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(54) **KINASE ANTAGONISTS**

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(57) **ABSTRACT**

The present invention provides novel compounds that are antagonists of PI3 kinase, PI3 kinase and tyrosine kinase, PI3 kinase and mTOR, or PI33 kinase, mTOR and tyrosine kinase.

Specification includes a Sequence Listing.

Figure 1.

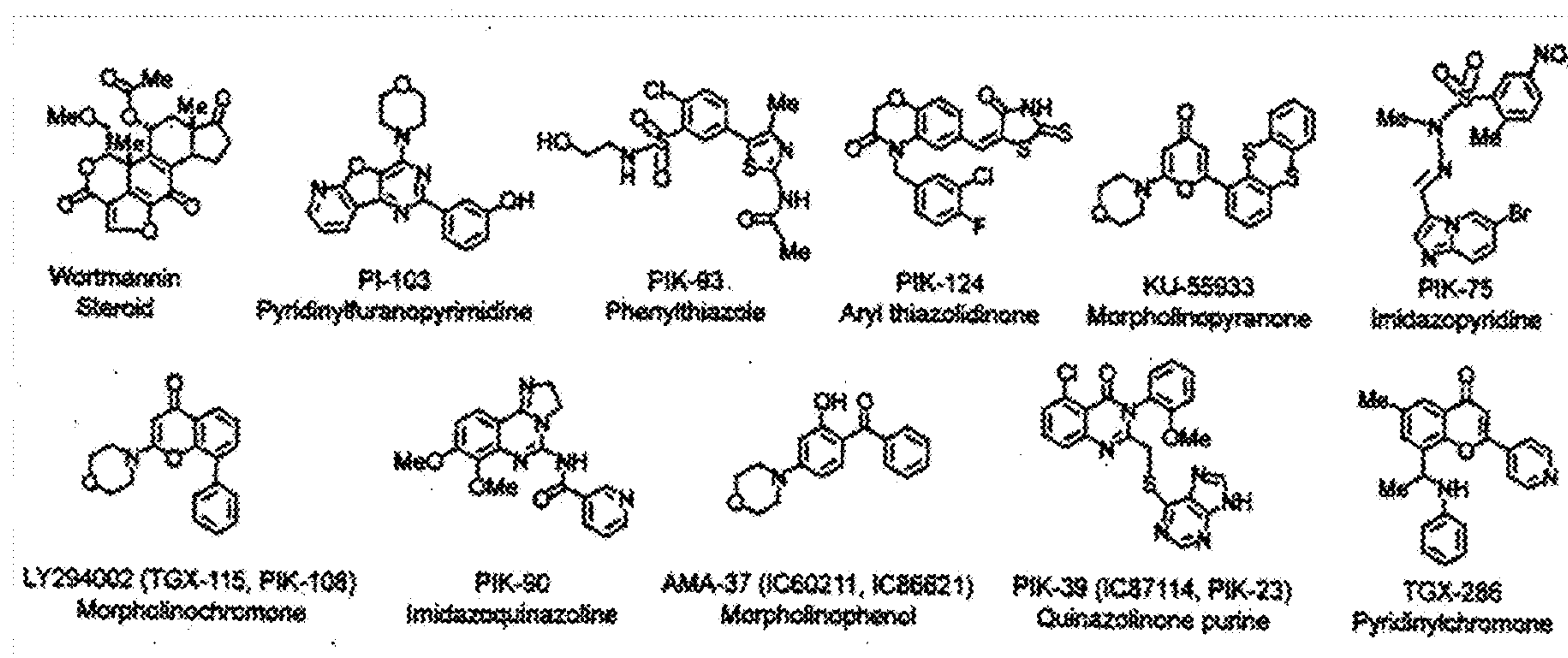


Figure 2.

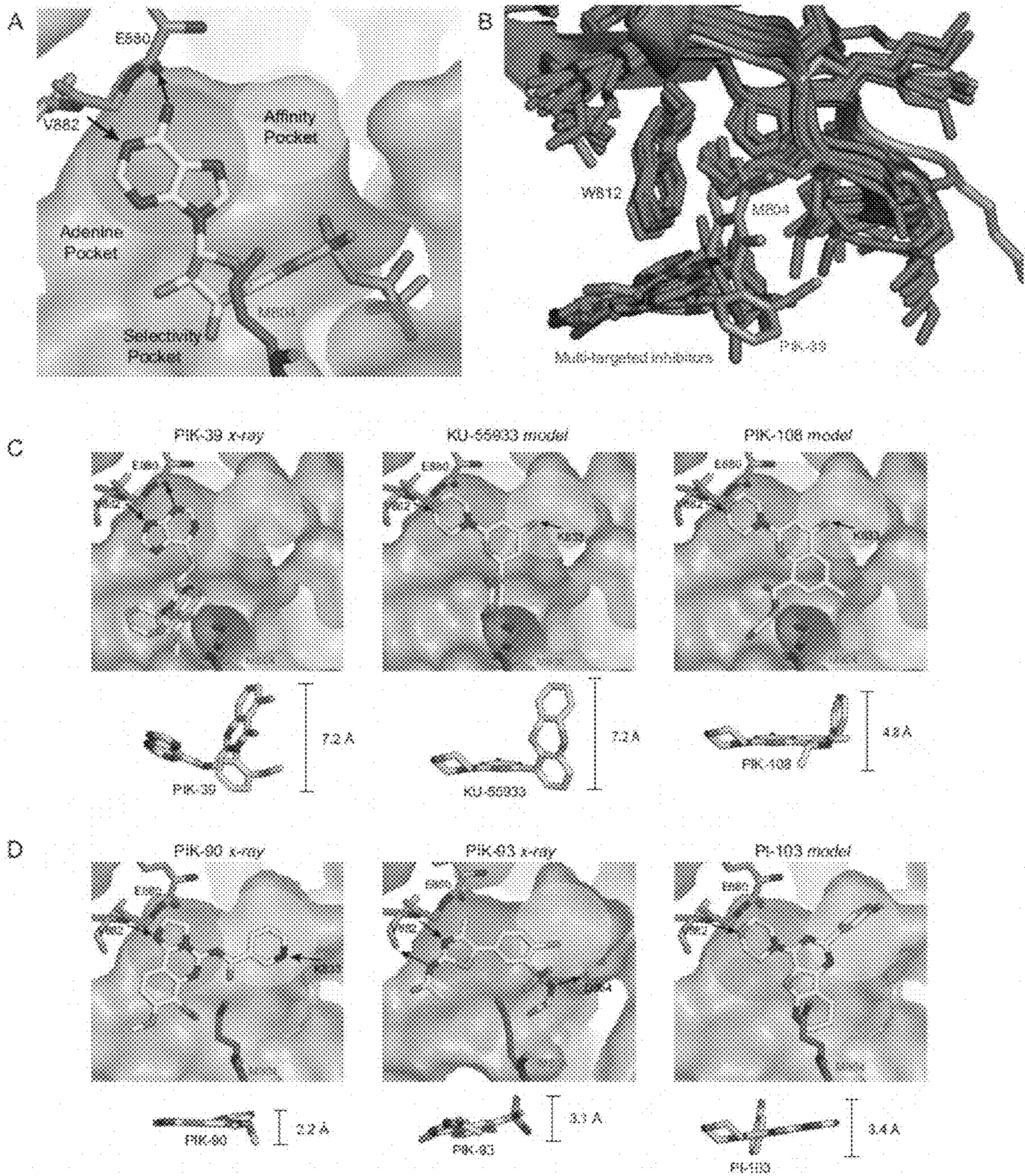


Figure 3.

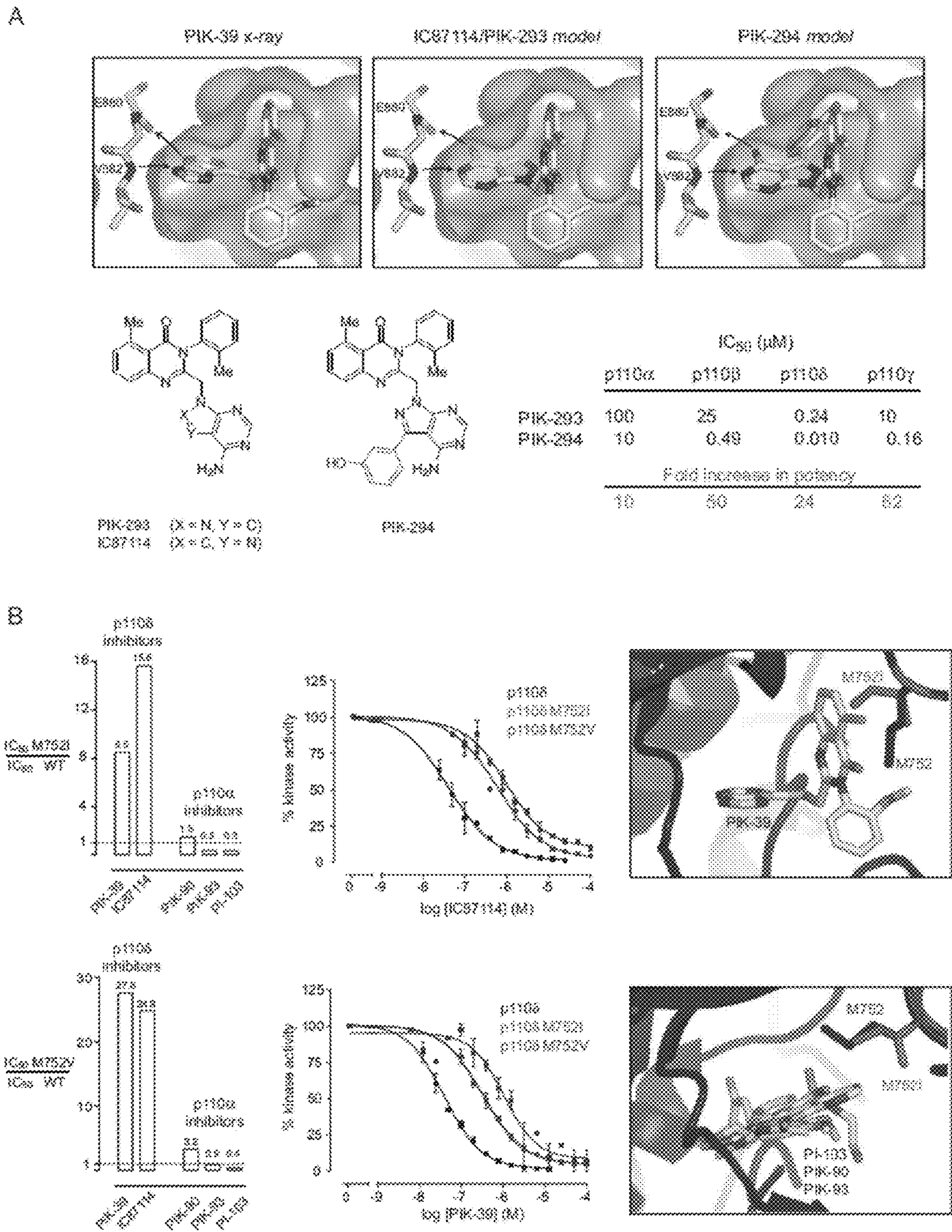
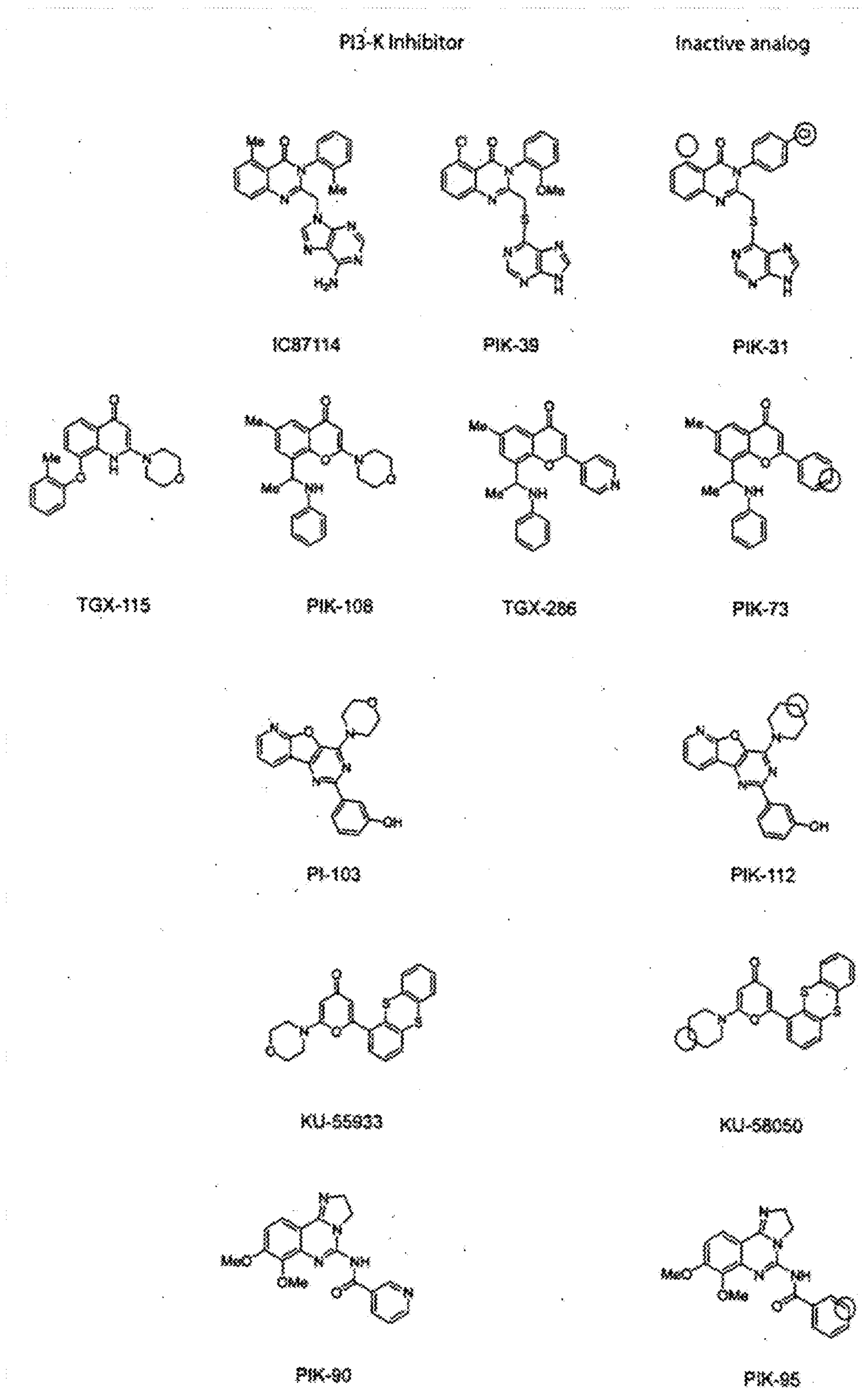


Figure 4.



[illegible]

Figure 6.

	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PI103	PIK124	KU55933
Abl	121.2	128.5	99.9	103.6	100.0	97.9	103.4	99.6	100.8	109.1	100.3
Abl (T315I)	141.2	127.4	110.5	99.4	108.5	121.6	111.3	126.0	108.1	87.5	105.3
Akt1	126.6	125.7	136.4	122.2	114.0	(10)	140.2	112.6	108.5	94.8	114.0
Akt1 (Δ PH)	91.4	77.3	81.0	89.6	94.7	(10)	122.4	122.2	123.1	93.3	116.5
Akt2	98.8	115.0	110.5	116.5	109.7	80.7	119.8	117.4	114.7	114.7	98.2
Akt2 (Δ PH)	104.4	94.4	111.3	117.8	117.3	95.0	108.5	110.7	112.6	98.7	100.2
Akt3	97.6	106.6	94.2	111.0	102.9	(2.9)	113.3	96.4	103.5	93.0	95.1
CamKII	111.4	121.9	122.1	115.4	118.8	119.8	116.1	120.4	127.6	135.5	121.8
CDK1/cyc.B	103.0	114.0	115.5	116.0	120.3	61.6	126.6	124.5	142.3	110.7	101.2
CDK2/cyc.A	105.3	99.7	105.6	102.4	103.1	(1.2)	100.9	98.1	98.5	104.9	97.4
Chk1	119.9	104.0	105.2	103.0	104.1	98.4	102.9	99.7	92.3	107.9	81.4
CK1	99.7	99.2	100.1	98.1	91.3	(3.0)	97.8	100.2	84.8	104.6	94.1
CK2	103.3	106.6	99.8	111.7	111.2	82.2	103.1	113.2	108.1	78.5	105.4
Erk1	96.7	99.3	97.6	93.7	99.0	77.9	98.8	98.6	92.0	97.8	104.6
Erk2	107.7	102.5	109.2	104.7	106.9	94.3	102.0	103.2	98.8	98.0	102.1
FAK	105.5	105.5	106.4	110.1	102.8	(10)	100.0	101.8	101.8	102.8	107.3
Fyn	145.7	131.3	115.7	105.3	111.3	(10)	126.1	127.2	114.2	113.4	116.0
GRK2	113.5	117.3	112.6	118.7	118.1	115.6	120.2	110.9	110.3	87.8	108.6
GSK3 β	114.0	107.3	101.5	104.7	96.1	(4.4)	85.6	104.0	105.5	97.6	102.0
Hck	104.9	102.2	101.1	93.0	84.9	(10)	94.7	94.9	94.9	87.2	104.1
Insulin R.	108.4	113.4	113.6	115.7	112.1	99.5	102.8	109.8	106.0	109.9	109.7
JNK1 α 1	99.9	95.6	92.1	88.6	93.8	97.8	94.2	87.2	83.6	96.9	99.6
JNK2 α 1	104.8	104.8	116.7	107.1	88.1	88.1	90.5	88.1	81.0	85.7	85.7
JNK2 α 2	95.4	101.6	90.8	87.7	89.3	86.2	83.1	98.5	76.9	89.3	95.4
IRAK4	112.7	98.9	100.1	93.1	95.0	(0.9)	94.9	95.9	105.6	175.4	74.2
NEK2	125.2	99.1	98.6	114.3	126.4	106.9	103.4	110.1	120.0	118.5	106.5
PKA	105.4	94.0	108.1	108.6	107.3	(10)	103.1	105.6	102.5	104.3	104.1
PKC δ	103.9	104.9	103.9	104.6	104.9	114.3	100.7	103.7	101.2	105.5	103.7
PKC ϵ	108.9	111.9	111.9	114.1	111.5	(10)	105.2	103.4	103.4	106.0	104.8
PDK1	111.2	101.9	97.4	113.4	114.4	111.0	110.4	118.7	107.5	109.4	130.7
PLK1	122.7	118.9	117.4	109.6	107.6	93.7	107.6	111.1	106.2	96.0	84.9
p38	101.2	102.8	106.5	104.1	100.9	100.3	98.5	102.9	99.8	102.6	101.4
Src	111.7	109.0	109.6	113.3	96.4	(10)	103.7	116.1	100.6	102.7	114.7
Src (T338I)	112.8	101.3	97.9	95.7	96.4	80.4	109.5	111.5	113.4	112.5	113.0
WNK1	107.5	108.0	109.6	109.0	119.3	101.1	108.6	110.0	104.1	108.3	104.7
Zap70	123.8	121.1	130.4	110.5	130.0	179.5	115.8	115.4	117.7	100.4	99.3

Figure 7.

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1  MPPGVDCPME FWTKEENQSV VVDFLLPTGV YLNFPVSRNA NLSTIKQLLW HRAQYEPFLH
61  MLSGPEAYVF TCINQTAEQQ ELEDEQRRLC DVQFFLPVLR LVAREGDRVK KLINSQISLL
121 IGRGLHEFDS LCDPEVNDPR AKMCQFCEEA AARRQQLGWE AWLQYSFPLQ LEPSAQTWGP
181 GTLRLPNRAL LVNVKFEGSE ESPTTFQVSTK DVFLALMACA LRKKATVFRQ PLVEQPEDYT
241 LQVNGRHEYL YGNYPLOQFQ YTCSCLSHSL TPHLTWVHSS SILAMRDEQS NPAPQVQKPR
301 AKPPPPIPAKK PSSVSLWSLE QPFRIELIQG SKVNADERMK LVVQAGLPHG NEMLCCTVSS
361 SEVSVCSEPV WKQRLEFDIN ICDLPRMARL CFALYAVIEK AKKARSTKKK SKKADCPIAW
421 ANLMLFDYKD QLKGTGERCLY MWPSVPDEKG ELLNPTGTVR SNPNTDSAAA LLICLPEVAF
481 HPVYYPALEK ILELGRHSEC VHVTEEEQLQ LAEILERRGS GELYEHKDL VWKLRHEVQE
541 HPPEALARLL LVTKWNKHED VAQMLYLLCS WPFLPVLSAL ELLDFSPFDC HVGSFAIKSL
601 RKLTDDELFO YLLQLVQVLK YESYLDCELT KFLLDRLAN RKIGHFLFWH LRSEMHVPSV
661 ALRFGILILEA YCRGSTHMK VLMKQGEALS KLKALNDFVK LSSQKTPKPO TKELMHLCMK
721 QEAYLEALSH LQSPDPSTL LAEVCVEQCT PMDSKMKPLW IMYSNEEAGS GGSVGLIFKN
781 GDDLKQDMLT LQMIQLMDVL WKQEGLDLRM TPYGCLEPTGD RTGLIEVVLR SDTIANIQLN
841 KSNMAATAAF NKDALLNWLK SKNPGEALDR AIEEFTLSCA GYCVATYVLG ICDRHSDNIM
901 IRESGQLFHI DFGHFLGNFK TKFGINRERV PFILTYDFVH VIQQGKTNNS EKFERFRGYC
961 ERAYTILRRH GLLFLHLFAL MRAAGLPELS CSKDIQYLKD SLALGKTEEE ALKHFRVKFN
1021 EALRESWRTK VNWLAHNVSK DNRQ
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(SEQ ID NO:3)

Figure 8.

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1  melenykqpv vlredncrrr rrmkprsaas slssmelipi efvlptsqrk ckspetalh
61  vaghgnvegm kaqvwirale tsvaadfyhr lgphhflily qkkgqwyey dkyqvvgtd
121 clrywkatrh spgqihlvqr hppseesqaf qrgltaligy dvtadvanhv delefttrrgl
181 vtpmaevas rdpklyamhp wvtskplpey lwkkiannoi fivihretts qtikvspddt
241 pgailqsfft kmakkkslmd ipesqseqdf vlrvccrday lvgetpiknf gwvrhclknq
301 eelhvvltdp pdpaldevrk eewplvddct gvtgyheqit ihgkdhsvf tvslwdcark
361 frvkiigidl pvlprntdlt vfveanighg qqvlcqrts pkpftteevlw nwlwefziki
421 kdlpkgaln lqiycgkapa laskasaesp sseskgkvql lyyvnlllid hrflrrgey
481 vlhmqisgk gedqgsfnad kltsatnpdk ensmsisill dnychpialp khqtpdpeg
541 drvraempnq lrkglealia tdpinpltae dkellwhfry eslkhpkayp klfskvkwgq
601 qeivaktyql larrevwdqs aldvgltmql ldenfsdenv raiavqkles ledddvlhyl
661 lqlvqavkfe pyhdsalarf llkrqlrnr ighflfwflr seiagsrhyq qrfavileay
721 lrgcgtamih dftgqvqvie mlqkvtdik slsaekydv sqvisqlkqk lenlqnsqk
781 esfrvpydpg lkagalalek ckvmaskkkp lwlefkcadp talnetigi ifkhgddlrq
841 dmlilqilri mesiwetesl dlcllpygci stgdkigmie ivkdattiak iqqstvgntg
901 afkdevlnhw lkekspteek fgaaverfvy scagycvatf vlgigdrhnd nimitatgnl
961 fhidfghilg nyksflgink ervpfvltpd flfvmgtsgk ktsphfqkfq dicvkaylal
1021 rhhtnllil fsmmlmtgmp qltskediay irdaltvgkn eedakkyfld qievcrdkgw
1081 tvqfnwflhl vlgikggekha sa
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(SEQ ID NO:4)

Figure 9.

1	MPPRPSSGEL	WGIHLMPPRI	LVECLLENGM	IVTLECLREA	TLITIKHELF	KEARKYFLHQ
61	LLQDESSYIF	VSVTQEAERE	EFFDETRRLC	DLRLFPQFPLK	VIEPVGNEEE	KILNREIGFA
121	IGMPVCEFDN	VKDPEVQDFR	RMILNVCKEA	VDLRDLNSPH	SRAMYVYPPN	VESSPELPHK
181	IYNKLDKGQI	IVVIWVIVSP	NNDKQKYTLK	INHDCVPEQV	TAEAIRKTR	SMLLSSEQLK
241	LCVLEYQGKY	ILKVCGCDEY	FLEKYPLSQY	KYIRSCIMLG	RMPNLMMLAK	ESLYSQLPMD
301	CFTMPSYSRR	ISTATPYMNG	ETSTKSLWVI	NSALRIKILC	ATYVNVNIRD	IDKIYVRTGI
361	YHGGEPLCDN	VNTQRVFCSN	PRWNEWLNVD	IYIPDLPRAA	RLCLSICSVK	GRKGAKKEHC
421	PLAWGNINLF	DYTDTLVSGK	MAINLWPFVH	GLEDLLNPIG	VTGSNPKNKT	PCLELEFDWF
481	SSVVKFPDMS	VIERHANWSV	SREAGFSYSH	AGLSNRLARD	NELRENDKEQ	LKAISTRDPL
541	SEITEQEKDF	LWSHRHYCVT	IPEILPKLLL	SVKWNRSDEV	AQMYCLVKDW	PPIKPEQAME
601	LLDCNYFDPM	VRGPAVECLE	KYLTDCKLSQ	YLIQLVQVLK	YEQYLDNLLV	RFLKALTN
661	QKIGHFFFWH	LKSEMHNKTV	SQRFGLLES	YCRACGMYLK	HLNRQVEAME	KLINLTDILK
721	QEKXDETQKV	QMKFLVEQMR	RPDFMDALQG	FLSPLNPAHQ	LGNLRELEECR	IMSSAKRPLW
781	LNWENPDIMS	ELLFQNEIIT	FKNGDELQD	MLTLQIIRIM	ENIWQNGGLD	LRMLPYGCLS
841	IGDCVGLIEV	VRNSHTIMQI	QCKGGLKGAL	QFNSHTLHQW	LKDKNKGEIY	DAAIDLFTRS
901	CAGYCVATFI	LGIGDRHNSN	IMVKDDGQLF	HIDFGHFLDH	KKKKFGYKRE	RVPPVLTQDF
961	LIVISKGAQE	CTKTREFERF	QEMCYKAYLA	IRQHANLFIN	LPSMMLQSGM	PELQSFDDIA
1021	YIRKTLALDK	TEQEALEYFM	KQMDANHHGG	WTTKMDWIFH	TIKQHALN	

(SEQ ID NO:5)

Figure 10.

1	MCFSPIMPPA	MADILDIWAV	DSQIASDGS	PVDFLLPTGI	YIQLEVPREA	TISYIKQMLW
61	KQVHNYPMFN	LLMDIDSYMF	ACVNQTAVYE	ELEDETRRLC	DVREPLPVLK	LVTRSCDPGE
121	KLDSKIGVLI	GKGLHEFDSL	KDPEVNEFRR	KMKFSEEEKI	LSLVGLSWMD	WLKQTYPPHEH
181	RPSIPENLED	KLYGCKLIYA	VHFENCQDVF	SFQVSPNMNP	IKVNELAIQK	RLTINGKEDE
241	VSPYDYVLQV	SGRVEYVFGD	HFLIQFQYIR	NCVMNRALPH	FILVECKIK	KMYEQEMIAI
301	EAAINRNSN	LPLPLPPKKT	RIISHVWENN	NPFQIVLVKG	NKLNTEETVK	VHVRAGLPHG
361	TELLCKTIVS	SEVSGKNDHT	WNEPLEFDIN	ICDLPRMARL	CFAVYAVLDK	VKTKKSTKTI
421	NPSKYQTIRK	AGKVHYPVAW	VNTMVFDFKG	QLRTGDIILH	SWSSFPDELE	EMLNPMGTVO
481	TNPHYTENATA	LHVKFPENKK	QPYYPFFDK	IIEKAAEIAS	SDSANVSSRG	GKKFLFVLKE
541	ILDRDPLSQL	CENEMDLINT	LRQDCREIFP	QSLPKLLLSI	KWNKLEDVAQ	LQALLQIWPK
601	LFPREALELL	DFNYPDQYVR	EYAVGCLROM	SDEELSOYLL	QLVQVLKYEP	FLDCALSRFL
661	LERALGNRRI	GQPLFWHLRS	EVHIPAVSVQ	FGVILEAYCH	GSVGHMKVLS	KQVEALNKLK
721	TLNSLIKINA	VKLNRAKGKE	AMHTCLKQSA	YREALSDLOS	PLNPCVILSE	LYVEKCKYMD
781	SKMKPLWLVI	NNKVFGEDSV	GVIFKNGDDL	RQDMLTLQML	RLMDLLWKEA	GLDLRMLPYG
841	CLATGDRSGL	IEVVSTSETI	ADIQLNSSNV	AAAAAFNKDA	LLNWLKEYNS	GDDLDRATIE
901	FTLSCAGYCV	ASYVLGIGDR	HSDNIMVKKT	GOLFHDIFGH	ILGNFKSKFG	IKRERVPPFIL
961	TYDFIHVIQQ	GKTGNTKFKG	RFRQCCEDAY	LILRRHGNLF	ITLFALMLTA	GLFELTSVKD
1021	IQYLKDSLAL	GKSEEEALKQ	FKQKFDALR	ESWTTKVNMW	AHTVRKDYRS	

(SEQ ID NO:6)

KINASE ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 11/732,856, filed Apr. 4, 2007, which in turn claims the benefit of U.S. Provisional Patent Application No. 60/744,269, filed Apr. 4, 2006, and U.S. Provisional Patent Application No. 60/744,270, filed Apr. 4, 2006, all of which are incorporated herein by reference in their entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] The present invention was supported by a grant from the National Institutes of Health (AI44009). The Government has certain rights to the invention.

BACKGROUND OF THE INVENTION

[0003] Phosphoinositide 3-kinases (PI3-Ks) catalyze the synthesis of the phosphatidylinositol (PI) second messengers PI(3)P, PI(3,4)P₂, and PI(3,4,5)P₃ (PIP₃) (Fruman et al., 1998). In the appropriate cellular context, these three lipids control diverse physiological processes including cell growth, survival, differentiation and chemotaxis (Katso et al., 2001). The PI3-K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation (Katso et al., 2001). The class I PI3-Ks (p110 α , p110 β , p110 δ , and p110 γ) are activated by tyrosine kinases or G-protein coupled receptors to generate PIP₃, which engages downstream effectors such as the Akt/PDK1 pathway, the Tec family kinases, and the Rho family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P₂. The PIKKs are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

[0004] The importance of these enzymes in diverse pathophysiology has made the PI3-K family the focus of intense interest as a new class of drug targets (Ward et al., 2003). This interest has been fueled by the recent discovery that p110 α is frequently mutated in primary tumors (Samuels et al., 2004) and evidence that the lipid phosphatase PTEN, an inhibitor of PI3-K signaling, is a commonly inactivated tumor suppressor (Cantley and Neel, 1999). Efforts are underway to develop small molecule PI3-K inhibitors for the treatment of inflammation and autoimmune disease (p110 δ , p110 γ , and mTOR), thrombosis (p110 β), viral infection (the PIKKs) and cancer (p110 α , mTOR, and others). Recently, the first selective inhibitors of these enzymes have been reported (Camps et al., 2005; Condliffe et al., 2005; Jackson et al., 2005; Knight et al., 2004; Lau et al., 2005; Sadhu et al., 2003).

[0005] Protein tyrosine kinases, protein serine/threonine kinases, and lipid kinases are distinct classes of proteins that play critical roles in regulation and proliferation of cellular activity. Small molecules that inhibit these protein classes have the potential to disrupt dysfunctional/pathological pathways at two distinct points. For example, signaling through tyrosine kinase receptors is known to be dysregulated in several types of cancer. This signaling pathway involves downstream proteins such as PI3 Kinase. Signaling

through the serine/threonine protein kinase mTOR (also known as the mammalian target of rapamycin) is known to regulate cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. Disruption of the mTOR pathway is implicated as a contributing factor to various human disease processes, especially various types of cancer. An inhibitor that blocks activity of protein tyrosine kinase and PI3 Kinase, mTOR and PI3Kinase, or mTOR, protein tyrosine kinase and PI3 Kinase, has the potential to stop the aberrant signaling at two or three different levels. Double or triple inhibition by a small molecule may magnify drug potency, increasing the compound's therapeutic potential.

[0006] The present invention meets these and other needs in the art by providing a new class of PI3 kinase antagonists, PI3 kinase and tryosine kinase antagonists, PI3Kinase and mTOR antagonists, and PI3Kinase, mTOR and tryosine kinase antagonists.

BRIEF SUMMARY OF THE INVENTION

[0007] It has been discovered that certain compounds described herein are potent antagonists of PI3 kinase, PI3 kinase and tryosine kinase, PI3Kinase and mTOR, or PI3Kinase, mTOR and tryosine kinase.

[0008] In one aspect, the present invention provides novel kinase antagonists that are PI3-Kinase affinity pocket binding antagonists (e.g. a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonist or a PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist). The PI3-Kinase affinity pocket binding antagonist is a compound containing a PI3-Kinase affinity pocket binding moiety. The PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists of the present invention are substituted pyrazolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety. Likewise, the PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists of the present invention are substituted pyrrolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety.

[0009] In another aspect, the present invention provides the novel kinase antagonists of Formula (I), defined below.

[0010] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3 Kinase (e.g. a p110 δ kinase). The method includes the step of contacting said PI3 kinase with an activity decreasing amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonists, or an antagonist of Formula I).

[0011] In another aspect, the present invention provides a method of treating a condition mediated by PI3 kinase activity, PI3 Kinase activity and tyrosine Kinase Activity, PI3 Kinase activity and mTOR activity, or PI3 Kinase activity, tyrosine kinase activity, and mTOR activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonists, or an antagonist of Formula I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 illustrates structures of representative compounds from eleven chemotypes of PI3-K inhibitors.

[0013] FIG. 2 illustrates structures of isoform-selective PI3-K inhibitors. A. Structure of ATP in the active site of

p110 γ , highlighting different regions of the ATP binding pocket. B. An alignment of all reported PI3-K inhibitor co-crystal structures. Met 804 adopts an up conformation in all structures except PIK-39. C. Structures or models of isoform-selective PI3-K inhibitors bound to p100 γ . D. Structures or models of multi-targeted PI3-K inhibitors bound to p110 γ .

[0014] FIG. 3 illustrates the probing of selectivity and an the PI3-Kinase affinity pocket. A. The structure of PIK-39 bound to p110 γ suggests a model for the binding of IC87114. PIK-293 and PIK-294 are pyrazolopyrimidine analogs of IC87114. PIK-294 projects a m-phenol into the affinity pocket, and this compound is more potent against the class I PI3-Ks. B. (Left) Ratio of IC50 values between mutant and wild-type for p110 δ inhibitors and p110 α /multi-targeted inhibitors. (Center) Dose response curves for binding of two p110 δ inhibitors to wild-type, M752I, and M752V p110 δ (Right) Models suggesting the impact of the M752I and M752V mutations in p110 δ on the binding of the different classes of inhibitors.

[0015] FIG. 4. Structures of additional PI3-K inhibitors and inactive analogs.

[0016] FIG. 5. IC50 values (μ M) for selected PI3-K inhibitors against lipid kinases.

[0017] FIG. 6. Inhibition of protein kinases by PI3-K inhibitors. Values represent % activity remaining in the presence of 10 μ M inhibitor. Values are average of triplicate measurements. IC50 values are in parenthesis where appropriate (μ M).

[0018] FIG. 7 sets forth the sequence of a human p110 δ kinase (SEQ ID NO: 3).

[0019] FIG. 8 sets forth the sequence of a human p110 γ kinase (SEQ ID NO: 4).

[0020] FIG. 9 sets forth the sequence of a human p110 α kinase (SEQ ID NO: 5).

[0021] FIG. 10 sets forth the sequence of a human p110 β kinase (SEQ ID NO:6).

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0022] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0023] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0024] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e. C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopente-

nyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

[0025] The term “alkylene” by itself or as part of another substituent means a divalent radical derived from an alkyl, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0026] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-$, $-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CHO}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedi-oxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})\text{OR}'-$ represents both $-\text{C}(\text{O})\text{OR}'-$ and $-\text{R}'\text{OC}(\text{O})-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like.

[0027] The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl,

cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidiny, 2-piperidiny, 3-piperidiny, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. The terms “cycloalkylene” and “heterocycloalkylene” refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

[0028] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0029] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (preferably from 1 to 3 rings) which are fused together (e.g. naphthyl) or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 6-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Thus, the term “heteroaryl” include fused ring structures in which at least one ring includes at least two double bonds. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms “arylene” and “heteroarylene” refer to the divalent radicals of aryl and heteroaryl, respectively.

[0030] For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxo, arylthioxo, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term “arylalkyl” is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphth-yloxy)propyl, and the like). However, the term “haloaryl,” as used herein is meant to cover only aryls substituted with one or more halogens.

[0031] Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. “3 to 7 membered”), the term “member” refers to a carbon or heteroatom.

[0032] The term “oxo” as used herein means an oxygen that is double bonded to a carbon atom.

[0033] Each of above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl,” and “heterocycloalkyl,” “aryl,” “heteroaryl” as well as their divalent radical derivatives) are meant to

include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0034] Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: —OR', —O, —NR', —N—OR', —NR'R'', —SR', —halogen, —SiR'R''R''', —OC(O)R', —C(O)R', —CO₂R', —C(O)NR'R'', —OC(O)NR'R'', —NR''C(O)R', —NR'—C(O)NR'R''', —NR''C(O)OR', —NR—C(NR'R'')=NR'', —S(O)R', —S(O)₂R', —S(O)₂NR'R'', —NRSO₂R', —CN and —NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an “alkoxy” group is an alkyl attached to the remainder of the molecule through a divalent oxygen radical. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, —NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., —CF₃ and —CH₂CF₃) and acyl (e.g., —C(O)CH₃, —C(O)CF₃, —C(O)CH₂OCH₃, and the like).

[0035] Similar to the substituents described for alkyl radicals above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, —OR', —NR'R'', —SR', —halogen, —SiR'R''R''', —OC(O)R', —C(O)R', —CO₂R', —C(O)NR'R'', —OC(O)NR'R'', —NR''C(O)R', —NR'—C(O)NR'R''', —NR''C(O)OR', —NR—C(NR'R'')=NR'', —NR—C(NR'R'')=NR'', —S(O)R', —S(O)₂R', —S(O)₂NR'R'', —NRSO₂R', —CN and —NO₂, —R', —N₃, —CH(Ph)₂, fluoro(C₁-C₄)alkoxo, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

[0036] Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula —T-C(O)—(CRR')_q-U-, wherein T and U are independently —NR—, —O—, —CRR'— or a single bond, and q is an

integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CRR'$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'$ or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''')_d-$, where s and d are independently integers of from 0 to 3, and X' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0037] As used herein, the term “heteroatom” or “ring heteroatom” is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0038] An “aminoalkyl” as used herein refers to an amino group covalently bound to an alkylene linker. The amino group is $-NR'R''$, wherein R' and R'' are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0039] A “substituent group,” as used herein, means a group selected from the following moieties:

[0040] (A) $-OH$, $-NH_2$, $-SH$, $-CN$, $-CF_3$, $-NO_2$, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0041] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0042] (i) oxo, $-OH$, $-NH_2$, $-SH$, $-CN$, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0043] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0044] (a) oxo, $-OH$, $-NH_2$, $-SH$, $-CN$, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0045] (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxo, $-OH$, $-NH_2$, $-SH$, $-CN$, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0046] A “size-limited substituent” or “size-limited substituent group,” as used herein means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4 - C_8

cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0047] A “lower substituent” or “lower substituent group,” as used herein means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5 - C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0048] The compounds of the present invention may exist as salts. The present invention includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0049] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0050] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0051] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)-

or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0052] The term “tautomer,” as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0053] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0054] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0055] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0056] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0057] The term “pharmaceutically acceptable salts” is meant to include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from

relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0058] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0059] The terms “a,” “an,” or “a(n)”, when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with “an” alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

[0060] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0061] The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer.

[0062] An “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. An “effective amount”

may also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) a disease, or reducing the likelihood of the onset (or reoccurrence) of a disease or its symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an osteoclast or leukocyte relative to the absence of the antagonist.

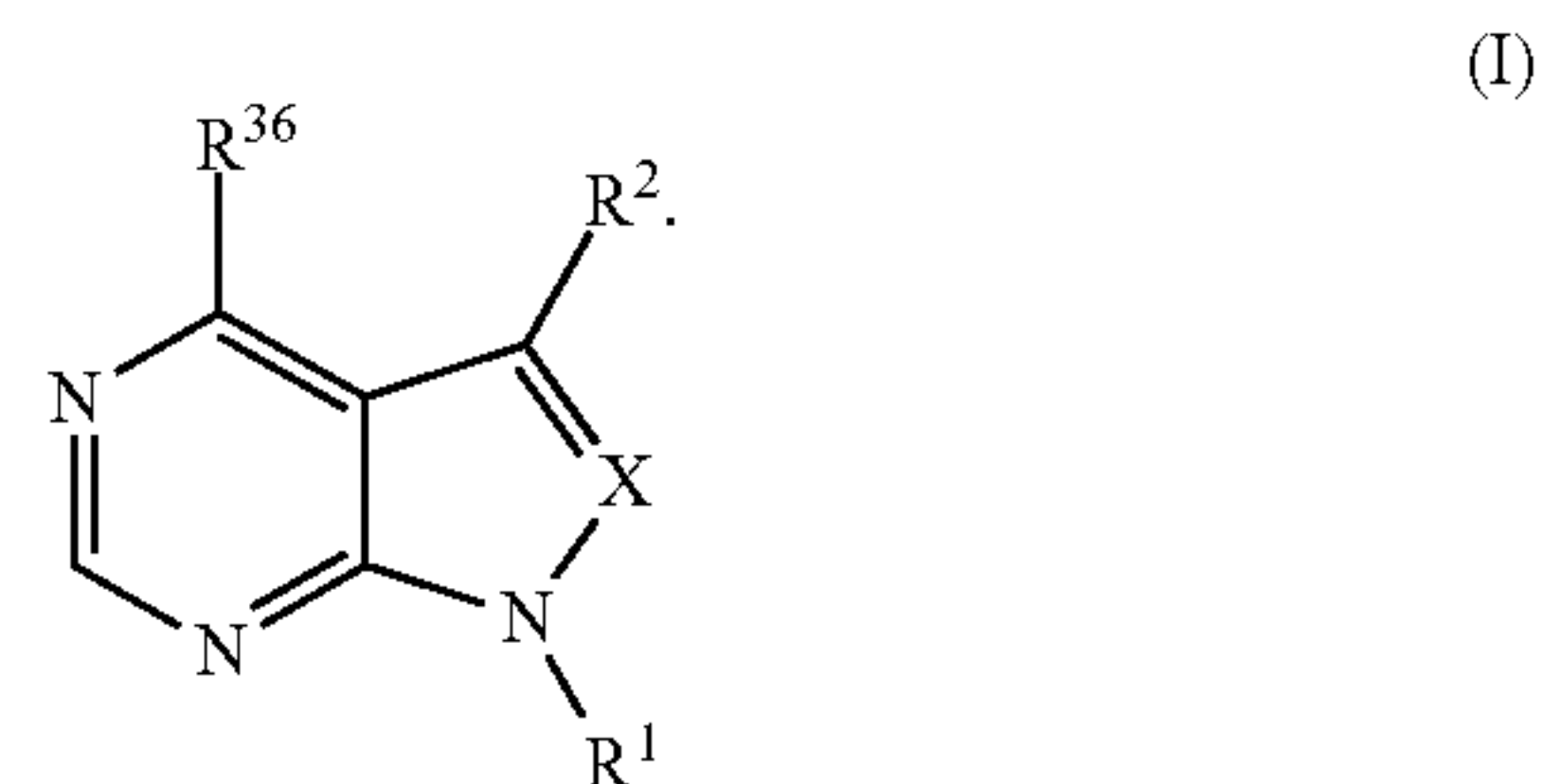
[0063] As used herein, the “antagonist” or “the compound of the present invention” refers to a compound of Formula (I), or a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or a PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist). A “compound of Formula (I)” includes the compounds of Formulae (I)-(X) as described below.

II. Kinase Antagonists

[0064] In one aspect, the present invention provides novel kinase antagonists. The kinase antagonists may be a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonist, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist) or a compound of Formula (I). The PI3-Kinase affinity pocket binding antagonists of the present invention are compounds containing a PI3-Kinase affinity pocket binding moiety. The PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists of the present invention are substituted pyrazolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety. Likewise, the PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists of the present invention are substituted pyrrolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety.

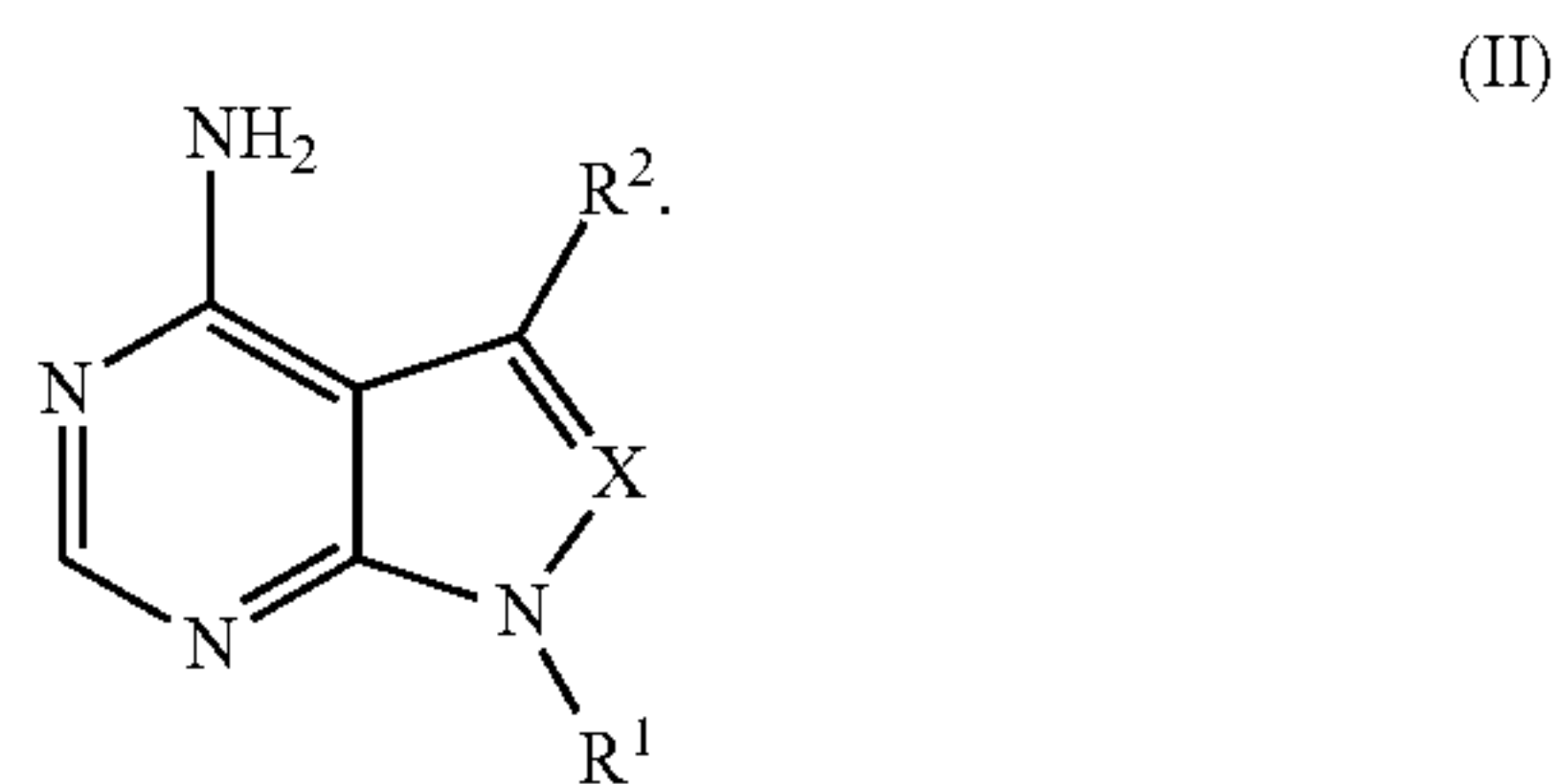
[0065] The PI3-Kinase affinity pocket binding moiety is a substituent which, upon contacting a p110 α , p110 β , p110 γ , or p110 δ kinase, fills space within the corresponding PI3-Kinase affinity pocket. In some embodiments, the PI3-Kinase affinity pocket binding moiety displaces at least one water molecule within the PI3-Kinase affinity pocket. The PI3-Kinase affinity pocket binding moiety may also interact with one or more amino acids that form part of the PI3-Kinase affinity pocket. A description of the PI3-Kinase affinity pocket and methods of determining whether a substituent fills space within the PI3-Kinase affinity pocket are set forth below.

[0066] In some embodiments, the kinase antagonist of the present invention has the formula:



In Formula (I), R¹ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R² is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X is =N— or =C(H)—. R³⁶ is halogen, —NR³⁷R³⁸, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R³⁷ and R³⁸ are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R³⁷ and R³⁸ are independently hydrogen, or unsubstituted alkyl. R² may be a PI3-Kinase affinity pocket binding moiety.

[0067] In some embodiments, R³⁶ is —NH₂. Thus, the kinase antagonist may have the formula:



[0068] In some embodiments, R¹, R², and X are as defined above in Formula (I). In certain embodiments, X is =N—.

[0069] In some embodiments of Formulae (I) and (II), R¹ is hydrogen, R³-substituted or unsubstituted alkyl, R³-substituted or unsubstituted heteroalkyl, R³-substituted or unsubstituted cycloalkyl, R³-substituted or unsubstituted heterocycloalkyl, R³-substituted or unsubstituted aryl, or R³-substituted or unsubstituted heteroaryl. R² is halogen, R⁴-substituted aryl, or substituted or unsubstituted heteroaryl;

[0070] R³ is halogen, —CN, —OR⁵, —S(O)_nR⁶, —NR⁷R⁸, —C(O)R⁹, =N—NH₂, —NR¹⁰—C(O)R¹¹, —NR¹²—C(O)—OR¹³, —C(O)NR¹⁴R¹⁵, —NR¹⁶S(O)₂R¹⁷, —S(O)₂NR¹⁸, R¹⁹-substituted or unsubstituted alkyl, R¹⁹-substituted or unsubstituted heteroalkyl, R¹⁹-substituted or unsubstituted cycloalkyl, R¹⁹-substituted or unsubstituted

heterocycloalkyl, R^{19} -substituted or unsubstituted aryl, or R^{19} -substituted or unsubstituted heteroaryl. Then symbol n is an integer from 0 to 2.

[0071] R^4 is halogen, $-\text{CN}$, $-\text{OR}^{20}$, $-\text{S}(\text{O})_q\text{R}^{21}$, $-\text{NR}^{22}\text{R}^{23}$, $-\text{C}(\text{O})\text{R}^{24}$, $=\text{N}-\text{NH}_2$, $-\text{NR}^{25}-\text{C}(\text{O})\text{R}^{26}$, $-\text{R}^{27}-\text{C}(\text{O})-\text{OR}^{28}$, $-\text{C}(\text{O})\text{NR}^{29}\text{R}^{30}$, $-\text{NR}^{31}\text{S}(\text{O})_2\text{R}^{32}$, $-\text{S}(\text{O})_2\text{NR}^{33}$, R^{34} -substituted or unsubstituted alkyl, R^{34} -substituted or unsubstituted heteroalkyl, R^{34} -substituted or unsubstituted cycloalkyl, R^{34} -substituted or unsubstituted heterocycloalkyl, R^{34} -substituted or unsubstituted aryl, or R^{34} -substituted or unsubstituted heteroaryl. The symbol q represents an integer from 0 to 2.

[0072] R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , and R^{33} are independently hydrogen, R^{35} -substituted or unsubstituted alkyl, R^{35} -substituted or unsubstituted heteroalkyl, unsubstituted cycloalkyl, R^{35} -substituted or unsubstituted heterocycloalkyl, R^{35} -substituted or unsubstituted aryl, or R^{35} -substituted or unsubstituted heteroaryl. R^{19} , R^{34} and R^{35} are independently hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0073] In some embodiments, R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , and R^{33} are independently hydrogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , and R^{33} may independently be hydrogen, unsubstituted alkyl, or unsubstituted heteroalkyl.

[0074] R^1 may be R^3 -substituted or unsubstituted alkyl, R^3 -substituted or unsubstituted cycloalkyl, or R^3 -substituted or unsubstituted aryl. R^1 may also be R^3 -substituted or unsubstituted alkyl, or R^3 -substituted or unsubstituted cycloalkyl. In some embodiments, R^1 is R^3 -substituted or unsubstituted C_1 - C_4 alkyl, or R^3 -substituted or unsubstituted C_3 - C_6 cycloalkyl. In other embodiments, R^1 is R^3 -substituted or unsubstituted C_1 - C_4 alkyl, or R^3 -substituted or unsubstituted cyclopentyl. R^1 may also be methyl or unsubstituted C_3 - C_6 branched alkyl (e.g. isopropyl, isobutyl, etc.).

[0075] In certain embodiments, R^3 is R^{19} -substituted or unsubstituted alkyl, R^{19} -substituted or unsubstituted cycloalkyl, or R^{19} -substituted or unsubstituted aryl. R^3 may also be R^{19} -substituted or unsubstituted alkyl, R^{19} -substituted or unsubstituted cycloalkyl, or R^{19} -substituted or unsubstituted aryl. In some embodiments, R^3 is R^{19} -substituted or unsubstituted alkyl, or R^{19} -substituted or unsubstituted cycloalkyl.

[0076] R^{19} may be unsubstituted alkyl or unsubstituted cycloalkyl. In some embodiments, R^{19} is unsubstituted C_1 - C_4 alkyl or unsubstituted cyclopentyl.

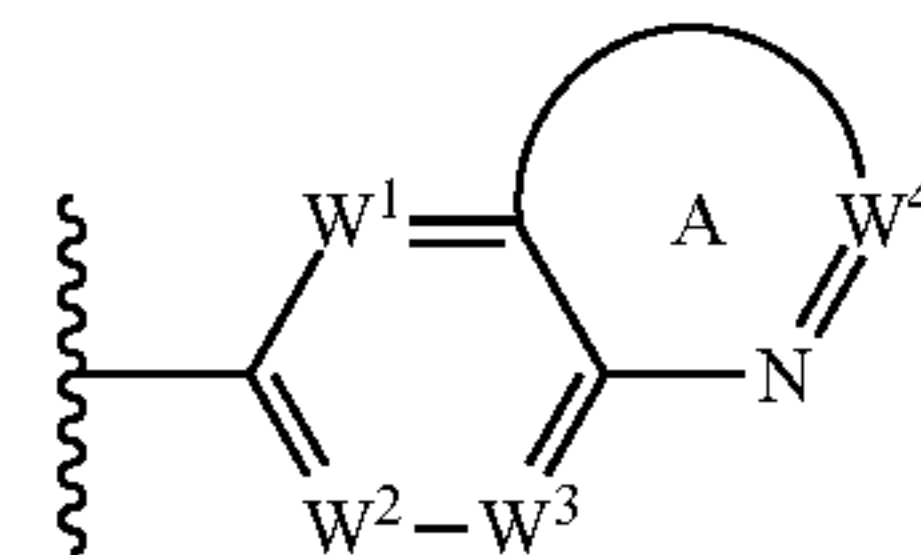
[0077] In some embodiments, R^2 is R^4 -substituted aryl, or R^4 -substituted or unsubstituted heteroaryl. R^2 may be R^4 -substituted phenyl, R^4 -substituted or unsubstituted naphthyl, R^4 -substituted or unsubstituted pyridinyl, R^4 -substituted or unsubstituted pyrimidinyl, R^4 -substituted or unsubstituted thiophenyl, R^4 -substituted or unsubstituted furanyl, R^4 -substituted or unsubstituted indolyl, R^4 -substituted or unsubstituted benzoxadiazolyl, R^4 -substituted or unsubstituted benzodioxolyl, R^4 -substituted or unsubstituted benzodioxanyl, R^4 -substituted or unsubstituted thianaphthanyl, R^4 -substituted or unsubstituted pyrrolopyridinyl, R^4 -substi-

tuted or unsubstituted indazolyl, R^4 -substituted or unsubstituted tetrahydronaphthalenyl, R^4 -substituted or unsubstituted quinolinyl, R^4 -substituted or unsubstituted quinoxalinyl, R^4 -substituted or unsubstituted pyridopyrazinyl, R^4 -substituted or unsubstituted quinazolinonyl, R^4 -substituted or unsubstituted chromenonyl, R^4 -substituted or unsubstituted benzoisoxazolyl, R^4 -substituted or unsubstituted imidazopyridinyl, R^4 -substituted or unsubstituted benzofuranyl, R^4 -substituted or unsubstituted dihydro-benzofuranyl, R^4 -substituted or unsubstituted dihydro-benzodioxinyl, R^4 -substituted or unsubstituted benzoimidazolonyl, or R^4 -substituted or unsubstituted benzothiophenyl.

[0078] In certain embodiments, R^2 is R^4 -substituted phenyl, R^4 -substituted or unsubstituted pyrrolopyridinyl, R^4 -substituted or unsubstituted quinolinyl, R^4 -substituted or unsubstituted indazolyl, R^4 -substituted or unsubstituted quinolinyl indolyl, or R^4 -substituted or unsubstituted naphthyl. R^4 may be halogen, $-\text{CN}$, $-\text{OR}^{20}$, or $-\text{NR}^{22}\text{R}^{23}$. R^4 may also simply be halogen, or $-\text{OR}^{20}$.

[0079] In certain embodiments, R^2 is has the formula:

(III)

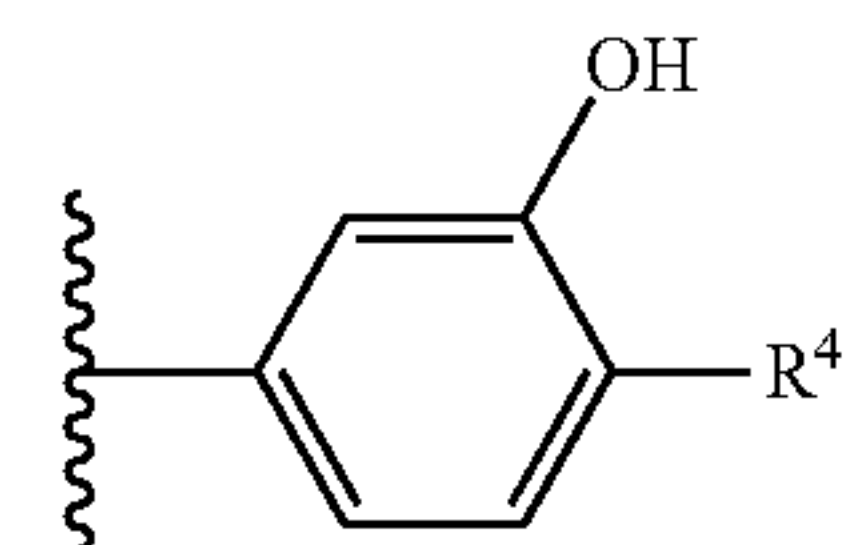


In Formula (III), W^1 , W^2 , W^3 , and W^4 are independently $=\text{CH}-$, $=\text{CR}^4-$, or $=\text{N}-$. Each R^4 is as defined above in the description of Formulae (I) and (II). Ring A is a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl. In some embodiments, ring A is a 6 to 7 membered heterocycloalkyl or 6 to 7 membered heteroaryl. Thus, in some embodiments, ring A is partially or fully unsaturated 6- or 7-membered ring.

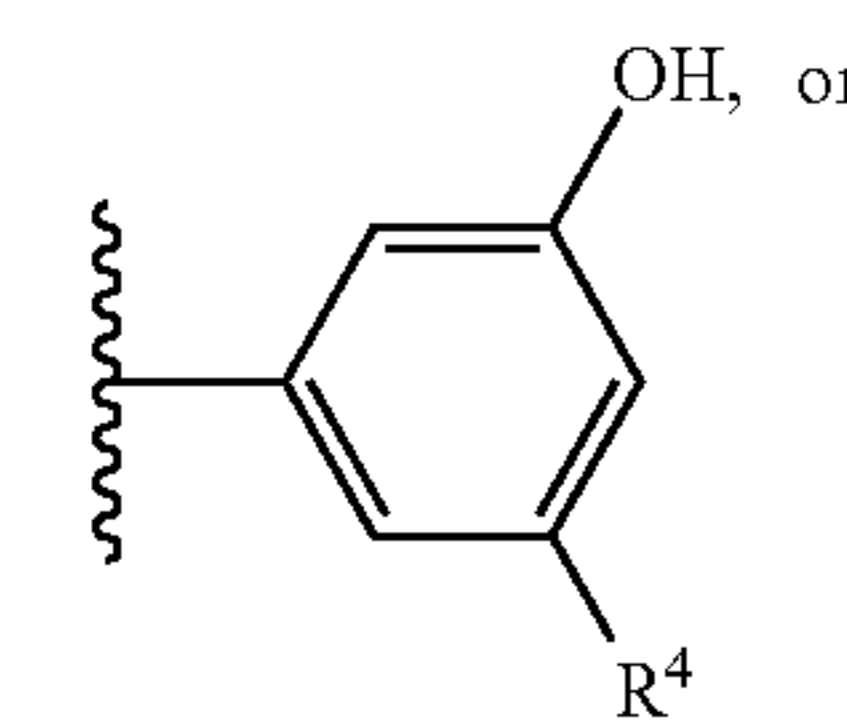
[0080] R^{20} may be hydrogen or unsubstituted C_1 - C_{10} alkyl. In some embodiments, R^{20} is hydrogen or unsubstituted C_1 - C_4 alkyl. R^{20} may also simply be hydrogen or methyl.

[0081] In some embodiments, R^2 has the formula:

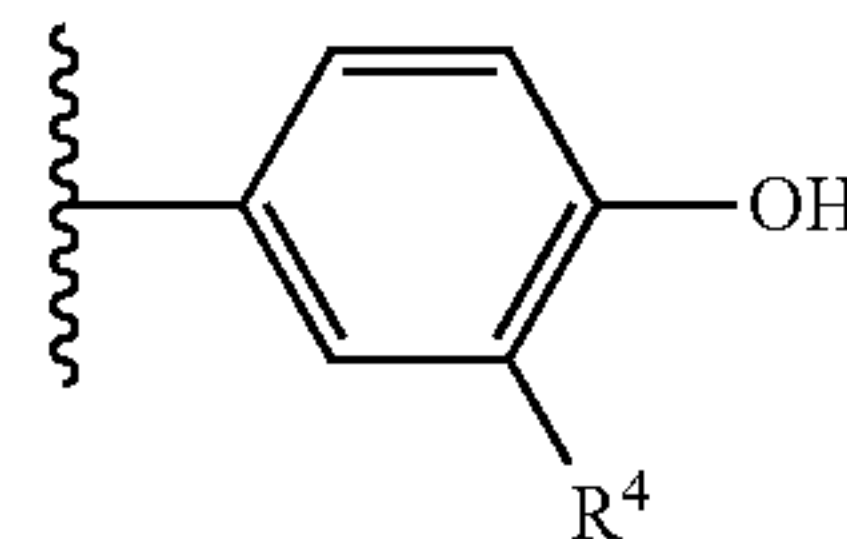
(IV)



(V)



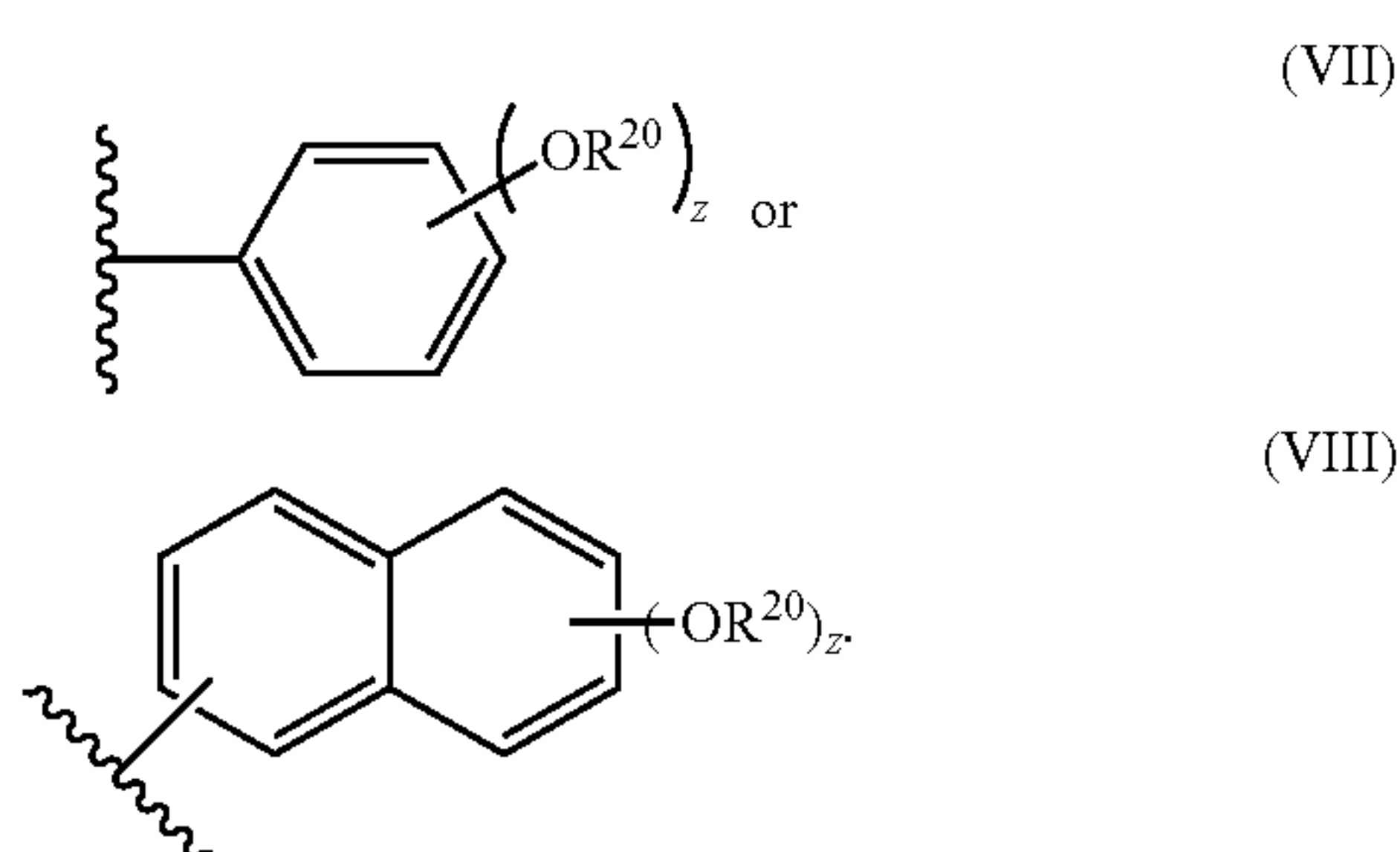
(VI)



In Formulae (IV), (V) and (VI), R^4 is absent, halogen, unsubstituted C_1 - C_4 alkyl, or $-OR^{20}$. The halogen may be F, Cl, or Br. In some embodiments, the halogen is F or Cl. In other embodiments, the halogen is F. R^{20} may be hydrogen or unsubstituted C_1 - C_4 alkyl.

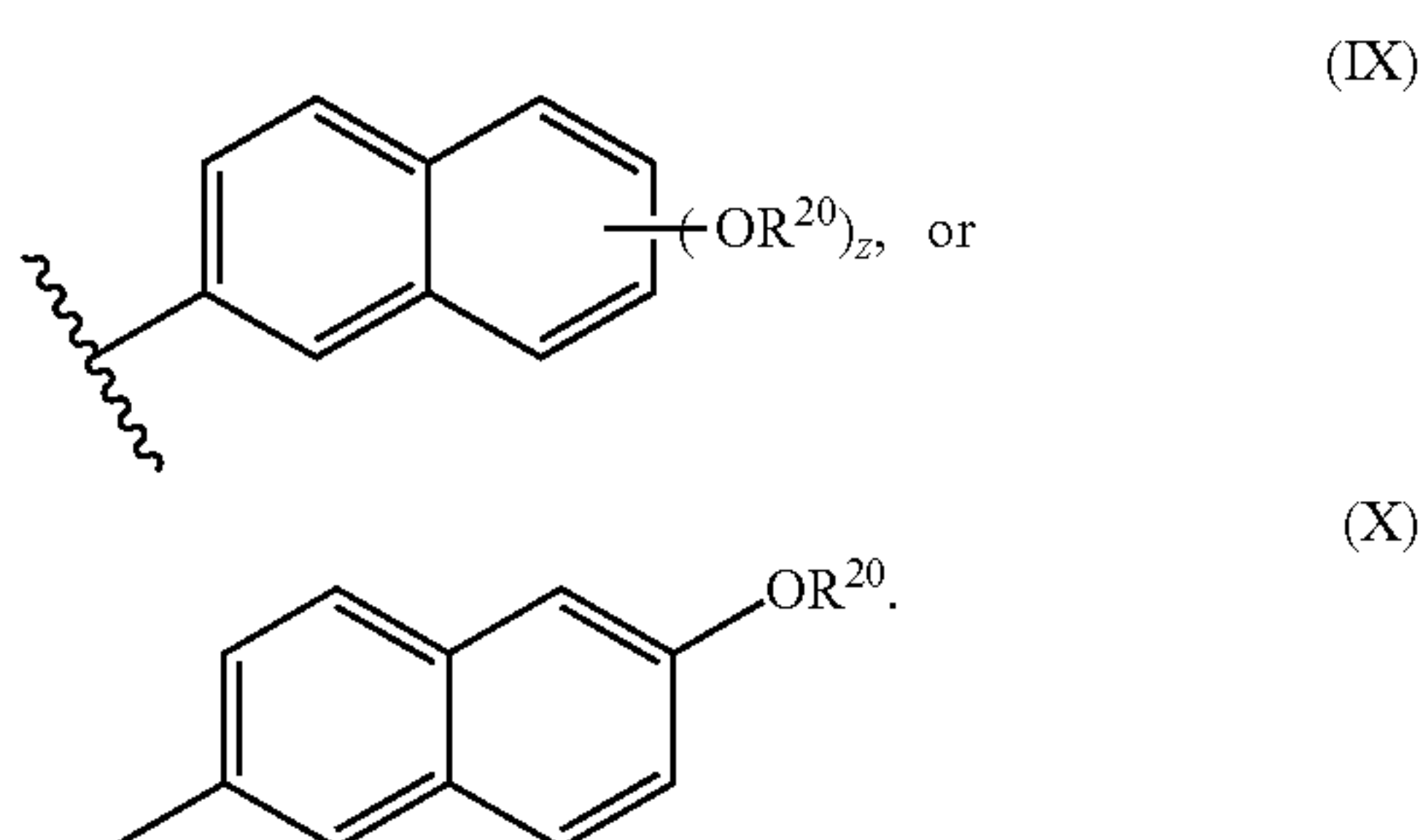
[0082] In some embodiments, R^2 is 6-hydroxynaphthyl, unsubstituted 7-azaindole, unsubstituted indolyl, unsubstituted indazolyl, or unsubstituted quinoliny.

[0083] In some embodiments, R^2 has the formula:



In Formulae (VII) and (VIII), R^{20} is as defined above. It is noted that, in accordance with the description of R^{20} above, each R^{20} is optionally different. The symbol z is an integer from 1 to 5 (e.g. 1 or 2). In some embodiments, R^{20} is hydrogen or unsubstituted C_1 - C_{10} alkyl (e.g. C_1 - C_5 alkyl such as methyl or ethyl).

[0084] In some embodiments, R^2 has the formula:



In Formulae (IX) and (X), above, R^{20} is as defined above, for example, in the description of Formulae (I), (II), (VI), and (VII) above.

[0085] In some embodiments, each substituted group described above for the compounds of the present invention is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, aryl(C_1 - C_6)alkyl, and heteroaryl(C_1 - C_6)alkyl described above is substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. Alternatively, at least one or all of these groups are substituted with at least one lower substituent group.

[0086] In other embodiments of the compounds described above, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4 - C_8

cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0087] Alternatively, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5 - C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0088] In another embodiment, the compounds of Formula (I) include any or all of the compounds listed in Table 1 below.

III. The PI3-Kinase Affinity Pocket

[0089] The term “PI3-Kinase affinity pocket,” as used herein, refers to a cavity within p110 α , p110 β , p110 γ , and p110 δ corresponding to the lightly shaded region shown in FIGS. 2A, 2C, and 2D labeled “Affinity Pocket.” FIGS. 2A, 2C, and 2D illustrate a computer model of the p110 γ crystal structure. In p110 γ , the surface of the PI3-Kinase affinity pocket is bound, at least in part, by the side chain of K833, D964, I879, and D841 (p110 γ numbering, see FIG. 8). The surface of the corresponding cavity in p110 δ is bound, at least in part, by the side chain of K779, D911, I825, and D787 (p110 δ numbering, see FIG. 7). The corresponding cavity within p110 α is bound, at least in part, by the side chains of K802, D933, I848, and D810 (p110 α numbering, see FIG. 9). The corresponding cavity within p110 β is bound, at least in part, by the side chains of K805, D937, I851, and D813 (p110 β numbering, see FIG. 10). The PI3-Kinase affinity pocket is not accessed by ATP.

[0090] The PI3-Kinase affinity pocket of p110 δ may be referred to herein as the p110 δ affinity pocket. Likewise, the PI3-Kinase affinity pocket of p110 γ may be referred to herein as the p110 γ affinity pocket. The PI3-Kinase affinity pocket includes lysine 779, which, according to computer models, forms a hydrogen bond with the pyridine nitrogen of PIK-90 and the phenol oxygen of PI 103 (FIG. 2D), both of which are inhibitors of p110 δ . Based on these computer modeling results, a novel antagonist was designed based on the chemical structure of PK-39 and IC87114, as detailed below.

[0091] As shown in FIG. 2C, PIK-39 does not contain a PI3-Kinase binding pocket moiety. And as shown in FIG. 3A, IC87114 maintains contacts to E880 and V882 in the ATP binding region of p110 δ , but is also missing a PI3-Kinase binding pocket moiety. By inserting m-phenol (a PI3-Kinase binding pocket moiety) at the C3 of the pyrazolopyrimidine of IC87114, the PI3-Kinase affinity pocket is accessed (FIG. 3A) resulting in a 60-fold increase in p110 δ inhibition potency.

[0092] As described above, a PI3-Kinase binding pocket moiety is a substituent which, upon contacting upon contacting p110 α , p110 β , p110 γ , or p110 δ , fills space within the corresponding PI3-Kinase binding pocket. For example, a PI3-Kinase affinity pocket binding moiety is a substituent which, upon contacting upon contacting p110 δ , fills space within the p110 α affinity pocket. Likewise, a p110 α affinity pocket binding moiety is a substituent which, upon contacting upon contacting p110 α , fills space within the p110 α , affinity pocket.

[0093] In some embodiments, the PI3-Kinase binding pocket moiety additionally interacts (e.g. bonds) with an amino acid that forms part of the PI3-Kinase binding pocket. In some related embodiments, the interaction is a hydrogen bond, van der Waals interaction, ionic bond, covalent bond (e.g. disulfide bond) or hydrophobic interaction.

IV. Determining Space Filling within the PI3-Kinase Affinity Pocket

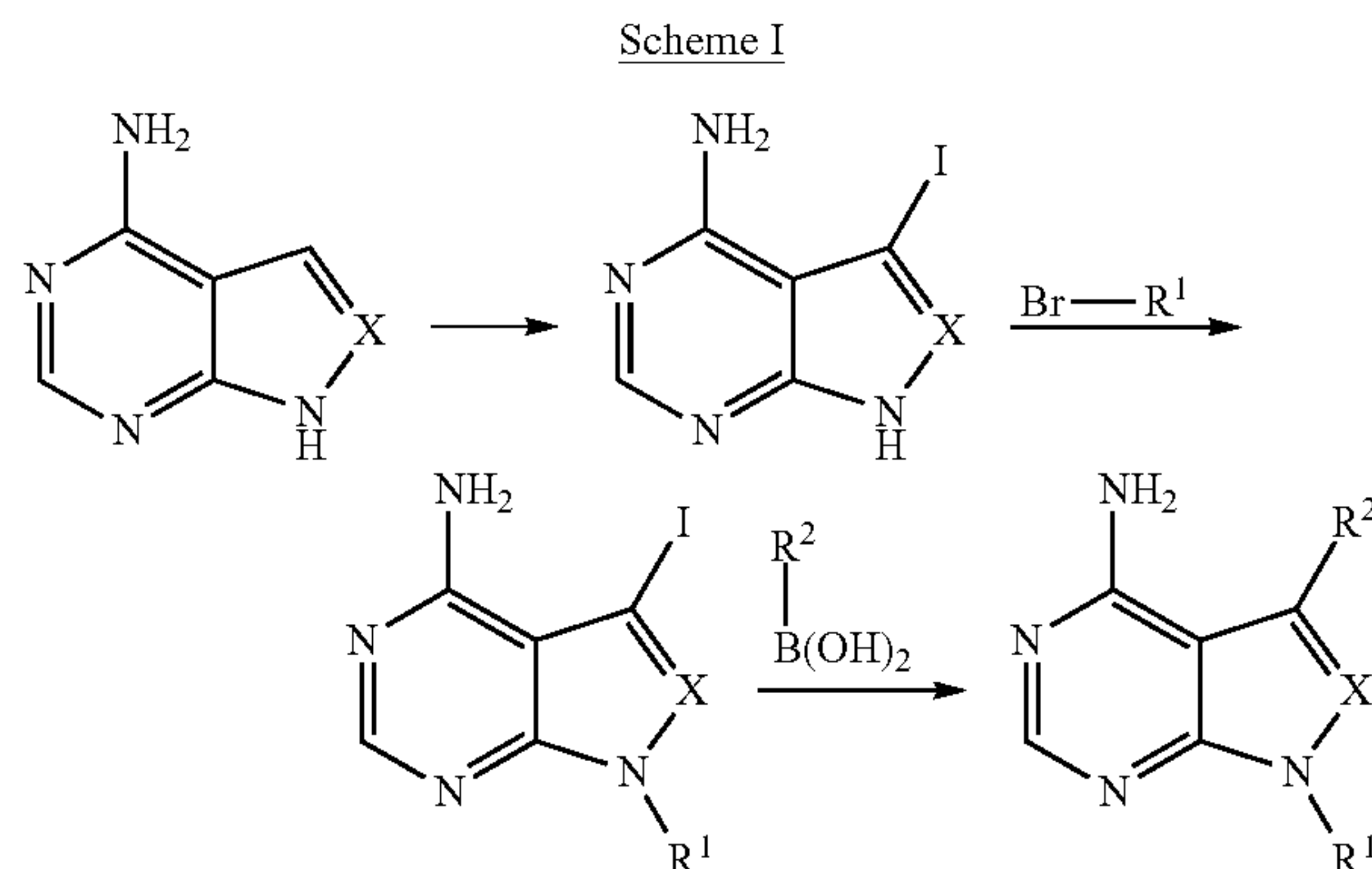
[0094] To determine whether the PI3-Kinase affinity pocket binding moiety fills space within the PI3-Kinase affinity pocket, computer modeling techniques are employed. A query PI3-Kinase affinity pocket binding antagonist (i.e. a test compound) is fit into a computer image of p110 γ . The p110 γ computer image is derived from the solved co-crystal structure of human p110 γ bound to PIK-39. The PyMOL Molecular Graphics System may be employed to generate the image. An example is presented in FIG. 3A, wherein IC87114 and PIK-294 are built into the computer image of p110 γ kinase, derived from the p110 γ -PIK-39 co-crystal. See Knight, et al., Cell 125: 733-745 (2006).

