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This is an appeal\(^1\,2\) under 35 U.S.C. § 134(a) involving claims to a radiolabeled Diels-Alder adduct of a trans-cyclooctene with a tetrazine. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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\(^1\) Appellants identify the Real Parties in Interest as the University of Delaware and the University of Southern California (see App. Br. 1).
Statement of the Case

Background

"Positron emission tomography (PET) is a non-invasive imaging modality that utilizes positron-emitting radionuclides . . . . For example, F-18 PET has a number of attributes that make it clinically attractive, including 100% positron efficiency, a very high specific radioactivity, and a short half-life of ~110 min" (Spec. 1:4–7). “The invention provides an extremely fast and reactive method for generating radionuclide labeled probes based on TTCO [tetrazine-trans-cyclooctene]-ligation, employing a Diels-Alder reaction between 3,6-diaryl-s-tetrazines and trans-cyclooctenes, one of which is labeled with a radionuclide, for example $^{18}$F” (Spec. 4:9–12).

The Claims

Claims 1, 4, 13, 14, and 20 are on appeal. Claims 1 and 20 are representative and read as follows:

1. A Diels-Alder adduct of a trans-cyclooctene with a tetrazine, wherein the adduct bears a substituent labeled with a radionuclide, wherein the substituent is a substituent on the trans-cyclooctene residue of the Diels-Alder adduct.

20. The compound according to structure 9

\[ \text{\includegraphics{structure_9.png}} \]

We limit our consideration of the merits of the appealed rejection to the elected species. See Ex parte Ohsaka, 2 USPQ2d 1460, 1461 (BPAI 1987). Thus, we read the claims as limited to compound 9 shown in claim 20 (see Response to Election/Restriction filed on June 29, 2015).
The Examiner rejected claims 1, 4, 13, 14, and 20 under 35 U.S.C. § 103(a) as obvious over Blackman, Royzen, Arstad, and Zhang (Ans. 2–6).

The Examiner finds Blackman teaches “strained click reactions that take advantage of intrinsic reactivity of cyclooctyne towards organic azides” that “could form the basis of powerful bioorthogonal reaction” (Ans. 2). The Examiner finds that Royzen teaches “synthesis of trans-cyclooctene derivative” and functionalization of that derivative with a hydroxy substituent (see Ans. 3–4).

The Examiner finds Arstad teaches “a need for labelling agents such as $^{18}$F-labelled prosthetic groups and methodologies, which allow rapid, chemoselective introduction of a label such as a radionuclide” (Ans. 4). The Examiner finds Zhang teaches a “labeling strategy has been developed for introducing $^{18}$F onto a target molecule by first attaching $^{18}$F to a prosthetic groups” (Ans. 5).

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4 We note that claim 10, identified as rejected in the Examiner’s Answer, was cancelled in an Amendment filed Nov. 16, 2015.


The Examiner finds:

It would have been obvious to one of ordinary skill in the art at the time of invention to modify the compounds taught by Blackman et al. (i.e., compounds transcyclooctene discussed above) by simply incorporating a $[^{18}\text{F}]$fluoroethyl radical as taught by Royzen et al., because it would advantageously enable inverse-electron-demand diels-alder reactivity with appropriate tetrazine bearing biomolecule in the absence of catalysis and in turn PET imaging.

(Ans. 6).

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that Blackman, Royzen, Arstad, and Zhang suggest the compound 9 of claim 20?

Findings of Fact

1. Blackman teaches “a bioorthogonal reaction that proceeds with unusually fast reaction rates without need for catalysis: the cycloaddition of $s$-tetrazine and $trans$-cyclooctene derivatives” (Blackman 13518, col. 1).

2. Blackman teaches “[b]ioorthogonal reactions, unnatural transformations that are unaffected by biological functionality, are broadly useful tools with applications that span synthesis, chemical biology, and materials science . . . and the enhanced reactivity enables applications for dynamic in vivo imaging” (Blackman 13518, col. 1).

3. Scheme 3a of Blackman is reproduced below:

\[
\begin{align*}
\text{a} & \quad \xrightarrow{hv \ 73\%} \\
\text{HO} & \quad \text{active removal on } \text{AgNO}_3\cdot\text{SiO}_2 \\
\text{4} & \quad \xrightarrow{} \\
\text{HO} & \quad \text{5}
\end{align*}
\]

Blackman teaches “$trans$-Cyclooctene derivative 5 is readily accessible from
cis-cyclooctene 4 by a photochemical protocol” (Blackman 13518, col. 2).

