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Progress with YAP/TAZ-TEAD inhibitors: a patent review (2018-present)

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Abstract

Introduction: The Hippo pathway represents a new opportunity for the treatment of cancer. Overexpression of Yes-associated protein (YAP) or transcriptional coactivator with PDZ-binding motif (TAZ) or TEAD has been demonstrated in cancers and YAP mediates resistance to cancer drugs. Since 2018, the potential of this pathway has been illustrated by numerous articles and patents and the first drugs entering in clinical trial phase 1.

Areas covered: This review is limited to published patent applications that have disclosed small molecule inhibitors of the YAP/TAZ–TEAD interaction.

Expert opinion: The YAP/TAZ–TEAD transcriptional complex is a promising target for the treatment of cancer. Approximately thirty international patents (Used data base: Sci-finder, query: TEAD; documents: patents; period: from 2017-january 2022) that disclose TEAD transcriptional inhibitors have been filled since 2018. The mechanism of action is not always described in the patents, we can divide the drugs into three different categories: (i) external TEAD ligands; (ii) non-covalent TEAD ligands of the palmitate pocket; (iii) covalent TEAD ligands which bind into the palmitate pocket. The first molecules in clinical trial phase 1 are non-covalent TEAD ligands. The selective TEAD ligand have also been patented, published and selectivity could be of great interest for personalized medicine.

Keywords: Transcriptional factors TEAD, Hippo pathway, selectivity, cancers, YAP/TAZ, NF2-deficiency

Article Highlights:

- A review of published patent applications (2018-january 2022) reporting small molecule YAP/TAZ-TEAD inhibitors from academics and pharmaceutical companies.
- After academics and biotech companies, big pharmas join the dance of patent applications.
- Three molecules entered in phase 1 clinical trial in 2021 for mesothelioma treatment.
- First selective ligands of TEAD were patented.

1. Introduction

The highly conserved Hippo pathway, discovered in *Drosophila* in 1995, controls organ size and cell differentiation through the regulation of cell proliferation, apoptosis and stem cell function [1]. Growing interest in the Hippo pathway has been firstly driven by its deregulation in many diverse cancers as reported in many reviews,[2,3] then found interest in regenerative medicine[4–6] to finally emerged in the field of neurodegenerative diseases.[7,8] The Hippo pathway is mainly composed of a series of kinases which after stimulation by upstream signals including metabolic regulators[9,10] causes the YAP (Yes-Associated Protein) /TAZ (transcriptional co-activator with PDZ-binding motif, also known as WWTR1 (WW domain-containing transcription regulator protein 1) phosphorylation to remain in the cytoplasm, eventually leading to its capture and degradation. Unphosphorylated YAP/TAZ enters the nucleus and promotes downstream genes expression through the formation of

transcriptional complexes mainly with TEAD1-4 transcription factors which are considered as the most important output of the Hippo pathway.

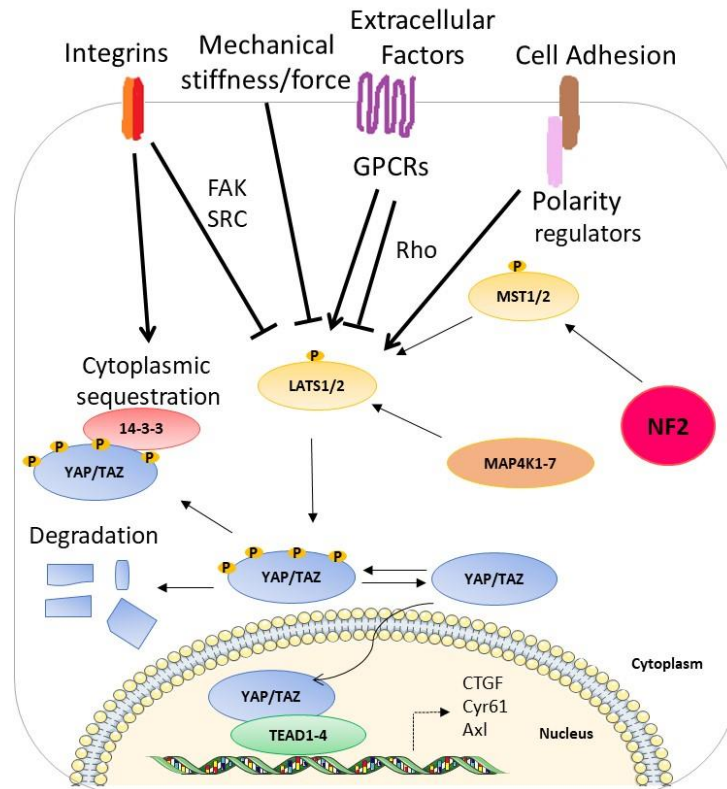


Figure 1: The Hippo pathway

YAP and TAZ bind to TEAD1-4 to drive expression of numerous target genes including CTGF, Cyr61 or Axl (cell proliferation), Survivin (Birc-5) (inhibition of apoptosis), Sox2, Nanog and Oct4 (stemness, pluripotency). Besides YAP/TAZ, the most studied coactivators of TEAD1-4 transcriptional activity, the Vestigial-like (VGLL) protein family, which consists in four members (VGLL1-4), has been shown to interact with TEAD to regulate distinct gene expression.[11] Although VGLL1-4 bind to the YAP/TAZ binding domain of TEAD1-4, VGLL1-3 and VGLL4 have distinct molecular functions and only VGLL4 has been reported to inhibit YAP/TAZ-TEAD interactions.

YAP/TAZ and TEADs form a complex through the interaction of the N-terminal domain of YAP (or TAZ) and the C-terminal domain of TEAD. Li *et al.*[12] (Figure 2) defined the three interfaces of contact between TEAD1²⁰⁹⁻⁴²⁶ and YAP⁵⁰⁻¹⁷¹ and their respective importance in the binding as follows: interface 3 (in light green on Figure 2A) > interface 2 (in plum) > interface 1 (in hot pink). The smaller fragment of YAP or TAZ which gives a nanomolar range binding constant corresponds to interfaces 2 and 3,[13] but mVGLL1²⁷⁻⁵⁶ was found to be equivalent to YAP and TAZ although VGLL do not interact with TEAD at the interface 3.[14] Interfaces 2 and 3 correspond to the external predicted druggable sites in plum and light green (Figure 2B).[15] In 2016, was reported for the first time, that C-terminal domain of TEAD2 and TEAD3 are palmitoylated in an internal hydrophobic pocket.[16,17] This internal pocket clearly appears as the third druggable site of TEAD (in light blue, Figure 2B).

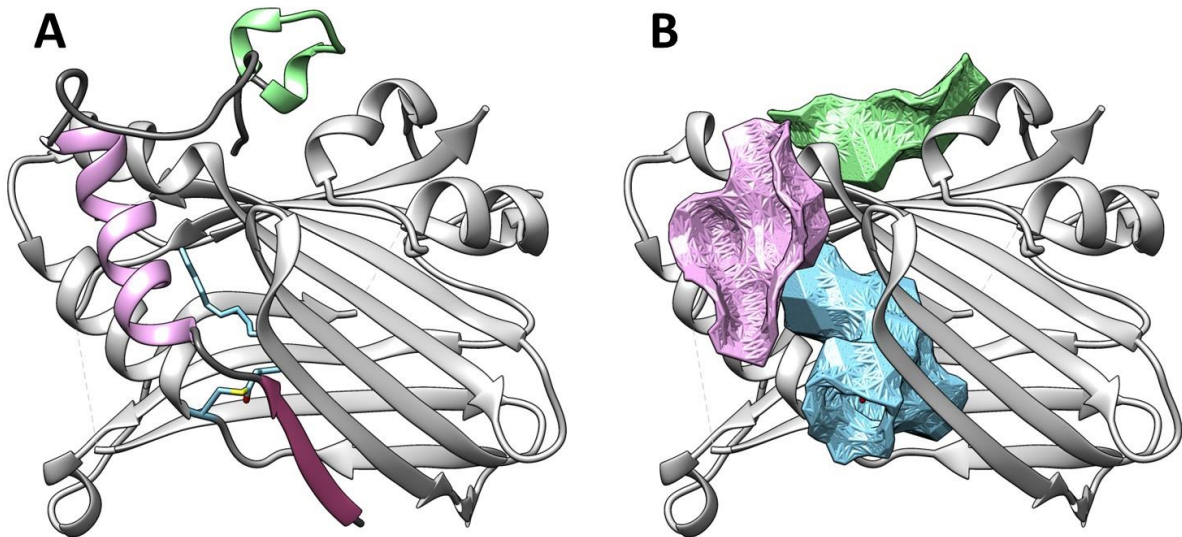


Figure 2: (A): The 3D-structure model built by superimposition of hYAP₂₅₀₋₁₇₁-hTEAD₁₂₀₉₋₄₂₆ complex (PDB code 3KYS) and hTEAD₂₂₁₇₋₄₄₇ (PDB code 5EMV) with interface 1 (hot pink), 2 (plum) and 3 (light green) and palmitate (light blue); (B): The three predicted druggable sites of TEAD (interface 2 (plum), interface 3 (light green) and internal pocket (light blue)). Structural figures were generated with Chimera 1.14 (UCSF) [18].

Dysregulation of the Hippo pathway may occur in many diseases, including cancers, neurodegenerative diseases and rare diseases.

YAP/TAZ phosphorylation regulates many hallmarks of cancer, including cancer cell proliferation, cancer stem cell fate, chemoresistance and metastasis. Elevated levels as well as the nuclear localizations of YAP/TAZ are observed in many human cancers where they are correlated with poor prognosis.

The activation of YAP or TAZ in the majority of these cancers is not associated with mutations in Hippo pathway components [2, 4-6], except for hepatocellular carcinomas [19] uveal melanoma [20], mesotheliomas [21], neurofibrosarcomas [22], pancreatic ductal adenocarcinomas [23] and glioblastomas [24] that can have genomic amplifications of YAP or TAZ and somatic mutations in components of the Hippo pathway.

Malignant mesothelioma (MM) constitutes a very aggressive tumor that arises from the pleural or peritoneal cavities. MM is usually diagnosed at advanced stages, surgery is no longer an option and conventional combination chemotherapy only extends the median overall survival for a few months. As many targeted therapies tested in clinical trials for this aggressive cancer without success, new therapeutics such as targeting YAP/TAZ-TEAD is highly pertinent in NF2-deficient or NF2-mutant mesotheliomas [25].

2. Patent evaluation

The database sci-finder (<https://scifinder-n-cas-org/>) has been queried (TEAD inhibitors/TEAD ligands) and the patent abstracts have been collected. We limited our study on international patent applications and analyzed the abstracts. The patents have been collected at the espacenet web site (<https://worldwide.espacenet.com>). During the manuscript revision, we repeated the procedure. We

finally analyzed 29 patent applications covering from 2017-january 2022 period. For an overview, TEAD patent applications discussed in this article are summarized in Table 1. When known, the reported drugs are classified into three different classes (external ligands, non-covalent internal pocket ligands and covalent internal pocket ligands).

Company/Institution	Patent	Target	Binding mode	Selectivity	Cancer cells	Ref.
Massachusetts General Hospital Harvard Medical School	WO2017053706	Internal pocket	Non covalent	Not discussed	92.1 (uveal melanoma) Huh7	[29]
Dana Farber Cancer Institute	WO2020081572	Internal pocket	Covalent	Not discussed	HEK293T PC-9	[30]
	WO2021133896				NCI-H226	[32]
	WO2021247634					[33]
Indianapolis University	WO2020087063	Internal pocket	Covalent (presumed)	Not discussed	HEK293 NSCLC	[35]
Inventiva	WO2017064277	Interface 3	Non covalent	Not discussed	HEK293 NCI-H2052	[36]
	WO2018185266					[37]
	WO2020070181					[38]
Vivace Therapeutics	WO2018204532	Internal pocket	Non covalent	TEAD1	NF2-deficient mesothelioma cell lines + <i>in vivo</i> mesothelioma tumor xenograft mouse models	[43]
	WO2019040380					[44]
	WO2019113236					[45]
	WO2019222431					[46]
	WO2020097389					[47]
	WO2020214734 WO2021102204					[48] [49]
Genentech	WO2019232216	Internal pocket	Non covalent	Not discussed	Biophysical test only	[51]
	WO2021108483		Non covalent	TEAD1/2/3	Biophysical test only	[52]
	WO2020051099		Non covalent and covalent	TEAD2/4	Detroit 562 cells	[54]
	WO2021097110		Non covalent and covalent	TEAD2/4	Biophysical test only	[55]
	WO2022020716		Non covalent and covalent	TEAD2/4	Biophysical test only	[56]
	WO2021178339		Non covalent	TEAD2/4	Biophysical test only	[57]
Ikena Oncology	WO2020243423	Not disclosed	Non covalent	Not discussed	11 different cancer cell lines + xenograft mice (NCI-H226 or MSTO211H)	[58]
Basilea Pharmaceutica	WO2021018869	C-ter domain	Non covalent	Not discussed	MCF-7, NCIH226 xenograft mice	[59]
Novartis	WO2021186324	Not disclosed	Non covalent	Not discussed	NCI-H2052 MKN-45	[61]
Sanofi	WO2021204823	Internal pocket	Covalent	Not discussed	Unspecified cancer cell lines	[63]
	WO2022023460					[64]
Merck	WO2021224291	Not disclosed	Non covalent	Not discussed	SK-HEP-1 NCI-H226 SW620 YAP KO	[65]
	WO2022018072					[66]

Astra-Zeneca and academic labs	ACS Chem Biol, (2019)	Internal pocket	Non covalent	Not discussed	HEK293, ACHN, MDA-MB-231, MCF-10A, PC-3	[67]
	Nat Commun, (2020)	Interface 2	Non covalent	Not discussed	RKO, and primary juvenile rat cardiomyocytes	[68]

Table 1. Overview of TEAD inhibitors and activators

2.1. Universities and Institutes

2.1.1. Massachusetts General Hospital – Harvard Medical School

In 2016, the presence of palmitate in an internal pocket of hTEAD2 or hTEAD3 was reported for the first time, which seems to increase the stability of the TEAD protein.[16] At the same time, Wu *et al.* disclosed the discovery of **MGH-CP-1** (Figure 3), a ligand of TEAD which crystallized in the TEAD internal pocket (PDB code of the crystal structure: 6CDY).[26] The main structural characteristics of the patented compounds (WO2017053706A1)[27] are the presence of an adamantyl group and a thiotriazole heterocycle at both ends mimicking the lipophilic and hydrophilic parts of fatty acids. Details concerning the patent are given in the previous patent review.[28] Following this first patent, the authors replaced the terminal heterocycle (triazole) by the more classical structure of flufenamic acid (**CP-58**) to yield **CP-55** which presents submicromolar activities on cell proliferation assays (92.1 (uveal melanoma) and Huh7 (liver carcinoma) cell lines). [29]

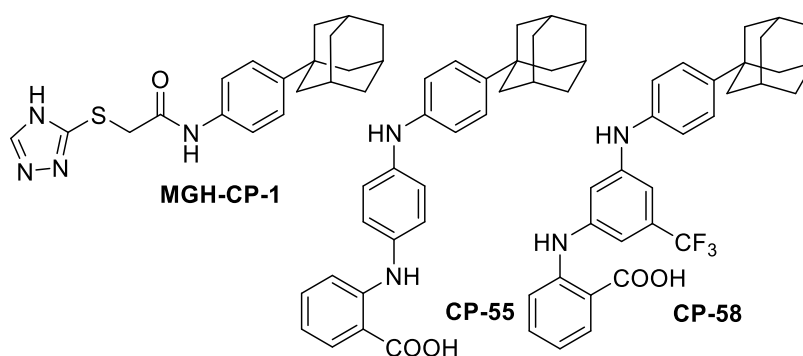


Figure 3: Structure of **MGH-CP-1**, **CP-55** and **CP-58**

2.1.2. Dana Farber Cancer Institute

Dana Farber Cancer Institute patented in three international patents two large families of di or tri substituted aromatics bearing reactive motifs. In the first patent (WO2020081572A1),[30] these reactive motifs are acryloyl and chloroacetyl groups linking to a non aromatic heterocyclic nitrogen atom (see Figure 4). In this first patent, the compounds were firstly evaluated on a TEAD transcription reporter assay (8xGTIIC) and then on the endogenous TEAD targets (Axl, CTGF, Cyr61 and Survivin) in MDA-MB-231 cell lines. While the structure of **MYF-01-037** (Figure 4) is protected in the first patent, the most of the data published by Kurppa *et al.*[31] is reported in the second patent (WO2021133896A1).[32] **MYF-01-037** inhibits YAP/TEAD interaction in HEK293T cells ($IC_{50} = 0.8 \mu M$) and reduced CTGF expression in PC-9 cells while it has roughly no effect on PC-9 transfected with TEAD1 C359S mutant which attests its target is effectively the palmitate pocket and its highly conserved cysteine residue. Ultimately, co-targeting EGFR, MEK and YAP/TEAD was applied on EGFR-mutant NSCLC to overcome the treatment-induced tumor dormancy through Hippo pathway.

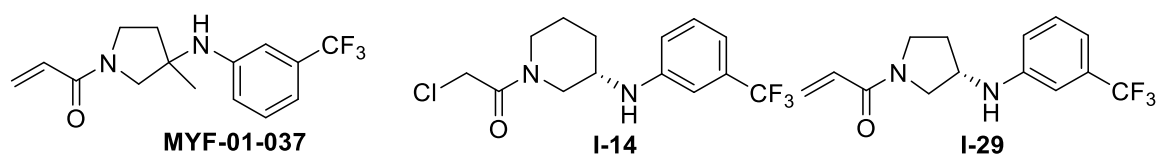


Figure 4: Structure of **MYF-01-037**, **I-14** and **I-29**

The authors claimed the global structure is directly inspired from the NSAID flufemamic acid with the 3-trifluoromethylaniline motif and the following patents reported mainly di or trisubstituted aromatic rings (WO2021133896A1)(compounds **I-A-02** and **II-1**)(Figure 5) with one of the substituent being an heteroaryl ring (WO2021247634A1)[33] (compounds **A-21** and **A-16**) (Figure 5). The IC_{50} of these compounds were measured in an anti-proliferation assay on NCI-H226 cells for 5 days and are in the micromolar range (compounds **I-A-02** and **II-1**) and in the nanomolar range (compounds **A-21** or **A-16**).

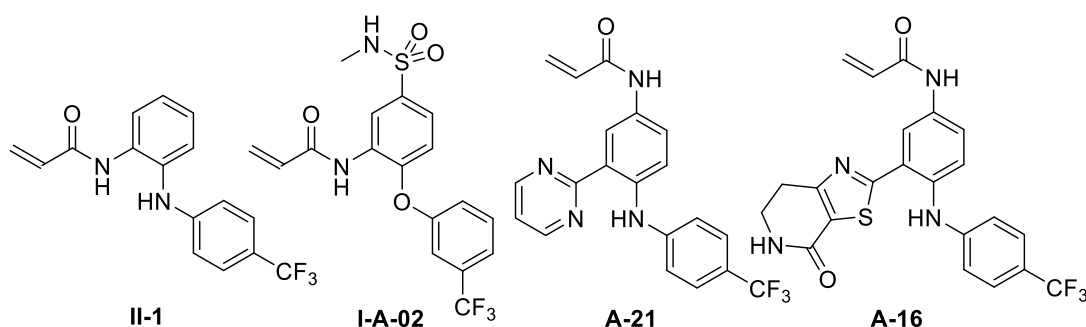


Figure 5: Structure of **I-A-02**, **II-1**, **A-21** and **A-16**

2.1.3. Indianapolis University

Bum-Erdene *et al.*[34] reported a small molecule (**TED-347**)(Figure 6) inhibiting YAP-TEAD complex transcriptional activity through the presumed formation of a covalent bond with the cysteine residue in the central pocket. The X-ray data are given but the electron density seems to us to correspond to palmitate. Using fluorescence polarization experiments, the authors were able to measure the inhibitory activity of their compounds for the YAP/TEAD4 interaction. **TED-347** possessed an EC_{50} of 5.9 μ M and a similar IC_{50} in a HEK293 cell-based assay but was found to be toxic in EGFR-mutant NSCLC cell [31] lines. **TED-347** is part of a patent [35] which cover general structure reported on Figure 6.

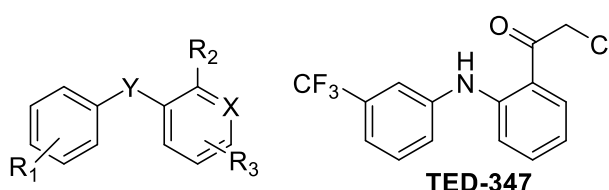


Figure 6: Structure of **TED-347** and general structures of patent WO2020087063A1

2.2. Biotech companies

2.2.1. Inventiva

Inventiva was the first company who protected its YAP/TAZ-TEAD inhibitors and the first patent [36] has been previously reviewed. [28] The protected structures correspond to diversely substituted benzo[d]isothiazole-1,1-dioxide (Figure 7) on which is branched at position 3 a N-substituted vanilline hydrazone motif. The following patent [37] is an extension of this first patent where the 4-hydroxy-3-methoxybenzylidene motif is replaced by disubstituted methylene motif yielding to the identification

of phenylboronic acid and ester moieties (**Ex 92** and **Ex 96**). Finally the most recent patent [38] explored the replacement of benzo[d]isothiazole-1,1-dioxide heterocycle by various fused heterocycles (**Ex 96**).

The compounds were tested on a transient transactivation assay on HEK293 cells using plasmids of hTEAD1, YAP mutant (S127A, S397A) and a luciferase reporter. The lowest IC₅₀ are at a submicromolar level. The tumor cell growth inhibitory activity of the YAP-TEAD inhibitors was tested on NCI-H2052 cell line, a mesothelioma cell line harboring a NF2 mutation. Best compound (**Ex 118**) exhibits a nanomolar IC₅₀ on NCI-H2052 cell line without showing any effect on Met5A cell line (a YAP independent mesothelioma cell line). The best compound of the first patent (**Ex 22**) was found to inhibit YAP-TEAD interaction by fluorescence polarization and the authors deduced **Ex 22** binds to interface 3.[39]

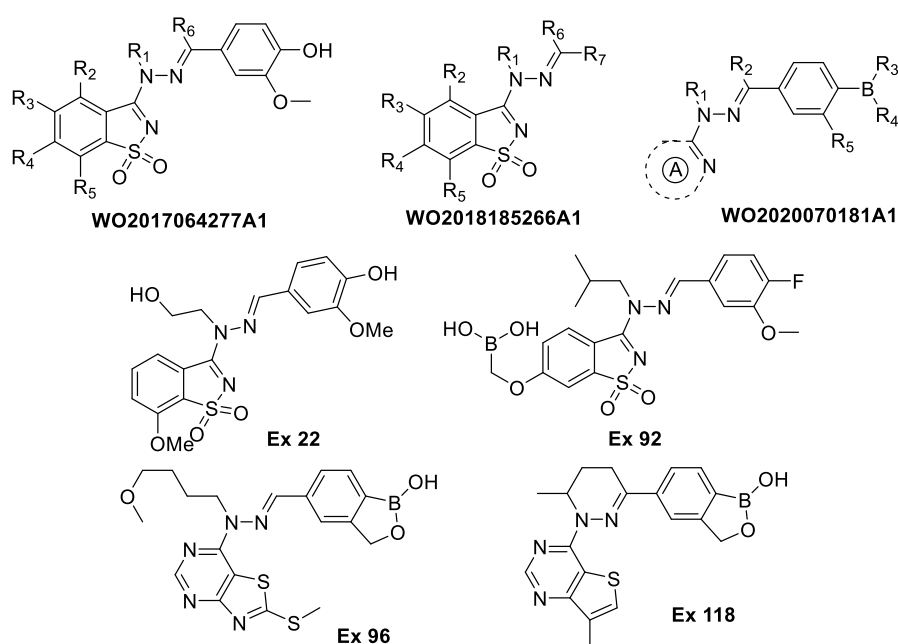


Figure 7: General structures of patents WO2017064277A1, WO2018185266A1 and WO2020070181A1 and some examples

2.2.2. Vivace Therapeutics

KL Guan, one of the co-founder of Vivace Therapeutics, patented 2,7-disubstituted-9H-fluorene-9-one oxime in 2013. [40] CA3 inhibits the expression of YAP1 and therefore the transcriptional activity in esophageal adenocarcinoma cell lines and in xenograft mouse model *in vivo*. It acts also synergistically with 5-FU in inhibiting growth of esophageal adenocarcinoma *in vivo*. [41] Extension of this patent on 2,7-disubstituted-9H-fluorene-9-one oxime was applied by Vivace Therapeutics in 2017.[42] Since 2018, Vivace Therapeutics has deposited seven recent patent applications, [43–49] and their lead molecule VT-3989 enters in phase 1 clinical trial (**NCT04665206**) in early 2021 (<https://clinicaltrials.gov/ct2/show/NCT04665206>). It is evaluated in patients with metastatic solid tumors enriched for tumors with NF2 gene mutations. Two distinct families have been patented. The first one is inspired from the flufenamic acid structure [43-46, 49] and the biological data of VT-103 [44] (Figure 8) have been detailed in a recent article. [50] Thermal shift assay on the four TEAD family members suggested a selectivity of VT-103 for TEAD1, which was confirmed by a TEAD palmitoylation assay. VT-103 inhibits cell proliferation of a panel of NF2-deficient mesothelioma cell lines at low nanomolar IC₅₀. VT-103 was evaluated in two malignant mesothelioma tumor xenograft mouse models with impressive outcomes, including an NCI-H226 model with TGI = 106% at 3 mg/kg p.o. and an NCI-

H2373 model with TGI = 126% at 10 mg/kg p.o. Favorable pharmacokinetics profile in mice VT-103 is also reported in this article. The second patented family consists of a substituted bicyclic aromatic ring, exemplified by VT-104 structure. [47, 49] VT-104 is part of the second family of substituted bicyclic aromatics substituted with an amide functional group. VT-104 is a pan-TEAD binder (TSA and palmitoylation assay), with low nanomolar IC₅₀ values in proliferation.

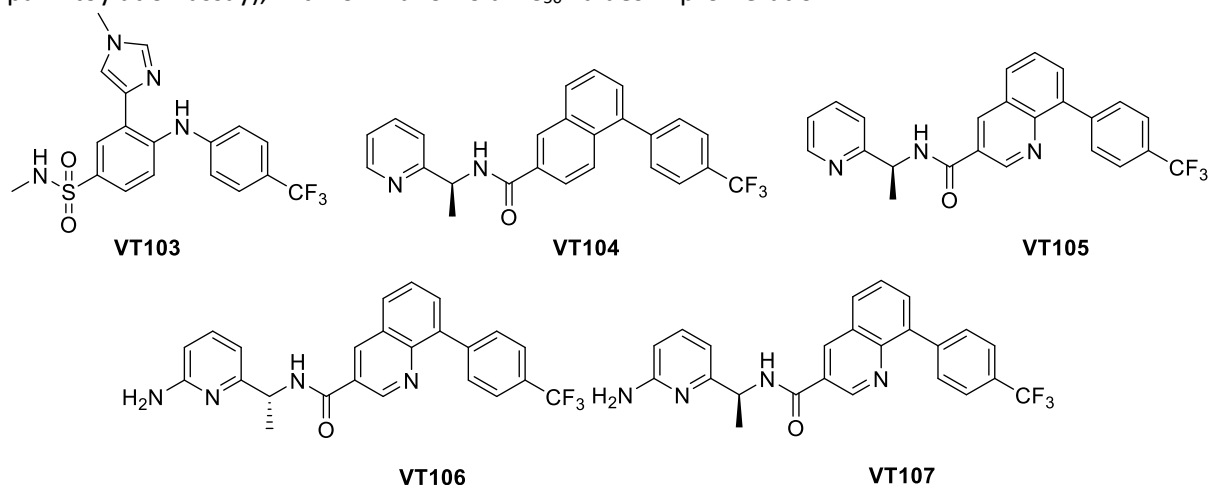


Figure 8: Structures of main compounds described in ref 42.

Crystal structure (PDB: 7CNL) of VT-105 in the TEAD3 internal pocket confirms the mode of action of this family. VT-104 also exhibits a favorable pharmacokinetics profile and a high efficacy on xenograft mice. The importance of the chirality is highlighted with the absence of biological activities of VT-106 compared to VT-107.

2.2.3. Genentech

Genentech released patent WO2019232216A1 [51] including 46 examples derived from the following general structure (Figure 9) as inhibitors of the YAP-TEAD interactions and therefore potential drugs to be used in YAP-TEAD mediated pathologies such as cancer. The general structure is composed of a pyrazolo[1,5-a]pyrimidin-7(4H)-one core bearing several substituents in position 2, 3 and 5. Position 2 can be substituted by halogens and (halo)alkyl chains. Position 3 bears an ester or an amide with chains covering various (cyclo)alkyl or (hetero)aryl. Position 5 bears a substituted (hetero)aryl moiety.

The compounds were evaluated in a TR-FRET binding assay on TEAD2₂₁₇₋₄₄₇ or TEAD3₂₁₇₋₄₄₇. The compounds demonstrating the best results are represented on Figure 9.

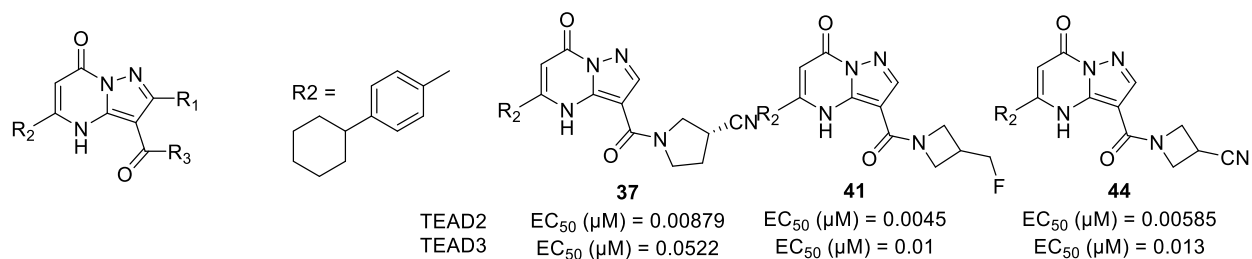


Figure 9: Structures of examples **37**, **41** and **44**.

They share structural similarities as for the three of them position 2 is unsubstituted, position 3 bears a fluoromethyl or cyano substituted azetidine/pyrrolidine amide and position 5 is a paracyclohexylphenyl fragment. The three of them were found to have similar affinity for TEAD2 with EC₅₀ values from 4.5 to 8.8 nM and for TEAD3 with EC₅₀ around 10 nM except for compound **37** for which it proved to be quite higher.

In patent WO2020051099A1, [52] Genentech reported two general structures (and 57 examples). The first one is centered around a variously polysubstituted six-membered aromatic/heteroaromatic ring bearing halo, cyano, alkyl, cycloalkyl, alkylcycloalkyl, haloalkyl or O-alkyl group. The compounds were evaluated as TEAD lipid pocket binders in a TEAD lipid assay followed by fluorescence polarization. A TEAD reporter activity inhibition assay performed on Detroit 562 cells (pharyngeal carcinoma) is also mentioned but the results are not to be included in the patent.

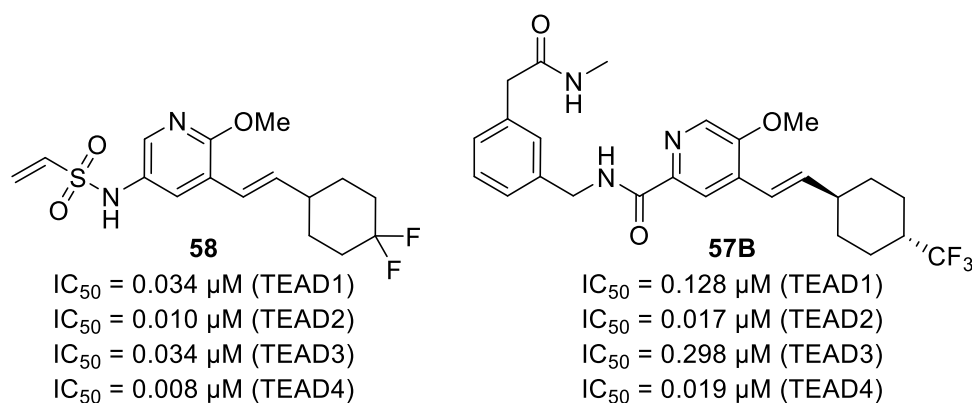


Figure 10: Structures of compounds **57B** and **58**.

Compound **58** (Figure 10) was found to have the best affinity for all TEADs with IC_{50} values ranging from 8 to 34 nM. Noticeably, it features a reactive vinylsulfonamide moiety as a Michael acceptor group. Compound **57B** (Figure 10) also demonstrated a quite good affinity for TEAD2 and TEAD4 (respectively 17 and 19 nM) but substantially less for TEAD1 and TEAD3 (respectively 128 nM and 298 nM) maybe due to a better selectivity towards TEAD2/4 than TEAD1/3. Detailed biological and biophysical properties of compound **58** have been disclosed in [53]. Although it inhibits TEAD palmitoylation by replacing palmitate in the internal pocket (PDB code: 6UYC), its mechanism of action could be *in vivo* (Detroit X1 562 xenograft model) by transforming TEAD into the dominant negative transcriptional repressor which blocks the TEAD interaction with chromatin.

In patent WO2021097110A1 [54] the protected general structure overlaps with the previous patent as it is derived from the best compounds previously identified. The 2-methoxy or 3-methoxypyridine is conserved for a majority of the compounds and variations are explored for the terminal group of the alkenyl chain, the chain in itself and other substituents on the ring as well. Most importantly, the vinylsulfonamide moiety in compound **58** and the amide chain in compound **57B** are now replaced with an optionally substituted acrylamide moiety, urea moiety or oxirane moiety. A few examples explore different core ring such as pyrimidine, dihydrobenzofurane, quinoline, 1,6-naphthyridine, benzoxazole and benzothiazole but keep the substituents pointing in the same general directions.

The compounds were evaluated in a biophysical TR-FRET assay and compounds **53**, **54** and **55** (Figure 11) were found to be the best TEAD2 and TEAD4 lipid pocket binders with IC_{50} in the nanomolar range.

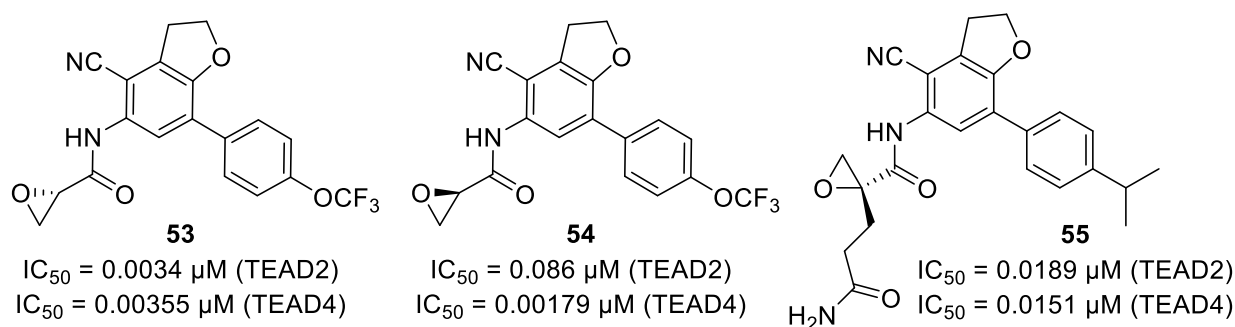


Figure 11: Structures of compounds **53**, **54** and **55** from patent WO2021097110A1. [54]

In patent WO2022020716A1 [55], the authors extended the previous one where the anilinic nitrogen is substituted by acrylic acid moiety.

Patent WO2021108483A1 [56] presents a second generation of compounds based on the structure of compound **41** from patent WO2019232216A1. [51] The second generation explores several modulations : the position 2 of the core platform is substituted with heterocycles, hydroxylated chains and amides, the apolar cyclohexyl group is modulated by other lipophilic fragments and further substitution of the azetidine/pyrrolidine cycle is also investigated.

The compounds were evaluated in a TR-FRET binding assay using all TEAD1/2/3/4 and biotinylated YAP₅₀₋₁₀₀ and TAZ₁₃₋₅₇. The best inhibitors (Figure 15) demonstrated nanomolar EC₅₀ for all the YAP or TAZ/TEAD1-4 except compound **70** which is selective of TEAD1,2,3 vs TEAD4. They all bear a pyrimidine or pyrazine heterocycle at the position 2 of the core structure. The phenyl in position 5 is para-substituted with a methylcyclopentane moiety or a 9 carbon chain. It appeared that the second generation of compounds did not show higher potency than the best hits from the first one at inhibiting the YAP/TAZ-TEAD interaction.

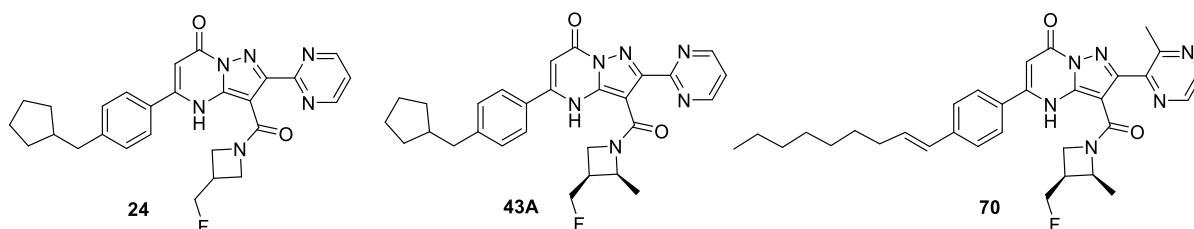


Figure 15: Structures of compounds **24**, **43A** and **70** from patent WO2021108483A1. [56]

In the continuity of patent WO2020051099A1, [52] patent WO2021178339A1 [57] presents heterobifunctional compounds derived from **57B** as TEAD inhibitors. The structure of **57B** is conserved but the terminal N-Me amide is replaced by a linker chain (carbon or PEG of variable length). The scope of this patent also extend to modifications of the linked structures. The compounds were evaluated in a biophysical TR-FRET assay. The authors pointed out the fact that the TR-FRET format allows more sensitive determination of affinity for the lipid pocket than the fluorescence polarization assay thanks to a lower concentration of TEAD protein for this test. Compound **17** was found to be the best TEAD lipid pocket binder with IC_{50} values as low as $0.04 \mu\text{M}$ for TEAD4 and $0.09 \mu\text{M}$ for TEAD2. Affinities for TEAD1 and especially TEAD3 were quite weaker. Noticeably, all the tested compounds showed poorer affinity for TEAD3 as **17** proved to have the lowest IC_{50} of all the tested compounds ($1.50 \mu\text{M}$).

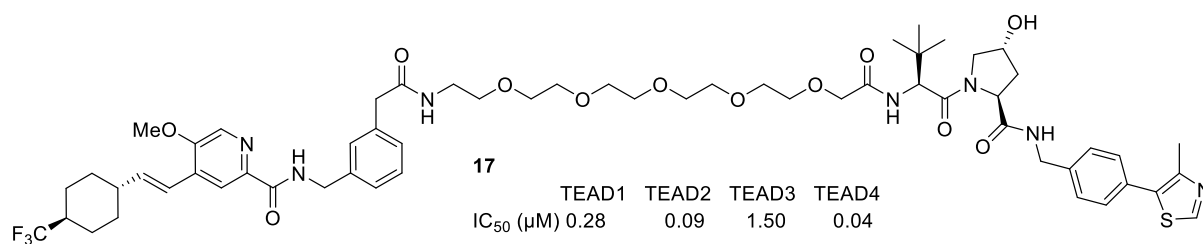


Figure 16: Structures of compound **17** from patent WO2021178339. [57]

2.2.4. Ikena Oncology

Ikena Oncology released patent WO2020243423A1 [58] presenting a series of around 500 examples, derived from the general structure presented in Figure 17.

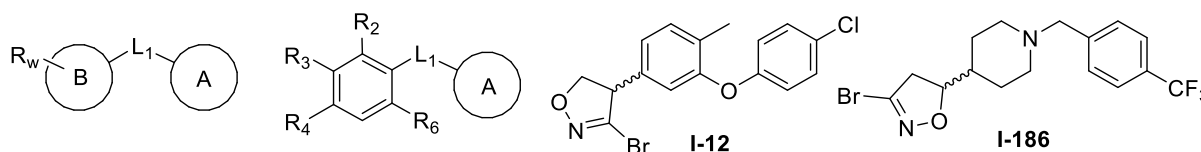


Figure 17: General structure of compounds from patent WO2020243423A1, [58] **I-12** and **I-186**

The compounds are constituted of two rings A and B connected with a linker L₁. Both A and B cycles can either be a phenyl group, a saturated or partially unsaturated carbocycle or heterocycle with 1 or 2 heteroatoms, an heteroaromatic ring with 1 to 4 heteroatoms (5- or 6-membered), a bicyclic aromatic or heteroaromatic ring with 1 to 5 heteroatoms (8- or 10-membered). The L₁ linker is a C1 to C6 linear or branched chain in which one to three CH₂ can be replaced by a connecting group (ether, thioether, amine, ketone, ester, amide, carbamate, urea, sulfoxide, sulfone, sulfonamide, thioketone, thionoester, thioamide or thiourea). When B cycle is a phenyl motif, it can be tetrasubstituted by various substituents. The patents present the results of an inhibition of TEAD reporter activity assay for certain compounds. The assay was conducted in MCF-7 TEAD reporter cells as well as H226 and H28 mesothelioma cell lines. Focusing on the TEAD reporter assay, a total of 67 compounds demonstrated EC₅₀ below 0.1 μM.

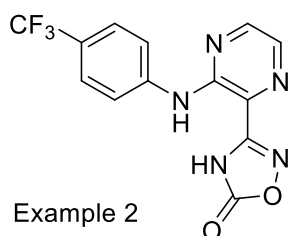
The authors state that isomer 2 of compound **I-12** (Figure 17) demonstrated inhibition of cell proliferation for NF2 mutant cell lines in particular and no effect seemed to be detectable on H28 cell line (non-deficient NF2 cell line). The compound showed EC₅₀ < 0.2 μM for the following cell lines: MSTO211H (biphasic mesothelioma), NCI-H1975 and NCI-H2085 (adenocarcinoma), NCI-H2052 and NCI-H226 (mesothelioma), SNU182 (hepatocellular carcinoma), U251 (glioblastoma) and YD8 (squamous cell carcinoma). Isomer 2 of **I-12** and isomer 1 of **I-186** were evaluated on NCI-H226 or MSTO211H xenograft mice. They both inhibited tumor growth without affected body weight and significantly decreased CTGF mRNA levels.

Ikena Oncology declared IK-930 clinical trial phase I launch in early 2022 (**NCT05228015**), (<https://clinicaltrials.gov/ct2/show/NCT05228015>).

2.2.5. Basilea Pharmaceutica

Basilea Pharmaceutica recently described in a patent application a series of 1,2,4-oxadiazol-5-one derivatives. [59] These molecules shared structural similarity with flufenamic acid, where the carboxylic acid group has been replaced with an 1,2,4-oxadiazol-5-one heterocycle. The patented

compounds presented interaction with hTEAD2 C-terminal domain as shown by TSA (thermal shift assay) with ΔT_m ranging from 0.4 to 18 °C and inhibited luciferase activity in the MCF-7 TEAD reporter gene assay with IC_{50} between 39 nM and 6 μ M. **Example 2** (Figure 18)(MCF-7 TEAD RGA IC_{50} = 41 nM, hTEAD2 ΔT_m = 10.6 °C, no PK data reported) is active *in vivo* in a 62-day murine NCIH226 xenograft efficacy model by showing dose-dependent activity and tumor stasis at the highest dose of 250 mg/kg p.o..



Example 2

- Thermal Shift Assay on hTEAD2: ΔT_m = 10.6 °C
- IC_{50} (TEAD reporter assay on MCF-7 cells) = 41 nM
- NCI-H226 xenograft mice: 60% decrease of tumor volume after 65 days (50 mg/kg po)

Figure 18: Structure of **Example 2** [59]

2.3. Big pharma

2.3.1. Novartis

Chène's team (from Novartis Oncology) largely contributes to a better understanding on the interaction between the C-terminal domain of TEAD and its co-factors (YAP, TAZ, VGLL and FAM) and published 12 articles and 17 crystal structures of wild-type or mutant hTEAD1 or 4. This team designed of potent peptide inhibitors of the YAP-TEAD interface 3. [60] Very recently, Novartis patented biaryl derivatives (WO2021186324A1) [61] as inhibitors of the protein-protein interaction between YAP/TAZ and TEAD with a total of 176 examples of biaryl compounds (Figure 19).

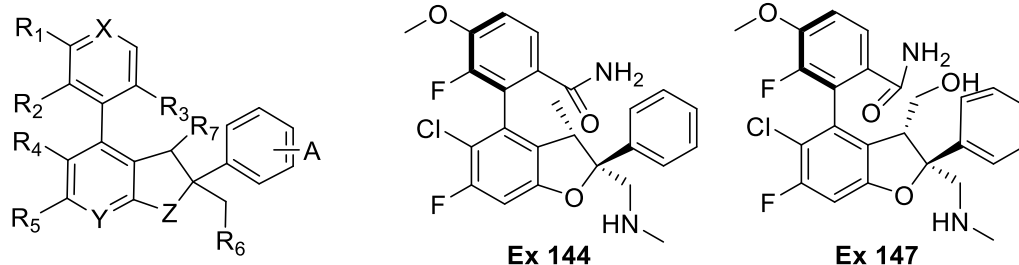


Figure 19: General structures of patented compounds [61] and structures of examples **144** and **147**.

The compounds are constituted of a central biaryl core with the first aryl being a phenyl (X = CH) or pyridinyl (X = N) ring substituted with R_1 , R_2 and R_3 . R_1 substituents range from simple hydrogen and halogens to alkyl, O-/NH-/S-alkyl with various substitutions on the alkyl chains (halo, hydroxy, alkoxy, carboxyl, morpholine and heterocycles). R_2 is either hydrogen or methyl but also fluorine and chlorine. R_3 covers a variety of rather polar groups such as nitrile, carboxamide, alkyl esters, carboxylic acid, alkyl/aryl-substituted amide, alkyl-substituted amine and O-hydroxyalkyl.

The second aryl moiety is generally a substituted 2,3-dihydrobenzofurane derivative (Z = O) but can be an indoline derivative (Z = NH) or an indane derivative (Z = CH_2). On this moiety, R_4 is generally a chlorine atom but can also be other halogens, halogenated alkyl chains or a cyano group. R_5 is either a hydrogen atom or an halogen atom. The position 2 of the five-membered ring is substituted with an aromatic or heteroaromatic ring that can optionally bear halo or haloalkoxy substituents. The same position 2 also holds a nitrogen bearing group (R_6 = NH_2 , alkylamine or cycloalkylamine). Finally, the

position 3 on the five membered ring, when substituted (R_7), can bear alkyl, hydroxyalkyl or alkoxyalkyl chains.

The compounds were evaluated in a biochemical TR-FRET. [62] The results show that most of the compounds are able to inhibit the interaction between hTEAD₂₁₇₋₄₃₄ and hYAP₆₀₋₁₀₀ with IC_{50} in the low nanomolar range. 134 compounds demonstrated $IC_{50} < 10$ nM and amongst them 5 demonstrated $IC_{50} < 1$ nM.

The compounds were also tested in two *in vitro* cellular assays. First, a luciferase-based reporter gene assay was conducted in NCI-H2052 mesothelioma cells in order to monitor YAP-dependent pathway activity. MKN-45 gastric adenocarcinoma cells (YAP-deleted) with constitutive luciferase expression were used as a specificity control. The same cell lines were used in a proliferation assay.

The two compounds showing the best activities in both tests are represented in Figure 12. They both demonstrated similar IC_{50} values (respectively 10 nM for example **144** and 11 nM for example **147**) as well as GI_{50} values (respectively 10 nM for example **144** and 5 nM for example **147**). Structurally, they share the same substituent pattern with $R_1 = OMe$, $R_2 = F$, $R_3 = CONH_2$ on the phenyl part of the biaryl and $R_4 = Cl$, $R_5 = F$ and $R_6 = NHMe$. Their sole difference lies with $R_7 = Me$ (**144**) or CH_2OH (**147**).

Novartis has initiated a phase I clinical study with **IAG933** (structure not disclosed) (**NCT04857372**) (<https://clinicaltrials.gov/ct2/show/NCT04857372>). The purpose of that study is to characterize the safety and tolerability of **IAG933** in patients with mesothelioma, NF2/LATS1/LATS2-mutated tumors compared to tumors with functional YAP/TAZ and to identify the maximum tolerated dose.

2.3.2. Sanofi

Sanofi patented (WO2021204823A1) [63] 1H-indolyl-acrylamide derivatives (general structure depicted on Figure 20).

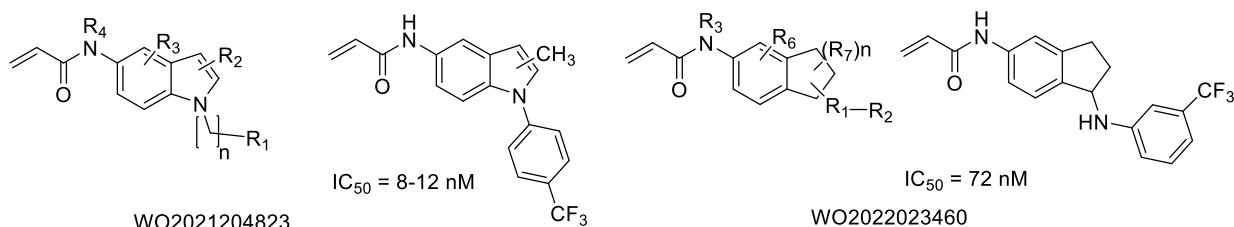


Figure 20: General patented structure [63, 64] and structure of the most active compounds

The core indole platform was conserved while various substituents at the indole nitrogen atom were incorporated. The scope encompassed benzyl, phenyl, alkyl and cycloalkyl chains, pyridinyl fragments and five-membered ring heterocycles. The acrylamide moiety was placed at the position 5 of the indole. The position of the acrylamide moiety was also modulated at the position 4, 6 or 7 of the indole ring.

The compounds were tested in a luciferase-based gene reporter assay to monitor YAP1-TEAD and TAZ-TEAD activity and investigate modulation of these activities in different human tumor cell lines with IC_{50} ranging from 1 nM to 10 μ M. The authors indicated that most of the compounds had IC_{50} values less than 1 μ M and particularly between 1 and 100 nM. Figure 20 shows the structures of the compounds with the best activities. The 5-acrylamide indole platform is substituted by a (4-

trifluoromethyl)phenyl moiety on the nitrogen atom and can either be unsubstituted or bear a methyl group in position 2 or 3 of the indole ring.

In a more recent patent (WO2022023460A1) [64], the indole motif has been replaced by an indane bicyclic system with an IC₅₀ of 72 nM for the example reported on Figure 20.

2.3.3. Merck

Merck Patented (WO2021224291A1) [65] and (WO2022018072A1) [66] a very large family of tricyclic heterocycles of formula depicted in Figure 21.

YAP-TEAD interaction inhibition was measured using a 8 x TEAD responsive elements driving the nanoLuc[®] luciferase gene on SK-HEP-1 cells (hepatocarcinoma). Viability assays were conducted on NCI-H226 mesothelioma (YAP-dependent) and on SW620 YAP KO colorectal (YAP-independent) cells.

Best results were obtained with 4-aryl-pyrazolo, oxazolo, thiazolo or triazolindole-7-carboxylic acids where the aryl group is substituted at para position by a trifluoromethyl group (IC₅₀ on SK-HEP-1 cells in the range of 1 nM to 10 nM; IC₅₀ on NCI-H226 cells in the range of 1 nM to 100 nM; IC₅₀ on SW620 YAP KO cells in the range > 30 μM).

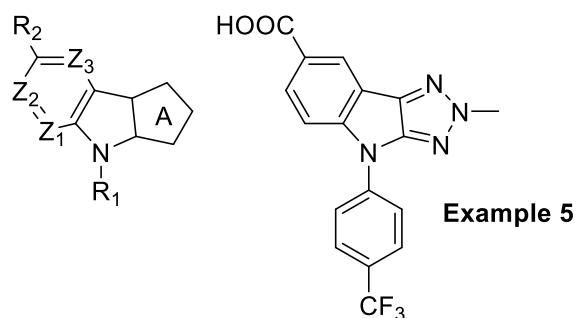


Figure 21: General patented structures [65, 66] and example of one the most active compounds

2.3.4. Astra-Zeneca and academic labs

Conversely to the other pharmaceutical companies, Astra-Zeneca appears in the field of activators of YAP/TAZ-TEAD interaction through collaborations with academics (Max Planck Institute for Molecular Physiology, Dortmund, Germany and A*STAR Institute of Molecular and Cell Biology, Singapore, Singapore mainly). While most reported palmitate pocket binders show inhibitory activity on TEAD palmitoylation and transcription, quinolinols were found to stimulate TEAD activity. [67] **Q2** (Figure 22) is supposed to occupy the TEAD central pocket as shown by SPR (Surface Plasmon Resonance) on wt-hTEAD2 compared to A231I mutant and increase expression levels of CTGF, CYR61 and ANKRD1. *In vivo*, quinolinol **Q2** accelerates cutaneous wound healing in mice to as soon as day 7. In another article, [68] the same collaboration between Astra-Zeneca and academics led to the design of an eicosapeptide **4E** (Figure 22) (derived from the VGL4 233-252 amino acid sequence by D to E replacement leading to crosslinked via lactamization of residues E235 and K250) linked to Tat sequence through a PEG2 linker presents a crosslink between the acid function of a glutamic residue and the ammonium function of a lysine residue. It binds to mTEAD4 (PDB code: 6SBA) at the interface 2 as previously published YAP/TAZ-TEAD inhibitors [69] but was found higher inhibitor of VGLL4 than YAP and therefore activates YAP-TEAD interaction, increases mRNA target genes levels (CYR61, CTGF, ANKRD1 and SEPINE1) in human cardiomyocytes and accelerates wound healing of RKO cells.

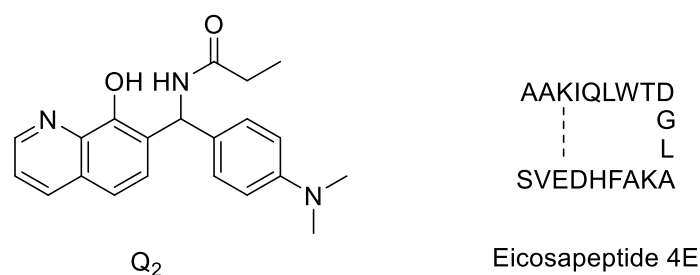


Figure 22: structures of Q2 and modified VGLL4 fragment (eicosapeptide 4E)

3. Expert opinion

In term of chemical structure, this review showed a large structural diversity with the omnipresence of fenamate family, including flufenamic acid and its trifluoromethyl group which appears in a large majority of YAP/TAZ-TEAD inhibitors, that have been firstly identified by Pobbati et al. [70] in 2015 as TEAD ligand occupying the internal pocket. The use of covalent warhead (chloroacetamide, acrylamide and vinylsulfamide) is also abundantly documented giving raise to high affinity in *in vitro* assay but not always translated as well in cellulo assays maybe due to problematic selectivity.

With the first articles published in 2010 on the crystal structures of YAP-TEAD [23] in hand, medicinal chemists firstly looked at disrupting protein-protein interaction and it was successful with modified peptides [60,67] but not with small molecules (with the exception of substituted pyrazoles). [66] Several compounds [34,71] proved to interact with TEAD at the internal pocket and competed with palmitate and the use of covalent warhead was justified by the existence of a conserved cysteine at the entry of the palmitate pocket which was found to be linked to the fatty acid by a thioester bond. [24] However, it is not the real purpose of a patent to determine the mechanism of action and we refered here to the numerous available crystal structures of TEAD with ligands in its internal pocket.

Ex 22 patented by Inventiva, [36] has been demonstrated to bind at the interface 3 of TEAD1 as measured by fluorescence polarization assay showing that it is able to compete with YAP (TMR-YAP₈₄₋₁₀₀) but litterature showed that internal pocket ligands may be found to inhibit YAP-TEAD *in vitro* by fluorescence polarization assay (using FAM-YAP₆₀₋₉₉ or FITC-YAP₅₀₋₁₀₀) [34,72] or in cells (Split gaussia luciferase assay or co-IP) [31,50] while other ligands have not effect on the YAP-TEAD interaction (TR-FRET or FP assay (using FITC-YAP₆₁₋₁₀₀). [53,73]

Specific dysregulation of TEAD in cancers is well-documented. TEAD1 is mainly implicated in prostate, cervical and breast cancers [74,75] whereas TEAD2 is a novel prognostic factor for hepatocellular carcinoma. [76] TEAD2 expression is increased during epithelial-mesenchymal transition in breast cancer cells [77] and it was found to be an independent prognostic factor in pancreatic ductal adenocarcinoma [78] and *NF-2* controls the invasiveness through YAP-TEAD2-dependent expression of Cyr61 in glioblastoma. [79] TEAD4 is implicated in colorectal cancer [80] and in hepatoblastoma [81] and elevated levels of a splicing isoform of TEAD4 associated with an increased rate of survival was also reported in cancer patients. [82] For these reasons, selectivity towards one member of the TEAD family found great interest in the context of personalized medicine. Vivace Therapeutics reported the first selective TEAD1 ligand [50] and Genentech reported selective TEAD2/4 ligands that found great interest in specific TEAD deregulated cancers. Nevertheless, pan-TEAD ligands would generally control upstream Hippo pathway dysregulation.

Finally, Astra-Zeneca and academic laboratories reported TEAD ligands able to activate transcriptional activity of TEAD which could find interest in the field of regenerative medicine (cardiac regeneration, wound healing) [6] and neurodegenerative diseases.[7] Sustained YAP/TAZ activation can induce tumor formation in cells that are facing different environmental stresses, such as inflammation, or that already have pre- malignant oncogenic mutations thus increasing the risk of malignant transformation. However, the tissue overgrowth and tumor formation resulting from transient activation of YAP are often reversible upon cessation of YAP activation. [83, 84] Thus, although the activation of YAP/TAZ can trigger undesired side effects, there might be a therapeutic window of YAP/TAZ activation that can be used to induce organ regeneration or wound healing.

Combination of transcriptomics, gain- and loss-of-function studies, and functional genomics led to the identification of RB1, an unanticipated tumor suppressor role for YAP and TAZ in many cancers and stratification into binary superclasses based on opposite pro- or anti-oncogenic activity of YAP/TAZ. [85] The YAP/TAZ-negative class consisted of blood cancers, many neural cancers and well-differentiated neuroendocrine cancers from many tissues, including lung, prostate, breast and the gastrointestinal tract whereas the YAP/TAZ-positive class consisted of solid cancers (adenocarcinoma, sarcoma, squamous cell cancers). [86] In this new partition, molecules which activate transcriptional activity found particular interest in certain cancers such as ER⁺ breast cancer leading to the identification by Vivace Therapeutics of new Lats1/2 inhibitor. [87]

With three molecules in phase 1 clinical trials, we are still far from a new anti-cancer drug available but knowledge of the biology of the Hippo pathway and downstream proteins YAP, TAZ and TEAD area is advancing by leaps and bounds. Knowledge on the structural interactions between TEAD1-4 and its different partners including YAP, TAZ and VGLL1-4 are still fragmented and new available data from AlphaFold2 (<https://alphafold.ebi.ac.uk/>) [88] will lead to a better understanding of the complex network governing activation or inhibition of transcriptional activity of TEAD1-4. [89] Selective ligands of each TEAD member should be at least of interest for a better understanding on the redundancy or complementarity of TEAD members [90, 91] but also for precision medicine.

In the future, YAP/TAZ-TEAD interaction inhibitors will probably find limited interest as monotherapy since the Hippo pathway is not considered as a major dysregulation pathway in cancers, but more likely in combination with other new therapeutic modalities (KRAS, mTOR, NOTCH pathways) or with the current chemotherapy to avoid/limit chemoresistance [92-94].

The new concept of binary pan-cancer classes will trigger greater interest for molecules that activate YAP/TAZ-TEAD interaction in addition to neurodegenerative disease, regenerative medicine and wound healing therapies and no doubt that in the future several patents will be deposited with this applications.

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Declaration of interest

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Author contributions

BZ and PC collected, analyzed and abstracted the patents. BZ, PM and PC wrote and revised the article.

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