[0095] The computer models are typically analyzed to prevent any gross steric clashes and to satisfy key hydrogen bonds between the query PI3-Kinase affinity pocket binding antagonist and the p110 γ protein (e.g. V882 and M804). In some embodiments, energy minimization calculations are performed to optimize binding energy. Using these techniques, one skilled in the art can easily determine whether a query PI3-Kinase affinity pocket binding antagonist includes a PI3-Kinase affinity pocket binding moiety that fills space within the PI3-Kinase affinity pocket.

[0096] In some embodiments, the query PI3-Kinase affinity pocket binding antagonist is analyzed to determine whether at least one bond (e.g. a hydrogen bond) is formed between the query PI3-Kinase affinity pocket binding antagonist and an amino acid that form part of the PI3-Kinase affinity pocket. Using a computer modeling technique as described above, the distance between one or more amino acids that form part of the PI3-Kinase affinity pocket and a potential contact point on the PI3-Kinase affinity pocket binding moiety is determined. Based on this distance, one skilled in the art may determine whether at least one bond is formed between one or more amino acids that form part of the PI3-Kinase affinity pocket and a PI3-Kinase affinity pocket binding moiety.

V. General Syntheses

[0097] The compounds of the invention are synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention. However, the discussion is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.



[0098] In Scheme I above, iodination of the pyrazolo- or pyrrolo-pyrimidine is accomplished using an appropriate iodination reagent, such as *n*-iodo-succinamide. Elaboration of the 1-position may be accomplished via halogen displacement of a brominated substituent (e.g. a substituted or unsubstituted alkylbromide). Palladium-catalyzed cross coupling between organoboronic acid and the iodo halide (i.e. Suzuki coupling), is then used to elaborate the 3-position. Recent catalyst and method developments have broadened the possible Suzuki coupling applications enormously, so that the scope of the reaction partners is not restricted to aryls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners. Further information regarding Suzuki coupling may be found, for example in Kudo et al., *Angew. Chem. Int. Ed* 45: 1282-1284 (2006); Kirchhoff et al., *J. Am. Chem. Soc.*, 124: 13662-13663 (2002); Wu et al., *J. Org. Chem.*, 68: 670-673 (2003); and Molander et al., *J. Org. Chem.*, 67:8424-8429 (2002).

VI. Methods

[0099] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3 Kinase (e.g. a p110 α kinase). The method includes the step of contacting the PI3 kinase with an activity decreasing amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I)). In some embodiments, the antagonist is capable of decreasing the catalytic activity of a tyrosine kinase. In some embodiments, the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists.

[0100] In some embodiments, the antagonist is specific to p110 α relative to the antagonist action against p110 δ , p110 β , and/or p110 γ . In some embodiments, the IC₅₀ for p110 α is at least 1.5, 2.0, 3.0, 4.0, 5.0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 fold lower than the IC₅₀ against p110 δ , p110 β , and/or p110 γ . In other embodiments, the IC₅₀ of the antagonist against the p110 α is less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M.

[0101] In some embodiments, the antagonist is specific to p110 α relative to the antagonist action against insulin receptor tyrosine kinase. In some embodiments, the IC₅₀ for p110 α is at least 1.5, 2.0, 3.0, 4.0, 5.0, 10, 20, 30, 40, 50, 60,

70, 80, 90, 100, 200, 500, or 1000 fold lower than the IC₅₀ against insulin receptor tyrosine kinase. In other embodiments, the IC₅₀ of the antagonist against the p110 α is less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M.

[0102] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase. In some embodiments, the IC₅₀ of the antagonist against the tyrosine kinase is less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M. Some tyrosine kinases include, for example, DNA-dependent protein kinase DNA-dependent protein kinase (pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and functional mutants thereof. In some embodiments, the tyrosine kinase is Abl, Bcr-Abl, EGFR, or Flt-3.

[0103] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of mTOR (PPAN AAI17167). In some embodiments, the IC₅₀ of the antagonist against mTOR is less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M.

[0104] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of mTOR and p110 α at an IC₅₀ of less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M. In other embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase and p110 α at an IC₅₀ of less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M. In other embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase, mTOR, and p110 α at an IC₅₀ of less than 100 μ M, 50 μ M, 40 μ M, 30 μ M, 20 μ M, 10 μ M, 5 μ M, 1 μ M, 0.5 μ M, 0.1 μ M, 50 nM, 10 nM, 1 nM, 0.5 nM, 0.1 nM, 50 μ M, 10 μ M, or 1 μ M.

[0105] In another aspect, the present invention provides a method of treating a disease or condition mediated by PI3 kinase activity, PI3 Kinase activity and Tyrosine Kinase Activity, PI3 Kinase activity and mTOR Activity, or PI3 Kinase activity, mTOR activity, and Tyrosine Kinase Activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of an antagonist. The antagonist is a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I). In some embodiments the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists.

[0106] The disease may also be a bone-resorption disorder, chronic myelogenous leukemia, abnormal inflammation, autoimmune disease, thrombosis, or asthma. The disease may also be a type of cancer or cancer metastasis, including, for example, leukemia, carcinomas and sarcomas, such as cancer of the brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus and Medulloblastoma. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insuloma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, and prostate cancer. In some embodiments, the disease is selected from disease is liver cancer, colon cancer, breast cancer, melanoma, acute myelogenous leukemia, chronic myelogenous leukemia, or non-small-cell lung cancer.

[0107] In another aspect, the present invention provides methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of the antagonist. The antagonist is a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I). In some embodiments the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonist, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist.

VII. Pharmaceutical Formulations

[0108] In another aspect, the present invention provides a pharmaceutical composition including an antagonist in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the PI3-Kinase antagonists of the present invention described above.

[0109] In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

[0110] The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A most preferable dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0111] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, cit-

rate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinolate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teo-clate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[0112] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articular, intra-sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

[0113] For injection, the agents of the invention may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0114] Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g. patient) to be treated.

[0115] For nasal or inhalation delivery, the agents of the invention may also be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances such as, saline, preservatives, such as benzyl alcohol, absorption promoters, and fluorocarbons.

[0116] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts

is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0117] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[0118] Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0119] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0120] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0121] Depending upon the particular condition, or disease state, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the inhibitors of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[0122] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers,

riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating diabetes such as insulin, insulin analogues, alpha glucosidase inhibitors, biguanides, and insulin sensitizers; and agents for treating immunodeficiency disorders such as gamma globulin.

[0123] These additional agents may be administered separately, as part of a multiple dosage regimen, from the composition. Alternatively, these agents may be part of a single dosage form, mixed together with the inhibitor in a single composition.

[0124] The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those having skill in the art from the foregoing description. Such modifications are intended to fall within the scope of the invention. Moreover, any one or more features of any embodiment of the invention may be combined with any one or more other features of any other embodiment of the invention, without departing from the scope of the invention. For example, the PI3-Kinase antagonists of the present invention described above are equally applicable to the methods of treatment and methods of inhibiting kinases described herein. References cited throughout this application are examples of the level of skill in the art and are hereby incorporated by reference herein in their entirety for all purposes, whether previously specifically incorporated or not.

VIII. Examples

[0125] The following examples are meant to illustrate certain embodiments of the invention, and not to limit the scope of the invention.

[0126] General Methods. All chemicals, reagents and solvents used were purchased commercially and used as received. dH₂O refers to deionized water. Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Compounds were purified by High Pressure Liquid Chromatography (HPLC) eluting with dH₂O-MeCN-trifluoroacetic acid, 50:50:0.1, unless otherwise indicated. Analysis of products was carried out on a Liquid Chromatography Mass Spectrometer (LCMS) using MeCN-0.1% formic acid (varying ratios) as eluent.

[0127] A. Selected Reaction Procedures.

[0128] Synthesis of 1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA18). A solution of 250 mL of formamide and 3-amino-4-pyrazolecarbonitrile (25 g, 0.231 mol) was heated to 180° C. overnight under an argon atmosphere. Reaction was cooled and 400 mL of dH₂O were added. The resulting solid was filtered and rinsed with cold dH₂O. White solid precipitate was collected and dried in vacuo overnight to yield BA18 (39 g, 100% yield). ESI-MS (M+H)⁺ m/z calcd 136.1, found 136.1.

[0129] Synthesis of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA19). A solution of 3H-pyrazolo[3,4-d]pyrimidin-4-amine (10 g, 0.074 mol) and n-iodo-succinamide (25 g, 0.111 mol) in DMF (80 mL) was heated to 80° C. overnight under an argon atmosphere. The resulting solid

was filtered and rinsed with cold EtOH. Product was dried in vacuo overnight to yield BA19 (24 g, 100% yield). ESI-MS (M+H)⁺ m/z calcd 262.0, found 262.0

[0130] Synthesis of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA12). A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 0.0077 mol) and K₂CO₃ (4.2 g, 0.031 mol) in DMF (50 mL) was brought to 80° C. under an argon atmosphere. Isopropylbromide (1.0 g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 mL) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH₂Cl₂, 5:95] yielding BA12 (1.68 g, 72% yield). ESI-MS (M+H)⁺ m/z calcd 304.0, found 304.1.

[0131] General Suzuki coupling. Preparation of final products (see Table 1 for final product names and structures).

[0132] 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol, 1 equivalent) was dissolved in DME (12 mL). Boronic acid (1.1 equivalent) was dissolved in EtOH (3.3 mL) and added to reaction mixture. Pd(PPh₃)₄ (30 mg, 0.026 mmol, 0.2 equivalents) and saturated Na₂CO₃ (1.9 mL) were added to the reaction mixture and heated to 80° C. under argon and refluxed for 8 hours. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined and solvent was removed. Resulting solid (or oil) was dissolved in dH₂O-MeCN-trifluoroacetic acid, 50:50:0.1 and purified by HPLC. Purified product (varying yields) was confirmed by LCMS.

[0133] Synthesis of 4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide (BA14). A solution of benzenesulfonamide-4-boronic acid pinacol ester (23 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA14 (2.2 mg, 10% yield). ESI-MS (M+H)⁺ m/z calcd 333.1, found 333.1.

[0134] Synthesis of 1-isopropyl-3-(3-methoxy-4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA15). A solution of 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (19 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA15 (4.3 mg, 20% yield). ESI-MS (M+H)⁺ m/z calcd 300.1, found 300.2.

[0135] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)naphthalen-2-ol (BA17). A solution of 6-hydroxynaphthalen-2-yl-2-boronic acid (15 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added

and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA15 (4.8 mg, 23% yield). ESI-MS (M+H)⁺ m/z calcd 320.1, found 320.1.

[0136] Synthesis of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20). A solution of 4 4-N-Boc-amino-3-methoxy-benzeneboronic acid (48 mg, 0.18 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.18 mmol) in DME (12 mL). Pd(PPh₃)₄ (40 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O: 0.1% TFA) to yield BA20. ESI-MS (M+H)⁺ m/z calcd 399.2, found 399.1.

[0137] Synthesis of 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA20d). A solution of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20) (20 mg, 0.05 mmol) in CH₂Cl₂, TFA, S(CH₂)₂, H₂O (45:45:5:5) (1 mL) was stirred at room temperature for 15 minutes. NaHCO₃ (2 mL) was added till reaction was alkaline. Reaction was extracted with H₂O and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.11% TFA) to yield BA20d.

[0138] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridine-2-carbonitrile (BA21). A solution of 2-cyanopyridine 5-boronic acid pinacol ester (18 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA21 (2.5 mg, 14% yield). ESI-MS (M+H)⁺ m/z calcd 280.1, found 280.1.

[0139] Synthesis of 3-(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. A solution of (3-Benzyloxy-5-fluorophenyl)boronic acid (29 mg, 5.80 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA22 (15.6 mg, 60% yield). ESI-MS (M+H)⁺ m/z calcd 378.1, found 378.0.

[0140] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol (BA22). A solution of -(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15 mg, 0.04 mmol) in MeOH (0.9 mL) was flushed with argon. Pd on activated carbon (10 mL) was carefully added while keeping reaction under an argon atmosphere. Reaction was flushed with H₂ gas and left under H₂ atmosphere overnight at room tem-

perature. The reaction was filtered through celite and rinsed with MeOH to yield BA22 (15 mg, 100% yield). ESI-MS (M+H)⁺ m/z calcd 288.1, found 288.1.

[0141] Synthesis of 1-isopropyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA23). A solution of 3,4-Dimethoxyphenylboronic acid (24 mg, 0.13 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.11% TFA) to yield BA23 (13.1 mg, 60% yield). ESI-MS (M+H)⁺ m/z calcd 314.0, found 314.1.

[0142] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol (BA26). A solution of (3-Hydroxymethylphenyl)boronic acid (24 mg, 0.13 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA26 (8.4 mg, 42% yield). ESI-MS (M+H)⁺ m/z calcd 283.1, found 284.2.

[0143] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-N-(4,5-dihydrothiazol-2-yl)benzamide (BA30). A solution of [3-((4,5-dihydrothiazol-2-yl)carbamoyl)phenyl]boronic acid (19 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O: 0.1% TFA) to yield BA30 (17.8 mg, 67% yield).

[0144] Synthesis of 1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (BA31). A solution of 4-Acetylphenylboronic acid (12.7 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA31 (12.9 mg, 62% yield).

[0145] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol (BA32). A solution of (4-Aminocarbonyl-3-chlorophenyl)boronic acid (16 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon

atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA32 (9.7 mg, 42% yield). ESI-MS (M+H)⁺ m/z calcd 331.1, found 331.1.

[0146] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylthiophene-2-carbaldehyde (BA34). A solution of 5-Formyl-3-methylthiophene-2-boronic acid (26 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA34 (14.7 mg, 38% yield). ESI-MS (M+H)⁺ m/z calcd 302.1, found 302.0.

[0147] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)furan-3-carbaldehyde (BA35). A solution of 4-Formylfuran-2-boronic acid (20 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA35 (13.5 mg, 39% yield). ESI-MS (M+H)⁺ m/z calcd 272.1, found 272.1.

[0148] Synthesis of N-[3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide (BA38). A solution of 3-Methanesulfonylaminophenylboronic acid (32 mg, 0.15 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O: 0.1% TFA) to yield BA38 (24.3 mg, 54% yield). ESI-MS (M+H)⁺ m/z calcd 347.1, found 347.0.

[0149] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzonitrile (BA39). A solution of 3-Cyanophenylboronic acid (23 mg, 0.15 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA39 (14.9 mg, 41% yield). ESI-MS (M+H)⁺ m/z calcd 279.1, found 279.0.

[0150] Synthesis of N-[4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide (BA40). A solution of 4-methanesulfonylaminophenylboronic acid (24 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]py-

rimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA40 (0.9 mg, 3% yield). ESI-MS (M+H)⁺ m/z calcd 347.1, found 347.0.

[0151] Synthesis of 3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide (BA41). A solution of benzenesulfonamide-3-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O: 0.1% TFA) to yield BA41 (9.2 mg, 28% yield). ESI-MS (M+H)⁺ m/z calcd 333.1, found 333.0.

[0152] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[b]thiophene-5-carbaldehyde (BA42). A solution of 5-Formylbenzo[b]thiophene-2-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O: 0.1% TFA) to yield BA42 (15.2 mg, 45% yield). ESI-MS (M+H)⁺ m/z calcd 338.1, found 338.0.

[0153] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-3-carbaldehyde (BA43). A solution of N-Boc-3-formyl-5-indoleboronic acid pinacol ester (40 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). The TFA from purification hydrolyzed the Boc to yield BA43. ESI-MS (M+H)⁺ m/z calcd 321.1, found 321.0.

[0154] Synthesis of 3-(benzo[c][1,2,5]oxadiazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA44). A solution of Benzo[c][1,2,5]oxadiazole-5-boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA44. ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0155] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile (BA45). A solution of (4-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA45. ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.1.

[0156] Synthesis of 2-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl) acetonitrile (BA46). A solution of (3-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA45. ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.1.

[0157] Synthesis of 1-isopropyl-3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA48). A solution of (4-methoxyphenyl)boronic acid (17 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.10% TFA) to yield BA48 (4.5 mg, 16% yield). ESI-MS (M+H)⁺ m/z calcd 284.1, found 284.1.

[0158] Synthesis of 1-isopropyl-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA49). A solution of 3-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.11% TFA) to yield BA49. ESI-MS (M+H)⁺ m/z calcd 284.1, found 284.0.

[0159] Synthesis of 1-isopropyl-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA52). A solution of 3-Pyridinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (15 mg, 0.015 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA52. ESI-MS (M+H)⁺ m/z calcd 255.1, found 255.0.

[0160] Synthesis of 1-isopropyl-3-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA53). A solution of 5-Pyrimidinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (15 mg, 0.015 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA53. ESI-MS (M+H)⁺ m/z calcd 256.1, found 256.1.

[0161] Synthesis of 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA54). A solution of 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (26 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA54 (6 mg, 15% yield). ESI-MS (M+H)⁺ m/z calcd 312.1, found 312.0.

[0162] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (BA55). A solution of 3-Acetylphenylboronic acid (23 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA55 (7 mg, 18% yield). ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0163] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (BA56). A solution of 4-Hydroxyphenylboronic acid (30 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 mL) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA56 (12 mg, 32% yield). ESI-MS (M+H)⁺ m/z calcd 270.1, found 270.1.

[0164] Synthesis of PI3-K/Tyrosine Kinase Dual Inhibitors

[0165] Synthesis of 1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA18). A solution of 250 ml of formamide and 3-amino-4-pyrazolecarbonitrile (25 g, 0.231 mol) was heated to 180° C. overnight under an argon atmosphere. Reaction was cooled and 400 ml of dH₂O were added. The resulting solid was filtered and rinsed with cold dH₂O. White solid precipitate was collected and dried in vacuo overnight to yield BA18 (39 g, 100% yield). ESI-MS (M+H)⁺ m/z calcd 136.1, found 136.1.

[0166] Synthesis of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA19). A solution of 3H-pyrazolo[3,4-d]pyrimi-

din-4-amine (10 g, 0.074 mol) and n-iodo-succinamide (25 g, 0.111 mol) in DMF (80 ml) was heated to 80° C. overnight under an argon atmosphere. The resulting solid was filtered and rinsed with cold EtOH. Product was dried in vacuo overnight to yield BA19 (24 g, 100% yield). ESI-MS (M+H)+ m/z calcd 262.0, found 262.0

[0167] Synthesis of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA12). A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 0.0077 mol) and K₂CO₃ (4.2 g, 0.031 mol) in DMF (50 ml) was brought to 80° C. under an argon atmosphere. Isopropylbromide (1.0 g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH₂Cl₂, 5:95] yielding BA12 (1.68 g, 72% yield). ESI-MS (M+H)+ m/z calcd 304.0, found 304.1.

[0168] Synthesis of 4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide (BA14). A solution of benzenesulfonamide-4-boronic acid pinacol ester (23 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA14 (2.2 mg, 10% yield). ESI-MS (M+H)+ m/z calcd 333.1, found 333.1.

[0169] Synthesis of 1-isopropyl-3-(3-methoxy-4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA15). A solution of 2 methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenol (19 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA15 (4.3 mg, 20% yield). ESI-MS (M+H)+ m/z calcd 300.1, found 300.2.

[0170] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)naphthalen-2-ol (BA17). A solution of 6-hydroxynaphthalen-2-yl-2-boronic acid (15 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA15 (4.8 mg, 23% yield). ESI-MS (M+H)+ m/z calcd 320.1, found 320.1.

[0171] Synthesis of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20). A solution of 4 4-N-Boc-amino-3-methoxy-benzeneboronic acid (48 mg, 0.18 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-

d]pyrimidin-4-amine (50 mg, 0.18 mmol) in DME (12 ml). Pd(PPh₃)₄ (40 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA20. ESI-MS (M+H)+ m/z calcd 399.2, found 399.1.

[0172] Synthesis of 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA20d). A solution of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20) (20 mg, 0.05 mmol) in CH₂Cl₂, TFA, S(CH₂)₂, H₂O (45:45:5:5) (1 ml) was stirred at room temperature for 15 minutes. NaHCO₃ (2 ml) was added till reaction was alkaline. Reaction was extracted with H₂O and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA20d.

[0173] Synthesis of 2-amino-5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (BA20dd). BA20 (tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate, 7 mg, 0.018 mmol) was dissolved in CH₂Cl₂ (2.5 ml) and stirred under an argon atmosphere at room temperature. BBr₃ (0.500 ml) was added slowly with a syringe. The reaction mixture was stirred overnight, under argon at room temperature. BBr₃ was removed in vacuo and the remaining solid was purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA20dd.

[0174] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridine-2-carbonitrile (BA21). A solution of 2-cyanopyridine 5-boronic acid pinacol ester (18 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA21 (2.5 mg, 14% yield). ESI-MS (M+H)+ m/z calcd 280.1, found 280.1.

[0175] Synthesis of 3-(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. A solution of (3-Benzyloxy-5-fluorophenyl)boronic acid (29 mg, 5.80 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA22 (15.6 mg, 60% yield). ESI-MS (M+H)+ m/z calcd 378.1, found 378.0.

[0176] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol (BA22). A solution of -(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15 mg, 0.04 mmol) in MeOH (0.9 ml) was flushed with argon. Pd on activated carbon (10 ml) was carefully added while keeping reaction under an argon atmosphere. Reaction was flushed with H₂ gas and left under H₂ atmosphere overnight at room temperature. The reaction was filtered through celite and rinsed

with MeOH to yield BA22 (15 mg, 100% yield). ESI-MS (M+H)⁺ m/z calcd 288.1, found 288.1.

[0177] Synthesis of 1-isopropyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA23). A solution of 3,4-Dimethoxyphenylboronic acid (24 mg, 0.13 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA23 (13.1 mg, 60% yield). ESI-MS (M+H)⁺ m/z calcd 314.0, found 314.1.

[0178] Synthesis of tert-butyl 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-(benzyloxy)-1H-indole-1-carboxylate (BA24). A solution of 5-Benzyloxy-1-BOC-indole-2-boronic acid (303 mg, 0.83 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [EtOAc:hexanes, 5:95] to yield BA24. ESI-MS (M+H)⁺ m/z calcd 499.2, found 499.2.

[0179] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indol-5-ol (BA24dd). BA24 (3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine, 30 mg, 0.10 mmol) was dissolved in a solution of formic acid (4.5 ml, 10 equivalents) and HCl (0.45 ml, 1 equivalent). The reaction was heated and stirred for one hour under an argon atmosphere. The reaction was then concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA24dd. ESI-MS (M+H)⁺ m/z calcd 309.1, found 309.1.

[0180] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl) methanol (BA26). A solution of (3-Hydroxymethylphenyl)boronic acid (24 mg, 0.13 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA26 (8.4 mg, 42% yield). ESI-MS (M+H)⁺ m/z calcd 283.1, found 284.2.

[0181] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-N-(4,5-dihydrothiazol-2-yl)benzamide (BA30). A solution of [3-((4,5-dihydrothiazol-2-yl)carbamoyl)phenyl]boronic acid (19 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concen-

trated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA30 (17.8 mg, 67% yield).

[0182] Synthesis of 1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (BA31). A solution of 4-Acetylphenylboronic acid (12.7 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA31 (12.9 mg, 62% yield).

[0183] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol (BA32). A solution of (4-Aminocarbonyl-3-chlorophenyl)boronic acid (16 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA32 (9.7 mg, 42% yield). ESI-MS (M+H)⁺ m/z calcd 331.1, found 331.1.

[0184] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylthiophene-2-carbaldehyde (BA34). A solution of 5-Formyl-3-methylthiophene-2-boronic acid (26 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA34 (14.7 mg, 38% yield). ESI-MS (M+H)⁺ m/z calcd 302.1, found 302.0.

[0185] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)furan-3-carbaldehyde (BA35). A solution of 4-Formylfuran-2-boronic acid (20 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA35 (13.5 mg, 39% yield). ESI-MS (M+H)⁺ m/z calcd 272.1, found 272.1.

[0186] Synthesis of N-[3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide (BA38). A solution of 3-Methanesulfonylaminophenylboronic acid (32 mg, 0.15 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (16 mg, 0.014 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic

phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA38 (24.3 mg, 54% yield). ESI-MS (M+H)⁺ m/z calcd 347.1, found 347.0.

[0187] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzonitrile (BA39). A solution of 3-Cyanophenylboronic acid (23 mg, 0.15 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA39 (14.9 mg, 41% yield). ESI-MS (M+H)⁺ m/z calcd 279.1, found 279.0.

[0188] Synthesis of N-[4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide (BA40). A solution of 4-Methanesulfonylaminophenylboronic acid (24 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA40 (0.9 mg, 3% yield). ESI-MS (M+H)⁺ m/z calcd 347.1, found 347.0.

[0189] Synthesis of 3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide (BA41). A solution of Benzenesulfonamide-3-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA41 (9.2 mg, 28% yield). ESI-MS (M+H)⁺ m/z calcd 333.1, found 333.0.

[0190] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[b]thiophene-5-carbaldehyde (BA42). A solution of 5-Formylbenzo[b]thiophene-2-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA42 (15.2 mg, 45% yield). ESI-MS (M+H)⁺ m/z calcd 338.1, found 338.0.

[0191] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-3-carbaldehyde (BA43). A solution of N-Boc-3-formyl-5-indoleboronic acid pinacol ester (40 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimi-

din-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). The TFA from purification hydrolyzed the Boc to yield BA43. ESI-MS (M+H)⁺ m/z calcd 321.1, found 321.0.

[0192] Synthesis of 3-(benzo[c][1,2,5]oxadiazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA44). A solution of Benzo[c][1,2,5]oxadiazole-5-boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA44. ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0193] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile (BA45). A solution of (4-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA45. ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.1.

[0194] Synthesis of 2-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile (BA46). A solution of (3-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA46. ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.1.

[0195] Synthesis of 1-isopropyl-3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA48). A solution of (4-Methoxyphenyl)boronic acid (17 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA48 (4.5 mg, 16% yield). ESI-MS (M+H)⁺ m/z calcd 284.1, found 284.1.

[0196] Synthesis of 1-isopropyl-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA49). A solution of 3-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in

EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA49. ESI-MS (M+H)⁺ m/z calcd 284.1, found 284.0.

[0197] Synthesis of 1-isopropyl-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA52). A solution of 3-Pyridinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (15 mg, 0.015 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA52. ESI-MS (M+H)⁺ m/z calcd 255.1, found 255.0.

[0198] Synthesis of 1-isopropyl-3-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA53). A solution of 5-Pyrimidinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (15 mg, 0.015 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA53. ESI-MS (M+H)⁺ m/z calcd 256.1, found 256.1.

[0199] Synthesis of 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA54). A solution of 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (26 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA54 (6 mg, 15% yield). ESI-MS (M+H)⁺ m/z calcd 312.1, found 312.0.

[0200] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (BA55). A solution of 3-Acetylphenylboronic acid (23 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA55 (7 mg, 18% yield). ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0201] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (BA56). A solution of 4-Hydroxyphenylboronic acid (30 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in

DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA56 (12 mg, 32% yield). ESI-MS (M+H)⁺ m/z calcd 270.1, found 270.1.

[0202] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol (BA59). A solution of 3-fluoro-4-hydroxyphenylboronic acid (103 mg, 0.66 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP using silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA59 (26 mg, 27% yield). ESI-MS (M+H)⁺ m/z calcd 288, found 288.

[0203] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylphenol (BA60). A solution of 4-hydroxy-2-methylphenylboronic acid (110 mg, 0.66 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA60 (42 mg, 22% yield). ESI-MS (M+H)⁺ m/z calcd 284, found 284.

[0204] Synthesis of 3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA62). A solution of 4-fluoro-3-methoxyphenylboronic acid (61 mg, 0.36 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (90 mg, 0.30 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA62 (40 mg, 44% yield). ESI-MS (M+H)⁺ m/z calcd 302, found 302.

[0205] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol (BA62d). A solution of BA62 (3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine, 30 mg, 0.10 mmol) was dissolved in CH₂Cl₂ (5 ml) and stirred under an argon atmosphere. BBr₃ (500 uL, 0.5 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 3 hours then concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA62d (23 mg, 44% yield). ESI-MS (M+H)⁺ m/z calcd 288.1, found 288.1.

[0206] Synthesis of 3-(2,5-difluoro-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA63). A solution of 2,5-difluoro-4-methoxyphenylboronic acid (84

mg, 0.45 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (54 mg, 0.18 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA63 (50 mg, 17% yield). ESI-MS (M+H)⁺ m/z calcd 320.1, found 320.0.

[0207] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2,5-difluorophenol (BA93). 3-(2,5-difluoro-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA63) (20 mg, 0.06 mmol) was dissolved in CH₂Cl₂ (2 ml) and BBr₃ (0.630 mL, 0.63 mmol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for overnight then concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA93 (6.7 mg, 35% yield). ESI-MS (M+H)⁺ m/z calcd 306.1, found 306.0.

[0208] Synthesis of 1-isopropyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA64). A solution of 3,4,5-trimethoxyphenylboronic acid (123 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA64 (70 mg, 89% yield). ESI-MS (M+H)⁺ m/z calcd 344.1, found 344.0.

[0209] Synthesis of 1-isopropyl-3-(2,3-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA65). A solution 2,3-dimethoxyphenylboronic acid (105 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA65 (63 mg, 88% yield). ESI-MS (M+H)⁺ m/z calcd 314.1, found 314.1.

[0210] Synthesis of 1-isopropyl-3-(2,4-dimethoxypyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA66). A solution 2,4-dimethoxypyrimidin-5-yl-5-boronic acid (106 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 2:98] to yield BA66. ESI-MS (M+H)⁺ m/z calcd 316.1, found 316.0.

[0211] Synthesis of 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA79). 3-fluoro-5-methoxybenzoic acid (5 g, 0.029 mol) was stirred in CH₂Cl₂ (50 ml) at 0° C. under an argon atmosphere.

DMF (9 drops, catalytic) was added, followed by oxalyl chloride (12.7 ml, 0.147 mol). Reaction was warmed to room temperature then stirred under argon for one hour. Reaction was concentrated in vacuo to yield 3-fluoro-5-methoxybenzoyl chloride (BA67).

[0212] A solution of malononitrile (2.87 g, 0.044 mol) in dry THF (50 ml) was stirred at 0° C. under an argon atmosphere. NaH in paraffin oil (4.64 g, 0.116 mol) was added piece-wise to solution. 3-fluoro-5-methoxybenzoyl chloride (BA67, 0.029 mol) was dissolved in 50 ml dry THF and added slowly to reaction. Reaction was warmed to room temperature and stirred under argon for 24 hours. 1N HCl (200 ml) was slowly added, then reaction mixture was extracted with EtOAc. Organic phases were combined, dried with magnesium sulfate, then concentrated in vacuo to yield 2-((3-fluoro-5-methoxyphenyl)(methoxy)methylene)malononitrile (BA69).

[0213] 2-((3-fluoro-5-methoxyphenyl)(methoxy)methylene)malononitrile (BA69, 0.029 mol) stirred in EtOH (20 ml) at room temperature under an argon atmosphere. Hydrazine (1.4 ml, 29 mmol) was added and reaction was left stirring for 90 minutes. Reaction mixture was concentrated in vacuo and dried on vacuum pump overnight to yield intermediate 5-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazole-4-carbonitrile (BA73). Formamide (20 ml) was added and reaction was heated to 180° C. under an argon atmosphere overnight. Reaction was cooled and dH₂O was added (40 ml) forcing a white precipitate out of solution. Precipitate was collected and washed with dH₂O. Solid was dried and purified by silica gel column chromatography [MeOH—CH₂Cl₂, 10:90] to yield 3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA75).

[0214] 3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA75, 100 mg, 0.386 mmol) was dissolved in DMF (10 ml). K₂CO₃ (250 mg, 1.54 mmol) was added and reaction was stirred at room temperature under an argon atmosphere. Iodocyclopentane (0.134 ml, 1.16 mmol) was added with a syringe and reaction was stirred for 2 hours. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA79.

[0215] Synthesis of 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA79d). 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA79, 0.386 mmol) was dissolved in CH₂Cl₂ (2 ml). BBr₃ (4 mL, 4 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 2 hours then concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA79 (69 mg, 57% yield).

[0216] Synthesis of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA80). A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (400 mg, 1.53 mmol) and K₂CO₃ (1 g, 6 mmol) in DMF (5 ml) was stirred at room temperature under an argon atmosphere. Iodocyclopentane (1.0 g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column

chromatography [MeOH—CH₂Cl₂, 5:95] yielding BA80 (300 mg, 60% yield). ESI-MS (M+H)⁺ m/z calcd 330.0, found 330.0.

[0217] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (BA81, BA81d & BA81dd). A solution of tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (200 mg, 0.76 mmol) in EtOH (3.3 ml) was added to a solution of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA80, 100 mg, 0.30 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH₂Cl₂, 5:95] yielding BA81. BA81 was dissolved in 50:50 CH₂Cl₂:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA81d. BA81d was dissolved in CH₂Cl₂ (2 ml) and BBr₃ (4 mL, 4 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 2 hours then concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA81dd.

[0218] Synthesis of 3-(3-bromo-5-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA85). A solution of 2-(3-bromo-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (137 mg, 0.43 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (65 mg, 0.216 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA85 (28 mg, 36% yield). ESI-MS (M+H)⁺ m/z calcd 362.1, found 362.0.

[0219] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-bromophenol (BA87). 3-(3-bromo-5-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA85, 0.1 mmol) was dissolved in CH₂Cl₂ (1 ml) and BBr₃ (1 mL, 1 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 35 minutes then concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA87 (10.7 mg, 31% yield). ESI-MS (M+H)⁺ m/z calcd 348.0, found 348.0.

[0220] Synthesis of tert-butyl 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA86). A solution of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (212 mg, 0.61 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (75 mg, 0.25 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA86 (9.3 mg, 9% yield). ESI-MS (M+H)⁺ m/z calcd 362.1, found 362.0.

[0221] Synthesis of 3-(1H-indol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA89). Tert-butyl 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA86, 9 mg, 0.022 mmol) was dissolved in 50:50 CH₂Cl₂:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA89 (4.8 mg, 75% yield). ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.0.

[0222] Synthesis of tert-butyl 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA88). A solution of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (130 mg, 0.38 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.15 mmol) in DME (12 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (1.9 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA88. ESI-MS (M+H)⁺ m/z calcd 419.2, found 419.1.

[0223] Synthesis of 3-(1H-indol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA94). Tert-butyl 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA88) was dissolved in 50:50 CH₂Cl₂:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA89 (6.3 mg). ESI-MS (M+H)⁺ m/z calcd 319.1, found 319.2.

[0224] Synthesis of 1-cyclopentyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA90). A solution of 3,4-dimethoxyphenylboronic acid (41 mg, 0.23 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.09 mmol) in DME (6 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O) to yield BA90 (8.4 mg, 28% yield). ESI-MS (M+H)⁺ m/z calcd 340.2, found 340.1.

[0225] Synthesis of 3-(1H-indol-4-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA91). A solution of 1H-indol-4-yl-4-boronic acid (40 mg, 0.25 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA91 (14.6 mg, 50% yield). ESI-MS (M+H)⁺ m/z calcd 293.1, found 293.1.

[0226] Synthesis of 1-cyclopentyl-3-(1H-indol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA92). A solution of 1H-indol-4-yl-4-boronic acid (30 mg, 0.19 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (25 mg, 0.076 mmol) in DME (6 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was

heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA92 (23 mg, 95% yield). ESI-MS (M+H)⁺ m/z calcd 319.2, found 319.1.

[0227] Synthesis of 3-(2,3-dihydrobenzofuran-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA95). A solution of 2,3-dihydro-1-benzofuran-5-ylboronic acid (38 mg, 0.23 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA95 (15.7 mg, 59% yield). ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0228] Synthesis of 3-(benzofuran-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA96). A solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzofuran (56 mg, 0.23 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh₃)₄ (30 mg, 0.03 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 80° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA96 (19 mg, 72% yield). ESI-MS (M+H)⁺ m/z calcd 296.1, found 296.1.

[0229] Synthesis of 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-ethoxyphenol (BA98). 1-cyclopentyl-3-(4-ethoxy-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK359, 25 mg, 0.071 mmol) was dissolved in CH₂Cl₂ (5 ml) and stirred at -10° C. under an argon atmosphere. After 30 minutes, reaction was brought to 0° C. and stirred for 2.5 hours. Reaction was stirred for additional 4 hours at room temperature, then concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA98 (3 mg, 13% yield). ESI-MS (M+H)⁺ m/z calcd 340.1, found 340.1.

[0230] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylamino)propan-1-ol (BA99). 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA20d) (30 mg, 0.10 mmol) was dissolved in DMF (0.400 ml). K₂CO₃ (55 mg, 0.4 mmol) was added and reaction was stirred at 70° C. 3-bromo-1-propanol (0.050 ml, 0.6 mmol) was added and reaction was stirred overnight. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA99 (8.4 mg, 24% yield). ESI-MS (M+H)⁺ m/z calcd 357.2, found 357.1.

[0231] Synthesis of 3-iodo-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA109). A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 7.69 mmol) and K₂CO₃ (4.25 g, 30.8 mmol) in DMF (5 ml) was stirred at room temperature under an argon atmosphere. Iodomethane (1.17 ml, 7.69 mmol) was added with a syringe. Reaction was

stirred under an argon atmosphere at room temperature for 2 hours. Solid K₂CO₃ was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH₂Cl₂, 5:95] yielding BA109 (212 mg, 10% yield). ESI-MS (M+H)⁺ m/z calcd 275.9, found 275.9.

[0232] General synthetic scheme for BA102, BA105-108, BA110, BA118, BA128-BA135, BA137, BA139-140, BA143, BA147, BA149-BA152, BA156, BA158, BA160-BA162. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA12, 1 equivalent) in DME (6 ml). Pd(PPh₃)₄ (15 mg, 0.15 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 90° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0233] General synthetic scheme for BA112, BA115, BA121, BA122, BA124, BA136, BA138, BA141, and BA144. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA80, 1 equivalent) in DME (6 ml). Pd(PPh₃)₄ (15 mg, 0.15 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 90° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0234] General synthetic scheme for BA111, BA114, BA116, BA117, BA119, and BA120. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA109, 1 equivalent) in DME (6 ml). Pd(PPh₃)₄ (15 mg, 0.15 mmol) and saturated Na₂CO₃ (0.95 ml) were added and the reaction was heated to 90° C. under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0235] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)quinolin-2-amine (BA146). 3-(2-chloroquinolin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA130, 50 mg, 0.15 mmol), acetamide (174 mg, 3.0 mmol) and K₂CO₃ (104 mg, 0.75 mmol) were combined and heated to 200° C. under an argon atmosphere for one hour. Reaction was cooled, then extracted with H₂O and CH₂Cl₂. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA146 (22 mg, 46% yield). ESI-MS (M+H)⁺ m/z calcd 320.2, found 320.4.

[0236] Synthesis of 3-(3-amino-1H-indazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA154). 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA150, 20 mg, 0.07 mmol) was dissolved in n-BuOH (2 ml). Hydrazine monohydrate (0.400 ml) was added and the reaction was heated to 110° C. under an argon atmosphere and left stirring over night. Reaction mixture was concentrated in vacuo and purified by RP-

HPLC (MeCN:H₂O:0.1% TFA) to yield BA154 (15 mg, 70% yield). ESI-MS (M+H)⁺ m/z calcd 309.2, found 309.4.

[0237] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-hydroxybenzonitrile (BA155_2). 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA150, 25 mg, 0.1 mmol) was dissolved in DMF (1 mL). t-BuOK (24 mg, 0.21 mmol) was added and the reaction was stirred at room temperature overnight. Reaction was then heated to 150° C. for 24 hours. The reaction was then concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA155_2 (21 mg, 89% yield). ESI-MS (M+H)⁺ m/z calcd 295.1, found 295.4.

[0238] Synthesis of 3-(3-aminobenzo[d]isoxazol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA157_2) & 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-hydroxybenzonitrile (BA157_3). 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA151, 20 mg, 0.07 mmol) was dissolved in DMF (1 mL). t-BuOK (24 mg, 0.21 mmol) was added and the reaction was stirred at room temperature overnight. Reaction was then heated to 150° C. for 24 hours. The reaction was then concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA157_2 (7 mg), ESI-MS (M+H)⁺ m/z calcd 295.1, found 295.4 and BA157_3 (8 mg), ESI-MS (M+H)⁺ m/z calcd 310.1, found 310.4.

[0239] Synthesis of 3-(3-amino-1H-indazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA159). 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2,6-difluorobenzaldehyde (BA149, 20 mg, 0.063 mmol) was dissolved in n-BuOH (1 mL). Hydrazine monohydrate (0.400 mL) was added and the reaction was heated to 100° C. under an argon atmosphere and left stirring for 2.5 hours. Reaction mixture was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield BA159 (15 mg, 77% yield). ESI-MS (M+H)⁺ m/z calcd 312.1, found 312.4.

[0240] Synthesis of 4-chloro-7-methyl-5-(naphthalen-2-yl)-7H-pyrrolo[2,3-d]pyrimidine (ZK102). A solution of 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (19 mg, 0.065 mmol), naphthalen-2-yl-2-boronic acid (12.2 mg, 0.071 mmol), Na₂CO₃ (68.9 mg, 0.65 mmol) and PdCl₂(dppf) (26.5 mg, 0.00325 mmol) in THE (3 mL) was heated to reflux overnight under an argon atmosphere. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield ZK102 (5 mg, 26% yield). ESI-MS (M+H)⁺ m/z calcd 294.1, found 294.3.

[0241] Synthesis of 4-chloro-7-methyl-5-(3-biphenyl)-7H-pyrrolo[2,3-d]pyrimidine (ZK103). A solution of 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (10 mg, 0.034 mmol), 3-biphenyl-boronic acid (7.4 mg, 0.038 mmol), Na₂CO₃ (36.1 mg, 0.34 mmol) and PdCl₂(dppf) (1.4 mg, 0.0017 mmol) in THE (10 mL) was heated to reflux overnight under an argon atmosphere. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA) to yield ZK103 (3 mg, 28% yield). ESI-MS (M+H)⁺ m/z calcd 320.1, found 320.0.

[0242] Synthesis of 3-(4-tert-butylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK125). 1-tert-butyl-3-(4-tert-butylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux for 2 hours. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:

H₂O:0.1% TFA) to yield ZK125 (quant.). ESI-MS (M+H)⁺ m/z calcd 268.2, found 268.4.

[0243] Synthesis of 3-(3-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK126). 1-tert-butyl-3-(3-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.16 mmol) was dissolved in a solution of formic acid (5 mL) and conc. HCl (0.1 mL) and heated to reflux for 2.5 hours. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 304.1, found 304.3.

[0244] Synthesis of 3-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK127). 1-tert-butyl-3-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (23 mg, 0.1 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.3 mL) and heated to reflux for 2.5 hours. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 226.1, found 226.3.

[0245] Synthesis of 3-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK128). 1-tert-butyl-3-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (23 mg, 0.055 mmol) was dissolved in a solution of formic acid (5 mL) and conc. HCl (0.1 mL) and heated to reflux for 2 hours. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 257.1, found 257.3.

[0246] Synthesis of 3-(benzo[d][1,3]dioxol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK129). 1-tert-butyl-3-(benzo[d][1,3]dioxol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (21 mg, 0.082 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.2 mL) and heated to reflux for 2 hours. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 256.1, found 256.3.

[0247] Synthesis of 3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK130). 1-tert-butyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (21 mg, 0.082 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 257.1, found 257.3.

[0248] Synthesis of 3-(3-(2,6-dichlorobenzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK131). 1-tert-butyl-3-(3-(2,6-dichlorobenzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19.5 mg, 0.05 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 386.1, found 386.2.

[0249] Synthesis of 3-(2,3-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK132). 1-tert-butyl-3-(2,3-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (34 mg, 0.14 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 240.1, found 240.4.

[0250] Synthesis of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (ZK133). 1-tert-butyl-2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (5 mg, 0.014 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was

concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 228.1, found 228.3.

[0251] Synthesis of 3-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK134). 1-tert-butyl-3-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 226.1, found 226.3.

[0252] Synthesis of 3-(3-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK135). 1-tert-butyl-3-(3-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 227.1, found 227.3.

[0253] Synthesis of 3-(3-(benzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK136). 1-tert-butyl-3-(3-(benzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19 mg, 0.052 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux for 30 min. Reaction yielded a mixture of ZK136 and 3-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (ZK138). Reaction was concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ZK136: ESI-MS (M+H)⁺ m/z calcd 318.1, found 318.3. ZK138: ESI-MS (M+H)⁺ m/z calcd 228.1, found 228.3.

[0254] Synthesis of 3-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK137). 1-tert-butyl-3-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (9 mg, 0.032 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.2 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 227.1, found 227.3.

[0255] Synthesis of 3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK139). 1-tert-butyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (9 mg, 0.029 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 266.1, found 266.4.

[0256] Synthesis of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (ZK140). 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (90 mg, 0.31 mmol) was taken up in 7N NH₃/MeOH and heated in a sealed tube at 110° C. overnight. Reaction was concentrated in vacuo to give a brown/off-white solid.

[0257] Synthesis of 3-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK141). 1-tert-butyl-3-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 226.1, found 226.3.

[0258] Synthesis of 3-(4-biphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK142). 1-tert-butyl-3-(4-biphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (22 mg, 0.066 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed

to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 288.1, found 288.3.

[0259] Synthesis of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK143). 1-tert-butyl-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19 mg, 54.1 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 304.1, found 304.3.

[0260] Synthesis of 1-benzyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK147). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (110 mg, 0.42 mmol) was dissolved in DMF (2 mL) and K₂CO₃ (220 mg, 1.6 mmol) and benzyl bromide (71.8 mg, 0.42 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration and then purified further by silica gel chromatography (5% MeOH/CH₂Cl₂) to yield a white solid.

[0261] Synthesis of 5-(4-(benzyloxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (ZK150). A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), 4-(benzyloxy)phenylboronic acid (21 mg, 0.091 mmol), K₃PO₄ (19.3 mg, 0.091 mmol) and Pd(PPh₃)₄ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C. under an argon atmosphere. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 331.1, found 331.3.

[0262] Synthesis of 5-(3-biphenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (ZK151). A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), 3-biphenylboronic acid (18 mg, 0.091 mmol), K₃PO₄ (19.3 mg, 0.091 mmol) and Pd(PPh₃)₄ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C. under an argon atmosphere. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 301.1, found 301.3.

[0263] Synthesis of 5-(benzo[b]thiophen-2-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (ZK152). A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), benzo[b]thiophen-2-yl-2-boronic acid (16 mg, 0.091 mmol), K₃PO₄ (19.3 mg, 0.091 mmol) and Pd(PPh₃)₄ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C. under an argon atmosphere. Reaction was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). ESI-MS (M+H)⁺ m/z calcd 281.1, found 281.3.

[0264] Synthesis of 3-(naphthalen-2-yl)-1-phenethyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK155). 2-(methoxy(naphthalen-6-yl)methylene)malononitrile (100 mg, 0.43 mmol) and phenethylhydrazine hydrogen chloride (58.5 mg, 0.43 mmol) were dissolved in EtOH (3 mL) and TEA (60 µL, 0.43 mmol) and heat to reflux for one hour. The product was extracted with diethylether and concentrated in vacuo. This concentrate was then dissolved in formamide (10 mL) and heated to 160-180° C. overnight. The following day the reaction was cooled, poured into water, and the precipitated product collected by filtration. ESI-MS (M+H)⁺ m/z calcd 366.2, found 366.2.

[0265] Synthesis of 1-isopropyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK156). 2-(methoxy

(naphthalen-6-yl)methylene)malononitrile (100 mg, 0.43 mmol) and isopropylhydrazine hydrogen chloride (47.3 mg, 0.43 mmol) were dissolved in EtOH (3 mL) and TEA (1 eq.) and heat to reflux for one hour. The product was extracted with diethylether and concentrated in vacuo. This concentrate was then dissolved in formamide (10 mL) and heated to 160-180° C. overnight. The following day the reaction was cooled, poured into water, and the precipitated product collected by filtration. ESI-MS (M+H)⁺ m/z calcd 304.2, found 304.2.

[0266] Synthesis of 1-ethyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK157). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.42 mmol) was dissolved in DMF (3 mL) and K₂CO₃ (220 mg, 1.6 mmol) and ethyl iodide (37 μ L, 0.46 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 290.1, found 290.2.

[0267] Synthesis of 1-cyclopentyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK158). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.42 mmol) was dissolved in DMF (3 mL) and K₂CO₃ (220 mg, 1.6 mmol) and cyclopentyl bromide (49.5 μ L, 0.46 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 330.2, found 330.2.

[0268] Synthesis of 1-allyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK159). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and allyl iodide (23 μ L, 0.25 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 302.1, found 302.2.

[0269] Synthesis of 2-(4-amino-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetamide (ZK162). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and iodoacetamide (46 mg, 0.25 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 319.1, found 319.2.

[0270] Synthesis of 1-(cyclopropylmethyl)-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK165). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and cyclopropyl methyl bromide (22 μ L, 0.25 mmol) were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 316.2, found 316.2.

[0271] Synthesis of 1-isopentyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK161). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and isobutyl bromide were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 332.2, found 332.3.

[0272] Synthesis of 3-(naphthalen-2-yl)-1-((E)-3-phenylprop-1-enyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK167). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and 1-((E)-3-bromoprop-1-enyl)benzene were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 378.2, found 378.2.

[0273] Synthesis of 3-(naphthalen-2-yl)-1-(prop-2-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK168). 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K₂CO₃ (110 mg, 0.8 mmol) and propargylbromide were added. The reaction was heated to 60° C. overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS (M+H)⁺ m/z calcd 300.1, found 300.2.

[0274] Synthesis of 3-ethoxy-4-methoxybenzoyl chloride (ZK299). 3-ethoxy-4-methoxybenzoic acid (5 g, 25.5 mmol) was added to a solution of CH₂CO₂ (40 mL) and benzene (20 mL) in a flame-dried 150 mL round bottom flask. Anhydrous DMF (9 drops) was added and the solution was cooled on ice. Oxalyl chloride (11 mL, 128 mmol) was added dropwise, and the reaction was then allowed to warm to RT. The reaction was stirred at RT for 90 minutes, then concentrated in vacuo yield an off-white solid. The solid was placed on a high-vacuum line for 2 hours, and then taken onto the next step without further characterization.

[0275] Synthesis of 2-((3-ethoxy-4-methoxyphenyl)(hydroxy)methylene)malononitrile (ZK301). NaH (2.2 g, 56 mmol, 60% dispersion in paraffin oil) was added to a solution of malononitrile (1.85 g, 28 mmol) in THE (30 mL) on ice. 3-ethoxy-4-methoxybenzoyl chloride (25.5 mmol) was dissolved in THE (50 mL) and added the first solution dropwise by syringe at 0° C. The ice was then removed and the reaction was allowed to proceed at RT for 60 min. 1N HCl (100 mL) was added and the solution was extracted three times with EtOAc. The organic phase was dried with MgSO₄, filtered, and concentrated in vacuo to give an orange solid that was taken onto the next step without further characterization.

[0276] Synthesis of 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile (ZK302). 2-((3-ethoxy-4-methoxyphenyl)(hydroxy)methylene)malononitrile (25.5 mmol) and sodium bicarbonate (17 g, 204 mmol) were combined in a solution of 1,4-dioxane (48 mL) and water (8 mL). Dimethylsulphate (17 mL, 178 mmol) was slowly added and the reaction was heated to 80-90° C. for 2 hours. The reaction was cooled to RT, water was added, and the aqueous phase extracted three times with EtOAc (200 mL). The organic phases were combined, dried with MgSO₄, and filtered to give a red oil. The oil was purified by silica gel chromatography (10% EtOAc/Hexanes, R_f~0.1) to give a white solid (3.59 g, 54.5% yield over three steps). ESI-MS (M+H)⁺ m/z calcd 259.1, found 259.0.

[0277] Synthesis of 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazole-4-carbonitrile (ZK303). 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile (200 mg, 0.78 mmol), isopropylhydrazine hydrogen chloride (86 mg, 0.78 mmol), and triethylamine (0.10 mL, 0.78 mmol) were combined in ethanol (5 mL) and heated to reflux for 90 minutes. The reaction was then cooled to RT, water was added and the aqueous phase was extracted

three times with EtOAc. The organic phase was concentrated and carried onto the next step without further characterization. ESI-MS (M+H)⁺ m/z calcd 301.1, found 301.0 [0278] Synthesis of 3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK305). 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazole-4-carbonitrile was dissolved in formamide (20 mL) and heated to 180° C. overnight. The next day the reaction was cooled to RT, water was added, and the precipitate was collected by filtration. The precipitate was then dissolved in CH₂Cl₂/MeOH and passed through a silica plug. The product was then lyophilized from benzene to yield an off-white solid (48 mg, 19% over two steps). ESI-MS (M+H)⁺ m/z calcd 328.2, found 328.0.

[0279] Synthesis of 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile (ZK304). 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile (200 mg, 0.78 mmol), 2-hydroxyethylhydrazine (0.056 mL, 0.78 mmol), and triethylamine (0.10 mL, 0.78 mmol) were combined in ethanol (5 mL) and heated to reflux for 90 minutes. The reaction was then cooled to RT, water was added and the aqueous phase was extracted three times with EtOAc, CH₂Cl₂, and CHCl₃. The organic phase was concentrated and carried onto the next step without further characterization. ESI-MS (M+H)⁺ m/z calcd 303.1, found 303.0.

[0280] 2-(4-amino-3-(3-ethoxy-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethanol (ZK306). 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile was dissolved in formamide (20 mL) and heated to 180° C. overnight. The next day the reaction was cooled to RT, water was added, and the precipitate was collected by filtration. The precipitate was then dissolved in CH₂Cl₂/MeOH and passed through a silica plug. The product was then lyophilized from benzene to yield a brown solid (6.4 mg, 2.5% over two steps). ESI-MS (M+H)⁺ m/z calcd 330.1, found 330.0.

[0281] B. Structural Studies

[0282] Crystal structures of p110γ have been reported, alone and in complex with ATP or pan-specific inhibitors such as LY294002 and wortmannin (Walker et al., 2000; Walker et al., 1999). To explore how potent and selective inhibitors bind, the crystal structures of PI3-K inhibitors from three chemotypes bound to human p110γ were determined at 2.5-2.6 Å resolution: the quinazoline purine PIK-39, the imidazopyridine PIK-90 and the phenylthiazole PIK-93 (FIG. 2).

[0283] Based on these co-crystal structures and a conserved arylmorpholine pharmacophore model, structural models were generated for three additional chemotypes bound to p110γ: the pyridinylfuranopyrimidine PI-103, the morpholinochromone PIK-108, and the morpholinopyranone KU-55933 (FIG. 2). Model-building for these inhibitors was guided by the observation that each compound contains the key arylmorpholine pharmacophore found in LY294002.

[0284] PIK-39 is an isoquinoline purine that inhibits p110δ at mid-nanomolar concentrations, p110γ and p110β at concentrations ~100-fold higher, and shows no activity against any other PI3-K family member, including p110α, at concentrations up to 100 μM (FIG. 5). The biochemical selectivity of this compound is achieved through an unusual binding mode revealed in its co-crystal structure with p110γ (FIG. 2C). Only the mercaptopurine moiety of PIK-39

makes contacts within the interior of the ATP binding pocket, and this ring system is rotated ~1100 and twisted ~35° out of the plane relative to the adenine of the ATP. In this orientation, it satisfies hydrogen bonds to the backbone amides of Val 882 and Glu 880 (thereby recapitulating the hydrogen bonds made by N1 and N6 of adenine).

[0285] In contrast to other PI3-K inhibitor structures, PIK-39 does not access the deeper pocket in the active site interior (FIG. 2C, lightly shaded area labeled as “Affinity Pocket”). Instead, the aryl-isoquinoline moiety of PIK-39 extends out to the entrance of the ATP binding pocket (FIG. 2B). In this region, the kinase accommodates the inhibitor by undergoing a conformational rearrangement in which Met 804 shifts from an “up” position, in which it forms the ceiling of the ATP binding pocket, to a “down” position which it packs against the isoquinoline moiety. The effect of this movement, which is unique to the PIK-39 structure (FIG. 2B), is to create a novel hydrophobic pocket between Met 804 and Trp 812 at the entrance to the ATP binding site. This induced-fit pocket buries ~180 Å² of solvent accessible inhibitor surface area, enabling PTK-39 to achieve nanomolar affinity despite limited contacts within the active site core.

[0286] Co-crystal structures of PIK-90 and PIK-93 compounds bound to p110γ were determined. PIK-90 and PTK-93 both make a hydrogen bond to the backbone amide nitrogen of Val 882 (FIG. 2D), an interaction conserved among all known PI3-K inhibitors (Walker et al., 2000). In addition to this hydrogen bond, PTK-93 makes a second hydrogen bond to the backbone carbonyl of Val 882 and a third between its sulphonamide moiety and the side chain of Asp 964. PTK-93 is one of the most polar inhibitors in our panel (clogP=1.69) and these extended polar interactions may compensate for its limited hydrophobic surface area.

[0287] PIK-90 binds in a mode similar to PIK-93, although this larger compound makes more extensive hydrophobic interactions, burying 327 Å² of solvent accessible surface area. To achieve this, PIK-90 projects its pyridine ring into a deeper cavity that is partially accessed by PIK-93 but not occupied by ATP (FIG. 2D, lightly shaded circle). In this region, the pyridine ring of PIK-90 is poised to make a hydrogen bond to Lys 833, and we find that replacement of this pyridine nitrogen with carbon results in a 100-fold loss in affinity (PIK-95, FIG. 4). PI-103, a third multi-targeted PI3K inhibitor, projects a phenol into the same pocket based on an arylmorpholine pharmacophore model (FIG. 2D).

[0288] Two structural features distinguish these potent, multi-targeted inhibitors from the more selective compounds in our panel. First, these compounds adopt a flat conformation in the ATP binding pocket, whereas highly selective inhibitors project out of the plane occupied by ATP (FIG. 2). Second, the most potent inhibitors project into a deeper binding pocket that is not accessed by ATP (FIG. 2A). Much of the surface of this affinity pocket is contributed by the side-chain of Ile 879.

[0289] The mercaptopurine in the PTK-39 structure was replaced with adenine to yield a model of IC87114 (FIG. 3A). This substitution provided the adenine of IC87114 in the correct orientation to make the same hydrogen bonds as the mercaptopurine of PIK-39, even though these two ring systems are rotated by 1100 with respect to each other.

[0290] Unlike other inhibitor chemotypes, PIK-39 does not exploit the PI3-kinase affinity pocket (FIG. 2C). The pyrazolopyrimidine analog of IC87114 (PIK-293) as well as

a novel analog containing an *m*-phenol (PTK-294, FIG. 3A) were then tested for inhibition of the class I PI3-Ks. PTK-294 was up to 60-fold more potent than PIK-293 (FIG. 3A).

[0291] The structure of PIK-39 bound to p110 γ reveals a conformational rearrangement of Met 804 that creates an induced pocket, and we have hypothesized that this conformational rearrangement underlies the selectivity of PIK-39 for p110 δ . A prediction of this model is that mutation of Met 804 should perturb the binding of p110 δ -selective inhibitors (which access the induced pocket), but not affect other classes of inhibitors (which do not access this pocket). Modeling suggests that mutation of Met 804 to a β -branched amino acid (such as valine or isoleucine) should restrict the pocket formed by rearrangement of that residue (FIG. 3B, right). Therefore, we mutated the corresponding residue in p110 δ (Met 752) to valine or isoleucine, expressed and purified these kinases, and tested them for sensitivity to PI3-K inhibitors (FIG. 3B). We find that M752I and M752V p110 δ are resistant to the p110 δ -selective inhibitors PIK-39 and IC87114, but retain sensitivity to the p110 α /multi-targeted inhibitors PIK-90, PIK-93, and PI-103. This chemotype-specific resistance supports the unique role of Met 752 in gating an inducible selectivity pocket.

[0292] Antagonist modeling was performed using the PyMOL Molecular Graphics System. All p110 γ crystal structures (PDB codes in parentheses), including the Apo (1E8Y), ATP (1E8X), Wortmannin (1E7U), LY294002 (1E7V), Quercetin (1E8W), Myricetin (1E90), and Staurosporine (1E8Z), PIK-90, PTK-93, and PTK-39 bound forms were structurally aligned using PyMOL's align function. Models for the inhibitors PIK-108, KU-55933, and PI-103 were built on top of the LY294002 arylmorpholine scaffold (1E7V) using PyMOL's fragment building function. A model for the inhibitor IC87114 was similarly built on top of the PIK-39 aryl-isoquinoline scaffold.

[0293] The model for PI-103 was built into the protein structure of p110 γ bound to PIK-90, because the PIK-90 structure contains the enlarged affinity pocket that is necessary to accommodate PIK-103's phenolic moiety (the PIK-90 p110 γ structure otherwise does not exhibit any conformational differences in the arylmorpholine-binding region in comparison to the LY294002-bound p110 γ structure). The models for PIK-108, KU-55933, and IC87114 were built into the protein structure of p110 γ bound to PIK-39 because these inhibitors possess bulky groups that project out of the adenine plane and are likely to exploit the unique "Met 804 down" induced-fit pocket. In all inhibitor models, the choice of protein structure and inhibitor binding mode is based on extensive biochemical SAR as well as inhibitor geometry. The protein structures and inhibitor models have not been minimized to optimize binding energy, but care was taken to prevent any gross steric clashes and to satisfy key hydrogen bonds.

[0294] C. p110 α /p85 α , p110 β /p85 α , p110 δ /p85 α , and p110 γ Assay

[0295] The class I PI3-Ks were either purchased (p110 α /p85 α , p110 μ /p85 α , p110 δ /p85 α from Upstate, and p110 γ from Sigma) or expressed as previously described (Knight et al., 2004). IC₅₀ values were measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions were performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM MgCl₂), and freshly

sonicated phosphatidylinositol (100 μ g/ml). Reactions were initiated by the addition of ATP containing 10 μ Ci of γ -³²P-ATP to a final concentration 10 or 100 μ M, as indicated in FIG. 5, and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions were then terminated by the addition of 105 μ l 1N HCl followed by 160 μ l CHCl₃:MeOH (1:1). The biphasic mixture was vortexed, briefly centrifuged, and the organic phase transferred to a new tube using a gel loading pipette tip precoated with CHCl₃. This extract was spotted on TLC plates and developed for 3-4 hours in a 65:35 solution of *n*-propanol:1M acetic acid. The TLC plates were then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity was measured at 10-12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μ M). For compounds showing significant activity, IC₅₀ determinations were repeated two to four times, and the reported value is the average of these independent measurements.

[0296] Results are set forth below in Table 2.

[0297] D. Abl Assay

[0298] Inhibitors (final concentration: 10 μ M) were assayed in triplicate against recombinant full-length Abl or Abl (T315I) (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 200 μ M ATP (2.5 μ Ci of γ -³²P-ATP), and 0.5 mg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK (SEQ ID NO:1) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0299] Results are set forth below in Table 3.

[0300] E. Hck Assay

[0301] Hck: Inhibitors (final concentration: 10 μ M) were assayed in triplicate against recombinant full-length Hck in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 200 μ M ATP (2.5 μ Ci of γ -³²P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK (SEQ ID NO:2) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0302] Results are set forth below in Table 3.

[0303] F. Insulin Receptor (IR) Assay

[0304] Inhibitors (final concentration: 10 μ M) were assayed in triplicate against recombinant insulin receptor kinase domain (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 10 mM MnCl₂, 200 μ M ATP (2.5 μ Ci of γ -³²P-ATP), and 0.5 mg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0305] Results are set forth below in Table 4.

[0306] G. Src Assay

[0307] Src, Src (T338I): Inhibitors (final concentration: 10 μ M) were assayed in triplicate against recombinant full-length Src or Src (T338I) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 200 μ M ATP (2.5 μ Ci of

γ -32P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK (SEQ ID NO:2) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0308] Results are set forth below in Table 3.

[0309] H. DNA-PK (DNAK) Assay

[0310] DNA-PK was purchased from Promega and assayed using the DNA-PK Assay System (Promega) according to the manufacturer's instructions.

[0311] Results are shown in Table 2.

[0312] I. mTOR Assay

[0313] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant mTOR (Invitrogen) in an assay containing 50 mM HEPES, pH 7.5, 1 mM EGTA, 10 mM MgCl₂, 2.5 mM, 0.01% Tween, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Rat recombinant PHAS-1/4EBP1 (Calbiochem; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0314] Results are set forth in Table 4 below.

[0315] J. Vascular Endothelial Growth Receptor

[0316] Vascular endothelial growth receptor 2(KDR): Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant KDR receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0317] Results are set forth in Table 3 below.

[0318] K Ephrin Receptor B4 (EphB4) Assay

[0319] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant Ephrin receptor B4 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0320] Results are set forth in Table 3 below.

[0321] L. Epidermal Growth Factor Receptor (EGFR) Assay

[0322] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant EGF receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M

NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0323] Results are set forth in Table 3 below.

[0324] M. KIT Assay

[0325] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant KIT kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 1 mM DTT, 10 mM MnCl₂, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0326] Results are set forth in Table 4 below.

[0327] N. RET Assay

[0328] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant RET kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5 mM DTT, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK (SEQ ID NO:1) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0329] Results are set forth in Table 4 below.

[0330] O. Platelet Derived Growth Factor Receptor (PDGFR) Assay

[0331] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant PDG receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5 mM DTT, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK (SEQ ID NO:1) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0332] Results are set forth in Table 4 below.

[0333] P. FMS-Related Tyrosine Kinase 3 (FLT-3) Assay

[0334] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant FLT-3 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5 mM DTT, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK (SEQ ID NO:1) was used as phosphoacceptor (200 μ M). Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0335] Results are set forth in Table 4 below.

[0336] Q. TEK Receptor Tyrosine Kinase (TIE2) Assay

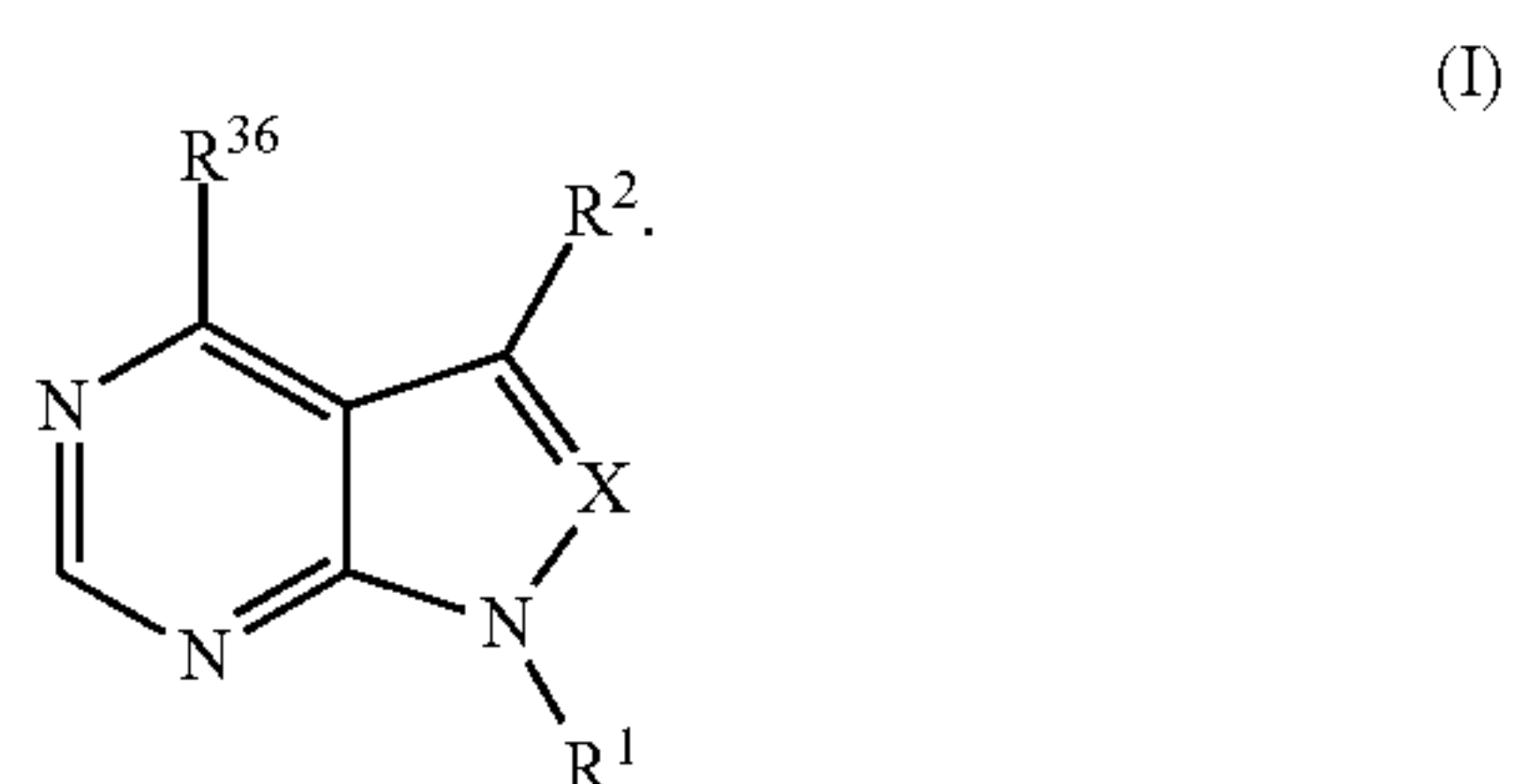
[0337] Inhibitors (final concentrations 50 μ M-0.003 μ M) were tested against recombinant TIE2 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2 mM DTT, 10 mM MnCl₂, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M

NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

Results are set forth in Table 4 below.

[0338] R. Results

[0339] In Table 1, the compounds have the formula:



R^1 and R^2 are as defined in Table 1. X is $=N-$ except where indicated. R^{36} is $-NH_2$ except where indicated.

