



(12) Translation of
European patent specification

(11) NO/EP 3390395 B1

NORWAY

(19) NO
(51) Int Cl.
C07D 405/14 (2006.01)
A61K 31/415 (2006.01)
A61K 31/4155 (2006.01)
A61P 35/00 (2006.01)
C07D 231/14 (2006.01)
C07D 401/04 (2006.01)
C07D 401/06 (2006.01)
C07D 403/04 (2006.01)
C07D 405/04 (2006.01)
C07D 405/06 (2006.01)
C07D 405/08 (2006.01)
C07D 413/06 (2006.01)

Norwegian Industrial Property Office

(45)	Translation Published	2020.12.07
(80)	Date of The European Patent Office Publication of the Granted Patent	2020.09.09
(86)	European Application Nr.	16816363.2
(86)	European Filing Date	2016.12.16
(87)	The European Application's Publication Date	2018.10.24
(30)	Priority	2015.12.16, GB, 201522245 2016.08.15, GB, 201613945
(84)	Designated Contracting States:	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
	Designated Extension States:	BA ; ME
	Designated Validation States:	MA ; MD
(73)	Proprietor	Loxo Oncology, Inc., Lilly Corporate Centre Indianapolis, Indiana 46285, USA
(72)	Inventor	GUISOT, Nicolas, c/o Redx Pharma PLCBlock 33F MeresideAlderley Park, Alderley EdgeCheshire SK10 4TG, Storbritannia
(74)	Agent or Attorney	ZACCO NORWAY AS, Postboks 488, 0213 OSLO, Norge

(54) Title **COMPOUNDS USEFUL AS KINASE INHIBITORS**

(56) References

Cited: WO-A1-2014/068527
WO-A1-2014/082598
WO-A1-2015/140566
US-B1- 7 718 662
WO-A2-2015/048662
CN-A- 105 085 474
US-A1- 2011 144 068
WO-A1-2015/189620

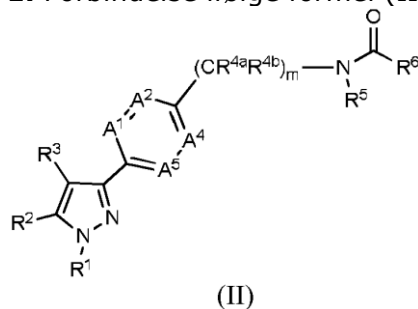
Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (<http://worldwide.espacenet.com>) or via the search engine on our website here: <https://search.patentstyret.no/>

[EP3390395]

1

Patentkrav

1. Forbindelse ifølge formel (II) eller farmasøytisk akseptable salter derav:



5 hvori

0, 1 eller 2 av A^1 , A^2 , A^4 og A^5 er uavhengig valgt fra N, og resten er CR^7 ;

R^1 representerer en gruppe valgt fra: C_{1-8} -alkyl, C_{1-8} -haloalkyl, C_{1-8} -alkoksy, C_{2-8} -alkyleter, $-C(O)R^A$, en C_{3-10} -karbosyklisk gruppe, en 3- til 10-leddet heterosyklisk gruppe, C_{1-8} -alkyl substituert med en C_{3-10} -karbosyklisk gruppe og et C_{1-8} -alkyl substituert med en 3- til 10-leddet heterosyklisk gruppe, hvori hver av de ovennevnte gruppene er usubstituert eller substituert med 1 til 5 substituent uavhengig valgt fra: halo, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{1-4} -alkoksy, C_{2-4} -alkyleter, $-OR^A$, $-NR^A R^B$, $=O$, $-OC(O)R^A$, $-C(O)R^A$, $-C(O)OR^A$, $-NR^A C(O)R^B$, $-C(O)NR^A R^B$, $-NR^A S(O)_2 R^B$, $-S(O)_2 NR^A R^B$, benzoyl, et 5- eller 6-leddet heterosykloaryl, en 3- til 6-leddet heterosykloalkylring, C_{1-4} -alkyl substituert med $-OR^A$ og C_{1-4} -alkoksy substituert med $-OR^A$, eller ett enkelt atom av R^1 er substituert to ganger for å danne en 3- til 6-leddet heterosykloalkyl- eller sykloalkylring;

R^2 er NH_2 ;

R^3 er $-C(O)NH_2$;

R^{4a} og R^{4b} er H;

R^5 er H eller C_{1-4} -alkyl;

R^6 er en gruppe valgt fra et substituert eller usubstituert: fenyl eller en 5- eller 6-leddet heteroarylring, hvori, når den er substituert, inneholder R^6 fra 1 til 5 substituent uavhengig ved hver forekomst valgt fra: halo, $-OR^I$, $-NR^I R^J$, $-CN$, C_{1-6} -alkyl, C_{1-6} -haloalkyl og C_{1-6} -alkyl substituert med $-OR^I$;

R^7 er valgt fra: H, halo, C_{1-6} -alkyl, C_{1-6} -haloalkyl, C_{1-6} -alkoksy, og C_{1-6} -alkyl substituert med $-OR^H$;

[EP3390395]

2

m er 1;

R^A og R^B ved hver forekomst avhengig er valgt fra: H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{1-4} -alkoksy, fenyl, benzyl eller C_{1-4} -alkyl substituert med $-OR^H$;

R^I , og R^J uavhengig ved hver forekomst er valgt fra: H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{1-4} -alkoksy og C_{1-4} -alkyl substituert med $-OR^H$; og

R^H er valgt fra H eller C_{1-4} -alkyl.

2. Forbindelsen ifølge krav 1, hvori A^2 , A^4 og A^5 er CH, og A^1 er CR^7 , og R^7 er valgt fra H, fluor, metyl, metoksy eller $-CH_2OH$.

3. Forbindelsen ifølge krav 1, hvori R^6 er en gruppe valgt fra et substituert: fenyl eller 6-leddet heteroarylring, eventuelt hvori R^6 er substituert med 1 eller 2 grupper uavhengig valgt fra: metyl, fluor eller metoksy.

4. Forbindelsen ifølge hvilket som helst foregående krav, hvori R^6 er 2-metoksyfen-1-yl eller 5-fluor-2-metoksyfen-1-yl.

5. Forbindelsen ifølge hvilket som helst foregående krav, hvori R^5 er H.

6. Forbindelsen ifølge hvilket som helst foregående krav, hvori R^1 representerer en gruppe valgt fra: C_{1-6} -alkyl, C_{1-6} -haloalkyl, C_{2-6} -alkyleter, $-C(O)R^A$, C_{3-10} -sykloalkyl, C_{6-10} -aryl, 3- til 10-leddet heterosykloalkyl, 3- til 10-leddet heteroaryl, C_{1-6} -alkyl substituert med C_{3-10} -sykloalkyl, C_{1-6} -alkyl substituert med C_{6-10} -aryl, C_{1-6} -alkyl substituert med 3- til 10-leddet heterosykloalkyl og C_{1-6} -alkyl substituert med 3- til 10-leddet heteroaryl, hvori hver av de ovennevnte gruppene er usubstituert eller substituert med 1 til 5 substituenten valgt fra: halo, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{1-4} -alkoksy, C_{2-4} -alkyleter, $-OR^A$, $=O$, $-C(O)OR^A$, $-C(O)NR^A R^B$, 5- eller 6-leddet heteroaryl, en 3- til 6-leddet heterosykloalkylring, C_{1-4} -alkyl substituert med $-OR^A$, C_{1-4} -alkoksy substituert med $-OR^A$ eller ett enkelt atom av R^1 er substituert to ganger for å danne en 3- til 6-leddet heterosykloalkyl- eller sykloalkylring.

[EP3390395]

7. Forbindelsen ifølge hvilket som helst foregående krav, hvori R^A er valgt fra: H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, benzyl eller C_{1-4} -alkyl substituert med $-OR^H$.

5 **8.** Forbindelsen ifølge hvilke som helst av kravene 1 til 5, hvori R^1 er valgt fra substituert eller usubstituert: metyl, etyl, iso-propyl, tert-heksyl, tert-butyl, trifluoretyl, propyleter, syklopropyl, syklobutyl, syklopentyl, sykloheksyl, indanyl, bisyklo[3.1.0]heksyl, oksetan, tetrahydropyranyl, fenyl, pyridyl, C_{1-8} -alkyl substituert med oksetan, C_{1-8} -alkyl substituert med morfolin, C_{1-8} -alkyl substituert med tetrazol, C_{1-8} -alkyl substituert med piperidin og C_{1-8} -alkyl substituert med
10 sykloheksyl,
hvori R^1 er substituert med 1 til 5 substituenten valgt fra: $-OH$, $=O$, $-OMe$, metyl, CF_3 , Cl, F, $-OBn$ eller $-CO_2Et$.

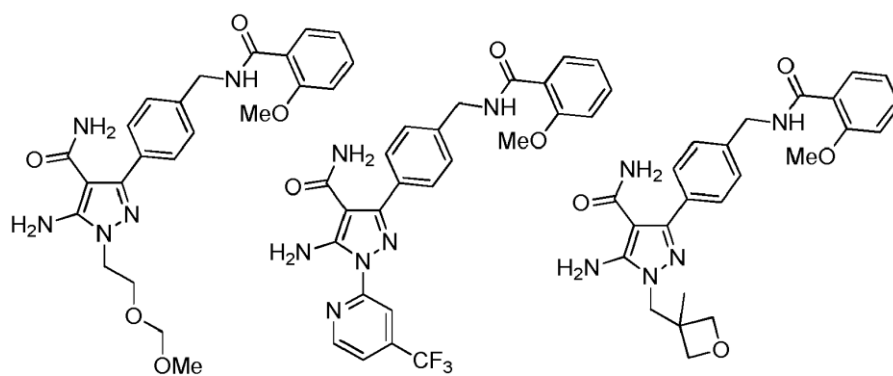
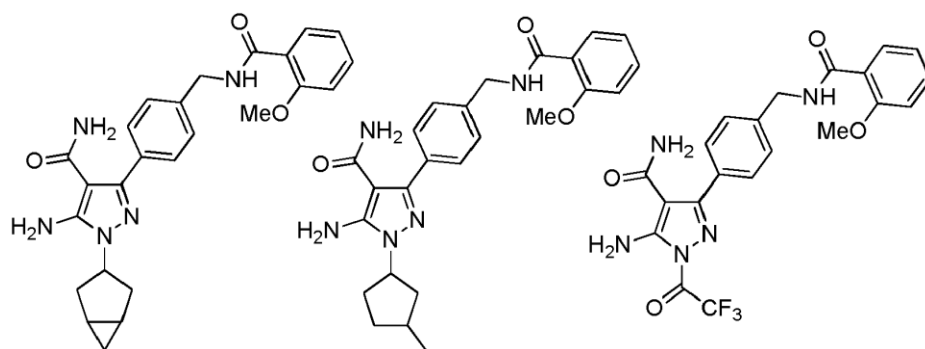
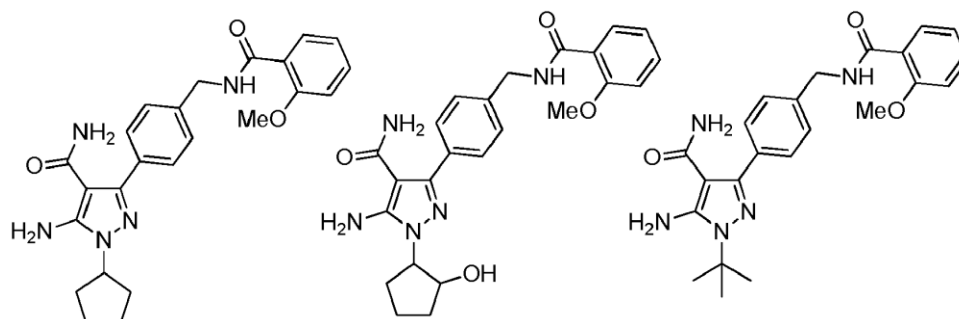
15 **9.** Forbindelsen ifølge hvilke som helst av kravene 1 til 5, hvori R^1 er valgt fra substituert eller usubstituert: metyl, etyl, iso-propyl, tert-heksyl, tert-butyl, trifluoretyl,
hvori R^1 er substituert med 1 til 5 substituenten valgt fra: $-OH$, $=O$, $-OMe$, metyl, CF_3 , Cl, F, $-OBn$ eller $-CO_2Et$.

