

Microwave-enhanced synthesis of 2,3,6-trisubstituted pyridazines: application to four-step synthesis of gabazine (SR-95531)[†]

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Microwave-enhanced, highly efficient protocols for the synthesis of synthetically and biologically important 2,3,6-trisubstituted pyridazine architectures have been developed by sequential amination/Suzuki coupling/alkylation reactions. This powerful strategy is an economical and highly chemoselective protocol for the synthesis of diversified pyridazines. The total synthesis of gabazine (SR-95531) has been achieved using a versatile strategy in four steps and 73% overall yield.

Introduction

The nitrogen containing heterocycle pyridazine¹ and its myriad of derivatives continue to attract significant attention in the pharmaceutical industry in the quest for new drugs. The 3-aminopyridazine pharmacophore has proven particularly interesting from a pharmacological point of view.^{2–7} For example, Minaprine (Cantor) is an antidepressant drug which acts as a short-acting monoamine oxidase (MAO) inhibitor.² The various Minaprine analogues and their metabolites act as cholinergic, dopaminergic, and serotonergic ligands as well as MAO and acetylcholinesterase inhibitors.^{2,3} Various 3-aminopyridazine derivatives which are extended analogues of γ -aminobutyric acid (GABA) act as competitive GABA_A receptor antagonists.⁴ Specifically, gabazine (SR-95531)⁵ has shows high specificity and potency towards both GABA_A and GABA_C receptors.⁶

There are few approaches for the construction of 3-amino-6-arylpyridazines.^{3b,5b,7a,8,9,13} Generally, the construction of 3-amino-6-arylpyridazines involves synthesis of the pyridazinone core based on the condensation of acetophenones with 1,4-dicarbonyl compounds in the presence of hydrazine,¹⁰ chlorination of pyridazinones with POCl₃,^{2e,3b,3e,11} followed by amination using ammonia or hydrazine.^{5b,8a} Moreover, there are also a few reports of palladium-catalyzed Suzuki cross-coupling reactions¹² on 3-amino-6-chloropyridazine moieties.^{7a,9} Recently, Favi *et al.* described a novel synthesis of diversely functionalized pyridazines from 4-chloro-1,2-diaza-1,3-butadienes by the Michael-type addition of active methylene compounds.¹³ Most approaches to the synthesis of diversified pyridazines have several disadvantages, including limited availability of suitable substrates, harsh reaction conditions, a high number of steps, inconvenient operations, time-consuming experimental procedures, use of toxic chemicals, lack of atom economy and poor yields. During the course of our ongoing research on the development of bioactive 3-aminopyridazine analogues, we found that diversified pyridazines can be efficiently

prepared by microwave-promoted sequential selective amination/Suzuki coupling/selective N(2)-alkylation reactions.

Microwave-assisted organic synthesis has demonstrated itself to be superior in many instances as compared to conventional heating reactions.¹⁴ We were interested in developing a general, efficient and an inexpensive approach to unsymmetrical 2,3,6-trisubstituted pyridazines. The synthesis of diversified 2,3,6-trisubstituted pyridazines were achieved from 3,6-dichloropyridazine through a sequence of reactions: selective amination of the 3,6-dichloropyridazine using aq. ammonium hydroxide, Suzuki coupling reaction of 3-amino-6-chloropyridazine with various boronic acids, followed by a selective N-alkylation at N(2) to introduce the third diversity point to furnish the corresponding 2,3,6-trisubstituted pyridazines (Fig. 1).

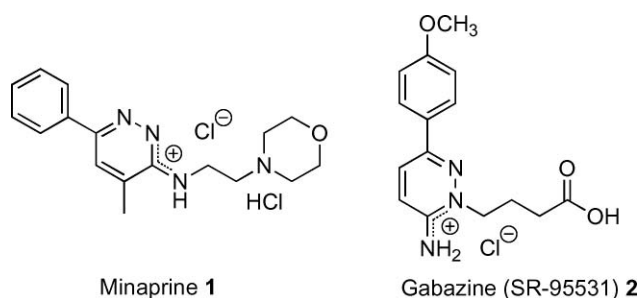


Fig. 1 Potential pharmaceutically important 3-aminopyridazine derivatives: minaprine 1 and gabazine 2.

