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Suzuki–Miyaura reactions of the soluble guanylate cyclase inhibitor NS2028: a non-product specific route to C-8 substituted analogues

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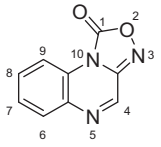
ABSTRACT

Both soluble guanylate cyclase (sGC) inhibitors ODQ **1** and NS2028 **2** are synthesized via improved protocols. In the former case treating 3,4-dihydroquinoxalin-2(1*H*)-one oxime **8**, which can be prepared in two steps from 1,2-benzenediamine, with 1,1′-carbonyldiimidazole (CDI) gives the dihydro-ODQ **10** that in the presence of $KMnO_4$ oxidises to give ODQ **1** in an overall yield of 46% starting from 1,2-benzenediamine. In the latter case, the synthesis affords NS2028 **2** from 2-amino-4-bromophenol **3** in three steps with an overall yield of 85% and avoids the need for chromatography. Furthermore, Suzuki–Miyaura reaction conditions are described that enable the preparation of 8-aryl and 8-heteroaryl derivatives of NS2028 directly from NS2028 **2**. Finally, demethylation of the 8-(methoxyphenyl) substituted analogues afforded the 8-(hydroxyphenyl) derivatives **40**–**42**. All new products are fully characterised.

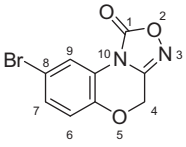
1. Introduction

Soluble guanylate cyclase (sGC) is the only known physiological receptor for nitric oxide (NO). On binding to NO the activity of sGC increases 400-fold, promoting the conversion of guanosine 5′-triphospate (GTP) to the second messenger guanosine 3′,5′-cyclic monophosphate (cGMP) and pyrophosphate. cGMP acts to regulate various effector proteins, including protein kinases, phosphodiesterases and ion channels.[1] As such inhibitors of sGC can be used to regulate NO related signalling processes and to lower cGMP activity.[2]

1*H*-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one, (ODQ) **1**, and 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]-benzoxazin-1-one (NS2028) **2** are specific inhibitors of soluble guanylate cyclase (sGC). Recent applications of NS2028 **2** include the development of inhibitors for lymphangiogenesis that can help prevent the metastasis of solid tumours,[3] for the treatment of dermatological diseases and in cosmetic skin care,[3,4] Furthermore, NS2028 has been used for neural thermoprotection against heat stroke or hyperthermia via inhibition of the PKG pathway,[5] and for the prevention and treatment of dental disorders.[6]



1 (ODQ)



2 (NS2028)

While ODQ **1** and NS2028 **2** were known for approximately 15 years, their synthesis was only fully reported recently.[7] Not surprisingly, only a few analogues have been prepared and as such the pharmacophore structure of these compounds remains unclear. Nevertheless replacing the 8-bromo substituent by 4-methoxyphenyl or by 3-trifluoromethylphenyl gave analogues with interesting biological profiles.[7] As such, modifying the C-8 position can be a starting point for studying structure activity relationships (SARs).

Since NS2028 **2** bears a bromine substituent at C-8 it would seem rational to target a non-product specific route to preparing a library of analogues for elucidating SARs via transition metal catalysed C–C coupling reactions. Interestingly, previous efforts to perform Suzuki–Miyaura reactions led to decomposition of the oxadiazole ring affording the oxime. To bypass this, the desired Suzuki–Miyaura coupling reaction was performed at an earlier stage of the synthesis, leading to a product specific synthesis.[7] During the time of the above disclosure we were working on a similar strategy and had also encountered problems with the late stage Suzuki–Miyaura

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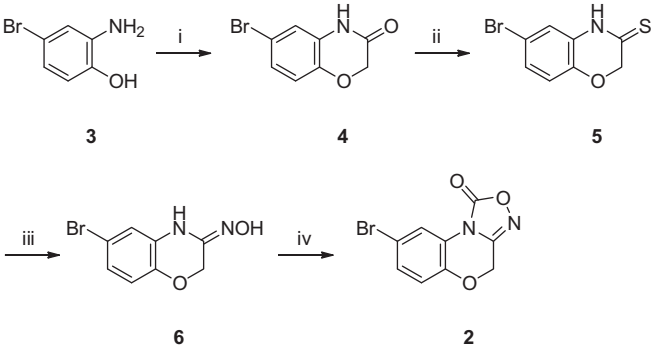
coupling. In light of these difficulties, we examined the stability of NS2028 **2** in acetonitrile (MeCN) towards various bases and identified Suzuki–Miyaura conditions using Hünig's base that afforded several 8-aryl and 8-heteroaryl substituted derivatives in moderate to high yields. Furthermore, alternative routes to both ODQ **1** and NS2028 **2** were developed providing these sGC inhibitors in higher overall yields than previously reported.

2. Results and discussion

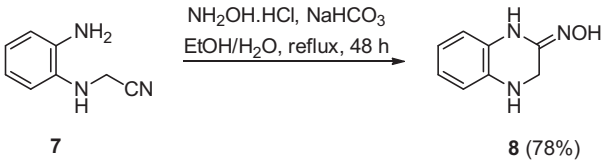
2.1. Synthesis of ODQ 1 and NS2028 2

The recently reported four step synthesis of NS2028 **2** started from available 2-amino-4-bromophenol **3** and gave the target compound in 64% overall yield.[7] The synthesis involved treatment of 2-amino-4-bromophenol **3** with 2-chloroacetyl chloride to afford the 1,4-benzoxazinone **4**, which was then sequentially converted into the thione **5**, then the oxime **6** and finally cyclised to afford the NS2028 **2** (Scheme 1). Furthermore, the last three steps of this synthesis required chromatography.



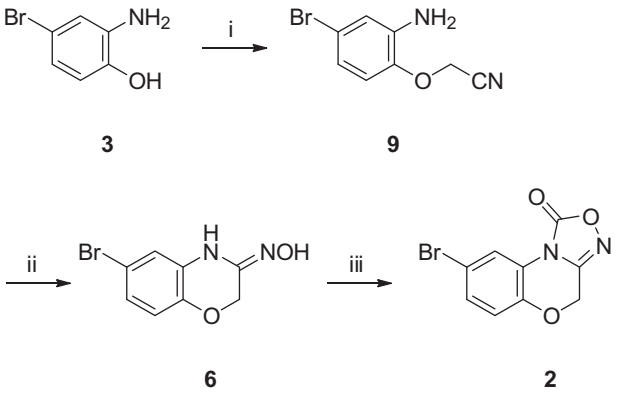
Scheme 1. Reagents: (i) $ClCH_2COCl$; (ii) Lawesson's reagent; (iii) $NH_2OH{\cdot}HCl$; (iv) CDI; overall yield 64%.[7]

We required an efficient and chromatography free route to NS2028 **2** that avoided the use of thionating agents. Aware of the reported cyclisation of 2-(2-aminophenylamino)acetonitrile **7** with hydroxylamine hydrochloride to give directly 3,4-dihydroquinoxalin-2(1*H*)-one oxime **8**,[8] we considered a similar strategy for the preparation of NS2028 **2**.



As such, cyanomethylation of 2-amino-4-bromophenol **3** using chloroacetonitrile gave 2-(2-amino-4-bromophenoxy)acetonitrile **9** in 93% yield, which on treatment with hydroxylamine hydrochloride gave the desired oxime **6** again in high yield (91%). Similar to the previous reported synthesis the final cyclisation using 1,1′-carbonyldiimidazole (CDI) gave the target NS2028 **2** in near quantitative yields. This three step synthesis required no chromatography and gave an overall yield of 85% (Scheme 2).

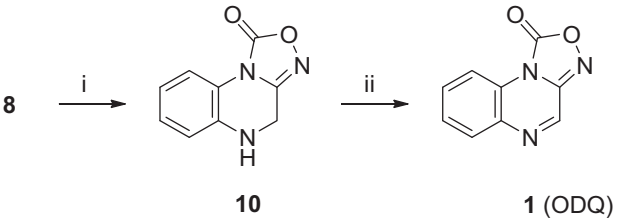
Interestingly, the related conversion of 3,4-dihydroquinoxalin-2(1*H*)-one oxime **8** into 4,5-dihydro-1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one **10** (dihydro-ODQ) has been reported using ethyl chloroformate and suffers from over ethylformylation of the remaining NH groups at the quinoxaline *N*3, furthermore no yields or experimental procedures were reported.[8] By treating 3,4-



Scheme 2. Reagents and conditions: (i) $ClCH_2CN$ (1.1 equiv), K_2CO_3 (2.2 equiv), MeCN, reflux, 12 h, 93%; (ii) $NH_2OH{\cdot}HCl$ (2 equiv), $NaHCO_3$ (2 equiv), H_2O/EtOH (17:25), reflux, 48 h, 91%; (iii) CDI (1.2 equiv), THF, reflux, 5 h, 100%.

dihydroquinoxalin-2(1*H*)-one oxime **8** with the milder reagent CDI in THF at reflux for 5 h we obtained the dihydro-ODQ **10** cleanly and in relatively good yield (67%).

The subsequent oxidation of dihydro-ODQ **10** to ODQ **1** using diethylazodicarboxylate (DEAD) was known[9] but failed in our hands, as such we considered alternative oxidants MnO_2 and $KMnO_4$. The use of MnO_2 (10 equiv) in MeOH at ca. 20 °C, led to incomplete conversion of the dihydro-ODQ **10** even after several days. While the reaction of dihydro-ODQ **10** with $KMnO_4$ (1.1 equiv) in MeCN at ca. 20 °C after 5 min gave ODQ **1** in good yield (88%) (Scheme 3).



Scheme 3. Reagents and conditions: (i) CDI (1.1 equiv), THF, reflux, 5 h, 67%; (ii) $KMnO_4$ (1.1 equiv), MeCN, ca. 20 °C, 5 min, 88%.

