

Supporting Information for

Discovery of Novel Succinate Dehydrogenase Inhibitors by the Integration of *in silico* Library Design and Pharmacophore Mapping

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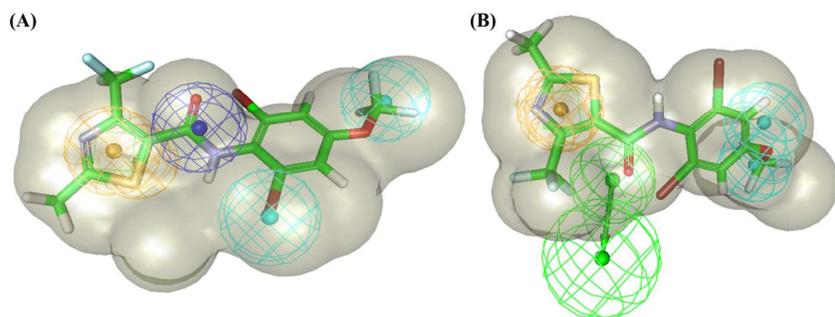


Figure S1. Comparison of Am-based and HBA-based pharmacophore model. The pharmacophore features are colored with cyan (“amide” feature), green (hydrogen bond acceptor), orange (aromatic ring), and blue (hydrophobic group).

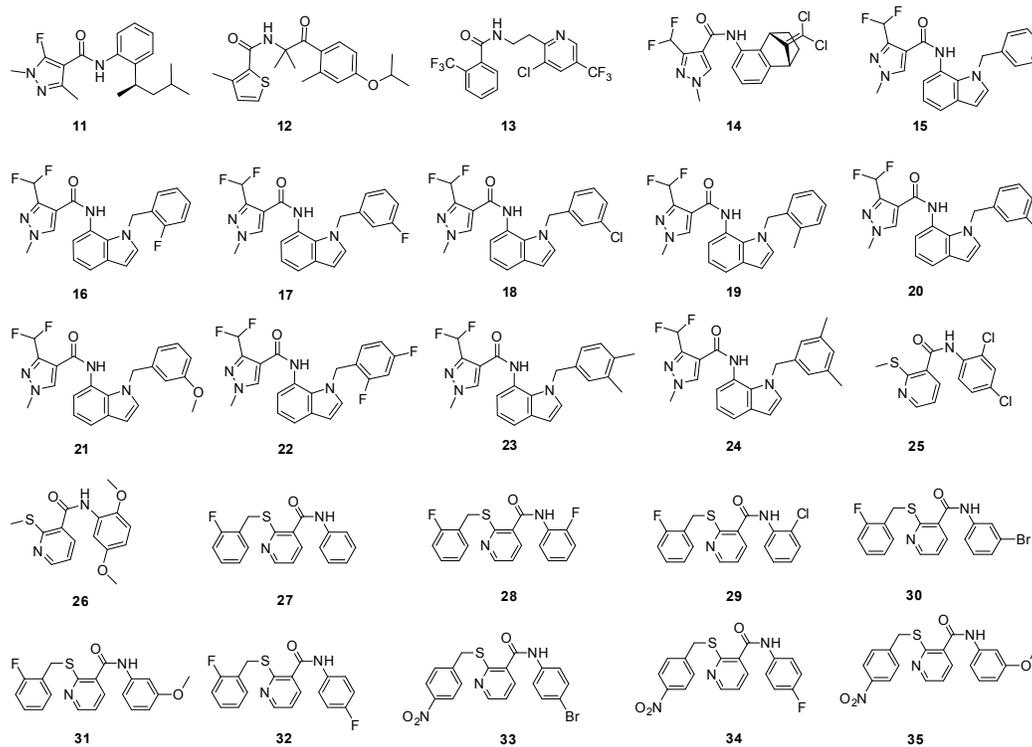


Figure S2. 25 known active SDH inhibitors for model validation.

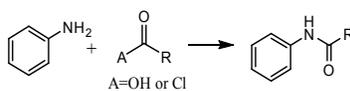


Figure S3. Reaction scheme for the library enumeration.

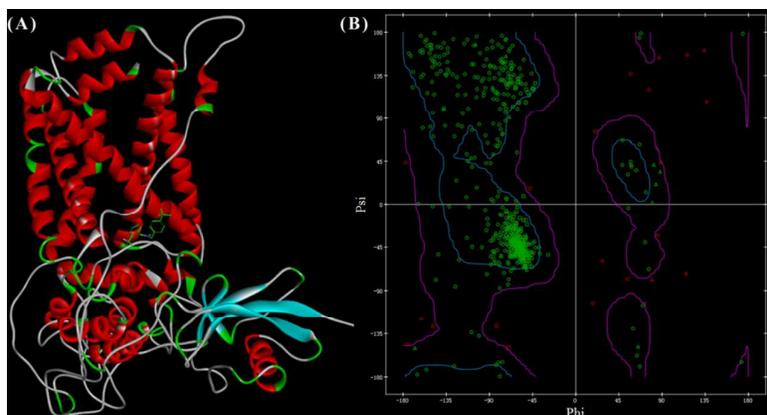


Figure S4. Homology model of *R*sSDH (A) and the Ramachandran plot (B).

