The term “heteroalkyl,” as used herein, refers to straight or branched chain, or cyclic carbon-containing radicals, or combinations thereof, containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P, Se, B, and S, wherein the phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

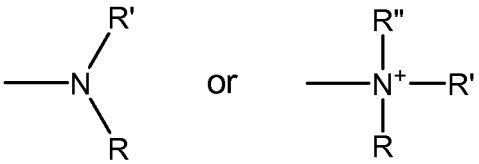
The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, and -S-alkynyl. Representative alkylthio groups include methylthio,

ethylthio, and the like. The term “alkylthio” also encompasses cycloalkyl groups, alkene and cycloalkene groups, and alkyne groups. “Arylthio” refers to aryl or heteroaryl groups. Alkylthio groups can be substituted as defined above for alkyl groups.

The terms "alkenyl" and "alkynyl", refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

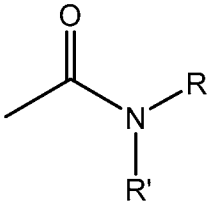
The terms "alkoxyl" or "alkoxy," as used herein, refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl is an ether or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, and -O-alkynyl. The terms “aroxy” and “aryloxy”, as used interchangeably herein, can be represented by –O-aryl or O-heteroaryl, wherein aryl and heteroaryl are as defined below. The alkoxy and aroxy groups can be substituted as described above for alkyl.

The terms "amine" and "amino" (and its protonated form) are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



wherein R, R’, and R” each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH2)_m-R_C$ or R and R’ taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_C represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In some embodiments, only one of R or R’ can be a carbonyl, e.g., R, R’ and the nitrogen together do not form an imide. In other embodiments, the term “amine” does not encompass amides, e.g., wherein one of R and R’ represents a carbonyl. In further embodiments, R and R’ (and optionally R”) each independently represent a hydrogen, an alkyl or cycloakly, an alkenyl or cycloalkenyl, or alkynyl. Thus, the term "alkylamine" as used herein means an amine group, as defined above, having a substituted (as described above for alkyl) or unsubstituted alkyl attached thereto, i.e., at least one of R and R’ is an alkyl group.

The term "amido" is art-recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R and R' are as defined above.

As used herein, "Aryl" refers to C_5-C_{10}-membered aromatic, heterocyclic, fused aromatic, fused heterocyclic, biaromatic, or bihetereocyclic ring systems. Broadly defined, "aryl", as used herein, includes 5-, 6-, 7-, 8-, 9-, and 10-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with one or more substituents including, but not limited to, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino (or quaternized amino), nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, and combinations thereof.

The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (i.e., "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic ring or rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocycles. Examples of heterocyclic rings include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, *2H,6H*-1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, *1H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl,

oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, and xanthenyl. One or more of the rings can be substituted as defined above for "aryl."

The term "aralkyl," as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

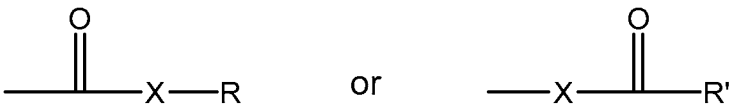
The term "aralkyloxy" can be represented by –O-aralkyl, wherein aralkyl is as defined above.

The term "carbocycle," as used herein, refers to an aromatic or non-aromatic ring(s) in which each atom of the ring(s) is carbon.

"Heterocycle" or "heterocyclic," as used herein, refers to a monocyclic or bicyclic structure containing 3-10 ring atoms, and in some embodiments, containing from 5-6 ring atoms, wherein the ring atoms are carbon and one to four heteroatoms each selected from the following group of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C_1-C_{10}) alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds and optionally substituted with one or more substituents. Examples of heterocyclic rings include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxepanyl, oxetanyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl,

piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, and xanthenyl. Heterocyclic groups can optionally be substituted with one or more substituents at one or more positions as defined above for alkyl and aryl, for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbonyl" is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R and R' are as defined above. Where X is an oxygen and R or R' is not hydrogen, the formula represents an "ester". Where X is an oxygen and R is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R is a hydrogen, the formula represents a "carboxylic acid." Where X is an oxygen and R' is hydrogen, the formula represents a "formate." In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiocarbonyl" group. Where X is a sulfur and R or R' is not hydrogen, the formula represents a "thioester." Where X is a sulfur and R is hydrogen, the formula represents a "thiocarboxylic acid." Where X is a sulfur and R' is hydrogen, the formula represents a "thioformate." On the other hand, where X is a bond, and R is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R is hydrogen, the above formula represents an "aldehyde" group.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Exemplary heteroatoms include, but are not limited to, boron, nitrogen, oxygen, phosphorus, sulfur, silicon, arsenic, and selenium.

As used herein, the term "nitro" refers to -NO_2; the term "halogen" designates -F, -Cl, -Br, or -I; the term "sulfhydryl" refers to -SH; the term "hydroxyl" refers to -OH; and the term "sulfonyl" refers to -SO_2-.

The term “substituted” as used herein, refers to all permissible substituents of the compounds described herein. In the broadest sense, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, but are not limited to, halogens, hydroxyl groups, or any other organic groupings containing any number of carbon atoms, *e.g.* 1-14 carbon atoms, and optionally include one or more heteroatoms such as oxygen, sulfur, or nitrogen grouping in linear, branched, or cyclic structural formats. Representative substituents include alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxyl, alkoxy, substituted alkoxy, phenoxy, substituted phenoxy, aroxy, substituted aroxy, alkylthio, substituted alkylthio, phenylthio, substituted phenylthio, arylthio, substituted arylthio, cyano, isocyano, substituted isocyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, sulfonyl, substituted sulfonyl, sulfonic acid, phosphoryl, substituted phosphoryl, phosphonyl, substituted phosphonyl, polyaryl, substituted polyaryl, C_3-C_{20} cyclic, substituted C_3-C_{20} cyclic, heterocyclic, substituted heterocyclic, amino acid, peptide, and polypeptide groups.

Heteroatoms, such as nitrogen, may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. It is understood that “substitution” or “substituted” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, i.e., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, “effective amount” refers to the amount of a composition described herein or pharmaceutical formulation described herein that will elicit a desired biological or medical response of a tissue, system, animal, plant, protozoan, bacteria or yeastor human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The desired biological response can be death, growth inhibition, reproductive inhibition, and/or development inhibition. The effective amount will vary depending on the exact chemical

structure of the composition or pharmaceutical formulation, the causative agent and/or severity of the infection, disease, disorder, syndrome, or symptom thereof being treated or prevented, the route of administration, the time of administration, the rate of excretion, the drug combination, the judgment of the treating physician, the dosage form, and the age, weight, general health, sex and/or diet of the subject to be treated.

Discussion

Malaria continues to be one of the most deadly diseases in the world, causing over half a million deaths in 2013. The reductions seen in annual mortality over the last 10 years are greatly welcomed, but these advances are at risk due to several factors. Chief among these risk factors is emerging resistance to existing antimalarial drugs, such as chloroquine and artemether. Thus, there is a pressing need to develop antimalarial drugs that engage new targets. Since the discovery that the malaria parasite *Plasmodium falciparum* carried an an apicoplast, there has been considerable interest in developing chemical agents that could specifically target this relict chloroplast, due to its unusual non-mammalian metabolism. Isoprenoid precursor biosynthesis in *P. falciparum* occurs in the apicoplast not via the mevalonate pathway, but rather through the methlerythritol phosphate (MEP) pathway. Supply of isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) is the sole essential function of this organelle during disease-causing asexual intraerythrocytic stages of the parasite and during gametocyte development, the malaria stages transmitted to the mosquito.

As the MEP pathway is absent in humans, agents targeting it could be both safe to the human host and effective. However, the MEP pathway is present in the human microbiome. Therefore, compounds that can selectively inhibit the *P. falciparum* enzymes are highly desirable to reduce their impact on the host microbiome. Fosmidomycin (FOS) was shown to inhibit 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR or IspC), the second enzyme in the MEP pathway, and it cured mice infected with *Plasmodium vinckei*. In combination with clindamycin, FOS was evaluated in clinical trials. However, FOS is unacceptable as a anti-malarial due to poor oral bioavailability. As such, there still exists a need for the development of selectively inhibit the *P. falciparum* enzymes for the development of anti-malarial compounds.

With that said, described herein are compositions and formulations thereof containing a MMV008138 derivative or analogue. Also described herein are methods of making and using the compositions, and formulations thereof described herein. The compositions, and

formulations thereof can, in some embodiments, inhibit the MEP pathway enzyme(s) and thus can be useful for treatment and/or prevention of organisms that utilize the MEP pathway. Other compositions, compounds, methods, features, and advantages of the present disclosure will be or become apparent to one having ordinary skill in the art upon examination of the following drawings, detailed description, and examples. It is intended that all such additional compositions, compounds, methods, features, and advantages be included within this description, and be within the scope of the present disclosure.

As used herein, "toxic" can refer to a effect that is the result of a composition or pharmaceutical formulation described herein, where the effect is detrimental to the life, growth, development, reproduction, and/or health of an organisim. For example, a composition that can inhibit the growth of an organism can be refered to herein as being toxic to that organism.

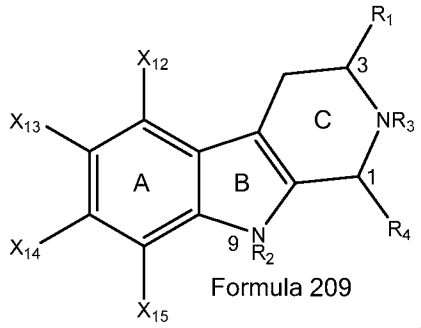
As used herein, "a MEP-obligate organism" refers to an organism that must have a functioning MEP pathway to grow, develop, reproduce, and/or survive.

Compositions

The apicoplast in *Plasmodium* is essential for both intraerythrocytic and intrahepatic development in a human host. Supply of the isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) is the sole essential function of this organelle in these life stages. Synthesis of these compounds in *Plasmodium* occurs via the MEP pathway, which is absent in humans. *Plasmodium* is an MEP-obligate organism as disruption of the MEP pathway results in an inability for the parasite to complete its life cycle.

Described herein are compositions that can inhibit or eliminate isoprenoid biosynthesis in an organism. The compositions can inhibit or ablate isoprenoid biosynthesis by targeting and/or inhibiting one or more enzymes in the methylerthritol phosphate (MEP) pathway. In some embodiments, the compositions can be toxic to an organism. In further embodiments, the compositions can selectively inhibit or eliminate isoprenoid biosynthesis in some organisms and not others.

The composition can have a structure according to formula 209. A compound having a structure according to Formula 209



Formula 209 ,

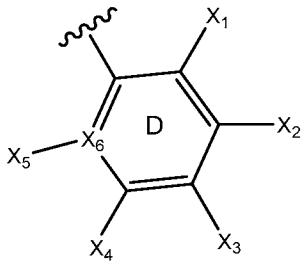
where R_1 can be H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 can be H or a C_1-C_6 alkyl,

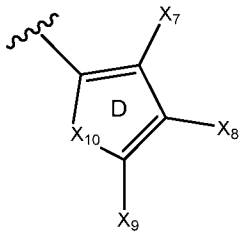
where R_3 can be H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} can each be independently selected from the group of: H and a halogen,

where R_4 can have a structure according to Formula 210 or 211



Formula 210



Formula 211 ,

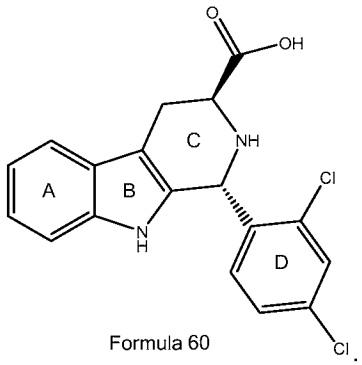
where X_1-X_5 can each be independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen,

where X_6 can be C or N,

where X_{10} can be selected from the group of O, S, and NX_{11}, where X_{11} can be selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} can be a halogen, and

where X_7-X_9 can each be independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} can be a halogen.

In some embodiments, the compound does not have a structure according to Formula 60.



Formula 60

Formula 209 is shown with 4 ring designations: A, B, C, and D. As such, it will be understood that when a portion of the compound of Formula 209 is referred to herein as the "D ring" it is referring to the ring labeled with "D" in formula 209. Some positions are numbered in Formula 209 for reference. As such, it will be understood that when numbers are used to describe a particular feature of a composition according to Formula 9, the numbers are referring to the location of the feature within the compositions. For example, the stereoisomer 1*R,* 3*S*, has the *R* isomer at the position designated with the "1" in Formula 209 and is the *S* isomer at the position designated with the "3" in Formula 209.

The composition can have a (1*R*,3*S*)-, (1*S*,3*S*)-, (1*R*,3*R*)-, or a (1*S*,3*R*)-configuration. In some embodiments the composition can have a (1*R*,3*S*)- configuration. In some embodiments, R4 is Formula 210. In these embodiments, X_1 and X_3 are each a halogen. The halogen can be F, Cl, Br, or I. X_1 and X_3 can be the same or different. X_1 and X_3 can each be independently selected from a halogen and a C_1-C_6 alkyl. The halogen can be F, Cl, Br, or I. The C_1-C_6 alkyl can be methyl. X_1 and X_3 can be the same or different. R_2 and R_3 can both be H.

In some embodiments, the composition can have a structure according to any one of Formulas 70, 74, 75, 66, 79, 80, 86, 90, 91, 84, 126,127, 128, 129, 131, 133, 138, 140, 182, 183, 184, 188, 189, 190, 194, 195, 196, 200, 201, or 203. In some embodiments, the composition can have a structure according to any one of formulas 70, 74, 75, 80, 90, 126, 127, 128, 129, 131, 133, 138, or 140. In some embodiments, the composition can have a structure according to any one of formulas 74, 80, 90, 126, 127, 128, 129, 133, 138, or 140. In some embodiments, the composition can have a strucutre according to Formula 60.

The compositions described herein can be toxic to an organism. The compositions described herein can inhibit the growth of an organism. The compositions describe herein can disrupt the reproduction cycle of an organism. The organism can be a plant, animal, protazoan bacteria, fungi, or yeast. The organism can synthesize isoprenoids via the MEP pathway. The organism can be a MEP-obligate organism. In some embodiments the organism can be from the genus *Plasmoidum*. In some embodiments, the organism can be *P. falciparum*, *P. malariae, P. ovale, P. vivax* or *P. knowlesi*. In other embodiments, the organism can be a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebisella, Acinetobacter, Pseudomonas, and Neisseria*. In further embodiments, the organism can be *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, and N. gonorrhoeae.*

The compositions described herein can inhibit or block the growth, development, and/or reproduction of an organism. In some embodiments, IC_{50} for growth inhibition of the organism can be about 1500 nM or less, about 1200 nM or less, or about 1000 nM or less. In some embodiments, the IC_{50} for growth inhibition of the organism can be about 880 nM or less. In other embodiments, the IC_{50} for growth inhibition of the organism can be about 650 nM or less.

In other embodiments, the organism can be a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebisella, Acinetobacter, Pseudomonas, and Neisseria*. In further embodiments, the organism can be *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, and N. gonorrhoeae.*

Pharmaceutical Formulations

The compositions described herein can be provided to a subject alone or as an ingredient, such as an active ingredient, in a pharmaceutical formulation or pharmaceutically acceptable salt thereof. It is to be understood that the term “pharmaceutical formulation”, as used herein, includes pharmaceutically acceptable salts thereof. Methods of making pharmaceutically acceptable salts are generally known in the art. As such, also described herein are pharmaceutical formulations that can contain one or more of the compositions described herein. In some embodiments, the pharmaceutical formulations can contain an

effective amount of a composition described herein. The pharmaceutical formulations can be administered to a subject in need thereof. In some embodiments, the subject in need thereof can be infected with or suspected of being infected with an organism that synthesizes isoprenoids via the MEP pathway. The subject in need thereof can be infected with or suspected of being infected with an organism that is a MEP-obligate organism. The compositions and pharmaceutical formulations described herein can be administered prophylactically to a subject in need thereof. In some embodiments, the subject in need thereof does not have any known exposure to an MEP-obligate organism.

In some embodiments, the organism can be from the genus *Plasmoidum*. In some embodiments, the organism can be *P. falciparum*, *P. malariae, P. ovale, P. vivax* or *P. knowlesi*. In other embodiments, the organism can be a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebisella, Acinetobacter, Pseudomonas, and Neisseria*. In some embodiments the organism can be a carbapenem-resistant enterobacteriaceae. In further embodiments, the organism can be *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, and N. gonorrhoeae.*

Any composition described herein can be included as a pharmaceutical formulation. In some embodiments, a composition included in the pharmaceutical formulation can have a structure according to any one of Formulas 60, 70, 74, 75, 66, 79, 80, 86, 90, 91, 84, 126,127, 128, 129, 131, 133, 138, 140, 182, 183, 184, 188, 189, 190, 194, 195, 196, 200, 201, or 203.

Pharmaceutically Acceptable Carriers and Auxiliary Ingredients and Agents

The pharmaceutical formulations containing an amount of a composition described herein can further include a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include, but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxyl methylcellulose, and polyvinyl pyrrolidone, which do not deleteriously react with the active composition.

The pharmaceutical formulations can be sterilized, and if desired, mixed with auxiliary agents, such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers,

salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances, and the like which do not deleteriously react with the active composition.

In addition to the effective amount of the compositions described herein, the pharmaceutical formulation can also include an effective amount of auxiliary active agents, including but not limited to, DNA, RNA, amino acids, peptides, polypeptides, antibodies, aptamers, ribozymes, guide sequences for ribozymes that inhibit translation or transcription of essential tumor proteins and genes, hormones, immunomodulators, antipyretics, anxiolytics, antipsychotics, analgesics, antispasmodics, anti-inflammatories, anti-histamines, anti-infectives, and chemotherapeutics.

Suitable hormones include, but are not limited to, amino-acid derived hormones (*e.g.* melatonin and thyroxine), small peptide hormones and protein hormones (*e.g.* thyrotropin-releasing hormone, vasopressin, insulin, growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone), eiconsanoids (*e.g.* arachidonic acid, lipoxins, and prostaglandins), and steroid hormones (*e.g.* estradiol, testosterone, tetrahydro testosteron cortisol).

Suitable immunomodulators include, but are not limited to, prednisone, azathioprine, 6-MP, cyclosporine, tacrolimus, methotrexate, interleukins (*e.g.* IL-2, IL-7, and IL-12), cytokines (*e.g.* interferons (*e.g.* IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, and IFN-γ), granulocyte colony-stimulating factor, and imiquimod), chemokines (*e.g.* CCL3, CCL26 and CXCL7), cytosine phosphate-guanosine, oligodeoxynucleotides, glucans, antibodies, and aptamers).

Suitable antipyretics include, but are not limited to, non-steroidal anti-inflammants (*e.g.* ibuprofen, naproxen, ketoprofen, and nimesulide), aspirin and related salicylates (*e.g.* choline salicylate, magnesium salicylae, and sodium salicaylate), paracetamol/acetaminophen, metamizole, nabumetone, phenazone, and quinine.

Suitable anxiolytics include, but are not limited to, benzodiazepines (*e.g.* alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, triazolam, and tofisopam), serotenergic antidepressants (*e.g.* selective serotonin reuptake inhibitors, tricyclic antidepresents, and monoamine oxidase inhibitors), mebicar , afobazole, selank,bromantane, emoxypine, azapirones, barbituates, hyxdroxyzine, pregabalin, validol, and beta blockers.

Suitable antipsychotics include, but are not limited to, benperidol, bromoperidol, droperidol, haloperidol, moperone, pipaperone, timiperone, fluspirilene, penfluridol, pimozide, acepromazine, chlorpromazine, cyamemazine, dizyrazine, fluphenazine,

levomepromazine, mesoridazine, perazine, pericyazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, thioproperazine, thioridazine, trifluoperazine, triflupromazine, chlorprothixene, clopenthixol, flupentixol, tiotixene, zuclopenthixol, clotiapine, loxapine, prothipendyl, carpipramine,, clocapramine, molindone, mosapramine, sulpiride, veralipride, amisulpride, amoxapine, aripiprazole, asenapine, clozapine, blonanserin, iloperidone, lurasidone, melperone, nemonapride, olanzaprine, paliperidone, perospirone, quetiapine, remoxipride, risperidone, sertindole, trimipramine, ziprasidone, zotepine, alstonie, befeprunox, bitopertin, brexpiprazole, cannabidiol, cariprazine, pimavanserin, pomaglumetad methionil, vabicaserin, xanomeline, and zicronapine.

Suitable analgesics include, but are not limited to, paracetamol/acetaminophen, non-steroidal anti-inflammants (*e.g.* ibuprofen, naproxen, ketoprofen, and nimesulide), COX-2 inhibitors (*e.g.* rofecoxib, celecoxib, and etoricoxib), opioids (*e.g.* morphine, codeine, oxycodone, hydrocodone, dihydromorphine, pethidine, buprenorphine), tramadol, norepinephrine, flupiretine, nefopam, orphenadrine, pregabalin, gabapentin, cyclobenzaprine, scopolamine, methadone, ketobemidone, piritramide, and aspirin and related salicylates (*e.g.* choline salicylate, magnesium salicylae, and sodium salicaylate).

Suitable antispasmodics include, but are not limited to, mebeverine, papverine, cyclobenzaprine, carisoprodol, orphenadrine, tizanidine, metaxalone, methodcarbamol, chlorzoxazone, baclofen, dantrolene, baclofen, tizanidine, and dantrolene.

Suitable anti-inflammatories include, but are not limited to, prednisone, non-steroidal anti-inflammants (*e.g.* ibuprofen, naproxen, ketoprofen, and nimesulide), COX-2 inhibitors (*e.g.* rofecoxib, celecoxib, and etoricoxib), and immune selective anti-inflammatory derivatives (*e.g.* submandibular gland peptide-T and its derivatives).

Suitable anti-histamines include, but are not limited to, H_1-receptor antagonists (*e.g.* acrivastine, azelastine, bilastine, brompheniramine, buclizine, bromodiphenhydramine, carbinoxamine, cetirizine, chlorpromazine, cyclizine, chlorpheniramine, clemastine, cyproheptadine, desloratadine, dexbromapheniramine, dexchlorpheniramine, dimenhydrinate, dimetindene, diphenhydramine, doxylamine, ebasine, embramine, fexofenadine, hydroxyzine, levocetirzine, loratadine, meclozine, mirtazapine, olopatadine, orphenadrine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, quetiapine, rupatadine, tripelennamine, and triprolidine), H_2-receptor antagonists (*e.g.*

cimetidine, famotidine, lafutidine, nizatidine, rafitidine, and roxatidine), tritoqualine, catechin, cromoglicate, nedocromil, and β2-adrenergic agonists.

Suitable anti-infectives include, but are not limited to, amebicides (*e.g.* nitazoxanide, paromomycin, metronidazole, tnidazole, chloroquine, and iodoquinol), aminoglycosides (*e.g.* paromomycin, tobramycin, gentamicin, amikacin, kanamycin, and neomycin), anthelmintics (*e.g.* pyrantel, mebendazole, ivermectin, praziquantel, abendazole, miltefosine, thiabendazole, oxamniquine), antifungals (*e.g.* azole antifungals (*e.g.* itraconazole, fluconazole, posaconazole, ketoconazole, clotrimazole, miconazole, and voriconazole), echinocandins (*e.g.* caspofungin, anidulafungin, and micafungin), griseofulvin, terbinafine, flucytosine, and polyenes (*e.g.* nystatin, and amphotericin b), antimalarial agents (*e.g.* pyrimethamine/sulfadoxine, artemether/lumefantrine, atovaquone/proquanil, quinine, hydroxychloroquine, mefloquine, chloroquine, doxycycline, pyrimethamine, and halofantrine), antituberculosis agents (*e.g.* aminosalicylates (*e.g.* aminosalicylic acid), isoniazid/rifampin, isoniazid/pyrazinamide/rifampin, bedaquiline, isoniazid, ethanmbutol, rifampin, rifabutin, rifapentine, capreomycin, and cycloserine), antivirals (*e.g.* amantadine, rimantadine, abacavir/lamivudine, emtricitabine/tenofovir, cobicistat/elvitegravir/emtricitabine/tenofovir, efavirenz/emtricitabine/tenofovir, avacavir/lamivudine/zidovudine, lamivudine/zidovudine, emtricitabine/tenofovir, emtricitabine/opinavir/ritonavir/tenofovir, interferon alfa-2v/ribavirin, peginterferon alfa-2b, maraviroc, raltegravir, dolutegravir, enfuvirtide, foscarnet, fomivirsen, oseltamivir, zanamivir, nevirapine, efavirenz, etravirine, rilpiviirine, delaviridine, nevirapine, entecavir, lamivudine, adefovir, sofosbuvir, didanosine, tenofovir, avacivr, zidovudine, stavudine, emtricitabine, xalcitabine, telbivudine, simeprevir, boceprevir, telaprevir, lopinavir/ritonavir, fosamprenvir, dranuavir, ritonavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, sawuinavir, ribavirin, valcyclovir, acyclovir, famciclovir, ganciclovir, and valganciclovir), carbapenems (*e.g.* doripenem, meropenem, ertapenem, and cilastatin/imipenem), cephalosporins (*e.g.* cefadroxil, cephradine, cefazolin, cephalexin, cefepime, ceflaroline, loracarbef, cefotetan, cefuroxime, cefprozil, loracarbef, cefoxitin, cefaclor, ceftibuten, ceftriaxone, cefotaxime, cefpodoxime, cefdinir, cefixime, cefditoren, cefizoxime, and ceftazidime), glycopeptide antibiotics (*e.g.* vancomycin, dalbavancin, oritavancin, and telvancin), glycylcyclines (*e.g.* tigecycline), leprostatics (*e.g.* clofazimine and thalidomide), lincomycin and derivatives thereof (*e.g.* clindamycin and lincomycin), macrolides and derivatives thereof (*e.g.* telithromycin, fidaxomicin, erthromycin, azithromycin, clarithromycin, dirithromycin, and troleandomycin), linezolid,

sulfamethoxazole/trimethoprim, rifaximin, chloramphenicol, fosfomycin, metronidazole, aztreonam, bacitracin, penicillins (amoxicillin, ampicillin, bacampicillin, carbenicillin, piperacillin, ticarcillin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, clavulanate/ticarcillin, penicillin, procaine penicillin, oxaxillin, dicloxacillin, and nafcillin), quinolones (*e.g.* lomefloxacin, norfloxacin, ofloxacin, qatifloxacin, moxifloxacin, ciprofloxacin, levofloxacin, gemifloxacin, moxifloxacin, cinoxacin, nalidixic acid, enoxacin, grepafloxacin, gatifloxacin, trovafloxacin, and sparfloxacin), sulfonamides (*e.g.* sulfamethoxazole/trimethoprim, sulfasalazine, and sulfasoxazole), tetracyclines (*e.g.* doxycycline, demeclocycline, minocycline, doxycycline/salicyclic acid, doxycycline/omega-3 polyunsaturated fatty acids, and tetracycline), and urinary anti-infectives (*e.g.* nitrofurantoin, methenamine, fosfomycin, cinoxacin, nalidixic acid, trimethoprim, and methylene blue).

Suitable chemotherapeutics include, but are not limited to, paclitaxel, brentuximab vedotin, doxorubicin, 5-FU (fluorouracil), everolimus, pemetrexed, melphalan, pamidronate, anastrozole, exemestane, nelarabine, ofatumumab, bevacizumab, belinostat, tositumomab, carmustine, bleomycin, bosutinib, busulfan, alemtuzumab, irinotecan, vandetanib, bicalutamide, lomustine, daunorubicin, clofarabine, cabozantinib, dactinomycin, ramucirumab, cytarabine, cytoxan, cyclophosphamide, decitabine, dexamethasone, docetaxel, hydroxyurea, decarbazine, leuprolide, epirubicin, oxaliplatin, asparaginase, estramustine, cetuximab, vismodegib, aspargainase erwinia chyrsanthemi, amifostine, etoposide, flutamide, toremifene, fulvestrant, letrozole, degarelix, pralatrexate, methotrexate, floxuridine, obinutuzumab, gemcitabine, afatinib, imatinib mesylatem, carmustine, eribulin, trastuzumab, altretamine, topotecan, ponatinib, idarubicin, ifosfamide, ibrutinib, axitinib, interferon alfa-2a, gefitinib, romidepsin, ixabepilone, ruxolitinib, cabazitaxel, ado-trastuzumab emtansine, carfilzomib, chlorambucil, sargramostim, cladribine, mitotane, vincristine, procarbazine, megestrol, trametinib, mesna, strontium-89 chloride, mechlorethamine, mitomycin, busulfan, gemtuzumab ozogamicin, vinorelbine, filgrastim, pegfilgrastim, sorafenib, nilutamide, pentostatin, tamoxifen, mitoxantrone, pegaspargase, denileukin diftitox, alitretinoin, carboplatin, pertuzumab, cisplatin, pomalidomide, prednisone, aldesleukin, mercaptopurine, zoledronic acid, lenalidomide, rituximab, octretide, dasatinib, regorafenib, histrelin, sunitinib, siltuximab, omacetaxine, thioguanine (tioguanine), dabrafenib, erlotinib, bexarotene, temozolomide, thiotepa, thalidomide, BCG, temsirolimus, bendamustine hydrochloride, triptorelin, aresnic trioxide, lapatinib, valrubicin, panitumumab, vinblastine, bortezomib, tretinoin, azacitidine, pazopanib, teniposide, leucovorin, crizotinib,

capecitabine, enzalutamide, ipilimumab, goserelin, vorinostat, idelalisib, ceritinib, abiraterone, epothilone, tafluposide, azathioprine, doxifluridine, vindesine, and all-trans retinoic acid.

Effective Amounts of the Compositions and Auxiliary Agents

The pharmaceutical formulations can contain an effective amount of a composition described herein and/or an effective amount of an auxiliary agent. In some embodiments, the effective amount ranges from about 0.001 pg of the composition described herein or auxiliary agent to about 1,000 g of the composition described herein or auxiliary agent composition. In some embodiments the effective amount of the composition described herein can be about 5 mg to about 5 g. In further embodiments, the effective amount of the composition described herein can be about 7 mg to about 3.5 g. In other embodiments, the concentration of the composition amount ranges from about 0.001 nM to about 100 mM. In some embodiments the effective amount of the composition described herein rages from about 0.001 mg/kg body weight to about 1,000 mg/kg body weight. In some embodiments, the effective amount can be at least 0.001 mg/kg body weight. In some embodiments, the effect amount of the composition can range from 0.1 mg/kg body weight to about 50 mg/kg body weight.

In embodiments where there is an auxiliary active agent contained in the pharmaceutical formulation in addition to the composition, the effective amount of the auxiliary active agent will vary depending on the auxiliary active agent. In some embodiments, the effective amount of the auxiliary active agent ranges from 0.001 micrograms to about 1 miligrams. In other embodiments, the effective amount of the auxiliary active agent ranges from about 0.01 IU to about 100,00 IU or more. In further embodiments, the effective amount of the auxiliary active agent ranges from 0.001 mL to about 100 mL or more. In yet other embodiments, the effective amount of the auxiliary active agent ranges from about 1% w/w to about 99% or more w/w of the total pharmaceutical formulation. In additional embodiments, the effective amount of the auxiliary active agent ranges from about 1% v/v to about 99% v/v of the total pharmaceutical formulation. In still other embodiments, the effective amount of the auxiliary active agent ranges from about 1% w/v to about 99% w/v of the total pharmaceutical formulation.

The auxiliary active agent can be included in the pharmaceutical formulation or can exist as a stand-alone compound or pharmaceutical formulation that is administered

contemporaneously or sequentially with a composition or pharmaceutical formulation described herein.

Dosage Forms

In some embodiments, the compositions or pharmaceutical formulations described herein may be in a dosage form. The dosage forms can be adapted for administration by any appropriate route. Appropriate routes include, but are not limited to, oral (including buccal or sublingual), rectal, intraocular, inhaled, intranasal, topical (including buccal, sublingual, transdermal, spraying, dusting, pre-emergent application, post-emergent application, and granule application), vaginal, intraurethral, parenteral, intracranial, subcutaneous, intramuscular, intravenous, and intradermal. .

Dosage forms adapted for oral administration can be discrete dosage units such as capsules, pellets or tablets, powders or granules, solutions, or suspensions in aqueous or non-aqueous liquids; edible foams or whips, or in oil-in-water liquid emulsions or water-in-oil liquid emulsions. In some embodiments, the bioactive formulations adapted for oral administration also include one or more agents which flavor, preserve, color, or help disperse the bioactive formulation. Dosage forms prepared for oral administration can also be in the form of a liquid solution that can be delivered as a foam, spray, or liquid solution. In some embodiments, the oral dosage form can contain at least 1 pg of the complexed compound, and in some embodiments, about 1 pg to about 1000 kg or more of a composition or pharmaceutical formulation described herein. In other embodiments, the oral dosage form can contain about 1 mg to about 1 g of a composition or pharmaceutical formulation described herein.

Where appropriate, the dosage forms described herein can be microencapsulated. The dosage form can also be prepared to prolong or sustain the release of any ingredient. In some embodiments, the complexed active agent can be the ingredient whose release is delayed. In other embodiments, the release of an auxiliary ingredient is delayed. Suitable methods for delaying the release of an ingredient include, but are not limited to, coating or embedding the ingredients in material in polymers, wax, gels, and the like. Delayed release dosage formulations can be prepared as described in standard references such as "Pharmaceutical dosage form tablets," eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These

references provide information on excipients, materials, equipment, and processes for preparing tablets and capsules and delayed release dosage forms of tablets and pellets, capsules, and granules. The delayed release can be anywhere from about an hour to about 3 months or more.

Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name EUDRAGIT® (Roth Pharma, Westerstadt, Germany), zein, shellac, and polysaccharides.

Coatings may be formed with a different ratio of water soluble polymer, water insoluble polymers, and/or pH dependent polymers, with or without water insoluble/water soluble non polymeric excipient, to produce the desired release profile. The coating is either performed on the dosage form (matrix or simple) which includes, but is not limited to, tablets (compressed with or without coated beads), capsules (with or without coated beads), beads, particle compositions, “ingredient as is” formulated as, but not limited to, suspension form or as a sprinkle dosage form.

Dosage forms adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, oils, and granules. In some embodiments for treatments of the eye or other external tissues, for example the mouth or the skin, the bioactive formulations are applied as a topical ointment or cream. When formulated in an ointment, the complexed active agent compound, auxiliary active ingredient can be formulated with a paraffinic or water-miscible ointment base. In other embodiments, the active ingredient can be formulated in a cream with an oil-in-water cream base or a water-in-oil base. Dosage forms adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

In some embodiments, such as for treatments of plants, the topical formulation of a composition or pharmaceutical formulation described herein can be further formulated as a spray and can include a suitable surfactant, wetting agent, adjuvants/surfactant (stickers, extender, plant penetrant, compatibility agents, buffers, drift control additives, and defoaming agents), or any combination thereof so as to formulated as a spray. The compounds, any optional auxiliary active ingredient, suitable surfactant, wetting agent, adjuvants, or any combination thereof can be formulated as a solution, suspension, or emulsion. The spray

dosage from can be administered through a spraying device. In some embodiments, the spraying device can be configured to generate the sprayable formulation as a liquid solution is contacted with the complexed active agent compound or formulation thereof. In other embodiments, the sprayable dosage form is pre-made prior to spraying. As such, the spraying device can act solely as an applicator for these embodiments.

In further embodiments, such as for treatments of plants (*e.g.* such as a herbicide), the topical formulation of composition or pharmaceutical formulation described herein thereof can be further formulated as a dust and can include a suitable dry inert carrier (*e.g.* talc chalk, clay, nut hull, volcanic ash, or any combination thereof so as to be formulated as a dust. The dust can contain dust particles of varying sizes. In some embodiments, the particle size can be substantially homogenous. In other embodiments, the particle size can be heterogeneous. Dosage forms adapted as a dust can contain one or more adjuvants/surfactants (stickers, extender, plant penetrant, compatibility agents, buffers, drift control additives, and defoaming agents).

In some embodiments, the dosage form for topical administration can be formulated as a bait. In these embodiments, the complexed active agent compound or other formulation thereof can be further formulated to include a food or other attractive substance that can attract one or more insect or other pest. The bait dosage form can be formulated as a dust, paste, gel, or granule. Dosage forms adapted as baits can contain one or more adjuvants/surfactants (stickers, extender, plant penetrant, compatibility agents, buffers, drift control additives, and defoaming agents).

In additional embodiments, the dosage form for topical administration can be formulated as granules or pellets that can be applied to the environment. These dosage formulations are similar to dust formulations, but the particles are larger and heavier. The granules can be applied to soil or other environmental area. Dosage forms adapted as granules or pellets can contain one or more adjuvants/surfactants (stickers, extender, plant penetrant, compatibility agents, buffers, drift control additives, and defoaming agents).

The dusts, granules, and pellets described herein can be formulated as wetable dusts, granules, and pellets, soluble dusts granules, and pellets, and/or water-dispersible granules, and/or dry flowables.

Dosage forms adapted for nasal or inhalation administration include aerosols, solutions, suspension drops, gels, or dry powders. In some embodiments, the composition or pharmaceutical formulation described herein, auxiliary active ingredient, and/or

pharmaceutically acceptable salt thereof can be in a dosage form adapted for inhalation can be in a particle-size-reduced form that is obtained or obtainable by micronization. In some embodiments, the particle size of the size reduced (e.g. micronized) compound or salt or solvate thereof, is defined by a D_{50} value of about 0.5 to about 10 microns as measured by an appropriate method known in the art. Dosage forms adapted for administration by inhalation also include particle dusts or mists. Suitable dosage forms wherein the carrier or excipient is a liquid for administration as a nasal spray or drops can include aqueous or oil solutions/suspensions of an active ingredient, which can be generated by various types of metered dose pressurized aerosols, nebulizers, or insufflators.

In some embodiments, the dosage forms can be aerosol formulations suitable for administration by inhalation. The aerosol formulation can contain a solution or fine suspension of the complexed active agent, auxiliary active ingredient, and/or pharmaceutically acceptable salt thereof a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multi-dose quantities in sterile form in a sealed container. For some of these embodiments, the sealed container can be a single dose or multi-dose nasal or an aerosol dispenser fitted with a metering valve (e.g. metered dose inhaler), which can be intended for disposal once the contents of the container have been exhausted.

Where the aerosol dosage form is contained in an aerosol dispenser, the dispenser can contain a suitable propellant under pressure, such as compressed air, carbon dioxide, or an organic propellant, including but not limited to a hydrofluorocarbon. The aerosol formulation dosage forms in other embodiments are contained in a pump-atomizer. The pressurized aerosol formulation can also contain a solution or a suspension of a composition described herein or pharmaceutical formulation thereof and/or auxilary agent. In further embodiments, the aerosol formulation also contains co-solvents and/or modifiers incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation. Administration of the aerosol formulation can be once daily or several times daily, for example 2, 3, 4, or 8 times daily, in which 1, 2, or 3 doses are delivered each time.

For some dosage forms suitable and/or adapted for inhaled administration, the composition or pharmaceutical formulation described herein can be a dry powder inhalable formulation. In addition to the composition, pharmaceutical formulation thereof, auxiliary active ingredient, and/or pharmaceutically acceptable salt thereof, such a dosage form can

contain a powder base such as lactose, glucose, trehalose, manitol, and/or starch. In some of these embodiments, the complexed active agent, auxiliary active ingredient, and/or pharmaceutically acceptable salt thereof is in a particle-size reduced form. In further embodiments, a performance modifier, such as L-leucine or another amino acid, cellobiose octaacetate, and/or metals salts of stearic acid, such as magnesium or calcium stearate.

In some embodiments, the aerosol formulations can be arranged so that each metered dose of aerosol contains a predetermined amount of a compound, such as the one or more of the complexed compounds described herein.

Dosage forms adapted for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations. Dosage forms adapted for rectal administration include suppositories or enemas.

Dosage forms adapted for parenteral administration and/or adapted for injection can include aqueous and/or non-aqueous sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, solutes that render the composition isotonic with the blood of the subject, and aqueous and non-aqueous sterile suspensions, which can include suspending agents and thickening agents. The dosage forms adapted for parenteral administration can be presented in a single-unit dose or multi-unit dose containers, including but not limited to sealed ampoules or vials. The doses can be lyophilized and resuspended in a sterile carrier to reconstitute the dose prior to administration. Extemporaneous injection solutions and suspensions can be prepared in some embodiments, from sterile powders, granules, and tablets.

Dosage forms adapted for ocular administration can include aqueous and/or non-aqueous sterile solutions that can optionally be adapted for injection, and which can optionally contain anti-oxidants, buffers, bacteriostats, solutes that render the composition isotonic with the eye or fluid contained therein or around the eye of the subject, and aqueous and non-aqueous sterile suspensions, which can include suspending agents and thickening agents.

The dosage form can be adapted for impregnating (saturating) an object or device, which then can be carried by, worn, or otherwise coupled to an organism in need thereof. In some embodiments, the dosage form can be impregnated onto a collar, bracelet, patch, adhesive tape, livestock ear tags, clothing, blankets, plastics, nets, and paints. The composition or pharmaceutical formulation thereof can be formulated and impregnated in the object or device such that the composition or pharmaceutical formulation evaporates over

time, which releases the composition and/or pharmaceutical formulation into the air and/or environment surrounding the organism and/or onto the organism, including an organism of the genus *Plasmodium* and/or an MEP-obligate organism.

The dosage form can be adapted as a fumigant, which is a formulation that forms a gas when utilized or applied. In some embodiments, the composition and/or pharmaceutical formulation thereof can be supplied as a liquid when packaged under pressure and change to a gas when they are released. In other embodiments, the composition and/or pharmaceutical formulation thereof can be supplied as a volatile liquid when enclosed in a container (not under pressure). Others can be formulated as solids that release gases when applied under conditions of high humidity or in the presence of high water vapor. Dosage forms adapted as fumigants can contain one or more adjuvants/surfactants (stickers, extender, plant penetrant, compatibility agents, buffers, drift control additives, and defoaming agents).

For some embodiments, the dosage form contains a predetermined amount of an the composition and/or pharmaceutical formulation thereof per unit dose. In an embodiment, the predetermined amount of the composition and/or pharmaceutical formulation thereof can be an amount of the complexed active agent to treat, prevent, and/or mitigate the symptoms of an infection with an organism described herein (such as, without limitation, a species of the genus *Plasmodium* or an MEP-obligate organism) or other disease or disorder. In other embodiments, the predetermined amount of a composition or pharmaceutical formulation described herein can be an appropriate fraction of the effective amount of the composition or pharmaceutical formulation. Such unit doses may therefore be administered once or more than once a day, more than once per week, more than once per month, or more than once per year. Such dosage forms can be prepared by any of the methods well known in the art.

Methods of Using the Compositions and Pharamceutical Formulations

The compositions and pharmaceutical formulations described herein can be used to treat and/or prevent infection with and/or infestation of an organism that uses the MEP pathway to generate isoprenoids. The compositions and pharmaceutical formulations described herein can be used to kill an organism that uses the MEP pathway to generate isoprenoids. The compositions and pharmaceutical formulations described herein can be used to inhibit or block the growth, development, and/or reproduction of an organism that uses the MEP pathway to generate isoprenoids. The compositions describe herein can disrupt the reproduction cycle of an organism.

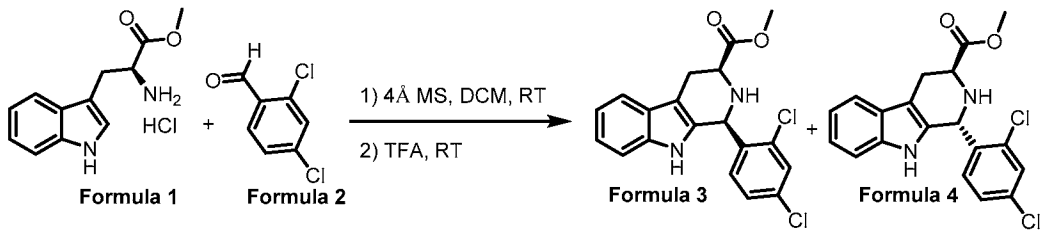
The organism that the compositions and pharmaceutical formulations can be used on or used to prevent infection by can be a plant, animal, protazoan bacteria, fungi, or yeast. The organism can synthesize isoprenoids via the MEP pathway. The organism can be a MEP-obligate organism. In some embodiments the organism can be from the genus *Plasmoidum*. In some embodiments, the organism can be *P. falciparum*, *P. malariae, P. ovale, P. vivax* or *P. knowlesi*. In other embodiments, the organism can be a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebisella, Acinetobacter, Pseudomonas, and Neisseria*. In further embodiments, the organism can be *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, and N. gonorrhoeae.*

EXAMPLES

Now having described the embodiments of the present disclosure, in general, the following Examples describe some additional embodiments of the present disclosure. While embodiments of the present disclosure are described in connection with the following examples and the corresponding text and figures, there is no intent to limit embodiments of the present disclosure to this description. On the contrary, the intent is to cover all alternatives, modifications, and equivalents included within the spirit and scope of embodiments of the present disclosure.

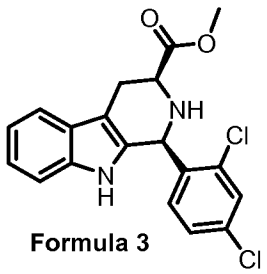
Example 1:

(1S,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 3) and (1R,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 4)



Scheme 1

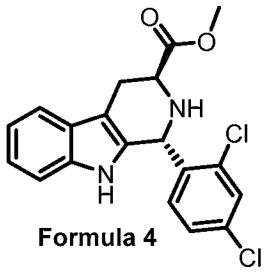
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (2.55 g, 10.0 mmol) and 4Å molecular sieve (5 g, powder form) in DCM (30 mL) was added 2,4-dichlorobenzaldehyde (**Formula 2**) (1.75 g, 10.0 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 20 hours at room temperature. TFA (1.53 mL, 20.0 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 44 hours. An aqueous solution of $NaHCO_3$ (2.40 g, 30 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 3** (1.88 g, 50 % yield) and **Formula 4** (1.30 g, 35 % yield).



Formula 3

(1S,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 3)

$[\alpha]_D^{21.0}$ = -33.0° (c = 2.08, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.49 (dd, J = 3.6 and 2.8 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.11 (m, 4H), 5.72 (s, 1H), 3.91 (dd, J = 10.8 and 4.0 Hz, 1H), 3.77 (s, 3H), 3.19 (ddd, J = 15.2, 4.0 and 2.4 Hz, 1H), 2.97 (ddd, J = 15.2, 10.8 and 2.4 Hz, 1H), 2.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.2, 136.1, 134.4, 134.0, 133.0, 131.3, 129.2, 127.8, 126.7, 122.0, 119.6, 118.1, 110.9, 109.2, 56.4, 53.7, 52.2, 25.3. HRMS (ESI) $[M+H]^+$ calculated for C19H17Cl2N2O2: 375.0662. Found: 375.0655.



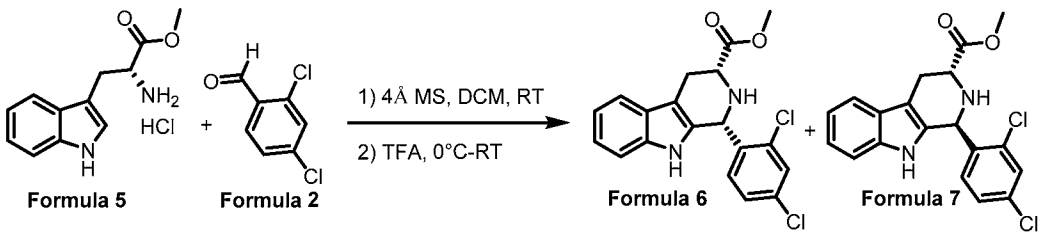
Formula 4

(1R,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 4)

$[\alpha]_D^{21.0}$ = -17.9° (c = 1.30, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.52 (dd, J = 7.2 and 2.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.12 (m, 3H), 7.04 (dd, J = 8.4 and 2.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.73 (s, 1H), 3.76 (dd, J = 8.0 and 4.8 Hz, 1H), 3.68 (s, 3H), 3.20 (ddd, J = 15.2, 4.8 and 0.8 Hz, 1H), 3.01 (ddd, J = 15.2, 8.0 and 0.8 Hz, 1H), 2.73 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.6, 136.2, 134.2, 131.3,130.8, 129.6, 127.0, 126.6, 122.1, 119.5, 118.2, 111.0, 109.5, 52.1, 51.9, 51.1, 24.8. HRMS (ESI) $[M+H]^+$ calculated for C19H17Cl2N2O2: 375.0662. Found: 375.0650.