20 **10.** Forbindelsen ifølge hvilke som helst av kravene 1 til 5, hvori R^1 er valgt fra substituert eller usubstituert: sykloheksyl, fenyl, syklobutyl, syklopentyl, bisyklo[3.1.0]heksyl, piperidiny, pyrrolidiny, tetrahydropyranyl, tetrahydrofuranyl, difluorisopropyl, trifluorisopropyl, (syklopropyl)etyl eller (tetrahydropyranyl)etyl.

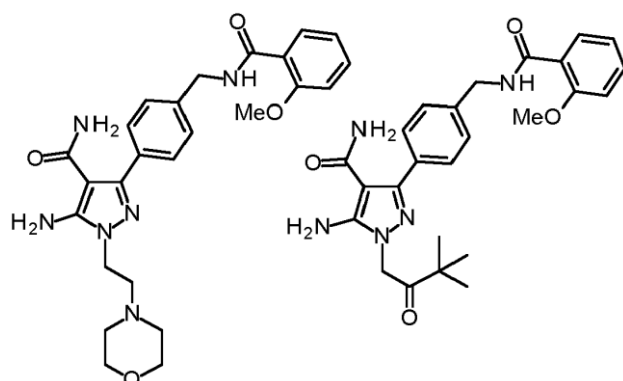
25 **11.** Forbindelsen ifølge krav 1, hvori forbindelsen er valgt fra gruppen bestående av:

[EP3390395]

4

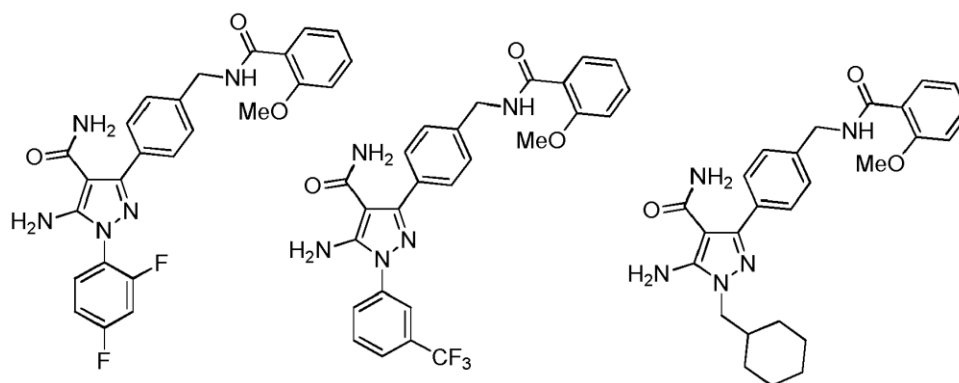
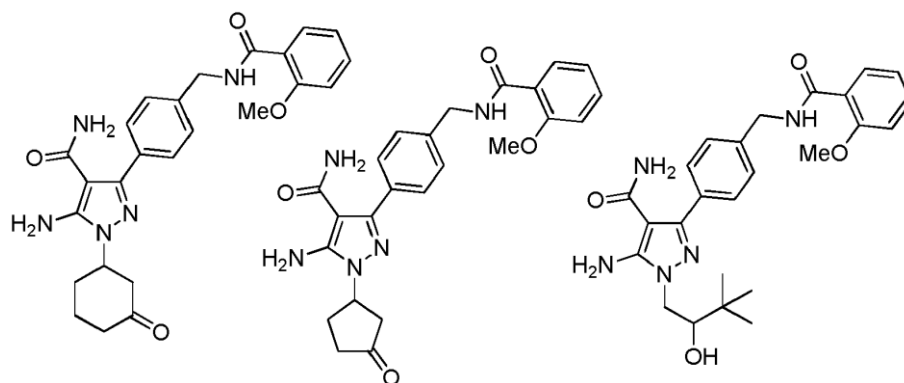


5

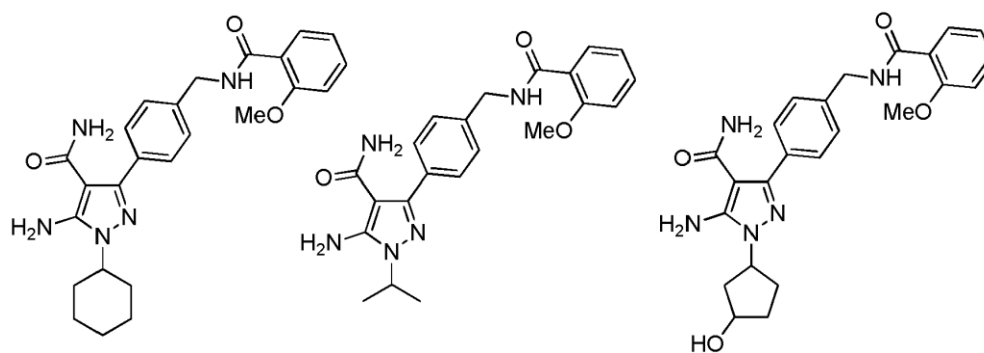


[EP3390395]

5

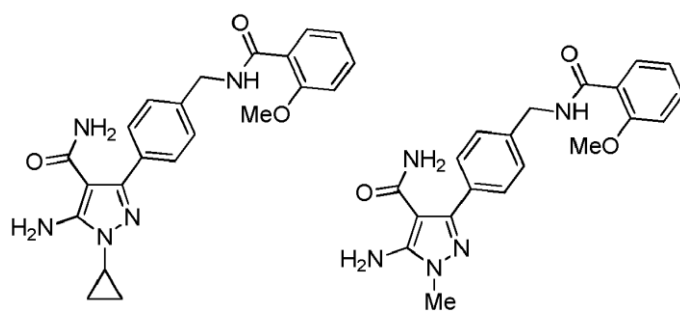
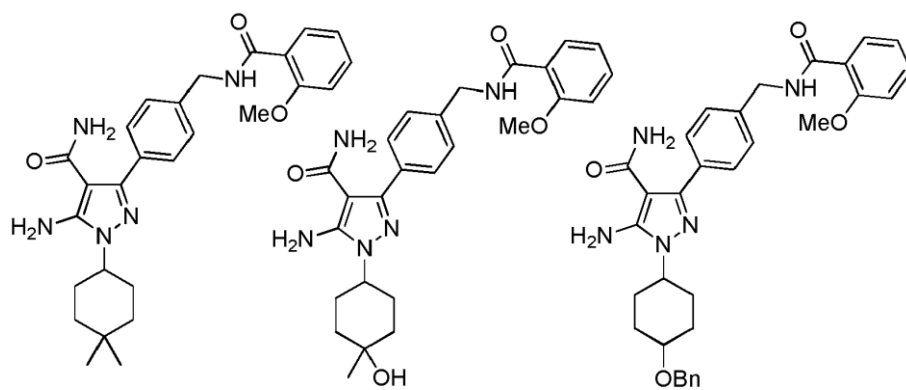
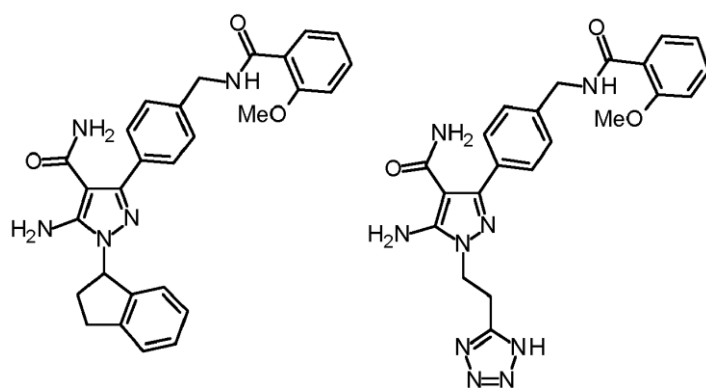
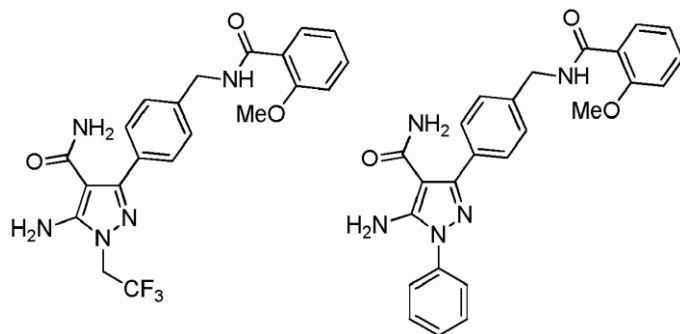


5



[EP3390395]

