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Iodine-promoted one-pot synthesis of 1,3,4-oxadiazole scaffolds *via* sp^3 C–H functionalization of azaarenes†

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An efficient iodine-mediated one-pot synthetic protocol for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole scaffolds has been developed *via* sp^3 C–H functionalization. Gratifyingly, this method involves oxidative amination with concomitant base-mediated cyclization of methylhetarenes and acylhydrazines by employing iodine and Cs_2CO_3. The key features of the present method include good functional group tolerance, a clean protocol, metal-free conditions and high yields, making this protocol an attractive strategy towards the synthesis of bioactive molecules and their key building blocks.

Introduction

In recent years, oxidative sp^3 C–H bond functionalization has attained significant attention in both industry and academia. Indeed, it is a powerful tool for the construction of C–C and C–heteroatom bonds in synthetic chemistry. Moreover, C–H functionalization offers a novel method of disconnecting the molecule using retrosynthetic analysis, thus providing a more efficient synthetic route from simple starting materials.[1] In this context, considerable attention has been paid to the oxidative functionalization of sp^3 C–H bonds to construct different heterocyclic motifs, and various methods have been developed. Among them, combinations of a metal catalyst with peroxide or molecular oxygen, such as copper/peroxide,[2] iron/O_2[3] and cobalt/O_2,[4] are the best catalytic systems for oxidative C–H bond functionalization. Other efficient approaches include using S_8 and iodine reagents with oxidants such as S_8/oxidant,[5] hypervalent iodine/azide,[6] and iodine reagents/peroxide.[7] However, these catalytic systems are usually limited exclusively to symmetrical alkanes and aryl methyl ketones. Thus, developing an efficient strategy for sp^3 C–H oxidative functionalization is challenging and a highly desirable target for synthetic chemists.

1,3,4-Oxadiazoles are important five-membered heterocyclic scaffolds in the realm of natural and synthetic chemistry, due to their wide range of biological and pharmaceutical activities. Currently available marketed drugs based on this oxadiazole nucleus are raltegravir (i, antiretroviral), tidazosin (ii, antihypertensive), furamizole (iii, antibiotic), and nesapidil (iv, antihypertensive), shown in Fig. 1.[8] Moreover, they are also reported to possess anticancer,[9] mycobacterial,[10] anti-inflammatory,[11] analgesic,[12] anti-diabetic,[13] anthelmenthic[14] and anticonvulsant properties.[15] The oxadiazole nucleus also acts as a good bioisostere for ester and amide functional groups, and moreover, it contributes to the pharmacological activity of drug molecules by participating in hydrogen-bonding interactions with several receptors. In a few instances, it acts as a flat aromatic linker to offer an appropriate orientation to the molecule.[16]

Numerous methods have been developed for the synthesis of 1,3,4-oxadiazoles, such as Cu(II)-catalyzed oxidation,[17] oxidative cyclization of acyl hydrazones using $Fe(NO_3)_3$,[18a] $FeCl_3$,[18b] Br_2,[18c] chloramine T,[18d] HgO/I_2,[18e] cerium ammonium nitrate,[18f] tetravalent lead reagents,[18g] hypervalent iodine reagents,[18h–j] and dehydrative cyclization of acyl hydrazines using $SOCl_2$, H_2SO_4 and PPA, *etc.*[19] Nevertheless, many of these synthetic methods

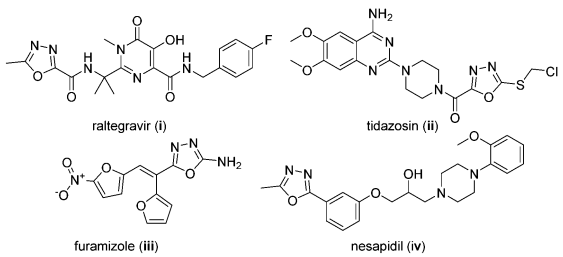

Fig. 1 Representative biologically active molecules containing 1,3,4-oxadiazole.

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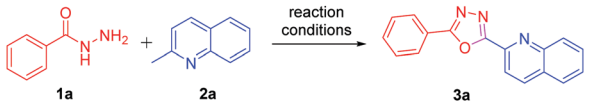
suffer from certain limitations, such as limited substrate scope, harsh reaction conditions, low yield, long reaction times, complicated work-up procedures leading to the production of toxic metal waste and problems with scalability. Therefore, the development of a facile, environmentally benign, metal-free method for the synthesis of these valuable heterocycles is highly desirable. In this context, iodine has attained significant attention from researchers due to its potential catalytic nature, as a greener alternative to transition metals. In 2013, Yu *et al.* developed a highly efficient I_2-mediated synthesis of 1,3,4-oxadiazoles *via* the oxidative cyclization of acylhydrazones.[20] However, this method exhibits certain disadvantages, such as the use of chemically unstable aldehydes as starting materials, involving the synthesis and isolation of an acyl hydrazone intermediate. Therefore, the development of an inexpensive, metal-free strategy for the synthesis of these heterocycles in a one-pot manner is urgently needed. Although numerous synthetic methods have been reported for the synthesis of 1,3,4-oxadiazoles, the concept of oxidative addition through sp^3 C–H bond amination with concomitant base-mediated cyclization has not yet been exploited. As part of our research program for the development of novel synthetic methodologies[21] towards medicinally important compounds in an environmentally friendly manner, and to overcome the limitations of previous approaches, herein, we communicate an oxidative benzylic C–H bond amination of heteroaromatic methanes to afford medicinally important 1,3,4-oxadiazoles in a one-pot manner.

