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Synthesis of 7-benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*]-[2,7]naphthyridin-1-ylamine and its analogs as bombesin receptor subtype-3 agonists

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ABSTRACT

The original structure of a high-throughput screening hit obtained from an external vendor was revised based on multiple NMR studies. The active compound was re-synthesized via a novel route and its structure and biological activity as a BRS-3 agonist were unambiguously confirmed. Multi-gram quantities of the hit were prepared for pharmacokinetic and efficacy studies. The synthetic strategy allowed for the preparation of multiple analogs for SAR exploration.

Obesity is a serious and chronic medical condition that has become a major global health issue. Current drugs approved for the chronic treatment of obesity have suboptimal tolerability and limited efficacy.[1] Hence, there is still unmet medical need in this therapeutic area and the search for more effective obesity treatments continues. Bombesin receptor subtype-3 (BRS-3 or BB3), a G-protein coupled receptor (GPCR) that belongs to the bombesin receptor family, has been recently validated as a potential target for the treatment of obesity.[2] In this Letter, we will describe part of our early efforts at identifying small molecule BRS-3 agonists.

A high throughput screening (HTS) campaign of the Merck sample collection identified an active compound against BRS-3 with the initial structure assignment **1** (Fig. 1) supplied from a commercial vendor. To confirm the structure, a series of NMR experiments such as COSY, HSQC, HMBC, and NOE difference, were conducted on a 500 MHz spectrometer using a microprobe. While a lot of information from proton NMR and HMBC spectra pointed to an isomeric structure **2** (Fig. 2), the strongest evidence came from a series of NOE experiments (Fig. 2). The benzyl group was determined to be on the nitrogen of the naphthyridine moiety rather than on the pyrazole because NOE effects were observed between the benzylic protons and both methylene groups attached to the nitrogen (Item a in Fig. 2). The nitrogen in the naphthyridine moiety was found to be at the 7-position instead of 8-position as depicted in the structure since there were NOE effects between the methylene at the 6-position and the α-methylene on the piperidinyl group (Item b in Fig. 2). The ring conjunction between the pyrazole and the pyridine should be pyrazolo[3,4-*c*]pyridine as suggested by NOE effects between the amino group and the methylene at the 9-position of the naphthyridine moiety (Item c in Fig. 2).

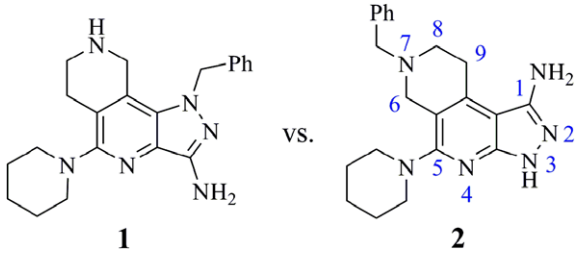

Figure 1. Original (**1**) and revised (**2**) structure assignments.

While compound **2** is also commercially available in milligram quantities, its synthesis has not been described in the literature. We needed an efficient route to prepare **2** in multi-gram quantities