By comparison with the recently reported two step synthesis of ODQ **1** from relatively expensive 2-chloroquinoxaline with an overall yield of 32%,[7] the above synthesis of ODQ **1** has an overall yield of ca. 46% starting from the comparatively cheap 1,2-diaminobenzene; n.b., cyanomethylation of 1,2-benzenediamine can be achieved in high yield (87%) by treating the diamine with formaldehyde, potassium cyanide in the presence of aqueous HCl.[10]

2.2. Suzuki–Miyaura coupling reactions of NS2028 2

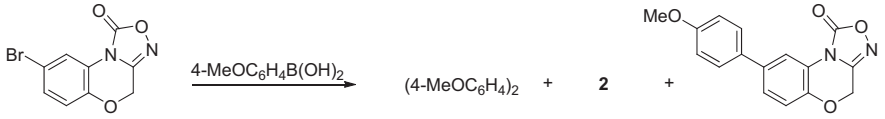
As reported above, attempted Suzuki reactions with NS2028 **2** led to decomposition of the oxadiazolone ring and recovery of the oxime **6**,[7] presumably due to base catalysed hydrolysis of the labile oxadiazolone. We considered a careful study of the reaction conditions, focussing initially on the choice of an appropriate base. As such, the stability of NS2028 **2** in MeCN towards various bases was examined: at room temperature treating an MeCN solution NS2028 **2** with aqueous NaOH or DBU rapidly led to decomposition, while with K_2CO_3, $KHCO_3$, KOAc, KF and Hünig's base, NS2028 **2** was stable at least for 12 h. This stability was also seen when the mixtures were heated to ca. 50 °C for 1 h, however, at ca. 90 °C after 1 h NS2028 **2** decomposed in the presence of K_2CO_3.

With this information in hand, we partially optimized the coupling by preparing a known compound, 8-(4-methoxyphenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **11** that did not co-run with the NS2028 **2** on TLC (SiO_2). Using $Pd(OAc)_2$ (5 mol %) as catalyst and

4-$MeOC_6H_4B(OH)_2$ (1.5 equiv), several bases that were tolerated by NS2028 at elevated temperatures and solvent systems were screened. An early observation showed that the Suzuki–Miyaura reaction proceeded to completion faster when aqueous solutions of dioxane or MeCN were used, regardless of the base chosen (Table 1). Attempts to use dry solvents, with or without the use of phase transfer catalysts inseparable by chromatography the target compound could not be isolated (entry 13). With pyrid-3-yl and pyrid-4-ylboronic acids no reaction was observed in either solvent systems affording only recovered NS2028 **2** (entries 16 and 17).

The conditions identified above led to the desired Suzuki–Miyaura coupling but depend on the choice of aryl or hetero-

Table 1
The Suzuki–Miyaura reaction of NS2028 **2** (0.186 mmol) with 4-$MeOC_6H_4B(OH)_2$ (1.5 equiv) in the presence of base (3 equiv) and $Pd(OAc)_2$ (5 mol %) in solvent (0.5 mL) at reflux



2 (NS2028) **12** **11**

Entry	Base	Solvent	Time (h)	Yields (%)		
				12[a]	**2**	**11**
1	K_2CO_3	Dioxane	2	61	28	51
2	K_2CO_3	MeCN	2	27	6	38
3	K_2CO_3	Dioxane/H_2O (4:1)	0.75	82	0	58
4	K_2CO_3	MeCN/H_2O (9:1)	2	32	6	42
5	$KHCO_3$	Dioxane/H_2O (4:1)	1.50	61	0	44
6	$KHCO_3$	MeCN/H_2O (9:1)	2	32	0	25
7	KOAc	Dioxane/H_2O (4:1)	2	73	24	60
8	KOAc	MeCN/H_2O (9:1)	2	83	0	65
9	KF	PhMe (18-C-6, 10 mol %)	18	88	20	58
10	KF	MeCN	18	71	0	73
11	KF	MeCN/H_2O (9:1)	2	57	10	71
12	KF	Dioxane/H_2O (4:1)	2	67	22	67
13	*i*-Pr_2NEt	Dioxane	2	40	6	62
14	*i*-Pr_2NEt	MeCN	2	50	6	60
15	*i*-Pr_2NEt	Dioxane/H_2O (4:1)	0.33	70	0	85
16	*i*-Pr_2NEt	MeCN/H_2O (9:1)	0.33	66	0	82
17	Py	Dioxane/H_2O (4:1)	18	43	66	9

[a] Yields of biaryl **12** based on 4-$MeOC_6H_4B(OH)_2$ not converted into compound **11**.

led to slow reactions. Furthermore, the reactions were always accompanied by moderate amounts of 4,4′-dimethoxybiphenyl **12** and attempts to overcome the formation of this side product by reducing the amount of 4-methoxyphenylboronic acid used (1.5→1 equiv) led to incomplete reactions and low product yields.

More important was the choice of base; inorganic bases, such as K_2CO_3, $KHCO_3$ and KOAc gave moderate yields of desired product (entries 1–8), while with KF the yields could be improved to a reasonable 67–73% depending on the choice of solvent system (entries 10–12). Switching to the sterically hindered organic Hünig's base (pK_b 2.6) was more fruitful, affording the desired product **11** rapidly (20 min) in good yields (82 and 85%) in either aqueous MeCN or dioxane (entries 16 and 15). Replacing Hünig's base by a less basic arylamine pyridine (pK_b 8.8) led to a poor conversion of starting NS2028 **2** and low yields of product (entry 17). Furthermore, in the presence of Hünig's base running the reactions at reflux in two solvent systems dioxane/water (4:1) and MeCN/water (9:1) was compatible affording short reaction times, high conversions of NS2028 **2** and moderate to good yields of coupled product.

With these conditions at hand we examined a variety of aryl, and heteroarylboronic acids as coupling partners for NS2028 **2** (Table 2). Both aryl and most heteroarylboronic acids reacted with NS2028 **2** to provide the 8-substituted NS2028 analogues **11**, **25**–**36** in moderate to good yields. With phenylboronic acid and the heteroarylboronic acids the MeCN/water (9:1) solvent mixture led to higher Suzuki–Miyaura product yields.

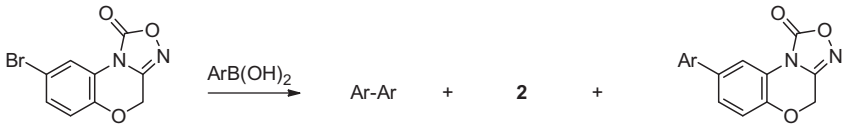
When nitrophenylboronic acid was used the reaction could not be driven to completion and at best the target compound **27** could be obtained in 50% based on 52% consumed NS2028 **2** (entry 4). While with thien-2-ylboronic acid the reaction could not be driven to completion and since both the product and NS2028 **2** were arylboronic acid. Since aryltrifluoroborates are more stable alternatives to arylboronic acids[11] we also investigated a selection with reaction of NS2028 **2** under similar conditions (Table 3).

The reaction of NS2028 **2** with the 2-methoxyphenyltrifluoroborates gave an exceptionally high yield of coupled product **26** (93%) in relatively short reaction time (10 min) (entry 1) which was not dissimilar to that obtained using 2-methoxyphenylboronic acid (91%, 20 min Table 2, entry 3). Similar high yielding reactions, however, were not forthcoming with other aryltrifluoroborates. In particular the simple phenyltrifluoroborate led to only a 51% yield of 8-phenylsubstituted NS2028 **28** (entry 4). Similarly, no significant advantage could be observed when 3-nitrophenyltrifluoroborate was used instead of 3-nitrophenylboronic acid (17 vs 26%). Allowing longer reaction times did result in the complete consumption of additional NS2028 **2** but unfortunately did not lead to higher yields of desired 8-substituted NS2028 derivatives.

2.3. Further functionalisation of NS2028 and its derivatives

With the Suzuki–Miyaura coupling of NS2028 **2** with various aryl and heteroarylboronic acids partially optimized the possibility of further modifications that can provide additional analogues was investigated. With ready access to the methoxyphenyl derivatives **11**, **25** and **26** we attempted demethylation using TMSCl (5 equiv), NaI (3 equiv) in refluxing MeCN, however, after 2 h only traces of unreacted starting material, iodine and baseline material could be observed by TLC. Nevertheless, treating an ice-cold DCM solution of the 8-methoxyphenyl substituted derivatives **11**, **25** and **26** dropwise with a 1 M solution of boron tribromide in DCM (3 equiv) and leaving the mixture to stir at ca. 20 °C for 6 h afforded the corresponding phenols **40**–**42** in good yields 93, 90 and 91%, respectively (Scheme 4).

Table 2
The Suzuki–Miyaura reaction of NS2028 **2** (0.186 mmol) with $ArB(OH)_2$ in the presence of *i*-Pr_2NEt (3 equiv) and $Pd(OAc)_2$ (5 mol %) in solvent (0.5 mL) at reflux

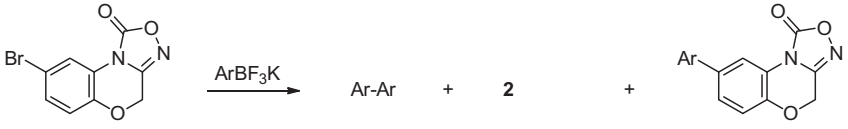


2 (NS2028) **12-24** **11, 25-36**

Entry	$ArB(OH)_2$ (equiv)	Solvent system	Time (min)	Yields (%)		
				12–24[a]	**2**	**11, 25–36**
1	4-$MeOC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	20	**12** (70)	0	**11** (85)
2	3-$MeOC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	20	**13** (60)	0	**25** (74)
3	2-$MeOC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	20	**14** (51)	8	**26** (91) (99)[b]
4	3-$O_2NC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	60	**15** (57)	48	**27** (26) (50)[b]
5	$PhB(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	60	**16** (61)	52	**28** (46) (97)[b]
6	$PhB(OH)_2$ (2)	MeCN/H_2O (9:1)	90	**16** (78)	2	**28** (75)
7	4-$ClC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	60	**17** (75)	0	**29** (54)
8	3-$ClC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	60	**18** (78)	0	**30** (57)
9	2-$ClC_6H_4B(OH)_2$ (1.5)	Dioxane/H_2O (4:1)	60	**19** (40)	0	**31** (66)
10	Fur-2-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	90	**20** (trace)	8	**32** (52)
11	Fur-3-yl$B(OH)_2$ (1.5)	MeCN/H_2O (9:1)	90	**21** (5)	4	**33** (38)
12	Thien-2-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	90	[c]	[c]	[c]
13	Thien-3-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	90	**22** (59)	2	**34** (47)
14	Indol-5-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	30	**23** (58)[d]	Traces	**35** (65)
15	Indol-6-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	30	**24** (58)[d]	Traces	**36** (65)
16	Pyrid-3-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	30	0	97	0
17	Pyrid-4-yl$B(OH)_2$ (2)	MeCN/H_2O (9:1)	30	0	97	0

[a] Yields of biaryls **12**–**24** based on $ArB(OH)_2$ not converted into 8-aryl substituted NS2028s.
[b] Yield based on recovered NS2028 **2**.
[c] Incomplete and inseperable reaction mixture.
[d] Indole observed (traces).