Example 2:

1R,3R)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 6) and (1S,3R)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 7)

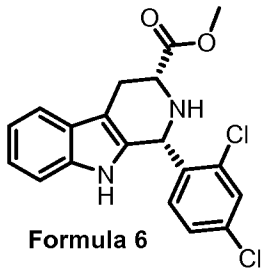


Formula 5 Formula 2 Formula 6 Formula 7

Scheme 2

To a suspension of D-Tryptophan methyl ester hydrochloride (**Formula 5**) (509 mg, 2.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2,4-dichlorobenzaldehyde (**Formula 2**) (385 mg, 2.2 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 21 hours at room temperature. The reaction mixture was cooled to 0 °C, and TFA (306 μL, 4.0 mmol) was then added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for another 6 hours. An aqueous solution of $NaHCO_3$ (420 mg, 5.0 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an

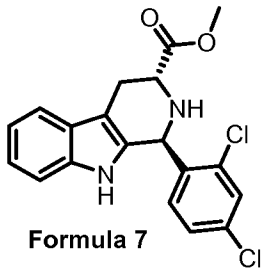
addition of EtOAc (60 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 6 (**446 mg, 60 % yield) and **Formula 7** (129 mg, 17 % yield).



Formula 6

(1R,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 6)

$[\alpha]_D^{21.0}$ = +28.4° (c = 1.92, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.53 (dd, J = 7.5 and 1.0 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.15 (m, 4H), 5.78 (s, 1H), 3.98 (dd, J = 11.0 and 4.0 Hz, 1H), 3.82 (s, 3H), 3.23 (ddd, J = 15.0, 4.0 and 2.0 Hz, 1H), 3.00 (ddd, J = 15.0, 11.0 and 2.0 Hz, 1H), 2.62 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 137.3, 136.2, 134.6, 134.1, 133.1, 131.4, 129.4, 128.0, 126.8, 122.2, 119.8, 118.2, 110.9, 109.4, 56.6, 53.8, 52.3, 25.4. HRMS (ESI) $[M+H]^+$ calculated for C19H17Cl2N2O2: 375.0662. Found: 375.0668.



Formula 7

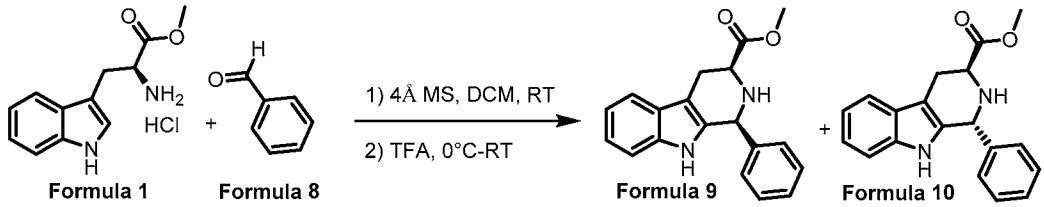
(1S,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 7)

$[\alpha]_D^{21.0}$ = +19.5° (c = 1.29, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 7.5 and 1.5 Hz, 1H), 7.13 (m, 2H), 7.07 (dd, J = 8.5 and 2.0 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.78 (s, 1H), 3.79 (dd, J = 8.0 and 5.0

Hz, 1H), 3.70 (s, 3H), 3.22 (ddd, J = 15.0, 5.0 and 1.0 Hz, 1H), 3.05 (ddd, J = 15.0, 8.0 and 1.0 Hz, 1H), 2.75 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 137.7, 136.2, 134.3, 134.2, 131.4, 130.8, 129.7, 127.1, 126.7, 122.2, 119.6, 118.3, 111.0, 109.6, 52.2, 52.0, 51.1, 24.8. HRMS (ESI) $[M+H]^+$ calculated for C19H17Cl2N2O2: 375.0662. Found: 375.0672.

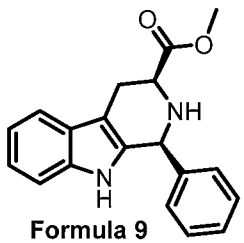
Example 3:

(1S,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 9) and (1R,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 10)



Scheme 3

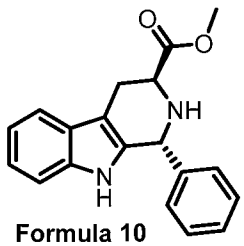
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (5 mL) was added benzaldehyde (**Formula 8**) (336 μL, 3.3 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 23 hours at room temperature. The reaction mixture was cooled to 0 °C, and TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was slowly warmed to room temperature and stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 9 (**612 mg, 67 % yield) and **Formula 10** (130 mg, 14 % yield).



Formula 9

(1S,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 9)

$[\alpha]_D^{21.0}$ = -57.0° (c = 0.17, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.4 and 2.4 Hz, 1H), 7.44 (br s, 1H), 7.36 (m, 5H), 7.13 (m, 3H), 5.22 (s, 1H), 3.96 (dd, J = 11.2 and 4.0 Hz, 1H), 3.80 (s, 3H), 3.22 (ddd, J = 14.8, 4.0 and 2.4 Hz, 1H), 3.00 (ddd, 14.8, 11.2 and 2.4 Hz, 1H), 2.40 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.7, 136.1, 134.7, 128.9, 128.6, 128.5, 127.1, 121.9, 119.6, 118.2, 110.9, 108.9, 58.7, 56.9, 52.2, 25.7. HRMS (ESI) $[M+H]^+$ calculated for C19H19N2O2: 307.1441. Found: 307.1443.



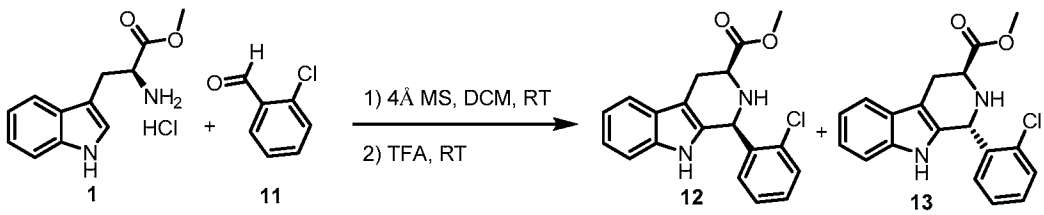
Formula 10

(1R,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 10)

$[\alpha]_D^{21.0}$ = -34.1° (c = 1.45, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.51 (dd, J = 6.4 and 2.0 Hz, 1H), 7.25 (m, 3H), 7.11 (m, 5H), 5.23 (s, 1H), 3.86 (dd, J = 7.2 and 6.0 Hz, 1H), 3.64 (s, 3H), 3.20 (ddd, J = 15.2, 5.2 and 1.2 Hz, 1H), 3.04 (ddd, J = 15.2, 7.2 and 1.2 Hz, 1H), 2.38 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 141.9, 136.1, 133.1, 128.6, 128.3, 127.9, 126.8, 121.8, 119.3, 118.1, 110.9, 108.3, 54.8, 52.2, 52.0, 24.7. HRMS (ESI) $[M+H]^+$ calculated for C19H19N2O2: 307.1441. Found: 307.1428.

Example 4:

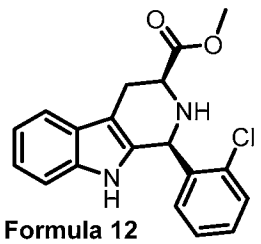
(1S,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 12) and (1R,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 13)



1 11 12 13

Scheme 4

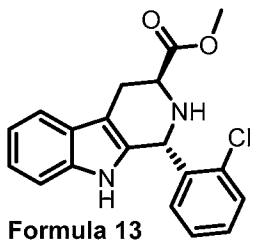
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2-chlorobenzaldehyde (**Formula 11**) (370 μL, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 :5 : 1 hexane / DCM / EtOAc) to give **Formula 12 (**601 mg, 59 % yield) and **Formula 13** (183 mg, 18 % yield).



Formula 12

(1S,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 12)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br s, 1H), 7.52 (dd, J = 7.2 and 2.0 Hz, 1H), 7.43 (dd, J = 8.0 and 1.2 Hz, 1H), 7.39 (dd, J = 7.6 and 1.6 Hz, 1H), 7.25 (td, J = 7.6 and 1.6 Hz, 1H), 7.18 (m, 2H), 7.11 (m, 2H), 5.81 (br s, 1H), 3.97 (dd, J = 11.2 and 4.0 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, J = 15.2, 4.0 and 2.0 Hz, 1H), 3.01 (ddd, J = 15.2, 11.2 and 2.0Hz, 1H), 2.61 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 138.5, 136.1, 133.6, 133.5, 130.3, 129.6, 129.4, 127.6, 126.9, 121.9, 119.6, 118.1, 110.9, 109.1, 56.6, 54.2, 52.2, 25.5.



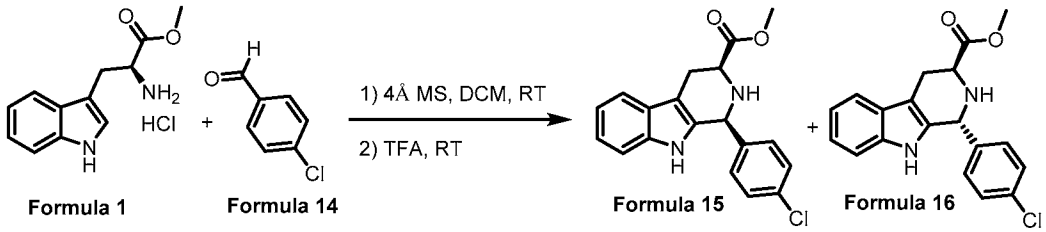
Formula 13

(1R,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 13)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.54 (dd, J = 7.2 and 1.6 Hz, 1H), 7.43 (dd, J = 8.0 and 1.2 Hz, 1H), 7.21 (m, 2H), 7.13 (m, 3H), 6.91 (dd, J = 7.6 and 1.6 Hz, 1H), 5.85 (s, 1H), 3.83 (dd, J = 8.0 and 4.8 Hz, 1H), 3.71 (s, 3), 3.24 (ddd, J = 15.2, 4.8 and 1.2 Hz, 1H), 3.06 (ddd, 15.2, 8.0, and 1.2 Hz, 1H), 2.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 139.0, 136.2, 133.7, 131.9, 130.0, 129.9, 129.2, 126.8, 126.8, 122.1, 119.5, 118.2, 110.9, 109.5, 52.1, 52.1, 51.6, 24.9.

Example 5:

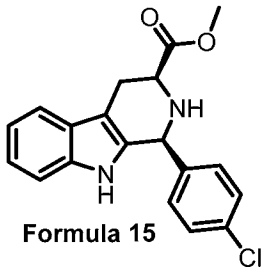
(1S,3S)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 15) and (1R,3S)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 16)



Formula 1 Formula 14 Formula 15 Formula 16

Scheme 5

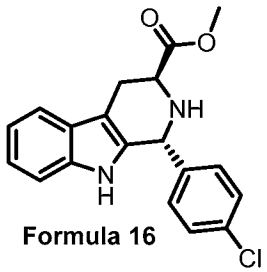
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (764 mg, 3.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 4-chlorobenzaldehyde (**Formula 14**) (464 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred for another 8 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 40 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 15 (**622 mg, 61 % yield) and **Formula 16** (204 mg, 20 % yield).



Formula 15

(1S,3S)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 15)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.29 (m, 4H), 7.14 (m, 3H), 5.17 (s, 1H), 3.92 (dd, J = 11.2 and 4.4 Hz, 1H), 3.79 (s, 3H), 3.20 (ddd, J = 15.2, 4.4 and 2.4 Hz, 1H), 2.98 (ddd, J = 15.2, 11.2 and 2.4 Hz, 1H), 2.41 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.3, 136.1, 134.3, 134.1, 129.9, 129.0, 127.0, 122.0, 119.7, 118.2, 110.9, 109.0, 58.0, 56.7, 52.2, 25.6.



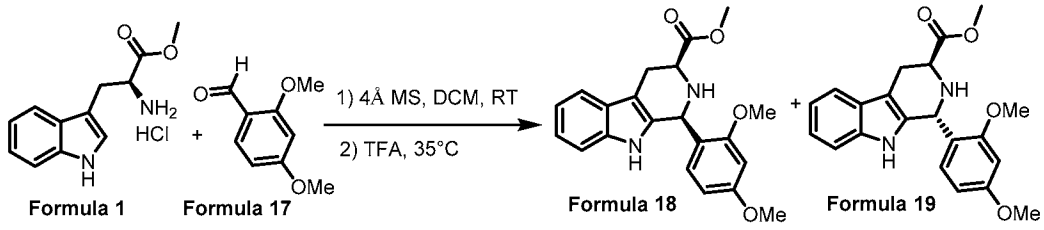
Formula 16

(1R,3S)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 16)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br s, 1H), 7.52 (dd, J = 7.2 and 2.0 Hz, 1H), 7.24 (m, 2H), 7.13 (m, 5H), 5.26 (s, 1H), 3.86 (dd, J = 7.2 and 5.2 Hz, 1H), 3.66 (s, 3H), 3.21 (ddd, J = 15.6, 5.2 and 1.2 Hz, 1H), 3.06 (ddd, J = 15.6, 7.2 and 1.2 Hz, 1H), 2.44 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 140.4, 136.1, 133.8, 132.6, 129.7, 128.7, 126.8, 122.0, 119.5, 118.2, 110.9, 108.4, 54.1, 52.3, 52.1, 24.6.

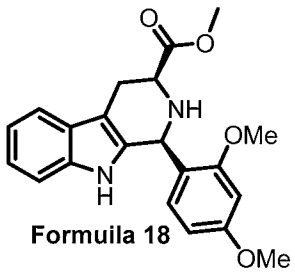
Example 6:

(1S,3S)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 18) and (1R,3S)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 19)



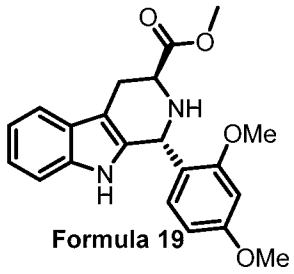
Scheme 6

To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (764 mg, 3.0 mmol) and 4Å molecular sieve (1.2 g, powder form) in DCM (20 mL) was added 2,4-dimethoxybenzaldehyde (**Formula 17**) (548 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at 35 °C for 4 days. An aqueous solution of $NaHCO_3$ (900 mg, 10.7 mmol, in 20 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (3 : 1 DCM / EtOAc) to give **Formula 18 (**209 mg, 19 % yield) and **Formula 19** (297 mg, 27 % yield).



(1S,3S)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 18)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.49 (dd, J = 6.4 and 2.4 Hz, 1H), 7.17 (m, 2H), 7.09 (m, 2H), 6.50 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.4 and 2.4 Hz, 1H), 5.59 (s, 1H), 3.92 (dd, J = 10.8 and 4.4 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 6H), 3.17 (ddd, J = 15.2, 4.4 and 2.4 Hz, 1H), 2.96 (ddd, J = 15.2, 10.4 and 2.4 Hz, 1H), 2.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 160.6, 158.3, 135.8, 135.2, 129.8, 127.1, 121.4, 121.3, 119.3, 117.9, 110.7, 108.3, 104.7, 98.7, 56.9, 55.6, 55.3, 52.0, 51.3, 25.7.



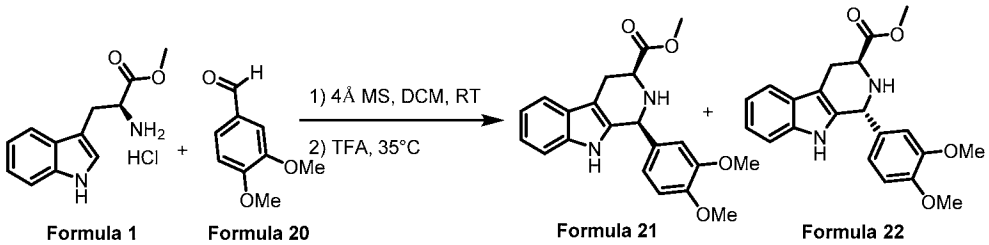
Formula 19

(1R,3S)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 19)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.50 (dd, J = 6.8 and 2.0 Hz, 1H), 7.20 (dd, J = 6.8 and 2.0 Hz, 1H), 7.09 (m, 2H), 6.61 (dd, J = 8.4 and 1.2 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.21 (dt, J = 8.4 and 2.4 Hz, 1H), 5.63 (s, 1H), 3.82 (s, 3H), 3.75 (dd, J = 9.2 and 4.4 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.16 (dd, J = 15.2 and 4.4 Hz, 1H), 2.92 (dd, J = 15.2 and 9.2 Hz, 1H), 2.75 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.4, 157.9, 136.1, 133.1, 129.6, 126.8, 122.4, 121.5, 119.1, 117.9, 110.8, 108.9, 103.3, 98.6, 55.3, 55.2, 51.9, 51.7, 48.8, 25.1.

Example 7:

(1S,3S)-methyl 1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 21) and (1R,3S)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 22)

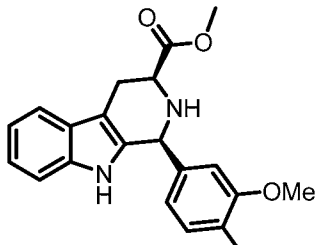


Formula 1 Formula 20 Formula 21 Formula 22

Scheme 7

To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (764 mg, 3.0 mmol) and 4Å molecular sieve (1.2 g, powder form) in DCM (20 mL) was added 3,4-dimethoxybenzaldehyde (**Formula 20**) (548 mg, 3.3 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 29 hours at room temperature. TFA (460 μL, 6.0 mmol) was then added dropwise. The reaction mixture was stirred at 35 °C for 4 days. An aqueous solution of $NaHCO_3$ (900 mg, 10.7 mmol, in 20 mL H_2O) was added dropwise at 0 °C,

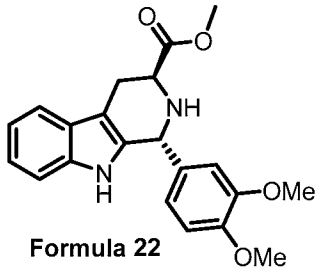
followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (2 : 1 DCM / EtOAc) to give **Formula 21 (**394 mg, 36 % yield) and **Formula 22** (448 mg, 41 % yield).



Formula 21

(1S,3S)-methyl 1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 21)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.52 (dd, J = 6.4 and 2.8 Hz, 1H), 7.20 (ddd, J = 6.8, 2.8 and 0.8 Hz, 1H), 7.11(m, 2H), 6.88 (dd, J = 8.4 and 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 8.4 Hz), 5.14 (s, 1H), 3.94 (dd, J = 11.2 and 4.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.20 (ddd, J = 15.2, 4.4 and 2.0 Hz, 1H), 2.99 (ddd, J = 15.2, 11.2 and 2.8 Hz, 1H), 2.39 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 149.3, 149.0, 136.1, 134.8, 133.2, 127.1, 121.8, 120.7, 119.4, 118.0, 111.2, 111.0, 110.9, 108.6, 58.5, 56.9, 55.8, 52.1, 25.6.



Formula 22

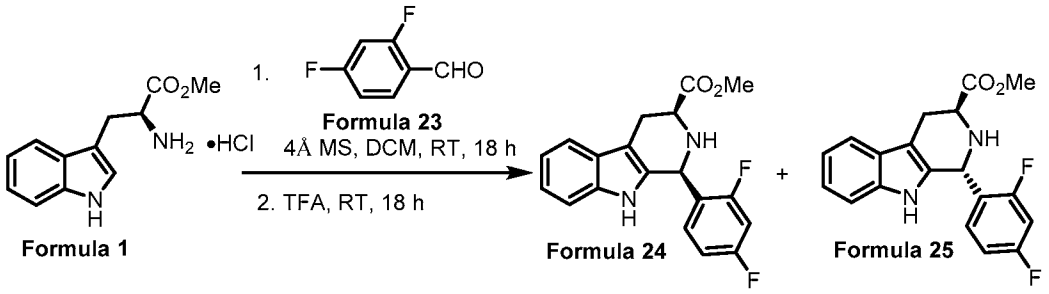
(1R,3S)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 22)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.54 (dd, J = 6.8 and 2.0 Hz, 1H), 7.22 (ddd, J = 6.8, 2.0 and 1.6 Hz, 1H), 7.12 (m, 2H), 6.82 (d, J = 1.6 Hz, 1H), 6.75 (m, 2H), 5.32 (s, 1H), 3.98 (t, J = 6.0 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.25 (ddd, J = 15.2, 6.0 and

1.6 Hz, 1H), 3.13 (ddd, J = 15.2, 6.0 and 1.6 Hz, 1H), 2.40 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 149.2, 148.8, 136.1, 134.5, 133.5, 127.0, 121.8, 120.6, 119.3, 118.1, 111.3, 110.9, 110.8, 108.0, 55.8, 54.6, 52.8, 52.0, 24.5.

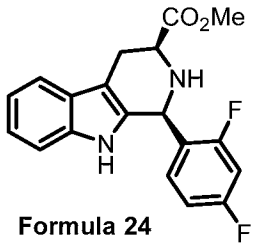
Example 8:

(1S,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 24) and (1R,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 25)



Scheme 8

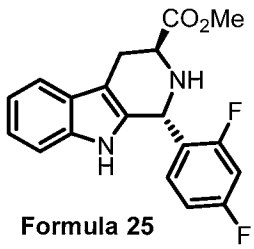
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (510 mg, 2.0 mmol) and 4Å molecular sieve (1.0 g, powder form) in DCM (10 mL) was added 2,4-difluorobenzaldehyde (**Formula 23**) (220 μL, 2.0 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 18 hours at room temperature. TFA (306 μL, 4.0 mmol) was then added dropwise. The reaction mixture was stirred for another 18 hours. An aqueous solution of $NaHCO_3$ (500 mg, 6.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 24 (**466 mg, 68 % yield) and **Formula 25** (203 mg, 30 % yield).



Formula 24

(1S,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 24)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br s, 1H), 7.51 (dd, J = 6.4 and 2.0 Hz, 1H), 7.31 (dt, J = 6.4 and 8.4 Hz, 1H), 7.20 (dd, J = 6.4 and 2.0 Hz, 1H), 7.11 (m, 2H), 6.84 (m, 2H), 5.60 (s, 1H), 3.94 (dd, J = 11.2 and 4.0 Hz, 1H), 3.80 (s, 3H), 3.20 (ddd, J = 15.2, 4.0 and 2.0 Hz, 1H), 2.97 (ddd, J = 15.2, 11.2 and 2.0 Hz, 1H), 2.46 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (s), 162.6 (dd, J = 249 and 12 Hz), 160.9 (dd, J = 248 and 12 Hz), 136.1 (s), 133.2 (s), 131.1 (dd, J = 10 and 5 Hz), 126.9 (s), 123.8 (dd, J = 13 and 4 Hz), 122.1 (s), 119.7 (s), 118.2 (s), 112.0 (dd, J = 21 and 4 Hz), 110.9 (s), 109.3 (s), 103.9 (t, J = 26 Hz), 56.7 (s), 52.2 (s), 50.4 (d, J = 3 Hz), 25.5 (s). ^{19}F NMR (376 MHz, CDCl3) δ -109.6 (pent, J = 7.5 Hz), -116.1 (q, J = 8.3 Hz).



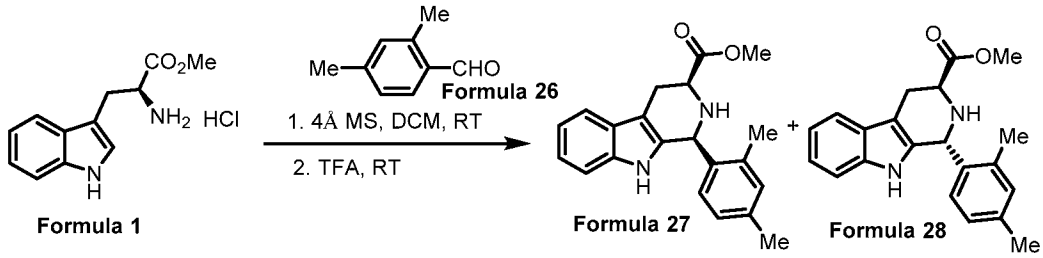
Formula 25

(1R,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 25)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.53 (dd, J = 8.4 and 1.2 Hz, 1H), 7.25 (ddd, J = 7.6, 1.6 and 0.8 Hz, 1H), 7.14 (m, 2H), 6.96 (dt, J = 6.4 and 8.4 Hz, 1H), 6.87 (ddd, J = 10.4, 8.8 and 2.4 Hz, 1H), 6.73 (ddd, J = 8.8, 2.4 and 0.8 Hz, 1H), 5.73 (s, 1H), 3.87 (dd, J = 8.0 and 4.8 Hz, 1H), 3.71 (s, 3H), 3.22 (ddd, J = 15.6, 4.8 and 1.2 Hz, 1H), 3.04 (ddd, J = 15.6, 8.0 and 1.2 Hz, 1H), 2.59 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7 (s), 162.5 (dd, J = 248 and 12 Hz), 160.8 (dd, J = 248 and 12 Hz), 136.2 (s), 131.5 (s), 130.6 (dd, J = 10 and 6 Hz), 126.8 (s), 125.1 (dd, J = 14 and 4 Hz), 122.2 (s), 119.7 (s), 118.2 (s), 111.1 (dd, J = 21 and 4 Hz), 110.9 (s), 109.3 (s), 104.1 (t, J = 25 Hz), 52.3 (s), 52.2 (s), 47.6 (d, J = 3 Hz), 24.8 (s). ^{19}F NMR (376 MHz, CDCl3) δ -110.3 (pent, J = 7.9 Hz), -115.2 (q, J = 9.0 Hz).

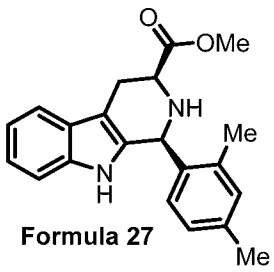
Example 9:

(1S,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 27) and (1R,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 28)



Scheme 9

To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (510 mg, 2.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2,4-dimethylbenzaldehyde (**Formula 26**) (310 μL, 2.0 mmol, in 5 mL DCM), followed by an addition of TFA (100 μL, 1.3 mmol). The resulting reaction mixture was stirred for 23 hours at room temperature. TFA (250 μL, 3.3 mmol) was then added dropwise. The reaction mixture was stirred for another 20 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 27 (**346 mg, 52 % yield) and **Formula 28** (266 mg, 40 % yield).

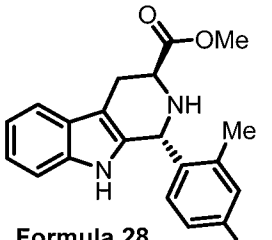


Formula 27

(1S,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 27)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 6.0 and 3.0 Hz, 1H), 7.47 (s, 1H), 7.10 (m, 6H), 5.42 (br s, 1H), 3.93 (dd, J = 11.0 and 4.0 Hz, 1H), 3.78 (s, 3H), 3.20 (ddd, J = 15.0, 4.0 and

1.5 Hz, 1H), 2.97 (ddd, J = 15.0, 11.0 and 2.0 Hz, 1H), 2.48 (br s, 3H), 2.31 (s, 3H), 2.18 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 138.0, 136.0, 135.5, 135.0, 131.6, 129.7, 127.3, 127.1, 121.7, 119.5, 118.0, 110.8, 108.9, 57.0, 53.5, 52.1, 25.8, 21.0, 19.0.



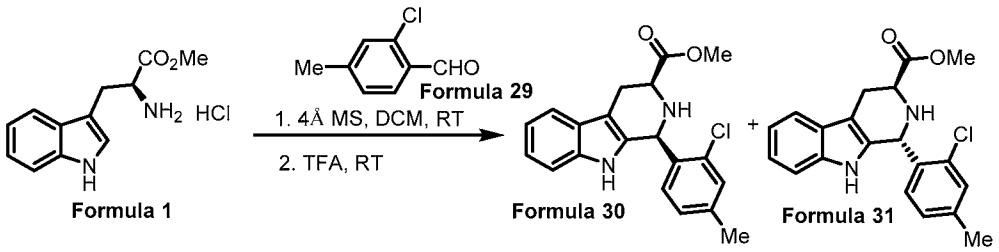
Formula 28

(1R,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 28)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.53 (dd, J = 8.0 and 2.0 Hz, 1H), 7.19 (dd, J = 6.5 and 2.0 Hz, 1H), 7.12 (m, 2H), 7.03 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.54 (s, 1H), 3.90 (dd, J = 7.0 and 5.0 Hz, 1H), 3.69 (s, 3H), 3.22 (ddd, J = 15.0, 5.0 and 1.5 Hz, 1H), 3.08 (ddd, J = 15.0, 7.0 and 1.5 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 2.23 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 137.6, 136.8, 136.3, 136.0, 133.6, 131.8, 128.8, 127.0, 126.5, 121.8, 119.4, 118.1, 110.8, 108.8, 52.4, 52.0, 51.4, 24.8, 20.9, 18.9.

Example 10:

(1S,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 30) and (1R,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 31)

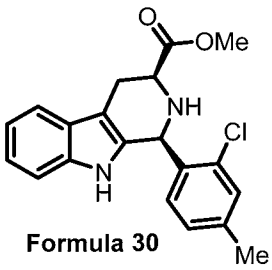


Formula 1 Formula 29 Formula 30 Formula 31

Scheme 10

To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (510 mg, 2.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2-chloro-4-methylbenzaldehyde (**Formula 29**) (309 mg, 2.0 mmol, in 5 mL DCM), followed by

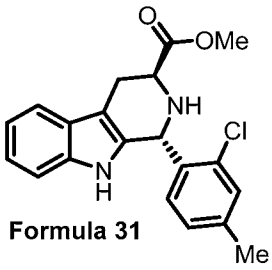
an addition of TFA (100 μL, 1.3 mmol). The resulting reaction mixture was stirred for 22 hours at room temperature. TFA (250 μL, 3.3 mmol) was then added dropwise. The reaction mixture was stirred for another 21 hours. An aqueous solution of $NaHCO_3$ (840 mg, 10.0 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 30 (**457 mg, 60 % yield) and **Formula 31** (290 mg, 40 % yield).



Formula 30

(1S,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 30)

^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.51 (dd, J = 6.5 and 2.0 Hz, 1H), 7.26 (s, 1H), 7.23 (d, J = 6.0 Hz, 1H), 7.19 (dd, J = 7.0 and 2.0 Hz, 1H), 7.10 (m, 2H), 7.10 (d, J = 3.0 Hz, 1H), 5.77 (s, 1H), 3.96 (dd, J = 11.0 and 4.0 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, J = 15.0, 4.0 and 2.0 Hz, 1H), 3.00 (ddd, J = 15.0, 11.0 and 2.5 Hz, 1H), 2.57 (br s, 1H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 139.8, 136.1, 135.3, 133.9, 133.2, 130.0, 130.0, 128.4, 126.9, 121.9, 119.6, 118.1, 110.9, 109.0, 56.7, 53.9, 52.2, 25.5, 20.8.



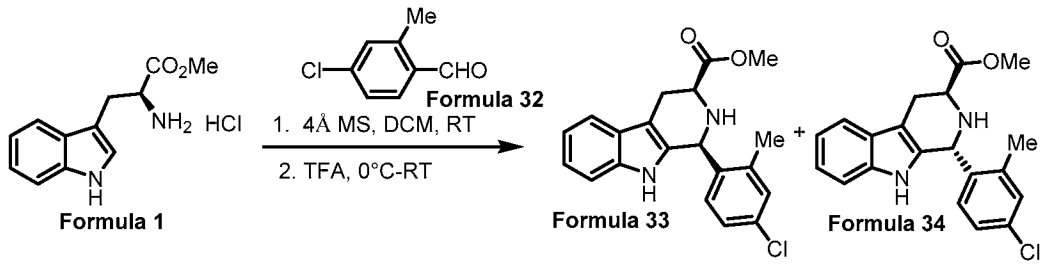
Formula 31

(1R,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 31)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.53 (dd, J = 7.0 and 1.0 Hz, 1H), 7.25 (d, J = 1.0 Hz, 1H), 7.21 (dd, J = 7.0 and 1.0 Hz, 1H), 7.12 (m, 2H), 6.88 (dd, J = 8.0 and 0.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.78 (s, 1H), 3.81 (dd, J = 8.0 and 5.0 Hz, 1H), 3.70 (s, 3H), 3.22 (ddd, J = 15.0, 5.0 and 1.0 Hz, 1H), 3.04 (ddd, J = 15.0, 8.0 and 1.5 Hz, 1H), 2.75 (br s, 1H), 2.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 139.5, 136.2, 135.8, 133.4, 132.1, 130.3, 129.7, 127.5, 126.8, 122.0, 119.5, 118.2, 110.9, 109.4, 52.1, 52.0, 51.4, 24.9, 20.7.

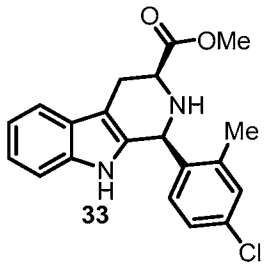
Example 11:

(1S,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 33) and (1R,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 34)



Scheme 11

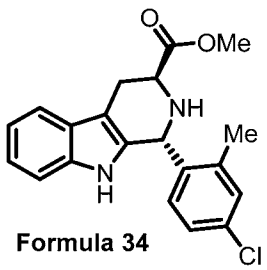
To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (330 mg, 1.3 mmol) and 4Å molecular sieve (270 mg, powder form) in DCM (8 mL) was added 4-chloro-2-methylbenzaldehyde (**Formula 32**) (200 mg, 1.3 mmol, in 3 mL DCM). The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (200 μL, 2.6 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. An aqueous solution of $NaHCO_3$ (542 mg, 6.5 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 33 (**168 mg, 37 % yield) and **Formula 34** (95 mg, 21 % yield).



33

(1S,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 33)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.18 (m, 2H), 7.11 (m, 4H), 7.54 (br s, 1H), 3.92 (dd, J = 11.2 and 4.4 Hz, 1H), 3.79 (s, 3H), 3.21 (ddd, J = 15.2, 4.4 and 2.0 Hz, 1H), 2.96 (ddd, J = 15.2, 11.2 and 2.8 Hz, 1H), 2.46 (br s, 3H), 2.22 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 136.9, 136.0, 134.1, 133.8, 130.6, 130.0, 127.0, 126.5, 121.9, 119.6, 118.1, 110.9, 56.8, 52.2, 25.7, 19.0. HRMS (ESI) $[M+H]^+$ calculated for C20H20ClN2O2: 355.1208. Found: 355.1218.



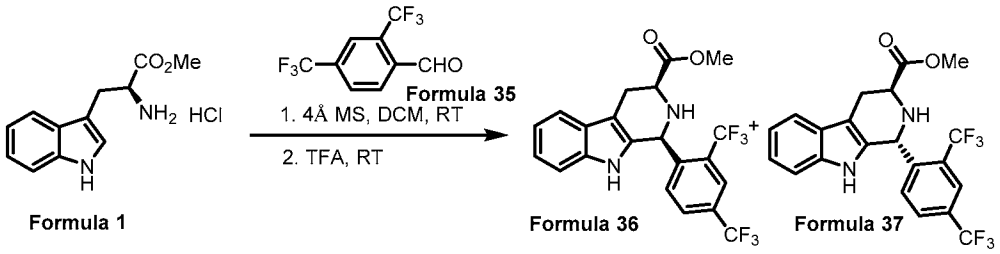
Formula 34

(1R,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 34)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.53 (dd, J = 7.2 and 1.6 Hz, 1H), 7.21 (m, 2H), 7.13 (m, 2H), 7.02 (dd, J = 8.4 and 2.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.52 (s, 1H), 3.87 (dd, J = 7.2 and 5.2 Hz, 1H), 3.69 (s, 3H), 3.22 (ddd, J = 15.2, 5.2 and 1.2 Hz, 1H), 3.08 (ddd, J = 15.2, 7.2 and 1.6 Hz, 1H), 2.43 (s, 3H), 2.27 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 139.0, 137.8, 136.1, 133.5, 132.8, 130.8, 130.2, 126.9, 125.9, 122.0, 119.6, 118.2, 110.9, 109.0, 52.4, 52.1, 51.2, 24.8, 18.8. HRMS (ESI) $[M+H]^+$ calculated for C20H20ClN2O2: 355.1208. Found: 355.1221.

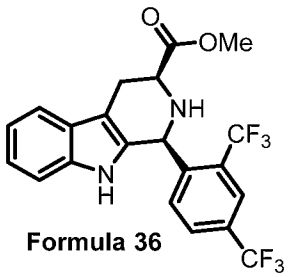
Example 12:

(1S,3S)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 36) and (1R,3S)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 37)



Scheme 12

To a suspension of L-Tryptophan methyl ester hydrochloride (**Formula 1**) (1.27 g, 5.0 mmol) and 4Å molecular sieve (1.0 g, powder form) in DCM (20 mL) was added 2,4-bis(trifluoromethyl)benzaldehyde (**Formula 35**) (818 μL, 5.0 mmol, in 5 mL DCM). The resulting reaction mixture was stirred for 18 hours at room temperature. TFA (130 μL, 1.7 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. TFA (500 μL, 6.5 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. An aqueous solution of $NaHCO_3$ (1.7 g, 20.2 mmol, in 15 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (100 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 36 (**1.39 g, 61 % yield) and **Formula 37** (0.76 g, 39 % yield).

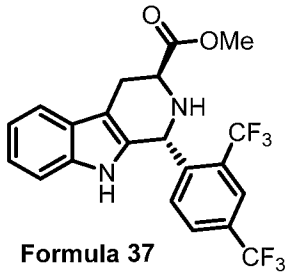


Formula 36

(1S,3S)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 36)

^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.4 and 1.2 Hz, 1H), 7.56 (dd, J = 6.4 and 2.0 Hz, 1H), 7.36 (s, 1H), 7.16 (m, 3H), 5.75 (s, 1H), 4.00 (dd,

J = 11.1 and 4.0 Hz, 1H), 3.83 (s, 3H), 3.27 (ddd, J = 15.2, 4.0 and 2.0 Hz, 1H), 3.07 (ddd, J = 15.2, 11.2 and 2.4 Hz, 1H), 2.81 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (s), 144.6 (s), 136.4 (s), 133.0 (s), 132.9 (s), 130.7 (q, J = 33 Hz), 129.4 (q, J = 31 Hz), 139.3 (q, J = 3 Hz), 126.6 (s), 126.4 (q, J = 273 Hz), 125.9 (q, J = 271 Hz), 122.6 (q, J = 4 Hz), 122.4 (s), 119.9 (s), 118.4 (s), 111.0 (s), 109.7 (s), 56.5 (s), 53.3 (q, J = 2 Hz), 52.4 (s), 25.3 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.4, -62.9.



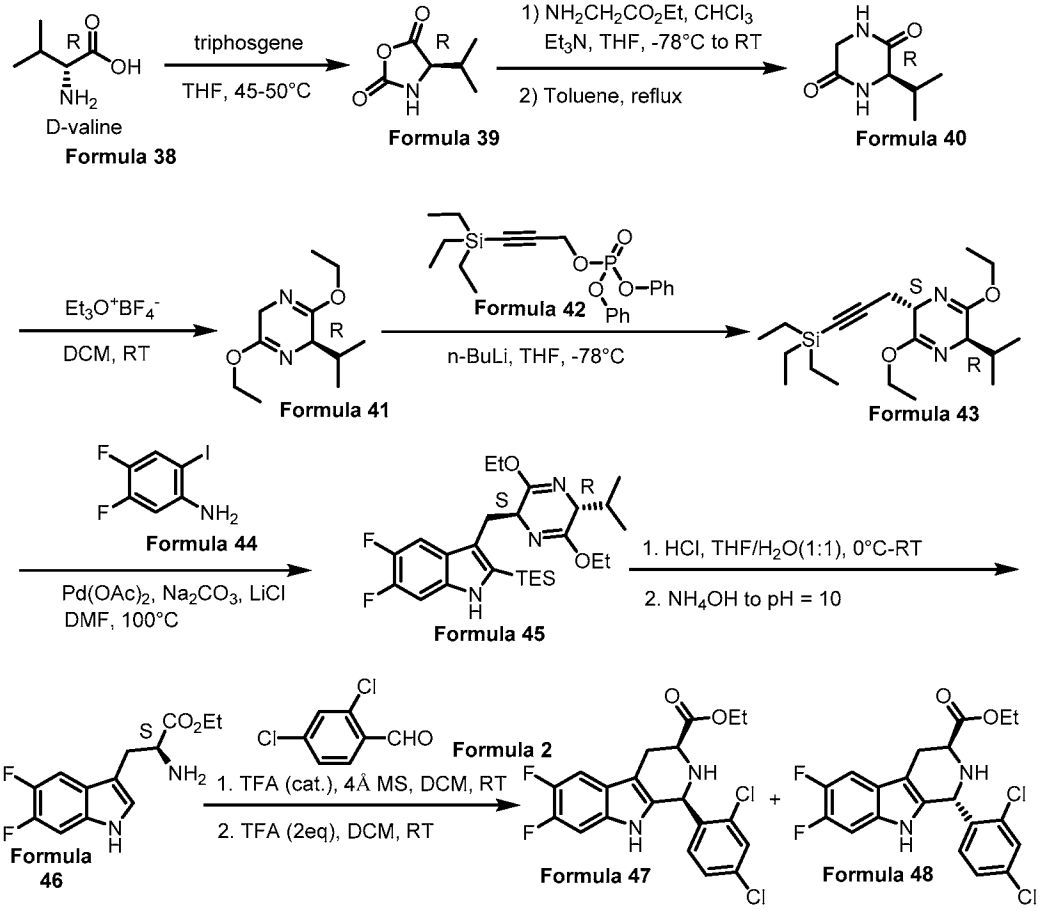
Formula 37

(1R,3S)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 37)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.54 (dd, J = 6.5 and 2.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.12 (m, 3H), 5.93 (s, 1H), 4.00 (t, J = 5.5 Hz, 1H), 3.67 (s, 3H), 3.30 (ddd, J = 15.5, 5.5 and 1.5 Hz, 1H), 3.23 (ddd, J = 15.5, 5.5 and 1.5 Hz, 1H), 2.70 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (s), 145.0 (s), 136.3 (s), 132.1 (s), 131.5 (s), 130.4 (q, J = 33 Hz), 129.3 (q, J = 31 Hz), 128.9 (q, J = 3 Hz), 126.6 (s), 123.7 (q, J = 273 Hz), 123.2 (q, J = 271 Hz), 123.0 (q, J = 4 Hz), 122.4 (s), 119.7 (s), 118.3 (s), 110.9 (s), 109.0 (s), 53.0 (s), 52.1 (s), 49.8 (s), 24.0 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.8, -62.9.

Example 13:

(1S,3S)-ethyl-1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (47) and (1R,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (48)



Scheme 13

To a suspension of D-Valine (**Formula 38**) (11.75 g, 100.0 mmol) in dry THF (100 mL) was added dropwise a solution of triphosgene (11.87 g, 40.0 mmol) in dry THF (50 mL) at 45 °C. When the addition was completed, the resulting suspension mixture was stirred at 50 °C for 16 hours until it became homogeneous. Removed the solvents under vacuum at 40 °C, 40 mL dry THF was added, removed the solvents again under vacuum at 40 °C. This flash evaporation was further repeated for three times. The residue was dissolved in 50 mL dry THF afforded D-Valine-N-carboxyanhydride **Formula 39**, which was kept in frige for the next step without further purification.

The above solution of **Formula 39** in THF was added dropwise to a stirred mixture of glycine ethyl ester hydrochloride (14.0 g, 100.0 mmol), triethylamine (32.0 mL, 226.0 mmol) and chloroform (140 mL) at -70 °C. After addition, the resulting mixture was stirred at -70 °C for 3 hours, then was slowly warmed to room temperature and stirred overnight. The

precipitate ($Et_3N\cdot$ HCl salt) was filtered. The filtrate was condensed under vacuum at 40 °C. The residue was added 80 mL of Et_2O, and the precipitate ($Et_3N\cdot$ HCl salt) was filtered again. The filtrate was condensed under vacuum at 40 °C. The residue was dissolved in 280 mL toluene. The resulting solution was stirred at reflux for 25 hours and then cooled to room temperature. The precipitate was filtered, washed with Et_2O (3×60 mL), and dried under vacuum at 80 °C to provide 12.25 g (78% yield based on D-valine) of (R)-3-isopropylpiperazine-2,5-dione (**Formula 40**). ^{1}H NMR (500 MHz, DMSO-d6) δ 8.18 (s, 1H), 8.00 (s, 1H), 3.81 (d, J = 17.5 Hz, 1H), 3.61 (dd, J = 17.5 and 3.0 Hz, 1H), 3.52 (t, J = 3.0 Hz, 1H), 2.10 (m, 1H), 0.92 (d, J =7.0 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 167.2, 166.0, 59.8, 44.1, 32.2, 18.5, 17.0.

(R)-3-isopropylpiperazine-2,5-dione (**Formula 40**) (1.72 g, 11.0 mmol) was added slowly (in portions) to a solution of triethyloxonium tetrafluoroborate (8.0 g, 42 mmol) in dry DCM (80 mL). The resulting reaction mixture became homogeneous after 30 minutes, and then was stirred at room temperature under N_2 for 3 days. The reaction mixture was cooled to 0 °C, quenched with 10 % ammonia aqueous solution (16 mL). The phases were separated. The aqueous layer was extracted with DCM (40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (6 : 4 : 1 hexane / DCM / EtOAc) to give (R)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine (**Formula 41**) (1.93 g, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 4.09 (m, 3H), 3.95 (m, 3H), 2.23 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.8, 61.0, 60.7, 46.8, 32.6, 19.0, 17.0, 14.3.

To a solution of (R)-3,6-diethoxy-2-isopropyl-2,5-dihydropyrazine (**Formula 41**) (1.61 g, 7.6 mmol) in dry THF (40 mL) was added n-BuLi (3.3 mL, 2.5 M in hexane, 8.4 mmol) dropwise at -78 °C. After being stirred at -78 °C for 1 hour, to the reaction mixture was added dropwise a solution of diphenyl 3-(triethylsilyl)prop-2-ynyl phosphate (**Formula 42**) (3.4 g, 8.4 mmol) in dry THF (10 mL), precooled to -78 °C. The resulting reaction mixture was stirred at -78 °C for 6 hours and then was slowly warmed to 0 °C. The reaction was quenched with water (2 mL), concentrated under vacuum, extracted with Et_2O (100 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (15 : 1 hexane / Et_2O) to give (2R,5S)-3,6-diethoxy-2-isopropyl-5-(3-(triethylsilyl)prop-2-ynyl)-2,5-dihydropyrazine (**Formula 43**) (1.60 g, 58 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (m, 5H), 3.97 (t, J = 3.6 Hz, 1H), 2.85 (dd, J = 16.4

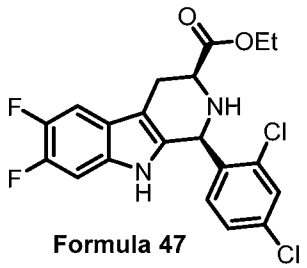
and 4.4 Hz, 1H), 2.69 (dd, J = 16.4 and 4.4 Hz, 1H), 2.27 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.71 (d, J = 6.8 Hz, 3H), 0.51 (q, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.1, 104.4, 83.5, 61.0, 60.7, 60.6, 54.6, 31.7, 26.5, 19.1, 16.7, 14.3, 14.3, 7.3, 4.4.

To a mixture of (2R,5S)-3,6-diethoxy-2-isopropyl-5-(3-(triethylsilyl)prop-2-ynyl)-2,5-dihydropyrazine (**Formula 43**) (689 mg, 1.9 mmol), 4,5-difluoro-2-iodoaniline (**Formula 44**) (483 mg, 1.9 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), and Na_2CO_3 (400 mg, 3.8 mmol) in dry DMF (22 mL) was added LiCl (3.8 mL, 0.5 M in THF, 1.9 mmol). The resulting reaction mixture was purged with N_2 for 1 hour and then heated in 103 °C oil bath for 47 hours. The reaction was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated and purified by flash chromatography (15 : 1 hexane / EtOAc), affording 3-(((2S,5R)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-5,6-difluoro-2-(triethylsilyl)-1H-indole (**Formula 45**) (691 mg, 74 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.56 (dd, J = 11.2 and 8.0 Hz, 1H), 7.07 (dd, J = 10.8 and 6.8 Hz, 1H), 4.10 (m, 5H), 3.91 (t, J = 3.6 Hz, 1H), 3.50 (dd, J = 14.4 and 3.2 Hz, 1H), 2.75 (dd, J = 14.4 and 10.0 Hz, 1H), 2.27 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.92 (m, 18H), 0.68 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (s), 163.1 (s), 148.1 (dd, J = 240 and 16 Hz), 145.9 (dd, J = 235 and 15 Hz), 133.7 (d, J = 4 Hz), 133.3 (d, J = 10 Hz), 125.0 (d, J = 8 Hz), 124.1 (dd, J = 4 and 1 Hz), 107.1 (d, J = 18 Hz), 97.9 (d, J = 21 Hz), 60.8 (s), 60.7 (s), 60.6 (s), 58.9 (s), 31.9 (s), 31.8 (s), 19.1 (s), 16.7 (s), 14.4 (s), 14.3 (s), 7.4 (s), 3.5 (s).

