Microwave-Assisted Solvent-Free Synthesis of Ipsapirone

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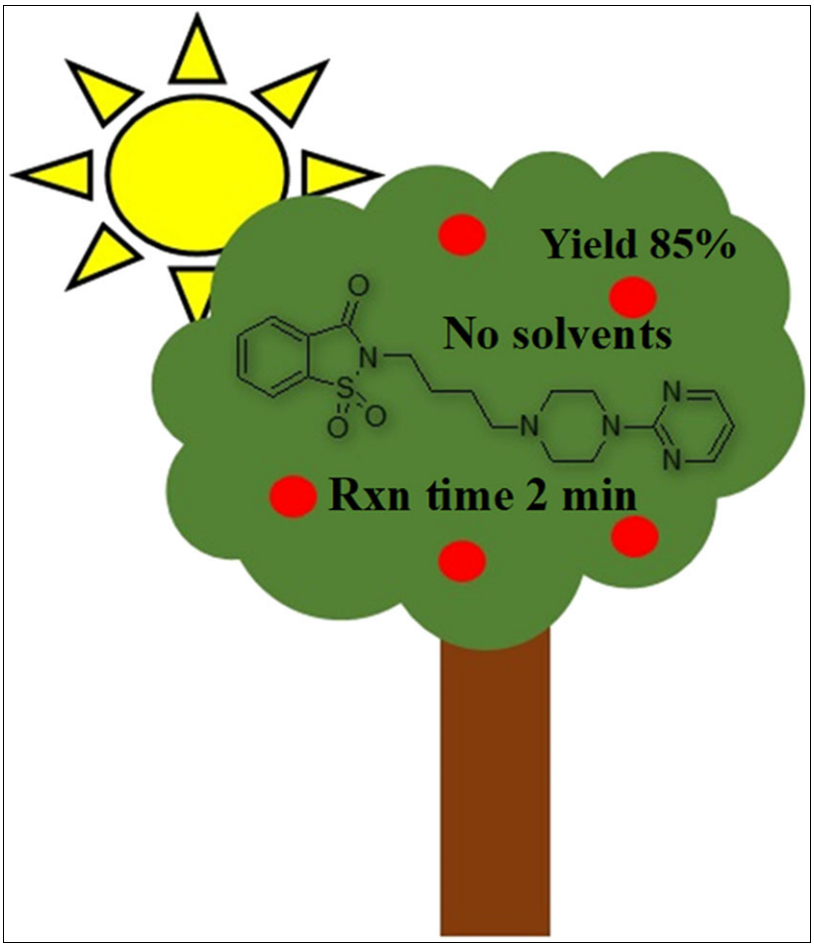


The currently applied synthetic methods of serotonin receptor ligands belonging to the group of long-chain arylpiperazines, including ipsapirone, require the use of toxic solvents and comprise numerous synthetic steps. Moreover, the reaction yield does not exceed 60% in the majority of cases. These factors lead to an increased energy consumption and negatively impact the environment. This paper describes a more environmentally friendly method of ipsapirone synthesis that we decided to use. Ipsapirone was obtained in two different methods. The first method involved *N*-alkylation of bromobutyl saccharin with 1-(2-pyrimidyl)piperazine dihydrochloride, while the second was a one-pot method. Neither of these requires the use of toxic and expensive solvents. A shortened synthesis time, not exceeding 10 min due to the use of microwave radiation, is also another advantage of these methods. The yield of the final product, ipsapirone, was 85% and 67% in the first and the second method, respectively. We also attempted to obtain ipsapirone using saccharin and arylpiperazine salt (method III) as starting materials, but to no avail in the tested conditions. As described herein, the green chemistry method for ipsapirone synthesis is rapid, cost-effective, and environment friendly.

