Tankyrase 1 Inhibitors with Drug-like Properties Identified by Screening a DNA-encoded Chemical Library

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ABSTRACT: We describe the design, synthesis and screening of a DNA-encoded chemical library (DECL) containing 76,230 distinct compounds. In this library design, sets of amine and carboxylic acid building blocks are directly linked producing the encoded compounds, which have compact structures as well as drug-like properties. Affinity-screening of this library yielded potent inhibitors of the potential pharmaceutical target tankyrase 1, a poly (ADP-ribose) polymerase (PARP). These compounds have drug-like characteristics and the most potent hit compound (X066/Y469) inhibited tankyrase 1 (TNKS1) with an IC_{50} value of 250 nM.

The development of novel drugs typically relies on the identification of molecules capable of selective binding to protein targets of interest, followed by structural optimization using medicinal chemistry methods. A widely used approach for hit discovery includes the screening of large sets of individual compounds one at a time using high-throughput technologies, which can be expensive, time-consuming and require complex logistics. In recent years, DNA-encoded chemical libraries (DECL) have emerged as alternative tools for drug-discovery, allowing for the screening of large compound libraries with an unprecedented level of speed and cost-efficiency.[1] Compounds in DECLs consist of building blocks serving as diversity elements (DE), which are assembled in a combinatorial fashion. Each compound is encoded by a conjugated DNA sequence, acting as an identification barcode.[2] DECL technology has yielded binders to diverse target proteins[2a,3] and is increasingly being used in drug discovery endeavors in industry and academia for the identification of hit compounds.[4]

Large DECLs have been constructed by incorporating three or more DEs for the synthesis of library members. This procedure, however, often results in molecules with a molecular weight >500 Da, while hit compounds for pharmaceutical development should preferentially fulfill the requirements of Lipinski's Rule of 5[5] in order to be orally available and, if possible, be smaller than 400 Da.[6] For this reason, there is a growing interest in developing encoded libraries of structurally-compact compounds with drug-like properties.[7]

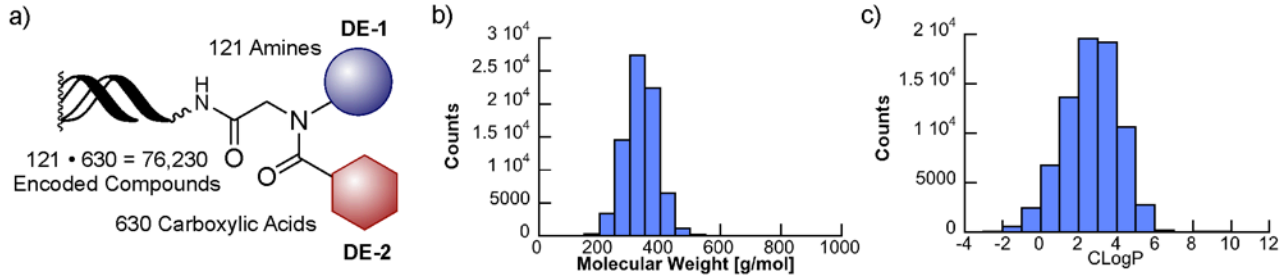

Figure 1. Structure and histogram analysis of selected properties of the DNA-encoded chemical library. a) Library design (DE: diversity element). Distribution of b) molecular weight and c) CLogP values of the encoded compounds.

Table 1. Chemical Properties of the Encoded Compounds.[a,b]

	Mean	Median	Threshold criteria[c]	Compliance[d]
MW [g/mol]	340	339	≤500	>99%
ClogP	2.7	2.8	≤5	96%
HA	2.9	3	≤10	100%
HD	1.5	1	≤5	>99%
PSA [Å^2]	63	60	≤140	>99%
RB	7.0	7	≤10	96%

a) MW: molecular weight; HA: number of hydrogen bond acceptors; HD: number of hydrogen bond donors; PSA: topological polar surface area; RB: rotatable bonds. b) Values were calculated for compounds assembled *in silico* by direct linkage of amine and carboxylic acid building blocks. c) Threshold criteria for drug-likeness.[5,8] d) Compliance: percentage of compounds in agreement with listed threshold criteria of drug likeness.

We here report on the design and synthesis of a novel DECL, based on the direct coupling of amine (DE-1) and carboxylic acid (DE-2) building blocks (Figure 1a). In our compound nomenclature, DE-1 and DE-2 are indicated by the letters X and Y, respectively. Directly connecting the DEs without the use of a scaffolding element produced very compact structures (>99% have a MW ≤500 Da; 89% have MW ≤400 Da) with drug-like properties (Figure 1 and Table 1).

The presented DECL library contains 76,230 encoded compounds consisting of 121 amines paired with 630 carboxylic acids, which were connected to individual DNA sequences by an acetamide linker (Figure 1a). The building blocks used were structurally diverse and generally adhered to the Rule of 3 for drug fragments.[9] *In silico* analysis of library members indicated that 96% of the molecules had a ClogP <5 (mean = 2.7) and that >95% of the encoded compounds fulfilled all four criteria for drug-likeness according to Lipinski's rule of 5.[5] 92% of all compounds had ≤10 rotatable bonds and a polar surface area of ≤140 Å^2 in addition to be compliant with the criteria of Lipinski's rule of 5 (Table 1 and Figure S3 in the Supporting Information).[8]

Synthesis of the compounds on DNA was achieved by a two-step split-and-pool protocol (Figure S2 in the SI). In a first step, amino-modified oligonucleotides attached to the solid support used for DNA synthesis were derivatized with chloroacetic acid, followed by the introduction of the amine building blocks by an S_N2-reaction.[10] The modified oligonucleotides were cleaved from the solid support, purified by HPLC and characterized by LC-MS. The conjugates were combined and split into separate reaction vessels for the attachment of the carboxylic acid building blocks via amide bond formation.[10,11] Each carboxylic acid building block was encoded using a protocol that was previously described (Figures S1 and S2 in SI)[3c,12] and combining the conjugates provided the final DECL.

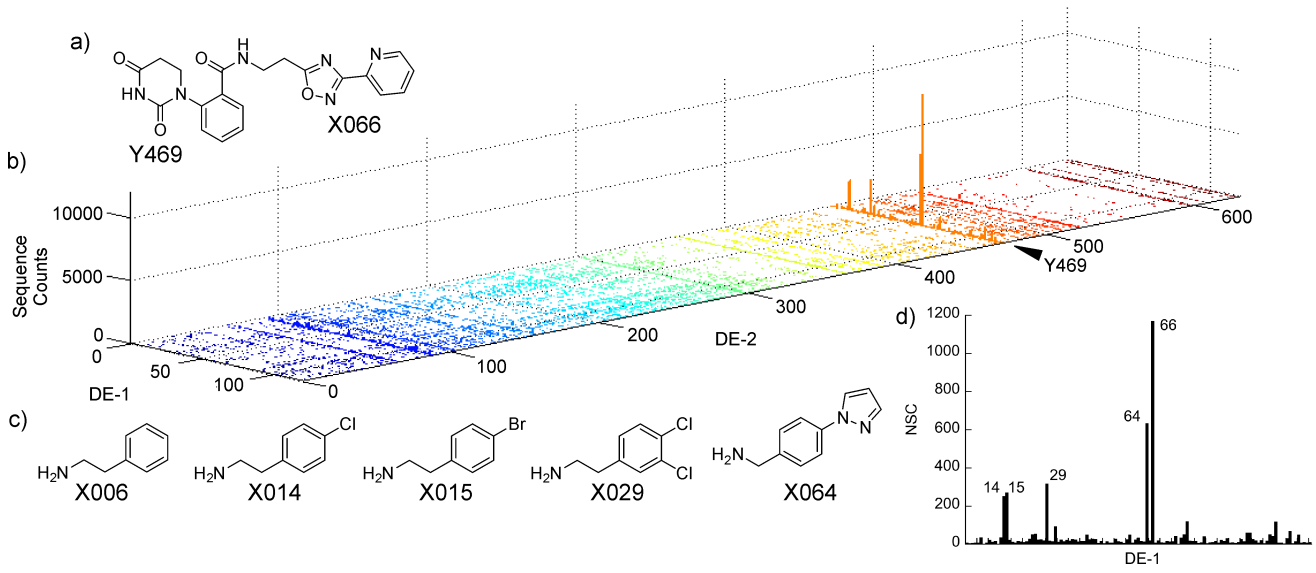

Figure 2. Identification of hit compounds for tankyrase 1 (TNKS1) from screening a DNA-encoded chemical library (DECL). a) Chemical structure of the most highly enriched hit compound X066/Y469. b) Affinity screening results for TNKS1. Each peak corresponds to an encoded compound identified by the building blocks in the x/y plane; the z-value corresponds to the number of obtained sequences. c) Structures of selected amines at DE-1 enriched in combination with Y469. d) Sequence enrichment of compounds with a conserved Y469 building block at DE-2 (NSC: normalized sequence counts).

Table 2. Chemical Properties and Potency of Enzyme Inhibition of Selected Compounds[a]

Compound	X066/Y469	X064/Y469	X029/Y469	X015/Y469	X014/Y469	X006/Y469	X064-Me/Y469
MW [g/mol]	406.4	389.4	406.3	416.3	371.8	377.4	403.4
ClogP	-1.34	0.55	2.06	1.49	1.34	0.63	0.52
PSA [Å^2]	124.8	94.1	78.5	78.5	78.5	78.5	85.3
RB	6	5	5	5	5	5	5
NSC	1167	633	315	269	251	33	-
log IC_{50} TNKS1 [μM]	6.61 ± 0.07 (0.25 μM)	6.48 ± 0.06 (0.33 μM)	6.17 ± 0.16 (0.7 μM)	6.46 ± 0.09 (0.35 μM)	6.24 ± 0.08 (0.57 μM)	5.33 ± 0.08 (4.6 μM)	5.61 ± 0.08 (2.5 μM)

[a] Dose-response curves are shown in Figure 3a and Figure S5 in the Supporting Information and all chemical structures are shown in Figure S5 in the SI.

The libraries were screened using a previously reported affinity-selection protocol.[7b] The biotinylated target proteins were immobilized on streptavidin-coated magnetic beads and incubated with the DECL. Conjugates with low target affinity could be washed away whereas affinity binders were retained on the solid support and could be identified by PCR amplification and high-throughput sequencing of the DNA barcodes.

We first tested the library by screening it against streptavidin and carbonic anhydrase IX, which were used as model target proteins as we have described previously (Figure S4).[3c,7b] Compounds containing Y087 (desthiobiotin) were considerably enriched in the streptavidin experiment (Figure S4b), which is in agreement with the high affinity of this protein-ligand pair. In the carbonic anhydrase IX selection (Figure S4c), four series of compounds containing aromatic sulfonamides at either the DE-1 or the DE-2 position (X032, Y138, Y157 and Y164) were enriched. The identification of ligands with previously known structural features for both proteins provided evidence for the quality of library synthesis and encoding.

We next turned our attention to tankyrase 1 (TNKS1; also known as PARP5a or ARTD5), a target of pharmaceutical interest. TNKS1 is a poly (ADP-ribose) polymerase (PARP) enzyme, which catalyzes the modification of proteins with poly (ADP-ribose) chains using NAD$^+$ as a cofactor. TNKS1 is a potential drug target[13] because it has been shown to be involved in the control of telomere maintenance[14] and was identified as a druggable element of the Wnt signaling pathway.[15] Several TNKS1 inhibitors have recently been described[16] and reports demonstrated that TNKS1 inhibitors can suppress tumor growth in animal models.[17]

Affinity-screening of the DECL for TNKS1 binders provided a series of structurally related compounds with highly enriched sequence counts (Figure 2). All compounds contained the carboxylic acid Y469 at DE-2, combined with different amines at DE-1, all of which featured aromatic groups in their structures (Figure 2). The same fragment (Y469) has recently been found independently by screening a different DECL for TNKS1.[7b] The identification of this fragment from two independent libraries emphasizes the potential of this structural element for the development of PARP inhibitors. There are no reports of PARP inhibitors identified by conventional screening techniques or the development of PARP inhibitors containing this fragment. In accordance with the library design, all compounds displayed drug-like properties. The most highly enriched compounds were all in agreement with Lipinski's rule of 5 and in particular had molecular masses <500 Da and ClogP values <5 (Table 2). Furthermore, these compounds also had polar surface areas of <140 Å^2 and ≤10 rotatable bonds.

Subsequently, we synthesized several hit compounds by amide bond formation between Y469 and the corresponding amines, omitting the acetamido moiety used for DNA-conjugation. We measured compound activity in an *in vitro* PARylation assay, using the catalytic domain of TNKS1.[18] All resynthesized compounds were found to be potent inhibitors of TNKS1, with IC_{50} values in the high nanomolar range (Table 2 and Figure S5). X066/Y469 was the most potent inhibitor, with an IC_{50} value of 250 nM (Figure 3a) followed by X064/Y469 with an IC_{50} value of 330 nM. Several 4-halogenated 2-phenylethylamines were strongly enriched and had nanomolar IC_{50} values (X015, 350 nM; X029, 700 nM; X014, 570 nM) in contrast to the moderately enriched control compound 2-phenylethyamine (X006/Y469), which had an IC_{50} value of 4.6 μM. These experimental results thus confirmed the predicted importance of the 4-halogen substituent for TNKS1 inhibition and illustrated the potential of DECL screening results to reveal structural features important for activity, in agreement with previous reports.[7b,19] In general, the inhibitory potencies of the enriched compounds roughly correlated with the sequence counts obtained in the screening experiment (Figure 3b), indicating that enrichment factors for individual library members may provide preliminary structure-activity information.[7b] To elucidate the contribution of the substituent on the nitrogen atom of the amide bond, we prepared and tested a N-methyl derivative of X064/Y469 (X064-Me/Y469), which is present as a mixture of cis/trans isomers, as confirmed by NMR analysis (Figure S16), in contrast to the conformationally-constrained primary amides. X064-Me/Y469 was a less potent inhibitor of TNKS1 with an IC_{50} value of 2.5 μM.

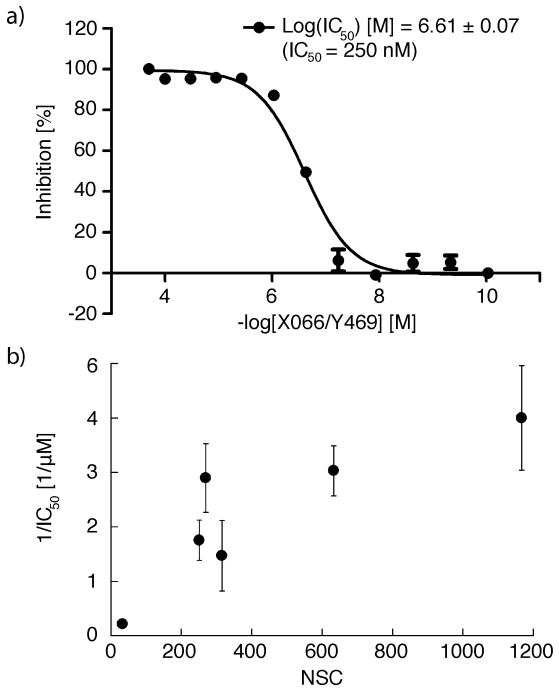

Figure 3. Inhibition of TNKS1 by identified hit compounds. a) Enzymatic inhibition data for X066/Y469. b) Scatter plot of normalized sequence counts[20] and enzymatic IC_{50} values.

In conclusion, a novel DECL was synthesized, containing 76,230 diverse and structurally compact compounds. Affinity-screening directly yielded nanomolar inhibitors of TNKS1, with drug-like properties and MW <410 Da. These results suggest that encoded libraries, based on two sets of small building blocks, may be useful for hit discovery applications, including family-wide approaches.[20-21]

EXPERIMENTAL SECTION

Library synthesis. The 121 amines at DE-1 were introduced on 5'-amino-modified DNA (Amino-modifier C12, Glen Research) on controlled pore glass (CPG) in a DNA-synthesis cartridge using a vacuum manifold. The amine-deprotected DNAs were incubated with a solution of chloroacetic acid (50 mM), HATU (50 mM) and DIPEA (150 mM) in DMF (0.5 mL) at room temperature for 2 h. The CPG was washed with DMF, MeCN, and DMSO (each 2 ×). A solution of the primary amine (1 M) in DMSO (1 mL) was added to the cartridge and allowed to react for 16 h. The CPGs were washed with DMSO, and MeCN (2 ×). The DNA-conjugate was cleaved from the CPG by incubating with conc. NH_3/$MeNH_2$ (0.5 mL; AMA) solution for twice 10 min and filtrated. The residual reaction solution was collected, incubated for 3 h, and concentrated under reduced pressure. The residue was dissolved in H_2O (200 μL) and the conjugate purified by HPLC. Product-containing fractions were collected, dried under reduced pressure and redissolved in H_2O (100 μL) and characterized by LC-ESI-MS.

Equimolar amounts of the 121 DNA-amine conjugates were combined and derivatized at DE-2 according to a modified literature protocol.[10,11] The combined conjugates (0.12 nmol) were immobilized on DEAE sepharose (0.1 mL of slurry). The resin was washed with 10 mM aq. AcOH (2 × 0.5 mL), H_2O (2 × 0.5 mL) and DMSO (2 × 0.5 mL). To the resin-immobilized DNA was added a solution of the corresponding carboxylic acid (50 mM), EDC (50 mM) and HOAt (5 mM) in DMSO (0.5 mL) and let react. The solution was removed and the resin washed with DMSO (1 × 0.5 mL) and treated with freshly activated reaction solution. These steps were repeated to reach three coupling steps of 2 × 2 h and 14 h reaction time. The reaction solution was removed and the resin washed with DMSO (2 × 0.5 mL) and 10 mM aq. AcOH (3 × 0.5 mL). The DNA was eluted from the resin by incubation with 3 M AcOH buffer (pH 4.75) for 5 min. The DNA-conjugates were isolated by ethanol-precipitation and the pellets redissolved in deionized water (50 μL). The conjugates were combined at equimolar quantities to provide the final DECL.

DECL affinity screening. Streptavidin-coated magnetic beads (40 pmol) were suspended in buffer (100 μL; 20 mM HEPES, 300 mM NaCl, 0.5 mM TCEP, 0.25 % Tween-20 pH 7.5 for TNKS1; 100 mM NaCl, 50 mM NaPi, 0.25 % Tween-20, pH 7.4 for streptavidin and carbonic anhydrase IX). Using a KingFisher magnetic particle processor, the magnetic beads were transferred to a solution of biotinylated proteins (40 pmol in 100 μL) and incubated for 20 min with continuous gentle mixing. Free streptavidin binding sites were blocked with biotin-containing buffer (3 × 100 μM) and the beads transferred to a solution of the DECL (5 nM total concentration in 100 μL) in buffer and the suspension incubated for 1 h with continuous gentle mixing. The beads were washed with buffer (5 × 30 s) and incubated with elution buffer (Buffer EB; Qiagen). DNA conjugates were released by heat denaturation of the proteins (96 °C for 5 min).

The coding DNA of oligonucleotide conjugates was amplified by PCR after selection experiments and submitted to the Functional Genomics Center Zurich for high-throughput DNA sequencing on an Illumina HiSeq 2000/2500.

Compound Synthesis. To a solution of Y469 (1.0 eq.) in anhyd. DMF (2.5 mL/mmol of Y469) was added EDC · HCl (1.0 eq) and N-Hydroxysuccinimide (1.0 eq.) and the mixture was stirred at room temperature for 2 h. A solution of the amine (1.1 eq.) and DIPEA (1.1 eq.) in DMF (2.5 mL/mmol of acid) was added to the activated carboxylic acid and the reaction mixture stirred overnight at room temperature. The DMF solution (slightly heated if product precipitated) was added drop by drop to stirred aq. citric acid (0.2 M; 45 mL/mmol of Y469) followed by cooling to 0 °C for 4 h. The precipitate was collected by filtration, the residue co-evaporated with DCE and dried under high-vacuum. The products were obtained in good purity (>95%); all compounds were further purified by recrystallization prior to performing enzymatic assays.

X066/Y469 (2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-N-(2-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)benzamide). Yield 84% (yield after recrystallization from CHCl/EtOH 47%). ^{1}H-NMR (400 MHz, DMSO-d6): 11.55 ppm (1 H, s), 8.73-8.75 ppm (1 H, m),

8.29-8.32 ppm (1 H, m), 7.97-8.08 ppm (3 H, m) 7.72 ppm (1 H, m), 7.59 ppm (1 H, m), 7.43 ppm (1 H, d, J = 8.5 Hz), 7.25 ppm (1 H, dd, $J_1 = J_2$ = 7.4 Hz), 4.23 ppm (2 H, t, J = 7.3 Hz), 3.51 ppm (2 H, m), 3.12 ppm (2 H, t, J = 6.8 Hz), 2.44 ppm (1 H, t, J = 7.4 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 178.66, 170.05, 167.55, 161.73, 150.23, 149.96, 145.79, 140.68, 137.63, 135.20, 127.59, 125.98, 123.26, 122.42, 115.74, 114.39, 38.94, 35.85, 33.25, 26.39 ppm. HRMS (MALDI) [M + H] calcd. 505.2082 m/z, found 505.2080 m/z.

