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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YASUYOSHI WATANABE, HIROTAKA ONOE, KAYO TAKAHASHI, MASAAKI SUZUKI, HISASHI DOI, and TAKAMITSU HOSOYA

Appeal 2015-003921
Application 13/381,078[1]
Technology Center 1600

Before DONALD E. ADAMS, ERIC B. GRIMES, and DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to labeled compounds suitable for use in connection with positron emission tomography ("PET"). The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a).

We affirm.

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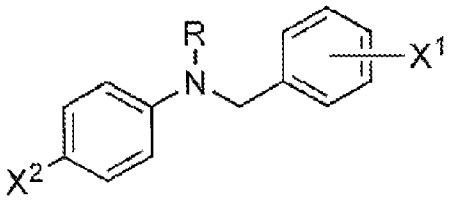
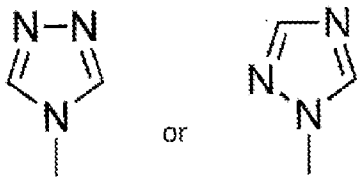
[1] According to Appellants, the real party in interest is Riken. App. Br. 3.

STATEMENT OF THE CASE

Claims 1, 2 and 4–13 are on appeal. Claim 1 is illustrative and reads as follows:

> 1. A compound, comprising a structure represented by formula (1)
>
> 
>
> ... (1)
>
> wherein X^1 is $^{11}CH_3$, $CH_2{}^{18}F$, or $CF_2{}^{18}F$, X^2 is CN or NO_2, and R is any one of the groups represented by
>
> 

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 5–7, 10, and 11 under 35 U.S.C. § 103(a) as unpatentable over Okada,[2] in view of Suzuki,[3] Schmidt,[4] Okada II[5], and/or Doi.[6]

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[2] Okada et al., *Studies on Aromatase Inhibitors II. Synthesis and Biological Evaluation of 1-Amino-1H-1,2,4-triazole Derivatives,* 45(2) CHEM. PHARM. BULL. 333-337 (1997) ("Okada").

[3] Suzuki et al., U.S. Patent No. 8,288,604 B2, issued Oct. 16, 2012 ("Suzuki").

[4] Schmidt et al., U.S. Patent Publication No. 2004/0241087 A1, published Dec. 2, 2004 ("Schmidt").

[5] Okada et al., U.S. Patent No. 5,674,886, issued Oct. 7, 1997 ("Okada II").

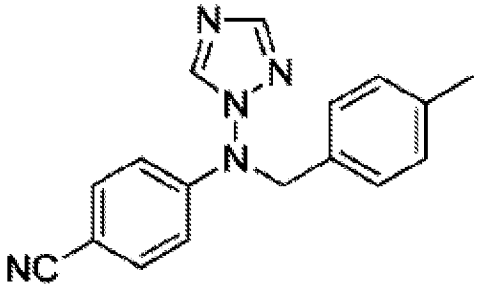
[6] Doi et al., *Paladium(0)-Mediated Rapid Methylation and Fluoromethylation on Carbon Frameworks by Reacting Methyl and Fluoromethyl Iodide with Aryl and Alkenyl Boronic Acid Esters: Useful for the Synthesis of $[^{11}C]CH_3$-C- and $[^{18}F]FCH_2$-C- Containing PET Tracers*

Claims 1, 2, and 4 under 35 U.S.C. § 103(a) as unpatentable over Okada II in view of Suzuki, Schmidt, Okada, and/or Doi.

Claims 8, 9, 12, and 13 under 35 U.S.C. § 103(a) as unpatentable over Takashini[7] in view of Okada, Suzuki, Schmidt, Okada II, and/or Doi.

