Pd(0)-Catalyzed Direct Inter- and Intramolecular C–H Functionalization of 4-Carboxyimidazoles

Steven Frippiat, Antoine Peresson, Thibaut Perse, Yvan Ramondenc, Cédric Schneider, Olivier Querolle, Patrick Angibaud, Virginie Poncelet, Lieven Meerpoel, Vincent Levacher, et al.

▶ **To cite this version:**

Steven Frippiat, Antoine Peresson, Thibaut Perse, Yvan Ramondenc, Cédric Schneider, et al.. Pd(0)-Catalyzed Direct Inter- and Intramolecular C–H Functionalization of 4-Carboxyimidazoles. SYNLETT, 2020, 31 (10), pp.1015-2021. 10.1055/s-0040-1708003 . hal-02548986

HAL Id: hal-02548986

https://normandie-univ.hal.science/hal-02548986

Submitted on 1 Dec 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Pd(0)-catalyzed direct inter- and intramolecular C-H functionalization of 4-carboxyimidazoles.

Journal:	*SYNLETT*
Manuscript ID	ST-2020-02-0075-L.R1
Manuscript Type:	Letter
Date Submitted by the Author:	n/a
Complete List of Authors:	Frippiat, Steven; Rouen University, Chemistry Peresson, Antoine; Rouen University, Chemistry Perse, Thibaut; Janssen Research and Development Val de Reuil, Chemistry Ramondenc, Yvan; Rouen University, Chemistry Schneider, Cedric; Normandie Univ, INSA Rouen, CNRS Querolle, Olivier; Janssen Research and Development Val de Reuil, Chemistry Poncelet, Virginie; Janssen Research and Development Val de Reuil, Chemistry Angibaud, Patrick; Janssen Research and Development Val de Reuil, Chemistry Meerpoel, Lieven; Janssen-Cilag NV/SA, chemistry Levacher, Vincent; Rouen University, UMR COBRA Bischoff, Laurent; Rouen University, Chemistry Baudequin, Christine; Rouen University, Chemistry Hoarau, Christophe ; UMR COBRA 6014, Heterocycles
Keywords:	catalysis, arylation, palladium, heterocycles, alkenation, C-H functionalization, palladium catalysis, imidazole, arylation, alkenylation
Abstract:	The palladium-catalyzed arylation and alkenylation of N-substituted methyl imidazole-4-carboxylates are described through inter- and intramolecular pathways. Both direct C2-H and C5-H arylation and alkenylation proceed under Pd(0) / Cu(I) cooperative catalysis and Pd(0) catalysis respectively using carbonate assistance in low-polarity 1,4-dioxane solvent. The methodology gives access to C2 (hetero)aryl- or alkenyl imidazoles as well as innovative C2 and C5 arylated fused imidazoles tricycles with a 5- to 7 membered middle ring.

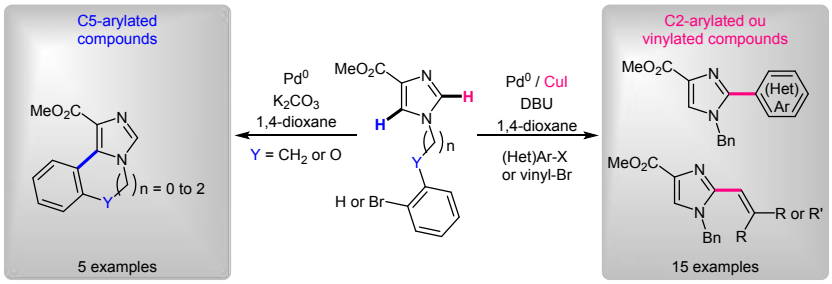
SCHOLARONE™
Manuscripts

Synlett Letter / Cluster / New Tools

Pd(0)-catalyzed direct inter- and intramolecular C-H functionalization of 4-carboxyimidazoles.

Steven Frippiat [a]
Antoine Peresson [a]
Thibaut Perse [b]
Yvan Ramondenc [a]
Cédric Schneider[a]
Olivier Querolle[b]
Patrick Angibaud[b]
Virginie Poncelet[b]
Lieven Meerpoel[c]
Vincent Levacher[a]
Laurent Bischoff[a]
Christine Baudequin*[a]
Christophe Hoarau*[a]

[a] Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.



Received:
Accepted:
Published online:
DOI:

Abstract The palladium-catalyzed arylation and alkenylation of *N*-substituted methyl imidazole-4-carboxylates are described through inter- and intramolecular pathways. Both direct C2-H and C5-H arylation and alkenylation proceed under Pd(0) / Cu(I) cooperative catalysis and Pd(0) catalysis respectively using carbonate assistance in low-polarity 1,4-dioxane solvent. The methodology gives access to C2 (hetero)aryl- or alkenyl imidazoles as well as innovative C2 and C5 arylated fused imidazoles tricycles with a 5- to 7 membered middle ring.

Key words C-H functionalization, palladium catalysis, imidazole, arylation, alkenylation

Imidazoles are abundantly present in various naturally-occurring and biologically active compounds,[1] pharmaceutics[2] and materials.[3] This class of azaheterocycle is employed to produce *N*-heterocyclic carbenes (NHC) used as ligands in various transition-metal complexes in homogeneous catalysis[4] and organocatalysis.[5] Imidazolium-based ionic liquids are also often considered as green reaction media due to their unique chemical and physical properties.[6]

In this context, concise synthetic access towards imidazole cores is of high importance. Since last decades, the synthesis of imidazoles over numerous standard condensation reactions has been intensively reported.[7] The main drawback arises from the introduction at an early stage of the adequate functional group which penalizes the subsequent cyclization sequence. One of modern synthetic alternative is focused on the late-stage palladium-catalyzed C-H functionalization reactions from C2, C4 & C5 unsubstituted imidazoles.[8,9,10,11,12] In particular, Pd(0)-catalyzed C-H (hetero)arylation of *N*-substituted imidazoles with aryl halides at C2 and/or C5 positions has been widely studied by Bellina and Rossi group.[12] As some remarkable progresses, the orthogonal C2-H versus C5-H arylation of *N*-substituted imidazoles have been developed respectively under base-assisted Pd(0) / Cu(I) cooperative catalysis and Pd(0)-catalyzed concerted metalation-deprotonation (CMD), taking advantage of the acidic and the nucleophilic specific characters of respectively C2 and C5 sites.[12b,i] Although being less reactive, the C4 position of the imidazole ring was also reached through rare C-H functionalization reactions methodology.[13] Inspired by the pioneering Suzuki work on intramolecular C-H arylation of *N*-bromophenyl imidazole-4-carboxamide[14] and, in line, with our ongoing interest for the regioselective Pd(0)-catalyzed C-H arylation and alkenylation with halides of (oxa)thiazole-4-carboxylates,[15] as well as imidazole-5-carboxylate,[16] we turned our attention to the 4-carboxyimidazole series. Unlike the parent imidazole, the presence of the ester function at the C4 site offers several new synthetic and methodologic opportunities. Indeed, the carboxylate group may be gracelessly easily removed by catalytic extrusion of volatile CO_2 or converted into wealth of other moieties, and can be used as leaving group in various decarboxylative coupling with formation of C-C or C-heteroatom bonds.[17] Herein, we turned our attention to an exhaustive study of selective C2-H and C5-H arylation of different methyl *N*-substituted imidazole-4-carboxylate with aryl halides under Pd(0) catalysis through both inter- and intramolecular pathways. The later one opens access to innovative non-aromatic imidazoles-based tricycles offering potential for applications in pharmaceutical sciences.

We started our investigations by selecting the *N*-benzyl methyl imidazole-4-carboxylate **1a** as substrate, which was readily prepared by *N*-benzylation of the commercially available methyl imidazole-4-carboxylate under S_N2-type nucleophilic substitution using NaH as base and benzylbromide as electrophilic reagent.[18,19] The first set of Pd(0)-catalyzed C-H arylation of **1a** with of 4-bromotoluene (1.2 equivalent) was carried out by using $Pd(OAc)_2$ catalyst, PPh_3 ligand (Table 1) and

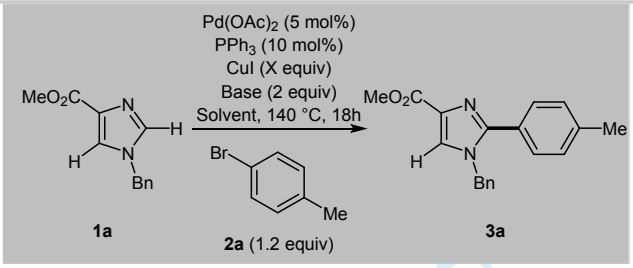
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

[a] Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France
E-mail: Christophe.hoarau@insa-rouen.fr

For Peer Review

Cu(I) as additive to reach selectively the C2 site in accordance to Bellina and Rossi reported work.[12i] In fact, the reaction was found poorly efficient in the standardly-used high polar DMF solvent with both potassium and cesium carbonates leading mainly to degradation of starting material **1a** (Table 1, entry 1). However in the less polar 1,4-dioxane solvent, the Pd(0)-catalyzed and CuI-assisted C-H arylation of **1a** with bromotoluene provided selectively the C2-H arylated imidazole-4-carboxylate **3a** in 34% yield (Table 1, entry 2).

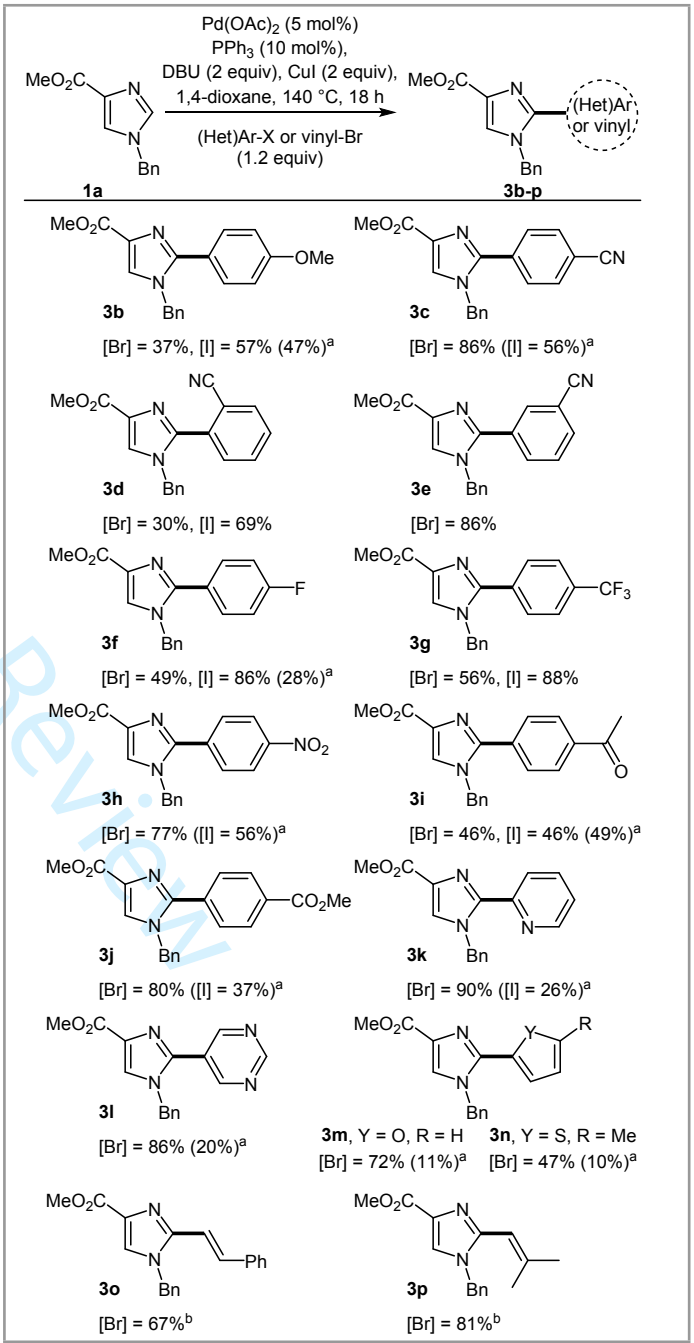
Table 1 Optimization of the palladium-catalysed intermolecular direct C-H arylation of **1a**



Entry	Base	Solvent[b]	CuI (n equiv)	Yield (%)[a]
1	K_2CO_3	DMF	2	< 5
2	K_2CO_3	1,4-dioxane	2	34
3	Cs_2CO_3	1,4-dioxane	2	4
4	CsF	1,4-dioxane	2	51
5	DBU	1,4-dioxane	2	76
6	DBU	1,4-dioxane	2	95[b]
7	DBU	1,4-dioxane	2	66[c]
8	DBU	1,4-dioxane	1	65
9	DBU	1,4-dioxane	-	<5
10	Cs_2CO_3	1,4-dioxane	--	< 5
11	K_2CO_3	1,4-dioxane	--	< 5

[a] Yield of isolated compound. [b] Using 4-iodotoluene (1.2 eq) as electrophilic reagent instead of 4-bromotoluene. [c] Reaction conditions: **1a** (1 eq), 4-iodotoluene (1 eq), $Pd(OAc)_2$ (5 mol %), $PCy_3.HBF_4$ (10 mol %), DBU (2 eq), CuI (2 eq), in 1,4-dioxane ([**1a**] = 0.16M), 210 °C, 20 min under microwave irradiation.

Three additional bases, Cs_2CO_3, CsF and DBU were then evaluated. Cs_2CO_3 proved to be deleterious to the CH arylation process leading mainly to degradation of the starting material **1a** (Table 1, entries 3). On the other hand, CsF and DBU were found more operating than K_2CO_3 base since the C2-arylated imidazole-4-carboxylate **3a** was produced in respectively 51 and 76% yields (Table 1, entries 4 and 5). Changing the electrophile for para-iodotoluene and keeping DBU as base led to the production of **3a** in excellent 95% isolated yield (Table 1, entries 6). Then, the C-H arylation of the methyl imidazole-4-carboxylate **1a** with para-iodotoluene was carried out under microwave irradiation using the optimal conditions. However, in this case, the use of PPh_3 as ligand which is prone to C-P cleavage reactions[20,21] led, as side product, to the introduction of a phenyl on the position 2 of the imidazole **1a**. As a replacement, $PCy_3.HBF_4$ ligand was then employed. In that case, the C2-arylated imidazole-4-carboxylate **3a** was obtained as single product in 66% yield after 20 min irradiation (Table 1, entry 7). As additional observations, lower amounts of CuI reduced the efficiency of the C-H arylation process with para-bromotoluene (Table 1, entry 8). Moreover, more importantly, without copper, very poor reactivity was observed (Table 1, entry 9-11) using DBU as well as Cs_2CO_3 and K_2CO_3 as bases suggesting that the standard carbonate-assisted palladium-catalyzed C-H arylation process is not operative.



Scheme 1 Scope of (hetero)aryl and alkenyl halides. [a] Yields obtained under microwave irradiation conditions (Table 1, entry 10) are given in brackets. [b] P(*o*-tolyl)$_3$ phosphine ligand was used instead of PPh_3.

With these optimal catalytic conditions in hands, the scope of the intermolecular arylation of the imidazole **1a** with different bromo- and iodoarenes as electrophiles was investigated.[22,23] Interestingly, the methodology revealed to be operative over a wide range of aryl bromides incorporating electron-withdrawing

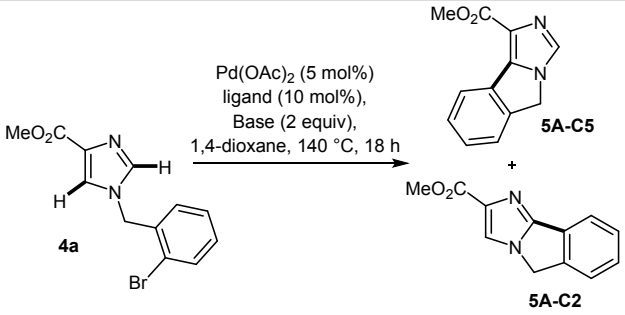
For Peer Review

groups and another electron-donating group. Notably, a broad series of C2-arylated imidazoles flanked with methyl (**3a**), methoxy (**3b**), cyano (**3c-e)**, fluoro (**3f**), trifluoromethyl (**3g**), nitro (**3h**), methylketone (**3i**) and methyl ester (**3j**) groups were successfully isolated in moderate to good yields (Scheme 1). The yields could be significantly improved by using aryliodides as electrophile reagents as exemplified for methyl C2-arylated imidazole-4-carboxylates **3b**, **3d**, **3g** and **3f**. Importantly, the protocol remained remarkably highly efficient with bromoheterocycles as electrophile reagents. Indeed, several methyl C2-heteroarylated-imidazole-4-carboxylates have been synthetized in presence of standard heterocycles such as pyridine (**3k**), pyrimidine (**3l**), furan (**3m**) and 5-methylthiophene (**3n**). As additional studies, some reactions were performed under microwave irradiation using iodoarenes. Although the time of the reaction was reduced to 20 min compared to conventional heating, in most of cases, lower performances were observed since methyl imidazole-4-carboxylates **3b-c,f,h-n** were obtained in a range of poor to moderate yields (10-56%).

As already mentioned, the regioselective direct arylation to afford the C2- or C5-arylated imidazole compounds has attracted a lot of attention during the past decades. However, the C2-H alkenylation of naked-imidazole has been less successful in contrast to their benzo-fused azole derivatives such as benzimidazole under Pd (with or without copper co-catalysis) catalysis from the corresponding alkenyl bromides.[24,25] Nevertheless, a Pd-catalyzed cross-dehydrogenative coupling reaction was successfully developed by Ong in 2014 to afford the corresponding C2-alkenylated imidazole.[26] In this context, the C-H alkenylation of 1a with alkenyl halides was then examined. However, applying strictly the above optimized protocol, the direct alkenylation of **1a** with the 2-bromostyrene failed. Meanwhile, in accordance with our previous observations in C-H alkenylation of 4,4'-dialkylimidazolone series,[27] the direct CH alkenylation reaction of 1a with the 2-bromostyrene was found immediately conclusive when replacing only the PPh_3 by P(o-tolyl)$_3$ as ligand. In this case, the expected alkenylated imidazoles **3o**-**p** were produced in 67% and 81% yields respectively from corresponding bromo-alkenes coupling partners (Scheme 1).

In continuation of this successful work on intermolecular selective C2-H (hetero)arylation of compound **1a**, we then turned our attention to the development of an intramolecular CH arylation protocol starting from methyl 1-(2-bromobenzyl)-1*H*-imidazole-4-carboxylate **4a**. First, the optimized protocol used for intermolecular C2-H arylation of **1a** revealed surprisingly ineffective. Other investigations under the same bis-catalytic mode but using carbonate bases were found also ineffective.[21] However, on the basis of our previous investigations in regioselective copper-free Pd(0)-catalyzed and carbonate-assisted arylation of oxa(thia)zole-4-carboxylates,[15f-g] intramolecular CH arylation of **4a** was achieved under standard catalysis based on the use of $Pd(OAc)_2$, carbonate bases and various phosphines in 1,4-dioxane. The results are summarized in table 2, and shows clearly that, under these conditions, a mixture of 4-carboxyimidazole-based tricyclic heterocycles possessing both imidazol-2-yl-aryl (**5A-C2**) and imidazole-5-yl-aryl (**5A-C5**) systems was identified with the isolated isomer **5A-C5** as the major one. Good performances of the direct C5-H arylation were observed using K_2CO_3 as a base and PPh_3 as well as electron-rich $PCy_3.HBF_4$ and electron-poor P(4-FC_6H_4)$_3$ as ligand providing the 4-carboxyimidazole-based tricyclic heterocycles **5A-C5** in a range of 70 to 81% isolated yields (Table 2, entries 1-3). Only the bidendate ligand dppb proved to be less effective (Table 2, entry 4). The observed C5-H selectivity using K_2CO_3 and electron-rich or electron-poor phosphines as optimal reagents are in favour a carbonate-assisted CMD-based process which, probably due to steric hindrance, was not effective for the intramolecular arylation of imidazole **1a** reported above. In accordance to our observations in (oxa)thiazole-4-carboxylate series, the acetate-assisted metalation-deprotonation process was found to be also ineffective with compound **4a** (Table 2, entry 5). In addition, with stronger bases such as Cs_2CO_3, the intramolecular C-H arylation of **4a** proceeded less efficiently as the 4-carboxyimidazole-based tricyclic heterocycle **5A-C5** was still isolated, as the main product but, in a poor 35% yield (Table 2, entry 6).

Table 2 Optimization of the reaction conditions of palladium-catalyzed intramolecular C-H arylation of **4a**

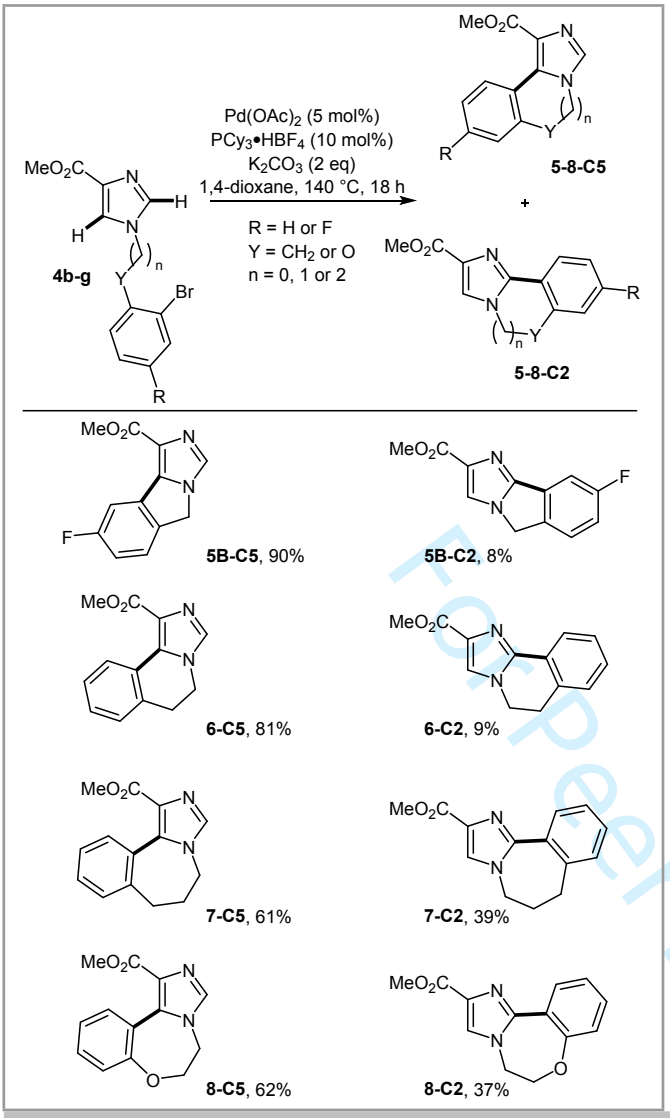


Entry	Ligand	Base	Yield (%)[a,b] **5A-C5**	Yield (%)[a,b] **5A-C2**
1	PPh_3	K_2CO_3	70	3
2	PCy_3•HBF_4	K_2CO_3	81	9
3	P(4-FC_6H_4)$_3$	K_2CO_3	81	17
4	dppb	K_2CO_3	42	nd
5	PCy_3•HBF_4	KOAc	nd	nd
6	PCy_3•HBF_4	Cs_2CO_3	35	3
7	P^{t}Bu$_2$Me•HBF_4	K_2CO_3	79	7
8	P^{t}Bu$_3$•HBF_4	K_2CO_3	23	27

[a]Conditions: **4a** (1 eq.), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (2 eq.), 1,4-dioxane (0.16 M), 140 °C, 18h. [b] Yield of isolated product.

Having previously highlighting the shift of selectivity from the most steric hindered C5 site to lower steric hindered C2 site through K_2CO_3-assited CMD-proceeding in oxazole and thiazole-4-carboxylates series by using bulky ligands,[15f-g] the behavior of the intramolecular C-H arylation of **4a** regarding the regioselectivity was examined when increasing phosphine bulkiness. First, P^{t}Bu$_2$Me gave predominantly the same **5A-C5** isomer in a good 79% yield (Table 2, entry 7). However, when further increasing the bulkiness of the phosphine and using the most steric hindered P^{t}Bu$_3$•HBF_4, the imidazole-based tricyclic heterocycle **5A-C2** was formed only in a slight excess compared to its regioisomer **5A-C5** (Table 2, entry 8).Therfore, full inversion of the regioselectivity was not observed as anticipated.

For Peer Review



Scheme 2 Synthesis of 4-carboxyimidazole-based tricyclic heterocycles

The production of 4-carboxyimidazole-based tricyclic heterocycles **5-8** embedding with an 5- and up to 7-membered central ring was finally investigated starting from various methyl *N*-alkylated imidazole-4-carboxylates **4b-g** and by selecting the optimized PCy_3•HBF_4 ligand. Results are depicted in Scheme 2. The para-fluorinated imidazole-based tricyclic heterocycles **5B-C5** was produced in excellent 90% yield, the **5B-C2** isomer being isolated in very few amounts (8%). Similarly, to the preparation of 5-membered medium ring models, the imidazole-based 6-membered tricyclic heterocyclic **6-C5** was also successfully obtained as the major product in excellent 81% yield. Again, the other isomer **6-C2** was produced as the only side product in 9% yield. Formation of compounds **6-C5** and **6-C2** has already been reported via a radical cyclisation although with lower yield and selectivity.[18a] With these promising results in hands, the preparation of imidazole-based 7-membered tricyclic heterocycles **7** and **8** were next investigated. However, in this case, we found that even the ring-closing reaction occurred mainly at the **C5** site of the imidazole ring leading to the **7-C5** and **8-C5** isomer in moderate 61 and 62% yields, a significant reduction of selectivity in favour of the less steric hindered C2-H site was observed and the **7-C2** and **8-C2** isomers were isolated in much more significant yields (39 and 37% respectively). Unfortunately, this methodology failed to prepare the imidazole-based 8-membered tricyclic heterocycles.

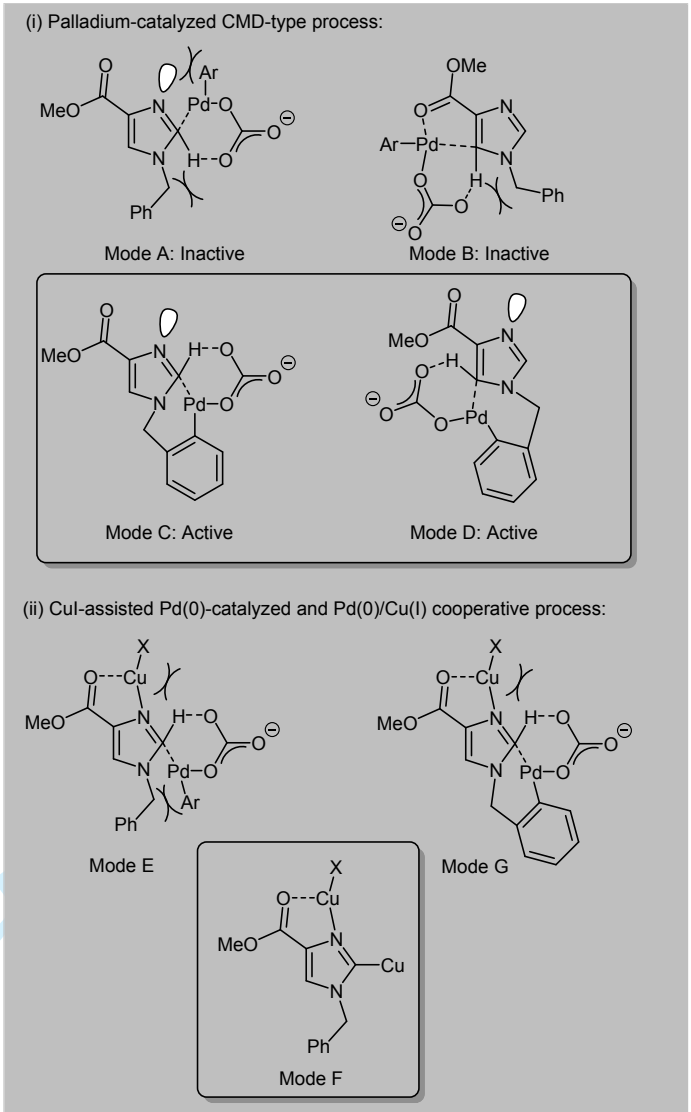


Figure 1 Plausible intermediates in catalytic C-H arylation

Finally, regarding the reactivity and the regioselectivity observed within this direct C-H arylation study in imidazole-4-carboxylate series through both intramolecular and intermolecular and using both Pd(0)- or Pd(0) / CuI cooperative catalysis, assumptions of the modes of carbonate-assisted metalation-deprotonation might be done (Scheme 3). First, we assumed that the standard K_2CO_3-assisted CMD-based reactivity could not proceed at both highly sterically hindered C2-H and C5-H sites of **1a** (model A and B) whilst, for the intramolecular pathway from compound **4a**, the reactivity could be recovered due to a decrease of the steric constraint. In that case, the C5-H vs C2-H competition was observed showing that the energetic barriers might be very closed (mode C and D). Naturally, the intramolecular direct C2-H arylation under Pd(0) / CuI cooperative catalysis pathway is penalized with the difficulty to achieve within the same molecule the consecutive generation of imidazole-2-yl copper as well as the oxidative addition of Pd(0) to the aryl halide moiety prefiguring the intramolecular transmetalation key step. On the other hands, the CuI co-catalyst being only efficient for intermolecular C2-H arylation of **1a**, the

For Peer Review

CMD mode from the *N*-(CuI)-chelated imidazole-4-carboxylate complex, reported by Gorelsky group (model E and G),[28] might be here discarded in favour of the generation of imidazole-2-yl copper intermediate (model F), in accordance to the Bellina/Rossi suggestion.[11f]

As summarized, this work reports the first full investigations of palladium-catalyzed direct C-H functionalization with halides in *N*-substituted imidazole-4-carboxyxlate series. In particular, the first selective direct C2-H (het)arylation and alkenylation of *N*-benzyl imidazole-4-carboxylate with bromo- and iodo(het)arenes and bromoalkenes under Pd(0)/Cu(I) cooperative catalysis was described giving a neat access to a broad library of C2-functionalized methyl imidazole-4-carboxylate compounds. By contrast to previous observations in 4-nitro *N*-substituted imidazole-4-carboxylate series,[29] in our case, the intermolecular CMD-based reactivity does not operate at C5 site when C4 site and nitrogen imidazole are both substituted. On almost the opposite, using *N*-(*ortho*-halogeno benzyl) imidazole-4-carboxylates as starting materials, the arylation took place successfully under K_2CO_3-assisted CMD-based conditions to produce new C5-arylated fused imidazoles with a 5- to 7 membered central rings as major products. As major mechanistic highlighting in direct C-H functionalization of heterocycle, the standard cooperative Pd(0)/Cu(I) catalysis revealed inoperative when driving through intramolecular pathway due to probably the difficulty of getting in the same first the formation of the imidazole-2-yl copper intermediate followed by the oxidative addition of Pd(0) to the aryl halide moiety. Moreover, a loss of C5-H vs C2-H selectivity was clearly observed during the preparation of 7-membered tricyclic imidazole-based heterocycles probably due to the more important size of the linker. Additional studies are currently ongoing to further functionalize these tricyclic scaffolds in order to generate chemical diversity.

For Peer Review

Funding Information

Click here to insert sources of funding, grant numbers, etc. Do not repeat the same in the acknowledgment.

Acknowledgment

This work has been partially supported by INSA Rouen, Rouen University, CNRS, EFRD, European INTERREG IV A France (Channel) and Labex SynOrg (ANR-11-LABX-0029). We also thank the CRIHAN for software optimization and technical support.

Supporting Information

Is there **Supporting Information** to be published? Click here, then the arrow, and choose YES or NO.

Primary Data

YES (this text will be updated with links prior to publication)

References and Notes

(1) (a) Wang, W.; Tang, X.; Hua, F.; Ling, T.-J.; Wan, X.-C.; Bao, G.-H. *Org. Lett.* **2018**, *20*, 2672. (b) Rodrigues de Carvalho, L.; de Brito, T. V.; Simiao da C. Junior, J.; Jose Dias Junior, G.; de Aguiar Magalhares, D.; Guimaraes Sousa, S.; Oliveira Silva, R.; Rodolfo Pereira da Silva, F.; Fernando Pereira Vasconcelos, D.; Maria Costa Veras, L.; de Sousa de Almeida Leite, J. R.; Santos Martins, D.; da Silva Martins, C.; Soares de Oliveira, J.; Barbosa, A. *Biomed. Pharmacother.* **2018**, *102*, 278. (c) Silva, V. G.; Silva, R. O.; Damasceno, S. R. B.; Carvalho, N. S.; Prudêncio, R. S.; Aragão, K. S.; Guimarães, M. A.; Campos, S. A.; Véras, L. M. C.; Godejohann, M.; Leite, J. R. S. A.; Barbosa, A. L. R.; Medeiros, J.-V. R. *J. Nat. Prod.* **2013**, *76*, 1071. (d) Ding, H.; Roberts A. G.; Harran, P. G. *Chem. Sci.* **2013**, *4*, 303. (e) Sato, S.; Iwata, F.; Takeo, J.; Kawahara, H.; Kuramoto, M.; Uno, H. *Chem. Lett.* **2011**, *40*, 186. (f) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1. (g) Iinuma, Y.; Kozawa, S.; Ishiyama, H.; Tsuda, M.; Fukushi, E.; Kawabata, J.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 1109. (h) Fresneda, P. M.; Molina, P.; Sanz M. A. *Tetrahedron Lett.* **2001**, *42*, 851.

(2) Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H.; *Med. Res. Rev.* **2014**, *34*, 340.

(3) For recent reviews, see: (a) Chen, W.-C.; Zhu, Z.-L.; Lee, C.-S. *Adv. Optical Mater.* **2018**, *6*, 1800258. (b) Anderson, E. B.; Long, T. E. *Polymer* **2010**, *51*, 2447.

(4) For reviews, see: (a) Liu, J.-Q.; Gou, X.-X.; Han, Y.-F. *Chem. Asian J.* **2018**, *13*, 2257. (b) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978. (c) Braband, H.; Kueckmann, T.; Theresa, I.; Abram, U. *J. Organomet. Chem.* **2005**, *690*, 5421. (d) Scott, N. M.; Nolan, S. P. *Eur. J. Inorg. Chem.* **2005**, 1815. (e) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.

(5) For recent reviews, see: (a) Wang, N.; Xu, J.; Lee, J. K. *Org. Biomol. Chem.* **2018**, *16*, 8230. (b) Wang, Z.; Pan, D.; Li, T.; Jin, Z. *Chem. Asian J.* **2018**, *13*, 2149.

(6) For leading references, see: (a) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, *0*, 965. (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (c) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772. (d) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (e) Karimi, B.; Tavakolian, M.; Akbari, M.; Mansouri, F. *ChemCatChem* **2018**, *10*, 3173.

(7) For recent reviews, see: (a) Rossi, R.; Angelici, G.; Casotti, G.; Manzini, C.; Lessi, M. *Adv. Synth. Catal.* **2019**, *361*, 2737. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (c) Kamijo, S.; Yamamoto, Y. *Chem. Asian J.* **2007**, *2*, 568.

(8) For selected C-H arylation of imidazoles or their ring fused analogues catalyzed by rhodium, copper or nickel metals, see: (a) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Accounts Chem. Res.* **2008**, *41*, 1013. (c) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2006**, 45, 1589. (d) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (e) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3296. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Accounts Chem. Res.* **2009**, *42*, 1074. (g) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (h) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (i) Muto, K.; Hatakeyama, T.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2015**, *6*, 6792.

(9) For reviews on this topic, see: (a) Ref 7a. (b) Bellina, F.; Rossi, R. *Adv. Synth. Catal.* **2010**, *352*, 1223. (c) De Ornellas, S.; Storr, T. E.; Williams, T. J.; Baumann, C. G.; Fairlamb, I. J. S. *Curr. Org. Synth.* **2011**, *8*, 79.

(10) For palladium-catalyzed intramolecular direct arylation of imidazole, see: (a) Xu, X.; Zhao, L.; Li, Y.; Soulé, J.-F.; Doucet, H. *Adv. Synth. Catal.* **2015**, *357*, 2869. (b) Laha, J. K.; Dayal, N.; Singh, S.; Bhimpuria, R. *Eur. J. Org. Chem.* **2014**, 5469. (c) Laha, J. K.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 8477. (d) Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron* **2010**, *66*, 1937. (e) Majumdar, K. C.; Debnath, P.; Taher, A.; Pal, A. K. *Can. J. Chem.* **2008**, *86*, 325. (f) Lee, H. S.; Kim, S. H.; Gowrisankar, S.; Kim, J. N. *Tetrahedron* **2008**, *64*, 7183. (g) Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, *18*, 3170. (h) Gracias, V.; Gasiecki, A. F.; Pagano, T. G.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8873. (i) Delest, B.; Tisserand, J.-Y.; Robert, J.-M.; Nourrisson, M.-R.; Pinson, P.; Duflos, M.; Le Baut, G.; Renard, P.; Pfeiffer, B. *Tetrahedron* **2004**,

60, 6079. (j) Kuroda, T.; Suzuki, F. *Tetrahedron Lett*. **1991**, *32*, 6915.

(11) For palladium-catalyzed intermolecular direct arylation of imidazole derivatives, see: (a) Vellakkaran, M.; Lingayya, R.; Kumar, B. N.; Nagaiah, K.; Poornachandra, Y.; Kumar, C. G. *RSC Adv*. **2015**, *5*, 8057. (b) Grosse, S.; Pillard, C.; Massip, S.; Marchivie, M.; Jarry, C.; Bernard, P.; Guillaumet, G. *J. Org. Chem*. **2015**, *80*, 8539.

(12) (a) Lessi, M.; Panzetta, G.; Marianetti, G.; Bellina, F. *Synthesis* **2017**, *49*, 4676. (b) Perego, L. A.; Grimaud, L.; Bellina, F. *Adv. Synth. Catal*. **2016**, *358*, 597. (c) Bellina, F. ; Lessi, M.; Manzini, C. *Eur. J. Org. Chem*. **2013**, 5621. (d) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060. (e) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem*. **2008**, 5436. (f) Bellina, F.; Cauteruccio, S.; Rossi, R. *Curr. Org. Chem*. **2008**, *12*, 774. (g) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (h) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem*. **2007**, *72*, 8543. (i) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem*. **2006**, 693. (j) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem*. **2005**, *70*, 3997.

(13) Joo, J. M.; Touré, B. B.; Sames, D. *J. Org. Chem*. **2010**, *75*, 4911.

(14) Kuroda, T.; Suzuki, F. *Tetrahedron Lett*. **1991**, *32*, 6915.

(15) (a) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008**, *10*, 2909. (b) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383. (c) Roger, J.; Verrier, C.; Le Goff, R.; Hoarau, C.; Doucet, H. *ChemSusChem* **2009**, *2*, 951. (d) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647. (e) Verrier, C.; Fiol-Petit, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2011**, *9*, 6215. (f) Théveau, L.; Verrier, C.; Lassalas, P.; Martin, T.; Dupas, G.; Querolle, O.; Van Hijfte, L.; Marsais, F.; Hoarau, C. *Chem. Eur. J.* **2011**, *17*, 14451. (g) Théveau, L.; Querolle, O.; Dupas, G.; Hoarau, C. *Tetrahedron* **2013**, *69*, 4375.

(16) Thireau, J.; Schneider, C.; Baudequin, C.; Gaurrand, S.; Angibaud, P.; Meerpoel, L.; Levacher, V.; Querolle, O.; Hoarau, C. *Eur. J. Org. Chem*. **2017**, 2491.

(17) For recent reviews, see: (a) Cai, X.-h.; Yang, M.; Xie, B. *Curr. Org. Chem*. **2018**, *22*, 1906. (b) Zhang, T.; Wang, N.-X.; Xing, Y. *J. Org. Chem*. **2018**, *83*, 7559. (c) Hosseinian, A.; Nasab, F. A. H.; Ahmadi, S.; Rahmani, Z.; Vessally, E. *RSC Adv*. **2018**, *8*, 26383. (d) Schwarz, J.; König, B., *Green Chem*. **2018**, *20*, 323. (e) Perry, G. J. P.; Larrosa, I. *Eur. J. Org. Chem*. **2017**, 3517. (f) Wie, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev*. **2017**, *117*, 8864. (g) Jin, Y.; Fu, H. *Asian J. Org. Chem*. **2017**, 6, 368. (h) Li, H.; Miao, T.; Wang, M.; Li, P.; Wang, L. *Synlett* **2016**, *27*, 1635.

(18) (a) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689. (b) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111.

(19) Two regioisomers were obtained, however concerning this study only methyl *N*-alkylated imidazole-4-carboxylates were evaluated.

(20) For recent references, see: (a) Baba, K.; Masuya, Y.; Chatani, N.; Tobisu, M. *Chem. Lett*. **2017**, *46*, 1296. (b) Zhou, H.; Li, J.; Yang, H.; Xia, C.; Jiang, G. *Org. Lett*. **2015**, *17*, 4628. (c) Zhou, Y.; Gan, Z.; Su, B.; Li, J.; Duan, Z.; Mathey, F. *Org. Lett*. **2015**, *17*, 5722. (d) Baba, K.; Tobisu, M.; Chatani, N. *Org. Lett*. **2015**, *17*, 70. (e) Karthik, V.; Gupta, V.; Anantharaman, G. *Organometallics* **2015**, *34*, 3713. (f) Baba, K.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed*. **2013**, *52*, 11892. (g) Li, Z.; Zhou, H.; Xu, J.; Wu, X.; Yao, H. *Tetrahedron* **2013**, *69*, 3281. (h) Ma, M.-T.; Lu, J.-M. *Tetrahedron* **2013**, *69*, 2102.

(21) See the supporting information for more details.

(22) **General procedure for Pd-catalyzed intermolecular direct C2-H arylation of methyl *N*-benzyl-1*H*-imidazole 4-carboxylate under thermic conditions:** Methyl 1-benzyl-1*H*-imidazole-4-carboxylate **1a** (80 mg, 0.37 mmol, 1 eq), the appropriate halide **2** (1.2 eq), $Pd(OAc)_2$ (18 µmol, 5 mol%), PPh_3 (37 µmol, 10 mol%), CuI (0.74 mmol, 2 eq) and anhydrous DBU (0.74 mmol 2 eq) were placed in a dry sealed tube containing a magnetic stir bar. The tube was evacuated and filled back with N2 three rime before adding anhydrous 1,4-dioxane (2.5 mL). The tube was sealed and heated to 140 °C for 18 hours. The reaction was filtered over a Celite® pad (washed with DCM and EtOAc). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (DCM to DCM/EtOAc 9-1).

(23) Compound **3a** was prepared according to the general procedure. The crude product was purified by flash chromatography to afford **3a** in 76% yield with aryl-bromide and 95% yield with aryl-iodide as a pale yellow solid. mp : 89-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H_{im}, H5), 7.46 (d, *J* = 8.0 Hz, 2H_{arom}), 7.35-7.33 (m, 3H_{benzyl}), 7.22 (d, *J* = 8.0 Hz, 2H_{arom}), 7.09-7.07 (m, 2H_{benzyl}), 5.19 (s, 2H), 3.89 (s, 3H, OMe), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 149.5 (C2, Cq_{im}), 139.7 (C4', Cq_{arom}), 135.9 (C1', Cq_{benzyl}), 132.9 (C4$_{im,}$ Cq), 129.3 (2×CH), 129.2 (2×CH), 129.1 (2×CH), 128.4 (CH_{benzyl}), 127.1 (C5, CH_{im}), 126.9 (2×CH_{benzyl}), 126.5 (Cq), 51.8 (OCH_3), 51.0 (N-CH_2), 21.4 (CH_3). IR (ATR ,cm^{-1}): 3125, 3079, 2920, 2850, 1689, 1549, 1330, 1227, 1004, 725 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{19}N_2O_2$: $[M+H]^+$ 307.1447, found 307.1455.

(24) (a) Vabre, R.; Chevot, F.; Legraverend, M.; Piguel, S. *J. Org. Chem*. **2011**, *76*, 9542. (b) Vabre, R.; Legraverend, M.; Piguel, S. *Dyes and Pigments* **2014**, 105, 145. (c) Baladi, T.; Granzhan, A.; Piguel, S. *Eur. J. Org. Chem*. **2016**, 2421.

(25) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem*. **2010**, 6097.

(26) Lee, W.-C.; Wang, T.-H.; Ong, T.-G. *Chem. Commun*. **2014**, *50*, 3671.

(27) (a) Museli, M.; Baudequin, C.; Perrio, C.; Hoarau, C.; Bischoff, L. *Chem. Eur. J*. **2016**, *22*, 5520. (b) Museli, M.; Baudequin, C.; Hoarau, C.; Bischoff, L. *Chem. Commun*. **2015**, *51*, 745.

(28) Gorelsky, S. I.; *Coordin. Chem. Rev*. **2013**, *257*, 153. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem*. **2012**, *77*, 658.

(29) Iaroshenko, V. O.; Gevorgyan, A.; Mkrtchyan, S.; Arakelyan, K.; Grigoryan, T.; Yedoyan, J.; Villinger, A.; Langer, P. *J. Org. Chem*. **2015**, *80*, 2103.

For Peer Review

Checklist (have these on hand for manuscript submission in ScholarOne):

- cover letter, including a statement of the work's significance
- full mailing address, telephone and fax numbers, and e-mail address of the corresponding author
- email address for each author
- original Word file

- original graphics files zipped into one zip file
- eye-catching graphical abstract as an individual file
- 5–8 key words
- separate Supporting Information file
- separate zipped Primary Data files including cover sheet (optional)

For Peer Review

Pd(0)-catalyzed direct inter- and intramolecular C-H functionalization of 4-carboxyimidazoles.

Steven Frippiat,[a] Antoine Peresson,[a] Thibault Perse,[b] Yvan Ramondenc,[a] Cédric Schneider,[a] Olivier Querolle,[b] Patrick Angibaud,[b] Virginie Poncelet,[b] Lieven Meerpoel,[c] Vincent Levacher,[b] Laurent Bischoff,[a] Christine Baudequin*[a] and Christophe Hoarau*[a]

[a] *Normandie University, COBRA UMR 6014 et FR 3038, University Rouen; INSA Rouen; CNRS, IRCOF 1 rue Tesnière 76821 Mont Saint Aignan, France.*

[b] *Janssen Research & Development, Division of Janssen-Cilag S. A., Campus de Maigremont, BP 615 27106 Val de Reuil Cedex, France.*

[c] *Janssen Research & Development, Division of Janssen-Cilag a division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340, Beerse, Belgium.*

For Peer Review

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Supporting Information

Table of Contents

General information

All reagents were purchased from commercial suppliers and were used without further purification. Extra dry 1,4-Dioxane and DMF were purchased from Sigma-Aldrich® in sealed bottles over 3Å or 4Å molecular sieves and stored under N_2.

The reactions were performed without any protection from the light and monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation (λ = 254 nm) and/or spraying TLC stain such as a $KMnO_4$ solution followed by heating at 200 °C. Flash chromatography columns were performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm).

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Brucker Advance spectrometer operating at 300 or 500 MHz, and 75 or -125 MHz respectively. Chemical shifts are given in parts per million and ^{1}H and ^{13}C NMR spectra were referenced using the solvent signal as an internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singulet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br: broad.

For Peer Review

Coupling constants (*J*) are reported in Hertz (Hz). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^{1}H-^{13}C-COSY (HSQC: Heteronuclear Single Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation).

HRMS were recorder on a LC Waters Acquity coupled to a Waters LCT Premier XE instrument

The infrared spectra of compounds were recorded on a Perkin Elmer Spectrum 100 FT IR spectrometers.

Melting points (mp [°C]) were taken on open capillary tubes and are uncorrected, performed on a Stuart SMP3.