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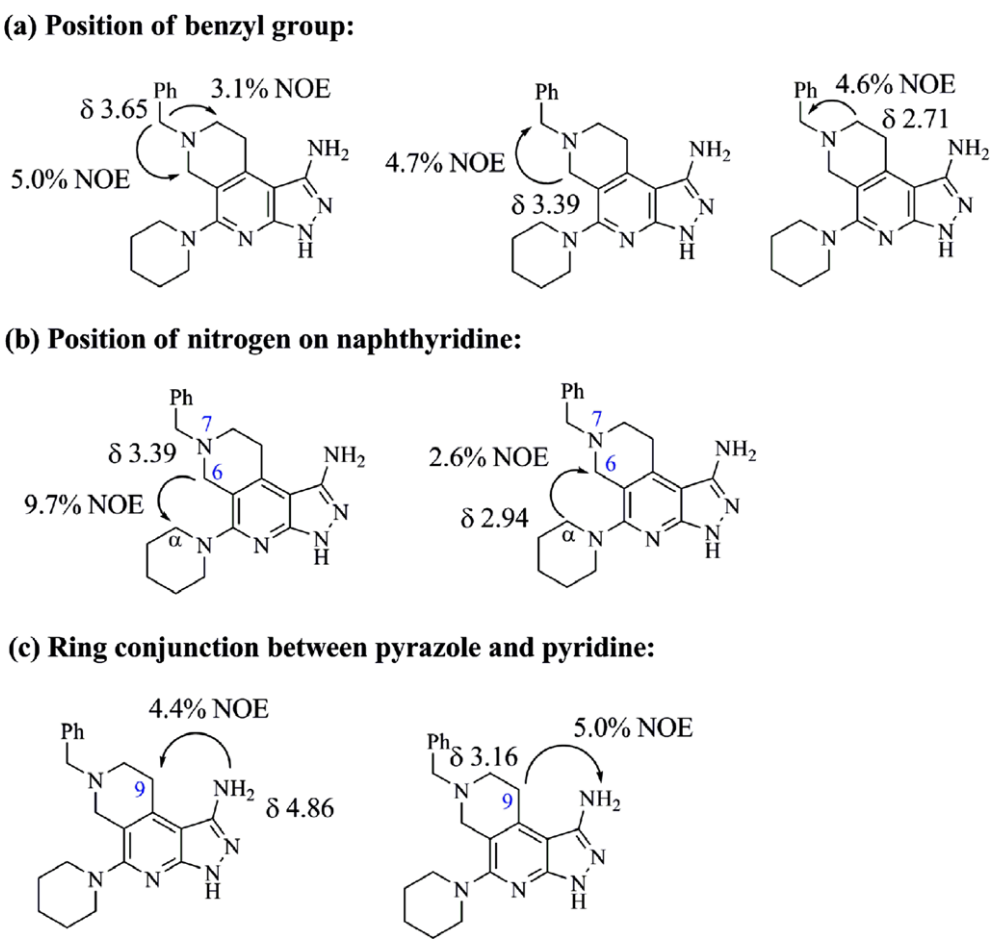
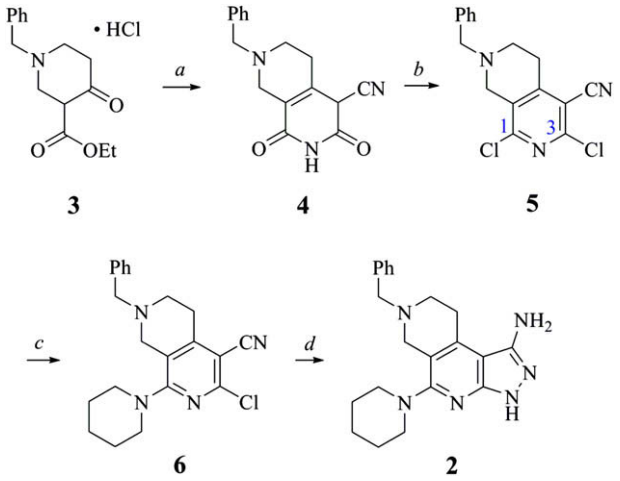


Figure 2. Summary of NOE experiments.

in order to confirm the structure of **2**, to evaluate it in pharmacokinetic and efficacy studies and for subsequent analog work. Retro-synthetic analysis indicated that **2** could be prepared in four steps from commercially available ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**3**) (Scheme 1). However, when considering the transformation of **5** into **6**, the selectivity of SN_{Ar} displacement between 1-chloro and 3-chloro in **5** was difficult to predict. In related examples, the selectivity of SN_{Ar} displacement between the 2-chloro and 6-chloro positions in 2,6-dichloro-3-cyanopyridine was heavily dependent on the substituent at either the 4- or 5-position of the pyridine.[3–6] To the best of our knowledge, no examples have been reported for SN_{Ar} displacement for substrates bearing substituents at both the 4- and 5-positions of the pyridine.