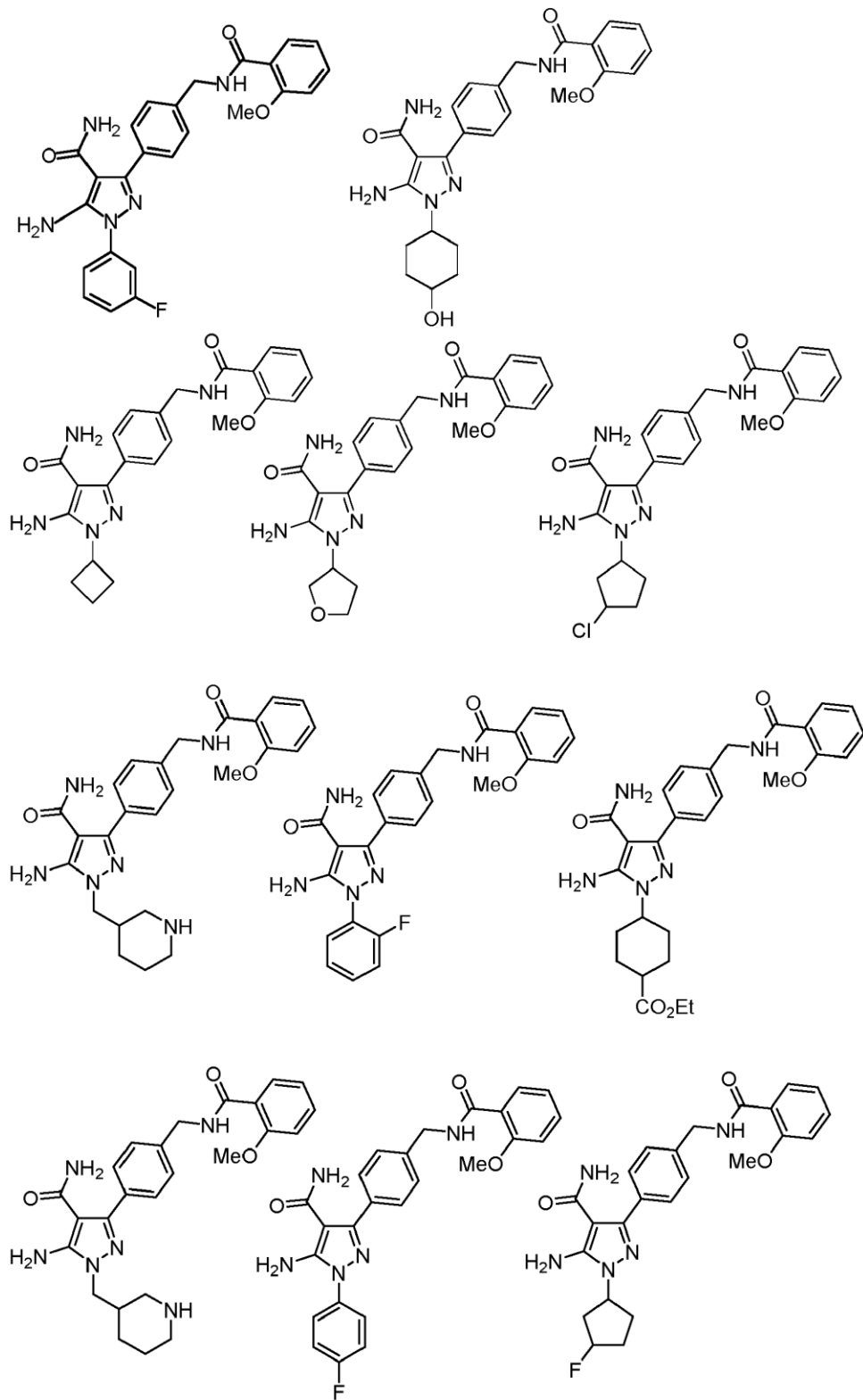
6



5

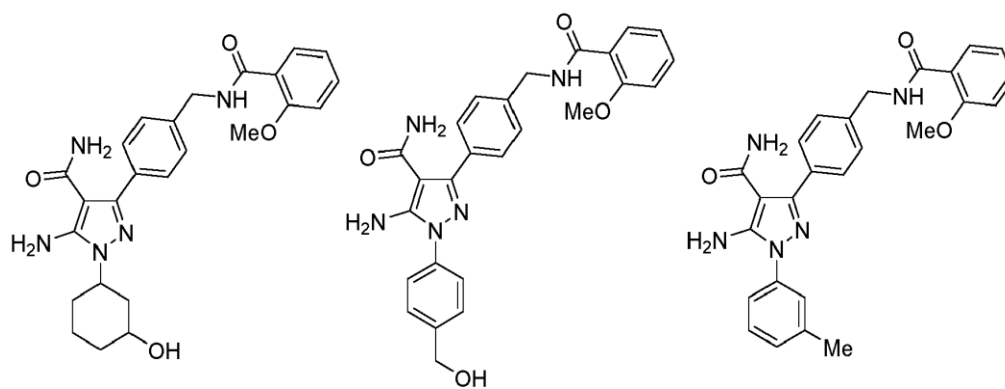
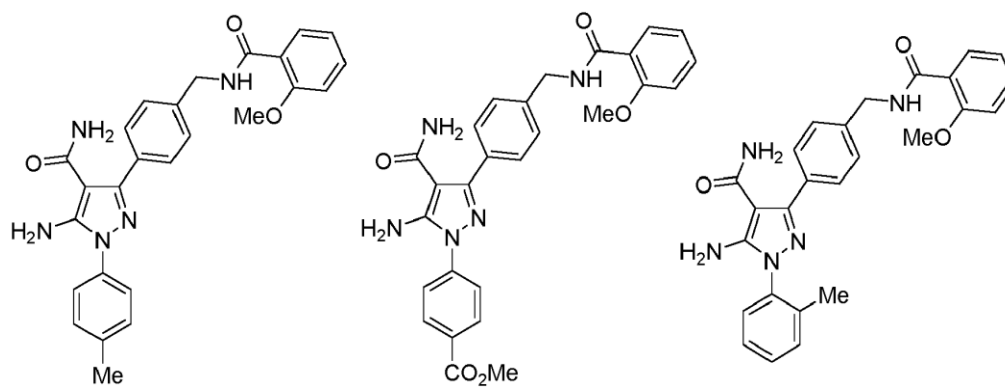
[EP3390395]

7

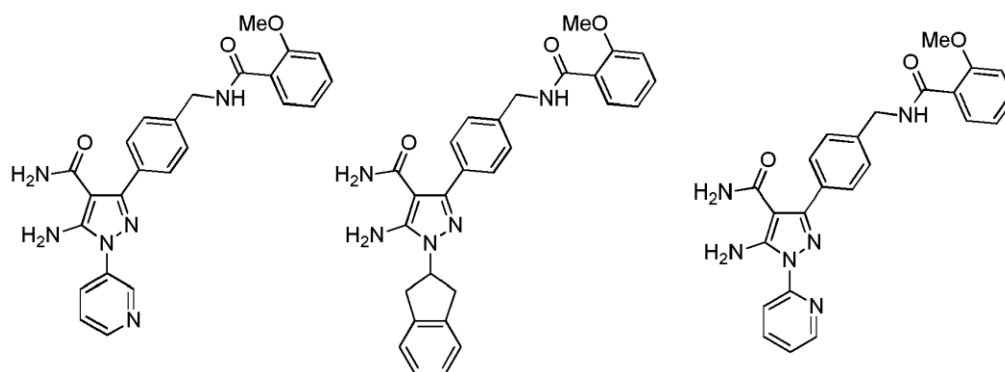


[EP3390395]

8

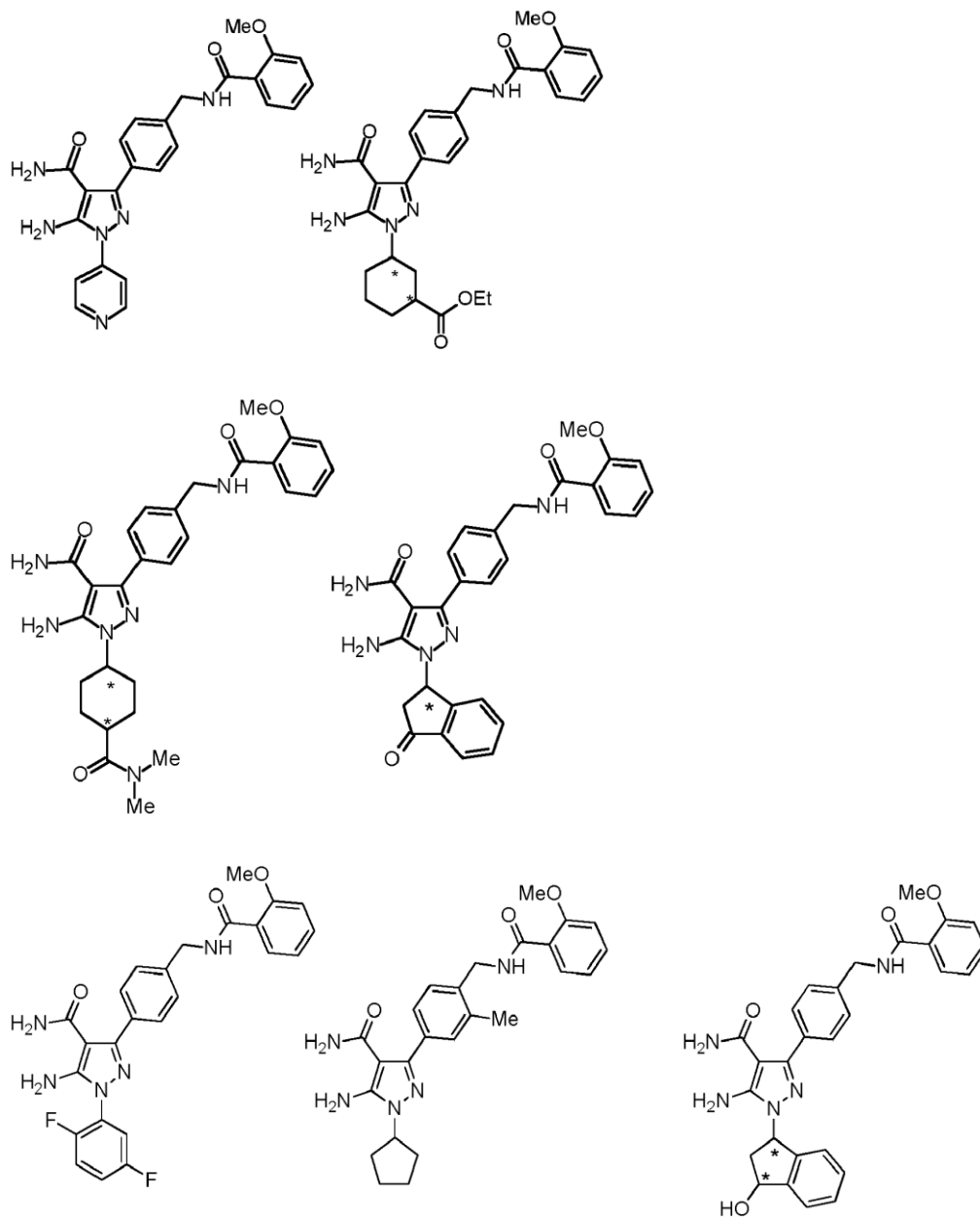


5



[EP3390395]

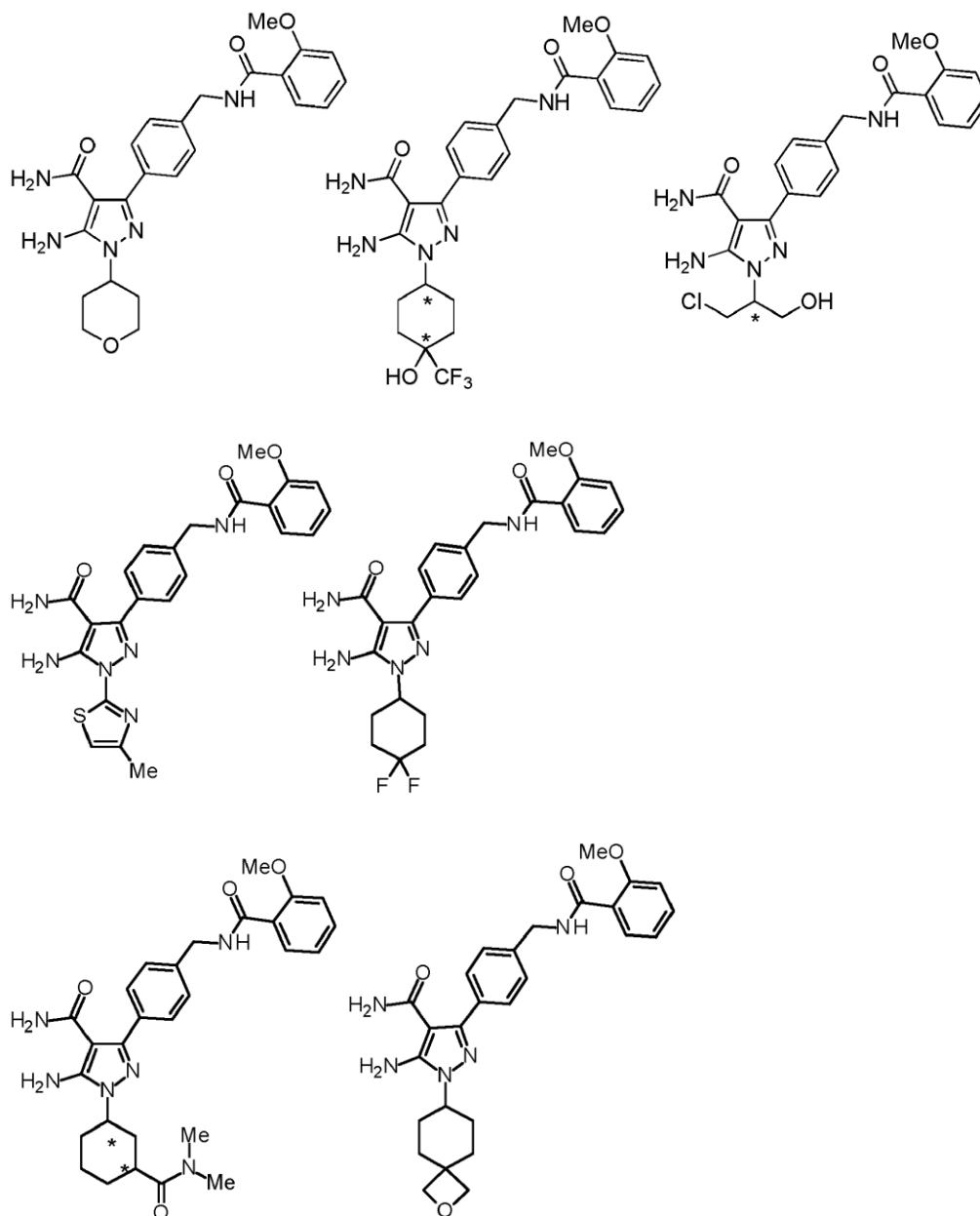
9



5

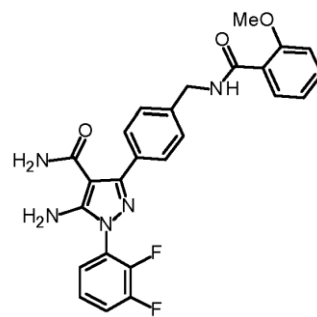
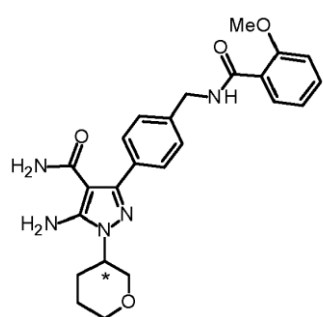
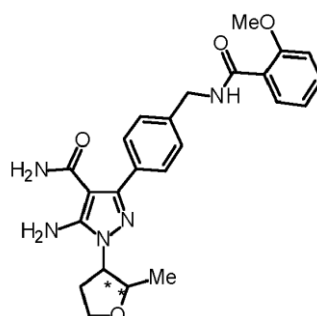
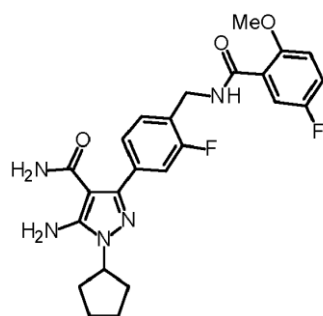
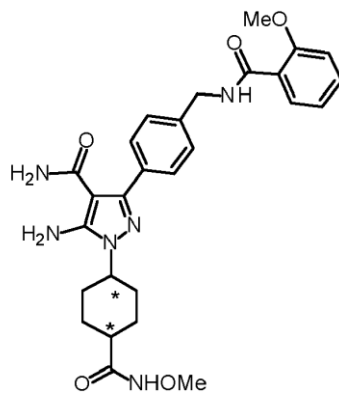
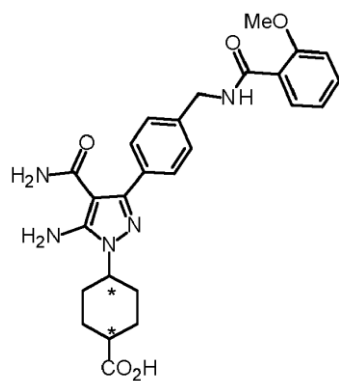
[EP3390395]

