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So that's why I -- my viewpoint in the document is -- favors simple discrete ester functionalities, hydrocarbon-based, without these types of reactive elements, moieties to them.

Q. Okay. Now, one of the ester examples that is provided in this section on esters in Bundgaard, I think you've got to go to Page 4, are these ampicillin prodrugs. Is that right?

A. Let me see.

Q. I think you refer to that example in your opinion.

A. Mm-hmm. Yes. I see it on Page 4.

Q. Now, ampicillin is -- the ampicillin prodrugs are more complicated than one-step conversions. Correct?

MS. WOOTEN: Objection. Form.

A. They're more complicated in what sense?

Q. Well --

A. In terms of the enzymatic conversion? Because they're basically -- they're de-esterification by enzymatic attack. So in that sense, they're not more complicated.

Q. Mm-hmm. Well, correct me if I'm wrong, but Bundgaard is citing ampicillin as an example

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of embodying a double-ester concept.

Do you see that at the first paragraph on Page 5?

A. Oh, in that sense, yes. We're not dealing here with fesoterodine, with the two-ester functionality. We're dealing with one.

Q. Right.

A. So in that sense, if you want to regard that as more complicated, certainly it's a difference.

Q. It's two steps?

A. It's a difference. Yes.

Q. Okay.

A. It's a difference.

Q. Two steps is more complicated than one step. Right?

A. Mm-hmm.

Q. Which is what you suggest --

A. Mm-hmm.

Q. -- one would design?

A. Mm-hmm.

Q. So would you agree that the ampicillin prodrugs are not necessarily suggestive of the compounds claimed in the patents?

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MS. WOOTEN: Objection. Form.

A. They're suggestive to the extent that in order for them to be activated and to produce the desired chemical therapeutic, they have to be transformed as -- their ester functionalities have to be transformed, have to be hydrolyzed by enzymatic hydrolysis by esterases.

So, in that sense, they have parallel to fesoterodine.

Q. Mm-hmm. But then they have to be further metabolized by a chemical process. Correct?

A. And that monoester is, in a sense, parallel chemically to the monoester of fesoterodine. That monoester would then be hydrolyzed to drug.

Q. Now, ampicillin had been known since the early 20th century. Correct?

A. I don't know the exact time, but certainly it's a venerable drug. It certainly would predate the OAB field in terms of fesoterodine and tolterodine.

Q. Right. And that is distinguished from 5-HMT, for which there was very little

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information. Correct?

MS. WOOTEN: Objection. Form.

A. Just as at one time, there was very little information about the cillins.

MR. TRAINOR: Okay. I'm going to have a couple of other questions related to the chemistry and Bundgaard, but let's just take a quick, short break --

THE WITNESS: Sure.

MR. TRAINOR: -- for five minutes or so.

THE VIDEOGRAPHER: The time now is 15:35, and we are now off the record.

(A recess was taken.)

THE VIDEOGRAPHER: The time now is 15:45, and we are back on the record.

BY MR. TRAINOR:

Q. Okay. Dr. Janero, staying with Exhibit 16, the Bundgaard text, on prodrugs --

A. Yes.

Q. -- you would agree with me that there are a number of alternative prodrugs to ester prodrugs that are disclosed in this text. Correct?

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A. That are disclosed, yes.

Q. Ethers would be one?

A. Yes.

Q. And carbamates. Correct?

A. Carbamate esters, yes.

Q. And carbonates?

A. Yes.

Q. There's also phosphate esters. Correct?

A. Yes.

Q. And Mannich bases?

A. Yes.

Q. My question is: Why wouldn't a person of ordinary skill in the art have considered those prosubstituents, if you will, to design a prodrug of 5-HMT?

MS. WOOTEN: Objection. Form.

A. They could be considered, theoretically. However, they would have to be considered in the context of the design parameters for the intended product, as well as for their applicability to the chemistry associated in the design.

For example, the Mannich bases, as quoted

here, are "potentially useful prodrug candidates for amine acidic compounds such as various amides, imides, carbamates, hydantoins and urea derivatives."

Well, that, for example, could be considered, but 5-HMT does not fit that chemical class. Therefore, that could be considered not a particularly attractive route, not a particularly attractive substitution to make in terms of derivatizing as a -- 5-HMT as a prodrug.

Q. And why is that? Because 5-HMT is basic?

A. It doesn't -- no, it simply doesn't fit any of these -- any of these descriptions. It's not an amide. It's not a carbamate. It's not a hydantoin, etc.

Q. Can you show me what you're pointing to?

A. Oh, yes. Pardon me. This is on Page 10, Paragraph 3.1 --

Q. Mm-hmm.

A. -- sentence one. So I'll use that to exemplify the idea that, yes, the table and -- in Chapter 1 does disclose and discuss various

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routes to prodrugs.

Q. Mm-hmm.

A. Many various chemical modifications that can yield prodrugs. However, these modifications are not necessarily attractive or even applicable in all cases.

Q. Okay. That's the Mannich bases?

A. Yes.

Q. Why wouldn't one of skill in the art have considered an ether prodrug?

A. I think it could be considered. However, ethers do have their own potential for reactivity as well, and that could impact their -- their attractiveness as that -- as a prodrug, as a moiety for a prodrug.

Q. Esters also can be reactive. No?

A. As a type of ester. A simple hydrocarbon ester, such as that in fesoterodine, would be -- doesn't have any reactive chemical moiety, other than the ability of that ester functionality to serve as a hydrolyzable substrate for an esterase and break that ester bond by introduction of water across the bond.

Q. Okay.

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A. In other words, the methyl groups themselves bear no reactivity, no significant reactivity.

Q. Okay. One of the other examples that you cite in your report of a prodrug is codeine. Correct?

A. I believe so. That's on Page 17, 54 paragraph.

Q. Yes. Thank you. Okay. Codeine is an ether prodrug. Correct?

A. It has an ether functionality, yes, but that's at the left-hand side of the molecule.

Q. Mm-hmm. So if codeine is relevant to suggest making a prodrug of 5-HMT, why is the teaching of the ether substituent not applicable to 5-HMT prodrugs?

MS. WOOTEN: Objection. Form.

A. I don't believe it's not applicable, because it exemplifies the conversion of an inactive to an active chemical by CYP2D6 hydrolysis.

Q. But that's exactly what you're trying to avoid by the design of a 5-HMT prodrug. Correct?

A. I don't think you would want to avoid that. You would need to activate -- you would need to activate the prodrug.

Q. Well, as I understand it, the rationale for designing a prodrug of 5-HMT is to avoid the CYP2D6 metabolism of tolterodine, which in CYP2D6-deficient people means that they don't convert to 5-HMT.

A. Mm-hmm. Mm-hmm.

Q. Correct?

A. Well, they convert less. In one paper we cited, it was 20 percent or so. Yes.

Q. Okay. So the morphine prodrug is the opposite. Right? You're actually trying to take advantage of CYP2D6 to go from codeine to morphine?

A. To activate. Right.

Q. Okay.

A. Right. My purpose in the example was to show that a conversion of an inactive to an inactive agent wasn't to analogize this conversion chemically. That this is the desired conversion for fesoterodine.

Q. Okay. So, in addition, as we

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mentioned, at least the codeine prodrug of morphine is an ether prodrug. Correct?

A. Yes. It has an ether functionality.

Q. And so why does codeine or why does a prodrug of morphine or -- strike that.

What did the example of the morphine prodrug teach a skilled artisan trying to develop a 5-HMT prodrug in 1998?

A. My opinion, it would teach the principle that the -- that the conversion could be made enzymatically from an inactive to an active agent --

Q. Okay.

A. -- by a discrete, one-step enzymatic conversion --

Q. Okay.

A. -- into, into an alcohol product, which is the type of product that one would aim for, desire in terms of the fesoterodine to 5-HMT conversion. In other words --

Q. Okay.

A. -- that that 2 prime -- that 2 position alcohol.

Q. Okay. So beyond the general principle

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that you can go from an inactive to an active compound, and the active compound being an alcohol form, would you agree that the other teachings of the morphine prodrug are not necessarily transferable to the design of 5-HMT prodrugs?

MS. WOOTEN: Objection. Form.

A. They could potentially be transferable if one wanted to follow the design in terms of an ether conversion.

Q. Right. Okay.

A. But, again, I have no internal knowledge of that.

Q. No. I understand. I'm saying if you're pointing to a prodrug of morphine as suggestive of designing fesoterodine as a prodrug of 5-HMT, why doesn't that also suggest using, making an ether prodrug?

A. It could. But my purpose was suggesting or illustrating the enzymatic conversion of an inactive compound to its active alcohol product.

Q. I understand that.

A. That was my aim in that example.

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Q. But wouldn't you agree that a person of ordinary skill trying to design a 5-HMT prodrug might not look to a prodrug activated by the CYP2D6 enzyme, given the circumstances of why you're making the 5-HMT prodrug?

A. Yes. It's a possibility.

MS. WOOTEN: Objection. Form.

THE WITNESS: Pardon me.

Q. And wouldn't you agree that if a person were to look at the morphine prodrug example, that they would be led toward employing an ether prodrug as opposed to an ester prodrug?

MS. WOOTEN: Objection. Form.

A. I don't necessarily agree with that conclusion. No.

Q. Okay. Well, how do I look at the example of the morphine prodrug and say, I'll disregard the ether substitution, and I'll use an ester prodrug?

A. I don't think this, per se, teaches away from that substitution. I think it teaches for the enzymatic conversion of an inactive prodrug to an active alcohol-based agent or alcohol agent, morphine.

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Q. Okay.

A. And that was the point in that illustration.

Q. Okay. Now, how about carbamates and carbonates, why wouldn't a person of ordinary skill in the art use those types of prodrugs as opposed to a simple ester prodrug?

A. The author, Bundgaard, indicates on Page 7 that carbamates of alcohols, in general, appear to be of no value in prodrug design due to the high stability. Certain activated carbamates may be useful.

Again, this depends on the specific, the specific chemical involved in terms of the derivatization. I can't, a priori, say that a person would not consider this. But I can say that as opposed to a simple hydrocarbon short chain ester, such as on fesoterodine, these are more complex molecules that have their, their limitations and their applications and are not necessarily, in my opinion most attractive for the 5-HMT fesoterodine application.

Q. Well, depending on how big your ester group; they're not necessarily more complexion.

Correct?

A. Well, that's one factor in complexity, and that is one of the considerations in terms of my proclivity toward the simple, short hydrocarbon ester functionality.