4. Royzen teaches the “unusual reactivity and well-defined chiral structure of trans-cyclooctene make it an attractive framework for stereocontrolled synthesis” (Royzen 3760, col. 1).

5. Royzen teaches compound 2b as reproduced below:

![Compound 2b](Royzen 3761, col. 1).

6. Royzen teaches functionalizing compound 2B in Figure 2a as reproduced below:

![Functionalization](Royzen 3761, col. 1).

“Figure 2. (a) Preparation and X-ray structure of a trans-cyclooctene with an axial substituent. 1,3-Diaxial interactions are highlighted” (Royzen 3761, col. 1).

7. Arstad teaches “a need for labelling agents such as $^{18}$F-labelled prosthetic groups and methodologies, which allow rapid, chemoselective introduction of a label such as a radionuclide, for example $^{18}$F, particularly into peptides” (Arstad 1:32 to 2:2).

8. Zhang teaches “fluorine-18 . . . is an important positron emitter for the imaging study using PET due to its optimal decay characteristics . . . So far, a number of methods for introducing $^{18}$F into a target molecule have
been developed” (Zhang 1817, col. 1).

**Principles of Law**

A prima facie case for obviousness requires “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Telexflex Inc.*, 550 U.S. 398, 418 (2007).

**Analysis**

Appellants contend that “Arstad does not discuss trans-cyclooctenes” and “provides no motivation to instead use an $^{18}$F-containing transcyclooctene, and particularly Appellants’ Compound 9” (App. Br. 4–5). Appellants contend “Zhang does not disclose or suggest making compounds where the $^{18}$F fluoroalkyl group is attached to oxygen, such as Appellants’ claimed compound 9” (id. at 5, emphasis omitted). Appellants contend “nothing in Zhang suggests substituting a trans-cyclooctene with an $[^{18}$F]fluoroethyl radical” and “motivation cannot come from Zhang, who does not discuss labeling biomolecules and provides no suggestion to do so. More particularly, Zhang provides no motivation to label a biomolecule indirectly via an $^{18}$F-containing trans-cyclooctene” (id.).

The Examiner responds that because “Arstad teaches click reactions that enable applications for in vivo dynamic imaging” and “$^{18}$F-labelled bioactive peptides have great clinical potential because of their utility in PET to quantitatively detect and characterize a wide range of diseases”,

it would have been obvious to a person of ordinary skill to incorporate $^{18}$F-label onto the diels-alden substrates of Blackman because it would advantageously enable applications for quantitative dynamic in vivo imaging and high yield conjugation without the need for a catalysis in organic solvents,
water, cell media, or cell lysate.

(Ans. 8).

We find that Appellants have the better position because the Examiner has not established a persuasive “reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” KSR, 550 U.S. at 418. While Blackman mentions in vivo imaging (FF 2) and Arstad and Zhang discuss the use of $^{18}$F in labeling agents (FF 78), the Examiner does not persuasively demonstrate why the ordinary artisan would have found it obvious to incorporate an $^{18}$F into the trans-cyclooctene compound 2b of Royzen. Royzen does not teach that compound 2b or compound 3 may be used in medical imaging. Royzen does not even teach that these compounds are used as biological linkers. Moreover, while Blackman generally discusses bioconjugation and medical imaging (FF 1–3), Blackman does not discuss labeling any compound, much less compound 5, with any type of label. Even the single mention of imaging in Blackman (FF 2) does not identify how the imaging occurs or provide any suggestion or reason to image using any type of label, much less a radioactive label such as $^{18}$F.

Thus, the Examiner’s prima facie case of obviousness is not persuasive because there is no persuasive evidence linking the $^{18}$F labeling teachings of Arstad and Zhang with the trans-cyclooctene compounds of Royzen and Blackman, sufficient to provide a reason to label a trans-cyclooctene compound with $^{18}$F.

Conclusion of Law

The evidence of record does not support the Examiner’s conclusion that Blackman, Royzen, Arstad, and Zhang suggest the compound 9 of claim
20.

SUMMARY

In summary, we reverse the rejection of claims 1, 4, 13, 14, and 20 under 35 U.S.C. § 103(a) as obvious over Blackman, Royzen, Arstad, and Zhang.

REVERSED