Multicomponent reactions: development, scope, and applications

Chandgude, Ajay

Chapter 4

Unconventional Passerini Reaction towards α-Aminoxy-amides

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A. L. Chandgude

A. Dömling,

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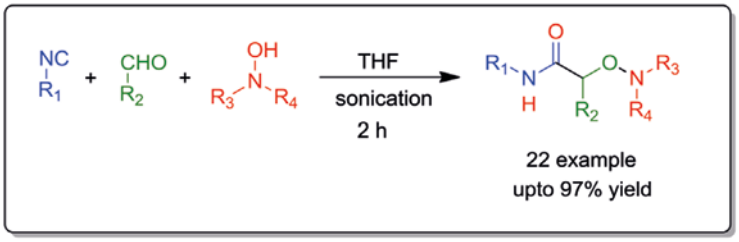


Abstract

The Passerini multicomponent reaction (P-3CR) towards the one-step synthesis of α-aminoxy-amide, by employing for the first time a *N*-hydroxamic acid component, has been reported. The sonication-accelerated, catalyst-free, simple, fast, and highly efficient Passerini reaction is used for the synthesis of diverse α-aminoxy-amides. The reaction is compatible with a vast range of aldehydes, isocyanides, and *N*-hydroxamic acids such as *N*-hydroxysuccinimides and phthalimides. The generated Passerini products can be easily converted into several follow-up products.

Introduction

Recently, the design and synthesis of peptidomimetics has gained attention in drug discovery, due to the potential structural and functional advantages over natural proteins.[1] Modified structures and functional groups increase the activity, selectivity and bioavailability. Also provide structural rigidity and stability.[2] Among the peptidomimetics, α-aminoxy-acids stand out as analogs of b-amino acids. The α-aminoxy-amides can adopt the structure of the secondary eight-membered N-O turn, which confers extra stability towards enzymatic degradation (Figure 1).[3] These peptidomimetic foldamers are used as building blocks to construct anion receptors and channels. e.g. to mimic anion recognition and transport processes.[4]

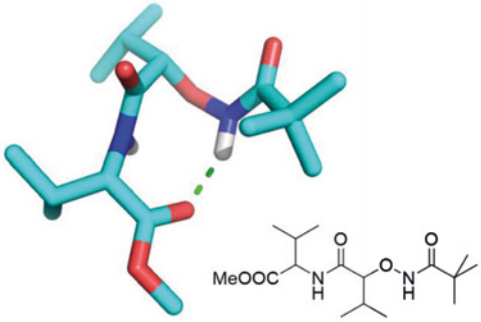
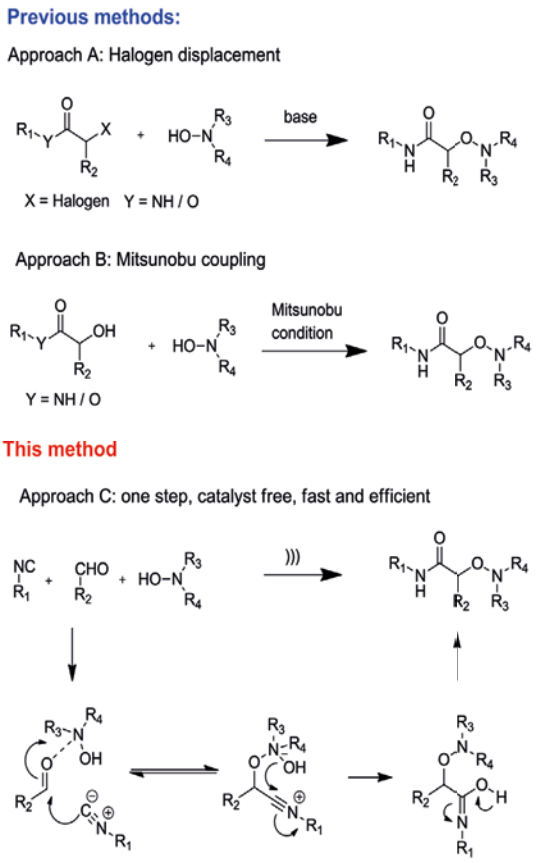


Figure 1. Model of an eight-membered turn involving α-aminoxy-amide.

Owing to the importance of α-aminoxy-amides, significant effort has been made towards their design and synthesis. The majority of α-aminoxy-amides synthesis methodologies can be categorized into two general approaches. The first is coupling between an a-halo acid, ester or amide with N-hydroxyphthalimide (NHPI) or N-hydroxysuccinimide (NHS)[5] (Scheme 1. Approach **A**). The second is the Mitsunobu reaction of a-hydroxy acid, ester or amide with NHPI or NHS[6,7] (Scheme 1. Approach **B**). These methods suffer from poor availability of starting materials, hence diversity in the products, lengthy multistep preparation, long reaction times, low yields, and also use of coupling reagents which require tedious work-up. Currently there is no known method to directly access the α-aminoxy-amides from simple starting materials, with high efficiency and scope. Isocyanide-based multicomponent reactions (IMCRs) have already been proven as a promising strategy for the synthesis of peptidomimetics.[8] This highly convergent approach provides pronounced diversity and complexity.[9]

We envisioned the use of N-hydroxamic acid as a novel acid isostere in the Passerini reaction, which is potentially suitable for the synthesis of α-aminoxy-amides. Surprisingly, the use of carboxylic acid-isosteres in the Passerini reaction is relatively unexplored,[10] with the exception of hydrogene azide,[11] nitro-phenol,[12] silanol[13] and phosphinic acid.[14] In the Passerini reaction, the acyl group of the carboxylic acid acts mechanistically as an electrophile while the OH group works as a nucleophile. Here we hypothesized that, in the Passerini reaction, the OH group of the hydroxamic acid acts as

the nucleophilic, and the imide-N as the electrophilic species towards the nitrilium intermediate. Weak hydroxamic acids such as NHS or NHPI (pK_a ~7.5) might be able to activate an aldehyde in the Passerini reaction to allow the attack of the the isocyanide. Further trapping of the resulting nitrilium intermediate by the hydroxamate affords the final product after the migration of the imide onto the oxygen atom, originating from the aldehyde (Scheme 1).