Q. Mm-hmm. But certainly the suggestion on Page 7 about carbamate esters suggests that carbonate -- excuse me, carbamate esters derived from phenols show high lability and strong enzymatic catylst -- catalysis, sorry, where most endI substituted carbamates prove highly stable --

A. Mm-hmm.

Q. -- as did carbamates of hydroxy compounds. Correct?

A. Yes. But you notice in illustration 11, for example, example 11, that's a much more complex situation with respect to the length of the hydrocarbon chain versus fesoterodine. And I don't know the specific compounds referenced in the citations given; specifically, citation 103.

Q. Mm-hmm.

A. So I can't do a direct comparison with these data between the two situations; namely,

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fesoterodine, 5-HMT, versus the library or few compounds that were made to substantiate this conclusion.

Q. Mm-hmm. Now, so in sum, I take it that your opinion is that a person of skill would look to esters first because of their simplicity. Is that right?

A. Short-chain hydrocarbon esters, because of their simplicity, in terms of lack of chemical reactivity, intrinsic chemical stability, and greater propensity to be accepted as substrates for enzymatic hydrolysis by esterases.

There are several interplay, interwoven factors.

Q. Right. But isn't it also true that the more simple the promoiety, or, in this case, the more simple the ester, the less likelihood that you'll get conversion?

MS. WOOTEN: Objection. Form.

A. No. I -- it again depends upon how the specific ester functionality, as chemically attached to the parent molecule in the prodrug form, can access the active site of the enzyme.

Q. But can't you determine that based upon

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what you know about the chemical structure of 5-HMT?

A. You could determine that based -- you could estimate that, a derivative of 5-HMT, you could conjecture, you could project that a chemical derivative of 5-HMT, if it were an ester, an esterified 5-HMT, the simpler the ester, the greater chance it would have for efficient conversion back to 5-HMT.

Q. Mm-hmm. But you would agree that there are many prodrug substitutions that can be designed to interact with an appropriate enzyme to yield an alcohol. Correct?

A. In theory, yes. Yes.

Q. Other than simple hydrocarbon esters. Correct?

A. Yes, indeed. Complex hydrocarbon esters, yes.

Q. Okay. And wouldn't you benefit from any complications of the non-simple hydrocarbon esters by using a carbon spacer with a different type of promoiety?

MS. WOOTEN: Objection. Form.

A. Not necessarily.

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Q. Okay. Why not?

A. An ester that's used is a simple methyl ester, for example, which has no spacer at all.

Q. Mm-hmm.

A. So a spacer, spacer requirement, again, this would depend upon the desired profile in terms of the in vivo exposure, pharmacokinetics, and so on.

I don't believe that the spacer would necessarily correlate with those desired therapeutic effects.

Q. Okay. You can use a phosphate ester to yield an alcohol. Correct?

A. Phosphate ester. Yes.

Q. You could use a carbamate to yield an alcohol. Correct?

A. As stated, yes.

Q. You could use a Mannich base to yield an alcohol?

A. It would vary, yes. With certain compounds, yes.

Q. Now, one of the other reasons that I believe you suggest the simple hydrocarbon ester would be used is because of the simple one-step

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metabolic process. Correct?

A. In a --

MS. WOOTEN: Objection. Form.

THE WITNESS: Pardon me.

A. In a monoester form, that would be a potential attraction. Yes.

Q. Mm-hmm. Okay. Now, but there are a number of different prodrugs, other than simple hydrocarbon esters, that metabolize in a one-step process. Correct?

A. Yes.

Q. Okay. And one of the other reasons, I believe, that you provided about the teaching toward ester prodrugs is because they had been previously used to improve lipophilicity in compounds similar in structure to 5-HMT. Is that right?

A. Or to alter the hydrophilicity and lipophilicity and desired properties. Yes.

Q. Okay. But with compounds of similar structure to 5-HMT?

A. Let me see exactly where that statement is.

Q. Okay.

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A. Small molecules, certainly, of which 5-HMT is. But I'm trying to find the exact chemical specification here.

Q. Okay. Well, what compounds are sufficiently similar in structure to 5-HMT, such that one would draw the parallel with the ester prodrugs of those other compounds?

MS. WOOTEN: Objection. Form.

A. In my opinion, the small molecule alcohol with comparable molecular weight.

Q. Mm-hmm. Are there any, in particular, that you can give as an example?

A. Not offhand, specifically. No.

Q. Okay. Now, in the Table 2 in Bundgaard, the Page 3 there --

A. I have it, yes.

Q. -- okay, now are any of these compounds on the left-hand side, in your opinion, structurally similar to 5-HMT?

MS. WOOTEN: Objection. Form.

A. I don't know the structures of all of them. However, I can state about two-thirds of the way down, phenols --

Q. Mm-hmm.

A. -- if we just take a small portion of 5-HMT, basically the alcohol ring, that's -- that could be considered separate from the major portion, the rest of the molecule, that 2 position hydroxyl on the phenyl ring, alone, so eliminating most of the molecule. That's phenol. But I do not know the structures of all of these compounds, offhand, to direct them specifically and compare them.

I could do that, had I had the structures in stick diagram, as I do for 5-HMT, in front of me.

Q. Okay. Well, if phenols are structurally similar, wouldn't the Bundgaard publication suggest to use an amino acid ester?

A. No. I'm not saying that the structure is similar. In fact, I made the point explicitly twice just now that we have to eliminate most of the 5-HMT molecule to derive at the phenol. The only thing I meant to say -- I said was that if we take the northwestern aromatic ring with the hydroxyl at the 2 position, that's the equivalent. That is phenol.

We would eliminate all of the rest of the molecule.

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Q. Well, if you eliminate all of the rest of the molecule, is it still a structurally similar molecule to 5-HMT?

A. No. That was not my point. I said -- my point is simply saying that this hydroxyl group is a reactive one that could be esterified, and that ring with the OH group at the 2 position would be phenol.

Q. Okay.

A. But the molecule itself does not resemble phenol. It has much more structure to it.

Q. Right.

A. It has another benzene -- another pi electron ring, for example, there and has another hydroxyl group.

Q. Right. And I think you said earlier that the decision on which ester to employ is a function of the structure of the molecule you're trying to convert to. Correct?

MS. WOOTEN: Objection. Form.

A. That's one of the factors. Yes.

Q. It's a pretty major factor. Right? There has to be compatibility. No?

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MS. WOOTEN: Objection. Object to the form.

A. Compatibility to?

Q. I mean, you can't just -- you can't just take the teaching about what ester to use from a completely dissimilar, structurally dissimilar molecule and draw parallels. Correct?

A. In my opinion, that would be tenuous, but one could do that. But I would not do that.

So that's why we focus here on the -- on either one of the two, the two or -- the methyl hydroxyl or the phenolic hydroxyl on 5-HMT.

Q. Okay.

A. As the reactive groups or the potentially derivatizable groups.

Q. Maybe I should ask it this way: How is it so obvious to use an ester or a specific type of ester based upon this disclosure in Bundgaard, without knowing how function -- structurally similar that ester has been successfully used in the past? Strike that.

I mean, what I'm saying is: How does Bundgaard teach you toward the ester, the isobutyryl ester in fesoterodine, if the compound

that is given as an example of a prior known ester drug is structurally dissimilar from 5-HMT?

MS. WOOTEN: Objection. Form.

A. Specifically, he would not do that because the drug is not listed. But he does, however, exemplify here cases where esters of various types are conjugated to various types of drugs to derive prodrugs.

So the exemplification here is ester conjugation or ester derivatization to derive at a prodrug, the esters of various chemical types, the promoiety of various chemical types.

Q. Okay. There is -- in this Table 2 here of these esters listed, there's no specific disclosure of an isobutyryl ester. Correct?

A. Correct.

Q. Okay. And you would agree that of the drugs listed as exemplary ester prodrugs, none of these are OAB prodrugs. Correct?

MS. WOOTEN: Objection. Form.

A. Not to my knowledge.

Q. Mm-hmm. And none of them are antimuscarinic drugs. Correct?

A. Not to my knowledge. Correct.

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Q. And none of them are diphenyl propylamines. Correct?

MS. WOOTEN: Objection. Form.

A. I would have to know the specific structures to determine that --

Q. Okay.

A. -- in a form that would be compatible with the 5-HMT structure drawn in the document.

Q. Well, when you determined that Bundgaard taught to make an ester prodrug of 5-HMT, did you consider what the structures of these compounds on the left-hand side were at some time?

A. Not every --

MS. WOOTEN: Objection. Form.

A. Not every one, individually. The general principle was in the teaching that esters could be used as a viable route for prodrugs, esters of various types, of various chemical constituencies with respect to the promoiety.

Q. But how do you know that they could be used without giving consideration to the structure of the metabolite?

MS. WOOTEN: Objection. Form.

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A. The idea is that these -- these are the active drugs. I don't necessarily have to -- I would not necessarily have to know the metabolite and metabolic profile, as long as this teaches that the ester, whatever the ester -- specific esters may be in each case, result in the drug mentioned.

Q. Okay. Could you turn to Paragraph 143 of Exhibit 1. It's on Page 47.

(Witness complies.)

A. I have it.

Q. Okay. And Paragraph 43 in the second sentence, it says, "Ester prodrugs were known in the art to improve lipophilicity and had been used to do so in compounds with a similar structure to 5-HMT."

And then there's a cite to Bundgaard and to Table 2 --

A. Mm-hmm.

Q. -- and Scheme 1.

A. Mm-hmm.

Q. So when you wrote that, I'm trying to figure out, what compounds are similar in structure to 5-HMT that had been previously made

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as ester prodrugs to improve lipophilicity?

A. They were small molecule compounds. They were basically the small molecules. The closest active group would be, as I say, with the phenol at the 2 position.

Q. Okay.

A. That was the concept that I was trying to get across in more general terms, and I should have not worded it in terms of similar structure to 5-HMT, because that implies all of the rest of the molecule.

Q. Okay. So -- so that it's not correct that the drugs identified in this exhibit are structurally similar to 5-HMT. Correct?

MS. WOOTEN: Objection. Form. It mischaracterizes testimony.

A. In the sense that they have -- they're low-molecular-weight agents that are estimable prodrugs, no. They have similarities. But in terms of exact chemical structure, they are dissimilar --

Q. Okay.

A. -- as I remember. Again, I don't have all of the structures in front of me at present.

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Q. Okay. So, to your recollection, the reference to compound with similar structure was a reference to the phenols?

A. Well, the -- I know the similarity, as I say, because the -- if we go back to the diagram on Page 7 of Exhibit 1, the moiety at the 2 position of 5-HMT, that hydroxyl attached to the aromatic ring, if we leave all of the rest of the molecule, that's a phenol group, phenol substituent, phenolic substituent.

Q. I understand that.

A. That's what --

Q. I'm just trying to understand, when you wrote this, I'm just trying to figure out what drugs, in Table 2 of Bundgaard, did you mean when you said, "The previous compounds with similar structure to 5-HMT had been made as ester prodrugs"?

