a)

b)

TCF/LEF binding site
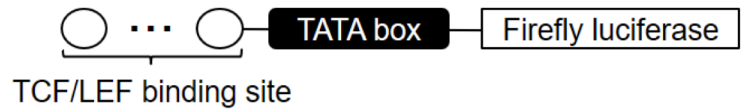
Supporting Figure 1 Wnt reporter cell line used for the study. a) Phase-contrast image of Leading Light Wnt Reporter Cell Line. b) Schematic of DNA construct stably expressed in the Leading Light Wnt Reporter Cell Line. The firefly luciferase reporter gene is under the control of a basal promoter element, TATA box, joined to tandem repeats of a proprietary and non-disclosed Wnt-responsive elements (TCF/LEF binding site).
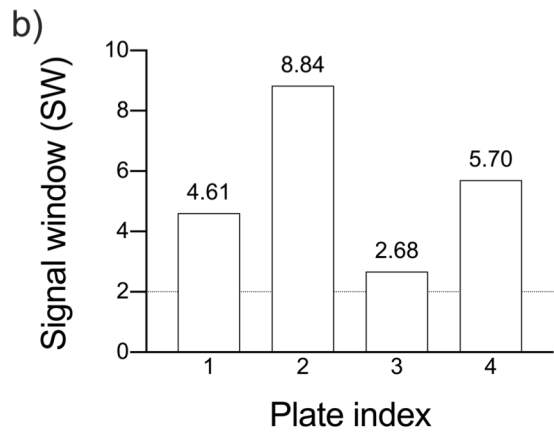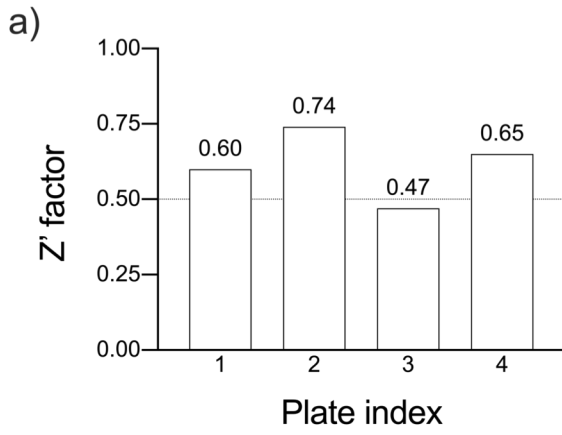
Supporting Figure 2 High-throughput assay quality metrics, calculated for each assay plate. a) Z' factor and b) signal window.
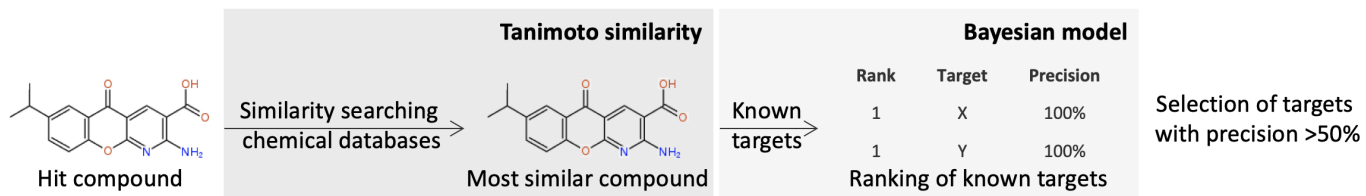
Supporting Figure 3 Schematic of HitPick protein target prediction strategy.
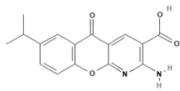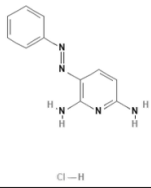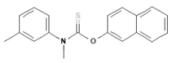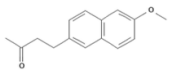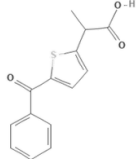
Supporting Table 1 Summary of promiscuity analysis of final five selected candidate drugs.

