Accepted Manuscript

Multicomponent access to novel dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium salts and indoles by means of Ugi/Bischler–Napieralski/heterocyclization two step strategy

Alessandra Silvani, Giordano Lesma, Sergio Crippa, Vito Vece

PII: S0040-4020(14)00615-2

DOI: 10.1016/j.tet.2014.04.081

Reference: TET 25531

To appear in: *Tetrahedron*

Received Date: 4 March 2014

Revised Date: 8 April 2014

Accepted Date: 25 April 2014

Please cite this article as: Silvani A, Lesma G, Crippa S, Vece V, Multicomponent access to novel dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium salts and indoles by means of Ugi/Bischler–Napieralski/ heterocyclization two step strategy, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.04.081.

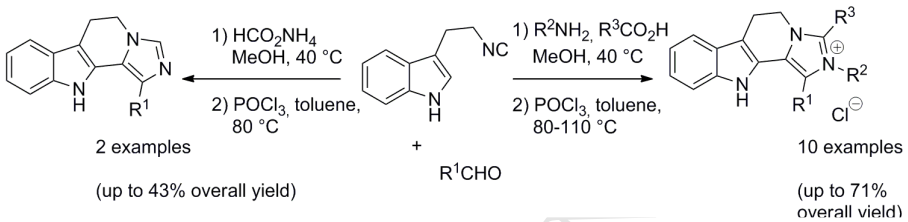
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Multicomponent access to novel dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium salts and indoles by means of Ugi/Bischler–Napieralski/heterocyclization two step strategy

Leave this area blank for abstract info.

Alessandra Silvani, Giordano Lesma,* Sergio Crippa, and Vito Vece*
Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi, 19, 20133 Milano (Italy)



Tetrahedron
journal homepage: www.elsevier.com

Multicomponent access to novel dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium salts and indoles by means of Ugi/Bischler–Napieralski/heterocyclization two step strategy

Alessandra Silvani, Giordano Lesma,* Sergio Crippa, and Vito Vece*

Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi, 19, 20133 Milano (Italy)

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
multicomponent reaction
Ugi reaction
isonitrile
carboline
imidazolium salt

ABSTRACT

A simple, efficient and general two step procedure, through a sequential Ugi reaction followed by a Bischler–Napieralski/heterocyclization tandem closure, to give novel 6,11-dihydro-5H-imidazo[1',5':1,2] pyrido[3,4-b]indol-2-ium salt derivatives, is described. By changing the amine and the acid components with ammonium formate, the same procedure affords 6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indole derivatives.

1. Introduction

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features to maximize structural complexity and convergence, while saving synthetic operations.[1] Since these highly step-economic reactions are particularly appealing in the context of diversity as well as target-oriented syntheses, they play an important role in drug discovery and biological probe chemistry. When coupled with post-MCR cyclizations, these reactions can lead to interesting heterocyclic scaffolds, becoming particularly useful for the construction of diverse arrays of drug-like molecules in medicinal chemistry. Among the several multicomponent protocols, the Ugi four-component reaction (Ugi-4CR)[2] has been, without any doubt, one of the most investigated in pharmaceutical industry and in academic research over the past two decades.[3]

In this context, we recently focused on tetrahydro-β-carboline (THBC)-based compounds[4] as privileged molecular targets, and on the Ugi reaction, as a powerful tool for the synthesis of related polycyclic structures.[5] Natural and synthetic products containing tryptophan-based pharmacophores exhibit a wide range of important bioactivities, particularly concerning the central nervous system. In particular, due to their unique rigid heterocyclic skeleton, THBC-based compounds are known to bind with high affinity to various receptor sites, such as the benzodiazepine (BzR), serotonin, and dopamine sites[6] and to inhibit monoamine oxidase A.[7] Moreover, some tetracyclic β-carbolines have been reported to act as selective inhibitors in the anticancer field,[8] or to be endowed with antimalarial properties.[9]

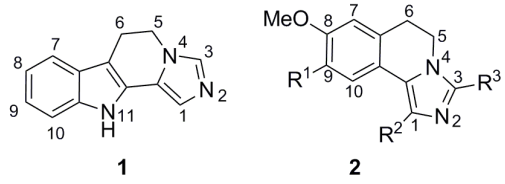


Fig. 1. The 6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indole and 5,6-dihydroimidazo[5,1-a]isoquinoline frameworks.

Recently, dihydroimidazo-fused THBC derivatives, in which the 6,11-dihydro-5H-imidazo [1',5':1,2]pyrido-[3,4-b]indole framework **1** has been incorporated (Figure 1), have shown particular interest because of their potential therapeutic properties,[10] mainly as agonists of 5HT-2 serotonin receptors,[10a,b]

* Corresponding author. Tel.: +039-02-50314079; e-mail: giordano.lesma@unimi.it

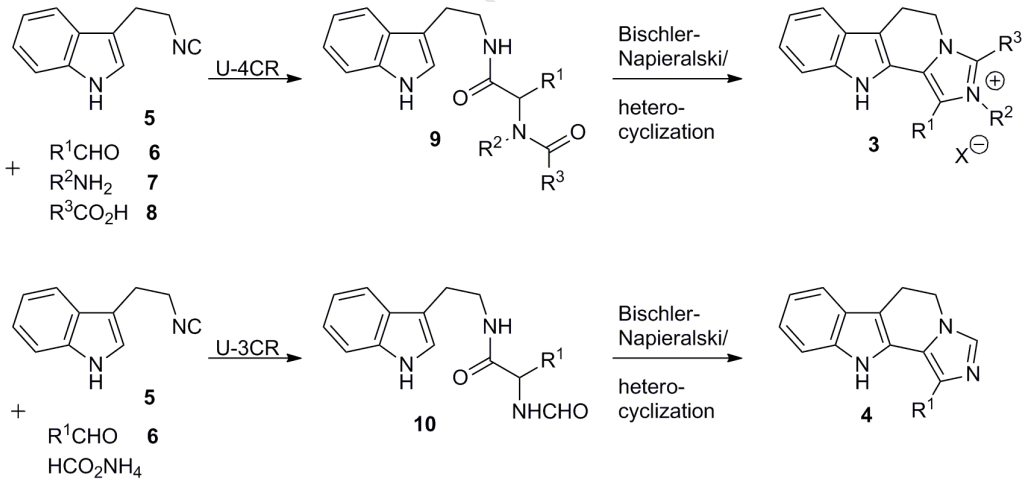
and as inhibitors of Mitogen-activated protein-Kinase-2.[11] Generally, available methods for the synthesis of type **1** compounds capitalized upon a conventional amidation/Bischler-Napieralski sequence which, however, do not allow for the rapid introduction of different functional groups onto the core structure. Yet, considerable recent progress has been represented by Seganish's synthesis[12] of the related 5,6-dihydroimidazo[5,1-a]isoquinolines **2**,[13] via an efficient Ugi/Bischler–Napieralski reaction sequence.

Imidazolium salts, which are made up of a discrete cation and anion pair, have found widespread utility as ionic liquids.[14] Several areas of bio-applications, including antitumor, antibacterials, antimicrobial, antioxidant activities and bioengineering applications, have also been reported.[15] Both imidazoles and imidazolium salts are ubiquitous in nature and play a critical role in many structures and functions due to their ability to interact electrostatically with biological systems.[16]

2. Results and discussion

As part of our ongoing interest in the development of MCRs-based heterocycles, we herein report the synthesis of diverse 1,2,3-trisubstituted 6,11-dihydro-5H-imidazo[1',5':1,2]pyrido [3,4-b]indol-2-ium salts **3** and 1-substituted 6,11-dihydro-5H-imidazo[1',5':1,2] pyrido[3,4-b]indoles **4**, via an Ugi/Bischler-Napieralski /heterocyclization two steps sequence (Scheme 1).

Notably, starting from a tryptamine-derived isocyanide, and aldehydes, carboxylic acids and amines as Ugi components, a non-conventional degree of chemical diversity could be introduced at the N-2 nitrogen atom of **1**, to afford imidazolium salts structures.



Scheme 1. Multicomponent Access to Novel Dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium Salts and Indoles.

Then, by a careful selection of starting materials, this two step strategy can, potentially, give access to a multitude of diversified molecules for testing of biological assays and catalytic ligand properties,[17] with improved synthetic efficiency. To the best of our knowledge, this represents the first protocol which allows to achieve unique indole-imidazolium structures, by means of a multicomponent approach.

The 3-(2-isocyano-ethyl)-1*H*-indole precursor **5** was prepared in 82% overall yield, by formylation of tryptamine followed by dehydration using triphenylphosphine and carbon tetrachloride in dichloromethane at room temperature.[18] It must be noted that any attempt to dehydrate *N*-formyl tryptamine by means of phosphoryl chloride[19] at room temperature only led to a fast decomposition of the starting material.

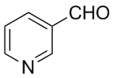
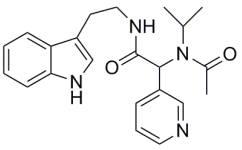
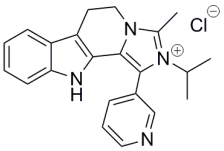
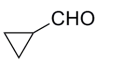
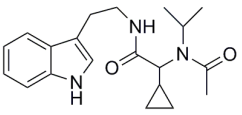
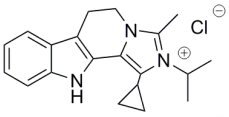
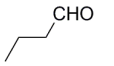
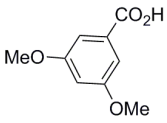
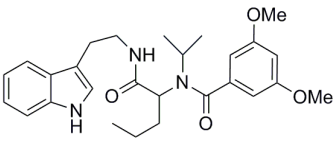
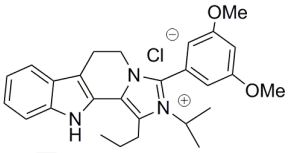
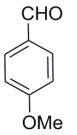
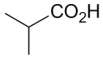
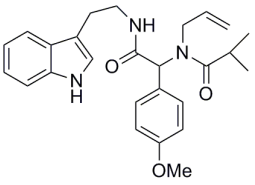
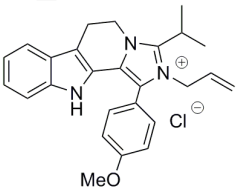
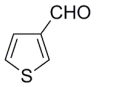
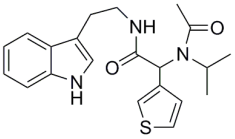
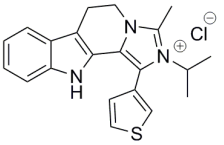
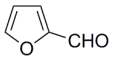
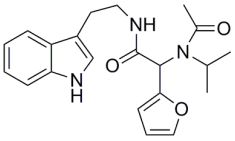
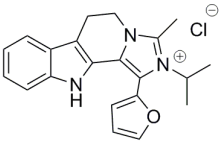
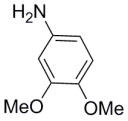
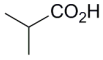
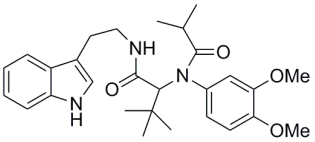
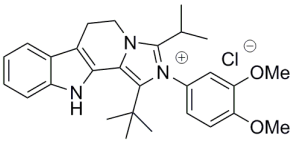
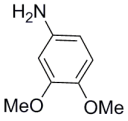
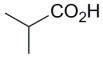
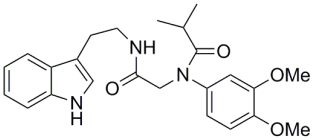
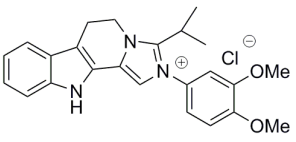
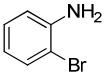
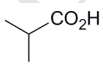
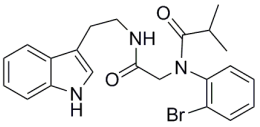
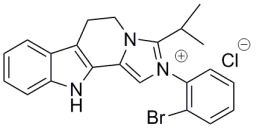
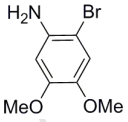
The Ugi reaction was undertaken following a general procedure, consisting of the sequential addition of aldehyde **6** (1.1 equiv), amine **7** (1.1 equiv), carboxylic acid **8** (1.1 equiv) and, finally, isocyanide **5** (1.0 equiv) in methanol. The mixture was stirred for 24-120 hours at 40 °C to provide intermediates **9** in moderate to good yields (Table 1). An investigation on temperature and solvent revealed that the use of methanol at 40 °C gave the optimal results both in terms of yields and reaction rates. When other solvents, such as CH_2Cl_2, CF_3CH_2OH or toluene, or higher reaction temperatures were applied, yields decreased significantly. This first multicomponent step was tolerant with a variety of aromatic (entries 1, 4-6) and aliphatic (entries 2-3, 7-10) aldehydes, having different electronic properties. Acid sensible furfural afforded smoothly the Ugi adduct in 77%. Notably, the steric hindrance of amine (entries 7, 8 and 10) as well as of acid (entries 3, 9) components does not play a determinant role in terms of reactivity and product yields.

The subsequent Bischler-Napieralski/ heterocyclization of Ugi-adducts **9** was carried out in toluene under nitrogen atmosphere at 80-110 °C, using a large excess of phosphoryl chloride (15 mol equiv) as dehydrating reagent for 60-360 minutes. Following this double dehydration protocol, we obtained the target products **3**, which could be easily isolated by standard aqueous work-up, followed by conventional flash chromatography as hydrochloride salts.

It should be noted that the reaction time and yields somewhat depend on the starting components of the Ugi step, which determine the structure of the R^{1-3} residues. In general, as for the Ugi reaction step, also in this case both aliphatic and aromatic residues, having different electronic properties, as well as those bearing bulky substituents showed to be suitable for the reaction.

An exception is the Ugi adduct **9f** containing a furan moiety: due to the acidic reaction conditions, we observed only a rapid degradation of the starting material with the production of unidentified by-products. Importantly, the reaction proceeded smoothly in the presence of electron-donating groups on the benzene ring (entries 7,8,10), where competition

Table 1. Ugi-Components, Products and Yields of Ugi-4CR and of the Bischler– Napieralski/Heterocyclization.

entry	R^1CHO(**6**)	R^2NH_2 (**7**)	R^3CO_2H (**8**)	Ugi product (**9**)[a]	(yield %)[b]	Cyclization product (**3**)[c]	(yield %)[b]
1			AcOH		**9a** (76)		**3a**[d] (94)
2			AcOH		**9b** (71)		**3b**[d] (70)
3					**9c** (64)		**3c**[e] (76)
4					**9d** (84)		**3d** (83)
5			AcOH		**9e** (81)		**3e**[e] (88)
6			AcOH		**9f** (77)		**3f** (nd)
7					**9g** (73)		**3g** (92)
8	$(CHO)_n$				**9h** (69)		**3h** (76)
9	$(CHO)_n$				**9i** (66)		**3i**[f] (77)
10	$(CHO)_n$				**9j** (68)		**3j**[g] (84)

[a]Reaction condition: see text and supporting informations.

[b]Isolated yields.

[c]Reaction conditions: **9**, $POCl_3$ (15 mol equiv), toluene, 60 min, 80 °C, (if not otherwise indicated).

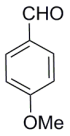
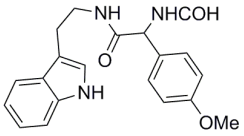
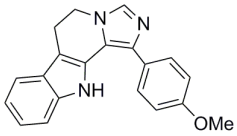
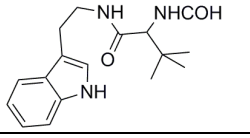
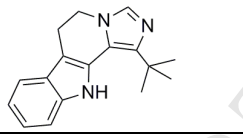
[d]Reaction time: 180 min.

[e]Reaction time: 90 min.

[f]Conditions: 300 min, 110 °C.

[g]Conditions: 360 min, 110 °C

Table 2. Aldehyde Ugi-Component, Products and Yields of Ugi-3CR and of the Bischler–Napieralski/Heterocyclization.

entry	R^1CHO (**6**)		Ugi product (**10**)[a]	(yield %)[b]	Cyclization product (**4**)[c]	(yield %)[b]
1		HCO_2NH_4[d]		**10a** (54)		**4a** (62)
2		HCO_2NH_4[d]		**10b** (58)		**4b** (74)

[a]Reaction condition: see text and supporting informations.

[b]Isolated yields.

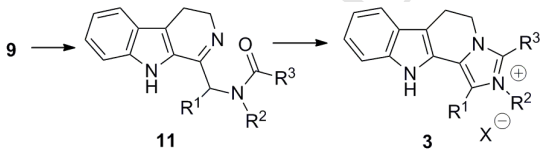
[c]Reaction conditions: **10**, $POCl_3$ (15 mol equiv), toluene, 60 min, 80 °C.

[d]Two equiv of the salt HCO_2NH_4 were used for the reaction.

of the electron-rich benzene ring to capture the transient Bischler-Napieralski iminium salt, can, in principle, occur. On the other hand, bulkiness seems to play a role in the rate of the tandem reaction, as highlighted by the higher temperature and longer reaction times required in the presence of an *ortho* substituent on the aniline-derived ring (entries 9,10).

We envisioned that the transformation of **9** to **3** might occur affording firstly mono-cyclized products **11** (Scheme 2) which, subsequently, could further cyclize to provide final compounds **3**. To gain support for this mechanistic proposal, on selected Ugi-products **9** the reaction was performed using a minor excess of phosphoryl chloride (5 mol equiv) at 50 °C. No cyclic intermediates **11** were observed, except for the cases of **9i** and **9j**, which afforded separable amounts of the corresponding **11i** and **11j**, as stable compounds. **11i** and **11j** were then cleanly converted to **3i** and **3j** by treatment with phosphoryl chloride, in toluene, at 80°C.

By employing ammonium formate as a solid source of ammonia in a three component Ugi reaction, we were able to obtain formamide derivatives **10a** and **10b** (entries 1 and 2, Table 2), albeit in moderate yields. The above described Bischler-Napieralski/heterocyclization protocol allowed to convert **10a** and **10b** into the imidazole derivatives **4a** and **4b**, thus endorsing this approach as a valid alternative for the synthesis of 1-substituted dihydroimidazo[1',5':1,2]pyrido[3,4-b]indoles.



Scheme 2. Plausible Mechanism.

3. Conclusion

In summary, we have described a two step Ugi/Bischler–Napieralski/heterocyclization sequence, providing a protocol for the synthesis of novel trisubstituted 5,6-dihydroimidazo[1',5':1,2]-pyrido[3,4-b]indol-2-ium salt derivatives and substituted dihydroimidazo-[1',5':1,2]pyrido[3,4-b]indoles, from readily available starting materials. The proposed sequence, which could be developed on multigram scale, can be applied to the synthesis of libraries of heterocyclic compounds, bearing up to three points of facile chemical diversity.

4. Experimental section

4.1. General

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography (FC) on silica gel 60 (230 - 400 mesh). IR spectra were recorded in the FTIR mode. ^1H NMR and ^{13}C NMR spectra were recorded with 300 and 400 MHz (^1H NMR) and 75 or 100 MHz (^{13}C NMR) spectrometers. Chemical shifts (δ) are expressed in ppm relative to TMS at δ = 0 ppm for ^1H NMR and relative to $CDCl_3$ at δ = 77.16 ppm for ^{13}C NMR. ^{13}C NMR spectra have been recorded using the APT pulse sequence; the signals of CH and CH_3 are positive while CH_2 and quarternary carbons are negative. High-resolution MS spectra were recorded with a FT-ICR (Fourier Transform Ion Ciclotron Resonance) instrument, equipped with an ESI source, or a standard MS instrument, equipped with an EI source.

4.2. Synthetic procedure for compound 5

A mixture of tryptamine (1.6 g, 10 mmol) in ethyl formate (8 mL) was refluxed for 18 hr. After concentration, the resulting crude residue was dissolved in anhydrous dichloromethane (20 mL) and triphenylphospine (14.41 g, 55 mmol), carbon tetrachloride (5.38 mL, 55 mmol) and triethylamine (15.4 mL, 110 mmol) were added in sequence. After being stirred at rt for 4h, the mixture was concentrated and the residue was purified by FC with 30% ethyl acetate-hexane, for elution, to give 3-(2-isocyanoethyl)-1*H*-indole **5** as an off-white solid (1.39 g, 82%): mp 74-75 °C (lit. 73-74.5 °C).[18b] Melting point and spectral properties (^1H and ^{13}C NMR) of the product are in agreement with the reported data.[18b]

4.3. General procedure for multicomponent isocyanide-based synthesis of compounds 9a-j

To a solution of the aldehyde **(6)** (2.59 mmol) in MeOH (4.7 mL), the amine **(7)** (2.59 mmol) and the carboxylic acid **(8)** (2.59 mmol) were added, followed by addition of 3-(2-isocyanoethyl)-1*H*-indole **(5)** (400 mg, 2.35 mmol). The resulting mixture was

stirred at 40 °C, for 24 to 120 h until the completion of the reaction, as indicated by TLC. The reaction mixture was cooled to room temperature and concentrated, and the residue was purified via FC as indicated below.

*4.3.1. N-(2-(1H-Indol-3-yl)ethyl)-2-(N-isopropyl cetamido)-2-(pyridin-3-yl)acetamide (**9a**).* Prepared according to the general procedure above from nicotinaldehyde, isopropylamine and acetic acid, for 48 h; FC: ethyl acetate-dichloromethane, 2:1; yield: 676 mg (76%); off-white solid; mp 129-131 °C; R_f = 0.46 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3334, 3309, 1669, 1642, 1516, 1456, 1422, 1373 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.47-8.41 (m, 2H), 8.30 (br, m, 1H), 7.56 (br, d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.16 (br, t, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 7.5 and 4.9 Hz, 1H), 7.07 (br, t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.54 (m, 1H), 4.76 (s, 1H), 4.08 (hept, *J* = 6.7 Hz, 1H), 3.58 (m, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.11. (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 169.7, 149.0, 148.7, 136.5, 135.9, 132.9, 127.3, 123.4, 122.7, 121.7, 119.0, 118.5, 112.0, 111.4, 60.0, 50.9, 40.2, 24.8, 22.6, 21.4, 20.8; HRMS (ESI) calculated for $C_{22}H_{27}N_4O_2$ [MH^+] 379.2134, found 379.2145.

4.3.2. *N-(2-(1H-Indol-3-yl)ethyl)-2-cyclopropyl-2-(N-isopropylacetamido)acetamide (**9b**).* Prepared according to the general procedure above from cyclopropanecarbaldehyde, isopropylamine and acetic acid, for 24 h; FC: ethyl acetate-dichloromethane, 2:1; yield: 569 mg (71%); white solid; mp 115-116 °C; R_f = 0.16 (ethyl acetate-hexane, 1:1.5); $\nu_{max}(CHCl_3)$ 3470, 3300, 1660, 1644, 1519, 1456, 1358 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (br, s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.32 (br, m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.06 (br, s, 1H), 3.93 (hept, *J* = 6.6 Hz, 1H), 3.59 (m, 2H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.78 (br, m, 1H), 2.09 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.55-0.48 (m, 1H), 0.34-0.28 (m, 2H), 0.19-0-15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.3, 136.6, 127.4, 124.6, 121.6, 118.9, 118.6, 112.2, 111.5, 63.7, 49.6, 40.1, 25.1, 22.9, 22.1, 21.0, 11.2, 5.5, 5.2; HRMS (ESI) calculated for $C_{20}H_{28}N_3O_2$ [MH^+] 342.2182, found 342.2173.

*4.3.3. N-(1-((2-(1H-Indol-3-yl)ethyl)amino)-1-oxopentan-2-yl)-N-isopropyl-3,5-dimethoxybenzamide **(9c).*** Prepared according to the general procedure above from *n*-butyraldehyde, isopropylamine and 3,5-dimethoxybenzoic acid, for 96 h; FC: ethyl acetate-hexane, 1:1; yield: 700 mg (64%); pale yellow solid; mp 118-122 °C; R_f = 0.22 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3475, 3294, 1656, 1594, 1543, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (br, m, 1H), 8.14 (br, m, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 7.8, 7.4 and 1.2 Hz, 1H), 7.14 (ddd, *J* = 7.8, 7.4 and 1.2 Hz, 1H), 7.12 (br, s, 1H), 6.51 (br, m, 1H), 6.39 (d, *J* = 2.1 Hz, 2H), 3.93 (br, m, 1H), 3.80 (s, 6H), 3.83-3.72 (m, 1H), 3.66 (q, *J* = 6.6 Hz, 2H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.32-2.09 (br, m, 2H), 1.49-1.30 (br, m, 2H), 1.18 (br, m, 3H), 1.10 (br, m, 3H), 0.97 (br, t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 173.4, 161.7 (2C), 139.6, 137.1, 128.1, 122.9, 122.5, 119.9, 119.4, 113.5, 111.9, 105.4, 104.8, 102.1, 62.1, 56.2 (2C), 53.1, 40.4, 32.8, 26.0, 21.6, 21.2, 21.0, 14.6; HRMS (ESI) calculated for $C_{27}H_{36}N_3O_4$ [MH^+] 466.2706, found 466.2694.

*4.3.4. N-(2-((2-(1H-Indol-3-yl)ethyl)amino)-1-(4-methoxyphenyl)-2-oxoethyl)-N-allylisobutyramide dimethylbutanamide **(9d).*** Prepared according to the general procedure above from anisaldehyde, allylamine and isobutyric acid, for 24 h; FC: ethyl acetate-dichloromethane, 1:1; yield: 855 mg (84%); off-white solid; mp 86-88 °C; R_f = 0.63 (ethyl acetate-hexane, 3:7); $\nu_{max}(CHCl_3)$ 3432, 3310, 1678, 1631, 1513, 1457, 1418 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.91 (br, s, 1H), 6.77 (d, *J* = 7.8 Hz, 2H), 5.88 (br, s, 2H), 5.44 (m, 1H), 4.97-4.90 (m, 2H), 3.93 (br, m, 2H), 3.77 (s, 3H), 3.57 (m, 2H), 2.91 (t, *J* = 6.8 Hz, 2H), 2.75 (hept, *J* = 6.6 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 170.1, 159.5, 136.4, 134.8, 130.9 (2C), 127.3, 122.5, 121.8, 119.1, 118.5, 116.0 (2C), 114.0 (2C), 112.3, 111.4, 61.3, 55.2, 48.4, 40.0, 31.0, 25.1, 19.7, 19.6; HRMS (ESI) calculated for $C_{26}H_{32}N_3O_3$ [MH^+] 434.2444, found 434.2453.

*4.3.5 N-(2-(1H-Indol-3-yl)ethyl)-2-(N-isopropylacetamido)-2-(thiophen-3-yl)acetamide (**9e**).* Prepared according to the general procedure above from thiophene-3-carbaldehyde, isopropylamine and acetic acid, for 24 h; FC: ethyl acetate; yield: 730 mg (81%); off-white solid; mp 159-162 °C; R_f = 0.12 (ethyl acetate-dichloromethane, 1.5:1); $\nu_{max}(CHCl_3)$ 3426, 3335, 1668, 1639, 1518, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, m, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.22 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.02 (m, 1H), 6.99 (br, s, 1H), 6.26 (br, m, 1H), 4.84 (br, s, 1H), 4.11 (hept, *J* = 6.7 Hz, 1H), 3.62 (dq, *J* = 12.9 and 6.4 Hz, 1H), 3.51 (dq, *J* = 12.9 and 6.4 Hz, 1H), 2.96 (m, 2H), 2.18 (s, 3H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.9, 138.0, 136.5, 128.2, 127.3, 126.1, 124.4, 122.6, 121.7, 119.1, 118.6, 112.4, 111.4, 57.4, 50.6, 40.2, 24.9, 22.5, 21.6, 21.0; HRMS (ESI) calculated for $C_{21}H_{26}N_3O_2S$ [MH^+] 384.1746, found 384.1738.

*4.3.6. N-(2-(1H-Indol-3-yl)ethyl)-2-(furan-2-yl)-2-(N-isopropylacetamido)acetamide (**9f**).* Prepared according to the general procedure above from furfural, isopropylamine and acetic acid, for 48 h; FC: ethyl acetate-dichloromethane, 1:1; yield: 664 mg (77%); white solid; mp 98-101 °C; R_f = 0.28 (ethyl acetate-dichloromethane, 1.5:1); $\nu_{max}(CHCl_3)$ 3429, 3333, 1674, 1642, 1520, 1456, 1372 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (br, m, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.27 (br, m, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.04 (br, s, 1H), 6.58 (br, m, 1H), 6.39 (br, d, *J* = 3.9 Hz, 1H), 6.27 (br, m, 1H), 4.87 (br, s, 1H), 4.04 (hept, *J* = 6.7 Hz, 1H), 3.63 (dq, *J* = 13.2 and 6.6 Hz, 1H), 3.51 (dq, *J* = 13.2 and 6.6 Hz, 1H), 2.95 (t, *J* = 6.6 Hz, 2H), 2.11 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 168.6, 150.5, 136.5 (2C), 127.4, 122.8, 121.7, 119.0, 118.6, 112.2, 111.5, 111.0, 109.9, 55.4, 50.4, 40.4, 25.0, 22.3, 21.2, 21.0; HRMS (ESI) calculated for $C_{21}H_{26}N_3O_3$ [MH^+] 368.1974, found 368.1982.