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Additive (equiv.)	Base (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	I_2 (1.0)	K_2CO_3 (3)	DMSO	100	12	5
2	I_2 (1.0)	Cs_2CO_3 (3)	DMSO	100	12	56
3	I_2 (1.0)	DBU (3)	DMSO	100	12	41
4	I_2 (1.0)	Et_3N (3)	DMSO	100	12	19
5	I_2 (1.0)	Cs_2CO_3 (3)	CH_3CN	80	12	NF
6	I_2 (1.0)	Cs_2CO_3 (3)	Toluene	100	12	NF
7	I_2 (1.0)	Cs_2CO_3 (3)	DMF	100	12	18
8	NIS (1.0)	Cs_2CO_3 (3)	DMSO	100	12	21
9	$PhI(OAc)_2$ (1.0)	Cs_2CO_3 (3)	DMSO	100	12	NF
10	TBAI (1.0)	Cs_2CO_3 (3)	DMSO	100	12	NF
11	I_2 (1.4)	Cs_2CO_3 (3)	DMSO	100	6	70
12	I_2 (1.8)	Cs_2CO_3 (3)	DMSO	100	5	82
13	I_2 (2.0)	Cs_2CO_3 (3)	DMSO	100	5	80
14	I_2 (1.8)	Cs_2CO_3 (5)	DMSO	100	5	74
15	I_2 (1.8)	Cs_2CO_3 (2)	DMSO	100	5	71
16	I_2 (1.8)	Cs_2CO_3 (3)	DMSO	120	5	84
17	I_2 (1.8)	Cs_2CO_3 (3)	DMSO	150	5	78
18	I_2 (1.8)	Cs_2CO_3 (3)	DMSO	80	12	45
19[c]	I_2 (1.8)	Cs_2CO_3 (3)	DMSO	120	5	89

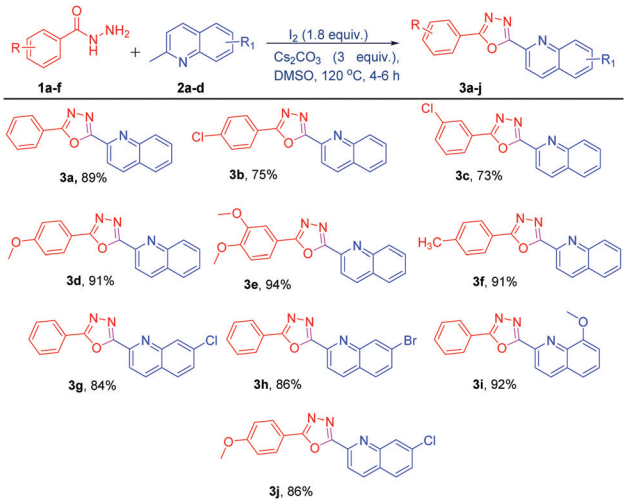
[a] All the reactions were performed using **1a** (1 mmol), **2a** (1 mmol). [b] Isolated yields. [c] Iodine (1.8 equiv.) was added to a solution of **2a** (1 mmol) in DMSO and was stirred for 1 h, followed by addition of **1a** along with base (Cs_2CO_3, 3 equiv.). DMSO: dimethyl sulfoxide; DMF: dimethyl formamide; NIS: *N*-iodosuccinimide; TBAI: tetrabutylammonium iodide.

