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(54) Titre : DERIVES DE PYRIDAZINONE UTILES EN TANT QU'INHIBITEURS DE SYNTHASE DE GLUCANE
(54) Title: PYRIDAZINONE DERIVATIVES USEFUL AS GLUCAN SYNTHASE INHIBITORS

(57) Abrégé/Abstract:
In its many embodiments, the present invention provides -substituted pyridazinone compounds as glucan synthase inhibitors, methods of preparing such compounds, pharmaceutical including one or more of such compounds, methods of preparing pharmaceutical formulations including one or more such compounds or one or more such compounds along with other antifungal agents, and methods of treatment, prevention, inhibition, or amelioration of one or more fungal infections associated with glucan synthase using such compounds or pharmaceutical compositions.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: PYRIDAZINONE DERIVATIVES USEFUL AS GLUCAN SYNTHASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides -substituted pyridazinone compounds as glucan synthase inhibitors, methods of preparing such compounds, pharmaceutical including one or more of such compounds, methods of preparing pharmaceutical formulations including one or more such compounds or one or more such compounds along with other antifungal agents, and methods of treatment, prevention, inhibition, or amelioration of one or more fungal infections associated with glucan synthase using such compounds or pharmaceutical compositions.

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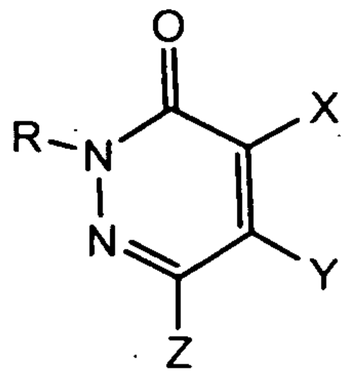
PYRIDAZINONE DERIVATIVES USEFUL AS GLUCAN SYNTHASE INHIBITORS

FIELD OF THE INVENTION

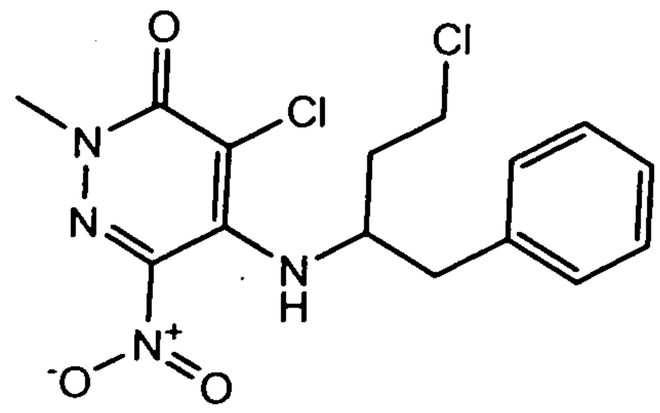
This invention relates to novel compounds, which are useful as glucan synthase inhibitors, pharmaceutical compositions containing the compounds, and methods of treating or preventing fungal infections. In one embodiment, the compounds are piperazine-substituted pyridazinone compounds.

BACKGROUND OF THE INVENTION

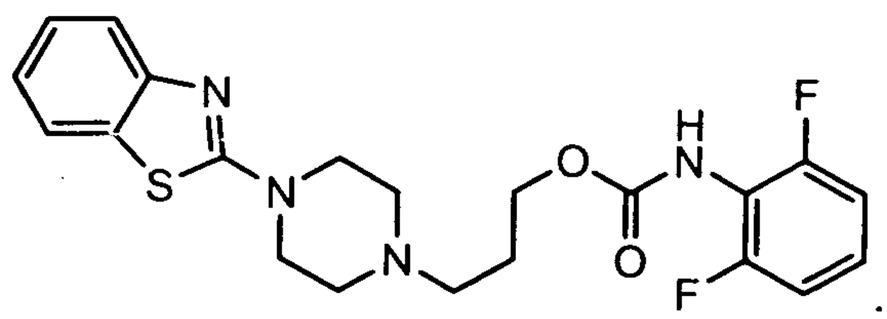
The enzymes involved in fungal cell wall biogenesis are attractive targets for antifungal intervention. These enzymes are unique to fungi and therefore provide highly selective antifungal targets. Furthermore, disruption of cell wall synthesis generally leads to a fungicidal response due to cell lysis induced by the osmotic instability of cells lacking an intact wall. Major structural components of fungal cell walls are β(1,3)-linked D-glucan polymers. These polymers are generated by β(1,3)-D-glucan synthase, an integral membrane protein complex that is required for fungal cell viability. Compounds described as inhibitors of glucan synthase have been described previously. Reference is made to Károlyházy, László et al. Arzneim.-Forsch./ Drug Res. **2003**, Vol. 53, No. 10, 738-743, which discloses 3-(2H)-pyridazinones of the formula:



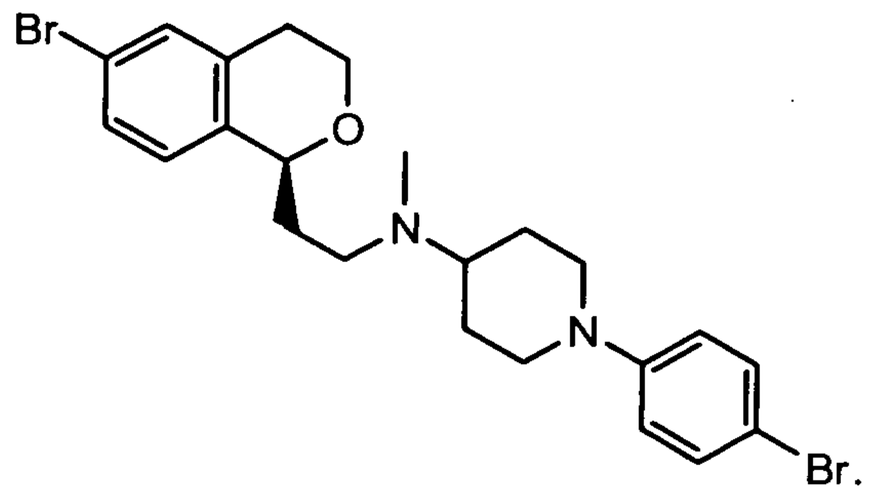
where the various elements are defined therein. An illustrative compound of that series is:



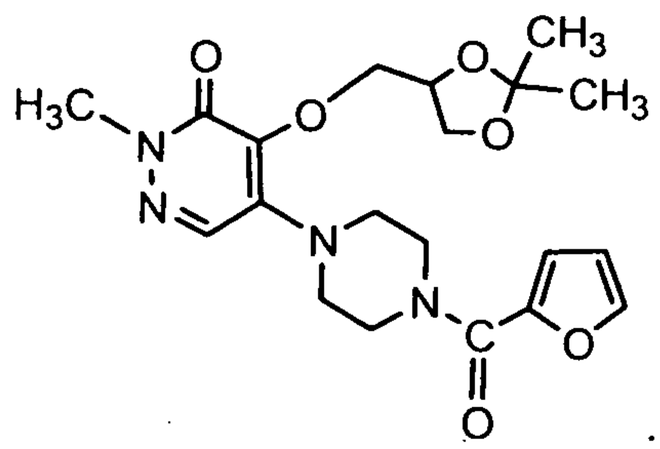
Reference is made to Kondoh, Osamu et al., Biol. Pharm. Bull. **2005**, 28, 2138-2141, which discloses piperazine propanol derivatives. An illustrative compound of that series is:



Reference is made to Brayman, Timothy et al., Antimicrobial Agents and Chemotherapy **2003** Vol. 47, No. 10, 3305-3310, which discloses the use of several compounds identified as glucan synthase inhibitors to test an assay for antifungal activity of glucan synthase inhibitors that uses germ tube formation in Candida albicans as an end point. An illustrative compound used to test the assay is:



Reference is made to Gomez, Gil et al., ES 540813 **1985**, which discloses 1,2-diazin -3(2H)-ones as compounds of pharmaceutical interest useful as antihypertensives, β-adrenergic blockers, antiulcer agents or as intermediates thereof. An illustrative compound of that series is:

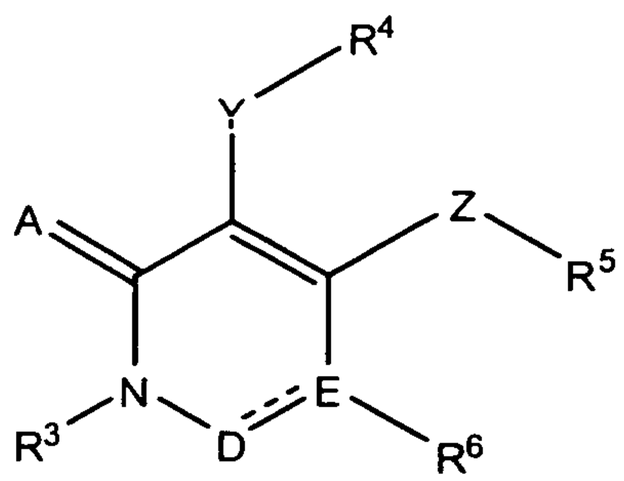


Reference is made to Pauline C. Ting and Scott S. Walker, "New Agents to Treat Life-Threatening Fungal Infections" in Current Topics in Medicinal Chemistry, 2008, which discloses Antifungals that are inhibitors of glucan synthase. These antifungals include cyclic hexapeptides that are either approved for antifungal chemotherapy (caspofungin, micafungin anidulafungin) or under clinical development (aminocandin).

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds, methods of preparing such compounds, pharmaceutical compositions comprising one or more of such compounds, pharmaceutical compositions comprising a combination of one or more of such compounds and other antifungal agents, bacterial agents, and steroids, methods of preparing pharmaceutical formulations comprising one or more of such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with glucan synthase using such compounds or pharmaceutical compositions.

A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

====== represents a double bond or a single bond, as permitted by the valency requirement, with the proviso that when E is N, the double bond is present and R^6 is absent;

A is O or S;

D and E are independently C or N,

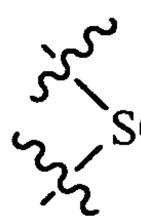
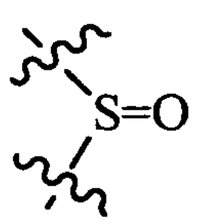
provided that when D is carbon, D is substituted with hydrogen, alkyl, -Oalkyl, -Nalkyl or –Salkyl;

R^3 is a moiety selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclenyl, heterocyclenylalkyl, heterocyclenylalkenyl , arylalkoxylalkyl, arylalkoxylalkenyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkenoxylalkyl, and cycloalkenyoxylalkenyl,

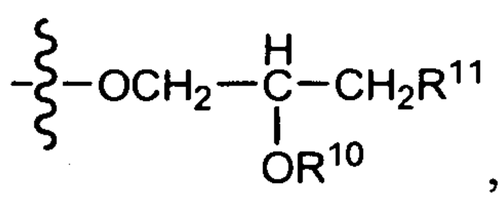
wherein each of said alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl,

cyclenylalkyl, cyclenylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclenyl, heterocyclenylalkyl, heterocyclenylalkenyl , arylalkoxylalkyl, arylalkoxylalkenyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9_2$, $-OR^9$, $-SR^9$, $-NO_2$, -CN, $-NR^{16}COR^9$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, $-CONR^9\,R^{16}$, and -N=C=O;

Y can be present or absent; or

Y is $-NR^9$, -O-, -S-,  or 

provided that when Y is O, Y-R^4 taken together is not alkoxyl of the formula



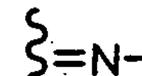
, wherein $-CH_2R^{11}$ and $-OR^{10}$ together with the CH to which they are attached, form a heterocyclyl that is substituted with one or more moieties, which can be the same or different , selected from the group consisting of alkyl and aryl, or

wherein R^{10} is H and R^{11} is hydroxyl or butylamine;

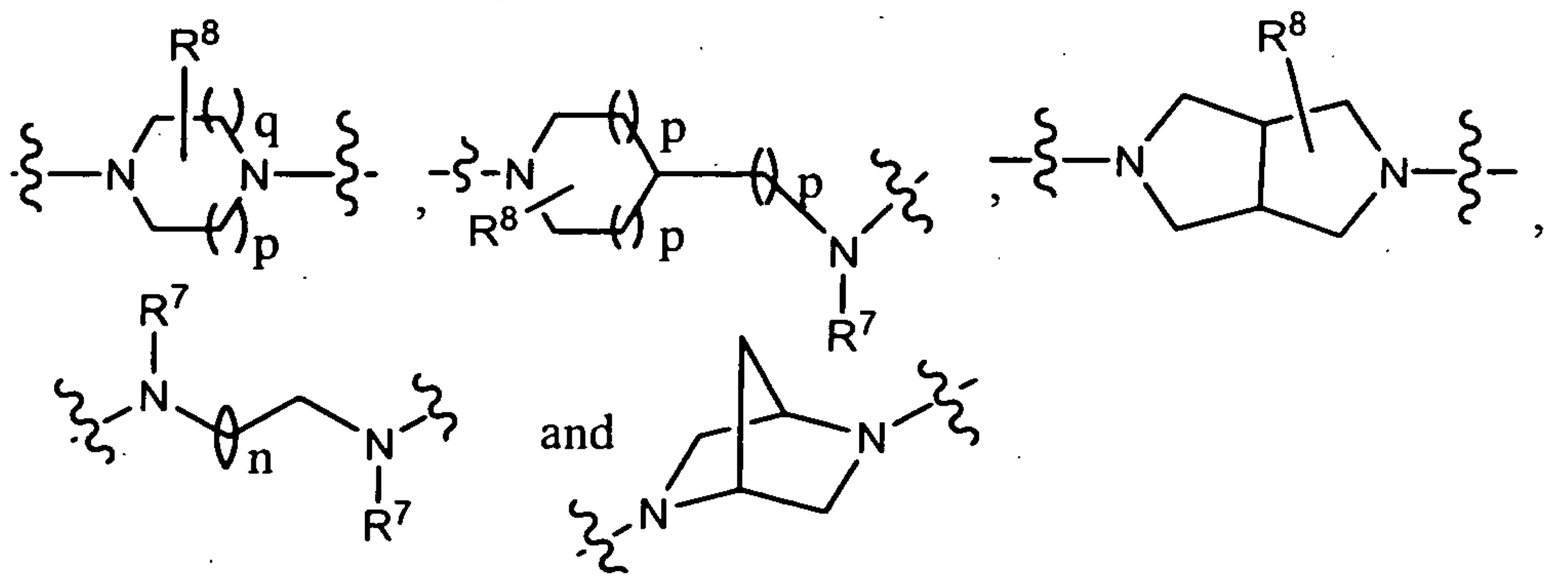
R^4 is alkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkenyl-O-alkyl, alkoxyalkenyl, alkenyl-O-alkenyl, alkynyl-O-alkyl, hydroxyalkyl, hydroxyalkenyl, alkyl-S-alkyl, alkenyl-S-alkyl, alkyl-S-alkenyl, alkenyl-S-alkenyl, alkyl-SO-alkyl, alkenyl-SO-alkyl, alkyl-SO-alkenyl, alkenyl-SO-alkenyl, alkyl-SO_2-alkyl, alkenyl-SO_2-alkyl, alkyl-SO_2-alkenyl, alkenyl-SO_2-alkenyl, alkyl-NR^9-alkyl, alkenyl-NR^9-alkyl, alkyl-NR^9-alkenyl, alkenyl-NR^9-alkenyl, alkyl-CO_2-alkyl, alkenyl-CO_2-alkyl, alkyl-CO_2-alkenyl, alkenyl-CO_2-alkenyl, alkyl-O_2C-alkyl, alkenyl-O_2C-alkyl, alkyl-O_2C-alkenyl, alkenyl-O_2C-alkenyl, alkyl-NCO-alkyl, alkenyl-NCO-alkyl, alkyl-NCO-alkenyl, alkenyl-NCO-alkenyl, alkyl-CON-alkyl, alkenyl-CON-alkyl, alkyl-CON-alkenyl, alkenyl-CON-alkenyl, alkyl-NCON-alkyl, alkenyl-NCON-alkyl, alkyl-NCON-alkenyl, alkenyl-NCON-alkenyl, alkyl-CO-alkyl, alkenyl-CO-alkyl, alkyl-CO-alkenyl, alkenyl-CO-alkenyl, cycloalkyl, cycloalkylalkyl, spiroheteroaryl, spiroheterocyclenyl,

spiroheterocyclyl, spiroheteroarylalkyl, spiroheteroarylalkenyl, spiroheterocyclenylalkyl, spiroheterocyclenylalkenyl, spiroheterocyclylalkyl, spiroheterocyclylalkenyl, spirocycloalkyl, spirocycloalkylalkyl, spirocycloalkylalkenyl, spirocyclenyl, spirocyclenylalkyl, spirocyclenylalkenyl, spiroaryl, spiroarylalkyl, spiroarylalkenyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylcycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl, heterocyclenyl, heterocyclenylalkyl heterocyclenylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, benzofused-cycloalkyl, benzofused-heterocycloalkyl, benzofused-cycloalkylalkyl or benzofused-heterocycloalkylalkyl;

wherein said alkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkenyl-O-alkyl, alkoxyalkenyl, alkenyl-O-alkenyl, alkynyl-O-alkyl, hydroxyalkyl, hydroxyalkenyl, alkyl-S-alkyl, alkenyl-S-alkyl, alkyl-S-alkenyl, alkenyl-S-alkenyl, alkyl-SO-alkyl, alkenyl-SO-alkyl, alkyl-SO-alkenyl, alkenyl-SO-alkenyl, alkyl-SO_2-alkyl, alkenyl-SO_2-alkyl, alkyl-SO_2-alkenyl, alkenyl-SO_2-alkenyl, alkyl-NR^9-alkyl, alkenyl-NR^9-alkyl, alkyl-NR^9-alkenyl, alkenyl-NR^9-alkenyl, alkyl-CO_2-alkyl, alkenyl-CO_2-alkyl, alkyl-CO_2-alkenyl, alkenyl-CO_2-alkenyl, alkyl-O_2C-alkyl, alkenyl-O_2C-alkyl, alkyl-O_2C-alkenyl, alkenyl-O_2C-alkenyl, alkyl-NCO-alkyl, alkenyl-NCO-alkyl, alkyl-NCO-alkenyl, alkenyl-NCO-alkenyl, alkyl-CON-alkyl, alkenyl-CON-alkyl, alkyl-CON-alkenyl, alkenyl-CON-alkenyl, alkyl-NCON-alkyl, alkenyl-NCON-alkyl, alkyl-NCON-alkenyl, alkenyl-NCON-alkenyl, alkyl-CO-alkyl, alkenyl-CO-alkyl, alkyl-CO-alkenyl, alkenyl-CO-alkenyl, cycloalkyl, cycloalkylalkyl, spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spiroheteroarylalkyl, spiroheteroarylalkenyl, spiroheterocyclenylalkyl, spiroheterocyclenylalkenyl, spiroheterocyclylalkyl, spiroheterocyclylalkenyl, spirocycloalkyl, spirocycloalkylalkyl, spirocycloalkylalkenyl, spirocyclenyl, spirocyclenylalkyl, spirocyclenylalkenyl, spiroaryl, spiroarylalkyl, spiroarylalkenyl, alkylcycloalkyl, alkylcycloalkylalkyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl, heterocyclenyl, heterocyclenylalkyl heterocyclenylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, benzofused-cycloalkyl, benzofused-heterocycloalkyl, benzofused-cycloalkylalkyl or benzofused-heterocycloalkylalkyl can be unsubstituted or substituted with at least one moiety

independently selected from the group consisting of alkyl, alkenyl, aryl, OR^9, arylalkyl, arylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkyl, cycloalkylalkenyl, alkylCO_2alkyl-, halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, cycloalkyl, cyclenyl, hydroxyalkyl, hydroxyalkenyl, thiohydroxyalkyl, thiohydroxyalkenyl, hydroxyalkenyl, heteroaryl, heteroarylalkyl, heterocyclenyl, heterocyclenylalkyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, -CN, $-NO_2$, $-OSiR^9_3$, $-NR^{16}COR^9$, $-OCONR^9_2$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2R^9$, $-NR^9_2$, -N=C=O,  , $-NR^{16}CO_2R^9$, $-COR^9$, $-CO_2R^9$, $-OCOR^9$, $-SO_2R^9$, $-SOR^9$, $-SR^9$, $-SO_2N(R^9)_2$ or $-CONR^9R^{16}$, wherein each of said alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkyl, cycloalkylalkenyl, halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, cycloalkyl, cyclenyl, hydroxyalkyl, hydroxyalkenyl, thiohydroxyalkyl, thiohydroxyalkenyl, hydroxyalkenyl, heteroaryl, heteroarylalkyl, heterocyclenyl, heterocyclenylalkyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from R^9;

Z is a linker attached at either end of said linker to the parent ring of Formula I, wherein said linker is selected from the group consisting of :

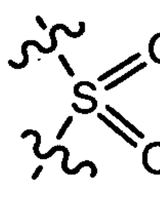
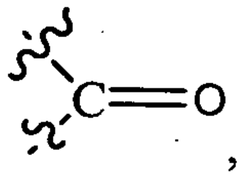
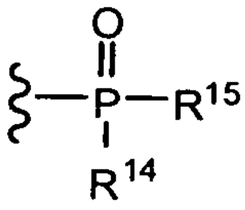
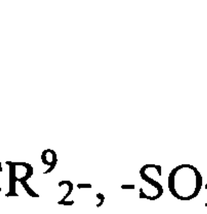


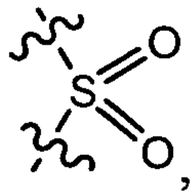
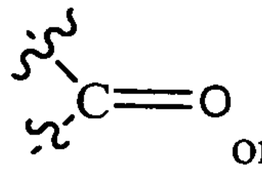
wherein

n is 1 to 4,

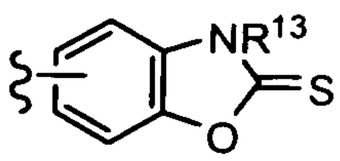
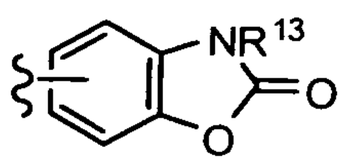
p is 0 to 2,

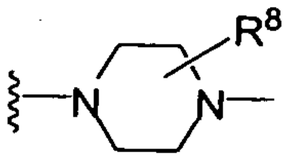
q is 1 to 3;

R^5 is  ,  ,  ,  , $-CR^9_2-$, $-SO_2NR^{13}$-alkyl-C(O)-aryl, or heteroaryl,

wherein each of said  ,  or $-CR^9_2-$ is attached at one end to Z and at the second end substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, $-OR^9$ and $-NR^9_2$,

further, wherein each of said alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, or heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, alkenyl, cycloalkyl, $-OR^9$, alkylOR^9, alkylCO_2R^9, alkyl$NR^{16}COR^9$, alkyl$NR^{16}CONR^9$, alkylSO_2R^9, alkylCOR^9, alkyl$SO_2NR^9_2$, alkylNR^9_2, alkylaryl, alkylheteroaryl, alkylSR^9, alkylSOR^9, -CN, $-CO_2R^9$, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^{16}COR^9$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2-R^{13}$, $-SO_2R^9$, $-COR^9$, $-NO_2$, $-SO_2NR^9_2$, aryl, heteroaryl, $-NR^9_2$, $-SR^9$, $-SOR^9$, $-C(=NOH)-NR^{13}$, , , ,

 and  ;

or Y-R^4 taken together are H, provided that R^6 is not H; or Y-R^4 taken together are H and R^6 is H, provided that when Z is  , R^8 is not H;

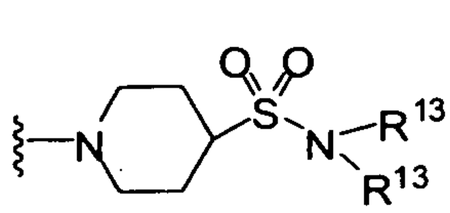
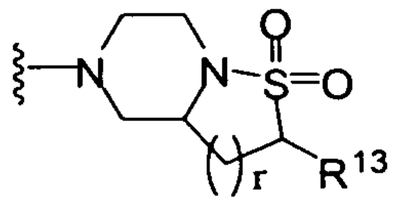
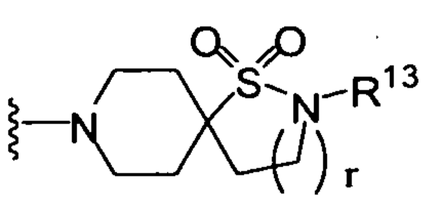
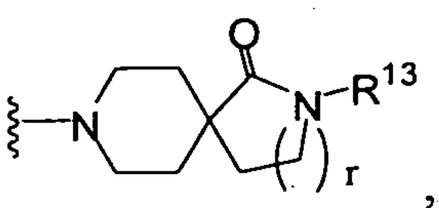
or when Y is –O- and R^5 is $–SO_2$-, R^4 and the second end substituent on R^5 together are –alkyl-, -alkenyl-, -alkyl-NH-,or –alkenyl-NH-, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

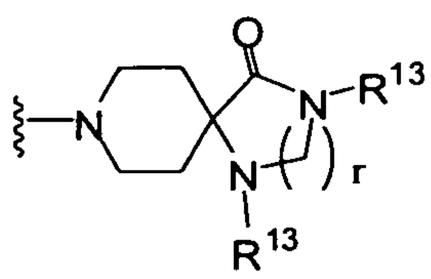
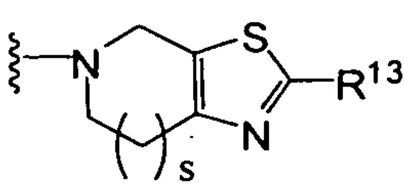
or when R^3 is a group having an $–OR^9$ substituent and Y is –O-, R^4 and the R^9 portion of the R^3 group together are a divalent alkyl group, forming a ring with the –O- atoms to which they are attached;

or when Y is –O- and R^5 is $–SO_2$-, R^4 and the second end substituent of R^5 together are an -alkyl-phenylene-alkyl-NR^{13}- group or an -alkyl-phenylene-alkyl- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or when Y is –O- and R^5 is $–SO_2$-, R^4 and the second end substituent of R^5 together are an -alkyl-heteroarylene-alkyl- group or an -alkyl-heteroarylene-alkyl-NR^{13}- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or Z and R^5 taken together is

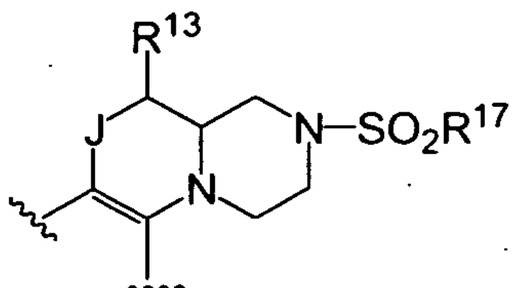

or

,

wherein

r is 1 or 2;

s is 0 or 1;

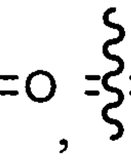
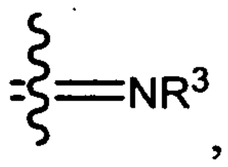
or -Y-R^4, -ZR^5 and the carbons to which they are attached form the group


, wherein J is –O-. –S- or $–NR^{13}$;