TABLE 1

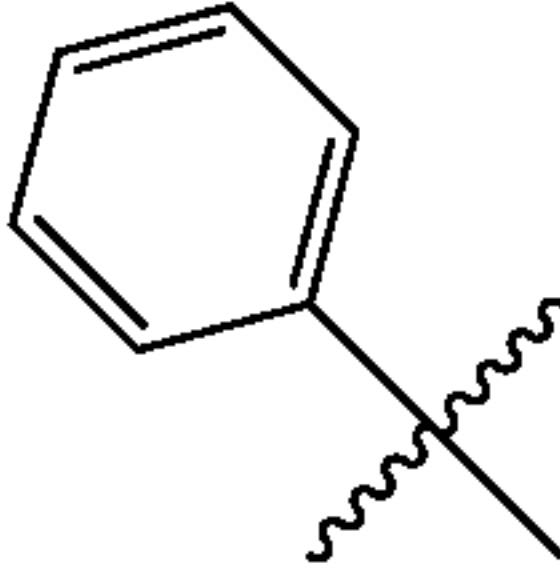
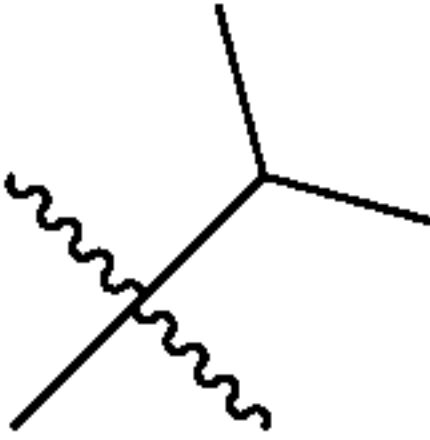
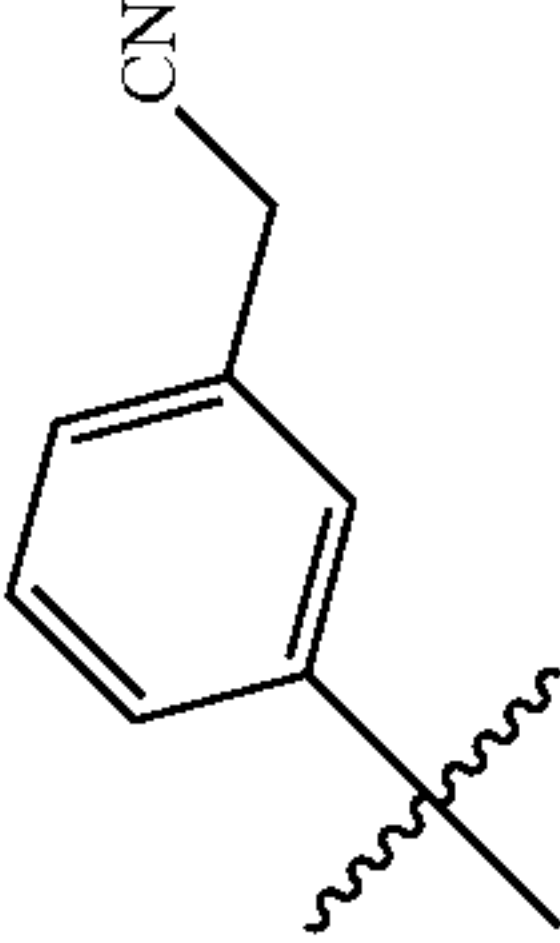
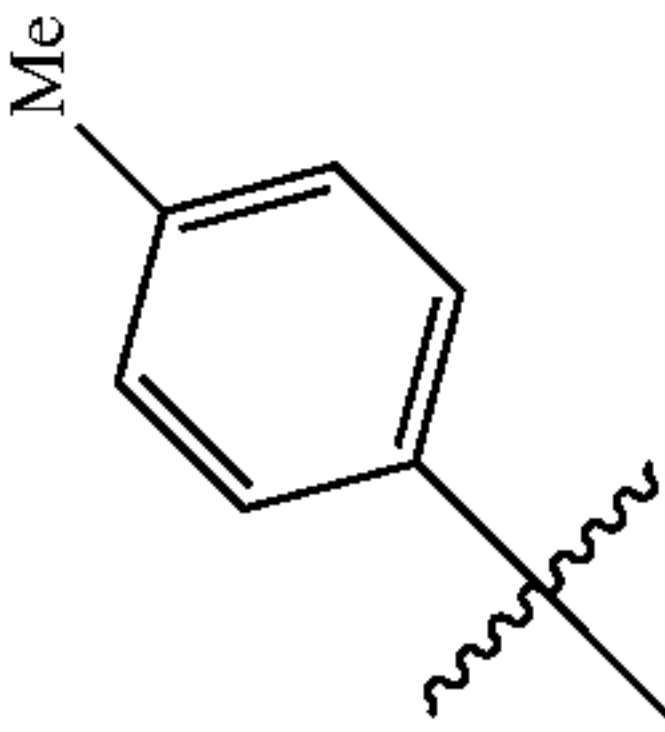
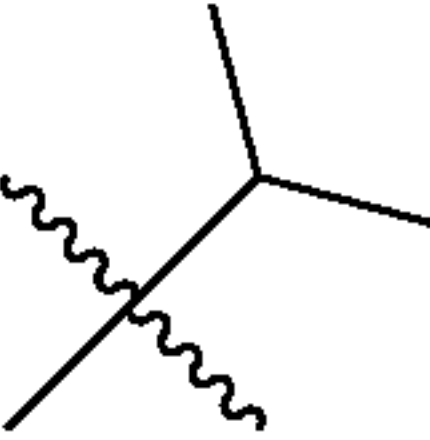
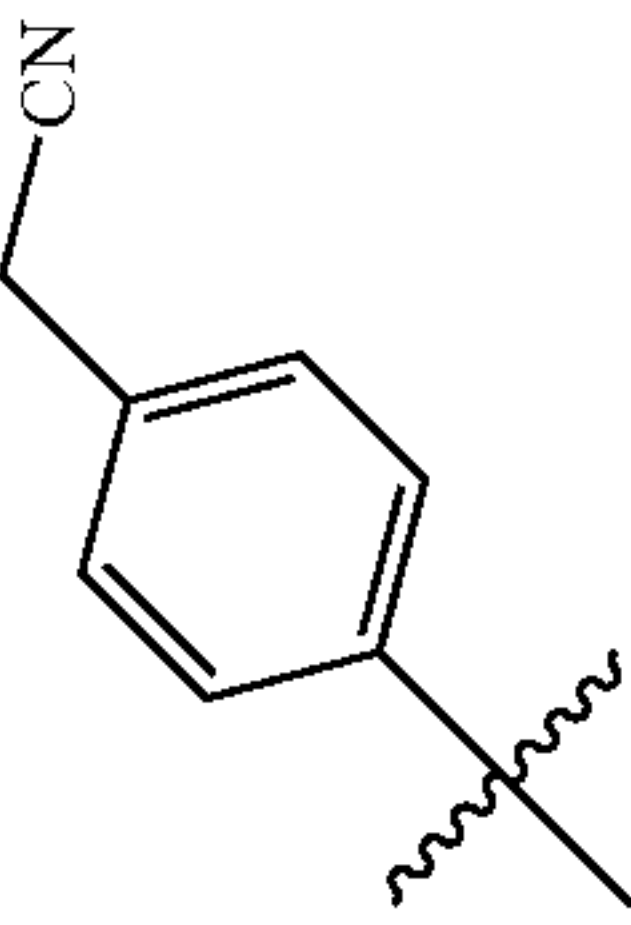
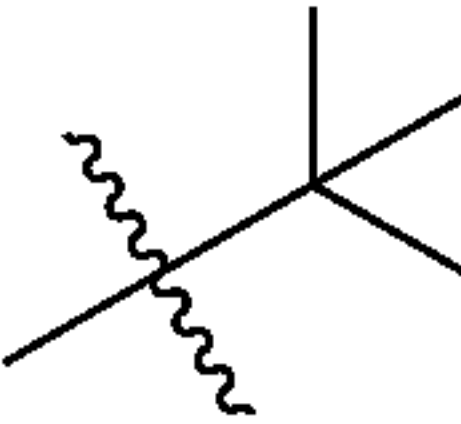
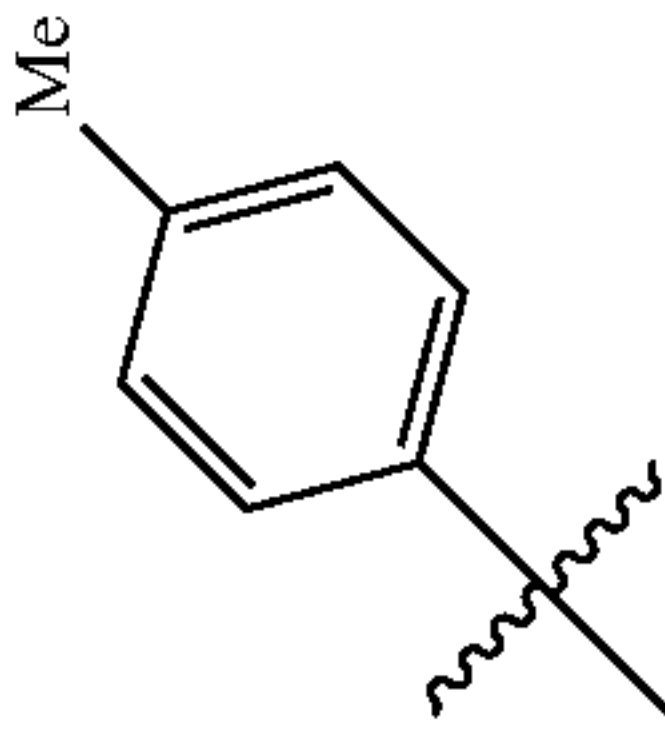
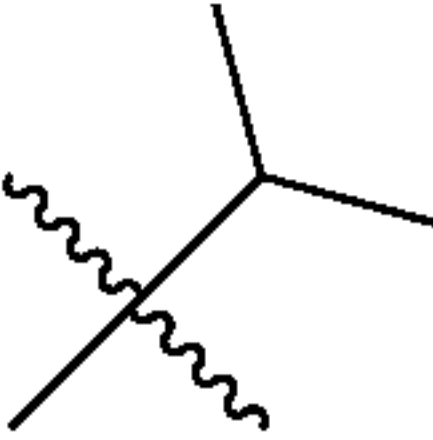
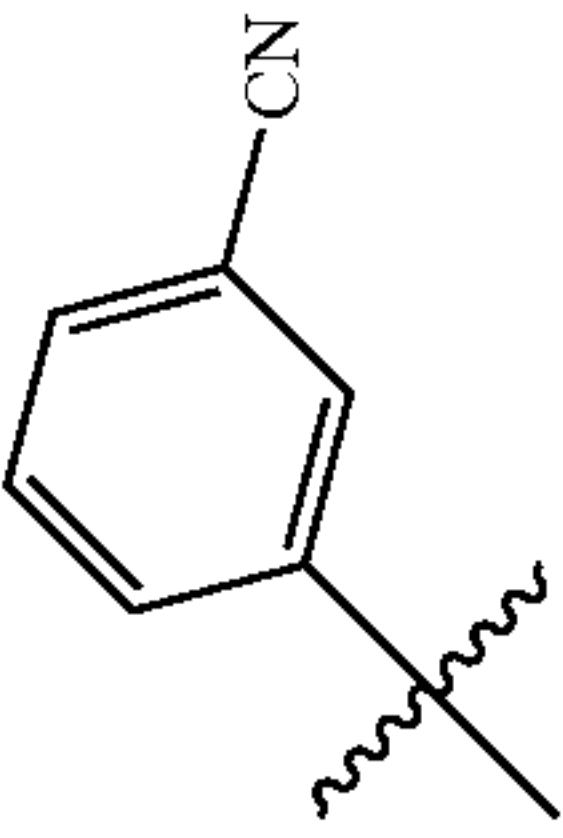
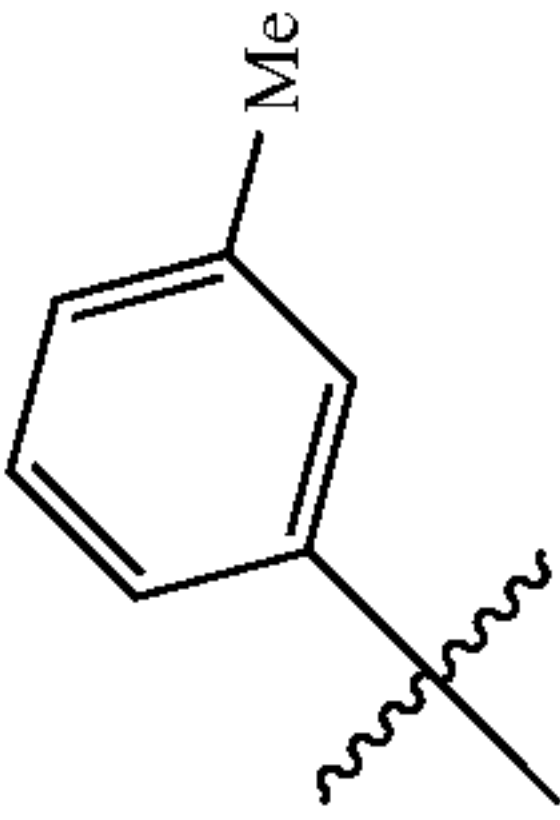
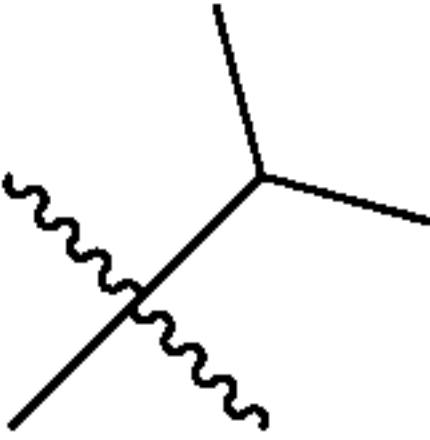
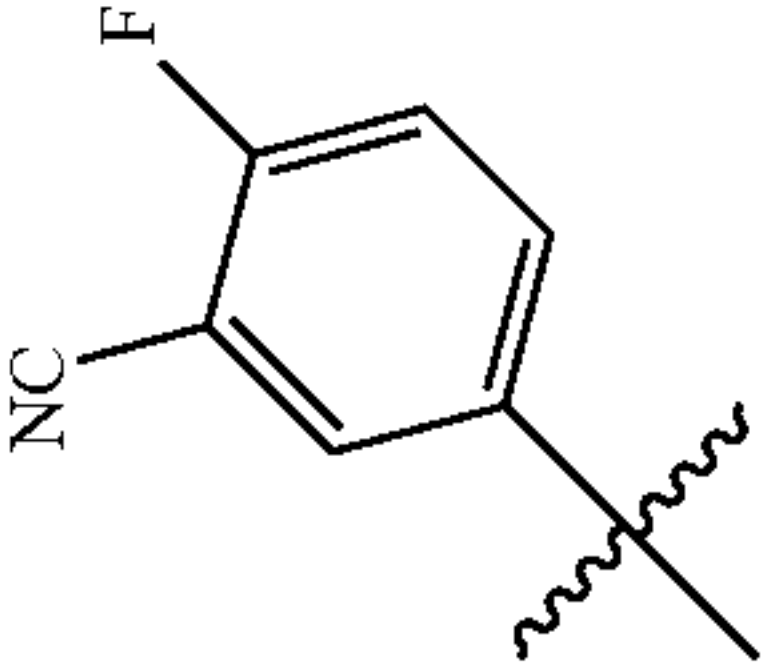
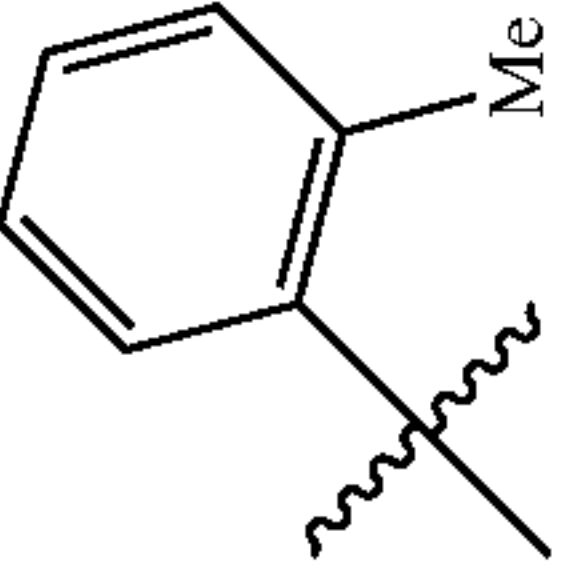
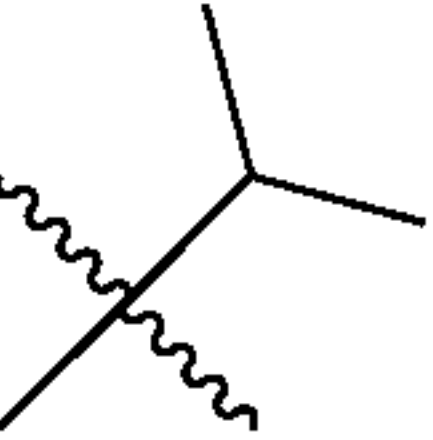
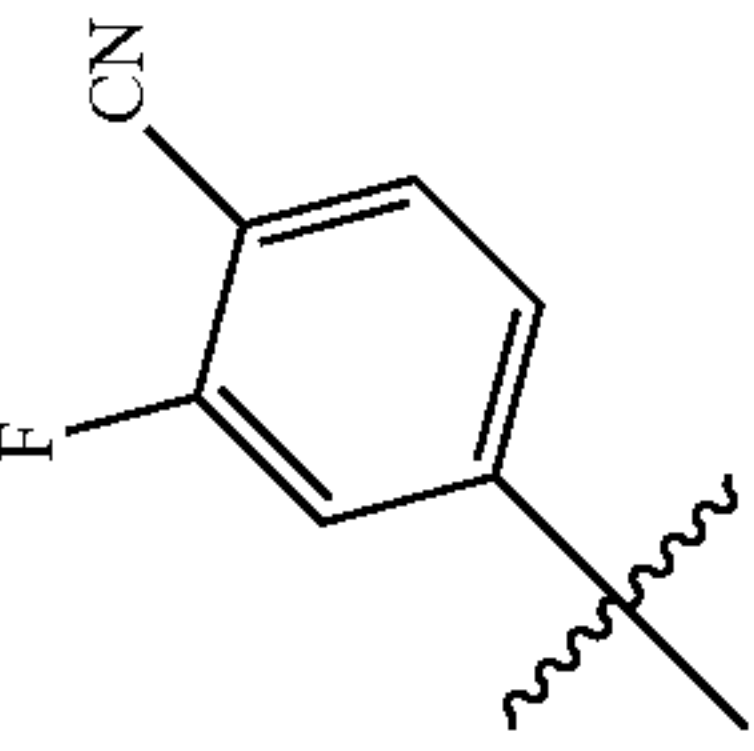
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TABLE 1-continued

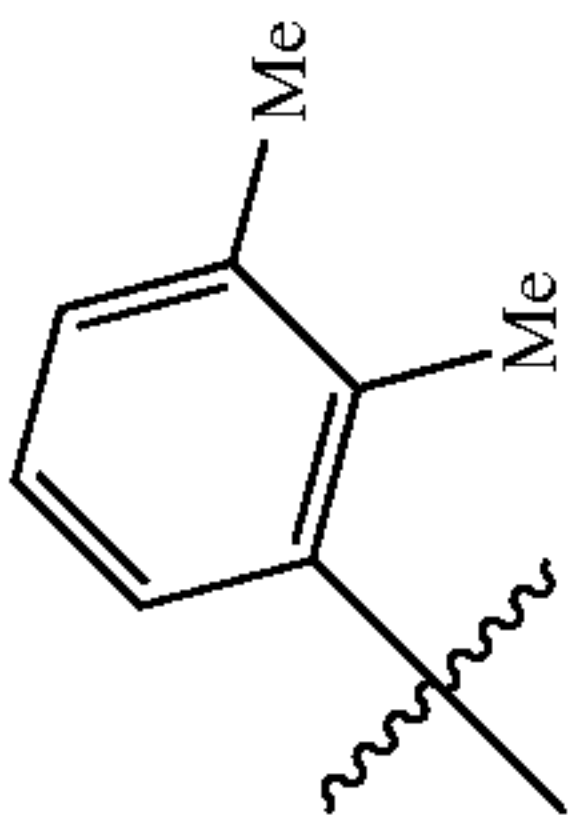
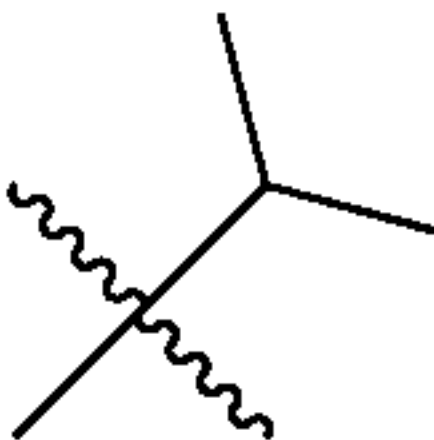
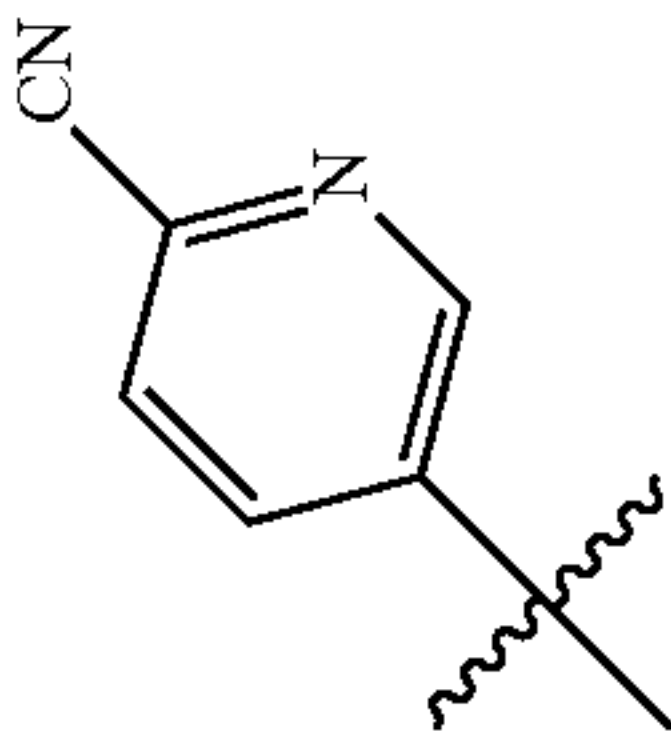
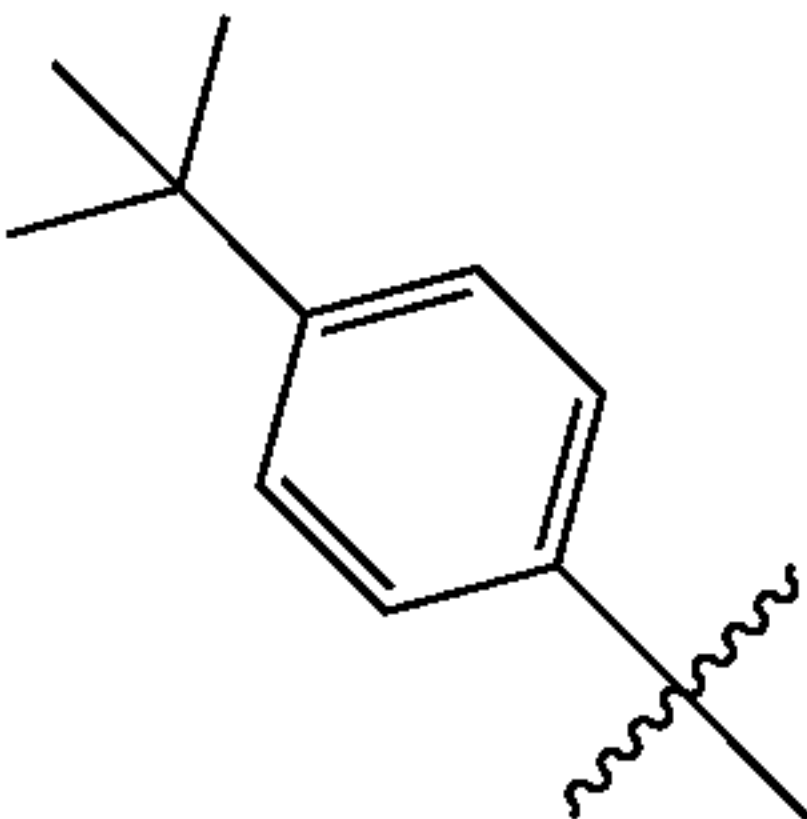
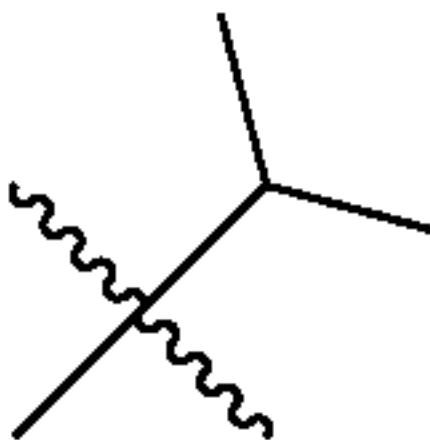
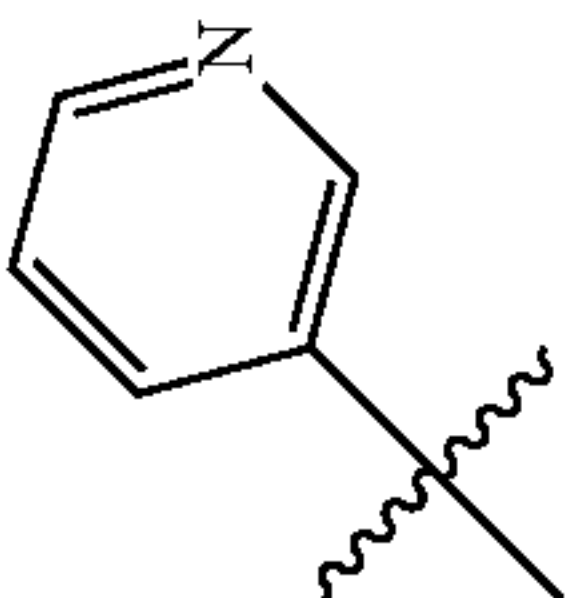
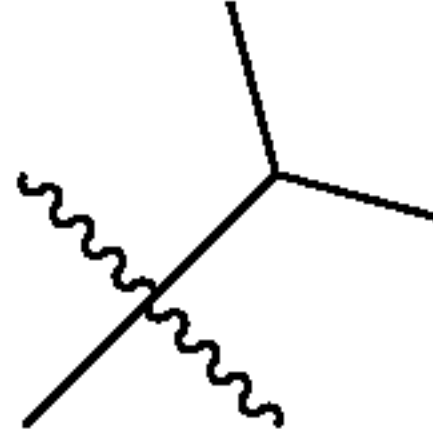
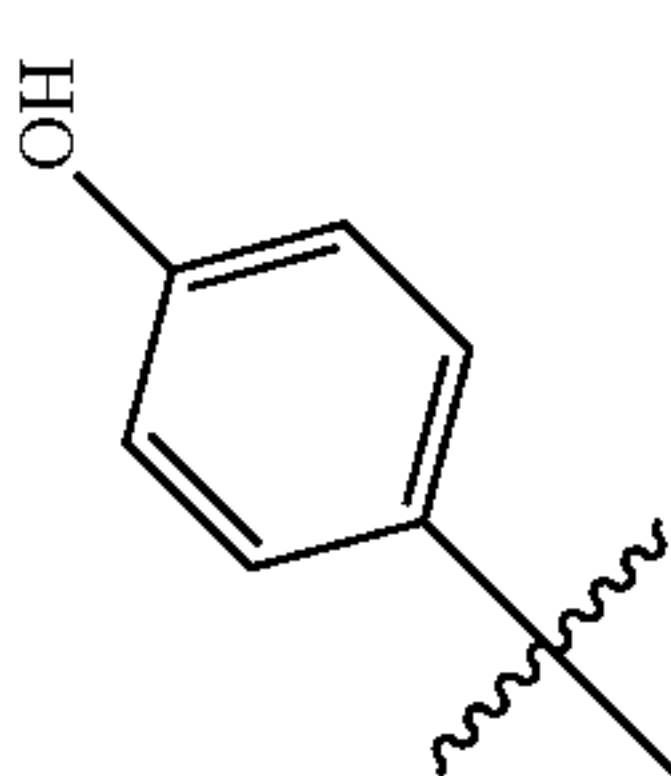
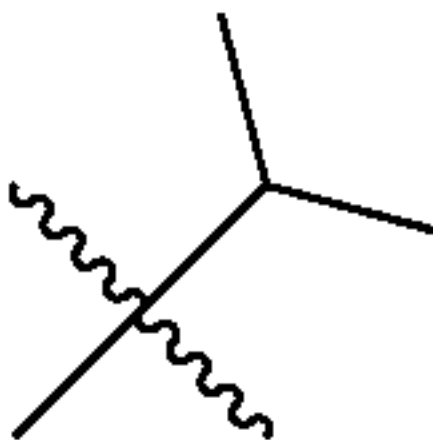
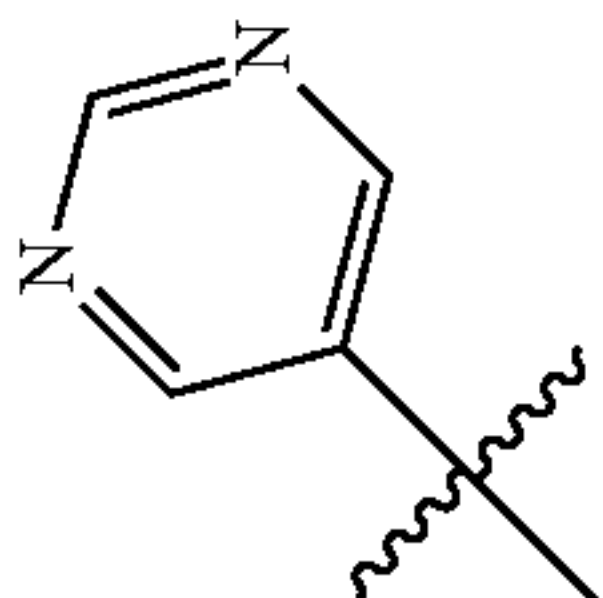
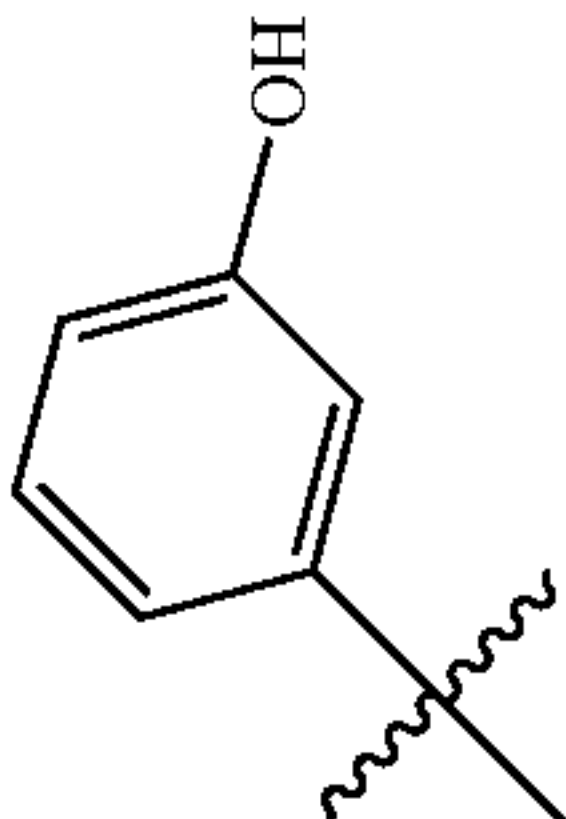
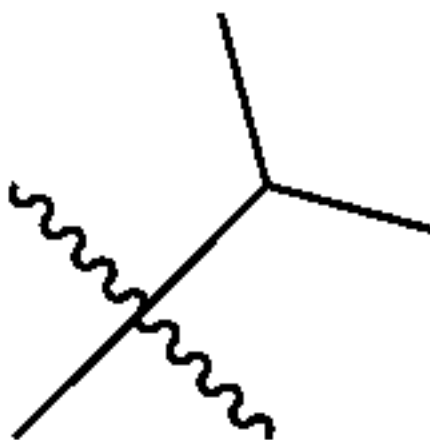
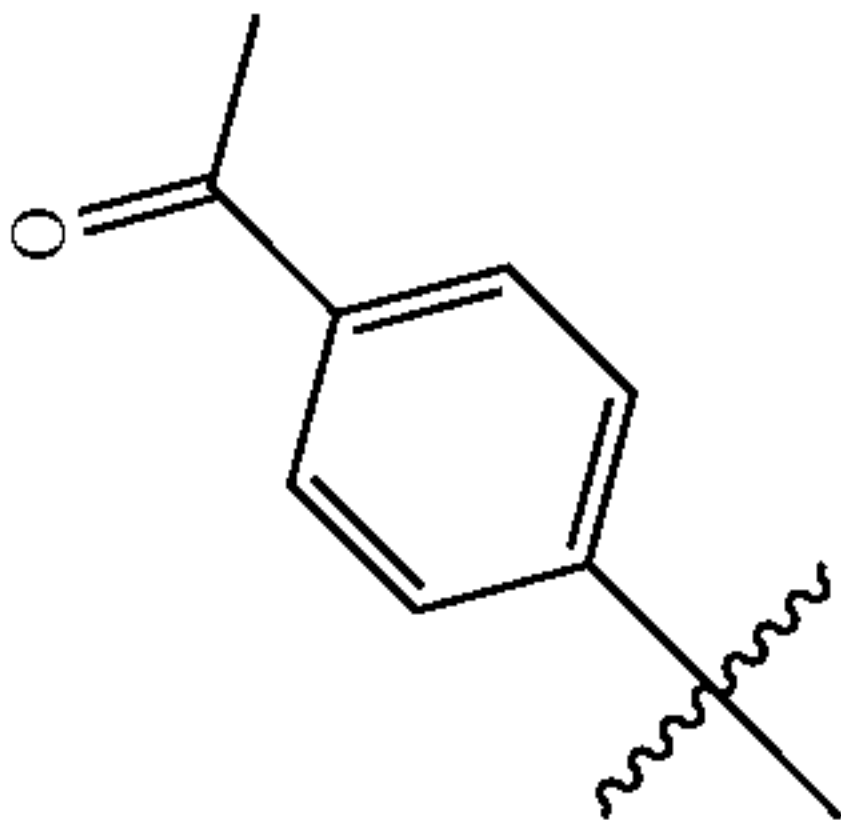
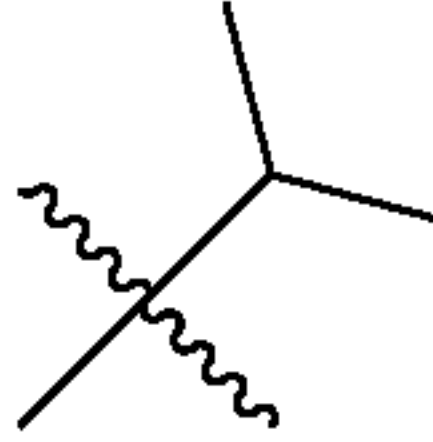
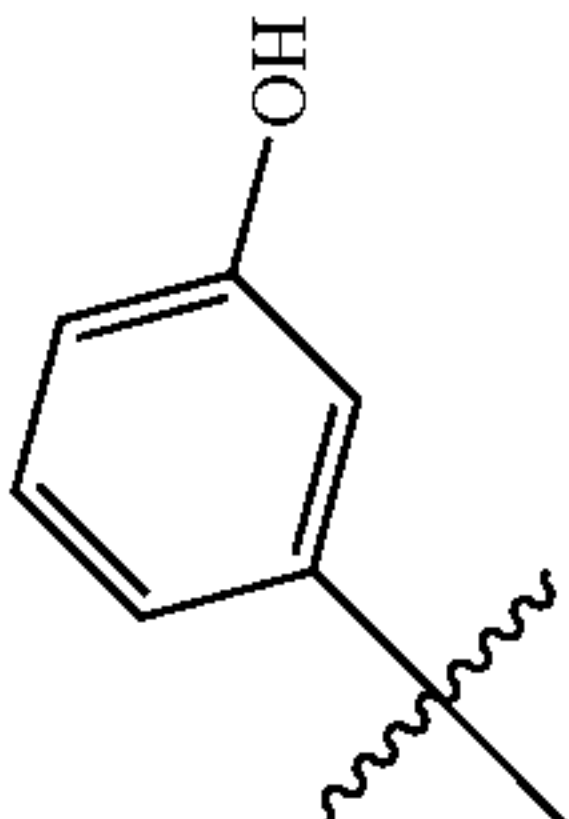
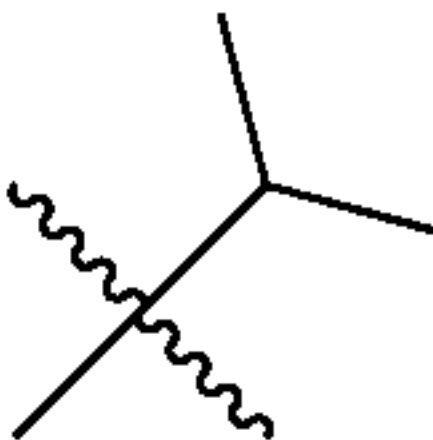
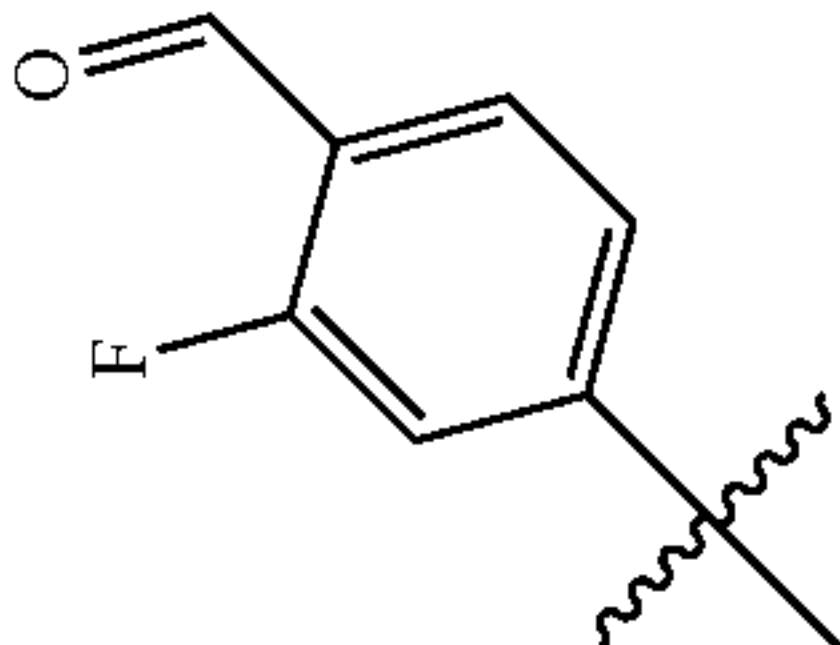
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK132	—H		BA21		
ZK125	—H		BA52		
BA56			BA53		
ZK138	—H		BA31		
KS287	 X = CH		BA152		

TABLE 1-continued

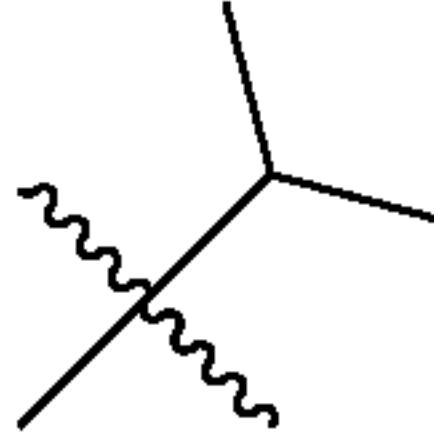
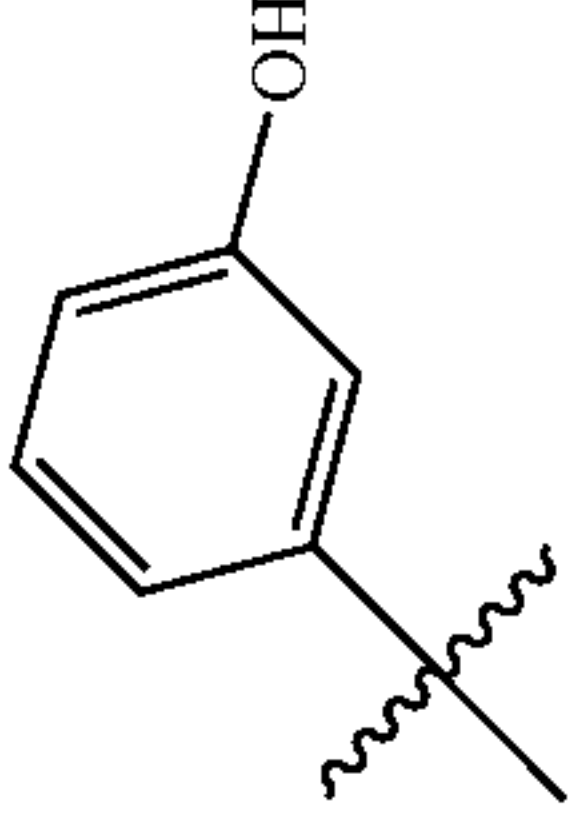
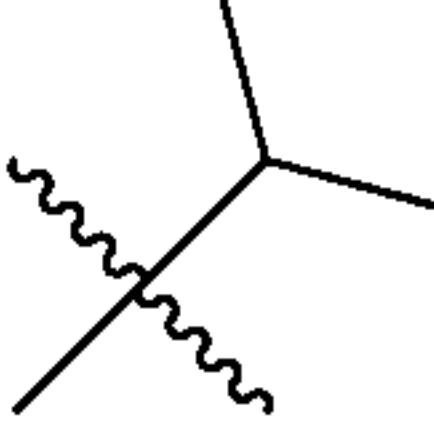
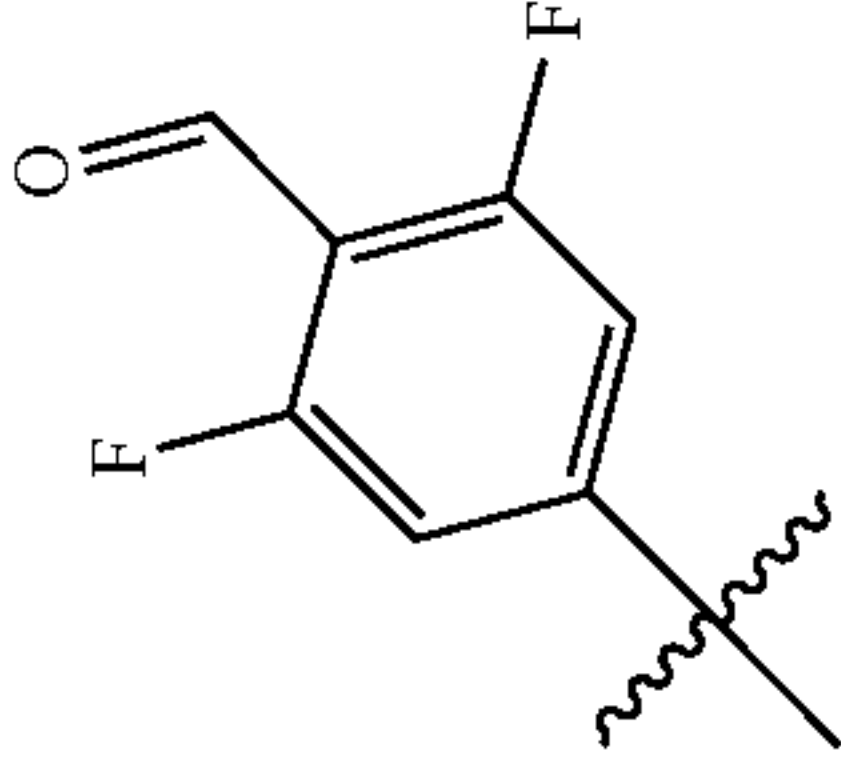
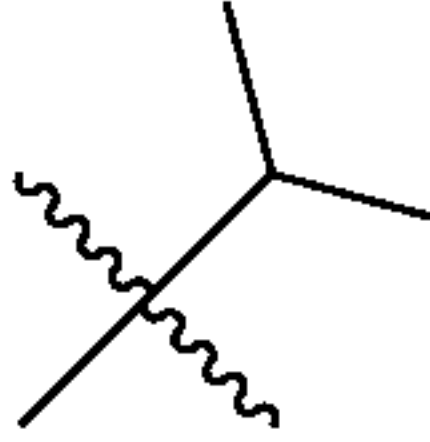
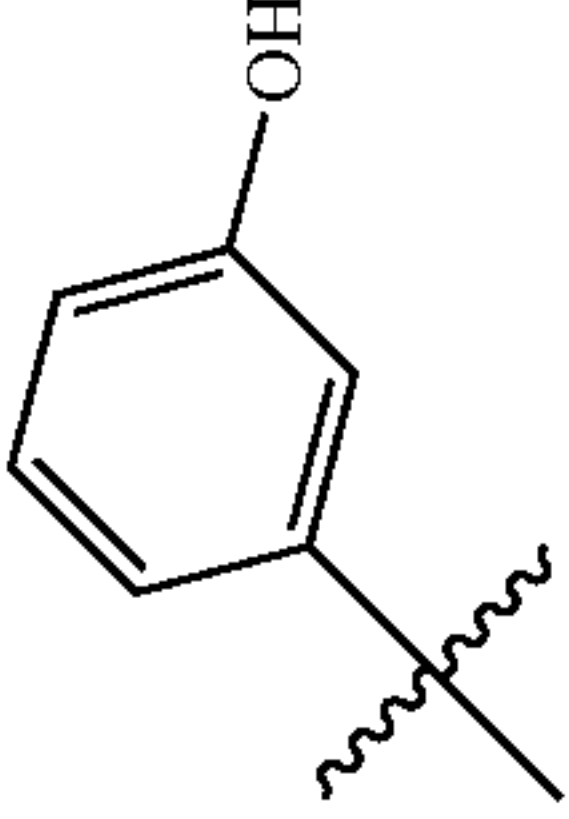
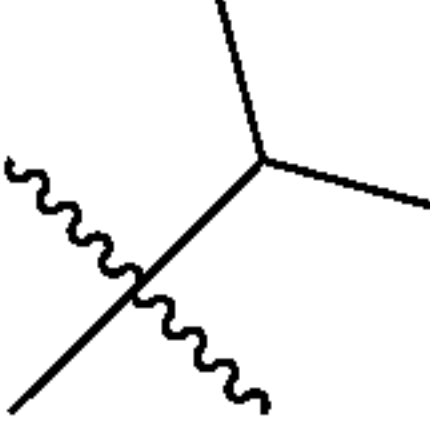
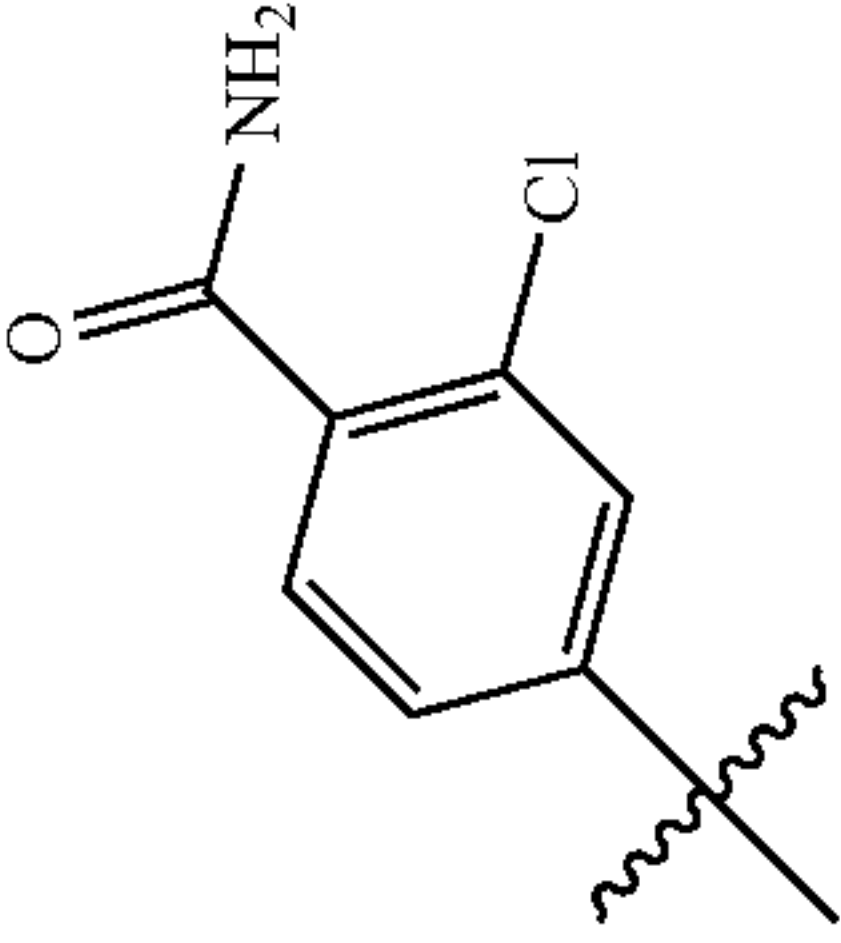
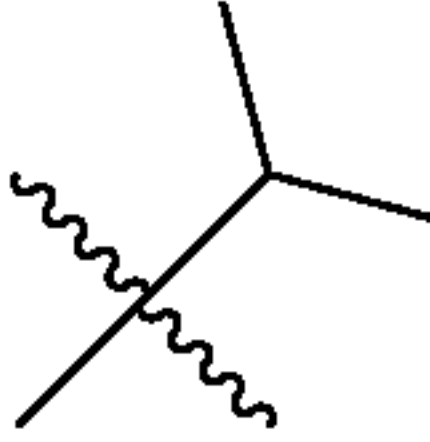
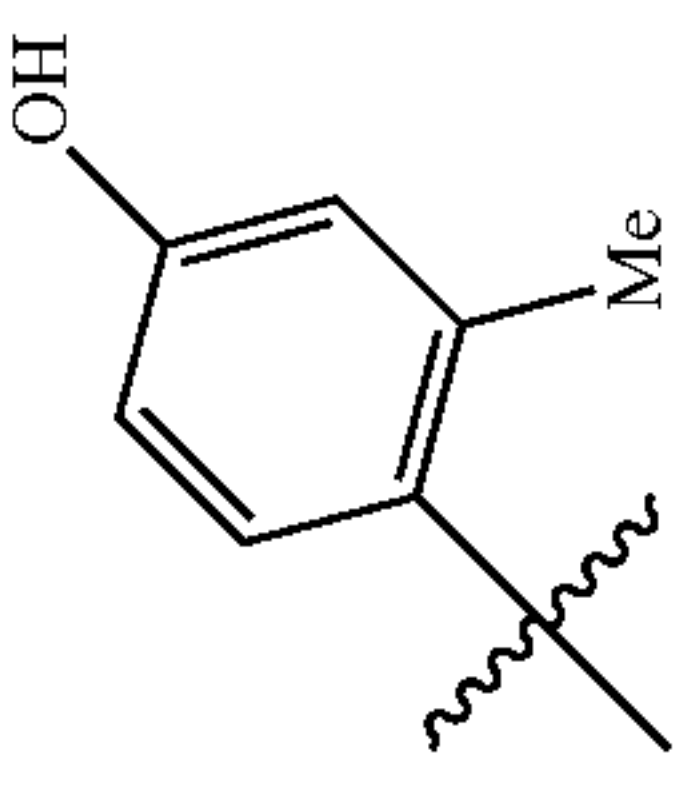
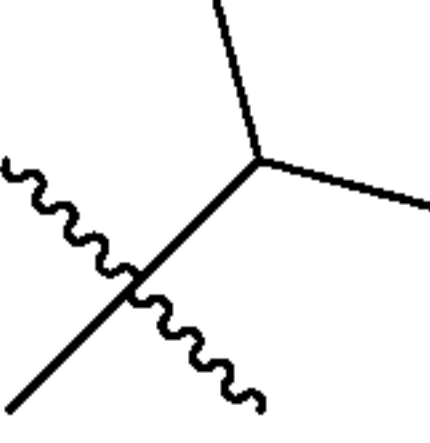
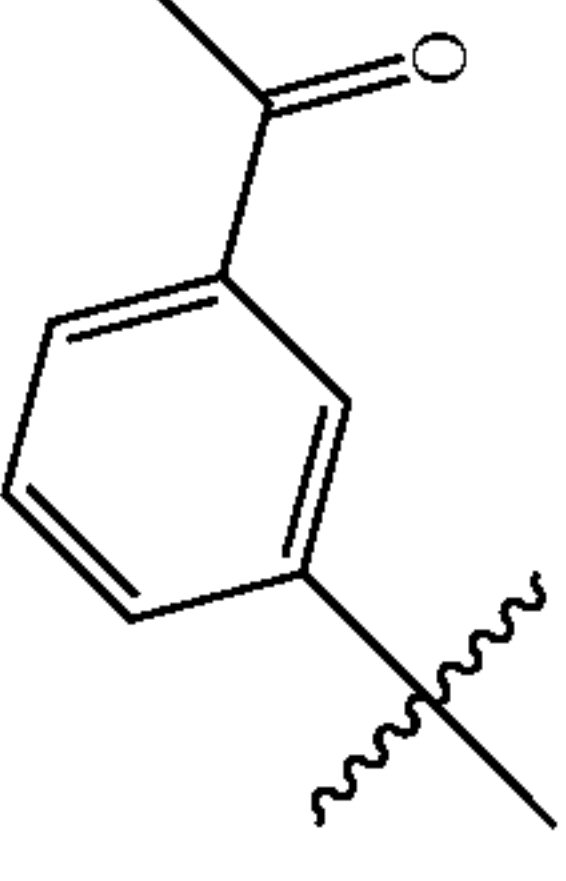
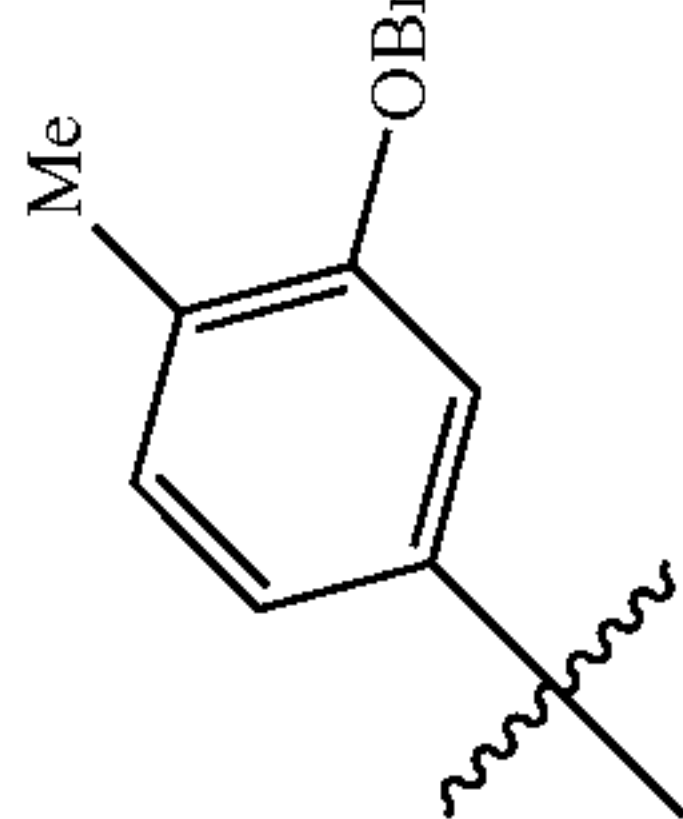
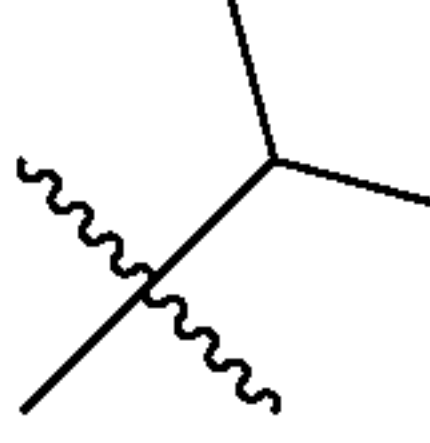
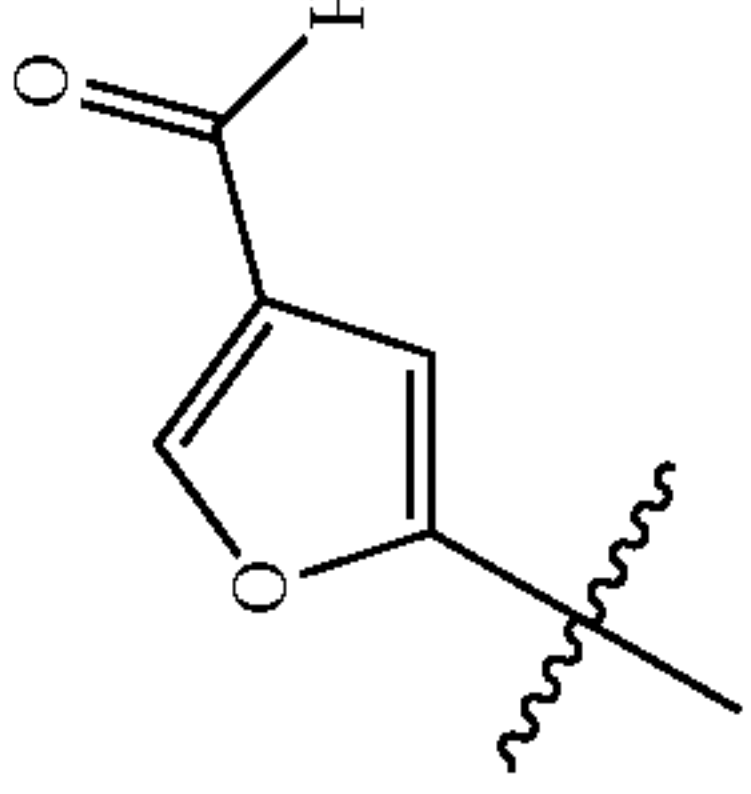
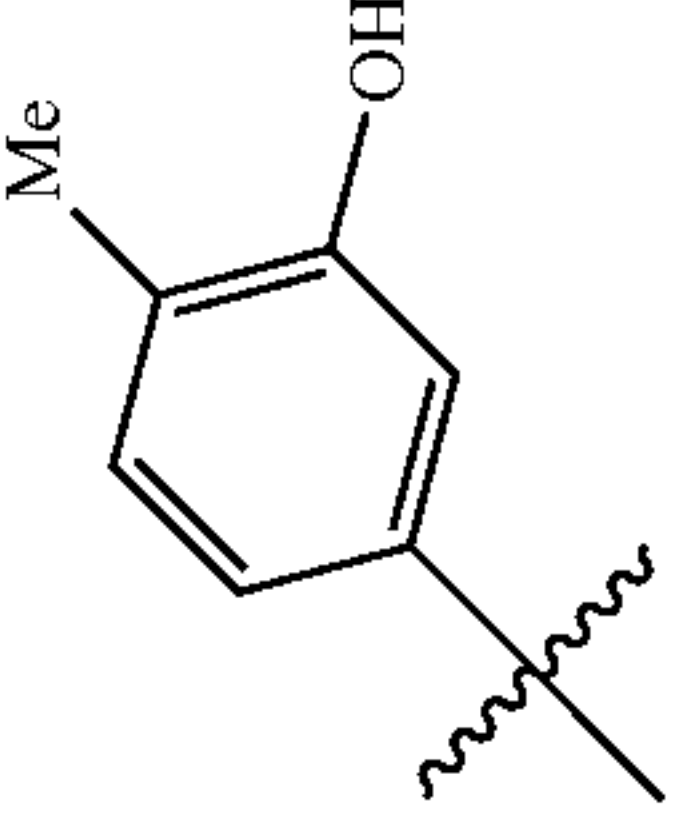
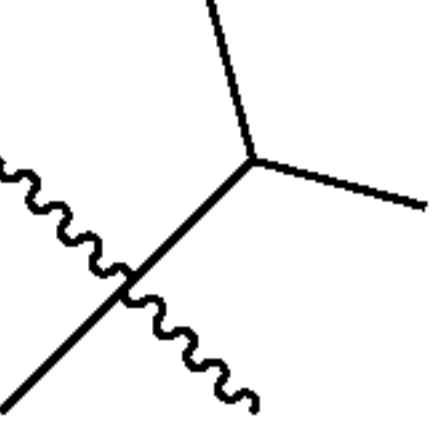
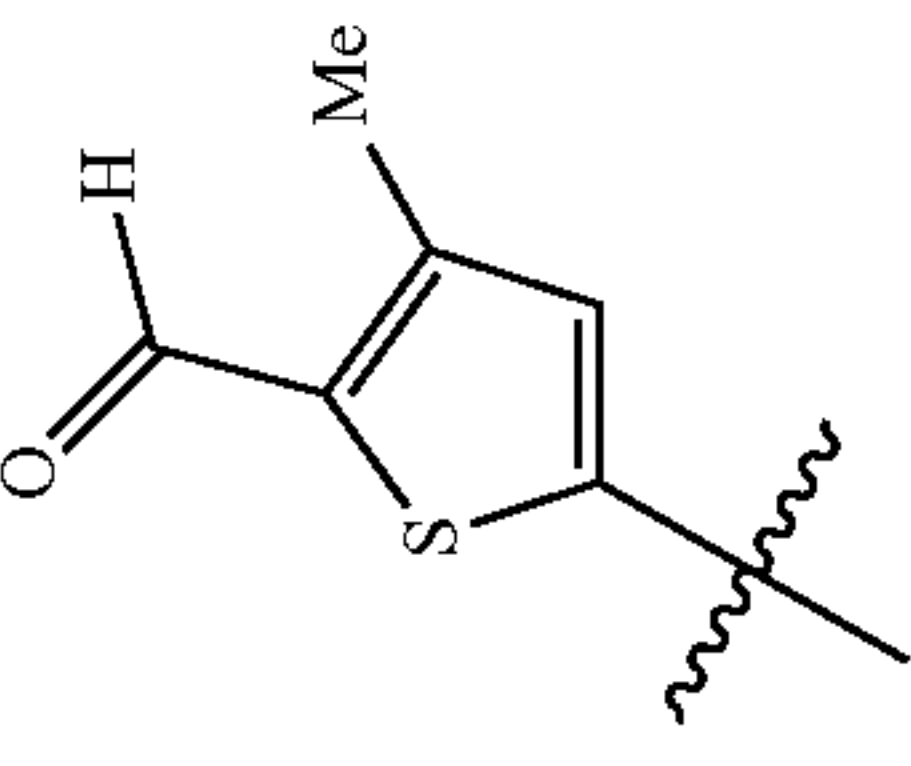
Cpd	R ¹	R ²	Cpd	R ¹	R ²
KS288	 R ³⁶ is N-Methyl		BA149		
KS284			BA32		
BA60			BA55		
ZK318	—H		BA35		
ZK320	—H		BA34		

TABLE 1-continued

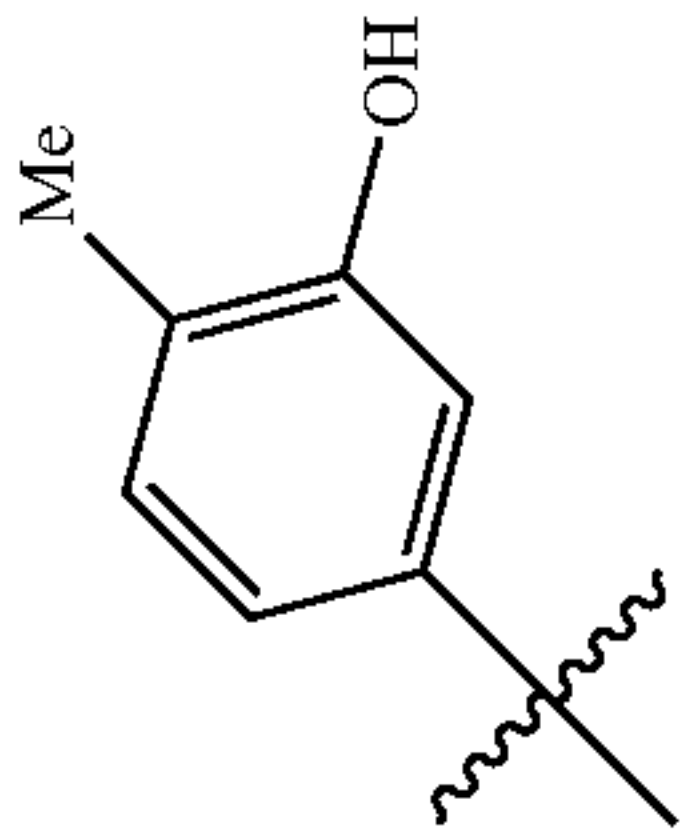
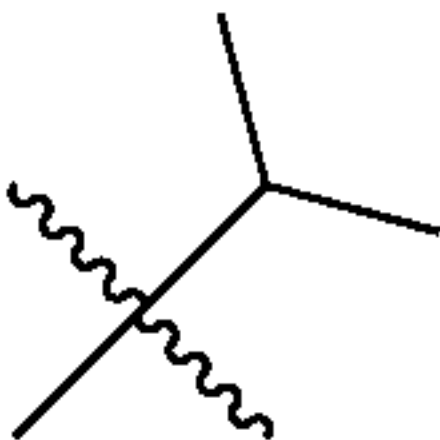
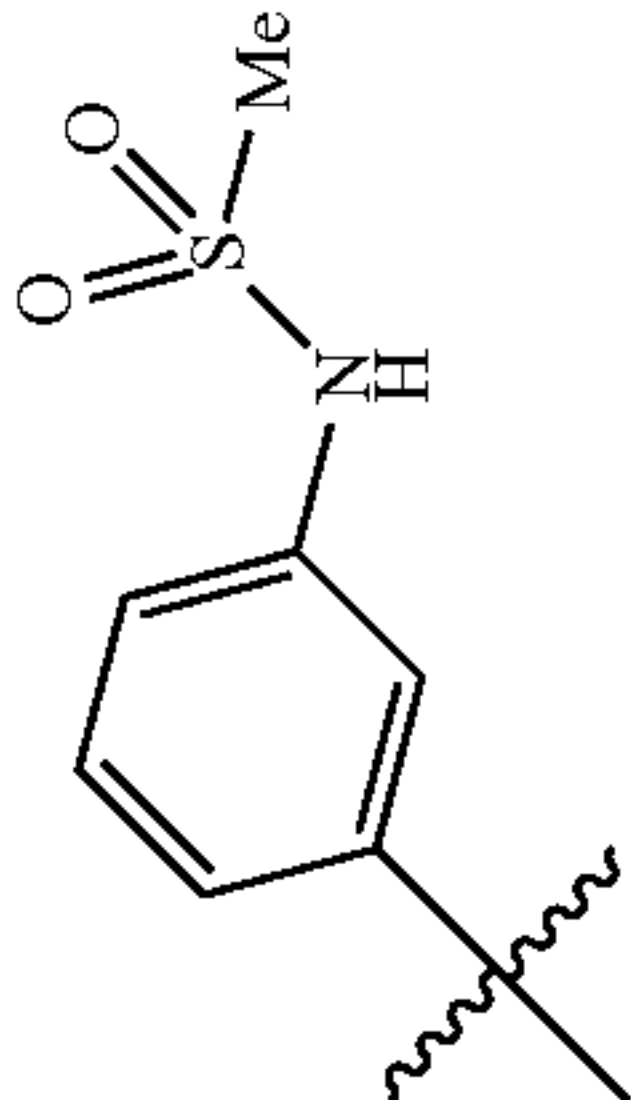
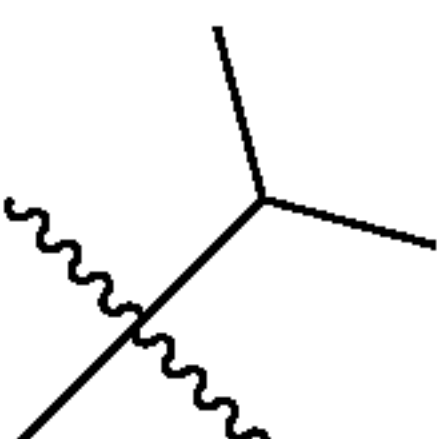
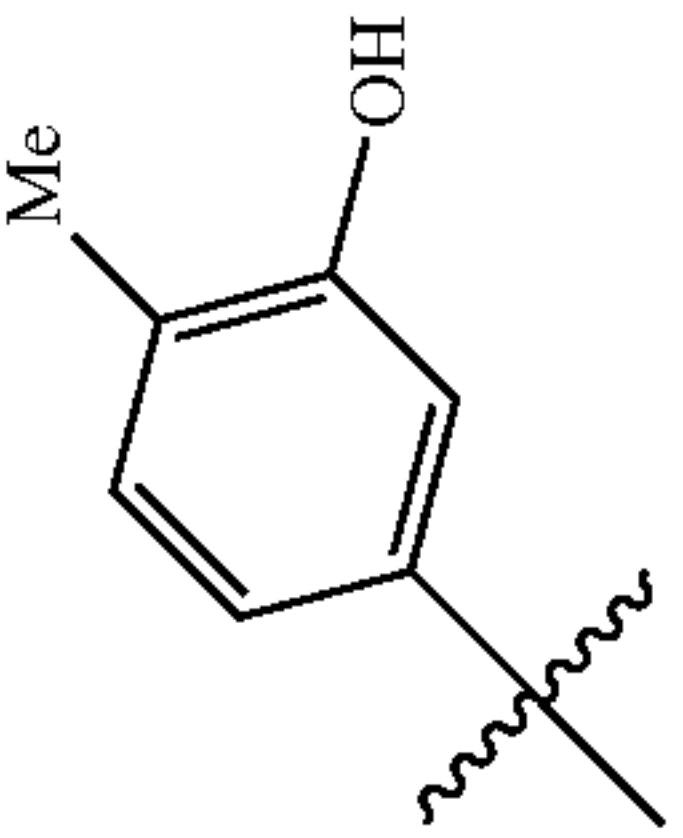
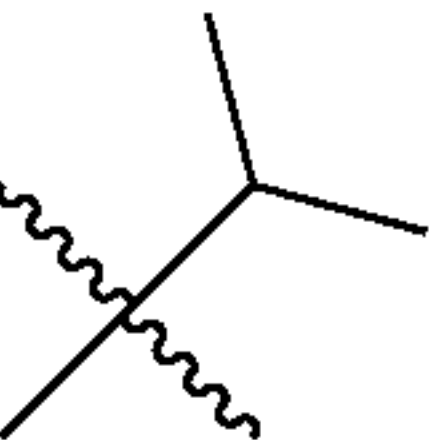
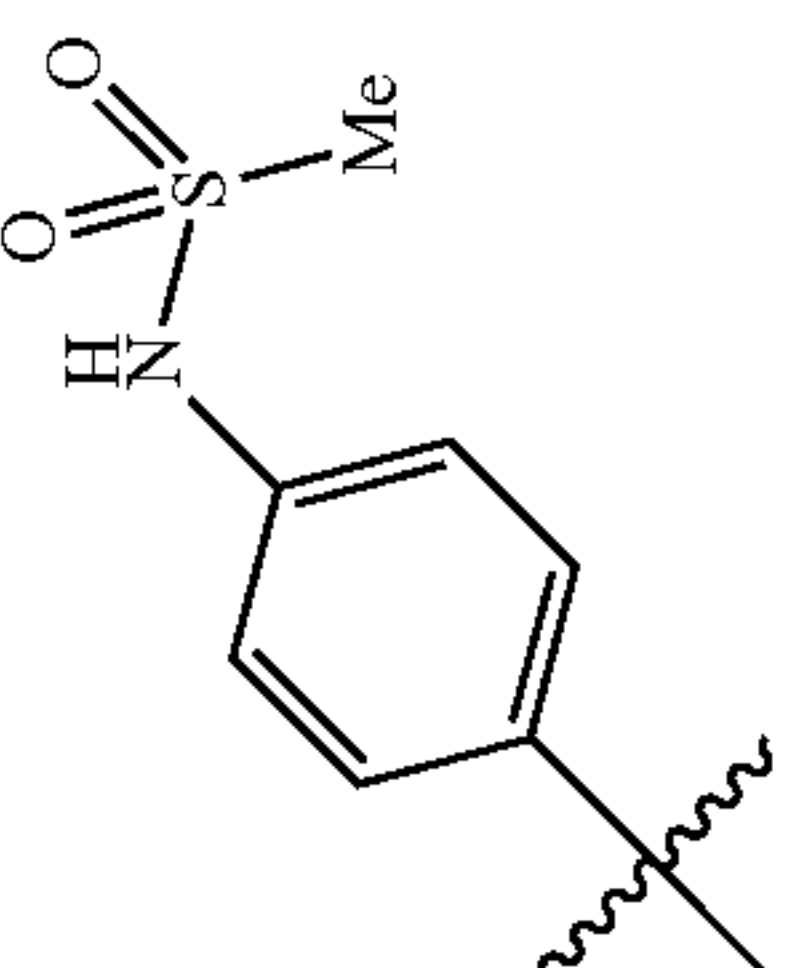
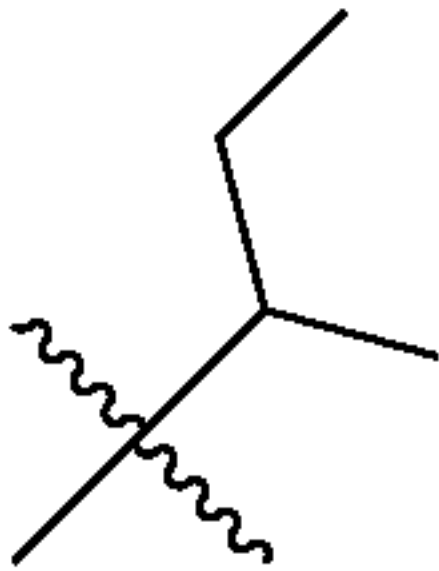
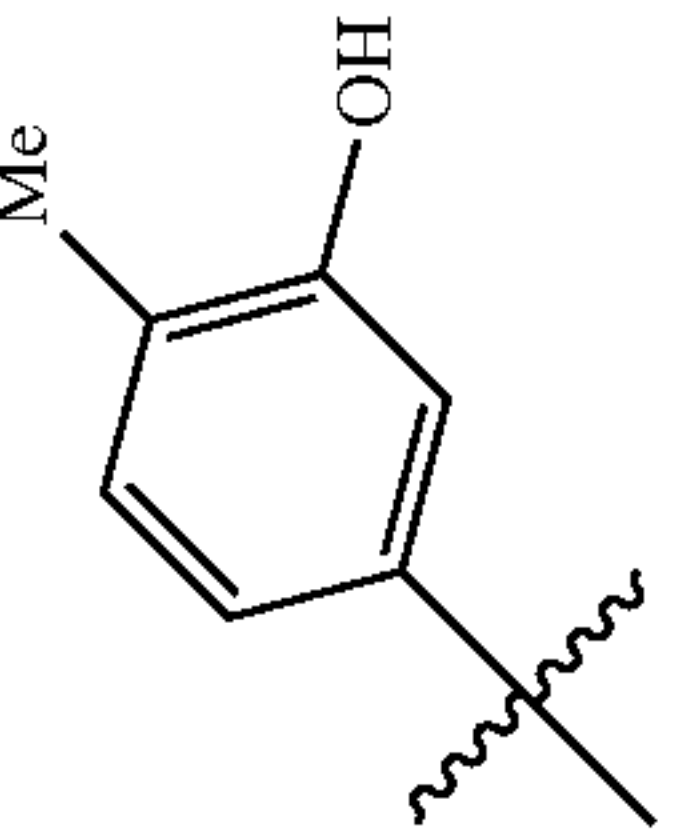
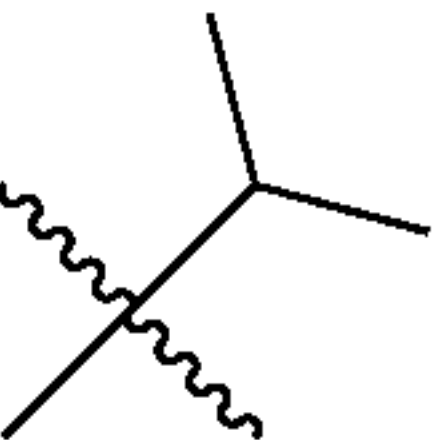
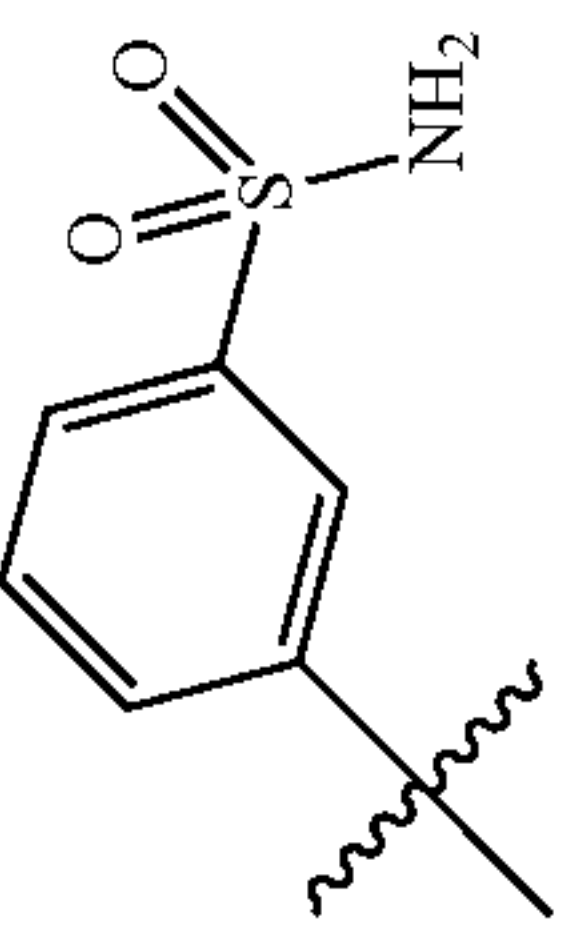
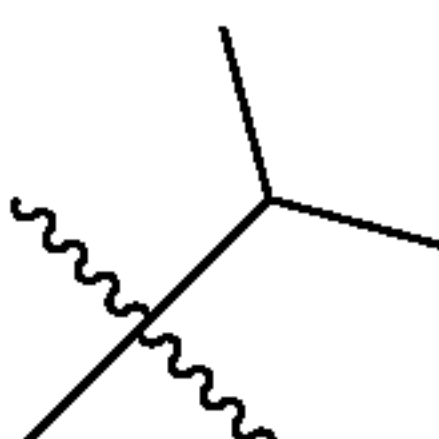
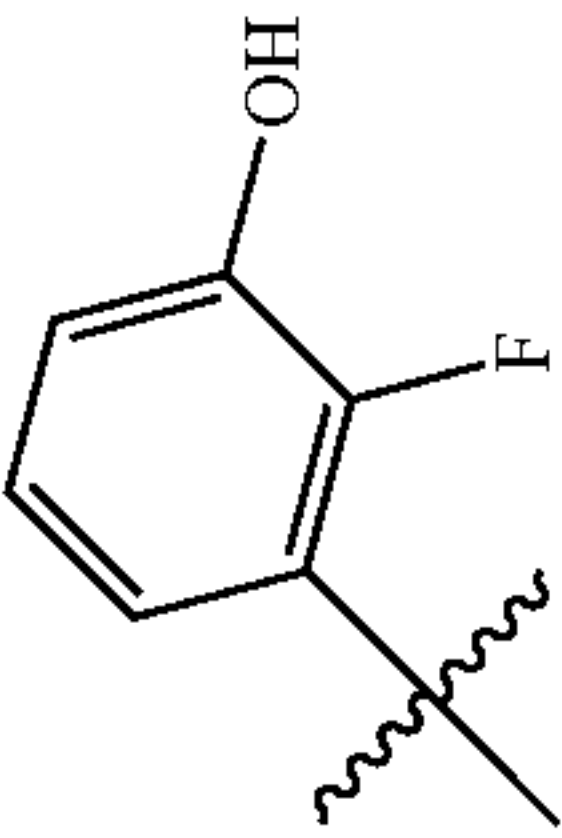
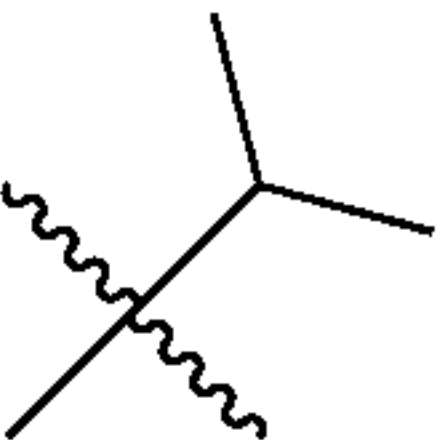
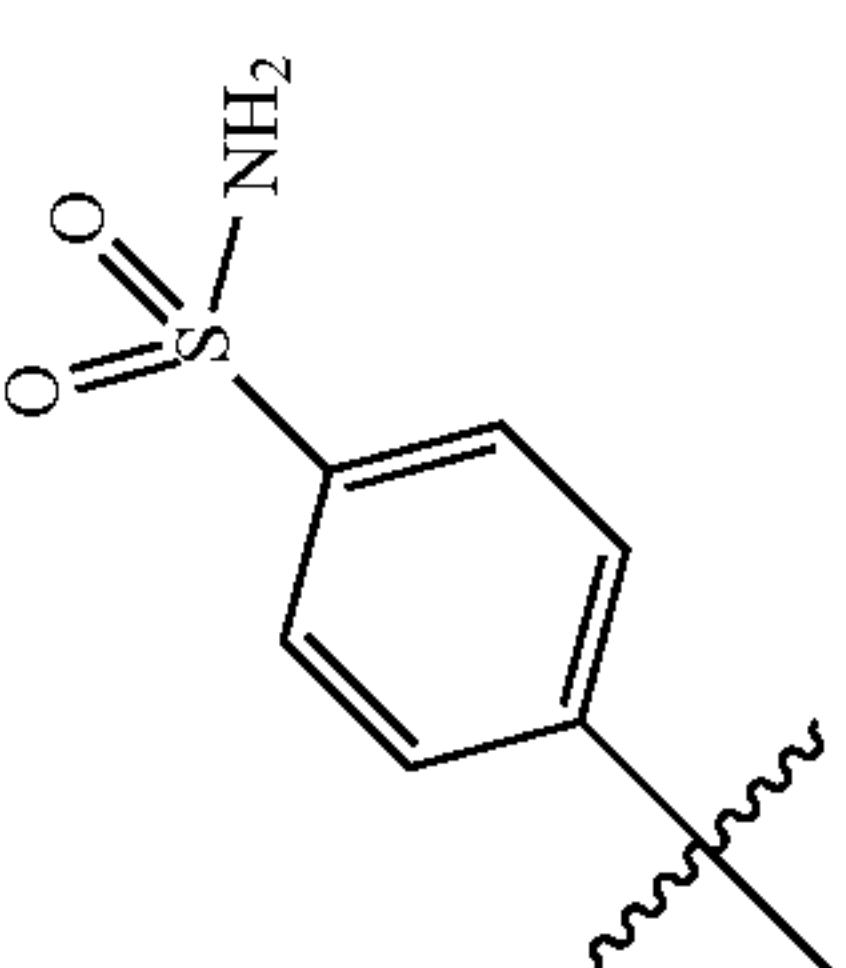
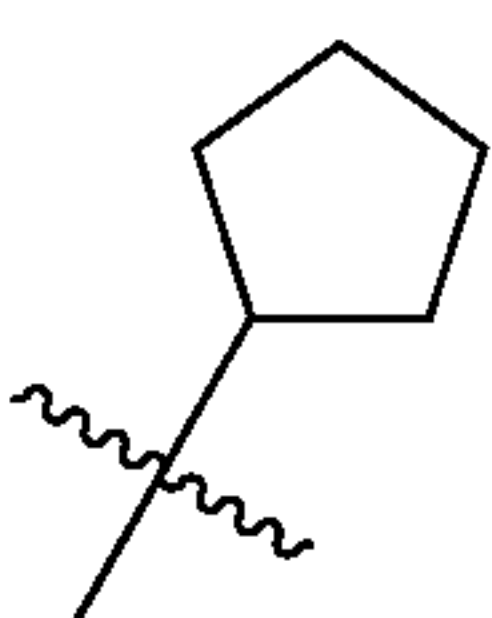
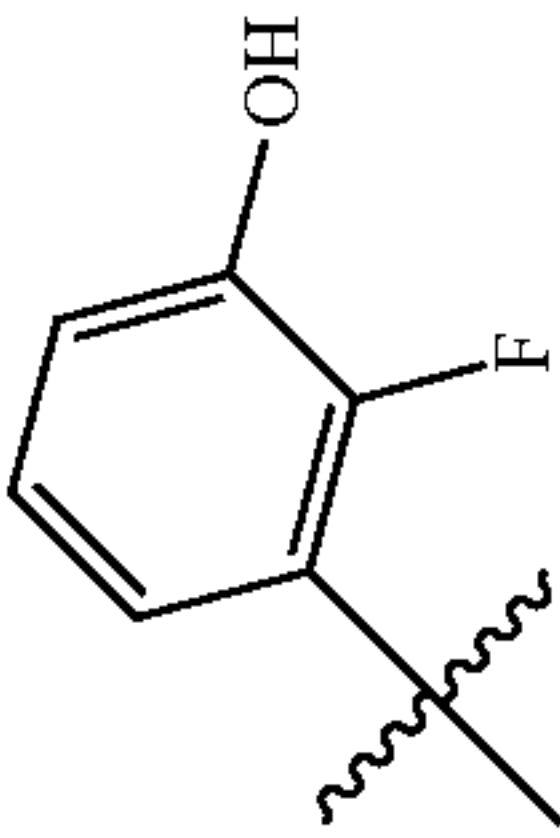
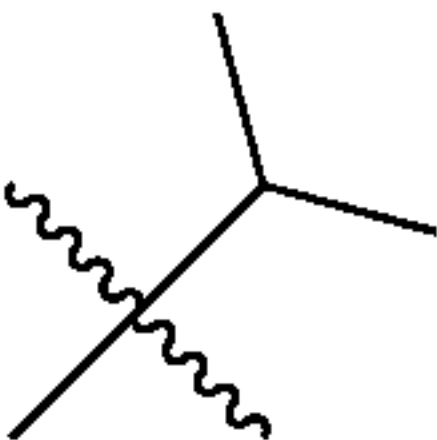
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK333	—Me		BA38		
ZK323			BA40		
ZK327			BA41		
BA77d			BA14		
BA78d			BA12		—I

TABLE 1-continued

Cpd	R ¹	R ²	Cpd	R ¹	R ²
BA22			BA30		
BA79d			ZK149	H	
BA85			ZK126	H	
BA87			ZK143	H	

TABLE 1-continued

Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK502			ZK150	$\begin{matrix} \text{---Me} \\ \text{X = CH} \end{matrix}$	
ZK489	---Me		ZK136	---H	
ZK487			ZK131	---H	
ZK491			ZK151	$\begin{matrix} \text{---Me} \\ \text{X = CH} \end{matrix}$	
ZK493			ZK142	---H	

