5. The Medicinal Chemistry of Phenethylamine Psychedelics

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I am sometimes asked, "how would you describe your research?" After many years my standard response has evolved to, "I design molecular probes of brain function." While the readers of this essay may know that I have worked with psychedelics for nearly thirty years, my laboratory also is studying the development of potential new treatments for depression, as well as carrying out significant efforts to create new therapies for end-stage Parkinson's disease. In each case, we are using relatively small chemical molecules to interact with various brain targets to gain information that may enhance our understanding of the underlying importance of those targets to normal brain function. In the latter two examples, it is clear what the end point should be. We should find better and faster ways to treat depression, and we should find new drugs to restore function to Parkinson patients who presently have no further hope. While the molecules we design often start out as experimental probes, if we have understood well the nature of our target, these structures may eventually become therapeutic entities.

What about probes of the brain receptors for hallucinogens? What is the end point there, and how is it relevant? There is one line of reasoning that says these peculiar substances can only be assayed in man, and that any other approach is inherently invalid. While off the record one may occasionally be forced to admit to the essential core truth of this premise, it does *not* necessarily follow that any other type of research is completely and utterly useless. Readers will find further confirmation of this fact in the chapter in this volume by Dr. Mark Geyer. I have occasionally been challenged that the structure-activity studies I carry out have no relevance to the real world; that studies in rats have no meaning. I do not believe this to be the case, and I shall explain why. We can very well use receptor assays, and models employing trained laboratory animals (mostly rats) to tell us whether a new molecule may have the essential molecular features that would ultimately allow it to be classified as a psychedelic, were it to be tested in man. What we cannot do with animals, or with any other nonhuman models, is to predict whether a particular molecule will open the gates of heaven or stoke up the fires of hell. We must maintain a clear distinction between these two positions. On the one hand, we can design and study molecules in model systems that allow us to predict that the structure will have psychedelic activity, but on the other we absolutely *cannot* know the full psychopharmacological complexity of their effects in the absence of clinical studies.

Discussions of psychedelics as chemical molecules, interacting with brain receptors, also tends to "demystify" psychedelics for those who view them as sacraments. It is not my mission to gore anyone's sacred cow. In the realm of psychedelics, hard core science will say that these substances simply activate certain parts of the brain that produce effects that might be predictable, if only we had a complete understanding of the brain and its neurobiology. At the other end of the spectrum are sincere people who believe that psychedelics are sacred substances, that can produce genuine nirvana, union with the cosmos, and the like--ecstatic states that they believe have very little to do with brain anatomy or chemistry. These are the folks who talk about a new paradigm of mind, quantum consciousness, and the like. I do not plan to enter this debate, but rather only to present a fundamentally reductionistic view of how these substances are now believed to interact with the physical brain. My objective in this essay is to provide some basic information about the medicinal chemistry of psychedelic agents.

At its heart, medicinal chemistry (what I do) attempts to draw clear and meaningful relationships between the molecular features of a chemical structure and the biological events subsequent to its administration to a living organism. Inherent in this approach is the assumption that a relationship exists between chemical structure and biological effect. In the context of psychedelic agents a relationship certainly exists. It is in clearly and explicitly defining this relationship that problems may arise.

Perhaps it would be helpful here to employ a crude analogy. One can clearly see that a relationship exists between gasoline and automobile travel. What one cannot predict is whether a particular tank of gasoline is destined to propel a car toward Canada, Mexico, the Northeast, etc. The outcome is dependent on the whims of the owner of the vehicle. Similarly, one can predict that

psychoactive substances such as LSD will move the psyche from what has been called consensus reality, to some altered state of consciousness. What cannot be predicted is the nature of that change or the "direction" the altered state will take. It is an erroneous assumption to believe that medicinal chemistry can design in elements of molecular structure that will lead the psyche in a particular direction. The state of the art in medicinal chemistry is not so advanced! This would be akin to assuming that a particular blend of gasoline could somehow determine the direction that the car will be driven.

What I am leading up to is the fact that there are key recognition elements within the structures of all psychedelic molecules that lead to their activity; phenethylamines have them, tryptamines have them, and LSD and other related ergolines have them. Essential chemical features of these molecular recognition elements activate a key brain target. This activation then "enables" the brain to shift its processing from ordinary waking consciousness and enter into whatever state is produced by all psychedelic drugs. Most scientists now believe the target, or "switch" for psychedelic molecules is a site known as the serotonin 5-HT_{2A} receptor (Nichols 1997). Just as turning on the power switch of a television enables the TV to display images, *but is not responsible for what is seen*, psychedelic molecules, by activating this brain receptor, "turn on" some other set of amplifiers and processors that allow nonordinary feelings and states of consciousness to occur.

