Scalable 9-Step Synthesis of the Splicing Modulator NVS-SM2

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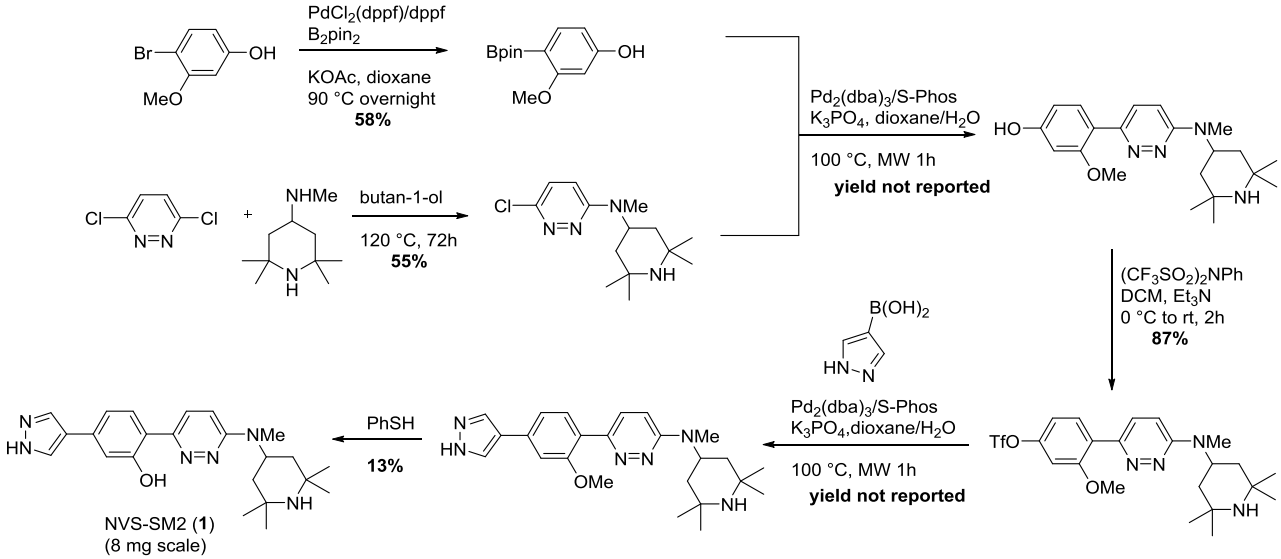
Supporting Information

ABSTRACT: NVS-SM2, the first activator of pre-mRNA splicing, displays remarkable pharmacological *in vivo* activities in models of spinal muscular atrophy. Herein we describe an improved approach to the synthesis of this compound, which features a convenient introduction of sterically encumbered amine moiety onto a fluoropyridazine intermediate.

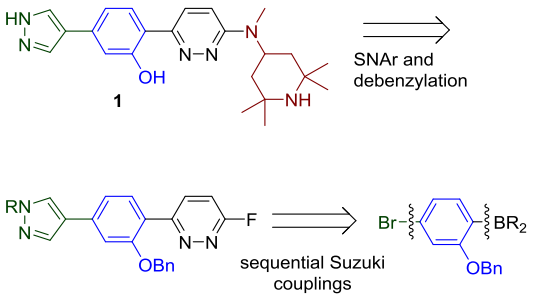
In 2015, Novartis scientists reported the discovery of NVS-SM2 (**1**, Scheme 1), the first activator of pre-mRNA splicing.[1] This orally active small molecule doubled life-span in a majority of treated mice in a model of spinal muscular atrophy (SMA). SMA is a major genetic cause of infant mortality caused by a mutation of the gene SMN that is essential to pre-mRNA splicing. The pharmacological investigation of **1** in SMA and other diseases is highly hindered by the availability of this compound. Indeed its preparation on an 8 mg scale has only been reported in one patent by Novartis' scientists.[2] The caveat in this synthesis lies in the deprotection of the phenol and the introduction of sterically hindered amine that respectively occurred with a 13 and 55% yield, and also with the Suzuki-Miyaura coupling of highly functionalized aryl and heteroaryl moieties, the yield of which was not reported (Scheme 1). In this communication, the execution of a 9-step, scalable synthesis of **1** is presented.

To overcome the limitation of the original synthesis of NVS-SM2, we explored several routes and we finally envisioned to protect the phenol as a benzyloxy and to introduce the congested amine onto a reactive fluoropyridazine. We considered also to assembly the aryl and heteroclic moieties Suzuki coupling under optimized reactions (Scheme 2).