Scheme 1. Previous and new synthesis of N-aminoxy amide and a proposed mechanism for P-3CR.

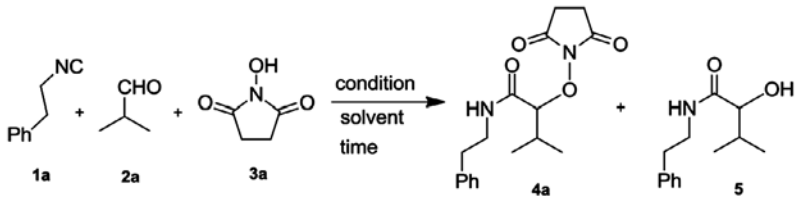
Results and Discussion

To test the feasibility of hydroxamic acids, we investigated the reaction between isobutyraldehyde (1.0 equiv), phenylethyl isocyanide (1.0 equiv), and N-hydroxysuccinimide (2.0 equiv) with different solvents and conditions (Table 1). When the reaction was performed in DCM, a promising 22% yield of a mixture of the expected product **4a** and the free hydroxyl-amide **5** was obtained (Table 1. Entry **1**). Use of catalysts such as $ZnCl_2$, PTSA or $BF_3.OEt_2$ then resulted in only trace product formation

(Table 1. Entries **2**–**4**). However, the reaction in CH_3CN and THF solvents gave desired product in moderate yields of 58%, after stirring overnight at room temperature (Table 1. Entries **5** and **6**).

Water is a known accelerator of the Passerini reaction.[15] However, use of water or a mixture with methanol as solvent in our case led to hydroxyl amide **5** as the major product. The expected product **4a** formed only in a trace amount even after increasing the temperature (Table 1. Entries **7**–**10**). Increase the temperature in THF solvent reduced the yields slightly to 50%, while in acetonitrile a considerable yield decrease to 38% was found (Table 1. Entries **11** and **12**). Recently we showed that, sonication greatly increased the efficiency of the Passerini reaction.[16] Applying sonication to our new reaction led to the α-hydroxy amide 5 as the major product in water and a water/methanol mixture (Table 1. Entries **14** and **15**). Remarkably, use of sonication together with THF as the solvent increased the yield to an almost quantitative 97%, and moreover the reaction required only 2 hours for completion. An equivalence study of NHS showed that 2 equivalents are necessary to get maximum yield. An increase or decrease in the NHS equivalents reduced the yield (Table 1. Entries **16**–**18**).

Table 1. Optimization conditions.[a]



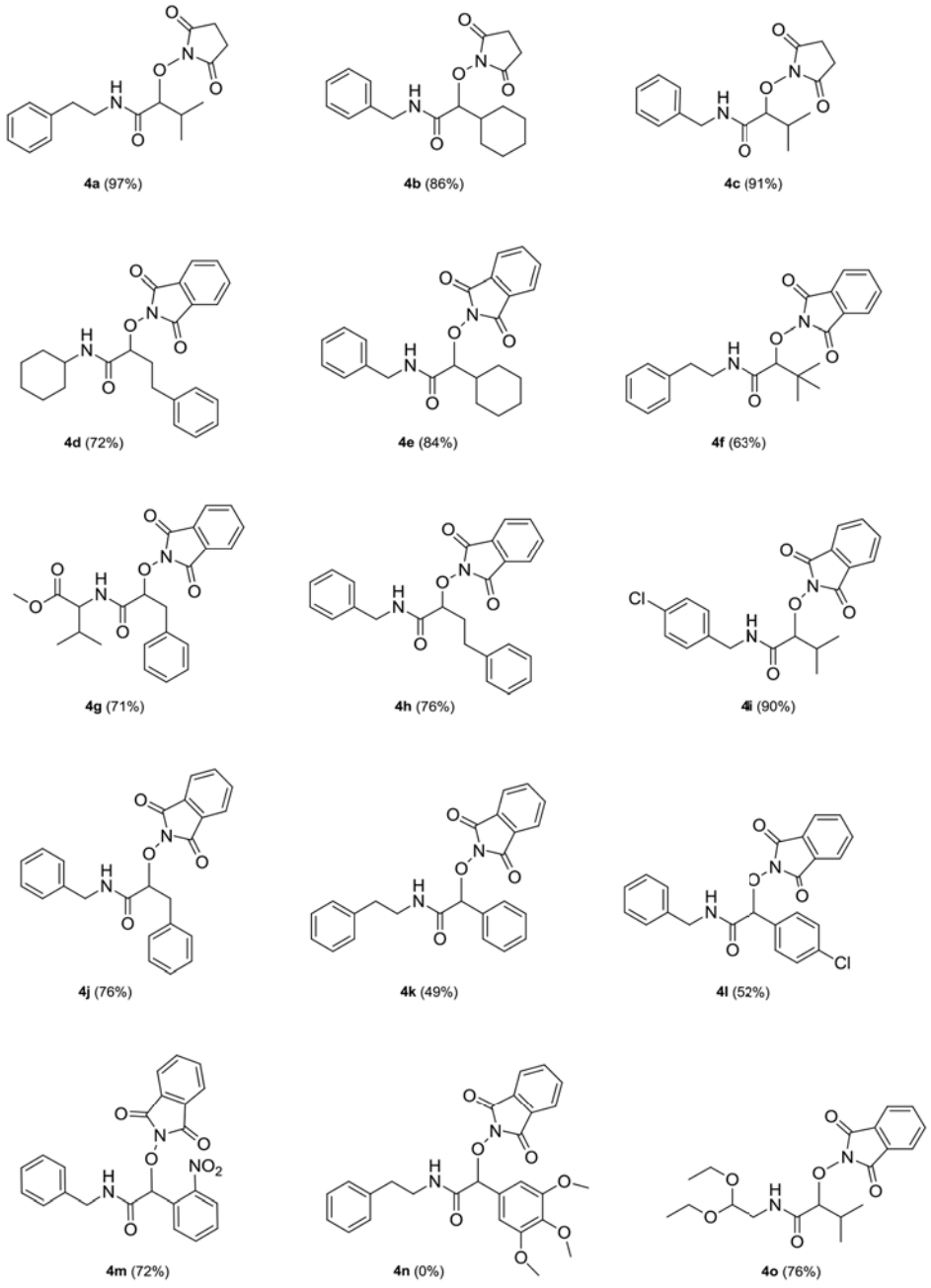
Entry	Solvent	Temp	Condition / catalyst	Time (h)	Yield (%)[c]
1	DCM	rt		12	22[f]
2[b]	DCM	rt	$ZnCl_2$	12	trace
3[b]	DCM	rt	PTSA	12	trace
4[b]	DCM	rt	$BF_3.OEt_2$	12	trace
5	CH_3CN	rt		12	58
6	THF	rt		12	58
7	MeOH : H_2O (1 : 1)	rt		12	56[f]
8	H_2O	rt		12	trace
9	MeOH : H_2O (1 : 1)	60 °C		12	35[f]
10	H_2O	60 °C		12	45[f]
11	THF	60 °C		12	50
12	CH_3CN	60 °C		12	38
13	DCM	60 °C		12	44[f]
14	MeOH : H_2O (1 : 1)	rt	sonication	2	76[f]
15	H_2O	rt	sonication	2	63[f]

