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Mechanochemical Synthesis Method for Drugs Used in the Treatment of CNS Diseases under PTC Conditions

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Abstract: Phase transfer catalysis (PTC) is an excellent possibility in the synthesis of organic compounds as it allows the reactions to be carried out under the conditions of green chemistry, while maintaining high yields and selectivity. The great advantage of these reactions is also the possibility of carrying out the reactions not only under conventional conditions, but also mechanochemically in solvent-free processes. Bearing this in mind, we decided to develop a new method for the synthesis of known biologically active compounds from the group of long-chain arylpiperazines (LCAPs). The first mortar trials were very promising and prompted us to carry out a series of ball mill reactions. One of the technological problems that we encountered while conducting reactions in the ball mill was the difficulty in extracting the post-reaction mixture. We tested the effects of additives improving the insulation of the product, such as, e.g., starch, zeolites, and silica. Research has proven that with appropriate process conditions using TBAB as a catalyst and in the presence of potassium carbonate and a small amount of Zeolite ZSM5 or silica, aripiprazole can be obtained with a yield of 90% in just five minutes. The obtained results are very promising and it is worth considering them as an alternative to the synthesis of other compounds from the LCAPS group.

Keywords: PTC catalysis; mechanochemistry; TBAB; solvent-free synthesis; green chemistry; aripiprazole; long-chain arylpiperazines

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Citation: Jaśkowska, J.; Drabczyk, A.K.; Michorczyk, P.; Kułaga, D.; Zaręba, P.; Jodłowski, P.; Majka, Z.; Jakubski, J.; Pindelska, E. Mechanochemical Synthesis Method for Drugs Used in the Treatment of CNS Diseases under PTC Conditions. *Catalysts* **2022**, *12*, 464. https://doi.org/10.3390/catal12050464

Academic Editor: Victorio Cadierno

Received: 18 March 2022
Accepted: 20 April 2022
Published: 21 April 2022

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1. Introduction

In recent years, research efforts have focused on the search for methods of the synthesis of the bioactive compounds that are characterized by simplicity of the individual stages of the process and the use of readily available and safe reagents, while maintaining high selectivity and efficiency. Moreover, a very important aspect is to limit the amount of harmful and environmentally toxic byproducts and waste, especially in larger-scale reactions. All these conditions are met by phase transfer catalysis (PTC). A wide variety of reactions can be carried out under PTC conditions, such as alkylation, oxidation, reduction, elimination, hydrolysis, aliphatic and aromatic substitution, multiple bond addition, carbonyl addition and many others. Additionally, it is possible to use PTC conditions both in standard methods of synthesis and in the presence of microwave irradiation, ultrasounds or in mechanochemistry. The obtained products, often even unpurified, are characterized by high purity, which is extremely important in the case of bioactive compounds. All these advantages of the PTC method mean that it is now used more and more often in the synthesis of bioactive compounds [1–14].

PTC is useful in a variety of reactions, such as reduction, oxidation, condensation, epoxidation, esterification, carbonylation and polymerization. It is a technique that does not require complicated equipment and enables the reaction to be carried out under mild conditions with high efficiency and selectivity. In addition, it allows the elimination or selection of a more convenient organic solvent, as well as the elimination of toxic reagents, which makes PTC one of the energy-saving, low-waste and environmentally friendly methods [14,15]. Due to these advantages, and despite the fact that phase transfer catalysis has been known since the 1960s, it still enjoys great interest and is still being developed.

Long-chain arylpiperazines (LCAPs) are bioactive substances, which are widely used in pharmacotherapy, mainly in the treatment of conditions of the Central Nervous System. These compounds have antipsychotic, antidepressant, and anxiolytic effects as they interact with specific serotonin or dopamine receptors in the brain [16–20]. Among this group, we can differentiate aripiprazole (7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one), trazodone (2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one), flibanserin (1-(2-{4-[3-(trifluoromethyl)phenyl] piperazin-1-yl}ethyl)-1,3-dihydro-2H-benzimidazol-2-one) or ipsapirone (1,1-dioxo-2-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-1,2-benzothiazol-3-one) (Figure 1) [20–24].

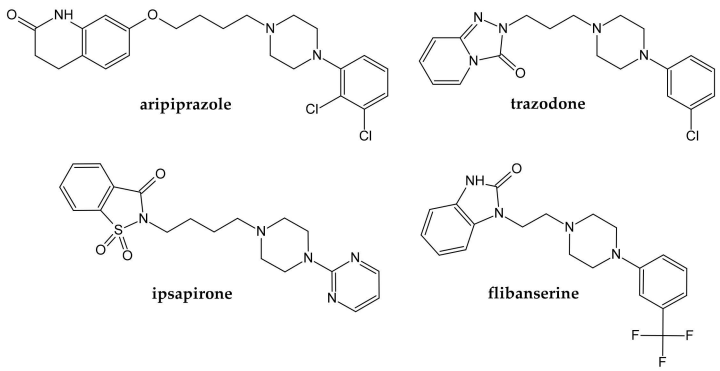


Figure 1. Examples of long-chain arylpiperazines: aripiprazole, trazodone, ipsapirone, flibanserine.