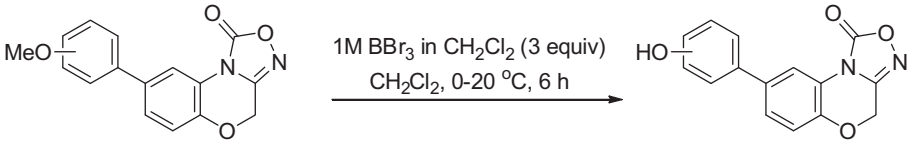
Table 3
The Suzuki–Miyaura reaction of NS2028 **2** (0.186 mmol) with $ArBF_3K$ (1.5 equiv) in the presence of *i*-Pr_2NEt (3 equiv) and $Pd(OAc)_2$ (5 mol %) in dioxane/H_2O (4:1) (0.5 mL) at reflux



2 (NS2028) **14-16**, **37**,**38** **26-28**, **39**

Entry	$ArBF_3K$	Time (min)	Yields (%)		
			Ar–Ar[a]	**2**	**26–28**, **39**
1	2-$MeOC_6H_4BF_3K$	10	**14** (44)	Traces	**26** (93)
2	3-$O_2NC_6H_4BF_3K$	150	**15** (27)	32	**27** (21) (30)[b]
3	3-$O_2NC_6H_4BF_3K$	180	**15** (40)	4	**27** (17)
4	$PhBF_3K$	120	**16** (35)	0	**28** (50)
5	2,6-$(MeO)_2C_6H_3BF_3K$	20	**37** (53)	60	**39** (25)
6	2,6-$(MeO)_2C_6H_3BF_3K$	60	**37** (53)	0	**39** (25)
7	2-$BrC_6H_4BF_3K$	30	**38** (traces)	90	0
8	VinylBF_3K	10	0	40	0

[a] Yields of biaryls **14**–**16**, **37** and **38** based on $ArBF_3K$ not converted into 8-aryl substituted NS2028s.
[b] Yield based on recovered NS2028 **2**.



11 (4-MeO)
25 (3-MeO)
26 (2-MeO)

40 (4-HO), 91%
41 (3-HO), 90%
42 (2-HO), 93%

Scheme 4.

However, attempts to reduce the 8-(3-nitrophenyl) substituted NS2028 **28** to access the anilino analogue using either Pd/C, H_2 in THF at ca. 20 °C for 15 min, or Zn dust in AcOH at ca. 20 °C, gave only complex mixtures.

3. Conclusion

Two modified synthetic routes to both ODQ **1** and NS2028 **2** have been developed that give these two sGC inhibitors in relatively good yields. In the latter case the synthesis affords NS2028 **2** from 2-amino-4-bromophenol (**3**) in three steps with an overall yield of 85% and avoids the need for chromatography. Furthermore, conditions have been developed that enable the 8-aryl and 8-heteroaryl derivatives of NS2028 to be prepared directly from NS2028 **2** using Suzuki–Miyaura reaction. The biological properties of these 20 new NS2028 analogues are currently under investigation.

4. Experimental

4.1. General methods and materials

DCM was freshly distilled from CaH_2 under argon. Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. Anhydrous Na_2SO_4 was used for drying organic extracts, and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). Melting and decomposition points were determined using either a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus or using a TA Instrument DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 °C/min. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin–Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with a Pike Miracle Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GC/MS with direct inlet probe. 2-Amino-4-bromophenol **3**,[12] 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]-benzoxazin-1-one (NS2028) **2**,[7] and 3,4-dihydro-2(1*H*)-quinoxalinone oxime **8**[8] were prepared using literature procedures.

4.2. Preparation of ODQ 1

*4.2.1. 4,5-Dihydro[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one **10**.* A stirred mixture of 3,4-dihydro-2(1*H*)-quinoxalinoneoxime **8** (499 mg, 3.06 mmol) and 1,1′-carbonyldiimidazole (CDI) (550 mg, 3.39 mmol) in dry THF (30 mL) was refluxed for 5 h. The reaction mixture was cooled to ca. 20 °C, and the volatiles removed in vacuo. The resulting solid was dissolved in DCM (50 mL), washed with water (2×25 mL), dried (Na_2SO_4), filtered and the volatiles evaporated in vacuo. Recrystallization of the residue gave the *title compound* **10** (388 mg, 67%) as pale yellow needles, mp (DSC) onset: 146 °C, peak max: 163 °C (decomp.) (from EtOH) (lit.,[8] 149–150 °C), R_f (DCM) 0.36; (found: C, 57.2; H, 3.6; N, 22.2. $C_9H_7N_3O_2$ requires C, 57.1; H, 3.7; N, 22.2%); ν_{max}/cm^{-1} 3379w and 3345br w (NH), 1776m, 1757s (C=O), 1713w, 1626m, 1599m, 1504s, 1454w, 1433s, 1348w, 1331s, 1314m, 1269w, 1217w, 1161w, 1121m, 1082w, 1069w, 988m, 934w, 883w, 785w, 766m; δ_H (300 MHz, $CDCl_3$) 8.04 (1H, d, *J* 9.0, Ar *H*), 7.11 (1H, dd, *J* 7.5, 7.5, Ar *H*), 6.92 (1H, dd, *J* 7.5, 7.5, Ar *H*), 6.82 (1H, d, *J* 9.0, Ar *H*), 4.38 (2H, s, CH_2), 4.24 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 154.9 (C_q), 152.3 (C_q), 134.7 (C_q), 127.4 (Ar *C*H), 120.5 (Ar *C*H), 120.0 (C_q), 116.5 (Ar *C*H), 115.5 (Ar *C*H), 38.5 (*C*H$_2$); *m*/*z* (EI) 189 (M^+, 69%), 144 (97), 118 (100), 105 (5), 91 (33), 77 (9), 63 (12), 51 (13).

*4.2.2. 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one **1**.* To a stirred solution of 4,5-dihydro-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one **10** (314 mg, 1.66 mmol) in MeCN (10 mL) at ca. 20 °C was added $KMnO_4$ (288 mg, 1.82 mmol). After 5 min no starting material remained (TLC), the colour of the reaction mixture changed from yellow to colourless and some brown precipitate appeared. The reaction mixture was poured into water (50 mL), extracted with DCM (3×20 mL), and the combined organic phases dried (Na_2SO_4), filtered and the volatiles evaporated in vacuo. Recrystallization of the residue gave the *title compound* **1** (273 mg, 88%) as colourless prisms, mp (DSC) onset: 162 °C, peak max: 163 °C (from EtOH) (lit.,[7] 164–166 °C), R_f (DCM) 0.49; (found: C, 57.9; H, 2.6; N, 22.5. $C_9H_5N_3O_2$ requires C, 57.8; H, 2.7; N, 22.5%); λ_{max} (DCM)/nm 234 (log ϵ 3.29), 254 inf (2.95), 287 inf (2.83), 296 (2.87), 310 (2.79), 331 inf (2.70), 345 (2.72), 360 inf (2.53); ν_{max}/cm^{-1} 3115w, 3084w and 3057w (Ar CH), 1782s, 1769s (C=O), 1614w, 1591w, 1574s, 1543w, 1487w, 1462s, 1423w, 1418w, 1360w, 1348m, 1192w, 1159m, 1117s, 1092w, 1084w, 991w, 986w, 959w, 912m, 901w, 874w, 858m, 775s, 758s; δ_H (300 MHz, $CDCl_3$) 8.70 (1H, s, *H*-4), 8.56 (1H, dd, *J* 8.1, 1.2, *H*-6 or 9), 7.94 (1H, dd, *J* 8.1, 1.5, *H*-6 or 9), 7.67 (1H, ddd, *J* 7.8, 7.8, 1.5, *H*-7 or 8), 7.56 (1H, ddd, *J* 8.1, 8.1, 1.5, *H*-7 or 8); δ_C (75 MHz, DMSO-d_6) 155.1 (C_q), 147.8 (C_q), 143.4 (C_q), 135.2 (Ar *C*H), 132.2 (Ar *C*H), 130.6 (Ar *C*H), 128.1 (Ar *C*H), 125.6 (C_q), 114.8 (Ar *C*H); *m*/*z* (EI) 187 (M^+, 59%), 143 (100), 116 (63), 102 (12), 89 (20), 75 (13), 63 (26), 51 (13).

