Supporting Information

N-Methyl-*N*-((1-methyl-5-(3-(1-(2-methylbenzyl)piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine, a New Cholinesterase and Monoamine Oxidase Dual Inhibitor

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QSAR Methods

The inhibiting MAO A/ B and AChE/BuChE activities (IC_{50}) of 30 indole derivatives were used for the QSAR study [(a) Bolea, I.; Gella, A.; Monjas, L.; Pérez, C.; Rodríguez-Franco, M. I.; Marco-Contelles, J. L.; Samadi, A.; Unzeta, M. The multipotent, permeable compound ASS234 inhibits Aβ aggregation, possesses antioxidant properties and protects from Aβ-induced apoptosis, *Curr. Alzheimer Res.* **2013**, *9*, 797-808; (b) V. Pérez, V.; Marco, J. L.; Fernández-Álvarez, E.; Unzeta, M. Relevance of benzyloxy group in 2-indolyl methylamines in the selective MAO-B inhibition, *Br. J. Pharmacol.* **1999**, *127*, 869-876, (c) Bautista-Aguilera, O. M.; Esteban, G.; Bolea, I.; Nikolic, K.; Agbaba, D.; Moraleda, I.; Iriepa, I.; Samadi, A.; Soriano, E.; Unzeta, M.; Marco-Contelles, J. Design, synthesis, pharmacological evaluation, qsar analysis, molecular modeling and admet of novel donepezil-indolyl hybrids as multipotent cholinesterase/monoamine oxidase inhibitors for the potential treatment of Alzheimer's disease, Eur. J. Med. Chem. 2014, 75, 82-95]. Negative logarithm of their IC_{50} i.e. (pIC_{50}) values were calculated.

Geometry optimization for the indole derivatives was performed by *ab initio* Hartree-Fock/3-21G method [Froese Fischer, C. F. The Hartree-Fock Method for Atoms: A Numerical Approach. John Wiley and Sons, New York. ISBN 047125990X (1977)] included in the Gaussian 98 program [Gaussian 98 (Revision A.7) Frisch MJ et al Gaussian, Inc., (1998), Pittsburgh PA.]. The selected Gaussian basis set methods have proven to be a very good choice for geometry optimization of related aromatic and organic compounds [(a) Filipic, S.; Nikolic, K.; Vovk, I.; Krizman, M.; Agbaba, D. Quantitative structure-mobility relationship analysis of imidazoline receptor ligands in CDs-mediated CE. *Electrophoresis* **2013**, *34*, 471–482; (b) Nikolic, K.; Ivković, B.; Bešović, Ž.; Marković, S.; Agbaba, D. A Validated Enantiospecific Method for

Determination and Purity Assay of Clopridogrel. *Chirality* **2009**, *21*, 878-885; (c) Remko M.; Swart, M.; Bickelhaupt, F.M. Theoretical study of structure, pKa, lipophilicity, solubility, absorption, and polar surface area of some centrally acting antihypertensives. *Bioorg. Med. Chem.* **2006**, *14*, 1715-1728; (d) Nikolic K.; Filipic, S.; Agbaba, D. *Bioorg. Med. Chem.* **2008**, *16*, 7134–7140; (e) Nikolic, K.; Filipic, S.; Agbaba, D. QSAR study of selective I1-imidazoline receptor ligands. *SAR QSAR Environ. Res.* **2008**, *20*, 133–144].

The pKa calculation and selection of dominant molecules/cations at physiological pH 7.4 was performed for the examined compounds using the MarvinSketch 5.5.1.0 program [ChemAxon MarvinSketch 5.5.1.0 program, Budapest, Hungary (2011) www.chemaxon.com/products.html]. Dominant forms at pH 7.4, were used for the 3D-QSAR study.

The 3D-QSAR studies of the indole derivatives were performed by use of the Pentacle 1.0.6 program [Pentacle, Version 1.0.6.; Molecular Discovery Ltd, Perugia, Italy (2009) http://www.moldiscovery.com/soft_pentacle.php].

The Pentacle is advanced software tool for obtaining alignment-independent 3D quantitative structure-activity relationships. The 3D-QSAR starts from computing highly relevant 3D maps of interaction energies (GRID based Molecular Interaction Fields-MIFs) between the examined molecule and four chemical probes: DRY (which represent hydrophobic interactions), O (sp^2 carbonyl oxygen, representing H-bond acceptor), N1 (neutral flat NH, like in amide, H-bond donor), and the TIP probe (molecular shape descriptor). The grid spacing was set to 0.5 Å and the MACC2 smoothing window to 1.6 (for 3D-QSAR (ChE) models) and the CLACC smoothing window to 1.6 (for 3D-QSAR (MAO) models). The number of filtered nodes was set to 100 with 50% relative weights within the ALMOND discretization.

The interaction energy between the probe and the target molecule is calculated at each point as the sum of Lennard-Jones (E_{lj}), hydrogen bond (E_{hb}), electrostatic interactions (E_{el}), and an entropic term: $E_{xyz} = \Sigma E_{lj} + \Sigma E_{el} + \Sigma E_{hb} + S$ [Pastor, M.; Cruciani, G.; McLay, I.; Pickett, S.; Clementi, S.; GRid-INdependent descriptors (GRIND): A novel class of alignment-independent three-dimensional molecular descriptors. *J. Med. Chem*. **2000**, *43*, 3233-3243].

The maps obtained are encoded into GRID Independent Descriptors (GRIND and GRIND2 descriptors) which are independent of the alignment of the series [Pastor, M.; Cruciani, G.; McLay, I.; Pickett, S.; Clementi, S.; GRid-INdependent descriptors (GRIND): A novel class of alignment-independent three-dimensional molecular descriptors. *J. Med. Chem*. **2000**, *43*, 3233-3243]. The GRIND approach aims to extract the information enclosed in the MIFs and compress it into new types of variables whose values are independent of the spatial position of the molecule studied by using an optimization algorithm with the intensity of the field at a node and the mutual node−node distances between the chosen nodes as a scoring function. Such variables constitute a matrix of descriptors that are analyzed using multivariate techniques, such as Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression analysis. The Principal Component Analysis was used for inspection of our series and for obtaining a map of our compounds describing their similarities and differences. The variables were used for development of 3D-QSAR models by use of the PLS regression [Eriksson, L.; Johansson, E.; Kettaneh-Wold, N.; Trygg, J.; Wikstrom, C.; Wold, S. (Eds.) Multi-and Megavariate Data Analysis. Basic Principles and Applications I, 2nd ed, Umetrics Academy, Umeå, 2001.].

Based on the Score Plots (t1 vs. t2 and t1 vs. u1) the data set of 30 MAO A/B inhibitors and data set of 35 AChE/BuChE inhibitors is divided on Training Set (23-29

compounds for QSAR models building) and Verification set (6-9 compounds for QSAR models validation) [Tropsha, A. Best practices for QSAR model development, validation, and exploitation. *Mol. Inf.* **2010**, *29*, 476–488]. The most important pharmacophores (GRID descriptors), responsible for the MAO A, MAO B, AChE, and BuChE inhibition, were selected by use of the PLS regression and used for the 3D-QSAR (MAO A, MAO B, AChE, BuChE) models building (Pentacle 1.0.6 program).

The quality of the 3D-QSAR models obtained was examined by use of: leave-one-out cross-validation (Q^2), correlation coefficient (R^2 Observed vs. Predicted), Root Main Squared Error of Estimation (RMSEE), and external validation (Root Main Squared Error of Prediction (RMSEP)) [(a) Wold, S.; Johansson, E.; Cocchi, M. 3D-QSAR in drug design, theory, methods, and applications. H. Kubinyi Ed., ESCOM Science Publishers: Leiden, 1993, pp 523–550; (b) Tropsha, A. Best practices for QSAR model development, validation, and exploitation. *Mol. Inf.* **2010**, *29*, 476–488]. Predictive power of the model is determined by Q^2, which is leave-one-out cross-validated version of R^2.

PLS models with $Q^2 \geq 0.5$ can be considered to have good predictive capability [(a) Allen, D.M. *Technometrics* **1974**, *16*, 125-127; (b) Wold, S.; Johansson, E.; Cocchi, M. 3D-QSAR in drug design, theory, methods, and applications. H. Kubinyi Ed., ESCOM Science Publishers: Leiden, 1993, pp 523–550].

The most significant variables of the 3D-QSAR (MAO A) model such as: v136: TIP-TIP, v162: TIP-TIP, v173: TIP-TIP, v271: DRY-TIP, v293: DRY-TIP, v365: O-TIP, v154: TIP-TIP, v317: O-N1, v400: N1-TIP, and v405: N1-TIP, are selected as pharmacophores with the strongest influence on MAO A inhibiting activity. The variables: v136: TIP-TIP, v162: TIP-TIP, v173: TIP-TIP, v271: DRY-TIP, v293: DRY-TIP, and v365: O-TIP are positively correlated with the MAO A inhibiting activity,

while variables such as: v154: TIP-TIP, v317: O-N1, v400: N1-TIP, and v405: N1-TIP, are negatively correlated with the MAO A inhibiting activity.

The most significant variables of the 3D-QSAR (MAO B) model such as: v136: TIP-TIP, v150: TIP-TIP, v181: DRY-O, v275: O-TIP, v356: O-TIP, v361: O-TIP, v48: O-O, v96: N1-N1, v167: TIP-TIP and v399: N1-TIP, are examined as pharmacophores with the strongest influence on MAO B inhibiting activity. The variables: v136: TIP-TIP, v150: TIP-TIP, v181: DRY-O, v275: DRY-TIP, v356: O-TIP and v361: O-TIP, are positively correlated with the MAO B inhibiting activity, while variables such as v48: O-O, v96: N1-N1, v167: TIP-TIP, and v399: N1-TIP, are negatively correlated with the MAO B inhibiting activity.

The most significant variables of the 3D-QSAR (AChE) model such as: v52: O-O, v96: N1-N1, v146: TIP-TIP, DRY-TIP, v283: DRY-TIP, v324: O-N1, v434: N1-TIP, v33: DRY-DRY, v62: O-O, v223: DRY-N, and v415: N1-TIP, are selected as pharmacophores with the strongest influence on AChE inhibiting activity. The variables such as: v52: O-O, v96: N1-N1, v146: TIP-TIP, DRY-TIP, v283: DRY-TIP, v324: O-N1, and v434: N1-TIP are positively correlated with the AChE inhibiting activity, while variables v33: DRY-DRY, v62: O-O, v223: DRY-N, and v415: N1-TIP, are negatively correlated with the AChE inhibiting activity.

The most significant variables of 3D-QSAR (BuChE) such as: v173: TIP-TIP, v448: N1-TIP, v21: DRY-DRY, v165: TIP-TIP, V204: DRY-O, V246/v251: DRY-N, V304: DRY-TIP, and V438/v425: N1-TIP, are examined as pharmacophores with the strongest influence on BuChE inhibiting activity. The variables v173: TIP-TIP, v448: N1-TIP are positively correlated with the BuChE inhibiting activity, while variables v21:

DRY-DRY, v165: TIP-TIP, V204: DRY-O, V246/v251: DRY-N, V304: DRY-TIP, and V438/v425: N1-TIP are negatively correlated with the BuChE inhibiting activity.

ADMET descriptors

Table S1. Calculated physicochemical and ADMET properties for compounds II and 2.[a,b]

Compound	Molecular weight	No. of H-bond donors	No. of H-bond acceptor	No. of Rotatable Bonds	logP (Moriguchi)[a,c]	logP[a]	TPSA (in Å^2)	No. violations Lipinski's rule	LogBB[a,d]	LogBB[b,d]	Peff (cm/s x 10^4)	Human intestinal absortion (%)[e]	In vitro Caco-2 perm (nm/sec)[f]	MDCK (cm/s x 10^7)[g]	% Plasma protein binding (in vitro)[h]	Toxicity[i]
II	443.64	0	4	10	3.83	5.88	20.64	1	0.25	0.31	5.63	100	32.71	216.59	60.53	hERG
2	457.66	0	4	10	4.17	6.19	20.64	1	0.39	0.54	5.71	100	34.52	225.08	64.99	hERG

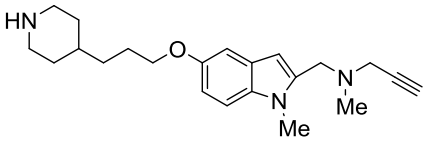
a AMET Predictor, v.6.5. *b* ACD/Percepta 14.0. *c* Moriguchi model. *d* High absorption to CNS: logBB more than 0.3; Middle absorption to CNS: logBB 0.3 ~ -1.0; Low absorption to CNS: logBB less than -1.0. *e* Human intestinal absorption is the sum of bioavailability and absorption evaluated from ratio of excretion or cumulative excretion in urine, bile, and feces. A value between 0 and 20% indicates poor absorption, 20−70% shows moderate absorption, and 70−100% indicates good absorption. *f* Caco-2 cells are derived from human colon adenocarcinoma and possess multiple drug transport pathways through the intestinal epithelium. A value <4 indicates low permeability, 4−70 shows middle permeability, and >70 indicates high permeability. *g* The MDCK cell system may be used as a good tool for rapid permeability screening. A value <25 indicates low permeability, 25−500 shows middle permeability, and >500 indicates high permeability. *h* The percent of drug binds to plasma protein. A value <90% indicates weak binding, and >90% indicates strong binding to plasma proteins. *i* hERG = hERG liability.

ADMET predictions

These predictions prompted us to carry out the virtual ADMET analysis of hybrid **2** by comparing it with compound **II**. The lipophilicity (expressed as logP) predicted for both compounds **II** and **2** is slightly higher than the traditionally cutoff value of 5 of the Lipinski's rules used in drug design (logP < 5 and/or mlogP < 4.1). CNS drugs have significantly reduced molecular weights compared with other therapeutics, and it has been suggested that molecular weight (MW) should be kept below 450 to facilitate brain penetration and to be lower than that for oral absorption. According to this, the structures show limit values (MW ≈ 450). The computed values predict a brain penetration sufficient for CNS activity, showing **2** with a better penetration profile than compound **II**. The structures show an adequate permeability to be good candidates (Peff > 0.1, MDCK > 25), and should be well absorbed compounds (% HIA). In addition, a middle Caco-2 cell permeability is suggested. Regarding toxicity, the structures lack hepatotoxicity, and show hERG liability. In summary, it can be concluded that hybrid **2** presents similar good drug-like characteristics and ADMET properties as compound **II**, and a slightly better brain penetration ability (Table S1, **Supporting Information**).

Chemistry

Structure of the synthesized compounds



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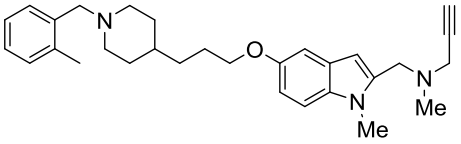

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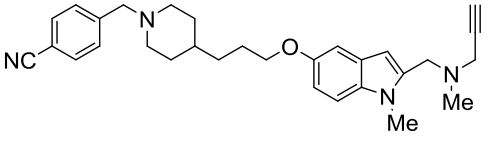

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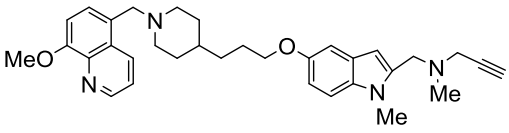

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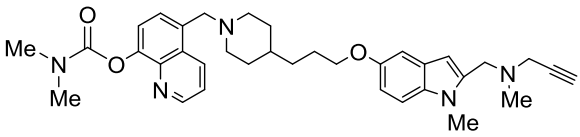

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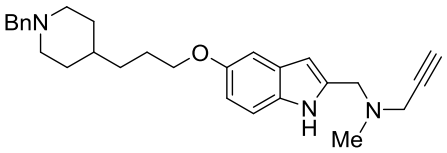

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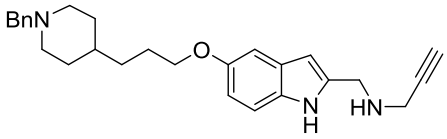

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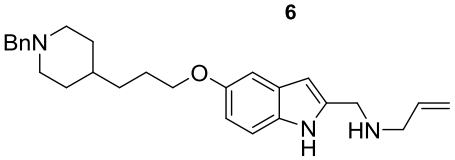

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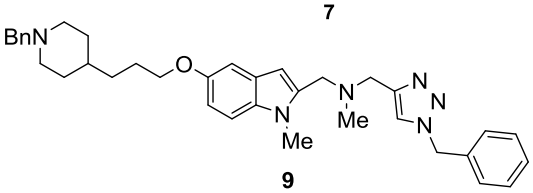

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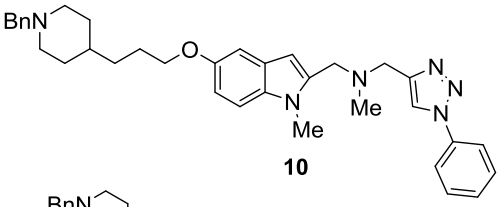

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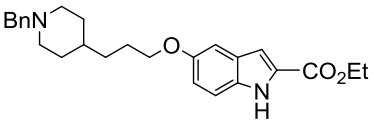

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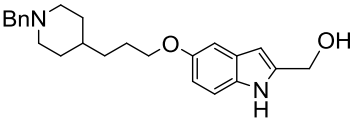

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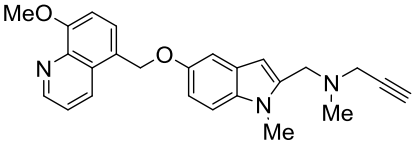

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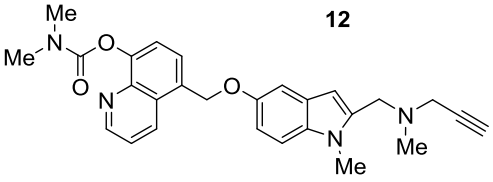

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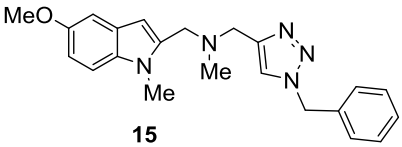

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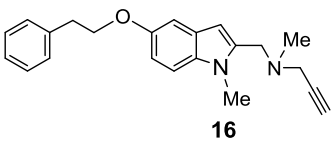

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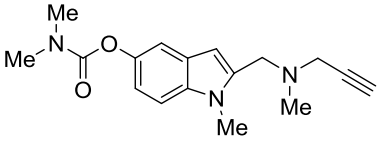

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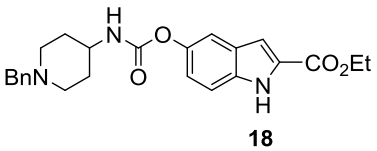

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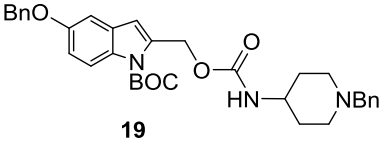

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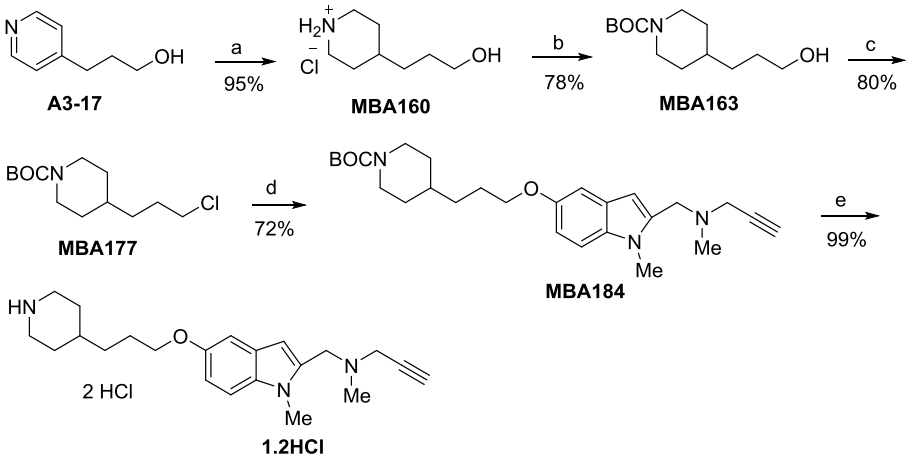
Experimental procedures

General Methods. Melting points were determined in a Koffler apparatus, and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 at 300, 400 or 500 MHz and at 75.4, 100.6 or 125.6 MHz, respectively, using solvent peaks [$CDCl_3$: 7.27 (*D*), 77.2 (*C*) ppm and DMSO-d_6 2.50 (D) and 39.7 (C) ppm] as internal references. The assignment of chemical shifts is based on standard NMR experiments (^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, HMBC, DEPT). Mass spectra were recorded on a GC/MS spectrometer with an API-ES ionization source. Elemental analyses were performed at the IQOG (CSIC, Spain). Tlc analyses were performed on silica F254 and detection by UV light at 254 nm, or by spraying with phosphomolybdic-H_2SO_4 dyeing reagent. Column chromatographies were performed on silica Gel 60 (230 mesh). "Chromatotron" separations were performed on a Harrison Research Model 7924. The circular disks were coated with Kieselgel 60 PF254 (E. Merck). The chlorydrate salts were prepared by solubilising the compound in a minimum of ether and a solution of ether saturated with HCl(*g*) was added dropwise. A white solid was formed immediately. The precipitated hydrochloride was separated by filtration, washer with ether and dried.

_N_-Methyl-_N_-((1-methyl-5-(3-(piperidin-4-yl)propoxy)-1_H_-indol-2-yl)methyl)prop-2-yn-1-amine (1)



Scheme 1. Reagents and conditions: (a) H_2, PtO_2 20%, Pd/C 10%, HCl/dioxane (4N), 45 psi; (b) $[(CH_3)_3COC(O)]_2O$, NaOH (3N), dioxane; (c) dry CCl_4, PPh_3, DCM; (d) 1-methyl-2-((methyl(prop-2-yn-1-yl) amino)methyl)-1*H*-indol-5-ol (**MBA176**), NaH, dry DMF; (e) HCl (g)/AcOEt.

3-(Piperidin-4-yl)propan-1-ol hydrochloride (MBA160). To a solution of commercial 3-(pyridin-4-yl)propan-1-ol (**A3-17**) (1.04 g, 7.6 mmol,) in dry ethanol (40 mL), chlorhydric acid in dioxane (1.4 mL, 4N), PtO_2 (0.208 gr), and Pd/C 20% (0.104 g) were added. The mixture was hydrogenated at rt and 45 psi for 48 h. After complete reaction (tlc analysis), the reaction mass was filtered over Celite, washed with methanol, and the solvent eliminated under vacuum, to give pure **MBA160** (1.30 g, 95%) as a yellow solid (R_f= 0.22, DCM/MeOH, 20%) (Egbertson, M. S.; Chang, C. T.-C.; Duggan, M. E.; Gould, R. J.; Halczenko, W.; Hartman, G. D.; Laswell, W. L.; Lynch, Jr., J. L.; Lynch, R. J.; Manno, P. D.; Naylor, A. M.; Prugh, J. D.; Ramjit, D. R.; Sitko, G. R.; Smith, R. S.; Turchi, L. M.; Zhang, G. Non-Peptide Fibrinogen Receptor Antagonists. 2. Optimization of a Tyrosine Template as a Mimic for Arg-Gly-Asp**,** *J. Med. Chem.* **1994,** *37***,** 2537-2551)

***tert*-Butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (MBA163**). To a solution of 3-(piperidin-4-yl)propan-1-ol hydrochloride (**MBA160**) (530 mg, 2.6 mmol) in dioxane (10 mL), NaOH 3N (3.6 mL) , di-*tert*-butyl dicarbonate (569 mg, 2.6 mmol) was added, and the mixture was stirred overnight at rt. After complete reaction (tlc analysis), the solvent was eliminated, ethyl ether (10 mL) was added, and the mixture was treated with aqueous 10% $KHSO_4$ (5 mL). After work-up, the organic phase was dried (Na_2SO_4), filtered and submitted to chromatography (hexane/AcOEt, 1:1) to give compound **MBA163** (566 mg, 78%) as an oil (R_f= 0.30, DCM/MeOH, 2%) (**1994JMC2546**).

***tert*-Butyl 4-(3-chloropropyl)piperidine-1-carboxylate (MBA177)**. To a solution of *tert*-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (**MBA163**) (180 mg, 0.74 mmol) and PPh_3 (388 mg, 1.48 mmol) in dry DCM (5 mL), CCl_4 (106 µL, 1.11 mmol) was added. The mixture was stirred at rt overnight. Next, the solvent was removed and the residue was purified by chromatography (hexane/AcOE, 5%) to yield **MBA177** (155 mg, 80%) as an oil (R_f= 0.28, hexane/AcOEt, 10%) (**ref. J2004MC711 :** Baraldi, P. G.; Romagnoli, R.; Núñez, M. C.; Perretti, M.; Paul-Clark, M. J.; Ferrario, M.; Govoni, M.; Benedini, F.; Ongini, E. Synthesis of nitro esters of prednisolone, new compounds combining pharmacological properties of both glucocorticoids and nitric oxide, *J. Med. Chem.* **2004,** *47*, 711−719).

***tert*-Butyl 4-(3-(1-methyl-2-((methyl(prop-2-ynyl)amino)methyl)-1*H*-indol-5-yloxy)propyl)piperidine-1-carboxylate (MBA184).** To a solution of *tert*-butyl 4-(3-chloropropyl)piperidine-1-carboxylate (**MBA177**) (152 mg, 0.58 mmol) and 1-methyl-2-[(methyl(prop-2-ynyl)amino)methyl]-1*H*-indol-5-ol (**MBA176**) (132 mg, 0.58 mmol) (**ref. 1991EJMC33:** Cruces, M. A.; Elorriaga, C.; Fernández-Álvarez, E. Acetylenic and allenic derivatives of 2-(5-benzyloxyindolyl) and 2-(5hydroxyindolyl)methylamines: synthesis and in vitro evaluation as monoamine oxidase inhibitors, *Eur. J. Med. Chem.* **1991**, *26*, 33-41), in dry DMF (10 mL), under argon, at rt, NaH (41.7 mg, 1.7 mmol, 60% dispersion in mineral oil) was slowly added, and the mixture stirred at rt overnight. Then, the solvent was removed, water (15 mL) was added, and the mass was extracted with DCM several times. The organic organic phase was dried (Na_2SO_4), filtered and submitted to chromatography (hexane/AcOEt, 10%) to afford indole **MBA184** (189 mg, 72%) as a white solid (R_f= 0.52, hexane/AcOEt, 40%): mp 88-90 ºC; IR (KBr) ν 3433, 3257, 2929, 1692, 1489, 1160, 1019 cm^{-1}; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.17 (d, *J*= 8.8 Hz, 1H, H7-indole), 7.02 (d, *J*= 2.5 Hz, 1H, H4), 6.84 (dd, *J*= 8.8, 2.5 Hz, 1H, H6), 6.32 (s, 1H, H3), 4.06 (br s, 2H, [BocN(C*Heq*$_2$CH$_2$)$_2$CH], 3.97 [t, *J*= 6.3 Hz, 2H, C(5)OC*H*$_2$CH$_2$CH$_2$], 3.73 [s, 3H, N(1)CH$_3$], 3.67 [br s, 2H, indoleC*H*$_2$NMe], 3.31 [d, *J*= 2.4 Hz, 2H, MeNCH$_2$C≡C*H*], 2.67 [br s, 2H, BocN(C*Hax*$_2$CH$_2$)$_2$CH], 2.33 (s, 3H, C*H*$_3$NCH$_2$C≡CH], 2.28 [t, 1 H, MeNCH$_2$C≡C*H*], 1.84-1.81 [m, 2H, C(5)OCH$_2$C*H*$_2$CH$_2$], 1.79-1.67 [m, 2H, BocN(CH$_2$C*Heq*$_2$)$_2$CH], 1.57 [m, 1H, BocN(CH$_2$CH$_2$)$_2$C*H*], 1.45 [s, 9H, C(CH$_3$)$_3$], 1.44-1.40 [m, 2H, C(5)OCH$_2$CH$_2$C*H*$_2$], 1.25-1.10 (m, 2H, H_2N^+(CH$_2$C*Hax*$_2$)$_2$CH]; ^{13}C NMR (125 MHz, CD_3Cl) δ 154.9 [N*C*O$_2$C(CH$_3$)$_3$], 153.2 (C5), 137.0 (C7a), 133.4 (C2),

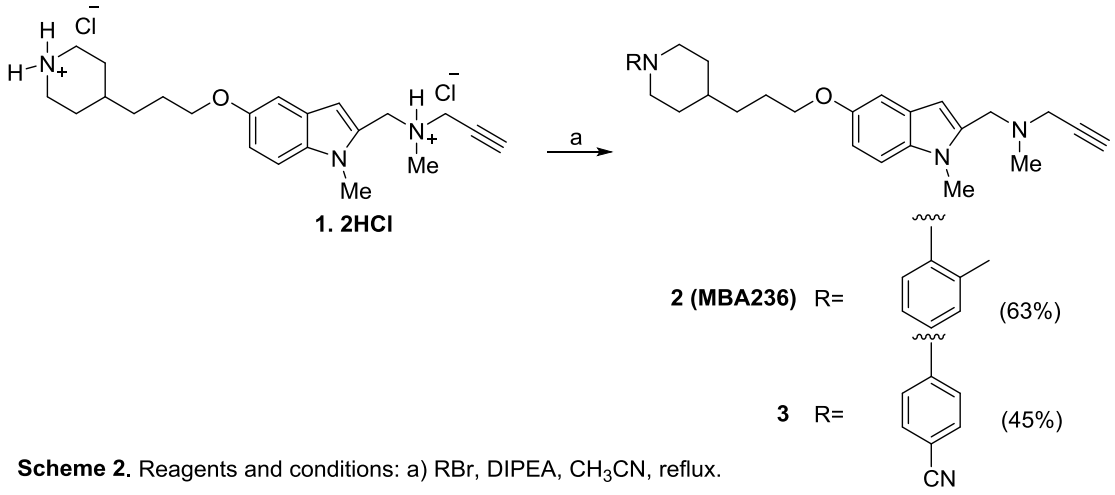
127.5 (C3a), 112.0 (C6), 109.6 (C7), 103.4 (C4), 102.0 (C3), 79.1 [MeNCH$_2$*C*≡CH], 78.4 [MeNCH$_2$C≡*C*H], 73.4 [NCO$_2$*C*(CH$_3$)$_3$], 68.9 [C(5)O*C*H$_2$CH$_2$CH$_2$], 51.8 [indole*C*H$_2$NMe], 44.7 [MeN*C*H$_2$C≡CH], 41.5 [*C*H$_3$NCH$_2$C≡CH], 35.8 [C(5)OCH$_2$CH$_2$*C*H$_2$], 32.9 [3C, BocN(*C*H$_2$CH$_2$)$_2$*C*H], 32.1 [2C, BocN(CH$_2$*C*H$_2$)$_2$CH], 29.8 [N(1)CH$_3$], 28.4 [NCO$_2$C(*C*H$_3$)$_3$], 26.6 [C(5)OCH$_2$*C*H$_2$CH$_2$]; MS (EI) *m*/*z* (%): 453 (48) [M]$^+$, 397 (22), 386 (29), 353 (25), 330 (100), 311 (11), 283 (38), 227 (16), 187 (12), 160 (98); HRMS (ESI): Calcd for $C_{27}H_{39}N_3O_3$: 453.2987. Found: 453.2991. Anal. Calcd for $C_{27}H_{39}N_3O_3.1/2H_2O$: C, 70.10; H, 8.71; N, 9.08. Found: 70.19; H, 8.48; N, 8.96.

***N*-Methyl-*N*-[(1-methyl-5-(3-(piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)]prop-2-yn-1-amine dihydrochloride (1.2HCl).** A saturated solution of AcOEt/HCl (4 mL) was slowly added to a solution of *tert*-butyl4-[3-(1-methyl-2-((methyl(prop-2-ynyl)amino)methyl]-1*H*-indol-5-yloxy)propyl)piperidine-1-carboxylate (**MBA184**) (24 mg, 0.053 mmol) in AcOEt (5 mL), cooled at 0 °C. The mixture was cooled in the freezer overnight. Then, the solid was filtered, washed with cold AcOEt and dried to afford compound **1.2HCl** (22 mg, 99%), as a white solid (R_f= 0.44, DCM/MeOH, 20%): mp 220-3 ºC; IR (KBr) ν 3435, 3189, 2934, 2505, 1485, 1469, 1250, 1209, 1161 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.35 (d, *J*= 9.0 Hz, 1H, H7), 7.08 (d, *J*= 2.4 Hz, 1H, H4), 6.92 (dd, *J*= 9.0, 2.4 Hz, 1H, H6), 6.74 (s, 1H, H3), 4.67 [br s, 2H, indoleC*H*$_2$N$^+$(H)Me], 4.16 [br s, 2 H, Me(H)N$^+$C*H*$_2$C≡CH], 4.00 [t, *J*= 6.3 Hz, 2H, C(5)OC*H*$_2$CH$_2$CH$_2$], 3.82 [s, 3H, N(1)CH$_3$], 3.49 [t, *J*= 2.5 Hz, 2H, Me(H)N$^+$CH$_2$C≡C*H*], 3.38 (d, *J*= 12.8 Hz, 2H, [H$_2$N$^+$(C*Heq*$_2$CH$_2$)$_2$CH], 2.98 [m, 2H, H$_2$N$^+$(C*Hax*$_2$CH$_2$)$_2$CH], 2.98 (s, 3H, C*H*$_3$(H)N$^+$CH$_2$C≡CH], 1.97 (m, 2H, H$_2$N$^+$(CH$_2$C*Heq*$_2$)$_2$CH], 1.82 [m, 2H, C(5)OCH$_2$C*H*$_2$CH$_2$], 1.68 [m, 1H, H$_2$N$^+$(CHax$_2$CH$_2$)$_2$C*H*], 1.52 [m, 2H, C(5)OCH$_2$CH$_2$C*H*$_2$], 1.42 (m, 2H, H$_2$N$^+$(CH$_2$C*Hax*$_2$)$_2$CH]; ^{13}C NMR (100 MHz, CD$_3$OD) δ 154.1 (C5), 134.1 (C7a), 127.6 (C2)*, 127.5 (C3a)*, 114.4 (C6), 110.8 (C7), 106.5 (C3), 103.1 (C4), 80.6 [Me(H)N$^+$CH$_2$*C*≡CH], 71.8 [Me(H)N$^+$CH$_2$C≡*C*H], 68.3 [C(5)O*C*H$_2$CH$_2$CH$_2$], 49.8 [indole*C*H$_2$N$^+$(H)Me], 44.2 [Me(H)N$^+$*C*H$_2$C≡CH], 44.1 [H$_2$N$^+$(*C*H$_2$CH$_2$)$_2$CH], 38.9 [*C*H$_3$(H)N$^+$CH$_2$C≡CH], 33.5 [H$_2$N$^+$(CH$_2$CH$_2$)$_2$*C*H], 32.5 [C(5)OCH$_2$CH$_2$*C*H$_2$], 29.5 [N(1)CH$_3$], 28.8 [H$_2$N$^+$(CH$_2$*C*H$_2$)$_2$CH], 26.2 [C(5)OCH$_2$*C*H$_2$CH$_2$]; MS (EI) *m*/*z* (%): 353 (61) [M]$^+$, 284 (61), 227 (20), 161 (100), 126 (84); HRMS (ESI): Calcd for

$C_{22}H_{31}N_3O$: 353.2481. Found: 392.2467. Anal. Calcd for $C_{22}H_{31}N_3O.2HCl.½\ H_2O$: C, 60.68; H, 7.87; N, 9.65. Found: 60.68; H, 7.62; N, 9.80.

***N*-Methyl-*N*-((1-methyl-5-(3-(1-(2-methylbenzyl)piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (2).**

4-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)benzonitrile (3).



Scheme 2. Reagents and conditions: a) RBr, DIPEA, CH_3CN, reflux.

General method for the *N*-alkylation of indole 1. To a solution of compound **1** in dry CH_3CN, under argon, at 0 ºC, di-isopropylethylamine (DIPEA) (4 equiv) and the corresponding 1-(bromomethyl)benzene derivative (1.08 equiv) were added, and refluxed overnight. After complete reaction (tlc analysis), the solvent was removed and purified by chromatography using hexane/AcOEt mixtures, to give the corresponding indole derivative.

***N*-Methyl-*N*-((1-methyl-5-(3-(1-(2-methylbenzyl)piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (2). Following the General method**, compound **1** (85 mg, 0.24 mmol) in CH_3CN (3.5 mL), was treated with DIPEA (0.17 mL, 0.96 mmol) and 1-(bromomethyl)-2-methylbenzene (36 µL, 0.26 mmol), to give **2** (70 mg, 63%), as an oil (R_f= 0.32, hexane/AcOEt, 20%), after chromatography (hexane/AcOEt, 10-50%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1H, *o*-CH_3-C_6H_4-CH_2N), 7.16 (d, *J*= 8.8 Hz, 1H, H7), 7.13-7.12 (m, 3H, *o*-CH_3-C_6H_4-CH_2N), 7.01 (d, *J*= 2.4 Hz, 1H, H4), 6.84 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.31 (s, 1H, H3), 3.95 (t, *J*= 6.6 Hz, 2H, O$CH_2CH_2CH_2$), 3.72 [s, 3H, N(1)CH_3], 3.65 [s, 2H, C(2)CH_2N(Me)], 3.40 [s, 2H, NCH_2(*o*-CH_3-C_6H_4], 3.30 [d,

J= 2.2 Hz, 2H, N(Me)CH_2C≡CH], 2.84 (d, *J*= 11.6 Hz, 2H, N[C(H_2)$_{eq}$(CH_2)$_2$CH], 2.34 [s, 3H, N(CH_3)CH_2C≡CH], 2.32 (s, 3H, *o*-CH_3-C_6H_4-CH_2N), 2.27 (t, *J*= 2.2 Hz, 1H, N(Me)CH_2C≡C*H*], 1.94 [t, *J*= 11.6 Hz,, 2H, N[CH_2)$_{ax}$$CH_2$)$_2$CH], 1.81-1.77 [m, 2H, OCH_2C$H_2$$CH_2$)], 1.66 [d, *J*= 9.9 Hz, 2H, N[(CH_2)$_2$CH_{2eq}CH], 1.41-1.36 (m, 2H, OCH_2CH_2CH_2), 1.29-1.24 [m, 3H, N(CH_2)$_2$CH_{2ax}C*H*)]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5 (C5), 137.6 (2C, C1', C2', *o*-CH_3-$C_6H_4CH_2$N), 137.2 (C2), 133.5 (C7a), 130.3 (C3', *o*-CH_3-$C_6H_4CH_2$N), 129.8 (C6', *o*-CH_3-$C_6H_4CH_2$N), 127.7 (C3a), 126.9, 125.6 (2C, C4', C5', *o*-CH_3-$C_6H_4CH_2$N), 112.2 (C6), 109.8 (C7), 103.5 (C4), 102.2 (C3), 78.6 (NCH_2*C*≡CH), 73.6 (NCH_2C≡*C*H)**,** 69.3 (O*C*$H_2CH_2CH_2$), 61.3 (*o*-CH_3-C_6H_4*C*H_2N), 54.3 [2CH_2, N(*C*H_2)$_2$(CH_2)$_2$CH], 52.0 [C(2)*C*H_2N(CH_3)CH_2C≡CH], 44.9 [C(2)CH_2N*C*H_2C≡CH], 41.8 [C(2)CH_2N(*C*H_3)CH_2C≡CH], 35.9 [N(CH_2)$_2$(CH_2)$_2$*C*H], 33.2 (OCH_2CH_2*C*H_2), 32.7 [2C, N(CH_2)$_2$(*C*H_2)$_2$CH], 30.1 [N(1)CH_3], 27.0 (OCH_2*C*H_2CH_2), 19.5 (*o*-*C*H_3-$C_6H_4CH_2$N); MS (ESI) *m/z* (%): 458 $(M+1)^+$. The bis-chlorhydrate was prepared as usual to give compound **2.2HCl**: mp 200-5 ºC; IR (KBr) ν 3433, 2927, 2510, 1485, 1468, 1210 cm^{-1}; MS (ESI) *m/z* (%): 458 $(M+1)^+$. Anal. $C_{30}H_{39}N_3O$.2HCl 1/2H_2O: C, 66.78; H, 7.85; N, 7.79. Found: C, 66.59; H, 7.59; N, 7.99.

4-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)benzonitrile (3). **Following the General method**, ompound **1** (200 mg, 0.56 mmol) in CH_3CN (4 mL), was treated with DIPEA (0.38 ml, 2.24 mmol), and 4-(bromomethyl)benzonitrile (133 mg, 0.67 mmol), to afford compound **3** (98 mg, 45%), as a white solid (R_f= 0.30, hexane/AcOEt, 40%), after chromatography (hexane/AcOEt, 30-70%): mp 75-8 ºC; IR (KBr) ν 3445, 3255, 2908, 2231, 1607, 1488, 1203, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J*= 8.3 Hz, 2H, H2', H6', CN-C_6H_4-CH_2N), 7.59 (d, *J*= 8.3 Hz, 2H, H3', H5', CN-C_6H_4-CH_2N), 7.17 (d, *J*= 8.8 Hz, 1H, H7), 7.01 (d, *J*= 2.5 Hz, 1H, H4), 6.84 (dd, *J*= 8.8, 2.5 Hz, 1H, H6), 6.32 (s, 1H, H3), 3.97 (t, *J*= 6.6 Hz, 2H, O*C*$H_2CH_2CH_2$), 3.73 [s, 3H, N(1)CH_3], 3.67 [s, 2H, C(2)CH_2N(Me)CH_2C≡CH], 3.51 (s, 2H, NCH_2-C_6H_4-CN), 3.31 [d, *J*= 2.2 Hz, 2H, C(2)CH_2N(Me)CH_2C≡CH], 2.81 (d, *J*= 11.8 Hz, 2H, N(CH_2)$_{eq}$], 2.34 [s, 3H, C(2)CH_2N(CH_3)CH_2C≡CH], 2.28 (t, *J*= 2.2 Hz, 1H, C(2)CH_2N(Me)CH_2C≡C*H*], 1.97 (tm, *J*= 11.8 Hz,, 2H, N(CH_2)$_{ax}$], 1.81-1.78 [m, 2H, OCH_2C$H_2$$CH_2$)], 1.70 [dm, J= 9.8 Hz, 2H, N(CH_2)$_2$(CH_2)$_{eq}$], 1.43-1.41 (m, 2H, OCH_2CH_2CH_2), 1.29-1.25 [m, 3H, N(CH_2)$_2$(CH_2)$_{ax}$C*H*]; ^{13}C NMR (126 MHz, $CDCl_3$) δ □153.2 (C5), 144.8 [C1', NC$C_6H_4CH_2$N], 137.0 (C2), 133.3 (C7a), 132.0 [2C, C2', C6', NC$C_6H_4CH_2$N], 129.4

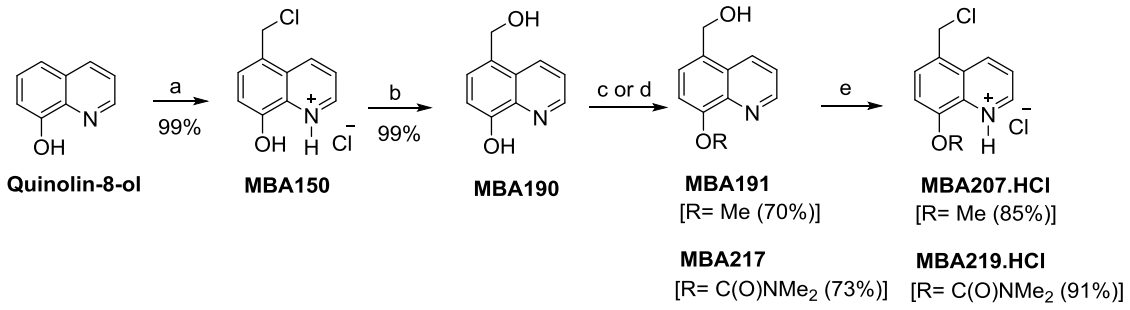
[2C, C3', C5', NC$C_6H_4CH_2$N], 127.5 (C3a), 119.0 (CN), 112.0 (C6), 110.6 [C4', NC$C_6H_4CH_2$N], 109.5 (C7), 103.4 (C4), 100.2 (C3), 78.4 (NCH_2C≡CH), 73.4 (NCH_2C≡CH), 69.0 (O$CH_2CH_2CH_2$), 62.9 [NC$C_6H_4CH_2$N], 54.0 [2CH_2, N(CH_2)$_2$(CH_2)$_2$CH], 51.8 [C(2)CH_2N(CH_3)CH_2C≡CH], 44.7 [C(2)CH_2NCH_2C≡CH], 41.5 [C(2)CH_2N(CH_3)CH_2C≡CH], 35.4 [N(CH_2)$_2$(CH_2)$_2$CH], 32.9 (O$CH_2CH_2CH_2$), 32.3 [2C, N(CH_2)$_2$(CH_2)$_2$CH], 29.8 [N(1)CH_3], 26.7 (O$CH_2CH_2CH_2$); MS (ESI) *m*/*z* (%): 469 $(M+1)^+$. Calcd for $C_{30}H_{36}N_4O$: C, 76.89; H, 7.74; N, 11.96. Found: C, 76.69; H, 7.62; N, 12.01.

5-(((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)methyl)quinolin-8-yl dimethylcarbamate (14).

***N*-((5-((8-Methoxyquinolin-5-yl)methoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (13)**.

***N*-((5-(3-(1-((8-Methoxyquinolin-5-yl)methyl)piperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (4)**.

5-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)quinolin-8-yl dimethylcarbamate (5).



Scheme 3. Reagents and conditions: (a) cc HCl, CH_2O/H_2O 37%; HCl (g), 0 ºC; (b) NH_3 30%, H_2O, rt; (c) CH_3I, NaH, dry DMF, rt; (d) $Cl(CO)NMe_2$, NaH, dry DMF; (e) $SOCl_2$, dry DCM, rt

5-(Chloromethyl)quinolin-8-ol hydrochloride (MBA150). To a solution of quinolin-8-ol (7.3 g, 50.3 mmol) and concentrated chlorhydric acid (22 mL), cooled at 0 ºC, aqueous formaldehyde (37%) (10 mL) was added, and HCl(g) was bubbled into the solution during 2 h at 0 º; then, the mixture was stirred at rt for 2 h more. The solid was

filtered, washed with cc HCl, and dried to give compound **MBA150** (11.4 g, 99%) as a yellow solid (R_f= 0.40, DCM/MeOH, 5%) (Li, L.; Xu, B. Synthesis and characterization of 5-substituted 8-hydroxyquinoline derivatives and their metal complexes, *Tetrahedron* **2008**, *64*, 10986–10995).

5-(Hydroxymethyl)quinolin-8-ol (MBA190). To a solution of 5-(hydroxymethyl)quinolin-8-ol (**MBA150**) (2.0 g, 8.7 mmol) in water (10 mL), aqueous NH_3 (30%) was added until pH 9-10. The mixture was stirred for 15 min, and the solid was washed with water, and filtered. Further purification by chromatography (DCM/methanol, 1-5 %, with 2% NH_3) gave compound **MBA190** (1.52 g, 99%) as a white solid (R_f= 0.35, DCM/ methanol, 10%, with 2.5% NH_3) (Li, L.; Xu, B. Synthesis and characterization of 5-substituted 8-hydroxyquinoline derivatives and their metal complexes, *Tetrahedron* **2008**, *64*, 10986–10995).

(8-Methoxyquinolin-5-yl)methanol (MBA191). To a solution of **MBA190** (500 mg, 2.8 mmol) in dry DMF (5 mL), cooled at 0 °C, under argon, NaH (75 mg, 3.1 mmol, 60% dispersion in mineral oil) and MeI (0.20 mL, 3.4 mmol) were added. The reaction mixture was stirred at rt for 6 h; then, the solvent was removed, the residue was suspended in water and extracted with DCM. The organic layer was dried (Na_2SO_4), dried and purified by chromatography (DCM/AcOEt, 50-70%) to give product **MBA191** (378 mg0, 70%), as white solid (R_f= 0.40, AcOEt) (Dimsdale, M. J. The formation of 2-alkoxyquinolines from quinoline *N*-oxides in alcoholic media, *J. Heterocyclic Chem*. **1979**, *16*, 1209-11).

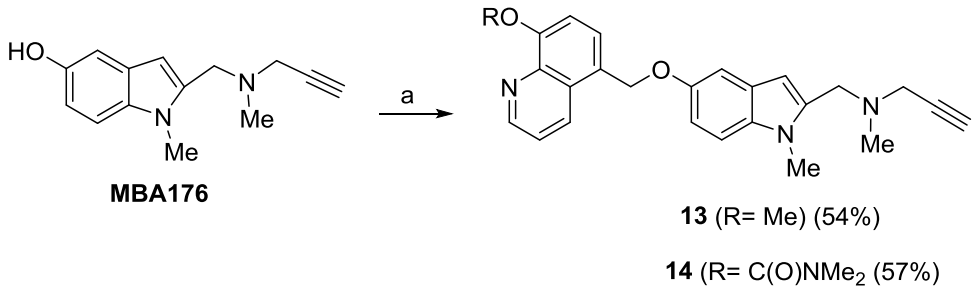
5-(Hydroxymethyl)quinolin-8-yl dimethylcarbamate (MBA217). To a solution of **MBA190** (510 mg, 2.9 mmol) in dry DMF (6 mL), under argon at 0 °C, NaH (84 mg, 3.5 mmol, 60% dispersion in mineral oil). After 10 min, dimethyl carbamoyl chloride (374 mg, 3.49 mmol) was added, and the mixture was stirred overnight. After complete reaction (tlc analysis), the solvent was removed and the residue suspended in water and extracted with DCM several times. The organic fraction was dried (Na_2SO_4), filtered and submitted to cromatography (DCM/methanol, 2%) to give compound **MBA217** (523 mg, 73%), as an amorphous solid (R_f= 0.38, DCM/methanol, 5%): IR (KBr) ν 3419, 2931, 1703, 1598, 1503, 1388, 1248, 1170, 1070, 1022 cm^{-1}; ^1H NMR (500 MHz, CD_3Cl) δ 8.90 (dd, *J*= 1.5, 3.9 Hz, 1H, H2), 8.44 (dd, *J*= 1.5, 8.5 Hz, 1H, H4), 7.46 7 (d, *J*= 7.9 Hz, 1H, H6), 7.41 (dd, *J*= 3.9, 8.5 Hz, 1H, H3), 7.37 (d, *J*= 7.9 Hz, 1H, H7), 5.00 (d, *J*= 5.8 Hz, 2H, CH_2OH), 3.28, 3.06 [s, s, 6H, $OC(O)N(CH_3)_2$], 2.23 (t, *J*= 5.8 Hz, 1H,

OH); ^{13}C NMR (100 MHz, CD_3Cl) δ □155.2 [$(CH_3)_2NOCO$], 150.1 (C2), 148.0 (C8), 142.2 (C8a), 134.3 (C4a), 132.5 (C4), 127.6 (C5), 125.5 (C6), 121.4 (C7), 120.9 (C3), 62.8 (CH_2OH), 36.8 [$(CH_3)_2NOCO$]; MS (EI) *m*/*z* (%): 247 $(M+1)^+$.

General Method for chlorination with $SOCl_2$. To a solution of the alcohol in dry DCM, under argon, at rt, $SOCl_2$ (1.58 equiv) was added, and the mixture was stirred at rt overnight. Then, the solvent was evaporated, and the solid was washed with dry DCM to isolate the corresponding chloride.

5-(Chloromethyl)-8-methoxyquinoline hydrochloride (**MBA207**). Following the **General Method for chlorination with $SOCl_2$**, (8-methoxyquinolin-5-yl)methanol **MBA191** (377 mg, 1.9 mmol) in dry DCM (4.5 mL) was treated with $SOCl_2$ (0.21 mL, 3.0 mmol), to give compound **MBA207** (413 mg, 85%) as a yellow solid: R_f= 0,05 AcOEt/methanol, 10%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10-9.06 (m, 2H, H2, H4), 8.03 (m, 1H, H3), 7.91 (d, *J*= 8.0 Hz, 1H, H6), 7.47 (d, 1H, H7), 5.32 (s, 2H, CH_2Cl), 4.09 (s, 3 H, OCH_3). [Himmelsbach, F.; Langkopf, E.; Eckhardt, M.; Mark, M.; Maier, R.; Lotz, R. R. H.; Tadayyon, M. Preparation of 8-[3-aminopiperidin-1-yl]xanthines as dipeptidylpeptidase-IV (DPP-IV) inhibitors. PCT Int. Appl. (2004), WO 2004018468 A2 20040304].

5-(Chloromethyl)quinolin-8-yl dimethylcarbamate hydrochloride (MBA219). Following the **General Method for chlorination with $SOCl_2$**, alcohol **MBA217** (303 mg, 1.23 mmol) in dry DCM (3 mL) was reacted with $SOCl_2$ (0.18 mL, 2.5 mmol) to give chloride **MBA219** (337 mg, 91%), as a beige solid (R_f= 0.35, DCM/methanol, 5%): mp 165-170 ºC, IR (KBr) ν 3544, 3443, 2930, 2499, 1737, 1550, 1385, 1296, 1249, 1162, 1022 cm^{-1}; ^{1}H NMR (500 MHz, CD_3Cl) δ 9.12 (br s, 1H, H2), 8.69 (br d, *J*= 4.9 Hz, 1H, H4), 7.66-7.65 (m, 2H, H3, H6), 7.53 (d, *J*= 7.8 Hz, 1H, H7), 5.00 (s, 2H, CH_2Cl), 3.34, 3.08 [s, s, 6H, $OC(O)N(CH_3)_2$]; ^{13}C NMR (126 MHz, CD_3Cl) δ □154.3 [$(CH_3)_2NOCO$], 148.7 (C2), 147.2 (C8), 135.4 (C8a), 130.9 (2C, C4, C4a), 128.9 (C6), 127.7 (C5), 122.8 (C7), 121.8 (C3), 42.8 (CH_2Cl), 37.2, 37.1 [$(CH_3)_2NOCO$]; MS (EI) *m*/*z* (%): 265 $(M+1)^+$, 267 $(M+3)^+$.



MBA176

13 (R= Me) (54%)

14 (R= C(O)NMe$_2$ (57%)

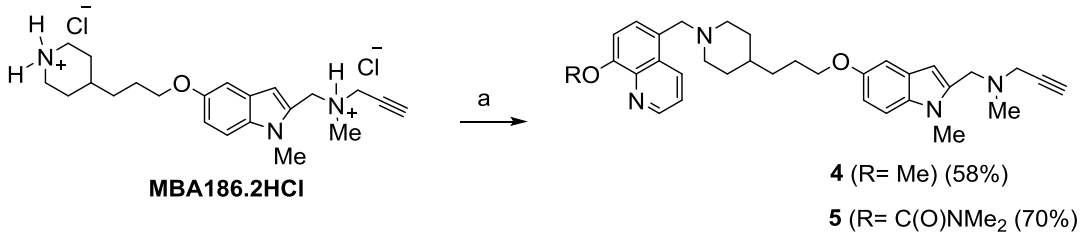
Scheme 4.Reagents conditions: (for **13**): (a) **MBA207** [5-(chloromethyl)-8-methoxyquinoline], NaH, dry DMF, rt; (for **14**): (a) **MBA219** [5-(chloromethyl)quinolin-8-yl dimethylcarbamate], NaH, dry DMF, rt;

General Method for the *O*-alkylation of indole MBA176. To a solution of compound **MBA176** in dry DMF, under argon, at 0 ºC, NaH (3 equiv, 60% dispersion in mineral oil) was added, and after 5 min, **MBA207** or **MBA219** (1 equiv) was added. The mixture was left stirring overnight at rt. The, the solvent was removed, and the residue was submitted to chromatography to afford the corresponding derivative.

***N*-((5-((8-Methoxyquinolin-5-yl)methoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (13)**. Following the **General method for the *O*-alkylation, MBA176** (134 mg, 0.58 mmol) in DMF (4 mL) was treated with NaH (42 mg, 1.74 mmol), and **MBA207** (122 mg, 0.58 mmol) to give compound **13** (125 mg, 54%), as a white solid (R_f= 0.26, AcOEt), after cromatography (hexane/AcOEt, 50-90%): mp 165-9 ºC, IR (KBr) ν 3435, 3301, 2939, 2912, 2834, 2793, 1617, 1572, 1505, 1487, 1470, 1401, 1374, 1313, 1205, 1105, 1014 cm^{-1}; ^{1}H NMR (400 MHz, CD_3Cl) δ 8.94 (dd, *J*= 1.6, 4.2 Hz, 1H, H2'), 8.43 (dd, *J*= 1.6, 8.6 Hz, 1H, H4'), 7.54 (d, *J*= 7.9 Hz, 1H, H6'), 7.45 (dd, *J*= 4.2, 8.6 Hz, 1H, H3'), 7.20-7.18 (m, 2H, H4, H7), 6.99 (d, *J*= 7.9 Hz, 1H, H7'), 6.90 (dd, *J*= 2.4, 9.0 Hz, 1H, H6), 6.34 (s, 1H, H3), 5.38 [s, 2H, (C5')CH_2O], 4.08 [s, 3H, C(8')OCH_3], 3.73 [s, 3H, C(1)NCH_3], 3.67 [s, 2H, CH_2N(Me)CH_2C≡CH], 3.29 [d, *J*= 2.4 Hz, 2H, CH_2N(Me) CH_2C≡CH], 2.33 [s, 3H, CH_2N(CH_3)CH_2C≡CH], 2.27 [t, *J*= 2.4 Hz, 1H, CH_2N(Me)CH_2C≡C*H*]; ^{13}C NMR (100 MHz, CD_3Cl) δ 156.0 (C5), 153.1 (C8'), 149.3 (C2'), 140.8 (C2), 137.5 (C8a'), 133.9 (C5'), 133.1 (C4'), 128.4 (C4a'), 128.2 (C6'), 127.2 (C3a)*, 125.1 (C7a)*, 122.1 (C3'), 112.4 (C6), 109.9 (C7), 108.7 (C7'), 104.2 (C4), 102.3 (C3), 78.6 [CH_2N(Me)CH_2*C*≡CH], 73.7 [CH_2N(Me)CH_2C≡*C*H], 69.4 [(C5')*C*H_2O)], 56.2 [C(8')O*C*H_3], 52.0 [*C*H_2N(Me)CH_2C≡CH], 44.9 [CH_2N(Me)*C*H_2C≡CH], 41.8 [CH_2N(*C*H_3)CH_2C≡CH],

30.5 [N(1)*C*H$_3$]; MS (EI) *m/z* (%): 172 (100) [M-C$_{14}$H$_{15}$N$_2$O$^{\cdot}$]$^+$, 399 (4) [M]$^+$. Anal. Calcd. for C$_{25}$H$_{25}$N$_3$O$_2$.H$_2$O: C, 71.92; H, 6.52; N, 10.06. Found: 71.72; H, 6.47; N, 9.80.

5-(((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)methyl)quinolin-8-yl dimethylcarbamate (14). Following the **General method for the *O*-alkylation, MBA176** (228 mg, 1.0mmol) in DMF (4 mL), was treated with NaH (120 mg, 3.0 mmol) and **MBA219** (316 mg, 1.2 mmol) to afford **14** (260 mg, 57%), as a white solid, after chromatography (hexane/AcOEt, 90%): R$_f$= 0.32, AcOEt; mp 145-8 ºC; IR (KBr) ν 3267, 2872, 1710, 1618, 1484, 1158 cm^{-1}; ^{1}H NMR (500 MHz, CD$_3$Cl) δ 8.95 (dd, *J*= 1.5, 4.0 Hz, 1H, H2'), 8.46 (dd, *J*= 1.5, 8.3 Hz, 1H, H4'), 7.62 (d, *J*= 7.4 Hz, 1H, H6'), 7.45-7.43 (m, 2H, H3', H7'), 7.25-7.20 (m, 2H, H4, H7), 6.92 (dd, *J*= 2.5, 8.8 Hz, 1H, H6), 6.36 (s, 1H, H3), 5.45 [s, 2H, (C5')C*H*$_2$O] , 3.75 [s, 3H, C(1)NC*H*$_3$], 3.69 [s, 2H, C*H*$_2$N(Me)CH$_2$C≡CH], 3.31 [d, *J*= 2.4 Hz, 2H, CH$_2$N(Me)C*H*$_2$C≡CH], 3.29, 3.07 [s, s, 6H, (CH$_3$)$_2$NOCO], 2.35 [s, 3H, CH$_2$N(C*H*$_3$)CH$_2$C≡CH], 2.29 [t, *J*= 2.4 Hz, 1H, CH$_2$N(Me)CH$_2$C≡C*H*]; ^{13}C NMR (126 MHz, CD$_3$Cl) δ 155.2 [(CH$_3$)$_2$NO*C*O], 152.8 (C5), 150.2 (C2'), 148.4 (C8'), 142.2 (C8a'), 137.3 (C2), 133.7 (C7a), 132.7 (C4'), 131.0 (C5'), 128.1 (C4a'), 127.5 (C3a), 126.9 (C6'), 121.5 (C3')*, 120.9 (C7')*, 112.1 (C6), 109.7 (C7), 104.7 (C4), 102.2 (C3), 78.3 [CH$_2$N(Me)CH$_2$*C*≡CH], 73.4 [CH$_2$N(Me)CH$_2$C≡*C*H], 69.0 [(C5')*C*H$_2$O], 51.8 [*C*H$_2$N(Me)CH$_2$C≡CH], 44.7 [CH$_2$N(Me)*C*H$_2$C≡CH], 41.5 [CH$_2$N(*C*H$_3$)CH$_2$C≡CH], 36.9 [2C, OCON(*C*H$_3$)$_2$], 29.9 [N(1)*C*H$_3$]; MS (ESI) *m/z* (%): 457 (M+1)$^+$. Anal. Calcd. for C$_{27}$H$_{28}$N$_4$O$_3$.1/3H$_2$O C, 70.11; H, 6.25; N, 12.11. Found: C, 70.04; H, 6.08; N, 12.26



Scheme 5. Reagents and conditions: (for **4**): (a) **MBA207** [5-(chloromethyl)-8-methoxyquinoline], DIPEA, CH$_3$CN, reflux; (for **5**): (a) **MBA219** [5-(chloromethyl)quinolin-8-yl dimethylcarbamate], DIPEA, CH$_3$CN, reflux.

***N*-((5-(3-(1-((8-Methoxyquinolin-5-yl)methyl)piperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (4)**. Following the **General method for the *N*-alkylation of indoles**, product **1** (80 mg, 0.18 mmol) in CH$_3$CN (3.0

mL), was treated with DIPEA (95 µl, 0.54 mmol) and **MBA207** (38 mg, 0.18 mmol) to give compound **4** (62 mg, 58%), as a white solid (R_f= 0.30, DCM/methanol, 5%) alter chromatography (DCM/methanol, 1%): mp 117-120 ºC, IR (KBr) ν 3301, 2934, 2849, 2793, 1620, 1574, 1504, 1487, 1475, 1454, 1205, 1161, 1103 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl) δ 8.90 (dd, *J*= 1.7, 4.1 Hz, 1H, H2'), 8.66 (dd, *J*= 1.7, 8.6 Hz, 1H, H4'), 7.42 (dd, *J*= 4.1, 8.6 Hz, 1H, H3'), 7.32 (d, *J*= 7.9 Hz, 1H, H6'), 7.14 (d, *J*= 8.8 Hz, 1H, H7), 6.99 (d, *J*= 2.4 Hz,1H, H4), 6.92 (d, *J*= 7.9 Hz, 1H, H7'), 6.81 (dd, *J*= 2.4, 8.8 Hz, 1H, H6), 6.29 (s, 1H, H3), 4.06 [s, 3H, C(8')OCH_3], 3.93 [t, *J*= 6.7 Hz, 2H, C(5)OC*H*$_2$$CH_2CH_2$], 3.74 [s, 2H, (C5')$CH_2$N], 3.71 [s, 3H, C(1)$NCH_3$], 3.64 [s, 2H, C*H*$_2$N(Me)$CH_2$C≡CH], 3.28 [d, *J*= 2.4 Hz, 2H, CH_2N(Me) C*H*$_2$C≡CH], 2.84 (d, *J*= 11.5 Hz, 2H, [N(C*Heq*$_2$$CH_2$)$_2$CH], 2.31 [s, 3H, CH_2N(C*H*$_3$)CH_2C≡CH], 2.26 [t, *J*= 2.4 Hz, 1H, CH_2N(Me)CH_2C≡C*H*], 1.95 [dd, *J*= 9.9, 11.5 Hz, 2H, N(C*Hax*$_2$$CH_2$)$_2$CH], 1.79-1.75 [m, 2H, C(5)OCH_2C*H*$_2$$CH_2$], 1.66-1.62 [m, 3H, N($CH_2$C*Heq*$_2$)$_2$C*H*], 1.39-1.34 [m, 2 H, C(5)OCH_2CH_2C*H*$_2$], 1.23-1.16 [m, 2H, N(CH_2C*Hax*$_2$)$_2$CH]; ^{13}C NMR (100 MHz, CD_3Cl) δ 155.1 (C5), 153.5 (C8'), 149.0 (C2'), 140.7 (C2), 137.2 (C8a'), 133.9 (C4'), 133.5 (C5'), 128.9 (C4a'), 127.9 (C6'), 127.7 (C3a)*, 126.8 (C7a)*, 121.4 (C3'), 112.2 (C6), 109.8 (C7), 106.5 (C7'), 103.5 (C4), 102.2 (C3), 78.6 [CH_2N(Me)CH_2*C*≡CH], 73.6 [CH_2N(Me)CH_2C≡*C*H], 69.2 [O*C*(5)$H_2CH_2CH_2$], 61.2 [(C5')*C*H_2N], 56.1 [C(8')O*C*H_3], 54.2 [N(*C*H_2CH_2)$_2$CH], 52.0 [*C*H_2N(Me)CH_2C≡CH], 44.9 [CH_2N(Me)*C*H_2C≡CH], 41.7 [CH_2N(*C*H_3)CH_2C≡CH], 35.9 [N(CH_2CH_2)$_2$*C*H], 33.1 [C(5)OCH_2CH_2*C*H_2], 32.6 [N(CH_2*C*H_2)$_2$CH], 30.1 [N(1)*C*H_3], 27.0 [C(5)OCH_2*C*H_2CH_2]; MS (EI) *m/z* (%): 172 (100) [M-$C_{11}H_{10}NO^{\cdot}]^+$, 283 (15) [M-$C_{18}H_{23}N_2O^{\cdot}]^+$, 442 (3) [$CH_2$N(Me)*C*$H_2$C≡CH]$^+$, 456 (6) [N(Me)*C*$H_2$C≡CH]$^+$, 485 (10) [M-*C*$H_2$C≡CH]$^+$, 524 (9) [M]$^+$ Anal. Calcd. for $C_{33}H_{40}N_4O_2$: C, 75.54; H, 7.68; N, 10.68. Found: 75.30; H, 7.49; N, 10.69.