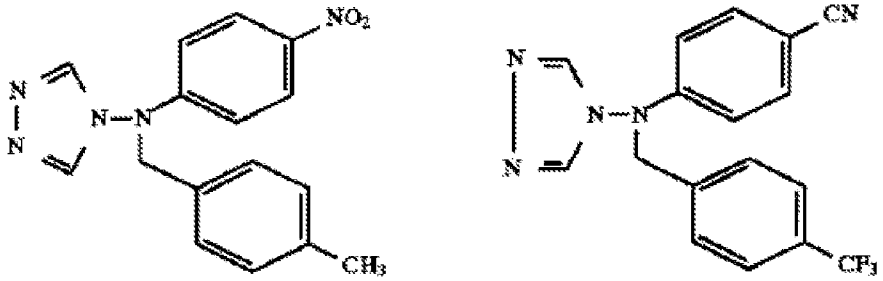
FINDINGS OF FACT

1. The Examiner finds that Okada discloses an aromatase inhibiting compound represented by the below formula.



Ans. 4 (citing Okada Table 1, compound 4j).

2. Okada II discloses aromatase inhibiting compounds represented by the below formulas.



Okada II Example 13 (above left) and Example 34 (above right).

(PET = Positron Emission Tomography), 15 CHEM. EUR. J. 4165–4171 (2009) ("Doi").

[7] Takashini et al., *Imaging of Aromatase Distribution in Rat and Rhesus Monkey Brains with [^{11}C]vorozole,* 33 NUCLEAR MEDICINE AND BIOLOGY 599–605 (2006).

3. Schmidt discloses:

> By the binding of one or several detectable groups to an aromatase inhibitor, surprising advantages are achieved by the invention. Firstly, an increased aromatase activity may represent an early occurring factor in tumor formation, which is very valuable for a desired early diagnosis of abnormal or pathological conditions. Since the estrogen supply of the tumor is prenominantly [sic] based on local synthesis, the aromatase enzyme is enriched in the tumor. In addition, the tumor tissue induces an enhanced generation of aromatase in its surroundings, so that the tumor and its surroundings are characterized by substantially more aromatase molecules than the surrounding healthy tissue.

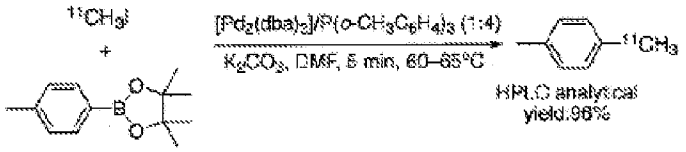
Schmidt ¶ 13.

4. Doi discloses: "The rapid methylation and fluoromethylation on aryl and alkenyl carbon frameworks by reacting methyl and fluoromethyl iodide with aryl and alkenyl boronates have been studied with the focus on the realization of the synthesis of $[^{11}C]CH_3$ and $[^{18}F]FCH_2$ labeled positron emission tomography (PET) tracers." Doi 4165.

5. Doi discloses "this boron protocol provides a firm chemical basis for the synthesis of ^{11}C and ^{18}F-incorporated PET tracers." *Id.*

6. Doi discloses: "Since synthetic methods for a variety of boron compounds have recently been developed due to the increased importance of these compounds in the synthesis of the carbon frameworks of complex natural products and artificial drug candidates, we can use organoboron chemistry for the synthesis of a PET tracer." *Id.* at 4168–69.

7. Scheme 3 of Doi, which shows "the synthesis of [^{11}C]xylene" provides as follows:



Scheme 3. Synthesis of a ^{11}C-labeled arene by rapid methylation.

Id. at 4168.

8. Doi discloses:

> [^{11}C]Celecoxib([^{11}C]-**10**), a clinically important COX-2 inhibitor, was successfully synthesized by using the corresponding pinacol arylborate under PET conditions in high yield. These methods will be applicable to the synthesis of ingenious [^{11}C]CH_3- and [^{18}F]FCH_2-incorporated heteroaromatic PET tracers, [^{11}C]-**11** and [^{18}F]-**12**, which exhibit extremely high affinity for metabotropic glutamate receptor subtype 5, starting from a common boronate precursor.

Id. at 4168–69 (reference citations omitted).