*4.3.7. N-(2-(1H-Indol-3-yl)ethyl)-2-(N-(3,4-dimethoxyphenyl)isobutyramido)-3,3-dimethylbutanamide **(9g).*** Prepared according to the general procedure above from pivalaldehyde, 3,4-dimethoxyaniline and isobutyric acid, for 24 h; FC: ethyl acetate-dichloromethane, 4:1; yield: 925 mg (73%); off-white solid; mp 148-149 °C; R_f = 0.83 (ethyl acetate-dichloromethane, 3:1); $\nu_{max}(CHCl_3)$ 3310 (br), 1674, 1632, 1513, 1465, 1418, 1386 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 8.19 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.07 (br, s, 1H), 6.85-6.67 (m, 3H), 4.86 (br, s, 1H), 3.88 (br, s, 3H), 3.85(s, 1H), 3.80 (s, 3H), 3.67-3.53 (m, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.60-2.46 (m, 1H), 1.02 (t, *J* = 6.9 Hz, 3H), 0.97 and 0.93 (two singlets, 9H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 171.9, 171.6, 149.8, 149.4, 137.1, 134.7, 127.8, 122.7, 122.6, 119.8, 119.2(2C), 113.2, 112.0, 111.9, 111.0, 56.6 and 56.5 (2C), 40.1,

34.8, 31.8, 28.5 (3C), 26.1, 20.3 (2C); HRMS (ESI) calculated for $C_{28}H_{38}N_3O_4$ [MH^+] 480.2862, found 480.2854.

*4.3.8.. N-(2-((2-(1H-Indol-3-yl)ethyl)amino)-2-oxoethyl)-N-(3,4-dimethoxyphenyl)isobutyramide (**9h**).* Prepared according to the general procedure above from paraformaldehyde, 3,4-dimethoxyaniline and isobutyric acid, for 48 h; FC: ethyl acetate-dichloromethane, 7:3; yield: 686 mg (69%); white solid; mp 116-118 °C; R_f = 0.33 (ethyl acetate-dichloromethane, 4:1); $\nu_{max}(CHCl_3)$ 3434, 3347, 1668, 1514, 1464, 1419 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 6.75-6.55 (m, 3H), 6.38 (br, t, *J* = 6.5 Hz, 1H), 4.16 (s, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.61 (q, *J* = 6.6 Hz, 2H), 2.96 (t, *J* = 6.7 Hz, 2H), 2.51 (hept, *J* = 6.7 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 169.0, 149.6, 148.8, 136.4, 135.6, 127.3, 122.3, 122.1, 119.8, 119.3, 118.6, 111.3 (2C), 112.5, 110.7, 56.0 (2C), 54.2, 39.5, 30.9, 25.2, 19.6 (2C); HRMS (ESI) calculated for $C_{24}H_{30}N_3O_4$ [MH^+] 424.2236, found 424.2228.

*4.3.9. N-(2-((2-(1H-Indol-3-yl)ethyl)amino)-2-oxoethyl)-N-(2-bromophenyl)isobutyramide (**9i**).* Prepared according to the general procedure above from paraformaldehyde, 2-bromoaniline and isobutyric acid, for 96 h; FC: ethyl acetate-hexane, 1:1.5; yield: 686 mg (66%); pale yellow solid mp 159-161 °C; R_f = 0.75 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3430, 3345, 1668, 1525, 1473, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (br, m, 1H), 7.65 (br, d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.28-7.20 (m, 4H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.11 (br, s, 1H), 6.47 (br, m, 1H), 4.68(d, *J* = 15.3 Hz, 1H), 3.74 (dq, *J* = 13.2 and 6.6 Hz, 1H), 3.60 (dq, *J* = 13.2 and 6.6 Hz, 1H), 3.59 (d, *J* = 15.3 Hz, 1H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.25 (hept, *J* = 6.7 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 168.7, 141.5, 136.5, 133.7, 130.7, 130.1, 129.0, 127.3, 123.3, 122.4, 122.1, 119.4, 118.7, 112.6, 111.3, 53.0, 39.5, 31.6, 25.1, 19.8, 19.2; HRMS (ESI) calculated for $C_{22}H_{25}BrN_3O_2$ [MH^+] 442.1130, found 442.1136.

*4.3.10. N-(2-((2-(1H-Indol-3-yl)ethyl)amino)-2-oxoethyl)-N-(2-bromo-4,5-dimethoxyphenyl)isobutyramide (**9j**).* Prepared according to the general procedure above from paraformaldehyde, 2-bromo-4,5-dimethoxyaniline and isobutyric acid, for 120 h; FC: ethyl acetate-dichloromethane, 7:3; yield: 803 mg (68%); off-white solid mp 198-200 °C (dec.); R_f = 0.62 (ethyl acetate); $\nu_{max}(CHCl_3)$ 3435, 3347, 1666, 1506, 1462, 1441 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d*6) δ 10.82 (s, 1H), 8.03 (bt, *J* = 6.5 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.35 (br, s, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.31 (br, s, 1H), 7.13 (br, s, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.45-3.34 (m, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.30 (hept, *J* = 6.6 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-*d*6) δ 176.8, 168.2, 149.7, 148.9, 136.7, 134.4, 127.7, 123.1, 121.4, 118.7 (2C), 115.7, 114.6, 113.6, 112.2, 111.8, 56.6, 56.4, 51.3, 40.2, 31.0, 25.6, 20.3, 19.6; HRMS (ESI) calculated for $C_{24}H_{29}BrN_3O_4$ [MH^+] 502.1341, found 502.1352.

4.4. General procedure for multicomponent isocyanide-based synthesis of compounds 10a,b

To a solution of 3-(2-isocyanoethyl)-1*H*-indole **(5)** (600 mg, 3.53 mmol) and aldehyde **(6)** (3.88 mmol) in MeOH (7 mL), ammonium formate (7.06 mmol) was added in one portion and the solution was stirred for 24 to 48 h until the completion of the reaction as indicated by TLC (eluent: ethyl acetate-hexane, 1:1). The solvent was evaporated under reduced pressure to give a residue, which was purified by FC with dichloromethane–ethyl acetate, 1:3.5, for elution.

*4.4.1. N-(2-(1H-Indol-3-yl)ethyl)-2-formamido-2-(4-methoxyphenyl)acetamide (**10a**).* Prepared according to the general procedure above from anisaldehyde. Yield: 670 mg (54%); off-white solid; mp 152-154 °C; R_f = 0.25 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3479, 3409 (br), 2937, 1674, 1671, 1611, 1512, 1486, 1457 cm^{-1}; ^1H NMR (300 MHz, DMSO-*d*6) δ 10.82 (s, 1H), 8.79 (d, *J*= 8.3 Hz, 1H), 8.42 (t, *J* = 5.6 Hz, 1H), 8.06 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.10-7.01 (m, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 2H), 5.45 (d, *J* = 8.3 Hz, 1H), 3.75 (s, 3H), 3.34 (br, m, 2H), 2.81 (t, *J*= 7.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.6, 160.4, 158.7, 136.2, 130.9, 128.2 (2C), 127.1, 122.8, 120.9, 118.3 (2C), 113.8 (2C), 111.6, 111.4, 55.1, 54.1, 39.9, 25.0; HRMS (ESI) calculated for $C_{20}H_{22}N_3O_3$ [MH^+] 352.1661, found 351.1668.

*4.4.2. N-(2-(1H-Indol-3-yl)ethyl)-2-formamido-3,3-dimethylbutanamide (**10b**).* Prepared according to the general procedure above from pivalaldehyde. Yield: 616 mg (58%); amorphous white solid; R_f = 0.31 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3475, 3400, 3332, 2887, 1670 (br), 1614, 1523, 1458 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.10 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.09-7.04 (m, 2H), 7.00 (t, *J* = 7.8 Hz, 1H), 4.24 (s, 1H), 3.49 (m, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 0.95 (s, 9H); ^{13}C NMR(75 MHz, CD_3OD) δ 173.0, 169.6, 139.1, 129.6, 124.4, 123.2, 120.5, 120.1, 114.0, 113.1, 61.8, 42.1, 36.0, 28.0 (3C), 27.1; HRMS (ESI) calculated for $C_{17}H_{24}N_3O_2$ [MH^+] 302.1869, found 302.1876.

4.5. General procedure for preparation of compounds 3a-j and 4a,b by tandem Bischler-Napieralski/heterocyclization

To a solution of the Ugi product **(9** or **10)** (1.0 mmol) in anhydrous toluene (10 mL) was added $POCl_3$ (1.37 mL, 15 mmol). Depending on the substrate, the reaction mixture was stirred at 80-110 °C for 60 to 360 min until the completion of the reaction as indicated by TLC. After cooling at rt, a 5% solution of Na_2CO_3 (10 mL) was added and the mixture extracted with dichloromethane (2 x 25 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by FC to yield the pure compound **(3** or **4)** as indicated below.

*4.5.1. 2-Isopropyl-3-methyl-1-(pyridin-3-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3a**).* Prepared according to the general procedure above from **9a**, for 180 min at 80 °C; FC: dichloromethane-ethyl acetate-methanol, 1:1.5:2.5; yield: 356 mg (94%); foam; R_f = 0.82 (dichloromethane-methanol, 4:1); $\nu_{max}(CHCl_3)$ 3155, 1641, 1586, 1533, 1456, 1432 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.88 (br, d, *J* = 3.9 Hz, 1H), 8.77 (br, s, 1H), 8.10 (br, d, *J* = 7.8 Hz, 1H), 7.75 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 4.56 (hept, *J* = 7.2 Hz, 1H), 4.47 (t, *J* = 6.9 Hz, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 2.90 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 153.1, 152.6, 146.0, 141.8, 139.8, 135.6, 133.3, 129.8, 126.9, 126.5, 125.3, 124.8, 122.8, 120.1, 113.5, 113.1, 53.2, 45.0, 22.0 (2C), 20.9, 12.2; HRMS (ESI) calculated for $C_{22}H_{23}N_4^+$ [M^+] 343.4443, found 343.4435.

*4.5.2. 1-Cyclopropyl-2-isopropyl-3-methyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3b**).* Prepared according to the general procedure above from **9b**, for 180 min at 80 °C; FC: dichloromethane-methanol, 9:1; yield: 239 mg (70%); pale yellow foam; R_f = 0.15 (dichloromethane-

methanol, 4:1); ν_{max}($CHCl_3$) 3299 (br), 1647, 1503, 1458, 1388 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 5.25 (hept, *J* = 6.8 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 2H), 3.23 (t, *J* = 6.8 Hz, 2H), 2.79 (s, 3H), 2.01 (m, 1H), 1.69 (d, *J* = 6.8 Hz, 6H), 1.37 (m, 2H), 0.84-0.74 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 144.5, 139.9, 128.7(2C), 127.0, 125.0, 123.6, 121.6, 120.0, 113.4, 111.4, 52.1, 44.7, 21.9, 21.6 (2C), 20.9, 12.3, 9.1 (2C); HRMS (ESI) calculated for $C_{20}H_{24}N_3^+$ [M^+] 306.1965, found 306.1973.

*4.5.3. 3-(3,5-Dimethoxyphenyl)-2-isopropyl-1-propyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3c**).* Prepared according to the general procedure above from **9c**, for 90 min at 80 °C; FC: dichloromethane-methanol, 9:1; yield: 354 mg (76%); pale yellow solid; mp 248-250 °C (dec.); R_f = 0.72 (ethyl acetate-methanol, 4:1); ν_{max}($CHCl_3$) 3164, 1635, 1597, 1541, 1460, 1424, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.0 (br, m, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.46 (br, d, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 7.8, 7.6 and 1.1 Hz, 1H), 7.08 (ddd, *J* = 7.8, 7.6 and 1.1 Hz, 1H), 6.77 (t, *J* = 2.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 2H), 4.58 (hept, *J* = 6.9 Hz, 1H), 3.97 (t, *J* = 6.9 Hz, 2H), 3.93 (s, 6H), 3.39 (br, t, *J* = 7.5 Hz, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 1.72 (sext, *J* = 7.5 Hz, 2H), 1.52 (d, *J* = 6.9 Hz, 6H), 1.14 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (2C), 145.7, 142.5, 139.6, 132.0, 131.5, 124.8, 124.0, 122.6, 120.6, 118.6, 114.5, 110.1, 109.3 (2C), 105.0, 56.6 (2C), 52.4, 45.2, 26.3, 23.8, 23.2 (2C), 20.7,14.7; HRMS (ESI) calculated for $C_{27}H_{32}N_3O_2^+$ [M^+] 430.2489, found 430.2495.

*4.5.4. 2-Allyl-3-isopropyl-1-(4-methoxyphenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3d**).* Prepared according to the general procedure above from **9d**, for 60 min at 80 °C; FC: dichloromethane-methanol, 4:1; yield: 360 mg (83%); white foam; R_f = 0.42 (dichloromethane-methanol, 4:1); ν_{max}($CHCl_3$) 3156, 1643, 1567, 1512, 1457, 1328 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 3H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.13-7.04 (m, 3H), 5.81 (ddt, *J* = 16.6, 10.7 and 4.9 Hz, 1H), 5.26 (d, *J* = 10.7 Hz, 1H), 4.97 (d, *J* = 16.6 Hz, 1H), 4.81 (br, d, *J* = 4.9 Hz, 2H), 4.50 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.70 (hept, *J* = 7.2 Hz, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 1.53 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 150.3, 137.8 (2C), 132.7 (2C), 132.0, 125.7, 124.6, 123.4, 122.0, 121.2, 119.3, 119.0, 116.7, 116.0 (2C), 112.6, 110.7, 55.6, 48.1, 45.5, 26.3 20.6, 19.7 (2C); HRMS (ESI) calculated for $C_{26}H_{28}N_3O^+$ [M^+] 398.2227, found 398.2222.

*4.5.5. 2-Isopropyl-3-methyl-1-(thiophen-3-yl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3e**).* Prepared according to the general procedure above from **9e**, for 90 min at 80 °C; FC: dichloromethane-methanol, 4:1; yield: 338 mg (88%); light yellow solid; mp 195-198 °C (dec.); R_f = 0.22 (ethyl acetate-methanol, 9:1); ν_{max}($CHCl_3$) 3301 (br), 1660, 1513, 1454, 1373, 1313 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.87 (dd, *J* = 2.9 and 1.2 Hz, 1H), 7.72 (d, *J* = 5.0 and 2.9 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 5.0 and 1.2 Hz, 1 H), 7.17 (br, t, *J* = 7.6 Hz, 1H), 7.09 (br, t, *J* = 7.6 Hz, 1H), 4.59 (hept, *J* = 7.0 Hz, 1H), 4.36 (t, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 7.1 Hz, 2H), 2.82 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 144.4, 138.9, 131.1, 129.7, 129.1, 128.3, 127.7, 126.1, 125.9, 124.2, 121.1, 120.8, 119.0, 112.6, 112.2, 52.2, 44.0, 21.0 (2C), 19.9, 11.0; HRMS (ESI) calculated for $C_{21}H_{22}N_3S^+$ [M^+] 348.1529, found 348.1522.

*4.5.6. 1-(tert-Butyl)-2-(3,4-dimethoxyphenyl)-3-isopropyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3g**).* Prepared according to the general procedure above from **9g**, for 60 min at 80 °C; FC: ethyl acetate-methanol, 9:1; yield: 442 mg (92%); pale yellow wax; R_f = 0.40 (ethyl acetate-methanol, 4:1); ν_{max}($CHCl_3$) 3138, 1655, 1576, 1563, 1455, 1413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.19 (br, t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.08 (m, 1 H), 6.98 (br, s, 2H), 4.17 (m, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 3.18 (m, 2H), 3.06 (hept, *J* = 7.0 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.7 (2C), 138.7, 136.5, 127.5 (2C), 124.8, 123.4, 122.8, 121.3, 120.2, 118.3, 113.9, 112.1, 111.4, 111.0, 56.7, 56.3, 45.1, 31.5 (3C), 29.6, 25.9, 20.4, 19.0 (2C); HRMS (ESI) calculated for $C_{28}H_{34}N_3O_2^+$ [M^+] 444.2646, found 444.2640.

*4.5.7. 2-(3,4-Dimethoxyphenyl)-3-isopropyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3h**).* Prepared according to the general procedure above from **9h**, for 60 min at 80 °C; FC: ethyl acetate-methanol, 9:1; yield: 295 mg (76%); off-white solid; mp 271-273 °C (dec.); R_f = 0.68 (ethyl acetate-methanol, 4:1); ν_{max}($CHCl_3$) 3122, 1601, 1516, 1463, 1421, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.41 (s, 1H), 8.27 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.06 (br, s, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.88 (dd, *J* = 8.8 and 2.0 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.37 (t, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.35 (hept, *J* = 6.7 Hz, 1H), 3.11 (t, *J* = 6.8 Hz, 2H), 1.40 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 150.1, 149.6, 137.9, 127.8, 126.2, 125.3, 123.5 (2C), 121.5, 120.0, 119.3, 118.9, 112.6, 111.5, 110.4, 108.4, 56.6, 56.6, 45.0, 26.3, 20.2, 20.0 (2C); HRMS (ESI) calculated for $C_{24}H_{26}N_3O_2^+$ [M^+] 388.2020, found 388.2029.

*4.5.8. 2-(2-Bromophenyl)-3-isopropyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3i**).* Prepared according to the general procedure above from **9i**, for 300 min at 110 °C; FC: dichloromethane-methanol, 3:1; yield: 341 mg (77%); pale yellow solid; mp 280-282 °C (dec.); R_f = 0.10 (ethyl acetate-methanol, 4:1); ν_{max}($CHCl_3$) 3178, 1645, 1597, 1541, 1460, 1427, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.7 (s, 1H), 8.36 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.53 (br, d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1 H), 7.07 (t, *J* = 7.7 Hz, 1H), 4.53 (t, J = 7.2 Hz, 2H), 3.24 (t, *J* = 7.2 Hz, 2H), 3.18 (hept, *J* = 7.0 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 149.1, 148.3, 138.0, 134.0, 132.8, 132.1, 129.7, 129.3, 129.2, 123.6, 121.2, 119.9, 118.5, 115.9, 113.0, 108.0, 45.0, 26.3, 20.1, 19.3, 19.2; HRMS (ESI) calculated for $C_{22}H_{21}BrN_3^+$ [M^+] 406.0919, found 406.0928.

*4.5.9. 2-(2-Bromo-4,5-dimethoxyphenyl)-3-isopropyl-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium chloride (**3j**).* Prepared according to the general procedure above from **9j**, for 360 min at 110 °C; FC: dichloromethane-methanol, 4:1; yield: 422 mg (84%); off-white solid; mp 298-301 °C (dec.); R_f = 0.38 (ethyl acetate-methanol, 4:1); ν_{max}($CHCl_3$) 3122, 1656, 1599, 1560, 1511, 1461, 1442, 1390 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 7.46 (br, s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.28 (br, t, *J* = 7.7 Hz, 1H), 7.17 (br, t, *J* = 7.7 Hz, 1H), 4.73 (m, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 3.43 (t, *J* = 7.1 Hz, 2H), 3.37 (hept, *J* = 7.0 Hz, 1H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 153.5, 151.8, 150.9, 139.0, 127.1 (2C), 126.2, 124.5, 121.5, 120.8, 119.3, 117.1, 115.7, 113.7, 112.3, 112.2, 110.9, 56.9, 56.8, 45.6, 26.9, 20.2, 18.7, 18.1; HRMS (ESI) calculated for $C_{24}H_{25}BrN_3O_2^+$ [M^+] 466.1125, found 466.1116.

*4.5.10. 1-(4-Methoxyphenyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indole (**4a**).* Prepared according

to the general procedure above from **10a**, for 60 min at 80 °C; FC: ethyl acetate-methanol, 9:1; yield: 195 mg (62%); white foam; R_f = 0.48 (ethyl acetate-methanol, 4:1); $\nu_{max}(CHCl_3)$ 3337, 1646, 1529, 1455, 1412, 1319 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (br, s, 1H), 7.75-7.62 (m, 3H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.19-7.09 (m, 2H), 7.02 (br, d, *J* = 7.1 Hz, 2H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.86 (s, 3H), 3.20 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 138.6, 129.0, 128.0 (2C), 126.8, 123.0, 120.8 (2C), 118.6, 115.1 (2C), 111.9 (2C), 111.7 (2C), 107.9, 55.4, 43.6, 21.8; HRMS (ESI) calculated for $C_{20}H_{18}N_3O^+$ [MH^+] 316.1450, found 316.1462.

*4.5.11. 1-(tert-Butyl)-6,11-dihydro-5H-imidazo[1',5':1,2]pyrido[3,4-b]indole (**4b**).* Prepared according to the general procedure above from **10b**, for 60 min at 80 °C; FC: ethyl acetate-hexane, 9:1; yield: 196 mg (74%); white foam; R_f = 0.68 (ethyl acetate-methanol, 9:1); $\nu_{max}(CHCl_3)$ 3298, 1638, 1533, 1437, 1424, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (br, s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.40 (s, 1H), 7.15 (td, *J* = 7.7 and 1.2 Hz, 1H), 7.10 (td, *J* = 7.7 and 1.2 Hz, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.07 (t, *J* = 6.7 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 136.5, 134.5, 126.7, 126.3, 122.0, 120.2, 118.5, 118.0, 111.3, 107.3, 43.6, 32.4, 31.0 (3C), 20.9; HRMS (ESI) calculated for $C_{17}H_{20}N_3^+$ [MH^+] 266.1657, found 266.1661.

4.6. General procedure for preparation of compounds 11i,j

To a solution of the Ugi product **(9)** (1.0 mmol) in anhydrous toluene (10 mL) was added $POCl_3$ (0.46 mL, 5 mmol). The reaction mixture was stirred at 50 °C, under a nitrogen atmosphere, until the complete consumption of the starting material. After cooling to rt, a 5% solution of Na_2CO_3 (10 mL) was added and the mixture extracted with dichloromethane (2 x 25 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by FC to yield the pure intermediate **(11)** as indicated below.

*4.6.1. N-(2-Bromophenyl)-N-((4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl)isobutyramide (**11i**).* Prepared according to the general procedure above from **9i**; FC: ethyl acetate-hexane, 1:1.5; yield: 59 mg (14%); thick syrup; R_f = 0.54 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3318, 1628, 1607, 1526, 1434, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (br, m, 1H), 7.70 (dd, *J* = 7.9 and 1.8 Hz, 1H), 7.63 (br, d, *J* = 7.9 Hz, 1H), 7.51 (br, d, *J* = 7.9 Hz, 1H), 7.37-7.24 (m, 3H), 7.18 (br, t, *J* = 7.8 Hz, 1H), 6.88 (br, d, *J* = 7.6 Hz, 1H), 5.38 (d, *J* = 14.3 Hz, 1H), 4.50-4.36 (br, m, 1H), 3.91 (dt, *J* = 15.8 and 7.3 Hz, 1H), 3.73 (br, ddd, *J* = 15.8, 11.4 and 7.6 Hz, 1H), 3.01-2.81 (m, 2H), 2.28 (hept, *J* = 6.7 Hz, 1H), 1.20 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 157.9, 141.4, 135.0, 133.1, 130.8, 129.5, 127.7, 127.5, 123.8, 123.5, 119.8, 119.0, 117.8, 114.4, 111.8, 52.9, 49.7, 32.1, 25.1, 19.8, 19.6; HRMS (ESI) calculated for $C_{22}H_{23}BrN_3O^+$ [MH^+] 424.1024, found 424.1029.

*4.6.2 N-(2-Bromo-4,5-dimethoxyphenyl)-N-((4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl)isobutyramide (**11j**).* Prepared according to the general procedure above from **9j**; FC: ethyl acetate-hexane, 1:1.5; yield: 111.5 mg (23%); thick oil; R_f = 0.41 (ethyl acetate-dichloromethane, 7:3); $\nu_{max}(CHCl_3)$ 3278 (br), 1632, 1618, 1512, 1466, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (br, m, 1H), 7.59 (br, d, *J* = 7.9 Hz, 1H), 7.47 (br, d, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.25 (br, s, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.07 (br, s, 1H), 5.31 (d, *J* = 13.7 Hz, 1H), 4.22 (d, *J* = 13.7 Hz, 1H), 3.88 (s, 3H), 3.86 (m, 2H), 3.68 (s, 3H), 2.87 (m, 2H), 2.83 (hept, *J* = 6.6 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 157.7, 150.2, 149.3, 137.1, 132.5, 127.9, 125.7, 125.0, 120.5, 120.2, 116.9, 116.0, 114.2, 113.0 (2C), 56.7, 56.5, 53.0, 49.2, 32.3, 30.1, 20.5, 19.8; HRMS (ESI) calculated for $C_{24}H_{27}BrN_3O_3^+$ [MH^+] 484.1236, found 484.1229.

References and notes

1. For an overview, see: (a) Zhu, J.; Bienaymé, H. Eds., Multicomponent reactions, Wiley-VCH, Weinheim, 2005. For recent reviews, see: (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234–6246. (c) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89. (d) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634.
2. Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267–268.
3. (a) Evans, C. G.; Smith, M. C.; Carolan, J. P.; Gestwicki, J. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2587–2590. (b) De Moliner, F.; Crosignani, S.; Banfi, L.; Riva, R.; Basso, A. *J. Comb. Chem.* **2010**, *12*, 613–616. (c) Riva, R.; Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Pani, M. *J. Org. Chem.* **2010**, *75*, 5134–5143. (d) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, 8444–8454. (e) Beaumont, S.; Retailleau, P.; Dauban, P.; Dodd, R. H. *Eur. J. Org. Chem.* **2008**, 5162–5175. (f) Constantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85. (g) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683–4686. (h) Weber, L. *Drug Discov.Today* **2002**, *7*, 143–147. (i) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
4. (a) Dominguez, G.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2011**, 7243–7253. (b) Singh, V.; Hutait, S.; Biswas, S.; Batra, S. *Eur. J. Org.* **2010**, 531–539. (c) Danieli, B.; Giovanelli, P.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *J. Comb. Chem.* **2005**, *7*, 458–462. (d) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231–261.
5. Lesma, G.; Cecchi, R.; Crippa, S.; Giovanelli, P.; Meneghetti, F.; Musolino, M.; Sacchetti, A.; Silvani, A. *Org. Biomol. Chem.* **2012**, *10*, 9004–9012.
6. (a) Khorana, N.; Smith, C.; Herrick-Davis, K.; Purohit, A.; Teitler, M.; Grella, B.; Dukat, M.; Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 3930–3937. (b) Abou-Gharbia, M.; Patel, U. R.; Webb, M. B.; Moyer, J. A.; Andree, T. H.; Muth, E. A. *J. Med. Chem.* **1987**, *30*, 1818–1823. (c) Oakley, N.; Jones, B. *Eur. J. Pharmacol.* **1980**, *68*, 381.
7. Callaway, J. C.; Gyntber, J.; Poso, A.; Airaksinen, M. M.; Vepsäläinen J. *J. Heterocycl. Chem.* **1994**, *31*, 431–435.
8. Jenkins, P. R.; Wilson, J.; Emmerson, D.; Garcia, M. D.; Smith, M. R.; Gray, S. J.; Britton, R. G.; Mahale, S.; Chaudhuri, B.; *Bioorg. Med. Chem.* **2008**, *16*, 7728–7739.
9. Gupta, L.; Srivastava, K.; Singh, S.; Puri, S. K.; Chauhan P. M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3306–3309.
10. (a) Fourtillan, J.-B.; Fourtillan, M.; PCT Int. Appl. (2008), WO 2008101824 A1 20080828. (b) Fourtillan, J.-B.; Fourtillan, M.; Jacquesy, J.-C; Karam, O.; Tafani, J.-P; Zunino, F.; PCT Int. Appl. (2002), WO 2002092598 A1. (c) Ostresh, J.M.; PCT Int. Appl. (1998), WO 9834112 A1 19980806. (d) Blondelle, S.: et al.; Peptides **2000**, Proceedings of the 26th European Peptide Symposium, Montpellier (Fr).
11. (a) Trujillo, J. I.; Meyers, M. J.; Anderson, D. R.; Hegde, S.; Mahoney, M. W.; Vernier, W. F.; Buchler, I. P.; Wu, K. K.; Yang, S; Hartmann, S. J.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4657–4663. (b) Meyers, M. J.; Trujillo, J. I.; Vernier, W. F.; Anderson, D. R.; Reitz, D. B.; Buchler, I. P.; Hedge, S. G.; Mahoney, M. W.; Wu, K. K. PTC Int. Appl. (2005), WO 2005009370 A2 20050203.
12. Seganish, W. M.; Bercovici, A.; Ho, G. D.; Loozen, H. J. J.; Timmers, C. M.; Tulshian, D. *Tetrahedron Lett.* **2012**, *53*, 903–905.
13. (a) Ho, G. D.; Seganish, W. M.; Bercovici, A.; Tulshian, D.; Greenlee, W. J.; Van Rijn, R.; Hruza, A.; Xiao, L.; Rindgen, D.; Mullins, D.; Guzzi, M.; Zhang, X.; Bleickardt, C.; Hodgson, R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2585–2589. (b) Knueppel, D.; Martin, S. F. *Tetrahedron* **2011**, *67*, 9765–9770.
14. Zhang, Y. G.; Chan, J. Y. G. *Energy Environ. Sci.*, **2010**, *3*, 408–417.

