Comments on the deposited data files for the figures presented in the manuscript.

Main Figures:

Figure 1	E	The axis title, units and sample name are provided in the file header; the column separator is a comma ",". File name: **Figure1E_IsPadC_dark_vs_light_Absorption_spectrum.csv**
	F	The axis title, units and sample name are provided in the file header; the column separator is a comma ",". This raw data was cordially provided by Heikki Takala as outlined in the Acknowledgements and was scaled to 1 at 398nm to be in accordance to the scaling of the other spectra shown in this work. File name: **Figure1F_AfAgp1_dark_vs_light_Absorption_spectrum.csv**
Figure 3	A	The file FSA_IsPadC_multistate_threshold72over35_mod.csv contains the IsPadC protein sequence in column 1and the raw data as output by the FSA script when launching the extra function in the script to create a "B-factor" table in column 2. **Value 0 corresponds to unlabeled, value 33 to functional, value 67 to adaptable and value 100 to structural**. The occurrence of these values is counted and plotted as pie chart. The column separator is ";".
	C+D S5A-D	The raw data for this figure is contained in the file **FSA_IsPadC_multistate_threshold72over35_mod.csv.** The column separator is ";". The graph is generated using the script **pie_chart_code.py**. Specify the file to be handled within the script. Launch the script in Linux typing "python3 pie_chart_code.py". It expects a two- column csv file with a protein sequence in column 1 and integer numbers in column 2. For each unique integer number (here 0, 33, 67, 100), a pie chart is generated which counts the occurrence of amino acids with this integer number.
Figure 4	A	Results of the FSA anaylsis plotted onto pdb 5llw. The values for this coloring approach are contained in the file **FSA_IsPadC_multistate_threshold72over35.csv**. It contains a single column containing the raw data as output by the FSA script when launching the extra function to create a "B-factor" table. The index/line number of each "B-factor" corresponds to an amino acid in 5llw with the same index. The file **IsPadC_FPS_P_value01_threshold72over35.pse** can be opened with Pymol and contains both views featured in Figure 4A. Activate the object "5llw" to show the dimeric front view and "ChainA" for the monomeric side view.
	B+D	The files **FSA_IsPadC_multistate_threshold72over35.csv** and **FSA_AfAgp1_multistate_threshold72over35.csv** contain raw data as output by the FSA script when launching the extra function to create a "B-factor" table. This was conducted for the proteins IsPadC and AfAgp1. **Value 0 corresponds to unlabeled, value 33 to functional, value 67 to adaptable and value 100 to structural**. Residues which are known to be important for phytochromes were checked in the raw files and checked for their assigned classification.
	C	A close up of selected second shell residues flagged as functional by the FSA analysis can be viewed in Pymol with the file **W174G_N175A_structure_context.pse**.
Figure 5	A+B C+D	Spectral characteristics for analyzed protein variants. The axis title, units and sample name are provided in the file header; the column separator is comma ",". File names: **Figure_5A_dark_spectra_Absorption.csv**; **Figure_5B_light_spectra_Absorption.csv**;

		Figure_5C_thermal_reversion.csv; Note the diverging time intervals for the different variants **Figure_5D_IsPadC_PSM_W174G_Absorption.csv**;
Figure 6	A	Mapping of changes in deuterium incorporation after 30 s of *Is*PadC PSM light versus dark. The differences in deuterium incorporation are plotted on pdb 5llw and can be visualized by Pymol and the corresponding session file **Figure_6A_WT_dark_vs_light.pse**. Within the file, the HDX data for all time points can be accessed (t1=10 s, t2=30 s, t3=3 min, t4=15 min, t5=60 min). The filtered raw data can be found in **IsPadC_PSM_WT_dark.yaml** and **IsPadC_PSM_WT_light.yaml**. The files can be opened using HXViewer, freely available from https://hx2.mr.mpg.de/. To visualize the HDX-MS data, tables containing the delta deuterium values are generated by providing a .yaml dataset containing single peptides spanning each region and setting the dark dataset as reference. The corresponding tables can be found under HDX_tables\WT_dark_vs_light. Using a script, these values are inserted into the B-factor column of a .pdb file and visualized with a custom color gradient.
	B	Mapping of changes in deuterium incorporation after 10 s of *Is*PadC PSM W174G dark versus WT dark. The differences in deuterium incorporation are plotted on pdb 5llw and can be visualized by Pymol and the corresponding session file **Figure_6B_WT_dark_vs_W174G_dark.pse**. Within the file, the HDX data for all time points can be accessed (t1=10 s, t2=30 s, t3=3 min, t4=15 min, t5=60 min). The filtered raw data can be found in **IsPadC_PSM_WT_dark.yaml** and **IsPadC_PSM_W174G_dark.yaml**. The files can be opened using HXViewer, freely available from https://hx2.mr.mpg.de/. To visualize the HDX-MS data, tables containing the delta deuterium values are generated by providing a .yaml dataset containing single peptides spanning each region and setting the dark dataset as reference. The corresponding tables can be found under HDX_tables\ WT_dark_vs_W174G_dark. Using a script, these values are inserted into the B-factor column of a .pdb file and visualized with a custom color gradient.
	C	Mapping of changes in deuterium incorporation after 3 min of *Is*PadC PSM N175A light versus WT light. The differences in deuterium incorporation are plotted on pdb 6et7 with the missing loop densitys filled up using the SWISS-MODEL webserver. The results can be visualized in Pymol using the corresponding session file **Figure_6C_WT_light_vs_N175A_light.pse** . Within the file, the HDX data for all time points can be accessed (t1=10 s, t2=30 s, t3=3 min, t4=15 min, t5=60 min). The filtered raw data can be found in **IsPadC_PSM_N175A_light.yaml** and **IsPadC_PSM_WT_light.yaml**. The files can be opened using HXViewer, freely available from https://hx2.mr.mpg.de/. To visualize the HDX-MS data, tables containing the delta deuterium values are generated by providing a .yaml dataset containing single peptides spanning each region and setting the dark dataset as reference. The corresponding tables can be found under HDX_tables\ WT_light_vs_N175A_light. Using a script, these values are inserted into the B-factor column of a .pdb file and visualized with a custom color gradient.

