

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MATHAI MAMMEN and DAVID OARE

Appeal 2008-2051
Application 10/426,270
Technology Center 1600

Decided: July 1, 2008

Before DONALD E. ADAMS, LORA M. GREEN, and
JEFFREY N. FREEDMAN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

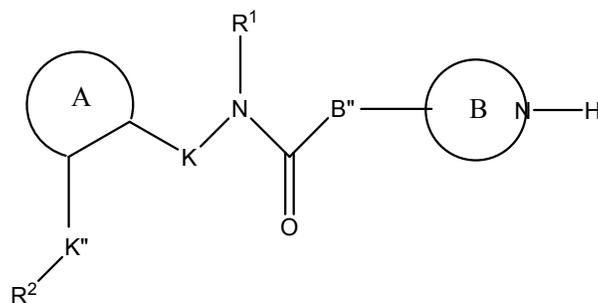
DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 50-63. Claim 64, the only remaining claim pending in this application, was “withdrawn from consideration as being drawn to a non-elected species and/or invention” (App. Br. 2). We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

Claims 50, 51, 55, 58, and 59 are illustrative:

50. A compound of the formula:



or a salt thereof; wherein

A is phenyl or pyridyl;

B is a heterocycloamino group selected from the group consisting of pyrrolidinyl, piperidinyl, hexahydroazepinyl, quinuclidinyl, 1-azabicyclo[2.2.1]heptyl and 1-azabicyclo[3.2.1]octyl;

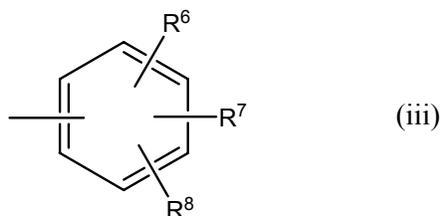
B'' is -NH-;

K is a bond or methylene group;

K'' is a bond;

R¹ is hydrogen or alkyl;

R² is a group of formula (iii):

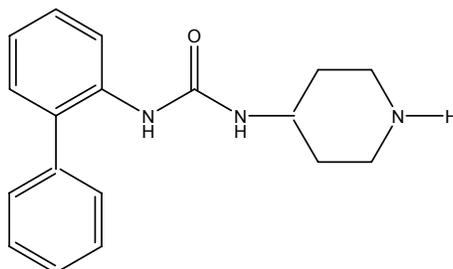


and

R⁶, R⁷, and R⁸ are independently selected from the group consisting of hydrogen, halo, hydroxyl, alkoxy, haloalkoxy, carboxy, alkoxy carbonyl and alkyl optionally substituted with one, two or three substituents selected from

halo, hydroxyl, carboxy, alkoxy, carbonyl, alkylthio, alkylsulfonyl, amino and substituted amino.

51. A compound of the formula:



or a salt thereof.

55. The compound of Claims 50, wherein B is pyrrolidinyl.

58. The compound of Claim 50, wherein B is 1-azabicyclo[2.2.1]heptyl.

59. The compound of Claim 50, wherein B is 1-azabicyclo[3.2.1]octyl.

The Examiner relies on the following prior art references to show unpatentability:

Mammen

US 7,238,709 B2

Jul. 3, 2007

J. Büchi, "The Constitution-Effect Relationships From a New Viewpoint," Deutsche Apotheker-Zeitung 1695-1700 (1966) (as translated Oct. 2002).

Charles H. Mitch, "Muscarinic Analgesics with Potent and Selective Effects on the Gastrointestinal Tract: Potential Application for the Treatment of Irritable Bowel Syndrome," 40 J. Med. Chem. 538-46 (1997).

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Ryo Naito, "Selective Muscarinic Antagonists. II. Synthesis and Antimuscarinic Properties of Biphenyllylcarbamate Derivatives," 46(8) Chem. Pharma. Bull. 1286-94 (1998).¹

David P. Marriott, "Lead Generation Using Pharmacophore Mapping and Three-Dimensional Database Searching: Application to Muscarinic M₃ Receptor Antagonists," 42 J. Med. Chem. 3210-16 (1999).

The rejection as presented by the Examiner is as follows:

1. Claims 50-63 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi.
2. Claims 50-63 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 51 of U.S. Patent 7,238,709 in view of Marriott, Mitch, Buchi, and Naito.