To a solution of 3-(((2S,5R)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-5,6-difluoro-2-(triethylsilyl)-1H-indole (**Formula 45**) (527 mg, 1.1 mmol) in 15 mL THF was added an aqueous HCl solution (6 N, 15 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 4 hours, and then at room temperature for 14 hours. The reaction was cooled to 0 °C and an aqueous ammonia solution (18%) was added dropwise till the pH = 9. The mixture was extracted with DCM (2 × 60 mL). The combined organic layers were dried over dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (15 : 1 DCM / EtOH) to give (S)-5,6-difluorotryptophan ethyl ester (**Formula 46**) (201 mg, 70 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.29 (dd, J = 11.0 and 8.0 Hz, 1H), 7.03 (dd, J = 11.0 and 7.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 4.17 (m, 2H), 3.78 (dd, J = 7.5 and 5.0 Hz, 1H), 3.17 (dd, J = 14.5 and 5.0 Hz, 1H), 2.99 (dd, J = 14.5 and 7.5 Hz, 1H), 1.89 (br s, 2H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (s), 147.8 (dd, J = 239

and 16 Hz), 126.0 (dd, J = 236 and 15 Hz), 131.1 (d, J = 10 Hz), 124.4 (d, J = 3 Hz), 122.6 (d, J = 8 Hz), 110.7 (s), 105.0 (d, J = 19 Hz), 99.0 (d, J = 21 Hz), 61.1 (s), 54.7 (s), 30.4 (s), 14.0 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -144.2 (ddd, J = 21.2, 10.3 and 8.0 Hz), -147.8 (ddd, J = 20.7, 10.3 and 6.6 Hz).

To a suspension of (S)-5,6-difluorotryptophan ethyl ester (**Formula 46**) (124 mg, 0.46 mmol) and 4Å molecular sieve (100 mg, powder form) in DCM (6 mL) was added 2,4-dichlorobenzaldehyde (**Formula 2**) (97 mg, 0.55 mmol, in 2 mL DCM), followed by an addition of TFA ((20 μL, 0.26 mmol). The resulting reaction mixture was stirred for 18 hours at room temperature. TFA (70 μL, 0.91 mmol) was then added dropwise. The reaction mixture was further stirred for 5 hours. An aqueous solution of $NaHCO_3$ (195 mg, 2.32 mmol, in 5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give (1S,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 47**) (78 mg, 40 % yield) and (1R,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 48**) (50 mg, 26 % yield).

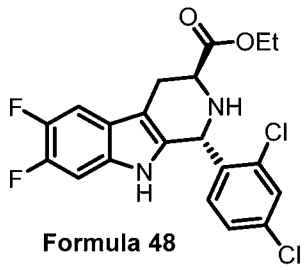


Formula 47

(1S,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 47)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.24 (dd, J = 10.8 and 2.8 Hz, 1H), 7.19 (dd, J = 8.4 and 2.0 Hz, 1H), 6.99 (dd, J = 10.8 and 2.4 Hz, 1H), 5.72 (s, 1H), 4.26 (m, 2H), 3.91 (dd, J = 11.2 and 4.0 Hz, 1H), 3.12 (ddd, J = 15.2, 4.0 and 2.0 Hz, 1H), 2.92 (ddd, J = 15.2, 11.2 and 2.4 Hz, 1H), 2.60 (br s, 1H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (s), 147.8 (dd, J = 239 and 16 Hz), 146.4 (dd, J = 237 and 15 Hz), 136.9 (s), 134.7 (d, J = 4 Hz), 134.7 (s), 133.9 (s), 131.3 (s), 131.0 (d, J = 10 Hz),129.4 (s), 128.0 (s), 122.1 (dd, J = 8 and 1 Hz), 109.4 (d, J = 3 Hz),

104.9 (d, J = 19 Hz), 99.0 (d, J = 22 Hz), 61.4 (s), 56.4 (s), 53.7 (s), 25.2 (s), 14.2 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -143.6 (pent, J = 9.9 Hz), -147.3 (ddd, J = 20.7, 10.8 and 6.6 Hz). HRMS (ESI) $[M+H]^+$ calculated for C20H17Cl2F2N2O2: 425.0630. Found: 425.0639



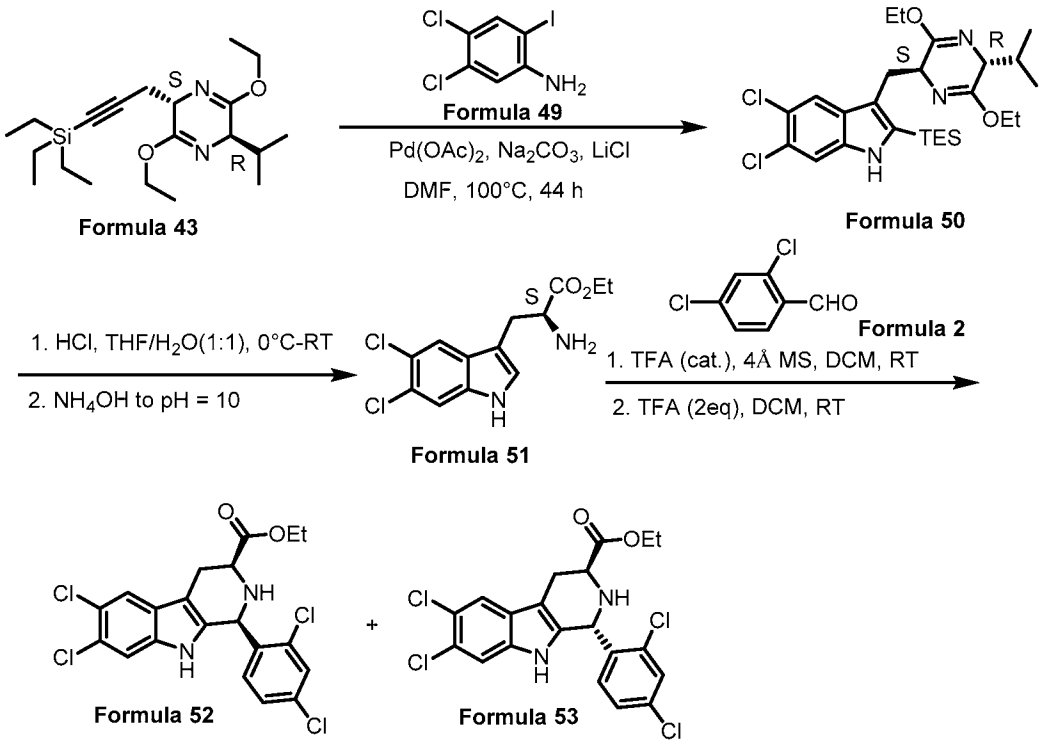
Formula 48

(1R,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 48)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 10.4 and 7.6 Hz, 1H), 7.13 (dd, J = 8.4 and 2.4 Hz, 1H), 7.03 (dd, J = 10.4 and 6.8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.78 (s, 1H), 4.17 (m, 2H), 3.80 (dd, J = 7.4 and 5.2 Hz, 1H), 3.16 (ddd, J = 15.2, 5.2 and 1.2 Hz, 1H), 3.00 (ddd, J = 15.2, 7.4 and 1.6 Hz, 1H), 2.76 (br s, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (s), 147.9 (dd, J = 240 and 16 Hz), 146.4 (dd, J = 237 and 15 Hz), 137.4 (s), 134.5 (s), 134.3 (s), 133.0 (d, J = 4 Hz), 131.1 (d, J = 10 Hz), 130.7 (s), 129.8 (s), 127.2 (s), 122.0 (dd, J = 8 and 2 Hz), 109.7 (dd, J = 4 and 2 Hz), 105.0 (d, J = 19 Hz), 99.1 (d, J = 25 Hz), 61.3 (s), 52.2 (s), 51.1 (s), 24.5 (s), 141.1 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -143.4 (ddd, J = 20.7, 10.3 and 7.5 Hz), -147.4 (ddd, J = 20.7, 10.3 and 6.6 Hz). HRMS (ESI) $[M+H]^+$ calculated for C20H17Cl2F2N2O2: 425.0630. Found: 425.0638

Example 14:

(1S,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 52) and (1R,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 53)



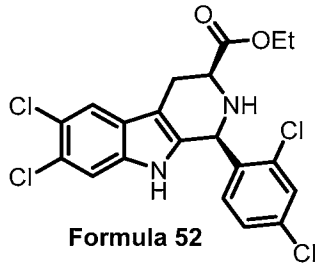
Scheme 14

To a mixture of (2R,5S)-3,6-diethoxy-2-isopropyl-5-(3-(triethylsilyl)prop-2-ynyl)-2,5-dihydropyrazine (**Formula 43**) (365 mg, 1.0 mmol), 4,5-dichloro-2-iodoaniline (**Formula 49**) (288 mg, 1.0 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), and Na_2CO_3 (212 mg, 2.0 mmol) in dry DMF (12 mL) was added LiCl (2.0 mL, 0.5 M in THF, 1.0 mmol). The resulting reaction mixture was purged with N_2 for 1.5 hour and then heated in 100 °C oil bath for 42 hours. The reaction was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated and purified by flash chromatography (20 : 1 hexane / EtOAc), affording 5,6-dichloro-3-(((2S,5R)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-2-(triethylsilyl)-1H-indole (**Formula 50**) (337 mg, 64 % yield).

To a solution of 5,6-dichloro-3-(((2S,5R)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)methyl)-2-(triethylsilyl)-1H-indole (**Formula 50**) (258 mg, 0.5 mmol) in 7 mL THF was added an aqueous HCl solution (6 N, 7 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then at room temperature for 23 hours. The reaction was cooled to 0 °C and an aqueous ammonia solution (18%) was added dropwise till the pH = 9. The mixture was extracted with DCM (2 × 30 mL). The combined organic layers were dried over dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (30 : 1

to 15 : 1 DCM / EtOH) to give (S)-5,6-dichlorotryptophan ethyl ester (**Formula 51**) (63 mg, 43 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.64 (s, 1H), 7.34 (s, 1H), 7.01 (d, J = 2.4 Hz, 1H), 4.17 (m, 2H), 3.79 (dd, J = 7.2 and 4.8 Hz, 1H), 3.17 (ddd, J = 14.8, 5.2 and 0.4 Hz, 1H), 3.02 (dd, J = 14.8 and 7.2 Hz, 1H), 1.66 (br s, 1H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 134.9, 127.2, 125.8, 125.0, 123.4, 119.7, 112.6, 110.7, 61.2, 54.7, 30.3, 14.1.

To a suspension of (S)-5,6-dichlorotryptophan ethyl ester (**Formula 51**) (63 mg, 0.21 mmol) and 4Å molecular sieve (100 mg, powder form) in DCM (10 mL) was added 2,4-dichlorobenzaldehyde (**Formula 2**) (40 mg, 0.23 mmol, in 2 mL DCM), followed by an addition of TFA ((20 μL, 0.26 mmol). The resulting reaction mixture was stirred for 22 hours at room temperature. Another TFA (20 μL, 0.26 mmol) was then added. The reaction mixture was further stirred for 20 hours. An aqueous solution of $NaHCO_3$ (160 mg, 1.9 mmol, in 5 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (60 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give (1S,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 52**) (51 mg, 53 % yield) and (1R,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 53**) (29 mg, 30 % yield).

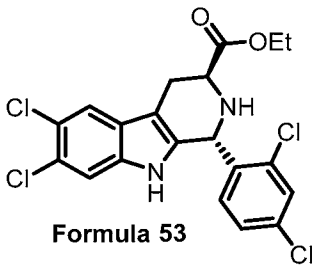


Formula 52

(1S,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 52)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.57 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.20 (dd, J = 8.4 and 2.0 Hz, 1H), 5.73 (br s, 1H), 4.26 (m, 2H), 3.92 (dd, J = 11.2 and 4.0 Hz, 1H), 3.14 (ddd, J = 15.2, 4.0 and 2.0 Hz, 1H), 2.92 (ddd, J = 15.2, 11.2 and 2.4 Hz, 1H), 2.64 (br s, 1H), 1.34 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 172.2, 136.7, 135.4, 134.8, 133.9, 131.3, 129.5, 129.4, 128.1, 126.7, 125.7, 123.8, 119.3, 112.4, 109.1, 61.5, 56.4, 53.7, 25.1, 14.2. HRMS (ESI) $[M+H]^+$ calculated for C20H17Cl4N2O2: 459.0015. Found: 459.0034.



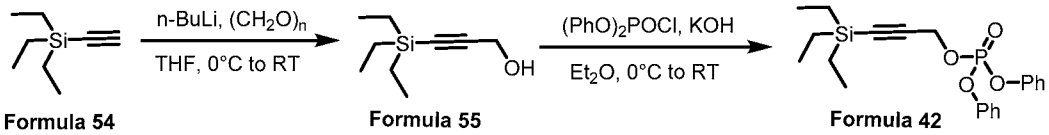
Formula 53

(1R,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (Formula 53)

^1H NMR (400 MHz, $CDCl_3$) δ 7,81 (br s, 1H), 7.61 (s, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.34 (s, 1H), 7.13 (dd, J = 8.4 and 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.82 (s, 1H), 4.12 (m, 2H), 3.82 (dd, J = 7.2 and 5.2 Hz, 1H), 3.17 (ddd, J = 15.2, 5.2 and 1.2 Hz, 1H), 3.02 (ddd, J = 15.2, 7.2 and 1.2 Hz, 1H), 2.77 (br s, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^3C NMR (100 MHz, $CDCl_3$) δ 172.9, 137.2, 134.9, 134.6, 134.3, 133.8, 130.7, 129.8, 127.3, 126.6, 125.9, 123.8, 119.4, 112.5, 109.3, 61.3, 52.2, 51.0, 24.4, 14.2. HRMS (ESI) $[M+H]^+$ calculated for C20H17Cl4N2O2: 459.0015. Found: 459.0046.

Example 15

diphenyl 3-(triethylsilyl)prop-2-ynyl phosphate (Formula 42)



Formula 54 Formula 55 Formula 42

Scheme 15

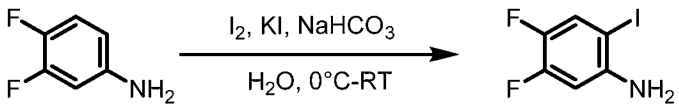
To a solution of triethyl(ethynyl)silane (**Formula 54**) (1.8 mL, 10.0 mmol) in dry THF (50 mL) was added n-BuLi (5.5 mL, 2.0 M in hexane, 11.0 mmol) dropwise at 0 °C. After being stirred at 0 °C for 1 hour, paraformaldehyde (1.9 g, 63.0 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 2 hours and then at room temperature 15 hours. The reaction mixture was poured into a saturated NH_4Cl aqueous solution (50 mL) at 0 °C. The mixture was extracted with Et_2O (2 × 60 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash

chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give 3-(triethylsilyl)prop-2-yn-1-ol (**Formula 55**) (1.69 g, 99 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (d, J = 6.0 Hz, 2H), 1.65 (t, J = 6.0 Hz, 1 H), 0.99 (t, J = 8.0 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.9, 88.1, 51.7, 7.4, 4.2.

To a solution of 3-(triethylsilyl)prop-2-yn-1-ol (**Formula 55**) (1.70 g, 10.0 mmol) and diphenyl chlorophosphate (2.5 mL, 12.0 mmol) in dry Et_2O at 0 °C was added KOH (3.53 g, 63.0 mmol). The resulting reaction mixture was stirred at room temperature for 20 hours, and then was cooled to 0 °C. Et_2O (200 mL) was added, followed an addition of H_2O (30 mL). The phases were separated. The organic layer was washed with brine (20 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (7 : 3 : 1 hexane / DCM / EtOAc) to give diphenyl 3-(triethylsilyl)prop-2-ynyl phosphate (**Formula 42**) (3.36 g, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 4H), 7.21 (m, 6H), 4.87 (d, J = 10.4 Hz, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 150.4, 129.7, 125.4, 125.4, 120.1, 120.1, 99.1, 99.0, 91.8, 57.2, 57.1, 7.3, 4.0.

Example 16:

4,5-difluoro-2-iodoaniline (Formula 44)



Formula 56 **Formula 44**

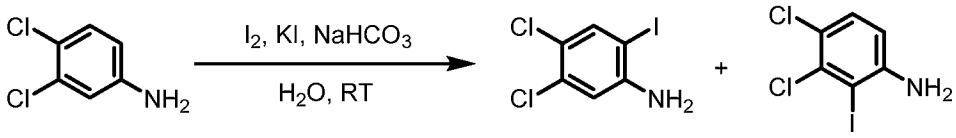
Scheme 16

To a mixture of $NaHCO_3$ (3.36 g, 40.0 mmol), H_2O (15 mL) and 3,4-difluoroaniline (**Formula 56**) (2.0 mL, 20.0 mmol) was added a solution of I_2 (5.48 g, 21.6 mmol) and KI (3.62 g, 21.8 mmol) in H_2O (6 mL) dropwise at 0 °C. After the addition, the resulting reaction mixture was stirred at room temperature for 18 hours, and then was cooled to 0 °C. 6 N HCl aqueous solution (3 mL) was added dropwise, followed an addition of EtOAc (150 mL). The phases were separated. The organic layer was washed with brine (30 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (15: 1 hexane / EtOAc) to give 4,5-difluoro-2-iodoaniline (**Formula 44**) (5.11 g, 99 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 9.6 and 8.8 Hz, 1H), 6.56 (dd, J = 12.4 Hz, 1H), 4.02 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0 (dd, J = 246 and 13 Hz), 143.7 (dd, J = 9 and 3 Hz), 143.1 (dd, J = 241 and 13 Hz), 126.4 (dd, J = 20 and 2 Hz), 102.6 (d, J = 21 Hz), 74.7 (dd, J = 7

and 4 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -136.4 (ddd, J = 20.7, 11.8 and 8.5 Hz), -149.3 (ddd, J = 21.6, 9.4 and 7.1 Hz).

Example 17:

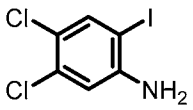
4,5-dichloro-2-iodoaniline (49)



Formula 57 **Formula 49** **Formula 58**

Scheme 17

To a mixture of $NaHCO_3$ (2.69 g, 32.0 mmol), H_2O (15 mL) and 3,4-dichloroaniline (**Formula 57**) (3.24 g, 20.0 mmol) was added a solution of I_2 (5.48 g, 21.6 mmol) and KI (3.62 g, 21.8 mmol) in H_2O (7 mL) dropwise at 0 °C. After the addition, the resulting reaction mixture was stirred at room temperature for 18 hours, and then was cooled to 0 °C. 6 N HCl aqueous solution (3 mL) was added dropwise, followed an addition of EtOAc (150 mL). The phases were separated. The organic layer was washed with brine (30 mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (30 : 1 to 15 : 1 hexane / EtOAc) to give 4,5-dichloro-2-iodoaniline (**Formula 49**) (3.46 g, 60 % yield) and 3,4-dichloro-2-iodoaniline (**Formula 58**) (1.73 g, 30 % yield).

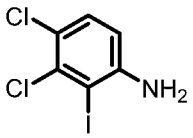


Formula 49

4,5-dichloro-2-iodoaniline (Formula 49)

^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.79 (s, 1H), 4.14 (br s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 138.9, 133.0, 121.4, 114.9, 80.9.



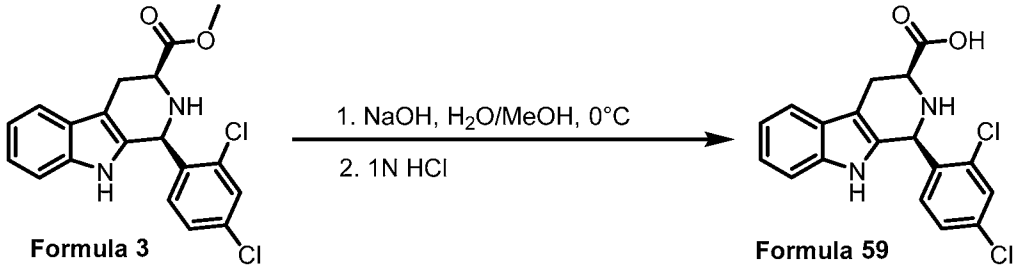
Formula 58

3,4-dichloro-2-iodoaniline (Formula 58)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.32 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 136.6, 130.1, 120.3, 112.8, 88.8.

Example 18

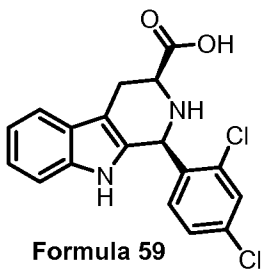
(1S,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 59)



Formula 3 **Formula 59**

Scheme 18

To a solution of **Formula 3** (100 mg, 0.27 mmol) in methanol (6 mL) was added an aqueous solution of NaOH (53 mg, 1.34 mmol, in 6 mL H_2O) dropwise at 0 °C. The resulting reaction mixture was stirred at 0 °C for 8 hours. The reaction was adjusted with 1 N HCl aqueous solution to pH = 3. The solvents were removed under vacuum. 10 mL methanol was added to the residue. After being stirred for 30 minutes, the precipitate was filtered off. The filtrate was condensed. To the residue, 5 mL methanol and 5 mL ethyl acetate were added. After being stirred for 30 minutes, the precipitate was filtered off. The filtrate was condensed to afford (1S,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 59**) (94 mg, 98 % yield).



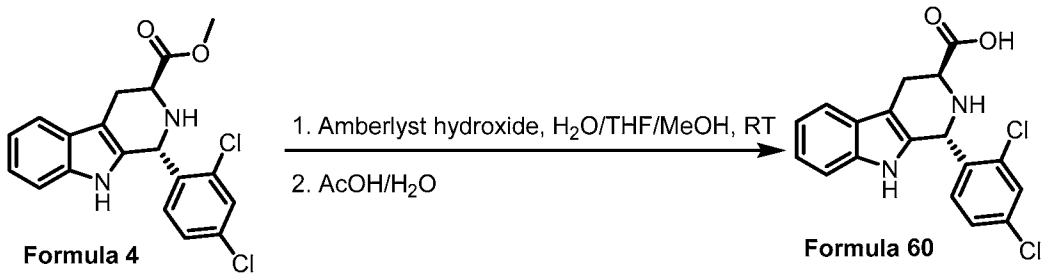
Formula 59

(1S,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 59)

$[\alpha]_D^{21.4}$ = -64.7° (c = 0.15, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.39 (dd, J = 8.0 and 2.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.0 and 1.0 Hz, 1H), 6.97 (td, J = 8.0 and 1.0 Hz, 1H), 5.66 (s, 1H), 3.83 (dd, J = 11.0 and 4.0 Hz, 1H), 3.05 (ddd, J = 15.0, 4.0 and 2.0 Hz, 1H), 2.81 (ddd, J = 15.0, 11.0, and 2.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.7, 138.2, 136.4, 134.2, 133.8, 132.9, 132.0, 128.7, 127.6, 126.4, 120.9, 118.5, 117.7, 111.2, 108.0, 56.1, 53.6, 25.1. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0512.

Example 19:

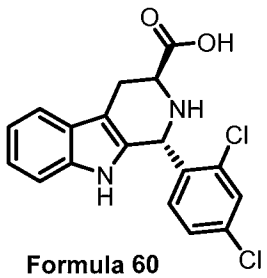
(1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 60)



Formula 4 **Formula 60**

Scheme 19

To a solution of **Formula 4** (518 mg, 1.38 mmol) in THF / MeOH / H_2O (10 mL / 10 mL / 10 mL) was added Amberlyst hydroxide resin (4.8 g, 20.2 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred at for 20 hours, the resin was filtered and washed with MeOH and DCM alternatively (4 × 10 mL). An aqueous solution of AcOH (50%) (20 mL) was added to cleave the product from the resin, the cleaving solution was collected by filtration. The cleavage step was repeated for other 3 times. The combined cleaving solutions were condensed under vacuum. The residue was added MeOH (6 mL), followed by addition of EtOAc (10 mL) and hexane (50 mL). The mixture was stirred for 2 hours and then filtered. The solid was washed with hexane to afford (1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 60**) (443 mg,89 % yield).



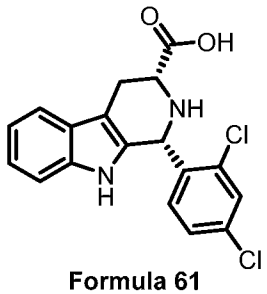
Formula 60

(1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (60)

$[\alpha]_D^{21.0}$ = -58.1° (c = 1.34, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (dd, J = 8.4 and 2.0 Hz, 1H), 7.25 (dt, J = 7.6 and 1.2 Hz, 1H), 7.06 (td, J = 6.8 and 1.2 Hz, 1H), 7.00 (td, J = 7.2 and 1.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 5.73 (s, 1H), 3.60 (dd, J = 8.4 and 4.8 Hz, 1H), 3.09 (dd, J = 15.2 and 4.8 Hz, 1H), 2.85 (ddd, J = 15.2, 8.4 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 138.7, 136.2, 134.1, 132.7, 132.3, 131.5, 129.0, 127.0, 126.4, 121.1, 118.5, 117.8, 111.1, 108.3, 51.4, 50.6, 24.7. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0514.

Example 20

(1R,3R)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 61)



Formula 61

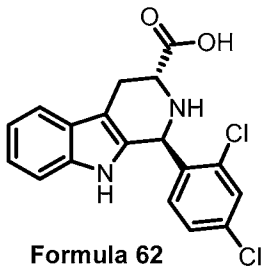
(1R,3R)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 61**) was prepared in 99 % yield from (1R,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 6**) following the procedure employed for preparation of **Formula 59**.

$[\alpha]_D^{21.4}$ = +64.1° (c = 0.22, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.39 (dd, J = 8.0 and 2.0 Hz, 1H), 7.29 (d, J = 8.0 Hz,

1H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.0 and 1.0 Hz, 1H), 6.97 (td, J = 8.0 and 1.0 Hz, 1H), 5.66 (s, 1H), 3.83 (dd, J = 11.0 and 4.0 Hz, 1H), 3.05 (ddd, J = 15.0, 4.0 and 2.0 Hz, 1H), 2.81 (ddd, J = 15.0, 11.0, and 2.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 138.2, 136.3, 134.2, 133.8, 132.9, 132.0, 128.7, 127.6, 126.4, 120.9, 118.5, 117.7, 111.2, 108.0, 56.1, 53.7, 25.1. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0511.

Example 21:

(1S,3R)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (62)



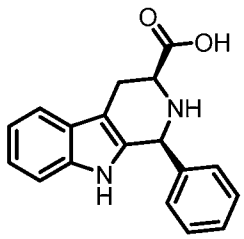
Formula 62

(1S,3R)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 62**) was prepared in 99 % yield from (1S,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 7**) following the procedure employed for preparation of **Formula 59**.

$[\alpha]_D^{21.6}$ = +53.5° (c = 1.10, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.30 (dd, J = 8.5 and 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 7.0 and 1.0 Hz, 1H), 6.99 (td, J = 8.0 and 1.0 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 5.71 (s, 1H), 3.57 (dd, J = 8.5 and 5.0 Hz, 1H), 3.08 (dd, J = 15.0 and 5.0 Hz, 1H), 2.84 (dd, J = 15.0 and 8.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 138.8, 136.2, 134.1, 132.7, 132.4, 131.4, 129.0, 127.0, 126.3, 121.1, 118.5, 117.8, 111.1, 108.3, 51.4, 50.6, 24.7. HRMS (ESI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0509.

Example 22:

(1S,3S)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 63)



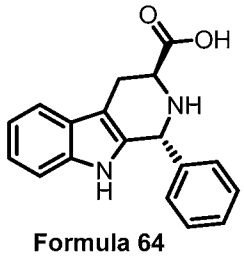
Formula 63

(1S,3S)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 63**) was prepared in 95 % yield from (1S,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 9**) following the procedure employed for preparation of **Formula 59**.

$[\alpha]_D^{21.0}$ = -49.5° (c = 2.00, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.51 (m, 6H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (td, J = 8.0 and 1.0 Hz, 1H), 7.03 (td, J = 8.0 and 1.0 Hz, 1H), 5.90 (s, 1H), 4.55 (dd, J = 11.5 and 4.0 Hz, 1H), 3.37 (dd, J = 15.5 and 4.0 Hz, 1H), 3.25 (ddd, J = 15.5, 11.5 and 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 136.8, 134.1, 130.5, 129.8, 129.1, 128.5, 125.5, 121.9, 119.1, 118.1, 111.6, 106.8, 57.6, 55.4, 22.2. HRMS (ESI) $[M+H]^+$ calculated for C18H17N2O2: 293.1285. Found: 293.1287.

Example 23:

(1R,3S)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 64)



Formula 64

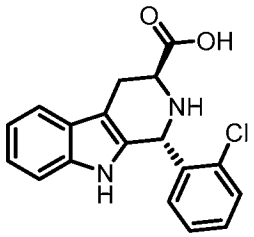
(1R,3S)-1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**64**) was prepared in 99 % yield from (1R,3S)-methyl 1-phenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**10**) following the procedure employed for preparation of **59**.

$[\alpha]_D^{21.0}$ = -51.4° (c = 0.14, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.42 (m, 5H), 7.30 (d, J = 7.6 Hz, 1H), 7.12 (td, J = 6.8 and 1.2 Hz, 1H), 7.05 (td, J = 7.6 and 0.8 Hz, 1H), 5.94 (s, 1H), 4.29 (dd, J = 7.2 and 7.0 Hz, 1H), 3.51 (dd, J = 16.0 and 7.0 Hz, 1H), 3.21 (dd, J = 16.0 and 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ

170.1, 136.6, 134.9, 130.3, 129.5, 128.6, 128.4, 125.5, 122.0, 119.0, 118.2, 111.5, 106.1, 54.5, 51.6, 22.1. HRMS (ESI) $[M+H]^+$ calculated for C18H17N2O2: 293.1285. Found: 293.1294.

Example 24:

(1R,3S)-1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (65)



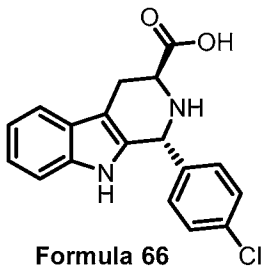
Formula 65

(1R,3S)-1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 65**) was prepared in 95 % yield from (1R,3S)-methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Figure 13**) following the procedure employed for preparation of **Figure 59**.

$[\alpha]_D^{21.0}$ = -19.5° (c = 1.32, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.58 (dd, J = 8.4 and 1.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.39 (td, J = 7.6 and 1.6 Hz, 1H), 7.25 (m, 2H), 7.08 (td, J = 6.8 and 1.2 Hz, 1H), 7.01 (td, J = 8.0 and 1.2 Hz, 1H), 6.92 (d, J = 6.8 Hz, 1H), 5.98 (s, 1H), 3.86 (br s, 1H), 3.28 (dd, J = 15.6 and 4.8 Hz, 1H), 2.97 (dd, J = 15.6 and 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 136.4, 133.7, 130.8, 130.1, 129.7, 127.1, 126.0, 121.5, 118.7, 117.9, 111.3, 107.6, 51.6, 51.0, 23.6. HRMS (ESI) $[M+H]^+$ calculated for C18H16ClN2O2: 327.0895. Found: 327.0898.

Example 25:

(1R,3S)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 66)



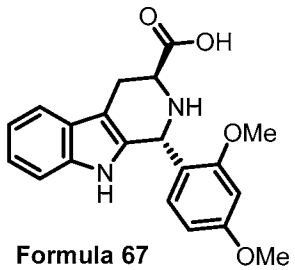
Formula 66

(1R,3S)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 66**) was prepared in 95 % yield from (1R,3S)-methyl 1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 16**) following the procedure employed for preparation of **Formula 59**.

$[\alpha]_D^{21.0}$ = -18.7° (c = 1.25, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 (dt, J = 8.4 and 2.0 Hz, 2H), 7.38 (dt, J = 8.4 and 2.0 Hz, 2H), 7.27 (dt, J = 8.0 and 1.2 Hz, 1H), 7.09 (td, J = 7.6 and 1.2 Hz, 1H), 7.01 (td, J = 8.0 and 1.2 Hz, 1H), 5.79 (s, 1H), 4.03 (t, J = 6.4 Hz, 1H), 3.35 (dd, J = 15.6 and 5.2 Hz, 1H), 3.09 (dd, J = 15.6 and 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 136.5, 136.1, 133.5, 131.7, 129.8, 128.4, 125.8, 121.7, 118.8, 118.1, 111.4, 106.6, 53.5, 51.8, 22.8. HRMS (ESI) $[M+H]^+$ calculated for C18H16ClN2O2: 327.0895. Found: 327.0906.

Example 26:

(1R,3S)-1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 67)



Formula 67

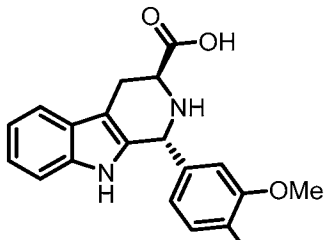
(1R,3S)-1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 67**) was prepared in 90 % yield from (1R,3S)-methyl 1-(2,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 19**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = +32.0° (c = 0.10, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.5 Hz,

1H), 6.70 (d, J = 2.0 Hz, 1H), 6.50 (dd, J = 8.5 and 2.0 Hz, 1H), 6.22 (s, 1H), 3.98 (s, 3H), 3.88 (br s, 1H), 3.80 (s, 3H), 3.46 (dd, J = 15.5 and 4.5 Hz, 1H), 3.18 (dd, J = 15.5 and 4.5 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 164.2, 160.1, 138.6, 132.6, 128.2, 127.3, 123.5, 120.5, 119.2, 115.9, 112.3, 109.3, 106.1, 99.7, 56.4, 56.0, 54.9, 51.3, 24.0. HRMS (ESI) $[M+H]^+$ calculated for C20H21N2O4: 353.1496. Found: 353.1489.

Example 27:

(1R,3S)-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 68)



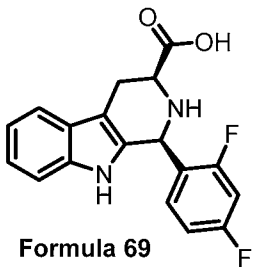
Formula 68

(1R,3S)-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 68**) was prepared in 86 % yield from (1R,3S)-methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 22**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -56.9° (c = 1.43, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.25 (dt, J = 8.0 and 1.2 Hz, 1H), 7.05 (m, 2H), 6.98 (td, J = 8.0 and 1.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.4 and 2.0 Hz, 1H), 5.48 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.66 (dd, J = 8.0 and 5.2 Hz, 1H), 3.11 (dd, J = 15.2 and 5.2 Hz, 1H), 2.93 (dd, J = 15.2 and 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 148.6, 148.6, 136.3, 132.5, 132.4, 126.3, 121.1, 120.9, 118.4, 117.8, 112.8, 111.3, 111.1, 107.2, 55.5, 55.5, 54.0, 52.1, 23.9. HRMS (ESI) $[M+H]^+$ calculated for C20H21N2O4: 353.1496. Found: 353.1500.

Example 28:

(1S,3S)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 69)



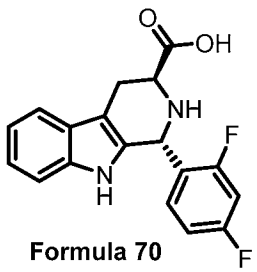
Formula 69

(1S,3S)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 69**) was prepared in 68 % yield from (1S,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 24**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -85.5° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 7.6 Hz, 1H), 7.43 (dt, J = 6.4 and 8.4 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.13 (m, 4H), 6.13 (s, 1H), 4.16 (dd, J = 12.0 and 4.8 Hz, 1H), 3.49 (dd, J = 16.0 and 4.8 Hz, 1H), 3.19 (ddd, J = 16.0, 12.0 and 2.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.3 (s), 165.5 (dd, J = 250 and 12 Hz), 163.4 (dd, J = 251 and 13 Hz), 138.7 (s), 133.7 (dd, J = 10 and 4 Hz), 128.9(s), 127.4 (s), 123.5 (s), 120.6 (s), 119.3 (dd, J = 13 and 4 Hz), 119.2 (s), 113.3 (dd, J = 22 and 4 Hz), 112.4 (s), 110.1 (s), 105.4 (t, J = 26 Hz), 60.5 (s), 52.1 (d, J = 5 Hz), 24.3 (s). ^{19}F NMR (376 MHz, CD_3OD) δ -108.5 (pent, J = 8.3 Hz), -113.2 (q, J = 8.3 Hz). HRMS (ESI) $[M+H]^+$ calculated for C18H15F2N2O2: 329.1096. Found: 329.1103.

Example 29:

(1R,3S)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 70)



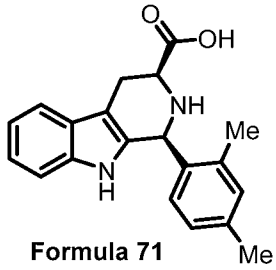
Formula 70

(1R,3S)-1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 70**) was prepared in 74 % yield from (1R,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 25**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -67.3° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dt, J = 8.0 and 0.8 Hz, 1H), 7.27 (dt, J = 8.4 and 0.8 Hz, 1H), 7.10 (m, 4H), 6.98 (td, J = 8.4 and 2.6 Hz, 1H), 6.28 (s, 1H), 4.02 (dd, J = 8.4 and 5.6 Hz, 1H), 3.49 (dd, J = 16.4 and 5.6 Hz, 1H), 3.26 (ddd, J = 16.4, 8.4 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.4 (s), 165.6 (dd, J = 247 and 12 Hz), 163.0 (dd, J = 248 and 13 Hz), 138.7 (s), 133.8 (dd, J = 10 and 4 Hz), 127.2 (s), 123.8 (s), 120.6 (s), 120.0 (dd, J = 14 and 4 Hz), 119.3 (s), 113.1 (dd, J = 22 and 4 Hz), 112.3 (s), 109.5 (s), 105.5 (t, J = 26 Hz), 55.1 (s), 49.1 (d, J = 4 Hz), 23.9 (s). ^{19}F NMR (376 MHz, CD_3OD) δ -108.6 (pent, J = 7.1 Hz), -113.7 (q, J = 9.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for C18H15F2N2O2: 329.1096. Found: 329.1094.

Example 30:

(1S,3S)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 71)



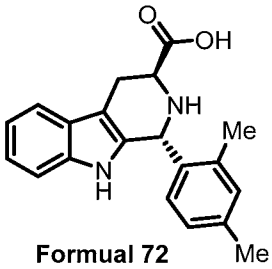
Formula 71

(1S,3S)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 71**) was prepared in 83 % yield from (1S,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 27**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -73.6° (c = 0.11, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.05 (s, 1H), 6.98 (m, 3H), 5.54 (s, 1H), 3.81 (dd, J = 11.0 and 4.0 Hz, 1H), 3.11 (dd, J = 15.0 and 4.0 Hz, 1H), 2.86 (t, J = 12.5 Hz, 1H), 2.35 (br s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.8, 137.0, 136.9, 136.4, 135.2, 134.3, 131.2, 129.2, 126.5, 126.4, 120.7, 118.4, 117.6, 111.2, 107.5, 57.1, 53.9, 24.8, 20.6, 18.9. HRMS (ESI) $[M+H]^+$ calculated for C20H21N2O2: 321.1598. Found: 321.1592.

Example 31:

(1R,3S)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 72)



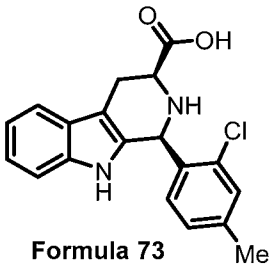
Formual 72

(1R,3S)-1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 72**) was prepared in 85 % yield from (1R,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 28**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -20.1° (c = 1.02, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.21 (dt, J = 7.6 and 0.8 Hz, 1H), 7.07 (d, J = 0.8 Hz, 1H), 7.03 (td, J = 7.2 and 1.2 Hz, 1H), 6.97 (td, J = 7.2 and 1.2 Hz, 1H), 6.88 (dd, J = 7.6 and 0.8 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.63 (s, 1H), 3.63 (dd, J = 7.2 and 5.2 Hz, 1H), 3.08 (dd, J = 15.2 and 5.2 Hz, 1H), 2.92 (dd, J = 15.2 and 7.2 Hz, 1H), 2.45 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 136.9, 136.7, 136.1, 136.0, 133.3, 131.2, 128.7, 126.4, 126.0, 120.9, 118.3, 117.6, 111.0, 107.4, 52.1, 50.6, 24.3, 20.6, 18.7. HRMS (ESI) $[M+H]^+$ calculated for C20H21N2O2: 321.1598. Found: 321.1596.

Example 32

(1S,3S)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 73)



Formula 73

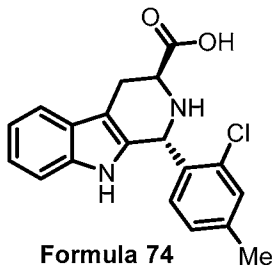
(1S,3S)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 73**) was prepared in 69 % yield from (1S,3S)-methyl 1-(2-chloro-4-

methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 30**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -59.7° (c = 0.66, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.36 (s, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.13 (m, 2H), 7.01 (td, J = 7.6 and 1.2 Hz, 1H), 6.95 (td, J = 7.2 and 1.2 Hz, 1H), 5.66 (s, 1H), 3.82 (dd, J = 11.2 and 4.0 Hz, 1H), 3.06 (ddd, J = 15.2, 4.0 and 1.2 Hz, 1H), 2.82 (ddd, J = 15.2, 11.2 and 2.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 139.3, 136.3, 135.7, 134.1, 133.0, 130.3, 129.6, 128.1, 126.5, 120.8, 118.4, 117.6, 111.2, 107.9, 56.3, 53.9, 25.2, 20.3. HRMS (ESI) $[M+H]^+$ calculated for C19H18ClN2O2: 341.1051. Found: 341.1046.

Example 33:

(1R,3S)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 74)



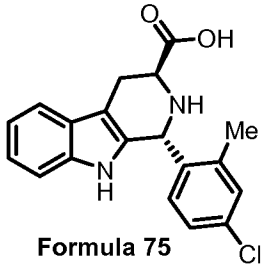
Formula 74

(1R,3S)-1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 74**) was prepared in 78 % yield from (1R,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 31**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -61.9° (c = 0.70, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 1.2 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.01 (m, 3H), 6.64 (d, J = 7.6 Hz, 1H), 5.69 (s, 1H), 3.56 (dd, J = 8.84 and 4.8 Hz, 1H), 3.08 (dd, J = 15.2 and 4.8 Hz, 1H), 2.83 (dd, J = 15.2 and 8.8 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 139.1, 136.2, 136.2, 132.8, 132.7, 129.9, 129.9, 127.4, 126.4, 121.0, 118.4, 117.7, 111.1, 108.2, 51.2, 51.0, 24.7, 20.2. HRMS (ESI) $[M+H]^+$ calculated for C19H18ClN2O2: 341.1051. Found: 341.1058.

Example 34:

(1R,3S)-1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (75)



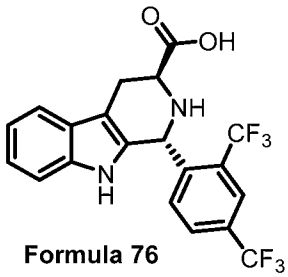
Formula 75

(1R,3S)-1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 75**) was prepared in 56 % yield from (1R,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 34**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -16.8° (c = 0.68, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.4 and 2.4 Hz, 1H), 7.04 (td, J = 7.6 and 1.2 Hz, 1H), 6.98 (td, J = 8.0 and 1.2 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 3.59 (t, J = 6.4 Hz, 1H), 3.06 (dd, J = 15.2 and 4.8 Hz, 1H), 2.88 (dd, J = 15.2 and 7.6 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 139.6, 138.9, 136.1, 133.3, 131.7, 130.4, 129.9, 126.5, 125.2, 120.9, 118.4, 117.7, 111.0, 107.7, 51.9, 50.3, 24.6, 18.5. HRMS (ESI) $[M+H]^+$ calculated for C19H18ClN2O2: 341.1051. Found: 341.1057.

Example 35:

(1R,3S)-1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (76)



Formula 76

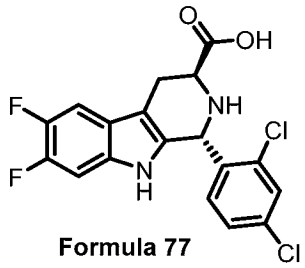
(1R,3S)-1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 76**) was prepared in 84 % yield from (1R,3S)-methyl 1-(2,4-

bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 37**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -70.6° (c = 2.04, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5 (s, 1H), 8.08 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.21 (J = 8.0 Hz, 1H), 7.05 (td, J = 8.0 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 5.87 (s, 1H), 3.86 (t, J = 5.6 Hz, 1H), 3.15 (dd, J = 15.2 and 4.8 Hz, 1H), 3.03 (dd, J = 15.2 and 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.9 (s), 146.4 (s), 136.4 (s), 132.6 (s), 132.5 (s), 129.2 (q, J = 2 Hz), 128.5 (q, J = 31 Hz), 128.4 (q, J = 33 Hz), 126.3 (s), 123.7 (q, J = 274 Hz), 123.5 (q, J = 271 Hz), 122.5 (q, J = 2 Hz), 121.2 (s), 118.6 (s), 117.9 (s), 111.2 (s), 107.7 (s), 52.2 (s), 49.4 (d, J = 2 Hz), 24.1 (s). ^{19}F NMR (470 MHz, DMSO-d_6) δ -56.6, -61.3. HRMS (ESI) $[M+H]^+$ calculated for C20H15F6N2O2: 429.1032. Found: 429.1019.

Example 36:

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 77)



Formula 77

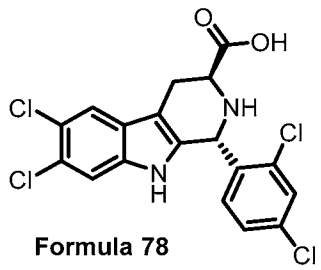
(1R,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 77**) was prepared in 88 % yield from (1R,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 48**) following the procedure employed for preparation of **Formula 60**.

$[\alpha]_D^{21.0}$ = -43.7° (c = 0.57, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.50 (dd, J = 11.2 and 8.0 Hz, 1H), 7.31 (dd, J = 8.1 and 2.0 Hz, 1H), 7.24 (dd, J = 11.2 and 5.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.69 (s, 1H), 3.56 (dd, J = 8.0 and 4.8 Hz, 1H), 3.04 (dd, J = 15.2 and 4.8 Hz, 1H), 2.80 (dd, J = 15.2 and 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4 (s), 146.4 (dd, J = 236 and 16 Hz), 145.0 (dd, J = 240 and 15 Hz), 138.6 (s), 134.5 (d, J = 3 Hz), 134.1 (s), 132.8 (s), 131.4 (s), 131.1 (d, J = 11 Hz), 129.0 (s), 127.1 (s), 121.7 (d, J = 7 Hz), 108.8 (d, J = 4 Hz), 104.7 (d, J = 19 Hz), 99.1 (d, J = 21 Hz), 51.3 (s), 50.5 (s), 24.6 (s). ^{19}F NMR (470 MHz, DMSO-d_6) δ -145.7 (ddd, J = 22.1, 10.8

and 8.0 Hz), -149.3 (ddd, J = 22.6, 11.3 and 7.1 Hz). HRMS (ESI) $[M+H]^+$ calculated for C18H13Cl2F2N2O2: 397.0317. Found: 397.0328.