While this may sound reductionistic to many readers, it may also be useful to envisage an analogy between this receptor and an automobile's ignition system, that must be switched on with a key before the car may go in any direction. It is up to the motivations of the driver, the power of the engine, the condition of the roads, etc. (i.e. the "set" and the "setting") to determine where and when the journey will actually begin and end.

It is believed that during ordinary circumstances the brain 5-HT_{2A} receptor is not highly activated. That is, the daily ebb and flow of serotonin molecules does not produce an LSD-like state in us because not many serotonin molecules are released by neurons onto these receptors. When a psychedelic molecule enters the brain however, it binds very tightly to these receptors, producing an extensive and prolonged activation state. In fact, the brain is so sensitive to activation of these receptors that when they are overstimulated, as for example when one ingests a psychedelic such as LSD, they quickly decline in density so as to reduce the numbers of targets for any additional neurotransmitter that might be released (or any additional LSD molecules that may happen to arrive). This is the reason that LSD loses its effects when taken too often. The number of receptors for it just rapidly decreases!

What my research has done is to focus on key sites in the brain, and attempt to identify the recognition elements that are necessary to bind to and activate them. This was a goal when I started research in this field in 1969, and it remains unattained in 1997. But, I think we are getting closer to understanding. To begin with, until a few years ago no one really had a good idea of what a receptor might look like. Today, we know that the vast majority of neurotransmitter receptors are bundles of protein helices embedded in and spanning the neuronal cell membrane. The receptor, therefore, can act as a "conduit" to allow information to pass *through* the neuronal membrane.

One of the stable forms that proteins can adopt is called an alpha helix. This is somewhat the shape of a Slinky toy, or the shape of the threads around a bolt. It is now widely believed that most of the serotonin receptors exist as a bundle of seven such alpha helices inserted into the neuron membrane. These seven helices are connected both on the outside and on the inside of the neuron membrane with continuing loops of proteins, so that the whole receptor, if it could be unwound and stretched out, would simply be one very long chain of amino acids, the basic building blocks of all proteins. A schematic view of this type of receptor is presented in figure 1.

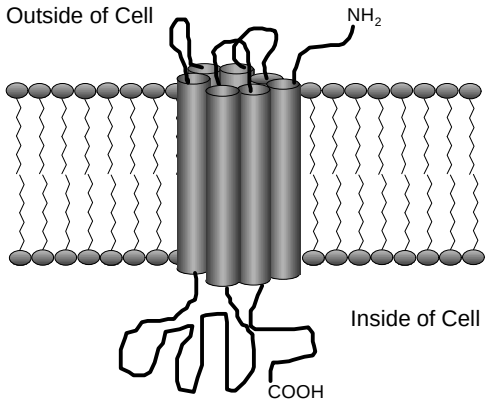

Figure 1. *A schematic representation of a membrane-bound G-protein coupled receptor, of which the serotonin 5-HT_{2A} receptor is an example. The receptor consists of 7 alpha helices, represented here by tubes, connected on the inside and outside with continuing loops of protein.*

The process of neurotransmission involves the release of neurotransmitter molecules from the terminal of a neuron. These diffuse through the solution in the space between the two neurons (called the synapse), and are attracted to the receptor, probably due to electrostatic fields generated by the charges on the amino acids in the receptor and charges on the neurotransmitter. The neurotransmitter molecule fits into the ligand recognition domain of the receptor, where a series of events is then initiated. It is believed that when the neurotransmitter "docks" into the receptor, the seven alpha helices rearrange the way they are oriented with respect to each other. That is, they twist, turn, and bend, undergoing what is called a "conformational change," in order to achieve a new packing arrangement that is compatible with the presence of the neurotransmitter in their midst. This is a reasonable hypothesis, and could be explained in a very technical way if time and space permitted.