We affirm.

DISCUSSION

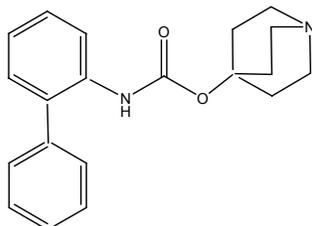
Obviousness:

Appellants provide separate arguments for the following five groups of claims: I. Claims 50, 52, 57, and 60-63; II. Claims 51, 53, and 54; III. Claims 55 and 56; IV. 58, and V. 59. Therefore, we limit our discussion to representative claims 50, 51, 55, 58, and 59. 37 C.F.R. § 41.37(c)(1)(vii).

¹ There are two Naito references of record and the Examiner's statement of the references relied upon appears to blend the title of the first with the journal, volume and page citation of the second. We have cited and relied upon the correct version of Naito herein.

Claim 50:

The Examiner finds that Naito teaches “many Muscarinic M₃ antagonists including YM-46303” (Ans. 4.) YM-46303 (compound 8I) has the following structure:



(Naito 1288: Table 2, compound 8I.)

The Examiner finds that YM-46303 “falls entirely within the scope of Appellants’ claims (wherein A + R² = biphenyl (i.e., R⁶, R⁷ and R⁸ = H), K = bond, R¹ = H and B = quinuclidinyl) with the exception that YM-46303 contains a carbamate linkage and not the requisite urea linkage” (Ans. 4). Stated differently, the Examiner finds that Naito fails “to teach an ‘NH’ at the B” position to form the requisite urea linkage (i.e., Naito et al. teach –NH-(C=O)-O- instead of –NH-(C=O)-NH-” (*id.*).

The Examiner relies on Marriott, Mitch and Büchi to make up for this deficiency in Naito. Specifically, the Examiner finds that:

[T]he combined references of Marriott et al., Mitch et al. and Buchi [sic] (e.g., see entire documents) teach the use of an “NH” group at the B” position to form a urea linkage (e.g., see Marriott et al., page 3213, column 1, last full paragraph, “Replacement of the oxygen atom for a nitrogen atom [i.e., formation of a urea] in the carbamate moiety . . . would lead to further combinatorial opportunities [for identification of a lead Muscarinic M₃ receptor antagonist]”; see also abstract, “By using Muscarinic M3 receptor antagonists as an example, we show that it is possible to identify potent novel lead compounds using this [combinatorial] approach”). In addition, the similar physicochemical properties would have been expected for the “NH” to “O” substitution at the B” position because this

represents an “isosteric” substitution (e.g., see Buchi [sic], page 3, Table 8, “O” and “NH” entries; see also paragraph bridging pages 2-3, “By exchanging isosteric groups in active-ingredient molecules [e.g., Muscarinic activity], it should be possible to produce effective analogs, since the electronic charge and physical/chemical properties of such a molecule should hardly change”).

(Ans. 5-6).

Based on this evidence the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the “NH” for the “O” at the B” position of YM-46303 as the “[r]eplacement of the oxygen atom for a nitrogen atom [i.e., formation of a urea] in the carbamate moiety . . . would lead to further combinatorial opportunities [for identification of a lead Muscarinic M₃ receptor antagonist]” (Ans. 8). According to the Examiner “one of ordinary skill in the art would have been motivated to use [sic] make such substitutions because ‘. . . it is possible to identify potent novel lead compounds’ using this approach” (*id.*). In addition, the Examiner finds that “a person of skill in the art would also have been motivated to produce these homologs as a result of their favorable physiochemical properties” (Ans. 9). In this regard, the Examiner finds that “[a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties’ *In re Payne*, 606 F.2d 303, 313 . . . (CCPA 1979)” (*id.*).

Appellants disagree. According to Appellants while Marriott suggests “the replacement of the oxygen atom for a nitrogen atom in compound 6 would lead to further combinatorial opportunities” and “that compounds

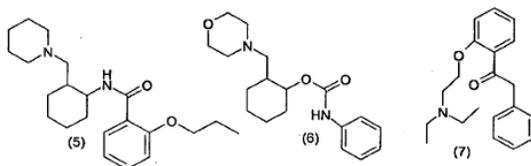
such as 5, 6 and 7^[2] should be amenable to further optimization in order to improve M₃ antagonist potency”, Appellants assert that “this is merely an invitation to modify these specific compounds in an attempt to optimize their properties” (App. Br. 9).

