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STRATEGIC AND TACTICAL APPROACHES TO THE SYNTHESIS OF 5,6-DIHYDRO-[1,2,4]OXADIAZINES

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Abstract – Three methods were developed for the synthesis of substituted 5,6-dihydro-4*H*-[1,2,4]oxadiazines. The desired oxadiazine rings were synthesised *via* reductive amination, addition to an iminium ion intermediate and by condensation of a diamine with an imidate. For all methods the scope with respect to the substituents that could be introduced was explored. It was found that the imidate condensation route was the most versatile and the products could be isolated in yields up to 91%. This route is also suitable for the introduction of chirality on the C5 and C6 position of the oxadiazine rings.

INTRODUCTION

Small heterocycles are important structures in pharmaceuticals and other bioactive compounds, as they provide a central scaffold around which substituents can be placed in a well-defined manner to probe the biological activity.¹ Therefore, the development of efficient and general methodology to access these heterocyclic scaffolds is an important endeavour.² As part of a medicinal chemistry program, the synthesis of 3,5-biaryl substituted 5,6-dihydro-4*H*-[1,2,4]oxadiazines was of interest. This heterocyclic scaffold has an already established pharmaceutical relevance and is for example present in a non-ATP-competitive MK2 inhibitor (**1**, Figure 1) to treat inflammatory diseases such as arthritis.³ In addition, it has been used as a central scaffold in a lead compound for the treatment of Alzheimer's disease (**2**)⁴ and in BRX-235 (Iroxanadine, **3**), a drug which acts as a potent cardioprotective agent.⁵

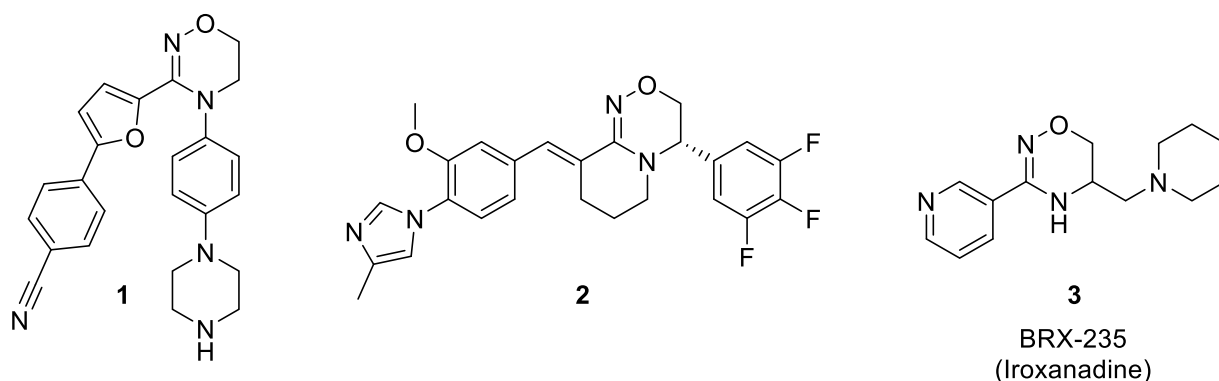
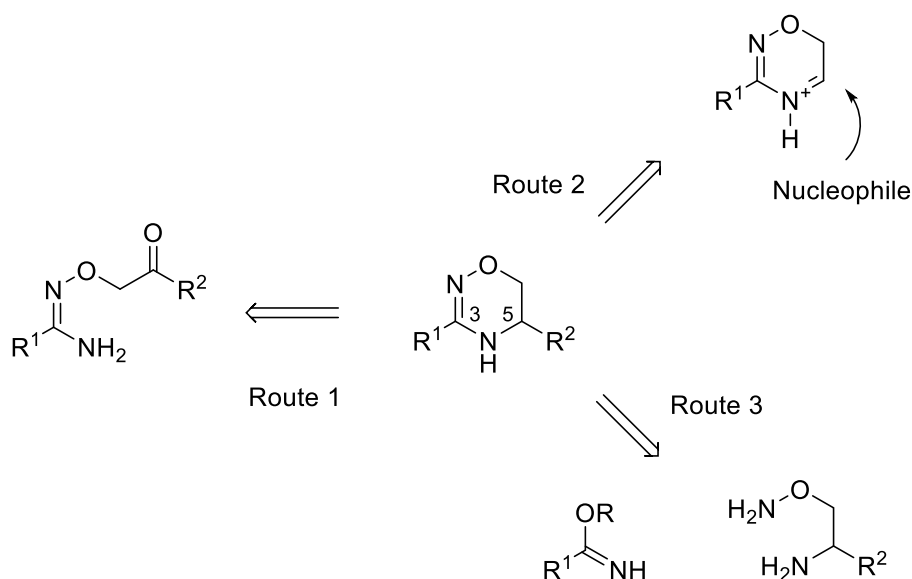


Figure 1. Examples of 1,2,4-oxadiazines in pharmaceuticals

A survey of the literature reveals a few early examples on the synthesis of 5,6-dihydro-4*H*-[1,2,4]oxadiazines.⁶ However, to the best of our knowledge, the first report in this field was contributed by Rajagopalan and Talaty.⁷ They developed a two-step procedure in which an 1-arylaziridine oxime undergoes ring-opening by hydrochloric acid, followed by a cyclization of the intermediate chloride under alkaline conditions. This strategy proved to be a useful synthetic method and was further elaborated by other groups.^{8,9} A modification of this approach was reported by Cho *et al.* who used the Lewis acid scandium(III) triflate in combination with chlorotrimethylsilane to promote ring opening and cyclization of aziridin-1-yl oximes to 5,6-dihydro-4*H*-[1,2,4]oxadiazines.¹⁰ Tabei and co-workers reported the synthesis of a mixture of geometrical isomers of 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4*H*-[1,2,4]oxadiazine derivatives *via* reaction of benzamide oximes with bromoacetoacetyl bromides.¹¹ Other approaches involve the reaction of aliphatic nitro compounds and acetyl chloride with β -diketones leading to tri-substituted [1,2,4]oxadiazine derivatives¹² and the condensation of benzamidoximes with glyoxal to furnish 3-aryl-*trans*-5,6-dihydroxy-5,6-dihydro-4*H*-[1,2,4]oxadiazines.¹³ More recent examples for the synthesis of the oxadiazine scaffold include ring expansion of fluorooxazolines with hydroxylamine hydrochloride,¹⁴ and cyclo-condensation reaction of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates with hydroxylamine.¹⁵

For our purposes we needed an approach where the substituent on the 5 position could be selectively introduced and easily modified. Based on a retrosynthetic analysis, three routes to the target oxadiazines were devised (Scheme 1).

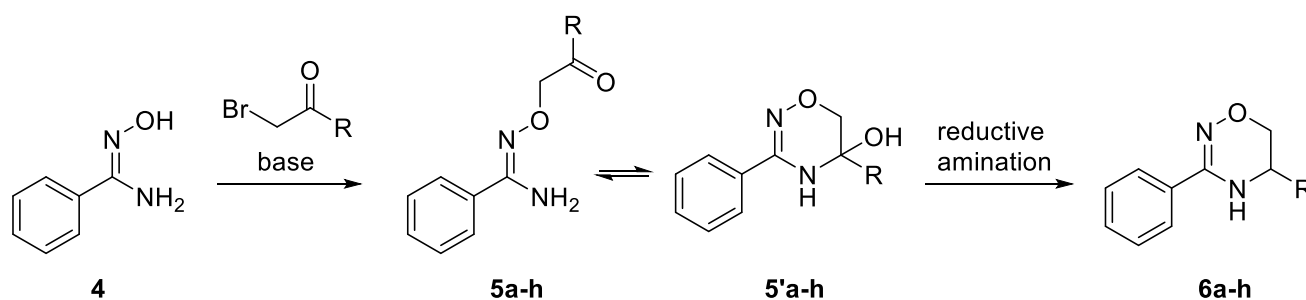


Scheme 1. Retrosynthetic approach to oxadiazines

The first route comprises a novel intramolecular reductive amination. The second route features a nucleophilic addition onto an *in situ* generated iminium ion. Additions to (*N*-acyl)iminium ions are well precedented in literature,¹⁶ but there are no known examples on an oxadiazine system. The third route is based on the condensation of an appropriate diamine onto an imidate building block. There are a few examples known for this type of cyclisation in literature, but only for simple diamines.¹⁷ As we envisioned these methods to be suitable for the introduction of a variety of R groups as well as the synthesis of chiral derivatives, the scope of these approaches was explored.

RESULTS AND DISCUSSION

First, the reductive amination approach was investigated (Table 1). Hydroxybenzimidamide **4** was alkylated with bromoacetophenone using sodium hydride in DMF to generate intermediate **5a**. Analysis of the reaction mixture by LCMS showed full consumption of **4** and formation of two products with correct mass. Analysis of the crude product by ¹H NMR showed this to be a mixture of **5a** and the corresponding cyclic aminal **5'a** in a 9:1 ratio. Attempts to isolate the intermediates by column chromatography were problematic, as the compounds co-eluted. Furthermore, only a low yield (25%) of the mixture **5a/5'a** was recovered after column chromatography, indicating the product to be instable on silica. Therefore, the crude mixture of the alkylation reaction was used in the subsequent reduction step and the yield was determined over the two steps.

Table 1. Synthesis of 5-substituted 3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* reductive amination

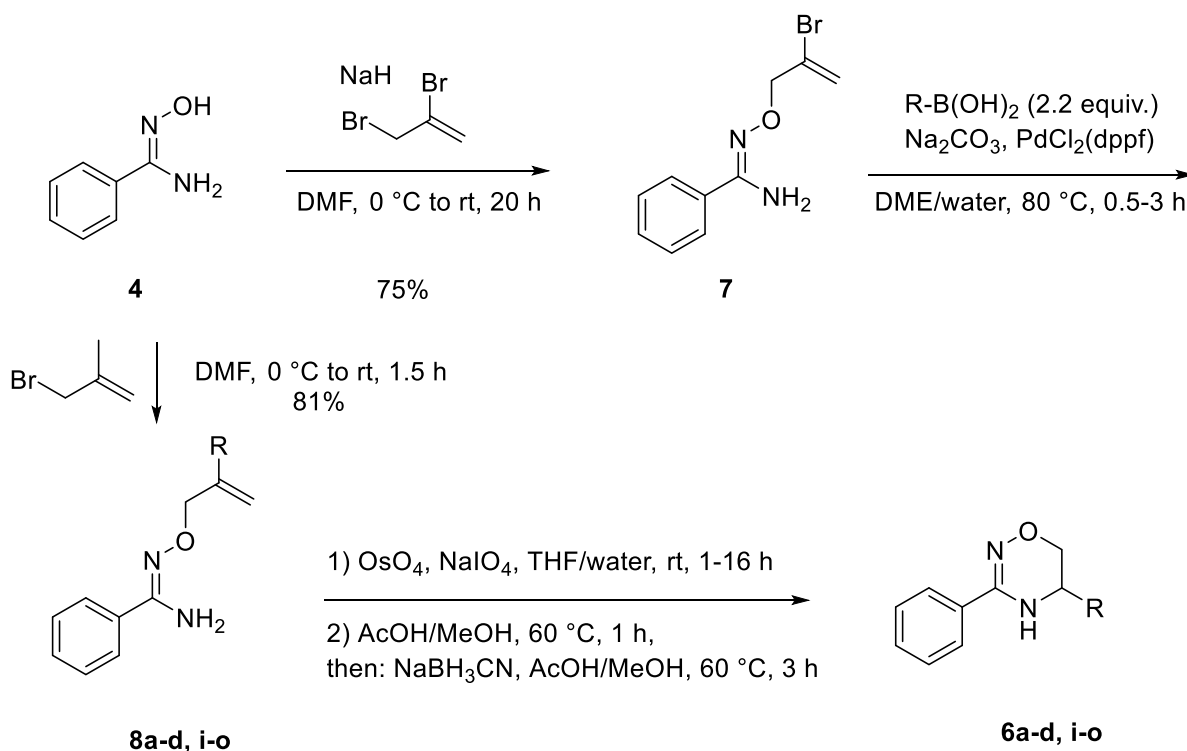
entry	R	Alkylation conditions	Reductive amination conditions	product	Yield (%) ^a
1	Ph	NaH, DMF, 0 °C to rt, 1 h (A)	NaBH ₄ , MeOH, rt, 16 h	6a	0
2	Ph	A	NaBH(OAc) ₃ , AcOH/MeOH, 60 °C, 3 h	6a	0
3	Ph	A	NaBH(OAc) ₃ , TFA, DCE, rt to 40 °C, 20 h	6a	traces
4	Ph	A	AcOH/MeOH, 60 °C, 1 h, then NaBH ₃ CN, 60 °C, 3 h (B)	6a	35
5	Ph	K ₂ CO ₃ , MeOH, rt to 60 °C, 3 h	B	6a	0
6	Ph	Cs ₂ CO ₃ , DMF, 60 °C, 3 h	B	6a	15
7	Ph	K ₂ CO ₃ , acetone, rt to 60 °C, 3 h	B	6a	16
8	Ph	PS-BEMP, MeCN, rt, 2 h (C)	B	6a	57
9	4-MeOPh	C	B	6b	40
10	4-ClPh	C	B	6c	0
11	Me ^b	C	B	6d	12
12	chex	C	B	6e	51
13	<i>t</i> Bu	C	B	6f	43
14	CO ₂ Me	C	B	6g	0
15	4-pyridyl	C	B	6h	0

^aIsolated yield over two steps. ^bChloroacetone was used in the alkylation.

The reduction of crude **5a/5'a** using NaBH₄ in MeOH failed and only starting material was observed (Table 1, entry 1). The reduction using NaBH(OAc)₃ in acetic acid/methanol also failed with mainly decomposition observed (entry 2). Treatment with NaBH(OAc)₃ in DCE with TFA as additive showed traces of product formation, but the reaction did not go to completion. Additionally, reduction of the

ketone of **5a** to the corresponding alcohol was observed by LCMS (entry 3). As the cyclisation to the imine/aminal intermediate appeared to be the problem and to prevent reduction of ketone **5a**, the mixture of **5a/5'a** was first heated in MeOH/AcOH to induce cyclisation. After heating at 60 °C for 1 hour, full conversion into a mixture of the corresponding imine/methoxyaminal was observed by LCMS. Addition of NaBH₃CN to the mixture afforded the product **6a** in 35% yield over the two steps (entry 4). Substitution of NaBH₃CN for NaBH(OAc)₃ or NaBH₄ under the same conditions gave lower yields. Despite the low yield, all the intermediate formed in the alkylation was converted into the product according to LCMS analysis, so the alkylation reaction was investigated in more detail. In order to assess the alkylation, the crude product from the alkylation reaction was converted into **6a** using conditions **B** and the overall yield over two steps was determined. A first test with K₂CO₃ in methanol failed with the formation of many undesired products as observed by LCMS (entry 5). The alkylation with Cs₂CO₃ in DMF proceeded somewhat better, although elevated temperature was needed and **6a** was isolated in low yield (entry 6). The use of K₂CO₃ in acetone afforded **6a** in a similar yield of 16% (entry 7). Finally, polystyrene supported 2-*tert*-butylimino-2-diethylimino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) was used as the base (entry 8). A fast and fairly clean reaction was observed by LCMS at room temperature and the intermediate mixture **5a/5'a** was conveniently isolated after filtration of the base and concentration. Upon reductive amination **6a** was isolated in a reasonable 57% yield over the two steps. The conditions in entry 8 were used in the subsequent reactions to determine the scope of this procedure. The 4-methoxyphenyl derivative **6b** was synthesised in 40% yield (entry 9), but introduction of an electron withdrawing 4-chlorophenyl group to obtain **6c** failed completely (entry 10), which was caused by a failed alkylation reaction as the intermediates **5c/5'c** were not observed by LCMS. Introduction of a methyl (entry 11), cyclohexyl (entry 12) or *t*Bu (entry 13) group afforded the products **6d**, **6e** and **6f** in 12%, 51% and 43% yields, respectively. Finally, introduction of an ester (entry 14) or a 4-pyridyl group (entry 15) was attempted, but the products could not be isolated. In the ester case some alkylation was observed, but the reduction failed. In the pyridine case, the alkylation did not work and the intermediates **5h/5'h** were not observed. Although this route gave access to a number of oxadiazine derivatives, the yields were not very high. Moreover, both the alkylation and reductive amination conditions seem to be substrate specific, hampering easy analogue generation. The low yield in the alkylation might be due to a proton transfer of the halo ketone to deprotonated **4**, resulting in a poor alkylation/side product formation. This would match the trend observed in the examples above, as the more easily enolisable halo ketones give lower yields or no reaction at all.