Example 37:

(1R,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 78)

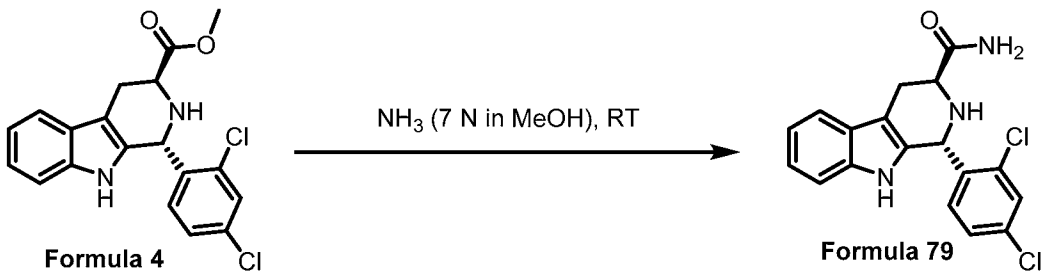


Formula 78

(1R,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 78**) was prepared in 77 % yield from (1R,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 53**) following the procedure employed for preparation of **Formula 60**. $[\alpha]_D^{21.0}$ = -30.0° (c = 0.10, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 7.76 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.48 (s, 1H), 7.31 (dd, J = 8.4 and 2.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.70 (s, 1H), 3.56 (dd, J = 7.6 and 4.8 Hz, 1H), 3.06 (dd, J = 15.2 and 4.8 Hz, 1H), 2.81 (dd, J = 15.2 and 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 138.4, 135.5, 135.0, 134.1, 132.8, 131.4, 129.0, 127.1, 126.4, 123.2, 121.2, 119.1, 112.6, 108.5, 51.3, 50.5, 24.5. HRMS (ESI) $[M+H]^+$ calculated for C18H13Cl4N2O2: 430.9702. Found: 430.9714.

Example 38:

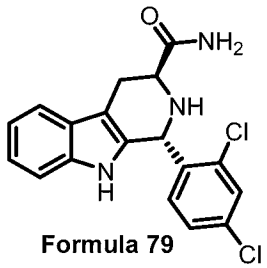
(1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (79)



Formula 4 **Formula 79**

Scheme 20

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (16.5 mg, 0.044 mmol) and ammonia solution in methanol (1.5 mL, 7 N, 10.5 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 24 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / MeOH) to give **Formula 79** (15.5 mg, 98 % yield).



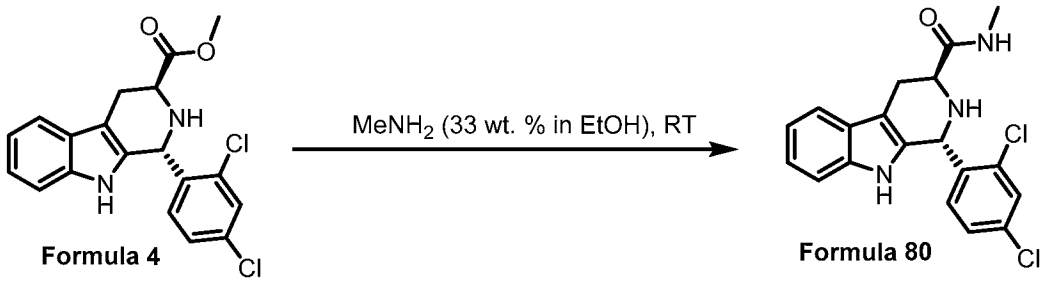
Formula 79

(1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 79**)

$[\alpha]_D^{21.0}$ = -25.7° (c = 0.32, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.30 (dd, J = 8.4 and 2.0 Hz, 1H), 7.26 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 7.06 (td, J = 8.4 and 1.6 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.57 (s, 1H), 3.34 (br s, 1H), 3.08 (br s, 1H), 3.03 (dd, J = 15.2 and 4.8 Hz, 1H), 2.70 (ddd, J = 15.2, 10.0 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 138.9, 136.1, 134.4, 132.6, 132.5, 131.2, 129.0, 126.8, 126.5, 121.1, 118.4, 117.7, 111.1, 109.1, 51.3, 50.7, 25.0. HRMS (ESI) $[M+H]^+$ calculated for C18H16Cl2N3O: 360.0665. Found: 360.0672.

Example 39:

(1R,3S)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (80)

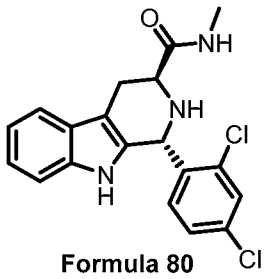


Formula 4

Formula 80

Scheme 21

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (36.0 mg, 0.096 mmol) and methylamine solution (2.0 mL, 33 wt. % in absolute ethanol, 16.1 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 16 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 80** (35.5 mg, 99 % yield).



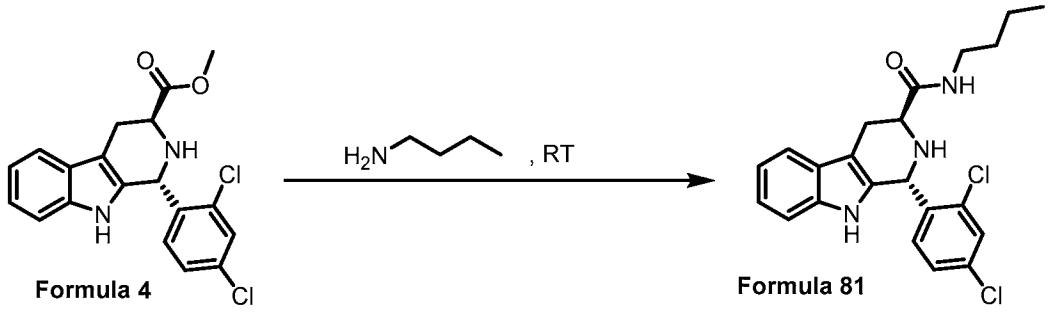
Formula 80

(1R,3S)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (80)

$[\alpha]_D^{21.0}$ = -41.4° (c = 0.63, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.20 (td, J = 7.0 and 1.0 Hz, 1H), 7.14 (td, J = 7.5 and 1.0 Hz, 1H), 7.05 (dd, J = 8.0 and 2.0 Hz, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.58 (s, 1H), 3.49 (dd, J = 10.0 and 5.0 Hz, 1H), 3.31 (dd, J = 15.5 and 4.5 Hz, 1H), 2.84 (ddd, J = 15.5, 10.0 and 1.0 Hz, 1H), 2.77 (d, J = 4.5 Hz, 3H), 2.05 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 136.8, 136.3, 135.0, 134.6, 131.4, 131.1, 129.9, 126.8, 122.5, 119.8, 118.5, 111.4, 111.0, 52.3, 51.9, 25.9, 24.8. HRMS (ESI) $[M+H]^+$ calculated for C19H18Cl2N3O: 374.0821. Found: 374.0830.

Example 40

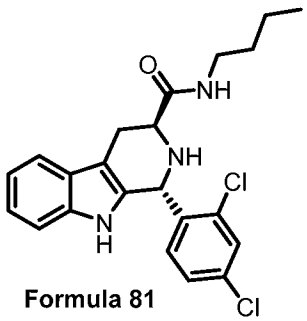
(1R,3S)-N-butyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 81)



Formula 4 Formula 81

Scheme 22

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (76.0 mg, 0.2 mmol) and n-butylamine (1.0 mL, 10.1 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 81 (**80.0 mg, 96 % yield).



Formula 81

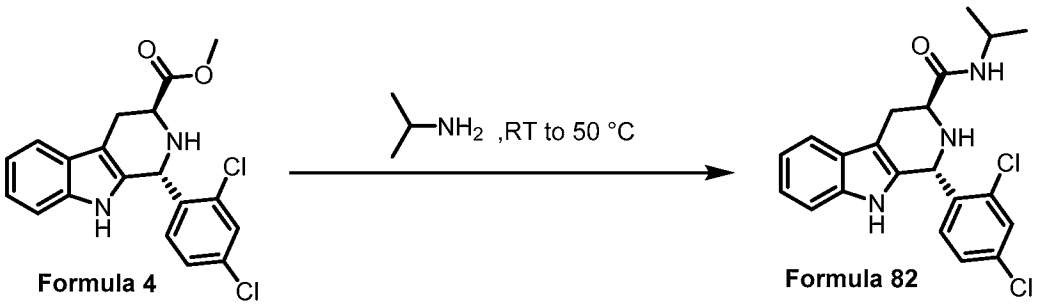
(1R,3S)-N-butyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 81)

$[\alpha]_D^{21.0}$ = -35.0° (c = 0.96, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.27 (dt, J = 8.0 and 0.8 Hz, 1H), 7.18 (td, J = 6.8 and 1.2 Hz, 1H), 7.11 (td, J = 7.6 and 1.2 Hz, 1H), 7.03 (dd, J = 8.0 and 2.0 Hz, 1H), 6.91 (t, J = 6.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.51 (s, 1H), 3.45 (dd, J = 10.0 and 4.8 Hz, 1H), 3.25 (dd, J = 16.0 and 4.8 Hz, 1H), 3.16 (m, 2H), 2.84 (ddd, J = 16, 10.0 and 1.2 Hz, 1H), 1.93 (br s, 1H), 1.45 (m, 2H), 1.30 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

172.4, 136.9, 136.3, 134.9, 134.4, 131.4, 131.0, 129.8, 126.8, 122.3, 119.6, 118.5, 111.1, 111.0, 52.4, 51.7, 38.9, 31.5, 24.7, 20.1, 13.7. HRMS (ESI) $[M+H]^+$ calculated for C22H24Cl2N3O: 416.1291. Found: 416.1275.

Example 41:

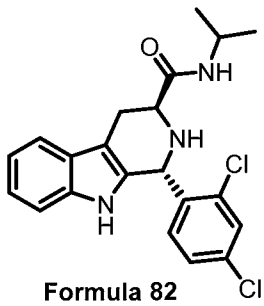
(1R,3S)-1-(2,4-dichlorophenyl)-N-isopropyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (82)



Formula 4 Formula 82

Scheme 23

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (76.0 mg, 0.2 mmol) and isopropylamine (1.0 mL, 58.8 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 24 hours and then at 50 °C for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 82 (**37.0 mg, 47 % isolated yield, 74 % brsm yield) and the starting material **Formula 4** (29.2 mg, 38 % yield).



Formula 82

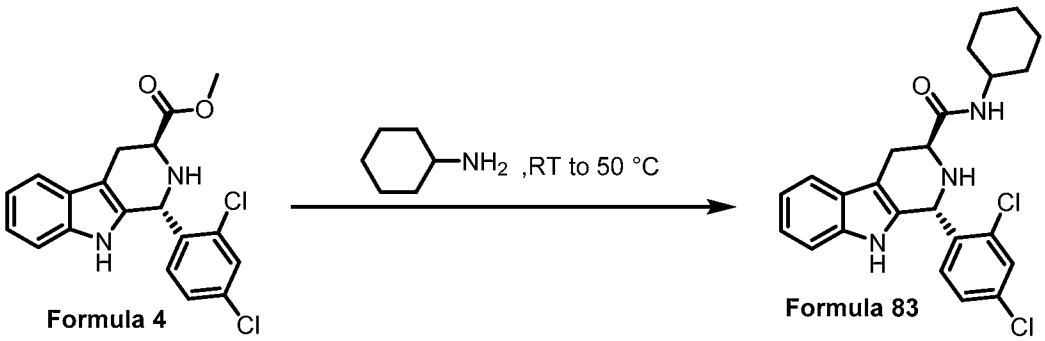
(1R,3S)-1-(2,4-dichlorophenyl)-N-isopropyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (82)

$[\alpha]_D^{21.0}$ = -33.8° (c = 0.77, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.27 (dt, J = 8.0 and 0.8 Hz, 1H), 7.18 (td, J = 7.2 and 1.2

Hz, 1H), 7.12 (td, J = 7.6 and 1.2 Hz, 1H), 7.06 (dd, J = 8.4 and 2.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.53 (s, 1H), 3.96 (m, 1H), 3.47 (dd, J = 9.2 and 4.8 Hz, 1H), 3.23 (dd, J = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, J = 16.0, 9.2 and 1.6 Hz, 1H), 1.91 (br s, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.9, 136.3, 134.9, 134.5, 131.3, 131.0, 129.9, 126.9, 126.8, 122.4, 119.7, 118.5, 111.0, 110.9, 52.4, 51.6, 41.1, 24.6, 22.7, 22.6. HRMS (ESI) $[M+H]^+$ calculated for C21H22Cl2N3O: 402.1134. Found: 402.1155.

Example 42:

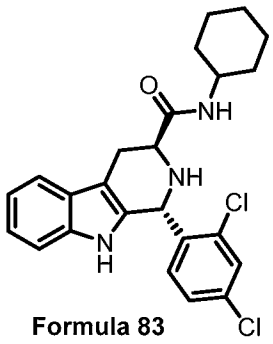
(1R,3S)-N-cyclohexyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (83)



Formula 4 **Formula 83**

Scheme 24

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (76.0 mg, 0.2 mmol) and cyclohexylamine (1.0 mL, 43.7 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 24 hours and then at 50 °C for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 83 (**53.0 mg, 60 % isolated yield, 96 % brsm yield) and the starting material **Formula 4** (29.0 mg, 38 % yield).



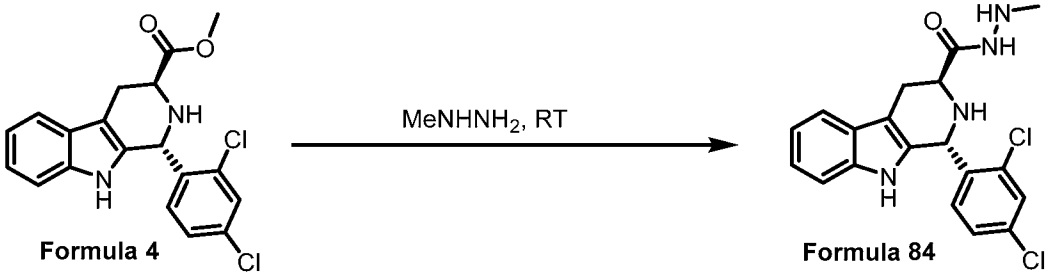
Formula 83

(1R,3S)-N-cyclohexyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (83)

$[\alpha]_D^{21.0}$ = -33.8° (c = 0.39, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.27 (dt, J = 8.0 and 0.8 Hz, 1H), 7.18 (td, J = 7.2 and 1.2 Hz, 1H), 7.11 (td, J = 8.0 and 1.2 Hz, 1H), 7.05 (dd, J = 8.4 and 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.50 (s, 1H), 3.66 (m, 1H), 3.47 (dd, J = 9.2 and 4.8 Hz, 1H), 3.22 (dd, J = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, J = 16.0, 9.2 and 1.6 Hz, 1H), 1.85 (m, 3H), 1.62 (m, 3H), 1.31 (m, 2H), 1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 136.9, 136.3, 134.9, 134.5, 131.4, 131.0, 129.8, 126.9, 126.8, 122.3, 119.6, 118.5, 111.0, 110.9, 52.5, 51.6, 47.7, 32.9, 32.8, 25.5, 24.7, 24.6, 24.5. HRMS (ESI) $[M+H]^+$ calculated for C24H26Cl2N3O: 442.1447. Found: 442.1448.

Example 43:

(1R,3S)-1-(2,4-dichlorophenyl)-N'-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbohydrazide (Formula 84)

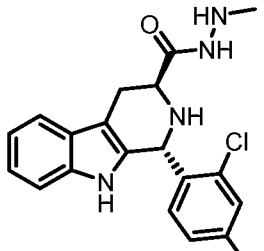


Formula 4 Formula 84

Scheme 24

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (76.0 mg, 0.2 mmol) and metylhydrazine (1.0 mL, 19.0 mmol). The vial was then closed tightly and the reaction

mixture was stirred at room temperature for 20 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (20 : 1 : 1 DCM / EtOAc / EtOH) to give **Formula 84 (**61.0 mg, 78 % yield).



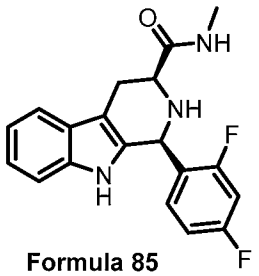
Formula 84

(1R,3S)-1-(2,4-dichlorophenyl)-N'-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbohydrazide (Formula 84)

$[\alpha]_D^{21.0}$ = -29.0° (c = 1.25, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.28 (dt, J = 8.0 and 0.8 Hz, 1H), 7.20 (td, J = 7.2 and 1.2 Hz, 1H), 7.15 (td, J = 8.0 and 1.2 Hz, 1H), 7.07 (dd, J = 8.4 and 2.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 3.55 (dd, J = 9.6 and 4.8 Hz, 1H), 3.29 (dd, J = 16.0 and 4.8 Hz, 1H), 2.88 (ddd, J = 16.0, 9.6 and 1.2 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.6, 136.2, 135.1, 134.6, 131.3, 131.0, 130.0, 126.9, 126.8, 122.5, 119.8, 118.5, 111.0, 110.9, 51.7 (2C), 39.3, 24.6. HRMS (ESI) $[M+H]^+$ calculated for C19H19Cl2N4O: 389.0930. Found: 389.0923.

Example 44:

(1S,3S)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 85)



Formula 85

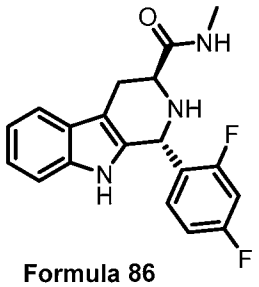
(1S,3S)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 85**) was prepared in 99 % yield from (1S,3S)-methyl 1-(2,4-

difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 24**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -41.6° (c = 0.90, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.14 (m, 3H), 6.87 (m, 3H), 5.54 (s, 1H), 3.71 (dd, J = 11.2 and 4.4 Hz, 1H), 3.35 (ddd, J = 16.0, 4.4 and 1.6 Hz, 1H), 2.83 (ddd, J = 16.0, 11.2 and 2.4 Hz, 1H), 2.82 (d, J = 5.2 Hz, 3H), 1.74 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (s), 162.8 (dd, J = 249 and 12 Hz), 161.2 (dd, J = 249, 12 Hz), 136.1 (s), 132.9 (s), 130.5 (dd, J = 10 and 5 Hz), 127.0 (s), 123.6 (dd, J = 14 and 4 Hz), 122.2 (s), 119.7 (s), 118.4 (s), 111.9 (dd, J = 21 and 4 Hz), 110.9 (s), 110.6 (s), 104.3 (t, J = 26 Hz), 58.0 (s), 51.5 (d, J = 3 Hz), 25.9 (s), 25.4 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -109.0 (pent, J = 8.0 Hz), -114.6 (q, J = 9.5 Hz) HRMS (ESI) $[M+H]^+$ calculated for C19H18F2N3O: 342.1412. Found: 342.1433.

Example 45:

(1R,3S)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 86)



Formula 86

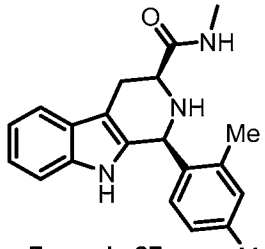
(1R,3S)-1-(2,4-difluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 86**) was prepared in 99 % yield from (1R,3S)-methyl 1-(2,4-difluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 25**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -70.4° (c = 0.75, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.76 (q, J = 4.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.29 (ddd, J = 10.4, 9.6 and 2.8 Hz, 1H), 7.25 (dt, J = 8.0 and 0.8 Hz, 1H), 7.06 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.94 (td, J = 8.4 and 2.4 Hz, 1H), 6.75 (dt, J = 6.8 and 8.4 Hz, 1H), 5.54 (s, 1H), 3.42 (br s, 1H), 3.11 (br s, 1H), 3.01 (dd, J = 15.2 and 4.8 Hz, 1H), 2.69 (ddd, J = 15.2, 10.0 and 0.8 Hz, 1H), 2.60 (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (s), 161.6 (dd, J = 244 and 12 Hz), 160.4 (dd, J = 248 and 12), 136.1 (s), 132.7 (s), 131.0 (dd, J = 10 and 6 Hz), 126.6

(s), 126.4 (dd, J = 14 and 4 Hz), 121.0 (s), 118.4 (s), 117.7 (s), 111.1 (s), 110.5 (dd, J = 21 and 4 Hz), 109.0 (s), 103.9 (t, J = 26 Hz), 51.6 (s), 47.3 (d, J = 2 Hz), 25.4 (s), 25.1 (s). ^{19}F NMR (376 MHz, CDCl3) δ -109.8 (pent, J = 7.8 Hz), -114.2 (q, J = 9.0 Hz). HRMS (ESI) $[M+H]^+$ calculated for C19H18F2N3O: 342.1412. Found: 342.1429.

Example 46:

(1S,3S)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 87)



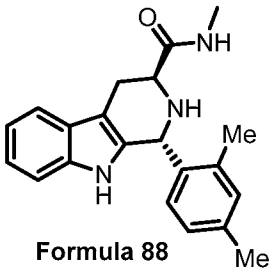
Formula 87

(1S,3S)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 87**) was prepared in 99 % yield from (1S,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 27**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -52.2° (c = 1.19, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.54 (dd, J = 6.8 and 1.6 Hz, 1H), 7.21 (dd, J = 6.8 and 1.6 Hz, 1H), 7.11 (m, 4H), 6.94 (m, 2H), 5.40 (s, 1H), 3.71 (dd, J = 11.2 and 4.4 Hz, 1H), 3.41 (ddd, J = 16.0, 4.4 and 2.0 Hz, 1H), 2.81 (ddd, J = 16.0, 11.2 and 2.8 Hz, 1H), 2.80 (d, J = 4.8 Hz, 3H), 2.48 (br s, 6H), 1.64 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 138.3, 137.2, 136.1, 135.5, 134.6, 131.8, 127.7, 127.2, 127.1, 121.9, 119.6, 118.3, 113.9, 110.8, 58.1, 54.7, 25.8, 25.4, 21.0, 19.0. HRMS (ESI) $[M+H]^+$ calculated for C21H24N3O: 334.1914. Found: 334.1910.

Example 47:

(1R,3S)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 88)



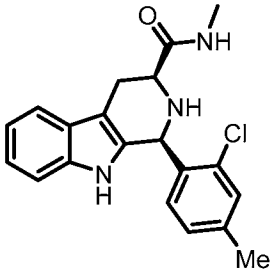
Formula 88

(1R,3S)-1-(2,4-dimethylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 88**) was prepared in 99 % yield from (1R,3S)-methyl 1-(2,4-dimethylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 28**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -46.5° (c = 0.99, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.24 (dt, J = 8.0 and 0.8 Hz, 1H), 7.16 (td, J = 6.8 and 1.2 Hz, 1H), 7.12 (td, J = 6.8 and 1.2 Hz, 1H), 7.05 (s, 1H), 6.87 (q, J = 5.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 5.31 (s, 1H), 3.53 (dd, J = 10.0 and 4.8 Hz, 1H), 3.31 (dd, J = 16.0 and 4.8 Hz, 1H), 2.82 (ddd, J = 16.0, 10.0 and 1.2 Hz, 1H), 2.73 (d, J = 5.2 Hz, 3H), 2.50 (s, 3H), 2.26 (s, 3H), 1.91 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 137.7, 136.9, 136.2, 135.5, 133.6, 131.6, 128.9, 127.0, 126.2, 122.0, 119.5, 118.3, 110.8, 110.7, 52.1, 52.0, 25.8, 24.6, 20.9, 19.0. HRMS (ESI) $[M+H]^+$ calculated for C21H24N3O: 334.1914. Found: 334.1898.

Example 48:

(1S,3S)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 89)



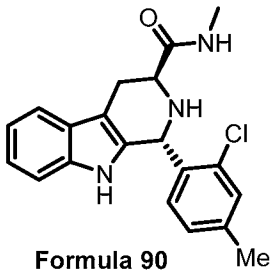
Formula 89

(1S,3S)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 89**) was prepared in 90 % yield from (1S,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 30**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -43.1° (c = 1.41, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 6.4 and 1.6 Hz, 2H), 7.32 (s, 1H), 7.23 (dt, J = 8.0 and 1.2 Hz, 1H), 7.10 (m, 5H), 5.72 (br s, 1H), 3.78 (dd, J = 11.2 and 4.4 Hz, 1H), 3.40 (ddd, J = 15.6, 4.4 and 2.0 Hz, 1H), 2.86 (ddd, J = 15.6, 11.2 and 2.4 Hz, 1H), 2.84 (d, J = 4.8 Hz, 3H), 2.35 (s, 3H), 1.78 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 140.2, 136.1, 134.0, 133.6, 130.5, 130.5, 129.2, 128.3, 127.1, 122.1, 119.7, 118.4, 110.9, 110.5, 58.1, 54.7, 25.9, 25.5, 20.9. HRMS (ESI) $[M+H]^+$ calculated for C20H21ClN3O: 354.1368. Found: 354.1371.

Example 49:

(1R,3S)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 90)



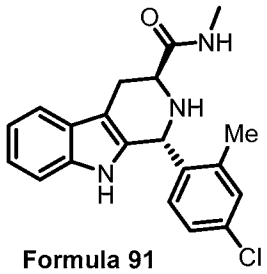
Formula 90

(1R,3S)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 90**) was prepared in 99 % yield from (1R,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 31**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -39.0° (c = 0.68, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.27 (s, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.17 (td, J = 7.2 and 1.2 Hz, 1H), 7.12 (td, J = 8.0 and 1.2 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.86 (dd, J = 7.6 and 0.8 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 5.57 (s, 1H), 3.54 (dd, J = 10.0 and 4.8 Hz, 1H), 3.28 (dd, J = 15.6 and 4.8 Hz, 1H), 2.85 (ddd, J = 15.6, 10.0 and 1.2 Hz, 1H), 2.75 (d, J = 4.8 Hz, 3H), 2.29 (s, 3H), 2.01 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 139.6, 136.2, 135.1, 133.9, 132.2, 130.4, 130.0, 127.3, 126.9, 122.1, 119.5, 118.4, 110.9, 110.8, 52.3, 51.9, 25.8, 24.7, 20.7. HRMS (ESI) $[M+H]^+$ calculated for C20H21ClN3O: 354.1368. Found: 354.1383.

Example 50:

(1R,3S)-1-(4-chloro-2-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 91)



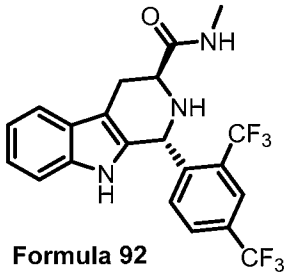
Formula 91

(1R,3S)-1-(4-chloro-2-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 91**) was prepared in 64 % yield from (1R,3S)-methyl 1-(4-chloro-2-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 34**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -47.9° (c = 0.63, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.27 (dt, J = 7.6 and 1.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.19 (td, J=8.0 and 1.6 Hz, 1H), 7.14 (td, J = 7.2 and 1.2 Hz, 1H), 6.95 (dd, J = 8.4 and 2.4 Hz, 1H), 6.80 (d, J = 4.8 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 5.34 (s, 1H), 3.49 (dd, J = 10.0 and 4.8 Hz, 1H), 3.33 (dd, J = 16.0 and 4.8 Hz, 1H), 2.82 (ddd, J = 16.0, 10.0 and 1.2 Hz, 1H), 2.76 (d, J = 4.8 Hz, 3H), 2.53 (s, 3H), 1.92 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 139.1, 137.0, 136.2, 133.5, 132.8, 130.7, 130.2, 126.9, 125.6, 122.3, 119.7, 118.4, 111.1, 110.9, 52.1, 52.0, 25.9, 24.7, 19.0. HRMS (ESI) $[M+H]^+$ calculated for C20H21ClN3O: 354.1368. Found: 354.1373.

Example 51:

(1R,3S)-1-(2,4-bis(trifluoromethyl)phenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 92)



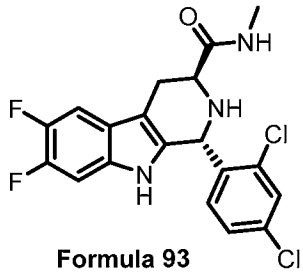
Formula 92

(1R,3S)-1-(2,4-bis(trifluoromethyl)phenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 92**) was prepared in 77 % yield from (1R,3S)-methyl 1-(2,4-bis(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 37**) following the procedure employed for preparation of **Formula 80**.

$[\alpha]_D^{21.0}$ = -57.9° (c = 0.71, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.75 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.28 (dt, J = 7.6 and 0.8 Hz, 1H), 7.21 (td, J = 7.6 and 1.2 Hz, 2H), 7.17 (td, J = 8.0 and 1.2 Hz, 1H), 6.83 (d, J = 5.2 Hz, 1H), 5.74 (s, 1H), 3.61 (dd, J = 13.2 and 8.8 Hz, 1H), 3.35 (dd, J = 16.0 and 5.2 Hz, 1H), 2.96 (ddd, J = 16.0, 9.2 and 1.6 Hz, 1H), 2.78 (d, J = 5.2 Hz, 3H), 2.18 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7 (s), 143.5 (s), 136.4 (s), 131.3 (s), 130.9 (q, J = 33 Hz), 130.8 (s), 129.7 (q, J = 31 Hz), 128.7 (q, J = 4 Hz), 126.8 (s), 124.2 (q, J = 4 Hz), 123.9 (q, J = 267 Hz), 123.1 (q, J = 266 Hz), 122.8 (s), 120.0 (s), 118.7 (s), 111.5 (s), 111.0 (s), 52.4 (s), 50.8 (s), 26.0 (s), 24.4 (s). ^{19}F NMR (470 MHz, $CDCl_3$) δ -58.4, -62.9. HRMS (ESI) $[M+H]^+$ calculated for C21H18F6N3O: 442.1349. Found: 442.1356.

Example 52:

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 93)



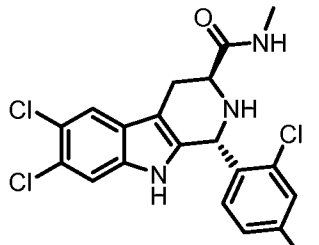
Formula 93

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 93**) was prepared in 97 % yield from (1R,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 48**) following the procedure employed for preparation of **Formula 80**. $[\alpha]_D^{21.0}$ = -38.6° (c = 1.52, MeOH). ^{1}H NMR (400 MHz, CD_3CN) δ 9.10 (s, 1H), 7.55(d, J = 2.0 Hz, 1H), 7.36 (dd, J = 11.2 and 8.0 Hz, 1H), 7.19 (dd, J = 11.2 and 6.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 4.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.59 (s, 1H), 3.42 (dd, J = 9.6 and 4.8 Hz, 1H), 3.04 (dd, J = 15.6 and 4.8 Hz, 1H), 2.73 (dd, J = 15.6 and 9.6 Hz, 1H), 2.65 (d, J = 4.8 Hz, 3H), 2.21 (br s, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 173.7 (s), 148.3 (dd, J = 236 and 16 Hz), 146.8 (dd, J = 233 and 15 Hz), 138.9 (s), 136.0 (s), 135.4 (d, J = 4 Hz), 134.5 (s), 132.3 (d, J = 10 Hz), 132.2 (s), 130.3 (s), 127.6 (s), 123.3 (d, J = 8 Hz), 111.7 (d, J = 3 Hz), 105.5 (d, J = 19 Hz), 100.1 (d, J = 22 Hz), 52.9 (s), 52.2 (s), 26.0 (s), 25.2 (s). ^{19}F NMR (470 MHz, CD_3CN) δ -146.5 (ddd, J = 19.7, 10.8 and 8.5 Hz), -150.3 (ddd, J = 19.7,

11.8 and 7.1 Hz). HRMS (ESI) $[M+H]^+$ calculated for C19H16Cl2F2N3O: 410.0633. Found: 410.0615.

Example 53:

(1R,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 94)

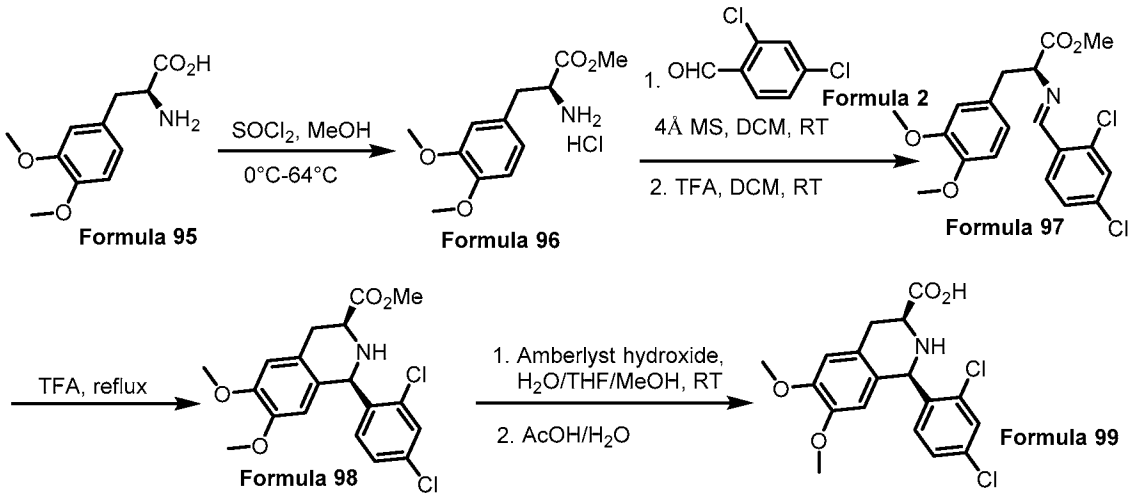


Formula 94

(1R,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 94**) was prepared in 81 % yield from (1R,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 53**) following the procedure employed for preparation of **Formula 80**. $[\alpha]_D^{21.0}$ = -32.1° (c = 0.14, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.21 (dd, J = 8.4 and 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.71 (s, 1H), 3.54 (dd, J = 10.0 and 4.8 Hz, 1H), 3.12 (dd, J = 15.6 and 4.8 Hz, 1H), 2.82 (ddd, J = 15.6, 10.0 and 1.6 Hz, 1H), 2.75 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 138.7, 137.0, 136.3, 135.9, 135.5, 132.3, 130.8, 128.0, 126.1, 123.8, 120.0, 113.6, 110.7, 53.1, 52.6, 26.3, 25.8. HRMS (ESI) $[M+H]^+$ calculated for C19H16Cl4N3O: 444.0018. Found: 442.0024.

Example 54:

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (99)



Scheme 25

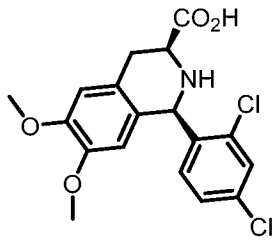
To a suspension of 3-(3,4-Dimethoxyphenyl)-L-alanine (**Formula 95**) (676 mg, 3.0 mmol) in absolute methanol (10 mL), thionyl chloride (450 μL, 6.0 mmol) was added dropwise at 0 °C. The resulting reaction mixture was then stirred at reflux for one hour. The reaction was cooled to room temperature and concentrated under vacuum. The residue was dissolved in 10 mL absolute ethanol and the condensed under vacuum again. This procedure was repeated for other twice to give 3-(3,4-Dimethoxyphenyl)-L-alanine methyl ester hydrochloride (**Formula 96**) (803 mg, 97 % yield).

To a suspension of 3-(3,4-Dimethoxyphenyl)-L-alanine methyl ester hydrochloride (**Formula 96**) (276 mg, 1.0 mmol) and 4Å molecular sieve (500 mg, powder form) in DCM (10 mL) was added 2,4-dichlorobenzaldehyde (**Formula 2**) (175 mg, 1.0 mmol, in 2 mL DCM). The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (150 μL, 2.0 mmol) was then added dropwise. The reaction mixture was stirred for another 24 hours. An aqueous solution of $NaHCO_3$ (500 mg, 6.0 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (60 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 (15 g), concentrated, then purified by flash chromatography (5 : 1 hexane / EtOAc) to give (S)-methyl 2-(2,4-dichlorobenzylideneamino)-3-(3,4-dimethoxyphenyl)propanoate (**Formula 97**) (146 mg, 37 % yield). ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 8.5 and 2.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.69 (dd, J = 8.0 and 1.5 Hz, 1H), 6.64 (d, J = 1.5 Hz, 1H), 4.20 (dd, J = 9.0 and 5.0 Hz, 1H), 3.83 (s,

3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.31 (dd, J = 13.5 and 5.0 Hz, 1H), 3.08 (dd, J = 13.5 and 9.0 Hz, 1H).

A solution of (S)-methyl 2-(2,4-dichlorobenzylideneamino)-3-(3,4-dimethoxyphenyl)propanoate (**Formula 97**) (146 mg, 0.37 mmol) in trifluoroacetic acid (8 mL) was stirred for 3 hours at reflux. The reaction was cooled to room temperature and concentrated under vacuum. The residue was dissolved in 60 mL EtOAc. The solution was washed with 10% $NaHCO_3$ aqueous solution (10 mL), brine (10 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give (1R,3S)-methyl 1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**Formula 98**) (110 mg, 75 % yield). $[\alpha]_D^{21.0}$ = +0.5° (c = 1.59, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.5 and 2.0 Hz, 1H), 6.65 (s, 1H), 6.16 (s, 1H), 5.64 (s, 1H), 3.87 (dd, J = 10.0 and 5.5 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.65 (s, 3H), 3.08 (m, 2H), 2.55 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 147.8, 147.5, 140.1, 134.4, 133.7, 131.9, 128.9, 128.5, 127.7, 126.2, 111.4, 109.8, 57.5, 56.1, 55.8, 55.7, 52.1, 31.9. HRMS (ESI) $[M+H]^+$ calculated for C19H20Cl2NO4: 396.0764. Found: 396.0768.

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**Formula 99**) was prepared in 95 % yield from (1R,3S)-methyl 1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**Formula 98**) following the procedure employed for preparation of **Formula 60**.



Formula 99

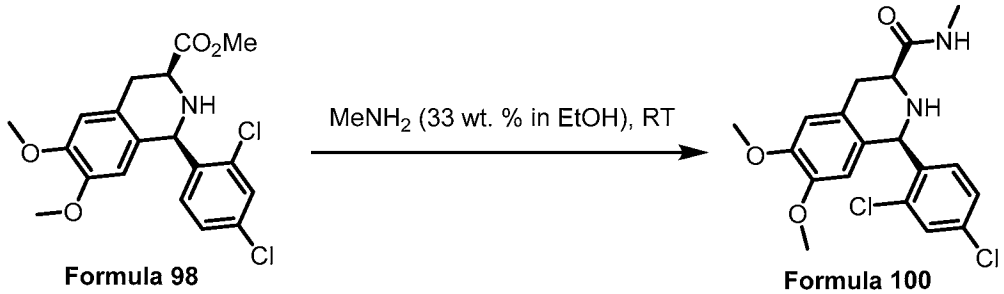
(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Formula 99)

$[\alpha]_D^{21.0}$ = -19.7° (c = 0.59, MeOH). ^{1}H NMR (400 MHz, DMSO-d6) δ7.65 (t, J = 1.2 Hz, 1H), 7.39 (s, 2H), 6.80 (s, 1H), 6.06 (s, 1H), 5.53 (s, 1H), 3.74 (dd, J = 8.4 and 4.4 Hz, 1H), 3.73 (s, 3H), 3.47 (s, 3H), 2.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 173.3, 147.7, 147.1,

140.6, 134.0, 132.6, 132.3, 128.5, 128.2, 127.7, 126.7, 112.3, 110.0, 57.0, 55.7, 55.6, 55.5, 31.4. HRMS (ESI) $[M+H]^+$ calculated for C18H18Cl2NO4: 382.0607. Found: 382.0605.

Example 55:

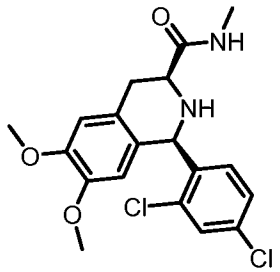
(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Formula 100)



Formula 98 **Formula 100**

Scheme 26

(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**Formula 100**) was prepared in 95 % yield from (1R,3S)-methyl 1-(2,4-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**Formula 98**) following the procedure employed for preparation of **Formula 80**.



Formula 100

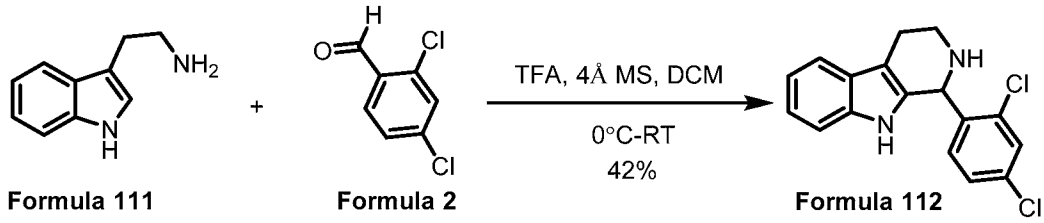
(1R,3S)-1-(2,4-dichlorophenyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (Formula 100)

$[\alpha]_D^{21.0}$ = -4.8° (c = 0.79, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 8.5 and 2.0 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 5.0 Hz, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 5.57 (s, 1H), 3.87 (s, 3H), 3.71 (dd, J = 11.0 and 4.5 Hz, 1H), 3.65 (s, 3H), 3.18 (dd, J = 16.0 and 4.5 Hz, 1H), 2.90 (dd, J = 16.0 and 11.0 Hz, 1H), 2.81 (d, J = 5.0 Hz, 3H), 1.84 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 148.1, 147.6, 139.8, 134.9, 134.0,

131.3, 129.5, 128.2, 127.6, 127.0, 111.6, 109.7, 58.0, 57.3, 55.9, 55.8, 32.0, 25.8. HRMS (ESI) $[M+H]^+$ calculated for C19H21Cl2N2O3: 395.0924. Found: 395.0911.

Example 56:

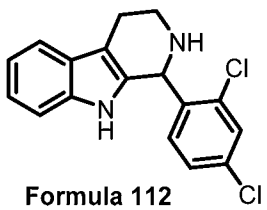
1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (Formula 112)



Formula 111 **Formula 2** **Formula 112**

Scheme 27

To a 50-mL flask charging with 4Å molecular sieve (500 mg, powder form) was added tryptamine (**Formula 111**) (320 mg, 2.0 mmol, in 5 mL DCM), and 2,4-dichlorobenzaldehyde (**Formula 2**) (420 mg, 2.4 mmol, in 5 mL DCM). 2 drops of TFA was added at 0 °C. The resulting reaction mixture was stirred for 17 hours at room temperature. The reaction was cooled to 0 °C and TFA (310 μL, 4.0 mmol) was added dropwise. The reaction mixture was further stirred for 7 hours at room temperature. Then the reaction was cooled to 0 °C again. An aqueous solution of $NaHCO_3$ (420 mg, 5.0 mmol, in 10 mL H_2O) was added dropwise, followed by an addition of EtOAc (80 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (20mL), dried over Na_2SO_4 (20 g), concentrated, then purified by flash chromatography (10 : 1 DCM / EtOH) to give 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**Formula 112**) (264 mg, 42 % yield).



Formula 112

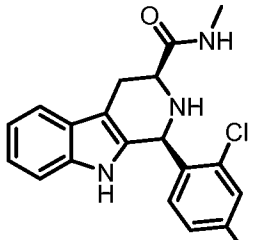
1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (Formula 112)

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.54 (dd, J = 7.6 and 1.6 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.22 (ddd, J = 7.6, 1.6 and 0.8 Hz, 1H), 7.14 (m, 3H), 7.02 (d, J = 8.4 Hz, 1H),

5.66 (s, 1H), 3.16 (m, 2H), 2.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 135.9, 134.5, 132.0, 131.2, 129.6, 127.3, 127.0, 122.1, 119.6, 118.3, 111.0, 110.9, 53.1, 41.4, 22.1. HRMS (ESI) $[M+H]^+$ calculated for C17H15Cl2N2: 317.0607. Found: 317.0628.

Example 57:

(1S,3S)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 113)



Formula 113

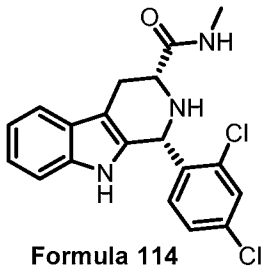
(1S,3S)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 113**) was prepared in 99 % yield from (1S,3S)-methyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 3**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (d, J = 2.0 Hz, 1H), 7.45 (dt, J = 7.2 and 1.2 Hz, 1H), 7.30 (dd, J = 8.4 and 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.21 (dt, J = 7.2 and 1.2 Hz, 1H), 7.05 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 7.2 and 1.2 Hz, 1H), 5.74 (s, 1H), 3.76 (dd, J = 11.2 and 4.4 Hz, 1H), 3.15 (ddd, J = 15.2, 4.4 and 2.0 Hz, 1H), 2.88 (ddd, J = 15.2, 11.2 and 2.0 Hz, 1H), 2.79 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 176.0, 138.9, 138.3, 136.3, 135.5, 134.4, 132.7, 130.4, 128.8, 128.2, 122.5, 119.9, 118.7, 112.1, 110.1, 59.2, 55.7, 26.8, 26.3.

Example 58:

(1R,3R)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 114)



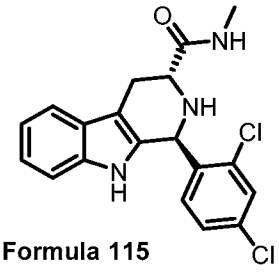
Formula 114

(1R,3R)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 114**) was prepared in 99 % yield from (1R,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 6**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (d, J = 2.0 Hz, 1H), 7.45 (dt, J = 7.2 and 1.2 Hz, 1H), 7.30 (dd, J = 8.4 and 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.21 (dt, J = 7.2 and 1.2 Hz, 1H), 7.05 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 7.2 and 1.2 Hz, 1H), 5.74 (s, 1H), 3.76 (dd, J = 11.2 and 4.4 Hz, 1H), 3.15 (ddd, J = 15.2, 4.4 and 2.0 Hz, 1H), 2.88 (ddd, J = 15.2, 11.2 and 2.0 Hz, 1H), 2.79 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD) δ 176.0, 138.9, 138.3, 136.3, 135.5, 134.4, 132.7, 130.4, 128.8, 128.2, 122.5, 119.9, 118.7, 112.1, 110.1, 59.2, 55.7, 26.8, 26.3. HRMS (MALDI) $[M+H]^+$ calculated for C19H18Cl2N3O: 374.0821. Found: 374.0843.

Example 59:
(1S,3R)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 115)



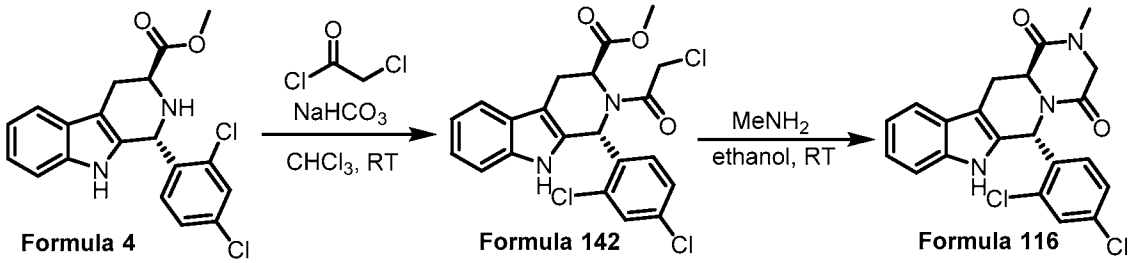
Formula 115

(1S,3R)-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 115**) was prepared in 83 % yield from (1S,3R)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 7**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.20 (td, J = 7.0 and 1.0 Hz, 1H), 7.14 (td, J = 7.5 and 1.0 Hz, 1H), 7.05 (dd, J = 8.0 and 2.0 Hz, 1H), 6.89 (d, J = 4.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.58 (s, 1H), 3.49 (dd, J = 10.0 and 5.0 Hz, 1H), 3.31 (dd, J = 15.5 and 4.5 Hz, 1H), 2.84 (ddd, J = 15.5, 10.0 and 1.0 Hz, 1H), 2.77 (d, J = 4.5 Hz, 3H), 2.05 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 136.8, 136.3, 135.0, 134.6, 131.4, 131.1, 129.9, 126.8, 122.5, 119.8, 118.5, 111.4, 111.0, 52.3, 51.9, 25.9, 24.8. HRMS (MALDI) $[M+H]^+$ calculated for C19H18Cl2N3O: 374.0821. Found: 374.0833.

Example 60:

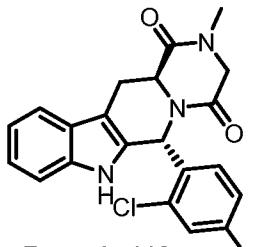
(6R-trans)-6-(2,4-dichlorophenyl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione (Formula 116)



Scheme 28

To a solution of **Formula 4** (105 mg, 0.28 mmol) in chloroform (1 mL) was added $NaHCO_3$ (28 mg, 0.34 mmol). After being stirred for 15 min, chloroacetyl chloride (30 μL, 0.34 mmol) was added. The resulting mixture was stirred for 20 hours and then purified by flash chromatography directly (silica gel, DCM/Et2O/hexane = 1 : 2 : 40) to afford the intermediate (1R,3S)-methyl 2-(2-chloroacetyl)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 142**) as a white solid (116 mg, 92 % yield).