Entry	Solvent	Temp	Condition / catalyst	time (h)	Yield (%)[c]
16	THF	rt	sonication	2	97
17[d]	THF	rt	sonication	2	82
18[e]	THF	rt	sonication	2	78

[d]The reaction was carried out with phenylethyl isocyanide (1.0 mmol), isobutyraldehyde (1.0 mmol) and N-hydroxysuccinimide (2.0 mmol). [b]10 mol % catalyst used. [c]Yield of isolated product **4a**. [d]1 equivalent NHS used. [e]**3** equivalent NHS used. [f]Total yield of **4a** and **5** as a mixture.

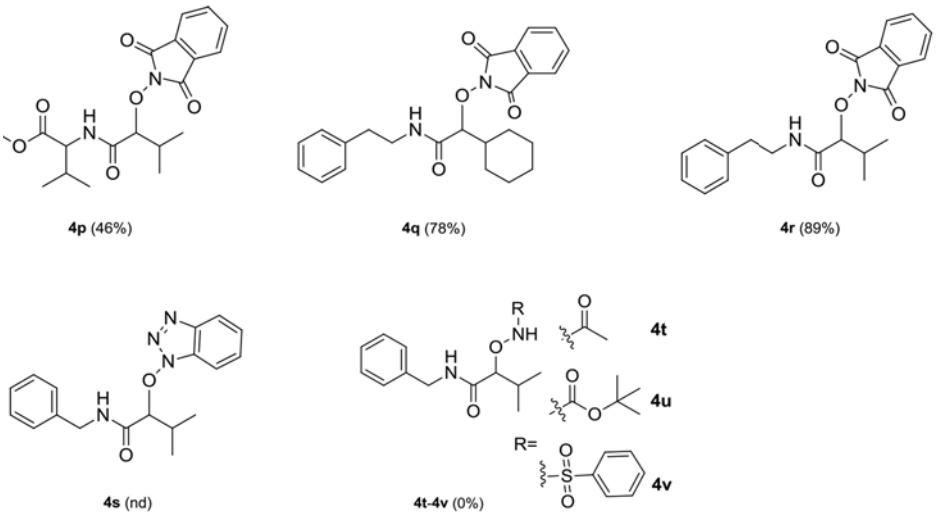
With these optimized conditions in hand, we then investigated the scope of this novel P-3CR by reacting different hydroxamic acids, aldehydes, and isocyanides (Scheme 2). NHS gave excellent yields with benzyl and phenylethyl isocyanides when used with different aldehydes **4a-4c**. Furthermore, we screened the NHPI. An 81% isolated yield obtained from 2 equivalents of NHPI with phenylethyl isocyanide and isobutylaldehyde, however 1.5 equivalents of NHPI provided the best yield, 89% **4r**. NHPI in 1 and 3 equivalents led to 74 and 63% yields, respectively. NHPI works well with aliphatic aldehydes such as isobutylaldehyde, cyclohexylcarbaldehyde or even bulky *tert*-butylaldehyde **4e**, **4f**, **4i**. Aliphatic aromatic aldehydes such as phenylacetaldehyde or phenylethylaldehydes gave good yields. Aromatic aldehydes also performed well in this reaction giving moderate to good yields **4k-m**. Aromatic aldehydes having electron-donating groups such as tri-methoxy moiety demonstrated very low reactivity, and their reactions did not produce any of the desired product **4n**. Different isocyanides were tested and found to be good substrates for this reaction. Protected isocyanides like valine ester isocyanide or 1,1-diethoxy-2-isocyanoethane isocyanide **4g**, **4o**, **4p** also provide moderate to good yields, which potentially allows for further modifications for synthesis of the diverse scaffolds and more complex peptide mimetics (Figure 1). Products **4g** and **4p** are formed as ~1 : 1 mixture of diastereomers. Halogen functionality on an isocyanide could also provide scope for further coupling reactions in the case of **4i**.

