United States Court of Appeals for the Federal Circuit

OTSUKA PHARMACEUTICAL CO., LTD.,
Plaintiff-Appellee,

v.

SANDOZ, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON BV, SYNTHON HOLDINGS BV, SYNTHON LABORATORIES, INC., AND SYNTHON PHARMACEUTICALS, INC.,
Defendants,

and

APOTEX INC. AND APOTEX CORP.,
Defendants-Appellants,

and

TEVA PHARMACEUTICALS USA, INC., BARR LABORATORIES, INC., AND BARR PHARMACEUTICALS, INC.,
Defendants-Appellants.

2011-1126, -1127

Appeal from the United States District Court for the District of New Jersey in Case No. 07-CV-1000, Judge Mary L. Cooper.

Decided: May 7, 2012

JAMES B. MONROE, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Washington, DC, argued for plaintiff-appellee. With him on the brief were MICHAEL J. FLIBBERT, PAUL M. BROWNING and DENISE MAIN. Of counsel on the brief were ROBERT L. BAECHTOLD and JOHN D. MURNANE, Fitzpatrick, Cella, Harper & Scinto, of New York, New York.

STEVEN E. FELDMAN, Husch Blackwell LLP, of Chicago, Illinois, argued for defendants-appellants Apotex Inc., et al. With him on the brief were DANIEL R. CHERRY and SHERRY L. ROLLO.

ELIZABETH J. HOLLAND, Kenyon & Kenyon LLP, of New York, New York, for defendants-appellants Teva Pharmaceuticals USA, Inc., et al. With her on the brief was MARIA LUISA PALMESE.

Before LOURIE, MOORE, and REYNA, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Apotex Inc., Apotex Corp., Teva Pharmaceuticals USA, Inc., Barr Laboratories, Inc., and Barr Pharmaceuticals, Inc. (collectively, the "Defendants") appeal from the final decision of the United States District Court for the District of New Jersey sustaining the validity of the asserted claims of U.S. Patent 5,006,528 (the "'528 patent) under 35 U.S.C. § 103 and under the doctrine of nonstatutory double patenting. We affirm.

BACKGROUND

Schizophrenia is a debilitating mental disease affecting about one percent of the human population. Despite

extensive research, the cause, mechanism, and etiology of schizophrenia remain unknown. Individuals with schizophrenia suffer from positive symptoms, negative symptoms, and cognitive deficits. Positive symptoms include hallucinations and delusions. Negative symptoms include flat affect, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation.

Drugs that treat schizophrenia are called antipsychotics. The first antipsychotic drug, chlorpromazine, was discovered by accident in the early 1950s. Subsequent research revealed that chlorpromazine's antipsychotic properties were due to its antagonism (blocking) of dopamine receptors in the brain. That finding resulted in the development of other "typical" antipsychotics, which treat positive symptoms but not negative symptoms and have a number of problematic side effects, including extrapyramidal symptoms ("EPS"), tardive dyskinesia, prolactin elevation (hyperprolactinemia), and sudden decrease in blood pressure (orthostatic hypotension). The United States Food and Drug Administration ("FDA") last approved a typical antipsychotic in 1975. Despite their drawbacks, typical antipsychotics are still used today.

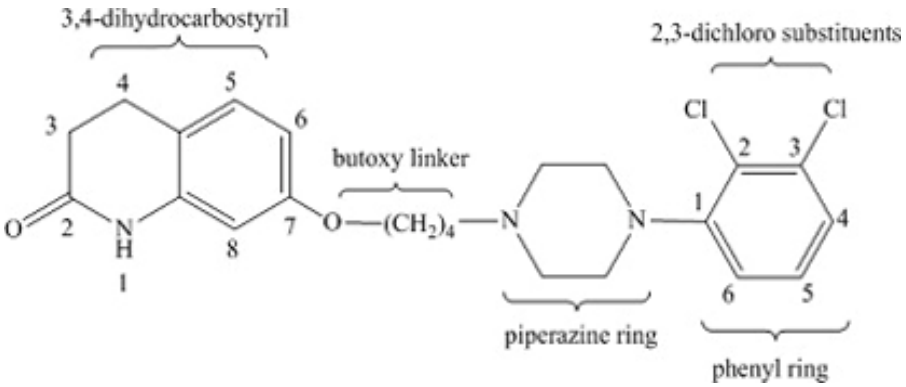
Researchers discovered clozapine in the early 1960s. Clozapine was the first "atypical" antipsychotic, in that it had a diminished propensity to cause EPS and was useful for treating both positive and negative symptoms of schizophrenia. Clozapine had serious potential side effects, however, including orthostatic hypotension, frank hypotension, and agranulocytosis (a life-threatening decrease in white blood cells). Due to those side effects clozapine was withdrawn from clinical trials in the 1970s, prompting scientists to seek an atypical antipsychotic drug similar to clozapine with respect to efficacy but lacking its toxicity and side effects. Researchers' efforts

were largely unsuccessful, however, and the FDA approved no new antipsychotic drugs between 1976 and 1989. The FDA finally approved clozapine in 1990, but only for treatment-resistant or treatment-intolerant patients, subject to rigorous blood testing.

The FDA approved risperidone, the first post-clozapine atypical antipsychotic, in 1994. Since then the FDA has approved seven other atypical antipsychotics: olanzapine (1996); quetiapine (1997); ziprasidone (2001); aripiprazole (2002); paliperidone (2007); asenapine (2009); and iloperidone (2009). Although clozapine remains the "gold standard" with respect to efficacy, the other atypical antipsychotics are considered at least as effective as typical antipsychotics for treating positive symptoms, while also treating negative symptoms and causing fewer EPS side effects. Every FDA-approved atypical antipsychotic has a chemical structure related either to clozapine or risperidone, with the sole exception of aripiprazole—the compound at issue in the present appeal.