Scheme 1. Novartis Synthesis of NVS-SM2



Scheme 2. Synthesis Plan for NVS-SM2 (1)



Our synthesis commenced with a palladium-catalyzed borylation[3] of iodide **2** that afforded a mixture (90:10) of boronates **3** and **3'**, which was directly used in a Suzuki-Miyaura coupling with iodopyridazine **4** to furnish adduct **5** (Scheme 3).[4] Initial attempts to perform this reaction using Fu's condition[5,6] did not yield the expected adduct **5** (entry 1, Table 1). Switching to other catalytic systems using S-Phos, X-Phos or PPh_3 as ligands provided the desired adduct with a conversion of 20-32% (entries 2-4). Ultimately, the air and moisture stable $PdCl_2$(dppf) proved to be particularly effective (entry 5). Finally, several other combinations of solvent and base were examined, and when the reaction was carried out in dioxane/H_2O with the use of K_3PO_4 as a base, a 70% yield could be achieved (entry 8). This preference for K^+ as a counteraction of the base suggests that this Suzuki coupling involves a fast oxidation step and a rate-determining transmetalation.[7]

Further continuation of the synthesis required the replacement of the methoxy by a benzyloxy that can be efficiently deprotected in the final step. Indeed, Novartis scientists reported in their patent that the demethylation at a latter step is performed with a 13% yield only.[2] Thus, demethylation with boron trichloride of **5**, followed by benzylation, gave the requisite intermediate **7** in a 98% yield.

Scheme 3. Synthesis of Intermediate 7

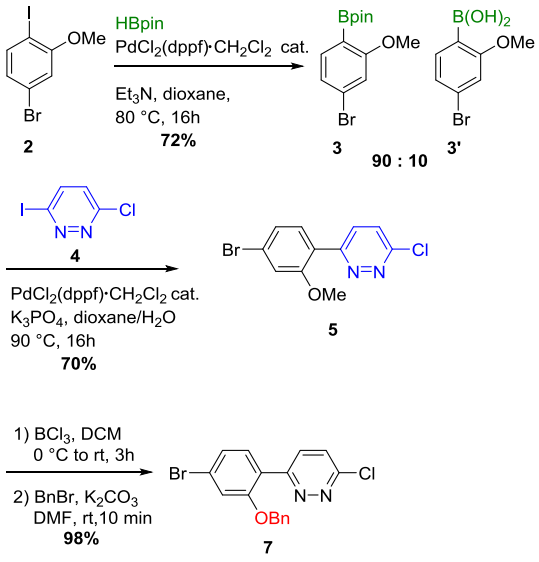
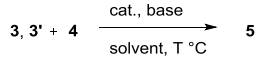


Table 1. Optimization of the First Suzuki-Miyaura Coupling



entry	cat.	base (eq)	solvent	T °C	yield (%)
1	$Pd_2(dba)_3$ (2 mol%) $P(tBu)_3$ (3 mol%)	KF (3)	THF	80	trace
2	$Pd(OAc)_2$ (10 mol%) S-Phos (20 mol%)	K_2CO_3 (2.2)	ACN/H_2O	110	20
3	$Pd(OAc)_2$ (10mol%) X-Phos (12 mol%)	K_3PO_4 (2)	*n*-BuOH/H_2O	110	21
4	$Pd(PPh_3)_4$ (5 mol%)	Na_2CO_3 (2)	EtOH/toluene/ H_2O	reflux	32
5	$PdCl_2$(dppf)·CH_2Cl_2 (10 mol%)	Na_2CO_3 (2)	DMF/H_2O	100	40
6	$PdCl_2$(dppf)·CH_2Cl_2 (10 mol%)	CsF (0.5)	DMF/H_2O	100	17
7	$PdCl_2$(dppf)·CH_2Cl_2 (10 mol%)	Na_2CO_3 (2)	THF/ACN/H_2O	100	12
8	$PdCl_2$(dppf)·CH_2Cl_2 (10 mol%)	K_3PO_4 (3)	dioxane/H_2O	90	70

With the intermediate **7** in hand, we proceeded to its coupling with the pyrazolylboronate moiety. Original attempts to perform this reaction using a pyrazolylboronate protected with a Boc were not satisfactory, due to the lability of the Boc in the examined conditions. To circumvent this issue, we incorporated a Trityl protecting group onto the pyrazolylboronate. This reagent was conveniently prepared in 3 steps from pyrazole **8** (Scheme 4).