What is not adequately represented in figure 1 is the relatively large piece of receptor protein that is used to connect the seven alpha helices on the *inside* of the receptor. These protein chains, particularly a large loop that connects helices 5 and 6, as well as the end of the protein chain that follows helix 7 on the inside of the receptor, adopt a shape that allows them to bind to another type of protein, called a GTP-binding protein (G protein for short). When the neurotransmitter molecule binds to its recognition domain in part of the receptor on the *outside* of the membrane, it causes changes in the shape of the receptor, and the movement of the receptor helices then apparently causes large shape changes in the loops and chains on the part of the receptor that is *inside* of the neuron. When this occurs, the G proteins dissociate from the receptor because the fit between them is no longer complementary, they bind to molecules of GTP in the cytoplasm, and then initiate a series of biochemical changes in the neuron that constitutes the actual "message" of the neurotransmitter; calcium levels in the neuron change, certain proteins are activated that attach phosphate groups to other proteins, etc. The whole process is a complex sequence of events known as a signaling cascade. All these biochemical changes produced in the interior alter the state of the neuron, making it more or less easy to send a signal itself. Ultimately, at least for psychedelics, these changes in brain biochemistry somehow lead to an alteration in consciousness. How this occurs will remain a mystery for many years to come, if we can ever discover it!

The assumption in my laboratory has been that all the various types of psychedelic agents, at a minimum, interact with brain serotonin 5-HT_{2A} receptors in this way, and what we have tried to do is to understand how the *chemical features* of these molecules lead to their binding to this receptor. We shall now move on to a more chemical discussion of what properties are possessed by the molecules themselves, that may allow them to activate receptors.

Following more than two decades of work, in several laboratories, there are now some ideas about what is required for activity, at least in some classes of molecules. For example, as a crude representation, figure 2 shows some of the structural features that may be important within the phenethylamine type hallucinogens for receptor recognition and activation (Monte et al. 1996). First of all, the cyclic hexagonal ring in the center of the figure is called a phenyl ring. The letter N in the NH_3 to the right of that represents the nitrogen atom. The lines connecting the two represent two carbon atoms attached together, called an ethyl group. Hence, these molecules, in general, are called phenethylamines or sometimes phenylethylamines: a phenyl ring separated by an ethyl grouping from an amine.

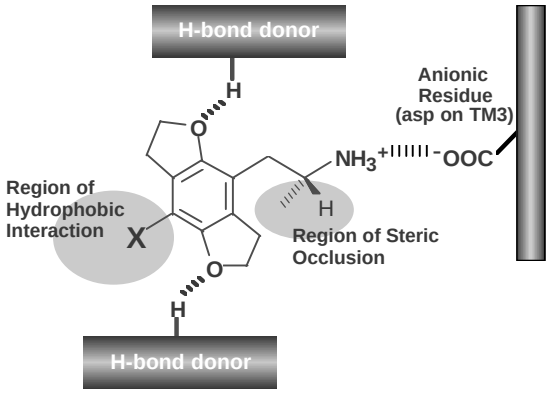

Figure 2*. A schematic representation of a phenethylamine hallucinogen similar to DOB interacting with the ligand binding domain of the serotonin 5-HT_{2A} receptor. Important sites for chemical interaction include the amino group, the two oxygen atoms, the hydrophobic "X" group, and the central phenyl ring itself. Taken from Monte et al. 1996*

The nitrogen atom has the property of being basic, in the context of acid-base chemical reactions. Ammonia is a common household base. Bases are neutralized by chemical reaction with acids.

Common household acids are vinegar and soft drinks. Since acids neutralize bases, in the body the basic amino group of the phenethylamines is also "neutralized" by reacting with weak acids. This means that the basic amino group, which is normally represented by an NH_2, has added an extra hydrogen atom, or proton (i.e. the acid), and now is an NH_3^+, the plus sign denoting that the hydrogen atom brought a positive charge with it to the molecule.

This positive charge is believed to lead to an attraction for an amino acid in the serotonin receptor called an aspartic acid residue. This key aspartic acid residue is located on one of the membrane-spanning alpha helices designated as transmembrane helix 3. This amino acid is a weak acid, similar in acidity to vinegar, but it too has lost it's hydrogen atom by neutralization in the body. The characteristic feature of weak organic acids is the presence of a COOH grouping of atoms. Since molecules prefer to be neutral, and not carry a charge on them, the departure of it's hydrogen atom with a positive charge left behind a corresponding negative charge. Thus, the aspartic acid is shown not as a -COOH, but rather as a $-COO^-$, indicating that the hydrogen atom is gone, and that a negative charge was left behind. It is the attraction between the amino group, with the positive charge, and the aspartic acid residue, with the negative charge, that is believed to be one of the most powerful forces in causing a neurotransmitter to bind to its receptor. This attraction is denoted by the series of short vertical lines between the NH_3^+ and the $-OOC^-$ in the figure. As a crude analogy, one can appreciate the force that occurs between the two poles of a magnet.