Results and discussion

The initial step of the synthesis involved the monoamination of 3,6-dichloropyridazine using 28–30% aq. ammonium hydroxide as the source for the amine functionality of 3-amino-6-chloropyridazine under microwave irradiation (Scheme 1). The amination proceeded rapidly and in good yield compared to traditional procedures,^{7a,15} providing an efficient synthesis of 3-amino-6-chloropyridazine.

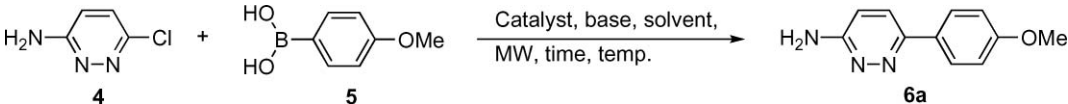
There have been a few reports on the synthesis of 3-amino-6-arylpyridazines using Suzuki coupling reactions^{7a,9} but the major drawbacks to this procedure are poor yields and/or long reaction times. For the purpose of optimization of the Suzuki coupling, we chose as a model reaction coupling between unprotected 3-amino-6-chloropyridazine with 4-methoxy phenylboronic acid (Table 1).

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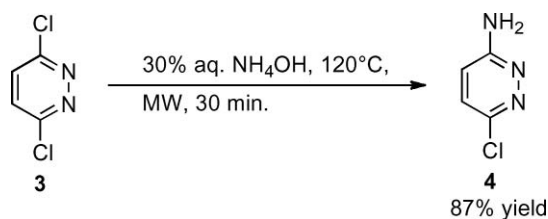
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Table 1 Optimization of microwave-enhanced Suzuki coupling of 3-amino-6-chloropyridazine with 4-methoxy phenylboronic acid^a

								
Entry	Catalyst	Mol (%)	Base	PTC ^b	Solvent	Time/min	T/°C	Conversion (%) ^c
1	Pd(PPh ₃) ₄	5	K ₂ CO ₃		Water	10	150	5
2	Pd(PPh ₃) ₄	5	K ₂ CO ₃	TBAB (100 mol%)	Water	10	150	69
3	Pd(PPh ₃) ₄	5	K ₂ CO ₃	SLS (20 mol%)	Water	10	150	36
4	Pd(PPh ₃) ₄	5	K ₂ CO ₃	SLS (100 mol%)	Water	10	150	74
5	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH	10	100	70
6	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH	10	120	98
7	Pd(PPh ₃) ₄	5	K ₂ CO ₃		toluene	10	120	77
8	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH–water (1 : 1)	10	120	80
9	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	100 (94) ^d
10	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH–water (4 : 1)	5	120	92
11	Pd(PPh ₃) ₄	3	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	82
12	Pd(PPh ₃) ₄	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	100	80
13	Pd(PPh ₃) ₄	5	K ₂ CO ₃		Toluene–water (4 : 1)	10	120	87
14	Pd(PPh ₃) ₄	5	K ₂ CO ₃		DME–water (4 : 1)	10	120	85
15	Pd(PPh ₃) ₄	5	K ₂ CO ₃		ACN–water (4 : 1)	10	120	83
16	Pd(PPh ₃) ₄	5	K ₂ CO ₃		Dioxane–water (4 : 1)	10	120	90
17	Pd(PPh ₃) ₄	5	K ₂ CO ₃		DMF–water (4 : 1)	10	120	89
18	Pd(PPh ₃) ₄	5	K ₂ CO ₃		[BMIM]BF ₄	10	120	12
19	Pd(OAc) ₂	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	2
20	PdCl ₂	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	4
21	10% Pd/C	10	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	0
22	Pd ₂ (dba) ₃	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	0
23	Pd(OAc) ₂ /dppp (1 : 1)	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	76
24	PdCl ₂ /PPh ₃ (1 : 1)	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	98
25	Pd ₂ (dba) ₃ /tfp (1 : 1)	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	5
26	NiCl ₂ (dppp)	5	K ₂ CO ₃		EtOH–water (4 : 1)	10	120	0
27	Pd(PPh ₃) ₄	5	Na ₂ CO ₃		EtOH–water (4 : 1)	10	120	90
28	Pd(PPh ₃) ₄	5	KF		EtOH–water (4 : 1)	10	120	86
29	Pd(PPh ₃) ₄	5	KOH		EtOH–water (4 : 1)	10	120	73
30	Pd(PPh ₃) ₄	5	K ₃ PO ₄		EtOH–water (4 : 1)	10	120	88
31	Pd(PPh ₃) ₄	5	Cs ₂ CO ₃		EtOH–water (4 : 1)	10	120	93