5-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)quinolin-8-yl dimethylcarbamate (5). Following the **General method for the *N*-alkylation of indoles**, compound **1** (66 mg, 0.15 mmol) in CH_3CN (3.5 mL) was reacted with DIPEA (0.1 mL, 0.6 mmol) and **MBA219** (41 mg, 0.15 mmol) to give product **5** (63 mg, 70%), as a white solid (R_f= 0.38, DCM/methanol 5%), after chromatography (DCM/methanol, 1%): mp 115-8 ºC, IR (KBr) ν 3434, 3281, 2915, 1722, 1486, 1390, 1170, 1072 cm^{-1}; ^1H NMR (400 MHz, CD_3Cl) δ 8.89 (dd, *J*= 1.7, 4.0 Hz, 1H, H2'), 8.69 (dd, *J*= 1.7, 8.4 Hz, 1H, H4'), 7.40-

7.37 (m, 2H, H3', H6'), 7.33 (d, *J*= 7.7 Hz, 1H, H7'), 7.15 (d, *J*= 8.8 Hz,1H, H7), 7.00 (d, *J*= 2.4 Hz, 1H, H4), 6.82 (dd, *J*= 2.4, 8.8 Hz, 1H, H6), 6.30 (s, 1H, H3), 3.94 [t, *J*= 6.6 Hz, 2H, C(5)OC*H*$_2$CH$_2$CH$_2$], 3.78 [s, 2H, (C5')CH$_2$N], 3.71 [s, 3H, C(1)NCH$_3$], 3.65 [s, 2H, C*H*$_2$N(Me)CH$_2$C≡CH], 3.28 [d, *J*= 2.4 Hz, 2H, CH$_2$N(Me)C*H*$_2$C≡CH], 3.36, 3.05 [s, s, 6H, (CH$_3$)$_2$NOCO], 2.85 (d, *J*= 11.5 Hz, 2H, [N(C*Heq*$_2$CH$_2$)$_2$CH], 2.32 [s, 3H, CH$_2$N(C*H*$_3$)CH$_2$C≡CH], 2.26 [t, *J*= 2.4 Hz, 1H, CH$_2$N(Me)CH$_2$C≡C*H*], 1.95 [td, *J*= 2.2, 11.5 Hz, 2H, N(C*Hax*$_2$CH$_2$)$_2$CH], 1.81-1.73 [m, 2H, C(5)OCH$_2$C*H*$_2$CH$_2$], 1.64 [br d, *J*= 12.5, 2H, N(CH$_2$C*Heq*$_2$)$_2$CH], 1.40-1.34 [m, 2 H, C(5)OCH$_2$CH$_2$C*H*$_2$], 1.33-1.24 [m, 1H, N(CH$_2$CH$_2$)$_2$C*H*], 1.21-1.15 [m, 2H, N(CH$_2$C*Hax*$_2$)$_2$CH]; ^{13}C NMR (100 MHz, CD$_3$Cl) δ □155.5 [(CH$_3$)$_2$NO*C*O], 153.5 (C5), 150.2 (C2'), 147.6 (C8'), 142.4 (C5'), 137.2 (C2), 133.9 (C4'), 133.5 (C7a), 133.1 (C8a'), 129.1 (C3a), 127.7 (C4a'), 127.3 (C6'), 121.1 (C3'), 120.8 (C7'), 112.2 (C6), 109.8 (C7), 103.5 (C4), 102.2 (C3), 78.6 [CH$_2$N(Me)CH$_2$*C*≡CH], 73.6 [CH$_2$N(Me)CH$_2$C≡*C*H], 69.2 [O*C*(5)H$_2$CH$_2$CH$_2$], 61.3 [(C5')*C*H$_2$N], 54.2 [N(*C*H$_2$CH$_2$)$_2$CH], 52.0 [*C*H$_2$N(Me)CH$_2$C≡CH], 44.9 [CH$_2$N(Me)*C*H$_2$C≡CH], 41.8 [CH$_2$N(*C*H$_3$)CH$_2$C≡CH], 37.0 [2C, OCON(*C*H$_3$)$_2$], 35.9 [N(CH$_2$CH$_2$)$_2$*C*H], 33.1 [C(5)OCH$_2$CH$_2$*C*H$_2$], 32.6 [N(CH$_2$*C*H$_2$)$_2$CH], 30.1 [N(1)*C*H$_3$], 27.0 [C(5)OCH$_2$*C*H$_2$CH$_2$]; MS (EI) *m*/*z* (%): 352 (97) [M-C$_{13}$H$_{13}$N$_2$O$_2$·]$^+$, 493 (4) [M-C$_3$H$_6$NO$_2$·]$^+$, 513 (18) [M-N(Me)CH$_2$C≡CH·]$^+$, 542 (26) [M-CH$_2$C≡CH·]$^+$, 581 (35) [M]$^+$. Anal. Calcd. for C$_{35}$H$_{43}$N$_5$O$_3$: C, 72.26; H, 7.45; N, 12.04. Found: C, 72.24; H, 7.20; N, 12.08.

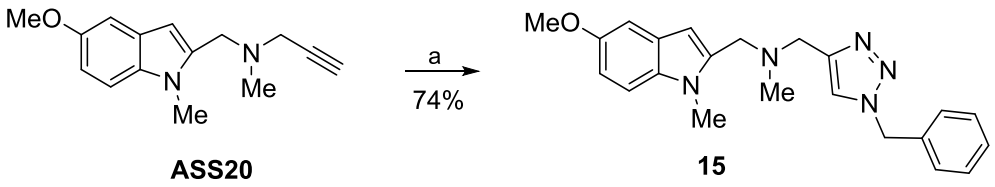
1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-methoxy-1-methyl-1*H*-indol-2-yl)methyl)-N-methylmethanamine (15).

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylmethanamine (9).

1-(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)-*N*-methyl-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)methanamine (10).

General Method for the synthesis of triazolindole derivatives. To a solution of the alkyne and the commercial azide (2 equiv) in a mixture of DMF and water (1:1), a solution of sodium ascorbate (0.4 equiv) and CuSO$_4$.7H$_2$O (0.17 equiv) in water was

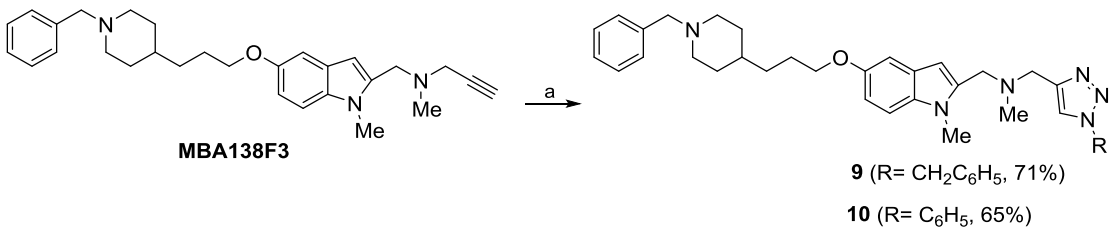
added. The mixture was stirred at 60 ºC overnight. Then, the solvents were evaporated, and the residue was purified by chromatography to give the pure molecules.



ASS20 **15**

Scheme 6. Reagents and conditions: (a) Benzylazide, sodium ascorbate,$CuSO_4.7H_2O$, DMF/H_2O, 60 ºC.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-methoxy-1-methyl-1*H*-indol-2-yl)methyl)-N-methylmethanamine (15). Following the **General Method for the synthesis of triazolindole derivatives**, a solution of **ASS20** (100 mg, 0.41 mmol), and benzylazide (1.61 mL, 0.82 mmol) in DMF and water (1:1, 10 mL), were reacted with a solution of sodium ascorbate (32 mg, 0.16 mmol) and $CuSO_4.7H_2O$ (18 mg, 0.07 mmol) in water (1.0 mL), to yield **15** (114 mg, 74%), as a white solid (R_f= 0.22, hexano/AcOEt, 70%), after chromatography (hexane/AcOEt, 50-70): mp 93-5 ºC; IR (KBr) ν 3436, 3130, 2912, 1489, 1209, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7-35 (m, 3H, H3'', H5'', H4'', $NCH_2C_6H_5$), 7.27 (s, 1H, H5'), 7.25-7.23 (m, H2'', H6'', 2 H, $NCH_2C_6H_5$), 7.14 (dd, *J*= 7.8 Hz, 1 H7), 7.01 (d, *J*= 2.5 Hz, 1H, H4), 6.82 (dd, 1H, H6), 6.27 (s, 1H, H3), 5.47 (s, 2H, $NCH_2C_6H_5$), 3.83 (s, 3H, OCH_3), 3.70 [s, 2H, $C(2)CH_2N(CH_3)CH_2$], 3.62 [s, 3H, $N(1)CH_3$], 3.61 [s, 2H, $C(2)CH_2N(CH_3)CH_2$], 2.24 [s, 3H, $C(2)CH_2N(CH_3)CH_2$]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9 (C5), 145.5 (C4'), 137.4 (C2), 134.7 (C1''), 133.3 (C7a), 129.1 (2C, C3'', C5'', $NCH_2C_6H_5$), 128.7 (C4'', $NCH_2C_6H_5$), 127.9 (2C, C2'', C6'', $NCH_2C_6H_5$), 127.5 (C3a), 122.3 (C5'), 11.3 (C6), 109.6 (C7), 102.1 (C3)*, 102.0 (C4)*, 55.9 (OCH_3), 54.0 ($NCH_2C_6H_5$), 53.5 [$C(2)CH_2N(CH_3)CH_2$], 51.9 [$C(2)CH_2N(CH_3)CH_2$], 42.3 [$C(2)CH_2N(CH_3)CH_2$], 29.8 [$N(1)CH_3$)]; MS (EI) *m/z* (%): 203 (100) [M-$C_{10}H_{10}N_3$·]$^+$, 174 (52) [M-$C_{11}H_{13}N_4$·]$^+$, 375 (38) [M]$^+$; Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.11; H, 6.59; N, 18.58.



Scheme 7. Reagents and conditions: (a) Benzylazide, sodium ascorbate, $CuSO_4.7H_2O$, DMF/H_2O, 60 ºC.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylmethanamine (9). Following the **General Method for the synthesis of triazolindole derivatives**, a solution of **MBA138F3** (107 mg, 0.24 mmol) and benzylazide (0.96 mL, 0.48 mmol) in DMF and water (1:1, 10 mL), were reacted with a solution of sodium ascorbate (19 mg, 0.09 mmol) and $CuSO_4.7H_2O$ (11 mg, 0.04 mmol) in water (1.5 mL), to give **9** (99 mg, 71%) as a white solid [R_f= 0.30, hexane/AcOEt70%, plus triethylamine (TEA) 1%], after cromatography (hexane/AcOEt, 50-70%, TEA 1%): mp 95-8 ºC; IR (KBr) ν 3468, 2935, 1487, 1206, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7-27 (m, 2H, $NCH_2C_6H_5$, triazole$NCH_2C_6H_5$], 7.23-7.21 (m, 3H, $NCH_2C_6H_5$, triazole$NCH_2C_6H_5$), 7.20 (s, 1H, H5''), 7.18-7.15 (m, 5H, $NCH_2C_6H_5$, triazole$NCH_2C_6H_5$), 7.06 (dd, *J*= 8.8 Hz, 1 H7), 6.92 (d, *J*= 2.5 Hz, 1H, H4), 6.75 (dd, 1H, H6), 6.18 (s, 1H, H3), 5.40 (s, 2H, triazole$NCH_2C_6H_5$), 3.87 (t, *J*= 6.3 Hz, 2H, $OCH_2CH_2CH_2$), 3.62 [s, 2H, $C(2)CH_2N(CH_3)CH_2$], 3.54 [s, 3H, $N(1)CH_3$], 3.53 [s, 2H, $C(2)CH_2N(CH_3)CH_2$], 3.41 (s, 2H, $NCH_2C_6H_5$), 2.80 [d, *J*= 11.2 Hz, 2H, $N(CH_2)eq(CH_2)ax(CH_2)_2CH$], 2.16 [s, 3H, $C(2)CH_2N(CH_3)CH_2$], 1.86 [t, *J*= 11.2 Hz, 2H, $N(CH_2)eq(CH_2)ax(CH_2)_2CH$], 1.73-1.70 (m, 2H, $OCH_2CH_2CH_2$), 1.61 [d, *J*= 9.3 Hz, 2H, $N(CH_2)_2(CH_2)eq(CH_2)axCH$], 1.35-1.31 (m, 2H, $OCH_2CH_2CH_2$), 1.26-1.20 [m, 3H, $N(CH_2)_2(CH_2)eq(CH_2)axCH$]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3 (C5), 145.5 (C4''), 138.6 (C1', $NCH_2C_6H_5$), 137.3 (C3a), 134.7 (C1''', triazole$NCH_2C_6H_5$), 133.3 (C7a), 129.2-127.5 (triazole$NCH_2C_6H_5$, $NCH_2C_6H_5$), 126.8 (C2), 122.3 (C5''), 111.9 (C6), 109.5 (C7), 103.3 (C4), 101.9 (C3), 69.1 ($OCH_2CH_2CH_2$), 63.5 ($NCH_2C_6H_5$), 54.0 $N(CH_2)_2(CH_2)_2CH$], 53.9 [$C(2)CH_2N(CH_3)CH_2$], 53.5 (triazole$NCH_2C_6H_5$), 51.9 [$C(2)CH_2N(CH_3)CH_2$], 42.3 [$C(2)CH_2N(CH_3)CH_2$], 35.5 [$N(CH_2)_2(CH_2)_2CH$], 32.9 ($OCH_2CH_2CH_2$), 32.4 [$N(CH_2)_2(CH_2)_2CH$], 29.8 [$N(1)CH_3$)], 26.8 ($OCH_2CH_2CH_2$); MS (EI) *m/z*: 404 (100) $[M\text{-}C_{10}H_{10}N_3^{\cdot}]^+$, 374 (74) $[M\text{-}C_{11}H_{13}N_4^{\cdot}]^+$, 576 (5) $[M]^+$. Calcd for $C_{36}H_{44}N_6O$: C, 74.97; H, 7.69; N, 14.57. Found: C, 74.72; H, 7.61; N, 14.47.

1-(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)-*N*-methyl-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)methanamine (10). Following the **General Method for the synthesis of triazolindole derivatives**, a solution of **MBA138F3** (119 mg, 0.23 mmol) and phenylazide (0.94 ml, 0.46 mmol), in DMF and water DMF and water (1:1, 10 mL), were reacted with a solution of sodium ascorbate (18 mg, 0.09 mmol) and $CuSO_4.7H_2O$ (11 mg, 0.04 mmol) in water (1.5 mL), to give compound **10** (100 mg, 65%), as a oil (R_f= 0.30, hexane/AcOEt, 70%; TEA, 1%), after chromatography (hexane/AcOEt, 50-70%; TEA, 1%), chracterized as the bis-chlorhydrate, prepared as usual: mp 215-218 ºC; IR (KBr) ν 3428, 2939, 2504, 1621, 1457, 1208, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.94 (br s, 1H, BnN^+Hpiperidine), 12.37 (br s, 1H, triazoleCH_2NMeN^+H), 8.95 (s, 1H, H5''), 7.78-7.76 (2H), 7.63-7.61 (2H), 7.55-7.52 (2H), 7.49-7.47 (1H), 7.43-7.42 (3H) [m, 10H, $NCH_2C_6H_5$, triazoleNC_6H_5], 7.21 (dd, *J*= 8.8 Hz, 1 H7), 7.01 (d, *J*= 2.8 Hz, 1H, H4), 6.91 (dd, 1H, H6), 6.87 (s, 1H, H3), 4.55 (br d, *J*= 13.8 Hz, 2H; 4.45 (br d, *J*= 11.1 Hz, 1 H; 4.39 (br d, *J*= 12.7, 1H: $C(2)CH_2N^+H(CH_3)CH_2$, $C(2)CH_2N^+H(CH_3)CH_2$], 4.12 (d, *J*= 4.4 Hz, 2H, $HN^+CH_2C_6H_5$), 3.94 (t, *J*= 6.3 Hz, 2H, $OCH_2CH_2CH_2$), 3.83 [s, 3H, $N(1)CH_3$], 3.46 [d, *J*= 11.1 Hz, 2H, $N(CH_2)eq(CH_2)ax(CH_2)_2CH$], 2.77 [s, 3H, $C(2)CH_2N(CH_3)CH_2$], 2.58 [dd, *J*= 11.1 and 10.5 Hz, 2H, $N(CH_2)eq(CH_2)ax(CH_2)_2CH$], 2-06 [dd, *J*= 11.7 and 14.1 Hz, 2H, $N(CH_2)_2(CH_2)eq(CH_2)axCH$], 1.86 [d, *J*= 14.1 Hz, 2H, $N(CH_2)_2(CH_2)eq(CH_2)axCH$], 1.80-1.74 (m, 2H, $OCH_2CH_2CH_2$), 1.53-1.47 [m, 3H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)eq(CH_2)axCH$]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7 (C5), 136.4 (C4''), 133.8 (C1', $HN^+CH_2C_6H_5$), 131.5 (C3a), 131.0 (C1''', $triazoleNCH_2C_6H_5$), 130.08 (C7a), 130.04, 129.8, 129.4, 129.2, 128.1, 127.1 ($triazoleNC_6H_5$, $NCH_2C_6H_5$), 126.2 (C2), 125.6 (C5''), 120.7 (2C, C2''', C6'''),114.7 (C6), 110.9 (C7), 107.6 (C3), 103.2 (C4), 68.2 ($OCH_2CH_2CH_2$), 60.9 ($N^+HCH_2C_6H_5$), 52.4 [$N(CH_2)_2(CH_2)_2CH$], 49.8 and 49.6 [2C: $C(2)CH_2N^+H(CH_3)CH_2$, $C(2)CH_2N^+H(CH_3)CH_2$], 38.8 [$C(2)CH_2N(CH_3)CH_2$], 34.0 [$N(CH_2)_2(CH_2)_2CH$], 31.9 ($OCH_2CH_2CH_2$), 30.9 [$N(1)CH_3$)], 28.9 [$N(CH_2)_2(CH_2)_2CH$], 26.2 ($OCH_2CH_2CH_2$); MS (EI) *m/z*: 404 (100) $[M-C_9H_8N_3^{\cdot}]^+$, 374 (85) $[M-C_{10}H_{12}N_4^{\cdot}]^+$, 216 (32) $[M-C_{20}H_{20}N_5O^{\cdot}]^+$, 174 (10) $[M-C_{23}H_{26}N_5O^{\cdot}]^+$. Calcd for $C_{35}H_{42}N_6O.2HCl.1/2H_2O$: C, 65.21; H, 7.04; N, 13.04. Found: C, 65.41; H, 6.88; N, 12.93.

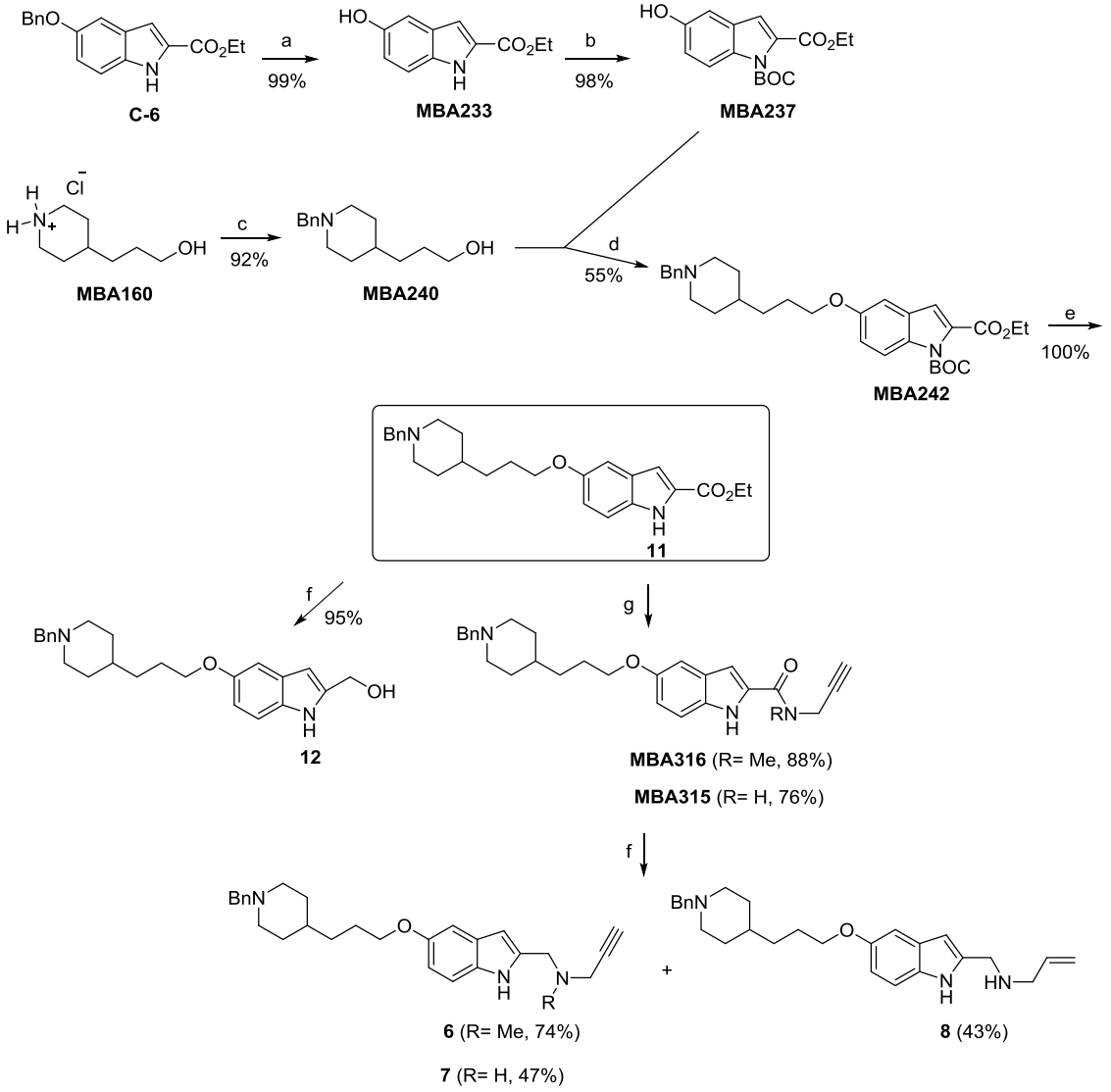
Ethyl 5-(3-(1-benzylpiperidin-4-yl)propoxy)-1*H*-indole-2-carboxylate hydrochloride (11).

(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methanol (12).

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (6)**.

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (7)**

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-en-1-amine (8)**.



Scheme 8. Reagents and conditions: (a) Pd/C (15%), TEA, dry THF, 40 psi, rt; (b) $(BOC)_2O$, TEA, dry dioxane; (c) BnBr, TEA, dry DCM; (d) DIAD, PPh_3, dry THF; (e) AcOEt/HCl; (f) $LiAlH_4$, THF; (g) $AlMe_3$, $HRNCH_2C{\equiv}CH$, THF.

Ethyl 5-hydroxy-1*H*-indole-2-carboxylate (MBA233). To a solution of commercial **C-6** (1.02 g, 3.4 mmol) in dry THF (15 mL), Pd/C (15%) (153 mg) and TEA (0.48 mL,

3.4 mmol) were added, and the mixture was hydrogenated at rt for 2 h at 45 psi. Then, the crude was filtered over Celite, the cake was washed with THF, and the solvent was removed, to give pure compound **MBA233** (701 mg, 99%; R_f= 0.35, hexane/AcOEt, 30%), as a yellow solid (Buchi, G.; Botkin, J. H.; Lee, G. C. M.; Yakushijin, K. A. Synthesis of methoxatin**,** *J. Am. Chem. Soc***. 1985,** *107*, 5555-6).

1-(*tert*-Butyl) 2-ethyl 5-hydroxy-1*H*-indole-1,2-dicarboxylate (MBA237). To a solution of **MBA233** (701 mg, 3.41 mmol) in dry dioxane (6 mL), TEA (0.70 mL, 5.10 mmol) and (*t*-BOC)$_2$O (1.12 g, 5.10 mmol), dissolved in dry dioxane (3.0 mL), were added. The mixture was stirred at 70 °C overnight. The, the solvent was removed, DCM and aqueous HCl (5%) were added till pH 6-7. The work-up was repeated several times and the organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was submitted to.chromatography (hexane/AcOEt, 10%) to yield compound **MBA237** (1.02 g, 98%, R_f= 0.31, hexane/AcOEt, 30%) (Akwabi-Ameyaw, A. Caravella, J.A.; Chen, L. Creech, K.L.; Deaton, D.N.; Madauss, K.P.; Marr, H.B.; Miller, A.B.; Navas, F. III; Parks, D.J.; Spearing, P. .; Todd, D. Williams, S.P.; Wisely, G. B. Conformationally constrained farnesoid X receptor (FXR) agonists: Alternative replacements of the stilbene, *Bioorg.Med.Chem.Lett*. **2011,** *21*, 6154-6160).

3-(1-Benzylpiperidin-4-yl)propan-1-ol (MBA240). To a suspension of **MBA160** (700 mg, 3.91 mmol) in dry DCM (5 mL), TEA (2.16 mL, 15.6 mmol) followed by benzyl bromide (0.58 mL, 4.88 mmol) were added. The reaction mixture was refluxed overnight. Then, the solvent was removed, and the crude was submitted to chromatography (hexane/AcOEt, 10%) to give product **MBA240** (838 mg, 92%) as an oil (R_f= 0.28, hexane/AcOEt, 50%) (Kitbunnadaj, R.; Zuiderveld, O. P.; De Esch, I. J. P.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M.-F.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. Synthesis and Structure-Activity Relationships of Conformationally Constrained Histamine H3 Receptor Agonists**,** *J. Med. Chem*. **2003**, *46*, 5445-5457).

Ethyl 5-(3-(1-benzylpiperidin-4-yl)propoxy)-1*H*-indole-2-carboxylate hydrochloride (11). To a solution of PPh_3 (1.20 g, 4.6 mmol) in dry THF (6 mL), under argon and at 0 °C, DIAD (0.90 mL, 4.6 mmol) was slowly added, and the mixture was stirred for 1 h; then, **MBA240** (527 mg, 2.30 mmol), followed by **MBA247** (700 mg, 2.30 mmol) were added, and stirred for 48 h at rt. The solvent was evaporated, and

the crude purified by cromatography (hexane/AcOEt, 10%) affording **1-(*tert*-butyl) 2-ethyl 5-(3-(1-benzylpiperidin-4-yl)propoxy)-1*H*-indole-1,2-dicarboxylate (MBA242)** {(656 mg, 55%) as an oil: R_f= 0.25 (hexane/AcOEt, 40%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J*= 2.5 Hz, 1H, H4), 7.36-7.25 (m, 7H, $NCH_2C_6H_5$, H7, H3), 7.14 (dd, *J*= 8.9, 2.5 Hz, 1H, H6), 4.51 [t, *J*= 7.6 Hz, 2H, $OCH_2(CH_2)_2$], 4.36 (q, *J*= 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.47 (s, 2H, $NCH_2C_6H_5$), 2.85 [d, *J*= 11.1 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 1.89 [t, *J*= 11.1 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 1.86-1.55 [m, 5H, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$, $OCH_2CH_2CH_2$)], 1.59 [s, 9H, $NCO_2C(CH_3)_3$], 1.39 (t, *J*= 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.28-1.21 [m, 4H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$]; MS (ESI) *m/z* (%): 520 $(M+H)^+$}. To a solution of **MBA242** (656 mg, 1.26 mmol) in AcOEt (5 mL), under argon and at 0 ºC, a saturated solution of HCl(g) in AcOEt (10 mL) was added. After stirring overnight, the solid was removed, washed with cold AcOEt, to give chlorhydrate **11** as a oil (529 mg, 100%): R_f= 0.25 (DCM/methanol, 10%/TEA,1%); IR (KBr) ν 3208, 2982, 2935, 1703, 1508, 1465, 1375, 1208, 1095, 1038 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.48-7.35 (m, 5H, $NCH_2C_6H_5$), 7.31 (d, *J*= 9.3 Hz, 1H, H7), 7.08 (s, 1H, H3), 6.94 (d, *J*= 2.5 Hz, 1H, H4), 6.89 (dd, *J*= 9.3, 2.5 Hz, 1H, H6), 4.52 [t, *J*= 7.4 Hz, 2H, $OCH_2(CH_2)_2$], 4.31 (q, *J*= 6.8 Hz, 2H, $CO_2CH_2CH_3$), 4.25 (s, 2H, $HN^+CH_2C_6H_5$), 3.44 [d, *J*= 11.8 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 2.93 [t, *J*= 11.8 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 1.92 [d, *J*= 14.2 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$], 1.78 (m, 2H, $OCH_2CH_2CH_2$), 15.9-153 [m, 1H, $N(CH_2)_2(CH_2)_2CH$)], 1.37 (t, *J*= 6.8 Hz, 3H, $CO_2CH_2CH_3$), 1.31-1.28 [m, 4H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$]; ^{13}C NMR (126 MHz, CD_3OD) δ 162.0 ($CO_2CH_2CH_3$), 153.3 (C5), 134.3 (C7a) 130.9 (C4', $NCH_2C_6H_5$), 129.8 (2xCH, C'3,.C5', $NCH_2C_6H_5$)*, 128.9 (3C: 2xCH, C2', C6', $NCH_2C_6H_5$; C'1)*, 127.1 (C3a),** 126.5 (C2)**, 115.8 (C6), 110.8 (C7), 109.0 (C3), 104.7 (C4), 60.3 ($HN^+CH_2C_6H_5$), 60.0 ($CO_2CH_2CH_3$), 52.3 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 43.8 ($CH_2CH_2CH_2O$), 33.0 [CH, $N(CH_2)_2(CH_2)_2CH$], 32.3 ($CH_2CH_2CH_2O$), 29.1 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 27.1 ($CH_2CH_2CH_2O$), 13.2 ($CO_2CH_2CH_3$); MS (EI) *m/z* (%): 420 (100) $[M]^+$, 347 (94) $[M-CO_2C_2H_5]^+$, 329 (17) $[M-CH2C6H5]^+$, 202 (89) $[M-C_{12}H_{12}NO_3^{\cdot}]^+$, 174 (15) $[M-C_{14}H_{16}NO_3^{\cdot}]^+$. Anal. Calcd. for $C_{26}H_{33}ClN_2O_3$. HCl.4/5H_2O: C, 66.24; H, 7.40; Cl, 7.52; N, 5.94. Found: C, 66.27; H, 7.41; N, 6.16.

(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methanol (12). To a suspension of LAH (54 mg, 1.42 mmol) in dry THF (3 mL), under argon at 0 ºC,

product **11** (150 mg, 0.35 mmol) was slowly added. Then, the mixture was refluxed 2 h. The reaction was cooled, and water added carefully. The solid was removed, washing the cake with AcOEt, and discarded. The solvent was evaporated and the crude was purified by chromatography (DCM/methanol, 1-5%) giving product **12** (128 mg, 95%; R_f= 0.35, DCM/methanol 10%): mp 135-7ºC; IR (KBr) ν 3280, 2922, 1620, 1468, 1372, 1253, 1201, 1182, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.25 (m, 5H, $NCH_2C_6\mathit{H}_5$), 7.13 (d, *J*= 8.8 Hz, 1H, H7), 6.95 (d, *J*= 2.5 Hz, 1H, H4), 6.95 (dd, *J*= 8.8, 2.5 Hz, 1H, H6), 6.30 (s, 1H, H3), 4.74 (s, 2H, CH_2OH), 4.11 [t, *J*= 6.6 Hz, 2H, $OC\mathit{H}_2(CH_2)_2$], 3.47 (s, 2H, $NC\mathit{H}_2Ph$), 2.87 [d, *J*= 11.7 Hz, 2H, $N(CH_2)_{2eq}$], 1.90 [tm, *J*= 11.7 Hz, 2H, $N(CH_2)_{2ax}$], 1.81-1.78 (m, 2H, $OCH_2C\mathit{H}_2CH_2$), 1.69-1.67 [m, 2H, $N(CH_2)_2(C\mathit{H}_2)_{3eq}$], 1.41-1.39 (m, 2H, $OCH_2CH_2C\mathit{H}_2$), 1.28-127 [m, 3H, $N(CH_2)_2(C\mathit{H}_2)_{ax}C\mathit{H}$)] (the N(1)H signal was not observed); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4 (C5-indol), 139.1 (2C, C2a, C1'-Ph), 132.7 (C7a), 129.3 (2C, C2', C6'-Ph), 128.1 (2C, C3', C5'-Ph), 127.8 (C3a), 126.9 (C4'-Ph), 111.7 (C6), 110.1 (C7), 105.1 (C4), 100.7 (C3), 63.4 (NCH_2Ph), 57.5 (CH_2OH), 53.7 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 44.0 ($CH_2CH_2CH_2O$), 35.5 [CH, $N(CH_2)_2(CH_2)_2CH$], 33.8 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 32.1 ($CH_2CH_2CH_2O$), 26.7 ($CH_2CH_2CH_2O$); MS (EI) *m*/*z* (%): 378 (53) $[M]^+$, 361 (19) $[M\text{-}OH^{\cdot}]^+$, 347 (100) $[M\text{-}CH_3O^{\cdot}]^+$, 202 (44) $[M\text{-}C_{10}H_{10}NO_2^{\cdot}]^+$. Anal. Calcd. for $C_{24}H_{30}N_2O_2.1/6\ H_2O$: C, 75.56; H, 8.01; N, 7.34. Found: C, 75.65; H, 7.83; N, 7.50.

5-(3-(1-Benzylpiperidin-4-yl)propoxy)-*N*-methyl-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (MBA316). To a solution of compound **11** (150 mg, 0.36 mmol) in dry THF (5 mL), under argon, *N*-methylpropargylamine (76 µL, 0.9 mmol) followed by trimethyl aluminium ($AlMe_3$) (2.0 M solution in hexanes) (0.80 mL, 1.6 mmol). This mixture was irradiated in a microwave apparatus (Biotage initiator 2.5) at 125 ºC for 30 min. The, the reaction mass was treated with some drops of an aqueous solution of HCl (1N), evaporated to dryness. The crude was submitted to column cromatography (DCM/methanol, 1-5%) to provide amine **MBA316** (139 mg, 88%) as an oil, R_f= 0.31, DCM/methanol, 10%): IR (KBr) ν 3428, 3291, 2925, 2851, 2802, 2758, 1630, 1526, 1453, 1404, 1374, 1225, 1201, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H, $NCH_2C_6\mathit{H}_5$), 7.09 (d, *J*= 8.8 Hz, 1H, H7), 6.90 (d, *J*= 2.2 Hz, 1H, H4), 6.76 (dd, *J*= 8.8, 2.2 Hz, 1H, H6), 6.55 (br s, 1H, H3), 4.34 (d, *J*= 2.2 Hz, 1H, $CONMeC\mathit{H}_2C{\equiv}CH$), 4.20 [t, *J*= 7.2 Hz, 2H, $OC\mathit{H}_2(CH_2)_2$], 3.52 (s, 2H, $NC\mathit{H}_2Ph$), 3.20 [s, 3H,$N(1)CH_3$], 2.90 [d, *J*= 11.3 Hz, 2H, $N(CH_2)_{2eq}$], 2.33 (br s, 1H, $CONMeCH_2C{\equiv}C\mathit{H}$), 1.93 [t, *J*=

10.9 Hz, 2H, $N(CH_2)_{2ax}$], 1.72-1.64 (m, 2H, $OCH_2CH_2CH_2$), 1.56 [br, *J*= 10.2 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.37-1.17 (m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)] (the N(1) H signal was not observed); MS (ESI) *m*/*z* (%): 444 $(M+H)^+$.

5-(3-(1-Benzylpiperidin-4-yl)propoxy)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (MBA315). Following the same method for the syntheis of compound **MBA313**, product **11** (130 mg, 0.30 mmol) and propargylamine (50 µL, 0.75 mmol) were reacted with $AlMe_3$ (0.67 mL, 1.35 mmol), to give amine **MBA315** (100 mg, 76%) as a solid (R_f= 0.35, DCM/methanol, 10%) after purification by cromatography (DCM/methanol, 1-5%): mp 73-6 ºC; IR (KBr) ν 3414, 3296, 2924, 2850, 2802, 2758, 1644, 1531, 1455, 1226, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.23 (m, 5H, $NCH_2C_6H_5$), 7.15 (d, *J*= 8.8 Hz, 1H, H7), 6.91 (d, *J*= 2.4 Hz, 1H, H4), 6.94 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.40 (s, 1H, H3), 6.41 (t, *J*= 5.2 Hz, 1H, $CONHCH_2C{\equiv}CH$), 4.43 [t, *J*= 7.3 Hz, 2H, $OCH_2(CH_2)_2$], 4.20 (dd, *J*= 2.4, 5.2 Hz, 1H, $CONHCH_2C{\equiv}CH$), 3.52 (s, 2H, NCH_2Ph), 2.90 [d, *J*= 10.9 Hz, 2H, $N(CH_2)_{2eq}$], 2.26 (t, *J*= 2.4 Hz, 1H, $CONHCH_2C{\equiv}CH$), 1.94 [t, *J*= 10.9 Hz, 2H, $N(CH_2)_{2ax}$], 1.81-1.64 (m, 2H, $OCH_2CH_2CH_2$), 1.58 [brd, *J*= 9.3 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.37-1.17 (m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)]; MS (ESI) *m*/*z* (%): 430 $(M+H)^+$.

General Method for the reduction of amides with LAH. To a suspensión of LAH (4.5 equiv) in dry THF (0.18M), under argon and at 0 ºC, the amide was slowly added, and refluxed for 1 h. The mixture was cooled at 0 ºC, and water was added to destroy the excess of LAH. Next, AcOEt was added and the salts was removed by filtration, and the solvent was evaporated to give a crude that was submitted to chromatography.

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (6)**. Following the **General Method for the reduction of amides with LAH**, a suspension of LAH (36 mg, 0.94 mmol) in THF (3 mL) was reacted with **MBA313** (70 mg, 0.16 mmol) to give compound **6** as an oil (50 mg, 74%; R_f= 0.36, DCM/methanol , 10%), after purification and separation by chromatography (DCM/methanol 1-5%): IR (KBr) ν 3413, 3292, 3028, 2923, 2851, 2797, 1620, 1480, 1455, 1416, 1360, 1203, 1183 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H, $NCH_2C_6H_5$), 7.08 (d, *J*= 8.8 Hz, 1H, H7), 6.91 (d, *J*= 2.4 Hz, 1H, H4), 6.70 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.25 (s, 1H, H3), 4.09 [t, *J*= 7.5 Hz, 2H, $OCH_2(CH_2)_2$], 3.64 [s, 2H, $C(2)CH_2NMe$], 3.54 (s, 2H, NCH_2Ph), 3.28 (d, *J*= 2.2 Hz, 1H, $NMeCH_2C{\equiv}CH$), 2.93 [d,

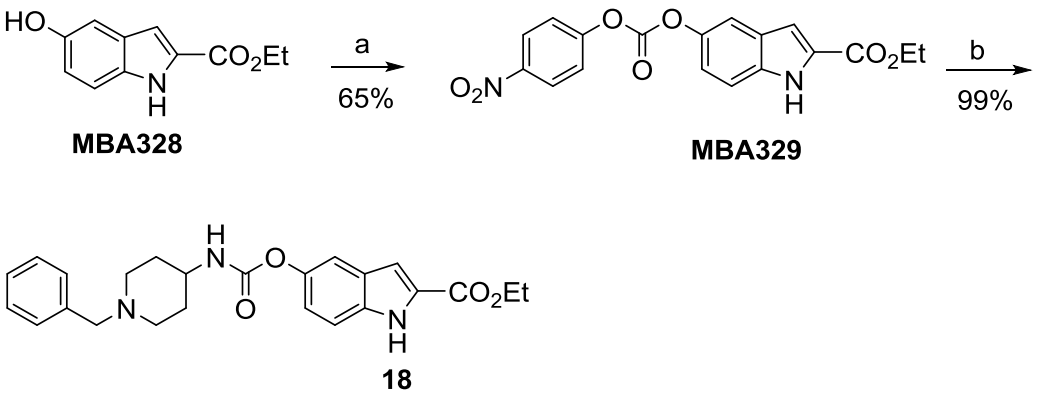
J= 11.3 Hz, 2H, $N(CH_2)_{2eq}$], 2.32 [s, 3H, NCH_3], 2.28 (t, 1H, $NMeCH_2C{\equiv}CH$), 1.96 [t, *J*= 11.3 Hz, 2H, $N(CH_2)_{2ax}$], 1.74-1.69 (m, 2H, $OCH_2CH_2CH_2$), 1.64 [d, *J*= 10.3 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.35-1.18 (m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)] (the N(1)H signal was not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8 (C5), 137.0, 136.6 (C2), 132.3 (C7a), 129.6 [2C, C2', C6', $C_6H_5CH_2N$] 128.2 [2C, C3', C5', $C_6H_5CH_2N$], 128.0 (C3a), 127.2 (C4'), 111.3 (C6), 109.8 (C7), 104.9 (C4), 101.8 (C3), 78.4 ($NCH_2C{\equiv}CH$), 73.5 ($NCH_2C{\equiv}CH$), 63.2 ($C_6H_5CH_2N$), 53.6 [2C,$N(CH_2)_2(CH_2)_2CH$], 51.9 [C(2) $CH_2NMeCH_2C{\equiv}CH_2$], 44.8 [C(2) $CH_2NMeCH_2C{\equiv}CH_2$], 43.8 ($OCH_2CH_2CH_2$), 41.6 ($N(1)CH_3$), 35.2 [$N(CH_2)_2(CH_2)_2CH$], 33.7 ($OCH_2CH_2CH_2$), 31.7 [2C,$N(CH_2)_2(CH_2)_2CH$], 27.3 ($OCH_2CH_2CH_2$); MS (ESI) *m*/*z* (%): 430 $(M+H)^+$. The bis-chlorhydrate was obtained as usual. **6.2HCl**: mp 140-5 ºC; IR (KBr) ν 3428, 2930, 2634, 1626, 1456, 1203 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.35-7.30 (m, 6H, $NCH_2C_6H_5$, H7), 6.96 (d, *J*= 2.4 Hz, 1H, H4), 6.78 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.60 (s, 1H, H3), 4.11 [t, *J*= 7.5 Hz, 2H, $OCH_2(CH_2)_2$], 4.06 [s, 2H, $C(2)CH_2N^+HMe$], 3.90 (d, *J*= 2.2 Hz, 1H, $N^+HMeCH_2C{\equiv}CH$), 3.25 [d, *J*= 16.4 Hz, 2H, $N(CH_2)_{2eq}$], 3.05 (t, 1H, $N^+HMeCH_2C{\equiv}CH$), 2.82 (s, 3H, NCH_3), 2.67 [t, *J*= 16.4 Hz, 2H, $N(CH_2)_{2ax}$], 1.68-1.45 (m, 4H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{eq}$], 1.22-0.90 (m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)] (the signal for $N^+HCH_2C_6H_5$ was not observed, surprisingly absent). Anal. Calcd for $C_{28}H_{35}N_3O.2HCl.5/2H_2O$: C, 61.42; H, 7.73; N, 7.67. Found: C, 61.60; H, 7.54; N, 7.86.

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (7) and *N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-en-1-amine (8)**. Following the **General Method for the reduction of amides with LAH**, a suspension of LAH (24 mg, 0.62 mmol) in THF (3.5 mL) was reacted with **MBA315** (60 mg, 0.14 mmol) to affor a mixture of compounds that were separated by column chromatography (DCM/methanol, 1-5%) to give pure products **7** as an oil (27 mg, 47%) and **8** as an oil (25 mg, 43%). **7**: R_f= 0.33 (DCM/methanol, 10%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.23 (m, 5H, $NCH_2C_6H_5$), 7.10 (d, *J*= 8.8 Hz, 1H, H7), 6.93 (d, *J*= 2.4 Hz, 1H, H4), 6.72 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.27 (s, 1H, H3), 4.09 [t, *J*= 7.6 Hz, 2H, $OCH_2(CH_2)_2$], 3.98 [s, 2H, $C(2)CH_2NH$], 3.48 (s, 2H, NCH_2Ph), 3.44 (d, *J*= 2.4 Hz, 1H, $NHCH_2C{\equiv}CH$), 2.86 [d, *J*= 11.2 Hz, 2H, $N(CH_2)_{2eq}$], 2.27 (t, 1H, $NHCH_2C{\equiv}CH$), 1.90 [t, *J*= 11.2 Hz, 2H, $N(CH_2)_{2ax}$], 1.74-1.70 (m, 2H, $OCH_2CH_2CH_2$), 1.63-.1.60 [m, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.30-1.18 [(m, 5H, $OCH_2CH_2CH_2$,

$N(CH_2)_2(CH_2)_{ax}CH$)] (the NH signals were not observed); MS (ESI) *m*/*z* (%): 416 $(M+H)^+$. The bis-chlorhydrate (**7.2HCl**) has been prepared as usual: mp 150-160 ºC; IR (KBr) ν 3428, 2932, 2726, 1626, 1456, 1199, 1154, 1030 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 7.35-7.23 (m, 6H, $NCH_2C_6H_5$, H7), 6.93 (d, *J*= 2.2 Hz, 1H, H4), 6.75 (dd, *J*= 8.8, 2.2 Hz, 1H, H6), 6.48 (s, 1H, H3), 4.39 [s, 2H, $C(2)CH_2NH_2^+$], 4.08-4.6 [4H, (m) $OCH_2(CH_2)_2$, (s) N^+HCH_2Ph], 3.79 (d, *J*= 2.5 Hz, 2H, $N^+H_2CH_2C{\equiv}CH$), 3.26 [d, *J*= 12.4 Hz, 2H, $N(CH_2)_{2eq}$], 2.88 (t, 1H, $N^+H_2CH_2C{\equiv}CH$), 2.69 [t, *J*= 12.4 Hz, 2H, $N(CH_2)_{2ax}$], 1.68-1.54 [m, 4H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{eq}$], 1.17-0.98 [m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)]. ^{13}C NMR (126 MHz, D_2O) δ 149.1 (C5), 132.3 (C7a), 130.9 [2C, C2', C6', $C_6H_5CH_2N^+H$], 129.9 (C4'), 129.8 (C2), 129.0 [2C, C3', C5', $C_6H_5CH_2N^+H$], 128.4 (C1'), 127.3 (C3a), 112.6 (C6), 111.6 (C7), 104.7 (C4), 103.2 (C3), 78.2 ($N^+H_2CH_2C{\equiv}CH$), 72.9 ($N^+H_2CH_2C{\equiv}CH$), 60.4 ($C_6H_5CH_2N^+H$), 52.2 [2C,$N^+H(CH_2)_2(CH_2)_2CH$], 43.2 (OCH2CH2CH2), 41.1 [C(2),$CH_2N^+H_2CH_2C{\equiv}CH$], 35.5 [C(2),$CH_2N^+H_2CH_2C{\equiv}CH$], 32.6 [2C,$N^+H(CH_2)_2(CH_2)_2CH$], 31.8 ($OCH_2CH_2CH_2$), 28.7 [2C,$N^+H(CH_2)_2(CH_2)_2CH$], 26.4 (OCH2CH2CH2) . Anal. Calcd for $C_{27}H_{33}N_3O.2HCl.2H_2O$: C, 62.45; H, 7.67; N, 7.80. Found: C, 62.31; H, 7.59; N, 8.04. **8**: R_f= 0.22 (DCM/methanol, 10%); IR (KBr) ν 3429, 3028, 2922, 2851, 2802, 2758, 1621, 1455, 1416, 1367, 1198, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.29 (m, 5H, $NCH_2C_6H_5$), 7.04 (d, *J*= 8.4 Hz, 1H, H7), 6.93 (d, *J*= 3.3 Hz, 1H, H4), 6.69 (dd, *J*= 8.4, 3.3 Hz, 1H, H6), 6.21 (s, 1H, H3), 5.92 (ddt, *J*= 6.0, 17.1, 10.3 Hz, 1H, $NHCH_2CH{=}CH_2$), 5.21 (dq, *J*= 1.7, 17.1 Hz, 1H, $NHCH_2CH{=}CH_2$), 5.12 (dq, *J*= 1.6, 10.3 Hz, 1H, $NHCH_2CH{=}CH_2$), 4.06 [t, *J*= 7.6 Hz, 2H, $OCH_2(CH_2)_2$], 3.87 [s, 2H, $C(2)CH_2NH$], 3.58 (s, 2H, NCH_2Ph), 3.32 (dt, *J*= 6.0, 1.4 Hz, 2H, $NHCH_2CH{=}CH_2$), 2.95 [d, *J*= 11.8 Hz, 2H, $N(CH_2)_{2eq}$], 2.02 [t, *J*= 11.8 Hz, 2H, $N(CH_2)_{2ax}$], 1.73-1.64 (m, 2H, $OCH_2CH_2CH_2$), 1.61 [d, *J*= 9.4 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.34-1.23 [(m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)]; MS (ESI) *m*/*z* (%): 91 (92) $[M-Bn]^+$, 347 (100) $[M-CH_2NHCH_2CH{=}CH_2]^+$, 361 (13) $[M-NHCH_2CH{=}CH_2]^+$, 376 (7) $[M-CH_2CH{=}CH_2]^+$, 417 (38) $[M]^+$. The mixed oxalate was prepared as usual to give **8.$C_2O_4H_2$:** mp 140-5 ºC; IR (KBr) ν 3426, 2934, 2852, 1719, 1624, 1456, 1404, 1279, 1204 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.35-7.25 (m, 6H, $NCH_2C_6H_5$, H7), 6.93 (d, *J*= 2.4 Hz, 1H, H4), 6.75 (dd, *J*= 8.4, 2.4 Hz, 1H, H6), 6.45 (s, 1H, H3), 5.74 (ddt, *J*= 6.9, 16.9, 10.3 Hz, 1H, $NHCH_2CH{=}CH_2$), 5.38 (d, *J*= 16.9 Hz, 1H, $NHCH_2CH{=}CH_2$), 5.36 (d, *J*= 10.3 Hz, 1H, $NHCH_2CH{=}CH_2$), 4.28 [s, 2H, $C(2)CH_2N^+H_2$], 4.06 (s, 2H, N^+HCH_2Ph), 4.04 [t, *J*= 6.8 Hz, 2H, $OCH_2(CH_2)_2$], 3.59 (d, *J*= 6.9, 1.4 Hz, 2H, $N^+H_2CH_2CH{=}CH_2$), 3.27 [d, *J*= 12.9

Hz, 2H, $N(CH_2)_{2eq}$], 2.69 [t, *J*= 12.9 Hz, 2H, $N(CH_2)_{2ax}$], 1.65 [d, *J*= 10.4 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}$], 1.59-1.51 (m, 2H, $OCH_2CH_2CH_2$), 1.34-0.98 [(m, 5H, $OCH_2CH_2CH_2$, $N(CH_2)_2(CH_2)_{ax}CH$)]. Anal.Calcd for $C_{27}H_{35}N_3O.2Oxal.H_2O$: C, 60.48; H, 6.71; N,6.83. Found: C, 60.36; H, 6.97; N, 6.68.

Ethyl 5-(((1-benzylpiperidin-4-yl)carbamoyl)oxy)-1*H*-indole-2-carboxylate (18).

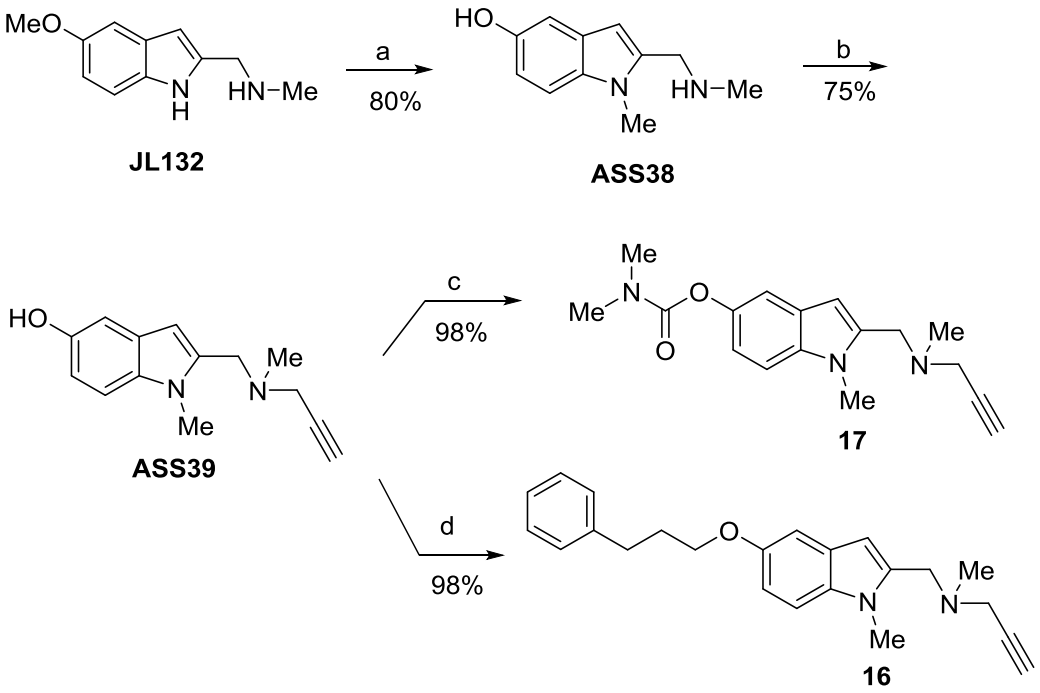


Scheme 9. Reagents and conditions: (a) 4-Nitrophenyl chloroformate, 4-methylmorpholine, THF; (b) 1-benzylpiperidin-4-amine, DMAP, THF.

Ethyl 5-(((4-nitrophenoxy)carbonyl)oxy)-1*H*-indole-2-carboxylate (MBA329). To a solution of ethyl 5-hydroxy-1*H*-indole-2-carboxylate (**MBA328**) (205 mg, 1 mmol) in dry THF (5 mL), under argon, 4-methylmorpholine (0.22 ml, 2 mmol) and 4-nitrophenyl cloroformate (402 mg, 2 mmol) were added, and stirred for 2 h, at rt. The solvent was evaporated and the crude purified by chromatography (hexane/AcOEt, 10-40%) to give carbonate **MBA329** (240 mg, 65%), as a white solid: R_f= 0.32 (hexane/AcOEt, 40%); mp 199-202 ºC; IR (KBr) ν 3435, 3336, 3076, 2851, 1765, 1698, 1531, 1351, 1260, 1247, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.02 (br s, 1H, NH), 8.31 (d, *J*= 9.4 Hz, 2H, H3', H5', 4'-$NO_2C_6H_4OCO$), 7.59 (s, 1H, H3), 7.50 (d, *J*= 9.4 Hz, 2H, H2', H6', 4'-$NO_2C_6H_4OCO$), 7.45 (d, *J*= 8.8 Hz, 1H, H7), 7.25-7.21 (m, 2H, H4, H6), 4.42 (q, *J*= 7.2 Hz, 2H, $CO_2CH_2CH_3$), 1.42 (q, *J*= 7.2 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5 ($CO_2CH_2CH_3$), 155.3 (C1')**, 151.6 (C5)**,), 145.5 (C4')*, 145.1 (C4'-$NO_2C_6H_4OCO$),* 134.7 (C2), 129.2 (C3a), 127.5 (C7a), 125.3 (2C, C3', C5', 4'-$NO_2C_6H_4OCO$), 121.7 (2C, C2', C6', 4'-$NO_2C_6H_4OCO$), 118.7 (C6), 113.7 (C3), 112.7 (C7), 108.7 (C4), 61.2 ($CO_2CH_2CH_3$, 14.3 ($CO_2CH_2CH_3$); MS (EI)

m/z (%): 370 (M^+, 100), 340 (3), 324 (19), 280 (49), 204 (19), 188 (9), 158 (49), 142 (29), 130 (25) 114 (22), 102 (14); MS (ESI): *m/z* (%): 371 $(M+H)^+$.

Ethyl 5-(((1-benzylpiperidin-4-yl)carbamoyl)oxy)-1*H*-indole-2-carboxylate (18). To a solution of commercial 4-amino-*N*-benzylpiperidine (60 µL, 0.29 mmol) in dry THF (3.5 mL), 4-dimethylaminopiridine (19 mg, 0.15 mmol) and ethyl 5-(((4-nitrophenoxy)carbonyl)oxy)-1*H*-indole-2-carboxylate (**MBA329**) (55 mg, 0.15 mmol) were added, and the mixture was stirred at rt for 1 h, under argon. The solvent was evaporated and the crude purified by chromatography (DCM/methanol, 0-2.5%) giving compound **18** (62 mg, 99%) as a white solid: R_f= 0.35 (DCM/methanol, 2.5%); mp 180-3 ºC; IR (KBr) ν 3325, 3028, 2936, 1701, 1521, 1249, 1204, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 [br s, 1H, N(1)H], 7.38 (d, *J*= 2.2 Hz, 1H, H4), 7.33-7.31 (m, 6H, $NCH_2C_6H_5$, H7), 7.15 (s, 1H, H3), 7.05 (dd, *J*= 9.0, 2.2 Hz, 1H, H6), 4.95 [br d, *J*= 7.7 Hz, NHC(O)O], 4.38 (q, *J*= 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.63-3.53 [m, 1H, $N(CH_2)_2(CH_2)_2CH$)NHC(O)O], 3.50 (s, 2H, $NCH_2C_6H_5$), 2.82 [d, *J*= 11.3 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 2.13 [t, *J*= 11.3 Hz, 2H, $N(CH_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 1.58-1.99 [d, *J*= 11.6 Hz, 2H, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$], 1.50 [m, 2H, $N(CH_2)_2(CH_2)_{eq}(CH_2)_{ax}CH$], 1.39 (t, *J*= 7.2 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 ($CO_2CH_2CH_3$), 154.6 [HNC(O)O], 145.4 (C5), 138.4 (C7a), 134.6 (C1', $NCH_2C_6H_5$), 129.3 (2xCH, C'3,.C5', $NCH_2C_6H_5$), 128.8 (C4', $NCH_2C_6H_5$), 128.4 (3C: 2xCH, C2', C6', $NCH_2C_6H_5$), 127.8 (C3a),* 127.3 (C2)*, 120.5 (C6), 114.5 (C4), 112.4 (C7), 108.8 (C3), 63.2 ($NCH_2C_6H_5$), 61.3 ($CO_2CH_2CH_3$), 52.3 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 48.6 [CH, $N(CH_2)_2(CH_2)_2CH$], 32.6 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 14.5 ($CO_2CH_2CH_3$); MS (EI) *m/z* (%): 368 (2), 236 (4), 217 (37), 205 (44), 159 (100), 139 (22), 125 (18); MS (ESI) *m/z* (%): 422 $(M+1)^+$. Anal. Calcd. for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.46; H, 6.73; N, 9.71.



Scheme 10. Reagents and conditions: (a) BBr_3, $CHCl_3$, -78 ºC; (b) Propargyl bromide, *t*-$BuNH_2$, THF, rt; (c) Me_2NCOCl, NaH, THF, 0 ºC; (d) $Ph(CH_2)_3Br$, NaH, DMF, reflux.

1-Methyl-2-((methylamino)methyl)-1*H*-indol-5-ol (ASS38). A solution of BBr_3 in CH_2Cl_2 (7.5 mL, 1M) was added to a stirred solution of **JL132** (1 g, 4.89 mmol) in anhydrous $CHCl_3$ (50 mL), cooled at -78 ºC, under argon. When the addition was complete, the reaction mixture was stirred at rt for 48 h, cooled at 0 ºC, and quenched with water, and neutralized by saturated $NaHCO_3$. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and after removing the solvent, the crude was purified by column chromatography (CH_2Cl_2/MeOH/TEA, 40/1/1% to 10/1/1%) to afford **ASS38** (0.742 g, 80%) as a white solid: R*f* = 0.34 (CH_2Cl_2/MeOH/TEA, 10/1/1 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3-NH), 3.66 (s, 3H, CH_3-N), 3.91 (s, 2H, CH_2), 6.21 (s, 1H, CH), 6.62 (dd, *J*= 2.3 and 8.7 Hz, 1H, CH), 6.79 (d, *J*= 2.2 Hz, 1H, CH), 7.18 (d, *J*= 8.7 Hz, 1H, CH), 8.66 (s, 1H, OH); MS (EI) *m/z* (%): 160 (100) $[M\text{-}HNMe]^+$, 173 (3) $[M\text{-}OH]^+$, 190 (48) $[M]^+$.

5-Hydroxy-*N*-[(1-methyl-1*H*-indol-2-yl)methyl]-*N*-methylprop-2-yn-1-amine (ASS39). To a solution of amine **ASS38** (0.31 g, 1.629 mmol) and *t*-$BuNH_2$ (0.25 mL, 2.44 mmol) in anhydrous THF (10 mL), cooled at 0-5 ºC, a solution of propargyl bromide (0.131 mL, 1.468 mmol) in THF (5 mL) was added. The reaction was stirred at rt overnight. Then, the solvent was removed in *vacuum* and the solid purified by colum

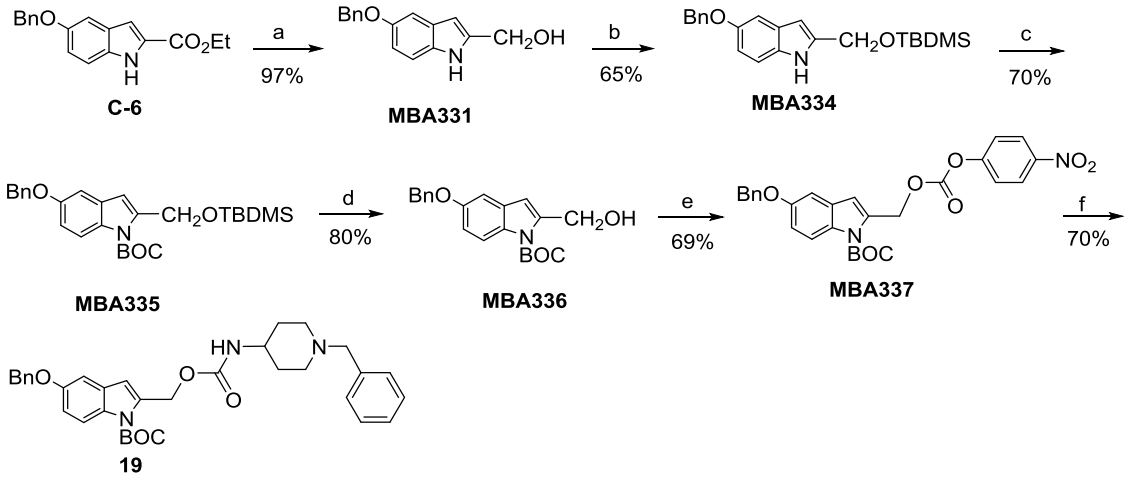
chromatography (CH_2Cl_2/EtOAc, 10/1) to afford **ASS39** (0.28 g, 75%) as a white solid: R*f* = 0.13 (CH_2Cl_2/EtOAc, 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H, CH_3),3.23 (m, CH), 3.29 (m, CH_2), 3.6 (s, 2H, CH_2), 3.64 (s, 3H, CH_3), 6.13 (s, CH), 6.6 (dd, *J*= 2.3 and 8.7 Hz,1H, CH), 6.78 (d, *J*= 2.2 Hz, 1H, CH), 8.7 (d, *J*= 8.7 Hz, CH), 8.64 (s, OH); MS (EI) *m/z* (%): 160 (100) $[M\text{-}HNMe]^+$, 228 (22) $[M]^+$.

1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl dimethylcarbamate (17). To an ice-cooled solution of **ASS39** (19 mg, 0.083 mmol) in dry CH_3CN (0.5 mL), NaH (3.3 mg, 0.083 mmol, 60% in mineral oil) was added under argon. The mixture was stirred at 0 ºC for 10 min. Then, to this mixture was added Me_2NCOCl (8 μL, 0.085 mmol, 1.02 equiv) in dry CH_3CN (0.5 mL). The reaction was stirred at 0 ºC for 4 h. Then, the reaction was evaporated in *vacuum*, and water (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2, and the combined extract was dried (Na_2SO_4), evaporated to dryness in *vacuum*, and the residue was purified by column chromatography (CH_2Cl_2/EtOAc, 10/1) to give compound **17** (24.4 mg, 98%). R*f* = 0.27 (CH_2Cl_2/AcOEt, 5/1/); mp 93-5 ºC; IR (KBr) ν 3283, 2940, 1704, 1486, 1394, 1191, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (t, *J*= 2.34 Hz, CH), 2.34 (s, 3H, CH_3), 3.02 (s, 3H, N-CH_3), 3.13 (s, 3H, N-CH_3), 3.31 (d, *J*= 2.36 Hz, 2H, CH_2), 3.69 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 6.38 (s, 1H, CH-3), 6.95 (dd, *J* = 8.76 and 2.28 Hz, 1H, CH-6), 7.24 (d, *J*= 8.79 Hz, 1H, CH-7), 7.26 (d, *J*= 2.25 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9 (N-CH_3), 36.4 (CON-CH_3), 36.6 (CON-CH_3), 41.4 (N-CH_3), 44.6 (*C*H_2-C≡CH), 51.7 (CH_2-N), 73.4 (C≡*C*H), 78.2 (-*C*≡C), 102.6 (CH-3), 109.0 (CH-7), 112.5 (CH-4), 115.8 (CH-6), 127.3 (C), 135.6 (C), 137.4 (C), 144.8 (C), 155.9 (CO); MS (EI) *m/z* (%): 72 (88) $[(CH_3)_2NCO]^+$, 232 (100) $[M\text{-}(CH_3NCH_2C{\equiv}CH)+H]^+$, 256 (6) $[M\text{-}CH_3)_2N]^+$, 299 (22) $[M]^+$. The free base was dissolved in dry ether (2 mL) and a solution of HCl/ether was added dropwise with stirring. The precipitate was separated by filtration, washed with ether and dried in *vacuum* to afford **17.HCl** as a white powder: mp 191-3 ºC; IR (KBr) ν 3230, 2920, 2619, 2499, 2418, 1722, 1713, 1477, 1390, 1198, 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, CH_3), 2.81 (s, 3H, CH_3), 2.97 (s, 3H, H_3), 3.02 (m, 1H, CH), 3.75 (s, 3H, CH_3), 3.87 (d, *J*= 2.4 Hz, 2H, CH_2), 4.44 (s, 2H, CH_2), 6.62 (s, 1H, CH), 6.89 (dd, *J*= 9 and 2.4 Hz, 1H), 7.18 (d, *J*= 2.4 Hz, 1H), 7.3 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0 (CH_3), 36.0 (CON-CH_3), 36.3 (CON-CH_3), 39.5 (N-CH_3), 44.5 (CH_2), 49.7 (CH_2), 71.6 (C≡CH), 80.5 (-C≡), 106.6 (CH-ind), 111.2 (CH-ind), 113.3 (CH), 117.9 (CH), 126.7 (C), 128.9 (C), 136.1 (C),

145.0 (C), 157.85 (CO). Anal. Calcd. for $C_{17}H_{21}N_3O_2$.HCl: C, 60.80; H, 6.60; N, 12.51. Found: C, 60.98; H, 6.77; N, 12.62.