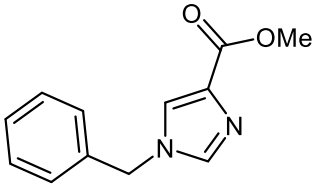
Experimental section

1. General procedure for alkylation

To a solution of methyl 4-imidazolecarboxylate (4 mmol, 1.0 eq) in anhydrous DMF (25 mL), sodium hydride (95% dry, 6 mmol, 1.5 eq) was introduced in small portions under argon atmosphere. The mixture was stirred at 80°C for 1 h. A solution of the alkylating agent (6 mmol, 1.5 eq) in 5 mL of DMF was introduced dropwise to the reaction mixture which was heated at 80°C for 12 h. The solution was cooled to room temperature and the salts were removed by filtration on a Celite® pad. The solution was evaporated under reduced pressure to afford two regioisomers which were separated by column chromatography using petroleum ether/ethyl acetate (1/4) as eluent.

All regioisomers methyl 1[(2-bromophenyl)alkyl)-1*H*-imidazole-5-carboxylate were previously prepared in our laboratory and reported.[1] In this paper, we do not used these regioisomers, also we have not reported the analysis of these compounds.

methyl 1-benzyl-1*H*-imidazole-4-carboxylate 1a:



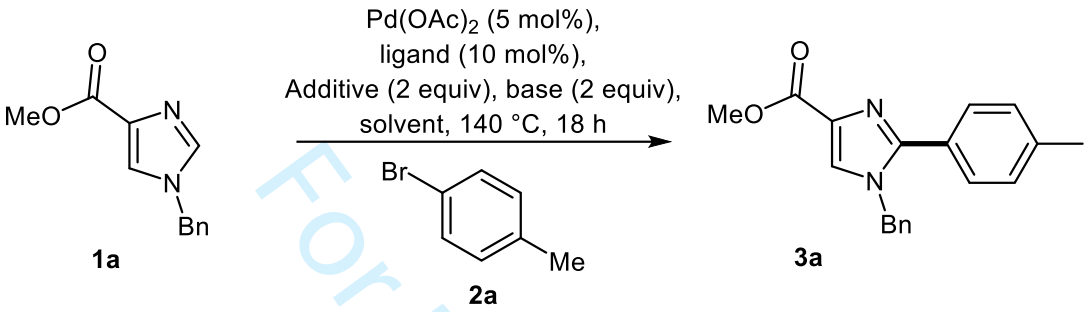
Compound **1a** was prepared according to the general procedure for alkylation. The crude product was purified by flash chromatography to afford **1a** in 74% (2.96mmol) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H$_{im}$, H5), 7.54 (s, 1H$_{im}$, H2), 7.37-7.33 (m, 3H$_{benzyl}$), 7.17-7.15 (m, 2H$_{benzyl}$), 5.12 (s, 2H), 3.86 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2

[1] Thireau, J.; Schneider, C.; Baudequin, C.; Gaurrand, S.; Angibaud, P.; Meerpoel, L.; Levacher, V.; Querolle, O.; Hoarau, C. *Eur. J. Org. Chem*., **2017**, 2491.

For Peer Review

(C=O), 138.1 (C2, CH_{im}), 134.9 ($C4_{im}$, Cq) 134.1 (C1', Cq_{benzyl}), 129.2 (C3', CH_{benzyl}), 128.7 (C4', CH_{benzyl}), 127.6 (C2', CH_{benzyl}), 125.4 (C5, CH_{im}), 51.7 (OCH_3), 51.4 ($N\text{-}CH_2$). IR (ATR ,cm^{-1}): 3417, 3112, 2950, 1715, 1546, 1378, 1223, 1178, 994, 767, 710 cm^{-1}. HRMS: Anal. Calcd for $C_{12}H_{12}N_2O_2$: $[M+H]^+$ 217.0977, found 217.0974.

2. Optimization of the Pd-catalyzed intermolecular direct C2-H arylation of the methyl 1-benzyl-1*H*-imidazole-4-carboxylate **1a** under thermic conditions:

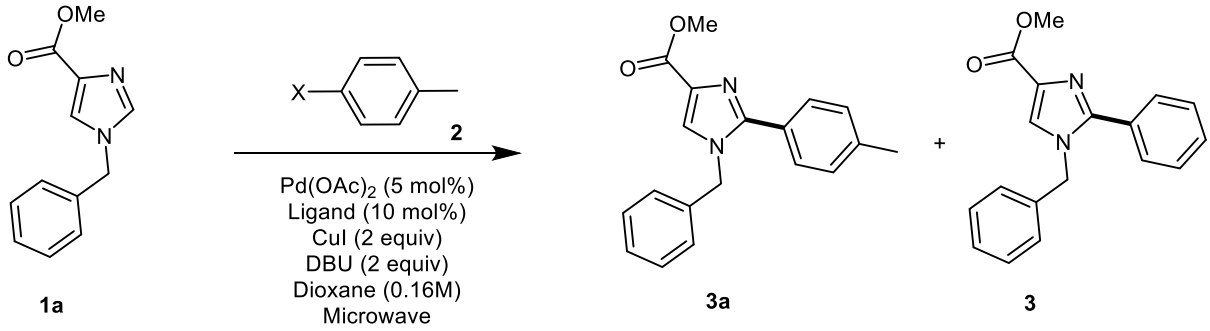


Entry	Ligand	Base (2eq.)	Additive (2eq.)	Solvent	Yield[b]
1	PPh_3	K_2CO_3	-	DMF	lc[a]
2	PPh_3	Cs_2CO_3	-	DMF	lc[a]
3	PPh_3	K_2CO_3	CuI	DMF	lc[a]
4	PPh_3	CsF	CuI	DMF	15
5	PPh_3	DBU	CuI	DMF	40
6	PPh_3	K_2CO_3	CuI	Dioxane	34
7	$PCy_3 \bullet HBF_4$	K_2CO_3	CuI	Dioxane	25
8	PPh_3	Cs_2CO_3	CuI	Dioxane	4
9	PPh_3	CsF	CuI	Dioxane	51
10	PPh_3	DBU	CuI	Dioxane	76
11	PPh_3	DBU	CuI (1eq)	Dioxane	65
12	PPh_3	DBU	CuI	Dioxane	95[c]

[a] lc: low conversion (determined by ^1H NMR). [b] Yield of isolated compound. [c] Using 4-iodotoluene as electrophilic reagent instead of 4-bromotoluene.

For Peer Review

3. Optimization of the Pd-catalyzed intermolecular direct C2-H arylation of the methyl 1-benzyl-1*H*-imidazole-4-carboxylate **1a** under microwave irradiation conditions:



Entry	Ligand	X	Temperature (°C)	Time (mn)	Formation of 3a (%)[a]	Yield 3a (%)
1	PPh_3	I	150	40	64[b]	Not isolated
2	PPh_3	I	210	20	68[b]	Not isolated
3	PCy_3	I	210	20	72	60
4	PCy_3•HBF_4	I	210	20	82	66
5	PCy_3•HBF_4	Br	210	20	90	45

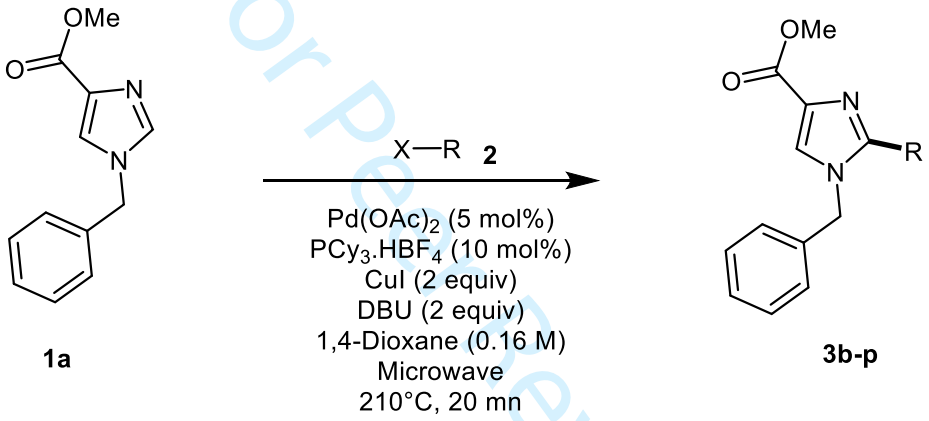
a: % of formation of compound **3a** was evaluated by Liquid Chromatography coupled to Mass Spectroscopy
b: mixture of compounds **3a** and **3**.
Entry 1: **3a**/**3**: 75/25
Entry 2: **3a**/**3**: 70/30

4. Pd-catalyzed intermolecular direct C-H arylation of methyl *N*-benzyl-1*H*-imidazole 4-carboxylate under thermic conditions or microwave irradiation conditions.

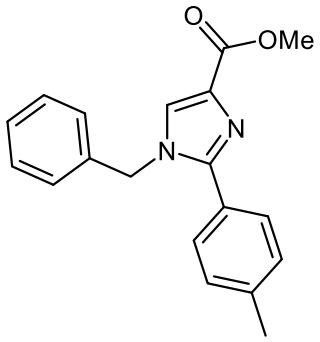
Method A. General procedure for Pd-catalyzed intermolecular direct C2-H arylation of methyl *N*-benzyl-1*H*-imidazole 4-carboxylate under thermic conditions: Methyl 1-benzyl-1*H*-imidazole-4-carboxylate **1a** (80 mg, 0.37 mmol, 1 eq), the appropriate halide **2** (1.2 eq), $Pd(OAc)_2$ (18 µmol, 5 mol%), PPh_3 (37 µmol, 10 mol%), CuI (0.74 mmol, 2 eq) and anhydrous DBU (0.74 mmol 2 eq) were placed in a dry sealed tube containing a magnetic stir bar. The tube was evacuated and filled back with N2 three rime before adding anhydrous 1,4-dioxane (2.5 mL). The tube was sealed and heated to 140 °C for 18 hours. The reaction was filtered over a Celite ® pad (washed with DCM and EtOAc). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (DCM to DCM/EtOAc 9-1).

For Peer Review

Method B. General procedure for Pd-catalyzed intermolecular direct C2-H arylation of methyl *N*-benzyl-1*H*-imidazole 4-carboxylate under microwave irradiation conditions: To a solution of compound **1a** in dioxane, in a septum sealed tube, were successfully added the appropriate halide (1.0 eq), ligand (10 mol%), CuI (2 eq) and DBU (2eq). Between each addition, the mixture was degassed and refilled with nitrogen. Then, $Pd(OAc)_2$ (5 mol%) in solution in 1,4-dioxane (final concentration of compound **1a** in 1,4-dioxane was 0.16M). Then, the tube was sealed and heated at 210°C using a single mode microwave (Biotage Initiator EXP60) with a power output ranging from 0 to 400W for 20mn. Then, the reaction mixture was diluted into dichloromethane and concentrated. The mixture was purified by reverse phase preparative chromatography (solid deposit with SiO_2 63-200 µm) using a gradient of NH_4CO_3 2g/L and acetonitrile.



methyl 1-benzyl-2-(p-tolyl)-1*H*-imidazole-4-carboxylate 3a:



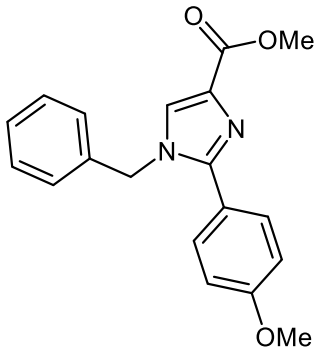
Compound **3a** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3a** in 76% yield with aryl-bromide and 95% yield with aryl-iodide as a pale yellow solid. mp : 89-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, $1H_{im}$, H5), 7.46 (d, J = 8.0 Hz, $2H_{arom}$), 7.35-7.33 (m, $3H_{benzyl}$), 7.22 (d, J = 8.0 Hz, $2H_{arom}$), 7.09-7.07 (m, $2H_{benzyl}$), 5.19 (s, 2H), 3.89 (s, 3H, OMe), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 149.5 (C2, Cq_{im}), 139.7 (C4', Cq_{arom}), 135.9 (C1', Cq_{benzyl}), 132.9 ($C4_{im,}$ Cq), 129.3 (2×CH),

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

For Peer Review

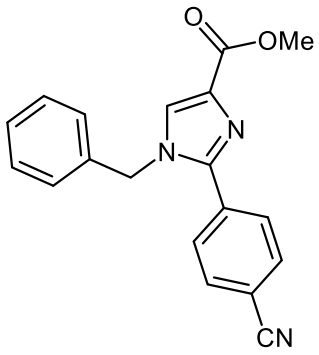
129.2 (2×CH), 129.1 (2×CH), 128.4 (CH_{benzyl}), 127.1 (C5, CH_{im}), 126.9 (2×CH_{benzyl}), 126.5 (Cq), 51.8 (OCH_3), 51.0 (N-CH_2), 21.4 (CH_3). IR (ATR ,cm^{-1}): 3125, 3079, 2920, 2850, 1689, 1549, 1330, 1227, 1004, 725 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{19}N_2O_2$: $[M+H]^+$ 307.1447, found 307.1455.

methyl 1-benzyl-2-(4-methoxyphenyl)-1*H*-imidazole-4-carboxylate 3b:



Compound **3b** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3b** in 57% as a pale yellow solid. mp : 70-71 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H_{im}, H5), 7.49 (d, *J* = 8.6 Hz, 2 H_{arom}), 7.35-7.33 (m, 3H_{benzyl}), 7.09-7.06 (m, 2H_{benzyl}), 6.92 (d, *J* = 8.6 Hz, 2H_{arom}), 5.18 (s, 2H), 3.89 (s, 3H, OMe), 3.82 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 160.6 (Cq_{arom}, C4'), 149.4 (C2, Cq_{im}), 135.8 (C1', Cq_{benzyl}), 132.8 ($C4_{im,}$ Cq), 130.7 (2×CH_{arom}, C2'), 129.2 (2×CH_{benzyl}), 128.4 (CH_{benzyl}), 127.0 (C5, CH_{im}), 126.9 (2×CH_{benzyl}), 121.7 (Cq), 114.1 (2×CH_{arom}, C3'), 55.4 (OCH_3), 51.8 (OCH_3), 51.0 (N-CH_2). IR (ATR ,cm^{-1}): 2948, 2838, 1713, 1611, 1538, 1481, 1347, 1328, 1251, 1175, 1004, 837 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{18}N_2O_3$: $[M+H]^+$ 323.1396, found 323.1404.

methyl 1-benzyl-2-(4-cyanophenyl)-1*H*-imidazole-4-carboxylate 3c:

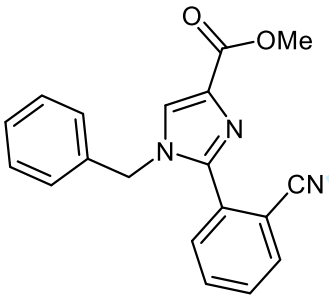


Compound **3c** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3c** in 86% as a white solid. mp : 160-161 °C (DCM/Pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.69 (m, 5H, 4H_{arom} and 1H_{im}, H5), 7.37-7.35 (m, 3H_{benzyl}),

For Peer Review

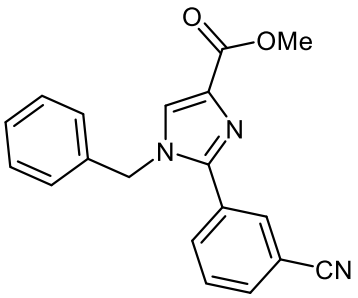
7.07-7.04 (m, 2H$_{benzyl}$), 5.24 (s, 2H), 3.90 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (C=O), 147.1 (C2, Cq$_{im}$), 135.1 (C1', Cq$_{benzyl}$), 133.7 (Cq), 133.7 (Cq), 132.4 (2×CH$_{arom}$), 129.7 (2×CH), 129.5 (2×CH), 128.8 (CH$_{benzyl}$), 128.3 (C5, CH$_{im}$), 126.7 (2×CH$_{benzyl}$), 118.3 (Cq), 113.3 (Cq), 52.0 (OCH_3), 51.3 (N-CH_2). IR : 3120, 3077, 2945, 2226, 1695, 1611, 1548, 1454, 1330, 1225, 1006, 723 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{15}N_3O_2$: $[M+H]^+$ 318.1243, found 318.1249.

methyl 1-benzyl-2-(2-cyanophenyl)-1*H*-imidazole-4-carboxylate 3d:



Compound **3d** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3d** in 69% as a pale yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 1H$_{arom}$), 7.68 (s, 1H$_{im}$, H5), 7.63 (d, *J* = 7.7 Hz, 1H$_{arom}$), 7.56 (t, *J* = 8.1 Hz, 2H$_{arom}$), 7.29-7.27 (m, 3H$_{benzyl}$), 7.09-7.06 (m, 2H$_{benzyl}$), 6.92 (d, *J* = 8.6 Hz, 2H$_{arom}$),7.01-6.99 (m, 2H), 5.10 (s, 2H), 3.87 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (C=O), 145.1 (C2, Cq$_{im}$), 134.8 (C1', Cq$_{benzyl}$), 133.5 (Cq), 133.3 (Cq), 133.2 (CH$_{arom}$), 132.9 (CH$_{arom}$), 131.8 (CH$_{arom}$), 130.3 (CH$_{arom}$), 129.2 (2×CH$_{benzyl}$), 128.7 (CH$_{benzyl}$), 127.4 (2×CH$_{benzyl}$), 127.2 (C5, CH$_{im}$), 117.2 (Cq), 113.6 (Cq), 51.9 (OCH_3), 51.4 (N-CH_2). IR : 3137, 2947, 2226, 1717, 1545, 1437, 1345, 1324, 1006, 814, 767, 713 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{15}N_3O_2$: $[M+H]^+$ 318.1243, found 318.1244.

methyl 1-benzyl-2-(3-cyanophenyl)-1*H*-imidazole-4-carboxylate 3e:



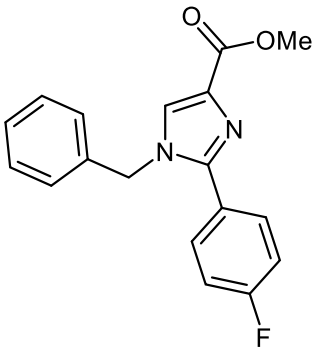
Compound **3e** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3e** in 86% as a pale yellow solid. mp : 160.1 -162.2 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H$_{arom}$, H2'), 7.79 (d, *J* = 7.9 Hz,

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

For Peer Review

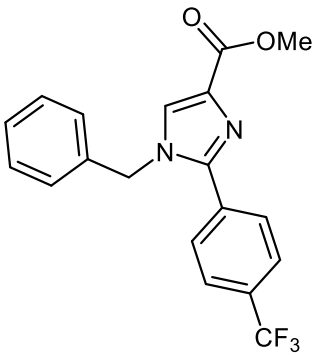
1H$_{arom}$, H6'), 7.70-7.68 (m, 2H, H$_{arom}$ 4'and H5), 7.52 (t, *J* = 7.8 Hz, 1H$_{arom}$, H5'), 7.36-7.34 (m, 3H$_{benzyl}$), 7.06-7.04 (m, 2H$_{benzyl}$), 5.21 (s, 2H), 3.89 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (C=O), 146.7 (Cq), 135.0 (C1', Cq$_{benzyl}$), 133.4 (Cq), 133.2 (CH$_{arom}$, C6'), 132.9 (CH$_{arom}$, C4'), 132.7 (CH$_{arom}$, C2'), 130.8 (Cq), 129.6 (Cq), 129.5 (CH$_{arom}$, C5'), 129.4 (2×CH$_{benzyl}$), 128.8 (CH$_{benzyl}$), 128.0 (C5, CH$_{im}$), 126.8 (2×CH$_{benzyl}$), 117.9 (Cq), 113.1 (Cq), 52.0 (OCH_3), 51.3 (N-CH_2). IR : 3066, 2947, 2229, 1731, 1460, 1436, 1347, 1179, 1010, 898, 720 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{15}N_3O_2$: $[M+H]^+$ 318.1243, found 318.1244.

methyl 1-benzyl-2-(4-fluorophenyl)-1*H*-imidazole-4-carboxylate 3f:



Compound **3f** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3f** in 86% as a yellow solid. mp : 116.3-118.1 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H$_{im}$, H5), 7.53 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.34-7.31 (m, 3H$_{benzyl}$), 7.10-7.02 (m, 4H), 5.16 (s, 2H), 3.87 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 163.5 (d, *J* = 248.6 Hz, Cq, C-F), 148.3 (Cq, C2$_{im}$), 135.5 (C1', Cq$_{benzyl}$), 133.0 (Cq, C4$_{im}$), 131.3 (d, *J* = 8.5 Hz, 2×CH$_{arom}$), 129.3 (2×CH$_{benzyl}$), 128.5 (CH$_{benzyl}$), 127.3 (C5, CH$_{im}$), 126.8 (2×CH$_{benzyl}$), 125.6 (d, *J* = 3.3 Hz, Cq$_{arom}$), 115.8 (d, *J* = 21.9 Hz, 2×CH$_{arom}$) 51.9 (OCH_3), 51.0 (N-CH_2). IR : 3129, 3079, 1694, 1551, 1454, 1332, 1223, 1006, 840, 731 cm^{-1}. HRMS : Anal. Calcd for $C_{18}H_{15}F_1N_2O_2$: $[M+H]^+$ 311.1196, found 311.1204.

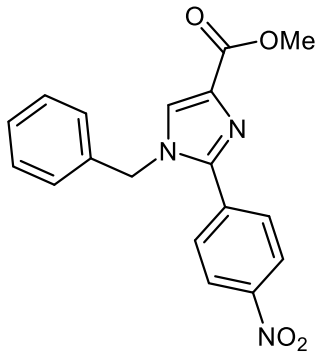
methyl 1-benzyl-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazole-4-carboxylate 3g:



For Peer Review

Compound **3g** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3g** in 88% as a white solid. mp : 123.1-123.8 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.64 (m, $4H_{arom}$), 7.69 (s, $1H_{im}$, H5), 7.36-7.34 (m, $3H_{benzyl}$), 7.08-7.05 (m, $2H_{benzyl}$), 5.22 (s, 2H), 3.89 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C=O), 147.7 (Cq, $C2_{im}$), 135.3 (C1', Cq_{benzyl}), 135.5 (Cq), 132.9 (d, J = 1.2 Hz, Cq), 131.5 (q, J = 32.8 Hz), 129.5 (2× CH), 129.4 (2×CH), 128.7 (CH), 127.9 (CH), 126.8 (2×CH_{benzyl}), 125.68 (q, J = 3.7 Hz, CH), 123.8 (q, J = 270.8 Hz, CF_3), 51.9 (OCH_3), 51.2 (N-CH_2). IR : 3126, 3079, 1695, 1547, 1456, 1325, 1230, 1166, 1109, 1071, 1007, 843, 730 cm^{-1}. HRMS : Anal. Calcd for $C_{19}H_{15}F_3N_2O_2$: $[M+H]^+$ 361.1164, found 361.1176.

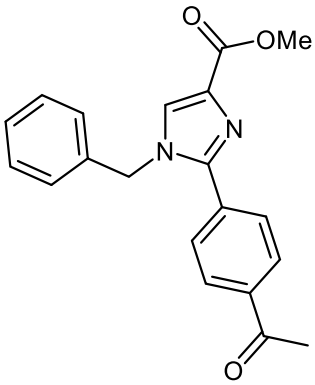
methyl 1-benzyl-2-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate 3h:



Compound **3h** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3h** in 77% as a pale yellow solid. mp :139.8-140.2 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, $2H_{arom}$), 7.77 (d, J = 8.8 Hz, $2H_{arom}$), 7.72 (s, $1H_{im}$, H5), 7.37-7.34 (m, $3H_{benzyl}$), 7.07-7.05 (m, $2H_{benzyl}$), 5.26 (s, 2H), 3.90 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (C=O), 148.2 (Cq), 146.7 (Cq), 135.5 (Cq), 135.0 (Cq), 133.7 (Cq), 129.9 (2× CH_{arom}), 129.4 (2×CH_{benzyl}), 128.8 (CH), 128.4 (CH), 126.9 (2×CH_{benzyl}), 123.8 (2× CH_{arom}), 52.0 (OCH_3), 51.4 (N-CH_2). IR : 3128, 2999, 1719, 1602, 1522, 1339, 1206, 1005, 852, 728 cm^{-1}. HRMS : Anal. Calcd for $C_{18}H_{15}N_4O_4$: $[M+H]^+$ 338.1141, found 338.1140.

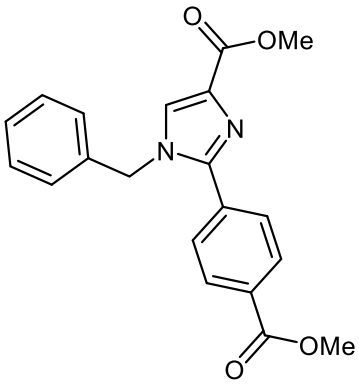
For Peer Review

methyl 2-(4-acetylphenyl)-1-benzyl-1*H*-imidazole-4-carboxylate 3i:



Compound **3i** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3i** in 46% as a pale brown solid. mp : 80.1-80.5 (Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, $2H_{arom}$), 7.68 (d, *J* = 8.3 Hz, $2H_{arom}$), 7.68 (s, $1H_{im}$, H5), 7.34-7.32 (m, $3H_{benzyl}$), 7.07-7.04 (m, $2H_{benzyl}$), 5.23 (s, 2H), 3.88 (s, 3H, OMe), 2.60 (s, 3H, COMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5 (C=OMe), 163.2 (C=O), 148.0 (Cq), 137.5 (Cq), 135.3 (Cq), 133.7 (Cq), 133.4 (Cq), 129.3 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 126.8 ($2\times CH_{benzyl}$), 51.9 (OCH_3), 51.2 ($N\text{-}CH_2$), 26.8 ($COCH_3$). IR : 3137, 2947, 1716, 1680, 1608, 1349, 1260, 1181, 1007, 844, 727 cm^{-1}. HRMS : Anal. Calcd for $C_{20}H_{18}N_2O_3$: $[M+H]^+$ 335.1396, found 335.1392.

methyl 1-benzyl-2-(4-(methoxycarbonyl)phenyl)-1*H*-imidazole-4-carboxylate 3j:

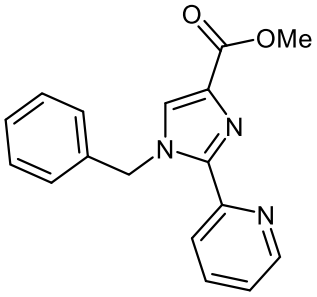


Compound **3j** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3j** in 80% as a pale brown solid. mp : 128.1-129-8 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, $2H_{arom}$), 7.69 (s, $1H_{im}$, H5), 7.66 (d, *J* = 8.3 Hz, $2H_{arom}$), 7.35-7.33 (m, $3H_{benzyl}$), 7.07-7.05 (m, $2H_{benzyl}$), 5.22 (s, 2H), 3.92 (s, 3H, OMe), 3.90 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C=O), 163.3 (C=O), 148.1 (Cq), 135.4 (Cq), 133.7 (Cq), 133.4 (Cq), 131.0 (Cq), 129.9 ($2\times CH_{arom}$), 129.3 ($2\times CH_{benzyl}$), 129.2 (CH), 128.6 (CH), 127.9 (CH), 126.9 ($2\times CH_{benzyl}$), 52.4 (OCH_3), 51.9

For Peer Review

(OCH_3), 51.2 (N-CH_2). IR : 3130, 2949, 1715, 1612, 1437, 1350, 1278, 1202, 1103, 1007, 863, 702 cm^{-1}. HRMS : Anal. Calcd for $C_{20}H_{18}N_2O_4$: $[M+H]^+$ 350.1345, found 335.1354.

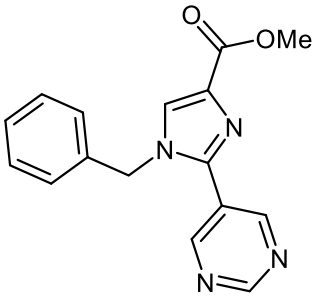
methyl 1-benzyl-2-(pyridin-2-yl)-1*H*-imidazole-4-carboxylate 3k:



Compound **3k** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3k** in 90% as a brown solid. mp : 128.2 -129.5 °C (DCM/Pentane).

^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (br d, *J*=4.73 Hz, $1H_{py}$,H_{15}), 8.30 (d, *J*=8.20 Hz, 1 H_{py}, H_{18}), 7.73-7.79 (m, 1 H_{py}, H_{17}), 7.65 (s, $1H_{im}$, H_5), 7.23-7.33 (m, $3H_{benzyl}$ and $1H_{py}$), 7.20 (br d, *J*=7.57 Hz, $2H_{benzyl}$, H_8 and H_{12}), 5.93 (s, 2H, N-CH_2), 3.90 (d, *J*=1.58 Hz, 3H, O-Me).
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 163.31 (C=O), 149.89 (CH_{py}, C_{15}), 148.24 (s, 1 Cq_{py}, C_{13}), 145.71 (Cq_{im}, C_2), 136.7 (CH_{py}, C_{17}), 136.7 (Cq_{benzyl}, C_7), 132.62 (Cq_{im}, C_4), 129.07 (CH_{im}, C_5), 128.86 ($2CH_{benzyl}$), 128.05 (CH_{benzyl}), 127.74 ($2CH_{benzyl}$), 123.79 (CH_{py}, C_{18}), 123.37 (CH_{py}, C_{16}), 52.34 (N-CH_2), 51.74 (O-Me).
IR : 3126, 2925, 1697, 1587, 1545, 1275, 1221, 1090, 1011, 777, 729, 706 cm^{-1}. HRMS : Anal. Calcd for $C_{17}H_{15}N_3O_2$: $[M+H]^+$ 294.1243, found 294.1246.

methyl 1-benzyl-2-(pyrimidin-5-yl)-1*H*-imidazole-4-carboxylate 3l:

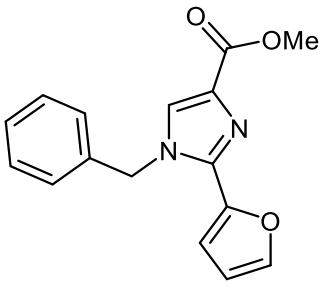


Compound **3l** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3l** in 86% as a yellow solid. mp : 166.9-167.8 °C (DCM/Pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, $1H_{py}$), 8.91 (s, $2H_{py}$), 7.75 (s, $1H_{im}$, H5), 7.35-7.32 (m, $3H_{benzyl}$), 7.05-7.02 (m, $2H_{benzyl}$), 5.24 (s, 2H), 3.89 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (C=O), 158.9 (CH_{py}), 156.4 ($2\times CH_{py}$), 143.0 C2, Cq_{im}), 134.6 (C1', Cq_{benzyl}), 134.1 ($C4_{im,}$ Cq), 129.5 ($2\times CH_{benzyl}$), 128.9 (CH), 128.5 (C5, CH_{im}), 126.6 ($2\times CH_{benzyl}$), 124.3 (Cq_{py}),

For Peer Review

52.0 (OCH_3), 51.4 ($N\text{-}CH_2$). IR : 3140, 2945, 1724, 1553, 1437, 1345, 1209, 1126, 1007, 728, 715 cm^{-1}. HRMS : Anal. Calcd for $C_{16}H_{14}N_4O_2$: $[M+H]^+$ 295.1195, found 295.1188.

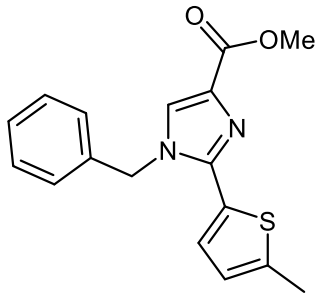
methyl 1-benzyl-2-(furan-2-yl)-1*H*-imidazole-4-carboxylate 3m:



Compound **3m** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3m** in 72% as a brown solid. mp : 121.6-123.4 °C (DCM/Pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, $1H_{im}$, H5), 7.47 (d, J = 8.8 Hz, 1H), 7.32-7.28 (m, $3H_{benzyl}$), 7.15-7.12 (m, $2H_{benzyl}$), 6.98 (d, J = 3.4 Hz, 1H), 6.47 (dd, J = 3.3, 1.8 Hz, 1H), 5.41 (s, 2H), 3.86 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (C=O), 144.5 (Cq_{fur}), 143.2 (CH_{fur}), 140.2 (C2, Cq_{im}), 135.4 (C1', Cq_{benzyl}), 133.0 ($C4_{im,}$ Cq), 129.1 ($2\times CH_{benzyl}$), 128.4 (CH_{benzyl}), 127.3 ($2\times CH_{benzyl}$), 127.2 (C5, CH_{im}), 111.7 (CH_{fur}), 111.5 (CH_{fur}), 51.8 (OCH_3), 51.5 ($N\text{-}CH_2$). IR : 3126, 2945, 1719, 1602, 1521, 1344, 1178, 1008, 767, 720 cm^{-1}. HRMS : Anal. Calcd for $C_{16}H_{14}N_2O_3$: $[M+H]^+$ 283.1083, found 283.1089.

For Peer Review

methyl 1-benzyl-2-(5-methylthiophen-2-yl)-1*H*-imidazole-4-carboxylate 3n:



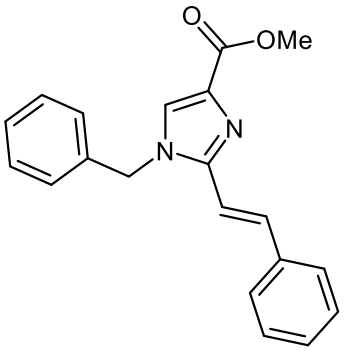
Compound **3n** was prepared according to the *method A*. The crude product was purified by flash chromatography to afford **3n** in 47% as a yellow solid. mp : 127.1 -127.9 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H$_{im}$, H5), 7.36-7.34 (m, 3H$_{benzyl}$), 7.10 (d, *J* = 7.6 Hz, 2H$_{benzyl}$), 7.05 (d, *J* = 3.4 Hz, 1H), 6.69 (d, *J* = 2.9 Hz, 1H), 5.30 (s, 2H), 3.88 (s, 3H, OMe), 2.48 (s, 3H Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 143.8 (Cq), 142.9 (Cq), 135.3 (C1', Cq$_{benzyl}$), 132.9 (C4$_{im,}$ Cq), 129.3 (2×CH$_{benzyl}$), 128.5 (CH$_{benzyl}$), 128.2 (CH$_{thio}$), 127.4 (C5, CH$_{im}$), 126.9 (2×CH$_{benzyl}$), 125.9 (CH$_{thio}$), 51.9 (OCH_3), 51.1 (N-CH_2), 15.3 (Me). IR : 3140, 2950, 1713, 1513, 1435, 1197, 1012, 793, 776, 764, 724, 709 cm^{-1}. HRMS : Anal. Calcd for $C_{17}H_{16}N_2O_2S$: $[M+H]^+$ 313.1011, found 313.1013.

5. Pd-catalyzed intermolecular direct C-H alkenylation of methyl *N*-benzyl-1*H*-imidazole 4-carboxylate.

Methyl 1-benzyl-1*H*-imidazole-4-carboxylate **1a** (0.5 mmol, 1 eq), the appropriate alkenylhalide (0.6 mmol, 1.2 eq), $Pd(OAc)_2$ (25 µmol, 5 mol%), P(*o*-tolyl)$_3$•HBF_4 (50 µmol, 10 mol%), CuI (1 mmol, 2 eq) and anhydrous DBU (1 mmol, 2 eq) were placed in a dry sealed tube containing a magnetic stir bar. The tube was evacuated and filled back with N_2 three rime before adding anhydrous 1,4-dioxane (3.0 mL). The tube was sealed and heated to 140 °C for 18 hours. The reaction was filtered over a Celite® pad (washed with DCM and EtOAc). The solvents were removed under reduced pressure and the crude product was then purified by column chromatography (DCM to DCM/EtOAc 9-1).

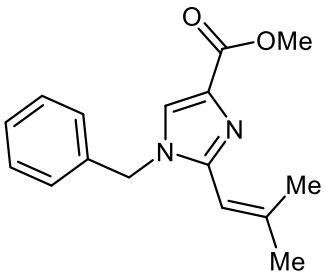
For Peer Review

methyl (E)-1-benzyl-2-styryl-1*H*-imidazole-4-carboxylate 3o:



Compound **3o** was prepared according to the general procedure for intermolecular direct C-H akenylation. The crude product was purified by flash chromatography to afford **3o** in 67% as yellow solid. mp : 131.4-133.5 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.9 Hz, $1H_{vinyl}$), 7.51 (s, $1H_{im}$, H5), 7.37 (d, *J* = 6.9 Hz, 2H), 7.29-7.18 (m, $5H_{benzyl}$), 7.08-7.05 (m, $2H_{benzyl}$), 6.75 (d, *J* = 15.9 Hz, $1H_{vinyl}$), 5.14 (s, 2H), 3.82 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (C=O), 146.8 (C2, Cq_{im}), 136.0 (Cq), 135.5 (CH_{vinyl}), 135.1 (Cq), 133.0 ($C4_{im,}$ Cq), 129.3 ($2\times CH_{benzyl}$), 128.8 ($3\times CH_{benzyl}$), 128.6 (CH), 127.0 ($2\times CH_{benzyl}$), 127.0 ($2\times CH_{benzyl}$), 126.9 (CH), 112.1 (CH_{vinyl}), 51.9 (OCH_3), 50.1 (N-CH_2). IR : 3131, 2924, 1714, 1543, 1436, 1327, 1234, 1012, 974, 754, 687 cm^{-1}. HRMS : Anal. Calcd for $C_{20}H_{18}N_2O_2$: $[M+H]^+$ 319.1447, found 319.1455.

methyl 1-benzyl-2-(2-methylprop-1-en-1-yl)-1*H*-imidazole-4-carboxylate 3p:



Compound **3p** was prepared according to the general procedure for intermolecular direct C-H akenylation. The crude product was purified by flash chromatography to afford **3p** in 81% as pale yellow solid. m.p. : 104.5-104.8 °C (DCM/Pentane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, $1H_{im}$, H5), 7.34-7.30 (m, $3H_{benzyl}$), 7.09-7.06 (m, $2H_{benzyl}$), 5.91 (s, $1H_{vinyl}$), 5.05 (s, 2H), 3.84 (s, 3H, OMe), 2.07 (s, 3H, Me_{vinyl}), 1.88 (s, 3H, Me_{vinyl}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 146.8 (C2, Cq_{im}), 146.5(Cq_{vinyl}), 135.4 (C1', Cq_{benzyl}), 132.1 ($C4_{im,}$ Cq), 129.1 ($2\times CH_{benzyl}$), 128.4 (CH_{benzyl}), 127.1 ($2\times CH_{benzyl}$), 125.5 (C5, CH_{im}), 110.6 (CH_{vinyl}), 51.7 (OCH_3), 50.2 (N-CH_2), 26.7 (Me_{vinyl}), 20.7 (Me_{vinyl}). IR : 3134, 2947, 1716, 1548, 1453, 1436,

For Peer Review

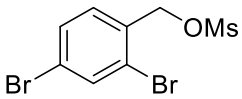
1325, 1010, 876, 765, 720, 699cm^{-1}. HRMS : Anal. Calcd for $C_{16}H_{18}N_2O_2$: $[M+H]^+$ 271.1447, found 271.1459.

For Peer Review

6. General procedure for the synthesis of 2-(2-bromophenyl)alkyl methanesulfonates

2-(2-bromophenyl)alkyl mesylates were prepared form the corresponding alcohols according to the procedure.[2] Methanesulfonyl chloride (5.6 mmol, 1.5 eq) was added dropwise to a solution of 2-(2-bromophenyl)alkyl alcohol (3.7 mmol) and triethylamine (11.1 mmol) in toluene (30 mL) at 0°C. The reaction mixture was further stirred at room temperature for 18 h and then poured into water and DCM. The aqueous phase was extracted with DCM (2×15 mL). The DCM layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the title product in quantitative yield. The crude sulfonates were used without purification.

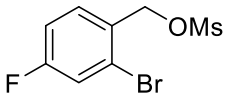
2,4-dibromobenzyl methanesulfonate



White solid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.37 (d, *J* = 8.3, 1H), 5.27 (s, 2H), 3.05 (s, 3H).

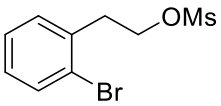
2-bromo-4-fluorobenzyl methanesulfonate



White solid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.36 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.08 (td, *J* = 8.3, 2.5 Hz, 1H), 5.28 (s, 2H), 3.02 (s, 3H).

2-(2-bromophenyl)ethyl methanesulfonate.[2]



Pale yellow oil

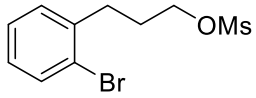
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.26-7.24 (m, 2H), 7.13-7.07 (m, 1H), 4.39 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 2.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.64 (Cq), 133.09 (CH), 131.63 (CH), 129.02 (CH), 127.79 (CH), 124.49 (Cq), 68.58 (CH_2), 37.30 (CH_3, OMs), 35.96 (CH_2). HRMS (TOF MS EI+): calcd. For $C_9H_{11}BrO_3S$ 277.9599;

[2] S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim, S. S. Rahman, *Tetrahedron*, **2005**, 61, 2689-2696.

For Peer Review

found 277.9612. This is a known compound and the spectral data are identical to those reported in literature.[2]

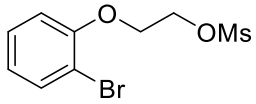
2-(2-bromophenyl)propyl methanesulfonate[3]



Yellow oil

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.27-7.24 (m, 2 H), 7.13-7.07 (m, 1H), 4.27 (t, *J* = 6.3 Hz, 2H), 3.04 (s, 3H), 2.88 (t, J = 7.7 Hz), 2.13-2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.65 (Cq), 132.96 (CH), 130.56 (CH), 128.13 (CH), 127.65 (CH), 124.31 (Cq), 69.15 (CH_2), 37.36 (CH_3, OMs), 32.03 (CH_2), 29.07 (CH_2). HRMS (TOF MS EI+): calcd. For $C_{10}H_{13}BrO_3S$ 291.97602; found 291.97688. This is a known compound and the spectral data are identical to those reported in literature.[3]

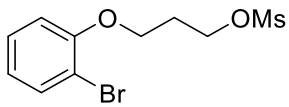
1-Bromo-2-(2-methanesulfonyloxyethyloxy)benzene



Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.91-6.85 (m, 2H), 4.59 (t, *J* = 4.3 Hz, 2H), 4.26 (t, *J* = 4.3 Hz, 2H), 3.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 (Cq), 133.4 (CH), 128.7 (CH), 122.8 (CH), 113.6 (CH), 111.9 (Cq), 68.3 (CH_2),66.8 (CH_2), 37.7 (CH_3, OMs).

3-(2-bromophenoxy)propyl methanesulfonate



Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.29-7.24 (m, 1 H), 6.92-6.83 (m, 2H), 4.53 (t, *J* = 6.0 Hz, 2 H), 4.16 (t, *J* = 5.7 Hz, 2 H), 3.00 (s, 3H), 2.28 (q, *J* = 5.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7 (Cq), 133.4 (CH_{arom}), 128.7 (CH_{arom}), 122.3 (CH_{arom}), 113.3 (CH_{arom}), 112.1 (Cq), 66.9 (CH_2), 64.2 (CH_2), 37.1 (CH_3, OMs), 28.9 (CH_2). HRMS (TOF MS ESI+): calcd. For $C_{10}H_{17}BrNO_4S$ $[M + NH_4]^+$ 326.0062; found 326.0067.

[3] L. Ripa, A. Hallberg, *J. Org. Chem*. **1998**, 63, 84-91.

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

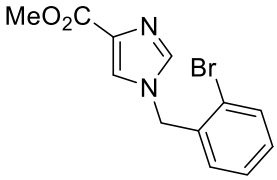
For Peer Review

7. General procedure for alkylation

To a solution of sodium hydride (95% dry, 6 mmol, 1.5 eq) in anhydrous DMF (25 mL), methyl 4-imidazolecarboxylate (4 mmol, 1eq) was introduced in small portions under argon atmosphere. The mixture was stirred at 80°C for 1 h. A solution of the alkylating agent (6 mmol, 1.5 eq) in 5 mL of DMF was introduced dropwise to the reaction mixture which was heated at 80°C for 12 h. The solution was cooled to room temperature and the salts were removed by filtration on a Celite® pad. The solution was evaporated under reduced pressure to afford two regioisomers which were separated by column chromatography using petroleum ether/ethyl acetate (1/4) as eluent.

All regioisomers methyl 1[(2-bromophenyl)alkyl)-1*H*-imidazole-5-carboxylate were previously prepared in our laboratory and reported.[4] In this paper, we do not used these regioisomers, also we have not reported the analysis of these compounds.

methyl 1[(2-bromophenyl)methyl]-1*H*-imidazole-4-carboxylate 4a :



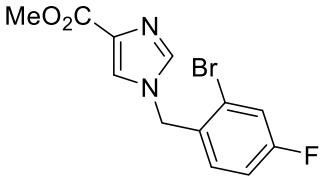
Compound **4a** was prepared from 1-bromo-2-(bromomethyl)benzene (commercial source) following the general procedure for alkylation.

White solid (51%). mp : 121-122 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.58 (m, 3H), 7.35-7.29 (m, 1H), 7.23 (td, *J* = 1.3 and 7.5 Hz, 1H), 7.05 (dd, *J* = 1.1 and 7.4 Hz, 1H, CH_{arom}, C6'), 5.24 (s, 2H, N-CH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 138.4 (C2, CH_{im}), 134.5 (Cq), 134.2 (Cq), 133.5 (C3', CH_{arom}), 130.6 (CH_{arom}), 129.7 (C6', CH_{arom}), 128.4 (CH_{arom}), 125.5 (C5, CH_{im}), 123.6 (C2', Cq-Br), 51.8 (OCH_3), 51.4 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{12}BrN_2O_2$ $[M + H]^+$ 295.0082; found 295.0088.

[4] J. Thireau, C. Schneider, C. Baudequin, S. Gaurrand, P. Angibaud, L. Meerpoel, V. Levacher, O. Querolle, C. Hoarau, *Eur. J. Org. Chem.*, **2017**, 2491-2494.

For Peer Review

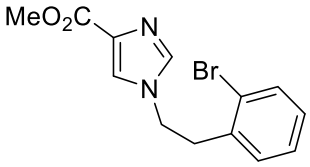
methyl 1-(2-bromo-4-fluorobenzyl)-1*H*-imidazole-4-carboxylate 4b :



This compound was prepared from the corresponding mesylate following the general procedure for alkylation.

White solid (32%). m.p = 112.8-113.5 °C (CH_2Cl_2/PE); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, $1H_{im}$, H5), 7.57 (s, $1H_{im}$, H2), 7.37 (dd, *J* = 1.6 and 7.5 Hz, $1H_{benzyl}$), 7.07-7.03 (m, $2H_{benzyl}$), 5.20 (s, 2H, N-CH_2), 3.86 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C=O), 162.5 (d, *J* = 253.6 Hz, Cq, C-F), 138.3 (C2, CH_{im}), 134.3 ($C4_{im,}$ Cq), 130.9 (d, *J* = 8.8 Hz, CH_{benzyl}), 130.5 (d, *J* = 3.6 Hz, Cq_{benzyl}), 125.2 (C5, CH_{im}), 123.9 (d, *J* = 9.6 Hz, Cq_{benzyl}), 121.0 (d, *J* = 24.7 Hz, CH_{benzyl}), 115.6 (d, *J* = 21.3 Hz), 51.8 (OCH_3), 50.7 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{11}Br^{(81)}FN_2O_2$ $[M + H]^+$ 314.9967; found 314.9969.

methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-4-carboxylate 4c :

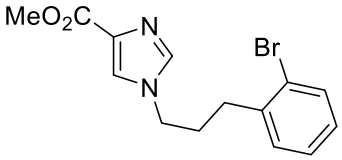


This compound was prepared from the corresponding mesylate following the general procedure for alkylation.