TABLE 1-continued

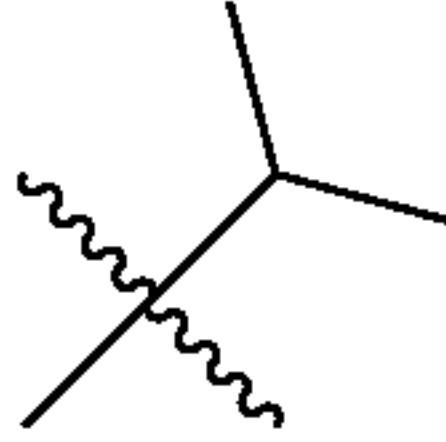
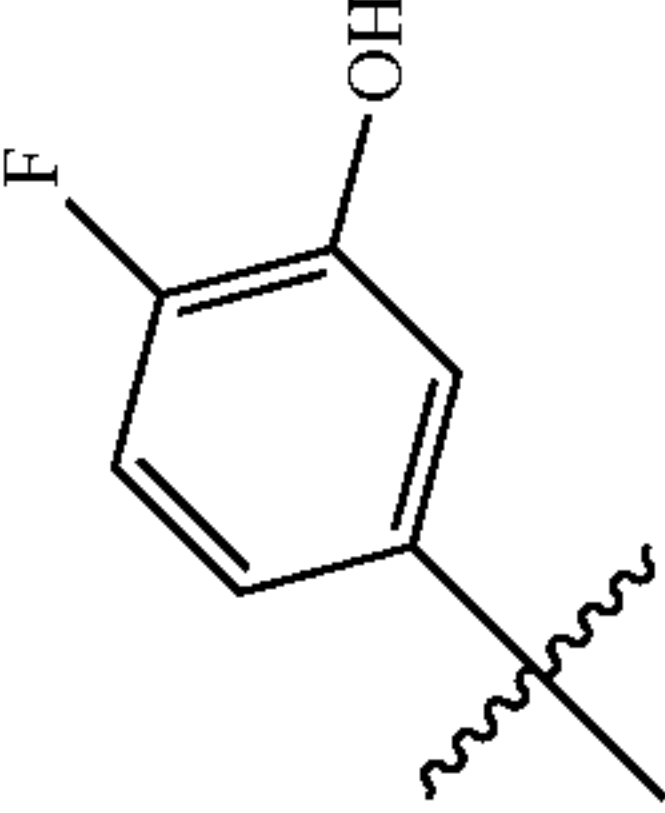
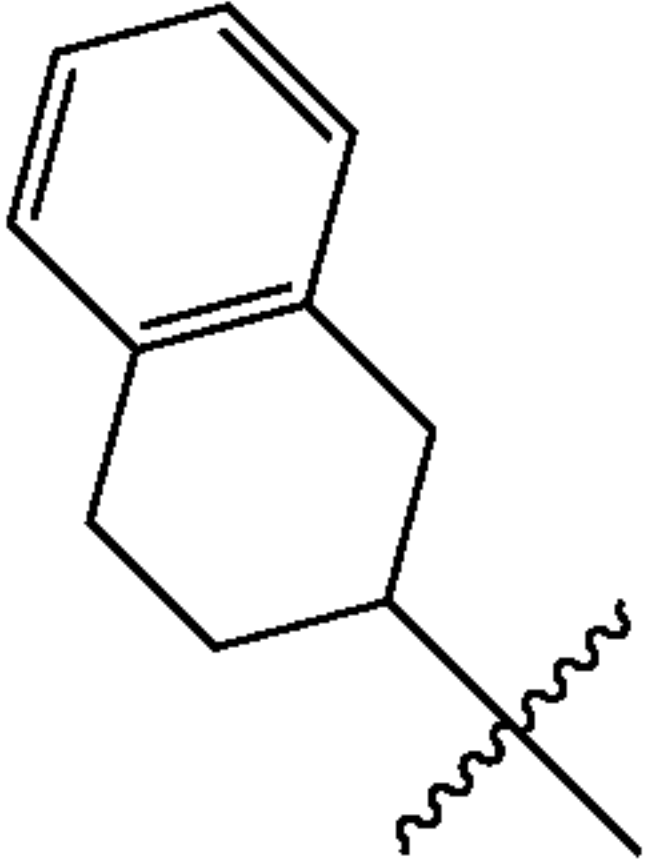
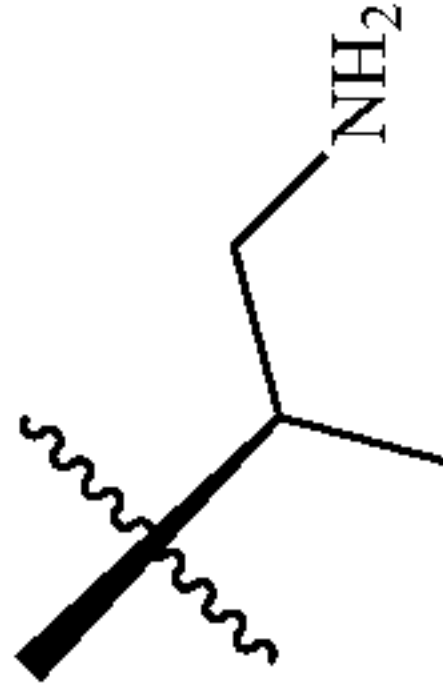
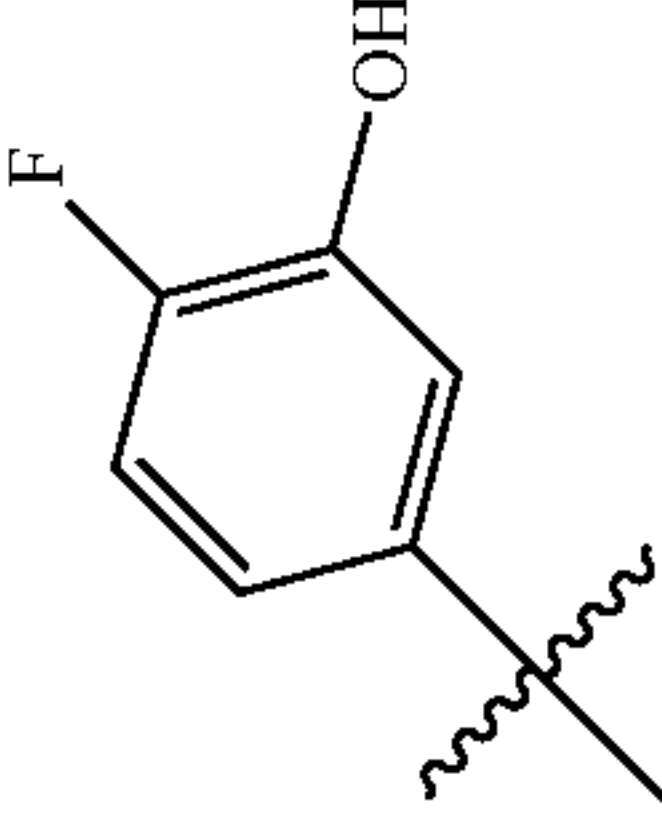
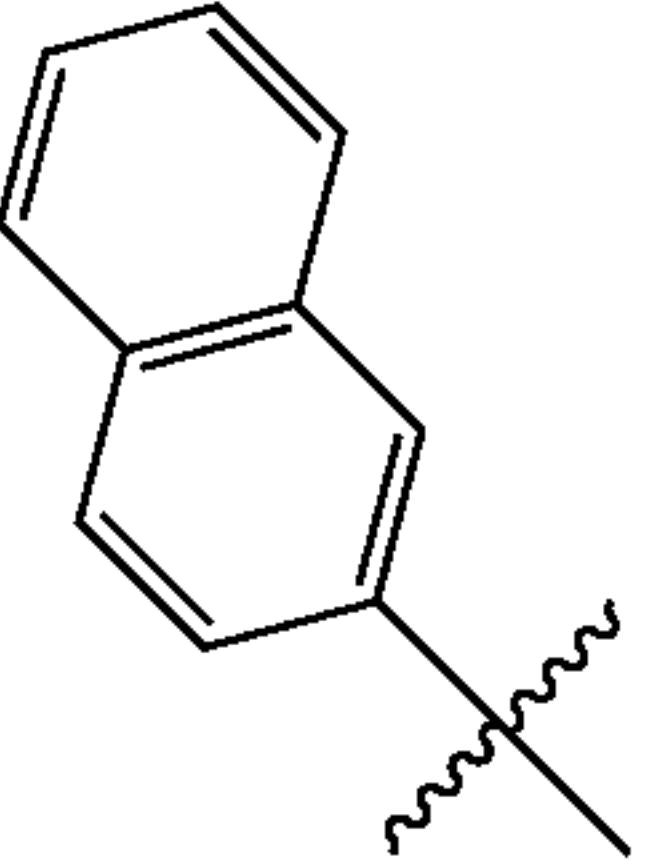
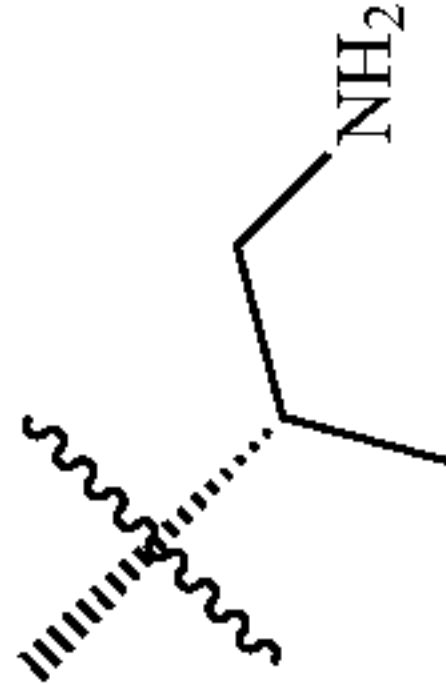
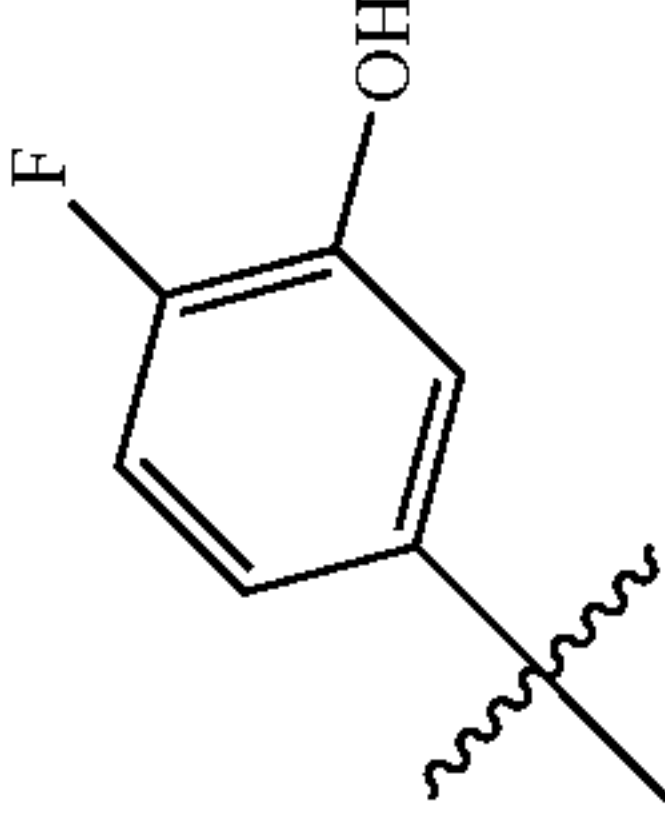
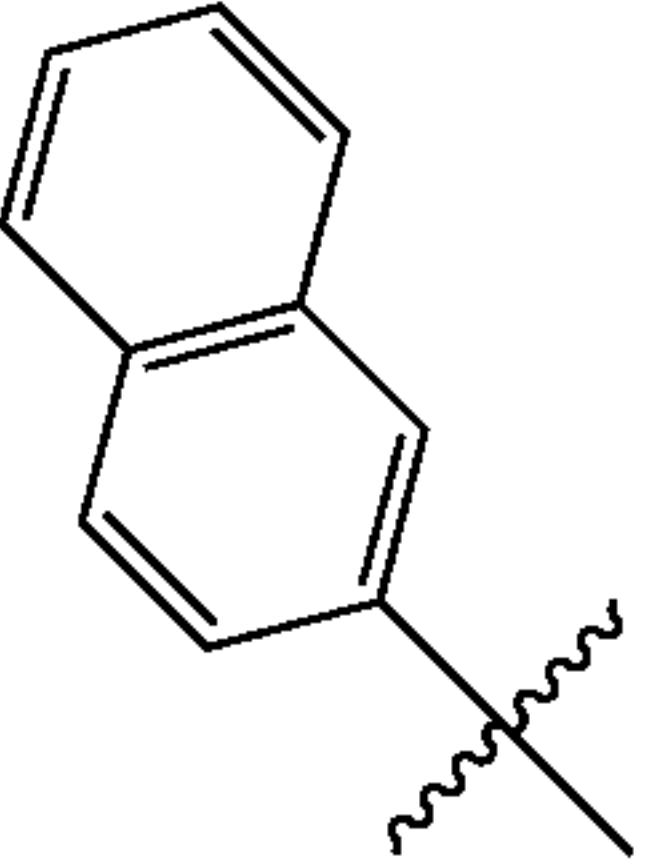
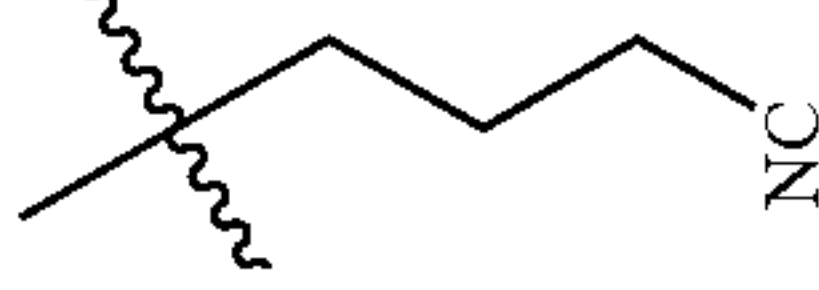
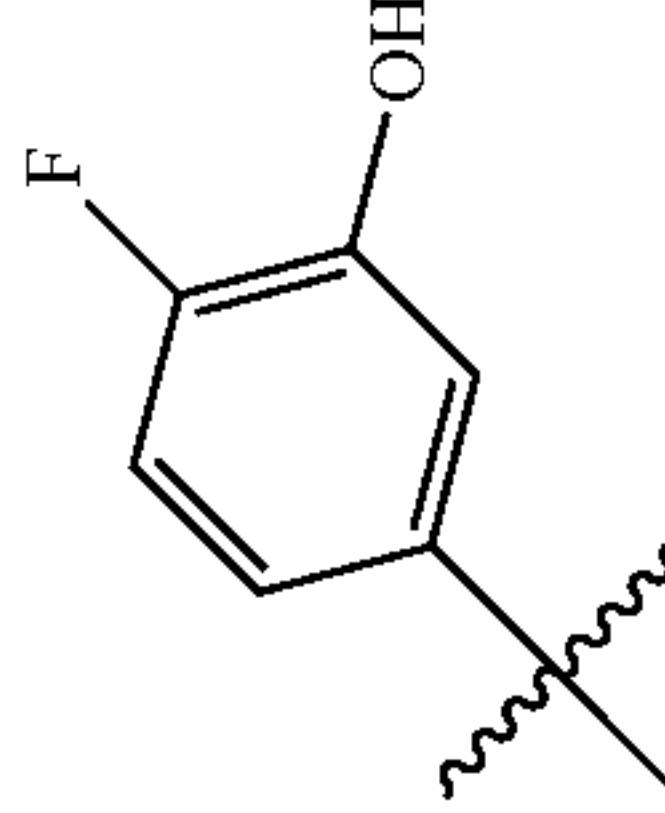
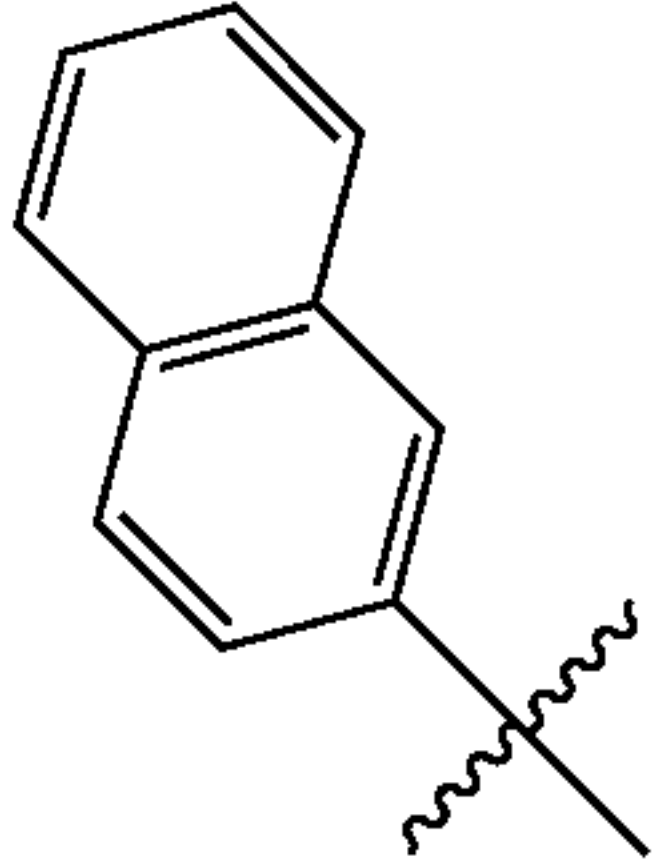
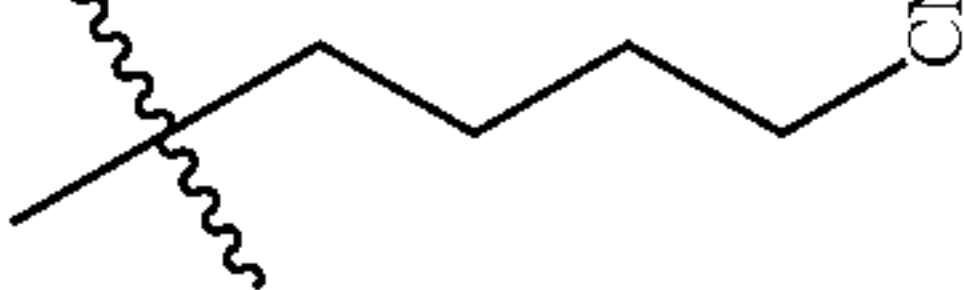
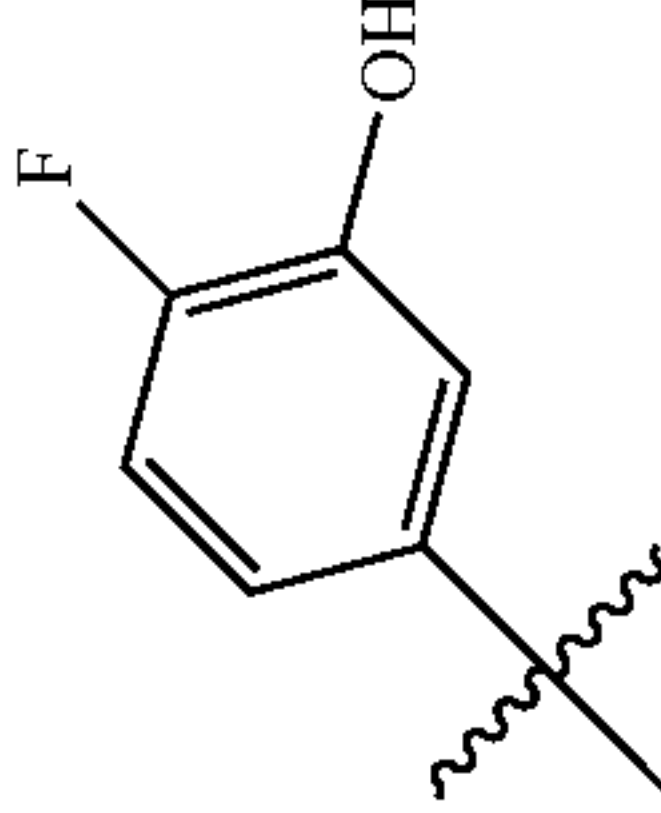
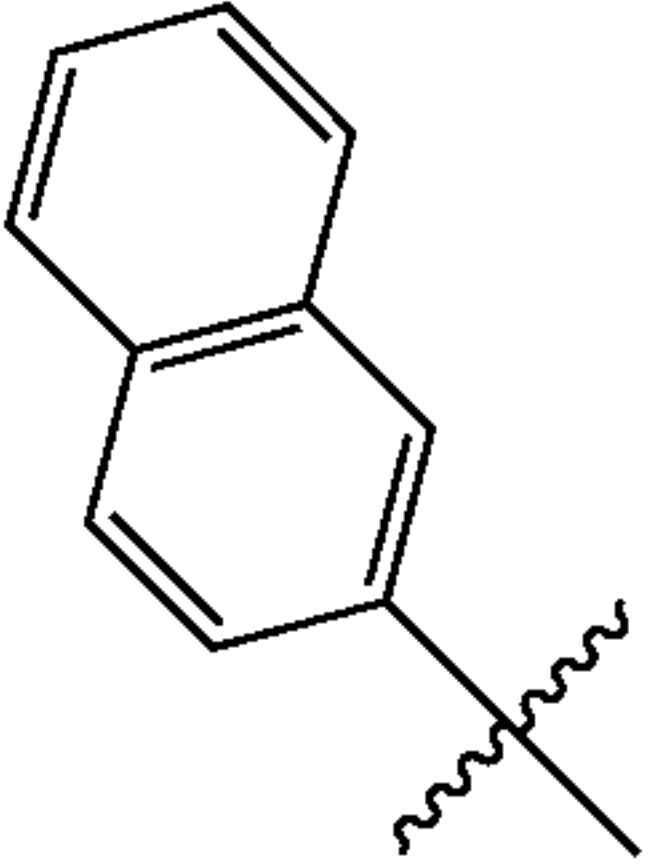
Cpd	R ¹	R ²	Cpd	R ¹	R ²
BA62d			ZK139	H	
ZK450			KS207	H	
ZK454			KS208	Me	
ZK469			ZK102	Me (R ³⁶ is Cl)	
ZK471			ZK157		

TABLE 1-continued

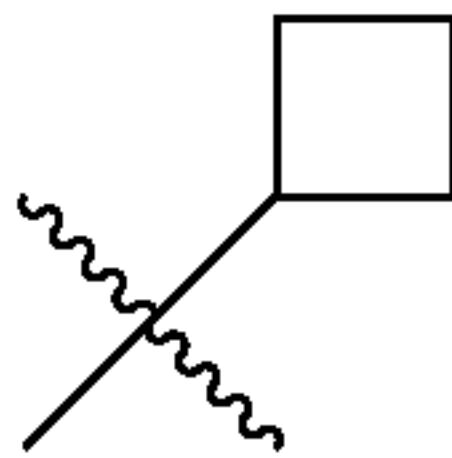
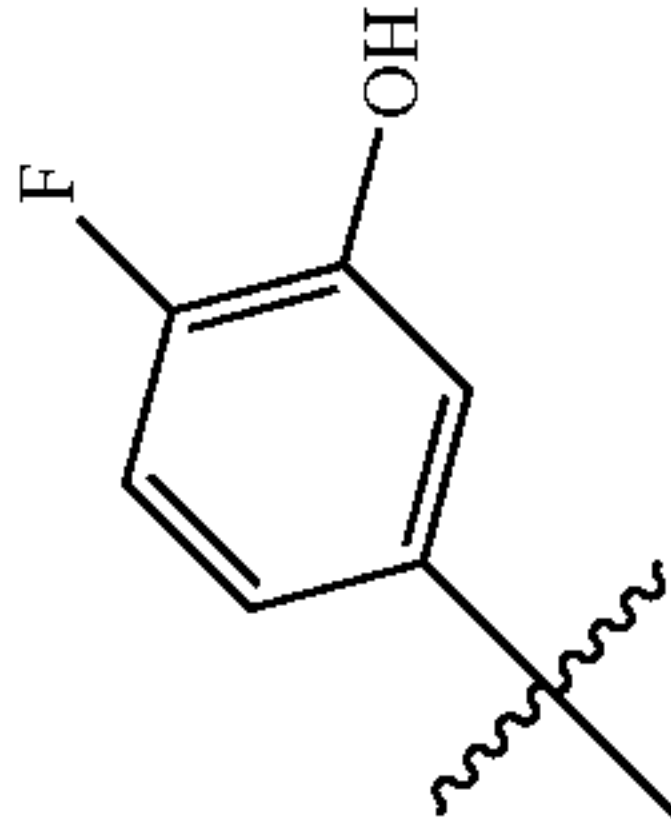
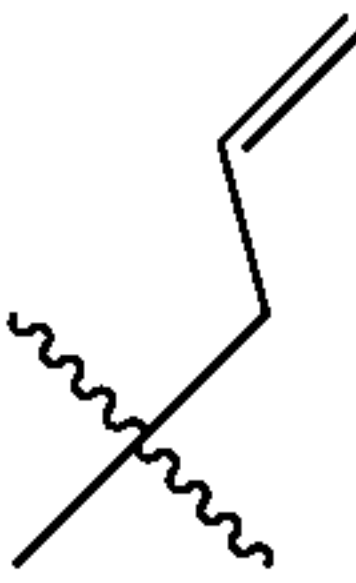
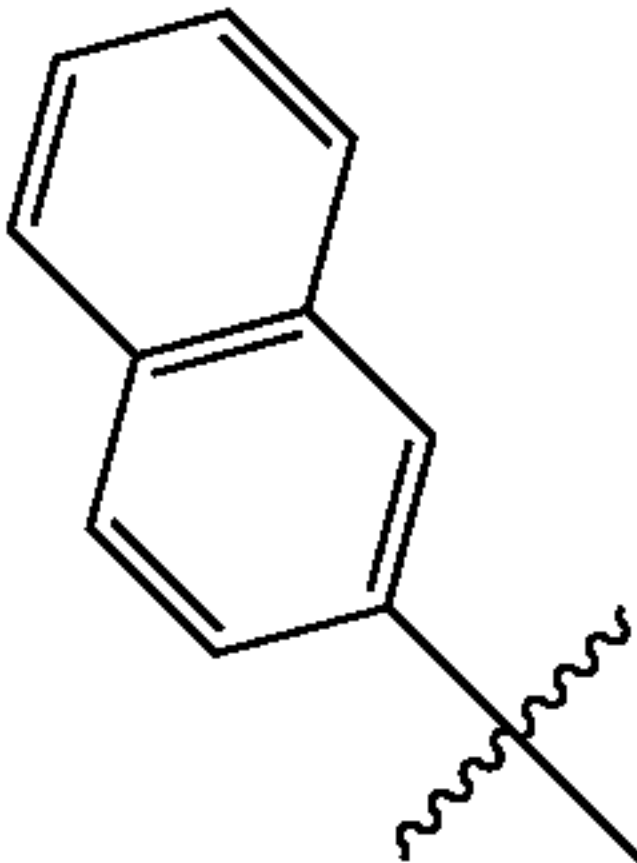
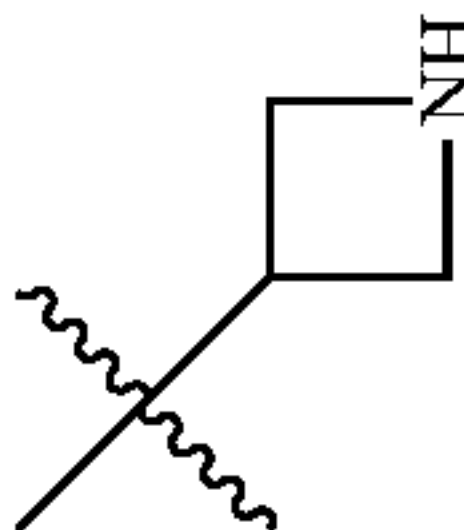
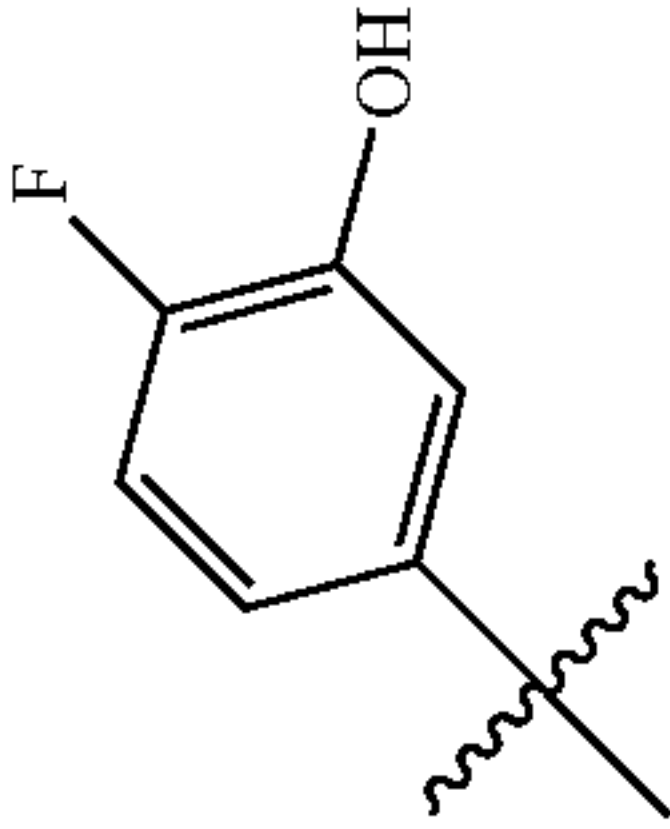
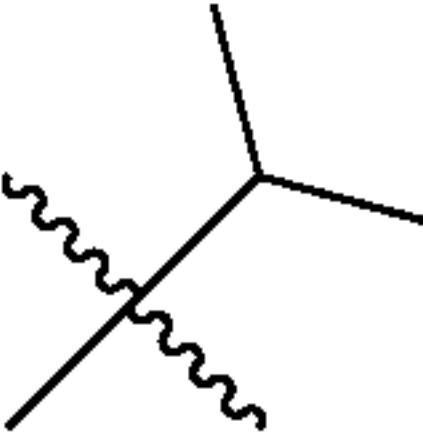
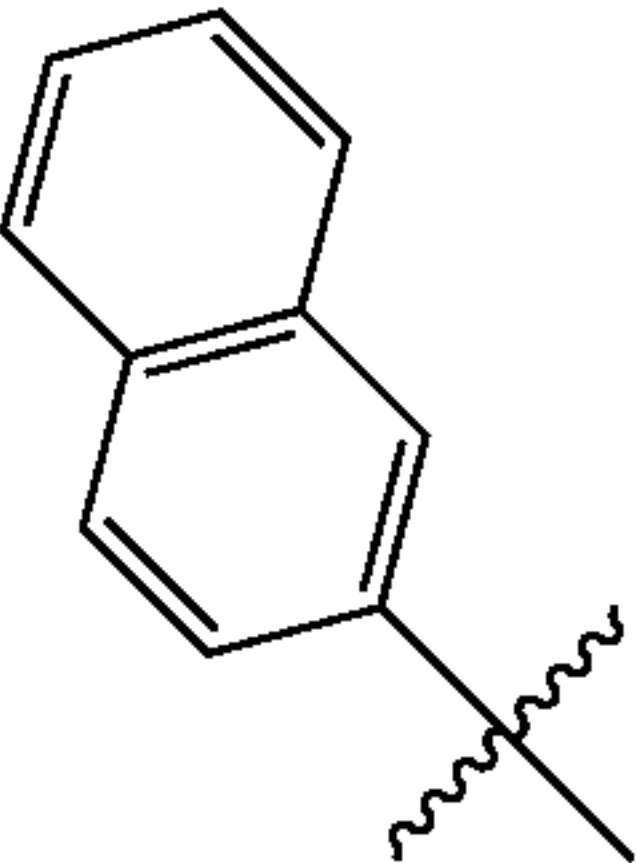
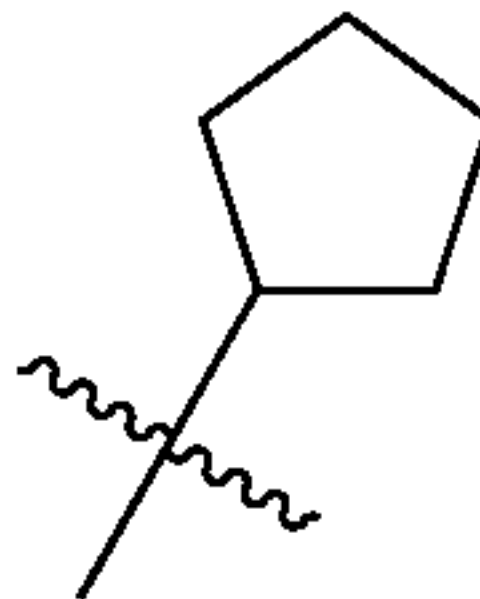
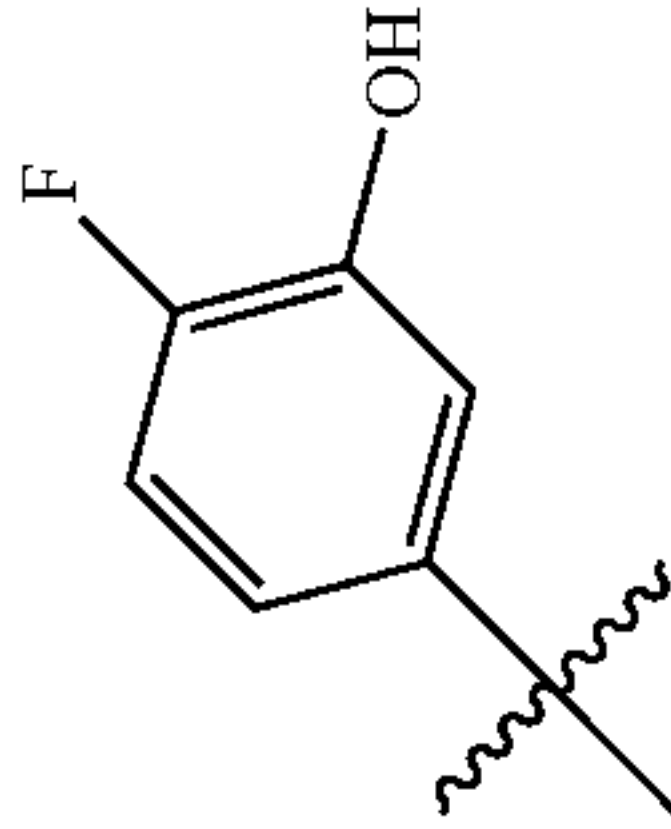
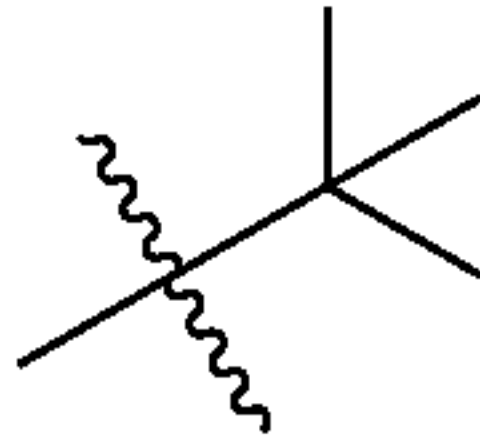
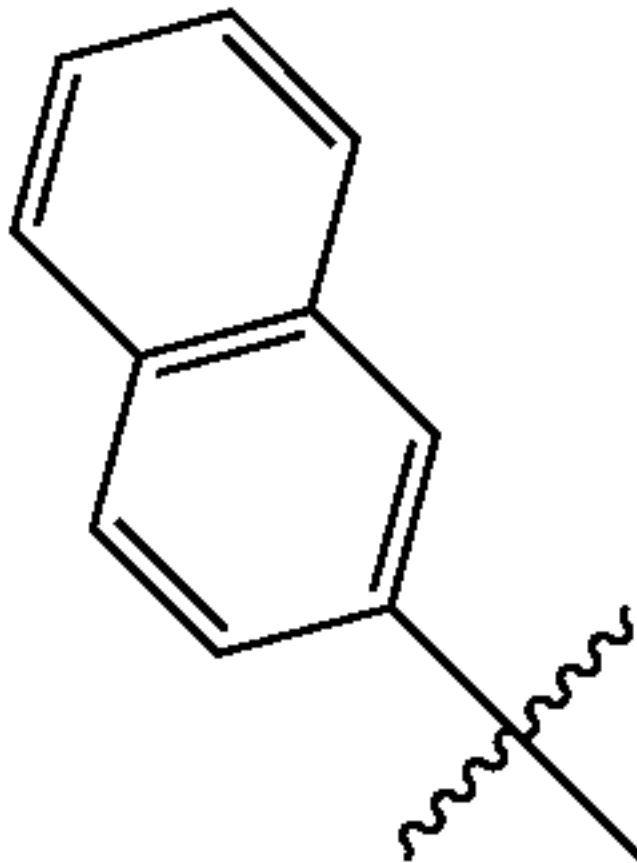
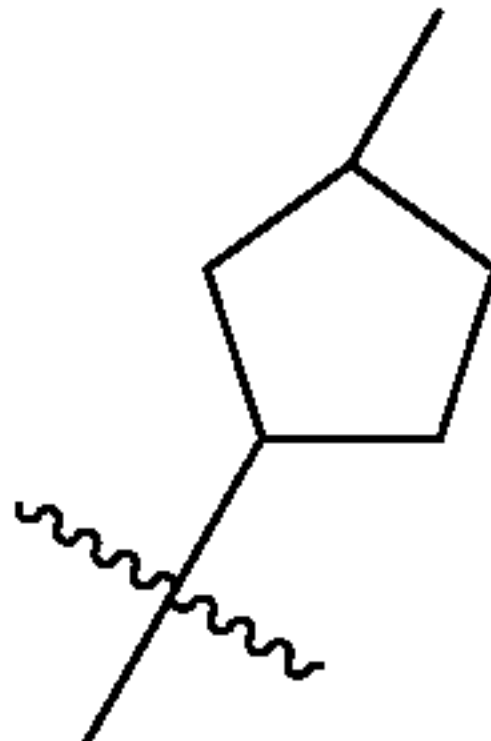
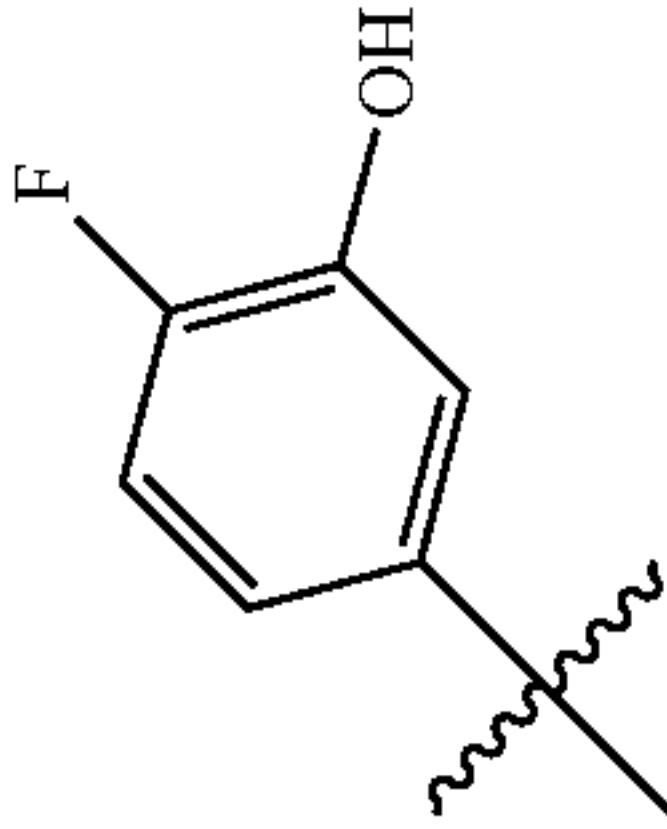
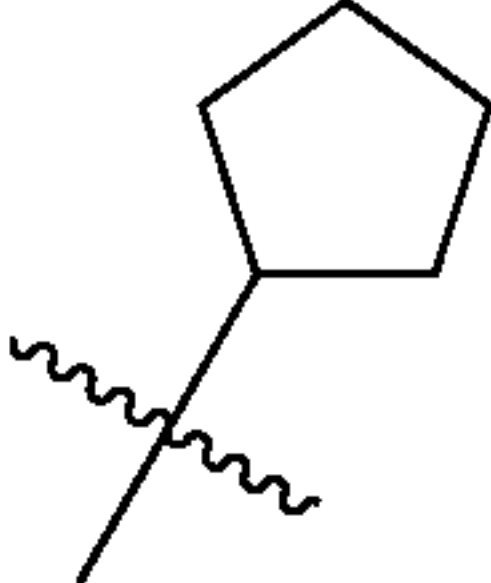
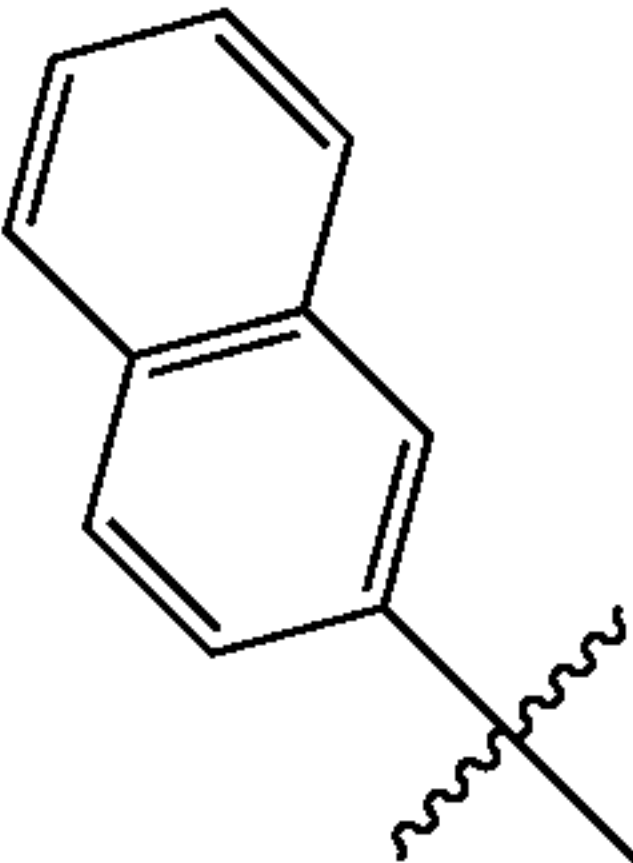
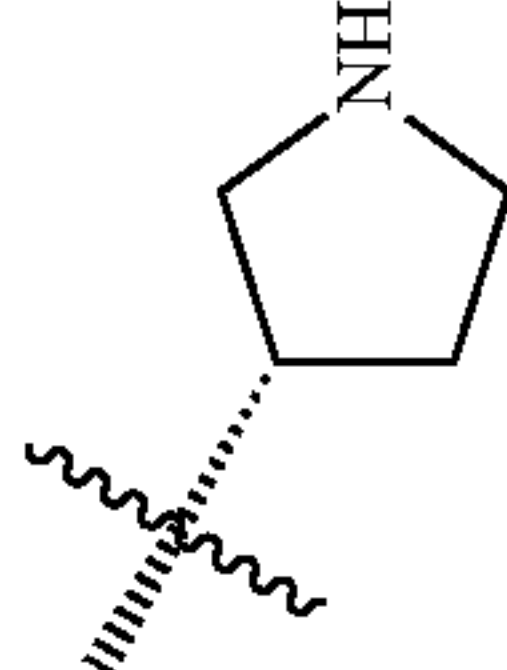
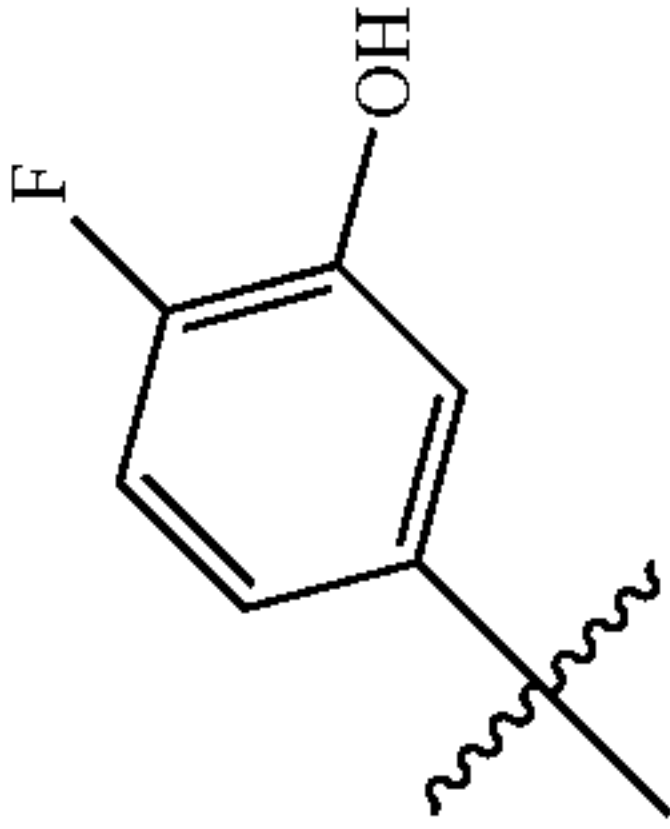
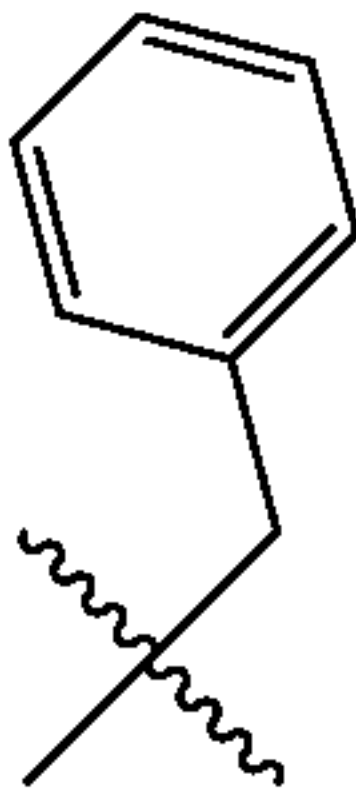
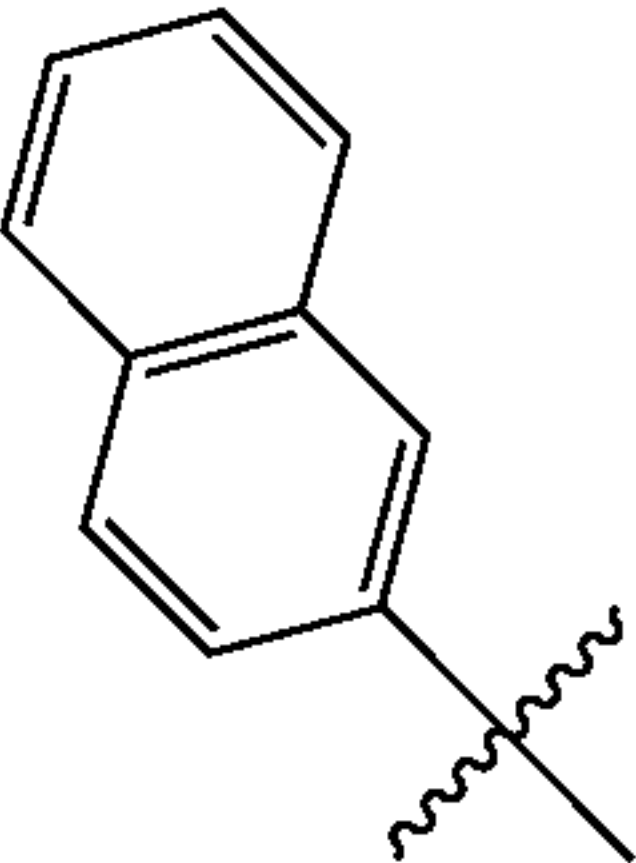
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK461			ZK159		
ZK413			ZK156		
ZK379			KS63		
ZK421			ZK158		
ZK403			ZK147		

TABLE 1-continued

Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK405			ZK155		
ZK432			ZK162		
ZK434			ZK165		
ZK465			ZK161		
ZK377			ZK167		

TABLE 1-continued

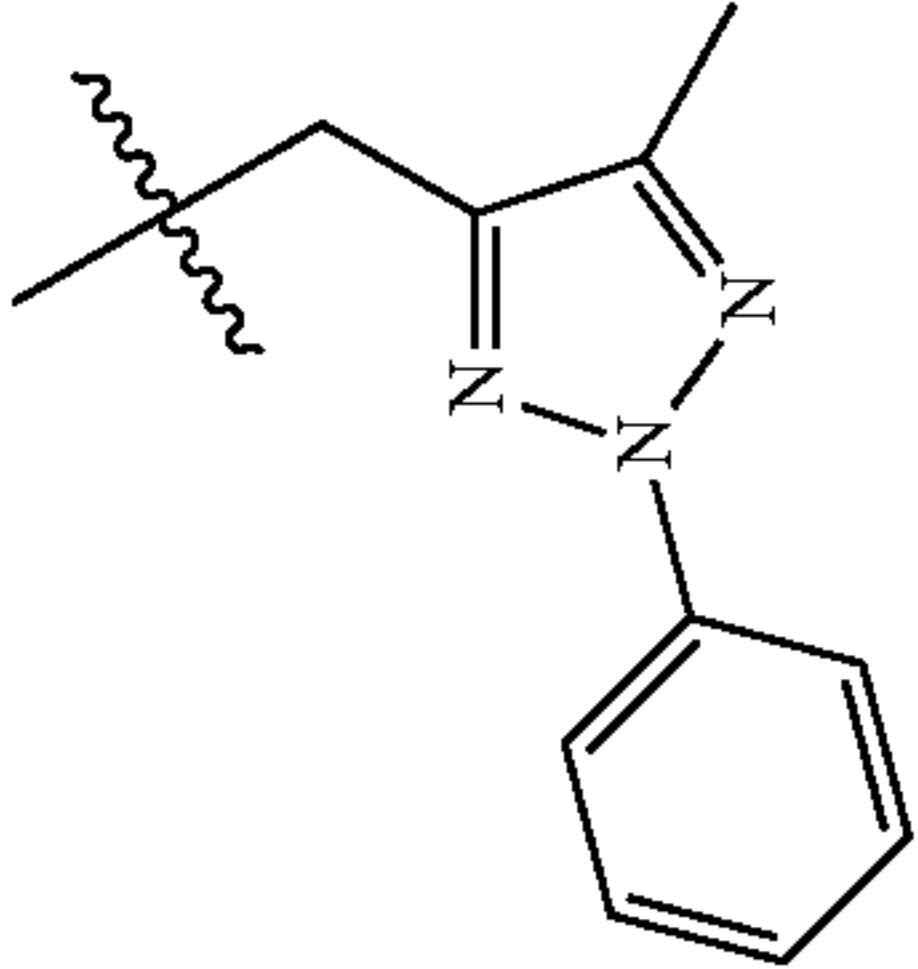
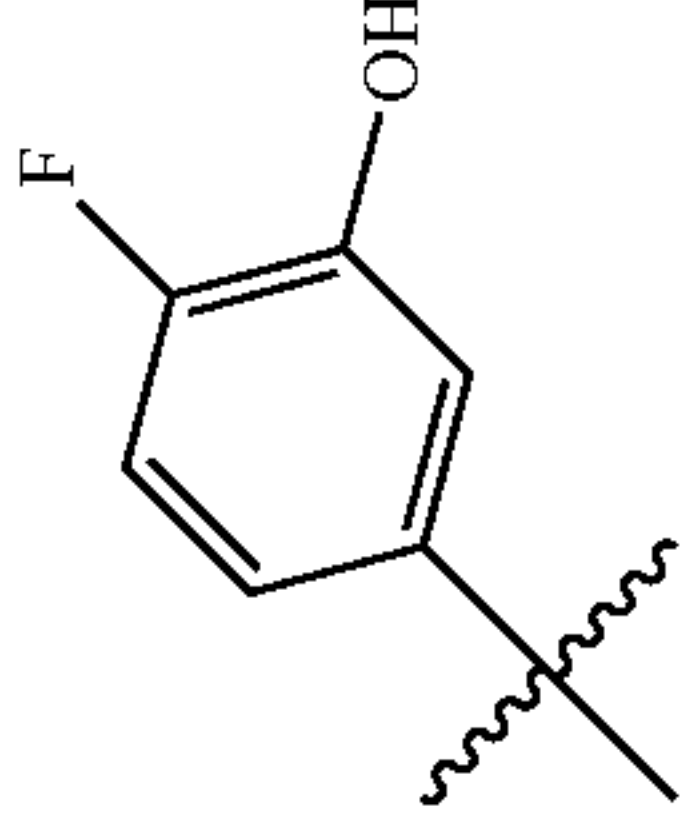
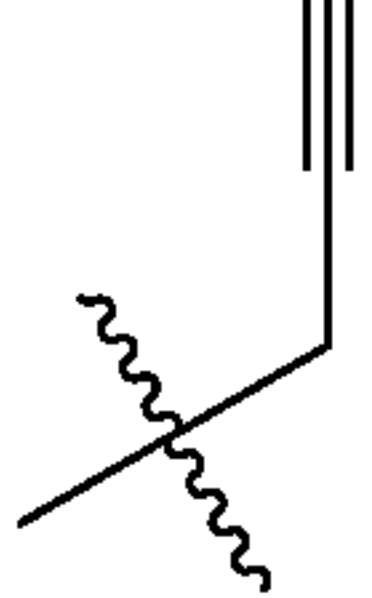
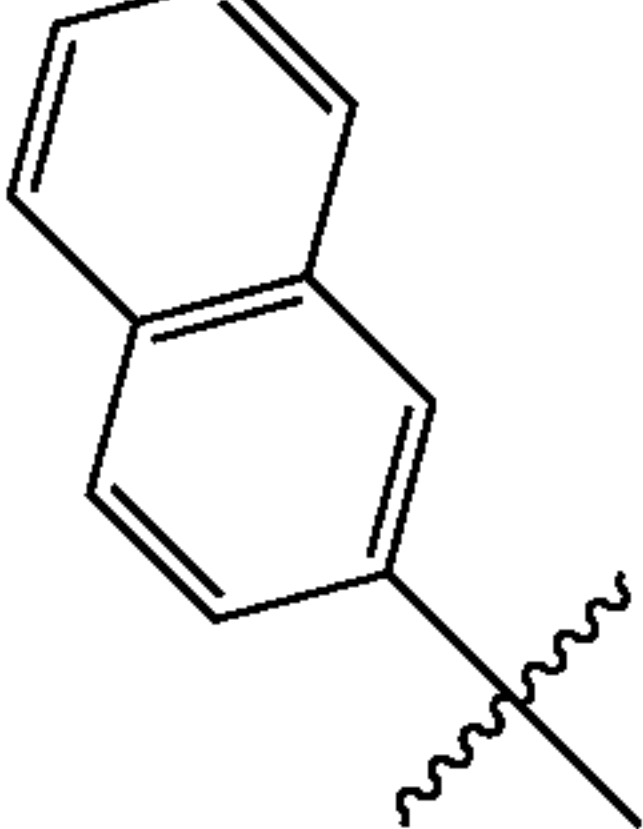
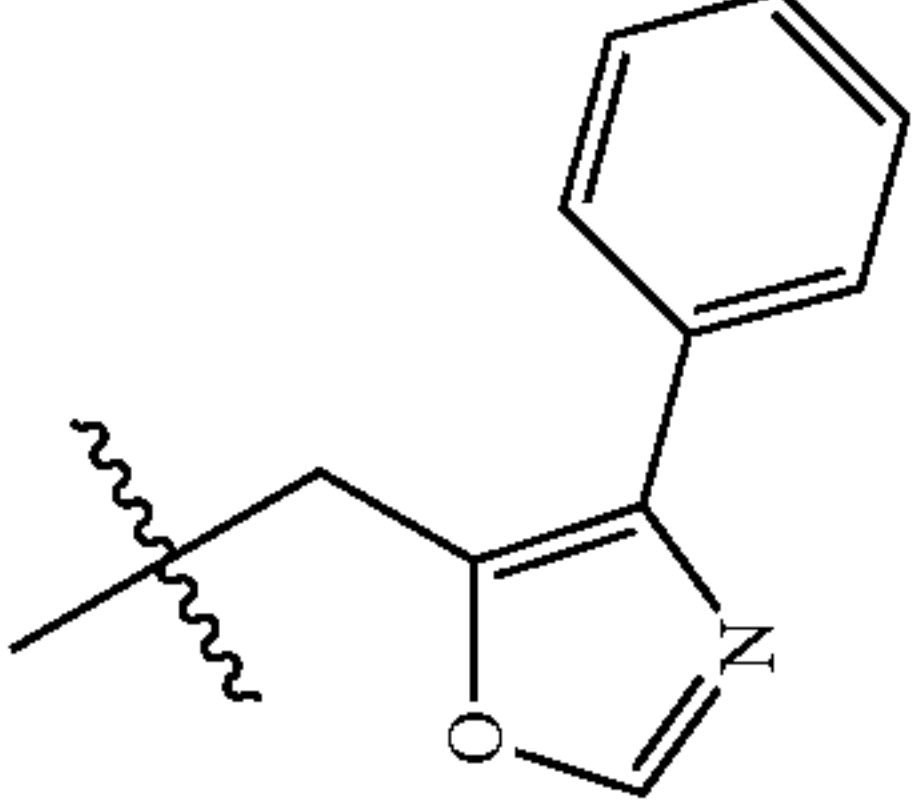
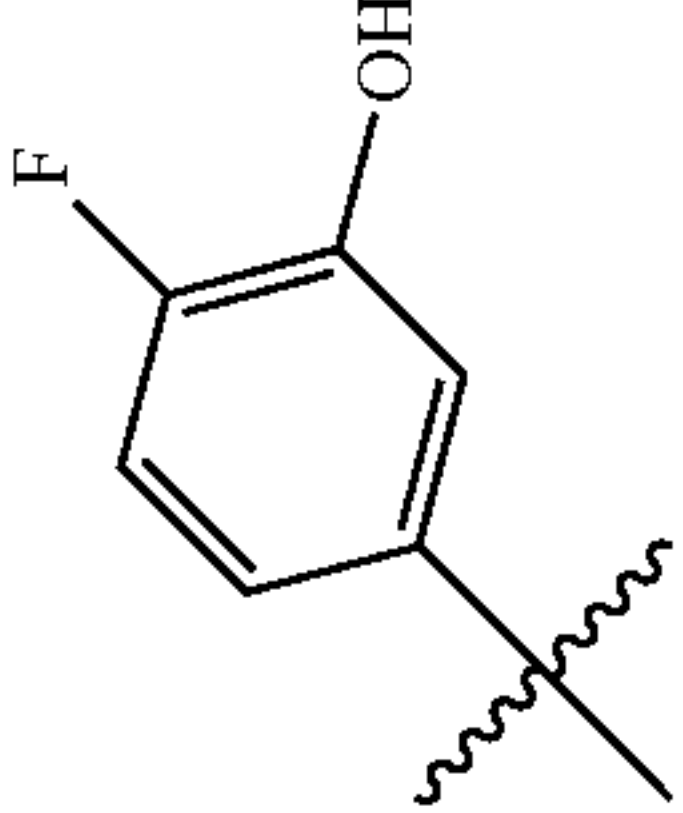
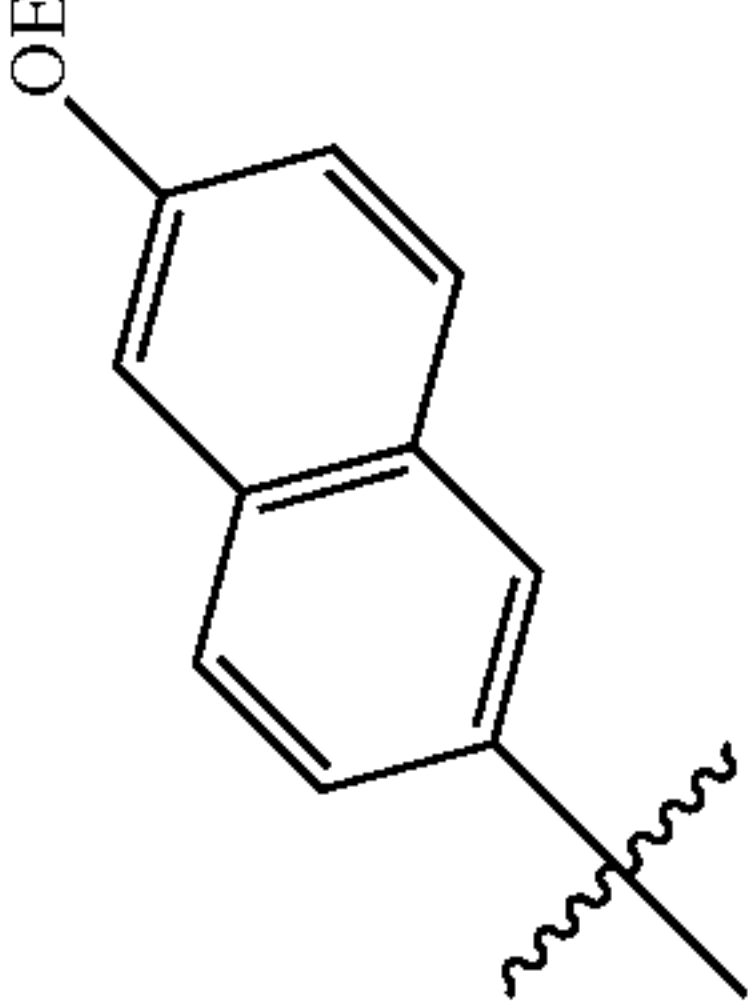
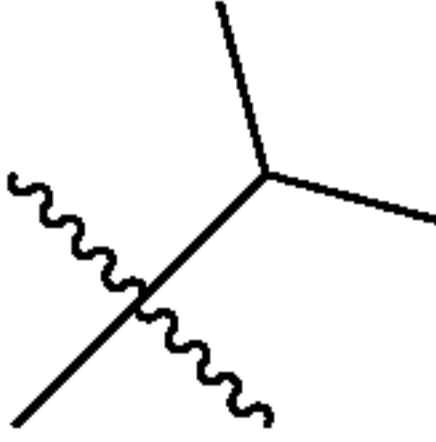
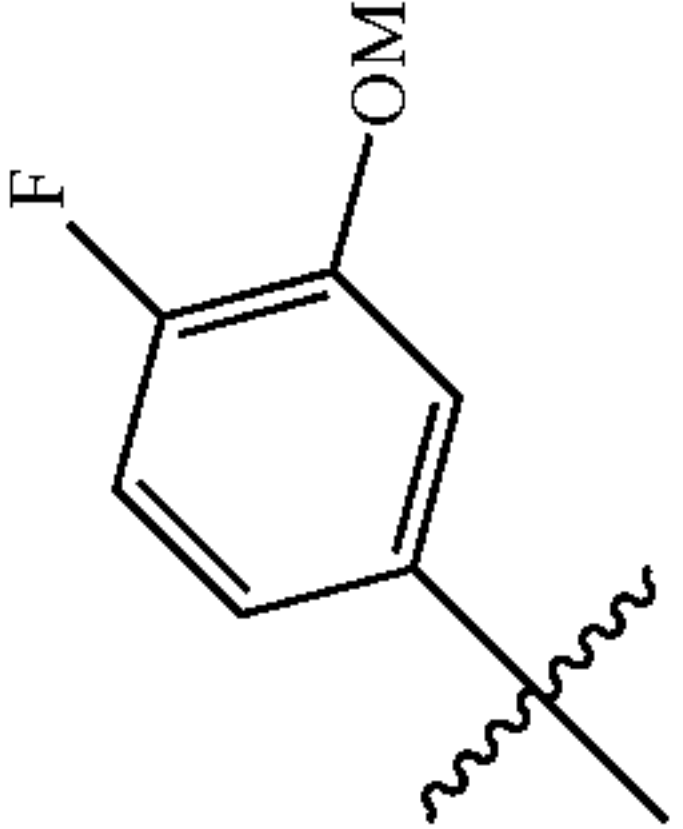
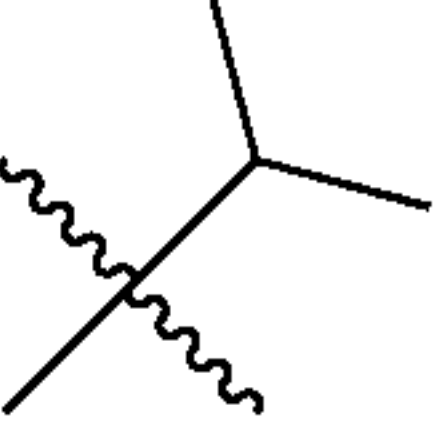
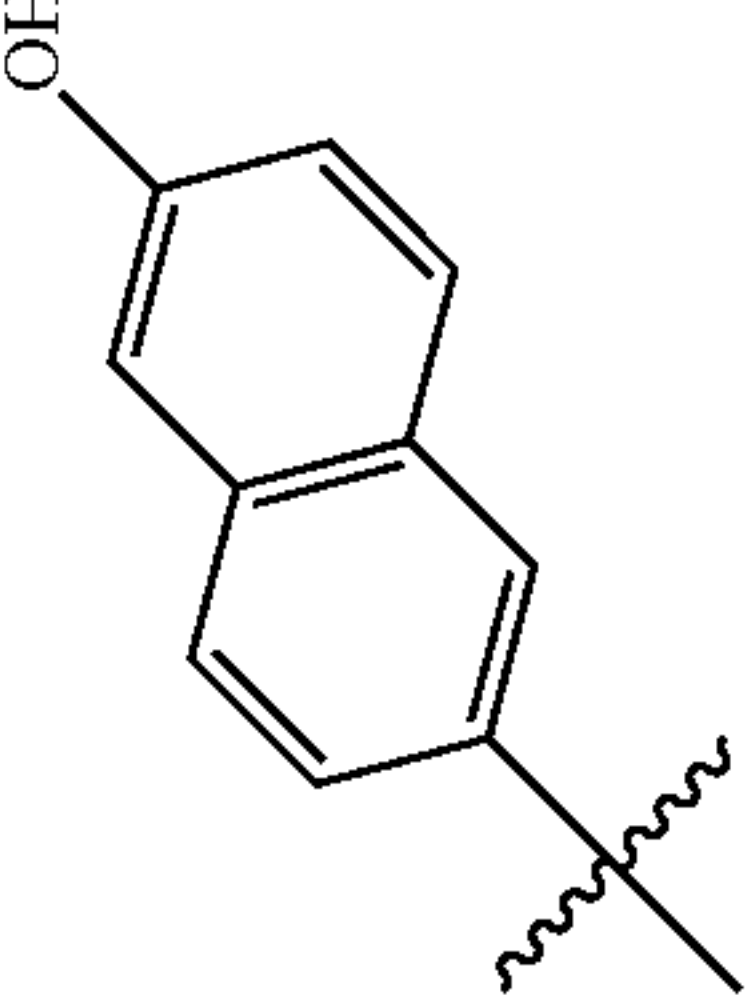
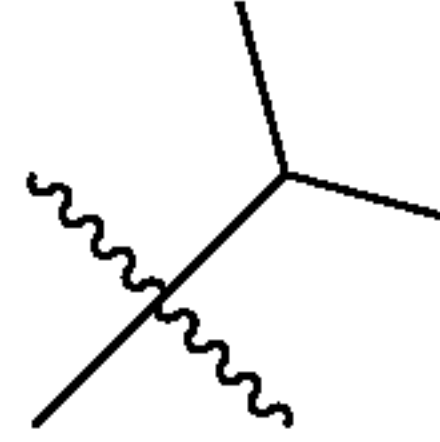
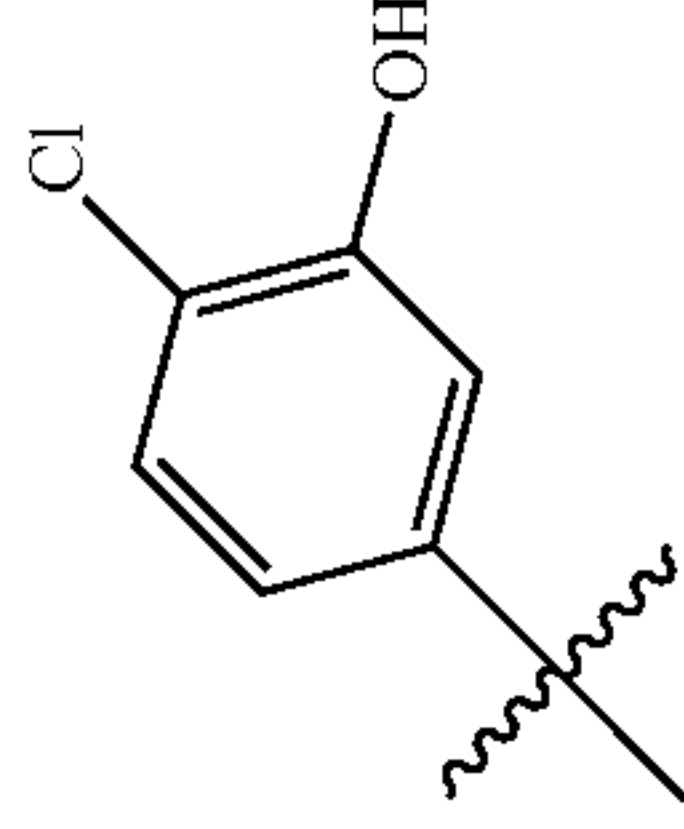
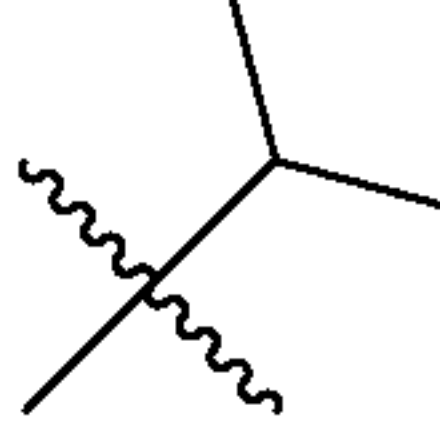
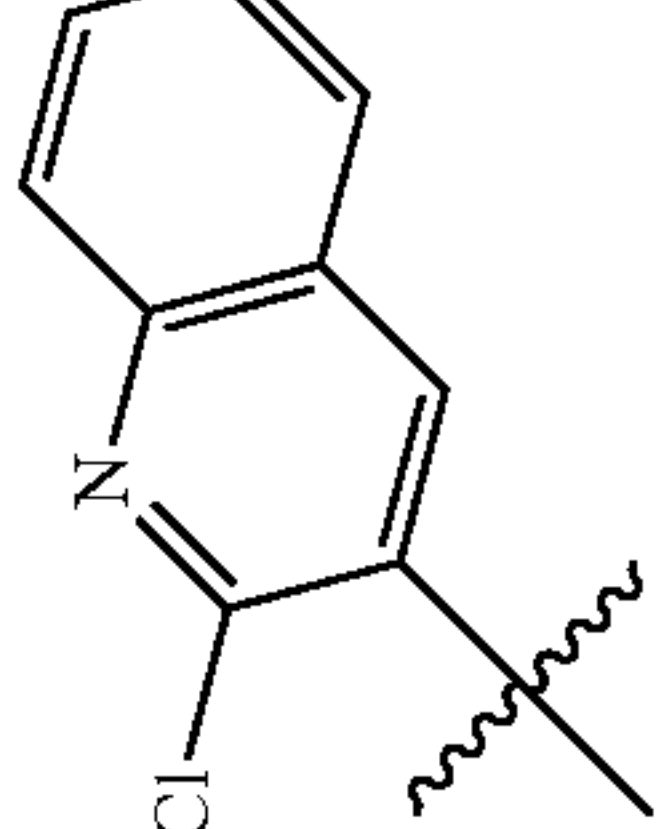
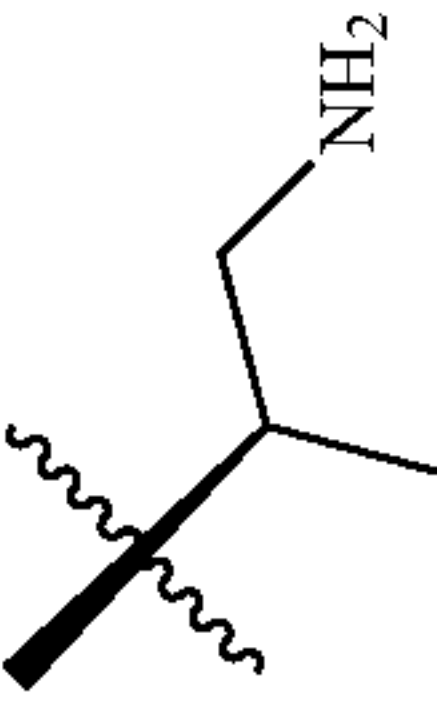
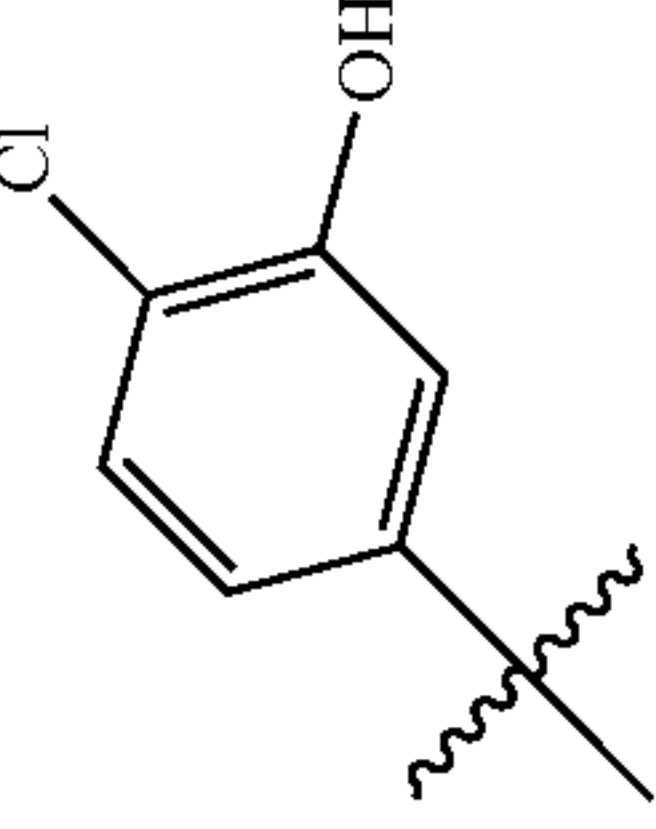
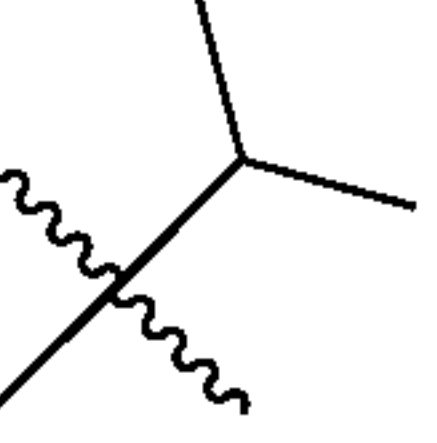
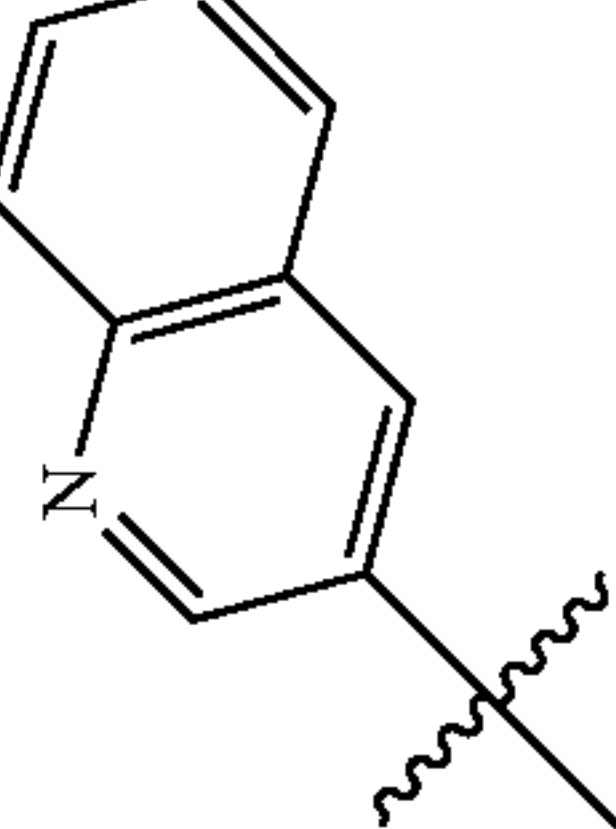
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ZK401			BA116		
BA62			BA17		
ZK358			BA134		
ZK452			BA105		