Scheme 4. Preparation of Tritylpyrazolylboronate 11

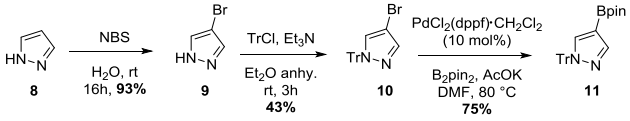
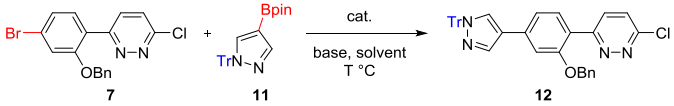
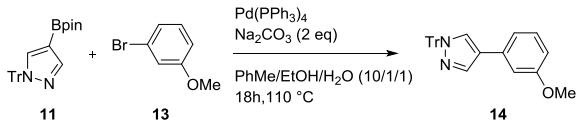


Table 2. Optimization of the Second Suzuki-Miyaura Coupling



entry	cat.	base (eq)	solvent	T°C	yield (%)
1	$Pd_2(dba)_3$ (3 mol%) $P(tBu)_3$ (7 mol%)	KF (3.3)	THF	70	0
2	$Pd_2(dba)_3$ (1 mol%) PCy_3 (2.4 mol%)	K_3PO_4 (1.7)	dioxane/H_2O	100	0
3	$Pd(PPh_3)_4$ (10 mol%)	Na_2CO_3 (2)	DME/H_2O (6/3)	MW 150	28
4	$Pd(PPh_3)_4$ (10 mol%)	Na_2CO_3 (2)	PhMe/EtOH/H_2O (10/1/1)	110	30

Table 3. Optimization of second Suzuki-Miyaura using 3-bromoanisole 13 as a substrate



11 13 14

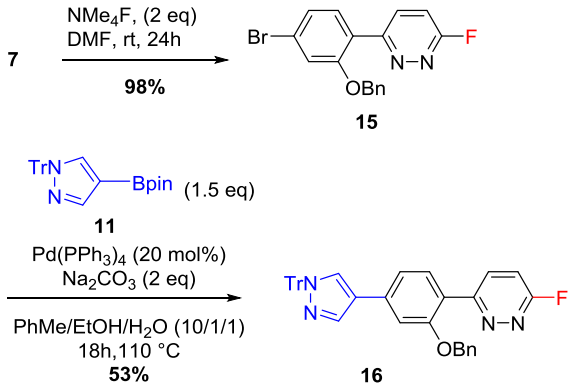
entry	**11** (eq)	$Pd(PPh_3)_4$ (mol%)	yield (%)
1	1.5	10	33
2	3	10	28
3	1.5	20	70

After extensive studies, we found that arylbromide **7** can be coupled in the presence of $Pd(PPh_3)_4$ with boronate **11** to prepare adduct **12** in a 30% yield (entries 3-4, Table 2). Initial attempts to use unprotected pyrazole-4-boronic acid did not deliver the expected adducts. When we examined this reaction with the reactant protected as a Boc, the yield was not reproducible and lied between 0 and 20%.

To improve this reaction condition, we examined the coupling of **11** with 3-bromoanisole **13** using $Pd(PPh_3)_4$, Na_2CO_3 in PhMe/EtOH/H_2O.[8] Our initial assay afforded the expected adduct in a 33% yield (entry 1, Table 3). Increasing the amount of boronate **11** did not modify the yield (entry 2). Gratefully, doubling the amount of catalyst improved the yield up to 70% (entry 3), suggesting that the catalyst is unstable in this condition.