Pale yellow oil (43 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8 and 0.7 Hz, 1H, CH_{arom}, C3'), 7.55 (s, 1H, C5, CH_{im}), 7.31 (s, 1H, C2, CH_{im}), 7.22-7.16 (m, 1H, CH_{arom}), 7.13 (td, *J* = 7.6, 1.9 Hz, 1H, CH_{arom}), 6.95 (dd, *J* = 7.3 and 1.7 Hz, 1H, CH_{arom}, C6'), 4.24 (t, *J* = 7.1 Hz, 2H, N-CH_2), 3.88 (s, 3H, OCH_3), 3.20 (t, *J* = 7.1 Hz, 2H, CH_2-Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C=O), 137.9 (C2, CH_{im}), 135.9 (C1'q, C_{arom}), 133.7 (Cq, C4, C_{im}), 133.2 (C3', CH_{arom}), 130.7 (C6', CH_{arom}), 129.1 (C5', CH_{arom}), 127.9 (C4', CH_{arom}), 125.1 (C5, CH_{im}), 124.1 (C2', Cq-Br), 51.7 (OCH_3), 46.9 (N-CH_2), 38.1 (CH_2-Ph). This is a known compound and the spectral data are identical to those reported in literature.[2]

For Peer Review

methyl 1[(2-bromophenyl)propyl]-1*H*-imidazole-4-carboxylate 4d :

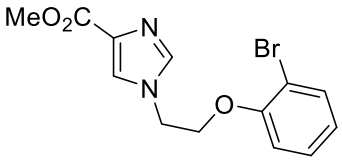


This compound was prepared from the corresponding mesylate following the general procedure for alkylation.

Yellow oil (13 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H, C5, CH_{im}), 7.55 (d, *J* = 7.8 Hz, 1H, CH_{arom}, C3'), 7.51 (s, 1H, C2, CH_{im}), 7.27-7.22 (m, 1H), 7.16-7.06 (m, 2H), 4.02 (t, *J* = 7.1 Hz, 2H, , N-CH_2), 3.89 (s, 3H, OCH_3), 2.75 (t, *J* = 7.7 Hz, 2H, CH_2-Ph), 2.16 (p, *J* = 7.3 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 139.3 (C1'q, C_{arom}), 137.9 (C2, CH_{im}), 133.9 (Cq, C4, C_{im}), 133.1 (CH_{arom}), 130.3 (CH_{arom}), 128.3 (CH_{arom}), 127.8 (CH_{arom}), 125.1 (C5, CH_{im}), 124.3 (C2', Cq-Br), 51.7 (OCH_3), 46.9 (N-CH_2), 33.0 (CH_2-Ph), 30.8 (CH_2). HRMS (TOF MS ESI+): calcd. For $C_{14}H_{16}Br^{(81)}N_2O_2$ $[M + H]^+$ 325.0375; found 325.0356.

methyl 1-(2-(2-bromophenoxy)ethyl)-1*H*-imidazole-4-carboxylate 4e :

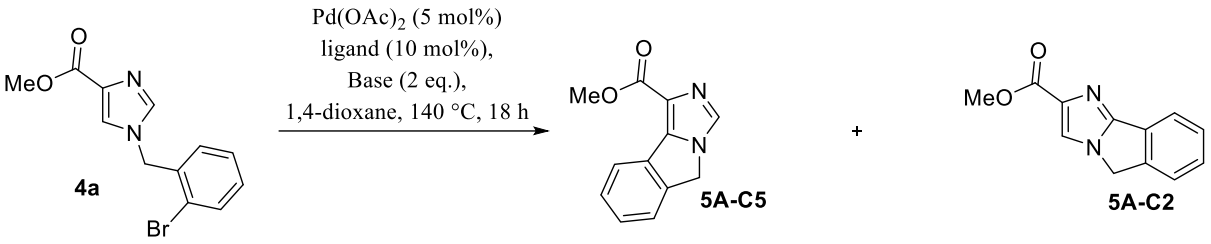


This compound was prepared from the corresponding mesylate following the general procedure for alkylation.

White solid (41 %). mp : 126.8-127.8 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.70 (s, 1H, C5, CH_{im}), 7.48 (dd, *J* = 7.9 and 1.3 Hz, 1H), 7.18 (td, *J* = 7.9 and 1.6 Hz, 1H), 6.82 (td, *J* = 7.7, 1.3 Hz, 1H), 6.75 (dd, *J* = 8.2, 1.3 Hz, 1H), 4.40 (t, *J* = 4.7 Hz, 2H, N-CH_2), 4.20 (t, *J* = 4.7 Hz, 2H, O-CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (C=O), 154.2, 138.8 (C2, CH_{im}), 133.7, 133.6, 128.6, 126.1 (C5, CH_{im}), 122.9, 113.0, 112.1, 67.9 (OCH_2), 51.6 (OCH_3), 46.9 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{13}H_{14}Br^{(81)}N_2O_3$ $[M + H]^+$ 327.0167; found 327.0167.

For Peer Review

8. Optimization of the Pd-catalyzed intramolecular direct C-H arylation of methyl mono-*N*-benzylimidazole-4-carboxylate 5A



Entry	Ligand	Base	Yield[b] **5A-C5** (%)	Yield[b] **5A-C2** (%)
1	PCy_3•HBF_4	Cs_2CO_3	35	3
2	PCy_3•HBF_4	KOAc	nd	nd
3	PCy_3•HBF_4	K_2CO_3	81	9
4	P*t*Bu_2Me•HBF_4	K_2CO_3	79	7
5	P*t*Bu_3•HBF_4	K_2CO_3	23	27
6	PPh_3	K_2CO_3	70	3
7	P(4-FC_6H_4)$_3$	K_2CO_3	81	17
8	dppb	K_2CO_3	42	nd

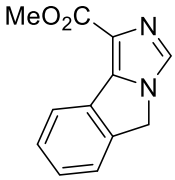
[a] Conditions: 4a (1 eq), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (2 eq), 1,4-dioxane (0.16 M), 140 °C, 18h.
[b] Yield of isolated compound.

9. General procedure for the Pd-catalyzed intramolecular direct C-H arylation of 2-bromo *N*-substituted-imidazoles.

Method C: Bromo *N*-substituted-imidazole **4a-e** (0.27 mmol, 1 equiv.) was placed in a dry sealed tube containing a magnetic stir bar with an appropriate $Pd(OAc)_2$ (3 mg, 13 µmol, 5 mol %), PCy_3•HBF_4 (10 mg, 27 µmol, 10 mol%), K_2CO_3 (75 mg, 0.54 mmol, 2.0 eq). The tube was evacued and filled back with N_2 three time before adding anhydrous 1,4-dioxane (final concentration of compound **5a-g** in dioxane was 0.12M). The tube was sealed and heated to 140 °C for 18 hours. The reaction mixture was filtered over a Celite® pad (washed with DCM and then EtOAc) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

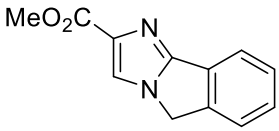
For Peer Review

Compound methyl 5*H*-imidazo[5,1-*a*]isoindole-1-carboxylate 5A-C5:



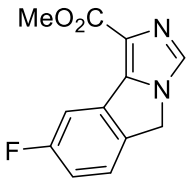
Compound **5A-C5** was prepared according to the *method C* using **4a** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **5A-C5** in 81% as a white solid. mp : 150.9-151.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.5 Hz, $1H_{arom}$), 7.69 (s, $1H_{im}$, H2), 7.49-7.37 (m, $3H_{arom}$), 5.04 (s, 2H), 3.97 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C=O), 144.3 (Cq), 141.5 (Cq), 132.5 (C2, CH_{im}), 129.4 (Cq), 128.9 (CH_{arom}), 128.5 (CH_{arom}), 124.1 (CH_{arom}), 123.4 (CH_{arom}), 123.2 (Cq), 51.7 (OCH_3), 49.1 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{11}N_2O_2$ $[M + H]^+$ 215.0821; found 215.0817.

Compound methyl 5*H*-imidazo[2,1-*a*]isoindole-2-carboxylate 5A-C2:



Compound **5A-C2** was prepared according to the *method C* using **4a** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **5A-C2** in 9% as a pale yellow solid. mp : 145.0-145.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.4 Hz, $1H_{arom}$), 7.91 (s, $1H_{im}$, H5), 7.49-7.38 (m, $3H_{arom}$), 4.97 (s, 2H), 3.94 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C=O), 154.5 (Cq), 141.8 (Cq), 137.7 (Cq), 129.1 (Cq), 129.0 (CH_{arom}), 128.7 (CH_{arom}), 123.6 (CH_{arom}), 122.3 (CH_{arom}), 121.2 (CH), 51.9 (OCH_3), 49.1 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{11}N_2O_2$ $[M + H]^+$ 215.0821; found 215.0823.

methyl 8-fluoro-5*H*-imidazo[5,1-*a*]isoindole-1-carboxylate 5B-C5 :

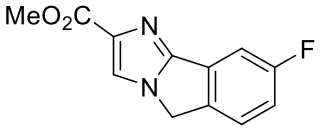


Compound **5B-C5** was prepared according to the *method C* using **4b** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **5B-C5** in 90% as a pale yellow solid. mp : 197.5 °C (degradation). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.7, 2.3 Hz, $1H_{arom}$), 7.74 (s, $1H_{im}$, H2), 7.41 (dd, *J* = 8.4, 4.7 Hz, 1H), 7.10 (td, *J* = 8.7, 2.6 Hz, 1H), 5.05 (s, 2H, N-CH_2), 4.00 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 163.3 (d, *J* =

For Peer Review

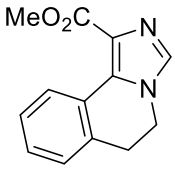
244.7 Hz, Cq, C-F), 143.30 (d, *J* = 4.0 Hz), 136.81 (d, *J* = 2.7 Hz, Cq_{arom}), 132.8 (C2, CH_{im}), 131.28 (d, *J* = 11.1 Hz), 124.69 (d, *J* = 9.1 Hz), 123.8 (Cq), 115.68 (d, *J* = 23.7 Hz), 111.48 (d, *J* = 25.9 Hz), 51.9 (OCH_3), 48.8 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{10}FN_2O_2$ [M + H]$^+$ 233.0726; found 233.0731.

methyl 8-fluoro-5*H*-imidazo[2,1-*a*]isoindole-2-carboxylate 5B-C2 :



Compound **5B-C2** was prepared according to the *method C* using **4b** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **5B-C2** in 8% as a pale yellow solid. mp : 177.0 °C (degradation). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, $1H_{im}$, H5), 7.61 (dd, *J* = 8.1, 2.0 Hz, $1H_{arom}$), 7.44 (dd, *J* = 8.3, 4.4 Hz, $1H_{arom}$), 7.11 (td, *J* = 8.8, 2.3 Hz, $1H_{arom}$), 4.95 (s, 2H, N-CH_2), 3.94 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 163.3 (d, *J* = 245.6 Hz, Cq, C-F), 153.4 (Cq), 137.9 (Cq), 137.1 (d, *J* = 2.7 Hz, Cq), 131.1 (d, *J* = 10.4 Hz, Cq), 125.0 (d, *J* = 9.1 Hz, CH), 122.5 (C5, CH_{im}), 115.9 (d, *J* = 23.7 Hz, CH_{arom}), 108.5 (d, *J* = 25.3 Hz, CH_{arom}), 52.0 (OCH_3), 48.9 (N-CH_2). HRMS (TOF MS ESI+): calcd. For $C_{12}H_{10}FN_2O_2$ [M + H]$^+$ 233.0726; found 233.0724.

methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate 6-C5 :

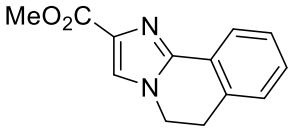


Compound **6-C5** was prepared according to the *method C* using **4c** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **6-C5** in 81% as a white solid (81 %). mp = 187.1-188.2 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 7.6 Hz, $1H_{arom}$), 7.53 (s, 1H, C2, CH_{im}) 7.42-7.37 (m, $1H_{arom}$) 7.34-7.26 (m, $2H_{arom}$), 4.16 (t, *J* = 6.5 Hz, 2H, N-CH_2), 3.95 (s, 3H, OMe), 3.09 (t, *J* = 6.6 Hz, 2H, CH_2-Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (C=O), 135.6 (C2, CH_{im}), 133.9 (Cq), 133.1 (Cq), 129.2 (CH_{arom}), 128.5 (CH_{arom}), 128.3 (Cq), 127.9 (CH_{arom}), 127.7 (CH_{arom}) , 126.0 (Cq), 52.0 (OCH_3), 42.6 (N-CH_2), 29.7 (CH_2-Ph). HRMS : Anal. Calcd for $C_{13}H_{13}N_2O_2$: [M+H]$^+$ 229.0977, found 229.0981. This is a known compound.[2]

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

For Peer Review

methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-2-carboxylate 6-C2 :

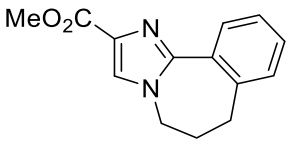


Compound **6-C2** was prepared according to the *method C* using **4c** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **6-C2** in 9% yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.16 (m, $1H_{arom}$), 7.65 (s, 1H, C5, CH_{im}), 7.38-7.29 (m, $2H_{arom}$), 7.26-7.23 (m, $1H_{arom}$), 4.23 (t, *J* = 6.9 Hz, 2H, N-CH_2), 3.93 (s, 3H, OMe), 3.19 (t, *J* = 6.9 Hz, 2H, CH_2-Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C=O), 145.1 (C2, Cq_{im}), 133.3 (Cq), 132.8 (Cq), 129.4 (CH_{arom}), 127.9 (CH_{arom}), 127.8 (CH_{arom}), 126.3 (Cq), 125.5 (CH), 124.7 (CH), 51.9 (OCH_3), 43.9 (N-CH_2), 28.4 (CH_2-Ph). This is a known compound.[2]

methyl 6,7-dihydro-5*H*-benzo[*c*]imidazo[1,5-*a*]azepine-1-carboxylate 7-C5 :

Compound **7-C5** was prepared according to the *method C* using **4d** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **7-C5** in 61%. mp : 185.7-186.2 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, $1H_{arom}$), 7.56 (s, 1H, C2, CH_{im}), 7.37-7.34 (m, $2H_{arom}$), 7.27-7.24 (m, $1H_{arom}$), 3.89-3.85 (m, 2H), 3.85 (s, 3H, OMe), 2.63 (t, *J* = 7.1 Hz, 2H), 2.25 (p, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (C=O), 138.4 (Cq), 138.2 (Cq), 136.3 (C2, CH_{im}), 131.5 (CH_{arom}), 129.7 (CH_{arom}), 128.9 (CH), 128.6 (Cq), 126.6 (CH_{arom}), 51.7 (OCH_3), 43.2 (N-CH_2), 31.3 (CH_2), 30.2 (CH_2). HRMS : Anal. Calcd for $C_{14}H_{15}N_2O_2$: $[M+H]^+$ 243.1134, found 243.1137.

methyl 6,7-dihydro-5*H*-benzo[*c*]imidazo[1,2-*a*]azepine-2-carboxylate 7-C2 :

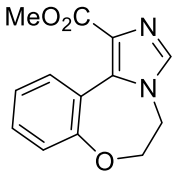


Compound **7-C2** was prepared according to the *method C* using **4d** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **7-C2** in 39%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, $1H_{arom}$), 7.72 (s, 1H, C5, CH_{im}), 7.36-7.33 (m, $2H_{arom}$), 7.25-7.23 (m, $1H_{arom}$), 3.94 (t, *J* = 6.9 Hz, 2H), 3.90 (s, 3H, OMe), 2.71 (t, *J* = 7.1 Hz, 2H), 2.33 (p, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C=O), 149.4 (C2, Cq_{im}), 138.0 (Cq), 132.5

For Peer Review

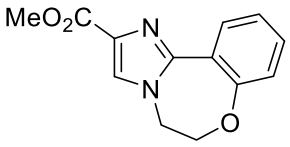
(Cq), 130.2 (Cq), 129.8 (CH_{arom}), 129.2 (CH_{arom}), 129.2 (CH_{arom}), 127.2 (CH_{arom}), 126.8 (C5, CH_{im}), 51.8 (OCH_3), 45.0 (N-CH_2), 31.0 (CH_2), 30.4 (CH_2).

methyl 5,6-dihydrobenzo[*f*]imidazo[1,5-*d*][1,4]oxazepine-1-carboxylate 8-C5 :



Compound **8-C5** was prepared according to the *method C* using **4e** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **8-C5** in 62% as a white solid. mp : 190.2-191.4 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.7, 1.5 Hz, $1H_{arom}$), 7.64 (s, $1H_{im}$, H2), 7.42 (td, *J* = 7.8, 1.6 Hz, $1H_{arom}$), 7.29 (t, *J* = 7.5 Hz, $1H_{arom}$), 7.18 (d, *J* = 8.0 Hz, $1H_{arom}$), 4.51 (t, *J* = 5.9 Hz, 2H, O-CH_2), 4.11 (t, *J* = 5.9 Hz, 1H, N-CH_2), 3.88 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C=O), 153.1 (Cq), 136.0 (Cq), 135.8 (CH), 132.3 (CH), 131.2 (CH), 129.4 (Cq), 124.6 (CH), 122.7 (Cq), 122.4 (CH), 74.0 (O-CH_2), 51.7 (OCH_3), 43.5 (N-CH_2). HRMS : Anal. Calcd for $C_{13}H_{13}N_2O_3$: $[M+H]^+$ 245.0926, found 245.0925.

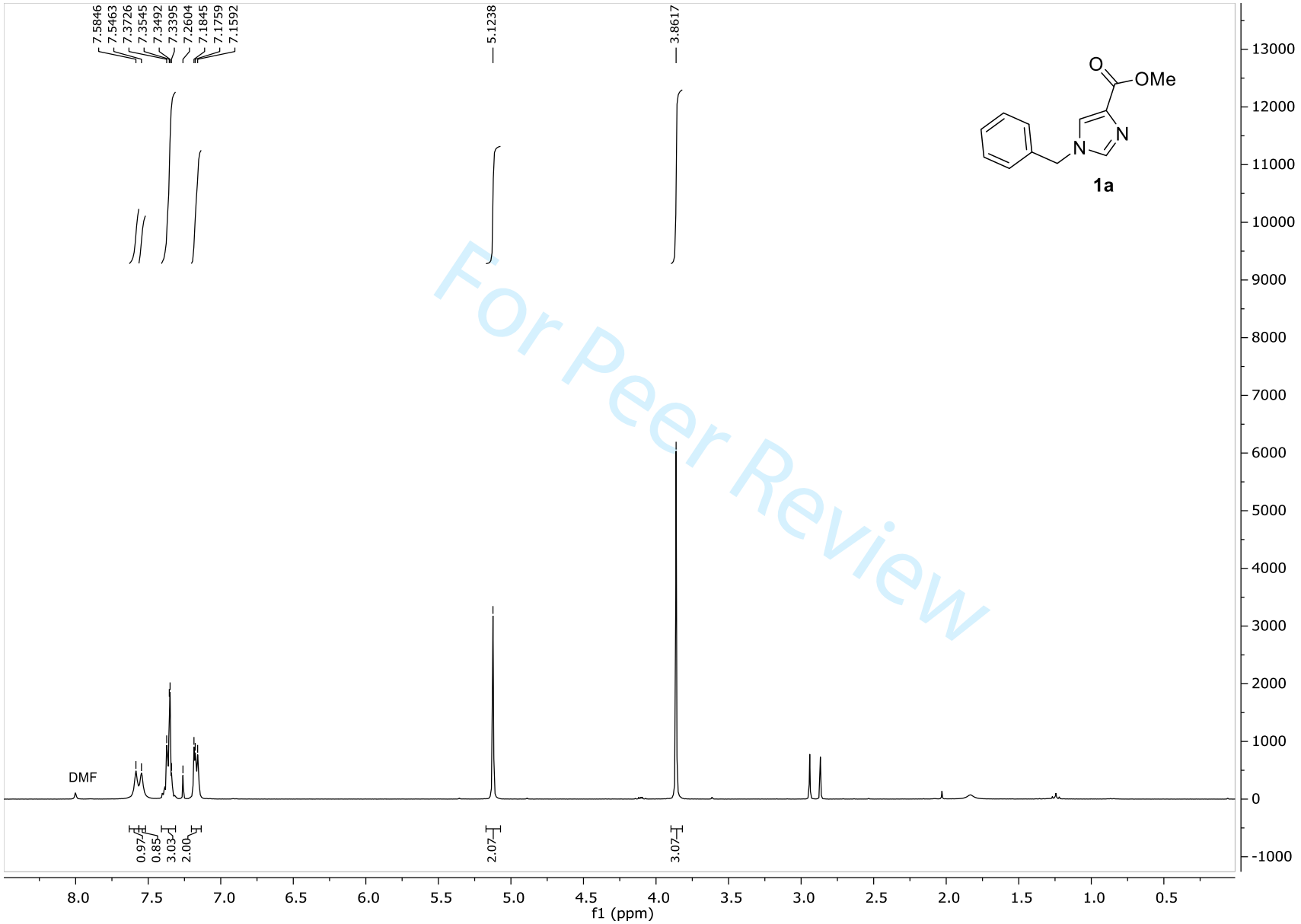
methyl 5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepine-2-carboxylate 8-C2 :



Compound **8-C2** was prepared according to the *method C* using **4e** (0.27 mmol). The crude product was purified by flash chromatography (EtOAc) to afford **8-C2** in 37% as a pale yellow solid. mp : 167.9-169.3 °C (CH_2Cl_2/PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.1 Hz, $1H_{arom}$), 7.66 (s, $1H_{im}$, H5), 7.28 (d, *J* = 8.0 Hz, $1H_{arom}$), 7.11 (t, *J* = 7.6 Hz, $1H_{arom}$), 7.02 (d, *J* = 8.1 Hz, $1H_{arom}$), 4.48-4.41 (m, 4H), 3.92 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (C=O), 155.7 (Cq_{arom}), 145.9 (C2, Cq_{im}), 133.2 (C4, Cq_{im}), 130.9 (CH_{arom}), 130.7 (CH_{arom}), 127.5 (C5, CH_{im}), 122.9 (CH_{arom}), 120.5 (CH_{arom}), 117.8 (Cq_{arom}), 68.3 (O-CH_2), 51.9 (OCH_3), 50.4 (N-CH_2). HRMS : Anal. Calcd for $C_{13}H_{13}N_2O_3$: $[M+H]^+$ 245.0926, found 245.0923.

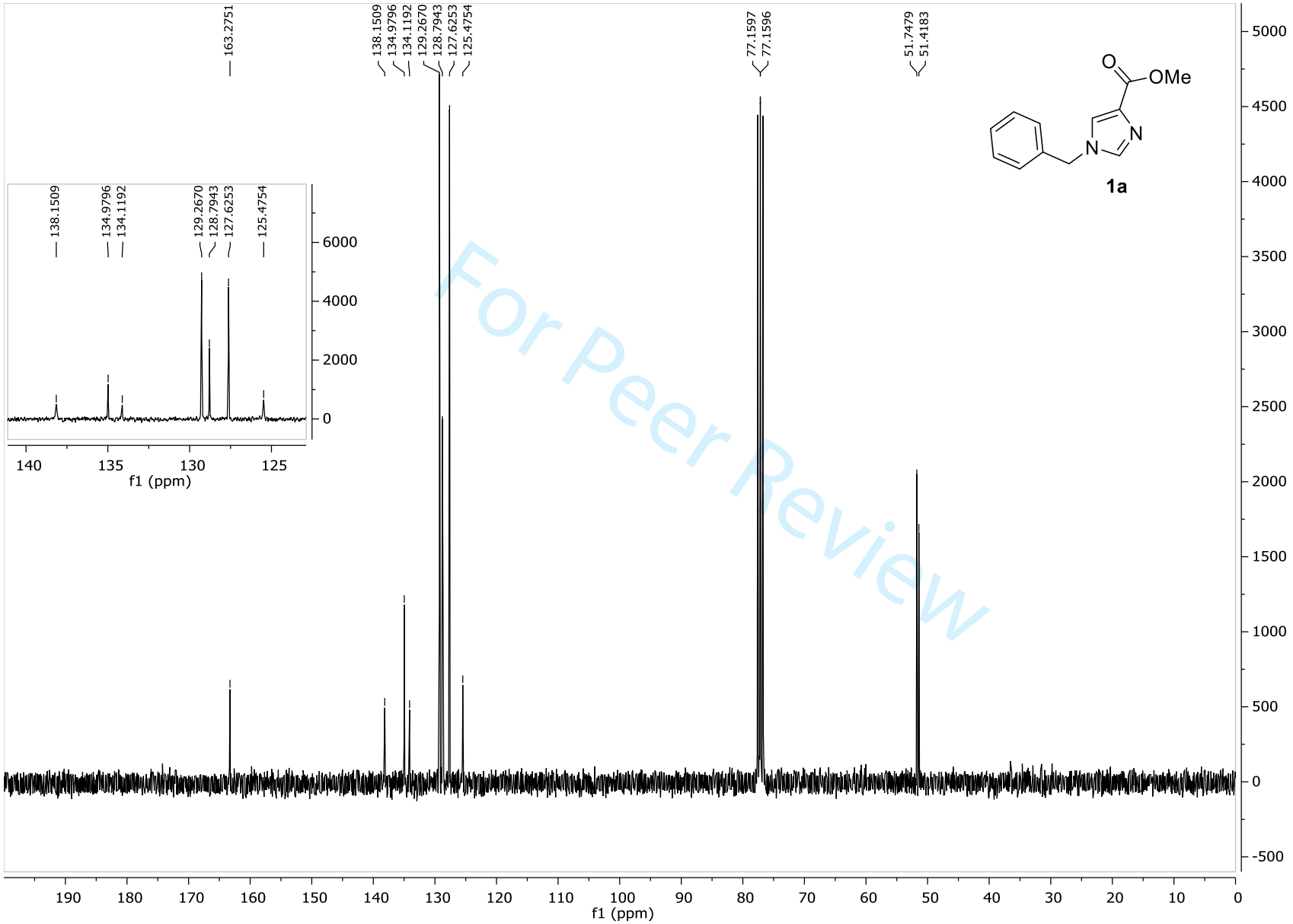
10. Copies of NMR Spectra

For Peer Review

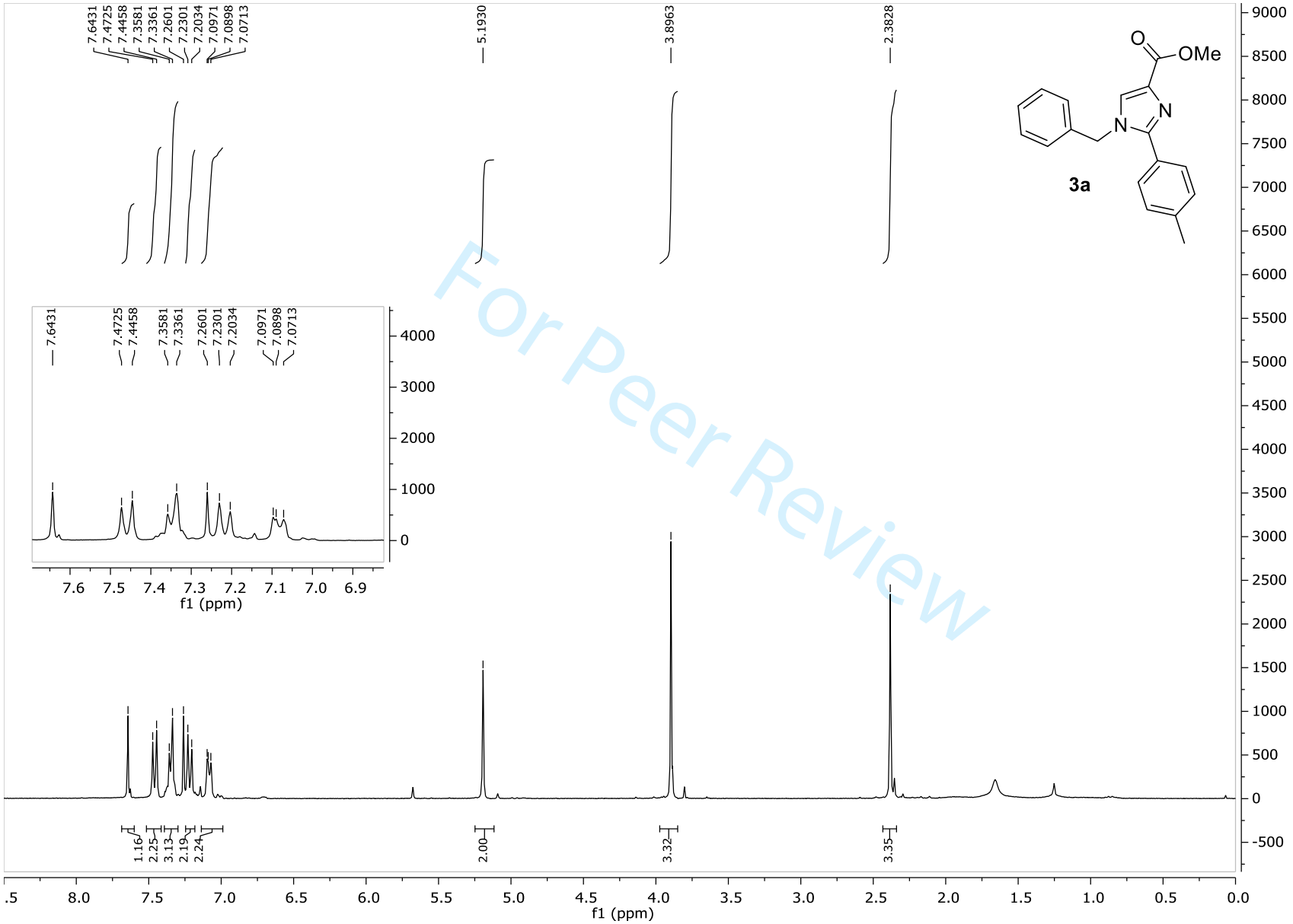


For Peer Review

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

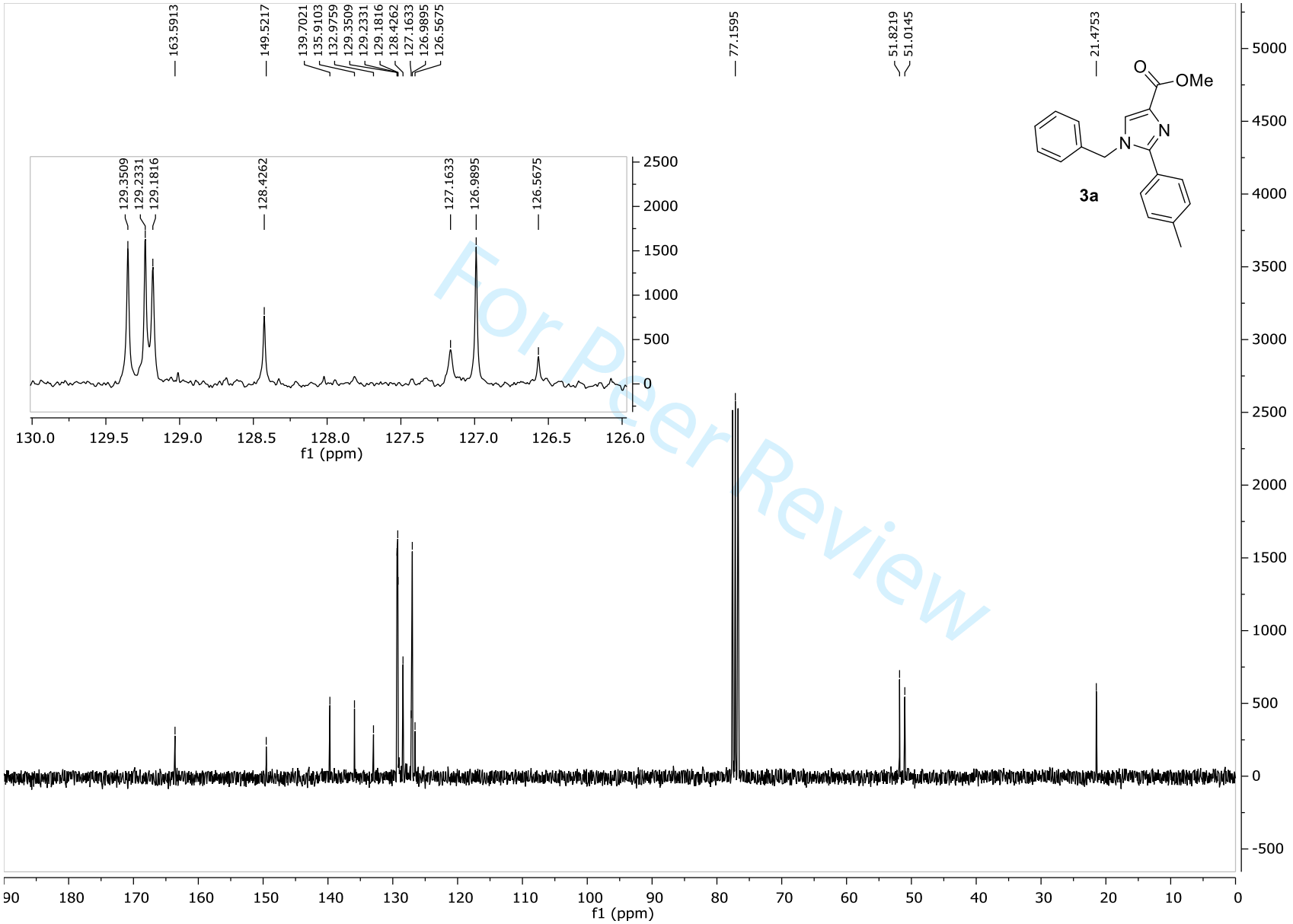


For Peer Review

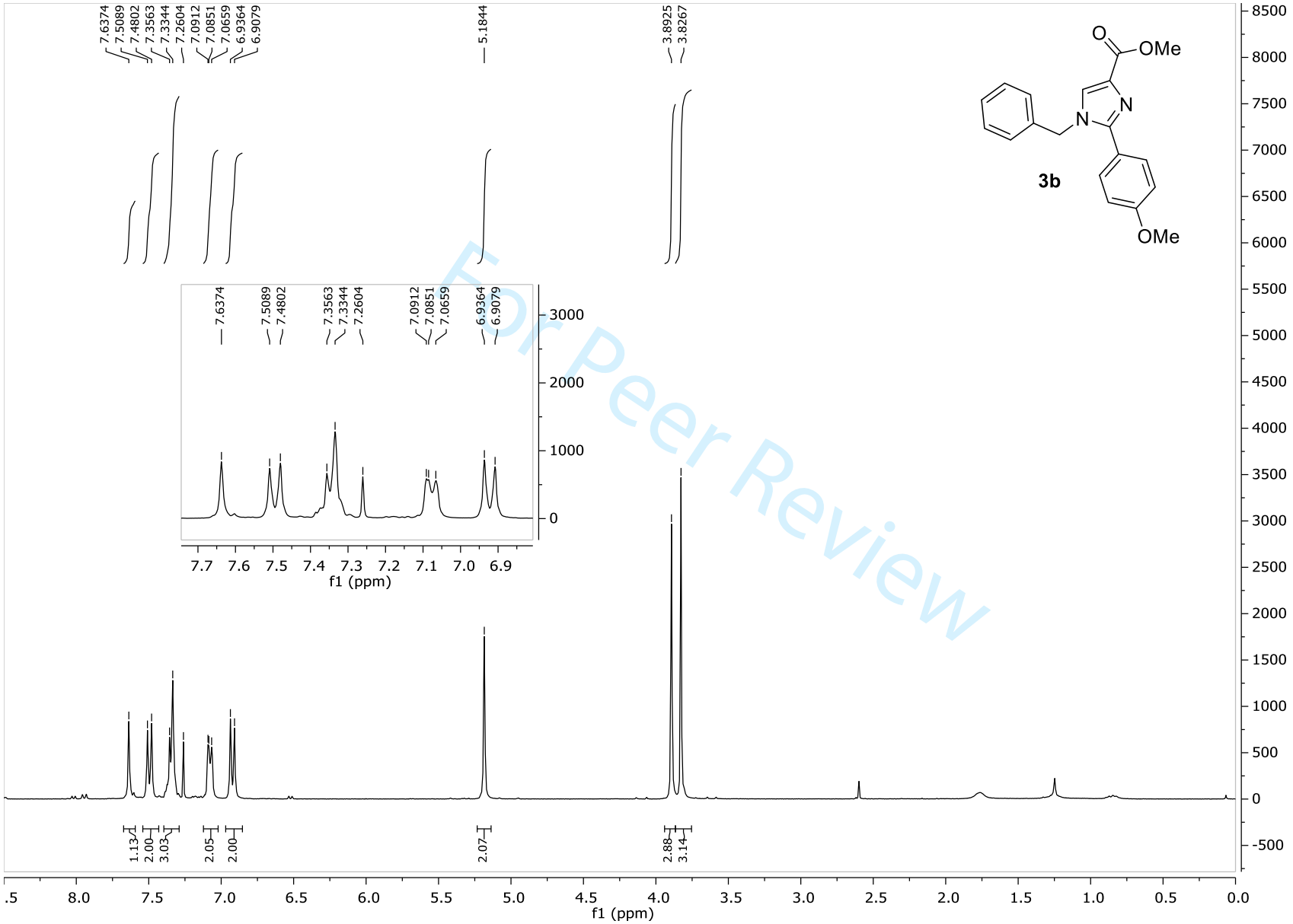


For Peer Review

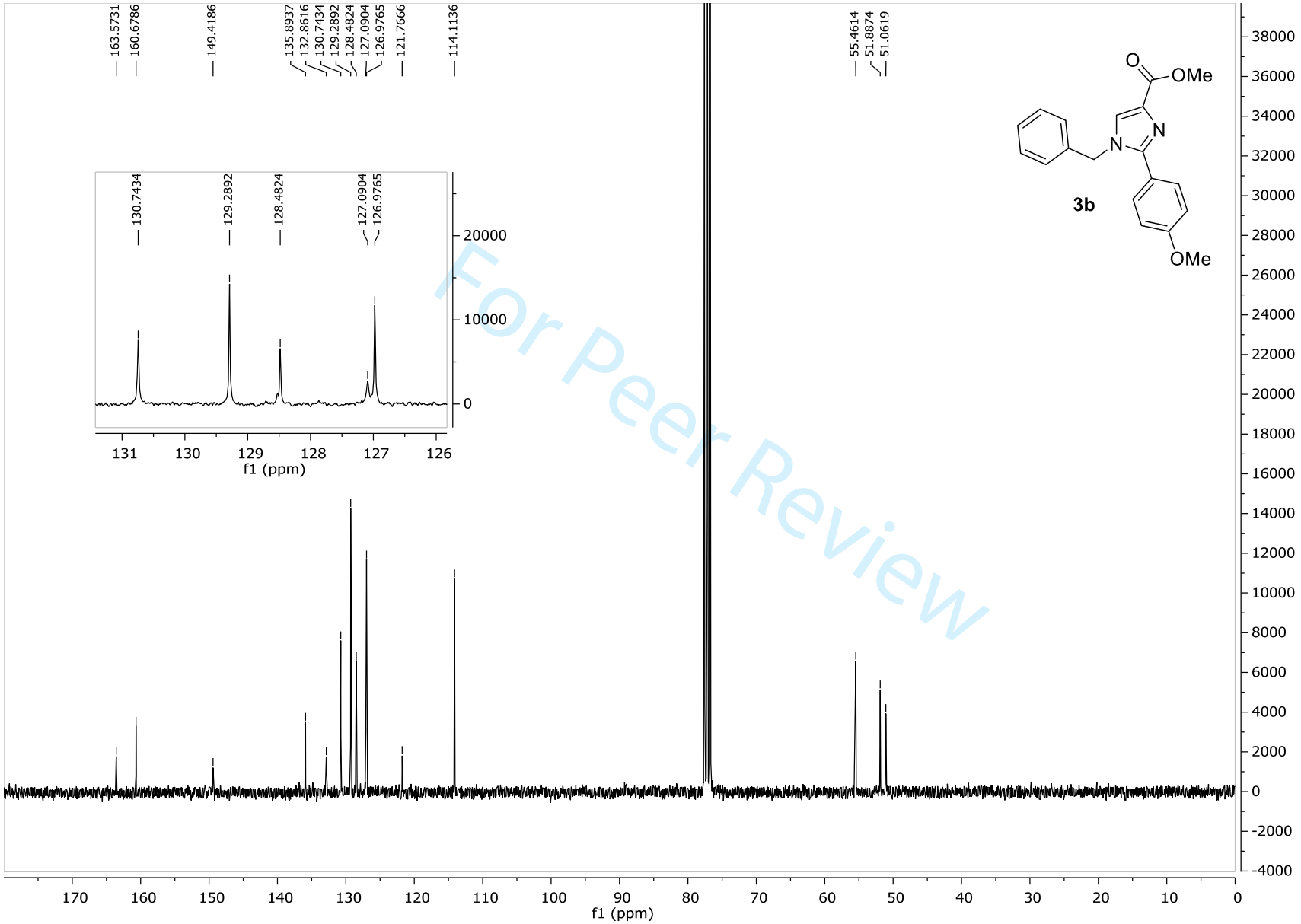
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