On the left side of the phenethylamine molecule, a large "X" is pictured above an elliptical area labeled as a "Region of Hydrophobic Interaction." Hydro is a prefix denoting water, and phobic comes from the same root as phobia, or fear of something. Thus, hydrophobic is a term meaning that something is "water-hating." Not surprisingly, therefore, hydrophobic molecules typically have an oily or greasy texture. This is an important place in the receptor that seems to prefer to bind to atoms or groups that have an oily, non-water soluble nature. Extremely potent phenethylamine hallucinogens have atoms attached at this position such as bromine, iodine, or sulfur. Indeed, if the rest of the structure is completely identical, the changing of what is attached only at this location of the phenyl ring can give compounds that begin to approach the potency of LSD on a dosage basis!

Another important feature of these compounds is the two oxygen atoms. These are shown near the top and bottom of the structure, as the letter O, with the dashed lines toward the Hs. These oxygen atoms are essential to binding and activation of the receptor. Alexander Shulgin carried out a number of studies where he replaced these oxygen atoms with other atoms such as sulfur, and in each case the activity was greatly reduced or lost completely. In the simplest compounds, these oxygen atoms are not part of a ring system, as shown here, but rather are freely swinging. They are hooked to the phenyl ring, and then another carbon atom called a methyl group is attached. This grouping looks like this: $-OCH_3$. Because of the numbering system for the locations around the phenyl ring, these methoxy groups are attached at positions numbered 2 and 5. The "X" group is attached at the position numbered 4. Thus, these compounds are often called 2,5-dimethoxy-4-substituted phenethylamines.

In figure 2, however, both oxygen atoms are shown incorporated into pentagonal rings (known as dihydrofurans), that have common edges with the central phenyl ring (i.e. they are "fused" to the phenyl ring). This has the effect of "locking" the oxygen atoms so they cannot undergo rotational movement. Experiments in my laboratory have shown that this gives the most active orientation of the oxygen atoms in producing hallucinogenic effects. We believe that the oxygen atoms interact with the receptor through hydrogen bonds, represented as the dashed lines connecting the oxygen atom to a hydrogen atom (denoted by the letter H) arising from a hydrogen bond donating site in the receptor. Because oxygen atoms have extra electrons in their outer shell, and certain types of hydrogen atoms attached to oxygen or nitrogen atoms have a slight "deficiency" of electrons, there is a fairly strong attraction between them that is called a hydrogen bond.

Finally, there is also a small area shown in figure 2 labeled "Region of Steric Occlusion." In the phenethylamines, there is only a hydrogen atom (H) at the end of the dashed line in this region. These are representatives of compounds that Shulgin has named 2C compounds (e.g. 2C-B, 2C-T, etc.). The 2C represents the fact that there are only two carbons between the phenyl ring and the amine. However, if a third carbon atom is attached, that is, a $-CH_3$ group is attached at the end of the dashed line that is lying over the region of steric occlusion, these compounds are typically called amphetamines. This carbon in the ethyl group is called the alpha position because it is the first carbon atom attached to the amine nitrogen. (The second carbon atom from the amine, next to the phenyl ring, is called the beta position.)

Nothing larger than a single carbon atom with its attached hydrogens, called a methyl group, can be attached here. In organic chemistry, the word steric is used to refer to the size or bulk of a portion of the molecule. We have therefore designated this portion of the receptor as an area that cannot tolerate steric bulk. In other words, it is a region of steric occlusion.

So, the molecule binds through a combination of forces, to the amino group, the two oxygen atoms, and the hydrophobic "X" group, and in addition, the receptor has many hydrophobic amino acid groups within the ligand binding domain that simply embrace the phenyl ring and the ethyl group which themselves are hydrophobic. The molecule just becomes as snug as a bug in a rug! In the process of being attracted to, and wrapping around the psychedelic molecule, the receptor changes and moves itself, and sets off the sequence of biochemical events described earlier.

The same thing cannot be said for molecules related to mescaline, however. We recently (Monte et al. 1997) showed that carrying out the same types of chemical modifications that led to high activity in the DOB type compounds, gave molecules that appear inactive in our animal models when applied to mescaline. Illustrated in figure 3 below are the relevant examples. Locking the methoxy groups of DOB into rings (as also shown earlier in the "receptor" model) gives an increase in potency. On the other hand, locking the distal methoxy groups of mescaline into rings in the same way led to inactive compounds!