Results and discussion

Initially, our investigation began with the reaction of benzohydrazide (**1a**) and 2-methyl quinoline (**2a**) in the presence of iodine (1 equiv.) and K_2CO_3 (3 equiv.) using DMSO as a solvent at 100 °C for 12 h, resulting in the formation of **3a** in 5% yield (entry 1, Table 1). To find optimum conditions for this reaction, various bases were initially screened, such as Cs_2CO_3, DBU and Et_3N (entries 2–4, Table 1). The results illustrated that Cs_2CO_3 exhibited the best conversion, and the desired product **3a** was obtained (entry 2, Table 1) in 56% yield. In order to improve the yield of **3a**, different solvents were also screened, including acetonitrile, toluene and dimethylformamide (entries 5–7, Table 1). These results encouraged us to use DMSO as a suitable solvent and may well imply that DMSO is involved in the oxidation of the C(sp^3)–H bond. Thereafter, different iodine sources, including *N*-iodosuccinimide (NIS), $PhI(OAc)_2$ and tetrabutylammonium iodide (TBAI), were used instead of I_2 in DMSO (entries 8–10, Table 1). However, these reagents were not effective and only NIS furnished the desired product **3a** (entry 8, Table 1) in 21% yield. Once we established an appropriate base and solvent, we then directed our attention towards fixing the quantity of iodine required for the reaction. Initially, we employed 1 equivalent of iodine and noticed 56% formation of the desired product **3a**. Interestingly, the product **3a** formation was increased to a greater extent by employing iodine at 1.8 equivalents (entries 11–12, Table 1). However, further increasing the amount of iodine led to a detrimental effect on the product yield of **3a** (entry 13, Table 1). Additionally, altering the quantity of base did not improve the yield of **3a** (entries 14–15, Table 1). This reaction was also tested at different temperatures to improve the reaction yield and 120 °C was found to be the optimum temperature (entries 16–18, Table 1). Gratifyingly, the reaction efficiency was further increased, providing the formation of **3a** in 89% yield when iodine was added to a solution of **2a** in DMSO and stirred for 1 h with subsequent addition of **1a** and base (entry 19, Table 1), followed by stirring at 120 °C for 5 h. Therefore, systematic screening of the reaction conditions revealed that the synthesis of 1,3,4-oxadiazoles was most efficient when I_2 (1.8 equiv.) and Cs_2CO_3 (3 equiv.) were employed in DMSO at 120 °C (entry 19, Table 1).

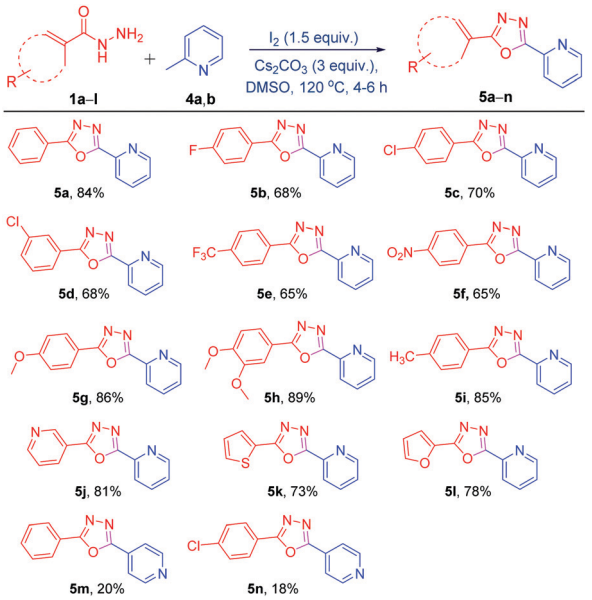
With the optimized conditions in hand, we then focused on investigating the substrate scope of the protocol towards the synthesis of different disubstituted 1,3,4-oxadiazoles. In this context, a wide range of acyl hydrazines and methylhetarenes bearing electron-withdrawing and electron-donating groups were successfully employed to study the substrate scope of the protocol. As depicted in Table 2, all the reactions proceeded smoothly to furnish the corresponding products in excellent yields ranging from 73 to 94%. The electronic nature of the substituents on acyl hydrazine and methylhetarenes had an influence on the reaction yields and reaction efficiency. For instance, acylhydrazines bearing electron-withdrawing groups such as methoxy (**3d**, 91%), dimethoxy (**3e**, 94%) and methyl (**3f**, 91%) reacted efficiently at a faster rate to afford the corresponding 1,3,4-oxadiazoles in excellent yields. However, acylhydrazines bearing an

Table 2 Iodine-catalyzed one-pot synthesis of various 1,3,4-oxadiazoles (**3a–j**) from acylhydrazines (**1a–f**) and 2-methylquinolines (**2a–d**)[a,b]

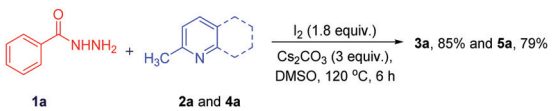


[a] All the reactions were performed with **1a–f** (1 mmol), **2a–d** (1 mmol), iodine (1.8 mmol), and Cs_2CO_3 (3 equiv.) in DMSO at 120 °C for 4–6 h. [b] Isolated yields.

Table 3 Iodine-mediated one-pot synthesis of various 1,3,4-oxadiazoles (**5a–n**) from acylhydrazines (**1a–l**) and 2-methylpyridines (**4a** and **b**)[a,b]



[a] All the reactions were performed with **1a–l** (1 mmol), **4a** and **b** (1 mmol), iodine (1.8 mmol) and Cs_2CO_3 (3 equiv.) in DMSO at 120 °C for 4–6 h. [b] Isolated yields.



Scheme 1 Gram-scale reaction for the synthesis of **3a** and **5a**.