^a General reaction conditions: 3-amino-6-chloropyridazine **4** (0.5 mmol), 4-methoxy phenylboronic acid **5** (1.2 equiv), catalyst (3–10 mol%), base (1.5 equiv), solvents (2 mL) and microwave irradiation at the given time, temperature using power 300 W. ^b Phase transfer catalyst. ^c GC-MS conversion based on comparison of starting material and product peak intensities. ^d The figure in parentheses is the isolated yield based upon an average of three reactions.

**Scheme 1** Selective mono-amination of 3,6-dichloropyridazine under microwave irradiation.

Due to environmental, economic and safety concerns, we screened water as a solvent for the Suzuki coupling. Unfortunately the transformation did not proceed, most likely due to poor substrate solubility in water (entry 1). In addition, we found that when water was used as a solvent with the addition of one equivalent of phase transfer catalyst (TBAB, tetrabutylammonium bromide or SDS, sodium dodecyl sulfate) to the reaction mixture it moderately facilitated the reaction but required higher temperatures and longer times to complete the coupling reaction (entries 2–4). However, an appropriately chosen solvent and co-solvent facilitated

the reaction, with the ratio of solvent to co-solvent determining the progress of the reaction. For example, the cross-coupling yield increased to 100% (GC-MS conversion yield) in ethanol and water (4 : 1) (entry 9) as compared to other solvent systems. Meanwhile, a one to one volumetric ratio of ethanol–water made the cross-coupling reaction sluggish (entry 8). Although ionic liquids have been used for cross-coupling reactions, surprisingly, [BMIM]BF₄ did not work in this reaction (entry 18). Among the catalysts tested, Pd(PPh₃)₄ was the most effective (entry 9). PdCl₂/PPh₃ and Pd(OAc)₂/dppp were also effective; however, Pd(OAc)₂, PdCl₂, Pd/C, Pd₂(dba)₃, Pd₂(dba)₃/tfp and NiCl₂(dppp) were inactive as catalysts in this case. An investigation of the influence of the base suggested that K₂CO₃ was the base of choice. Other bases such as Na₂CO₃, KF, KOH, K₃PO₄ and Cs₂CO₃ also led to moderate to good yields (entries 27–31). We have screened various catalysts, solvents, bases and microwave irradiation conditions (temperature and time) to optimize the Suzuki coupling reaction of unprotected 3-amino-6-chloropyridazine with 4-methoxy phenylboronic acid. Finally, we found that reaction of 3-amino-6-chloropyridazine (1.0 equiv), arylboronic acid (1.2 equiv), K₂CO₃ (1.5 equiv), and 5 mol% Pd(PPh₃)₄ in ethanol–water (4 : 1, 2 mL) under microwave

Table 2 Suzuki coupling of 3-amino-6-chloropyridazine with diversified boronic acids under microwave irradiation^a

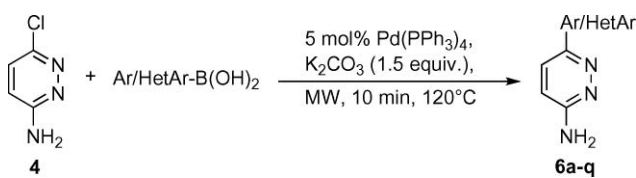
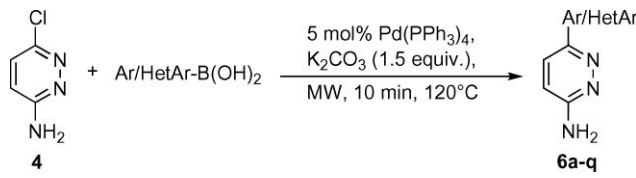
			
Entry	Ar/HetAr-B(OH) ₂	Product (6a–q)	Yield (%) ^b
a			94
b			88
c			95
d			86
e			90
f			92
g			88
h			92
i			84
j			82
k			92
l			90
m			86
n			91
o			87

Table 2 (Cont.)