A. Well, the phenol would fit in terms of an ester prodrug, because hydrolysis of an ester phenol would give you back the alcohol, and that is, in essence, what happens when fesoterodine is hydrolyzed by an esterase.

We get the alcohol back at the 2 position,

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which is 5-HMT.

Q. So the answer is that, in your view, a phenol is structurally similar to 5-HMT?

MS. WOOTEN: Objection. Form.

A. No. I'm saying, in my view, there's a parallel between the hydrolysis of a phenolic ester to gain back the phenol and the hydrolysis of fesoterodine to gain back the phenol moiety of the 5-HMT.

Q. Okay. So do you agree or disagree that a phenol is a similar structure to 5-HMT?

MS. WOOTEN: Objection. Form. Asked and answered.

A. As I mentioned, there's a phenol moiety in 5-HMT.

Q. Does that make it a similar structure, in your opinion?

A. In terms of that particular component, there's a commonality.

Q. Okay. Are there any other such similarities among the drugs in Table 2?

A. I would have to refresh my memory of the other structures.

Q. Mm-hmm. Okay. Now, assuming that

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there are no other structurally similar drugs in Table 2 of Bundgaard, other than phenols, would you agree that the disclosure of the esters used can't teach toward the appropriate prodrug of 5-HMT?

MS. WOOTEN: Objection. Form. Facts not in evidence.

A. This document gives, in my opinion, no consideration or no treatment whatsoever as to the appropriateness of anything associated with the drug therapeutic properties of 5-HMT or fesoterodine.

Q. "This document," meaning the Bundgaard reference?

A. The Bundgaard. Yes.

Q. Now --

A. Exhibit 16. Yes.

Q. Now, you talked a little bit about the placement of the functional groups in a prodrug candidate needing to be optimized to fit the binding pocket. Do you recall that?

A. Yes. To be hydrolyzed by esterase, yes.

Q. So when you talk about the binding

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pocket, you're talking about binding to the esterase, not binding to the muscarinic receptor. Correct?

A. In terms of conversion of the prodrug to the desired product, yes.

Q. Okay. Okay. Now, if a structure is not similar to 5-HMT, then the placement of the functional groups on a different structure wouldn't necessarily teach you anything about where to -- which functional groups to substitute on 5-HMT. Correct?

MS. WOOTEN: Objection. Form.

A. If the same functional group were to be substituted on 5-HMT and substituted on, say, a low molecular weight, a different, but the same potentially hydrolyzable ester group --

Q. Mm-hmm.

A. -- and they were run in parallel or they were -- they were examined in an esterase preparation, the S9 supinate and what have you, then one could glean from either case the notion that or the susceptibility of that particular moiety to esterase activation, to esterase hydrolysis, qualitatively.

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Q. Okay.

A. It would -- would it mean quantitatively the extent of conversion would be the same among identical esters of various chemicals? No, not necessarily.

Q. Mm-hmm.

A. But it certainly would give you positive data to guide you forward that at least that functionality was recognizable by some esters.

Q. Right. But if you can't --

A. Esterases, sorry.

Q. -- if you can't draw parallels with respect to the quantitative conversion, that's pretty significant. Right? Because, qualitatively, you can have a structurally dissimilar compound with the same functional group, and it converts in a very low percentage.

That wouldn't be a very good prodrug, would it?

MS. WOOTEN: Objection. Form.

A. That would depend upon the structure of the rest of the molecule. That's why I qualified my statement and my answer by saying that those

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two -- the comparators would have to be within relative striking distance of molecular mass, solubility and so on.

I wouldn't take something that had a molecular mass of something, say, 400 molecular weight, which had the simple ester functionality, and something that had 4000 molecular weight, and compare those.

Q. Okay. I see. So what you're saying is in a structurally dissimilar compound, you might be able to glean that the same functional group will cleave, but you can't say anything about the extent of conversion --

MS. WOOTEN: Objection. Form.

Q. -- as applied to a different compound?

A. Well, you could say that you would expect that there would be some conversion. But could you quantify that conversion, based upon another compound? No.

Q. Okay.

A. Not absolutely, no.

Q. And, now, the other classes of esters that are, for example, disclosed in Table 2 --

A. Mm-hmm.

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Q. -- well, first of all, you'd agree with me that what is being described under the ester column is a number of different classes of esters. Correct?

A. A wide variety. Yes.

Q. Okay. And what informs whether to use one class of ester over another, according to Bundgaard or to your own opinion?

MS. WOOTEN: Objection. Form.

A. According to Bundgaard, it depends upon, for example, potential reactivity of the ester group itself, potential ability to conjugate that ester functionality to the parent compound.

We used the example earlier of the Mannich bases that are potentially useful prodrug candidates for certain amino acidic compounds, but they wouldn't necessarily be general agents to derivatize any compound.

So there has to be a chemical match there as well as a stability and a property of the ester group, once hydrolyzed, once released, not to have, in a particular situation, in vivo biological activity, at least undesired

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biological activity.

Q. Mm-hmm. Now, in the class of -- the classes of esters provided in Table 2 that we're looking at, is there a class or particular classes that are superior to others?

MS. WOOTEN: Objection. Form.

A. The superiority would reflect their properties, but reflect their properties conjugated to specific molecules. So, a priori, there would be no way to answer that question.

Q. Because it's specific to the compound structure that it's conjugated to?

A. Well, these examples are only given to specific compounds.

Q. Okay. And --

A. In other words, I could not generalize from this table all carbon-made esters. The carbon-made ester here, for example, in the second line is paracetamol.

Q. Okay. With respect to structure of 5-HMT, are there esters or is there an ester class or classes of esters that are preferable on this list to others?

MS. WOOTEN: Objection. Form.

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A. In my opinion, as I stated earlier, simple, nonreactive hydrocarbon ester would be most attractive. So something like aromatic ester, in my opinion, would be not attractive.

Q. Okay. And what about 5-HMT suggests to you that that's -- that aromatic esters are not attractive?

A. Nothing about the molecule, per -- well, there are two things. One, a large bulky group, particularly at the 2 hydroxyl of that phenyl ring, could cause steric hindrance in the rest of the molecule. It would be a very bulky group at that end.

So that would be one consideration that I would bring into play to limit that area and limit the derivatization at that area.

The second one is that if you have the -- the electronic configuration of an aromatic group could lead to other routes of metabolism and other reactions at that aromatic group.

Q. Okay. Now, but that assumes that you have to make the substitution at the 2 position. Correct?

MS. WOOTEN: Objection. Form.

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A. Yes. That is -- that is the example because of the link with fesoterodine and with the fact that tolterodine itself has the hydroxyl at that position. It does not have one at the opposing position, 5.

Q. Okay. But that's with the benefit of seeing fesoterodine?

A. Mm-hmm.

Q. If you only just look at 5-HMT, why would the substitution of aromatic esters not be attractive, given the possibilities for substitution?

A. Because of the potential steric bulk at the 2 position and either at the 2 position or the 5 position, which would be at the opposite position to the 2, that would also introduce -- could introduce the potential for further reactivity as a result of that phenol ring.

Q. At the 5 position?

A. In either position.

Q. What do you mean by "further reactivity"?

A. Because the phenolic group is electron rich. It has three unsaturated bonds, and those

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unsaturated bonds could react further with other molecules.

Q. Mm-hmm.

A. Or could drive the metabolism of 5-HMT elsewhere or could provide a bulky substituent that might be less attractive to esterase cleavage.

Again, I go back to my principle that a simple moiety, nonreactive hydrocarbon, in my opinion, is most attractive.

Q. Okay. Now, you've mentioned in your report, probably more than once, that even the smallest modification to a molecule can affect the properties of a compound. Correct?

A. Any modification can. Yes.

Q. Okay. And if that's the case, then why would a skilled artisan limit his or herself to, you know, a limited number of substitutions or limited number of promoieties?

MS. WOOTEN: Objection. Form.

A. Because someone skilled in the art, in my opinion, would realize that limiting the options, promoieties to simple, nonreactive promoieties that would have the potential to fit

into, easily, as conjugated to the parent structure, the esterases for cleavage and for return or obtaining the parent compound again.

That would be an attractive scenario.

Q. Okay.

A. So, in other words, this arrangement, this constellation of factors, would be metabolically attractive, from a prodrug standpoint, to obtain the active desired compound.

Q. Okay. Now, Dr. Janero, did you have an opportunity to consider the expert report of Dr. Rauch?

A. I did.

Q. Okay. Now, do you recall Dr. Rauch says if you assume -- if you just sort of limit the possible experimental choices of ester substitution to C2 through C6 carbons, there are at least 86 different possibilities.

Do you recall that, generally?

A. Generally, I do. Yes.

Q. And I think, in your report here, you suggest, in reality, that number would be much smaller. Do you recall that?

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I'm sorry. Let me help you out here. It's my fault.

A. Sure. I don't recollect I quoted an exact number, but we have to see the text.

Q. Yeah. I'll help you with that. It is 67.

A. Oh, 67. Here we are. Thank you.

Q. Mm-hmm. I think, more specifically, I'm getting at what you've got there in the second sentence that says -- after saying that, "theoretically, there may be 86 different phenolic monoester substitutions at the 2 position."

But then you said, "There is a much smaller number of potential substitutions that would have favorable properties, such as not being susceptible to chemical transformation or reactivity."

A. Mm-hmm.

Q. Okay. "Or substitutions that would create a polar molecule bearing an ionic charge that may compromise absorption and bioavailability."

A. Yes.

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Q. Okay. So, first of all, I don't see any citation to any prior art references or anything like that. So I'm just wondering, what is the basis for suggesting that the number is much smaller than 86?

A. Practically, the basis would be knowing that you'd want to limit the steric molecule. You want to limit the size of that promoiety. Someone skilled in the art, in my opinion, would start with the most simple, unreactive hydrocarbon.

If I remember correctly, in fact, in the literature that was available, Dr. Mog and the group actually started with a methyl ester --

Q. Mm-hmm.

A. -- which is the simplest of the hydrocarbon esters --

Q. Mm-hmm.

A. -- and did the comparisons among relatively simple esters of a few carbons, not going up to six, seven, multiple carbons.

The other factors, not only the number of carbons, but the positioning of the carbons in the promoiety; for example, in fesoterodine,

there's -- you have three, you have a three-carbon group. But the -- it's an isopropyl functionality. So you have three carbons. You could have three linear carbons and so on.

So that number doesn't necessarily represent different numbers of carbons. It can also -- it also represents different arrangements of the same number of carbons.

Q. Mm-hmm.

A. So that number is -- is increased in that way as well.

The thrust of this reasoning was that one would have, theoretically, far greater, but my opinion, someone skilled in the art would start with the more structurally simple promoieties, fewer carbons, with no unsaturated bonds that could be reactive, for example, could be oxidized, for example.