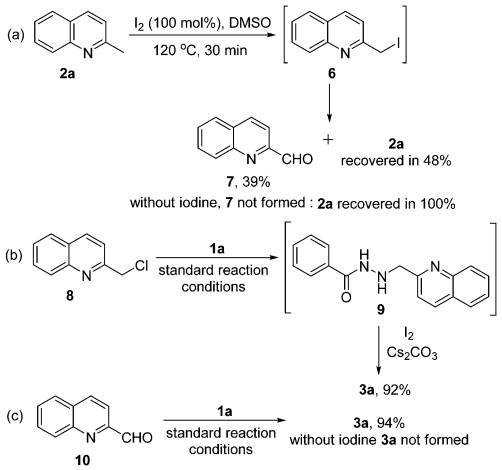
electron-withdrawing group such as chloro furnished **3b** and **3c** in moderate yields of 75% and 73%, respectively. Interestingly, chloro group substitution at the 4th position obtained the corresponding product with a slightly higher yield (**3b**, 75%) when compared to substitution at the 3rd position (**3c**, 73%). Subsequently, we focused our attention on the substrate scope diversity of other components, *i.e.* 2-methylquinolines. Substituted 2-methylquinolines (chloro, bromo and methoxy) were employed, as they were expected to furnish the corresponding products with excellent yields (**3g–j**, Table 2). Interestingly, a reaction performed with methoxy-substituted acylhydrazine and chloro-substituted 2-methylquinoline also proceeded well to afford the corresponding product **3j** in 86% yield.

Later, we were also interested to explore this protocol by employing 2-methyl pyridine as a substrate to deliver the different 1,3,4-oxadiazole scaffolds. To our delight, 2-methyl pyridine was amenable to this reaction and reacted well with various substituted acylhydrazines to afford the products **5a–n** in moderate to good yields (Table 3). The electronic nature of acylhydrazine had an effect on the reaction rate and reaction yields. Substrates bearing an electron-withdrawing group, such as chloro, bromo, trifluoromethyl, and nitro functionalities, delivered the 1,3,4-oxadiazoles **5b–f** in moderate yields after prolonged reaction times, whereas electron-donating groups, such as methoxy, dimethoxy and methyl groups, furnished the products **5g–i** in good yields in a shorter reaction time (Table 3). Investigations with heteroaryl acylhydrazines, such as pyridyl, thiophene and furan, were also found to be fruitful and delivered the products **5j–l** in 81%, 73% and 78% yields, respectively (Table 3). In order to explore the synthetic applicability and efficiency of the presented method, we executed the reaction with 4-methylpyridine and acylhydrazine. However, the reaction proceeded in a very sluggish manner and furnished the corresponding products **5m** and **5n** in lower yields.

In order to extend the synthetic applicability of the present protocol, a gram scale synthesis was performed by reacting the substrates **2a** (5.2 g, 36.7 mmol) and **4a** (4.9 g, 36.7 mmol) with **1a** (5 g, 36.7 mmol) under standard conditions. The quantitative yield of the products **3a** and **5a** (Scheme 1) in 85% and 79% yield in a gram scale revealed that this protocol has the potential for utility in industrial scale-up operations.

To elucidate the reaction pathway for the formation of the various disubstituted 1,3,4-oxadiazoles, a few control experiments were performed (Scheme 2). Initially, we performed a reaction with 2-methyl quinoline (**2a**) in the presence of iodine (1.0 equiv.) in DMSO at 120 °C for 30 min without using acyl hydrazine (**1a**) and obtained a quinoline-2-carbaldehyde (**7**) in 39% yield. The starting material **2a** (48%) was recovered, whereas **7** was not detected in the absence of iodine and **2a** was completely recovered (Scheme 2a).

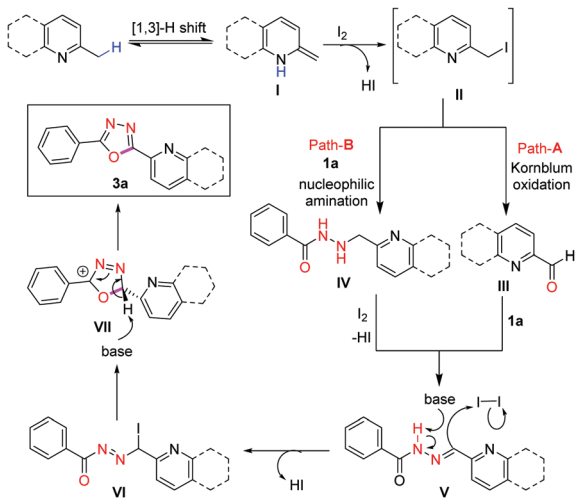
Considering that previous literature reports[22] revealed that the nucleophilic reactivity of 2-methyl quinoline (**2a**) is mediated by iodine, 2-methyl quinoline might undergo a nucleophilic halogenation in the presence of iodine to furnish a 2-iodomethyl quinoline (**6**). However, the iodo intermediate **6** is unstable and cannot be isolated, and it undergoes a Kornblum oxidation leading to the formation of quinoline-2-carbaldehyde (**7**), in agreement with a report from Wu *et al.*[23] To avoid the Kornblum oxidation step for the formation of quinoline 2-carbaldehyde (**7**), **6** could