To a one-dram vial was added (**Formula 142**) (45 mg, 0.1 mmol) and methylamine solution (2.0 mL, 33 wt. % in absolute ethanol, 16.1 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 23 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give (6R-trans)-6-(2,4-dichlorophenyl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione (**Formula 116**) (41 mg, 99 % yield).



Formula 116

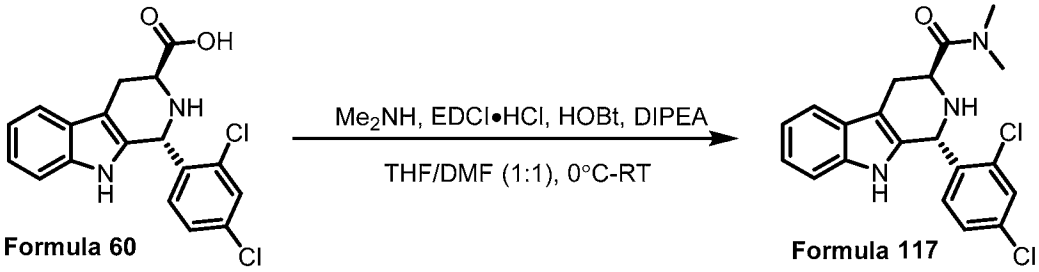
(6R-trans)-6-(2,4-dichlorophenyl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione (**Formula 116**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.34 (m, 2H), 7.13 (td, J = 6.8 and 1.2 Hz, 1H), 7.10 (s, 1H), 7.04 (td, J = 6.8 and 1.2 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 4.27 (d, J = 18.0 Hz, 1H), 4.09 (d, J = 18.0 Hz, 1H), 3.98 (dd, J = 11.6 and 4.4 Hz, 1H), 3.23 (dd, J = 15.6 and 4.4 Hz, 1H), 3.04 (dd, J = 15.6 and 11.6 Hz, 1H), 2.85 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 164.0, 136.2, 134.8, 134.2, 134.0, 132.4, 129.6, 129.5, 127.3, 125.9, 121.9, 119.0, 118.2, 111.5, 108.0, 52.4, 50.6, 48.6, 32.4, 26.1.

Example 61:

(1R,3S)-1-(2,4-dichlorophenyl)-N,N-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 117)

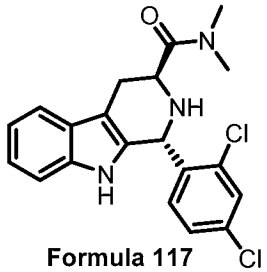


Formula 60 Formula 117

Scheme 29

To a solution of **Formula 60** (100 mg, 0.28 mmol) in THF/DMF (1 : 1, 5 mL) was added EDCI hydrochloride (69 mg, 0.36 mmol) at 0°C, the resulting mixture was stirred for 15 minutes at same temperature. A solution of dimethylamine (277μL, 2 M in methanol, 0.55 mmol) and DIPEA (96 μL, 0.55 mmol) in THF (1 mL) was added dropwise at 0°C. After being stirred for 2 hours at 0°C, the reaction mixture was warmed slowly to RT, and was stirred for 21 hours. The solvents was removed under vacuum, the residue was purified by flash chromatography (silica, DCM/EA = 10 : 1, then DCM/EA/MeOH = 100 : 7 : 1) to afford

(1R,3S)-1-(2,4-dichlorophenyl)-N,N-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 117**) (66 mg, 62 % yield.



Formula 117

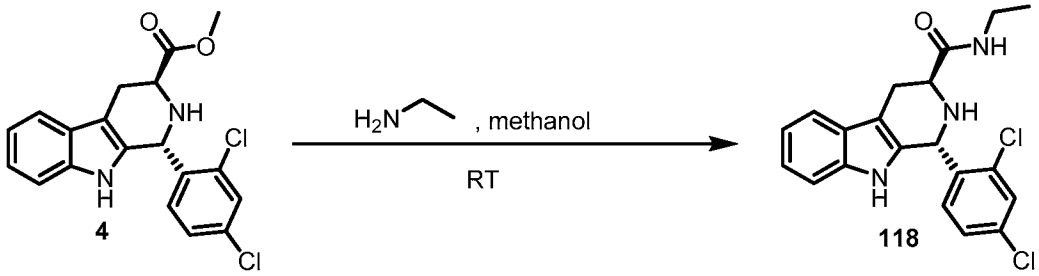
(1R,3S)-1-(2,4-dichlorophenyl)-N,N-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 117**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.28 (dd, J = 8.4 and 2.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.06 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.53 (d, J = 4.4 Hz, 1H), 3.66 (td, J = 11.2 and 5.2 Hz, 1H), 3.11 (dd, J = 11.2 and 4.0 Hz, 1H), 2.81 (m, 4H), 2.66 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 138.7, 136.1, 134.7, 132.5, 132.4, 131.3, 129.0, 126.7, 126.6, 121.1, 118.4, 117.8, 111.1, 109.5, 50.8, 47.8, 35.8, 35.1, 24.1.

Example 62:

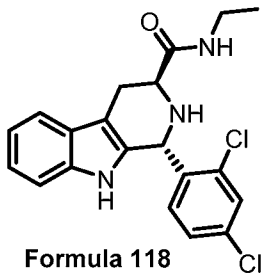
(1R,3S)-1-(2,4-dichlorophenyl)-N-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (118)



Scheme 30

To a one-dram vial was added (1R,3S)-methyl 1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 4**) (62.0 mg, 0.17 mmol) and ethylamine (2.0 mL, 2 M in methanol, 4.0 mmol). The vial was then closed tightly and the reaction mixture was stirred at room temperature for 30 hours. The reaction was

concentrated under vacuum and then purified by flash chromatography (10 : 1 DCM / EtOAc) to give **Formula 118** (58.0 mg, 90 % yield).



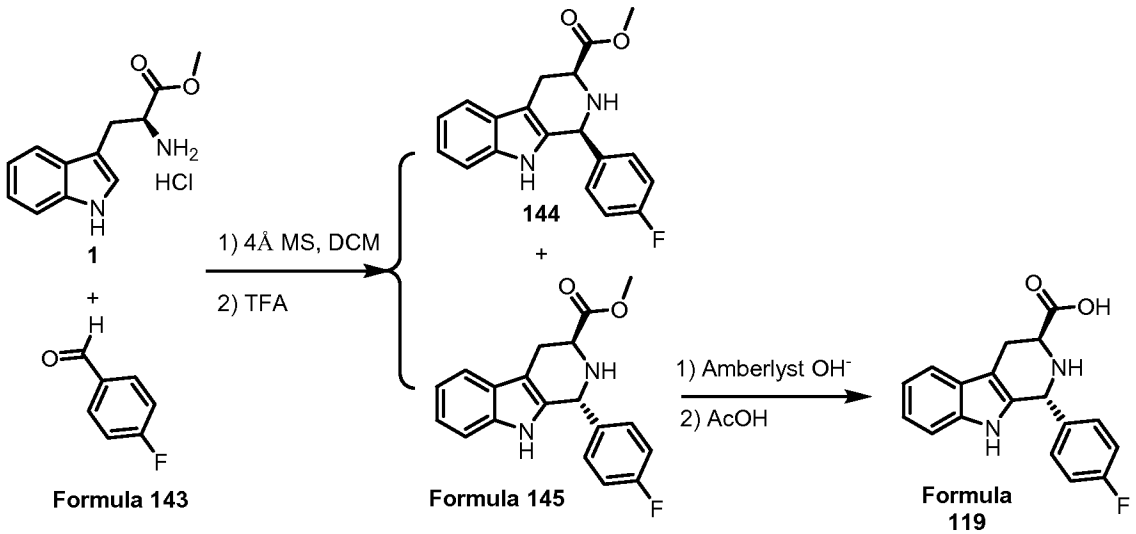
Formula 118

(1R,3S)-1-(2,4-dichlorophenyl)-N-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 118**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.79 (t, J = 4.8 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.31 (dd, J = 8.4 and 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 8.0 and 1.2 Hz, 1H), 6.99 (td, J = 7.6 and 1.2 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.56 (d, J = 4.8 Hz, 1H), 3.37 (dd, J = 9.2 and 4.4 Hz, 1H), 3.10 (m, 3H), 2.99 (dd, J = 15.2 and 4.4 Hz, 1H), 2.70 (dd, J = 15.2 and 9.2 Hz, 1H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.1, 138.9, 136.1, 134.4, 132.6, 132.5, 131.2, 129.0, 126.8, 126.5, 121.1, 118.5, 117.7, 111.1, 109.1, 51.4, 50.6, 33.3, 25.2, 14.7..

Example 63:

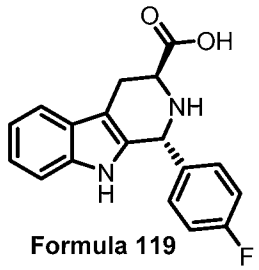
(1R,3S)-1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 119)



Scheme 31

(1S,3S)-methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 144**) and (1R,3S)-methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 145**) were prepared in 77 % and 19 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**formula 1**) and 4-fluorobenzaldehyde (**formula 143**) following the procedure employed for preparation of **formula 3** and **Formula 4**.

(1R,3S)-1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 119**) was prepared in 99 % yield from (1R,3S)-methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 145**) following the procedure employed for preparation of **Formula 60**.

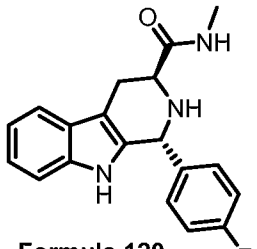


Formula 119

(1R,3S)-1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**119**) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.30 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.16 (td, J = 9.2 and 2.0 Hz, 2H), 7.05 (td, J = 7.2 and 1.2 Hz, 1H), 6.98 (td, J = 8.0 and 1.2 Hz, 1H), 5.45 (s, 1H), 3.64 (dd, J = 7.6 and 4.8 Hz, 1H), 3.09 (dd, J = 15.2 and 4.8 Hz, 1H), 2.91 (dd, J = 15.2 and 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7 (s), 161.6 (d, J = 242 Hz), 137.8 (d, J = 2 Hz), 136.2 (s), 133.1 (s), 130.5 (d, J = 8Hz), 126.4 (s), 121.0 (s), 118.4 (s), 117.8 (s), 114.9 (d, J = 21 Hz), 111.1 (s), 107.2 (s), 53.3 (s), 51.8 (s), 24.3 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -115.1 (tt, J = 9.6 and 6.0 Hz).

Example 64:

(1R,3S)-1-(4-fluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 120)



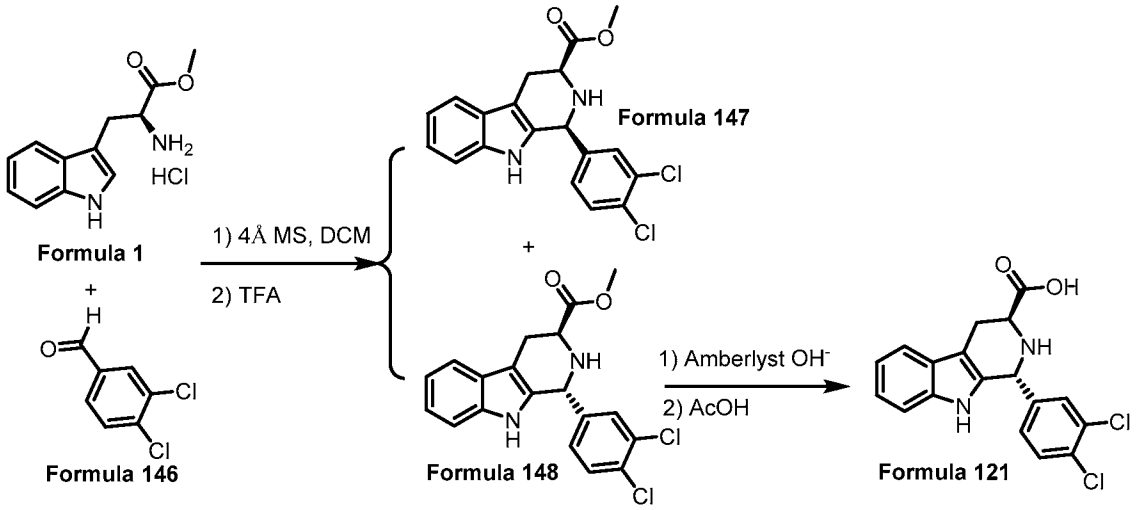
Formula 120

(1R,3S)-1-(4-fluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 120**) was prepared in 99 % yield from (1R,3S)-methyl 1-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 145**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.8 (s, 1H), 7.81 (q, J = 4.8 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.26 (m, 3H), 7.14 (tt, J = 8.8 and 2.0 Hz, 2H), 7.05 (td, J = 7.6 and 1.2 Hz, 1H), 6.97 (td, J = 7.6 and 1.2 Hz, 1H), 5.22 (s, 1H), 3.36 (dd, J = 8.4 and 4.4 Hz, 1H), 3.11 (br s, 1H), 2.94 (dd, J = 15.2 and 4.4 Hz, 1H), 2.71 (ddd, J = 15.2, 9.2 and 1.2 Hz, 1H), 2.60 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.9 (s), 161.2 (d, J = 241 Hz), 139.1 (d, J = 3 Hz), 136.0 (s), 134.3 (s), 130.1 (d, J = 8 Hz), 126.7 (s), 120.9 (s), 118.3 (s), 117.6 (s), 114.6 (d, J = 21 Hz), 111.0 (s), 108.0 (s), 53.1 (s), 51.6 (d, J = 2 Hz), 25.3 (s), 25.0 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -116.0 (tt, J = 9.6 and 6.0 Hz).

Example 65:

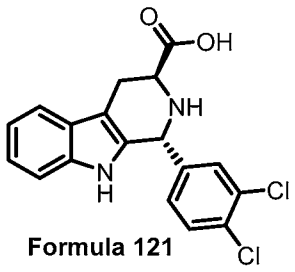
(1R,3S)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 121)



Scheme 32

(1S,3S)-methyl 1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 147**) and (1R,3S)-methyl 1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 148**) were prepared in 70 % and 23 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 3,4-dichlorobenzaldehyde (**Formula 146**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 121**) was prepared in 95 % yield from (1R,3S)-methyl 1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 148**) following the procedure employed for preparation of **Formula 60**.



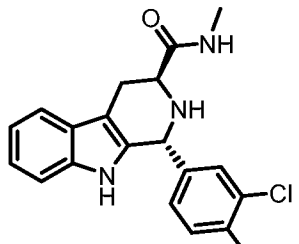
(1R,3S)-1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**121**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7. 53 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.05 (td, J = 8.0 and 1.2 Hz, 1H), 6.98

(td, J = 8.0 and 1.2 Hz, 1H), 5.40 (s, 1H), 3.68 (dd, J = 6.8 and 4.8 Hz, 1H), 3.07 (dd, J = 15.2 and 4.8 Hz, 1H), 2.90 (dd, J = 15.2 and 6.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 143.9, 136.2, 133.0, 130.8, 130.3, 130.2,129.8, 128.7, 126.4, 121.1, 118.5, 117.8, 111.1, 107.2, 53.0, 51.9, 24.4. HRMS (MALDI) $[M+H]^+$ calculated for C18H15Cl2N2O2: 361.0505. Found: 361.0483.

Example 66:

(1R,3S)-1-(3,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 122)



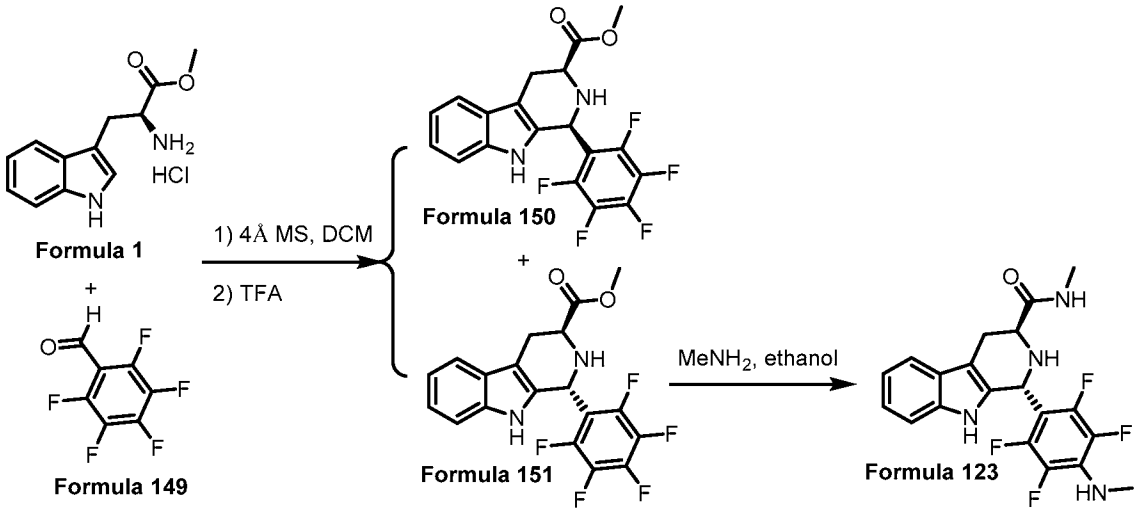
Formula 122

(1R,3S)-1-(3,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 122**) was prepared in 99 % yield from (1R,3S)-methyl 1-(3,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 148**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.8 (s, 1H), 7.85 (q, J = 4.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 6.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 8.0 and 2.0 Hz, 1H), 7.06 (td, J = 7.6 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 5.23 (s, 1H), 3.36 (dd, J = 9.2 and 4.8 Hz, 1H), 3.21 (br s, 1H), 2.93 (dd, J = 15.2 and 4.8 Hz, 1H), 2.72 (ddd, J = 15.2, 9.2 and 1.2 Hz, 1H), 2.61 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 144.2, 136.0, 133.3, 130.7, 130.2, 130.1, 129.5, 128.5, 126.6, 121.1, 118.4, 117.8, 111.1, 108.3, 52.8, 51.8, 25.5, 24.9..

Example 67:

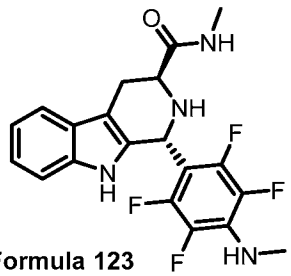
(1R,3S)-N-methyl-1-(2,3,5,6-tetrafluoro-4-(methylamino)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 123)



Scheme 33

(1S,3S)-methyl 1-(perfluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 150**) and (1R,3S)-methyl 1-(perfluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 151**) were prepared in 58 % and 41 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 2,3,4,5,6-pentafluorobenzaldehyde (**Formula 149**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-N-methyl-1-(2,3,5,6-tetrafluoro-4-(methylamino)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 123**) was prepared in 93 % yield from (1R,3S)-methyl 1-(perfluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 151**) following the procedure employed for preparation of **Formula 80**.



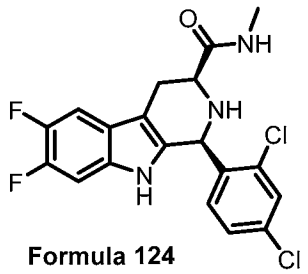
Formula 123

(1R,3S)-N-methyl-1-(2,3,5,6-tetrafluoro-4-(methylamino)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 123**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.87 (q, J = 4.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.21 (dd, J = 7.2 and 0.8 Hz, 1H), 7.02 (td, J = 7.2 and 0.8 Hz, 1H), 6.95 (td, J = 7.2 and 0.8 Hz, 1H), 5.92 (t, J = 2.4 Hz, 1H), 5.56 (s, 1H), 3.60 (dd, J = 9.2 and 4.4 Hz, 1H), 3.18 (br s, 1H), 2.94 (m, 4H), 2.74 (dd, J = 14.8 and 4.4 Hz, 1H), 2.61 (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, carbons on the tetrafluorobenzene ring were not shown) δ 173.0 (s), 135.9 (s), 133.0 (s), 126.7 (s), 120.7 (s), 118.2 (s), 117.6 (s), 110.9 (s), 107.1 (s), 53.2 (s), 44.4 (s), 31.9 (s), 25.5 (s), 24.9 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -146.0 (d, J = 16.4 Hz, 2F), -161.9 (d, J = 16.4 Hz, 2F).

Example 68:

(1S,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 124)



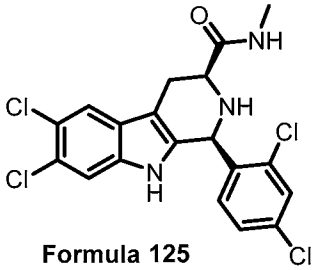
Formula 124

(1S,3S)-1-(2,4-dichlorophenyl)-6,7-difluoro-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 124**) was prepared in 95 % yield from (1S,3S)-ethyl 1-(2,4-dichlorophenyl)-6,7-difluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 47**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.79 (q, J = 4.8 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 11.2 and 8.0 Hz, 1H), 7.41 (dd, J = 8.4 and 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 11.2 and 6.8 Hz, 1H), 5.56 (d, J = 7.6 Hz, 1H), 3.62 (m, 1H), 2.98 (ddd, J = 15.2, 4.0 and 1.6 Hz, 1H), 2.71 (m, 2H), 2.63 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3 (s), 146.2 (dd, J = 235 and 16 Hz), 144.9 (dd, J = 233 and 15 Hz), 137.9 (s), 136.1 (d, J = 4 Hz), 134.3 (s), 133.0 (s), 131.9 (d, J = 9 Hz), 131.2 (d, J = 11 Hz), 128.8 (s), 127.6 (s), 121.9 (d, J = 7 Hz), 109.0 (s), 104.4 (d, J = 18 Hz), 99.0 (d, J = 21 Hz), 57.3 (s), 53.9 (s), 25.5 (s), 25.3 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -145.9 (pent, 10.0 Hz), -149.2 (ddd, J = 24.0, 12.0 and 7.6 Hz).

Example 69:

(1S,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 125)

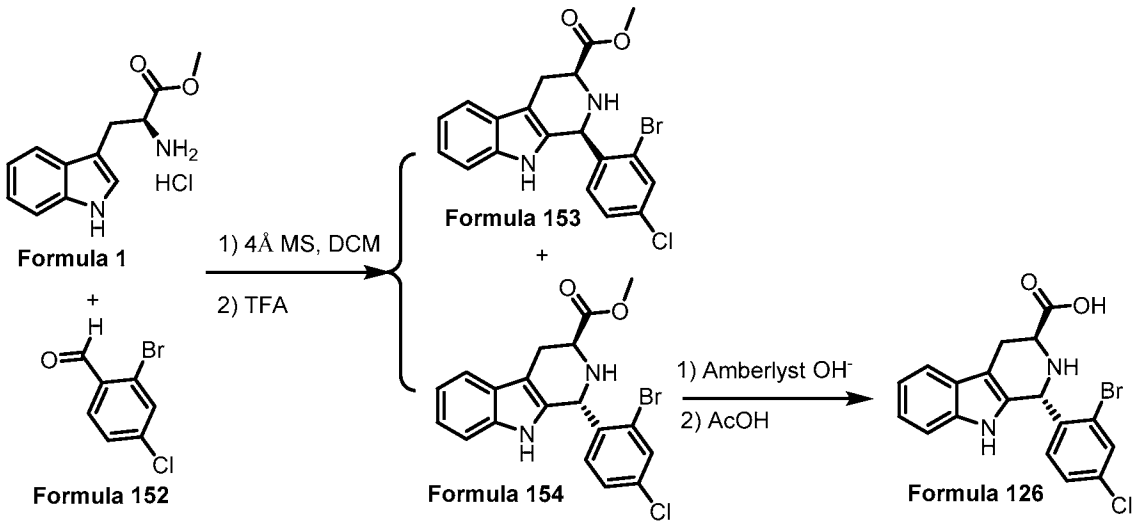


Formula 125

(1S,3S)-6,7-dichloro-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 125**) was prepared in 92 % yield from (1S,3S)-ethyl 6,7-dichloro-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 52**) following the procedure employed for preparation of **Formula 80**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.8 (s, 1H), 7.79 (q, J = 4.4 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.71 (s, 1H), 7.41 (dd, J = 8.4 and 2.4 Hz, 1H), 7.40 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 5.57 (d, J = 8.0 Hz, 1H), 3.63 (m, 1H), 3.00 (ddd, J = 15.2, 4.0 and 1.6 Hz, 1H), 2.73 (m, 2H), 2.63 (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 137.6, 137.0, 135.1, 134.3, 133.1, 131.9, 128.9, 127.7, 126.6, 122.9, 121.1, 118.9, 122.6, 108.8, 57.2, 48.6, 25.5, 25.1.

Example 70:

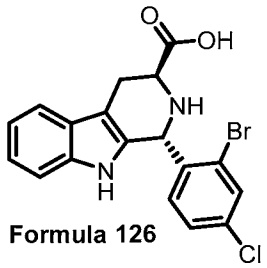
(1R,3S)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 126)



Scheme 34

(1S,3S)-methyl 1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 153**) and (1R,3S)-methyl 1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 154**) were prepared in 51 % and 42 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 2-bromo-4-chlorobenzaldehyde (**Formula 152**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 126**) was prepared in 96 % yield from (1R,3S)-methyl 1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 154**) following the procedure employed for preparation of **Formula 60**.



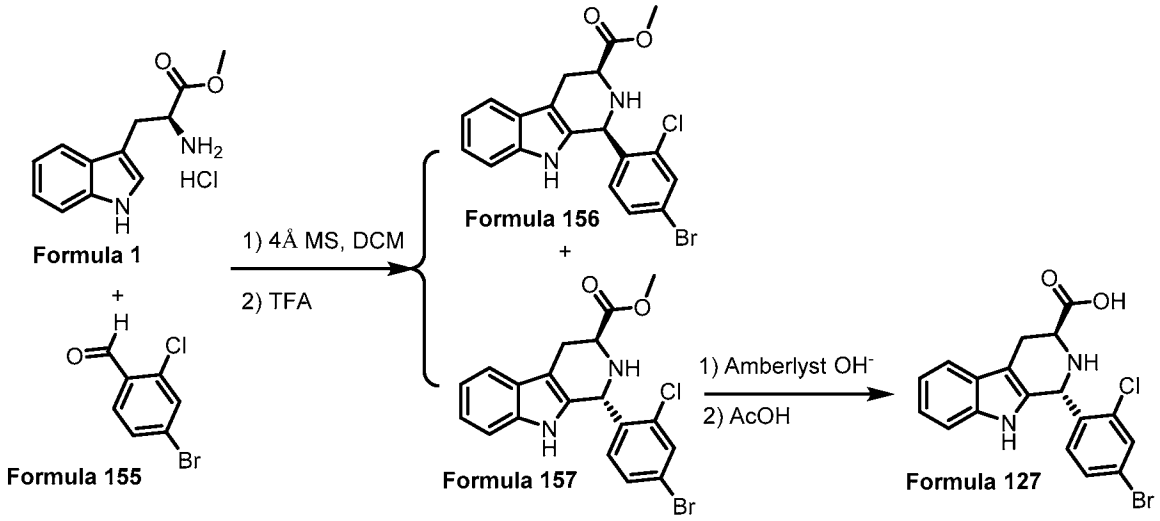
Formula 126

(1R,3S)-1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 126**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.34 (dd, J = 8.0 and 2.0 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.06 (td, J = 8.0 and 1.2 Hz, 1H), 6.99 (td, J = 7.2 and 1.2 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.67 (s, 1H), 3.57 (dd, J = 8.0 and 4.8 Hz, 1H), 3.09 (dd, J = 15.2 and 4.8 Hz, 1H), 2.85 (dd, J = 15.2 and 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 140.2, 136.2, 132.9, 123.4, 132.0, 131.5, 127.5, 126.3, 124.5, 121.2, 118.5, 117.8, 111.2, 108.3, 53.1, 51.3, 24.7. HRMS (MALDI) $[M+H]^+$ calculated for C18H15BrClN2O2: 405.0000. Found: 405.0000.

Example 71:

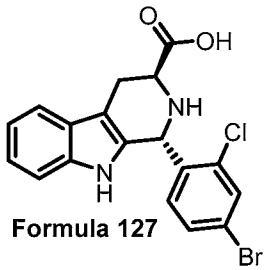
(1R,3S)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (127)



Scheme 35

(1S,3S)-methyl 1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 156**) and (1R,3S)-methyl 1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 157**) were prepared in 52 % and 37 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 4-bromo-2-chlorobenzaldehyde (**Formula 155**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 127**) was prepared in 99 % yield from (1R,3S)-methyl 1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 157**) following the procedure employed for preparation of **Formula 60**.

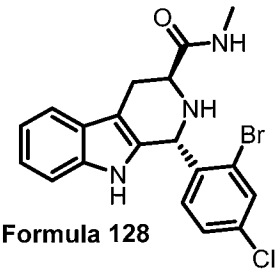


(1R,3S)-1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 127**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.4 and 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.70 (s, 1H), 3.58 (dd, J = 8.0 and 4.8 Hz, 1H), 3.08 (dd, J = 15.2 and 4.8 Hz, 1H), 2.84 (ddd, J = 15.2, 8.0 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 139.6, 136.6, 134.7, 132.7, 132.2, 132.1, 130.4, 126.8, 121.6, 121.4, 118.9, 118.2, 111.6, 108.7, 51.8, 51.1, 25.2. HRMS (MALDI) $[M+H]^+$ calculated for C18H15BrClN2O2: 405.0000. Found: 405.0000.

Example 72:

(1R,3S)-1-(2-bromo-4-chlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 128)



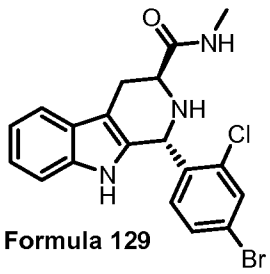
Formula 128

(1R,3S)-1-(2-bromo-4-chlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 128**) was prepared in 94 % yield from (1R,3S)-methyl 1-(2-bromo-4-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 154**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.72 (q, J = 4.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 8.4 and 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 8.0 and 1.2 Hz, 1H), 6.99 (td, J = 7.6 and 1.2 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.51 (d, J = 4.4 Hz, 1H), 3.35 (m, 1H), 3.31 (dd, J = 9.2 and 4.8 Hz, 1H), 2.99 (dd, J = 15.2 and 4.8 Hz, 1H), 2.69 (ddd, J = 15.2, 9.2 and 0.8 Hz, 1H), 2.60 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.7, 140.3, 136.1, 132.7, 132.6, 132.1, 131.2, 127.2, 126.5, 124.9, 121.1, 118.5, 117.7, 111.1, 109.1, 53.1, 51.3, 25.4, 25.1. HRMS (MALDI) $[M+H]^+$ calculated for C19H18BrClN3O: 418.0316. Found: 418.0316.

Example 73:

(1R,3S)-1-(4-bromo-2-chlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 129)



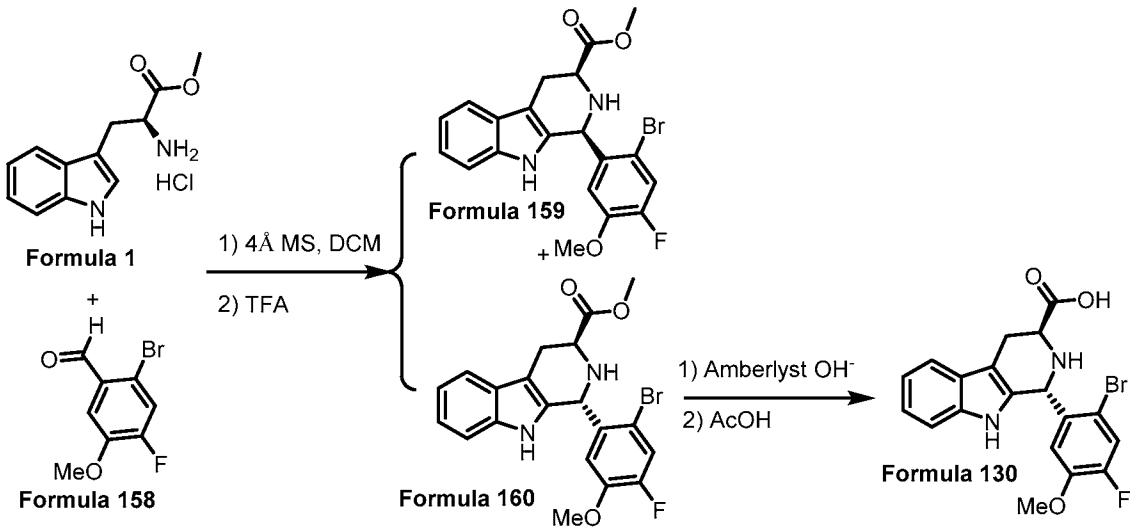
Formula 129

(1R,3S)-1-(4-bromo-2-chlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 129**) was prepared in 95 % yield from (1R,3S)-methyl 1-(4-bromo-2-chlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 157**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.72 (q, J = 4.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.4 and 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 7.6 and 0.8 Hz, 1H), 6.99 (td, J = 7.6 and 0.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.55 (d, J = 4.8 Hz, 1H), 3.35 (m, 1H), 3.10 (dd, J = 9.6 and 4.4 Hz, 1H), 2.99 (dd, J = 15.2 and 4.4 Hz, 1H), 2.68 (dd, J = 15.2 and 9.6 Hz, 1H), 2.59 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 139.2, 136.1, 134.7, 132.6, 131.7, 131.6, 129.7, 126.5, 121.1, 120.1, 118.4, 117.7, 111.1, 109.2, 51.4, 50.8, 25.4, 25.2.

Example 74:

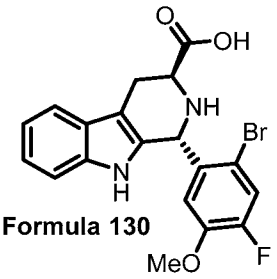
(1R,3S)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 130)



Scheme 36

(1S,3S)-methyl 1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 159**) and (1R,3S)-methyl 1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 160**) were prepared in 56 % and 30 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 2-bromo-4-fluoro-5-methoxybenzaldehyde (**Formula 158**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 130**) was prepared in 99 % yield from (1R,3S)-methyl 1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 160**) following the procedure employed for preparation of **Formula 60**.



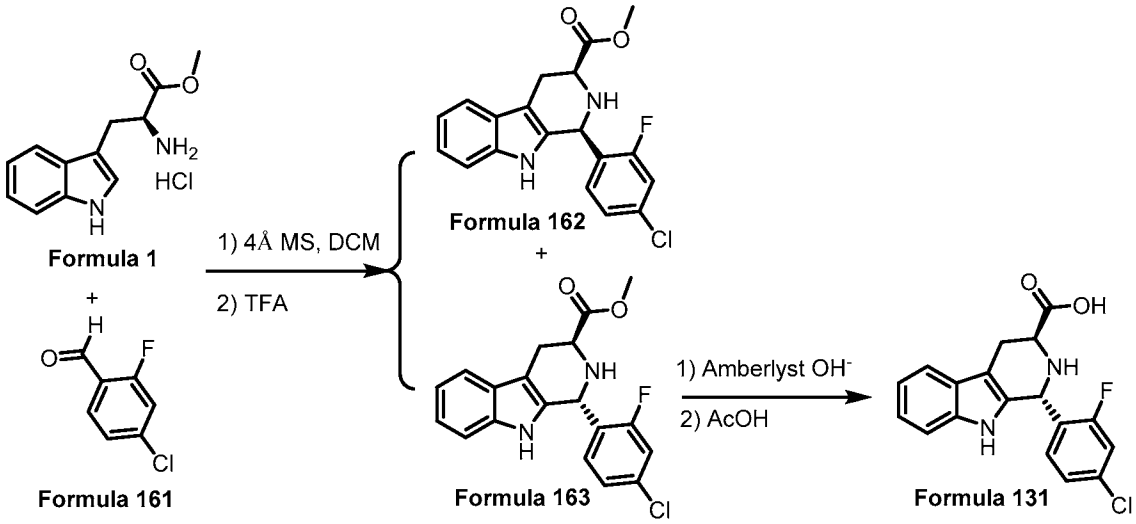
Formula 130

(1R,3S)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 130**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.05 (td, J = 6.8 and 1.2 Hz, 1H), 6.98 (td, J = 8.0 and 1.2 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 5.70 (s, 1H), 3.77 (dd, J = 7.2 and 5.2 Hz, 1H), 3.55 (s, 3H), 3.12 (ddd, J = 15.2, 5.2 and 0.8 Hz, 1H), 2.91 (ddd, J = 15.2, 7.2 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6 (s), 150.7 (d, J = 247 Hz), 146.2 (d, J = 10 Hz), 137.8 (d, J = 3 Hz), 136.3 (s), 132.7 (s), 126.3 (s), 121.1 (s), 120.1 (d, J = 21 Hz), 118.4 (s), 117.8 (s), 115.0 (s), 13.1 (d, J = 9 Hz), 111.2 (s), 107.9 (s), 56.1 (s), 53.3 (s), 51.8 (s), 24.4 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -134.0 (t, J = 10.0 Hz). HRMS (MALDI) $[M+H]^+$ calculated for C19H17BrFN2O3: 419.0401. Found: 419.0392.

Example 75:

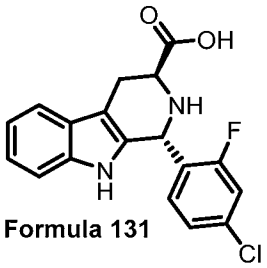
(1R,3S)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 131)



Scheme 37

(1S,3S)-methyl 1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 162**) and (1R,3S)-methyl 1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 163**) were prepared in 39 % and 47 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 4-chloro-2-fluorobenzaldehyde (**Formula 161**) following the procedure employed for preparation of **Formula 3** and **4**.

(1R,3S)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 131**) was prepared in 96 % yield from (1R,3S)-methyl 1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 163**) following the procedure employed for preparation of **Formula 60**.



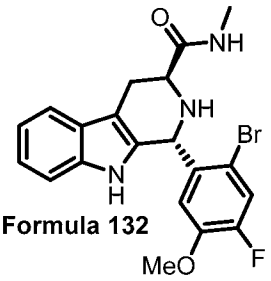
(1R,3S)-1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (131)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.49 (dd, J = 10.0 and 2.0 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 8.4 and 2.0 Hz, 1H), 7.05 (td, J = 8.0 and

1.2 Hz, 1H), 6.99 (td, J = 8.0 and 0.8 Hz, 1H), 6.89 (t, J = 8.0 Hz, 1H), 5.68 (s, 1H), 3.65 (dd, J = 8.0 and 4.8 Hz, 1H), 3.08 (dd, J = 15.2 and 4.8 Hz, 1H), 2.87 (ddd, J = 15.2, 8.0 and 0.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4 (s), 160.3 (d, J = 248 Hz), 136.2 (s), 132.8 (d, J = 10 Hz), 132.2 (s), 131.4 (d, J = 5 Hz), 128.7 (d, J = 14 Hz), 126.4 (s), 124.3 (d, J = 3 Hz), 121.1 (s), 118.5 (s), 117.8 (s), 116.0 (d, J = 26 Hz), 111.1 (s), 107.9 (s), 51.8 (s), 46.9 (d, J = 3 Hz), 24.6 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -116.2 (t, J = 9.0 Hz).

Example 76:

(1R,3S)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 132)

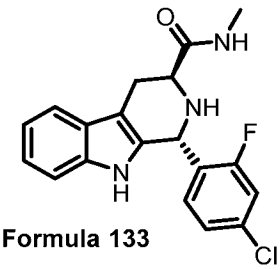


Formula 132

(1R,3S)-1-(2-bromo-4-fluoro-5-methoxyphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 132**) was prepared in 94 % yield from (1R,3S)-methyl 1-(2-bromo-4-fluoro-5-methoxyphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 160**) following the procedure employed for preparation of **Formula 80**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.74 (q, J = 4.8 Hz, 1H), 7.66 (d, J = 10.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.05 (td, J = 7.6 and 0.8 Hz, 1H), 6.98 (td, J = 7.6 and 0.8 Hz, 1H), 6.45 (d, J = 8.8 Hz, 1H), 5.49 (d, J = 5.6 Hz, 1H), 3.53 (s, 3H), 3.51 (m, 1H), 3.08 (dd, J = 9.2 and 4.4 Hz, 1H), 3.02 (dd, J = 15.2 and 4.4 Hz, 1H), 2.76 (dd, J = 15.2 and 9.2 Hz, 1H), 2.62 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8 (s), 150.6 (d, J = 247 Hz), 146.0 (d, J = 10 Hz), 137.9 (d, J = 4 Hz), 136.2 (s), 132.9 (s), 126.5 (s), 121.1 (s), 120.2 (d, J = 21 Hz), 118.4 (s), 117.8 (s), 115.1 (d, J = 2 Hz), 113.6 (d, J = 8 Hz), 111.1 (s), 109.0 (s), 56.2 (s), 53.3 (s), 51.8 (s), 25.4 (s), 24.8 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -134.4 (t, J = 10.5 Hz).

Example 77:

(1R,3S)-1-(4-chloro-2-fluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (133)



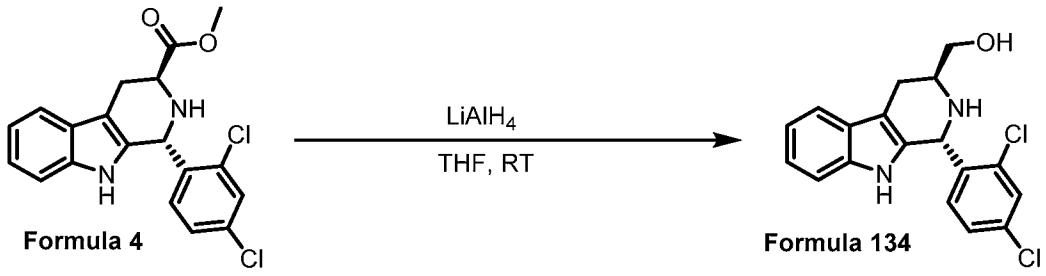
Formula 133

(1R,3S)-1-(4-chloro-2-fluorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 133**) was prepared in 99 % yield from (1R,3S)-methyl 1-(4-chloro-2-fluorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 163**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.74 (q, J = 4.4 Hz, 1H), 7.48 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.4 and 2.0 Hz, 1H), 7.05 (td, J = 7.2 and 1.2 Hz, 1H), 6.99 (td, J = 8.0 and 1.2 Hz, 1H), 6.73 (t, J = 8.4 Hz, 1H), 5.52 (d, J = 4.8 Hz, 1H), 3.39 (m, 1H), 3.12 (dd, J = 10.4 and 4.8 Hz, 1H), 2.99 (dd, J = 15.2 and 4.8 Hz, 1H), 2.67 (ddd, J = 15.2, 10.4 and 1.2 Hz, 1H), 2.59 (d, J = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8 (s), 160.2 (d, J = 249 Hz), 136.1 (s), 132.6 (d, J = 11 Hz), 132.4 (s), 131.2 (d, J = 5 Hz), 129.1 (d, J = 14 Hz), 126.5 (s), 124.0 (d, J = 3 Hz), 121.1 (s), 118.4 (s), 117.7 (s), 116.0 (d, J = 25 Hz), 111.1 (s), 109.0 (s), 51.6 (s), 47.3 (d, J = 2 Hz), 25.4 (s), 25.1 (s). ^{19}F NMR (376 MHz, DMSO-d_6) δ -115.3 (t, J = 9.4 Hz).

Example 78:

((1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)methanol (Formula 134)

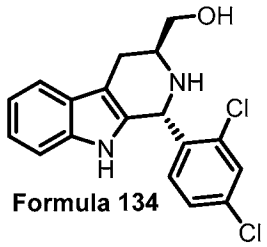


Formula 4 Formula 134

Scheme 38

To a suspension of $LiAlH_4$ (5.7 mg, 0.15 mmol) in dry THF (1 mL) was added a solution of **Formula 4** (25 mg, 0.066 mmol) in dry THF (1 mL) at RT. The resulting reaction mixture was stirred for 80 minutes at RT. The reaction was quenched with H_2O/THF (0.2 mL

H_2O and 1 mL THF). The mixture was condensed to dry and purified by flash chromatography (silica gel, DCM/MeOH = 10 : 1) to afford ((1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)methanol (**Formula 134**) (17 mg, 75% yield).



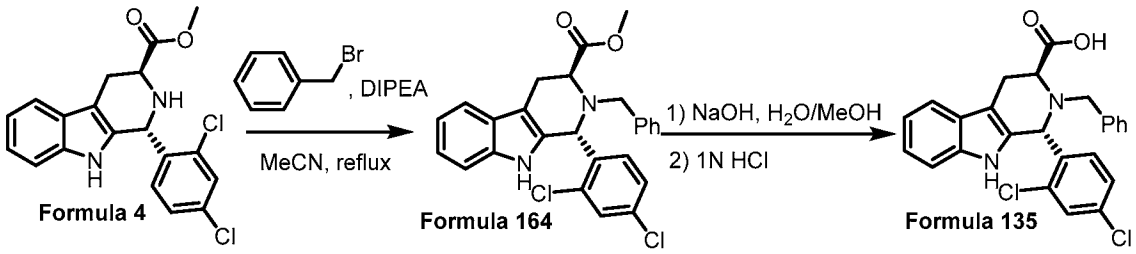
Formula 134

((1R,3S)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)methanol (Formula 134)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.15 (m, 2H), 7.05 (dd, J = 8.0 and 2.0 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.59 (s, 1H), 3.71 (dd, J = 10.8 and 4.0 Hz, 1H), 3.52 (dd, J = 10.8 and 8.4 Hz, 1H), 3.07 (hep, d = 2.0 Hz, 1H), 2.82 (dd, J = 15.2 and 4.0 Hz, 1H), 2.52 (dd, J = 15.2 and 10.4 Hz, 1H), 2.43 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 136.3, 134.6, 134.3, 131.7, 130.9, 129.8, 126.9, 126.7, 122.3, 119.7, 118.3, 111.0, 110.8, 65.4, 51.5, 50.0, 24.2.

Example 79:

(1R,3S)-2-benzyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 135)



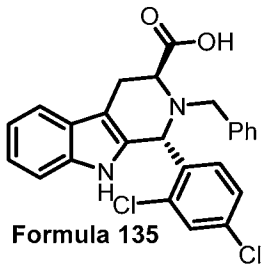
Formula 4 **Formula 164** **Formula 135**

Scheme 39

To a solution of **Formula 4** (194 mg, 0.52 mmol) and benzyl bromide (74 μL, 0.62 mmol) in dry acetonitrile (5 mL) was added DIPEA (135 μL, 0.78 mmol) at RT. The resulting reaction solution was reflux for 6 hours, and then concentrated. The residue was added 5 mL water and extracted with ethyl acetate (80 mL). The organic layer was washed with brine

(10 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (10 : 1 hexane / EtOAc) to give **Formula 164** (238 mg, 99 % yield).

To a solution of **Formula 164** (73 mg, 0.16 mmol) in methanol (1 mL) was added an aqueous solution of NaOH (31 mg, 0.8 mmol, in 1 mL H_2O) dropwise at 0 °C. The resulting reaction mixture was stirred at RT for 45 hours. The solvents were removed under vacuum. 5 mL of water was added to the residue. The resulting solution was adjusted with 1 N HCl aqueous solution to pH = 1. After being stirred for 30 minutes, the precipitate was filtered, washed with water to afford (1R,3S)-2-benzyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 135**) (38 mg, 52 % yield).



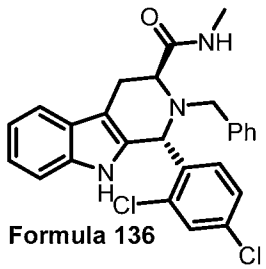
Formula 135

(1R,3S)-2-benzyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 135**)

^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.24 (m, 7H), 7.02 (td, J = 7.2 and 1.2 Hz, 1H), 6.97 (td, J = 7.2 and 0.8 Hz, 1H), 6.13 (s, 1H), 4.05 (d, J = 13.6 Hz, 1H), 3.85 (dd, J = 6.0 and 3.2 Hz, 1H), 3.73 (d, J = 13.6 Hz, 1H), 3.24 (dd, J = 15.2 and 2.0 Hz, 1H), 3.16 (ddd, J = 15.2, 6.0 and 1.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.4, 140.3, 140.2, 138.6, 136.8, 135.0, 133.9, 129.9, 129.8, 129.4, 128.7, 128.3, 127.9, 122.3, 119.8, 118.6, 112.0, 107.3, 57.9, 57.7, 55.8, 25.7.