Aripiprazole belongs to the group of atypical antipsychotic drugs. It is a partial agonist of dopamine D_2 and serotonin 5-HT_{1A} receptors and an antagonist of dopamine D_3 and serotonin 5-HT_{2A} receptors, and is used in the treatment of schizophrenia and bipolar disorder. Trazodone acts as an antagonist of 5-HT_{2A} serotonin receptors and as a serotonin reuptake inhibitor (SARI). It is a well-known antidepressant and serotonin reuptake inhibitor. Ipsapirone exhibits activity as a selective partial 5-HT_{1A} and D_2 agonist and has antidepressant and anxiolytic effects. Another interesting drug from the LCAP group is flibanserin. It acts as an agonist of postsynaptic 5-HT_{1A} receptors and antagonist to other serotoninergic receptors (5-HT_{2A} and 5-HT_{2B} as well as 5-HT_{2C}). However, its medical indication is different from the above-mentioned compounds as flibanserin is recommended for the treatment of hypoactive sexual desire disorder in pre-menopausal women [20,25–27].

The methods described so far in the literature of obtaining aripiprazole (IIIa) can be carried out with *N*-alkylation of hydrochloride of 2,3-dichloro arylpiperazine of 7-(4-bromobutoxy)-3,4-dihydro-1H-quinolin-2-one in organic solvents such as DMF [28–31], dimethyl sulfoxide (DMSO), dioxane, tetrahydrofuran (THF), benzene, toluene, xylene, or alcohols [32–35] in the presence of bases such as triethylamine, pyridine, sodium or potassium hydroxides, or potassium, sodium or cesium carbonates [31–34,36–38]. Other reactions—carried out in accordance with green chemistry principles—reported in the literature involve microwave (MW) radiation with or without a solvent [27].

The synthesis of trazodone by alkylation of hydrochloride of 3-chloro arylpiperazine can be carried out with solvents such as toluene [39,40] or acetonitrile [41] in the presence of triethylamine [39,40] or potassium carbonate [41]. A green chemistry synthesis method

is also known, where no solvent is used and the reaction is carried out under microwave radiation with potassium carbonate and tetrabutylammonium bromide (TBAB) [42].

In the case of ipsapirone, the reaction can be carried out by alkylation of 4-(pyrimidin-2-yl)piperazine with alkyl halide derivatives (1,1-dioxo)-1,2-benzothiazol-3-one. The reaction is carried out in chlorobenzene under nitrogen atmosphere and in the presence of potassium carbonate by heating the reaction mixture for 8 h [43]. The synthesis can also be performed out under microwave radiation with potassium carbonate and TBAB [44].

The synthesis of flibanserin by *N*-alkylation of hydrochloride of 3-trifluoromethyl arylpiperazine can be conducted in solvents such as water, DMF, acetonitrile [45] or ethanol [46]. This reaction is most often performed with potassium carbonate and sodium iodide [45]. In another known method, flibanserin is obtained in the presence of sodium carbonate and sodium iodide in alcohol by heating the mixture with a reflux condenser in 18 h [47].

Mechanochemical reactions in organic chemistry have been known for years. The reactions carried out, not only in mortars, but also in ball mills, are becoming more and more popular [48–50]. The mechanochemical *N*-alkylation described so far in the literature concern the reactions with urea [51], hydrazone [52], imines [53,54], imides [55], pyridines [56], pyrimidines [57], imidazoles [58], and secondary amines [59]. Some of these processes are carried out under PTC conditions [54,59]. All the above-mentioned reactions were carried out under solvent-free conditions, which make it possible to reduce toxic reagents and treat the reactions as having met green chemistry principles. Our research work has proven that it is possible to obtain *N*-alkyl derivatives of piperazine including aripiprazole, trazodone, flibanserin and ipsapirone belonging to the group of LCAPs pharmacologically active substances under solvent-free conditions in mechanochemical synthesis under phase-transfer catalysis (PTC) conditions.

2. Results

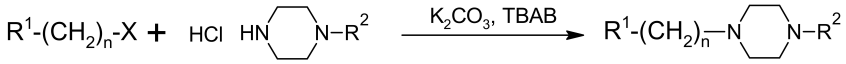
The reaction obtaining compound from the LCAPs family was carried out in the process by *N*-alkylation arylpiperazin according to the SN2 reaction mechanism, at room temperature (20–25 °C) in the presence of potassium carbonate (K_2CO_3), a phase-transfer catalyst—TBAB, and an additive facilitating the isolation of the product from the reaction mixture, i.e., zeolites (zeolite A, zeolite Y, ZSM-5, Zeosil MP 1165), boehmite (dispersal), starch or silica sands in mechanochemical synthesis carried out in a mortar or a ball mill (Table 1). As the process is run in a mortar for 30 min, it is possible to obtain expected products at a yield of 22–46%. In contrast, once the process is run in a ball mill, it is possible to obtain products with a twice higher yield of 64–86%. After the synthesis is finished, the mixture is transferred to a beaker with water, which is then cooled down to 4 °C. Afterwards, the sediment obtained is drained under reduced pressure to obtain the raw product. It should be noted, however, that although initially all the reactants are solid, the aryl piperazine hydrochlorides under the influence of the alkaline reaction medium transform into the alkaline phase, which is liquid, so in fact the reaction takes place in the liquid-solid system (L-S).