Drugs	Promiscuity in bioassays (%)	
	PubChem	ChemBank
Amlexanox	6,9 (active in 35 of 501 screens)	-
Phenazopyridine hydrochloride	7,5 (active in 86 of 1189 screens)	4,1 (active in 29 of 697 screens)
Tolnaftate	2,7 (active in 33 of 1219 screens)	2,7 (active in 18 of 654 screens)
Nabumetone	2,8 (active in 33 of 1154 screens)	1,7 (active in 11 of 647 screens)
Tiaprofenic acid	-	-
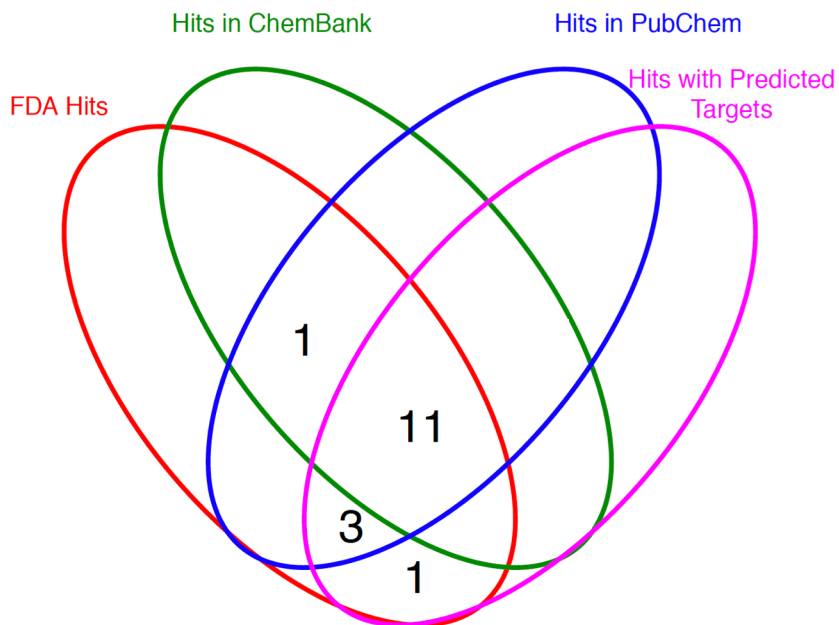
**Supporting Figure 4** Venn diagram showing the overlap of hits to compounds tested in ChemBank and PubChem bioassay databases, as well as compounds with predicted targets.

Supporting Table 2 Summary of final five selected candidate drugs.

