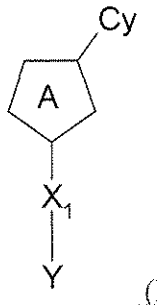
(Svensson et al. 2002 and Mangla et al 2004). Similarly, the clinical efficacy observed with a neutralizing antibody to the B cell stimulating factor BlyS supports a role for B cells in the pathophysiology of systemic lupus erythematosus (SLE) (La Cava 2010). Given the necessity for BTK for the production of autoantibodies, including anti-DNA antibodies, in murine models of SLE (Steinberg et al., 1982; Golding et al., 1983; Scribner et al., 1987; Seldin et al.,1987; Satterthwaite et al., 1998; Takeshita et al., 1998;Whyburn et. al., 2003), BTK inhibitors may offer therapeutic benefit to SLE patients.

Within myeloid cells, BTK signal transduction is necessary for the stimulated release of inflammatory cytokines such as TNF from stimulated monocytes (Horwood, J Exp Med, 2003, 1603-xxx) and for optimal actin cytoskeletal organization and lacunar bone resorption in isolated osteoclasts (Danks, 2011, J Bone and Mineral Research, 26, 182–192). Bone marrow derived mast cells lacking BTK exhibit impaired activation-induced degranulation and cytokine release (ref). Given the role of BTK in signal transduction processes across multiple cell types implicated in the pathogenesis of autoimmune and allergic disorders, inhibition of BTK activity may provide clinical benefit in diseases such as RA, MS, SLE, asthma and allergic disorders.

SUMMARY ~~OF THE INVENTION~~

The ~~invention~~ disclosure comprises a novel class of heteroaromatic compounds and methods for making and using the same. These compounds are useful for the treatment of autoimmune and allergic disorders in that they exhibit good inhibitory effect upon BTK.

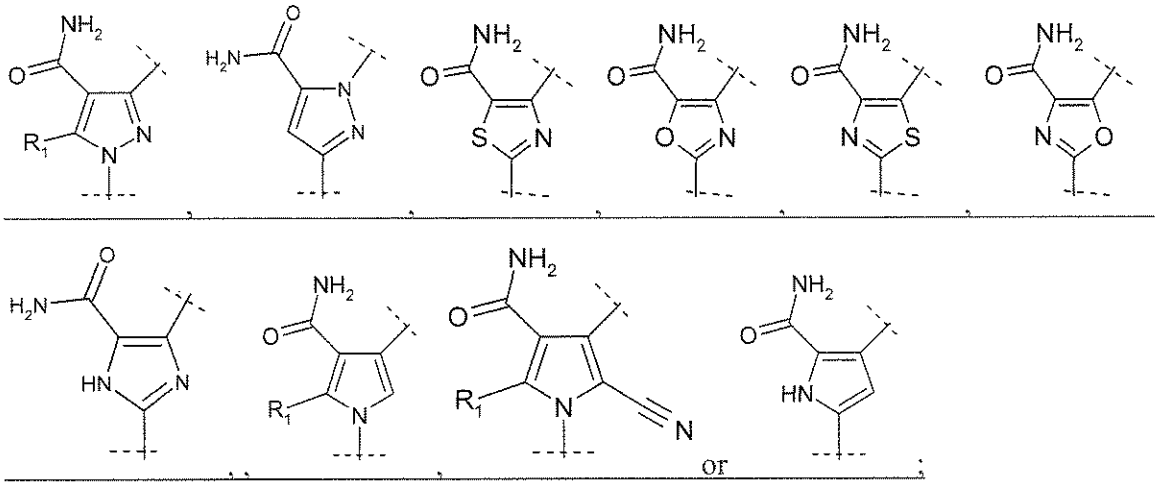
In a first aspect, there is provided a compound of the formula (I)



(I)

wherein

A ring is:



R_1 is $N(R_3)_2$ or hydrogen;

Cy is aryl or heteroaryl each is substituted by R_2 and optionally substituted by halogen, halo C_{1-4} alkyl, C_{1-4} alkyl and C_{1-4} alkoxy;

R_2 is chosen from:

L-Ar, C_{1-6} alkyl and C_{1-6} alkoxy, each Ar, C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted by halogen, halo C_{1-4} alkyl, C_{1-4} alkyl, R_3-$S(O)_m$-, -CN, -C(O)-$N(R_3)_2$ or C_{1-4} alkoxy;

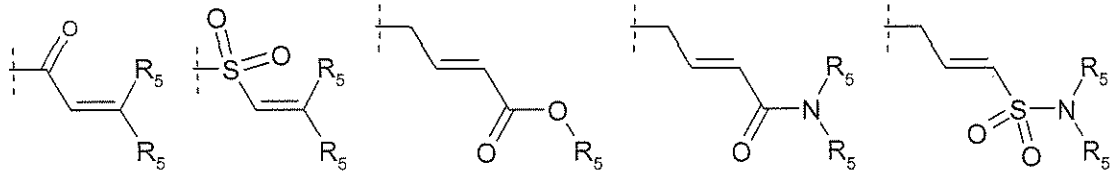
L is a linker chosen from a bond, O, >C(O). -$(CH_2)_n$-, -O-$(CH_2)_n$-, -$N(R_3)$-, -$N(R_3)$-$(CH_2)_n$-, -$(CH_2)_n$-$N(R_3)$-, -C(O)-$N(R_3)$-, -C(O)-$N(R_3)$-$(CH_2)_n$-,-$N(R_3)$-C(O)-$N(R_3)$-, -$N(R_3)$-C(O)-, -$S(O)_m$-$N(R_3)$- and -$N(R_3)$-$S(O)_m$-, wherein the -CH_2- in each L can have 1-2 hydrogens replaced by C_{1-3} alkyl, said C_{1-3} alkyl groups can optionally cyclize to form a C_{3-6} cycloalkyl ring;

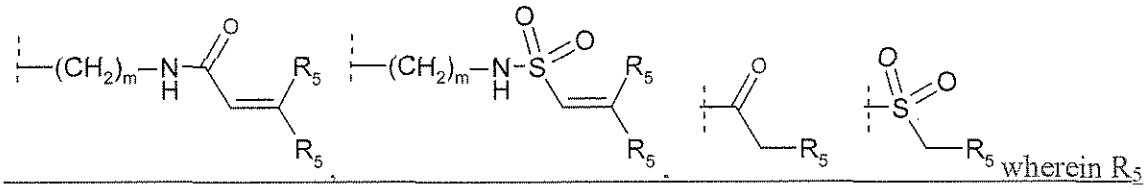
Ar is carbocycle, heterocycyl or heteroaryl;

X_1 is a linker chosen from a bond, $-(CH_2)_n-$;

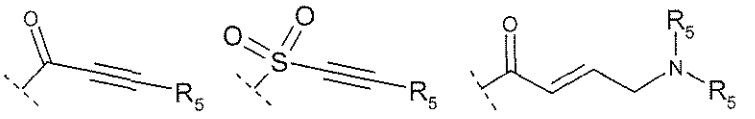
Y is chosen from C_7-C_{10} spirocycle optionally containing 0-1 ring nitrogen atoms, a nitrogen containing mono- or bi-cyclic heterocycle, carbocycle, aryl, each substituted by one R_4;

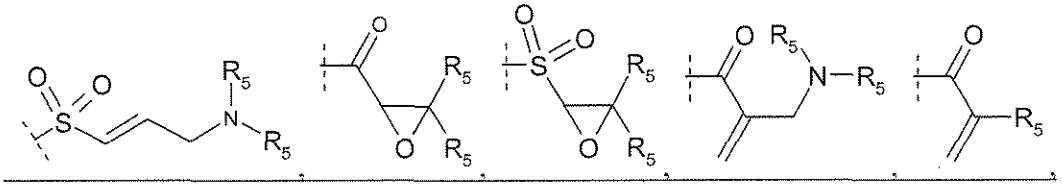
R_4 is

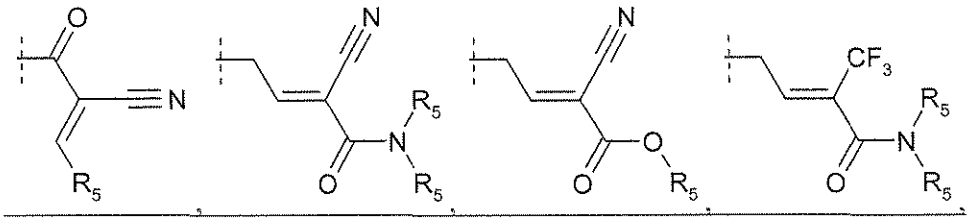


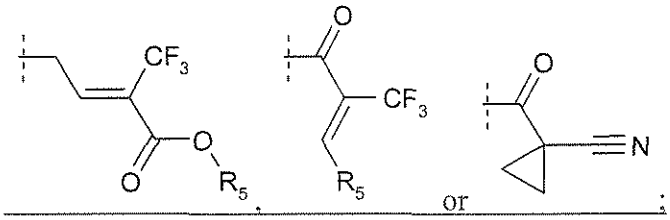


wherein R_5 cannot be hydrogen,









or

;

each n is independently 1-4;

each m is independently 0-2;

