**Response to Editorial Comments:**

• **Protocol Language:** The JoVE protocol should be almost entirely composed of numbered short steps (2-3 related actions each) written in the imperative tense (as if you are telling someone how to do the technique, i.e. "Do this", "Measure that" etc.). Any text that cannot be written in the imperative tense may be added as a brief “Note” at the end of the step (please limit notes). Please edit your protocol section accordingly. Descriptive sections of the protocol (e.g. Lines 321-331 can be moved to introduction, Representative Results or Discussion. The JoVE protocol should be a set of instructions rather a report of a study. Any reporting should be moved into the representative results.

*1) Editor re-wrote some of your protocol steps (in section 1) in the imperative tense.*

We thank the editor for rewording some of our protocol steps. We have also carefully examined the rest of the protocol and converted the protocol steps to imperative tense.

*2) There are numerous notes, please limit notes in number and their length.  
3) Notes should be written out as steps wherever appropriate. As an example see the tracked changes to the Note following 1.2 (now step 1.3)*

The notes have been either condensed, or written out as steps, as suggested.

*4) Several steps need to be rewritten in the imperative tense: 2.5*

The steps in section 2.5 have been modified accordingly, as suggested.

*•****Protocol Detail:****Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video.****Please add more details to the following protocol steps.****There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.*

*1) 1.2.1: What is the sample used? What is its source?*

The source has been added and the steps modified to include references. We have also replaced ‘sample’ with ‘deuterium reaction’ for a more accurate description.

*2) 1.4: When is the quench solution added to the sample?*Details of addition of quench have been included.

*3) 2.2 Note: This should be converted into steps.*

The note has been converted to protocol steps.

*4) 2.5,3.1: Please mention what button is clicked on in the software to do this, or which menu items need to be selected.*

These are vendor specific information and hence the interface and ‘methods’ that need to be set differ between different Mass Spectrometry vendors and hence it is difficult to indicate a specific button or menu item. However, continuous calibration is an option that is available during adding a ‘Mass Spectrometry method’ in most of the vendor-provided software. These steps have also been modified to appeal to a general mass spectrometry reader.

*5) 3.2,3.4 : Please cite references for each step.*

References have been added for these steps.

*6) 4.1: Is quenching done as in Section 1?’*

Yes, the quenching is done as in section 1 and the section has been referenced in this step for ease of readability.

*7) 4.3: Please mention what button is clicked on in the software to do this, or which menu items need to be selected.*

These are again vendor specific details that are difficult to add since they have vastly difference interfaces. However, we have modified the steps to include ‘MS/MS mode’ option details that are common across different Mass spectrometer providers.

*8) 4.4: How is this done? Please add a reference.*

We have added references to a few such analysis soft wares and to studies where such analyses have been detailed.

*9) 4.5: What are the denaturants you use? Please provide examples. Please cite the referenced steps by the step number.*

We have provided examples and referenced the steps by step numbers.

*10) 5.1: What is the quantity of ligands, protein and buffers? At what time points?*

We have added the details of ligands, protein and buffers ratios used, to this step to aid in continuity and improved readability.

*11) 5.2: Incubate at what temperature? For what duration? At what time points?*

We have added details of incubation temperature, deuteration time points etc to this step.

*12) 5.3: How is the data analyzed? Perhaps cite a reference?*The data analysis has been discussed in earlier steps, and references to those steps have been added.

*13) 5.4: How?*

Details of classification of orthosteric reporters have been added.

*14) 5.5: Needs a reference.*

This has been moved to 5.4 and a reference has been added.

*15) 6.2: Mention the steps by number.*

Step numbers have been added.

*16) 6.3: Needs a reference for the data analysis.What do you analyze for?*

These have been described in earlier steps and hence we have mentioned the relevant step numbers and added more details of what we analyze for.

*17) 7.2,7.5: Needs a reference.*

These have been moved to 5.4 and 7.3, respectively, and references have been added.