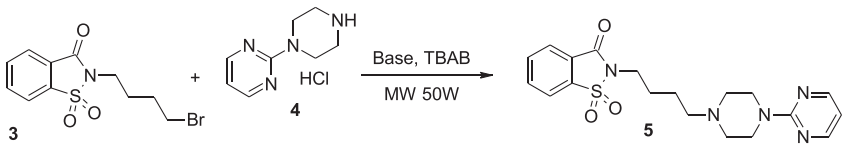
INTRODUCTION

According to reports by the World Health Organization [1], depression and diseases affecting the central nervous system (CNS) will be one of the main burdens hindering the functioning of the human population [2,3]. Modern methods of treatment for these conditions include using a wide range of medications acting on the CNS, but each of them can cause side effects, and as much as 30% of patients do not respond to treatment at all. One of the known compounds that can be used in the treatment of CNS diseases is ipsapirone, belonging to the class of azapirones [4]. Ipsapirone, 2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl) butyl)benzo[*d*]isothiazol-3(2*H*)-one1,1-dioxide, is a known ligand with anxiolytic, anti-depressive [3], and anti-aggressive effects, and a partial antagonist of the 5-HT_{1A} receptor [5]. It can also be used to treat alcohol dependence [6]. From a chemical point of view, the discussed compound is a long-chain arylpiperazine, composed of a pyrimidylpiperazine linked *via* a butyl moiety to saccharin. Ipsapirone synthesis has not been widely described in the literature and patents. One of several known methods of ipsapirone synthesis, claimed in a patent, consists of a four-step reaction [7]. Such synthesis, however, requires the use of toxic and expensive solvents such as dimethylformamide (DMF) or oxygenate-derived reagents, and the entire process is long, taking about 24 h. The total yield of ipsapirone is less than 40%. In turn, another patent reports that ipsapirone can be synthesized by an alkylation reaction of *N*-bromobutyl saccharin and 1-(2-pyrimidyl)piperazine dihydrochloride [6]. Similarly to the previous patent, the inventors use toxic DMF as a solvent, and the synthesis time is 1 h, with yield amounting to 34%. The scientific literature provides a general method for the synthesis of ipsapirone analogues [8–10] (but not ipsapirone itself) by alkylation of saccharin with a suitable alkylarylpiperazine salt. As already described herein, the standard method requires mixing substrates with potassium carbonate and a suitable solvent, such as DMF [9] or ACN [11] to obtain a product with a yield below 60%. However, ipsapirone can be obtained in another reaction. *N*-Alkylation of bromobutyl saccharin with 1-(2-pyrimidyl)piperazine dihydrochloride (Scheme 1) appears to be the most obvious route. Moreover, ipsapirone can also be synthesized in a one-pot approach by reacting saccharin, 1,4-dibromobutane, and 1-(2-pyrimidyl) piperazine dihydrochloride (Scheme 2). This approach is advantageous by lack of need for intermediate isolation, and resulting improvement of economic aspects of the entire process. Having considered the previously described economic and ecological aspects, we decided to employ a cost-effective, innovative, and environmentally friendly method: a solvent-free microwave-assisted reaction, simultaneously being part of a green chemistry trend.

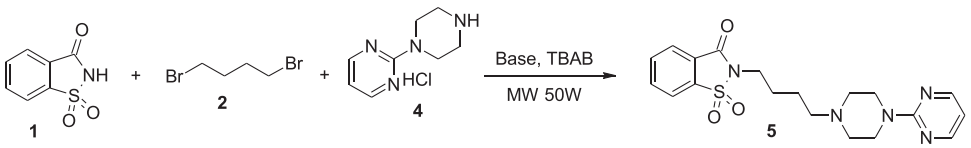
RESULTS AND DISCUSSION

Chemistry. ***N-alkylation of saccharine.*** The initial stage of our research involved the development of an efficient method for the synthesis of *N*-bromobutyl saccharin **3** in a solvent-free microwave-assisted reaction. In our previous papers, we described *N*-alkylation of imides under conventional methodology, in a solvent-free conditions [12]. Fiorinoa et al. [13] describes a microwave-assisted *N*-alkylation of saccharin **1**, however, with the use of solvents. In this paper, we decided to combine these two methods and obtain an alkylated saccharin **3** in solvent-free, microwave-assisted conditions (Scheme 3). We have started our research with determining the appropriate molar amounts of reactants. As a starting point, 1 eq of saccharin **1**, 3 eq of K_2CO_3 as a base, and 1.1 eq of alkylating agent **2** were used. Because reagents do not mix with each other, a phase transfer catalyst, that is, 0.1 eq *tert*-butylammonium bromide (TBAB), was used to facilitate the reaction. The

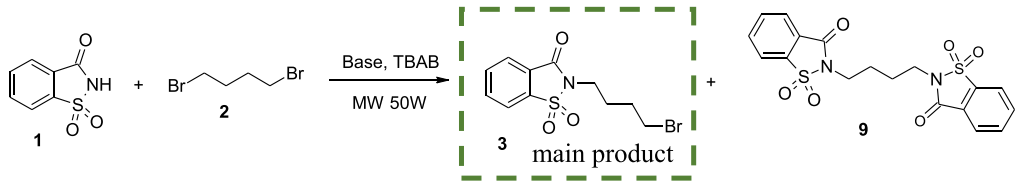
Scheme 1. Synthesis of ipsapirone according to method 1.



Scheme 2. Synthesis of ipsapirone according to (one-pot) method 2.



Scheme 3. *N*-Alkylation of saccharine. [Color figure can be viewed at wileyonlinelibrary.com]



reaction was carried out in the presence of 1 wt% DMF relative to saccharin **1**, which was used as a medium to transfer microwave energy [14]. The synthesis time was 50 s. The results are summarized in Table 1 (items 1–4). The progress of the reaction was monitored by thin-layer chromatography (TLC). Average yield of reaction (item 1) is caused by formation of significant amounts of the disubstituted product **9**. Excess of 1,4-dibromobutane (item 2) increases the selectivity of the reaction toward the formation of *N*-bromobutyl saccharine **3**. Impurities observed in TLC were not isolated. It has been determined that the optimal excess of alkylation agent is 2.5 eq. Larger excess does not have a major effect on the reaction progress and may cause problem issues with the crystallization of the product. Because Jaśkowska et al. [12] report that the optimal amount of potassium carbonate in the *N*-benzylation of phthalimide is 3 eq, while Fiorinoa et al. [13] uses only 1.5 eq of K_2CO_3 in the alkylation reaction of saccharin **1**, we decided to study and describe the effect of the amount of base on the reaction yield. The results are shown in Table 1 (items 5–8). Based on the TLC analysis, an increased amount of potassium carbonate promotes formation of impurities. When 1.5 eq of K_2CO_3 was used, we observed only spots attributable to *N*-bromobutyl saccharin **3** and traces of disubstituted product **9**. In addition, we decided to evaluate the effect of DMF addition; therefore, a complete synthesis of *N*-bromobutyl saccharine **3** was run without DMF addition. Having analyzed by TLC, the reaction mixture after 50 s of reaction, partial formation of product **3**, and significant amount of unreacted saccharin **1** were noticed. The reaction was then continued for 2 min. After this time, TLC indicated the presence of the desired product **3** a by-product **9** and other impurities. In this case, *N*-bromobutyl-saccharin **3** was not isolated. Our research also compared the effects of addition of ACN instead of DMF, and NaOH and Et_3N instead of K_2CO_3 as a base, as well as the catalytic amounts of KI instead of TBAB. In all the reactions with ACN, formation of numerous by-products was observed in TLC. The desired product was not isolated. Using NaOH as a base, TLC analysis indicated that during the first 10 s of heating, only product **3** was formed and the presence of unreacted substrate **1** was observed as before, while longer reaction times caused degradation of product **3** and led to formation of vast amounts of impurities; in this case, the product has not been isolated as well. Satisfactory results (85% yield) were observed only in the case of using triethylamine instead of potassium carbonate.

Table 1

Impact of 1,4-dibromobutane and base amounts on the yield in *N*-alkylation reaction of saccharine.

Item	1,4-Dibromobutane (eq)	K_2CO_3 (eq)	Yield (%)
1	1.1	3	45
2	2.0	3	67
3	2.5	3	79
4	3.0	3	80
5	2.5	1.0	70
6	2.5	1.5	94
7	2.5	2.0	85
8	2.5	2.5	80

Synthesis of ipsapirone: Method 1. Ipsapirone analogues obtained by N-alkylation were presented as an examples of the conventional method, and microwave-assisted method between appropriate bromoalkylimide and 1-(2-pyrimidyl)piperazine dihydrochloride **4** and are well known in the literature [15,16]. However, both of these synthetic approaches need toxic solvents to be used. Reaction times are also relatively long and, in microwave syntheses, often exceed 1 h. The initial step of ipsapirone **5** synthesis using a solvent-free method supported by microwave radiation is similar to this of *N*-bromobutyl saccharin **3** synthesis described previously. In this experiment, we determined the effect of addition of various bases on the reaction yield, and the results are presented in Table 2 (items 9–18). Values listed in the table show that the synthesis of ipsapirone **5** gives higher yields (of about 80%) in the presence of weak inorganic bases, such as potassium carbonate or calcium hydroxide. Carrying out the reaction in these conditions is also advantageous in the context of reaction time, as the use of K_2CO_3 shortened the reaction time to 1 min, while reaction in the presence of $Ca(OH)_2$ took 2 min. TLC analysis indicated the presence of the main product ipsapirone **5** and traces of 1-(2-pyrimidyl)piperazine dihydrochloride **4**, which was used in 10% molar excess. Using stronger inorganic bases, such as sodium hydroxide or potassium hydroxide, decreased the reaction yield to a point where no final product was isolated. TLC analysis revealed the presence of ipsapirone **5** traces and

Table 2

Impact of various bases and solvents (DMF/ACN) on the yield in Ipsapirone synthesis.

Item	Base (3 eq)	DMF (wt%)[b]	ACN (wt%)[c]	Yield (%)[a]
9	K_2CO_3	0.1	—	85
10	K_2CO_3	—	0.1	0
11	K_2CO_3	—	—	43
12	Et_3N	0.1	—	83
13	Et_3N	—	0.1	0
14	Et_3N	—	—	35
15	NaOH	0.1	—	0
16	NaOH	—	0.1	0
17	$Ca(OH)_2$	0.1	—	75
18	$Ca(OH)_2$	—	0.1	0

[a]Hydrochloride salt crystallized from acetone.
[b]Reaction time of up to 2 min.
[c]Reaction time of up to 10 min.

vast amounts of polar impurities. The mentioned weak inorganic bases can be considered as environmentally friendly, cost-effective, and easily available. Using triethylamine as a base for ipsapirone **5** synthesis allowed to obtain good yields over the reaction time of 2 min. However, due to the toxicity of this compound, this synthetic approach is not recommended. Investigating the effects of using DMF as a medium facilitating the reaction yielded interesting results. Reacting compounds in the presence of DMF accelerated the process very efficiently. In the case of K_2CO_3, the content of 1 wt% of DMF allowed to obtain the final product **5** with an 85% yield, while its absence reduced the yield of the reaction by 43%. When DMF was changed to ACN, no reaction progress was seen. Attempts to obtain ipsapirone **5** in the presence of ACN were repeated with addition of K_2CO_3, $Ca(OH)_2$, NaOH, and Et_3N gave no measurable effects. The final product was absent in the TLC analysis, even after prolonged heating for up to 10 min, although over this period, some mixtures get burned.

Table 3

Impact of various bases on the reaction yield.

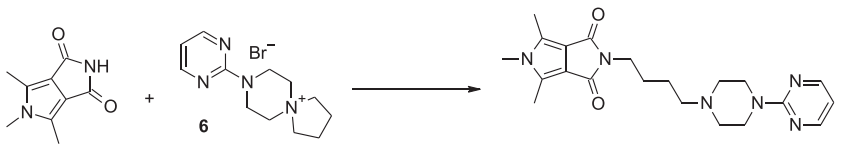
Item	Base (3 eq)	Yield (%)[a]
19	K_2CO_3[b]	52
20	Et_3N[c]	67
21	$Ca(OH)_2$[b]	60

[a]Hydrochloride salt crystallized from acetone.
[b]Reaction time of up to 2 min.
[c]Reaction time of up to 10 min.

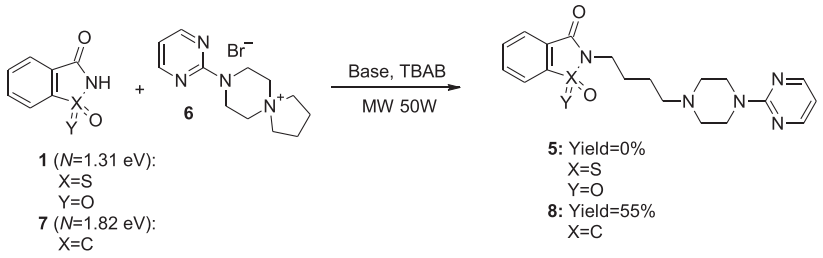
Synthesis of ipsapirone: Method 2 (one pot). So-called one-pot synthesis is one of the approaches in organic synthesis, which follows the principles of green chemistry, allowing one to obtain compounds in a clean, effective, economical, and quick manner [17]. In the case of ipsapirone **5**, the isolation step of *N*-bromobutyl-saccharine **3** can be omitted, thus shortening the synthesis time. Cybulski et al. [18] described the method for synthesis buspirone derivatives by a simultaneous reaction of 1-(2-pyrimidyl)piperazine dihydrochloride, 1,4-dibromobutane, and the corresponding imide. They reported high reaction yields for the final product with using xylene as a solvent and heating the mixture in a flask. Encouraged by this report, we decided to obtain ipsapirone **5** in a one-step reaction, without any solvents used for enhancing the microwave-assisted reaction; 1 eq of saccharin **1**, 2.5 eq of 1,4-dibromobutane **2**, and 1.1 eq of 1-(2-pyrimidyl)piperazine dihydrochloride **4** were used for the synthesis. The results are shown in Table 3. Ipsapirone **5** yield (52%) was slightly lower compared with the two-step synthesis, yet still acceptable. Lower yield is mainly attributable to a troublesome removal of 1,4-dibromobutane **2** excess upon the purification stage. TLC analysis of the reaction mixture revealed that addition of potassium carbonate as a base leads to formation of a greater number of impurities when compared with using triethylamine.

Synthesis of ipsapirone: Method 3. An alternative version of the *N*-alkylation reaction allowing to obtain ipsapirone **5** is a reaction between of 8-(pyrimidin-2-yl)-5,8-diazaspiro[4.5]decan-5-ium bromide **6** and saccharin **1**. Using a similar approach, Malinka et al. [19] obtained a series of imide derivatives (Scheme 4) with a high yield (60–80%), using potassium carbonate as a base and xylene as a solvent. Based on this report, we decided to check the yield of ipsapirone **5**. First, we obtained 8-(pyrimidin-2-yl)-5,8-diazaspiro[4.5]decan-5-ium bromide **6** by a conventional method described in the literature [19,20]. For this part of the research, we applied the same method as the one used for synthesis of *N*-bromobutyl saccharin **3**. The use of K_2CO_3 in line with the literature reports failed to give the product of interest. However, having exchanged K_2CO_3 to NaOH, we obtained the desired product with an 83% yield. In this case, 1 wt% addition of DMF was essential. Upon the

Scheme 4. Imide derivatives obtained by Cybulski et al. [18].



Scheme 5. Synthesis of ipsapirone and analogue according to method 3.



next stage, a possibility to obtain ipsapirone **5** was tested in accordance with Scheme 5, with determination of the effect of used bases (K_2CO_3, Et_3N, and $Ca(OH)_2$) and the reaction time (1, 2, 5, and 10 min.) on the reaction yield. Ipsapirone **5** was not formed in any of the tested conditions, as shown by TLC and HPLC. Saccharin **1**, classified as moderately nucleophilic, is not as easily alkylated as its analogue, phthalimide **7**, which is the probable reason for the observed outcome. To check this further, we decided to perform a similar synthesis with phthalimide **7** instead of saccharin **1** (Scheme 5). In this reaction, 50% of the substrate was converted to the desired product after just a 1 min. Conversion was confirmed by TLC and UPLC-MS analyses. It was determined that the potentially attractive way for ipsapirone **5** synthesis using 8-(pyrimidin-2-yl)-5,8-diazaspiro[4.5]decan-5-ium bromide **6** is not achievable in the tested conditions. This phenomenon can be explained by the molecular electron density theory [21], which in recent years has been successfully used to explain the reactivity of components in numerous different types of bimolecular reactions [22–24]. The global nucleophilicity descriptors needed for this purpose (*N*) were obtained by calculating B3LYP/6-31G (d), using the equation proposed by Domingo [25]:

$$N = E_{HOMO} - E_{HOMO(\text{tetracyanoethene})}$$

The calculated value of *N* index for saccharine **1** was 1.31 eV, which classifies this compound as a marginal nucleophile. On the other hand, phthalimide **7** belongs to the group of moderate nucleophiles (*N* = 1.82 eV) on the Domingo reactivity scale [26]. This differentiation clearly explains why phthalimide **7** reacts in mild conditions, while the desired product cannot be obtained from saccharin **1**.

CONCLUSION

Ipsapirone **5**, a ligand acting on the CNS, was obtained in line with the green chemistry principles, with reduction or complete elimination of toxic and expensive solvents. Implementing a microwave-assisted approach shortened the synthesis time from a few hours to minutes. The most efficient method for synthesis of ipsapirone **5** is a two-step *N*-alkylation of saccharin **1** in the first step and then *N*-bromobutyl saccharin **3** in the next. The one-pot method also seems to be fast and somehow efficient; however, difficulties with product separation may occur, as 1,4-dibromobutane **2** is hard to eliminate. Conversely, we failed to obtain ipsapirone **5** using method 3 due to the moderate nucleophilic index for saccharin **1**, preventing it from reacting. This conclusion was confirmed by quantum chemical calculations and the successful reaction in which saccharin **1** was replaced by phthalimide **7** (Scheme 5).

EXPERIMENTAL

All the reactants were purchased from commercial available suppliers. ^{1}H NMR spectra were recorded using Bruker 300 and 400 MHz apparatuses with TMS as an internal standard. Melting points were determined with Böetius apparatus. Waters UPLC with a PDA detector and 1.7 μm Aquity HPLC BEH C18 column was used for UPLC-MS analyses. Knauer HPLC with DAD detector and C18 1.4 μm column was used in HPLC analysis, with MeOH : H2O + formic acid (4:6 + 0.1%) as a mobile phase. Analytical TLC was performed using 0.2 mm silica gel precoated aluminum sheets (60 F254, Merck), and UV light at 254 nm was used for visualization. SAMSUNG ME73M at 300–450 W of power was used for all the microwave-assisted reactions.

2-(4-Bromobutyl)benzo[d]isothiazol-3(2H)-one1,1-dioxide (3). Saccharine **1** (1 g, 5.46 mmol), potassium carbonate (1.13 g, 8.18 mmol), and TBAB (0.17 g, 0.53 mmol) were ground in the mortar. Next, 1,4-dibromobutane **2** (1.6 mL, 13.62 mmol) was added, followed by 53 μL of DMF. Mixture was reacted in a microwave reactor at 300 W for 50 s. After this time, TLC indicated that the reaction was completed. Mixture was purified *via* flash chromatography using 100% hexane to 100% methanol as eluents. Methanol phase was evaporated to dryness, and crude product was crystallized from MeOH to give 1.65 g of pure product. Melting point 71–72°C (ref. 71–72°C [27]); yield 95%; white solid; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.09–8.04 (m, 1H), 7.95–7.81 (m, 3H), 3.83 (t, J = 6.7 Hz, 2H), 3.46 (t, J = 6.2 Hz, 2H), 2.05–1.97 (m, 4H). UPLC-MS: 98.9%, m/z = 318.

Ipsapirone (5) (method 1). 2-(4-Bromobutyl)benzo[*d*] isothiazol-3(2*H*)-one1,1-dioxide **3** (0.2 g, 0.63 mmol), potassium carbonate (0.26 g, 1.89 mmol), TBAB (0.029 g, 0.063 mmol), and 1-(2-pyrimidyl)piperazine dihydrochloride **4** (0.15 g, 0.63 mmol) were ground in the mortar; 6.45 μL of DMF was added, and the mixture was reacted in the microwave reactor at on 300 W for 60 s. After this time, TLC indicated that the reaction was completed. Mixture was diluted with water, extracted with ethyl acetate (3 × 10 mL), and organic phases were combined and evaporated. Crude product was dissolved in acetone, acidified with 4 M HCl in dioxane and cooled down in a freezer to obtain white crystals. The desired product was obtained as a hydrochloride salt. Melting point: 217–220°C (ref. 221–222°C [28]); yield 85%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.45 (d, J = 4.8 Hz, 2H), 8.16–7.97 (m, 4H), 6.77 (t, J = 4.8 Hz, 1H), 4.69 (d, J = 14.1 Hz, 2H), 3.79 (t, J = 6.6 Hz, 3H), 3.58–3.51 (d, J = 12 Hz, 2H), 3.43–3.36 (d, J = 20 Hz, 2H), 3.18 (m, 2H), 3.02 (dd, J = 20.6 Hz, 8.9 Hz, 2H), 1.82 (m, 4H). UPLC-MS: 93%, m/z = 401.14.

Ipsapirone (5) ("one-pot" method 2). Saccharine **1** (0.5 g, 2.73 mmol), potassium carbonate (1.13 g, 8.18 mmol), and TBAB (0.087 g, 0.27 mmol) were ground in the mortar. Next, 1,4-dibromobutane **2** (0.8 mL, 6.9 mmol) was added, followed by 33 μL of DMF. Mixture was reacted in the microwave reactor at 300 W for 50 s, then 1-(2-pyrimidyl)piperazine dihydrochloride **4** (0.15 g, 0.63 mmol) was added and mixed in with a spatula. Mixture was placed again in the microwave reactor and reacted at 300 W for 120 s. After this time, TLC indicated that the reaction was completed. Mixture was diluted with water and extracted with ethyl acetate (3 × 10 mL), and organic phases were combined and evaporated. Crude product was dissolved in acetone, acidified with 4 M HCl in dioxane and cooled down in a freezer. The desired product was obtained as a hydrochloride salt. Melting point: 216–219°C (ref. 221–222°C [28]); yield 50%; white solid; UPLC-MS: 90%, m/z = 401.52.

8-(Pyrimidin-2-yl)-5,8-diazaspiro[4.5]decan-5-ium bromide (6). 2-(Piperazin-1-yl)pyrimidine dihydrochloride **4** (1 g, 4.24 mmol), sodium hydroxide (0.5 g, 12.5 mmol), and TBAB (0.13 g, 0.40 mmol) were ground in the mortar. Next, 1,4-dibromobutane 2 (1.22 mL, 10.54 mmol) was added, followed by 38 μL of DMF. Mixture was reacted in the microwave reactor at 450 W for 2 × 60 s. After this time, TLC indicated that the reaction was completed. The reaction mixture was cooled down to room temperature, diluted with i-PrOH, and boiled for a few minutes. Insoluble inorganics were filtered off, and the filtrate was evaporated to dryness. The resulting semi-solid material was crystallized from i-PrOH. Melting point 245–247°C (ref. 241.5–242.5°C [29]); yield 83%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 4.8 Hz, 2H), 6.70 (t, J = 4.8 Hz, 1H), 4.22 (t, J = 7.2 Hz, 4H), 4.13 (t, J = 7.2 Hz, 4H), 3.82 (t, J = 3.9 Hz, 4H), 2.44–2.39 (m, 4H). UPLC-MS = 100%, m/z = 219 [M-Br$^-$].

Synthesis of ipsapirone (5) (method 3). 8-(Pyrimidin-2-yl)-5,8-diazaspiro[4.5]decan-5-ium bromide **6** (0.3 g, 1 mmol), potassium carbonate (0.41 g, 2.97 mmol), TBAB (0.032 g, 0.1 mmol), and saccharine **1** (0.36 g, 2 mmol) were ground in the mortar; 23 μL of DMF was added to the mixture, and the mixture was placed in the microwave reactor and reacted at 300 W for 120 s. After this time, TLC and UPLC-MS indicated the presence of starting materials only.

2-(4-(4-(Pyrimidin-2-yl)piperazin-1-yl)butyl)isoindoline-1,3-dione (8). 8-(Pyrimidin-2-yl)-5,8-diazaspiro[4.5] decan-5-ium bromide **6** (0.3 g, 1 mmol), potassium carbonate (0.41 g, 2.97 mmol), TBAB (0.032 g, 0.1 mmol), and phthalimide **7** (0.29 g, 2 mmol) were ground in the mortar; 22 μL of DMF was added to the mixture, and the mixture was placed in the microwave reactor and reacted at 300 W for 60 s. After this time, TLC indicated the presence of the desired product, unreacted substrates, and impurities. Mixture was diluted with water and extracted with ethyl acetate (3 × 10 mL), and organic phases were combined and evaporated. Crude product was crystallized from MeOH to give pure product. Melting point 137–139°C (ref. 138–139°C [30]); 55% yield; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.78 (d, J = 36.8 Hz, 4H), 6.47 (s, 1H), 3.77 (d, J = 25.4 Hz, 6H), 2.45 (d, J = 22.6 Hz, 6H), 1.66 (d, J = 47.0 Hz, 2H). UPLC-MS = 92%, m/z = 366 [m + H].

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