**Supplementary Table 1.** Small molecule screening data

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| **Category** | **Parameter** | **Description** |
| Assay | Type of assay | Viability and apoptosis |
|  | Target | NA |
|  | Primary measurement | % response |
|  | Key reagents | CellTiterGlo and caspase glo (promega) |
|  | Assay protocol | As described in the methods section, SI and online via the Pubchem database (AID # 1259257). |
|  | Additional comments |  |
| Library | Library size | 1912 |
|  | Library composition | Approved and investigational drugs |
|  | Source | Various sources |
|  | Additional comments |  |
| Screen | Format | Single agent and combination |
|  | Concentration(s) tested | Custom to each agent |
|  | Plate controls | DMSO (negative) and bortezomib (positive) |
|  | Reagent/ compound dispensing system | Acoustic dispenser (EDC Biosystems, Fremont CA) |
|  | Detection instrument and software | ViewLux reader (Perkin-Elmer, Waltham MA) |
|  | Assay validation/QC | Custom (see <https://tripod.nih.gov/matrix-client/>) |
|  | Correction factors | Custom (see <https://tripod.nih.gov/matrix-client/>) |
|  | Normalization | Custom (see <https://tripod.nih.gov/matrix-client/>) |
|  | Additional comments |  |
| Post-HTS analysis | Hit criteria | Single agent actives are based upon achievement of class -1.1, -1.2 and -2.1 curves in all four cell lines (Fig. 1a, Supplementary Fig. 1a)(see Inglese et al. for curve class definitions(ref. 33)). |
|  | Hit rate | 679 agents possessed this criteria (35%) |
|  | Additional assay(s) |  |
|  | Confirmation of hit purity and structure | Key agents were QC’d utilizing 1H, 13C NMR and HRMS |
|  | Additional comments |  |