ENHANCING DRUG SAFETY ASSESSMENT WITH AUTOMATED INSTRUMENTATION IN SECONDARY PHARMACOLOGY





Poster Number: P157

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Abstract

In pharmaceutical development, early assessment of drug candidate safety is critical to mitigate post-market withdrawals and reduce risks. Approximately 75% of adverse drug reactions (ADRs) are dose-dependent (Type A), often linked to off-target interactions. To address this, we have introduced ICESTP SAFETYPANEL® 44, a product comprising 44 screening models designed to assess target safety across critical areas such as the central nervous system, cardiovascular system, metabolism, and immunity. This panel has already successfully screened over 700 different types of compounds. Building on this initial product, we have further developed two new products: ICESTP SAFETYPANEL® 77 and ICESTP SAFETYPANEL® PLUS, as shown in Figure 1, which are cutting-edge functional safety assessment panels designed to revolutionise drug development. By evaluating the agonist or antagonist effects of compounds on these targets through functional activity screening, we assess compound safety and provide reference criteria for later stages of drug development. We tested pegolide and three antidepressant and two anticancer compounds on the ICESTP SAFETYPANEL® 77. The results demonstrated that our panel provides a competitive advantage by enabling the early identification of potential off-target ADRs and supporting informed decision-making, ultimately driving safer and more effective drug development.