***N*-Methyl-N-((1-methyl-5-(3-phenylpropoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine** (**16**). A solution of **ASS39** (15 mg, 0.0657 mmol) in DMF (0.5 mL) was treated with NaH (4 mg, 0.1 mmol, 60% in mineral oil), and then with 4-phenyl-1-bromopropane (13 mg, 0.0657 mmol) for 30 min at reflux. The reaction mixture was diluted with water, and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure to afford compound **ASS50** (22.2 mg, 98%). R*f* = 0.66 (CH_2Cl_2/AcOEt, 10/1); mp 74-76 ºC; IR (KBr) ν 3281, 2953, 2932, 2854, 1618, 1488, 1472, 1396, 1209, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12 (m, 2H, CH_2), 2.28 (t, *J*= 3.0Hz, CH), 2.34 (s, 3H, CH_3), 2.84 (t, *J*= 7.3 Hz, CH_2), 3.31 (d, *J*= 3.0 Hz, CH_2), 3.67 (s, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.00 (t, *J*= 6.3 Hz, 2H, CH_2), 6.32 (s, CH-3), 6.88 (dd, *J*= 2.4 and 8.8 Hz,1H, CH-6), 7.02 (d, *J*= 2.3 Hz, 1H, CH-4), 7.16-7.3 (m, CHind + 5Har); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (CH_3), 31.0 (CH_2), 32.2 (CH_2), 41.6 (CH_3), 44.6 (CH_2), 51.7 (CH_2), 67.7 (CH_2), 73.4 (C), 78.3 (CH), 102.0 (CH-3), 103.4 (CH-4), 109.5 (CH-7), 112.0 (CH-6), 125.7 (CH-Ph), 127.4 (C), 128.3 (2xCH-Ph), 128.3 (2xCH-Ph), 133.3 (C), 137.0 (C), 141.7 (C), 153.2 (C); MS (EI) *m/z* (%): 160 (73) [M-HNMe – $Ph(CH_2)_3$]$^+$, 279 (100) [M- HNMe]$^+$, 346 (36) [M]$^+$. The free base was dissolved in diethyl ether and treated with a solution of ether saturated with HCl with stirring; the precipitate was collected by filtration, triturated with fresh ether, and filtered again. Drying in *vacuum* afforded **16.HCl** as a white powder: mp 185-7 ºC; IR (KBr) ν 3196, 2933, 2561, 2512, 1486, 1473, 1207 cm^{-1}. Anal. Calcd. for $C_{23}H_{26}N_2O$.HCl: C, 72.14; H, 7.11; N, 7.32. Found: C, 72.01; H, 7.08; N, 7.43.

***tert*-Butyl 5-(benzyloxy)-2-((((1-benzylpiperidin-4-yl)carbamoyl)oxy)methyl)-1*H*-indole-1-carboxylate (19)**.



Scheme 10. Reagents and conditions: (a) LAH, THF, rt; (b) TBDMSiCl, imidazole, DCM; (c) (*t*-BOC)$_2$O, DMAP, TEA, DCM; (d) AcOH, H_2O, THF; (e) 4-Nitrophenyl chloroformate, 4-methylmorpholine, THF; (f) 1-benzylpiperidin-4-amine, DMAP, THF.

(5-(Benzyloxy)-1*H*-indol-2-yl)methanol (MBA331). To a suspension of LAH (228 mg, 6 mmol) in dry THF (4 mL), under argon at a 0 ºC, commercial ethyl 5-(benzyloxy)-1*H*-indole-2-carboxylate (**C-6**) (60 mg, 0.14 mmol) was slowly added. Then, the mixture was refluxed for 2 h, cooled at 0 ºC, and treated with some drops of water. AcOEt was added and the mass was filtered, washed with more AcOEt. The solvent was evaporated, and the residue was purified by chromatography (DCM/methanol, 1-5%) to give compound **MBA331** (211 mg, 97%) (Marco, Jose L. Improved preparation of N-propargyl-2-(5-benzyloxyindolyl)methylamine, *J. Heterocyclic Chem*.**1998**, *35*, 475-476).

5-(Benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1*H*-indole (MBA334). To a solution of 5-(benzyloxy)-1*H*-indol-2-yl)methanol (**MBA331**) (210 mg, 0.83 mmol) in dry DCM (4 mL), *tert*-butyldimethylsilyl chloride (149 mg, 0.96 mmol) and imidazole (71 mg, 1.05 mmol) were added, and at stirred at rt for 24 h. Then, the solvent was removed, and the crude was submitted to cromatography (hexane/AcOEt, 5-10%) to yield compound **MBA334** (198 mg, 65%) {^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 [br s, 1H, N(1)H], 7.54-7.41 (m, 5H, $OCH_2C_6H_5$), 7.28 (d, *J*= 8.8 Hz, 1H, H7), 7.16 (d, *J*= 2.4 Hz, 1H, H4), 6.96 (dd, *J*= 8.8, 2.4 Hz, 1H, H6), 6.29 (s, 1H, H3), 5.14 (s, 2H, $OCH_2C_6H_5$), 4.89 [s, 2H, C(2)CH_2OTBDMS], 1.00 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 0.16 [s, 6H, $Si(CH_3)_2C(CH_3)_3$]} [Seehra, Jasbir S.; Kaila, Neelu; McKew, John C.; Lovering, Frank; Bemis, Jean E.; Xiang, Yibin, Preparation of indole derivatives as phospholipase enzyme inhibitors, PCT Int. Appl. (1999), WO 9943651].

***tert*-Butyl 5-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1*H*-indole-1-carboxylate (MBA335)**. 5-(Benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1*H*-indole (**MBA334**) (198 mg, 0.42 mmol) was dissolved in dry DCM (5 mL) and treated with (*tert*-BOC)$_2$O (114 mg, 0.52 mmol), TEA (88 µL, 0.64 mmol) and DMAP (13 mg, 0.10 mmol) at rt for72 h. Then, the solvent was evaporated,and the resulting crude purified by column chromatography (hexane/AcOEt, 1-5%) affording compound **MBA335** (176 mg, 70%) {^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J*= 9.0 Hz, 1H, H7), 7.50-7.34 (m, 5H, $OCH_2C_6H_5$), 7.09 (d, *J*= 2.6 Hz, 1H, H4), 6.97 (dd, *J*= 9.0, 2.6 Hz, 1H, H6), 6.63 (s, 1H, H3), 5.14 (s, 2H, $OCH_2C_6H_5$), 5.04 [s, 2H, $C(2)CH_2OTBDMS$], 1.70 [s, 9H, $N(1)CO_2C(CH_3)_3$], 1.02 [s, 9H, $Si(CH_3)_2C(CH_3)_3$], 0.18 [s, 6H, $Si(CH_3)_2C(CH_3)_3$]} [Seehra, Jasbir S.; Kaila, Neelu; McKew, John C.; Lovering, Frank; Bemis, Jean E.; Xiang, Yibin, Preparation of indole derivatives as phospholipase enzyme inhibitors, PCT Int. Appl. (1999), WO 9943651].

***tert*-Butyl 5-(benzyloxy)-2-(hydroxymethyl)-1*H*-indole-1-carboxylate (MBA336)**. *tert*-Butyl 5-(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1*H*-indole-1-carboxylate (**MBA335**) (176 mg, 0.38 mmol) was dissolved in a mixture of cc AcOH (5.6 mL), H_2O (1.88 mL) and THF (1.88 mL) and the mixture was stirred at rt overnight.. Then, the solvents were evaporated, and the crude purified by chromatography (hexane/AcOEt, 10%) affording product **MBA336** (107 mg, 80%) {^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J*= 8.9 Hz, 1H, H7), 7.48-7.34 (m, 5H, $OCH_2C_6H_5$), 7.06 (d, *J*= 2.6 Hz, 1H, H4), 6.99 (dd, *J*= 8.9, 2.6 Hz, 1H, H6), 6.51 (s, 1H, H3), 5.12 (s, 2H, $OCH_2C_6H_5$), 4.97 [s, 2H, $C(2)CH_2OH$], 3.62 (br s, 1H, OH), 1.73 [s, 9H, $N(1)CO_2C(CH_3)_3$]} [Seehra, Jasbir S.; Kaila, Neelu; McKew, John C.; Lovering, Frank; Bemis, Jean E.; Xiang, Yibin, Preparation of indole derivatives as phospholipase enzyme inhibitors, PCT Int. Appl. (1999), WO 9943651].

***tert*-Butyl 5-(benzyloxy)-2-((((4-nitrophenoxy)carbonyl)oxy)methyl)-1*H*-indole-1-carboxylate (MBA337)**. To a solution of *tert*-butyl 5-(benzyloxy)-2-(hydroxymethyl)-1*H*-indole-1-carboxylate (**MBA336**) (105 mg, 0.29 mmol) in dry THF (5 mL), 4-methylmorpholine (66 µL, 0.6 mmol) and 4-nitrophenyl cloroformate (119 mg, 0. mmol) were added and the mixture was stirred at rt for 2.5 h, under argon. Then, the solvents were evaporated, and the crude purified by chromatography (hexane/AcOEt, 10%) to give compound **MBA337** (107 mg, 69%), as a oil: R_f= 0.30 (hexane/AcOEt, 30%); IR (KBr) ν 3367, 2923, 1731, 1615, 1525, 1452, 1369, 1325, 1260, 1212, 1159, 1121, 1095,

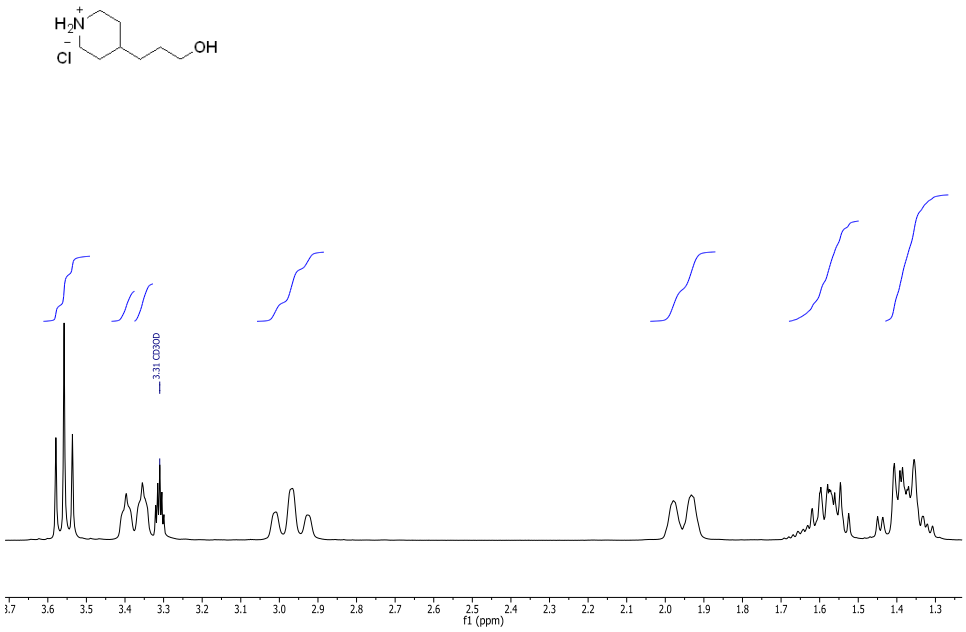
1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J*= 9.3 Hz, 2H, H3', H5', 4'-$NO_2C_6H_4OCO$), 8.02 (d, *J*= 9.0 Hz, 1H, H7), 7.48-7.33 (m, 7H: 2H, H2', H6', 4'-$NO_2C_6H_4OCO$; 5H, $OCH_2C_6\mathit{H}_5$), 7.08-7.02 (m, 2H, H4, H6), 6.69 (s, 1H, H3), 5.64 [s, 2H, C(2)CH_2OC(O)O], 5.12 ($C_6H_5OC\mathit{H}_2$), 1.70 [s, 9H, N(1)COC$(CH_3)_3$]; MS (EI) *m/z* (%): 139 (14), 236 (48), 280 (100), 327 (11), 418 (22, M-BOC+H^+); MS (ESI) *m/z* (%): 518 (M+23, M+Na)$^+$.

***tert*-Butyl 5-(benzyloxy)-2-((((1-benzylpiperidin-4-yl)carbamoyl)oxy)methyl)-1*H*-indole-1-carboxylate (19)**. To a solution of commercial 4-amino-*N*-benzylpiperidine (84 µL, 0.41 mmol) in dry THF, DMPA (25 mg, 0.20 mmol) and *tert*-butyl 5-(benzyloxy)-2-((((4-nitrophenoxy)carbonyl)oxy)methyl)-1*H*-indole-1-carboxylate (**MBA337**) (107 mg, 0.20 mmol) were added,and the mixture was stirred for 3 h, at rt, under argon. Then, the solvent was evaporated, and the crude purified by chromatography (DCM/methanol, 1%) leading to product **19** (83 mg, 70%) as an oil: R_f= 0.39 (DCM/methanol, 2%); IR (KBr) ν 3338, 2928, 1730, 1531, 1476, 1452, 1370, 1123, 1042, 850, 738, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J*= 8.8 Hz, 1H, H7), 7.37 (d, *J*= 7.4 Hz, 1H, aromatic), 7.30 (t, *J*= 7.3 Hz, 1H, aromatic), 7.25-7.16 (m, 8H, $C_6\mathit{H}_5OCH_2$, $NCH_2C_6\mathit{H}_5$), 6.95 (d, *J*= 2.0 Hz, 1H, H4), 6.90 (dd, *J*= 8.8, 2.0 Hz, 1H, H6), 6.64 (s, 1H, H3), 5.31 [s, 2H, C(2)CH_2OC(O)NH], 5.02 ($C_6H_5OC\mathit{H}_2$), 4.63 [br d, *J*= 7.3 Hz, NHC(O)O], 3.49-3.47 [m, 1H, $N(CH_2)_2(CH_2)_2C\mathit{H}$)NHC(O)O], 3.44 (s, 2H, $NC\mathit{H}_2C_6H_5$), 2.74 [m, 2H, $N(C\mathit{H}_2)_{eq}(CH_2)_{ax}(CH_2)_2CH$], 2.07 [t, *J*= 10.3 Hz, 2H, $N(CH_2)_{eq}(C\mathit{H}_2)_{ax}(CH_2)_2CH$], 1.88 [d, *J*= 10.8 Hz, 2H, $N(CH_2)_2(C\mathit{H}_2)_{eq}(CH_2)_{ax}CH$], 1.58 [s, 9H, N(1)COC$(CH_3)_3$], 1.45-1.42 [m, 2H, $N(CH_2)_2(CH_2)_{eq}(C\mathit{H}_2)_{ax}CH$]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2 (C5), 155.0 [HNC(O)O]*, 149.9 [N(1)*C*(O)OC$(CH_3)_3$], 137.2 (C7a), 136.1 and 131.7 (2C, 2xC1', C_6H_5), 129.4, 129.1, 128.8, 128.5, 128.2 (10C, CH, $C_6H_5CH_2O$, $NCH_2C_6H_5$), 127.4 (C3a),* 127.1 (C2)*, 116.4 (C7), 113.9 (C6), 109.3 (C3), 104.1 (C4), 84.4 [N(1)C(O)OC$(CH_3)_3$], 70.5 ($C_6H_5OCH_2$), 62.9 ($NCH_2C_6H_5$), 61.2 [C(2)*C*H_2OC(O)NH], 52.1 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 48.1 [CH, $N(CH_2)_2(CH_2)_2CH$], 32.3 [2xCH_2, $N(CH_2)_2(CH_2)_2CH$], 28.1 [N(1)*C*(O)OC(CH_3)$_3$]; MS (EI) *m/z* (%) 233 (100) [M-$C_{21}H_{22}NO_3$]$^+$, 469 (4)$^{\cdot}$[MH-BOC]$^+$, 217 (12) [M-$C_{21}H_{22}NO_4^{\cdot}$]$^+$. The oxalate was obtained as usual to give compound **19-Oxal**: mp 102-5 ºC; IR (KBr) ν 3422, 2978, 2550, 1725, 1618, 1453, 1371, 1194, 1125 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, *J*= 9.1 Hz, 1H, H7), 7.53 (d, *J*= 6.5 Hz, 1H, aromatic), 7.46-7.31 (m, 9H, $C_6\mathit{H}_5OCH_2$, $N^+HCH_2C_6\mathit{H}_5$), 7.18 (d, *J*= 2.5 Hz, 1H, H4), 6.98 (dd, *J*=

9.1, 2.5 Hz, 1H, H6), 6.64 (s, 1H, H3), 5.25 [s, 2H, C(2)C*H*$_2$OC(O)NH], 5.10 (C$_6$H$_5$OC*H*$_2$), 3.99 (s, 2H, N$^+$HC*H*$_2$C$_6$H$_5$), 3.54 [m, 1H, N(CH$_2$)$_2$(CH$_2$)$_2$C*H*)NHC(O)O], 3.12 [m, 2H, N(C*H*$_2$)$_{eq}$(CH$_2$)$_{ax}$(CH$_2$)$_2$CH], 2.72 [m, 2H, N(CH$_2$)$_{eq}$(C*H*$_2$)$_{ax}$(CH$_2$)$_2$CH], 1.88 [d, *J*= 13.2 Hz, 2H, N(CH$_2$)$_2$(C*H*$_2$)$_{eq}$(CH$_2$)$_{ax}$CH], 1.58 [s, 9H, N(1)COC(CH$_3$)$_3$; m, 2H, N(CH$_2$)$_2$(CH$_2$)$_{eq}$(C*H*$_2$)$_{ax}$CH]; MS (EI) *m/z* (%): 378 (1), 280 (1),172 (2), 146 (1), 91 (100); MS (ESI) *m/z* (%): 569 (M+1)$^+$. Anal. Calcd for C$_{34}$H$_{39}$N$_3$O$_5$.Oxal: C, 65.54; H, 6.26; N, 6.37. Found: C, 65.51; H, 6.34; N, 6.33.

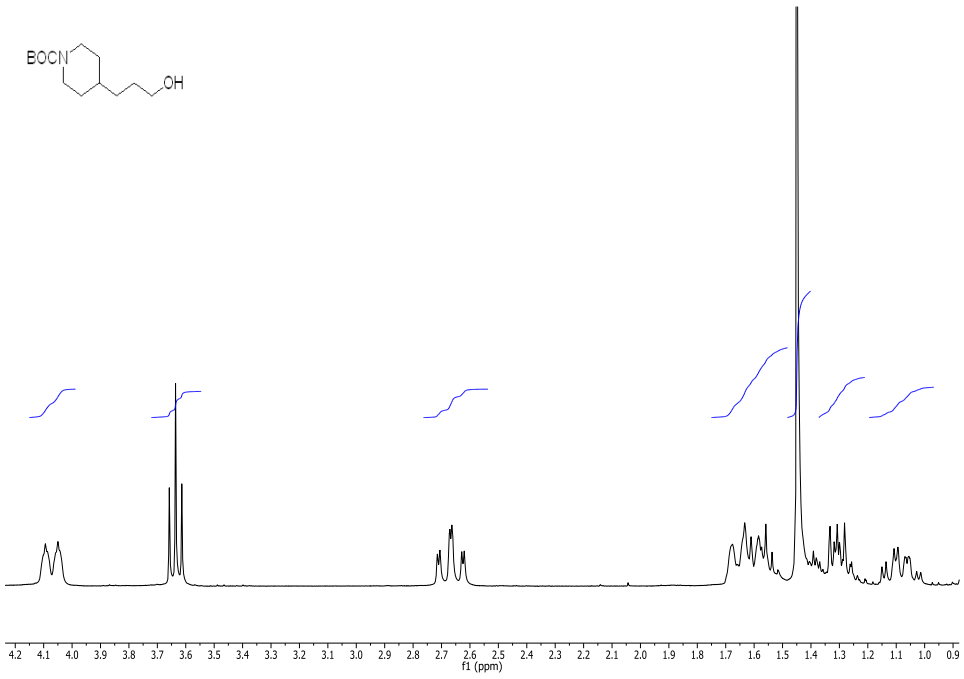
^{1}H and ^{13}C NMR spectra

3-(Piperidin-4-yl)propan-1-ol hydrochloride (MBA160).



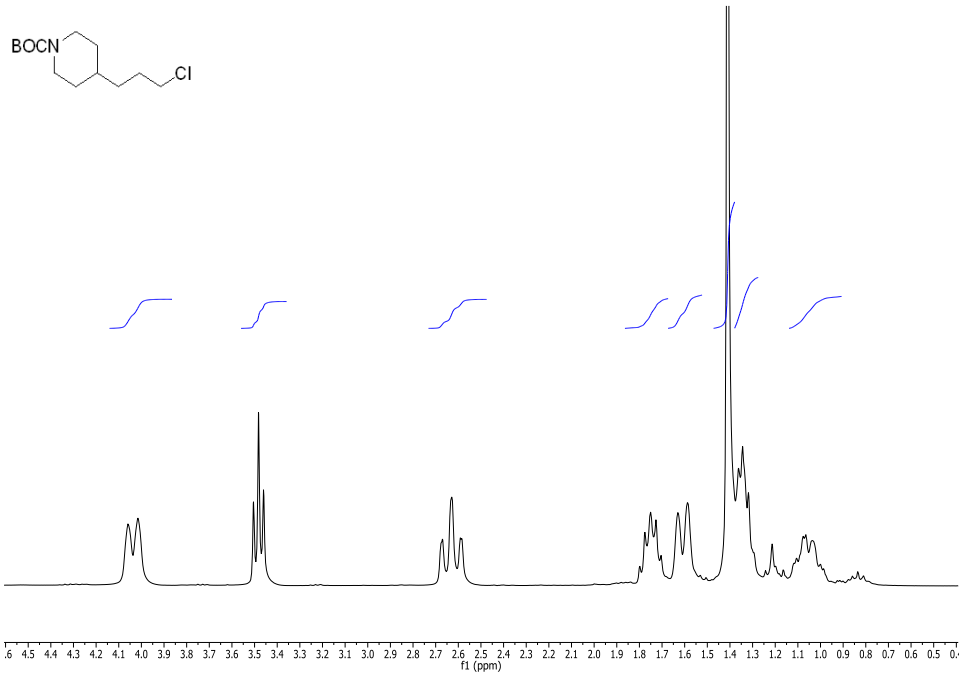
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA160.**

tert-Butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (MBA163).



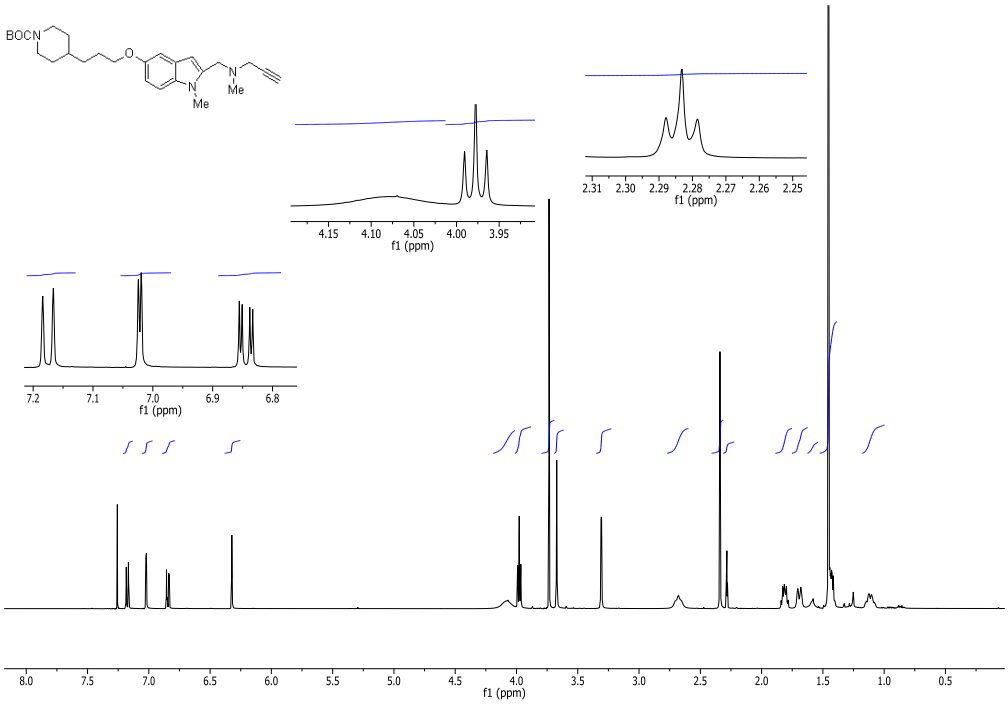
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA163.**

***tert*-Butyl 4-(3-chloropropyl)piperidine-1-carboxylate (MBA177)**.

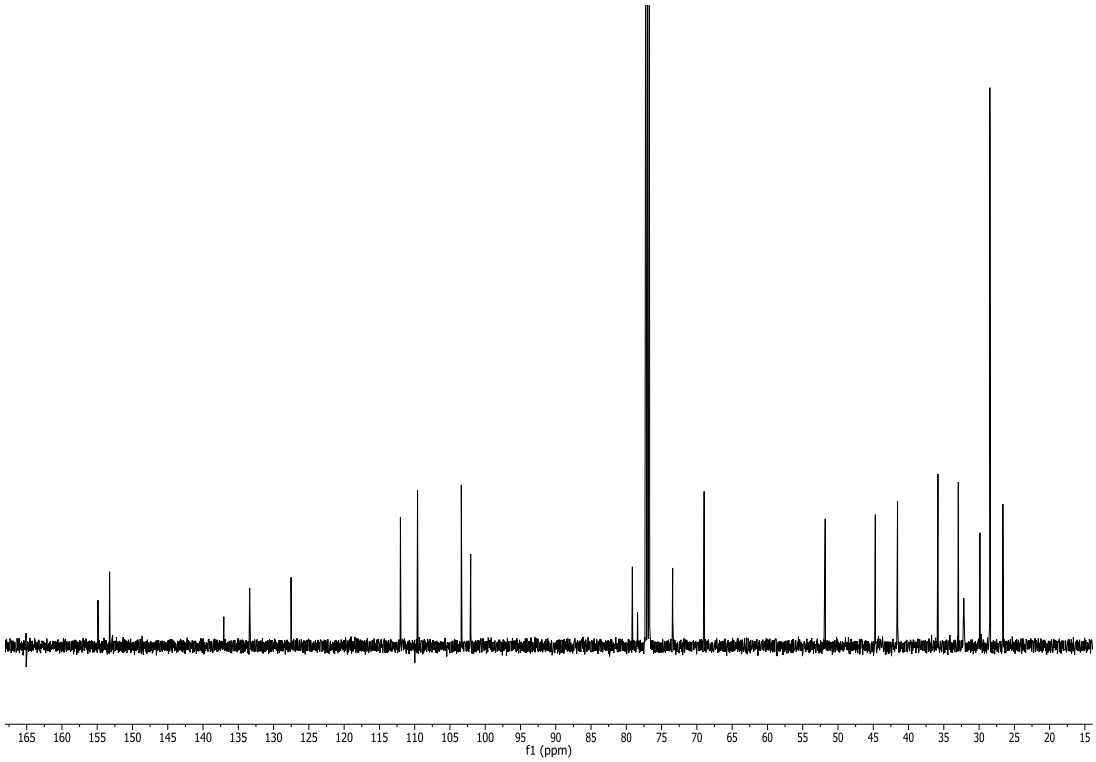


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA177.**

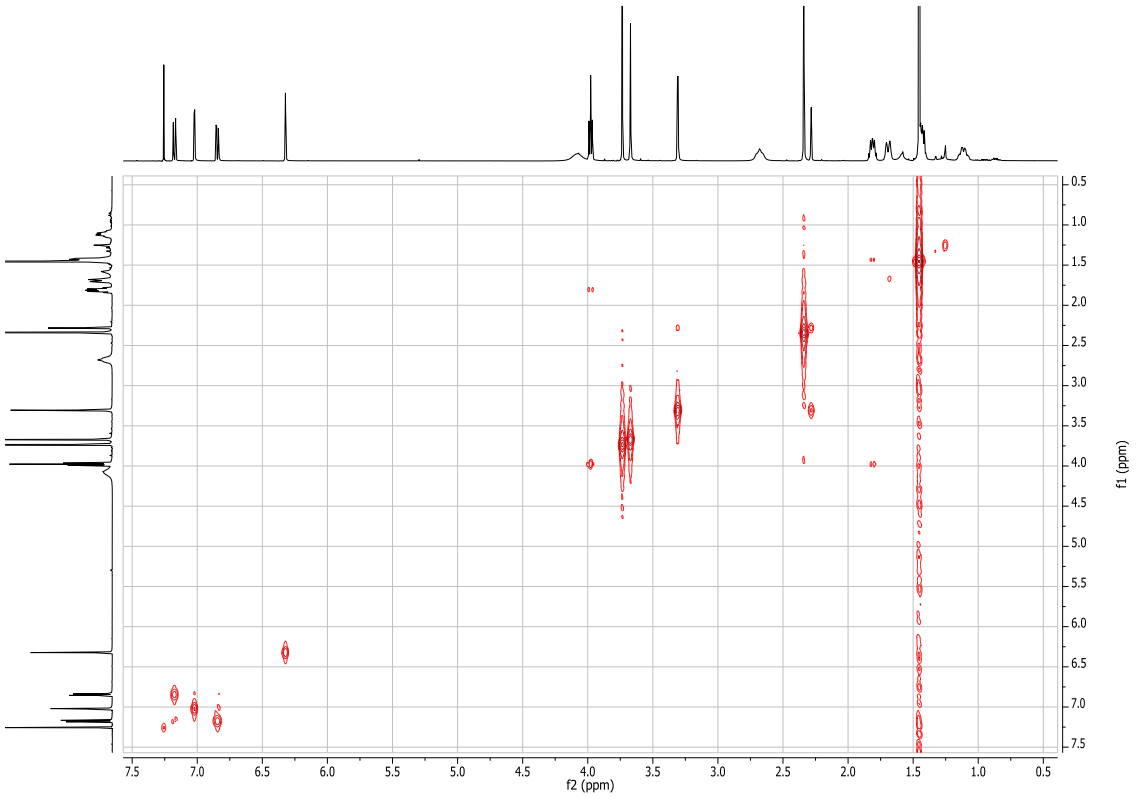
***tert*-Butyl 4-(3-(1-methyl-2-((methyl(prop-2-ynyl)amino)methyl)-1*H*-indol-5-yloxy)propyl)piperidine-1-carboxylate (MBA184).**



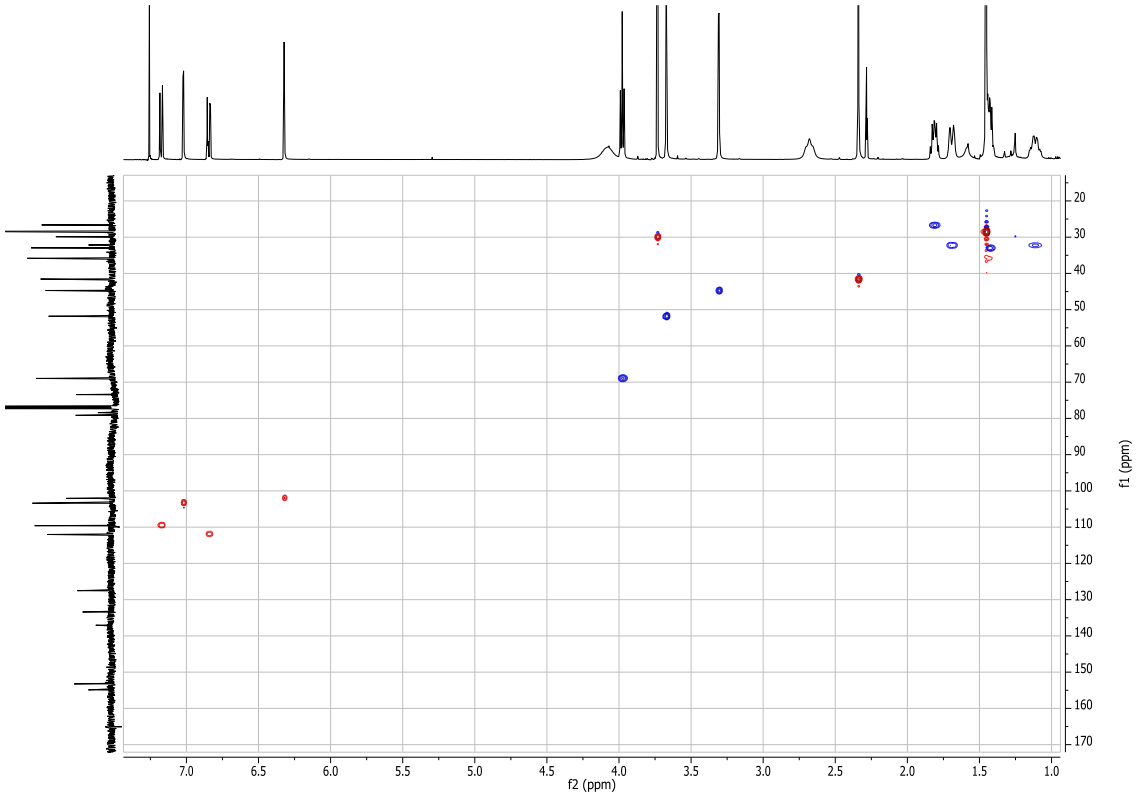
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **MBA184.**



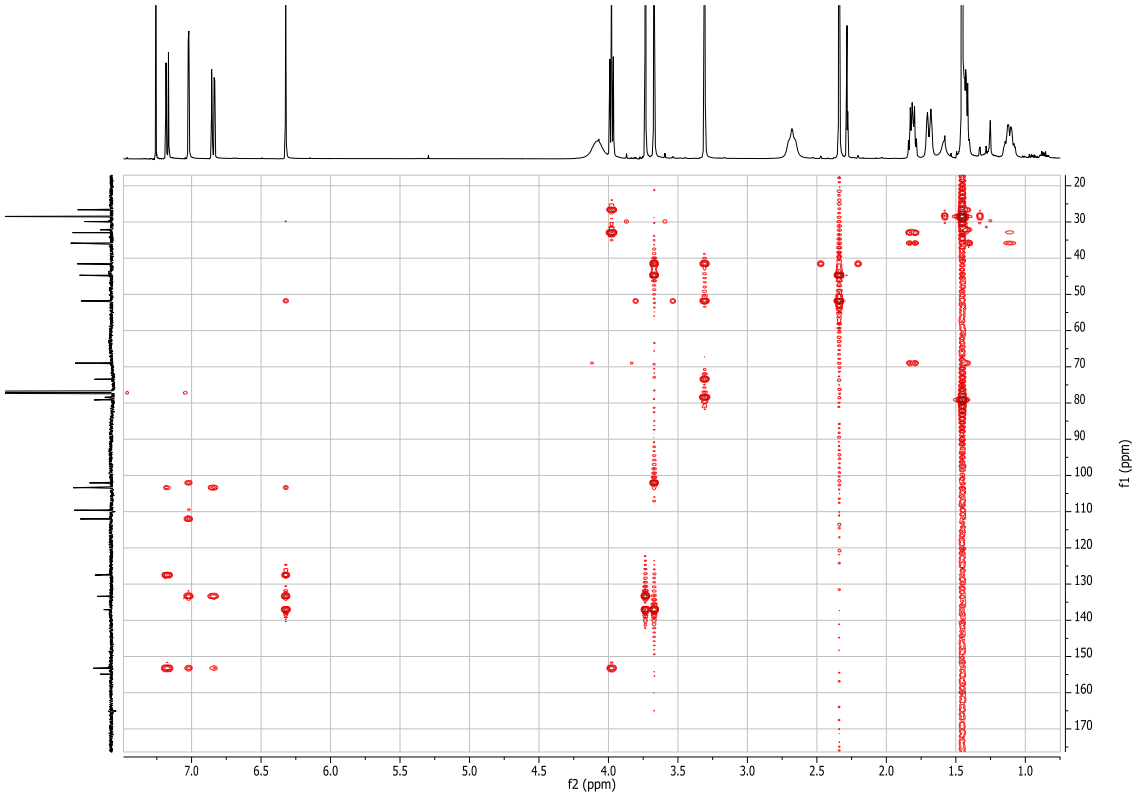
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **MBA184.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **MBA184.**

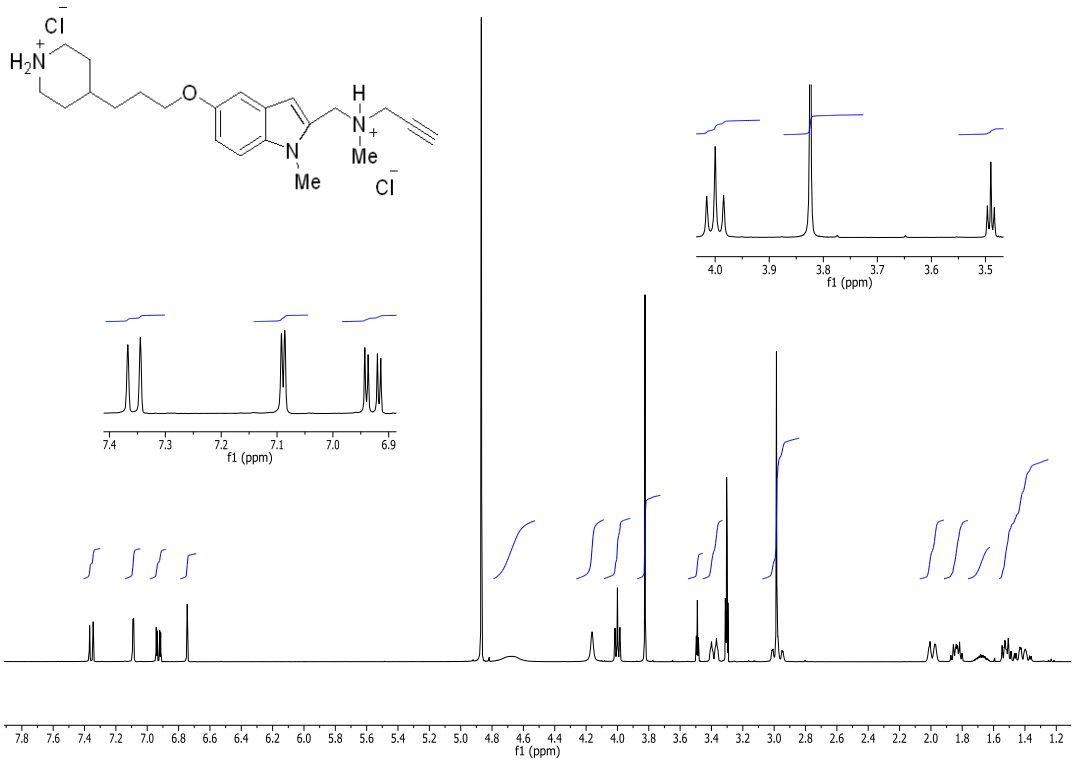


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **MBA184.**

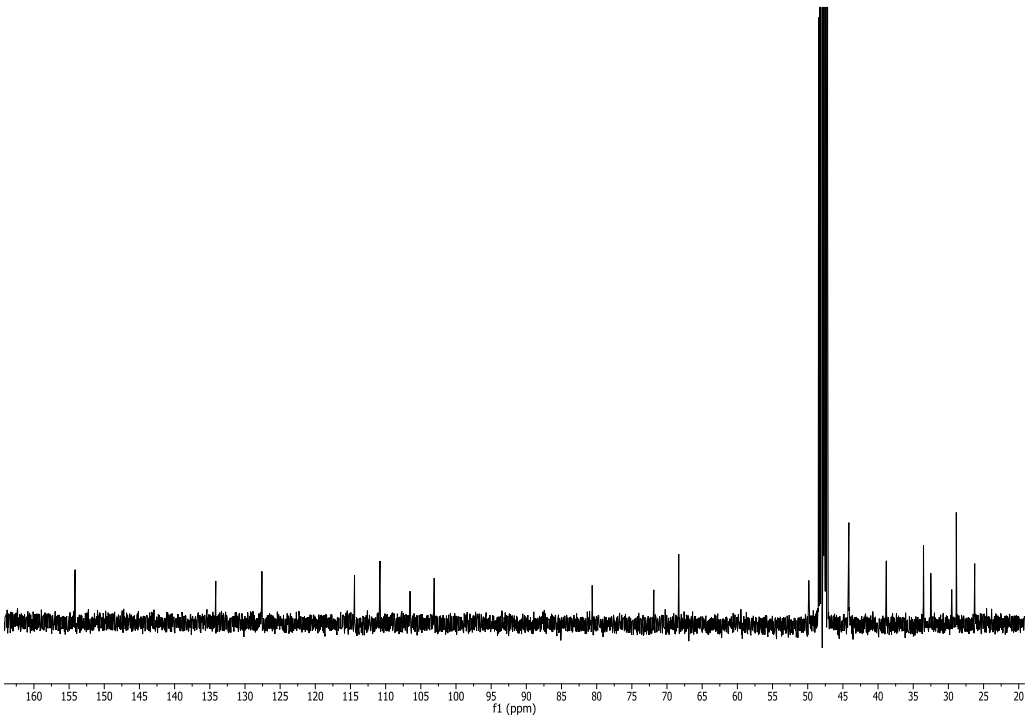


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **MBA184.**

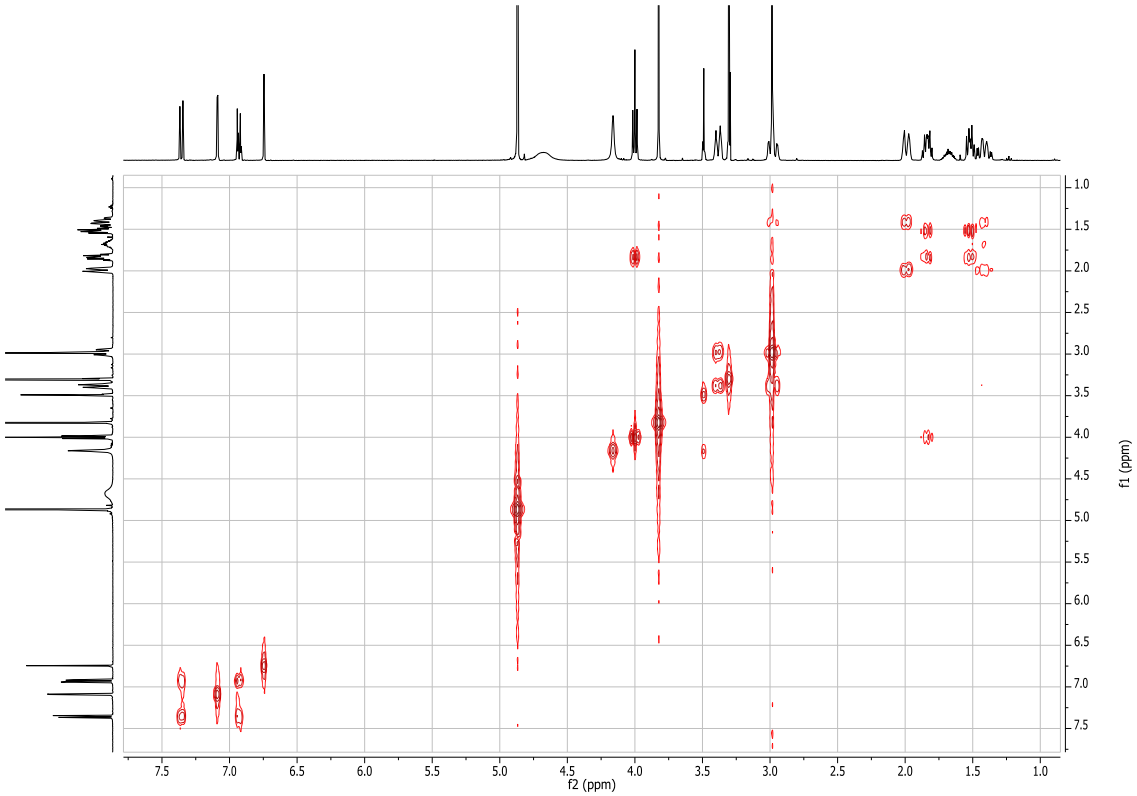
***N*-Methyl-*N*-[(1-methyl-5-(3-(piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)]prop-2-yn-1-amine dihydrochloride (1.2HCl).**



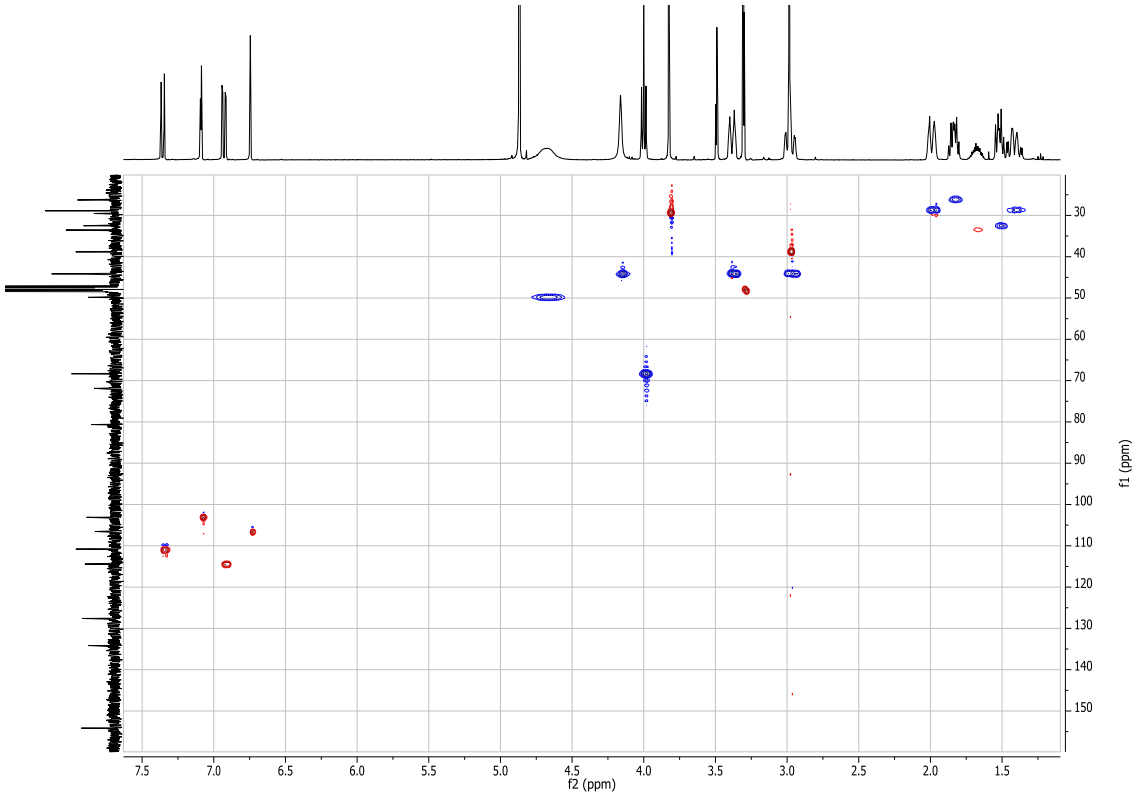
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **1.2HCl.**



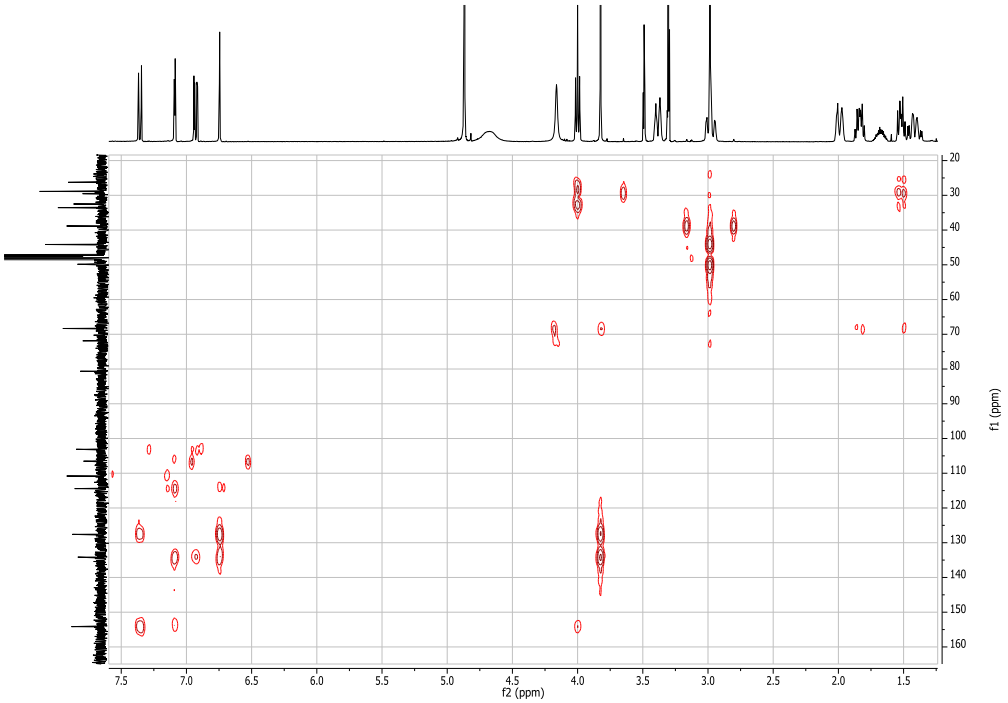
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **1.2HCl.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **1.2HCl.**

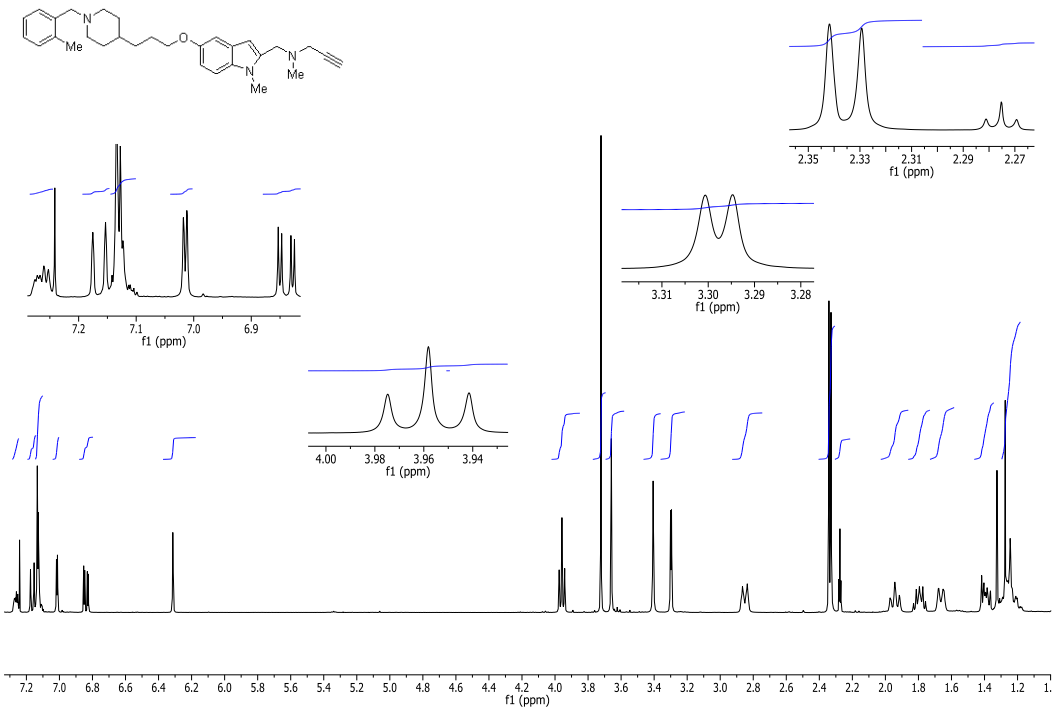


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **1.2HCl.**

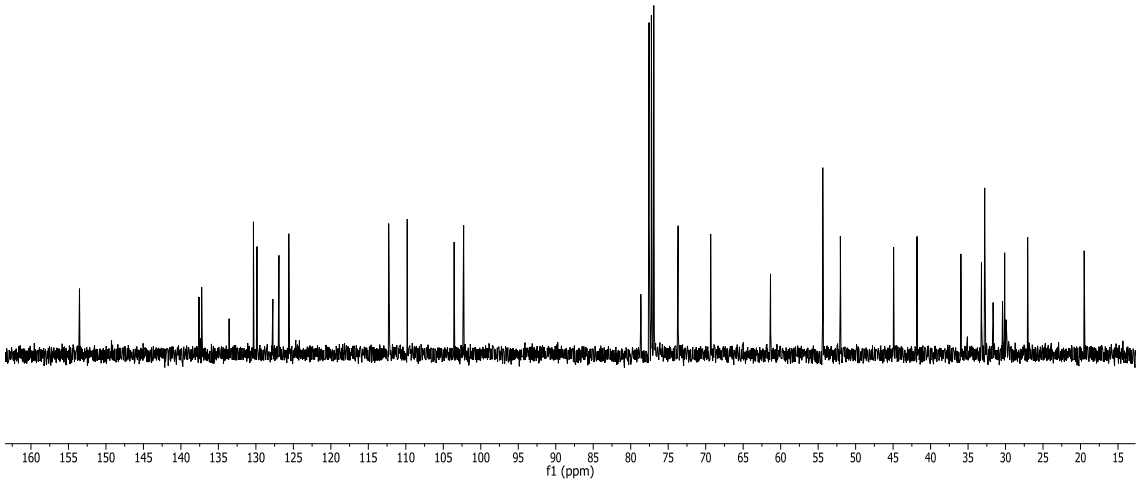


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **1.2HCl.**

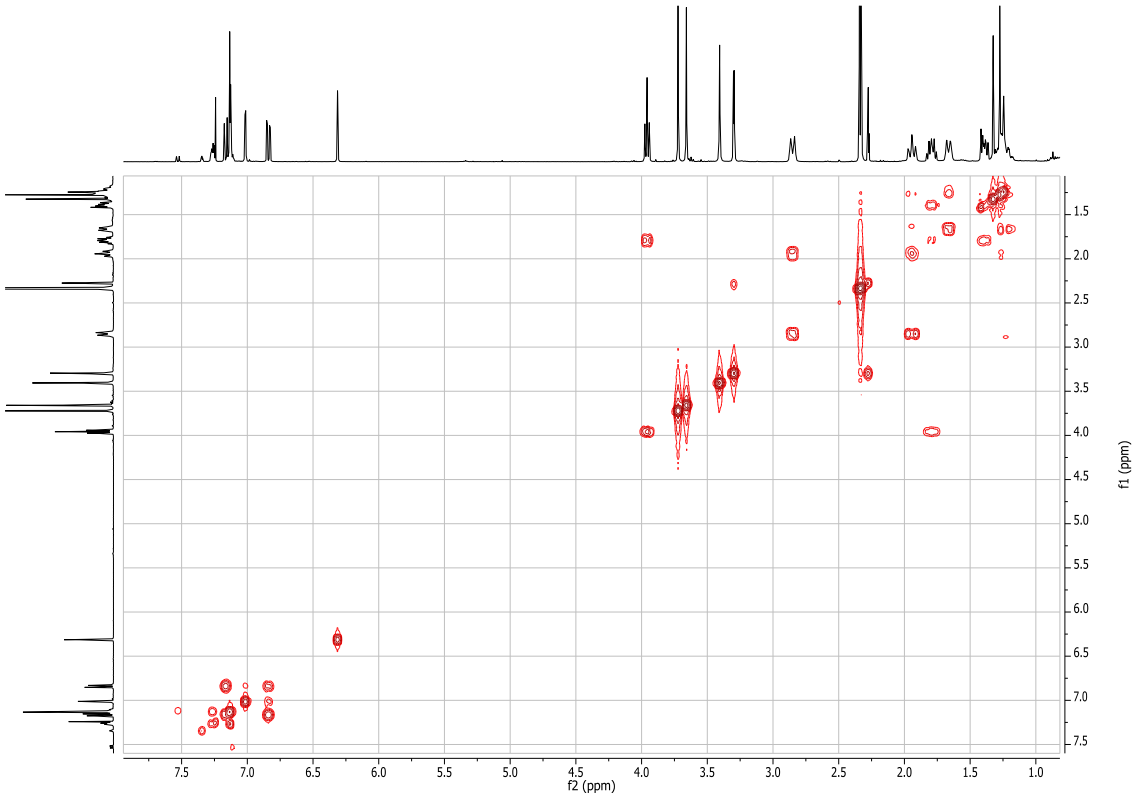
***N*-Methyl-*N*-((1-methyl-5-(3-(1-(2-methylbenzyl)piperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (2).**



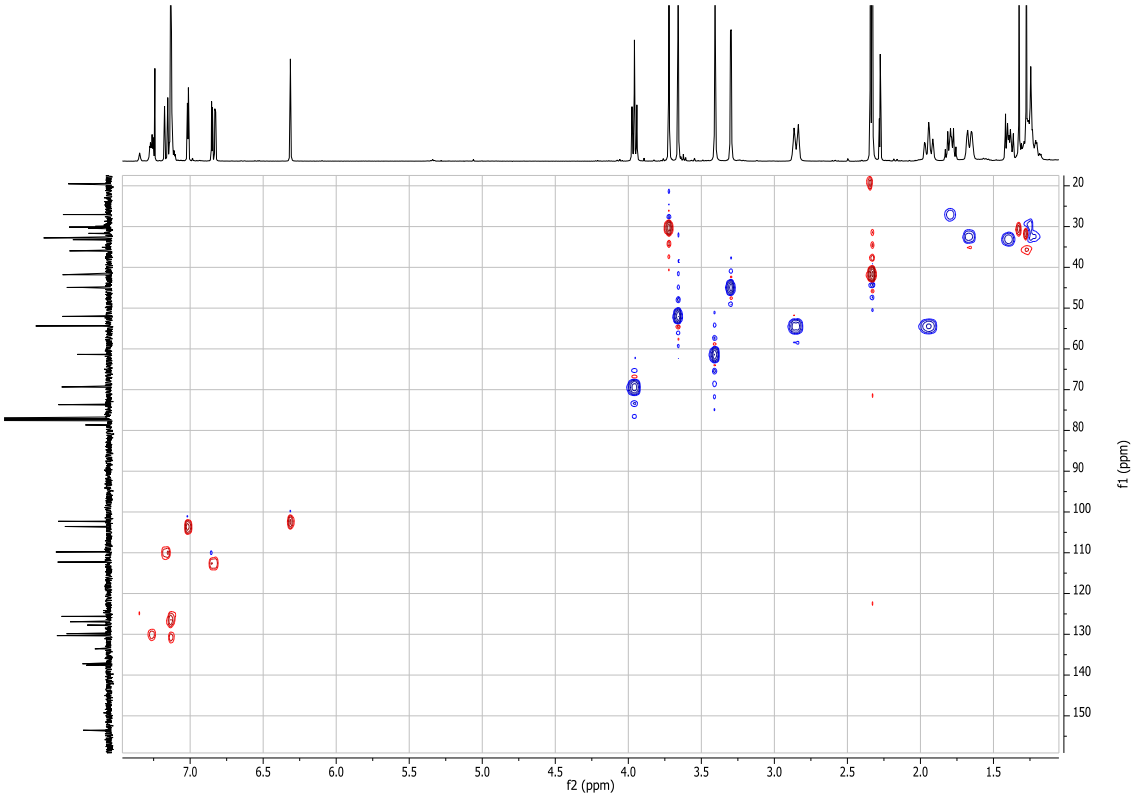
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **2.**



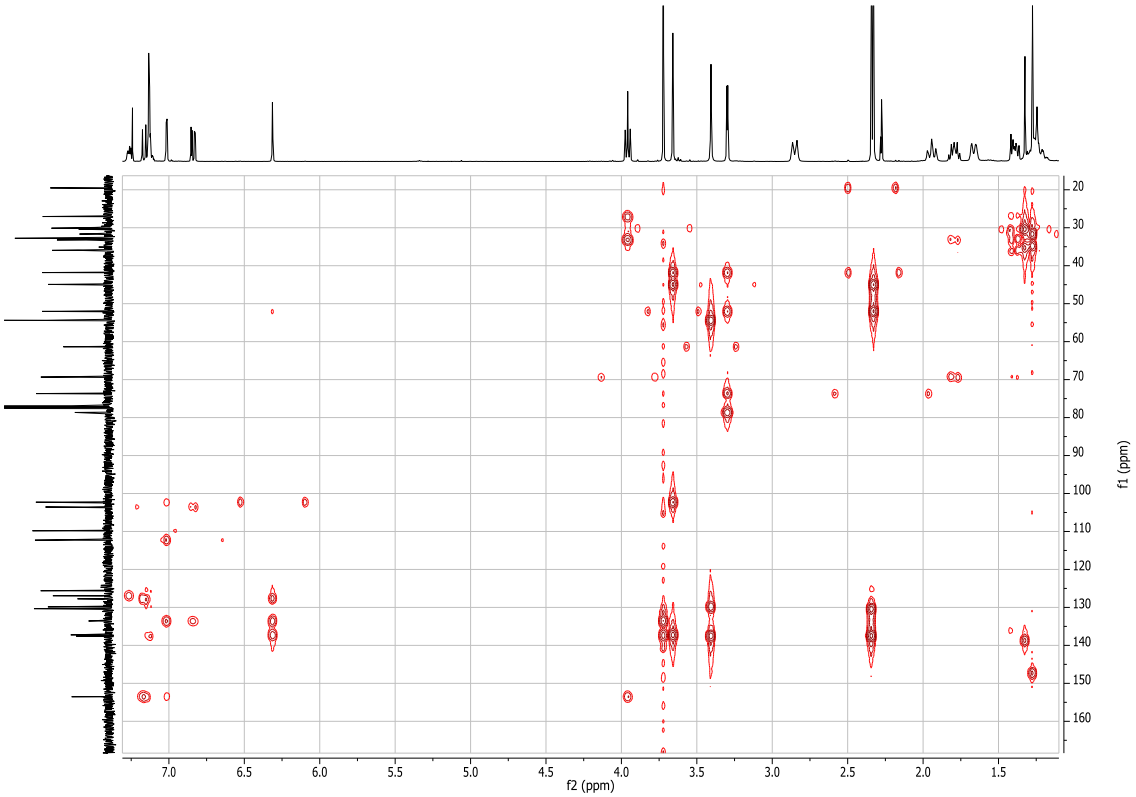
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **2.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **2.**

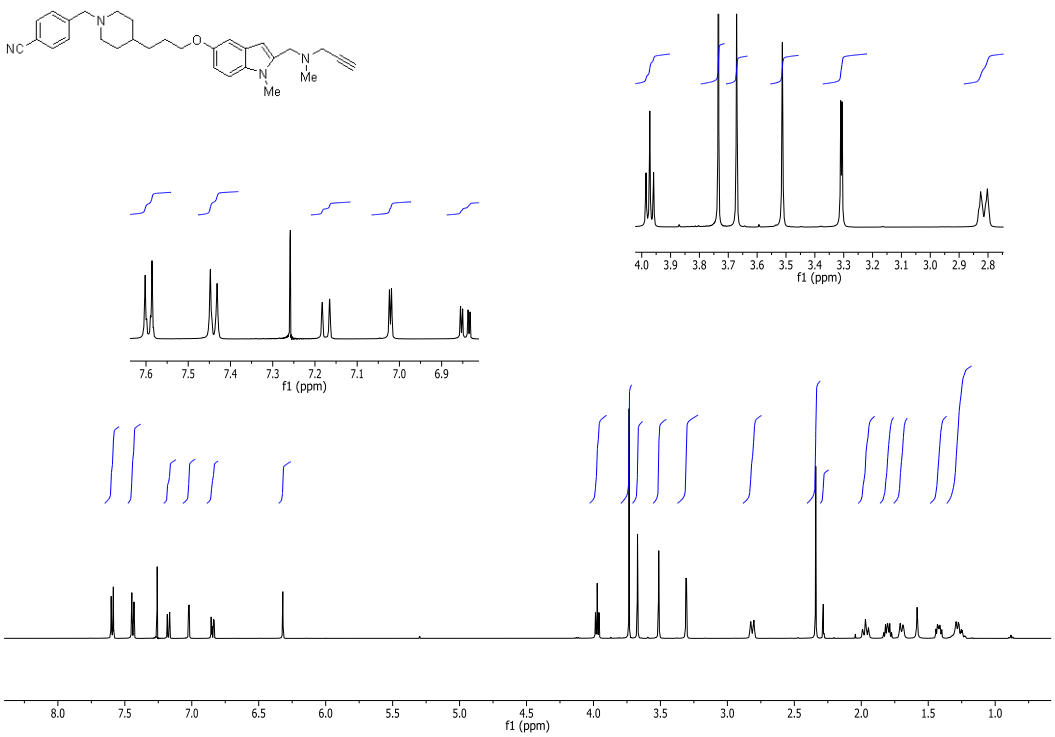


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **2.**

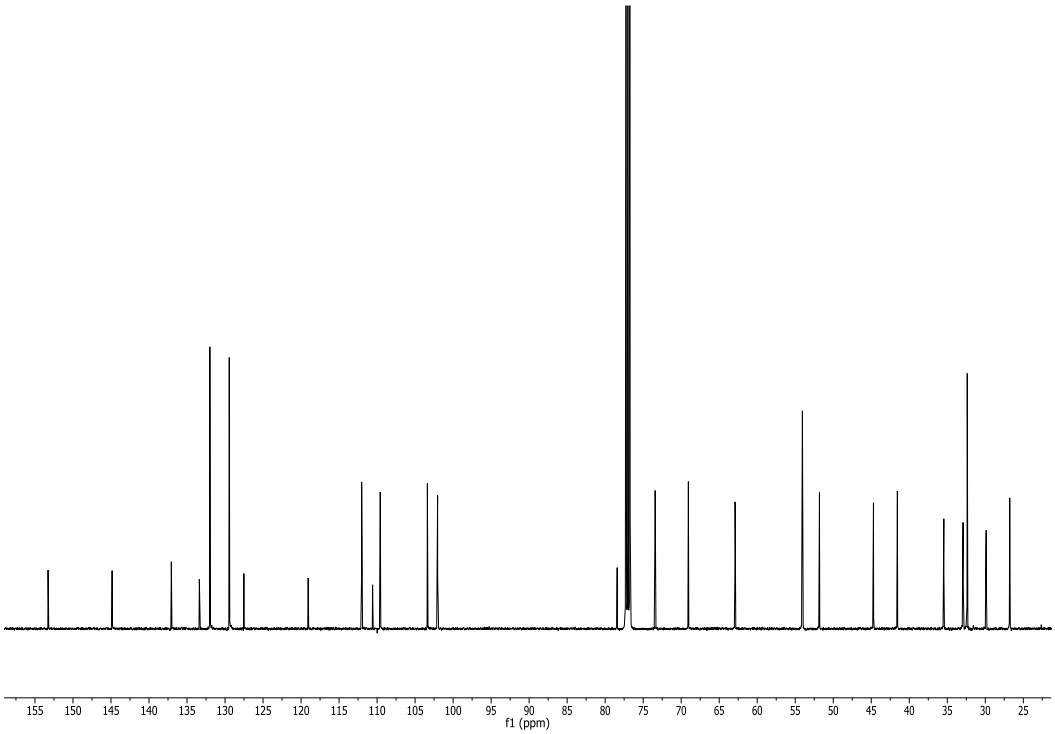


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **2.**

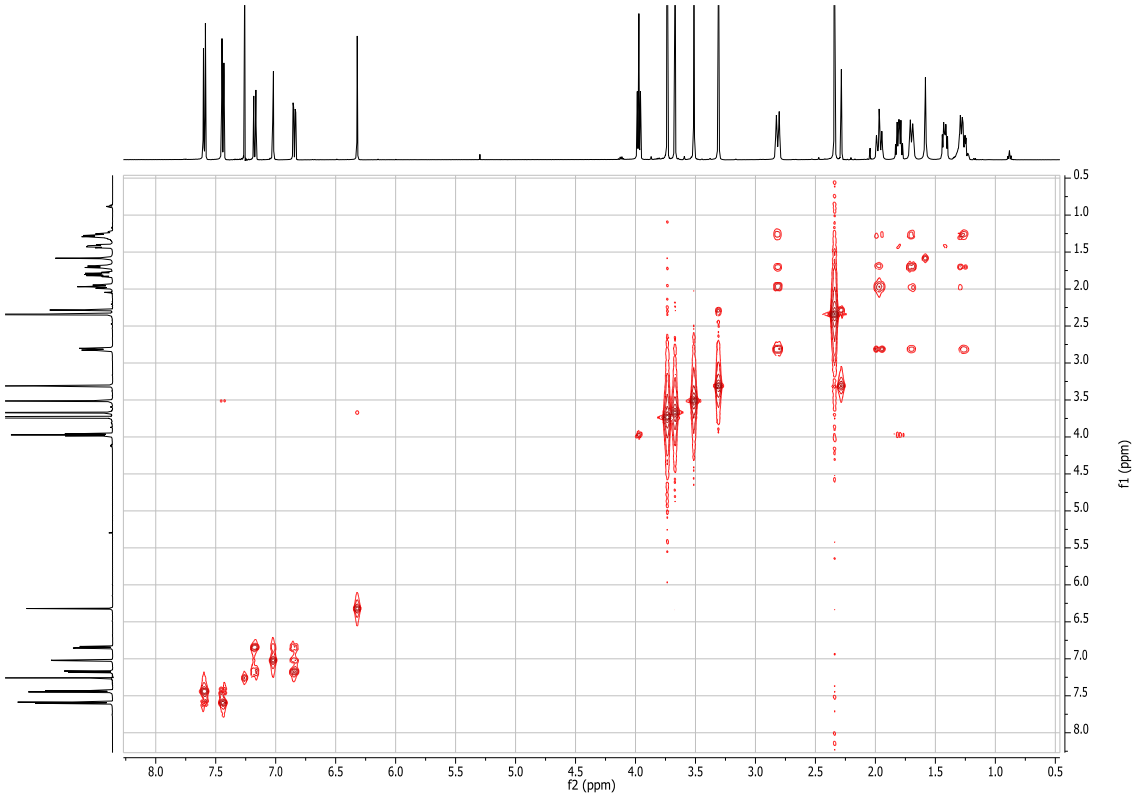
4-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)benzonitrile (3).