10

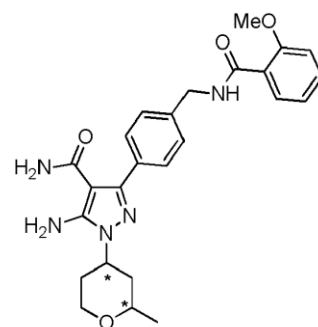
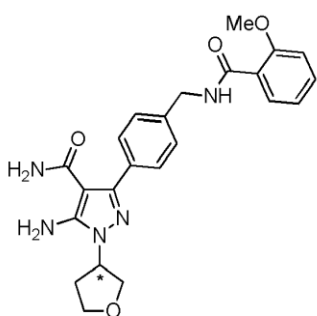
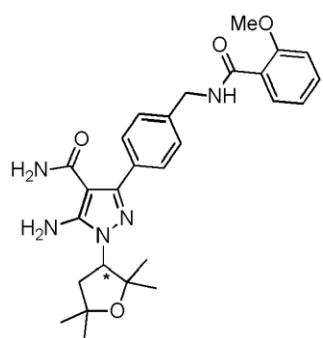


[EP3390395]

11

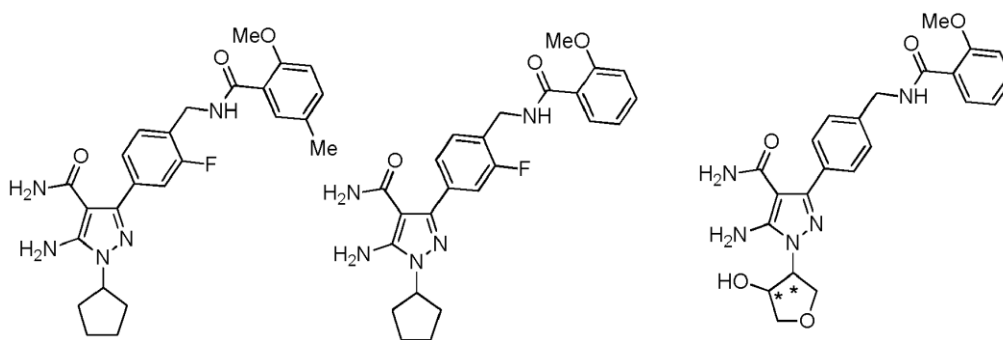
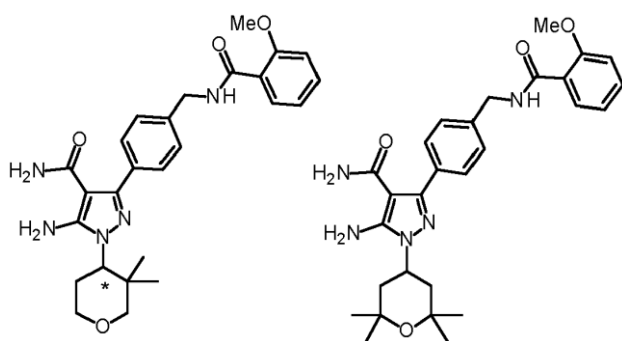
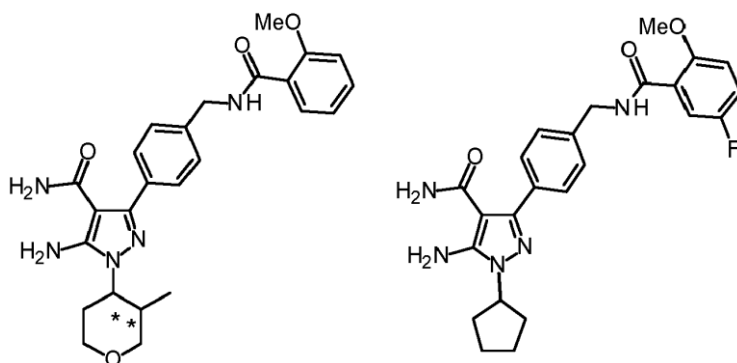


5

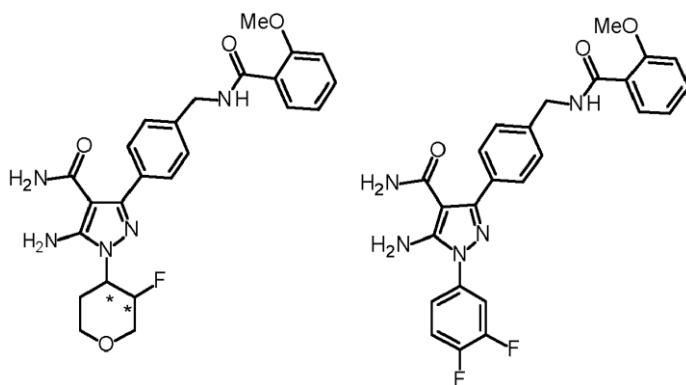


[EP3390395]

12

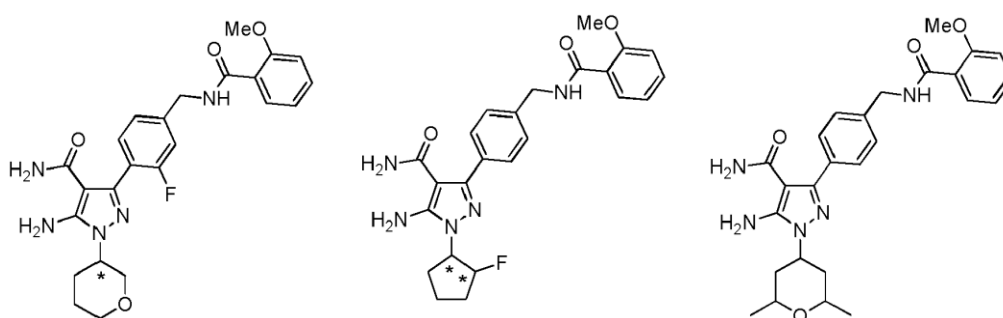
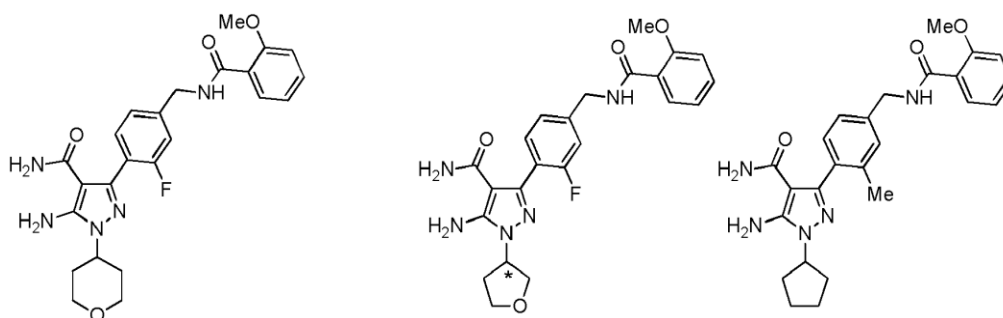


5

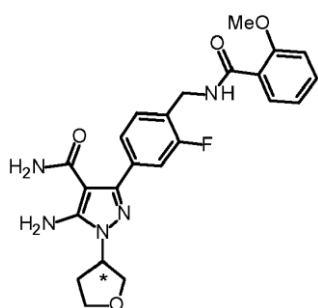
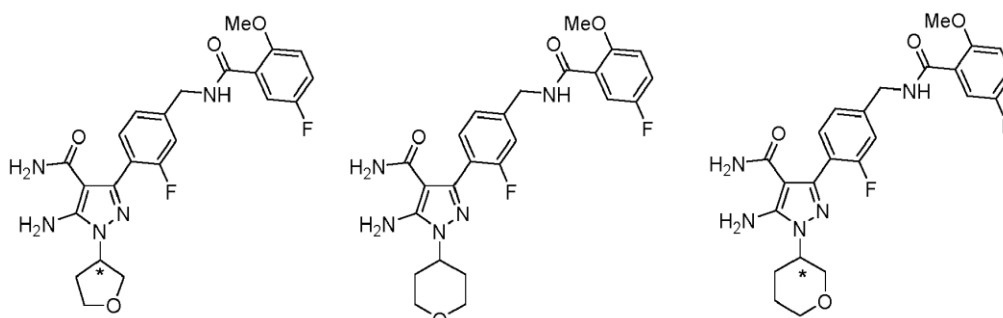


[EP3390395]

13

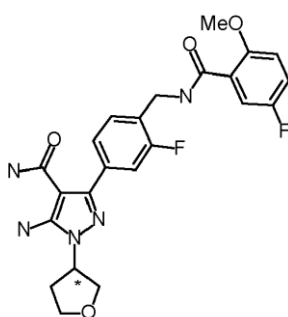
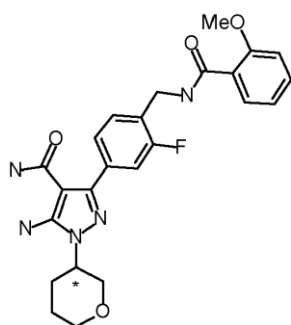
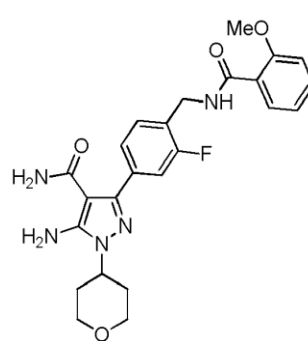
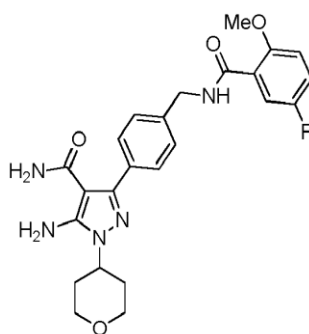
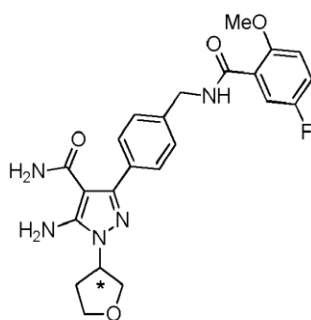
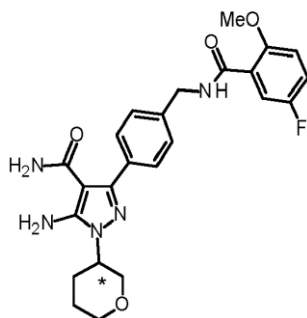
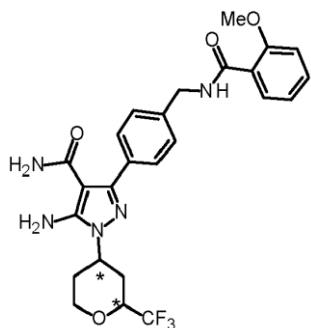


5

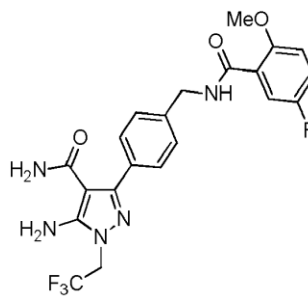
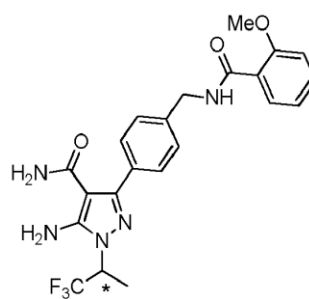
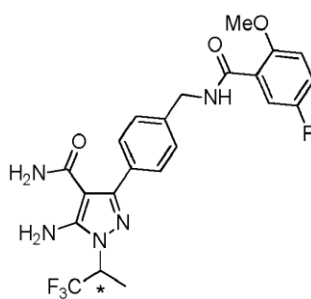