In the reaction with HOBt it was found that the product (as confirmed by mass spectroscopy) is relatively unstable during silica or neutral alumina column chromatography and converts to α-hydroxy amides **4s**. To further investigate the scope of hydroxamic acids, we tested the free NH hydroxamic acids, but disappointingly they did not form the desired products **4t-4v**. These results show that the nitrogen of the hydroxamic acids should not be acidic to give the product.



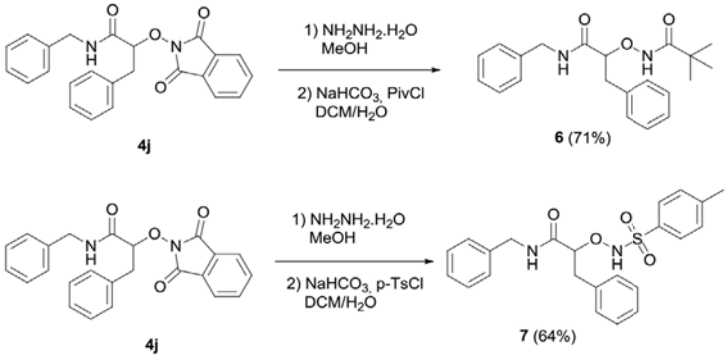
Scheme 2. Substrate scope of the synthesis of α-aminoxy amides from isocyanide, aldehyde and N-hydroxamic acid.[a]

[a]Reaction conditions: 1.0 mmol **1**, 1.0 mmol **2**, 2.0 mmol NHS, HOBT, N-hydroxamic acids, 1.5 mmol NHPI **3**, and 1 ml THF. nd = not determined.



Scheme 2. *(Continued)*

Next we used our P-3CR towards the preparation of the oxyamines, which are important intermediates for the synthesis of peptidomimetics as well as different scaffolds like oxime ethers and benzofurans.[17] When 2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-N-phenethylbutanamide **4j** was treated with hydrazine for 5 hours at room temperature, it forms the oxy-amine which was further used for the synthesis of an amide and sulphonamide (Scheme 3). We obtained 71% product with pivaloyl chloride coupling 6 and 64% with p-TsCl 7.[18]



Scheme 3. Deprotection towards O-hydroxylamines and acylation/sulfonylation.

Conclusion

In conclusion, we have introduced for the first time N-hydroxamic acids in the Passerini three-component reaction. We developed a novel, catalyst-free, mild, work-up free, efficient and general hydroxamic acid based Passerini reaction to gain access to α-aminoxy-amides. This methodology is applicable to a wide range of isocyanides and aldehydes. Functional group compatibility in this methodology provides easy access for further modifications. This modified-Passerini reaction has the ability to expand the scope of substrate for investigation as peptidomimetic design and has the potential to become a preferred method for the synthesis of complex α-aminoxy amides.

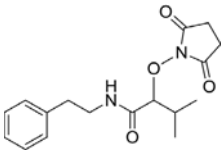
Experimental Procedures and Spectral Data

General procedure for the synthesis of α-aminoxy amides

A 10 ml tube was charged with aldehyde (1.0 mmol) and isocyanide (1.0 mmol) and NHS/HOBT/N-hydroxamic acids (2 mmol) or NHPI (1.5 mmol) with THF (1 ml). The mixture was sonicated in the water bath of an ultrasonic cleaner (frequency of 50/60 Hz, 220/240V, 25 Amps) at room temperature till completion of the reaction (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

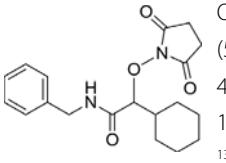
Spectral Data

2-((2,5-dioxopyrrolidin-1-yl)oxy)-3-methyl-*N*-phenethylbutanamide (**4a**)



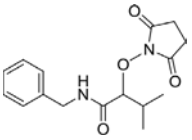
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 154 mg (97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.19 (t, *J* = 7.3, 1H), 7.14 (d, *J* = 7.2, 2H), 4.16 (d, *J* = 8.2, 1H), 3.76 – 3.61 (m, 2H), 3.38 (s, 1H), 2.74 (td, *J* = 6.8, 2.5, 2H), 2.59 (s, 4H), 2.16 – 1.98 (m, 1H), 1.06 (d, *J* = 6.6, 3H), 0.97 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 155.3, 139.8, 129.0, 128.2, 126.1, 72.2, 48.2, 37.2, 32.2, 25.5, 18.5, 18.3. MS (ESI) m/z calculated $[M+H]^+$: 319.37; found $[M+H]^+$: 319.28. HRMS (ESI) m/z calculated $[M+H]^+$: 319.16523; found $[M+H]^+$: 319.16483.

N-benzyl-2-cyclohexyl-2-((2,5-dioxopyrrolidin-1-yl)oxy)acetamide (**4b**)



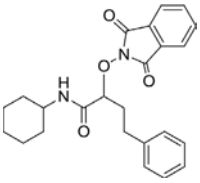
Obtained from 1 mmol reaction as a white solid, yield: 296 mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.20 (t, *J* = 7.3, 1H), 7.13 (d, *J* = 7.5, 2H), 4.64 (s, 2H), 4.36 (br s, 1H), 3.68 (d, *J* = 4.4, 1H), 2.71 (s, 4H), 2.10 (d, *J* = 12.4, 1H), 1.90 – 1.60 (m, 5H), 1.33 – 1.20 (m, 2H), 1.20 – 1.12 (m, 1H), 1.12 – 0.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 156.7, 139.5, 128.3, 126.7, 126.6, 71.8, 50.4, 41.5, 28.8, 28.5, 26.3, 25.9, 25.7, 25.6. MS (ESI) m/z calculated $[M+H]^+$: 345.40; found $[M+H]^+$: 345.30. HRMS (ESI) m/z calculated $[M+H]^+$: 345.18088; found $[M+H]^+$: 345.18024.