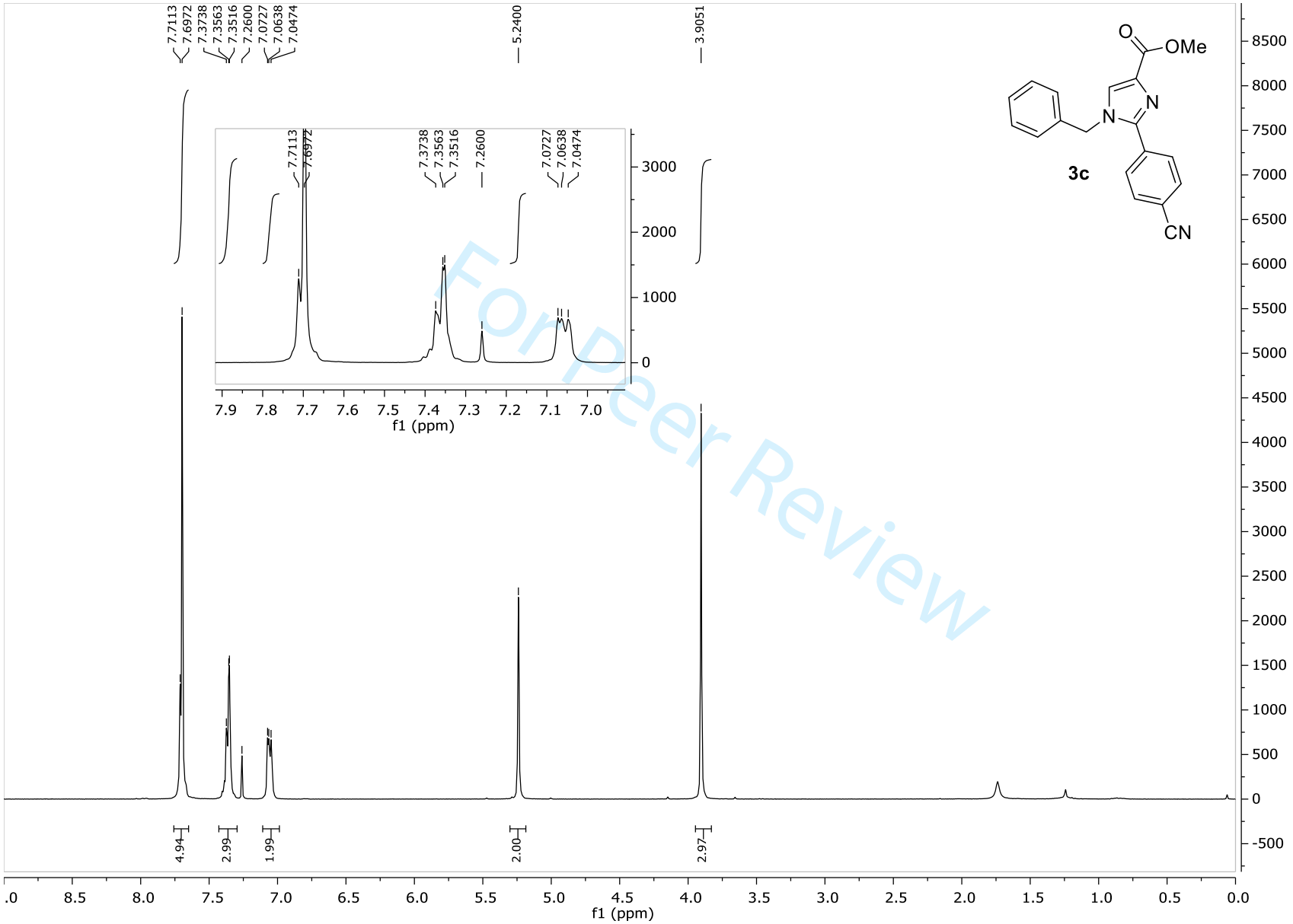
For Peer Review



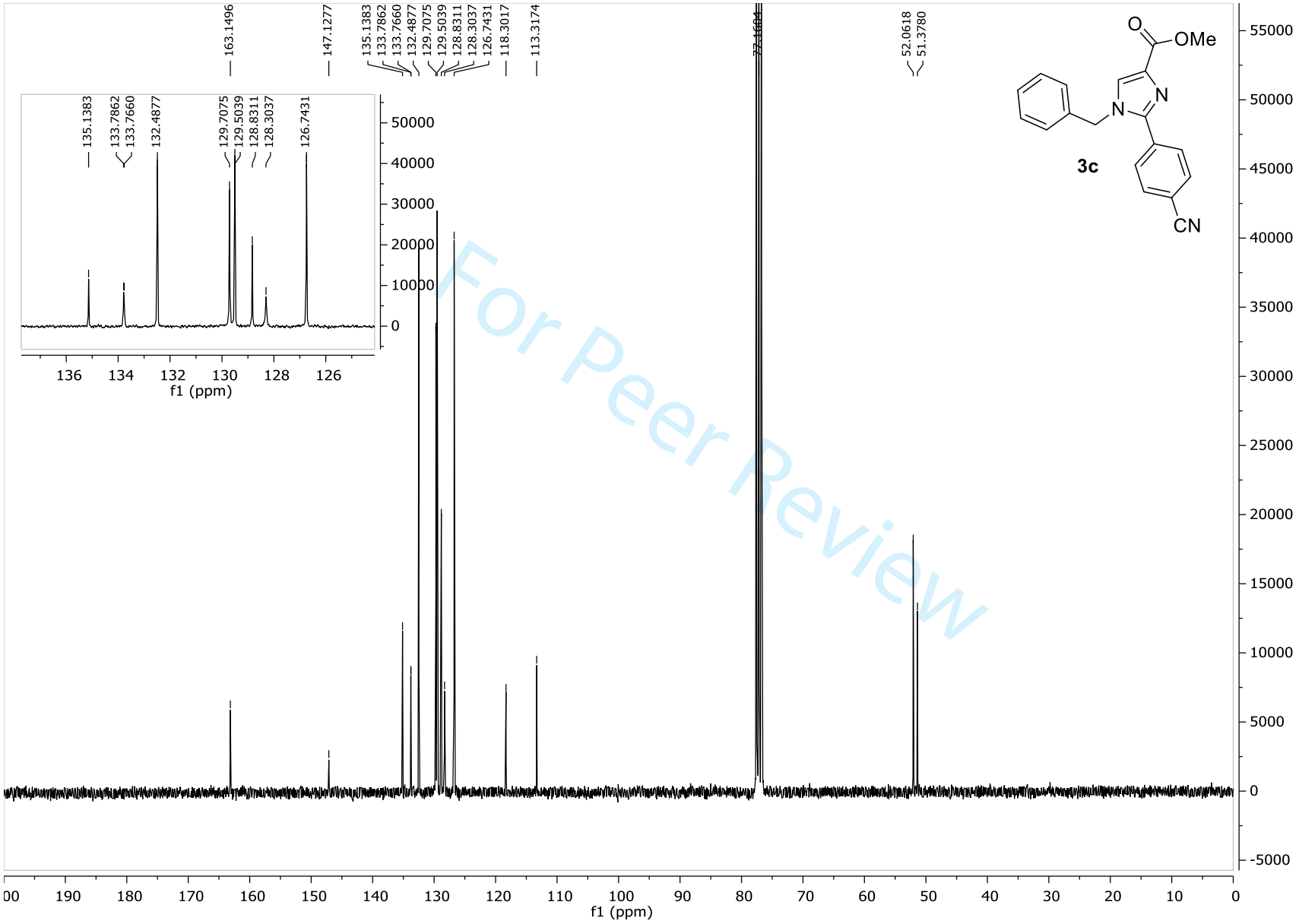
For Peer Review



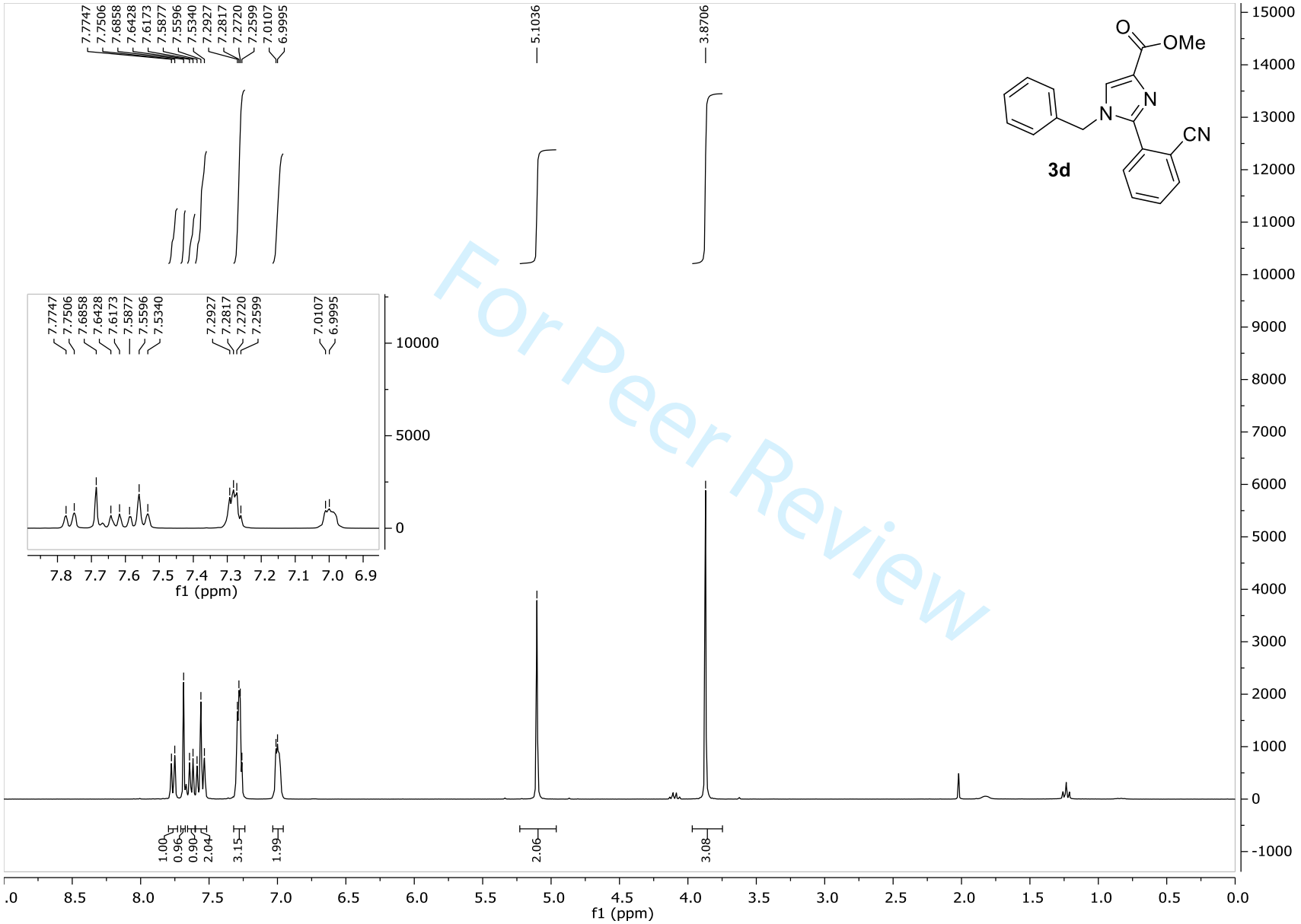
For Peer Review



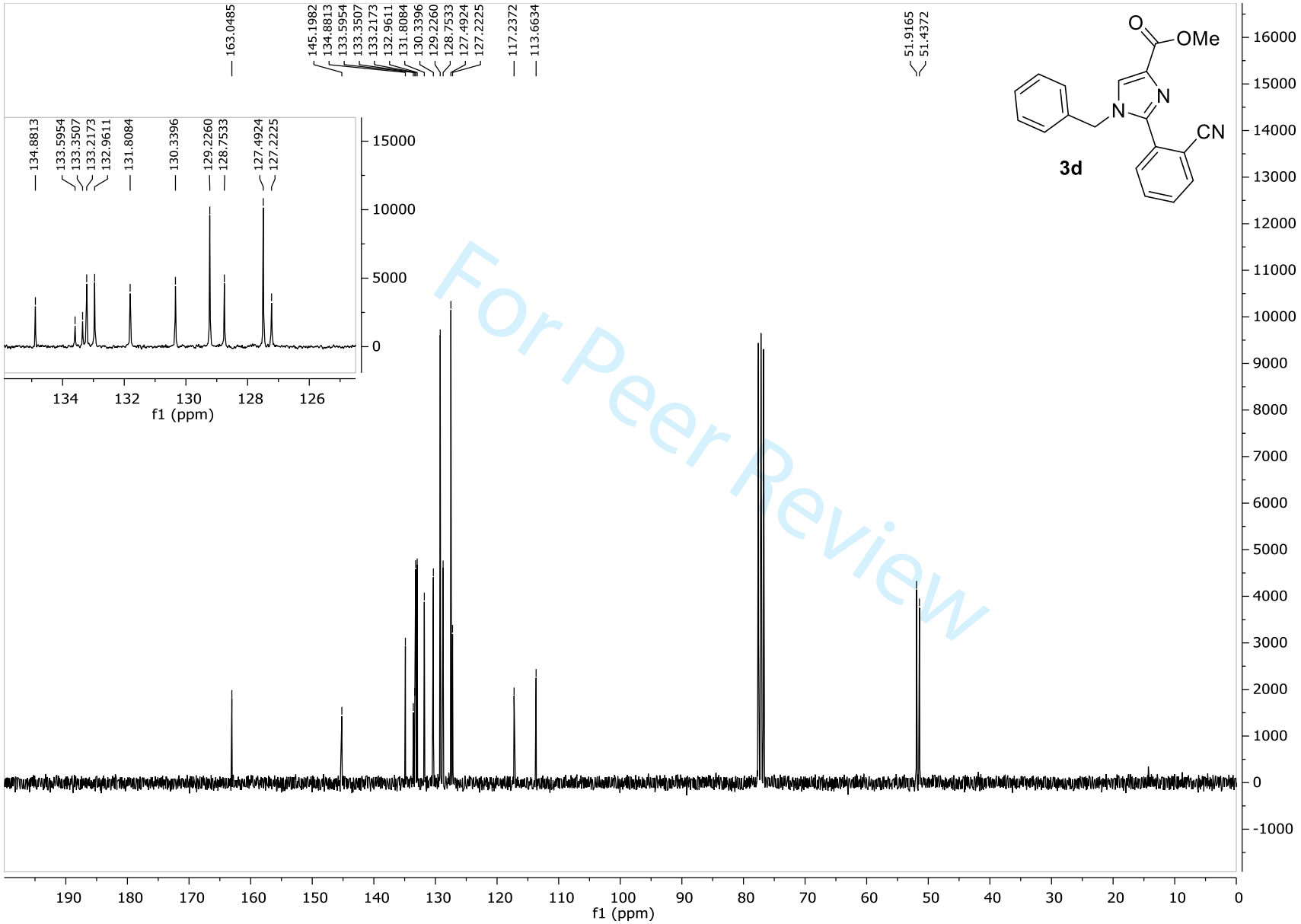
For Peer Review



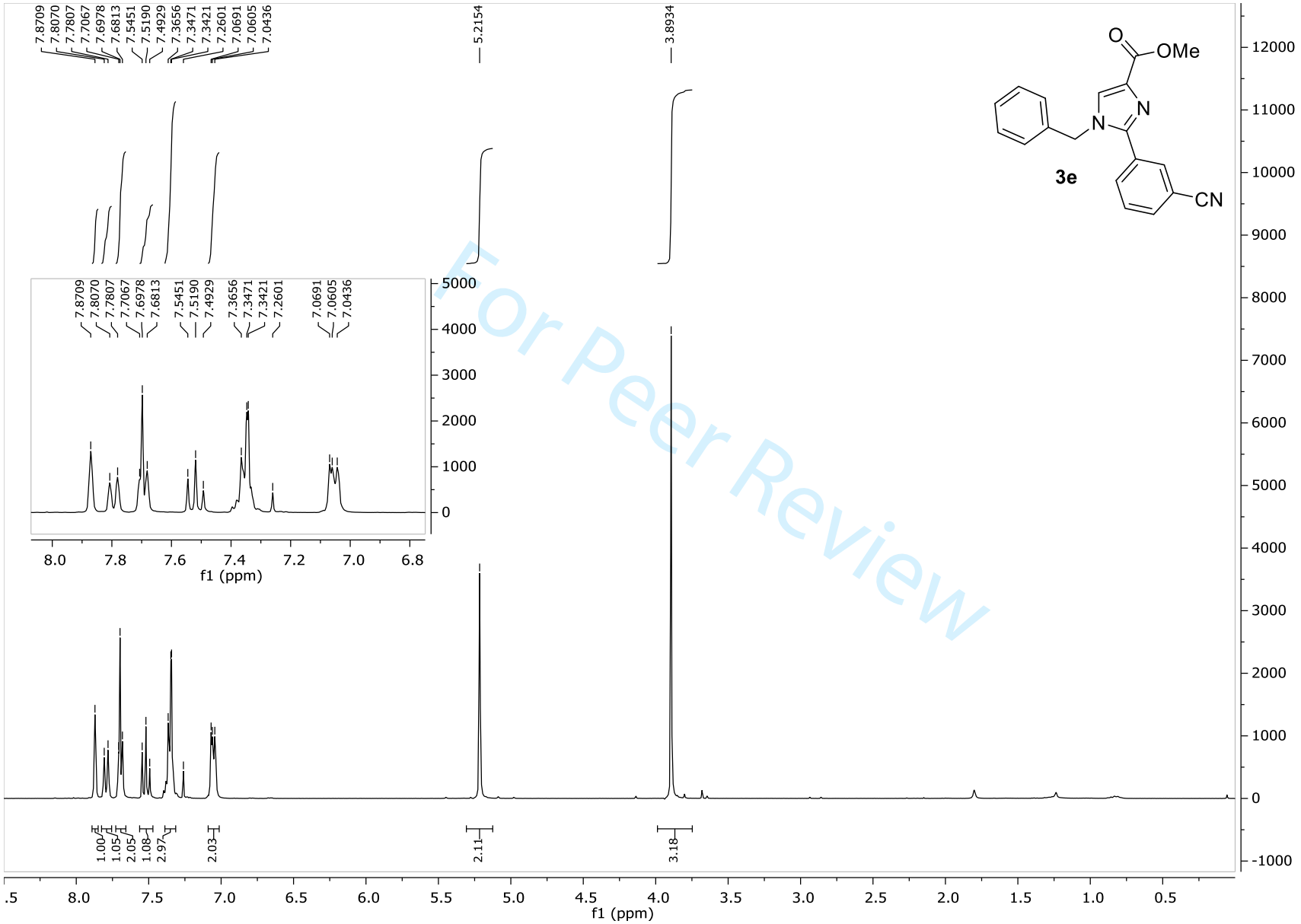
For Peer Review



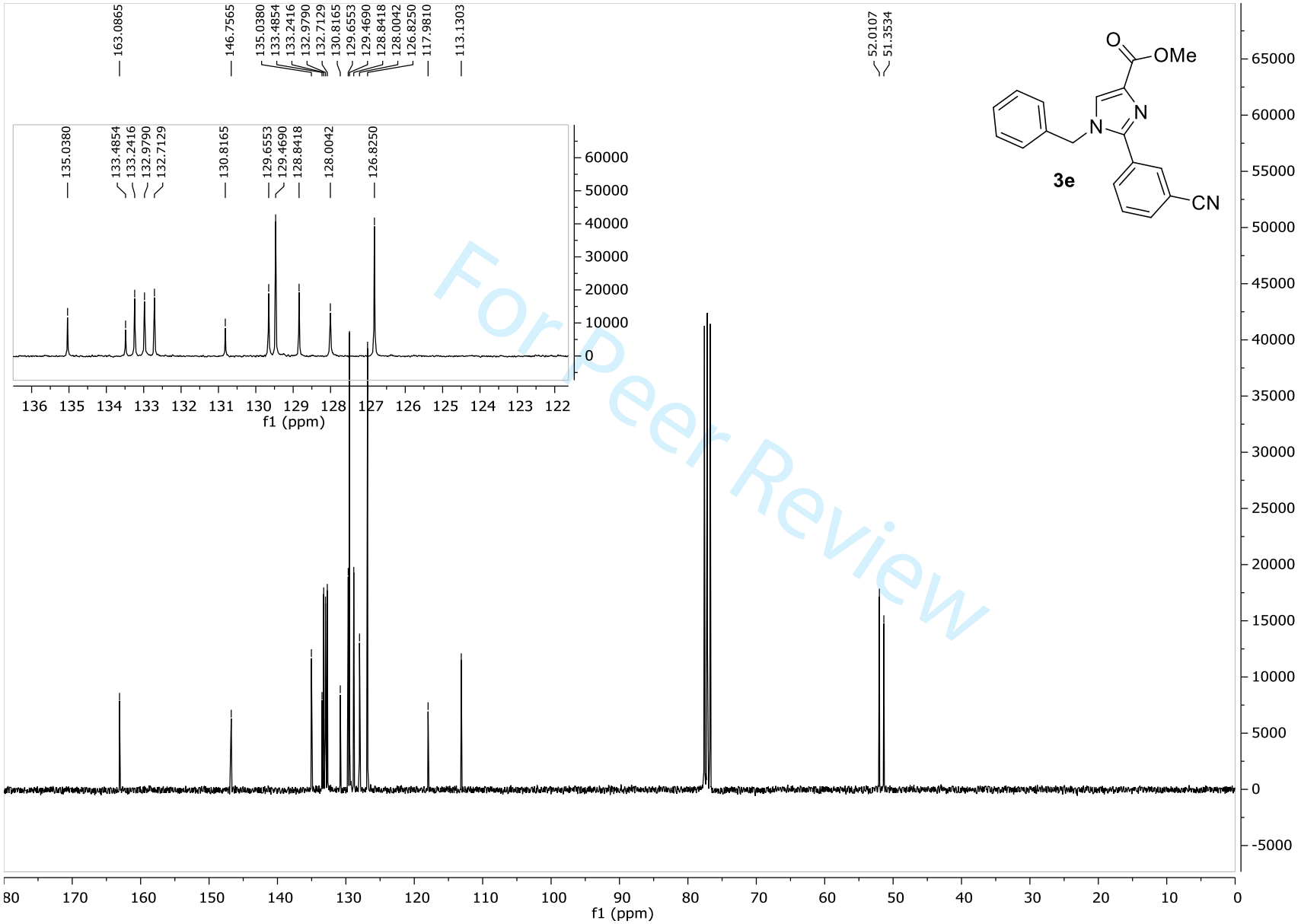
For Peer Review



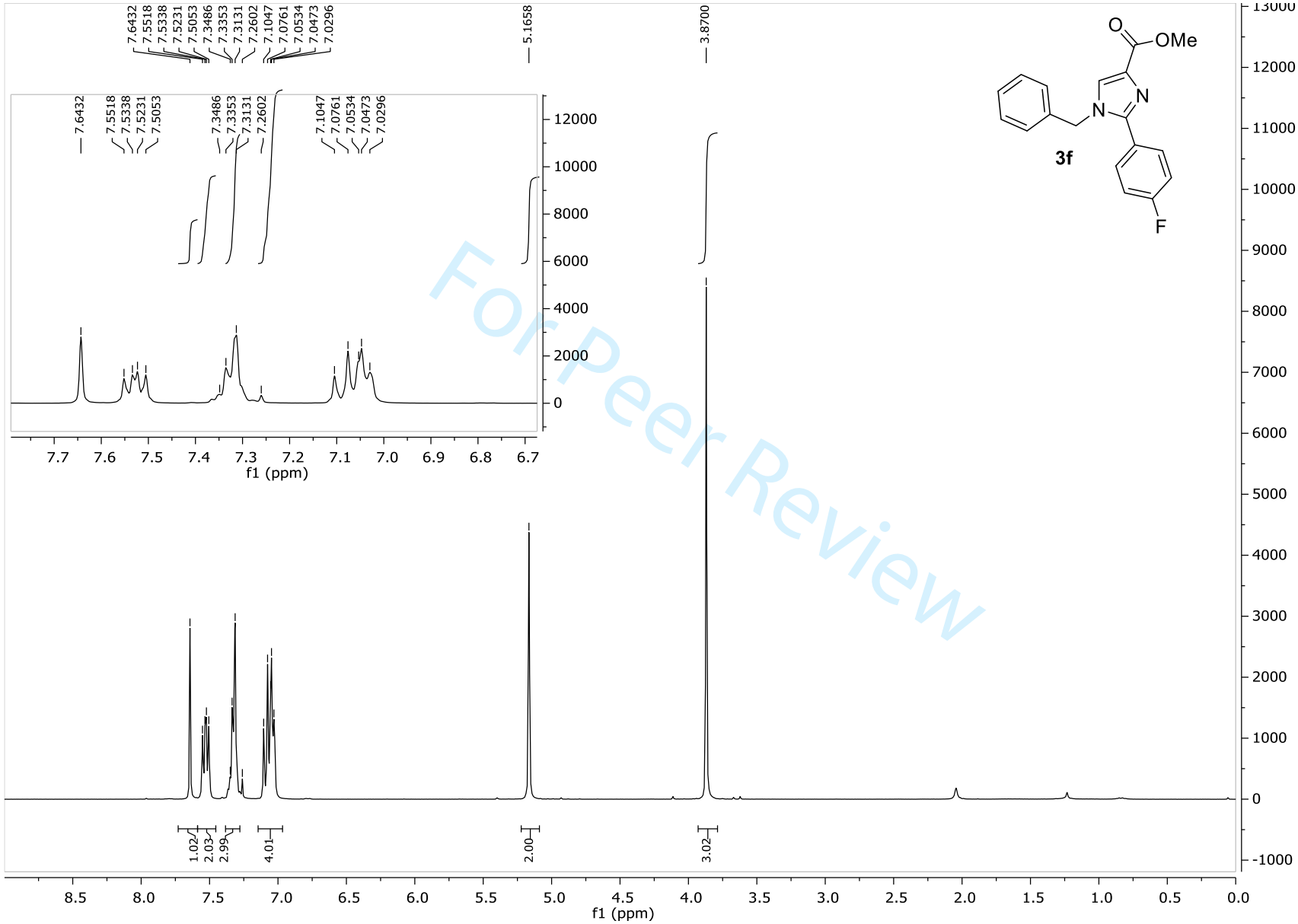
For Peer Review



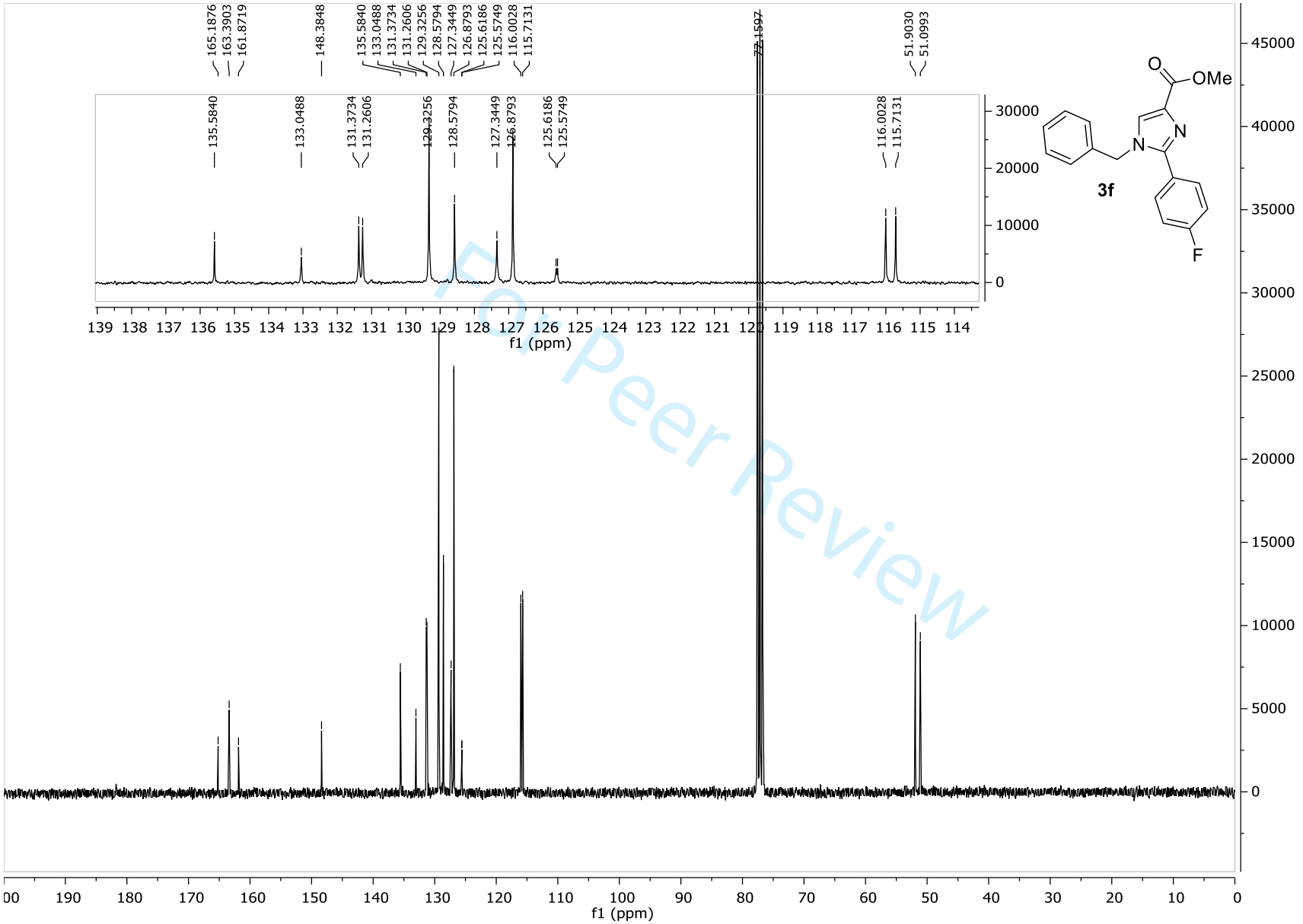
For Peer Review



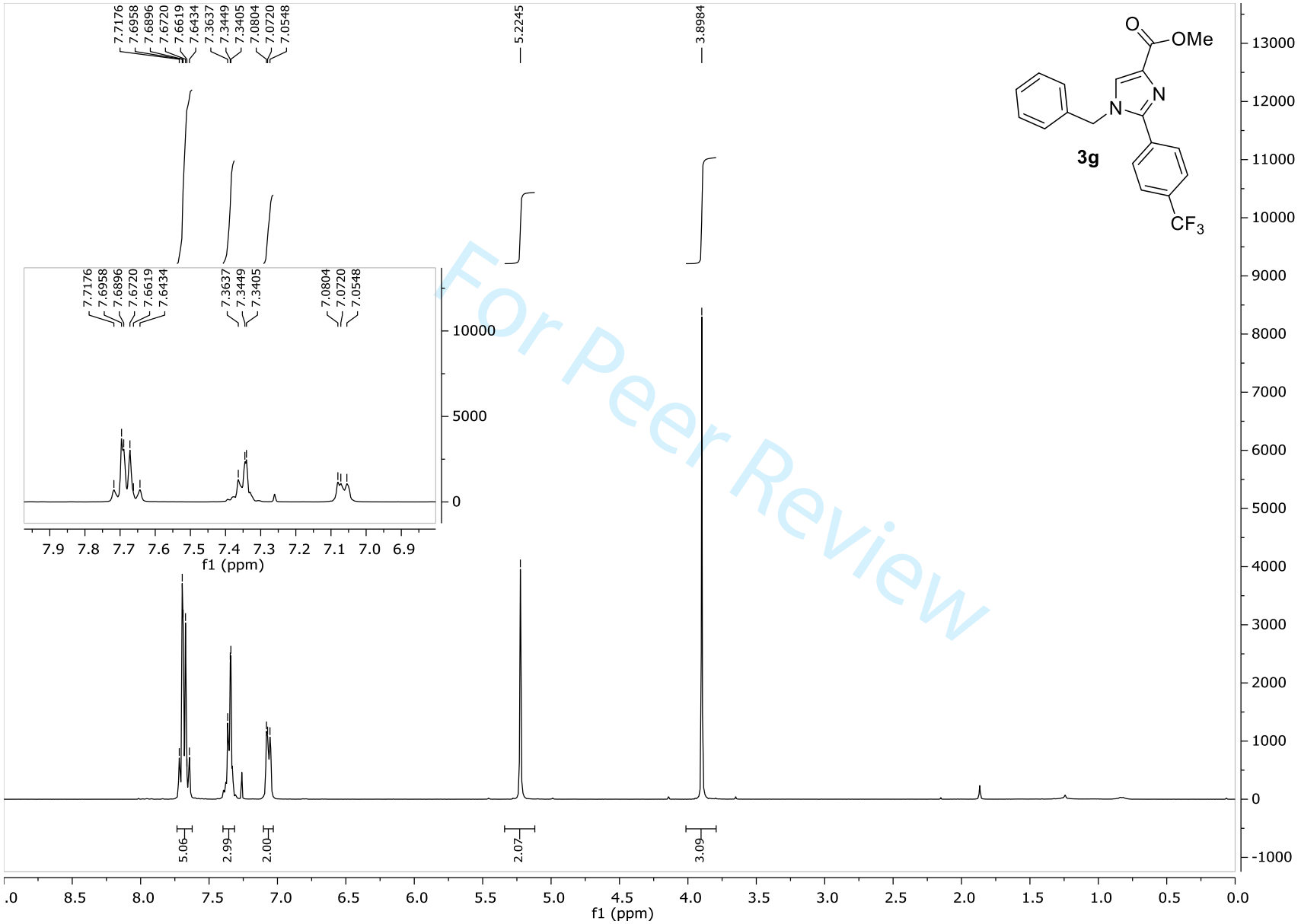
For Peer Review



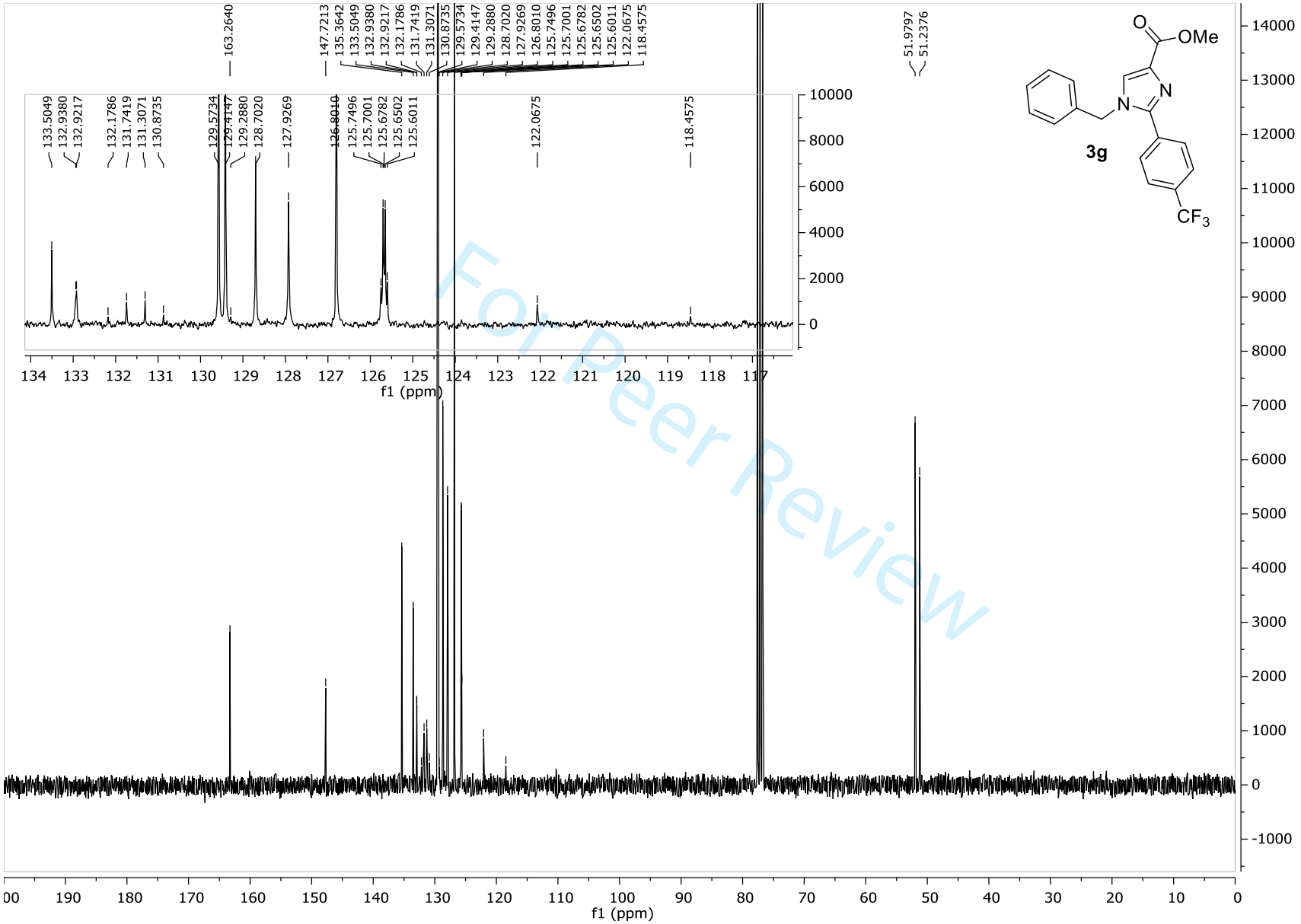
For Peer Review



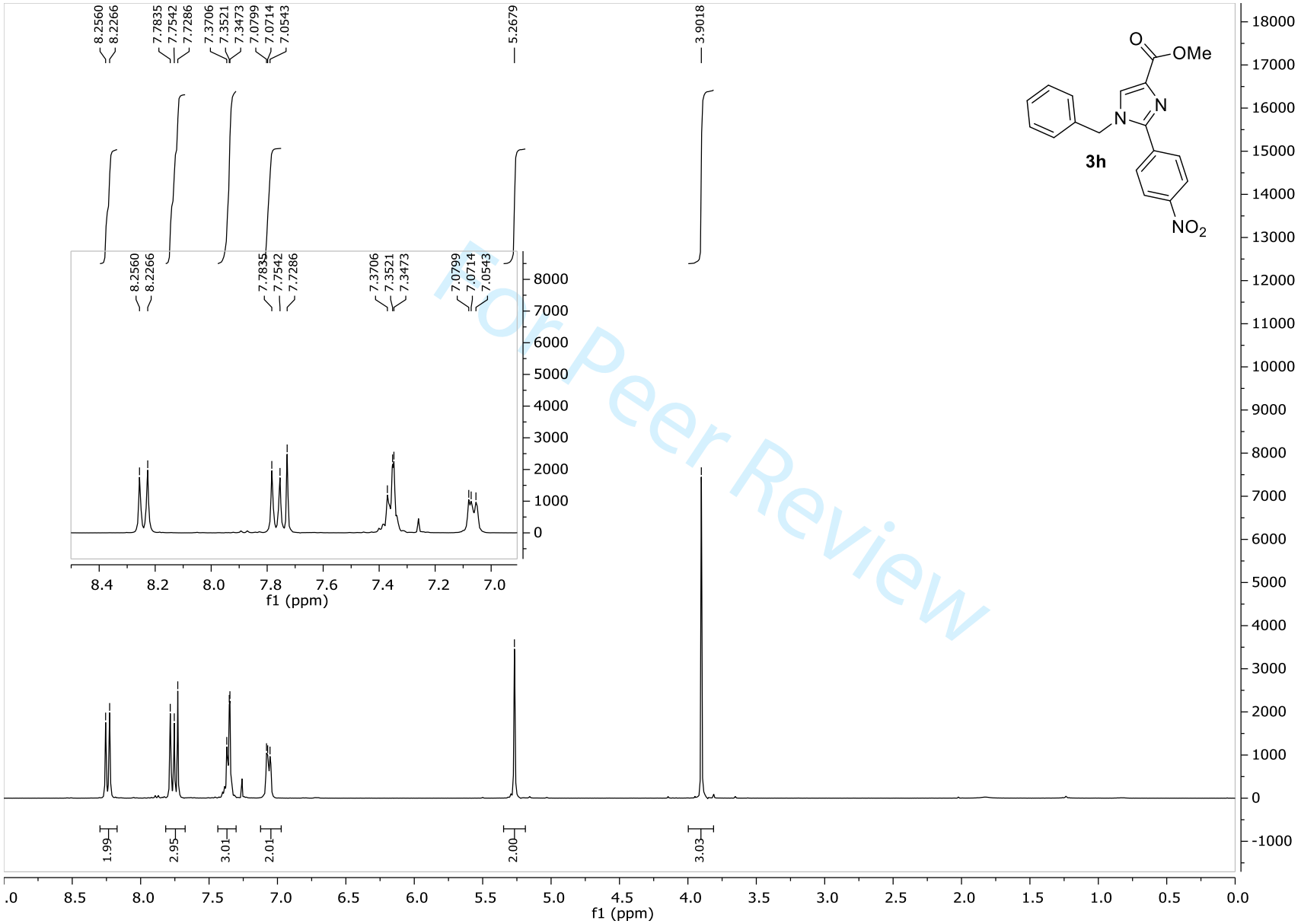
For Peer Review



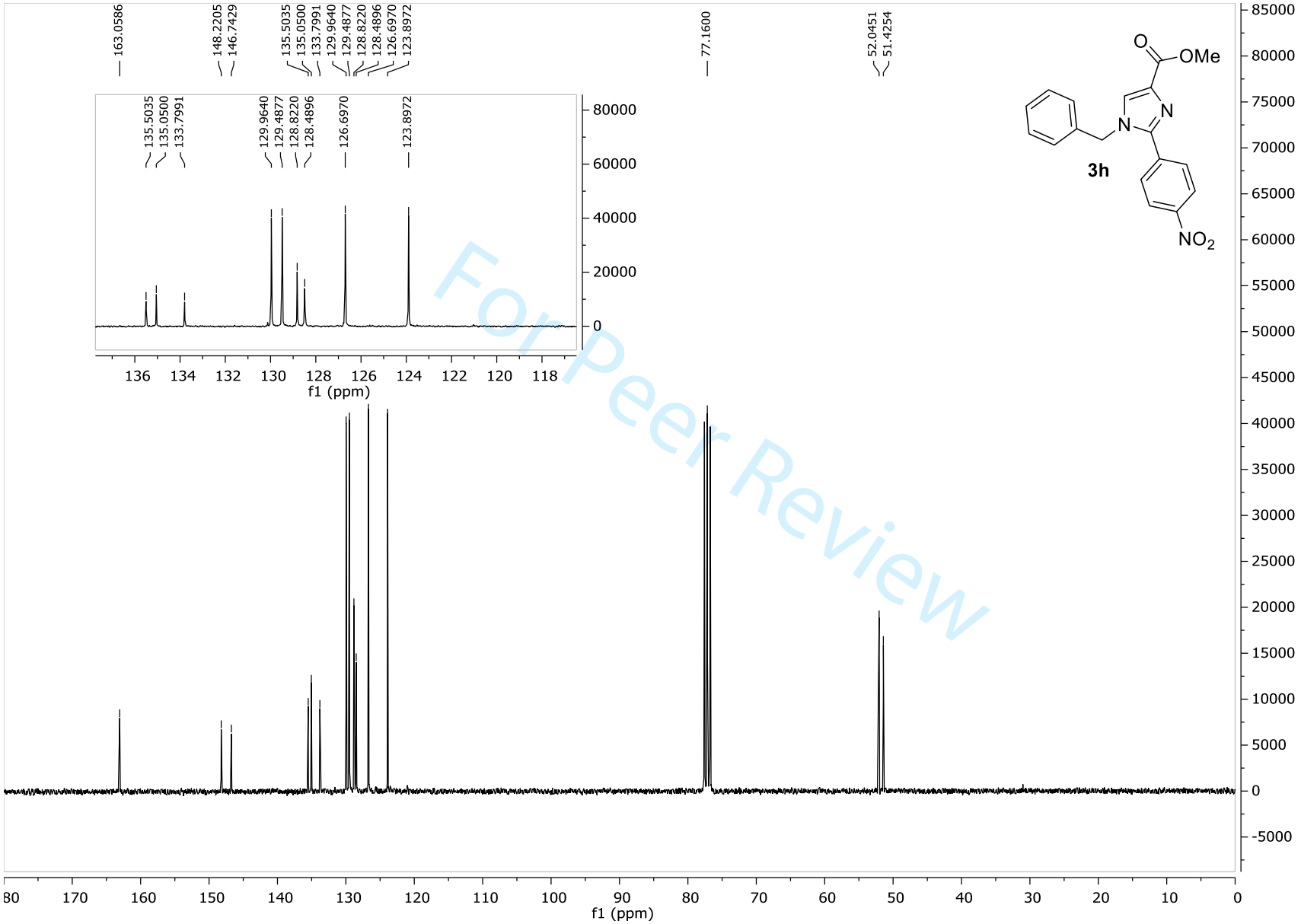
For Peer Review



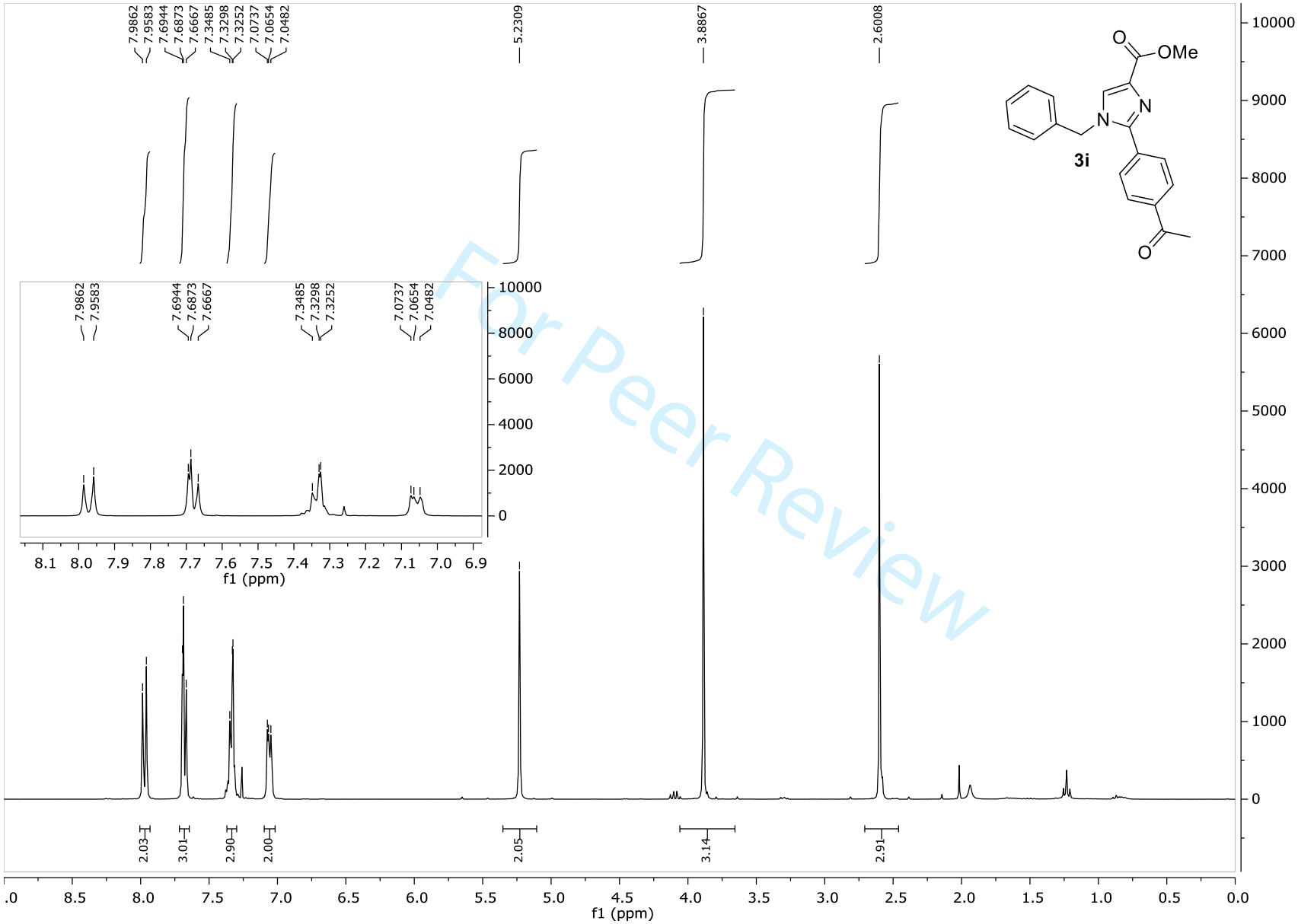
For Peer Review



For Peer Review

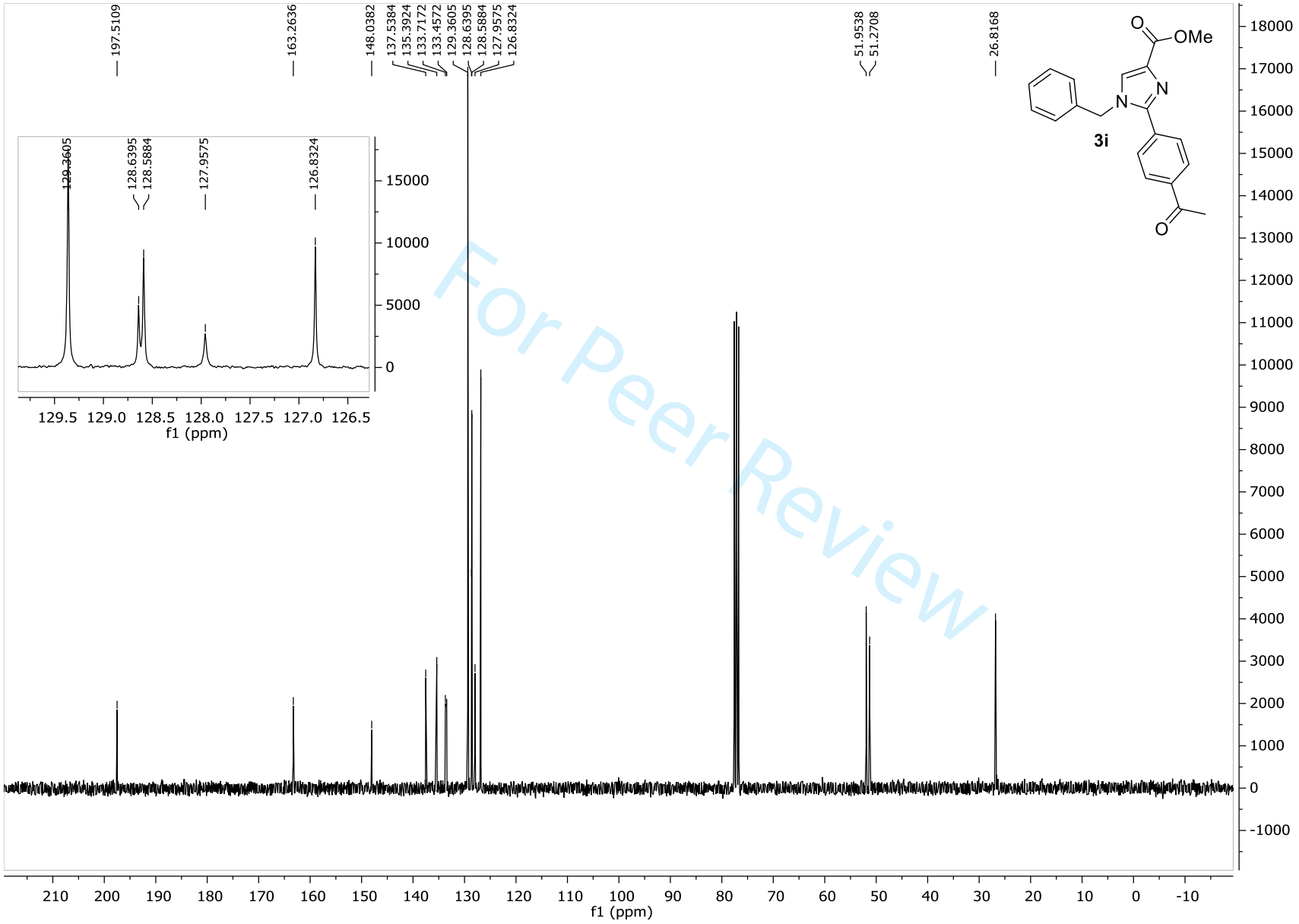


For Peer Review

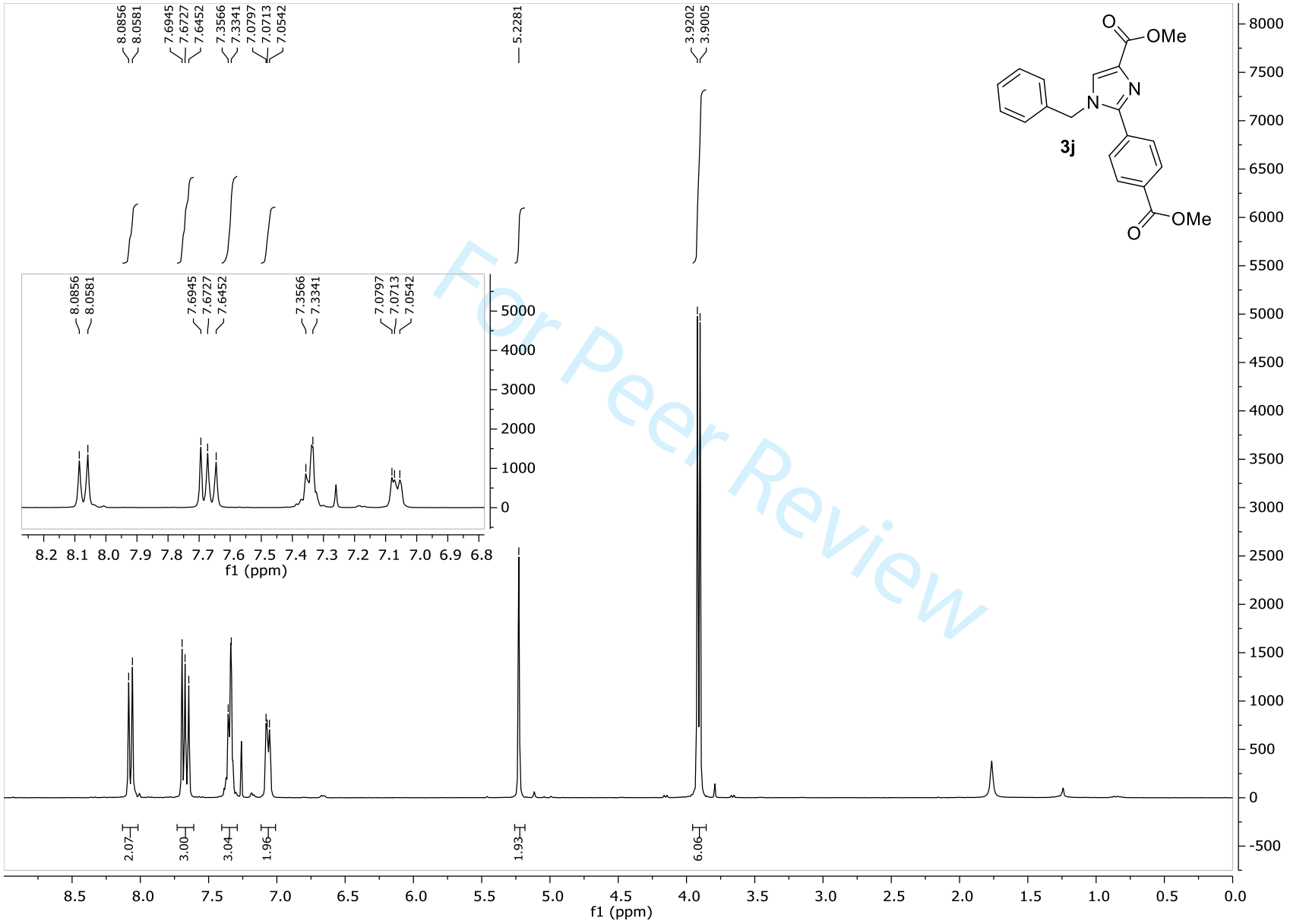


For Peer Review

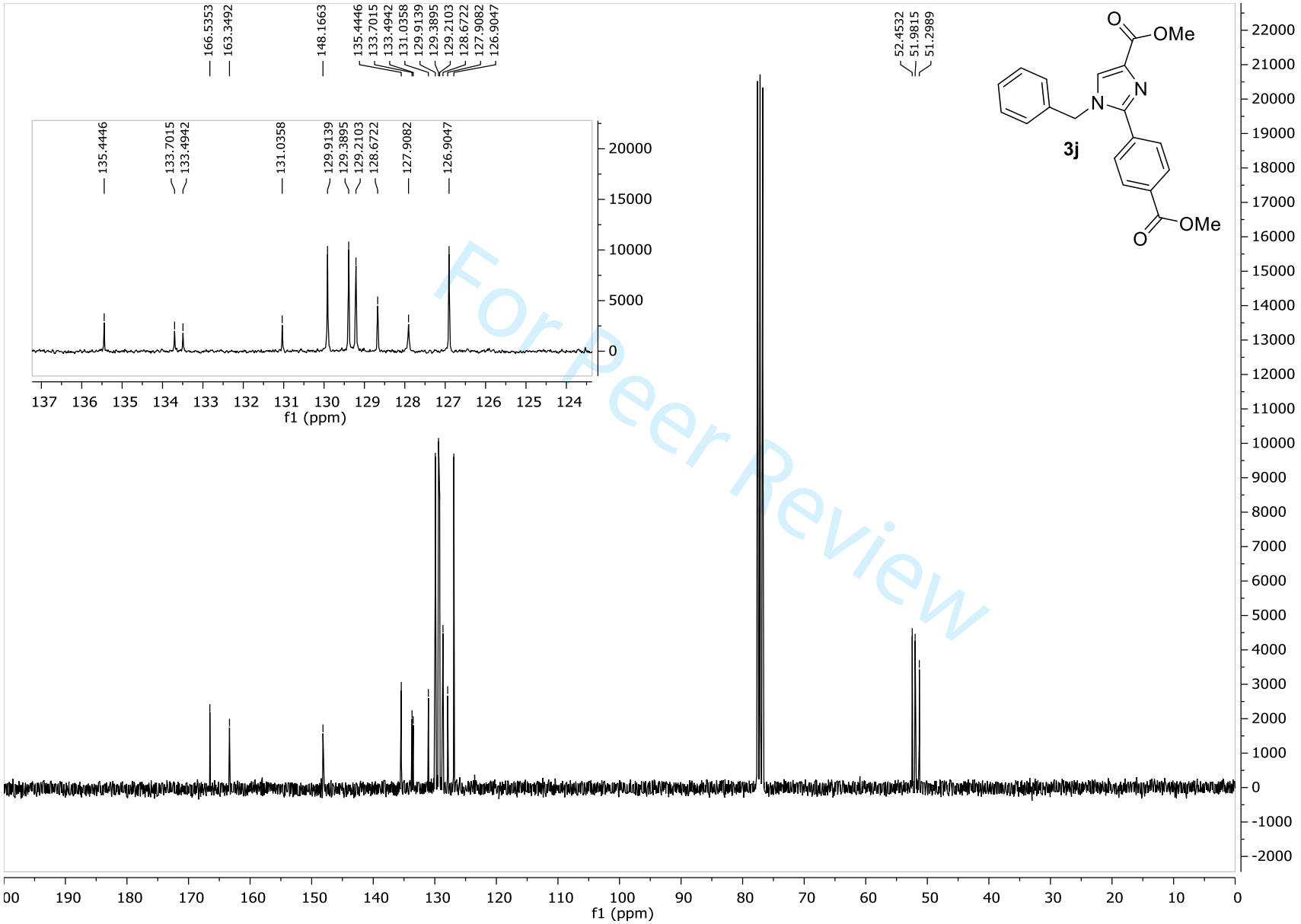
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