Aripiprazole is the active ingredient in the antipsychotic drug marketed by Otsuka Pharmaceutical Co., Ltd. ("Otsuka") under the brand name Abilify®. The culmination of several decades of drug development efforts, Abilify® was approved in 2002 by the FDA and is marketed for the treatment of schizophrenia, bipolar disorder, irritability associated with autistic disorder in pediatric patients, and as an add-on treatment for depression. Abilify® has been commercially successful; since 2005 its annual sales have exceeded a billion dollars, and in 2009 its sales were $3.3 billion.

Aripiprazole has the chemical name 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril and has the following chemical structure:



aripiprazole

Otsuka Pharm. Co. v. Sandoz, Inc., No. 3:07-cv-1000, 2010 U.S. Dist. LEXIS 132595, at *15 (D.N.J. Dec. 15, 2010). Aripiprazole is a "carbostyril derivative," that is, its chemical structure contains a quinolinone fused ring (labeled as "3,4-dihydrocarbostyril" in the structure above). Aripiprazole's carbostyril ring is referred to as "3,4-dihydro" because it has two hydrogen atoms (not shown in the structure above) connected to the 3 and 4 positions, and thus has a single bond between these two carbon atoms. In contrast, a "carbostyril" moiety has only one hydrogen atom at the 3 and 4 positions and a resulting double bond between the carbon atoms. Researchers refer to both variants as "carbostyril derivatives." Connected to the 7-position of aripiprazole's carbostyril core is a "butoxy linker" consisting of four methylene ($–CH_2–$) units. A "propoxy linker," in contrast, consists of only three methylene units. Connected to aripiprazole's butoxy linker is a piperazine ring and a phenyl ring. The terminal phenyl ring of aripiprazole is "2,3-dichloro" substituted, meaning that it has chlorine atoms connected to the 2 and 3 positions.

Otsuka is the assignee of the '528 patent, which has a foreign priority date of October 31, 1988, was filed on

October 20, 1989, and issued on April 9, 1991. The exclusivity afforded by the '528 patent, including a five-year patent term extension and a six-month period of pediatric exclusivity, will expire on April 20, 2015. *Id.* at *14. Claim 12 of the '528 patent claims aripiprazole using its chemical name. '528 patent col.19 ll.18–19. Claim 16 claims "[a] pharmaceutical composition for treating schizophrenia containing, as the active ingredient, a carbostyril compound . . . ," *id.* col.19 l.16–col.20 l.3, and claim 17 claims "[t]he pharmaceutical composition of claim 16 wherein the carbostyril compound" is aripiprazole, *id.* col.20 ll.4–7. Claim 23, which was added during re-examination of the '528 patent, claims a method of treating schizophrenia comprising administering a pharmaceutical composition containing aripiprazole as an active ingredient. Ex Parte Reexamination Certificate, '528 patent col.2 ll.13–16.

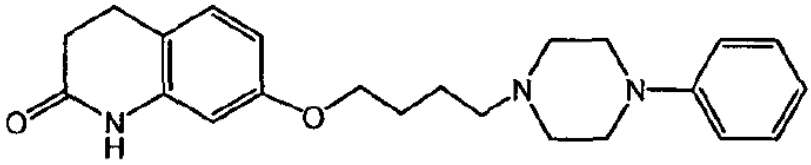
The Defendants and several other companies submitted Abbreviated New Drug Application ("ANDA") filings to the FDA for approval to engage in the commercial manufacture, use, or sale of generic aripiprazole products. Otsuka brought actions against these generic drug manufacturers for patent infringement; most of those actions were consolidated into the case now before us on appeal. *See Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *3–5. Otsuka asserted that the Defendants infringed claims 12, 17, and 23 of the '528 patent under 35 U.S.C. § 271(e)(2)(A). The Defendants conceded that their ANDA filings constituted literal infringement but asserted in defense and counterclaimed that the claims were invalid for obviousness and obviousness-type double patenting.[1]

[1] The Defendants also asserted an ultimately unsuccessful inequitable conduct defense and counterclaim, which are not at issue on appeal.

The district court held a bench trial from August 5 through August 26, 2010, and heard closing arguments on October 21, 2010. The court entered its Amended Memorandum Opinion on December 15, 2010. *See id.* at *5.

On the issue of obviousness under § 103, the court concluded that the Defendants failed to prove by clear and convincing evidence that the asserted claims would have been obvious to one of ordinary skill. In its analysis, the court considered the known carbostyril derivatives, with particular emphasis on the three purported "lead compounds" asserted by the Defendants. *Id.* at *53.

The first of the Defendants' alleged lead compounds is 7-[4-(4-phenylpiperazinyl)-butoxy]-3,4-dihydrocarbostyril, which has the following chemical structure:



"unsubstituted butoxy"

Br. Defs.-Appellants Apotex, at 12. The parties refer to this compound as the "unsubstituted butoxy," because its phenyl ring is unsubstituted and it has a butoxy linker connecting the 7-position of its carbostyril core to its piperazine ring.

The unsubstituted butoxy is disclosed and claimed in Otsuka's earlier U.S. Patent 4,734,416 (the "'416 patent"), which the parties agree is prior art to the '528 patent. The '416 patent issued on March 29, 1988, and expired on March 29, 2005. Entitled "Pharmaceutically Useful Carbostyril Derivatives," the '416 patent teaches a broad genus encompassing "approximately nine trillion compounds." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *12.

The '416 patent discloses that "[c]arbostyril derivatives having antihistaminic action and central nervous controlling action are useful as antihistaminic agents or central nervous controlling agents." '416 patent abstract. The patent further discloses that the compounds:

> are useful for central nervous controlling agents such as central muscle relaxing agents, sleep-inducing agents, pre-operative drugs, antischizophrenia agents, sedatives, antianxiety drugs, antimanic depressive psychosis agents, antipyretic agents, analgetic agents and depressors, without showing side-effects such as the feeling of thirst, constipation, tachycordia [sic], parkinsonism, and/or delayed dyscinesia [sic] which exist with conventional central nervous controlling agents.