4.3. Preparation of NS2028 precursors

*4.3.1. 2-(2-Amino-4-bromophenoxy)acetonitrile **9**.* To a stirred mixture of 2-amino-4-bromophenol **3** (20.1 g, 107 mmol) and K_2CO_3 (32.5 g, 235 mmol) in dry MeCN (300 mL) was added chloroacetonitrile (8.88 g, 7.43 mL, 117.6 mmol) and the suspension was stirred and heated at reflux for 12 h. After cooling to ca. 20 °C, the suspension was filtered (Celite) and the Celite rinsed with acetone. The filtrate and acetone rinses were combined, the volatiles removed in vacuo and the solid residue was dissolved in DCM, passed through a thin layer of silica and rinsed with DCM to give a light yellow solution. Removal of the volatiles in vacuo and recrystallization of the residue gave the *title compound* **9** (22.5 g, 93%) as tawny plates, mp (DSC) onset: 108 °C, peak max: 109 °C (from $CHCl_3$), R_f (DCM) 0.49; (found: C, 42.4; H, 3.1; N, 12.4. $C_8H_7BrN_2O$ requires C, 42.3; H, 3.1; N, 12.3%); λ_{max} (DCM)/nm 243 (log ϵ 2.75), 296 (2.48); ν_{max}/cm^{-1} 3472w and 3377m (NH_2), 3206w, 3067w (Ar CH), 2913w, 2264w (C≡N), 1630m, 1593w, 1504s, 1439w, 1420w, 1375w, 1296w, 1275w, 1248w, 1207s, 1144w, 1092w, 1065w, 1045m, 1007w, 949w, 887w, 854m, 799w, 779s; δ_H (300 MHz, acetone-d_6) 6.97–6.88 (2H, m, *H*-3 and 6), 6.73 (1H, dd, *J* 8.5, 2.5, *H*-5), 5.05 (2H, s, CH_2O), 4.86 (2H, br s, NH_2); δ_C (75 MHz, acetone-d_6) 144.0 (C_q), 141.3 (C_q), 119.5 (Ar *C*H), 118.0 (Ar *C*H), 116.7 (C_q), 116.3 (C_q), 115.7 (Ar *C*H), 55.0 (*C*H$_2$); *m*/*z* (EI) 228 (M^++2, 34%), 226 (M^+, 36), 188 (100), 186 (99), 160 (54), 158 (56), 145 (2), 131 (3), 107 (10), 90 (5), 78 (32), 63 (8), 52 (34).

*4.3.2. 6-Bromo-2H-1,4-benzo[b][1,4]oxazin-3(4H)-one oxime **6**.* A mixture of hydroxylamine hydrochloride (12.4 g, 178 mmol) and $NaHCO_3$ (15.0 g, 178 mmol) in water (85 mL) was stirred at ca. 20 °C for 30 min. To this mixture a solution of 2-(4-bromo-2-aminophenoxy)-acetonitrile **9** (20.2 g, 89.0 mmol) in EtOH (125 mL) was

added and the resulting mixture was heated at reflux for 48 h. After cooling to ca. 3–5 °C the precipitate that formed was filtered off, washed (cold water), dried under vacuum at ca. 60 °C and recrystallized to give the *title compound* **6** (19.7 g, 92%) as tawny prisms, mp (DSC) onset: 177 °C, peak max: 184 °C (decomp.) (from EtOH/H_2O) (lit.,[7] 196–198 °C); R_f (Et_2O) 0.75; (found: C, 39.6; H, 2.8; N, 11.5. $C_8H_7BrN_2O_2$ requires C, 39.5; H, 2.9; N, 11.5%); λ_{max} (DCM)/nm 229 (log ϵ 3.17), 261 (2.95), 299 (2.55); ν_{max}/cm^{-1} 3366m (NH), 3103br w, 2804br w, 1670s, 1603s, 1495s, 1439m, 1385m, 1358m, 1302w, 1279m, 1250w, 1198s, 1119m, 1072w, 1030w, 1007m, 945s, 887m, 856m, 824s, 777s; δ_H (300 MHz, DMSO-d_6) 10.04 (1H, s, N*H*), 9.58 (1H, s, O*H*), 7.24 (1H, d, *J* 2.1, *H*-5), 6.88 (1H, dd, *J* 8.5, 2.1, H-7), 6.81 (1H, d, *J* 8.5, H-8), 4.48 (2H, s, CH_2O); δ_C (75 MHz, DMSO-d_6) 143.4 (C_q), 140.9 (C_q), 130.7 (C_q), 122.5 (Ar *C*H), 118.1 (Ar *C*H), 117.5 (Ar *C*H), 113.7 (Ar *C*H), 63.6 (CH_2); *m*/*z* (EI) 244 (M^++2, 97%), 242 (M^+, 100), 226 (37), 224 (33), 213 (9), 211 (8), 199 (46), 197 (50), 184 (4), 172 (62), 170 (75), 158 (14), 144 (9), 132 (6), 117 (16), 104 (20), 90 (34), 78 (48), 63 (100), 51 (68).

4.4. Suzuki coupling of NS2028 with arylboronic acids [dioxane/water (4:1) solvent system]

*4.4.1. 8-(4-Methoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one **11** (typical procedure, see Table 2).* To a stirred mixture of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]-benzoxazin-1-one **2** (50.0 mg, 0.186 mmol) and 4-methoxyphenylboronic acid (42.3 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) was added dropwise *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol). The stirred reaction mixture was then immersed into a preheated oil bath at ca. 110 °C until all the solids dissolved and then $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) was added in one portion. The reaction mixture was then allowed to stir at ca. 110 °C for 20 min and then cooled to ca. 20 °C. The volatiles were removed in vacuo and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give 4,4′-dimethoxybiphenyl **12** as colourless needles (9 mg, 70%), mp 170–171 °C (lit.,[13] 173–174 °C), R_f (DCM) 0.62; identical to an authentic sample. Further elution (DCM) gave the *title compound* **11** (46.8 mg, 85%) as colourless prisms, mp (DSC) onset: 207 °C, peak max: 209 °C (from 1,2-dichloroethane) (lit.,[7] 209 °C), R_f (DCM) 0.42; (found: C, 64.8; H, 4.0; N, 9.4. $C_{16}H_{12}N_2O_4$ requires C, 64.9; H, 4.1; N, 9.5%); λ_{max} (DCM)/nm 242 (log ϵ 3.40), 273 (3.43); ν_{max}/cm^{-1} 3078w (Ar CH), 3015w, 2957w, 2934w, 2914w, 2833w, 1769s (C═O), 1634m, 1609m, 1499s, 1474s, 1443w, 1425m, 1393w, 1344m, 1300m, 1275m, 1256m, 1240s, 1227m, 1182m, 1152m, 1121s, 1092w, 1043m, 1026m, 1018s, 893w, 880w, 843w, 822s, 787w; δ_H (300 MHz, $CDCl_3$) 8.26 (1H, d, *J* 2.3, H-9), 7.51 (2H, d, *J* 9.0, Ar *H*), 7.41 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.15 (1H, d, *J* 8.5, *H*-6), 6.98 (2H, d, *J* 9.0, Ar *H*), 5.12 (2H, s, CH_2O), 3.85 (3H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 159.5 (C_q), 154.1 (C_q), 150.8 (C_q), 143.4 (C_q), 137.1 (C_q), 131.7 (C_q), 128.0 (Ar *C*H), 125.8 (Ar *C*H), 121.4 (C_q), 118.1 (Ar *C*H), 114.4 (Ar *C*H), 114.3 (Ar *C*H), 60.1 (CH_2O), 55.4 (CH_3O); *m*/*z* (EI) 296 (M^+, 79%), 252 (35), 237 (100), 209 (58), 182 (7), 169 (5), 155 (9), 153 (10), 140 (10), 127 (28), 114 (7), 101 (7), 89 (6), 77 (17), 63 (14), 51 (6).

*4.4.2. 8-(3-Methoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one **25**.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo [3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 3-methoxyphenylboronic acid (42.3 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 20 min gave on chromatography (DCM) 3,3′-dimethoxybiphenyl **13** as a colourless oil (9 mg, 60%) (lit.,[14] oil), R_f (DCM) 0.62; *m*/*z* (EI) 214 (M^+, 100%), 171 (67), 154 (31), 141 (31), 139 (28), 128 (55), 115 (29); identical to an authentic sample. Further elution (DCM) gave the *title compound* **25** (40.8 mg, 74%) as colourless prisms, mp (DSC) onset: 171 °C, peak max: 173 °C (from 1,2-dichloroethane), R_f (DCM) 0.42; (found: C, 64.8; H, 3.9; N, 9.6. $C_{16}H_{12}N_2O_4$ requires C, 64.9; H, 4.1; N, 9.5%); λ_{max} (DCM)/nm 230 (log ϵ 3.61), 262 (3.32), 286 inf (3.15); ν_{max}/cm^{-1} 3015w, 2997w, 2916w, 2832w, 1776s (C═O), 1634m, 1599m, 1582w, 1510m, 1489m, 1472m, 1447w, 1429w, 1404w, 1342w, 1283w, 1267w, 1250w, 1225s, 1190w, 1161w, 1150w, 1123m, 1092m, 1053vw, 1036m, 1020m, 1005w, 899w, 883w, 874m, 866w, 833m, 814w, 795m, 783s, 762w, 752w; δ_H (300 MHz, $CDCl_3$) 8.31 (1H, d, *J* 2.1, *H*-9), 7.45 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.37 (1H, dd, *J* 7.9, 7.9, Ar *H*), 7.17 (1H, d, *J* 8.5, *H*-6), 7.18–7.13 (1H, m, Ar *H*), 7.09 (1H, dd, *J* 2.3, 2.3, Ar *H*), 6.92 (2H, ddd, *J* 8.3, 2.4, 0.8, Ar *H*), 5.14 (2H, s, CH_2O), 3.87 (3H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 160.1 (C_q), 154.1 (C_q), 150.8 (C_q), 144.0 (C_q), 140.7 (C_q), 137.2 (C_q), 130.0 (Ar *C*H), 126.4 (Ar *C*H), 121.4 (C_q), 119.5 (Ar *C*H), 118.1 (Ar *C*H), 115.0 (Ar *C*H), 113.1 (Ar *C*H), 112.9 (Ar *C*H), 60.2 (CH_2O), 55.4 (CH_3O); *m*/*z* (EI) 296 (M^+, 100%), 252 (55), 222 (9), 209 (26), 195 (10), 182 (5), 169 (13), 155 (9), 153 (9), 140 (17), 127 (25), 114 (6), 101 (5), 89 (4), 77 (11), 63 (11), 51 (5).