Table S1. Features, rank values and max fit features for the Am-based pharmacophore models.

NO.	features ^a	rank	direct hit	partial hit	max fit
1 ^b	RAmHH	60.26	1111111	0	4
2	RAmHH	60.05	1111111	0	4
3	RAmHH	59.88	1111111	0	4
4	RAmHH	58.93	1111111	0	4
5	RHHA	58.85	1111111	0	4
6	RHHA	58.61	1111111	0	4
7	RHHA	58.55	1111111	0	4
8	RHHA	57.88	1111111	0	4
9	RHHA	57.81	1111111	0	4
10	AmHHH	57.61	1111111	0	4

^aAm: amide feature; R: ring aromatic feature; H: hydrophobic feature; A: hydrogen bond acceptor feature. ^bPharmacophore model that was selected for validation and virtual screening.

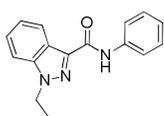
Table S2. Pesticide-likeness values of potent VS hits.

No.	MW ^a	logP ^b	HBA ^c	HBD ^d	ROB ^e	ARB ^f
A1	265	3.2	2	1	3	3
A4	247	3.5	1	1	2	3
A5	241	3.1	2	1	3	2
A8	205	3.4	1	1	6	1
A9	250	2.9	1	2	3	3
A12	211	3.1	1	1	2	2
A14	257	2.6	3	1	4	2
A16	311	3.7	2	1	3	3

^aMolecular weight; ^bpredicted octanol/water partition coefficient; ^cnumber of H-bond acceptor; ^dnumber of H-bond donor; ^enumber of rotatable bonds; ^fnumber of aromatic bonds.

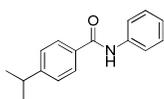
General procedure for the synthesis of target amides A1~A16 and A16a~o. To a solution of selected acid (1 mmol) in acetonitrile (20 ml) was added HATU (456 mg, 1.2 mmol) and aniline (140 mg, 1.5 mmol), the resulting mixture was heated at 40 °C for 6 h, and subsequently cooled down to room temperature. All of the solvent was removed under reduced pressure and partitioned between water and dichloromethane. The organic fraction was then separated, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to provide the title compound.

1-ethyl-N-phenyl-1H-indazole-3-carboxamide (A1). White solid; yield 65%;



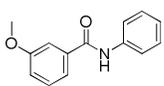
m.p.=120 - 122 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.90 (s, 1H, CONH), 8.47 (d, J = 8.2 Hz, 1H, Ar-H), 7.79 (dd, J = 8.5, 0.9 Hz, 2H, Ar-H), 7.47 - 7.43 (m, 2H, Ar-H), 7.41 (dt, J = 8.4, 4.7 Hz, 2H, Ar-H), 7.32 (m, 1H, Ar-H), 7.19 - 7.12 (m, 1H, Ar-H), 4.47 (q, J = 7.3 Hz, 2H, CH_2CH_3), 1.57 (t, J = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, CDCl_3) δ 160.48, 140.54, 138.02, 137.06, 128.98, 126.80, 123.85, 122.99, 122.79, 122.78, 119.60, 109.24, 44.32, 14.79. HR-MS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_3\text{NaO}$ $[\text{M} + \text{Na}]^+$: 288.1113; found: 288.1103.

4-isopropyl-N-phenylbenzamide (A2). Pale yellow solid; yield 80%; m.p. = 130 -



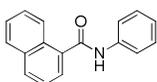
132 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.96 (s, 1H, CONH), 7.91 - 7.82 (m, 3H, Ar-H), 7.65 (d, J = 7.7 Hz, 2H, Ar-H), 7.61 - 7.52 (m, 2H, Ar-H), 7.38 (dd, J = 10.8, 5.1 Hz, 2H, Ar-H), 7.17 (m, 1H, CHMe_2) 1.63 (s, 6H, CHMe_2). ^{13}C NMR (125 MHz, CDCl_3) δ 165.60, 149.08, 137.87, 133.91, 129.11, 127.26, 125.90, 124.65, 120.27, 83.72, 26.11. HR-MS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}$ $[\text{M} + \text{H}]^+$: 240.1388 ; found: 240.1025.