Example 80:

(1R,3S)-2-benzyl-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 136)



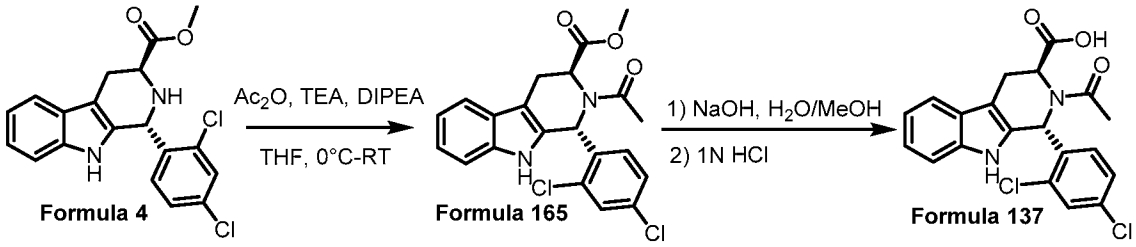
Formula 136

(1R,3S)-2-benzyl-1-(2,4-dichlorophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 136**) was prepared in 81 % yield from (1R,3S)-methyl 2-benzyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 164**) following the procedure employed for preparation of **Formula 80**, except for the reaction time was 41 hours.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.68 (dd, J = 8.4 and 1.6 Hz, 1H), 7.33 (m, 4H), 7.22 (m, 5H), 7.04 (dd, J = 8.4 and 1.6 Hz, 1H), 6.79 (q, J = 4.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 5.38 (s, 1H), 3.79 (d, J = 12.8 Hz, 1H), 3.75 (dd, J = 10.0 and 6.0 Hz, 1H), 3.21 (m, 2H), 2.85 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 137.5, 136.6, 135.3, 134.5, 132.2, 130.5, 130.0, 128.2, 127.7, 126.9, 126.7, 122.5, 120.0, 118.8, 111.1, 110.6, 56.5, 55.9, 53.1, 25.9, 18.5.

Example: 81

(1R,3S)-2-acetyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 137)

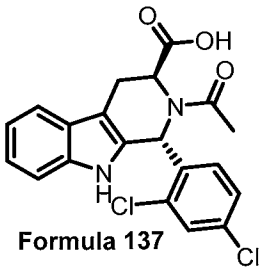


Scheme 40

To a solution of **Formula 4** (188 mg, 0.5 mmol) in dry THF (10 mL) was added Ac_2O (56 μL, 0.55 mmol) at 0°C. After being stirred for 10 min at the same temperature, TEA (76 μL, 0.55 mmol) was added. The resulting reaction mixture was stirred for 24 hours at RT, and then DIPEA (96 μL, 0.55 mmol) was added. The reaction mixture was further stirred for 48 hours and then concentrated. The residue was added 5 mL water and extracted with ethyl acetate (80 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 (10 g), concentrated, then purified by flash chromatography (5: 5 : 1 hexane / DCM / EtOAc) to give **Formula 165** (166 mg, 80 % yield).

(1R,3S)-2-acetyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 137**) was prepared in 80 % yield from (1R,3S)-methyl 2-acetyl-1-

(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 165**) following the procedure employed for preparation of **Formula 135**.



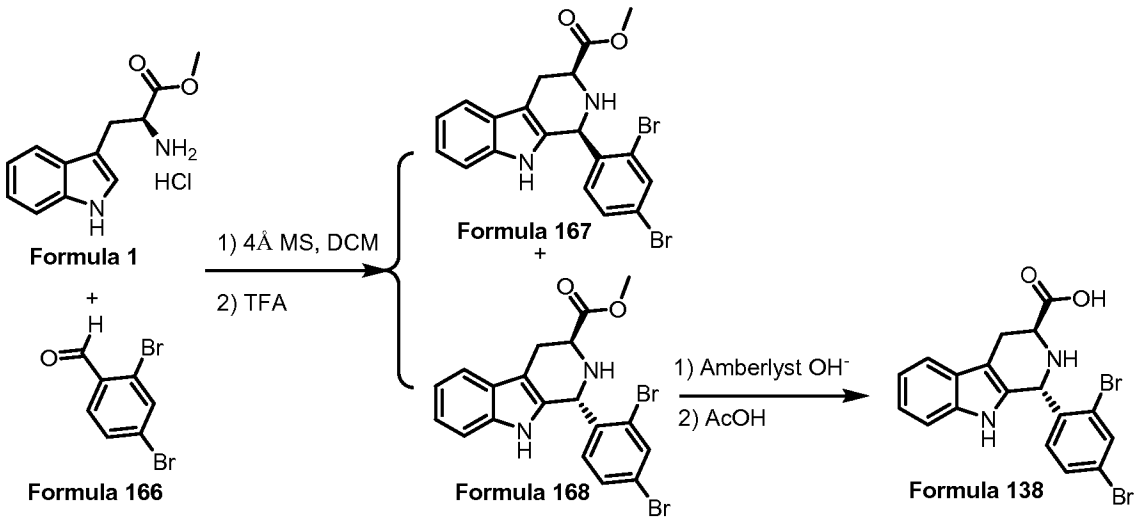
Formula 137

(1R,3S)-2-acetyl-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 137)

^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (m, 2H), 7.26 (m, 2H), 7.05 (m, 3H), 6.58 (s, 0.3H), 6.51 (s, 0.7H), 5.28 (dd, J = 5.2 and 2.0 Hz, 1H), 3.69 (dd, J = 15.2 and 1.2 Hz, 0.7H), 3.50 (m, 1.3H), 2.17 (s, 2.1H), 2.05 (s, 0.9H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.9, 175.3, 174.7, 174.6, 142.0, 140.1, 138.7, 138.6, 135.5, 134.4, 134.3, 134.1, 133.6, 133.3, 131.1, 130.7, 129.9, 129.4, 128.5, 127.4, 127.3, 123.2, 122.9, 120.5, 120.3, 118.9, 118.9, 118.8, 112.5, 112.4, 107.7, 106.0, 59.3, 56.4, 55.7, 54.5, 24.7, 23.6, 22.9, 22.5.

Example 82:

(1R,3S)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 138)

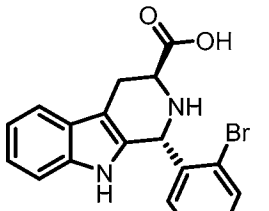


Formula 1 + **Formula 166** → **Formula 167** + **Formula 168** → **Formula 138**

Scheme 41

(1S,3S)-methyl 1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 167**) and (1R,3S)-methyl 1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 168**) were prepared in 60 % and 38 % yields, respectively, from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 2,4-dibromobenzaldehyde (**Formula 166**) following the procedure employed for preparation of **Formula 3** and **Formula 4**.

(1R,3S)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 138**) was prepared in 95 % yield from (1R,3S)-methyl 1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 168**) following the procedure employed for preparation of **Formula 60**.



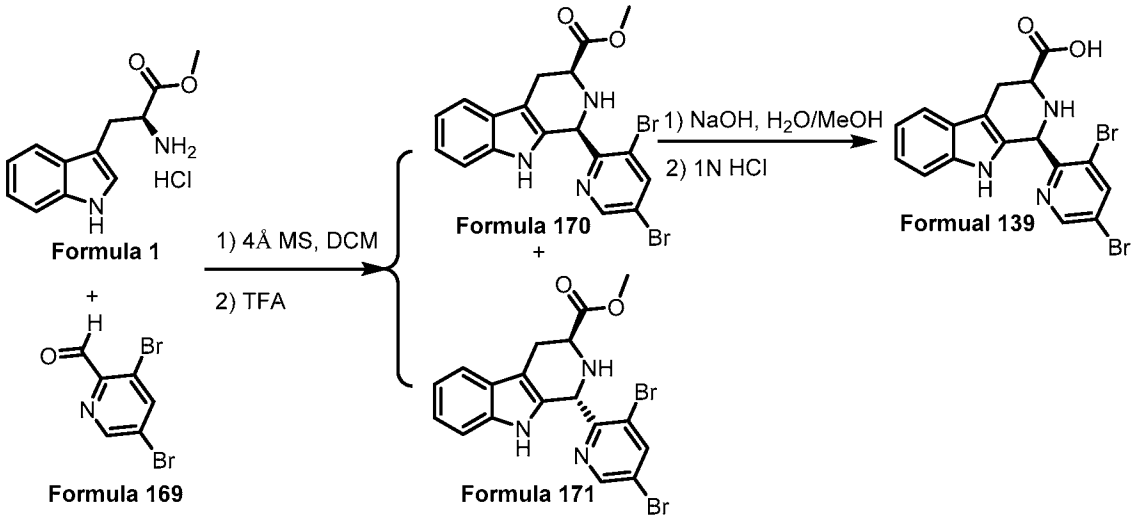
Formula 138

(1R,3S)-1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 138)

^{1}H NMR (100 MHz, CD_3OD) δ 8.00 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.0, 1H), 7.52 (dd, J = 8.4 and 2.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.15 (td, J = 7.2 and 1.2 Hz, 1H), 7.07 (td, J = 7.2 and 1.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.37 (s, 1H), 3.96 (dd, J = 8.4 and 5.6 Hz, 1H), 3.47 (dd, J = 16.0 and 5.6 Hz, 1H), 3.22 (dd, J = 16.0 and 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.6, 138.7, 136.9, 135.5, 133.9, 132.6, 127.8, 127.4, 127.2, 125.6, 123.8, 120.6, 119.3, 112.4, 109.7, 55.2, 54.9, 24.0.

Example 83

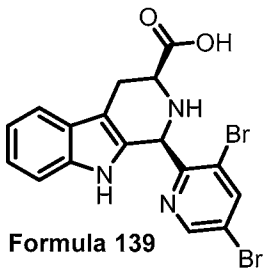
(1R,3S)-1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 139)



Scheme 42

(1R,3S)-methyl 1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 170**) and (1S,3S)-methyl 1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 171**) were prepared from L-Tryptophan methyl ester hydrochloride (**Formula 1**) and 3,5-Dibromopyridine-2-carboxaldehyde (**Formula 169**) following the procedure employed for preparation of **Formula 3** and **Formula 4**. However, only some of the crystalline (1R,3S)-methyl 1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 170**) was successfully isolated by recrystallization from DCM/hexane in 13 % yield.

To a solution of **Formula 170** (50 mg, 0.11 mmol) in methanol (4 mL) and was added an aqueous solution of NaOH (28 mg, 0.7 mmol, in 1 mL H_2O) dropwise at 0 °C. The resulting reaction mixture was stirred at RT for 20 hours. The solvents were removed under vacuum. 5 mL of water was added to the residue. The resulting solution was adjusted with 0.7 mL of 1 N HCl aqueous solution to pH = 2-3. After being stirred for 30 minutes, the precipitate was filtered, washed with cold water to afford (1R,3S)-1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (**Formula 139**) (48 mg, 99 % yield).



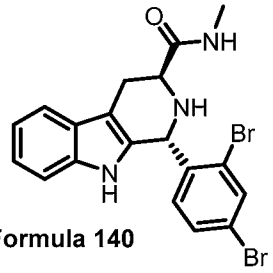
Formula 139

(1R,3S)-1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid (Formula 139)

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.4 (s, 1H), 8.69 (d, J = 0.8 Hz, 1H), 8.61 (d, J = 0.8 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 5.83 (s, 1H), 3.98 (dd, J = 6.0 and 2.4 Hz, 1H), 3.08 (dd, J = 15.2 and 2.8 Hz, 1H), 2.81 (dd, J = 15.2 and 9.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 149.1, 142.8, 136.2, 126.3, 121.6, 121.1, 119.5, 118.6, 117.7, 113.9, 111.2, 109.5, 107.5, 56.0, 55.6, 25.2.

Example 84:

(1R,3S)-1-(2,4-dibromophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 140)



Formula 140

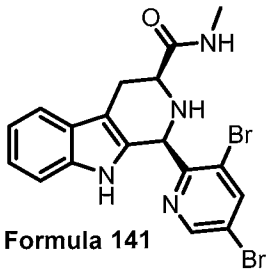
(1R,3S)-1-(2,4-dibromophenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 140**) was prepared in 85 % yield from (1R,3S)-methyl 1-(2,4-dibromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 168**) following the procedure employed for preparation of **80**.

^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 8.4 and 2.0 Hz, 1H), 7.24 (dd, J = 7.6 and 1.2 Hz, 1H), 7.09 (td, J = 7.2 and 1.2 Hz, 1H), 7.02 (td, J = 7.6 and 1.2 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.67 (s, 1H), 3.52 (dd, J = 10.4 and 4.4 Hz, 1H), 3.17 (dd, J = 15.2 and 4.4 Hz, 1H), 2.85 (ddd, J = 15.2, 10.4 and 1.2 Hz,

1H), 2.75 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.8, 141.1, 138.3, 136.6, 132.8, 131.4, 128.0, 126.5, 123.1, 122.8, 120.0, 118.8, 112.1, 110.7, 55.3, 53.2, 26.3, 26.2.

Example 85:

(1R,3S)-1-(3,5-dibromopyridin-2-yl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (Formula 141)



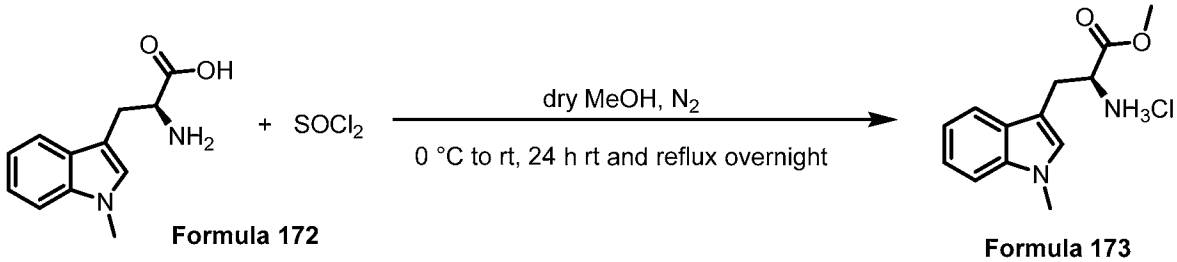
Formula 141

(1R,3S)-1-(3,5-dibromopyridin-2-yl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (**Formula 141**) was prepared in 77 % yield from (1R,3S)-methyl 1-(3,5-dibromopyridin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 170**) following the procedure employed for preparation of **Formula 80**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (s, 1H), 8.68 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.0 Hz, 1H), 7.94 (q, J = 4.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.2 and 1.2 Hz, 1H), 6.95 (td, J = 7.6 and 1.2 Hz, 1H), 5.76 (d, J = 8.0 Hz, 1H), 3.72 (m, 1H), 2.98 (dd, J = 15.2 and 4.0 Hz, 1H), 2.71 (ddd, J = 15.2, 11.2 and 2.4 Hz, 1H), 2.64 (d, J = 4.4 Hz, 3H), 2.45 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 156.1, 149.2, 142.7, 136.1, 133.8, 126.6, 121.6, 121.0, 119.3, 118.5, 117.6, 111.2, 108.1, 56.6, 56.3, 25.4, 25.3.

Example 86:

methyl 1-methyl-*L*-tryptophanate hydrochloride (Formula 173)



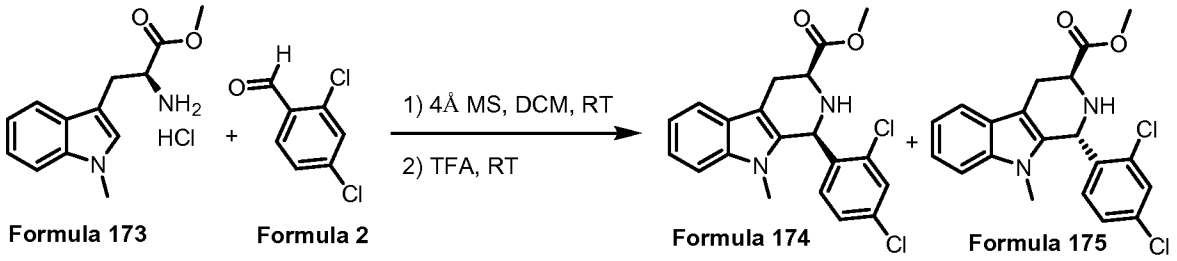
Formula 172 Formula 173

Scheme 43

To methyl 1-methyl-*L*-tryptophan (0.6 g, 2.75 mmol) was added dry MeOH (8 mL) under nitrogen atmosphere. $SOCl_2$ (0.4 mL, 5.5 mmol) was then added dropwise in an ice bath and the solution was stirred at 0 °C for 1 hour and then warmed up to room temperature and continued to stir for 24 hours. After completion of the reaction MeOH was evaporated and Et_2O (15 mL) was added and the mixture was stirred for 20 mins and filtered and washed with cold Et_2O to yield methyl 1-methyl-*L*-tryptophanate hydrochloride (0.7 g, 95%). ^1H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.13 – 7.07 (m, 1H), 4.32 (dd, *J* = 7.1, 5.6 Hz, 1H), 3.80 – 3.79 (s, 6H), 3.44 (dd, *J* = 15.2, 5.4 Hz, 1H), 3.35 (dd, *J* = 15.3, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.20, 146.13, 138.77, 136.69, 130.81, 128.27, 127.70, 119.29, 115.05, 62.19, 62.14, 41.92, 35.39. HRMS (ESI) $[M+H]^+$ calculated for $C_{13}H_{16}N_2O_2$: 233.1285. Found: 233.1272

Example 87:

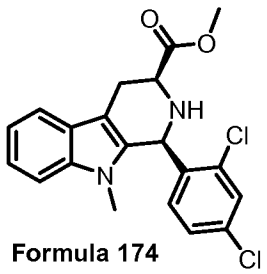
methyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 174) and methyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 175)



Formula 173 Formula 2 Formula 174 Formula 175

Scheme 44

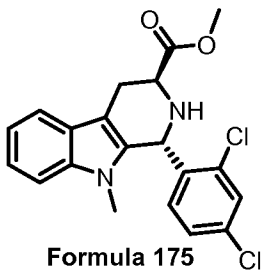
To methyl 1-methyl-*L*-tryptophanate hydrochloride (**Formula 173**), (0.693 g, 2.98 mmol) 2,4-dichlorobenzaldehyde (**Formula 2**) (0.52 g, 2.6 mmol) and 4Å molecular sieve (1.4 g, powder form) DCM/MeOH (4:1.5 mL) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 32 hours at room temperature. TFA (0.46 mL, 5.97 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 72 hours. An aqueous solution of $NaHCO_3$ (0.75 g, 8.94 mmol, in 6 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (12 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ (1 g), concentrated, then purified by flash chromatography (5 : 5 : 0.1 hexane / DCM / THF) to give **Formula 174** (0.107 g, 10 % yield) and **Formula 175** (0.27 g, 26 % yield) and **Formula 173** (0.2 g, 29%) was obtained back.



Formula 174

methyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 174)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.09 (ddd, *J* = 8.0, 6.6, 1.5 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.77 (s, 1H), 3.86 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.72 (s, 3H), 3.21 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.14 (s, 3H), 3.00 (ddd, *J* = 15.1, 10.2, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.63, 138.09, 137.77, 135.16, 134.87, 134.11, 131.57, 129.96, 128.50, 126.75, 122.35, 119.80, 118.58, 109.77, 109.44, 56.37, 53.53, 52.59, 30.61, 25.95.



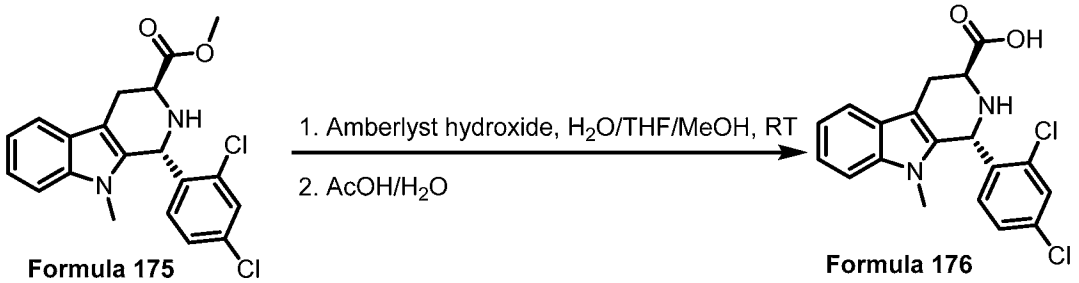
Formula 175

methyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 175)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 9.5 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.27 (m, 2H), 7.17 (ddd, *J* = 8.0, 6.5, 1.7 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 5.80 (s, 1H), 3.76 (s, 3H), 3.70 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.28 (s, 3H), 3.28 (dd, *J* = 15.2, 4.6 Hz, 1H), 3.01 (dd, *J* = 16.3, 10.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.47, 137.46, 136.92, 134.58, 134.43, 132.84, 130.72, 130.21, 127.01, 126.49, 121.97, 119.46, 118.48, 109.18, 109.14, 52.37, 51.23, 51.10, 29.71, 25.52.

Example 88:

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (176)



Formula 175 **Formula 176**

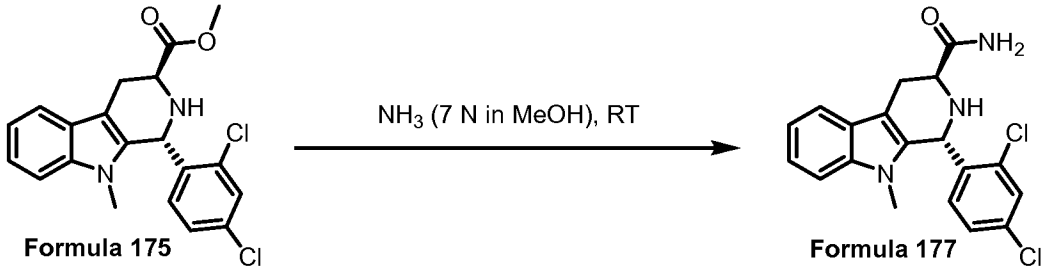
Scheme 45

To a solution of **Formula 175** (39.0 mg, 0.1 mmol) in THF / MeOH / H_2O (1 mL / 1 mL / 1 mL) was added Amberlyst hydroxide resin (0.63 g, 2.65 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 20 hours, the resin was filtered and washed with MeOH and DCM alternatively (4 × 1 mL). An aqueous solution of AcOH (50%) (2 mL) was added to cleave the product from the resin, the cleaving solution was collected by filtration. The cleavage step was repeated for other 4 times. The combined cleaving solutions were condensed under vacuum. The residue was added MeOH (0.15 mL), followed by addition of Et_2O (1.5 mL) and hexane (4.5 mL). The mixture was stirred for 30 mins and then filtered. The solid was washed with hexane to afford (1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**Formula 176**) (30 mg, 80 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 2.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.31 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.86

(d, *J* = 8.4 Hz, 1H), 6.21 (s, 1H), 3.81 (bs, 1H), 3.44 (d, *J* = 15.4 Hz, 1H), 3.19 (s, 3H), 3.07 (t= 15.5 Hz, 1H).^{13}C NMR (126 MHz, CD_3OD) δ 174.85, 139.40, 137.49, 136.55, 133.82, 133.20, 131.27, 129.96, 129.11, 127.10, 123.76, 120.78, 119.57, 110.26, 109.72, 53.79, 51.81, 29.83, 24.78.

Example 89:

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (Formula 177)



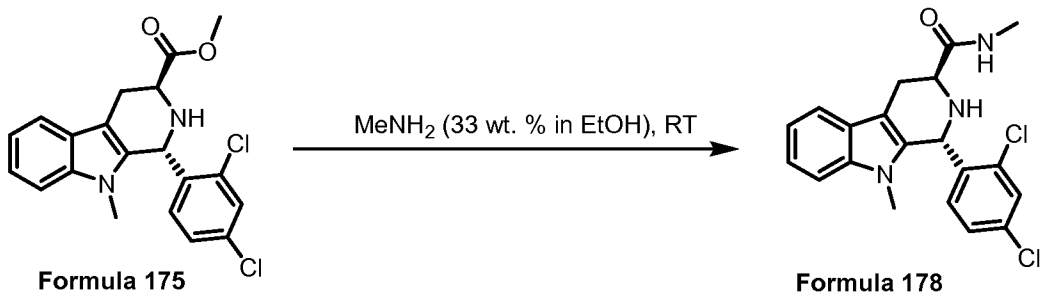
Formula 175 Formula 177

Scheme 46

To a round bottom flask was added (**175**) (39.0 mg, 0.1 mmol) and ammonia solution in methanol (3.4 mL, 7 N, 23.8 mmol). The solution was stirred at room temperature for 24 hours. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 0.1 DCM / MeOH) to give **177 (**37 mg, 99 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.18 (td, *J* = 5.7, 0.7 Hz, 2H), 7.08 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 5.76 (s, 1H), 3.54 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.25 (s, 3H), 3.24 (dd, *J* = 15, 4.5 Hz, 1H), 2.85 (dd, *J* = 14.3, 11.0 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 177.85, 138.98, 137.98, 136.09, 135.70, 133.96, 132.27, 131.06, 128.13, 127.77, 122.96, 120.28, 119.08, 110.41, 110.04, 52.52, 52.02, 32.75, 26.43.

Example 90:

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-*N*,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (Formula 178)



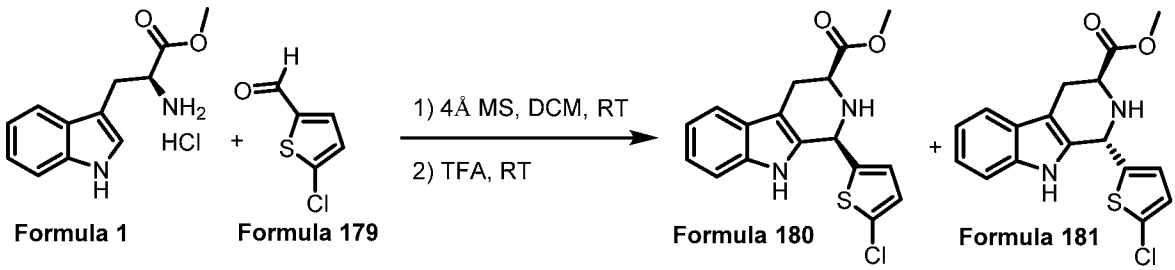
Formula 175 Formula 178

Scheme 47

To a round bottom flask was added (**Formula 175**) (39.0 mg, 0.1 mmol) and methylamine solution (2.12 mL, 33 wt. % in absolute ethanol, 16.7 mmol). The vial was then closed tightly and the solution was stirred at room temperature for 4 days. The reaction was concentrated under vacuum and then purified by flash chromatography (10 : 0.1 DCM / MeOH) to give **Formula 178 (**36 mg, 95 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 – 7.08 (m, 2H), 6.62 (d, *J* = 8.3 Hz, 1H), 5.69 (s, 1H), 3.48 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.28 (dd, *J* = 6.4, 4.5 Hz, 1H), 3.26 (s, 3H), 2.88 – 2.82 (m, 1H), 2.79 (s, 3H), 2.77 (dd, *J* = 27.8, 3.9 Hz, 1H).^{13}C NMR (101 MHz, CD_3OD) δ 174.97, 138.08, 137.03, 135.39, 135.20, 133.52, 131.53, 130.68, 127.42, 127.04, 122.50, 119.86, 118.77, 110.06, 109.58, 52.22, 51.58, 29.79, 26.18, 25.81.

Example 91:

methyl (1*R*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (180) and methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (181)

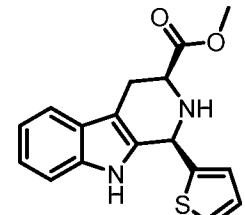


Formula 1 Formula 179 Formula 180 Formula 181

Scheme 48

To of L-Tryptophan methyl ester hydrochloride (**Formula 1**), (1.25 g, 5 mmol), 4Å molecular sieve (2.5 g, powder form) in DCM (15 mL), 5-chlorothiophene-2-carbaldehyde

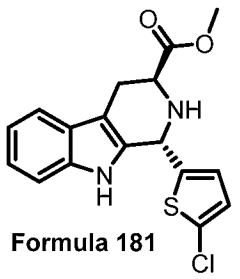
(**Formula 179**) (0.53 mL, 5 mmol) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 6 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ (2 g), concentrated, then purified by flash chromatography (5 : 5 : 0.6 hexane / DCM / EtOAc) to give **Formula 180** (0.134 g, 8 % yield) and **Formula 175** (1.04 g, 60 % yield) and **Formula 181** (0.52 g, 30%).



Formula 180

methyl (1*R*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 180)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.20 – 7.10 (m, 2H), 6.95 (d, *J* = 3.7 Hz, 1H), 6.82 (d, *J* = 3.8 Hz, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 3.92 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.83 (s, 3H), 3.20 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 2.98 (ddd, *J* = 15.1, 11.2, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.75, 144.61, 136.32, 131.82, 129.70, 126.26, 125.45, 125.21, 121.70, 118.89, 117.85, 111.00, 109.86, 107.16, 51.96, 51.75, 50.64, 24.61.



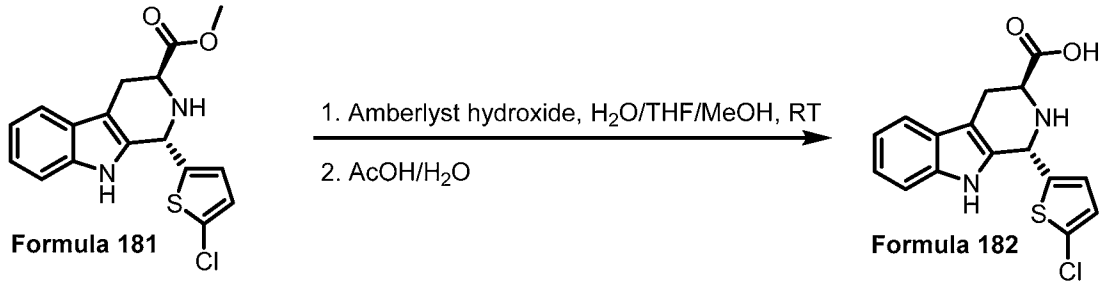
Formula 181

methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 181)

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.9, 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.75 (dd, *J* = 15.4, 5.0 Hz, 2H), 5.55 (s, 1H), 4.01 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.78 (dd, *J* = 15.1, 9.1 Hz, 3H), 3.23 (dd, *J* = 15.4, 5.0 Hz, 1H), 2.99 (dd, *J* = 15.6, 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CD_3OD/CDCl_3$) δ 173.75, 144.61, 136.32, 131.82, 129.70, 126.26, 125.45, 125.21, 121.70, 118.89, 117.85, 111.00, 109.86, 107.16, 51.96, 51.75, 50.64, 24.61.

Example 92:

(1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (182)



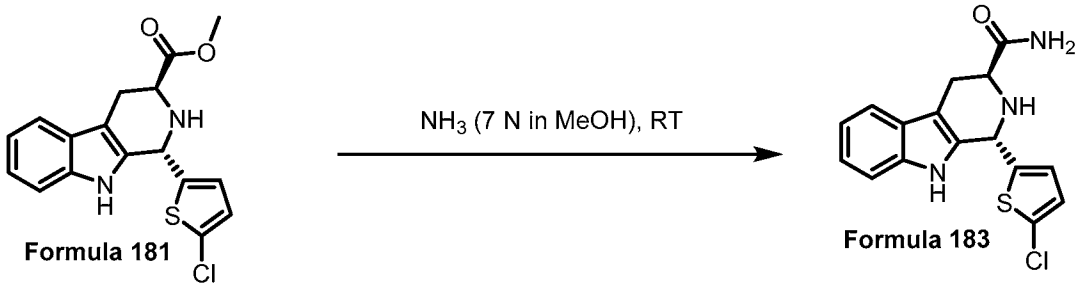
Formula 181 **Formula 182**

Scheme 49

To a solution of **Formula 181** (39.0 mg, 0.2 mmol) in THF / MeOH / H_2O (2 mL / 2 mL / 2 mL) was added Amberlyst hydroxide resin (0.90 g, 3.78 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 3 days, the resin was filtered and washed with MeOH and DCM alternatively (4 × 2 mL). An aqueous solution of AcOH (50%) (4 mL) was added to cleave the product from the resin, the cleaving solution was collected by filtration. The cleavage step was repeated for other 4 times. The combined cleaving solutions were condensed under vacuum. The residue was added MeOH (0.5 mL), followed by addition of DCM (2 mL), Et_2O (5 mL) and hexane (10 mL). The mixture was stirred for 30 mins and then filtered. The solid was washed with hexane to afford (**Formula 182**) (58 mg, 88 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.91 – 6.82 (m, 2H), 5.90 (s, 1H), 3.97 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.31 (dd, *J* = 16.0, 2.7 Hz, 1H), 3.06 (dd, *J* = 15.5, 10.8 Hz, 1H). ^{13}C NMR (101 MHz, cd_3od) δ 177.38, 141.52, 138.44, 132.48, 130.44, 129.64, 127.63, 127.39, 123.48, 120.38, 119.29, 112.33, 109.14, 54.80, 51.94, 24.96.

Example 93:

(1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (Formula 183)

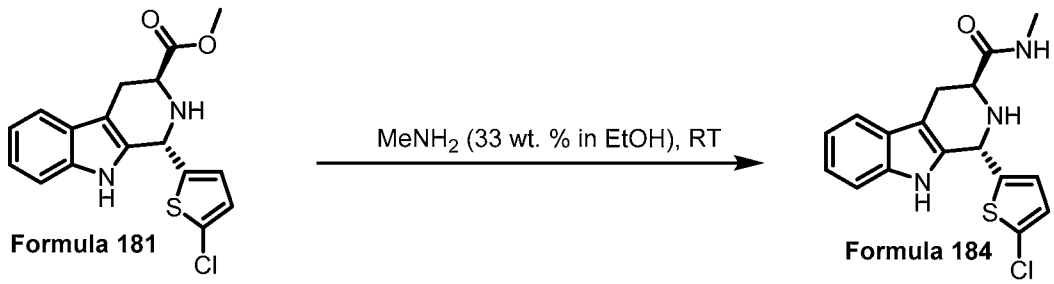


Scheme 50

(1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (**Formula 183**) was prepared in 100 % yield from methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 181)** following the procedure employed for preparation of **Formula 177**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.72 (d, *J* = 3.8 Hz, 1H), 6.63 (dd, *J* = 3.8, 1.1 Hz, 1H), 5.41 (s, 1H), 3.71 (dd, *J* = 10.8, 4.7 Hz, 1H), 3.15 (dd, *J* = 15.6, 4.7 Hz, 1H), 2.78 (ddd, *J* = 15.6, 10.8, 1.3 Hz, 1H).^{13}C NMR (101 MHz, CD_3OD) δ 176.46, 144.80, 136.07, 131.94, 128.83, 126.13, 125.05, 124.84, 121.10, 118.29, 117.28, 110.49, 107.59, 51.56, 50.72, 24.27.

Example 94:

(1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (184)

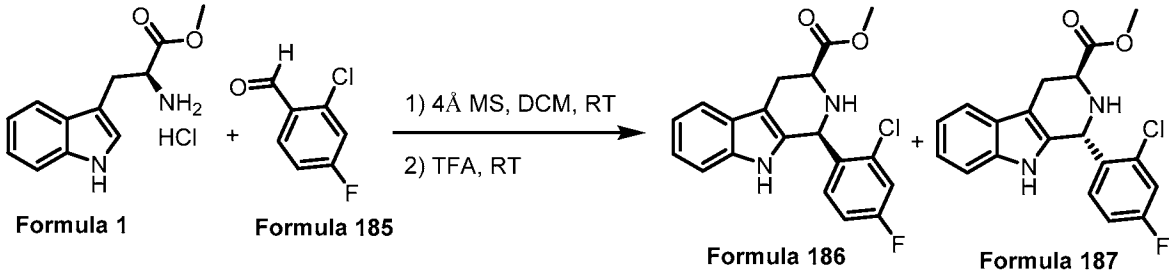


Scheme 51

(1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide **(Formula 184)** was prepared in 100 % yield from methyl (1*S*,3*S*)-1-(5-chlorothiophen-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 181)** following the procedure employed for preparation of **Formula 178**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.31 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.68 (d, *J* = 3.8 Hz, 1H), 6.59 (dd, *J* = 3.8, 1.2 Hz, 1H), 5.37 (s, 1H), 3.65 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.14 (dd, *J* = 15.7, 4.7 Hz, 1H), 2.80 (s, 3H), 2.73 (ddd, *J* = 15.6, 10.9, 1.3 Hz, 1H).^{13}C NMR (101 MHz, CD_3OD) δ 175.28, 145.80, 137.20, 133.16, 130.12, 127.33, 126.22, 126.09, 122.38, 119.57, 118.58, 111.77, 109.00, 52.97, 52.00, 26.19, 25.48.

Example: 95

methyl (1*S*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (186) and methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (187)

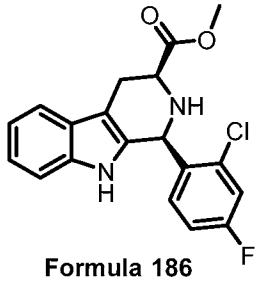


Formula 1 Formula 185 Formula 186 Formula 187

Scheme 52

To a solution of L-Tryptophan methyl ester hydrochloride (**Formula 1**), (1.27 g, 5 mmol), 4Å molecular sieve (2.5 g, powder form) and 2-chloro-4-fluorobenzaldehyde (**Formula 185**) (0.79 g, 5 mmol), DCM (18 mL) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (15 mL), dried over

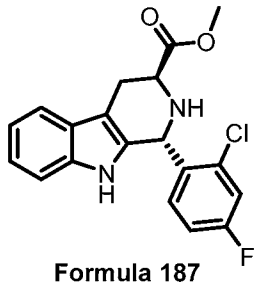
$MgSO_4$ (2 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / EtOAc) to give **Formula 186** (1.0 g, 56 % yield) and **Formula 187** (0.7 g, 40 % yield).



Formula 186

methyl (1*S*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula186)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.55 (d, *J* = 6.4 Hz, 1H), 7.40 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.25 – 7.10 (m, 4H), 6.95 (td, *J* = 8.3, 2.6 Hz, 1H), 5.79 (s, 1H), 3.99 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.83 (s, 3H), 3.25 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.02 (ddd, *J* = 15.0, 11.0, 2.5 Hz, 1H), 2.60 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.23 (q, *J* = 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.11, 162.15 (d, *J* = 251.0 Hz), 136.26, 134.77, 134.25 (d, *J* = 10.4 Hz), 133.50, 131.82 (br s), 126.99, 122.23, 119.84, 118.34, 117.03 (d, *J* = 25.3 Hz), 115.13 (d, *J* = 21.0 Hz), 111.06, 109.43, 56.72, 53.88, 52.43, 25.55.



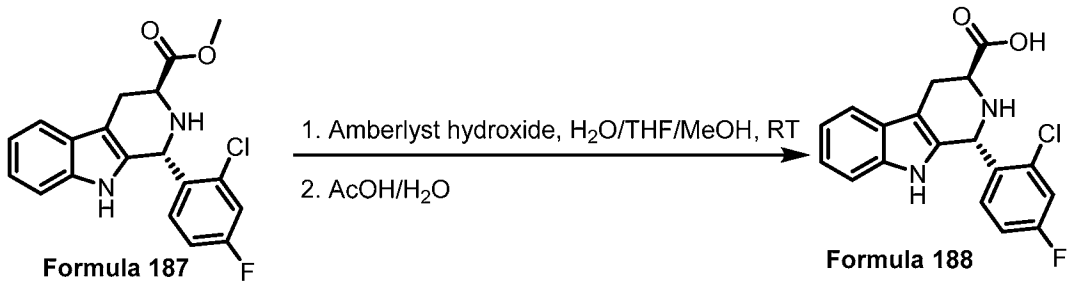
Formula 187

methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 187)

^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.13 (dtd, *J* = 21.2, 7.2, 1.3 Hz, 2H), 6.89 – 6.75 (m, 2H), 5.80 (s, 1H), 4.22 (s, 3H), 3.75 (dd, *J* = 14.2, 4.2 Hz, 1H), 3.75 (s, 3H), 3.27 (dd, *J* = 15.4, 4.7 Hz, 1H), 3.03 (ddd, *J* = 15.4, 9.4, 1.5 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -112.15 (q, *J* = 7.9 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.45, 161.88 (d, *J* = 250.6 Hz), 136.48, 134.59 (d, *J* = 3.6 Hz), 134.20 (d, *J* = 10.4 Hz), 131.23 (d, *J* = 8.8 Hz), 128.84, 126.33, 121.77, 119.04, 117.86, 117.10 (d, *J* = 24.9 Hz), 113.57 (d, *J* = 20.9 Hz), 111.06, 108.83, 52.09, 51.28, 51.22, 24.71.

Example 96:

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (Formula 188)



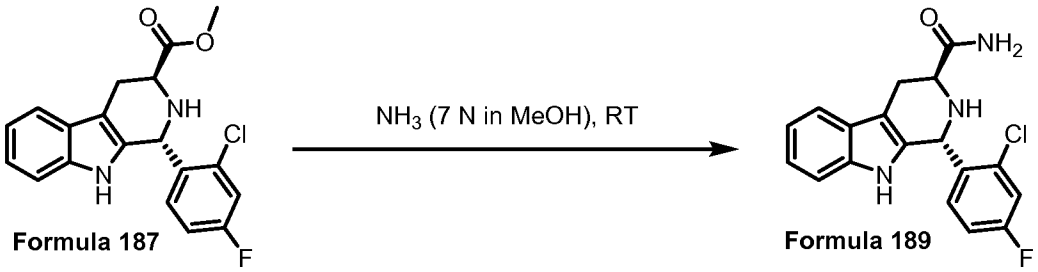
Formula 187 **Formula 188**

Scheme 53

To a solution of **Formula 187** (108.0 mg, 0.3 mmol) in THF / MeOH / H_2O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.26 g, 5.3 mmol, Aldrich, loading: 4.2 mmol/g) at room temperature. The reaction mixture was stirred for 36 hours, the resin was filtered and washed with MeOH and DCM alternatively (4 × 3 mL). An aqueous solution of AcOH (50%) (6 mL) was added to cleave the product from the resin, the cleaving solution was collected by filtration. The cleavage step was repeated for other 4 times. The combined cleaving solutions were condensed under vacuum. The residue was added MeOH (0.5 mL), followed by addition of DCM (2 mL), Et_2O (5 mL) and hexane (10 mL). The mixture was stirred for 30 mins and then filtered. The solid was washed with hexane to afford (**Formula 188**) (97 mg, 94 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.44 (s, 1H), 3.99 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.50 (dd, *J* = 16.8, 5.7 Hz, 1H), 3.26 (ddd, *J* = 16.3, 8.5, 1.4 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -110.50 (q, *J* = 7.4 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 172.01, 163.24 (d, *J* = 252.3 Hz), 137.29, 136.12 (d, *J* = 10.8 Hz), 132.75 (d, *J* = 9.5 Hz), 129.07 (d, *J* = 3.8 Hz), 126.18, 125.76, 122.38, 119.18, 117.88, 117.20 (d, *J* = 25.6 Hz), 114.56 (d, *J* = 21.8 Hz), 110.91, 108.15, 53.63, 51.02, 22.43.

Example 97:

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3 carboxamide (189)

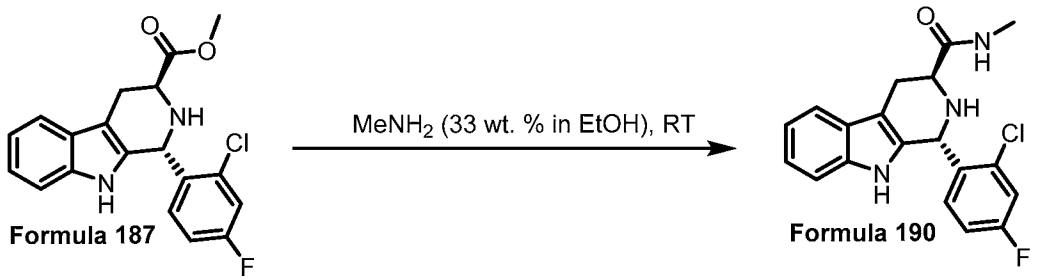


Scheme 54

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3 carboxamide (**Formula 189**) was prepared in 93 % yield from methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 187)** following the procedure employed for preparation of **Formula 177**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.26 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.08 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.02 (ddd, *J* = 7.7, 7.1, 1.1 Hz, 1H), 6.90 (dddd, *J* = 8.6, 8.1, 2.6, 0.4 Hz, 1H), 6.75 (dd, *J* = 8.6, 6.2 Hz, 1H), 5.72 (s, 1H), 3.56 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.21 (dd, *J* = 15.3, 4.6 Hz, 1H), 2.86 (ddd, *J* = 15.3, 10.3, 1.4 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -114.34 (td, *J* = 8.4, 6.3 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 178.02, 163.38 (d, *J* = 248.8 Hz), 138.22, 136.48 (d, *J* = 3.5 Hz), 136.12 (d, *J* = 10.5 Hz), 133.03, 132.68 (d, *J* = 8.9 Hz), 128.00, 122.75, 119.97, 118.81, 118.19 (d, *J* = 25.2 Hz), 114.51 (d, *J* = 21.1 Hz), 112.08, 110.57, 52.84, 52.72, 26.30.

Example 98:

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (Formula 190)



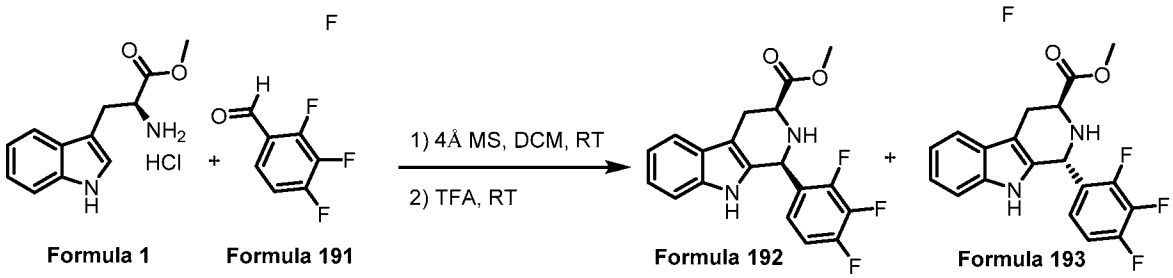
Scheme 55

(1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide **(190)** was prepared in 93 % yield from methyl (1*R*,3*S*)-1-(2-chloro-4-fluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(187)** following the

procedure employed for preparation of **Formula 178**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.31 (dt, *J* = 8.5, 1.9 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.5, 7.1 Hz, 1H), 6.73 (t, *J* = 6.6, 5.6 Hz, 1H), 5.70 (s, 1H), 3.52 (dd, *J* = 10.0, 3.9 Hz, 1H), 3.17 (d, *J* = 15.5 Hz, 1H), 2.82 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.73 (s, 3H).^{19}F NMR (376 MHz, CD_3OD) δ -114.34 (q, *J* = 8.0 Hz).^{13}C NMR (101 MHz, CD_3OD) δ 175.78, 163.36 (d, *J* = 248.9 Hz), 138.20, 136.42 (d, *J* = 3.1 Hz), 136.19 (d, *J* = 10.4 Hz), 133.02, 132.70 (d, *J* = 8.9 Hz), 127.98, 122.76, 119.97, 118.81, 118.18 (d, *J* = 25.2 Hz), 114.50 (d, *J* = 21.1 Hz), 112.09, 110.53, 53.09, 52.70, 26.26, 26.20.

Example 99:

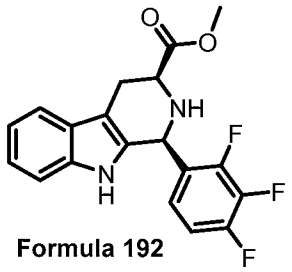
methyl (1*S*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (192) and methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (193)



Formula 1 **Formula 191** **Formula 192** **Formula 193**

Scheme 56

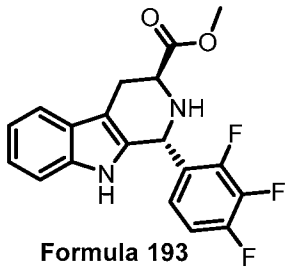
To of L-Tryptophan methyl ester hydrochloride (**Formula 1**), (1.27 g, 5 mmol), 4Å molecular sieve (2.5 g, powder form) and 2,3,4-trifluorobenzaldehyde (**Formula 191**) (0.8 g, 5 mmol), DCM (18 mL) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ (2 g), concentrated, then purified by flash chromatography (5 : 5 : 1 hexane / DCM / Et_2O) to give **Formula 192** (1.02 g, 56 % yield) and **Formula 193** (0.60 g, 34 % yield).