To check this hypothesis, an alternative route was devised, where an allyl group was introduced as a masked ketone (Table 2). First, hydroxybenzimidamide **4** was alkylated with 3-bromo-2-methylpropene allyl bromide to afford alkene **8d** in 81% yield. In this case, NaH/DMF afforded the product in higher

Table 2. Synthesis of 5-substituted 3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* alkene oxidation/reductive amination

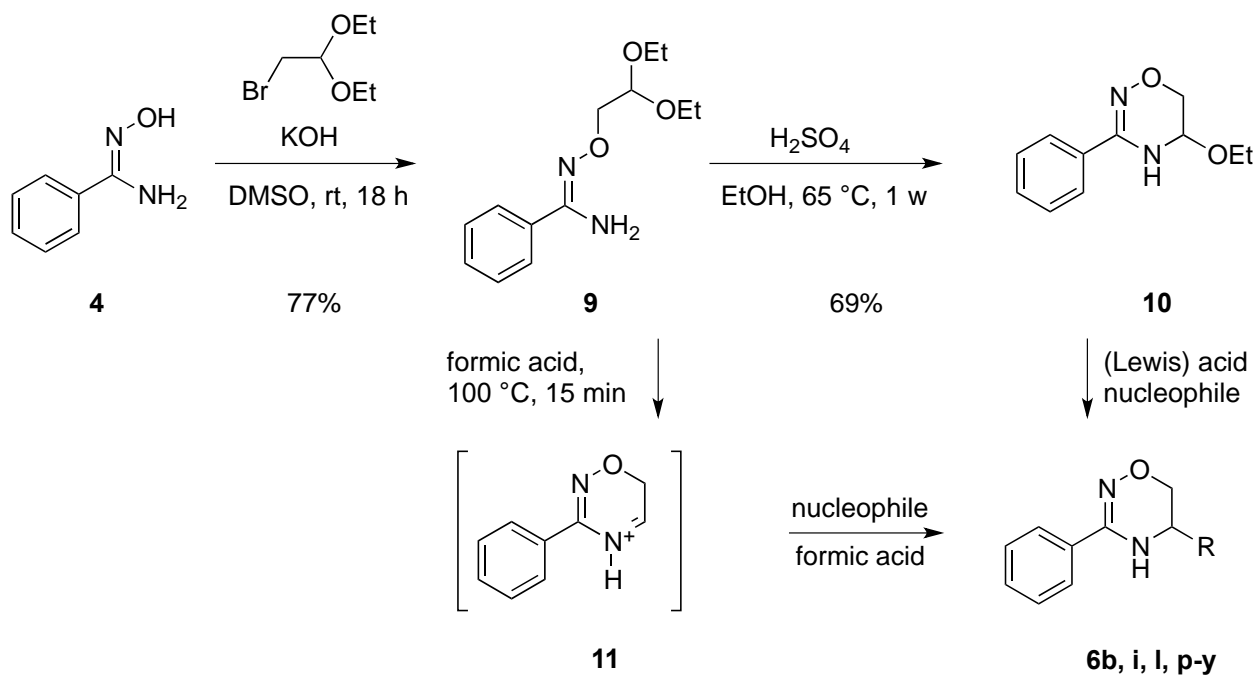
entry	R	Suzuki reaction yield (%) ^a	product	Oxidation/reduction yield (%) ^b	product
1	Me	-	8d	57	6d
2	Ph	72	8a	80	6a
3	4-MeOPh	61	8b	59	6b
4	4-MePh	60	8i	68	6i
5	4-ClPh	63 ^c	8c	66	6c
6	4-FPh	61	8j	71	6j
7	3-MeOPh	62	8k	75	6k
8	3-ClPh	55 ^c	8l	66	6l
9	3-benzofuran	66	8m	38	6m
10	2-(<i>N</i> -Me-indole)	97	8n	0	6n
11	3-pyridyl	62	8o	22	6o

^aIsolated yield, reactions were monitored by LCMS and stopped as soon as full conversion was observed.

^bIsolated yield over two steps. ^cReaction performed at 70 °C using 1.1 equiv. of boronic acid.

yield than PS-BEMP in acetonitrile. Next, the double bond was converted into the ketone using OsO₄/NaIO₄.¹⁸ Clean conversion was observed by LCMS and the crude product (100% yield) was used directly in the reductive amination to provide **6d** in 57% yield over two steps (entry 1). This approach indeed confirmed that the problem is the alkylation step and not the reduction, as the initial procedure afforded the product in only 12% yield. In order to synthesize derivatives, **4** was alkylated with 2,3-dibromoprop-1-ene affording building block **7** in 75% yield. The introduction of a phenyl group was

effected by a Suzuki reaction to afford **8a** in an acceptable 72% yield. The double bond was oxidised to afford the intermediate mixture **5a/5a'** (see Table 1) in quantitative yield. Subsequent purification by column chromatography again led to partial decomposition resulting in an isolated yield of only 30%. As expected, direct reduction of the crude intermediate afforded **6a** in 80% yield (entry 2). Although this route is one step longer, it does give access to additional targets as a plethora of R groups can be introduced by palladium catalysis. To explore the scope, a few simple phenyl derivatives with electron donating and withdrawing groups were synthesized. The substituent at the 4-position of the phenyl ring did not have much influence on the Suzuki reaction as the introduction of a 4-methoxy-, 4-methyl-, 4-chloro- and 4-fluorophenyl proceeded in similar yields of 60–63% (entries 3–6, products **8b**, **8i**, **8c** and **8j**, respectively). For the 4-chloro derivative **8c**, however, the Suzuki reaction was run at 70 °C using 1.1 equivalent of boronic acid to prevent the formation of oligomers (entry 5). Gratifyingly, the subsequent oxidations/reductive aminations proceeded in 59–71% yields, now allowing access to electron poor aromatic substituents as well. The introduction of a 3-methoxy- and 3-chlorophenyl afforded alkenes **8k** (entry 7) and **8l** (entry 8) in 62% and 55% yield, respectively. Subsequent oxidation/reduction afforded the corresponding oxadiazines **6k** and **6l** in 75% and 66% yield, respectively. Next, the introduction of heteroaryls was tested. Introduction of a 3-benzofuran gave the precursor **8m** in 66% yield (entry 9). The subsequent ketone formation gave clean conversion, but in the reductive amination several small unidentified impurities formed, resulting in only 38% isolated yield of **6m**. A 2-(*N*-methyl)indole was introduced in almost quantitative yield (entry 10). While the conversion into the ketone proceeded smoothly, the reductive amination failed to deliver the product. Several unidentified products formed and after tedious purification, some over-reduced **6n** (reduction of the indole to the indolinyl) was isolated in 12% yield.¹⁹ Finally, introduction of a pyridine was attempted and the Suzuki reaction afforded **8o** in 62% yield (entry 11). The oxidative cleavage to the ketone went slowly and took 16 hours to reach completion. The subsequent reductive amination afforded product **6o** in only 22% yield. The synthesis of the corresponding 4-pyridyl derivative was also attempted, but failed as the synthesis of the intermediate alkene by either Suzuki or Stille reaction did not work. This strategy provides an improvement over the initial alkylation/reductive amination procedure, but still takes four steps and therefore a shorter approach was investigated: the direct introduction of nucleophiles on the 5-position by nucleophilic attack on an iminium ion intermediate (Table 3).

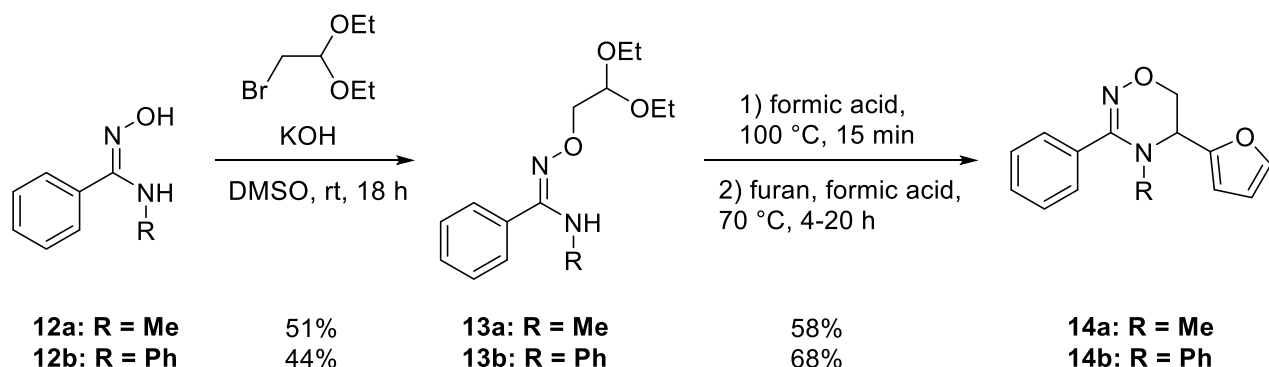
Table 3. Synthesis of 5-substituted 3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* iminium ion reactions

entry	starting material	nucleophile	temp (°C)	time (h)	R	product	Yield (%) ^d
1 ^a	10	furan	rt	20	2-(furan)	6p	92
2 ^a	9	furan	rt	20	2-(furan)	6p	88
3 ^a	9	indole	rt	20	3-(indole)	6q	70
4 ^a	9	<i>N</i> -Me-indole	rt	20	3-(<i>N</i> -Me-indole)	6r	86
5 ^a	9	indazole	rt	84	3-(indazole)	6s	87
6 ^a	9	benzofuran	100	2.5	2-(benzofuran)	6t	53
7 ^a	9	benzo[<i>b</i>]thiophene	100	4	2-(benzo[<i>b</i>]thiophene)	6u	69
8 ^a	9	benzo[<i>d</i>][1,3]dioxole	100	4.5	5-(benzo[<i>d</i>][1,3]dioxole)	6v	74
9 ^a	9	anisole	100	2.5	2-(methoxyphenyl) 4-(methoxyphenyl)	6w 6b	20 67
10 ^a	9	toluene	100	21	4-(methylphenyl)	6i	trace
11 ^a	9	chlorobenzene	100	21	3-(chlorobenzene)	6l	0
12 ^b	10	allylTMS	rt	20	allyl	6x	64
13 ^c	10	trimethyl((1-phenyl-vinyl)oxy)silane	rt	48	2-(1-phenyl-ethan-1-one)	6y	33

^aReaction performed in formic acid using 5 equiv. of nucleophile. ^bReaction performed in DCM using 5 equiv. of nucleophile and 5 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$. ^cReaction performed in DCM using 2.5 equiv. of nucleophile and 0.1 equiv. of $\text{Sc}(\text{OTf})_3$. ^dIsolated yield.

In order to test Route 2, compound **4** was *O*-alkylated with bromoacetaldehyde diethyl acetal to afford compound **9**. Next, prolonged stirring with sulfuric acid in ethanol gave the cyclic ethoxy aminal **10** in 69% yield after column chromatography. The coupling of **10** with furan as the nucleophile in formic acid afforded the product **6p** in 92% yield (Table 3, entry 1). In order to shorten the route, intermediate **9** was heated for 15 minutes in formic acid to generate the intermediate iminium ion **11** *in situ*. The mixture was

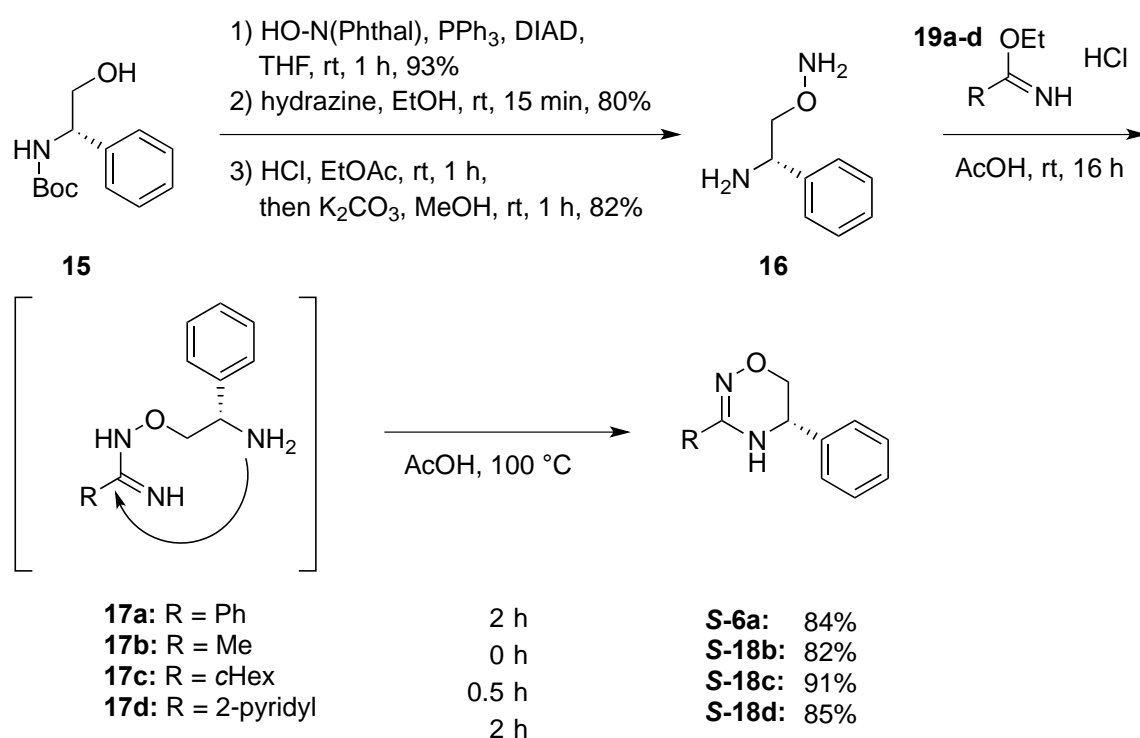
cooled to room temperature and furan was added as the nucleophile again. Gratifyingly, product **6p** was isolated in similar yield of 88% (entry 2). Next, a set of (hetero)aromatic nucleophiles was added to screen the scope of this reaction starting from **9**. As expected, both indole (entry 3) and *N*-methyl-indole (entry 4) could be coupled in good yields at room temperature to afford products **6q** and **6r**. Additionally, indazole also reacted at room temperature to afford the product **6s** in 87% yield (entry 5). The addition of benzofuran (entry 6) required heating to afford the product **6t** in 53% yield. Benzo[*b*]thiophene (entry 7) was added in good yield as well resulting in the formation of 2-isomer **6u** in 69% yield. Formation of some additional regioisomers was also observed by LCMS, but these could not be isolated in pure form. The coupling of benzo[*d*][1,3]dioxole afforded the product **6v** in 74% yield as a single 5-isomer (entry 8). As expected, anisole also reacted, leading to the formation of the 2- and 4-methoxy regioisomeric products **6w** and **6b** in a 1:3.3 ratio in 87% overall yield (entry 9). The limit of this addition was reached using toluene as the nucleophile (entry 10). A trace of product **6i** was observed in the reaction mixture by LCMS, but over time side product formation was observed. As expected, the reaction with the more electron poor chlorobenzene to obtain **6l** failed completely (entry 11). Next, the addition of some non-aromatic nucleophiles was tested starting from **10** using $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis acid in dichloromethane, conditions commonly used in the coupling of nucleophiles with *N*-acyliminium ions.²⁰ Introduction of an allyl unit was effected in 64% yield to afford product **6x** (entry 12). Although there is an electron withdrawing hydroxylimine group attached to the intermediate iminium ion, the reaction was quite slow and needed 20 hours to reach completion. A reaction with the silyl enol ether of acetophenone was initially tested with $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis acid. A rapid reaction was observed, but the initial product reacted with the excess nucleophile resulting in the formation of oligomers. When $\text{Sc}(\text{OTf})_3$ was used as the Lewis acid, the ketone **6y** could be isolated in 33% yield.