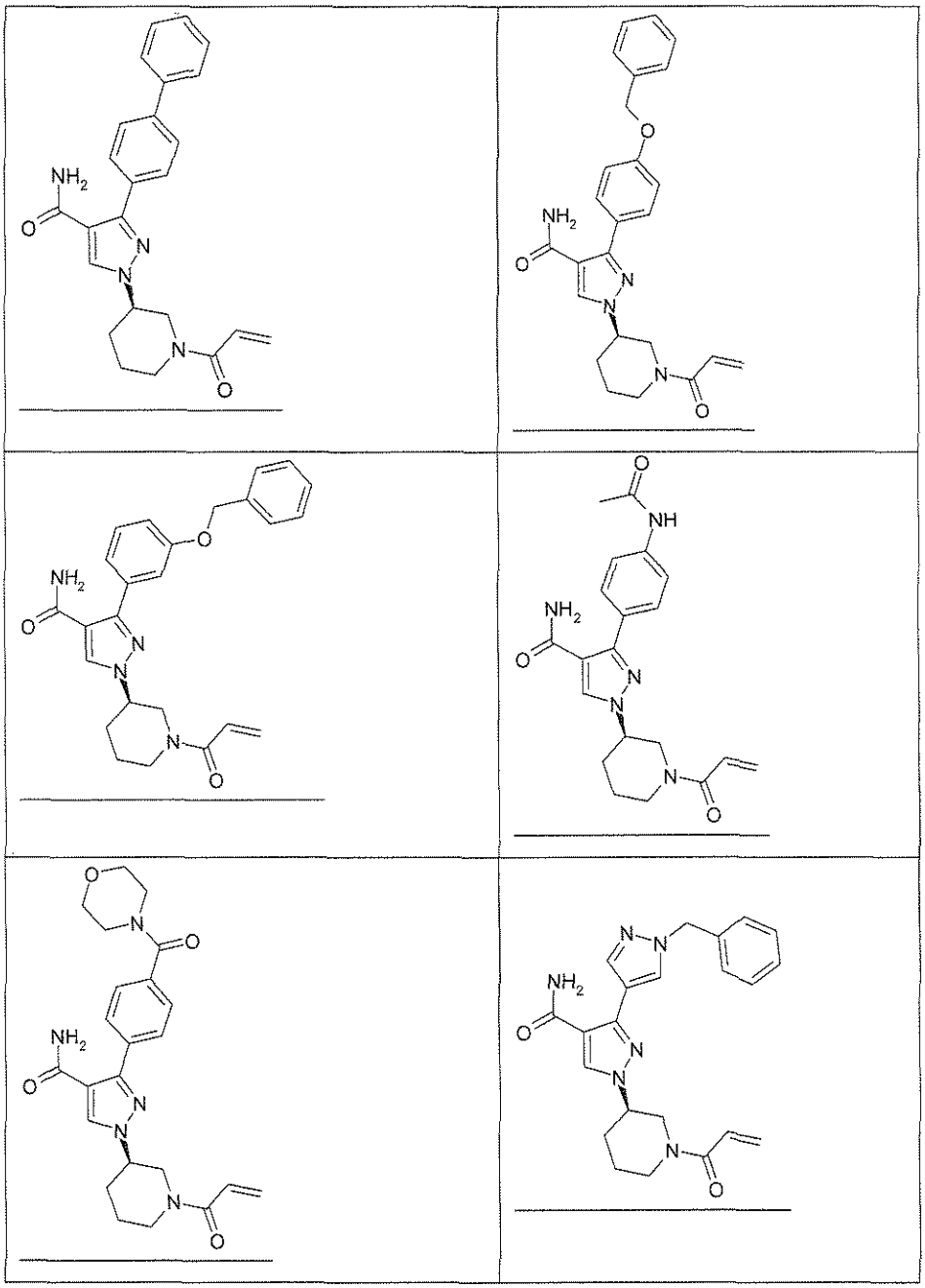
each R_3 is independently chosen from hydrogen or C_{1-4} alkyl;

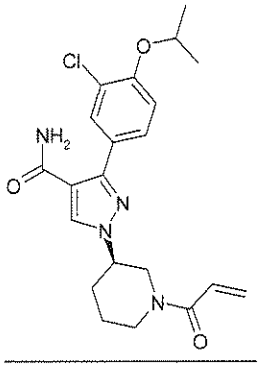
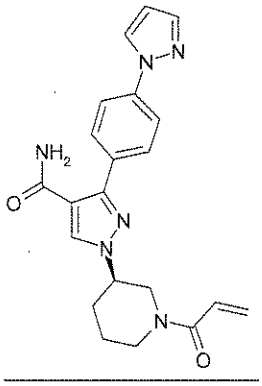
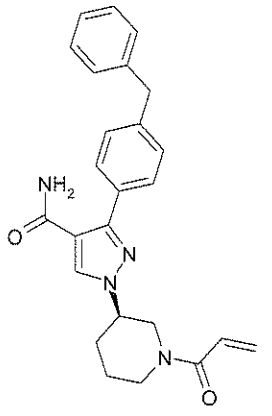
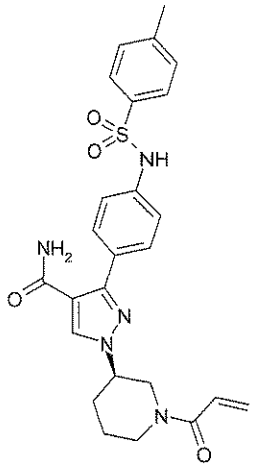
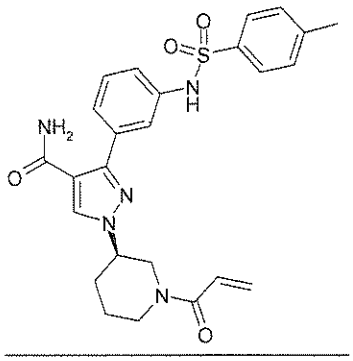
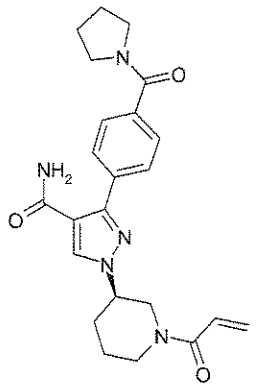
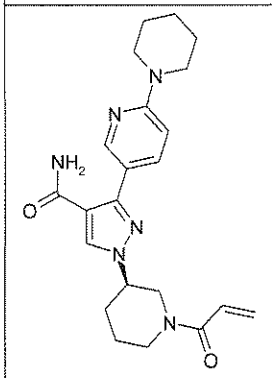
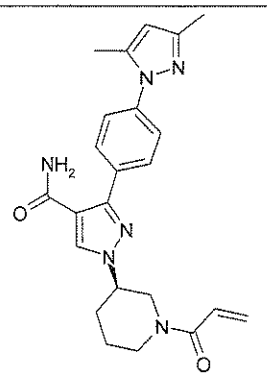
each R_5 is independently chosen from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylC_{1-4} alkoxy, -$(CH_2)_n$-heterocycle and heterocycle each heterocycle optionally substituted by halogen, OH or R_3-$S(O)_m$-;

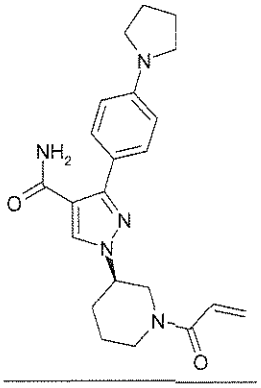
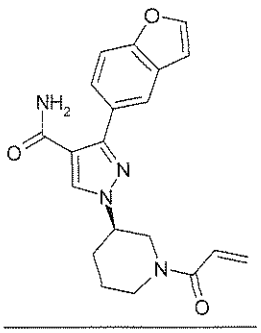
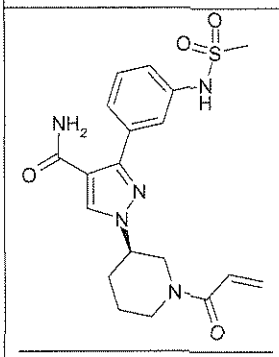
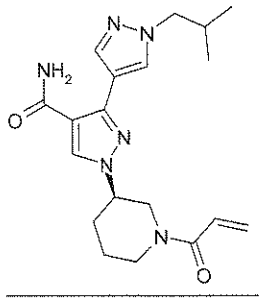
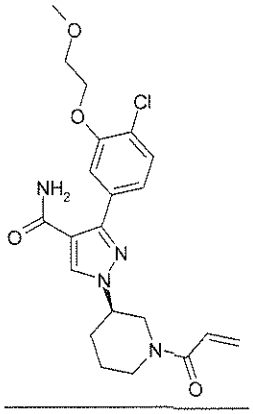
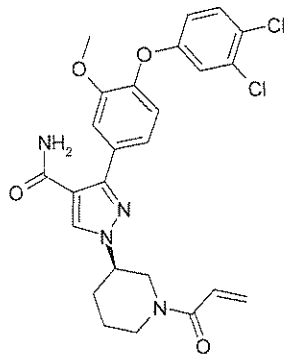
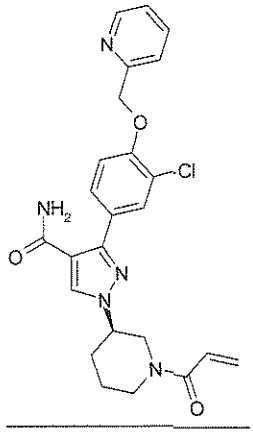
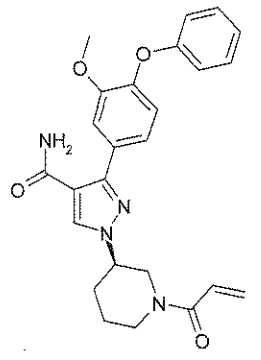
each group defined above for Cy, R_1-R_5, X_1 and Y can be where possible partially or fully halogenated;