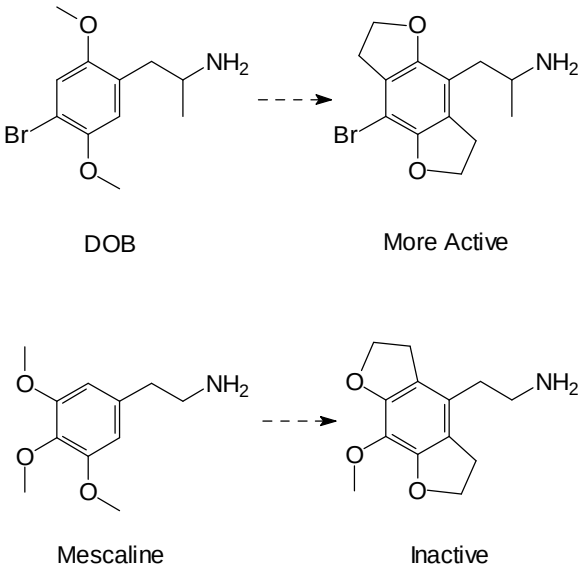

Figure 3. *Rigidification of the methoxy groups in DOB leads to compounds with increased activity while a similar transformation in mescaline leads to inactive compounds.*

While it has generally been assumed that mescaline activates the same receptors as all of the other types of psychedelics, there are clearly some important differences when one actually looks at the molecular architecture of mescaline compared with DOB-like molecules. This is an issue that continues to perplex us, and will be the focus of additional studies as we attempt to identify the active shape of mescaline-like molecules when they bind to the receptor.

These might appear, at first glance, to be easy questions to solve, but in fact the design of molecular probes to study this question is quite problematic. When a change is made in the structure of a molecule, many variables are changed simultaneously and one often cannot know which one was responsible for the observed effect. For example, in figure 3, incorporation of the methoxy groups into the pentagonal furan rings does not simply "lock" the orientation of the oxygen atom. It also introduces new pieces of molecular 'baggage.' That is, a methoxy group is $-OCH_3$, while the corresponding part of the furan ring structure is $-OCH_2CH_2-$. Furthermore, in mescaline, the positions in the phenyl ring (the hexagonal central ring) that are adjacent to the ethylamine chain are occupied only by hydrogen atoms, while in the rigid analogue on the right, they serve as the anchor points for the cyclic ring structures. In the usual circumstance, one cannot know what effect these additional modifications have on overall activity. Our analogy to the DOB molecule however, suggests that incorporation of the oxygen atoms into these ring structures should not affect activity, *if the oxygen atom in the methoxy group possesses the same orientation as in the ring structure upon binding to the receptor*. Our extension of this approach to mescaline, leading to inactive compounds, suggests therefore that the oxygen atoms of mescaline do not adopt the orientation of the rigid analog shown on the right, and that perhaps the methoxy groups of mescaline may rotate into some different, and as yet undefined orientation. What is this orientation? That is a question we will attempt to address in future studies.

What's next?

The missing piece(s) of the puzzle are now the links between these biochemical events, and the parts of the brain that must be involved in changing consciousness. It will probably be a long time before this connection can be made. In the meantime, however, there are a number of scientifically valid approaches that will give useful information. Recently, for example, we have "stumbled" upon a simple phenethylamine molecule that has affinity for the 5-HT_{2A} receptor nearly 100-fold higher than any other compound discovered to date, including LSD itself! There is no particular reason to search for more potent compounds, but often such molecules prove to be quite useful as research tools. For example, when a molecule has very high affinity for a receptor, it is often possible to introduce radioactive atoms into the molecule that allow one to visualize sites where the molecule binds in the brain. This has already been done with molecules such as DOB, DOI, and LSD. However, a molecule with even higher affinity can be used at lower concentrations and dosages to detect and visualize receptors. This new molecule, with exceedingly high affinity for the 5-HT_2 class of receptors will no doubt be useful to label and visualize these receptors in the brain. Indeed, we have already begun discussions with a firm that supplies radioactive molecules to prepare radioactive forms of this molecule for evaluation.

Literature reports now also suggest that a tentative 3-dimensional structure for the family of G-protein coupled receptors may not be far off. This is the receptor family to which nearly all of the serotonin receptors belong. Perhaps within the next year or two a good structure may become available. With that event, we would begin computer modeling studies to dock our molecules into this receptor structure in attempts to gain an appreciation of which structural features of the molecule are necessary for binding and activation of the receptor. If this can be accomplished, we should also be able to design new molecules to test hypotheses about which molecular features are necessary for receptor binding. That would be a very exciting development because it would be the first time that it might become possible to design a molecule, *de novo*, to fit a particular receptor. Clearly, if we can retain our research funding, the most exciting developments in the medicinal chemistry of psychedelic agents are yet to come.

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