Scheme 2. Synthesis of *N*-substituted 3-phenyl-5-furyl-5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* iminium ion reactions

Although the oxadiazines can be *N*-alkylated, the iminium ion reaction sequence was also tested for the synthesis of *N*-substituted derivatives (Scheme 2). This way, the position of the *N*-alkyl group is

unambiguous and it allows for the introduction of R groups that might be difficult to install afterwards. Starting from intermediates **12a** and **12b**, the iminium ion precursors **13a** and **13b** were synthesized. The subsequent introduction of a furan group did not proceed at room temperature as before with the unsubstituted derivative **9**, but required additional heating. The methyl derivative **14a** was isolated in 58% yield after heating for 4 hours at 70 °C. The phenyl derivative required heating overnight to provide product **14b** in 68% yield. Although giving access to a variety of 5-substituted oxadiazine targets, this approach is limited to the use of electron rich nucleophiles and also does not give access to optically pure derivatives. Therefore, the synthesis of a chiral diamine **16** was started to test the construction of oxadiazines by condensation with an imidate (Scheme 3).



Scheme 3. Synthesis of 5-phenyl 3-substituted-5,6-dihydro-4H-[1,2,4]oxadiazines *via* condensation of diamines with imidates

The commercially available *N*-Boc-phenylglycinol **15** was converted into the diamine **16** in 3 steps. Next, the diamine was stirred at room temperature overnight with ethyl benzimidate hydrochloride **19a** leading to intermediate **17a**. Upon heating to 100 °C for 2 hours, intramolecular attack of the nitrogen onto the imidate, followed by elimination of ammonia led to clean conversion into **S-6a** and the product was isolated in 84% yield. The free amine must be used in the reaction, attempts to perform the cyclisation reaction with the initially isolated dihydrochloride salt of **16** failed as the intermediate did not form. Starting the reaction at 100 °C directly also afforded the product, but in lower yield. At higher temperature the amine of the intermediate can react with a second equivalent of the imidate leading to side product formation. Gratifyingly, chiral HPLC analysis showed no racemization had taken place in

the synthesis of **S-6a**. Considering the number of (optically pure) amino alcohols/amino acids available, this route gives access to an array of (optically pure) oxadiazines. As expected, variation on the 3 position could easily be effected by changing the starting imidate. The methyl derivative **S-18b** already cyclised by stirring at room temperature overnight in 82% yield. Both the cyclohexyl (**S-18c**) and 2-pyridyl (**S-18d**) derivatives required some additional heating to give the products in 91% and 85% yield, respectively.

Encouraged by these results, the scope with respect to the diamines that can be used in the cyclization was explored using ethyl benzimidate hydrochloride **19a** as the imidate (Table 4). The unsubstituted oxadiazine derivative **21a** was obtained in 63% yield (entry 1). Either a 4-, 5-, or 6-methyl group was installed on the oxadiazine starting from the appropriate diamine to afford **21b** (entry 2, 74%), **6d** (entry 3, 77%) and **21d** (entry 4, 57% yield), respectively. The somewhat lower yield for **21d** was the result of double addition of the diamine to the imidate, caused by the increased nucleophilicity of the *N*-methylated amine. A [5-6] *cis* (**21e**, 53%, entry 5), or *trans* (**21f**, 71%, entry 6) annulated cyclohexyl ring was installed on the oxadiazine in reasonable yields. A smaller [5-6] *cis* annulated cyclopentyl ring (**21g**, entry 7) could be introduced in 78% yield as well. As expected, the cyclization to the corresponding *trans* annulated derivative **21h** was more difficult (entry 8), but the product could be isolated in 25% yield after heating for 48 hours. Introduction of a [4-5] annulated ring was also possible in high yield starting from the prolinol derived diamine **20i** to afford **21i** in 80% yield (entry 9). Finally, introduction of a quaternary center was probed. The 5,5-dimethyl substituted oxadiazine **21j** was synthesized in 83% yield starting from amine **20j** (entry 10). Starting from diamine **20k**, the spiro-fused oxadiazine **21k** was synthesized in 87% yield (entry 11). Based on these results, the synthesis of a large number of substituted oxadiazines can conveniently be accomplished starting from easily accessible diamines.

In summary, three approaches for the synthesis of substituted 5,6-dihydro-4*H*-[1,2,4]oxadiazines were investigated. The first approach *via* alkylation with a haloketone, followed by reductive amination, gave moderate to low yields. Additionally, the procedure was found to have a limited scope. These problems could partly be alleviated by a multi-step approach involving alkylation with 2,3-dibromoprop-1-ene, followed by introduction of R groups *via* a Suzuki reaction, oxidative cleavage of the double bond and reductive ring closure. The direct introduction of substituents at the 5-position by addition to an iminium ion provided new analogues in one synthetic step; however, the scope was limited to electron rich nucleophiles. The condensation of a diamine with an imidate was found to be the most versatile route. This route allowed for variation of substituents at the 3, 4, 5 and 6 position of the oxadiazine in good yields. Furthermore, depending on the diamine used, optically pure oxadiazines could be prepared.

Table 4. Synthesis of a series of 3-phenyl-substituted-5,6-dihydro-4*H*-[1,2,4]oxadiazines

$\text{Ph}-\text{C}(\text{OEt})=\text{NH} + \text{HCl} \xrightarrow[\text{AcOH, rt to } 100\text{ }^\circ\text{C}]{\text{diamine (20a-k)}} \text{Ph}-\text{C}(\text{R}^2)=\text{N}-\text{O}-\text{C}(\text{R}^3)-\text{N}(\text{R}^1)-\text{H}$

19a **6d, 21a, b, d-k**

entry	diamine	time (h) ^a	product	yield (%) ^b
1		2		63%
2		3		74%
3		2		77%
4		4		57%
5		8		53%
6		3		71%
7		2		78%
8		48		25%
9		16		80%
10		24		83%
11		5		87%

^aThe reaction mixtures were stirred at rt for 16 h to form the intermediate and then stirred at 100 °C for the indicated time for the cyclisation. ^bIsolated yield.

EXPERIMENTAL

General Experimental Methods. All solvents and reagents were used as purchased from commercial suppliers without further purification. Starting materials which were not commercially available were synthesized by previously reported methods. Flash column chromatography was performed using prepacked silica gel (20–40 mesh) columns. Analytical thin-layer chromatography was performed on Merck 60 F254 glass plates. Visualization was accomplished with UV light, iodine, anisaldehyde or potassium permanganate, followed by heating. Melting points were measured on a calibrated standard melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ on a 300 or 400 MHz Bruker spectrometer and are reported in ppm using TMS (0.00 ppm) as an internal standard. Proton-decoupled ^{13}C NMR spectra were recorded on a 101 MHz Bruker spectrometer and are reported in ppm using the internal solvent residual signal as an internal standard. Optical rotations were measured in MeOH on a polarimeter with a 100 mm cell (*c* given in g/100 mL) operating at $\lambda = 589$ nm, corresponding to the sodium D line, at the indicated temperatures. Basic preparative HPLC was performed on a Reveleris Prep system: Detection: UV (220/254 nm), Column: XSelectTM CSH C18, 145x25 mm, particle size 10 μm , Flow: 40 mL/min, Eluent A: 10 mM ammonium bicarbonate in water pH = 9.0; Eluent B: 99% acetonitrile + 1% 10 mM ammonium bicarbonate in water; 5% B to 100% B gradient. Acidic preparative HPLC was performed on a Reveleris Prep system: Detection: ELSD, UV 220 nm/254 nm), Column: Phenomenex Luna C18, 150x25 mm, particle size 10 μm , Flow: 40 mL/min, Eluent A: 0.1% (v/v) Formic acid in water, Eluent B: 0.1% (v/v) Formic acid in acetonitrile, 5% B to 100% B gradient. The product containing fractions were lyophilized to obtain the products.

General procedure **A** for the synthesis of 5-substituted 3-phenyl-5,6-dihydro-4*H*[1,2,4]oxadiazines via alkylation and reductive amination. To a solution of *N*'-hydroxybenzimidamide **4** (250 mg, 1.84 mmol) in MeCN (4 mL), PS-BEMP (2.2 mmol/g, 1.2 equiv, 1 g) was added. After stirring for 15 min at rt, the bromo- or chloroketone (1.5 equiv.) in MeCN (2 mL) was added and the mixture was stirred for 2 h. The solids were removed by filtration and the filtrate was concentrated to afford the crude alkylated intermediate. This was dissolved in a mixture of MeOH (9 mL) and acetic acid (3 mL), heated to 60 °C for 1 h, sodium cyanoborohydride (127 mg, 2.02 mmol, 1.1 equiv.) was added and the mixture was stirred at 60 °C for an additional 3 h. The mixture was poured into an aqueous 1M NaOH solution (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried using Na_2SO_4 and concentrated to afford the crude product, that was further purified as described.

3,5-Diphenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6a). General procedure **A** was followed, using 2-bromo-1-phenylethan-1-one. Purification by silica flash column chromatography (30% EtOAc in *n*-heptane) afforded compound **6a** (254 mg, 57% yield) as a crystalline solid; mp 110 – 111 °C; ^1H NMR

(400 MHz, CDCl₃) δ 7.72 – 7.67 (m, 2H), 7.49 – 7.34 (m, 8H), 5.05 (s, 1H), 4.76 – 4.69 (m, 1H), 4.33 – 4.23 (m, 1H), 3.76 (dd, $J = 11.1, 7.4$ Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 152.9, 138.8, 130.5, 129.2, 128.9, 128.8, 127.0, 126.0, 77.5, 69.8, 54.4; HRMS (ESI-TOF) m/z Calcd for C₁₅H₁₅N₂O 239.1184 [M + H]⁺; Found 239.1190; Chiral HPLC: t_R : 8.58 and 13.24 min, 1:1 mixture (column: Chiralpak AD-H, 250 x 4.6 mm, 5 μ m, eluent: 20% EtOH in heptane, flow: 1 mL/min, temp: 25 °C); IR (ν_{\max} , cm⁻¹): 3289, 1599; Anal. Calcd for C₁₅H₁₄N₂O: C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.78; H, 6.13; N, 12.01%.

5-(4-Methoxyphenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6b). General procedure A was followed using 2-bromo-1-(4-methoxyphenyl)ethan-1-one. Purification by silica flash column chromatography (35% EtOAc in *n*-heptane) followed basic preparative HPLC afforded compound **6b** (200 mg, 40% yield) as an amorphous solid; ¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.64 (m, 2H), 7.48 – 7.37 (m, 3H), 7.32 – 7.26 (m, 2H), 6.96 – 6.89 (m, 2H), 5.02 (s, 1H), 4.70 – 4.61 (m, 1H), 4.29 – 4.19 (m, 1H), 3.81 (s, 3H), 3.70 (dd, $J = 11.0, 7.6$ Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 160.0, 152.9, 132.9, 130.8, 130.4, 128.8, 128.2, 126.0, 114.6, 69.9, 55.5, 53.8; HRMS (ESI-TOF) m/z Calcd for C₁₆H₁₇N₂O₂ 269.1287 [M + H]⁺; Found 269.1290; IR (ν_{\max} , cm⁻¹): 3318, 1604; Anal. Calcd for C₁₆H₁₆N₂O₂: C, 71.62; H, 6.01; N, 10.44%. Found: C, 71.67; H, 6.26; N, 10.56%.

5-Methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6d). General procedure A was followed using 1-chloropropan-2-one. Purification by silica flash column chromatography (30% EtOAc in *n*-heptane) followed by basic preparative HPLC afforded compound **6d** (41 mg, 12% yield) as an amorphous solid; ¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.56 (m, 2H), 7.51 – 7.34 (m, 3H), 4.60 (s, 1H), 4.19 – 4.06 (m, 1H), 3.85 – 3.65 (m, 1H), 3.50 (dd, $J = 10.8, 7.1$ Hz, 1H), 1.27 (d, $J = 6.4$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 152.5, 133.2, 130.3, 128.8, 126.0, 69.4, 45.8, 18.6; HRMS (ESI-TOF) m/z Calcd for C₁₀H₁₃N₂O 177.1028 [M + H]⁺; Found 177.1030; IR (ν_{\max} , cm⁻¹): 3232, 1603; Anal. Calcd for C₁₀H₁₂N₂O: C, 68.16; H, 6.86; N, 15.90%. Found: C, 67.87; H, 7.26; N, 16.11%.

5-Cyclohexyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6e). General procedure A was followed using 2-bromo-1-cyclohexylethan-1-one. Purification by trituration from EtOAc afforded compound **6e** (233 mg, 51% yield) as a crystalline solid; mp 165 – 166 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.60 (m, 2H), 7.46 – 7.36 (m, 3H), 4.73 (s, 1H), 4.07 (dd, $J = 11.0, 3.4$ Hz, 1H), 3.81 (dd, $J = 11.0, 6.0$ Hz, 1H), 3.38 – 3.30 (m, 1H), 1.91 (d, $J = 12.2$ Hz, 1H), 1.86 – 1.76 (m, 3H), 1.76 – 1.67 (m, 1H), 1.57 – 1.48 (m, 1H), 1.35 – 1.16 (m, 3H), 1.16 – 1.01 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 152.8, 133.3, 130.2, 128.7, 126.0, 66.0, 55.0, 40.6, 29.1, 28.9, 26.4, 26.0; HRMS (ESI-TOF) m/z Calcd for C₁₅H₂₁N₂O 245.1654 [M + H]⁺; Found 245.1654; IR (ν_{\max} , cm⁻¹): 3360, 1606; Anal. Calcd for C₁₅H₂₀N₂O: C, 73.74; H, 8.25; N, 11.47%. Found: C, 73.70; H, 8.41; N, 11.09%.