			
Entry	Ar/HetAr-B(OH) ₂	Product (6a–q)	Yield (%) ^b
p			79
q			75

^a Reaction conditions: 3-amino-6-chloropyridazine **4** (1 mmol), aryl/heteroaryl boronic acid (1.2 equiv), Pd(PPh₃)₄ (5 mol%), K₂CO₃ (1.5 equiv), EtOH–H₂O (4:1, 2 mL) and microwave irradiation for 10 min at 120 °C using power 300 W. ^b Yields of the isolated products.

irradiation (CEM Discover S-Class microwave reactor: equipped with single mode reactor and fiber optic temperature control; method: dynamic mode at power 300 W) at 120 °C with stirring for 10 min gave the best result (**6a** in 100% GC-MS conversion and 94% isolated yield, entry 9).

As shown in Table 2, we utilized different boronic acids to synthesize the corresponding 3-amino-6-arylpyridazines under the optimized conditions. We were pleased to observe excellent reactivity for a variety of electron-deficient (entries b–f and p), electron-rich (entries a, g, j, k–m and q) and sterically hindered arylboronic acids (entries h–j), as well as heteroaromatic boronic acids (entries m–o) with yields being uniformly good to excellent. For more challenging electronically unactivated and deactivated arylboronic acids, the corresponding coupling products were obtained in good to excellent yields (For example, entries a and h–j). Also, a good yield (75%) was obtained for the coupling reaction with unprotected 4-amino phenylboronic acid (entry q). Chloro and amino substituents on the boronic acid and amino substituent on the pyridazine ring were well tolerated under the reaction conditions, which could extend the scope for further functionalization of the pyridazine ring. Therefore, these results reveal the broad substrate scope and high efficiency of microwave-assisted protocol for the Suzuki coupling of unprotected 3-amino-6-chloropyridazine, which are better than those reported to date with conventional heating.

The alkylation of the *endo* amidinic system of 3-amino-6-arylpyridazines with alkyl halides^{4f,5a,b} (Table 3) using microwave irradiation was also explored. Under solvent and catalyst free conditions, we obtained exclusively N(2)-alkylated 3-amino-6-(4'-methoxyphenyl)pyridazine. We found excellent reactivity for alkyl halides bearing esters, phosphinates and nitriles with reactions proceeding rapidly in uniformly good to excellent yields. Interestingly, we also observed selective N(2) alkylation of 3-amino-6-(4'-methoxyphenyl)pyridazine with 3-bromo-1-propanol without protecting hydroxy group (entry h). The selective N(2) alkylations were confirmed by IR and NMR. Selective N(2) alkylation of 3-amino-6-(4'-methoxyphenyl)pyridazine is thought to be due to both steric effects of the phenyl ring and the electron-attracting effect of the phenyl ring at the 6-position which makes the N(1)

Table 3 Selective N(2)-alkylation of 3-amino-6-(4'-methoxyphenyl) pyridazine under microwave irradiation^a

Entry	R ¹ -X	Product (7a-h)	Yield (%) ^b
a		R ¹ = (CH ₂) ₃ COOEt; X=Cl, (7a)	84
b		R ¹ = (CH ₂) ₃ COOEt; X=Br, (7b)	95
c		R ¹ = (CH ₂) ₂ COOEt; X=Br, (7c)	93
d		R ¹ = (CH ₂) ₄ COOEt; X=Br, (7d)	96
e		R ¹ = (CH ₂) ₃ PO(OEt) ₂ ; X=Br, (7e)	90
f		R ¹ = (CH ₂) ₃ CN; X=Br, (7f)	84 (92) ^c
g		R ¹ = (CH ₂) ₄ ; X=Br, (7g)	93
h		R ¹ = (CH ₂) ₃ OH; X=Br, (7h)	52 ^d