R^6 is H, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, arylalkoxylalkyl, arylalkoxylalkenyl, arylalkoxyl, cycloalkoxyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkylalkoxyl, cycloalkenoxyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl, -NR^9_2, -OR^9, -NO_2, -$NR^{16}COR^9$, -$NR^{16}CON(R^{17})_2$, -$NR^{16}SO_2R^9$, -COR^9, -CO_2R^9 or -$CONR^9R^{16}$;

wherein each of said alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, arylalkoxylalkyl, arylalkoxylalkenyl, arylalkoxyl, cycloalkoxyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkylalkoxyl, cycloalkenoxyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9{}_2$, $-OR^9$, $-SR^9$, $-NO_2$, -CN, $-NR^{16}COR^9$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, $-CONR^9R^{16}$ and $-NR^{16}CON(R^{17})_2$;

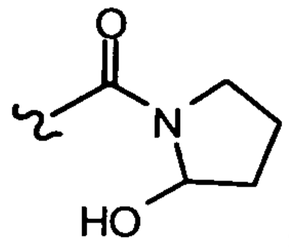
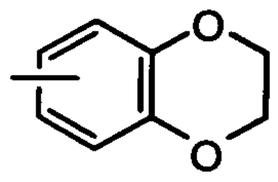
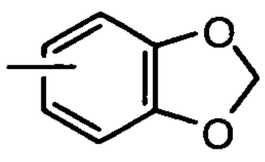
each R^7 is independently selected from the group consisting of H and alkyl;

R^8 is one or more moieties, which can be the same or different, each being independently selected from the group consisting of H, aryl, arylalkyl, alkyl, ,  ,  , arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, alkenyl, alkynyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9{}_2$, $-OR^9$, $-SR^9$, $-NR^{16}COR^9$, $-NR^{16}CON(R^{17})_2$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, and $-CONR^9R^{16}$,

wherein each of said aryl, arylalkyl, alkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, alkenyl and alkynyl can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9{}_2$, $-OR^9$, $-SR^9$, $-NO_2$, -CN, $-NR^{16}COR^9$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, $-CONR^9R^{16}$ and $-NR^{16}CON(R^{17})_2$;

R^9 is one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heteroalkyl, heterocycloalkyl, heterocyclenyl, heteroaryl, hydroxyalkyl, hydroxyalkenyl, alkylthioalkyl, alkylthioalkenyl, alkenylthioalkyl, alkenylthioalkenyl, alkoxylalkyl, arylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, arylalkenyl, cycloalkyalkenyl, cyclenylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl,

alkoxyaryl, trihaloalkyl, trihaloalkenyl, dihaloalkyl, dihaloalkenyl, monohaloalkyl, and monohaloalkenyl,

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heterocycloalkyl, heterocyclenyl, heteroaryl, hydroxyalkyl, hydroxyalkenyl, alkoxylaikyl, arylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, arylalkenyl, cycloalkyalkenyl, cyclenylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, and alkoxyaryl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, trihaloalkenyl, dihaloalkenyl, monohaloalkenyl, hydroxyl, alkoxy, hydroxyalkyl, $-N(R^{12})_2$, aikyl, alkynyl , cycloalkyl, alkenyl, cyclenyl, aryl, heteroaryl, heterocycloalkyl, heterocyclenyl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, heterocyclenylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heteroarylalkenyl, heterocycloalkylalkenyl, heterocyclenylalkenyl, -CN, $-NO_2$, $-SO_2R^{17}$, $-C(O)N(R^{20})_2$, $-CO_2R^{19}$,  , $-NR^{16}-C(O)R^{19}$, $-NR^{16}CON(R^{17})_2$, $-NR^{16}SO_2R^{17}$, trihaloalkoxy, dihaloalkoxy, monohaloalkoxy,  and  ;

further wherein when two R^9 moieties are attached to a N, the two R^9 moieties, together with the N to which they are attached, can form a heterocyclyl or heterocyclenyl ring of 4 to 7 members, wherein 1 or 2 of said ring members can be –O-, -S- or $-NR^{18}$-, provided that there are no heteroatoms adjacent to each other; and wherein the heterocyclyl or heterocyclenyl ring is optionally substituted on 1 or 2 ring carbon atoms by a substituent independently selected from the group consisting of alkyl, alkoxy, -OH and $-NR^{16}$, or two hydrogen atoms on the same carbon are replaced by =O;

each R^{12} is independently selected from the group consisting of H, alkyl, aryl and arylalkyl;

each R^{13} is independently selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl;

R^{14} is alkyl or alkoxy;

R^{15} is aryl, arylalkyl, -N(R^{13})-aryl, -N(R^{13})-alkylaryl, -O-aryl or –O-alkylaryl;

R^{16} is independently selected from the group consisting of H and alkyl;

R^{17} is alkyl, aryl or arylalkyl;

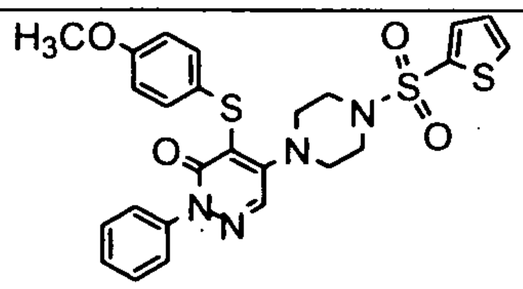
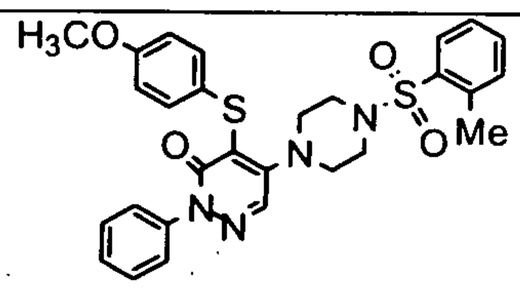
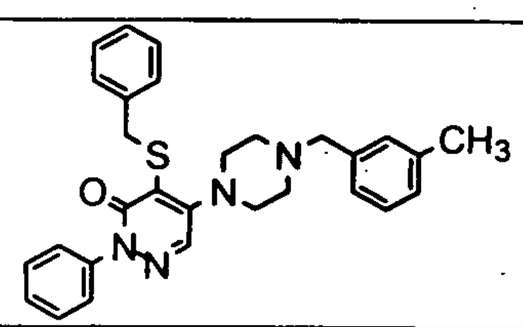
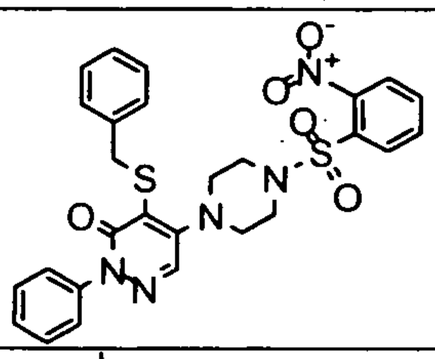
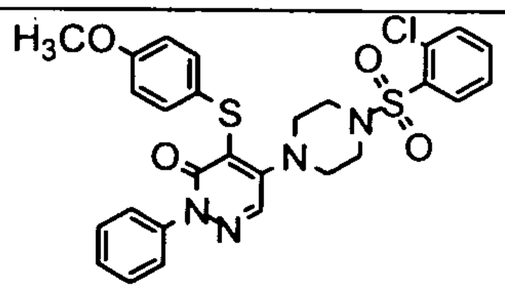
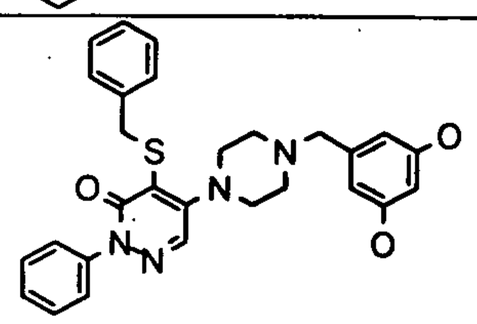
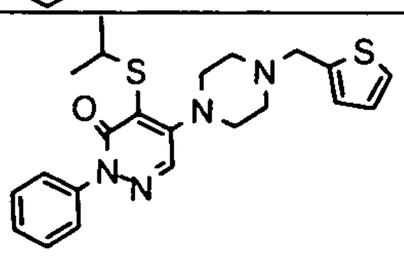
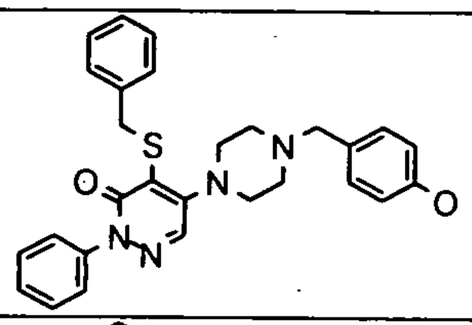
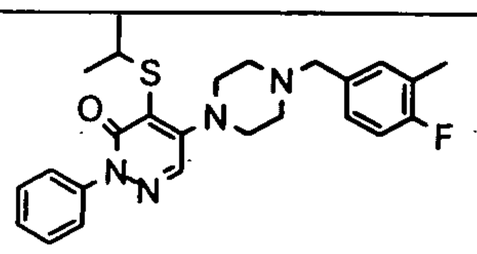
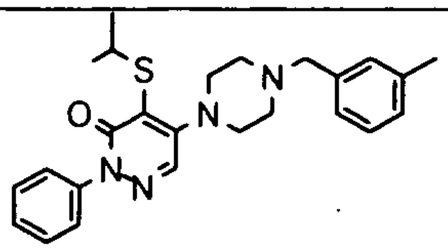
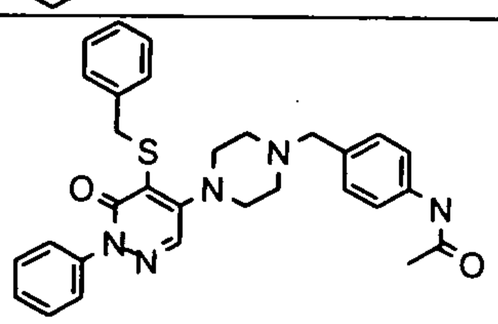
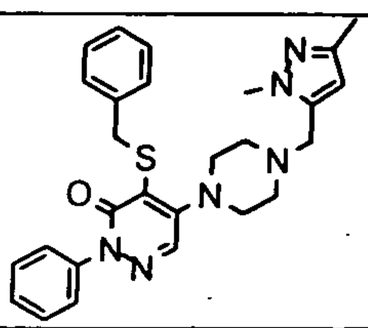
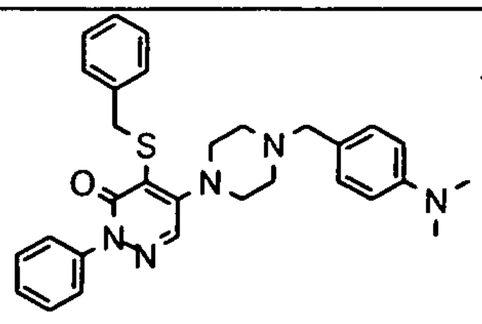
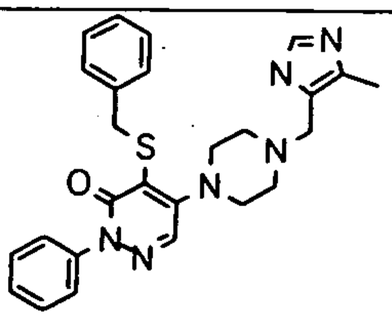
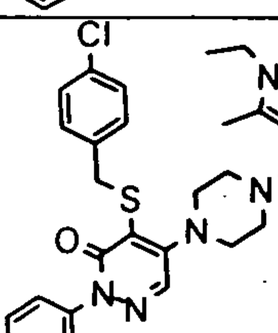
R^{18} is H, alkyl, –COOR^{19}, -COR^{17} or –CON(R^{17})$_2$;

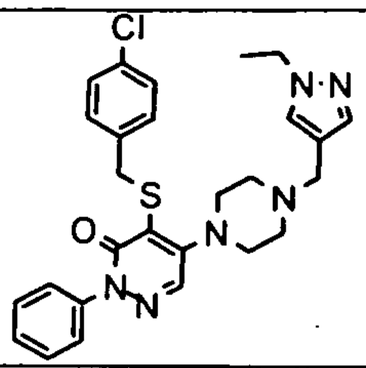
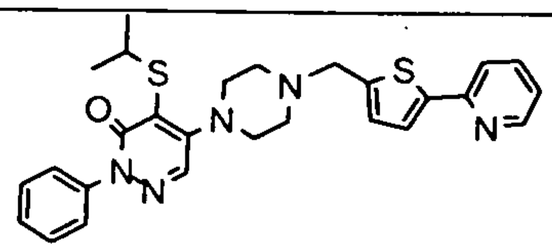
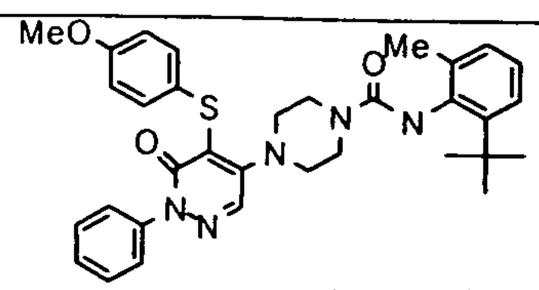
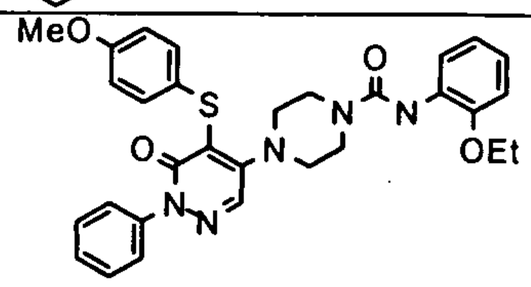
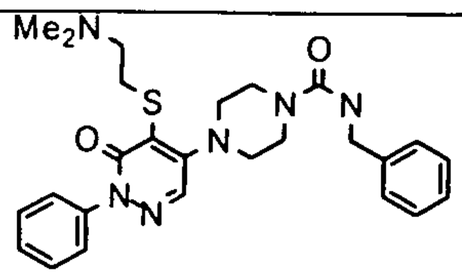
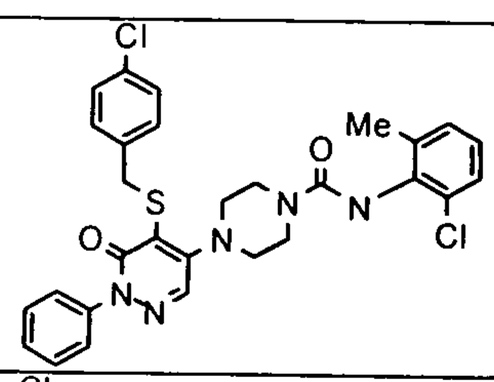
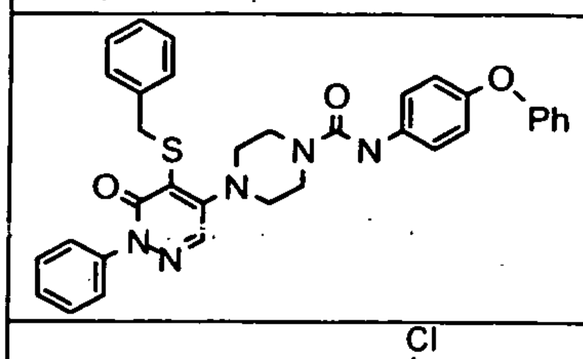
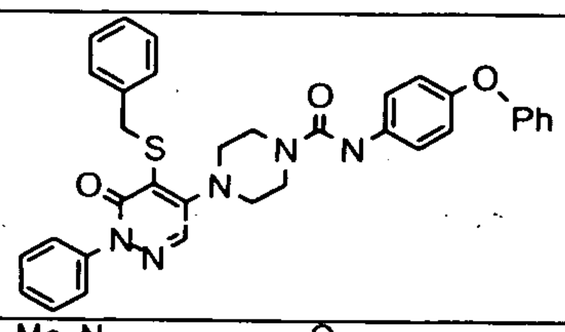
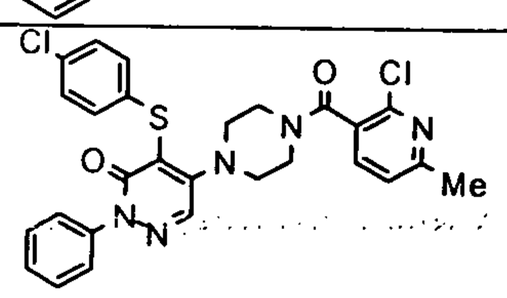
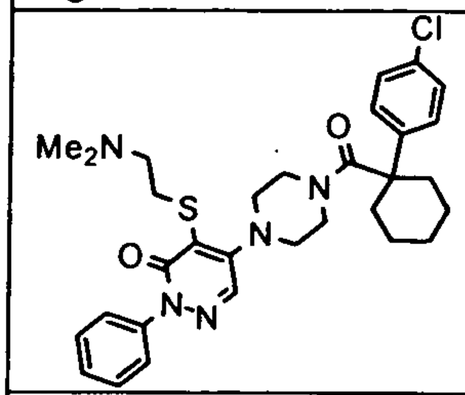
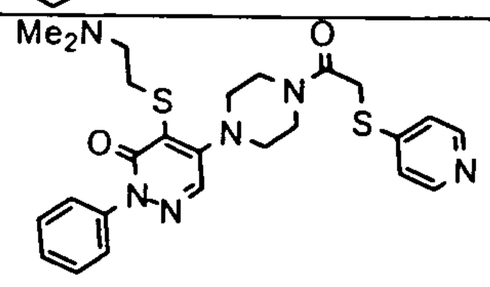
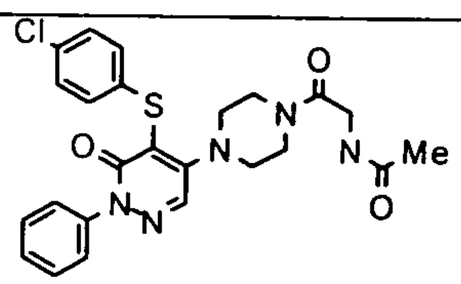
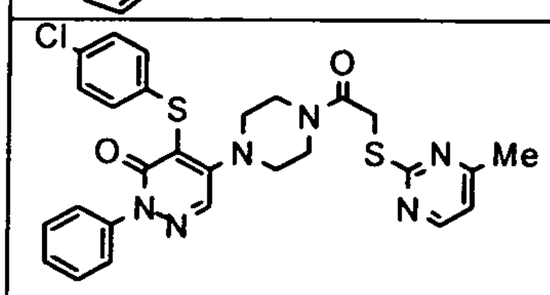
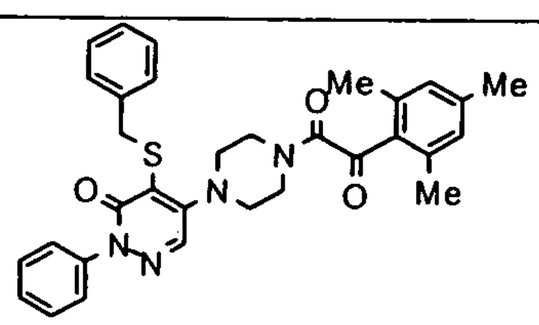
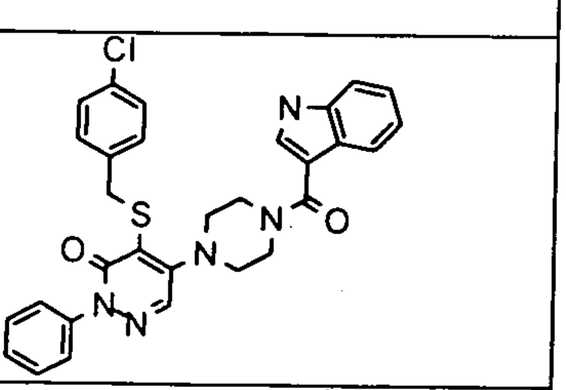
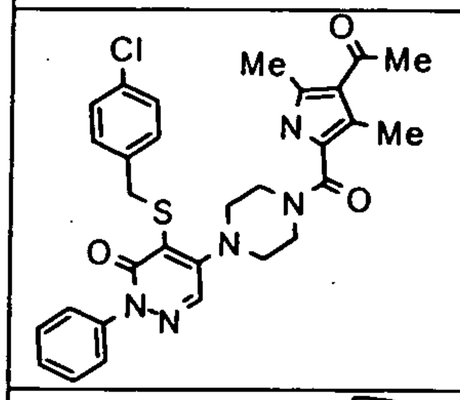
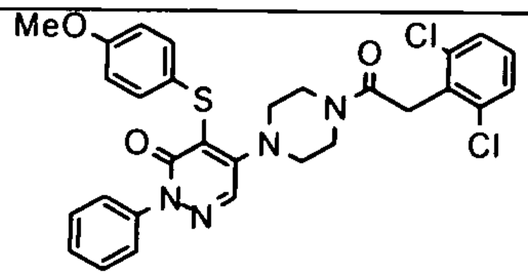
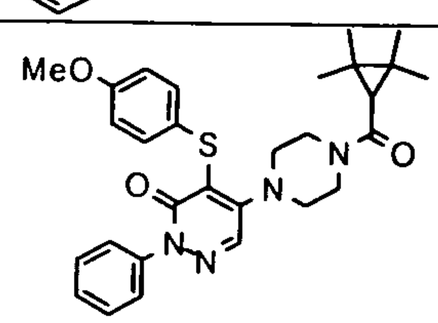
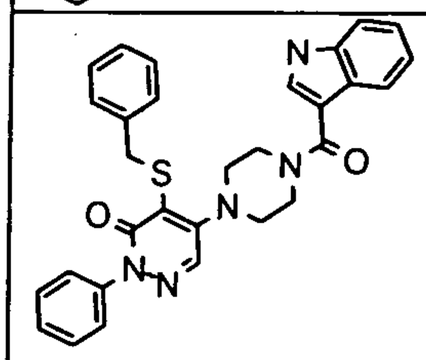
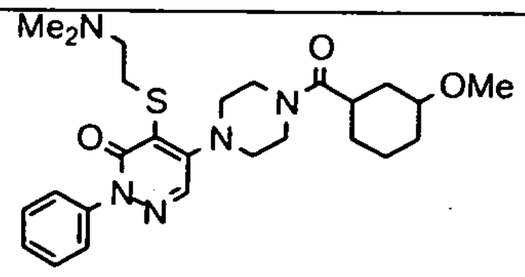
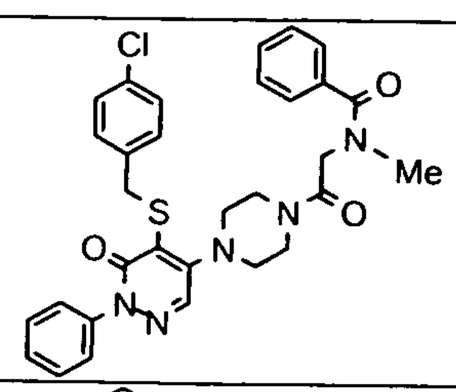
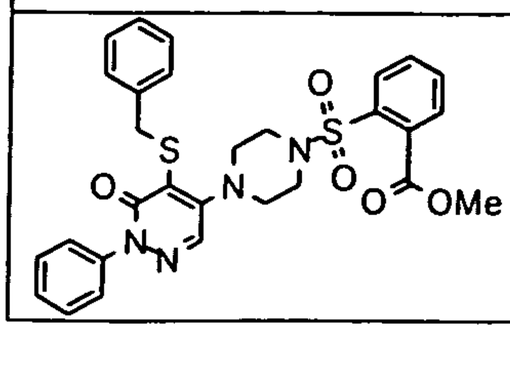
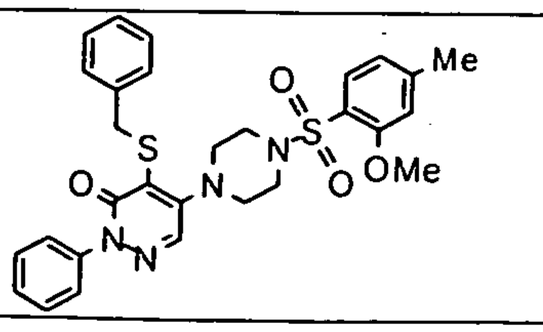
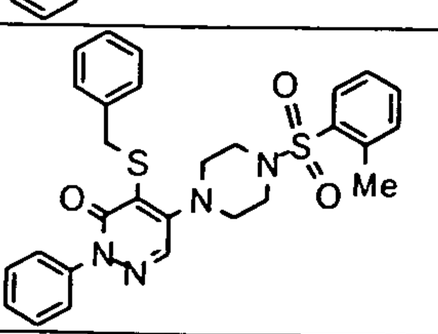
each R^{19} is independently selected from the group consisting of H, alkyl and arylalkyl;