Formula 192

methyl (1*S*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 192)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.53 (dd, *J* = 8.1, 2.8 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.18 – 7.05 (m, 3H), 6.91 (tdd, *J* = 9.1, 6.9, 2.1 Hz, 1H), 5.62 (s, 1H), 3.95 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.82 (s, 3H), 3.22 (ddd, *J* = 15.1, 4.1, 1.9 Hz, 1H), 2.98 (ddd, *J* = 15.2, 11.1, 2.5 Hz, 1H), 2.48 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.86 – -134.01 (m), -140.58 (dt, *J* = 19.5, 6.6 Hz), -159.70 (tdd, *J* = 20.4, 6.9, 2.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.06, 151.73 (ddd, *J* = 252.2, 9.6, 3.0 Hz), 149.31 (ddd, *J* = 250.3, 8.7, 2.8 Hz), 139.84 (dt, *J* = 252.5, 15.5 Hz), 136.32, 132.59, 126.97, 125.61 (dd, *J* = 9.4, 3.5 Hz), 123.73 (dd, *J* = 8.1, 4.2 Hz), 122.41, 119.95, 118.38, 112.88 (dd, *J* = 17.4, 3.7 Hz), 111.09, 109.75, 56.69, 52.47, 50.52, 25.55.



Formula 193

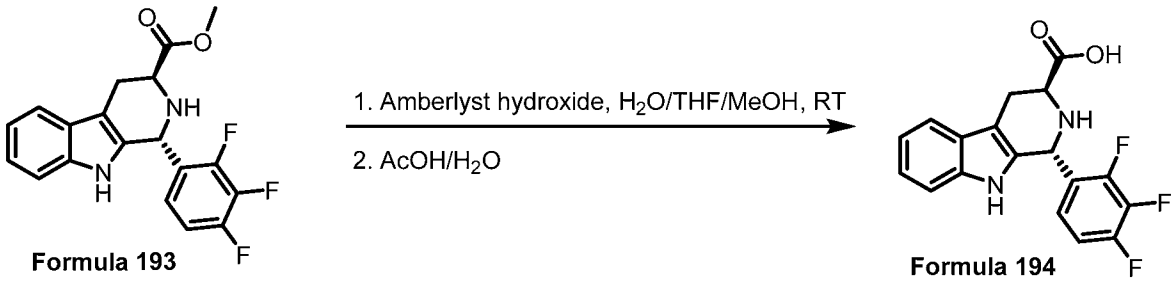
methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 193)

^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.21 – 7.09 (m, 2H), 6.87 – 6.77 (m, 1H), 6.72 – 6.64 (m, 1H), 5.70 (s, 1H), 3.85 (dd, *J* = 8.2, 5.0 Hz, 1H), 3.73 (s, 3H), 3.22 (dd, *J* = 15.4, 5.0 Hz, 1H), 3.02 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.52 (s, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -134.32 (dq, *J* = 22.1, 7.0 Hz), -139.72 (dt, *J* = 19.9, 6.9 Hz), -159.72 (tdd, *J* = 20.3, 7.6, 1.7 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.69, 151.51 (ddd, *J* = 250.7, 10.5, 4.6 Hz), 148.93 (ddd, *J* = 250.2, 10.1, 3.4 Hz), 139.98 (dt, *J* = 252.4, 15.3 Hz), 136.23, 130.79, 126.67, 126.66 (ddd, *J* = 11.4, 3.3, 1.7 Hz), 123.15 (dt, *J* =

8.3, 4.2 Hz), 122.38, 119.74, 118.29, 111.77 (dd, *J* = 17.1, 3.7 Hz), 111.03, 109.60, 52.25, 52.13, 47.79, 24.85.

Example 100:

(1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (194)



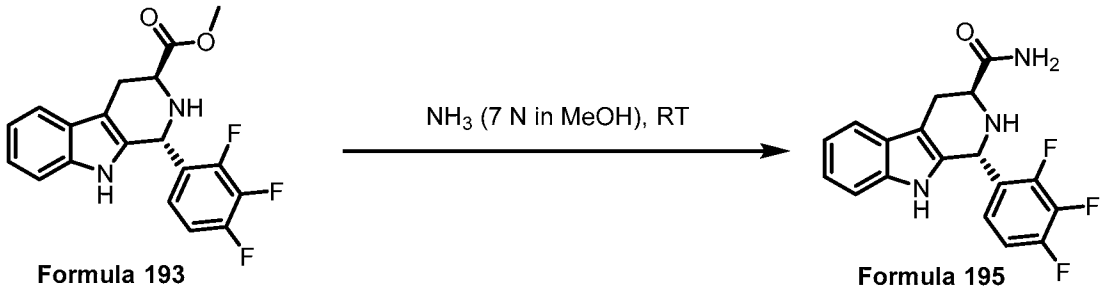
Formula 193 **Formula 194**

Scheme 57

(1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**Formula 194**) was prepared in 76% yield from methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 193)** following the procedure employed for preparation of **(Formula 188)**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.08 (t, *J* = 7.6, 6.9 Hz, 1H), 6.93 – 6.81 (m, 1H), 6.25 (s, 1H), 4.00 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.48 (dd, *J* = 16.3, 5.5 Hz, 1H), 3.35 (s, 1H), 3.24 (dd, *J* = 16.3, 8.6 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -133.83 – -134.04 (m), -138.38 (dt, *J* = 18.3, 8.3 Hz), -162.48 (td, *J* = 19.5, 7.1 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.54, 154.54 (ddd, *J* = 249.8, 8.5, 2.8 Hz), 151.19 (ddd, *J* = 251.7, 9.2, 2.6 Hz), 141.28 (dt, *J* = 249.0, 17.8 Hz), 138.68, 127.22, 126.99, 126.77 – 126.29 (m), 123.87, 122.15 (dd, *J* = 12.5, 1.6 Hz), 120.65, 119.34, 113.89 (d, *J* = 21.6 Hz), 112.35, 109.77, 54.92, 54.81, 24.01.

Example 101:

(1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (Formula 195)



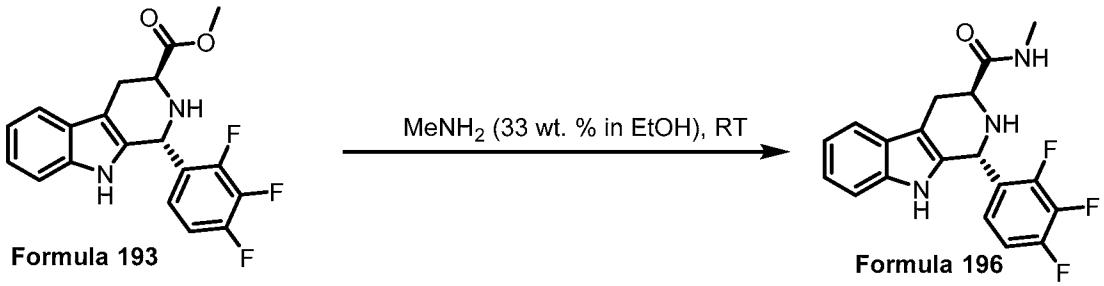
Formula 193 Formula 195

Scheme 58

(1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (**Formula 195**) was prepared in 74 % yield from methyl (1*R*,3*S*)-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 193)** following the procedure employed for preparation of **(Formula 177).** ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.00 (q, *J* = 8.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 5.82 (s, 1H), 4.51 (s, 1H), 3.74 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.50 (t, *J* = 2.2 Hz, 2H), 3.38 (dd, *J* = 16.0, 3.7 Hz, 1H), 3.01 (dd, *J* = 15.2, 10.9 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -136.32 (ddt, *J* = 19.9, 9.6, 6.8 Hz), -140.36 (dt, *J* = 19.1, 7.4, 6.3 Hz), -162.24 (tdd, *J* = 19.9, 7.0, 2.3 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 176.69, 138.66 (dt, *J* = 251.2, 16.0, 14.7 Hz), 136.67, 130.83, 126.73 (dd, *J* = 11.8, 3.0 Hz), 126.54, 123.61 (d, *J* = 7.9 Hz), 121.67, 118.83, 117.69, 111.10 (dd, *J* = 17.2, 3.9 Hz), 110.98, 109.99, 109.57, 51.66, 48.26, 24.90.

Example 102:

(1*R*,3*S*)-*N*-methyl-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (196)



Formula 193 Formula 196

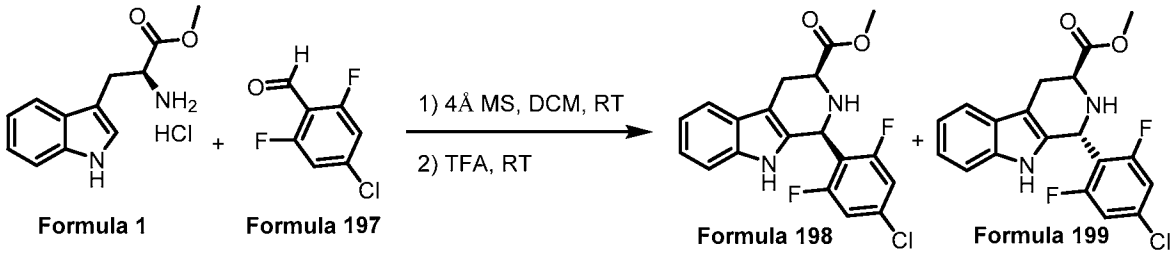
Scheme 59

(1*R*,3*S*)-*N*-methyl-1-(2,3,4-trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide **(Formula 196)** was prepared in 87 % yield from methyl (1*R*,3*S*)-1-(2,3,4-

trifluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 193)** following the procedure employed for preparation of **Formula 178**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.27 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.11 (td, *J* = 7.9, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.90 – 6.80 (m, 1H), 6.53 (ddd, *J* = 8.0, 5.8, 2.4 Hz, 1H), 5.64 (s, 1H), 3.53 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.20 (dd, *J* = 15.5, 4.6 Hz, 1H), 2.81 (ddd, *J* = 15.5, 10.6, 1.5 Hz, 1H), 2.75 (s, 3H).^{19}F NMR (376 MHz, CD_3OD) δ -136.39 (ddt, *J* = 20.0, 9.6, 6.9 Hz), -140.23 (dt, *J* = 19.9, 7.5, 6.8 Hz), -162.29 (tdd, *J* = 20.0, 7.1, 2.3 Hz).^{13}C NMR (101 MHz, CD_3OD) δ 175.29, 152.84 (ddd, *J* = 250.4, 9.5, 3.6 Hz), 150.50 (ddd, *J* = 251.7, 9.5, 3.6 Hz), 140.78 (dt, *J* = 250.8, 15.5, 14.9 Hz), 137.54, 131.72, 127.62 (ddd, *J* = 11.6, 3.4, 0.8 Hz), 127.42, 124.51 (dt, *J* = 8.3, 4.1 Hz), 122.53, 119.69, 118.55, 111.85 (dd, *J* = 17.3, 3.8 Hz), 111.84, 110.52, 52.72, 49.14, 26.18, 25.78.

Example 103:

methyl (1*S*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (198) and methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (199)

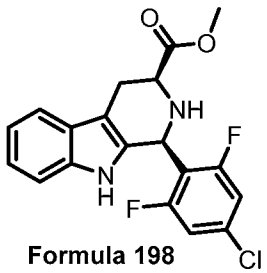


Formula 1 **Formula 197** **Formula 198** **Formula 199**

Scheme 60

To a solution of L-Tryptophan methyl ester hydrochloride (**Formula 1**), (1.27 g, 5 mmol), 4Å molecular sieve (2.5 g, powder form) and 4-chloro-2,6-difluorobenzaldehyde (**Formula 197**) (0.88 g, 5 mmol), DCM (18 mL) was added under nitrogen atmosphere. The resulting reaction mixture was stirred for 24 hours at room temperature. TFA (0.77 mL, 10 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 4 days. An aqueous solution of $NaHCO_3$ (1.2 g, 14.3 mmol, in 10 mL H_2O) was added dropwise at 0 °C, followed by an addition of EtOAc (40 mL). The mixture was stirred for 15 minutes. The phases were separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ (2 g), concentrated, then purified by flash chromatography (5 : 3 : 1 : 1 hexane /

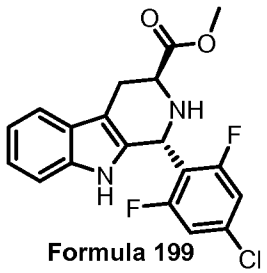
DCM / $CHCl_3$ / Et_2O) to give **Formula 198** (1.20 g, 64% yield) and **Formula 199** (0.59 g, 31 % yield).



Formula 198

methyl (1*S*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 198)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.56 – 7.50 (m, 1H), 7.25 – 7.10 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 2H), 5.69 (s, 1H), 3.96 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.82 (s, 3H), 3.23 (ddd, *J* = 15.3, 4.4, 1.9 Hz, 1H), 2.97 (ddd, *J* = 15.2, 11.2, 2.6 Hz, 1H), 2.49 (br s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.40 (d, *J* = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.19, 161.64 (dd, *J* = 253.9, 8.9 Hz), 136.01, 135.70 (t, *J* = 13.6 Hz), 132.50, 127.15, 122.19, 119.89, 118.29, 114.88 (t, *J* = 18.3 Hz), 113.77 – 113.16 (m), 111.06, 108.56, 57.28, 52.44, 47.98 (t, *J* = 4.1, 2.6 Hz), 25.85.



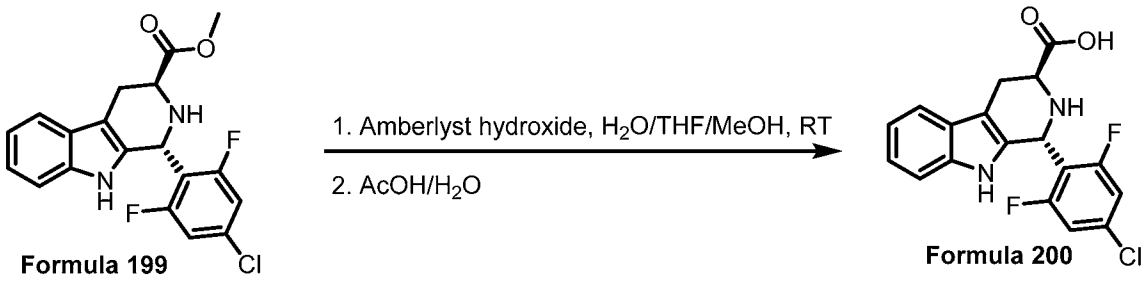
Formula 199

methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (Formula 199)

^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.06 (dtd, *J* = 17.0, 7.1, 1.3 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 5.84 (s, 1H), 4.17 (s, 1H), 4.05 (t, *J* = 5.8 Hz, 1H), 3.70 (s, 3H), 3.23 (ddd, *J* = 15.4, 5.3, 1.5 Hz, 1H), 3.10 (ddd, *J* = 15.4, 6.5, 1.7 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.72 (d, *J* = 8.4 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 173.95, 161.35 (dd, *J* = 253.1, 9.2 Hz), 136.26, 134.80 (t, *J* = 13.7 Hz), 131.08, 126.56, 121.37, 118.84, 117.74, 116.43 (t, *J* = 16.3 Hz), 112.84 (dd, *J* = 27.9, 2.8 Hz), 110.87, 106.71, 53.43, 52.04, 44.31 (t, *J* = 2.8 Hz), 24.36.

Example 103:

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (200)



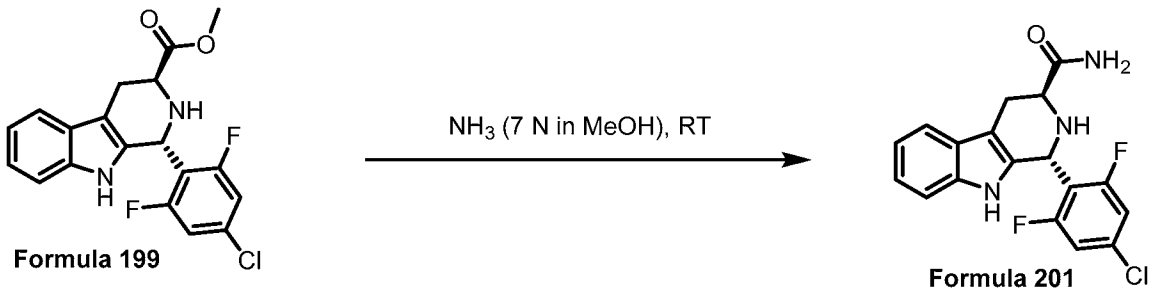
Formula 199 **Formula 200**

Scheme 61

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**Formula 194**) was prepared in 97% yield from methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 199)** following the procedure employed for preparation of **(Formula 188)**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 7.9 Hz, 1H), 7.28 – 6.97 (m, 5H), 6.23 (s, 1H), 4.07 (t, *J* = 6.0 Hz, 1H), 3.41 – 3.23 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ -110.99. (br s). ^{13}C NMR (101 MHz, CD_3OD) δ 175.84, 162.85 (dd, *J* = 254.3, 8.3 Hz), 138.08, 137.85 (t, *J* = 13.8 Hz), 128.70, 127.43, 122.93, 120.11, 118.91, 114.25 (dd, *J* = 26.8, 2.9 Hz), 113.64 (t, *J* = 17.7, 17.2 Hz), 112.04, 107.83, 56.45, 45.62, 24.11.

Example 104:

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (201)



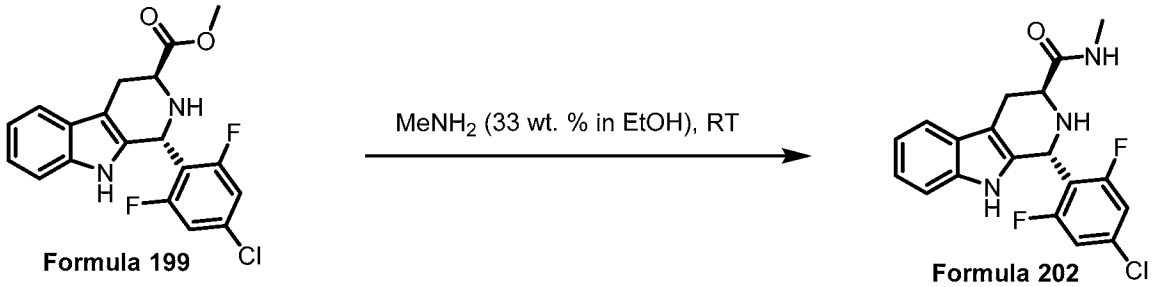
Formula 199 **Formula 201**

Scheme 62

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3 carboxamide (**Formula 201**) was prepared in 96% yield from methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 199)** following the procedure employed for preparation of **(Formula 177)**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.23 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H), 7.03 – 6.97 (m, 3H), 5.74 (s, 1H), 3.88 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.19 (ddd, *J* = 15.4, 4.9, 1.0 Hz, 1H), 2.97 (ddd, *J* = 15.4, 8.5, 1.8 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ -112.11 (d, *J* = 8.0 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 176.68, 161.46 (dd, *J* = 252.4, 9.3 Hz), 136.57, 134.67 (t, *J* = 13.9 Hz), 131.49, 126.75, 121.13, 118.55, 117.49, 116.67 (t, *J* = 16.7 Hz), 112.73 (dd, *J* = 28.6, 2.7 Hz), 110.77, 107.21, 53.51, 44.65, 24.63.

Example 105:

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (202)



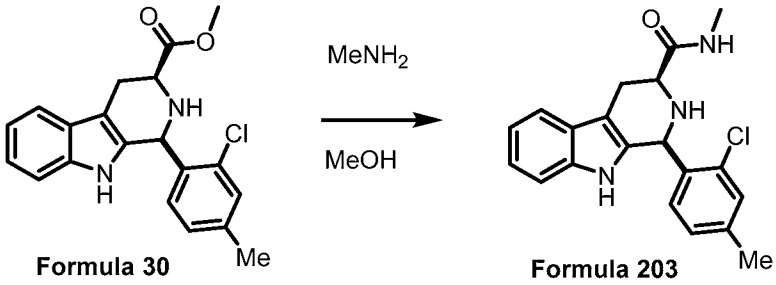
Formula 199 **Formula 202**

Scheme 63

(1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-*N*-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide **(Formula 202)** was prepared in 86 % yield from methyl (1*R*,3*S*)-1-(4-chloro-2,6-difluorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate **(Formula 199)** following the procedure employed for preparation of **Formula 178**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.23 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.10 – 6.98 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 1H), 3.81 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.17 (ddd, *J* = 15.4, 4.9, 0.9 Hz, 1H), 2.93 (ddd, *J* = 15.5, 8.7, 1.8 Hz, 1H), 2.76 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -111.85 (d, *J* = 8.0 Hz). ^{13}C NMR (101 MHz, CD_3OD) δ 174.43, 161.40 (dd, *J* = 252.5, 9.3 Hz), 136.51, 134.67 (t, *J* = 13.9 Hz), 131.59, 126.77, 121.23, 118.64, 117.61, 116.65, 112.78 (dd, *J* = 28.1, 1.8 Hz), 110.86, 107.43, 53.78, 44.77 (t, *J* = 3.7, 2.9 Hz), 25.49, 24.65.

Example 106:

(1S,3S)-1-(2-chloro-4-methylphenyl)-N-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxamide (203)



Formula 30 **Formula 203**

Scheme 64

Formula 203 was prepared in 90% yield from (1S,3S)-methyl 1-(2-chloro-4-methylphenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (**Formula 30**) following the procedure employed for preparation of **Formula 90**.

Example 107:

It was first reported that the growth inhibitory activity of antimalarial compound MMV008138 was due to blockade of the MEP pathway (Bowman, J. D.; Merino, E. F.; Brooks, C. F.; Striepen, B.; Carlier, P. R.; Cassera, M. B. Antiapicoplast and Gametocytocidal Screening To Identify the Mechanisms of Action of Compounds within the Malaria Box. *Antimicrob. Agents. Chemother.* 2014, *58*, 811-819). This discovery was made by screening the Malaria Box with a previously developed IPP rescue assay (Yeh, E.; DeRisi, J. L. Chemical Rescue of Malaria Parasites Lacking an Apicoplast Defines Organelle Function in Blood-Stage *Plasmodium falciparum*. *PLoS. Biol.* 2011, *9*, e1001138). In the IPP rescue assay, if growth inhibition activity of a compound can be abrogated by supplementation with IPP (200 μM), then compound must be preventing synthesis of IPP and DMAPP. Prior to this work, fosmidomycin (FOS) **(Formula 204)** was the only known inhibitor that targets the MEP pathway in malaria parasites, and it served as the positive control. As shown in Table1 below, FOS is toxic to the parasites (IC_{50} = 880 ± 70 nM), and its toxicity at 5 uM is completely eliminated by supplementation with 200 uM IPP.

Out of 200 drug-like and 200 probe-like compounds in the malaria box, only MMV008138 showed significant rescue by IPP supplementation. Since the relative and absolute stereochemistry of commercially available MMV008138 was not known, all four

possible stereoisomers of MMV008138 for evaluation in the phenotypic assay. As described in detail below, Pictet-Spengler reactions of (*S*)- and (*R*)-tryptophan methyl esters were performed with 2,4-dichlorobenzaldehyde, to afford the four diastereomeric esters; in these compounds the C3 stereochemistry is defined by the starting enantiomer of tryptophan methyl ester. The relative configuration of the C1 substituent (*cis* or *trans*) in these compounds was determined by ^{13}C NMR spectroscopy, using the empirical rule of Cook (Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. General method for the assignment of stereochemistry of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines by carbon-13 spectroscopy. *J. Am. Chem. Soc.* 1980, *102*, 6976-6984). Hydrolysis was performed using Amberlyst hydroxide resin and acidification, affording the four stereoisomers of MMV008138.

As shown in Table 1 below, only the (1*R*, 3*S*)-stereoisomer of the structure of MMV008138 (Formula 60) was significantly cytocidal towards the malaria parasite (IC_{50} = 186 ± 2 nM), and its toxicity at 5 μM was rescued to about 91% of control by supplementation with about 200 μM IPP. The (1*S*, 3*S*)- and (1*S*, 3*R*)-stereoisomers (Formulas 59 and 62) showed no toxicity at about 10,000 nM; the (1*R*, 3*R*)-stereoisomer (Formula 61) possessed an IC_{50} of 3,000 ± 200 nM, with about 60% rescue by about 200 μM IPP (5 about μM drug). Thus the order of potency was (1*R*, 3*S*) >> (1*R*, 3*R*) >> (1*S*, 3*S*), (1*S*, 3*R*). ^1H NMR spectroscopic analysis of a commercial sample of MMV008138 revealed a single diastereomer (*trans*), and given the wide disparity of cytocidal activities of *trans*-acids Formulas 60 and 62, it was concluded that actual structure of commercial MMV008138 is that of Formula d 60.

In this Example, 88 analogs of 60 have been synthesized and screened *in vitro* for cytocidal activity to Dd2 *Plasmodium falciparum* in the absence and presence of IPP supplementation (metabolic rescue to ensure apicoplast-targeting specificity) (see Table 1 below). Most of these analogs interrogated variation in substituents of the D ring, and replacement of the 3-carboxyl group. Several close analogs possessed growth inhibitory similar to 60, including i) 74, which featured 2'-chloro-4'-methyl substitution (IC_{50} = 434 ± 54 nM); ii) compound 126, which featured 2'-Br, 4'-Cl substitution (IC_{50} = 359 nM); iii) compound 127, which featured 2'-Cl, 4'-Br substitution (IC_{50} = 320 nM); and iv) compound 138, which featured 2',4'-Br_2 substitution (IC_{50} = 586 nM). All of these compounds demonstrated 100% rescue by about 200 uM IPP at about 2.5 – 5 μM drug, indicating growth inhibition was due to MEP pathway blockade.

Replacement of the carboxyl group of compound 60 by a proton was observed to lead to a dramatic loss of cytocidal activity (compound 112), as did conversion to the methyl ester (compound 4). Replacement of the carboxyl group by a primary amide also caused a loss of activity (compound 79, IC_{50} = 1,200 ± 100), with only 50% rescue by 200 uM IPP. However, replacement of the carboxyl group with a methyl amide was not observed to lead to a significant loss in potency: i) compound 80, featuring 2',4'-Cl_2 substitution (IC50 = 170 ± 30 nM); ii) compound 90, featuring 2'-Cl, 4'-Me substitution; iii) compound 128, featuring 2'-Br,4'-Cl substitution (IC_{50} = 341 nM); iv) compound 129, featuring 2'-Cl,4'-Br substitution (IC_{50} = 300 nM); v) compound 133, featuring 2'-F,4'-Cl substitution (IC_{50} = 632 nM); vi) compound 140, featuring 2',4'-Br_2 disubstitution (IC_{50} = 520 nM). All of these compounds demonstrated 100% rescue by about 200 uM IPP at 2.5 – 5 μM drug, indicating growth inhibition was due to MEP pathway blockade. X-ray crystallography (anomalous dispersion) of compound 80 confirmed (1*R*, 3*S*)-configuration. Since compound 80 is derived from 60, this X-ray analysis provides independent confirmation of the (1*R*, 3*S*)-configuration of compound 60 (Figure 1).

Finally, since the erectile dysfunction drug tadalafil (Formula 208) also possesses a 1-aryl-3-carboxamido-tetrahydro-β-carboline structure, it was also tested it in the phenotypic assay. At about 20,000 nM, this drug had no toxicity to Dd2 *P. falciparum*. Without being bound to theory, this lack of cytocidal activity is likely due to three factors: i) the presence of an additional ring (diketopiperazine), which reduces the basicity of the nitrogen atom in 60, and may cause steric problems; ii) the non-ideal (*R*, *R*) configuration; and iii) 3,4-disubstitution on the D-ring, instead of 2',4'-disubstitution. The investigation demonstrated in this Example of 3',4'-disubstituted analogs (compounds 68, 121, 122) confirms that this substitution pattern can reduce growth inhibition potency within the compound 60 scaffold. Formula 116 represents a hybrid between 60 and tadalafil, and demonstrates that even with (1*R*,3*S*)-configuration and 2',4'-Cl_2 substitution of the D-ring, the diketopiperazine functionality abrogates growth inhibition.

Since *E. coli* also uses the MEP pathway to synthesize IPP and DMAPP, a number of compounds for growth inhibition of *E. coli* were also tested. As shown in Table 1, none of the compounds tested (including promising anti-malarial compounds 60, 74, 80, 90, 126, 127, 128, 129, 133, 138, 140) at 250 – 500 μM affected growth of *E. coli* for up to 18 h. This data suggest that these drugs might be unlikely to affect Gram-negative gut flora, an advantageous property for a antimalarial chemoprophylactic drug. In addition, since it is now

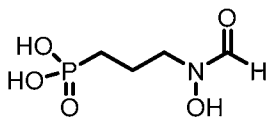
known that the *Plasmodium* target of MMV008138 is IspD (Wu, W.; Herrera, Z.; Ebert, D.; Baska, K.; Cho, S. H.; DeRisi, J. L.; Yeh, E. A chemical rescue screen identifies a Plasmodium falciparum apicoplast inhibitor targeting MEP isoprenoud precursor biosynthesis. *Antimicrob. Agents. Chemother.* 2015, *59*, 356-364 and Imlay, L. S.; Armstrong, C. M.; Masters, M. C.; Li, T.; Price, K. E.; Edwards, R., L.; Mann, K. M.; Li, L. X.; Stallings, C. L.; Berry, N. G.; O'Neill, P. M.; Odom, A. R. Plasmodium IspD (2-C-methyl-D-erythritol 4-phosphate cytidyltransferase), an essential and druggable antimalarial target. *ACS Infect. Dis.* 2015, *1*, 0000), the fourth enzyme in the MEP pathway, selected compounds were tested for inhibition of *P. falciparum* IspD. As shown in Table 1, in every case tested, potent growth inhibitory compounds are potent inhibitors of *Pf*IspD, and weak growth inhibitors are weak inhibitors of *Pf*IspD. Finally, *in vitro* ADME-tox analysis of Formula 60 (Pharmaron) revealed excellent solubility, plasma stability, plasma protein-binding, and Caco-2 permeability. It has no significant liabilities (i.e., > 30 uM IC_{50}) at hERG, Cyp2D6, and Cyp3A4. It has no general cytotoxicity (HepG2 IC_{50} > 150 uM) and it is Ames negative at the two strains tested.

Biossay procedures and Results

Cytocidal (*P. falciparum, E. coli*) and rescue assays were carried out as follows: Growth of asexual blood stages were measured as described previously using the SYBR green assay.[2, 7] Briefly, ring-stage parasite cultures (1% hematocrit and 1% parasitemia) were incubated for 72 h with 10,000 – 1 nM drug (0.1% DMSO) under normal culture conditions. The % growth was normalized to that of untreated control parasites in the presence of 0.1% DMSO. Background determinations were made using uninfected erythrocytes. Compounds having $IC_{50} \leq 50$ nM were reassayed at 2.5 μM in the presence of 200 μM IPP to confirm MEP pathway inhibition as the mechanism of action. To select against possible adverse interaction with human gut flora, compounds will then be tested at 100 μM for growth inhibition of *E. coli* strain BL21(DE3) as described previously (Yao, Z.-K.; Krai, P. M.; Merino, E. F.; Simpson, M. E.; Slebodnick, C.; Cassera, M. B.; Carlier, P. R. Determination of the active stereoisomer of the MEP pathway-targeting antimalarial agent MMV008138, and initial structure-activity studies. *Bioorg. Med. Chem. Lett.* 2015, *25*, 1515-1519). Briefly, a 20,000-fold dilution of an overnight culture of *E. coli* will be performed into Luria-Bertani broth medium containing the test compounds at three concentrations (100 μM, 50 μM, and 25 μM) with a final concentration of 5% DMSO. Cultures will be incubated for 18

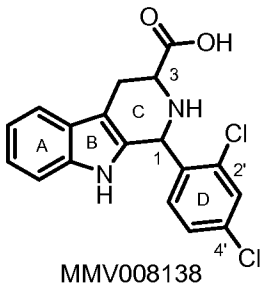
h at 37 °C with agitation. A 100 μM FOS treatment and 5% DMSO alone will be used as control. Bacteria growth will be measured using a cell density meter.

Inhibition of PfIspD was determined for several of these compounds according to the following procedure: We expressed recombinant *N*-terminal His-tagged *Pf*IspD in *E. coli* using the published codon-optimized gene (Imlay *et al.*, 2015). Inhibition of *Pf*IspD by 1a is reported to be CTP-competitive and independent of [MEP] (Imlay *et al.*, 2015). We have successfully expressed recombinant *Pf*IspD, and measured kinetic parameters (K_m^{MEP} = 12 μM, k_{cat}^{MEP} = 7.65 s^{-1}, K_m^{CTP} = 9.3 μM, k_{cat}^{CTP} = 11.7 s^{-1}) using PhosphoWorks™ Fluorimetric Pyrophosphate Assay Kit (AAT Bioquest®, Inc.). Note that this method directly measures pyrophosphate (PP_i) released from the IspD-catalyzed reaction (MEP + CTP → CDPME + PP_i, Fig. 1). Our K_m values are lower than those reported by other groups (K_m^{MEP} =60.6 μM, k_{cat}^{MEP} = 0.16 s^{-1}) (Wu *et al.*, 2015) and (K_m^{CTP} = 58.7 μM, k_{cat}^{CTP} = 0.4 s^{-1}) (Imlay *et al.*, 2015). These determinations used a coupled assay to ultimately measure P_i (EnzChek Phosphate Assay Kit, Molecular Probes); we have found that the coupled assay offers lower sensitivity than the direct measurement of PP_i referenced above. We thus used this coupled assay to measure IC_{50} values ([*Pf*IspD] = 60 nM, [CTP] = 50 μM, [MEP] = 60 μM, 100 mM NaCl, 23 mM Tris (pH 7.0), 75 mM $MgCl_2$, 37 °C) (Imlay *et al.*, 2015) of selected analogs of Formula 60.



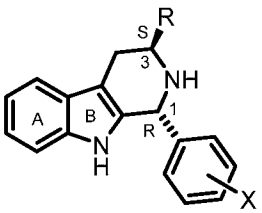
FOS

Formula 204



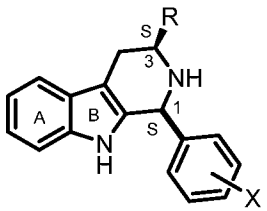
MMV008138

Formula 205



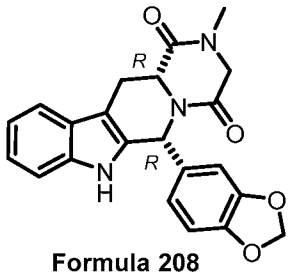
Formula 206

(1*R*, 3*S*)-configured except for **Formulas 182-184** for which it is (1*S*,3*S*)



Formula 207

(1*S*, 3*S*)-configured



Formula 208

Tadalafil
(PDE5 inhibitor)

Table 1

Formula	A, B ring	R and N2/N9 substitution (if any)	X	configuration	*P. falciparum* growth inhibition IC_{50} (nM)[b]	% Recovery (5 uM drug + 200 uM IPP)	*Pf*lspD IC_{50} (nM)[c]	*E. coli* growth inhibition (18 h)[d]
FOS (204)	NA	NA	NA	NA	880 ± 70	100	ND	
MMV008138 (205)	indole	CO_2H	2',4'-Cl_2	not disclosed	135 ± 5	100	ND	
Tadalafil (208)	indole	NA	NA	(*R*,*R*)	>20,000	ND		
60	indole	CO_2H	2',4'-Cl_2	(1*R*,3*S*)	186 ± 2	91 ± 10	43 (35-57)	0 @ 250 µM
59	indole	CO_2H	2',4'-Cl_2	(1*S*,3*S*)	>10,000	ND		
62	indole	CO_2H	2',4'-	(1*S*,3*R*)	>10,000	ND	0% inh.	0 @ 250

			Cl_2				@ 500 nM	µM
61	indole	CO_2H	2',4'-Cl_2	(1*R*,3*R*)	3,000 ± 200	60%		
64	indole	CO_2H	H	(1*R*,3*S*)	>10,000	ND	0% inh. @ 500 nM	0% @ 250 µM
63	indole	CO_2H	H	(1*S*,3*S*)	>10,000	ND		
70	indole	CO_2H	2',4'-F_2	(1*R*,3*S*)	868 ± 22	94 ± 6	115	0% @ 250 µM
69	indole	CO_2H	2',4'-F_2	(1*S*,3*S*)	>10,000	ND		
74	indole	CO_2H	2'-Cl,4'-Me	(1*R*,3*S*)	434 ± 54	116 ± 33	23.4	0% @ 500 µM
73	indole	CO_2H	2'-Cl,4'-Me	(1*S*,3*S*)	>10,000	ND		
72	indole	CO_2H	2',4'-Me_2	(1*R*,3*S*)	67% inhibition @ 10,000	ND		
71	indole	CO_2H	2',4'-Me_2	(1*S*,3*S*)	>10,000	ND		
75	indole	CO_2H	2'-Me, 4'-Cl	(1*R*,3*S*)	717 ± 54	83 ± 1	21.7	0% @ 500 µM
65	indole	CO_2H	2'-Cl	(1*R*,3*S*)	3,280 ± 989	60% @ 10 uM	144	0% @ 250 µM
66	indole	CO_2H	4'-Cl	(1*R*,3*S*)	1,170 ± 60	50% @ 10 uM	188	0% @ 250 µM
67	indole	CO_2H	2',4'-$(OMe)_2$	(1*R*,3*S*)	>20,000	ND		
76	indole	CO_2H	2',4'-$(CF_3)_2$	(1*R*,3*S*)	>10,000	ND		
68	indole	CO_2H	3',4'-$(OMe)_2$	(1*R*,3*S*)	>20,000	ND		
78	5,6-	CO_2H	2',4'-	(1*R*,3*S*)	>10,000	ND		

	dichloro-indole		Cl_2					
77	5,6-difluoro-indole	CO_2H	2',4'-Cl_2	(1*R*,3*S*)	73% @ 10,000	ND		
99	5,6-dimethoxy-phenyl	CO_2H	2',4'-Cl_2	(1*R*,3*S*)	>10,000	ND		
112	indole	H	2',4'-Cl_2	1*RS*	10,000 ± 1,600	0% @ 20 uM		
79	indole	$CONH_2$	2',4'-Cl_2	(1*R*,3*S*)	1,200 ± 100	50		
80	indole	CONHMe	2',4'-Cl_2	(1*R*,3*S*)	155 ± 9	100	48 (29-81)	0% @ 500 μM
86	indole	CONHMe	2',4'-F_2	(1*R*,3*S*)	1237 ± 44	87 ± 4		0% @ 500 μM
90	indole	CONHMe	2'-Cl, 4'-Me	(1*R*,3*S*)	351 ± 40	117 ± 3	126	0% @ 500 μM
88	indole	CONHMe	2',4'-Me2	(1*R*,3*S*)	67% @ 10,000	ND		
91	indole	CONHMe	2'-Me,4'-Cl	(1*R*,3*S*)	1,209 ± 257	50 ± 10		
84	indole	CONHNHMe	2'-Me,4'-Cl	(1*R*,3*S*)	1,746 ± 216	78 ± 4		
82	indole	CONH*i*-Pr	2',4'-Cl_2	(1*R*,3*S*)	47% @ 10,000	ND		
81	indole	CONHBu	2',4'-Cl_2	(1*R*,3*S*)	82% @ 10,000	ND		
83	indole	CONHc-C_6H_{11}	2',4'-Cl_2	(1*R*,3*S*)	2,633 ± 461	0 % @ 10 uM		

4	indole	CO_2Me	2',4'-Cl_2	(1*R*,3*S*)	6,760 ± 1446	~ 20 % @ 20 uM		
3	indole	CO_2Me	2',4'-Cl_2	(1*S*,3*S*)	11,960 ± 3,650	~15% @ 20 uM		
7	indole	CO_2Me	2',4'-Cl_2	(1*S*,3*R*)	7,730 ± 1,410	0% @ 20 uM		
6	indole	CO_2Me	2',4'-Cl_2	(1*R*,3*R*)	~10,000	0% @ 20 uM		
10	indole	CO_2Me	H	(1*R*,3*S*)	~20% @ 20,000	ND		
9	indole	CO_2Me	H	(1*S*,3*S*)	>10,000	ND		
203	indole	CONHMe	2'-Cl, 4'-Me	(1*S*,3*S*)	>10,000	ND		
85	indole	CONHMe	2',4'-F_2	(1*S*,3*S*)	>10,000	ND		
87	indole	CONHMe	2',4'-Me_2	(1*S*,3*S*)	>10,000	ND		
92	indole	CONHMe	2',4'-$(CF_3)_2$	(1*R*,3*S*)	>10,000	ND		
94	5,6-dichloro-indol	CONHMe	2',4'-Cl_2	(1*R*,3*S*)	74% @ 10,000	ND		
93	5,6-difluoro-indol	CONHMe	2',4'-Cl_2	(1*R*,3*S*)	1189 ± 95	33 ± 4		
100	5,6-dimethoxy-phenyl	CONHMe	2',4'-Cl_2	(1*R*,3*S*)	>10,000	ND		
113	indole	CONHMe	2',4'-Cl_2	(1*S*,3*S*)-	5 – 10 μM			
114	indole	CONHMe	2',4'-Cl_2	(1*R*,3*R*)	~ 10 μM			
115	indole	CONHMe	2',4'-	(1*S*,3*R*)	3,55 μM			

			Cl_2					
116	indole	CON(Me)CH2-N2, i.e. diketopiperazine linked to N2	2',4'-Cl_2	(1*R*,3*S*)	3.7 μM			
117	indole	CONMe2	2',4'-Cl_2	(1*R*,3*S*)	> 20 μM			
118	indole	CONHEt	2',4'-Cl_2	(1*R*,3*S*)	~5 μM	ND		
119	indole	CO2H	4'-F	(1*R*,3*S*)	60% inh. @ 5 μM	ND		
120	indole	CONHMe	4'-F	(1*R*,3*S*)	> 10 μM	ND		
121	indole	CO2H	3',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND	0% inh @ 500 nM	9% @ 250 μM
122	indole	CONHMe	3',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND	0% inh @ 500 nM	0% @ 250 μM
123	indole	CONHMe	2',3',5',6'-F_4-4'-NHMe	(1*R*,3*S*)	>10 μM	ND		
124	5,6-difluoro indole	CONHMe	2',4'-Cl_2	(*1S*,3*S*)	>10 μM	ND		
125	5,6-dichloroindole	CONHMe	2',4'-Cl_2	(1*S*,3*S*)	>10 μM	ND		
126	indole	CO_2H	2'-Br,4'-Cl	(1*R*,3*S*)	359 (294-437)	100% @ 5 μM	41 (31-53)	7% @ 125 μM
127	indole	CO_2H	2'-Cl, 4'-Br	(1*R*,3*S*)	320 (218-468)	100% @ 5 μM	33 (26-42)	0% @ 250 μM
128	indole	CONHMe	2'-Br, 4'-Cl	(1*R*,3*S*)	341 (238-486)	100% @ 5 μM	33 (15-70)	0% @ 250 μM

129	indole	CONHMe	2'-Cl,4'-Br	(1*R*,3*S*)	300 (233-387)	95% @ 5 μM	39 (31-48)	0% @ 250 μM
130	indole	CO_2H	2'-Br, 4'-F, 5'-OMe	(1*R*,3*S*)	>10 μM	ND		
131	indole	CO_2H	2'-F, 4'-Cl	(1*R*,3*S*)	860 (718-1030)	100% @ 5 μM	85	0% @ 250 μM
132	indole	CONHMe	2'-Br, 4'-F, 5'-OMe	(1*R*,3*S*)	>10 μM	ND		
133	indole	CONHMe	2'-F, 4'-Cl	(1R,3S)	632 (575-697)	100% @ 5 μM	63	0% @ 250 μM
134	indole	CH_2OH	2',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND		
135	indole	CO_2H, N2-benzyl	2',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND	0% inh. @ 500 nM	0% @ 250 μM
136	indole	CONHMe, N2-benzyl	2',4'-Cl_2	(1*R*,3*S*)	2.5 – 5 μM	ND	0% inh. @ 500 nM	0% @ 250 μM
137	indole	CO_2H, N2-acetyl	2',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND		
138	indole	CO2H	2',4'-Br_2	(1*R*,3*S*)	586 (522-578)	100% @ 10 μM	88	
139	indole	CO2H	3',5'-Br_2-pyridin-2'-yl	(1*R*,3*S*)	>10 μM	ND		
140	indole	CONHMe	2',4'-Br_2	(1*R*,3*S*)	520 (468-578)	80% @ 10 μM	48	
141	indole	CONHMe	3',5'-Br_2-pyridin-2'-yl	(1*R*,3*S*)	~20 μM	ND		
176	indole	CO_2H N9-Me	2',4'-Cl_2	(1*R*,3*S*)	>10 μM	ND		

177	indole	$CONH_2$ N9-Me	2',4'-Cl_2	(1*R*,3*S*)	~20 μM	ND		
178	indole	CONHMe N9-Me	2',4'-Cl_2	(1*R*,3*S*)	~10 μM	ND		
182	indole	CO_2H	5'-Cl-thiophen-2'-yl	(1*S*,3*S*)				
183	indole	$CONH_2$	5'-Cl-thiophen-2'-yl	(1*S*,3*S*)				
184	indole	CONHMe	5'-Cl-thiophen-2'-yl	(1*S*,3*S*)				
188	indole	CO_2H	2'-Cl,4'-F	(1*R*,3*S*)				
189	indole	$CONH_2$	2'-Cl,4'-F	(1*R*,3*S*)				
190	indole	CONHMe	2'-Cl, 4'-F	(1*R*,3*S*)				
194	indole	CO_2H	2',3',4'-F_3	(1*R*,3*S*)				
195	indole	$CONH_2$	2',3',4'-F_3	(1*R*,3*S*)				
196	indole	CONHMe	2',3',4'-F_3	(1*R*,3*S*)				
200	indole	CO_2H	2',6'-F_2,4'-Cl	(1*R*,3*S*)				
201	indole	$CONH_2$	2',6'-F_2,4'-Cl	(1*R*,3*S*)				
202	indole	CONHMe	2',6'-F_2,4-Cl	(1*R*,3*S*)				

Note: Formula 206 is (1R,3S)-configured except for certain examples that feature heteroaromatic replacement of the D-ring, for which it is (1S,3S). Formula 207 is (1S,3S)-configured except for certain examples that feature heteroaromatic replacement of the D-ring, for which it is (1R,3S).

Example 108:

Diastereomers **2a** and **3a** (Fig. 2) derive from (S)-Trp-OMe and were easily separated by column chromatography; the relative configuration of the Cl substituent (cis- or *trans-)* in each compound was determined by ^{13}C NMR spectroscopy, using the empirical rule of Cook.[14] Similarly (*R*)-Trp-OMe provided *ent*-**2a** and *ent*-**3a** (Fig. 2). Hydrolysis of the esters using an Amberlyst resin catch and release protocol[15] gave the desired stereoisomers of MMV008138, **4a, 5a,** ent-**4a,** and ent-**5a,** (Fig. 2) free from inorganic salt contamination. 'H NMR spectroscopic analysis of commercial MMV008138 indicated that it was >95% trans-configured, like **4a** or ent-**4a** (Fig. 2). The four stereoisomers were then examined for growth inhibitory activity and reversal of growth inhibition by 200 uM IPP (Fig. 2), using MMV008138 and FOS as controls. As can be seen, **4a** (IC_{50} = 250 ± 70 nM) was by far the most potent stereoisomer of the four (Fig, 2, entries 3, 4, 15 and 16). Compounds **5a** and ent-**4a** (Fig. 2) showed no inhibition of growth at the highest concentration tested (10,000 nM), and ent-**5a** (Fig. 2) had an IC_{50} of 3000 nM.