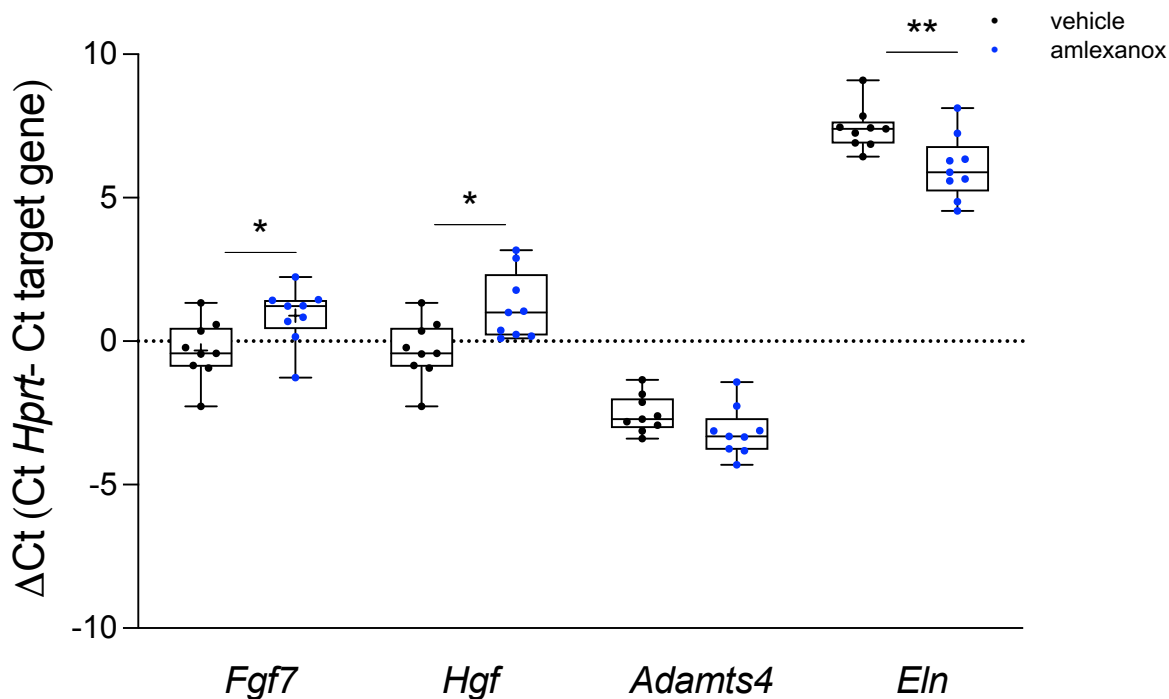| Drug	Therapeutic class	Formula	Structure	Luciferase activity
Amlexanox	Allergology	$C_{16}H_{14}N_2O_4$		8.6
Phenazopyridine hydrochloride	Central Nervous System	$C_{11}H_{12}ClN_5$		4.8
Tolnaftate	Infectiology	$C_{19}H_{17}NOS$		4.5
Nabumetone	Central Nervous System	$C_{15}H_{16}O_2$		4.3
Tiaprofenic acid	Central Nervous System	$C_{14}H_{12}O_3S$		3.1
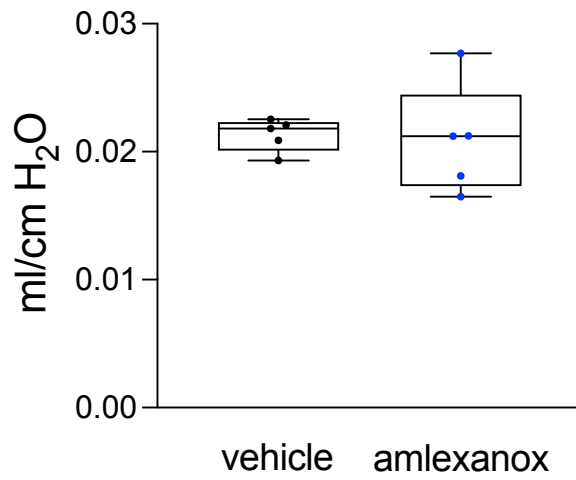
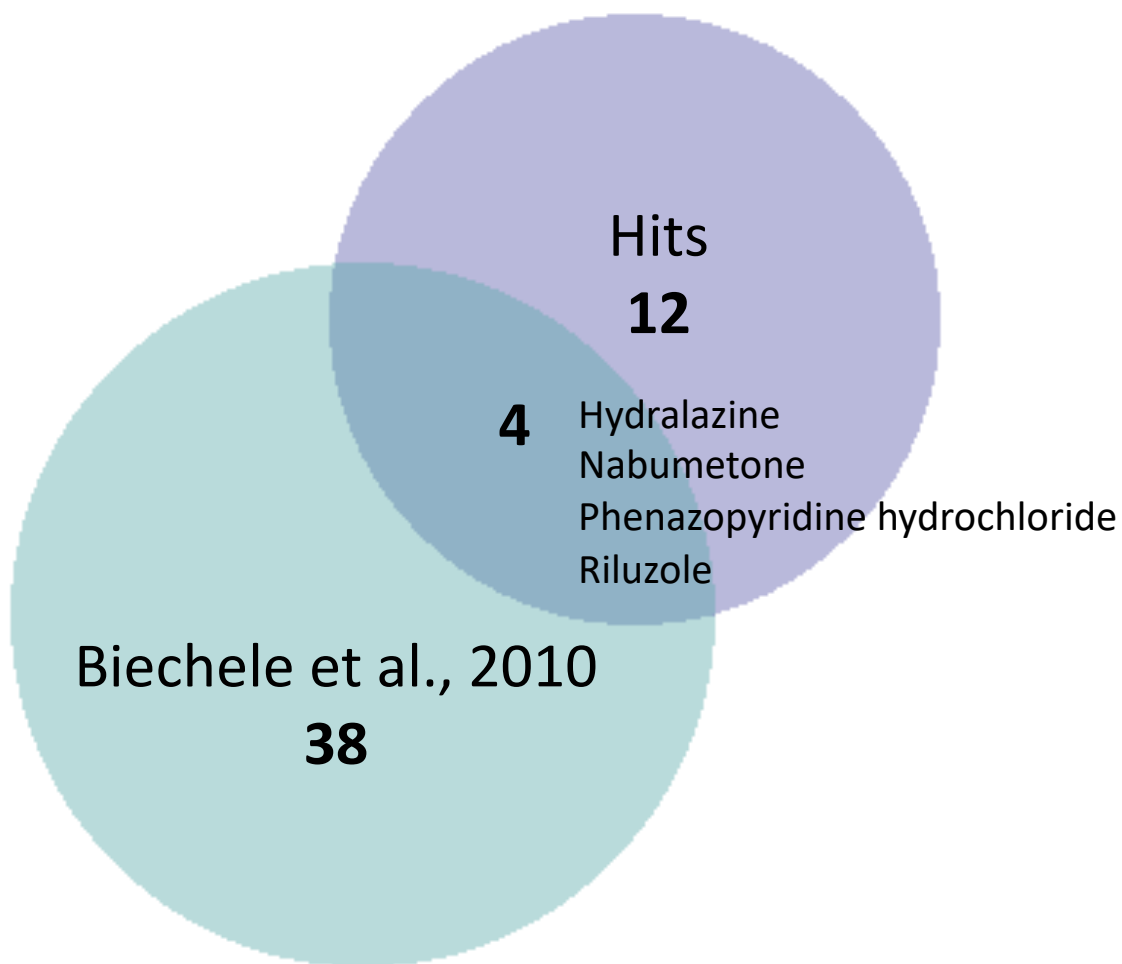**Supporting figure 5** Dynamic compliance from lung function analysis of control mice (saline challenged) treated with either vehicle or 50 mg kg^{-1} of amlexanox. n=5. Data is presented as mean ± SD.