3-methoxy-N-phenylbenzamide (A3). White solid; yield 65%; m.p. = 98 - 100 °C. ^1H



NMR (500 MHz, CDCl_3) δ 8.39 (s, 1H, CONH), 7.75 - 7.59 (m, 3H, Ar-H), 7.42 - 7.40 (m, 1H, Ar-H), 7.38 (dd, J = 7.9, 3.4 Hz, 1H, Ar-H), 7.36 - 7.31 (m, 2H, Ar-H), 7.28 (dd, J = 10.9, 4.9 Hz, 1H, Ar-H), 7.17 - 7.12 (m, 1H, Ar-H), 7.03 (m, J = 8.2, 2.6, 0.8 Hz, 1H, Ar-H), 3.78 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, CDCl_3) δ 166.00, 159.57, 137.87, 136.26, 129.58, 128.92, 124.53, 120.44, 118.86, 117.95, 112.41, 55.35. HR-MS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$ $[\text{M} + \text{H}]^+$: 228.1024; found: 228.1017.

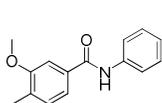
N-phenyl-1-naphthamide (A4). White solid; yield 67%; m.p. = 158-160 °C. ^1H NMR



(500 MHz, CDCl_3) δ 8.33 (dd, J = 5.9, 3.7 Hz, 1H, CONH), 7.94 (d, J

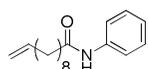
= 8.1 Hz, 2H, Ar-H), 7.90 - 7.80 (m, 1H, Ar-H), 7.74 - 7.65 (m, 3H, Ar-H), 7.59 - 7.52 (m, 2H, Ar-H), 7.48 - 7.42 (m, 1H, Ar-H), 7.39 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.19 (t, $J = 7.4$ Hz, 1H, Ar-H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.63, 138.05, 134.42, 133.72, 130.96, 130.04, 129.10, 128.40, 127.30, 126.55, 125.24, 125.08, 124.68, 124.64, 120.04. HR-MS (ESI): m/z calcd. for $\text{C}_{17}\text{H}_{14}\text{NO}$ [$\text{M} + \text{H}$] $^+$: 248.1075; found: 248.1066.

3-methoxy-4-methyl-N-phenylbenzamide (A5). White solid; yield 63%; m.p. = 118 -



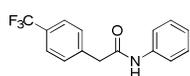
120 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.41 (s, 1H, CONH), 7.69 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.38 (d, $J = 1.2$ Hz, 1H, Ar-H), 7.31 (m, 3H, Ar-H), 7.20 - 7.04 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (125 MHz, CDCl_3) δ 166.02, 157.94, 138.10, 133.67, 131.05, 130.31, 128.91, 124.33, 120.34, 118.17, 109.10, 55.28, 16.27. HR-MS (ESI): m/z calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$: 242.1181; found: 242.1173.

N-phenylbut-3-enamide (A6). Pale yellow solid; yield 61%; m.p. = 64 - 66 °C; ^1H



NMR (500 MHz, CDCl_3) δ 8.01 (s, 1H, CONH), 7.54 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.29 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.09 (t, $J = 7.4$ Hz, 1H, Ar-H), 5.93 - 5.71 (m, 1H, $\text{CH}_2=\underline{\text{C}}\text{H}$), 5.10 - 4.85 (m, 2H, $\underline{\text{C}}\text{H}_2=\text{CH}$), 2.44-2.04 (m, 6H, undec-1-ene-H), 1.81 - 1.33 (m, 10H, undec-1-ene-H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.02, 157.94, 138.10, 133.67, 131.05, 130.31, 128.91, 124.33, 120.34, 118.17, 109.10, 55.28, 16.27. HR-MS (ESI): m/z calcd. for $\text{C}_{17}\text{H}_{25}\text{NNaO}$ [$\text{M} + \text{Na}$] $^+$: 282.1834 ; found: 282.2798.

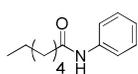
N-phenyl-2-(4-(trifluoromethyl)phenyl)acetamide (A7). White solid; yield 68%; m.p.



= 100 - 102 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.63 (d, $J = 8.1$ Hz, 2H, CONH), 7.59 - 7.34 (m, 5H, Ar-H), 7.29 (dd, $J = 14.0, 5.8$ Hz, 2H, Ar-H), 7.12 (t, $J = 7.4$ Hz, 1H, Ar-H), 3.75 (s, 2H, CH_2). ^{13}C NMR (125 MHz,

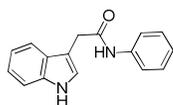
CDCl₃) δ 168.20, 138.51, 137.46, 129.96, 129.75, 129.01, 125.91, 125.88, 125.13, 124.76, 122.96, 120.08, 44.26. HR-MS (ESI): m/z calcd. for C₁₅H₁₃F₃NO [M + H]⁺: 280.0949; found: 280.0943.