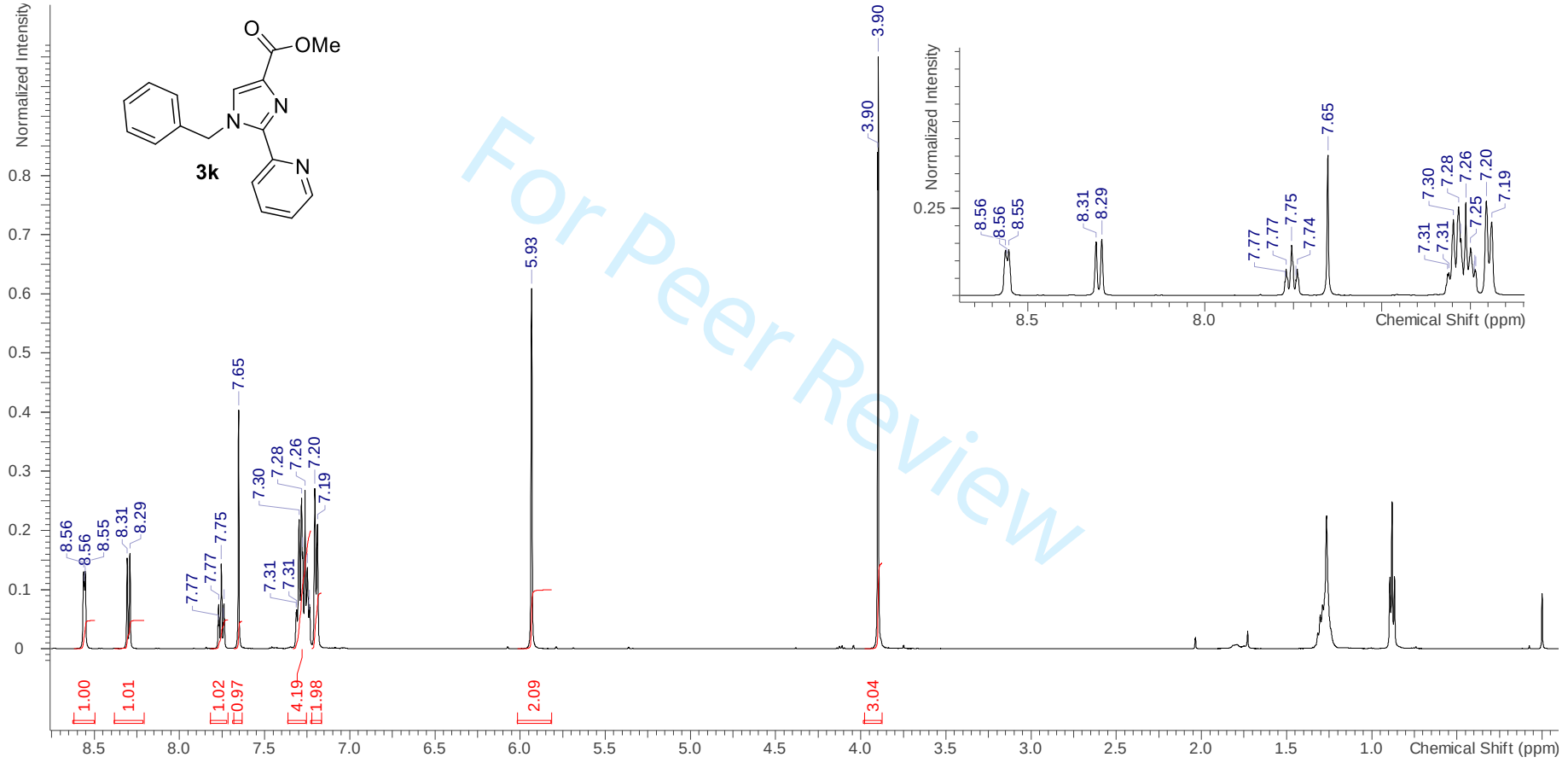
For Peer Review



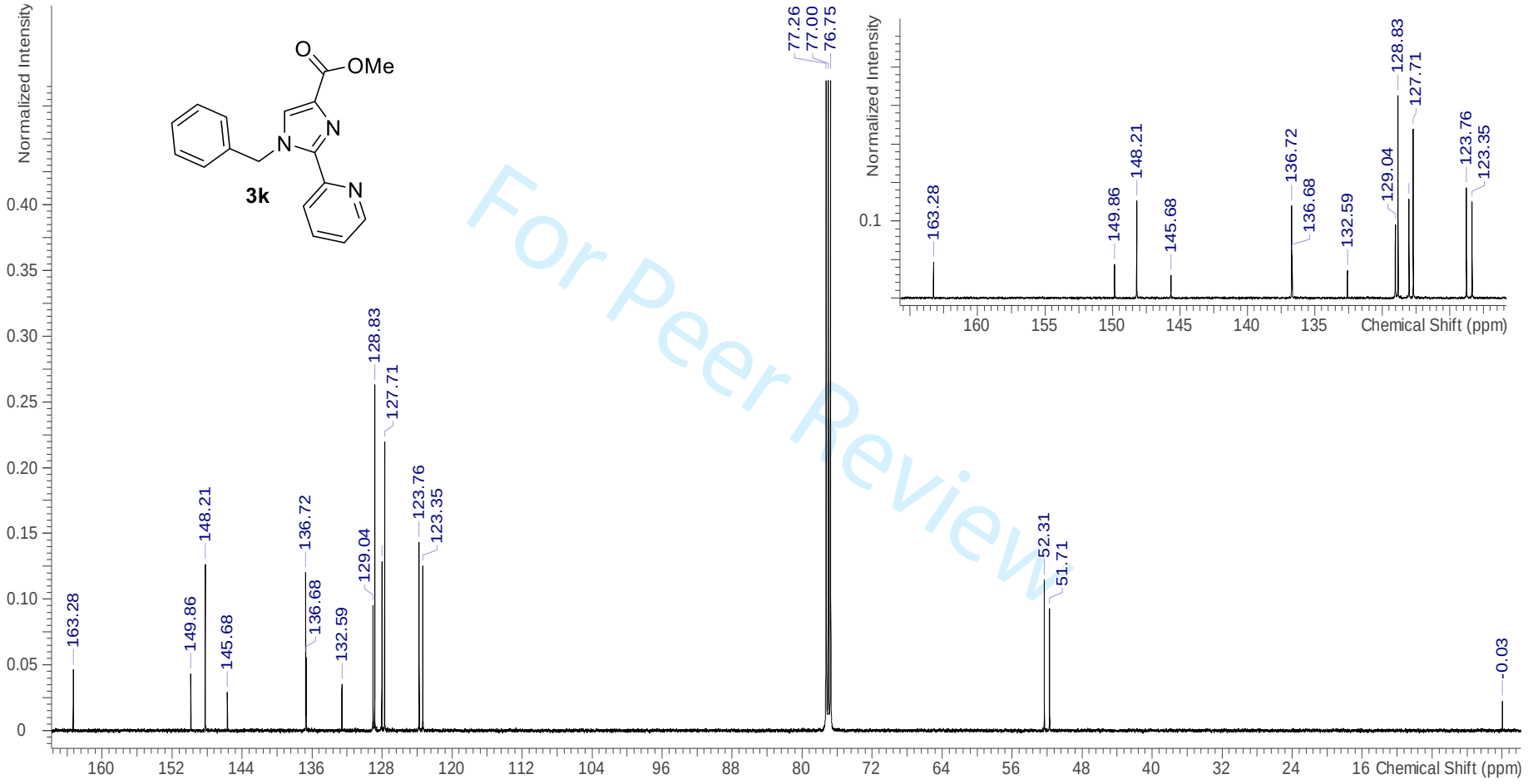
For Peer Review



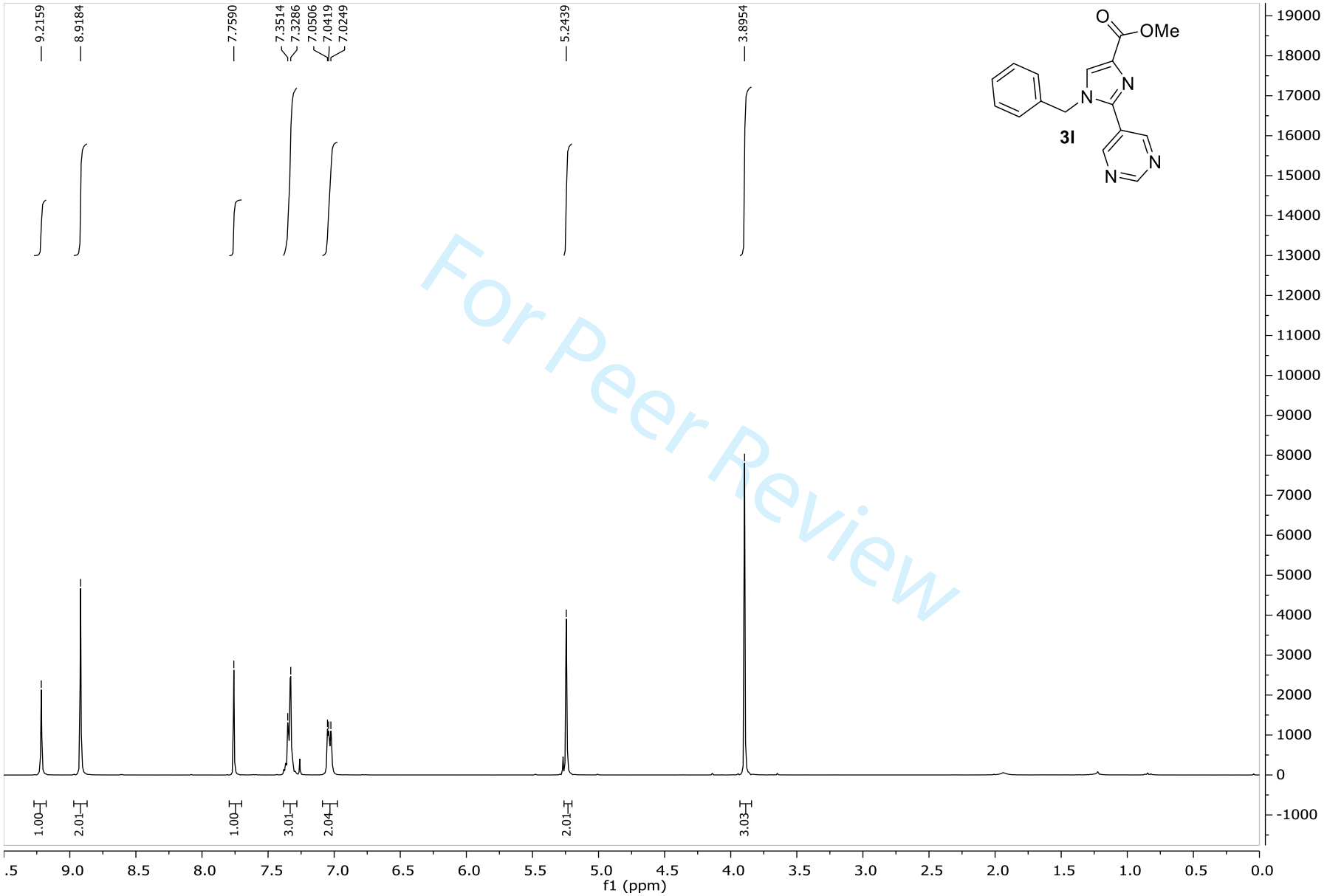
For Peer Review



For Peer Review

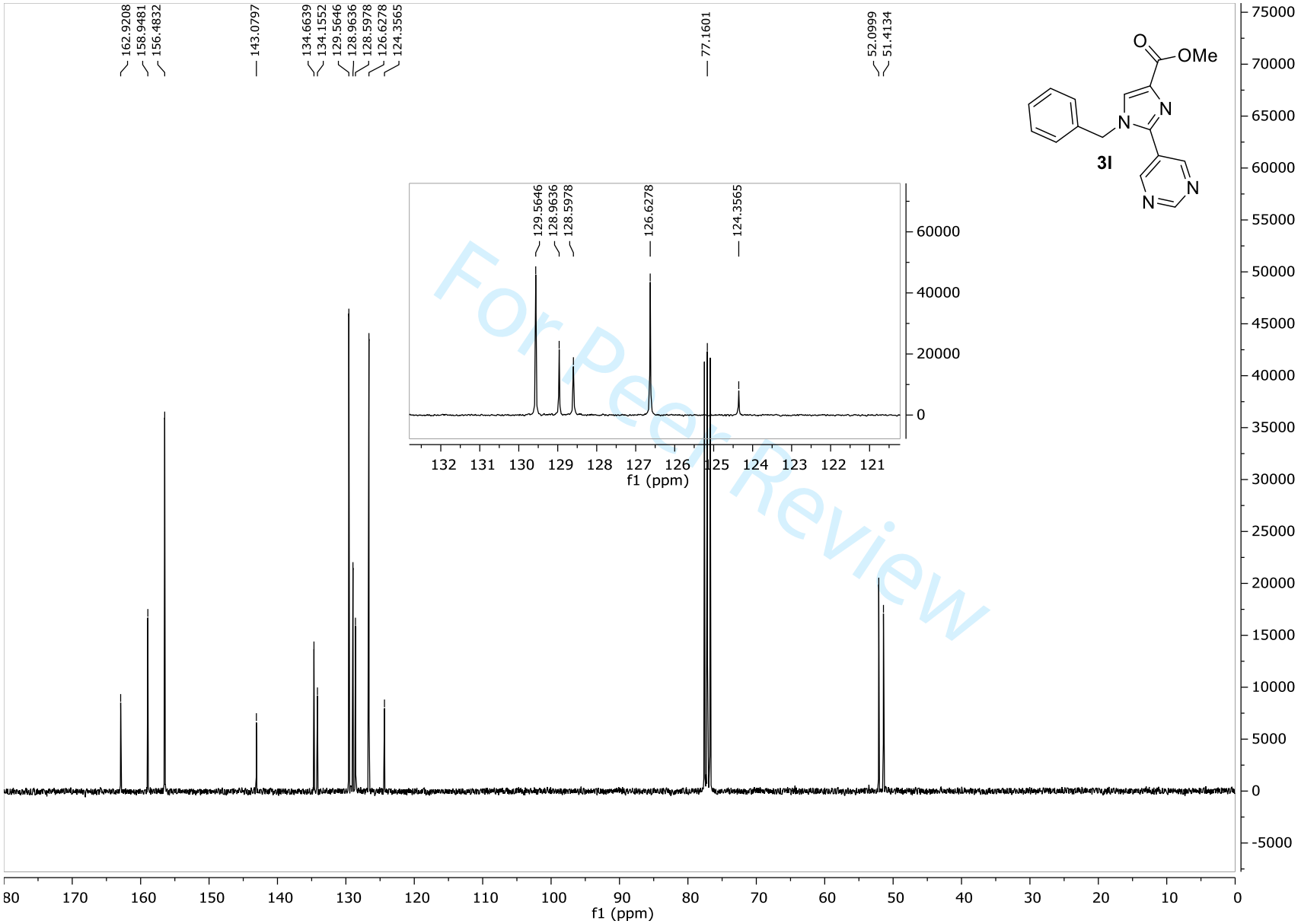


For Peer Review

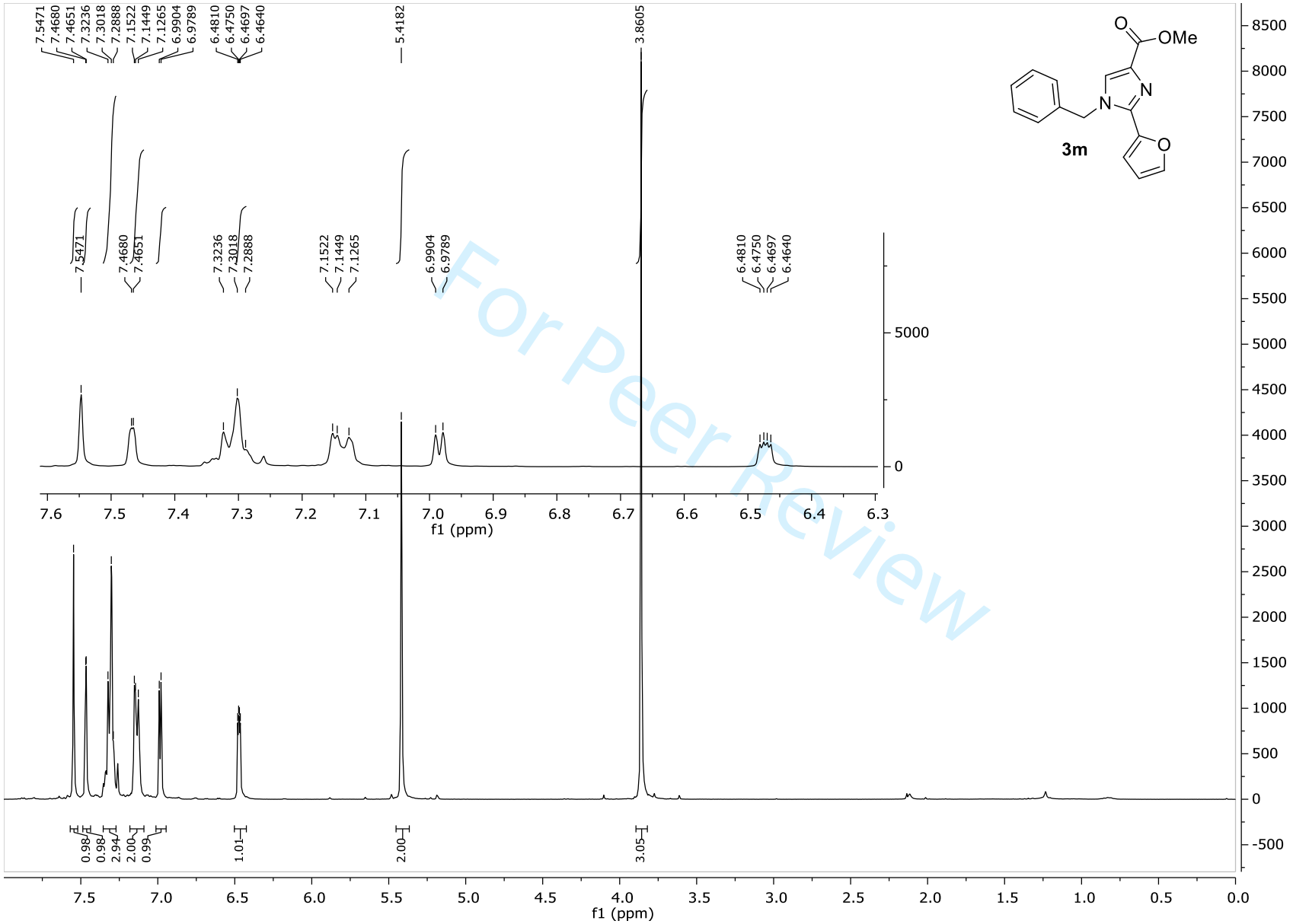


For Peer Review

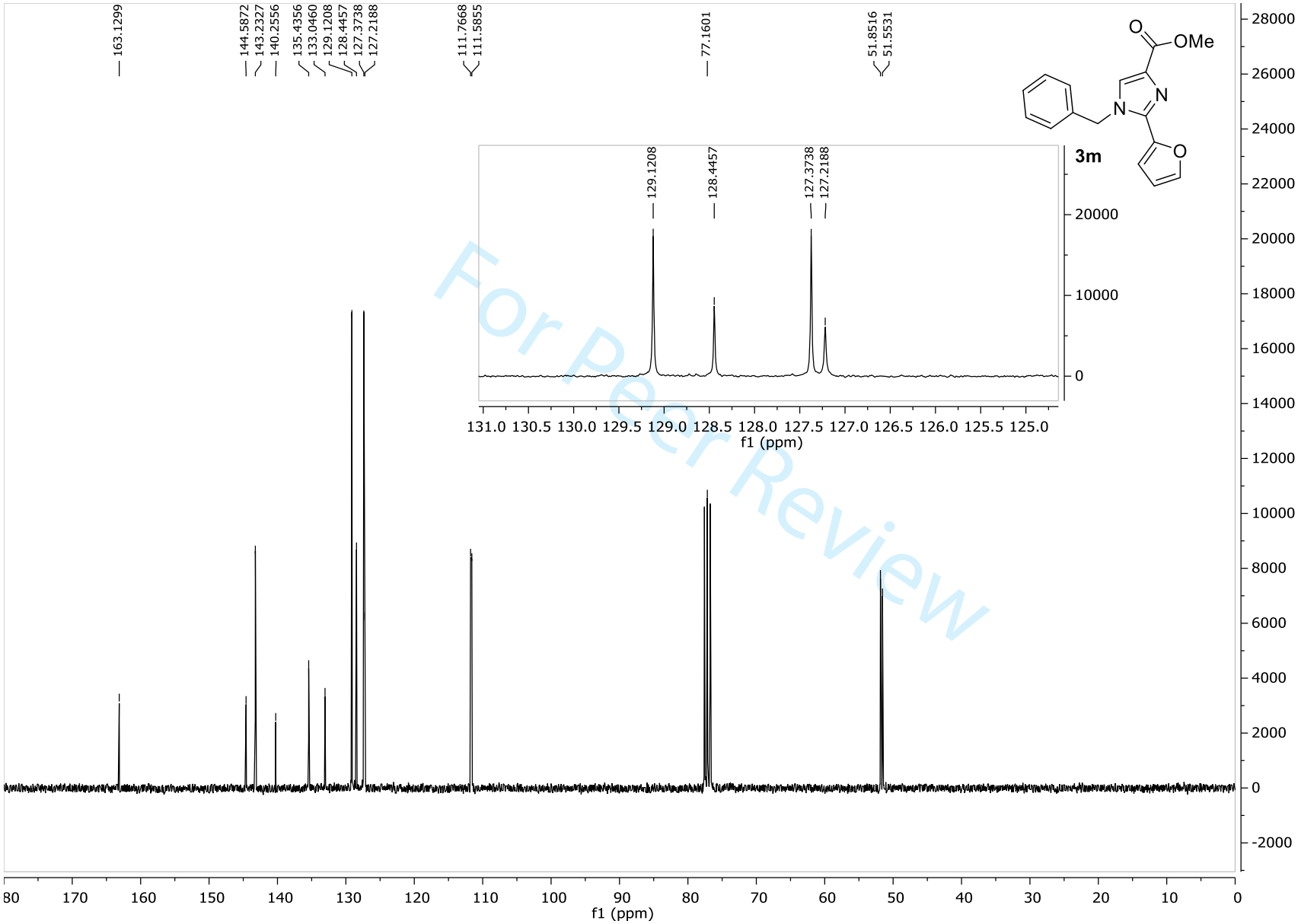
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



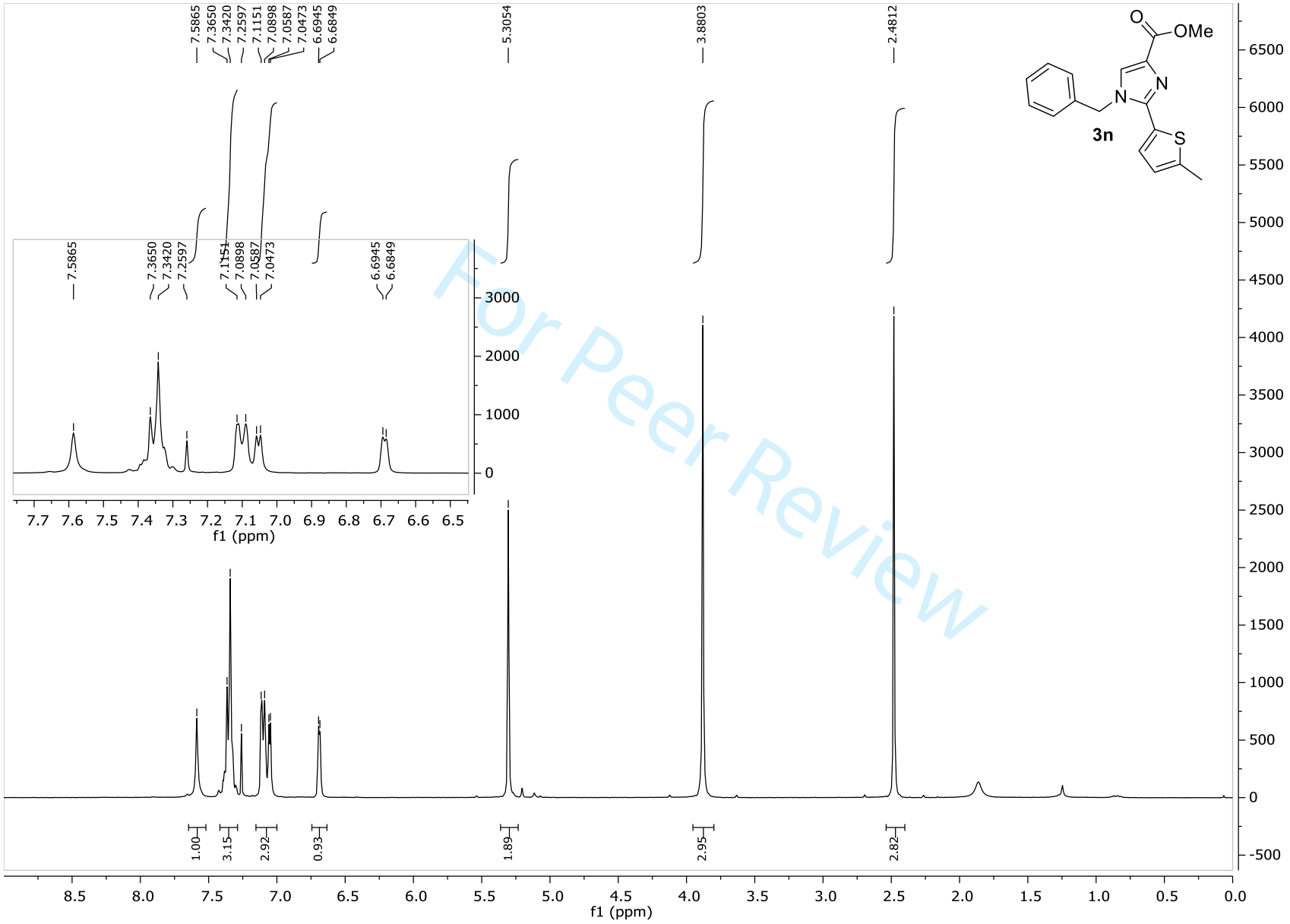
For Peer Review



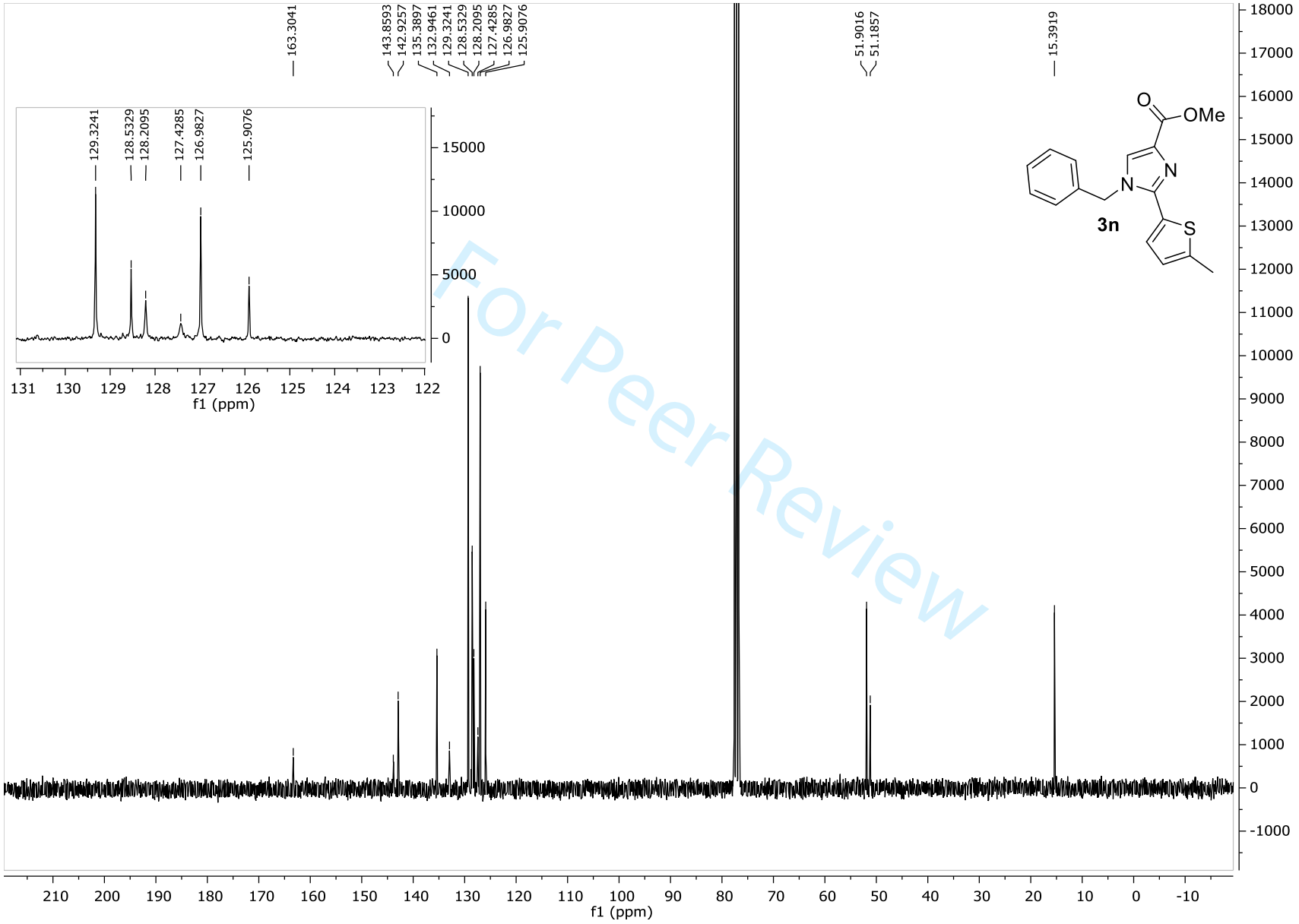
For Peer Review



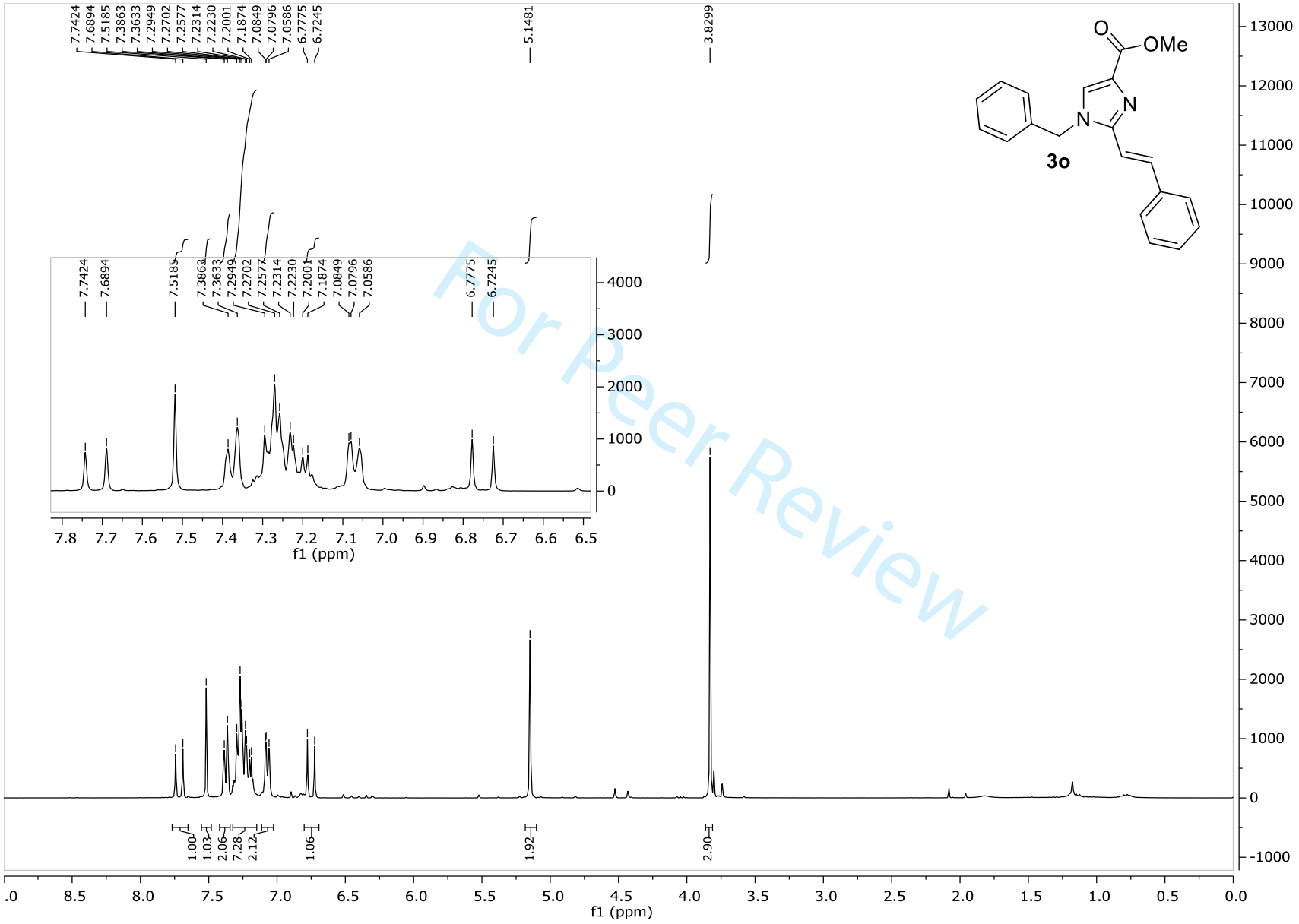
For Peer Review



For Peer Review

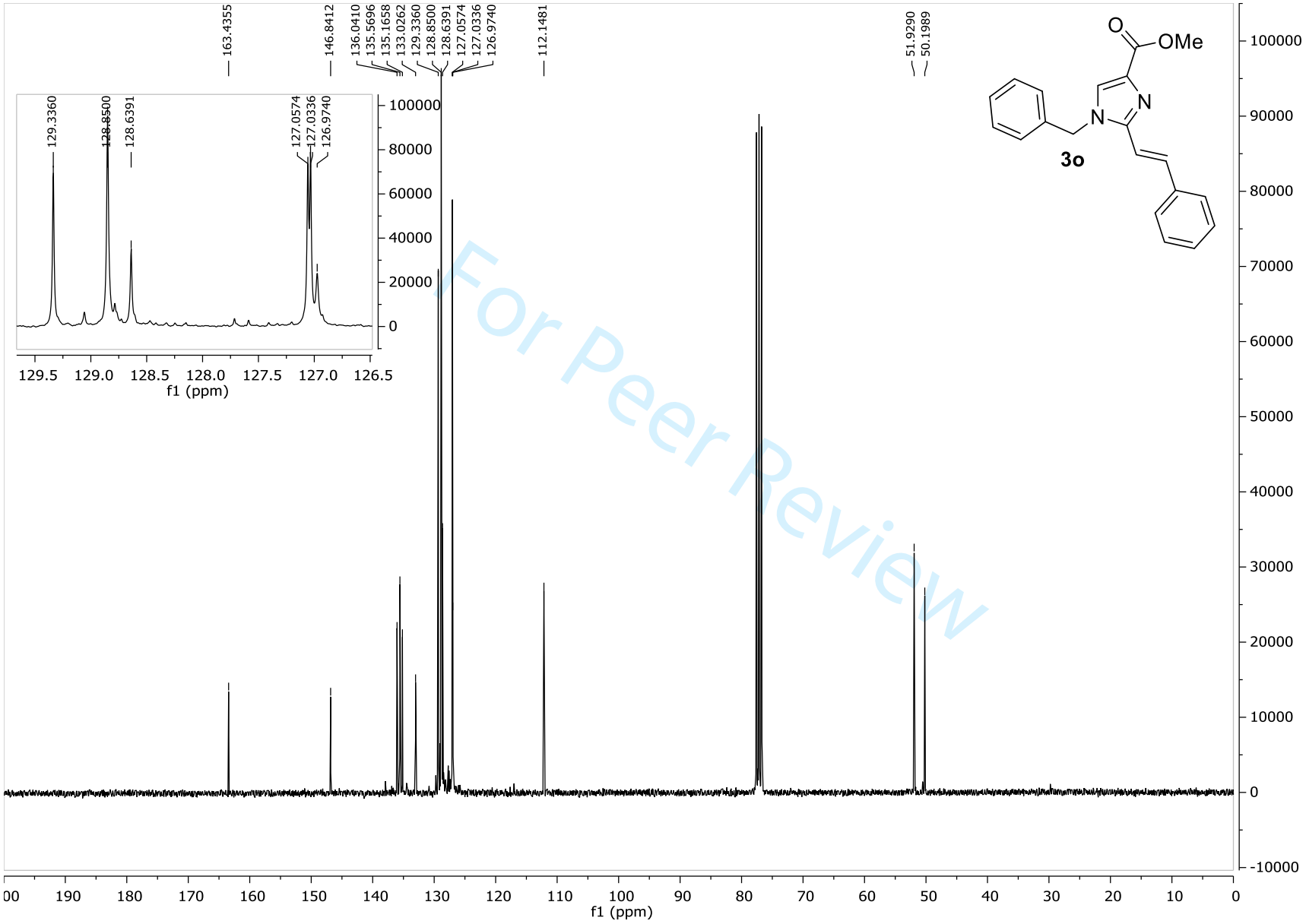


For Peer Review

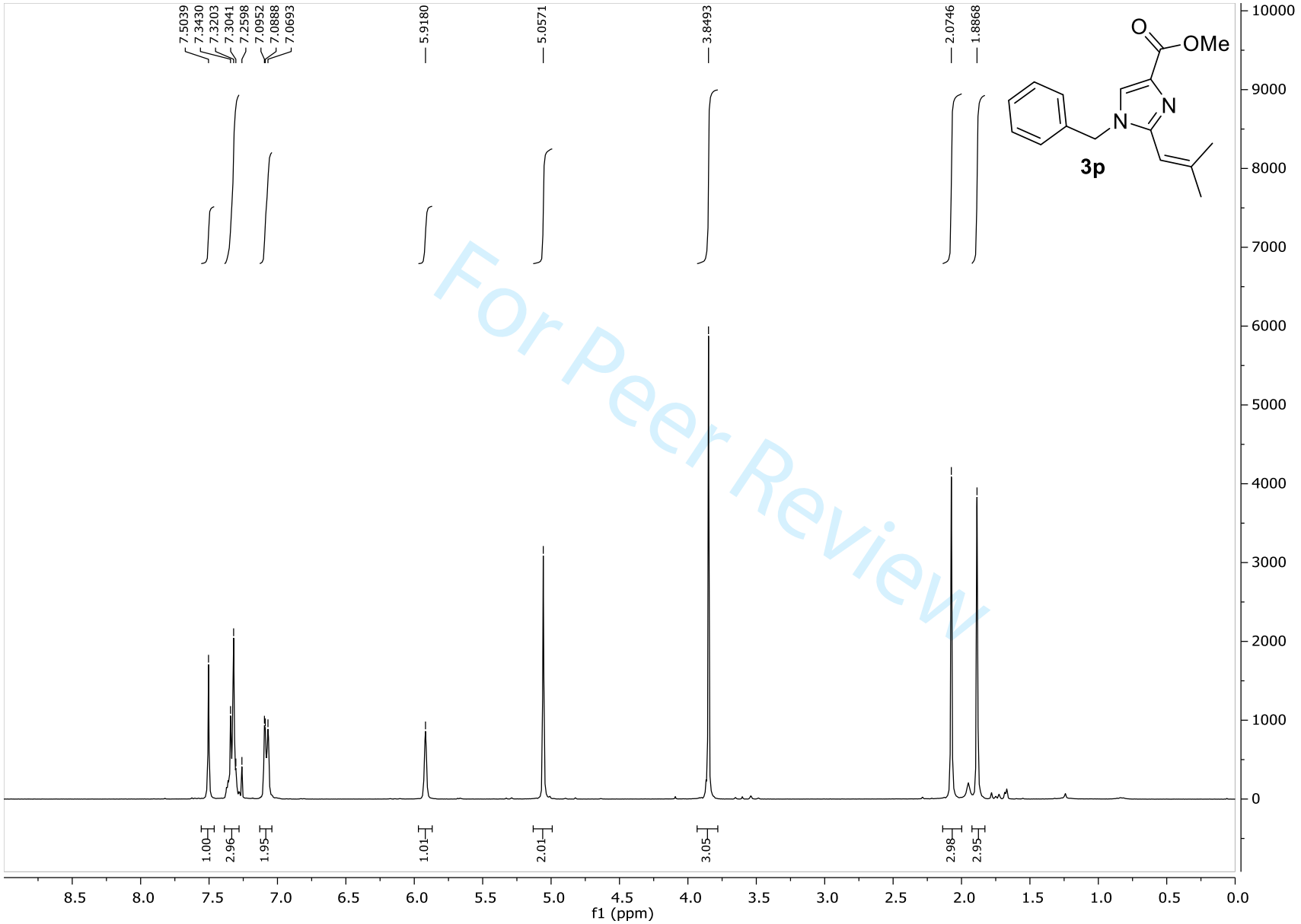


For Peer Review

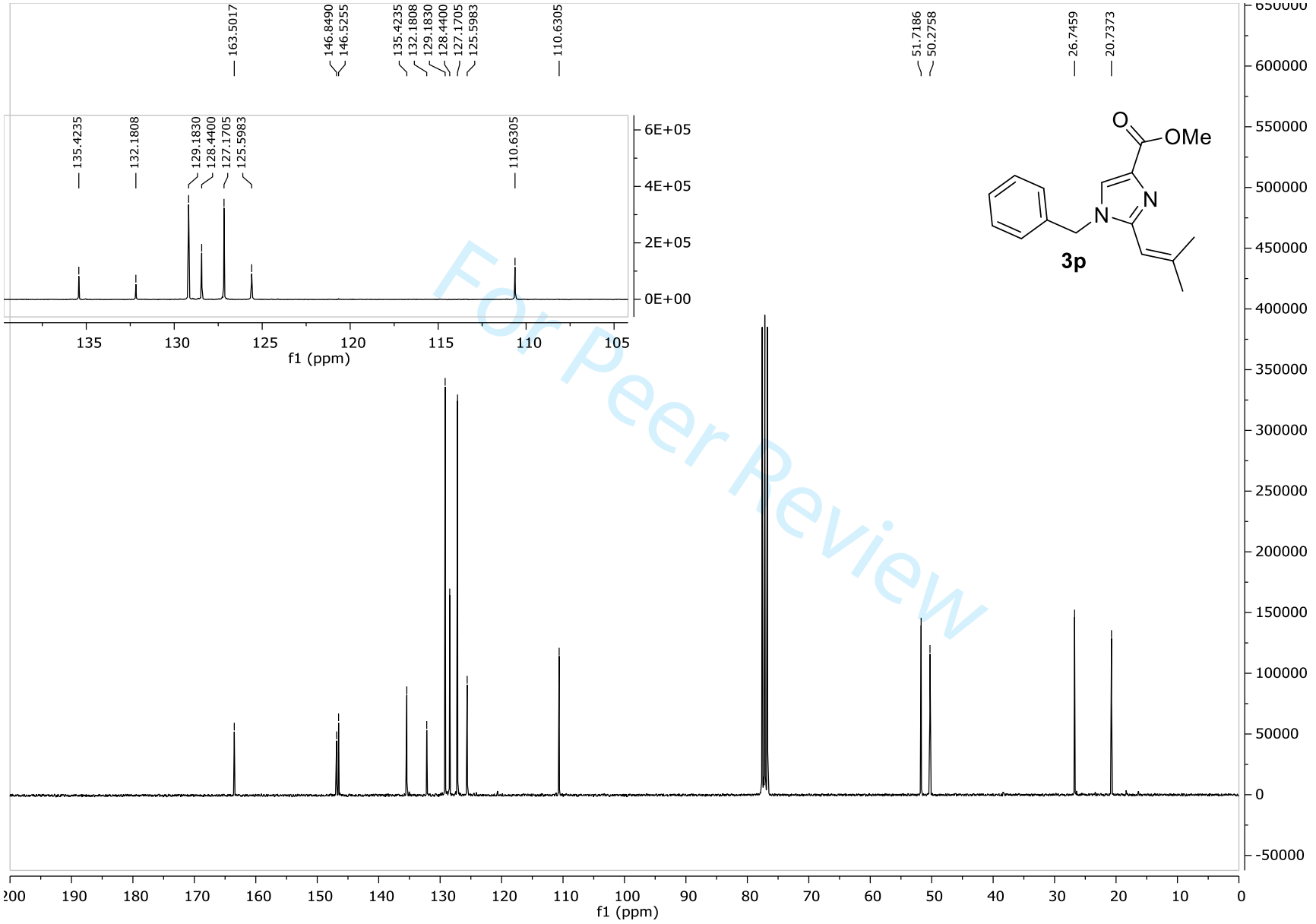
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