The synthesis of **2** (Scheme 1) began with condensation of the free base of ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**3**) with 2-cyanoacetamide to give 7-benzyl-1,3-dioxo-1,2,3,4,5,6,7,8-octahydro-2,7-naphthyridine-4-carbonitrile (**4**)[7] in 71% yield, which was converted to 7-benzyl-1,3-dichloro-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**5**)[7] using phosphorus oxychloride. Both **4** and **5** were used directly in the following step without purification. We were pleased to find that reaction of **5** with piperidine was completely selective, producing only the desired 7-benzyl-3-chloro-1-(piperidin-1-yl)-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**6**)[7] in 49% yield over two steps after purification by recrystallization. The structure of **6** was confirmed by an NOE experiment. Treatment of **6** with hydrazine monohydrate in ethanol provided 7-benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*][2,7]naphthyridin-1-ylamine



Scheme 1. Reagents and conditions: (a) (i) aqueous $NaHCO_3$, CH_2Cl_2; (ii) $NCCH_2CONH_2$, KOH, MeOH, reflux, 71%; (b) $POCl_3$, sealed tube, 180 °C; (c) piperidine, Et_3N, DMF, rt, 49% from **4**; (d) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 92%.

(**2**)[7] in 92% yield, purified by trituration with ethanol. The entire synthesis did not involve column chromatography, thus making it amenable to multi-gram scale preparation. The structure of **2** was confirmed by NOE experiments and other NMR experiments (HMBC, HSQC, COSY) to be identical to the structure of the hit from the HTS.

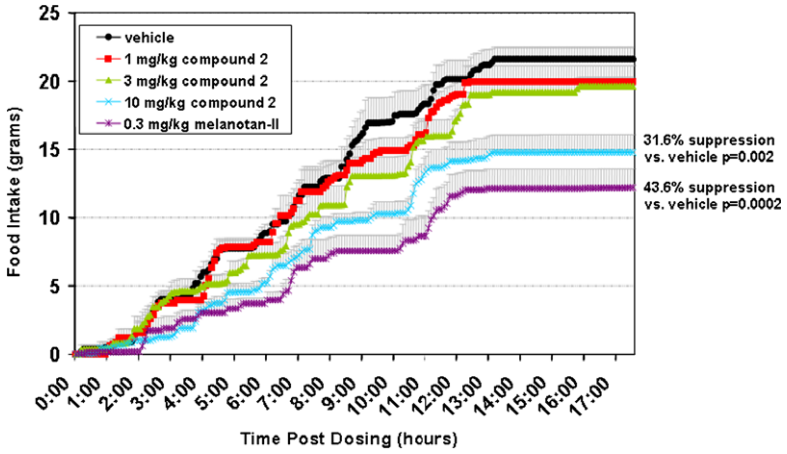


Figure 3. Food intake effects of **2** in DIO rats.

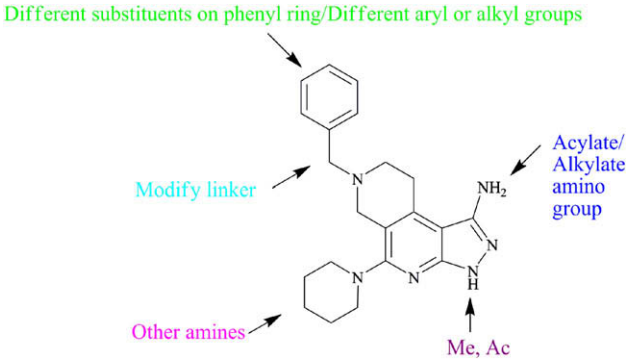
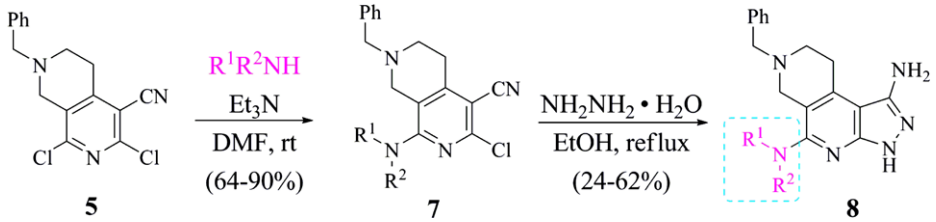


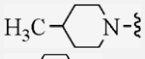
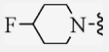
Figure 4. SAR strategy.