N-phenylbutyramide (**A8**). Pale yellow liquid; yield 71%; ¹H NMR (500 MHz, CDCl₃)



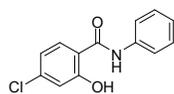
δ 9.08 (s, 1H, CONH), 7.62 (d, J = 7.9 Hz, 2H, Ar-H), 7.27 (t, J = 7.9 Hz, 2H, Ar-H), 7.09 (t, J = 7.4 Hz, 1H, Ar-H), 2.38 (q, J = 7.4 Hz, 2H, heptane-H), 1.78 - 1.60 (m, 2H, heptane-H), 1.41 - 1.24 (m, 6H, heptane-H), 0.96 - 0.86 (m, 3H, heptane-H). ¹³C NMR (125 MHz, CDCl₃) δ 172.71, 138.12, 128.48, 123.86, 120.26, 37.24, 31.36, 28.74, 25.61, 22.28, 13.78. HR-MS (ESI): m/z calcd. for C₁₃H₂₀NO [M + H]⁺: 206.1545; found: 206.1536.

2-(1*H*-indol-3-yl)-*N*-phenylacetamide (**A9**). Pale yellow solid; yield 71%; m.p. = 132



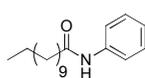
- 134 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, J = 8.3 Hz, 1H, CONH), 7.99 - 7.84 (m, 2H, Ar-H, NH), 7.54 (m, 4H, Ar-H), 7.34 (d, J = 7.9 Hz, 2H, Ar-H), 7.31 - 7.20 (m, 2H, Ar-H), 7.06 (t, J = 7.3 Hz, 1H, Ar-H), 4.17 (s, 2H, CH₂). ¹³C NMR (125 MHz, CDCl₃) δ 172.71, 138.12, 128.48, 123.86, 120.26, 37.24, 31.36, 28.74, 25.61, 22.28, 13.78. HR-MS (ESI): m/z calcd. for C₁₆H₁₅N₂O [M + H]⁺: 251.1184; found: 251.1176.

4-chloro-2-hydroxy-*N*-phenylbenzamide (**A10**). White solid; yield 77%; m.p. = 213-



214 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, J = 45.7 Hz, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.44 (d, J = 26.3 Hz, 2H, Ar-H), 7.27 (s, 2H, Ar-H), 7.13 - 6.77 (m, 3H, Ar-H), 3.50 (s, 1H, OH). ¹³C NMR (125 MHz, CDCl₃) δ 129.28, 127.94, 126.42, 126.18, 125.63, 121.32, 120.14, 119.47, 119.06, 118.75, 117.87. HR-MS (ESI): m/z calcd. for C₁₃H₉ClNO₂ [M-H]⁻: 246.0322; found: 246.0315.

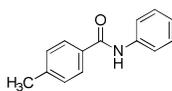
N-phenylbutyramide (**A11**). Yellow solid; yield 68%; m.p. = 52 - 54 °C. ¹H NMR



(500 MHz, CDCl₃) δ 7.53 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.41 (s, 1H, CONH), 7.32 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.10 (t, *J* = 7.4 Hz, 1H, Ar-H),

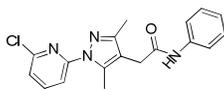
2.36 (td, *J* = 7.5, 4.0 Hz, 4H, dodecane-H), 1.81 - 1.60 (m, 4H, dodecane-H), 1.27 (s, 10H, dodecane-H), 0.89 (t, *J* = 6.8 Hz, 5H, dodecane-H). ¹³C NMR (125 MHz, CDCl₃) δ 171.64, 137.96, 128.97, 124.19, 119.85, 37.84, 34.03, 31.91, 29.60, 29.49, 29.44, 29.39, 29.33, 29.28, 29.25, 29.09, 25.67, 24.74, 22.69, 14.11. HR-MS (ESI): *m/z* calcd. for C₁₈H₃₀NO [M + H]⁺: 276.2327; found: 276.1620.

4-methyl-*N*-phenylbenzamide (**A12**). Pale yellow solid; yield 78%; m.p. = 92 - 94 °C.



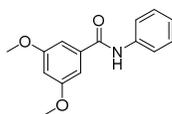
¹H NMR (500 MHz, CDCl₃) δ 8.10 - 7.96 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.36 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.30 - 7.24 (m, 2H, Ar-H), 7.15 (t, *J* = 7.4 Hz, 1H, Ar-H), 2.42 (s, 3H, CH₃). HR-MS (ESI): *m/z* calcd. for C₁₄H₁₄NO [M + H]⁺: 212.1075; found: 212.9806.

2-(1-(6-chloropyridin-2-yl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-phenylacetamide (**A13**).



Yellow gum; yield 64%. ¹H NMR (500 MHz, CDCl₃) δ 8.43 (dd, *J* = 4.7, 1.4 Hz, 1H, CONH), 8.07 (s, 1H, Ar-H), 7.85 (dd, *J* = 8.0, 1.4 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.02 (t, *J* = 7.4 Hz, 1H, Ar-H), 3.48 (s, 2H, CH₂), 2.25 (s, 3H, CH₃), 2.13 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 168.65, 149.24, 148.51, 146.98, 139.54, 139.38, 137.51, 128.72, 128.60, 125.04, 124.11, 119.85, 110.78, 32.06, 11.82, 9.83. HR-MS (ESI): *m/z* calcd. for C₁₄H₁₄NNaO [M + Na]⁺: 363.0989; found: 363.3614.