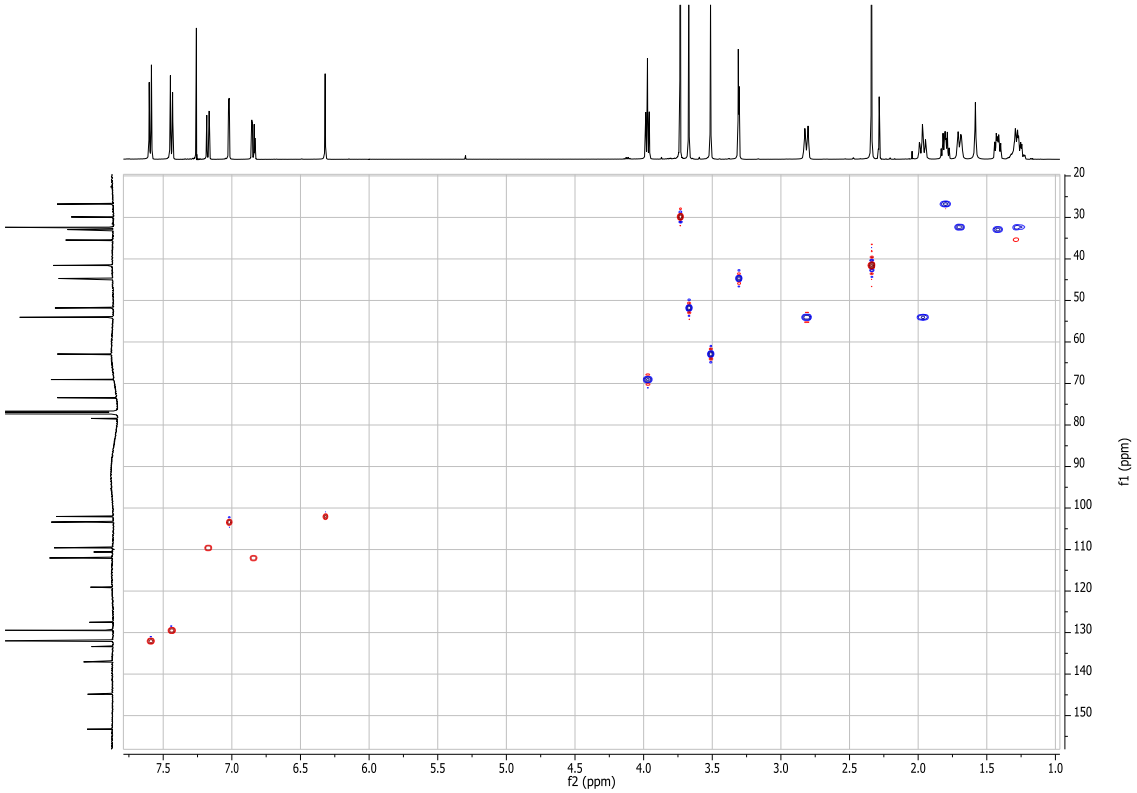
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **3**.



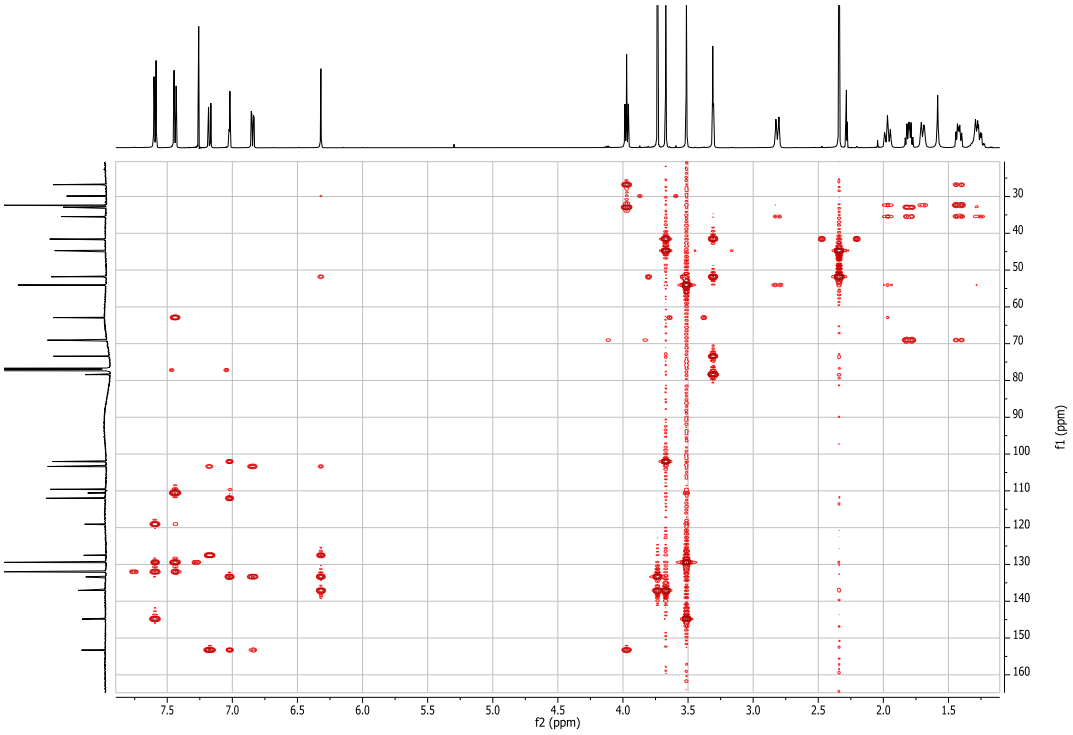
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **3**.



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **3**.

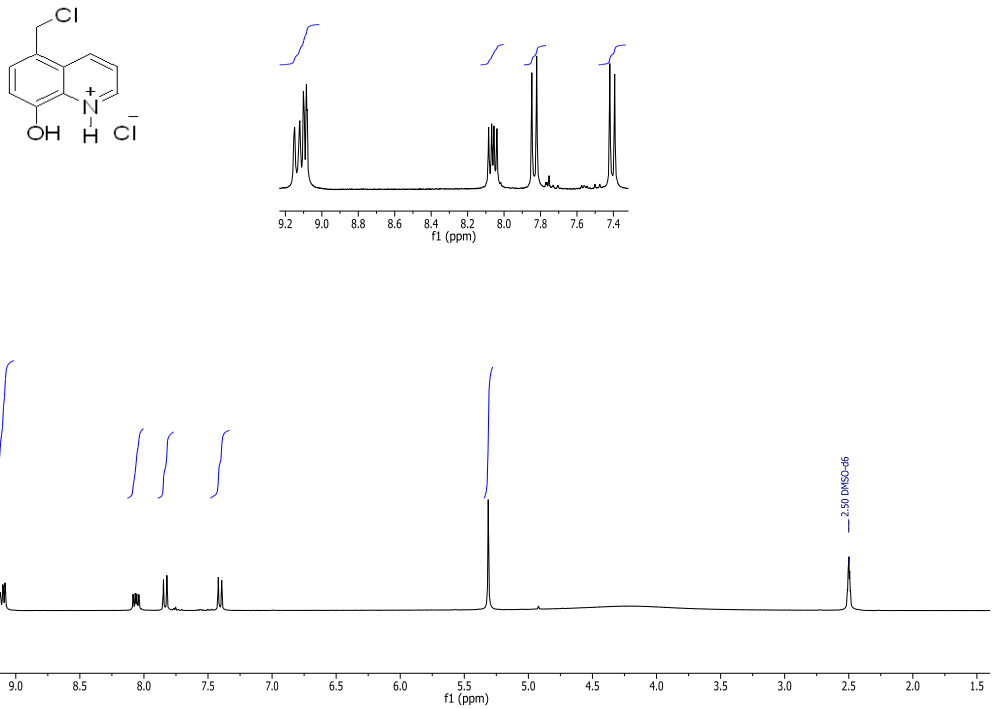


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **3**.



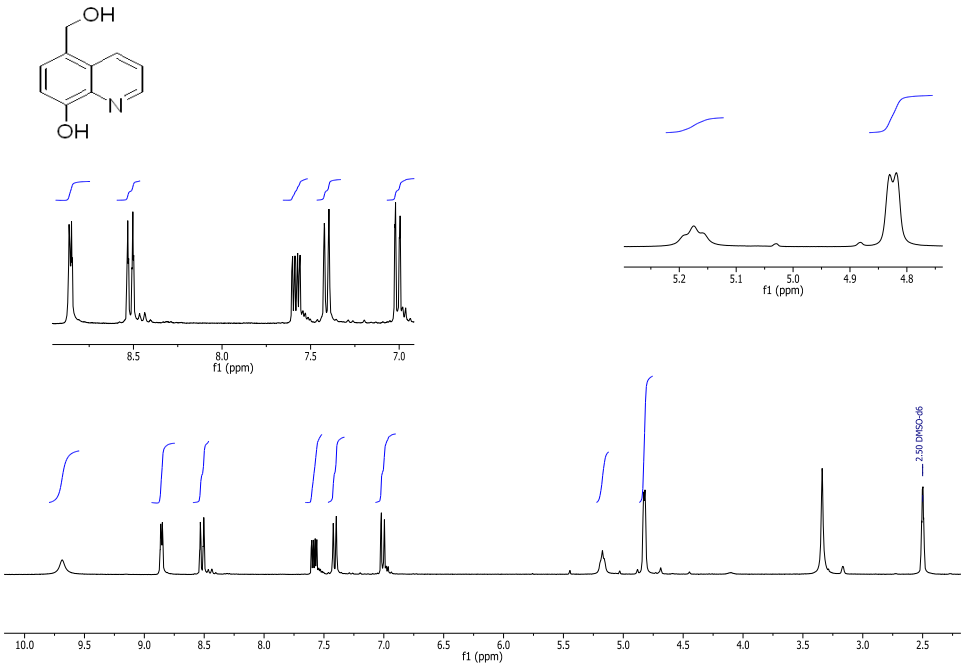
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **3**.

5-(Chloromethyl)quinolin-8-ol (MBA150).



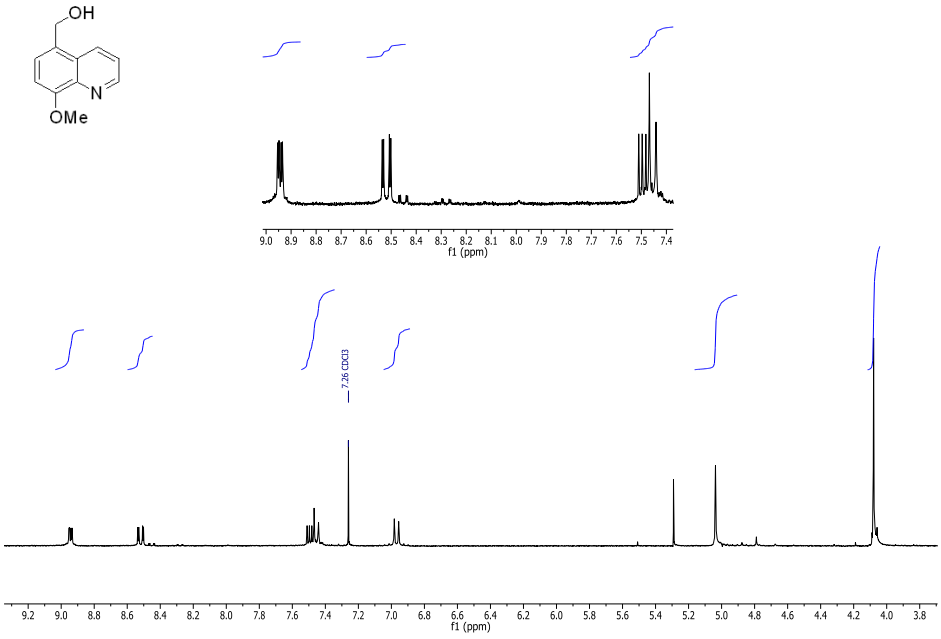
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA150.**

5-(Hydroxymethyl)quinolin-8-ol (MBA190).



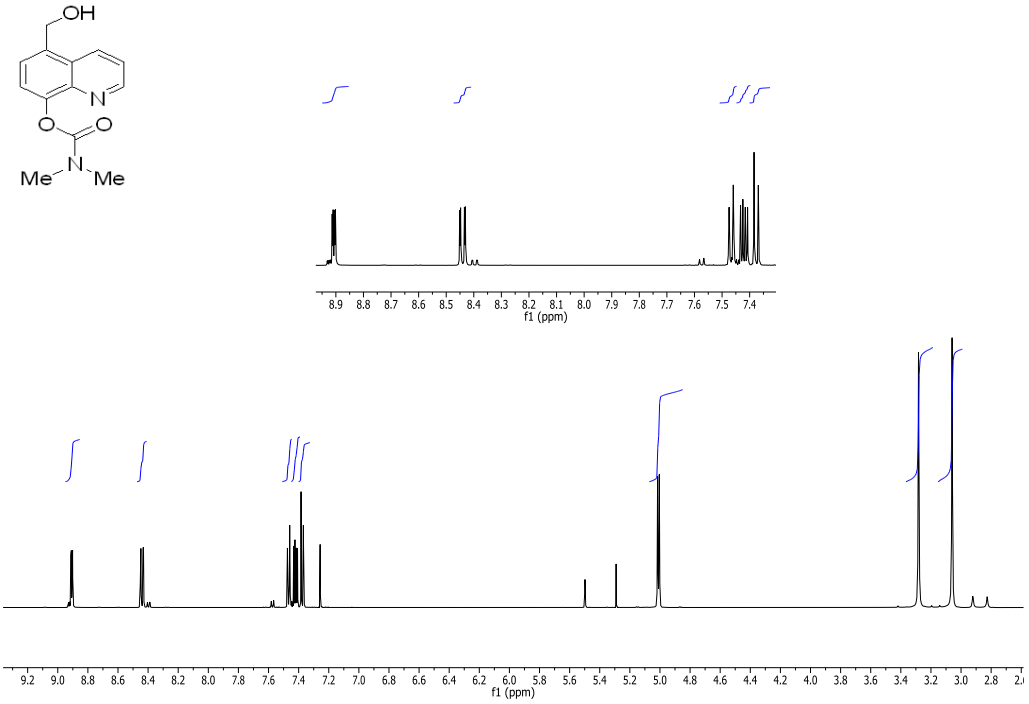
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA190.**

(8-Methoxyquinolin-5-yl)methanol (MBA191).

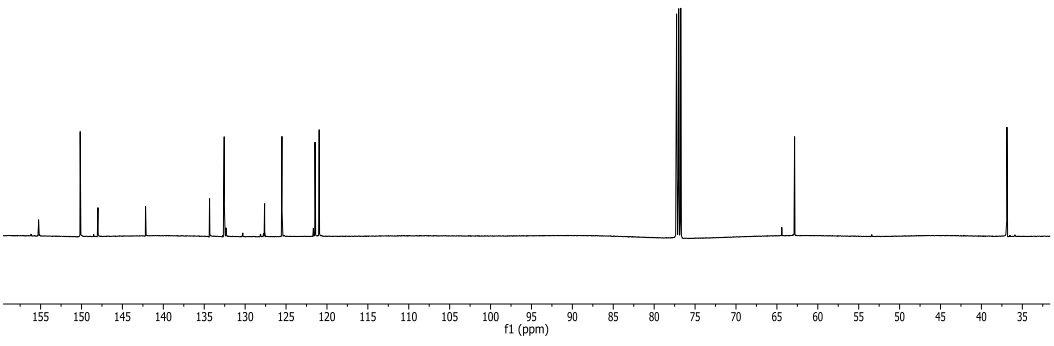


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA191.**

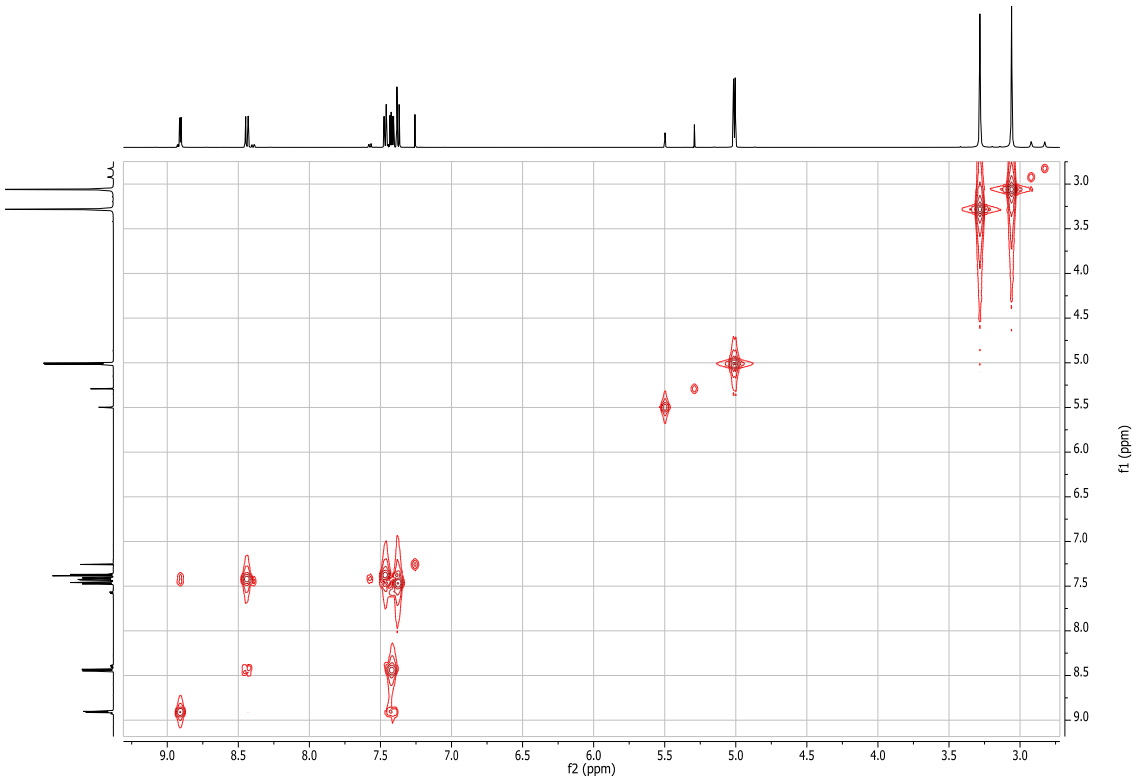
5-(Hydroxymethyl)quinolin-8-yl dimethylcarbamate (MBA217).



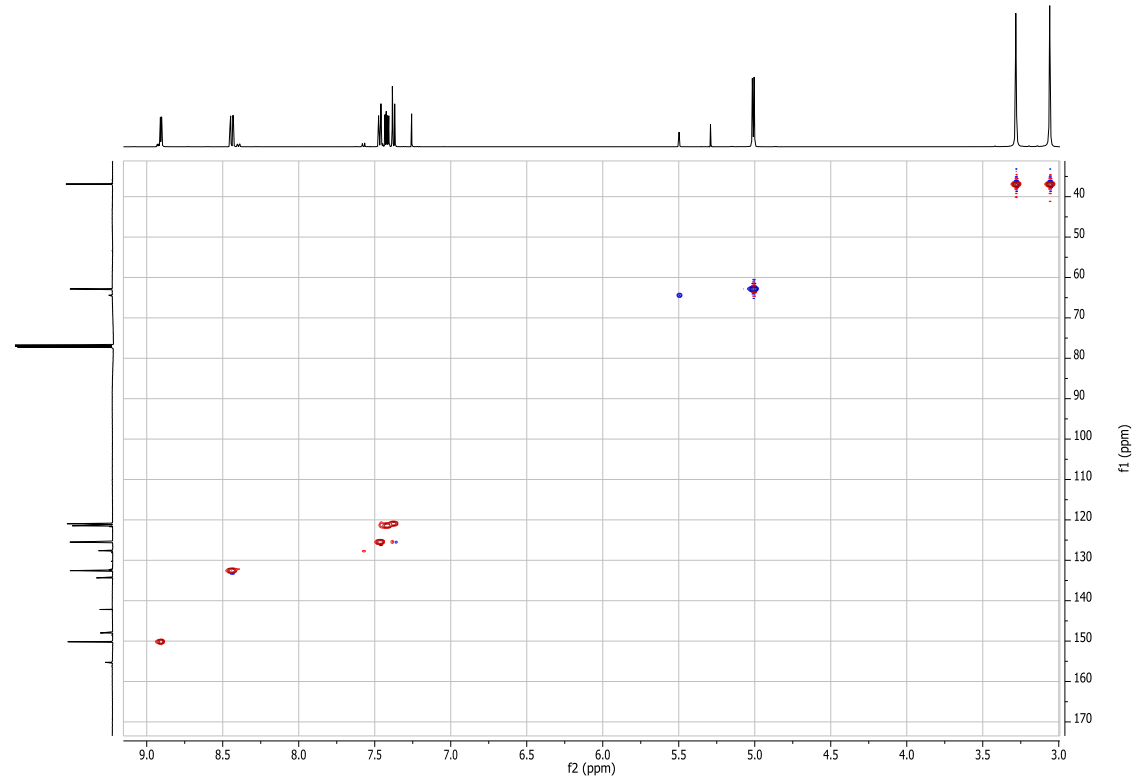
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **MBA217.**



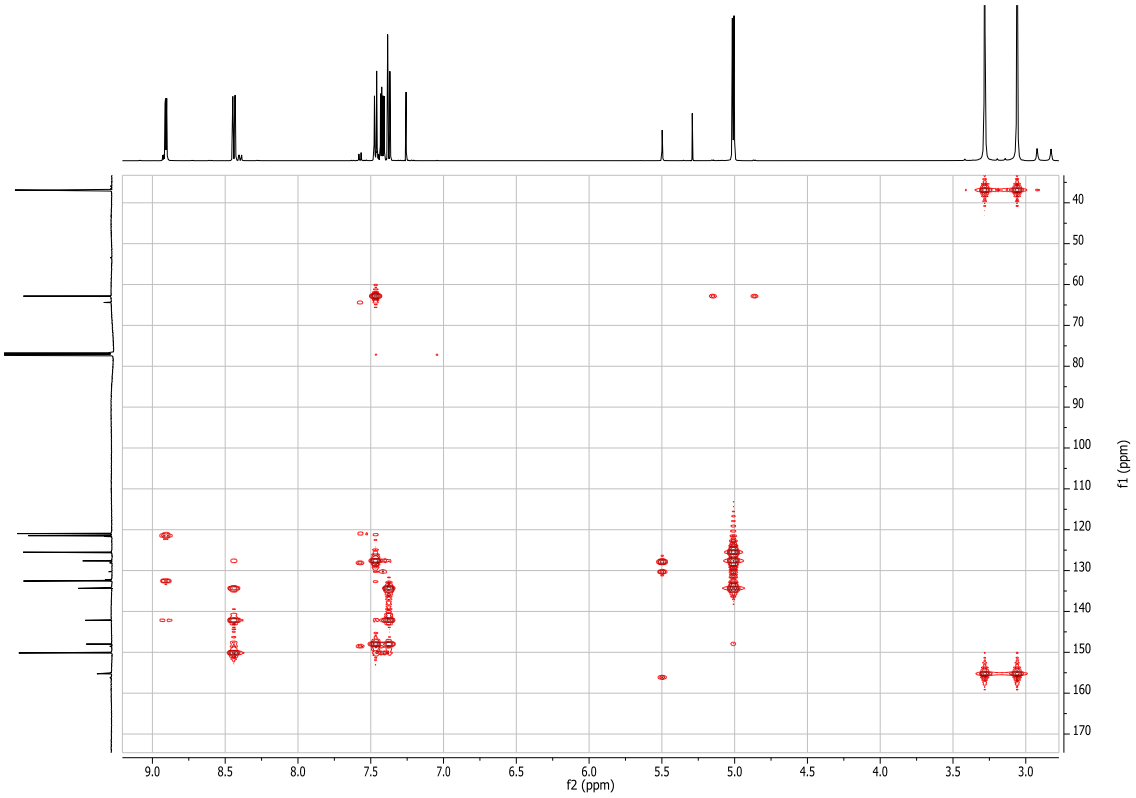
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **MBA217.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **MBA217.**

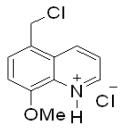


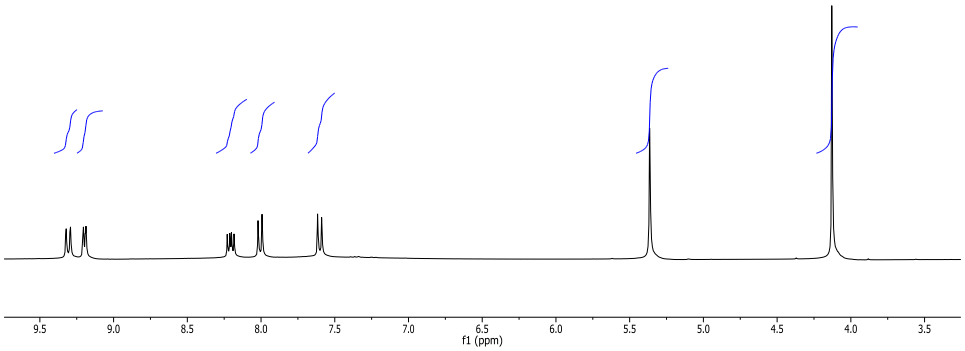
^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **MBA217.**



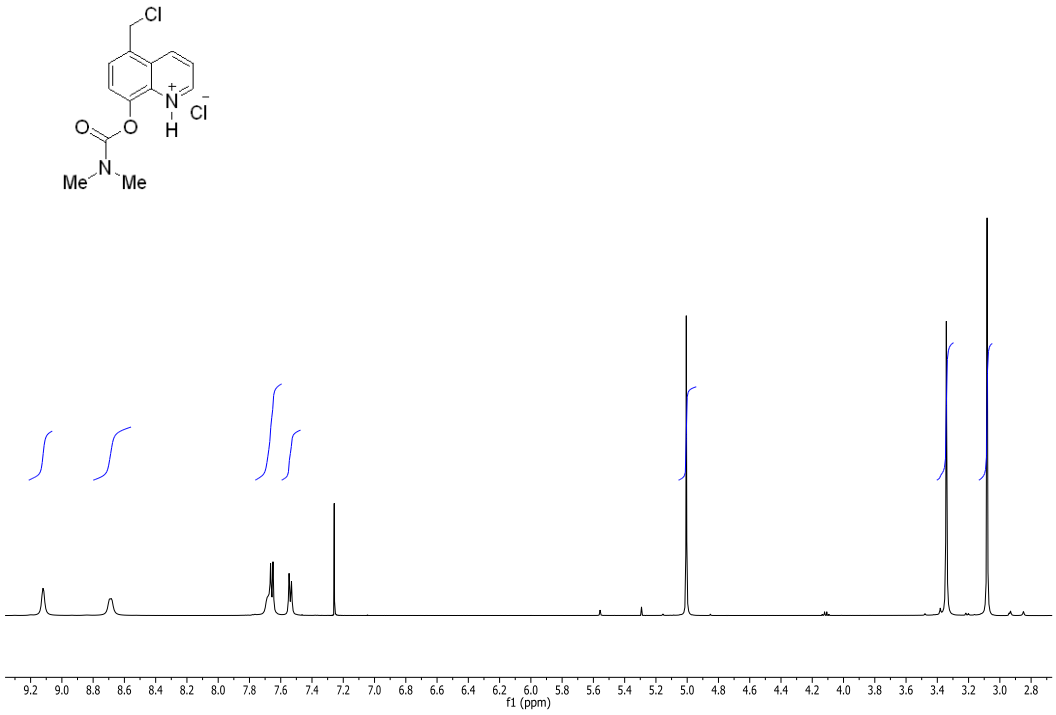
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **MBA217.**

5-(Chloromethyl)-8-methoxyquinoline (MBA207).

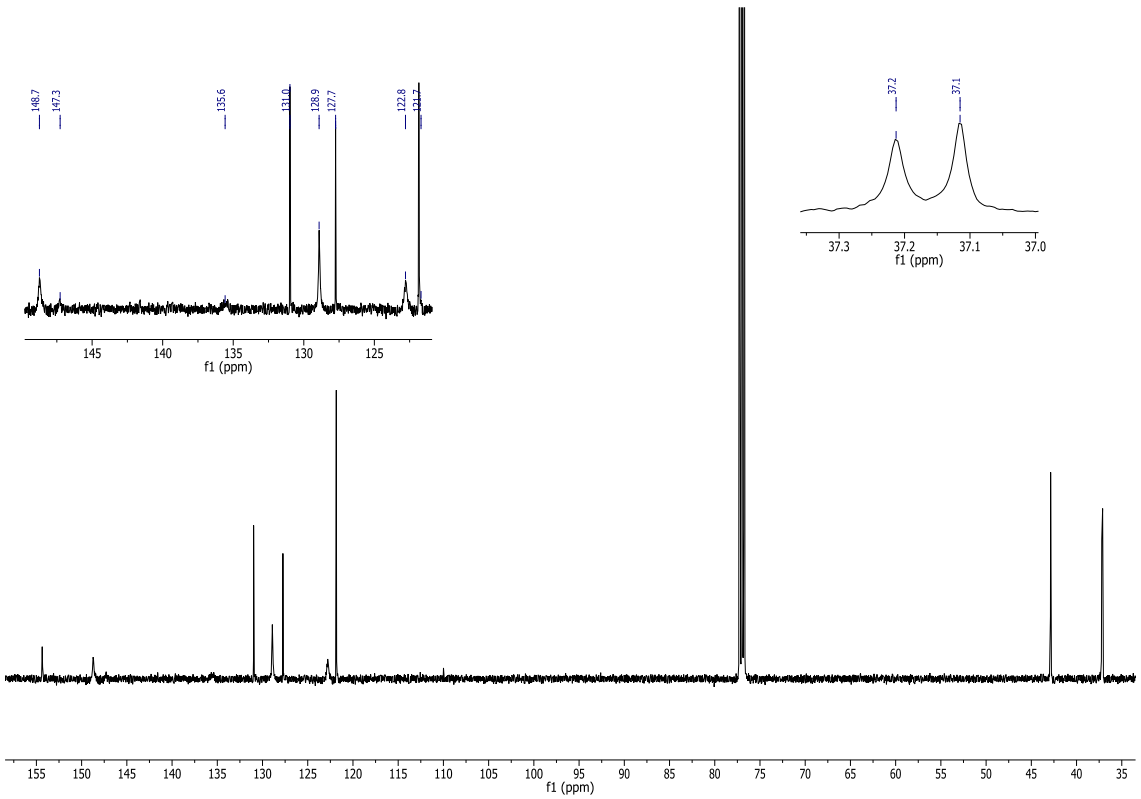




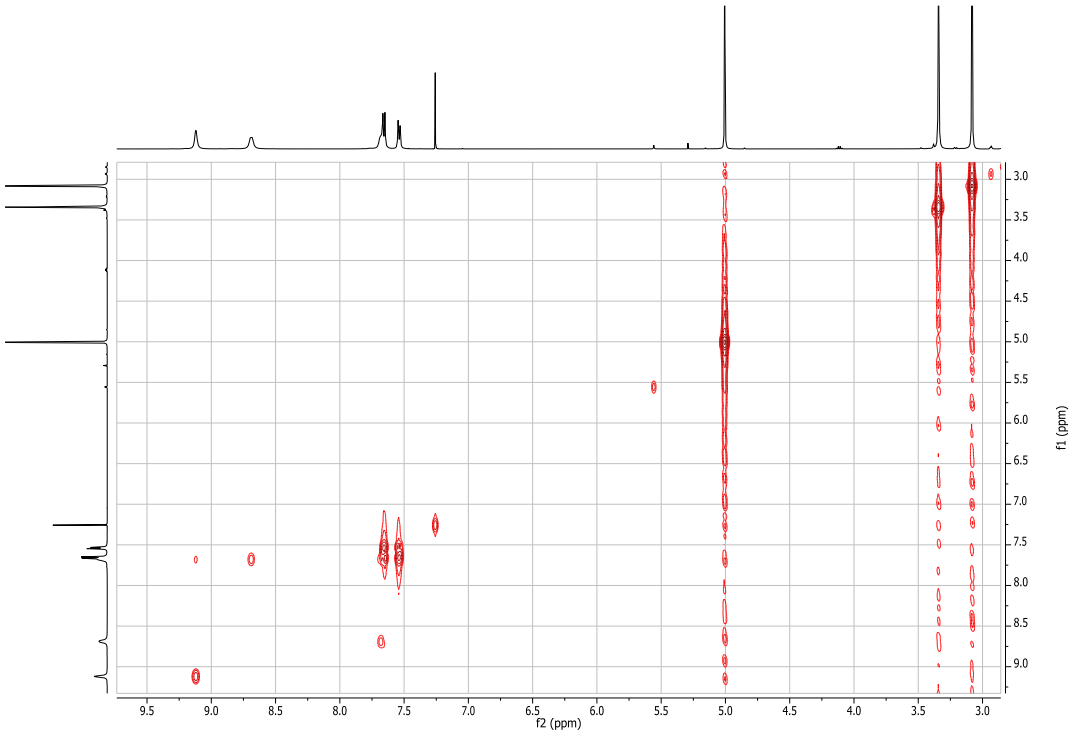
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA207.**



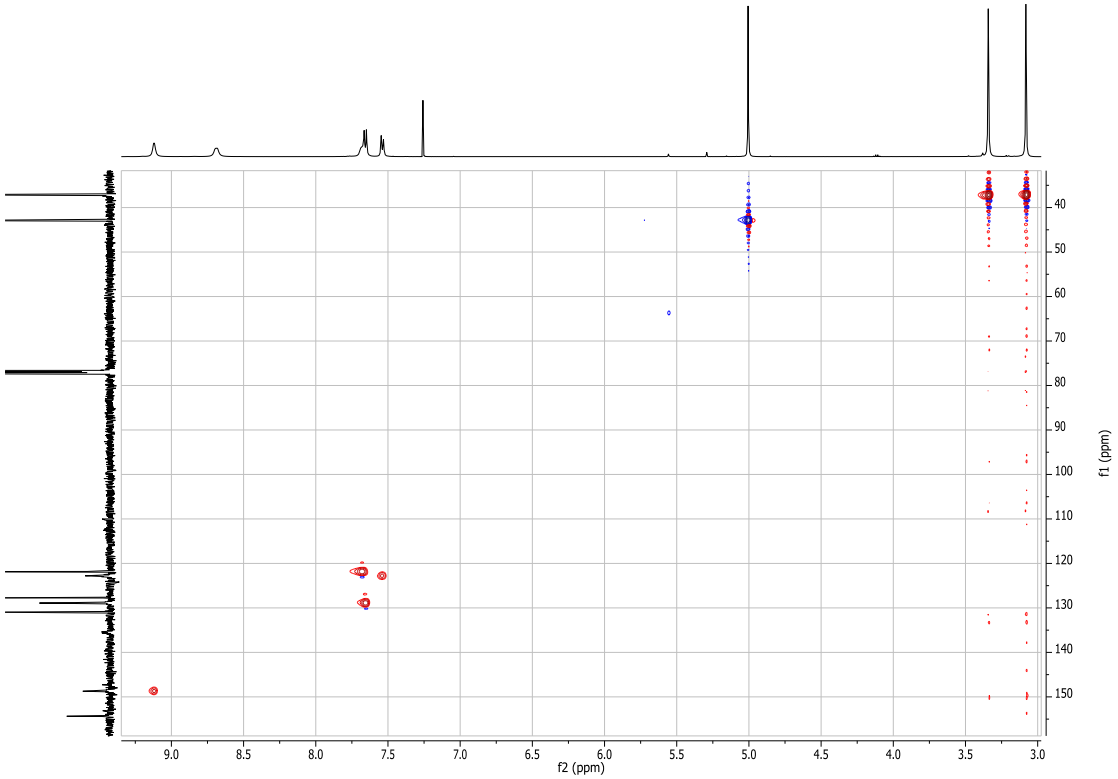
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **MBA219.**



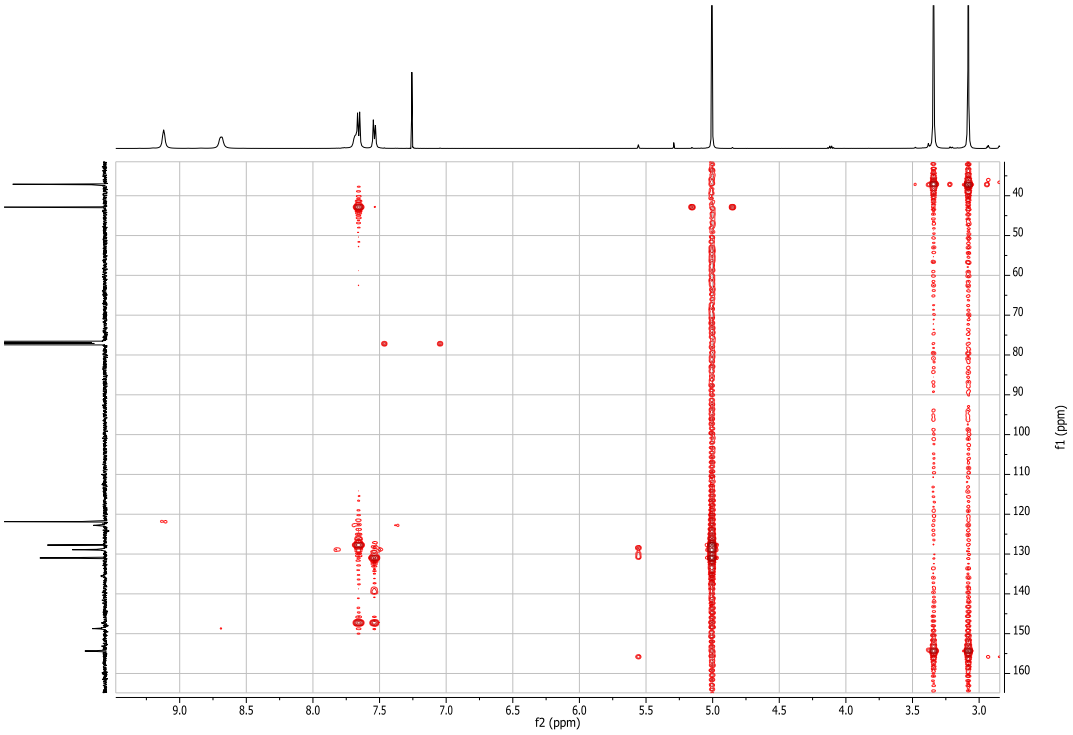
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **MBA219.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **MBA219.**

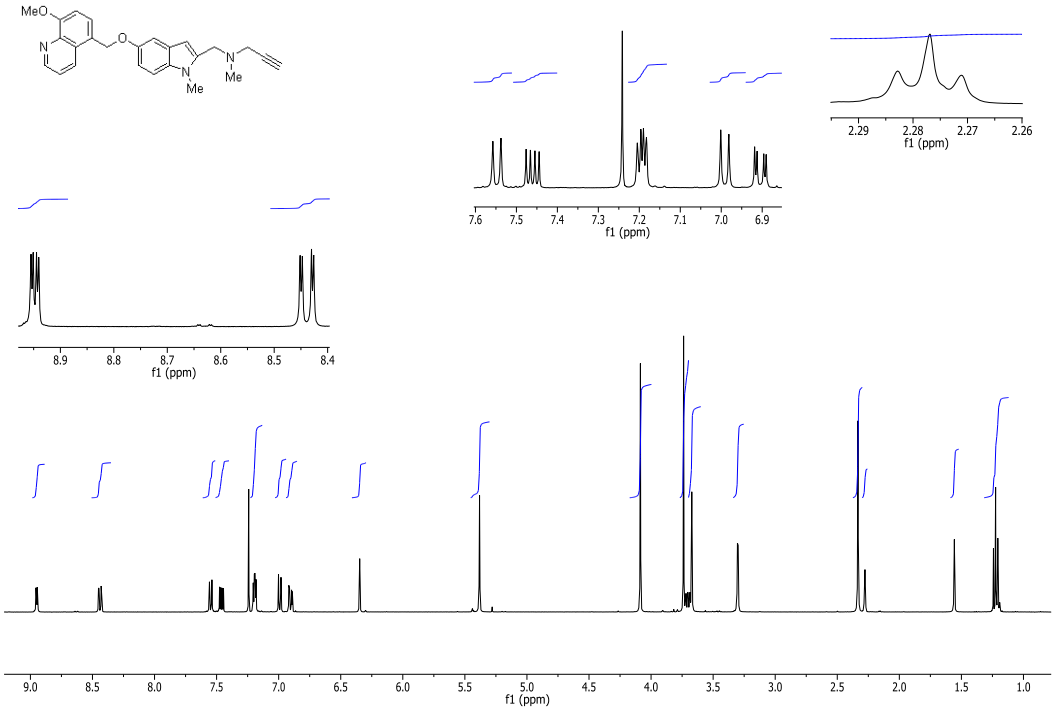


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **MBA219.**

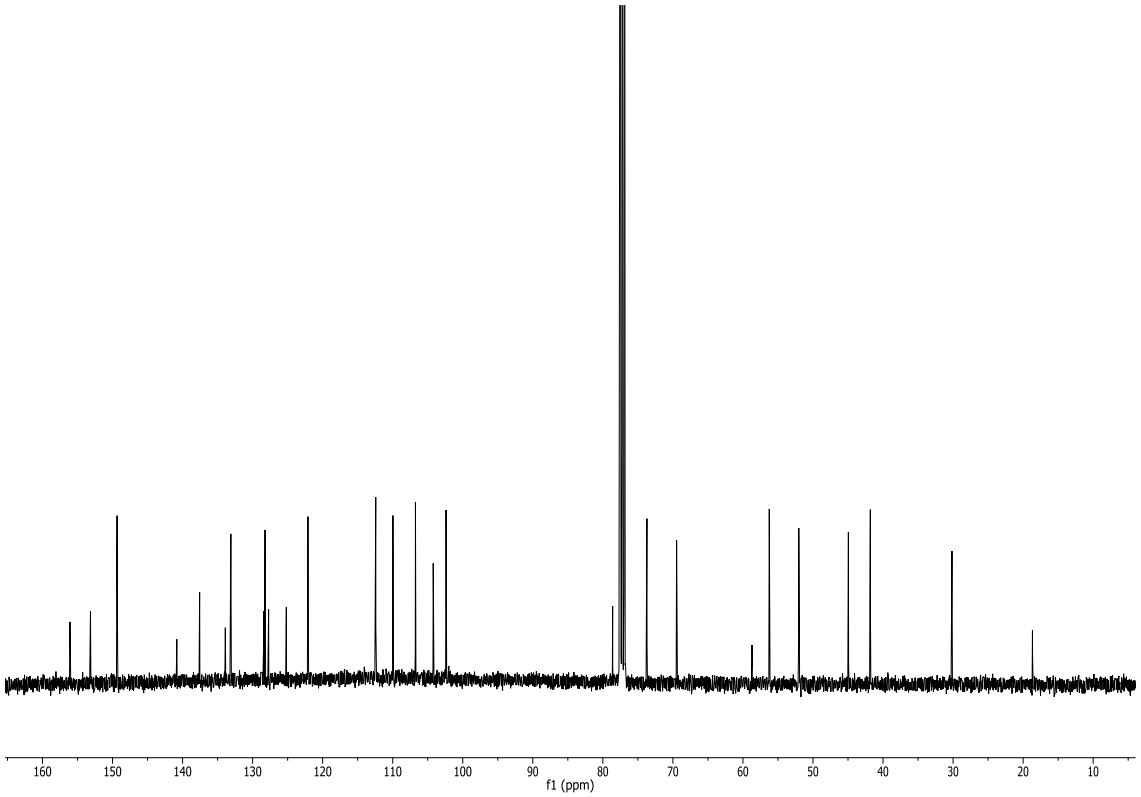


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **MBA219.**

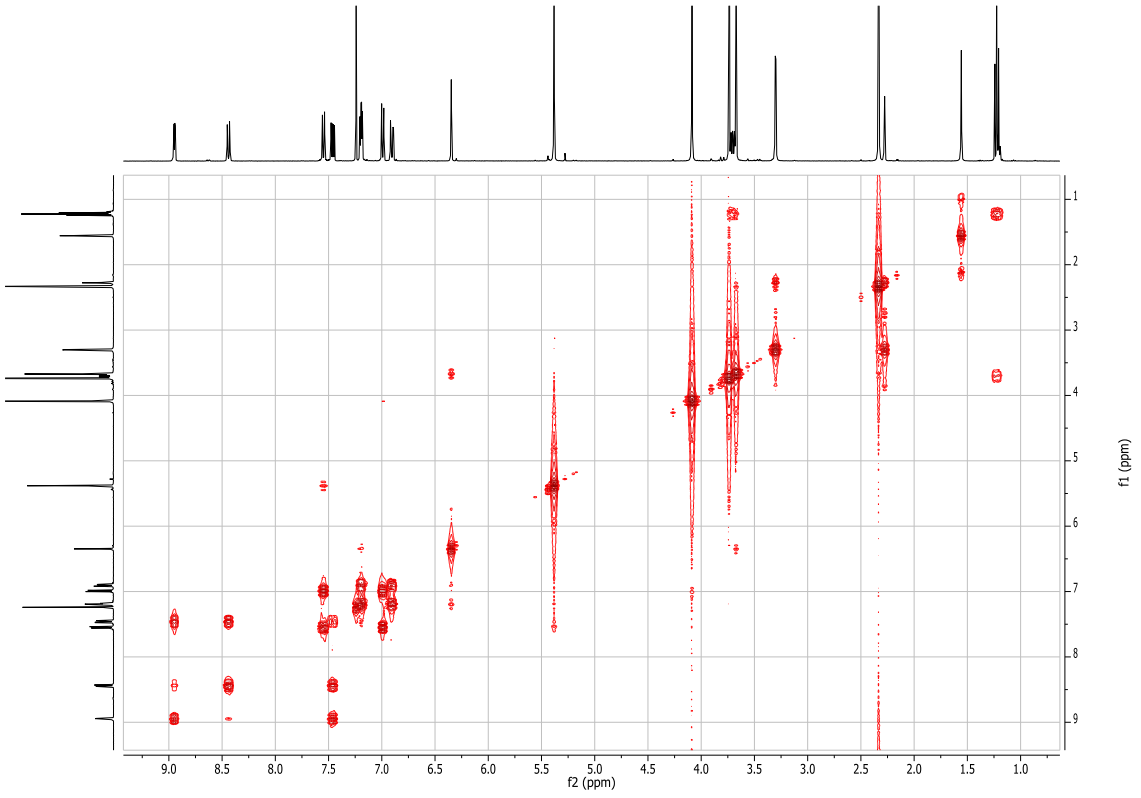
***N*-((5-((8-Methoxyquinolin-5-yl)methoxy)-1-methyl-1H-indol-2-yl)methyl)-N-methylprop-2-yn-1-amine (13)**.



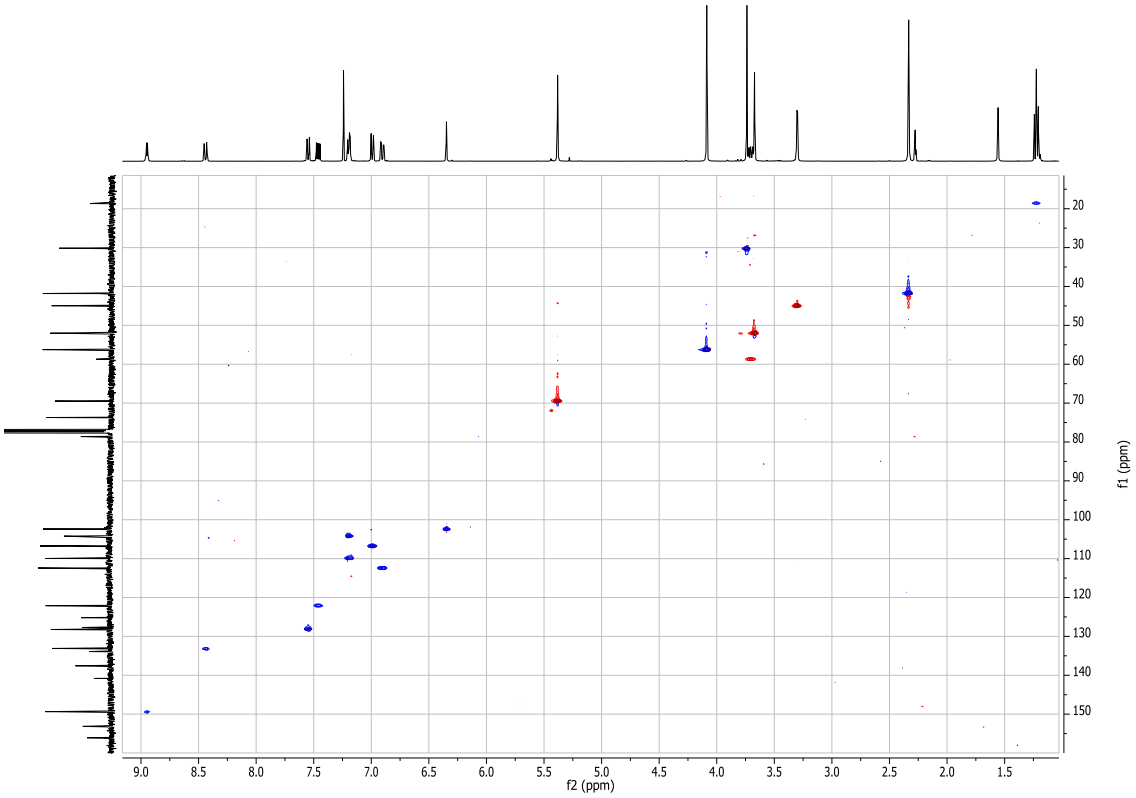
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **13**.



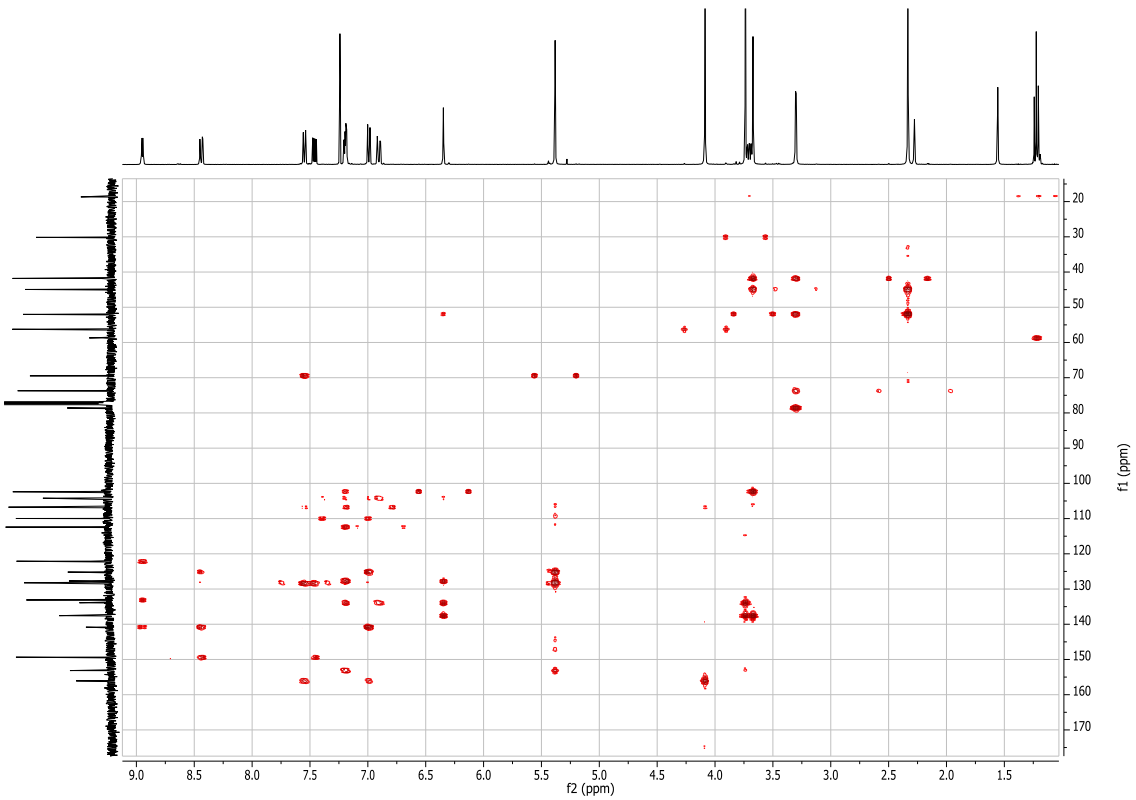
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **13**.



^{1}H-^{1}H *g*-COSY (400 MHz, $CDCl_3$) spectrum of compound **13**.

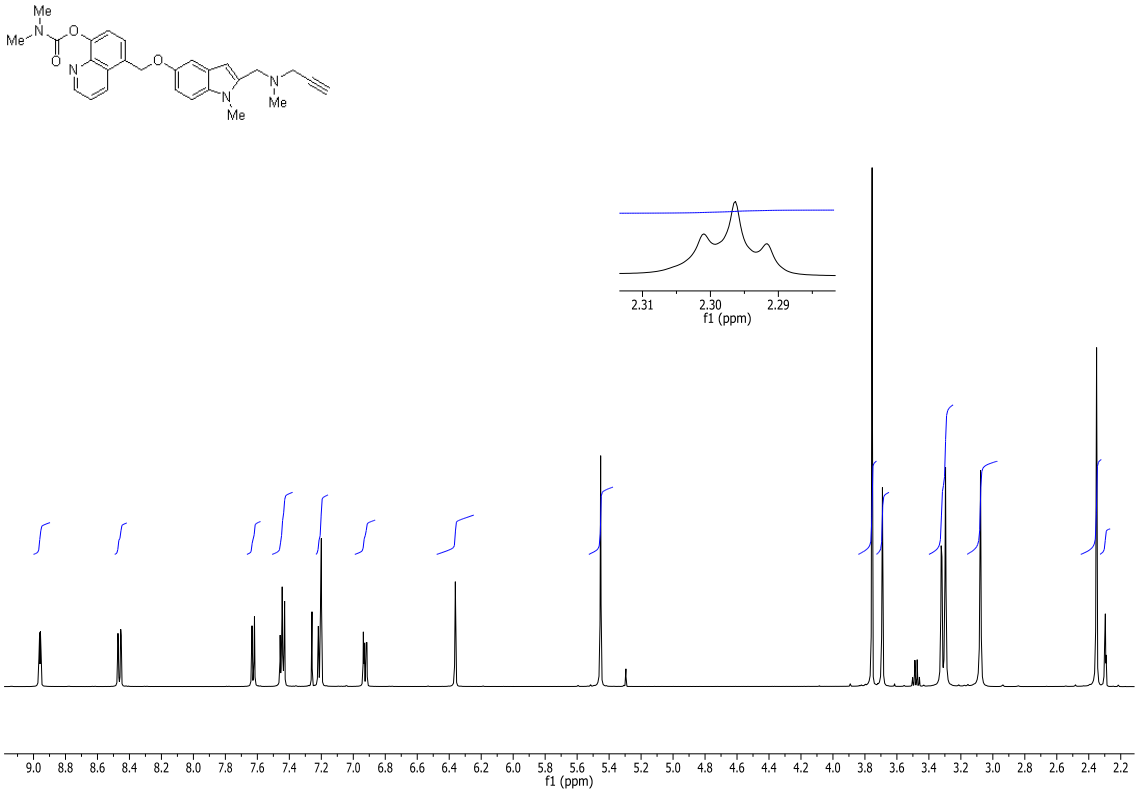


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **13**.

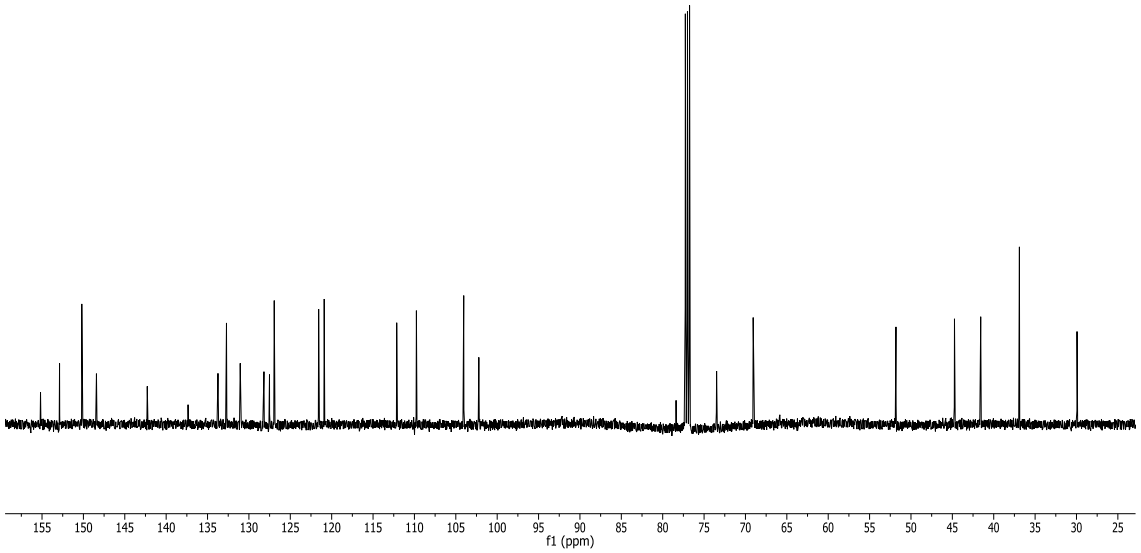


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **13**.

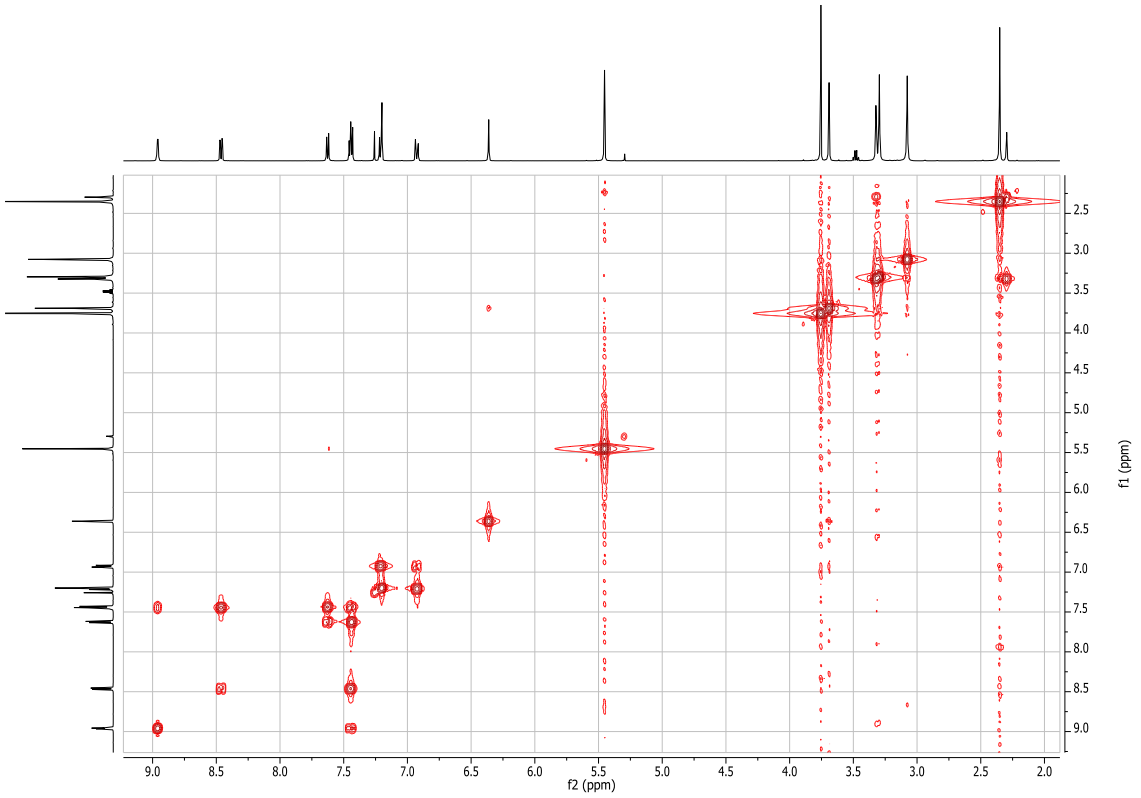
5-(((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)methyl)quinolin-8-yl dimethylcarbamate (14)



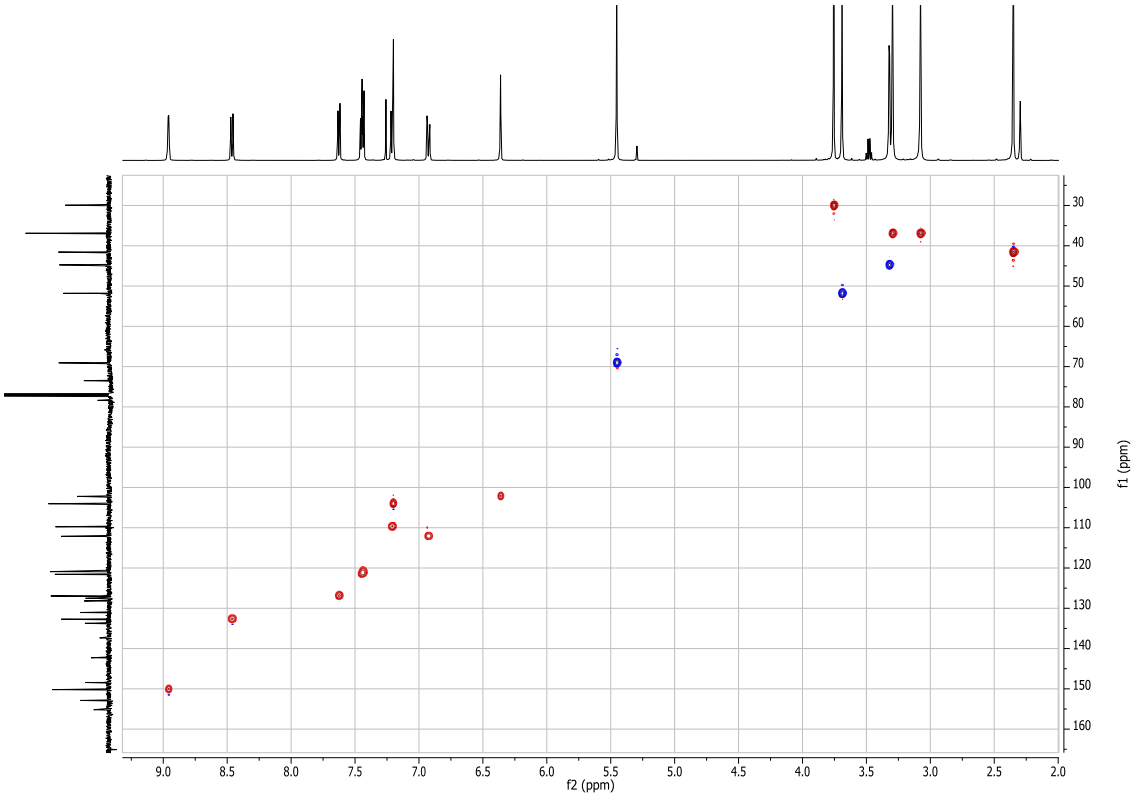
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **14**.