[EP3390395]

14

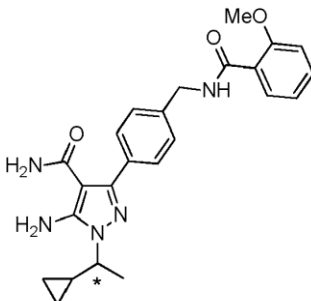
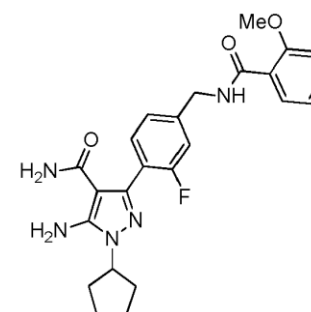
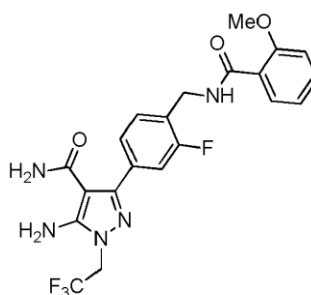
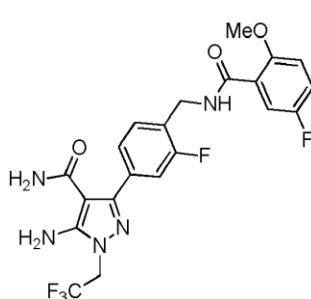
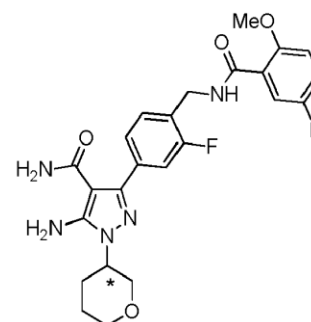
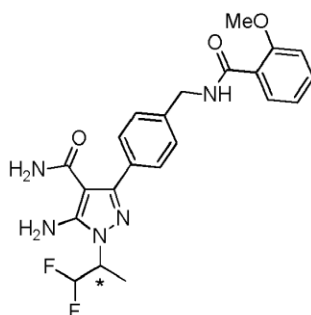
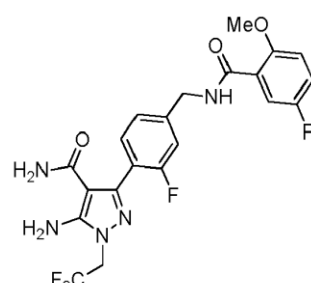
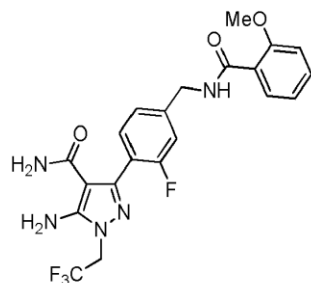
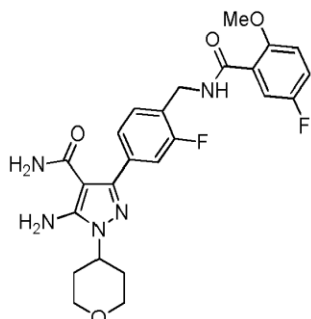


5

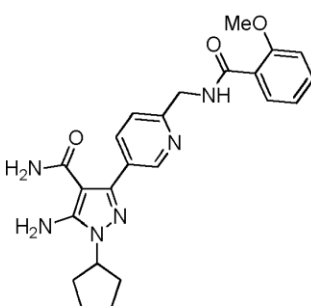
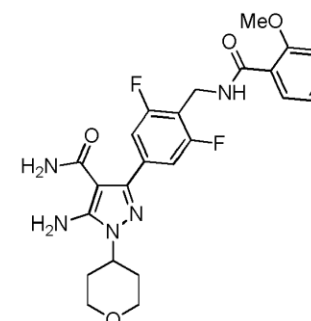
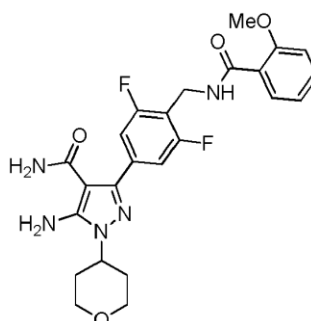


[EP3390395]

15

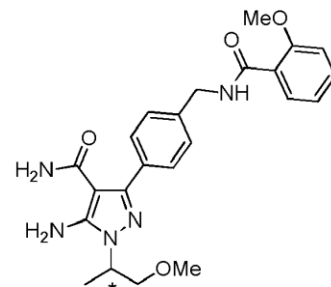
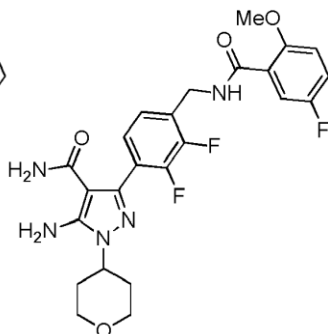
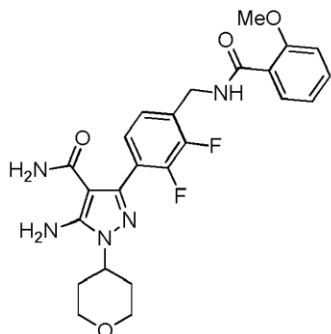
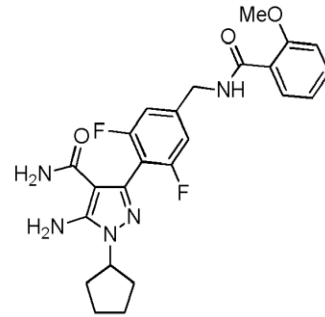
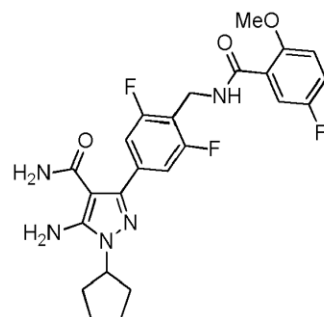
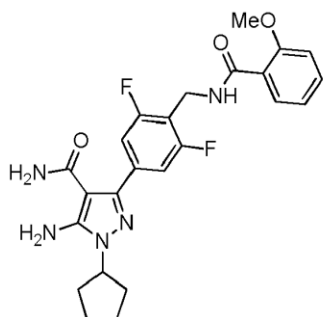
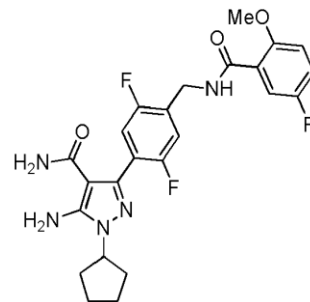
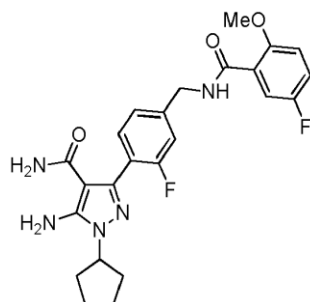
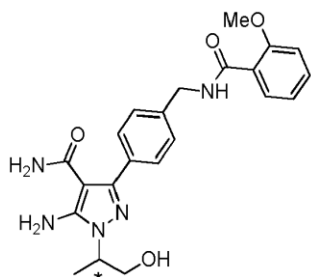


5

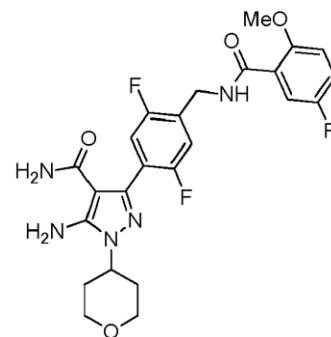
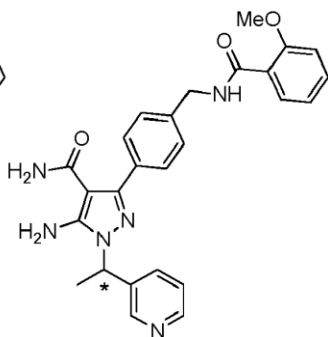
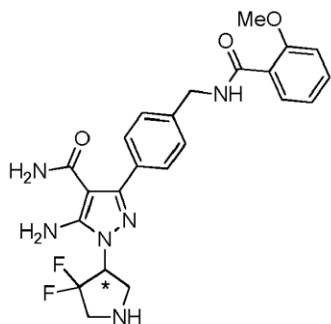


[EP3390395]

16

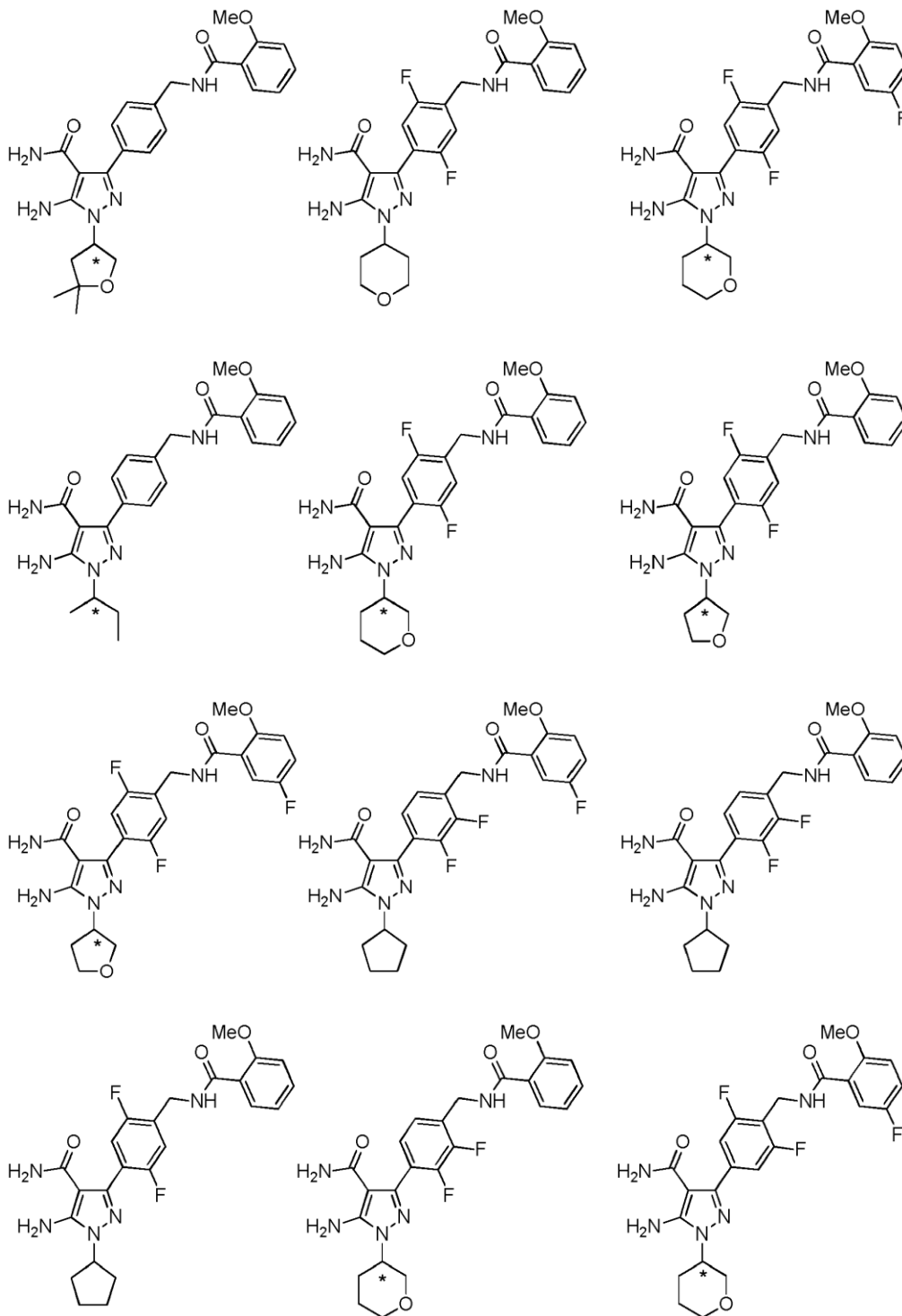


5



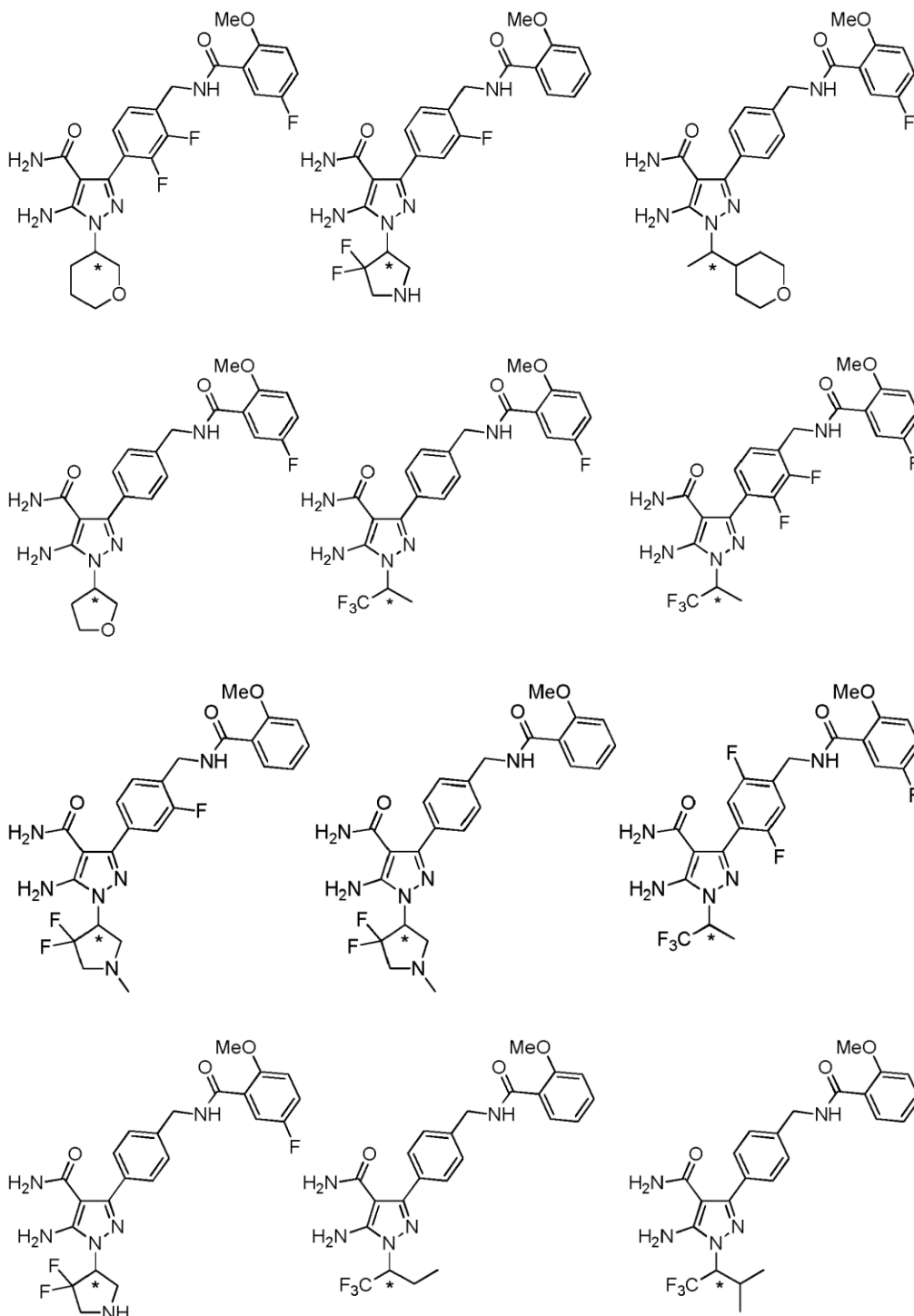
[EP3390395]

17



[EP3390395]

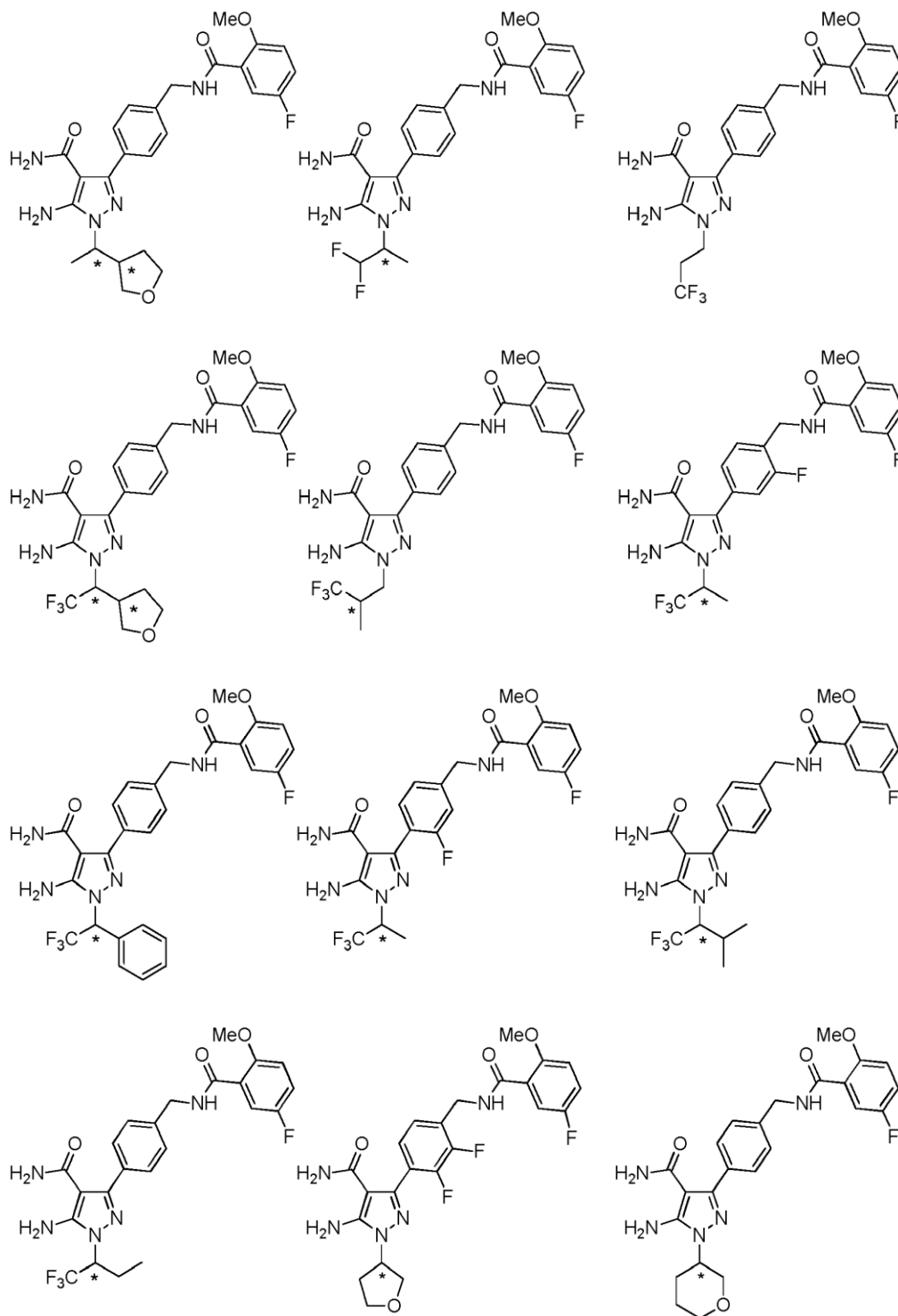
18



5

[EP3390395]

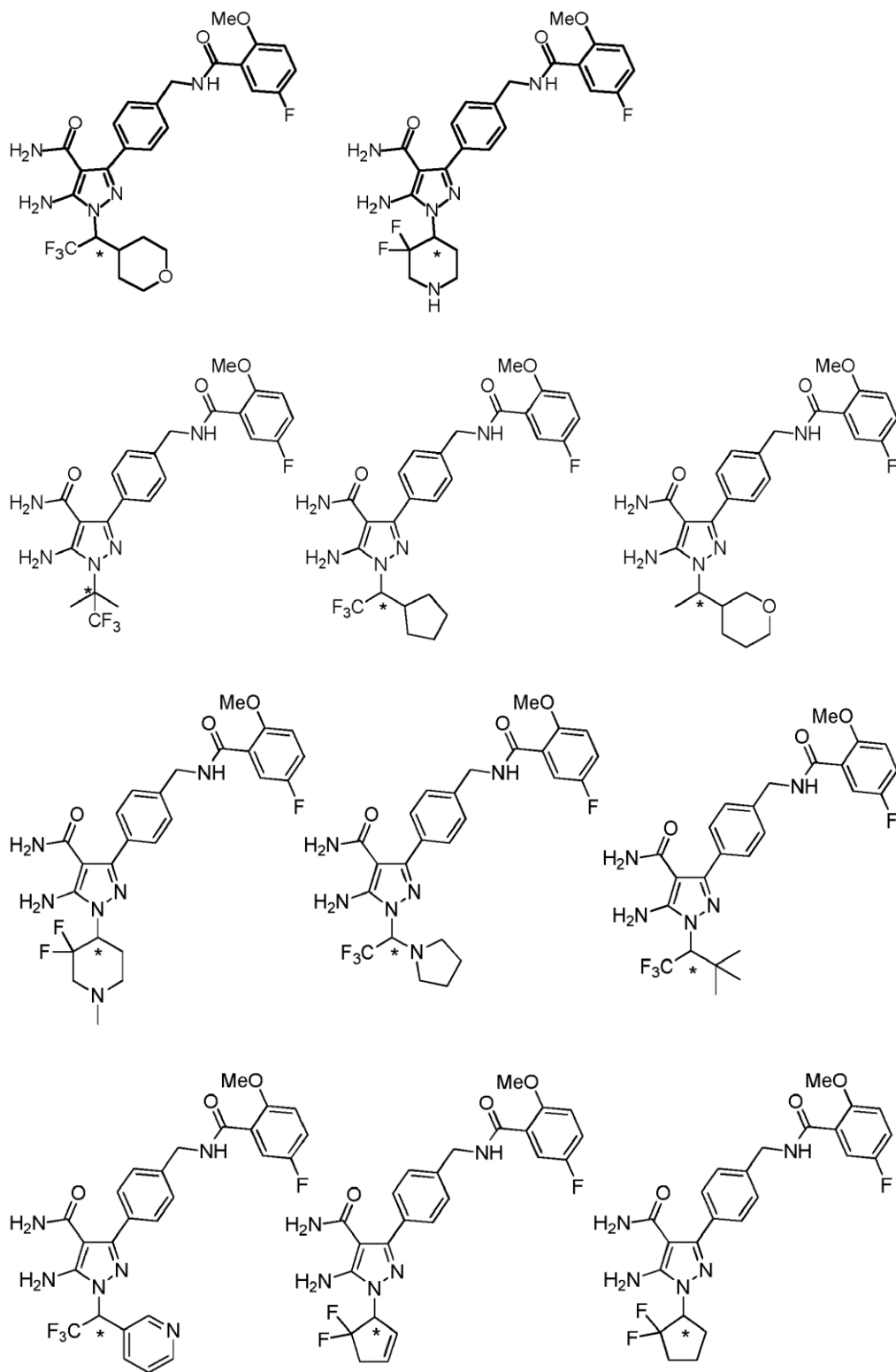
19



5

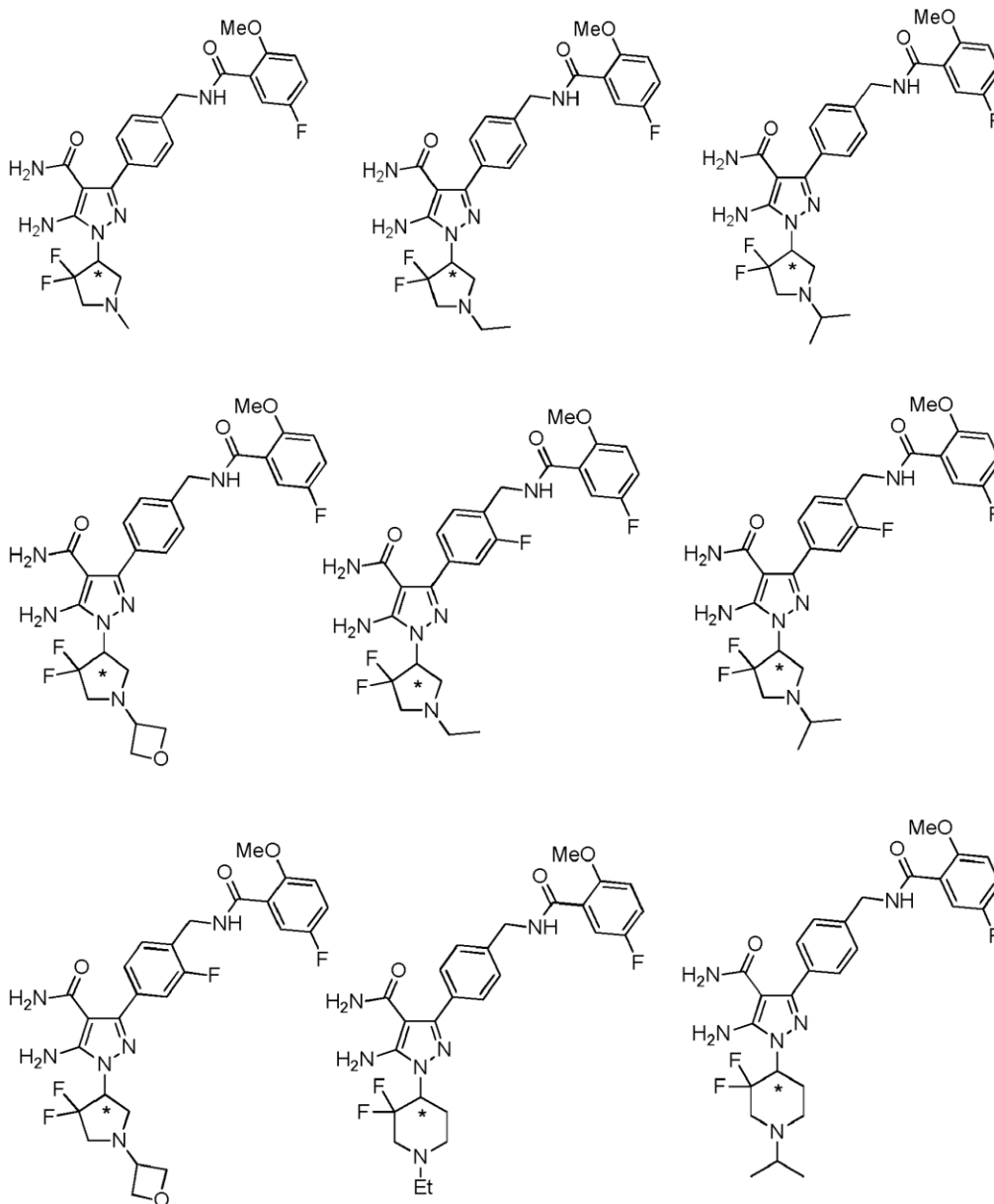
[EP3390395]

20



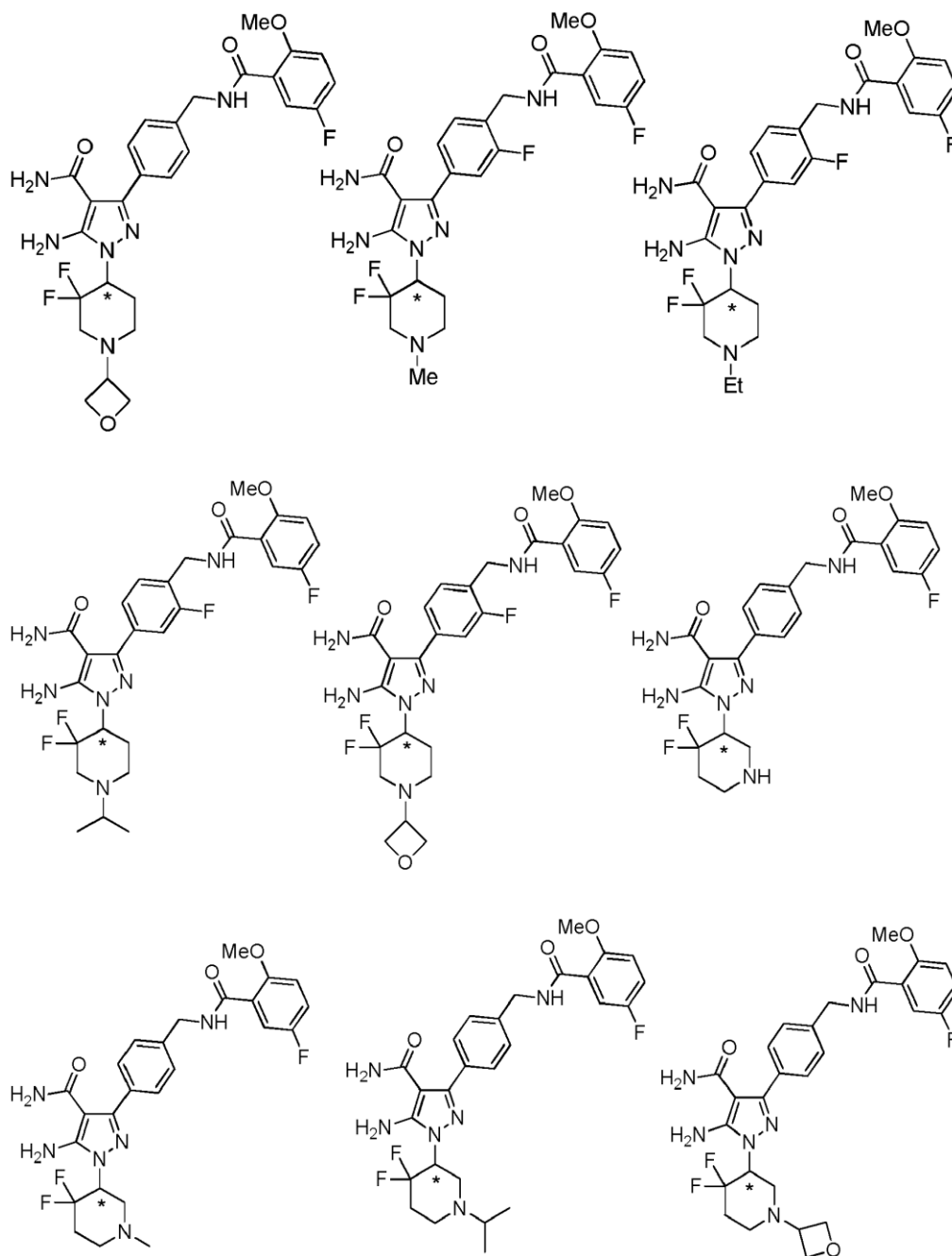
[EP3390395]

21



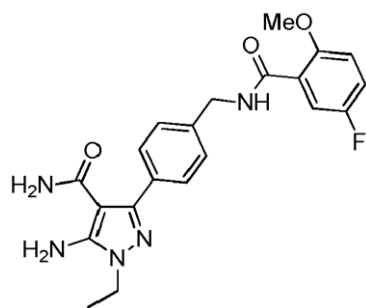
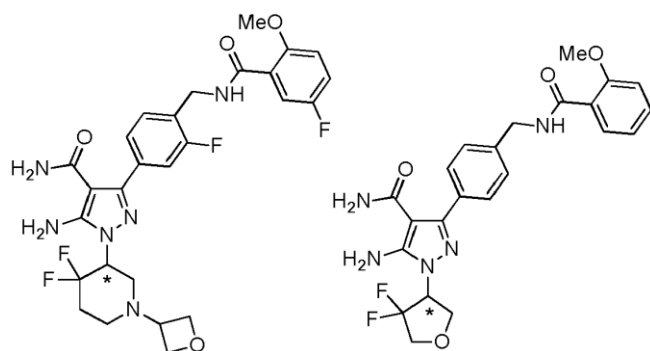
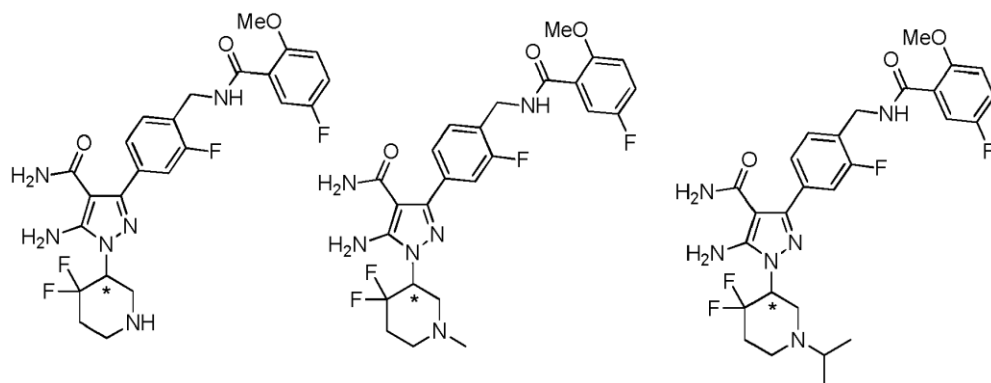
[EP3390395]

22

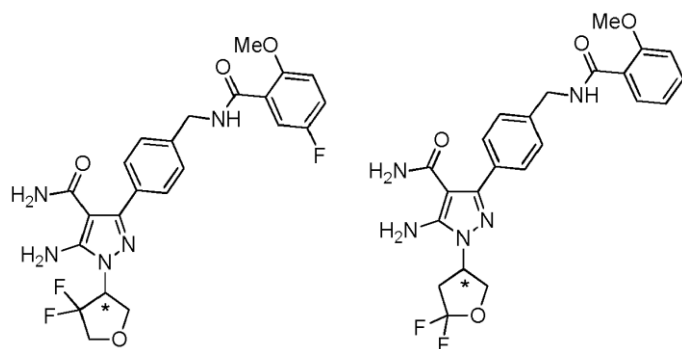


[EP3390395]

23

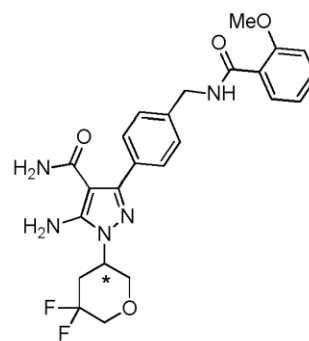
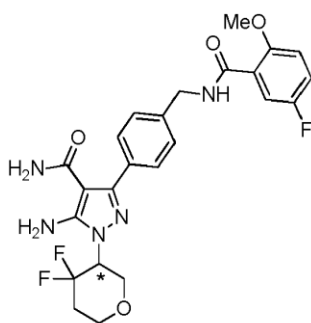
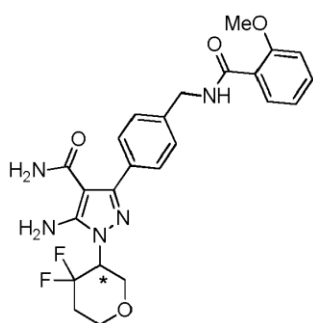
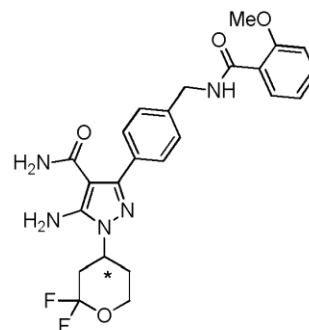
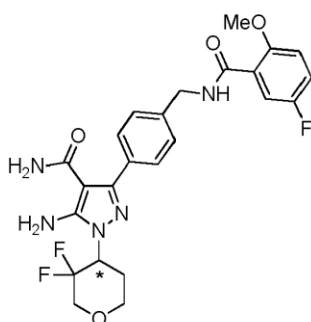
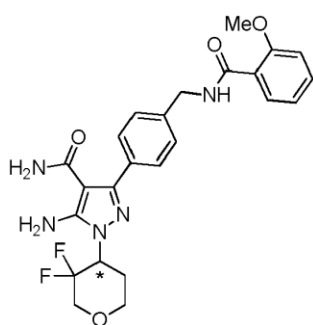
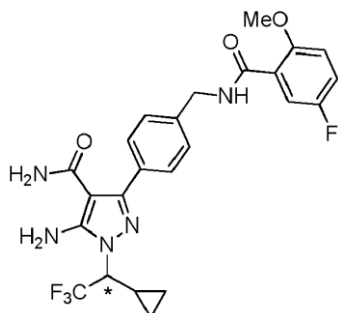