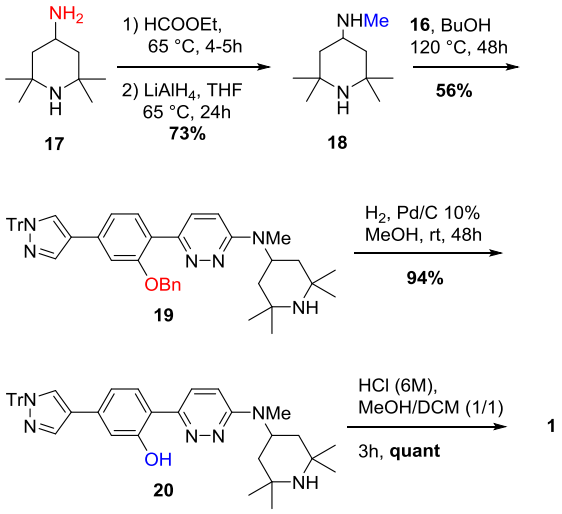
With an optimized Suzuki-Miyaura coupling of boronate **11** in hand, an efficient route to synthesize advanced intermediate **16** was developed (Scheme 5). First, the iminochloride **7** was treated with anhydrous tetramethylammonium fluoride under Sanford's condition[9] to smoothly furnish fluoropyridazine **15**, in 98% yield. The latter has two main advantages compared to the cognate chloropyridazine **7**: the iminofluoride moiety is resistant to Suzuki coupling, and importantly, it is much more reactive in SNAr reactions. The coupling of boronate **11** with **15** delivered adduct **16** in 53% yield.

Scheme 5. Synthesis of advanced intermediate



The synthesis of diamine **18** was conveniently achieved by formylation of **17** with ethyl formate and reduction of the obtained formamide with $LiAlH_4$. Its condensation with fluoropyridazine **16** gave aminopyridazine **19** in a satisfactory yield (56%) (Scheme 6). We originally considered performing this reaction with a chloropyridazine, but all of our attempts failed to deliver the expected adduct. Completion of the synthesis was accomplished by a double deprotection of the phenol and pyrazole moieties with a 94% yield for both steps.

Scheme 6. Endgame of the Synthesis



In conclusion, the synthesis of NVS-SM2 has been accomplished in 9 linear steps with an overall yield of 14% (average yield: 82%). It involves few more steps that the original one, however we optimized all the steps and some of them can be carried a very convenient manner with a near quantitative yield. For example, the conversion of 5 into 7 was performed in 2 steps with an overall yield of 98% and the intermediate of this sequence was directly used in the second step without purification. Actually, this sequence can be easily achieved in half a day. The fluoridation (**7** → **15**) and deprotection (**19** → **20** → **1**) steps are also performed in high yield in a very expedient manner.

Thus, this route can satisfy the global demand for NVS-SM2 to examine in detail its therapeutic potential to treat SMA and other diseases associated with alterations in RNA splicing. In addition, the efficacy of the synthesis reported herein offers an opportunity to explore further the pharmacological effects of chemical modifications in the structure of NVS-SM2.

■ EXPERIMENTAL SECTION

All commercial reagents were used without purification. All the anhydrous solvents used are commercial or are conserved on molecular sieves. All reactions sensitive to moisture or oxygen were carried out under argon atmosphere and in flasks dried at 110 °C. Reactions were stirred with a magnetic stirrer. Temperatures for the reactions refer to bath temperatures. Reactions were monitored by TLC (0.2 mm, Merck DC Platten Kieselgel 60 F_{254}) with detection by UV light (λ = 254 nm) and treatment with anisaldehyde and potassium permanganate-stain. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected.

NMR spectras were acquired on a Bruker DRX-400 spectrometer in $CDCl_3$ (referenced to 7.26 ppm for 1H and 77.0 ppm for ^{13}C), $(CD_3)_2SO$ (referenced to 2.50 ppm for ^1H and 39.5 ppm for ^{13}C) or CD_3OD (referenced to 3.31 ppm for ^1H and 49 ppm for ^{13}C) as solvents. Coupling constants (J) are in Hz. Chemical shifts are reported in parts per million (ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet. High resolution mass spectra were recorded on a Bruker MicroTOF-Q (ESI Q-TOF) spectrometer.

3-(4-Bromo-2-methoxyphenyl)-6-chloropyridazine (5)

1,1'-Bis(diphenylphosphinoferrocene)-palladium (II) dichloride CH_2Cl_2 complex (574 mg, 0.70 mmol) was added to a dioxane (19 mL) / H_2O (1 mL) solution of iodopyridazine **4** (1.86 g, 7.73 mmol), boronates (**3, 3'**) (2.2 g, 7.03 mmol) and potassium phosphate (4.48 g, 21.08 mmol) at room temperature under argon atmosphere (the flask was evacuated and refilled with argon five times before adding of Pd complex). The reaction was heated at 90 °C for 16h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL), filtered through celite with copious washings, and then concentrated. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel using DCM (100%) as eluent to give **5** (1.63 g, 70%) as a white solid ; mp = 133-136 °C ; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 7.16 (1H, d, *J* = 1.4 Hz), 7.26 (1H, dd, *J* = 1.4, 8.3 Hz), 7.49 (1H, d, *J* = 9 Hz), 7.84 (1H, d, *J* = 8.3 Hz), 7.98 (1H, d, *J* = 9 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 115.0, 123.6, 124.6, 125.4, 127.2, 130.3, 132.2, 155.1, 157.1, 157.6 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{11}H_9BrClN_2O$ 298.9581 ; found 298.9571.