9. Suzuki discloses:

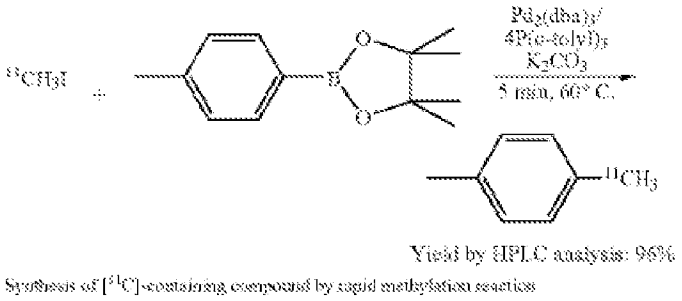
> A method of rapid methylation of an aromatic compound or an alkenyl compound, which is capable of obtaining an aromatic compound or an alkenyl compound labeled with a methyl group or a fluoromethyl group under a mild condition rapidly in high yield using an organic boron compound whose toxicity is not so high as a substrate.

Suzuki Abstract.

10. Suzuki discloses: "The method of methylation can be generally applied to a wide range of aromatic rings." Suzuki col. 6, ll. 38–40.

11. Suzuki discloses kits for carrying out its method of rapid methylation. Suzuki col. 6, l. 53 – col. 7, l. 3.

12. Suzuki illustrates the synthesis of a [^{11}C] containing compound by rapid methylation reaction as follows:



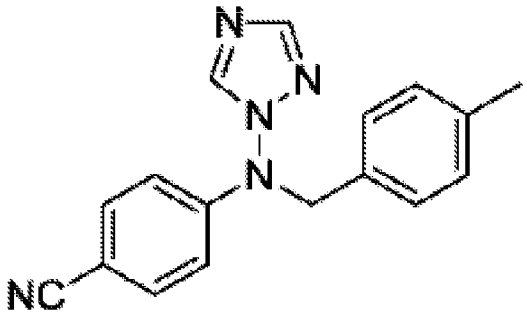
Synthesis of [^{11}C]-containing compound by rapid methylation reaction

Id. at col. 14, ll. 35–45.

REJECTION OF CLAIMS 1, 5–7, 10, AND 11 AS OBVIOUS OVER OKADA IN VIEW OF SUZUKI, SCHMIDT, OKADA II, AND/OR DOI

Appellants argue claims 1, 5–7, 10, and 11 together as a group. We designate claim 1 as representative for claims 1, 5–7, 10, and 11.

The Examiner found that Okada taught an aromatase inhibiting compound represented by the formula:

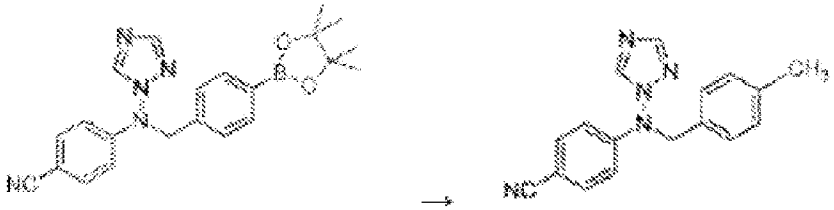
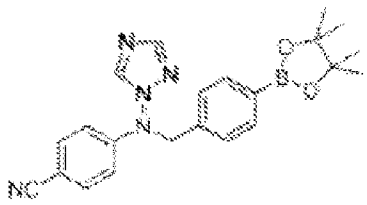


Ans. 4 (hereafter, "the Okada Compound"). The Examiner determined, however, that Okada did not teach a compound where X^1 is $^{11}CH_3$, $CH_2{}^{18}F$, or $CF_2{}^{18}F$, as recited in claim 1. *Id.*

The Examiner found that it would have been obvious to "incorporate an ^{11}C or ^{18}F at the methyl position of the Okada Compound because it would advantageously enable a predictable aromatase binding PET

radiotracer for early stage diagnosis of pathological conditions, such as tumor formation." *Id.* at 14. The Examiner found the motivation for this substitution in Schmidt, which taught that "increased aromatase activity may represent an early occurring factor in tumor formation, which is very valuable for an early stage diagnosis of abnormal and pathological conditions." *Id.* The Examiner found that the means to make this substitution were provided by Suzuki and/or Doi, both of which taught "rapid Pd-catalyzed coupling of [^{11}C]Mel and [^{18}F]FMel into PET tracer." *Id.*