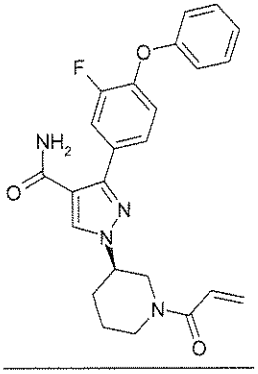
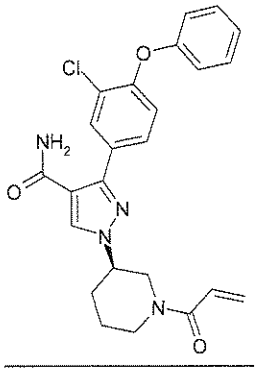
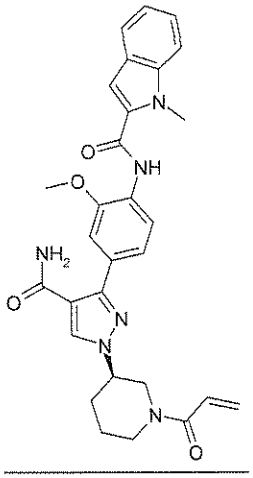
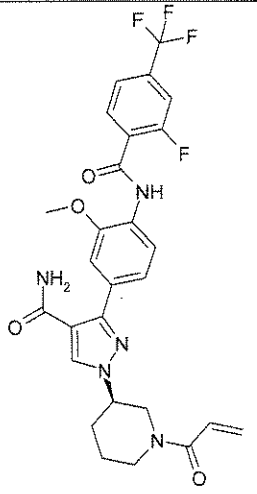
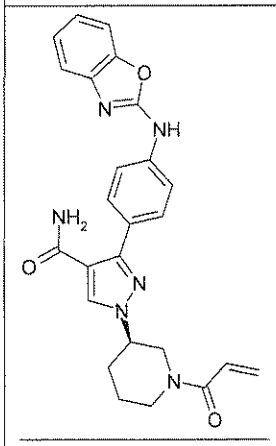
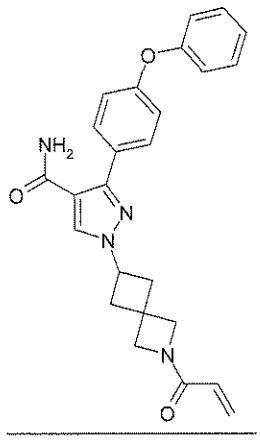
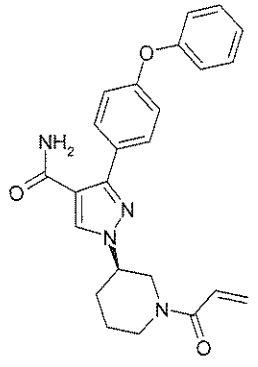
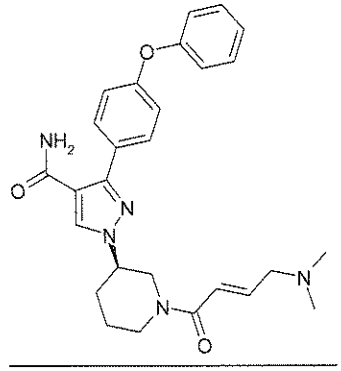
or a pharmaceutically acceptable salt thereof.

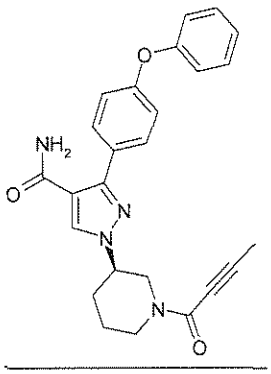
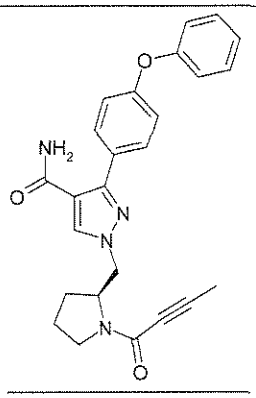
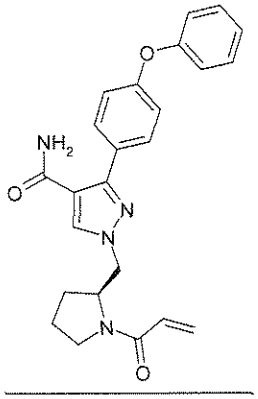
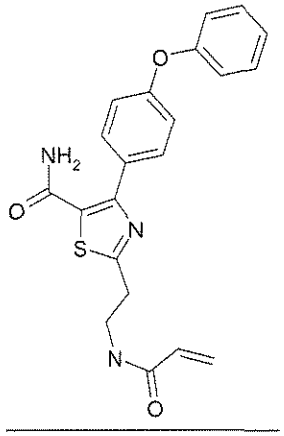
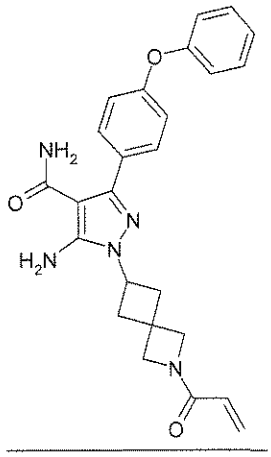
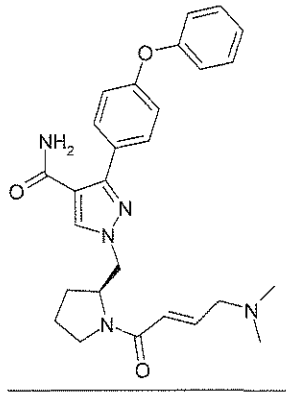
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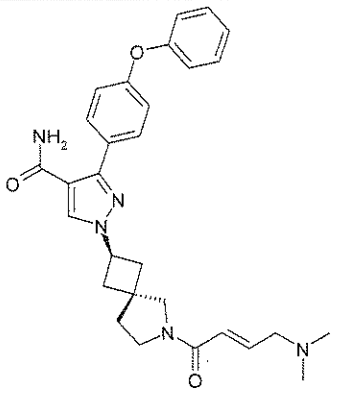


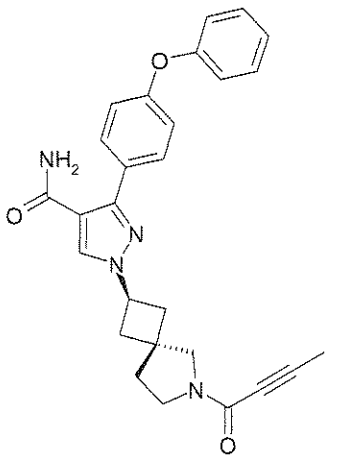
	
	
	
	

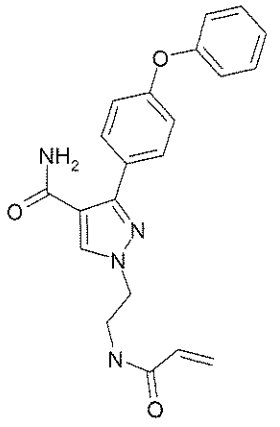
	
	
	
	

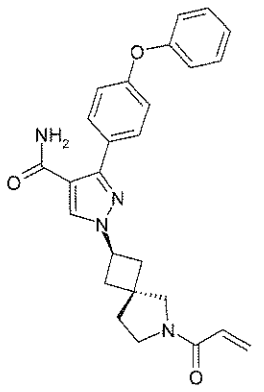
	
	
	
	

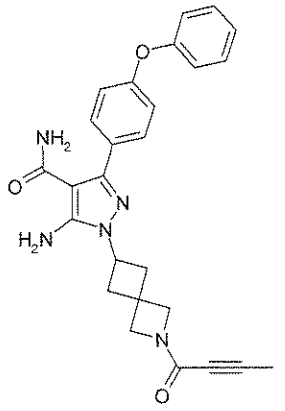
	
	
	

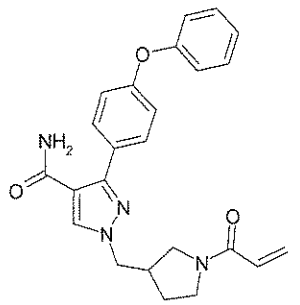


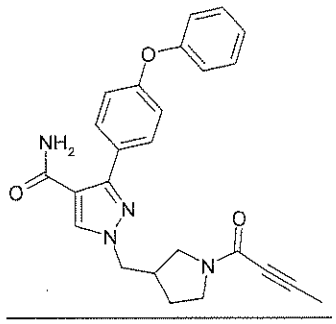


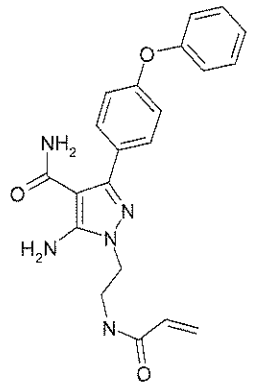


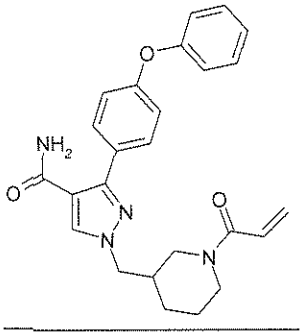
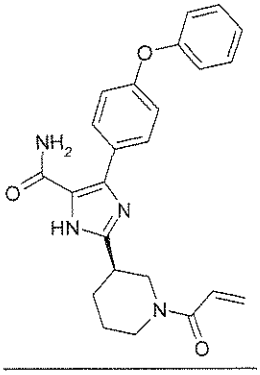
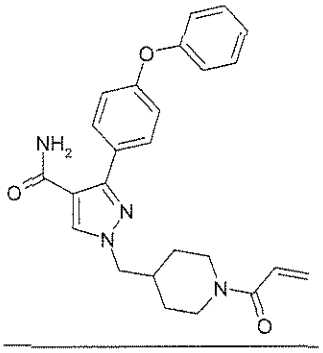
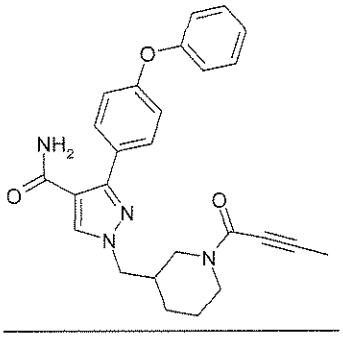
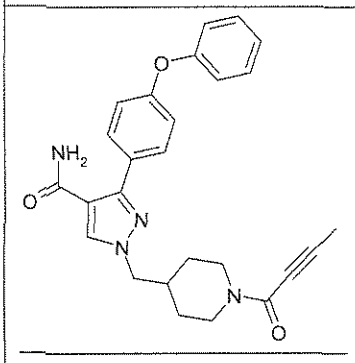
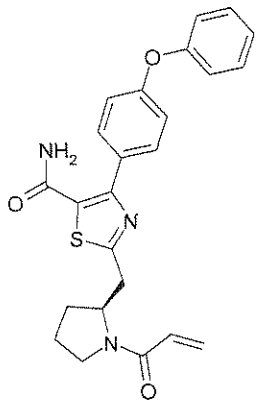
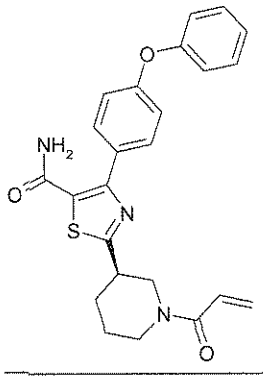
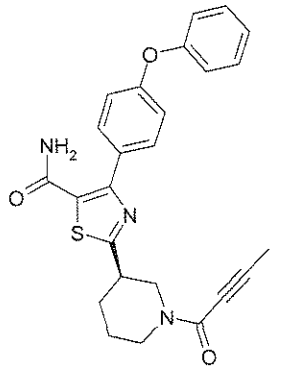