X064/Y469 (N-(4-(1H-pyrazol-1-yl)benzyl)-2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamide). Yield after recrystallization from $CHCl_3$/EtOH 53 %. ^{1}H-NMR (400 MHz, DMSO-d6): 11.58 ppm (1 H, s), 8.59 ppm (1 H, t, J = 5.8 Hz), 8.46 ppm (1 H, d, J =2.52 Hz), 8.00 ppm (1 H, dd, J = 7.84 Hz, J = 1.64 Hz), 7.67-7.75 ppm (4 H, m), 7.49 ppm (1 H, d, J = 8.48 Hz), 7.40 ppm (1 H, t, J =7.84 Hz), 7.25 ppm (1 H, t, J = 7.48 ppm), 7.13 ppm (1 H, d, J = 7.64 Hz), 6.54 ppm (1 H, dd, J = 2.44, J = 1.76 Hz), 4.27-4.33 ppm (4 H, m), 2.55 ppm (2 H, t, J = 7.42 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 169.80, 161.79, 150.02, 140.90, 140.76, 139.71, 135.26, 129.44, 127.67, 127.60, 125.00, 122.46, 117.41, 116.79, 115.76, 114.57, 107.82, 42.04, 39.02, 33.31 ppm. HRMS (MALDI) [M + H] calcd. 390.1561 m/z; found 390.1560 m/z.

X029/Y469 (N-(2,4-dichlorophenethyl)-2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamide). Yield 84% (yield after recrystallization from $CHCl_3$/EtOH 47%). ^{1}H-NMR (400 MHz, DMSO-d6): 11.58 ppm (1 H, s), 8.12 ppm (1 H, t, J = 5.7 Hz), 8.01 ppm (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 7.72-7.78 ppm (1 H, m), 7.57 ppm (1 H, d, J = 2.2 Hz), 7.44 ppm (1 H, d, J = 8.5 Hz), 7.33 ppm (1 H, dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 7.24-7.29 ppm (2 H, m), 4.22 ppm (2 H, t, J = 7.42 Hz), 3.25 ppm (2 H, m), 2.76 ppm (2 H, t, J = 7.0 Hz), 2.41 ppm (2 H, t, J = 7.38 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 169.69, 161.78, 149.98, 140.74, 135.96, 135.24, 134.04, 132.34, 131.69, 128.60, 127.61, 127.25, 122.47, 115.75, 114.49, 38.99, 38.08, 33.34, 32.19. Elemental analysis: calcd. % C, 56.17; H, 4.22; N, 10.34; found % C, 56.02; H, 4.17; N, 10.31.

X015/Y469 (N-(4-bromophenethyl)-2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamide). Yield 84% (yield after recrystallization from $CHCl_3$, 20% EtOH and Et_2O 62%). ^{1}H-NMR (400 MHz, DMSO-d6): 11.56 ppm (1 H, s), 8.07 ppm (1 H, t, J = 5.5 Hz), 8.00 ppm (1 H, d, J = 7.8 Hz), 7.74 ppm (1 H, dd, $J_1 = J_2$ = 7.8 Hz), 7.41-7.45 ppm (3 H, m), 7.25 ppm (1 H, dd, $J_1 = J_2$ = 7.5 Hz), 7.09 ppm (2 H, d, J = 8.3 Hz), 4.21 ppm (2 H, t, J = 7.3 Hz), 3.18-3.23 ppm (2 H, m), 2.59 ppm (2 H, t, J = 7.1 Hz), 2.41 ppm (2 H, t, J = 7.3 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 169.64, 161.78, 149.98, 140.76, 138.91, 135.23, 131.07, 130.91, 127.60, 122.46, 119.15, 115.75, 114.54, 39.87, 39.04, 34.24, 33.38 ppm. Elemental analysis: calcd. % C, 54.82; H, 4.36; N, 10.09; found % C, 54.98; H, 4.30; N, 10.10.

X014/Y469 (N-(4-chlorophenethyl)-2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamide). Yield 86% (yield after recrystallization from $CHCl_3$, 20% EtOH and Et_2O 67%). ^{1}H-NMR (400 MHz, DMSO-d6): 11.56 ppm (1 H, s), 8.07 ppm (1 H, t, J = 5.5 Hz), 8.00 ppm (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.74 ppm (1 H, dt, J_1 = 7.9, J_2 = 1.6 Hz), 7.44 ppm (1 H, d, J = 8.5 Hz), 7.29 ppm (2 H, d, J = 8.4 Hz), 7.25 ppm (1 H, t, J = 7.5 Hz), 7.15 ppm (2 H, d, J = 8.4 Hz), 4.21 ppm (2 H, t, J = 7.3 Hz), 3.18-3.24 ppm (2 H, m), 2.61 ppm (2 H, t, J = 7.1 Hz), 2.41 ppm (2 H, t, J = 7.3 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 169.64, 161.78, 149.98, 140.76, 138.48, 135.23, 130.69, 130.49, 128.15, 127.60, 122.46, 115.75, 114.54, 39.93, 39.04, 34.18, 33.38 ppm. Elemental Analysis: calcd. % C, 61.38; H, 4.88; N, 11.30; found: C, 61.52; H, 4.79; N, 11.27.

X009/Y469 (2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-N-phenethylbenzamide). Yield 91% (yield after further recrystallization from $CHCl_3$, 20% EtOH and Et_2O 58%). H-NMR (400 MHz, DMSO-d6): 11.56 ppm (1 H, s), 8.10 ppm (1 H, t, J = 5.5 Hz), 8.00 ppm (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.74 ppm (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.45 ppm (1 H, d, J = 8.5 Hz), 7.23-7.28 ppm (3 H, m), 7.12-7.19 ppm (3 H, m), 4.21 ppm (2 H, t, J = 7.4 Hz), 3.19 – 3.25 ppm (2 H, m), 2.62 ppm (2 H, t, J = 7.4 Hz), 2.42 ppm (2 H, t, J = 7,3 Hz). ^{13}C-NMR (100 MHz, DMSO-d6): 169.58, 161.79, 149.98, 140.77, 139.42, 135.23, 128.57, 128.26, 127.59, 126.04, 122.45, 115.76, 114.54, 40.20, 39.06, 34.97, 33.40 ppm. Elemental Analysis: calcd. % C, 67.64; H, 5.68; N, 12.45; found: C, 67.79; H, 5.61; N, 12.57.

X064-Me/Y469 (N-(4-(1H-pyrazol-1-yl)benzyl)-2-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-N-methylbenzamide). Yield 71 % (recrystalized from MeCN/H_2O). In the ^{1}H- and ^{13}C-NMR-spectra the product appeared as a mixture of two isomers in a ratio of approx. 2:1, likely corresponding to the cis/trans isomers of the amide bond. ^{1}H-NMR (400 MHz, DMSO-d6): 11.60 and 11.55 ppm (1 H, 2 s), 8.46-8.47 ppm (1 H, m), 8.00-8.03 ppm (1 H, m), 7.75-7.85 ppm (4 H, m), 7.20-7.54 ppm (4 H, m), 6.53-6.55 ppm (1 H, m), 4.58 and 4.55 ppm (2 H, 2 s), 4.27-4.33 ppm (2 H, m), 2.90 and 2.85 ppm (3 H, 2 s), 2.27-2.81 ppm (2 H, m). ^{13}C-NMR (100 MHz, DMSO-d6): 170.15, 170.11, 161.78, 161.74, 150.02, 149.97, 140.91, 140.84, 140.77, 140.68, 138.84, 138.72 138.84, 135.61, 135.43, 135.31, 135.10, 128.74, 127.69, 127.64, 127.58, 122.47, 122.40, 118.47, 118.64, 115.73, 114.61, 114.38, 107.80, 107.74, 51.72, 49.30, 38.62, 34.51, 33.26, 30.36, 30.03 ppm. Elemental Analysis: calcd. % C, 65.50; H, 5.25; N, 17.36. Found: C, 65.31; H, 5.15; N, 17.56.

ASSOCIATED CONTENT

Supporting information includes general information and detailed experimental procedures, synthetic protocols and supplementary figures S1-S5. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no financial conflict of interest.

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ABBREVIATIONS

DECL, DNA-encoded chemical library; DE, diversity element; TNKS1, tankyrase 1; NSC, normalized sequence count; CPG, controlled pore glass; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOAt, 1-hydroxybenzotriazole; HATU, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; DIPEA, *N,N*-diisopropylaminoethylamine; TCEP, tris-(carboxyethyl)phosphine; HEPES, 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid; PCR, polymerase chain reaction.

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