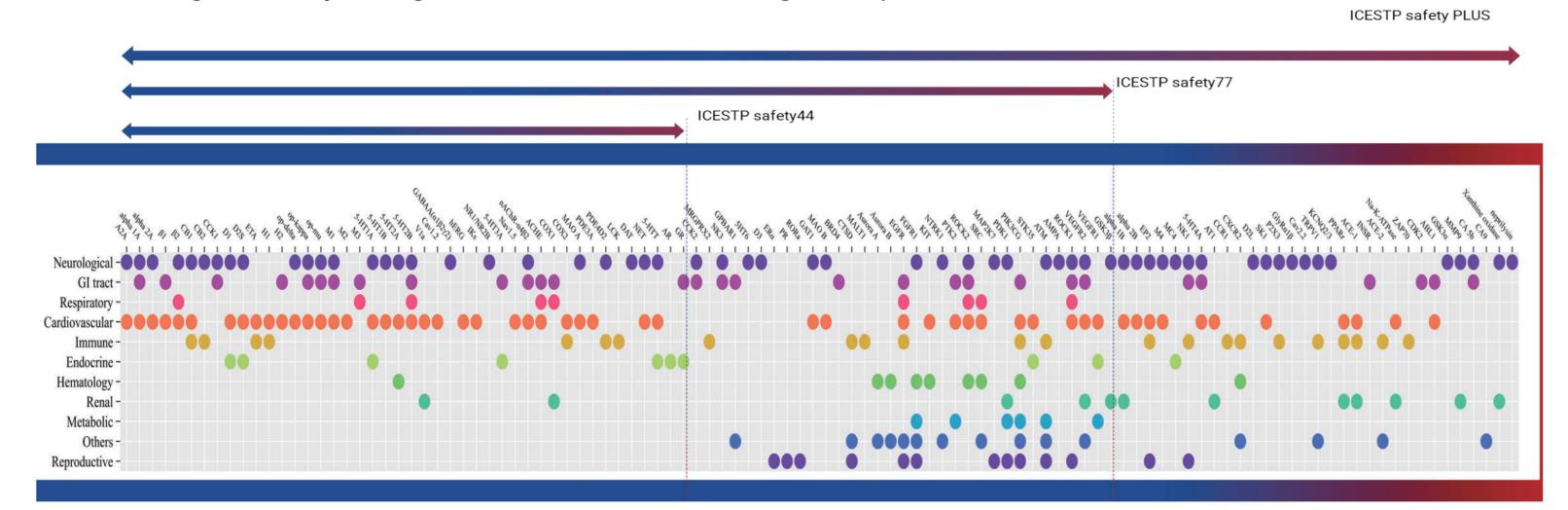


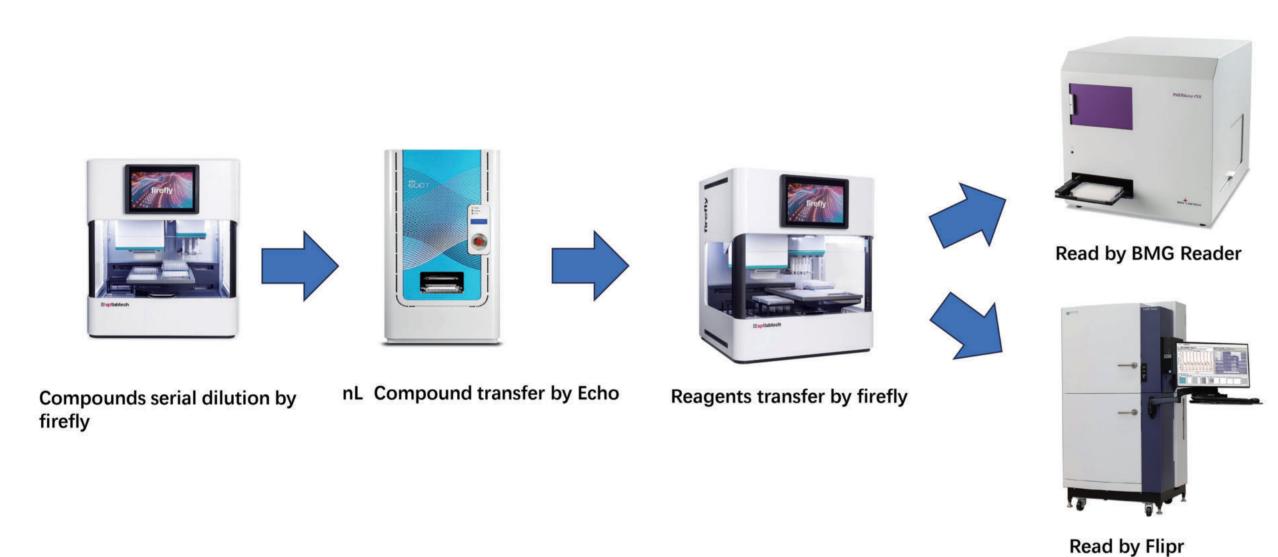
Figure 1. Organ systems at risk related to target activity in our three panels.

ICESTP SAFETYPANEL® 44: Target composition of the in vitro secondary pharmacology panel of 44 targets suggested by Bowes et al.

ICESTP SAFETYPANEL® 77: Add more comprehensive toxicity risk targets suggested by Richard et al.

ICESTP SAFETYPANEL® PLUS: Add more risk targets from our own targets database.

Methods



Automated systems and workflow supporting the ICESTP SAFETYPANEL® 77 Dose Response

The ICESTP SAFETYPANEL® 77 Dose Response comprises 116 assays, integrating both single-point and dose-response screening methodologies within a functional assay framework, including techniques such as FLIPR Calcium Flux, HTRF, ADP-Glo, FP, etc. The utilization of SPT Labtech's firefly® automated liquid handling platform and acoustic liquid handler ECHO655 for high-throughput sample processing, thereby enhancing the efficiency and precision of safety assessments for the The ICESTP SAFETYPANEL® 77 Dose Response.

Compound Name	Trade Name(s)	Class	Clinical Application	Side effects
Amitriptyline	Elavil; Endep	Tricyclic antidepressant	An inhibitor of serotonin reuptake transporter and noradrenaline reuptake transporter. It weakly binds to dopamine reuptake transporter. Amitriptyline also inhibits adrenergic, muscarinic. histamine and 5-HT receptors. Amitriptyline has antidepressant activity.	hypothermia, respiratory depression, seizures, abnormal tendon reflexes, disorientation, agitation, myoclonic jerks, coma,pyramidal signs, arrhythmias, bundle branch block, cardiac arrest.hypotension, circulatory collapse, mydriasis, blurred vision,tachycardia,vasodilation, urinaryretention, decreased gastrointestinal motility, decreased bronchial secretions, and dry mucous membranes and skin.
Bupropion	Welbutrin; Zyban	Tricyclic antidepressant	It block dopamine uptake or Metham- phetamine-induced dopamine release.It's an atypical antidepressant of the aminoketone group.Bupropion hydrochloride can be used for the research of smoking cessation aid.	hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias.Lethargy,grogginess, tremors, jitteriness, confusion,lightheadedness, paresthesias, visual hallucinations, blurred vision, nausea,and vomiting
Fluoxetine	Prozac	SSRI (Selective Serotonin Reuptake Inhibitor)	It inhibits the uptake of serotonin by a nerve cells (neurons) and helps people with depression, panic, anxiety, or ob- sessive. compulsive symptoms.	excessive salivation and eye-watering in low doses, followed by muscle spasms and ultimately death
Osimertinib	Tagrisso	Antineoplastic agent; Third-generation EGFR TKI	A covalent, orally active, irreversible, and mutant-selective EGFR inhibitor. Osimertinib overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer	hepatotoxicity