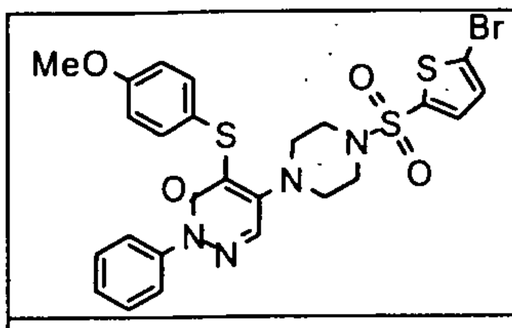
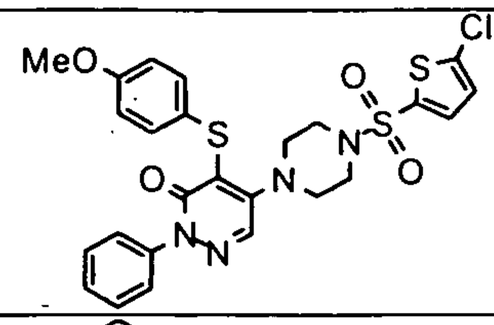
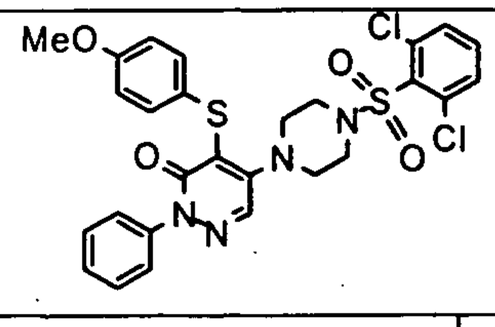
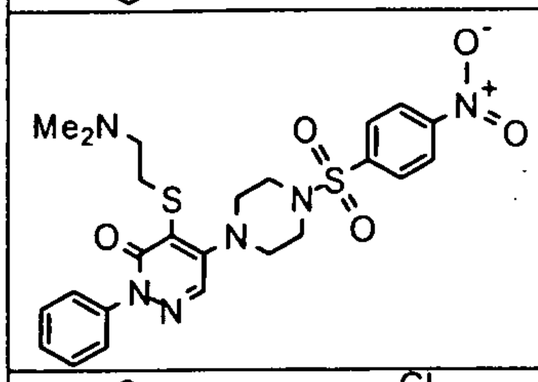
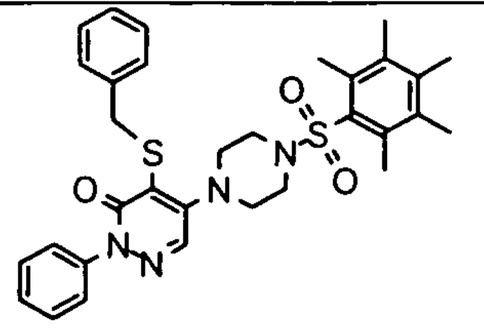
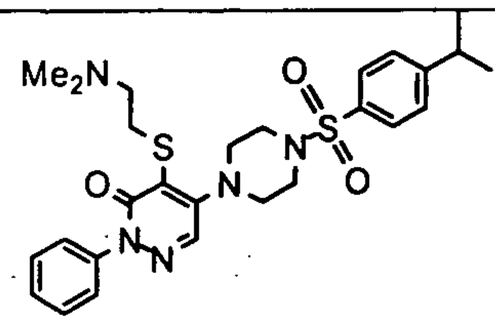
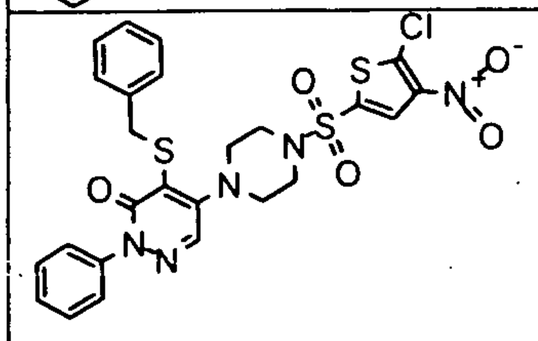
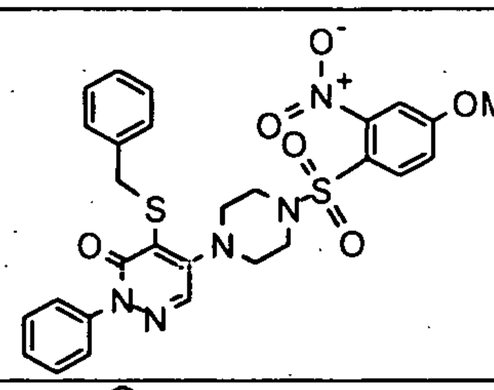
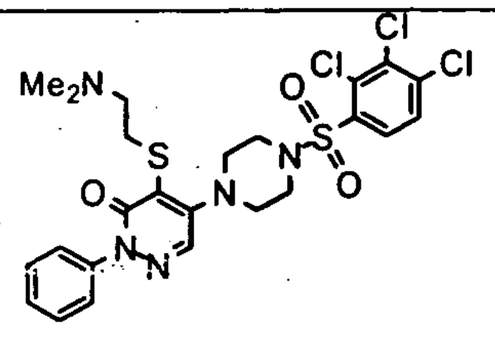
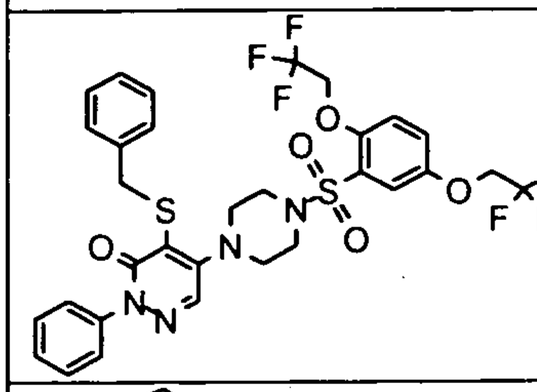
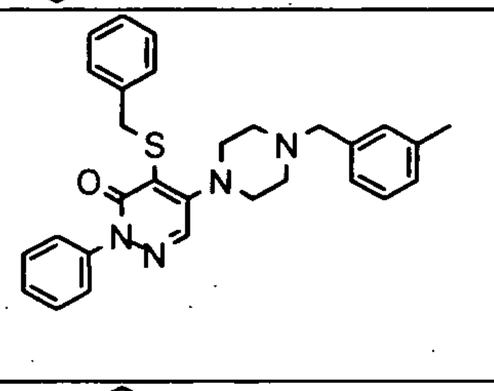
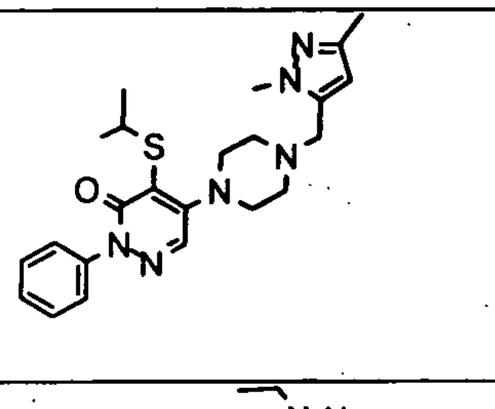
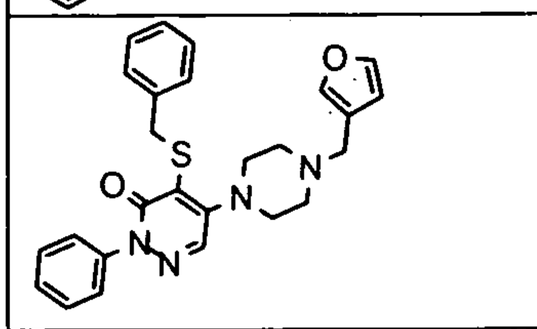
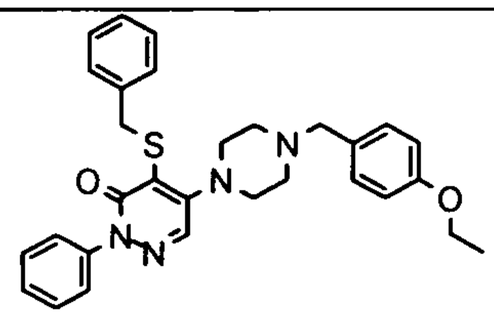
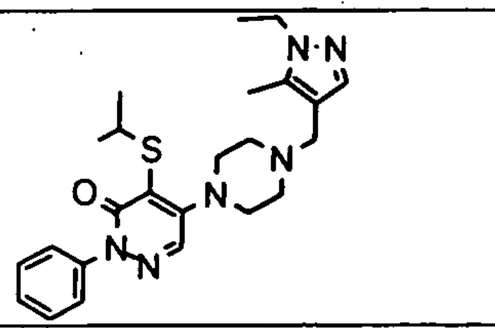
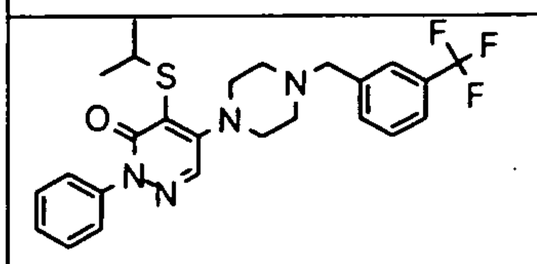
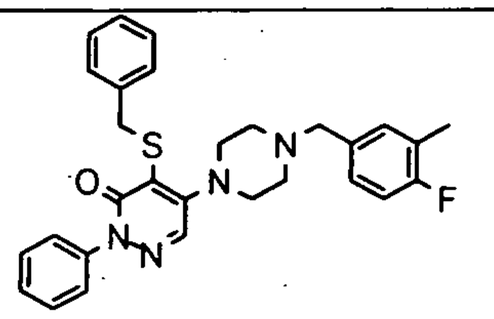
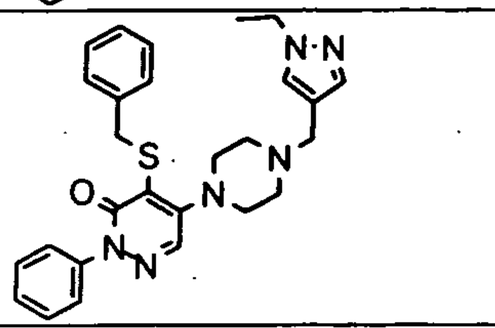
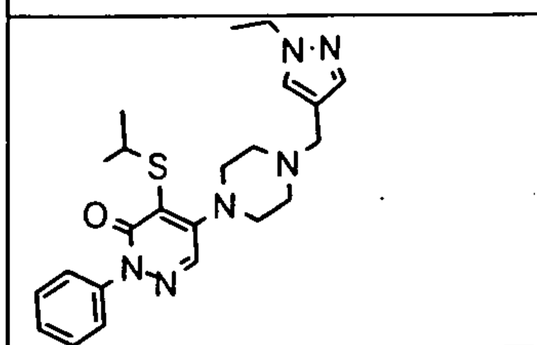
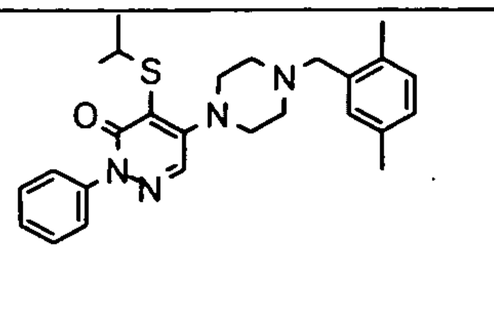
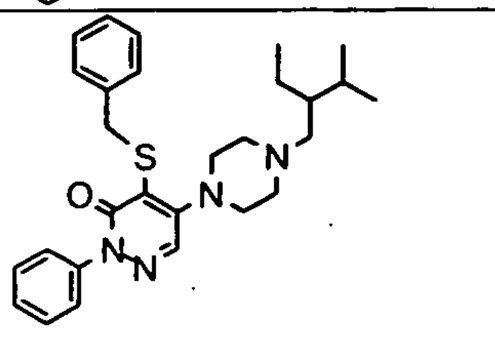
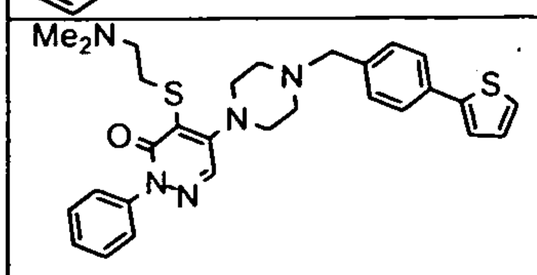
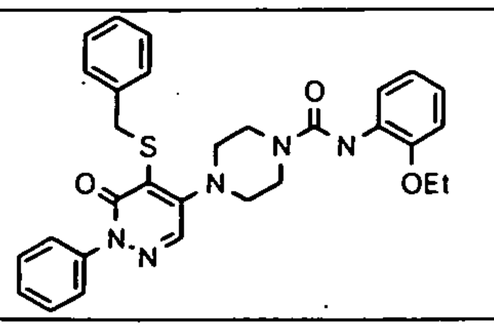
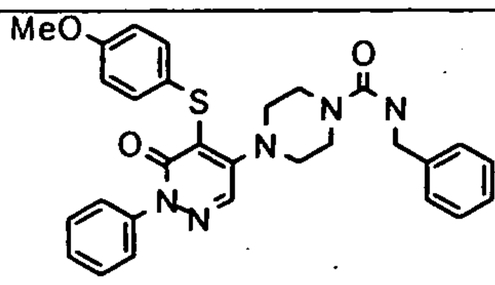
each R^{20} is is independently selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, and alkoxyalkyl;

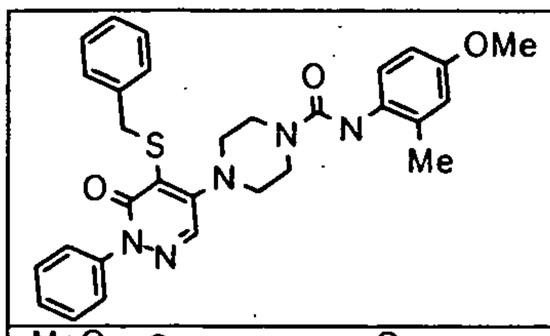
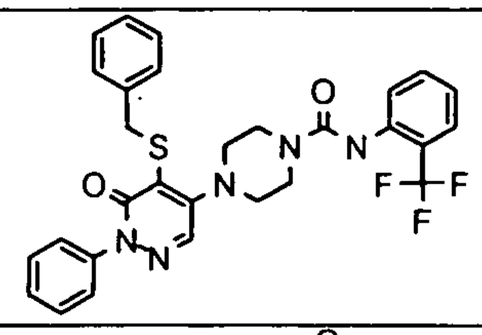
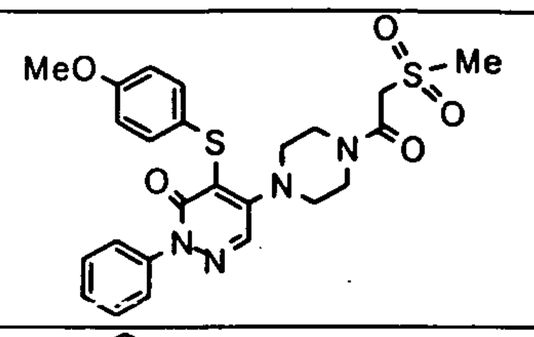
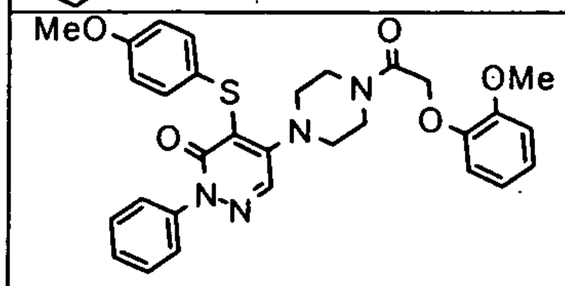
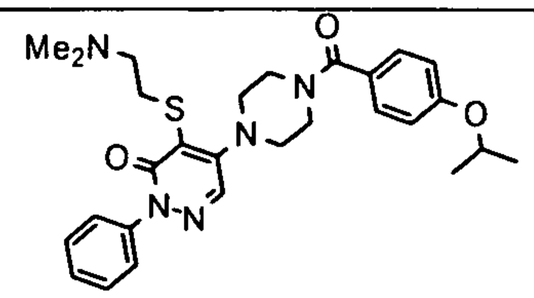
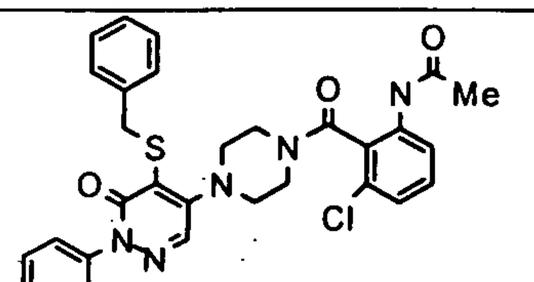
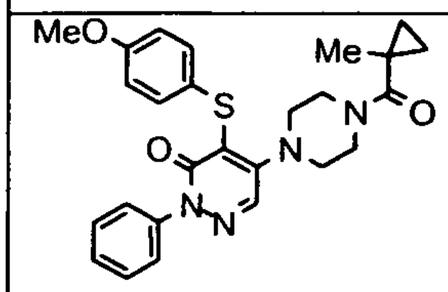
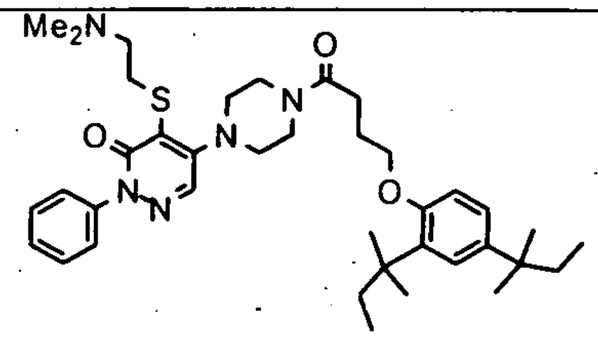
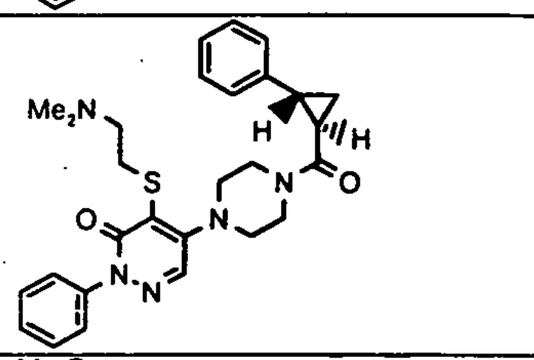
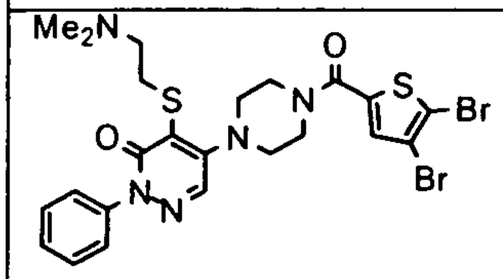
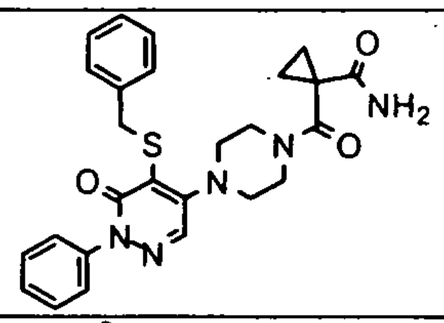
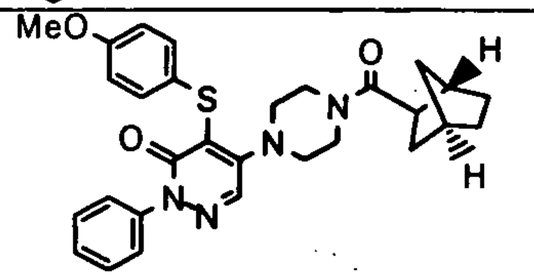
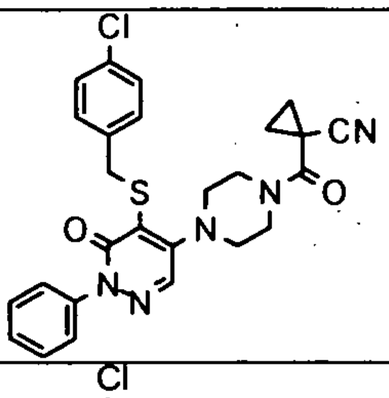
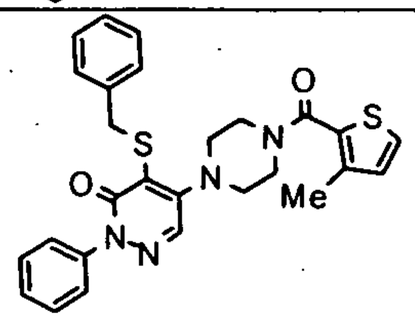
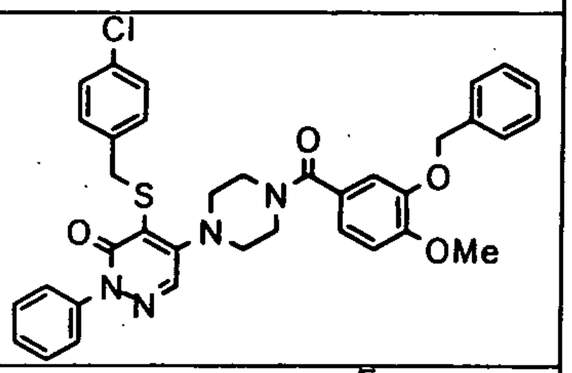
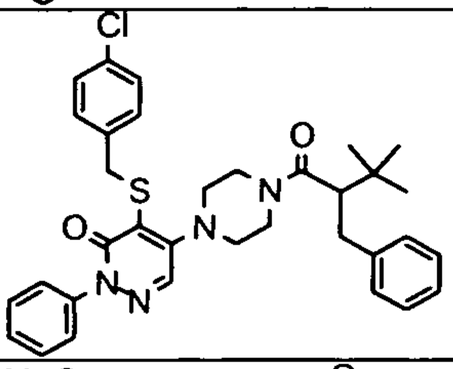
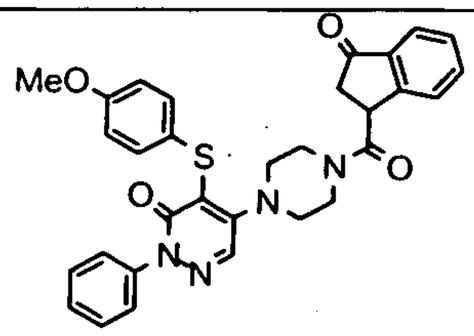
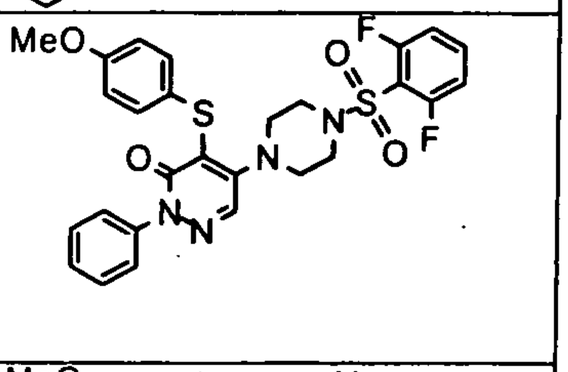
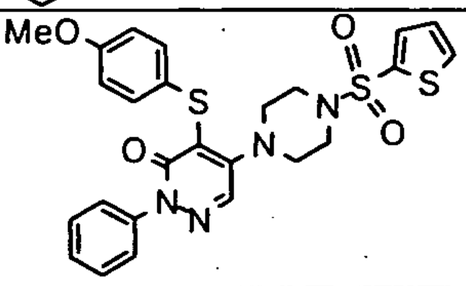
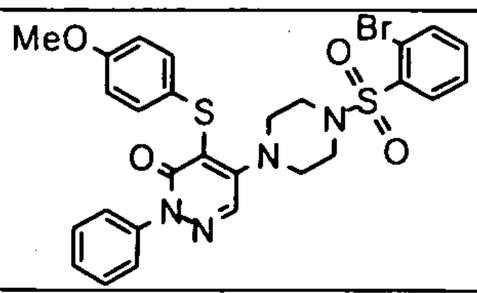
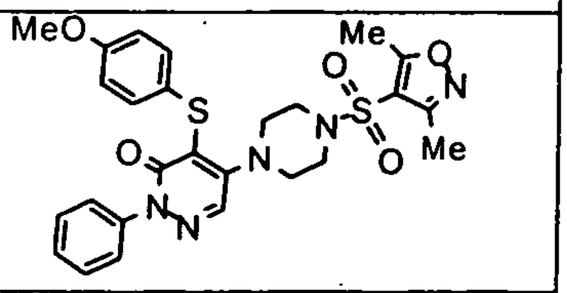
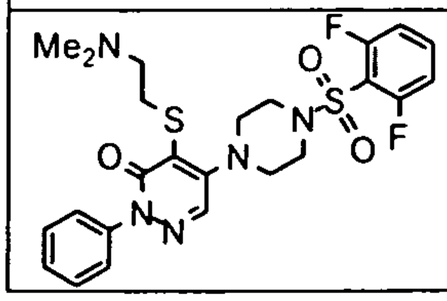
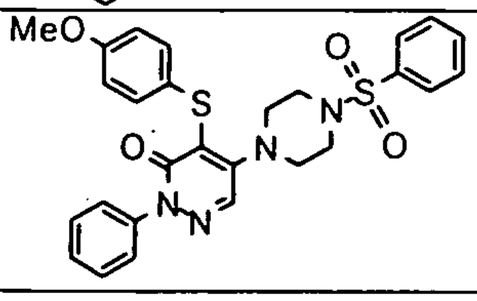
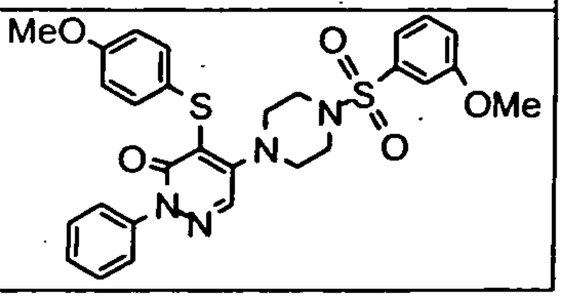
provided that Formula I does not include the compounds of Table A:

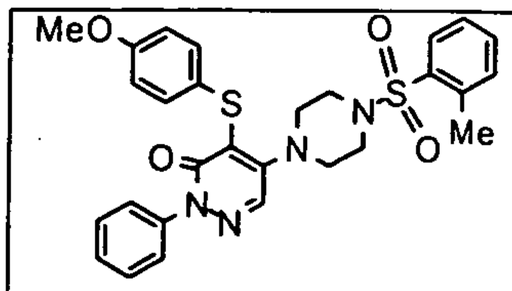
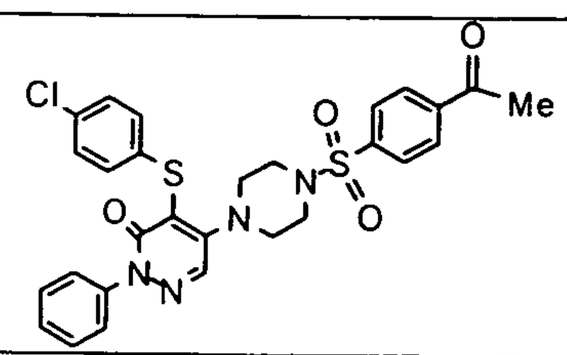
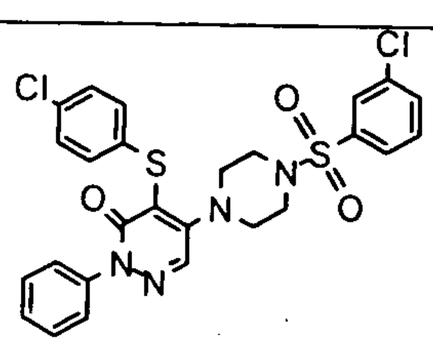
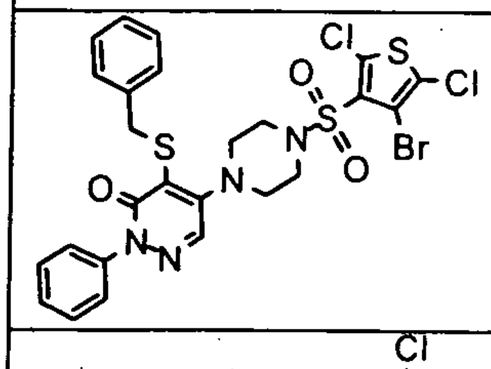
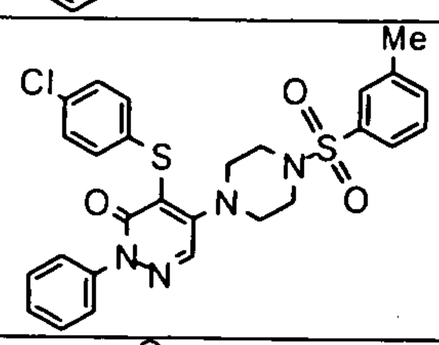
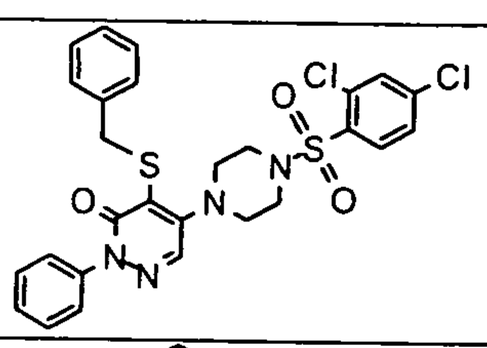
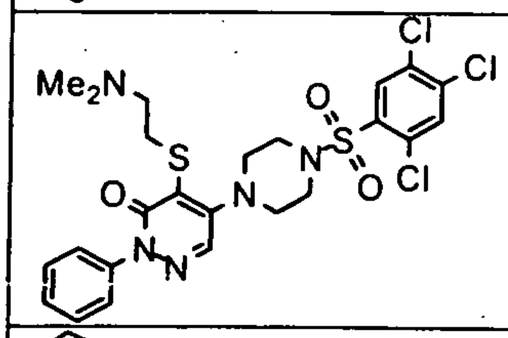
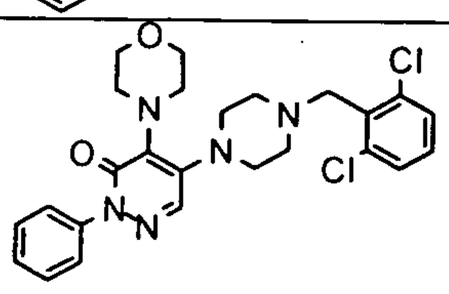
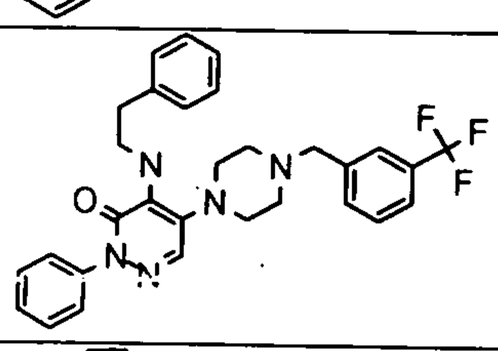
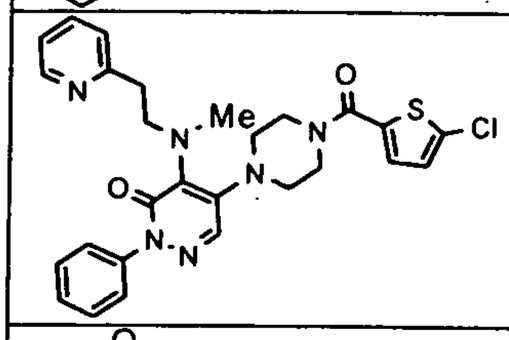
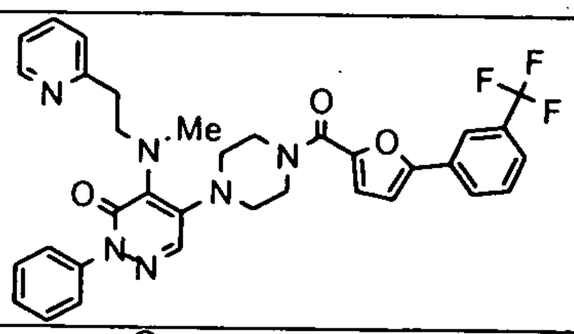
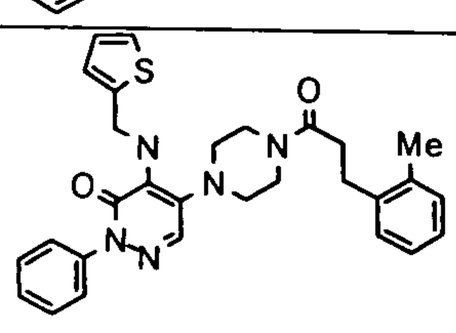
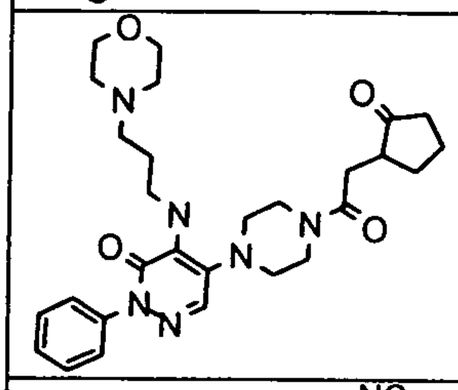
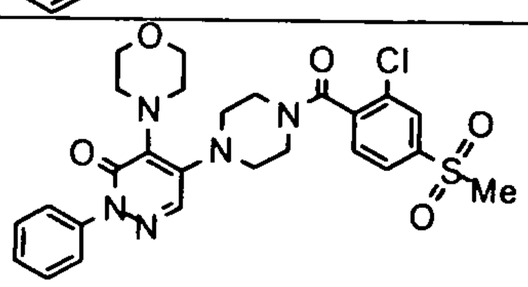
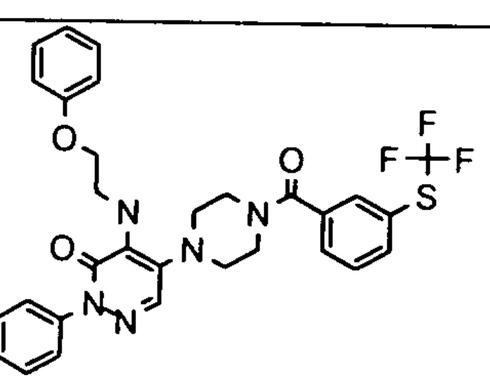
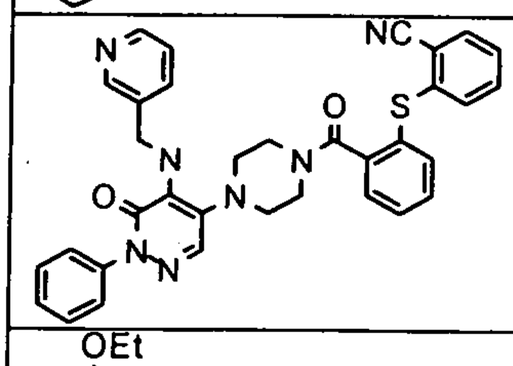
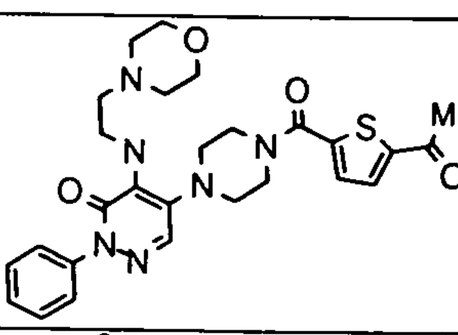
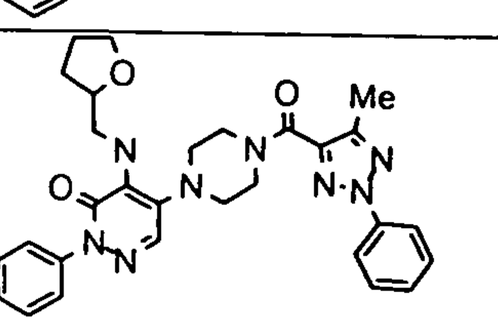
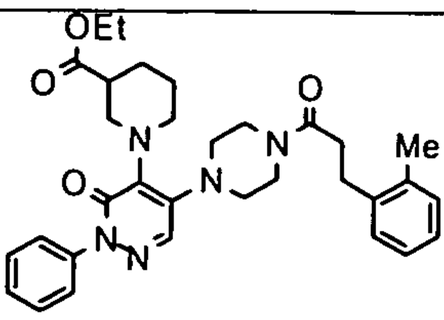
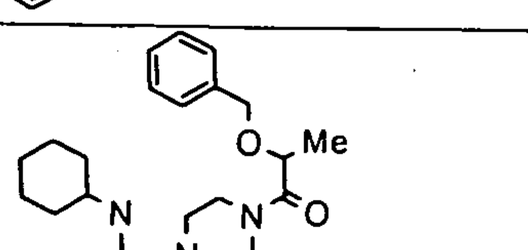
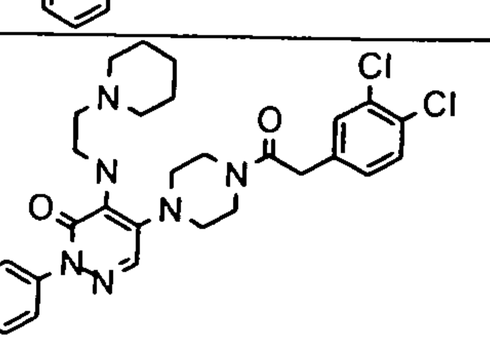
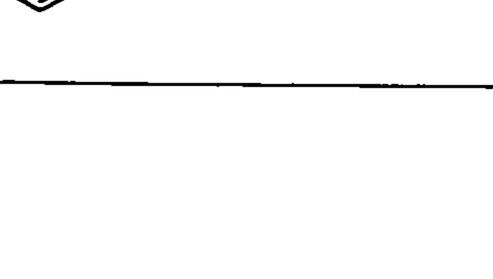
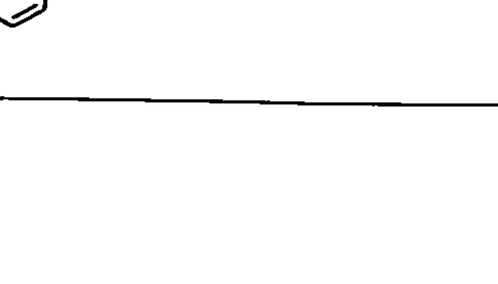
Table A:

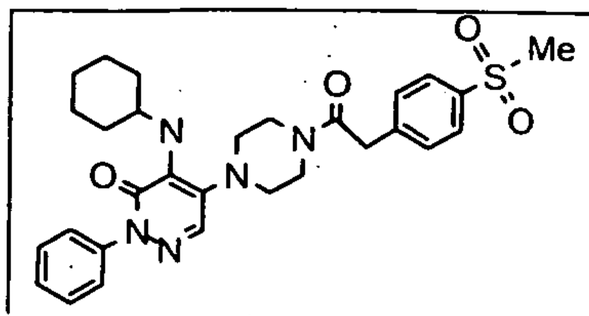
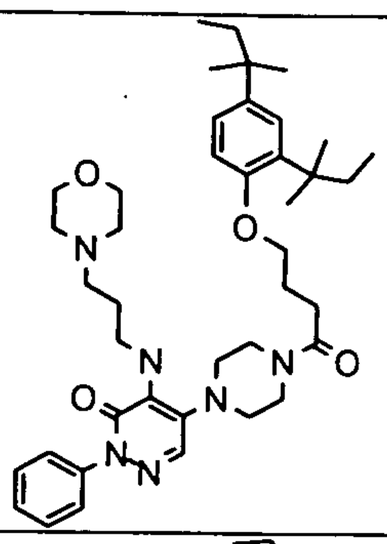
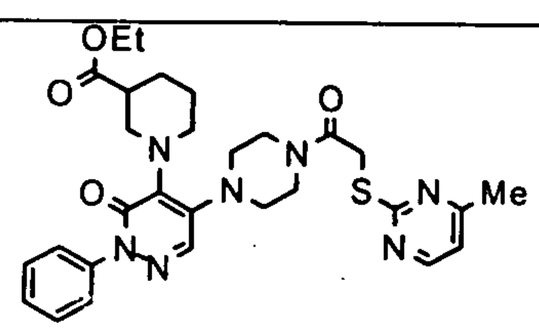
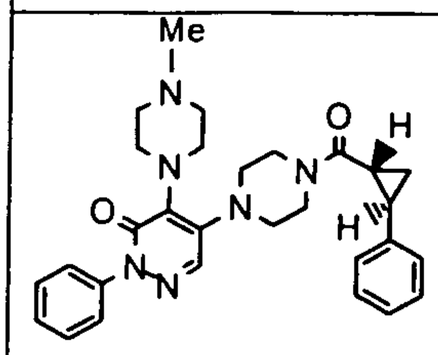
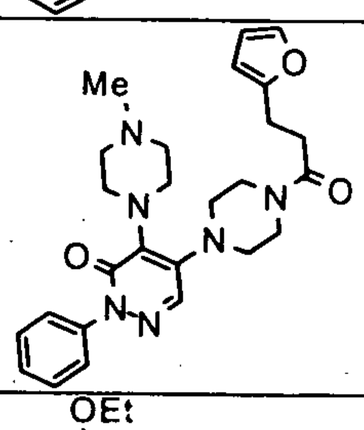
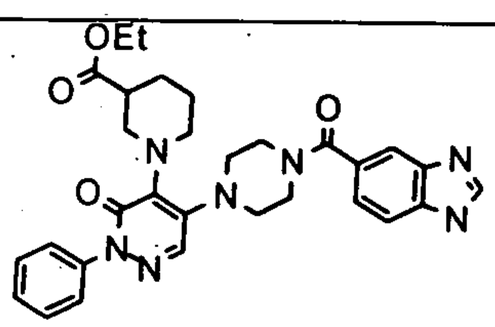
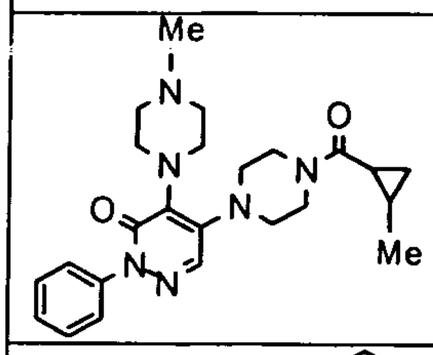
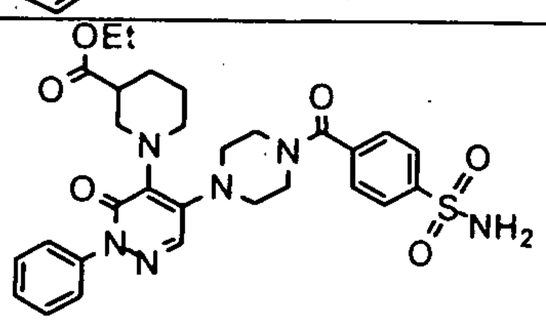
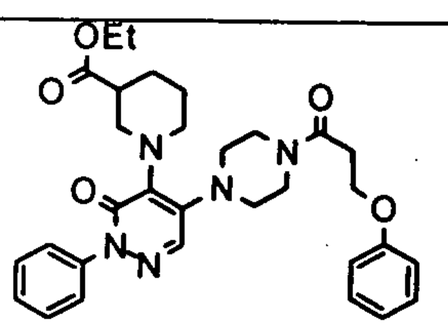
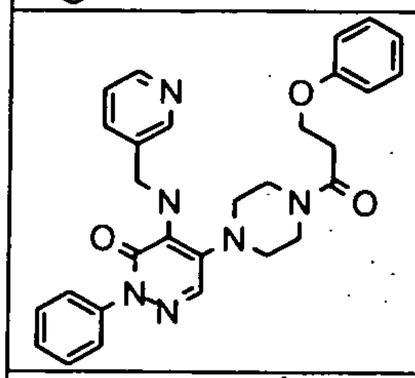
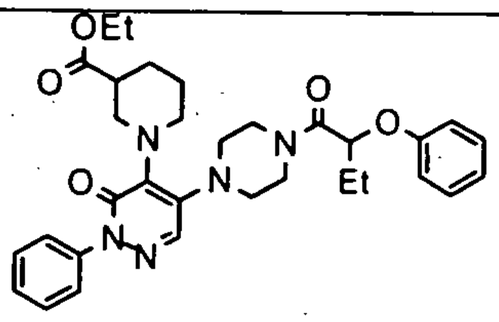
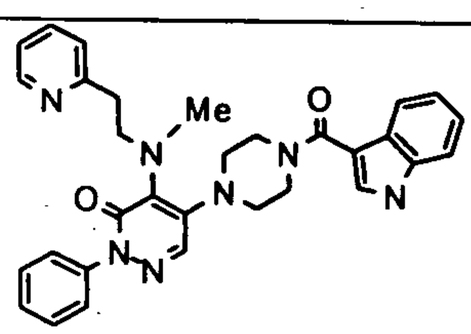
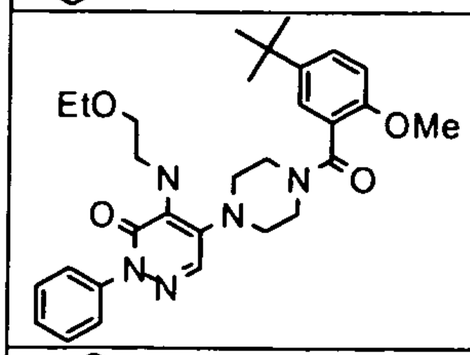
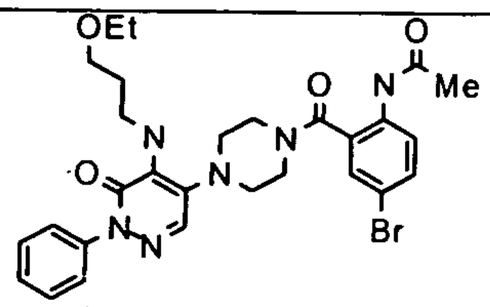
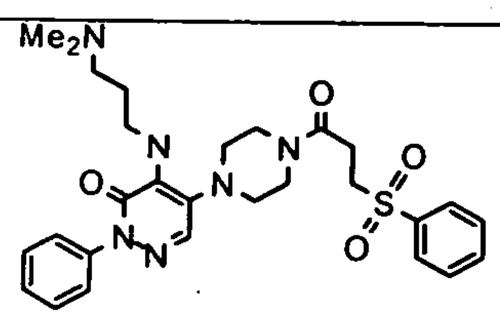
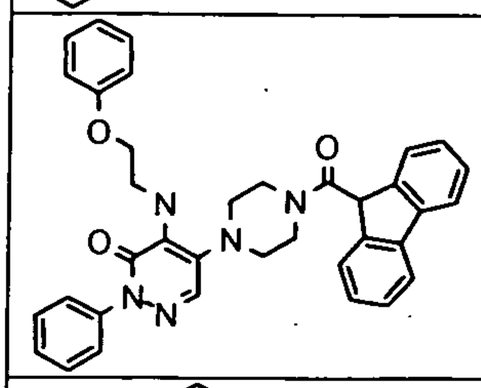
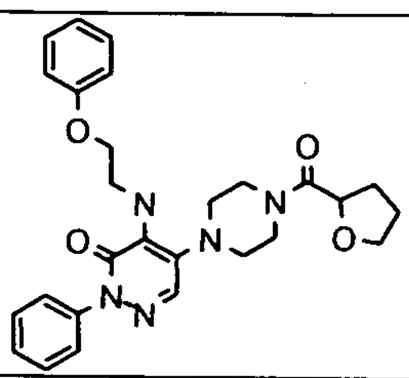
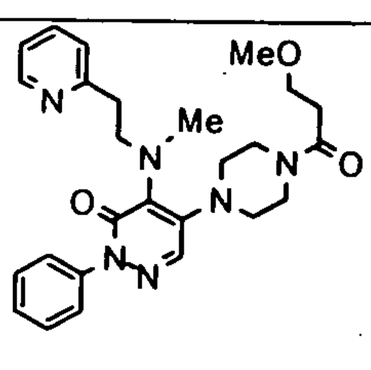
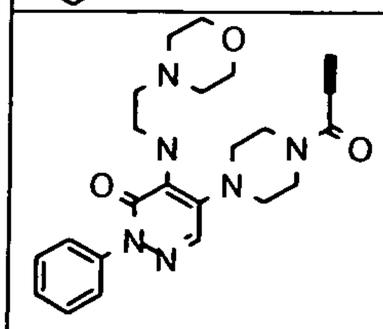
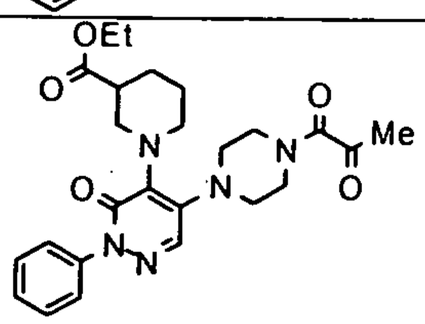
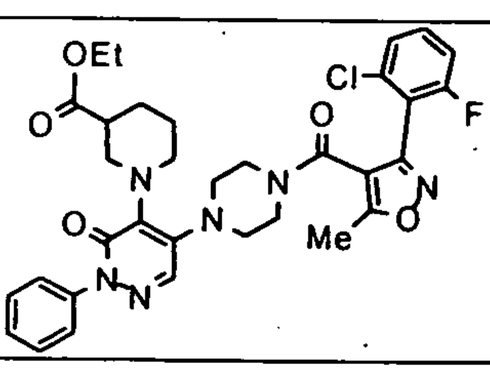
		
		
		
		
		

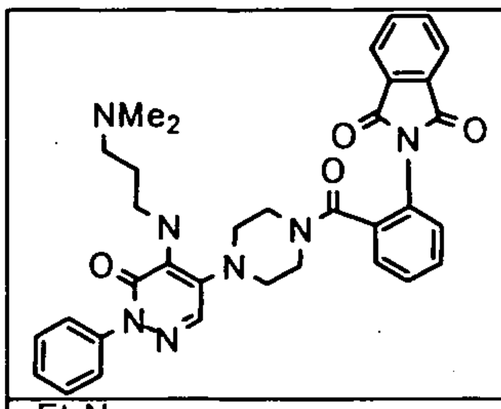
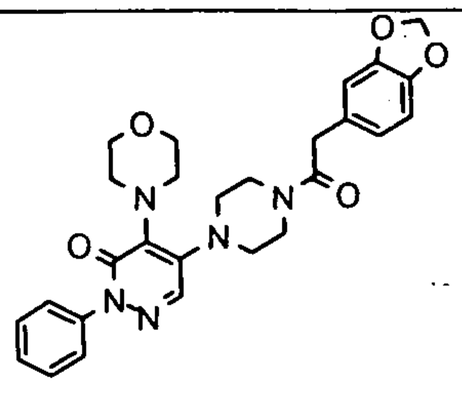
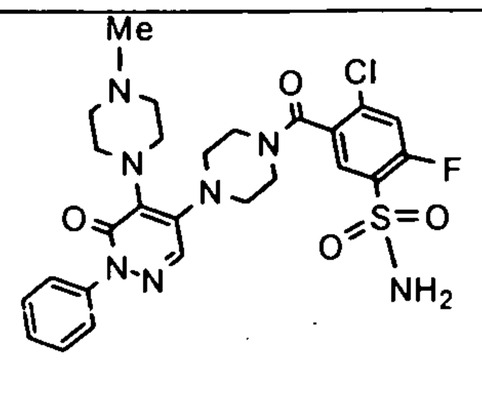
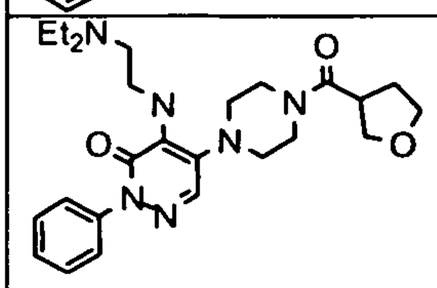
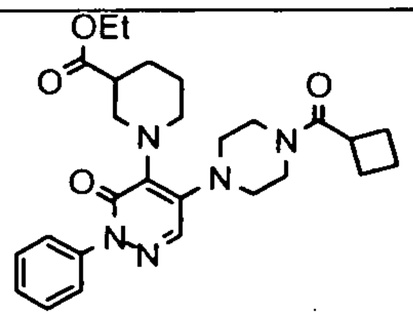
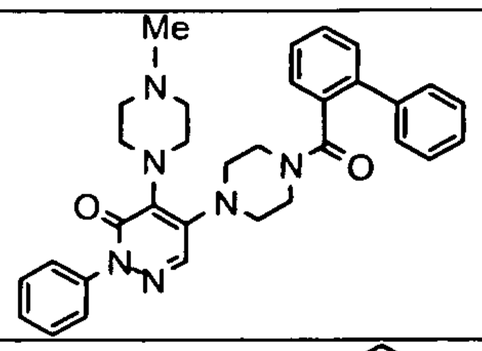
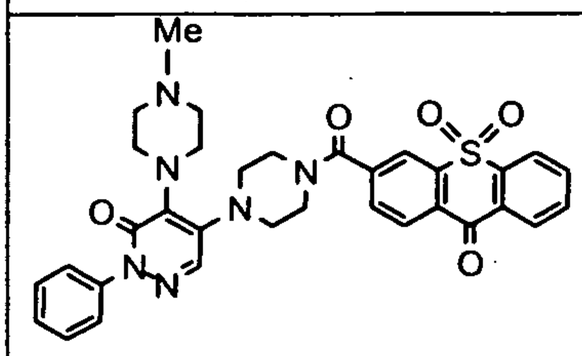
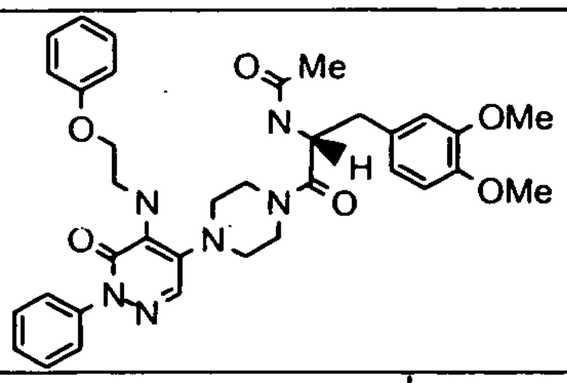
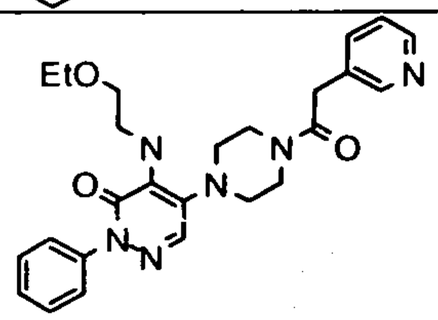
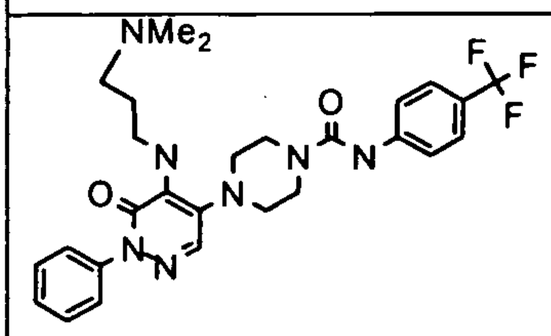
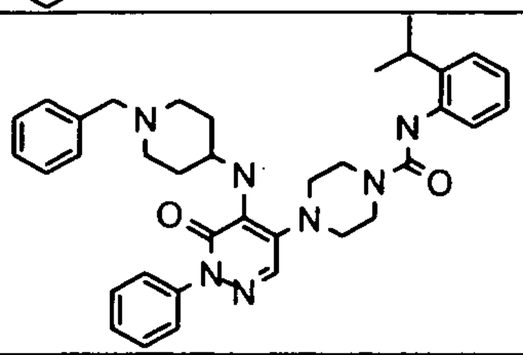
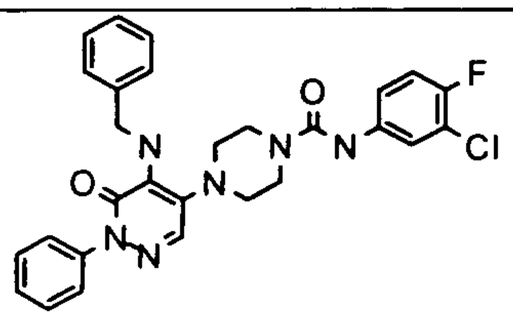
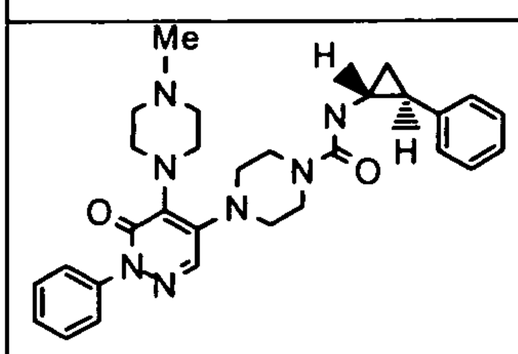
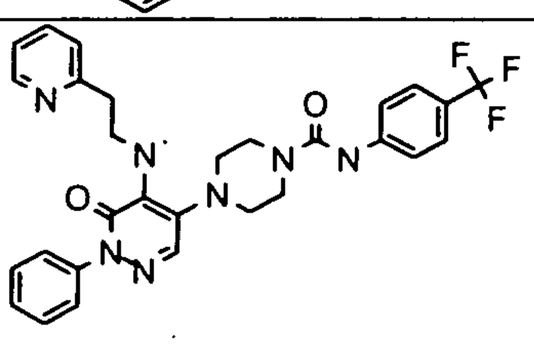
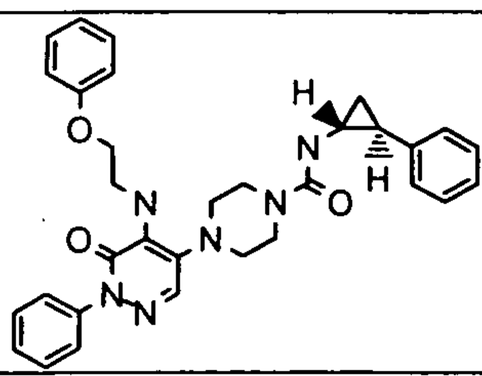
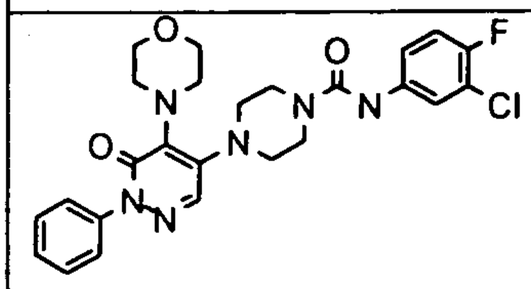
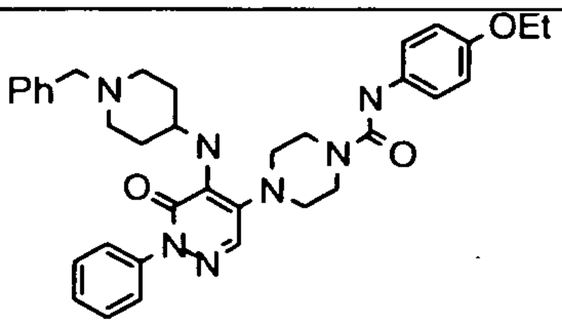
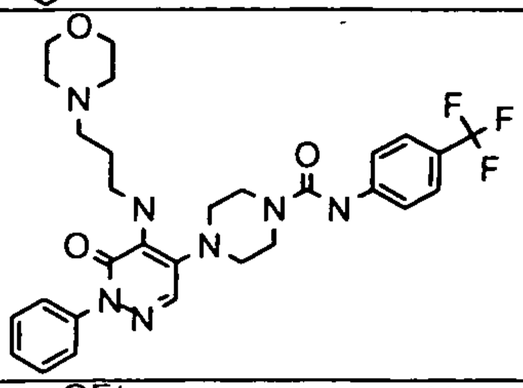
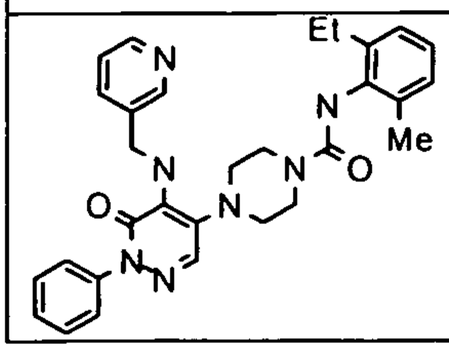
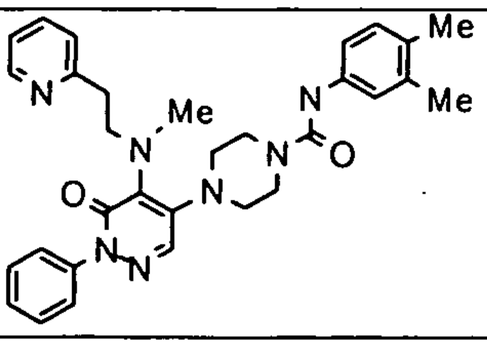
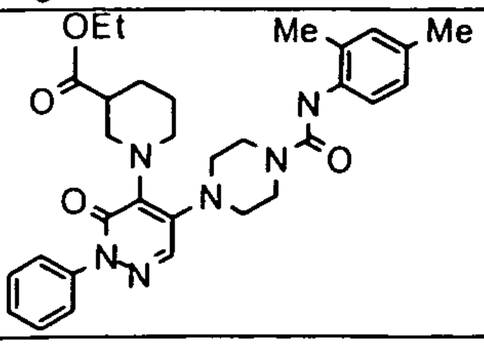
		