5-(*tert*-Butyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6f). General procedure A was followed using 1-bromo-3,3-dimethylbutan-2-one. Purification by silica flash column chromatography (35%

EtOAc in *n*-heptane) followed by basic preparative HPLC afforded compound **6f** (178 mg, 43% yield) as an amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.56 (m, 2H), 7.51 – 7.34 (m, 3H), 4.74 (s, 1H), 4.17 – 4.03 (m, 1H), 3.83 (dd, $J = 11.2, 6.6$ Hz, 1H), 3.41 – 3.23 (m, 1H), 1.03 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.4, 133.3, 130.3, 128.8, 126.0, 64.9, 58.6, 33.6, 26.0; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}$ 219.1498 $[\text{M} + \text{H}]^+$; Found 219.1497; IR (ν_{max} , cm^{-1}): 3204, 1606; Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$: C, 71.53; H, 8.31; N, 12.83%. Found: C, 71.21; H, 8.65; N, 12.78%.

***N'*-((2-Bromoallyl)oxy)benzimidamide (7)**. To a solution of *N'*-hydroxybenzimidamide **4** (2.28 g, 16.8 mmol) in dry DMF (15 mL) under nitrogen atmosphere at 0 °C, was added sodium hydride (60% dispersion in mineral oil, 738 mg, 18.4 mmol). The resulting suspension was stirred at rt for 20 min, 2,3-dibromoprop-1-ene (3.69 g, 18.4 mmol) was added and the mixture was stirred at rt for 20 h. The reaction mixture was poured into water and was extracted with EtOAc twice. The combined organic layers were washed with brine, dried using Na_2SO_4 , concentrated and the crude product was purified by silica flash column chromatography (10% to 60% EtOAc in *n*-heptane) to afford compound **7** (3.2 g, 75% yield) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.57 (m, 2H), 7.45 – 7.33 (m, 3H), 5.97 – 5.91 (m, 1H), 5.66 – 5.60 (m, 1H), 4.89 (s, 2H), 4.72 – 4.65 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.8, 132.2, 130.1, 129.7, 128.6, 126.0, 117.6, 77.0; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{10}\text{H}_{12}\text{BrN}_2\text{O}$ 255.0133 $[\text{M} + \text{H}]^+$; Found 255.0130.

***N'*-((2-Methylallyl)oxy)benzimidamide (8d)**. To a solution of *N'*-hydroxybenzimidamide **4** (500 mg, 3.67 mmol) in dry DMF (15 mL) under nitrogen atmosphere, sodium hydride (60% dispersion in mineral oil, 154 mg, 3.86 mmol) was added in portions and the resulting suspension was stirred at rt for 30 min. Then, a solution of 3-bromo-2-methylpropene (992 mg, 7.34 mmol) in dry DMF (5 mL) was added and the resulting mixture was stirred at rt for 1 h. The mixture was diluted with water and extracted with EtOAc twice. The combined organic layers were washed with water, brine, dried using Na_2SO_4 , concentrated and purified by silica flash column chromatography (20% EtOAc in *n*-heptane) to afford compound **8d** (579 mg, 81% yield) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 7.71 – 7.55 (m, 2H), 7.45 – 7.30 (m, 3H), 5.09 – 4.96 (m, 1H), 5.00 – 4.89 (m, 1H), 4.83 (s, 2H), 4.54 (s, 2H), 1.89 – 1.73 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.0, 142.6, 132.7, 130.0, 128.7, 126.0, 112.2, 19.9; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}$ 191.1184 $[\text{M} + \text{H}]^+$; Found 191.1180.

General procedure **B** for the synthesis of *N'*-((2-substituted allyl)oxy)benzimidamides via Suzuki cross-coupling. Through a 0.2 M solution of **7**, Na_2CO_3 (3 equiv.) and the appropriate boronic acid (2.2 equiv.) in DME/water (2:1, v/v), nitrogen was bubbled for 10 min. Then, 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.05 equiv.) was added and the mixture was heated at the indicated temperature for the indicated time. The reaction was cooled to rt, partitioned

between water and EtOAc, the organic layer was separated, dried using Na₂SO₄ and concentrated to afford the crude product that was purified as indicated.

***N'*-((2-Phenylallyl)oxy)benzimidamide (8a).** General procedure **B** was followed starting from **7** (250 mg, 0.98 mmol) using phenylboronic acid and stirring at 80 °C for 30 min. Purification by silica flash column chromatography (5% to 35% EtOAc in *n*-heptane) afforded compound **8a** (180 mg, 72% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.43 – 7.19 (m, 6H), 5.57 (s, 1H), 5.41 (s, 1H), 5.01 (s, 2H), 4.74 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 152.4, 144.3, 139.0, 132.6, 130.0, 128.7, 128.4, 127.8, 126.2, 126.0, 114.9, 75.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₆H₁₇N₂O 253.1341 [M + H]⁺; Found 253.1341.

***N'*-((2-(4-Methoxyphenyl)allyl)oxy)benzimidamide (8b).** General procedure **B** was followed starting from **7** (250 mg, 0.98 mmol) using 4-methoxyphenylboronic acid and stirring at 80 °C for 30 min. Purification by basic preparative HPLC afforded compound **8b** (169 mg, 61% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.33 (m, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.50 (s, 1H), 5.32 (s, 1H), 4.99 (s, 2H), 4.76 (s, 2H), 3.81 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.3, 152.2, 143.4, 132.5, 131.4, 129.9, 128.6, 127.3, 125.9, 113.7, 113.2, 75.7, 55.3; HRMS (ESI-TOF) *m/z* Calcd for C₁₇H₁₉N₂O₂ 283.1457 [M + H]⁺; Found 283.1446.

***N'*-((2-(4-Chlorophenyl)allyl)oxy)benzimidamide (8c).** General procedure **B** was followed starting from **7** (209 mg, 0.82 mmol) using 1.1 equiv. of 4-chlorophenylboronic acid and stirring at 70 °C for 30 min. Purification by silica flash column chromatography (5% to 30% EtOAc in *n*-heptane) afforded compound **8c** (148 mg, 63% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 7.7 Hz, 2H), 7.49 – 7.34 (m, 5H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.56 (s, 1H), 5.43 (s, 1H), 4.98 (s, 2H), 4.74 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 152.4, 143.3, 137.4, 133.6, 132.5, 130.1, 128.8, 128.6, 127.6, 126.1, 115.6, 75.5; HRMS (ESI-TOF) *m/z* Calcd for C₁₆H₁₆ClN₂O 287.0958 [M + H]⁺; Found 287.0951.

***N'*-((2-(4-Methylphenyl)allyl)oxy)benzimidamide (8i).** General procedure **B** was followed starting from **7** (150 mg, 0.59 mmol) using 4-methylphenylboronic acid and stirring at 80 °C for 1 h. Purification by basic preparative HPLC afforded compound **8i** (94 mg, 60% yield) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.48 – 7.31 (m, 5H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.54 (s, 1H), 5.36 (s, 1H), 4.99 (s, 2H), 2.34 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 152.3, 144.0, 137.6, 136.0, 132.6, 130.0, 129.1, 128.7, 126.1, 126.0, 114.0, 75.6, 21.2; HRMS (ESI-TOF) *m/z* Calcd for C₁₇H₁₉N₂O 267.1497 [M + H]⁺; Found 267.1500.

***N'*-((2-(4-Fluorophenyl)allyl)oxy)benzimidamide (8j).** General procedure **B** was followed starting from **7** (150 mg, 0.59 mmol) using 4-fluorophenylboronic acid and stirring at 80 °C for 1 h. Purification by basic preparative HPLC afforded compound **8j** (97 mg, 61% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.43 – 7.31 (m, 3H), 7.06 – 6.97 (m, 2H), 5.50 (s,

1H), 5.38 (s, 1H), 4.75 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 162.5 (d, *J* = 246.6 Hz), 152.4, 143.4, 135.0 (d, *J* = 3.2 Hz), 132.5, 130.1, 128.7, 127.9 (d, *J* = 8.0 Hz), 126.0, 115.3 (d, *J* = 21.3 Hz), 114.9, 75.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₆H₁₆FN₂O 271.1247 [M + H]⁺; Found 271.1245.

***N'*-((2-(3-Methoxyphenyl)allyl)oxy)benzimidamide (8k)**. General procedure **B** was followed starting from **7** (150 mg, 0.59 mmol) using 3-methoxyphenylboronic acid and stirring at 80 °C for 1 h. Purification by basic preparative HPLC afforded compound **8k** (103 mg, 62% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.44 (m, 2H), 7.33 – 7.22 (m, 3H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.99 – 6.94 (m, 1H), 6.74 (dd, 1H), 5.47 (s, 1H), 5.32 (d, *J* = 1.2 Hz, 1H), 4.90 (s, 2H), 4.68 (s, 2H), 3.69 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.6, 152.3, 144.2, 140.5, 132.5, 129.9, 129.3, 128.6, 126.0, 118.7, 115.1, 113.2, 112.0, 75.5, 55.3; HRMS (ESI-TOF) *m/z* Calcd for C₁₇H₁₉N₂O₂ 283.1447 [M + H]⁺; Found 283.1450.

***N'*-((2-(3-Chlorophenyl)allyl)oxy)benzimidamide (8l)**. General procedure **B** was followed starting from **7** (150 mg, 0.59 mmol) using 1.1 equiv. of 3-chlorophenylboronic acid and stirring at 70 °C for 1 h. Purification by basic preparative HPLC afforded compound **8l** (93 mg, 55% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.55 (m, 3H), 7.51 (s, 1H), 7.45 – 7.32 (m, 6H), 7.29 – 7.21 (m, 4H), 5.57 (s, 1H), 5.45 (d, 2H), 4.97 (s, 3H), 4.75 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 152.4, 143.4, 140.9, 134.4, 132.5, 130.1, 129.7, 128.7, 127.8, 126.5, 126.1, 124.5, 116.2, 75.4; HRMS (ESI-TOF) *m/z* Calcd for C₁₆H₁₆ClN₂O 287.0951 [M + H]⁺; Found 287.0950.

***N'*-((2-(Benzofuran-3-yl)allyl)oxy)benzimidamide (8m)**. General procedure **B** was followed starting from **7** (250 mg, 0.98 mmol) using benzofuran-3-boronic acid and stirring at 80 °C for 2 h. Purification by silica flash column chromatography (20% EtOAc in *n*-heptane) afforded compound **8m** (270 mg, 66% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.80 (m, 2H), 7.63 – 7.59 (m, 2H), 7.49 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.33 – 7.25 (m, 2H), 5.79 (s, 1H), 5.56 – 5.51 (m, 1H), 4.95 (s, 2H), 4.81 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 155.6, 152.3, 142.9, 136.4, 132.5, 130.1, 128.7, 126.2, 126.0, 124.5, 123.1, 121.2, 119.6, 115.1, 111.7, 76.5; HRMS (ESI-TOF) *m/z* Calcd for C₁₈H₁₇N₂O₂ 293.1290 [M + H]⁺; Found 293.1289.

***N'*-((2-(1-Methyl-1*H*-indol-2-yl)allyl)oxy)benzimidamide (8n)**. General procedure **B** was followed starting from **7** (250 mg, 0.98 mmol) using 1-methyl-2-indoleboronic acid pinacol ester and stirring at 80 °C for 90 min. Purification by silica flash column chromatography (20% EtOAc in *n*-heptane) afforded compound **8n** (296 mg, 97% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.53 (m, 3H), 7.45 – 7.33 (m, 3H), 7.34 – 7.28 (m, 1H), 7.27 – 7.18 (m, 1H), 7.14 – 7.07 (m, 1H), 6.55 (s, 1H), 5.70 (d, *J* = 1.3 Hz, 1H), 5.38 (s, 1H), 4.94 (s, 2H), 4.74 (s, 2H), 3.77 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 152.5, 139.1, 138.5, 137.5, 132.6, 130.1, 128.7, 126.0, 121.9, 120.7, 119.8, 117.9, 109.6, 101.4, 76.2, 31.3; HRMS (ESI-TOF) *m/z* Calcd for C₁₉H₂₀N₃O 306.1606 [M + H]⁺; Found 306.1611.

***N'*-((2-(Pyridin-3-yl)allyl)oxy)benzimidamide (8o)**. General procedure **B** was followed starting from **7** (200 mg, 0.78 mmol) using pyridine-3-boronic acid and stirring at 80 °C for 3 h. Purification by silica flash column chromatography (45% EtOAc in *n*-heptane) afforded compound **8o** (126 mg, 62% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.78 (s, 1H), 8.52 (d, *J* = 3.9 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.47 – 7.33 (m, 3H), 7.31 – 7.22 (m, 1H), 5.62 (s, 1H), 5.51 (s, 1H), 5.00 (s, 2H), 4.77 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 148.9, 141.9, 133.6, 132.5, 130.1, 128.7, 126.1, 116.8, 75.3; HRMS (ESI-TOF) *m/z* Calcd for C₁₅H₁₆N₃O 254.1293 [M + H]⁺; Found 254.1290.

General procedure **C** for the synthesis of 5-substituted 3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* oxidative cleavage and reductive amination. To a 0.15 M solution of the appropriate *N'*-allyloxy-benzimidamide in THF/water (3:1, v/v), osmium tetroxide (4 wt% in water, 0.05 equiv.) and sodium periodate (3.5 equiv.) were added. The mixture was stirred at rt for 1 h (unless indicated otherwise), diluted with water and extracted with DCM twice. The combined organic layers were washed with brine, dried using Na₂SO₄ and concentrated to afford the crude intermediate. A 0.15 M solution of crude intermediate in MeOH/acetic acid (3:1, v/v) was heated to 60 °C for 1 h and sodium cyanoborohydride (1.1 equiv.) was added. The mixture was stirred at 60 °C for 3 h, poured into a 1M sodium hydroxide solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried using Na₂SO₄ and concentrated to afford the crude product which was purified as described.

3,5-Diphenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6a). General procedure **C** was followed using *N'*-((2-phenylallyl)oxy)benzimidamide **8a** (150 mg, 0.55 mmol). Purification by silica flash column chromatography (30% EtOAc in *n*-heptane) afforded compound **6a** (104 mg, 80% yield) as a solid.

5-(4-Chlorophenyl)-3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6b). General procedure **C** was followed using *N'*-((2-(4-methoxyphenyl)allyl)oxy)benzimidamide **8b** (137 mg, 0.49 mmol). Purification by silica flash column chromatography (35% EtOAc in *n*-heptane) afforded compound **6b** (77 mg, 59% yield) as a solid.

5-(4-Chlorophenyl)-3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6c). General procedure **C** was followed using *N'*-((2-(4-chlorophenyl)allyl)oxy)benzimidamide **8c** (117 mg, 0.41 mmol). The oxidative cleavage was stirred for 2 h. Purification by silica flash column chromatography (30% EtOAc in *n*-heptane) afforded compound **6c** (75 mg, 66% yield) as a solid; ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.61 (m, 2H), 7.50 – 7.35 (m, 5H), 7.35 – 7.28 (m, 2H), 5.07 (s, 1H), 4.82 – 4.61 (m, 2H), 4.30 – 4.17 (m, 1H), 3.77 (dd, *J* = 11.1, 6.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 152.9, 137.9, 134.3, 132.6, 130.5, 129.2, 128.8, 128.3, 126.0, 69.4, 53.5; HRMS (ESI-TOF) *m/z* Calcd for C₁₅H₁₄ClN₂O 273.0793 [M + H]⁺; Found 273.0795; IR (ν_{max}, cm⁻¹): 3297, 1601; Anal. Calcd for C₁₅H₁₃ClN₂O: C, 66.06; H, 4.80; N, 10.27%. Found: C, 65.73; H, 4.51; N, 10.24%.

5-Methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6d). General procedure C was followed using *N'*-((2-methylallyl)oxy)benzimidamide **8d** (575 mg, 3.0 mmol). Purification by silica flash column chromatography (35% EtOAc in *n*-heptane) afforded compound **6d** (311 mg, 57% yield) as a solid.