In the case of the synthesis of flibanserin (**IIIc**), it is necessary to remove the isopropylene fragment present in the **Ic** substrate. Our experiments proved that it is possible only with the application of an additional step, i.e., the formation of flibanserin hydrochloride. For this purpose, the crude product obtained after the reaction (1-(prop-1-en-2-yl)-3-(2-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2(3H)-one) must be dissolved in isopropanol and acidified. The resulting mixture is heated, then cooled, and ethyl acetate is added. The mixture is alkylated with a water solution of a strong base (NaOH) until strongly alkaline pH is obtained. Next, it is stirred and the organic layer is separated from water, drained, and evaporated under reduced pressure.

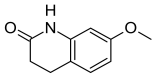
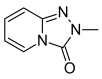
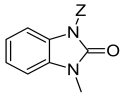
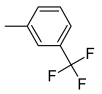
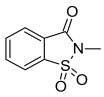
The first attempts to synthesize compounds from the LCAPs group using a mechanochemical method were carried out in a mortar for 30 min. The reactions were carried out with

an equimolar ratio of the reactants in the presence of potassium carbonate and catalytic amounts of TBAB (Table 1).

Table 1. Synthesis of aripiprazole, trazodone, fibanserin and ipsapirone in the presence of potassium carbonate and TBAB in a mortar. The molar ratio **Ia-d**:**IIa-d**:K_2CO_3:TBAB 0.01:0.011:0.03:0.001.



Ia-d **IIa-d** **IIIa-d**

Symbol	R^1	n	X	R^2	Name	Reaction Conditions	Yield [%]
a		4	Br		aripiprazole	K_2CO_3, TBAB mortar, 30 min	37
b		3	Br, Cl		trazodone		46
c		2	Br		flibanserin		22
d		4	Br		ipsapirone		25

Z = prop-1-en-2-yl (for substrate) or H (for the product).

Then, similar reactions of the synthesis of aripiprazole and trazodone were carried out in a planetary ball mill (rotation speed 300 rpm, stainless steel balls with a size Ø10 mm, Planetary Ball Mill PM 100-RETSCH) (Table 2).

Table 2. Synthesis of aripiprazole, trazodone in the presence of potassium carbonate and TBAB in a ball mill (rotation speed 300 rpm, stainless steel balls with a size Ø10 mm, Planetary Ball Mill PM 100-RETSCH). The molar ratio **Ia-b**:**IIa-b**:K_2CO_3:TBAB 0.01:0.011:0.03:0.001.

	Name	Reaction Conditions	Yield [%]
IIIa	aripiprazole	K_2CO_3, TBAB ball mill, 30 min	86
IIIb	trazodone		64

During the process, a technological problem arose: it became difficult to isolate the product from the reaction mixture as the post-reaction mixture adhered to the walls of the vessel and the steel balls. As a result, in subsequent stages we added starch (soluble starch, CHEMPUR) zeolites to eliminate this problem. Further research was carried out focusing only on the synthesis of aripiprazole (Table 3). It was observed that the addition of starch zeolites A or Y significantly affects the course of the insulation of products from the reaction mixture, as the mixture is looser. As a result, the effect of other readily available zeolites and boehmite alumina powder (disperal) in the amount of 8% mass was also assessed (Table 3, entry 11–14). In the case of using additives to the water-insoluble reaction mixture (e.g., starch, zeolites, bentonite), water was added after the reaction, the product was filtered and

dried, and further purified by crystallization from isopropanol. The reaction results were very satisfactory (Y = 77–84%) and the purity of the products was 100% (HPLC).

Table 3. Synthesis of aripiprazole in the presence of potassium carbonate, TBAB and additives improving the insulation of the product in a ball mill (rotation speed 300 rpm, stainless steel balls with a size Ø10 mm, Planetary Ball Mill PM 100-RETSCH). The molar ratio **Ia**:**IIa**:K_2CO_3:TBAB 0.01:0.011:0.03:0.001.

Entry	Reaction Conditions			
	Additives Improving the Insulation of the Product	% by Mass of the Additive		Yield [%]
1	Starch	23	K_2CO_3, TBAB ball mill, 300 rpm, 30 min	62
2		32		62
3	Zeolite A [1]	3		44
4		5.5		48
5		8		70
6		15		57
7	Zeolite Y [2]	3		43
8		5.5		50
9		8		63
10		15		50
11	Zeolite Y [3]	8		77
12	Zeolite ZSM-5 [4]	8		79
13	Zeosil 1165 [5]	8		84
14	Disperal [6]	8		81

[1] obtained according to the method described in [60]; [2] obtained according to the method described in [61]; [3] Zeolite Y, sodium powder 5:1:1 SiO_2:Al_2O_3, ALFA AESAR; [4] Zeolite ZSM-5, ACROS ORGANICS; [5] Zeosil 1165, SOLVAY; [6] Boehmite alumina powder, Disperal, SASOL.