TABLE 1-continued

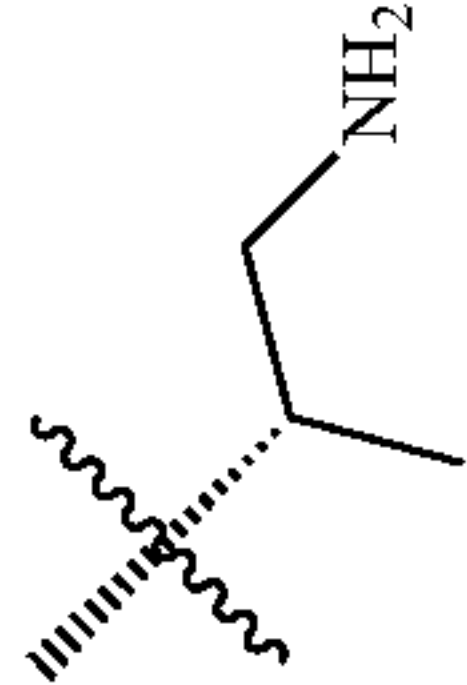
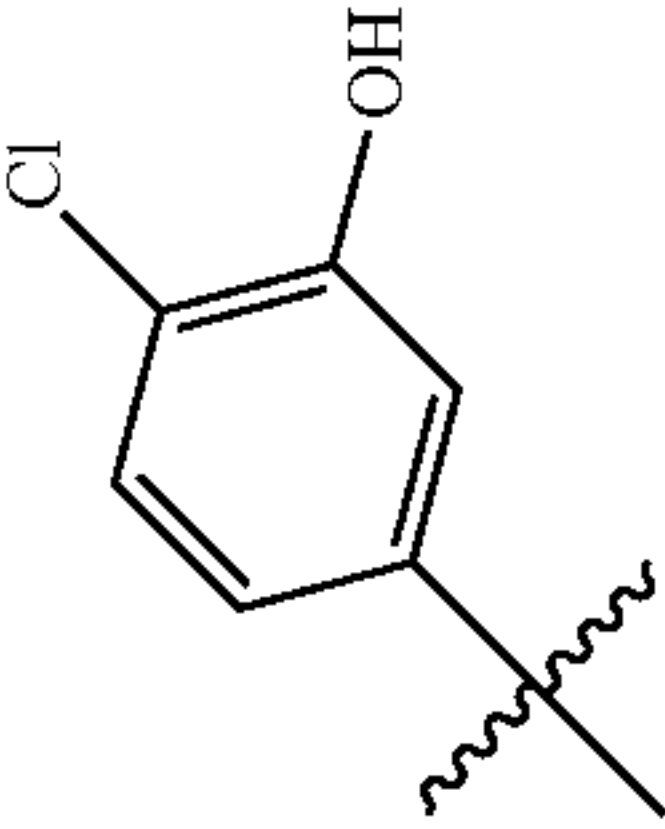
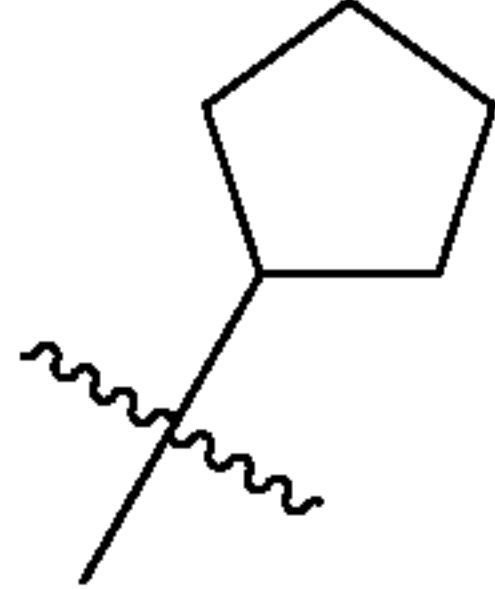
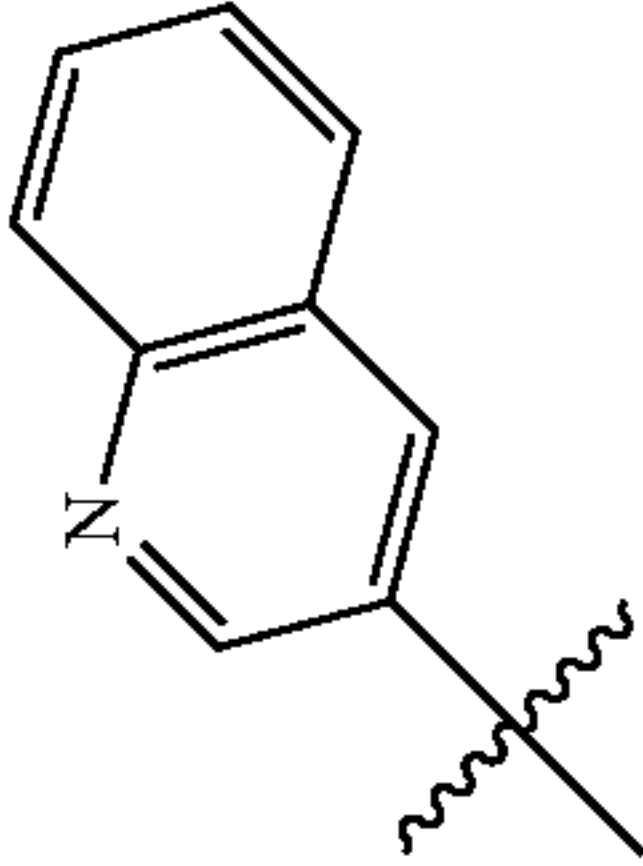
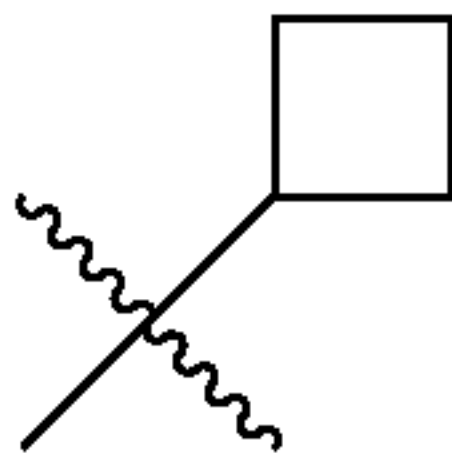
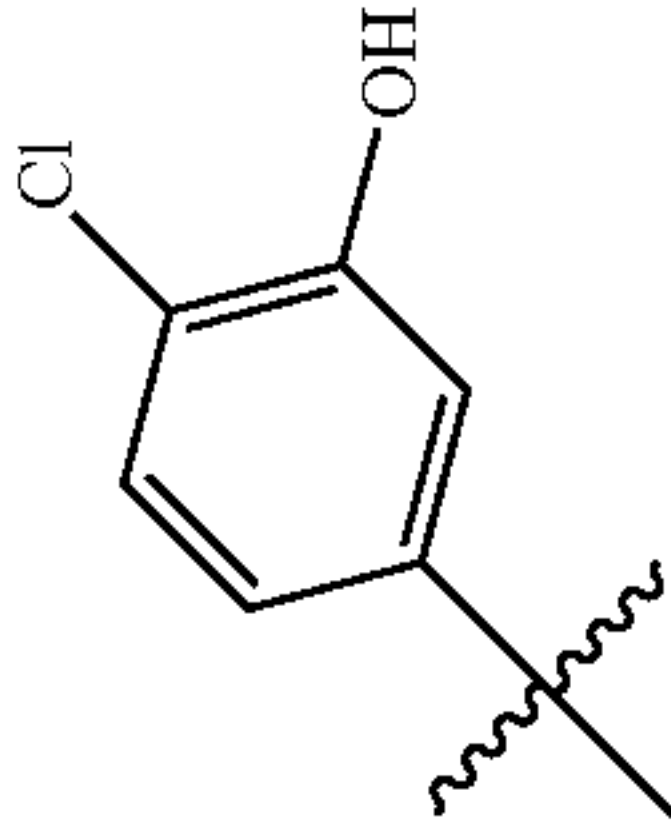
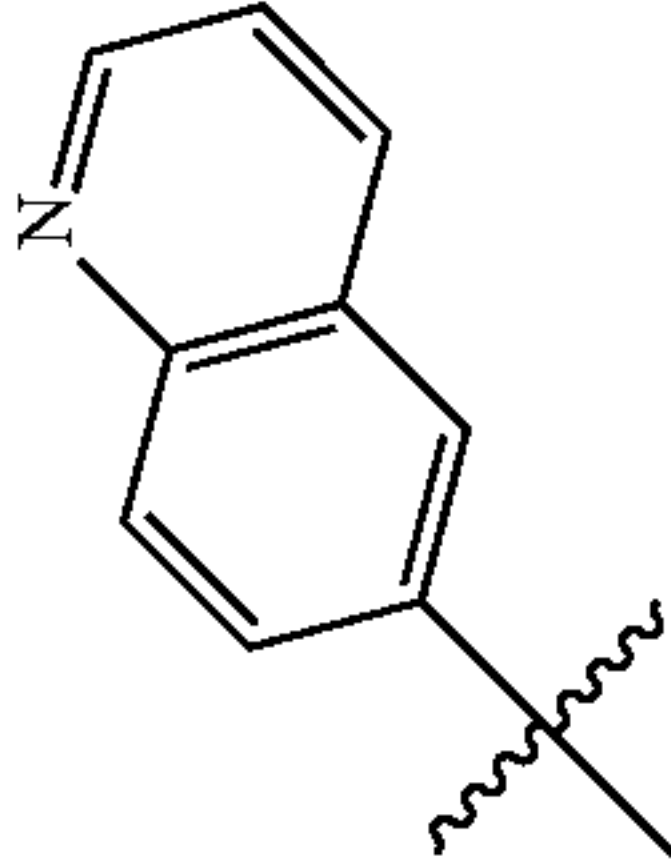
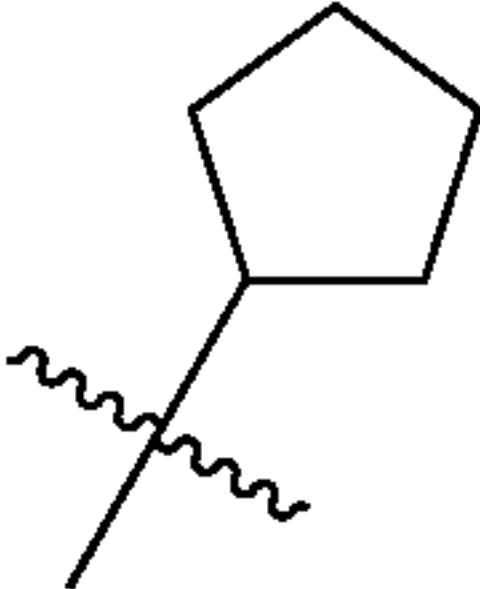
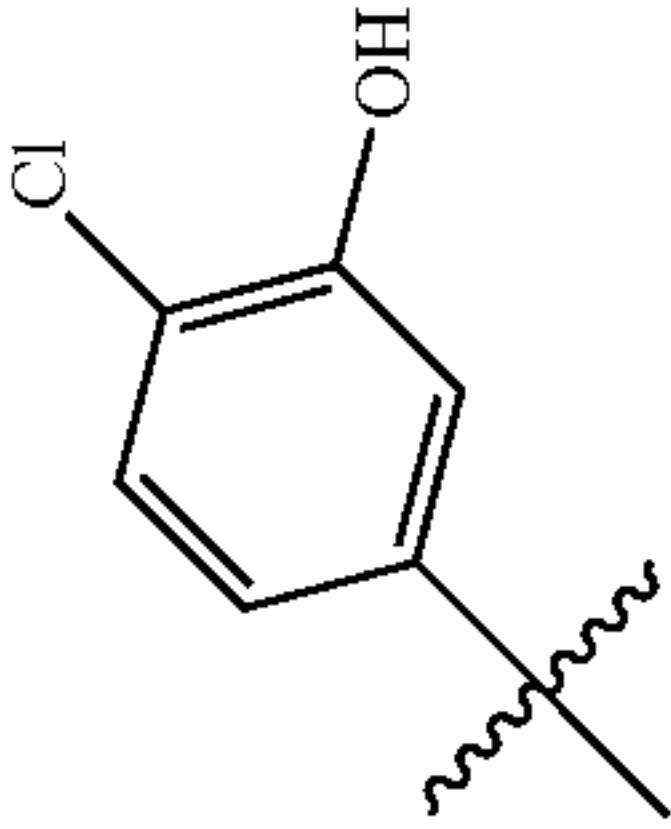
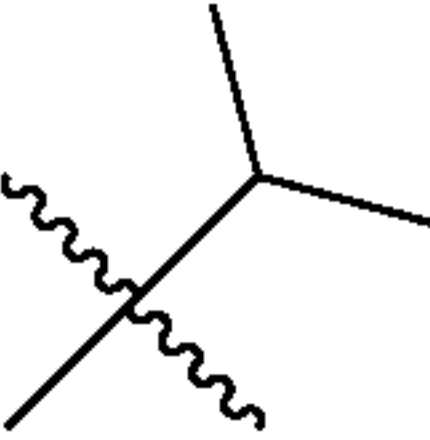
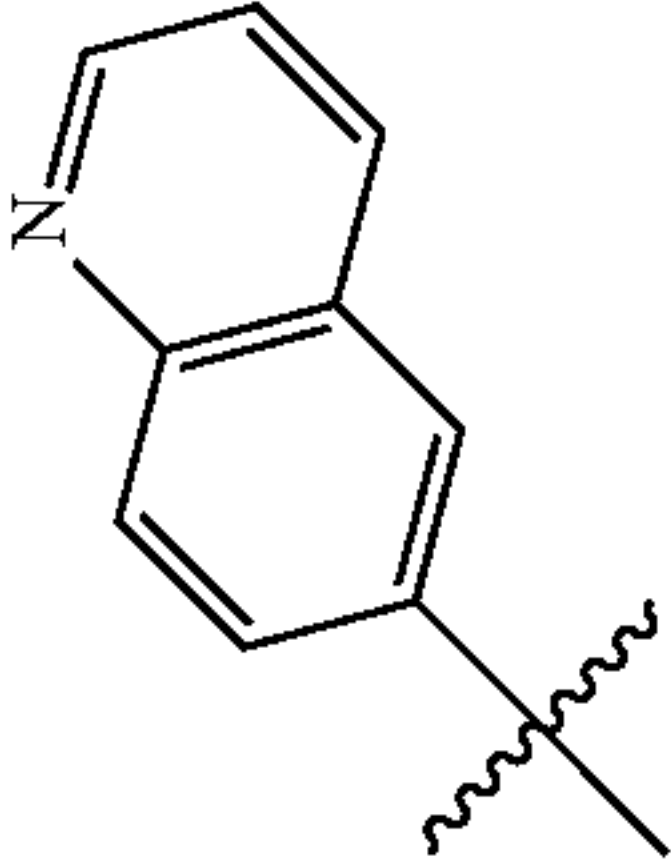
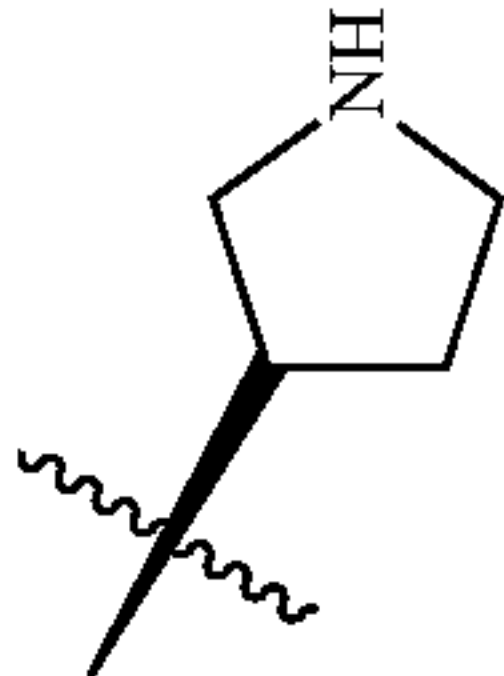
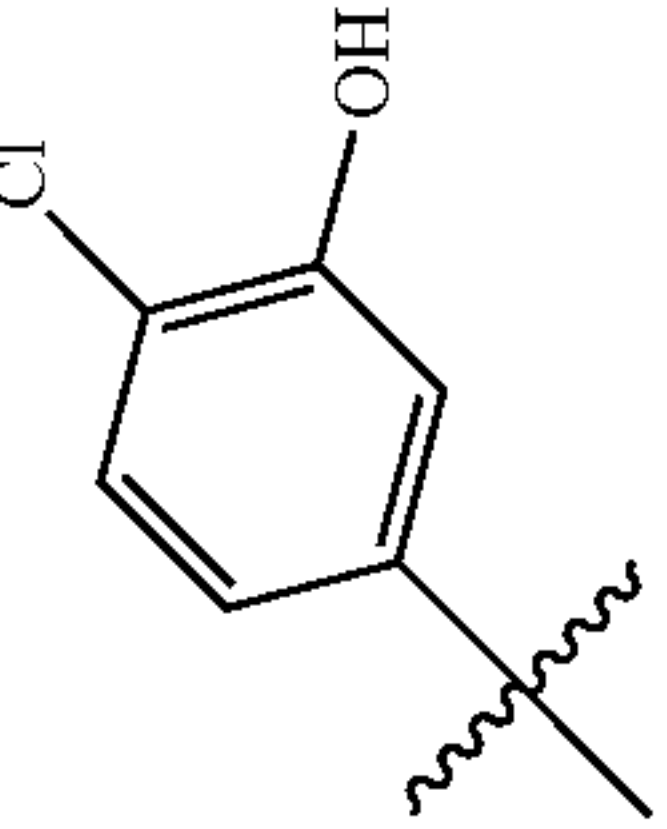
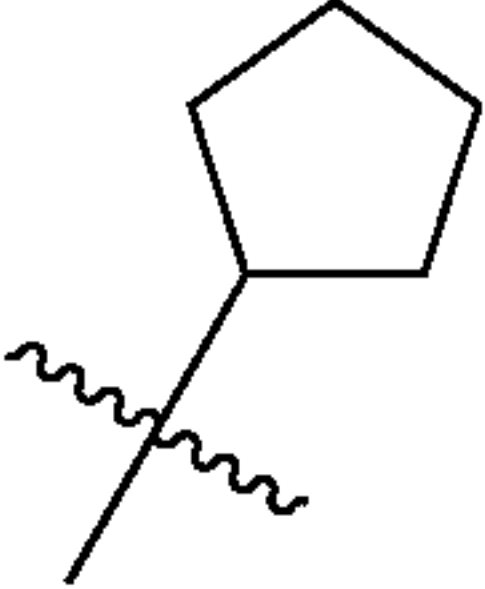
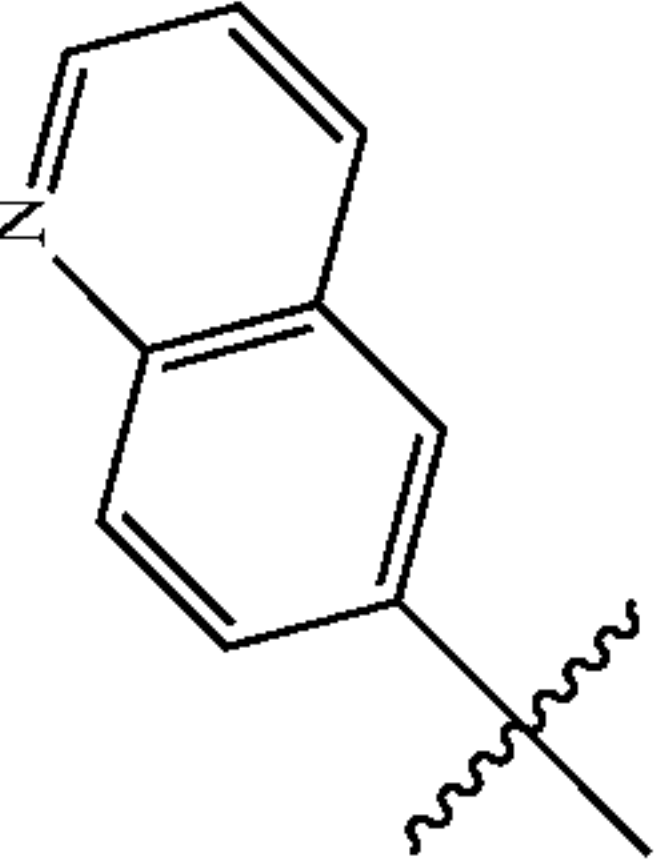
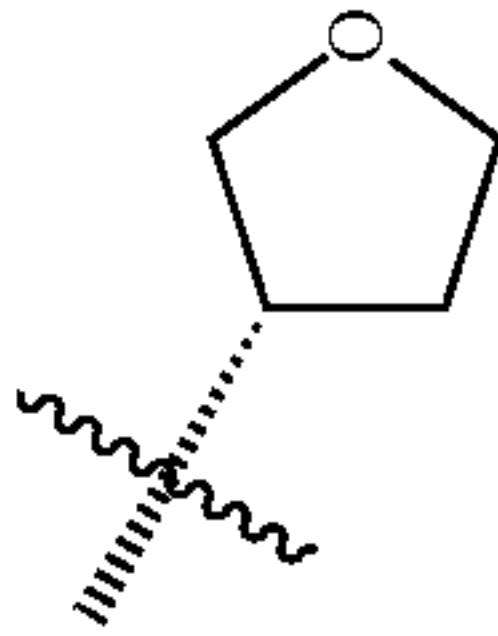
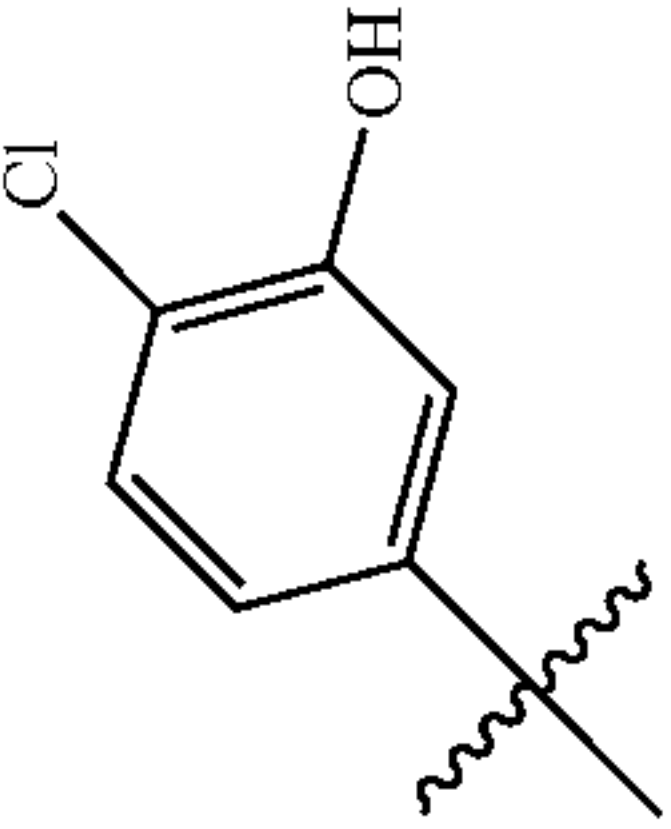
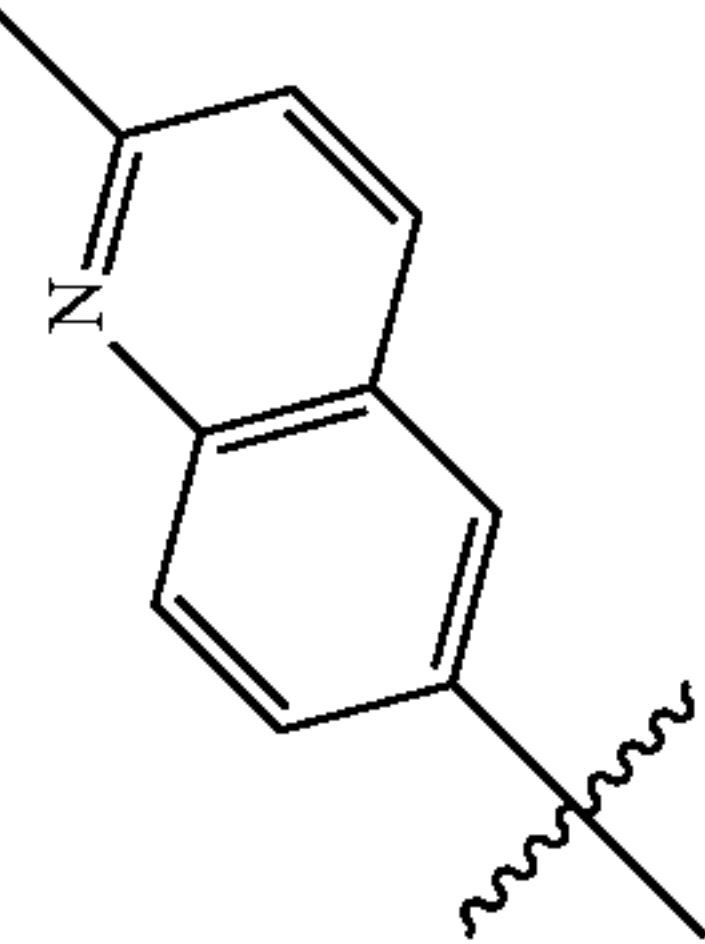
Cpd	R ¹	R ²	Cpd	R ¹	R ²
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ZK463			BA111	—Me	
ZK371			BA102		
ZK409			BA112		
ZK428			BA118		

TABLE 1-continued

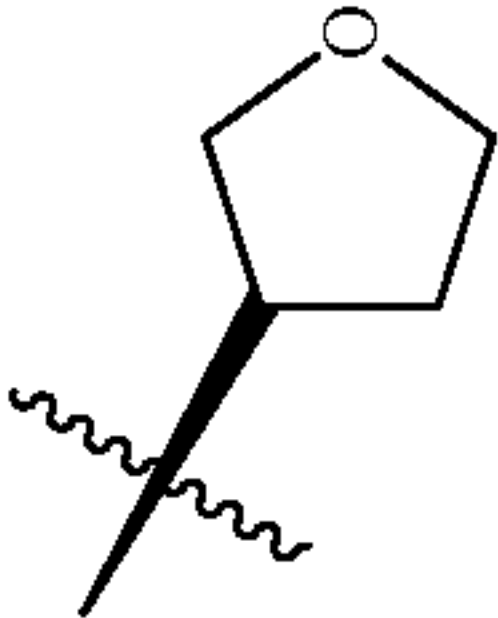
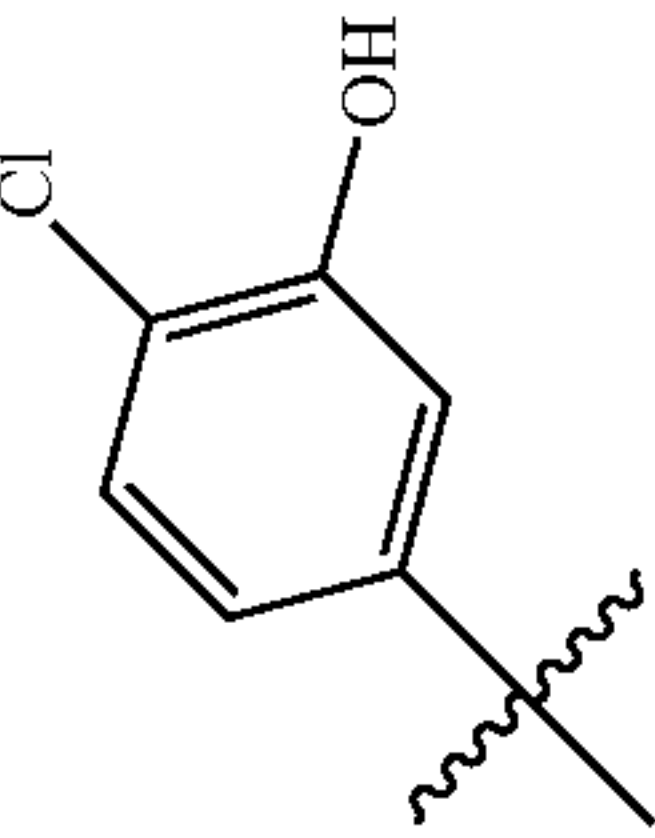
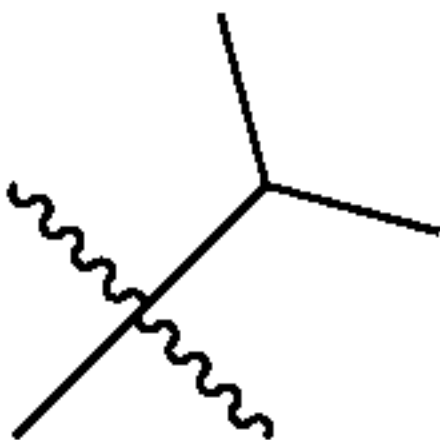
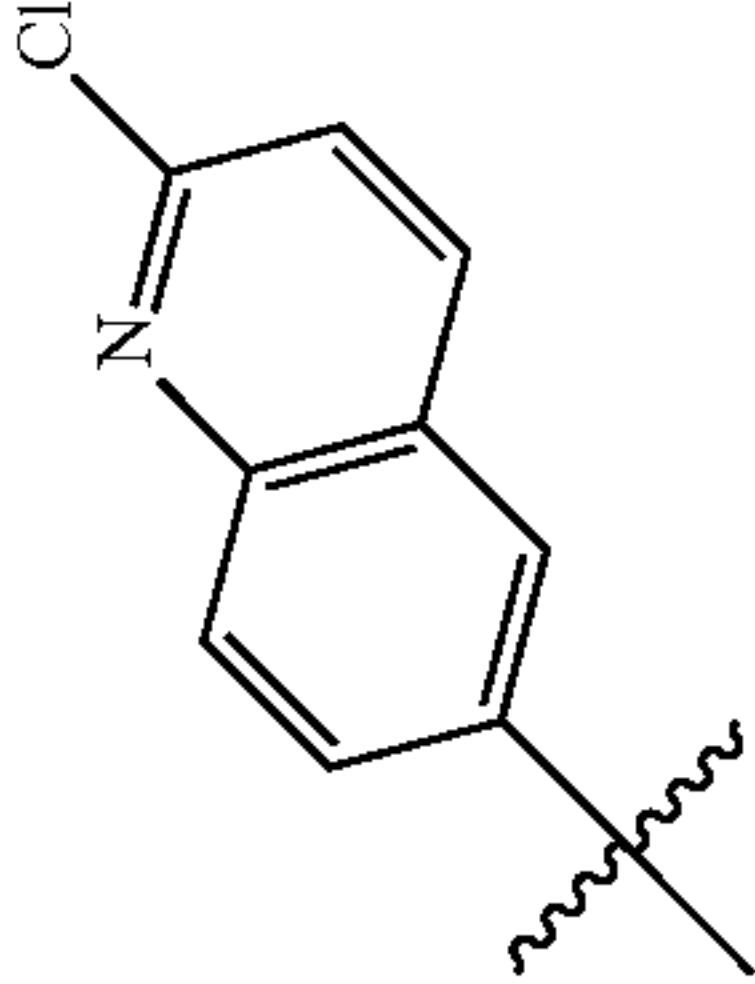
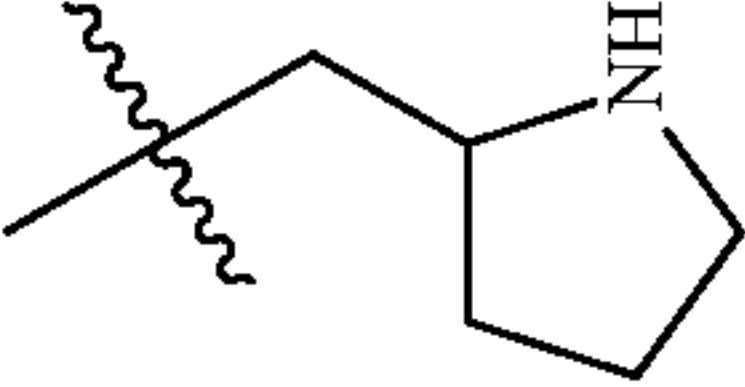
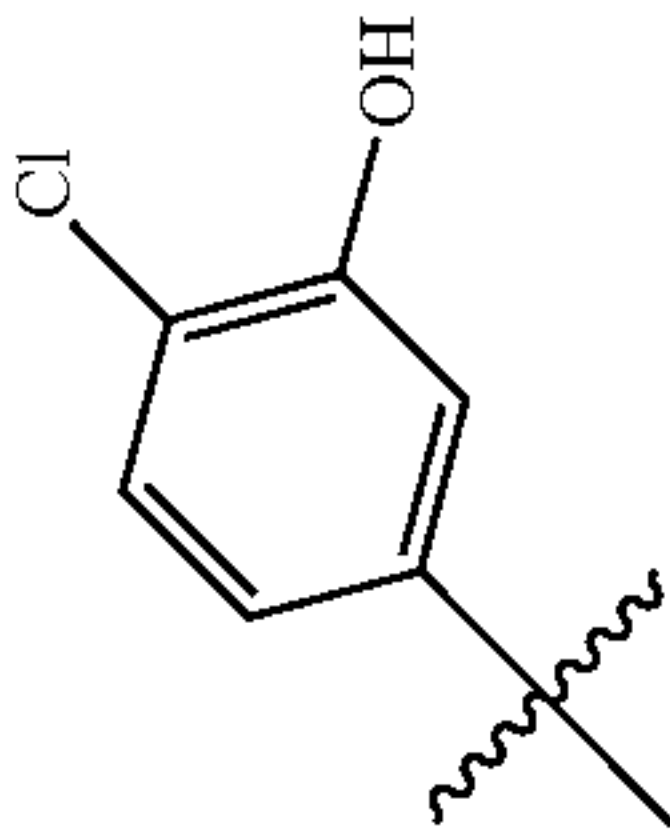
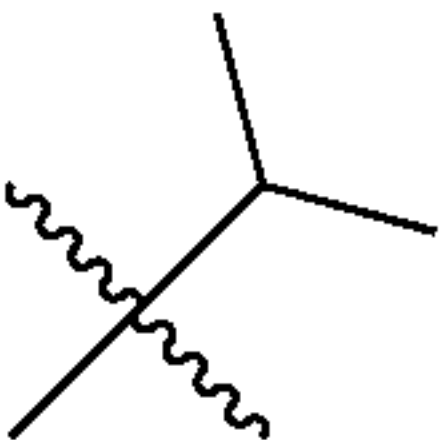
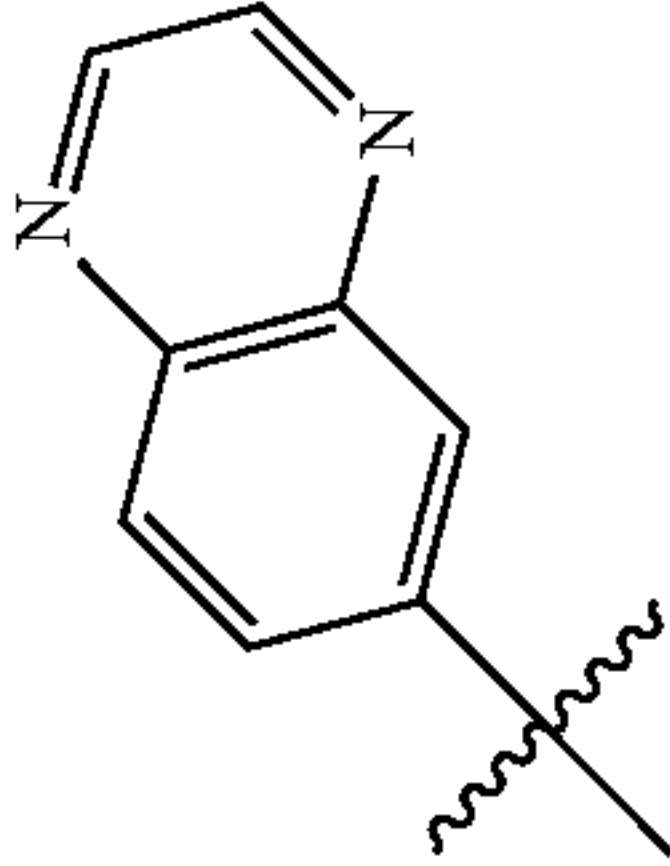
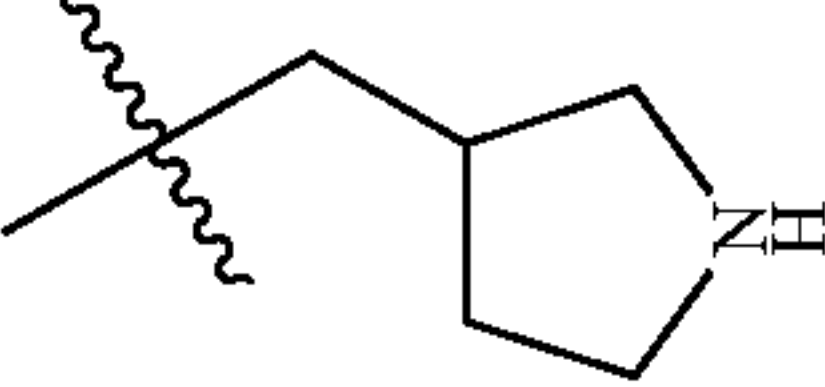
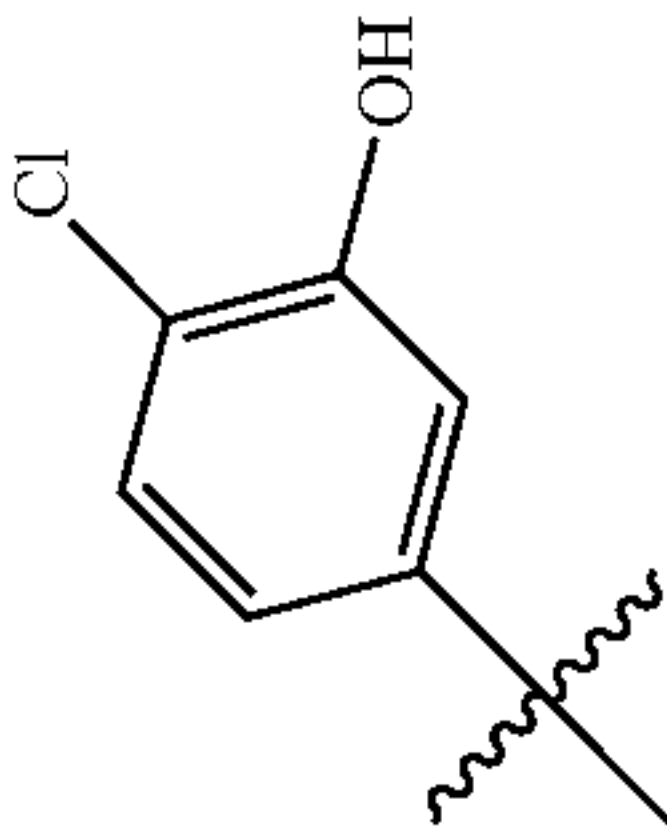
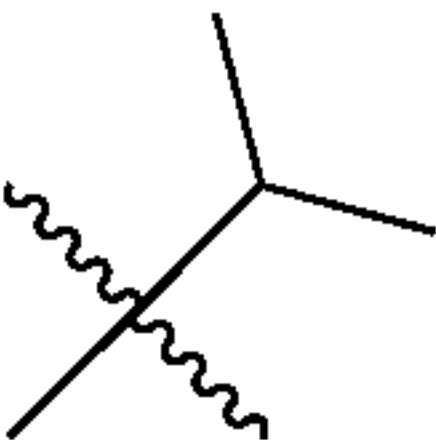
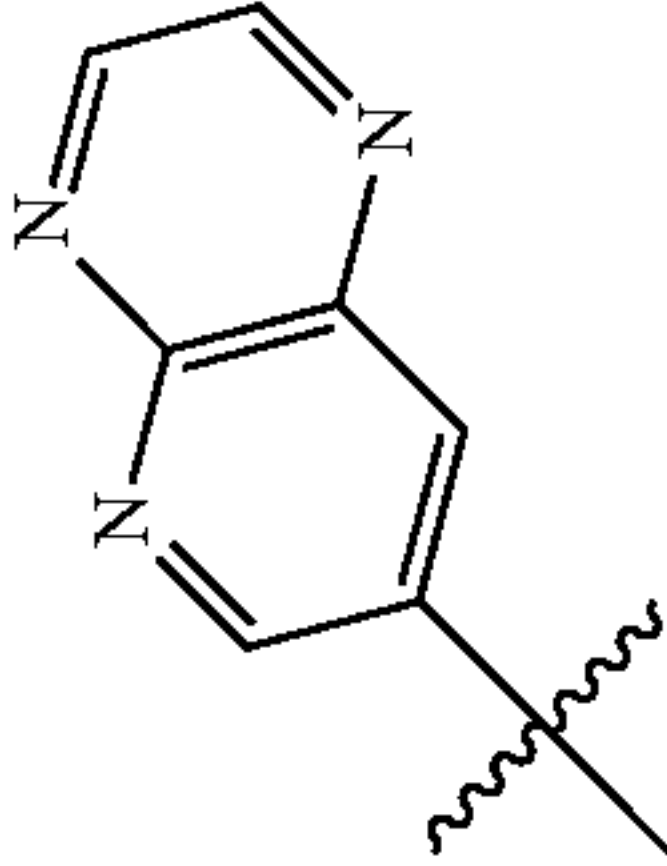
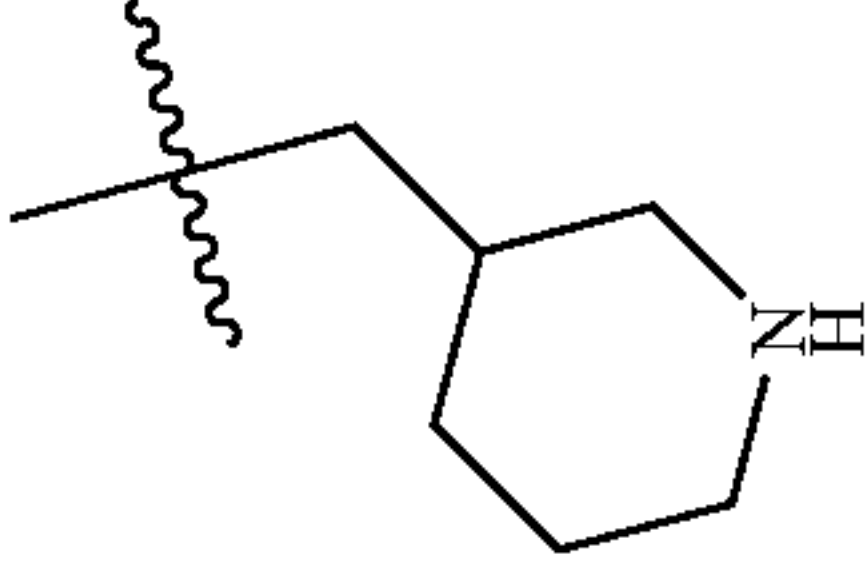
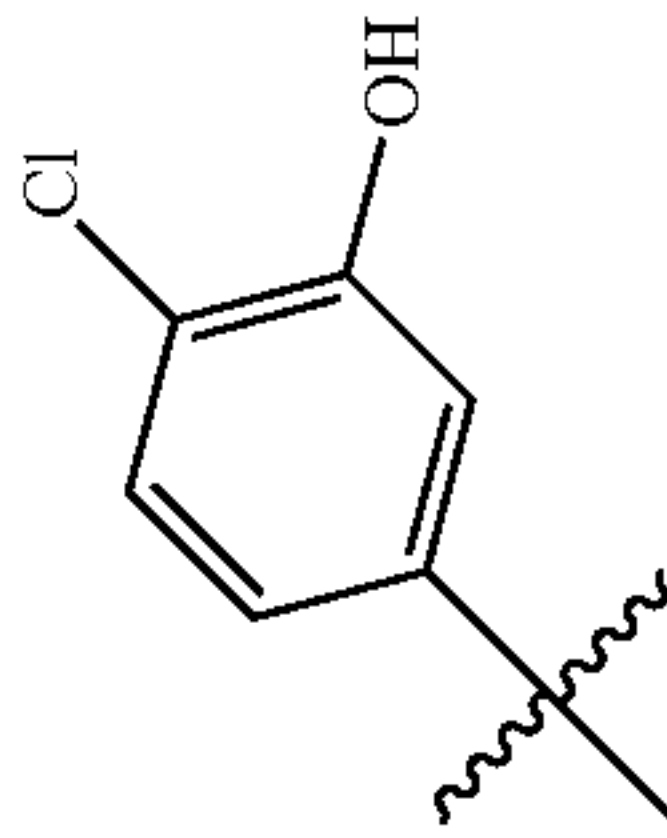
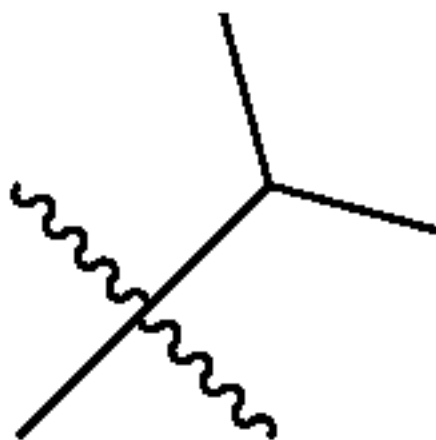
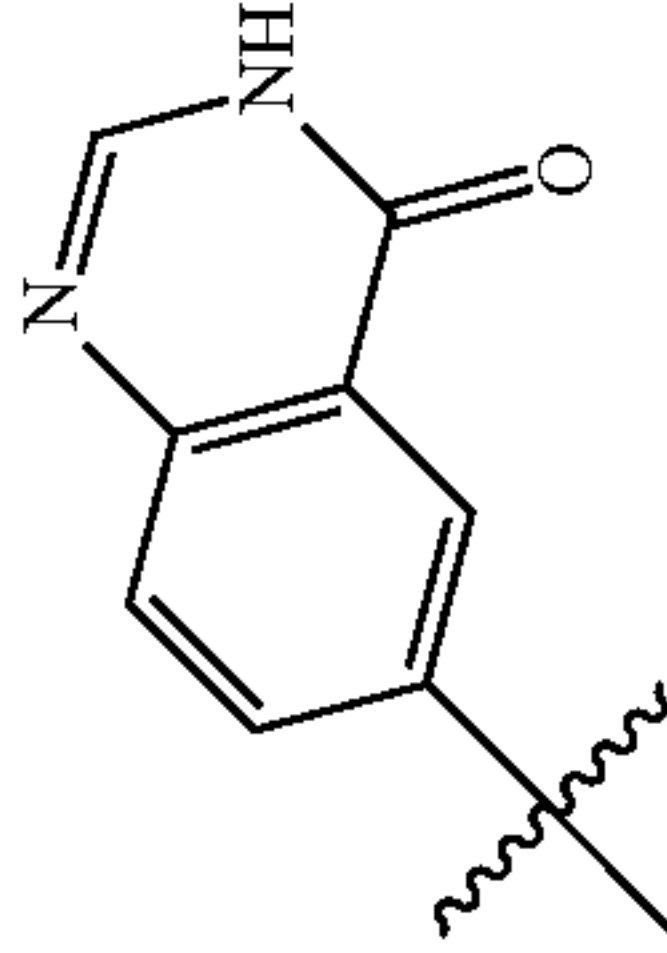
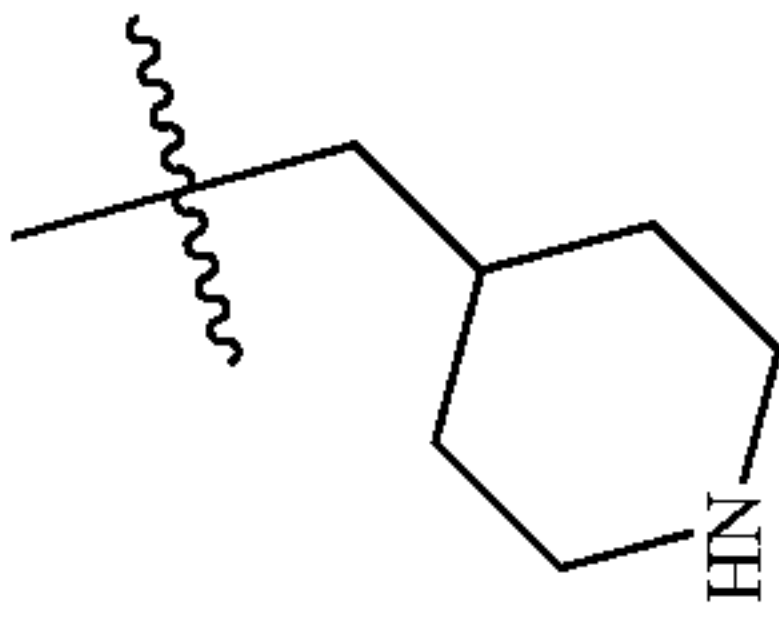
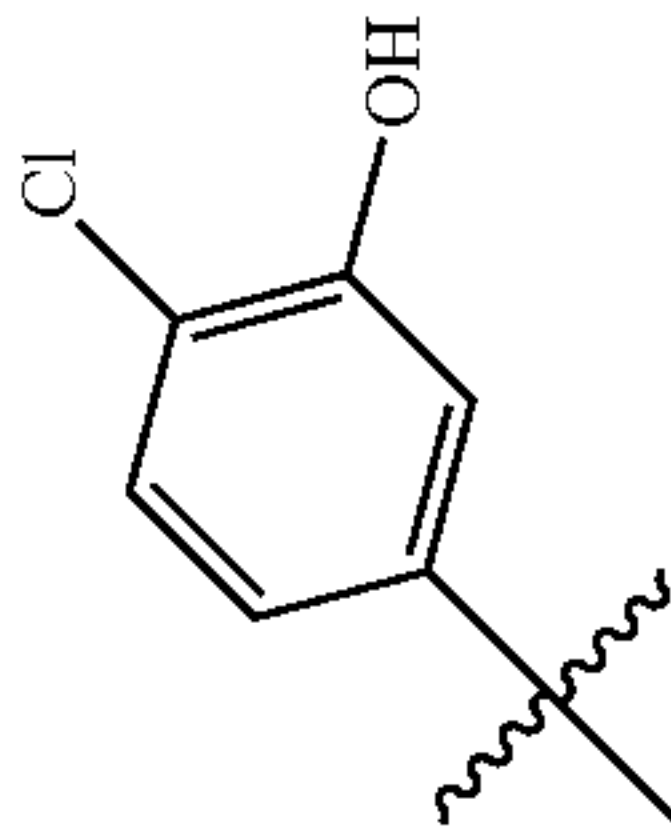
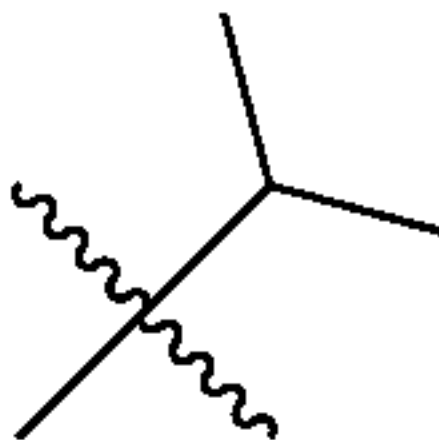
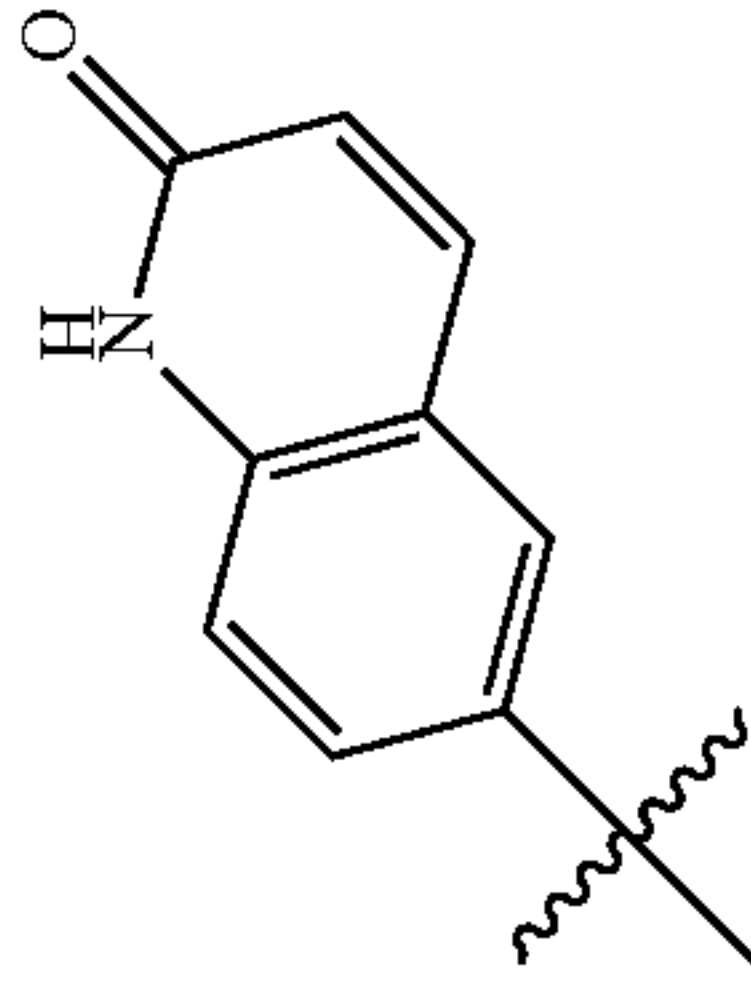
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK430			BA130		
ZK387			BA132		
ZK389			BA139		
ZK369			BA158		
ZK385			BA140		

TABLE 1-continued

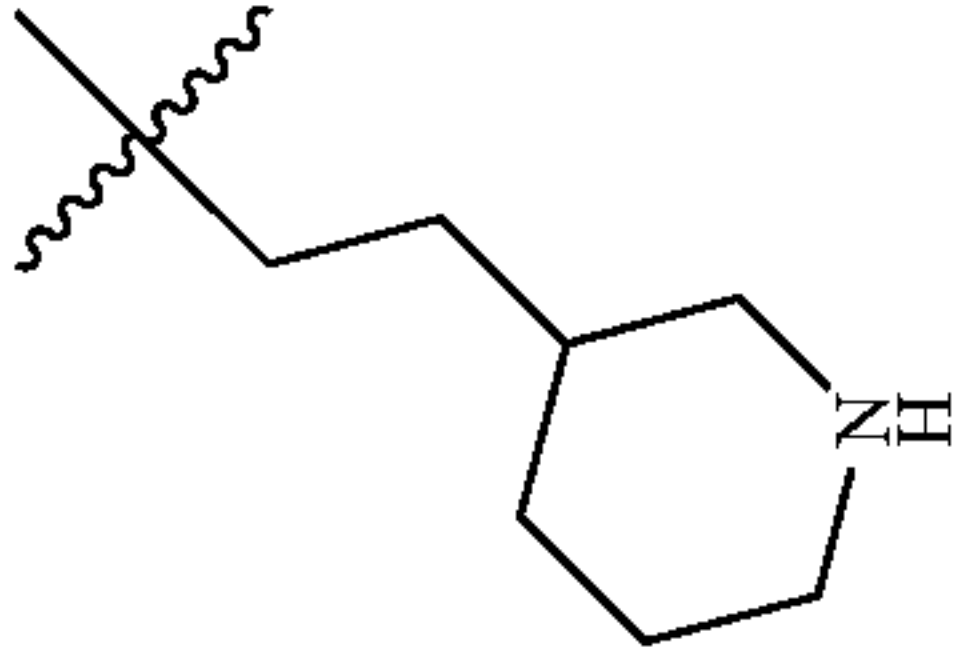
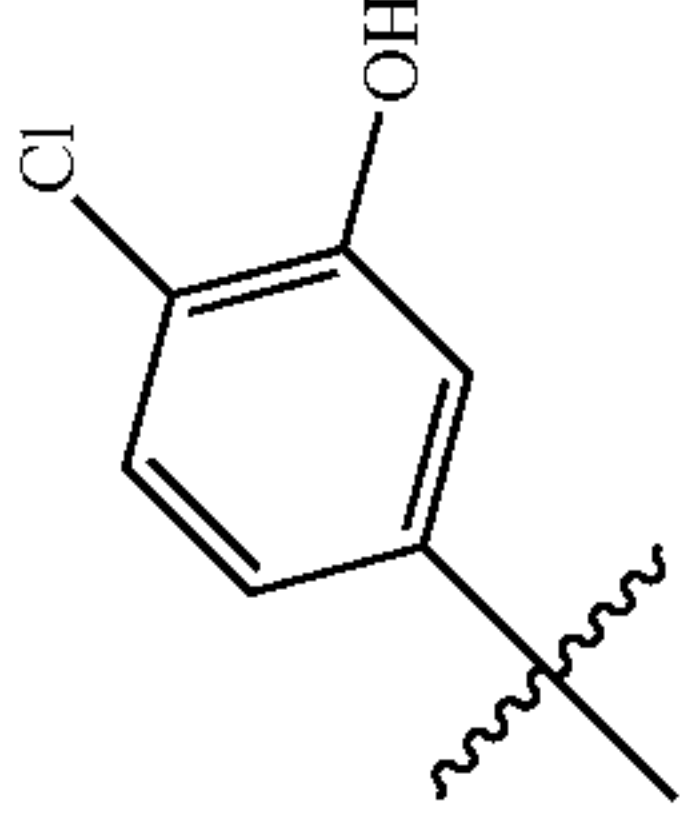
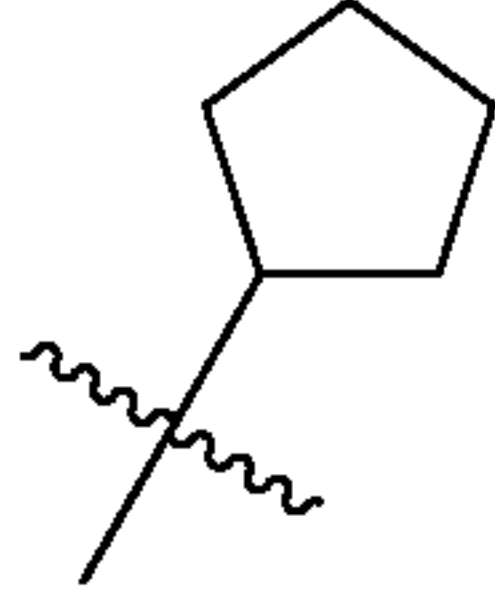
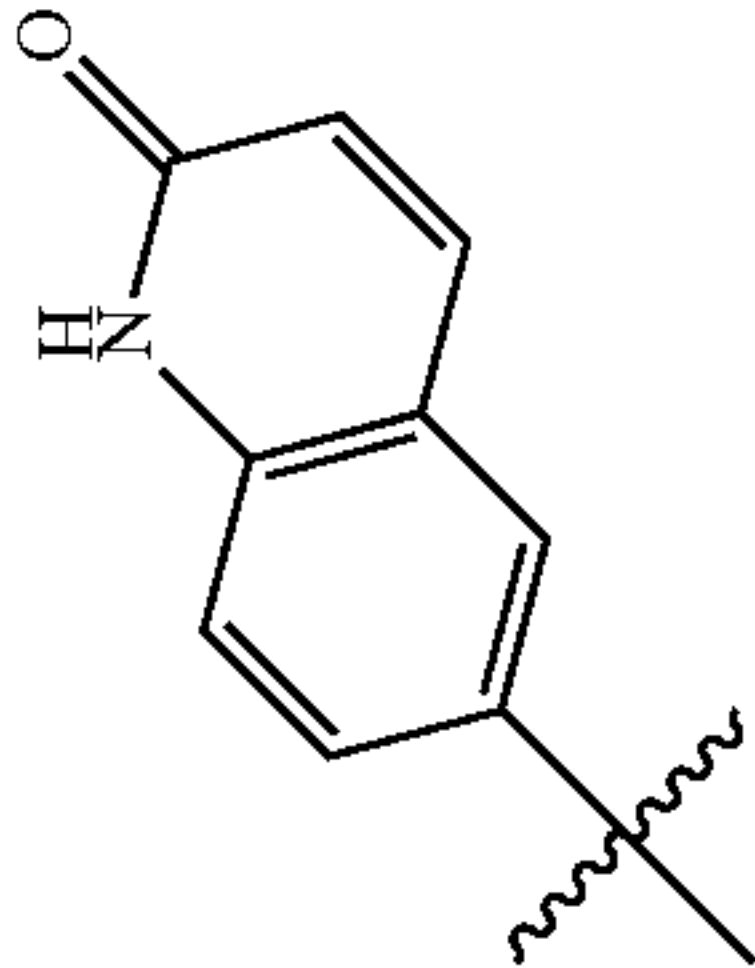
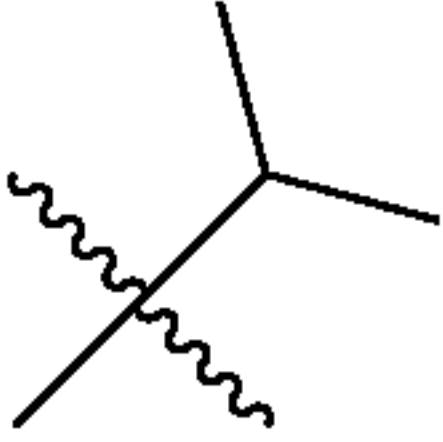
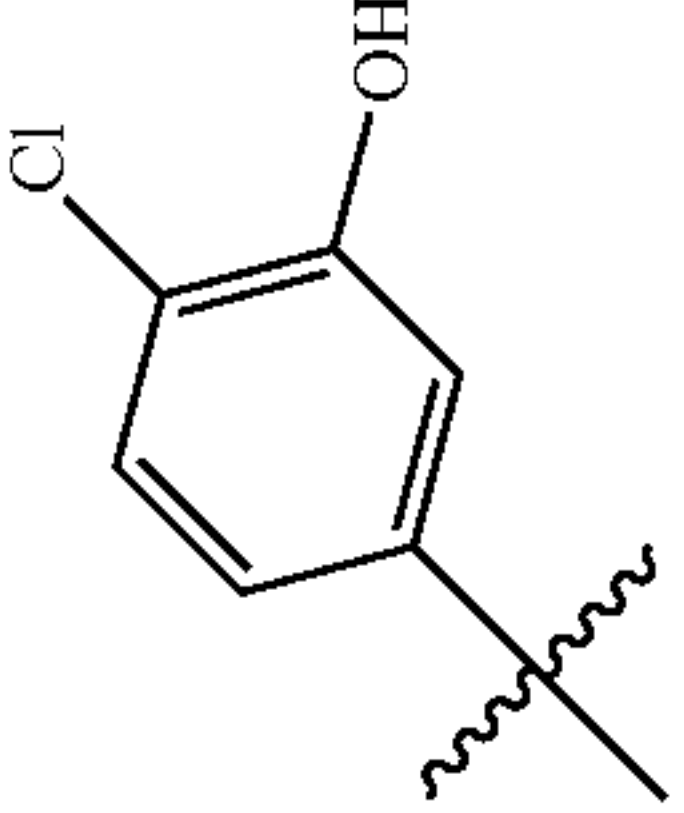
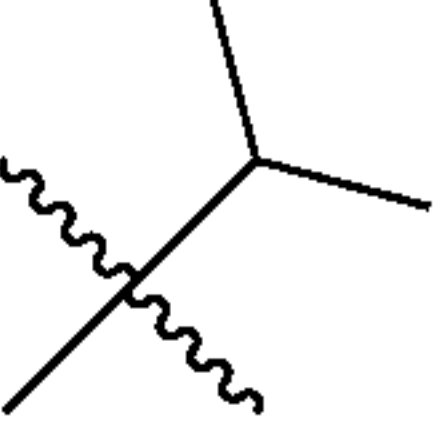
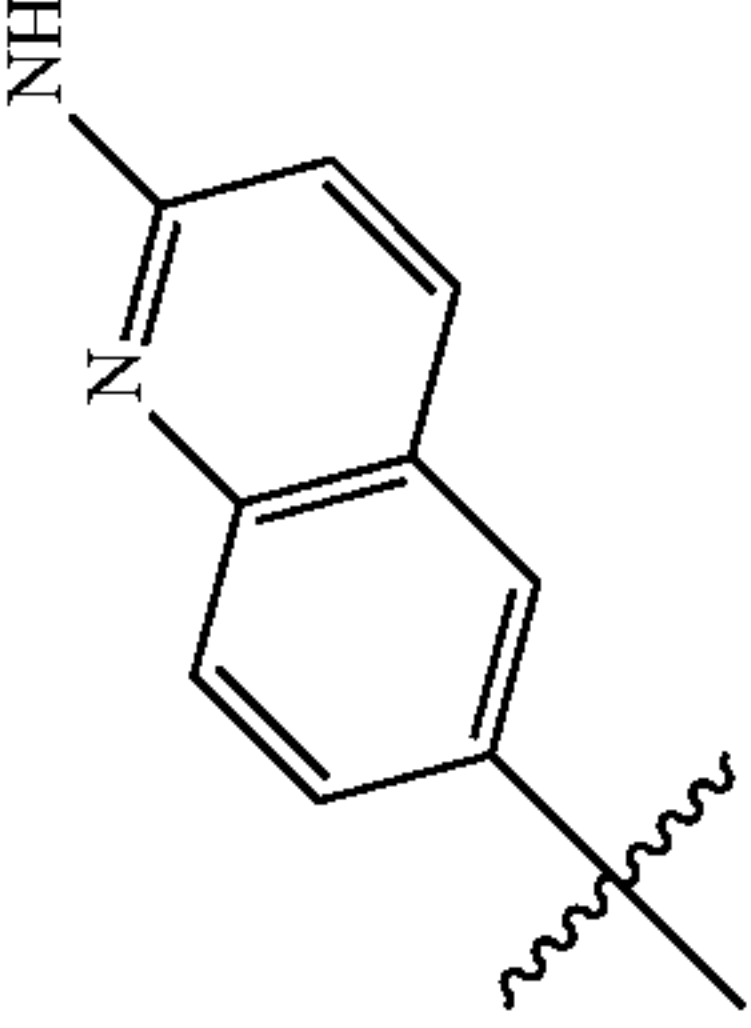
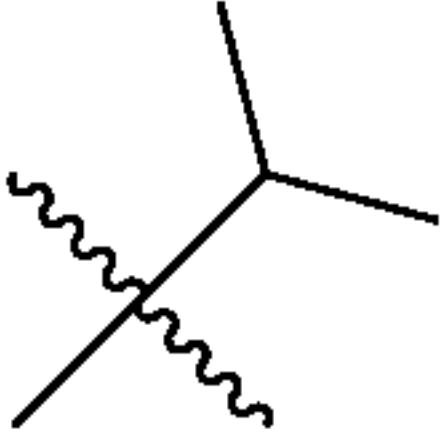
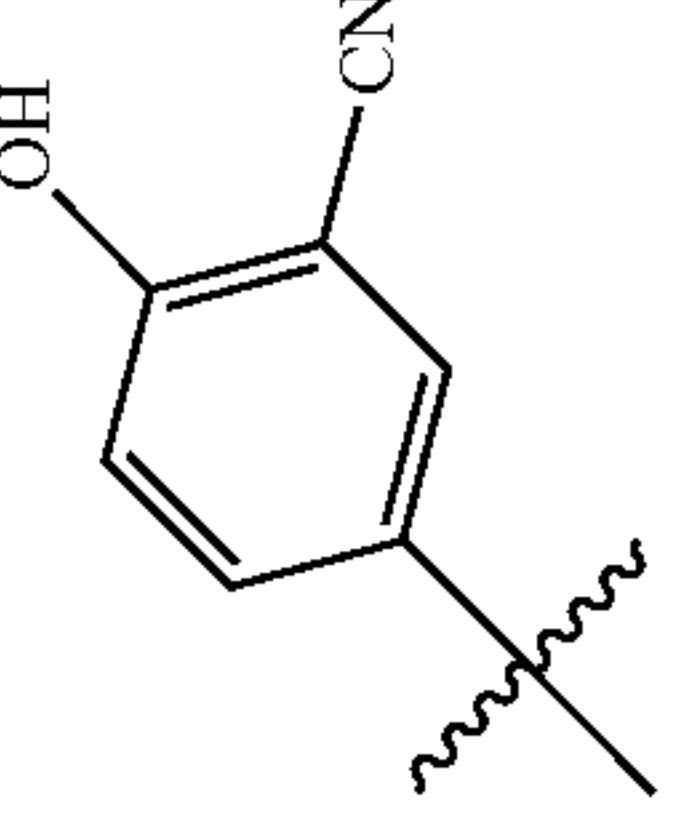
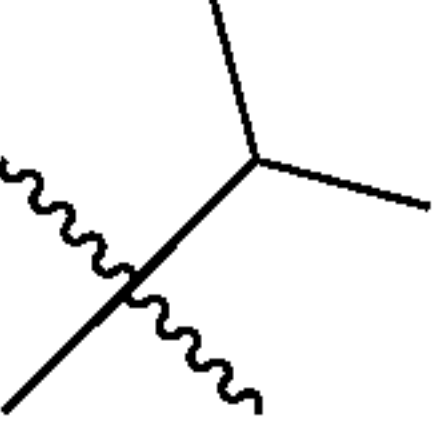
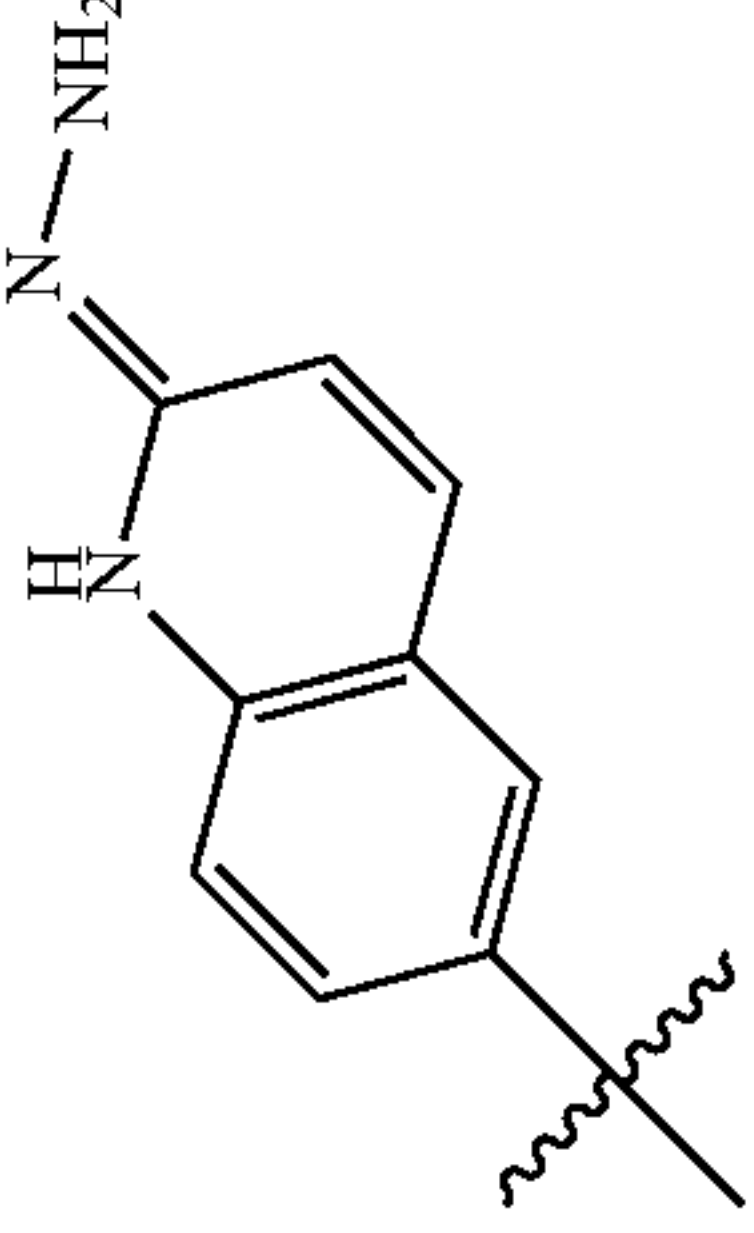
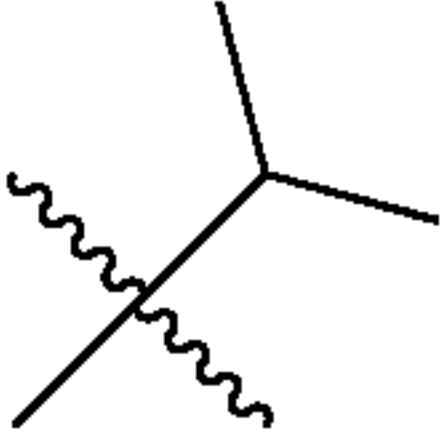
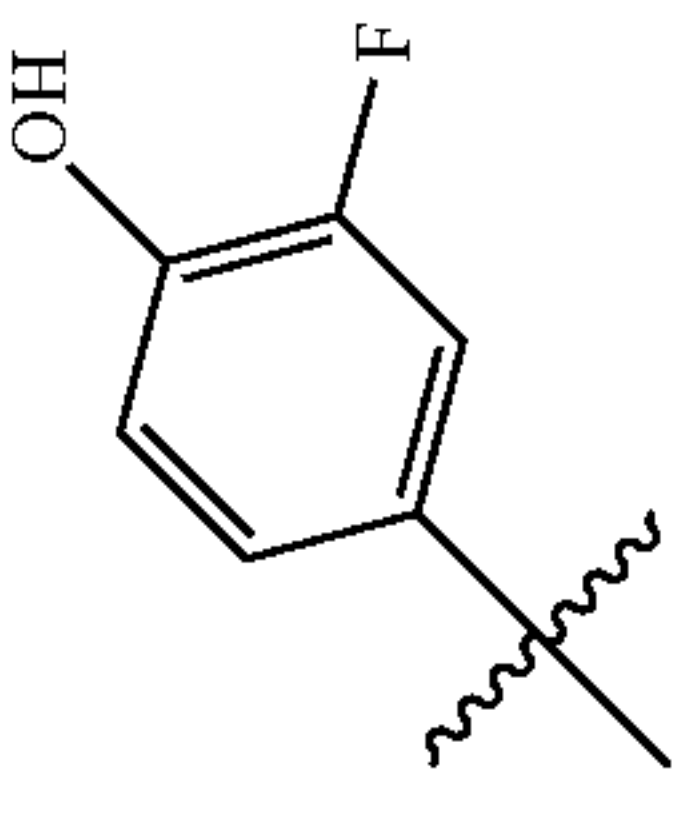
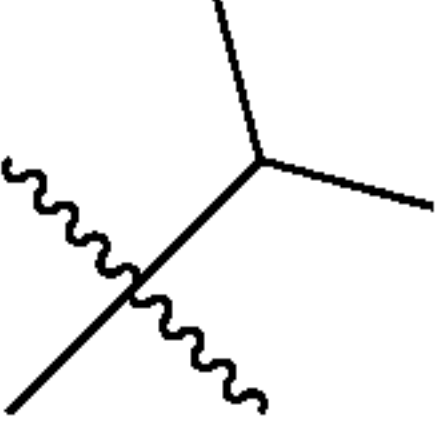
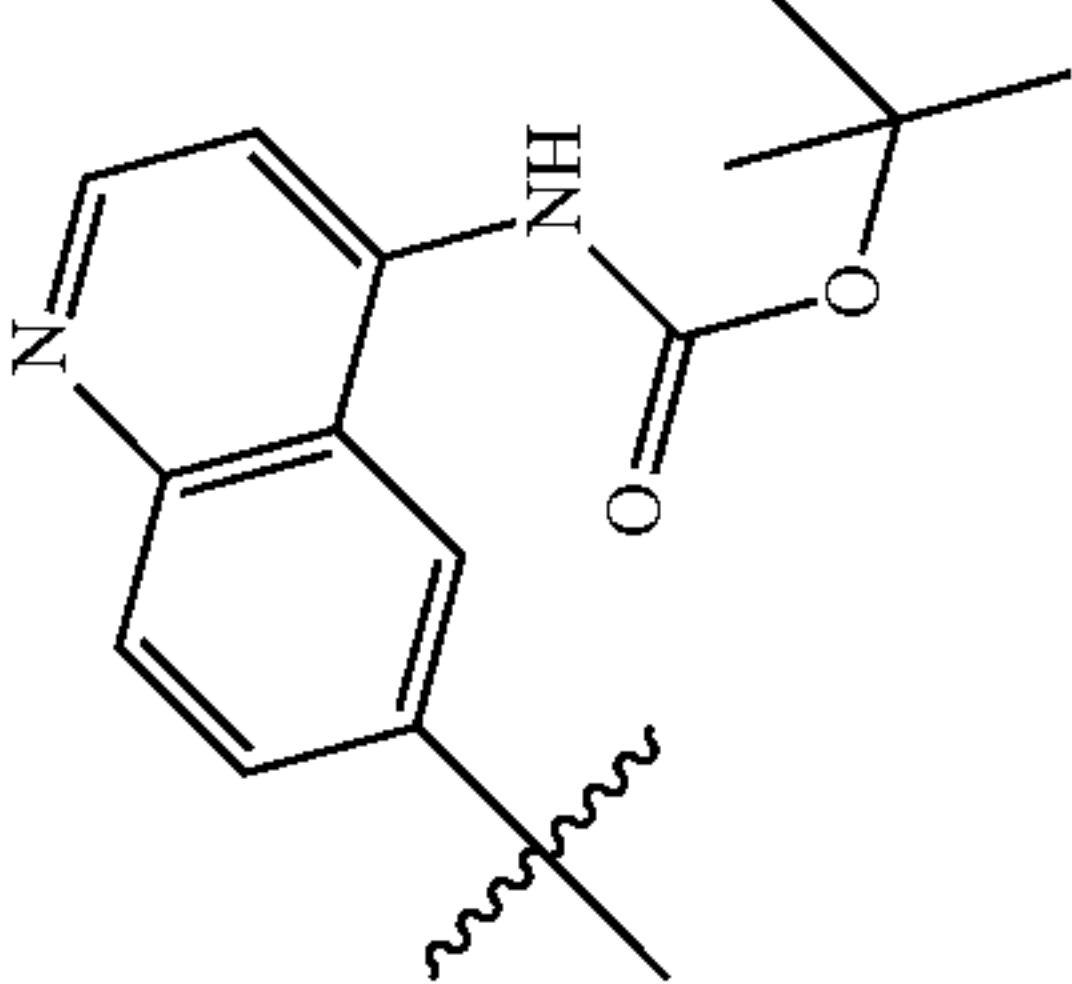
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK391			BA141		
BA155_2			BA146		
BA157_2			BA142		
BA59			BA145		