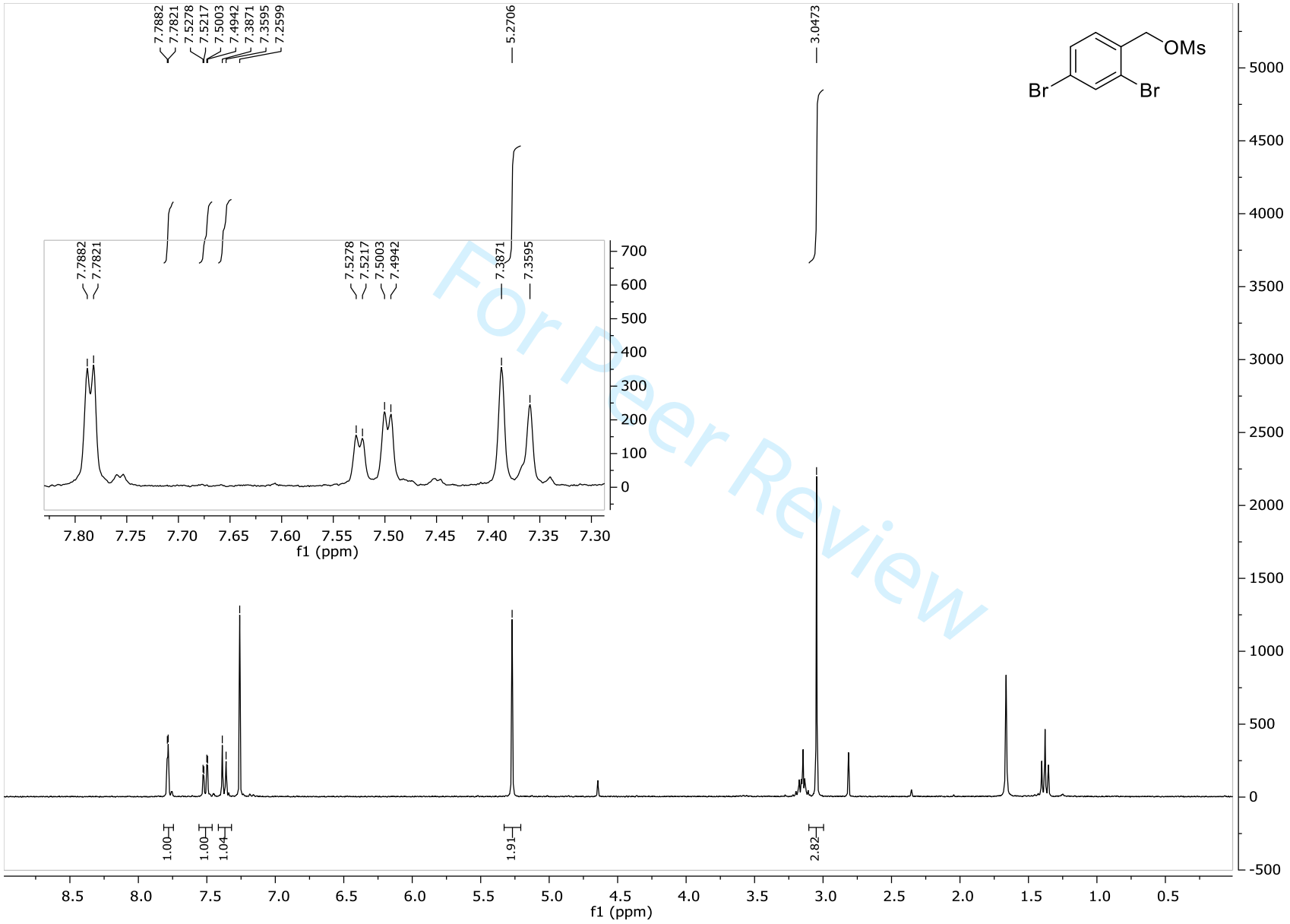
For Peer Review



For Peer Review

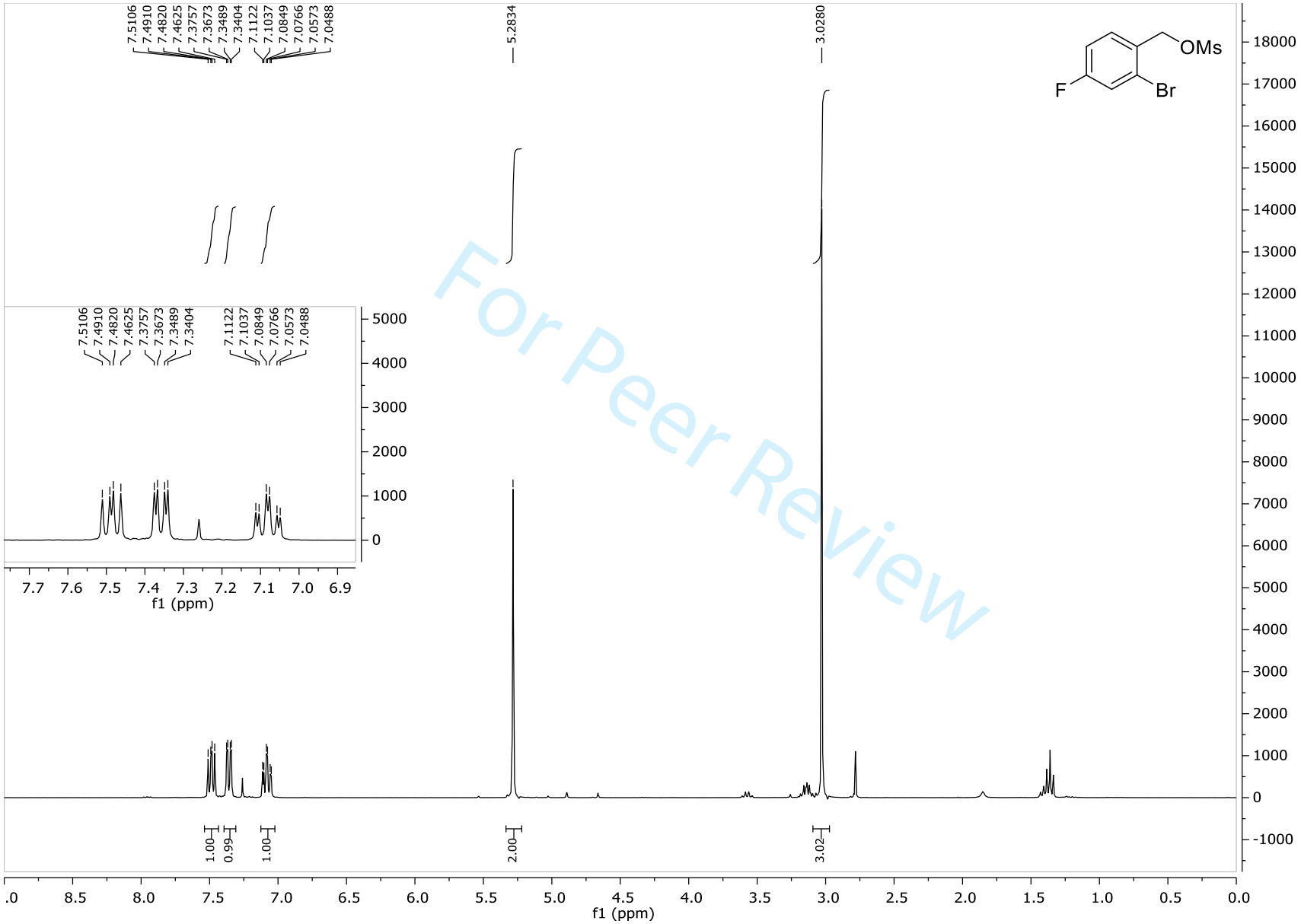


For Peer Review

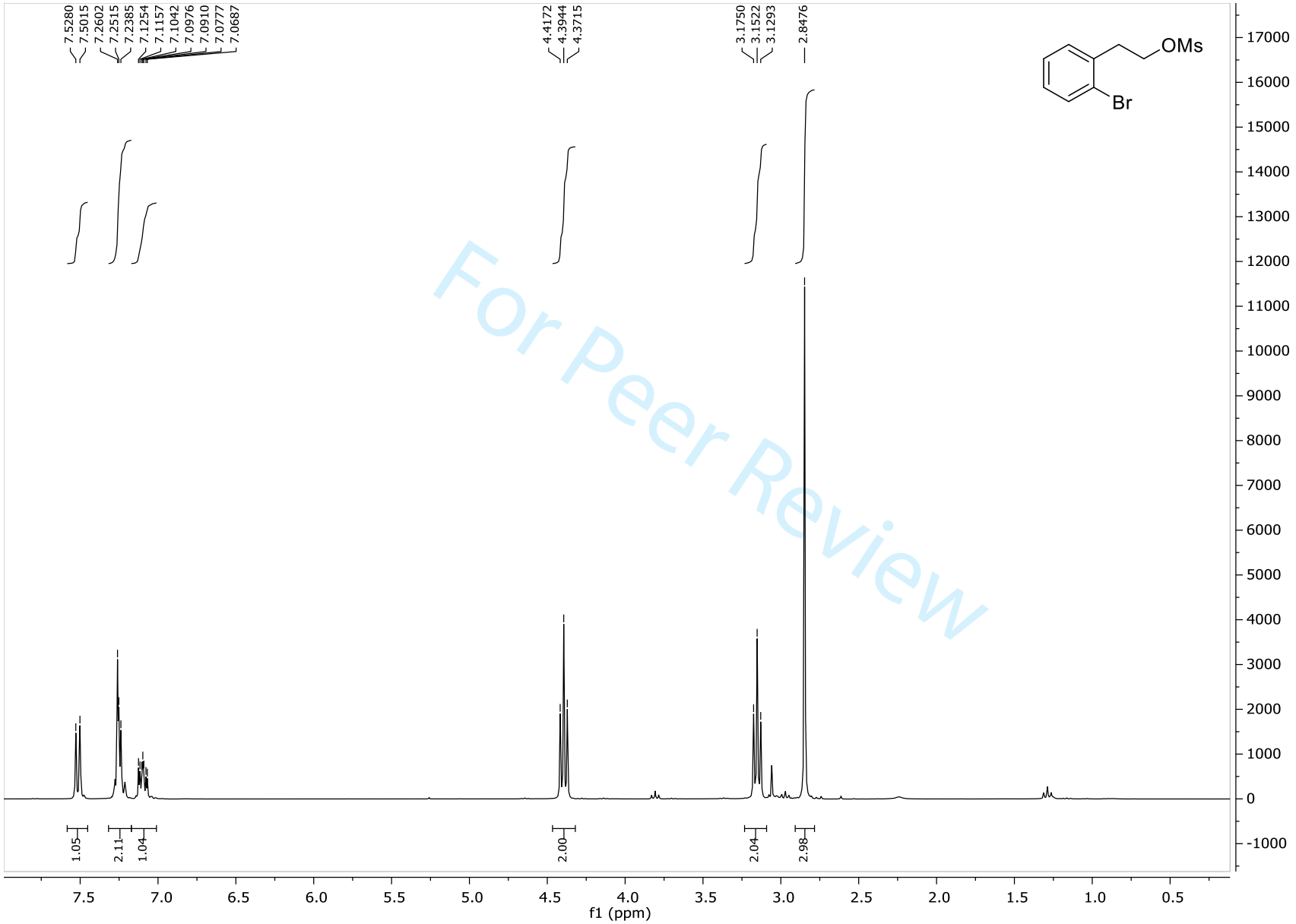


For Peer Review

Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

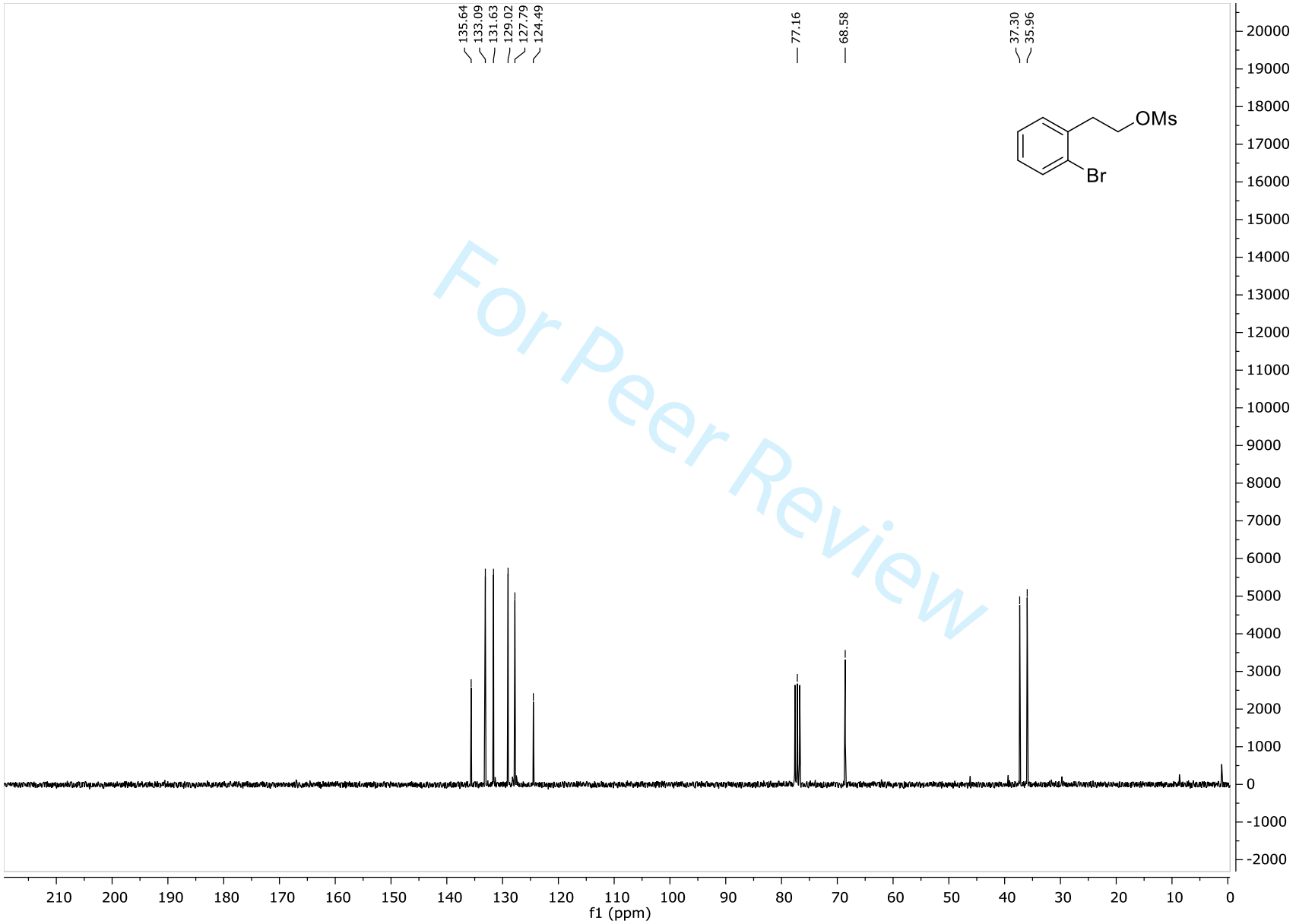


For Peer Review

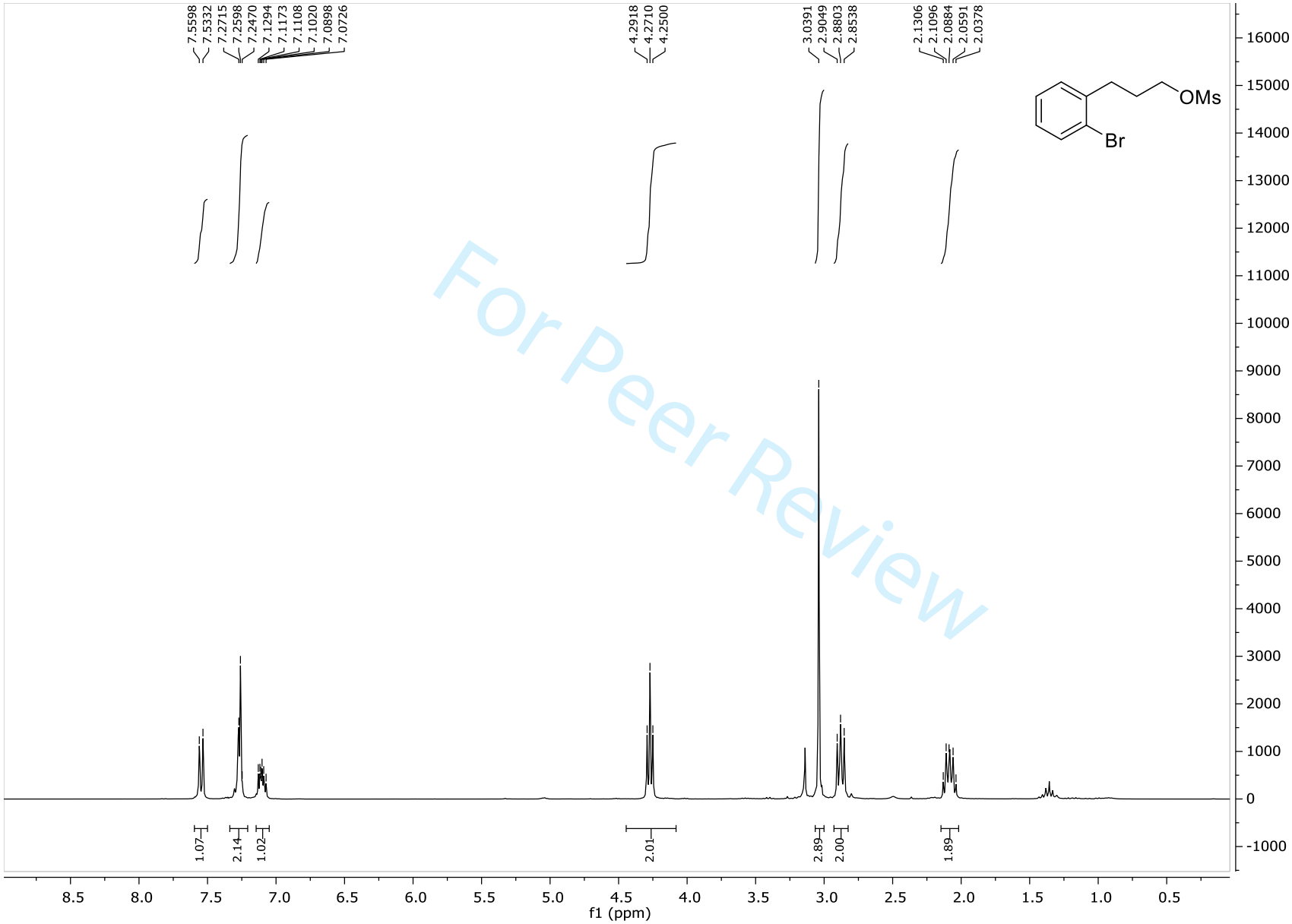


For Peer Review

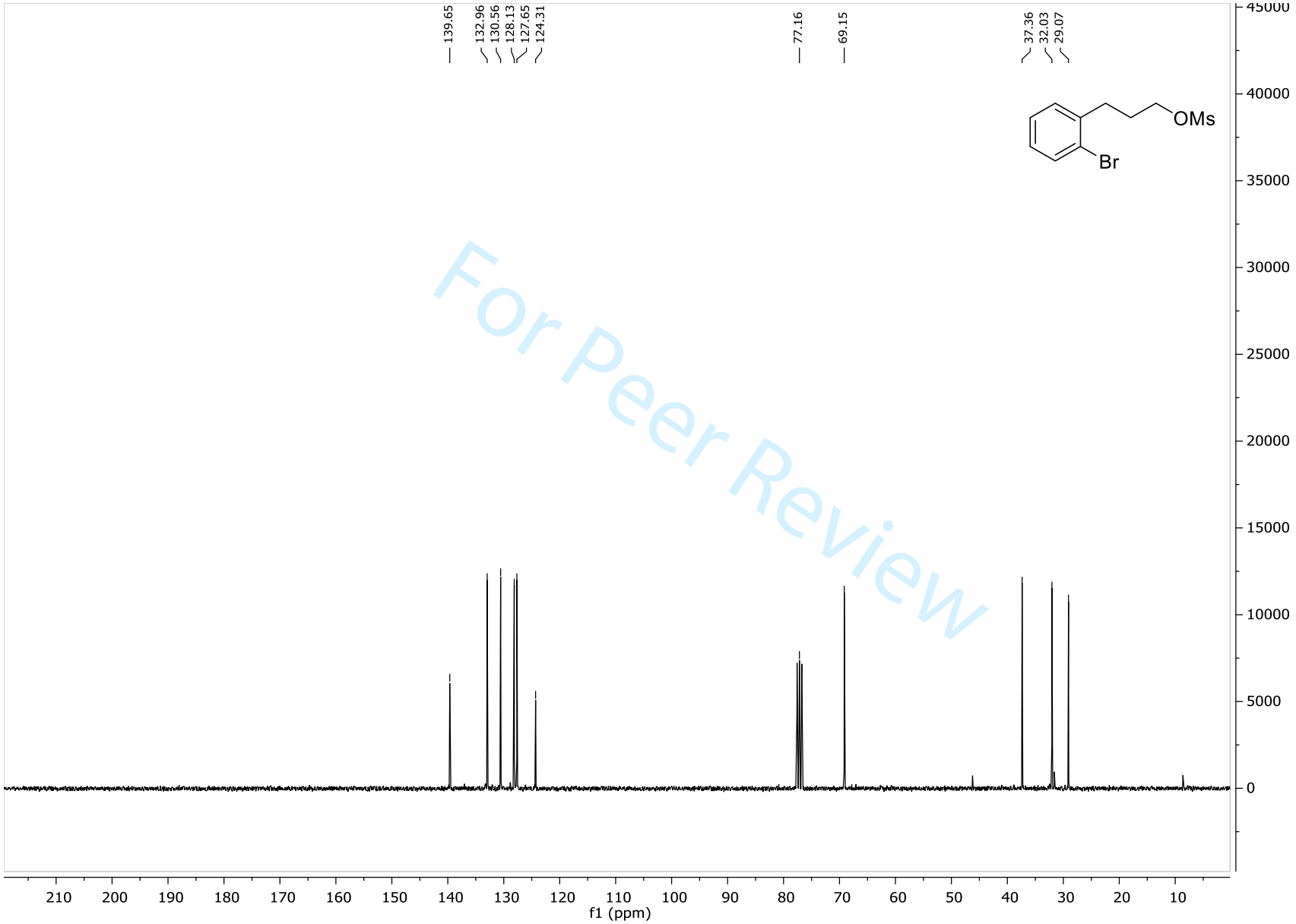
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



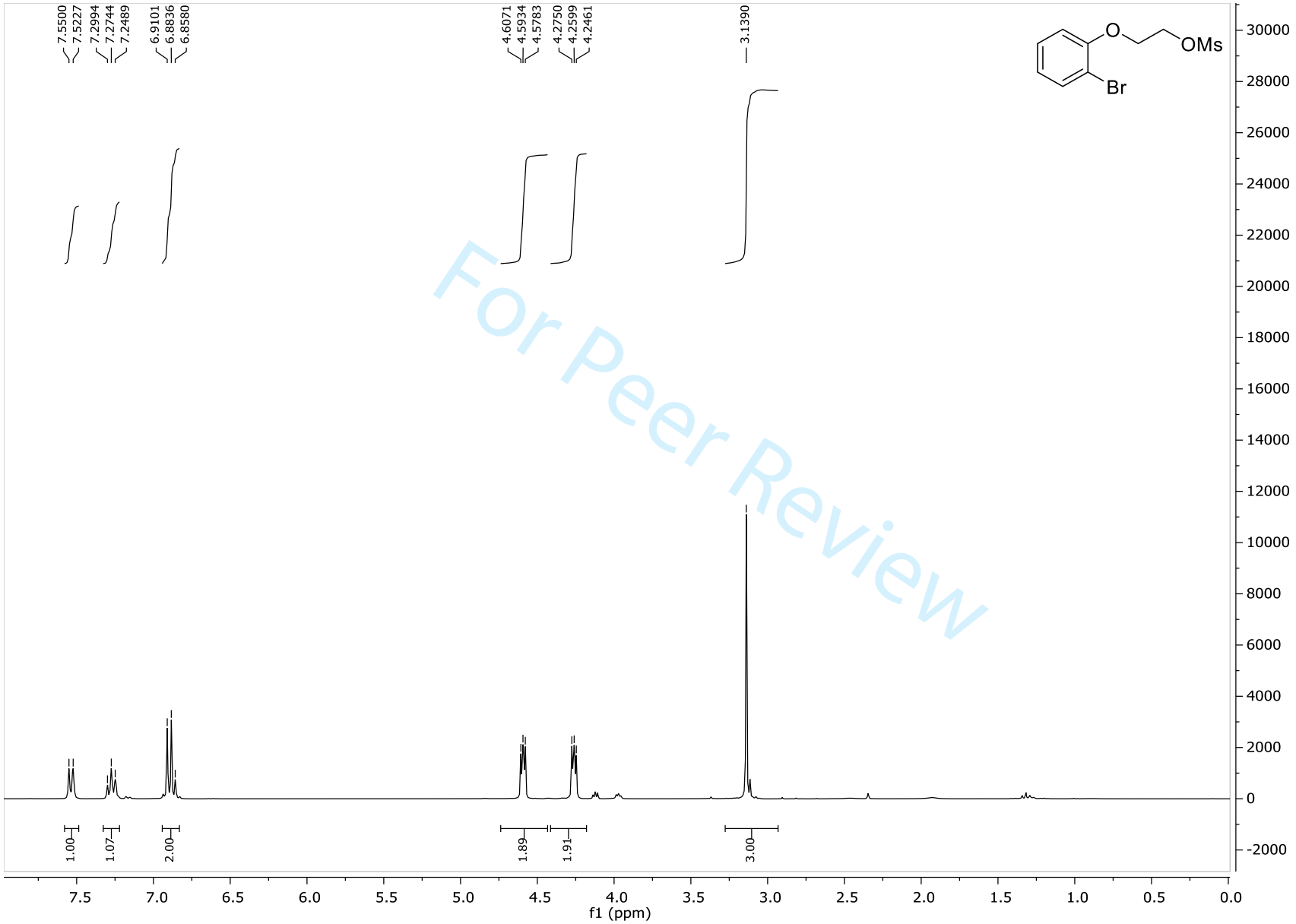
For Peer Review



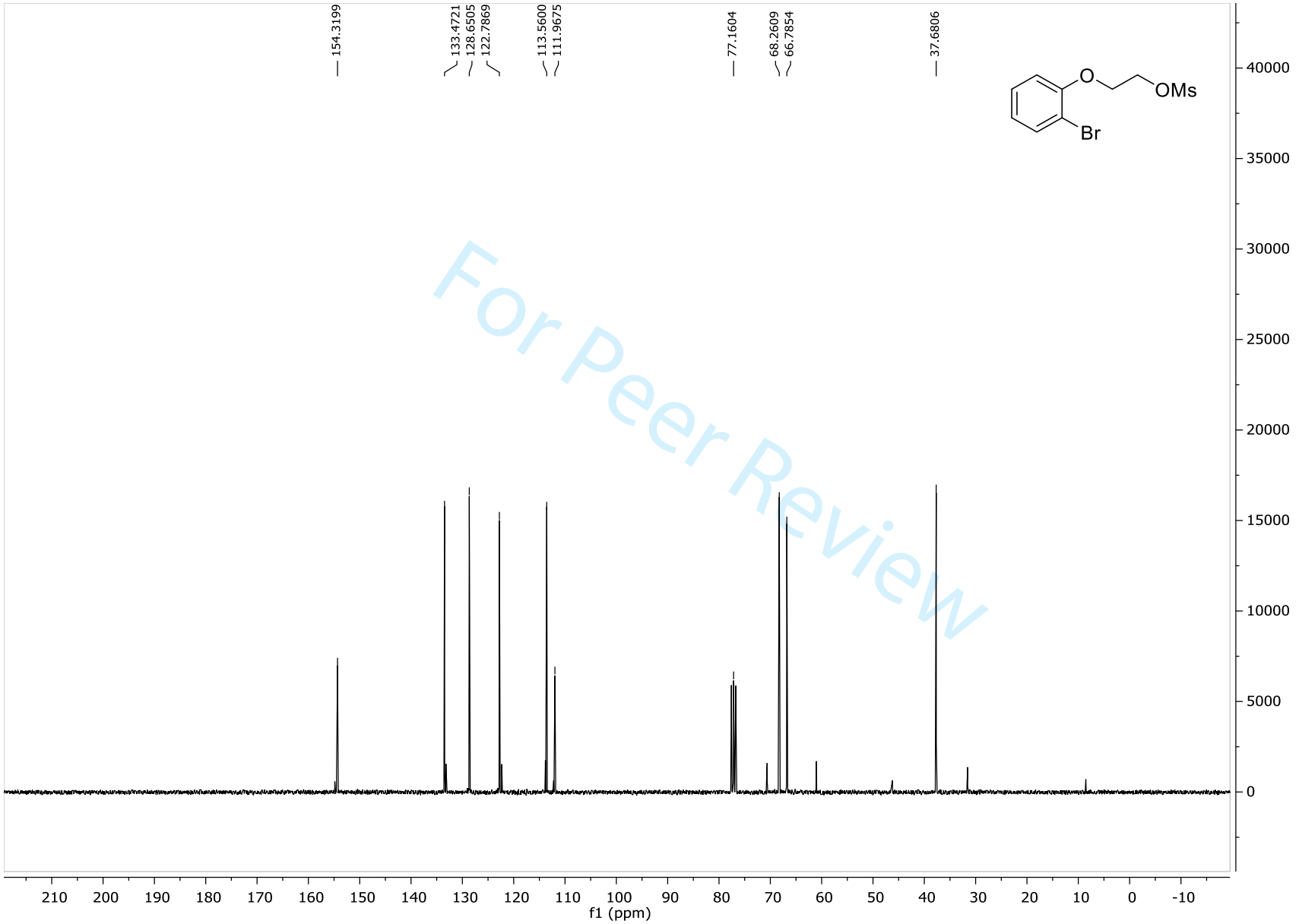
For Peer Review



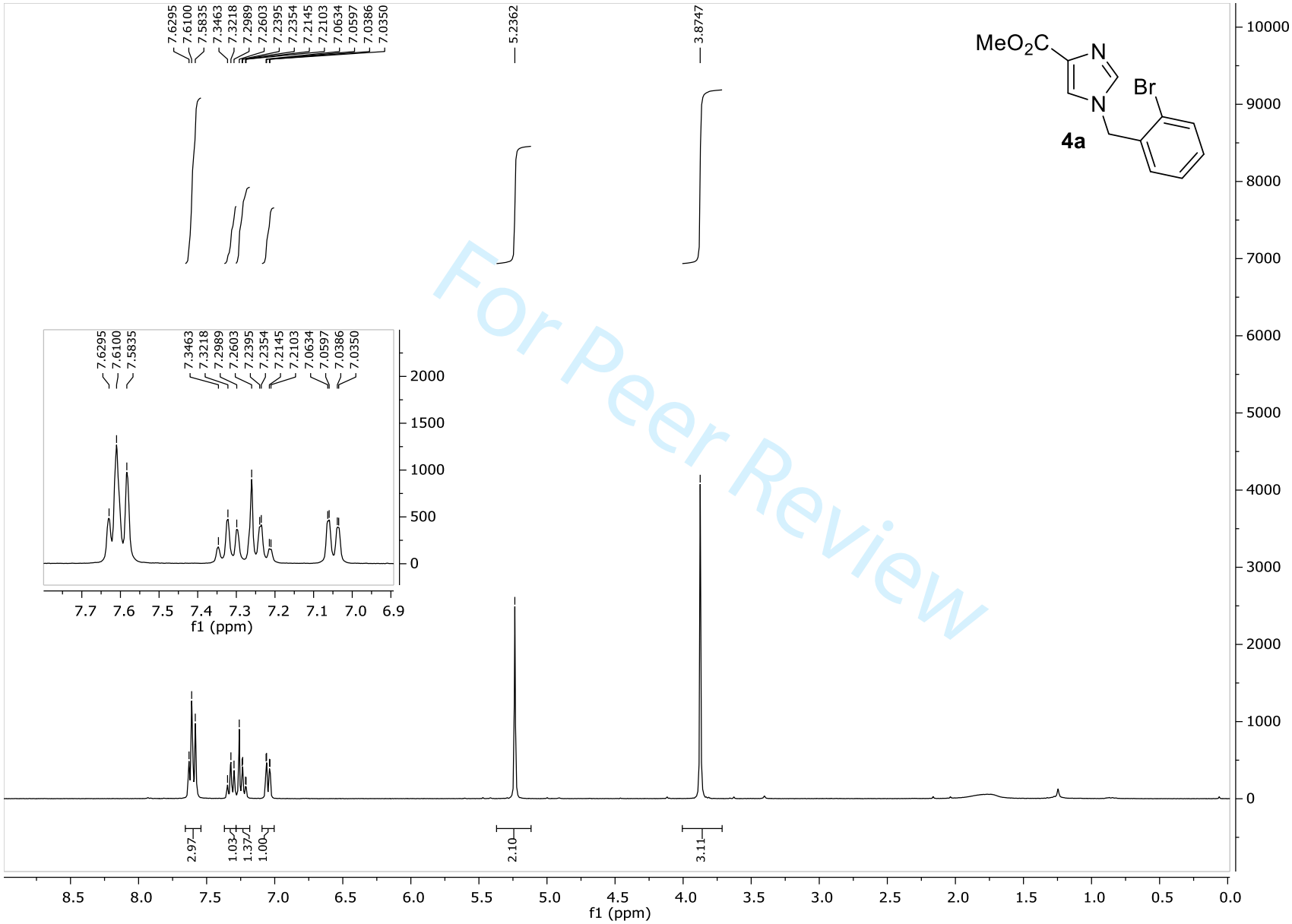
For Peer Review



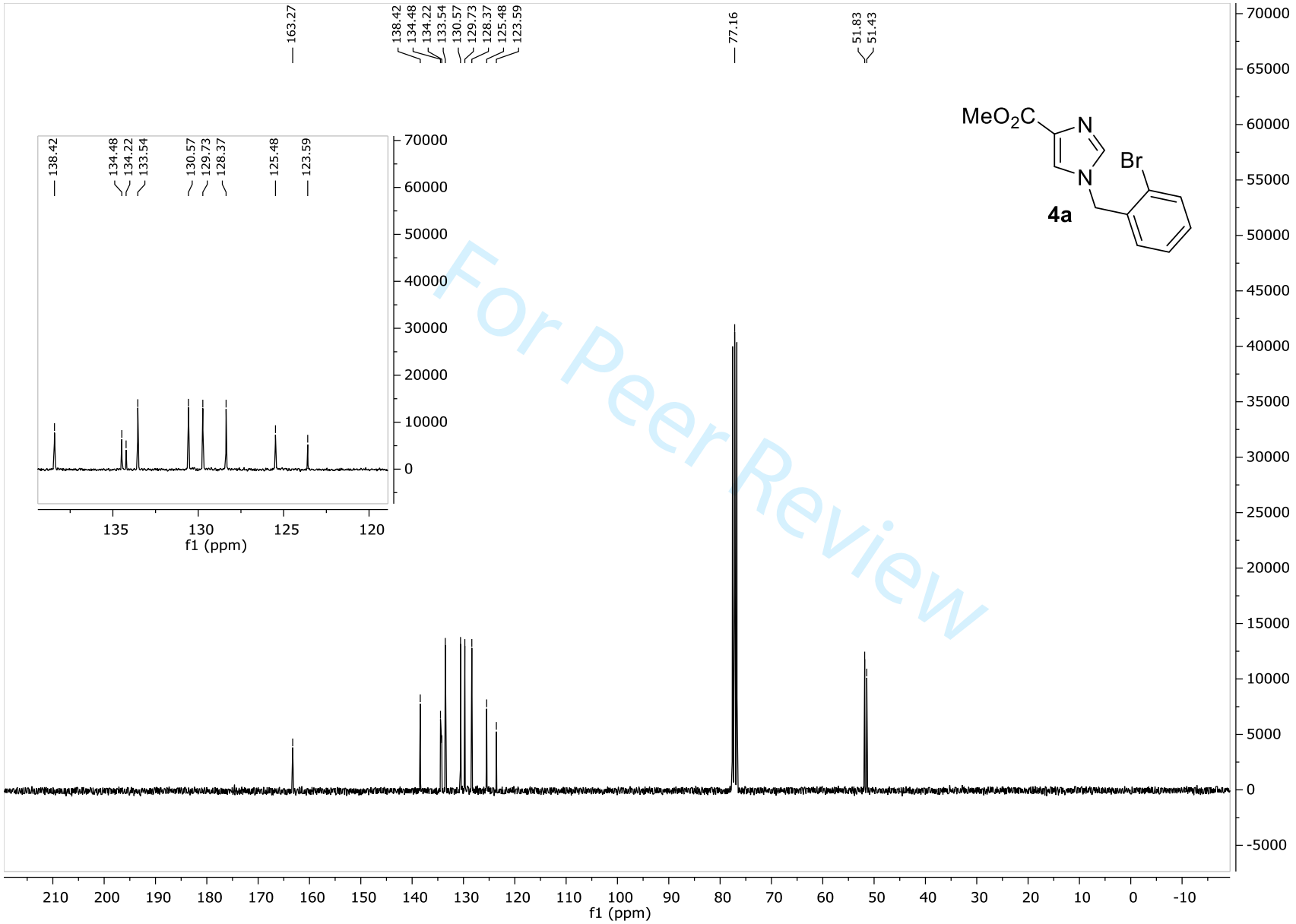
For Peer Review



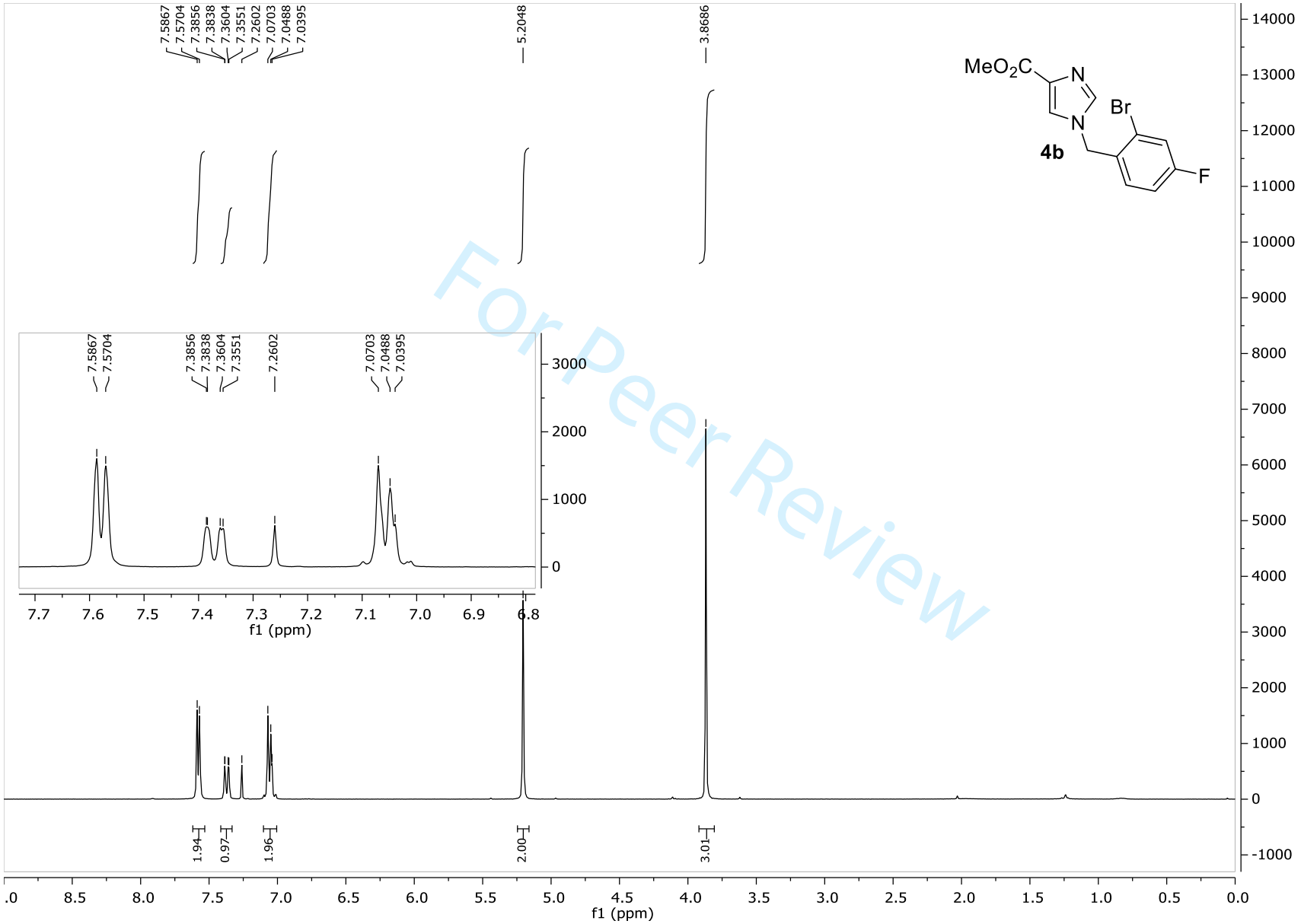
For Peer Review



For Peer Review

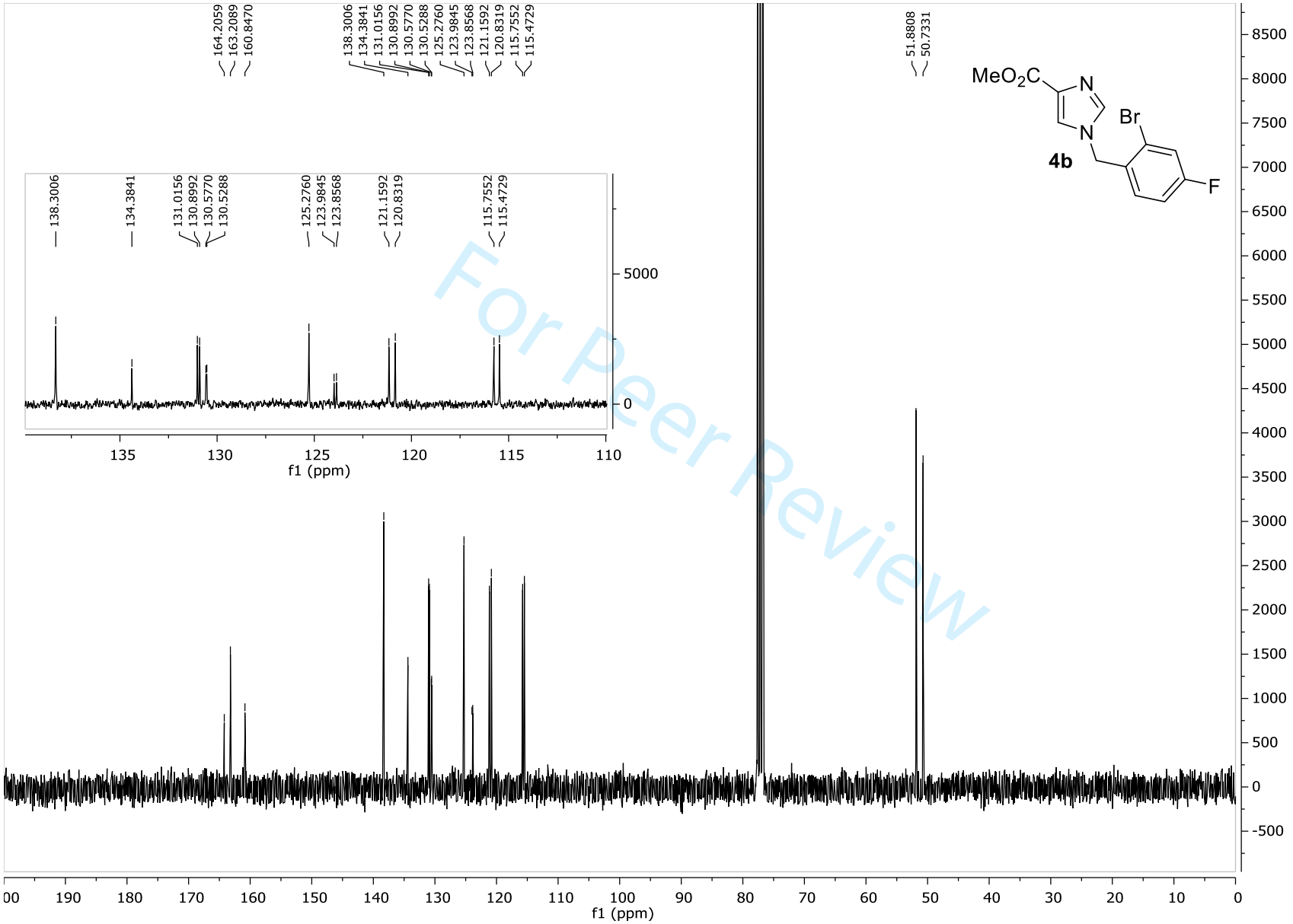


For Peer Review

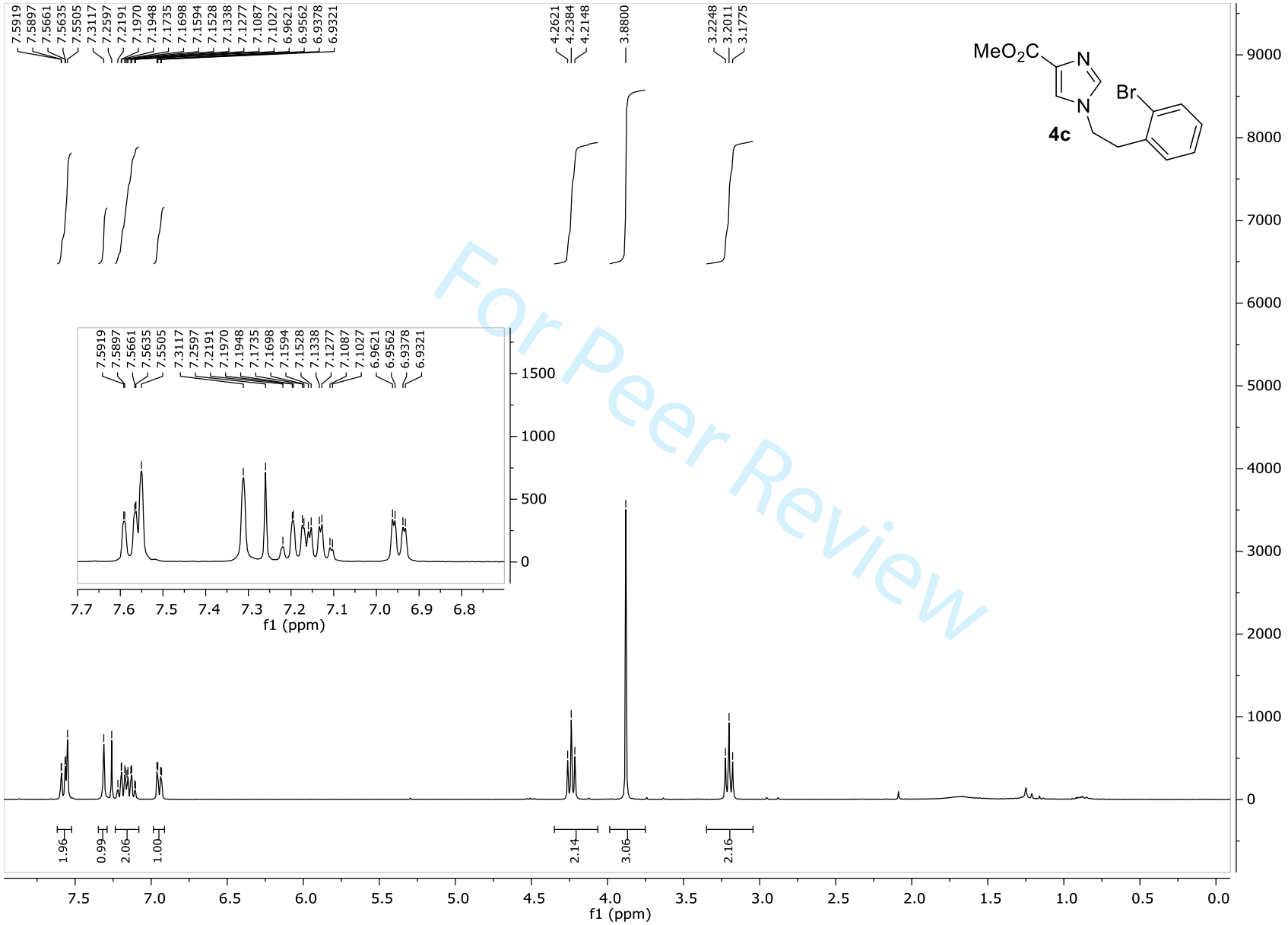


For Peer Review

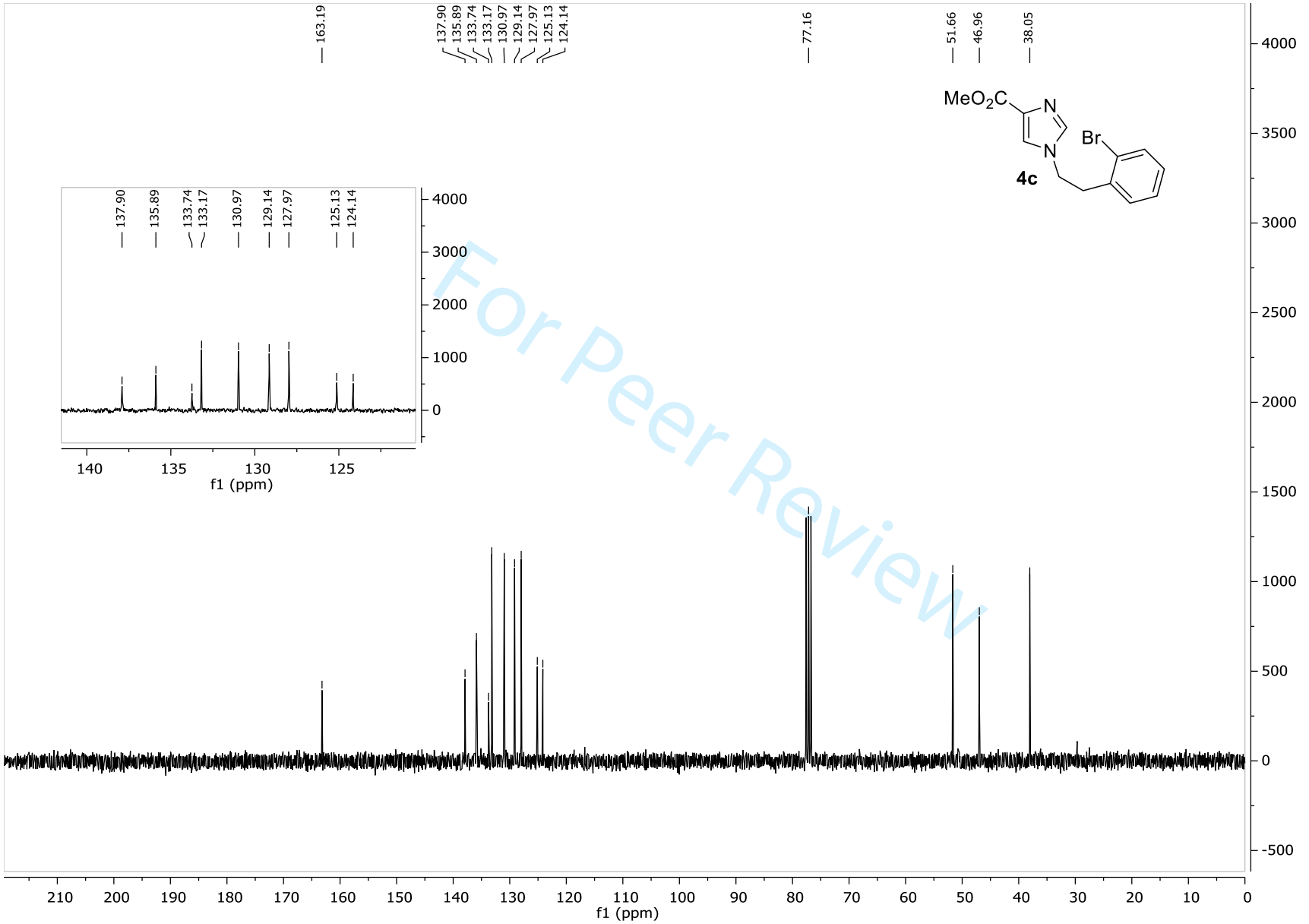
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