*4.4.3. 8-(2-Methoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one **26**.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo [3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 2-methoxyphenylboronic acid (42.3 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 20 min gave on chromatography (DCM) 2,2′-dimethoxybiphenyl **14** as colourless needles (6 mg, 51%), mp 154–155 °C (lit.,[13] 156–157 °C), R_f (DCM) 0.62; identical to an authentic sample. Further elution (DCM) gave unreacted starting material **2** (NS2028) (4 mg, 8%) followed by the *title compound* **26** (50.1 mg, 91%) as colourless prisms, mp (DSC) onset: 164 °C, peak max: 165 °C (from 1,2-dichloroethane), R_f (DCM) 0.42; (found: C, 64.7; H, 4.0; N, 9.5. $C_{16}H_{12}N_2O_4$ requires C, 64.9; H, 4.1; N, 9.5%); λ_{max} (DCM)/nm 231 (log ϵ 3.47), 289 (3.07); ν_{max}/cm^{-1} 3076w (Ar CH), 2949w, 2905w, 2835w, 1778s (C═O), 1634m, 1607w, 1510w, 1487s, 1472s, 1454m, 1439w, 1404m, 1342w, 1296w, 1256s, 1240m, 1221w, 1184w, 1152m, 1119s, 1088m, 1061w, 1036m, 1024s, 891w, 885w, 849w, 831m, 810w, 783w; δ_H (300 MHz, $CDCl_3$) 8.28 (1H, d, *J* 1.9, *H*-9), 7.40 (1H, dd, *J* 8.5, 2.1, *H*-7), 7.38–7.28 (2H, m, Ar *H*), 7.15 (1H, d, *J* 8.5, *H*-6), 7.07–6.97 (2H, m, Ar *H*), 5.12 (2H, s, CH_2O), 3.84 (3H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 156.3 (C_q), 154.1 (C_q), 150.9 (C_q), 143.5 (C_q), 134.5 (C_q), 130.6 (Ar *C*H), 129.2 (Ar *C*H), 128.9 (Ar *C*H), 128.6 (C_q), 120.9 (Ar *C*H), 120.7 (C_q), 117.5 (Ar *C*H), 117.4 (Ar *C*H), 111.2 (Ar *C*H), 60.1 (CH_2O), 55.5 (CH_3O); *m*/*z* (EI) 296 (M^+, 100%), 251 (9), 223 (13), 209 (29), 196 (8), 183 (51), 169 (13), 155 (32), 140 (9), 127 (23), 115 (8), 101 (5), 89 (4), 77 (14), 63 (11), 51 (5).

*4.4.4. 8-(3-Nitrophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one **27**.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 3-nitrophenylboronic acid (46.5 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1 h gave on chromatography (DCM) 3,3′-dinitrobiphenyl **15** as yellow plates (16 mg, 57%), mp 200–201 °C (lit.,[13] mp 201–202 °C), R_f (DCM) 0.80; identical to an authentic sample. Further elution (DCM) gave unreacted starting material **2** (NS2028) (24.0 mg, 48%) and then the *title compound* **27** (15.1 mg, 26%) as colourless cotton needles, mp (DSC) onset: 220 °C, peak max: 221 °C (from DCM/pentane), R_f (DCM) 0.53; (found: C, 57.9; H, 3.0; N, 13.4. $C_{15}H_9N_3O_5$ requires C, 57.9; H, 2.9; N, 13.5%); λ_{max} (DCM)/nm 238 (log ϵ 3.59), 257 inf (3.49); ν_{max}/cm^{-1} 3107w, 3082w, and 3011w (Ar CH), 2943w, 2862w, 1775s (C═O), 1622w, 1607w, 1530s, 1512s, 1483s, 1437m, 1396w, 1352s, 1314w, 1298m, 1269w, 1260m, 1244m, 1233m, 1159w, 1126m, 1088m, 1049w, 1022s, 907w, 883s, 837m, 829m, 804s; δ_H (300 MHz, $CDCl_3$) 8.41 (1H, dd, *J* 2.0, 2.0, Ar *H*), 8.35 (1H, d, *J* 2.3, *H*-9), 8.22 (1H, ddd, *J* 8.3, 2.1, 0.9, Ar *H*), 7.90 (1H, ddd, *J* 7.7, 0.9, 0.9, Ar *H*), 7.63 (1H, dd, *J* 8.1, 8.1, Ar *H*), 7.50 (1H, dd, *J* 8.6, 2.2, *H*-7),

7.25 (1H, d, *J* 8.6, *H*-6), 5.18 (2H, s, CH_2O); δ_C (75 MHz, DMSO-d_6) 154.0 (C_q), 151.4 (C_q), 148.4 (C_q), 145.0 (C_q), 140.2 (C_q), 132.9 (Ar *C*H), 132.8 (C_q), 130.7 (Ar *C*H), 126.1 (Ar *C*H), 122.4 (Ar *C*H), 121.9 (C_q), 120.8 (Ar *C*H), 118.4 (Ar *C*H), 113.8 (Ar *C*H), 59.9 (*C*H_2O); *m*/*z* (EI) 311 (M^+, 100%), 267 (68), 240 (7), 221 (20), 209 (14), 193 (52), 167 (59), 153 (14), 139 (80), 126 (15), 113 (8), 100 (4), 89 (7), 75 (7), 70 (6), 63 (10), 50 (4).

4.4.5. 8-(4-Chlorophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***29****.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 4-chlorophenylboronic acid (43.6 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 60 min gave on chromatography (DCM) 4,4′-dichlorobiphenyl **17** as colourless needles (15 mg, 75%), mp 141–143 °C (lit.,[13] 149–154 °C), R_f (DCM) 0.82; identical to an authentic sample. Further elution (DCM) gave the *title compound* **29** (30.2 mg, 54%) as colourless prisms, mp (DSC) onset: 210 °C, peak max: 211 °C (from 1,2-dichloroethane), R_f (DCM) 0.67; (found: C, 59.9; H, 3.0; N, 9.4. $C_{15}H_9ClN_2O_3$ requires C, 59.9; H, 3.0; N, 9.3%); λ_{max} (DCM)/nm 241 (log ϵ 3.52), 266 (3.41); ν_{max}/cm^{-1} 3065w (Ar CH), 2997w, 2928w, 1773s (C=O), 1636m, 1609w, 1520w, 1487s, 1445w, 1420m, 1389w, 1373w, 1346w, 1292w, 1283w, 1269w, 1256w, 1248w, 1234m, 1153w, 1117s, 1092m, 1040w, 1016s, 895w, 881w, 856w, 822s, 808m; δ_H (300 MHz, $CDCl_3$) 8.28 (1H, d, *J* 2.1, *H*-9), 7.50 (2H, d, *J* 8.7, Ar *H*), 7.45–7.38 (3H, m, Ar *H* & *H*-7), 7.19 (1H, d, *J* 8.5, *H*-6), 5.14 (2H, s, CH_2O); δ_C (75 MHz, DMSO-d_6) 153.9 (C_q), 151.4 (C_q), 144.4 (C_q), 137.4 (C_q), 133.8 (C_q), 132.5 (C_q), 129.0 (Ar *C*H), 128.1 (Ar *C*H), 125.5 (Ar *C*H), 121.7 (C_q), 118.2 (Ar *C*H), 113.4 (Ar *C*H), 59.9 (*C*H_2); *m*/*z* (EI) 302 (M^++2, 30%), 300 (M^+, 86), 258 (31), 256 (82), 229 (17), 216 (4), 202 (46), 200 (20), 188 (5), 174 (8), 164 (12), 153 (19), 139 (100), 126 (16), 113 (10), 101 (12), 87 (9), 75 (17), 69 (8), 63 (17), 51 (8).

4.4.6. 8-(3-Chlorophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***30****.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 3-chlorophenylboronic acid (43.6 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1 h gave on chromatography (DCM) 3,3′-dichlorobiphenyl **18** as a colourless oil (15 mg, 78%) (lit.,[15] oil), R_f (DCM) 0.82; *m*/*z* (EI) 222 (M^+, 100%), 186 (7), 152 (90); identical to an authentic sample. Further elution gave the *title compound* **30** (31.9 mg, 57%) as colourless prisms, mp (DSC) onset: 143 °C, peak max: 145 °C (from 1,2-dichloroethane), R_f (DCM) 0.67; (found: C, 60.0; H, 2.9; N, 9.3. $C_{15}H_9ClN_2O_3$ requires C, 59.9; H, 3.0; N, 9.3%); λ_{max} (DCM)/nm 232 (log ϵ 3.51), 262 inf (3.31); ν_{max}/cm^{-1} 3061w (Ar CH), 2909w, 1778s (C=O), 1632w, 1611w, 1597w, 1564w, 1508w, 1477s, 1439w, 1429w, 1389w, 1342w, 1288w, 1260w, 1240w, 1223w, 1152w, 1113m, 1097w, 1047m, 1020m, 1007w, 995w, 964w, 897w, 885w, 853w, 839m, 810w, 787s, 762m; δ_H (300 MHz, $CDCl_3$) 8.29 (1H, d, *J* 2.1, *H*-9), 7.55 (1H, dd, *J* 1.6, 1.6, Ar *H*), 7.47–7.32 (4H, m, Ar *H* and *H*-7), 7.20 (1H, d, *J* 8.5, *H*-6), 5.15 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 154.1 (C_q), 150.6 (C_q), 144.3 (C_q), 141.0 (C_q), 135.9 (C_q), 134.9 (C_q), 130.2 (Ar *C*H), 127.9 (Ar *C*H), 127.0 (Ar *C*H), 126.4 (Ar *C*H), 125.2 (Ar *C*H), 121.5 (C_q), 118.4 (Ar *C*H), 114.9 (Ar *C*H), 60.2 (*C*H_2O); *m*/*z* (EI) 302 (M^++2, 36%), 300 (M^+, 100), 258 (30), 256 (85), 229 (18), 216 (5), 202 (48), 200 (16), 188 (4), 177 (5), 164 (12), 153 (19), 139 (78), 126 (14), 113 (9), 101 (9), 87 (7), 75 (16), 69 (11), 63 (17), 51 (8).