Further Appellants assert that:

Marriott only suggests modifying one of its compounds by changing the carbamate to a urea in the context of generating a larger and more diverse combinatorial library. However, one skilled in the art would not necessarily have a reasonable expectation that the compounds in the library would have the desired properties.

(App. Br. 9-10.) In this regard, Appellants “point out that Marriott found only 3 of the 172 hit compounds to have any significant muscarinic activity” and while “absolute predictability is not required . . . an obviousness determination does require a reasonable expectation of success” (App. Br. 10). According to Appellants “one skilled in the art, observing Marriott’s less than 2% success rate, would not have a reasonable expectation of success of discovering a muscarinic antagonist should they choose to combine the Marriott teachings with those of the Naito reference” (*id.*). We disagree. Appellants’ position is contrary to Marriott who teaches that the three compounds [structures 5, 6, 7] they identified “were found to exhibit potency in our screen” and the “hit rate for leads from this study is . . .

² The structure of Marriott’s compounds 5, 6, and 7 are as follows:



(see App. Br. 9.)

several orders of magnitude greater than from high-throughput screening” (Marriott 3213: col. 2, ll. 26-28).

Therefore, the question before us is not whether a person of ordinary skill in the art would obtain compounds from a library based on a core molecule that is taught by the references relied upon. To the contrary, the question before us is whether the claimed compound is prima facie obvious to a person of ordinary skill in the art. On this record, the evidence relied upon by the Examiner teaches a muscarinic M₃ antagonist that differs from the claimed compound by containing a carbamate linkage and not the requisite urea linkage (Ans. 4). Marriott “sought to identify novel antagonists of the muscarinic M₃ receptor” (Marriott 3210: col. 2, ll. 13-14). Marriott teaches that “[p]harmacophore generation based on the structures of known M₃ receptor antagonists, 3D database searching, and medium-throughput screening were used successfully to identify a small set of simple, novel lead compounds” (Marriott 3211: col. 1, ll. 28-32). Marriott found three compounds (compounds 5, 6, and 7) “constitute quality lead structures ripe for optimization” (Marriott 3213: col. 2, ll. 25-26). Like the claimed compound, Marriott’s compound 6 contains a carbamate moiety. Marriott teaches that the “[r]eplacement of the oxygen atom for a nitrogen atom in the carbamate moiety of structure 6, such that a central urea moiety is generated, would lead to further combinatorial opportunities, with various amine libraries open to exploration” (Marriott 3213: col. 1, ll. 28-32).

Thus, a person of ordinary skill in the art reading Naito and Marriott in combination would realize that Naito’s compound (a M₃ receptor antagonist) can be used as a lead compound, as taught by Marriott, and that by replacing the oxygen atom for a nitrogen atom in the carbamate moiety

further combinatorial opportunities would be open to exploration as taught by Marriott. In sum, we agree with the Examiner's conclusion that the claimed compound would have been prima facie obvious in view of the combined teachings of Naito and Marriott.

Appellants' arguments concerning the reasonable expectation of successfully identifying other M₃ receptor antagonists from a library based on a compound taught by the combined teachings of Naito and Marriott puts the cart before the horse. The issue is not whether it would have been obvious to try screening a library based on such a compound in the hope of identifying other M₃ receptor antagonists. To the contrary, the issue is whether the combination of prior art relied upon by the Examiner teaches the claimed compound. For the foregoing reasons, we find that it does.

Accordingly, we are not persuaded by Appellants' assertion's regarding the reasonable expectation of success in "discovering a muscarinic antagonist should they choose to combine the Marriott teachings with those of the Naito reference" (App. Br. 10). For the same reasons we are not persuaded by Appellants' assertion that "even if the secondary Marriott and/or Büchi references were combined with Naito, there is no reasonable expectation of success. While combinatorial chemistry is an excellent research tool, it is no a roadmap to success." (App. Br. 11).