3,5-dimethoxy-*N*-phenylbenzamide (**A14**). Pale yellow solid; yield 67%; m.p. = 94 -



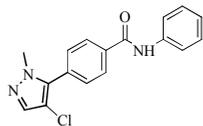
96 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.35 (s, 1H, CONH), 7.64 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.32 (dd, *J* = 10.9, 5.0 Hz, 2H, Ar-H), 7.13 (t, *J*

= 7.4 Hz, 1H, Ar-H), 6.96 (d, $J = 2.3$ Hz, 2H, Ar-H), 6.56 (t, $J = 2.2$ Hz, 1H, Ar-H), 3.75 (s, 6H, OMe₂). ¹³C NMR (125 MHz, CDCl₃) δ 168.65, 149.24, 148.51, 146.98, 139.54, 139.38, 137.51, 128.72, 128.60, 125.04, 124.11, 119.85, 110.78, 32.06, 11.82, 9.83. HR-MS (ESI): m/z calcd. for C₁₅H₁₆NO₃ [M + H]⁺: 258.1130; found: 258.1121.

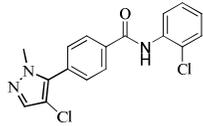
4-bromo-1-(3-chloropyridin-2-yl)-N-phenyl-1H-pyrazole-3-carboxamide (**A15**).

 Yellow crystal; yield 62%; m.p. = 66 - 68 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.38 (s, 1H, CONH), 7.63 (d, $J = 7.7$ Hz, 2H), 7.58 (dd, $J = 7.6, 1.4$ Hz, 1H, Ar-H), 7.36 (m, 4H, Ar-H), 7.31 - 7.23 (m, 1H, Ar-H), 7.16 (t, $J = 7.4$ Hz, 1H, Ar-H). ¹³C NMR (125 MHz, CDCl₃) δ 164.78, 137.61, 135.26, 131.34, 130.61, 130.13, 129.78, 128.90, 126.97, 124.64, 120.16. HR-MS (ESI): m/z calcd. for C₁₅H₁₀BrClN₄NaO [M + Na]⁺: 398.9625; found: 398.9613.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-phenylbenzamide (**A16**). White solid; yield

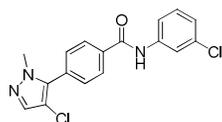
 = 63%; m.p. = 110 - 112 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.37 (s, 1H, CONH), 7.98 (d, $J = 8.3$ Hz, 2H, Ar-H), 7.67 (d, $J = 7.7$ Hz, 2H, Ar-H), 7.53 (s, 1H, Ar-H), 7.49 (d, $J = 8.3$ Hz, 2H, Ar-H), 7.36 (t, $J = 7.9$ Hz, 2H, Ar-H), 7.17 (t, $J = 7.4$ Hz, 1H, Ar-H), 3.79 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 165.23, 138.40, 137.76, 137.24, 135.50, 131.10, 129.84, 129.05, 127.56, 124.81, 120.49, 109.16, 38.36. HR-MS (ESI): m/z calcd. for C₁₇H₁₅ClN₃O [M + H]⁺: 312.0903; found: 312.0894.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(2-chlorophenyl)benzamide (**A16a**).

 Colorless liquid; yield = 67%. ¹H NMR (500 MHz, CDCl₃) δ 8.54 - 8.41 (m, 1H, CONH), 8.17 (s, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 8.03 (d, $J = 1.7$ Hz, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.22 (dd, $J = 11.8, 5.0$ Hz, 1H, Ar-H), 7.19 - 7.09 (m, 2H, Ar-H), 3.86 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 164.70, 153.77, 151.84, 138.35, 137.33,

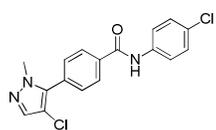
135.07, 131.60, 131.12, 130.34, 130.11, 127.57, 126.24, 121.98, 115.01, 114.86, 109.33, 38.47. HR-MS (ESI): m/z calcd. for $C_{17}H_{13}Cl_2N_3NaO$ $[M + Na]^+$: 368.0334; found: 368.2589.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(3-chlorophenyl)benzamide (A16b). Pale