4.4.7. 8-(2-Chlorophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***31****.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 2-chlorophenylboronic acid (43.6 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1 h gave on chromatography (DCM) 2,2′-dichlorobiphenyl **19**, as colourless needles (7 mg, 40%), mp 55–56 °C (lit.,[13] 57–58 °C), R_f (DCM) 0.82; identical to an authentic sample. Further elution (DCM) gave the *title compound* **31** (36.9 mg, 66%) as colourless prisms, mp (DSC) onset: 180 °C, peak max: 180 °C (from 1,2-dichloroethane), R_f (DCM) 0.67; (found: C, 60.1; H, 3.0; N, 9.2. $C_{15}H_9ClN_2O_3$ requires C, 59.9; H, 3.0; N, 9.3%); λ_{max} (DCM)/nm 232 (log ϵ 3.51), 281 inf (2.81); ν_{max}/cm^{-1} 3051w (Ar CH), 2911w, 1769s (C=O), 1632m, 1609w, 1510m, 1485s, 1464w, 1433m, 1402m, 1358w, 1346w, 1294w, 1277w, 1256w, 1240w, 1221m, 1161w, 1123m, 1090m, 1070m, 1036m, 1020s, 993w, 966w, 955w, 891w, 881w, 847m, 833w, 808w, 766s; δ_H (300 MHz, $CDCl_3$) 8.17 (1H, d, *J* 2.1, *H*-9), 7.52–7.44 (1H, m, Ar *H*), 7.36–7.29 (4H, m, Ar *H* and *H*-7), 7.19 (1H, d, *J* 8.5, *H*-6), 5.16 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 1 Ar CH missing 154.0 (C_q), 150.7 (C_q), 144.0 (C_q), 138.5 (C_q), 135.3 (C_q), 132.4 (C_q), 131.2 (Ar *C*H), 130.0 (Ar *C*H), 129.1 (Ar *C*H), 129.0 (Ar *C*H), 127.0 (Ar *C*H), 120.7 (C_q), 117.5 (Ar *C*H), 60.1 (*C*H_2O); *m*/*z* (EI) 302 (M^++2, 34%), 300 (M^+, 100), 258 (26), 256 (73), 229 (19), 216 (5), 202 (51), 177 (6), 164 (13), 153 (20), 139 (76), 126 (14), 113 (8), 101 (7), 87 (8), 75 (15), 69 (9), 63 (16), 51 (8).

4.5. Suzuki coupling of NS2028 with arylboronic acids [MeCN/H_2O (9:1), solvent system]

4.5.1. 8-Phenyl-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***28*** *(typical procedure, see Table 2).* To a stirred mixture of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol) and phenylboronic acid (45.3 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) was added dropwise *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol). The stirred reaction mixture was then immersed into a preheated oil bath at ca. 110 °C until all the solids dissolved and then $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) was added in one portion. The reaction mixture was then allowed to stir at ca. 110 °C for 1.5 h and then cooled to ca. 20 °C. The volatiles were removed in vacuo and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give biphenyl **16** as colourless prisms (14 mg, 78%), mp 65–67 °C (lit.,[13] mp 67–69 °C), R_f (DCM) 0.78; identical to an authentic sample. Further elution (DCM) gave crude product, which co-ran with small amount of unreacted starting material (ca. 2% based on ^{1}H NMR data). Recrystallization of crude product gave *title compound* **28** (37.1 mg, 75%) as colourless prisms, mp (DSC) onset: 176 °C, peak max: 177 °C (from 1,2-dichloroethane), R_f (DCM) 0.67; (found: C, 67.6; H, 3.7; N, 10.4. $C_{15}H_{10}N_2O_3$ requires C, 67.7; H, 3.8; N, 10.5%); λ_{max} (DCM)/nm 236 (log ϵ 3.54), 258 inf (3.35); ν_{max}/cm^{-1} 3063w and 3034w (Ar CH), 2907w, 1775s (C=O), 1634m, 1609w, 1576w, 1508w, 1485s, 1474m, 1445m, 1400m, 1368w, 1341w, 1287w, 1275w, 1258w, 1246w, 1227m, 1148m, 1111s, 1090m, 1076w, 1043m, 1018s, 1001w, 989w, 889w, 883w, 841m, 827m, 808w, 760s; δ_H (300 MHz, $CDCl_3$) 8.33 (1H, d, *J* 2.1, *H*-9), 7.62–7.55 (2H, m, Ar *H*), 7.50–7.42 (3H, m, Ar *H* and *H*-7), 7.41–7.34 (1H, m, Ar *H*), 7.19 (1H, d, *J* 8.5, *H*-6), 5.14 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 154.1 (C_q), 150.8 (C_q), 143.9 (C_q), 139.1 (C_q), 137.3 (C_q), 129.0 (Ar *C*H), 127.9 (Ar *C*H), 127.0 (Ar *C*H), 126.3 (Ar *C*H), 121.4 (C_q), 118.2 (Ar *C*H), 114.9 (Ar *C*H), 60.2 (*C*H_2O); *m*/*z* (EI) 266 (M^+, 100%), 222 (71), 195 (17), 182 (6), 168 (43), 166 (27), 153 (9), 139 (74), 127 (27), 115 (9), 111 (10), 102 (9), 89 (8), 77 (18), 70 (13), 63 (20), 51 (15).

4.5.2. 8-(Fur-2-yl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***32****.* Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), fur-2-ylboronic acid (41.6 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1.5 h gave on chromatography (DCM) 2,2′-bifuran **20** (trace) as a volatile colourless oil (lit.,[16] oil), *m*/*z* (EI) 134 (M^+, 100%), 105 (32), 78 (58), 51 (31), 77 (14), 52 (14), 50 (11) 39

(17), identical to an authentic sample. Further elution (DCM) gave unreacted starting material (NS2028) (4 mg, 8%) and then the *title compound* **28** (25.3 mg, 53%) as brown needles, mp (DSC) onset: 185 °C, peak max: 187 °C (from DCM/pentane), R_f (DCM) 0.67; (found: C, 61.0; H, 3.0; N, 10.8. $C_{13}H_8N_2O_4$ requires C, 60.9; H, 3.2; N, 10.9%); λ_{max} (DCM)/nm 238 (log ϵ 3.32), 289 (3.43); ν_{max}/cm^{-1} 3009w (Ar CH), 1798m, 1780s (C=O), 1645w, 1632m, 1614m, 1557w, 1539w, 1514m, 1495s, 1470s, 1410m, 1344m, 1288m, 1261m, 1246w, 1227m, 1148m, 1111m, 1092m, 1049m, 1016s, 995m, 912w, 883m, 829m, 818m, 812m, 800m, 760s; δ_H (300 MHz, $CDCl_3$) 8.36 (1H, d, *J* 1.9, H-9), 7.53 (1H, dd, *J* 8.7, 1.9, *H*-7), 7.48 (1H, d, *J* 1.1, Ar *H*), 7.13 (1H, d, *J* 8.5, *H*-6), 6.68 (1H, d, *J* 3.4, Ar *H*), 6.48 (1H, dd, *J* 3.4, 1.9, Ar *H*), 5.12 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 154.0 (C_q), 152.1 (C_q), 150.7 (C_q), 143.5 (C_q), 142.5 (Ar CH), 127.2 (C_q), 123.0 (Ar *C*H), 121.4 (C_q), 118.2 (Ar *C*H), 111.9 (Ar *C*H), 111.7 (Ar *C*H), 105.7 (Ar *C*H), 60.1 (*C*H$_2$O); *m*/*z* (EI) 256 (M$^+$, 100%), 212 (32), 183 (41), 172 (3), 156 (39), 130 (26), 116 (9), 106 (6), 102 (54), 89 (17), 75 (17), 63 (20), 51 (17).

4.5.3. 8-(Fur-3-yl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***33***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), fur-2-ylboronic acid (41.6 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1.5 h gave on chromatography (DCM) 3,3′-bifuran **21** as colourless needles (1 mg, 5%), mp 41–43 °C (lit.,[17] 44–45 °C), R_f (DCM) 0.82; identical to an authentic sample. Further elution (DCM) gave unreacted starting material (NS2028) (2 mg, 4%) and then the *title compound* **33** (18.1 mg, 38%) as yellow cotton needles, mp (DSC) onset: 183 °C, peak max: 185 °C (from DCM/pentane), R_f (DCM) 0.67; (found: C, 60.8; H, 3.0; N, 10.9. $C_{13}H_8N_2O_4$ requires C, 60.9; H, 3.2; N, 10.9%); λ_{max} (DCM)/nm 231 (log ϵ 3.42), 263 inf (2.99), 298 (2.48); ν_{max}/cm^{-1} 3157w (Ar CH), 1776s (C=O), 1632m, 1611w, 1585w, 1558w, 1512m, 1495w, 1477m, 1449w, 1414w, 1373w, 1362w, 1341w, 1300w, 1269w, 1248w, 1227m, 1155m, 1121m, 1092m, 1057w, 1026m, 1009w, 932w, 883w, 874m, 837w, 818w, 799m, 787s; δ_H (300 MHz, $CDCl_3$) 8.17 (1H, d, *J* 2.1, *H*-9), 7.73 (1H, dd, *J* 1.1, 1.1, furyl *H*), 7.48 (1H, dd, *J* 1.7, 1.7, furyl *H*), 7.33 (1H, dd, *J* 8.5, 2.1, *H*-7), 7.11 (1H, d, *J* 8.5, *H*-6), 6.68 (1H, dd, *J* 1.7, 0.9, furyl *H*), 5.10 (2H, s, CH_2O); δ_C (75 MHz, $CDCl_3$) 154.1 (C_q), 150.7 (C_q), 144.0 (Ar *C*H), 143.4 (C_q), 138.8 (Ar *C*H), 128.8 (C_q), 125.1 (Ar *C*H), 125.0 (C_q), 121.4 (C_q), 118.2 (Ar *C*H), 113.6 (Ar *C*H), 108.7 (Ar *C*H), 60.1 (*C*H$_2$O); *m*/*z* (EI) 256 (M$^+$, 100%), 212 (49), 183 (28), 172 (3), 158 (16), 156 (25), 140 (3), 129 (14), 116 (10), 102 (51), 89 (20), 75 (20), 63 (24), 51 (18).