Table 1: General information on tested compounds in theICESTP SAFETYPANEL® 77 Dose Response

Selected active compounds corresponds to the marketed drugs from various antidepressant and antineoplastic classes with known clinical applications and adverse drug reactions.

Results

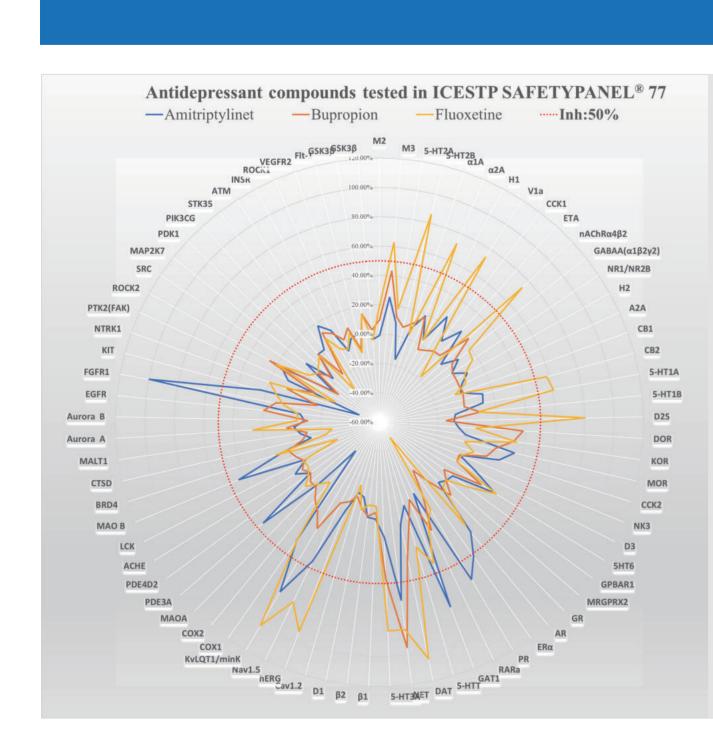
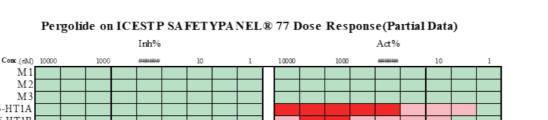
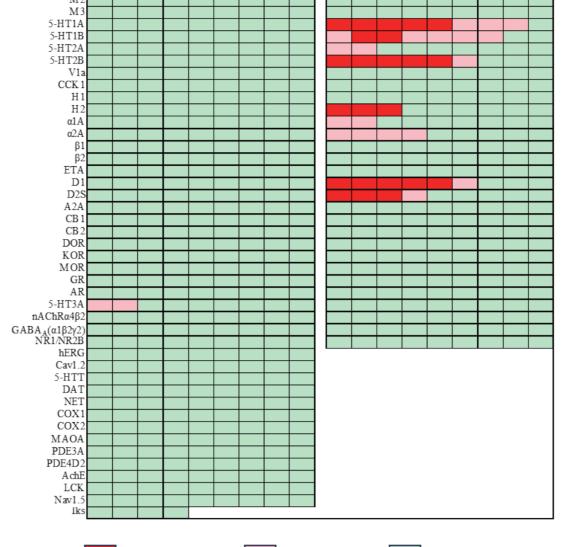
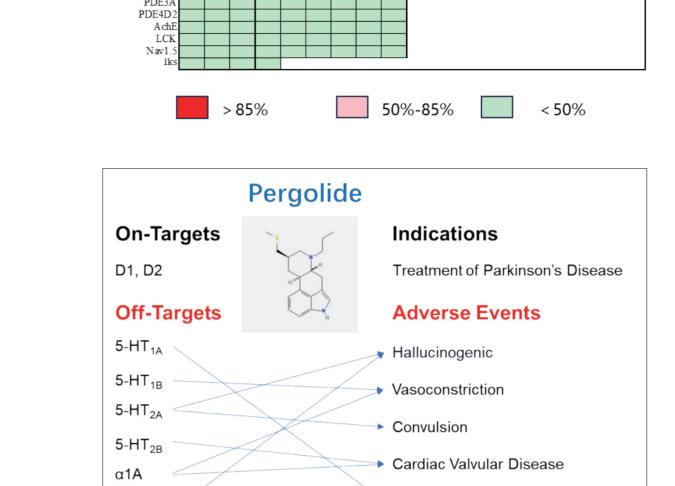