Q. But you don't know the reactivity of a compound until you test it. Right?

A. But you know -- you know, in most cases, the potential to susceptibility of that to reactivity. For example, a saturated bond couldn't be advantageously oxidized,

carbon-carbon bond, whereas an unsaturated bond could be.

Q. And where do you get the support for that?

A. In terms of basic fatty acid metabolism, unsaturated fatty acid bond, when it's oxidized, chemically or enzymatically, forms a different product with different metabolic activity.

That's how a polyunsaturated fatty acid or acetonic acid can become a lipid-signaling intermediate; leukotriene, for example, prostaglandin.

Q. Now, you mention the simple methyl is the best option, and I think you also just recalled that that's how the inventors started. Correct?

A. I can't say that the inventors started, but I believe it was an early specification in the -- in the documents that I reviewed. And I don't know that it was the best, but certainly it is the simplest, in terms of a small, hydrocarbon ester.

Q. Okay.

A. In other words, having one ester carbon, the methyl.

Q. And fesoterodine doesn't have a methyl ester. Correct?

A. No. Fesoterodine has an -- an isopropyl ester group.

Q. Mm-hmm. So if the person of skill would start with the simple methyl option, how, in your view, would you end up arriving at the isobutyryl of fesoterodine?

A. Perhaps the methyl ester was not stable, was not -- was hygroscopic, attracted atmospheric water so that it couldn't be solidified. Or when it was solidified, it was not -- it didn't remain a solid.

In fact, I believe those were some of the factors that came into play. But, be that as it may, regardless of any knowledge of that, those could be some -- those would be some of the practical considerations to explore other esters. But, at the same time, keep that ester functionality as limited as possible.

Q. Mm-hmm. I understand that. But there is no teaching in the art as to how stable, for

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example, a particular ester substitution will render the prodrug. Correct?

MS. WOOTEN: Objection. Form.

A. Stable in terms of chemical stability, as a neat compound?

Q. Yes.

A. That's true.

Q. And I just want to understand your opinion with regard to why it was obvious to substitute only at the 2 position, as opposed to the 5 position or both.

A. Mm-hmm.

Q. Can you just explain that to me?

A. Yes. Both, I think we covered to some degree earlier; namely, the -- I would disregard that, and I would suggest that a person, a skilled person at that time would also have because of the need to have multiple enzymatic conversions to derive or to arrive at 5-HMT.

Q. Mm-hmm.

A. So if we take that into consideration, then we can view the 2 versus 5 hydroxl. As I mentioned in the di -- in the text, following the diagram, yes, they're both hydroxyl groups. But

they're not chemically equivalent.

The hydroxyl at the 2 position, 5-HMT, is the same hydroxyl in tolterodine.

The methyl hydroxyl at the 5 position actually is a result of the -- of the metabolism of tolterodine to 5-HMT.

Secondly, the difference is that the 2 hydroxyl is relatively more acidic than the 5. And, therefore, under standard conditions, would be more readily converted to a simple ester, in terms of the synthetic chemistry, the chemical transformation to a stable ester. I --

Q. Where do you get that the 2 hydroxyl is relatively more acidic than the 5?

A. Because it's conjugated to the pi substituents, the pi ring of the phenyl moiety, whereas the 5 is not. It's separated by one methyl group.

Q. And, from that, you concluded it's more acidic?

A. Yes, because the electronic configuration, as shown in these diagrams, is actually not as rigid here. You have a pi electron ring that basically can be moved toward

the electron-rich ring that alters the acidity, that makes that direct link between the 2 hydroxyl and that pi ring system more acidic.

The lack of that direct link with respect to the 5 position, by virtue of that carbon spacer, so to speak, makes that relatively less acidic, because it's not in communication, direct communication with the pi electron system of the phenyl ring.

Q. Okay. Now, you had mentioned -- well, if you look at the figure that you've been pointing to, which is on -- what is it, seven?

A. Seven, yes.

Q. And you are -- strike that.

You agree that both tolterodine and 5-HMT are active in and of themselves. Correct? They have, they share antimuscarinic properties. Correct?

A. Yes.

Q. And the fact that what is common to those two molecules is the hydroxyl in the 2 position, in addition to the amine group, wouldn't that suggest to a person of ordinary skill in the art the likelihood that that

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molecular configuration is important to the muscarinic receptor binding?

MS. WOOTEN: Objection. Form.

A. Not in terms of the binding data I've seen that show that both tolterodine and 5-HMT are high affinity ligands for that receptor.

Q. Okay. But that structural commonality, wouldn't that suggest to one of skill in the art that that's involved with the binding?

MS. WOOTEN: Objection. Form.

A. Not -- not in and of itself, no.

Q. Okay.

A. Because there are so many -- for example, there are so many other commonalities; namely, the tertiary amine, for example. The entire right side of the molecule, from the stereoselective hydrogen over to the right, are also common.

Q. Mm-hmm.

A. And if memory serves, I believe that the amine region is a very critical determinant of the interaction of these types of ligands with muscarinic receptors.

Q. Okay. Fair enough. It could be the

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amine, the common amine structure. But the other common structure is the hydroxyl at 2. Correct?

MS. WOOTEN: Objection. Form.

A. Between tolterodine and 5-HMT, yes.

Q. And that being one of the two common structural features between these two compounds, which you know work, wouldn't that suggest to a person of skill in the art that that 2-positioned hydroxyl is important towards driving the activity of these compounds?

A. No. Because I believe there's precedent for the amine region to be particularly critical, but also there are not -- there are many more than two common chemical similarities between tolterodine and 5-HMT.

We could go around the molecule and count them. But the entire 3-position moiety from the phenol group is common to both. And that has several chemical entities associated with it.

Q. Okay.

A. In fact, that has -- the bulk of the molecule is there.

Q. Mm-hmm. Now, I believe that you reviewed the deposition transcript of Dr. Sparf,

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one of the inventors. Correct?

A. I believe so, yes.

Q. And do you recall that initially the inventors were attempting to make the prodrug by substitution at the 5 position?

A. I don't actually recall that, specifically.

MR. TRAINOR: Okay. I'd like to show you this. And what I've marked as Janero Exhibit 17 is United States Patent 5,382,600 --

(Document Bates-stamped MYLB_FESO_00027703 through -7722 marked Exhibit 17.)

Q. -- to Jönsson, et al. And I believe if you look at Page 6 of your report, this is another one of the documents that you considered, as you see in the table there --

A. Yes.

Q. -- in Paragraph 14.

A. Yes.

Q. So do you understand that this document, this U.S. patent is the patent that covers tolterodine?

A. The '600. That's my understanding.

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MS. WOOTEN: Objection. Calls for a legal conclusion.

Q. Okay. Now, if you -- did you review this patent?

A. I did.

Q. Okay. If you look at Column 29, which is pretty close to the end of the patent --

A. Got it.

Q. Okay. In the second full sentence, it says -- oh, sorry, in the first full sentence, it says, "The test procedures are described below, and the test results are reported in Table 1," which starts on the next page. And I'll get to that.

But before we get to that, it says, "For comparison purposes, the testing also included the commercially available drug terodiline and a structurally similar compound," which it names, and states that it's disclosed in the prior art and other patents.

And then the paragraph concludes, "The test results clearly show that the compounds according to the invention are superior to the known compounds, especially as regards selectivity

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between the desired anticholinergic activity and the undesired side effects."

Do you see that?

A. I see that.

Q. Okay. So if you go to Table 1, you see the first two compounds are these compounds that were described in that passage I just read as the prior art compounds.

A. Yes.

Q. Terodiline and this GBA compound?

A. Yes.

Q. And, in particular, terodiline is a diphenylpropylamine that is completely unsubstituted. Do you see that? On the rings?

A. The phenyls are unsubstituted except for the --

Q. Okay. And then the rest of Table 1 are examples of the compounds claimed in this patent. And my question is just, looking at those structures numbered 1 through 13 in the patent, would you agree with me that the one common feature of all of these compounds is either the hydroxyl or methoxy at the 2 position of one of the phenyl rings?

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MS. WOOTEN: Objection. Form.

A. A common feature, yes. Ether hydroxy or methoxy. Yes.

Q. Okay. Now, and you'll note that the amine groups vary from compound to compound. Correct?

A. They do.

Q. And there are some compounds that are substituted or have additional substitution on the rings or are substituted on both rings?

A. Yes.

Q. But, again, the one common feature is the 2-position substitution of hydroxyl for methoxy. Correct?

A. In at least one of the rings, if not --

Q. Yeah.

A. -- both.

Q. Right. It should be clear, because you have it in your -- Page 7 of your report, but just represent that compound four is tolterodine. So I'll ask you the question again.

Having seen this, and also considering the structure of 5-HMT, does that suggest to you that the substitution of a hydroxy or, I guess, in a

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few cases a methoxy at the 2 position may be important to the activity of these compounds?

MS. WOOTEN: Objection. Form.

A. Well, let's consider compound four.

Q. Mm-hmm.

A. And let's consider its direct analog where the substitution is at the 5 position with a hydroxyl, only a methoxy --

Q. Mm-hmm.

A. -- and what number would that be?

Q. Eight. That's a different amine group.

A. No.

Q. I'm sorry?

A. No. I said, "No". It is a different amine group. Sorry.

Q. But I'm just asking you --

A. See --

Q. -- for the benefit of --

A. Right.

Q. -- they're all analogs. Right? And 5-HMT is an analog of these as well?

A. Right. Some are, as you alluded to earlier, for example, example ten, compound ten is a cyclic analog. So there are various --

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there are multiple changes.

What I was looking for was the direct comparison between 4 --

Q. Mm-hmm.

A. -- at the 2 position and versus the direct comparator at the 5 position.

Q. Right. But that's kind of my point, which is that you don't have that. That tolterodine, in its analogs and 5-HMT, the one thing they all have in common is that there's this substitution at the 2 position.

So my question is: Don't you think that would suggest to someone reviewing the prior art, in 1998, that there's something significant about the substituent at that specific 2 position on these analogs?

MS. WOOTEN: Objection. Form.

A. As I say, I can't see the exact equivalent that is substituted only at the 5 position with the hydroxy. I'm not seeing that to make that comparison. I see a diphenolic, but I don't see the equivalent to make that comparison directly in terms of anticholinergic, antimuscarinic, what have you.

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Q. Mm-hmm.

A. I'm not seeing that comparison. So, from this -- from these data alone, from this data set, I could not -- I could not agree with that statement, because I don't see a direct comparator here.

Q. Well, wouldn't you agree that one possible reason is that the 5-position substitution you're looking for is not the significant structural characteristic of all these analogs?

MS. WOOTEN: Objection. Form.