The conducted research proved that when zeolites are used, the problem of ball sticking, which is observed after the reaction, can be eliminated. When no additives were used, or when starch and disperal were used, the balls were firmly stuck with the post-reaction mixture (Figure 2). In this respect, the best results were obtained in the case of the use of zeolites, where it was observed that the post-reaction mixture is still loose, does not stick to the balls, creates few lumps between the balls, but is mainly at the bottom of the vessel. In these cases, removing the post-reaction mixture from the ball mill was not problematic.

In the next stage of research, attempts were made to assess the possibility of carrying out the reaction on a planetary mill with the possibility of using faster rotations (500–700rpm) (Table 4). The reactions were carried out as before in the solid phase, only in two cases water was used as the solvent (entry 7–8, Table 4).

Zeosil 1165 and TBAB were selected for the tests in the first stage. It was observed that the increase in the speed to 500 rpm allows the reactions to be carried out in a third of the time, i.e., 10 min, obtaining the yield at the level of 58–63% (entry 1–2, Table 4). Increasing the speed to 700 rpm means that after five minutes the product is obtained with the yield of 68%, and the process extension, even up to 15 results, gives a slight increase in the yield to 74% (entry 3–6, Table 4). Interestingly, aripiprazole synthesis reactions can be successfully carried out with the use of water, which allows us to obtain the expected product with a yield of 62–66% within five minutes (entry seven–eight, Table 4) or aluminum oxide, which allows us to obtain aripiprazole from a yield of 71% (entry nine, Table 4). Interestingly, we also conducted trials with the use of TBAB, where we used silica sand instead of the ZSM-5, the results are very promising (entry 10–11, Table 4). In the case of silica sand (2), we achieved a yield of 90%, and the resulting mixture could be easily removed from the

ball mill. This is a very interesting option, which we will certainly develop in the future as the use of sands solves an important technological problem, and at the same time it is an accessible, cheap and easy method to be used both in laboratory and industrial conditions.

A **B**

Figure 2. Examples of post-reaction mixture when no additives are used and with the addition of starch or disperal (**A**) post-reaction mixture sticks to the balls, and when additional zeolites (**B**) are used post-reaction mixture is at the bottom of the vessel or it additionally forms dense lumps, only a few balls are sticky.

We also assessed the influence of the PTC catalyst by conducting the reactions in the presence of Zeosil 1165 and the commonly available commercially available zeolite ZSM-5, achieving yields of 65–67% (entry 12–13, Table 4), but the disadvantage of these reactions is the fact that the product, despite crystallization, is contaminated with unreacted BBQ. Interestingly, in the case of the ZSM-5 zeolite, the addition of the PTC catalyst in the form of TBAB resulted in obtaining the yield of 90% within five minutes with the use of 700 rpt (entry 16, Table 4), and in the case of lower speeds at the level of 500 rtp, a slightly lower yield was observed at 85–86% (entry 14–15, Table 4).

These studies prompted us to evaluate the effects of other PTC catalysts as well: TEBA (benzyltriethylammonium chlorid), TMAB (tetramethylammonium borohydride), TEAC (tetraethylammonium chloride), BTBAC (benzyltributylammonium chloride), CTAB (cetrimonium bromide) (entry 17–21, Table 4) and DABCO (1,4-diazabicyclo [2.2.2] octane), which is not a PT catalyst (entry 22, Table 4). In the case of TEBA, TMAB, DABCO, the yield was also above 80%, while in the case of TEAC and BTBAC, the yield was above 70%. The lowest yield was obtained with CTAB (46%).

Table 4. Synthesis of aripiprazole in the presence of potassium carbonate and catalysts PTC in a ball mill (zirconium oxide balls with a size of Ø20 mm, Planetary Ball Mill Pulverisette 7 premium line, Fritsch GmbH). The molar ratio **Ia**:**IIa**:K_2CO_3:TBAB 0.01:0.011:0.03:0.001.

Entry	Reaction Conditions			Time [min]	Yield [%]
	Additives Improving the Insulation of the Product (8% Mass)	rpm	Cat. PT		
1	Zeosil 1165 [1]	500	TBAB	10	58
2	Zeosil 1165 [1]	500 *	TBAB	10	63
3	Zeosil 1165 [1]	700	TBAB	5	68
4	Zeosil 1165 [1]	700	TBAB	7	72
5	Zeosil 1165 [1]	700	TBAB	10	69
6	Zeosil 1165 [1]	700	TBAB	15	74