Figure 2: Results of antidepressant compounds tested by ICESTP **SAFETYPANEL® 77 Dose Response**

We tested three antidepressant compounds in ICESTP SAFETYPAN-EL® 77 Dose Response. The results displayed the inhibition percentage of each target's activity by the tested compounds at 10 μ M.

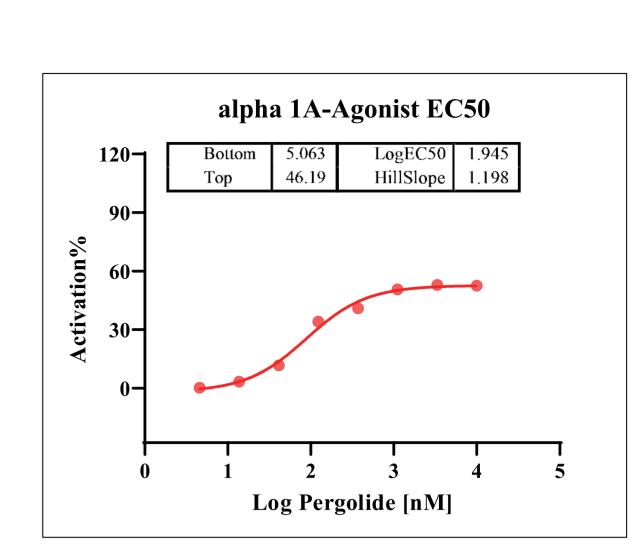






α2Α

H2



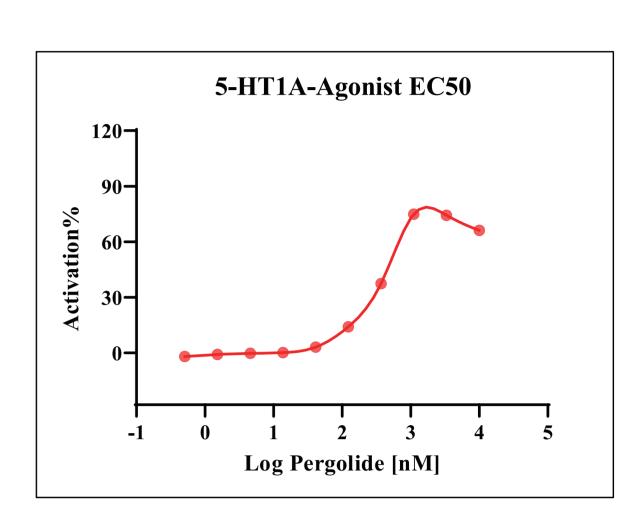
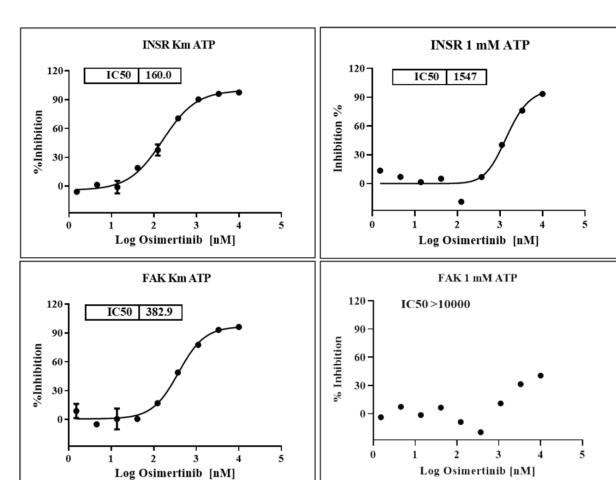


Figure 3: Pergolide with functional assay format ICESTP SAFETYPANEL® 77 Dose Response.