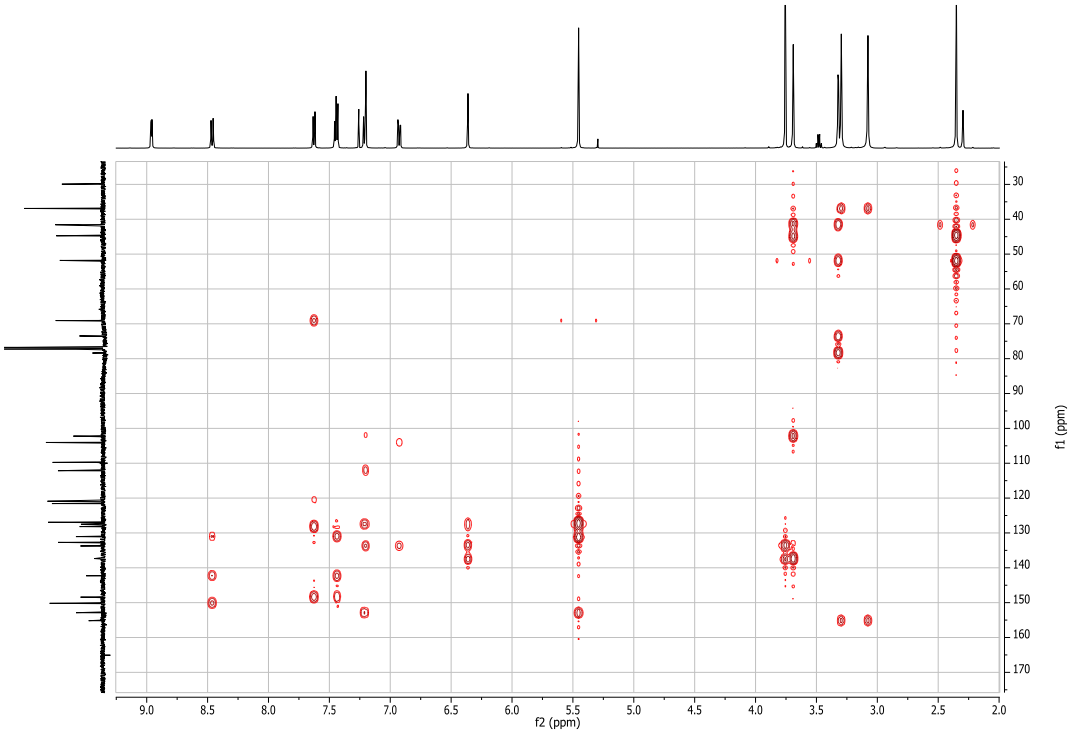
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **14**.



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **14**.

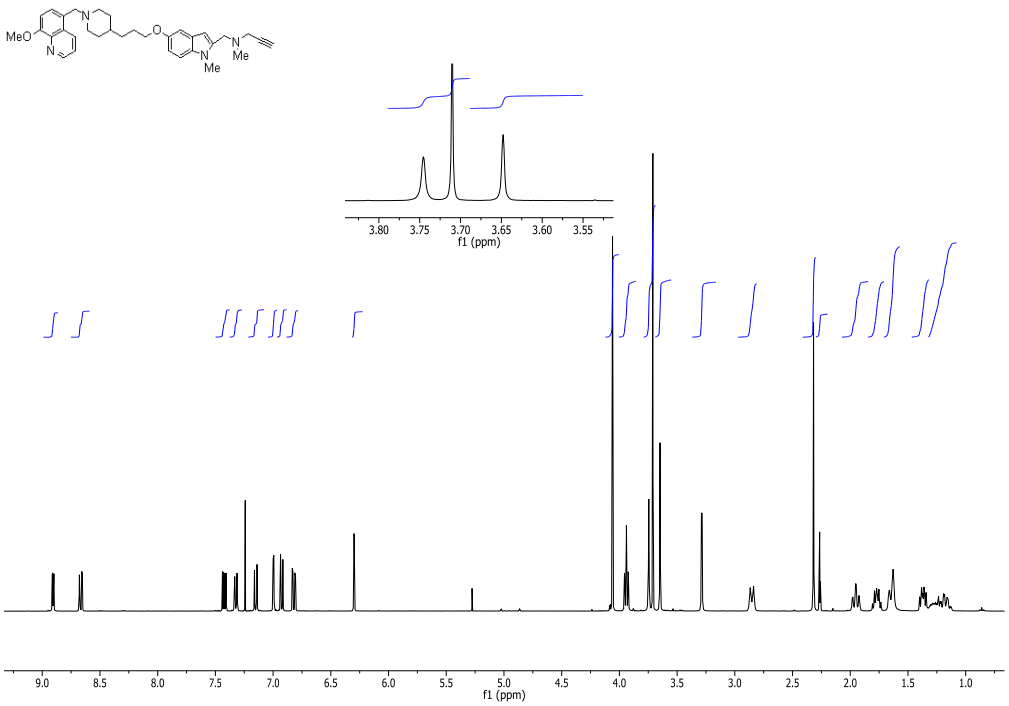


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **14**.

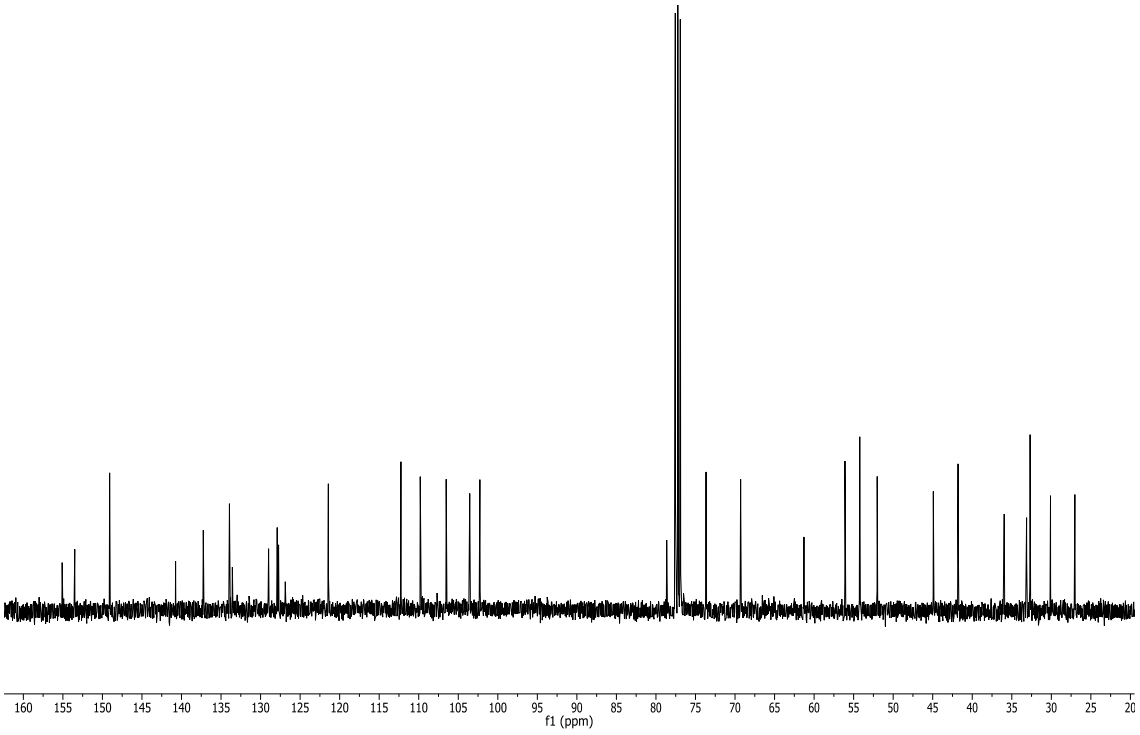


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **14**.

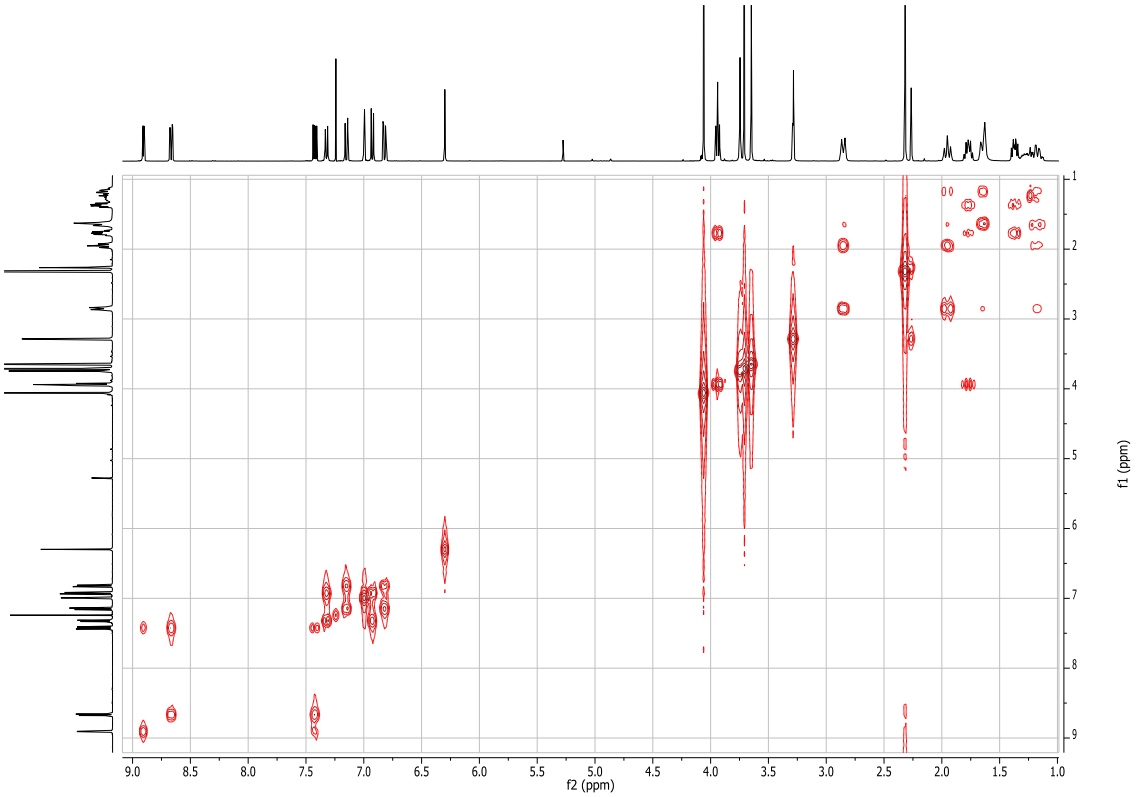
***N*-((5-(3-(1-((8-Methoxyquinolin-5-yl)methyl)piperidin-4-yl)propoxy)-1-methyl-1H-indol-2-yl)methyl)-N-methylprop-2-yn-1-amine (4)**.



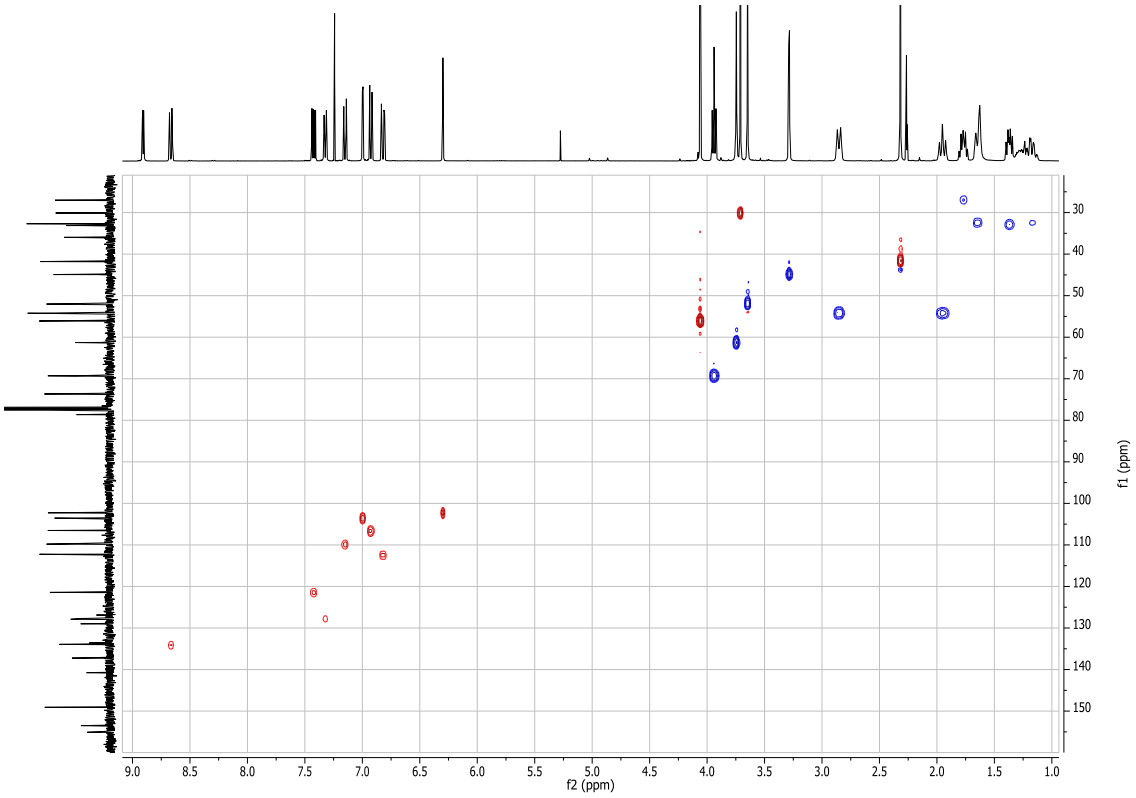
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **4.**



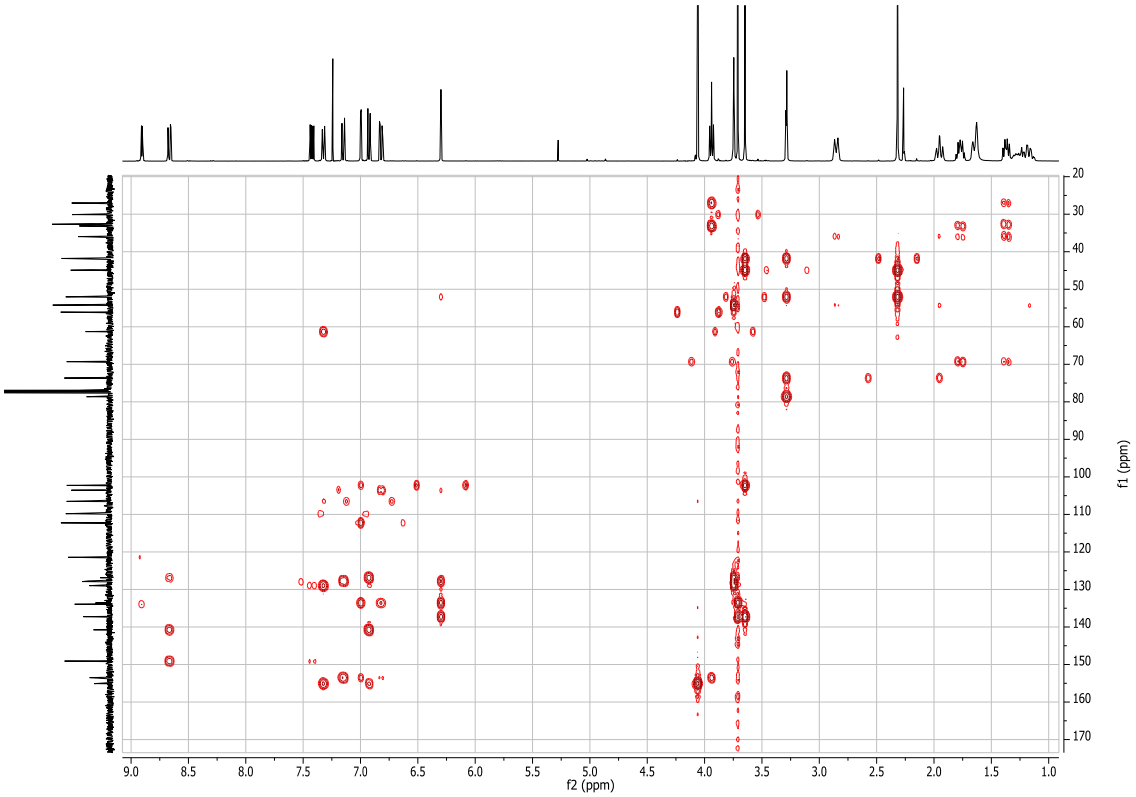
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **4.**



^{1}H-^{1}H *g*-COSY (400 MHz, $CDCl_3$) spectrum of compound **4.**

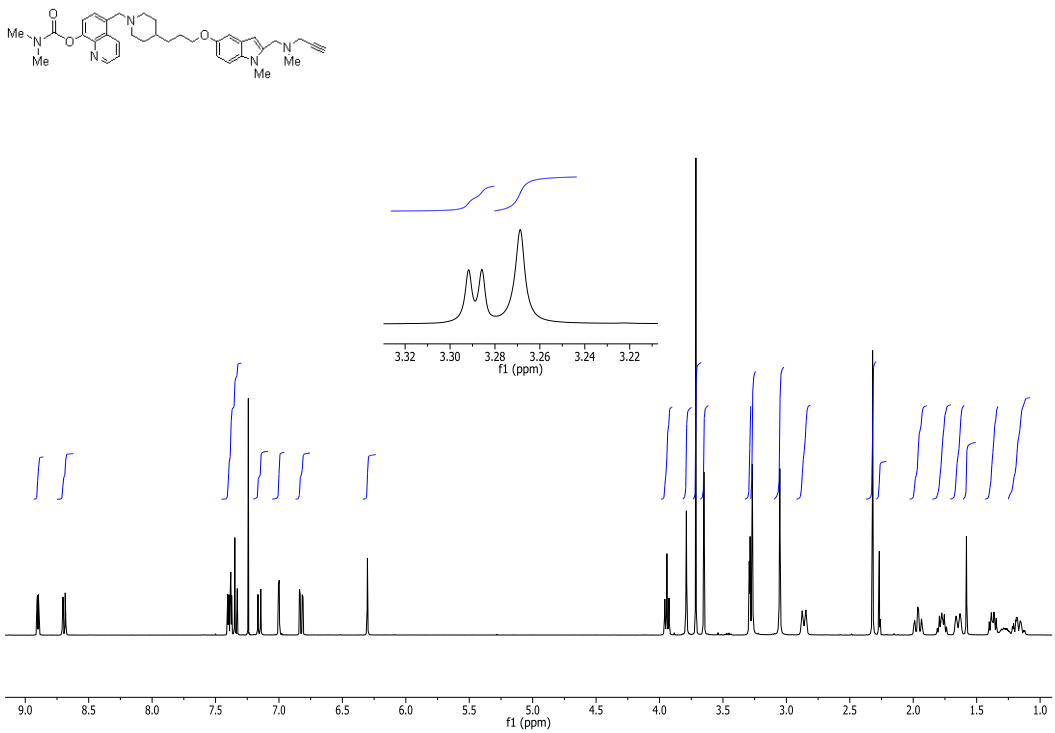


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **4.**

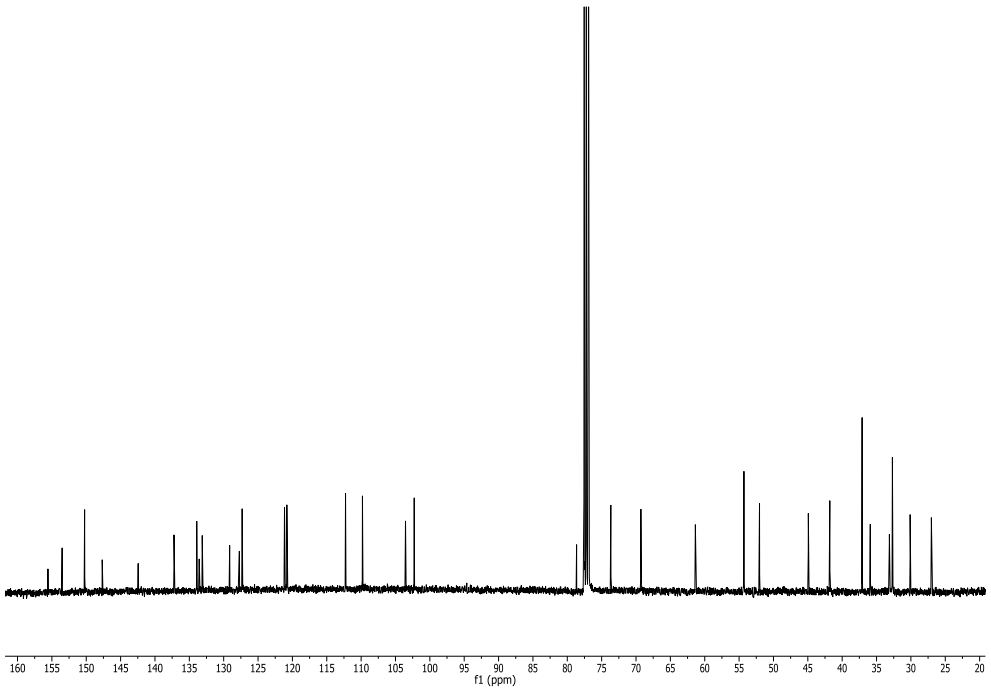


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **4.**

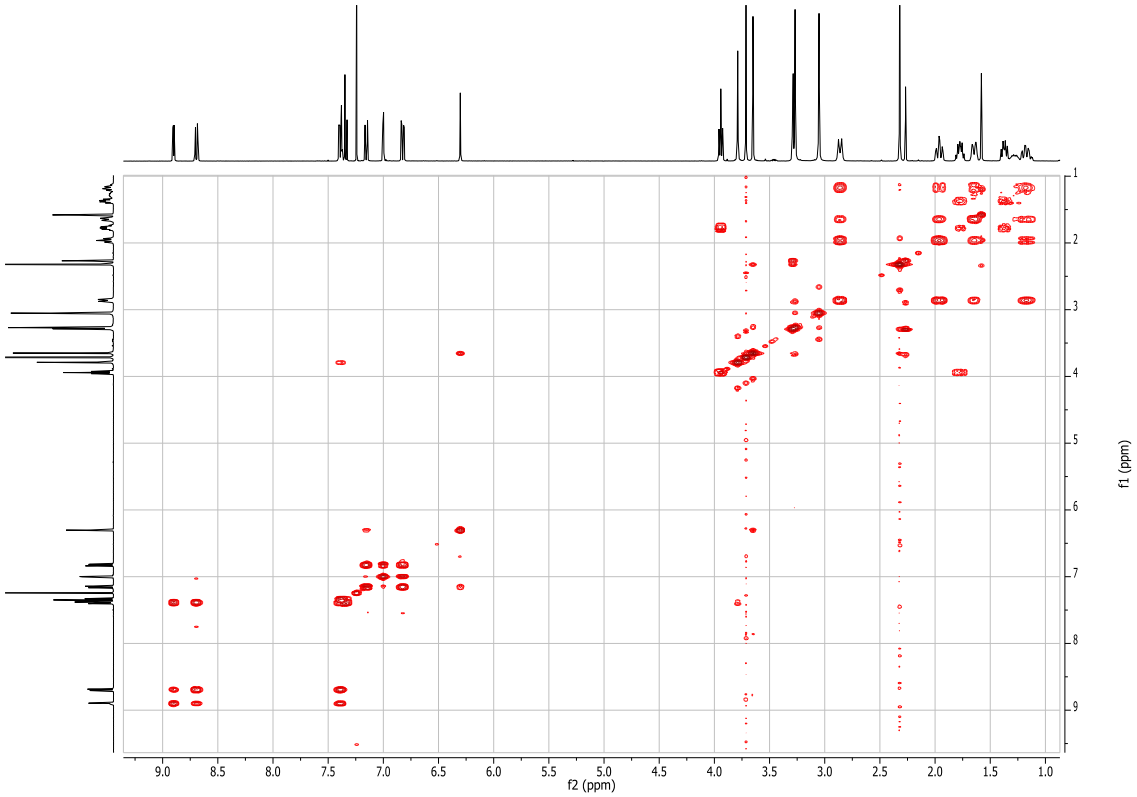
5-((4-(3-((1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl)oxy)propyl)piperidin-1-yl)methyl)quinolin-8-yl dimethylcarbamate (5).



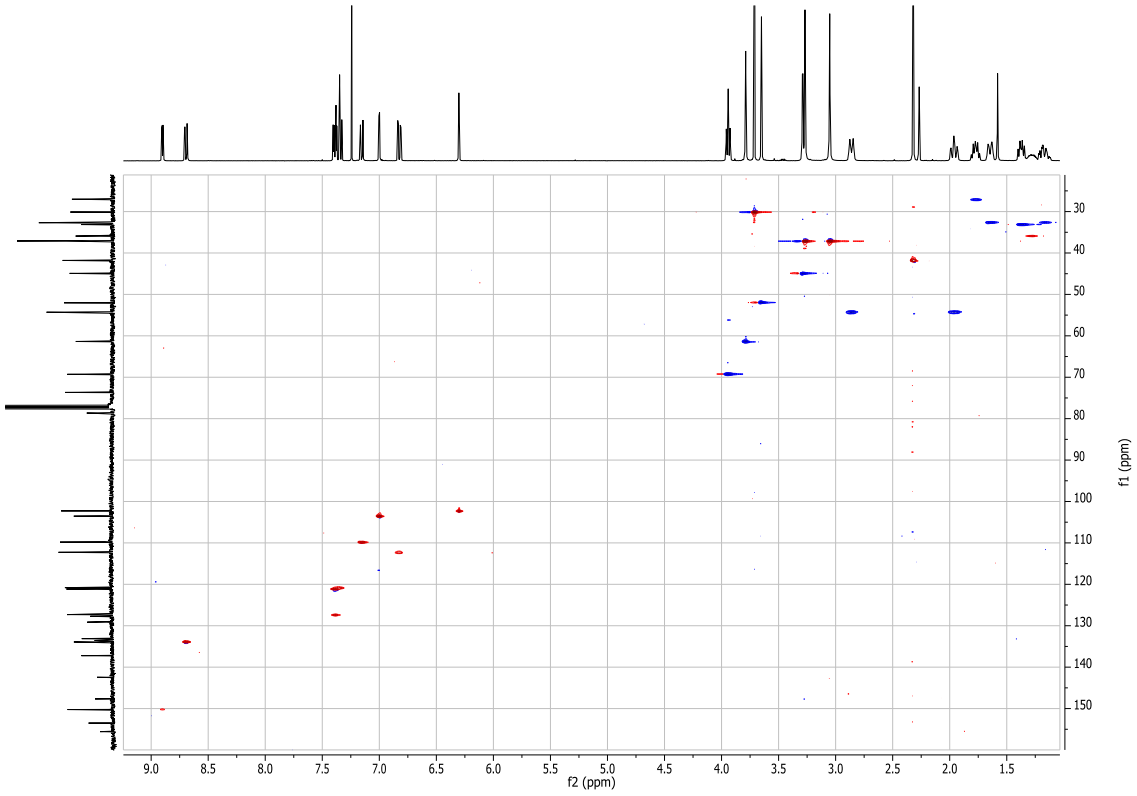
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5.**



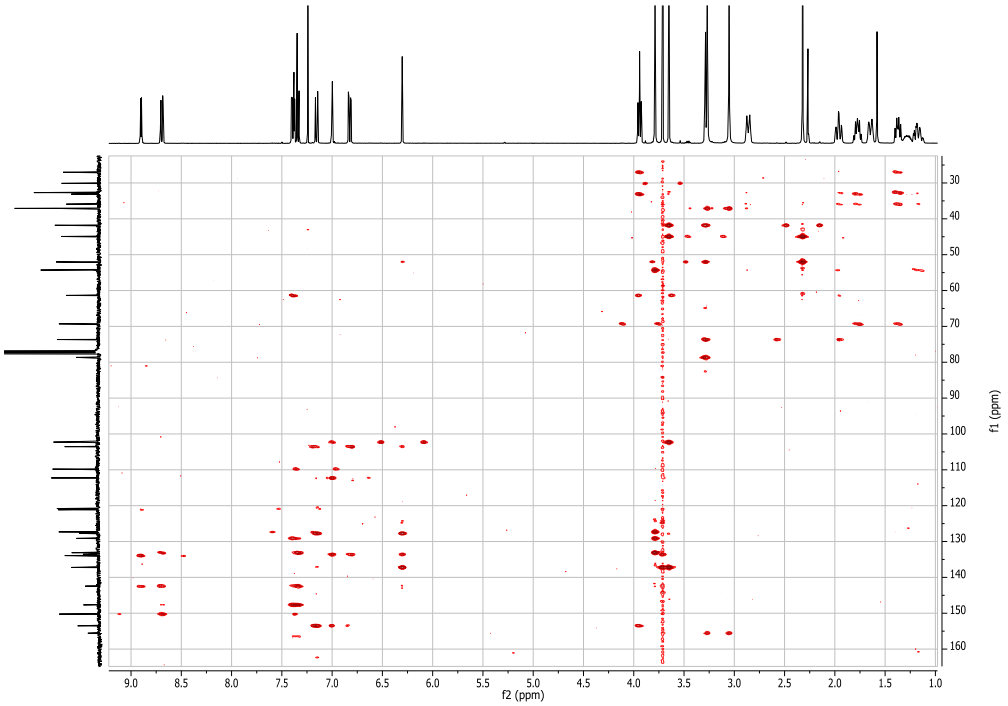
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **5.**



^{1}H-^{1}H *g*-COSY (400 MHz, $CDCl_3$) spectrum of compound **5.**

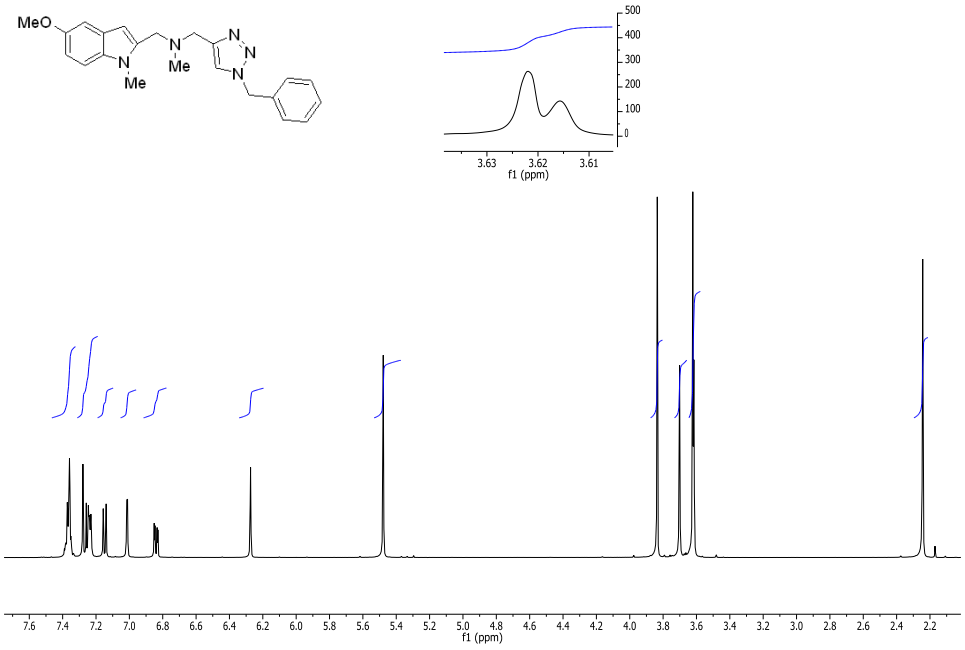


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **5.**

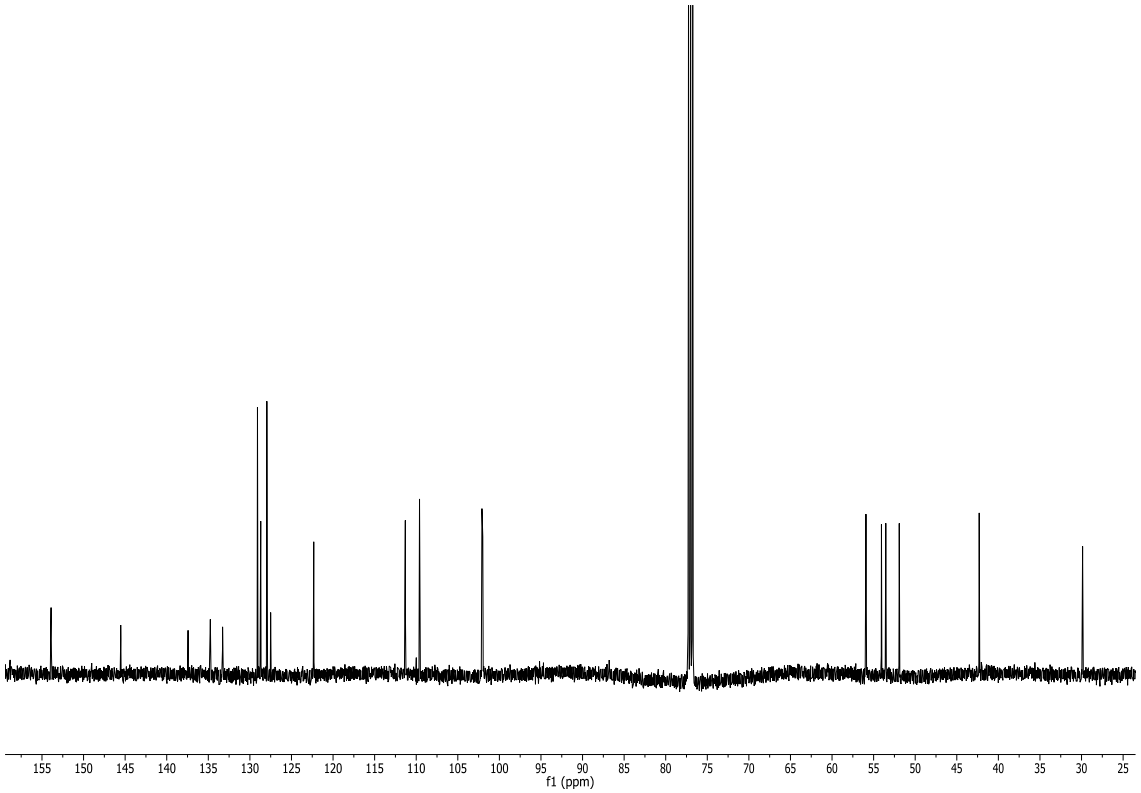


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **5.**

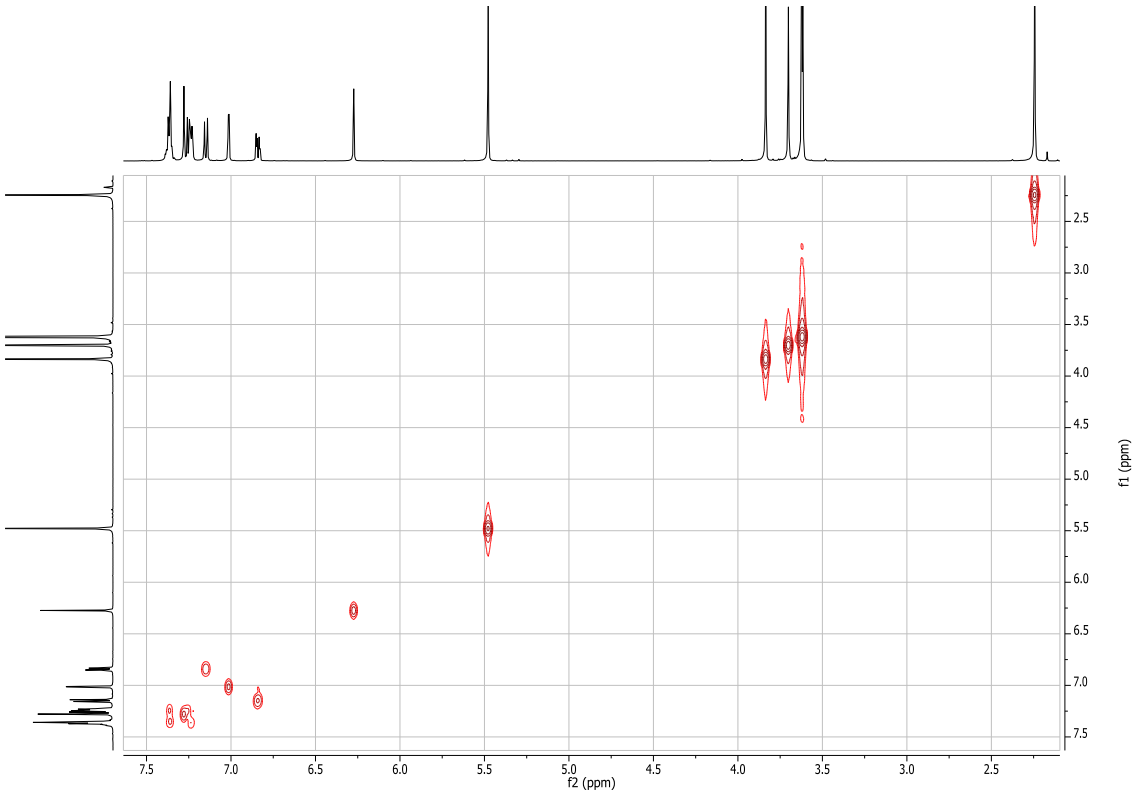
1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-methoxy-1-methyl-1*H*-indol-2-yl)methyl)-N-methylmethanamine (15).



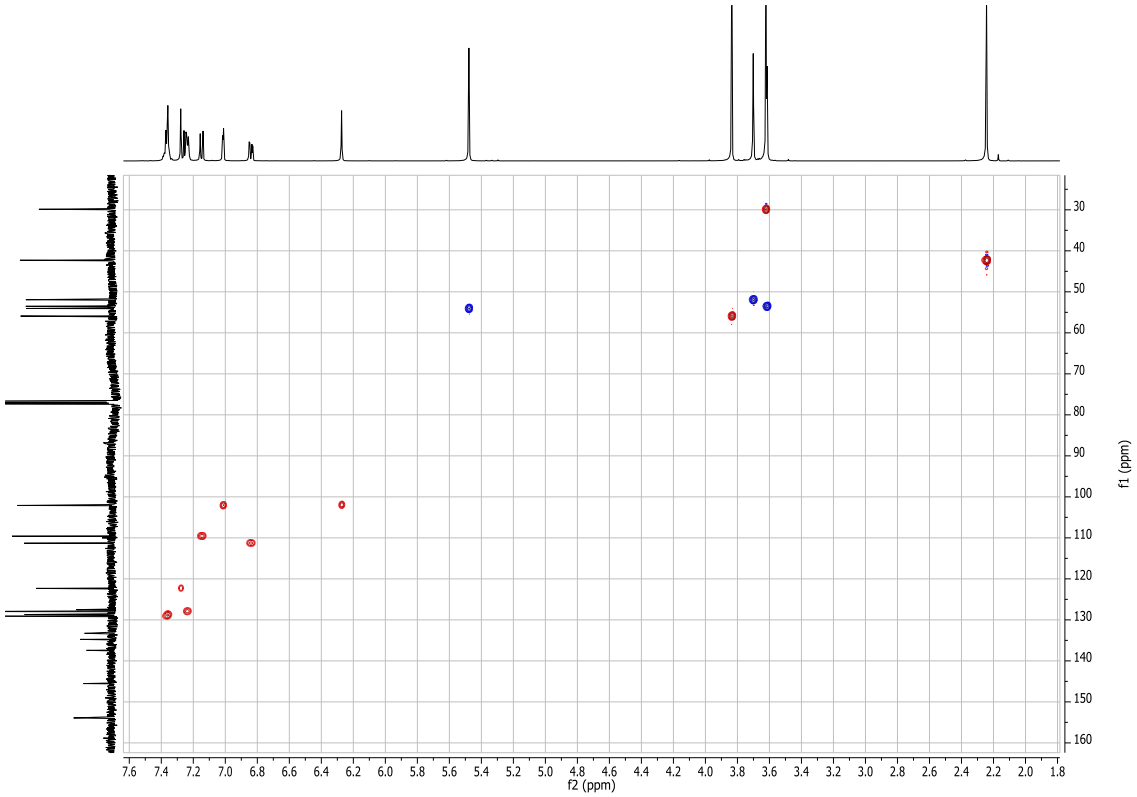
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **15.**



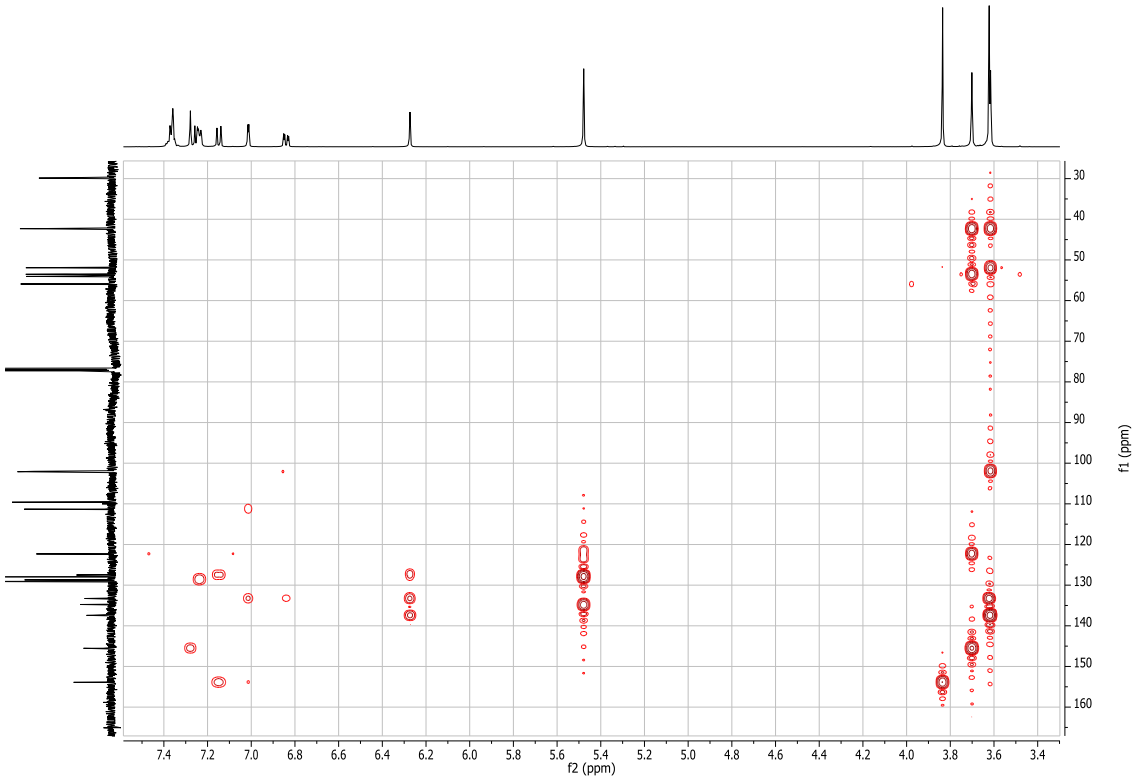
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **15.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **15.**

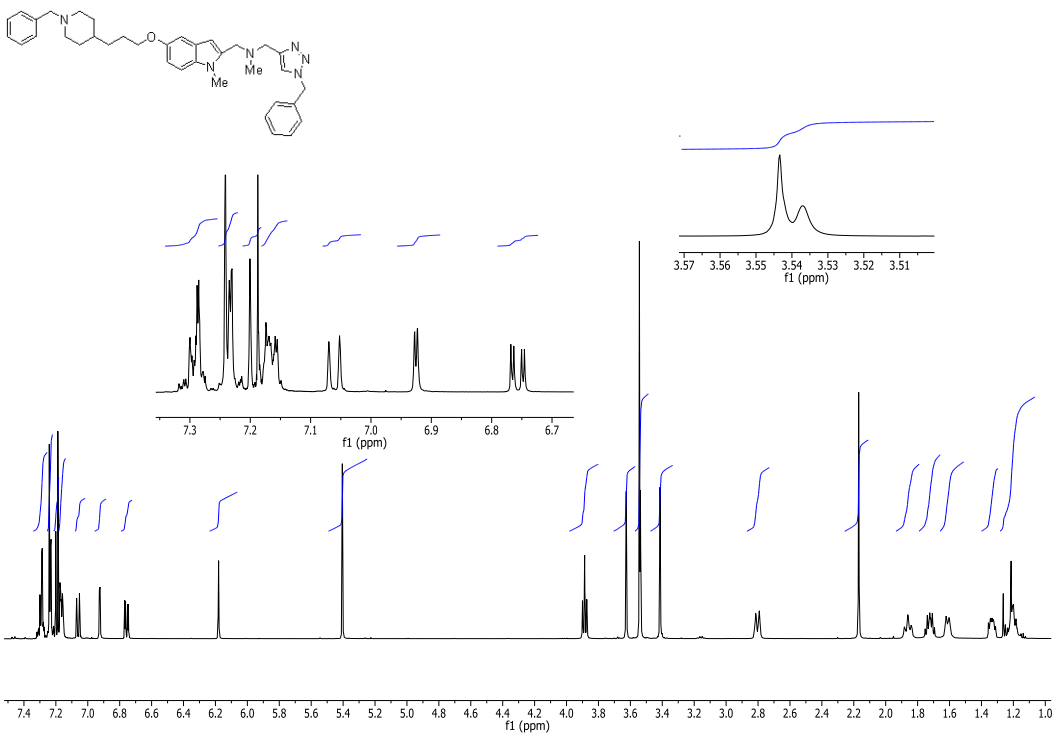


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **15.**

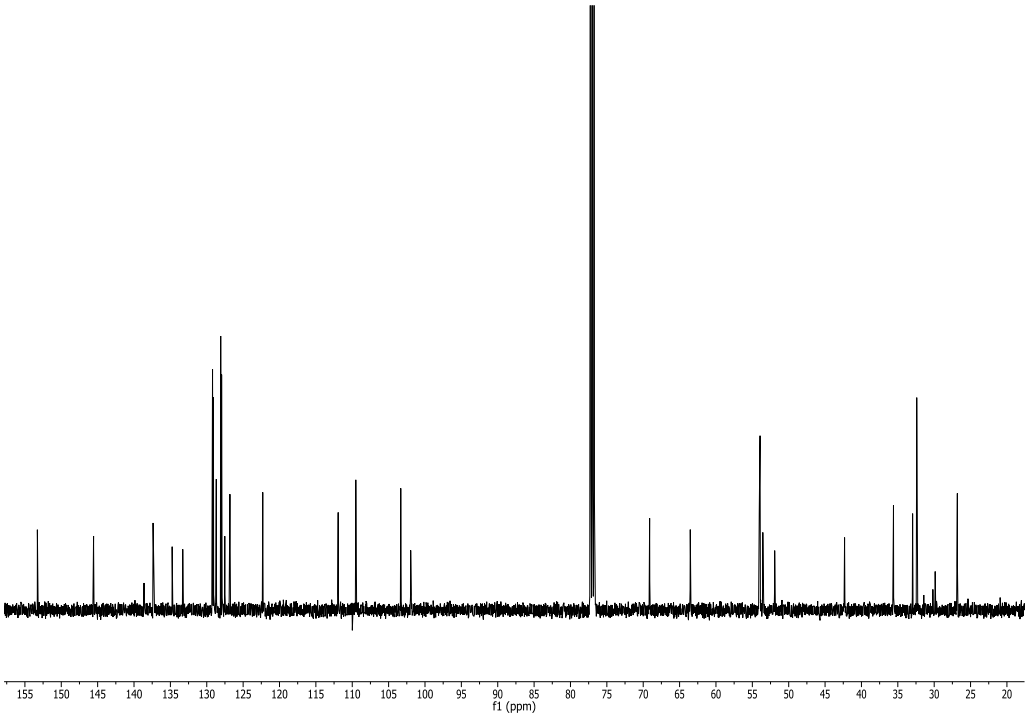


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **15.**

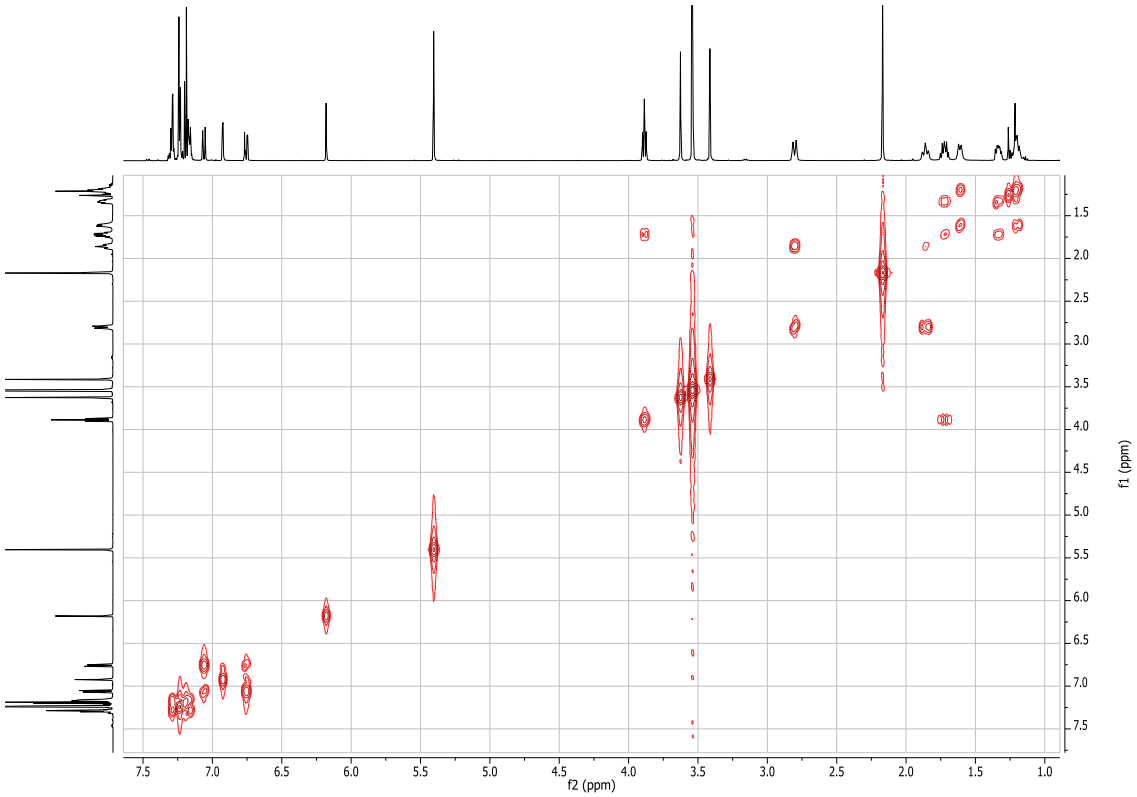
1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((5-(3-(1-benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)methyl)-*N*-methylmethanamine (9).



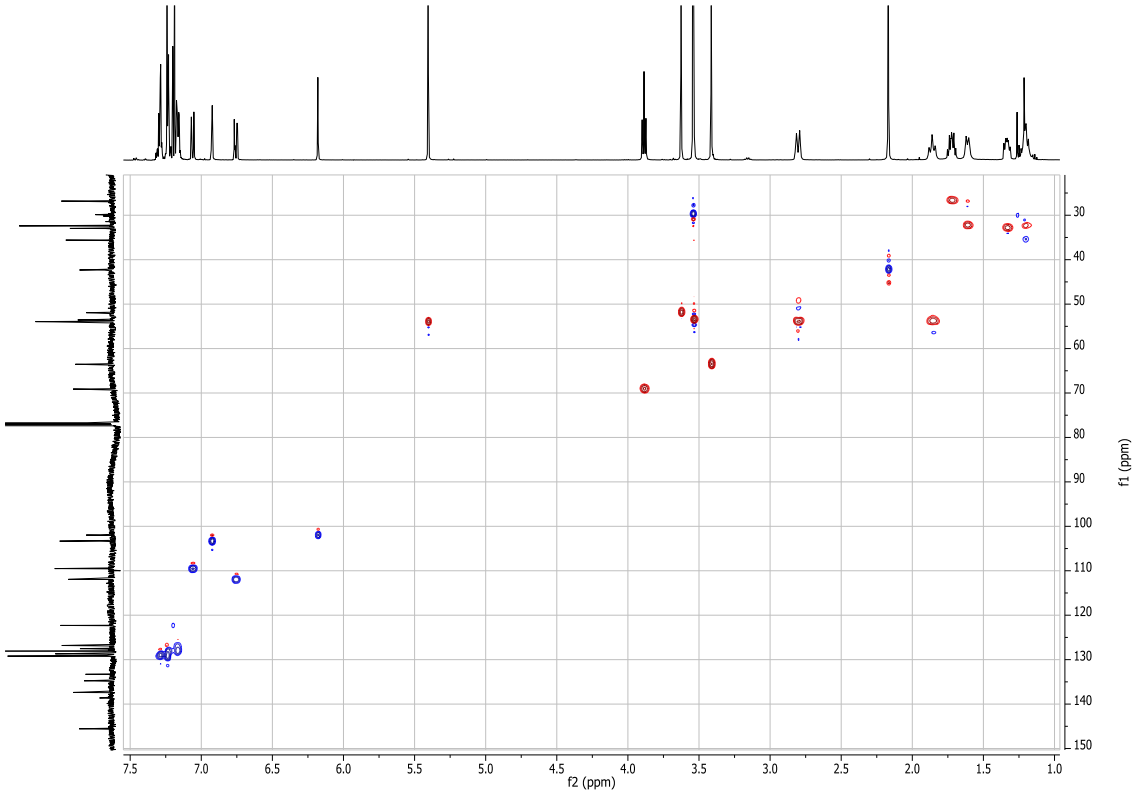
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **9.**



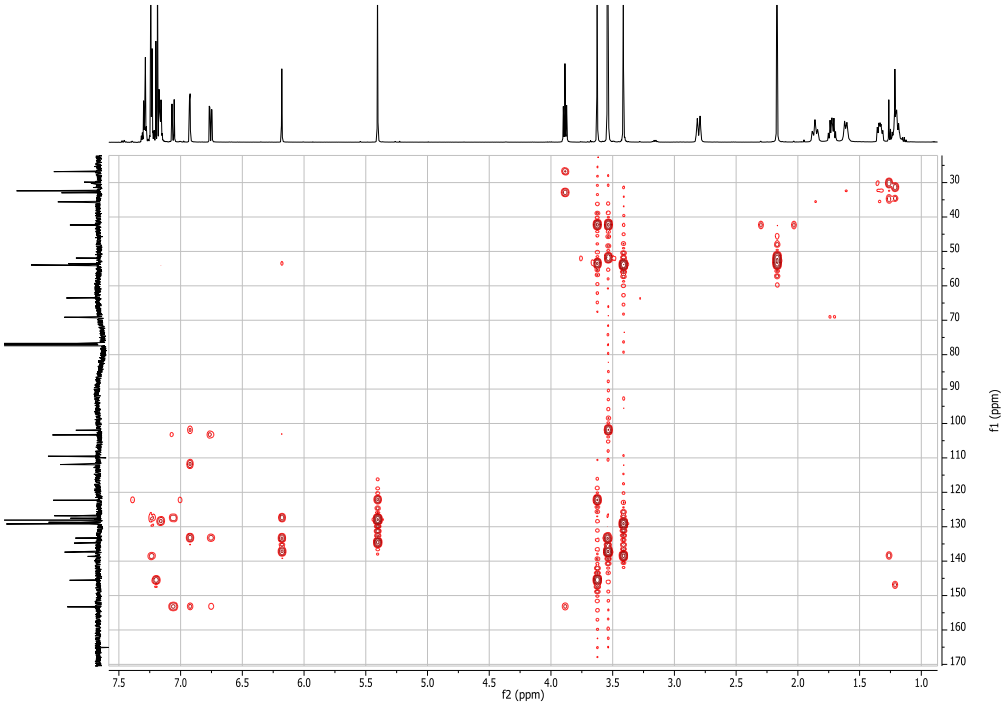
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **9.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **9.**

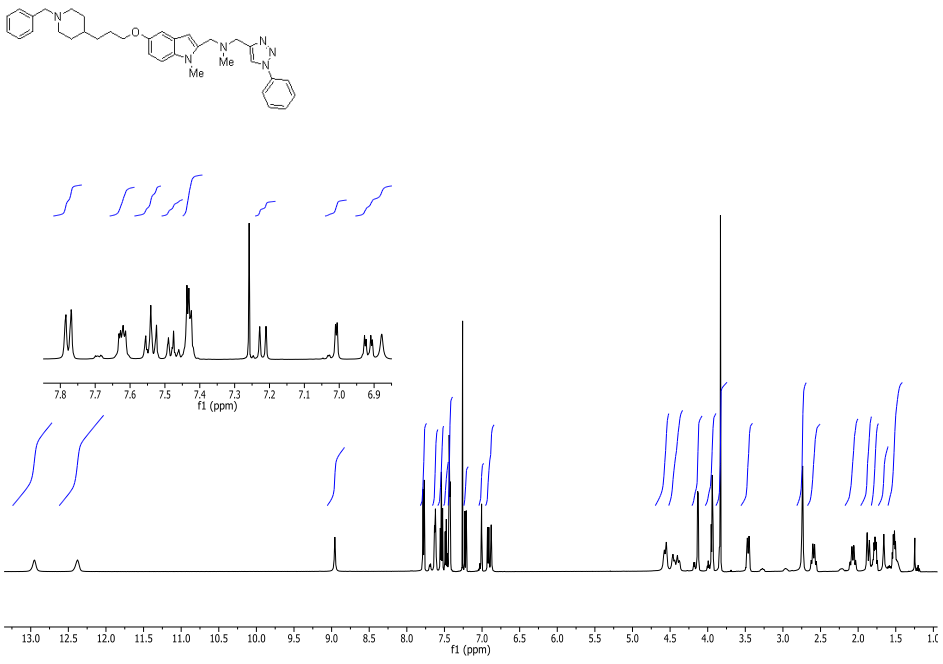


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **9.**

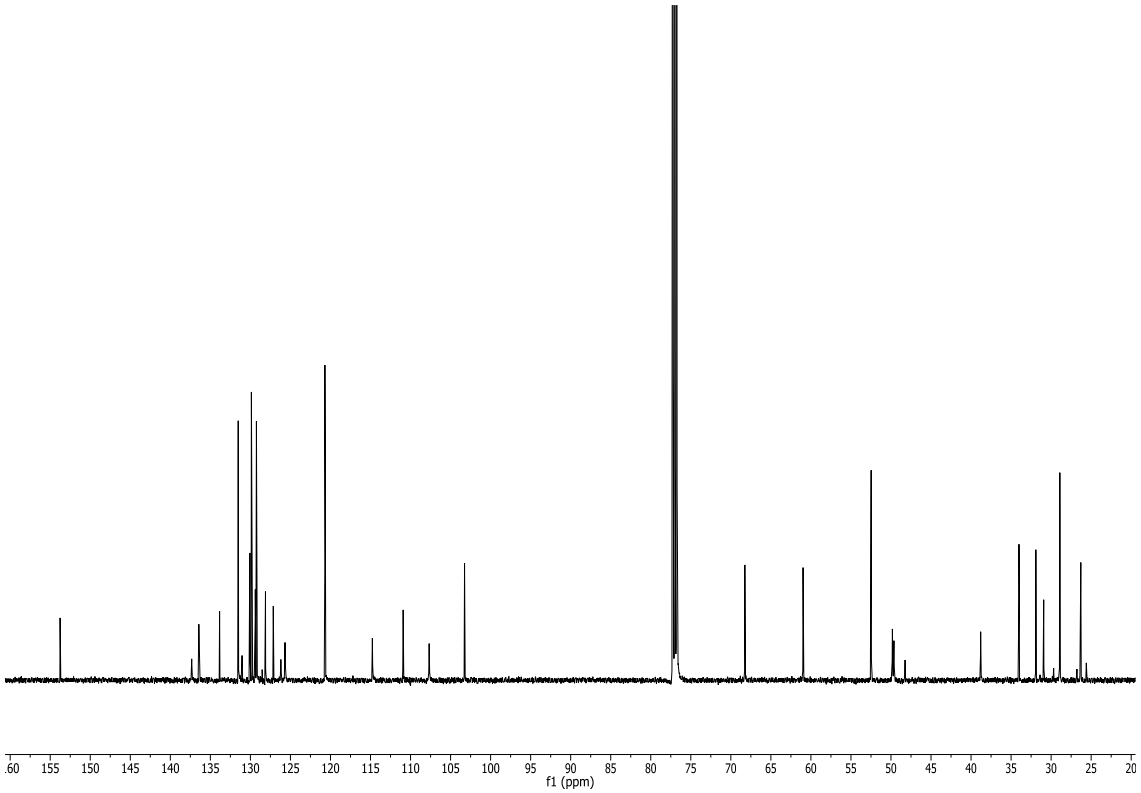


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **9.**

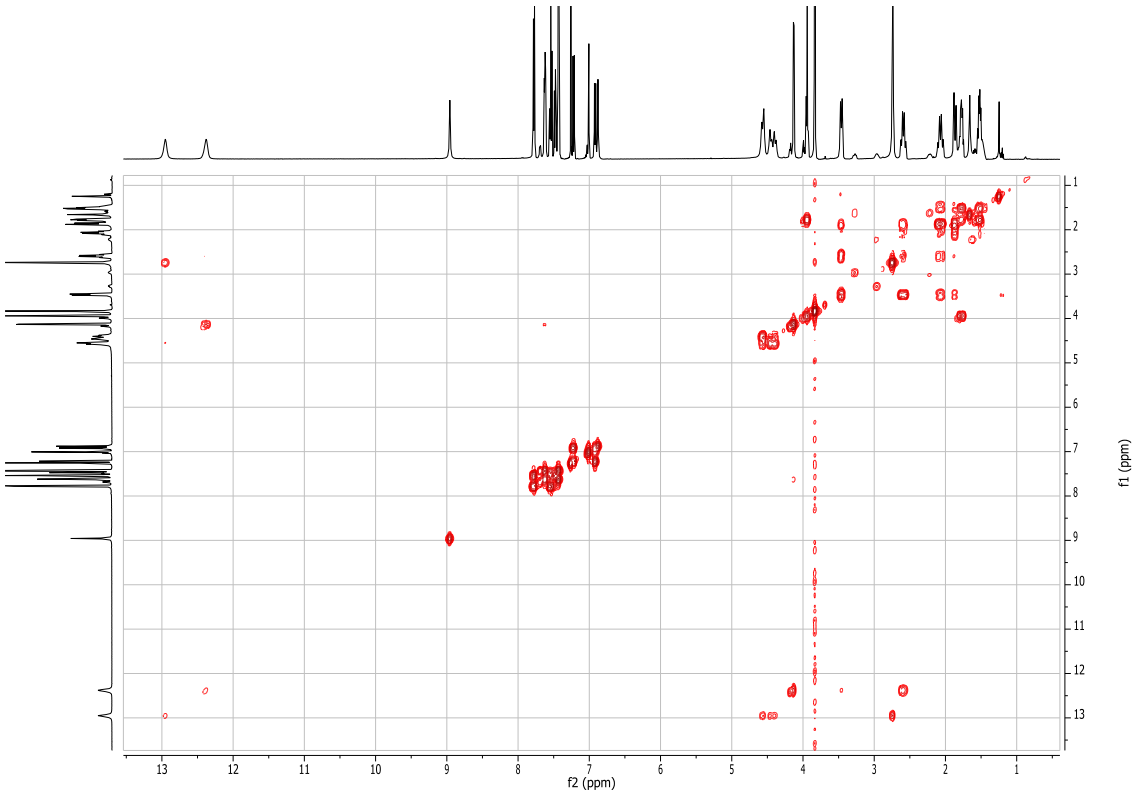
1-(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1-methyl-1*H*-indol-2-yl)-*N*-methyl-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)methanamine hydrochloride (10.2HCl).



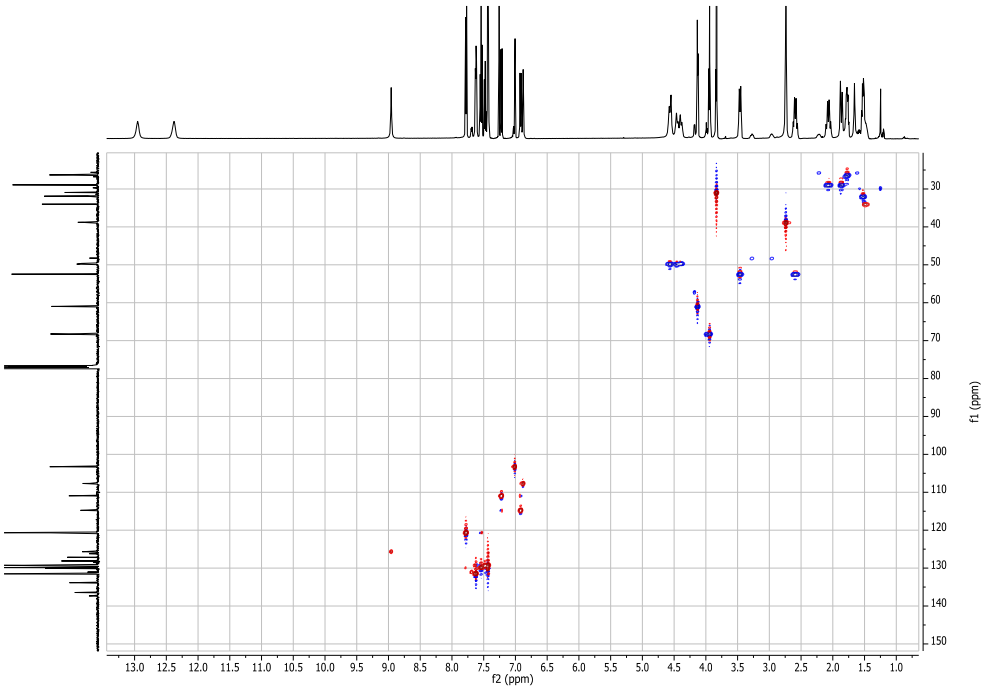
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **10.2HCl.**



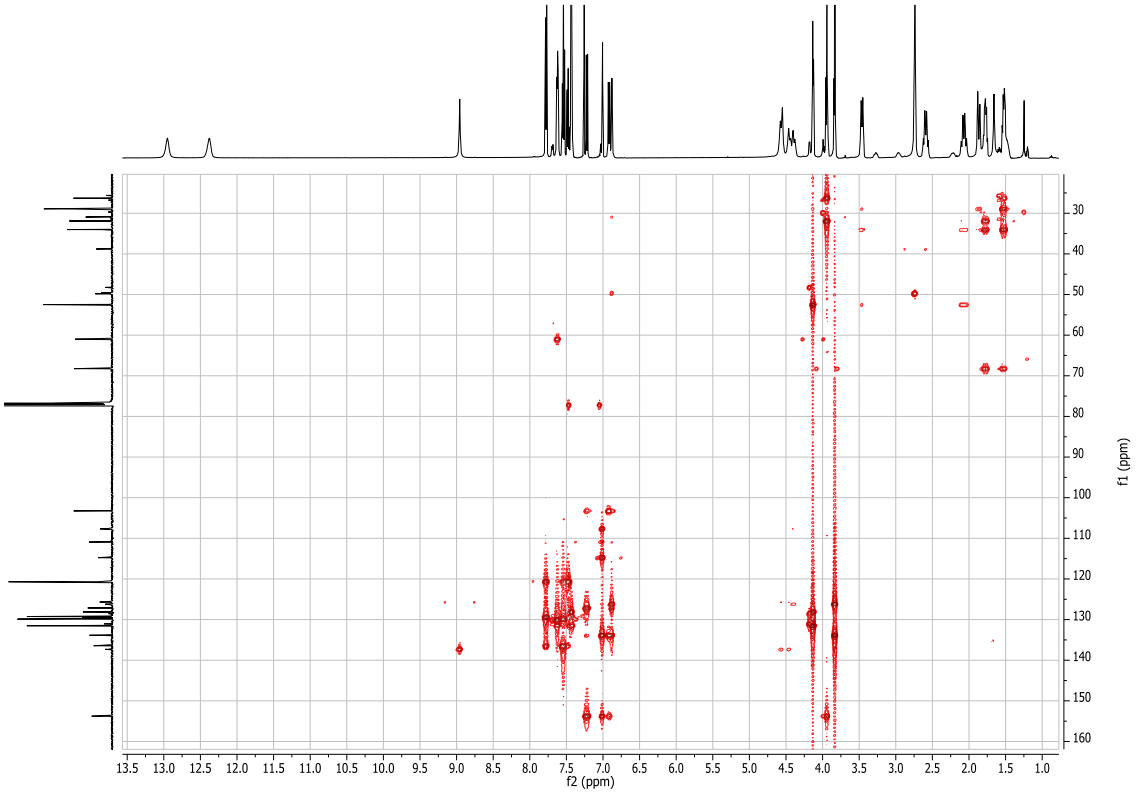
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **10.2HCl.**



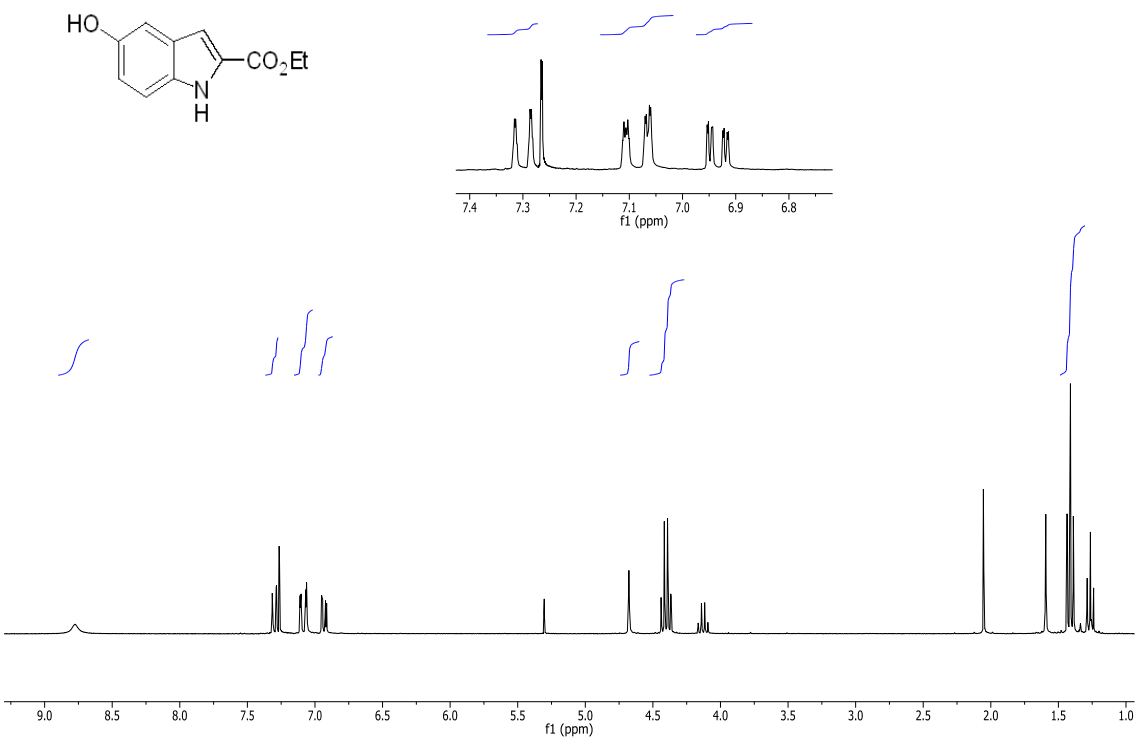
^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **10.2HCl.**



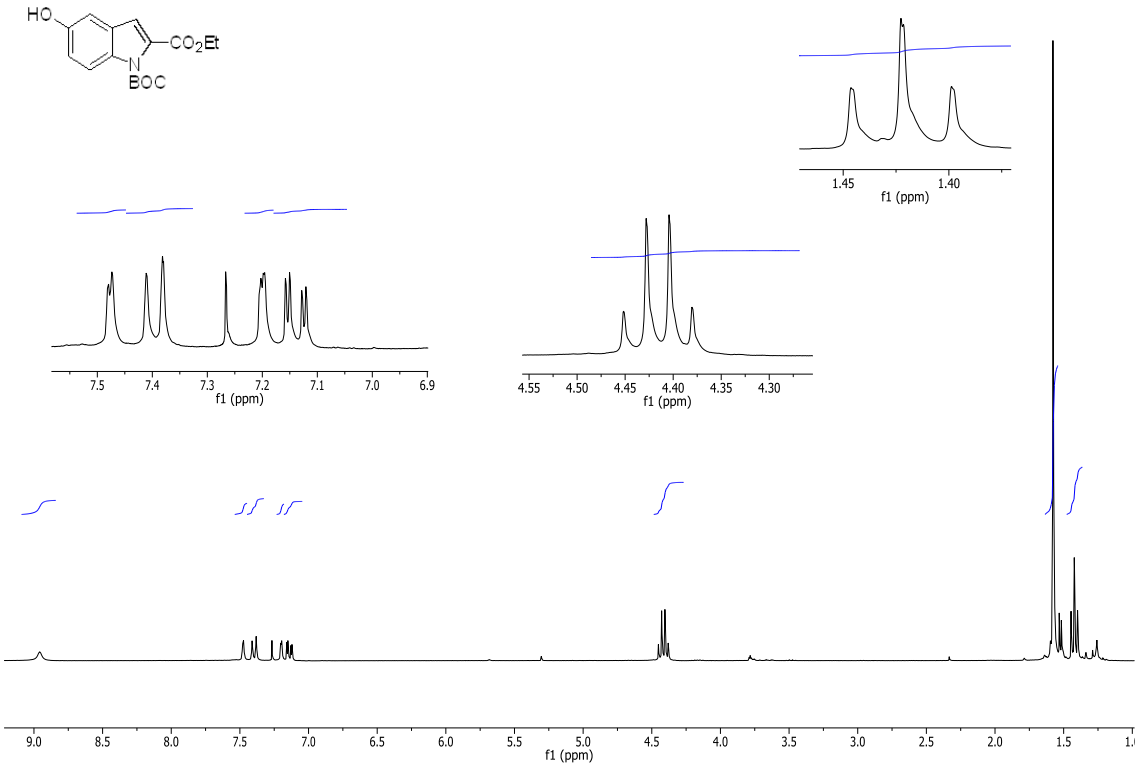
^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **10.2HCl.**



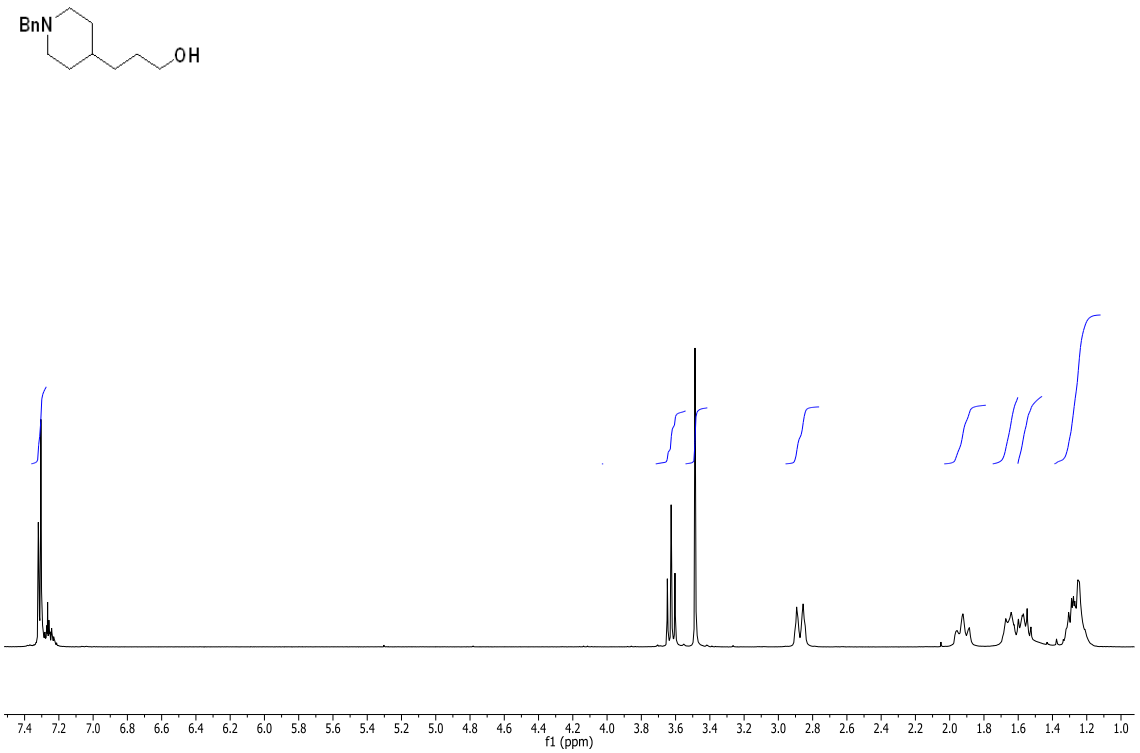
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **10.2HCl.**



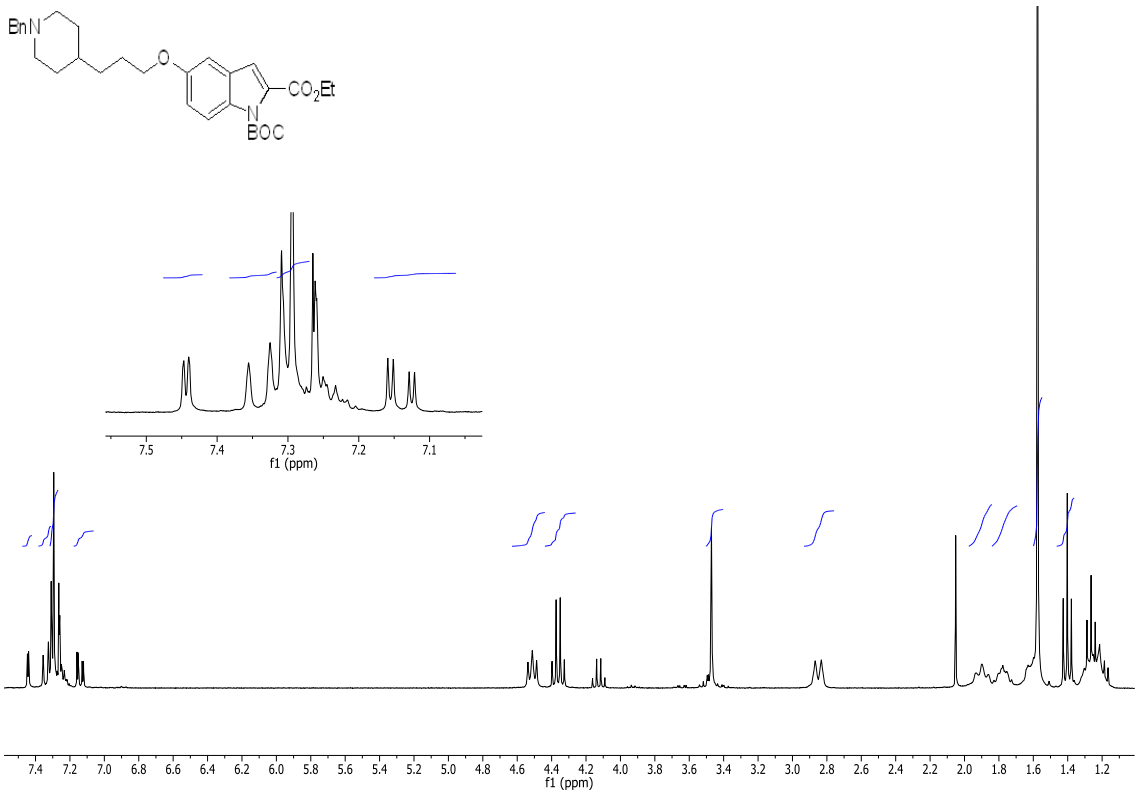
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA233.**



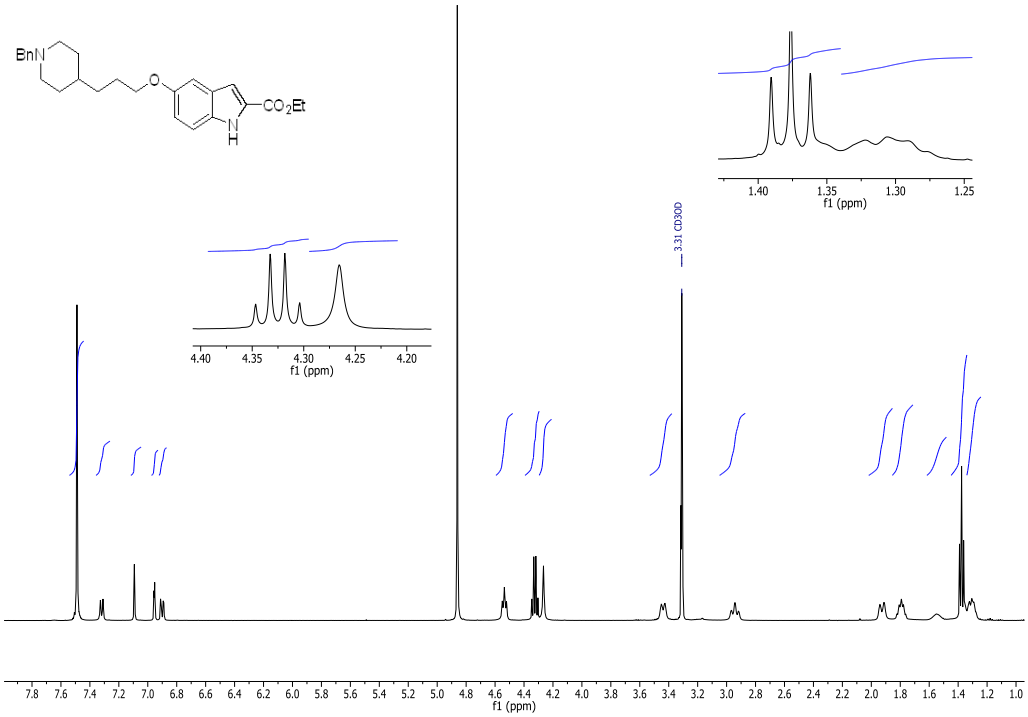
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA237.**



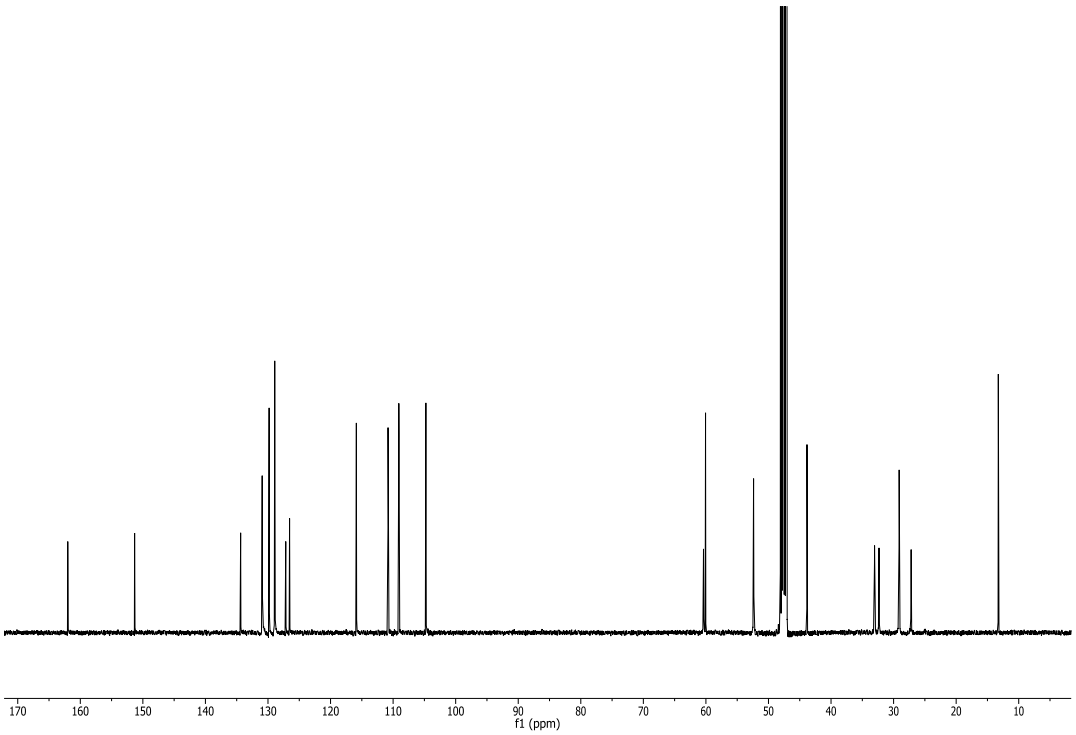
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA240.**



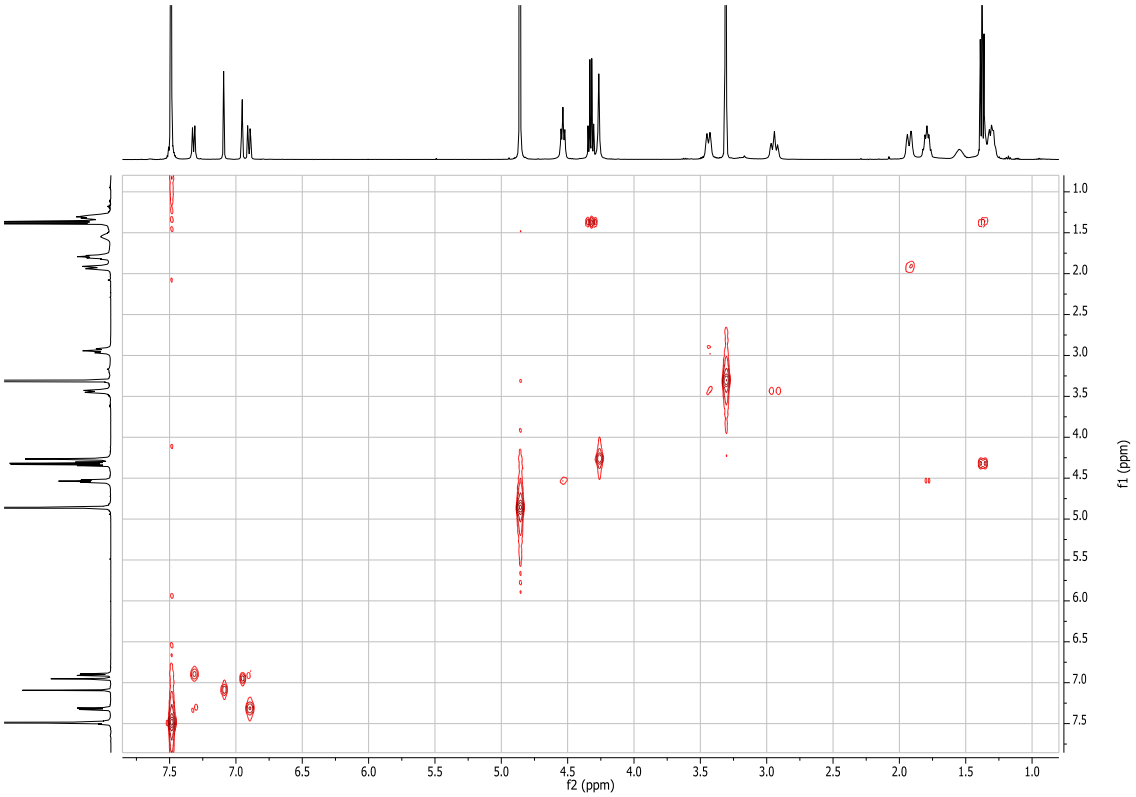
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA242.**



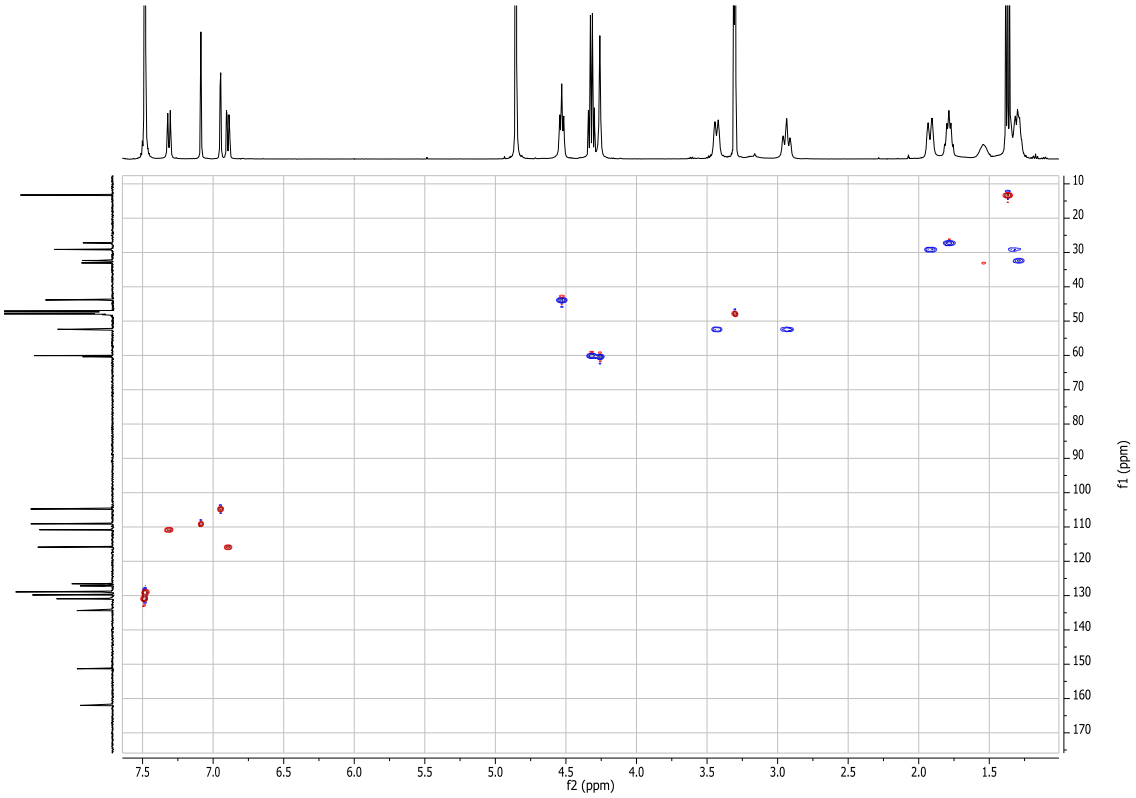
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **11.**



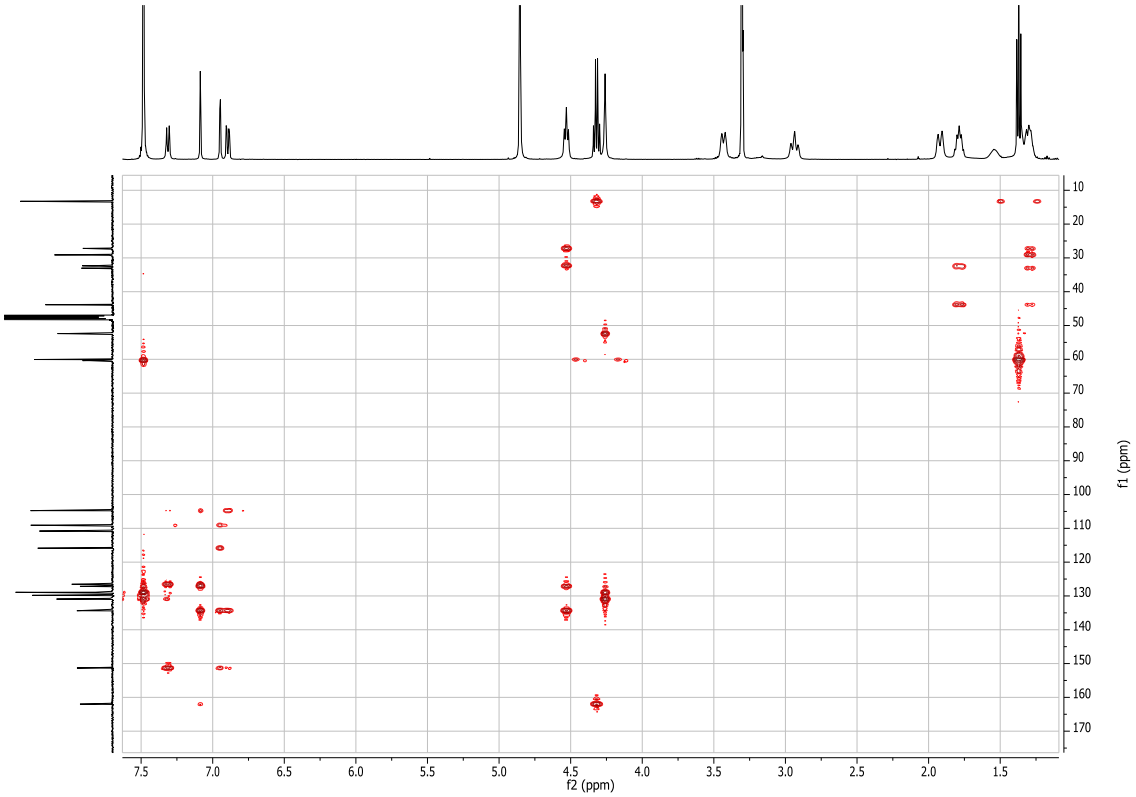
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **11.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **11.**

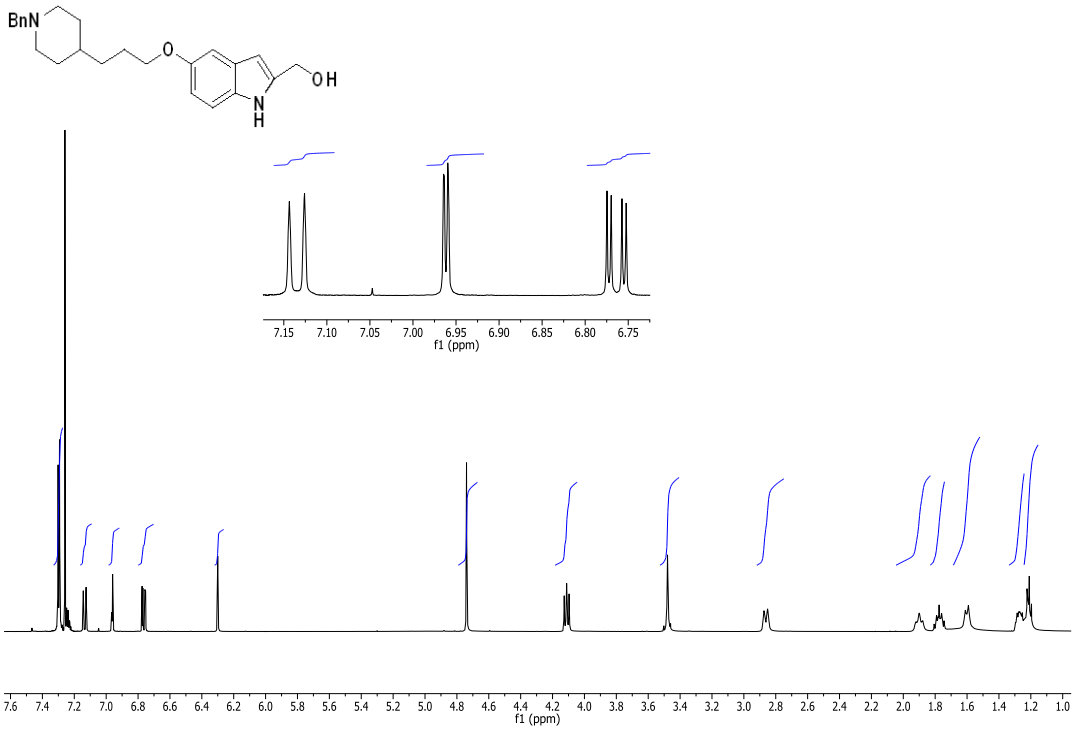


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **11.**

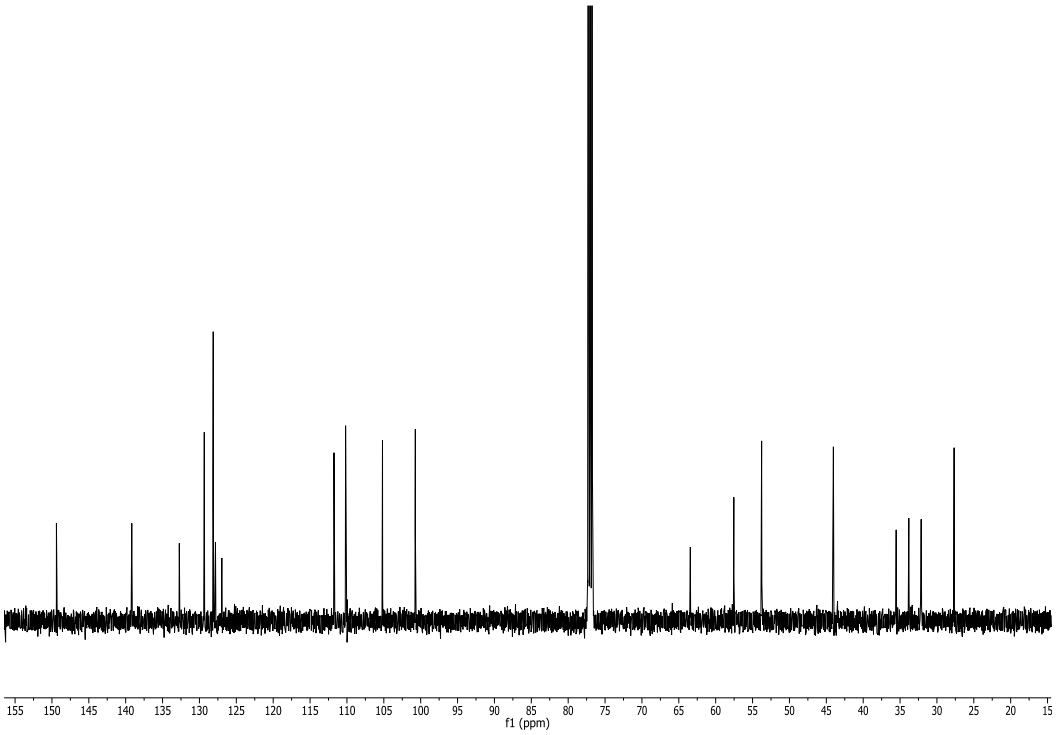


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **11.**

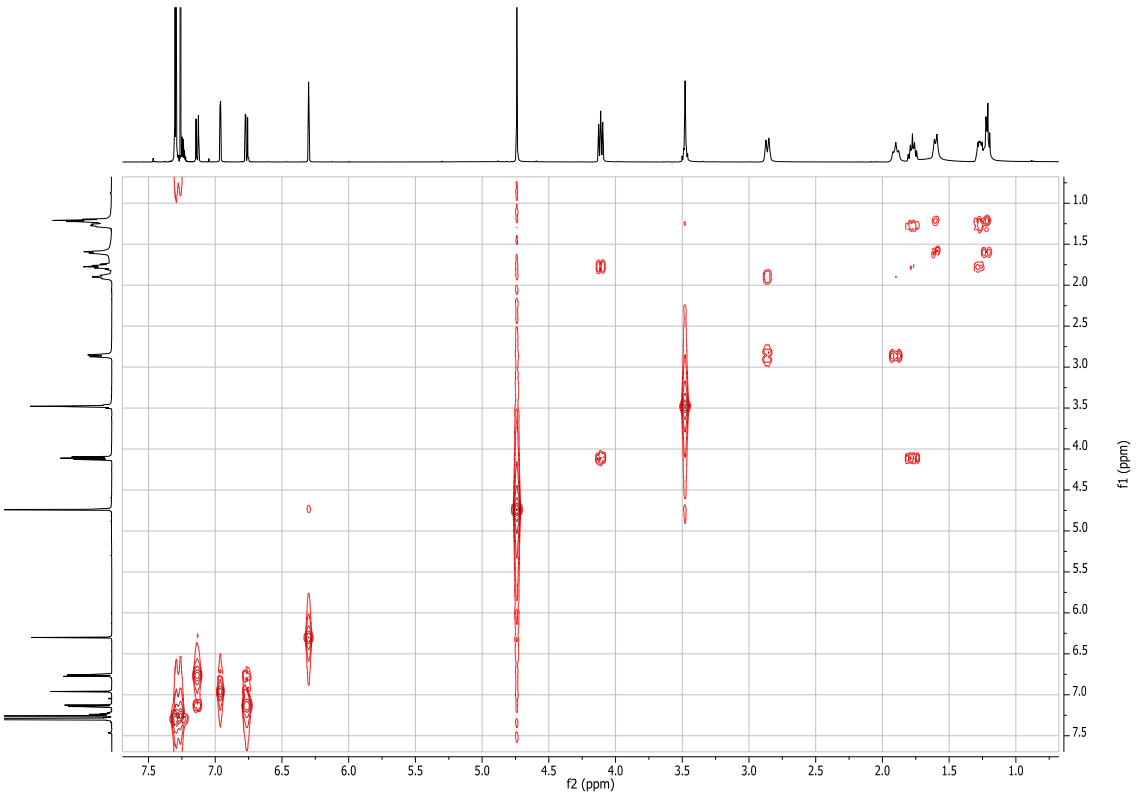
(5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methanol (12).



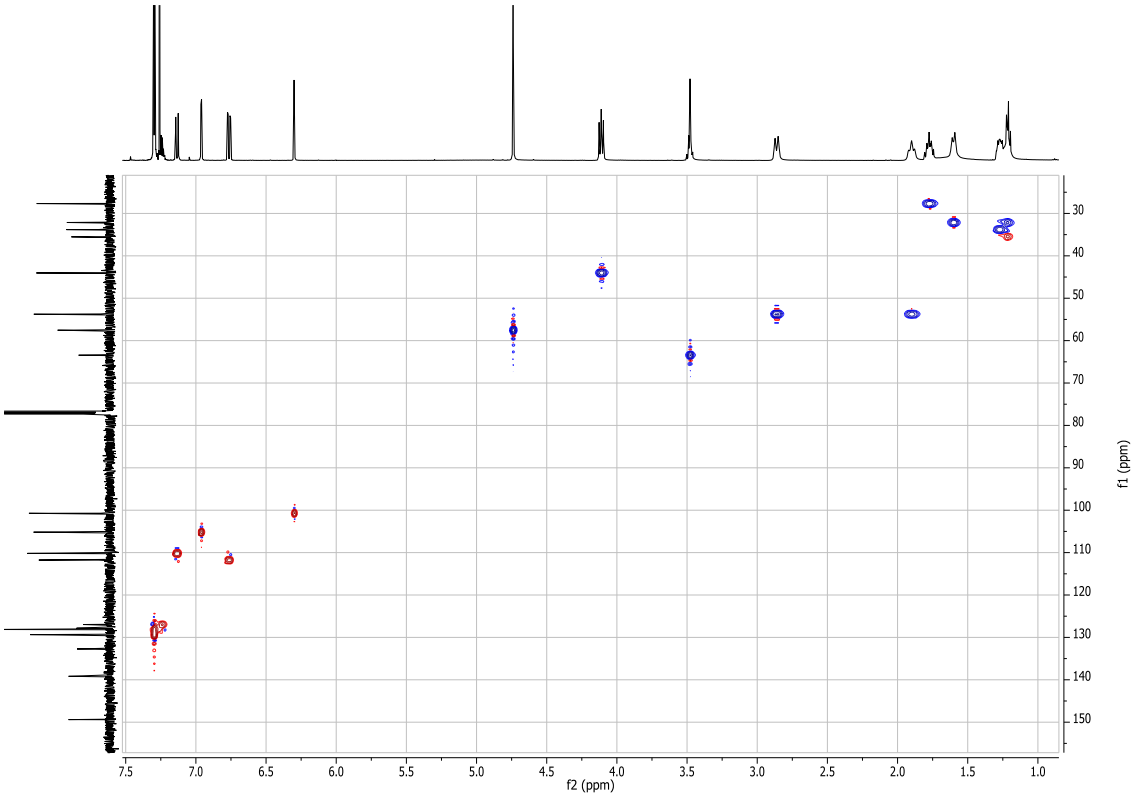
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **12.**



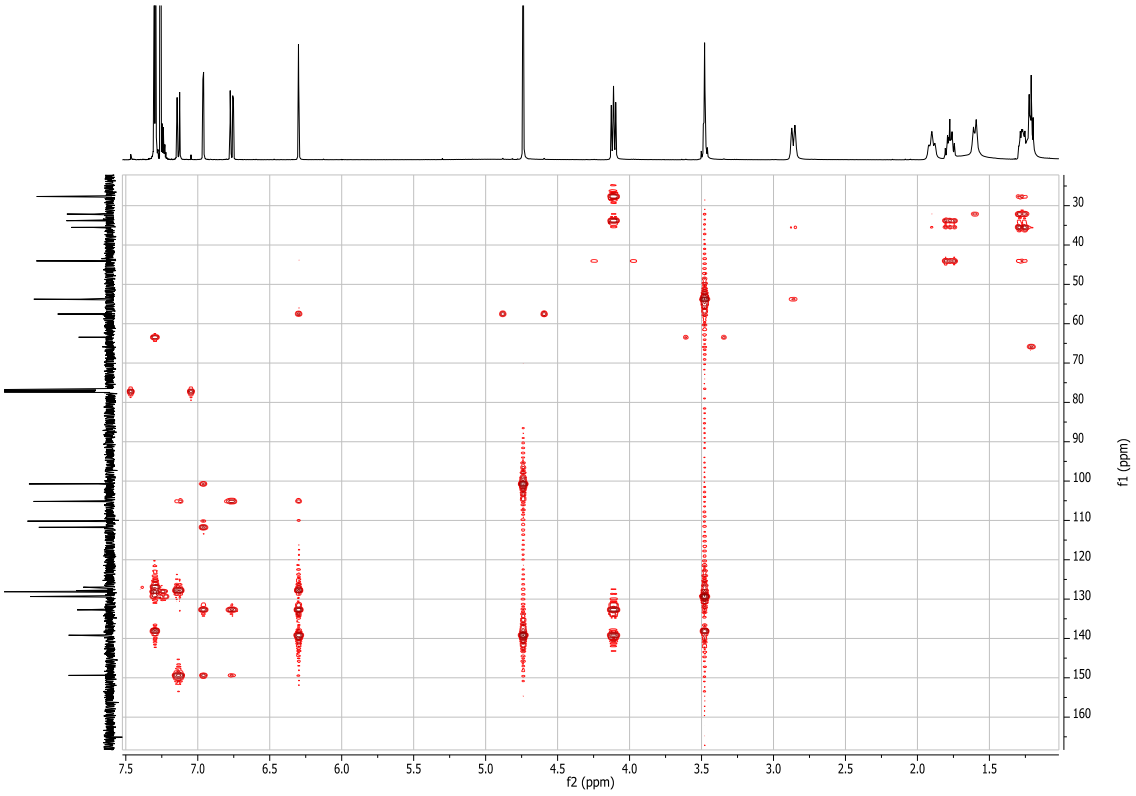
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **12.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **12.**

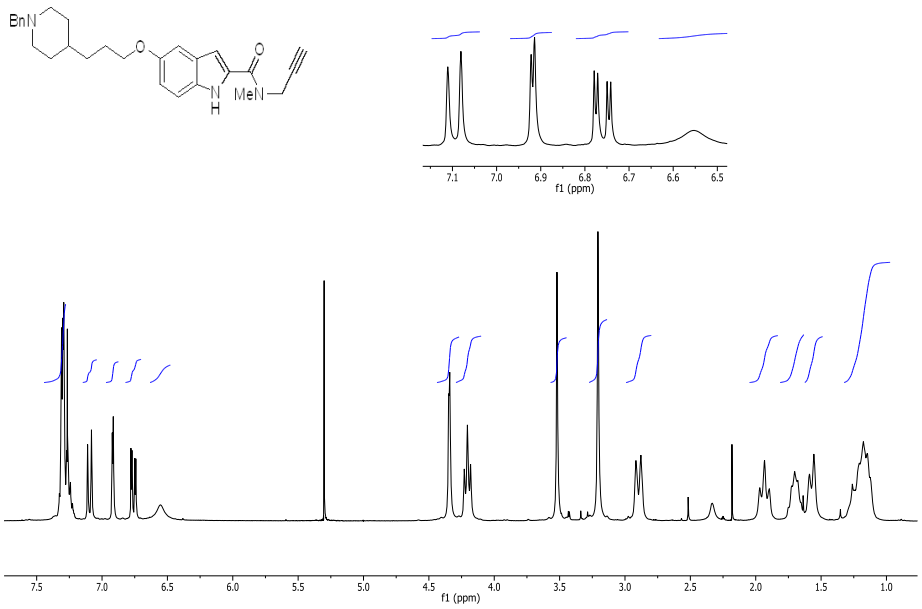


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **12.**



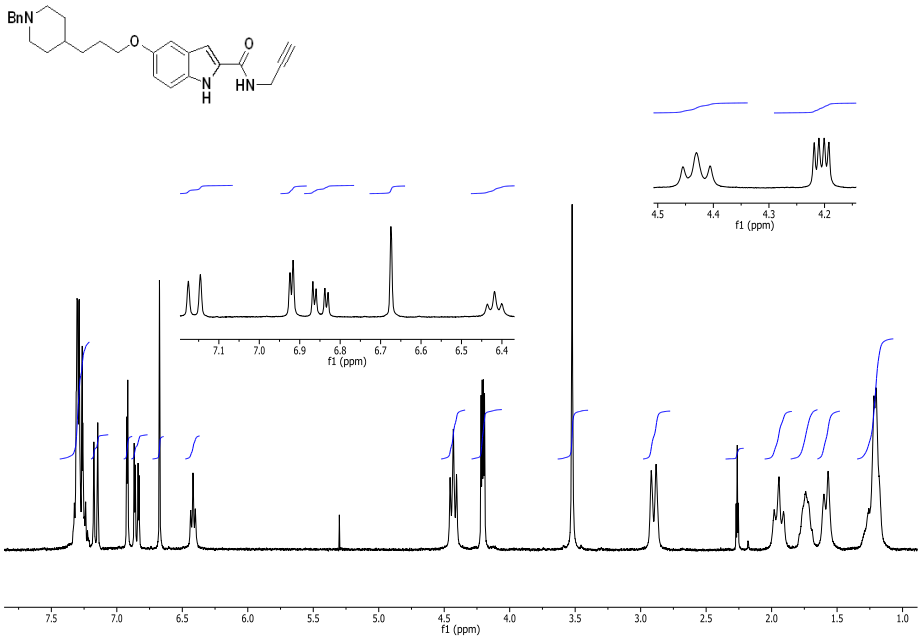
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **12.**

5-(3-(1-Benzylpiperidin-4-yl)propoxy)-*N*-methyl-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (MBA316).



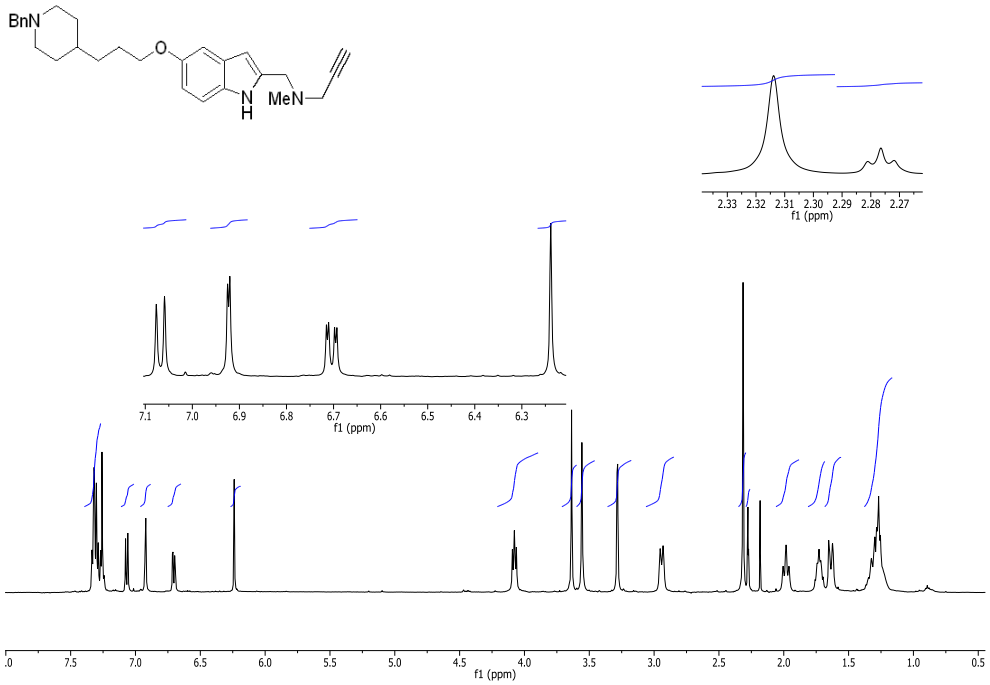
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA316.**

5-(3-(1-Benzylpiperidin-4-yl)propoxy)-*N*-(prop-2-yn-1-yl)-1*H*-indole-2-carboxamide (MBA315).

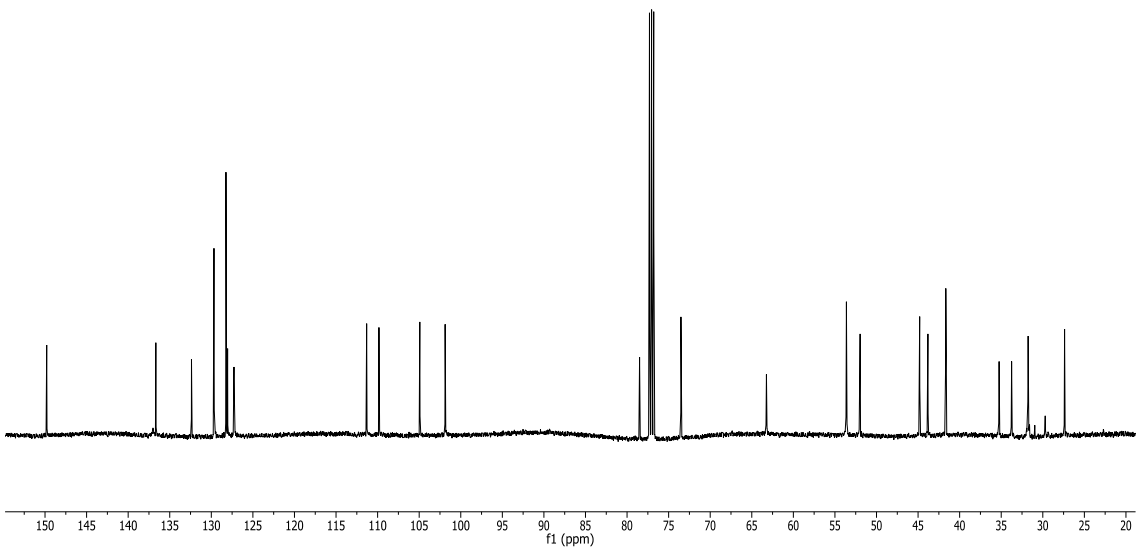


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA315.**

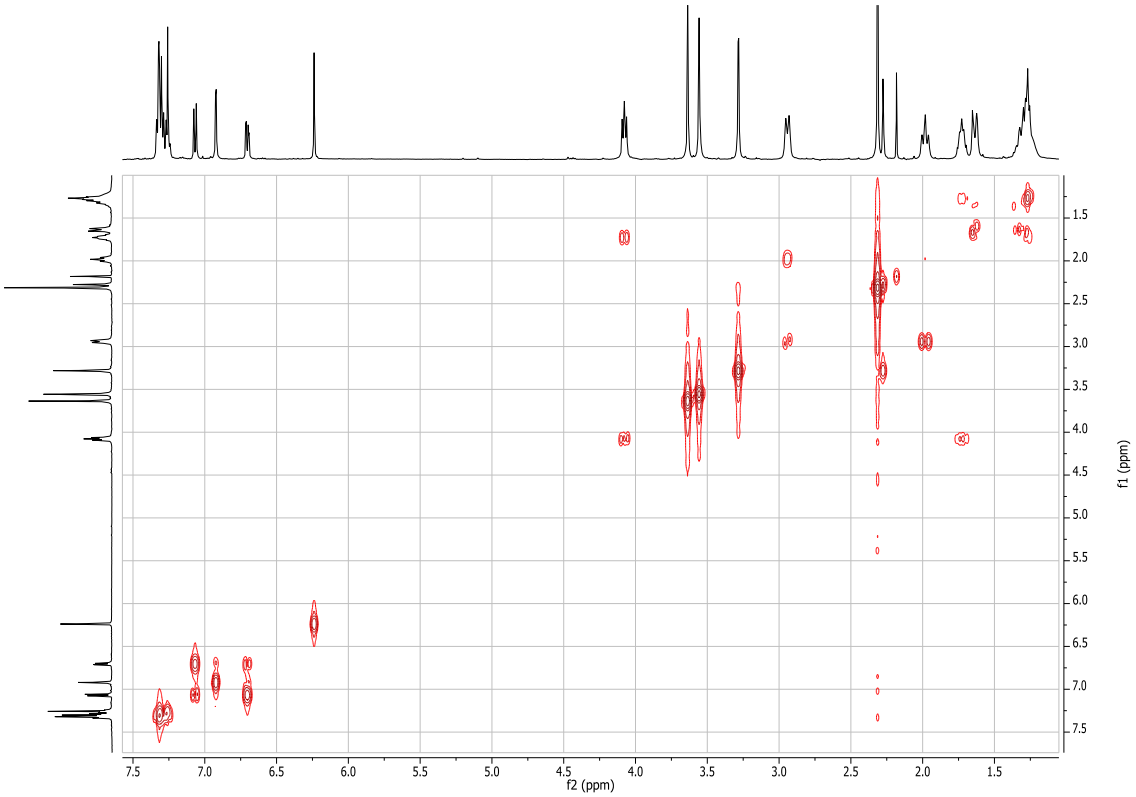
***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (6).**



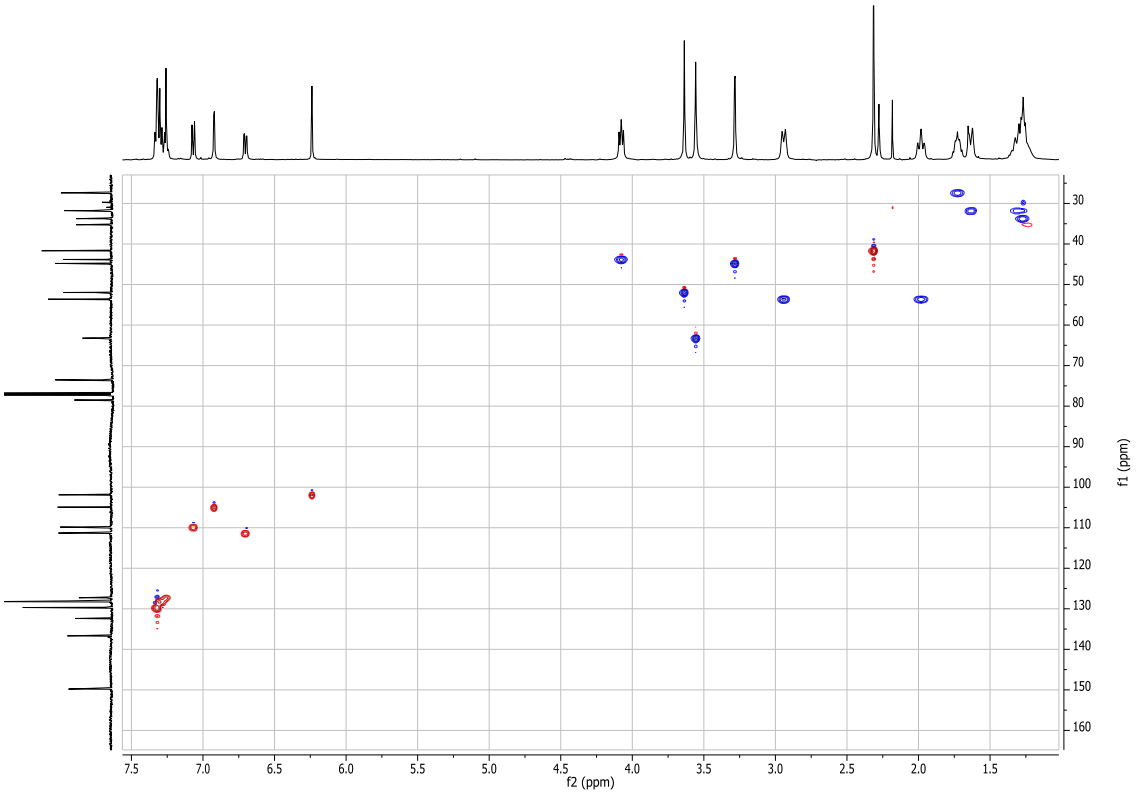
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **6.**



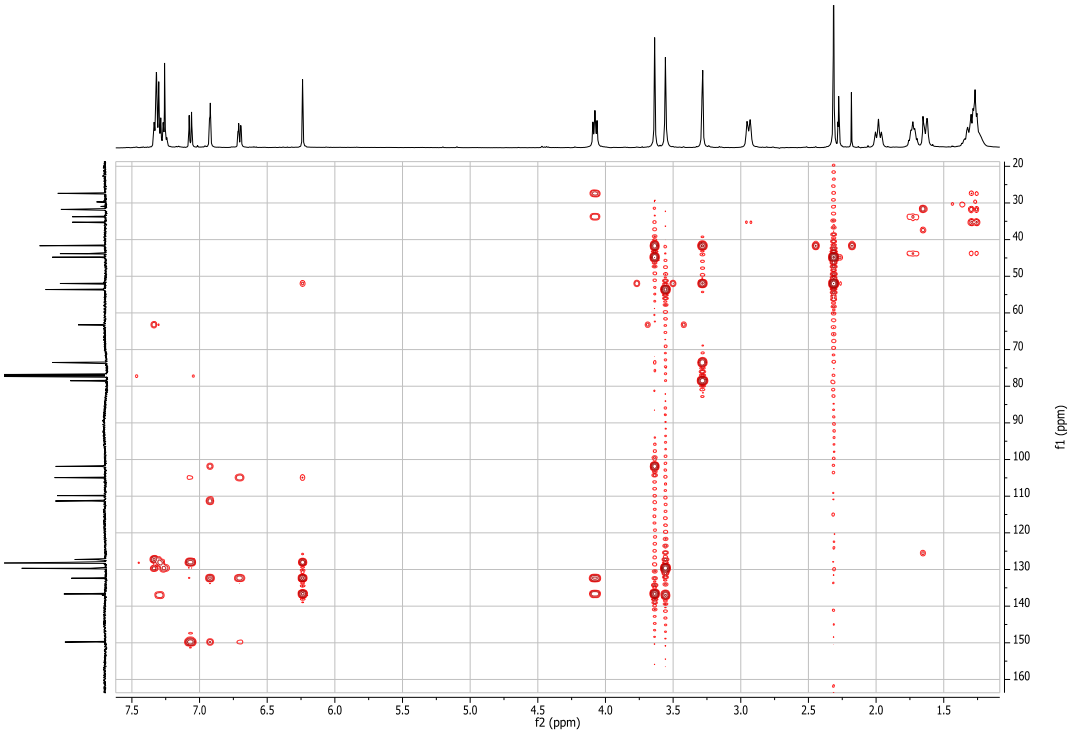
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **6.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **6.**

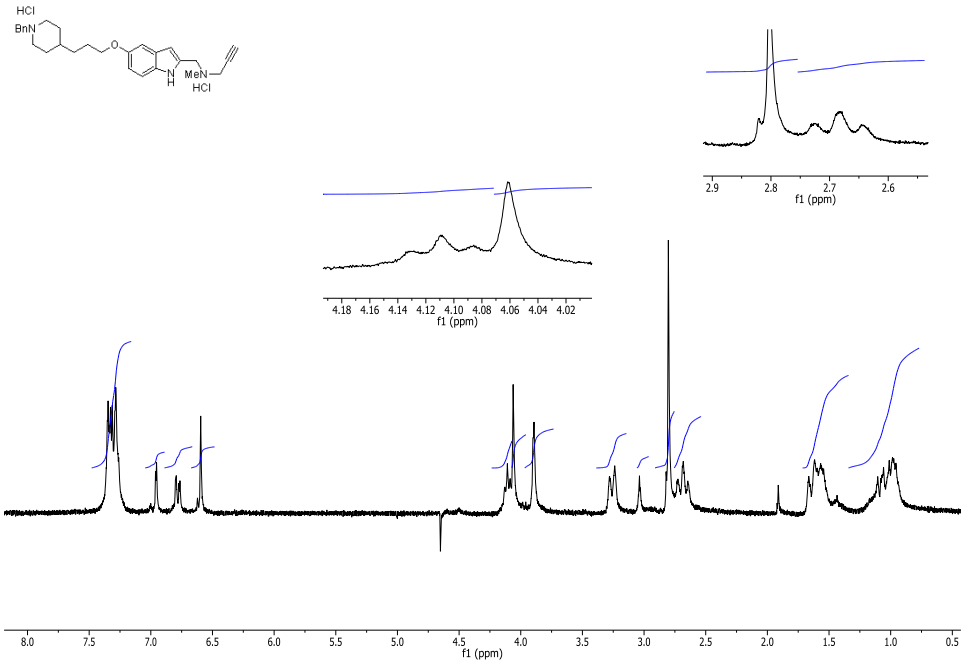


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **6.**



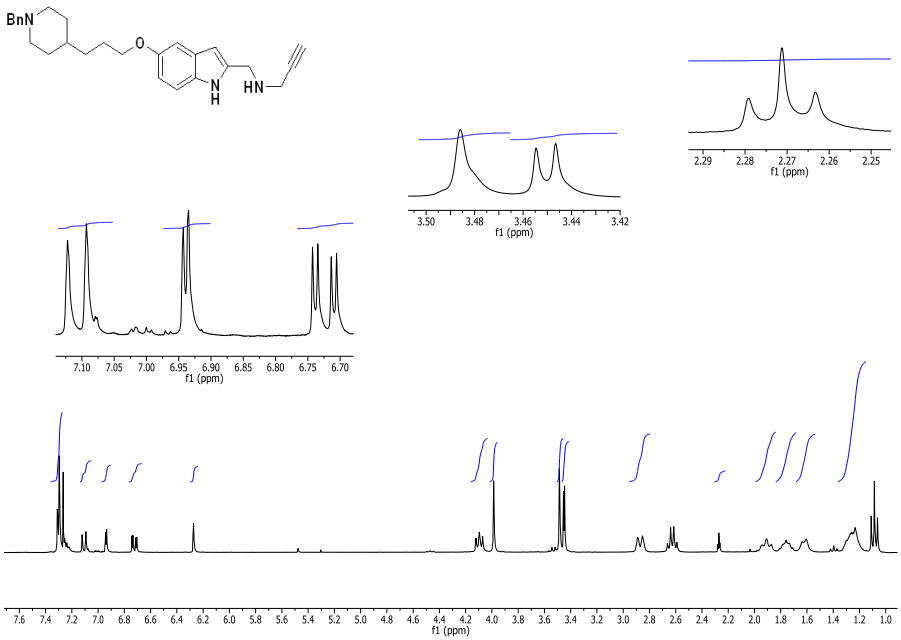
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **6.**

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)-*N*-methylprop-2-yn-1-amine (6.2HCl)**



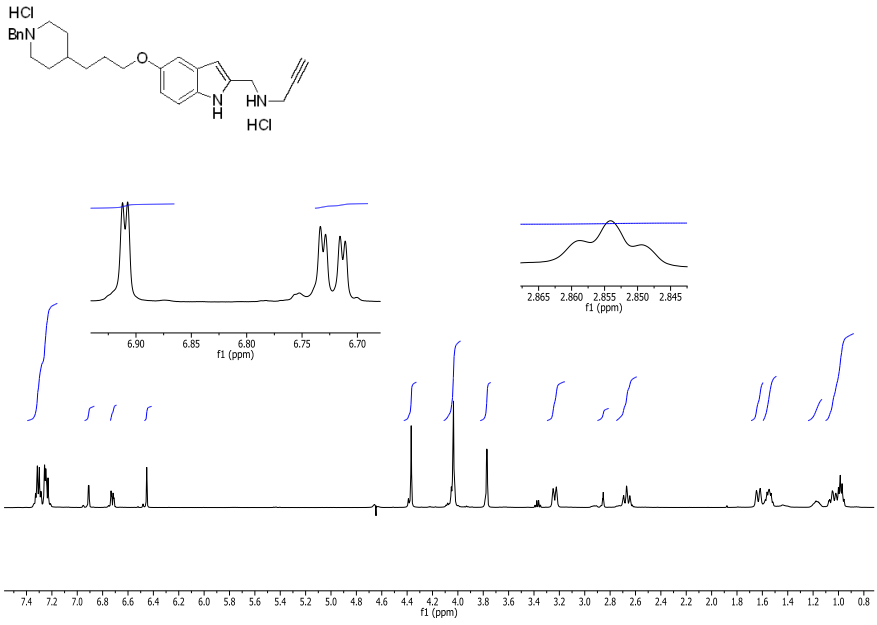
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **6.2HCl.**

_N_-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1_H_-indol-2-yl)methyl)prop-2-yn-1-amine (7).

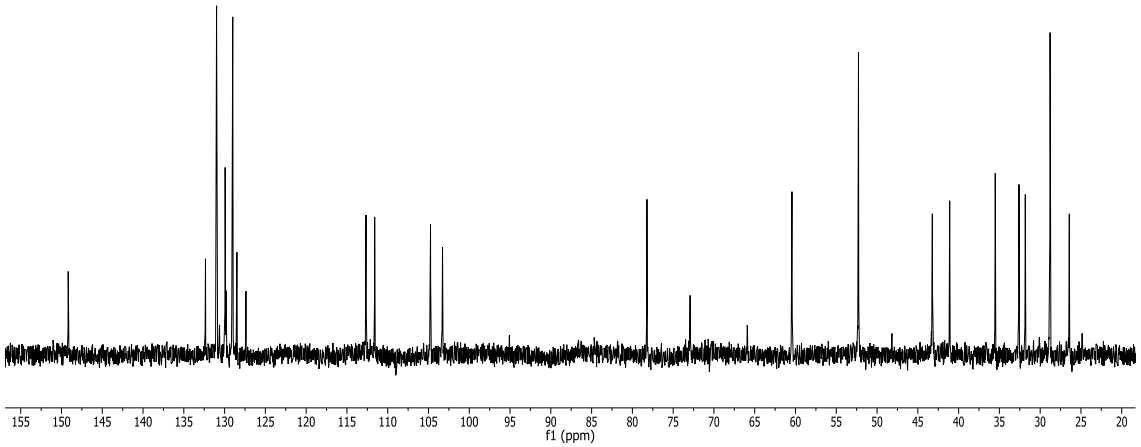


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **7.**

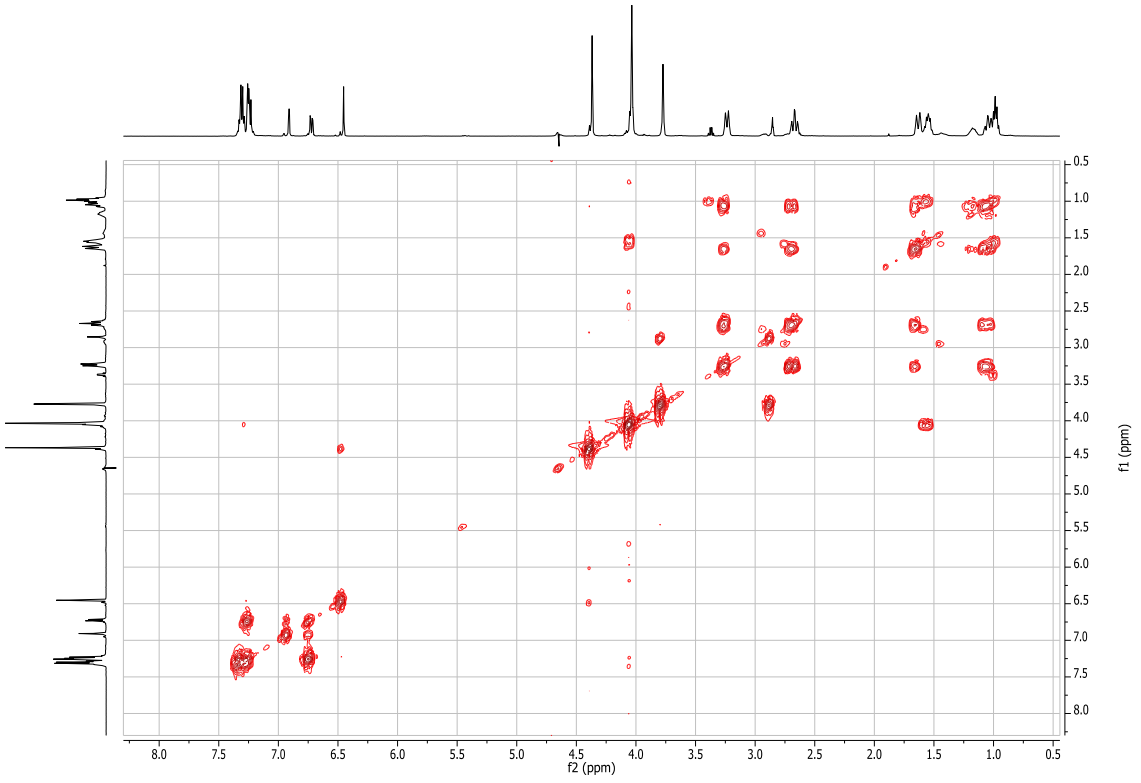
_N_-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1_H_-indol-2-yl)methyl)prop-2-yn-1-amine (7.2HCl).



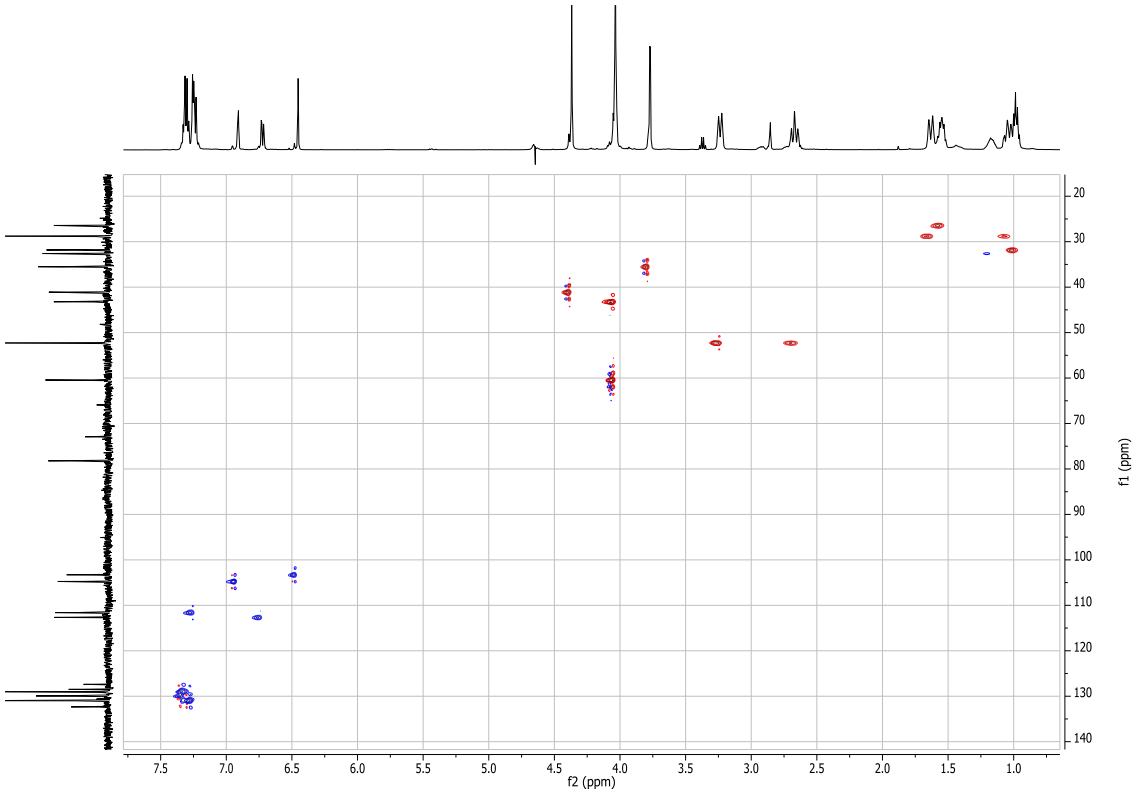
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **7.2HCl.**



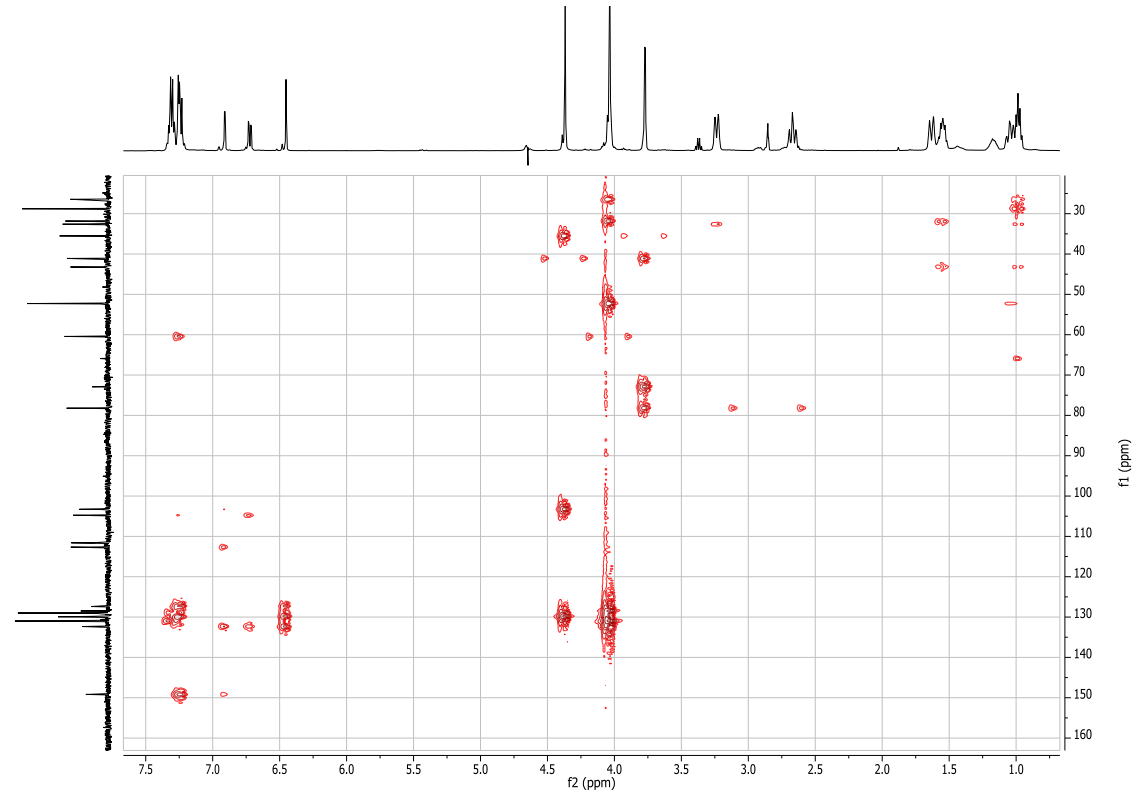
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **7.2HCl.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **7.2HCl.**

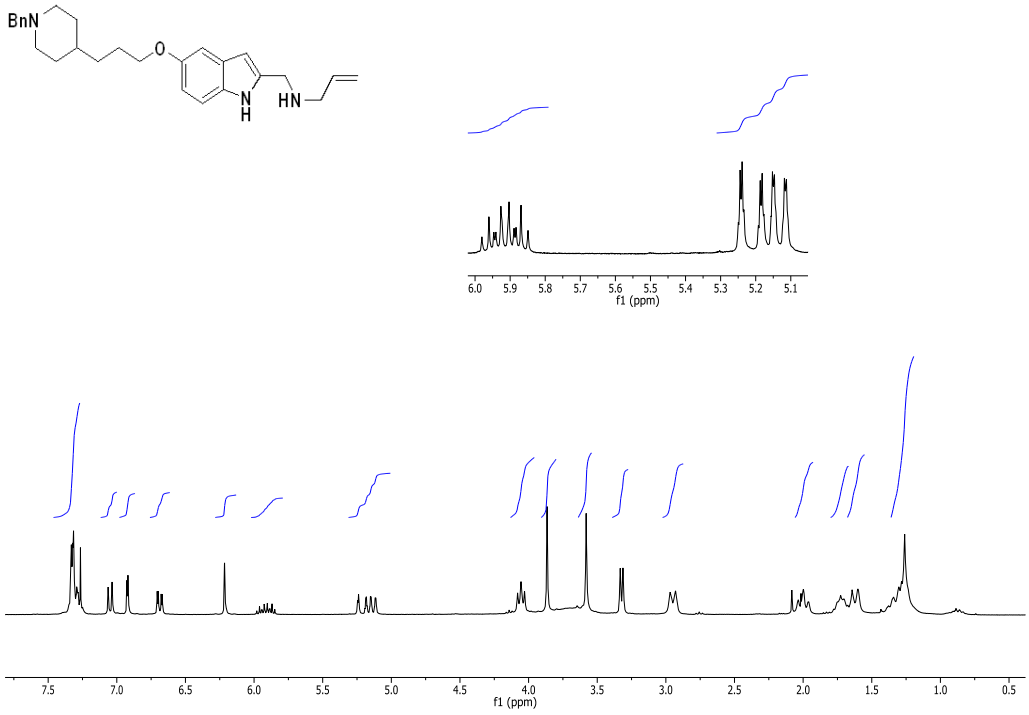


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **7.2HCl.**

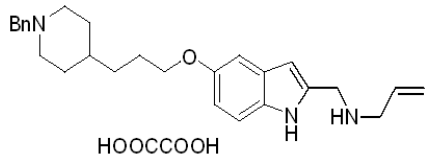


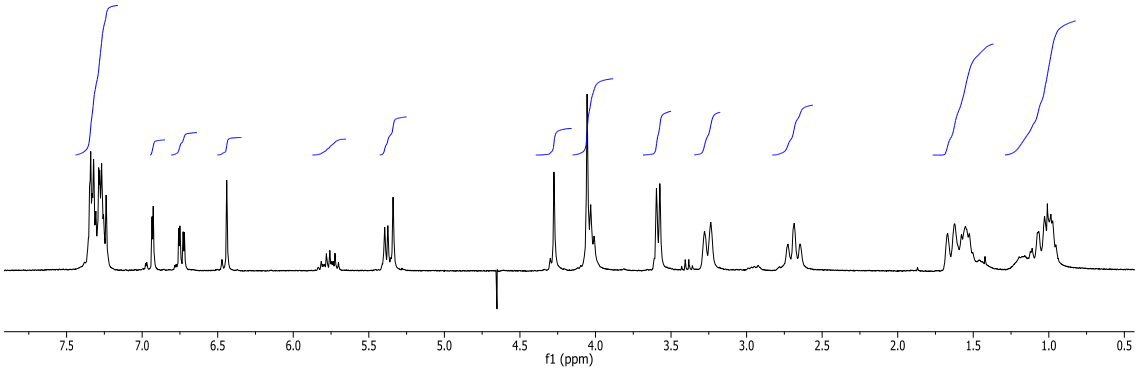
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **7.2HCl.**

***N*-((5-(3-(1-Benzylpiperidin-4-yl)propoxy)-1*H*-indol-2-yl)methyl)prop-2-en-1-amine (8)**.

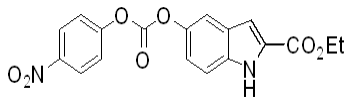


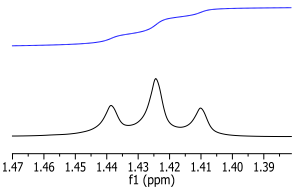
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **8.**

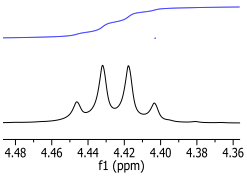


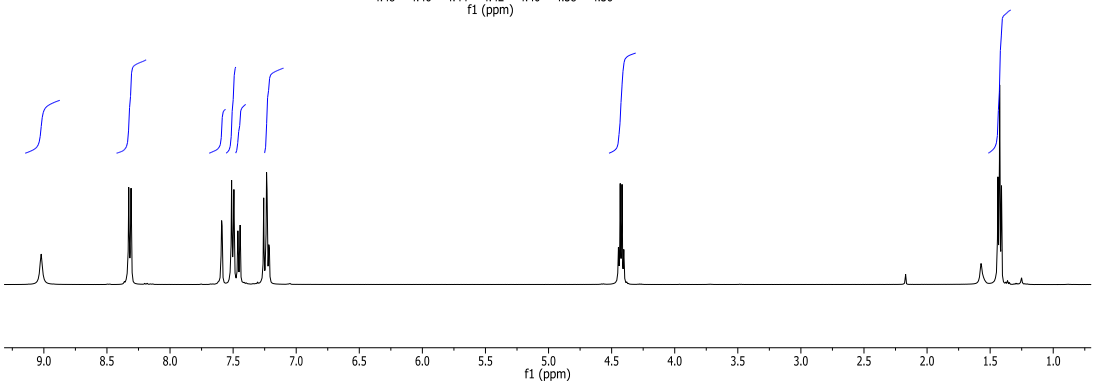


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **8.Oxal.**

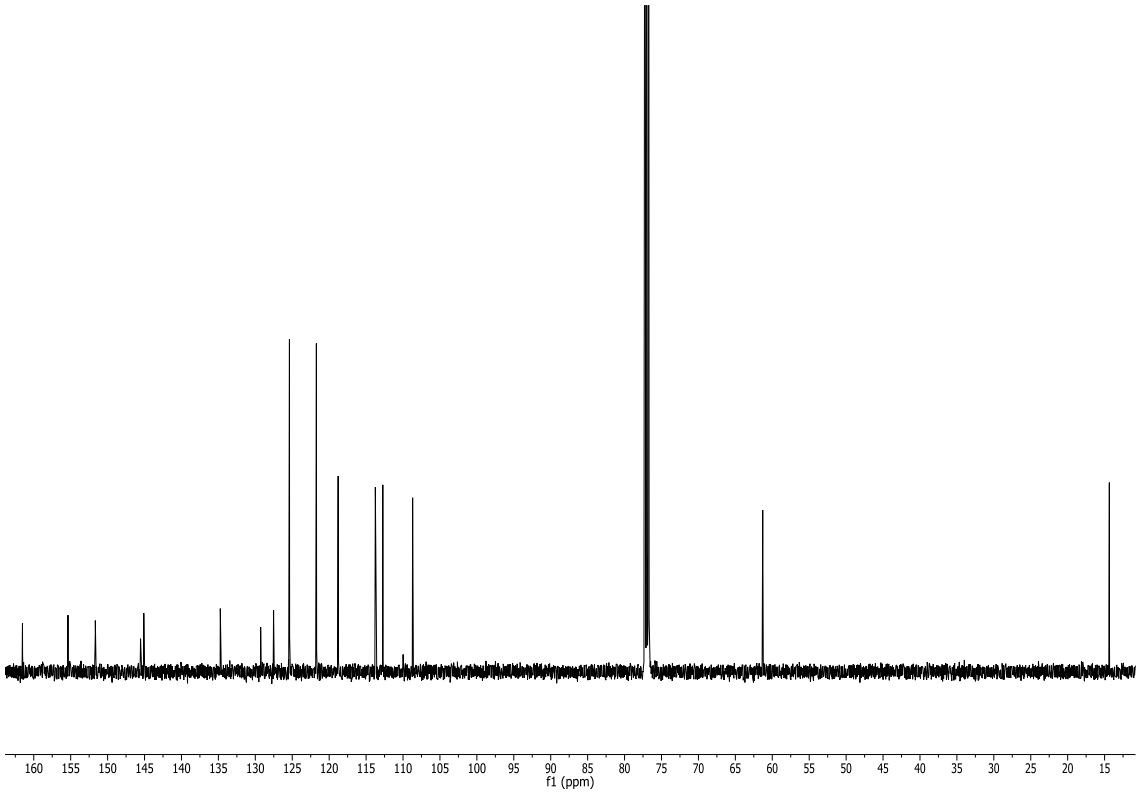




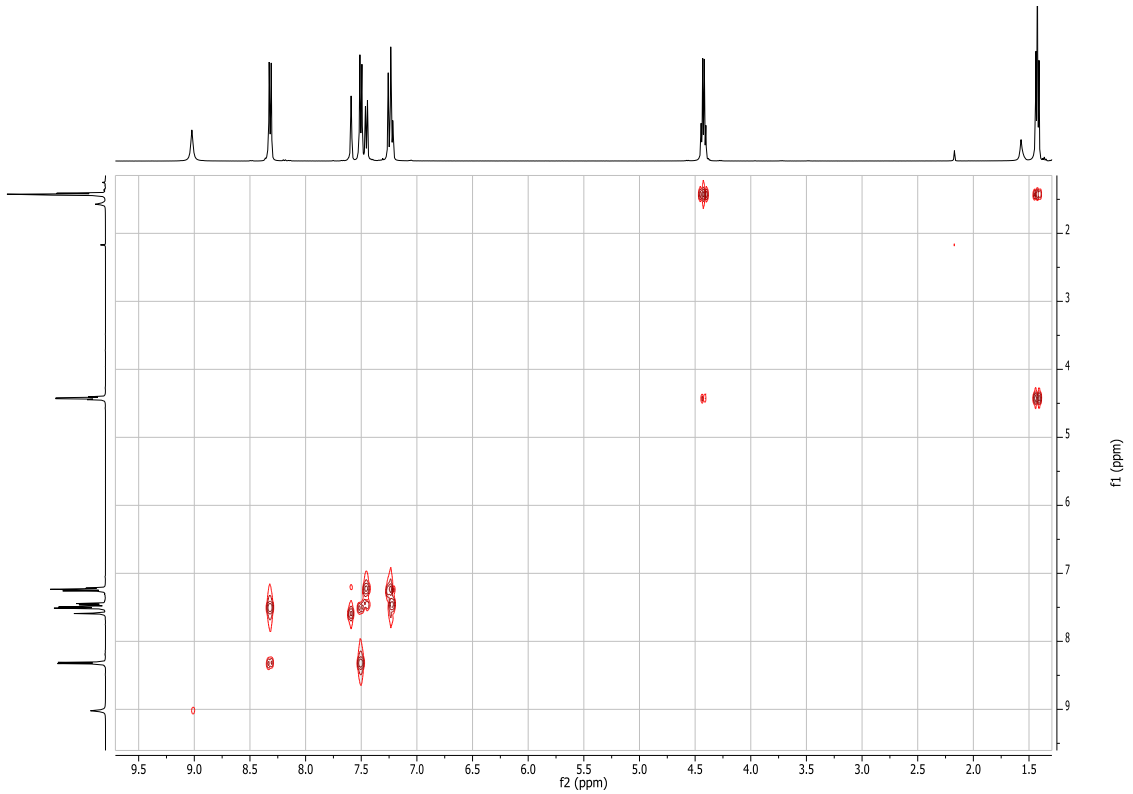




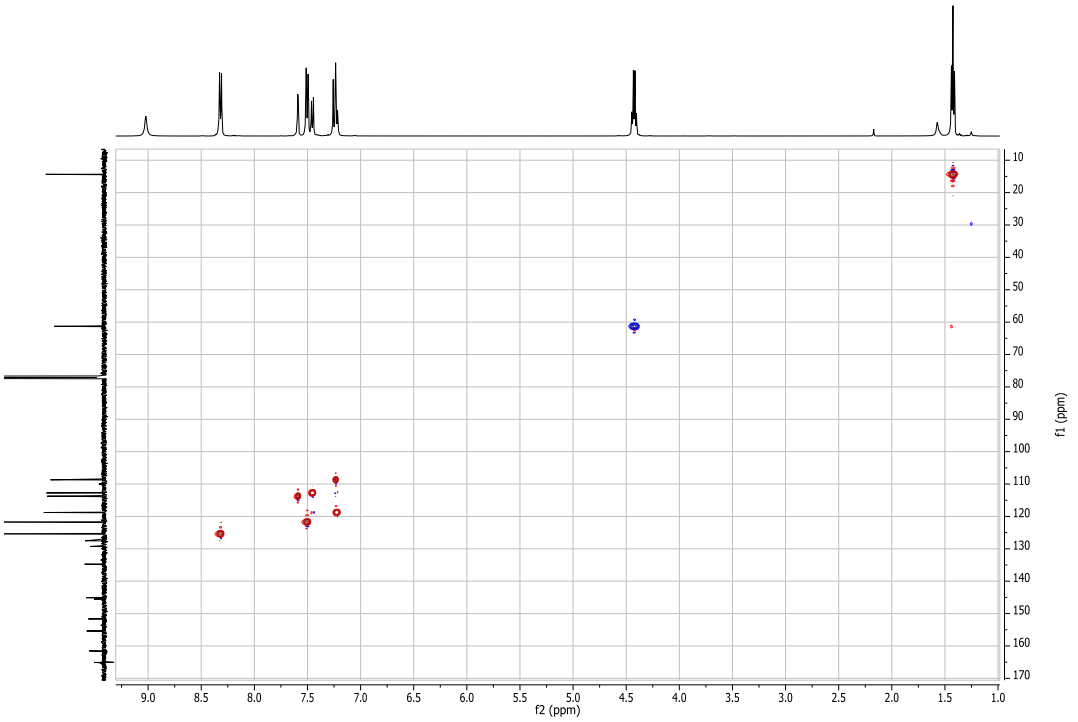
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **MBA329.**



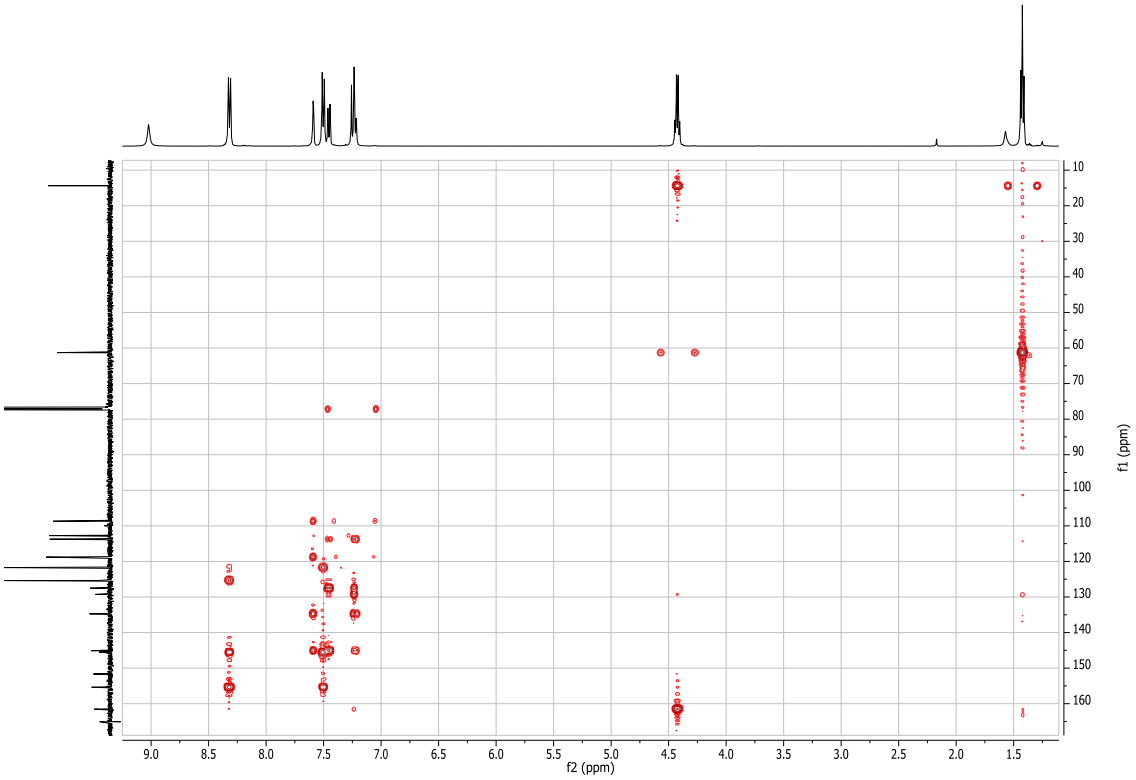
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **MBA329.**



^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **MBA329.**

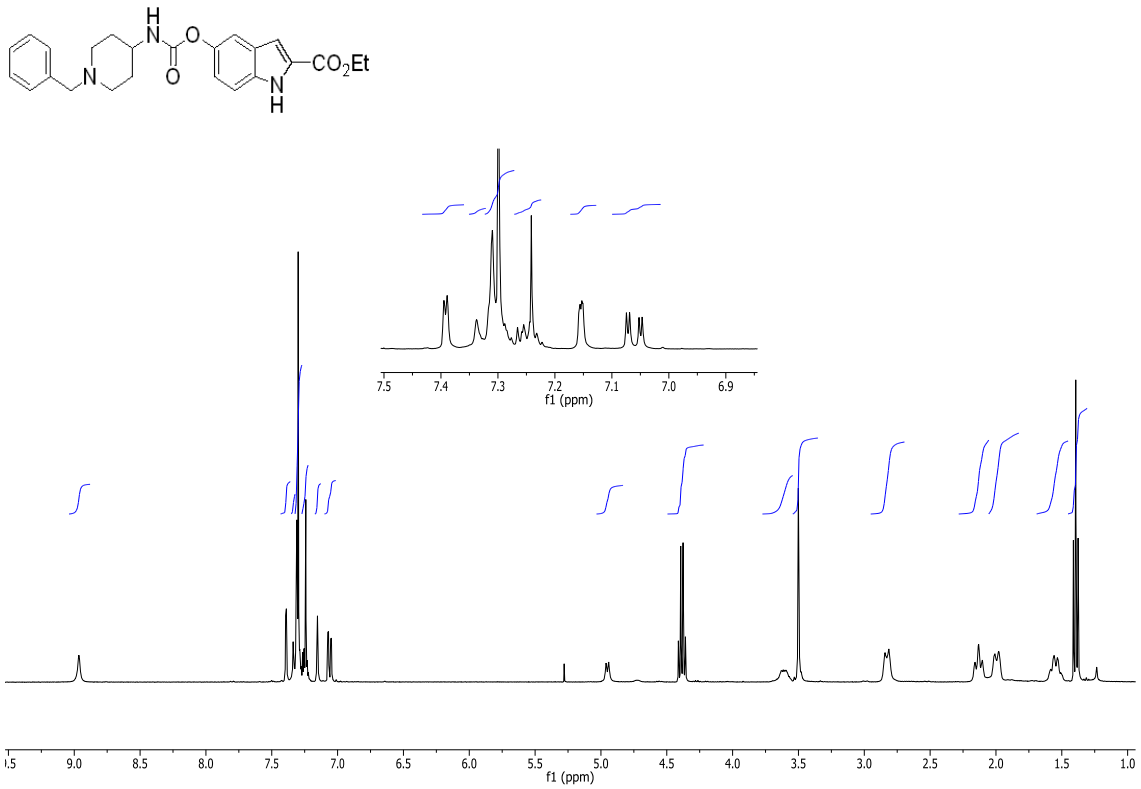


^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **MBA329.**

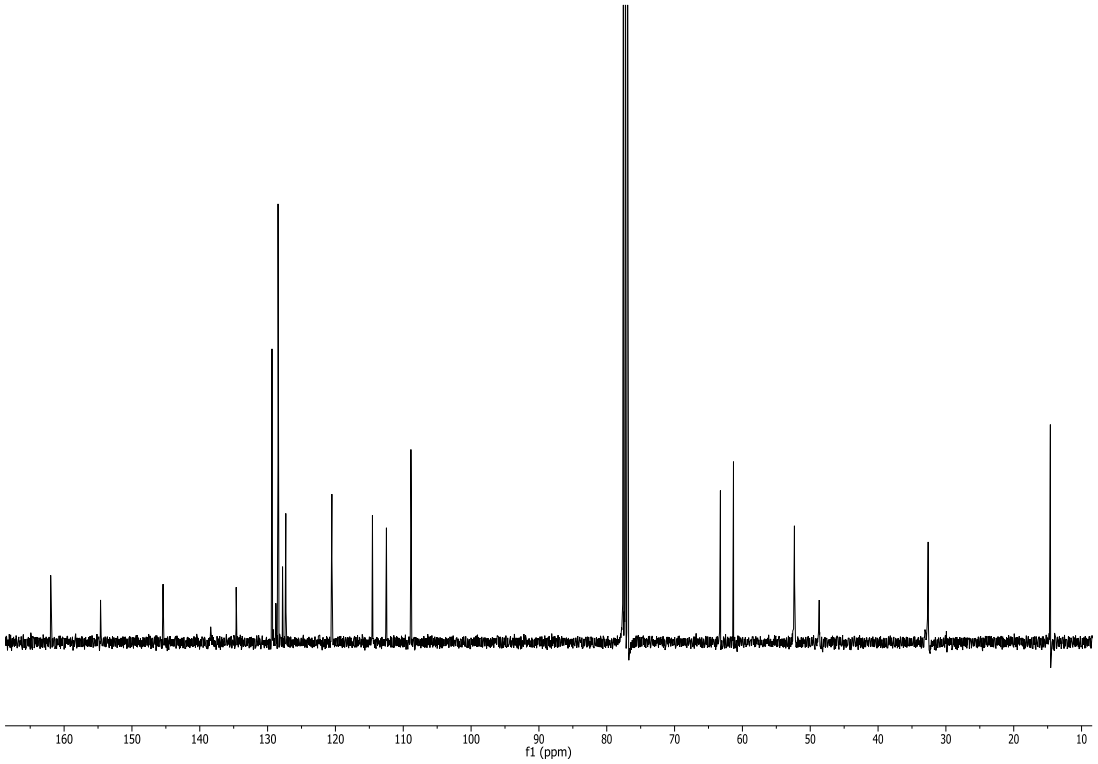


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **MBA329.**

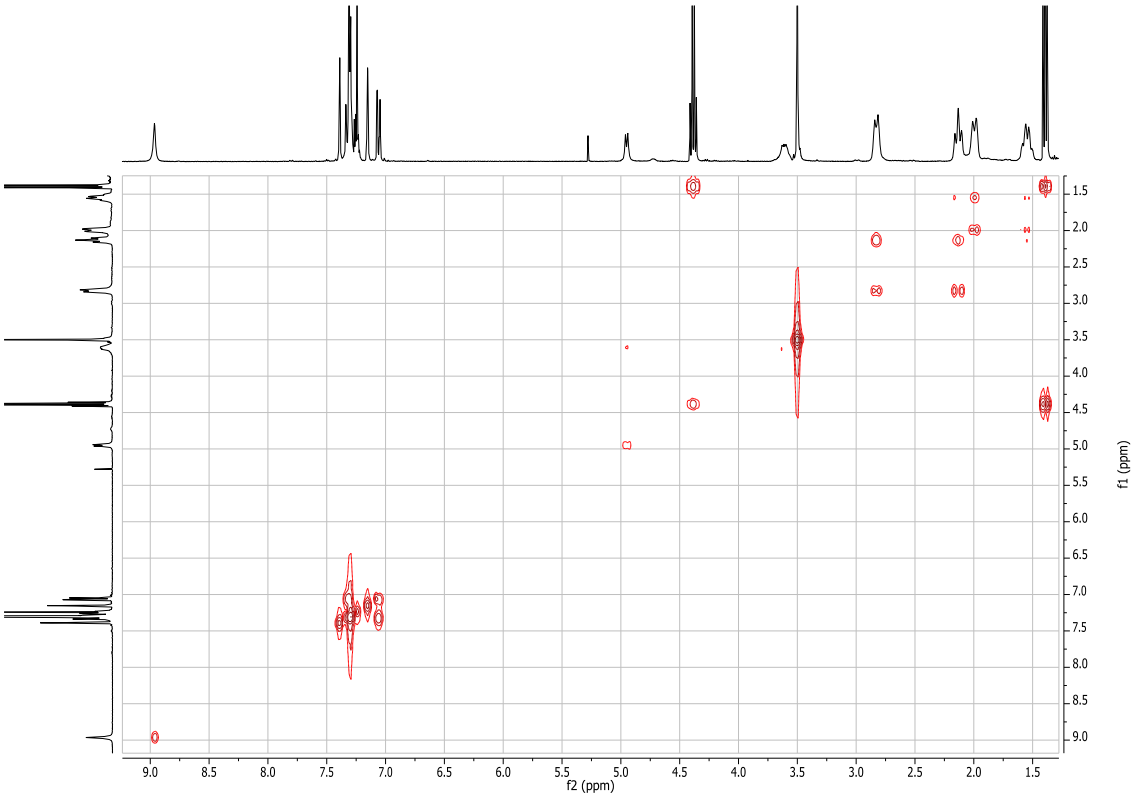
Ethyl 5-(((1-benzylpiperidin-4-yl)carbamoyl)oxy)-1*H*-indole-2-carboxylate (18).



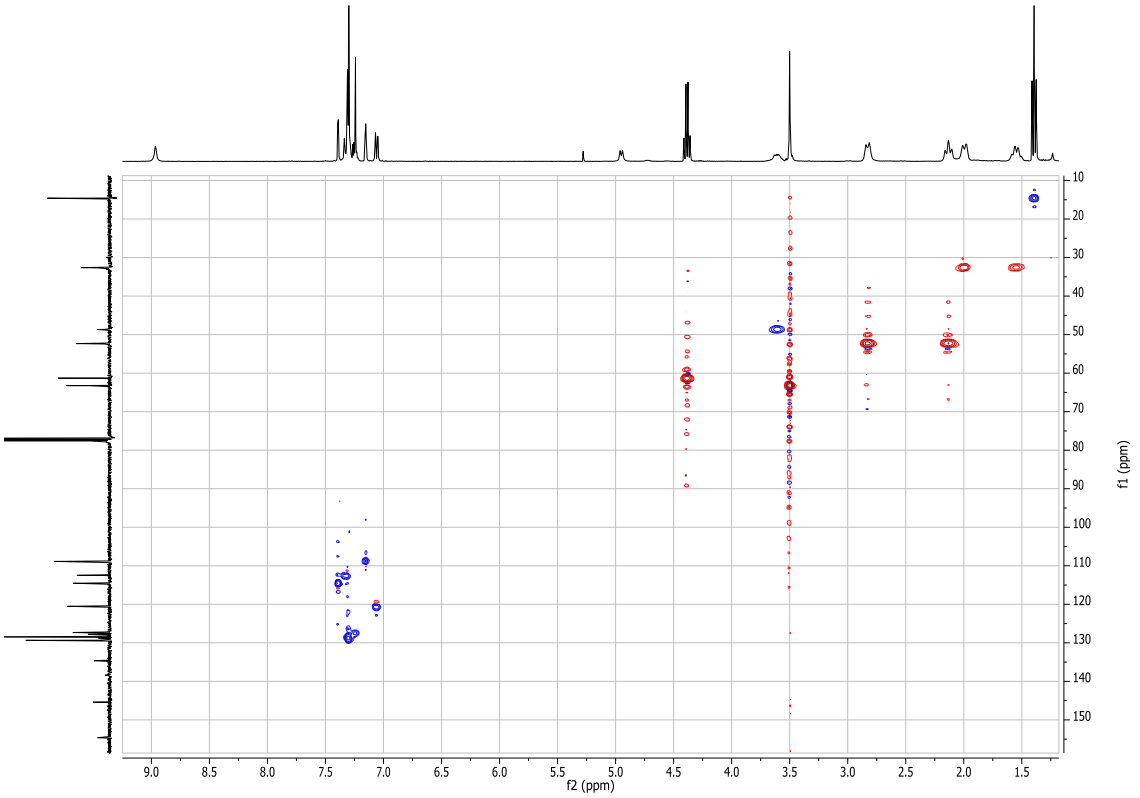
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **18.**



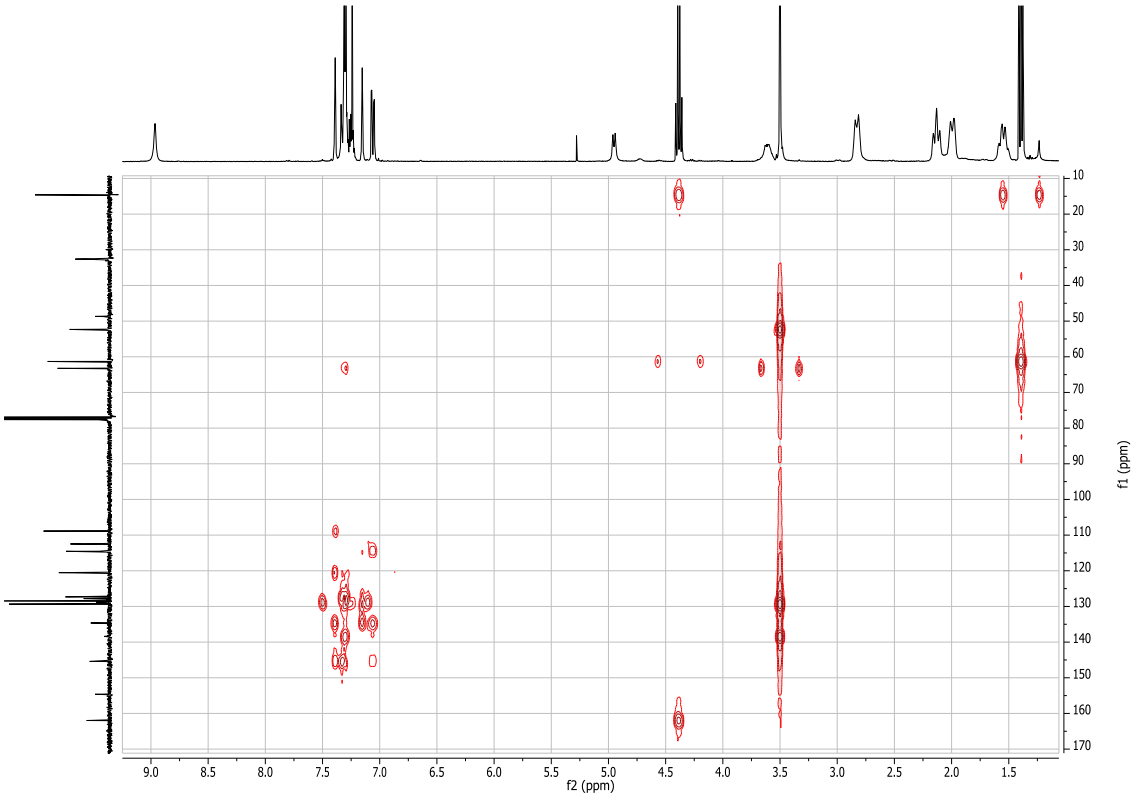
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **18.**



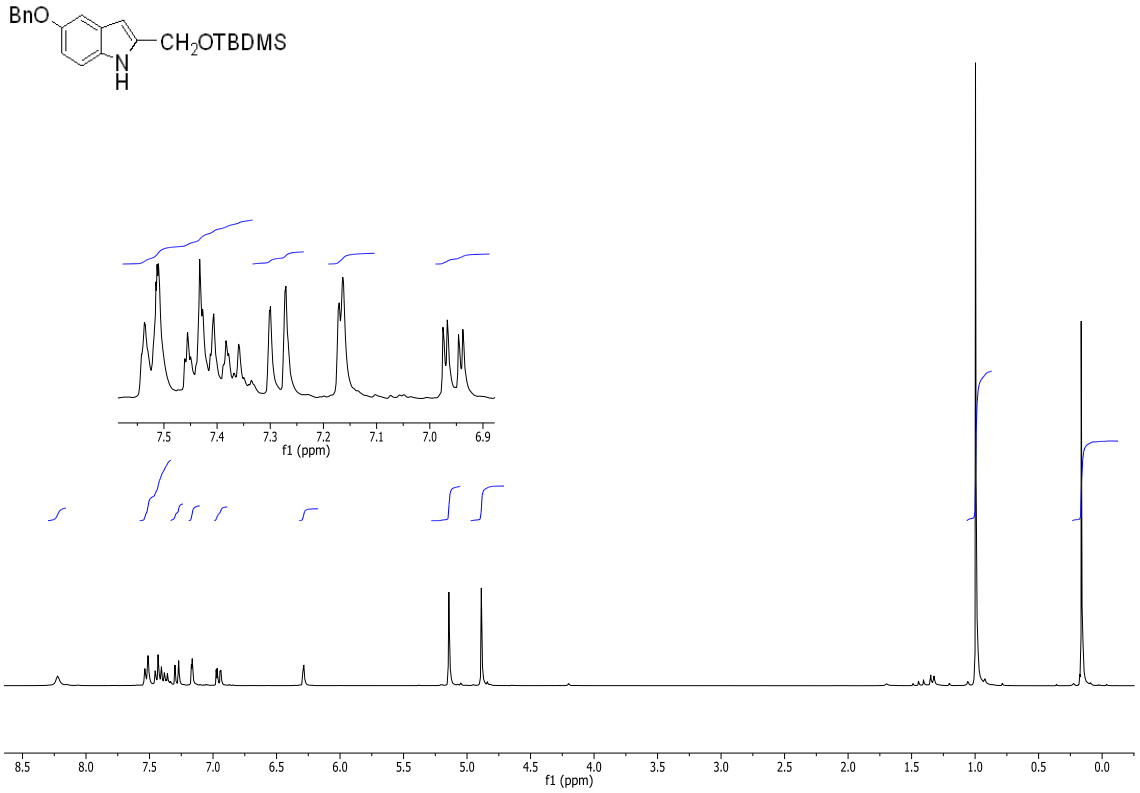
^{1}H-^{1}H *g*-COSY (400 MHz, $CDCl_3$) spectrum of compound **18.**



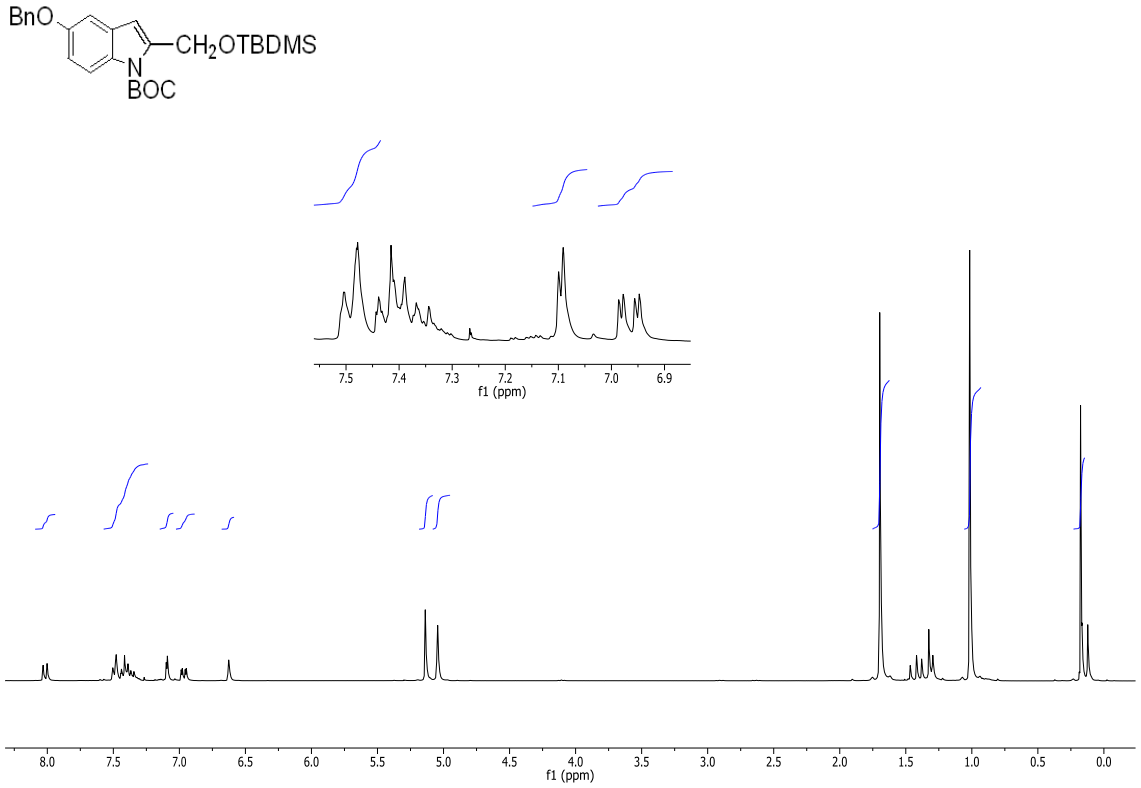
^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **18.**



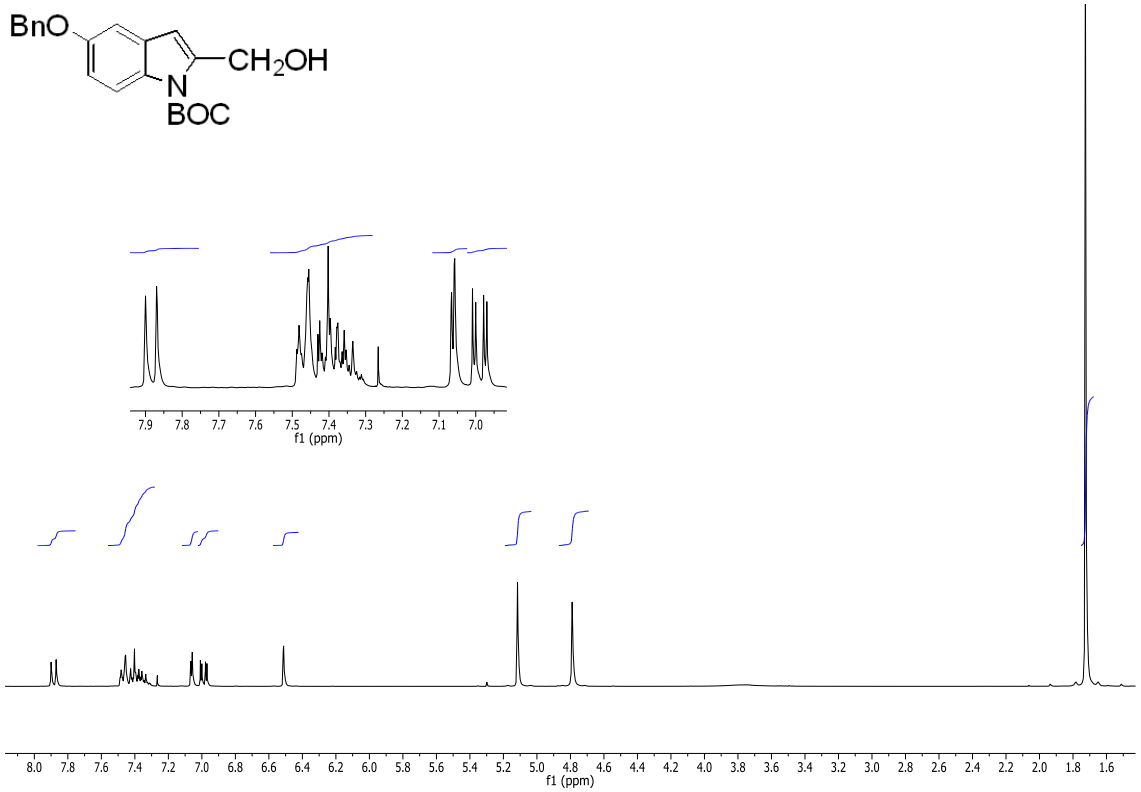
^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **18.**



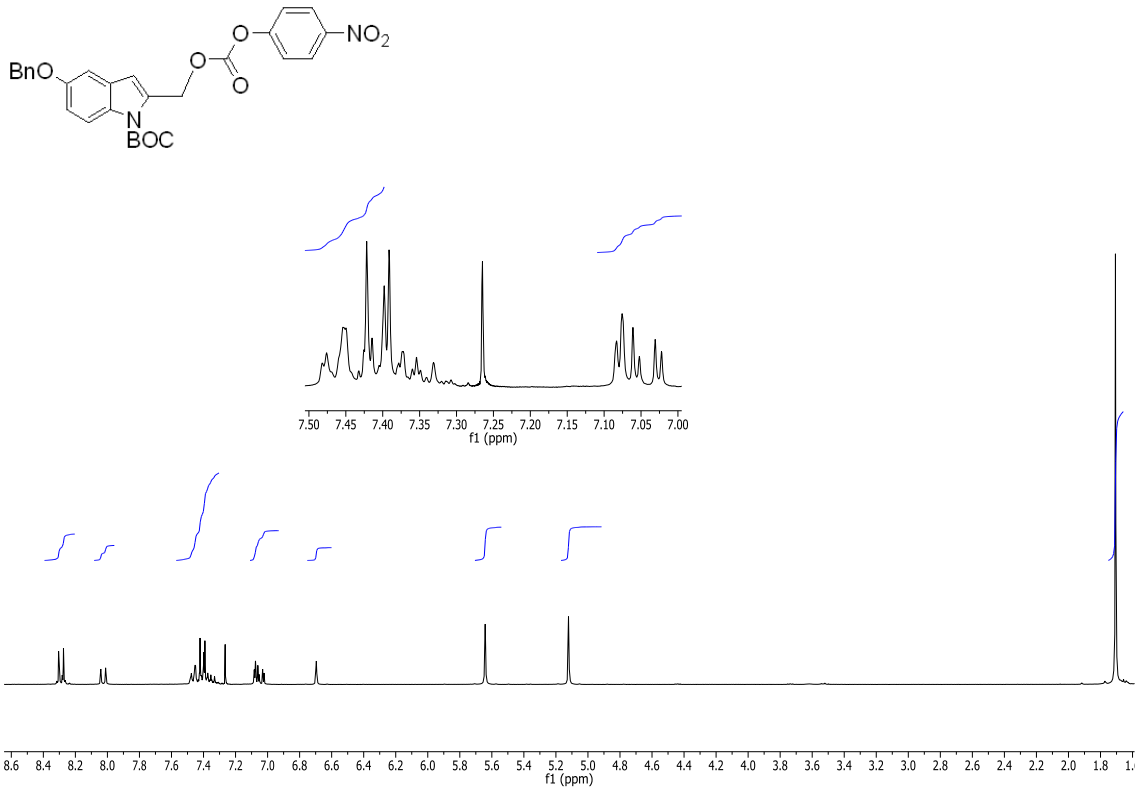
^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA334.**



^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA335.**

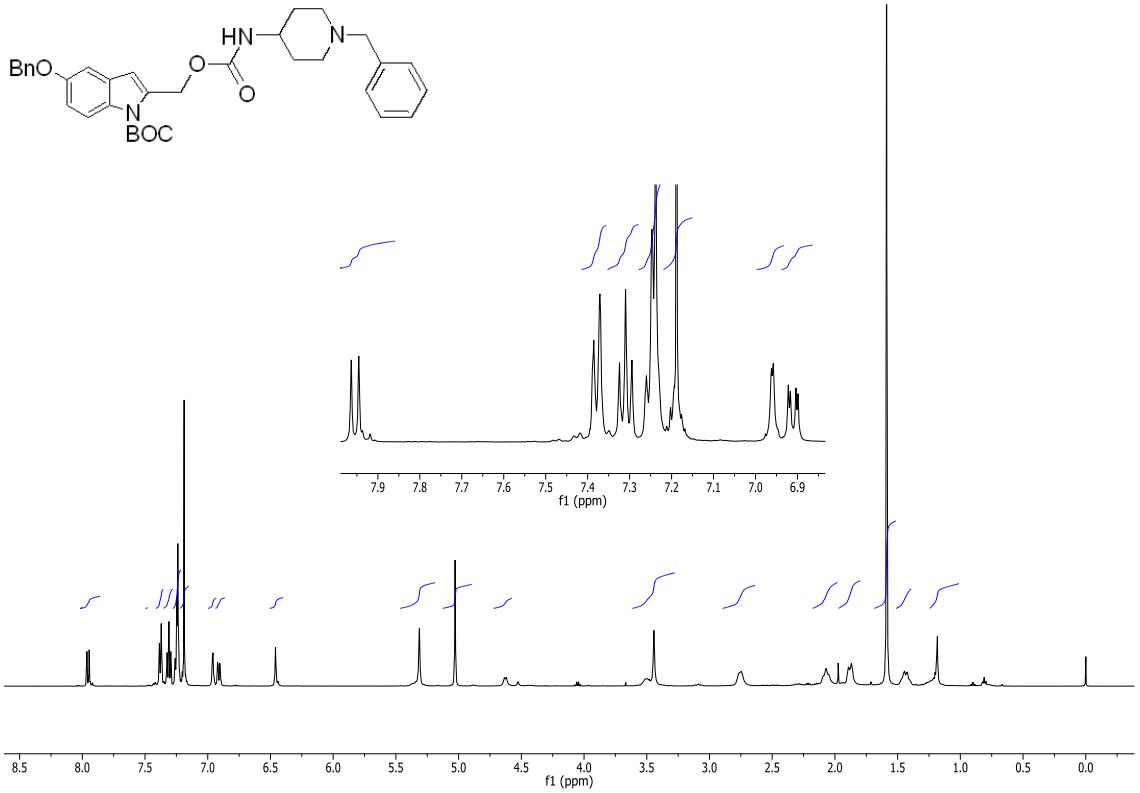


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA336.**

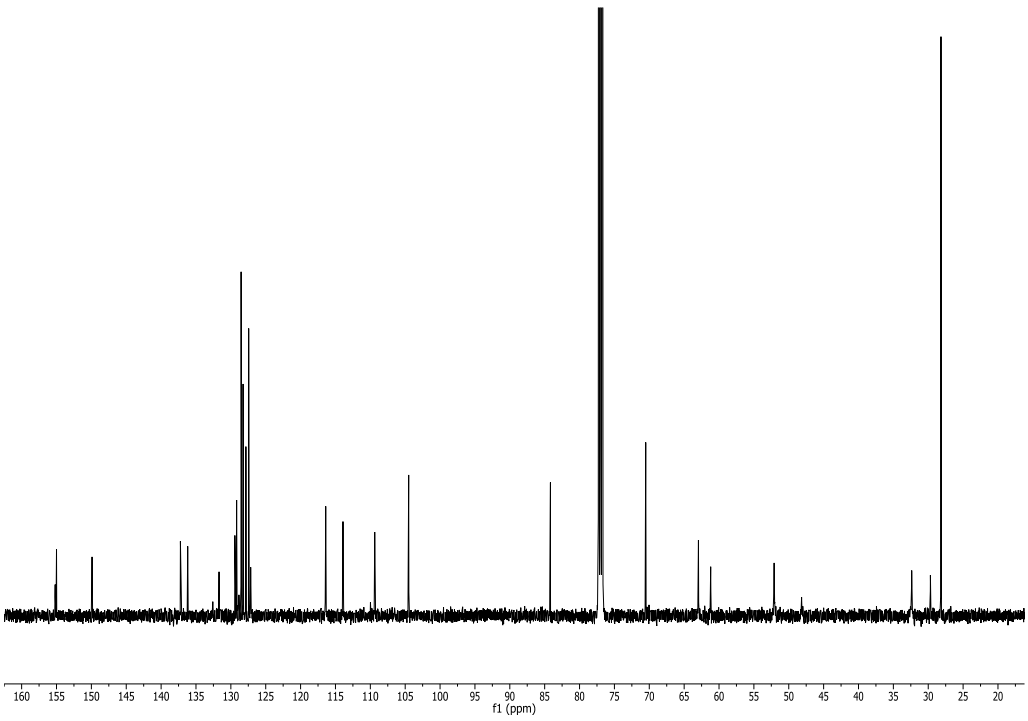


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **MBA337.**

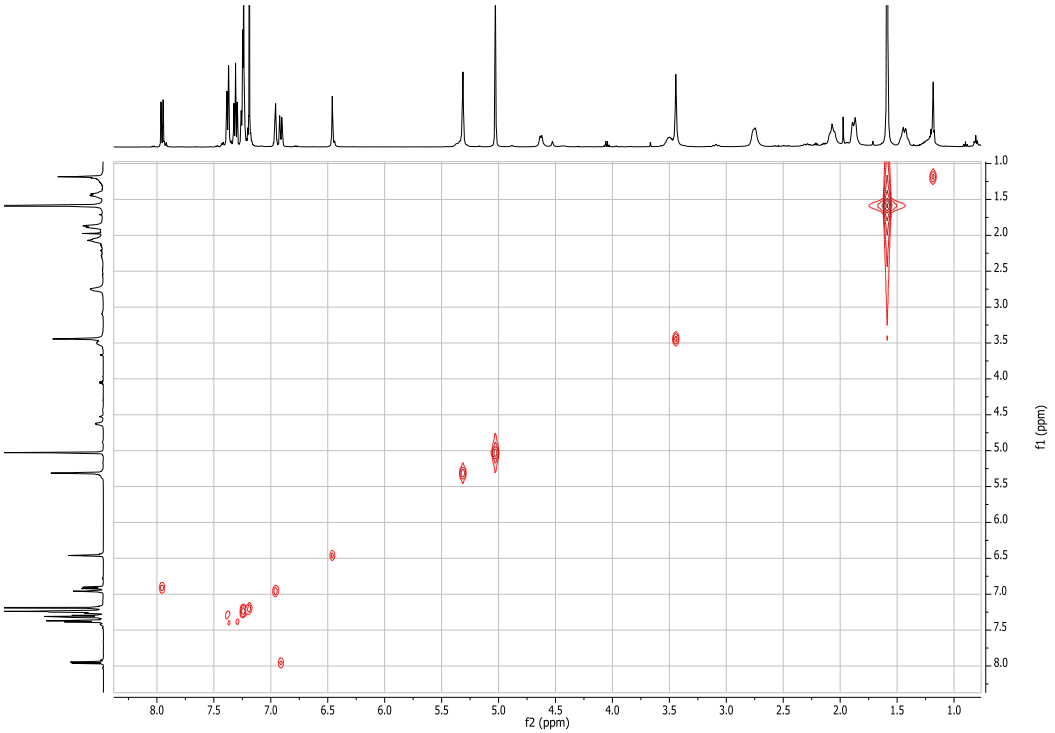
***tert*-Butyl 5-(benzyloxy)-2-((((1-benzylpiperidin-4-yl)carbamoyl)oxy)methyl)-1*H*-indole-1-carboxylate (19)**.