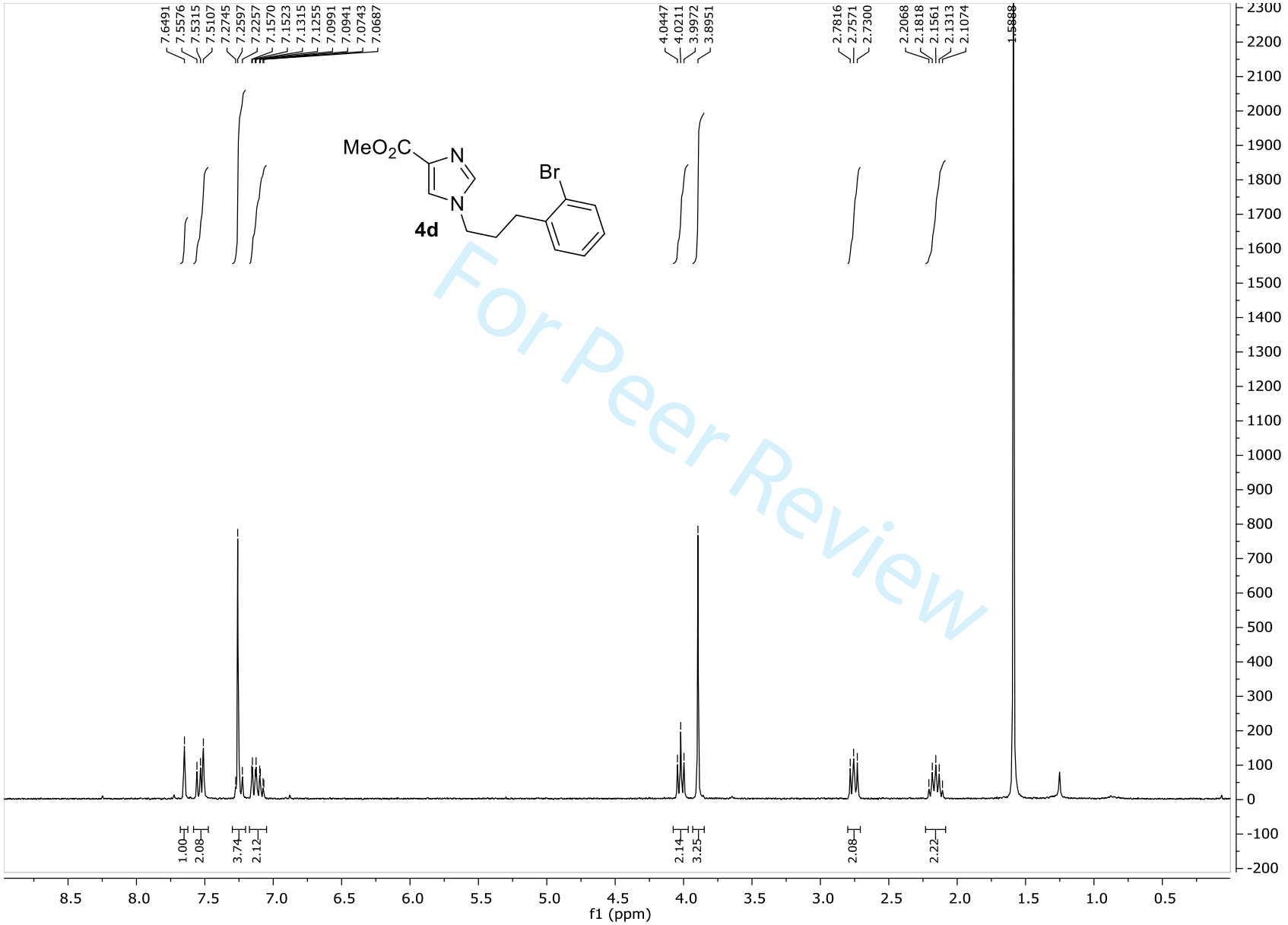
For Peer Review



For Peer Review

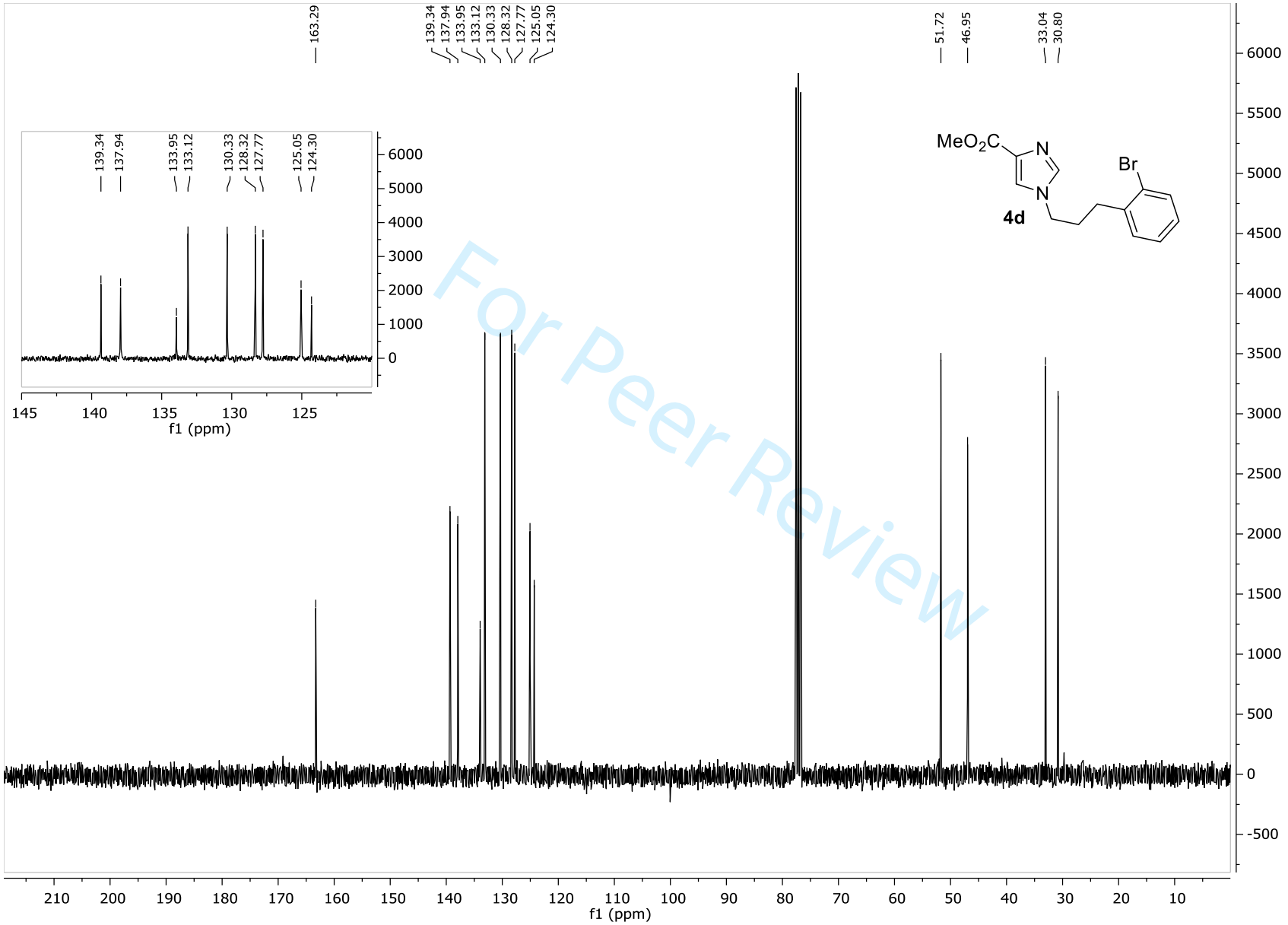


For Peer Review

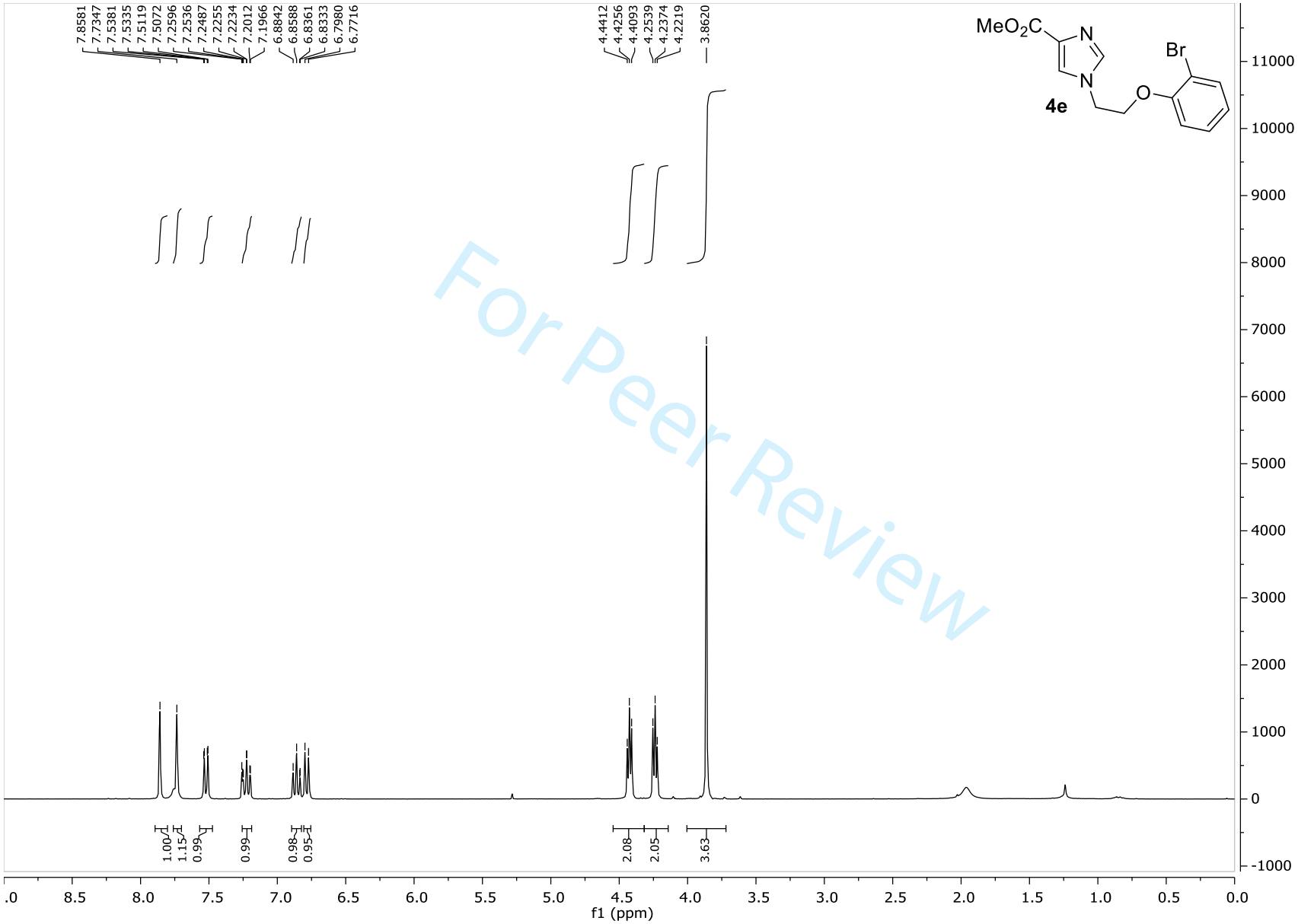


For Peer Review

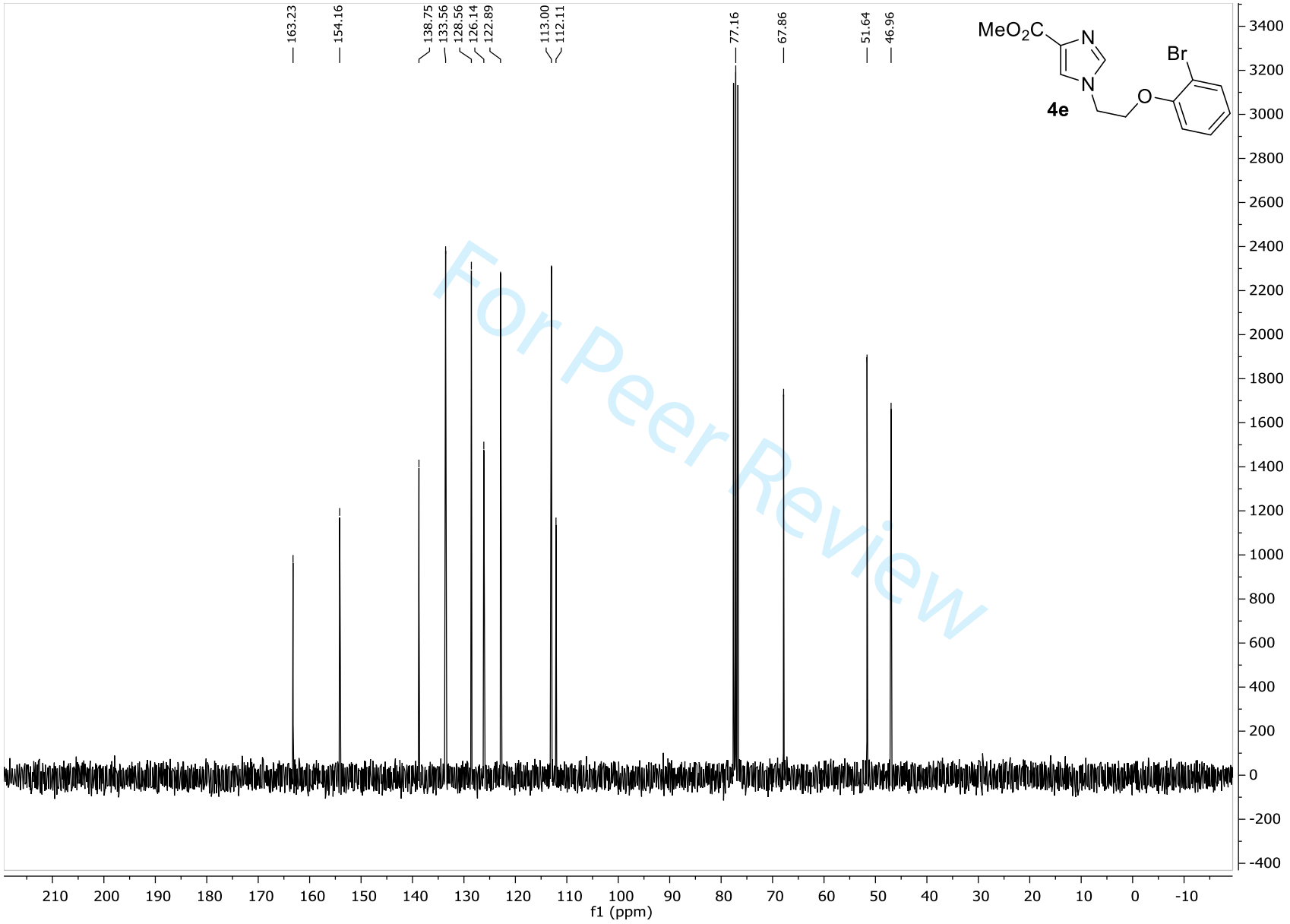
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



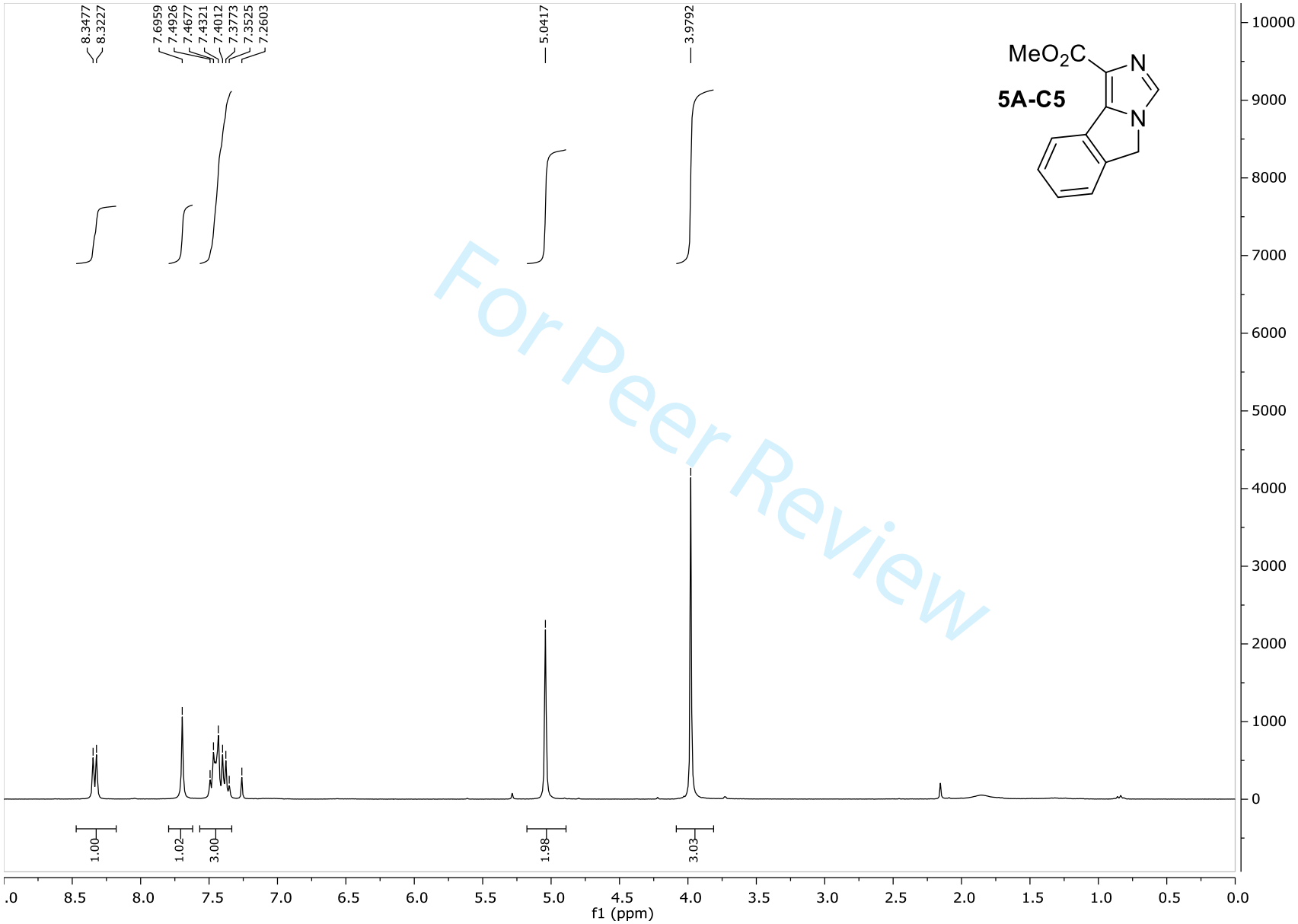
For Peer Review



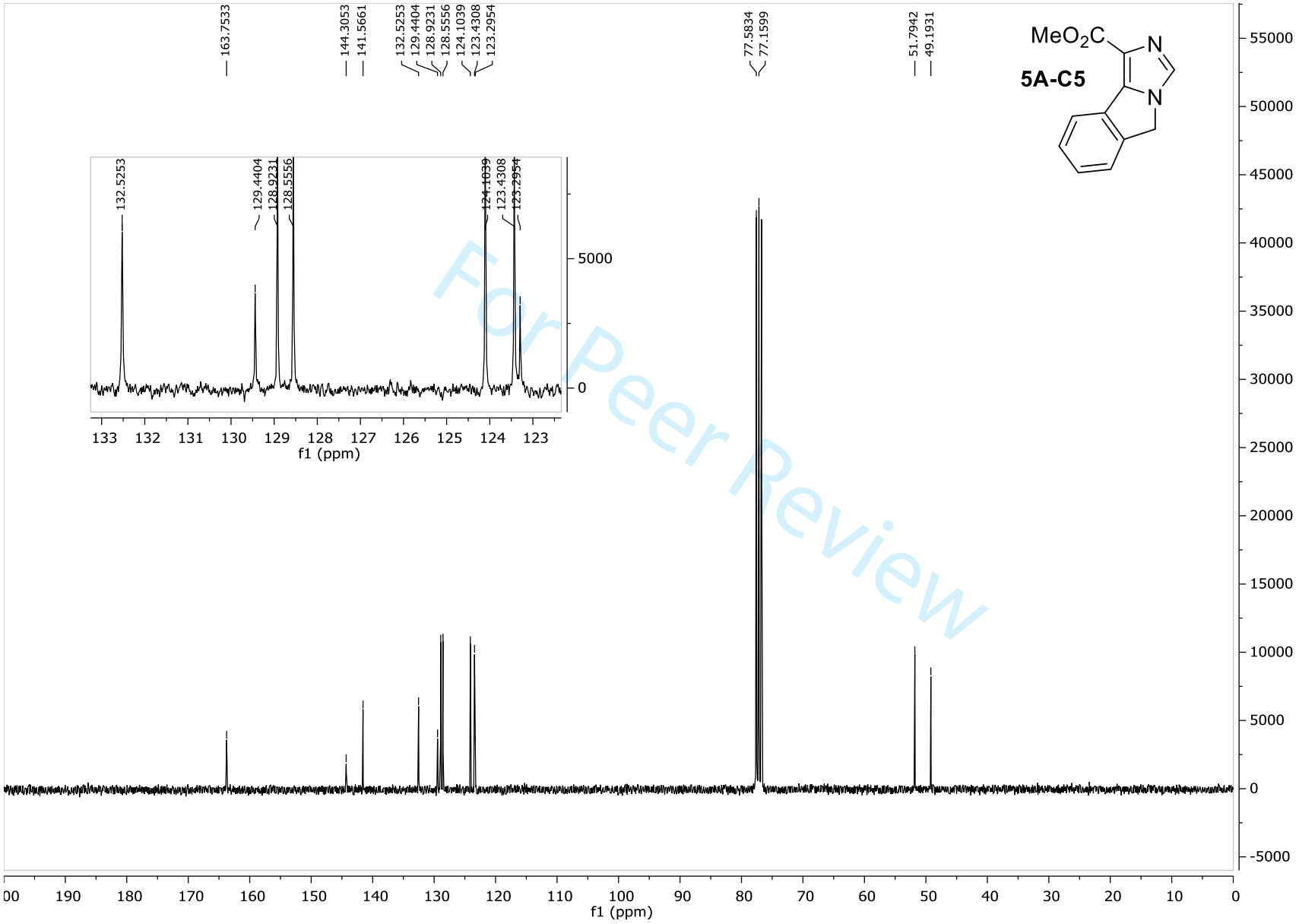
For Peer Review



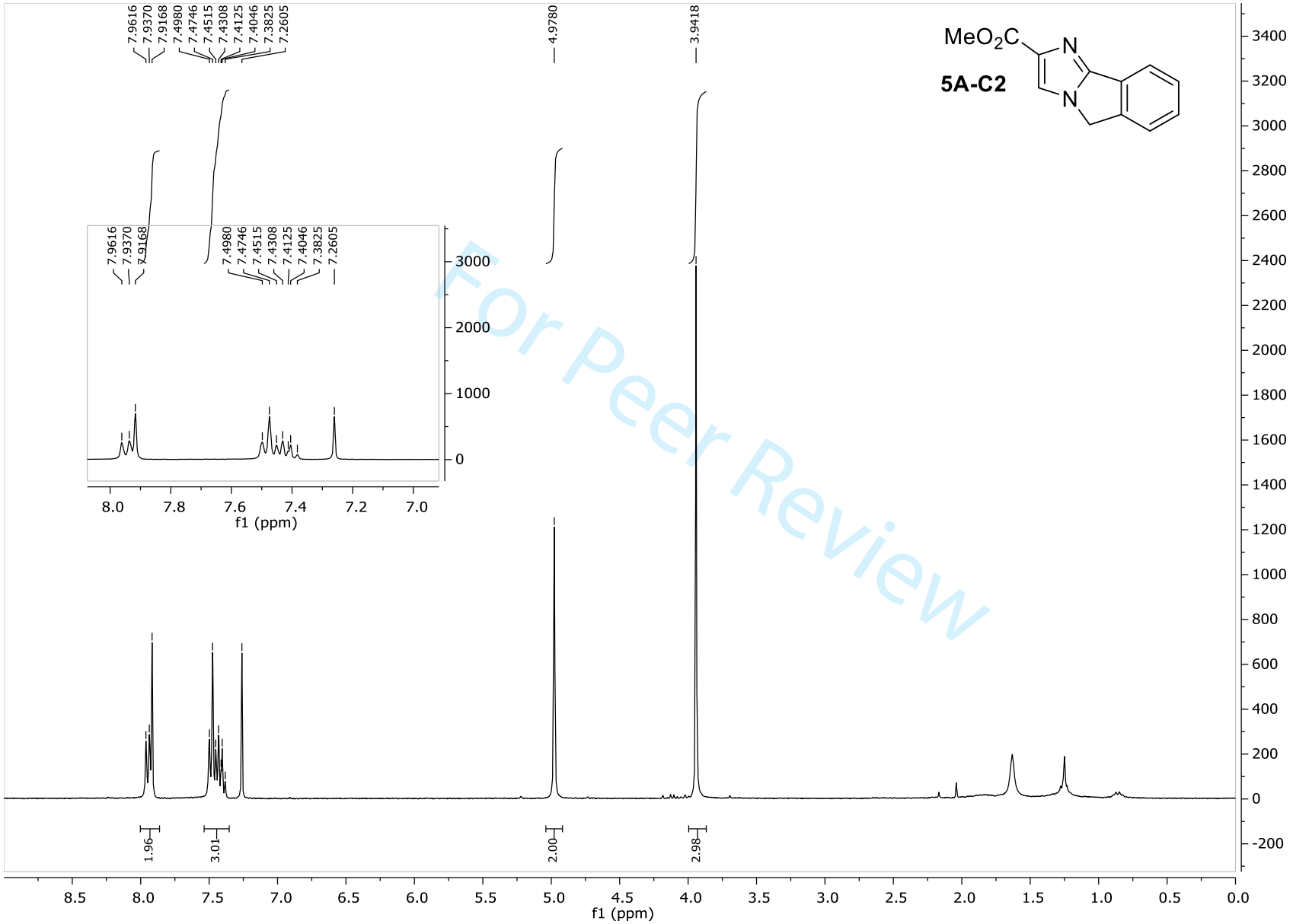
For Peer Review



For Peer Review

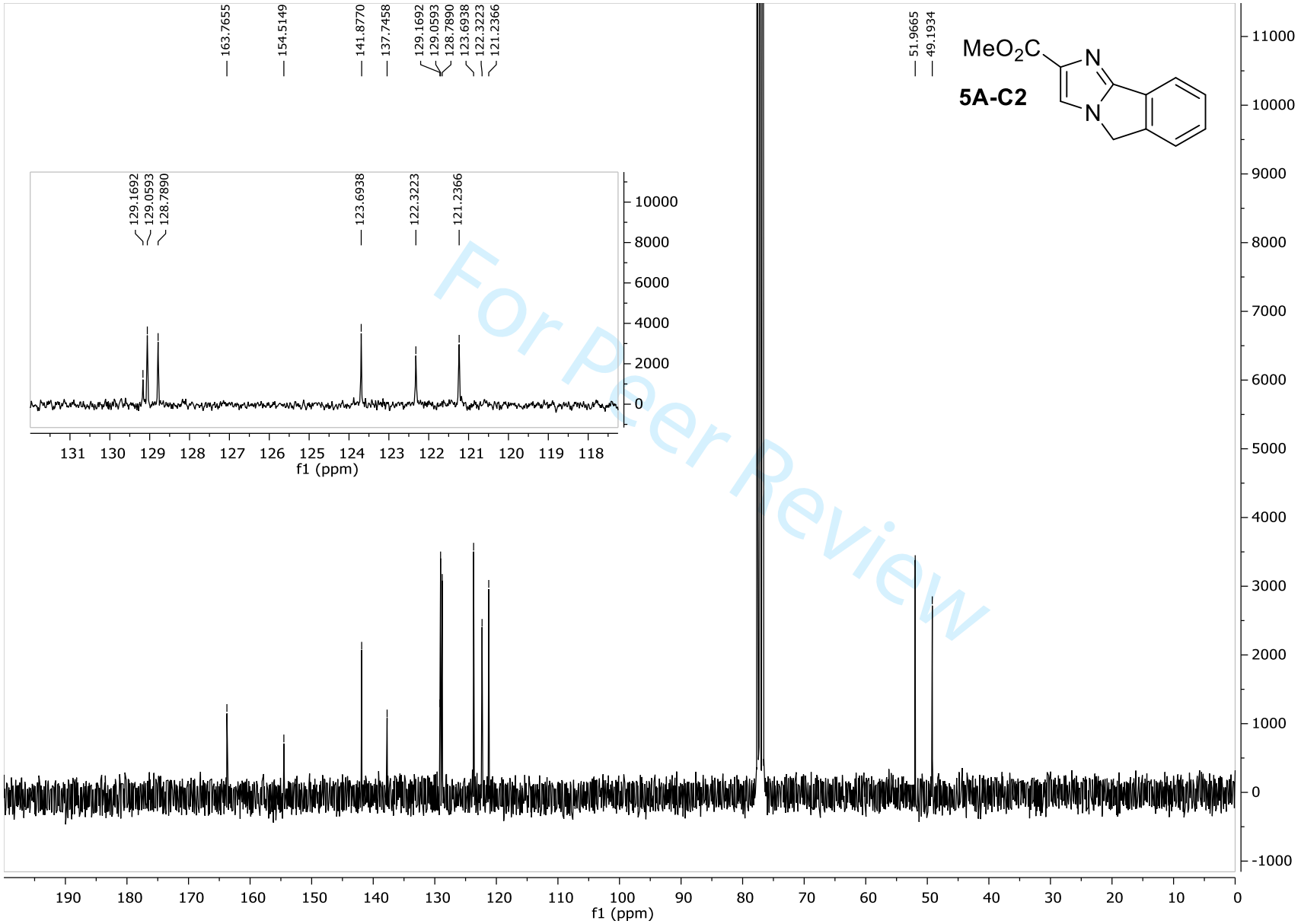


For Peer Review

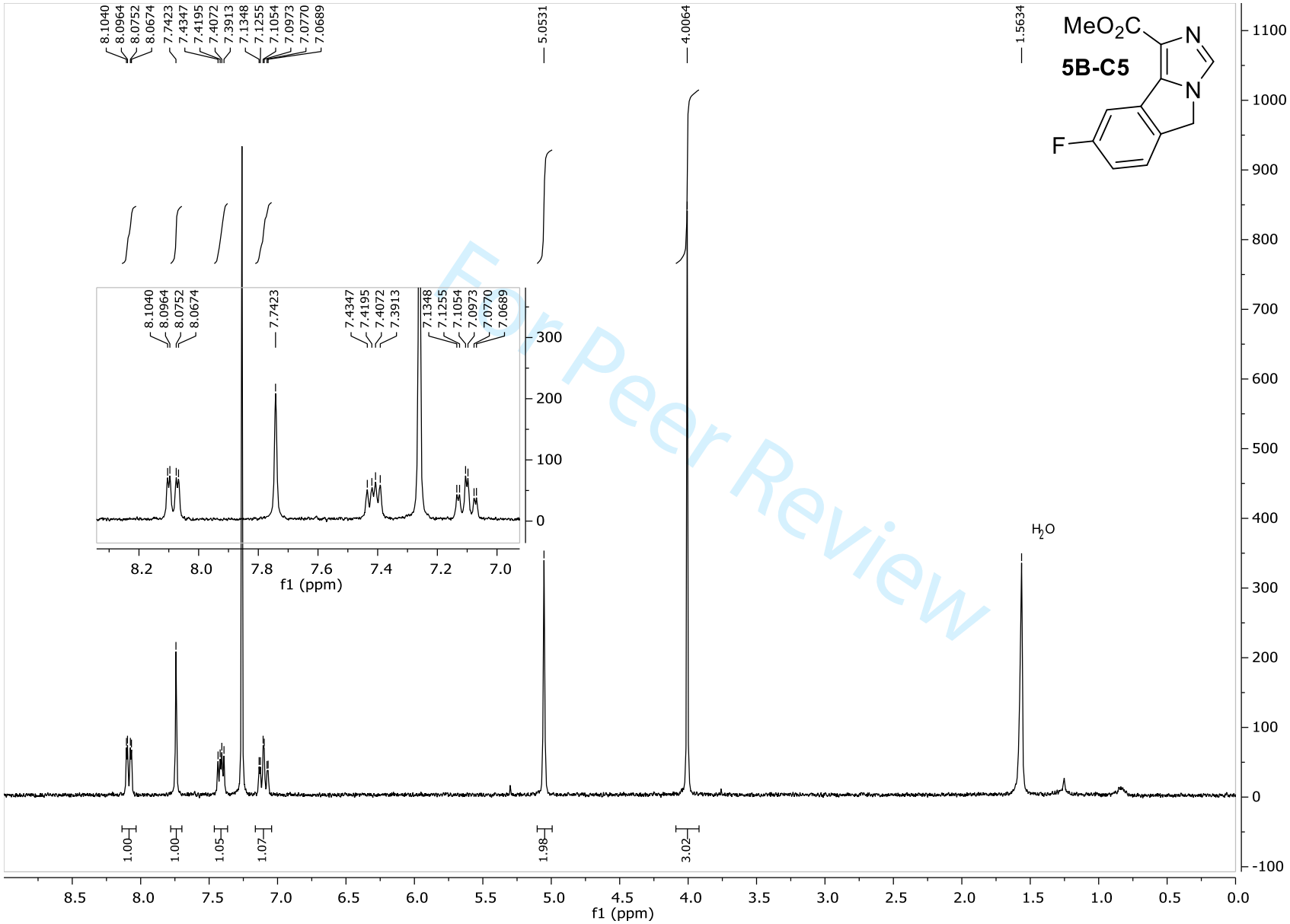


For Peer Review

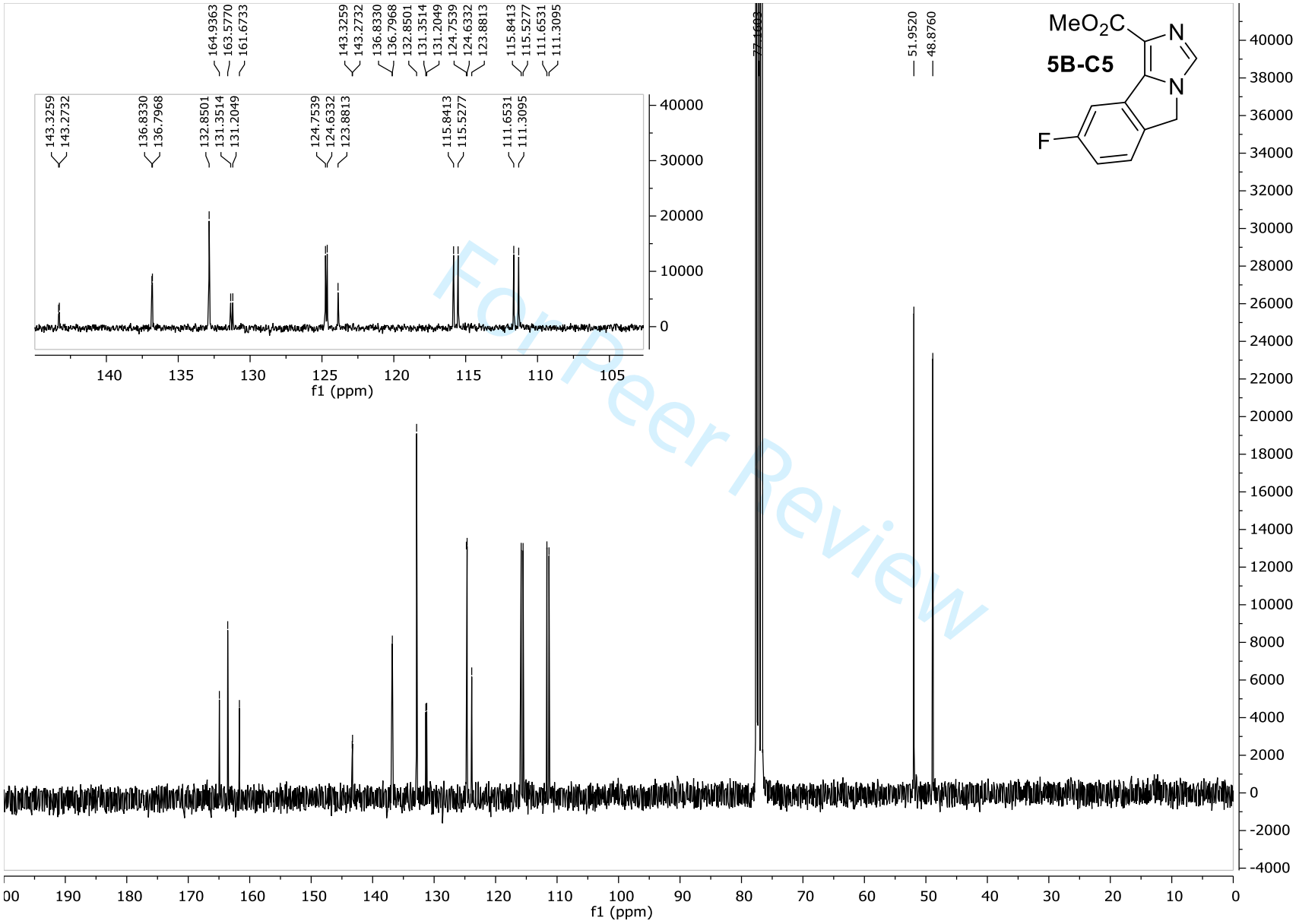
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