N-benzyl-2-((2,5-dioxopyrrolidin-1-yl)oxy)-3-methylbutanamide (**4c**)



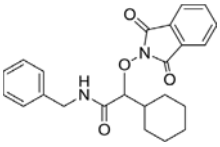
Obtained from 1 mmol reaction as a white viscus liquid, yield: 276 mg (91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5, 2H), 7.19 (t, *J* = 7.3, 1H), 7.13 (d, *J* = 7.5, 2H), 4.65 (s, 2H), 4.31 (d, *J* = 7.9, 1H), 3.87 (s, 1H), 2.71 (s, 4H), 2.25 – 2.07 (m, 1H), 1.10 (d, *J* = 6.6, 3H), 1.03 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 156.8, 139.5, 128.3, 126.7, 126.6, 72.6, 50.3, 32.3, 25.6, 18.4. MS (ESI) m/z calculated $[M+H]^+$: 305.34; found $[M+H]^+$: 305.23. HRMS (ESI) m/z calculated $[M+H]^+$: 305.14958; found $[M+H]^+$: 305.14966.

N-cyclohexyl-2-((1,3-dioxoisoindolin-2-yl)oxy)-4-phenylbutanamide (**4d**)



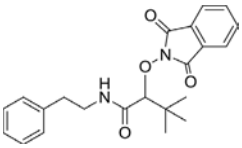
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 147 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.1, 2H), 7.81 – 7.74 (m, 2H), 7.39 – 7.08 (m, 6H), 4.64 (brs, 1H), 3.44 (brs, 1H), 2.88 (brs, 2H), 2.28 – 2.04 (m, 2H), 1.41 (brs, 5H), 1.09 (brs, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 153.6, 141.1, 134.5, 129.4, 128.6, 128.5, 126.1, 123.6, 66.0, 54.7, 36.5, 33.8, 31.2, 25.5, 23.4. MS (ESI) m/z calculated $[M+H]^+$: 407.47; found $[M+H]^+$: 407.30. HRMS (ESI) m/z calculated $[M+H]^+$: 407.19653; found $[M+H]^+$: 407.19626.

N-benzyl-2-cyclohexyl-2-((1,3-dioxoisoindolin-2-yl)oxy)acetamide (**4e**)



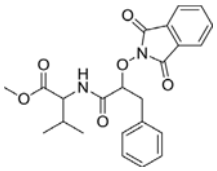
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 165 mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 2H), 7.76 – 7.68 (m, 2H), 7.17 – 7.06 (m, 3H), 6.99 (d, *J* = 7.2, 2H), 4.65 (s, 2H), 4.51 – 4.41 (m, 1H), 3.64 (d, *J* = 6.0, 1H), 2.15 (d, *J* = 12.4, 1H), 2.01 – 1.87 (m, 2H), 1.84 – 1.75 (m, 2H), 1.68 (d, *J* = 12.5, 1H), 1.33 – 1.07 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 157.2, 139.3, 134.5, 129.3, 128.1, 126.6, 126.4, 123.7, 72.0, 50.3, 41.7, 28.9, 28.5, 26.3, 25.9, 25.8. MS (ESI) m/z calculated $[M+H]^+$: 393.45; found $[M+H]^+$: 393.25. HRMS (ESI) m/z calculated $[M+H]^+$: 393.18088; found $[M+H]^+$: 393.18088.

2-((1,3-dioxoisoindolin-2-yl)oxy)-3,3-dimethyl-*N*-phenethylbutanamide (**4f**)



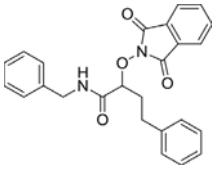
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 119 mg (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H), 7.81 – 7.74 (m, 2H), 7.15 – 7.06 (m, 3H), 6.99 (d, *J* = 6.5, 2H), 4.25 (s, 1H), 3.65 – 3.54 (m, 2H), 2.67 – 2.56 (m, 2H), 1.91 (s, 1H), 1.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 155.2, 139.5, 134.4, 129.3, 128.9, 128.8, 128.1, 126.0, 123.6, 74.3, 49.4, 37.2, 35.7, 26.0, 25.9. MS (ESI) m/z calculated $[M+H]^+$: 381.44; found $[M+H]^+$: 381.28. HRMS (ESI) m/z calculated $[M+H]^+$: 381.18088; found $[M+H]^+$: 381.18069.

methyl 2-(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-phenylpropanamido)-3-methylbutanoate (**4g**)



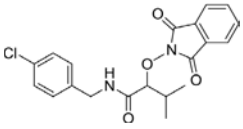
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 150 mg (71%) as a mixture of diastereomers (1:1.14); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 4H), 7.83 – 7.75 (m, 4H), 7.38 (t, *J* = 9.0, 4H), 7.35 – 7.30 (m, 4H), 7.24 (t, *J* = 7.5, 2H), 4.82 (s, 1H), 4.70 (t, *J* = 7.0, 1H), 4.15 (s, 1H), 3.91 (s, 1H), 3.62 (s, 3H), 3.55 (s, 3H), 3.39 – 3.26 (m, 3H), 3.25 – 3.12 (m, 2H), 3.03 (s, 1H), 2.01 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H), 0.66 (brs, 3H), 0.47 (brs, 6H), 0.36 (brs, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 171.6, 163.5, 163.5, 158.4, 136.1, 136.0, 134.7, 134.5, 129.8, 129.7, 129.7, 129.4, 128.7, 128.6, 127.0, 127.0, 123.8, 123.6, 69.4, 68.9, 64.1, 63.8, 52.0, 51.9, 40.9, 40.2, 31.5, 31.3, 19.2, 19.2. MS (ESI) m/z calculated $[M+H]^+$: 425.45; found $[M+H]^+$: 425.20. HRMS (ESI) m/z calculated $[M+H]^+$: 425.17071; found $[M+H]^+$: 425.17065.

