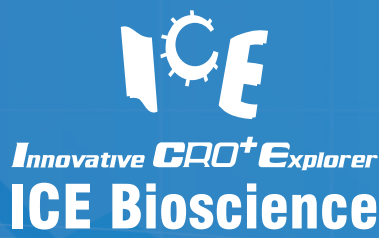


ENHANCING DRUG SAFETY ASSESSMENT WITH AUTOMATED INSTRUMENTATION
IN SECONDARY PHARMACOLOGY

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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 pergolide 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.

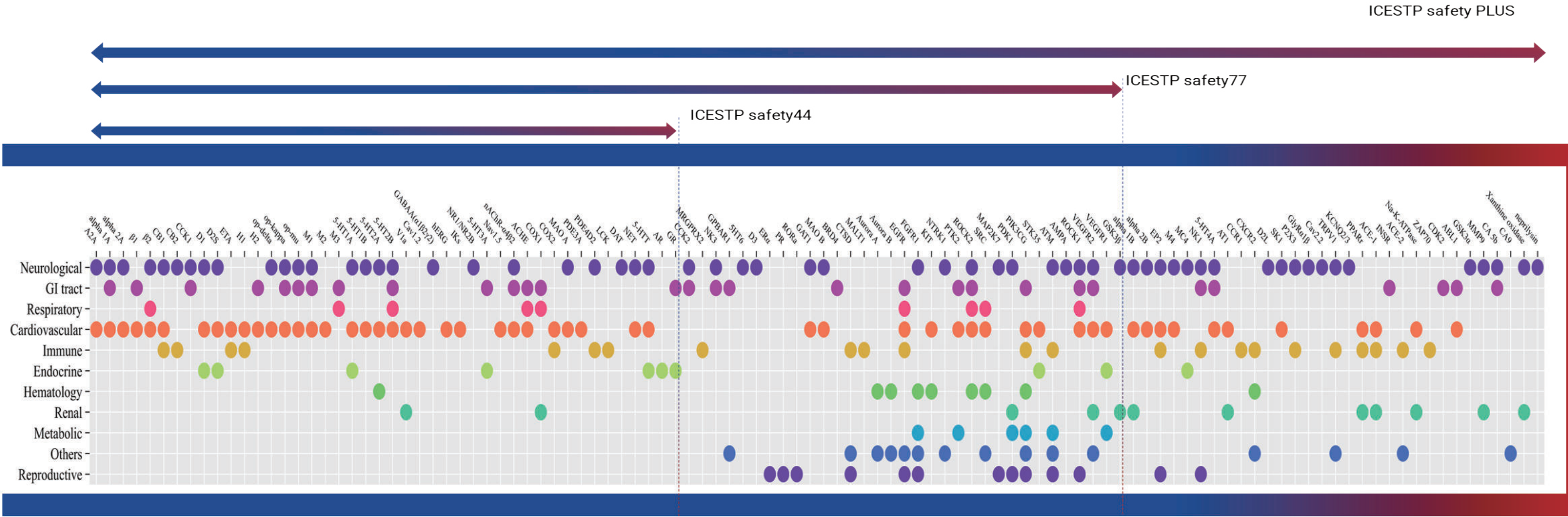
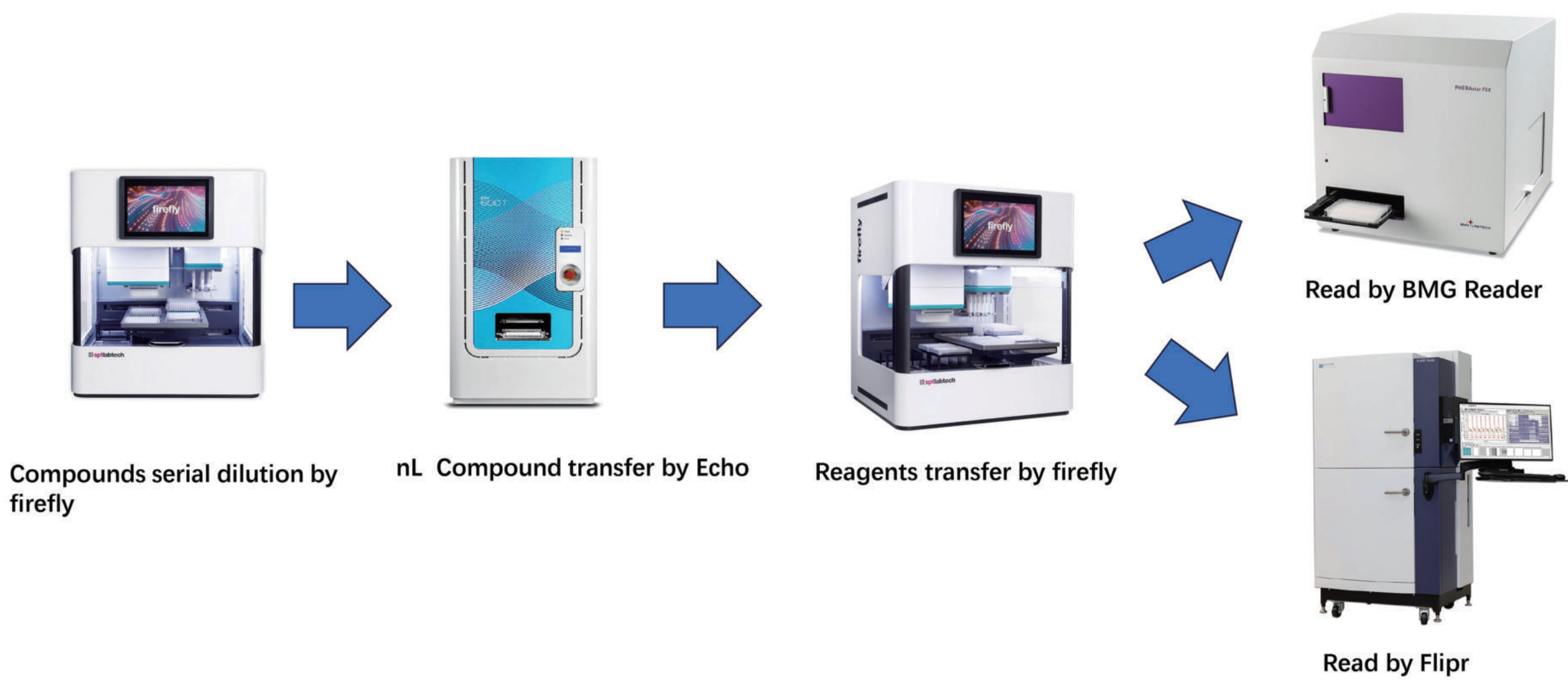