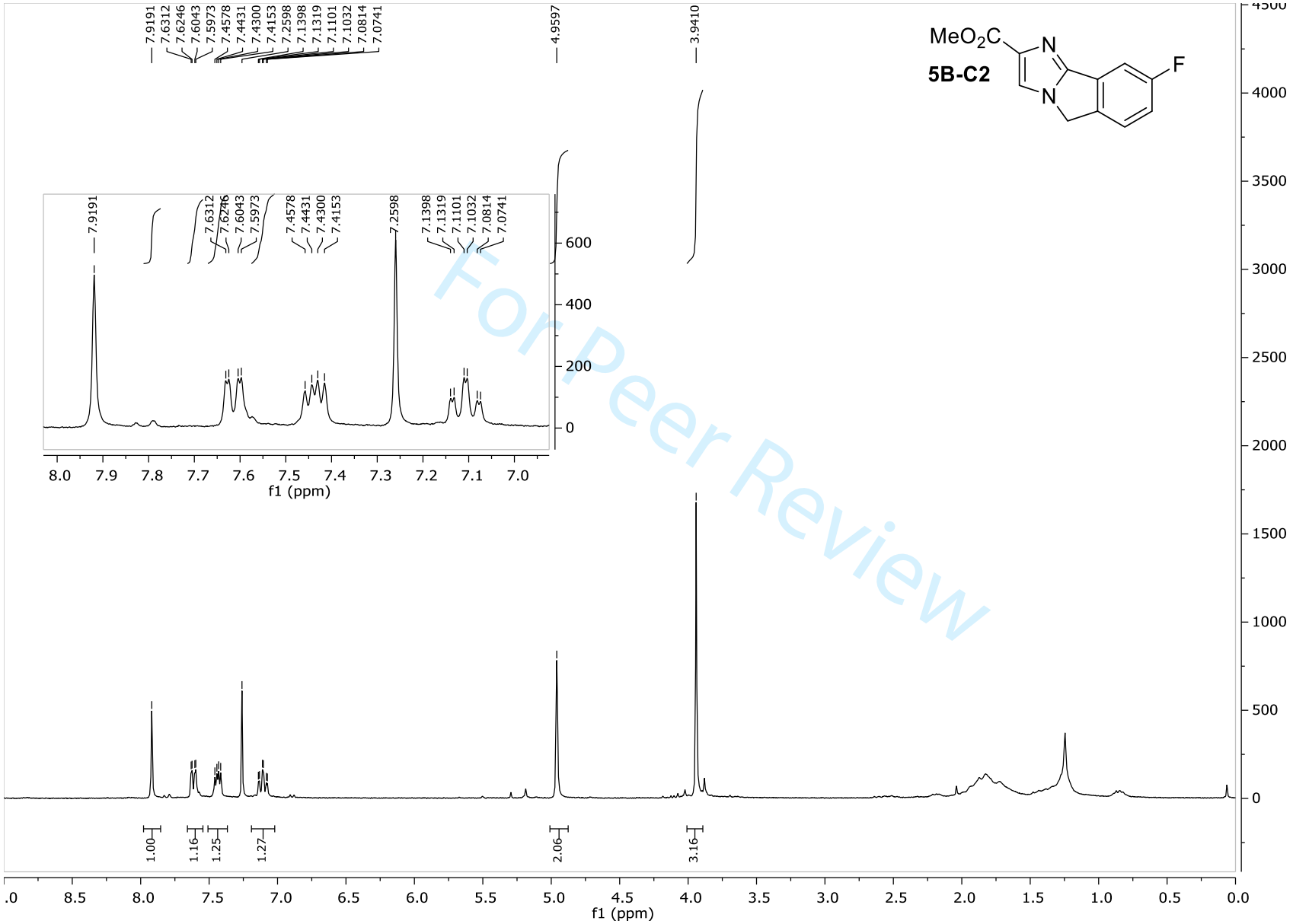
For Peer Review



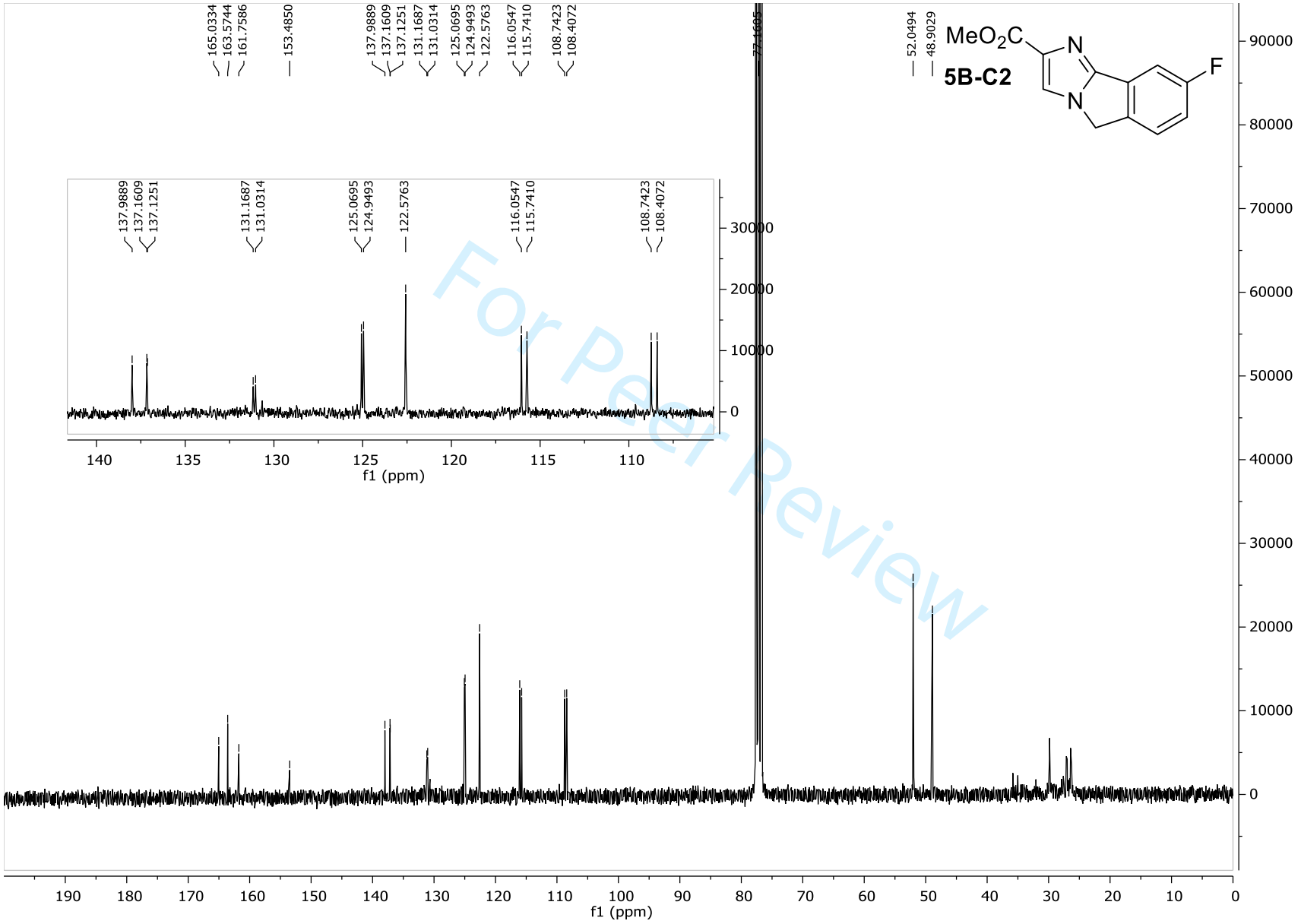
For Peer Review



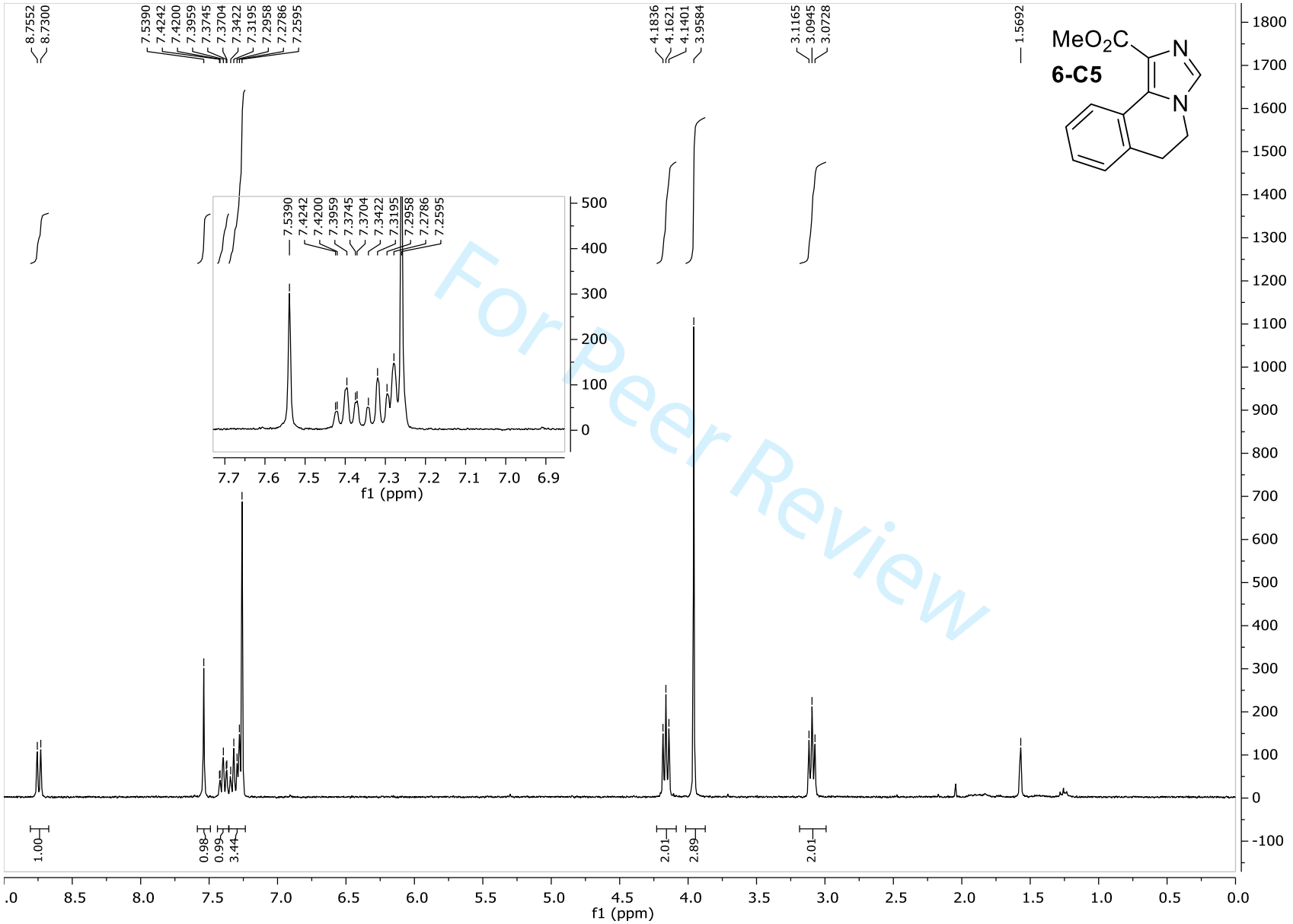
For Peer Review



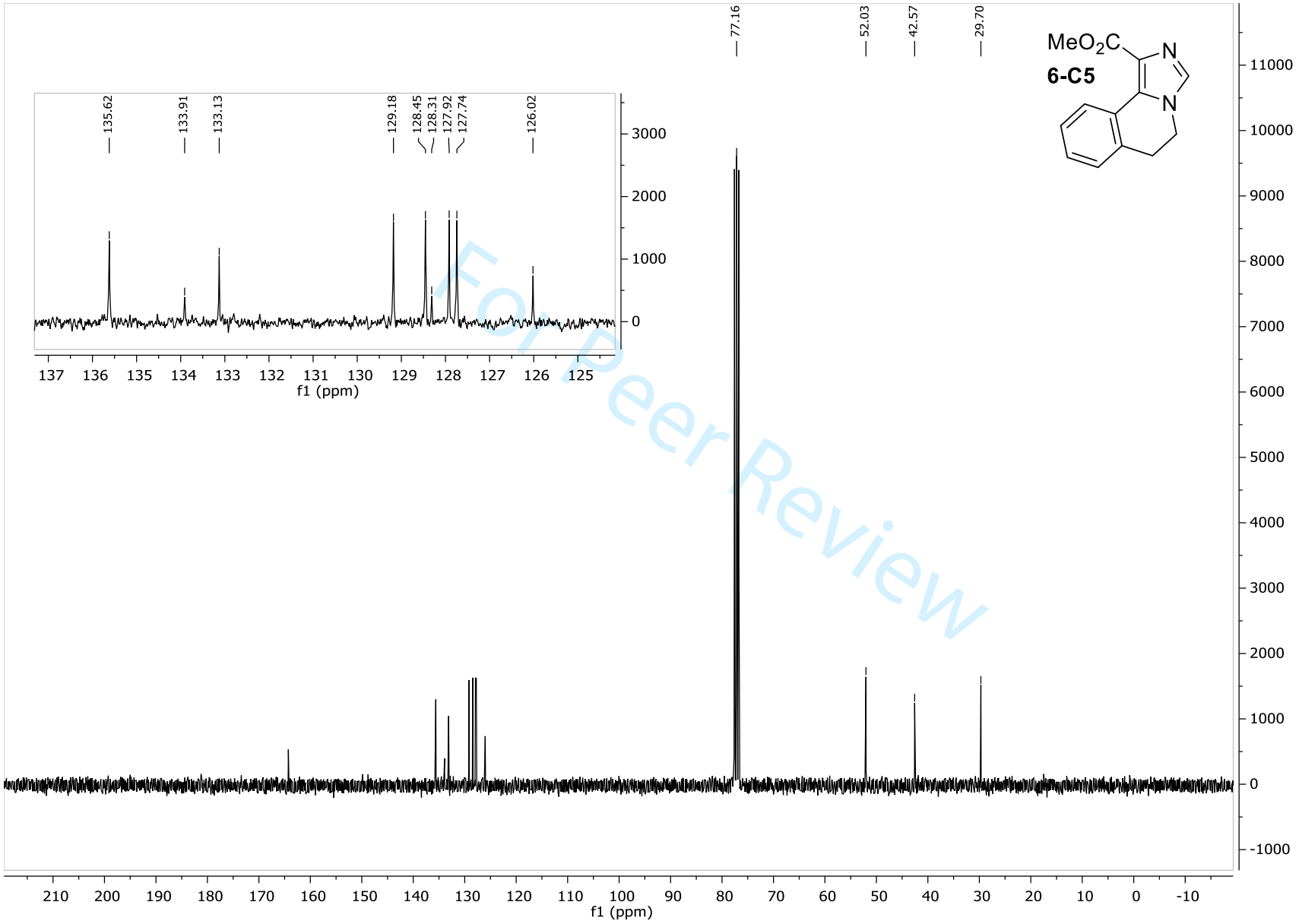
For Peer Review



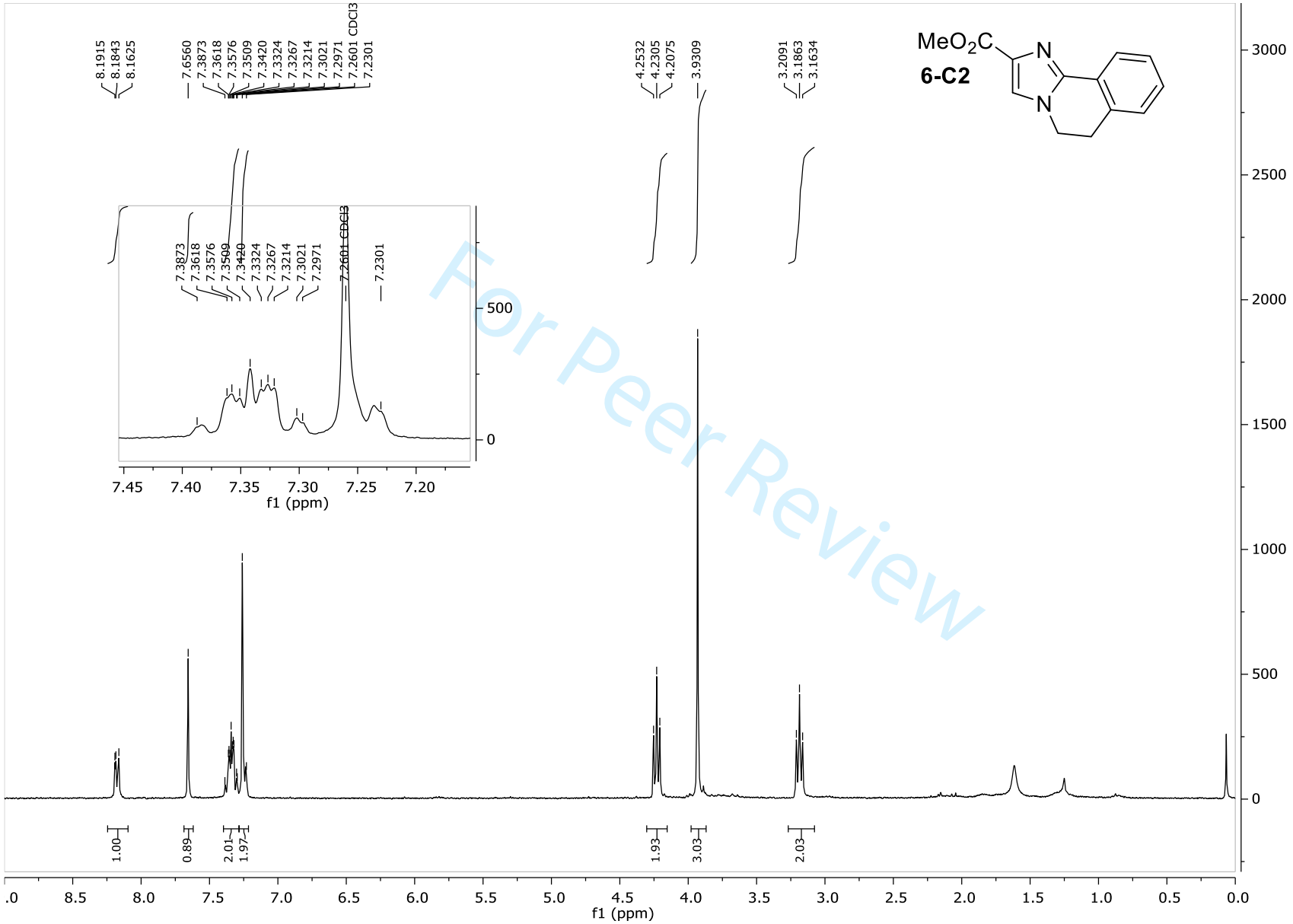
For Peer Review



For Peer Review

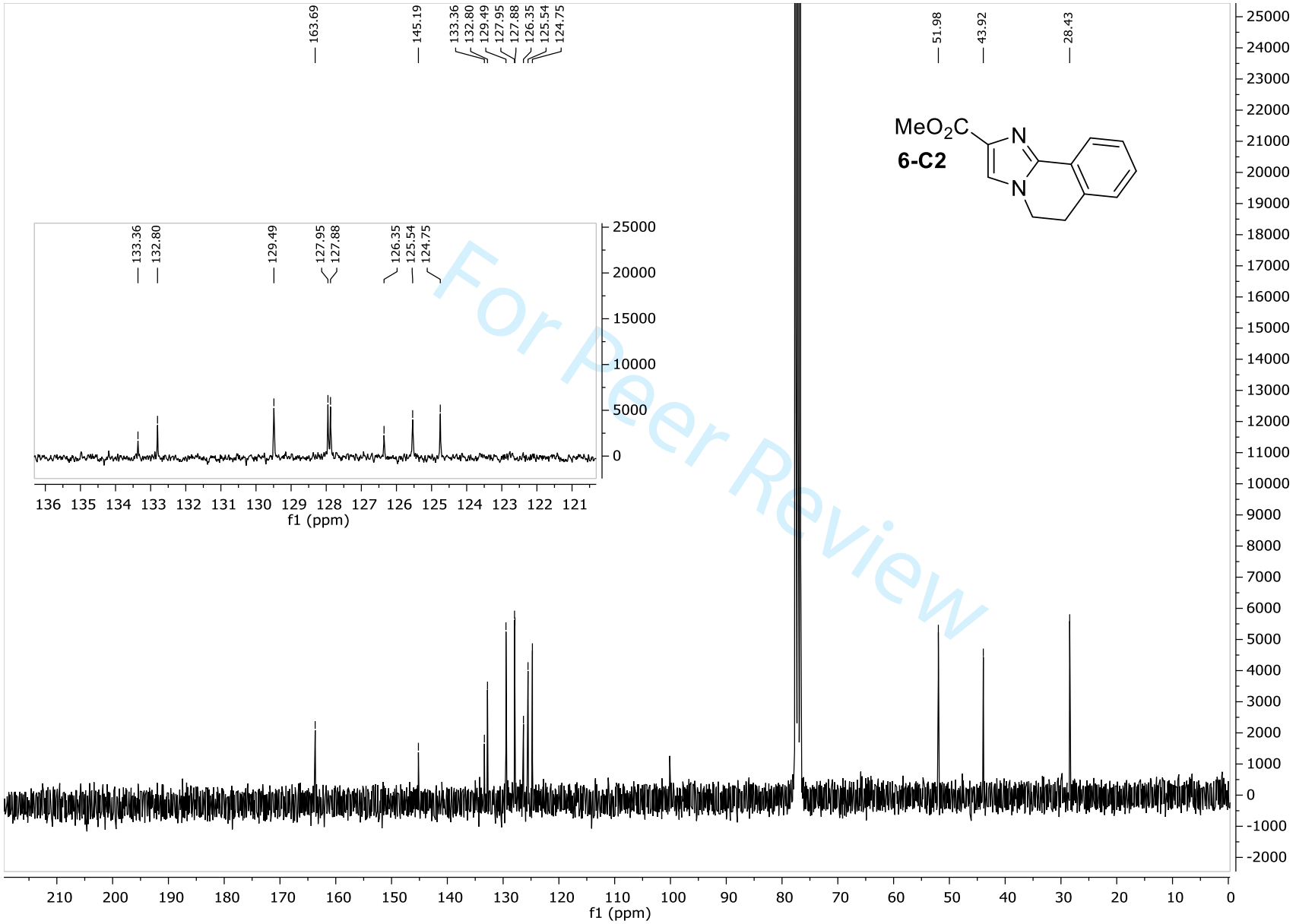


For Peer Review

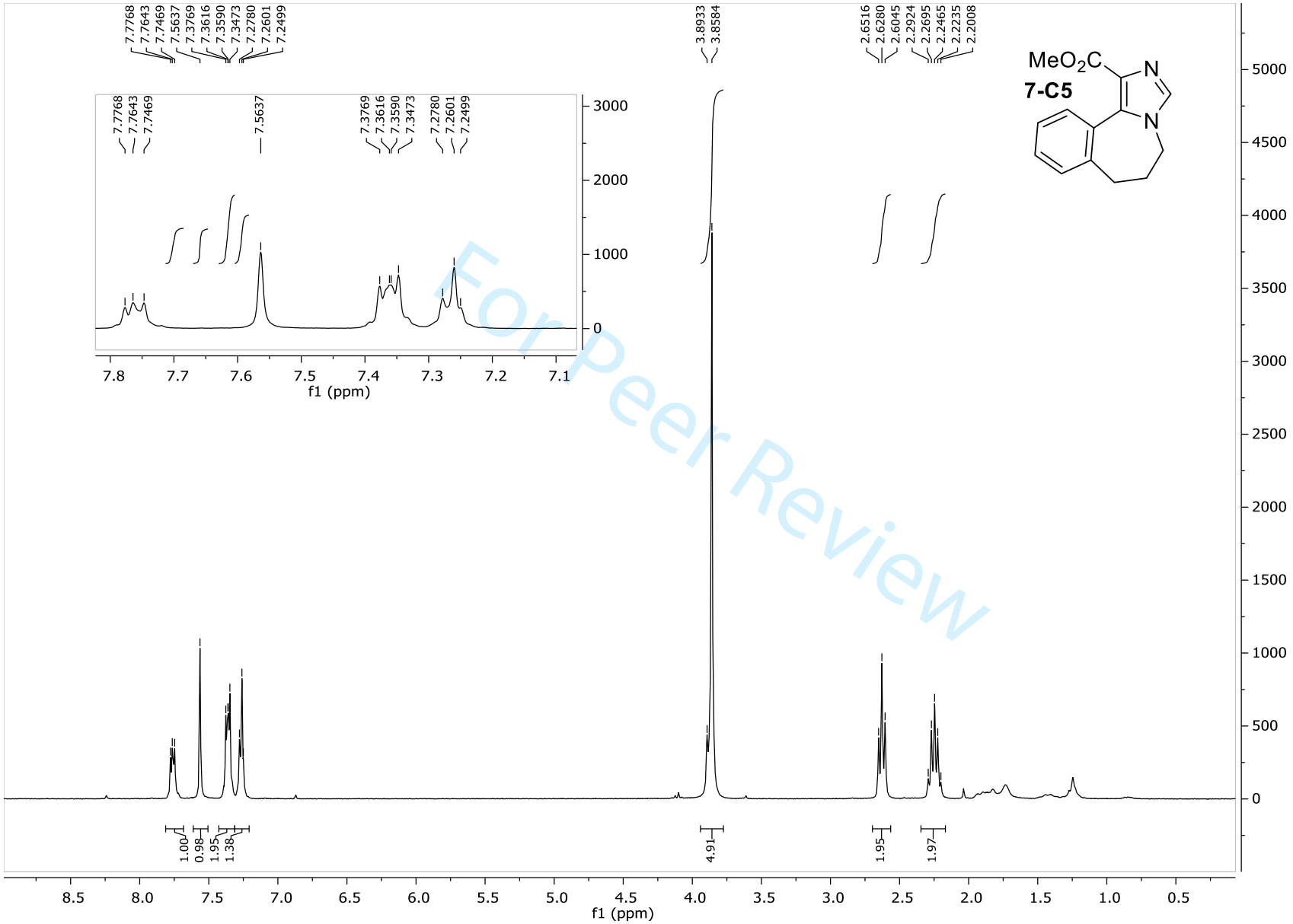


For Peer Review

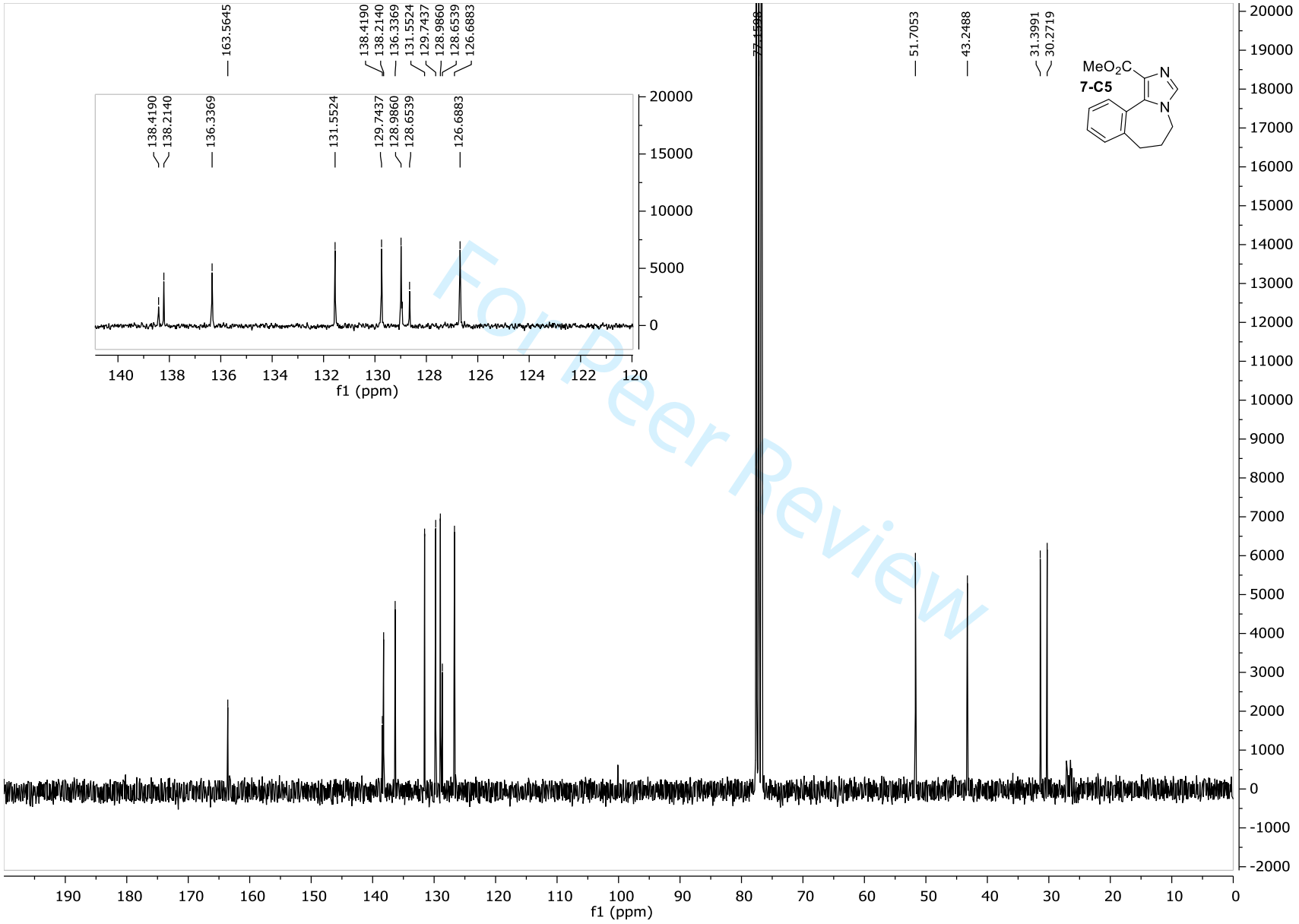
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



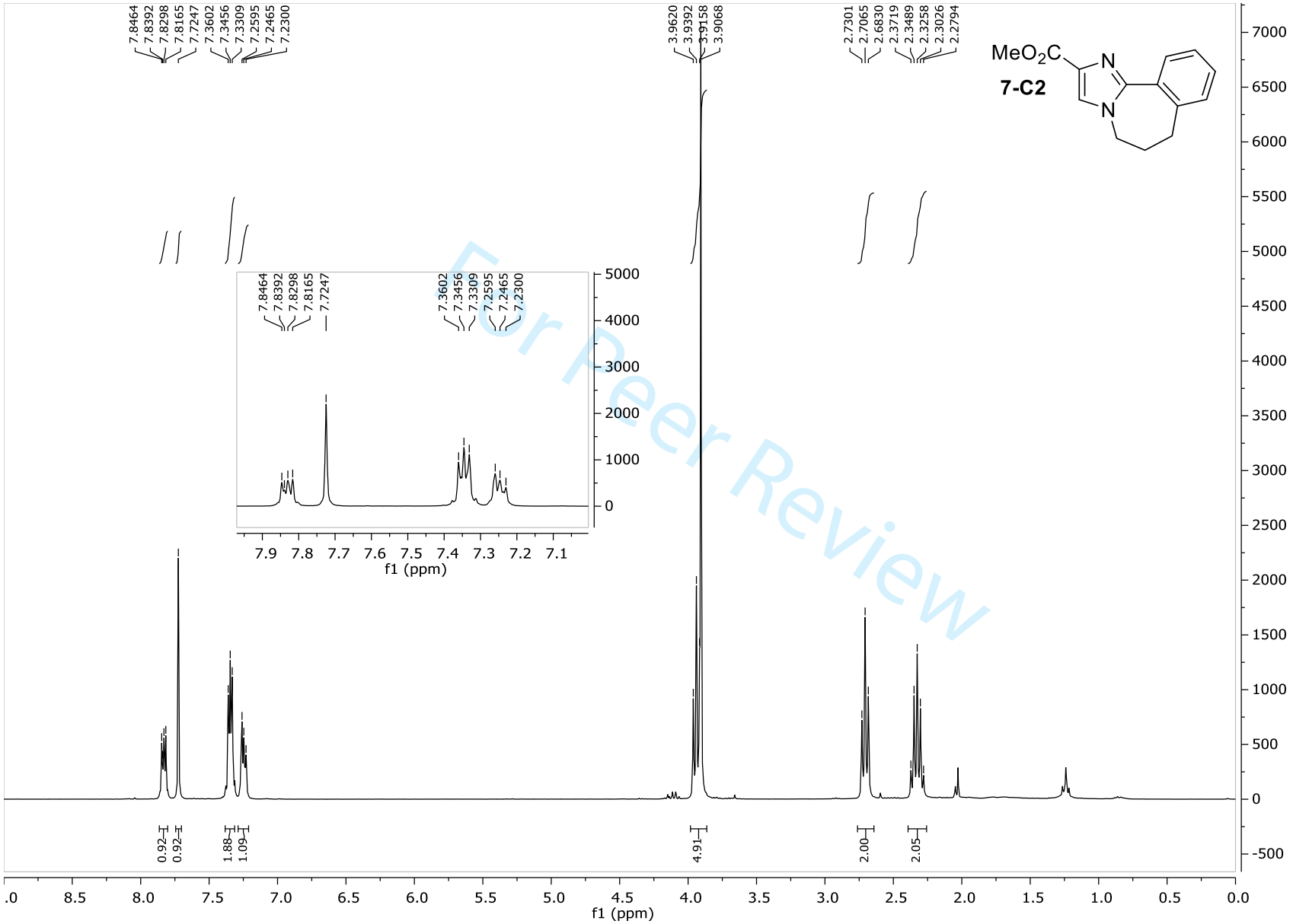
For Peer Review



For Peer Review

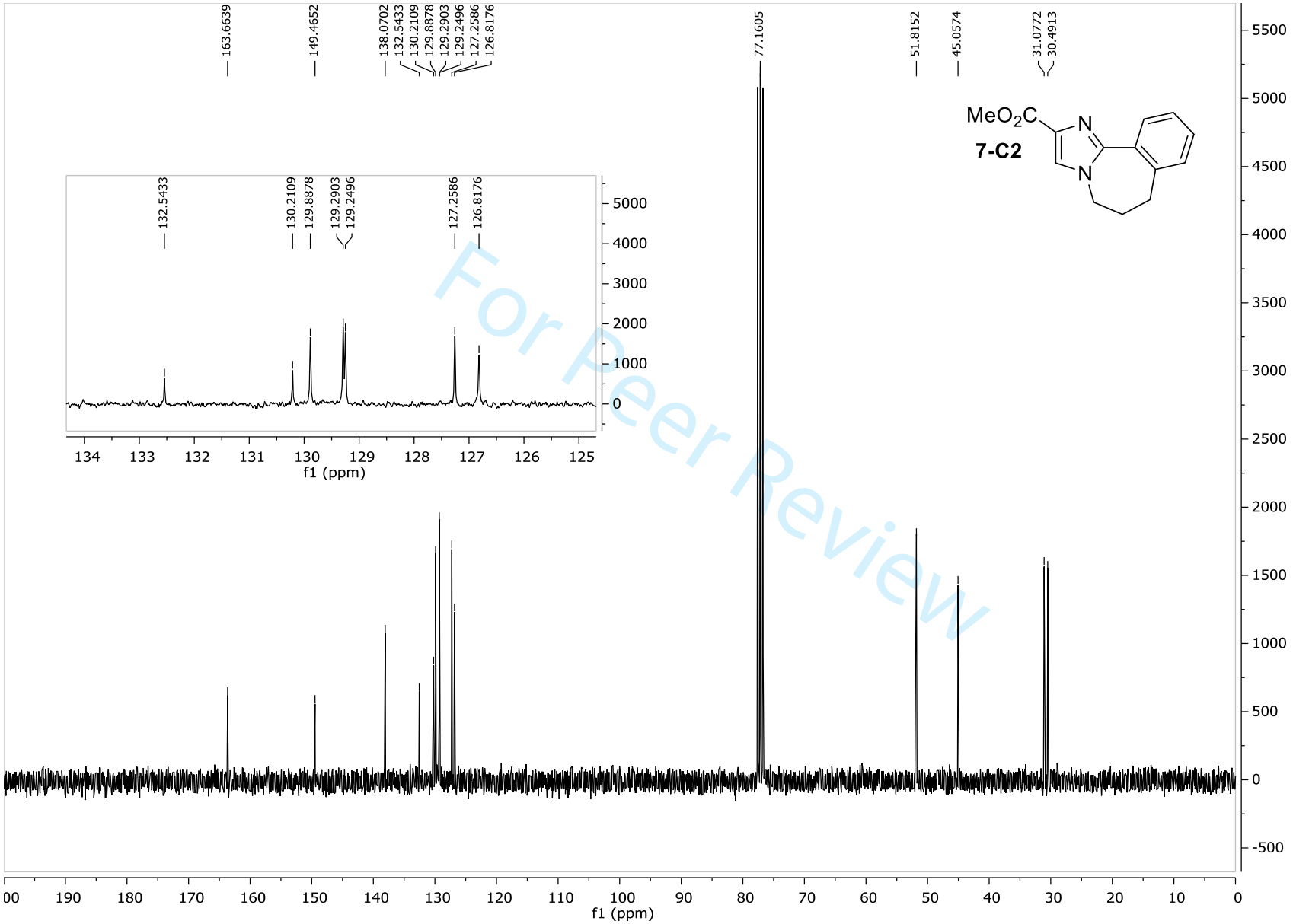


For Peer Review

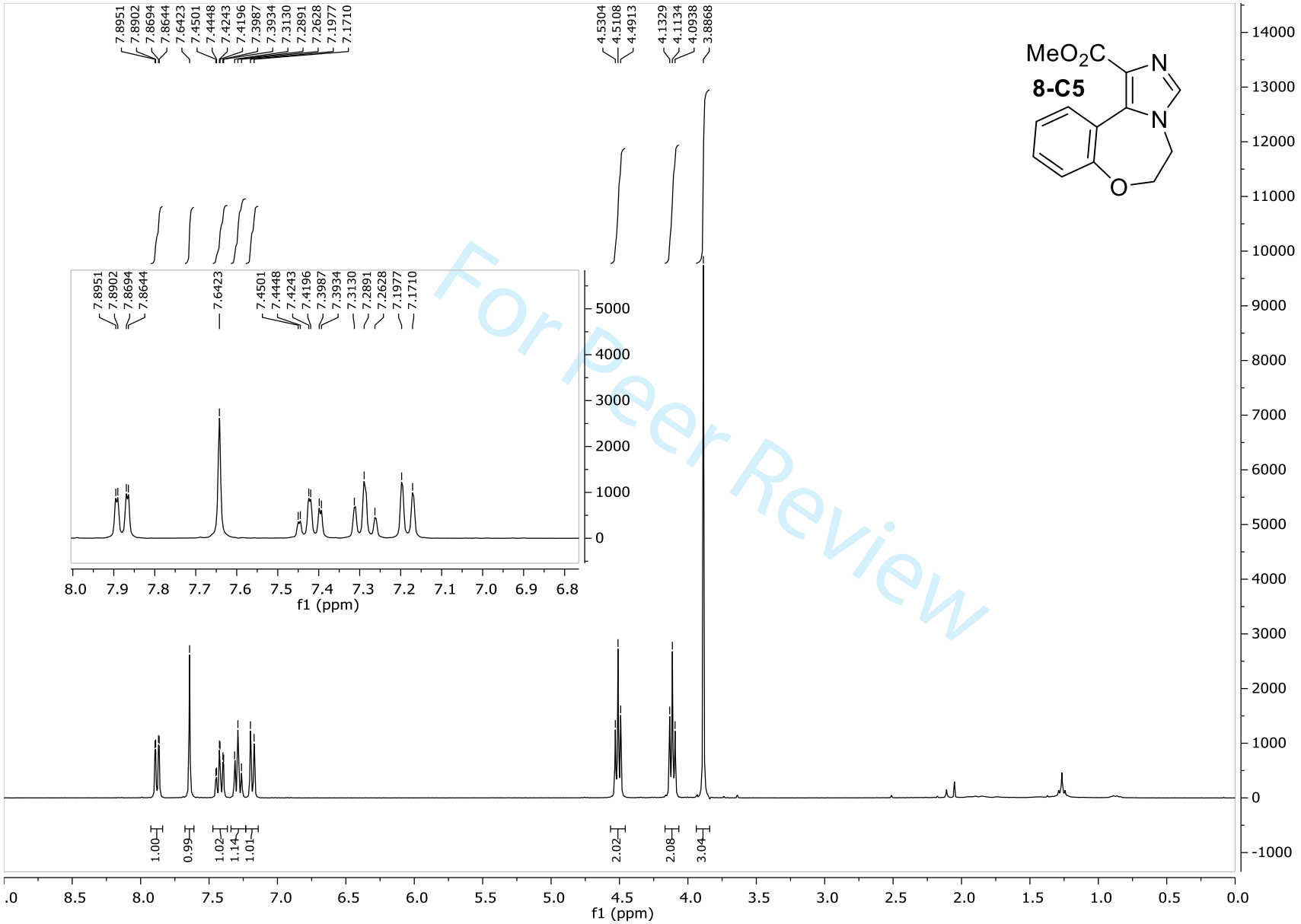


For Peer Review

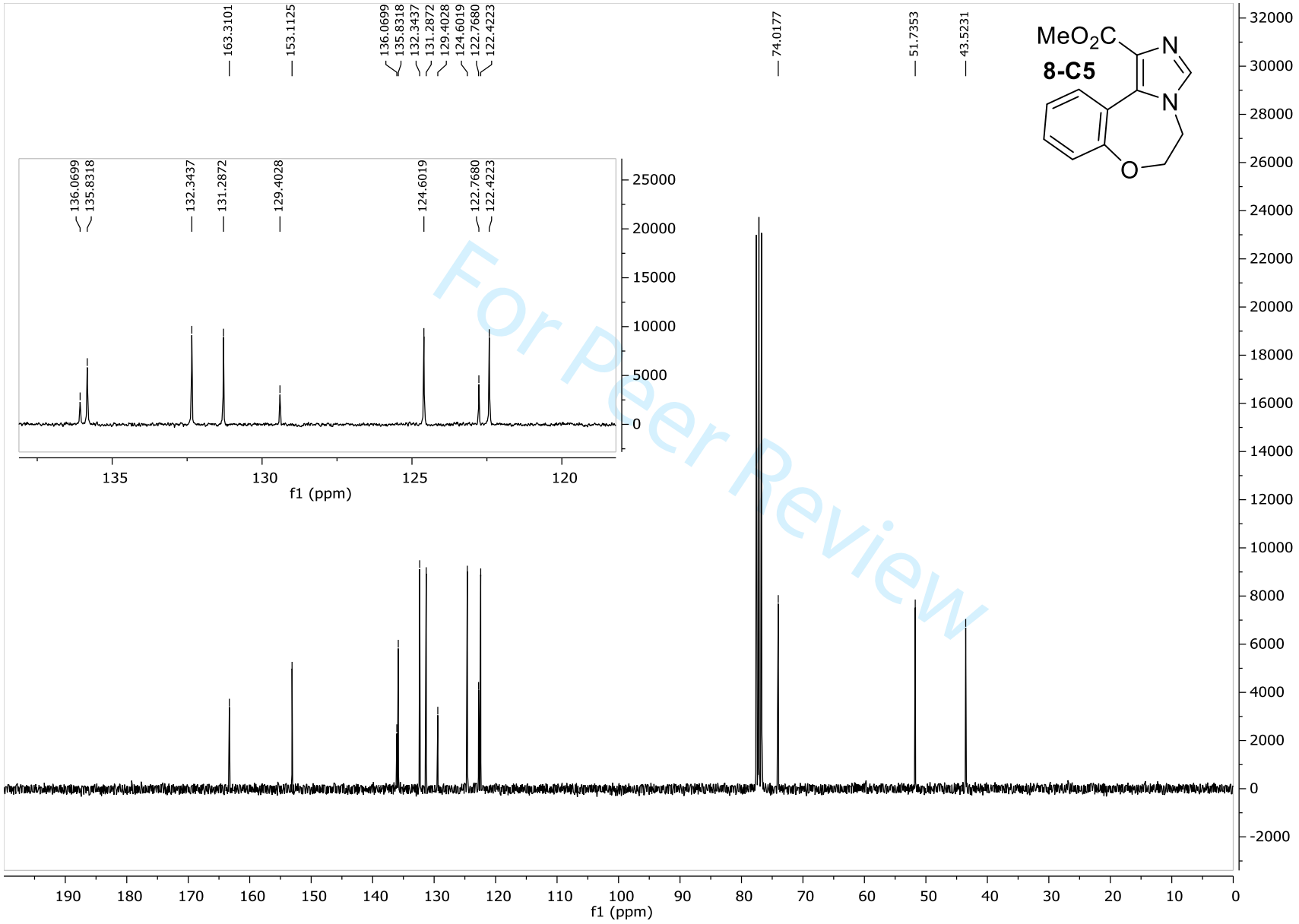
Georg Thieme Publishers KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



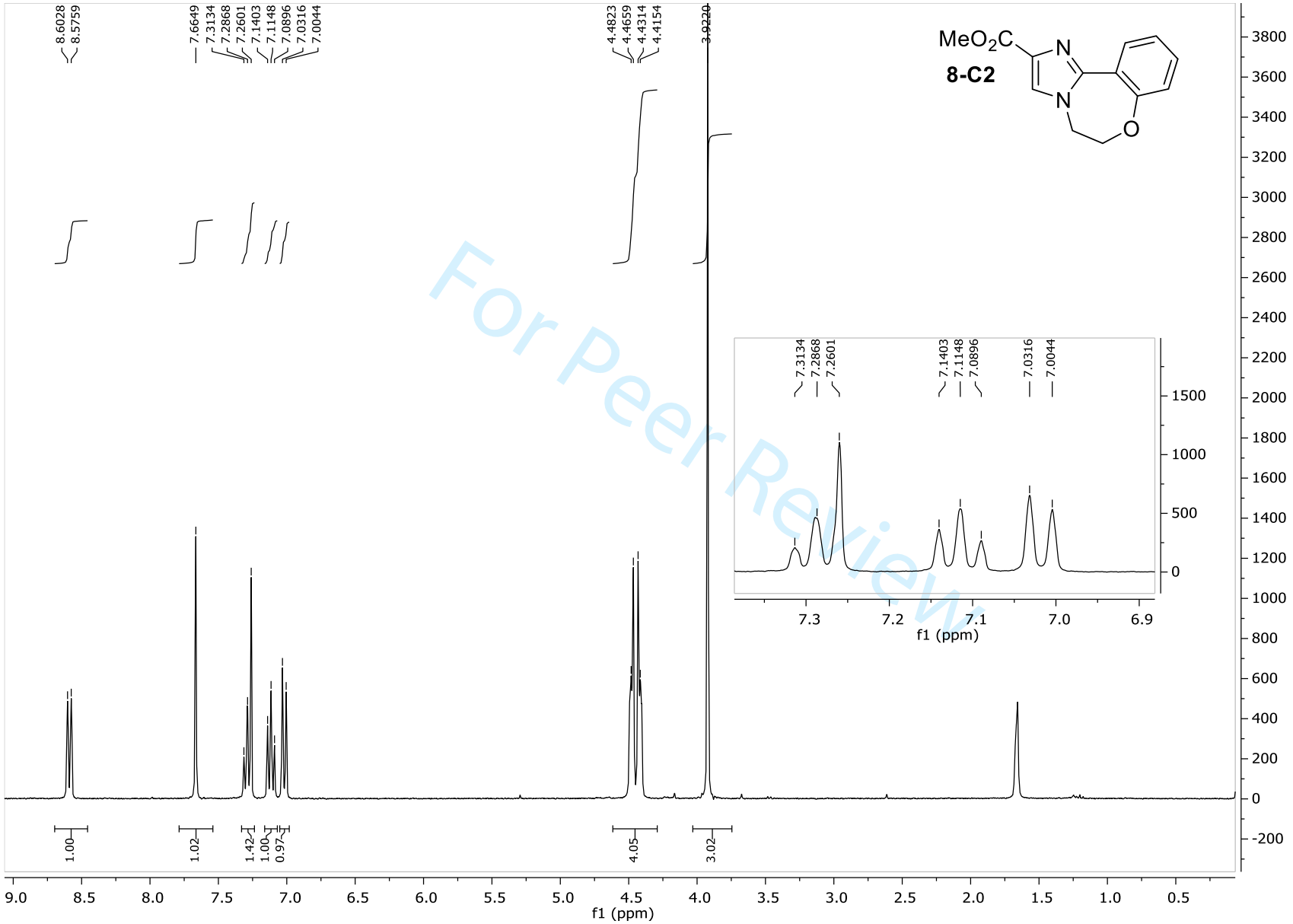
For Peer Review



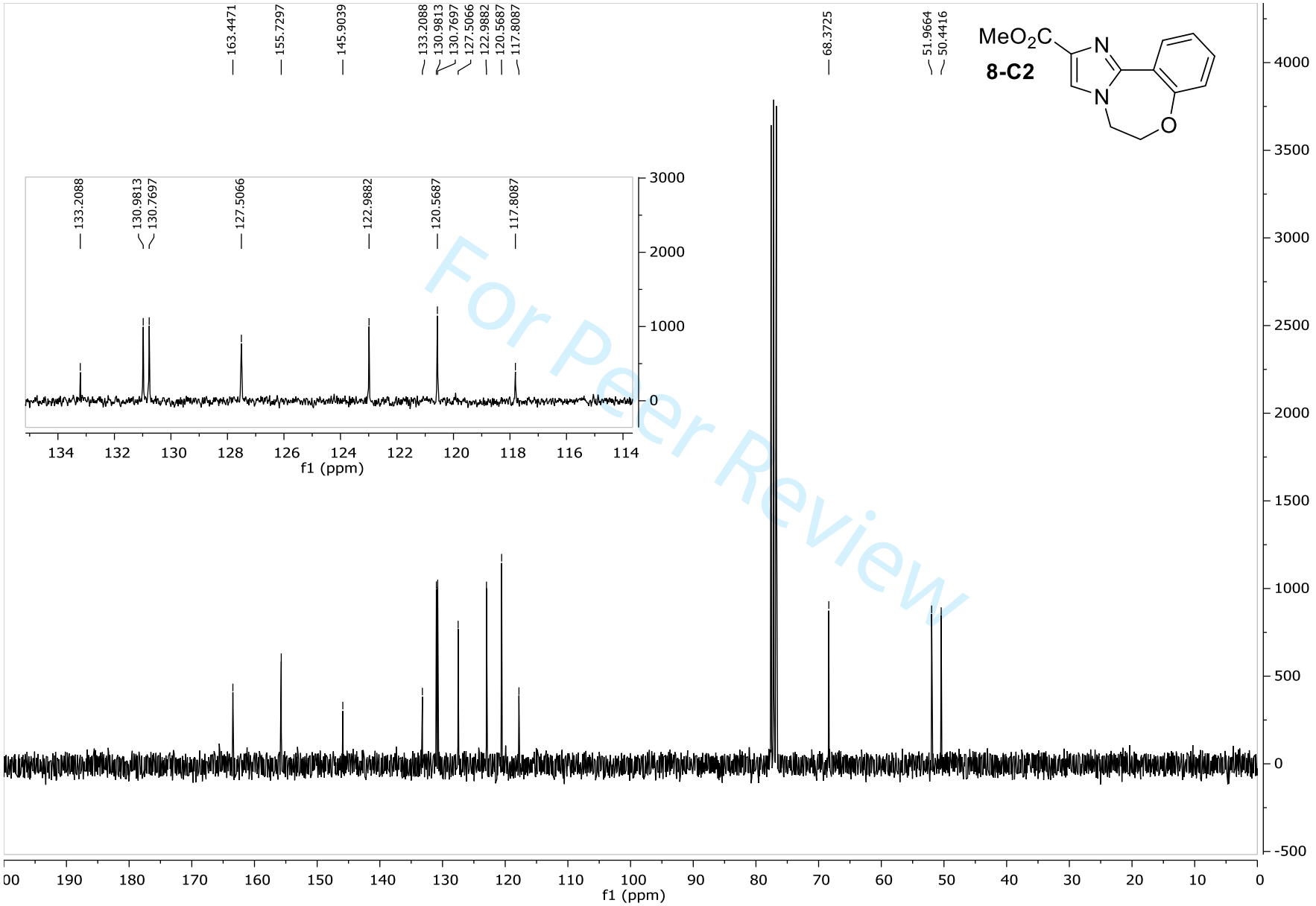
For Peer Review



For Peer Review



For Peer Review



For Peer Review