4.5.4. 8-(Thien-3-yl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***34***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 3-thienylboronic acid (47.5 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 1.5 h gave on chromatography (DCM) 3,3′-bithiophene **22** as colourless needles (14 mg, 59%), mp 129–130 °C (lit.,[18] 130–131 °C), R_f (DCM) 0.84; identical to an authentic sample. Further elution (DCM) gave unreacted starting material **2** (NS2028) (1 mg, 2%) and then the *title compound* **34** (23.8 mg, 47%) as colourless needles, mp (DSC) onset: 197 °C, peak max: 198 °C (from 1,2-dichloroethane), R_f (DCM) 0.58; (found: C, 57.5; H, 2.8; N, 10.2. $C_{13}H_8N_2O_3S$ requires C, 57.4; H, 3.0; N, 10.3%); λ_{max} (DCM)/nm 232 (log ϵ 3.54), 270 (3.24); ν_{max}/cm^{-1} 3117w and 3011w (Ar CH), 2990w, 2930w, 1773s (C=O), 1630w, 1609w, 1537w, 1504m, 1474m, 1449w, 1420m, 1400w, 1364w, 1354w, 1337w, 1271w, 1244w, 1229m, 1196m, 1148w, 1121m, 1092w, 1084w, 1042m, 1022m, 1003w, 870m, 839w, 827m, 814w, 777s; δ_H (300 MHz, $CDCl_3$) 8.31 (1H, d, *J* 2.1, *H*-9), 7.48–7.44 (2H, m, Ar *H* and *H*-7), 7.41 (1H, dd, *J* 5.1, 3.0, thienyl *H*-5), 7.37 (1H, dd, *J* 5.1, 1.2, thienyl *H*-2), 7.14 (1H, d, *J* 8.7, *H*-6), 5.13 (2H, s, CH_2O); δ_C (75 MHz, DMSO-d_6) 153.9 (C_q), 151.5 (C_q), 143.7 (C_q), 139.9 (C_q), 130.4 (C_q), 127.5 (Ar *C*H), 125.8 (Ar *C*H), 125.0 (Ar *C*H), 121.6 (C_q), 121.1 (Ar *C*H), 118.0 (Ar *C*H), 112.8 (Ar *C*H), 59.8 (*C*H$_2$O); *m*/*z* (EI) 272 (M$^+$, 100%), 228 (69), 200 (29), 188 (4), 174 (27), 172 (20), 160 (4), 146 (20), 134 (5), 116 (9), 102 (33), 89 (10), 75 (5), 69 (7), 63 (8), 51 (5).

4.5.5. 8-(1H-Indol-5-yl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***35***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 1*H*-indol-5-ylboronic acid (59.8 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 30 min gave on chromatography (DCM) indole (trace), then 5,5′-biindole **23** as grey needles (17 mg, 58%), mp 198–200 °C (lit.,[19] mp 200–202 °C), R_f (DCM) 0.56; identical to an authentic sample. Further elution (DCM) gave the *title compound* **35** (36.9 mg, 65%) as tawny needles, mp (DSC) onset: 240 °C, peak max: 247 °C (decomp.) (from DCM/pentane), R_f (DCM) 0.44; (found: C, 66.7; H, 3.5; N, 13.6. $C_{17}H_{11}N_3O_3$ requires C, 66.9; H, 3.6; N, 13.8%); λ_{max} (DCM)/nm 245 (log ϵ 3.70), 284 inf (3.28); ν_{max}/cm^{-1} 3379br w (NH), 3134w and 3115w (Ar CH), 1786s (C=O), 1634m, 1607w, 1578w, 1520w, 1504m, 1474s, 1454w, 1427w, 1402w, 1346m, 1312w, 1300w, 1258w, 1238w, 1221m, 1179w, 1155w, 1142w, 1117s, 1103m, 1092m, 1042w, 1034w, 1024w, 1013m, 997w, 897w, 883m, 874m, 808s, 773s; δ_H (300 MHz, acetone-d_6) 10.33 (1H, br s, N*H*), 8.32 (1H, d, *J* 1.9, *H*-9), 7.83 (1H, br s, Ar *H*), 7.57 (1H, dd, *J* 8.7, 2.3, *H*-7), 7.53 (1H, d, *J* 8.7, Ar *H*), 7.43–7.35 (2H, m, Ar *H*), 7.22 (1H, d, *J* 8.7, *H*-6), 6.56 (1H, br s, Ar *H*), 5.33 (2H, s, CH_2O); δ_C (75 MHz, acetone-d_6) 155.2 (C_q), 152.6 (C_q), 144.5 (C_q), 139.1 (C_q), 136.9 (C_q), 131.7 (C_q), 129.7 (C_q), 126.7 (Ar *C*H), 126.5 (Ar *C*H), 122.9 (C_q), 121.4 (Ar *C*H), 119.3 (Ar *C*H), 118.7 (Ar *C*H), 115.0 (Ar *C*H), 112.7 (Ar *C*H), 102.9 (Ar *C*H), 61.0 (*C*H$_2$O); *m*/*z* (EI) 305 (M$^+$, 100%), 261 (58), 233 (33), 205 (15), 192 (6), 178 (22), 164 (4), 152 (11), 139 (4), 131 (6), 117 (3), 104 (14), 89 (13), 76 (10), 70 (5), 63 (7), 58 (5).

4.5.6. 8-(1H-Indol-6-yl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***36***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), 1*H*-indol-6-ylboronic acid (59.8 mg, 0.372 mmol) in MeCN/water (9:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 30 min gave on chromatography (DCM) indole (trace), then 6,6′-biindole **24** as grey needles (17 mg, 58%), mp 281–284 °C (from acetone/pentane) (lit.,[20] 285 °C), R_f (DCM) 0.56; identical to an authentic sample. Further elution (DCM) gave the *title compound* **36** (36.9 mg, 65%) as tawny needles, mp (DSC) onset: 234 °C, peak max: 239 °C (decomp.) (from DCM/pentane), R_f (DCM) 0.44; (found: C, 67.0; H, 3.7; N, 13.6. $C_{17}H_{11}N_3O_3$ requires C, 66.9; H, 3.6; N, 13.8%); λ_{max} (DCM)/nm 240 (log ϵ 3.71), 294 (3.54); ν_{max}/cm^{-1} 3341br w (NH), 1761s (C=O), 1634m, 1609w, 1566w, 1522w, 1508w, 1477m, 1458w, 1433w, 1418m, 1352m, 1315w, 1261w, 1244m, 1231w, 1196w, 1161w, 1132m, 1123m, 1105m, 1094m, 1038m, 1022m, 1003w, 897w, 887w, 878w, 856m, 835w, 822w, 806s, 779w, 764m; δ_H (300 MHz, acetone-d_6) 10.35 (1H, s, N*H*), 8.33 (1H, d, *J* 1.9, *H*-9), 7.72–7.63 (2H, m, Ar *H*), 7.58 (1H, dd, *J* 8.5, 2.1, *H*-7), 7.40 (1H, dd, *J* 2.5, Ar *H*), 7.32 (1H, d, *J* 8.3, Ar *H*), 7.22 (1H, d, *J* 8.5, *H*-6), 6.50 (1H, br s, Ar *H*), 5.33 (2H, s, CH_2O); δ_C (75 MHz, acetone-d_6) 155.2 (C_q), 152.6 (C_q), 144.7 (C_q), 138.8 (C_q), 137.8 (C_q), 133.7 (C_q), 128.8 (C_q), 126.8 (Ar *C*H), 126.5 (Ar *C*H), 122.9 (C_q), 121.6 (Ar *C*H), 119.2 (Ar *C*H), 118.8 (Ar *C*H), 114.9 (Ar *C*H), 110.2 (Ar *C*H), 102.3 (Ar *C*H), 61.0 (*C*H$_2$O); *m*/*z* (EI) 305 (M$^+$, 84%), 261 (59), 233 (29), 205 (14), 192 (5), 178 (22), 164 (4), 151 (9), 140 (4), 131 (5), 126 (3), 114 (3), 104 (14), 89 (11), 76 (10), 63 (6), 58 (30).

4.6. Suzuki coupling of NS2028 with potassium trifluoroborates

4.6.1. 8-(2,6-Dimethoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***39*** *(typical procedure, see Table 3).* To a stirred solution

of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*]-[1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol) and potassium (2,6-dimethoxyphenyl)-trifluoroborate (68.1 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) was added dropwise *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol). The stirred reaction mixture was then immersed into a preheated oil bath ca. 110 °C until all the solids dissolved and then in one portion was added $Pd(OAc)_2$ (2.09 mg, 9.30 μmol). The reaction mixture was then allowed to stir at ca. 110 °C for 1 h. On cooling to ca. 20 °C the volatiles were removed in vacuo and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give 2,2′,6,6′-tetramethoxybiphenyl **37** as colourless needles (17 mg, 53%), mp 173–175 °C (lit.,[13] 175–177 °C), R_f (DCM) 0.78; identical to an authentic sample. Further elution (DCM) gave the *title compound* **39** (15.2 mg, 25%) as colourless needles, mp (DSC) onset: 178 °C, peak max: 179 °C (from 1,2-dichloroethane), R_f (DCM) 0.58; (found: C, 62.6; H, 4.3; N, 8.5. $C_{17}H_{14}N_2O_5$ requires C, 62.6; H, 4.3; N, 8.5%); λ_{max} (DCM)/nm 229 (log ϵ 3.40), 239 inf (3.29), 270 inf (2.93); ν_{max}/cm^{-1} 3103w and 3017w (Ar CH), 2967w, 2837w, 1778s (C=O), 1632w, 1607w, 1593w, 1582w, 1510w, 1487w, 1468m, 1433w, 1404w, 1341w, 1298w, 1281w, 1244s, 1225m, 1173w, 1152w, 1119m, 1105s, 1088m, 1036w, 1020m, 887w, 835w, 827m, 806w, 789m; δ_H (300 MHz, $CDCl_3$) 8.07 (1H, d, *J* 1.9, *H*-9), 7.30 (1H, dd, *J* 8.4, 8.4, Ar *H*), 7.20 (2H, dd, *J* 8.4, 1.8, *H*-7), 7.14 (1H, d, *J* 8.5, *H*-6), 6.65 (2H, d, *J* 8.3, Ar *H*), 5.12 (2H, s, CH_2O), 3.75 (6H, s, CH_3O); δ_C (75 MHz, $CDCl_3$) 157.6 (C_q), 154.2 (C_q), 151.1 (C_q), 143.3 (C_q), 130.6 (Ar *C*H), 130.2 (C_q), 129.3 (Ar *C*H), 120.6 (C_q), 119.1 (Ar *C*H), 117.4 (C_q), 117.2 (Ar *C*H), 104.1 (Ar *C*H), 60.1 (CH_2O), 55.9 (CH_3O); *m*/*z* (EI) 326 (M^+, 100%), 281 (4), 267 (3), 253 (8), 239 (15), 224 (10), 213 (30), 196 (9), 185 (19), 170 (13), 159 (6), 155 (6), 140 (13), 127 (11), 114 (12), 101 (6), 88 (7), 77 (11), 63 (11), 55 (7).