5-Bromo-2-(6-chloropyridazin-3-yl)phenol (6)

To a stirred solution of **5** (500 mg, 1.67 mmol) in dry DCM (50 mL), BCl_3 (5 mL, 5 mmol, 1M in DCM) was added dropwise at 0 °C under argon atmosphere. The resulting reaction mixture was stirred over 3h at room temperature then quenched with water. The aqueous layer was extracted with DCM (2 × 50 mL). Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give **6** (470 mg, 99%) as a pale-yellow solid which was used without further purification ; mp = 161-164 °C ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10 (1H, dd, *J* = 1.5, 8.5 Hz), 7.29 (1H, d, *J* = 1.5 Hz), 7.52 (1H, d, *J* = 8.5 Hz), 7.67 (1H, d, *J* = 9.3 Hz), 8.01 (1H, d, *J* = 9.3 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.9, 122.4, 122.9, 125.7, 127.1, 127.5, 130.1, 155.0, 159.5, 160.5 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_7BrClN_2O$ 284.9425 ; found 284.9420.

3-[2-(Benzyloxy)-4-bromophenyl]-6-chloropyridazine (7)

To a stirred solution of phenol **6** (130 mg, 0.45 mmol) in dry DMF (1.5 mL), was added potassium carbonate (126 mg, 0.9 mmol) and then benzyl bromide (86 mg, 0.5 mmol) at room temperature under argon atmosphere. The resulting reaction mixture was stirred over 10 min at the same temperature and then diluted with DCM (15 mL). The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated to give chloropyridazine **7** (167 mg, 98%) as a white solid which was used without further purification ; mp = 177-180 °C ; ^1H NMR (400 MHz, $CDCl_3$): δ 5.12 (2H, s), 7.27-741 (8H, m), 7.89 (1H, d, *J* = 8.3 Hz), 7.98 (1H, d, *J* = 9 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.4, 116.6, 124.1, 125.1, 125.4, 127.2, 127.5, 128.6, 128.9, 130.4, 132.5, 135.6, 155.2, 156.9, 157.1 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}BrClN_2O$ 374.9894 ; found 374.9883.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-trityl-1*H*-pyrazole (11)

To a stirred solution of 4-bromo-tritylpyrazole **10** (2 g, 5.14 mmol) and bis(pinacolato)diboron (1.44 g, 5.65 mmol) in DMF(14 ml), was added 1,1'-bis(diphenylphosphinoferrocene)-palladium (II) dichloride CH_2Cl_2 complex (420 mg, 0.51 mmol) and potassium acetate (1.51g, 15.42 mmol) at room temperature under argon atmosphere. The resulting mixture was heated at 80 °C for 16h. After cooling to room temperature, the reaction mixture was diluted with DCM (50 mL). The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel using pentane / Et_2O (10/0 to 8/2) as eluent to give boronate **11** (1.8 g, 75%) as a white solid ; mp = 190-193 °C ; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (12H, s), 7.13-7.20 (6H, d, m), 7.28-7.34 (9H, d, m), 7.79 (1H, s), 7.98 (1H, s) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 78.8, 83.4, 127.7, 127.8, 130.2, 138.8, 143.2, 145.9 ; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{28}H_{29}BN_2NaO_2$ 459.2214 ; found 459.2210.