A. Or the possibility exists, given the other changes in the structures, including what I would consider are radical changes in terms of cyclization around the nitrogen, that those may be determining factors, or the interaction of those.

There's no way, in my opinion, of concluding -- of answering that question without the direct comparator, and I don't see it in this table. I'm sorry.

Q. I'm not suggesting that you could conclude that. I'm not even suggesting that a

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person of ordinary skill would conclude that.

I'm just saying, wouldn't it possibly occur to them that there is some significance?

It may or may not be true, but given that you've got 11 -- 13 compounds here, plus 5-HMT, and all of them are substituted at the 2 position, wouldn't it be possible the person of ordinary skill in the art would consider maybe that is important to the function of these analogs?

MS. WOOTEN: Objection. Form. Asked and answered.

A. Well, I'll accept that the prior art.

Q. Correct.

A. And that has an anticholinergic effect, if I read this, of 5 times 10 to the minus 7 molar, as I see, 50.

Q. Right.

A. So that's a -- that's a -- that's about half. Let's say 5.2. 5.2, 5.5. So that's about fourfold difference between 4. But still you're in the -- you're in the submicromolar range with virtually all of these.

Q. Okay.

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A. So from this, alone, I stand by my conclusion that I would -- I could not isolate, without direct comparator, the contribution of that specific position on the phenol ring to the overall profile given here of these compounds.

Q. Okay. That's fine. Let me ask it to you this way: Let's assume that a person of ordinary skill in the art had a different view, and it occurred to them that there's something significant about the 2 substitution.

I want you to assume that. You may not agree with it. I want you to assume that that's what the thinking would be.

Assuming that the person of ordinary skill in the art did consider that, wouldn't you agree that they would be less likely to make the prodrug substitution at that position that may be important, and, instead, consider substitution at the 5 position?

MS. WOOTEN: Objection. Form.

A. If there were data to show that assumption were true, then, in my opinion, the 2 position would be less favored.

Q. Okay.

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A. But a substitution at the 2 position, having said that, would not necessarily change in an adverse way, per se, the activity of that compound or its ability to be hydrolyzed as a prodrug, an ester substitution.

Q. Okay. Okay. Fair enough. But you would agree that it would be reasonable for a person of ordinary skill to say, I want to avoid a prodrug substitution at the 2 position, because it might be important, and I don't want to interfere with the importance of keeping the hydroxyl there or the methoxy?

MS. WOOTEN: Objection. Form.

A. Given that assumption --

Q. Yes.

A. -- and given comparator proof that the -- that that 2-position hydroxyl were absolutely necessary for the activity --

Q. Mm-hmm.

A. -- those data, not being in the document before me, in the table, but with those as suppositions and given, then that would be a reasonable conclusion, in my opinion.

Q. Okay. Now, I just want to ask a few

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more questions about this -- some of this molecular modification opinions.

So going back to -- you know, it begins on Page 21, I think. Actually, it goes back a little further. So let's look at Paragraph 62, for example.

A. I have it.

Q. Now, here in Paragraph 62, you express your opinion that the skilled artisan would not be motivated to di substitute at both 2 and 5. Do you see that?

A. I do.

Q. Okay. One of the reasons that you provide -- or sort of at the end of Paragraph 62, is that the -- a higher molecular weight and/or dual esterification is not desired, because that would reduce the propensity for esterases to act on the molecule. Do you see that?

A. I do.

Q. What is the basis for suggesting that an increase in molecular weight correlates with a reduction in the propensity to esterize or for esterases to act on the molecule?

A. The higher molecular weight, in this

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case, as I referred to earlier in the paragraph, would derive from the increase in complexity of the promoiety.

Q. Mm-hmm.

A. So we're keeping the parent moiety, so to speak, the same.

Q. Mm-hmm.

A. So we have enzymes whose active sites can accommodate only so much bulk, molecular bulk --

Q. Mm-hmm.

A. -- molecular weight, molecular mass.

If we increase this -- and, by the way, these enzymes are water-soluble enzymes.

So if we increase the molecular weight, a person skilled in the art would invite, would consider inviting -- that this would invite less ability of the higher-molecular-weight species to interact with the catalytic site in such a way that they would be transformed, that they would be acted upon by the enzyme to -- as prodrugs, to result in the desired active product.

Q. So where is the support for that? That the heavier the prodrug, the less likely it is

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that the esterase will act on it?

A. Let's take an example. If we have a fatty ester --

Q. Mm-hmm.

A. -- let's say 16, 18, 20 carbons, versus a short chain ester, two, three carbons, simple linear chain, saturated, no problem --

Q. Mm-hmm.

A. -- and we expose an S9 preparation from liver to the very long chain lipid ester versus the short chain --

Q. Mm-hmm.

A. -- the long chain ester would not be recognized by this type of es- -- of enzyme, in terms of enzymatic hydrolysis. It would be recognized by another type that's membrane associated that takes that type of fatty molecule, but it would not be recognized by this type of water-soluble esterase that we're talking about here acting on a small molecule.

This is why, if one assays esterase activity from commercial reagents, this type of esterase, the commercial substrates, are small molecules. And the ester- -- the esterase converts them into

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a product that forms color, that emits light, that fluoresces, and that's how this type of assay is done in terms of determining esterase activity.

It's not -- it's not performed, but with a high molecular weight, long-chain fatty ester. These experiments I have actually done myself.

Q. Okay. At what point -- is there a threshold of molecular weight that you need to stay under?

A. Not that I know of.

Q. And this is not a memory test, but I'll represent to you, I think the molecular weight of 5-HMT is about 341.

A. I would say that's reasonable.

Q. Would you agree that you don't run the risk of -- I mean, that it would take quite a bit to go over that threshold? In other words, to add to the molecular weight of 341, at what point does it become too big, where it becomes the problem that you're envisioning?

MS. WOOTEN: Objection. Form.

A. I wouldn't know that, but it's not only in terms of the steric bulk. It's in terms of

now changing the molecular properties.

If one introduces a very extensive hydrocarbon chain onto 5-HT --

Q. Mm-hmm.

A. -- HMT, you have a situation where you're now making the molecule very lipophilic, very greasy.

Q. Okay.

A. And these molecules -- these enzymes, these esterases are water soluble. They -- their active sites are well hydrated. They don't act upon this type of high-molecular-weight molecule.

They wouldn't act upon this because you've changed, not only molecular weight increased, by doing so, you've increased the lipophil- -- you made them actually into lipid-like molecules.

So it's not only the molecular mass. Other factors come in as well when one increases the complexity, the chemical complexity of this ester profunction.

Q. Okay. In the next paragraph, Paragraph 63 --

A. Yes.

Q. -- I probably should have brought you

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here before, but there's a discussion of these other types of common ester groups --

A. Mm-hmm.

Q. -- that can be considered. Phosphate esters, ethers --

A. Yes.

Q. -- carbamates and carbonates.

And just to paraphrase, the opinion that you express there is that these types of ester groups invite changes to the charge of the parent molecule.

Do you see that?

A. Yes, but not in all cases. The phosphate ester may, because it may have a negative charge. But not all of them.

Q. Carbonates and carbamates, they don't even have a charge. Correct?

A. At certain pHs, they don't.

Q. Okay.

A. The point here is not to -- my point was not to assign specific reactivity or charges to any specific groups here. The idea that by introducing certain types of esters, such as these, these functionalities have in themselves

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chemical reactivities that would not be displayed by simple hydrocarbons, such as that on a methyl ester, such as that on an isopropyl ester.

Q. Mm-hmm.

A. And that, to me, and to someone skilled in the art at that time, in '98, would make such a simple ester, hydrocarbon ester, more attractive versus these esters in a discovery program.

Q. Okay. But the reasoning of inviting charge, just sticking with that for a moment --

A. Sure.

Q. -- if carbamates and carbonates don't have charge, that wouldn't be a reason not to consider them as the ester groups for a 5-HMT prodrug. Correct?

A. Right, if under those conditions. But it could be under conditions where they have their own reactivities, chemical reactivities as carbamates or carbonates or ethers, for example.

Q. And even if any of these other alternative esters were charged, wouldn't you agree that the body takes care of charges all the time?

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A. No. I wouldn't agree with that.

Q. Okay. Is every amino acid in the human body charged?

A. No.

Q. Okay. And tolterodine and 5-HMT at the physiological pH, are they charged?

A. They would not be, in my opinion. No.

Q. And the -- there's another reference to inviting local changes to the tissue pH --

A. Yes.

Q. -- if these esters are employed?

A. Mm-hmm. Mm-hmm.

Q. Okay. And --

A. Again, not all esters, but this is a potential for some esters that would have more acidic chemical reactivity or basic reactivity.

Q. Okay. But the inciting local charges -- or the risk of inciting local changes in the tissue pH --

A. Mm-hmm.

Q. -- that you suggest would be brought on by these alternative ester promoieties --

A. Mm-hmm.

Q. -- doesn't that fail to account for the

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fact that human serum is a buffer in and of itself?

A. It's --

MS. WOOTEN: Objection, form.

THE WITNESS: Pardon me.

A. It's an extraordinarily weak buffer.

Q. Okay.

A. And it's not what one would call a general buffer. It's an extraordinarily weak buffer. And this is why, for example, intervenous or intramuscular drugs are not interjected at pH 1.

Q. Mm-hmm.

A. They're not administered at pH 12. If it were such a good buffer, the pH of these preps wouldn't matter at all.

Q. Okay. And regardless of whether a prodrug of the type described in Paragraph 63 is employed, once the active molecule is released from the prodrug, it's going to have the same reactivity, no matter what. Correct?

MS. WOOTEN: Objection. Form.

A. This would depend upon whether the prodrug did alter, for example, the metabolism of

that drug and produced, for instance, other byproducts that were active or may have interfered with the activity of that drug.

So that's not -- that's the optimal scenario, but I could see it would not necessarily be the case.

Q. Okay. And the -- I believe that -- okay. Let me just see if there's anything else on this and then -- now, the -- going back to Bundgaard, a number of the compounds that are listed in that Table 2, they are -- some of them are di substituted, some of them are tri substituted.

How is it that Bundgaard would suggest only a mono substitution for a 5-HMT prodrug?

A. Well, there are some that are monoesters that are specified here, and they are prodrugs for drugs containing a hydroxyl group, and that is in parallel with 5-HMT.

Q. Mm-hmm.

A. In terms of monoester, one would have to go -- versus -- one would have to go back into these independently and assess that situation.

I don't know the specific basis, nor would I

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conclude that a monoester would be favored from this table, alone. I gave other reasons earlier, as well as in the document, why I would think a person skilled in the art at that time would favor a monoester.

Q. Mm-hmm. Despite examples in the prior art of a number of prodrugs that are -- have multiple substitutions?

MS. WOOTEN: Objection to form.