N-benzyl-2-((1,3-dioxoisoindolin-2-yl)oxy)-4-phenylbutanamide (**4h**)



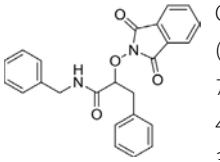
Obtained from 1 mmol reaction as a colorless liquid, yield: 314 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.66 (m, 4H), 7.41 – 7.21 (m, 5H), 7.17 – 7.06 (m, 3H), 6.96 (d, *J* = 7.0, 2H), 4.72 (d, *J* = 5.8, 1H), 4.56 (s, 2H), 3.18 (d, *J* = 4.7, 1H), 3.00 – 2.74 (m, 2H), 2.50 – 2.14 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 157.4, 140.9, 139.1, 134.6, 129.3, 128.6, 128.5, 128.2, 126.5, 126.1, 123.8, 66.6, 50.1, 35.9, 31.1. MS (ESI) m/z calculated $[M+H]^+$: 415.45; found $[M+H]^+$: 415.24. HRMS (ESI) m/z calculated $[M+H]^+$: 415.16523; found $[M+H]^+$: 415.16541.

N-(4-chlorobenzyl)-2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbutanamide (**4i**)



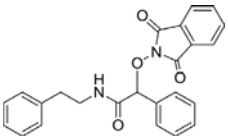
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 174 mg (90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.2, 3.1, 2H), 7.78 (dd, *J* = 5.2, 3.1, 2H), 7.10 (d, *J* = 8.1, 2H), 6.93 (d, *J* = 8.0, 2H), 4.62 (s, 2H), 4.37 (t, *J* = 7.2, 1H), 3.07 (d, *J* = 5.8, 1H), 2.34 – 2.14 (m, 1H), 1.16 (d, *J* = 6.6, 3H), 1.09 (d, *J* = 6.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 157.4, 137.7, 134.6, 132.2, 129.2, 128.3, 127.9, 123.7, 73.0, 49.7, 32.6, 18.4. MS (ESI) m/z calculated $[M+H]^+$: 387.83; found $[M+H]^+$: 387.01. HRMS (ESI) m/z calculated $[M+H]^+$: 387.11012; found $[M+H]^+$: 387.11029.

N-benzyl-2-((1,3-dioxoisoindolin-2-yl)oxy)-3-phenylpropanamide (**4j**)



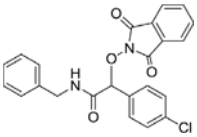
Obtained from 4 mmol reaction as a white solid, yield: 1210 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 3.0, 2H), 7.74 (d, *J* = 2.8, 2H), 7.37 (d, *J* = 7.1, 2H), 7.29 (t, *J* = 7.2, 2H), 7.23 – 7.18 (m, 1H), 7.08 (d, *J* = 6.8, 3H), 6.85 (d, *J* = 6.2, 2H), 4.90 (brs, 1H), 4.29 (d, *J* = 16.1, 1H), 4.08 (d, *J* = 16.1, 1H), 3.32 (brs, 1H), 3.28 – 3.18 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 156.3, 139.0, 135.8, 134.5, 129.8, 129.3, 128.7, 128.1, 127.1, 126.5, 126.4, 123.8, 68.7, 49.9, 41.0. MS (ESI) m/z calculated $[M+H]^+$: 401.43; found $[M+H]^+$: 401.07. HRMS (ESI) m/z calculated $[M+H]^+$: 401.14958; found $[M+H]^+$: 401.14911.

2-((1,3-dioxoisoindolin-2-yl)oxy)-*N*-phenethyl-2-phenylacetamide (**4k**)



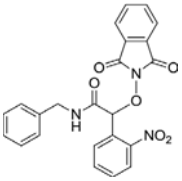
Obtained from 0.5 mmol reaction as a colourless liquid, yield: 98 mg (49%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 3.0, 2H), 7.77 (dd, *J* = 4.6, 3.2, 2H), 7.41 (t, *J* = 8.1, 2H), 7.36 – 7.31 (m, 2H), 7.07 (brs, 3H), 6.88 (brs, 2H), 5.63 (s, 1H), 3.58 – 3.47 (m, 2H), 2.52 (t, *J* = 6.7, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 164.7, 138.5, 135.6, 134.5, 133.6, 129.8, 129.0, 128.8, 128.8, 128.7, 128.6, 127.3, 126.6, 123.7, 75.9, 40.3, 35.5. MS (ESI) m/z calculated $[M+H]^+$: 401.43; found $[M+H]^+$: 401.19. HRMS (ESI) m/z calculated $[M+H]^+$: 401.14958; found $[M+H]^+$: 401.14987.