Figure 1. Organ systems at risk related to target activity in our three panels.
ICESTP SAFETYPANEL® 44 : Target composition of the in vitro secondary pharmacology panel of 44 targets suggested by Bowes et al.
ICESTP SAFETYPANEL® 77 : Add more comprehensive toxicity risk targets suggested by Richard et 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, urinary retention, decreased gastrointestinal motility, decreased bronchial secretions, and dry mucous membranes and skin.
Bupropion	Wellbutrin; Zyban	Tricyclic antidepressant	It blocks dopamine uptake or Methamphetamine-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 cell (neurons) and helps people with depression, panic, anxiety, or obsessive-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 the ICESTP SAFETYPANEL® 77 Dose Response
Selected active compounds correspond to the marketed drugs from various antidepressant and antineoplastic classes with known clinical applications and adverse drug reactions.

Results

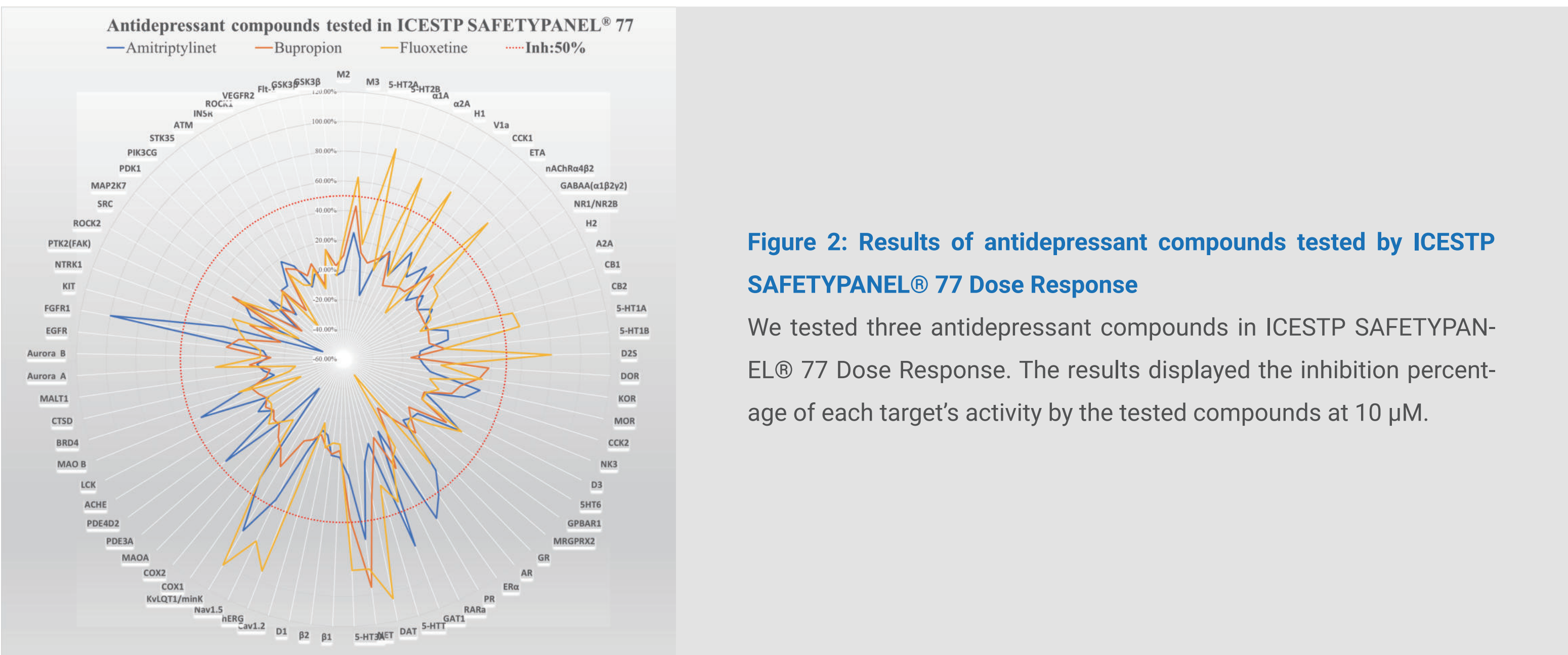


Figure 2: Results of antidepressant compounds tested by ICESTP SAFETYPANEL® 77 Dose Response
We tested three antidepressant compounds in ICESTP SAFETYPANEL® 77 Dose Response. The results displayed the inhibition percentage of each target's activity by the tested compounds at 10 µM.