5-(4-Methylphenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6i). General procedure C was followed using *N'*-((2-(4-methylphenyl)allyl)oxy)benzimidamide **8i** (71 mg, 0.27 mmol). Purification by silica flash column chromatography (0% to 60% EtOAc in *n*-heptane) followed by lyophilization afforded compound **6i** (46 mg, 68% yield) as an amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.65 (m, 2H), 7.48 – 7.36 (m, 3H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 5.08 (s, 1H), 4.69 – 4.62 (m, 1H), 4.22 (dd, $J = 11.0, 4.0$ Hz, 1H), 3.69 (dd, $J = 11.0, 7.5$ Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.9, 138.6, 135.8, 132.9, 130.4, 129.8, 128.8, 126.9, 126.0, 69.8, 54.0, 21.2; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}$ 253.1341 $[\text{M} + \text{H}]^+$; Found 253.1337; IR (ν_{max} , cm^{-1}): 3332, 1606.

5-(4-Fluorophenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6j). General procedure C was followed using *N'*-((2-(4-fluorophenyl)allyl)oxy)benzimidamide **8j** (85 mg, 0.31 mmol). Purification by silica flash column chromatography (0% to 60% EtOAc in *n*-heptane) followed by lyophilization afforded compound **6j** (57 mg, 71% yield) as an amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.60 (m, 2H), 7.48 – 7.35 (m, 3H), 7.35 – 7.28 (m, 2H), 7.12 – 7.02 (m, 2H), 5.29 (s, 1H), 4.72 – 4.61 (m, 1H), 4.15 (dd, $J = 11.1, 3.8$ Hz, 1H), 3.70 (dd, $J = 11.1, 6.6$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.8 (d, $J = 247.2$ Hz), 152.9, 135.1 (d, $J = 3.1$ Hz), 132.7, 130.4, 128.8, 128.6 (d, $J = 8.2$ Hz), 126.0, 116.0 (d, $J = 21.7$ Hz), 69.5, 53.5; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{15}\text{H}_{14}\text{FN}_2\text{O}$ 257.1090 $[\text{M} + \text{H}]^+$; Found 257.1088; IR (ν_{max} , cm^{-1}): 3344, 1602; Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}$: C, 70.30; H, 5.11; N, 10.93%. Found: C, 70.06; H, 5.03; N, 10.90%.

5-(3-Methoxyphenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6k). General procedure C was followed using *N'*-((2-(3-methoxyphenyl)allyl)oxy)benzimidamide **8k** (83 mg, 0.29 mmol). Purification by silica flash column chromatography (0% to 60% EtOAc in *n*-heptane) followed by lyophilization afforded compound **6k** (59 mg, 75% yield) as an amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 7.77 – 7.61 (m, 2H), 7.52 – 7.36 (m, 3H), 7.37 – 7.28 (m, 1H), 6.95 (d, $J = 7.7$ Hz, 1H), 6.92 – 6.85 (m, 2H), 5.10 (s, 1H), 4.73 – 4.60 (m, 1H), 4.25 (dd, $J = 11.0, 4.0$ Hz, 1H), 3.81 (s, 3H), 3.74 (dd, $J = 11.0, 7.3$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 160.3, 152.8, 140.5, 132.9, 130.4, 130.3, 128.8, 126.0, 119.1, 113.8, 112.8, 69.7, 55.4, 54.2; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2$ 269.1290 $[\text{M} + \text{H}]^+$; Found 269.1288.

5-(3-Chlorophenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6l). General procedure C was followed using *N'*-((2-(3-chlorophenyl)allyl)oxy)benzimidamide **8l** (83 mg, 0.29 mmol). Purification by silica flash column chromatography (0% to 60% EtOAc in *n*-heptane) followed by lyophilization afforded compound **6l** (52 mg, 66% yield) as an amorphous solid; ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.59 (m,

2H), 7.48 – 7.36 (m, 3H), 7.35 – 7.29 (m, 3H), 7.25 – 7.19 (m, 1H), 5.33 (s, 1H), 4.70 – 4.61 (m, 1H), 4.14 (dd, $J = 11.1, 3.8$ Hz, 1H), 3.73 (dd, $J = 11.1, 6.3$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.9, 141.5, 135.0, 132.6, 130.5, 130.4, 128.8, 128.7, 127.1, 126.0, 125.1, 69.3, 53.7; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{15}\text{H}_{14}\text{ClN}_2\text{O}$ 273.0795 $[\text{M} + \text{H}]^+$; Found 273.0791.

5-(Benzofuran-3-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6m). General procedure **C** was followed using *N*'-((2-(benzofuran-3-yl)allyl)oxy)benzimidamide (**8m**) (190 mg, 0.65 mmol). Purification by silica flash column chromatography (30% EtOAc in *n*-heptane) afforded compound **6m** (67 mg, 38% yield) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 7.63 – 7.54 (m, 4H), 7.49 (d, $J = 8.3$ Hz, 1H), 7.44 – 7.37 (m, 1H), 7.36 – 7.28 (m, 3H), 7.26 – 7.20 (m, 1H), 5.44 (s, 1H), 4.95 – 4.86 (m, 1H), 4.19 (dd, $J = 11.1, 4.0$ Hz, 1H), 3.98 (dd, $J = 11.1, 6.7$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.8, 152.9, 142.8, 132.6, 130.4, 128.7, 126.0, 125.6, 125.0, 123.1, 119.9, 119.0, 112.0, 67.5, 46.6; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_2$ 279.1134 $[\text{M} + \text{H}]^+$; Found 279.1132.

5-(Pyridin-3-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6o). General procedure **C** was followed using *N*'-((2-(pyridin-3-yl)allyl)oxy)benzimidamide (**8o**) (310 mg, 1.22 mmol). The oxidative cleavage was stirred for 16 h. Purification by silica flash column chromatography (5% MeOH in DCM) afforded compound **6o** (66 mg, 22% yield) as an off white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.53 – 8.42 (m, 2H), 7.68 – 7.58 (m, 3H), 7.47 – 7.39 (m, 1H), 7.39 – 7.31 (m, 2H), 7.27 (dd, $J = 7.9, 4.8$ Hz, 1H), 5.96 (d, $J = 2.2$ Hz, 1H), 4.74 – 4.62 (m, 1H), 4.08 (dd, $J = 11.1, 3.7$ Hz, 1H), 3.78 (dd, $J = 11.1, 5.3$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.2, 149.6, 148.3, 135.7, 134.7, 132.5, 130.5, 128.7, 126.0, 123.9, 68.8, 51.8; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}$ 240.1137 $[\text{M} + \text{H}]^+$; Found 240.1138.

General procedure **D** for the alkylation of (*N*-substituted) *N*'-hydroxybenzimidamides. To a solution of the appropriate *N*'-hydroxybenzimidamide and 1-bromo-2,2-diethoxyethane (1.1 equiv.) in DMSO was added KOH (1.2 equiv.) and the mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with water, extracted with EtOAc, the combined organic extracts were washed twice with 0.1 M aqueous sodium hydroxide solution and once with brine. The organic layer was dried over Na_2SO_4 , concentrated and the crude product was purified by silica flash column chromatography using the indicated gradient.

***N*'-(2,2-Diethoxyethoxy)benzimidamide (9).** General procedure **D** was followed using *N*'-hydroxybenzimidamide **4** (10.0 g, 73.7 mmol) in 100 mL of DMSO. Purification by silica flash column chromatography (15% to 30% EtOAc in *n*-heptane) afforded compound **9** (14.3 g, 77% yield) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.57 (m, 2H), 7.47 – 7.33 (m, 3H), 4.86 (t, $J = 5.3$ Hz, 3H), 4.11 (d, $J = 5.4$ Hz, 2H), 3.76 (dq, $J = 9.5, 7.1$ Hz, 2H), 3.61 (dq, $J = 9.4, 7.0$ Hz, 2H), 1.24 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.5, 132.6, 130.1, 128.7, 126.0, 100.5, 73.6, 62.6, 15.5; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$ 275.1372 $[\text{M} + \text{Na}]^+$; Found 275.1374.

5-Ethoxy-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (10). To a solution of *N'*-(2,2-diethoxyethoxy)benzimidamide **9** (5.0 g, 19.8 mmol) in EtOH (200 mL), H₂SO₄ (1.94 g, 19.8 mmol) in water (10 mL) was added and the mixture was stirred at 65 °C for 1 week. The reaction mixture was quenched using solid sodium bicarbonate. When gas evolution had ceased, the reaction mixture was concentrated to approximately 50 mL volume and partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with water, brine, dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (45% to 65% EtOAc in *n*-heptane) to afford compound **10** (2.8 g, 69% yield) as a solid; mp 112 – 113 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (d, *J* = 5.0 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.51 – 7.37 (m, 3H), 4.86 – 4.78 (m, 1H), 4.07 – 3.98 (m, 1H), 3.76 – 3.64 (m, 1H), 3.54 – 3.38 (m, 2H), 1.15 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.2, 132.5, 129.9, 128.3, 125.9, 77.2, 65.9, 61.2, 15.1; HRMS (ESI-TOF) *m/z* Calcd for C₁₁H₁₅N₂O₂ 207.1134 [M + H]⁺; Found 207.1139.

***N'*-(2,2-Diethoxyethoxy)-*N*-methylbenzimidamide (13a).** General procedure **D** was followed using *N'*-hydroxy-*N*-methylbenzimidamide **12a** (488 mg, 3.25 mmol) in 5 mL of DMSO. Purification by silica flash column chromatography (0% to 30% EtOAc in *n*-heptane) afforded compound **13a** (444 mg, 51% yield) as a pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.30 (m, 5H), 5.47 – 5.12 (m, 1H), 4.06 (d, *J* = 5.4 Hz, 2H), 3.75 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.60 (dq, *J* = 9.5, 7.1 Hz, 2H), 2.71 (d, *J* = 5.3 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 157.6, 131.2, 129.7, 128.8, 128.6, 100.5, 73.3, 62.6, 30.8, 15.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₄H₂₂N₂NaO₃ 289.1528 [M + Na]⁺; Found 289.1529.

***N'*-(2,2-Diethoxyethoxy)-*N*-phenylbenzimidamide (13b).** General procedure **D** was followed using *N'*-hydroxy-*N*-phenylbenzimidamide **12b** (577 mg, 2.72 mmol) in 5 mL of DMSO. Purification by silica flash column chromatography (8% to 30% EtOAc in *n*-heptane) afforded compound **13b** (392 mg, 44% yield) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.39 (m, 2H), 7.39 – 7.21 (m, 4H), 7.14 – 7.04 (m, 2H), 6.95 – 6.87 (m, 1H), 6.68 – 6.60 (m, 2H), 4.89 (t, *J* = 5.4 Hz, 1H), 4.17 (d, *J* = 5.4 Hz, 2H), 3.83 – 3.71 (m, 2H), 3.68 – 3.56 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 152.0, 139.9, 131.2, 129.8, 128.9, 128.6, 128.5, 122.8, 121.4, 100.4, 73.7, 62.7, 15.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₉H₂₄N₂NaO₃ 351.1684 [M + Na]⁺; Found 351.1705.

General procedure **E** for the synthesis of 5-substituted 3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazines *via* iminium ion additions. A 0.25 M solution of *N'*-(2,2-diethoxyethoxy)benzimidamide (**9**) in formic acid was heated to 100 °C for 15 min and then cooled to rt. Next, 5 equivalents of nucleophile were added and the mixture was stirred at the indicated temperature for the indicated time. The mixture was concentrated, co-evaporated with DCM twice and the product was purified as indicated.

5-(Furan-2-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6p). General procedure **E** was followed starting from **9** (1.14 g, 4.52 mmol) using furan as the nucleophile and stirring at rt for 20 h. Purification

by silica flash column chromatography (20% to 40% EtOAc in *n*-heptane) afforded compound **6p** (0.91 g, 88% yield) as a solid; mp 115 – 116 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 – 7.59 (m, 4H), 7.49 – 7.36 (m, 3H), 6.44 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.40 – 6.32 (m, 1H), 4.77 (q, *J* = 3.7 Hz, 1H), 4.01 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.91 (dd, *J* = 11.0, 3.5 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 153.6, 151.8, 142.3, 132.7, 129.8, 128.2, 126.0, 110.5, 106.9, 65.8, 47.2; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₃N₂O₂ 229.0977 [M + H]⁺; Found 229.0985; IR (ν_{max}, cm⁻¹): 3377, 1605; Anal. Calcd for C₁₃H₁₂N₂O₂: C, 68.21; H, 5.10; N, 12.07%. Found: C, 67.97; H, 4.82; N, 11.88%. Compound **6p** was also synthesised from **10** by stirring with furan for 20 h at rt in 92% yield.

5-(1*H*-Indol-3-yl)-3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6q). General procedure **E** was followed starting from **9** (106 mg, 0.42 mmol) using indole as the nucleophile (2 equiv. added directly, an additional 2 equiv. after 30 min, followed by an additional 1 equiv. after 1 h) and stirring at rt for 20 h. Purification by silica flash column chromatography (15% to 50% EtOAc in *n*-heptane) followed by basic preparative HPLC afforded compound **6q** (82 mg, 70% yield) as an amorphous solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 7.76 – 7.67 (m, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.48 – 7.32 (m, 5H), 7.14 – 7.05 (m, 1H), 7.04 – 6.95 (m, 1H), 5.02 – 4.93 (m, 1H), 4.11 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.85 (dd, *J* = 10.8, 6.6 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.4, 136.5, 133.1, 129.6, 128.2, 126.1, 125.5, 123.6, 121.2, 118.8, 118.7, 113.4, 111.7, 68.1, 47.0; HRMS (ESI-TOF) *m/z* Calcd for C₁₇H₁₆N₃O 278.1293 [M + H]⁺; Found 278.1294; IR (ν_{max}, cm⁻¹): 3310, 1607; Anal. Calcd for C₁₇H₁₅N₃O: C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.36; H, 5.44; N, 15.14%.

5-(1-Methyl-1*H*-indol-3-yl)-3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6r). General procedure **E** was followed starting from **9** (109 mg, 0.43 mmol) using 1-methylindole as the nucleophile (3 equiv. added directly, an additional 2 equiv. after 1 h) and stirring at rt for 20 h. Purification by acidic preparative HPLC afforded compound **6r** (108 mg, 86% yield) as a yellow amorphous solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 – 7.68 (m, 2H), 7.68 – 7.61 (m, 1H), 7.52 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.37 (m, 4H), 7.35 (s, 1H), 7.21 – 7.12 (m, 1H), 7.08 – 7.00 (m, 1H), 5.01 – 4.93 (m, 1H), 4.09 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.85 (dd, *J* = 10.8, 6.2 Hz, 1H), 3.77 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.3, 136.8, 133.1, 129.7, 128.2, 127.8, 126.1, 125.9, 121.3, 119.0, 118.8, 112.8, 109.9, 68.1, 46.7, 32.4; HRMS (ESI-TOF) *m/z* Calcd for C₁₈H₁₈N₃O 292.1449 [M + H]⁺; Found 292.1448; IR (ν_{max}, cm⁻¹): 3180, 1606; Anal. Calcd for C₁₈H₁₇N₃O: C, 74.20; H, 5.88; N, 14.42%. Found: C, 73.84; H, 6.10; N, 14.61%.