Table 4. *Cont.*

Entry	Reaction Conditions			Time [min]	Yield [%]
	Additives Improving the Insulation of the Product (8% Mass)	rpm	Cat. PT		
7	H_2O	500	TBAB	5	62
8	H_2O	700	TBAB	5	66
9	α-Al_2O_3	700	TBAB	10	71
10	Silica sand (1) [2]	500	TBAB	5	70
11	Silica sand (2) [3]	500	TBAB	5	90
12	Zeosil 1165 [1]	700	-	5	65
13	Zeolite ZSM-5 [4]	700	-	5	67
14	Zeolite ZSM-5 [4]	300	TBAB	5	86
15	Zeolite ZSM-5 [4]	500	TBAB	5	85
16	Zeolite ZSM-5 [4]	700	TBAB	5	90
17	Zeolite ZSM-5 [4]	500	TEBA [5]	5	83
18	Zeolite ZSM-5 [4]	500	TMAB [6]	5	82
19	Zeolite ZSM-5 [4]	500	TEAC [7]	5	78
20	Zeolite ZSM-5 [4]	500	BTBAC [8]	5	71
21	Zeolite ZSM-5 [4]	500	CTAB [9]	5	46
22	Zeolite ZSM-5 [4]	500	DABCO [10*]	5	88

* Zirconium oxide balls with a size of Ø1 mm; [1.] Zeosil 1165, SOLVAY; [2.] Silica sand 3K (binder content max 1.0%, SiO_2 > 96%, $Fe2O_3$ < 1%, carbonates < 0.5%), D_{50} = 0.20 mm (Standard: Foundry molding materials - Molding sands. PN-H-11001: 1985); [3.] Silica sand, SIBELCO, 1K (binder content max 0.2%, SiO_2 > 98%, Fe_2O_3 < 0.5%, carbonates < 0.3%), D_{50} = 0.25 mm (Standard: Foundry molding materials—Molding sands. PN-H-11001: 1985); [4.] Zeolite ZSM-5, ACROS ORGANICS; [5.] TEBA—benzyltriethylammonium chlorid; [6.] TMAB—tetramethylammonium borohydride; [7.] TEAC—tetraethylammonium chloride; [8.] BTBAC—benzyltributylammonium chloride; [9.] CTAB—hexadecyltrimethylammonium bromide; [10*.] DABCO—1,4-diazabicyclo [2.2.2] octane (is not a PT catalyst).

3. Conclusions

As mentioned in the introduction, conventional methods of aripiprazole synthesis are characterized by a long reaction time and the need to use toxic solvents or reagents. For example, aripiprazole can be obtained by an analogous reaction to that described in our experiments, however it is necessary to use solvents such as, for example, acetonitrile, which allows the expected product to be obtained in 53–97% yield within 4–10 h [36,62,63]. There are also known reactions, in which alcohols as solvents, e.g., isopropanol, can be used, which allows us to obtain 88% yield within five hours [64]. There are also known syntheses of aripiprazole where, e.g., DMF or water is used, however, like in other reactions, the synthesis time is several hours (DMF: Y = 94% [28], 4 h; H_2O: Y = 88–98%, 3–8 h [65–67]). All these syntheses are accompanied by a long synthesis time and the need to heat the reaction mixture. Moreover, an undoubtedly significant problem in the synthesis of bioactive compounds is the need to obtain compounds of high purity. For many of the described methods for the synthesis of aripiprazole, and other LCAPs compounds, it is necessary to purify the crude product by chromatography, which is very difficult or even impossible to apply to compounds used on a large scale in the pharmaceutical industry.

Mechanochemical reactions are a very interesting alternative of synthesis compared to classical methods, taking into account the possibility of carrying out the reactions under green chemistry. Carrying out the process under PTC catalysis conditions allows for the synthesis to be carried out in a short time, with high yield and high purity of products, which is particularly important in the case of the synthesis of bioactive compounds.

Our experiments have proven that even with the use of such simple laboratory equipment as a mortar, in the presence of potassium carbonate and TBAB, it is possible to obtain active substances such as aripiprazole (**IIIa**), trazodone (**IIIb**), flibanserine (**IIIc**) or ipsapirone (**IIId**) within 30 min with a yield of 22–46%. The use of a planetary ball mill

for synthesis allows us to significantly increase the yield (increase by 20–40%, 300 rpm), however, there is a technological problem in the fact that the post-batch mixture sticks to the balls. Subsequent tests were carried out with additives such as starch, Zeolite A, Zeolite Y, Zeolite ZSM-5, Zeosil 1165, Disperal (Boehmite alumina powder), which are to eliminate this problem. Aripiprazole synthesis was chosen as a model reaction to evaluate the influence of these parameters on the course of the process. The research proved that when zeolites are used in the amount of 8% by weight, the post-reaction mixture does not stick to the balls, but remains at the bottom of the vessel or forms few lumps. Bearing in mind that the highest yield was obtained with the use of Zeosil 1165 (Y = 84%) and Zeolite ZSM-5 (Y = 79%), further studies were carried out with the use of these additives. In the next stage of the research, we assessed the possibility of carrying out the reaction with a larger number of revolutions (500–700 rpm), which translated into a significant reduction in reaction time (up to 5–10 min). At this stage, we also tested the possibility of using alumina, water or silica sand as an additive to the reaction mixture, which also brought interesting results—especially in the case of silica sand where a yield of 90% was achieved. However, looking from the point of view of isolating the final product from the reaction mixture, it is definitely the easiest to do in the case of Zeosil 1165 and Zeolite ZSM-5. The conducted experiments proved that the highest yield of aripiprazole (80–90%) in the shortest time (five minutes) is obtained by using a planetary ball mill (700 rpm) with in the presence of potassium carbonate and additives improving product insulation (Zeolite ZSM-5, Zeolite 1165) in the presence of PT catalysts such as TBAB, TMAB or in the presence DABCO. The obtained results are very promising as the reagents used are non-toxic and readily available, and thanks to the mechanochemical synthesis, the product can be easily isolated using only water. Bearing in mind that aripiprazole belongs to a large family of compounds from the LCPs group, the developed method may also be used in the synthesis of other important bioactive compounds.