Compound **2** was confirmed in vitro for BRS-3 agonist functional potency in an aequorin bioluminescence assay:[2a] rEC_{50} = 380 nM (105% activation), hEC_{50} = 4525 nM (60% activation). These EC_{50} values were consistent with those obtained in the HTS. In a pharmacokinetic study in rats, compound **2** showed low bioavailability (F = 5.7%), short half life ($t_{1/2}$ = 0.73 h), and high clearance (Cl = 45 mL/min/kg). Compound **2** achieved good brain/plasma ratios and respectable brain drug level in rats (1 mg/kg IV) which was important due to the predominant location of BRS-3 receptors in the central nervous system:[8] 4.4 at 0.25 h (1.21 μM total concentration in brain), 3.2 at 1 h (0.39 μM total concentration in brain), 3.4 at 2 h (0.14 μM total concentration in brain). In an efficacy study, significant acute food intake effect of compound **2** (31.6% suppression vs vehicle) was observed in diet-induced obese rats at 10 mg/kg IV, using melanotan-II[9] as the positive control (Fig. 3).

Table 1
SAR results at 5-position in **2**



5 7 8

ID	R^1R^2N	Rat functional EC_{50} (nM) (%activation)	Human functional EC_{50} (nM) (%activation)
2		380 (105%)	4525 (60%)
8a		965 (99%)	10,000 (12%)
8b		1442 (100%)	10,000 (9%)
8c		10,000 (51%)	10,000 (3.7%)
8d		854 (96%)	10,000 (6.8%)
8e		481 (96%)	10,000 (10%)

(*continued on next page*)

Table 1 (*continued*)

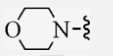
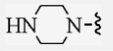
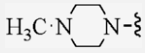
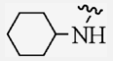
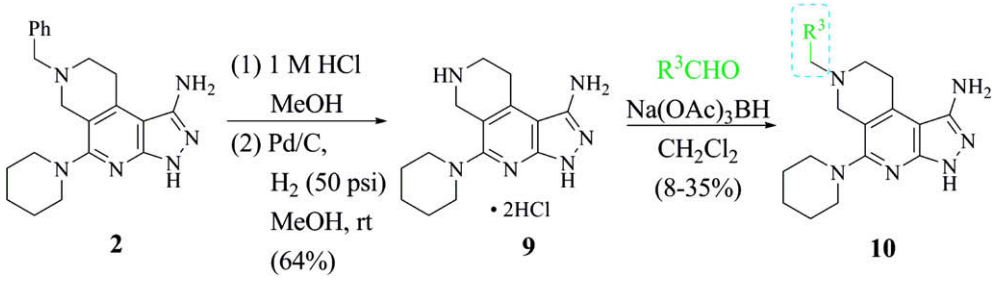
ID	R^1R^2N	Rat functional EC_{50} (nM) (%activation)	Human functional EC_{50} (nM) (%activation)
8f		3557 (82%)	10,000 (1.3%)
8g		10,000 (31%)	10,000 (0.1%)
8h		10,000 (21%)	10,000 (0.2%)
8i	$(CH_3)_2N$–	8954 (59%)	10,000 (0.9%)
8j	*i*-PrNH–	7652 (55%)	10,000 (1.8%)
8k		10,000 (50%)	10,000 (1%)
8l	PhNH–	10,000 (60%)	10,000 (1.5%)