5-(1*H*-Indazol-3-yl)-3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (6s). General procedure **E** was followed starting from **9** (110 mg, 0.44 mmol) using indazole as the nucleophile and stirring at rt for 84 h. Purification by silica flash column chromatography (20% to 50% EtOAc in *n*-heptane) afforded compound **6s** (106 mg, 87% yield) as a solid; mp 172 – 174 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (d, *J* = 4.7 Hz, 1H), 8.15 (d, *J* = 0.9 Hz, 1H), 7.83 – 7.69 (m, 3H), 7.63 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.54 – 7.42

(m, 3H), 7.40 – 7.32 (m, 1H), 7.20 – 7.11 (m, 1H), 6.43 – 6.35 (m, 1H), 4.24 (dd, $J = 11.7, 2.7$ Hz, 1H), 4.03 (dd, $J = 11.7, 3.1$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 152.7, 138.5, 133.4, 131.9, 130.3, 128.5, 126.2, 126.0, 124.4, 120.9, 120.8, 110.8, 66.5, 65.0; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_4\text{O}$ 279.1246 $[\text{M} + \text{H}]^+$; Found 279.1248; IR (ν_{max} , cm^{-1}): 3191, 1611; Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}$: C, 69.05; H, 5.07; N, 20.13%. Found: C, 68.88; H, 4.86; N, 20.07%.

5-(Benzofuran-2-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6t). General procedure E was followed starting from **9** (111 mg, 0.44 mmol) using benzofuran as the nucleophile and stirring at 100 °C for 2.5 h. Purification by SCX chromatography, basic preparative HPLC, followed by acidic preparative HPLC afforded compound **6t** (65 mg, 53% yield) as an amorphous solid; ^1H NMR (400 MHz, DMSO- d_6) δ 7.88 (d, $J = 4.2$ Hz, 1H), 7.76 – 7.66 (m, 2H), 7.66 – 7.59 (m, 1H), 7.59 – 7.53 (m, 1H), 7.52 – 7.40 (m, 3H), 7.33 – 7.19 (m, 2H), 6.87 – 6.81 (m, 1H), 4.96 (q, $J = 3.5$ Hz, 1H), 4.22 (dd, $J = 11.1, 3.4$ Hz, 1H), 3.98 (dd, $J = 11.1, 3.4$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 156.8, 154.2, 151.8, 132.7, 129.9, 128.3, 128.0, 126.0, 124.1, 122.9, 121.0, 111.1, 103.9, 65.3, 47.6; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_2$ 279.1133 $[\text{M} + \text{H}]^+$; Found 279.1130; IR (ν_{max} , cm^{-1}): 3323, 1603; Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$: C, 73.37; H, 5.07; N, 10.07%. Found: C, 72.82; H, 4.90; N, 9.97%.

5-(Benzo[b]thiophen-2-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6u). General procedure E was followed starting from **9** (0.51 g, 2.0 mmol) using benzo[b]thiophene as the nucleophile and stirring at 100 °C for 4 h. Purification by silica flash column chromatography (25% acetone in *n*-heptane) afforded a mixture of isomers. Further purification by silica flash column chromatography (18% to 40% EtOAc in *n*-heptane) afforded **6u** (408 mg, 69%) as a solid; mp 87 – 89 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 8.06 – 8.01 (m, 1H), 8.01 – 7.95 (m, 1H), 7.78 (d, $J = 3.4$ Hz, 1H), 7.77 – 7.70 (m, 2H), 7.66 – 7.61 (m, 1H), 7.51 – 7.37 (m, 5H), 5.19 (q, $J = 3.7$ Hz, 1H), 4.08 (dd, $J = 11.0, 3.6$ Hz, 1H), 3.96 (dd, $J = 11.0, 4.6$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 152.3, 140.2, 136.9, 135.5, 132.9, 129.8, 128.3, 126.1, 124.6, 124.5, 124.3, 123.1, 121.9, 66.9, 48.2, HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{OS}$ 295.0905 $[\text{M} + \text{H}]^+$; Found 295.0906; IR (ν_{max} , cm^{-1}): 3310, 1605; Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{OS}$: C, 69.36; H, 4.79; N, 9.52%. Found: C, 69.22; H, 4.53; N, 9.22%.

5-(Benzo[d][1,3]dioxol-5-yl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6v). General procedure E was followed starting from **9** (110 mg, 0.44 mmol) using 1,3-benzodioxole as the nucleophile and stirring at 100 °C for 4.5 h. Purification by silica flash column chromatography (40% to 65% EtOAc in *n*-heptane) afforded compound **6v** (91 mg, 74% yield) as a solid; mp 155.5 – 156.5 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 7.75 – 7.66 (m, 2H), 7.62 (d, $J = 2.9$ Hz, 1H), 7.50 – 7.38 (m, 3H), 6.97 – 6.88 (m, 2H), 6.85 (dd, $J = 8.1, 1.5$ Hz, 1H), 6.00 (s, 2H), 4.63 (q, $J = 3.6$ Hz, 1H), 3.95 (dd, $J = 10.9, 3.6$ Hz, 1H), 3.70 (dd, $J = 10.9, 5.0$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 152.3, 147.3, 146.5, 134.9, 132.9, 129.8, 128.3, 126.0, 120.0, 108.1, 107.2, 100.9, 68.9, 52.1; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_3$

283.1082 [M + H]⁺; Found 283.1088; IR (ν_{\max} , cm⁻¹): 3320, 1604; Anal. Calcd for C₁₆H₁₄N₂O₃: C, 68.07; H, 5.00; N, 9.92%. Found: C, 67.67; H, 4.67; N, 9.79%.

5-(2-Methoxyphenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6w) and **5-(4-methoxyphenyl)-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6b)**. General procedure E was followed starting from **9** (110 mg, 0.44 mmol) using anisole as the nucleophile and stirring at 100 °C for 2.5 h. Purification by silica flash column chromatography (20% to 40% EtOAc in *n*-heptane) and lyophilization afforded compound **6w** (23 mg, 20% yield) as an amorphous yellow solid and compound **6b** (79 mg, 67% yield) as an amorphous pink solid; **6w**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.77 – 7.67 (m, 2H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.33 – 7.25 (m, 1H), 7.22 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.04 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.01 – 6.92 (m, 1H), 4.97 (q, *J* = 3.6 Hz, 1H), 3.92 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.84 (s, 3H), 3.78 (dd, *J* = 10.8, 3.6 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.9, 152.5, 133.0, 129.8, 128.6, 128.4, 128.3, 127.3, 125.9, 120.2, 110.7, 67.0, 55.5, 47.2; HRMS (ESI-TOF) *m/z* Calcd for C₁₆H₁₇N₂O₂ 269.1290 [M + H]⁺; Found 269.1287; IR (ν_{\max} , cm⁻¹): 3382, 1603; Anal. Calcd for C₁₆H₁₆N₂O₂: C, 71.62; H, 6.01; N, 10.44%. Found: C, 71.51; H, 5.97; N, 9.99%.

5-Allyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6x). To a solution of **10** (250 mg, 1.21 mmol) in DCM (5 mL) at 0 °C under nitrogen atmosphere allyltrimethylsilane (693 mg, 6.06 mmol) and BF₃·OEt₂ (860 mg, 6.06 mmol) were added. The mixture was allowed to come to rt and stirred for 20 h. It was poured out onto sat. aq. sodium bicarbonate, the layers were separated, the organic layer was dried using Na₂SO₄, concentrated and purified by silica flash column chromatography (0% to 50% EtOAc in *n*-heptane) to afford compound **6x** (156 mg, 64% yield) as an oil that solidified upon standing; ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.55 (m, 2H), 7.47 – 7.31 (m, 3H), 5.91 – 5.73 (m, 1H), 5.25 – 5.21 (m, 1H), 5.21 – 5.17 (m, 1H), 4.92 (s, 1H), 4.18 – 4.02 (m, 1H), 3.73 – 3.54 (m, 2H), 2.50 – 2.36 (m, 1H), 2.33 – 2.17 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 152.5, 133.0, 133.0, 130.2, 128.7, 125.9, 119.3, 67.6, 48.8, 37.5; HRMS (ESI-TOF) *m/z* Calcd for C₁₂H₁₅N₂O 203.1184 [M + H]⁺; Found 203.1182; IR (ν_{\max} , cm⁻¹): 3323, 1607; Anal. Calcd for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.09; H, 7.20; N, 13.65%.

1-Phenyl-2-(3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazin-5-yl)ethan-1-one (6y). 1-Phenyl-1-trimethylsilyloxyethylene (242 mg, 1.26 mmol) was slowly added to a suspension of **10** (200 mg, 0.97 mmol) and scandium trifluoromethanesulfonate (48 mg, 0.10 mmol) in DCM (5 mL) at 0 °C under an argon atmosphere. The mixture was allowed to come to rt and stirred for 24 h. Additional 1-phenyl-1-trimethylsilyloxyethylene (242 mg, 1.26 mmol) was added and stirring was continued for 24 h. The mixture was concentrated under reduced pressure and the residue was purified by silica flash chromatography (10% to 60% EtOAc in *n*-heptane) to afford compound **6y** (90 mg, 33% yield) as a gum; ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.93 (m, 2H), 7.66 – 7.56 (m, 3H), 7.55 – 7.45 (m, 2H), 7.45 – 7.33

(m, 3H), 5.65 (s, 1H), 4.38 – 4.22 (m, 1H), 4.12 – 3.97 (m, 2H), 3.57 (dd, $J = 18.0, 9.8$ Hz, 1H), 3.28 (dd, $J = 18.0, 3.3$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 198.9, 153.1, 136.5, 133.9, 132.7, 130.4, 128.9, 128.8, 128.2, 126.0, 67.3, 46.4, 43.0; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$ 281.1290 $[\text{M} + \text{H}]^+$; Found 281.1293; IR (ν_{max} , cm^{-1}): 3207, 1684, 1608; Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.76; N, 9.99%. Found: C, 73.08; H, 5.75; N, 10.02%.

5-(Furan-2-yl)-4-methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (14a). General procedure E was followed starting from **13a** (198 mg, 0.74 mmol) using furan as the nucleophile and stirring at 70 °C for 4 h. Purification by silica flash column chromatography (0% to 50% EtOAc in *n*-heptane), followed by basic preparative HPLC afforded compound **14a** (105 mg, 58% yield) as an amorphous solid; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.69 (dd, $J = 1.8, 0.9$ Hz, 1H), 7.55 – 7.34 (m, 5H), 6.53 – 6.43 (m, 2H), 4.71 (t, $J = 3.9$ Hz, 1H), 4.15 (dd, $J = 11.3, 4.2$ Hz, 1H), 4.03 (dd, $J = 11.3, 3.7$ Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 156.1, 151.6, 142.8, 132.5, 129.4, 128.6, 128.4, 110.6, 107.9, 66.4, 54.3, 37.8, HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_2$ 243.1133 $[\text{M} + \text{H}]^+$; Found 243.1139; IR (ν_{max} , cm^{-1}): 1591; Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$: C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.04; H, 5.73; N, 11.69%.

5-(Furan-2-yl)-3,4-diphenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (14b). General procedure E was followed starting from **13b** (171 mg, 0.52 mmol) using furan as the nucleophile and stirring at 70 °C for 20 h. Purification by silica flash column chromatography (0% to 50% EtOAc in *n*-heptane), followed by basic preparative HPLC afforded compound **14b** (108 mg, 68% yield) as an amorphous solid; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.69 (dd, $J = 1.8, 0.9$ Hz, 1H), 7.55 – 7.34 (m, 5H), 6.53 – 6.43 (m, 2H), 4.71 (t, $J = 3.9$ Hz, 1H), 4.15 (dd, $J = 11.3, 4.2$ Hz, 1H), 4.03 (dd, $J = 11.3, 3.7$ Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 151.9, 151.0, 144.9, 142.7, 133.5, 129.0, 128.2, 128.1, 125.1, 125.0, 110.7, 107.7, 66.3, 55.4; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2$ 305.1290 $[\text{M} + \text{H}]^+$; Found 305.1286; IR (ν_{max} , cm^{-1}): 1588; Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2$: C, 74.98; H, 5.30; N, 9.20%. Found: C, 74.80; H, 5.27; N, 9.17%.

(S)-2-(Aminoxy)-1-phenylethan-1-amine (16). At 0 °C, diisopropyl azodicarboxylate (1.79 g, 8.85 mmol, 1.72 mL) was added to a solution of *tert*-butyl (*S*)-(2-hydroxy-1-phenylethyl)carbamate **15** (2.00 g, 8.43 mmol), *N*-hydroxyphthalimide (1.44 g, 8.85 mmol) and triphenylphosphine (2.32 g, 8.85 mmol) in THF (50 mL). The mixture was stirred at rt for 1 h, concentrated and the residue was purified by silica flash chromatography (5% to 25% EtOAc in *n*-heptane) to obtain a solid. Further purification by silica flash chromatography (0% to 2% MeOH in DCM) afforded *tert*-butyl (*S*)-(2-((1,3-dioxoisindolin-2-yl)oxy)-1-phenylethyl)carbamate (3.01 g, 93%) as a solid; ^1H NMR (400 MHz, CDCl_3) δ 7.83 – 7.77 (m, 2H), 7.77 – 7.70 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 1H), 5.92 (s, 1H), 5.04 (s, 1H), 4.60 – 4.41 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.5, 155.6, 138.6, 134.7, 128.8, 128.7, 127.7, 126.6, 123.7, 80.4, 80.0, 28.5. Hydrazine

monohydrate (0.433 g, 8.66 mmol, 0.422 mL) was added to a suspension of *tert*-butyl (*S*)-2-((1,3-dioxoisindolin-2-yl)oxy)-1-phenylethyl)carbamate (3.01 g, 7.87 mmol) in EtOH (25 mL) and the mixture was stirred at rt for 15 min. The solids were filtered off, the filtrate was concentrated and the residue was purified by silica flash column chromatography (1% to 6% MeOH in DCM) to obtain the crude product. Further purification by silica flash column chromatography (20% to 100% EtOAc in *n*-heptane) afforded *tert*-butyl (*S*)-2-(aminooxy)-1-phenylethyl)carbamate (1.60 g, 80%) as a solid; ¹H NMR (400 MHz, DMSO-*d*₆) as a mixture of rotamers δ 7.42 – 7.26 (m, 5H), 7.26 – 7.18 (m, 1H), 6.04 (s, 2H), 4.89 – 4.75 (m, 0.9H), 4.75 – 4.59 (m, 0.1H), 3.63 (dd, *J* = 10.6, 8.3 Hz, 1H), 3.55 (dd, *J* = 10.7, 5.5 Hz, 1H), 1.47 – 1.13 (m, 9H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.2, 141.3, 128.1, 126.8, 126.8, 77.8, 52.8, 28.2; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₂₁N₂O₃ 253.1552 [M + H]⁺; Found 253.1569. Saturated hydrochloric acid in EtOAc (10 mL) was added to a solution of *tert*-butyl (*S*)-2-(aminooxy)-1-phenylethyl)carbamate (1.55 g, 6.14 mmol) in EtOAc (10 mL). The mixture was stirred at rt for 1 h and concentrated. The residue was dissolved in MeOH (20 mL), K₂CO₃ (2.0 g, 18.4 mmol) was added and the mixture was stirred at rt for 1 h. The solids were filtered off, the filtrate was concentrated and purified by silica flash column chromatography (10% (7M NH₃ in MeOH) in DCM) to afford compound **16** (764 mg, 82%) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.32 (m, 4H), 7.29 – 7.25 (m, 1H), 4.29 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.79 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.67 (dd, *J* = 10.3, 8.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 142.6, 128.6, 127.5, 126.9, 81.9, 54.5; HRMS (ESI-TOF) *m/z* Calcd for C₈H₁₃N₂O 153.1028 [M + H]⁺; Found 153.1038.