Q. Correct.

A. The multiple substitution in those would not necessarily guarantee that the same multiple substitution would be appropriate for 5-HMT.

Q. Mm-hmm.

A. For example, some of those drugs need not have been modified at a hydroxyl group.

Q. Mm-hmm. Okay. Now, but you would agree that the Bundgaard publication teaches a number of successful diesters. Correct?

MS. WOOTEN: Objection. Form.

A. Successful, in terms of?

Q. Prodrugs functioning as they should.

A. No. I would disagree with that.

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Q. Okay. You have epinine, albuterol, terbutaline, epinephrine, dobutamine. Those are all diesters?

A. Right. But in contrast to what you stated, I would say that the table represents various -- in terms of successful, to use the terminology, conversions of ester prodrugs to active drugs that are listed in the left-hand column --

Q. Mm-hmm.

A. -- and in the references.

It gives me no indication as to the pharmacological profile of the resultant drugs in terms of their therapeutic success or therapeutic limitation for adverse events or lack of adverse events.

Q. Okay. Okay. There are, I think, a number of indications in this section about the molecular modifications that a person of ordinary skill would make, and I think a couple of times you make a reference to preserving the metabolic pathway of 5-HMT.

Does that sound familiar to you?

A. It does sound familiar. I'd like a

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specific example, though --

Q. Mm-hmm.

A. -- because it may be very contextual.

Q. Well, let me see here. Why don't I just ask you this question, which is: Regardless of what prodrug you design of 5-HMT, once it converts to 5-HMT, the metabolic pathway of 5-HMT is what it is. It's not going to change or be affected by the way you've designed the prodrug. Correct?

MS. WOOTEN: Objection. Form.

A. Once the conversion is to 5-HMT --

Q. Mm-hmm.

A. -- 5-HMT would be expected to be inactivated, metabolized, by two cytochromes, two essentially inactive products --

Q. Mm-hmm.

A. -- yes. That are known.

However, the derivatization of 5-HMT into a prodrug could alter such things as the rate of conversion. It could alter the site of conversion and so forth. But where, if I understand your question, it starts at point of 5-HMT --

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Q. Okay.

A. -- if I have that right.

Q. Okay. And one more question about Bundgaard.

There are also a number of examples of prodrugs made with substitutions at the aliphatic positions. Correct?

A. Yes.

Q. I think quinapril is one. What else? And there's prodrugs of IDU. Those are not in the table, but they are in this chapter?

A. Mm-hmm.

Q. But would you agree that Bundgaard discloses prodrugs where the ester substitution is at the aliphatic position?

MS. WOOTEN: Objection. Form.

A. There are specified examples in Table 2. Yes.

Q. Okay. And is there any reason why those disclosures or teaching of Bundgaard wouldn't suggest substituting at the aliphatic position in designing a 5-HMT prodrug?

A. Well, given knowledge at the time, and I believe, if memory serves, this goes back to

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oxybutynin, in itself, the aliphatic region of these -- of these antimuscarinic agents is very critical to their engagement at the receptor, at the muscarinic receptor.

So I would use that information, combined, yes, there's a possibility to derivatize at the aliphatic region of 5-HMT, but I would temper that information with the knowledge that the substituents around the ring, in fact, this nitrogen region to the right, is very critical in terms of recognition of these antimuscarinic agents and their engagement by target receptor that is known to be involved in the relaxation of the bladder smooth muscle, so I would say that that information would teach someone skilled in the art away from -- away from substitution at that region, the aliphatic region, rather than toward.

MR. TRAINOR: Okay. Why don't we take a quick break.

THE VIDEOGRAPHER: The time now is 17:17, and we're off the record.

(A recess was taken.)

THE VIDEOGRAPHER: The time now is

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17:29, and we're back on the record.

BY MR. TRAINOR:

Q. I know it's getting late. Just finishing up on the opinions you have with respect to the specific molecular design of the 5-HMT prodrug, is it fair to say that your opinions are based on -- strike that.

Is it fair to say that your opinion is that a person of ordinary skill would start with small hydrocarbon esters, because they are less complex and keep the molecules simple -- that that's your opinion. Correct? That the person of skill would start, reasonably, with that particular choice of ester?

MS. WOOTEN: Objection. Form.

A. Those are two factors, but there are other factors as well, as I alluded to. In other words, the ability of these simpler esters to be hydrolyzed by required enzymes, to regain the parent compound from the prodrug, the attractiveness of the more conservative esters, I think would not change the intrinsic properties of the molecule, physiochemical properties, for example, making them more lipophilic; as an

example, I showed fatty, to the extent that they might have alternative activities or might engender metabolic products that would have other perhaps unwanted activities and so forth. So those reasons that you cite are part of a larger picture, but they are reasons, so yes.

Q. So my question is really: Would you agree that nonester prodrugs such as the ones we discussed in Bundgaard or other classes of esters, ester prodrugs, like carbonates and carbamates, would you agree that they may also be converted, notwithstanding that they may be more complex and less simple?

In other words, it's not your opinion that other types of prodrugs wouldn't work to convert 5-HMT. Correct?

A. I cannot say that, because I don't know to what extent a derivative of 5-HMT would be -- would be -- those other types of derivatives would be, a priori, susceptible to hydrolysis.

Experiments would say that, but I don't know that, just based upon the chemical structure, other than if we keep the promoiety relatively conservative, my guesstimate would be that they

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would have a good chance of being converted. But I would not know that.

Q. Right. And I think that's my point.

It's your opinion that you would start with these conservative hydrocarbon esters because of their simplicity and the likelihood that they may work. Correct?

A. And lack of intrinsic chemical reactivity.

Q. Right. And all I'm asking you is: It doesn't necessarily follow that nonester prodrugs or more complex ester prodrugs couldn't also work as a solution. Correct?

MS. WOOTEN: Objection. Form.

A. Not necessarily from -- correct.

Q. Right.

A. But the data on the ester prodrug, per se, would not necessarily be predictive of either another type of ester "working," quote/unquote, or not.

Q. Okay. Now, with respect to the design choices that faced the skilled artisan with respect to making a prodrug of 5-HMT, are there any particular rules or teachings in the art

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which suggest which types of prodrugs or which types of esters are likely to render the prodrug inactive?

A. If we go back to the prior context and reasoning --

Q. Mm-hmm.

A. -- the prodrug would be rendered inactive in a scenario where it would not be hydrolyzed at all or hydrolyzed efficiently by ester prodrug.

So going back to a former example, if we were to derivatize a relatively low molecular weight, of around 400ish or so, molecule with a very large, aliphatic hydrocarbon, greasy, lipid ester group, that stands very little chance of being hydrolyzed by this type of water-soluble esterase, then, yes, that would have great impact, perhaps decisive impact on the ability.

Q. Right. I think we're -- I may have confused you.

I'm talking about to the extent that the prodrug does not get hydrolyzed, and I'm sure you would agree with me that no matter what the prodrug is and no matter what the drug is, there

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will always be some unconverted prodrug, itself. Right?

A. I wouldn't say always, no.

Q. Okay. And, obviously, you wouldn't want that. But to the extent -- I mean, the teaching about Bundgaard and the definition of the prodrug being inactive, that's important, correct, to the extent that not all of the prodrug gets converted?

MS. WOOTEN: Objection. Form.

A. In the classic definition that Bundgaard gives as a prodrug, that is a prerequisite. That is a characterization, a characterizing factor of the prodrug, yes.

Q. Right. And that's because, for any unconverted prodrug, you don't want to run the risk of it having activity that could be adverse or affect other targets. Correct?

MS. WOOTEN: Objection. Form.

A. Well, but by definition of the prodrug that we're using here, the prodrug would have no significant biological activity.

Q. I agree. I understand. That's -- that is the definition of a prodrug, that the prodrug

itself doesn't have activity.

And my question is: Are there any particular teachings as to how to modify or design a prodrug to ensure that if the prodrug is not converted, it's still inactive?

MS. WOOTEN: Objection. Form.

A. If it's not converted --

Q. Correct.

A. -- it's still inactive?

Q. Correct.

A. Well, other than to try to ensure that it is not a substrate of esterases, because if a prodrug is not a substrate or a very poor substrate of esterases; i.e., not risked by the enzyme's active site to be converted, then you would end up in this paradigm with mainly or only inactive prodrug. So...

Q. Well, once -- it's preferably inactive, but you don't necessarily know that. Correct? Lets take a look at the three structures in front of you, Page 7.

A. Mm-hmm.

Q. Okay. You would agree with me, tolterodine is active?

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MS. WOOTEN: Objection. Form.

A. It has muscarinic activity, yes.

Q. Right. And 5-HMT is active as well?

A. It has muscarinic activity, yes.

Q. And so isn't it fair to assume that there's a risk in designing a prodrug being an analog of those two active antimuscarinics, that the prodrug you design converts, but, unfortunately, it's active also and doesn't solve the problem of the two active agents?

MS. WOOTEN: Objection. Form.

A. If I understand the question correctly, the risk would be mitigated by the conservative nature of the substitution.

Q. It would be mitigated. So --

A. Could be.

Q. Okay. That's what I wanted to ask you. So your -- your testimony is that a conservative ester is likely to lead to a compound that's inactive?

A. No.

MS. WOOTEN: Objection. Form.

A. The opposite. A conservative ester would likely be a substrate of esterases, and,

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therefore, would likely end up with a com- -- if the compound is active, it would likely be activated, it would likely be transformed by the esterase.

A conservative ester substitution of the parent compound, a priori, need not necessarily lead to an inactive prodrug.

Q. Right. What I'm saying --

A. That's --

Q. What I'm saying is the two structural analogs of fesoterodine, 5-HMT and tolterodine --

A. Yes.

Q. -- they're active?

A. Yes.

Q. If I create a prodrug that is not completely converted, and the unconverted analog of those two is active --

A. Mm-hmm.

Q. -- then I haven't designed a prodrug, by definition. Correct?

A. The classic definition --

MS. WOOTEN: Objection. Form. Asked and answered.

A. That's true, because the classic

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definition that we're following here is the prodrug has no significant biological activity.

Q. Right. And so what I'm asking you is when you're doing this design --

A. Yes.

Q. -- before you know whether it converts or anything like that, before you've done any testing of its qualities as a prodrug --

A. Mm-hmm.

Q. -- what is it in the prior art, if anything, that teaches you what substitutions to make to ensure that, unlike its two analogs, it is not also active?

MS. WOOTEN: Objection. Form. Asked and answered.

Q. Or is that something you just have to test?

A. The nonempirical way to do it would be to make the derivatives and profile them, of course --

Q. Right.

A. -- and quantify the rate and extent of conversion.

Q. Mm-hmm.

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A. The mere derivatization of a compound, an active pharmacological agent --

Q. Mm-hmm.

A. -- to any type of ester need not guarantee that that derivatization has inactivated that compound.

Q. That's what I was asking you. And so on that point, is there anything that a medicinal chemist or a drug designer can do that will tend to result in an inactive prodrug, as opposed to a drug which converts, and in unconverted form, remains active?