Scheme 2 Control experiments.

instead undergo nucleophilic amination directly with acyl hydrazine (**1a**) to produce an intermediate **9**. Hence, we conducted a control experiment with acylhydrazine (**1a**) and 2-chloromethylquinoline (**8**) under standard conditions, which affords the desired product **3a** in 92% yield (Scheme 2b). This reaction may be advanced through the *in situ* halide exchange of the chloro group in 2-chloromethylquinoline (**8**) with an iodo group in the presence of iodine to form a 2-iodomethyl quinoline (**6**). Subsequently, we performed a reaction with **1a** and quinoline-2-carbaldehyde (**7**) using two cases in the presence and absence of iodine, which furnished the product **3a** only in the presence of iodine, whereas product **3a** was not detected in the latter case, *i.e.* in the absence of iodine (Scheme 2c). Therefore, control experimental data revealed that 2-iodomethyl quinoline (**6**) and quinoline 2-carbaldehyde (**7**) might be the potential intermediates in this reaction process.

Based on the literature reports and control experimental results, a plausible mechanistic pathway for the synthesis of 1,3,4-oxadiazole is depicted in Scheme 3. At the onset, 2-methylazaarene exists in equilibrium with the more nucleophilic enamine *via* imine–enamine tautomerization *via* [1,3]H-shift, which subsequently undergoes a nucleophilic halogenation with iodine to form a 2-iodomethyl azaarene **II**. Next, in path-**A**, intermediate **II** is further oxidized to provide aldehyde **III** *via* Kornblum oxidation with DMSO,[24] followed by condensation with acylhydrazine (**1a**) to afford an acyl hydrazone **V**. Alternatively, in path-**B**, intermediate **II** undergoes subsequent nucleophilic amination with acyl hydrazine to form an intermediate **IV**, which is oxidized further with iodine to furnish intermediate **V**. Finally, **V** undergoes a base-promoted oxidative iodination to furnish the iodinated intermediate **VI**, which subsequently undergoes S_N2 type cyclization to form a C–O bond, followed by deprotonation with base to furnish the desired product **3a**. The base neutralizes the HI which is generated in the reaction medium.



Scheme 3 Plausible reaction mechanism.

Conclusion

In conclusion, an efficient I_2-mediated oxidative amination with concomitant base-mediated cyclization for the synthesis of various disubstituted 1,3,4-oxadiazoles has been developed in a one-pot manner. This method employs Cs_2CO_3 as an efficient base, which plays an important role in the cyclization process. The key features of this methodology are operational simplicity, high yields, good functional group tolerance and low environmental impact. Additionally, this method utilizes a wide range of substrates and progresses under metal-free conditions using DMSO as an efficient oxidant. Moreover, a gram-scale synthesis was also achieved and this protocol may find significant applications in the design of new chemical entities (NCEs) in the drug discovery process for various therapeutic purposes.

Experimental section

General information

All the reagents and chemicals were obtained from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed with silica gel (MERCK silica gel 60-F254; 0.5 mm) precoated glass plates. TLC plates were visualized by exposure to ultraviolet light. Column chromatography was performed using 100–200 mesh silica gel, and the eluent was as a mixture of ethyl acetate and *n*-hexane. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz NMR instrument in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and coupling constants (J) are reported in parts per million (ppm) and Hertz (Hz), respectively. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; ddd, doublet of doublet of doublet. Melting points were determined using an electrothermal apparatus (Model IA9200) and are uncorrected. High-resolution mass spectra (HRMS) were recorded on LC-QTOF mass spectrometer.

General procedure for the synthesis of 1,3,4-oxadiazole (3a–j, 5a–n)

In a 25 ml round bottomed flask, methyl quinoline (1 mmol) and iodine (1.8 mmol) in DMSO were refluxed at 120 °C

followed by the addition of acylhydrazine (1 mmol) after 1 h, and continued refluxing at 120 °C for 3–5 h. After completion of the reaction (monitored with TLC), the reaction mixture was quenched with a saturated solution of sodium thiosulphate and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by silica-gel column chromatography using ethyl acetate–hexane as the eluent in increasing polarity to afford the desired 1,3,4-oxadiazoles **3a–j** and **5a–n**.

2-Phenyl-5-(quinolin-2-yl)-1,3,4-oxadiazole (3a). 242 mg (89%) of **3a** was obtained as a yellow solid; R_f = 0.766 (ethyl acetate/*n*-hexane, 1 : 1); Mp. 164–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, J = 8.5 Hz, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.31–8.27 (m, 3H), 7.91 (d, J = 8.1 Hz, 1H), 7.85–7.80 (m, 1H), 7.69–7.64 (m, 1H), 7.62–7.54 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.96, 164.08, 147.80, 143.28, 137.64, 132.12, 130.68, 130.00, 129.08, 128.74, 128.36, 127.81, 127.52, 123.63, 119.88; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}N_3NaO$ $[M + Na]^+$ 296.0794, found 296.0810.