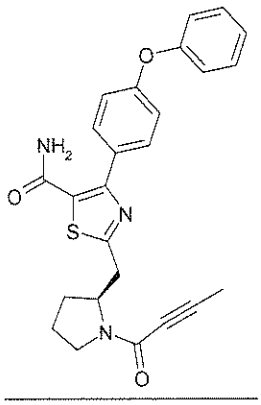
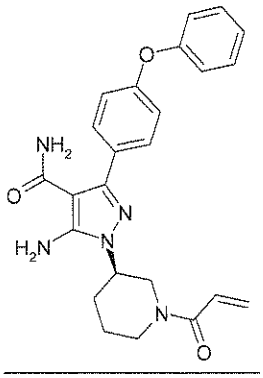
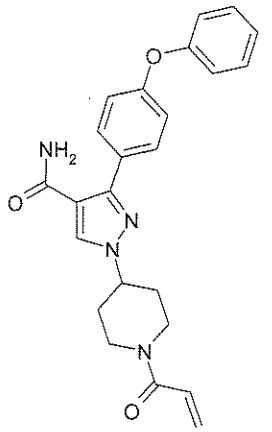
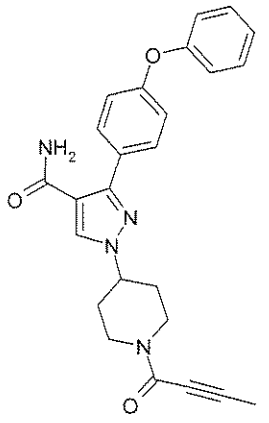
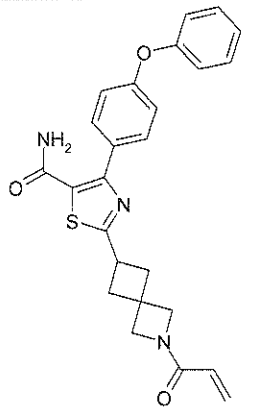
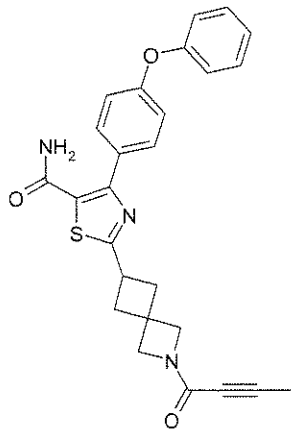


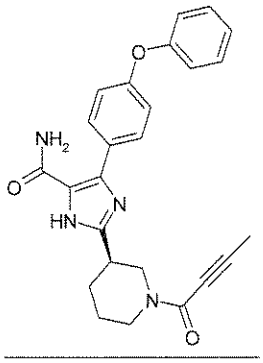
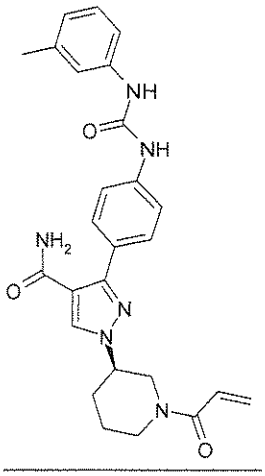
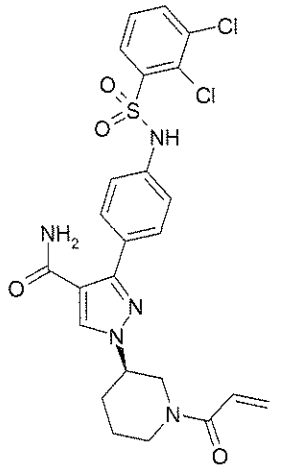
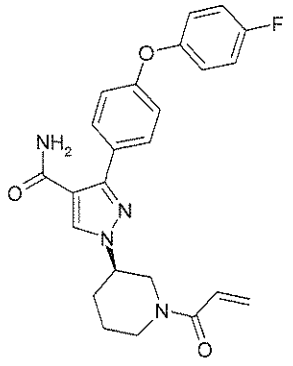
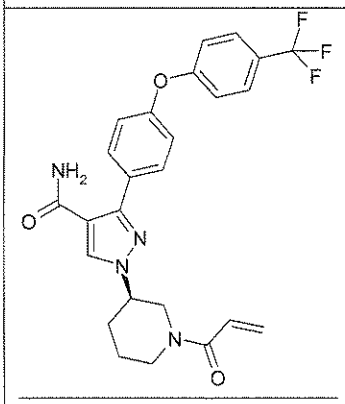
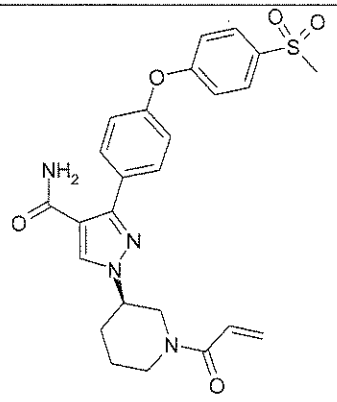


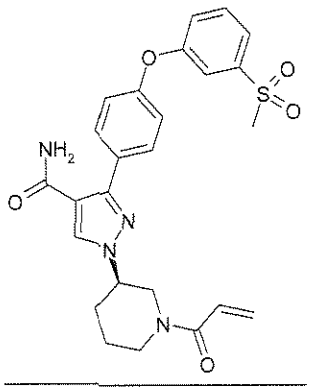
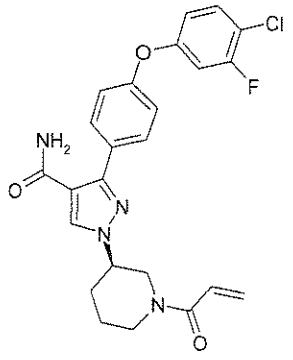
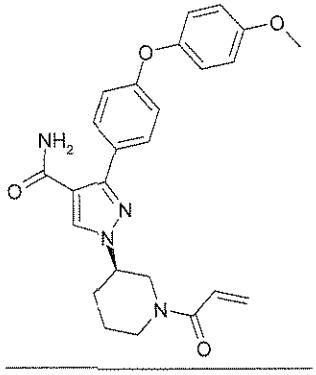
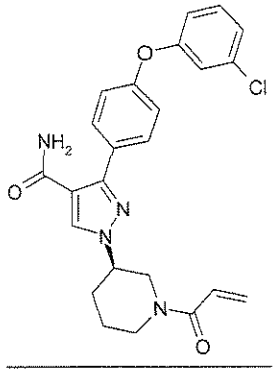
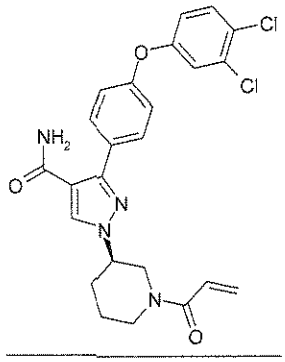
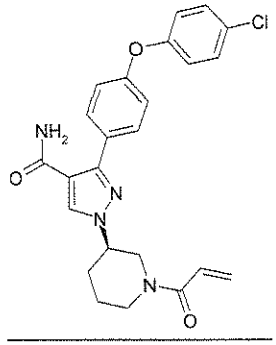
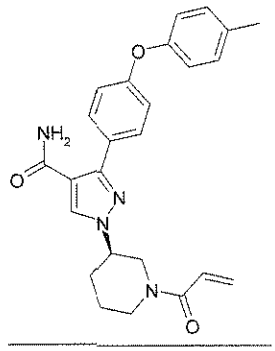
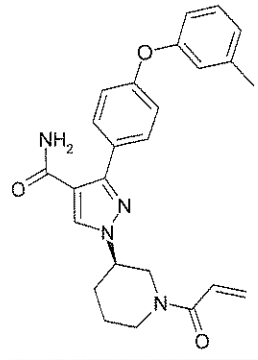


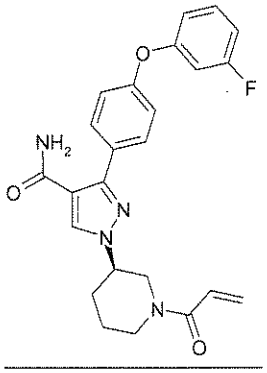
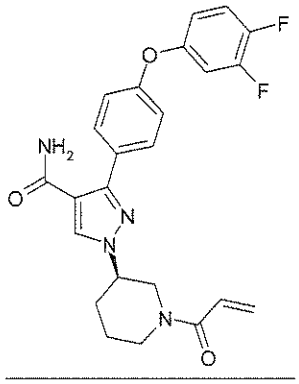
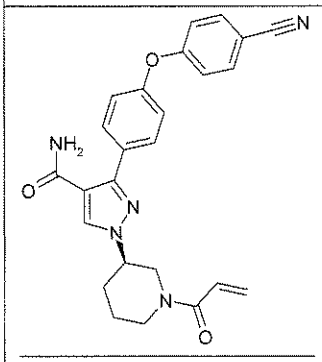
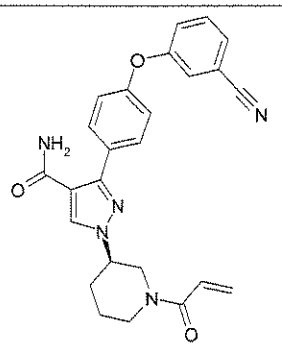
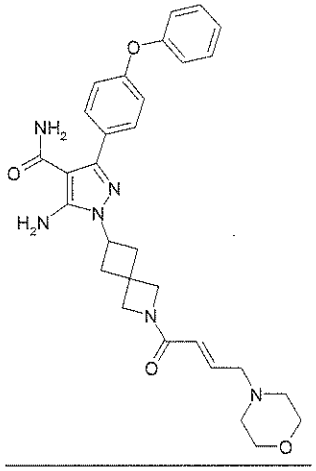
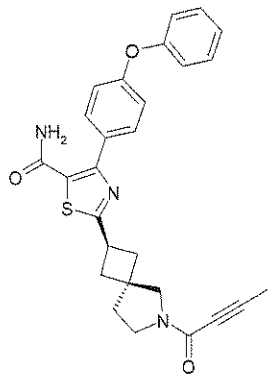
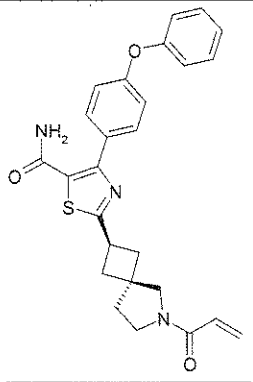
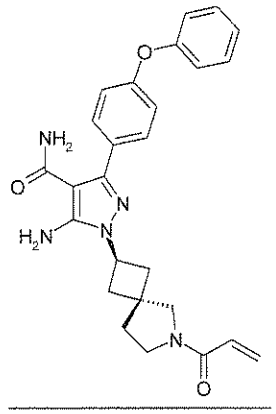


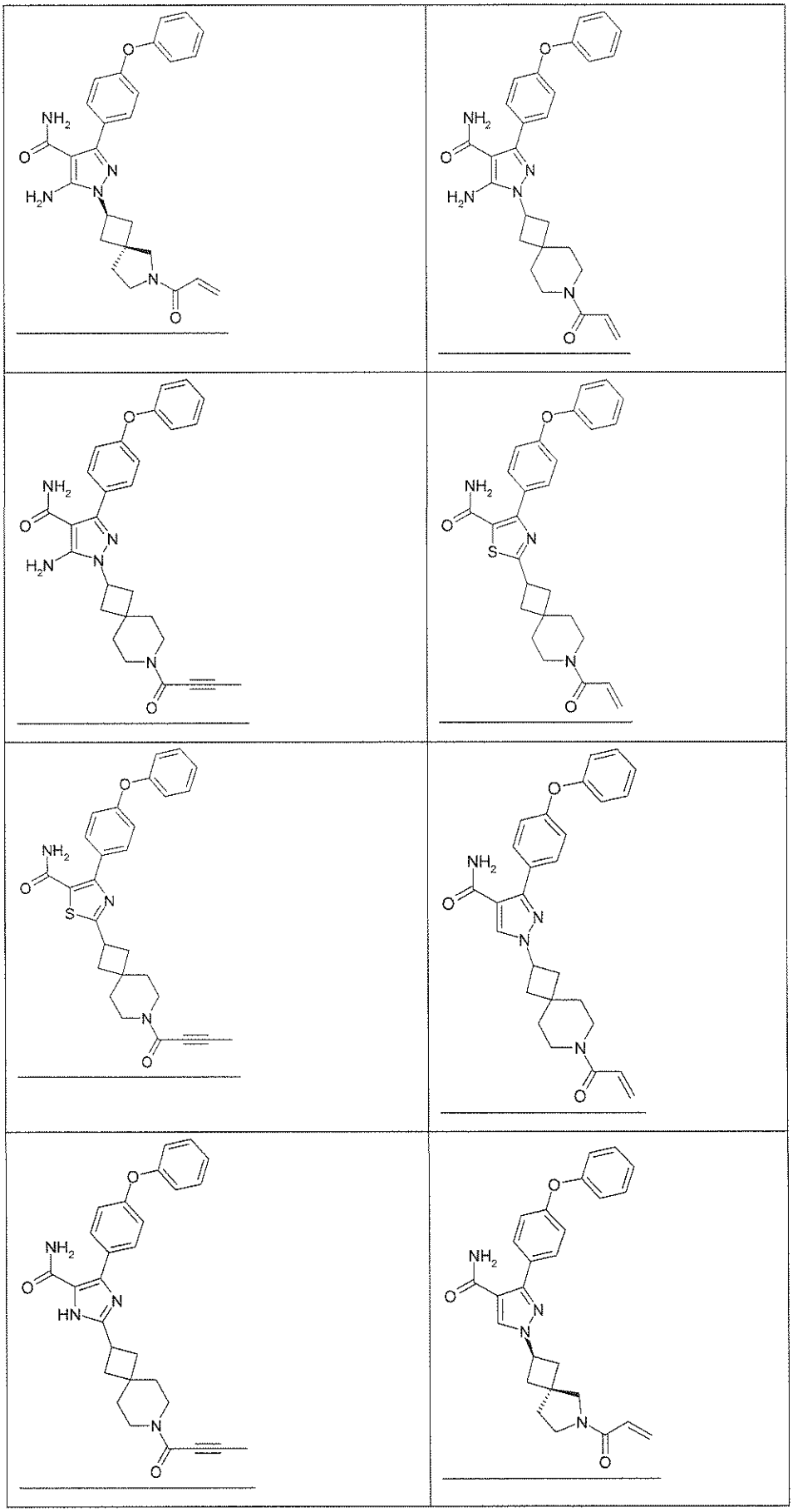
	
	
	
	

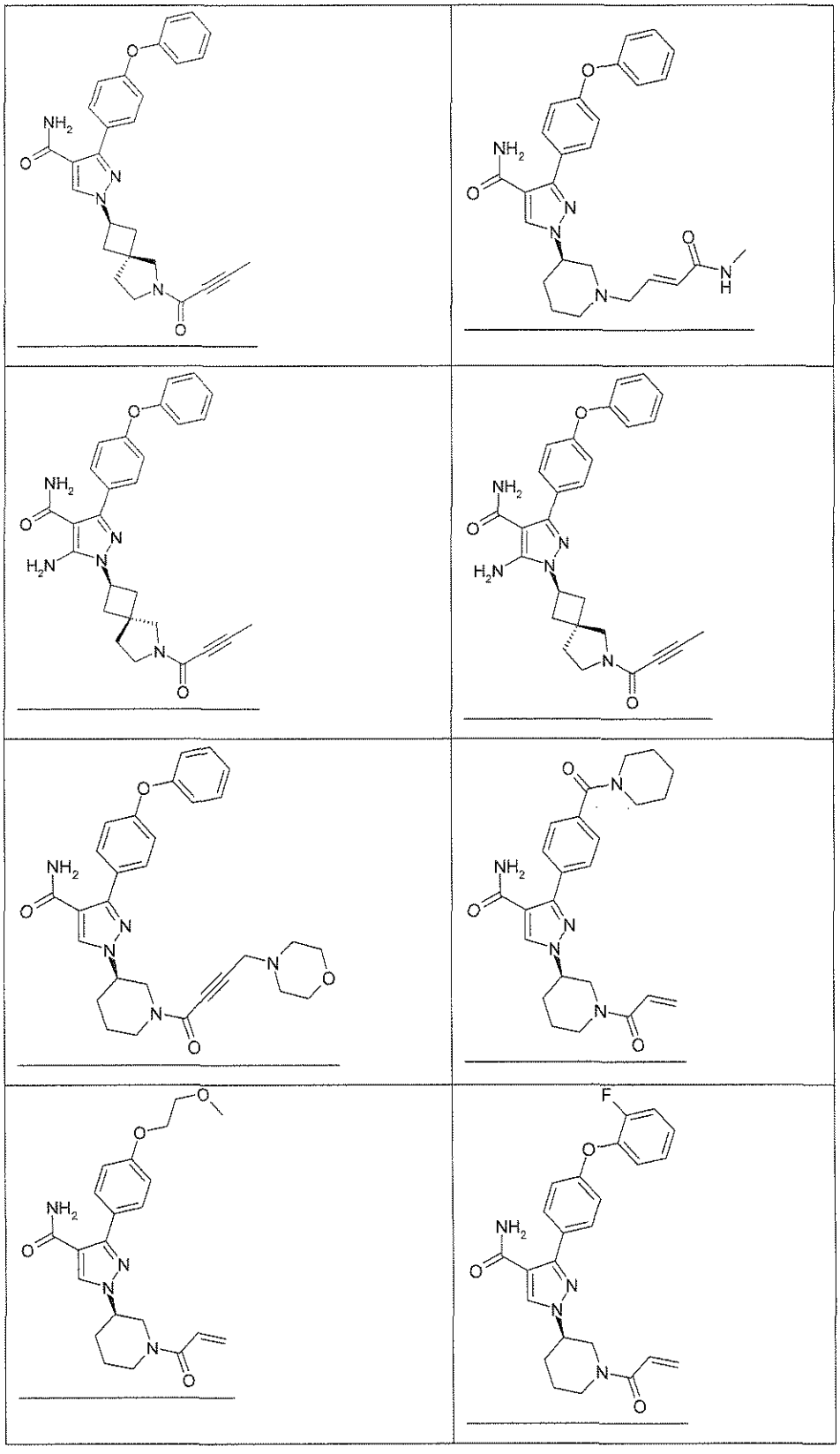
	
	
	
	



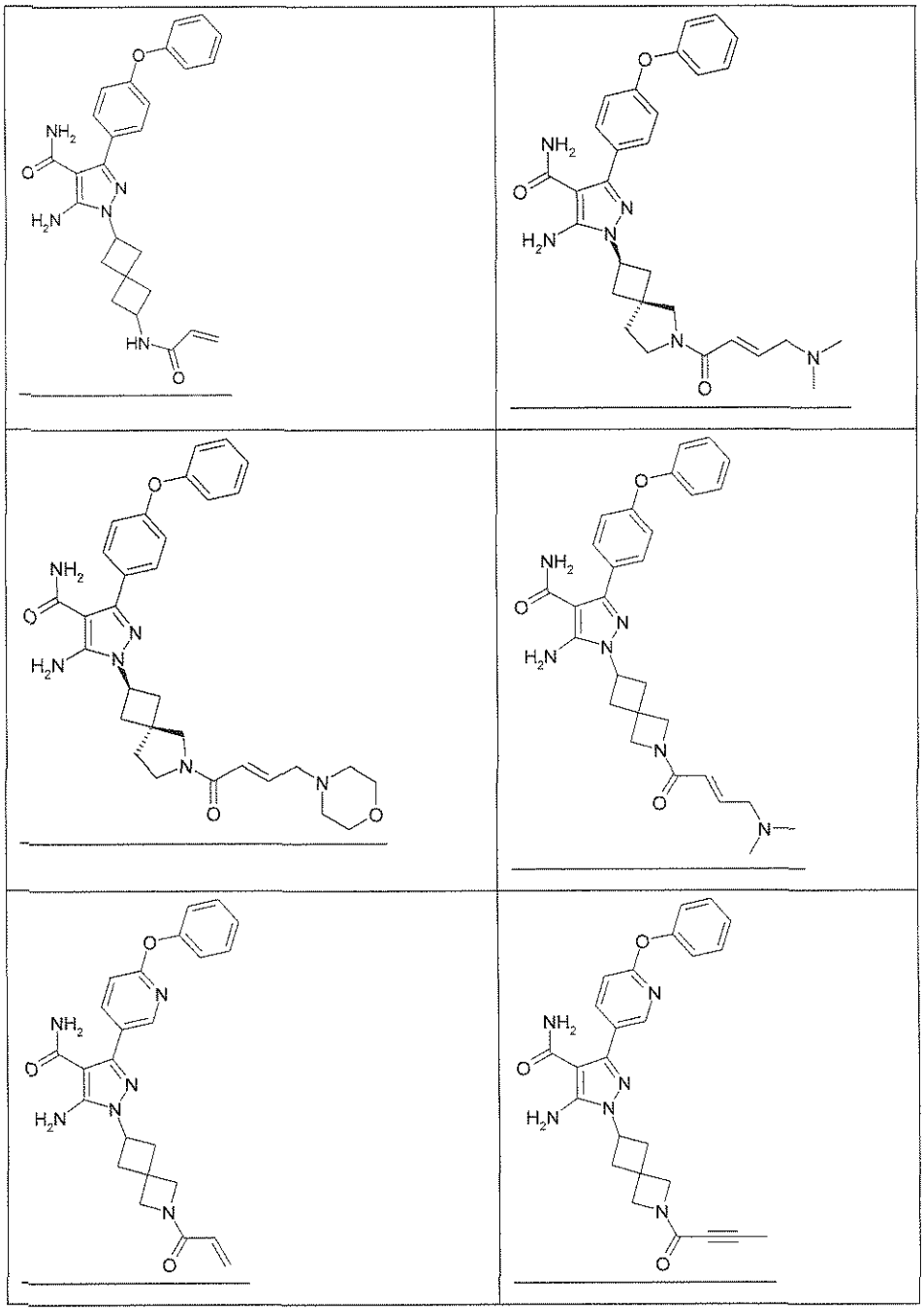
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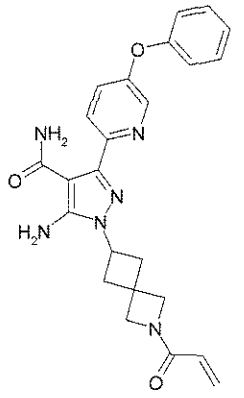
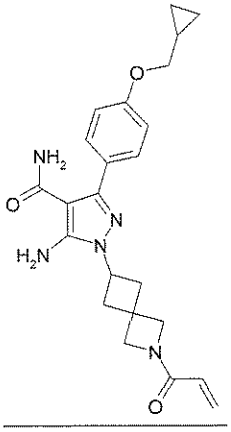
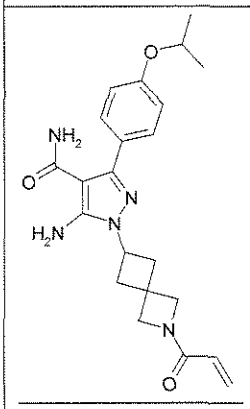
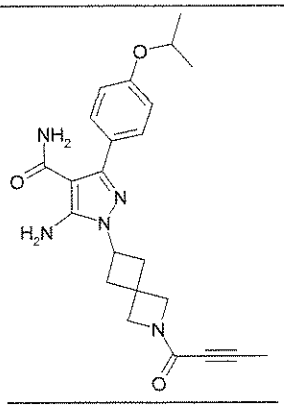
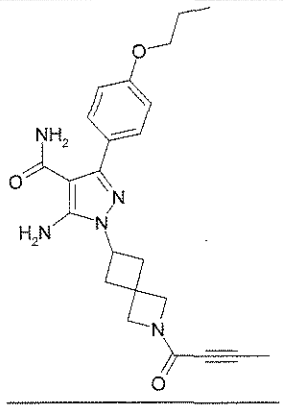
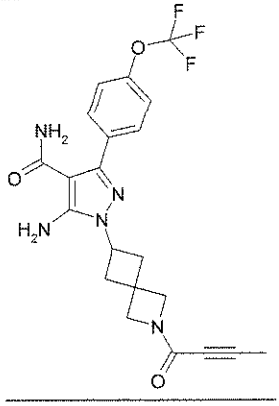
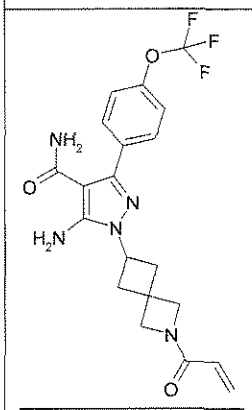
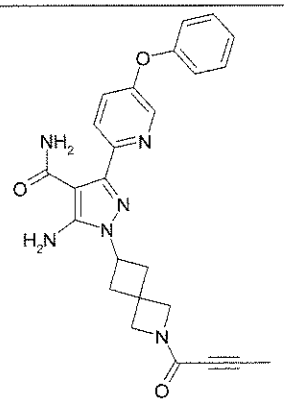
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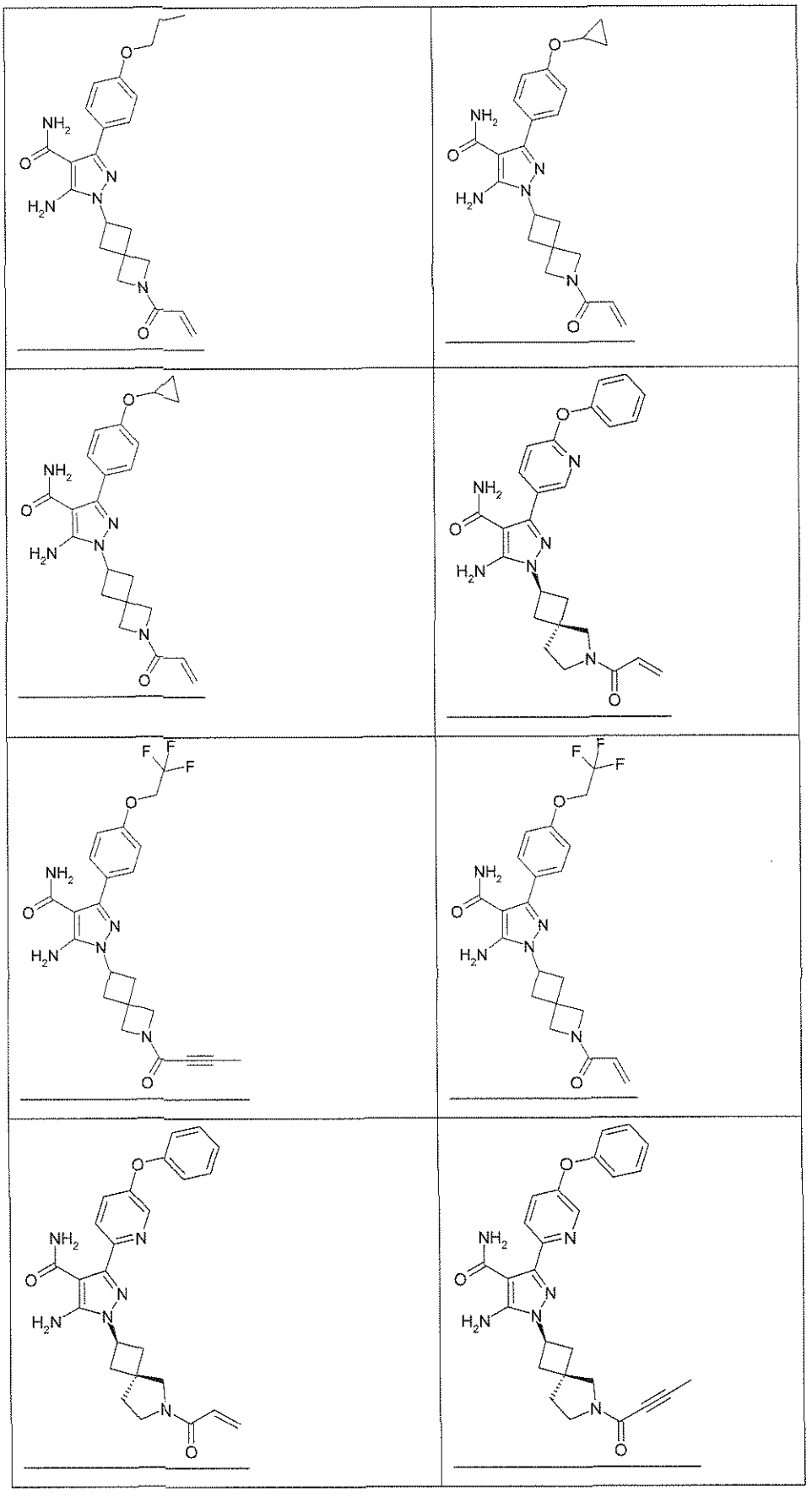


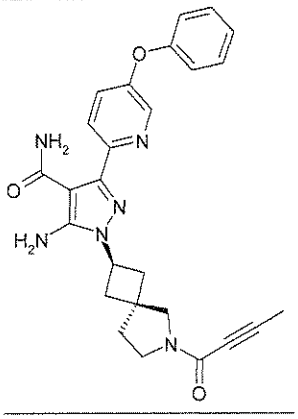
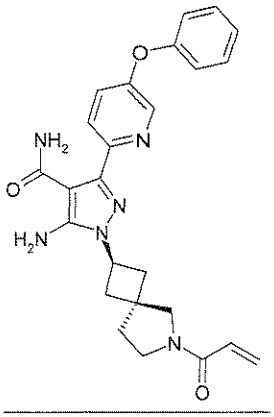
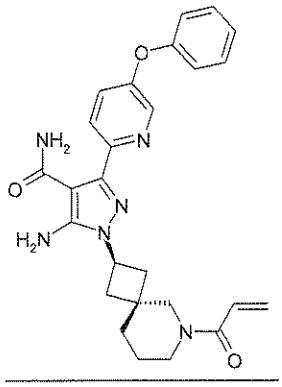
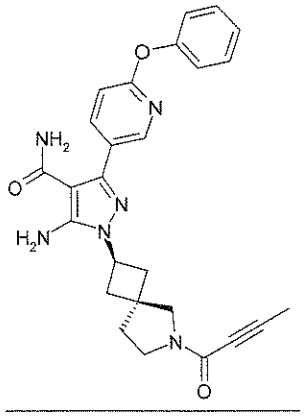
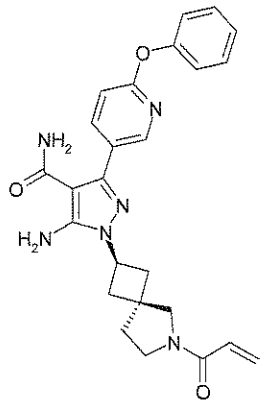
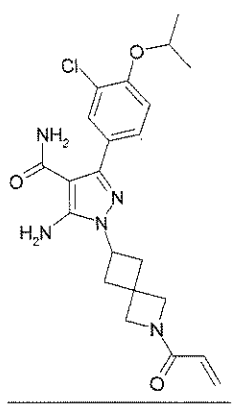
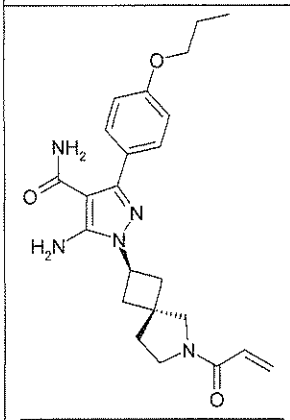
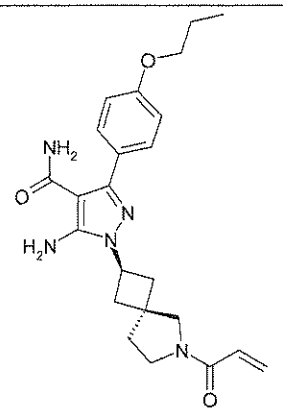
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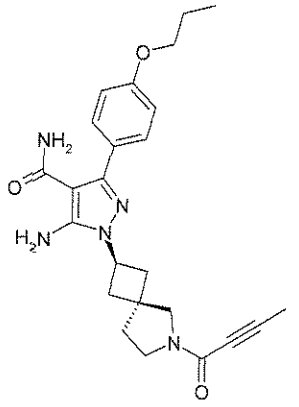
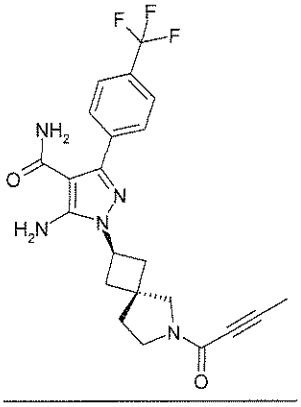
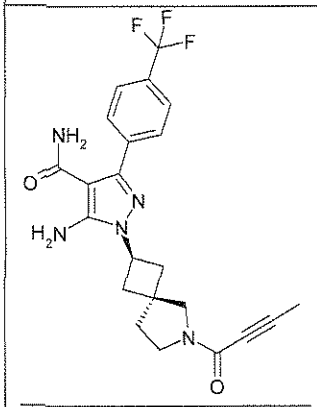
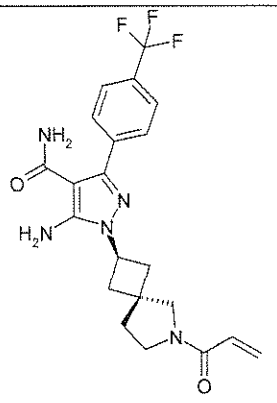
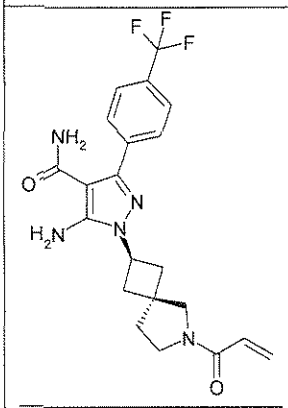
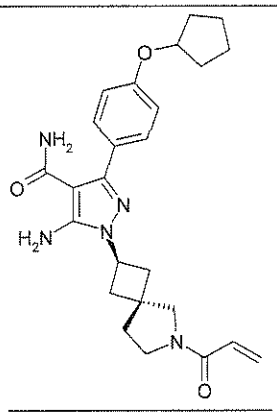
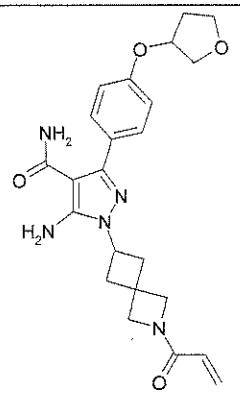
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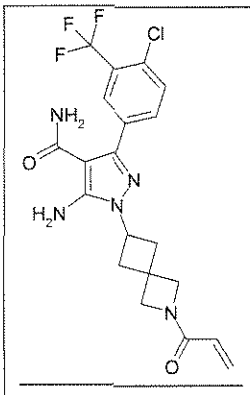
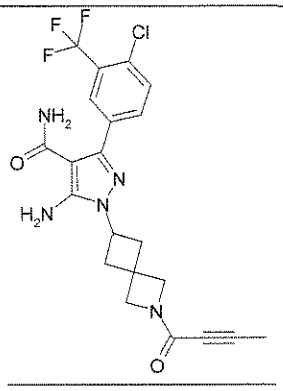
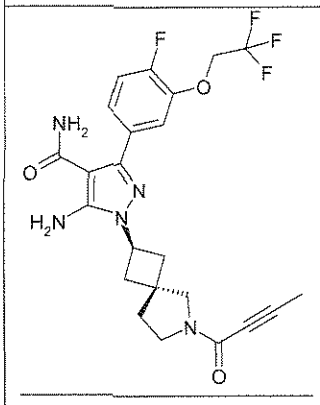
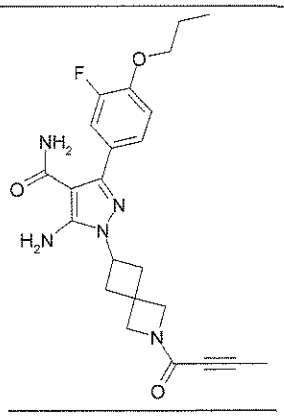
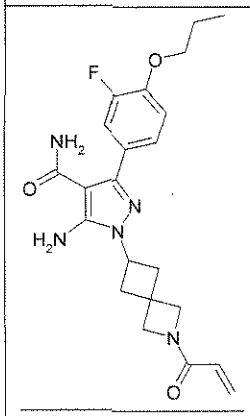
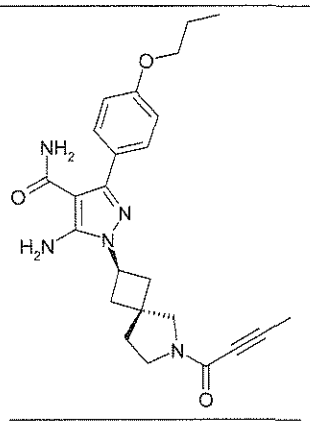
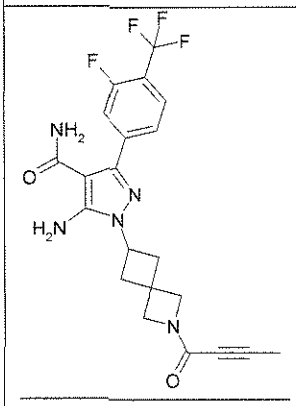
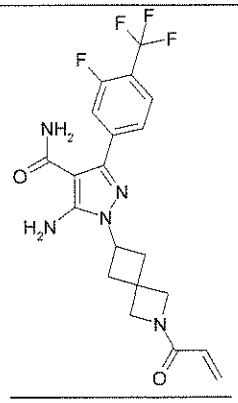


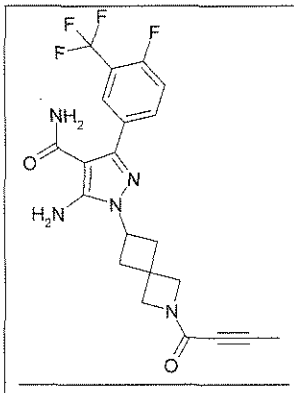
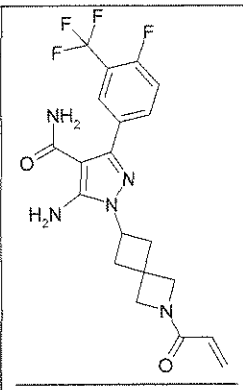
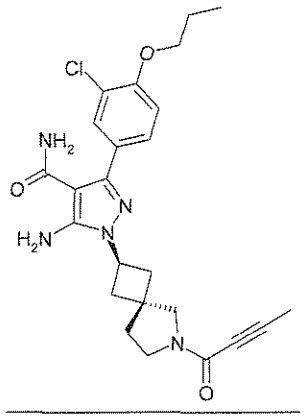
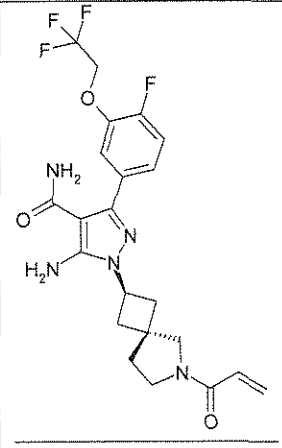
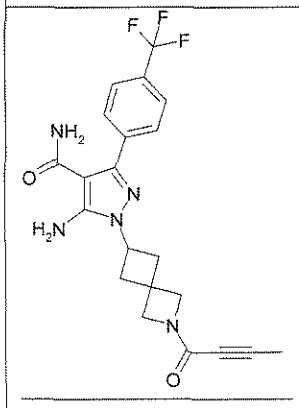
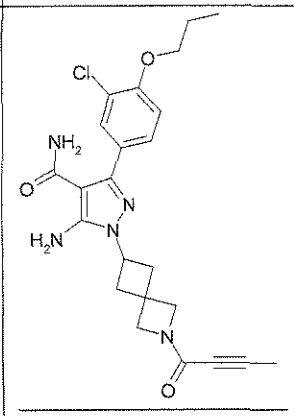
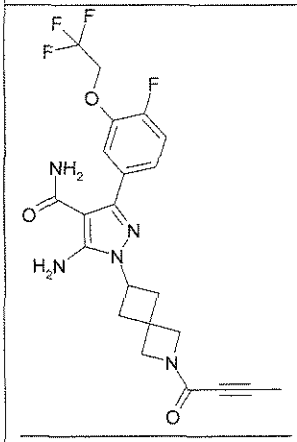
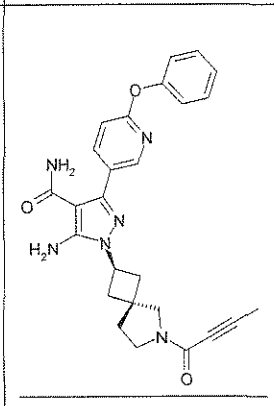
	