MS. WOOTEN: Objection to form.

Q. Do you understand my question?

A. Right. If one knew, for example, that there were a certain reactive molecule, not the prodrug, that were essential to its pharmacological action, such that if that region were altered, abrogated, changed in some way, as a prodrug, as an ester prodrug, however, chemically, then negatively affected the activity, that one could design around that region to limit the activity as a prodrug.

But, at the same time, introduce a promoiety

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that would be susceptible to metabolic conversion to regain that compound back.

Q. Mm-hmm.

A. And in the design rationale, that would support the idea of inactivating or limiting the activation in the classic sense, inactivating that original molecule and then expressing the activity with metabolic conversion as a prodrug.

So that would be one way one could do that.

Q. Okay. I guess my question is: This presents a good example on Page 7, but with respect to any prodrug that you're trying to design to get back to an active metabolite, for example, you're necessarily creating an analog of the active compound. Correct?

A. Chemical analog. Yes.

Q. And so wouldn't a person of ordinary skill in the art be concerned that any analog of an agent I know is active might also be active?

MS. WOOTEN: Objection. Form. Asked and answered.

A. That would be potential. Yes, it would be a potential outcome.

Q. Right. And I apologize if you answered

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this already. I'm just saying, were there any teachings or rules that existed in 1998 that dictated how you might design a closed structural analog to, conversely, be inactive?

MS. WOOTEN: Objection. Form.

A. You would have to look at the specific compound in question in terms of a data set that I was -- prior art that I was describing earlier, with respect to regions of the molecule that had been changed and that had affected activity.

In this case, you would want the activity to have been affected adversely or reduced so that you could then leverage that information in terms of then reducing the activity or eliminating the activity in a prodrug, whether it be an ester or some other promoiety.

Q. Okay. And I take it from your answer about needing to understand what parts of the active molecule are involved in the activity, that the fact that fesoterodine is inactive suggests that that 2 position probably is involved in the activity of both tolterodine and 5-HMT. Correct?

MS. WOOTEN: Objection. Form.

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Mischaracterizes testimony.

A. No. It simply suggests that the structure around that region, but not necessarily the 2 position, may -- may be a determinant of the fit of that skeleton into the binding pocket of the muscarinic receptor.

Q. Okay. And you testified earlier that you're not aware of what parts of the 5-HMT or tolterodine molecules are responsible for the activity. Correct?

A. I believe that one component that's important in the engagement of this type of molecule is the derivatized nitrogen in this class of molecules, so there is something known about it.

Q. Mm-hmm.

A. I don't know that this literature that has picked apart each individual group around these -- around these molecules sequentially, and given the same substitution all around or similar substitution, to prove that point experimentally.

Q. But if the amine group of tolterodine and 5-HMT were important to the activity, wouldn't a person of ordinary skill in the art

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try to alter the amine, the amine group to ensure that the prodrug would be inactive, to the extent not converted?

MS. WOOTEN: Objection. Form.

A. But then, in my opinion, you'd run the situation of either an inefficient conversion or conversion to something else.

I would say that that would teach away, that would teach to preserve that region, not derivatize the region as being essential for engagement to the target receptor that's involved in the disease.

Q. Okay. In any event, in the -- the answer to my question of how do you make design choices to best ensure inactivity of the prodrug, is it correct that the answer is, if you know, you try to design around the parts of the compound responsible for the activity? Is that right?

MS. WOOTEN: Objection. Form.

A. That's one approach, but certainly not the only approach.

Q. Mm-hmm.

A. You -- by doing that, as I just

mentioned, you run the risk of having a limited regain of reactivity upon conversion, if conversion occurs at all.

Q. Mm-hmm.

A. You need -- if you have an essential moiety in your parent compound and you derivatize that to something else that may be theoretically convertible, you would have to return that moiety to exactly the same position, exactly at the same hydration, exactly the same ester chemistry in order for the prodrug approach to have worked.

If you take a less -- a region of the molecule that is less involved, less critical, and derivatize that, that, to me, would be more attractive in terms of a prodrug design.

Q. Okay. Let me just have one last question on this.

A. Sure.

Q. Looking at those three compounds on Page 7 of your report, tolterodine, 5-HMT, fesoterodine, and you agree with me that fesoterodine has been proven to be inactive in and of itself. Correct?

A. All that I've seen would support that,

yes.

Q. Do you have a view as to why fesoterodine is inactive in and of itself?

MS. WOOTEN: Objection. Form.

A. One possibility is that this region of the tertiary amine may be somehow shielded from its interaction with the receptor, but at the same time, the conservative nature of this ester modification allows this intact molecule, as fesoterodine, to be recognized by esterases for cleavage and for return back to 5-HMT as a prodrug --

Q. Okay.

A. -- oxidation to the alcohol.

Q. Okay. So if a person of ordinary skill in the art, in 1998, or any time, has an understanding of how the active agent or the desired agent binds or otherwise affects its activity, then that is something you would consider in the design of a prodrug. Correct?

A. That would be one element of the information, yes.

MR. TRAINOR: Okay. That's great. Thanks.

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Q. Now, I just want to ask you about your opinions with respect to the obviousness of the fumarate salt --

A. Salt, yes.

Q. -- of fesoterodine.

A. Yes.

Q. One of the papers that you cite in support is this Berge paper. Let me just give it to you, so you have it in front of you.

MR. TRAINOR: Can you just pass me that.

Q. Actually, before I get to that, let me just ask you: Now, assuming that the person of ordinary skill makes a prodrug and designs to make a conservative hydrocarbon ester prodrug, how is it, in your view, that the person of ordinary skill in the art would have obviously come to the specific isobutyryl substitution of fesoterodine?

MS. WOOTEN: Objection. Form. Asked and answered.

A. It would comply with those specifications as a conservative hydrocarbon, unreactive modification. That would be one of

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other possible, but that would certainly be, in my opinion, someone -- a skilled artisan, at that time, or any time, to be a prime candidate.

Q. So why is isobutyryl a prime candidate, aside from being conservative?

A. It has limited hydrocarbon. It doesn't even have a hydrocarbon chain, isobutyl, short molecule. It has three carbons, and that would satisfy the specifications that I would consider attractive in terms of modifying at that -- as a hydrocarbon ester.

Q. Right. But there's still a number of other esters that fit that description. Correct?

A. Yes.

Q. Okay. So my question is: Why isobutyryl specifically? Where is the teaching specifically to isobutyryl?

MS. WOOTEN: Objection. Form.

A. I believe that the ultimate teaching would come from experimental comparative data with respect to, say, turnover of esterases.

Q. Okay. So you'd agree that there's no specific teaching to use isobutyryl in connection with 5-HMT or molecules structurally similar to

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5-HMT. Rather, it would be a function of trial and error?

MS. WOOTEN: Objection. Form. Mischaracterizes testimony.

A. No. I would say that the teaching would restrict the potential derivatization to small conservative modifications of nonreactive hydrocarbon esters, a prime candidate of which, a prime specimen of which, a prime example of which is the isopropyl.

Q. Right. And all I'm saying is that that's -- but you would arrive there by virtue of testing a number of other conservative esters that fit that description, including isobutyryl. Correct?

MS. WOOTEN: Objection. Form.

A. No. I would arrive at that by taking into account those parameters and knowing that isobutyl fit those parameters, as did methyl. So they would be, in my opinion, for someone experienced in the art at that time, any time, prime candidates to derivatize such an agent.

Q. I understand that. But there are a number of candidates. Correct?

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A. Well --

MS. WOOTEN: Objection. Form.

A. -- there would be a number of candidates, chemically, that would fit that description, yes.

Q. Right. And aside from it being inside this group of candidates, you're not aware of any teaching in the prior art that said specifically isobutyryl is the ester to use with a compound structurally similar to 5-HMT?

A. No. I am not aware of that.

Q. Okay. And now I'll turn to this question of salt.

A. The salt.

Q. The -- thank you.

MR. TRAINOR: This is number 18. So I'm asking the court reporter to mark as Janero -- let me put it up here, Janero Exhibit 18, another publication from the Journal of Pharmaceutical Sciences, a review article entitled "Pharmaceutical Salts." And the lead author is Berge or Berge (pronunciation). This is -- bears Mylan Bates numbers -26914 to -933.

(Document Bates-stamped

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MYLB_FESO_00026914 through -6933 marked Exhibit 18.)

Q. Now, you recognize this publication, Dr. Janero?

A. I do.

Q. Exhibit 18?

A. I do.

Q. Okay. Now, would you agree that it is from this publication that you concluded that the fumarate salt of fesoterodine would have been obvious to a skilled artisan in 1999?

MS. WOOTEN: Objection. Form.

A. Could you repeat the question, please.

Q. So the relevance of this publication to your opinions is that, in your view, this publication, Exhibit 18, teaches the fumarate salt of fesoterodine?

MS. WOOTEN: Objection. Form.

A. I believe it teaches that fumarate salt is a very attractive salt, from both a commercial marketing standpoint, as well as biocompatibility standpoints, to be used in formation of a salt.

Q. Mm-hmm.

A. It does not, to my recollection,

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specify fesoterodine or any antimuscarinic agent in that class, per se.

Q. Okay. And on the first page of this article, and the paragraph in the second column that begins -- the second column that begins, "Salt forming agents are often chosen empirically."

A. Yes.

Q. Do you see that?

A. Yes, I do.

Q. About halfway down, we can see there's a sentence that begins, "Unfortunately, there's no reliable way of predicting the influence of particular salt species on the behavior of a parent compound."

A. I see that.

Q. Do you see that?

A. Yes, I do.

Q. Do you agree with that, that that was the case in 1998 or 1999?

A. Yes. I would agree with that.

Q. Okay. And then it continues, "Furthermore, even after many salts of the same basic agent have been prepared, no efficient

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screening techniques exist to facilitate the selection of the salt most likely to exhibit the desired pharmacokinetic solubility and formulation profiles."

Do you see that?

A. I do.

Q. Okay. Did you agree that that statement was accurate as of 1998 or 1999?

A. I don't know what the qualifier "efficient" means, but certainly there are techniques that existed then, and certainly exist now, to facilitate selection of a salt.

Q. Okay.

A. Experimental techniques, screening techniques.

Q. Okay. Now, what was it about fesoterodine fumarate that would have suggested to a skilled artisan that it would be biocompatible with a 5-HMT prodrug?

MS. WOOTEN: Objection. Form.

A. Well, the fumarate salt itself, the fumarate itself, as a known fumaric acid, is known to be biocompatible. It's actually a metabolite.