2-(4-Chlorophenyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole (3b). 230 mg (75%) of **3b** was obtained as a white solid; R_f = 0.866 (ethyl acetate/*n*-hexane, 1 : 1); Mp. 184–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, J = 8.5 Hz, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.25–8.21 (m, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.86–7.81 (m, 1H), 7.70–7.65 (m, 1H), 7.57–7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.08, 164.32, 147.94, 143.18, 138.43, 137.51, 130.64, 130.08, 129.48, 128.75, 128.73, 128.38, 127.82, 122.12, 119.87; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}ClN_3O$ $[M + H]^+$ 308.0585, found 308.0597.

2-(3-Chlorophenyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole (3c). 224 mg (73%) of **3c** was obtained as a yellow solid; R_f = 0.666 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 146–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (q, J = 8.5 Hz, 2H), 8.29 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 6.9 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.1 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.32, 164.22, 147.76, 143.04, 137.82, 133.67, 132.69, 131.68, 131.26, 130.79, 130.06, 128.84, 128.50, 127.80, 127.12, 123.07, 119.93; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{10}ClN_3NaO$ $[M + Na]^+$ 330.0405, found 330.0416.

2-(4-Methoxyphenyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole (3d). 275 mg (91%) of **3d** was obtained as a white solid; R_f = 0.530 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 167–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.25–8.19 (m, 2H), 7.90 (d, J = 8.1 Hz, 1H), 7.85–7.79 (m, 1H), 7.68–7.63 (m, 1H), 7.08–7.04 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.88, 163.76, 162.69, 147.93, 143.55, 137.38, 130.50, 130.07, 129.30, 128.66, 128.17, 127.77, 119.83, 116.14, 114.52, 55.48; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}N_3NaO_2$ $[M + Na]^+$ 326.0900, found 326.0911.

2-(3,4-Dimethoxyphenyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole (3e). 275 mg (91%) of **3e** was obtained as a white solid; R_f = 0.322 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 184–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (t, J = 6.3 Hz, 2H), 8.36 (d, J = 8.8 Hz, 1H), 7.92 (dd, J = 8.2, 1.0 Hz, 1H), 7.86–7.82 (m, 1H), 7.69–7.65 (m, 1H), 7.44 (d, J = 2.3 Hz, 2H), 6.67 (t, J = 2.3 Hz, 1H), 3.91 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.87, 164.21, 161.24, 148.02, 143.42, 137.40, 130.54, 130.15, 128.72, 128.29, 127.78, 125.15, 119.89, 105.23, 104.96, 55.74; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{16}N_3O_3$ $[M + H]^+$ 334.1186, found 334.1202.

2-(Quinolin-2-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole (3f). 261 mg (91%) of **3f** was obtained as a white solid; R_f = 0.233 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 176–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.1 Hz, 1H), 7.86–7.80 (m, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.13, 164.07, 148.10, 143.67, 142.72, 137.37, 130.51, 130.23, 129.81, 128.76, 128.24, 127.81, 127.51, 121.01, 119.94, 21.71; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{14}N_3O$ $[M + H]^+$ 288.1131, found 288.1134.

2-(7-Chloroquinolin-2-yl)-5-phenyl-1,3,4-oxadiazole (3g). 257 mg (84%) of **3g** was obtained as a pale yellow solid; R_f = 0.800 (ethyl acetate/*n*-hexane, 1 : 1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 8.6 Hz, 1H), 8.28 (dd, J = 4.2, 1.7 Hz, 2H), 8.27–8.25 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.62–7.59 (m, 1H), 7.59–7.57 (m, 2H), 7.57–7.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.06, 163.96, 148.34, 144.41, 137.27, 136.60, 132.20, 129.33, 129.12, 129.07, 128.96, 127.51, 127.05, 123.58, 120.09; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}ClN_3O$ $[M + H]^+$ 308.0585, found 308.0598.

2-(7-Bromoquinolin-2-yl)-5-phenyl-1,3,4-oxadiazole (3h). 301 mg (86%) of **3h** was obtained as a white solid; R_f = 0.699 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 194–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, J = 8.6 Hz, 1H), 8.30–8.24 (m, 3H), 8.16 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 9.0, 2.2 Hz, 1H), 7.62–7.54 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.06, 163.79, 146.33, 143.56, 136.61, 134.27, 132.23, 131.56, 129.90, 129.69, 129.12, 127.52, 123.49, 122.64, 120.75; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{10}BrN_3NaO$ $[M + Na]^+$ 373.9899, found 373.9908.

2-(8-Methoxyquinolin-2-yl)-5-phenyl-1,3,4-oxadiazole (3i). 278 mg (92%) of **3i** was obtained as a white solid; R_f = 0.350 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.32–8.29 (m, 2H), 7.62–7.53 (m, 4H), 7.50–7.46 (m, 1H), 7.18–7.13 (m, 1H), 4.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.93, 164.25, 155.72, 142.31, 139.92, 137.39, 131.99, 129.94, 128.95, 128.79, 127.58, 123.67, 120.58, 119.50, 108.70, 56.16; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{13}N_3NaO_2$ $[M + Na]^+$ 326.0900, found 326.0906.