General procedure **F** for the synthesis of substituted 5,6-dihydro-4*H*-[1,2,4]oxadiazines *via* condensation of a diamine with an imidate. A 0.25 M solution of a diamine and an imidate (1 equiv.) was stirred in acetic acid at rt for 16 h, followed by heating to 100 °C for the indicated time. The mixture was concentrated, dissolved in DCM, washed with sat. NaHCO₃, dried using Na₂SO₄, concentrated and the crude product was purified as described. When the diamine was a HCl salt, the free base was first prepared by stirring the compound in MeOH with K₂CO₃ (3 equiv.) for 30 min, followed by filtration and concentration of the filtrate, assuming quantitative yield.

(*S*)-3,5-Diphenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine (*S*-6a). General procedure **F** was followed using (*S*)-2-(aminooxy)-1-phenylethan-1-amine **16** (93 mg, 0.61 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 2 h. Purification by silica flash column chromatography (50% EtOAc in *n*-heptane) afforded compound **S-6a** (123 mg, 84% yield) as a crystalline solid; mp 129 – 131 °C; [α]_D^{23.5} = 109.3 (*c* 1, MeOH); Chiral HPLC: *t*_R: 13.31 min, 100% (column: Chiralpak AD-H, 250 x 4.6 mm, 5 μm, eluent: 20% EtOH in heptane, flow: 1 mL/min, temp: 25 °C).

(*S*)-3-Methyl-5-phenyl-5,6-dihydro-4*H*[1,2,4]oxadiazine (*S*-18b). General procedure **F** was followed using (*S*)-2-(aminooxy)-1-phenylethan-1-amine **16** (161 mg, 1.06 mmol) and ethyl acetimidate

hydrochloride, additional heating was not required. Purification by silica flash column chromatography (1% to 6% MeOH in DCM) afforded compound **S-18b** (152 mg, 82% yield) as a solid; mp 154 – 155.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.25 (m, 5H), 4.89 (s, 1H), 4.62 – 4.46 (m, 1H), 4.20 – 3.99 (m, 1H), 3.60 (dd, *J* = 11.1, 7.2 Hz, 1H), 1.95 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 151.3, 139.0, 129.0, 128.6, 126.8, 69.5, 54.2, 18.4; HRMS (ESI-TOF) *m/z* Calcd for C₁₀H₁₃N₂O 177.1028 [M + H]⁺; Found 177.1024; IR (ν_{max}, cm⁻¹): 3198, 1615; Anal. Calcd for C₁₀H₁₂N₂O: C, 70.28; H, 5.48; N, 17.56%. Found: C, 70.58; H, 5.45; N, 18.03%; [α]_D²⁴ 60.0 (*c* 1.1, MeOH).

(S)-3-Cyclohexyl-5-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (S-18c). General procedure **F** was followed using (*S*)-2-(aminoxy)-1-phenylethan-1-amine **16** (177 mg, 1.16 mmol) and ethyl cyclohexanecarbimide hydrochloride and stirring at 100 °C for 30 min. Purification by silica flash column chromatography (10% to 60% EtOAc in *n*-heptane) afforded compound **S-18c** (258 mg, 91% yield) as a solid; mp 105 – 106 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.33 (m, 3H), 7.33 – 7.29 (m, 2H), 4.64 – 4.54 (m, 1H), 4.51 (s, 1H), 4.28 – 4.04 (m, 1H), 3.60 (dd, *J* = 11.1, 7.5 Hz, 1H), 2.23 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.06 – 1.93 (m, 2H), 1.93 – 1.79 (m, 2H), 1.78 – 1.69 (m, 1H), 1.54 – 1.14 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 158.0, 139.3, 129.1, 128.5, 126.8, 69.9, 54.2, 42.0, 31.0, 30.8, 26.22, 26.18, 26.0; HRMS (ESI-TOF) *m/z* Calcd for C₁₅H₂₁N₂O 245.1654 [M + H]⁺; Found 245.1657; IR (ν_{max}, cm⁻¹): 3229, 1609; Anal. Calcd for C₁₅H₂₀N₂O: C, 73.74; H, 8.25; N, 11.47%. Found: C, 73.50; H, 8.47; N, 11.54%; [α]_D²⁴ 47.6 (*c* 1, MeOH).

(S)-5-Phenyl-3-(pyridin-2-yl)-5,6-dihydro-4H-[1,2,4]oxadiazine (S-18d). General procedure **F** was followed using (*S*)-2-(aminoxy)-1-phenylethan-1-amine **16** (161 mg, 1.06 mmol) and methyl picolinimide and stirring at 100 °C for 2 h. Purification by silica flash column chromatography (10% to 60% EtOAc in *n*-heptane) afforded compound **S-18d** (215 mg, 85% yield) as a solid; mp 105 – 106.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, *J* = 4.7 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.75 (td, *J* = 7.8, 1.7 Hz, 1H), 7.47 – 7.28 (m, 6H), 6.94 (s, 1H), 4.84 – 4.66 (m, 1H), 4.40 – 4.24 (m, 1H), 3.74 (dd, *J* = 10.9, 7.0 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 150.2, 148.7, 148.2, 139.0, 136.9, 129.1, 128.5, 126.9, 124.9, 120.3, 70.2, 53.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₄H₁₄N₃O 240.1137 [M + H]⁺; Found 240.1138; IR (ν_{max}, cm⁻¹): 3398, 1618; Anal. Calcd for C₁₄H₁₃N₃O: C, 70.28; H, 5.48; N, 17.56%. Found: C, 70.58; H, 5.45; N, 17.83%; [α]_D²⁴ 145.5 (*c* 1.1, MeOH).

2-(Aminoxy)propan-1-amine dihydrochloride (20b). *tert*-Butyl (2-(aminoxy)propyl)carbamate²¹ (500 mg, 2.63 mmol) was added to a 4 M solution of HCl in EtOAc (10 mL) and stirred for 1 h at rt. Evaporation of the reaction mixture afforded compound **20b** (420 mg, 98%) as a solid; mp 194 – 195 °C (decomp.); ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (s, 3H), 8.37 (s, 3H), 4.62 – 4.44 (m, 1H), 3.07 (m, 2H), 1.33 (d, *J* = 6.3 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 77.21, 41.23, 16.45; HRMS (ESI-TOF) *m/z* Calcd for C₃H₁₁N₂O 91.0864 [M + H]⁺; Found 91.0871.

(1R,2S)-2-(Aminoxy)cyclohexan-1-amine (20e). To a solution of *tert*-butyl ((1R,2R)-2-hydroxycyclohexylcarbamate (1.0 g, 4.64 mmol) and *N*-hydroxyphthalimide (909 mg, 5.57 mmol) in dry THF (70 mL) was added triphenylphosphine (1.83 g, 6.96 mmol) and diisopropyl azodicarboxylate (1.35 mL, 6.96 mmol) and the mixture was stirred at rt for 3 h. The mixture was diluted with water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica flash column chromatography (40% EtOAc in *n*-heptane) to afford *tert*-butyl ((1R,2S)-2-((1,3-dioxoisindolin-2-yl)oxy)cyclohexyl)carbamate (1.18 g, 71%) as a solid; ¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.84 (m, 2H), 7.80 – 7.75 (m, 2H), 5.85 (br d, *J* = 7.0 Hz, 1H), 4.36 (s, 1H), 3.69 (br s, 1H), 2.27 – 2.23 (m, 1H), 1.97 – 1.69 (m, 4H), 1.60 – 1.35 (m, 12H); ¹³C NMR (101 MHz, CDCl₃) δ 164.2, 155.7, 134.7, 129.0, 123.7, 87.2, 79.2, 51.7, 29.4, 28.5, 27.6, 24.4, 19.6. To a solution of *tert*-butyl ((1R,2S)-2-((1,3-dioxoisindolin-2-yl)oxy)cyclohexyl)carbamate (450 mg, 1.25 mmol) in DCM (40 mL) was added TFA (20 mL) and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated and the residue was coevaporated with toluene (3 × 25 mL), DCM (25 mL) and Et₂O (25 mL) to give an off-white foam as residue. This was dissolved in EtOH (35 mL), hydrazine monohydrate (0.47 mL, 9.6 mmol) was added and the mixture was stirred at rt for 16 h. The solids were filtered off, the filtrate was concentrated on silica and purified by silica flash column chromatography (10% (7M NH₃ in MeOH) in DCM) to afford **20e** (116 mg, 65%) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 3.70 (dt, *J* = 6.9, 3.2 Hz, 1H), 3.23 (m, 1H), 1.92 – 1.86 (m, 1H), 1.72 – 1.44 (m, 5H), 1.38 – 1.31 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 82.2, 50.5, 29.8, 26.5, 22.2, 21.6; HRMS (ESI-TOF) *m/z* Calcd for C₆H₁₅N₂O 131.1184 [M + H]⁺; Found 131.1195.

(1R,2R)-2-(Aminoxy)cyclohexan-1-amine (20f). To a solution of *tert*-butyl ((1R,2S)-2-hydroxycyclohexylcarbamate (0.5 g, 2.32 mmol) and *N*-hydroxyphthalimide (568 mg, 3.48 mmol) in dry THF (40 mL) was added triphenylphosphine (914 mg, 3.48 mmol) and diisopropyl azodicarboxylate (0.67 mL, 3.48 mmol) and the mixture was stirred at rt for 72 h. The mixture was diluted with water (70 mL) and extracted with DCM (3 × 70 mL). The combined organic layers were washed with brine (70 mL), dried over Na₂SO₄, concentrated and purified by silica flash column chromatography (45% EtOAc in *n*-heptane) to afford *tert*-butyl ((1R,2R)-2-((1,3-dioxoisindolin-2-yl)oxy)cyclohexyl)carbamate (563 mg, 67%) as a solid; ¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.82 (m, 2H), 7.78 – 7.74 (m, 2H), 5.61 (br s, 1H), 3.98 – 3.91 (m, 1H), 3.64 – 3.57 (m, 1H), 2.41 (br d, *J* = 10.5 Hz, 1H), 2.19 – 2.15 (m, 1H), 1.83 – 1.60 (m, 3H), 1.44 (s, 9H), 1.40 – 1.18 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.3, 155.9, 134.7, 128.9, 123.7, 88.7, 79.3, 53.2, 31.8, 30.5, 28.6, 23.9, 23.7. To a solution of *tert*-butyl ((1R,2R)-2-((1,3-dioxoisindolin-2-yl)oxy)cyclohexyl)carbamate (540 mg, 1.49 mmol) in DCM (40 mL) was added TFA (20 mL) and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated

and the residue was coevaporated with toluene (3 × 25 mL), DCM (25 mL) and Et₂O (25 mL) to give an off-white foam as residue. This was dissolved in EtOH (35 mL), hydrazine monohydrate (0.6 mL, 12.3 mmol) was added and the mixture was stirred at rt for 16 h. The solids were filtered off, the filtrate was concentrated on silica and purified by silica flash column chromatography (10% (7M NH₃ in MeOH) in DCM) to afford **20f** (115 mg, 55%) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 3.15 (ddd, *J* = 10.2, 9.3, 4.2 Hz, 1H), 2.62 (ddd, *J* = 10.8, 9.3, 4.4 Hz, 1H), 2.20 – 2.17 (m, 1H), 1.89 – 1.84 (m, 1H), 1.76 – 1.73 (m, 1H), 1.67 – 1.63 (m, 1H), 1.27 – 1.11 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 89.0, 53.7, 34.3, 29.6, 24.8, 24.5; HRMS (ESI-TOF) *m/z* Calcd for C₆H₁₅N₂O 131.1184 [M + H]⁺; Found 131.1196.

1-(Aminoxy)-2-methylpropan-2-amine dihydrochloride (20j). Under an argon atmosphere, potassium bis(trimethylsilyl)amide (1 M in THF, 29.8 mL, 29.8 mmol) was added to a solution of acetone oxime (2.18 g, 29.8 mmol) in dry DMF (100 mL). A solution of 4,4-dimethyl-2-(trifluoromethyl)-4,5-dihydrooxazole²² (3.33 g, 19.9 mmol) in dry DMF (25 mL) was added and the mixture was heated at 80 °C for 2 h. The mixture was quenched with saturated aqueous NH₄Cl and extracted with EtOAc twice. The combined organic layers were washed with water, brine, dried over Na₂SO₄, concentrated and the residue was purified by silica flash column chromatography (5% to 25% EtOAc in *n*-heptane) to afford 2,2,2-trifluoro-*N*-(2-methyl-1-((propan-2-ylideneamino)oxy)propan-2-yl)acetamide (3.45 g, 68%) as a pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 3.93 (s, 2H), 1.89 (s, 3H), 1.88 (s, 3H), 1.43 (s, 6H). A solution of 2,2,2-trifluoro-*N*-(2-methyl-1-((propan-2-ylideneamino)oxy)propan-2-yl)acetamide (3.45 g, 13.5 mmol) and sodium hydroxide (2.5 g, 42 mmol) in MeOH (75 mL) and water (75 mL) was heated at 55 °C for 16 h in a closed flask. The mixture was extracted with DCM (4 × 75 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford propan-2-one *O*-(2-amino-2-methylpropyl) oxime (1.95 g, 95%) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 3.82 (s, 2H), 1.89 (s, 3H), 1.88 (s, 3H), 1.13 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 154.7, 83.4, 53.6, 50.9, 50.4, 27.5, 22.0, 15.7. A solution of propan-2-one *O*-(2-amino-2-methylpropyl) oxime (1.95 g, 12.8 mmol) in 2 M aqueous HCl (100 mL) was heated at 90 °C for 16 h. The mixture was concentrated under reduced pressure and triturated from EtOH (30 mL) to afford **20j** (1.30 g, 57%) as a solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.28 (bs, 3H), 7.91 (bs, 3H), 4.08 (s, 2H), 1.31 (s, 6H), spectral data identical to literature.²³