Id. col.3 ll.14–22. Claim 13 of the '416 patent claims the unsubstituted butoxy using its chemical name. *Id.* col.70 ll.62–63. Claim 50 claims "[a] method of producing an antihistaminic effect in a mammal comprising the step of administering to the mammal for producing said antihistaminic effect a pharmaceutical composition containing a suitable amount of a carbostyril derivative" having a general chemical formula, *id.* col.76 ll.1–60, and claim 116 claims "[t]he method of claim 50, wherein the carbostyril derivative is selected from the group consisting of" nine specific carbostyril derivatives, including the unsubstituted butoxy, *id.* col.84 ll.29–46.

The unsubstituted butoxy is also disclosed in a declaration submitted during the prosecution of the '416 patent by one of that patent's co-inventors, Dr. Kazuyuki Nakagawa (the "Nakagawa declaration"). J.A. 3792–3807. The Nakagawa declaration discloses three sets of test data comparing certain carbostyril derivatives. The first two measure the compounds' antihistaminic activity. The

third involves a test for "Activity for inhibiting jumping behavior in mouse induced by Methamphetamine and L-DOPA." J.A. 3803. Although the Nakagawa declaration nowhere mentions schizophrenia or antipsychotic activity, and despite conflicting evidence regarding the use of mouse jumping test data in antipsychotic drug discovery, the district court found that Dr. Nakagawa's mouse jumping data "could be indicative of potential antipsychotic activity to the skilled artisan." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *34.

The Nakagawa declaration provides mouse jumping test data for nine carbostyril derivative test compounds and two prior art reference compounds. The potency of the compounds is indicated with an effective dosage ("ED_{50}") value measured in milligrams per kilogram, wherein a lower value indicates greater potency in the mouse jumping test. The following table summarizes the data for the test compounds.

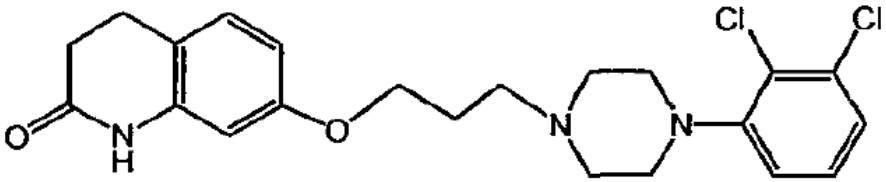
Compound No.	**Chemical Name**	**ED_{50}**
5	5-[3-(4-phenylpiperazinyl)propoxy]-3,4-dihydrocarbostyril dihydrochloride	2.1
6	7-[3-(4-phenylpiperazinyl)propoxy]-3,4-dihydrocarbostyril dihydrochloride	9.3
16	7-{3-[4-(4-chlorophenyl)piperazinyl]propoxy}-3,4-dihydrocarbostyril	15.1

39	7-{3-[4-(3-chlorophenyl)piperazinyl]propoxy}-3,4-dihydrocarbostyril	2.5
41	7-[4-(4-phenyl-1-piperazinyl)butoxy]-3,4-dihydrocarbostyril ("unsubstituted butoxy")	5.5
42	1-methyl-7-[3-(4-phenyl-1-piperazinyl)propoxy]-3,4-dihydrocarbostyril	10.7
43	7-{3-[4-(2-chlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril	3.4
44	5-{3-[4-(2-ethoxyphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril	0.53
45	5-{3-[4-(4-methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril	8.1

J.A. 3794, 3796, 3805. The two most potent carbostyril derivatives tested in the mouse jumping study have a 5-propoxy linker, *i.e.*, a propoxy substituent connected at the 5-position of the carbostyril core. Compound 44, the most potent derivative with an ED_{50} of 0.53, has a 5-propoxy linker and an ethoxy substituent ($–OCH_2CH_3$) at the 2-position of its phenyl ring. Compound 5, the second most potent derivative with an ED_{50} of 2.1, has a 5-propoxy linker and an unsubstituted phenyl ring. Of the 7-linked carbostyril derivatives for which Dr. Nakagawa provided mouse jumping data, Compound 39, a 3-chloro

substituted propoxy,[2] had an ED_{50} of 2.5; Compound 43, a 2-chloro substituted propoxy, had an ED_{50} of 3.4; Compound 41, the unsubstituted butoxy, had an ED_{50} of 5.5; Compound 6, an unsubstituted propoxy, had an ED_{50} of 9.3; and Compound 16, a 4-chloro substituted propoxy, had an ED_{50} of 15.1. Thus, the best compounds in this test were the propoxys, not the butoxy.

The second alleged lead compound considered by the district court is a carbostyril derivative with the chemical name 7-{3-[4-(2,3-dichlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril and the chemical structure depicted below:



"2,3-dichloro propoxy"

Br. Defs.-Appellants Apotex, at 9. The parties refer to this compound as the "2,3-dichloro propoxy" because its phenyl ring is substituted with a chlorine atom at the 2 and 3 positions and it has a propoxy linker connecting its carbostyril core and its piperazine ring. The 2,3-dichloro propoxy was disclosed in two prior art foreign counterparts to Otsuka's '416 patent: German Patent 2,912,105 (the "DE '105 patent"), J.A. 3808–930, at 3926 (example 317); and Swedish Patent Publication 434,945 (the "SE '945 application"), J.A 6396–565, at 6556 (example 134). Like the '416 patent, the SE '945 application teaches that its carbostyril derivatives "can be used as antihistamines

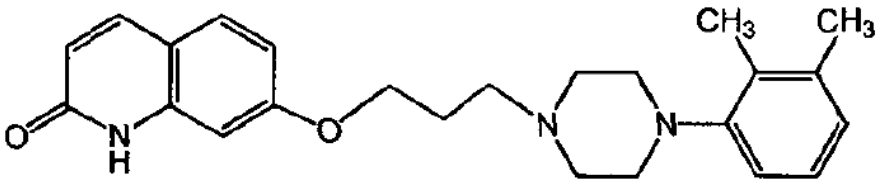
[2] Elsewhere in its opinion the district court referred to Compound 39 as "OPC-4139." *See Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *42.

or agents having a regulating action in the central nervous system," J.A. 6495, and discloses numerous examples of agents in the latter category:

> The compounds according to the present invention are therefore useful as means of controlling the central nervous system as muscle relaxants, sleeping agents, presurgery drugs, antischizophrenia agents, sedatives, anxiolytics, drugs for manic-depressive psychosis, fever-lowering agents, analgesics and "depressors" without showing side effects such as thirst, constipation, tachycardia, parkinsonism and/or delayed dyschezia, which are displayed by conventional agents which act on the central nervous system.