3-(2-(Benzyloxy)-4-(1-trityl-1*H*-pyrazol-4-yl)phenyl)-6-chloropyridazine (12)

$Pd(PPh_3)_4$ (31 mg, 0.027 mmol) was added to a stirred solution of chloropyridazine **7** (100 mg, 0.27 mmol), boronate **11** (174 mg, 0.40 mmol) and Na_2CO_3 (117 mg, 0.53 mmol) in PhMe (3 ml) / EtOH (0.3 ml) / H_2O (0.3 ml) at room temperature under argon atmosphere (the flask was purged five times with argon before adding the Pd complex). The resultant mixture was stirred at the same temperature for 5 min and then at 110 °C for 18h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL). The organic layer was washed with water, brine, dried over $MgSO_4$, concentrated and purified by column chromatography on silica gel using pentane / Et_2O (8/2 to 5/5) as eluent to give chloropyridazine **12** (50 mg, 30%) as a white solid ; mp = 216-219 °C ; ^1H NMR (400 MHz, $CDCl_3$): δ 5.07 (2H, s), 7.05 (1H, d, *J* = 0.9 Hz), 7.07-7.20 (8H, m), 7.21-7.35 (14H, m), 7.60 (1H, s), 7.88 (1H, s), 7.90 (1H, d, *J* = 8 Hz), 7.96 (1H, d, *J* = 9 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.1, 79.1, 110.2, 119.1, 121.0, 123.0, 127.0, 127.5, 127.9, 128.0, 128.3, 128.8, 129.6, 130.2, 130.5, 131.7, 136.3, 137.4, 143.0, 154.7, 156.9, 157.6 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{39}H_{30}ClN_4O$ 605.2103 ; found 605.2108.

4-(3-Methoxyphenyl)-1-trityl-1*H*-pyrazole (14)

The title compound was prepared similarly to the synthesis of chloropyridazine **12** starting from 3-bromoanisole **13** (80 mg, 0.054 mmol), boronate **11** (281 mg, 0.64 mmol), sodium carbonate (91 mg, 0.86 mmol), $Pd(PPh_3)_4$ (100 mg, 0.086 mmol) and PhMe (3 ml) / EtOH (0.3 ml) / H_2O (0.3 ml). The crude product was purified by chromatography on silica gel using pentane / Et_2O (10/0 to 80/20) as eluent to give pyridazine **14** (126 mg, 70%) as a white solid ; mp = 120-123 °C ; ^1H NMR

(400 MHz, $CDCl_3$): δ 3.82 (3H, s), 6.75 (1H, ddd, *J* = 1.0, 2.6, 8.4 Hz), 7.96 (1H, dd, *J* = 1.4, 2.6 Hz), 7.03 (1H, ddd, *J* = 1, 1.4, 7.7 Hz), 7.20-7.25 (7H, m), 7.30-7.35 (9H, m), 7.61 (1H, d, *J* = 0.8 Hz), 7.93 (1H, d, *J* = 0.8 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 78.9, 111.4, 111.6, 118.2, 121.5, 127.8, 127.9, 129.3, 129.8, 130.2, 134.0, 137.3, 143.1, 160.0 ; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{29}H_{24}N_2NaO$ 439,1786 ; found 439,1768.

3-[2-(Benzyloxy)-4-bromophenyl]-6-fluoropyridazine (15)

To a stirred solution of chloropyridazine **7** (750 mg, 1.99 mmol) in dry DMF (12 mL), anhydrous NMe_4F (375 mg, 3.98 mmol) was added at room temperature under argon atmosphere. The resulting reaction mixture was stirred at the same temperature for 24h before it was diluted with DCM (70 mL). The organic layer was washed with water (3 × 120 mL), brine (1 × 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give fluoropyridazine **15** (700 mg, 98%) as a white solid which was used without further purification ; mp = 167-170 °C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (2H, s), 7.13 (1H, dd, *J* =1.5, 9.2 Hz), 7.27-7.40 (7H, m), 7.8 (1H, d, *J* = 8.2 Hz), 8.12 (1H, dd, *J* = 7.5, 8.2 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.3, 114.7 (d, *J* = 33 Hz), 116.5, 124.2, 125.1, 125.2, 127.5, 128.6, 128.9, 132.5, 133.7 (d, *J* = 7 Hz), 135.6, 156.7, 157.6 (d, *J* = 2.7 Hz), 165.7 (d, *J* = 245 Hz) ; ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): -81.27 (1F, s) ; ^{19}F NMR coupled ^{1}H (376 MHz, $CDCl_3$): -81.27 (1F, d, *J* = 7.5 Hz) ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}BrFN_2O$ 359.0190 ; found 359.0192.