We are also not persuaded by Appellants' assertion that "there is nothing in Büchi that teaches that ureas and carbamates are interchangeable" or "that such isosteric changes can be done in a linker positioned at the core of a complex structure" (App. Br. 10). Marriott addresses both of these points by teaching the "[r]eplacement of the oxygen atom for a nitrogen atom in the carbamate moiety of structure 6, such that a central urea moiety

is generated, would lead to further combinatorial opportunities, with various amine libraries open to exploration” (Marriott 3213: col. 1, ll. 28-32).

We recognize Appellants assertion that Mitch fails to support “that an ‘NH’ for ‘O’ substitution should be made for compounds with M₃ Muscarinic activity” (App. Br. 12). However, as the Examiner points out “Mitch is not being relied upon to show the obviousness of the O/N substitution” (Ans. 24). Accordingly, we are not persuaded by Appellants’ arguments regarding Mitch.

For the foregoing reasons we find no error in the Examiner’s prima facie case of obviousness. Accordingly, we affirm the rejection of claim 50 under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi. Claims 52, 57, and 60-63 fall together with claim 50.

Claim 51:

The compound of claim 51 is similar to that of Naito’s muscarinic M₃ antagonists YM-46303 except that the bicycle[2.2.2]octane groups is replaced by a piperidin-4-yl group and YM-46303 contains a carbamate linkage and not the requisite urea linkage. Naito does, however, teach a compound (compound 14) which contains a piperidin-4-yl group in the appropriate location (Naito 1287: Chart 3). Naito further illustrates this compound as an intermediate in the formulation of compounds 15a-o (*id.*). Accordingly, the question is whether it would have been prima facie obvious to substitute the carbamate linkage with an urea linkage. For the reasons discussed above, based on the teachings of Marriott we find that it would have been prima facie obvious to make this substitution. Accordingly, we

disagree with Appellants' assertion that "there is nothing to suggest combining the teachings of Marriott and Naito" (App. Br. 15).

For the foregoing reasons we affirm the rejection of claim 51 under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi. Claims 53 and 54 fall together with claim 51.

Claim 55:

The Examiner finds that the pyrrolidinyl ring is a homolog "of the piperidinyl ring disclosed by Niato et al. (e.g., see Naito et al., Table 3, compound 14)" (Ans. 7).

In response, Appellants assert that the change in ring structure, coupled with "[t]he additional 'carbamate to urea' change that is required, diminishes any possibility that homologous portions may function in a similar manner" (App. Br. 17). We are not persuaded. Marriott teaches the carbamate to urea substitution. Therefore, the question is whether the modification of the piperidin-4-yl ring in compound 14 of Naito for a pyrrolidinyl ring would have been obvious to a person of ordinary skill in the art. In this regard, we note that:

Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para).

In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Similarly, in *Shetty* the Examiner noted that the claimed compound differed from the prior art compound by “a mere methylene group . . . and concluded that ‘this minor molecular modification would clearly be obvious to the pharmaceutical chemist.’” The *Shetty* court, agreed with the Examiner’s position, finding “that a person skilled in chemical and/or pharmaceutical arts would not hesitate to extend the alkylene linkage of the prior art compound.” *In re Shetty*, 566 F.2d 81, 85 (CCPA 1977). Accordingly, absent evidence to the contrary, which there is none, we are not persuaded by Appellants’ argument. Attorney argument cannot take the place of evidence lacking in the record. *Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977).

For the reasons set forth above, we are not persuaded by Appellants arguments concerning Büchi.

Accordingly, we affirm the rejection of claim 55 under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi. Claim 56 falls together with claim 55.

Claim 58:

The Examiner finds that “the 1-azabicyclo[2.2.2]octyl portion of the YM-46303 muscarinic antagonist disclosed by Naito et al. represents, for example, a [homology] of the currently claimed 1-azabicyclo[2.2.1]heptyl ‘B’ group” (Ans. 7).

Appellants assert that “more modifications have to be made to the Naito compound to render the claimed compound obvious. The additional ‘carbamate to urea’ change that is required, diminishes any possibility that homologous portions may function in a similar manner” (App. Br. 18). For

the reasons set forth above, we disagree. For the same reasons we are not persuaded by Appellants' arguments regarding Büchi.

Accordingly, we affirm the rejection of claim 58 under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi.