15. Riduan, S. N.; Zhang, Y. *Chem. Soc. Rev*. **2013**, *42*, 9055–9070 and references cited therein.
16. (a) Rawat, K.; Bohidar, H. B. *J. Phys. Chem. B* **2012**, *116*, 11065–11067. (b) Geng, F.; Zheng, L.; Yu, L.; Li, G.; Tung, C. *Process Biochem*. **2010**, *45*, 306–311.
17. Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem*. **2008**, *73*, 1983–1986.
18. (a) Maiorana, S.; Baldoli, C.; Licandro, E.; Casiraghi, L.; de Magistris, E.; Paio, A.; Provera, S.; Seneci, P. *Tetrahedron Lett*. **2000**, *41*, 7271–7275. (b) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem*. **1986**, *51*, 1159–1165.
19. D□mling, A. and Ugi, I., *Angew*. *Chem. Int. Ed*. **2000**, *39*, 3168–3210.

Supplementary Material

^{1}H NMR and ^{13}C NMR copies of all synthesized compounds. Supplementary data associated with this article can be found in the online version.

Supporting information

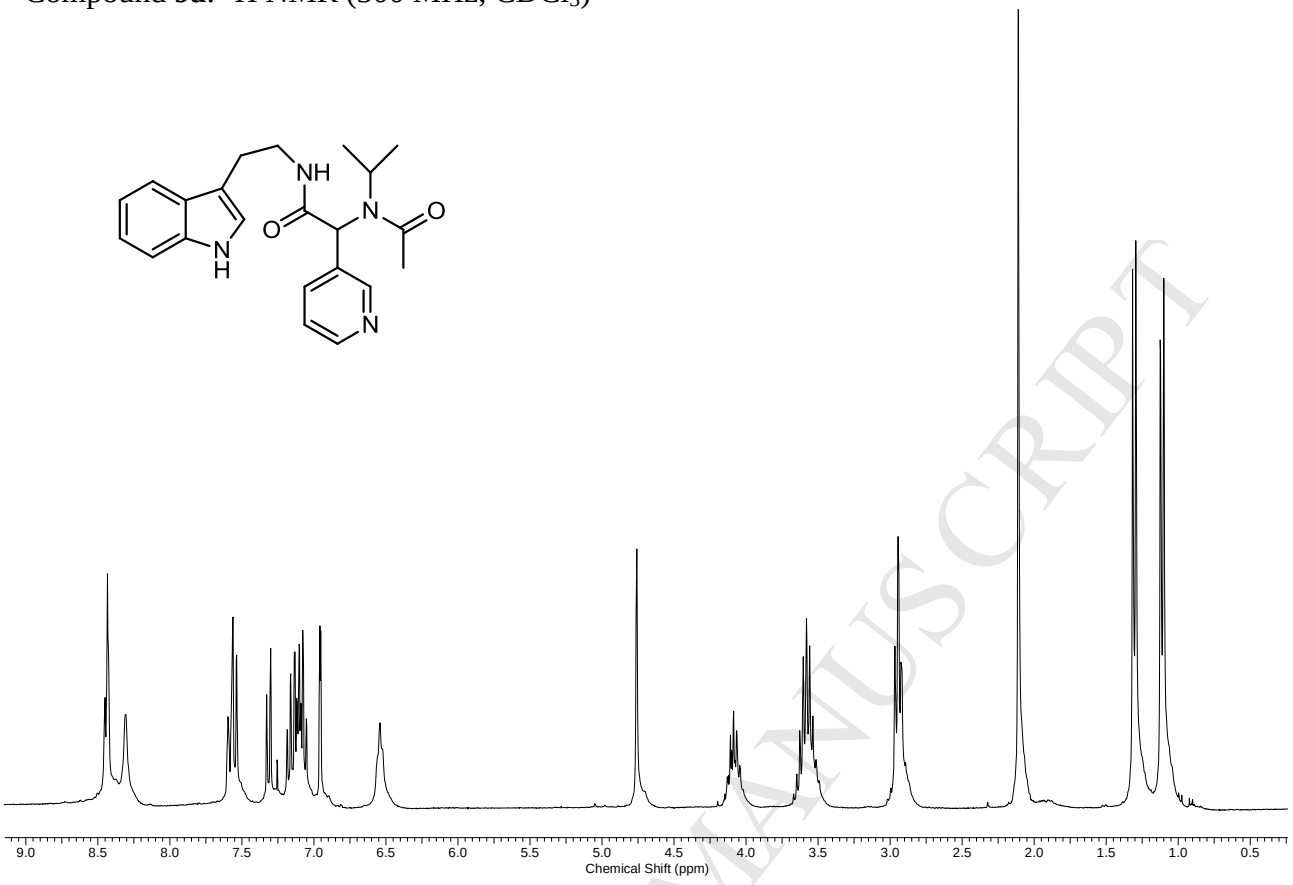
Multicomponent Access to Novel Dihydroimidazo[1',5':1,2]pyrido[3,4-b]indol-2-ium Salts and Indoles by means of Ugi/Bischler–Napieralski/Heterocyclization Two Step Strategy

Alessandra Silvani, Giordano Lesma,* Sergio Crippa, and Vito Vece*

Dipartimento di Chimica, Università degli Studi di Milano, via C. Golgi, 19 20133 Milano (Italy)

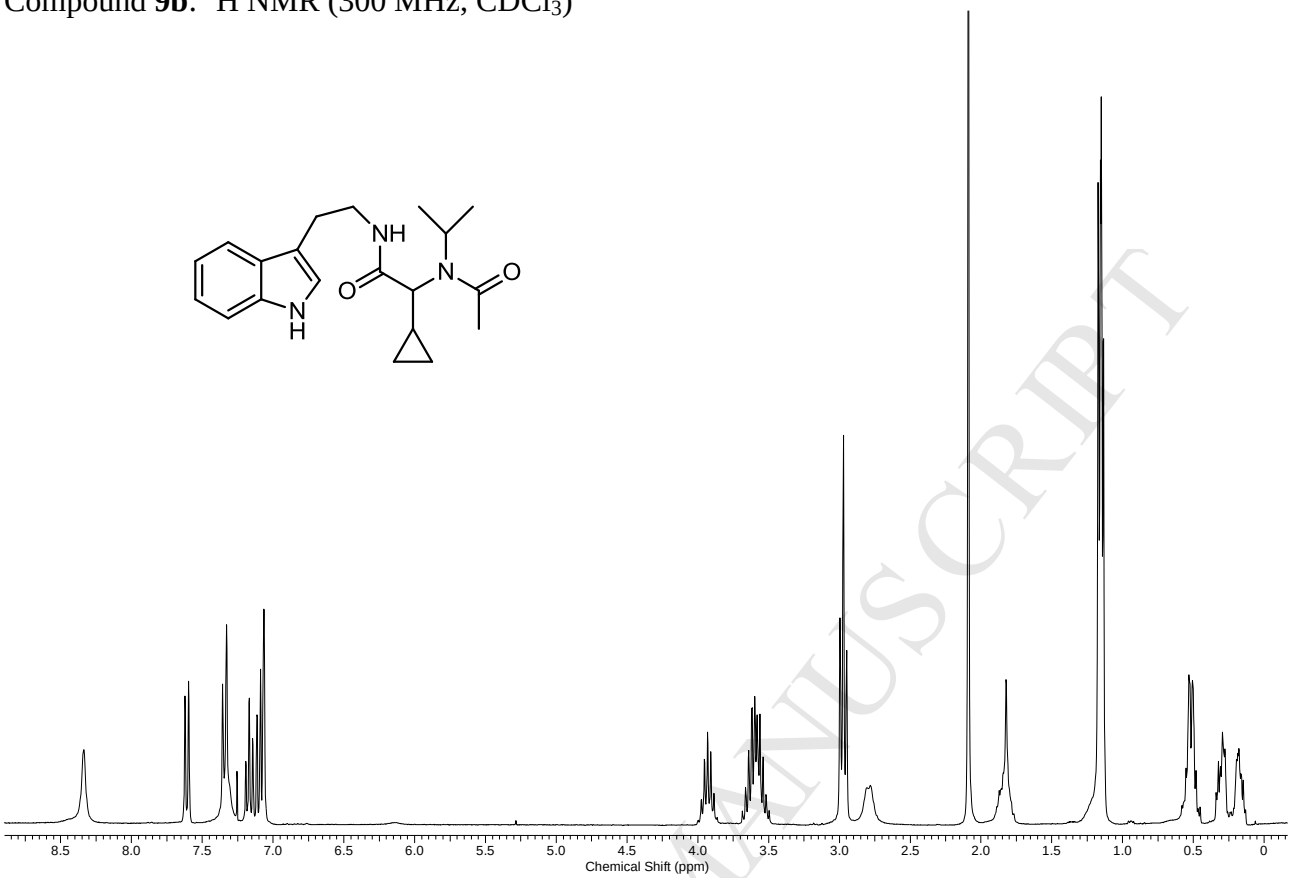
email: giordano.lesma@unimi.it

Compound **9a**: ^{1}H NMR (300 MHz, $CDCl_3$)

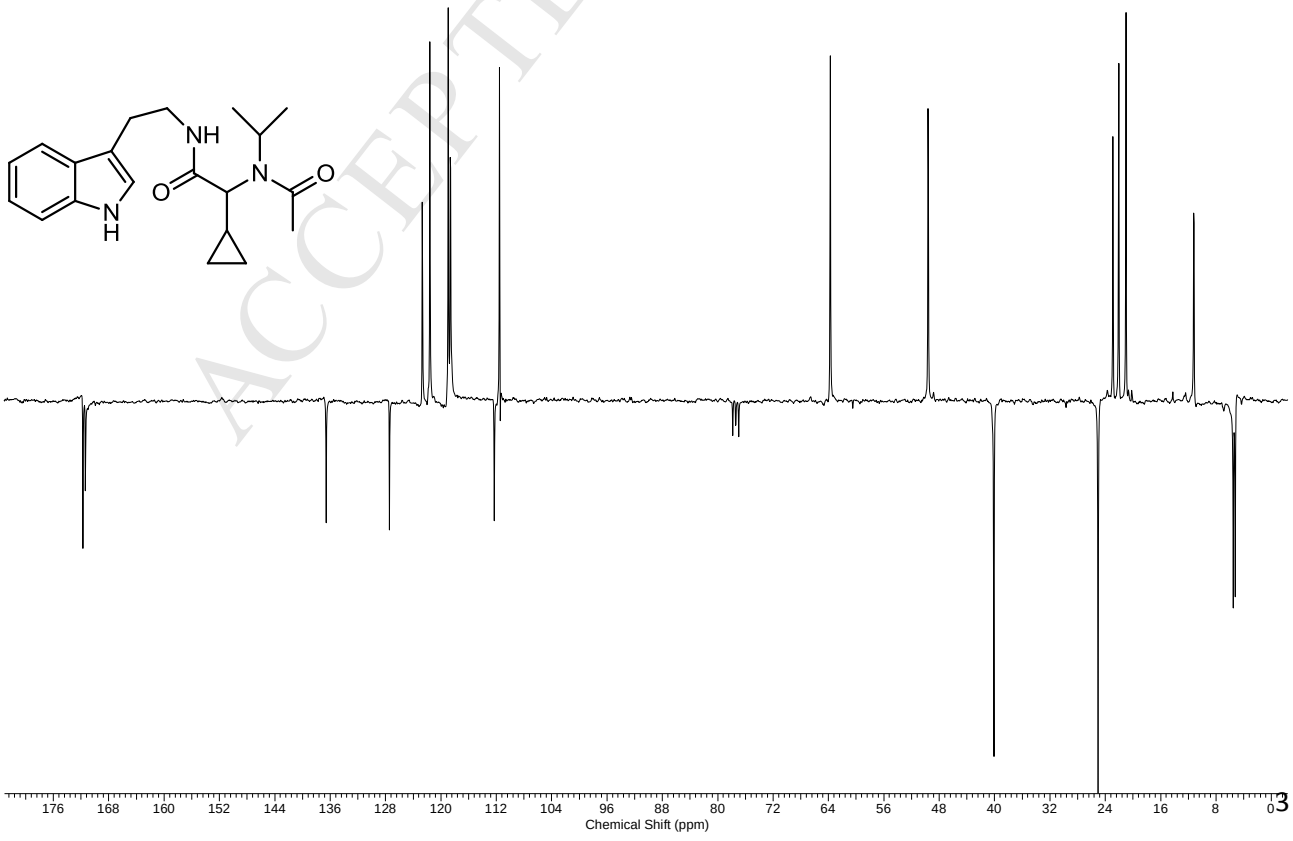


Compound **9a**: ^{13}C NMR (75 MHz, $CDCl_3$)

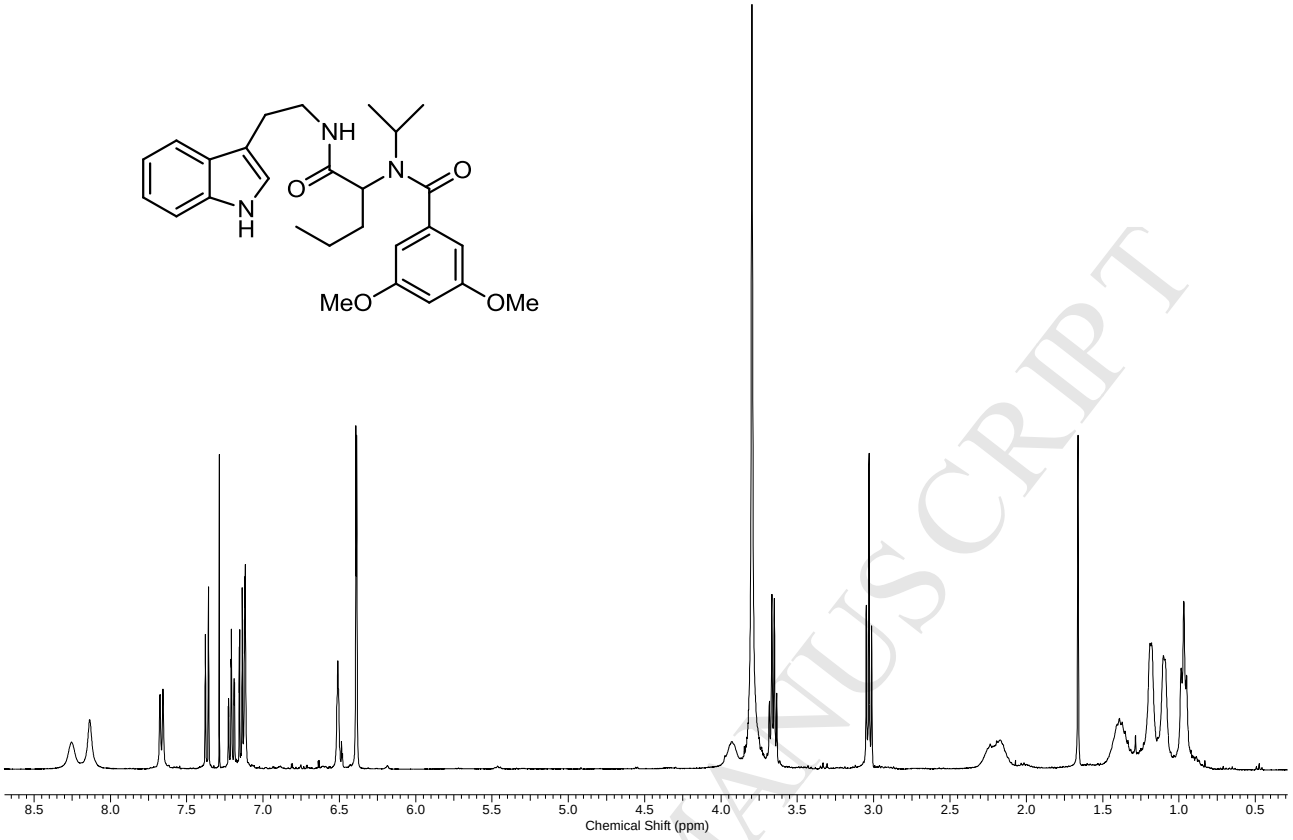
Compound **9b**: ^{1}H NMR (300 MHz, $CDCl_3$)



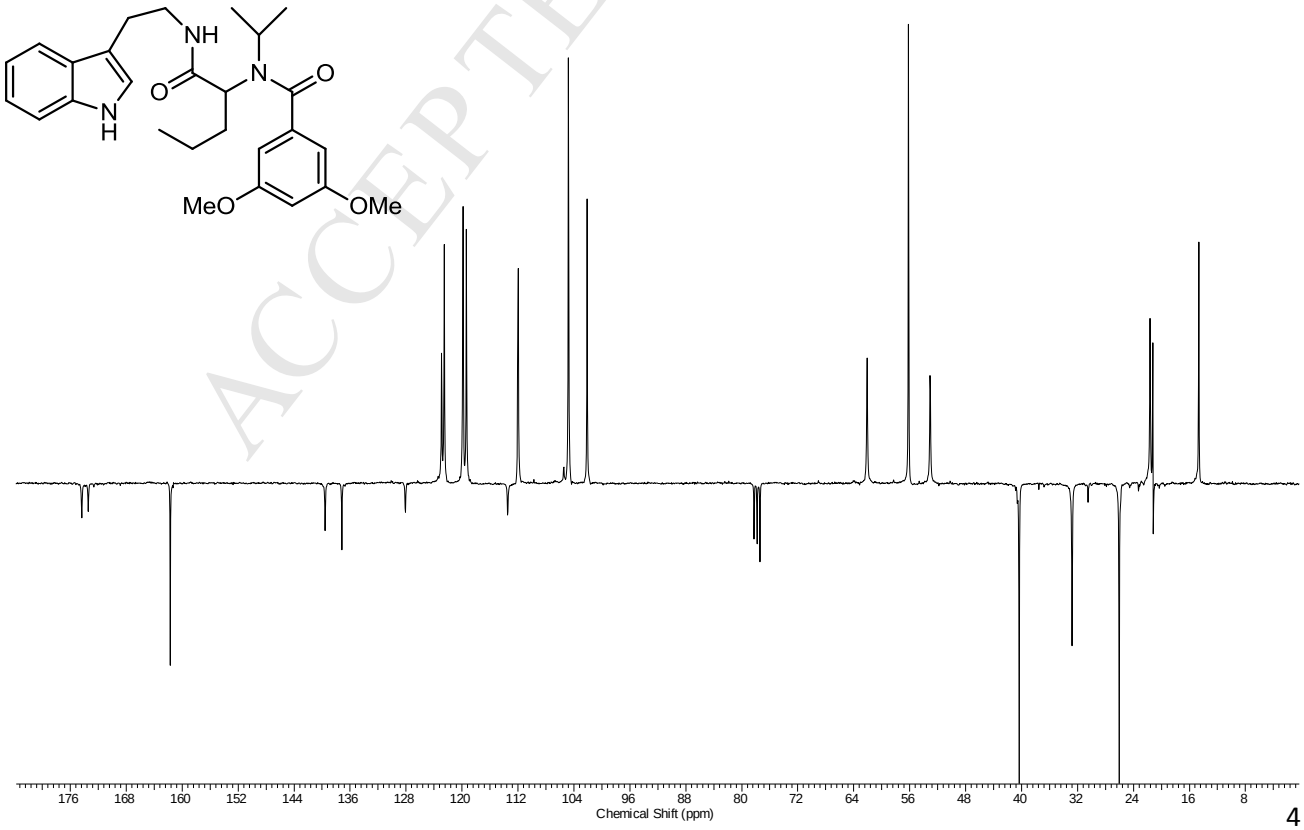
Compound **9b**: ^{13}C NMR (75 MHz, $CDCl_3$)



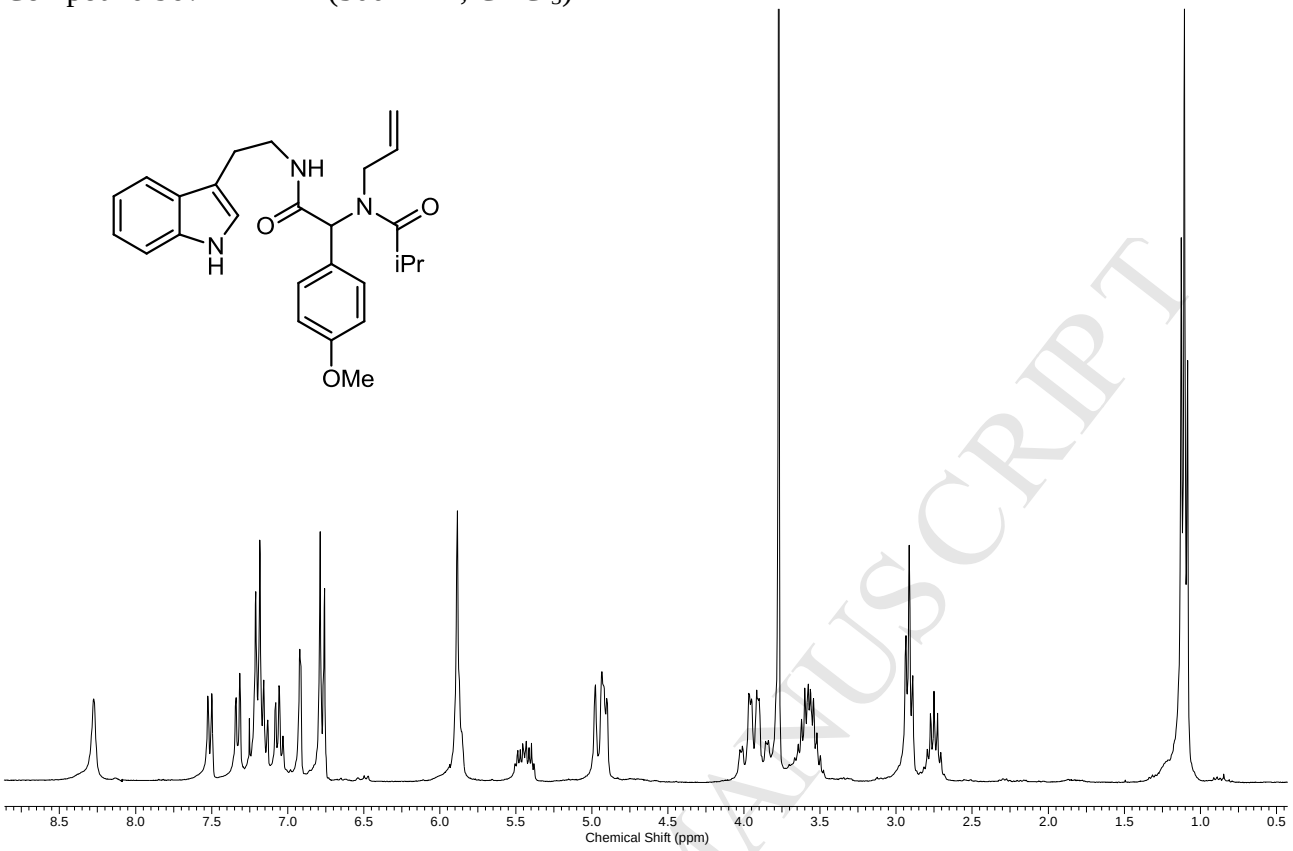
Compound **9c**: ^{1}H NMR (400 MHz, $CDCl_3$)



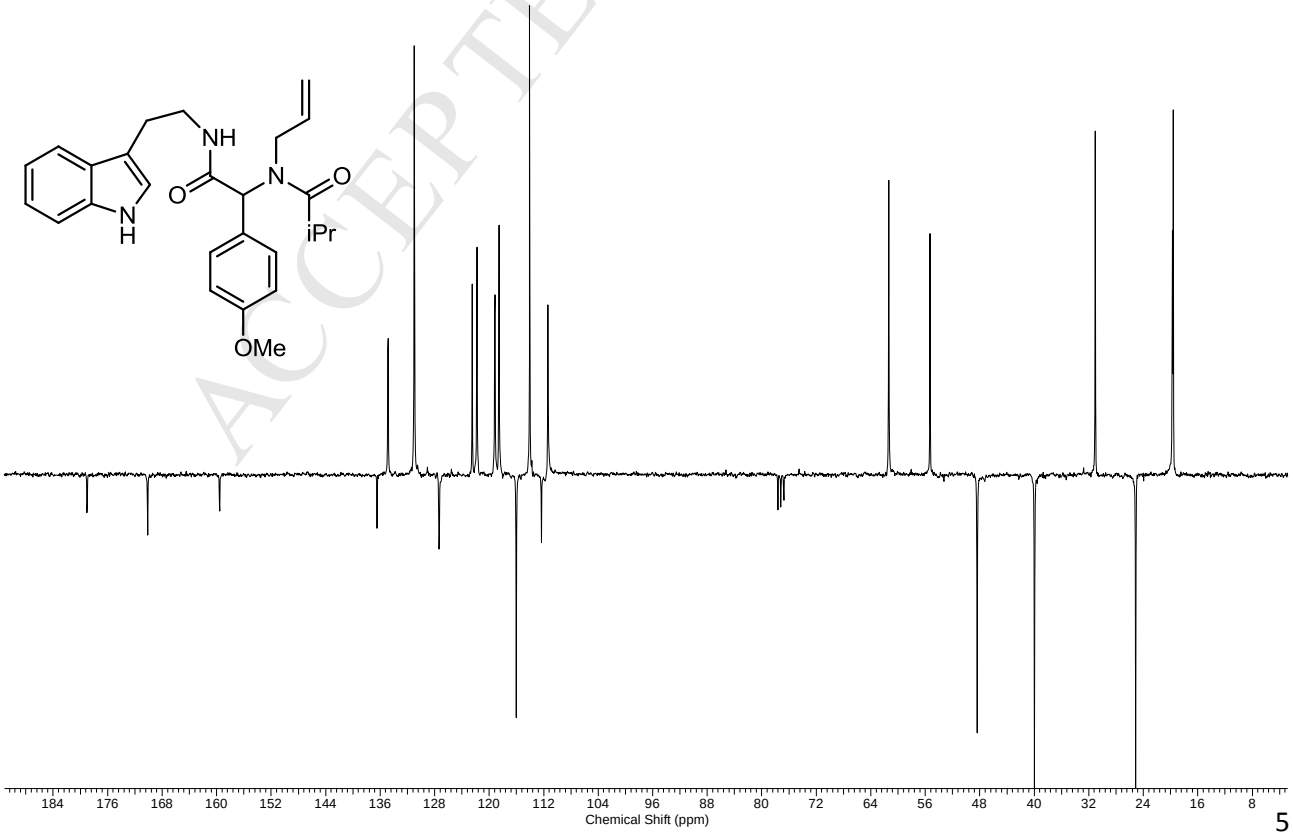
Compound **9c**: ^{13}C NMR (75 MHz, $CDCl_3$)



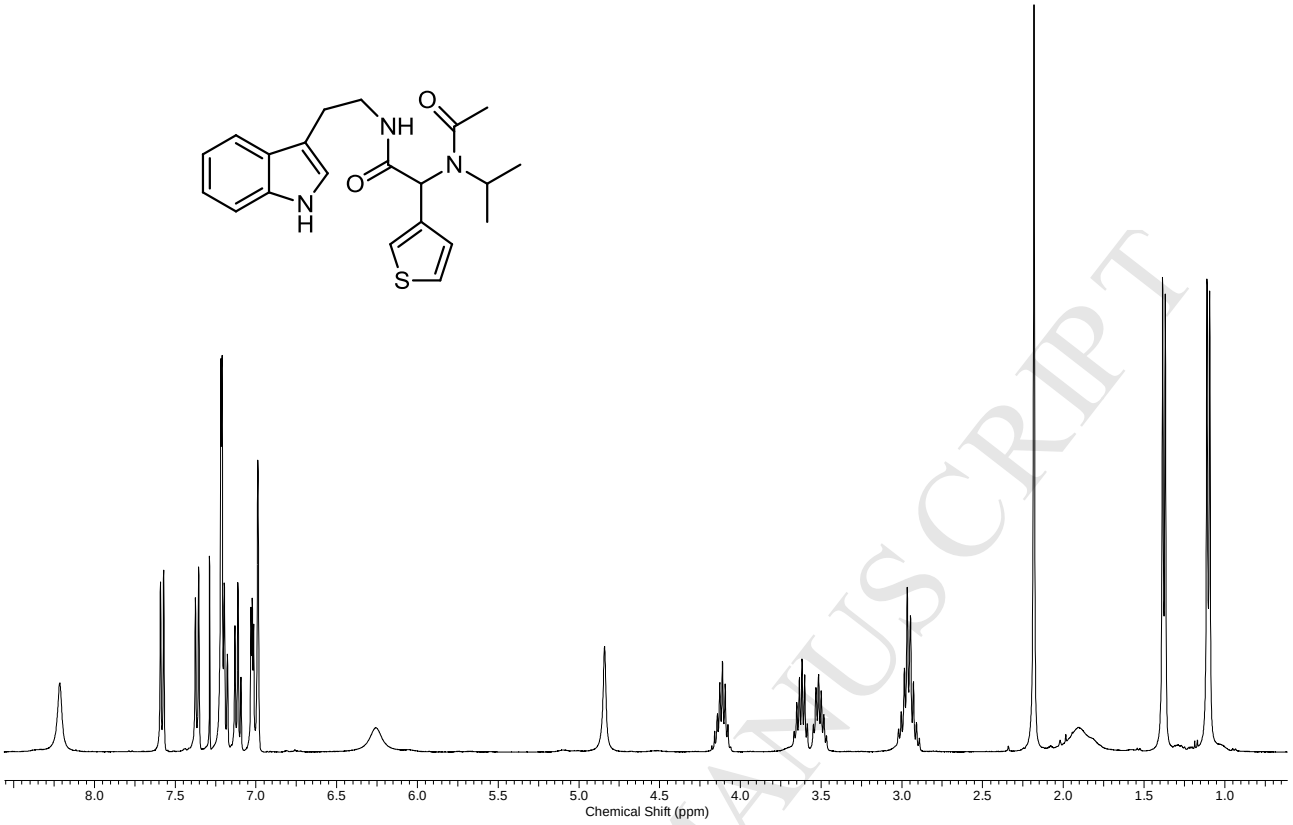
Compound **9d**: ^{1}H NMR (300 MHz, $CDCl_3$)