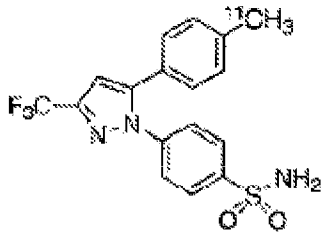
Appellants argue that none of the cited art teaches a method for synthesizing the starting compound necessary to perform the rapid Pd-catalyzed coupling reaction of Suzuki and Doi. App. Br. 10. Appellants thus contend:

> [W]hile Suzuki et al. in view of Doi et al., arguably teaches that it would be possible for a person skilled in the art to carry out a reaction represented by:
>
> 
>
> neither Suzuki et al. nor Doi et al. disclose or suggest a procedure to obtain the starting compound for such a reaction:
>
> 

Id. at 10–11. Appellants further contend that "the Examiner has not pointed to anything within Schmidt et al. that suggests any motivation for one of

skill in the art to modify the compositions of Okada et al. (1997) to arrive at the presently claimed compounds." *Id.* at 13.

Based on the record before us, we find that the Examiner has the better position. Doi discloses that its methylation and fluoromethylation method has broad applicability, providing a "firm chemical basis for the synthesis of ^{11}C and ^{18}F-incorporated PET tracers." FF5.[8] Doi further suggests that methods for synthesizing the boronate precursor compounds used in its method are known. *See,* FF6 ("synthetic methods for a variety of boron compounds have recently been developed" allowing the "use [of] organoboron chemistry for the synthesis of a PET tracer."). Doi also provides an example in which its method was used to incorporate an ^{11}C label in a COX2-inhibitor compound having the below formula.



[^{11}C]-10

FF7; Doi 4169.

Appellants do not identify any evidence or provide any argument explaining why a person of ordinary skill in the art would be unable to use the method of Doi to incorporate an ^{11}C and ^{18}F label in the Okada Compound. Instead, Appellants find fault with the Examiner's analysis, contending that the Examiner failed to sufficiently identify a method for obtaining the precursor compound to be used for applying the method of Doi

[8] Doi and Suzuki both disclose similar methods of rapid palladium catalyzed labeling of PET tracers. *See,* FF7 and FF12. To simplify our analysis, we focus principally on one reference, Doi.

to the Okada Compound. App. Br. 10 ("the Examiner has not demonstrated…"); *see also,* App. Br. 11 ("the Examiner has not pointed to anything…"). We are not persuaded. The Examiner provided evidence of a labeling method taught to be broadly applicable to PET tracers. FF5. Appellants provide no persuasive argument or evidence to support a conclusion that a person of ordinary skill in the art would be unable to synthesize the necessary precursors for Doi's methylation and fluoromethylation method. This is particularly true given Doi's suggestion that methods of synthesizing boronates were known. FF6.

To the extent there is something unique about synthesis of the particular boronate precursor needed to use Doi's methylation and fluoromethlyation method on the Okada Compound that places its synthesis outside the skill of the ordinary artisan, Appellants are in the better position to provide evidence to this effect. *See, In re Antor Media Corp.,* 689 F.3d 1282, 1289 (Fed. Cir. 2012) ("an examiner, who has no access to experts or laboratories, is not in a position to test each piece of prior art for enablement in citing it, and requiring him to do so would be onerous, if not impossible").

Appellants contend that the prior art does not provide a motivation to "modify the compositions of Okada et al. (1997) to arrive at the presently claimed compounds." App. Br. 13. We disagree. Okada teaches that the Okada Compound is an aromatase inhibitor. FF1. And Schmidt teaches that "[b]y the binding of one or several detectable groups to an aromatase inhibitor, surprising advantages are achieved." FF3. Most significantly, using a labeled aromatase inhibiting compound may allow for "early diagnosis of abnormal or pathological conditions." *Id.* We find that this

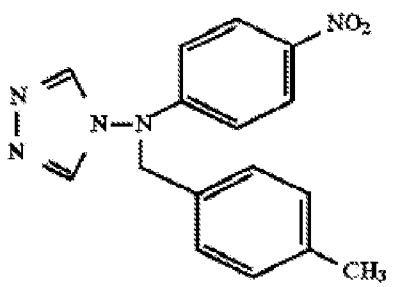
teaching would provide sufficient motivation to modify the Okada Compound with a detectable group like an ^{11}C or ^{18}F label.