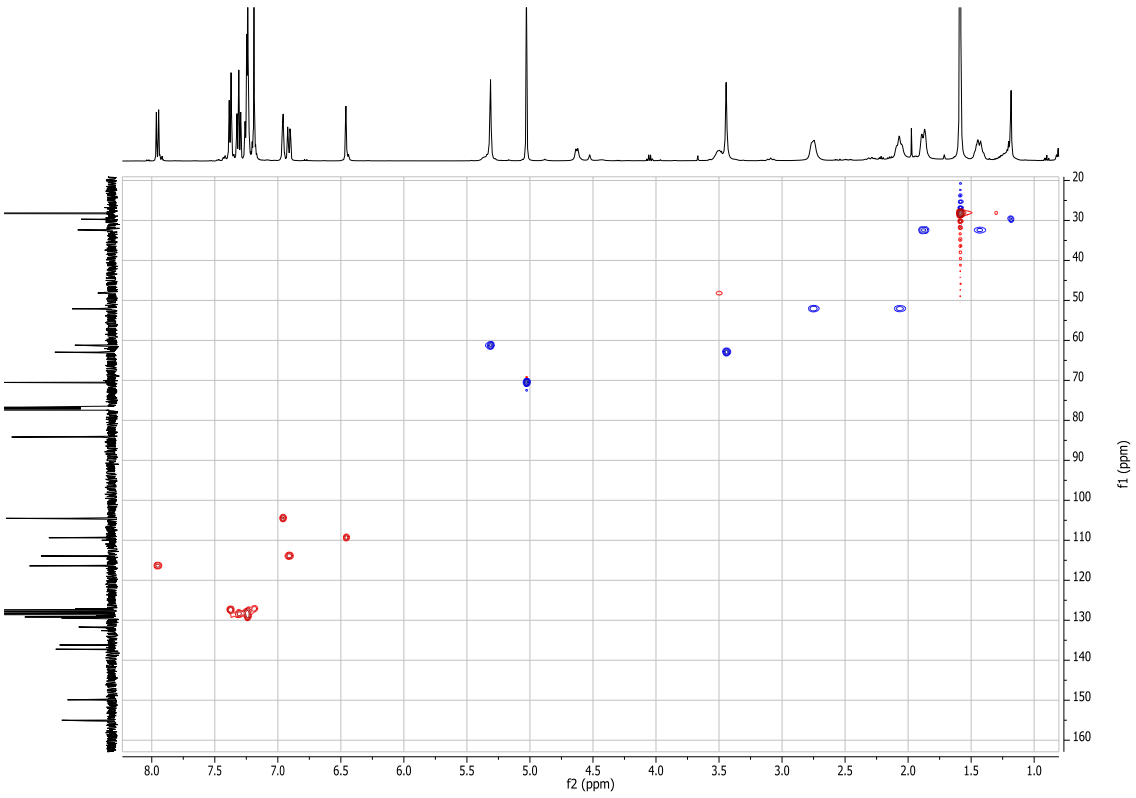
^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of compound **19.**



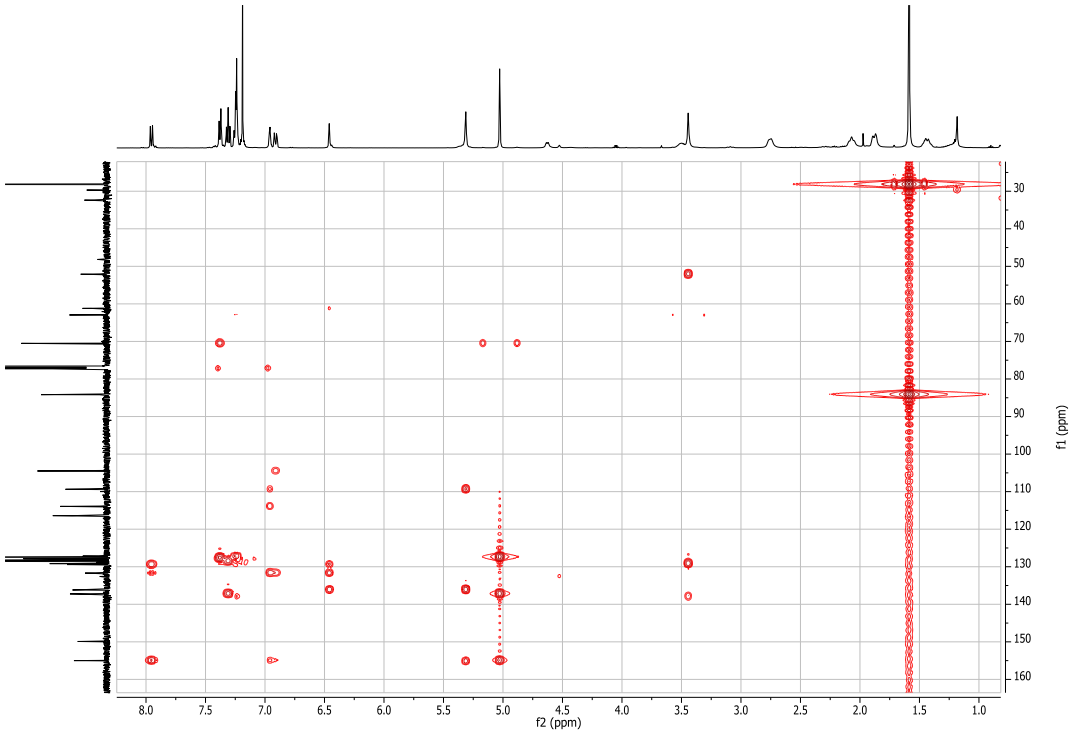
^{13}C NMR (126 MHz, $CDCl_3$) Spectrum of compound **19.**



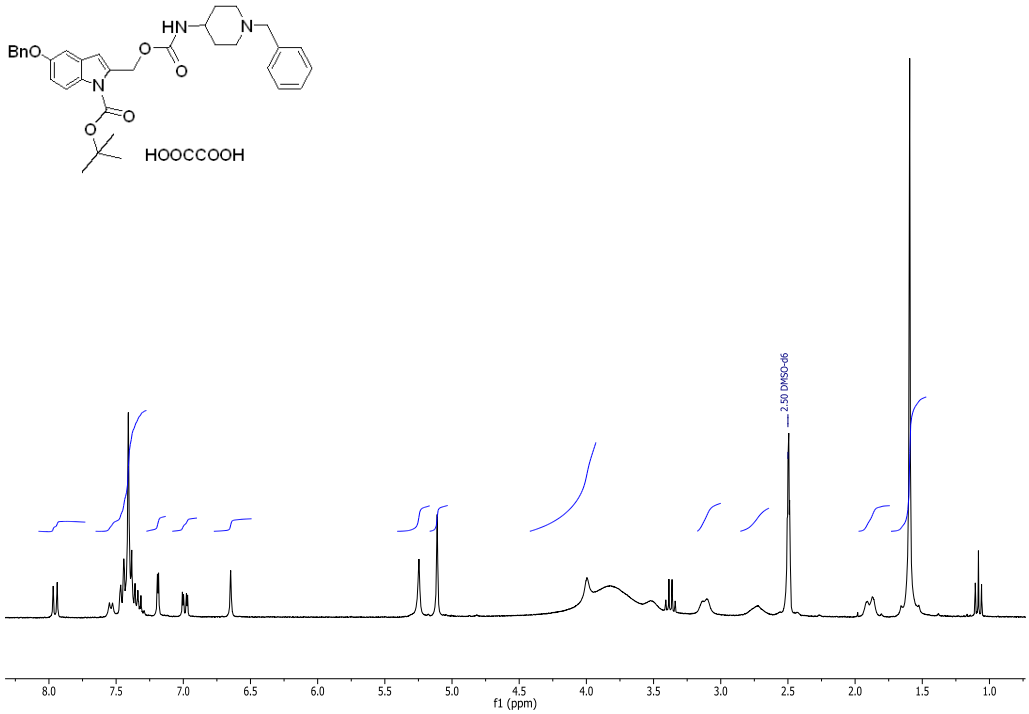
^{1}H-^{1}H *g*-COSY (500 MHz, $CDCl_3$) spectrum of compound **19.**



^{1}H-^{13}C *g*-HSQC ($CDCl_3$) spectrum of compound **19.**

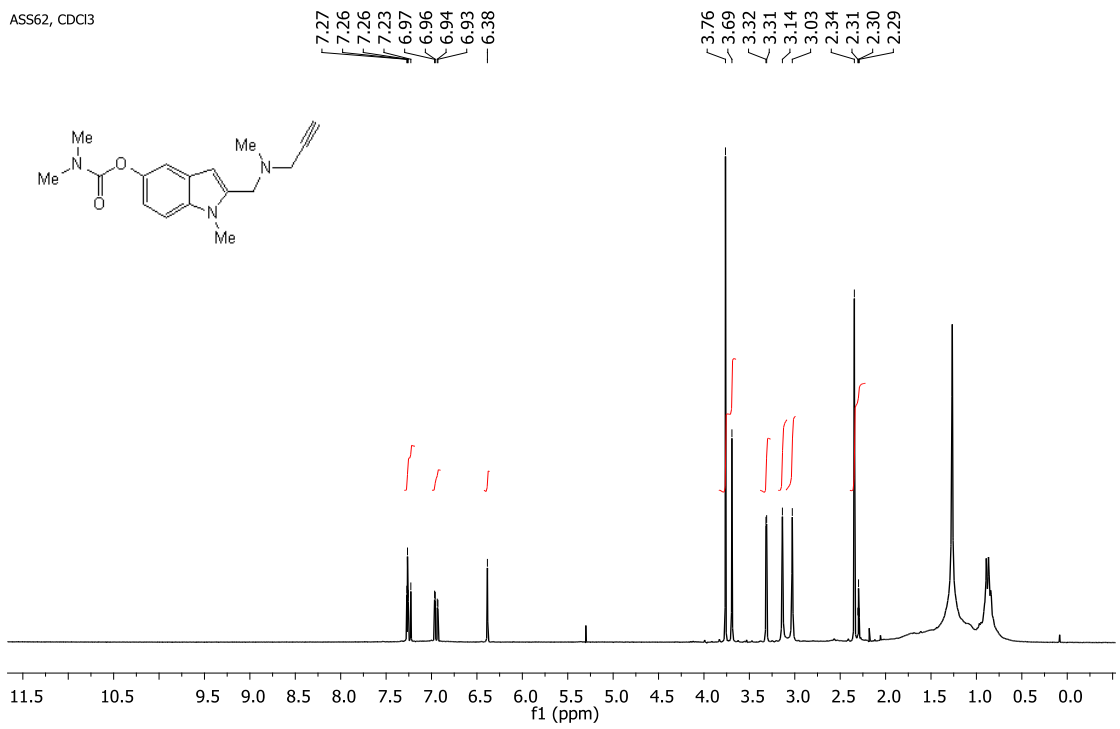


^{1}H-^{13}C *g*-HMBC ($CDCl_3$) spectrum of compound **19.**

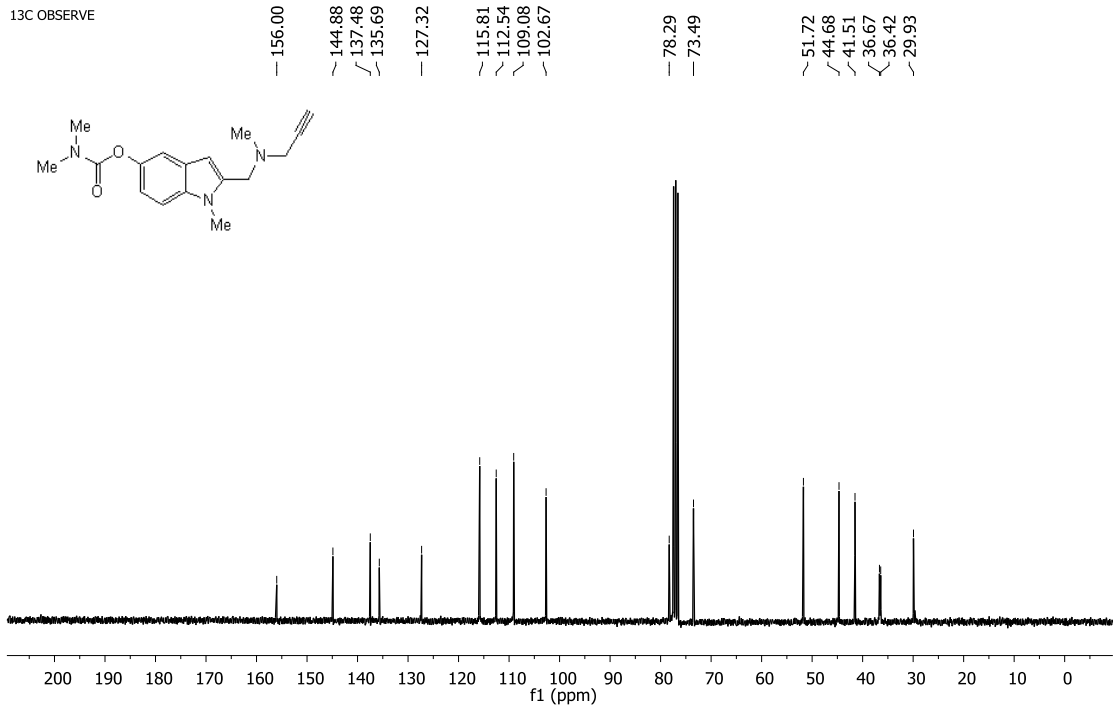


^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **19-Oxal.**

1-Methyl-2-((methyl(prop-2-yn-1-yl)amino)methyl)-1*H*-indol-5-yl dimethylcarbamate (17)

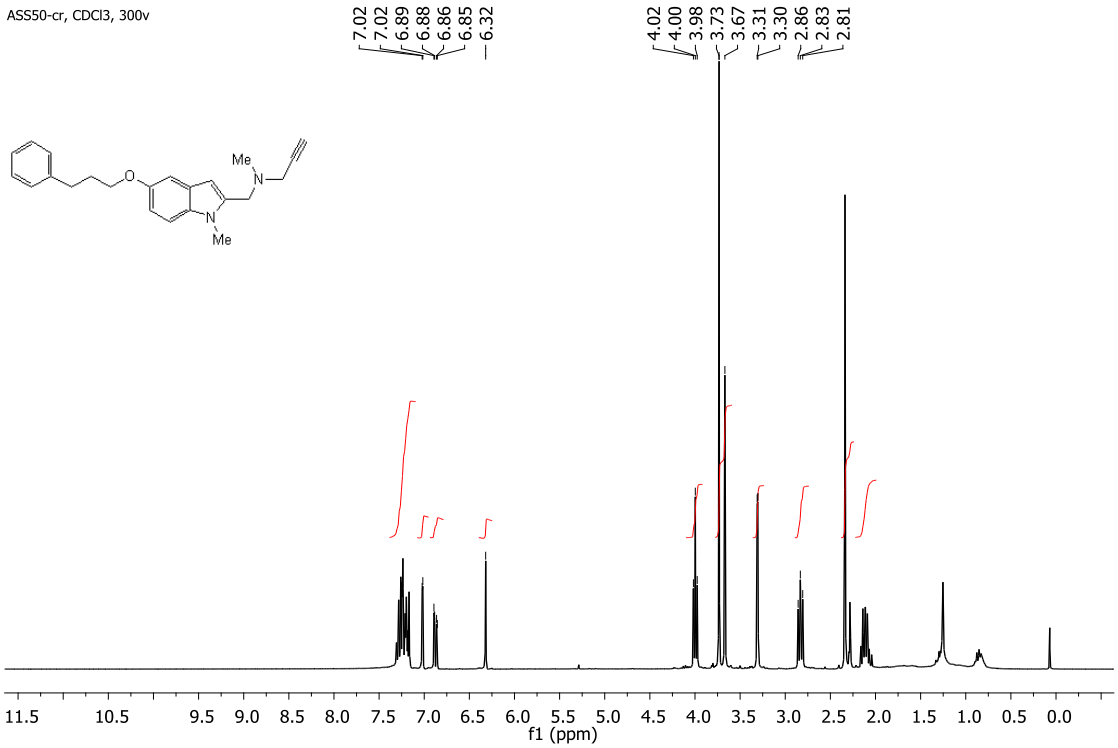


^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of compound **17.**

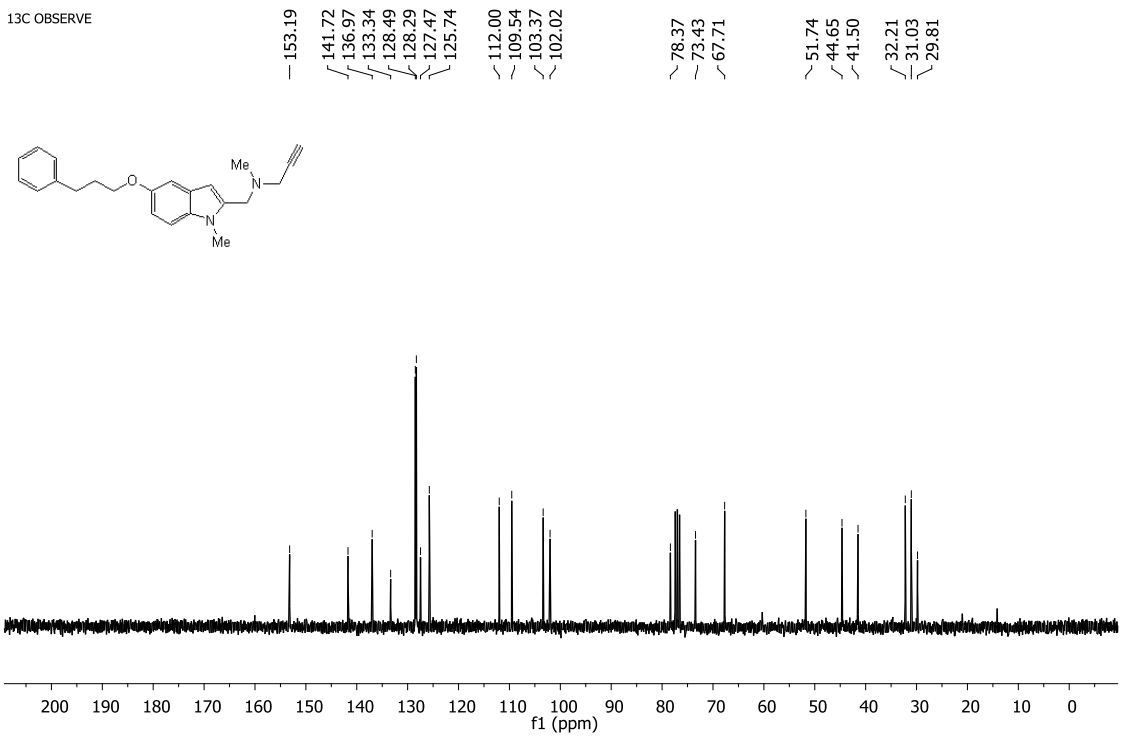


^{13}C-NMR (100 MHz, $CDCl_3$) spectrum of compound **17**

***N*-Methyl-*N*-((1-methyl-5-(3-phenylpropoxy)-1*H*-indol-2-yl)methyl)prop-2-yn-1-amine (16)**



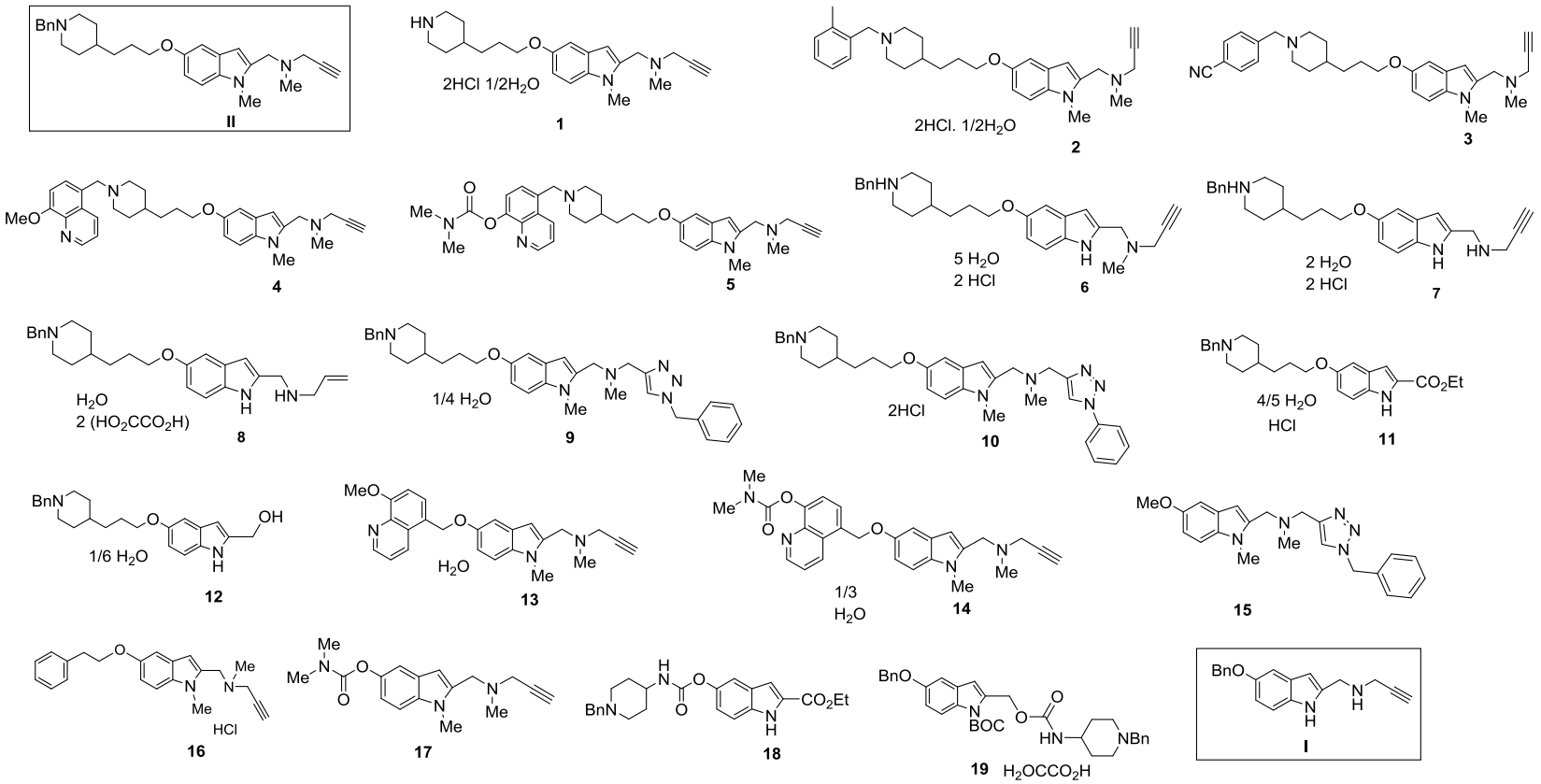
^{1}H-NMR (300 MHz, $CDCl_3$) spectra of compound **16.**



^{13}C-NMR (100 MHz, $CDCl_3$) spectra of compound **16.**

Biological Evaluation

Table S2. IC_{50} values and MAO-B selectivity ratios [IC_{50} (MAO-A)]/[IC_{50} (MAO-B)] for the inhibitory effects of test compounds (new compounds **1**-**19**, and reference inhibitors) on the enzymatic activity of hMAO isoforms expressed in baculovirus infected BTI insect cells. IC_{50} values for the inhibitory effects of test compounds (all new compounds and reference inhibitors) on the enzymatic activity of recombinant acetylcholinesterase (hAChE) and butyrylcholinesterase (hBuChE) expressed in HEK 293 cells.



CMPD	hMAO-A	hMAO-B	Ratio	hAChE	hBuChE	Ratio
II	58.2 ± 1.2 nM[a]	1.2 ± 0.1 µM	0.05	3.4 ± 0.2 µM	3.3 ± 0.2 µM	1.03
1	127.6 ± 13.5 nM[a]	1.2 ± 0.1 µM	0.11	**	**	
2	6.3 ± 0.4 nM[a]	183.6 ± 7.4 nM	0.03	2.8 ± 0.1 µM	4.9 ± 0.2 µM	0.57
3	443.2± 36.2 nM[a]	18.6 ± 1.5 nM	23.8	***	**	
4	10.1 ± 1.5 nM	8.2 ± 0.6 nM	1.2	***	**	
5	257.6 ± 11.4 nM[b]	196.3 ± 7.8 nM	1.3	8.4 ± 0.9 µM	5.9 ± 0.4 µM	1.4
6	9.1 ± 0.7 µM[b]	35.1 ± 2.8 µM	0.26	15.4 ± 0.9 µM	7.1 ± 0.5 µM	2.2
7	19.2 ± 1.3 µM[b]	33.6 ± 1.5 µM	0.57	4.9 ± 0.3 µM	7.3 ± 0.8 µM	0.67
8	45.3 ± 1.6 µM[b]	21.3 ± 1.9 µM	2.1	4.6 ± 0.3 µM	40.6 ± 2.2 µM	0.11
9	***	***		1.4 ± 0.1 µM	4.3 ± 0.3 µM	0.32
10	***	**		0.8 ± 0.06 µM	2.6 ± 0.2 µM	0.30
11	876.3 ± 25.2 nM	1.0 ± 0.02 µM	0.87	9.6 ± 0.8 µM	9.7 ± 0.7 µM	0.99
12	9.1 ± 0.3 µM	13.5 ± 1.1 µM	0.67	13.6 ± 1.4 µM	31.2 ± 3.1 µM	0.43
13	630.1 ± 16.1 nM[a]	164.7 ± 12.1 nM	3.8	**	**	
14	310.6 ± 17.1 µM	273.1 ± 8.9 nM	1.1	**	**	
15	***	**		**	56.1 ± 2.1 µM	> 1.7
16[c]	1.383 ± 0.099 µM	1.001 ± 0.205 µM	0.7	> 100	> 100	-
17[c]	3.2 ± 0.7 nM	5.2 ± 1.8 nM	1.6	> 100[d]	> 100[e]	-

18	**	***		31.47 ± 4.65 µM	**	
19	**	**		***	**	
I	287.3 ± 11.2 nM[a]	4.1 ± 0.7 nM	70	**	**	
Clorgyline	4.7 ± 0.2 nM[a]	65.8 ± 1.6 µM	$0.71x10^{-3}$	**	**	
(-)-Deprenyl	63.6 ± 1.3 µM[a]	18.2 ± 0.9 nM	3,494	**	**	
Iproniazide	6.3 ± 0.7 µM	7.5 ± 0.5 µM	0.84			
Moclobemide	366.4 ± 28.8 µM	*	<0.37[#]			
Eserine				122.6 ± 10.3 nM	165.6 ± 4.9 nM	0.74
Tacrine				427.9 ± 35.2 nM	146.8 ± 9.5 nM	2.9

MAO: All IC_{50} values shown in this Table are the mean ± SD. from five experiments. Level of statistical significance: [a]$P < 0.01$ or [b]$P < 0.05$ versus the corresponding IC_{50} values obtained against MAO-B, as determined by ANOVA/Dunnett´s.
* Inactive at 1 mM (highest concentration tested).
** Inactive at 100 µM (highest concentration tested).
*** 100 µM inhibits the corresponding MAO activity by approximately 40-50%. At higher concentration the compounds precipitate.
[#] Values obtained under the assumption that the corresponding IC_{50} against MAO-A is the highest concentration tested (1 mM).
ChE: All IC_{50} values shown in this Table are the mean ± SD from five experiments.
** Inactive at 100 µM (highest concentration tested).
*** 100 µM inhibits the corresponding ChE activity by approximately 40%. At higher concentration the compounds precipitate.
[c] We thank Dr. Irene Bolea (UAB, Barcelona) for these analyses.[d] *Ee*AChE.[e] eqBuChE.

Methods

Determination of MAO isoform activity. The potential effects of compounds on MAO activity were investigated by measuring their effects on the production of H_2O_2 from *p*-tyramine, using the Amplex® Red MAO assay kit (Molecular Probes, Inc., Eugene, Oregon, USA) and membrane MAO isoforms prepared from insect cells (BTI-TN-5B1-4) infected with recombinant baculovirus containing cDNA inserts for human MAO-A or MAO-B (Sigma-Aldrich Química S.A., Alcobendas, Spain). The production of H_2O_2 catalysed by MAO isoforms can be detected using 10-acetyl-3,7-dihydroxyphenoxazine (Amplex® Red reagent), a non-fluorescent, highly sensitive and stable probe, which reacts with H_2O_2 in the presence of horseradish peroxidase to produce a fluorescent product, resorufin. MAO activity was evaluated by the above mentioned coupled assay, previously described but with several modifications (Yáñez, M.; Fraiz, N.; Cano, E.; Orallo, F.; *Biochem. Biophys. Res. Commun*. **2006**, *344*, 688-695).

Briefly, 0.1 mL of sodium phosphate buffer (0.05 M, pH 7.4) containing compounds or reference inhibitors and pure MAO-A or MAO-B required to oxidize (in the control group) 165 pmol of *p*-tyramine/min were incubated for 15 min at 37 °C in corresponding wells from a 96-well plate (BD, NJ, USA) already placed into the dark fluorimeter chamber. After this incubation period, reaction was started by adding (final concentrations) 200 μM Amplex® Red reagent, 1 U/mL horseradish peroxidase and 1 mM *p*-tyramine as a common substrate for both MAO A/ B. The production of H_2O_2 and, consequently, of resorufin was quantified at 37 °C in an spectrometer FLX800™ Multi-Detection microplate reader (Biotek Instruments, Inc, Vermont, USA) on the basis of the fluorescence generated (excitation 545 nm, emission 590 nm) over a 15 min period, a period in which fluorescence increased linearly from the beginning.

Control experiments were carried out simultaneously by replacing the test compounds with appropriate dilutions of the vehicles. In addition, the possible capacity of the above-mentioned test compounds to directly react with Amplex® Red reagent was determined by adding these compounds to solutions containing only the Amplex® Red reagent in a sodium phosphate buffer.

The specific fluorescence emission (used to obtain the final results) was calculated after subtraction of background activity which was determined from vials containing all components with the exception of the MAO isoforms, which were replaced by a sodium phosphate buffer solution.

For reversibility assays, a 100X concentration of the enzyme used in the above described experiments was incubated with a concentration of inhibitor equivalent to 10-fold its IC_{50}. After 30 min, the mixture was diluted 100-fold into reaction buffer containing Amplex® Red reagent, horseradish peroxidase and p-tyramine and reaction was monitored for 15 min. Control tests were carried out by pre-incubating and diluting in the absence of inhibitor (Copeland, R. A. Evaluation of Enzyme Inhibitors in Drug Discovery, Wiley-Interscience, Hoboken, NJ, 2005).

Enzyme kinetic assays were performed by testing four different concentrations of compound in the presence of four independent amounts of substrate p-tyramine. Slopes achieved in each experiment were registered and the data analyzed by global non linear regression.

Ki values were obtained in kinetic assays testing four different concentrations of compound in the presence of four independent amounts of substrate *p*-tyramine. Rates were recorded and the data analyzed by global non linear regression.

IC_{50} values for irreversible and reversible inhibition were determined by measuring the remaining activity after a 15 min incubation time of compound **2** in saturated substrate conditions (irreversible), or without preincubation at a substrate concentration equal to 2xKm (reversible).

Determinations of cholinesterases activities. The cholinesterase assay method of Ellman (Ellman, G. L.; Courtney, K. D.; Andres, B. J.; Featherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88) was used to determine the *in vitro* cholinesterase activity. The activity was measured by the increase in absorbance at 412 nm due to the yellow color produced from the reaction of acetylthiocholine iodide with the dithiobisnitrobenzoate (DTNB) ion. Acetylcholinesterase recombinant expressed in HEK 293 cells and butyrylcholinesterase from human serum was obtained from Sigma. Enzyme activity was measured using a FLUOstar Optima microplate reader. The assay medium contained phosphate buffer, pH 8.0, 20 mM DTNB, 0.165 U/mL of enzyme, 0.75 µM substrate (acetylthiocholine iodide or butyrylthiocholine iodide). The activity was determined by measuring the increase in absorbance at 412 nm at 1 min intervals for 10 min at 37 °C. In dose-dependent inhibition studies, the substrate was added to the assay medium containing enzyme, buffer, and DTNB with inhibitor after 10 min of incubation time. All experiments were carried out in duplicate and expressed as mean ± SEM. The relative activity is expressed as percentage ratio of enzyme activity in the absence of inhibitor.

Reversibility was checked by measuring the restoration of the enzyme after a quiclky dilution into reaction buffer containing acetylthiocholine iodide and DTNB. Control tests were carried out by pre-incubating and diluting in the absence of inhibitor.

Enzyme kinetic assays were performed by testing four different concentrations of compound in the presence of four independent amounts of acetylthiocholine iodide. Slopes achieved in each individual experiment were registered and data were analyzed by global non-linear regression.

Statistical assay. Unless otherwise specified, results shown in the text and Tables are expressed as mean ± standard error (SD) from *n* experiments. Significant differences between two means were determined by one-way analysis of variance (ANOVA) followed by the Dunnett's *post-hoc* test. Graph Pad Prism Software (GraphPad Software, San Diego, California, USA) was used to perform statistical analyses and to calculate IC_{50} values and kinetic parameters.

Molecular modeling

The hMAO-A and MAO-B enzyme models have been obtained from crystallographic structures deposited in the Protein Data Bank (PDB)[1] with codes 2Z5X[2] and 4CRT[3] respectively. These PDB entries have been selected because the first one represents the highest hMAO-A X-ray resolution model available while the second reports the covalent adduct between a partially resolved structure of compound **II** and the hMAO-B. The molecular modeling study started building a complete model of compound **II** hMAO-B adduct by means of the addition of the benzylpiperidine moiety onto the 4CRT inhibitor structure while, for hMAO-A, the inhibitor, after removing the original ligand, has been manually designed into the catalytic site of the PDB model 2Z5X. The geometries of both theoretical models have been energy minimized. In order investigate the difference between the interaction of compounds **II** and **2** with MAO, on the previous optimized structures, one *ortho* hydrogen atom of the inhibitor benzylpiperidine moiety has been replaced by a methyl group.

A better positioning of the inhibitors into both hMAO-A and MAO–B catalytic sites has been achieved submitting the four covalent adduct models to a conformational search. Three and five possible conformations of compound **II** were highlighted with hMAO-A and hMAO–B, respectively. The Boltzman population analysis, carried out on the internal energies of above reported structure, revealed probabilities equal to 98.65% and 67.28%, for the existence of the global minimum energy adduct models with hMAO-A and hMAO–B, respectively. In the case of the theoretical models with **2**, a narrow conformational space appeared; actually only one proposed structure was found for hMAO-A and two for hMAO-B, with a global miminum population equal to 96.11%. The graphical inspection of the conformational search results highlighted similar binding modes of compounds **II** and **2** in the MAO clefts. Both inhibitors were

observed in folded conformations in hMAO-A, but were linear in MAO–B, respectively (Figure S1).

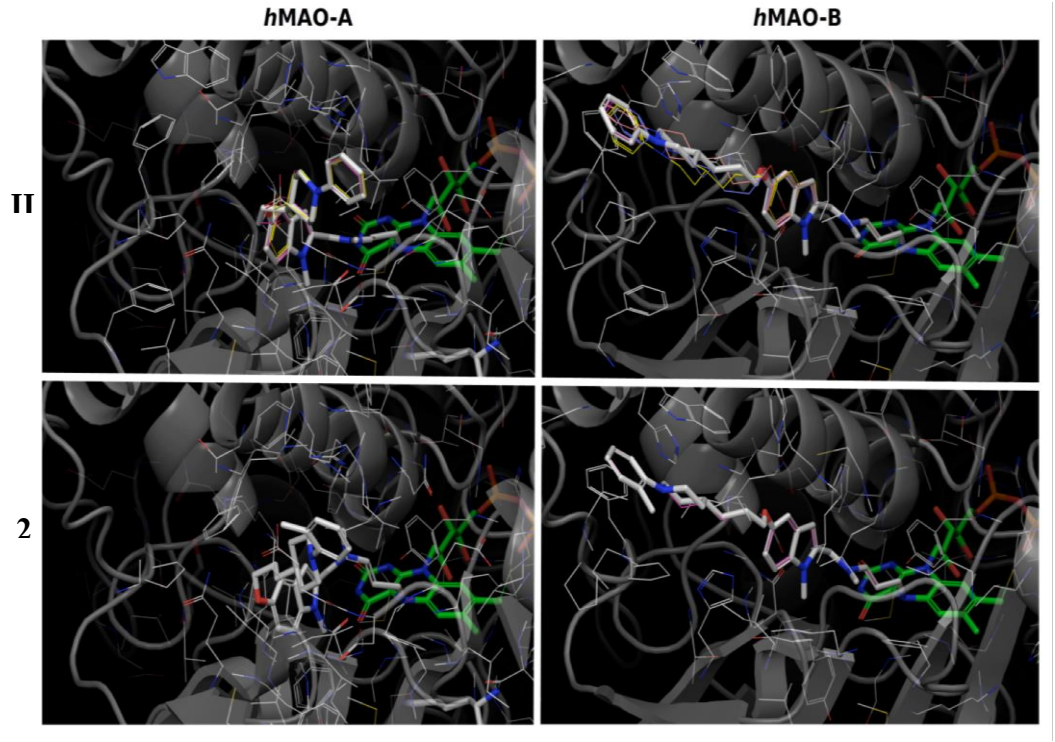


Figure S1. Global minimum energy structures of compounds **II** and **2** covalently bound to hMAO-A and hMAO-B. The FAD cofactor is shown in green and inhibitors are depicted in white polytube with colored carbons. Interacting residues are showed in white carbons wireframe. Higher energy conformers of the inhibitors are reported in various colored wireframe and superposed to the global minimum one.

The reasons for the differential recognition by the isozymes could be mainly due to the hMAO-A Phe208 replaced by Ile199 in hMAO-B. In hMAO-B, Ile199 allowed the positioning of the benzylpiperidine moiety of the inhibitor into a lipophilic cage delimited by Phe103, His115 and Val106 whereas, in hMAO-A, the bulkier Phe173 directed the same inhibitor moiety toward Glu327. Taking into account the protonation state at pH 7, the Glu327 side chain has established a strong electrostatic interaction to the positively charged nitrogen of the piperidine ring. The conformations of the inhibitors in hMAO-A revealed other productive hydrophobic interaction to Phe173,

Ile176 and Ile180. Overall, the interactions between compounds **II**, **2** and the MAOs are driven by both steric hindrance and hydrophobic contribution. Only in the case of hMAO-A is an additional electrostatic term highlighted.

Taking into account that covalent interactions can be established only after a non bonding recognition, the MC global minimum energy structures have been modified to design the corresponding reversible complexes. In order to improve our investigation, MC global minimum energy covalent adducts and derived reversible complexes have been submitted to 100 ns of molecular dynamics (MD) simulations. The evaluation of the MD trajectories has been carried out considering the structure modification during the simulation. A root means square deviation (RMSd) matrix has been computed comparing, one each other, all sampled structures for each MD run. The RMSd calculation has been applied to both inhibitor and enzyme atoms revealing small perturbation (Figures S2 and S3). The effect of the methyl group, both on the inhibitor and on the enzyme conformation, has been qualitatively correlated to the percentage of compound **2** RMSd matrix included values lower than the corresponding hybrid **II**. As reported in Table S3, in all cases the methyl group has remarkably improved the conformation stability of both inhibitors and targets.

Table S3. Conformation stabilizing effect of compound **2** methyl group as a percentage.

	Enzyme		**Inhibitor**	
	Adduct	**Complex**	**Adduct**	**Complex**
hMAO-A	71.83	98.17	37.35	81.95
hMAO-B	28.28	27.68	75.29	48.85

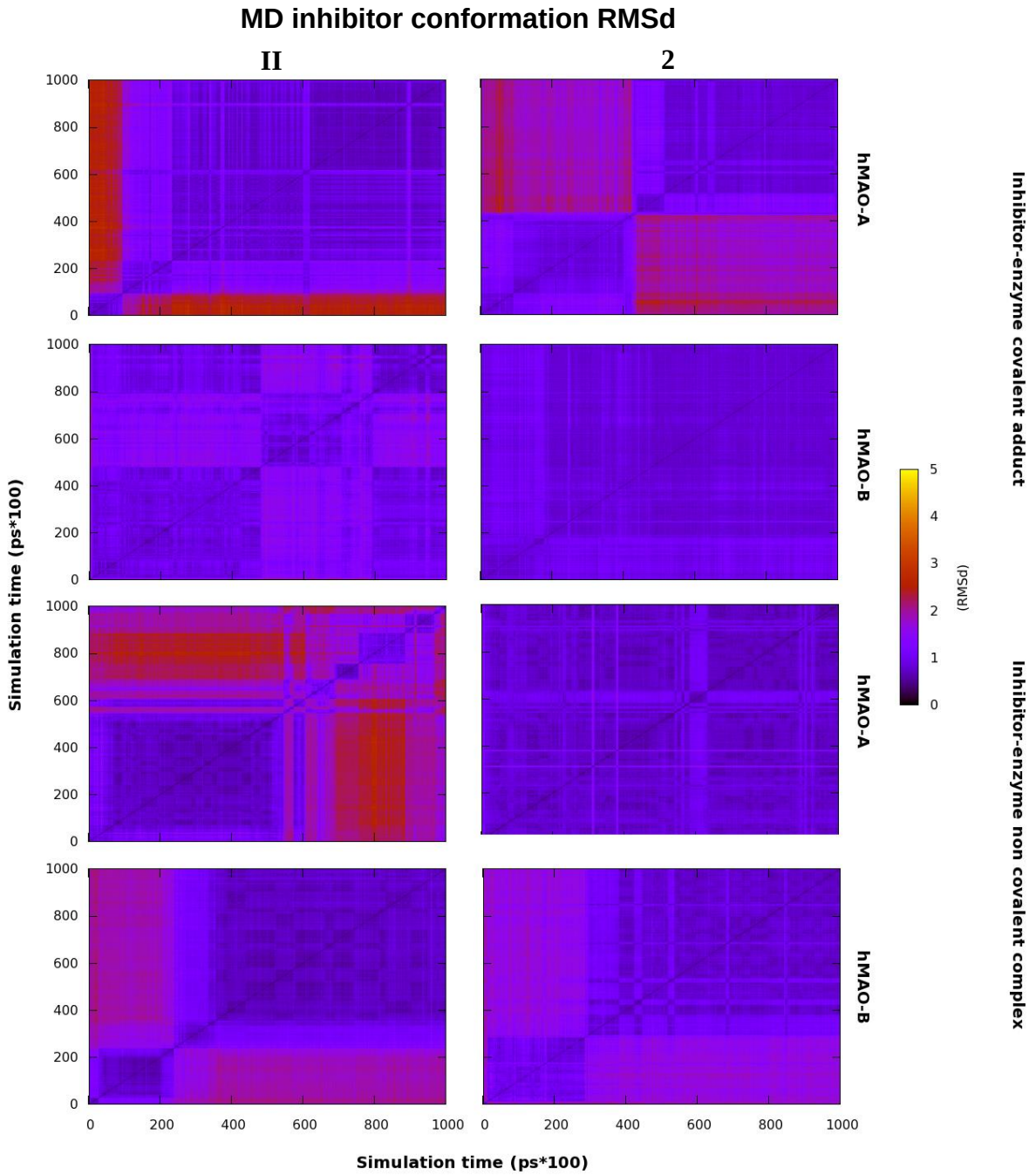


Figure S2. Molecular dynamics inhibitor atomic fluctuation. RMSd is reported in Å.

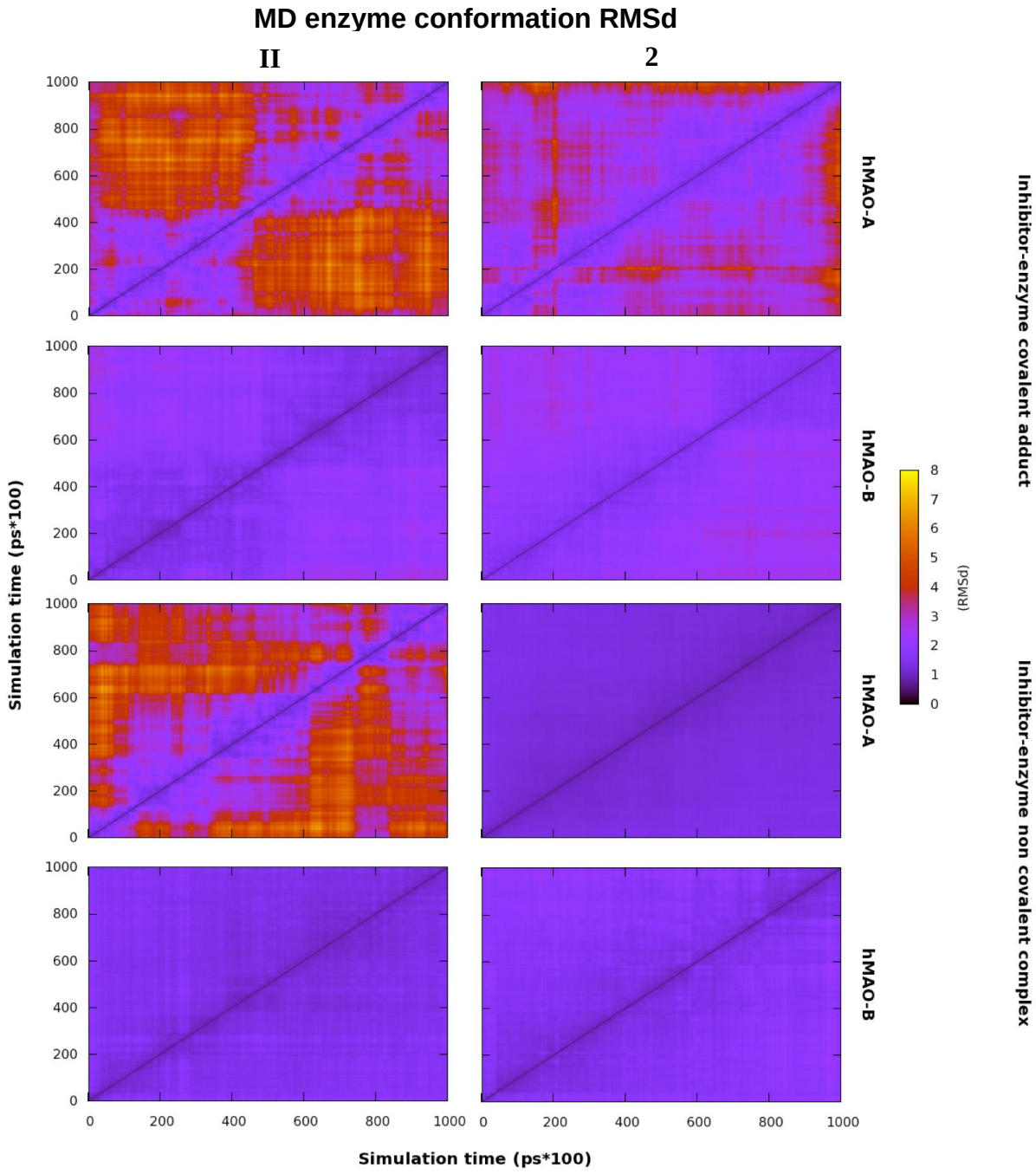


Figure S3. Molecular dynamics enzyme atomic fluctuation. RMSd is reported in Å.

Using the target RMSd matrix, each MD trajectory has been clustered in nine groups. The representative structure that reported the lowest RMSd value for that group, has been superposed to the initial conformation. The visual inspection of the ten

structures for each inhibitor with each enzyme clearly indicates the conformation stabilizing effect of the methyl group (Figure S4).

The analysis of MD simulation performed on the non-covalent complexes has provided an estimation of the thermodynamic difference between the recognition of compounds **II** and **2** by the MAOs. The enzyme-ligand interaction energies have been computed after each 10 ps of MD simulations. Coupled to Boltzman population analysis at 300° K, the energies highlight a good qualitative accord to IC_{50} experimental data (Table S4).

Table S4. Boltzman population weighted average MAOs interaction energies in kcal/mol.

	II	**2**
***h*MAO-A**	-68.91	-75.47
***h*MAO-B**	-63.30	-64.18

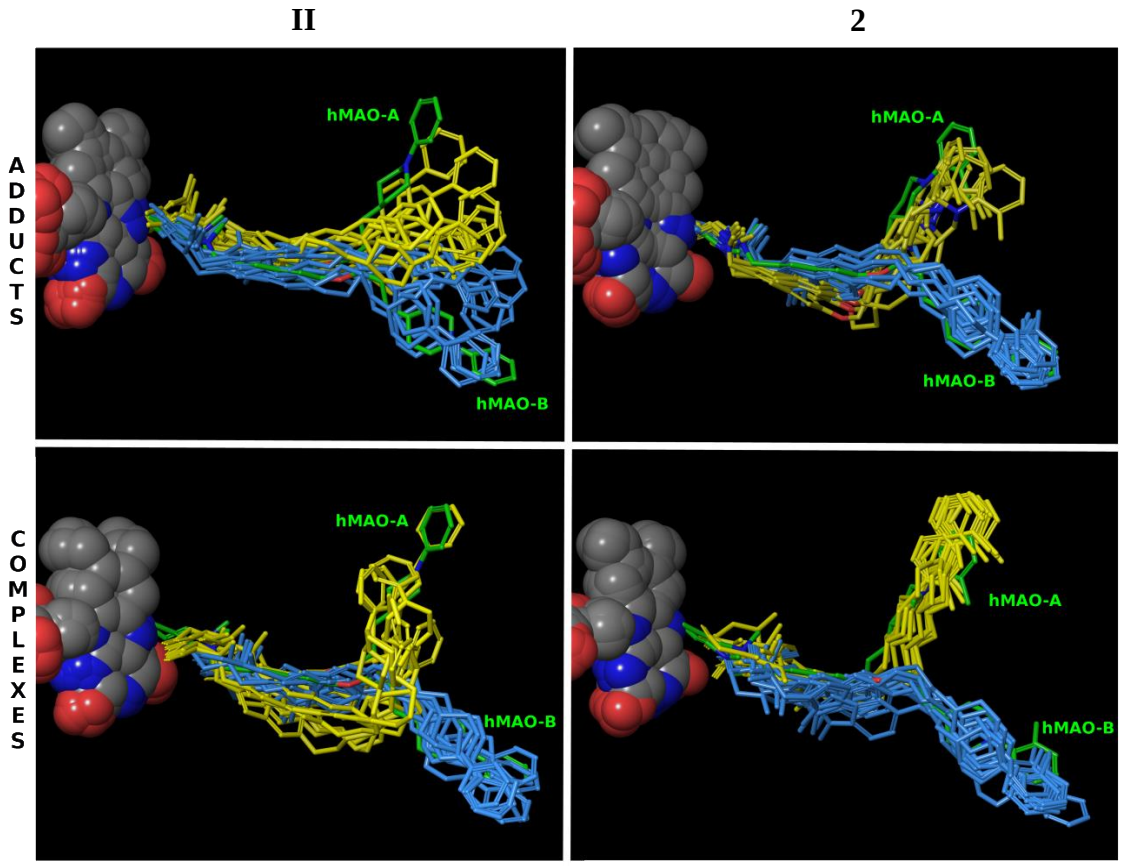


Figure S4. Superimposition of inhibitors in MAO: the starting conformation (green polytube) and the representative structures of the nine MD clusters in hMAO-A (yellow) and hMAO-B (light blue).

Both inhibitors reported better interaction energies in the hMAO-A case.The stabilizing effect of the methyl group, suggested by the MD geometry analysis, has been confirmed by thermodynamics data. The role of this substituent can be attributed to its productive contribution to the hydrophobic interaction driving the recognition of compounds **II** and **2** by both hMAO-A and hMAO-B.

A molecular modeling study on hAChE and hBuChE has been conducted by means of docking experiments. Biochemical experiments have demonstrated that compounds **II** and **2** are reversible inhibitors of ChEs and their mechanism of action is based on non-covalent interaction with these enzymes. The evident structural similarity with the known AChEI donepezil suggested that compounds **II** and **2** could analogously

interact to ChE targets. The catalytic sites of human AChE and BuChE are quite similar: the main difference is found at the entrance gorge where the hAChE Trp286 is replaced by Ala277 in hBuChE. This mutation enlarges the entrance gorge allowing the recognition of substrates bulkier than acetylcholine. Moreover, this residue is the basis of the donepezil selectivity, because its indanone moiety establishs π-π interaction to the Trp286 sidechain. It is also known that the conformation of a conserved Tyr residue, 341 in AChE and 332 in BuChE, plays a pivotal role for the binding of known inhibitors such as donepezil and tacrine. The Tyr conformation adopted for the interaction with tacrine is not compatible with the donepezil binding mode and *viceversa*.

Aiming to take into account the enzyme conformation flexibility, we decided to consider several receptor models for both targets in docking simulations. The PDB was searched for wild type structures of hAChE and hBuChE. The resulting PDB entries were refined, discarding those models reporting complexes of the enzymes with macromolecules (such as fasciculin). Finally, our receptor models have been built, in the case of AChE, from PDB entries 3LII,[4] 4EY4,[5] 4EY5,[5] 4EY6,[5] 4EY7,[5] 4M0E[6] and 4M0F[6] and for BuChE, 1P0M,[7] 1P0P,[7] 2J4C,[8] 2PM8[9] and 4BDS.[10] The docking results analysis revealed similar binding modes of compounds **II** and **2** in both AChE and BuChE receptor models. PDB structures 4EY7 and 1P0P, reporting AChE·donepezil and BuChE·butyrylthiocholine complexes, respectively, have been the better recognized by our ligands. The docking scoring function best values have been in partial accord with the experimental data. In the AChE case, donepezil-like binding modes (Figure S5) are shown by both inhibitors with the docking scores indicating an advantage for the compound **2** recognition equal to 3.32 kcal/mol with respect to hybrid **II**. Such a result can be attributed to the improved π-π stacking of the **2** *o*-methyl benzyl moiety

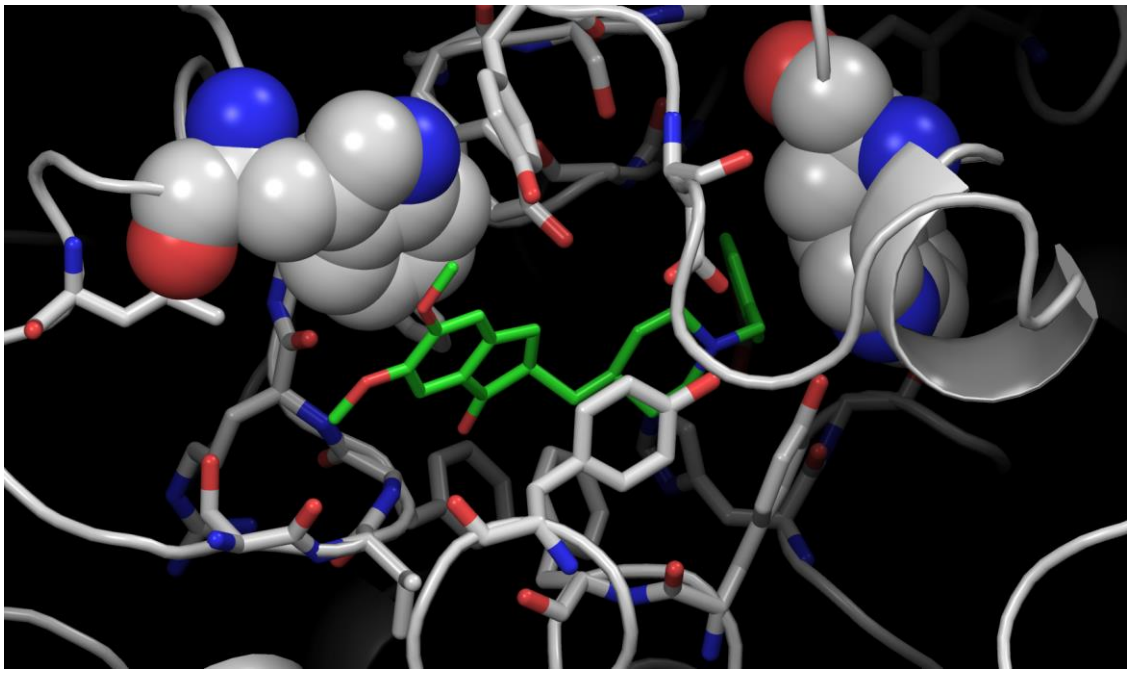


Figure S5. Donepezil recognition in human AChE (PDB: 4EY7). The ligand is depicted in green carbons polytube. Trp86 (inner side) and Trp286 (outer side) are reported in spacefill cpk colored notation. Hydrophobically interacting residues are showed in polytube white carbon atoms.

to the Trp86 sidechain compared to the compound **II** unsubstituted benzyl ring. The remaining interactions of compounds **II** and **2** to the AChE can be considered equivalent. In both cases we observed one hydrogen bond between the inhibitors ether oxygen atom and the backbone of Phe295, hydrophobic contacts to Phe338 and Tyr341 have been also reported. In addition, productive electrostatic interaction was observed between the positively charged piperidine moiety of the ligands and the Asp74 side chain (Figure S6).

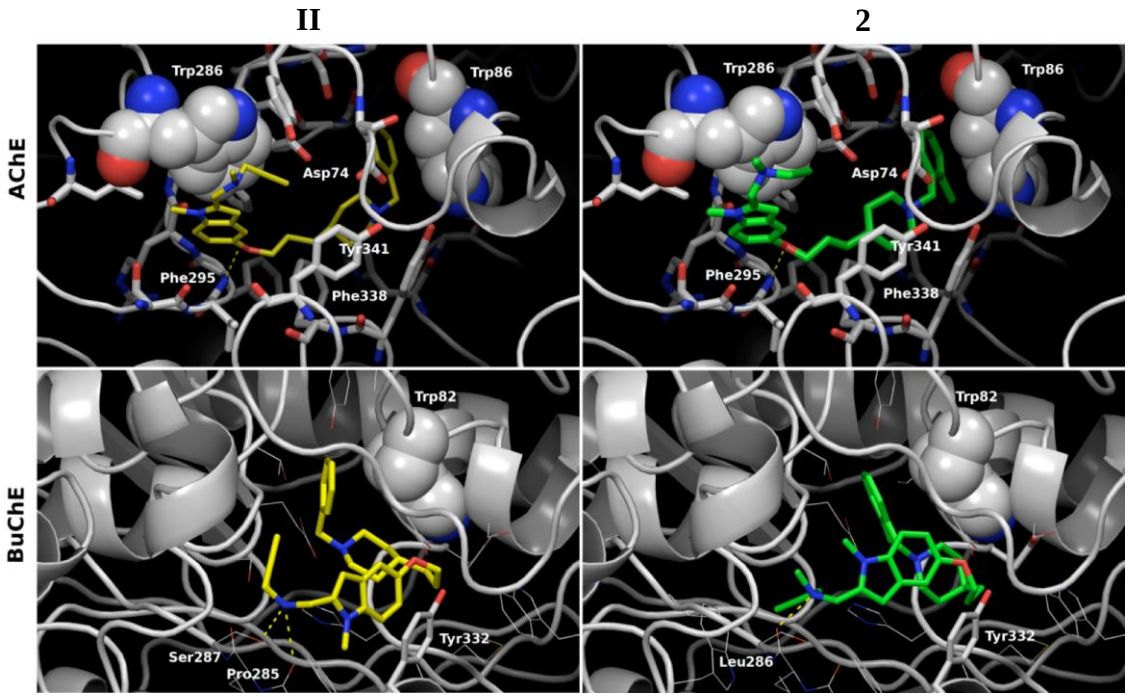


Figure S6. Cholinestarases recognition of compounds **II** and **2**. Yellow dotted lines indicate hydrogen bonds. Most relevant inhibitor-interacting residues are labeled.

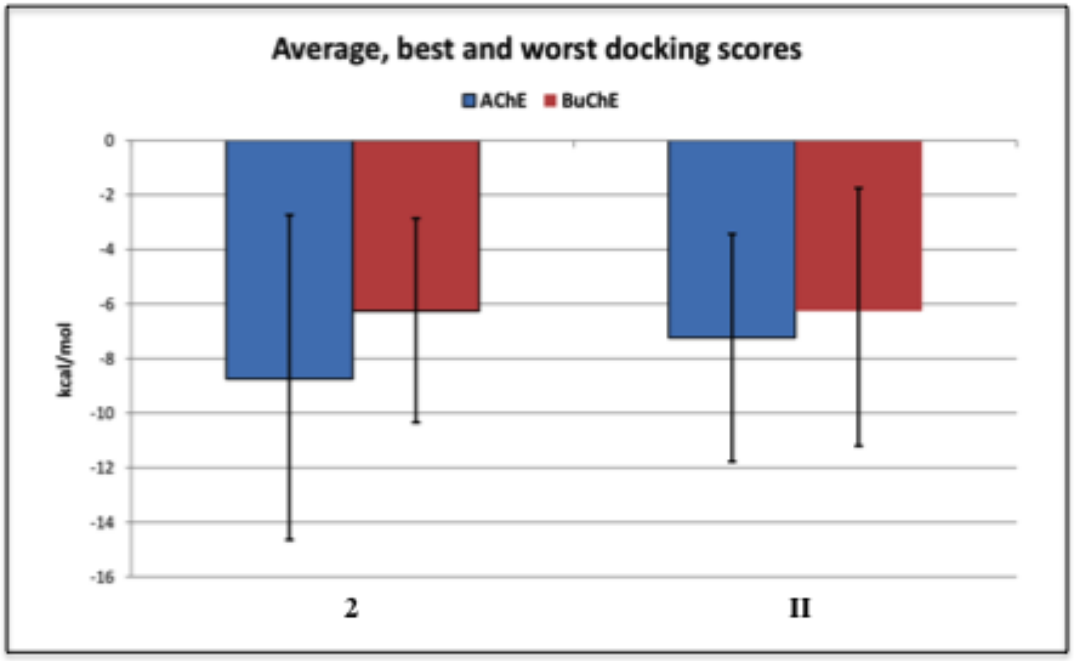


Figure S7. Compounds **2** and **II** docking average score of with respect to all AChE (blue) and BuChE (red) receptor models. The bars indicate the best and worst values.

The docking simulations performed on the BuChE receptor models indicated, for both ligands, a less productive recognition with respect to the previously reported

AChE. Actually docking score, either computed as average on all receptor models and best and worst values, highlighted BuChE interaction energies higher than the corresponding AChE. (Figure S7).

The poses analysis confirmed the remarkable ligand recognition stabilizing contribution of AChE Trp286. In fact, its replacement with the Ala277 in BuChE produced deleterious effects: A ligand·enzyme recognition favorable π-π stacking has been lost and the corresponding increased volume of the entrance gorge has allowed the ligand to assume a folded conformation for reducing its solvent exposition. The best poses of both inhibitors have shown that only hydrogen bonds (HB) provided specific interaction to the target. In particular, compound **II** has donated HB either to the Ser287 sidechain and to the backbone of Pro285, while compound **2** established this interaction to Leu286 backbone only. The observed folded conformation of both inhibitors, geometrically prevented the stacking between the ligands benzyl moiety and inner site Trp82 (Trp86 in AChE) limiting the recognition contribution of such a residue to a weak generic hydrophobic interaction.

For building the complete hMAO–B compound **II** adduct model a multi step procedure has been followed. First of all, the benzylpiperidine moiety not resolved in the X-ray data has been added to the 4CRT PDB entry inhibitor structure. All missinng hydrogen atoms have been included and FAD cofactor and ligand bonds order has been fixed. The final structure (Figure S8), including X-ray water molecules, has been energy minimised using the OPLS-2005[11] force field. Water enviroment effects have been mimicked by means of the implicit solvtion model GB/SA.[12] In order to prevent unrealistic distorsion of the targets, a costant force equal to 100 kJ/mol·$Å^{-1}$ has been

applied to the enzyme backbone atoms. The optimisation procedure has been carried out using Schrodinger Suite.[12]

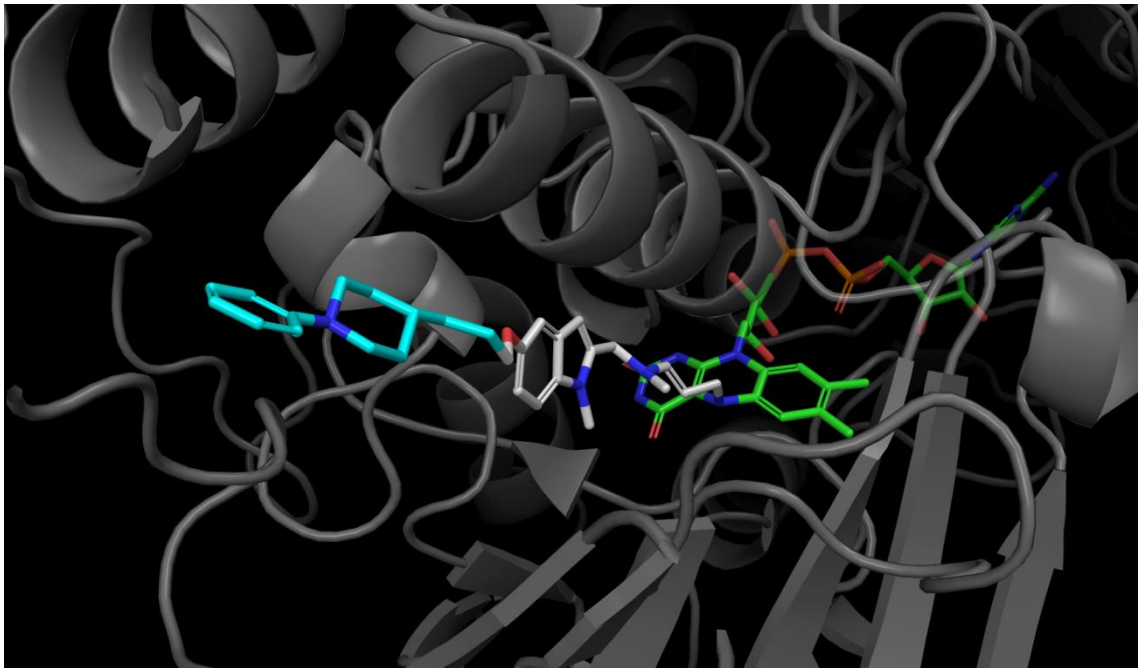


Figure S8. Preliminary structure of compound **II** hMAO-B convalent adduct model. FAD cofactor, green carbons colored, and covalently bound inihibitor, are displayed in polytube. The compound **II** manually added moiety is depicted in cyan carbons, the original X-ray in white carbons. The hMAO-B structure is reported as gray cartoon.

A similar approach has been followed for building the hMAO-A compound **II** covalent adduct model: harmine, the orginal X-ray ligand, has been removed from the 2Z5X catalytic site and manually replaced by compound **II** bound to FAD.

The conformational search of compounds **II** and **2** covalently bound to hMAO-A and hMAO-B has been carried out by means of MonteCarlo (MC) method. [12] Previously reported optimized models have been considered as starting structures. 2000 inhibitor conformations were randomly generated by moving each ligand rotatable bond in a range equal to ±180°. The conformations generated were energy minimised using the same protocol as previously reported. For each adduct model, the MC optimised geometries have been compared by superimposition after taking into account the root

means square deviation (RMSd) computed, on the atoms other than hydrogen. Structures were considered identical if their RMSd was lower than 0.5 Å.

The design of compounds **II** and **2** non covalent complexes of the MAOs active sites, started from the corresponding MC global minimum energy structures by removing the covalent bond between the inhibitors and the FAD. The complexes so generated, after fixing FAD and inhibitor bond order and adding the required hydrogen atoms, have been submitted to the energy optimisation procedure previously described (Figure S9).

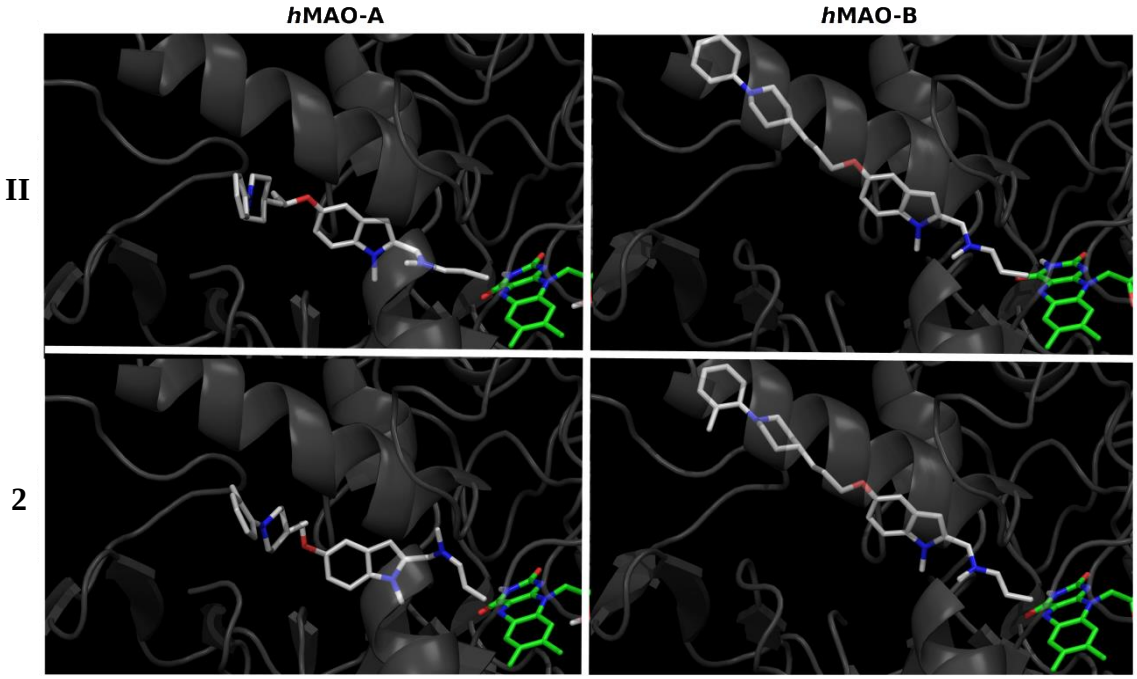


Figure S9. Optimised structures of compounds **II** and **2** non-convalent complexes with MAO. The FAD cofactor (green) carbons colored, and the inihibitors (white) are displayed in polytube. The enzymes are reported as gray cartoon.

Molecular dynamics experiments have been performed on both covalent adducts and complexes of compounds **II** and **2** in the hMAO-A and MAO-B catalytic sites. All simulation have been carried out up to 100 ns at 300° K. The pressure was fixed at 1 atm and the integration time step was equal to 2 fs. Trajectories snapshots have been

sampled at regular time intervals of 100 ps. The energy evaluation has been based on the OPLS-2005 force field and SPC explicit solvation model has been adopted to take into account watern environment effects. All molecular dynanimcs simulations have been computed by means of Desmond software.[13-15]

Docking simulations of compounds **II** and **2** with respect to human AChE and BuChE receptor models have been performed using Glide software.[16-19] All selected PDB structures have been modified by removing co-crystallised water molecules and ligands. According to the force field OPLS-2005, missing hydrogen atoms have been added and energy minimised. For those PDB structures reporting enzyme dimeric forms, both chains have been, separately, taken into account. The binding site core of each receptor model has been defined by means of a regular box of 1000 $Å^3$ centered onto the catalytic Ser residue. Ligand flexible docking alghoritm has been adopted and theoretical complexes have been evaluated using the extra-precision (XP) Glide scoring function.

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***In Vitro* Blood–Brain Barrier Permeation Assay (PAMPA-BBB)**.

Prediction of the brain penetration was evaluated using a parallel artificial membrane permeation assay (PAMPA-BBB), in a similar manner as previously described (López-Iglesias, B.; Pérez, C.; Morales-García, J. A.; Alonso-Gil, S.; Pérez-Castillo, A.; Romero, A.; López, M. G.; Villarroya, M.; Conde, S.; Rodríguez-Franco, M. I. New melatonin-*N*,*N*-dibenzyl(*N*-methyl)amine hybrids: potent neurogenic agents with antioxidant, cholinergic, and neuroprotective properties as innovative drugs for Alzheimer's disease. *J. Med. Chem.* **2014,** *57*, 3773-3785). Pipetting was performed with a semi-automatic pipettor (CyBi®-SELMA) and UV reading with a microplate spectrophotometer (Multiskan Spectrum, Thermo Electron Co.). Commercial drugs, phosphate buffered saline solution at pH 7.4 (PBS), and dodecane were purchased from Sigma, Aldrich, Acros, and Fluka. Millex filter units (PVDF membrane, diameter 25 mm, pore size 0.45 μm) were acquired from Millipore. The porcine brain lipid (PBL) was obtained from Avanti Polar Lipids. The donor microplate was a 96-well filter plate (PVDF membrane, pore size 0.45 μm) and the acceptor microplate was an indented 96-well plate, both from Millipore. The acceptor 96-well microplate was filled with 200 μL of PBS:ethanol (70:30) and the filter surface of the donor microplate was impregnated with 4 μL of porcine brain lipid (PBL) in dodecane (20 mg mL^{-1}). Compounds were dissolved in PBS: ethanol (70:30) at 100 μg mL^{-1}, filtered through a Millex filter, and then added to the donor wells (200 μL). The donor filter plate was carefully put on the acceptor plate to form a sandwich, which was left undisturbed for 120 min at 25 ºC. After incubation, the donor plate is carefully removed and the concentration of compounds in the acceptor wells was determined by UV-Vis spectroscopy. Every sample is analyzed at five wavelengths, in four wells and at least in three independent

runs, and the results are given as the mean ± standard deviation. In each experiment, 11 quality control standards of known BBB permeability were included to validate the analysis set.