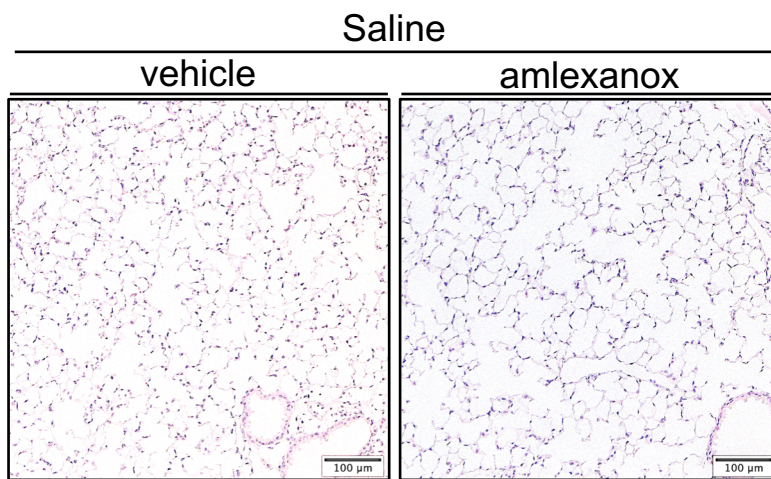
Supporting figure 6 Representative histological images of control mice (saline challenged) treated with either vehicle or 50 mg kg^{-1} of amlexanox lung sections stained with hematoxylin and eosin. n=4-5. Scale bar =100 μm.

Supporting figure 7 Gene expression analysis of Wnt, tissue repair and COPD related genes *Fgf7*, *Hgf, Adamts4* and *Eln* of elastase challenged mouse lungs treated with either vehicle or 25 mg kg^{-1} of amlexanox. n=9. Data is presented as mean ± SD. Mann-Whitney test, *p<0.05, **p<0.01.

Supporting Figure 8 Venn diagram with comparison of our hits with the hits with previous publication.