		
		
		
		
		
		
		

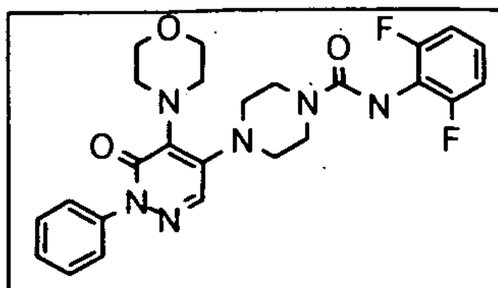
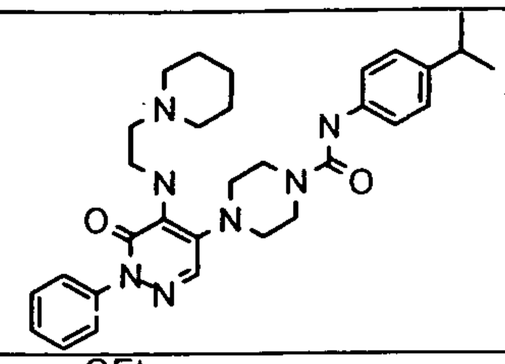
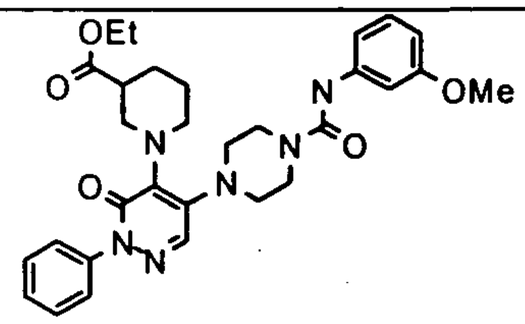
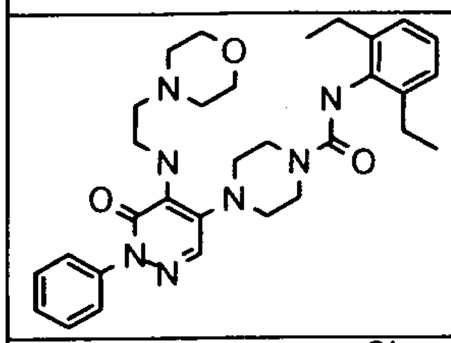
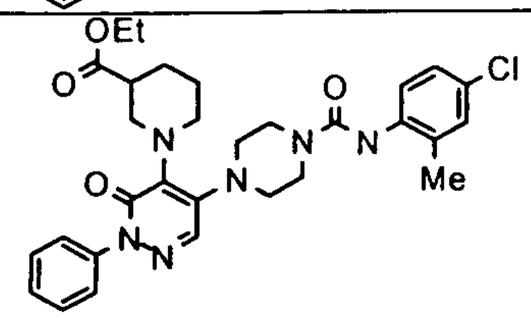
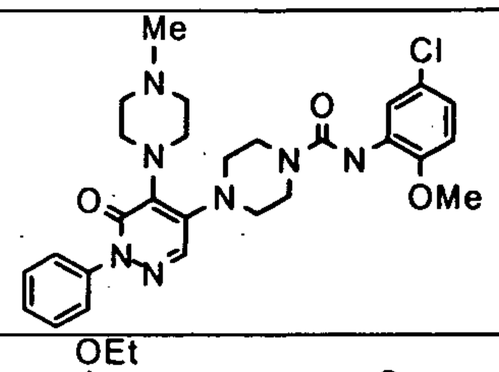
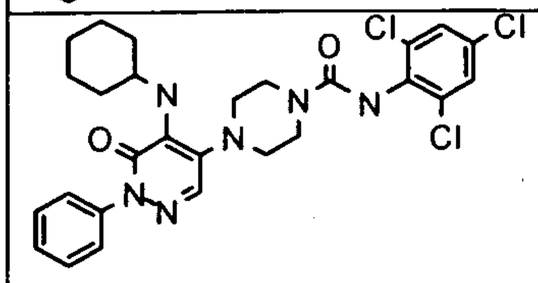
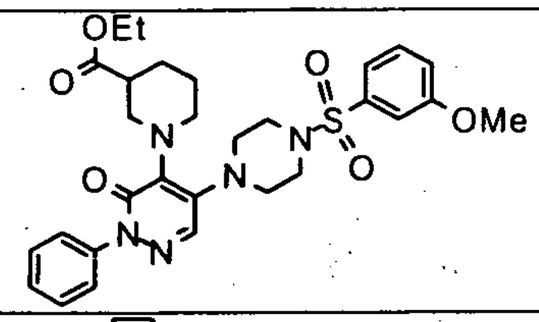
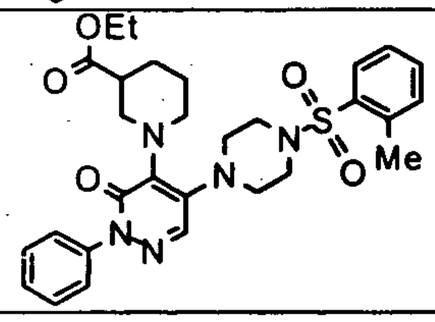
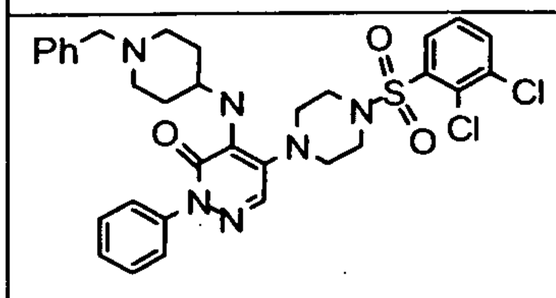
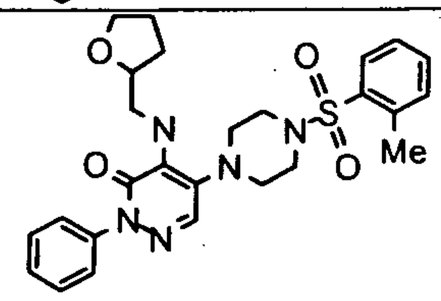
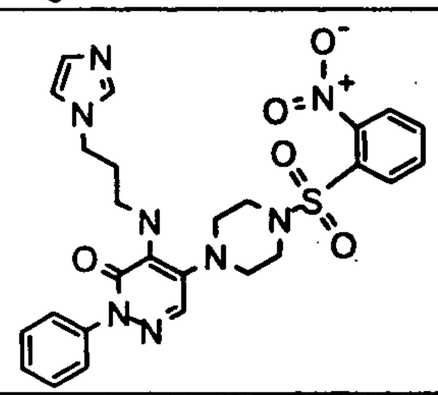
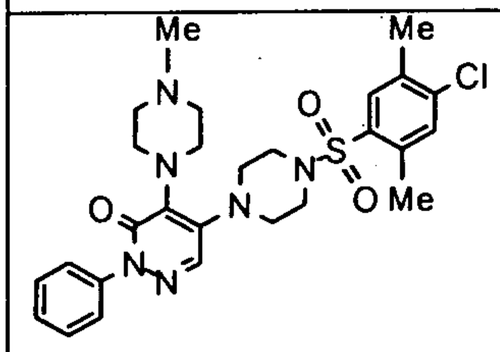
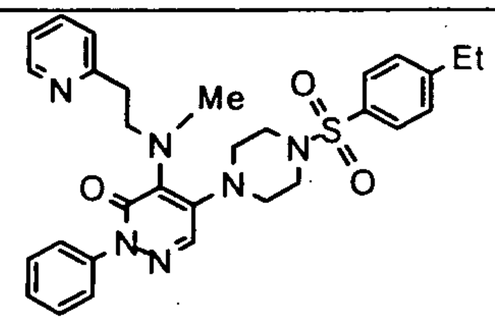
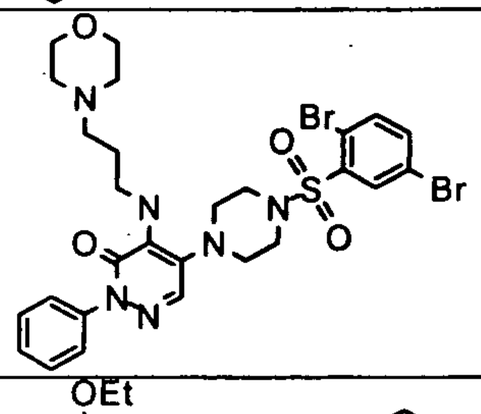
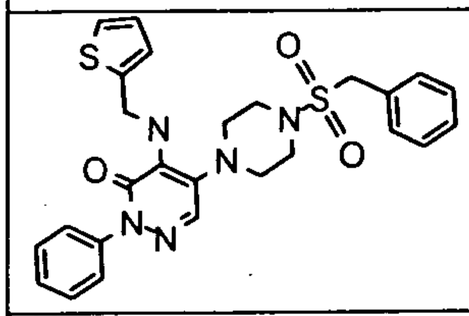
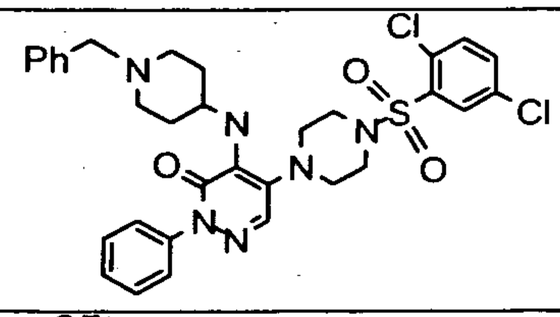
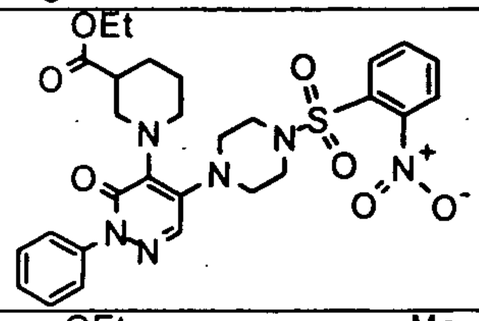
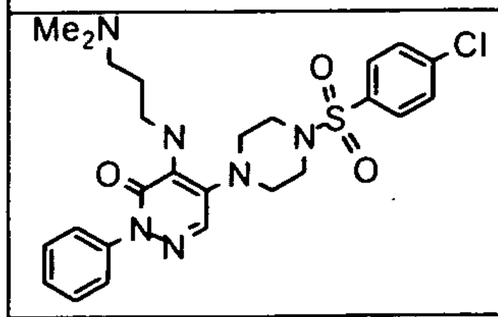
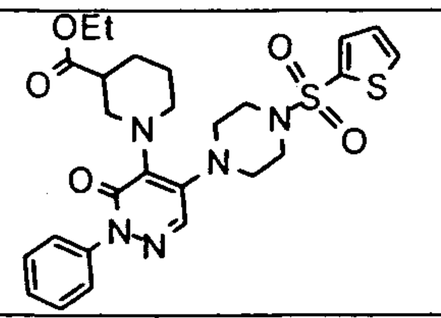
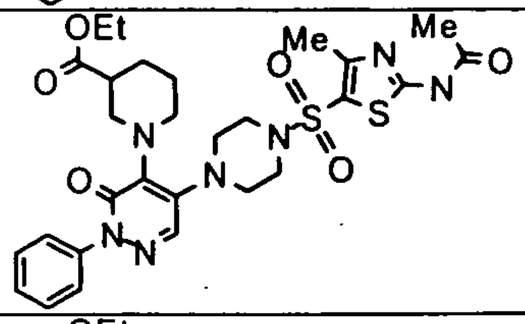
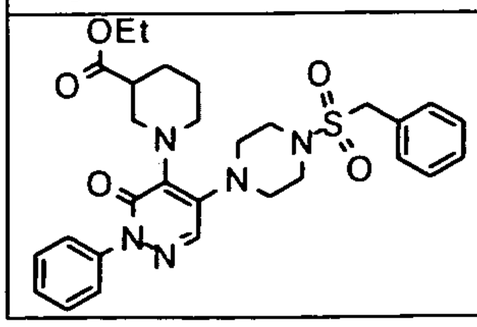
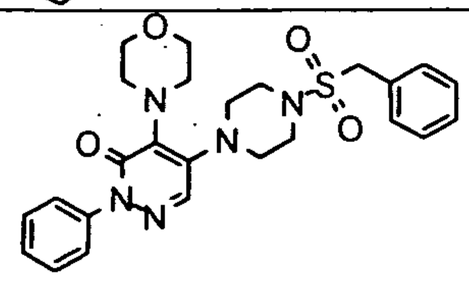
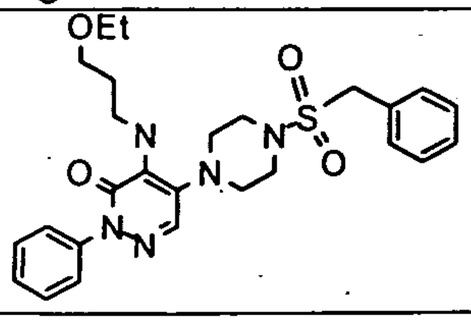
		
		
		
		
		
		
		
		

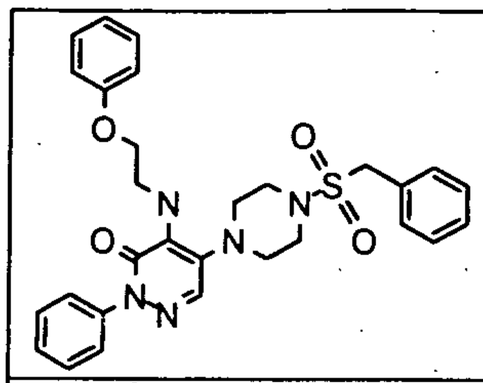
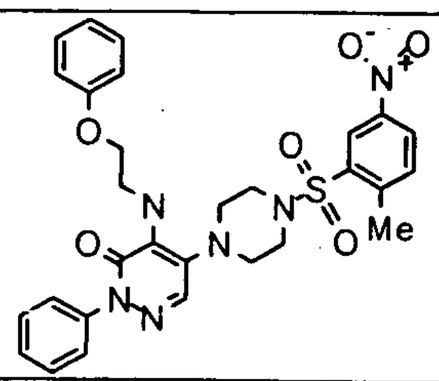
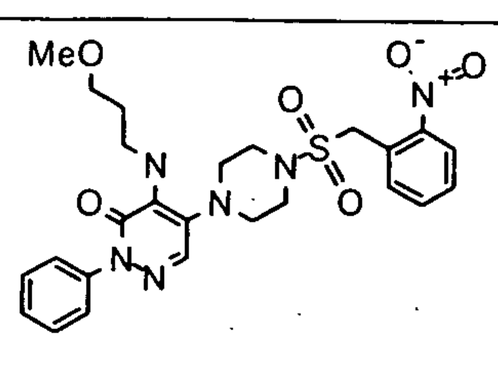
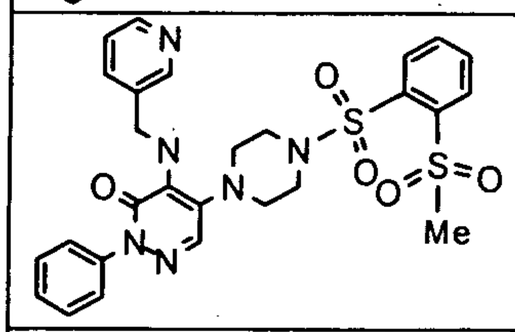
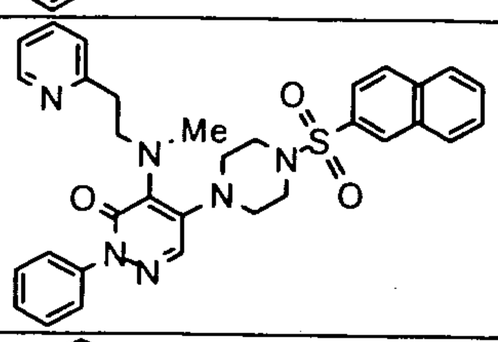
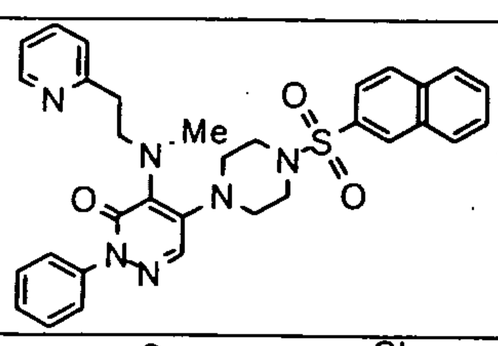
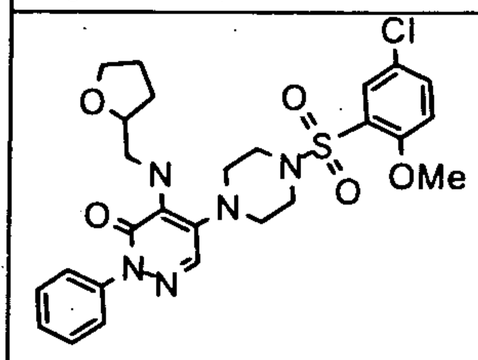
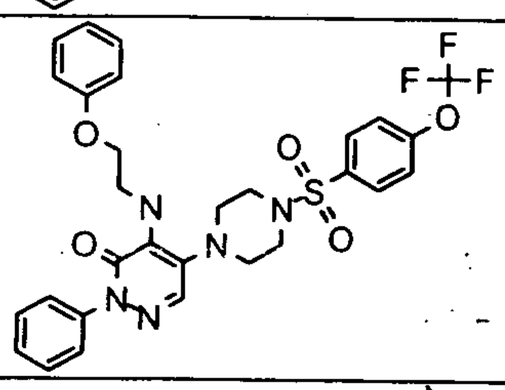
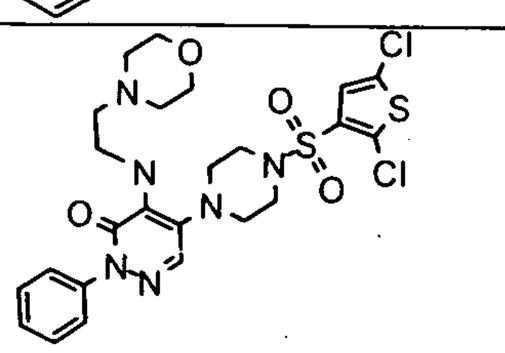
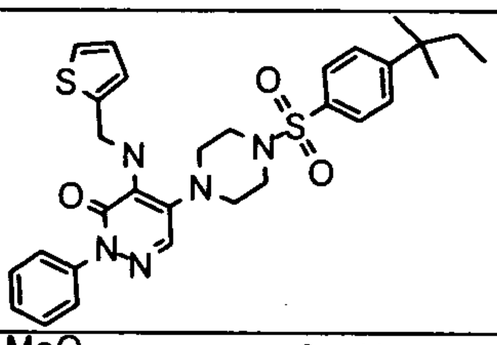
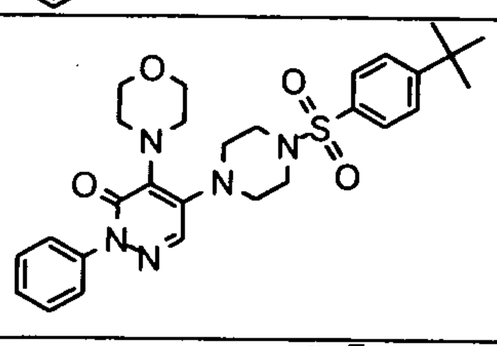
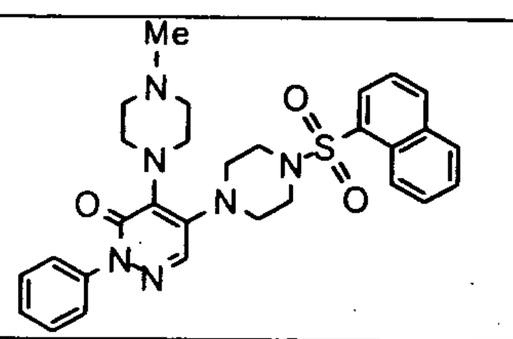
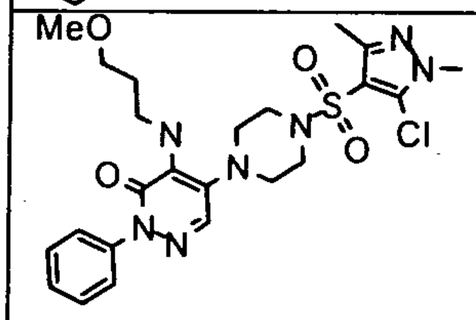
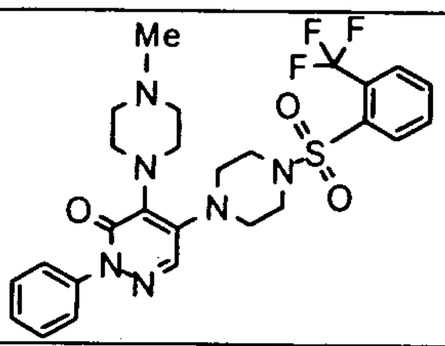
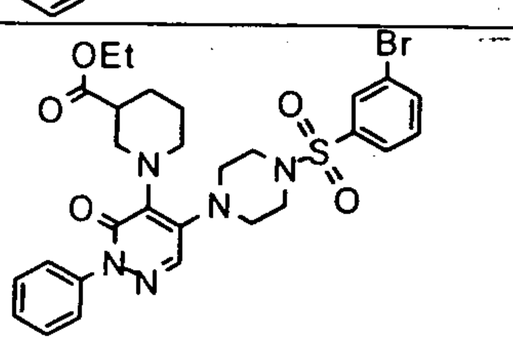
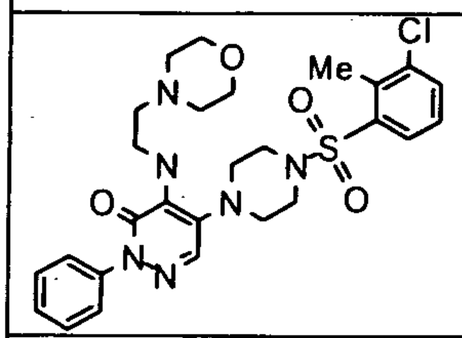
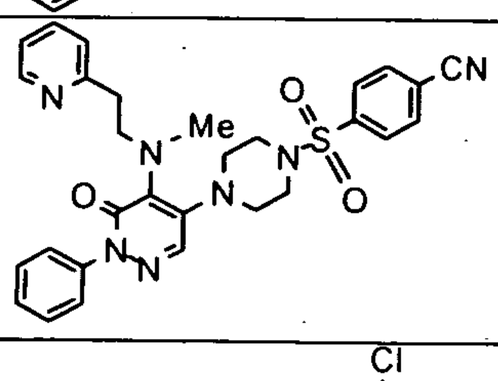
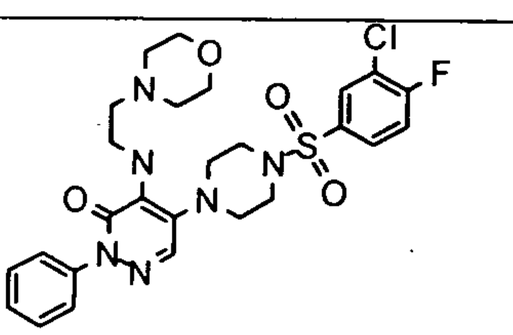
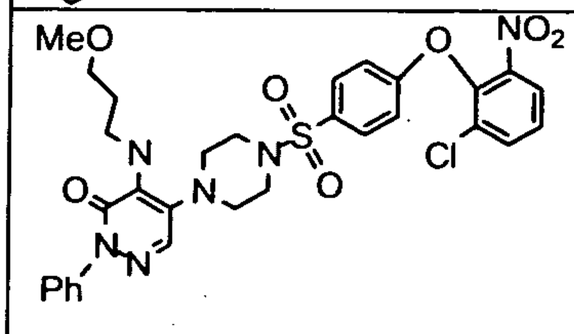
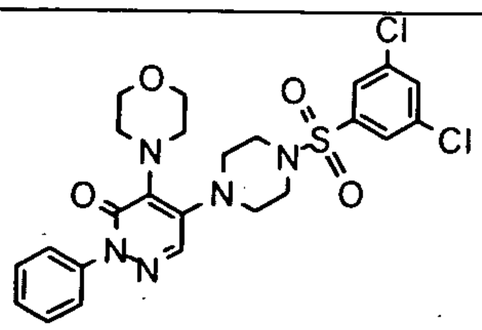
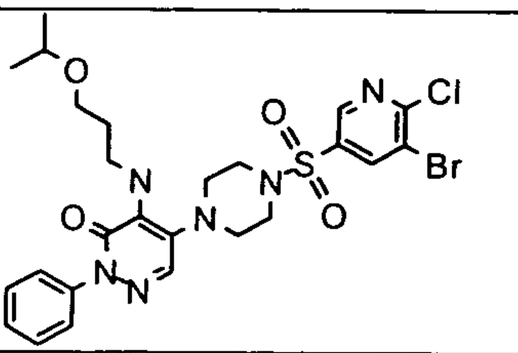
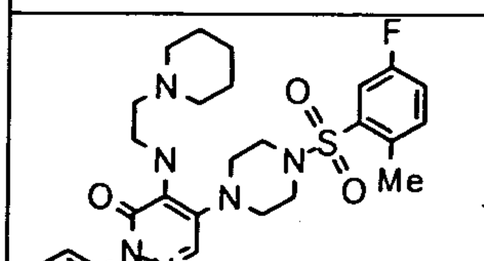
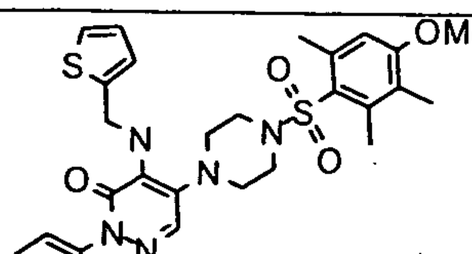
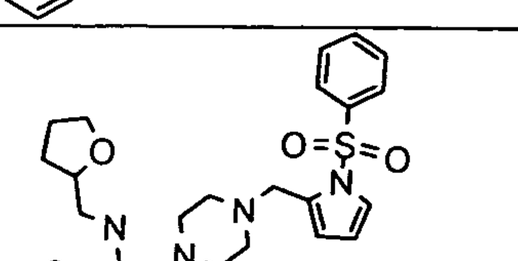
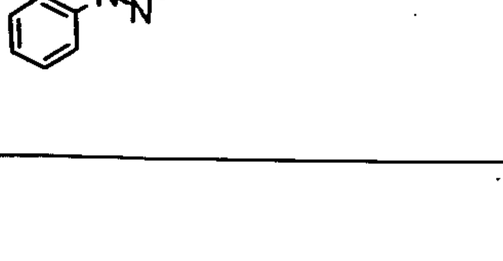
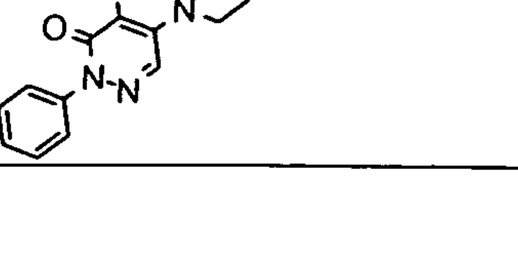
		