^a Reaction conditions: 3-amino-6-(4'-methoxyphenyl)pyridazine **6a** (1 mmol), alkyl halide (1.2 equiv) and microwave irradiation for 15 min at 80 °C using power 300 W. ^b Yields of the isolated products. ^c The reaction was carried out in the presence of 0.1 mL DMF. ^d The reaction was carried out for 1 h in the presence of 0.1 mL DMF.

nitrogen less nucleophilic.^{5b} The solvent-free, metal-free, non-hazardous experimental condition, short reaction times, ease of product isolation/purification and high yields fulfilled the triple bottom-line philosophy of green chemistry and made the present methodology environmentally benign.

We demonstrated the synthetic utility of the powerful strategy for the four-step synthesis of neuroactive gabazine (SR-95531) **2**. An efficient and inexpensive total synthesis of gabazine **2** was achieved using the versatile strategy in four steps and 73% overall yield (Scheme 2). To date, there is only one report by Wermuth *et al.* (1987),^{5b} which describes a seven-step conventional strategy for the preparation of gabazine **2** which involves the synthesis of the pyridazinone intermediate.

Conclusions

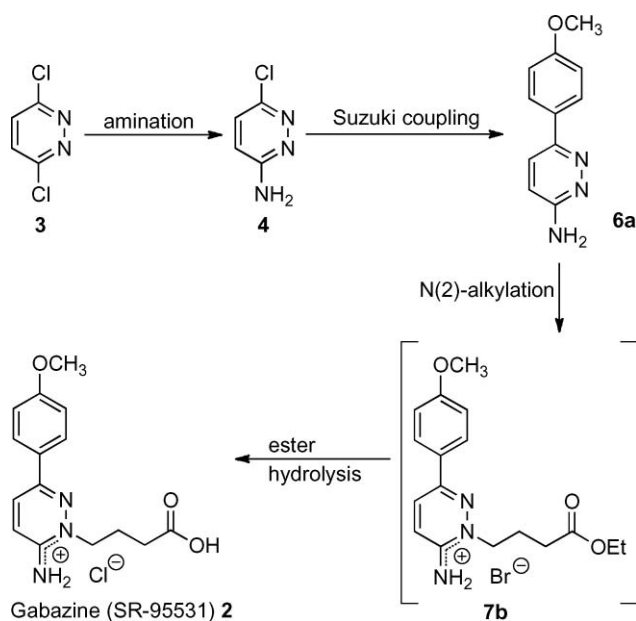
In conclusion, we have successfully developed an efficient and versatile protocol for the synthesis of diversified 2,3,6-trisubstituted pyridazines under microwave irradiation. The synthesis of synthetically and biologically important 2,3,6-trisubstituted pyridazine architectures have been developed by sequential selective amination/Suzuki coupling/selective N(2) alkylation reactions. Furthermore, The significance of the approach is demonstrated by synthesizing neuroactive gabazine **2** in four steps and in high yield. Finally, these aminopyridazine frameworks can provide a

useful scaffold for the synthesis of novel gabazine analogues with demonstrated biological activity at GABA receptors.

Experimental section

General details

All glass apparatus were oven dried prior to use. All chemicals used were purchased from Aldrich Chemical Co. Ltd. (St Louis, MO), Boron Molecular Inc. (NC, USA) and were of highest commercially available purity. All solvents were distilled by standard techniques prior to use. Where stated, reactions were performed under an inert atmosphere of nitrogen. Melting points were measured on a Stuart SMP10 (UK) melting point apparatus. ¹H NMR spectra were recorded at 400 MHz using a Varian (Palo Alto, CA) Gemini 400 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), referenced externally to tetramethylsilane at 0 ppm. ¹³C NMR spectra were recorded at 100 MHz using a Varian (USA) 400 MI spectrometer. Chemical shifts (δ) are quoted in ppm, referenced internally to CDCl₃ at 77.0 ppm. All coupling constants (*J*) are given in Hertz. Low Resolution Mass Spectra (LRMS) was carried out using a Bruker (USA) Daltronics BioApexII with a 7T superconducting magnet and an analytical ESI source. High Resolution Mass Spectra (HRMS) were obtained by the Mass Spectrometry Unit at the School of Chemistry, The University of Sydney, on a



Scheme 2 Total synthesis of gabazine (SR-95531) **2**.