2-(7-Chloroquinolin-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3j). 257 mg (84%) of **3j** was obtained as a white solid; R_f = 0.800 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 206–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, J = 8.5 Hz, 1H), 8.36 (t, J = 6.7 Hz, 2H), 8.26–8.22 (m, 2H), 7.86 (d, J = 8.7 Hz, 1H), 7.62 (dd, J = 8.7, 2.0 Hz, 1H), 7.10–7.05 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.05, 163.42, 162.78, 148.16, 144.40, 137.32, 136.60, 129.35, 129.24, 128.96, 128.90, 126.97, 120.02, 115.96, 114.57, 55.52; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{12}ClN_3NaO_2$ $[M + Na]^+$ 360.0510, found 360.0517.

2-Phenyl-5-(pyridin-2-yl)-1,3,4-oxadiazole (5a). 187 mg (84%) of **5a** was obtained as a white solid; R_f = 0.233 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 121–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (dd, J = 4.7, 0.5 Hz, 1H), 8.35–8.32 (m, 1H), 8.25–8.21

(m, 2H), 7.95–7.89 (m, 1H), 7.60–7.51 (m, 3H), 7.51–7.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.72, 163.50, 149.91, 143.19, 137.74, 132.09, 129.08, 127.38, 125.95, 123.53, 123.38; HRMS (ESI): *m*/*z* calcd for $C_{13}H_9N_3NaO$ $[M + Na]^+$ 246.0638, found 246.0645.

2-(4-Fluorophenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5b). 163 mg (68%) of **5b** was obtained as a white solid; R_f = 0.173 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 156–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85–8.79 (m, 1H), 8.36–8.30 (m, 1H), 8.27–8.19 (m, 2H), 7.96–7.89 (m, 1H), 7.52–7.47 (m, 1H), 7.26–7.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.04 (d, J = 253.76 Hz), 164.88, 163.62, 150.03, 143.21, 137.64, 129.71 (d, J = 9.0 Hz), 125.98, 123.37, 119.89 (d, J = 3.28 Hz), 116.46 (d, J = 22.3 Hz); HRMS (ESI): *m*/*z* calcd for $C_{13}H_8FN_3NaO$ $[M + Na]^+$ 264.0544, found 264.0552.

2-(4-Chlorophenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5c). 179 mg (70%) of **5c** was obtained as a white solid; R_f = 0.260 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, J = 3.7 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.6 Hz, 2H), 7.93 (t, J = 7.6 Hz, 1H), 7.56–7.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.85, 163.84, 150.23, 143.34, 138.42, 137.49, 129.50, 128.62, 126.01, 123.41, 122.07; HRMS (ESI): *m*/*z* calcd for $C_{13}H_8ClN_3NaO$ $[M + Na]^+$ 280.0248, found 280.0259.

2-(3-Chlorophenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5d). 174 mg (68%) of **5d** was obtained as a white solid; Mp. 164–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, J = 4.7 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.11 (dd, J = 7.8, 1.6 Hz, 1H), 7.96–7.89 (m, 1H), 7.61–7.56 (m, 1H), 7.54–7.47 (m, 2H), 7.46–7.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.10, 163.86, 150.36, 143.41, 137.39, 133.52, 132.62, 131.50, 131.25, 127.08, 125.98, 123.39, 123.01; HRMS (ESI): *m*/*z* calcd for $C_{13}H_8ClN_3NaO$ $[M + Na]^+$ 280.0248, found 280.0255.

2-(Pyridin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (5e). 191 mg (65%) of **5e** was obtained as a white solid; R_f = 0.533 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 137–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87–8.82 (m, 1H), 8.39–8.34 (m, 3H), 7.99–7.91 (m, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.55–7.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.52, 164.02, 150.03, 142.93, 137.79, 133.67 (q, J = 32.94), 127.70, 126.78, 123.59, 123.55 (q, J = 271.89 Hz), 126.23, 126.14 (q, J = 3.74 Hz); HRMS (ESI): *m*/*z* calcd for $C_{14}H_8F_3N_3NaO$ $[M + Na]^+$. 314.0512, found 314.0522.

2-(4-Nitrophenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5f). 174 mg (65%) of **5f** was obtained as a yellow solid; R_f = 0.225 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 180–182 °C; ^{1}H NMR (500 MHz, DMSO): δ 8.85 (d, J = 3.7 Hz, 1H), 8.47 (dd, J = 7.2, 3.8 Hz, 2H), 8.39 (dd, J = 6.1, 2.7 Hz, 2H), 8.32 (dd, J = 7.3, 4.2 Hz, 1H), 8.16–8.09 (m, 1H), 7.76–7.64 (m, 1H); ^{13}C NMR (125 MHz, DMSO): δ 164.75, 163.82, 150.90, 149.80, 142.98, 138.44, 129.28, 128.67, 127.19, 125.14, 123.87; HRMS (ESI): *m*/*z* calcd for $C_{13}H_8N_4NaO_3$ $[M + Na]^+$. 291.0489, found 291.0492.