N-benzyl-2-(4-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)oxy)acetamide (**4l**)



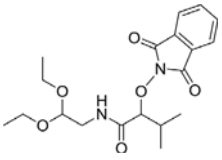
Obtained from 0.5 mmol reaction as a white solid, yield: 109 mg (52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.8, 2H), 7.79 – 7.76 (m, 2H), 7.60 (d, *J* = 8.1, 2H), 7.40 (d, *J* = 8.1, 2H), 7.14 – 7.05 (m, 4H), 6.90 (d, *J* = 6.1, 2H), 5.79 (s, 1H), 4.57 (d, *J* = 15.8, 1H), 4.47 (d, *J* = 15.9, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 156.1, 138.7, 135.8, 135.2, 134.7, 134.5, 129.2, 129.1, 128.2, 127.9, 126.5, 123.9, 69.2, 50.0. MS (ESI) m/z calculated $[M+H]^+$: 421.85; found $[M+H]^+$: 421.16. HRMS (ESI) m/z calculated $[M+H]^+$: 421.09496; found $[M+H]^+$: 421.09506.

N-benzyl-2-((1,3-dioxoisoindolin-2-yl)oxy)-2-(2-nitrophenyl)acetamide (**4m**)



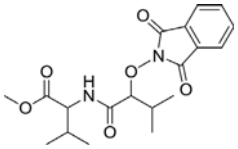
Obtained from 0.5 mmol reaction as a brown solid, yield: 156 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 33.5, 7.7, 2H), 7.87 – 7.68 (m, 7H), 7.55 (t, *J* = 7.4, 1H), 7.20 – 7.07 (m, 3H), 7.03 (d, *J* = 6.4, 2H), 6.53 (s, 1H), 4.77 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 154.4, 147.5, 138.9, 134.7, 134.2, 133.6, 129.4, 129.2, 129.1, 128.2, 126.8, 126.6, 125.3, 123.8, 66.1, 50.9. MS (ESI) m/z calculated $[M+H]^+$: 432.40; found $[M+H]^+$: 432.13. HRMS (ESI) m/z calculated $[M+H]^+$: 432.11901; found $[M+H]^+$: 432.11879.

N-(2,2-diethoxyethyl)-2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbutanamide (**4o**)



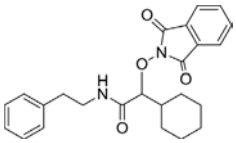
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 143 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, 2H), 7.81 – 7.75 (m, 2H), 4.41 – 4.25 (m, 2H), 3.82 (d, *J* = 2.2, 1H), 3.73 (dd, *J* = 12.5, 5.6, 1H), 3.67 – 3.55 (m, 2H), 3.53 – 3.46 (m, 1H), 3.46 – 3.36 (m, 2H), 2.35 – 2.19 (m, 1H), 1.15 – 1.08 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 158.5, 134.4, 129.3, 123.6, 102.0, 72.6, 63.5, 63.1, 50.4, 31.9, 18.5, 18.2, 15.1, 15.1. MS (ESI) m/z calculated $[M+H]^+$: 379.42; found $[M+H]^+$: 379.39. HRMS (ESI) m/z calculated $[M+H]^+$: 379.18636; found $[M+H]^+$: 379.1857.

methyl 2-(2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methylbutanamido)-3-methylbutanoate (**4p**)



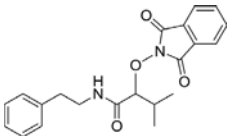
Obtained from 0.5 mmol reaction as a colorless liquid, yield: 86 mg (46%) as a mixture of diastereomers (1:1.05); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 4H), 7.78 (dd, *J* = 5.4, 3.1, 4H), 4.37 (d, *J* = 4.0, 1H), 4.27 (d, *J* = 4.0, 2H), 4.13 (d, *J* = 8.6, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 3.25 (s, 1H), 3.03 (s, 1H), 2.32 – 2.15 (m, 2H), 2.13 – 2.02 (m, 2H), 1.18 – 1.02 (m, 13H), 0.73 (dd, *J* = 15.3, 5.8, 6H), 0.49 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 171.9, 171.7, 163.7, 163.6, 163.6, 163.6, 159.5, 134.7, 134.4, 129.4, 129.4, 123.6, 123.6, 73.8, 73.8, 64.6, 64.3, 64.2, 52.0, 51.9, 32.7, 32.7, 31.8, 31.8, 31.5, 31.2, 31.2, 19.3, 19.2, 18.5, 18.5, 18.5, 18.4 . MS (ESI) m/z calculated $[M+H]^+$: 377.40; found $[M+H]^+$: 377.37. HRMS (ESI) m/z calculated $[M+H]^+$: 377.17071; found $[M+H]^+$: 377.17036.

2-cyclohexyl-2-((1,3-dioxoisoindolin-2-yl)oxy)-*N*-phenethylacetamide (**4q**)



Obtained from 1 mmol reaction as a colorless liquid, yield: 316 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H), 7.80 – 7.72 (m, 2H), 7.16 – 7.04 (m, 3H), 6.99 (d, *J* = 6.8, 2H), 4.30 – 4.14 (m, 1H), 3.70 – 3.52 (m, 2H), 2.73 (d, *J* = 5.3, 1H), 2.69 – 2.53 (m, 2H), 2.09 (d, *J* = 12.5, 1H), 1.88 – 1.64 (m, 5H), 1.36 – 1.23 (m, 2H), 1.22 – 1.11 (m, 1H), 1.10 – 0.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 156.1, 139.6, 134.4, 129.2, 128.9, 128.1, 126.0, 123.6, 71.5, 48.8, 41.5, 37.2, 28.9, 28.4, 26.3, 25.9, 25.7. MS (ESI) m/z calculated $[M+H]^+$: 407.47; found $[M+H]^+$: 407.37. HRMS (ESI) m/z calculated $[M+H]^+$: 407.19653; found $[M+H]^+$: 407.19595.