5

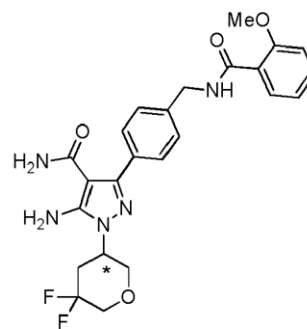
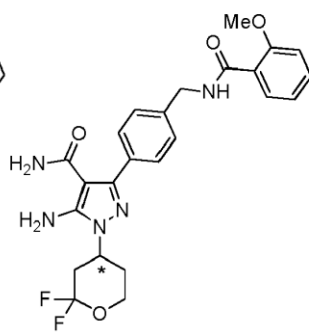
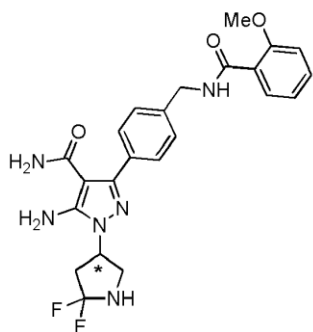


[EP3390395]

24

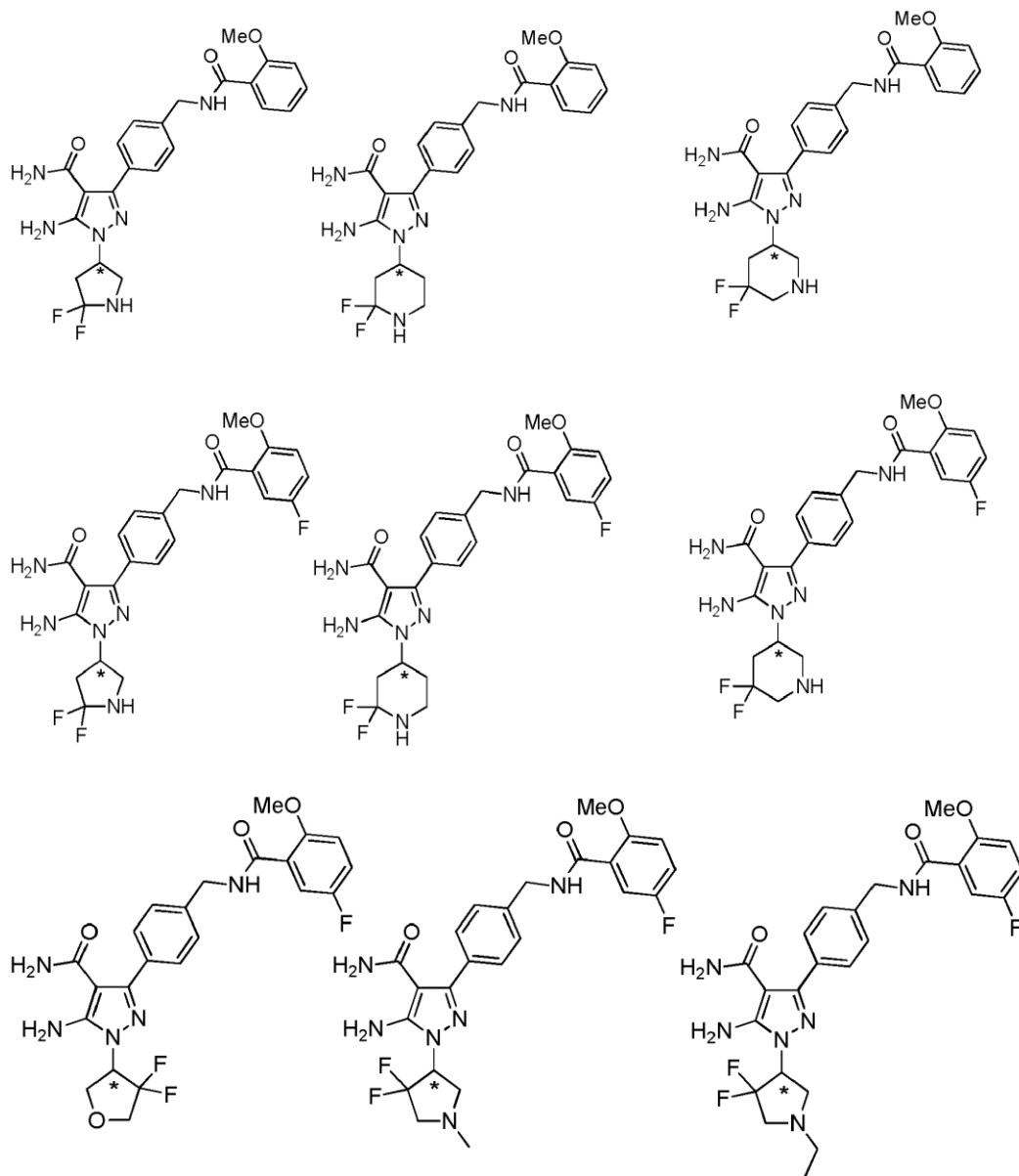


5



[EP3390395]

25



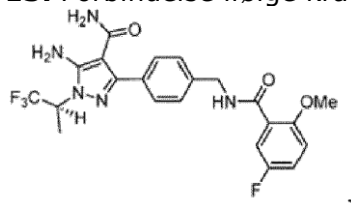


[EP3390395]

27

eller et farmasøytisk akseptabelt salt derav.

13. Forbindelse ifølge krav 1, hvori forbindelsen er:



5 eller et farmasøytisk akseptabelt salt derav.

14. Forbindelse ifølge hvilket som helst foregående krav for anvendelse som medikament.

10 **15.** Forbindelse ifølge hvilke som helst av kravene 1 til 13 for anvendelse i behandling av en tilstand som er modulert av BTK, hvori tilstanden som er modulert av BTK, er valgt fra gruppen bestående av: kreft, lymfom, leukemi, autoimmune sykdommer, inflammatoriske lidelser, heteroimmune tilstander eller fibrose.

15 **16.** Forbindelse for anvendelse ifølge krav 15, hvori tilstanden som er modulert av BTK, er valgt fra: B-celle-malignitet, B-celle-lymfom, diffust storcellet B-celle-lymfom, kronisk lymfocytteleukemi, non-Hodgkins lymfom, ABC-DLBCL, kappecellelymfom, follikulært lymfom, hårcelleleukemi B-celle-non-Hodgi-
20 lymfom, Waldenströms makroglobulinemi, multippelt myelom, benkreft, benmetastase, artritt, multippel sklerose osteoporose, irritabel tarm-syndrom, inflammatorisk tarmsykdom, Crohns sykdom, Sjögrens syndrom og lupus.

25 **17.** Forbindelse ifølge hvilke som helst av kravene 1 til 13 for anvendelse i behandling av: kreft, lymfom, leukemi, autoimmune sykdommer, inflammatoriske lidelser, heteroimmune tilstander eller fibrose.

18. Forbindelse ifølge hvilke som helst av kravene 1 til 13 for anvendelse i behandling av en tilstand valgt fra gruppen bestående av: B-celle-malignitet, B-

[EP3390395]

celle-lymfom, diffust storcellet B-celle-lymfom, kronisk lymfocytteleukemi, non-Hodgkins lymfom, ABC-DLBCL, kappecellelymfom, follikulært lymfom, hårcelleleukemi, B-celle-non-Hodgkins lymfom, Waldenströms makroglobulinemi, multipelt myelom, benkreft, benmetastase, follikulært lymfom, kronisk lymfocytisk lymfom, B-celle-prolymfocytteleukemi, lymfoplasmacyttisk lymfom, splenisk marginalsonelymfom, plasmacellemyelom, plasmacytom, ekstranodalt marginalsone-B-celle-lymfom, nodalt marginalsone-B-celle-lymfom, mediastinalt (thymisk) storcellet B-celle-lymfom, intravaskulært storcellet B-celle-lymfom, primært effusjonslymfom, burkittlymfom/leukemi, lymfomatoid granulomatose, inflammatorisk tarmsykdom, artritt, lupus, reumatoid artritt, psoriatisk artritt, osteoartritt, Stills sykdom, juvenil artritt, diabetes, myasthenia gravis, Hashimotos tyreoiditt, Ords tyreoiditt, Graves sykdom Sjögrens syndrom, multippel sklerose, Guillain-Barres syndrom, akutt disseminert encefalomyelitt, Addisons sykdom, opsoclonus-myoclonus-syndrom, ankyloserende spondylitt, antifosfolipid-antistoffsyndrom, aplastisk anemi, autoimmun hepatitt, cøliaki, Goodpastures syndrom, idiopatisk trombocytopenisk purpura, optisk nevritt, sklerodermi, primær biliær cirrhose, Reiters syndrom, Takayusus artritt, temporal artritt, varm autoimmun hemolytisk anemi, Wegeners granulomatose, psoriasis, alopecia universalis, Behcets sykdom, kronisk utmattelse, dysautonomi, endometriose, interstitiell cystitt, omyotoni, sklerodermi, vulvodyni, graft-versus-verts-sykdom, transplantasjon, transfusjon, anafylakse, allergi, type I-hypersensitivitet, allergisk konjunktivitt, allergisk rhinitt, atopisk dermatitt, astma, appendicitt, blefaritt, bronkiolitt, bronkitt, bursitt, cervicitt, kolangitt,olecystitt, kolitt, konjunktivitt, cystitt, dakryoadenitt, dermatitt, dermatomyositt, encefalitt, endokarditt, endometritt, enteritt, enterokolitt, epikondylitt, epididymitt, fasciitt, fibrositt, gastritt, gastroenteritt, hepatitt, hidradenitis suppurativa, laryngitt, mastitt, meningitt, myelitis myocarditis, myositt, nefritt, ooforitt, orkitt, osteitt, otitt, pankreatitt, parotitt, perikarditt, peritonitt, faryngitt, pleuritt, flebitt, pneumonitt, pneumoni, proktitt, prostatitt, pyelonefritt, rhinitt, salpingitt, sinusitt, stomatitt, synovitt, tendonitt, tonsillitt, uveitt, vaginitt, vaskulitt, vulvitt, pulmonal fibrose, idiopatisk pulmonal fibrose (IPF), usual interstitial pneumonitis (UIP), interstitiell lungesykdom, kryptogen fibroserende alveolitt (CFA), bronchiolitis obliterans, bronkiektasi, fettleversykdom, steatose

[EP3390395]

ikke-alkoholisk steatohepatitt (NASH), kolestatisk leversykdom, primær biliær cirrhose (PBC), cirrhose, alkoholindusert leverfibrose, galleveisskade, biliær fibrose, kolestase, kolangiopatier, hepatisk eller lever-fibrose, hepatisk fibrose assosiert med alkoholisme, virusinfeksjon, hepatitt C, B eller D, autoimmun hepatitt, ikke-alkoholisk fettleversykdom (NAFLD), progressiv massiv fibrose, eksponering for toksiner eller irriterende stoffer, nyrefibrose, kronisk nyrefibrose, nefropatier assosiert med skade/fibrose kroniske nefropatier assosiert med diabetes, diabetisk nefropati, lupus, sklerodermi i nyrene, glomerulær nefritt, fokal segmental glomerulosklerose, IgA-nefropati nyrefibrose assosiert med human kronisk nyresykdom (CKD), kronisk progressiv nefropati (CPN), tubulointerstitiell fibrose, ureteral obstruksjon, kronisk uremi, kronisk interstitiell nefritt, strålingsnefropati, glomerulosklerose, progressiv glomerulonefrose (PGN), endotelial/trombotisk mikroangiopatiskade, HIV-assosiert nefropati, fibrose assosiert med eksponering for et toksin, et irriterende stoff eller et kjemoterapeutisk middel, fibrose assosiert med sklerodermi; strålingsindusert tarmfibrose; fibrose assosiert med en inflammatorisk lidelse i fremre tarm, Barretts øsofagus og kronisk gastritt, fibrose assosiert med en inflammatorisk lidelse i bakre tarm, inflammatorisk tarmsykdom (IBD), ulcerøs kolitt og Crohns sykdom, aldersrelatert makuladegenerering, diabetisk retinopati, retinopati ved prematuritet og neovaskulært glaukom.

19. Forbindelse ifølge hvilke som helst av kravene 1 til 13 for anvendelse samtidig med, sekvensielt med eller separat fra et ytterligere anti-tumor-middel, i behandling av kreft, lymfom, leukemi, autoimmune sykdommer, inflammatoriske lidelser, heteroimmune tilstander eller fibrose.

20. Farmasøytisk sammensetning, hvori den farmasøytiske sammensetningen omfatter en forbindelse ifølge hvilke som helst av kravene 1 til 13 og farmasøytisk akseptable eksipienter.

21. Farmasøytisk sammensetning ifølge krav 20, hvori sammensetningen er et kombinasjonsprodukt og omfatter et ytterligere farmasøytisk aktivt middel.