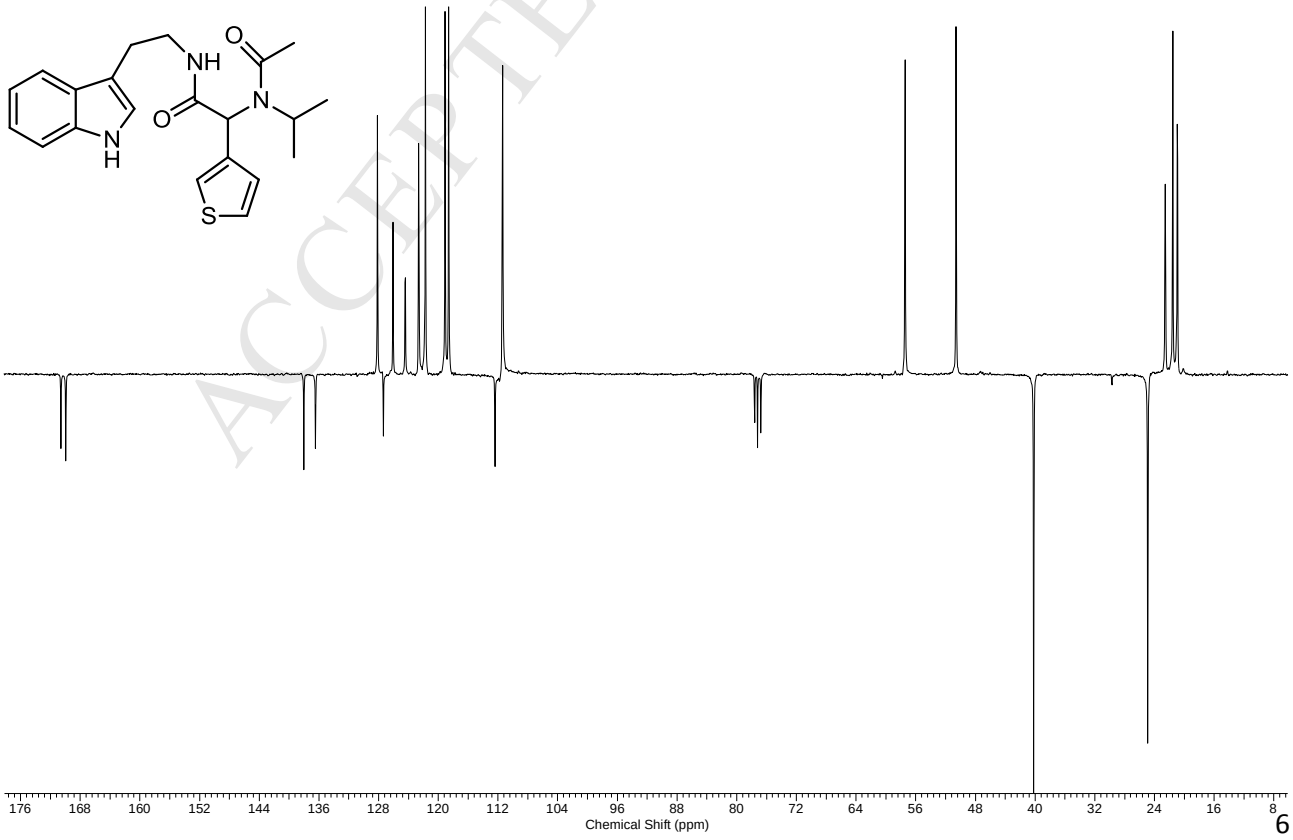
Compound **9d**: ^{13}C NMR (75 MHz, $CDCl_3$)



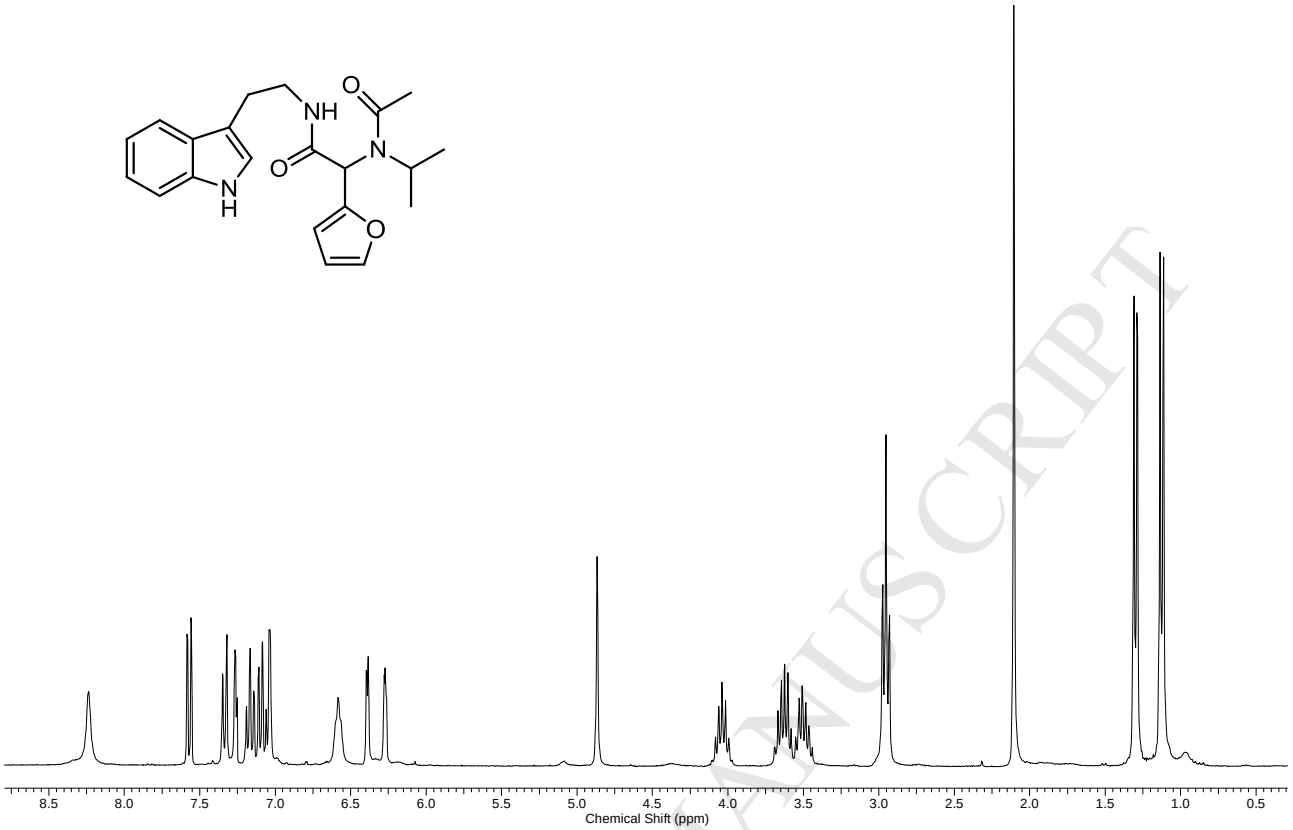
Compound **9e**: ^{1}H NMR (400 MHz, $CDCl_3$)



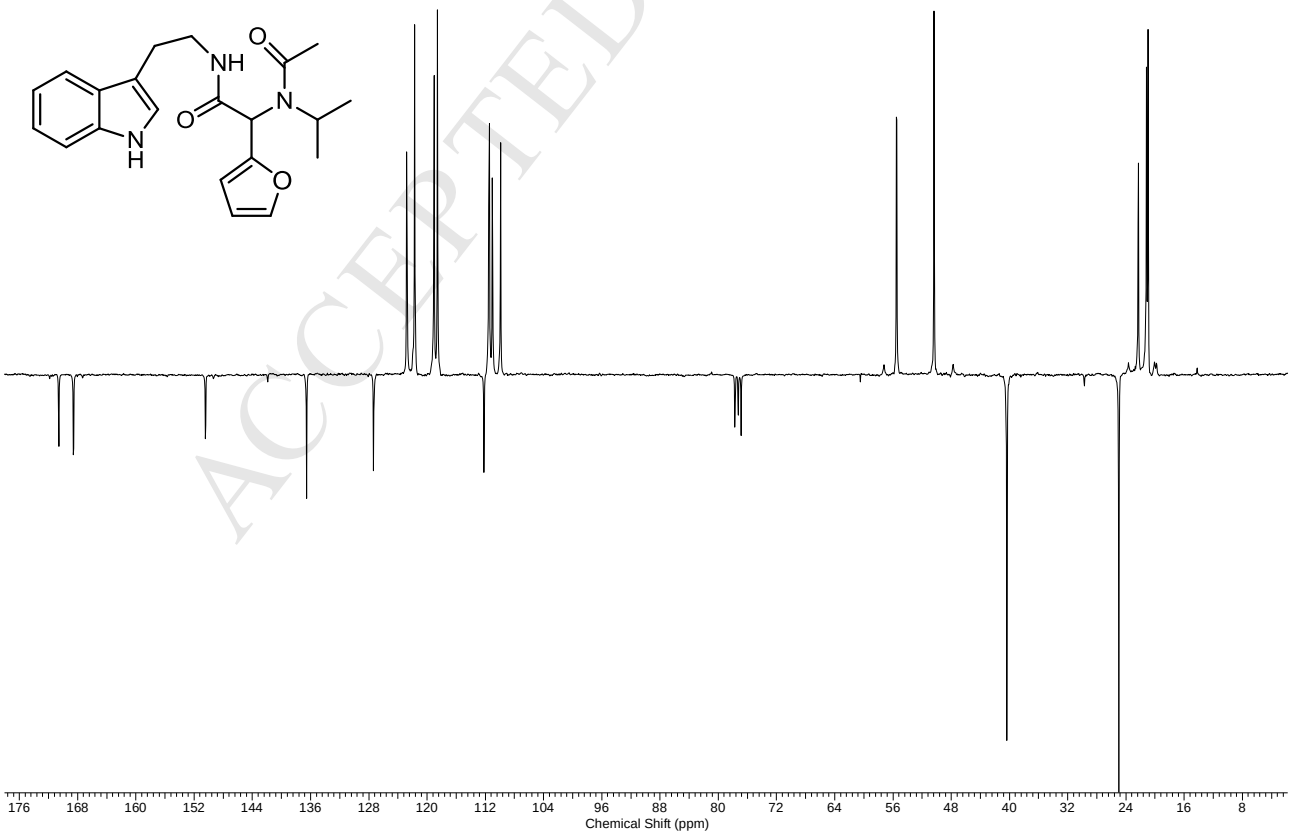
Compound **9e**: ^{13}C NMR (75 MHz, $CDCl_3$)



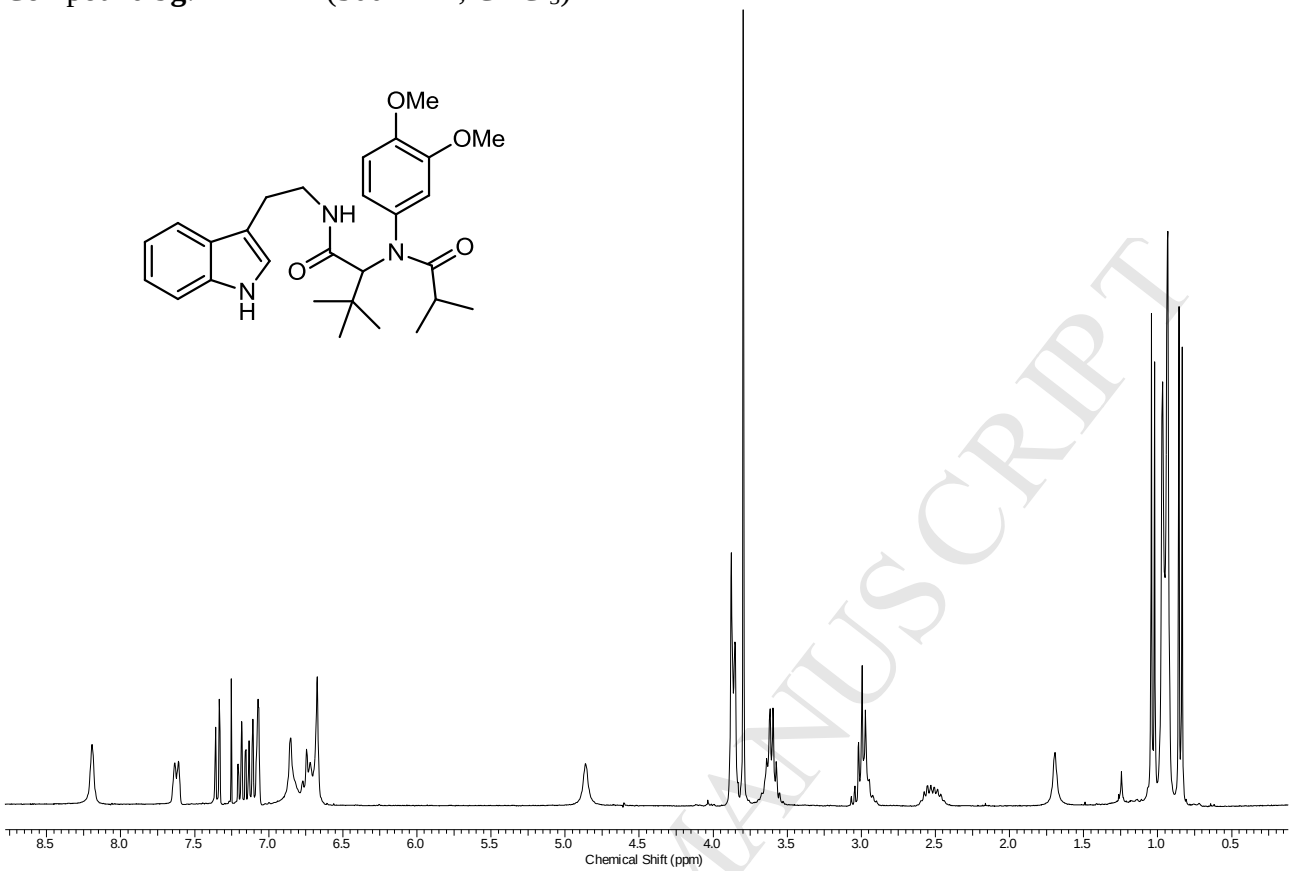
Compound **9f**: ^{1}H NMR (300 MHz, $CDCl_3$)



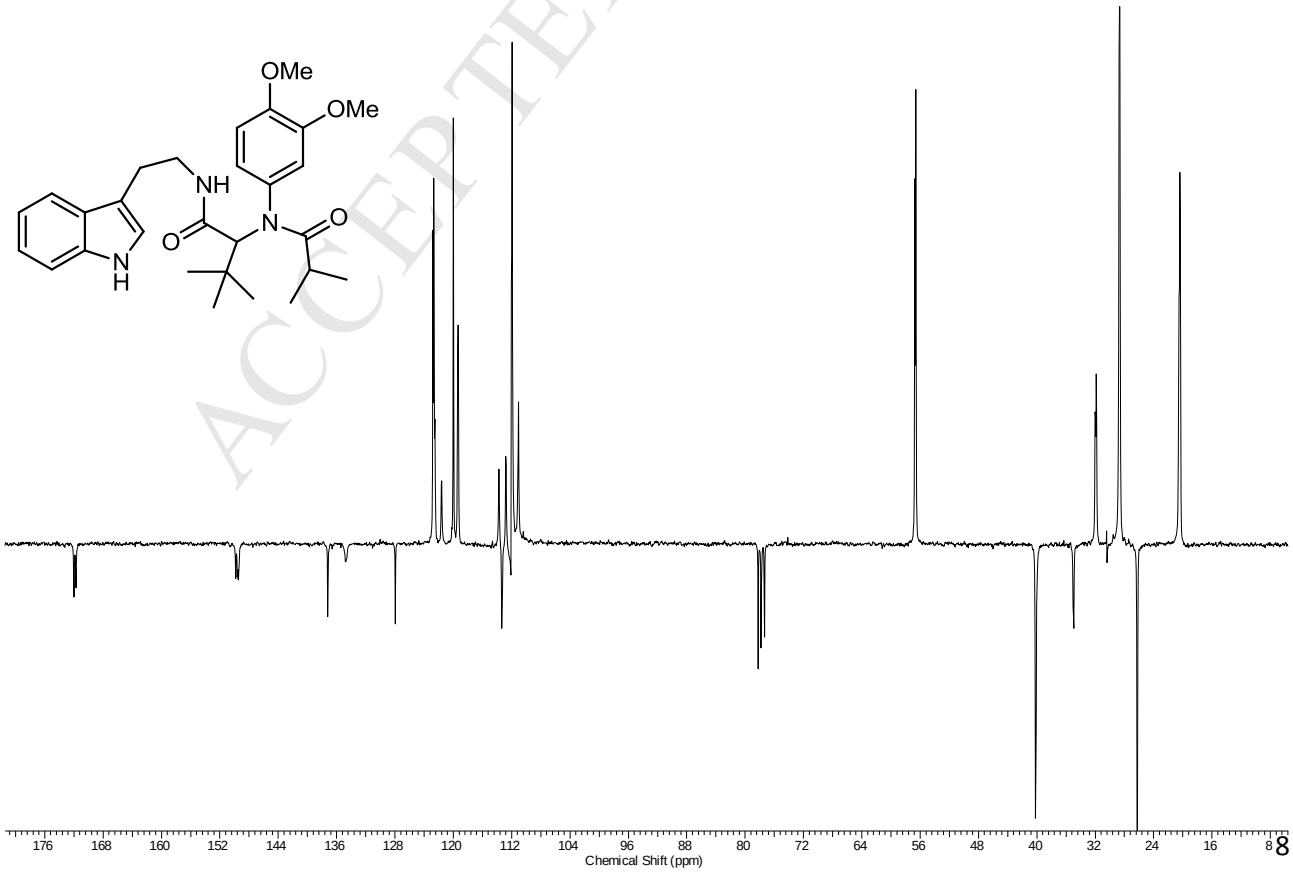
Compound **9f**: ^{13}C NMR (75 MHz, $CDCl_3$)



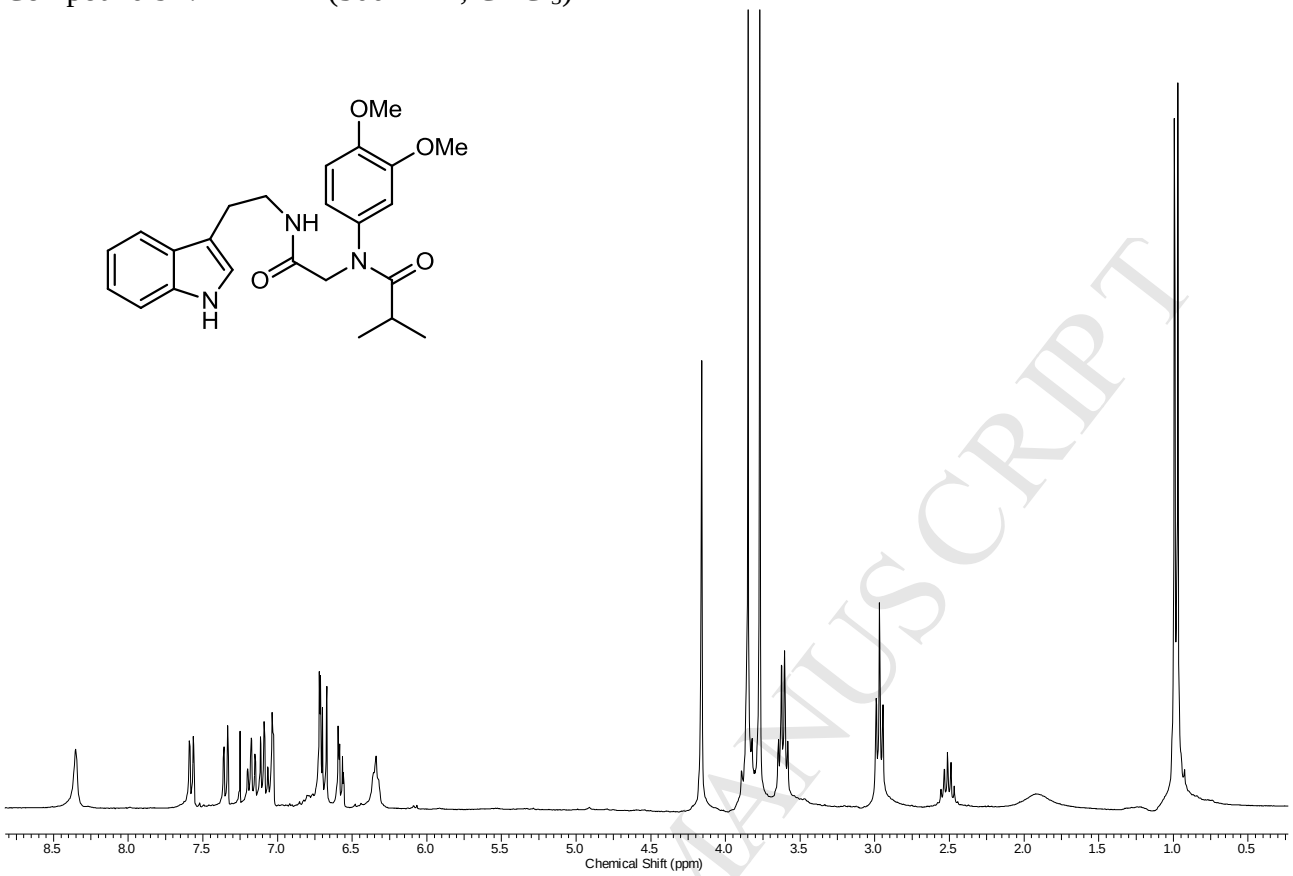
Compound **9g**: ^{1}H NMR (300 MHz, $CDCl_3$)



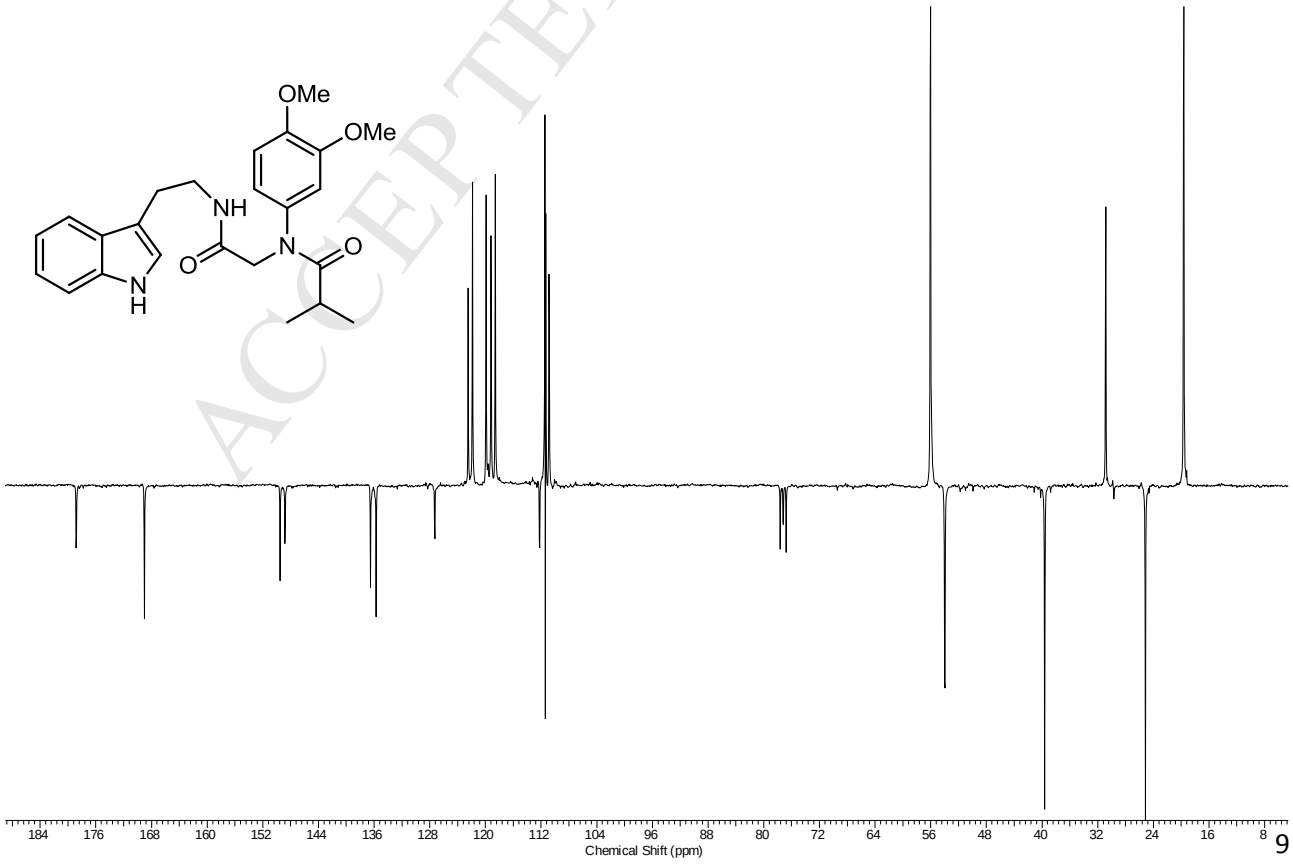
Compound **9g**: ^{13}C NMR (75 MHz, $CDCl_3$)



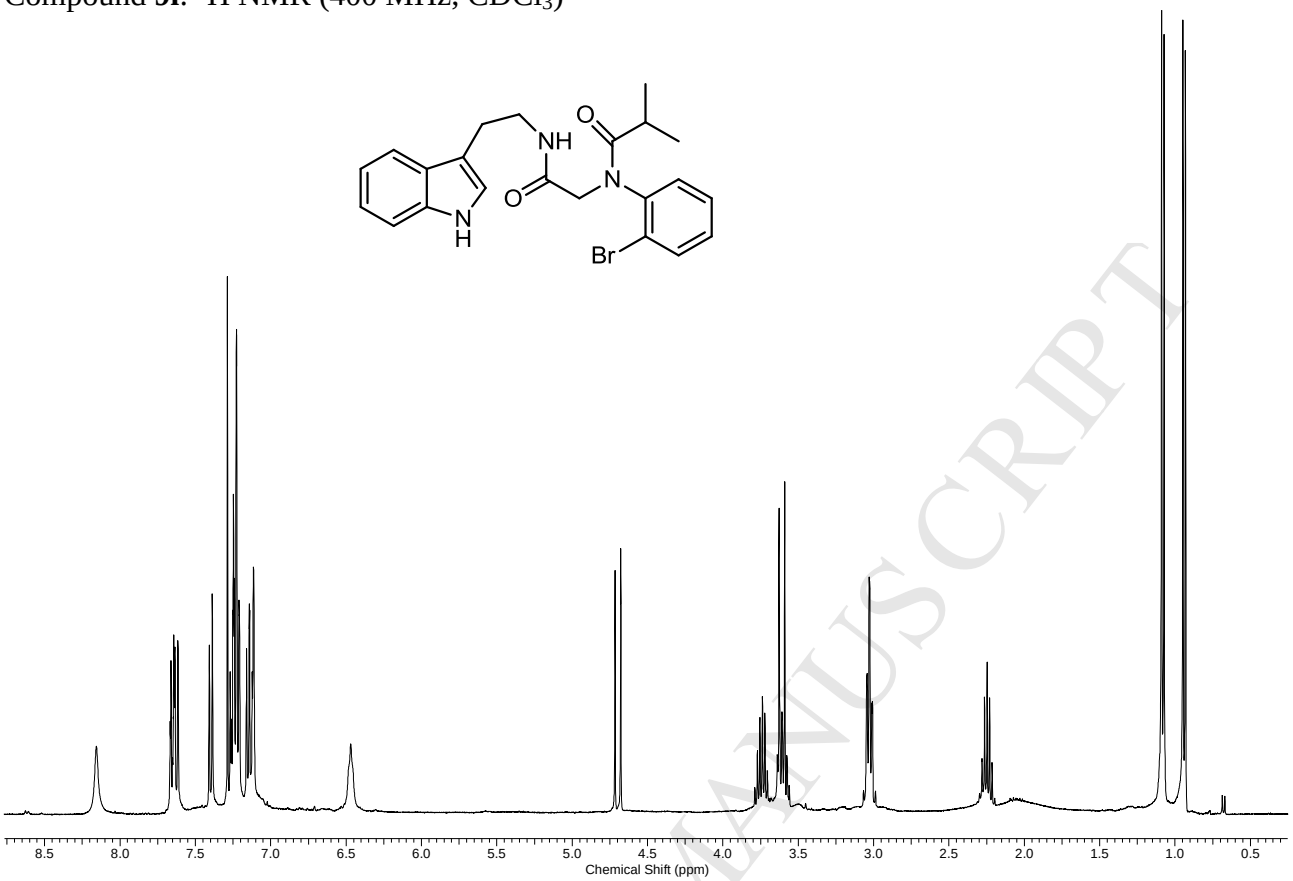
Compound **9h**: ^{1}H NMR (300 MHz, $CDCl_3$)



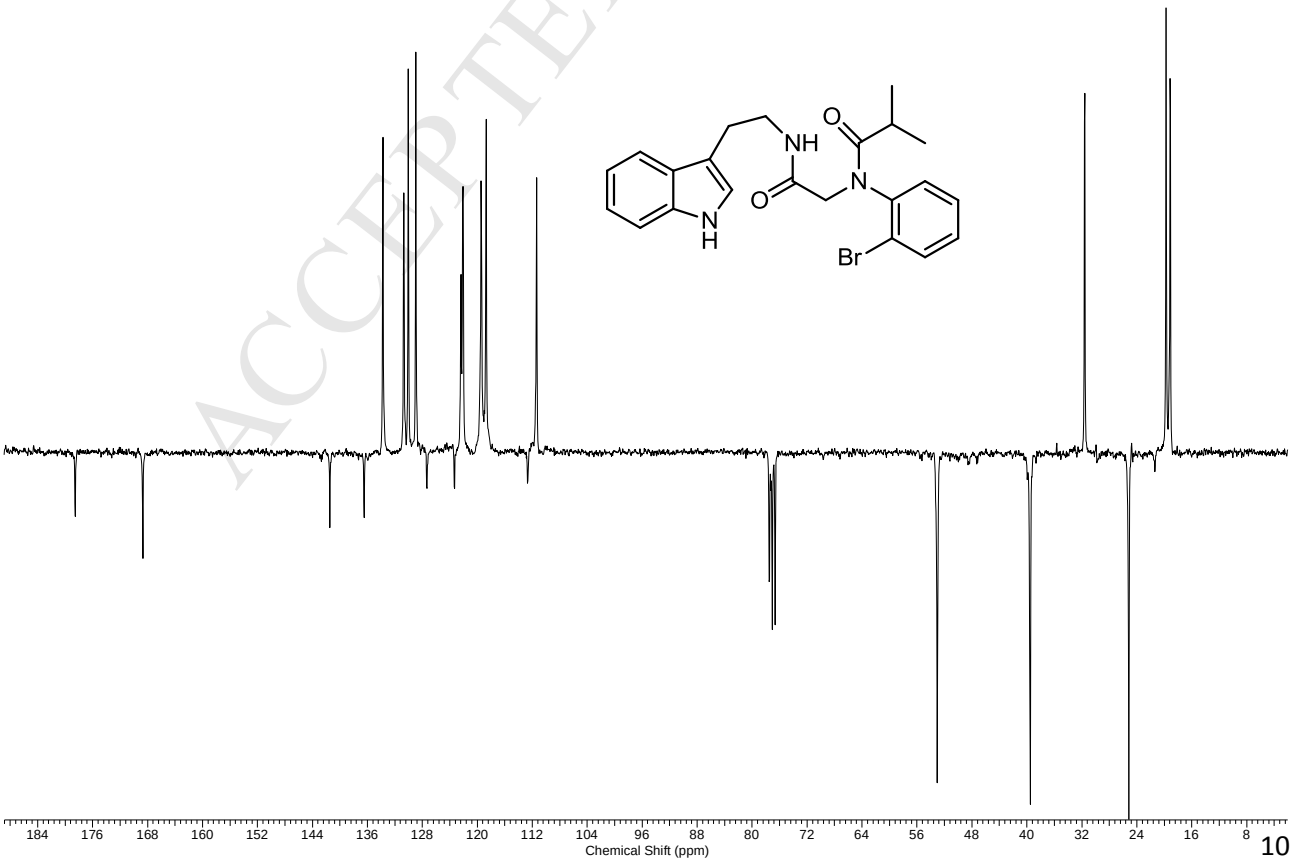
Compound **9h**: ^{13}C NMR (75 MHz, $CDCl_3$)



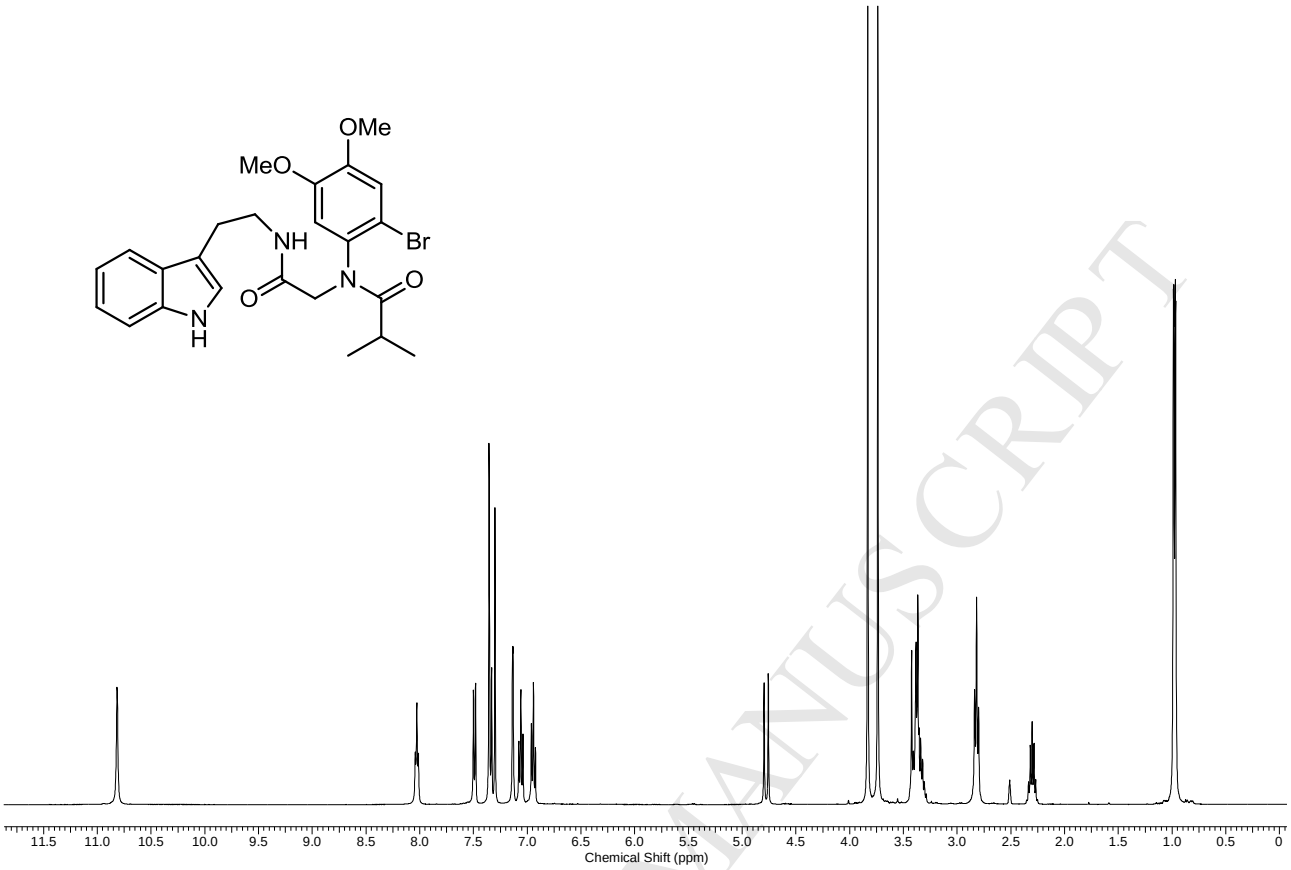
Compound **9i**: ^{1}H NMR (400 MHz, $CDCl_3$)



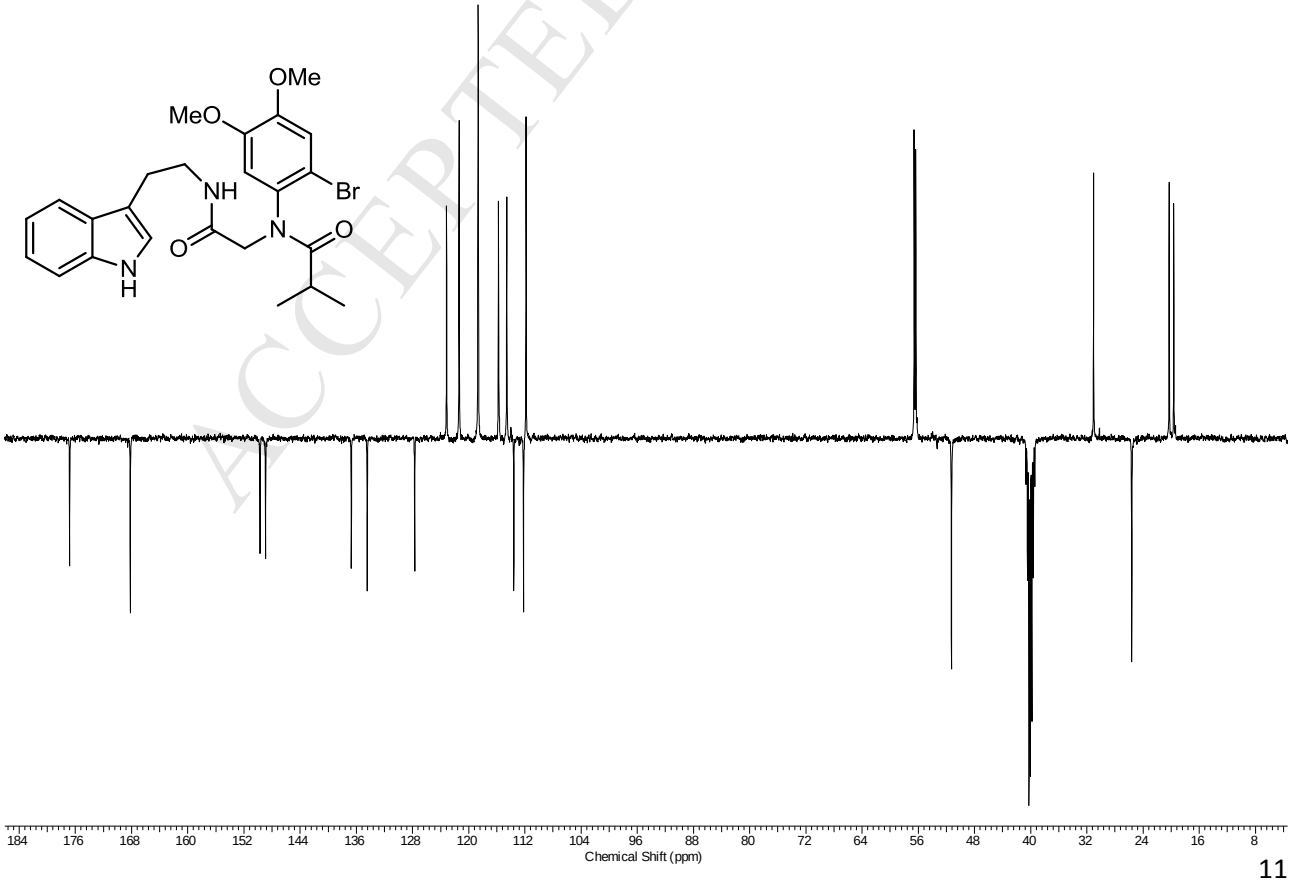
Compound **9i**: ^{13}C NMR (75 MHz, $CDCl_3$)



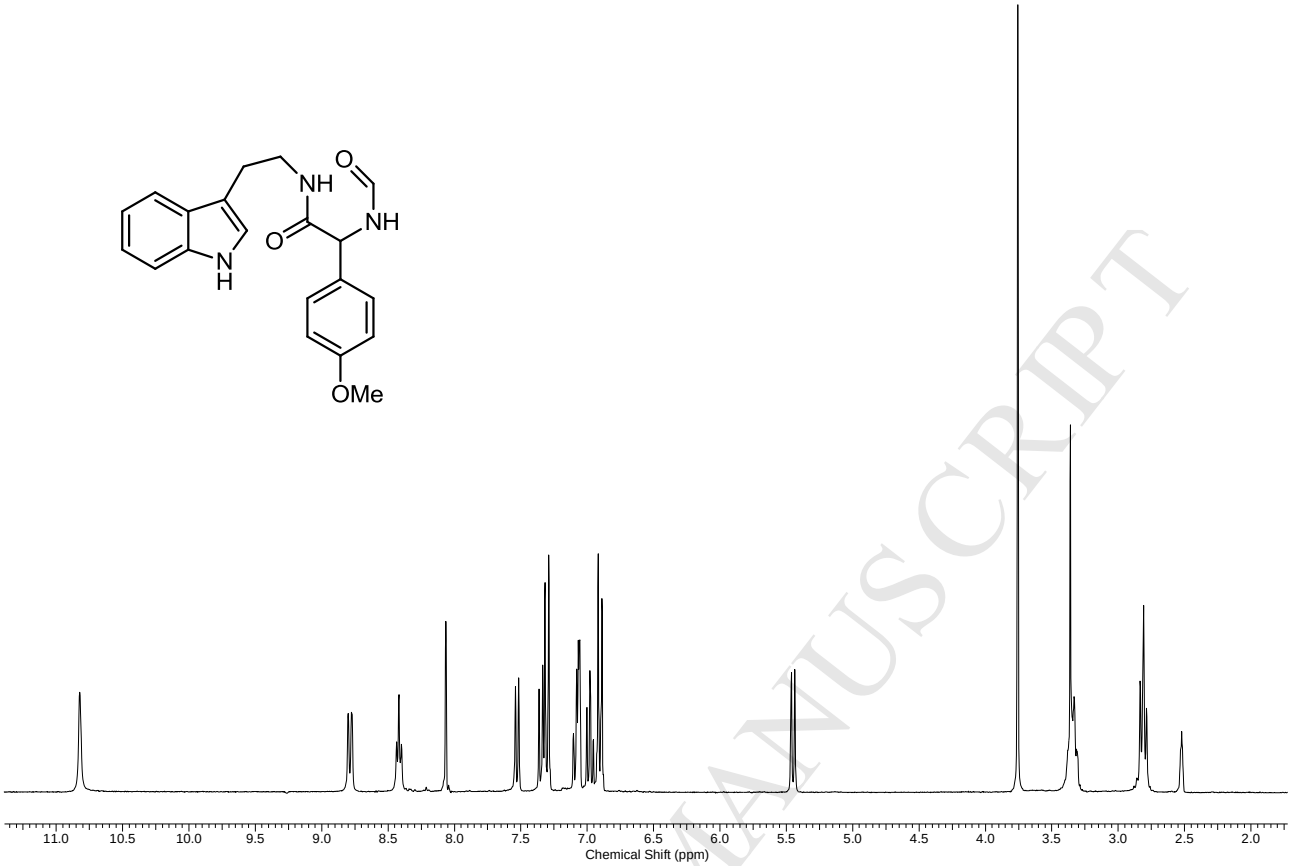
Compound **9j**: ^{1}H NMR (300 MHz, DMSO-*d*6)



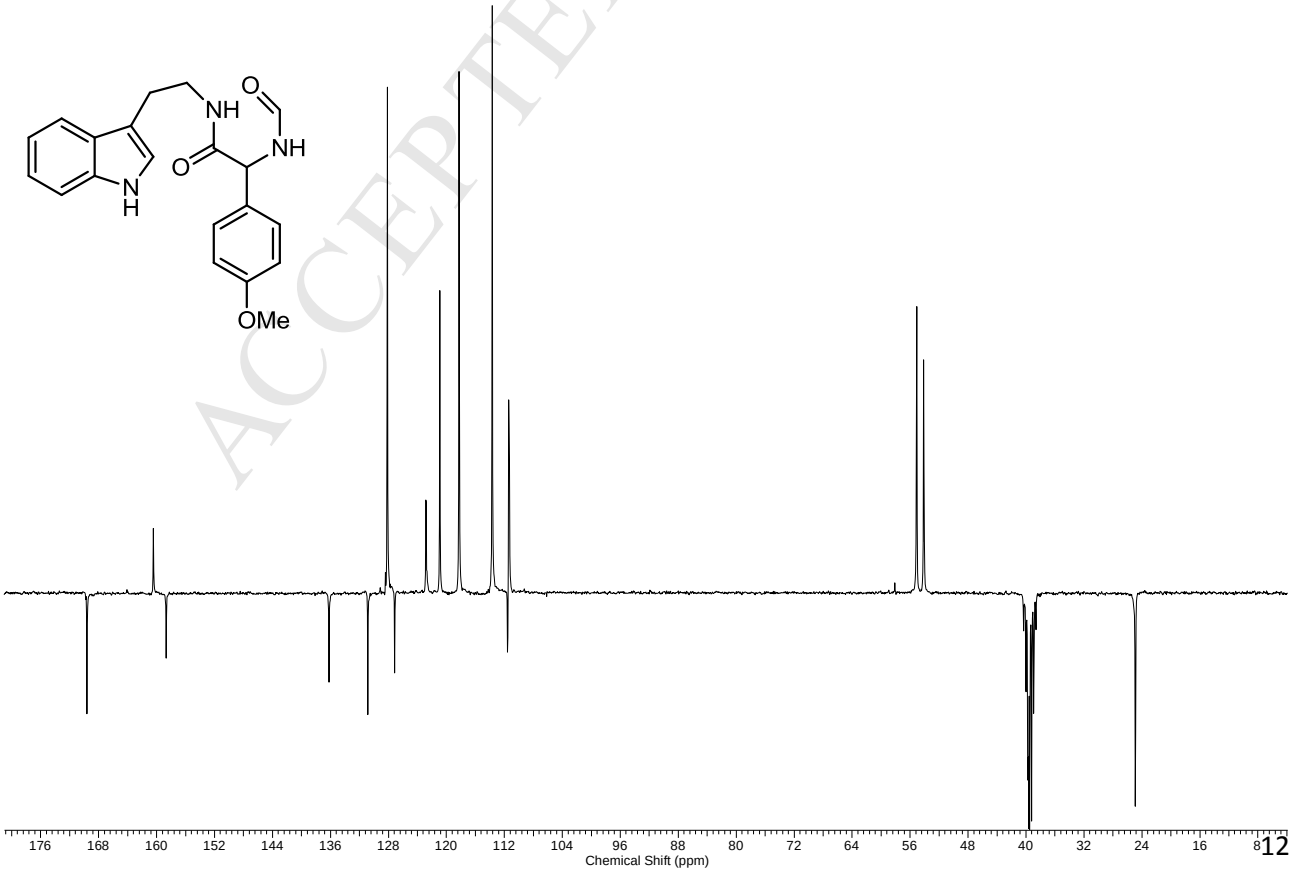
Compound **9j**: ^{13}C NMR (100 MHz, DMSO-*d*6)



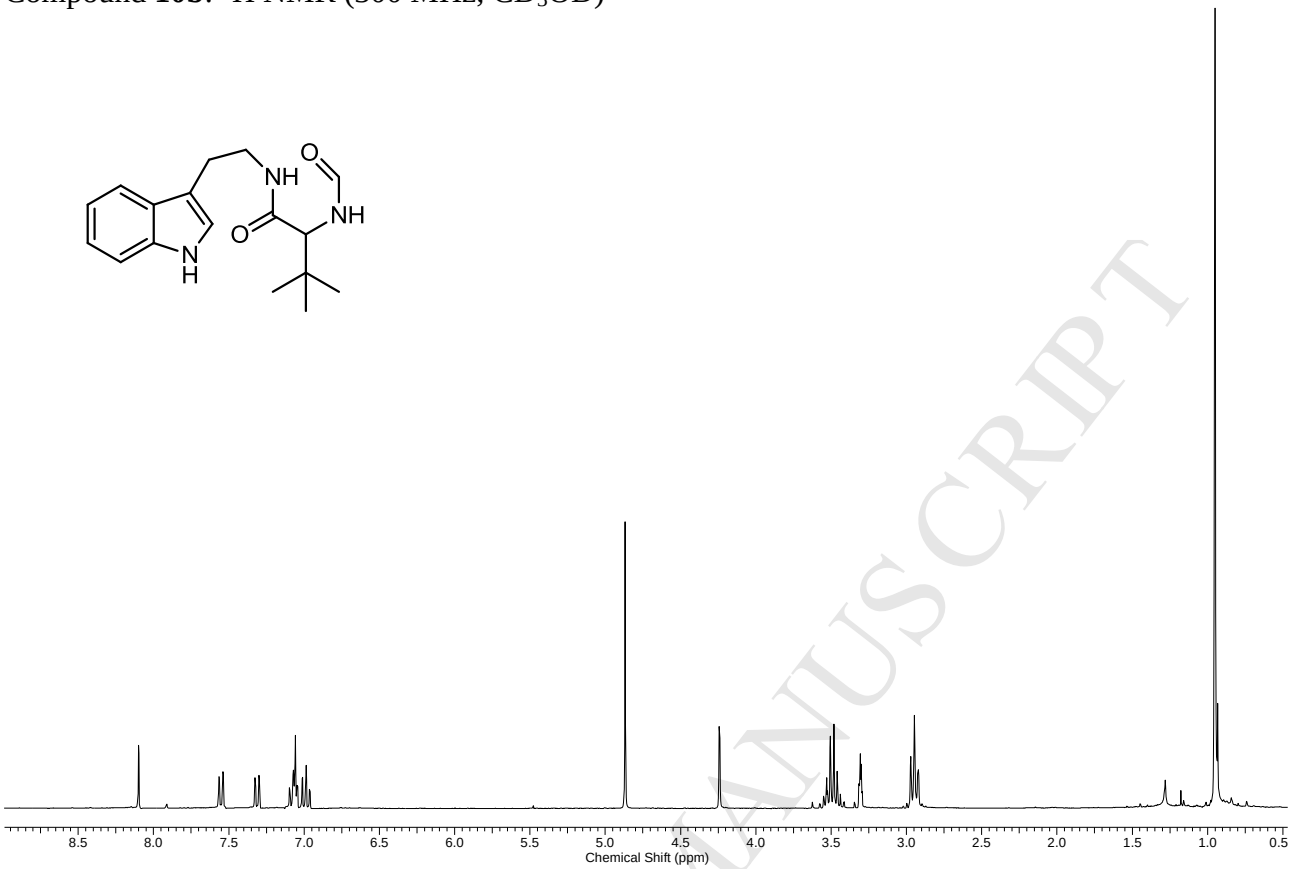
Compound **10a**: ^{1}H NMR (300 MHz, DMSO-*d*6)



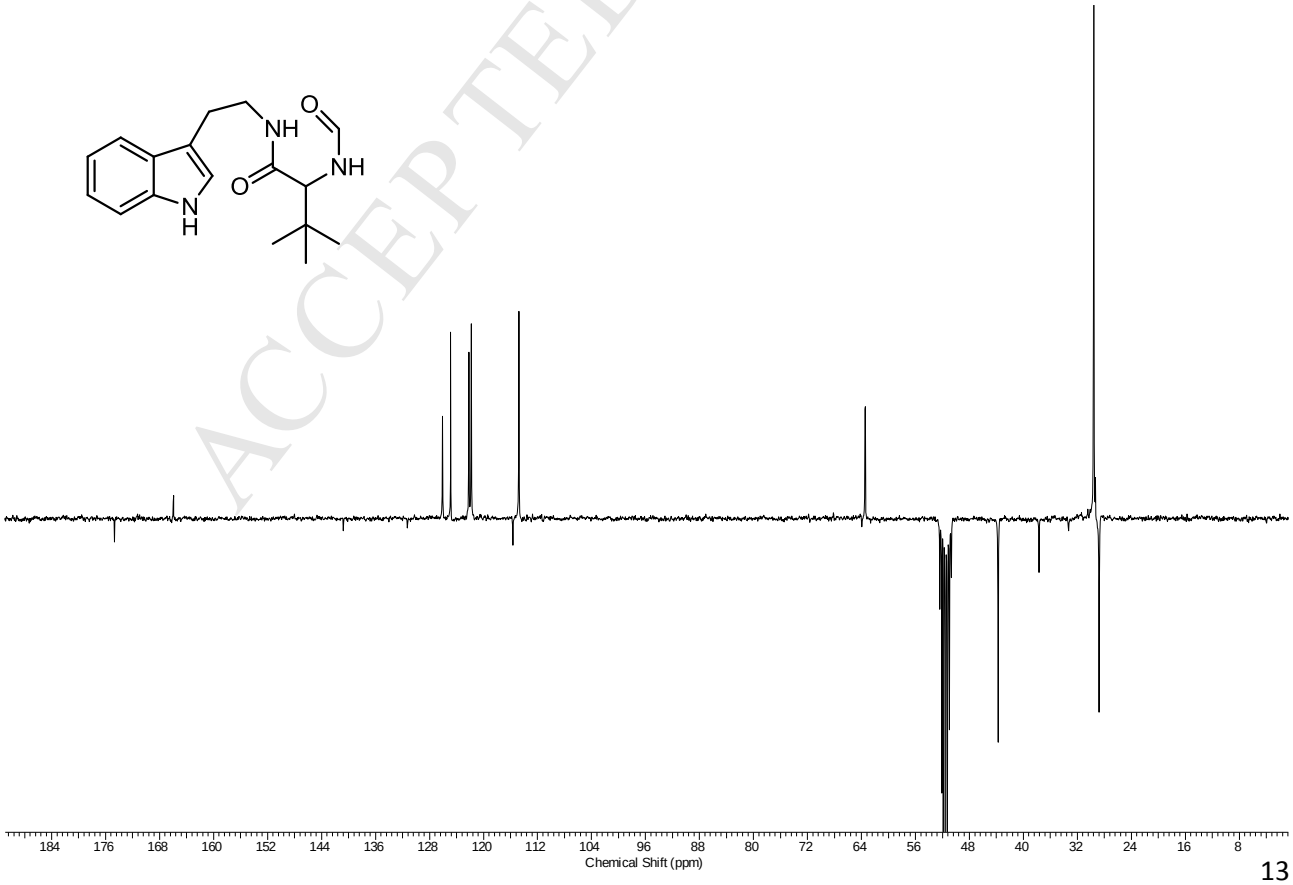
Compound **10a**: ^{13}C NMR (75 MHz, DMSO-*d*6)



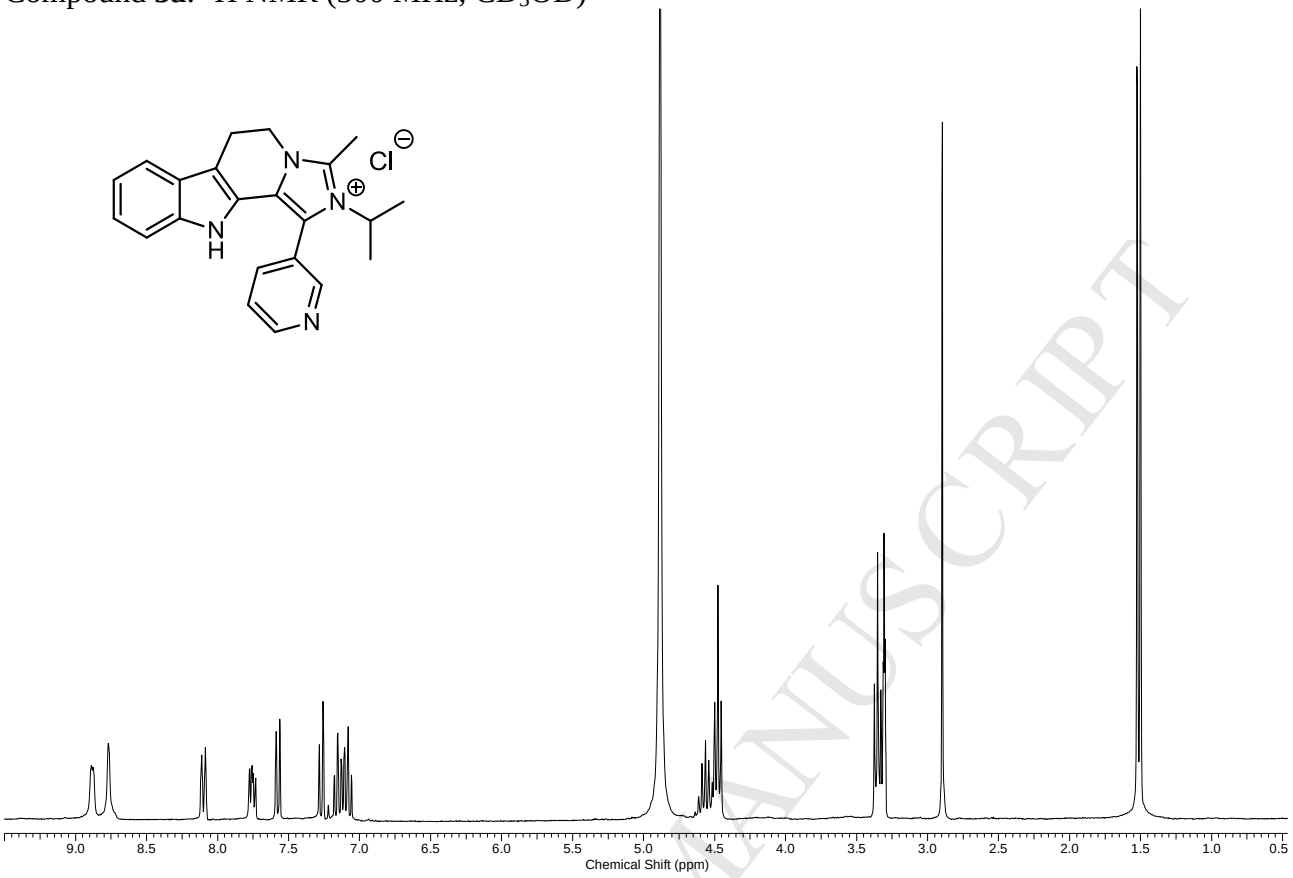
Compound **10b**: ^{1}H NMR (300 MHz, CD_3OD)



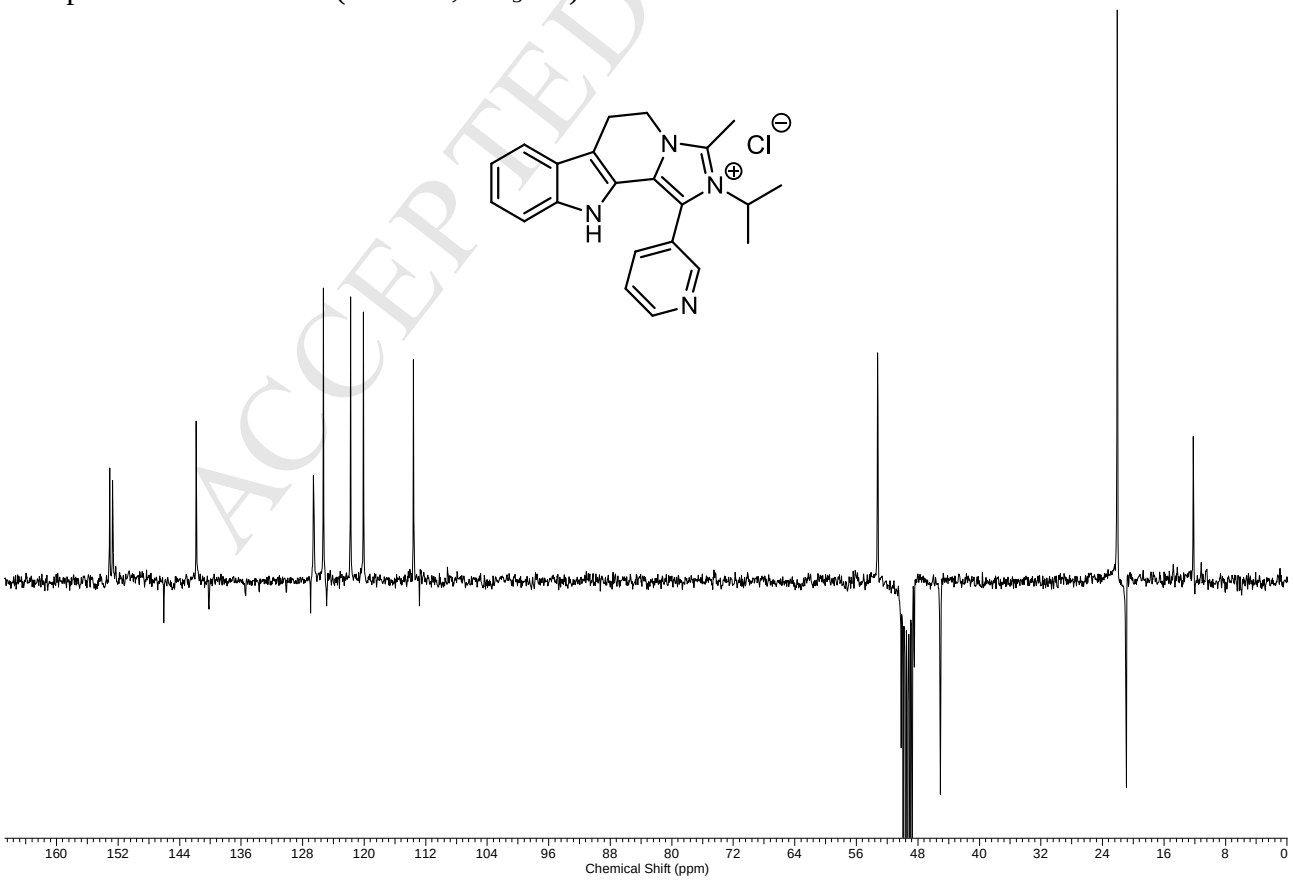
Compound **10b**: ^{13}C NMR (75 MHz, CD_3OD)



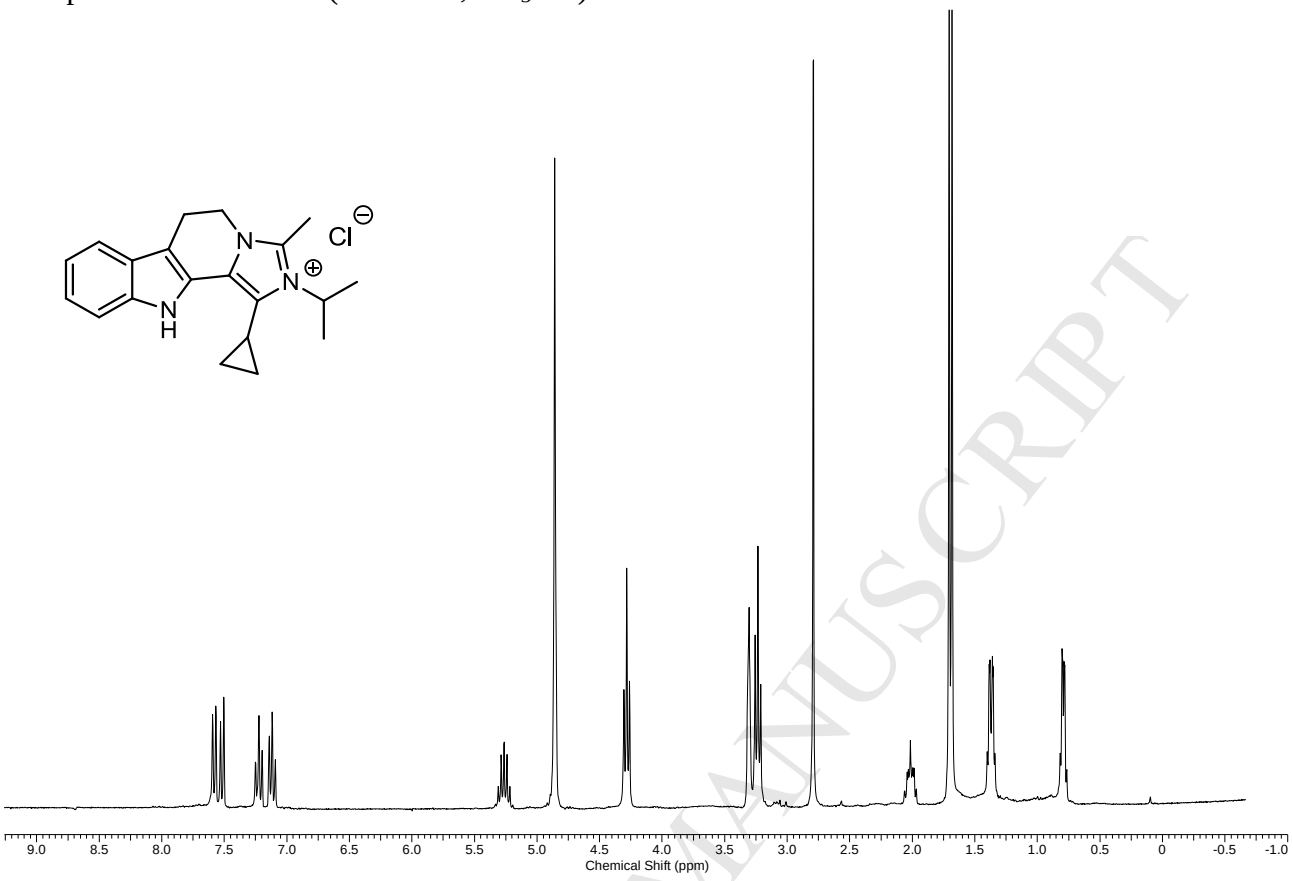
Compound **3a**: ^{1}H NMR (300 MHz, CD_3OD)



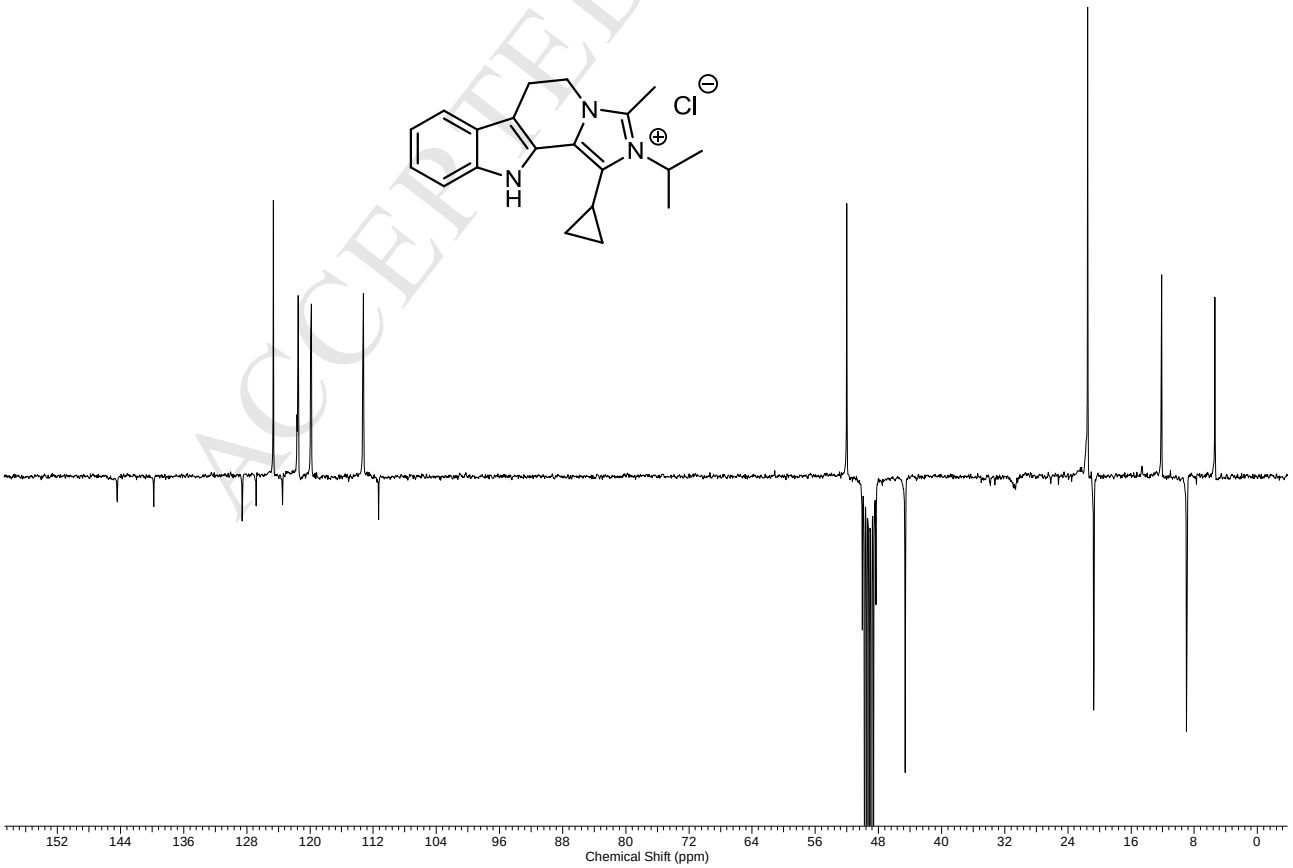
Compound **3a**: ^{13}C NMR (75 MHz, CD_3OD)



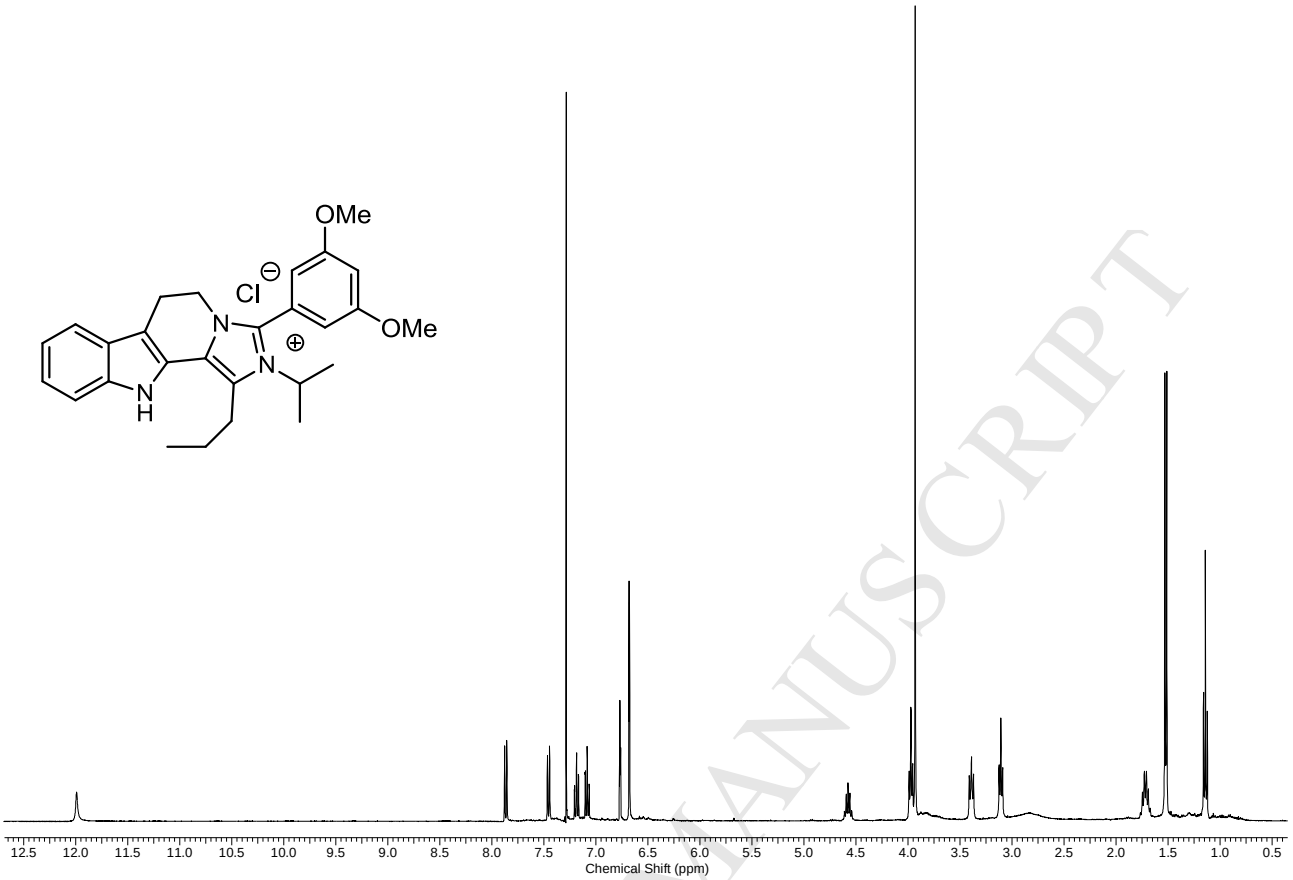
Compound **3b**: ^{1}H NMR (300 MHz, CD_3OD)



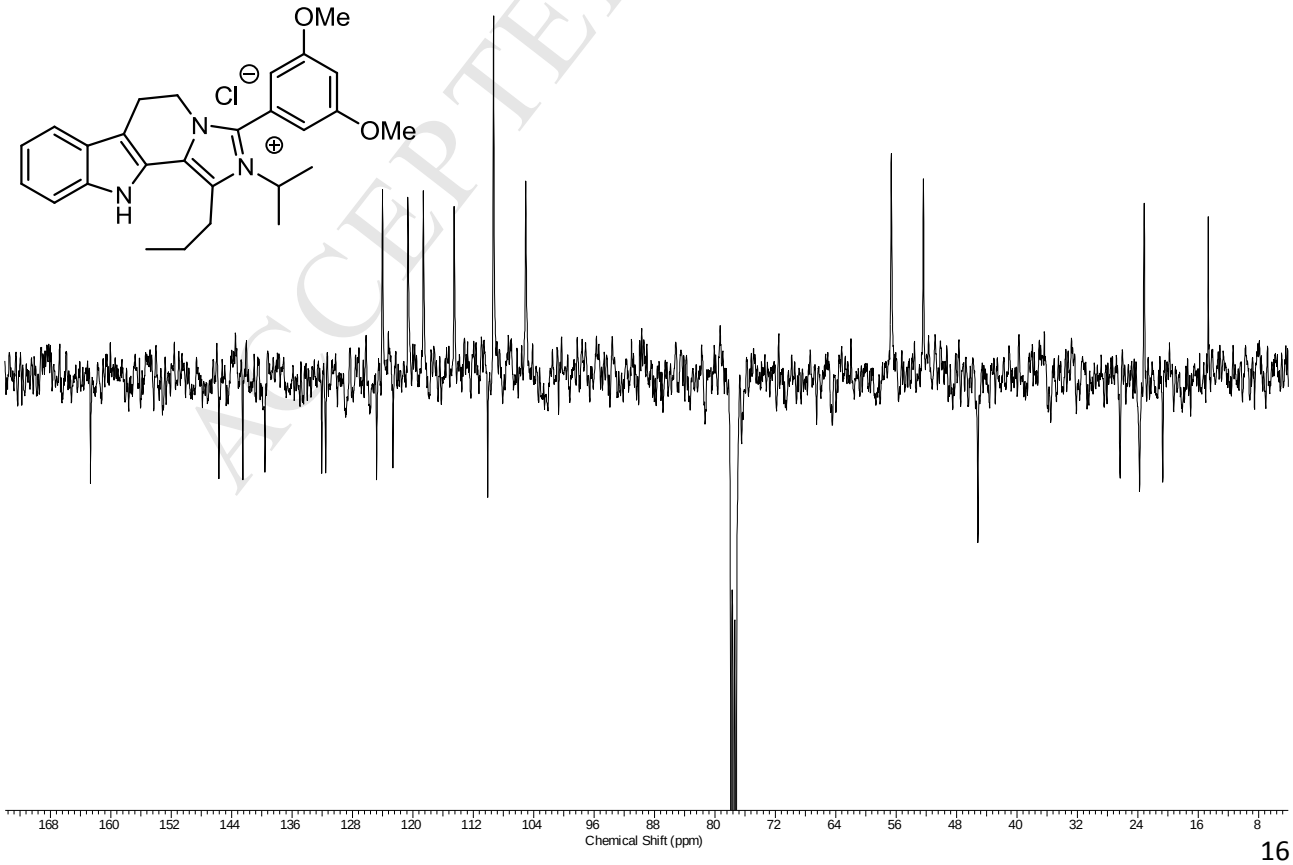
Compound **3b**: ^{13}C NMR (75 MHz, CD_3OD)



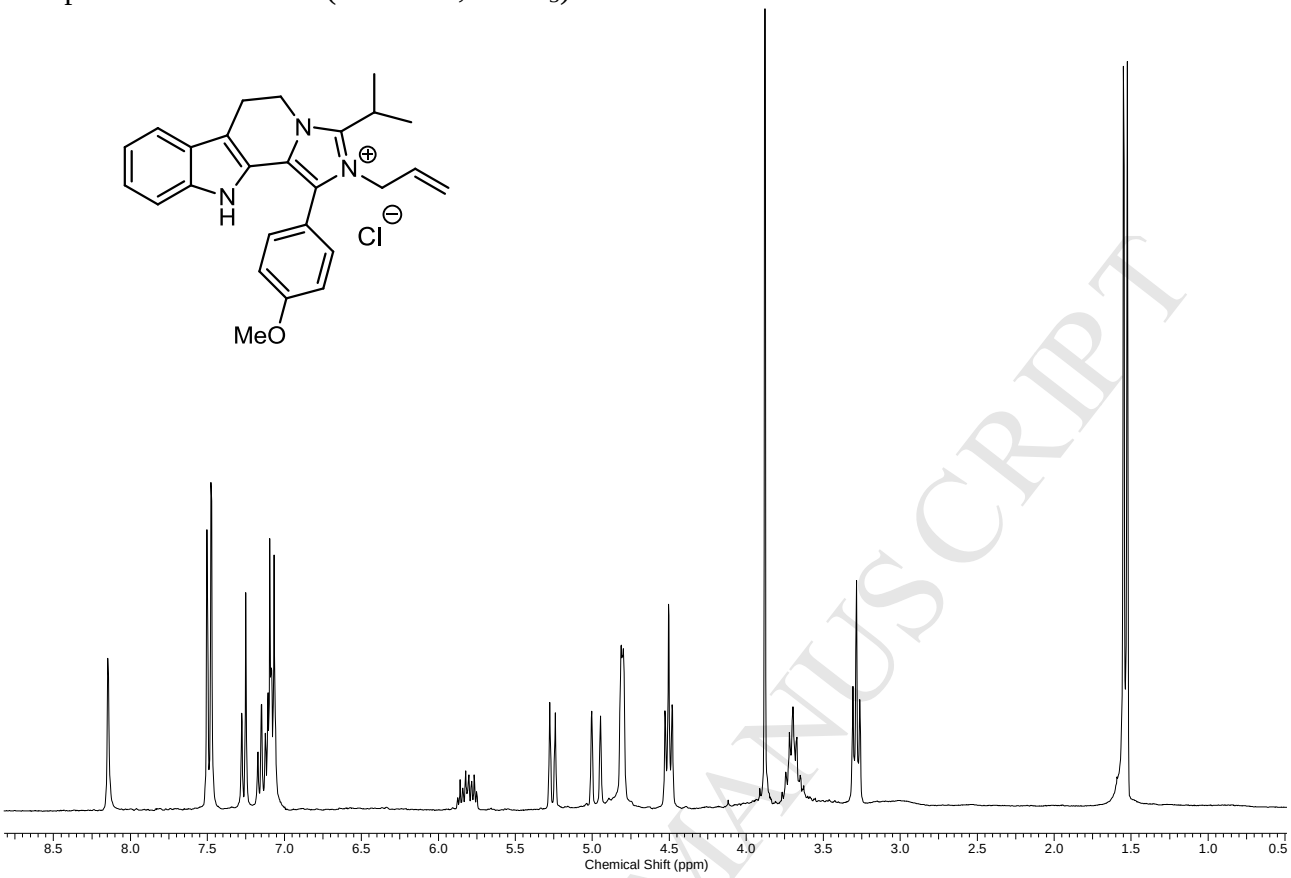
Compound **3c**: ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **3c**: ^{13}C NMR (100 MHz, $CDCl_3$)

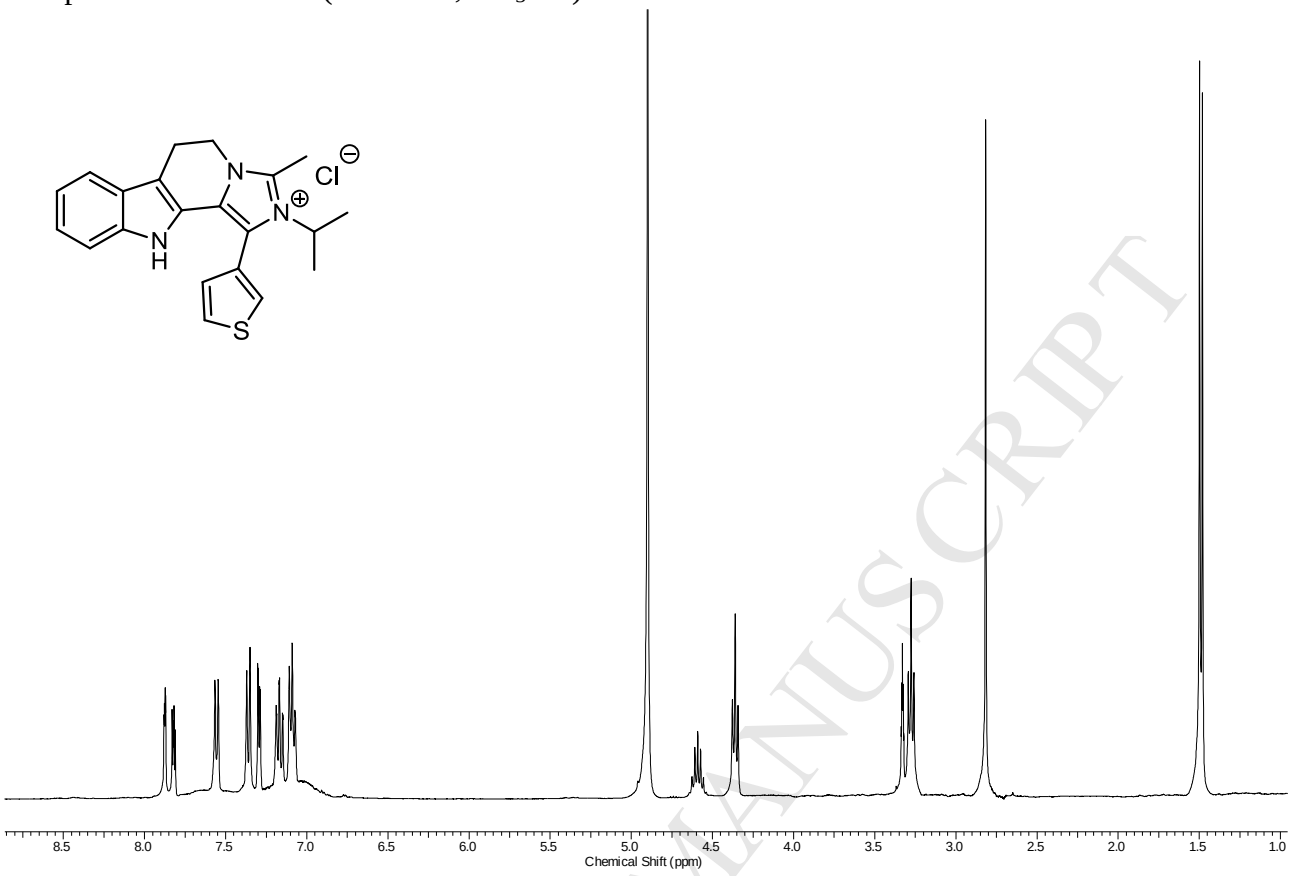


Compound **3d**: ^{1}H NMR (300 MHz, $CDCl_3$)