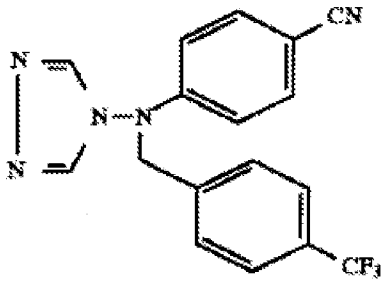
Accordingly, we affirm the Examiner's rejection of claim 1 as unpatentable over Okada, in view of Suzuki, Schmidt, Okada II, and/or Doi. Because they were not argued separately, claims 5–7, 10, and 11 fall with claim 1.

REJECTION OF CLAIMS 1, 2, AND 4 AS OBVIOUS OVER OKADA II IN VIEW OF SUZUKI, SCHMIDT, OKADA, AND/OR DOI

Appellants argue claims 1, 2 and 4 together as a group. We designate claim 1 as representative for claims 1, 2 and 4.

The Examiner's rejection of claims 1, 2 and 4 differs from the Examiner's first obviousness rejection (rejecting claims 1, 5–7, 10, and 11) principally in that the Examiner relied on a different starting compound. In rejecting claims 1, 2 and 4, the Examiner relied upon the aromatase inhibiting compound disclosed in Examples 13 and 34 of Okada II (reproduced below) as starting compounds. Final Act. 8–9.





Example 13 (above left) discloses "4-[N-(4-methylbenzyl)-N-(4-nitrophenyl)amino]-4H-1,2,4-triazole." Okada II, col. 20, ll. 12–13. Example 34 (above right) discloses "4-[N-(4-cyanophenyl)-N-[(4-trifluoromethyl)benzyl]-amino]-4H-1,2,4-triazole." *Id.* at col. 33, ll. 45–46. The Examiner determined that it would have been obvious to modify the compounds of Examples 13 and 34 to incorporate an ^{11}C or ^{18}F at the methyl

(or trifluoromethyl) position for the reasons discussed in connection with the Examiner's first obviousness rejection. Final Act. 8–9; Ans. 15.

Appellants argue that claim 1, 2 and 4 are non-obvious for the same reasons that claims 1, 5–7, 10, and 11 are non-obvious. App. Br. 13–14. For the reasons discussed with respect to claims 1, 5–7, 10, and 11, Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the obviousness of claim 1 over Okada II, in view of Suzuki, Schmidt, Okada and/or Doi. Because they were not argued separately, claims 2 and 4 fall with claim 1.

REJECTION OF CLAIMS 8, 9, 12, AND 13 AS OBVIOUS OVER TAKASHINI IN VIEW OF OKADA, SUZUKI, SCHMIDT, OKADA II, AND/OR DOI

Appellants argue claims 8, 9, 12, and 13 together as a group. We designate claim 8 as representative for claims 8, 9, 12, and 13.

Claims 8, 9, 12, and 13 add limitations relating to methods of diagnosis using a compound of claim 1. To address these additional limitations, the Examiner relied upon Takashini, which the Examiner found to teach "methods of diagnosing aromatase linked disorders comprising administering labeled aromatase inhibitor." Ans. 10. Appellants argue that claims 8, 9, 12, and 13 are non-obvious for the same reasons that claims 1, 5–7, 10, and 11 are non-obvious. App. Br. 14–15. For the reasons discussed with respect to claims 1, 5–7, 10, and 11, Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the obviousness of claim 8 over Takashini in view of Okada, Suzuki, Schmidt, Okada II, and/or Doi. Because they were not argued separately, claims 9, 12, and 13 fall with claim 8.

SUMMARY

For these reasons and those set forth in the Examiner's Answer, the Examiner's final decision to reject claims 1, 2, and 4–13 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED