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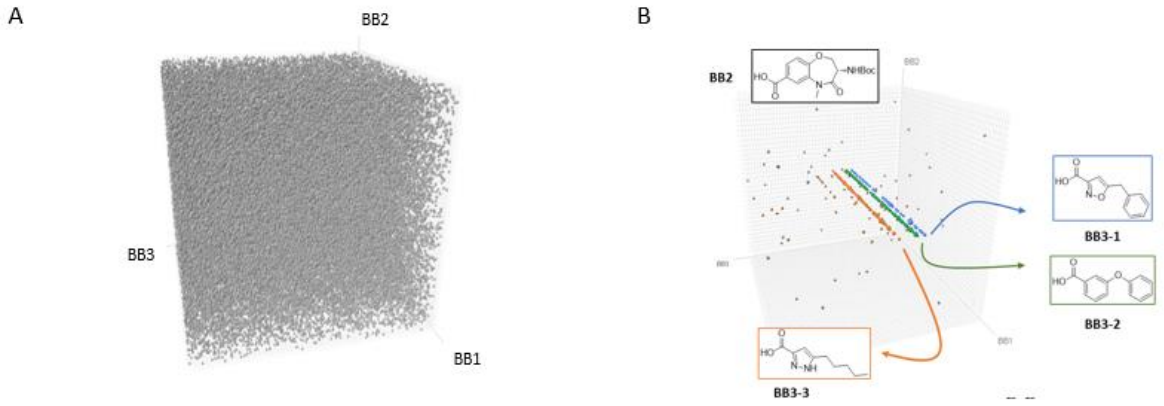
Supplementary information

DNA-encoded chemical libraries

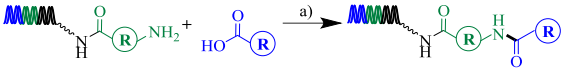
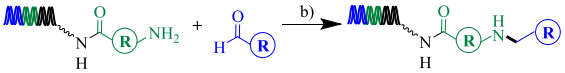
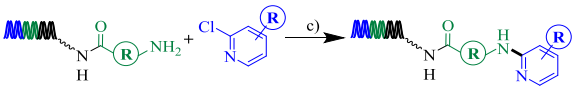
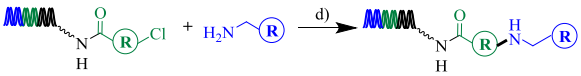
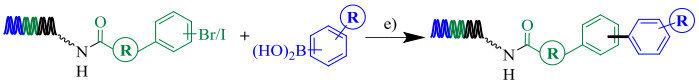
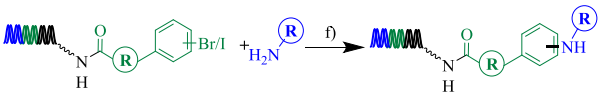
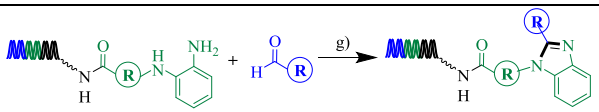
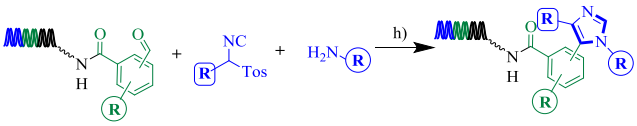
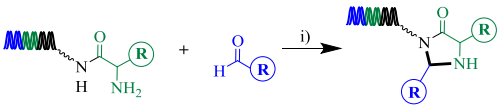
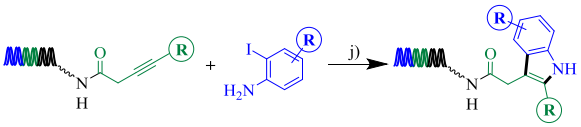
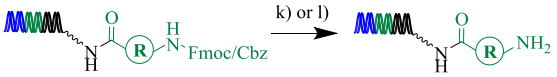
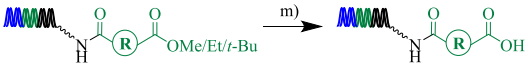
In the format provided by the authors and unedited

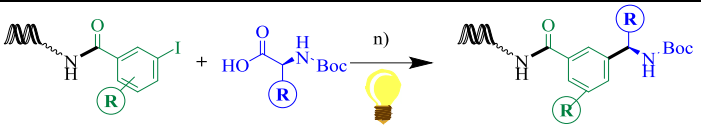
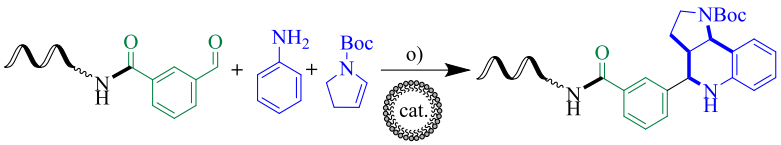
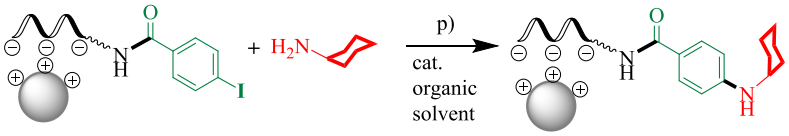
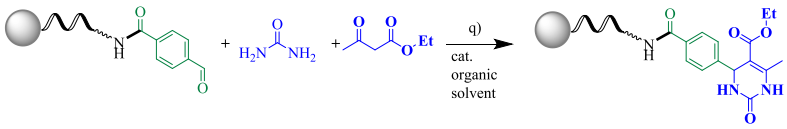


Supplementary Figure 1. Visualization of cube plot before and after removal of background signal and weakly enriched molecules.

(A) The visualized data prior to removal of library molecules with weak enrichment or enrichment against the no-target control selection. (B) The remaining visualized data, allowing for observation of potential ligand clusters.

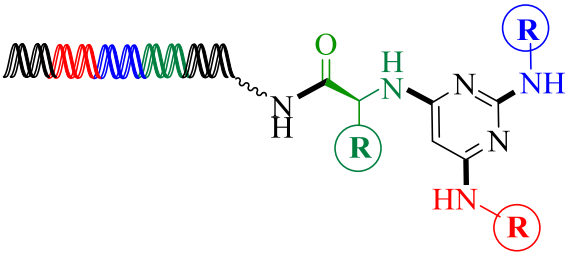
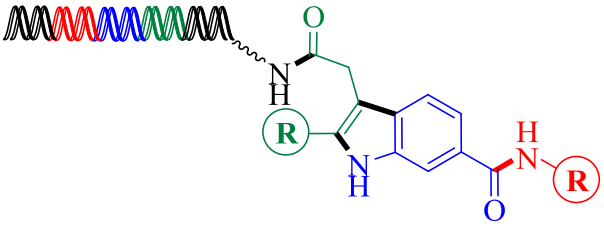
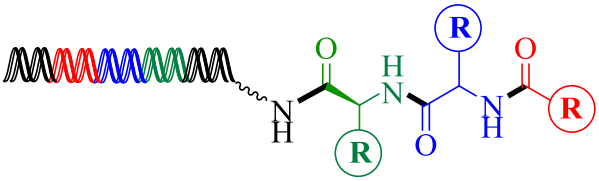
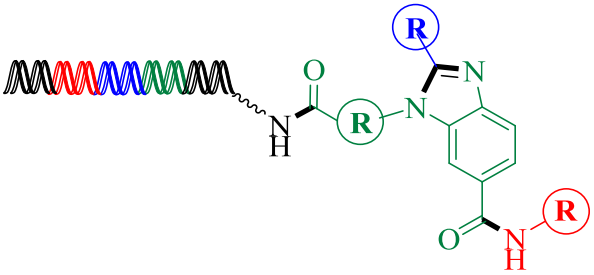
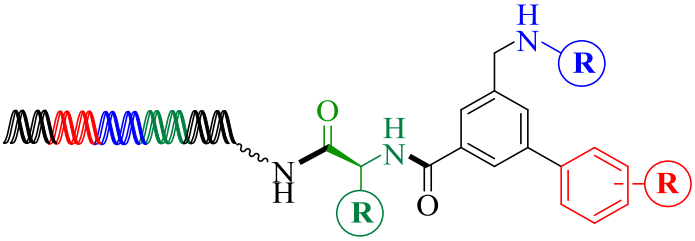
Supplementary Table 1. Exemplary reactions on DNA-encoded substrates

No	reaction	generic scheme	ref
coupling reactions			
1.	amide synthesis		1,2
2.	reductive amination		3
3.	S_nAR		1
4.	nucleophilic substitution		4
5.	Suzuki coupling		5
6.	Ullmann coupling		6
heterocyclic chemistries			
7.	benzimidazole synthesis		3,7
8.	van-Leusen reaction		8
9.	pyrazolidinone synthesis		3,9
10.	Larock indole synthesis		10
protective group chemistry			
11.	amines		1
12.	carboxylic acids		3,9

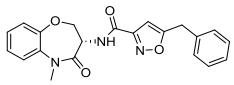
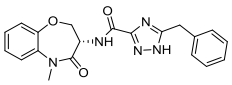
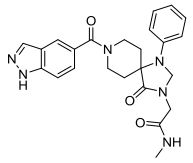
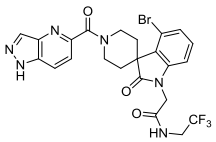
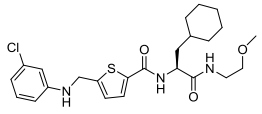
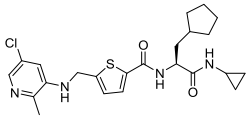
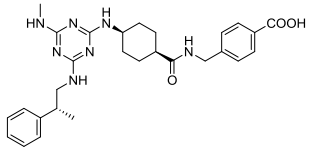
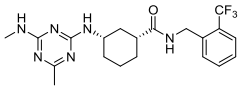
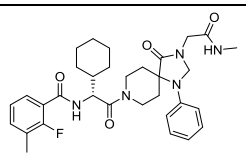
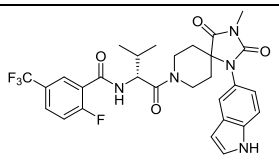
strategies for reaction scope expansion			
13.	photoredox chemistry		11
14.	micellar reactions		12
15.	on-resin reactions		13
16.	CPG solid phase		14

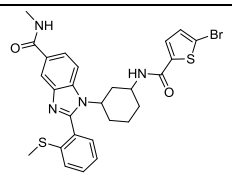
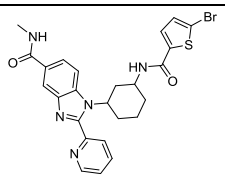
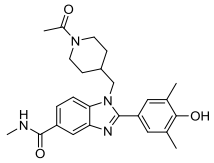
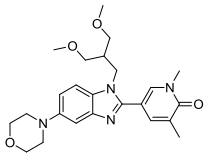
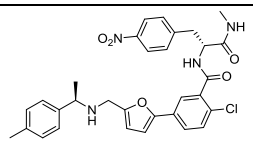
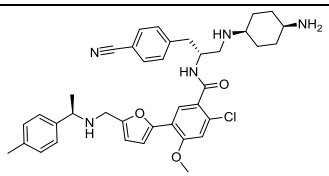
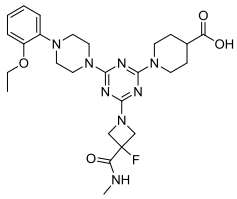
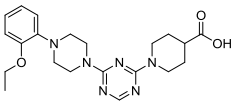
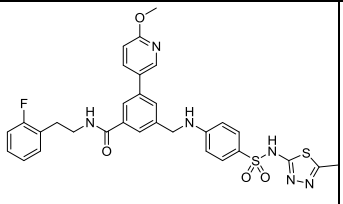
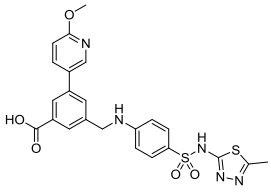
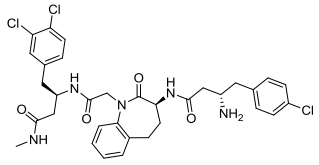
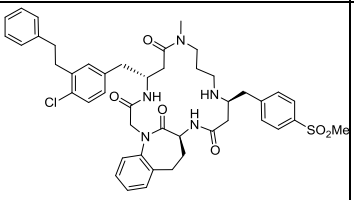
Reaction conditions: a) coupling reagents such as EDC, DM-MMT, HBTU; b) $NaCNBH_3$; c,d) no catalyst, heating in aqueous solution; e,j) Pd(0)/ligands; f) Cu(I)/ligands; g,h,i) no catalyst, heating in aqueous solution; k) piperidine in water (for Fmoc), $Pd/NaCNBH_3$ (for Cbz); m) dilute aqueous NaOH; n) Iridium catalyst; o) designer surfactant or copolymer catalyst; p) various reactions shown e.g. ; q) BINOL-phosphoric acid. CPG: controlled pore glass.

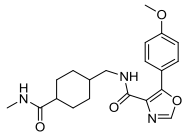
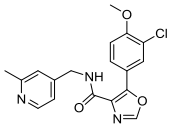
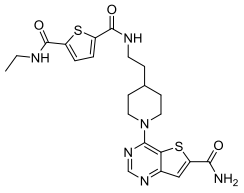
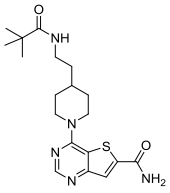
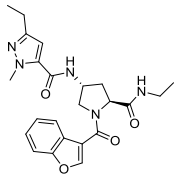
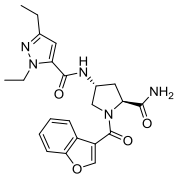
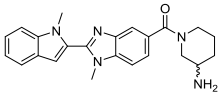
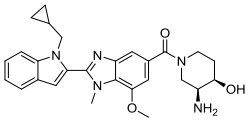
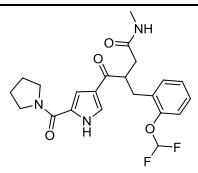
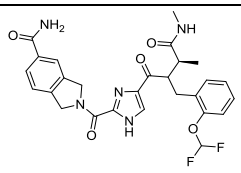
Supplementary Table 2. Exemplary library designs that led to validated bioactive compounds.

No	structure	DECL design	ref
1.	S_nAR-DECL		1
2.	indole-DECL		10
3.	capped triamide-DECL		15
4.	benzimidazole-DECL		16
5.	biaryl-DECL		17

Supplementary Table 3. Published examples of DECL hit molecules before and after medicinal chemistry optimization.

