**Name:**

**Institution:**

**Address:**

**E-mail:**

**Title:**

*This 5-page document should outline the scientific nature and rationale of the proposed project. For additional information, please refer to the Solicitation Instructions. Additional material can be uploaded as appendices described in the instructions.*

**Background**

|  |
| --- |
| *Replace text with the requested information…* |

**Therapeutic Hypothesis**

|  |
| --- |
| *Replace text with the requested information…* |

**Current State of Project**

|  |
| --- |
| *Replace text with the requested information…* |

**Proposed Development Strategy**

|  |
| --- |
| *Replace text with requested information…* |

**Justification**

|  |
| --- |
| *Replace text with requested information…* |

**Timeline and Milestones**

|  |
| --- |
| *Replace text with requested information…* |

**Appendix 1:**

Provide data on the proposed lead compound using the following tables:

1. **Compound Properties Profile:**

*Lead Compound*

*Structure or Composition*

|  |  |  |
| --- | --- | --- |
| **Calculated Properties** | **Value** | **Goal** |
| **Compound ID** | *Provide data* | **N/A** |
| **MW** | *Provide data* | **< 500** |
| **Log D7.4, cLog P** | *Provide data* | **1-3, 1-4.5** |
| **TPSA** | *Provide data* | **< 140 (oral), < 90 (CNS)** |
| **Ligand Efficiency (LE, LELP)** | *Provide data* | **> 0.29, <10** |
| **Rotatable Bonds** | *Provide data* | **≤ 10** |
| **N + O (HBA)** | *Provide data* | **≤ 10** |
| **NH + OH (HBD)** | *Provide data* | **≤ 5** |

|  |  |  |  |
| --- | --- | --- | --- |
| ***In Vitro* Properties** | **Units** | **Value & Class** | **Goal** |
| **Compound ID** | **N/A** | *Provide data* | **N/A** |
| **Solubility (pH, media )** | **(g/mL)** | *Provide data* | **> 60** |
| **Stability - Microsomes (species)** | **t1/2 (min)** | *Provide data* | **> 30** |
| **CLint (mL/min/mg)** | *Provide data* | **< 10** |
| **Stability – Hepatocytes (species)** | **t1/2 (min)** | *Provide data* | **> 120** |
| **CLint, L/min/106 cells** | *Provide data* | **< 5** |
| **Stability – Plasma (species)** | **% Remaining at 3 hr** | *Provide data* | **> 80%** |
| **Stability – Solution (media)** | **% Remaining at 24 hr** | *Provide data* | **> 80%** |
| **CYP450 Inhibition (isozymes)** | **% Inhibition at 3 M** | *Provide data* | **< 15%** |
| **IC50 (M)** | *Provide data* | **> 10** |
| **Cmax at MED / Ki** | *Provide data* | **< 0.1** |
| **Plasma Protein & Tissue Binding (species)** | **Fu, plasma (%)** | *Provide data* |  |
| **Fu, tissue (%)** | *Provide data* |  |
| **Permeability - PAMPA** | **Pe (10-6 cm/s)** | *Provide data* | **> 1** |
| **Permeability - PAMPA-BBB** | **Pe (10-6 cm/s)** | *Provide data* | **> 4** |
| **Permeability - Caco-2** | **Papp (a-b, 10-6 cm/s)** | *Provide data* | **> 10** |
| **Efflux Ratio** | *Provide data* | **< 3** |
| **Permeability - MDR1-MDCKII** | **Papp (a-b, 10-6 cm/s)** | *Provide data* | **> 20** |
| **Pgp Efflux Ratio** | *Provide data* | **< 2** |
| **hERG - (method)** | **IC50 (M)** | *Provide data* | **> 10** |
| **IC50 / Free Cmax** | *Provide data* | **> 30** |
| **Free Cmax - Plasma** | **Total Cmax (M) \* Fu, plasma** | *Provide data* |  |
| **Free Cmax - Tissue** | **Total Cmax (M) \* Fu, plasma** | *Provide data* |  |
| **Screening Ames** | **Positive / Negative** | *Provide data* | **Negative** |

1. **Compound Efficacy Profile:**

|  |  |  |  |
| --- | --- | --- | --- |
| ***In Vitro* Biology** | **Units** | **Value & Class** | **Goal** |
| **Compound ID** | **N/A** |  | **N/A** |
| **Activity** |  |  |  |
| **(Assay 1) - IC50** | **nM** | *Provide data* | **< 1000** |
| **(Assay 1) - Ki** | **nM** | *Provide data* | **< 1000** |
| **(Assay 2) - IC50** | **nM** | *Provide data* | **< 1000** |
| **(Assay 2) – Ki** | **nM** | *Provide data* | **< 1000** |
| **Selectivity** |  |  |  |
| **(Assay 1) - IC50 / Fold selectivity** | **nM** | *Provide data* | **> 100** |
|  |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| ***In Vivo* Biology** | **Units** | **Value & Class** | **Goal** |
| **Compound ID** | **N/A** |  |  |
| **(Species, dose, route) – MED** | **nM** | *Provide data* |  |
| **(Species, dose, route) - MED** | **nM** | *Provide data* |  |
| **(Species, dose, route) - MED** | **nM** | *Provide data* |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **Other Biology** | **Units** | **Value & Class** | **Goal** |
|  |  |  |  |
|  |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PK Properties** | **Units** | **Dose (mpk), Route, Species** | **Dose (mpk), Route, Species** | **Goal** |
| **Compound ID** | **N/A** |  |  | **N/A** |
| **t1/2** | **hr** | *Provide data* | *Provide data* | **> 3** |
| **AUC0-∞, total, unbound** | **hr\*ng/mL** | *Provide data* | *Provide data* | **> 500 (PO)** |
| **CL** | **mL/min/kg** | *Provide data* | *Provide data* | **< 25% HBF** |
| **Cmax, total, unbound** | **ng/mL (nM)** | *Provide data* | *Provide data* |  |
| **Tmax** | **hr** | *Provide data* | *Provide data* |  |
| **Vd** | **L/kg** | *Provide data* | *Provide data* |  |
| **F** | **%** | *Provide data* | *Provide data* | **> 20%** |

**Appendix 2: References for *In Vitro* ADME Assays and *In Vivo* Pharmacokinetics**

General References

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1. “Physicochemical high throughput screening: Parallel artificial membrane permeability assay in the desc. of passive absorp. processes”, Kansy, M., *et al.,* (1998), *J. Med. Chem.* *41*, 1007-1010.
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Permeability – PAMPA-BBB

1. “High Throughput Artificial Membrane Permeability Assay for Blood-Brain Barrier”, L. Di, *et al.*, *Eur. J. Med. Chem.* (2003) 38, 223-232.
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