Bruker 7T Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. GCMS was performed on a PolarisQ GC-MS-MS ion trap mass spectrometer coupled to a Trace GC and automated injections were performed on an AS2000 Autosampler. Thin layer chromatography was performed on Merck aluminium backed plates, precoated with silica (0.2 mm, 60F₂₅₄), which were developed using one of the following techniques: UV fluorescence (254 nm), alkaline potassium permanganate solution (0.5% w/v) or ninhydrin (0.2% w/v) and Iodine vapors. Flash chromatography was performed on silica gel (Merck silica gel 60H, particle size 5–40 µm).

Microwave details

All microwave irradiation reactions were conducted by using CEM Discover S-Class microwave reactor (single mode reactor, method: dynamic mode at power 300 W). The microwave reactor is equipped with fiber optic temperature control.

Synthesis of 3-amino-6-chloropyridazine (4)

To a thick-wall borosilicate glass vial (30 mL) were added 3,6-dichloropyridazine **3** (1.5 g) and NH₄OH solution (5 mL; NH₃ content: 28 to 30%). The vial was sealed with a lid and placed in the microwave reactor for 30 min at 120 °C (power: 300 W). After cooling down, the precipitate that deposited was filtered off, washed with ethyl acetate–hexane (3:7), dried to give as a light yellowish-white solid of 3-amino-6-chloropyridazine **4** (87% yield, require no further purification). mp 229–232 °C. ¹H NMR (400 MHz, DMSO): δ 7.35 (d, 1H, *J* = 9.2 Hz), 6.83 (d, 1H, *J* = 9.2 Hz), 6.59 (s, 2H). ¹³C NMR (100 MHz, DMSO): δ 160.76, 145.45, 129.43, 117.99. MS (ESI) *m/z* = 130.46 [*M* + 1]. HRMS (ESI) calcd for C₄H₄N₃Cl [*M*⁺] 129.5477, found 129.5662.

Representative procedure for the synthesis of 6a–q: 3-amino-6-(4'-methoxyphenyl)pyridazine (6a)^{9c}

To a thick-wall borosilicate glass vial (10 mL) were added 3-amino-6-chloropyridazine **4** (129 mg, 1 equiv.), K₂CO₃ (206 mg, 1.5 equiv.), 4-methoxy phenylboronic acid **5** (181 mg, 1.2 equiv.), Pd(PPh₃)₄ (57 mg, 5 mol%) and ethanol–water (4:1, 2 mL). The mixture was degassed with nitrogen for 5 min and then vial was sealed with a lid. The reaction mixture was pre-stirred for 1 min to ensure sufficient mixing of the reagents. The reaction mixture was irradiated at 120 °C for 10 min at the maximum power of 300 W. The reaction mixture is filtered and extracted with ethyl acetate (the product can also be purified without extraction by flash chromatography: the reaction mixture is dried under reduced pressure and crude mixture is directly loaded on flash chromatography for purification). The collected organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography [EtOAc–MeOH (98:2)/TFA 2%] to furnish 3-amino-6-(4'-methoxyphenyl)pyridazine **6a** (white solid, 94%). mp 195–198 °C. ¹H NMR (400 MHz, DMSO): δ 7.88 (d, 2H, *J* = 8.8 Hz), 7.73 (d, 1H, *J* = 9.2 Hz), 7.00 (d, 2H, *J* = 8.8 Hz), 6.81 (d, 1H, *J* = 9.2 Hz), 6.34 (s, 2H), 3.78 (s, 3H). MS (ESI) *m/z* = 202.33 [*M* + 1]. HRMS (ESI) calcd for C₁₁H₁₁N₃O [*M*⁺] 201.0902, found 201.0904.