Vomiting

Decreased Blood Pressure

Using Pergolide as a case study, we tested its off-target profile in ICESTP SAFETYPANEL® 77 Dose Respon (showed in Figure. 3). The heatmap (Figure 3a) showed the inhibition and activation rates of Pergolide on the targets within the panel. We found that pergolide is a partial agonist of the alpha1 A target (Figure. 3b). Interestingly, we found that Pergolide exhibits an agonist effect on 5-HT1A with a bell-shaped curve (Figure 3c), which cannot be determined under a single-concentration condition. and subsequently utilized the off-target representation to elucidate its ADR mechanisms (Figure. 3d). It provides valuable information for safety-related prediction tasks.



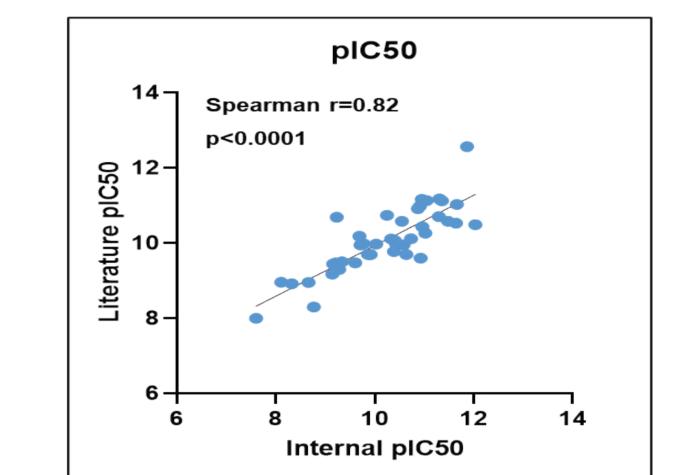


Figure 4: Pergolide with functional assay format ICESTP SAFETYPANEL® 77 Dose Response.

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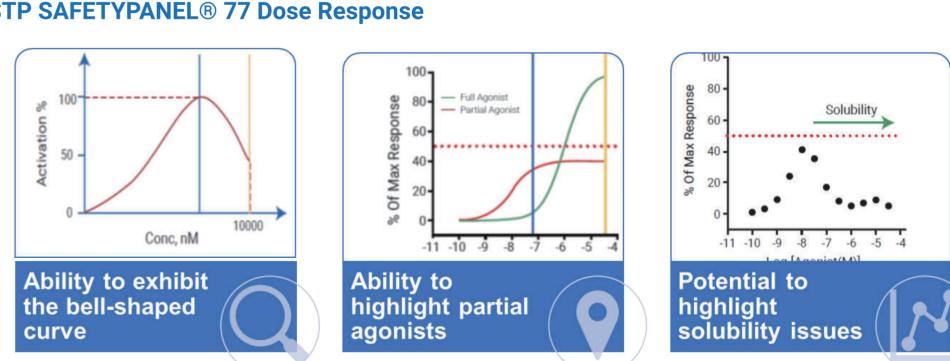
Figure 5: Nonparametric correlation analysis between literature and experimental data.

For inhibitor and antagonist of each target in ICESTP SAFETYPANEL® 77, a dose-response curve was plotted using 10 points to calculate the IC50. The molar value was linearized by calculating the negative logarithm to obtain pIC50. The same conversion was applied to the literature data.

Summary

Functional assay format	Curve-based screening
Ability to distinguish agonist and antagonist	Robust /reproducible data
Ability to detect allosteric pharmacology	Ability to highlight partial agonists
Closed to the physiological situation. (1 mM ATP used in kinase assays)	Potential to highlight solubility issues
Provide for a more stringent analysis, resulting in fewer follow-up studies.	Quickly correlate with in vivo exposure values
Efficient and time-saving	Efficient and time-saving

Table 2: Advantages of ICESTP SAFETYPANEL® 77 Dose Response



Our results demonstrate that ICESTP SAFETYPANEL® 77 Dose Response is a valuable tool in in vitro pharmacology profiling, which may help reduce the rate of drug molecule elimination related to safety during drug discovery and development, thereby enabling efficient and cost-effective early decision-making.

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