		
		
		
		
		
		
		

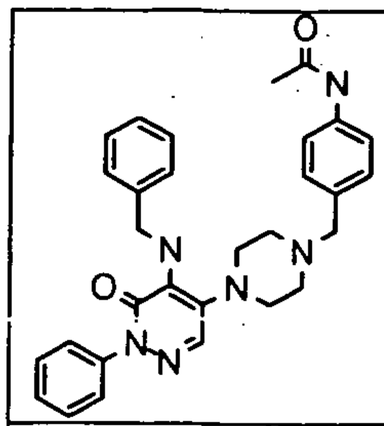
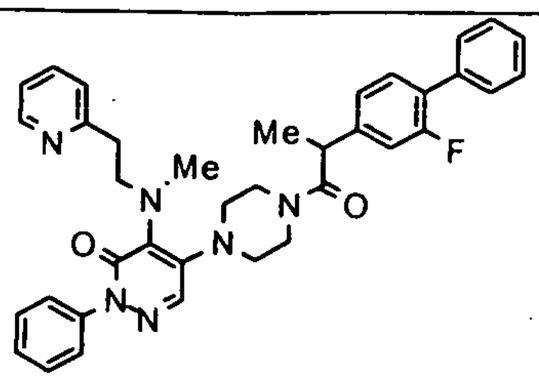
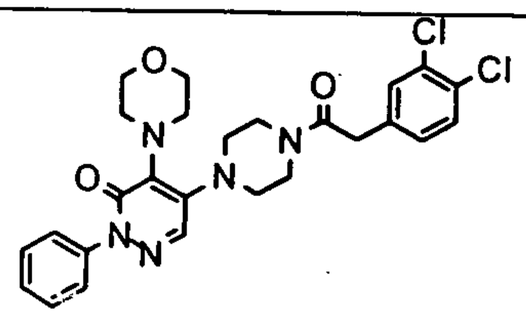
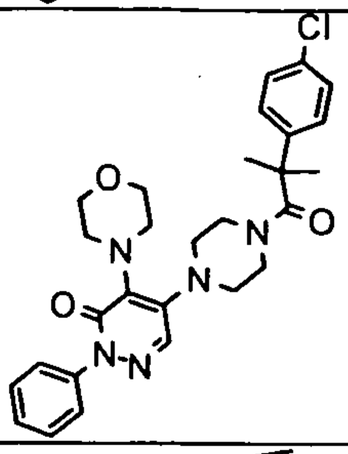
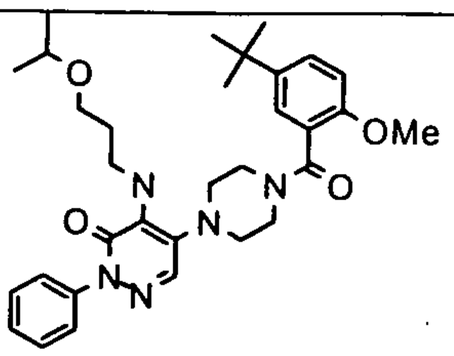
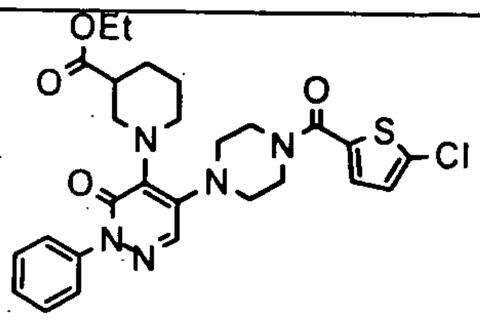
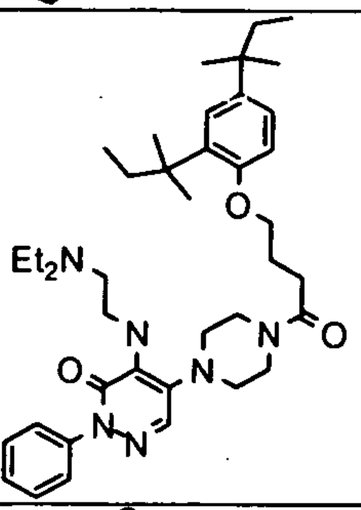
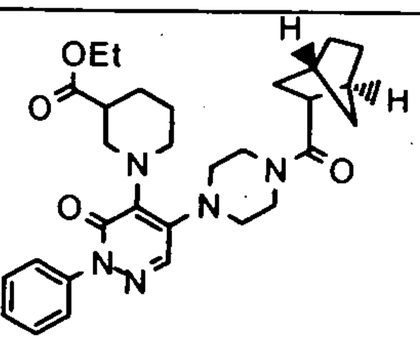
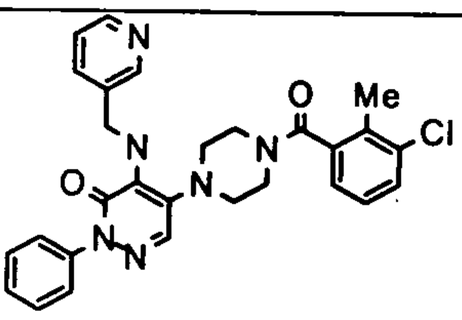
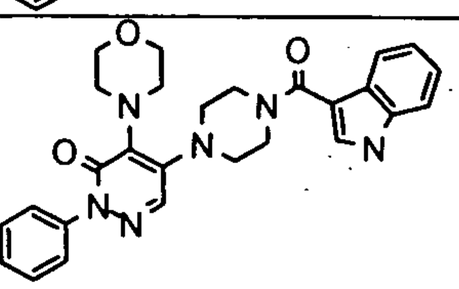
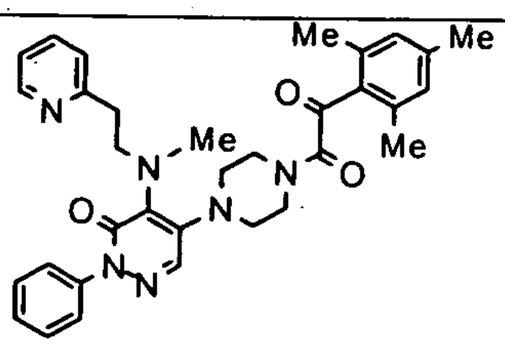
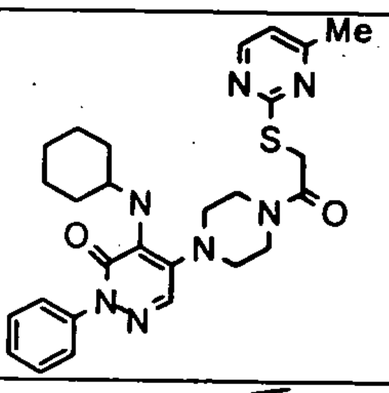
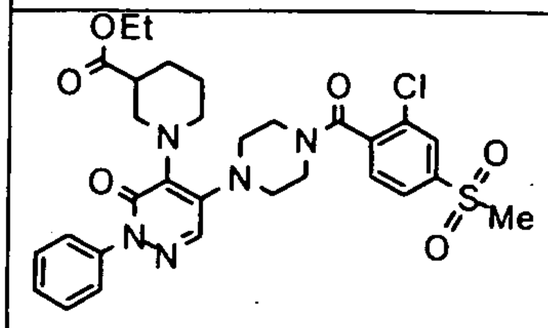
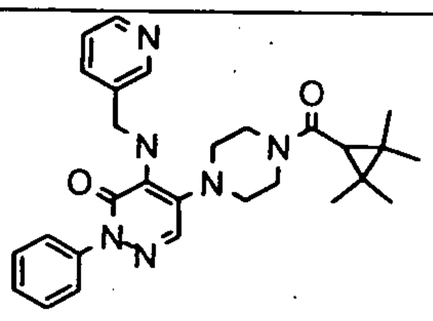
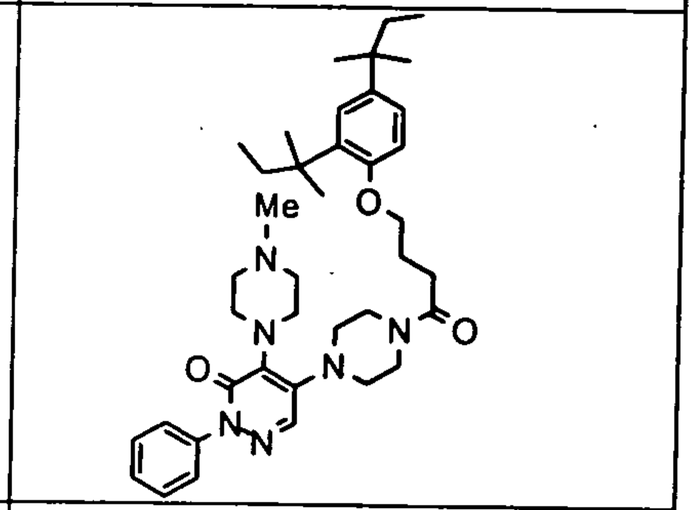
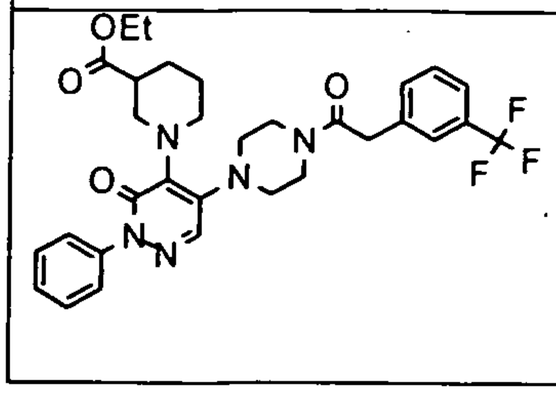
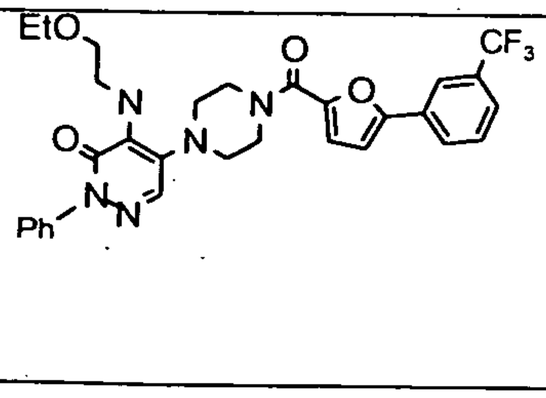
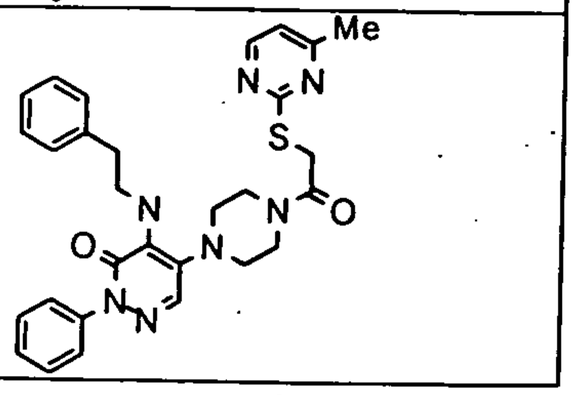
		
		
		
		
		
		
		
		

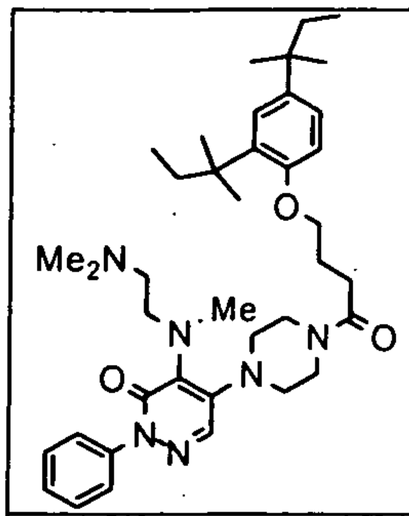
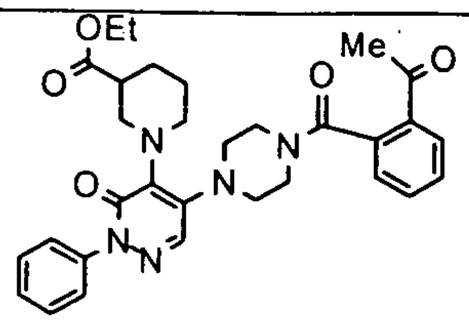
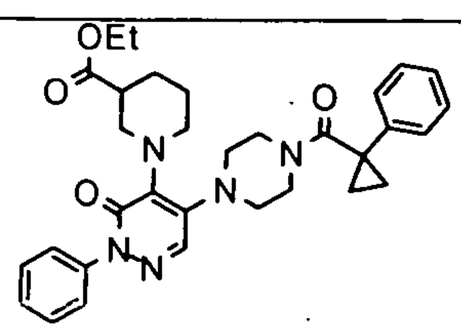
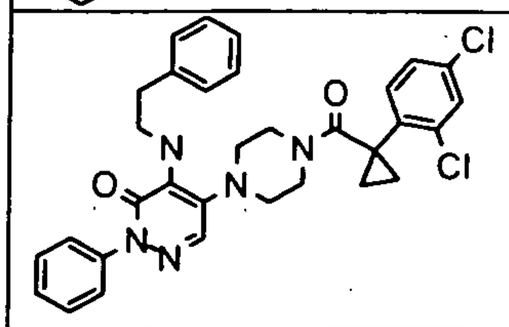
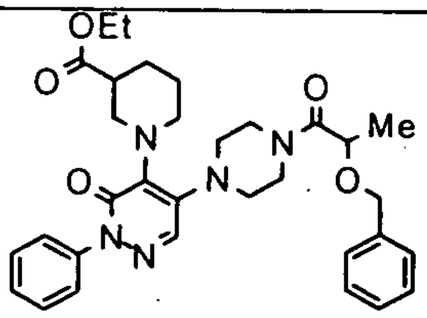
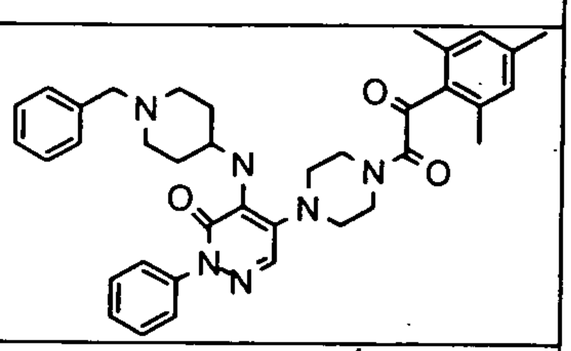
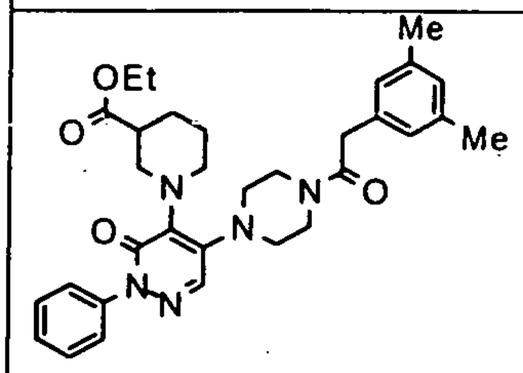
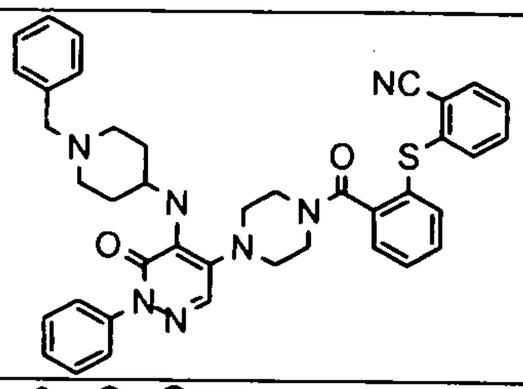
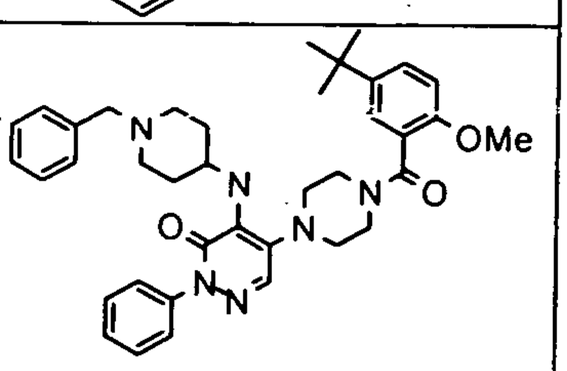
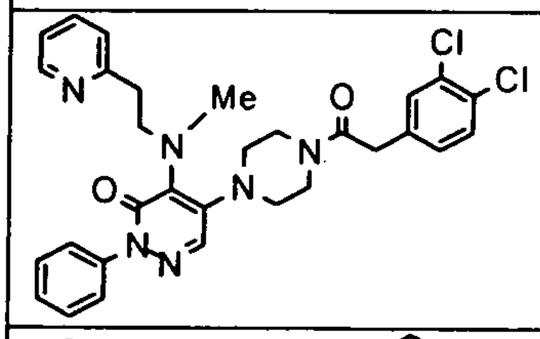
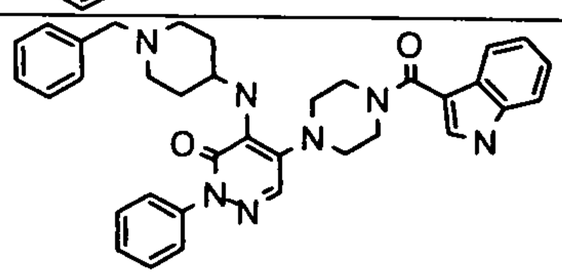
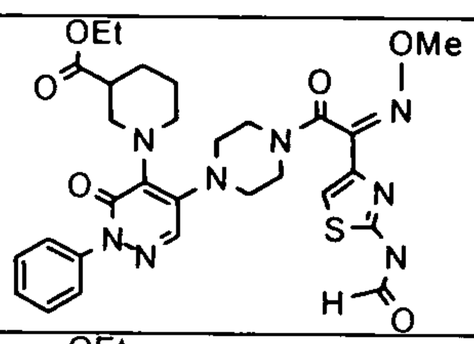
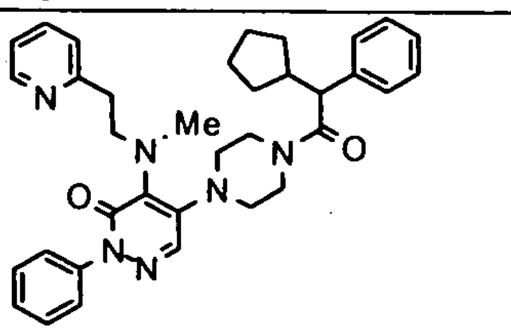
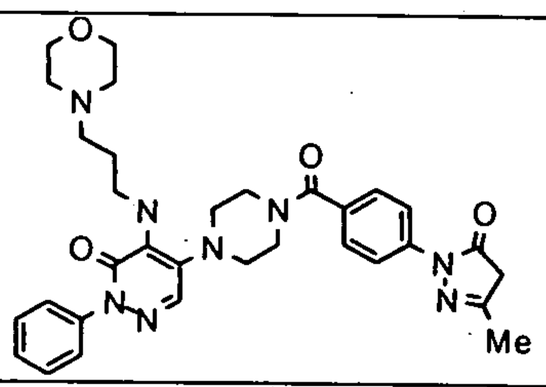
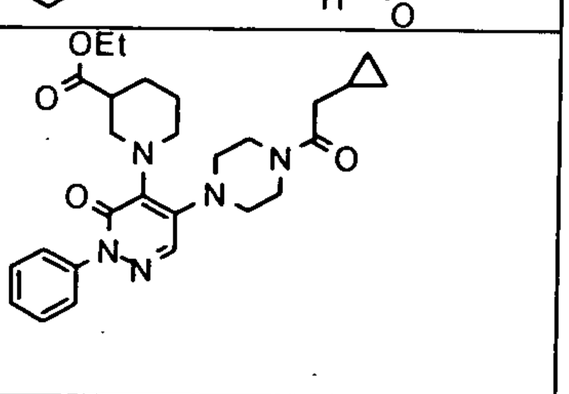
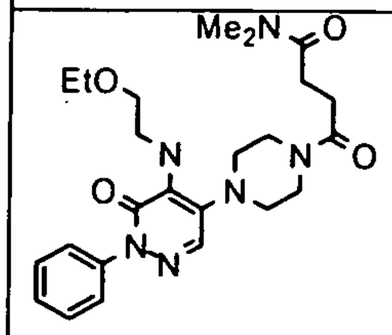
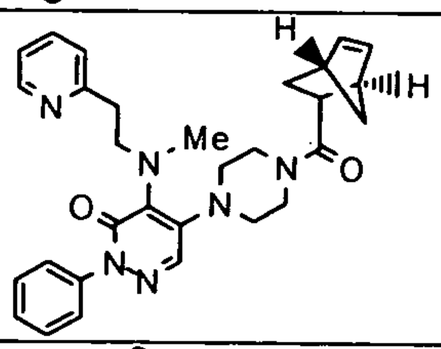
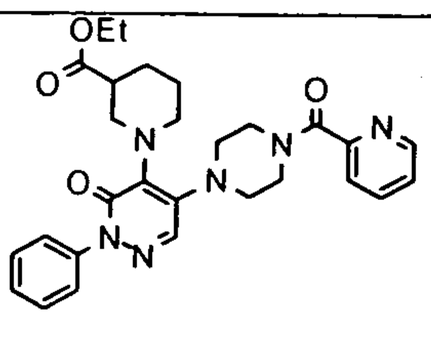
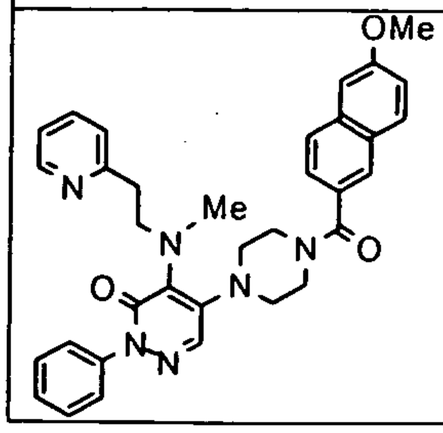
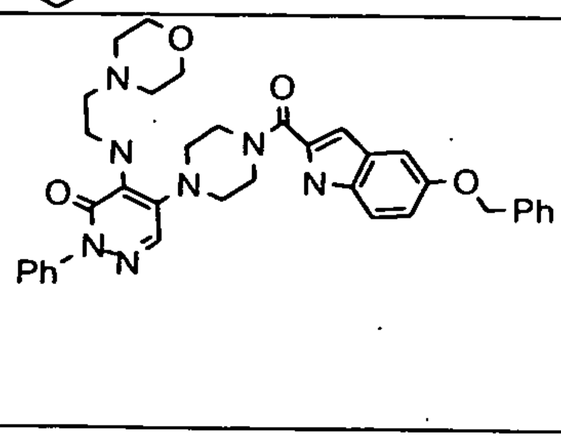
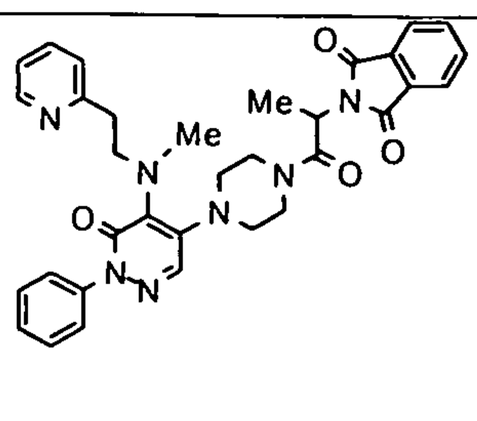
		
		
		
		
		
		
		

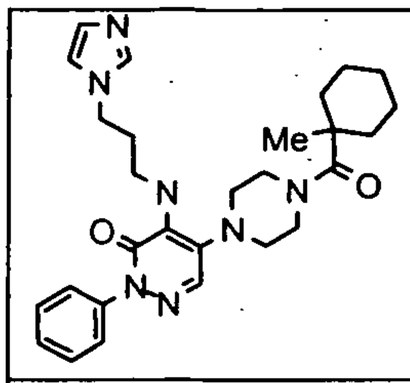
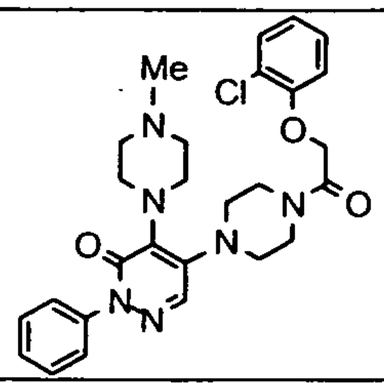
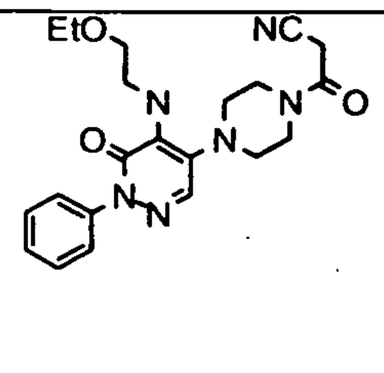
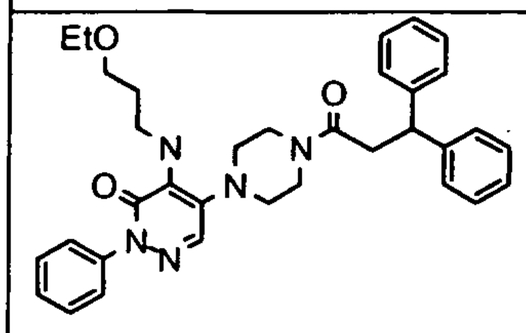
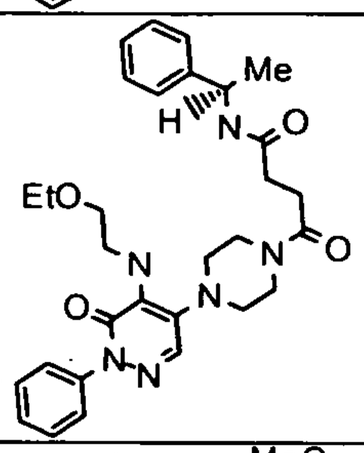
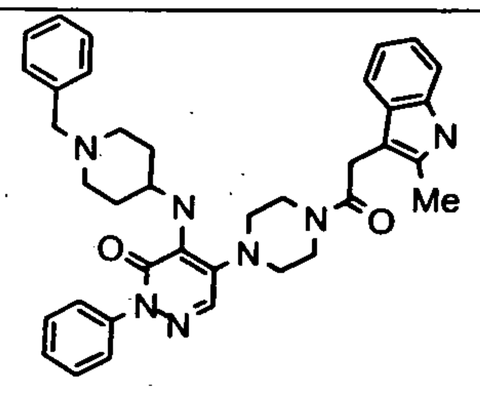
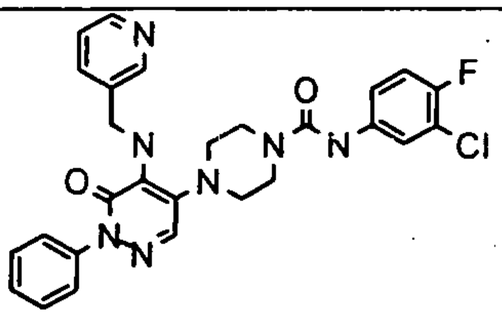
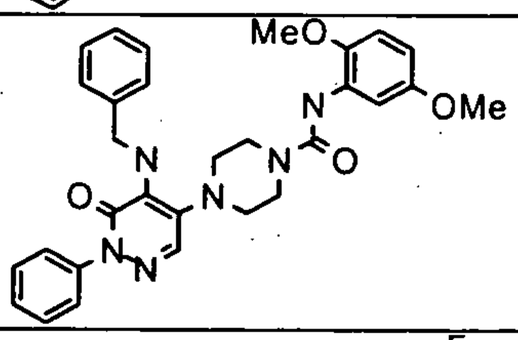
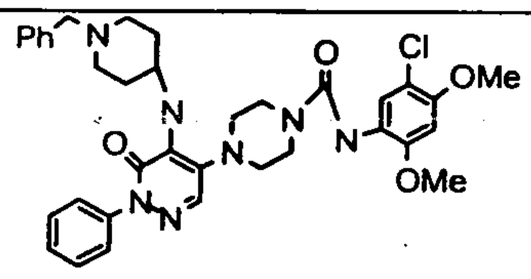
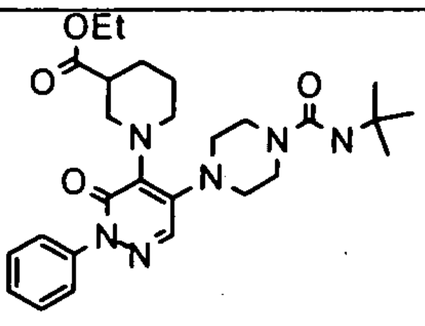
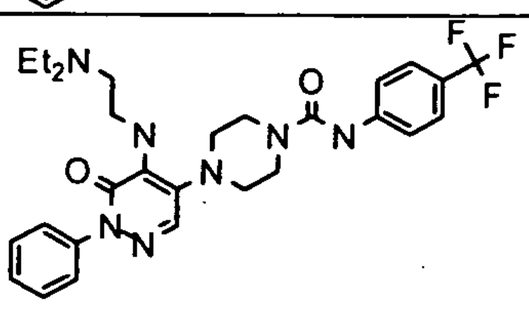
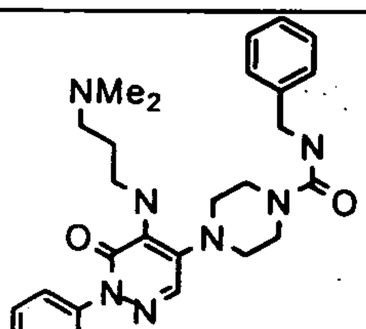
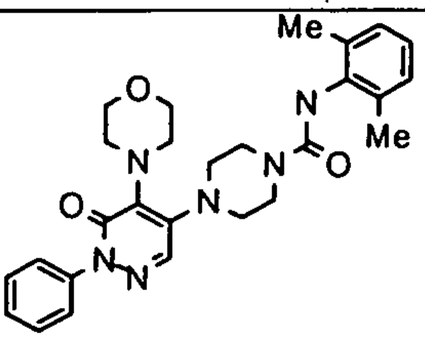
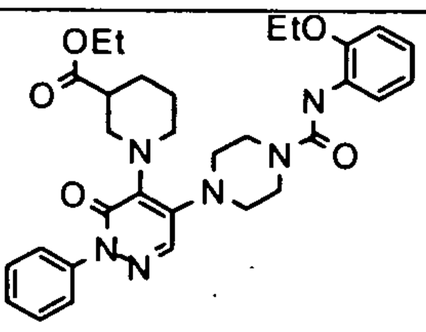
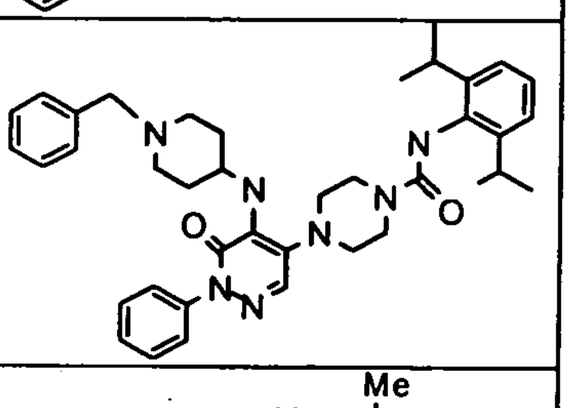
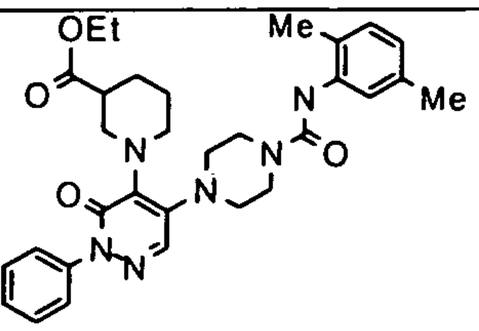
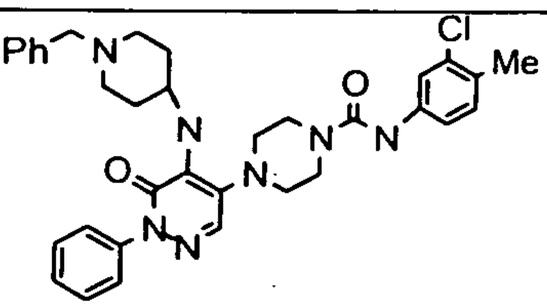
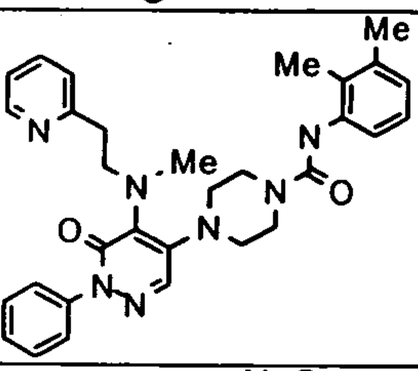
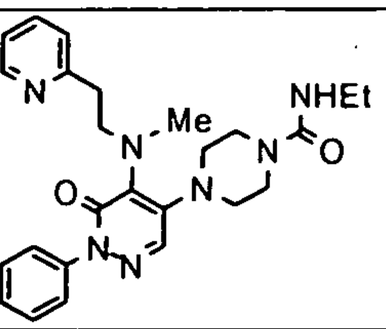
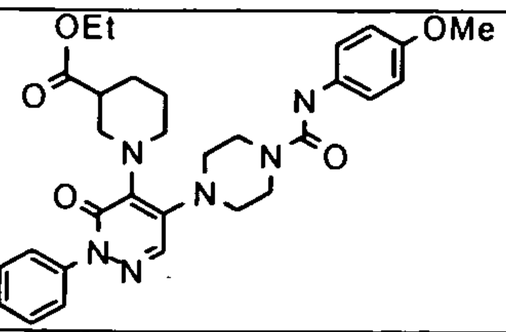
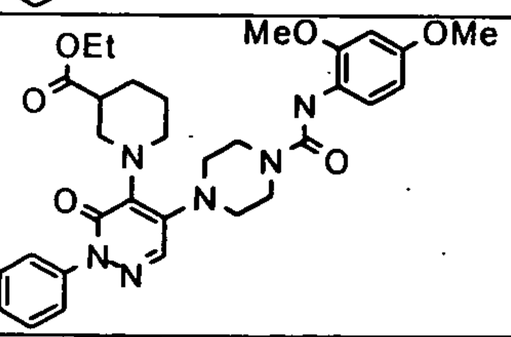
		
		
		
		
		
		
		

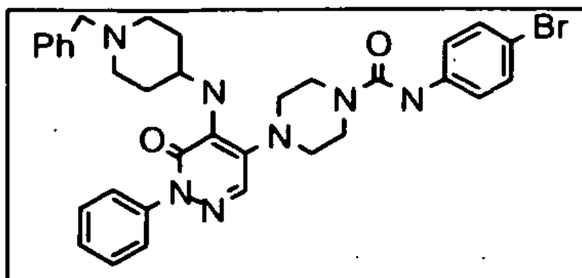
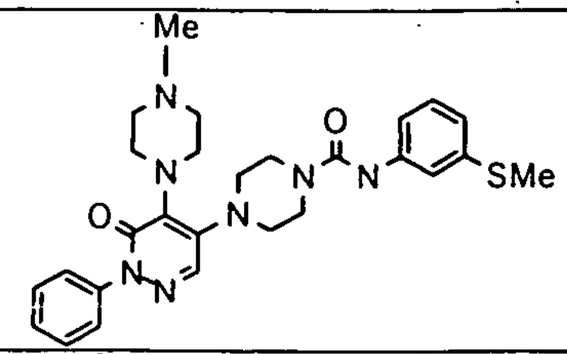
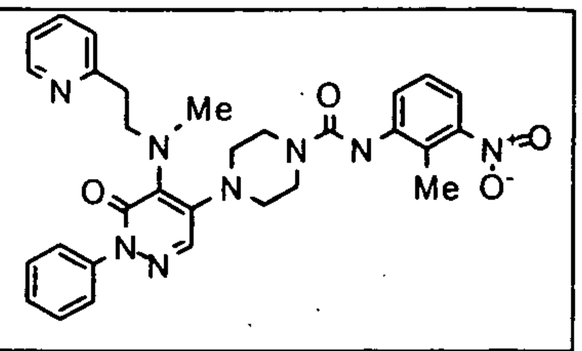
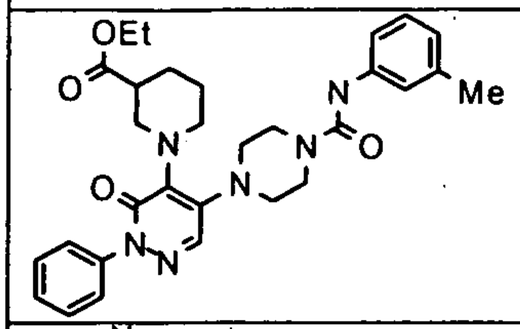
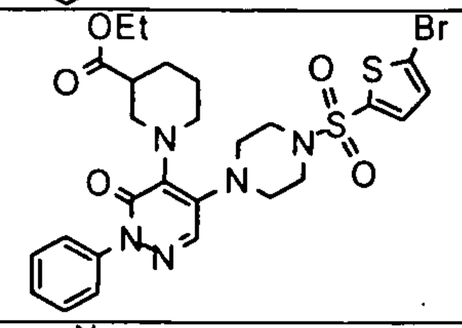
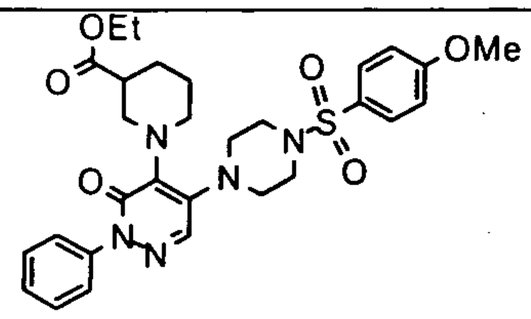
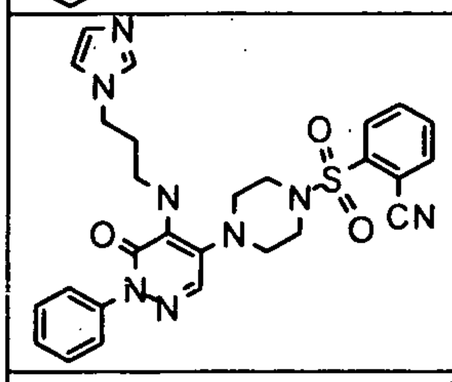
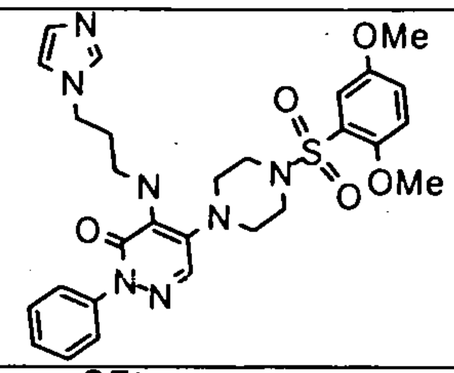
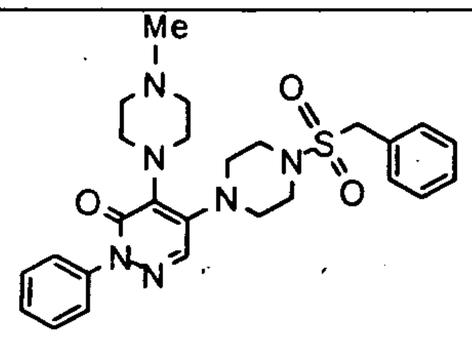
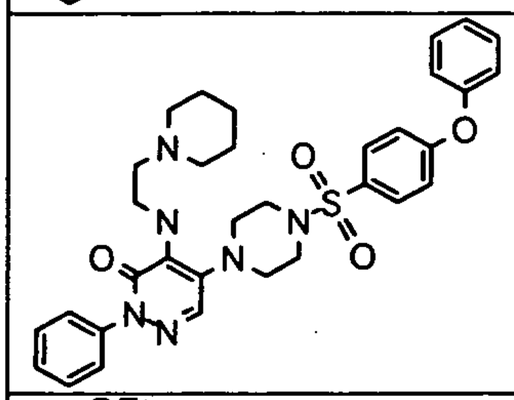
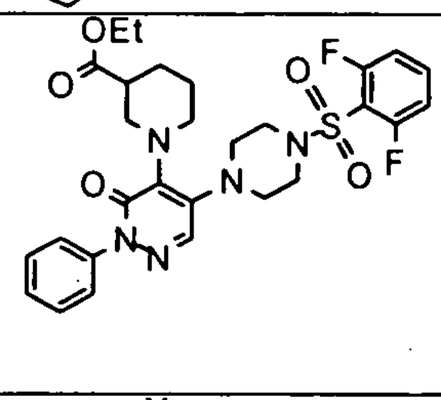
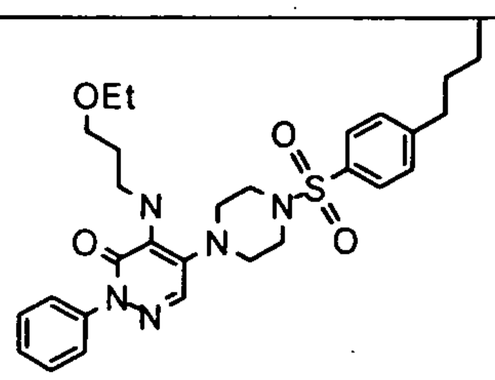
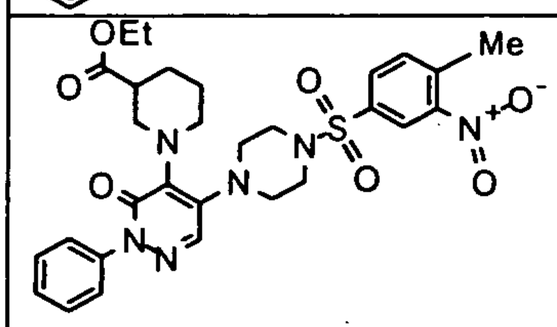
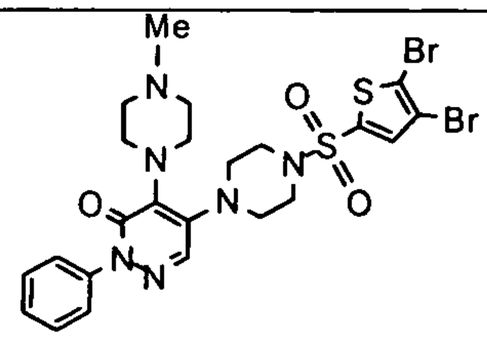
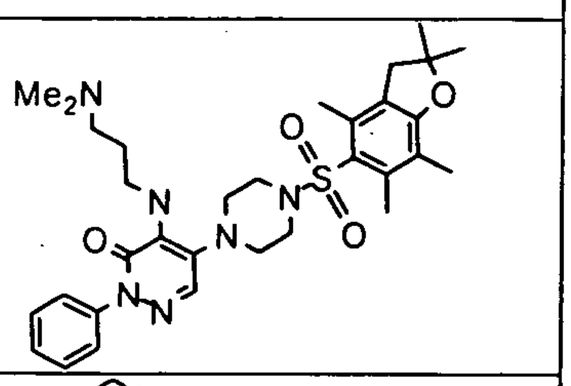
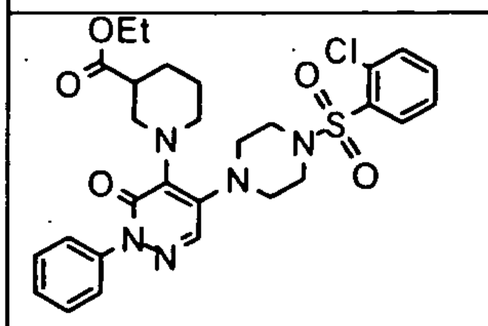
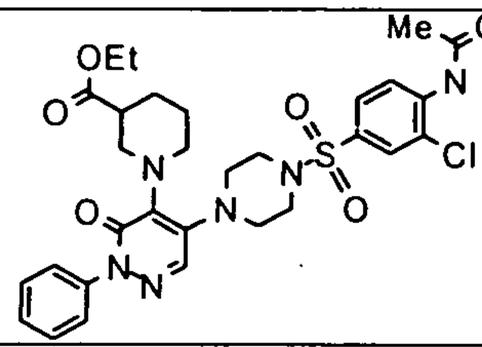
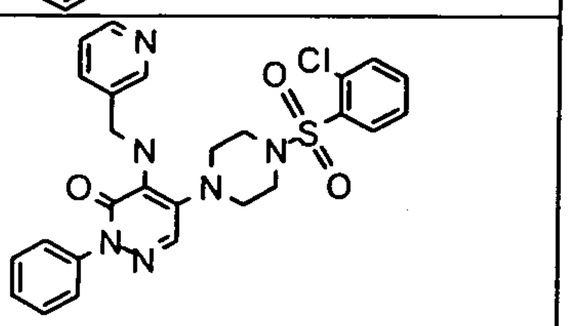
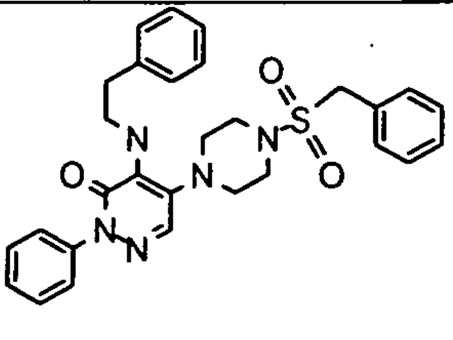
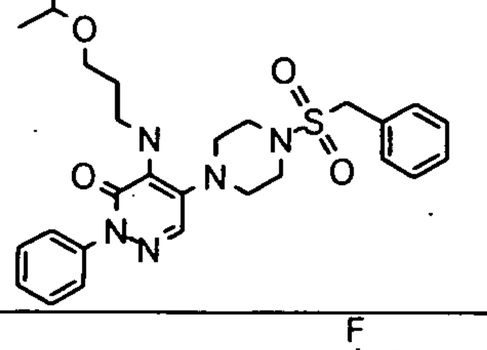
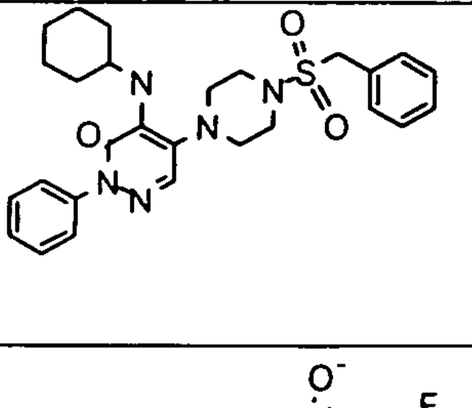
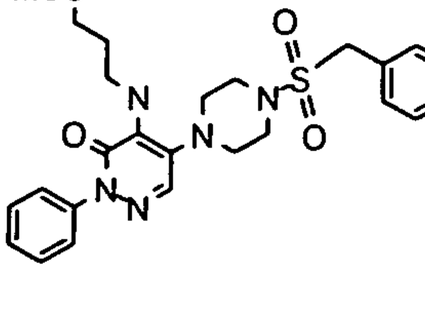
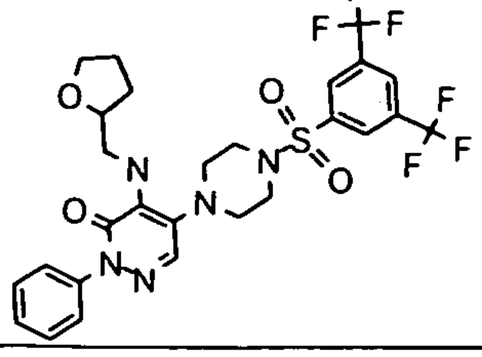
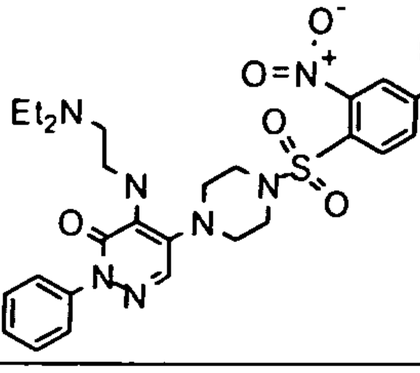
		
		
		
		
		
		
		
		