Representative procedure for the synthesis of 7a–h: ethyl-4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl]butanoic acid hydrobromide (7b)

To a thick-wall borosilicate glass vial (10 mL) were added 3-amino-6-(4-methoxyphenyl)pyridazine **6a** (200 mg, 1 equiv.), ethyl 4-bromobutanoate (0.17 mL, 1.2 equiv.). The vial was sealed with a lid and then reaction mixture was pre-stirred for 1 min to ensure sufficient mixing of the reagents. The reaction mixture was irradiated at 80 °C for 15 min at the maximum power of 300 W. The hot solution was poured with stirring into ethyl acetate (30 mL), affording a crystalline compound to give ethyl-4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl]butanoic acid hydrobromide **7b** (off-white solid, 95% yield). mp 239–242 °C. ¹H NMR (400 MHz, DMSO): δ 9.00 (brs, 2H), 8.38 (d, 1H, *J* = 9.2 Hz), 7.93 (d, 2H, *J* = 9.2 Hz), 7.62 (d, 1H, *J* = 9.6 Hz), 7.11 (d, 2H, *J* = 9.2 Hz), 4.35–4.31 (t, 2H, *J* = 6.8 Hz), 3.96–3.91 (q, 2H), 3.82 (s, 3H), 2.12–2.03 (m, 2H), 1.09–1.05 (t, 3H, *J* = 6.8 Hz). ¹³C NMR (100 MHz, DMSO): δ 172.64, 161.90, 152.48, 149.66, 131.47, 128.45, 126.22, 125.46, 115.10, 60.49, 55.94, 55.54, 30.57, 21.97, 14.42. MS (ESI) *m/z* = 317.27 [*M* + 1]; HRMS (ESI) calcd for C₁₇H₂₂N₃O₃ [*M* + Br] 316.1661, found 316.1655.

Synthesis of gabazine (SR-95531) **2**

To a solution of ethyl-4-[6-imino-3-(4-methoxyphenyl)pyridazin-1-yl]butanoic acid hydrobromide **7b** (500 mg) in water (1.5 mL) was added NaOH (208 mg) at room temperature. The resulting mixture was stirred for 2 h, maintaining 40–45 °C using conventional heating. After cooling to 10 °C, to the reaction mixture was added water (5 mL) and ethyl acetate (10 mL). The aqueous layer was separated, washed with ethyl acetate (2.5 mL) and treated with 17.5% hydrogen chloride in water to adjust the pH to 0.5–1.0 at 20–25 °C. The resulting mixture was further stirred at 0–5 °C for 1 h, and the precipitate was filtered off and washed with water.

(1 mL). Drying under reduced pressure afforded crude gabazine **2** (375 mg, 90% yield) of 95% purity as a light yellowish solid. The crude gabazine **2** (375 mg) was treated with carbon (15 mg) in a mixture of 2-propanol (2 mL) and water (1 mL) at 80 °C. The filtrate was cooled to 0 °C, and the precipitate was filtered off and washed with a mixture of 2-propanol (0.5 mL) and water (0.3 mL), and successively water (0.5 mL). Drying under reduced pressure afforded purified gabazine **2** (347 mg, 85% yield) of 100% purity as a white solid. mp 219–222 °C. ¹H NMR (400 MHz, DMSO): δ 12.25 (brs, 1H), 8.95 (brs, 2H), 8.37 (d, 1H, *J* = 9.6 Hz), 7.93 (d, 2H, *J* = 9.2 Hz), 7.58 (d, 1H, *J* = 9.6 Hz), 7.11 (d, 2H, *J* = 9.2 Hz), 4.33–4.29 (t, 2H, *J* = 6.8 Hz), 3.82 (s, 3H), 2.42–2.38 (t, 2H, *J* = 14.4 Hz), 2.09–2.02 (m, 2H). ¹³C NMR (100 MHz, DMSO): δ 174.18, 161.88, 152.48, 149.73, 131.51, 128.51, 126.18, 125.54, 115.10, 55.92, 55.54, 30.65, 22.14. MS (ESI) *m/z* = 288.07 [*M*⁺]; HRMS (ESI) calcd for C₁₅H₁₈N₃O₃ [*M*⁺ – Cl] 288.1348, found 288.1337.

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