Supporting data

Figure S1		Weblogo depiction of a multiple sequence alignment of the PadC protein family. Find the aligned sequences in **IsPadC_natural_sequence_alignment.fasta**
Figure S2		Weblogo depiction of multiple sequence alignment of ProteinMPNN generated sequences based on IsPadC input coordinates. Find the aligned sequences in **IsPadC_multistate_ProteinMPNN_sequences.fa.** Note: ProteinMPNN is run on a dimeric input structure hence the output also contains multiple chains with the same sequence for each design. To better visualize the sequences, these additional sequences were removed in the file.
Figure S3		Weblogo depiction of multiple sequence alignment of the protein family containing AfAgp1. Find the aligned sequences in **AfAgp1_natural_sequence_alignment.fasta**
Figure S4		Weblogo depiction of multiple sequence alignment of ProteinMPNN generated sequences based on AfAgp1 input coordinates. Find the aligned sequences in **AfAgp1_multistate_ProteinMPNN_sequences.fa.** Note: ProteinMPNN is run on a dimeric input structure hence the output also contains multiple chains with the same sequence for each design. To better visualize the sequences, these additional sequences were removed in the file.
Figure S5		The raw data for this figure is contained in the file **FSA_IsPadC_multistate_threshold72over35_mod.csv.** The column separator is ";". The graph is generated using the script **pie_chart_code.py**. Specify the file to be handled within the script. Launch the script in Linux typing "python3 pie_chart_code.py". It expects a two- column csv file with a protein sequence in column 1 and integer numbers in column 2. For each unique integer number (here 0, 33, 67, 100), a pie chart is generated which counts the occurrence of amino acids with this integer number.
Figure S6	A	Comparison of FSA results of the original approach using ProteinMPNN and a trial using ligand-containing input structures and LigandMPNN. In the file **FSA_IsPadC_multistate_threshold72over35.csv**, the raw output of the FSA method is shown for the protein IsPadC as published in the main text. In the file **IsPadC_multistate_ligand_MPNN_threshold72over35.csv** the FSA method was conducted with LigandMPNN. The direct comparison between the two files is shown as Sankey diagram, generated with the script Sankey_diagram_script_FSA_final.ipynb, open with Jupyter notebook and check that all dependencies are installed. Changes from functional to structural for the same residues between the datasets were noted down and entered into the script by hand according to the documentation in the script. **0 unlabelled, 33 functional, 67 adaptability, 100 structural**
	B	Residues in the vicinity of the cofactor which change their classification due to LigandMPNN being aware of the cofactor provided during the experiment. Look up residues which changed from functional (33) to structural (100) in the .csv files mentioned for Figure S6A.
	C	Biliverdin binding cavity in top view (from the GGDEF domain down) and up view colored according to the results of the FSA method using either ProteinMPNN or LigandMPNN. Raw data can be found in the files described in Figure S6A. Open the file **comparison_FSA_ProteinMPNN_Ligand_MPNN_BV_cavity_top_view.pse** in Pymol. The object Protein_MPNN corresponds to the upper Panel on the