3-[2-(Benzyloxy)-4-(1-trityl-1*H*-pyrazol-4-yl)phenyl]-6-fluoropyridazine (16)

The title compound was prepared similarly to the synthesis of chloropyridazine **12** starting from fluoropyridazine **15** (200 mg, 0.55 mmol), boronate **11** (364 mg, 0.83 mmol), sodium carbonate (117 mg, 1.1 mmol), $Pd(PPh_3)_4$ (129 mg, 0.11 mmol) and PhMe (5 ml) / EtOH (0.5 ml) / H_2O (0.5 ml). The crude product was purified by chromatography on silica gel using pentane / Et_2O (8/2 to 5/5) as eluent to give fluoropyridazine **16** (172 mg, 53%) as a white solid ; mp = 203-206 °C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (2H, s), 7.13 (1H, dd, *J* = 1.5, 9.2 Hz), 7.18 (7H, d, *J* = 1.5 Hz), 7.22 (1H, d, *J* = 8.3 Hz), 7.24-7.3 (6H, m), 7.32-7.43 (14H, m), 7.73 (1H, s), 7.99 (1H, dd, *J* = 1.4, 8.2 Hz), 8.00 (1H, s), 8.21 (1H, dd, *J* = 7.5, 8.3 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.1, 79.1, 110.2, 114.5 (d, *J* = 33 Hz), 119.1, 121.0, 123.1, 127.4, 127.9, 128.0, 128.3, 128.7, 129.5, 130.2, 131.8, 133.6 (d, *J* = 6.8 Hz), 136.1, 132.3, 137.5, 143.0, 156.6, 158.1 (d, *J* = 2.5 Hz), 165 (d, *J* = 244 Hz) ; ^{19}F NMR decoupled ^{1}H (376 MHz, $CDCl_3$): -81.99 ; ^{19}F NMR coupled ^{1}H (376 MHz, $CDCl_3$): -81.99 (dd, *J* = 1.4, 7.5 Hz) ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{39}H_{29}FN_4O$ 589.2398 ; found 589.2395.

***N*,2,2,6,6-pentamethylpiperidin-4-amine (18)**

A solution of **17** (4.4 mL, 0.026 mmol) in ethyl formate (6.5 mL, 0.078 mmol) was heated at 65 °C for 4-5 h. The resulting thick, white suspension was cooled to room temperature and filtered. After the filter cake was washed with EtOAc (20 mL), the solid was dried under vacuum to give 3.8 g (79 % yield) of *N*-(2,2,6,6-tetramethylpiperidin-4-yl)formamide, which was used directly in the next step. A 250 mL round bottom flask equipped with a large Teflon-coated stir bar was charged with $LiAlH_4$ (1.17 g, 31 mmol), fitted with a reflux condenser, and purged with argon. THF (40 mL) was added and the resulting suspension was cooled to 0 °C. A *N*-(2,2,6,6-tetramethylpiperidin-4-yl)formamide (3.8 g, 20.6 mmol) was added in portion over 10 min (CAUTION: hydrogen gas evolution!). The cooling bath was replaced with an oil bath and the colorless solution was heated at 65 °C for 24h under a slow stream of argon. The resulting white suspension was cooled to 0 °C and then carefully quenched by dropwise addition of water (10 mL; CAUTION: violently exothermic reaction, evolution of hydrogen gas!) followed by a 20% aq NaOH solution (20 mL). The resulting suspension was stirred at room temperature for 15 min. MeOH (40 mL) was added then the mixture was filtered on celite. The filtrate was concentrated and then the residue was dissolved with EtOAc (50 mL). The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give diamine **18** (3.25 g, 93%) as a yellow liquid which was used without further purification ; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 0.72 (2H, t, *J* = 11.8 Hz), 1.00 (6H, s), 1.09 (6H, s), 1.68 (2H, dd, *J* = 3.4, 12.3 Hz), 2.26 (3H, s), 2.6 (1H, tdd, *J* = 3.5, 11.5, 11.5 Hz) ; ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 28.5, 32.5, 34.3, 44.5, 49.7, 50.6 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{23}N_2$ 171.1856 ; found 171.1853.