4. Materials and Methods

All chemicals were purchased from Sigma-Aldrich and all solvents used in the synthesis were from POCH.

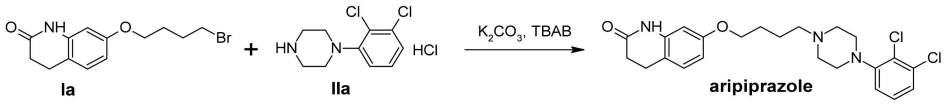
The progress of all reactions was monitored by TLC (Thin Layer Chromatography)—Sigma-Aldrich silica plates: 200 μm, pore diameter: 60 A, fluorescence index: 254 nm. Chloroform: methanol eluent—9:1 v/v. UV light, λ = 254 nm (Jeulin lamp, Enceinte UV 701435) was used for detection. Melting point measurement—performed on a Böetius apparatus. IR spectra were performed on an FTS-165 (FTIR Biorad) spectrometer. Analytical chromatograph by Perkin Elmer 200, XTerra RP C-18 column, mobile phase, isocratic: CH_3OH:H_2O 60:40 with 0.1% HCOOH and standards were used for analyses by high performance liquid chromatography (HPLC). Furthermore, system Waters Acquity UPLC system coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole), PDA detector, Acquity UPLC BEH C18, 1.7, 2.1 × 100 mm column (Waters Corporation, Milford, MA, USA), mobile phase: methanol:water + formic acid (4:6 + 0.1%, v/v)—were used for analyses with ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS).

5. Synthesis

5.1. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) in a Mortar

First, 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (**Ia**) (0.01 mol, 2.98 g), 1-(2,3-dichlorophenyl) piperazine hydrochloride (**IIa**) (0.011 mol, 2.94 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g) was weighed, placed in a mortar and ground for 30 min, then the mixture was transferred to a beaker containing 50 cm^3 of water, stirred and cooled to 4 °C. After 24h, the crude aripiprazole (**IIIa**) was filtered off under reduced pressure, washed with water and air dried. 1.66 g (Y = 37%) **IIIa** was obtained,

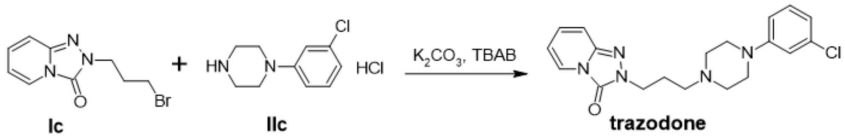
TLC R_f = 0.48, HPLC R_t = 2.06 min. (matching the pattern).UPLC-MS R_t = 4.98 min., m/z = 448 [M+H] (Scheme 1).



Scheme 1. Synthesis of Aripiprazole.

5.2. Synthesis of Trazodone (2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo [4,3-a]pyridin-3-one) (IIIb) in a Mortar

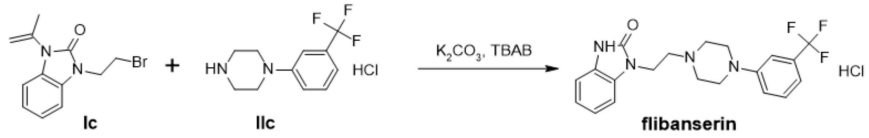
The process was carried out in the same way as described in point 5.1, using 2-(3-chloropropyl)-1,2,4-triazolo [4,3-a]pyridin-3-(2H)-one (**Ib**) (0.01 mol, 2.12 g), 1-(3-chlorophenyl) piperazine (**IIb**) hydrochloride (0.011 mol, 2.56 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g). 1.71 g (Y = 46%) **IIIb** was obtained, TLC R_f = 0.75, HPLC R_t = 1.66 min. (matching the pattern) (Scheme 2).



Scheme 2. Synthesis of Trazodone.

5.3. Synthesis of Flibanserin (1-(2-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-1, 3-dihydro-2H-benzimidazol-2-one) (IIIc) in a Mortar

First, 1-(2-bromoethyl)-3-(prop-1-en-2-yl)-1H-benzo[b]imidazol-2(3H)-one (**Ic**) (0.01 mol, 2.81 g), 3-trifluoromethylphenylpiperazine hydrochloride (**IIc**) (0.011 mol, 2.93 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g) was weighed, placed in a mortar and ground for 30 min, then the mixture was transferred to a beaker containing 50 cm^3 of water, stirred and cooled to 4 °C. After 24 h, the precipitate ((1-(prop-1-en-2-yl)-3-(2-(4-(3-(trifluoromethyl)phenyl)-piperazin-1-yl)ethyl)-1H-benzo[d]imidazol-2(3H)-one) was filtered off under reduced pressure, washed with water and air dried. The precipitate was then dissolved in isopropanol (10 cm^3) and concentrated hydrochloric acid was added until the pH was strongly acid, then the reaction mixture was heated to 70 °C and stirred for 2 h. The mixture was then cooled and ethyl acetate (about 3 cm^3) and a 20% aqueous sodium hydroxide solution added until the pH was strongly basic and stirred for 30 min. The organic layer was separated from the aqueous layer and dried over anhydrous magnesium sulfate and then evaporated under reduced pressure. 0.86 g (Y = 22%) of flibanserin (**IIIc**) was obtained. TLC R_f = 0.65, HPLC R_t = 3.20 min. (matching the pattern) (Scheme 3).