		left whereas the object Ligand_MPNN corresponds to the upper panel on the right. Open the file **comparison_FSA_ProteinMPNN_Ligand_MPNN_BV_cavity_up_view.pse** in Pymol. The object Protein_MPNN corresponds to lower Panel on the left whereas the object Ligand_MPNN corresponds to the lower panel on the right.
Figure S7		Spectral characterization of individual *Is*PadC PSM variants with dark, 30s 660 nm illuminated and light-dark difference spectra. The axis title, units and sample names are provided in the file header; the column separator is comma ",". File names: **FigS7_IsPadC_PSM_E173A_dark_vs_light.csv** **FigS7_IsPadC_PSM_F259M_dark_vs_light.csv** **FigS7_IsPadC_PSM_M190Y_dark_vs_light.csv** **FigS7_IsPadC_PSM_M190Y_F259M_dark_vs_light.csv** **FigS7_IsPadC_PSM_N175A_dark_vs_light.csv** **FigS7_IsPadC_PSM_P172A_dark_vs_light.csv** **FigS7_IsPadC_PSM_R177Q_dark_vs_light.csv** **FigS7_IsPadC_PSM_W174G_dark_vs_light.csv** **FigS7_IsPadC_PSM_WT_dark_vs_light.csv**
Figure S8		Fluorescence characteristics of IsPadC PSM variants WT, W174G, N175A. The axis title, units and sample names are provided in the file header; the column separator is comma ",". File names: **FigS8_fluorescence_data.csv**
Figure S9	A-D	Hydrogen-deuterium exchange MS results plotted against time points for three example peptides. Find the filtered raw data in the following .yaml files which can be opened using HXViewer within the Hexicon2 package, freely available from https://hx2.mr.mpg.de/. File names: **IsPadC_PSM_WT_dark.yaml** **IsPadC_PSM_WT_light.yaml** **IsPadC_PSM_W174G_dark.yaml** **IsPadC_PSM_W174G_light.yaml** **IsPadC_PSM_N175A_dark.yaml** **IsPadC_PSM_N175A_light.yaml**
Figure S10	A, left	See Figure 6B, the Pymol session file showing the difference in deuterium incorporationplotted on the structure is renamed to **Figure_S10A_left_WT_dark_vs_W174G_dark.pse** for consistency.
	A, right	Mapping of changes in deuterium incorporation after 10 s of *Is*PadC PSM W174G light versus WT light. The differences in deuterium incorporation are plotted on pdb 6et7 with the missing loop densitys filled up using the SWISS-MODEL webserver. The results can be visualized in Pymol using the corresponding session file **Figure_S10A_right_WT_light_vs_W174G_light.pse**. Within the file, the HDX data for all time points can be accessed (t1=10 s, t2=30 s, t3=3 min, t4=15 min, t5=60 min). The filtered raw data can be found in **IsPadC_PSM_WT_light.yaml** and **IsPadC_PSM_W174G_light.yaml**. The files can be opened using HXViewer, freely available from https://hx2.mr.mpg.de/. To visualize the HDX-MS data, tables containing the delta deuterium values are generated by providing a .yaml dataset containing single peptides spanning each region and setting the dark dataset as reference. The corresponding tables can be found under HDX_tables\WT_light_vs_W174G_light. Using a script, these values are

		inserted into the B-factor column of a .pdb file and visualized with a custom color gradient.
	B, left	Mapping of changes in deuterium incorporation after 3 min of *Is*PadC PSM N175A dark versus WT dark. The differences in deuterium incorporation are plotted on pdb 5llw and can be visualized by Pymol and the corresponding session file **Figure_S10B_left_WT_dark_vs_N175A_dark.pse**. Within the file, the HDX data for all time points can be accessed (t1=10 s, t2=30 s, t3=3 min, t4=15 min, t5=60 min). The filtered raw data can be found in **IsPadC_PSM_N175A_dark.yaml** and **IsPadC_PSM_WT_dark.yaml**. The files can be opened using HXViewer, freely available from https://hx2.mr.mpg.de/. To visualize the HDX-MS data, tables containing the delta deuterium values are generated by providing a .yaml dataset containing single peptides spanning each region and setting the dark dataset as reference. The corresponding tables can be found under HDX_tables\WT_dark_vs_N175A_dark. Using a script, these values are inserted into the B-factor column of a .pdb file and visualized with a custom color gradient.
	B, right	See figure 6C, the Pymol session file showing differences in deuterium incorporation plotted on the structure is renamed to **Figure_S10B_right_WT_light_vs_N175A_light.pse** for consistency.
Figure S11		Comparison of results for IsPadC obtained with the FSA method and the method published by Cagaida et al., 2023. The file **comparison_FSA_versus_cagiada.csv** contains 2 columns; column 1 contains the results of FSA method on IsPadC represented as numerical values, column 2 contains the results from the tool published by Cagiada et al., converted to the FSA nomenclature used in this publication. **0 unlabelled, 33 functional, 67 adaptability, 100 structural**