2-(4-Methoxyphenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5g). 317 mg (86%) of **5g** was obtained as a white solid; R_f = 0.140 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 158–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.35 (d, J = 7.78 Hz, 1H), 8.19 (d, J = 8.9 Hz, 2H), 7.97 (t, J = 7.5 Hz, 1H), 7.60–7.48 (m, 1H), 7.04 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.82, 162.85, 162.74, 149.60, 143.04, 137.87, 129.37, 125.76, 123.48, 115.90, 114.62, 55.75; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}N_3NaO_2$ $[M + Na]^+$ 276.0743, found 276.0747.

2-(3,4-Dimethoxyphenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5h). 251 mg (89%) of **5g** was obtained as a white solid; R_f = 0.128 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 179–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.33 (d, J = 7.8 Hz, 1H), 7.94 (t, J = 7.7 Hz, 1H), 7.55–7.48 (m, 1H), 7.37 (d, J = 1.5 Hz, 2H), 6.64 (d, J = 1.5 Hz, 1H), 3.88 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.75, 163.52, 161.25, 149.91, 143.22, 137.72, 125.95, 125.03, 123.43, 105.08, 55.78; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}N_3O_3$ $[M + H]^+$ 284.1030, found 284.0949.

2-(Pyridin-2-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole (5i). 201 mg (85%) of **5h** was obtained as a white solid; R_f = 0.173 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, J = 4.3 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 8.2 Hz, 2H), 7.95–7.90 (m, 1H), 7.49 (dd, J = 7.0, 4.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.83, 163.45, 150.11, 143.53, 142.69, 137.47, 129.78, 127.33, 125.80, 123.27, 120.80, 21.68; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}N_3NaO_3$ $[M + Na]^+$. 260.0794, found 260.0803.

2-(Pyridin-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (5j). 181 mg (81%) of **5i** was obtained as a yellow solid; R_f = 0.130 (ethyl acetate/*n*-hexane, 4 : 1); Mp. 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.82 (d, J = 4.4 Hz, 2H), 8.56 (dt, J = 8.0, 1.7 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.93 (td, J = 7.8, 1.7 Hz, 1H), 7.59–7.53 (m, 1H), 7.53–7.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.35, 163.46, 152.44, 150.42, 148.04, 143.31, 137.34, 134.67, 126.12, 123.89, 123.48, 120.33; HRMS (ESI): *m*/*z* calcd for $C_{12}H_9N_4O_3$ $[M + H]^+$ 225.0771, found 225.0774.

2-(Pyridin-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (5k). 167 mg (73%) of **5j** was obtained as a white solid; R_f = 0.100 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 3.3 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.94–7.87 (m, 2H), 7.58 (dd, J = 5.0, 1.2 Hz, 1H), 7.47 (dd, J = 6.9, 5.0 Hz, 1H), 7.18 (dd, J = 5.0, 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.26, 161.88, 150.02, 143.28, 137.46, 130.75, 130.61, 128.27, 125.90, 124.80, 123.33; HRMS (ESI): *m*/*z* calcd for $C_{11}H_7N_3NaOS$ $[M + Na]^+$ 252.0202, found 252.0208.

2-(Furan-2-yl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (5l). 166 mg (78%) of **5k** was obtained as a white solid; R_f = 0.133 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.93–7.84 (m, 1H), 7.69–7.62 (m, 1H), 7.52–7.42 (m, 1H), 7.34–7.29 (m, 1H), 6.61 (dd, J = 3.5, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.11, 158.31, 150.35, 146.10, 143.22, 139.17, 137.29, 125.96, 123.34, 114.92, 112.32; HRMS (ESI): *m*/*z* calcd for $C_{11}H_7N_3NaO_2$ $[M + Na]^+$ 236.0430, found 236.0438.

2-Phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazole (5m). 44 mg (20%) of **5l** was obtained as a white solid; R_f = 0.166 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.84 (d, J = 5.8 Hz, 2H), 8.18–8.11 (m, 2H), 8.03–7.97 (m, 2H), 7.62–7.52 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.52, 162.75, 150.78, 132.31, 131.17, 129.24, 127.17, 123.37, 120.37; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$ 224.0818, found 224.0905.

2-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (5n). 46 mg (18%) of **5m** was obtained as a white solid; R_f = 0.200 (ethyl acetate/*n*-hexane, 2 : 3); Mp. 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.86 (d, J = 5.8 Hz, 2H), 8.13–8.08 (m, 2H), 8.04 –8.00 (m, 2H), 7.57–7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.76, 162.84, 150.66, 138.75, 131.13, 129.68, 128.43, 121.81, 120.43; HRMS (ESI): *m*/*z* calcd for $C_{13}H_9ClN_3O$ $[M + H]^+$ 258.0429, found 258.0480.

Conflicts of interest

There are no conflicts to declare.

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