4.6.2. 8-(2-Methoxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***26***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo [3,4-*c*][1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), potassium 2-methoxyphenyltrifluoroborate (59.7 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 10 min gave on chromatography (DCM) 2,2′-dimethoxybiphenyl **14** as colourless needles (5 mg, 44%), mp 154–155 °C (lit.,[13] 156–157 °C), R_f (DCM) 0.62; identical to an authentic sample. Further elution (DCM) gave the *title compound* **26** (51.3 mg, 93%) as colourless prisms, mp (DSC) onset: 164 °C, peak max: 165 °C (from 1,2-dichloroethane), R_f (DCM) 0.42; identical to the sample described above.

4.6.3. 8-(3-Nitrophenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***27***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*] [1,4]benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), potassium 3-nitrophenyltrifluoroborate (63.8 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 3 h gave on chromatography (DCM) 3,3′-dinitrobiphenyl **15** as colourless cotton needles (12 mg, 40%), mp 200–201 °C (lit.,[13] mp 201–202 °C), R_f (DCM) 0.80; identical to an authentic sample. Further elution (DCM) gave unreacted starting material **2** (NS2028) (2 mg, 4%) followed by the *title compound* **27** (9.8 mg, 17%) as colourless needles, mp (DSC) onset: 220 °C, peak max: 221 °C (from DCM/pentane), R_f (DCM) 0.53; identical to the sample described above.

4.6.4. 8-Phenyl-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***28***. Similar treatment of 8-bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4] benzoxazin-1-one **2** (50.0 mg, 0.186 mmol), potassium phenyltrifluoroborate (51.3 mg, 0.279 mmol) in dioxane/water (4:1) (0.5 mL) with *N*-ethyldiisopropylamine (96.4 μL, 0.557 mmol) and $Pd(OAc)_2$ (2.09 mg, 9.30 μmol) at ca. 110 °C for 2 h gave on chromatography (DCM) biphenyl **16** as colourless prisms (5 mg, 35%), mp 65–67 °C (lit.,[13] mp 67–69 °C), R_f (DCM) 0.78; identical to an authentic sample. Further elution (DCM) gave the *title compound* **28** (24.8 mg, 50%) as colourless prisms, mp (DSC) onset: 176 °C, peak max: 177 °C (from 1,2-dichloroethane), R_f (DCM) 0.67; identical to the sample described above.

4.7. Demethylation of 8-(methoxyphenyl)-4*H*-[1,2,4] oxadiazolo[3,4-*c*][1,4]benzoxazin-1-ones

4.7.1. 8-(4-Hydroxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***40*** *(typical procedure, see Scheme 4).* To a stirred ice-cold solution of 8-(4-methoxyphenyl)-4*H*-[1,2,4]oxadiazolo[3,4-*c*] [1,4]benzoxazin-1-one **11** (150 mg, 0.506 mmol) in DCM (5 mL) was added dropwise a 1 M solution of BBr_3 in DCM (1.52 mL, 1.52 mmol). The reaction mixture was then allowed to stir at ca. 20 °C for 6 h and then adsorbed onto silica and chromatographed (Et_2O) to give the *title compound* **40** (130 mg, 91%) as colourless plates, mp (DSC) onset: 218 °C, peak max: 224 °C (decomp.) (from acetone/pentane), R_f (Et_2O) 0.62; (found: C, 64.0; H, 3.4; N, 9.8. $C_{16}H_{12}N_2O_4$ requires C, 63.8; H, 3.6; N, 9.9%); λ_{max} (DCM)/nm 242 (3.47), 271 (log ϵ 3.47); ν_{max}/cm^{-1} 3356br w (OH), 3063w (Ar CH), 1784m, 1759s (C=O), 1634m, 1611m, 1593m, 1499s, 1474m, 1441s, 1402w, 1366w, 1348m, 1298w, 1265s, 1240m, 1217s, 1180m, 1163m, 1124s, 1092m, 1043m, 1022s, 995w, 974w, 883m, 858w, 845m, 827s, 818m, 804m; δ_H (300 MHz, acetone-d_6) 8.52 (1H, s, O*H*), 8.21 (1H, d, *J* 2.3, *H*-9), 7.52–7.45 (3H, m, Ar *H* and H-7), 7.20 (1H, d, *J* 8.7, *H*-6), 6.94 (2H, d, *J* 8.7, Ar *H*), 5.33 (2H, s, CH_2O); δ_C (75 MHz, acetone-d_6) 158.3 (C_q), 155.2 (C_q), 152.5 (C_q), 144.7 (C_q), 137.3 (C_q), 131.6 (C_q), 128.7 (Ar *C*H), 125.9 (Ar *C*H), 122.9 (C_q), 118.8 (Ar *C*H), 116.8 (Ar *C*H), 114.3 (Ar *C*H), 61.0 (CH_2O); *m*/*z* (EI) 282 (M^+, 100%), 238 (85), 210 (35), 184 (17), 182 (29), 170 (4), 155 (18), 140 (10), 128 (37), 115 (17), 102 (10), 89 (12), 77 (18), 63 (15).

4.7.2. 8-(3-Hydroxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***41***. Similar treatment of 8-(3-methoxyphenyl)-4*H*-[1,2,4] oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **25** (150 mg, 0.506 mmol) with BBr_3 (1.52 mL, 1.52 mmol) at ca. 20 °C for 6 h gave the *title compound* **41** as colourless prisms (129 mg, 90%), mp (DSC) onset: 241 °C, peak max: 243 °C (from acetone/pentane), R_f (Et_2O) 0.62; (found: C, 64.0; H, 3.5; N, 10.0. $C_{16}H_{12}N_2O_4$ requires C, 63.8; H, 3.6; N, 9.9%); λ_{max} (DCM)/nm 233 (log ϵ 3.48), 262 (3.26), 284 inf (3.11); ν_{max}/cm^{-1} 3464w (OH), 1755s (C=O), 1636w, 1614w, 1591w, 1578w, 1512w, 1489m, 1466m, 1408m, 1352w, 1317w, 1302m, 1288w, 1269w, 1244w, 1225w, 1194m, 1153m, 1124m, 1096w, 1047w, 1020s, 966w, 903w, 885w, 862w, 841m, 818w, 802m, 783s; δ_H (300 MHz, acetone-d_6) 8.50 (1H, s, O*H*), 8.26 (1H, d, *J* 2.1, H-9), 7.53 (1H, dd, *J* 8.5, 2.3, *H*-7), 7.30 (1H, dd, *J* 8.1, 8.1, Ar *H*), 7.23 (1H, d, *J* 8.5, *H*-6), 7.13–7.07 (1H, m, Ar *H*), 6.86 (1H, ddd, *J* 8.1, 2.3, 0.8, Ar *H*), 5.35 (2H, s, CH_2O); δ_C (75 MHz, acetone-d_6) 158.9 (C_q), 155.2 (C_q), 152.4 (C_q), 145.4 (C_q), 141.7 (C_q), 137.2 (C_q), 131.0 (Ar *C*H), 126.5 (Ar *C*H), 122.9 (C_q), 118.9 (Ar *C*H), 118.7 (Ar *C*H), 115.6 (Ar *C*H), 114.9 (Ar *C*H), 114.3 (Ar *C*H), 61.0 (CH_2O); *m*/*z* (EI): 282 (M^+, 100%), 238 (80), 211 (15), 184 (31), 170 (3), 155 (19), 140 (9), 127 (34), 115 (17), 102 (10), 89 (10), 77 (17), 63 (15), 51 (13).

4.7.3. 8-(2-Hydroxyphenyl)-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one ***42***. Similar treatment of 8-(2-methoxyphenyl)-4*H*-[1,2,4] oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **26** (150 mg, 0.506 mmol) with BBr_3 (1.52 mL, 1.52 mmol) at ca. 20 °C for 6 h gave the *title compound* **42** as colourless needles (133 mg, 93%), mp (DSC) onset: 166 °C, peak max: 167 °C (from DCM/pentane), R_f (Et_2O) 0.62; (found: C, 64.0; H, 3.5; N, 9.9. $C_{16}H_{12}N_2O_4$ requires C, 63.8; H, 3.6; N, 9.9%); λ_{max} (DCM)/nm 232 (log ϵ 3.45), 287 (3.04); ν_{max}/cm^{-1} 3354br w (OH), 3076w and 3032w (Ar CH), 1748s (C=O), 1628w, 1603w, 1508w, 1495m, 1470m, 1450m, 1398w, 1346m, 1294w, 1279m, 1267w, 1236m, 1196w, 1161w, 1126m, 1107w, 1092w, 1051w, 1034w, 1022m, 997w, 887w, 878w, 858w, 847w, 831m, 814w, 799w, 752s; δ_H (300 MHz, $CDCl_3$) 8.33 (1H, d, *J* 1.9, *H*-9), 7.46 (1H, dd, *J* 8.5, 1.9,

H-7), 7.38–7.28 (3H, m, Ar *H*), 7.12–6.97 (2H, m, Ar *H* and *H*-6), 5.21 (2H, s, CH_2O), 5.15 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 154.0 (C_q), 152.3 (C_q), 150.7 (C_q), 143.9 (C_q), 133.6 (C_q), 130.5 (Ar *C*H), 129.5 (Ar *C*H), 128.5 (Ar *C*H), 126.4 (C_q), 121.3 (C_q), 121.2 (Ar *C*H), 118.2 (Ar *C*H), 117.3 (Ar *C*H), 116.1 (Ar *C*H), 60.2 (*C*H_2O); *m*/*z* (EI) 282 (M^+, 100%), 238 (17), 210 (12), 184 (52), 170 (7), 155 (25), 139 (9), 128 (38), 115 (21), 102 (16), 89 (11), 77 (18), 63 (17), 55 (15), 51 (16).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.003.

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