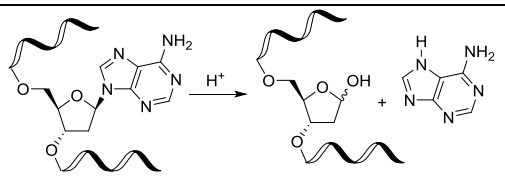
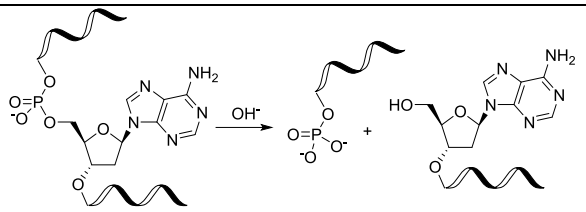
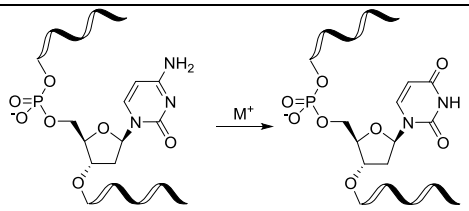
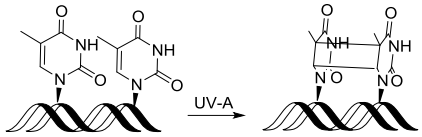
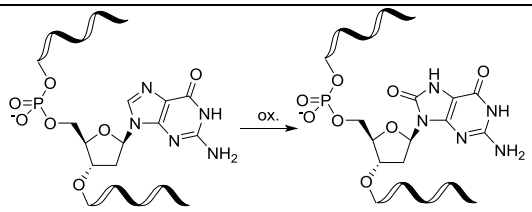
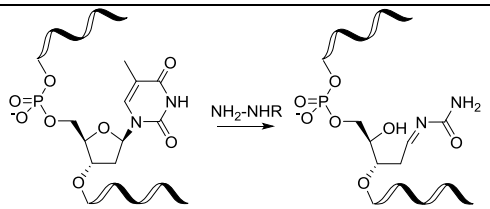
Target	DECL hit molecule		After Med Chem	
RIP1[18]		MW = 377.4 cLogP = 2.31 hba = 7 hbd = 1 rb = 4 tpsa = 84.7 aring = 3 IC50 = 1.6 nM		MW = 377.4 cLogP = 2.02 hba = 8 hbd = 2 rb = 4 tpsa = 100.2 aring = 3 IC50 = 1.0 nM
DDR1[19]		MW = 446.5 cLogP = 0.69 hba = 9 hbd = 2 rb = 5 tpsa = 101.6 aring = 3 IC50 = 1.5 μM		MW = 565.4 cLogP = 1.85 hba = 9 hbd = 2 rb = 5 tpsa = 111.3 aring = 3 IC50 = 0.029 μM
WIP1[20]		MW = 478.1 cLogP = 5.2 hba = 6 hbd = 3 rb = 11 tpsa = 79.5 aring = 2 IC50 = 13 nM		MW = 461.0 cLogP = 4.6 hba = 6 hbd = 3 rb = 9 tpsa = 83.1 aring = 2 IC50 = 6 nM
sEH[21]		MW = 517.6 cLogP = 2.33 hba = 10 hbd = 5 rb = 10 tpsa = 141.2 aring = 3 pIC50 = 8.1		MW = 422.4 cLogP = 4.12 hba = 7 hbd = 3 rb = 8 tpsa = 90.4 aring = 2 IC50 = 27 pM
ATX[22]		MW = 577.7 cLogP = 3.25 hba = 9 hbd = 2 rb = 8 tpsa = 102.1 aring = 2 IC50 = 86 nM		MW = 587.2 cLogP = 3.38 hba = 9 hbd = 2 rb = 8 tpsa = 85.0 aring = 3 IC50 = 55 nM