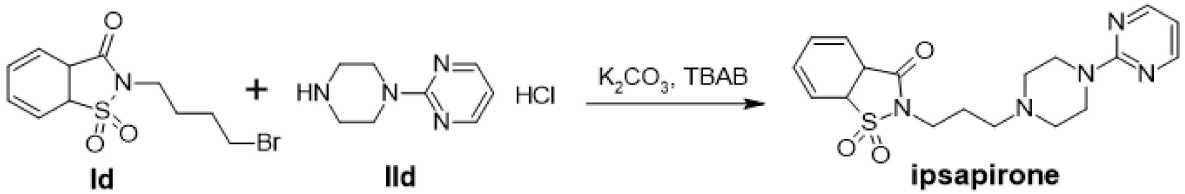


Scheme 3. Synthesis of Flibanserin.

5.4. Synthesis of Ipsapirone (9,9-Dioxo-8-[4-(4-pyrimidin-2-yl-piperazin-1-yl)butyl]o-9λ6-thia-8-azabicyclo [4.3.0]nona-1,3,5-trien-7-one) (IIId) in a Mortar

The process was carried out in the same way as described in point 5.1, using 2-(4-bromobutyl)-1H-1λ6,2-benzothioazole-1,1,3 (2H)-trione (**Id**) (0.01 mol, 3.19 g), dihydrochlo-

ride 2-(piperazin-1-yl)pyrimidine (**IId**) (0.011 mol, 2.61 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g). 1.00g (Y = 25%) **IIIa** was obtained, TLC R_f = 0.74, HPLC R_t = 1.43 min. (matches the pattern). UPLC-MS R_t = 3.49 min, *m/z* = 402 [M+H] (Scheme 4).



Scheme 4. Synthesis of Ipsapirone.

5.5. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl) piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

First, 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (**Ia**) (0.01 mol, 2.98 g), 1-(2,3-dichlorophenyl)piperazine hydrochloride (**IIa**) (0.011 mol, 2.94 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g) was weighed, placed in a ball mill and ground for 30 min, then the mixture was transferred to a beaker containing 50 cm^3 of water, stirred and cooled to 4 °C. After 24h, the crude aripiprazole (**IIIa**) was filtered off under reduced pressure, washed with water and air dried. 3.85g (Y = 86%) **IIIa** was obtained, TLC R_f = 0.48, HPLC R_t = 1.93 min. (matching the pattern). FT-IR 3189, 2942, 2809, 1674, 1593-1446, 1174, 779 cm^{-1}.

5.6. Synthesis of Trazodone (2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo [4,3-a]pyridin-3-one) (IIIb) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.5, using 2-(3-chloropropyl)-1,2,4-triazolo [4,3-a]pyridin-3-(2H)-one (**Ib**) (0.01 mol, 2.12 g), 1-(3-chlorophenyl) piperazine (**IIb**) hydrochloride (0.011 mol, 2.56 g), potassium carbonate (0.03 mol, 4.14 g) and TBAB (0.001 mol, 0.32 g). 2.38 g (Y = 64%) (**IIIb**) was obtained, TLC R_f = 0.75, HPLC R_t = 1.65 min. (matching the pattern). FT-IR 2950, 2828, 1702, 1594, 1463, 1441, 1342, 1258 cm^{-1}.

5.7. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Starch (23% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

First, 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (**Ia**) (0.01 mol, 2.98 g), 1-(2,3-dichlorophenyl) piperazine hydrochloride (**IIa**) (0.011 mol, 2.94 g), potassium carbonate (0.03 mol, 4.14 g), TBAB (0.001 mol, 0.32 g) and 0.5 g of starch was weighed, placed in a ball mill and ground for 30 min, then the mixture was transferred to a beaker containing 50 cm^3 of water, stirred and cooled to 4 °C. After 24 h, the crude aripiprazole (**IIIa**) was filtered off under reduced pressure, washed with water and air dried. After crystallization from isopropanol, 2.77 g (Y = 62%) **IIIa** was obtained, TLC R_f = 0.48, HPLC R_t = 1.96 min. (matching the pattern).

5.8. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Starch (32% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 1.0 g of starch. After crystallization from isopropanol, 2.78g (Y = 62%) **IIIa** was obtained, TLC R_f = 0.48, HPLC R_t = 2.06 min. (matching the pattern).