J.A. 6499. The SE '945 application "discloses dozens of carbostyril compounds," and the 2,3-dichloro propoxy "is just one of ninety-six different compounds disclosed in Example 134 alone." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *37–38. The DE '105 patent "is substantially the same as the SE '945 application except that the DE '105 Patent omits any mention of potential antipsychotic activity." *Id.* at *38.

The final purported lead compound considered by the district court is OPC-4392. This carbostyril derivative, which has the following chemical structure, has a 2,3-dimethyl substituted phenyl ring, a propoxy linker, and a carbostyril ring containing a double bond at the 3,4-position:



"OPC-4392"

Br. Defs.-Appellants Apotex, at 10. OPC-4392 is an Otsuka development compound and, as of the priority date of the '528 patent, was the only carbostyril derivative tested in humans as a potential antipsychotic. A prior art article published in 1987 describes OPC-4392 as "a totally new compound that is an anti-psychotic drug being developed." Mitsukuni Murasaki, *New Psycho-Neuro Agents*, 16 Japanese J. Clinical Psychiatry 1515, 1517 (1987) ("Murasaki 1987"); J.A. 5891–919, at 5907. The Murasaki 1987 article further notes that "the anti-psychotic action was not strong but the strength of the activating action stood out," that "improvements were observed in the negative symptoms," and that "the extra-pyramidal disturbances are extremely weak." J.A. 5907. A prior art publication from January 1988 by the same author stated that OPC-4392 was "expected to have some advantageous effects different from those of conventional antipsychotic drugs," such as chlorpromazine. Mitsukuni Murasaki, *Phase 1 Study of a New Antipsychotic Drug, OPC-4392*, 12 Progress Neuro-Psychopharmacology & Biological Psychiatry 793, 802 (1988) ("Murasaki 1988"); J.A. 10396–406, at 10405. Although the article stated that OPC-4392 was "expected to have fewer side effects than conventional drugs of the same class," it also reported that subjects receiving a 5-milligram dose of OPC-4392 "experienced sleeplessness, stagger, weakness, fatigability, heavy headedness, lack of motivation and disturbed concentration, which were so severe that they were not able to perform daily routine work." J.A. 10397, 10401.

Evaluating the differences between the claimed invention and the prior art, the district court found that the asserted prior art did not teach one of ordinary skill to select the unsubstituted butoxy, the 2,3-dichloro propoxy, or OPC-4392 as a lead compound for further antipsychotic research. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *59,

*64, *70. Rather, the court found that a structure like clozapine or risperidone—both of which are structurally dissimilar to aripiprazole—would have been an attractive lead compound. *Id.* at *76. The court thus concluded that the Defendants failed to prove by clear and convincing evidence that one of ordinary skill would have been motivated to combine the asserted prior art to make aripiprazole and would have had a reasonable expectation of success in doing so. *Id.* at *76–77.

The court then turned to the issue of nonstatutory obviousness-type double patenting. The court considered whether aripiprazole and its uses are not patentably distinct from the unsubstituted butoxy in claim 13 of the '416 patent. *Id.* at *88. Noting the structural differences between aripiprazole and the unsubstituted butoxy, the court found that the prior art did not teach one of ordinary skill to achieve antipsychotic activity by modifying the unsubstituted butoxy with a 2,3-dichloro substitution on its phenyl ring to make aripiprazole. *Id.* at *90–91. The court thus concluded that the Defendants failed to prove by clear and convincing evidence that the asserted claims were invalid for nonstatutory double patenting. *Id.* at *92.

On December 15, 2010, the court entered its Amended Order and Final Judgment in favor of Otsuka. *Otsuka Pharm. Co. v. Sandoz, Inc.*, No. 3:07-cv-1000 (D.N.J. Dec. 15, 2010). The Defendants timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A patent is invalid if an alleged infringer proves, by clear and convincing evidence, that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the pertinent art. 35 U.S.C. §§ 103(a), 282(2); *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011). Obviousness is a question of law with underlying factual findings, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence such as commercial success, long-felt need, and the failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Similarly, nonstatutory obviousness-type double patenting is a question of law with underlying findings of fact. *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985).

Following a bench trial, we review the district court's conclusions of law *de novo* and its findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

I

We first address the Defendants' arguments that the district court erred by failing to hold the asserted claims invalid for obviousness under § 103.[3]

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[3] Defendants-Appellants Apotex Inc. and Apotex Corp. submitted one set of appellate briefs addressing the issues of § 103 obviousness and nonstatutory double patenting. Defendants-Appellants Teva Pharmaceuticals USA, Inc., Barr Laboratories, Inc., and Barr Pharmaceuticals, Inc., submitted another set of briefs that addressed only nonstatutory double patenting, but joined in full the principal and reply briefs filed by Apotex. For purposes of this opinion we will refer to the arguments in both sets of briefs as the Defendants' arguments.