Furthermore, the P. *falciparum* toxicity of **4a** (Fig. 2) was reversed (100% at 2.5 μM) by supplementation with IPP, similar to MMV008138. These observations and the similar measured IC_{50} values for MMV008138 and **4a** (Fig. 2) (210 ± 90 and 250 ± 70 nM, entries 2 and 3, respectively (Fig. 2) confirm that MMV008138 is the pure (1R,3S)-stereoisomer and is thus properly depicted as **4a** (Fig. 2) or **Formula 60.**

To ascertain the structural determinants of the apicoplast-targeting growth inhibitory activity of **4a** (Fig. 2)**,** we explored the effect of variation of the D-ring substituents. With slight modification, the same synthetic methods were used to prepare (1R,3S)-configured acid derivatives **4b-k** from benzaldehydes **lb-k** (Fig. 2)**,** and a smaller number of (1S,3S)-configured acids **5b, e, g, h** (Fig. 2) were also investigated (Table 2). Bioassays of **4b-k** (Fig. 2) revealed that potent growth inhibition requires 2',4'-disubstitution of the D-ring. Compound **4b** lacking D-ring substitution has no toxicity to *P. falciparum* at 10,000 nM (Fig. 2, entry 5). Growth inhibitory activity was regained with a 2'-Cl **(4c)** or a 4'-Cl **(4d)** substituent (Fig. 2 entries 6-7). Among the 2',4'-disubstitution patterns explored, the relatively conservative 2'-chloro-4'-methyl **(4e,** Fig. 2 entry 8) and 2'-methyl-4'-chloro **(4f,** Fig. 2 entry 9) substitutions came closest to recapitulating the activity of **4a** (Fig. 2)**.** Although **4e** (IC_{50} = 410 ± 40 nM) (Fig. 2) was not observed to be as potent as **4a** (cf. Table 1 entries 8 and 3), it demonstrated full rescue by 200 uM IPP supplementation. The 2',4'-difluoro analog **(4h,** Fig. 2 entry 11) was observed to be more potent than the 2',4'-dimethyl analog **(4g,** Fig. 2 entry

10), and both the 2',4'-dimethoxy and 2', 4'-bis(trifluoromethyl) analogs failed to demonstrate growth inhibitory activity at 10,000 or 20,000 nM **(4i** and **4j,** Fig. 2 entries 12- 13). The sole case of 3',4'-disubstitution explored **(4k,** Fig. 2 entry 14) did not inhibit parasite growth at 20,000 nM. Without being bound to theory, it could be that the 2'- and 4'-substituents complement the shape of a rather tight binding pocket. In addition, the presence of the 2'-substituent could also constrain the D-ring to lie perpendicular to the C-ring.

Example 109:

Various synthesis schemes and isolated yields for D-ring variants of Formulas 4 and 3 (2a and 3a respectively in Fig. 3) are demonstrated in Fig. 3.

Example 110:

Since the carboxylic acid group is often considered a liability in drug development, aseries of analogs of **Formula 60** that varied in the C3 substituent (Fig. 4) were examined. **Fomula 4** (Compound 2a in Fig. 4), the methyl ester precursor of **Formula 60** (compound 4a in Fig. 4) had only weak growth inhibitory activity (IC_{50} = 6800 ± 1400 nM, Fig. 4, entry 1. Thus it appears that the methyl ester group cannot recapitulate the binding of the carboxylic acid/ carboxylate of **Formula 60**. A number of other esters were examined and found to not inhibit *P. falciparum* growth; in particular Formulas 7 and 4 (*ent*-2a and 2b, respectively in Fig. 4**)** (the methyl ester precursors of **Formulas 62** and **64**(*ent*-4a and 4b, respectively in Fig. 4) had little growth inhibitory activity (Fig. 4, entries 2-3). Tryptamine was condensed with **Ia** to yield **Formula 112** ((±)-6a in Fig. 4) in 42% yield, which lacks a C3-substituent (Fig. 5). As can be seen in Fig. 4, **Formula 112** ((±)-6a in Fig. 4) appears to be a weak inhibitor of parasite growth (entry 4).

More success was obtained with amide and hydrazide derivatives, that were simply prepared by treatment of the requisite methyl ester with the desired amine or hydrazine (Fig. 5). The primary amide of **Formula 79** (7a in Fig. 4) was observed to be weakly potent, but methylamide **Formula 80** (8a in Fig. 4) was observed to be slightly more potent than **Formula 60** (IC_{5O} = 190±30nM, Fig. 4 entry 6, $p<0.04$ ANOVA test) and exhibited 100% rescue upon IPP supplementation. X-ray crystallography of **Formula 80** confirmed (lR,3S)-configuration (Fig. 2). Methylamide Formula 90 (8e in Fig. 4) featuring a 2'-chloro-4'-methylphenyl group in place of 2',4'-dichlorophenyl also showed good potency (IC_{50} = 340 ±

50 nM, Fig. 4 entry 7); methy-lamides **Formulas 86, 88,** and **91** (8f-h in Fig. 4) were observed to be less potent as to growth inhibition.

Example 111:

To assess possible off-target effects of potent inhibitors **4a (F. 60)** and **8a (F. 80)** we explored their parasite growth inhibition activity in the presence of 200 uM IPP (Figs 2, 4, 6A and 6B). As can be seen, the presence of 200 uM IPP raises the IC_{50} values of these compounds to roughly 10,000 nM. Similar results were seen for **4e, 4f,** and **4h**. Thus the off-target *P. falciparum* growth inhibition activity of these compounds occurs at concentrations roughly 40-fold higher than those that target the MEP pathway. Additionaly, when tested at 10-20 uM, many of the weakly potent (micromolar IC_{50} values) analogs in Figs. 2 and 4 did not show full rescue upon IPP supplementation (*e.g.,* **4c,d,** enr**-5a, 2a,** ent**-2a, (±)-6a, 7a, 8f, 11a, 12a)** (Fig. 4). While not being bound to theory, it could be that the same off-target toxic mechanisms are also operative for these compounds.

As mentioned above, the MEP pathway is present in the human microbiome and specificity of these inhibitors to the malaria parasite is highly desirable. Therefore, compounds **4a, 4e, 4f, 4h, 8a, 8e,** and **8h,** (Figs. 3-4) were tested for antibacterial activity against *Escherichia coli*. In order to investigate the effect of selected compounds against *E. coli*, strain BL21(DE3), an overnight culture of *E. coli* (37 °C, 200 rpm agitation) was diluted 100-fold into LB broth medium and incubated to an OD_{600} of ~0.6. The culture was then diluted 10,000-fold into LB broth medium. Then 750 µL of this *E. coli* inoculum was inoculated into a culture tube containing 750 µL of the test compounds previously diluted in LB broth medium at three concentrations (500 µM, 250 µM, and 125 µM). The final DMSO concentration was 5%. Cultures were incubated for 18 h at 37 °C and 200 rpm agitation. The following controls were performed: 100 µM fosmidomycin (FOS) treatment which targets the MEP pathway in *E. coli*, media without inoculum, 5% DMSO (vehicle of MMV008138 analogs), and control with inoculum alone (untreated). After 18h incubation, bacteria growth was measured using a cell density meter. The percentage of growth was normalized to that of untreated control bacteria and potential inhibition of growth of MMV008138 analogs was determined by comparison to the 5% DMSO control.

None of these seven compounds inhibited *E. coli* growth at 500 µM (Fig. 9).

Example 112:

The effect of MMV008138 analogs was evaluated against asexual blood stages of *P. falciparum* parasites using the SYBR green assay as described previously.[8] The antimalarial activity of MMV008138 analogs was first evaluated against asexual parasites using four-point dilutions ranging from 10 μM to 1.25 μM. For active compounds, the half maximal inhibitory concentration (IC_{50}) were determined using eight- or ten-point dilutions at concentrations ranging from 20 μM to 0.02 μM in constant 0.1% DMSO (vehicle). The percentage of growth was normalized to that of untreated control parasites in the presence of 0.1% DMSO. Background determinations were made using uninfected erythrocytes. Two or more independent experiments were performed. The IC_{50} values were calculated with GraphPad Prism 6 (GraphPad Software Ltd.) using nonlinear regression curve fitting with variable slope (four parameters) and represent the average of two or more independent experiments and their standard deviation (S.D.). To assess whether compounds were specifically targeting the apicoplast, the recovery of growth in the presence of inhibitor and IPP was performed as described previously (Bowman, J. D.; Merino, E. F.; Brooks, C. F.; Striepen, B.; Carlier, P. R.; Cassera, M. B. Antiapicoplast and Gametocytocidal Screening To Identify the Mechanisms of Action of Compounds within the Malaria Box. *Antimicrob. Agents. Chemother.* 2014, *58*, 811-819). Briefly, parasites were grown in the presence or absence of 200 μM IPP along with a serial dilution (10 μM to 0.02 μM) or single concentration (10 or 20 μM) of MMV008138 analogs. All conditions were set in 96-well half area plates using ring-stage parasite cultures (100 μl/well with 1% hematocrit and 1% parasitemia) and incubated for 72 h under normal culture conditions. Parasite growth was measured by a SYBR green assay.

The results are demonstrated in Figs. in 6A and 6B. Figs. 6A and 6B show graphs demonstrating the effects of compounds according to Formula 60 (Fig. 6A) and Formula 80 (Fig. 6B) on *P. falciparum* Dd2 strain growth in the absence and presence of 200 μM IPP (72 h incubation). Data represent the average and standard error of five independent experiments.

Example 113:

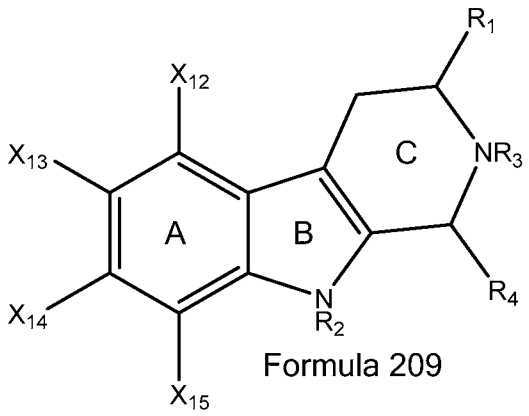
Fig. 7 shows a table demonstrating *in vitro* ADME Toxicity of compounds according to Formulas 60 and 80. Assays were performed by Pharmaron Corp., according to industry-standard procedures.

Example 114:

Fig. 8 shows a graph demonstrating pharmokinetics of a compound according to Formula 60 in the Mouse via oral (PO) (40 mg/kg) or intravenous (IV) administration (10 mg/kg). using 20% DMSO, 60% PEG400 and 20% sulfobutyl ether$_7$ β-cyclodextrin (SBE-β-CD, 30% w/v) as vehicle. Three male CD1 mice were used for each study. PO administration was by oral gavage, and IV administration was via tail vein injection. Studies were performed by Pharmaron.

We claim:

1. A composition according to Formula 209



Formula 209

,

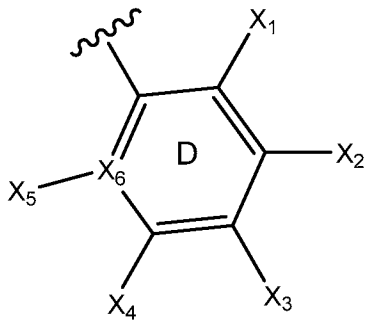
where R_1 is H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$ alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 is H or a C_1-C_6 alkyl,

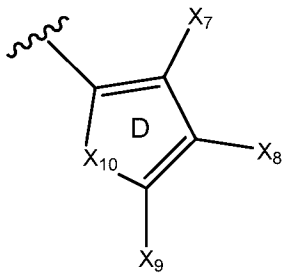
where R_3 is H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} are each independently selected from the group of: H and a halogen,

where R_4 has a structure according to Formula 210 or 211



Formula 210



Formula 211

,

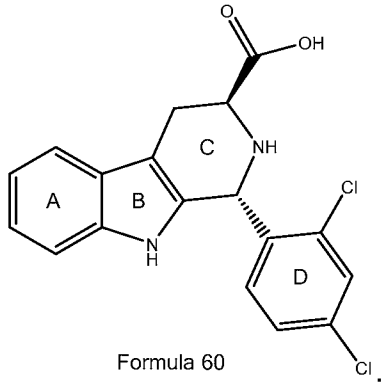
where X_1-X_5 are each independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} is a halogen,

where X_6 is C or N,

where X_{10} is selected from the group of O, S, and NX_{11}, where X_{11} is selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} is a halogen,

where X_7-X_9 are each independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} is a halogen, and

where the composition does not have a structure according to Formula 60



Formula 60

2. The composition of claim 1, wherein the compsition has a (1*R*,3*S*) configuration.

3. The compsition of claim 1, wherein the compsition has an R_4 of Formula 210.

4. The composition of claim 1, wherein the halogen is F, Cl, Br, I.

5. The composition of claim 1, wherein X_1 and X_3 are each a halogen.

6. The compsition of claim 4, wherein the halogen is F, Cl, Br, or I.

7. The compsition of claim 1, wherein X_1 and X_3 are each independently selected from a halogen and a C_1-C_6 alkyl.

8. The compsition of claim 7, wherein the halogen is F, Cl, Br, or I and the C_1-C_6 alkyl is methyl.

9. The compsition of any of claims 1-8, wherein R_1 is COOH or $CONHCH_3$.

10. The compsition of claim 9, wherein the compsition inhibits an enzyme of the methylerythritol phosphate pathway.

11. The compsition of claim 9, wherein the compsition is toxic to an organism of the genus *Plasmodium*.

12. The compsition of claim 11, wherein the toxicity at 5 μM of compsition is at least partially eliminated by supplementation with an amount of isopentenyl diphosphate (IPP).

13. The compsition of claim 12, wherein the toxicity at 5 μM of compsition is completely eliminated by supplementation with an amount of IPP.

14. The compsition of claim 1, wherein the compound is according to Formula 70, 74, 75, 80, 90, 126, 127, 128, 129, 131, 133, 138, or 140.

15. The compsition of claim 1, wherein the compsition is according to Formula 74, 80, 90, 126, 127, 128, 129, 133, 138, or 140.

16. The compsition of any one of claims 1-8, wherein the compsition inhibits an enzyme of the MEP pathway.

17. The compsition of claim 16, wherein the compound inhibits an enzyme of the methylerythritol phosphate pathway.

18. The compsition of claim 16, wherein the compound is toxic to an organism of the genus *Plasmodium*.

19. The compsition of claim 18, wherein the IC_{50} for growth inhibition of the organisim is about 880 nM or less.

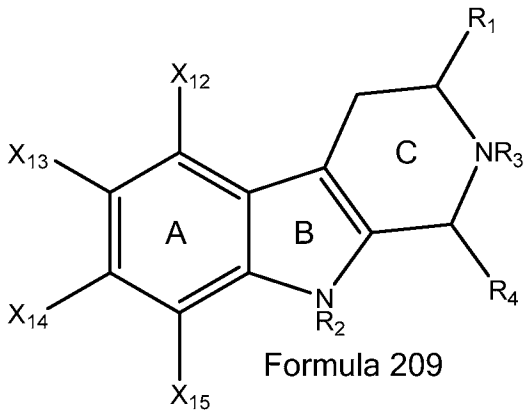
20. The compsition of claim 18, wherein the IC_{50} for growth inhibition of the organism is about 650 nM or less.

21. The compsition of claim 18, wherein the toxicity at 5 μM of compsition is at least partially eliminated by supplementation with an amount of isopentenyl diphosphate (IPP).

22. The compsition of claim 18, wherein the toxicity at 5 μM of compsition is completely eliminated by supplementation with an amount of isopentenyl diphosphate (IPP).

23. A pharmaceutical formulation comprising:

a composition according to Formula 209



Formula 209 ,

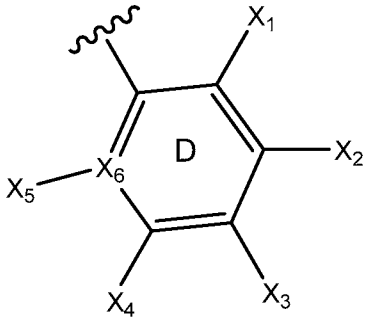
where R_1 is H, $COOCH_3$, COOEt, COOH, $CONH_2$, $CONHCH_3$, a $CONHC_{1-6}$ alkyl, $CONH(CH)_{1-5}(CH_3)_2$, $CON(C_6H_{11})$, $CONHNHCH_3$, $CON(CH_3)_2$, or CH_2OH,

where R_2 is H or a C_1-C_6 alkyl,

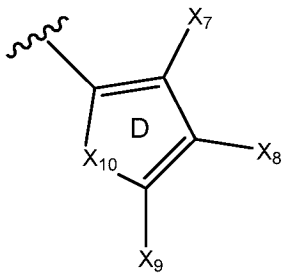
where R_3 is H, a C1-C6 alkyl group, a benzyl, $COCH_3$,or a diketopiperazine formed between N_2 and R_1,

where X_{12}-X_{15} are each independently selected from the group of: H and a halogen,

where R_4 has a structure according to Formula 210 or 211



Formula 210



Formula 211

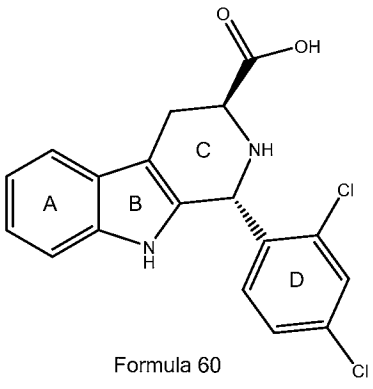
where X_1-X_5 are each independently selected from the group of H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} is a halogen,

where X_6 is C or N,

where X_{10} is selected from the group of O, S, and NX_{11}, where X_{11} is selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$, where X_{16} is a halogen,

where X_7-X_9 are each independently selected from the group of: H, a halogen, a C_1-C_6 alkyl, a C_1-C_6 alkoxy, $NHCH_3$, and $C(X_{16})_3$ where X_{16} is a halogen, and

where the composition does not have a structure according to Formula 60



Formula 60; and

a pharmaceutically acceptable carrier.

24. The pharmaceutical formulation of claim 23, wherein the compound has a 1*R*, 3*S* configuration.

25. The pharmaceutical formulation of claim 23, wherein the compound has an R_4 of Formula 210.

26. The pharmaceutical formulation of claim 23, wherein the halogen is F, Cl, Br, I.

27. The pharmaceutical formulation of claim 23, wherein X_1 and X_3 are each a halogen.

28. The pharmaceutical formulation of claim 27, wherein the halogen is F, Cl, Br, or I.

29. The pharmaceutical formulation of claim 23, wherein X_1 and X_3 are each independently selected from a halogen and a C_1-C_6 alkyl.

30. The pharmaceutical formulation of claim 29, wherein the halogen is F, Cl, Br, or I and the C_1-C_6 alkyl is methyl.

31. The pharmaceutical formulation of any of claims 23-30, wherein R_1 is COOH or $CONHCH_3$.

32. A method comprising:

administering a composition according to any one of claims 1-22 or a pharmaceutical formulation according to any one of claims 23-31 to a subject in need thereof.

33. The method of claim 32, wherein the subject is infected with or is suspected of being infected with a methylerythritol phosphate (MEP) pathway obligate organism.

34. The method of claim 32, wherein the composition or pharmaceutical formulation is administered prophylactically to prevent infection by a methylerythritol phosphate (MEP) pathway obligate organism.

35. The method of any one of claims 33-34, wherein the organism is a species of the genus *Plasmodium*, *Toxoplasma, Mycobacterium*, *Baccillus*, *Vibrio*, *Clostriduium*, *Helicobacter*, *Campylobacter*, *Chlamydia, Brucella*, *Eimeria, Klebsiella, Acinetobacter, Pseudomonas,* or *Neisseria*.

36. The method of any one of claims 33-34, wherein the organism is *P. falciparum*, *P. malariae, P. ovale, P. vivax* or *P. knowlesi*.

37. The method of any one of claims 33-34, wherein the organism is *T. gondii*, *M. tuberculosis*, *B. anthracis*, *V. cholera*, *C. difficile*, *C. botulinum*, *H. pylori*, *C. jejuni*, *C. trachomatis 434/Bu*, *C. pneumoniae*, *B. abortus*, *E. tenella. K. pneumoniae, A. baumanii, P. aeruginosa, or N. gonorrhoeae.*

38. The method of any one of claims 32-34, wherein the composition or pharmaceutical formulation is administered orally, intramuscularly, intravenously, topically or subcutaneously.

39. A method comprising:

contacting an organism with an amount of a composition according to any one of claims 1-22 or a pharmaceutical formulation according to any one of claims 23-31.

40. The method of claim 39, wherein the organism is a methylerythritol phosphate (MEP) pathway obligate organism.

41. The method of claim 39, wherein the organism uses the methylerythritol phosphate (MEP) pathway to synthesize isopentenyl diphosphate (IPP).

42. The method of any one of claims 39-41, wherein the organism is a plant.

43. The method of any one of claims 39-41, wherein the organism is a protazoan.

44. The method of any one of claims 39-41, wherein the organism is a bacterium.

45. A method comprising:

administering a composition according to Formula 60 or a pharmaceutical formulation comprising a composition according to Formula 60 to a subject in need thereof,

where the subject in need thereof is infected with or is suspected of being infected with a methylerythritol phosphate (MEP) pathway obligate organism.

46. A method comprising:

prophylactically adminstering.a composition according to Formula 60 or a pharmaceutical formulation comprising a composition according to Formula 60 to a subject in

need thereof to prevent infection by a methylerythritol phosphate (MEP) pathway obligate organism.

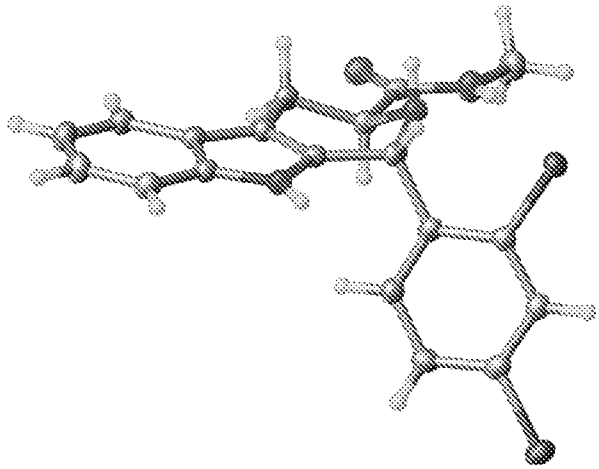
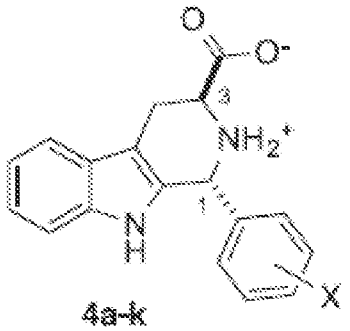
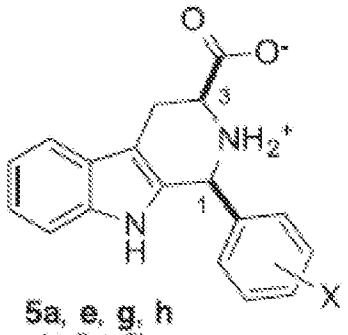


FIG. 1



4a-k
(1*R*,3*S*)-

&



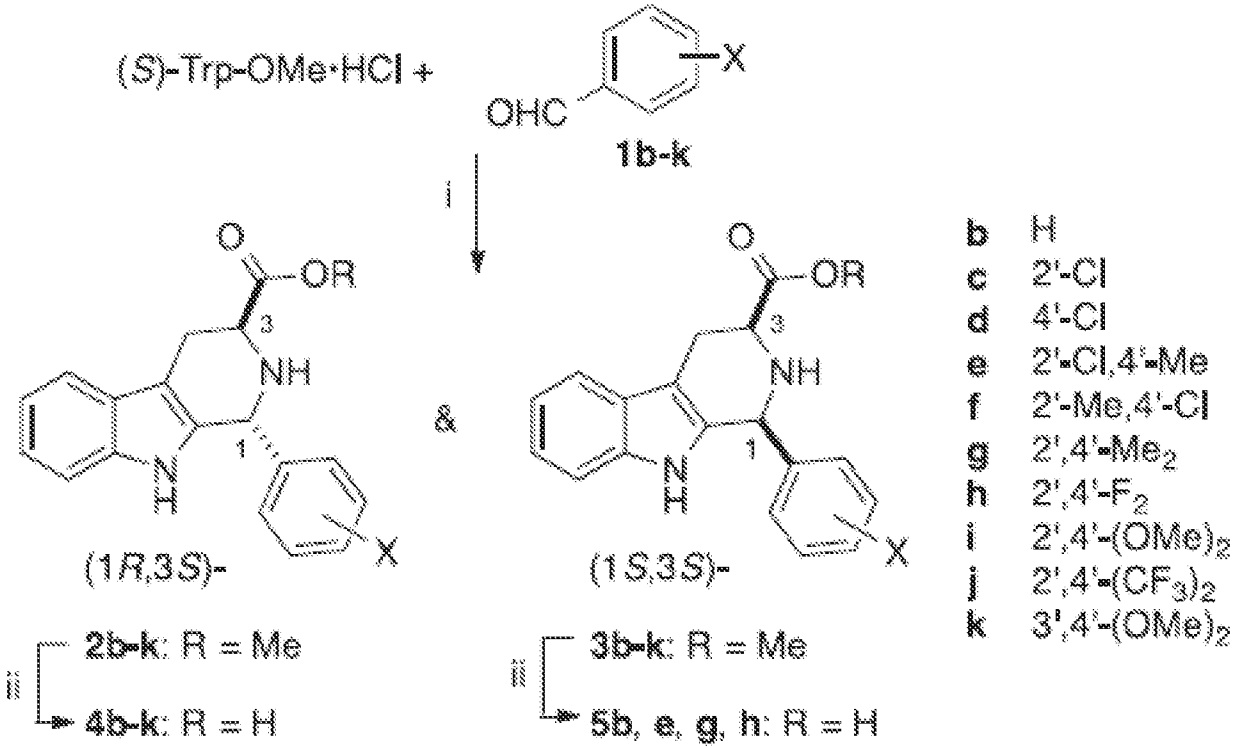
5a, e, g, h
(1*S*,3*S*)-

Entry	Compound	X	*P. falciparum* Dd2 strain[a] IC_{50} (nM)	% rescue (+ 200 μM IPP)[b]
1	FOS		880 ± 70	100 @ 10 μM
2	MMV008138	2′,4′-Cl_2	210 ± 90	100 @ 2.5 μM
3	**4a**	2′,4′-Cl_2	250 ± 70	100 @ 2.5 μM
4	*ent*-**4a**	2′,4′-Cl_2	>10,000	ND
5	**4b**	H	>10,000	ND
6	**4c**	2′-Cl	3280 ± 990	60 @ 10 μM
7	**4d**	4′-Cl	1170 ± 60	50 @ 10 μM
8	**4e**	2′-Cl, 4′-Me	410 ± 40	100 @ 2.5 μM
9	**4f**	2′-Me, 4′-Cl	700 ± 90	100 @ 2.5 μM
10	**4g**	2′,4′-Me_2	70% inhibition @ 10,000	ND
11	**4h**	2′,4′-F_2	780 ± 175	100 @ 5 μM
12	**4i**	2′,4′-$(OMe)_2$	>20,000	ND
13	**4j**	2′,4′-$(CF_3)_2$	>10,000	ND
14	**4k**	3′,4′-$(OMe)_2$	>20,000	ND
15	**5a**	2′,4′-Cl_2	>10,000	ND
16	*ent*-**5a**	2′,4′-Cl_2	3000 ± 200	60 @ 10 μM
17	**5b**	H	>10,000	ND
18	**5e**	2′-Cl, 4′-Me	>10,000	ND
19	**5g**	2′,4′-Me_2	>10,000	ND
20	**5h**	2′,4′-F_2	>20,000	ND

[a] MRA-150, chloroquine-resistant (intermediate), pyrimethamine-resistant, mefloquine-resistant.

[b] Drug at indicated concentration; ND signifies 'not determined.'

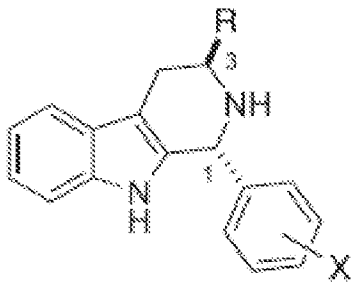
FIG. 2



i) 4 Å molecular sieves, DCM, RT, 24 h; TFA (2 equiv) 8 - 23 h.
ii) NaOH (aq, 6 equiv), 2 hr; HCl (aq) *or* Amberlyst hydroxide, THF/MeOH/H_2O; AcOH, H_2O.

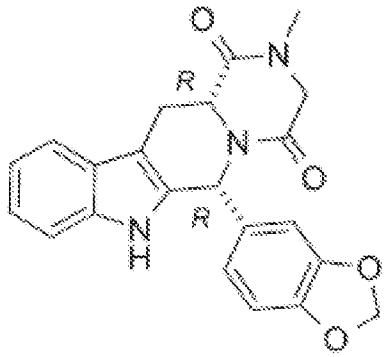
	%Yield		%Yield		%Yield		%Yield
2b	14	**3b**	67	**4b**	99	**5b**	95
2c	18	**3c**	59	**4c**	95		
2d	20	**3d**	61	**4d**	95		
2e	40	**3e**	60	**4e**	78	**5e**	69
2f	21	**3f**	37	**4f**	56		
2g	40	**3g**	52	**4g**	85	**5g**	83
2h	30	**3h**	68	**4h**	74	**5h**	68
2i	27	**3i**	19	**4i**	90		
2j	39	**3j**	61	**4j**	84		
2k	41	**3k**	36	**4k**	86		

FIG. 3



2, 6-12

	X
a	2',4'-Cl_2
b	H
e	2'-Cl, 4'-Me
f	2'-Me, 4'-Cl
g	2',4'-Me_2
h	2',4'-F_2
j	2',4'-$(CF_3)_2$



Tadalafil

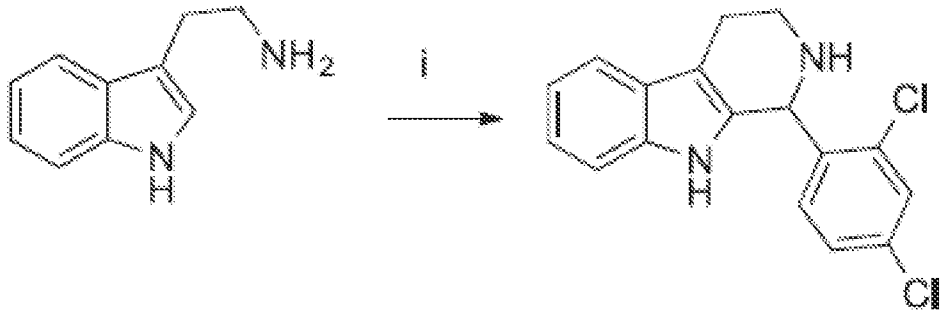
Entry	Compound	R	*P. falciparum* Dd2 strain[a] IC_{50} (nM)	% Rescue (+200 μM IPP)[b]
1	**2a**	CO_2Me	6800 ± 1400	~20 @ 20 μM
2	*ent*-**2a**	CO_2Me	7700 ± 1400	0 @ 20 μM
3	**2b**	CO_2Me	~20% inhibition @ 20,000	ND
4	(±)-**6a**	H	10,000 ± 1600	0 @ 20 μM
5	**7a**	$CONH_2$	1200 ± 100	50 @ 10 μM
6	**8a**	CONHMe	190 ± 30	100 @ 2.5 μM
7	**8e**	CONHMe	340 ± 50	100 @ 2.5 μM
8	**8f**	CONHMe	1850 ± 600	50 @ 10 μM
9	**8g**	CONHMe	70% inhibition @ 10,000	ND
10	**8h**	CONHMe	1200 ± 100	100 @ 2.5 μM
11	**8j**	CONHMe	>10,000	ND
12	**9a**	CONHi-Pr	50% inhibition @ 10,000	ND
13	**10a**	CONHBu	80% inhibition @ 10,000	ND
14	**11a**	CONHc-C_6H_{11}	2830 ± 500	0 @ 10 μM
15	**12a**	CONHNHMe	1940 ± 200	80 @ 10 μM
16	Tadalafil	NA[c]	>20,000	ND

[a] MRA-150, chloroquine-resistant (intermediate), pyrimethamine-resistant, mefloquine-resistant.

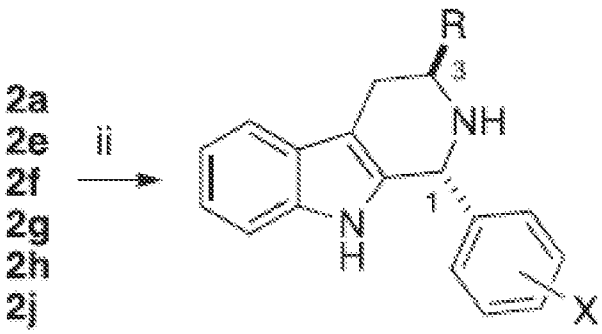
[b] Drug at indicated concentration; ND signifies 'not determined.'

[c] Not applicable.

FIG. 4



(±)-**6a** (42%)



	R	% yield
7a	$CONH_2$	98
8a	CONHMe	99
8e	CONHMe	99
8f	CONHMe	64
8g	CONHMe	99
8h	CONHMe	99
8j	CONHMe	77
9a	CONH*i*-Pr	47
10a	CONHBu	96
11a	CONH*c*-C_6H_{11}	60
12a	CONHNHMe	78

FIG. 5

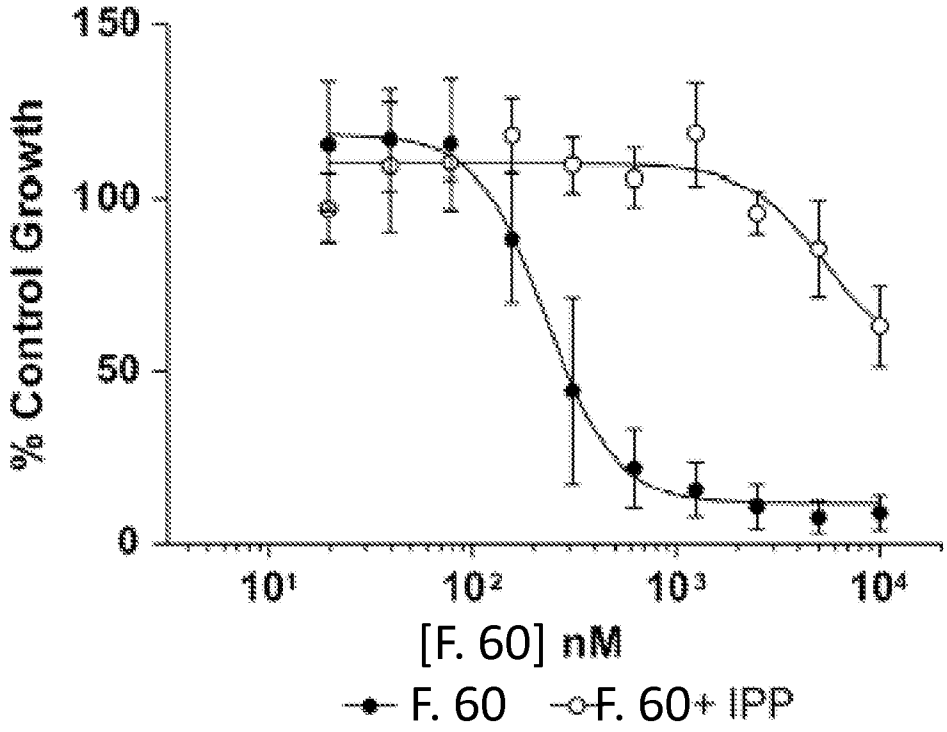

150
100
50
0
% Control Growth
10¹
10²
10³
10⁴
[F. 60] nM
F. 60
F. 60+ IPP

FIG. 6A

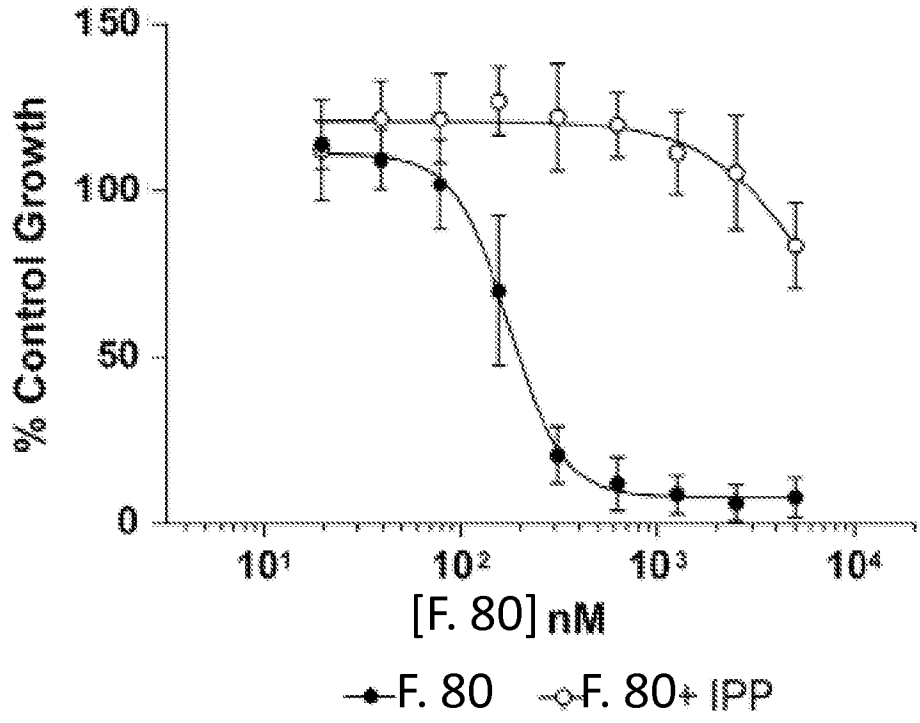

150
100
50
0
% Control Growth
10¹
10²
10³
10⁴
[F. 80] nM
F. 80
F. 80+ IPP

FIG. 6B

Table 2. *In Vitro* ADME-Tox Study (Pharmaron)

Assay	Unit	F. 60	F. 80
Thermodynamic Solubility pH 7.4	mg/mL	1.05	0.0006
Chemical Stability	%	105	nd
Plasma stability (m, 2 h)	%	108	97
PPB (*m*, 1, 10 µM)	%	93.7, 93.4	97.0, 96.1
Caco2 P_{app}(A-B)	10^{-6} cm/s	4.13	13.2
Caco2 P_{app}(B-A)	10^{-6} cm/s	6.19	7.4
Efflux ratio (B/A)		1.5	0.56
Male mouse liver microsomes $t_{1/2}$	min^{-1}	14.5	19.3
HepG2 cytotoxicity	µM	182	152
hERG IC_{50}	µM	>30	16.2
2C9 IC_{50}	µM	12.7	nd
2D6, 3A4 (m), 3A4 (t) IC_{50}	µM	all >50	nd

FIG. 7

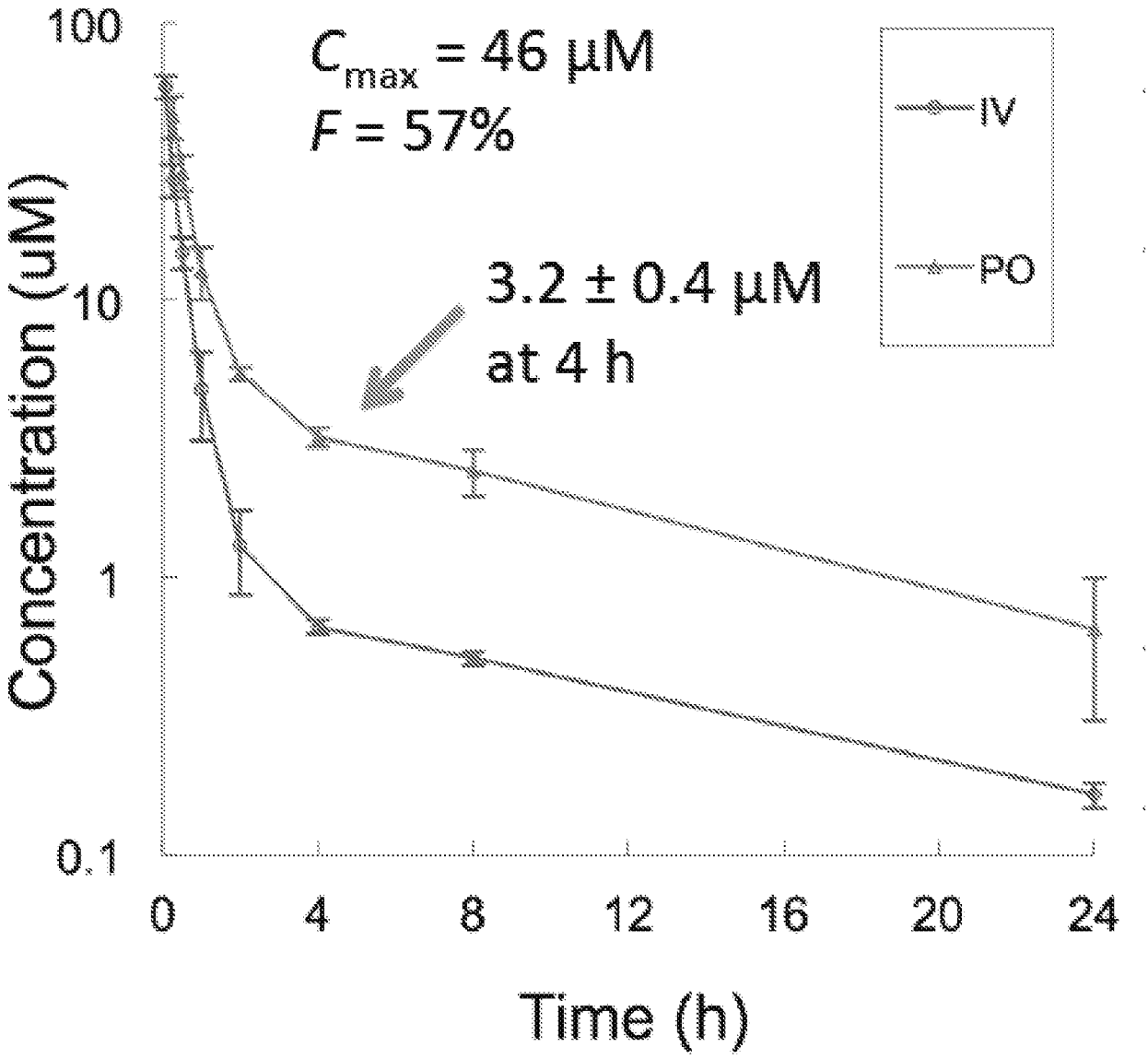

100
10
1
0.1
Concentration (uM)
C_{max} = 46 µM
F = 57%
3.2 ± 0.4 µM
at 4 h
IV
PO
0
4
8
12
16
20
24
Time (h)

FIG. 8

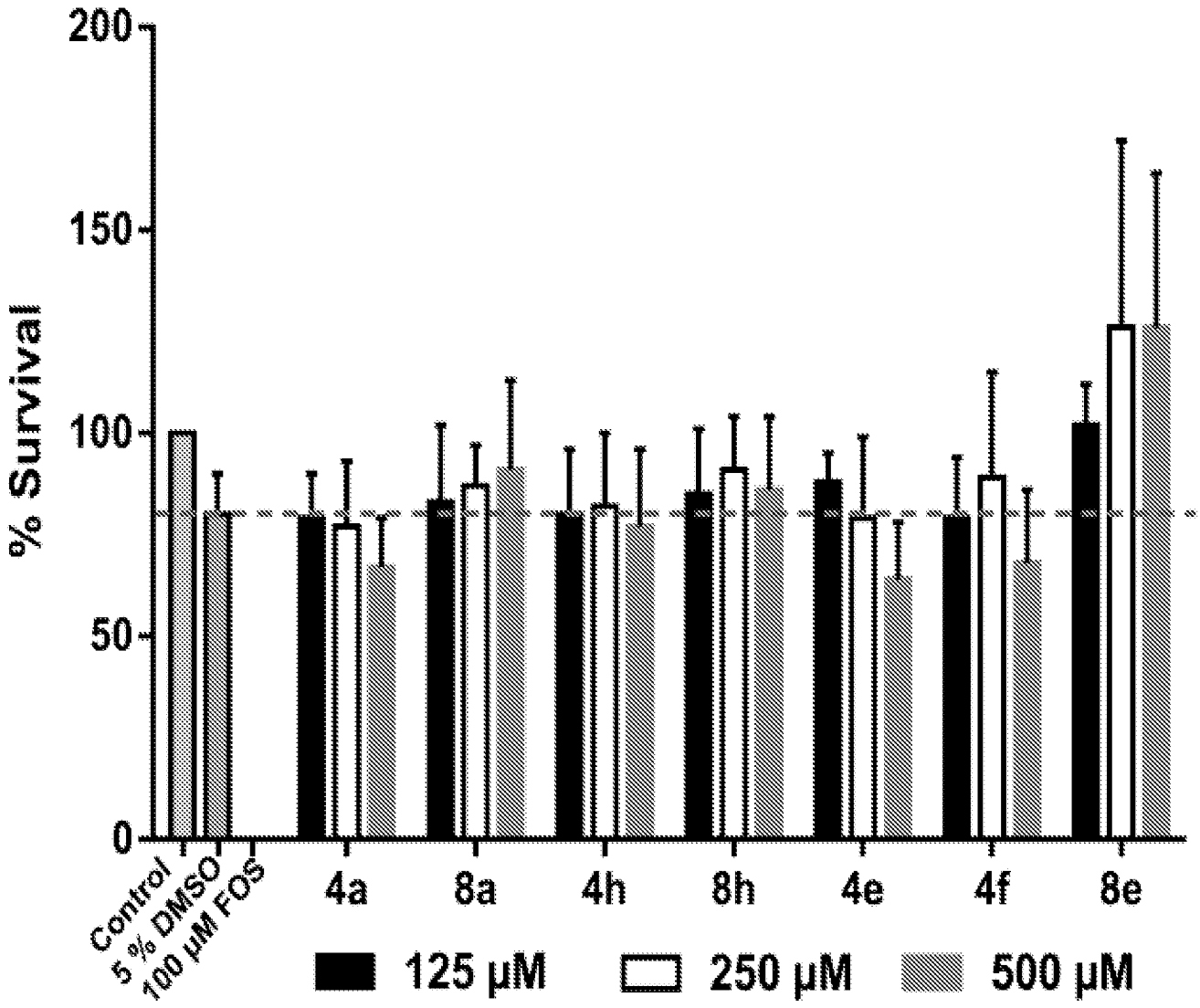

200
150
100
50
0
% Survival
Control
5 % DMSO
100 µM FOS
4a
8a
4h
8h
4e
4f
8e
125 µM
250 µM
500 µM

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/58157

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4545; C07D 471/04 (2015.01)
CPC - A61K 31/4545; C07D 471/04
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)
IPC(8): A61K 31/4545; C07D 471/04 (2015.01)
CPC: A61K 31/4545; C07D 471/04

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: MEP, methylerythritol, phosphate, pathway, inhibit, isopentenyl, diphosphate, toxic, organism, plasmodium, infection

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2013/0171103 A1 (DAVIS, T et al.) 04 July 2013; paragraphs [0026], [0032]-[0034], [0039], [0052], [0086], [0089]-[0097], [0103]-[0104], [0253]-[0254], [0291]-[0292], [0359], [0378]; table 1	1-8, 9/1-8, 14-15, 23-30, 31/23-30 ---------- 10/9/1-8, 11/9/1-8, 12/11/9/1-8, 13/12/11/9/1-8, 16/1-8, 17/16/1-8, 18/16/1-8, 19/18/16/1-8, 20/18/16/1-8, 21/18/16/1-8, 22/18/16/1-8, 45-46
Y	WO 2012/135064 A2 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 04 October 2012; paragraphs [0011], [0022], [0034]; figures 1A, 1B	10/9/1-8, 11/9/1-8, 12/11/9/1-8, 13/12/11/9/1-8, 16/1-8, 17/16/1-8, 18/16/1-8, 19/18/16/1-8, 20/18/16/1-8, 21/18/16/1-8, 22/18/16/1-8
Y	US 2013/0065857 A1 (SONG, Y) 14 March 2013; abstract; paragraph [0018]	45-46

☒ 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
"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	Date of mailing of the international search report
04 December 2015 (04.12.2015)	21 JAN 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/071074 A1 (INVISTA NORTH AMERICA S.A. R.I.) 16 May 2013; entire document	1-8, 9/1-8, 10/9/1-8, 11/9/1-8, 12/11/9/1-8, 13/12/11/9/1-8, 14-15, 16/1-8, 17/16/1-8, 18/16/1-8, 19/18/16/1-8, 20/18/16/1-8, 21/18/16/1-8, 22/18/16/1-8, 23-30, 31/23-30, 45-46
A	US 2012/0178707 A1 (CAO, L et al.) 12 July 2012; entire document	1-8, 9/1-8, 10/9/1-8, 11/9/1-8, 12/11/9/1-8, 13/12/11/9/1-8, 14-15, 16/1-8, 17/16/1-8, 18/16/1-8, 19/18/16/1-8, 20/18/16/1-8, 21/18/16/1-8, 22/18/16/1-8, 23-30, 31/23-30, 45-46

International application No.
PCT/US15/58157

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 32-44
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.