	
	
	

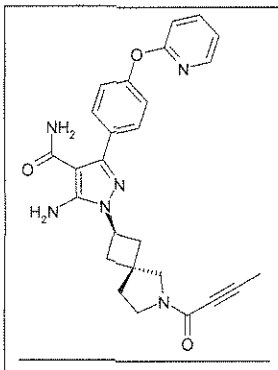
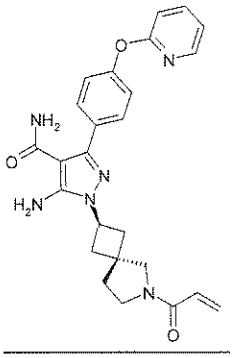
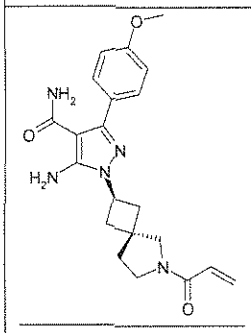
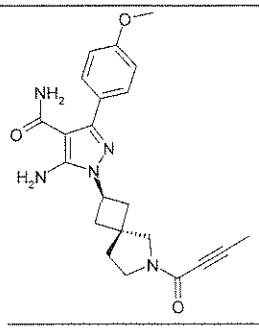
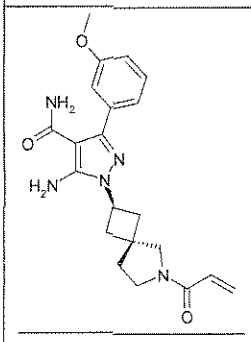
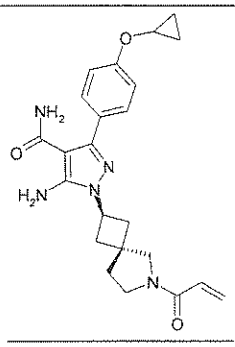
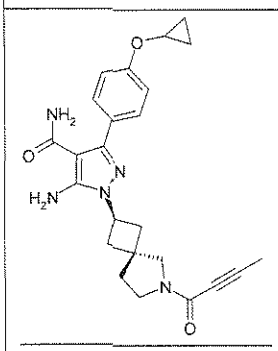
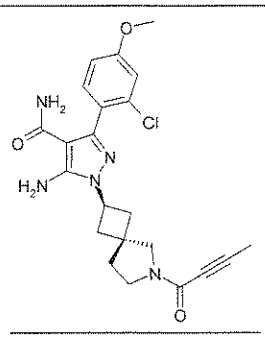
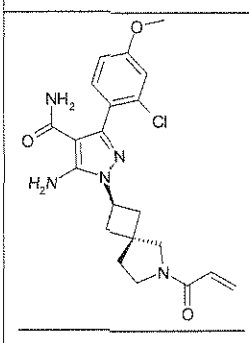
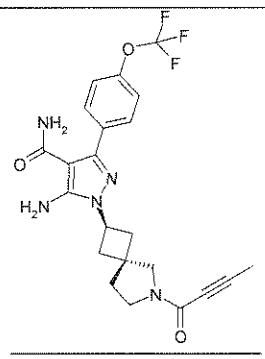


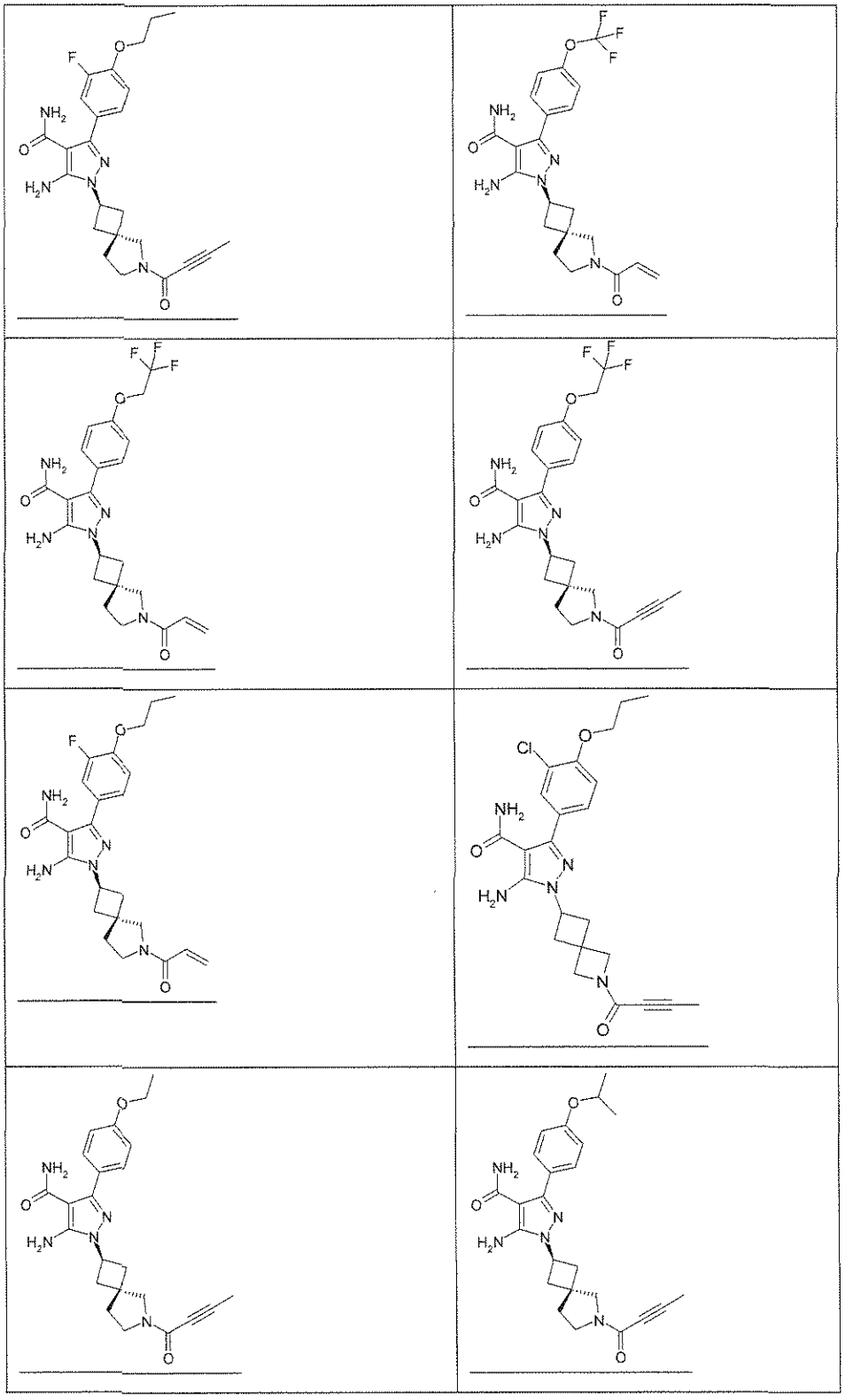
	
	
	
	



or the pharmaceutically acceptable salts thereof.

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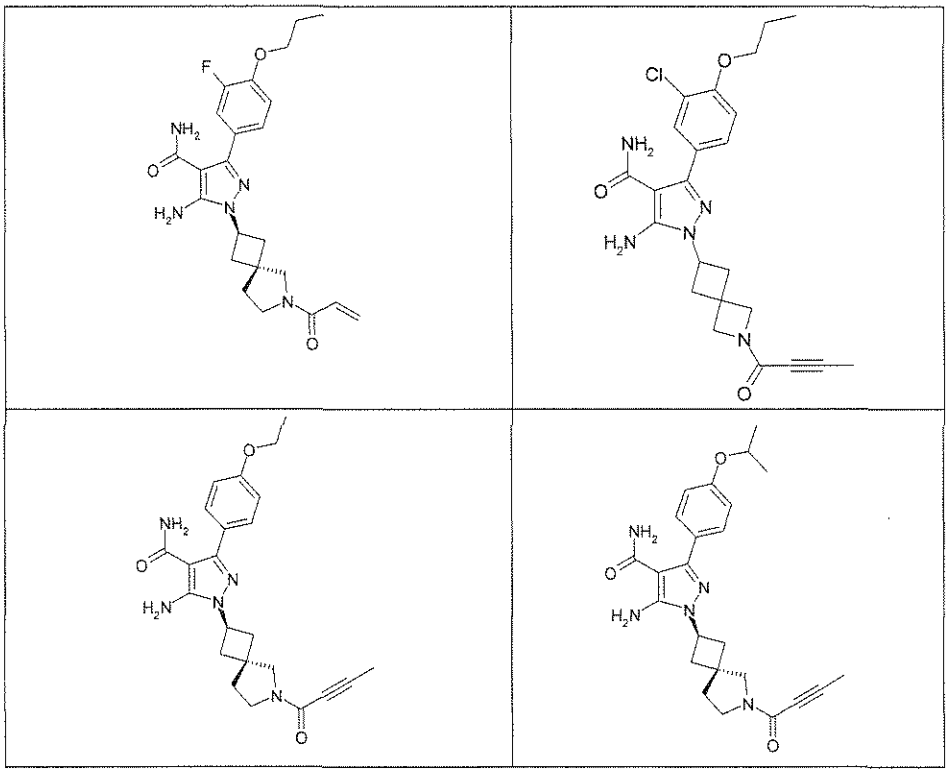
In a fourth aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined herein or a pharmaceutically acceptable salt thereof.

In a fifth aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof for use in the treatment of a disease chosen from rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.

In a sixth aspect, there is provided use of a compound as defined herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease chosen from rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.

DETAILED DESCRIPTION OF THE INVENTION

In a first generic embodiment, there is provided a compound of the formula (I)



or the pharmaceutically acceptable salts thereof.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

21. A ~~method of treating a disease chosen from rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis, comprising administering to a patient a therapeutically effective amount of a~~ compound according to claim 1 or a pharmaceutically acceptable salt thereof for use in the treatment of a disease chosen from rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.

22. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease chosen from rheumatoid arthritis, systemic lupus erythromatosis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.