The Defendants contend that aripiprazole would have been obvious over the prior art carbostyril derivative compounds at the time aripiprazole was invented. They assert that the lead compound analysis applied by the district court violates our precedent and "fall[s] into a rigid obviousness analysis precluded by *KSR*." Br. Defs.-Appellants Apotex, at 35–36. In this regard, the Defendants allege that the court erred by assuming that "only the most obvious choice could serve as a lead." *Id.* at 34. According to the Defendants, prior art compounds, including the 2,3-dichloro propoxy, the unsubstituted butoxy, and OPC-4392, were known to have antipsychotic activity, and it would have been obvious to chemically modify them in the ways necessary to make aripiprazole. Finally, they argue that aripiprazole's properties and other secondary considerations do not render aripiprazole nonobvious.

Otsuka, in response, argues that the district court correctly rejected the Defendants' obviousness contentions, which are based on improper hindsight bias. Otsuka points out that no carbostyril derivative had been shown to effectively treat schizophrenia as of the priority date of the '528 patent. Otsuka also contends that the district court did not require proof that aripiprazole was the "most obvious" compound, but rather evaluated all of the potential choices available to one of ordinary skill and determined that the prior art did not suggest that the unsubstituted butoxy, 2,3-dichloro propoxy, or OPC-4392 would be suitable lead compounds. Otsuka also asserts that secondary considerations support the court's conclusion of nonobviousness.

For the following reasons, we hold that the district court correctly determined that the Defendants failed to prove by clear and convincing evidence that the asserted claims would have been obvious under § 103.

A. The District Court's "Lead Compound" Analysis

In cases involving the patentability of a new chemical compound, *prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds. *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010). The Defendants assert that the district court erred by employing a "lead compound" analysis as part of its determination under the third *Graham* factor. We reject that contention. New compounds may be created from theoretical considerations rather than from attempts to improve on prior art compounds. In this case, however, the parties' arguments focus on selecting and modifying particular prior art compounds, designated as lead compounds.

Our case law demonstrates that whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."). A lead compound, as we have explained, is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). As such, a lead compound is "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). In recent cases involving the alleged obviousness of a new

chemical compound, the parties have frequently focused upon the notion that a chemist must select one or more lead compounds. *E.g.*, *Daiichi*, 619 F.3d at 1352; *Altana*, 566 F.3d at 1007; *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *Eisai*, 533 F.3d at 1357; *Takeda*, 492 F.3d at 1357; *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000); *cf. Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1362 (Fed. Cir. 2011) ("[T]he term "reference composition" is more appropriate than "lead compound" when considering obviousness for a chemical composition."). In such cases our analysis focuses on those proposed lead compounds that the alleged infringer has attempted to prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art. *Daiichi*, 619 F.3d at 1354.

In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties. *See Eli Lilly*, 471 F.3d at 1378; *In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984). Such properties may include positive attributes such as activity and potency, *Altana*, 566 F.3d at 1008; *Eli Lilly*, 471 F.3d at 1379; *Yamanouchi*, 231 F.3d at 1345; adverse effects such as toxicity, *Takeda*, 492 F.3d at 1358, and other relevant characteristics in evidence, *see Eisai*, 533 F.3d at 1358 (considering a prior art compound's lipophilicity and low molecular weight); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363 (Fed. Cir. 2007) (considering the "strength, solubility, and other known chemical characteristics" of a prior art salt-forming acid). Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound

does not inform the lead compound selection. *See Daiichi*, 619 F.3d at 1354; *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc) ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, *where the prior art gives reason or motivation to make the claimed compositions*, creates a *prima facie* case of obviousness." (emphasis added)). Were it otherwise, the analysis would impermissibly rely upon *ex post* reasoning. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.").

The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Takeda*, 492 F.3d at 1357 ("[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."); *Pfizer*, 480 F.3d at 1361 ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."); *Dillon*, 919 F.2d at 692.

In keeping with the flexible nature of the obviousness inquiry, the reason or motivation for modifying a lead compound may come from any number of sources and need not necessarily be explicit in the prior art. *Eisai*, 533 F.3d at 1357 (citing *KSR*, 550 U.S. at 415); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d

1293, 1301 (Fed. Cir. 2007). Again, pertinent properties guide the analysis, for "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Daiichi*, 619 F.3d at 1354 ("Potent and promising activity in the prior art trumps mere structural relationships."); *see also Eli Lilly*, 471 F.3d at 1378 ("[P]atentability for a chemical compound does not depend only on structural similarity."); *In re Stemniski*, 444 F.2d 581, 586 (CCPA 1971). As we have explained, "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis*, 499 F.3d at 1301 (quoting *Dillon*, 919 F.2d at 692); *see also In re Wilder*, 563 F.2d 457, 460 (CCPA 1977).

In the present case, in assessing whether aripiprazole would have been *prima facie* obvious in view of the prior art compounds asserted by the Defendants, the district court summarized the applicable law as requiring inquiry into

> the hypothetical person of skill in the art's identification of a lead compound, structural differences between the proposed lead compound and the claimed invention, motivation or teachings in the prior art to make the necessary changes to arrive at the claimed invention, and whether the person of skill in the art would have a reasonable expectation of success in making such structural changes.

Otsuka, 2010 U.S. Dist. LEXIS 132595, at *52–53. We discern no error in the district court's recitation of the applicable law. Moreover, the court did not require, as the Defendants allege, that only "the most obvious choice"

could serve as the lead. Rather, the district court concluded that two compounds—clozapine and risperidone—would have been considered viable lead compounds. *Id.* at *76. These were the only marketed antipsychotic compounds at the time the present inventors began their work. They were the natural and obvious lead compounds whose structures one would have considered to modify to obtain improved antipsychotic compounds. At the relevant time, there were no carbostyril compounds that were marketed as antipsychotics or were publicly known to have potent antipsychotic activity with minimal side effects. Carbostyrils were thus not plausible lead compounds, except in retrospect, and the district court did not clearly err in concluding that they were not.

As for the Defendants' purported lead compounds, the district court carefully considered each compound and correctly rejected the contention that a skilled artisan would have selected those compounds for further antipsychotic drug research efforts.