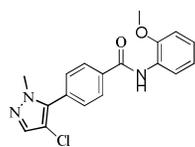
yellow solid; yield=62%; m.p. = 134 – 136 °C. 1H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H, CONH), 8.00 (s, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 7.80 (t, J = 1.9 Hz, 1H, Ar-H), 7.57 - 7.50 (m, 4H, Ar-H), 7.29 (dd, J = 13.5, 5.4 Hz, 1H, Ar-H), 7.15 (dd, J = 7.9, 1.3 Hz, 1H, Ar-H), 3.83 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.13, 138.89, 138.33, 137.33, 135.09, 134.80, 131.50, 131.12, 130.35, 130.11, 130.03, 127.56, 124.88, 120.47, 118.33, 109.30, 38.44. HR-MS (ESI): m/z calcd. for $C_{17}H_{14}Cl_2N_3O$ $[M + H]^+$: 346.0514; found: 346.0500.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(4-chlorophenyl)benzamide (A16c). White



solid; yield = 75%; m.p. = 148 - 150 °C. 1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H, CONH), 7.98 (d, J = 1.7 Hz, 1H, Ar-H), 7.96 (d, J = 1.8 Hz, 1H, Ar-H), 7.63 - 7.61 (m, 1H, Ar-H), 7.61 - 7.58 (m, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.51 (d, J = 1.8 Hz, 1H, Ar-H), 7.50 (d, J = 1.8 Hz, 1H, Ar-H), 7.35 - 7.31 (m, 1H, Ar-H), 7.32 - 7.29 (m, 1H, Ar-H), 3.80 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.18, 138.31, 137.29, 136.32, 135.12, 131.36, 129.92, 129.86, 129.09, 127.55, 121.71, 109.23, 38.39. HR-MS (ESI): m/z calcd. for $C_{17}H_{13}Cl_2N_3O$ $[M - H]^+$: 344.0358; found: 344.0373.

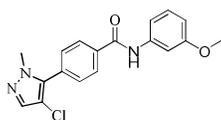
4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(2-methoxyphenyl)benzamide (A16d). White



solid; yield = 71%; m.p.= 142 - 144°C. 1H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H, CONH), 8.55 (dd, J = 8.0, 1.5 Hz, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 8.03 (d, J = 1.8 Hz, 1H, Ar-H), 7.58 (d, J = 1.8 Hz, 1H, Ar-H), 7.57 (d, J = 1.8 Hz, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.12 (td, J = 7.8, 1.6 Hz

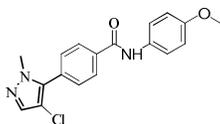
z, 1H, Ar-H), 7.05 (td, $J = 7.8, 1.2$ Hz, 1H, Ar-H), 6.95 (dd, $J = 8.1, 1.2$ Hz, 1H, Ar-H), 3.95 (s, 3H, CH₃), 3.85 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 164.39, 148.18, 138.47, 137.27, 135.87, 131.12, 129.98, 127.56, 127.48, 124.17, 121.22, 119.93, 110.00, 109.19, 55.83, 38.44. HR-MS (ESI): m/z calcd. for C₁₈H₁₇ClN₃O₂ [M + H]⁺: 342.1009; found: 342.1002.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(3-hydroxyphenyl)benzamide (A16e).



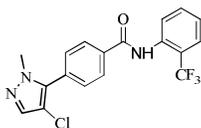
Colorless liquid; yield = 65%; ¹H NMR (500 MHz, CDCl₃) δ 8.42 (s, 1H, CONH), 8.01 – 7.97 (m, 2H, Ar-H), 7.53 (s, 1H, Ar-H), 7.52 – 7.49 (m, 2H, Ar-H), 7.45 (t, $J = 2.1$ Hz, 1H, Ar-H), 7.25 (d, $J = 8.1$ Hz, 1H, Ar-H), 7.17 (dd, $J = 8.0, 1.1$ Hz, 1H, Ar-H), 6.72 (m, 1H, Ar-H), 3.81 (d, $J = 3.7$ Hz, 6H, OCH₃, CH₃). ¹³C NMR (126 MHz, CDCl₃) δ 165.72, 165.20, 160.17, 139.06, 138.42, 137.25, 135.53, 131.12, 129.87, 129.74, 127.57, 112.56, 110.55, 109.16, 106.17, 55.30, 38.56, 38.39. HR-MS (ESI): m/z calcd. for C₁₈H₁₇ClN₃O₂ [M + H]⁺: 342.1009; found: 342.1001.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(4-methoxyphenyl)benzamide (A16f). Off-



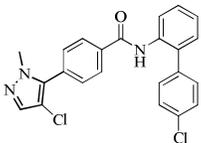
white solid; yield = 65%; m.p. = 126 - 128°C. ¹H NMR (500 MHz, CDCl₃) δ 8.38 (s, 1H, CONH), 7.97 (s, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 6.90 - 6.87 (m, 1H, Ar-H), 6.87 - 6.84 (m, 1H, Ar-H), 3.79 (s, 3H, OCH₃), 3.78 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 165.11, 156.75, 138.43, 137.21, 135.51, 130.92, 130.81, 129.77, 127.53, 122.41, 114.17, 109.10, 55.43, 38.34. HR-MS (ESI): m/z calcd. for C₁₈H₁₇ClN₃O₂ [M + H]⁺: 342.1009; found: 342.0994.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(2-(trifluoromethyl)phenyl)benzamide