6-[2-(Benzyloxy)-4-(1-trityl-1*H*-pyrazol-4-yl)phenyl]-*N*-methyl-*N*-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (19)

To a stirred solution of **16** (230 mg, 0.39 mmol) in butan-1-ol (4 ml), diamine **18** (133 mg, 0.78 mmol) was added at room temperature under argon atmosphere. The mixture was heated at 120 °C for 48h. After cooling to room temperature, butan-1-ol was removed using rotary evaporator, then the residue was diluted with DCM (50 mL). The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography on silica gel using DCM / MeOH (10/0 to 8/2) as eluent to give **19** (160 mg, 56%) as a yellow solid ; mp = 105-108 °C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (6H, s), 1.35 (6H, s), 1.38 (2H, m), 1.70 (2H, dd, *J* = 2.1, 12 Hz), 2.96 (3H, s), 5.13 (2H, s), 5.15 (1H, m), 6.72 (1H, d, *J* = 9.7 Hz), 7.07 (1H, d, *J* =1.3 Hz), 7.14 (1H, dd, *J* = 1.3, 8 Hz), 7.17-7.25 (6H, m), 7.28-7.4 (14H, m), 7.63 (1H, s), 7.84 (1H, d, *J* = 9.5 Hz), 7.92 (1H,s), 7.98 (1H, d, *J* = 8 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.8, 29.2, 35.3, 41.9, 47.5, 51.5, 71.0, 79.0, 110.4, 119.0, 121.4, 125.3, 127.3, 127.8, 127.9, 128.6, 129.2, 129.4, 130.2, 130.9, 134.1, 137.0, 137.4, 143.1, 149.1, 156.3, 158.2 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{49}H_{51}N_6O$ 739.4119 ; found 739.4138.

2-[6-[Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]pyridazin-3-yl]-5-(1-trityl-1*H*-pyrazol-4-yl)phenol (20)

To a stirred solution of **19** (110 mg, 0.15 mmol) in MeOH (7 ml), catalytic amount of 10% palladium on carbon was added under H_2 atmosphere. The mixture was stirred for 48h at room temperature and then filtered on celite. The filtrate was concentrated and purified by flash chromatography on silica gel using DCM / MeOH (10/0 to 8/2) as eluent to give phenol **20** (90 mg, 94%) as a yellow solid ; mp = 132-135 °C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (6H, s), 1.35 (6H, s), 1.40 (2H, t, *J* = 12.3 Hz), 1.69 (2H, dd, *J* = 2, 12 Hz), 3.00 (3H, s), 4.88 (1H,

m), 6.98 (1H, d, *J* = 9.8 Hz), 7.01 (1H, d, *J* = 8.1 Hz), 7.11 (1H, s), 7.16-7.23 (6H, m), 7.29-7.37 (9H, m), 7.52 (1H, d, *J* = 8.3 Hz), 7.66 (1H, s), 7.92 (1H, s), 7.79 (1H, d, *J* = 9.8 Hz), 7.98 (1H, s) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.4, 35.3, 42.0, 48.4, 51.5, 79.1, 113.9, 114.8, 116.0, 116.8, 121.2, 124.5, 125.4, 128.0, 129.7, 130.3, 134.8, 137.5, 143.2, 151.6, 157.9, 159.4 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{42}H_{45}N_6O$ 649.3649 ; found 649.3634.

2-[6-[Methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]pyridazin-3-yl]-5-(1*H*-pyrazol-4-yl)phenol (1)

To a stirred solution of **20** (80 mg, 0.12 mmol) in THF (2 ml) / MeOH (2 ml), 2 ml of HCl (6M) was added at room temperature. The mixture was stirred at the same temperature. After 3h, solvents were removed using rotary evaporator. The yellow product obtained in salt form was dissolved in DCM / MeOH (50/50) and neutralized with addition of solid $NaHCO_3$. Then the mixture was filtered through celite. The filtrate was concentrated and purified by flash chromatography using DCM / MeOH (10/0 to 8/2) as eluent to give NVS-SM2 (**1)** (48 mg, quant.) as a yellow solid ; mp = 146-149 °C ; ^{1}H NMR (400 MHz, MeOD): δ 1.22 (6H, s), 1.35 (6H, s), 1.48-1.65 (4H, m), 2.87 (3H, s), 4.98 (1H, m), 7.04-7.17 (3H, m), 7.59 (1H, d, *J* = 7.4 Hz), 7.89 (1H, d, *J* = 9.4 Hz), 7.97 (2H, s) ; ^{13}C NMR (100 MHz, MeOD): δ 27.5, 29.8, 33.6, 41.3, 54, 115, 116.3, 117.2, 117.6, 123, 126.4, 127.3, 136.2, 152.8, 159.2, 159.9 ; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}N_6O$ 407.2554 ; found 407.2550.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Spectral data for compounds described herein (PDF)

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Notes

The authors declare no competing financial interest.

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