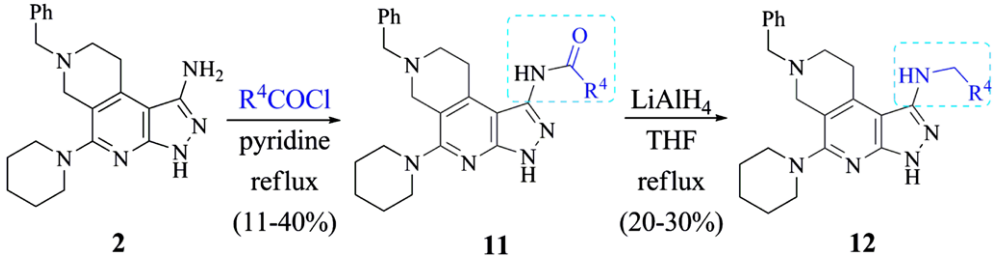
Table 2
SAR results at 7-position in **2**



ID	R^3	Rat functional EC_{50} (nM) (%activation)	Human functional EC_{50} (nM) (%activation)
2	Ph	380 (105%)	4525 (60%)
9[7]	H*	>10,000 (15%)	>10,000 (0.3%)
10a[7]	2-Pyridyl	346 (94%)	6779 (46%)
10b	2-Cl-Ph	342 (121%)	5567 (67%)
10c	4-F-Ph	3859 (64%)	10,000 (1.7%)
10d	4-MeO-Ph	10,000 (8%)	10,000 (0.55%)
10e	3-CF_3-Ph	10,000 (38%)	10,000 (0.3%)
10f	Piperonyl	402 (94%)	10,000 (1.6%)
10g	Cyclohexyl	10,000 (49%)	10,000 (12%)
10i	*i*-Pr	10,000 (61%)	10,000 (10%)
10j	*t*-Bu	1057 (91%)	10,000 (22%)
10k	$PhCH_2$	7906 (51%)	10,000 (3.3%)
10l[7]	4-F-Benzoyl*	>10,000	>10,000

* Directly attached to the 7-nitrogen in compound **10**.

Table 3
SAR results at 1-amino in **2**



ID	R^4	Rat functional EC_{50} (nM) (%activation)	Human functional EC_{50} (nM) (%activation)
2		380 (105%)	4525 (60%)
11a	CH_3–	129 (94%)	3164 (31%)
11b	CH_3CH_2–	123 (103%)	3474 (19%)
11c	$(CH_3)_2CH$–	99 (102%)	4763 (37%)
11d	$(CH_3)_3C$–	63 (105%)	1542 (37%)
11e[7]	$(CH_3)_3CCH_2$–	433 (93%)	1234 (52%)
11f	Cyclopentyl	413 (99%)	704 (61%)
11g	$CH_3CH_2C(CH_3)_2$–	212 (96%)	543 (78%)
12a	CH_3–	471 (105%)	10,000 (53%)
12b	$(CH_3)_3C$–	680 (94%)	4149 (29%)

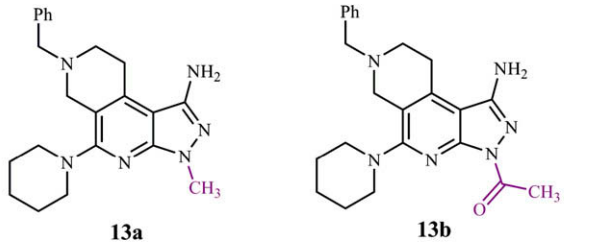


Figure 5. SAR results at 3-position in **2**.

The newly established synthetic route provided access to key analogs of **2** for SAR study in hit-to-lead efforts. Figure 4 outlines the SAR strategy on compound **2** aiming to improve potency and pharmacokinetics while maintaining a favorable brain/plasma ratio.

Selective replacement of the 1-chloro group in versatile intermediate **5** with various amines followed by reaction with hydrazine provided analogs **8**. These compounds showed tight SAR as even minor changes resulted in decrease of potency (Table 1).