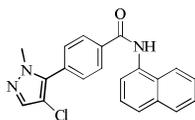
(**A16g**). White solid; yield = 67%; m.p.= 124 – 126 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.43 (d, *J* = 1.8 Hz, 1H, CONH), 8.03 (s, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 7.89 (t, *J* = 11.2 Hz, 1H, Ar-H), 7.54 (dd, *J* = 5.3, 3.0 Hz, 3H), 7.52 - 7.45 (m, 2H, Ar-H), 7.42 (d, *J* = 7.8 Hz, 1H, Ar-H), 3.82 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 165.30, 138.35, 137.33, 134.95, 131.58, 131.12, 130.35, 130.04, 129.69, 127.61, 123.44, 121.23, 120.55, 109.32, 38.43. HR-MS (ESI): *m/z* calcd. for C₁₈H₁₂ClF₃N₃O [M - H]⁺: 378.0828; found: 378.0624.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(4'-chloro-[1,1'-biphenyl]-2-yl)benzamide



(**A16h**). White solid; yield=63%; m.p. = 160 - 162 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.42 (d, *J* = 8.2 Hz, 1H, CONH), 7.96 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.57 - 7.44 (m, 6H, Ar-H), 7.41 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.34 - 7.24 (m, 2H, Ar-H), 3.82 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 164.40, 138.28, 137.28, 136.54, 135.06, 134.46, 134.34, 131.83, 131.35, 130.65, 130.15, 130.04, 129.42, 128.94, 127.28, 125.08, 122.23, 109.23, 38.45. HR-MS (ESI): *m/z* calcd. for C₂₃H₁₆Cl₂N₃O [M - H]⁺: 420.0671; found: 420.0673.

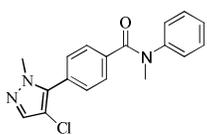
4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-(naphthalen-1-yl)benzamide (**A16i**). White



solid; yield = 65%; m.p. = 193 - 195°C. ¹H NMR (500 MHz, CDCl₃) δ 8.43 (s, 1H, CONH), 8.11 (s, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 8.01 - 7.87 (m, 3H, Ar-H), 7.78 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.61 - 7.47 (m, 6H, Ar-H), 3.85 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃) δ 138.46, 137.33, 135.29, 134.19, 132.20, 131.34, 130.02, 128.83, 127.70, 126.49, 126.15, 125.72, 121.74, 1

20.87, 109.27, 38.46. HR-MS (ESI): m/z calcd. for $C_{21}H_{15}ClN_3O$ $[M - H]^+$: 360.0904; found: 360.0907.

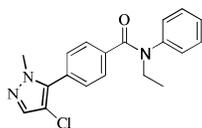
4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-methyl-N-phenylbenzamide (A16j). White g



um; yield = 66%. 1H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H, Ar-H), 7.43 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.30 - 7.22 (m, 4H, Ar-H), 7.18 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.09 (d, $J = 7.6$ Hz, 2H, Ar-H), 3.73 (s, 3H,

CH_3), 3.54 (s, 3H, CO-N CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.78, 144.55, 138.68, 137.16, 136.64, 129.28, 129.05, 129.00, 126.93, 126.83, 108.93, 38.42, 38.32. HR-MS (ESI): m/z calcd. for $C_{18}H_{17}ClN_3O$ $[M + H]^+$: 326.1060; found: 326.1057.

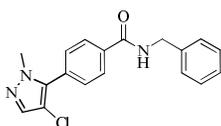
4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-ethyl-N-phenylbenzamide (A16k). White



gum; yield = 66%. 1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.54 - 7.41 (m, 3H, Ar-H), 7.38 (t, $J = 6.6$ Hz, 3H,

Ar-H), 7.32 (dd, $J = 11.6, 5.4$ Hz, 1H, Ar-H), 7.20 (d, $J = 5.8$ Hz, 1H, Ar-H), 4.69 (d, $J = 104.8$ Hz, 2H, CH_2CH_3), 3.81 (d, $J = 7.9$ Hz, 3H, CH_3), 3.00 (d, $J = 67.8$ Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.38, 170.67, 138.60, 137.13, 136.87, 136.30, 129.69, 129.15, 128.90, 128.72, 128.13, 127.57, 127.43, 127.23, 126.66, 55.17, 50.83, 38.35, 36.97, 33.28, 21.75. HR-MS (ESI): m/z calcd. for $C_{19}H_{19}ClN_3O$ $[M + H]^+$: 340.1216; found: 340.1224.

