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Antibody-drug conjugates with pyrrole-based KSP inhibitors as the payload class

Hans-Georg Lerchen*[a], Sven Wittrock[b], Beatrix Stelte-Ludwig[a], Anette Sommer[b], Sandra Berndt[b], Nils Griebenow[c], Anne-Sophie Rebstock[d], Sarah Johannes[a], Yolanda Cancho-Grande[a], Christoph Mahlert[a], Simone Greven[a] and Carsten Terjung[a]

Abstract: The number of cytotoxic payload classes successfully employed in antibody-drug conjugates (ADCs) is still rather limited. The identification of ADC payloads with a novel mode of action will increase therapeutic options and potentially increase the therapeutic window. Herein, we describe the utilization of kinesin spindle protein inhibitors (KSPi) as a novel payload class providing highly potent ADCs against different targets, for instance cerbB2/HER-2 or TWEAKR/Fn14. Aspects of technical optimization comprise the development of different linker attachment sites, the stabilization of ADC linkage to avoid payload deconjugation and finally, the tailor-made design of active metabolites with a long lasting intracellular exposure in the tumor matching the mode of action of KSP inhibition. These KSP-ADCs are highly potent and selective *in vitro* and demonstrate *in vivo* efficacy in a broad panel of tumor models including complete regressions in a patient-derived urothelial cancer model.

The recent clinical success and approval of brentuximab vedotin (Adcetris, 2011) in relapsed Hodgkin lymphoma and anaplastic large cell lymphoma[1], trastuzumab emtansine (Kadcyla, 2013) in HER-2 positive metastatic breast cancer[2], as well as re-approval of gemtuzumab ozogamicin (Mylotarg) and approval of inotuzumab ozogamicin (Besponsa) in 2017[3] stimulated extensive research efforts in the ADC field. Goals of technical innovation include the identification of novel targets and the improvement of the ADC components, antibody, linker and payload, which resulted in a pipeline with currently more than 60 ADCs in clinical trials.[4] The ADC payload classes presently tested in clinical trials are dominated by microtubule binders and DNA binding agents. Key challenges of those are hydrophobicity leading to aggregation as well as the management of off-target toxicities.[5] Despite tremendous efforts, the success rate in the discovery of cytotoxic payload classes with a novel mode of action resulting in ADCs with an improved therapeutic window has been rather low.

Kinesin spindle protein (KSP, synonyms: Eg5, KIF11) is an ATP-dependent motor protein involved in the separation of centrosomes in the G_2/M phase of the cell cycle.[6] The blockade of this essential event in mitosis with small molecule KSP inhibitors (KSPis) such as ispinesib results in high antitumor potency which raised great excitement to this compound class.[7] However, transferring the preclinical potency of SMOL KSP inhibitors into highly efficient clinical regimens with an acceptable therapeutic window has remained challenging.[8] Inspired by previous work of Abrams and Wang et al.[9], we discovered a new pyrrole subclass of KSPis, i.e. compound A, showing sub-nanomolar potency against a large panel of tumor cell lines (Scheme 1 and Table 1, column 4) which we investigated for their applicability as a novel payload class for ADCs. For initial investigations of technical aspects such as finding appropriate attachment sites for the linker and optimization of the effector chemistry with a focus on ADC stability we selected the monoclonal antibody (mAb) employed in trastuzumab emtansine (Kadcyla).[2a] For our investigations we used an in house produced version of trastuzumab called BAY-865 having the same protein sequence as trastuzumab. Optimized effector chemistries were subsequently employed in ADCs which are targeting the receptor of TWEAK (tumor necrosis factor [TNF]-like weak inducer of apoptosis). The TWEAK receptor (TWEAKR, Fn14), the smallest member of the TNF receptor superfamily is a tumor antigen which is overexpressed in several solid tumor indications including non-small cell lung, bladder, colorectal and pancreatic cancer.[10] This raised our interest in exploring TWEAKR-targeted ADCs with the KSPi payload as anticancer agents and results are also described in this manuscript.

The KSPi with a pyrrole core (compound A) was synthesized starting with the benzylation of the methyl 4-bromo-1H-pyrrole-2-carboxylate educt followed by Suzuki coupling with (2,5-difluorophenyl)boronic acid, a reduction-oxidation sequence and an enantioselective installation of the amino and *tert.*-butyl moiety via Ellmann's *tert.*-butanesulfinamide methodology[11] (Scheme 1 and Supporting Information). For applicability of compound A as payload in ADCs, we investigated different positions in the molecule which are compatible with the attachment of cleavable and/or non-cleavable linkers. Initial SAR studies with regard to linker attachment retaining the strong binding affinity to KSP, revealed two appropriate positions marked by the arrows in scheme 1, whereas the basic amino group is important for binding (data not shown). Reductive alkylation of intermediate A with suitably protected amino acid derived aldehydes, acylation and partial deprotection allowed for the synthesis of either intermediate B or intermediate C. These intermediates were further modified with a variety of linkers carrying thiol reactive groups. For ADC synthesis, the anti-HER2 antibody BAY-865 has been incubated with Tris(2-carboxyethyl)phosphine (TCEP) in PBS phosphate buffer at pH 7 to reduce the 4 interchain disulfide bridges and subsequently reacted with 6-8 equivalents of the electrophilic precursor molecules to provide the ADCs. The drug-to-antibody ratios (DARs) are given in scheme 1 and details of the synthesis are

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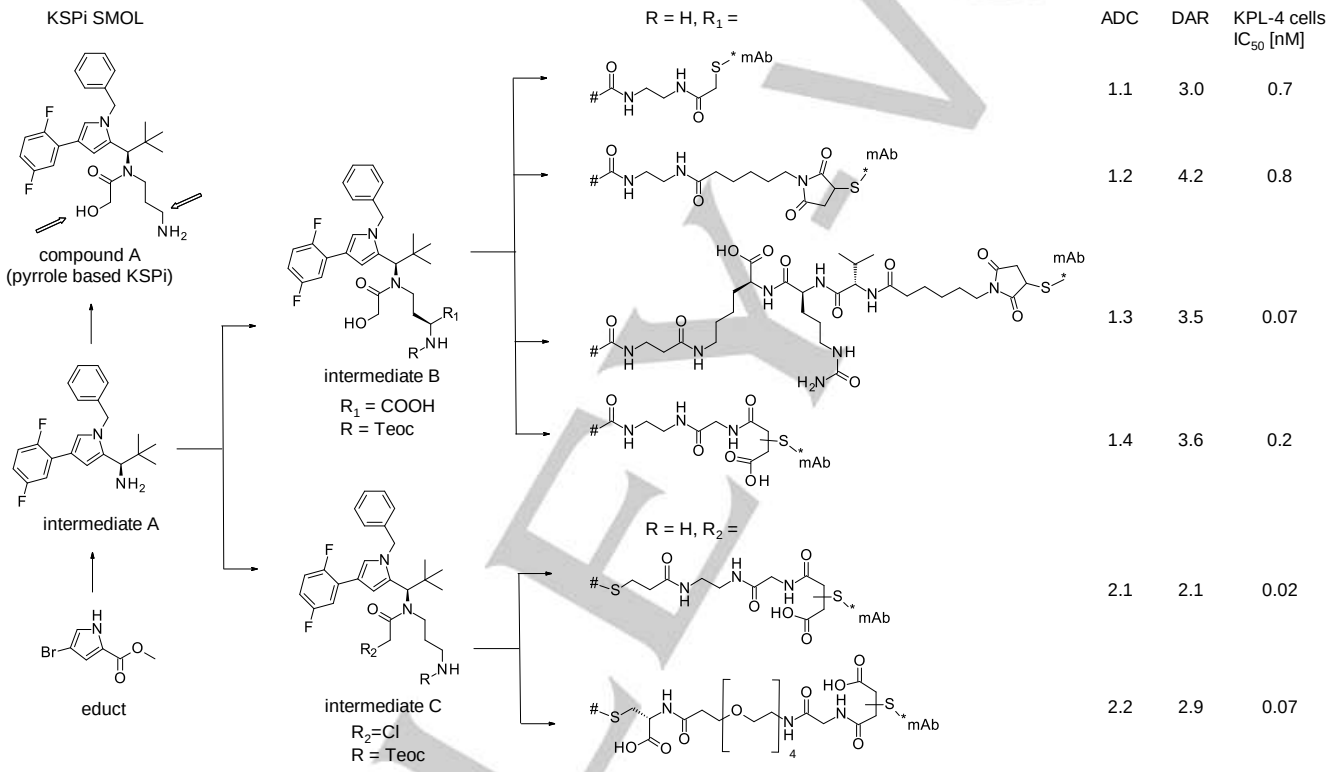
provided in the supporting information. All ADCs were highly potent against the HER2 positive breast cancer cell line KPL-4 with IC_{50} values in the picomolar range.

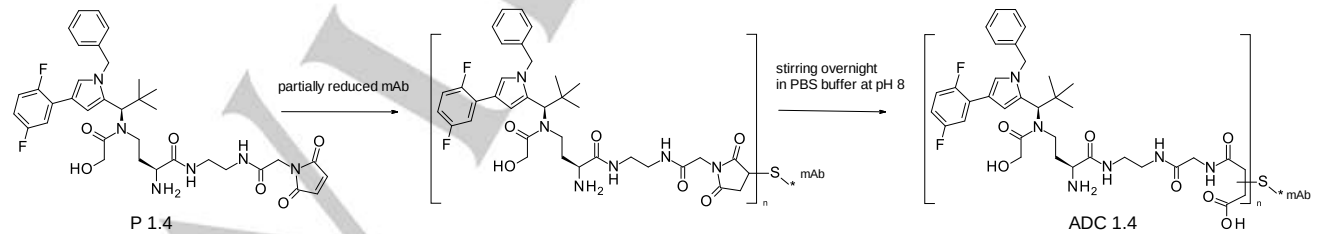
Cysteine-linked ADCs conjugated via maleidocaproyl linker as employed in many ADCs in the clinic and also in ADC 1.2. are susceptible to de-conjugation by retro-Michael reaction which may be associated with off-target side effects.[12] Since ring-opened succinimides are no longer susceptible to retro-Michael type reactions, ring opening was strived for by e.g. Tumey et al. via stirring ADCs for 48 h at a pH of 9.2 at elevated temperatures.[13] Lyon et al. described the utilization of adjacent amino groups to provide self-hydrolizing maleimides under much milder conditions which, however, adds additional complexity.[14] With KSP ADCs we observed that the ease of hydrolysis of the succinimide thioether very much depends on the length of the alkyl chain between succinimide and amide bond. When ADC precursor P1.4 with a maleidoacetyl amide linker is conjugated to the HER2 antibody, nearly quantitative ring-opening of the obtained ADC is achieved under mild conditions just by stirring overnight in PBS buffer at pH 8 and room temperature providing the ADC 1.4 (Scheme 1b). In contrast, no ring opening was found under the same conditions with the chain-elongated ADC 1.2

Consequently, the ADC 1.4 with the ring-opened succinic acid amide linker does not show significant de-conjugation upon stirring for 12 days in TRIS-buffer in the presence of *N*-acetylcysteine. In contrast, under the same conditions, a loss of ~60% of its initial drug load was observed with ADC 1.2 (Fig. S5).

a) Synthesis of KSPi SMOL (compound A) and ADCs (exemplified for HER-2 ADCs)



b) Synthesis of ring-opened ADCs conjugated via succinimido acetamides



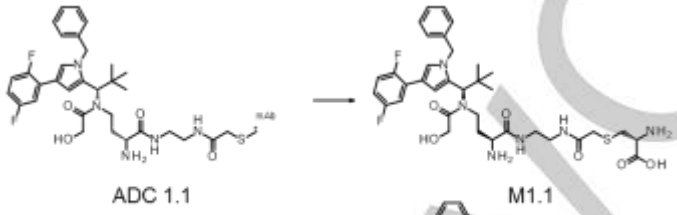
Scheme 1a. Pyrrole-based inhibitors of kinesin spindle protein (KSP) and exploration of appropriate attachment sites and linker chemistries for highly potent HER-2-targeting ADCs. Drug-to-antibody ratios (DARs) and potency of the ADCs in the HER2 positive breast cancer cell line KPL-4. **Scheme 1b.** Ring-opening of ADCs conjugated via succinimido acetamides under mild conditions (exemplified for HER2 KSP ADC 1.4) providing stable ADCs (Fig. S4 and S5).

Inspired by the favorable technical profile of HER-2 targeted KSP-ADCs with BAY-865 and particularly by the strong potency observed in HER-2 positive tumor cells, we investigated the extension to tumor targets so far unexplored in the ADC setting such as the TWEAK receptor (TWEAKR / Fn14). By IHC, we confirmed the TWEAKR antigen expression described for different solid tumor indications also in a broad panel of cancer cell lines representative for these tumors (Table 1 and Table S1,

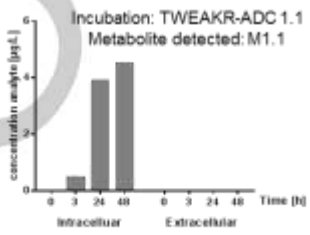
columns 1-3). Furthermore, the small molecule KSPi compound A was also found to be highly potent with IC_{50} values in the picomolar range against the cell panel (Table 1 and Table S1, column 4).

For ADC synthesis, the fully humanized anti-TWEAKR hIgG1 antibody was prepared in its aglycosylated form (BAY-356)[15] and showed good binding affinity (K_d ~ 13 nM) to TWEAKR and TWEAKR-dependent internalization (Fig. S6). The thiol reactive ADC precursor molecules were coupled to the anti-TWEAKR antibody BAY-356 in analogy to the BAY-865-conjugated ADCs described above. Ring-opening of the anti-TWEAKR ADCs 1.4, 2.1, and 2.2 after stirring overnight at pH 8 and room temperature was higher than 90% for all ADCs. The DARs were in the range of 3.4 - 4.6 without significant formation of aggregates (Supporting Information). Overnight stirring at pH 8 had no significant influence on IEF profiles of the antibodies showing that these conditions were well tolerated by the antibodies (Figure S3).

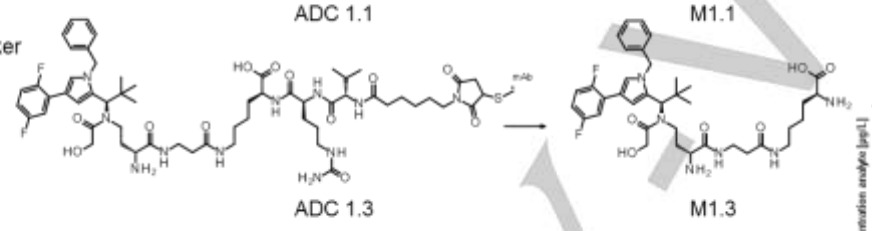
a) non-cleavable linker



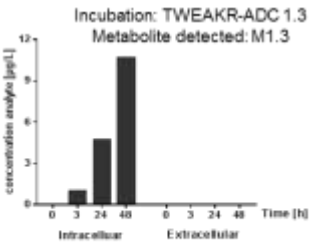
ADC 1.1 M1.1



b) cleavable linker



ADC 1.3 M1.3



c) metabolite profile

		Compound A	M1.1	M1.3
Biochemical KSP assay	IC_{50} [nM]	1.1	0.62	2.6
Cytotoxicity assay against NCI-H292	IC_{50} [nM]	0.17	21	120
Transport B → A in Caco-2 cell assay	[nm/s]	213	6	2

Scheme 2a and 2b. Intracellular metabolism of ADCs 1.1 or 1.3 and detection of metabolites M1.1 and M1.3, respectively. After incubation of NCI-H292 cells in vitro for 3, 24, or 48 h with the TWEAKR-ADCs 1.1 (DAR=1.8) or 1.3 (DAR=3.7) concentration of metabolites M1.1 and M1.3, respectively, increases over time in the intracellular compartment and remains below the lower limit of quantitation (LLOQ=1µg/L) in the extracellular compartment. **Scheme 2c.** In vitro potency and permeability profile of pyrrole-containing KSPi compound A and intracellularly formed metabolites M1.1 and M1.3.

Most of the ADCs exemplified in scheme 1 have non-cleavable linkers, while ADC 1.3 contains a cathepsin B cleavable linker. Representative routes of ADC metabolism after internalization and trafficking into the lysosomal compartment are shown in scheme 2a and 2b. Formation of the cysteine metabolite M1.1 is expected after complete antibody degradation of ADC 1.1 in the lysosomes, while metabolite M1.3 is formed upon cathepsin B mediated cleavage of ADC 1.3.

The profile of these metabolites has been investigated in comparison to the KSPi compound A (Scheme 2c). Similar to compound A, metabolites M1.1 and M1.3 are highly potent in an enzymatic KSP inhibition assay indicating that linker or linker fragments attached to the KSPi molecule at that particular position do not negatively impact KSP inhibition. However, when cytotoxicity against tumor cells such as NCI-H292 is measured, compound A is highly potent, whereas M1.1 is 100-fold and M1.3 even 1000-fold less active. The reason for these pronounced differences are different membrane permeabilities which have been investigated in a Caco-2 assay as a surrogate. In this assay, compound A shows high passive permeability and pronounced transporter-mediated efflux, whereas both M1.1 and M1.3 display very low permeability and low active efflux. These different membrane permeability profiles of KSPi ADC metabolites offer a great flexibility in adapting ADC performance to the requirements of individual targets. Metabolites with low permeability are trapped intracellularly thus enabling a long lasting exposure inside the tumor cell and at the same time reduce off-target toxicities due to low permeability into normal cells. In contrast, metabolites with high permeability like compound A may induce by-stander killing in tumors with heterogeneous target expression.

In scheme 2a and 2b it is shown that upon incubation of NCI-H292 cells with ADCs 1.1 and 1.3 the expected metabolites M1.1 and M1.3 can be detected in a time-dependent manner only in the intracellular fraction and not in the supernatant. These findings are in alignment with the permeability data from the Caco-2 assay and indicate an intracellular trapping of the metabolites after binding and internalization of the ADCs. Taken together, this profile allows for a long lasting intracellular exposure of cytotoxic metabolites and may help to extend activity also against cancer cells entering the G_2/M phase of the cell cycle relevant for KSP inhibition at a later point in time.

All TWEAKR ADCs were active against the TWEAKR-positive NSCLC cell line NCI-H292, the pancreatic cancer cell line BxPC3, and the colorectal cancer cell line LoVo. In this panel, the TWEAKR ADCs 1.4 and 2.2 showed a very consistent potency in the picomolar range with ~1000-fold selectivity versus

respective isotype control ADCs containing identical linkers and payloads (Table 1). Antigen-dependency of ADC potency was furthermore shown by comparing the TWEAKR-negative cell line NCI-H520 and the same cell line stably transfected with TWEAKR. While the SMOL KSP inhibitor compound A is highly potent in both cell lines, the TWEAKR ADC is selectively potent in the transfected target positive variant only, clearly indicating that target antigen expression is required for anti-tumor activity (table S2). Extended *in vitro* testing confirmed the high potency of the TWEAKR ADCs 1.4 and 2.2 in further tumor cell lines from various solid cancer indications (Table S1).

Cancer type	Cancer cell line	IHC Anti-TWEAKR	SMOL KSPi Compound A IC_{50} [M]	TWEAKR-KSP-ADC 1.1 IC_{50} [M]	TWEAKR-KSP-ADC 1.2 IC_{50} [M]	TWEAKR-KSP-ADC 1.3 IC_{50} [M]	TWEAKR-KSP-ADC 1.4 IC_{50} [M]	TWEAKR-KSP-ADC 2.1 IC_{50} [M]	TWEAKR-KSP-ADC 2.2 IC_{50} [M]	Control-KSP-ADC 1.4 IC50 [M]	Control-KSP-ADC 2.2 IC50 [M]
NSCLC	NCI-H292	+++	3.5E-10	4.1E-10	4.4E-8	7.4E-10	3.0E-10	3.1E-10	9.4E-11	>1.0E-07	>1.0E-07
Pancreatic cancer	BxPC3	+++	<3.0E-11	9.7E-10	6.6E-9	8.7E-10	8.7E-10	1.1E-09	1.6E-10	>1.0E-07	>1.0E-07
CRC	LoVo	+++	<3.0E-11	6.0E-07	6.0E-07	6.0E-07	8.5E-11	3.7E-10	6.2E-11	5.8E-08	5.6E-08

Table 1. *In vitro* potency of SMOL KSPi compound A and of TWEAKR-KSP ADCs 1.1., 1.2, 1.3, 1.4, 2.1, and 2.2 in TWEAKR-expressing cell lines versus selected respective isotype control ADCs 1.4 and 2.2 with same linker payload chemistry

In vivo efficacy of the TWEAKR targeting ADCs was investigated in the non-small cell lung cancer (NSCLC) model NCI-H292. Tumor regressions were observed after 3 treatments with ADC 1.4 (5 and 10 mg/kg) or ADC 2.2 (10 mg/kg; Figure 1a). The isotype control ADC of 2.2 was ineffective at the same doses and ispinesib, a small molecule KSPi which had been tested in clinical trials, had only moderate efficacy at doses of 10 mg/kg. The repeated doses of ADC did not induce a body weight loss of the mice. In the TWEAKR-expressing patient-derived urothelial cell cancer (UCC) xenograft model BXF 1218, the KSP ADC 1.4 administered at 5 or 7.5 mg/kg showed high efficacy with complete tumor eradication with both dose levels. Ispinesib as SMOL KSP inhibitor at 10 mg/kg and gemcitabine (standard of care in UCC) showed moderate activity whereas the isotype control ADC was inactive which again demonstrates the specificity of the ADC induced tumor cell killing (Figure 1b).

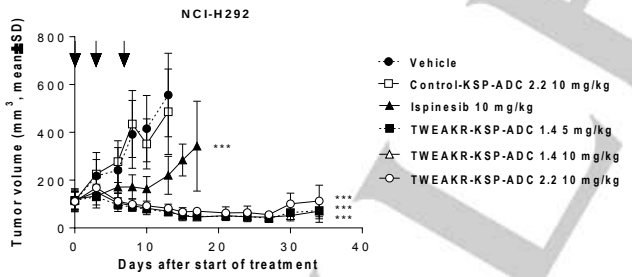


Figure 1a. Efficacy of TWEAKR-ADCs 1.4 and 2.2 with aglycosylated TWEAKR mAb BAY-356 in the NCI-H292 NSCLC xenograft model in NMRI nude mice.

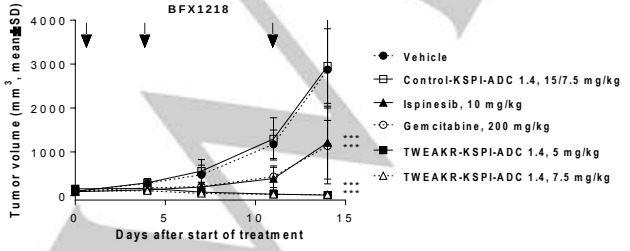


Figure 1b. Efficacy of TWEAKR-KSP ADC 1.4 in the BXF1218 UCC PDX model in NMRI nude mice.

In conclusion, we have shown that KSPis are a versatile new payload class for the generation of highly potent and selective ADCs against different targets as shown for HER-2 and the TWEAK receptor. The small molecule KSPi (compound A) offers high flexibility in terms of linker attachment site and linker composition. The stability of cysteine-linked KSPi ADCs is improved by ring-opening of thiosuccinimide which can be achieved under mild conditions by stirring overnight at pH 8 when maleimido acetyl amide linkers are employed.

Variation of the linker chemistry of KSPi ADCs allows for a flexible design of intracellularly formed active metabolites with high affinity to the KSP enzyme and different membrane permeability profiles. KSPi metabolites with low efflux accumulate in tumor cells intracellularly after ADC administration, which may extend activity and reduce off-target toxicities. KSP-ADCs targeting TWEAKR demonstrate potent and selective anti-proliferative activity in a panel of TWEAKR-positive cancer cell lines *in vitro* and high antitumor efficacy *in vivo*. Thus, ADCs with KSPi as payload offer a promising new approach for tumor treatment and further evaluation in additional cancer types is warranted and will be reported elsewhere.

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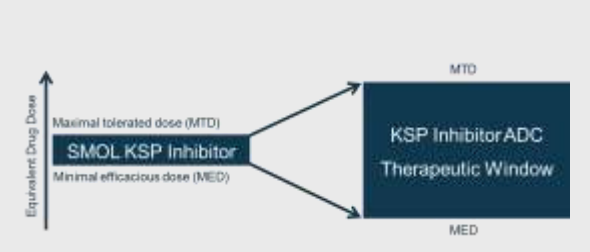

Flexible - Stable - Potent! Inhibitors of kinesin spindle protein (KSP) have been developed as a novel payload class in antibody drug conjugates (ADC) to increase the therapeutic window. Flexibility in linker attachment and tuning of the profile of active metabolites fitting to the KSPi mode of action as well as high linker stability provide potent ADCs against different targets.

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Antibody-drug conjugates with pyrrole-based KSP inhibitors as the payload class