1-((Aminoxy)methyl)cyclopentan-1-amine (20k). To a solution of (1-aminocyclopentyl)methanol (1.60 g, 13.9 mmol) and *N,N*-diisopropylethylamine (3.59 g, 27.8 mmol) in DCM (75 mL) at 0 °C, trifluoroacetic anhydride (3.79 g, 18.06 mmol) was slowly added and the resulting mixture was stirred at rt for 90 min. Saturated aqueous NaHCO₃ was added, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄, concentrated under reduced pressure and the residue was purified by silica flash column chromatography (10% to 50% EtOAc in

n-heptane) to obtain 2,2,2-trifluoro-*N*-(1-(hydroxymethyl)cyclopentyl)acetamide (2.68 g, 91% yield) as a solid; ^1H NMR (400 MHz, CDCl_3) δ 6.42 (s, 1H), 3.71 (s, 2H), 2.49 (s, 1H), 2.00 – 1.75 (m, 6H), 1.75 – 1.61 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 157.3 (q, $J = 36$ Hz), 115.9 (q, $J = 288$ Hz), 67.0, 66.7, 34.9, 24.3. At 0 °C, diisopropyl azodicarboxylate (2.69 g, 13.3 mmol) was added to a solution of 2,2,2-trifluoro-*N*-(1-(hydroxymethyl)cyclopentyl)acetamide (2.68 g, 12.7 mmol) and triphenylphosphine (3.50 g, 13.3 mmol) in DCM (100 mL). The mixture was stirred at rt for 30 min, concentrated, pentane (100 mL) was added and the mixture was stirred vigorously for 1 h. The solids were filtered off, washed with pentane and concentrated to afford 2-(trifluoromethyl)-3-oxa-1-azaspiro[4.4]non-1-ene as a yellow oil, which was used crude in the next step. Under an argon atmosphere potassium bis(trimethylsilyl)amide (1 M in THF, 18.1 mL, 18.1 mmol) was added to a solution of acetone oxime (1.32 g, 18.1 mmol) in dry DMF (40 mL). A solution of 2-(trifluoromethyl)-3-oxa-1-azaspiro[4.4]non-1-ene from the previous step in dry DMF (20 mL) was added and the mixture was heated at 80 °C for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layer was washed with water, brine, dried over Na_2SO_4 , concentrated and the residue was purified by silica flash column chromatography (5% to 25% EtOAc in *n*-heptane) to afford 2,2,2-trifluoro-*N*-(1-(((propan-2-ylideneamino)oxy)methyl)cyclopentyl)acetamide (2.83 g, 71% over 2 steps) as a pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (s, 1H), 3.98 (s, 2H), 2.19 – 2.07 (m, 2H), 1.99 – 1.89 (m, 2H), 1.88 (s, 3H), 1.87 (s, 3H), 1.80 – 1.68 (m, 2H), 1.67 – 1.54 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.40, 156.1 (q, $J = 36$ Hz), 116.0 (q, $J = 289$ Hz), 75.9, 66.1, 33.3, 25.0, 21.7, 15.6; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2\text{Na}$ 289.1140 $[\text{M} + \text{Na}]^+$; Found 289.1144. A solution of 2,2,2-trifluoro-*N*-(1-(((propan-2-ylideneamino)oxy)methyl)cyclopentyl)acetamide (2.23 g, 8.38 mmol) and sodium hydroxide (1.68 g, 41.9 mmol) in MeOH (75 mL) and water (75 mL) was heated at 55 °C for 16 h in a closed flask. The mixture was extracted with DCM (4 \times 75 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to afford propan-2-one *O*-((1-aminocyclopentyl)methyl) oxime (1.42 g, 99%) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 3.92 (s, 2H), 1.88 (s, 3H), 1.87 (s, 3H), 1.84 – 1.73 (m, 2H), 1.73 – 1.57 (m, 4H), 1.49 – 1.38 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 154.6, 81.7, 61.5, 38.0, 24.5, 21.8, 15.6; HRMS (ESI-TOF) m/z Calcd for $\text{C}_9\text{H}_{19}\text{N}_2\text{O}$ 171.1497 $[\text{M} + \text{H}]^+$; Found 171.1492. A solution of propan-2-one *O*-((1-aminocyclopentyl)methyl) oxime (1.22 g, 7.15 mmol) in 2 M aqueous hydrochloric acid (100 mL) was heated at 90 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by silica flash chromatography (5% to 10% (7M NH_3 in MeOH) in DCM) to afford **20k** (724 mg, 79%) as an oil; ^1H NMR (400 MHz, CDCl_3) δ 3.58 (s, 2H), 1.88 – 1.69 (m, 2H), 1.69 – 1.51 (m, 4H), 1.51 – 1.34 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 84.9, 61.4, 38.3, 24.5; HRMS (ESI-TOF) m/z Calcd for $\text{C}_6\text{H}_{15}\text{N}_2\text{O}$ 131.1184 $[\text{M} + \text{H}]^+$; Found 131.1188.

3-Phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (21a). General procedure **F** was followed using 2-(aminooxy)ethan-1-amine dihydrochloride **20a**²⁴ (194 mg, 1.30 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 3 h. Purification by silica flash column chromatography (15% to 60% EtOAc in *n*-heptane) afforded compound **21a** (132 mg, 63% yield) as a solid; mp 130 – 132 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.54 (m, 2H), 7.47 – 7.33 (m, 3H), 4.80 (s, 1H), 4.07 – 3.98 (m, 2H), 3.60 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 130.3, 128.7, 126.0, 63.1, 40.9; HRMS (ESI-TOF) *m/z* Calcd for C₉H₁₀N₂O 163.0872 [M + H]⁺; Found 163.0871; IR (ν_{max}, cm⁻¹): 3299, 1599; Anal. Calcd for C₉H₁₀N₂O: C, 66.65; H, 6.21; N, 17.27%. Found: C, 66.46; H, 6.41; N, 17.50%.

6-Methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (21b). General procedure **F** was followed using 2-(aminooxy)propan-1-amine dihydrochloride **20b** (200 mg, 1.22 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 3 h. Purification by silica flash column chromatography (15% to 60% EtOAc in *n*-heptane) afforded compound **21b** (161 mg, 74% yield) as a solid; mp 133 – 133.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.55 (m, 2H), 7.46 – 7.33 (m, 3H), 4.79 (s, 1H), 3.90 – 3.76 (m, 1H), 3.54 – 3.45 (m, 1H), 3.31 – 3.15 (m, 1H), 1.34 (d, *J* = 6.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 152.2, 133.1, 130.2, 128.7, 126.0, 67.8, 46.7, 17.6; HRMS (ESI-TOF) *m/z* Calcd for C₁₀H₁₃N₂O 177.1028 [M + H]⁺; Found 177.1024; IR (ν_{max}, cm⁻¹): 3341, 1604; Anal. Calcd for C₁₀H₁₂N₂O: C, 68.16; H, 6.86; N, 15.90%. Found: C, 67.79; H, 7.32; N, 16.24%.

5-Methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (6d). General procedure **F** was followed using 1-(aminooxy)propan-2-amine dihydrochloride **20c**²³ (176 mg, 1.07 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 3 h. Purification by silica flash column chromatography (15% to 60% EtOAc in *n*-heptane gradient) afforded compound **6d** (145 mg, 77% yield) as a solid.

4-Methyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (21d). A modified general procedure **F** was followed using 2-(aminooxy)-*N*-methylethan-1-amine dihydrochloride **20d**^{17b} (200 mg, 1.23 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 4 h. The methanol solution of the free base was not concentrated, but used as such for the formation of the intermediate as the diamine was volatile. Upon complete formation of the intermediate (rt, 16 h), the mixture was concentrated and the cyclisation was performed in AcOH as usual. Purification by silica flash chromatography (20% to 100% EtOAc in *n*-heptane) afforded compound **21d** (123 mg, 57%) as an oil; ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.34 (m, 5H), 4.18 – 4.07 (m, 2H), 3.49 – 3.40 (m, 2H), 2.75 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.4, 132.6, 129.6, 128.8, 128.4, 63.8, 48.37, 39.7; HRMS (ESI-TOF) *m/z* Calcd for C₁₀H₁₃N₂O 177.1028 [M + H]⁺; Found 177.1030; IR (ν_{max}, cm⁻¹): 1590; Anal. Calcd for C₁₀H₁₂N₂O: C, 68.16; H, 6.86; N, 15.90%. Found: C, 67.31; H, 7.08; N, 15.71%.

(4a*R*,8a*S*)-3-Phenyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[*e*][1,2,4]oxadiazine (21e). General procedure **F** was followed using (1*R*,2*S*)-2-(aminooxy)cyclohexan-1-amine **20e** (100 mg, 0.77 mmol) and ethyl

benzimidate hydrochloride and stirring at 100 °C for 3 h. Purification by silica flash column chromatography (50% EtOAc in *n*-heptane) afforded compound **21e** (88 mg, 53% yield) as a solid; mp >190 °C (decomp.); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.63 – 7.60 (m, 2H), 7.44 – 7.37 (m, 3H), 7.18 (d, *J* = 4.1 Hz, 1H) 3.71 (q, *J* = 3.5 Hz, 1H), 3.44 – 3.39 (m, 1H), 1.90 – 1.83 (m, 1H), 1.70 – 1.53 (m, 4H), 1.50 – 1.23 (m, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 150.3, 133.1, 129.4, 128.2, 125.7, 69.8, 48.5, 29.7, 27.9, 22.5, 20.4; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₇N₂O 217.1341 [M + H]⁺; Found 217.1342; IR (ν_{max}, cm⁻¹): 3324, 1604; Anal. Calcd for C₁₃H₁₆N₂O: C, 72.19; H, 7.46; N, 12.95%. Found: C, 72.34; H, 7.85; N, 12.87%; [α]_D²³ = -46.7 (*c* = 1, MeOH).

(4aR,8aR)-3-Phenyl-4a,5,6,7,8,8a-hexahydro-4H-benzo[e][1,2,4]oxadiazine (21f). General procedure F was followed using (1*R*,2*S*)-2-(aminoxy)cyclohexan-1-amine **20f** (100 mg, 0.77 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 3 h. Purification by silica flash column chromatography (50% EtOAc in *n*-heptane) afforded compound **21f** (118 mg, 71% yield) as a solid; mp 141 – 142 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 – 7.62 (m, 2H), 7.44 – 7.37 (m, 3H), 6.97 (s, 1H), 3.12 (ddd, *J* = 11.4, 7.8, 4.0 Hz, 1H), 3.02 – 2.96 (m, 1H), 2.02 – 1.91 (m, 2H), 1.77 (m, 1H), 1.67 (d, *J* = 12.2 Hz, 1H), 1.43 – 1.15 (m, 4H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.3, 133.2, 129.5, 128.1, 125.9, 76.2, 53.5, 29.7, 28.3, 24.1, 23.3; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₇N₂O 217.1341 [M + H]⁺; Found 217.1341; IR (ν_{max}, cm⁻¹): 3334, 1600; Anal. Calcd for C₁₃H₁₆N₂O: C, 72.19; H, 7.46; N, 12.95%. Found: C, 72.45; H, 7.38; N, 12.81%; [α]_D^{23.5} = -78.5 (*c* = 1, MeOH).

(4aS,7aR)-3-Phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[e][1,2,4]oxadiazine (21g). General procedure F was followed using (1*S*,2*R*)-2-(aminoxy)cyclopentan-1-amine **20g**²⁵ (184 mg, 1.54 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 2 h. Purification by silica flash column chromatography (5% to 60% EtOAc in *n*-heptane) afforded compound **21g** (243 mg, 78% yield) as a solid; mp 195 – 195.5 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 – 7.60 (m, 2H), 7.49 – 7.31 (m, 4H), 3.72 – 3.61 (m, 1H), 3.61 – 3.55 (m, 1H), 2.06 – 1.90 (m, 2H), 1.79 – 1.63 (m, 2H), 1.61 – 1.39 (m, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.3, 132.9, 129.6, 128.2, 125.7, 72.7, 53.9, 31.8, 28.8, 20.1; HRMS (ESI-TOF) *m/z* Calcd for C₁₂H₁₅N₂O 203.1184 [M + H]⁺; Found 203.1180; IR (ν_{max}, cm⁻¹): 3311, 1602; Anal. Calcd for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85%. Found: C, 70.81; H, 7.44; N, 13.99%; [α]_D²⁴ 102.2 (*c* 1.01, MeOH).

(4aS,7aS)-3-Phenyl-4,4a,5,6,7,7a-hexahydrocyclopenta[e][1,2,4]oxadiazine (21h). General procedure F was followed using (1*S*,2*S*)-2-(aminoxy)cyclopentan-1-amine dihydrochloride **20h**²⁵ (280 mg, 1.48 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 48 h. Purification by silica flash column chromatography (10% to 50% EtOAc in *n*-heptane) afforded compound **21h** (75 mg, 25% yield) as a solid; mp 140 – 141 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.63 (m, 2H), 7.46 – 7.34 (m, 3H), 4.91 (s, 1H), 3.67 (dt, *J* = 11.2, 7.5 Hz, 1H), 3.30 – 3.13 (m, 1H), 2.22 – 2.04 (m, 2H), 2.02 – 1.82 (m,

2H), 1.78 – 1.62 (m, 1H), 1.53 – 1.40 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 151.6, 133.2, 130.2, 128.7, 126.3, 80.3, 54.1, 26.6, 25.3, 18.1; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$ 203.1184 $[\text{M} + \text{H}]^+$; Found 203.1190; IR (ν_{max} , cm^{-1}): 3179, 1595; Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.14; H, 7.44; N, 14.08%; $[\alpha]_{\text{D}}^{23}$ -109.0 (c 0.77, MeOH).

(S)-4-Phenyl-6,7,8,8a-tetrahydro-1H-pyrrolo[1,2-*d*][1,2,4]oxadiazine (21i). General procedure F was followed using (*S*)-*O*-(pyrrolidin-2-ylmethyl)hydroxylamine **20i**²³ (322 mg, 2.58 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 16 h. Purification by silica flash column chromatography (5% to 70% EtOAc in *n*-heptane) afforded compound **21i** (419 mg, 80% yield) as a solid; mp 138.5 – 140 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.47 (m, 2H), 7.47 – 7.33 (m, 3H), 4.43 (dd, J = 10.4, 3.9 Hz, 1H), 3.74 – 3.58 (m, 1H), 3.58 – 3.47 (m, 1H), 3.18 (dd, J = 10.4, 9.2 Hz, 1H), 3.10 – 2.93 (m, 1H), 2.31 – 2.10 (m, 1H), 1.89 – 1.69 (m, 2H), 1.69 – 1.55 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.7, 133.8, 129.6, 128.5, 128.3, 68.6, 54.2, 51.3, 28.5, 22.9; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$ 203.1184 $[\text{M} + \text{H}]^+$; Found 203.1179; IR (ν_{max} , cm^{-1}): 1538; Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.29; H, 7.06; N, 13.65%. $[\alpha]_{\text{D}}^{23}$ 32.2 (c 0.99, MeOH).

5,5-Dimethyl-3-phenyl-5,6-dihydro-4H-[1,2,4]oxadiazine (21j). A modified general procedure F was followed using 1-(aminooxy)-2-methylpropan-2-amine dihydrochloride **20j** (250 mg, 1.41 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 24 h. The methanol solution of the free base was not concentrated, but used as such for the formation of the intermediate as the diamine was volatile. Upon complete formation of the intermediate (rt, 16 h), the mixture was concentrated and the cyclisation was performed in AcOH as usual. Purification by silica flash column chromatography (5% to 60% EtOAc in *n*-heptane) afforded compound **21j** (223 mg, 83%) as a solid; mp 139 – 140 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.58 (m, 2H), 7.47 – 7.35 (m, 3H), 4.54 (s, 1H), 3.68 (s, 2H), 1.32 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.0, 133.2, 130.2, 128.6, 126.0, 73.6, 49.4, 26.4; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}$ 191.1184 $[\text{M} + \text{H}]^+$; Found 191.1179; IR (ν_{max} , cm^{-1}): 3255, 1595; Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$: C, 69.45; H, 7.42; N, 14.73%. Found: C, 69.68; H, 7.37; N, 14.57%.

7-Phenyl-9-oxa-6,8-diazaspiro[4.5]dec-7-ene (21k). General procedure F was followed using 1-((aminooxy)methyl)cyclopentan-1-amine **20k** (162 mg, 1.22 mmol) and ethyl benzimidate hydrochloride and stirring at 100 °C for 5 h. Purification by silica flash column chromatography (5% to 50% EtOAc in *n*-heptane) afforded compound **21k** (229 mg, 87% yield) as a solid; mp 113 – 113.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.55 (m, 2H), 7.48 – 7.32 (m, 3H), 4.70 (s, 1H), 3.75 (s, 2H), 1.97 – 1.77 (m, 4H), 1.77 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 152.1, 130.2, 128.7, 126.1, 71.7, 60.2, 37.9, 23.9; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}$ 217.1341 $[\text{M} + \text{H}]^+$; Found 217.1339; IR (ν_{max} , cm^{-1}): 3232, 1601; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$: C, 72.19; H, 7.46; N, 12.95%. Found: C, 72.50; H, 7.73; N, 13.21%

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