The benzyl group in **2** was successfully removed by hydrogenation to provide **9**. Installation of different groups on the naphthyridine nitrogen in **10** was achieved by either selective reductive alkylation of **9** with aldehydes or acylation.[10,11] Table 2 summarizes the SAR of modifying the 7-position of compound **2**. While minor modification like 2-picolyl (**10a**), 2-chlorobenzyl (**10b**) and piperonyl (**10f**) retained activities against BRS-3 receptor, other modifications caused loss of potency. Modification at the linker decreased potency (compounds **10k** and **10l**).

The amino group in **2** could be acylated to give amides **11**. Reduction with lithium aluminum hydride provided analogs **12**, which had various alkyl groups attached to the amino nitrogen. Moderate improvement in potency (2- to 6-fold) was observed in amides **11**, while potency was retained in alkylated analogs **12** (Table 3).

Two 3-substituted analogs **13a** and **13b** were prepared.[12] Neither compound showed improvement in potency (Fig. 5).

In summary, the revision of the original structure assignment of compound **2** demonstrated the importance of structure confirmation in the hit-to-lead process. A concise synthesis of 7-benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*][2,7]naphthyridin-1-ylamine (**2**) in gram quantity was achieved in four steps with 32% overall yield starting from commercially available materials. Preliminary SAR work at the 1-, 3-, 5- and 7-positions of **2** showed a generally tight SAR with only limited improvement in potency against BRS-3 receptor. Priority for further development was thus given to other more promising hits within the program.[2]