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So when a salt form of a compound is placed into water and dissolutes, the compound results and fumarate would result, fumarate being a biocompatible molecule that would argue for the compatibility of the salt form, biocompatibility of the salt form.

Q. Oh, okay. Then I should ask you, what do you mean by "biocompatible"?

A. That the dissolution of the salt form into its salt and other agents -- agents, that the salt itself does not engender adverse event -- adverse evex -- adverse events and that it can be readily eliminated or metabolized by the -- by the organism treated.

(Reporter clarification.)

A. By the organism, by the living entity treated.

Q. Okay. Now, would you agree that in 1999, or 1998, you could not predict whether one could actually make a fumarate salt of a specific fesoterodine molecule?

MS. WOOTEN: Objection. Form.

A. Based upon the knowledge at that time that a salt form of a closely-related compound

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could be made, I would conclude that knowledge would argue that a salt form could be made.

Q. So --

A. Or would be likely to be made, to be able to be made.

Q. Okay. Even assuming that's true, does it follow that the fumarate salt form specifically could be made of a 5-HMT analog?

A. From that evidence, alone, no.

Q. Okay. And would you agree that while one may make -- one may be capable of making some salt of a given compound, that it doesn't necessarily follow that that salt is sufficient to make that compound viable as a pharmaceutical?

MS. WOOTEN: Objection. Form.

A. If I understand the question correctly, are you asking whether a specific salt form can guarantee that that salt form of a compound ensures its viability as a drug?

Q. Correct.

A. That is correct. There would be no absolute assurance of that.

Q. Okay. In other words, for example, would you agree you could take any compound and

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possibly make some salt of it, but if the salt is amorphous or unstable, the fact that you can make that salt doesn't mean that that's an attractive drug candidate. Correct?

MS. WOOTEN: Objection. Form.

A. It would depend upon the product that resulted from the salt.

In other words, if you had a substance, for example, a salt form of a substance that were hygroscopic, in and of itself; in other words, that absorbed water molecules from the air --

Q. Mm-hmm.

A. -- that, a priori, would not necessarily rule it out as a drug. That perceived potential limitation could be eliminated by, for example, correct formulation or storage under heavy gas; argon, for example, or in a desiccated manner prior to administration.

Q. Okay. And the -- is there any significance to the fumarate salt as among all the other salts that are described in Exhibit 18, that made it particularly likely to form a salt of a 5-HMT analog?

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MS. WOOTEN: Objection. Form.

A. No. Other than its attractiveness that it does have a pKa that would -- that would support its salt formation, but not necessarily specifically with fesoterodine.

Q. Okay. And the -- when you say the "pKa," you mean the pKa of the 5-HMT analog or the pKa of the salt?

A. The salt.

Q. Okay. And would you agree that there are a good number of salts with a pKa range that, theoretically, would provide for a salt of a 5-HMT analog in this paper?

MS. WOOTEN: Objection. Form.

A. I haven't quantified the number, so I can't address whether the number is good or not, but I can say that there are alternatives mentioned in the paper that would have a pKa within the range of 3 to 5, say.

Q. Okay. And would you agree that this disclosure in this Berge publication suggests that the optimal salt selection is informed by the structure and properties of the compound itself?

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A. The ultimate salt resulting is -- reflects properties of the interaction between the salt and the parent compound.

Q. Okay.

A. So, therefore, there is an interaction between the two. Is one a determinant versus the other or a more definitive determinant versus the other? No, I can't say that.

Q. Okay. Now, this text goes on for quite a bit and discusses certain specific salts of specific compounds. And, as far as I can see, there's no treatment in the text beyond its identification in the table of the fumarate salt, specifically.

Does that seem correct to you? I mean, I don't want to make you read the whole thing. I've read it. I don't think there's any discussion of fumarate salt with any particular compound in this paper, but if you're aware of any, perhaps you could point that out to me.

A. I would have to reread it to point that out or do a computer word search of the PDF.

Q. Okay.

A. But I don't -- I haven't memorized

text.

Q. I'm not sure we could get a PDF of this one, 1977.

A. Venerable. Yes.

Q. The -- there is a -- in the Table 3, "Potentially Useful Salts," do you see that on Page 5 of the article?

A. I do.

Q. Okay. There is, in the second column, there's a description of the compound modified for a particular salt example.

Do you see that?

A. I do.

Q. Okay. So if you look, for example, maybe six up from the bottom, there's a reference to the compound being formed as a salt, as various amines. Do you see that?

A. I see that.

Q. Would analogs of 5-HMT fall into the category of "various amines"?

A. 5-HMT does have a tertiary amine functionality.

Q. So my question -- and the salt that corresponds to that in this table is tannic acid.

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Do you see that?

A. I do see that.

Q. Okay. Do you have -- strike that.

In your opinion, having read this publication, Exhibit 18, and trying to design a salt form of a 5-HMT analog or prodrug, wouldn't -- wouldn't this publication suggest to look to tannic acid, for example?

MS. WOOTEN: Objection. Form.

A. Well, in prior testimony, I did allude to the idea that the amine functionality would not be one that I would submit a person skilled in the art at the time would be interested in modifying, because the amine functionality of this class of compounds; specifically, the tertiary amine functionality is -- seems to be important for engagement of these ligands at muscarinic receptors.

Q. Right. But we're not --

A. So I am not --

Q. -- modifying the compound. Right? We're just selecting the salt. Correct?

A. Well, but you -- that's true, but you have got -- it says here "the top compound

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modified."

Q. Mm-hmm.

A. So I presume that this is -- I would not regard "modified compound." It's -- you're introducing another amine into the -- into the mixture.

So if that's the case, we have a dissolutable amine, then I would say that this, to me, to someone experienced in this field, would teach away, because you would be introducing, potentially, an amine interference by introducing another amine into the salt.

Q. That's how you read this table?

A. That's how I read it.

Q. Let's just -- if you start at the top, right --

A. Yes.

Q. -- the compound identified as doxycycline.

A. Oh, I'm sorry. The tannic acid is the com- -- is the salt-forming agent --

Q. Right.

A. -- so you'd have a tannate salt. You have a tannate salt of an amine. Okay. Then my

first statement would hold, because I wouldn't want to, in any way, do -- have any interaction with an essential amine group that would be critical, very important for interaction of that molecule with the receptor, with the target receptor.

Q. But they're not doing away with an amine group.

A. I understand that.

Q. Let's look at the first example of doxycycline.

A. Mm-hmm.

Q. Don't you read this to say this is just an example, in the art, of a salt that was successful for use with doxycycline?

A. I do.

Q. Right. So coming back to the various amines, what this table is saying is there are examples of amine compounds that have been successfully formed as tannate salts?

A. I see. I agree with that. Yes. Yes.

Q. Okay. So my question is: If a person of ordinary skill in the art was looking at this reference and trying to determine what salt form

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to make the 5-HMT prodrug --

A. Mm-hmm.

Q. -- would you agree that that person would, with the benefit of this article, look to tannate salts?

MS. WOOTEN: Objection. Form.

A. I wouldn't necessarily agree with that, because I would argue that the dissolution of the tannic acid salt forming the hydrated tannic acid could tend to alter the pH, the local pH of the tissue adversely, because you would have a -- you would have an acid in solution as a result of that salt dissolution.

Q. Okay. Well, wouldn't the same be true for fumarate acid?

A. But fumarate is a metabolic product, and it's easily -- it's not as strong an acid, I believe, as tannic acid.

Q. Okay. So you don't believe that, based on this disclosure, the person of skill might look to tannic acid before looking at fumarate acid?

MS. WOOTEN: Objection. Form. Asked and answered.

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A. It's a possibility, but I don't know that this would be, in my opinion, looked at preferably to an alternative acid that is a natural metabolite of cells, tissue, and organs.

Q. Okay. And if you look a few pages on, Page 10 of the article, there's a section on "Bioavailability." Do you see that?

A. I do.

Q. And then further on, under this larger heading on the next page, there's a section about "Absorption Alteration."

A. I do. I see that.

Q. Okay. Now, if the premise for developing a prodrug of 5-HMT is to enhance or ensure it's the absorption of 5-HMT to the system, would you agree that a skilled artisan might look to the disclosures about successful salts in conjunction with achieving sufficient absorption?

A. Yes. Provided those other examples had similar physicochemical properties to the parent compound in question here.

Q. Okay. And under that section, we can kind of just go through what -- there are a

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number of examples discussed in the first paragraph. It's theophylline, isopropyl -- isopropanol amine.

There's a potassium salt discussed, two paragraphs down; estolate salt on the next page, stearate salt, potassium, hydro amine.

So a number of salts and examples of compounds where the salt was used to ensure absorption. So do you see that as you run through?

A. Yes. In some cases to ensure, but I would say to alter the -- to affect the absorption one way or another.

Q. Okay. Wasn't that an objective of developing a 5-HMT prodrug, in your view?

MS. WOOTEN: Objection. Form.

A. I don't know if the objection [sic] were to increase, I think the absorption of the prodrug would be to ensure its absorption --

Q. Mm-hmm.

A. -- not to enhance absorption, necessarily.

Q. Okay. So you wouldn't look to any of these salt examples in selecting a salt for a

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5-HMT prodrug over looking to the fumarate salt, which is not discussed here?

MS. WOOTEN: Objection. Form.

A. The fact that these salt forms in these specific instances, with these specific molecules, alter the absorption would not necessarily translate in a beneficial way to an effect on the absorption of fesoterodine --

Q. Okay.

A. -- in my opinion.

Q. Was there any information in the prior art that suggested that the fumarate salt, specifically, would translate to effective absorption?

MS. WOOTEN: Objection. Form.

Q. That you're aware of?

A. Not that I'm aware of.

Q. Okay. I guess I've got one other question. In your rebuttal report, which is Exhibit 2 -- we could look at it, but let me see if you recall this opinion.

You have an opinion that the -- with respect to fesoterodine not exhibiting unexpected results over tolterodine, do you recall that, generally?

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A. I really would like to see the context before I address that.

Q. Yeah. So Exhibit 2 --

A. Yes.

Q. -- this is actually a pretty short report. So there is an opinion that says -- I'll tell you right now -- that it was not unexpected that fesoterodine could be effectively dosed at 8 milligrams, given what was known about tolterodine. And, I'm sorry, this is not my version.

(Discussion off the record.)

MS. MEDINA: Paragraph 37?

MR. TRAINOR: 37? No. Sorry, that's not it.

A. Let me go back then and try to find it.

Q. Well, let me just try to ask you the question, so we can get out of here.

You would agree that tolterodine and 5-HMT have dose-dependent antimuscarinic effects. Correct?

MS. WOOTEN: Objection. Form.

A. Yes.

Q. Okay. And one of the antimuscarinic