B. The Unsubstituted Butoxy Compound

In evaluating the differences between the claimed invention and the prior art, the district court first considered the unsubstituted butoxy compound disclosed in the prior art '416 patent and the Nakagawa declaration. The Defendants contend that the court erred by finding that a skilled artisan would not have selected the unsubstituted butoxy as a lead compound for antipsychotic drug discovery. We disagree.

As the court noted, the claims of the prior art '416 patent explicitly disclose the unsubstituted butoxy as producing an antihistaminic effect. This clear teaching controls over the far more nebulous disclosure that the trillions of carbostyril compounds encompassed by the '416 patent "have antihistaminic and central nervous

controlling effects." '416 patent col.2 ll.50–51. As explained by Dr. Bryan Roth, whom the court credited as an expert in schizophrenia, antipsychotic drug discovery, and psychopharmacology, one of ordinary skill in the art would not have understood the '416 patent's "laundry list" of potential central nervous system controlling effects to mean that every carbostyril derivative disclosed in the '416 patent is a potential antipsychotic. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *26, *31.

The Nakagawa declaration similarly fails to support the Defendants' contentions. As an initial matter, Otsuka argues in a footnote to its brief that the Nakagawa declaration is not eligible as prior art because the Defendants failed to prove that a chemist seeking to develop a new antipsychotic drug would have consulted the unindexed file history of the prior art '416 patent in the course of his or her research. Br. Pl.-Appellee Otsuka, at 24 n.1. Arguments raised only in footnotes, however, are waived. *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006). Although we may exercise our discretion to consider improperly raised arguments, we decline to do so here. *See Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 800 (Fed. Cir. 1990). We therefore assume, without deciding, that the Nakagawa declaration qualifies as prior art.

Although Nakagawa's mouse jumping data "could be indicative of potential antipsychotic activity to the skilled artisan," *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *34, that alone does not resolve the matter. Rather, we must consider the contents of the declaration as a whole, as the district court correctly did. In doing so, we focus in particular on the compounds' disclosed properties because, as the district court found, "[g]enerally, a skilled artisan would be attracted to the most potent compounds in

selecting a lead compound for development." *Id.* at *54; *see also Daiichi*, 619 F.3d at 1354.

Of the nine carbostyril test compounds for which the Nakagawa declaration supplied mouse jumping data, the unsubstituted butoxy was inferior to four other test compounds and thus "was only of middling potency." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *65. Significantly, the four more potent test compounds were all propoxy-linked, including Compound 44, which, with an ED_{50} of 0.53 milligrams per kilogram, "was by far the most potent of the compounds tested." *Id.* at *54. One of the Defendants' own experts conceded that the activity of Compound 44 was "striking," and Dr. Roth testified that if a skilled artisan were to select any compound from the Nakagawa declaration, it would be Compound 44. *Id.* at *54, *56. The Defendants do not allege obviousness over the structurally dissimilar Compound 44, which, unlike aripiprazole, has a propoxy linker connected at the 5-position of its carbostyril core and a 2-ethoxy substituent on its phenyl ring. As the district court found, the Nakagawa declaration would, if anything, have taught one of ordinary skill to select a 5-linked propoxy carbostyril derivative as a lead compound. *See id.* at *57 (comparing the ED_{50} value of 2.1 for a 5-linked unsubstituted propoxy and the ED_{50} value of 9.3 for a 7-linked unsubstituted propoxy and finding that this "significant" difference "would teach the skilled artisan the superiority of 5-linked propoxy compounds over 7-linked propoxy compounds").

Thus, neither the '416 patent nor the Nakagawa declaration supports the Defendants' position that one of ordinary skill would have selected the prior art unsubstituted butoxy compound as a lead compound for further antipsychotic research.

C. The 2,3-Dichloro Propoxy Compound

According to the Defendants, the district court erred by failing to find that aripiprazole would have been obvious over the SE '945 application, which taught that the 2,3-dichloro propoxy compound had antipsychotic activity. We disagree. The Defendants' argument "strains the scope of the SE '945 application." *Id.* at *62. As the district court correctly found, the SE '945 application lists the 2,3-dichloro propoxy compound "as one among hundreds of examples that may be useful for an extensive list of potential central nervous system controlling activities," *id.*, and fails to tie the 2,3-dichloro propoxy to any meaningful suggestion of antipsychotic activity.

The Defendants, citing *Pfizer*, 480 F.3d 1348, allege that the SE '945 application's generic disclosure "is all that is required for obviousness." Br. Defs.-Appellants Apotex, at 37. In *Pfizer*, this court held that the claimed amlodipine besylate salt would have been obvious in view of the known chemical structure of amlodipine and a prior art group of salt-forming anions including benzene sulphonate (which combines with amlodipine to form the besylate salt). *Pfizer*, 480 F.3d at 1372. This court premised its conclusion on findings that the prior art not only provided "ample motivation to narrow the [prior art] genus of . . . salt-forming anions . . . to a few [species]," *id.* at 1363, but also "predicted the results," *id.* at 1367. In the present case, in contrast to *Pfizer*, the Defendants failed to make an analogous showing. The district court thus correctly found that one of ordinary skill in the art would not have selected the 2,3-dichloro propoxy compound as a lead compound for further antipsychotic research.

Furthermore, as Otsuka points out, the Defendants' theory that aripiprazole would have been obvious over the

unsubstituted butoxy and the 2,3-dichloro propoxy rested in large part upon an asserted "bracketing theory"—*i.e.*, that one would have combined those two asserted compounds to arrive at aripiprazole, which shares some structural features of both. The district court found that the Defendants' theory constituted "an improper hindsight analysis." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *64. The Defendants do not on appeal challenge the district court's finding or re-assert their bracketing theory. Accordingly, we conclude that the Defendants failed to prove by clear and convincing evidence that aripiprazole would have been obvious over the 2,3-dichloro propoxy.