TABLE 1-continued

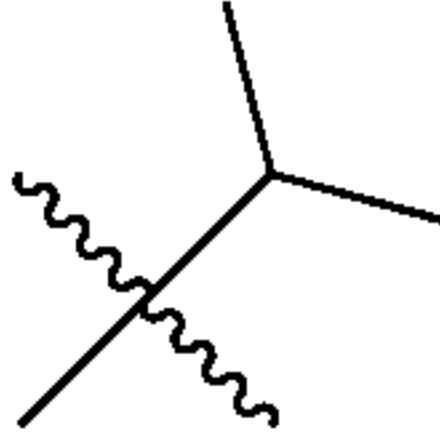
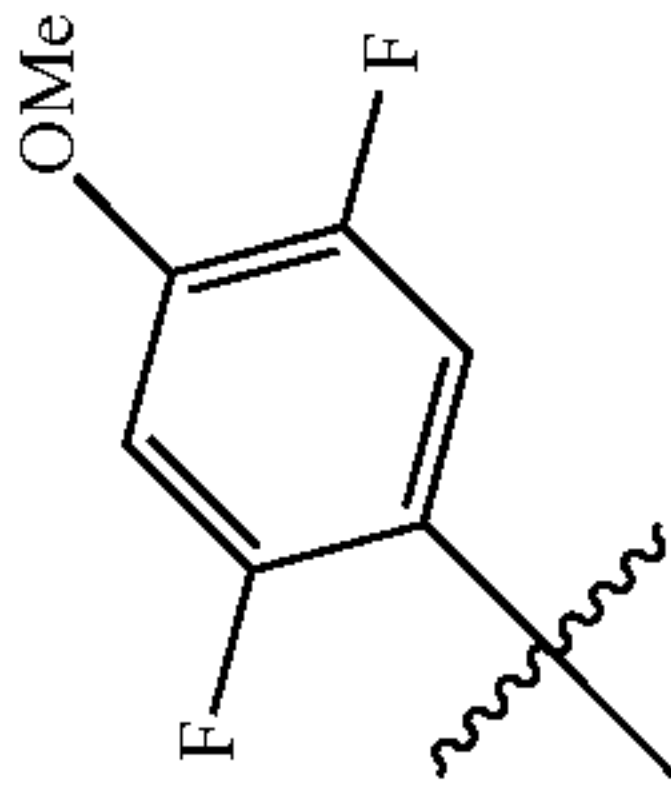
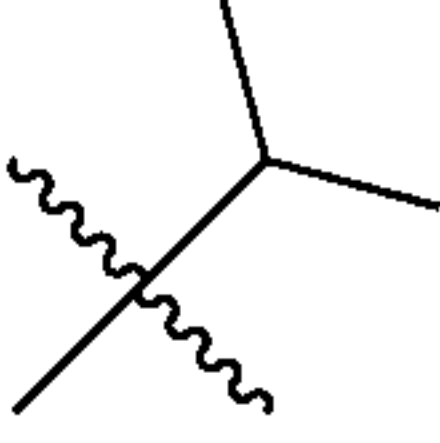
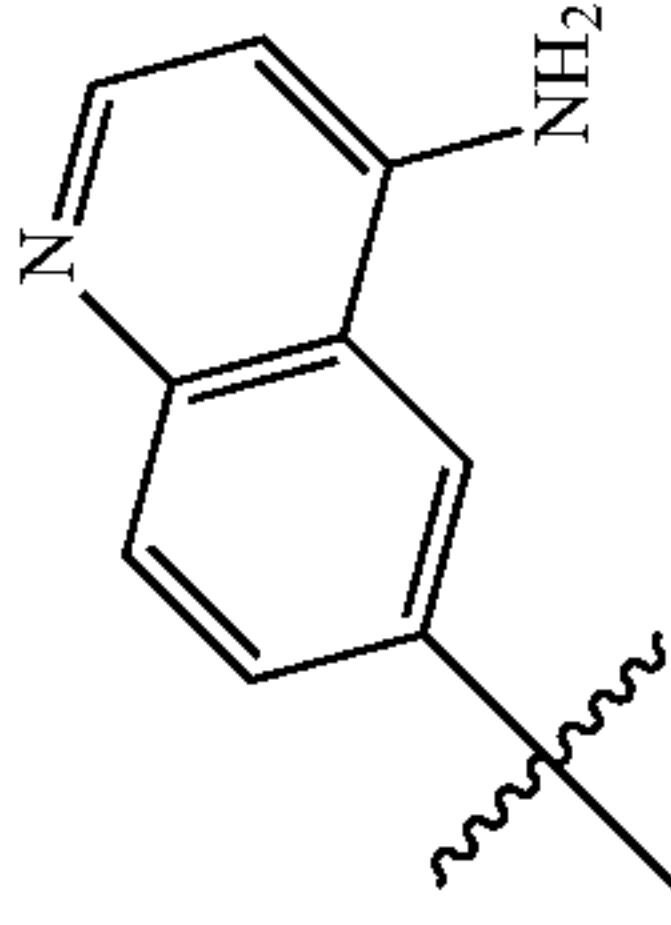
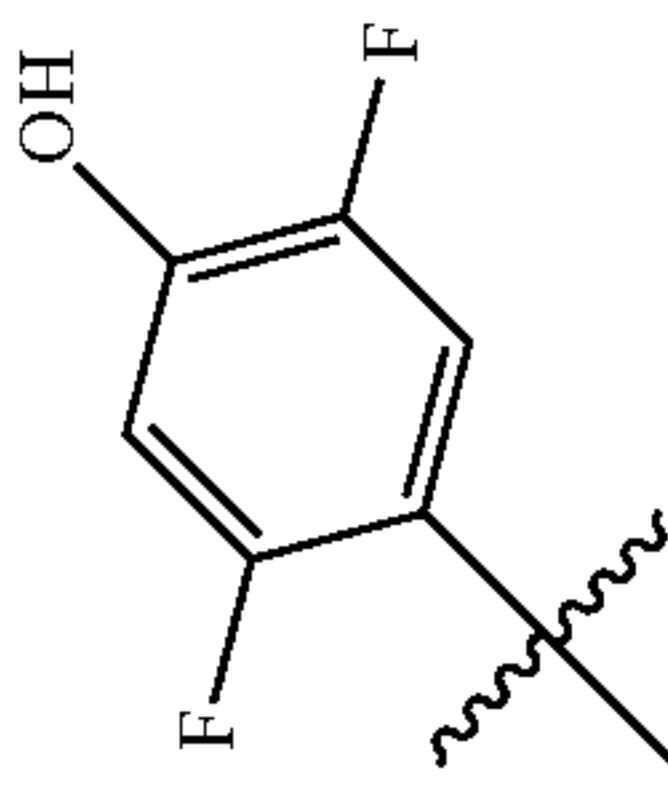
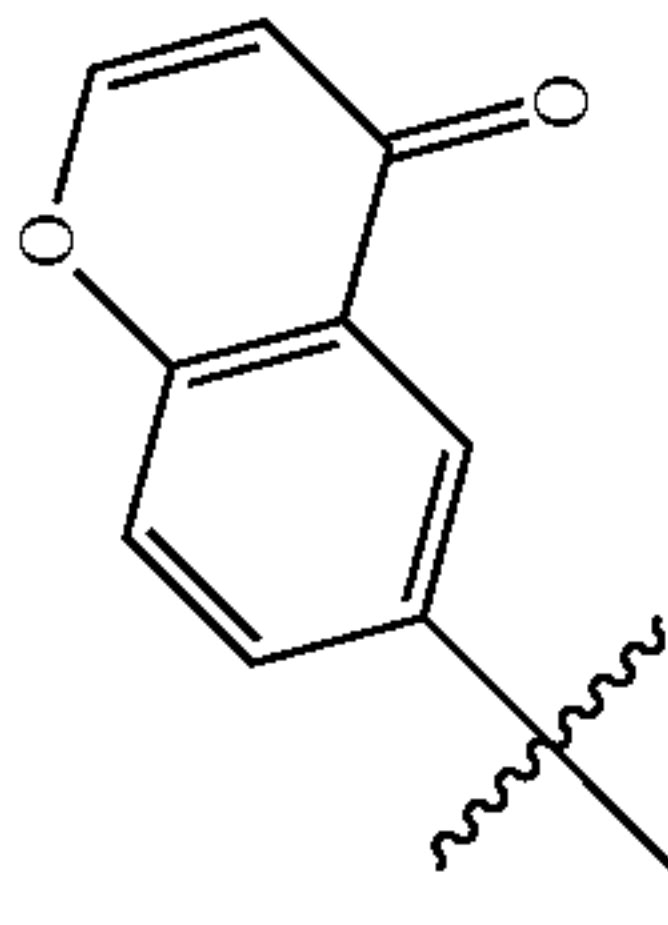
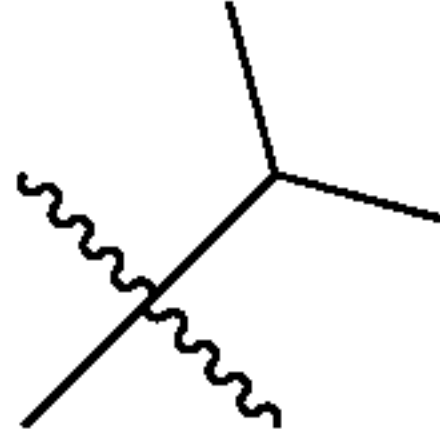
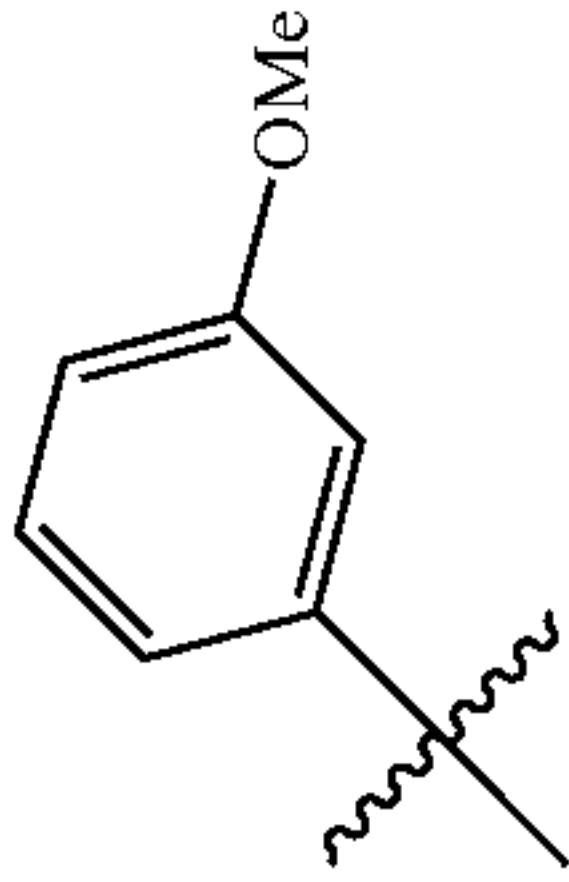
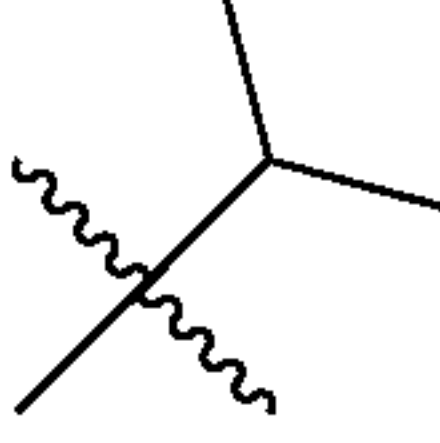
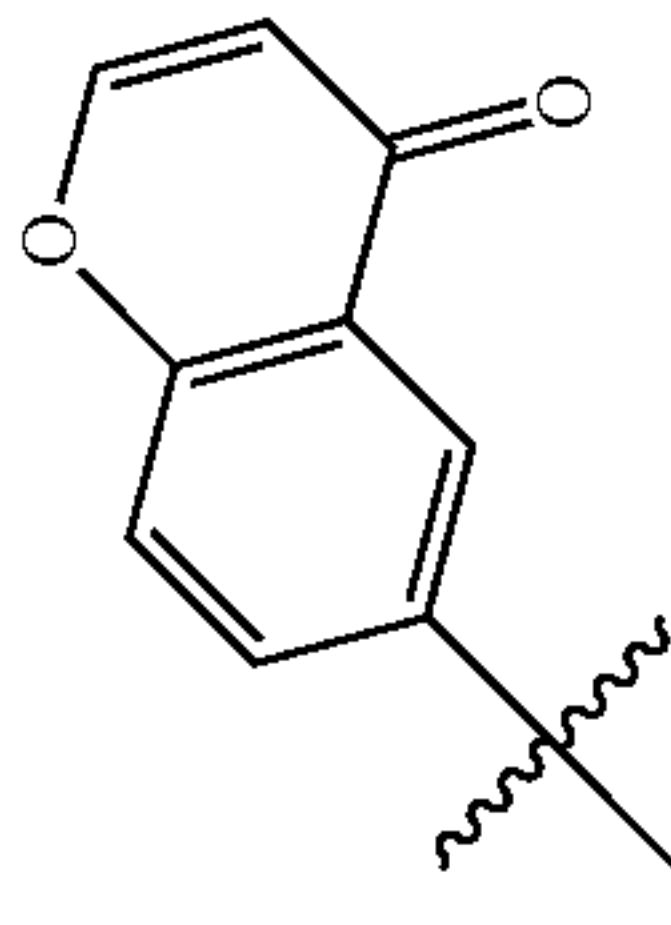
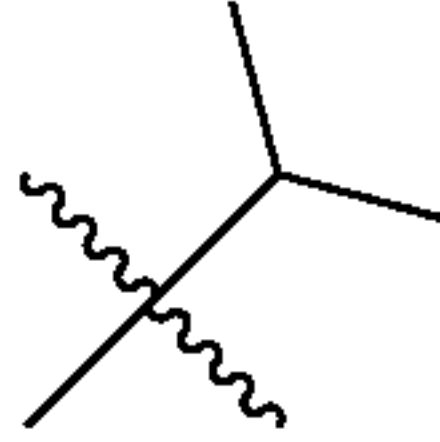
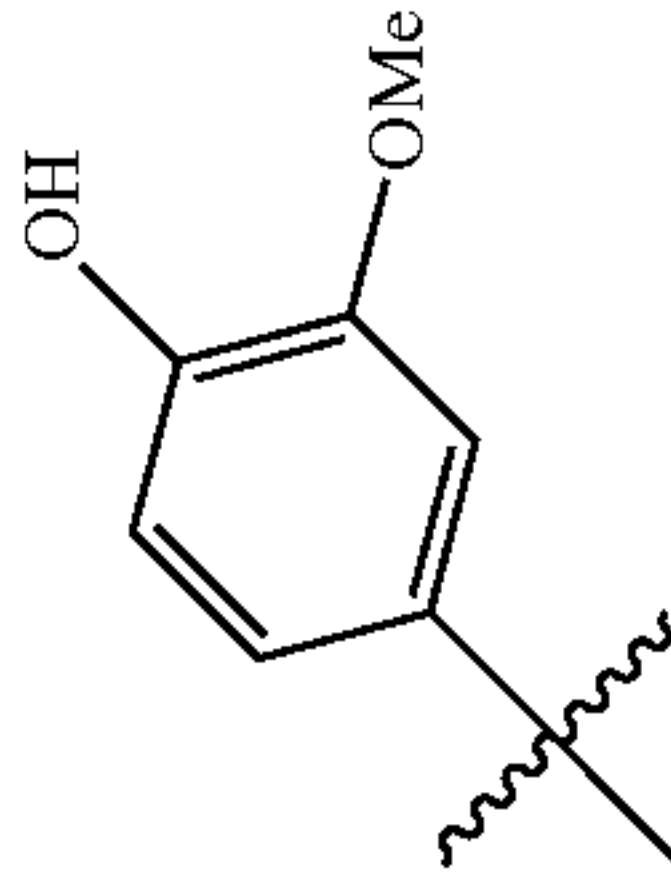
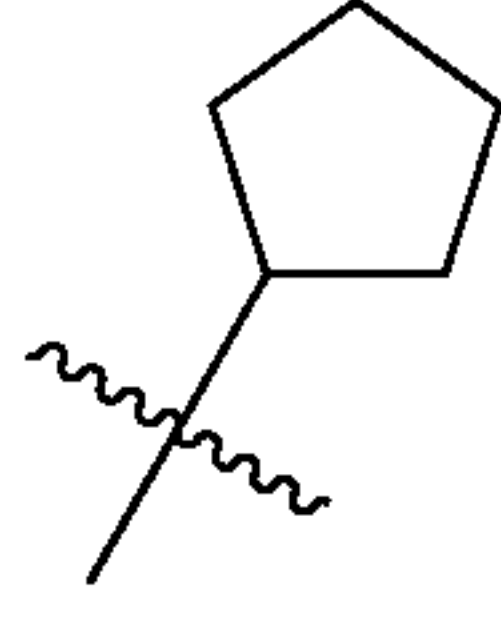
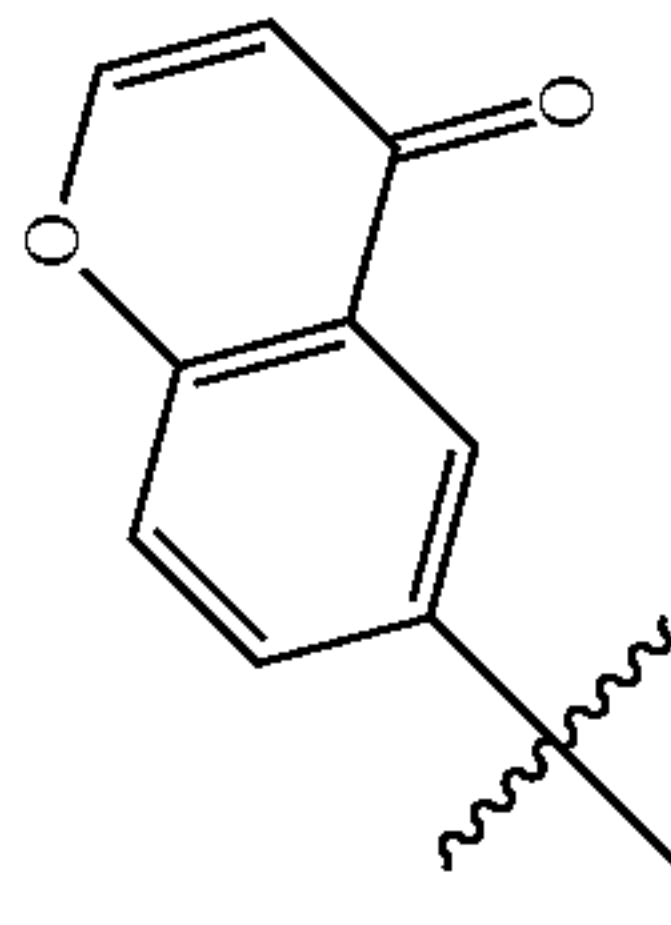
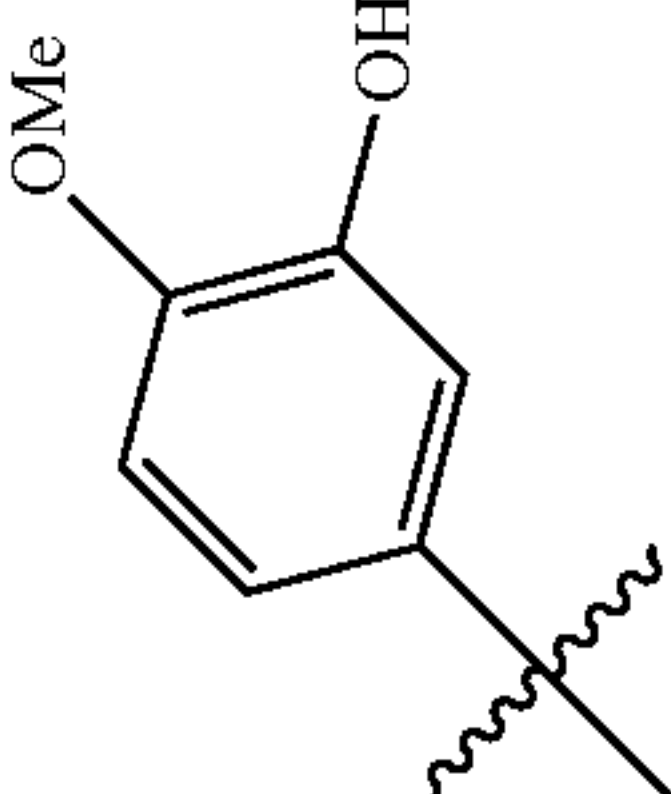
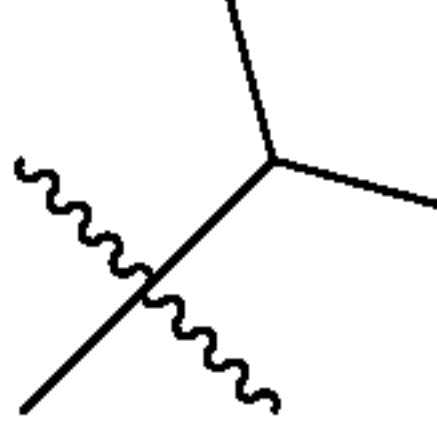
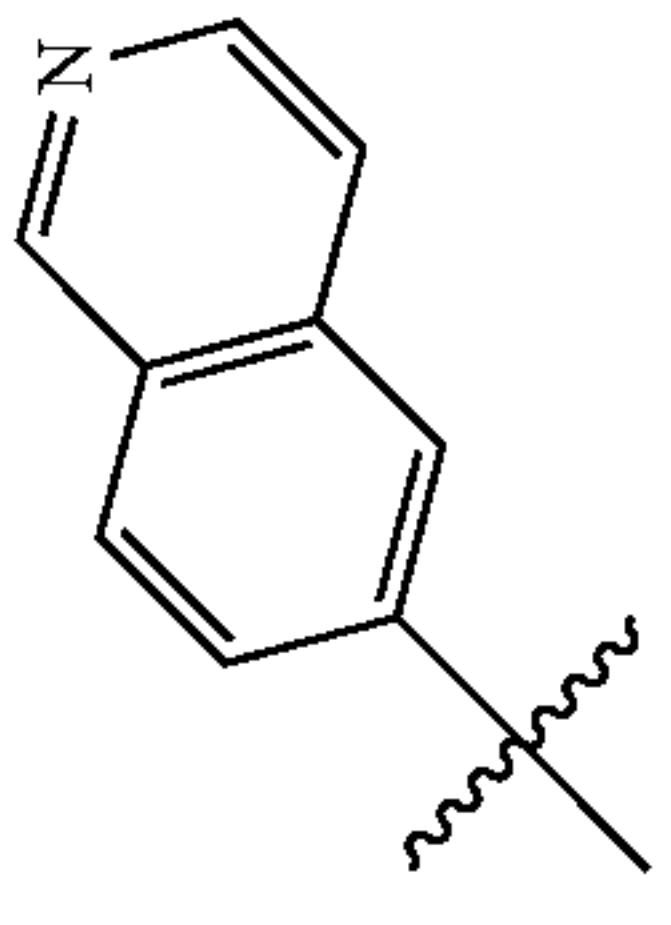
Cpd	R ¹	R ²	Cpd	R ¹	R ²
BA63			BA147		
BA93			BA148	—Me	
BA49			BA143		
BA15			BA144		
ZK321	—H		BA129		

TABLE 1-continued

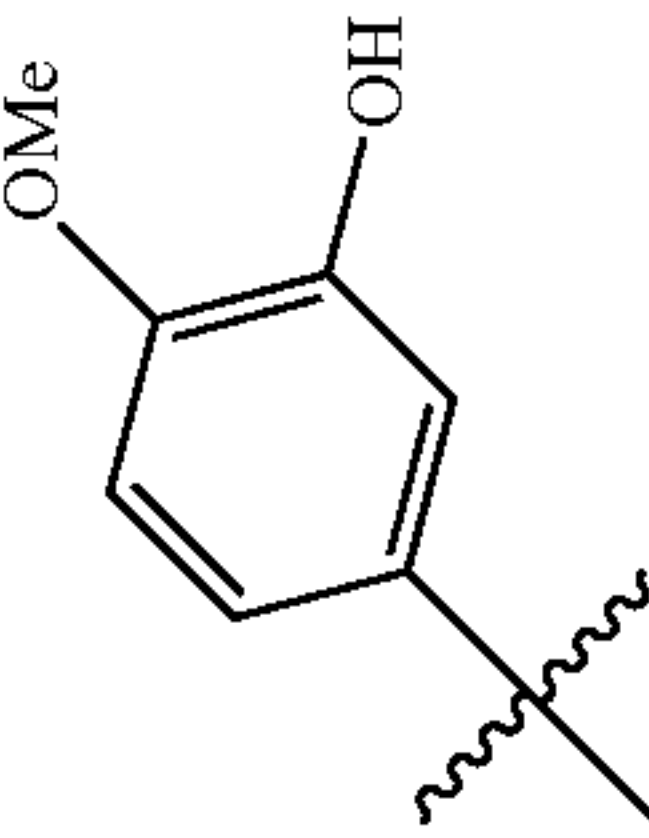
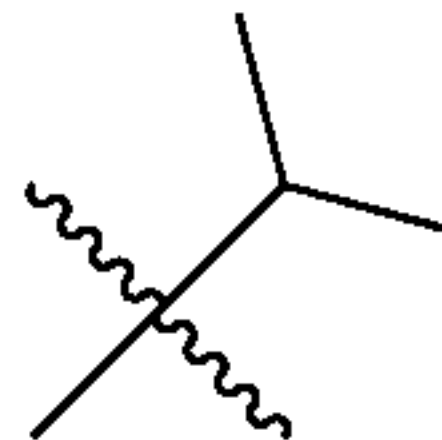
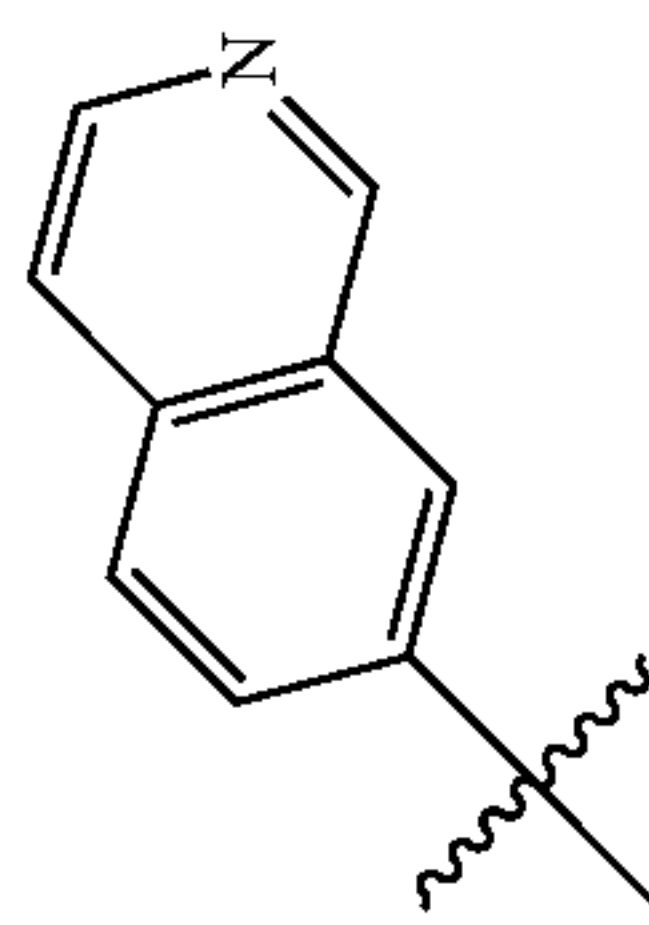
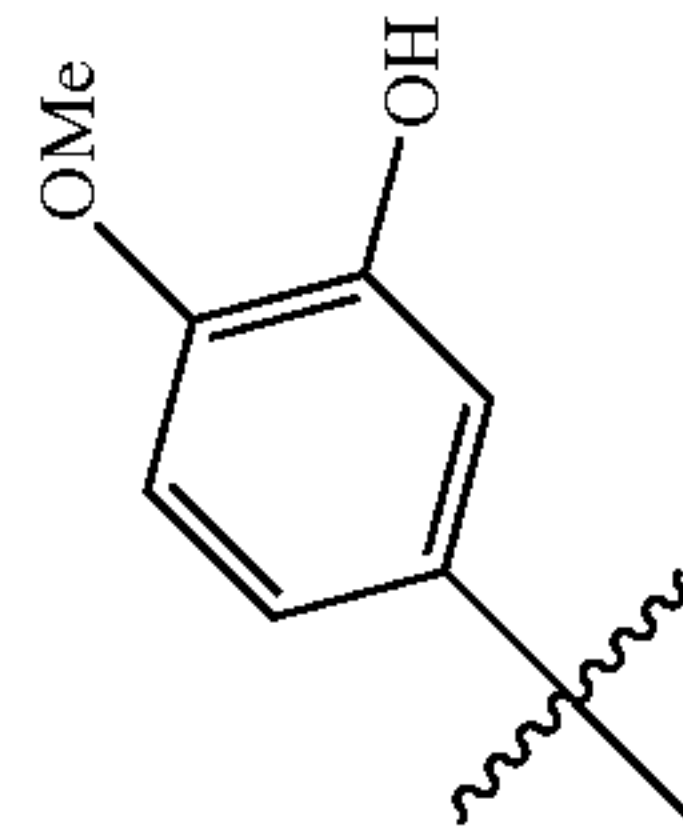
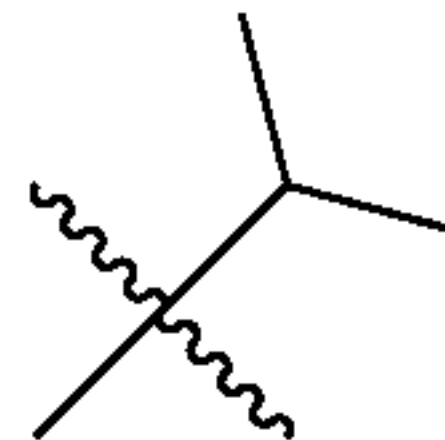
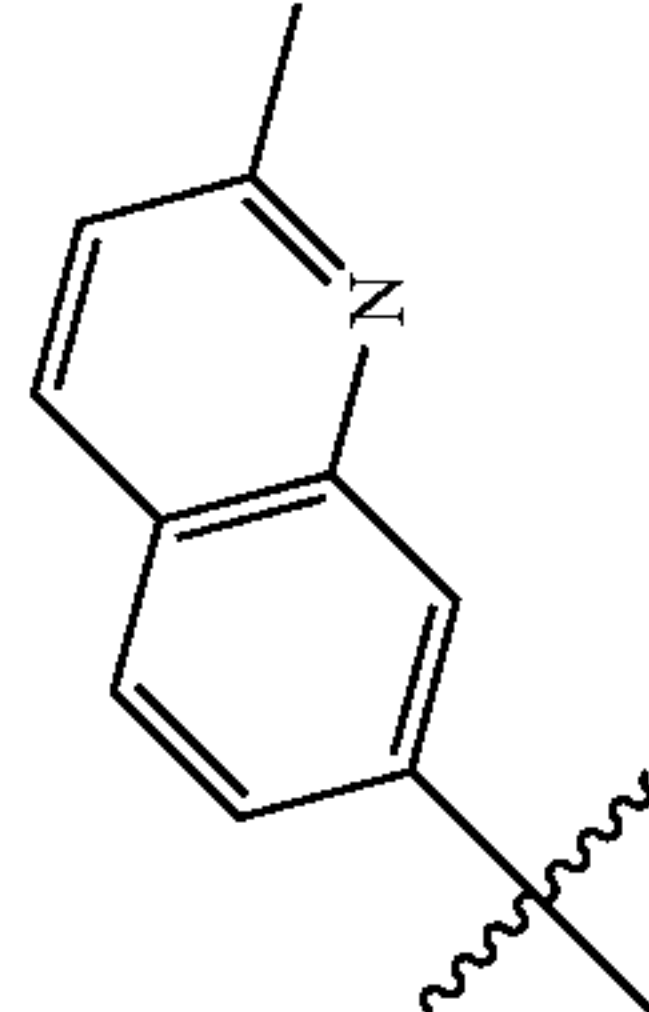
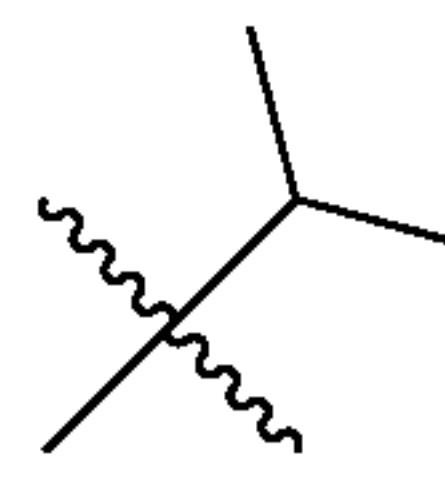
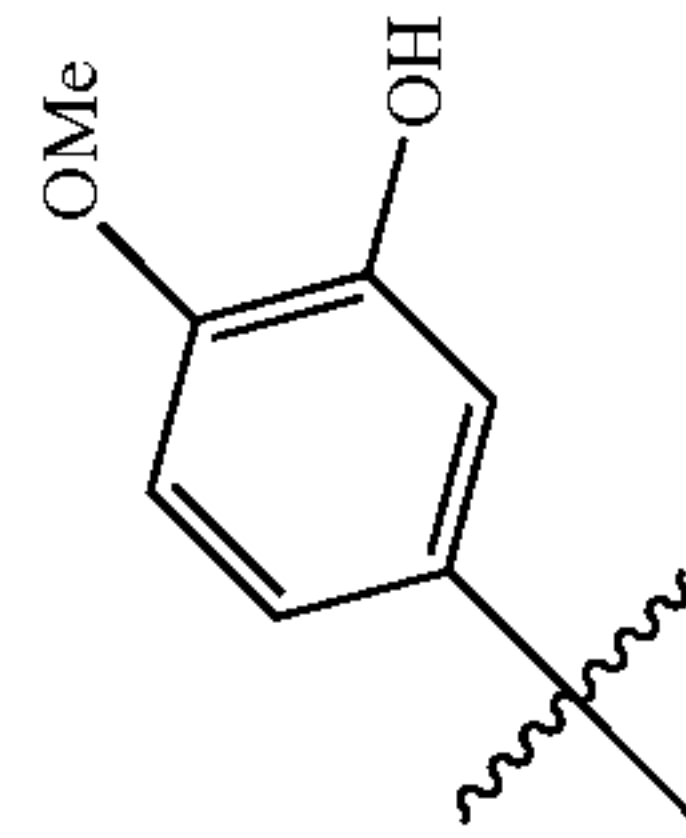
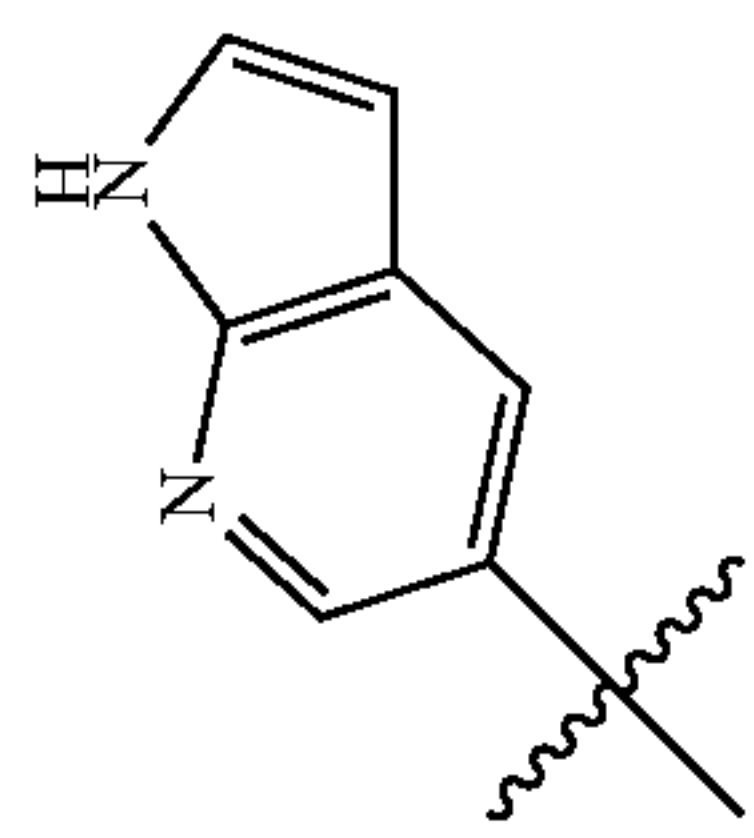
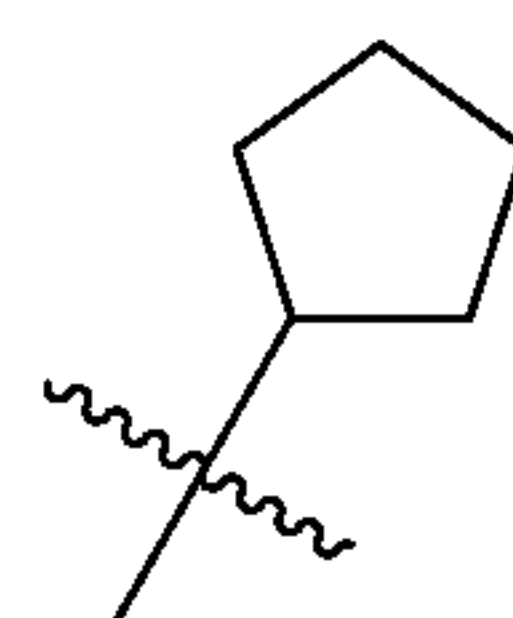
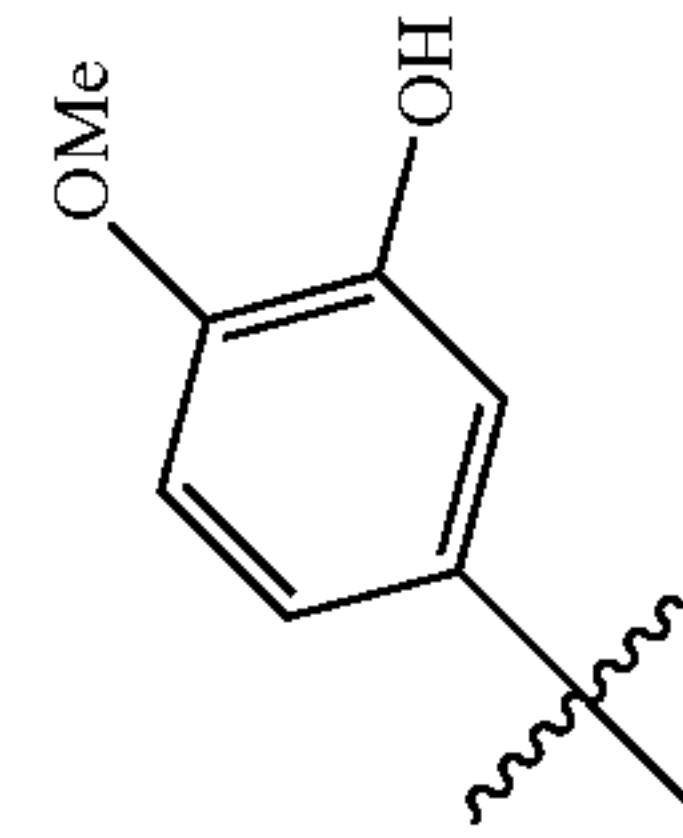
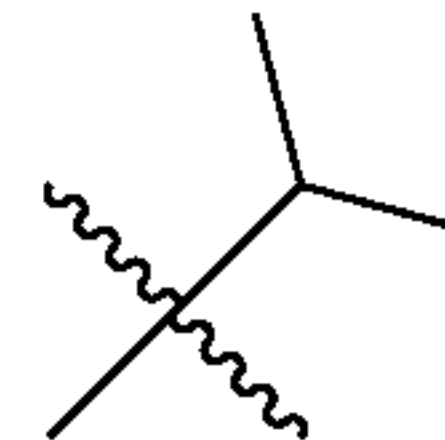
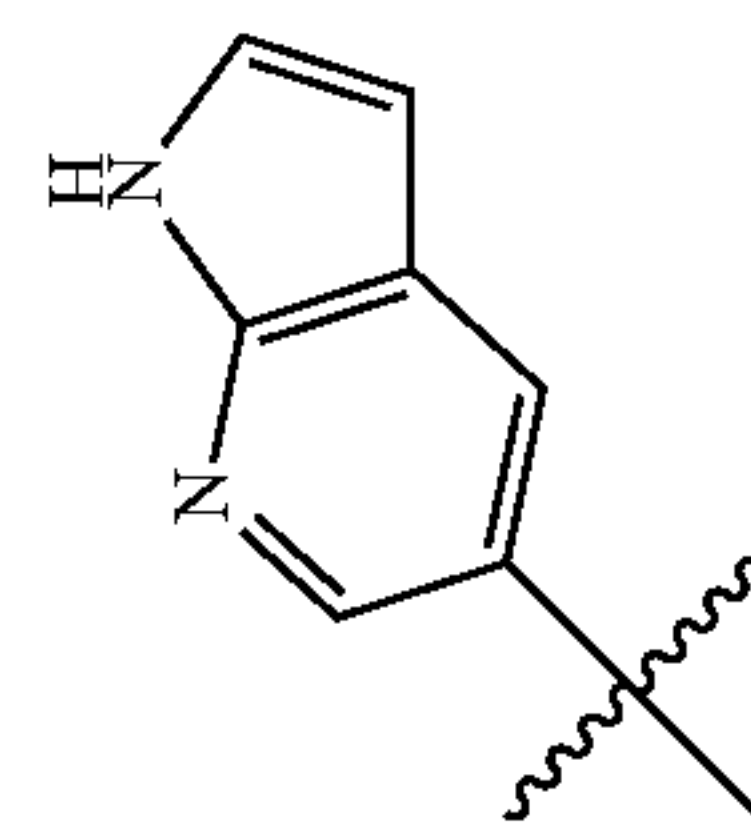
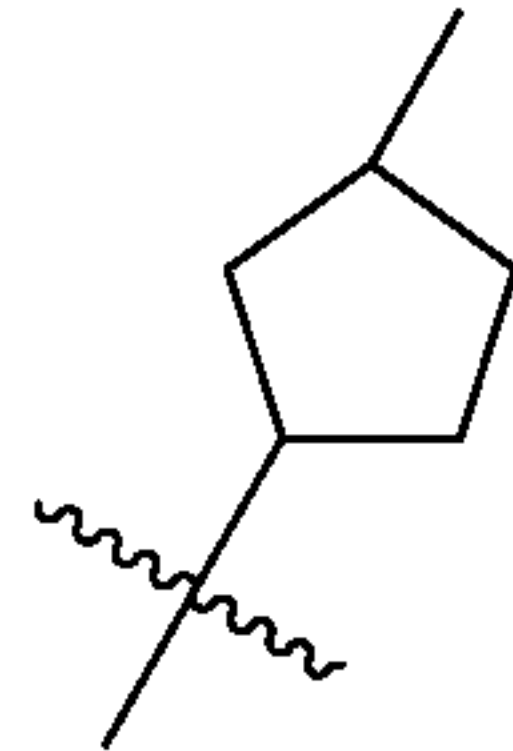
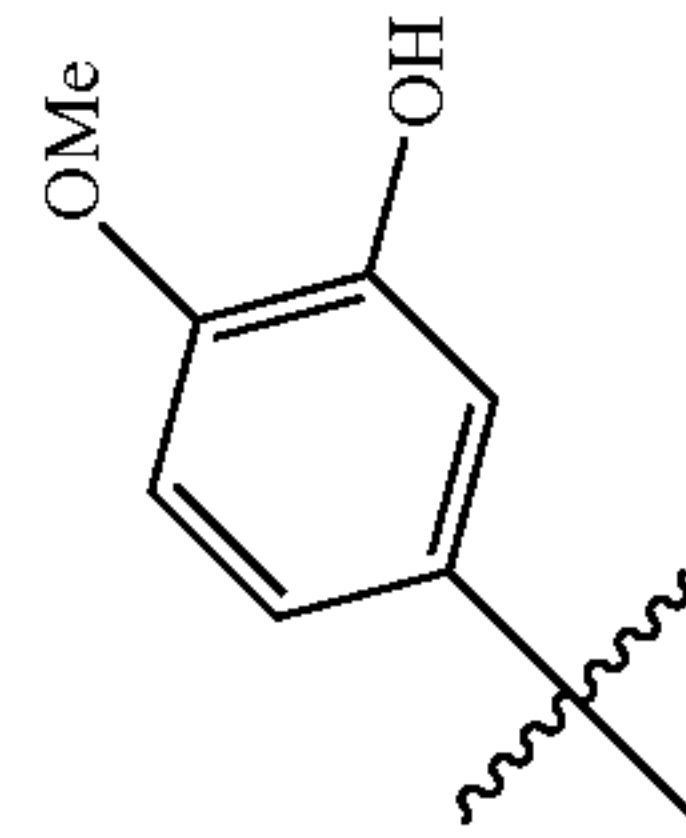
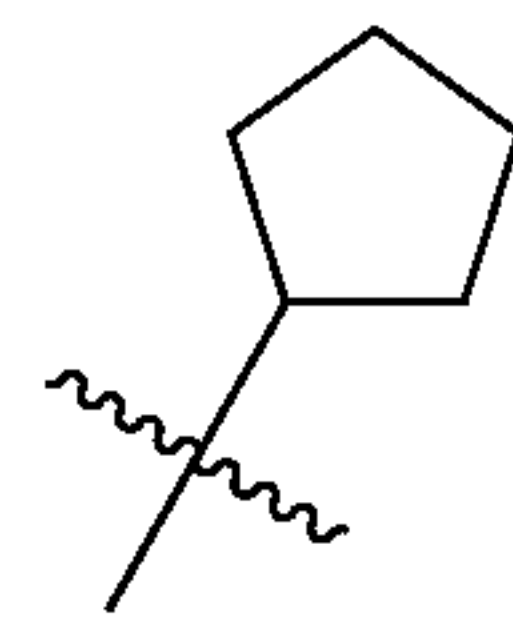
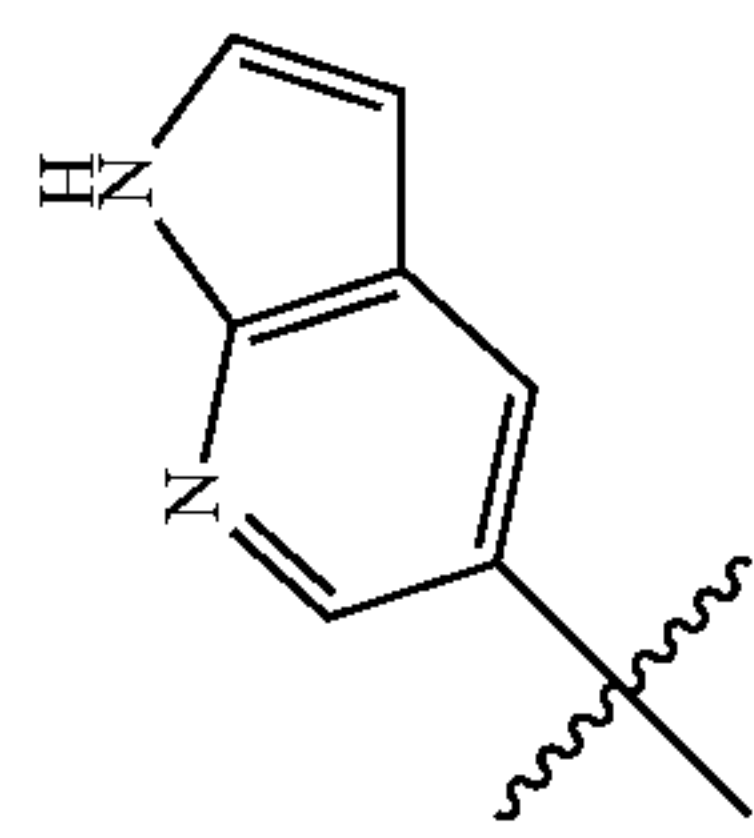
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK337	—Me		BA131		
ZK347			BA133		
ZK325			BA120	—Me	
ZK349			BA108		
ZK423			BA121		

TABLE 1-continued

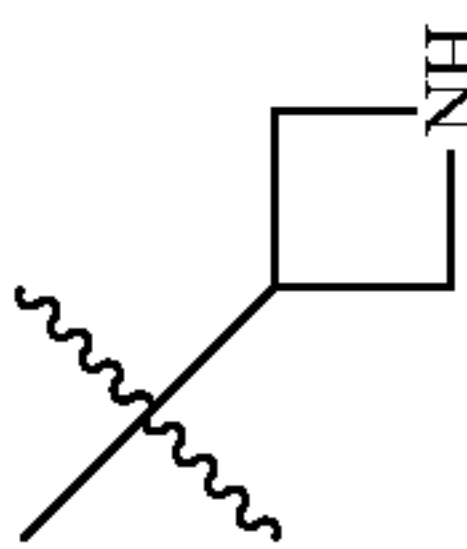
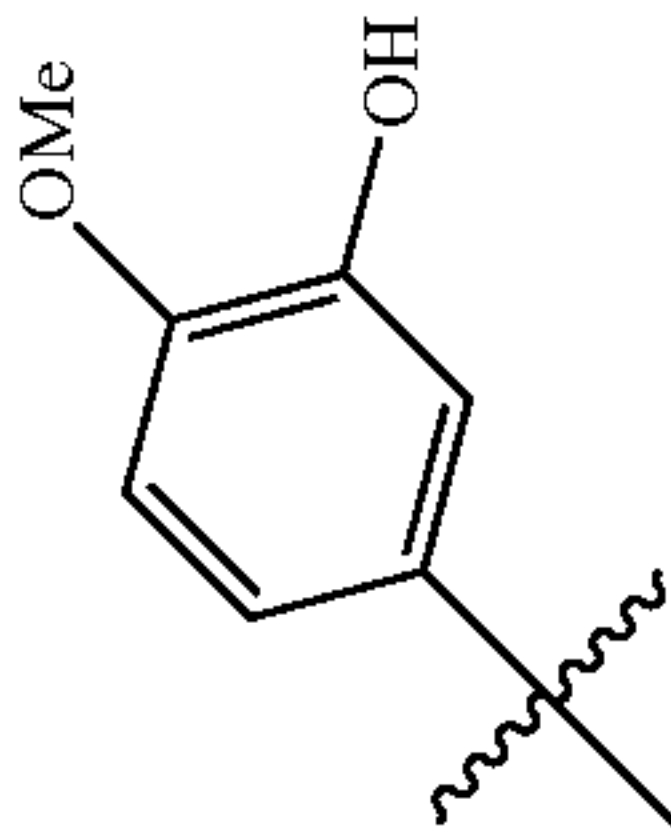
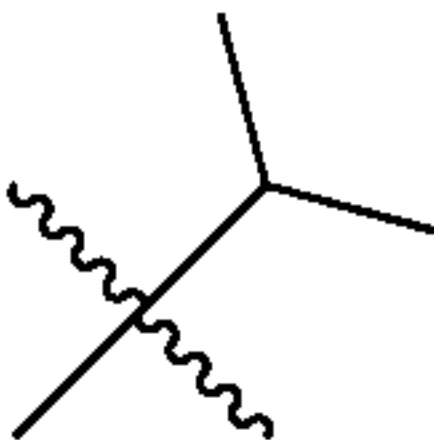
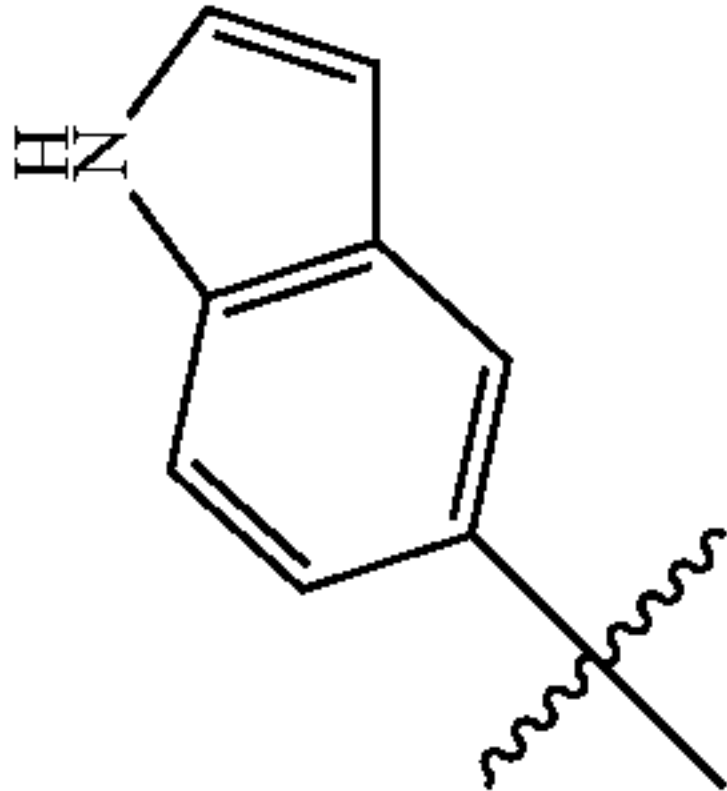
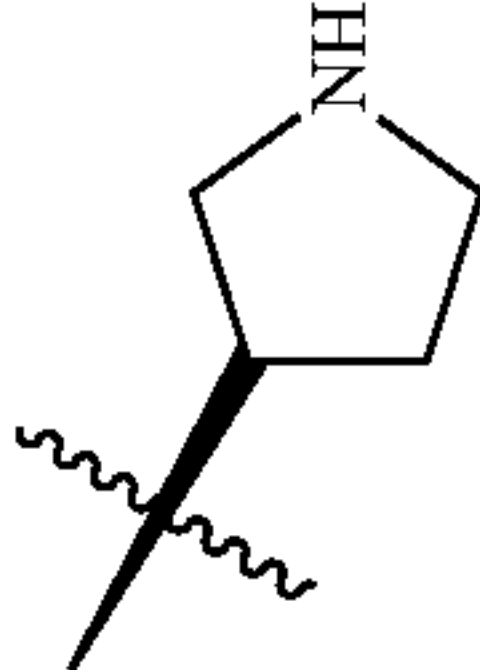
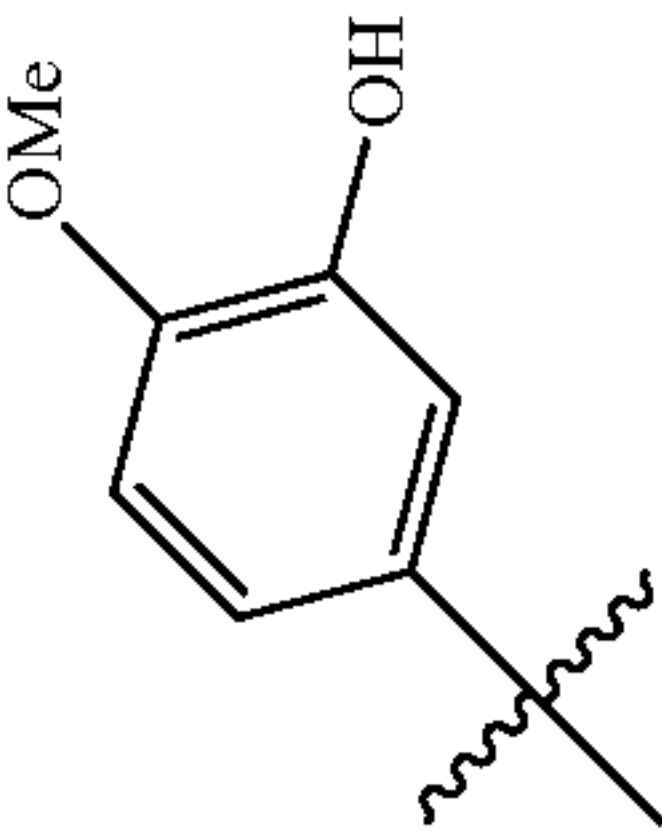
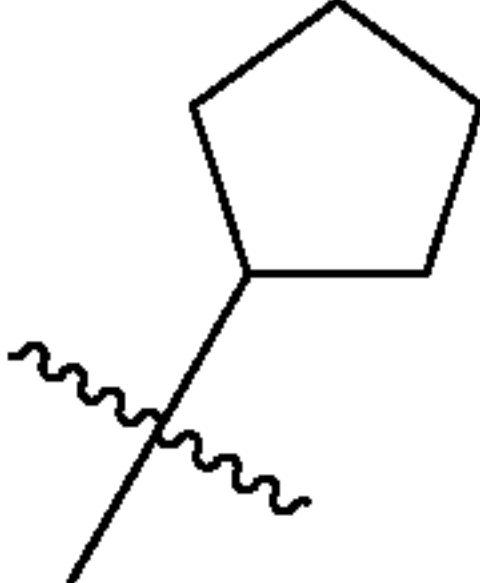
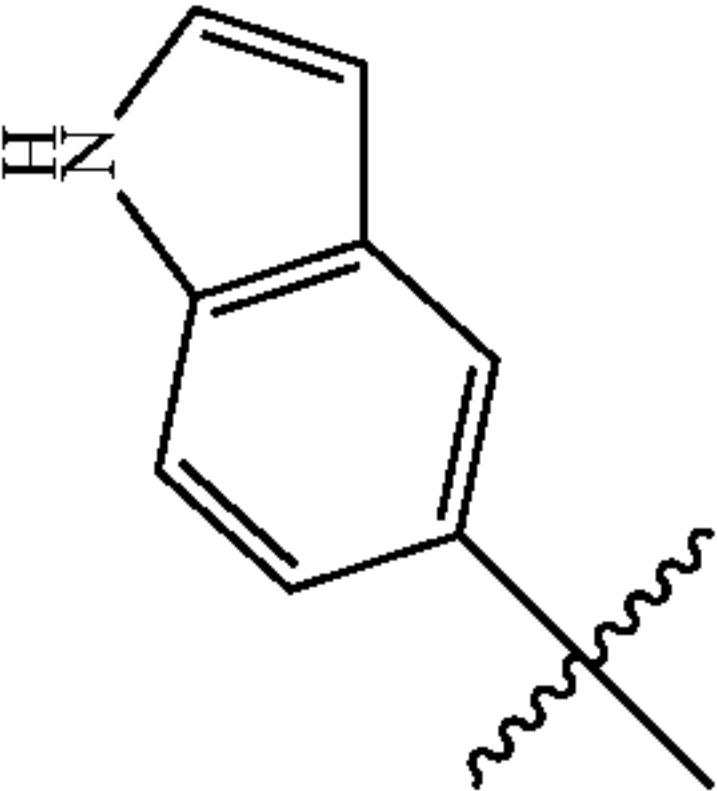
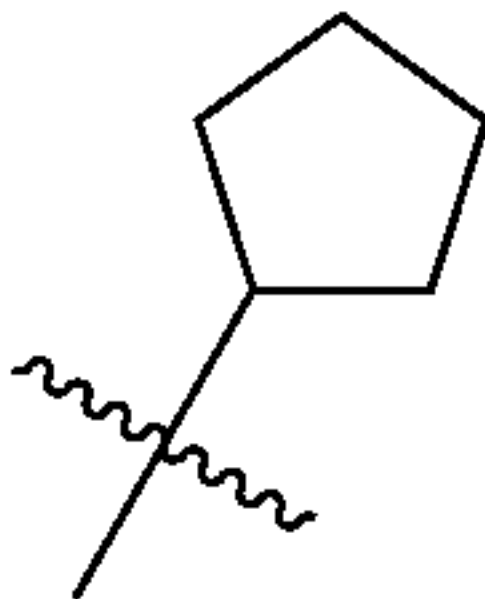
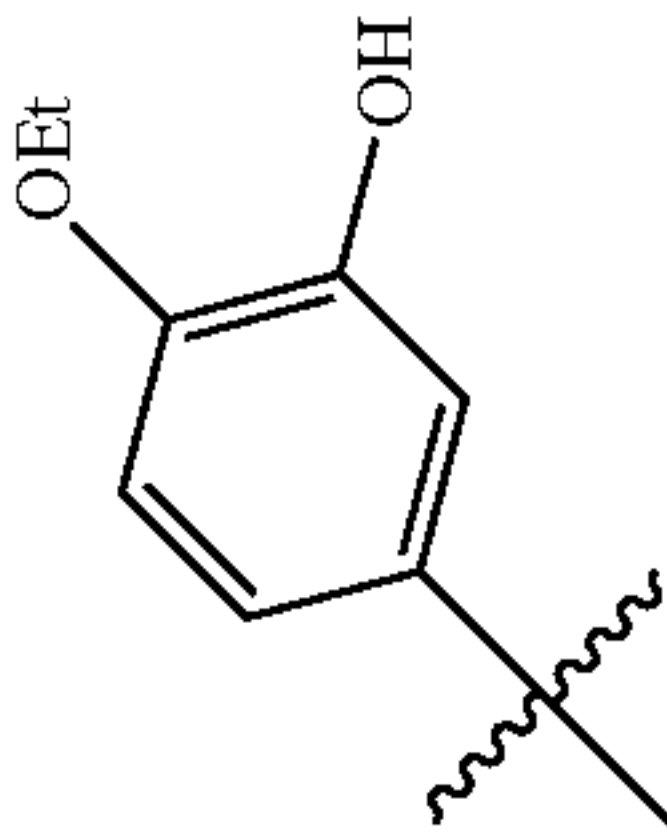
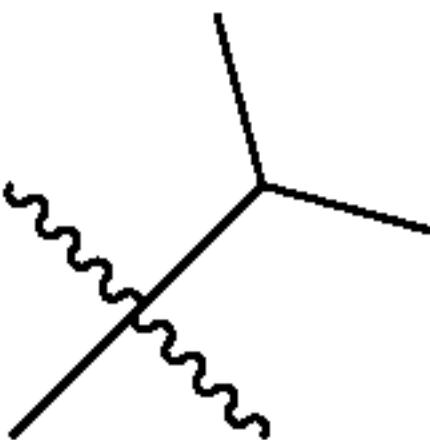
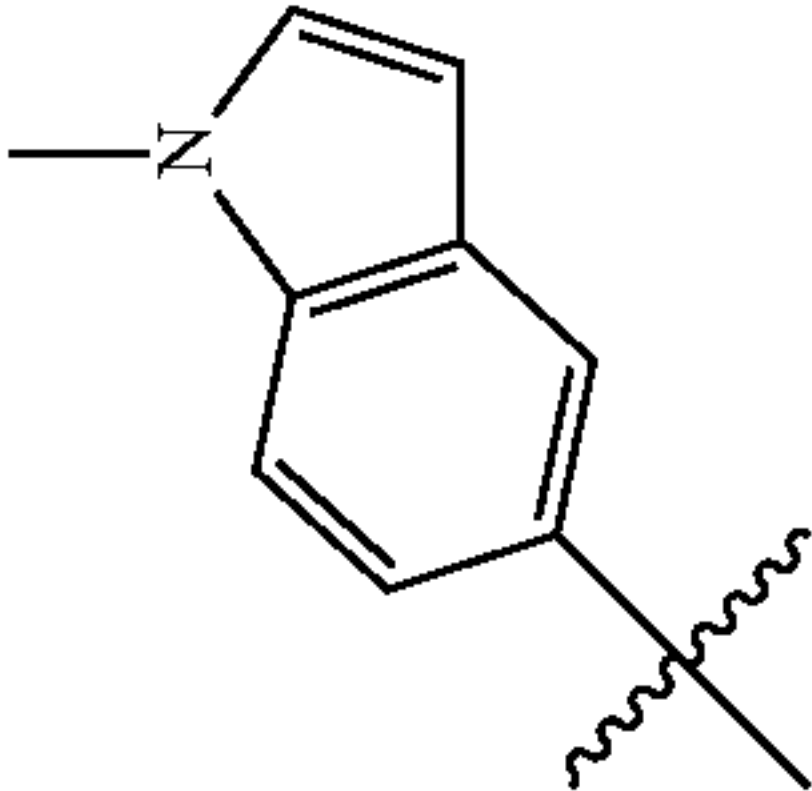
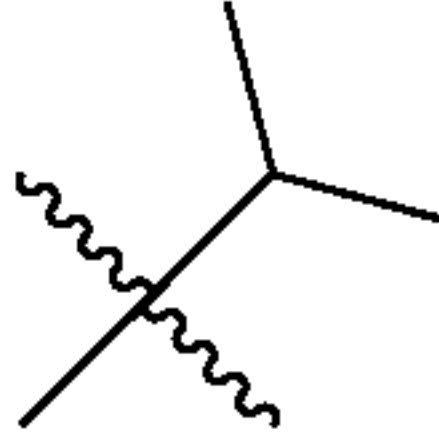
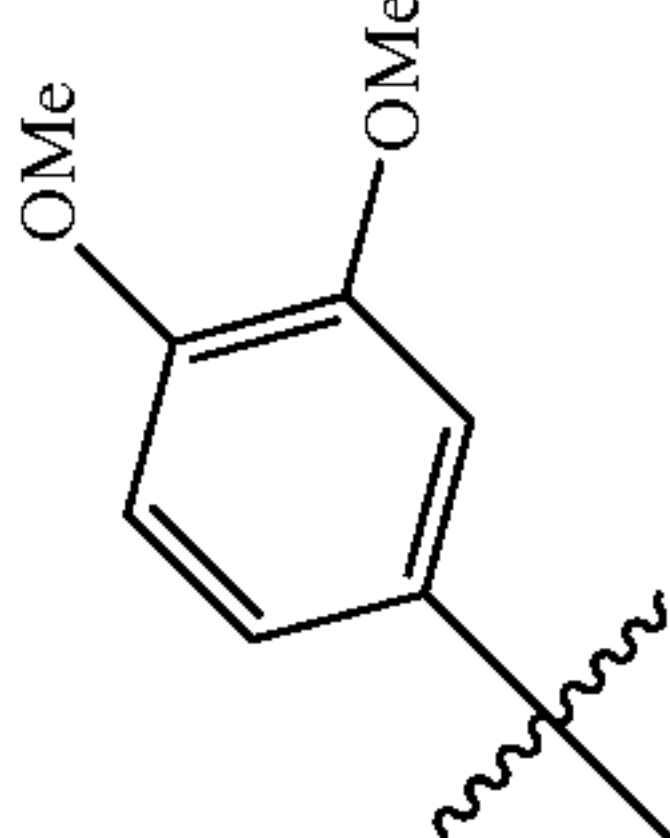
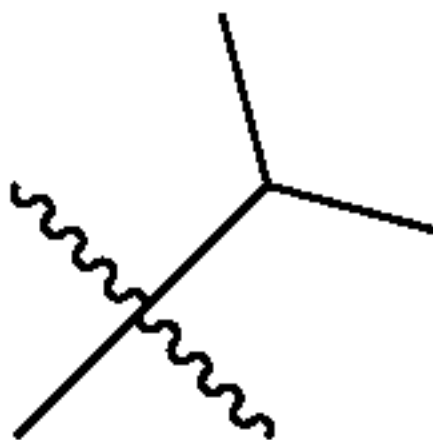
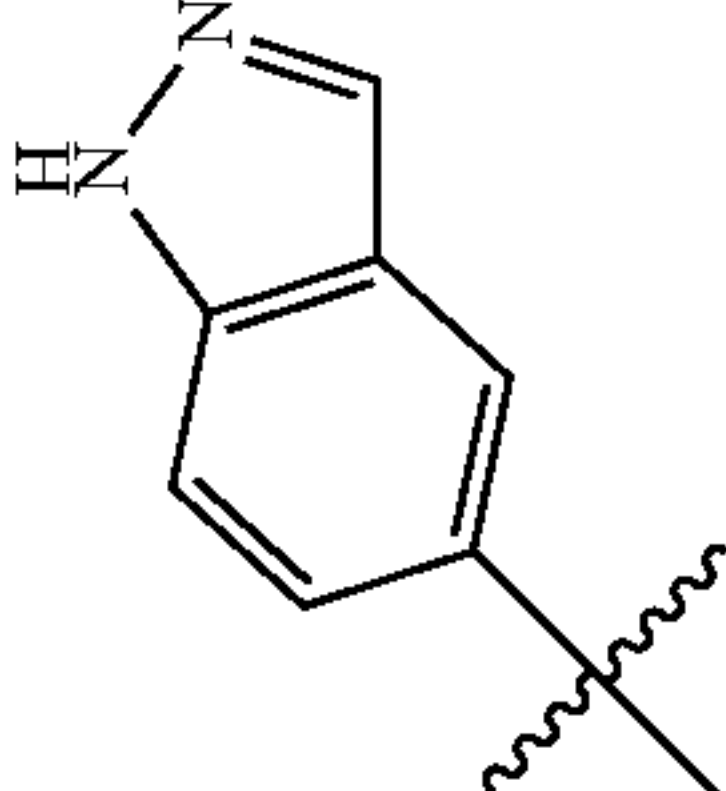
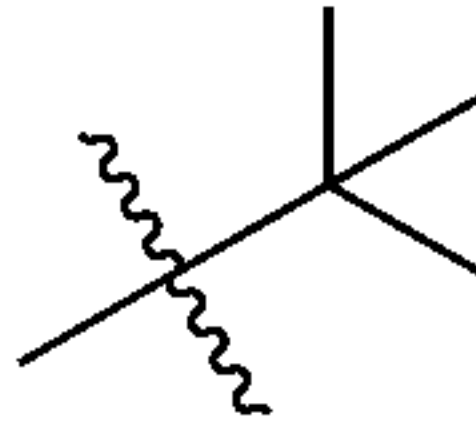
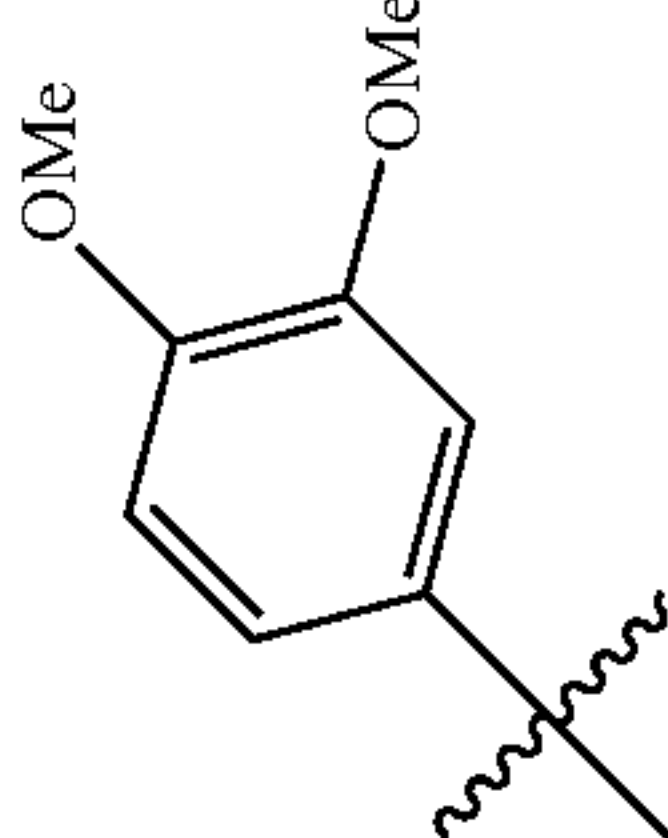
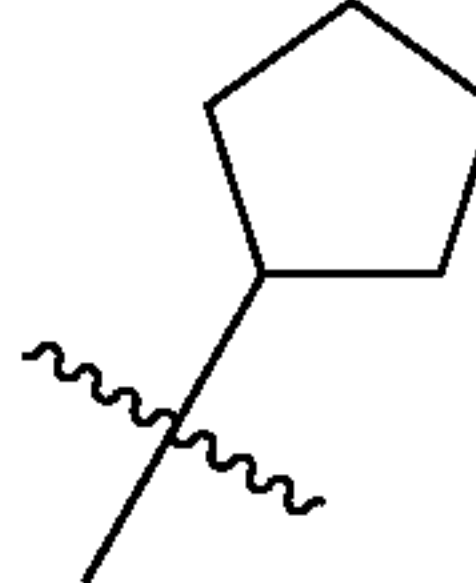
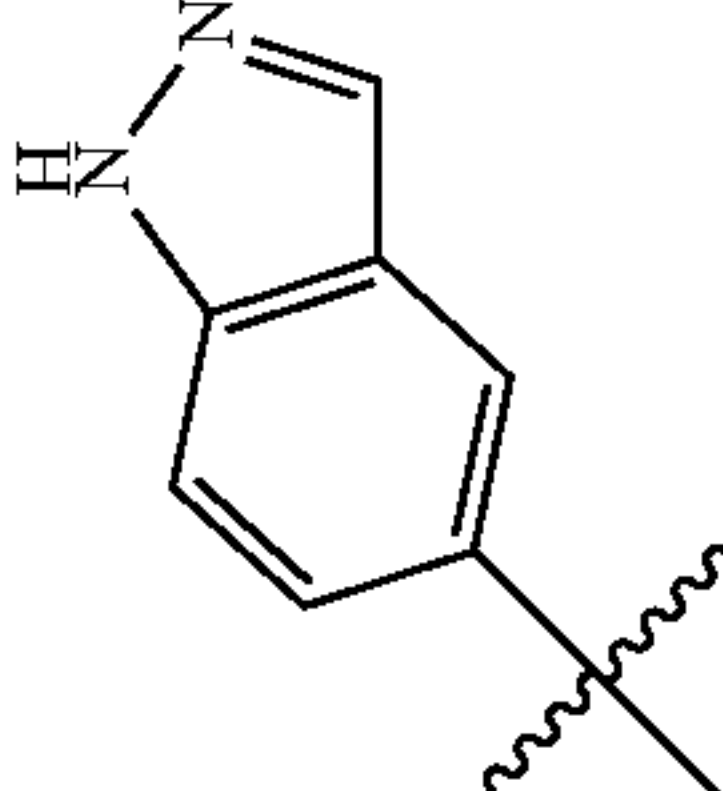
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK411			BA89		
ZK407			BA94		
BA98			BA135		
BA23			BA137		
ZK485			BA138		

TABLE 1-continued

Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK495			BA160		
ZK496			BA157_3		
ZK494			BA154		
BA90			BA110		
ZK341	—H		BA115		

TABLE 1-continued

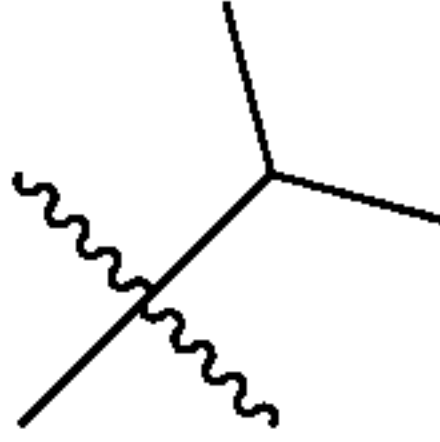
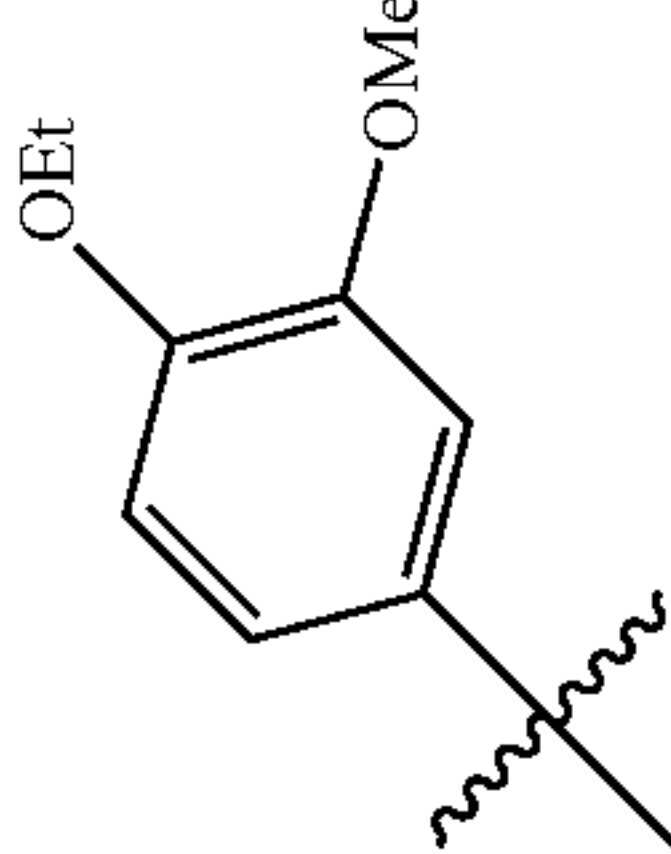
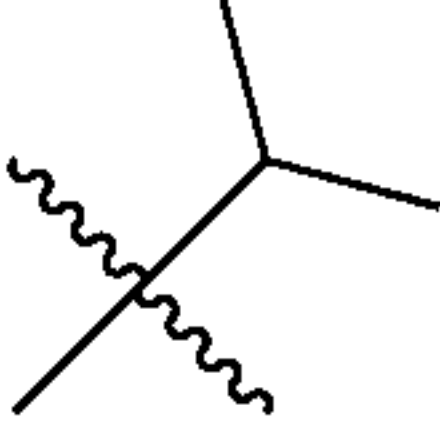
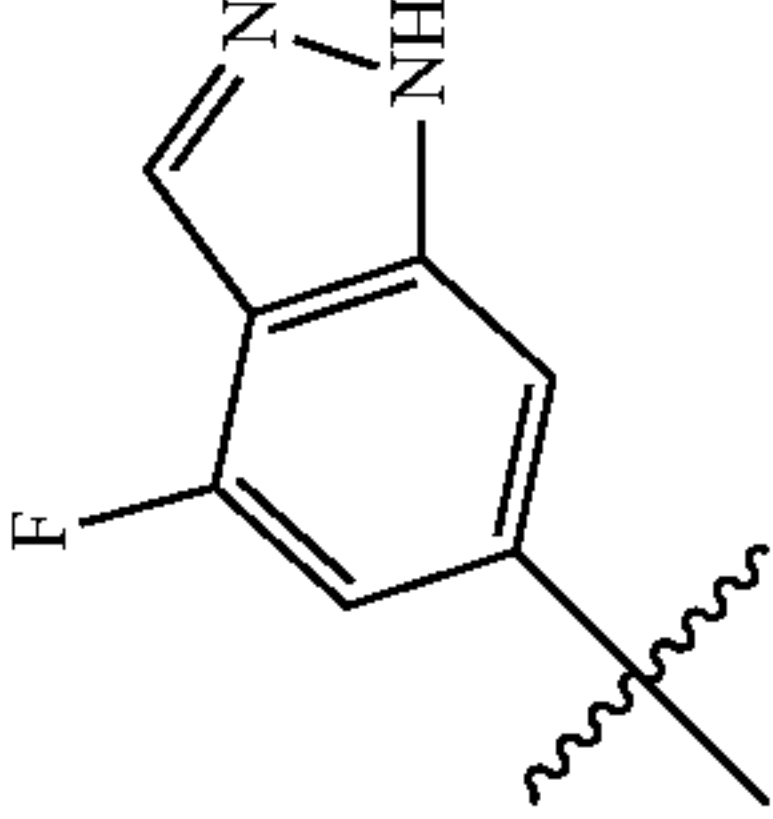
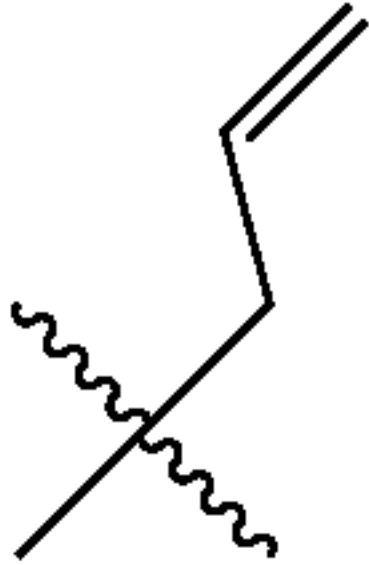
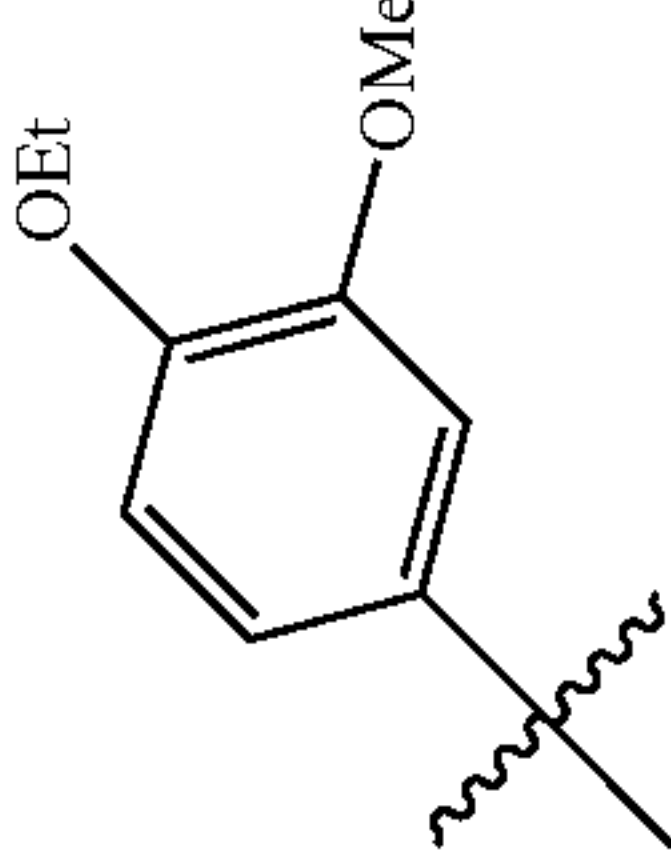
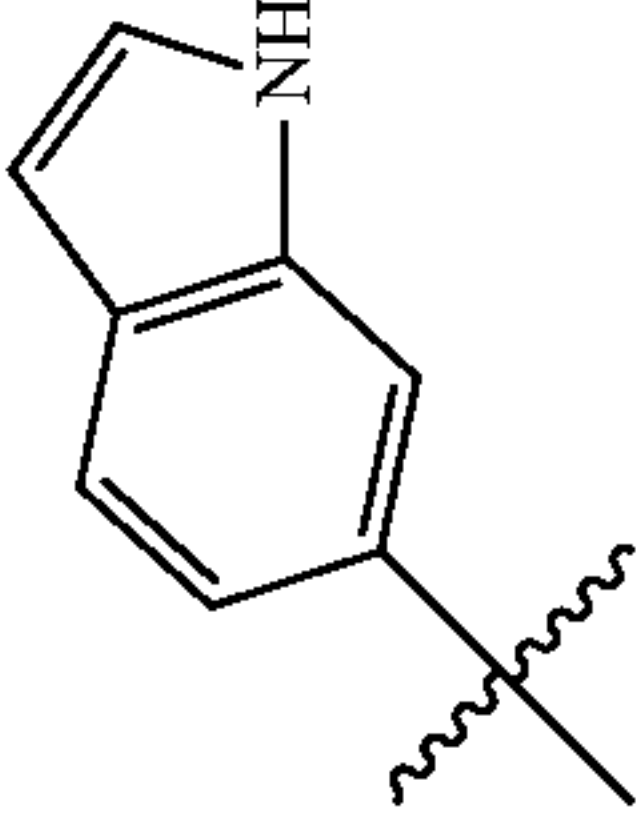
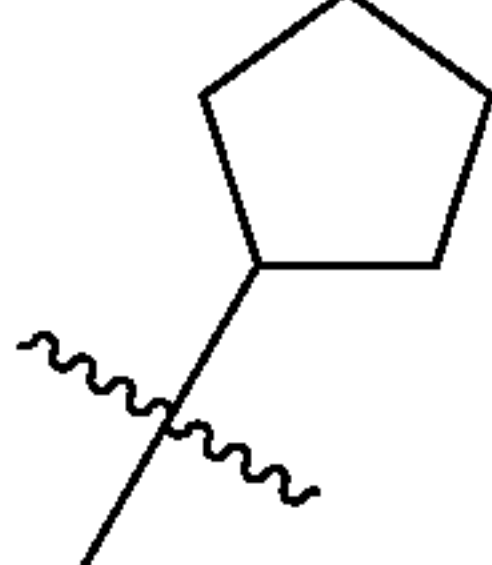
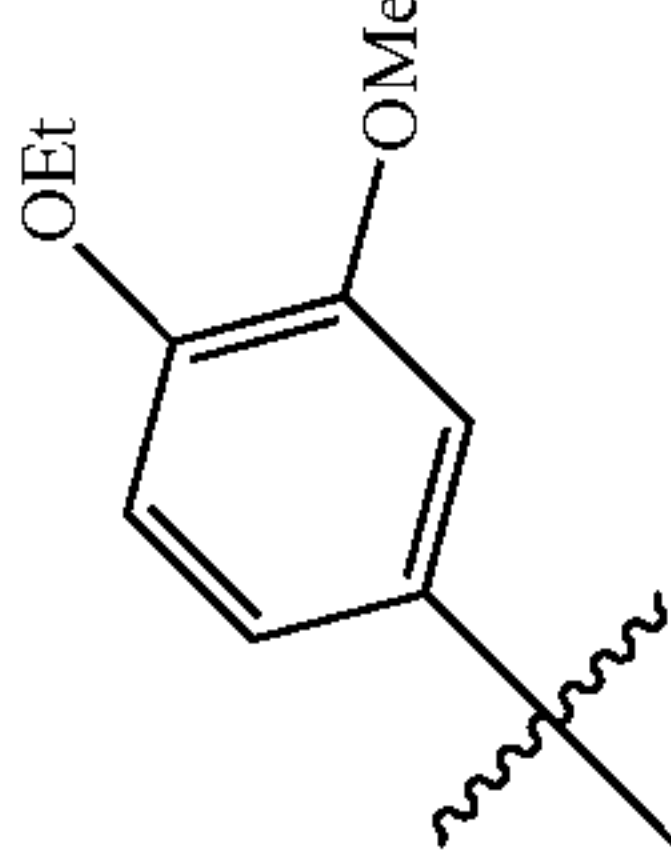
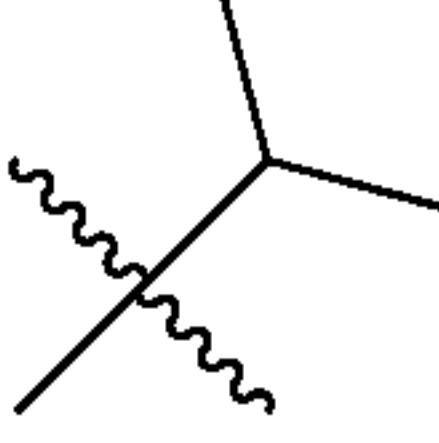
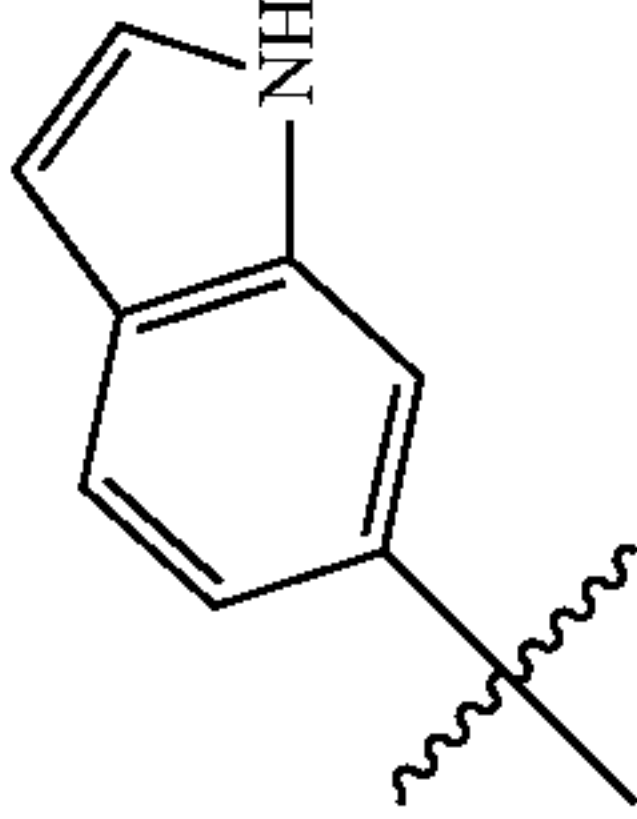
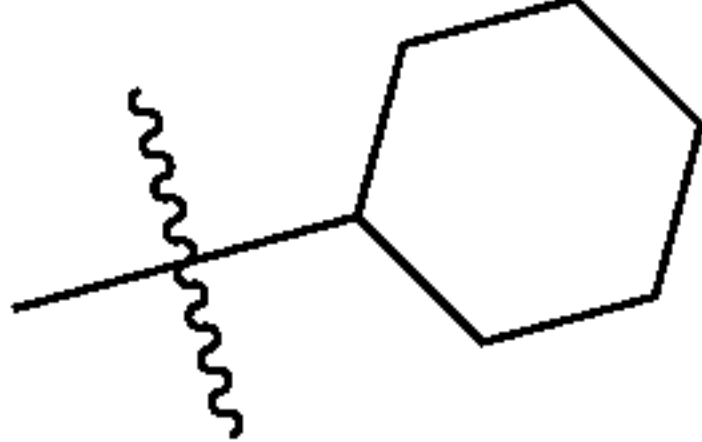
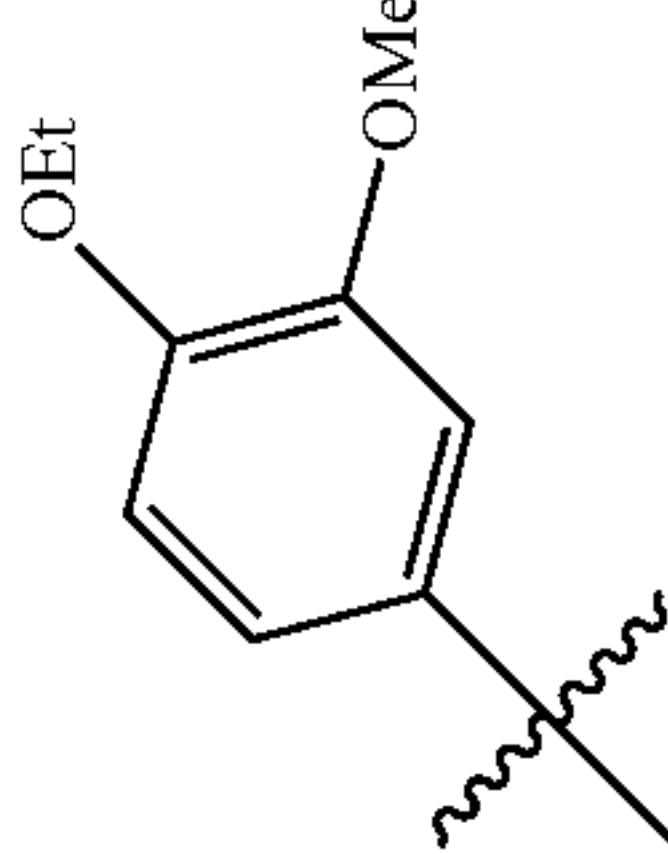
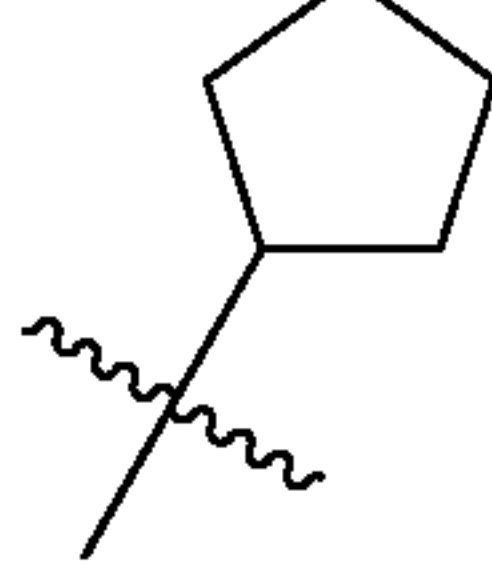
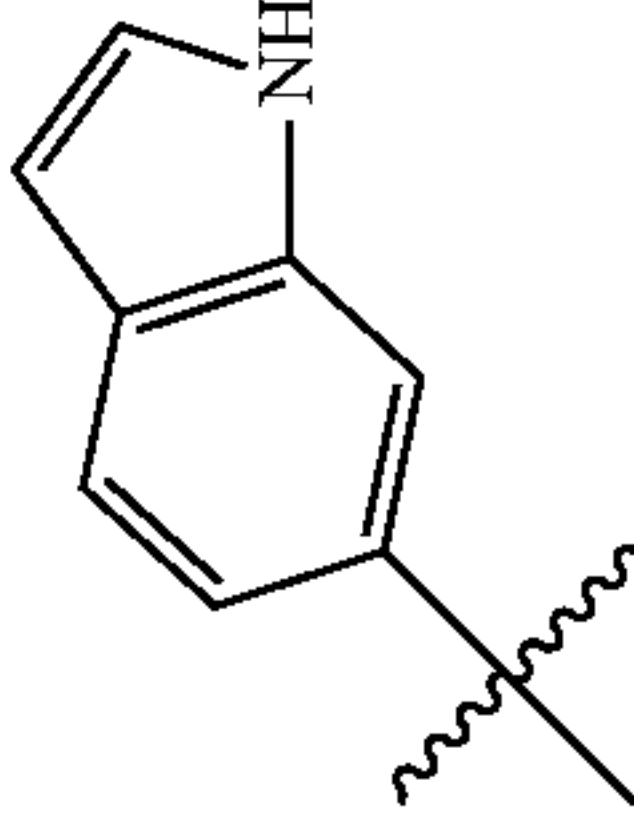
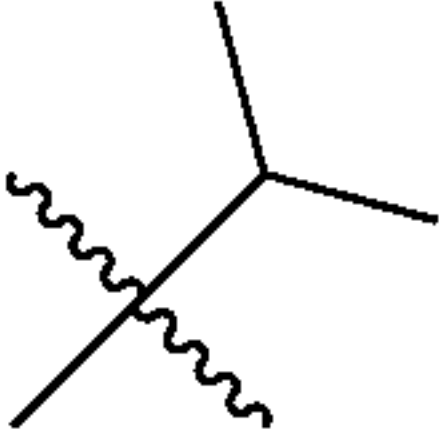
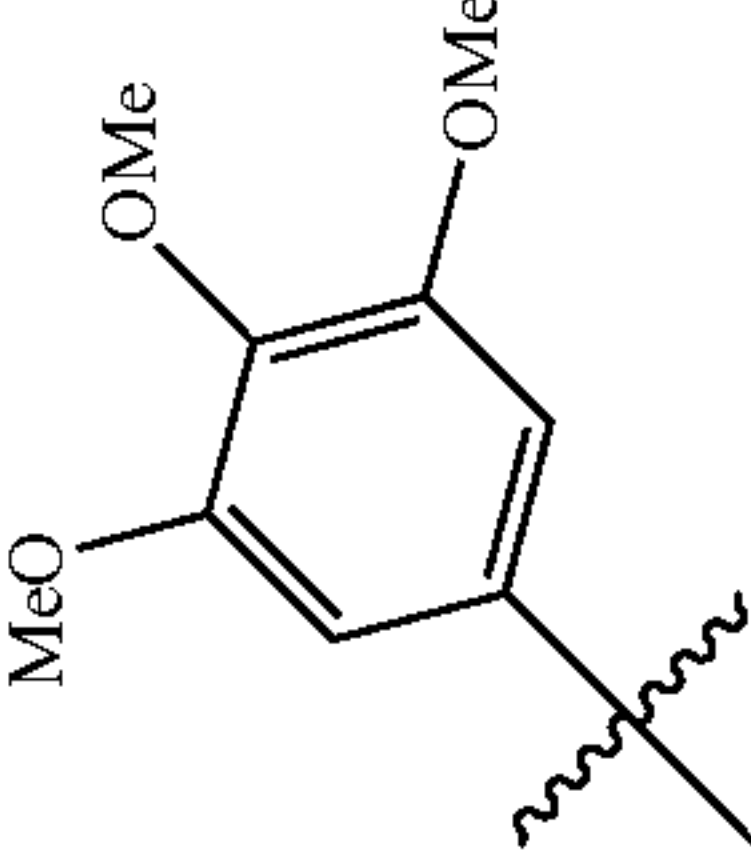
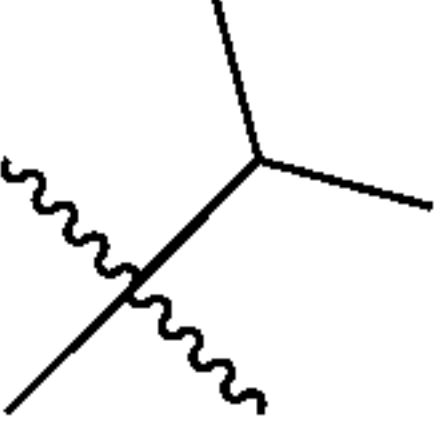
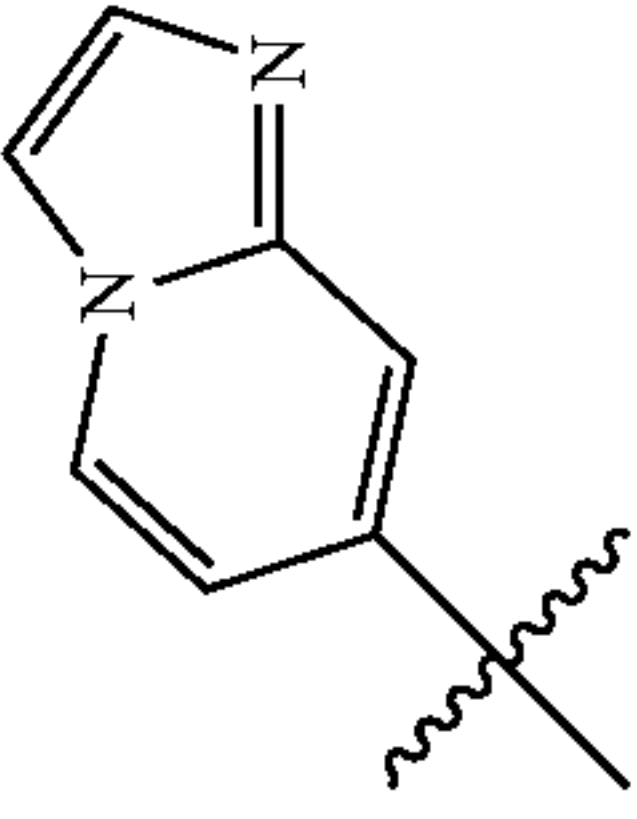
Cpd	R ¹	R ²	Cpd	R ¹	R ²
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ZK361			BA119		
ZK359			BA107		
ZK362			BA124		
BA64			BA161		

TABLE 1-continued

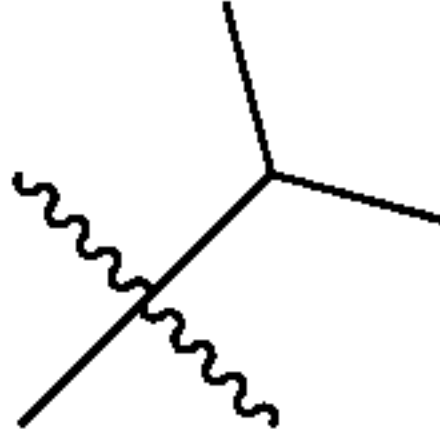
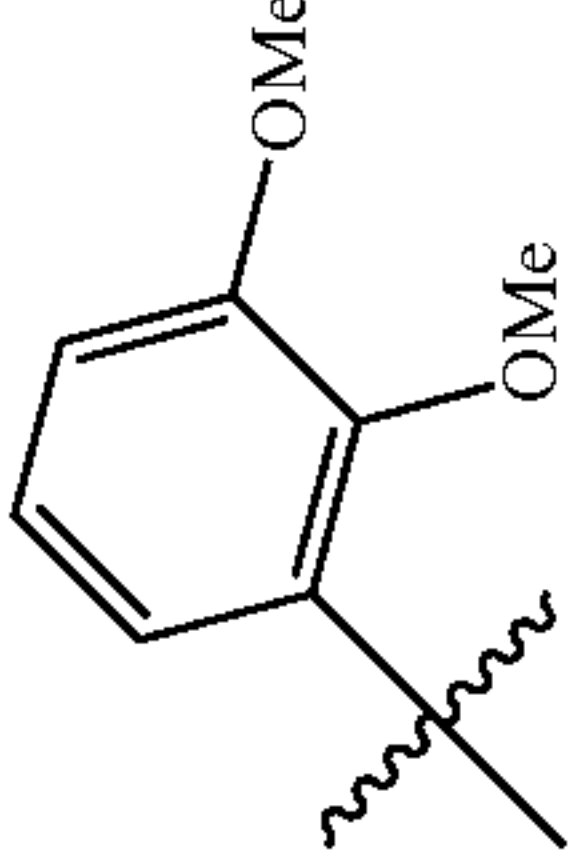
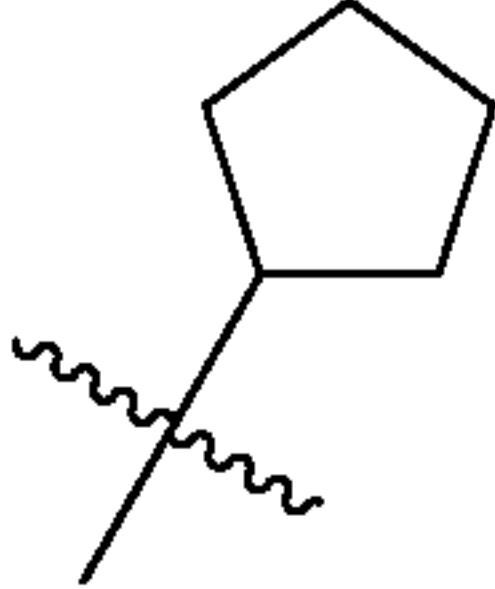
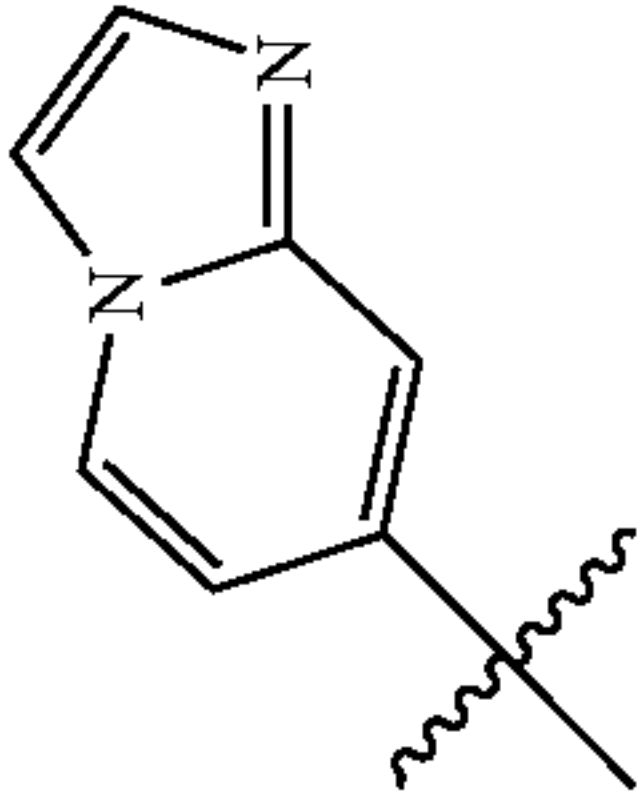
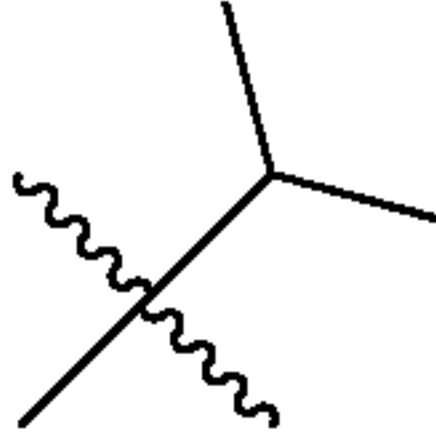
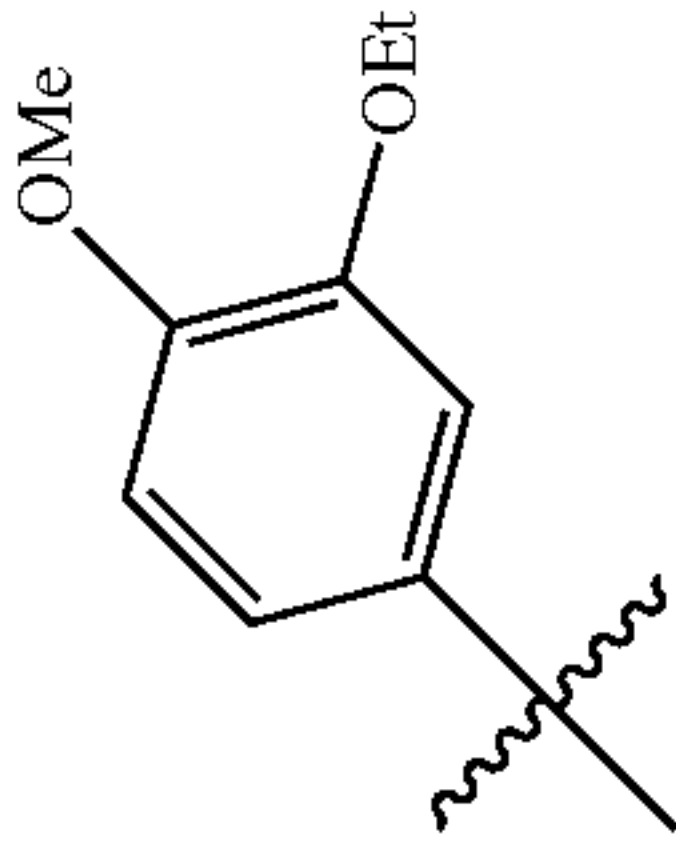
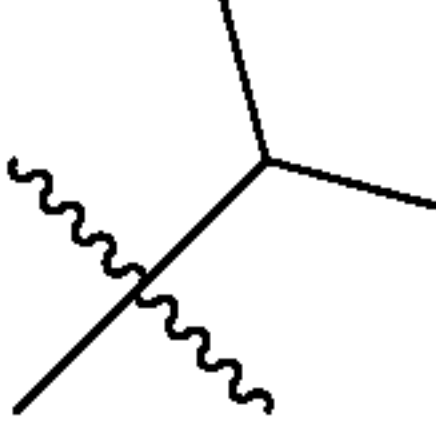
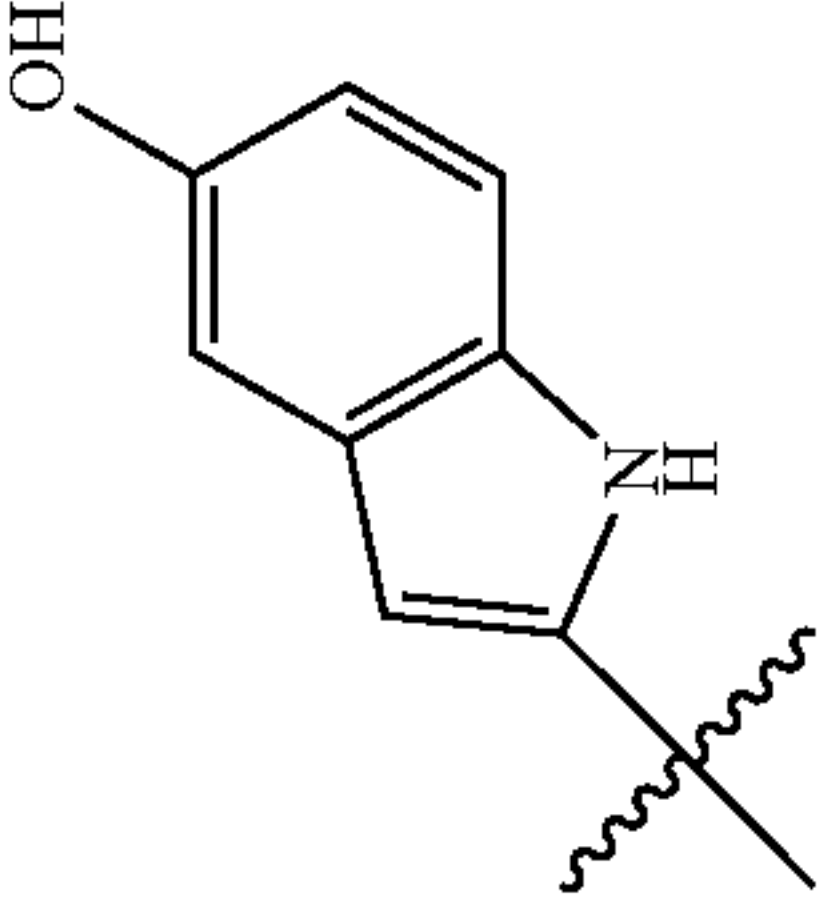
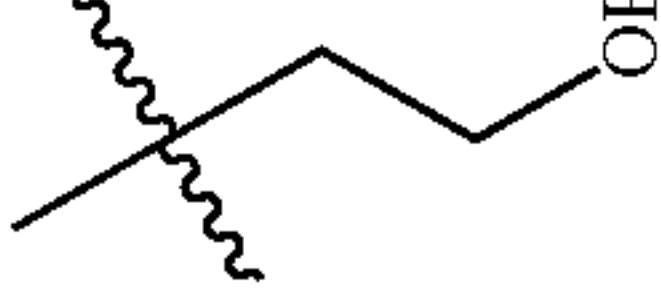
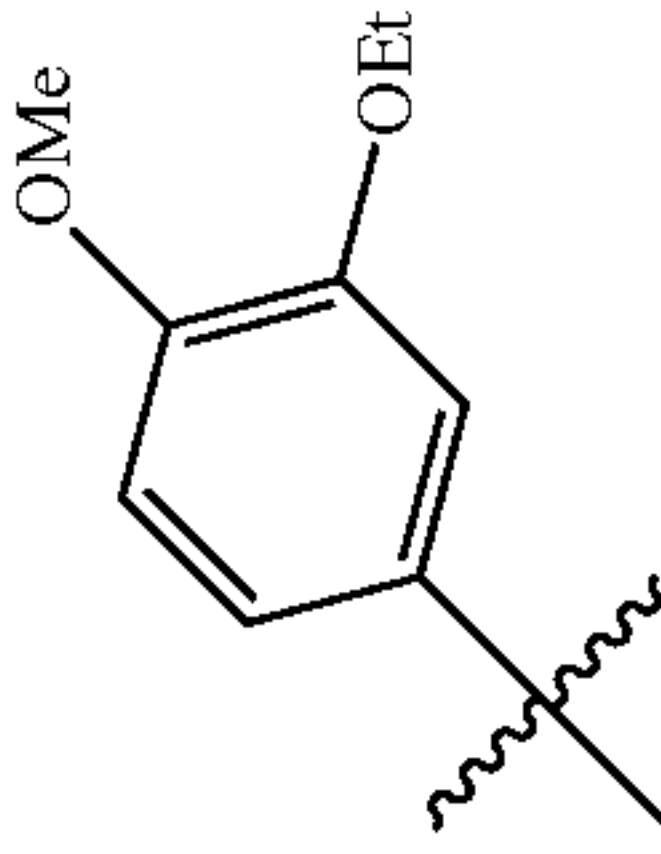
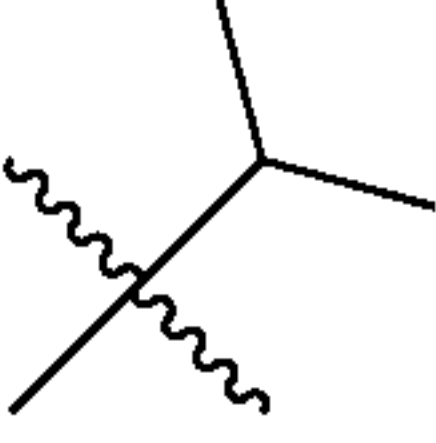
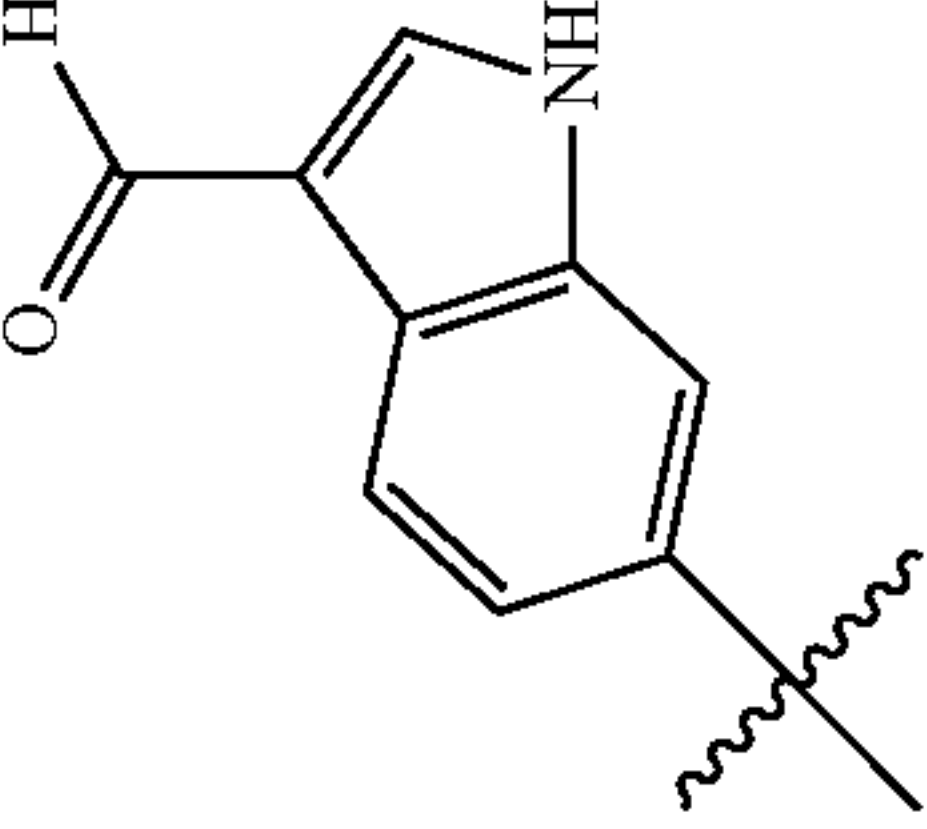
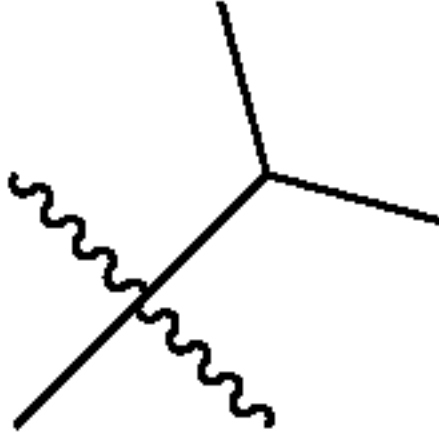
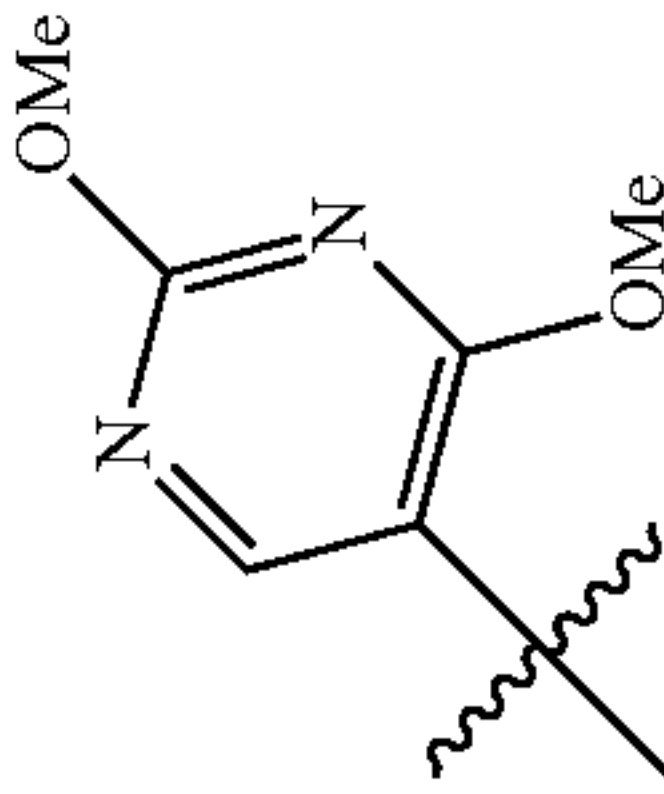
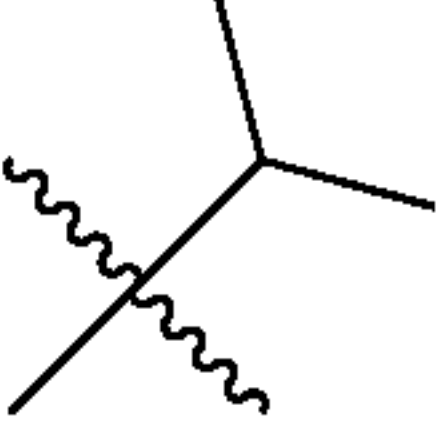
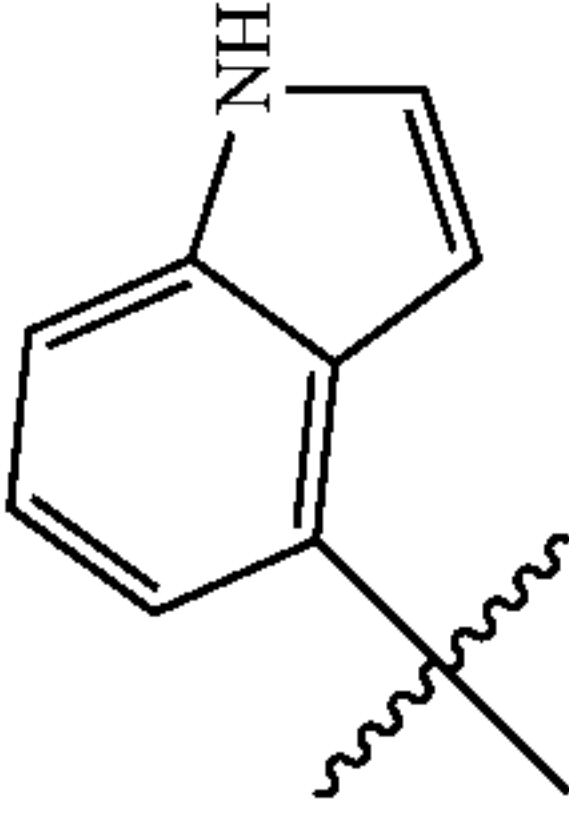
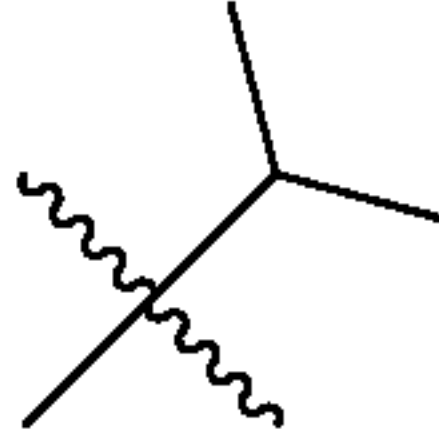
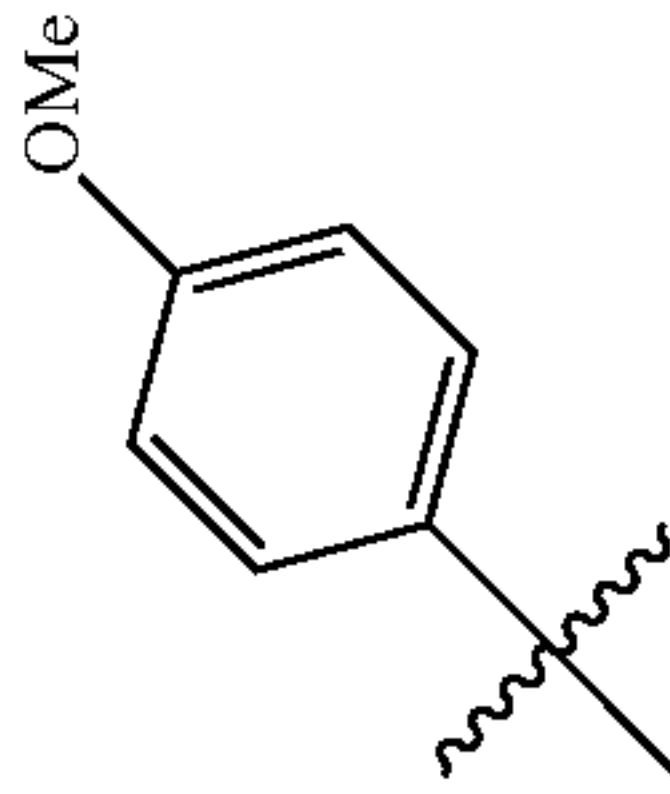
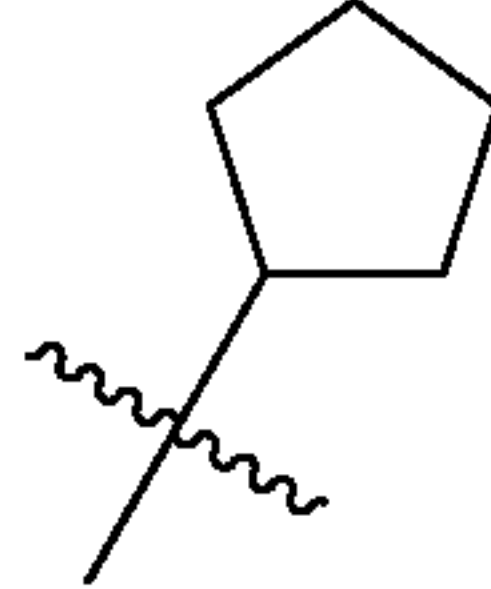
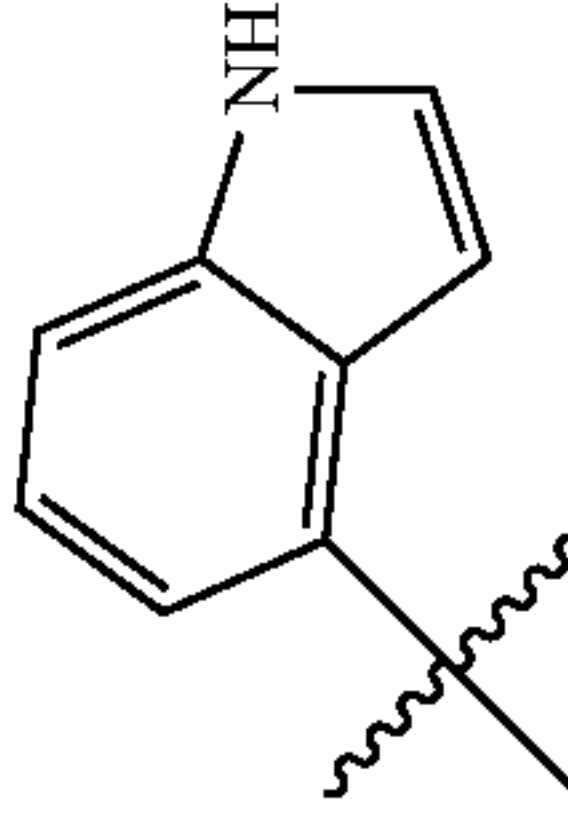
Cpd	R ¹	R ²	Cpd	R ¹	R ²
BA65			BA162		
ZK305			BA24dd		
ZK306			BA43		
BA66			BA91		
BA48			BA92		

TABLE 1-continued

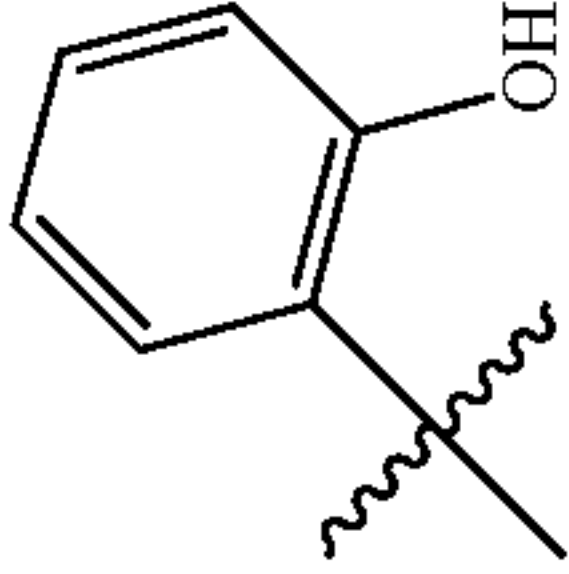
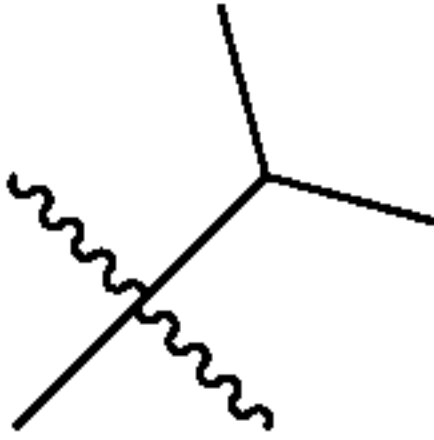
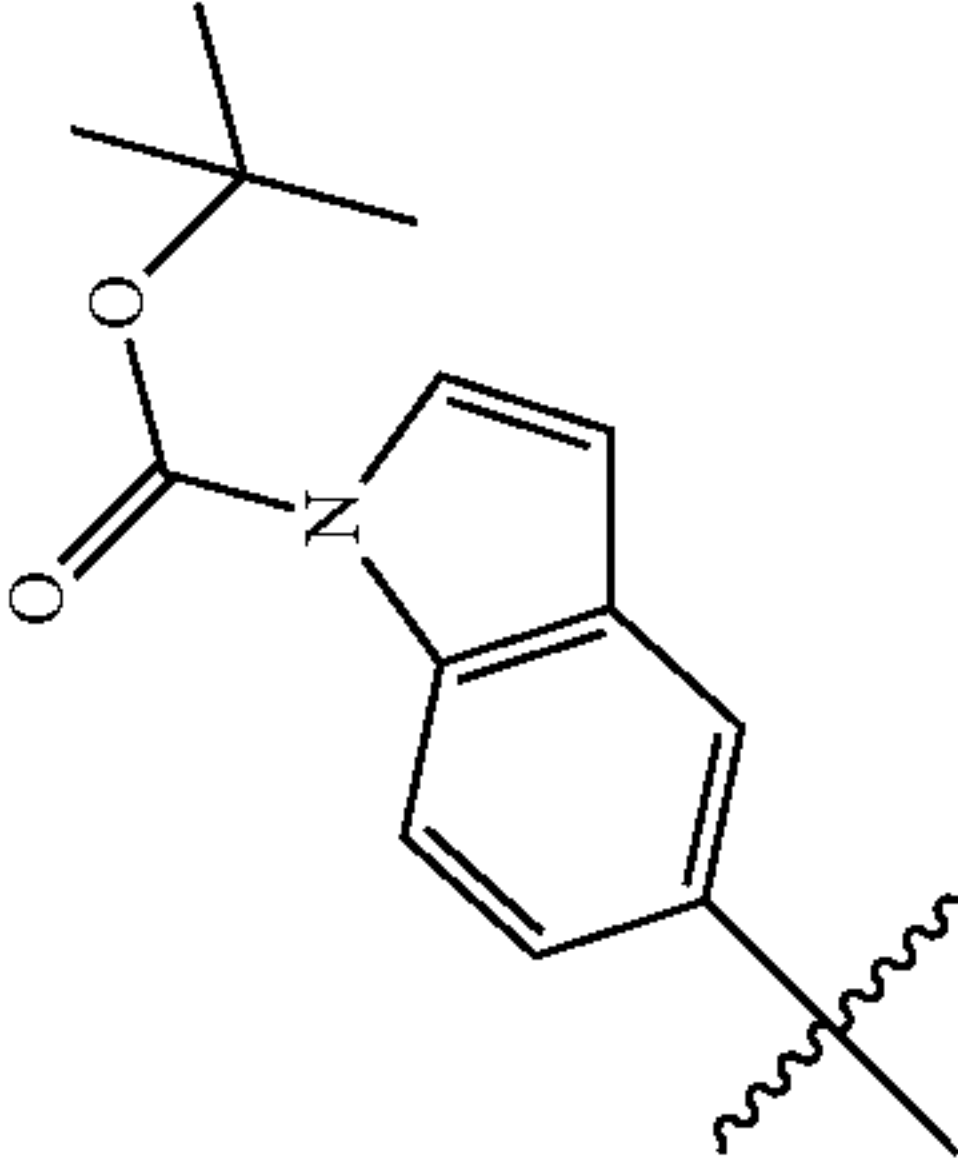
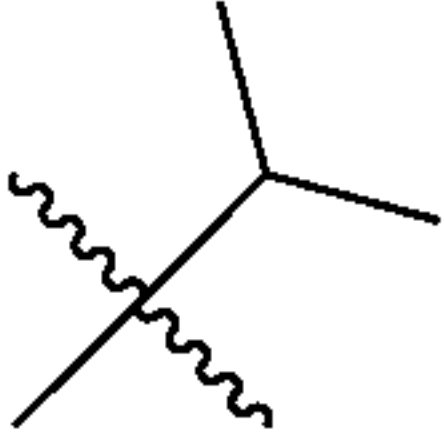
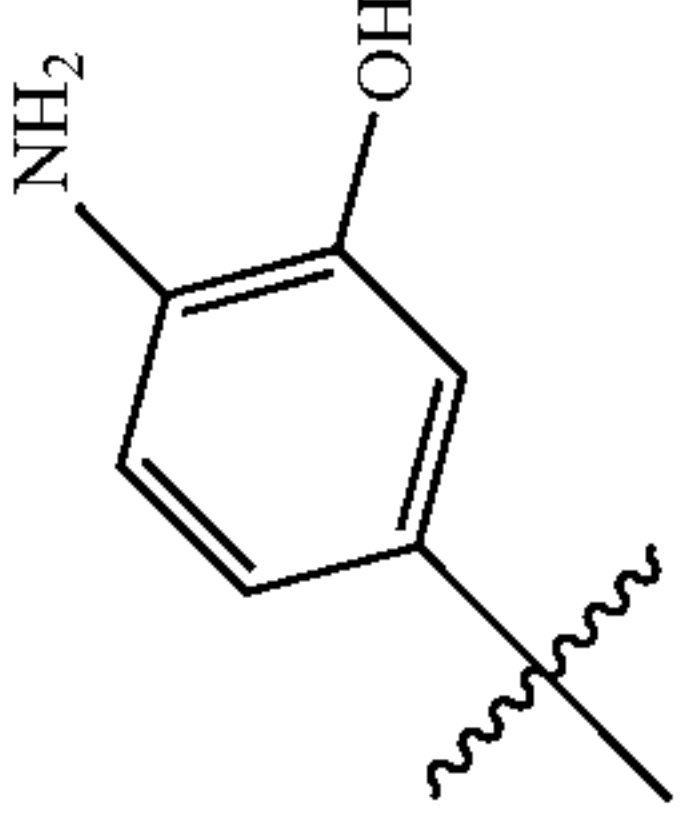
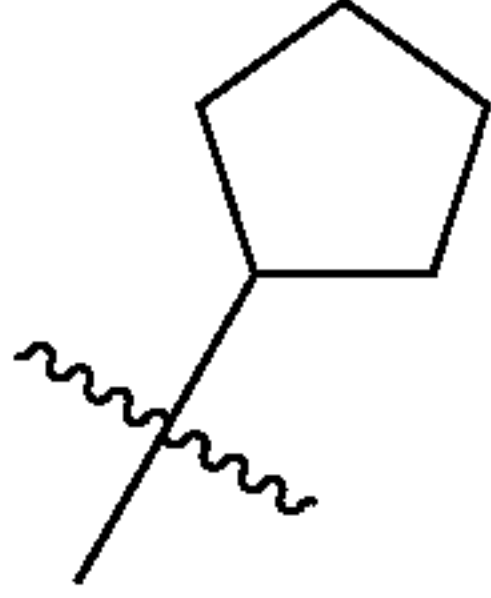
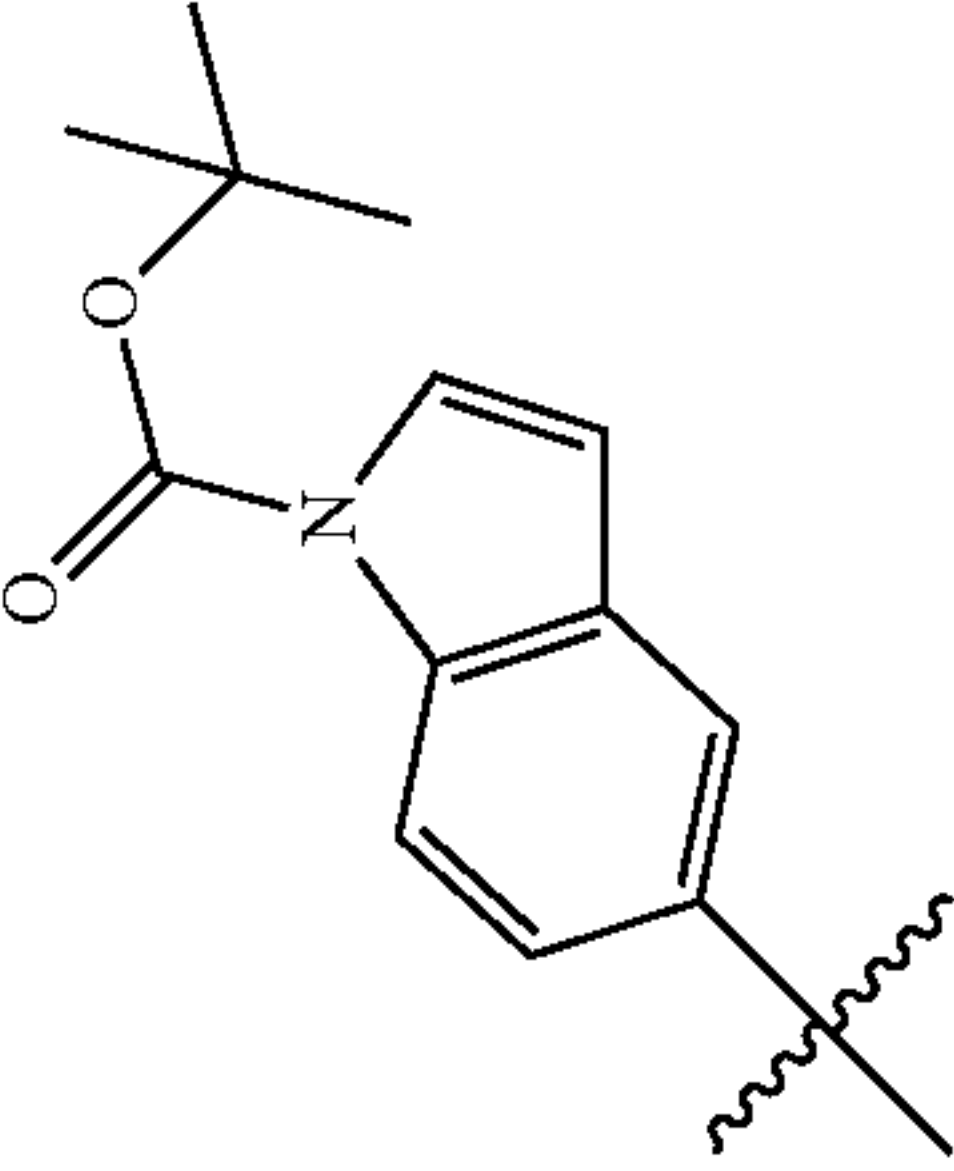
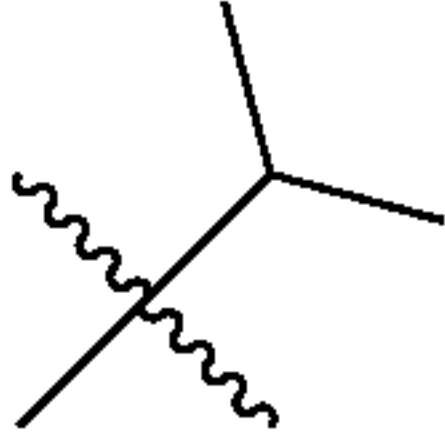
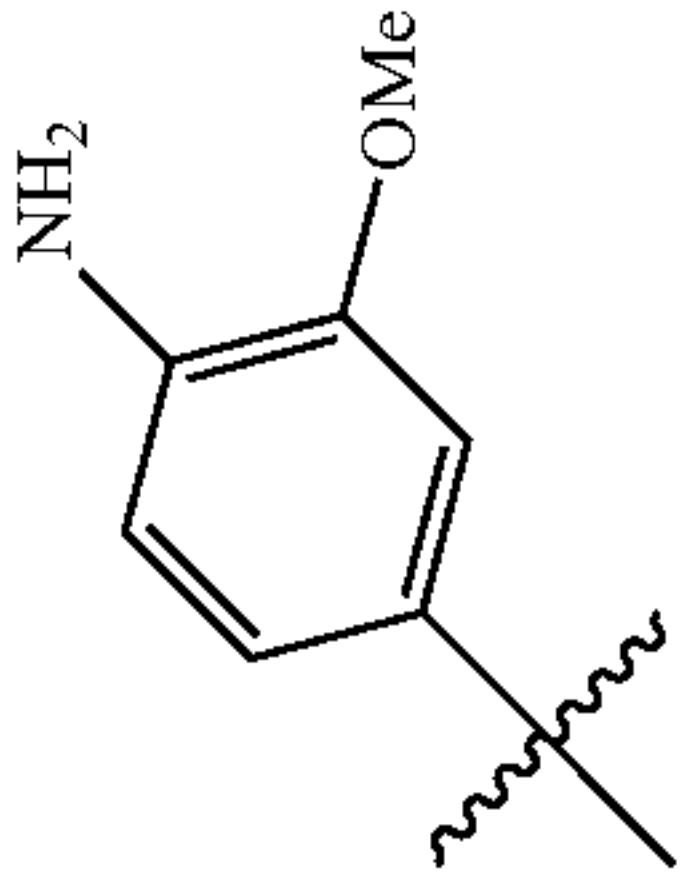
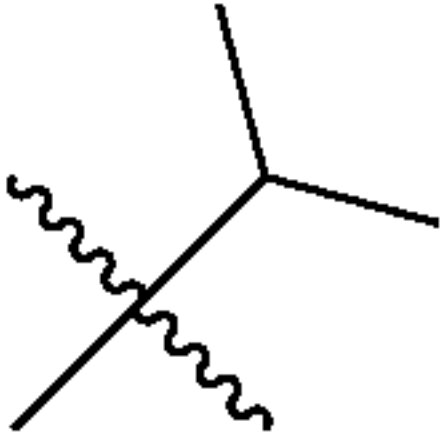
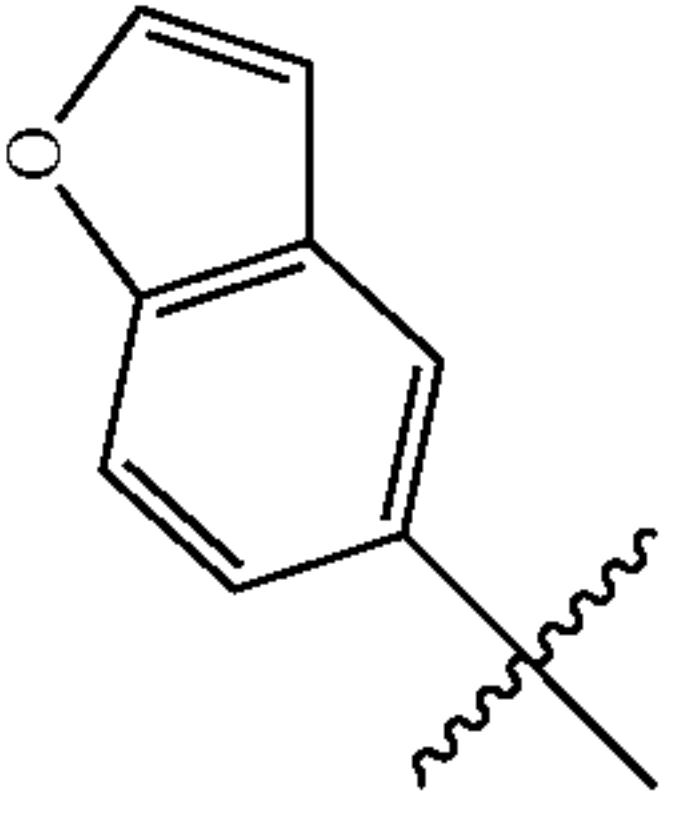
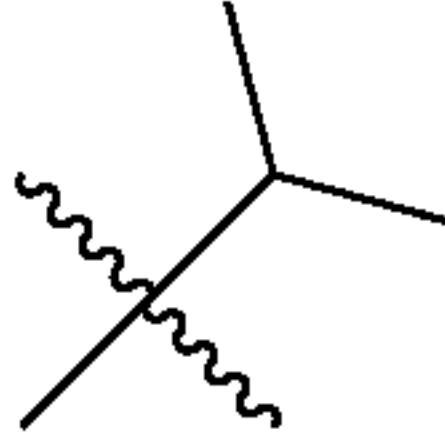
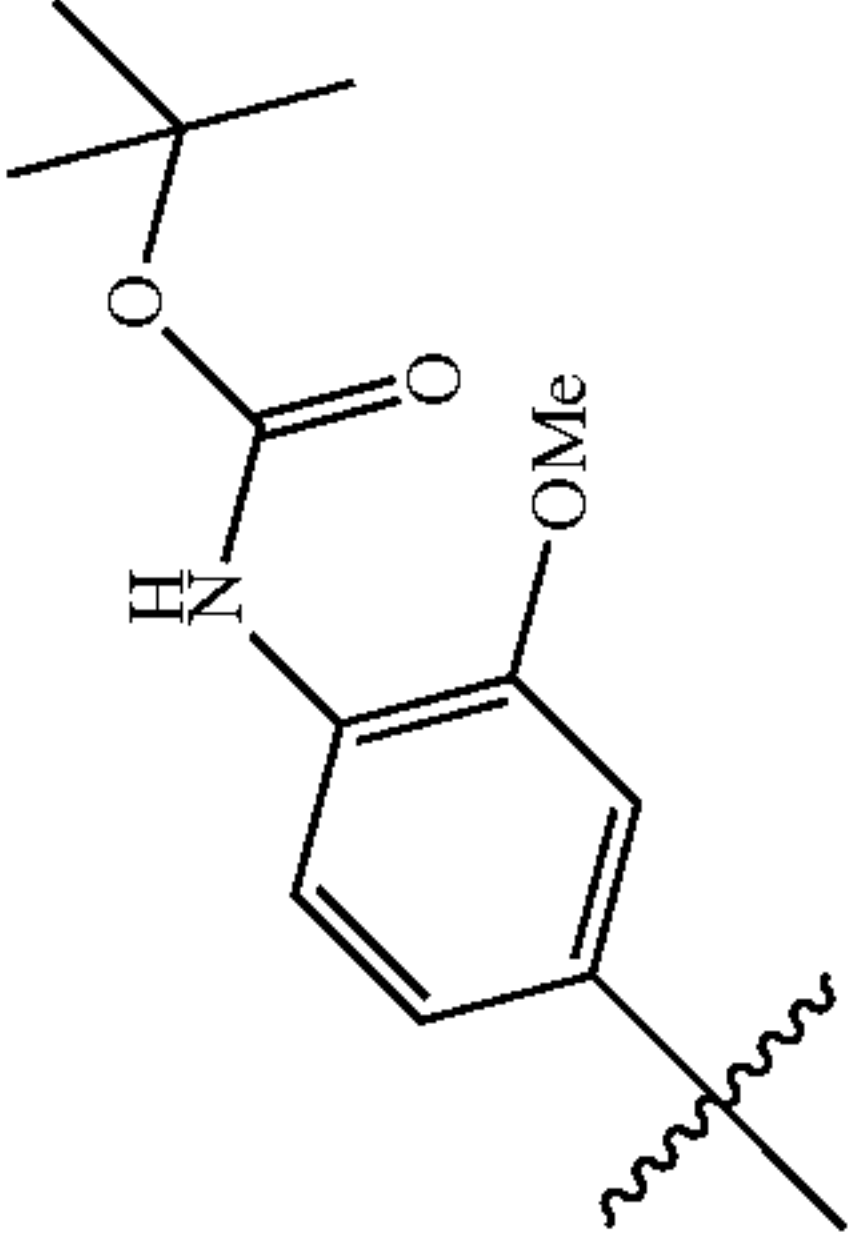
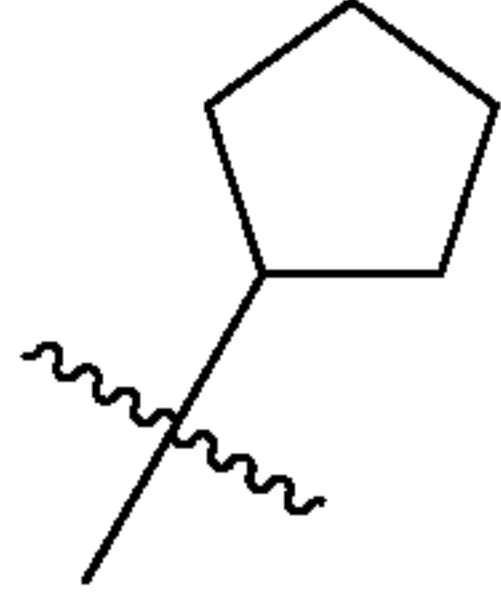
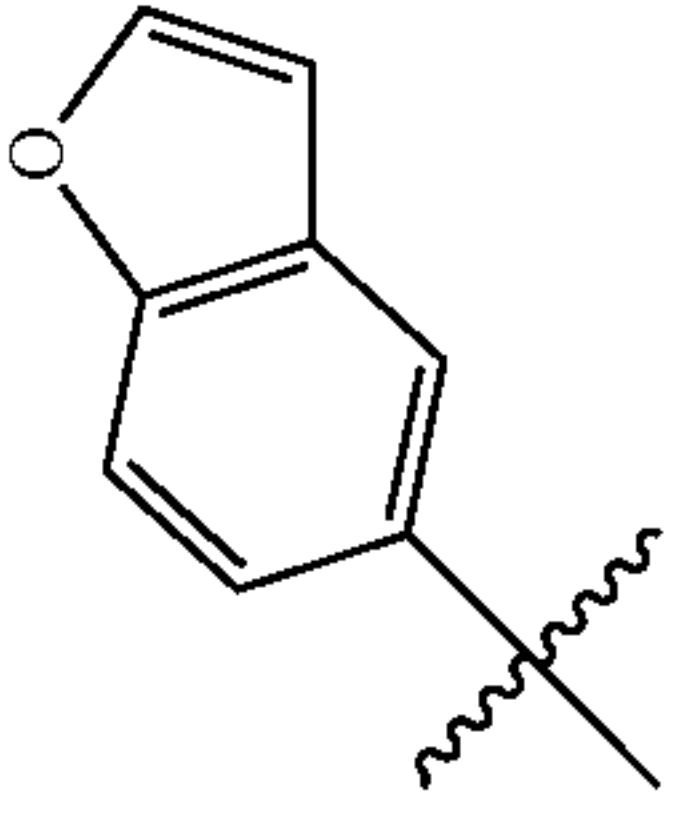
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK133	—H		BA86		
BA20dd			BA88		
BA20d			BA96		
BA20			BA97		

TABLE 1-continued

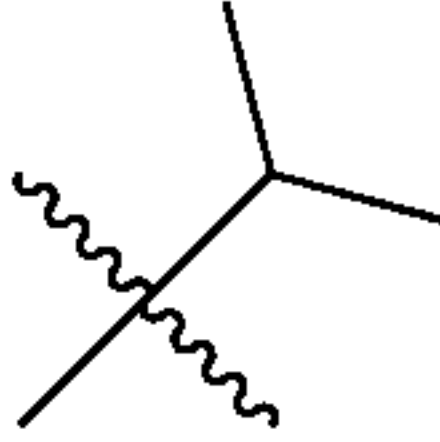
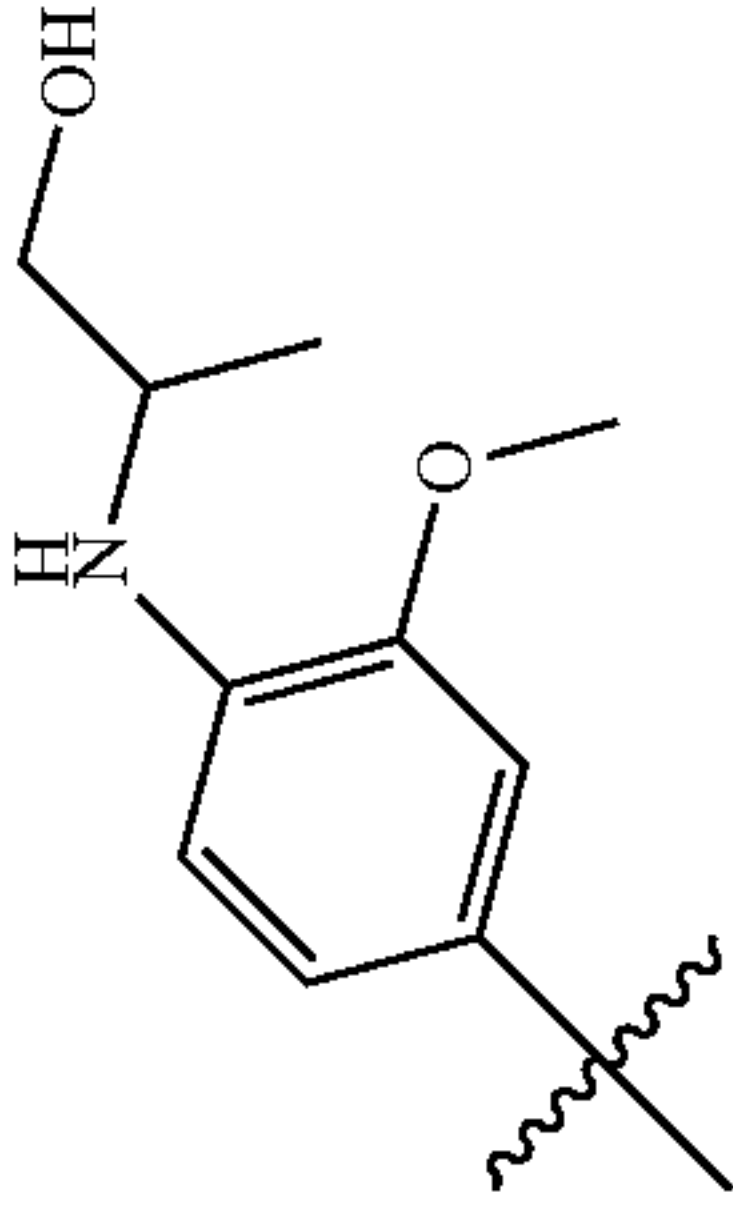
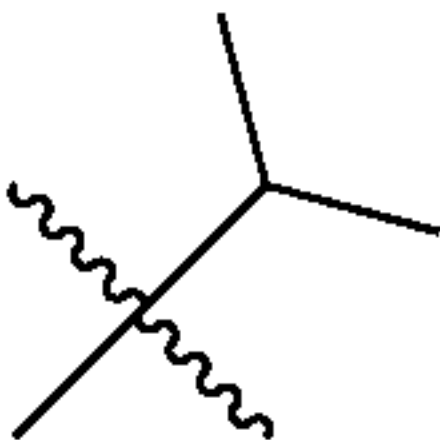
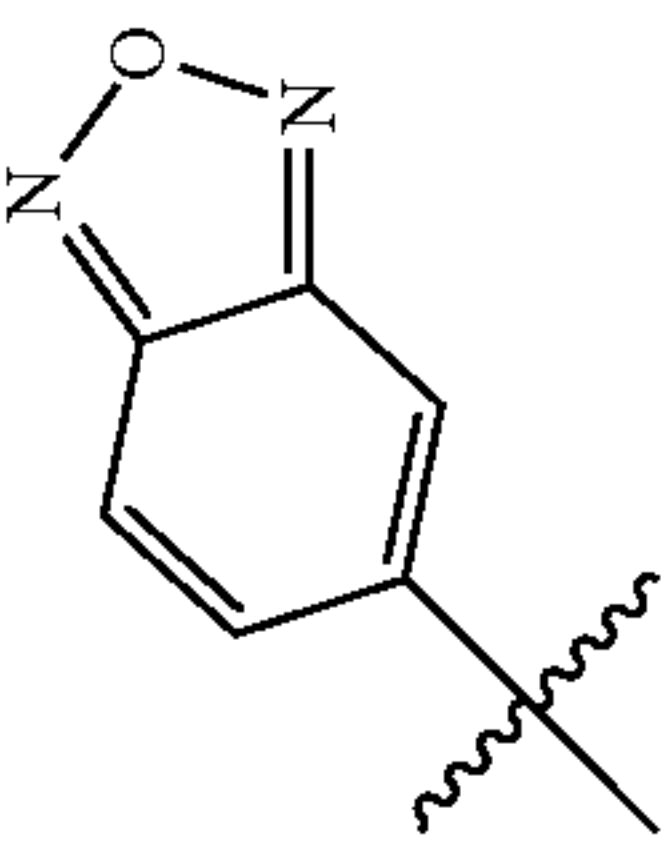
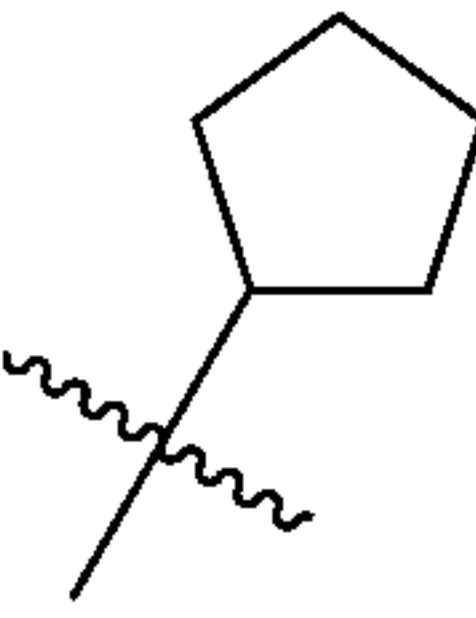
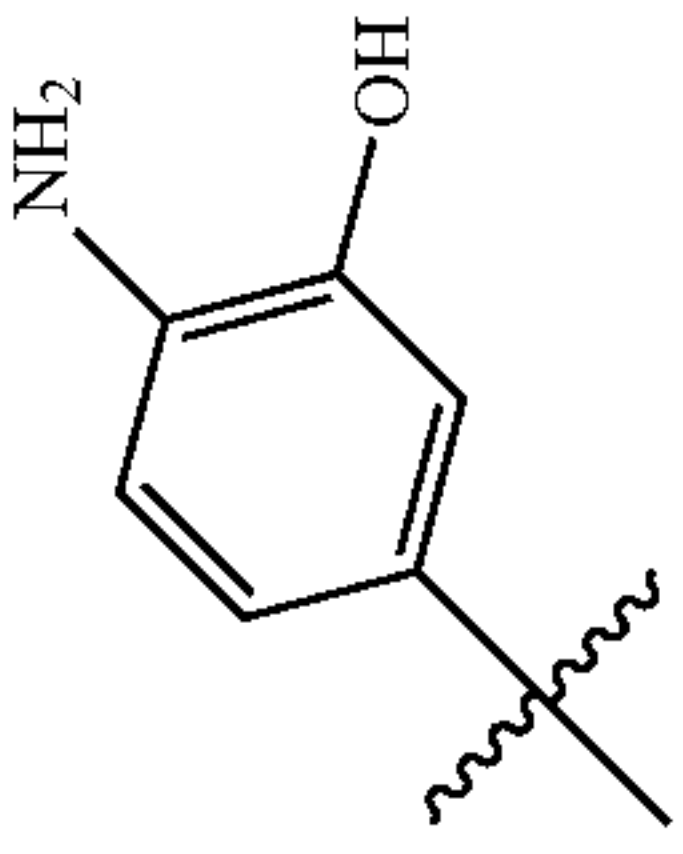
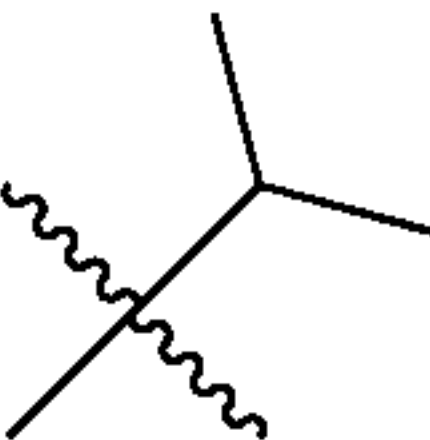
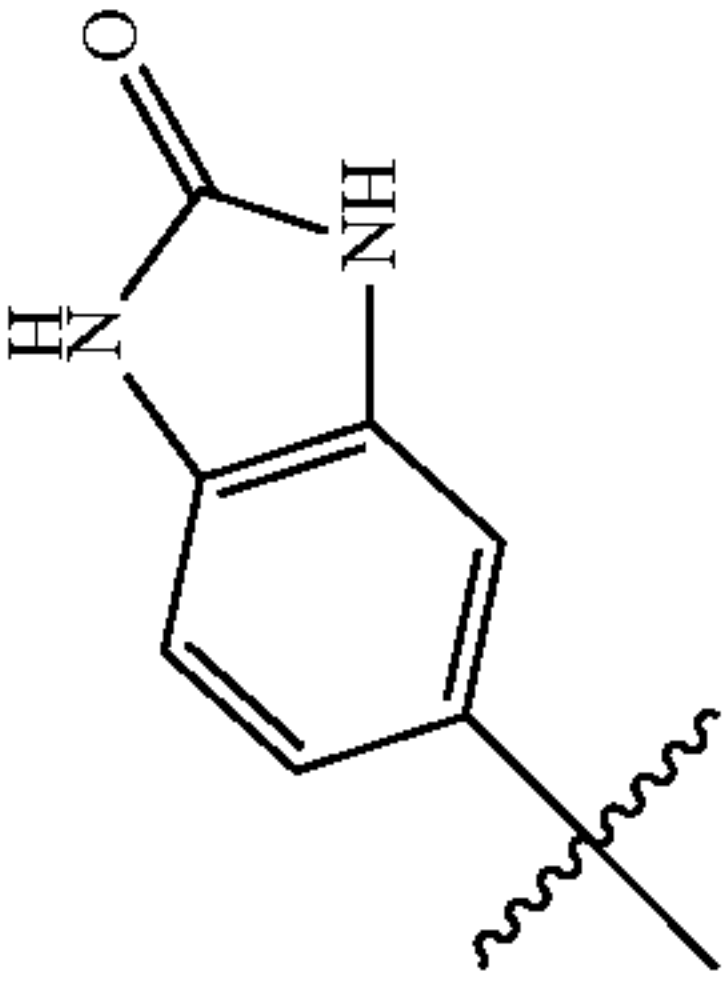
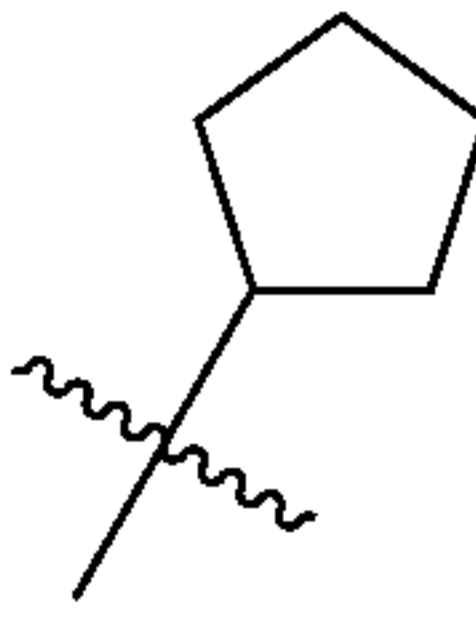
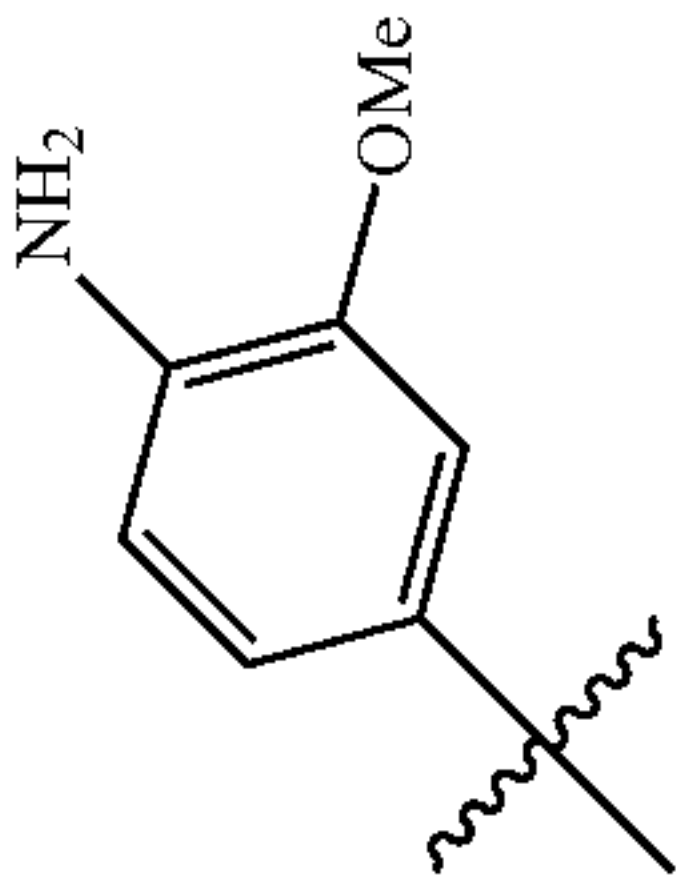
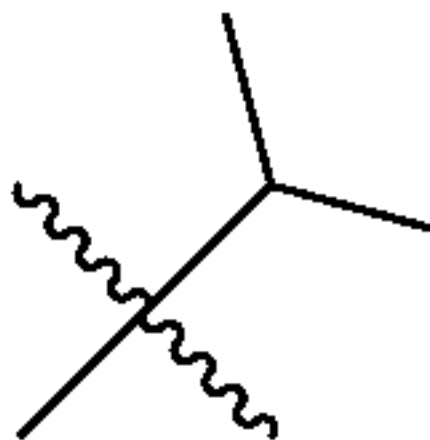
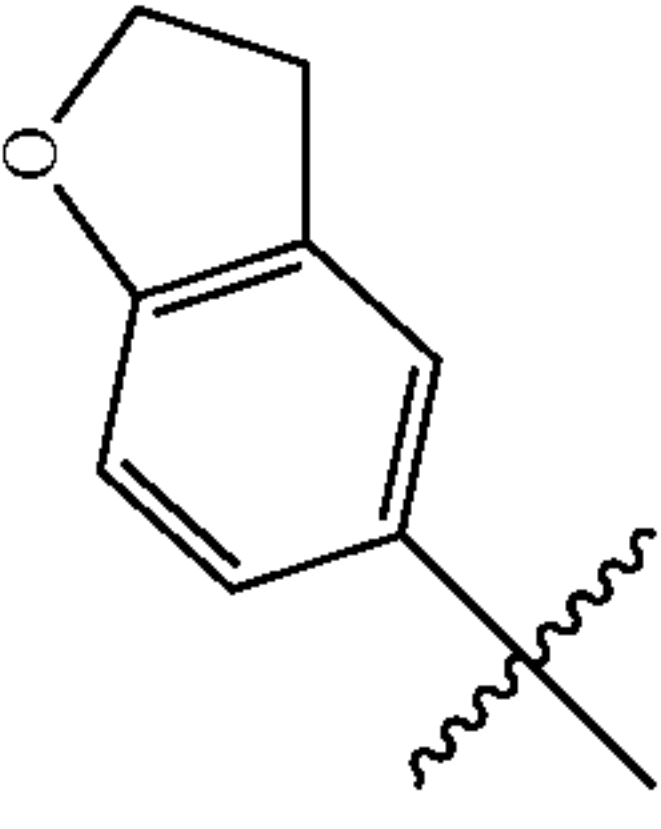
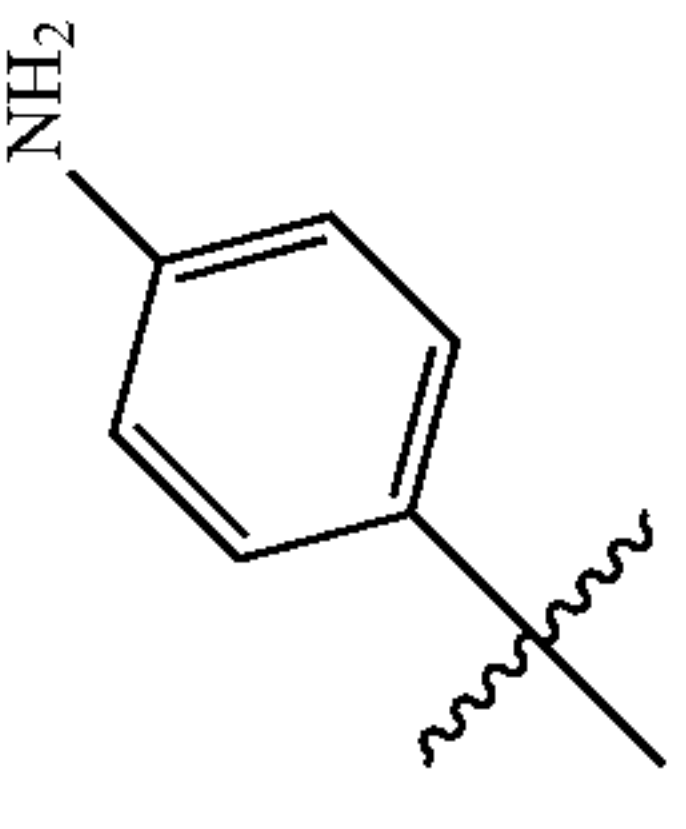
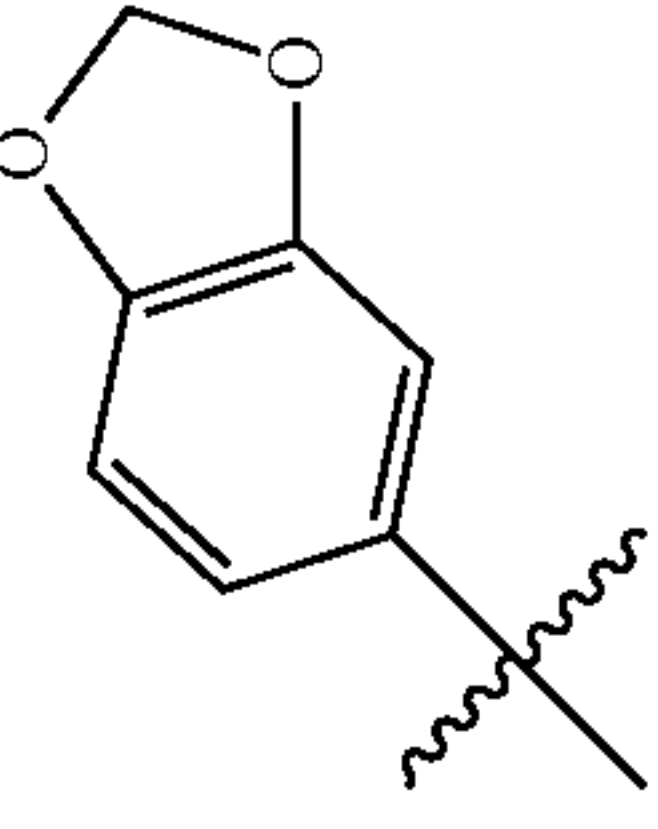
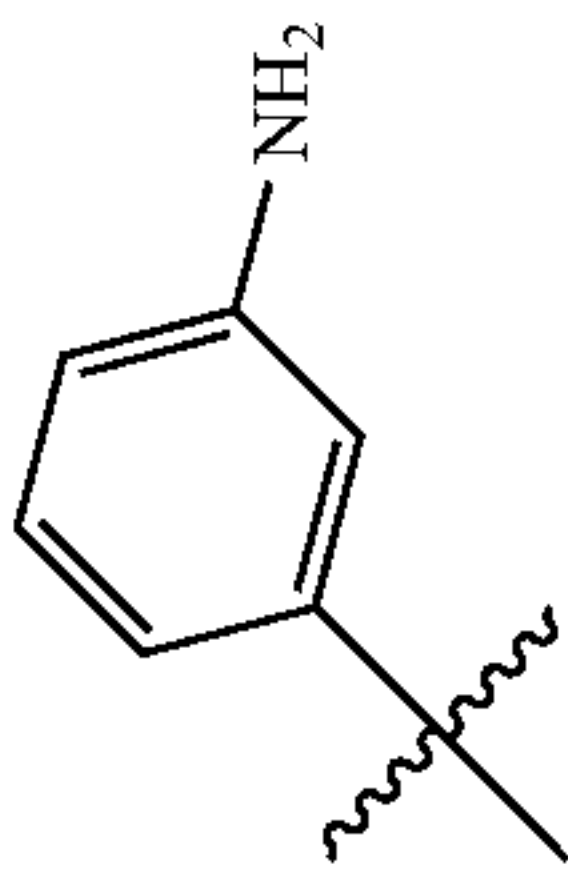
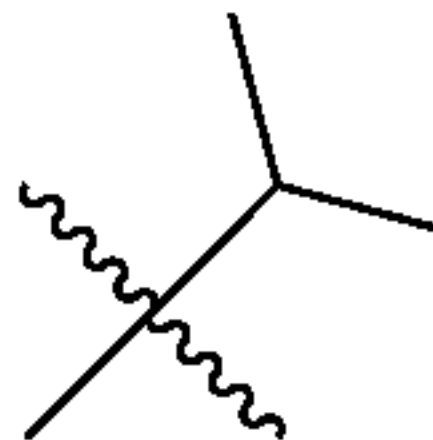
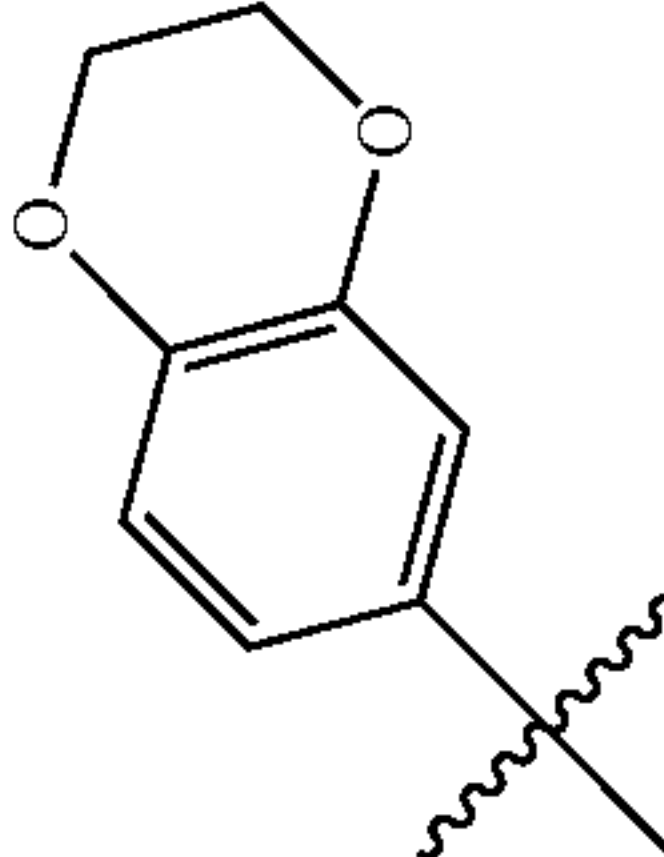
Cpd	R ¹	R ²	Cpd	R ¹	R ²
BA99			BA44		
BA81dd			BA156		
BA81d			BA95		
ZK137	—H		ZK129	$\begin{matrix} \text{—Me} \\ \text{X = CH} \end{matrix}$	
ZK135	—H		BA54		

TABLE 1-continued

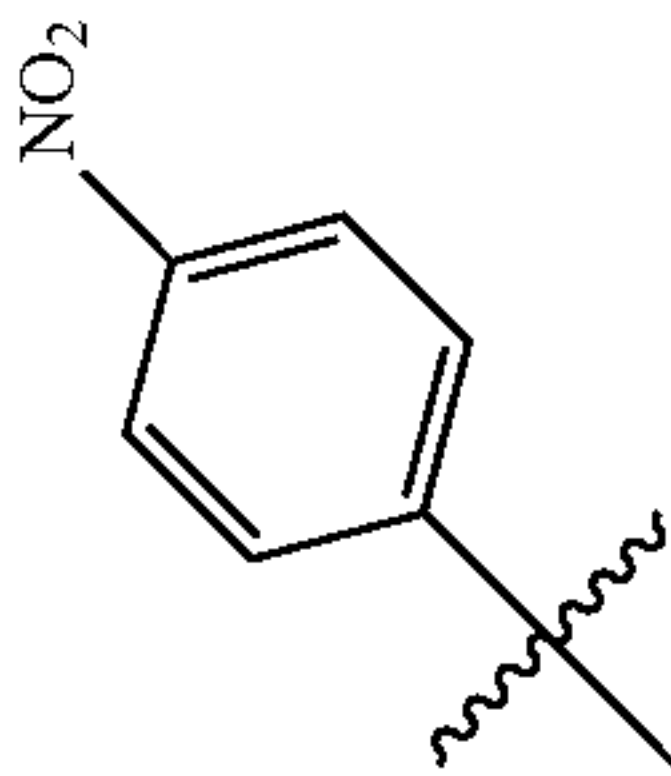
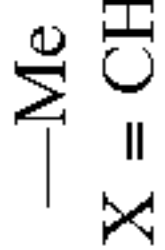
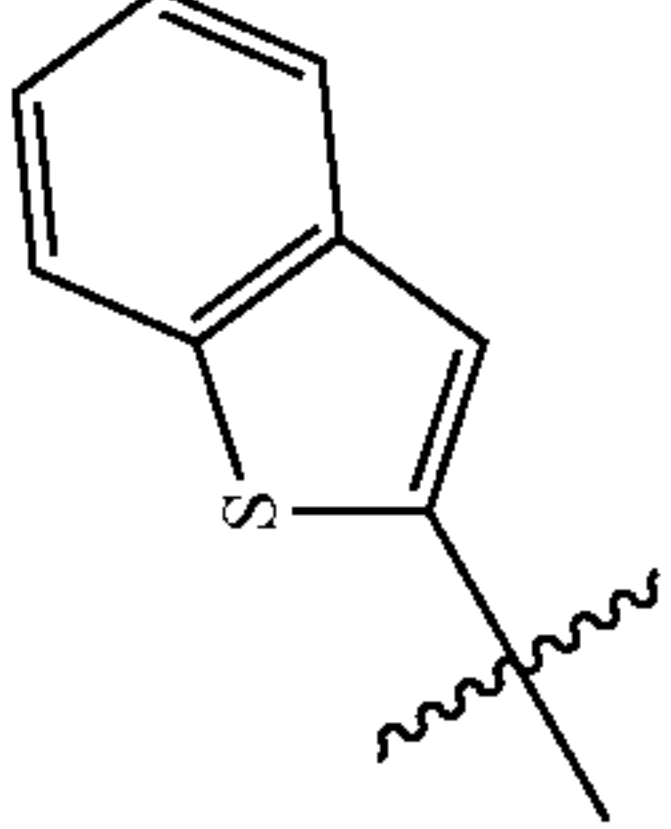
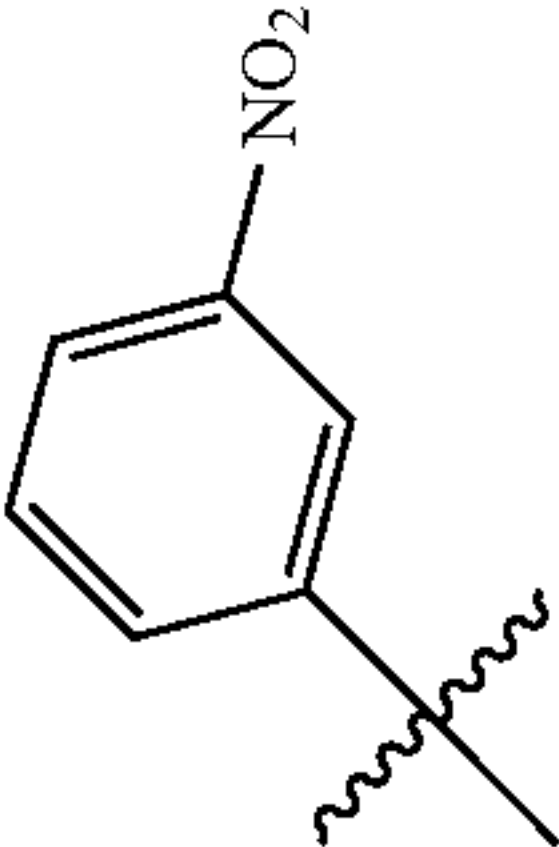
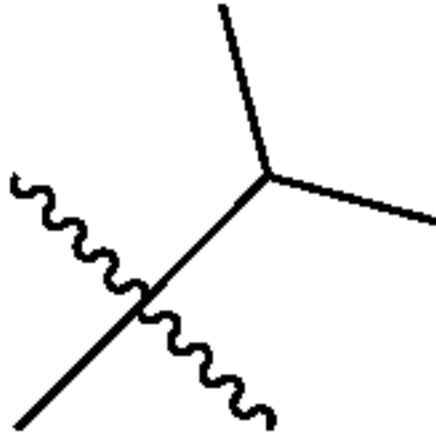
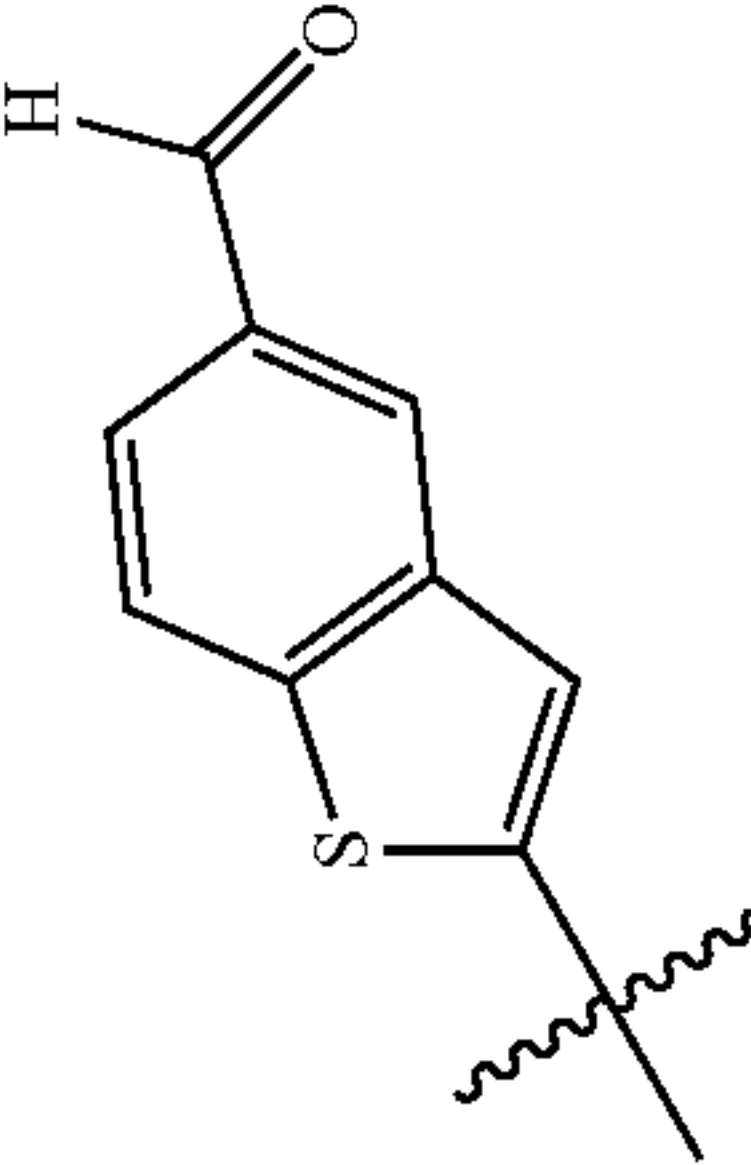
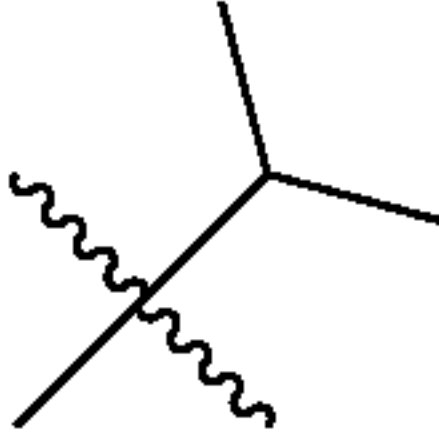
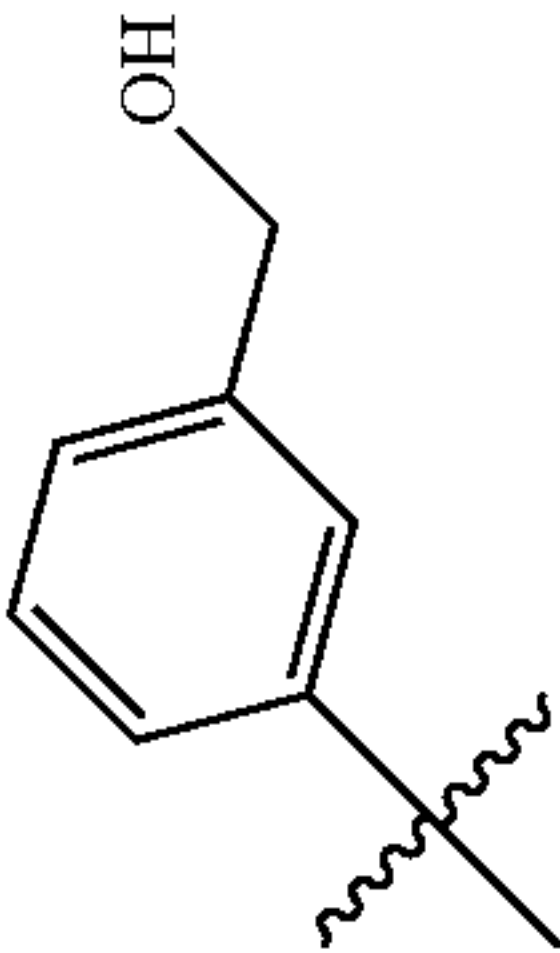
Cpd	R ¹	R ²	Cpd	R ¹	R ²
ZK130	—H		ZK152	 —Me X = CH	
ZK128	—H		BA42		
BA26					

TABLE 2

Cpd	110□	110□	110□	110□	DPK	Cpd	110□	110□	110□	110□	DPK
KS167	++	+	++	++	++	BA46	++	++	+++	++	+++
ZK141	++	++	++	++	+++	BA45	++	+	++	++	++
KS84	++	+	++	+	+++	BA39	++		+++	++	++
ZK127	++	++	++	++	+++	BA150	++	+	++	++	++
ZK134	++	+	++	++	+++	BA151	++	+	++	++	++
ZK132	++	++	++	++	+++	BA21	++	++	++		++
ZK125	++	+	++	++	+++	BA52	++	++	++	++	++
BA56	+++	+++	+++	+++	+++	BA53	++	+	+	+	++
ZK138	++	++	++	++	+++	BA31	++	++	+++	+++	++
KS287	++	++	++	++	++	BA152	++	++	+++	++	+++
KS288		+	+	+	+++	BA149	++	++	++	++	+
KS284	+++	++	+++	++	+++	BA32	++	++	+++		+++
BA60	++	++	+++	++	+++	BA55	++	++	+++	++	++
ZK318	++	+	++	++	++	BA35	++		+++	+++	+++
ZK320	++	++	+++	+++	++	BA34	++	++	+++	++	+++
ZK333	+++	++	+++	+++	+++	BA38	++		+++	+++	+++
ZK323	+++	++	+++	+++	+++	BA40	++		++	++	+++
ZK327	+++	++	+++	+++	+++	BA41	++	++	+++	+++	+++
BA77d	++	++	+++	++	++	BA14	++	++	+++	++	+++
BA78d	++	++	+++	++	+++	BA12	++	++	+++	++	++
BA22	+++	+++	+++	+++	+++	BA30	++	++	+++	+++	+++
BA79d	+++	+++	+++	+++	+++	ZK149	+	++	++	++	+
BA85	++	++	++	++	+++	ZK126	++	+	++	+	++
BA87	+++	+++	+++	+++	+++	ZK143	+	+	+	+	+
ZK502	++	++	+++	++	+++	ZK150	++	+	+	+	++
ZK489	+++	+++	+++	+++	+++	ZK136	++	+	+	++	+++
ZK487	+++	+++	+++	+++	+++	ZK131	+	+	+	+	+
Zk491	+++	+++	+++	+++	++	ZK151	+	+	+	+	+++
Zk493	+++	+++	+++	+++	+++	ZK142	+	+	+	+	+
BA62d	+++	+++	+++	+++	++	ZK139	+	+	+	++	++
ZK450	++	++	++	+++	+	KS207	++	+	+++	+++	+++
ZK454	++	++	++	+++	+++	KS208	++	++	++	+++	+++
ZK469	+++	+++	++	+++	+++	ZK102	+	+	+	+	+++
ZK471	+++	+++	+++	+++	++	ZK157			+++		+++
ZK461	+++	++	+++	++	++	ZK159	++	++	++	++	+++
ZK413	++	+++	+++	+++	+++	ZK156	++	++	++	++	+++
ZK379	+++	++	+++	+++	+++	KS63	+	+	+	+	+++
ZK421	+++	++	+++	+++	+++	ZK158	++	++	++	++	+++
ZK403	++	+++	+++	+++	++	ZK147	+	++	++	++	++
ZK405	++	++	+++	++	+++	ZK155	++	++	++	++	+++
ZK432	+++	++	+++	+++	+++	ZK162	++	+	++	++	+++
ZK434	+++	+++	+++	+++	+++	ZK165	++	+	++	++	+++
ZK465	+++	+	+++	+++	+++	ZK161	++	+	++	++	++
ZK377	++	++	++	++	+++	ZK167			++		++
ZK399	++	++	+++	++	+++	ZK168			++		+++
ZK401	++	+	++	+	+++	BA116	+	++	++	++	+++
BA62	+++	++	+++	+++	+++	BA17	+++	++	+++	++	+++
ZK358	+++	++	+++	+++	+++	BA134	++	+	++	+	++
ZK452	++	++	++	+++	+++	BA105	++	++	+++	++	+++
ZK456	+++	++	++	+++	+++	BA122	++	++	+++	++	+++
ZK463	+++	++	+++	+++	+++	BA111	+++	++	+++	+++	+++
ZK371	+++	+++	+++	+++	+++	BA102	+++	+++	+++	+++	+++
ZK409	+++	+++	+++	+++	+++	BA112	+++	++	+++	+++	+++
ZK428	+++	+++	+++	+++	+++	BA118	+++	++	+++	+++	+++
ZK430	+++	+++	+++	+++	+++	BA130	+++	++	+++	+++	+++
ZK387	++	++	++	++	+++	BA132	+++	+++	+++	+++	+++
ZK389	++	+++	+++	++	+++	BA139	++	++	+++	+	++
ZK369	++	+	++	++	++	BA158	+++	+++	+++	+++	+++
ZK385	++	++	+++	++	+++	BA140	+	++	+	+	++
ZK391	++	++	+++	++	+++	BA141	+	+	+	+	+
BA155_2	+++	+++	+++	+++	+++	BA146	+++	+++	+++	+++	+++
BA157_2	+++	+++	+++	+++	+++	BA142	+++	++	++	+++	+++
BA59	+++	++	+++	+++	+++	BA145	++	++	++	++	++
BA63		++		+++	+++	BA147	++	++	++	++	++
BA93	+++	++	+++	+++	+++	BA148	++	++	++	++	+++
BA49	++	+	++	++	++	BA143	++	++	++	++	+++
BA15	+++	++	+++	+++	+++	BA144	+++	++	+++	+++	+++
ZK321	+++	++	+++	+++	+++	BA129	++	+	++	+	++
ZK337	+++	+++	+++	+++	+++	BA131	+++	++	+++	+++	+++
ZK347	+++	+++	+++	+++	+++	BA133	+++	+++	+++	+++	+++
ZK325	+++	+++	+++	+++	+++	BA120	+++	++	+++	+++	+++
ZK349	+++	+++	+++	+++	+++	BA108	+++	++	+++	++	+++
ZK423	+++	+++	+++	+++	+++	BA121	+++	++	+++	++	+++
ZK411	++	+++	+++	+++	+++	BA89	+++	++	+++	+++	+++
ZK407	++	+++	+++	++	++	BA94	+++	++	+++	+++	+++

TABLE 2-continued

Cpd	110□	110□	110□	110□	DPK	Cpd	110□	110□	110□	110□	DPK
BA98	+++	+++	+++	+++	+++	BA135	+++	+++	+++	+++	+++
S1	++	+	++	+	+	BA136	+++	++	+++	++	+++
BA23	+++	+++	+++	+++	+++	BA137	+++	+++	+++	+++	+++
ZK485	+++	+++	+++	++	++	BA138	+++	++	+++	+++	+++
ZK495	+++	++	+++	++	+++	BA160	++	++	+++	+++	+++
ZK496	++	++	+++	++	+++	BA157_3	+++	++	+++	+++	+++
ZK494	+++	+++	+++	+++	+++	BA154	+++	+++	+++	+++	+++
BA90	+++	+++	+++	+++	+++	BA110	+++	++	+++	+++	+++
ZK341	++	++	+++	+++	++	BA115	+++	++	+++	+++	+++
ZK343	+++	++	+++	++	+++	BA159	+++	+++	+++	+++	++
ZK361	++	++	+++	+++	+++	BA119	++	++	+++	++	+++
ZK359	+++	+++	+++	+++	+++	BA107	++	++	+++	++	+++
ZK362	+++	+++	+++	+++	++	BA124	++	++	+++	++	+++
BA64	+	+	++	+	++	BA161	+	+	+	+	+++
BA65	+	+	++	+	++	BA162	++	++	++	++	+++
ZK305	+++	+++	+++	+++	+++	BA24dd	++	++	+++	++	+++
ZK306	++	+	++	++	++	BA43	+++		+++	+++	+++
BA66	++	++	+++	++	+++	BA91	++	++	++	++	+++
BA48	++	++	+++	++	+++	BA92	++	++	+++	++	+++
ZK133	+	+	+	++	++	BA86	++	++	++	+++	+++
BA20dd	++	++	++	++	+++	BA88	+	+	++	+++	+++
BA20d	++	++	+++	+++	+++	BA96	++	+	+++	+++	+++
BA20	++		++	++	++	BA97	++	++	+++	+++	+++
BA99	++	+	++	+	++	BA44	++	+++	++	++	++
BA81dd	+++	++	+++	+++	+	BA156	++	++	++	++	+++
BA81d	+++	++	+++	+++	+++	BA95	++	++	+++	+++	+++
ZK137	++	+	++	++	+++	ZK129	++	++	++	++	+++
ZK135	++	+	+	++	++	BA54	++	++	++	++	+++
ZK130	+	+	+	+	+	ZK152	++	++	++	++	+++
ZK128	++	+	++	++	++	BA42	++	++	++	++	+++
BA26	++	++	+++	+++	++	PIK294	++	+++	+++	+++	++
SU11248	++	+	++	++	+	Iressa	+	+	+	+	+
BAY43-9006	++	+	+	+	+	PIK103	+++	+++	+++	+++	+++
Dasatinib	++	+	++	+	++	PIK90	+++	+++	+++	+++	+++

TABLE 3

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
KS84	+++	+++	+++	++	+++	+++	+++
BA56	++	+++	+++	++	++	+++	++
KS284	+++	+++	+++	++	+++	+++	+++
BA60	++	+++	+++	+++	++	+	++
ZK318	++	++	+++	++	+		++
ZK320	+++	+++	+++	++	+++	++	++
ZK333	+++	+++	+++	++	+++	++	++
ZK323	+++	+++	+++	+++	+++	+++	+++
ZK327	+++	+++	+++	++	+++	++	++
BA77d	+++	+++	+++	++	++	++	+++
BA78d	+++	+++	+++	++	+++	++	++
BA22	+++	+++	+++	++	+++	+++	+++
BA79d	+++	+++	+++	++	+++	+++	+++
BA85	++	+++	+++	++	++	++	++
BA87	+++	+++	+++	+++	+++	+++	+++
ZK502	+++	+++	+++	++	++	++	+
ZK489	+++	+++	+++	+	++	+	++
ZK487	+++	+++	+++	++	+++	+++	+++
Zk491	+++	+++	+++	++	+++	+++	+++
Zk493	+++	+++	+++	++	+++	+++	+++
BA62d	+++	+++	+++	+++	+++	++	+++
ZK450	+++	+++	+++	+	++	+	++
ZK454	+++	++	+++	+	++	++	+
ZK469	+++	+++	+++	+	++	++	++
ZK471	+++	+++	+++	+	++	++	+
ZK461	+++	+++	+++	+	+++	++	++
ZK413	+++	+++	+++	+	++	++	
ZK379	+++	+++	+++	++	+++	+++	+++
ZK421	+++	+++	+++	+++	+++	+++	+++
ZK403	+++	+++	+++	++	+++	++	+++
ZK405	+++	+++	+++	++	++	++	+
ZK432	+++	+++	+++	++	+++	++	+++

TABLE 3-continued

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
ZK434	+++	+++	+++	++	+++	++	+++
ZK465	+++	+++	+++	+	+++	+++	+++
ZK377	++	++	+++	+	++	+	+
ZK399	+++	+++	+++	+	+	+	++
ZK401	+++	+++	+++	+	+	+	+
BA62	+++	+++	+++	+	+	++	+++
ZK358	+++	+++	+++	++	+++	+++	+++
ZK452	+++	+++	+++	++	+++	++	++
ZK456	+++	+++	+++	+	++	++	++
ZK463	+++	+++	+++	++	+++	++	++
ZK371	+++	+++	+++	++	+++	+++	+++
ZK409	+++	+++	+++	++	+++	++	+++
ZK428	+++	+++	+++	++	+++	++	+++
ZK430	+++	+++	+++	++	+++	++	+++
ZK387	+++	+++	+++	+	++	++	++
ZK389	+++	+++	+++	++	+++	++	+++
ZK369	++	++	+++	+	++	++	+
ZK385	++	+++	+++	+	++	+	++
ZK391	++	+++	+++	+	++	++	++
BA155_2	++	+++	+++	++	++	++	++
BA157_2	++	++	++	++	++	++	++
BA59	+++	+++	+++	+++	++	++	+++
BA63	++	+++	+++	++	++	++	++
BA93	++	+++	+++	++	++	++	++
BA49	++	+++	+++	++	+	++	+++
BA15	++	+++	+++	++	+	+++	++
ZK321	+++	+++	+++	++	++	+	++
ZK337	+++	+++	+++			+	++
ZK347	+++	+++	+++	++	+++	++	++
ZK325	+++	+++	+++	++	+++	++	+++
ZK349	+++	+++	+++	+++	+++	+++	+++
ZK423	+++	+++	+++	++	+++	+++	+++

TABLE 3-continued

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
ZK411	++	++	+++	+	++	++	++
ZK407	++	+++	+++	+	+++	++	+
BA98	+++	+++	+++	++	+++	+++	++
S1	+++	+	++	+	+	+	+
BA23	++	++	+++	++	+	++	++
ZK485	++	+++	+++	+	+	++	++
ZK495	++	+++	++	++	+	++	++
ZK496	++	++	++	++	++	++	++
ZK494	+++	+++	+++	++	++	++	++
BA90	++	+++	+++	++	++	++	++
ZK341	++	++	+	+	+	+	+
ZK343	++	+++	+++	+	++	++	++
ZK361	++	++	++	+	+	++	+
ZK359	+++	+++	+++	++	++	++	+++
ZK362	++	+++	+++	+	+	++	+
BA64	+++	+++	+++	++	+	++	+++
BA65	++	+++	+++	++	++	++	++
ZK305	++	++	++	++	+	+	++
ZK306	+	++	++	++	++	++	+
BA66	++	++	++	+		+	++
BA48	++	+++	+++	++	++	++	++
BA20dd	+++	+++	+++	++	++	++	++
BA20d	+++	+++	+++	++	++	++	++
BA20	+++	+++	+++	+++	++	+++	+
BA99	++	+++	+++	++	+++	++	++
BA81dd	+++	+++	+++	++	+++	+++	+++
BA81d	+++	+++	+++	++	+++	+++	+++
BA26	++	++	+++	++	+	+	+
BA46	++	++	++	+	++	++	++
BA45	++	+++	+++	++	++	++	+
BA39	++	++	++	++	++	+	++
BA150	++	++	++	+	++	+	++
BA151	++	++	++	+	+	++	++
BA21	++	++	++	+	+	+	+
BA52	++	++	++	+	+	+	+
BA53	++	++	++	+	+	+	+
BA31	++	++	++	+	+	++	+
BA152	+++	+++	+++	+	++	++	++
BA149	++	+++	+++	++	++	++	++
BA32	++	++	++	+	+	+	++
BA55	++	++	++	+	+	++	++
BA35	++	++	++	++	++	++	++
BA34	++	++	++	++	++	++	++
BA38	++	++	++	++	+	+	+
BA40	++	++	++	++	++	++	+
BA41	++	++	++	++	++	+	++
BA14	++	++	++	++	+	+	++
BA12	++	++	++	++	++	++	++
BA30	++	++	++	++	++	+++	++
KS208	++	+++	++	++	++	+++	++
BA116	++	+++	++		+++	++	++
BA17	+++	+++	+++	+++	+++	+++	+++
BA134	++	++	++	++	+	+	++
BA105	++	+++	++	++	++	++	++
BA122	+++	+++	+++	++	++	+++	+++
BA111	+	+	++	++	++	++	++
BA102	+++	+++	+++	++	+++	+++	+++
BA112	++	+++	+++	++	++	++	++
BA118	++	++	+	++	++	+	++
BA130	++	+++	++	++	+++	+	++
BA132	++	+++	++	+	++	++	++
BA139	++	++	++	+	++	++	+
BA158	+++	+++	+++	++	++	++	++
BA140	++	++	++	++	+	++	++
BA141	+	++	+	+	+	++	+
BA146	++	++	++	+	++	++	++
BA142	++	++	+++	+	++	++	++
BA145	+	++	++	+	+	+	++
BA147	++	++	++	+	++	+	++
BA148	+	++	++	+	+	++	+
BA143	++	++	++	++	+	++	++
BA144	++	++	+++	+	++	+	++
BA129	++	+	+++	+	++	++	++
BA131	++	++	11	+	++	+	++
BA133	++	++	+++	+	+	++	++

TABLE 3-continued

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
BA120	+++	+++	+++	++	+++	++	++
BA108	+++	+++	+++	+++	+++	+++	+++
BA121	+++	+++	+++	+++	+++	+++	+++
BA89	+++	+++	+++	+++	+++	+++	+++
BA94	+++	+++	+++	+++	+++	+++	+++
BA135	+++	+++	+++	++	+++	+++	+
BA136	+++	+++	+++	++	+++		++
BA137	+++	+++	+++	+++	+++	++	++
BA138	+++	+++	+++	+++	+++	+++	++
BA160	+++	+++	+++	++	++	+++	++
BA157_3	++	+++	+++	++	+	++	++
BA154	+++	+++	+++	++	++	++	++
BA110	+++	+++	+++	++	+++	++	++
BA115	+++	+++	+++	+++	+++	+++	
BA159	+++	+++	+++	++	+++	++	++
BA119	++	+++	+++	++	++	++	++
BA107	+++	+++	+++	++	+++	+++	+++
BA124	+++	+++	+++	+++	+++	+++	+++
BA161	++	+	++	+	+	++	+
BA162	++	++	++	+	+	++	++
BA24dd	++	++	++	++	++	++	++
BA43	++	+++	++	++	++	++	++
BA91	++	++	+++	++	++	++	++
BA92	++	+++	+++	++	++	++	++
BA86	+++	+++	+++	+++	+++	+++	+++
BA88	+++	+++	+++	+++	+++	+++	+++
BA96	+++	+++	+++	++	++	+++	+++
BA97	+++	+++	+++	++	++	+++	+++
BA44	++	++	++	++	+	++	+
BA156	++	++	++	++	++	+++	++
BA95	++	+++	++	+	+	++	++
BA54	++	++	+++	++	++	++	++
BA42	+	++	++	++	++	+	++
SU11248	+++	+++	+++	+++	+++	++	+
BAY43-9006	+++	+++	+++	+++	+++	+	++
Dasatinib				++	+	+++	
Iressa	++	+++	+++	++	++		++
PIK103	+	+	+	+	+	+	+
PIK90	+	+	+	+	+	+	+
PIK294	++	+	++	+	+	+	+

TABLE 4

Cpd	cKIT	Tie2	FLT3	PDGFR	RET	IR	mTOR
ZK358	+++	++	+++	+++	+++	++	+++
ZK487	+++	+++	+++	+++	+++	+	+++
ZK349	+++	+++	+++	+++	+++	++	+++
ZK494	+++	++	++	+++	+++	+	+++
BA102	+++	+++	+++	+++	+++	+	+++
BA121	+++	+++	+++	+++		++	+++
KS84	+++	+	+++	+++	+++	++	++
SU11248	+++	++	+++	+++	+++	++	+
BAY43-9006	+++	+++	+	+++	+++	++	+
Dasatinib	+++	++	+++	+++	++	+	+
Iressa	+	++	+++	+++	++	+	+

[0340] In Tables 2-4 above, a +++ indicates an IC50 of less than 1 μM; a ++ indicates an IC50 of from 1 μM to 50 μM; and a + indicates and IC50 of more than 50 μM.

IX. REFERENCES

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Cys	Arg	Arg	Arg	Arg	Arg	Met	Lys	Pro	Arg	Ser	Ala	Ala	Ala	Ser	Leu	
			20					25					30			
Ser	Ser	Met	Glu	Leu	Ile	Pro	Ile	Glu	Phe	Val	Leu	Pro	Thr	Ser	Gln	
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Arg	Lys	Cys	Lys	Ser	Pro	Glu	Thr	Ala	Leu	Leu	His	Val	Ala	Gly	His	
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Gly	Asn	Val	Glu	Gln	Met	Lys	Ala	Gln	Val	Trp	Leu	Arg	Ala	Leu	Glu	
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Thr	Ser	Val	Ala	Ala	Asp	Phe	Tyr	His	Arg	Leu	Gly	Pro	His	His	Phe	
				85					90					95		
Leu	Leu	Leu	Tyr	Gln	Lys	Lys	Gly	Gln	Trp	Tyr	Glu	Ile	Tyr	Asp	Lys	
			100					105					110			
Tyr	Gln	Val	Val	Gln	Thr	Leu	Asp	Cys	Leu	Arg	Tyr	Trp	Lys	Ala	Thr	
		115					120					125				
His	Arg	Ser	Pro	Gly	Gln	Ile	His	Leu	Val	Gln	Arg	His	Pro	Pro	Ser	
	130					135					140					
Glu	Glu	Ser	Gln	Ala	Phe	Gln	Arg	Gln	Leu	Thr	Ala	Leu	Ile	Gly	Tyr	
145					150					155					160	
Asp	Val	Thr	Asp	Val	Ser	Asn	Val	His	Asp	Asp	Glu	Leu	Glu	Phe	Thr	
				165					170					175		
Arg	Arg	Gly	Leu	Val	Thr	Pro	Arg	Met	Ala	Glu	Val	Ala	Ser	Arg	Asp	
			180					185					190			
Pro	Lys	Leu	Tyr	Ala	Met	His	Pro	Trp	Val	Thr	Ser	Lys	Pro	Leu	Pro	
		195					200					205				
Glu	Tyr	Leu	Trp	Lys	Lys	Ile	Ala	Asn	Asn	Cys	Ile	Phe	Ile	Val	Ile	
	210					215					220					
His	Arg	Ser	Thr	Thr	Ser	Gln	Thr	Ile	Lys	Val	Ser	Pro	Asp	Asp	Thr	
225					230					235					240	
Pro	Gly	Ala	Ile	Leu	Gln	Ser	Phe	Phe	Thr	Lys	Met	Ala	Lys	Lys	Lys	
				245					250					255		
Ser	Leu	Met	Asp	Ile	Pro	Glu	Ser	Gln	Ser	Glu	Gln	Asp	Phe	Val	Leu	
			260					265					270			
Arg	Val	Cys	Gly	Arg	Asp	Glu	Tyr	Leu	Val	Gly	Glu	Thr	Pro	Ile	Lys	
		275					280					285				
Asn	Phe	Gln	Trp	Val	Arg	His	Cys	Leu	Lys	Asn	Gly	Glu	Glu	Ile	His	
	290					295					300					
Val	Val	Leu	Asp	Thr	Pro	Pro	Asp	Pro	Ala	Leu	Asp	Glu	Val	Arg	Lys	
305					310					315					320	
Glu	Glu	Trp	Pro	Leu	Val	Asp	Asp	Cys	Thr	Gly	Val	Thr	Gly	Tyr	His	
				325					330					335		
Glu	Gln	Leu	Thr	Ile	His	Gly	Lys	Asp	His	Glu	Ser	Val	Phe	Thr	Val	
			340					345					350			
Ser	Leu	Trp	Asp	Cys	Asp	Arg	Lys	Phe	Arg	Val	Lys	Ile	Arg	Gly	Ile	
		355					360					365				
Asp	Ile	Pro	Val	Leu	Pro	Arg	Asn	Thr	Asp	Leu	Thr	Val	Phe	Val	Glu	
	370					375					380					
Ala	Asn	Ile	Gln	His	Gly	Gln	Gln	Val	Leu	Cys	Gln	Arg	Arg	Thr	Ser	
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Pro	Lys	Pro	Phe	Thr	Glu	Glu	Val	Leu	Trp	Asn	Val	Trp	Leu	Glu	Phe	
				405					410					415		
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			420					425					430			
Ile	Tyr	Cys	Gly	Lys	Ala	Pro	Ala	Leu	Ser	Ser	Lys	Ala	Ser	Ala	Glu	
		435					440					445				
Ser	Pro	Ser	Ser	Glu	Ser	Lys	Gly	Lys	Val	Gln	Leu	Leu	Tyr	Tyr	Val	
	450					455					460					

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Asn	Leu	Leu	Leu	Ile	Asp	His	Arg	Phe	Leu	Leu	Arg	Arg	Gly	Glu	Tyr	
465					470					475					480	
Val	Leu	His	Met	Trp	Gln	Ile	Ser	Gly	Lys	Gly	Glu	Asp	Gln	Gly	Ser	
				485					490					495		
Phe	Asn	Ala	Asp	Lys	Leu	Thr	Ser	Ala	Thr	Asn	Pro	Asp	Lys	Glu	Asn	
			500					505					510			
Ser	Met	Ser	Ile	Ser	Ile	Leu	Leu	Asp	Asn	Tyr	Cys	His	Pro	Ile	Ala	
		515					520					525				
Leu	Pro	Lys	His	Gln	Pro	Thr	Pro	Asp	Pro	Glu	Gly	Asp	Arg	Val	Arg	
	530					535					540					
Ala	Glu	Met	Pro	Asn	Gln	Leu	Arg	Lys	Gln	Leu	Glu	Ala	Ile	Ile	Ala	
545					550					555					560	
Thr	Asp	Pro	Leu	Asn	Pro	Leu	Thr	Ala	Glu	Asp	Lys	Glu	Leu	Leu	Trp	
				565					570					575		
His	Phe	Arg	Tyr	Glu	Ser	Leu	Lys	His	Pro	Lys	Ala	Tyr	Pro	Lys	Leu	
			580					585					590			
Phe	Ser	Ser	Val	Lys	Trp	Gly	Gln	Gln	Glu	Ile	Val	Ala	Lys	Thr	Tyr	
		595					600					605				
Gln	Leu	Leu	Ala	Arg	Arg	Glu	Val	Trp	Asp	Gln	Ser	Ala	Leu	Asp	Val	
	610					615					620					
Gly	Leu	Thr	Met	Gln	Leu	Leu	Asp	Cys	Asn	Phe	Ser	Asp	Glu	Asn	Val	
625					630					635					640	
Arg	Ala	Ile	Ala	Val	Gln	Lys	Leu	Glu	Ser	Leu	Glu	Asp	Asp	Asp	Val	
				645					650					655		
Leu	His	Tyr	Leu	Leu	Gln	Leu	Val	Gln	Ala	Val	Lys	Phe	Glu	Pro	Tyr	
			660					665					670			
His	Asp	Ser	Ala	Leu	Ala	Arg	Phe	Leu	Leu	Lys	Arg	Gly	Leu	Arg	Asn	
		675					680					685				
Lys	Arg	Ile	Gly	His	Phe	Leu	Phe	Trp	Phe	Leu	Arg	Ser	Glu	Ile	Ala	
	690					695					700					
Gln	Ser	Arg	His	Tyr	Gln	Gln	Arg	Phe	Ala	Val	Ile	Leu	Glu	Ala	Tyr	
705					710					715					720	
Leu	Arg	Gly	Cys	Gly	Thr	Ala	Met	Leu	His	Asp	Phe	Thr	Gln	Gln	Val	
				725					730					735		
Gln	Val	Ile	Glu	Met	Leu	Gln	Lys	Val	Thr	Leu	Asp	Ile	Lys	Ser	Leu	
			740					745					750			
Ser	Ala	Glu	Lys	Tyr	Asp	Val	Ser	Ser	Gln	Val	Ile	Ser	Gln	Leu	Lys	
		755					760					765				
Gln	Lys	Leu	Glu	Asn	Leu	Gln	Asn	Ser	Gln	Leu	Pro	Glu	Ser	Phe	Arg	
	770					775					780					
Val	Pro	Tyr	Asp	Pro	Gly	Leu	Lys	Ala	Gly	Ala	Leu	Ala	Ile	Glu	Lys	
785					790					795					800	
Cys	Lys	Val	Met	Ala	Ser	Lys	Lys	Lys	Pro	Leu	Trp	Leu	Glu	Phe	Lys	
				805					810					815		
Cys	Ala	Asp	Pro	Thr	Ala	Leu	Ser	Asn	Glu	Thr	Ile	Gly	Ile	Ile	Phe	
			820					825					830			
Lys	His	Gly	Asp	Asp	Leu	Arg	Gln	Asp	Met	Leu	Ile	Leu	Gln	Ile	Leu	
		835					840					845				
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	850					855					860					
Leu	Pro	Tyr	Gly	Cys	Ile	Ser	Thr	Gly	Asp	Lys	Ile	Gly	Met	Ile	Glu	

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865					870					875					880
Ile	Val	Lys	Asp	Ala	Thr	Thr	Ile	Ala	Lys	Ile	Gln	Gln	Ser	Thr	Val
				885					890					895	
Gly	Asn	Thr	Gly	Ala	Phe	Lys	Asp	Glu	Val	Leu	Asn	His	Trp	Leu	Lys
			900					905					910		
Glu	Lys	Ser	Pro	Thr	Glu	Glu	Lys	Phe	Gln	Ala	Ala	Val	Glu	Arg	Phe
		915					920					925			
Val	Tyr	Ser	Cys	Ala	Gly	Tyr	Cys	Val	Ala	Thr	Phe	Val	Leu	Gly	Ile
	930					935					940				
Gly	Asp	Arg	His	Asn	Asp	Asn	Ile	Met	Ile	Thr	Glu	Thr	Gly	Asn	Leu
945					950					955					960
Phe	His	Ile	Asp	Phe	Gly	His	Ile	Leu	Gly	Asn	Tyr	Lys	Ser	Phe	Leu
				965					970					975	
Gly	Ile	Asn	Lys	Glu	Arg	Val	Pro	Phe	Val	Leu	Thr	Pro	Asp	Phe	Leu
			980					985					990		
Phe	Val	Met	Gly	Thr	Ser	Gly	Lys	Lys	Thr	Ser	Pro	His	Phe	Gln	Lys
		995					1000					1005			
Phe	Gln	Asp	Ile	Cys	Val	Lys	Ala	Tyr	Leu	Ala	Leu	Arg	His	His	
	1010					1015					1020				
Thr	Asn	Leu	Leu	Ile	Ile	Leu	Phe	Ser	Met	Met	Leu	Met	Thr	Gly	
	1025					1030					1035				
Met	Pro	Gln	Leu	Thr	Ser	Lys	Glu	Asp	Ile	Glu	Tyr	Ile	Arg	Asp	
	1040					1045					1050				
Ala	Leu	Thr	Val	Gly	Lys	Asn	Glu	Glu	Asp	Ala	Lys	Lys	Tyr	Phe	
	1055					1060					1065				
Leu	Asp	Gln	Ile	Glu	Val	Cys	Arg	Asp	Lys	Gly	Trp	Thr	Val	Gln	
	1070					1075					1080				
Phe	Asn	Trp	Phe	Leu	His	Leu	Val	Leu	Gly	Ile	Lys	Gln	Gly	Glu	
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			20					25					30		
Thr	Leu	Glu	Cys	Leu	Arg	Glu	Ala	Thr	Leu	Ile	Thr	Ile	Lys	His	Glu
		35					40					45			
Leu	Phe	Lys	Glu	Ala	Arg	Lys	Tyr	Pro	Leu	His	Gln	Leu	Leu	Gln	Asp
	50					55					60				
Glu	Ser	Ser	Tyr	Ile	Phe	Val	Ser	Val	Thr	Gln	Glu	Ala	Glu	Arg	Glu
65					70					75				80	
Glu	Phe	Phe	Asp	Glu	Thr	Arg	Arg	Leu	Cys	Asp	Leu	Arg	Leu	Phe	Gln
			85						90					95	
Pro	Phe	Leu	Lys	Val	Ile	Glu	Pro	Val	Gly	Asn	Arg	Glu	Glu	Lys	Ile
		100						105					110		

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Leu	Asn	Arg	Glu	Ile	Gly	Phe	Ala	Ile	Gly	Met	Pro	Val	Cys	Glu	Phe	
	115						120					125				
Asp	Met	Val	Lys	Asp	Pro	Glu	Val	Gln	Asp	Phe	Arg	Arg	Asn	Ile	Leu	
	130					135				140						
Asn	Val	Cys	Lys	Glu	Ala	Val	Asp	Leu	Arg	Asp	Leu	Asn	Ser	Pro	His	
145					150					155					160	
Ser	Arg	Ala	Met	Tyr	Val	Tyr	Pro	Pro	Asn	Val	Glu	Ser	Ser	Pro	Glu	
				165					170					175		
Leu	Pro	Lys	His	Ile	Tyr	Asn	Lys	Leu	Asp	Lys	Gly	Gln	Ile	Ile	Val	
			180					185					190			
Val	Ile	Trp	Val	Ile	Val	Ser	Pro	Asn	Asn	Asp	Lys	Gln	Lys	Tyr	Thr	
		195					200					205				
Leu	Lys	Ile	Asn	His	Asp	Cys	Val	Pro	Glu	Gln	Val	Ile	Ala	Glu	Ala	
	210					215					220					
Ile	Arg	Lys	Lys	Thr	Arg	Ser	Met	Leu	Leu	Ser	Ser	Glu	Gln	Leu	Lys	
225					230					235					240	
Leu	Cys	Val	Leu	Glu	Tyr	Gln	Gly	Lys	Tyr	Ile	Leu	Lys	Val	Cys	Gly	
				245					250					255		
Cys	Asp	Glu	Tyr	Phe	Leu	Glu	Lys	Tyr	Pro	Leu	Ser	Gln	Tyr	Lys	Tyr	
			260					265					270			
Ile	Arg	Ser	Cys	Ile	Met	Leu	Gly	Arg	Met	Pro	Asn	Leu	Met	Leu	Met	
		275					280					285				
Ala	Lys	Glu	Ser	Leu	Tyr	Ser	Gln	Leu	Pro	Met	Asp	Cys	Phe	Thr	Met	
	290						295				300					
Pro	Ser	Tyr	Ser	Arg	Arg	Ile	Ser	Thr	Ala	Thr	Pro	Tyr	Met	Asn	Gly	
305					310					315					320	
Glu	Thr	Ser	Thr	Lys	Ser	Leu	Trp	Val	Ile	Asn	Ser	Ala	Leu	Arg	Ile	
				325					330					335		
Lys	Ile	Leu	Cys	Ala	Thr	Tyr	Val	Asn	Val	Asn	Ile	Arg	Asp	Ile	Asp	
			340					345					350			
Lys	Ile	Tyr	Val	Arg	Thr	Gly	Ile	Tyr	His	Gly	Gly	Glu	Pro	Leu	Cys	
		355					360					365				
Asp	Asn	Val	Asn	Thr	Gln	Arg	Val	Pro	Cys	Ser	Asn	Pro	Arg	Trp	Asn	
	370					375					380					
Glu	Trp	Leu	Asn	Tyr	Asp	Ile	Tyr	Ile	Pro	Asp	Leu	Pro	Arg	Ala	Ala	
385					390					395					400	
Arg	Leu	Cys	Leu	Ser	Ile	Cys	Ser	Val	Lys	Gly	Arg	Lys	Gly	Ala	Lys	
				405					410					415		
Glu	Glu	His	Cys	Pro	Leu	Ala	Trp	Gly	Asn	Ile	Asn	Leu	Phe	Asp	Tyr	
			420					425					430			
Thr	Asp	Thr	Leu	Val	Ser	Gly	Lys	Met	Ala	Leu	Asn	Leu	Trp	Pro	Val	
		435					440					445				
Pro	His	Gly	Leu	Glu	Asp	Leu	Leu	Asn	Pro	Ile	Gly	Val	Thr	Gly	Ser	
	450					455					460					
Asn	Pro	Asn	Lys	Glu	Thr	Pro	Cys	Leu	Glu	Leu	Glu	Phe	Asp	Trp	Phe	
465					470					475					480	
Ser	Ser	Val	Val	Lys	Phe	Pro	Asp	Met	Ser	Val	Ile	Glu	Glu	His	Ala	
				485					490					495		
Asn	Trp	Ser	Val	Ser	Arg	Glu	Ala	Gly	Phe	Ser	Tyr	Ser	His	Ala	Gly	
		500						505					510			
Leu	Ser	Asn	Arg	Leu	Ala	Arg	Asp	Asn	Glu	Leu	Arg	Glu	Asn	Asp	Lys	

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515						520						525					
Glu	Gln	Leu	Lys	Ala	Ile	Ser	Thr	Arg	Asp	Pro	Leu	Ser	Glu	Ile	Thr		
	530						535				540						
Glu	Gln	Glu	Lys	Asp	Phe	Leu	Trp	Ser	His	Arg	His	Tyr	Cys	Val	Thr		
545					550					555					560		
Ile	Pro	Glu	Ile	Leu	Pro	Lys	Leu	Leu	Leu	Ser	Val	Lys	Trp	Asn	Ser		
				565					570					575			
Arg	Asp	Glu	Val	Ala	Gln	Met	Tyr	Cys	Leu	Val	Lys	Asp	Trp	Pro	Pro		
			580					585					590				
Ile	Lys	Pro	Glu	Gln	Ala	Met	Glu	Leu	Leu	Asp	Cys	Asn	Tyr	Pro	Asp		
	595						600					605					
Pro	Met	Val	Arg	Gly	Phe	Ala	Val	Arg	Cys	Leu	Glu	Lys	Tyr	Leu	Thr		
	610					615					620						
Asp	Asp	Lys	Leu	Ser	Gln	Tyr	Leu	Ile	Gln	Leu	Val	Gln	Val	Leu	Lys		
625					630				635						640		
Tyr	Glu	Gln	Tyr	Leu	Asp	Asn	Leu	Leu	Val	Arg	Phe	Leu	Leu	Lys	Lys		
				645					650					655			
Ala	Leu	Thr	Asn	Gln	Arg	Ile	Gly	His	Phe	Phe	Phe	Trp	His	Leu	Lys		
			660				665						670				
Ser	Glu	Met	His	Asn	Lys	Thr	Val	Ser	Gln	Arg	Phe	Gly	Leu	Leu	Leu		
	675						680					685					
Glu	Ser	Tyr	Cys	Arg	Ala	Cys	Gly	Met	Tyr	Leu	Lys	His	Leu	Asn	Arg		
	690					695					700						
Gln	Val	Glu	Ala	Met	Glu	Lys	Leu	Ile	Asn	Leu	Thr	Asp	Ile	Leu	Lys		
705					710				715						720		
Gln	Glu	Lys	Lys	Asp	Glu	Thr	Gln	Lys	Val	Gln	Met	Lys	Phe	Leu	Val		
				725					730					735			
Glu	Gln	Met	Arg	Arg	Pro	Asp	Phe	Met	Asp	Ala	Leu	Gln	Gly	Phe	Leu		
			740					745					750				
Ser	Pro	Leu	Asn	Pro	Ala	His	Gln	Leu	Gly	Asn	Leu	Arg	Leu	Glu	Glu		
	755						760					765					
Cys	Arg	Ile	Met	Ser	Ser	Ala	Lys	Arg	Pro	Leu	Trp	Leu	Asn	Trp	Glu		
	770					775					780						
Asn	Pro	Asp	Ile	Met	Ser	Glu	Leu	Leu	Phe	Gln	Asn	Asn	Glu	Ile	Ile		
785					790					795					800		
Phe	Lys	Asn	Gly	Asp	Asp	Leu	Arg	Gln	Asp	Met	Leu	Thr	Leu	Gln	Ile		
				805					810					815			
Ile	Arg	Ile	Met	Glu	Asn	Ile	Trp	Gln	Asn	Gln	Gly	Leu	Asp	Leu	Arg		
			820					825					830				
Met	Leu	Pro	Tyr	Gly	Cys	Leu	Ser	Ile	Gly	Asp	Cys	Val	Gly	Leu	Ile		
	835						840					845					
Glu	Val	Val	Arg	Asn	Ser	His	Thr	Ile	Met	Gln	Ile	Gln	Cys	Lys	Gly		
	850					855					860						
Gly	Leu	Lys	Gly	Ala	Leu	Gln	Phe	Asn	Ser	His	Thr	Leu	His	Gln	Trp		
865					870					875					880		
Leu	Lys	Asp	Lys	Asn	Lys	Gly	Glu	Ile	Tyr	Asp	Ala	Ala	Ile	Asp	Leu		
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Phe	Thr	Arg	Ser	Cys	Ala	Gly	Tyr	Cys	Val	Ala	Thr	Phe	Ile	Leu	Gly		
			900					905					910				
Ile	Gly	Asp	Arg	His	Asn	Ser	Asn	Ile	Met	Val	Lys	Asp	Asp	Gly	Gln		
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Leu	Phe	His	Ile	Asp	Phe	Gly	His	Phe	Leu	Asp	His	Lys	Lys	Lys	Lys	
930						935					940					
Phe	Gly	Tyr	Lys	Arg	Glu	Arg	Val	Pro	Phe	Val	Leu	Thr	Gln	Asp	Phe	
945					950					955					960	
Leu	Ile	Val	Ile	Ser	Lys	Gly	Ala	Gln	Glu	Cys	Thr	Lys	Thr	Arg	Glu	
				965					970					975		
Phe	Glu	Arg	Phe	Gln	Glu	Met	Cys	Tyr	Lys	Ala	Tyr	Leu	Ala	Ile	Arg	
			980					985					990			
Gln	His	Ala	Asn	Leu	Phe	Ile	Asn	Leu	Phe	Ser	Met	Met	Leu	Gly	Ser	
			995				1000					1005				
Gly	Met	Pro	Glu	Leu	Gln	Ser	Phe	Asp	Asp	Ile	Ala	Tyr	Ile	Arg		
1010						1015					1020					
Lys	Thr	Leu	Ala	Leu	Asp	Lys	Thr	Glu	Gln	Glu	Ala	Leu	Glu	Tyr		
1025						1030					1035					
Phe	Met	Lys	Gln	Met	Asn	Asp	Ala	His	His	Gly	Gly	Trp	Thr	Thr		
1040						1045					1050					
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Asp	Phe	Leu	Leu	Pro	Thr	Gly	Ile	Tyr	Ile	Gln	Leu	Glu	Val	Pro	Arg	
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Glu	Ala	Thr	Ile	Ser	Tyr	Ile	Lys	Gln	Met	Leu	Trp	Lys	Gln	Val	His	
50						55					60					
Asn	Tyr	Pro	Met	Phe	Asn	Leu	Leu	Met	Asp	Ile	Asp	Ser	Tyr	Met	Phe	
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Ala	Cys	Val	Asn	Gln	Thr	Ala	Val	Tyr	Glu	Glu	Leu	Glu	Asp	Glu	Thr	
			85						90					95		
Arg	Arg	Leu	Cys	Asp	Val	Arg	Pro	Phe	Leu	Pro	Val	Leu	Lys	Leu	Val	
			100					105					110			
Thr	Arg	Ser	Cys	Asp	Pro	Gly	Glu	Lys	Leu	Asp	Ser	Lys	Ile	Gly	Val	
		115					120					125				
Leu	Ile	Gly	Lys	Gly	Leu	His	Glu	Phe	Asp	Ser	Leu	Lys	Asp	Pro	Glu	
130						135					140					
Val	Asn	Glu	Phe	Arg	Arg	Lys	Met	Arg	Lys	Phe	Ser	Glu	Glu	Lys	Ile	
145						150				155					160	
Leu	Ser	Leu	Val	Gly	Leu	Ser	Trp	Met	Asp	Trp	Leu	Lys	Gln	Thr	Tyr	
				165					170					175		
Pro	Pro	Glu	His	Glu	Pro	Ser	Ile	Pro	Glu	Asn	Leu	Glu	Asp	Lys	Leu	
			180					185					190			
Tyr	Gly	Gly	Lys	Leu	Ile	Val	Ala	Val	His	Phe	Glu	Asn	Cys	Gln	Asp	
	195						200					205				
Val	Phe	Ser	Phe	Gln	Val	Ser	Pro	Asn	Met	Asn	Pro	Ile	Lys	Val	Asn	

-continued															
210				215				220							
Glu	Leu	Ala	Ile	Gln	Lys	Arg	Leu	Thr	Ile	His	Gly	Lys	Glu	Asp	Glu
225					230					235				240	
Val	Ser	Pro	Tyr	Asp	Tyr	Val	Leu	Gln	Val	Ser	Gly	Arg	Val	Glu	Tyr
				245					250					255	
Val	Phe	Gly	Asp	His	Pro	Leu	Ile	Gln	Phe	Gln	Tyr	Ile	Arg	Asn	Cys
			260					265					270		
Val	Met	Asn	Arg	Ala	Leu	Pro	His	Phe	Ile	Leu	Val	Glu	Cys	Cys	Lys
		275					280					285			
Ile	Lys	Lys	Met	Tyr	Glu	Gln	Glu	Met	Ile	Ala	Ile	Glu	Ala	Ala	Ile
	290					295					300				
Asn	Arg	Asn	Ser	Ser	Asn	Leu	Pro	Leu	Pro	Leu	Pro	Pro	Lys	Lys	Thr
305					310					315					320
Arg	Ile	Ile	Ser	His	Val	Trp	Glu	Asn	Asn	Asn	Pro	Phe	Gln	Ile	Val
				325					330					335	
Leu	Val	Lys	Gly	Asn	Lys	Leu	Asn	Thr	Glu	Glu	Thr	Val	Lys	Val	His
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Val	Arg	Ala	Gly	Leu	Phe	His	Gly	Thr	Glu	Leu	Leu	Cys	Lys	Thr	Ile
		355					360					365			
Val	Ser	Ser	Glu	Val	Ser	Gly	Lys	Asn	Asp	His	Ile	Trp	Asn	Glu	Pro
	370					375					380				
Leu	Glu	Phe	Asp	Ile	Asn	Ile	Cys	Asp	Leu	Pro	Arg	Met	Ala	Arg	Leu
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Cys	Phe	Ala	Val	Tyr	Ala	Val	Leu	Asp	Lys	Val	Lys	Thr	Lys	Lys	Ser
				405					410					415	
Thr	Lys	Thr	Ile	Asn	Pro	Ser	Lys	Tyr	Gln	Thr	Ile	Arg	Lys	Ala	Gly
			420					425					430		
Lys	Val	His	Tyr	Pro	Val	Ala	Trp	Val	Asn	Thr	Met	Val	Phe	Asp	Phe
		435					440					445			
Lys	Gly	Gln	Leu	Arg	Thr	Gly	Asp	Ile	Ile	Leu	His	Ser	Trp	Ser	Ser
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Thr	Asn	Pro	Tyr	Thr	Glu	Asn	Ala	Thr	Ala	Leu	His	Val	Lys	Phe	Pro
				485					490					495	
Glu	Asn	Lys	Lys	Gln	Pro	Tyr	Tyr	Tyr	Pro	Pro	Phe	Asp	Lys	Ile	Ile
			500					505					510		
Glu	Lys	Ala	Ala	Glu	Ile	Ala	Ser	Ser	Asp	Ser	Ala	Asn	Val	Ser	Ser
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Asp	Pro	Leu	Ser	Gln	Leu	Cys	Glu	Asn	Glu	Met	Asp	Leu	Ile	Trp	Thr
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Leu	Arg	Gln	Asp	Cys	Arg	Glu	Ile	Phe	Pro	Gln	Ser	Leu	Pro	Lys	Leu
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Leu	Leu	Ser	Ile	Lys	Trp	Asn	Lys	Leu	Glu	Asp	Val	Ala	Gln	Leu	Gln
			580					585					590		
Ala	Leu	Leu	Gln	Ile	Trp	Pro	Lys	Leu	Pro	Pro	Arg	Glu	Ala	Leu	Glu
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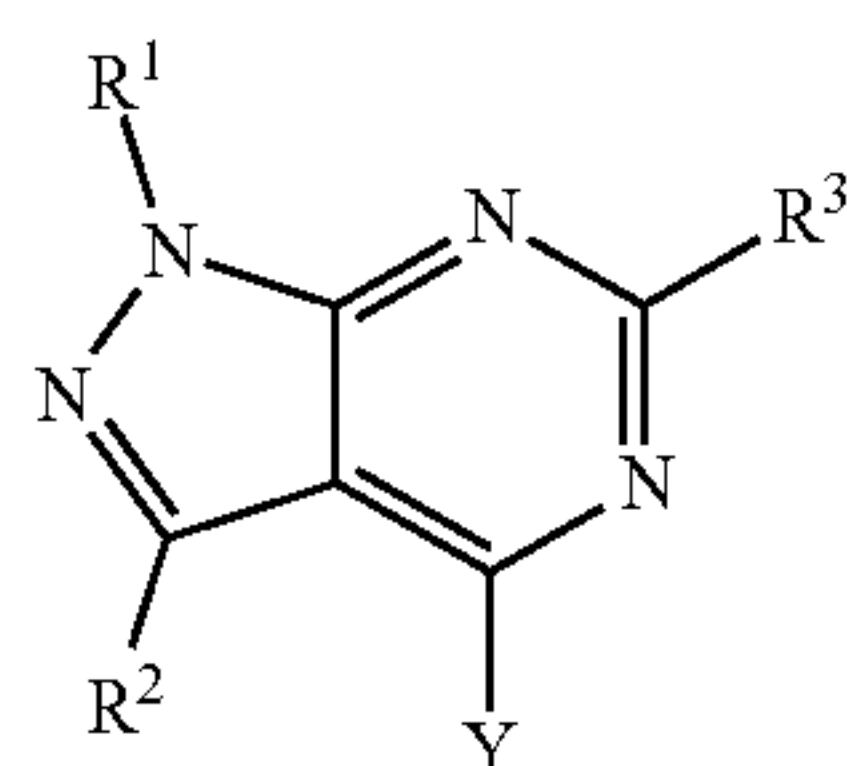
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Ser	Arg	Phe	Leu	Leu	Glu	Arg	Ala	Leu	Gly	Asn	Arg	Arg	Ile	Gly	Gln
			660					665					670		
Phe	Leu	Phe	Trp	His	Leu	Arg	Ser	Glu	Val	His	Ile	Pro	Ala	Val	Ser
		675					680					685			
Val	Gln	Phe	Gly	Val	Ile	Leu	Glu	Ala	Tyr	Cys	Arg	Gly	Ser	Val	Gly
	690					695					700				
His	Met	Lys	Val	Leu	Ser	Lys	Gln	Val	Glu	Ala	Leu	Asn	Lys	Leu	Lys
705					710					715					720
Thr	Leu	Asn	Ser	Leu	Ile	Lys	Leu	Asn	Ala	Val	Lys	Leu	Asn	Arg	Ala
				725					730					735	
Lys	Gly	Lys	Glu	Ala	Met	His	Thr	Cys	Leu	Lys	Gln	Ser	Ala	Tyr	Arg
			740					745					750		
Glu	Ala	Leu	Ser	Asp	Leu	Gln	Ser	Pro	Leu	Asn	Pro	Cys	Val	Ile	Leu
		755					760					765			
Ser	Glu	Leu	Tyr	Val	Glu	Lys	Cys	Lys	Tyr	Met	Asp	Ser	Lys	Met	Lys
	770					775					780				
Pro	Leu	Trp	Leu	Val	Tyr	Asn	Asn	Lys	Val	Phe	Gly	Glu	Asp	Ser	Val
785					790					795					800
Gly	Val	Ile	Phe	Lys	Asn	Gly	Asp	Asp	Leu	Arg	Gln	Asp	Met	Leu	Thr
				805					810					815	
Leu	Gln	Met	Leu	Arg	Leu	Met	Asp	Leu	Leu	Trp	Lys	Glu	Ala	Gly	Leu
			820					825					830		
Asp	Leu	Arg	Met	Leu	Pro	Tyr	Gly	Cys	Leu	Ala	Thr	Gly	Asp	Arg	Ser
		835					840					845			
Gly	Leu	Ile	Glu	Val	Val	Ser	Thr	Ser	Glu	Thr	Ile	Ala	Asp	Ile	Gln
	850					855					860				
Leu	Asn	Ser	Ser	Asn	Val	Ala	Ala	Ala	Ala	Ala	Phe	Asn	Lys	Asp	Ala
865					870					875					880
Leu	Leu	Asn	Trp	Leu	Lys	Glu	Tyr	Asn	Ser	Gly	Asp	Asp	Leu	Asp	Arg
				885					890					895	
Ala	Ile	Glu	Glu	Phe	Thr	Leu	Ser	Cys	Ala	Gly	Tyr	Cys	Val	Ala	Ser
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Tyr	Val	Leu	Gly	Ile	Gly	Asp	Arg	His	Ser	Asp	Asn	Ile	Met	Val	Lys
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Phe	Lys	Ser	Lys	Phe	Gly	Ile	Lys	Arg	Glu	Arg	Val	Pro	Phe	Ile	Leu
945					950					955					960
Thr	Tyr	Asp	Phe	Ile	His	Val	Ile	Gln	Gln	Gly	Lys	Thr	Gly	Asn	Thr
				965					970					975	
Glu	Lys	Phe	Gly	Arg	Phe	Arg	Gln	Cys	Cys	Glu	Asp	Ala	Tyr	Leu	Ile
			980					985					990		
Leu	Arg	Arg	His	Gly	Asn	Leu	Phe	Ile	Thr	Leu	Phe	Ala	Leu	Met	Leu
			995				1000					1005			
Thr	Ala	Gly	Leu	Pro	Glu	Leu	Thr	Ser	Val	Lys	Asp	Ile	Gln	Tyr	
	1010					1015					1020				

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Leu	Lys	Asp	Ser	Leu	Ala	Leu	Gly	Lys	Ser	Glu	Glu	Glu	Ala	Leu
1025						1030					1035			
Lys	Gln	Phe	Lys	Gln	Lys	Phe	Asp	Glu	Ala	Leu	Arg	Glu	Ser	Trp
1040						1045					1050			
Thr	Thr	Lys	Val	Asn	Trp	Met	Ala	His	Thr	Val	Arg	Lys	Asp	Tyr
1055						1060					1065			
Arg	Ser													
1070														

What is claimed is:

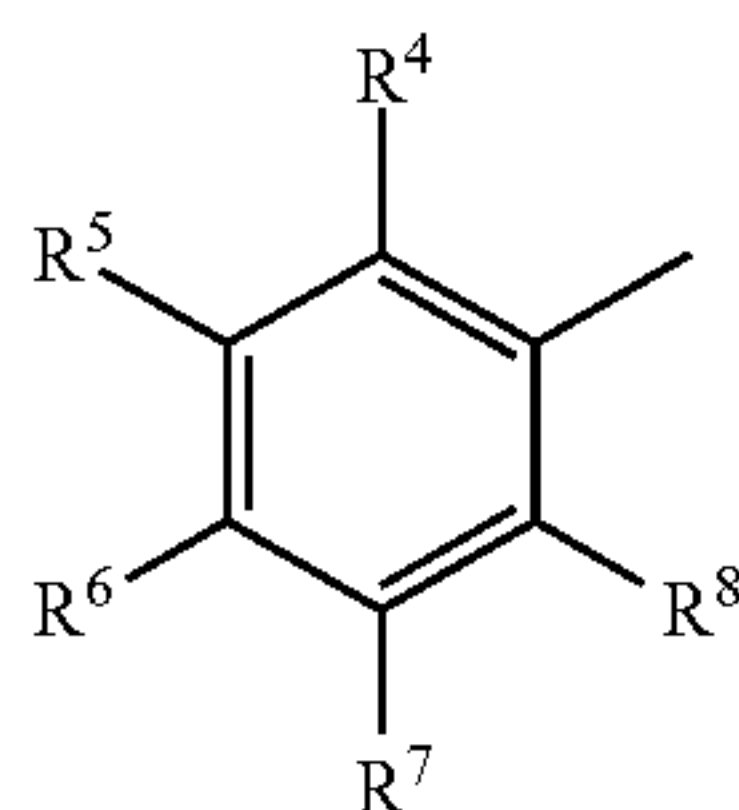
1. A compound of formula (I)



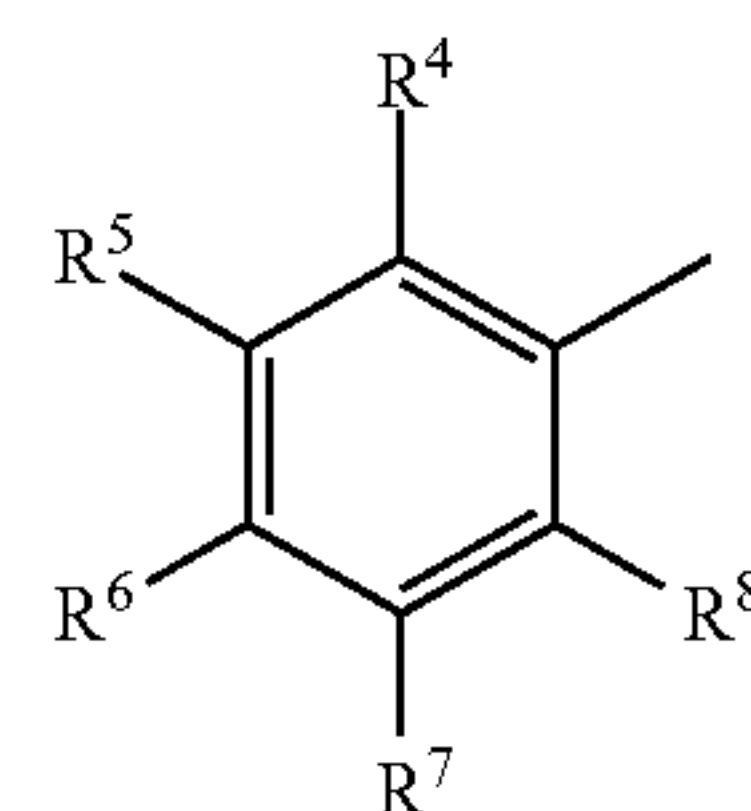
(I)

or a pharmaceutically acceptable salt thereof, wherein:

- R¹ is unsubstituted alkyl;
- R² is substituted aryl, or substituted or unsubstituted heteroaryl;
- R³ is hydrogen;
- Y is —NH₂.

2. The compound of claim 1, wherein R¹ is unsubstituted C₁-C₁₀ alkyl.3. The compound of claim 1, wherein R¹ is unsubstituted C₁-C₄ alkyl.4. The compound of claim 1, wherein R¹ is unsubstituted C₁-C₃ alkyl.5. The compound of claim 1, wherein R¹ is methyl, ethyl, n-propyl, or isopropyl.6. The compound of claim 1, wherein R² has a fused ring structure.7. The compound of claim 1, wherein R² is phenyl having the substitution pattern,

wherein the R² phenyl is fused at R⁴-R⁵, R⁵-R⁶, R⁶-R⁷ or R⁷-R⁸ by a substituted or unsubstituted heteroaryl group or a 6-membered heterocyclyl group.

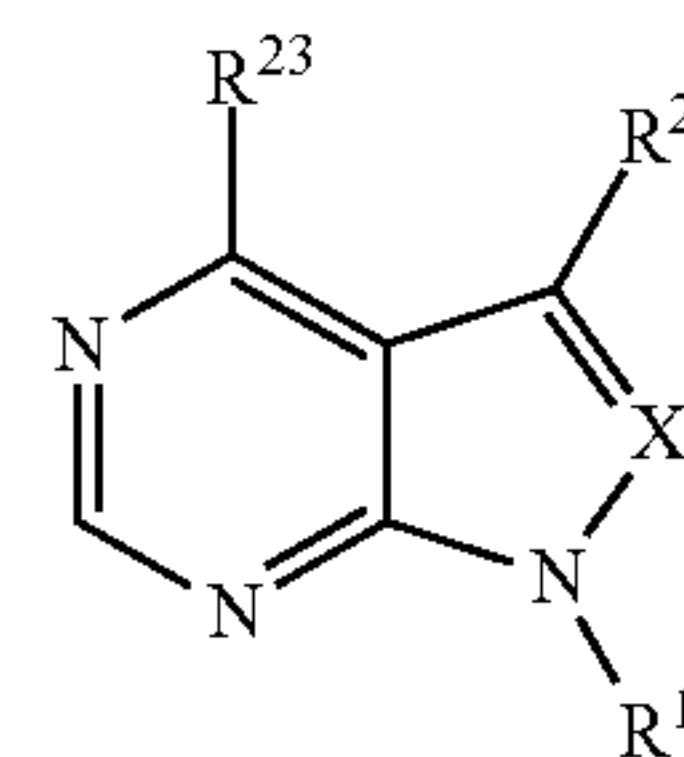
8. The compound of claim 1, wherein R² is phenyl having the substitution pattern,

wherein the R² phenyl is fused at R⁴-R⁵, R⁵-R⁶, R⁶-R⁷ or R⁷-R⁸ by a substituted or unsubstituted heteroaryl group or a 6-membered heterocyclyl group; and wherein any R⁴-R⁸ group that is not part of the fused ring structure is hydrogen.

9. The compound of claim 7, wherein the R² phenyl is fused at R⁵-R⁶ by a substituted or unsubstituted heteroaryl group or a 6-membered heterocyclyl group.10. The compound of claim 7, wherein the R² phenyl is fused at R⁵-R⁶ by a substituted or unsubstituted five-membered heteroaryl group.11. The compound of claim 7, wherein the R² phenyl is fused at R⁴-R⁵, R⁵-R⁶, R⁶-R⁷ or R⁷-R⁸ by a heteroaryl group substituted by one or more of hydroxyl, cyano, unsubstituted alkyl, or amino.12. The compound of claim 1, wherein R² is substituted or unsubstituted indolyl, or substituted or unsubstituted benzodioxanyl.13. The compound of claim 1, wherein R² comprises 5-indolyl or 5-benzothiazolyl.

14. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof.

15. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

- X is N;
- R¹ is unsubstituted alkyl;

c) R^2 is substituted or substituted aryl, or substituted or unsubstituted heteroaryl; and

d) R^{23} is NH_2 .

16. The compound of claim **15**, wherein R^1 is unsubstituted C_1 - C_{10} alkyl.

17. The compound of claim **15**, wherein R^1 is unsubstituted C_1 - C_4 alkyl.

18. The compound of claim **15**, wherein R^1 is unsubstituted C_1 - C_3 alkyl.

19. The compound of claim **15**, wherein R^1 is methyl, ethyl, n-propyl, or 2 isopropyl.

20. The compound of claim **15**, wherein R^2 has a fused ring structure.

21. The compound of claim **15**, wherein R^2 is R^4 -substituted aryl, wherein R^4 is unsubstituted heterocycloalkyl.

22. The compound of claim **15**, wherein R^2 is substituted or unsubstituted indolyl, or substituted or unsubstituted benzodioxanyl, wherein when indolyl or benzodioxanyl are substituted, the substituent is selected from CN, OR^{10} wherein R^{10} is hydrogen, unsubstituted alkyl, and $NR^{12}R^{13}$, wherein R^{12} and R^{13} are independently hydrogen or unsubstituted alkyl.

23. The compound of claim **15**, wherein R^2 comprises 5-indolyl or 5-benzothiazolyl.

24. A pharmaceutical composition comprising the compound of claim **15** or a pharmaceutically acceptable salt thereof.

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