N-benzyl-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)benzamide (A16l). Colorless gum;

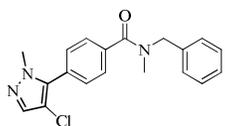


yield=70%. 1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H, CONH), 7.92 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.34 (d, $J = 4.4$ Hz, 4H, Ar-H), 7.32 - 7.26 (m, 1H,

Ar-H), 6.98 (t, $J = 5.1$ Hz, 1H, Ar-H), 4.64 (d, $J = 5.7$ Hz, 2H, CH_2), 3.77 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.68, 138.47, 138.00, 137.16, 134.90, 130.83,

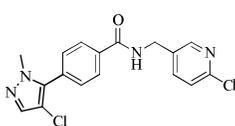
129.71, 128.70, 127.75, 127.56, 127.45, 109.06, 44.08, 38.29. HR-MS (ESI): m/z calcd. for $C_{18}H_{17}ClN_3O$ $[M + H]^+$: 326.1060; found: 326.1049.

N-benzyl-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-*N*-methylbenzamide (**A16m**).



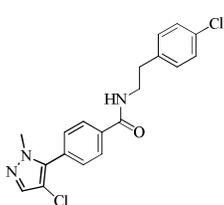
Colorless liquid; yield = 69%. 1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.54 - 7.42 (m, 3H, Ar-H), 7.42 - 7.33 (m, 3H, Ar-H), 7.33 - 7.30 (m, 1H, Ar-H), 7.21 (d, $J = 6.1$ Hz, 1H), 4.69 (d, $J = 105.0$ Hz, 2H, CH_2), 3.81 (s, 3H, CH_3), 3.01 (s, 3H, CO- NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.39, 170.70, 138.61, 137.14, 136.92, 136.30, 129.70, 129.16, 128.92, 128.73, 128.13, 127.60, 127.44, 127.23, 126.66, 108.96, 55.17, 50.84, 38.35, 36.98, 33.29. HR-MS (ESI): m/z calcd. for $C_{19}H_{19}ClN_3O$ $[M + H]^+$: 326.1060; found: 326.1049.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-*N*-((6-chloropyridin-3-yl)methyl)benzamide



(**A16n**). Colorless gum; yield = 77%. 1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, $J = 2.3$ Hz, 1H, CONH), 7.94 (s, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.70 (dd, $J = 8.2, 2.5$ Hz, 1H, Ar-H), 7.54 - 7.43 (m, 3H, Ar-H), 7.32 - 7.22 (m, 2H, Ar-H), 4.62 (d, $J = 6.0$ Hz, 2H, CH_2), 3.79 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.98, 150.43, 148.81, 138.64, 138.30, 137.13, 134.18, 133.05, 131.13, 129.74, 127.49, 124.25, 109.05, 40.69, 38.32. HR-MS (ESI): m/z calcd. for $C_{17}H_{15}Cl_2N_4O$ $[M + H]^+$: 361.0623; found: 361.0961.

4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-*N*-(4-chlorophenethyl)benzamide (**A16o**).



White solid; yield = 62%; m.p. = 164 - 166°C. 1H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H, CONH), 7.82 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 6.47 (s, 1H, Ar-H), 3.79 (s, 3H, CH_3), 3.71 (q, $J = 6.6$ Hz, 2H, CH_2), 2.93 (t, $J = 6.9$

Hz, 2H, CH₂). ¹³C NMR (125 MHz, CDCl₃) δ 166.80, 138.44, 137.22, 137.21, 135.04, 132.43, 130.89, 130.09, 129.79, 128.79, 127.26, 109.10, 41.13, 38.36, 34.98. HR-MS (ESI): m/z calcd. for C₁₉H₁₈Cl₂N₃O [M + H]⁺: 374.0827; found: 374.0817.

Homology Modeling. The target sequences of *Rhizoctonia solani* were retrieved from Swiss-Prot database (entry code: CUA71217, KEP51148, CUA73959.1).¹ The sequences were then subjected to template search using the BLAST. Thus, the crystal structure of SDH from porcine (entry code: 4YXD), avian (entry code: 1YQ3) and *Ascaris suum* SDH (entry code: 3VR8) were applied as templates. Homology modeling of RsSDH was carried out using MODELER. The “copy ligand” option was activated in order to transfer flutolanil and hemoglobin from template to the final homology models. Finally, the best model was chosen based on the DOPE score. The quality of the established model was evaluated by the Ramachandran plot approaches.² The derived model was further minimized employing the Generalized Born with a simple SWitching (GBSW) solvent model until a RMS gradient of 0.1 was satisfied.

References:

1. Gasteiger, E.; Gattiker, A.; Hoogland, C.; Ivanyi, I.; Appel, R. D.; Bairoch, A., ExPASy: the proteomics server for in-depth protein knowledge and analysis. *Nucleic Acids Research* **2003**, *31*, 3784-3788.
2. Parchansky, V.; Kapitan, J.; Kaminsky, J.; Sebestik, J.; Bour, P., Ramachandran Plot for Alanine Dipeptide as Determined from Raman Optical Activity. *Journal of Physical Chemistry Letters* **2013**, *4*, 2763-2768.