D. OPC-4392

The Defendants also assert that the district court erred by rejecting OPC-4392 as a lead compound. Again, we disagree. The Defendants rely selectively on the disclosure in Murasaki 1987 that OPC-4392 was "an antipsychotic drug," J.A. 5907, and the fact that OPC-4392 proceeded to Phase II clinical trials. Taken as a whole, however, the prior art taught away from using OPC-4392 as a starting point for further antipsychotic research.

For example, Murasaki 1987 teaches that "the antipsychotic action [of OPC-4392] was not strong." *Id.* Based on that teaching, together with other prior art of record that focuses only on the effects of OPC-4392 on schizophrenia's negative symptoms, a skilled artisan would have concluded that OPC-4392 did not treat positive symptoms. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *68–69. The district court also credited the testimony of one of the Defendants' witnesses, who stated that clinical studies of OPC-4392 showed that it "lacked [an] antipsychotic component." *Id.* at *68. Furthermore, Murasaki 1987 taught that "the strength of the activating action [of

OPC-4392] stood out," J.A. 5907, a property that Dr. Roth testified would have been a "red flag" indicating that the drug was likely to cause patients to act out on their delusions and hallucinations. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *69. Another prior art reference, Murasaki 1988, taught that OPC-4392, even at a "very low dose," *id.* at *41, caused "severe" side effects, J.A. 10401. In light of the totality of the evidence before the district court, we perceive no clear error in the conclusion that OPC-4392 was "considered a failure insofar as it did not treat the positive symptoms of schizophrenia and was not well-tolerated in modest doses." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *70. The court thus did not err in concluding that one of ordinary skill in the art would not have selected OPC-4392 as a lead compound for further antipsychotic research.

Even assuming that one would have selected OPC-4392 as a lead compound, the district court found that the Defendants failed to prove that the prior art would have directed one to make the various modifications necessary to convert OPC-4392 into aripiprazole. Those modifications include: (1) converting OPC-4392's carbostyril core into a dihydrocarbostyril; (2) changing OPC-4392's propoxy linker to a butoxy; and (3) replacing OPC-4392's 2-methyl and 3-methyl groups with 2-chloro and 3-chloro substituents. On appeal, the Defendants rely in large part on the inventors' and Otsuka's own development efforts in an attempt to prove that aripiprazole would have been obvious. *E.g.*, Br. Defs.-Appellants Apotex, at 46–47 (arguing that Otsuka's aripiprazole development involved a "short timeline" and only "took a few months"). Those arguments cannot trump the district court's careful fact finding, however. The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordi-

nary skill in the art would have followed, as evidenced by the pertinent prior art. *See* 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."). We therefore agree with the district court that the Defendants failed to provide clear and convincing evidence that the skilled artisan would have known how to modify OPC-4392 to increase antipsychotic activity. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *70.

E. Conclusion

In summary, the district court's careful analysis exposed the Defendants' obviousness case for what it was—a poster child for impermissible hindsight reasoning. Because we agree with the district court that the Defendants failed to prove that claim 12 of the '528 patent would have been *prima facie* obvious over the asserted prior art compounds, we need not address the court's findings regarding objective evidence of nonobviousness. In addition, because the Defendants' arguments for obviousness of dependent claims 17 and 23 rely on a determination of obviousness for independent claim 12, we need not separately analyze the court's finding that the Defendants failed to prove invalidity for the asserted dependent claims.

II

We now turn to the Defendants' contention that the district court erred by failing to hold the asserted claims of the '528 patent invalid for nonstatutory obviousness-type double patenting in view of the unsubstituted butoxy compound of claim 13 of the '416 patent.

An inventor may obtain "a patent" for an invention pursuant to 35 U.S.C. § 101; the statute thus "permits only one patent to be obtained for a single invention." *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997). The double patenting doctrine "precludes one person from obtaining more than one valid patent for either (a) the 'same invention,' or (b) an 'obvious' modification of the same invention." *Longi*, 759 F.2d at 892. Nonstatutory double patenting is a judicially created doctrine grounded in public policy that "prevent[s] the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Id.*

As an initial matter, the parties disagree over the legal test for nonstatutory double patenting. Otsuka contends that there is no difference between obviousness under § 103 and obviousness-type double patenting. That is not entirely correct. We have noted that "a double patenting of the obviousness type rejection is analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. § 103." *Id.* at 892 n.4 (internal quotation marks omitted). Important differences remain, however. The patent principally underlying the double patenting rejection need not be prior art. *Id.* Moreover, when analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the issue is not whether a skilled artisan would have selected the earlier compound as a lead compound. That is so because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, lead compound or not. *See Ortho Pharma. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992) ("[I]t is the claims that are compared when assessing double patenting.").

The Defendants assert that, unlike an analysis under § 103, the test for obviousness-type double patenting never asks whether the prior art would have supplied a motivation to modify the earlier claimed compound. That is also incorrect. Unless the earlier claim anticipates the later claim under § 102, the question whether the two claimed compounds are "patentably distinct" implicates the question of obviousness under § 103, *Longi*, 759 F.2d at 892, which in the chemical context requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success, *see Takeda*, 492 F.3d at 1357, 1361.

The Defendants rely on *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377 n.1 (Fed. Cir. 2003), which states in a footnote that "[o]bviousness requires inquiry into a motivation to modify the prior art; nonstatutory double patenting does not." *Geneva*, however, involved nonstatutory double patenting based on anticipation, not obviousness. *Id.* ("This genus-species relationship makes the claims patentably indistinct, because the earlier species . . . anticipates the later genus . . . ."). For anticipation, of course, motivation in the prior art is unimportant. *See, e.g.*, *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1347 (Fed. Cir. 2009) (noting that, in an "anticipation argument, . . . motivation to combine is not an issue"). The statement from *Geneva* was later recited in dictum in *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009), in which we concluded under § 103 that there would have been no motivation to modify the prior art compound, *id.* at 995, and then stated: "Having concluded that [the asserted compound] was not obvious under 35 U.S.C. § 103, we *similarly conclude* that the [asserted] patent is not invalid for obviousness-type double patenting," *id.* at

999 (emphasis added). Contrary to the Defendants' arguments, neither *Geneva* nor *Procter & Gamble* stands for the proposition that, in considering whether one compound is an obvious variant of another for purposes of nonstatutory double patenting, analyzing the compound of the prior claim for a reason or motivation to modify is irrelevant.