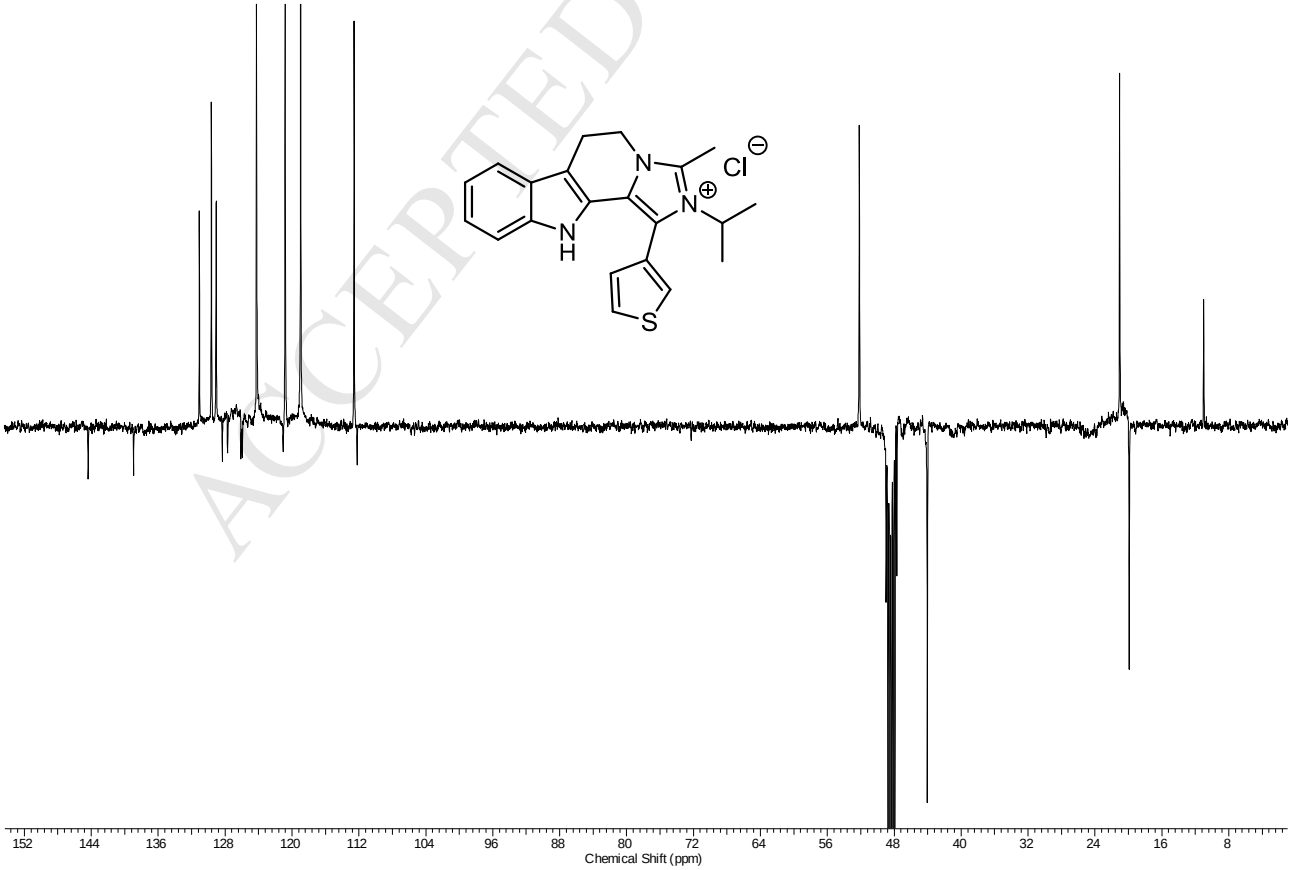


Compound **3d**: ^{13}C NMR (75 MHz, $CDCl_3$)

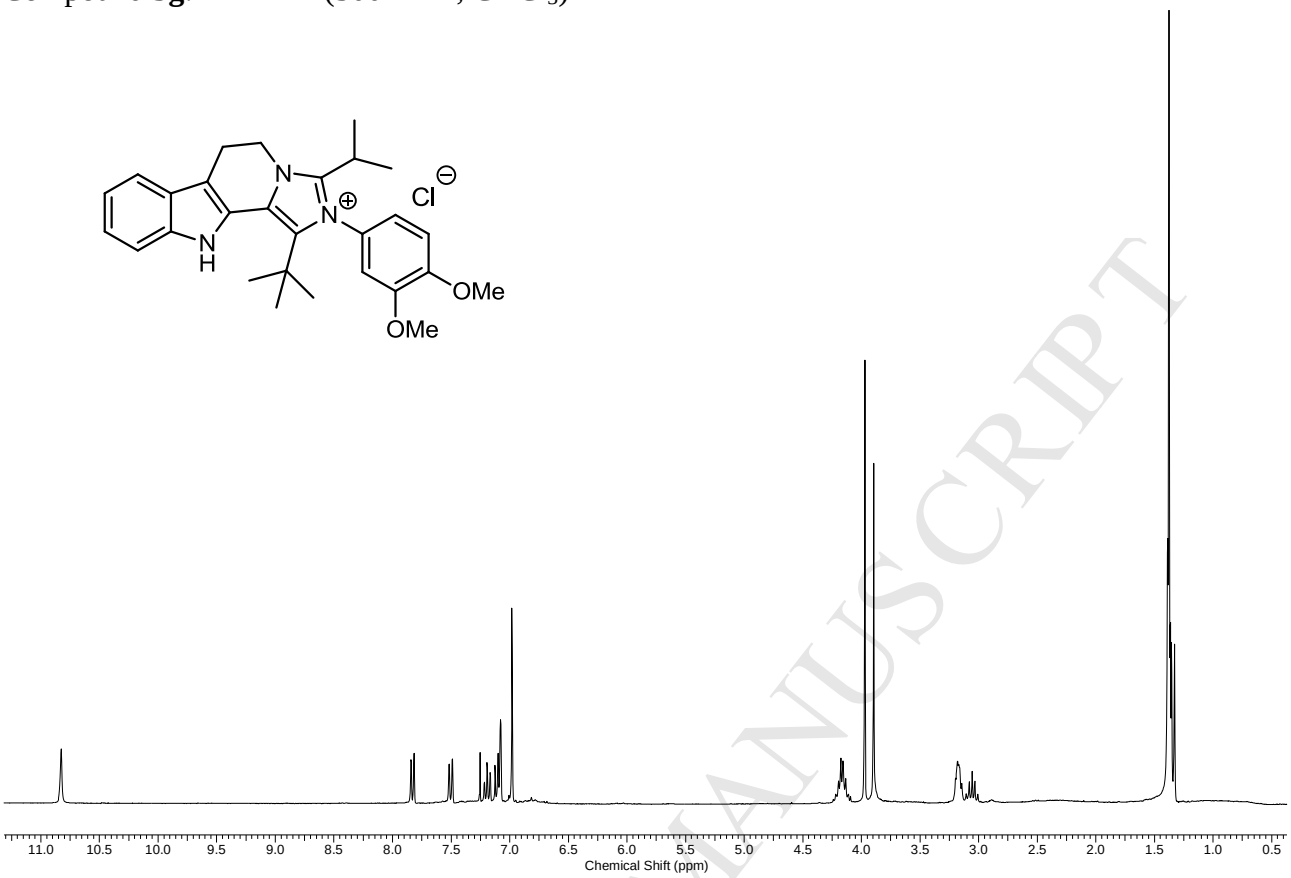
Compound **3e**: ^{1}H NMR (400 MHz, CD_3OD)



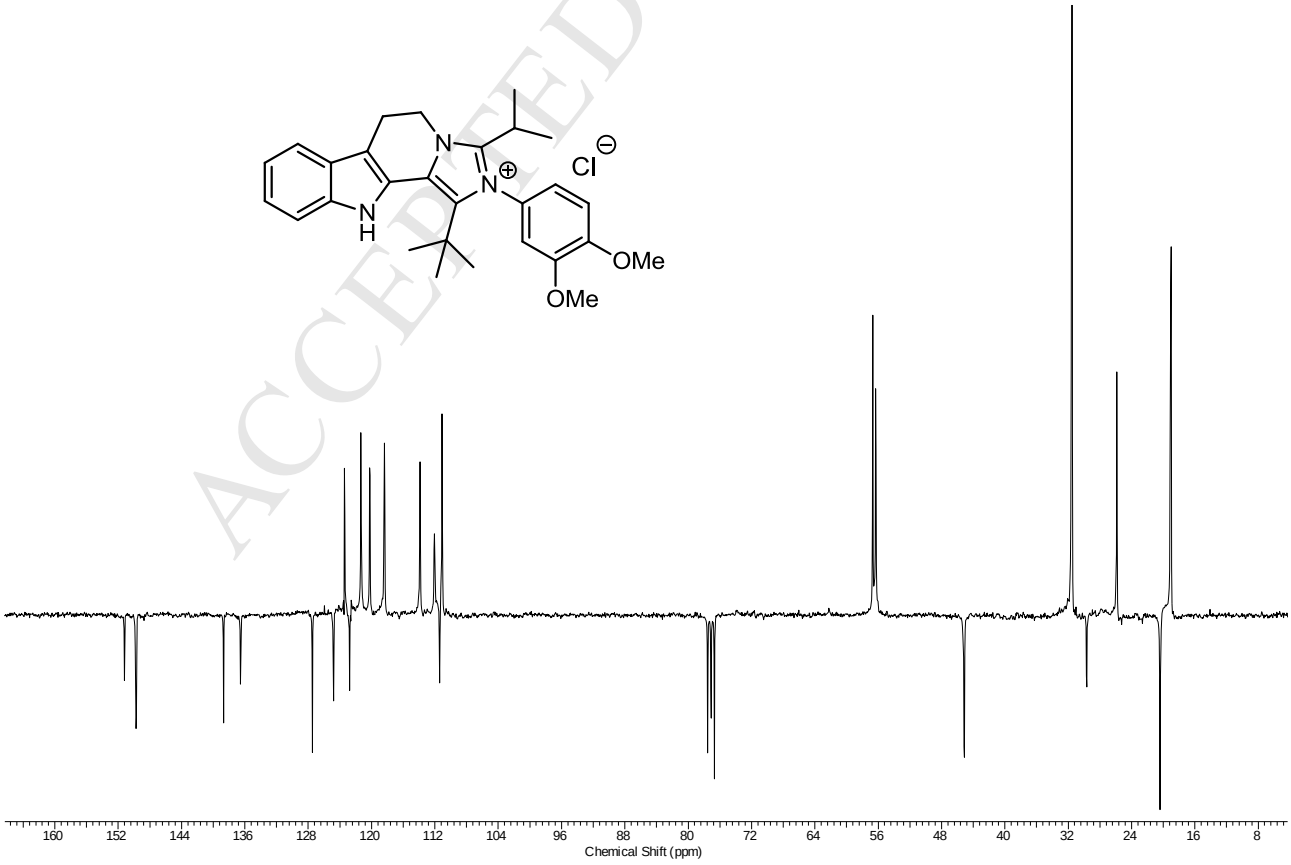
Compound **3e**: ^{13}C NMR (100 MHz, CD_3OD)



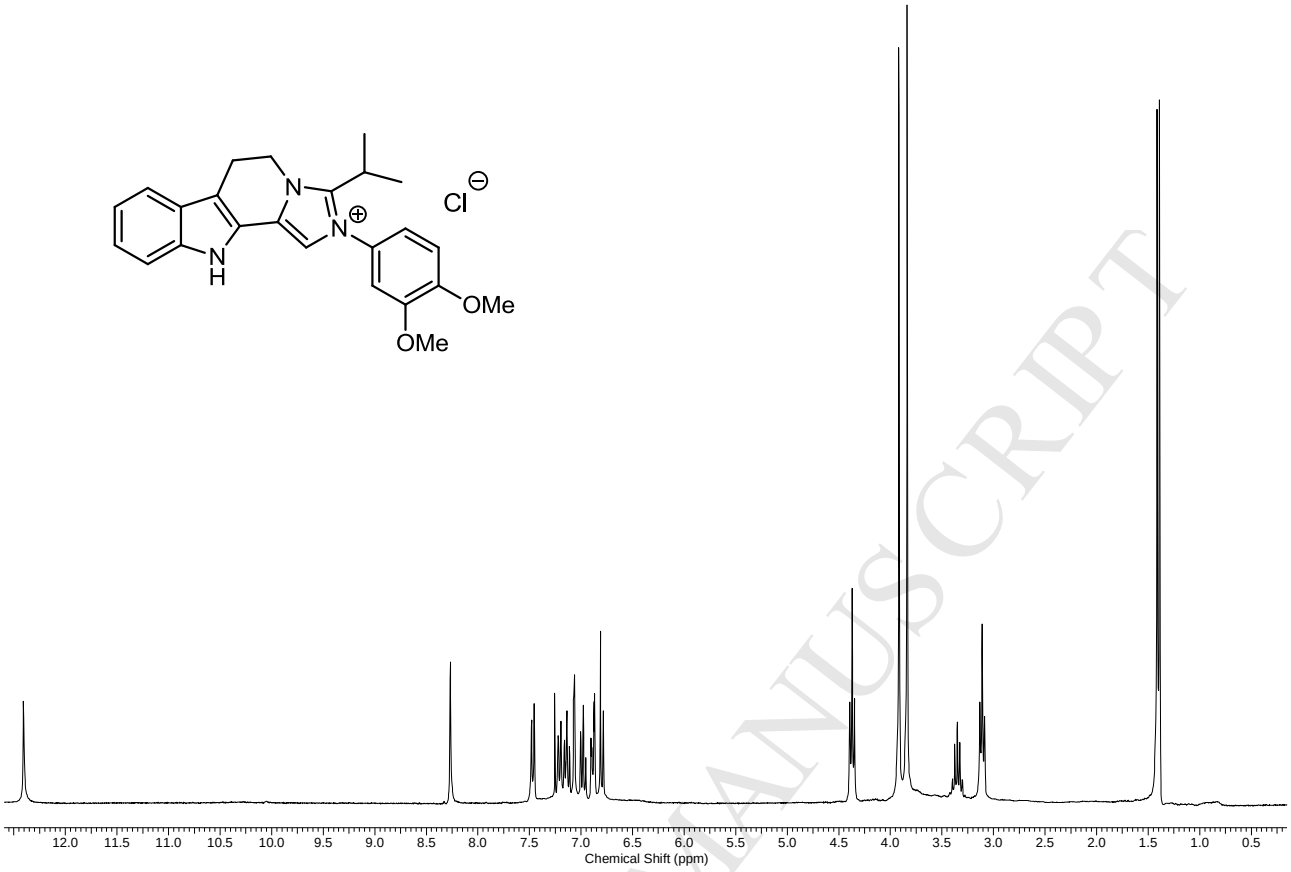
Compound **3g**: ^{1}H NMR (300 MHz, $CDCl_3$)



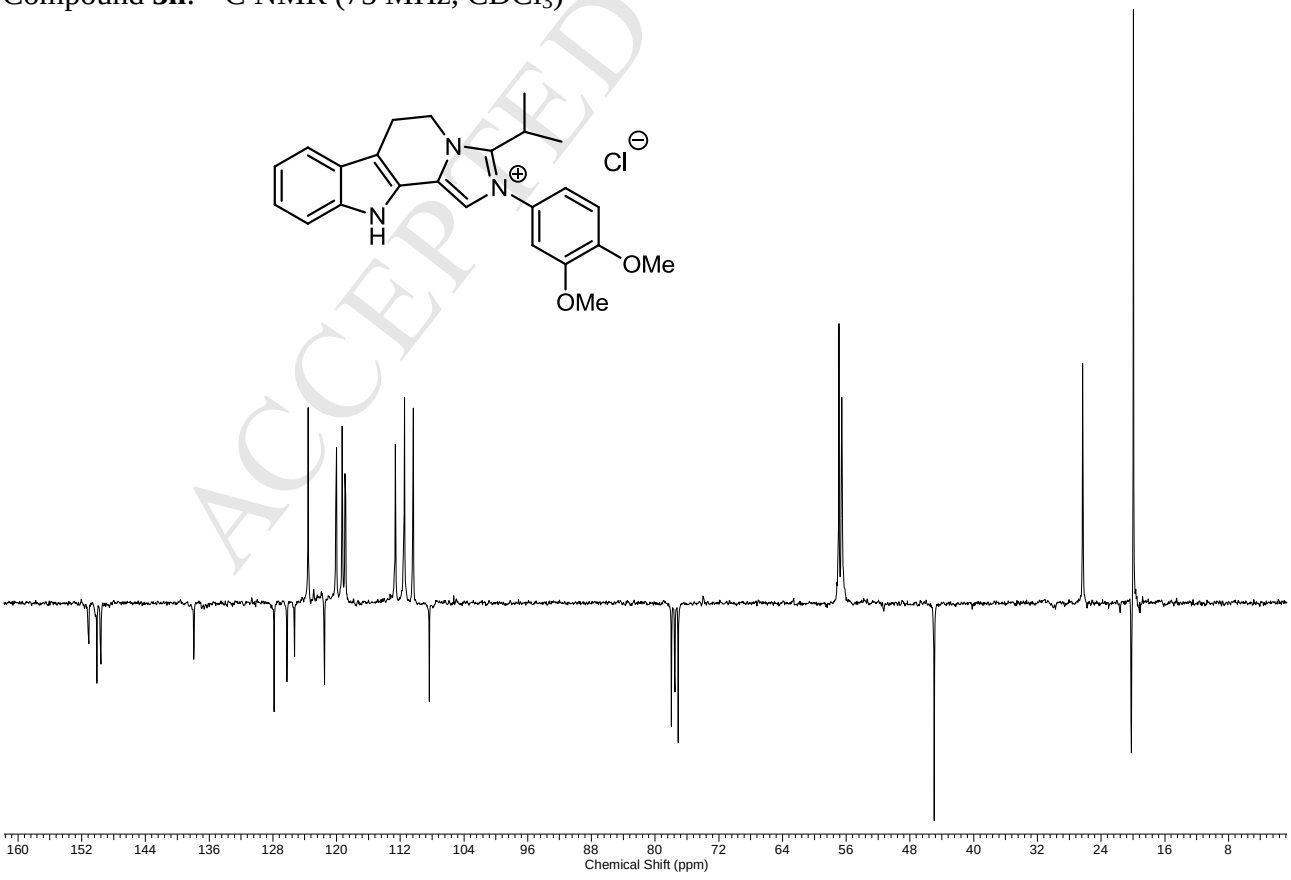
Compound **3g**: ^{13}C NMR (75 MHz, $CDCl_3$)



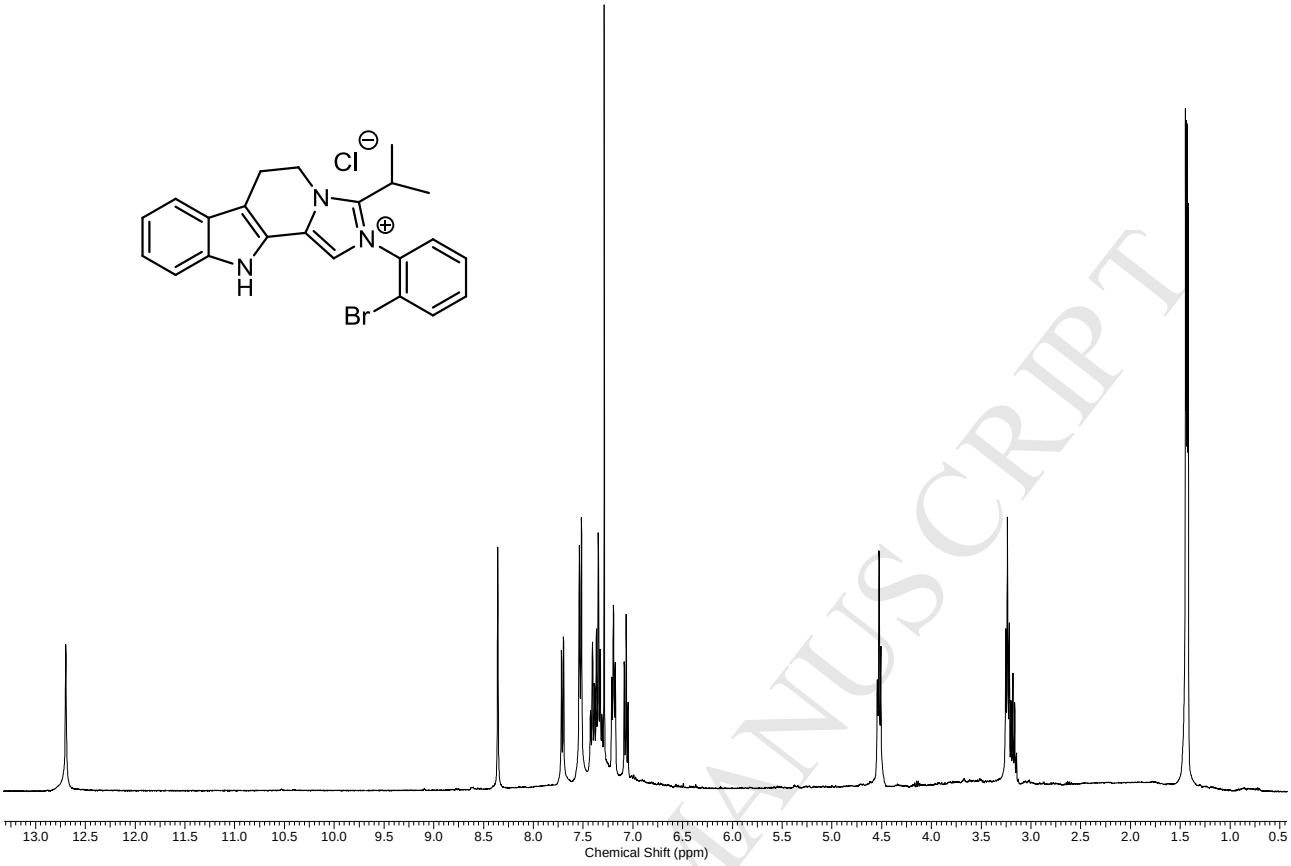
Compound **3h**: ^{1}H NMR (300 MHz, $CDCl_3$)



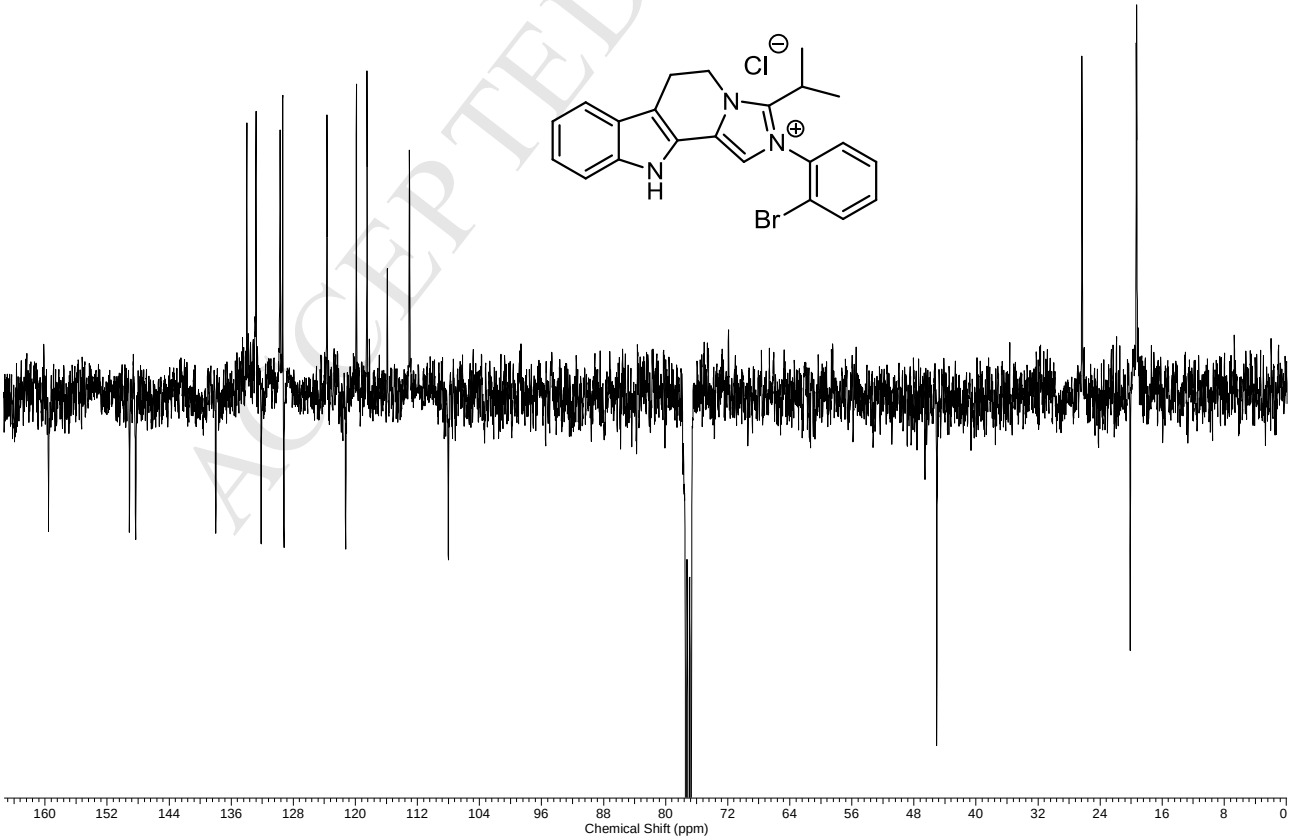
Compound **3h**: ^{13}C NMR (75 MHz, $CDCl_3$)



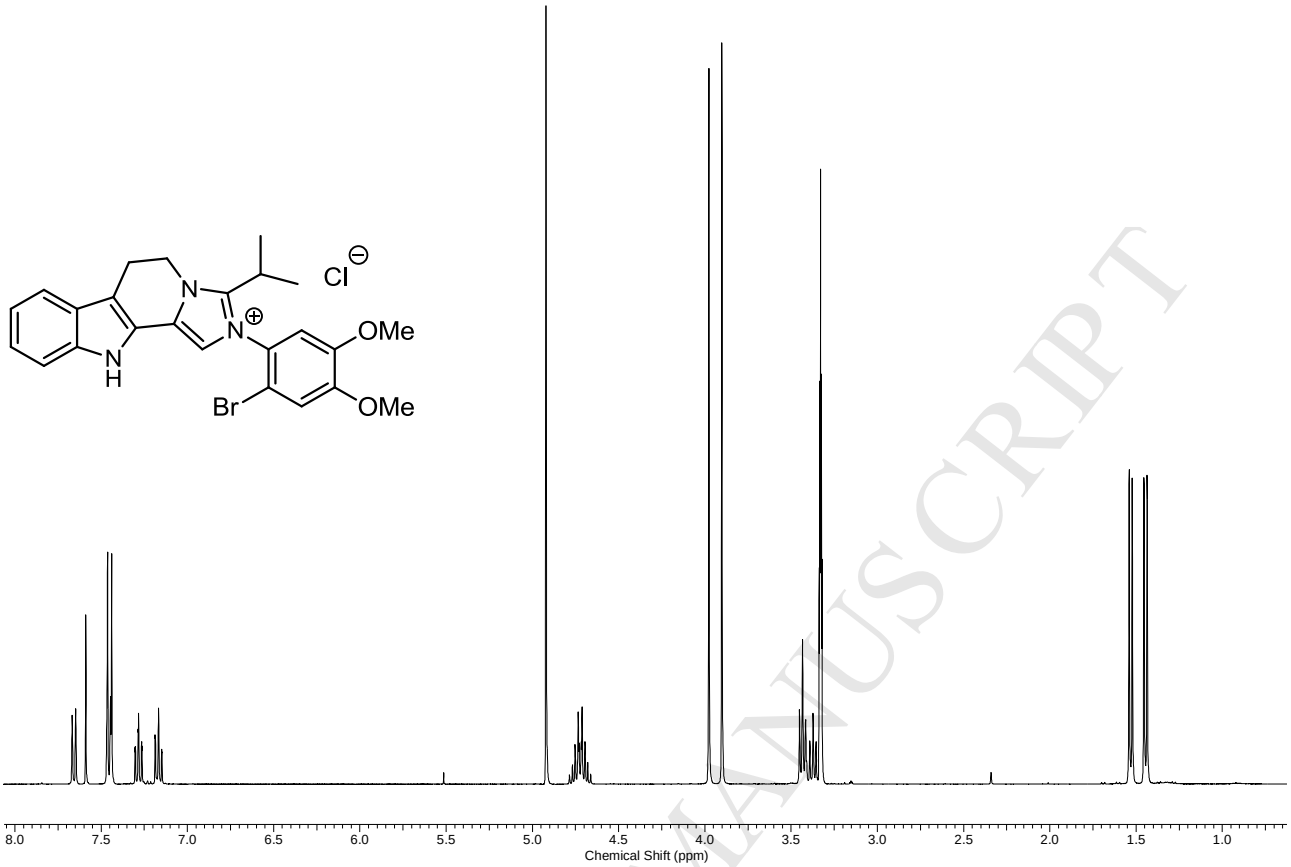
Compound **3i**: ^{1}H NMR (300 MHz, $CDCl_3$)