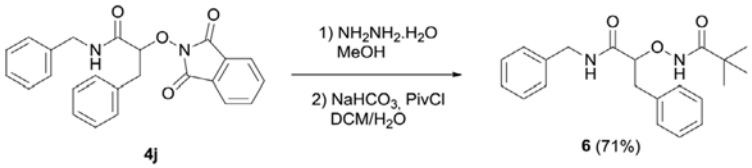
2-((1,3-dioxoisoindolin-2-yl)oxy)-3-methyl-*N*-phenethylbutanamide (**4r**)



Obtained from 1 mmol reaction as a colorless liquid, yield: 324 mg (89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.81 – 7.74 (m, 2H), 7.18 – 7.06 (m, 3H), 7.00 (d, *J* = 6.9, 2H), 4.24 – 4.08 (m, 1H), 3.71 – 3.52 (m, 2H), 2.75 – 2.55 (m, 3H), 2.14 – 1.99 (m, 1H), 1.09 (d, *J* = 6.5, 3H), 1.00 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 156.1, 139.6, 134.4, 129.2, 128.9, 128.2, 126.1, 123.7, 72.2, 48.8, 37.2, 32.3, 18.5, 18.3. MS (ESI) m/z calculated $[M+H]^+$: 367.41; found $[M+H]^+$: 367.23. HRMS (ESI) m/z calculated $[M+H]^+$: 367.16523; found $[M+H]^+$: 367.16522.

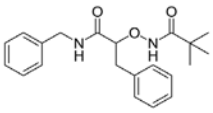
Procedure for the synthesis of O-hydroxylamines and acylation/ sulfonylation

Procedure for the synthesis of *N*-benzyl-3-phenyl-2-(pivalamidooxy)propanamide (6)[1]



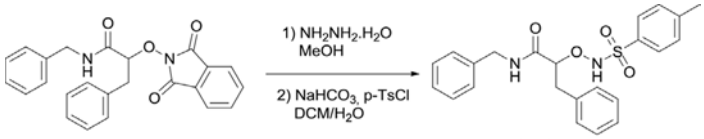
To a solution of 4j (200 mg, 0.5 mmol) in 5 ml of methanol was added 200 µl of hydrazine hydrate. This mixture was stirred at room temperature over 5 h, at the end of which the solvent was removed and dissolved the residue in 15 ml of DCM and washed it with 3% $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and then concentrated to afford colorless oil which was subjected to the next step without further purification. To the solution of above crude product in 2 ml of DCM/H_2O (3 : 1) was added 207 mg of K_2CO_3 (3 equivalent), and followed by 61 µl of pivaloyl chloride (0.5 mmol) at 0°C. The resulting mixture was stirred for 12 h, and then 10 ml of DCM added to it and organic layer was separated and after washed with brine dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent to afford **6**.
([1]: D. W. Zhang, Z. Luo, G. J. Liu and L. H. Weng, Tetrahedron, 2009, 65, 9997-10001.)

N-benzyl-3-phenyl-2-(pivalamidooxy)propanamide (**6**)



Obtained as a white solid, yield: 126 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.29 – 7.27 (m, 2H), 7.26 – 7.23 (m, 3H), 7.21 (d, *J* = 7.3, 2H), 6.76 (s, 1H), 4.48 (dd, *J* = 14.7, 6.0, 1H), 4.45 – 4.34 (m, 2H), 3.27 (dd, *J* = 13.9, 4.1, 1H), 2.95 (dd, *J* = 13.9, 8.2, 1H), 1.26 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 172.2, 137.9, 136.6, 132.1, 129.6, 128.9, 128.7, 127.8, 127.6, 127.1, 73.0, 43.2, 40.9, 27.5, 27.1, 27.0. MS (ESI) m/z calculated $[M+H]^+$: 355.44; found $[M+H]^+$: 355.26.

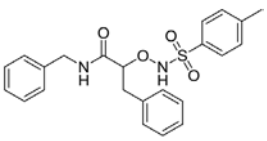
Synthesis of *N*-benzyl-2-((4-methylphenylsulfonamido)oxy)-3 phenylpropanamide (**7**)



4j **7** (64%)

To a solution of **4j** (200 mg, 0.5 mmol) in 5 ml of methanol was added 200 µl of hydrazine hydrate. This mixture was stirred at room temperature over 5 h, at the end of which the solvent was removed and dissolved the residue in 15 ml of DCM and washed it with 3% $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and then concentrated to afford colorless oil which was subjected to the next step without further purification. To the solution of above crude product in 2 ml of DCM/H_2O (3 : 1) was added 207 mg of K_2CO_3 (3 equivalent), and followed by 80 mg of p-TsCl (0.5 mmol) at 0 °C. The resulting mixture was stirred for 12 h, and then 10 ml of DCM added to it and organic layer was separated and after washed with brine dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc-hexane as eluent to afford 7.

***N*-benzyl-2-((4-methylphenylsulfonamido)oxy)-3-phenylpropanamide (7)**



Obtained as a white solid, yield: 135 mg (64%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2, 2H), 7.34 (d, *J* = 8.1, 2H), 7.32 – 7.27 (m, 4H), 7.27 – 7.21 (m, 4H), 7.18 (d, *J* = 7.1, 2H), 6.87 (brs, 1H), 5.87 (s, 1H), 4.45 (dd, *J* = 14.8, 6.1, 1H), 4.41 – 4.31 (m, 2H), 3.24 (dd, *J* = 13.9, 4.0, 1H), 2.93 (dd, *J* = 13.9, 8.2, 1H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.6, 137.8, 136.8, 133.1, 130.0, 129.6, 128.7, 128.7, 128.4, 128.2, 127.8, 127.5, 127.0, 72.9, 43.1, 40.9, 21.6. MS (ESI) m/z calculated $[M+H]^+$: 425.51; found $[M+H]^+$: 425.45.

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