We therefore reject the Defendants' contention that the district court legally erred by relying in part on its findings under § 103 in its subsequent double patenting analysis. The court in this case applied the correct test for nonstatutory obviousness-type double patenting: In the context of claimed chemical compounds, an analysis of nonstatutory obviousness-type double patenting—like an analysis under § 103—entails determining, *inter alia*, whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success. There is no other way to consider the obviousness of compound B over compound A without considering whether one of ordinary skill would have had reason to modify A to make B. That is traditional obviousness analysis.

Turning to the particulars of the district court's decision on nonstatutory double patenting, the Defendants contend that the court improperly treated claim 13 of the '416 patent in isolation without considering prior art, such as the Nakagawa declaration, which would have taught a skilled artisan to substitute a phenyl ring with chlorine atoms at the 2- and 3-positions to make aripiprazole. Otsuka, in response, argues that the court, after considering the Nakagawa declaration in detail, correctly concluded that aripiprazole was not an obvious variant of the unsubstituted butoxy.

We agree with the district court that the asserted claims are not invalid for nonstatutory double patenting. As we explained above, aripiprazole differs structurally from the unsubstituted butoxy of claim 13 of the '416 patent. Aripiprazole has chlorine substituents at the 2 and 3 positions of its phenyl ring, whereas the unsubstituted butoxy has hydrogens at those positions—*i.e.*, it is "unsubstituted." In its double patenting analysis, the court determined "that the prior art, including the Nakagawa Declaration, . . . did not teach the person of ordinary skill in the art to pursue a 2,3-dichloro substitution on the phenyl ring to achieve antipsychotic activity." *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *90–91; *see also id.* at *64. The evidence before the district court supports this finding. For example, the court credited evidence demonstrating the high degree of unpredictability in antipsychotic drug discovery as of the priority date. *Id.* at *48, *61. Experts testified that the discovery of new antipsychotic drugs in the 1980s was "very unpredictable," J.A. 30660, and that antipsychotic research at that time was "notoriously unsuccessful," J.A. 30453. As *KSR* makes clear, predictability is a vital consideration in the obviousness analysis. 550 U.S. at 421; *see also Procter & Gamble*, 566 F.3d at 996 ("[T]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on . . . 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." (quoting *Eisai*, 533 F.3d at 1359)).

As the district court correctly held, the prior art would not have provided a skilled artisan with a reason to make the necessary structural changes to the unsubstituted butoxy to yield aripiprazole. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *91. The Defendants posit that substitution with chlorine atoms at the 2- and 3-positions of the phenyl ring "would have been a logical and routine modi-

fication." Br. Defs.-Appellants Apotex, at 66. The evidence indicates otherwise. The Nakagawa declaration neither disclosed nor would have suggested a 2,3-dichloro substituted antipsychotic compound. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *62; J.A. 30689. And, as we noted above, although other prior art including the SE '945 application disclosed 2,3-dichloro substituted compounds, those references failed to tie that disclosure to any meaningful suggestion of antipsychotic activity. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *62. As Dr. David Nichols, an expert in both medicinal chemistry and pharmacology, testified at trial: "There was no known antipsychotic drug, successful or otherwise, that had those two particular [chlorine] substituents arranged in a 2,3 . . . orientation," and, further, "[t]here's no teaching that suggests that a dichlorination pattern like that would lead to a safe atypical antipsychotic, or even an antipsychotic, period, atypical or otherwise." J.A. 30688–89. In short, we perceive no clear error in the district court's finding that one of ordinary skill would not have been motivated to pursue a 2,3-dichloro substitution on the phenyl ring as would have been required to convert the unsubstituted butoxy to aripiprazole.

Finally, the nonstatutory double patenting issue in this case is not, as the Defendants argue, controlled by *In re Zickendraht*, 319 F.2d 225 (CCPA 1963). In *Zickendraht*, one of our predecessor courts reviewed a decision of the Board of Patent Appeals and Interferences (the "Board") rejecting a claimed metalliferous azodyestuff compound for nonstatutory double patenting over a similar compound claimed in an issued patent. The two compounds were identical but for the presence or absence of a methyl group. *Id.* at 1534. In affirming the Board's rejection, the *Zickendraht* court noted that "[i]t has not been shown that this [chemical] difference has any effect

on the dyeing characteristics of the compound." *Id.* at 1531. The court also pointed out that the earlier "patent disclosure would suggest to one skilled in the art" reacting particular starting components, which "should result in production of the dye claimed" in the pending application. *Id.* at 1532. Unlike in *Zickendraht*, the evidence here not only demonstrates the unpredictability of minor structural changes on a compound's antipsychotic properties, but also indicates that the prior art would not have provided the skilled artisan with a reason to make the necessary structural changes to the unsubstituted butoxy to yield aripiprazole. *Otsuka*, 2010 U.S. Dist. LEXIS 132595, at *61, *91. *Zickendraht*, therefore, is distinguishable from the present case.

Because we agree with the district court that the prior art would not have provided one of ordinary skill with a reason or motivation to make aripiprazole from the unsubstituted butoxy compound, we need not examine Otsuka's evidence of secondary considerations of nonobviousness. Moreover, the Defendants do not advance separate double patenting arguments for the asserted dependent claims of the '528 patent. We therefore conclude that the district court correctly determined that all of the asserted claims of the '528 patent are not invalid for nonstatutory obviousness-type double patenting over claim 13 of the '416 patent.

CONCLUSION

For the foregoing reasons, we *affirm* the judgment of the district court.

AFFIRMED