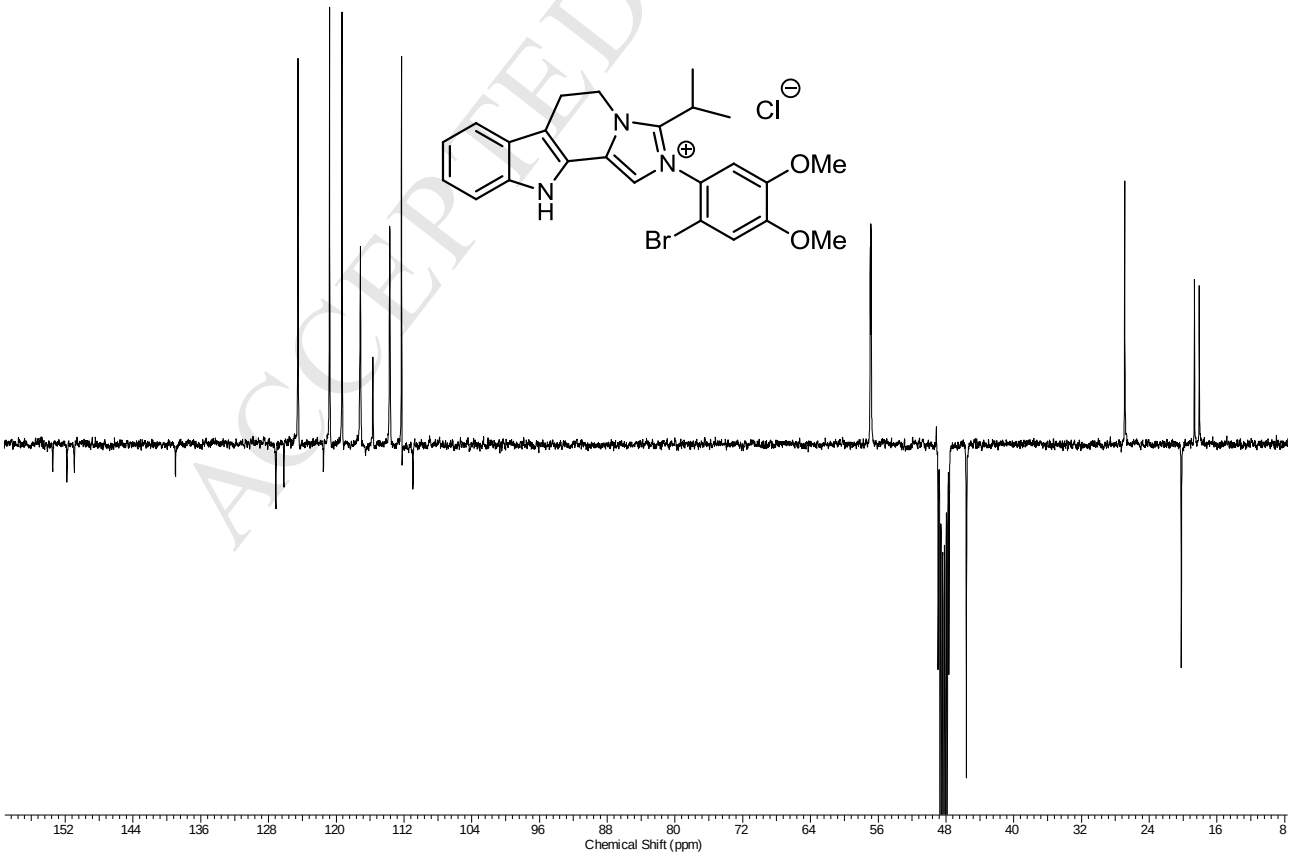
Compound **3i**: ^{13}C NMR (75 MHz, $CDCl_3$)



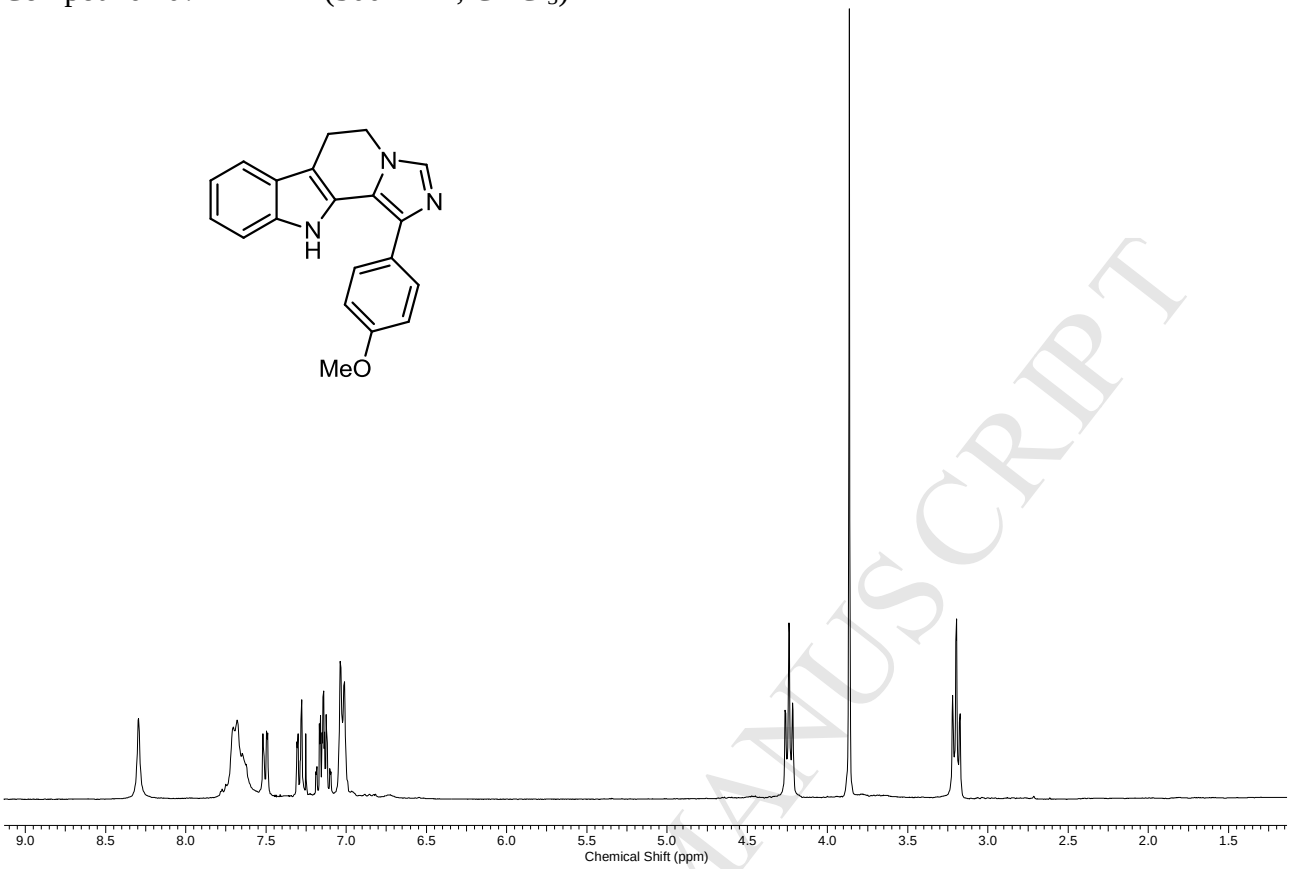
Compound **3j**: ^{1}H NMR (400 MHz, CD_3OD)



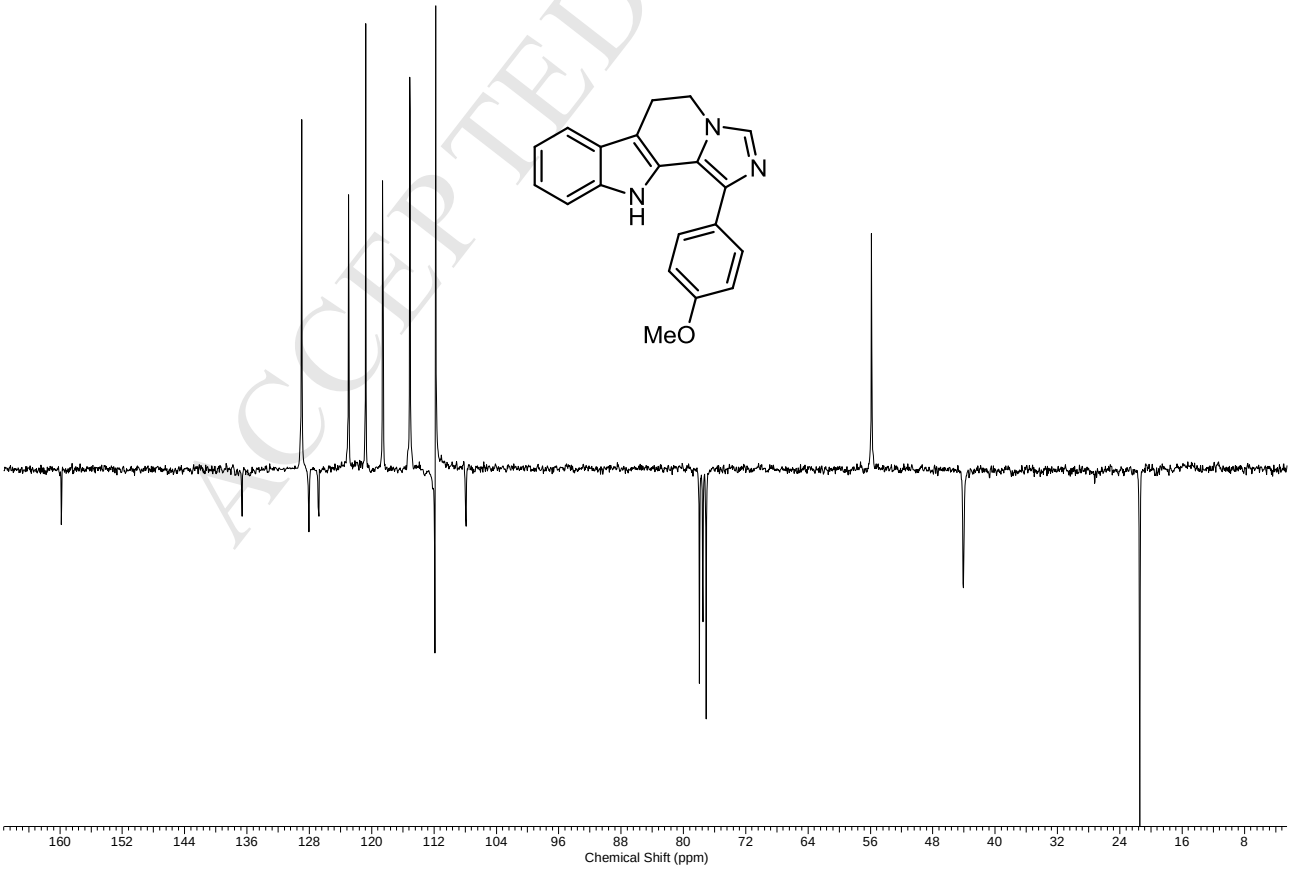
Compound **3j**: ^{13}C NMR (100 MHz, CD_3OD)



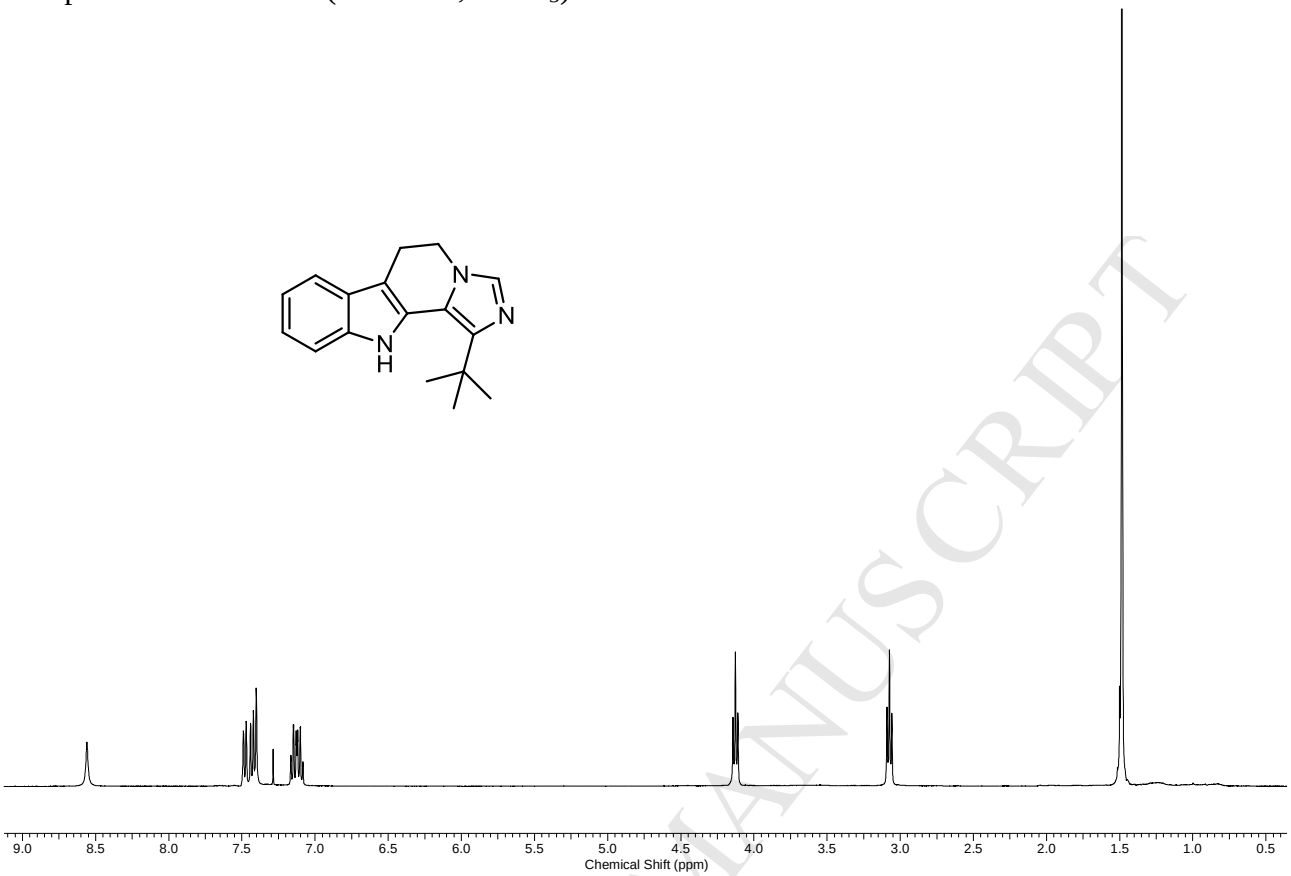
Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$)



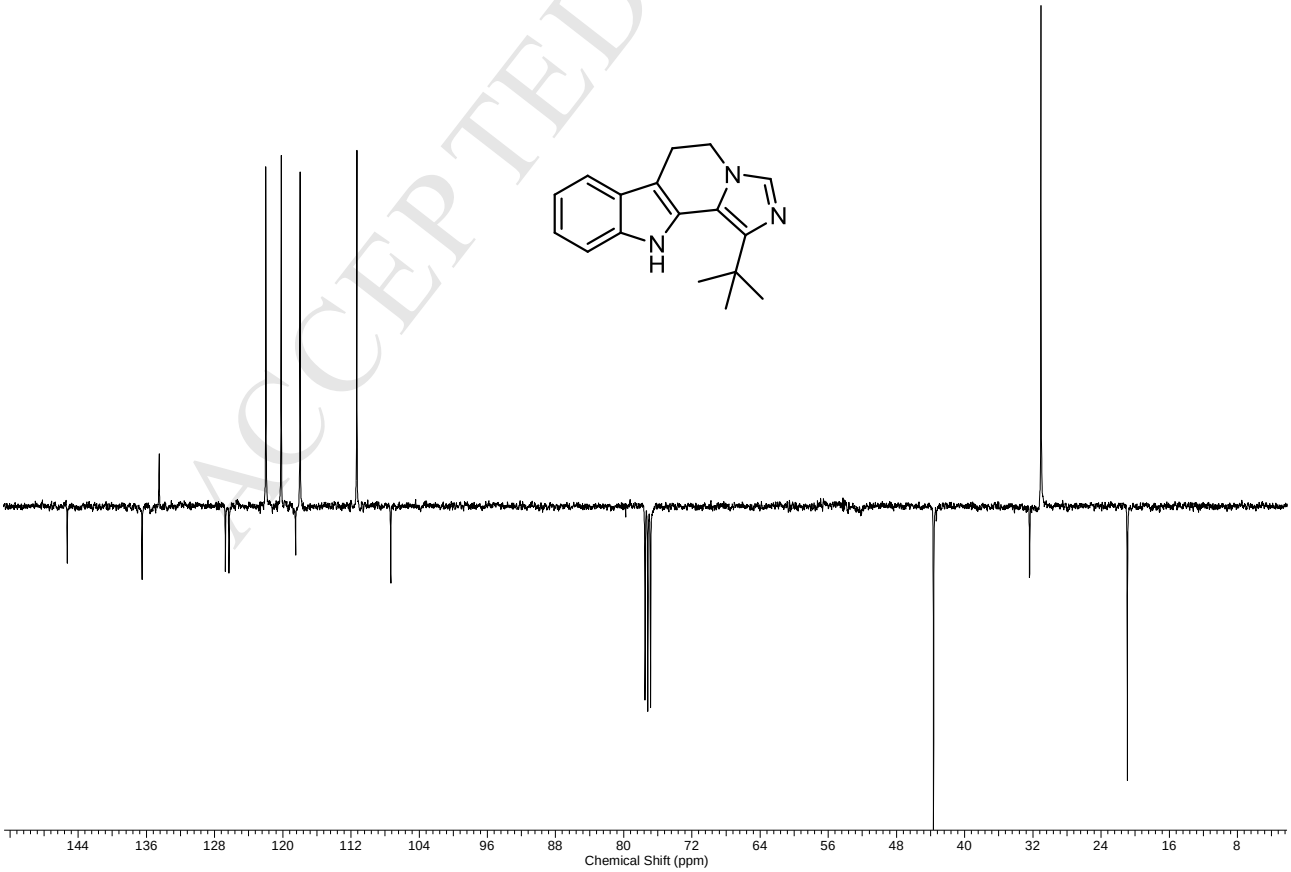
Compound **4a**: ^{13}C NMR (75 MHz, $CDCl_3$)



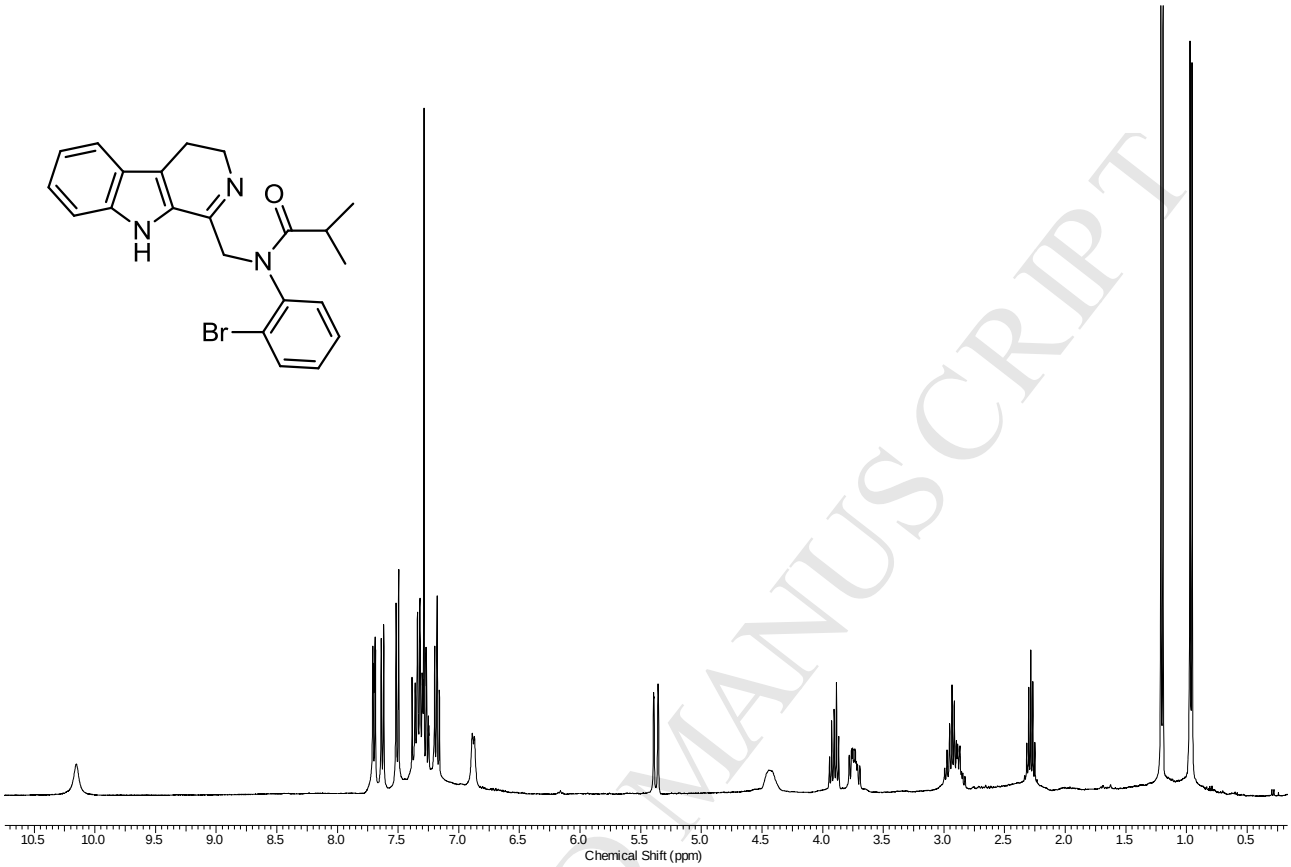
Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$)



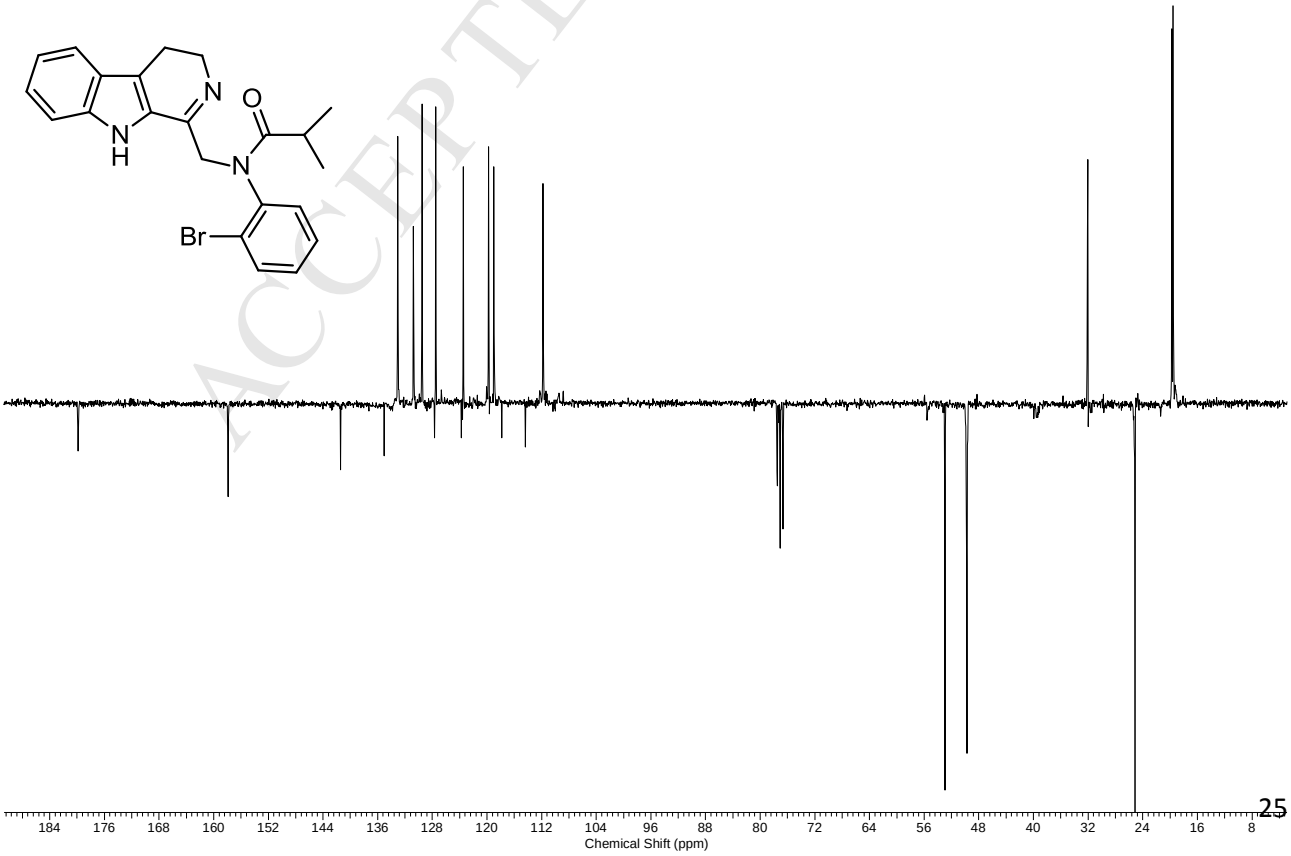
Compound **4b**: ^{13}C NMR (100 MHz, $CDCl_3$)



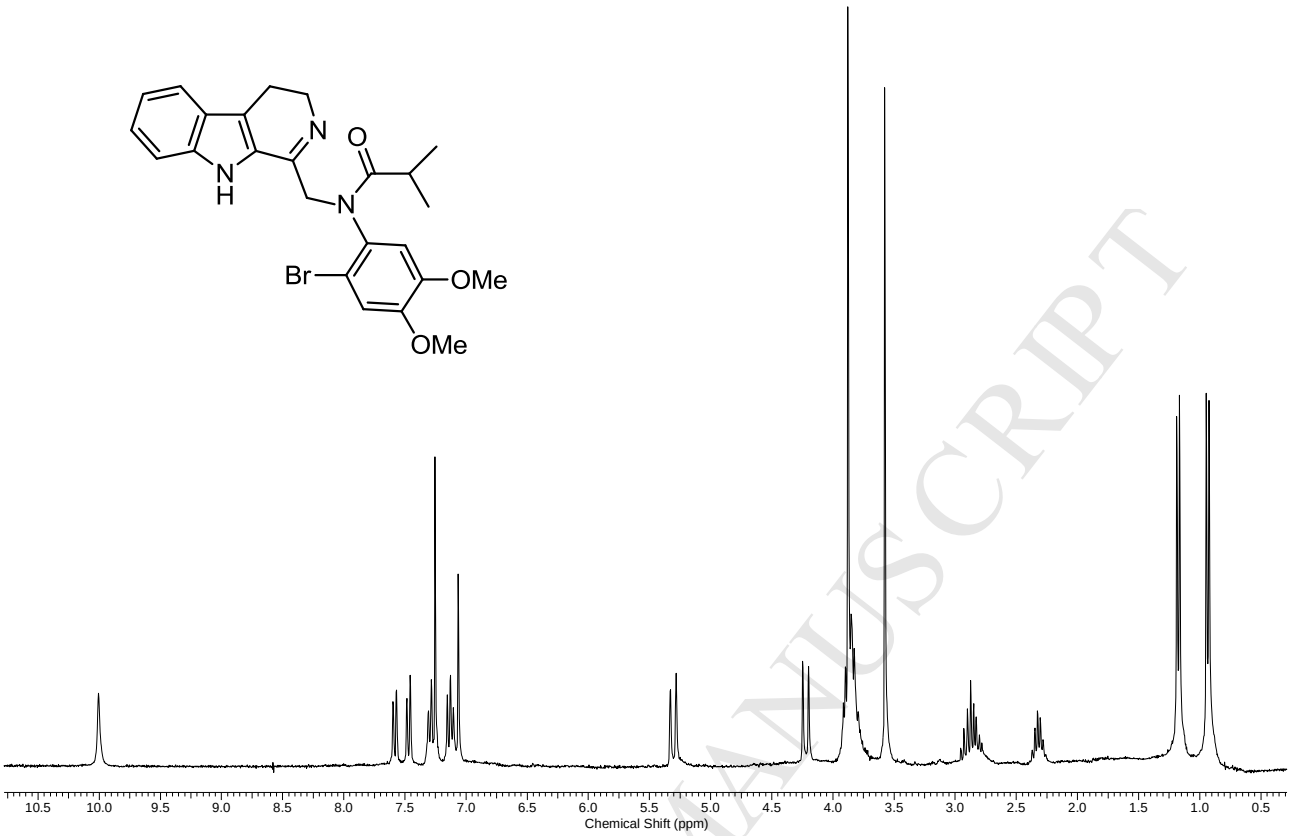
Compound **11i**: ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **11i**: ^{13}C NMR (75 MHz, $CDCl_3$)



Compound **11j**: ^{1}H NMR (300 MHz, $CDCl_3$)



Compound **11j**: ^{13}C NMR (75 MHz, $CDCl_3$)