BCATm[2] 3		MW = 583.6 cLogP = 5.96 hba = 6 hbd = 2 rb = 6 tpsa = 76.0 aring = 4 pIC50 6.6		MW = 538.5 cLogP = 4.50 hba = 7 hbd = 2 rb = 5 tpsa = 88.9 aring = 4 pIC50 7.3
BRD4[24]		MW = 434.5 cLogP = 3.02 hba = 7 hbd = 2 rb = 5 tpsa = 87.5 aring = 3 pIC50 = 6.6		MW = 440.5 cLogP = 1.89 hba = 8 hbd = 0 rb = 8 tpsa = 70.8 aring = 3 pIC50 = 7.9
ATAD2[2] 5		MW = 575.1 cLogP = 5.55 hba = 9 hbd = 3 rb = 10 tpsa = 126.5 aring = 4 IC50 not reported		MW = 654.3 cLogP = 6.20 hba = 8 hbd = 4 rb = 13 tpsa = 125.3 aring = 4 IC50 = 166 nM
OXA- 48[26]		MW = 542.6 cLogP = 1.26 hba = 12 hbd = 2 rb = 7 tpsa = 127.3 aring = 2 Ki = 0.9 μM		MW = 412.5 cLogP = 1.81 hba = 9 hbd = 1 rb = 5 tpsa = 94.9 aring = 2 Ki = 0.53 μM
PI3Ka[17]		MW = 632.7 cLogP = 4.34 hba = 10 hbd = 3 rb = 10 tpsa = 135.2 aring = 5 IC50 6.5 nM		MW = 511.6 cLogP = 2.56 hba = 10 hbd = 3 rb = 6 tpsa = 143.4 aring = 4 IC50 10 nM
Mcl-1[27]		MW = 673.0 cLogP = 3.96 hba = 9 hbd = 4 rb = 12 tpsa = 133.6 aring = 3 IC50 = 2 μM		MW = 826.5 cLogP = 4.68 hba = 11 hbd = 3 rb = 8 tpsa = 145.0 aring = 4 IC50 < 3 nM

GSK-3b[28]		MW = 371.4 cLogP = 1.54 hba = 7 hbd = 2 rb = 5 tpsa = 93.5 aring = 2 pIC50 = 6.5		MW = 357.8 cLogP = 2.03 hba = 6 hbd = 1 rb = 5 tpsa = 77.3 aring = 3 pIC50 = 7.5
SIRT1[29]		MW = 486.6 cLogP = 1.92 hba = 9 hbd = 3 rb = 8 tpsa = 129 aring = 3 IC50 = 3.6 nM		MW = 389.5 cLogP = 2.65 hba = 7 hbd = 2 rb = 5 tpsa = 101.2 aring = 2 IC50 = 15 nM
InhA[30]		MW = 437.5 cLogP = 1.64 hba = 9 hbd = 2 rb = 7 tpsa = 109.5 aring = 3 IC50 = 34 nM		MW = 423.5 cLogP = 1.4 hba = 9 hbd = 2 rb = 7 tpsa = 123.5 aring = 3 IC50 = 4 nM
PAD4[31]		MW = 387.5 cLogP = 2.72 hba = 6 hbd = 1 rb = 3 tpsa = 69.1 aring = 4 IC50 = 3.2 μM		MW = 473.6 cLogP = 2.19 hba = 8 hbd = 2 rb = 6 tpsa = 98.5 aring = 4 IC50 = 50 nM
TAK1[32]		MW = 433.5 cLogP = 2.37 hba = 7 hbd = 2 rb = 10 tpsa = 91.5 aring = 2 IC50 = 1.3 μM		MW = 539.5 cLogP = 2.48 hba = 10 hbd = 3 rb = 11 tpsa = 147.5 aring = 3 IC50 = 2 nM

MW = molecular weight (g/mol)
cLogP = calculated logarithm of its partition coefficient between n-octanol and water
hba = number hydrogen bond acceptors
hbd = number hydrogen bond doners
rb = number rotatable bonds
tpsa = topological polar surface area (angstroms squared)
aring = number aromatic rings
IC50 = Half-maximal inhibitory concentration

Supplementary Table 4. DNA damage reactions that limit the reaction scope for DECL design

No	type	reaction	reaction conditions/reagents
1.	depurination		pH < 4, Lewis/Brønsted acids and heat
2.	fragmentation		pH > 14 and heat
3.	deamination[a]		metal ions, heating
4.	2+2 cycloaddition[b]		irradiation
5.	oxopurine formation		oxidants, radicals
6.	nucleophile addition		hydrazines, hydroxylamines

[a] Cytosine most susceptible, but purines may deaminate, too; [b] at wavelengths of ca 260 nm, catalysts may facilitate cycloaddition at higher wavelengths (see literature on photodynamic therapy)

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