Claim 59:

The Examiner finds that:

The 1-azabicyclo[2.2.2]octyl portion of the YM-46303 muscarinic antagonist disclosed by Naito et al. represents, for example, a positional isomer with regard to the bridgehead linkage (bound either meta or para to the ring nitrogen). Compounds that are position isomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457 . . . (CCPA 1977).

(Ans. 7-8.)

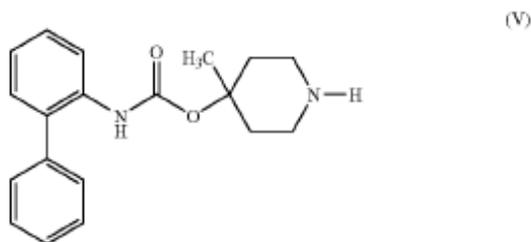
Appellants assert that that “the combined teachings do not suggest taking the Naito muscarinic antagonist, changing its carbamate to a urea, and then substituting the 1-azabicyclo[2.2.2]octyl group with a 1-azabicyclo[3.2.1]octyl group to arrive at the claimed compound” and “there is no reasonable expectation of success” in doing so (App. Br. 19). For the reasons set forth above, we disagree.

Accordingly, we affirm the rejection of claim 59 under 35 U.S.C. § 103(a) as unpatentable over the combination of Naito, Marriott, Mitch, and Büchi.

Obviousness-type double patenting:

Claims 50-63 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 26³ of U.S. Patent 7,238,709 in view of Marriott, Mitch, Büchi, and Naito.

Claim 26 of the '709 patent is drawn to a compound having formula (V)



or a salt thereof.

The Examiner finds that claim 26 of the '709 patent recites "a species of Muscarinic antagonists that read (in part) on the currently claimed invention. For example, claim [26 of '709] . . . recites N-[1,1'-biphenyl]-2-yl-N'-4-methyl-4-piperidiny]l-carbamate which reads (in part) on the currently claimed ureas when R²=phenyl, K''=bond, A=phenyl, R¹=hydrogen and B=piperidiny]" (Ans. 12). The Examiner finds that the muscarinic antagonist of '709's claim 26 differs from the compound of claim 50 by "reciting a 'carbamate' linkage instead of the requisite 'urea' linkage[]" and "a '4-methyl-4-piperidiny]l' group instead of the requisite 'piperidiny]l' group" (*id.*).

The Examiner relies on Marriott, Mitch, Büchi, and Naito to teach the substitution of an urea linkage for the carbamate in the compound of '709's

³ As the Examiner explains U.S. Patent Application No. 09/732,241 issued as U.S. Patent No. 7,238,709 (Ans. 11). Claim 51 of the '241 application was renumbered as claim 26 in the '709 patent.

claim 26. For the reasons discussed above, we find no error in the Examiner's conclusion that this substitution would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made (Ans. 12-13). The Examiner finds that piperidinyl is a homolog of 4-methyl-4-piperidinyl and therefore the substitution of a 4-methyl-4-piperidinyl group for a piperidinyl group would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made (Ans. 12-14). For the reasons set forth above, we find no error in the Examiner's prima facie case of obviousness.

In response, Appellants question why "one skilled in the art [would] select the particular fragments mentioned by the Examiner from all the possible fragments that could be used, to modify the teachings of the ['709 patent] . . . or Naito, both of which describe compounds having central carbamates" (App. Br. 23). For the reasons set forth above, we are not persuaded.

The compound of '709's claim 26 differs from Naito's compound 14 by a methylene. Accordingly, a person of ordinary skill in the art would have found it prima facie obvious to remove the methylene group from the compound of '709's claim 26 to use it as taught by Naito. As for the substitution of the carbamate with an urea, as discussed above, Marriott provides a person of ordinary skill in this art with a reason to make this modification.

Absent evidence to the contrary, which there is none, we find no error in the Examiner's prima facie case.

Accordingly, we affirm the rejection of claim 50 under the judicially created doctrine of obviousness-type double patenting as being unpatentable

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over claim 26 of U.S. Patent 7,238,709 in view of Marriott, Mitch, Büchi, and Naito. Since they were not argued separately, claims 51-63 fall together with claim 50. 37 C.F.R. § 41.37(c)(1)(vii).

CONCLUSION

In summary, we affirm the rejections of record.

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

AFFIRMED; 37 C.F.R. § 41.50(b)

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