5.9. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite A (3% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.1 g of Zeolite A. After crystallization from isopropanol, 1.94g (Y = 44%) **IIIa** was obtained, TLC R_f = 0.48, HPLC R_t = 2.34 min. (matching the pattern).

5.10. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite A (5.5% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.2 g of Zeolite A.

As such, 2.13 g (Y = 48%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.44 min. (matching the pattern).

5.11. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite A (8% by weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Zeolite A.

As such, 3.13 g (Y = 70%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.45 min. (matching the pattern).

5.12. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite A (15% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.6 g of Zeolite A.

As such, 2.56 g (Y = 57%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.50 min. (matching the pattern).

5.13. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite Y (3% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.1 g of Zeolite Y.

As such, 1.99 g (Y = 44%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.43 min. (matching the pattern).

5.14. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite Y (5.5% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.2 g of Zeolite Y.

As such, 2.24 g (Y = 50%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.35 min. (matching the pattern).

5.15. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite Y (8% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Zeolite Y.

As such, 2.82 g (Y = 63%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.48 min. (matching the pattern).

5.16. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite Y (15% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.6 g of Zeolite Y.

As such, 2.23 g (Y = 50%) **IIIa** was obtained, TLC R_f = 0.47, HPLC R_t = 2.48 min. (matching the pattern).

5.17. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite Y (Sodium Powder 5:1:1 SiO_2:Al_2O_3, ALFA AESAR) (8% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Zeolite Y (sodium powder 5:1:1 SiO_2:Al_2O_3, ALFA AESAR).

As such, 3.45 g (Y = 77%, purity 85%) **IIIa** was obtained. After crystallization from isopropanol, the purity was 100%. TLC R_f = 0.47, UPLC-MS R_t = 4.98 min., *m/z* = 448 [M+H].

5.18. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeolite ZSM-5 (ACROS ORGANICS) (8% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Zeolite ZSM-5 (ACROS ORGANICS).

As such, 3.54 g (Y = 79%, purity 85%) **IIIa** was obtained. After crystallization from methanol, the purity was 100%. TLC R_f = 0.47, UPLC-MS R_t = 4.95 min., *m/z* = 448 [M+H].

5.19. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Zeosil 1165 (Solvay) (8% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Zeosil 1165 (Solvay).

As such, 3.76 g (Y = 74%, purity 85%) **IIIa** was obtained. After crystallization from isopropanol, the purity was 100%. TLC R_f = 0.47, UPLC-MS R_t = 4.97 min., *m/z* = 448 [M+H].

5.20. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Boehmite Alumina Powder (Disperal, SASOL) (8% by Weight) in a Ball Mill (Planetary Ball Mill PM 100-RETSCH)

The process was carried out in the same way as described in point 5.7, using 0.3 g of Disperal.

As such, 3.62 g (Y = 81%, purity 85%) **IIIa** was obtained. After crystallization from methanol, the purity was 100%. TLC R_f = 0.47, UPLC-MS R_t = 4.98 min., *m/z* = 448 [M+H].

5.21. Synthesis of Aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) (IIIa) with the Addition of Additives Improving the Insulation of the Product (8% by Weight) in a Ball Mill (Planetary Ball Mill Pulverisette 7 Premium Line, Fritsch GmbH)

General procedure: 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (**Ia**) (0.01 mol, 2.98 g), 1-(2,3-dichlorophenyl) piperazine hydrochloride (**IIa**) (0.011 mol, 2.94 g), potassium carbonate (0.03 mol, 4.14 g), phase transfer catalyst (0.001 mol) and 8% by weight *of* additives improving the insulation of the product, which was weighed, placed in a ball mill and ground for 30 min. Then, the mixture was transferred to a beaker containing 50 cm^3 of water, stirred and cooled to 4 °C. After 24h, the crude aripiprazole (**IIIa**) was filtered off under reduced pressure, washed with water and air dried. The presence of aripiprazole (**IIIa**) was determined each time by TLC and UPLC-MS. TLC R_f = 0.47, UPLC-MS R_t = 4.95–4.98 min., *m/z* = 448 [M+H].

6. Patents

Part of the results are described in the patent application: Jaśkowska J., Jodłowski P., Drabczyk A. K., Kułaga D., Zaręba P., Pindelska E. Method for the production of *N*-substituted aryl piperazines PL434376 (A1)—20 December 2021.

Author Contributions: Conceptualization, supervision, methodology, investigation, resources, writing—original draft, J.J. (Jolanta Jaśkowska); synthesis in mortar, selection and preparation of reagents J.J. (Jolanta Jaśkowska), A.K.D., D.K. and P.Z.; synthesis in ball mill, selection and preparation of reagents J.J. (Jolanta Jaśkowska), A.K.D., E.P., P.J., P.M., Z.M. and J.J. (Jarosław Jakubski); analysis of physico-chemical data, confirmation of the identity of the molecules, J.J. (Jolanta Jaśkowska), A.K.D., D.K. and P.Z.; HPLC and FT-IR analyzes A.K.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data has not been archived anywhere. Some of the results are published as a patent application, which is described in the appropriate section.

Conflicts of Interest: The authors declare no conflict of interest.

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