Acknowledgment

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6. Miyamoto, T.; Egawa, H.; Matsumoto, J.-I. *Chem. Pharm. Bull.* **1987**, *35*, 2280.
7. *Analytical data for representative compounds*:
7-Benzyl-1,3-dioxo-1,2,3,4,5,6,7,8-octahydro-2,7-naphthyridine-4-carbonitrile (**4**): A light yellow solid: mp 258–260 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.95 (s, 1H), 9.71 (br s, 1H), 7.51–7.47 (m, 5H), 4.48–4.34 (m, 2H), 3.83 (d, 1H, J = 14.4 Hz), 3.63–3.56 (m, 2H), 3.24 (m, 1H), 2.71 (m. 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.8, 162.6, 146.0, 131.1, 129.9, 129.6, 129.0, 120.6, 96.7, 73.5, 58.5, 48.4, 48.0, 24.6; MS (ESI): m/z 282 (M+H)$^+$.
7-Benzyl-1,3-dichloro-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**5**): An off-white solid: mp 220–223 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.58–7.31 (m, 5H), 4.30 (s, 2H), 4.11 (s, 2H), 3.30 (t, 2H, J = 5.2 Hz), 3.20 (t, 2H, J = 5.2 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.3, 150.3, 149.2, 131.1, 129.5, 128.9, 125.1, 113.0, 109.1, 57.8, 56.0, 48.1, 45.5, 25.2; MS (ESI): m/z 318 (M+H, 2 × ^{35}Cl)$^+$, 320 (M+H, ^{35}Cl + ^{37}Cl)$^+$, 322 (M+H, 2 × ^{37}Cl)$^+$.
7-Benzyl-3-chloro-1-(piperidin-1-yl)-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**6**): An off-white solid: mp 120–122 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.34–7.27 (m, 5H), 3.66 (s, 2H), 3.31 (s, 2H), 3.22 (s, 4H), 2.89 (t, 2H, J = 5.8 Hz,), 2.74 (t, 2H, J = 5.8 Hz), 1.50 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.0, 150.6, 149.5, 137.5, 129.3, 128.7, 127.7, 119.3, 115.5, 100.6, 62.6, 53.6, 50.3, 49.3, 29.1, 26.1, 24.5; MS (ESI): m/z 367(M+H, ^{35}Cl)$^+$, 369 (M+H, ^{37}Cl)$^+$; HPLC t_R = 14.3 min, >99% (area percent).
7-Benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-ylamine (**2**): A white solid: mp 219–222 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.51 (s, 1H), 7.39–7.30 (m, 4H), 7.30–7.23 (m, 1H), 4.86 (s, 2H), 3.65 (s, 2H), 3.39 (s, 2H), 3.16 (t, 2H, J = 5.6 Hz), 2.94 (s, 4H), 2.71 (t, 2H, J = 5.9 Hz), 1.51 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.3, 150.8, 148.3, 140.2, 138.3, 129.6, 128.6, 127.5, 114.5, 100.8, 62.2, 52.8, 51.3, 49.8, 26.6, 26.0, 24.4; MS (ESI): m/z 363 (M+H)$^+$; HPLC t_R = 11.7 min, >99% (area percent).
5-(Piperidin-1-yl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-ylamine (**9**): A light yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.14 (br s, 2H), 4.16–4.14 (m, 4H), 3.43–3.40 (m, 4H), 3.06-3.04 (m, 4H), 1.67–1.63 (m, 6H); ^{13}C NMR (D_2O, 125 MHz) δ 159.6, 148.0, 146.5, 144.6, 108.8, 98.0, 66.6, 51.1, 42.6, 40.0, 25.3, 23.4, 23.3; MS (ESI): m/z 273 (M+H)$^+$; HPLC t_R = 6.5 min, 98.3% (area percent).
5-(Piperidin-1-yl)-7-(pyridin-2-ylmethyl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-amine hydrochloride (**10a**): A yellow solid: mp 228–230 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.55 (br s, 1H), 11.00 (br s, 1H), 8.70 (dd, J = 4.7, 0.7 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.54–7.50 (m, 1H), 4.63 (s, 2H), 4.29 (s, 2H), 3.69–3.67 (m, 2H), 3.60–3.58 (m, 2H), 3.16 (s, 2H), 2.98 (br s, 4H), 1.54 (br s, 6H); ^{13}C NMR ($CDCl_3$/CD_3OD, 125 MHz) δ 165.1, 153.2, 150.7, 150.6, 148.2, 140.7, 139.3, 125.8, 125.6, 111.2, 98.0, 59.9, 51.8, 49.8, 49.7, 26.7, 25.1, 24.6; MS (ESI): m/z 364 (M+H)$^+$; HPLC t_R = 8.2 min, >99% (area percent).
7-(4-Fluorobenzoyl)-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-ylamine (**10l**): An off-white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.70 (s, 1H), 7.51–7.46 (m, 2H), 7.33–7.26 (m, 2H), 5.01 (br s, 2H), 4.69–4.46 (m, 2H), 4.11 (br s, 2H), 3.88–3.62 (m, 2H), 3.06–2.82 (m, 4H), 1.69–1.37 (m, 6H); MS (ESI): m/z 395 (M+H)$^+$; HPLC t_R = 11.7 min, 98.6% (area percent).
N-(7-Benzyl-5-(piperidin-1-yl)-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c][2,7]naphthyridin-1-yl)-3,3-dimethylbutanamide (**11e**): An off-white solid: mp 263–265 °C (dec.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.85 (s, 1H), 9.72 (s, 1H), 7.38–7.25 (m, 5H), 3.65 (s, 2H), 3.41–3.39 (m, 2H), 3.04–2.99 (m, 6H), 2.71–2.69 (m, 2H), 2.20 (s, 2H), 1.53 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.9, 163.6, 140.6, 138.4, 131.0, 130.6, 129.5, 128.7, 118.9, 106.8, 63.6, 54.0, 52.5, 50.8, 50.4, 32.1, 30.4, 27.3, 27.0, 25.7; MS (ESI): m/z 461 (M+H)$^+$; HPLC t_R = 12.9 min, >99% (area percent).
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12. Compound **13a** was prepared by refluxing of **6** with methylhydrazine in ethanol. Compound **13b** was prepared by acylation of the 3-nitrogen in **2** using acetyl chloride and triethylamine in dichloromethane at 0 °C.