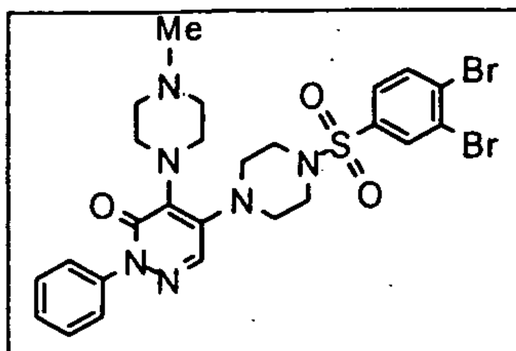
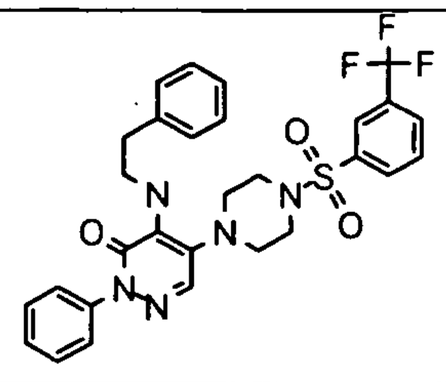
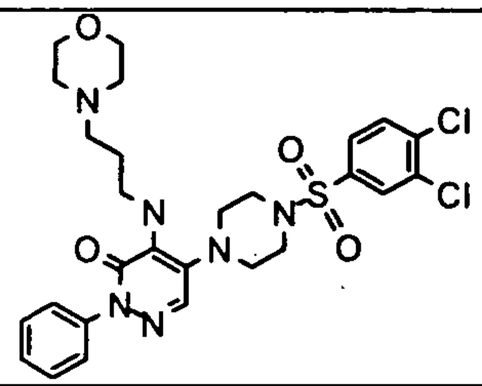
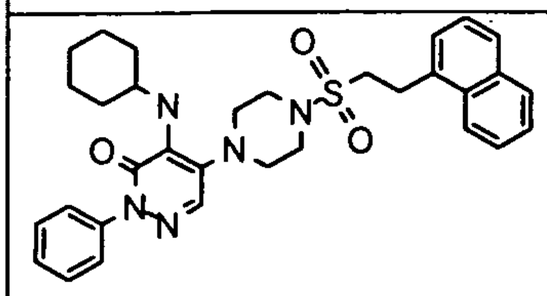
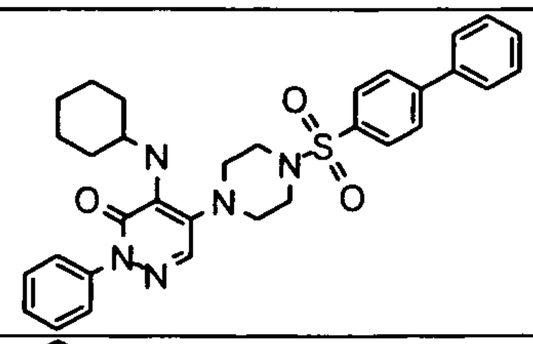
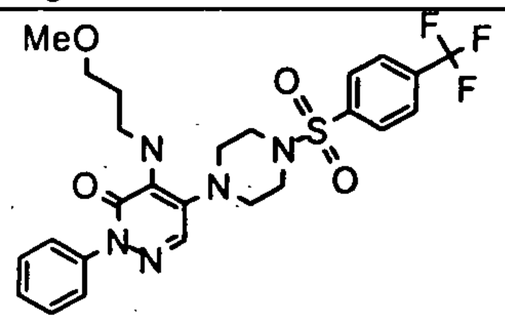
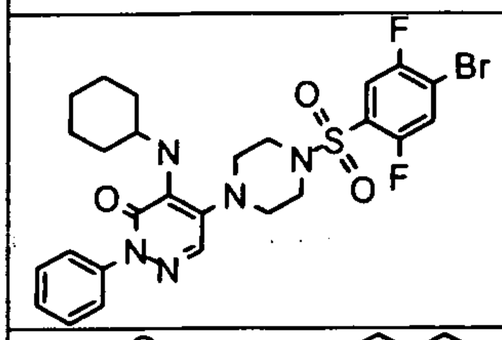
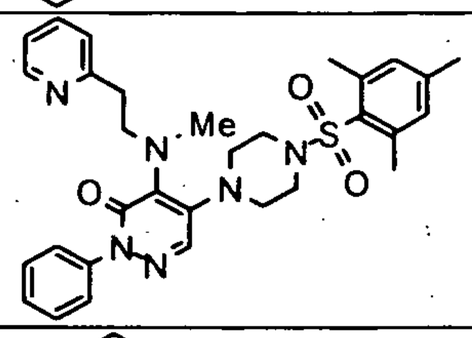
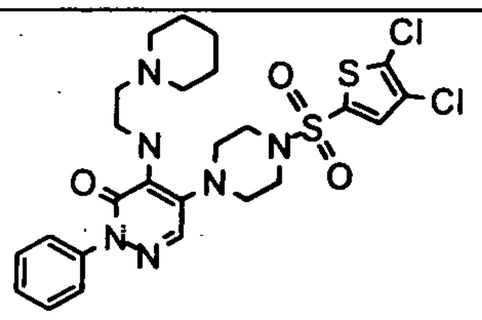
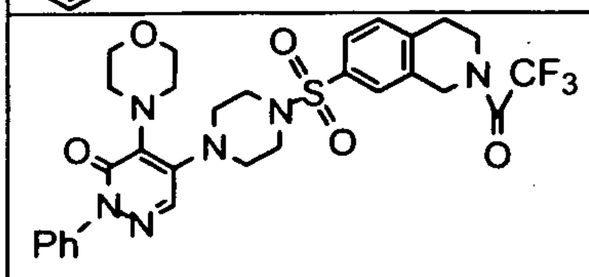
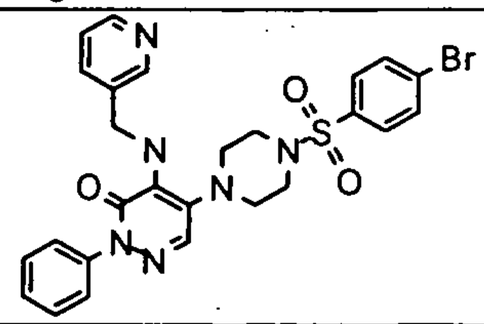
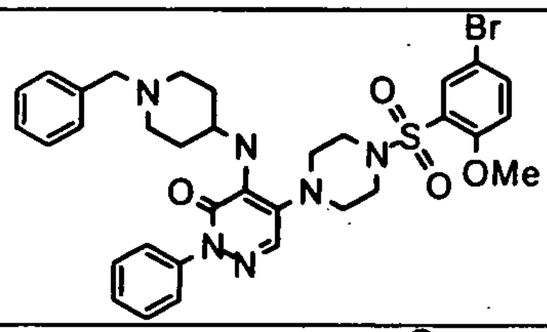
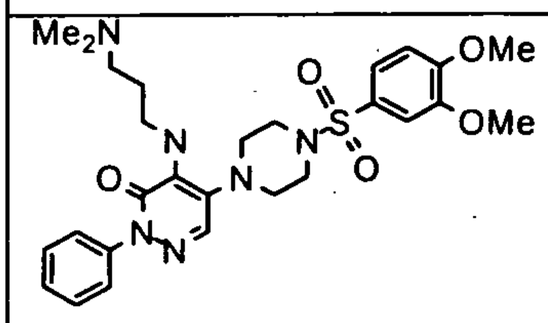
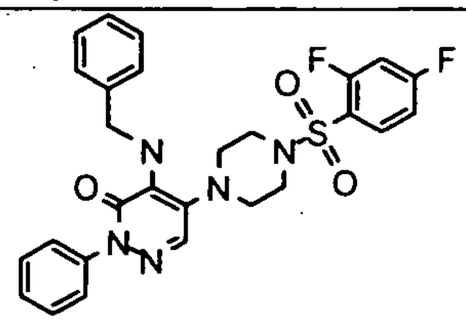
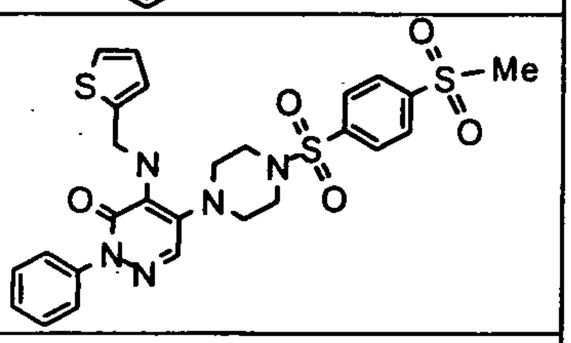
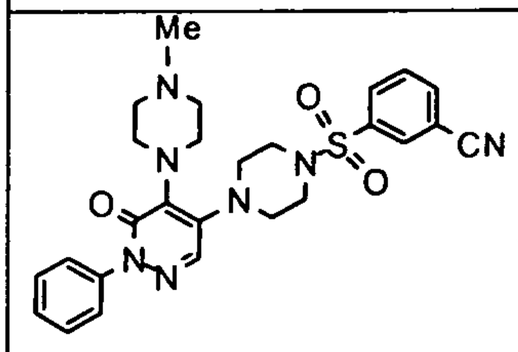
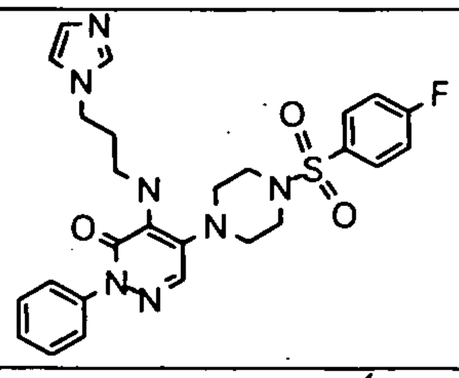
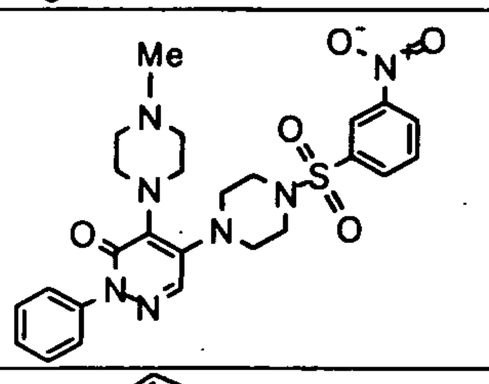
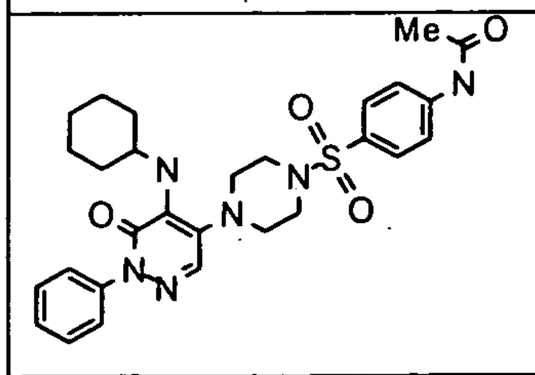
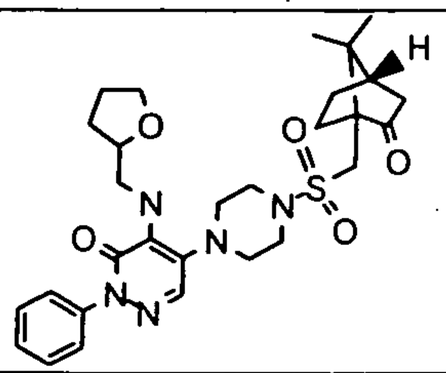
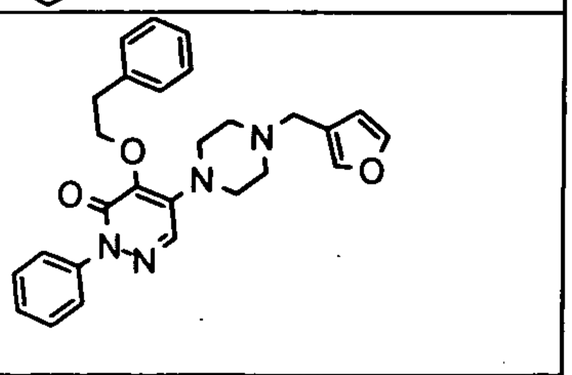
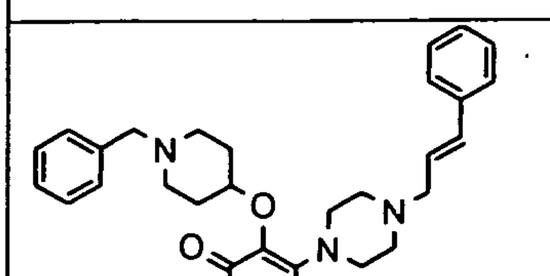
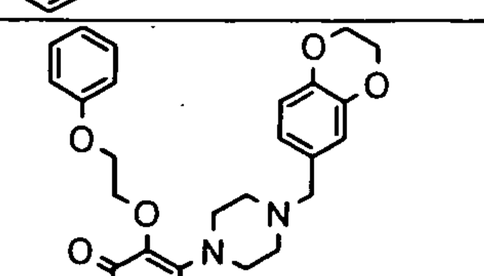
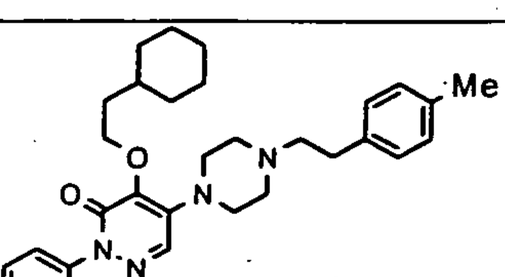
		
		
		
		
		
		
		
		
		

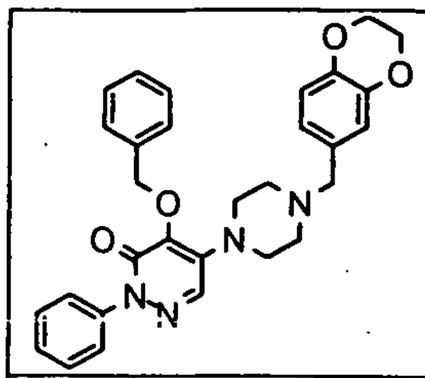
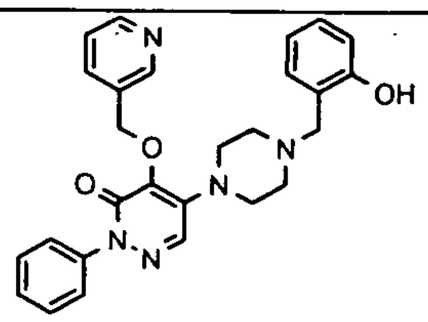
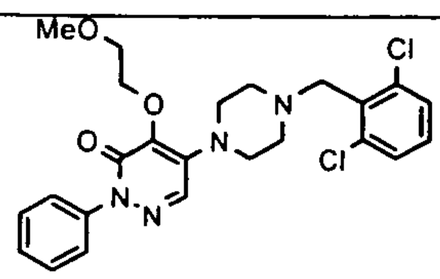
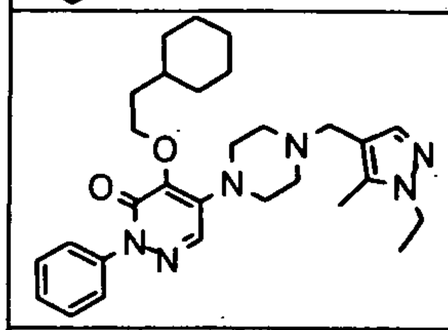
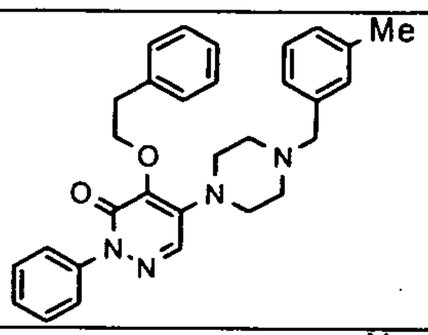
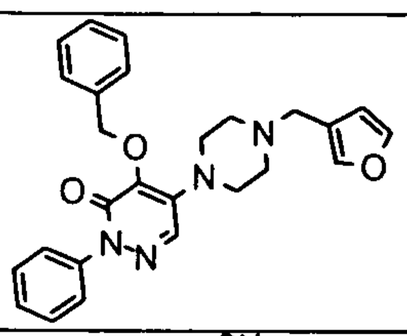
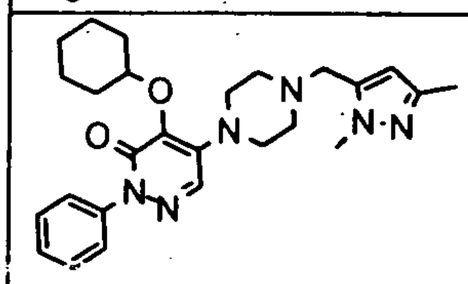
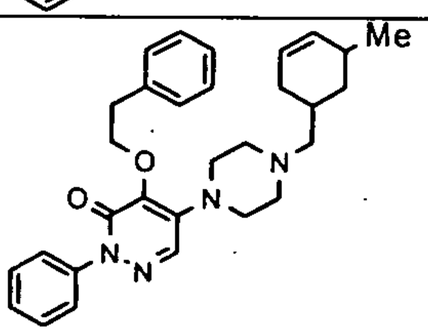
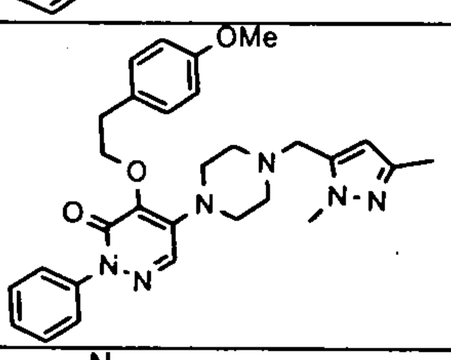
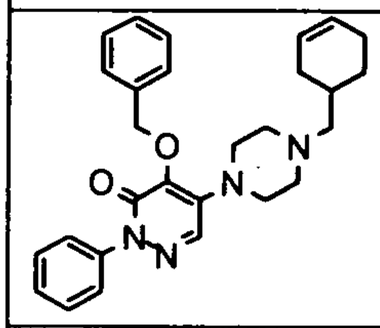
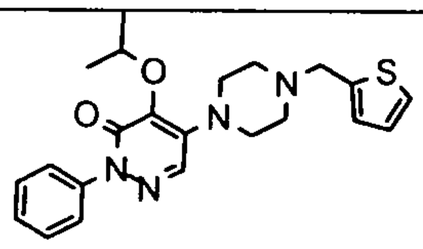
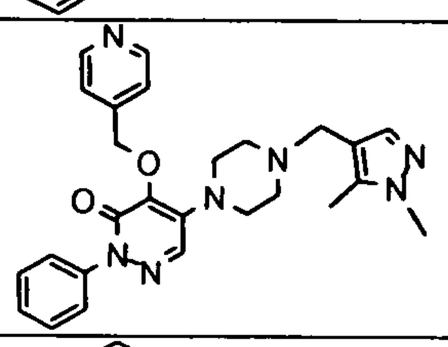
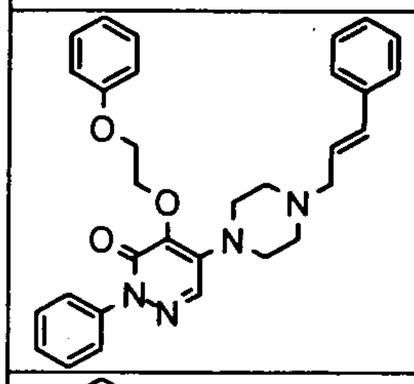
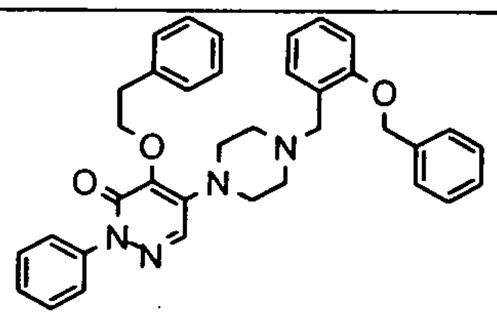
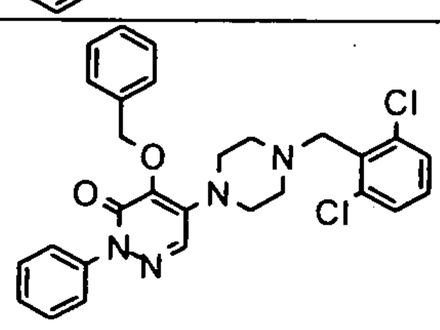
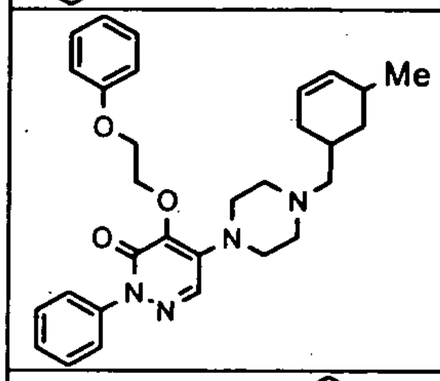
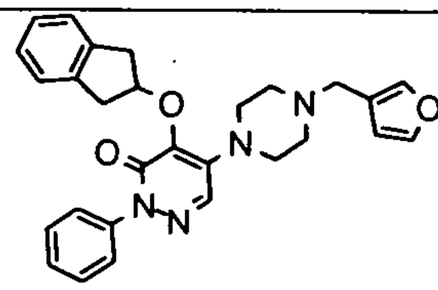
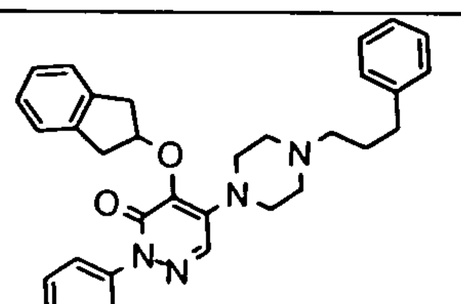
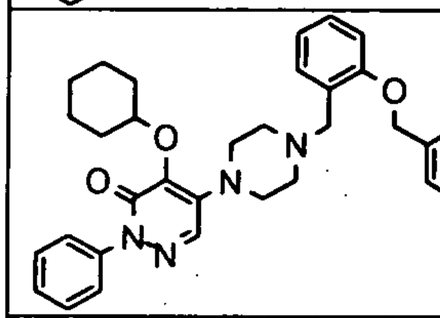
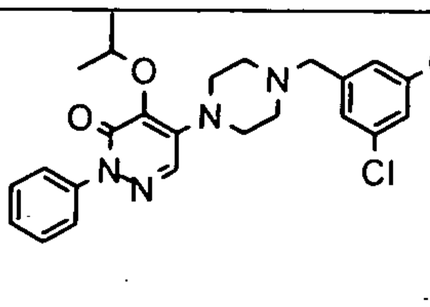
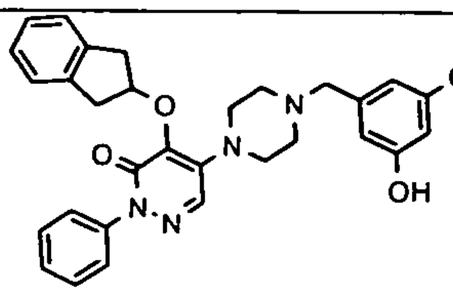
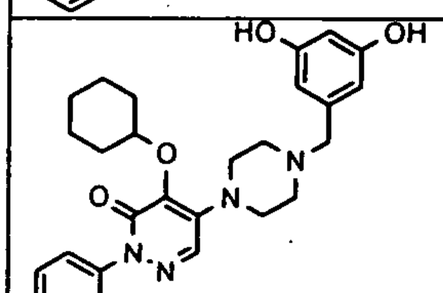
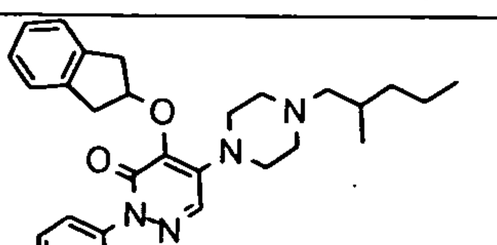
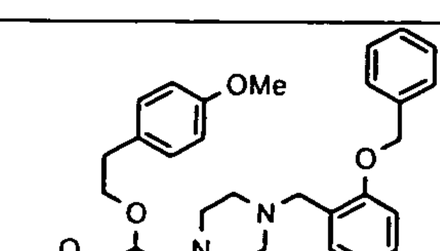
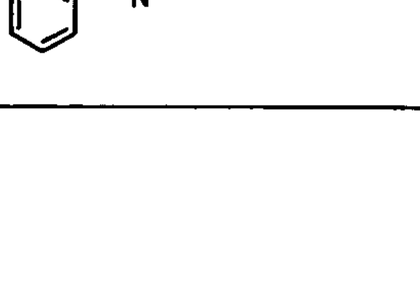
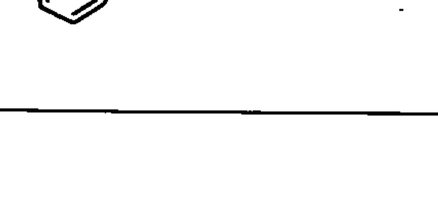
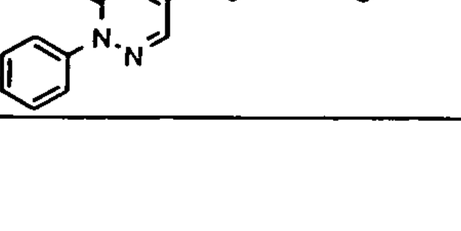
		
		
		
		
		
		

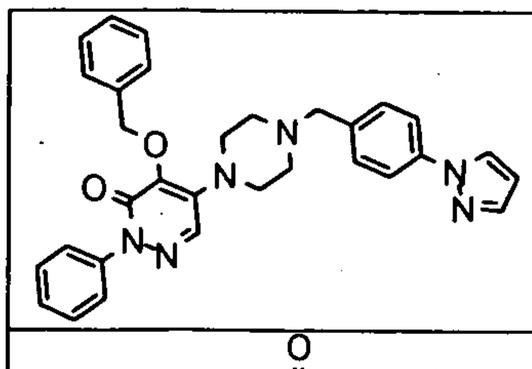
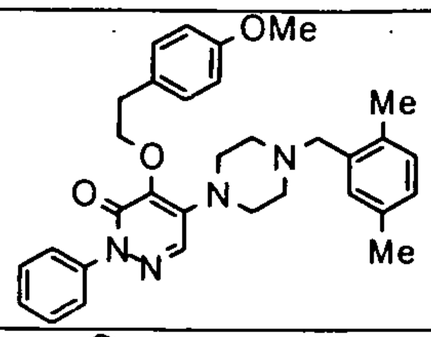
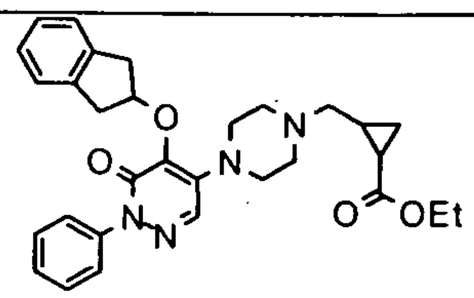
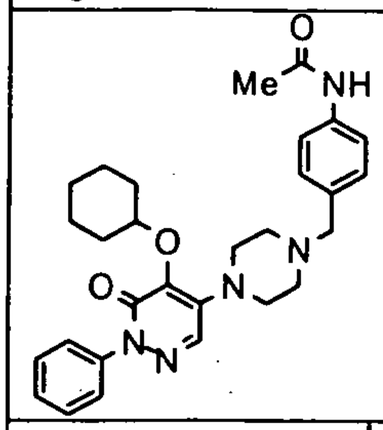
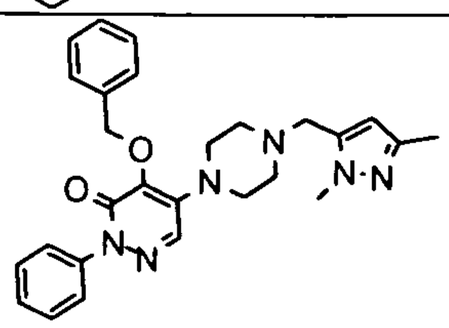
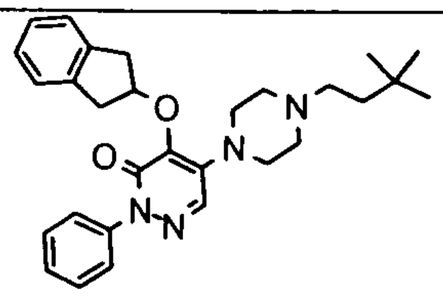
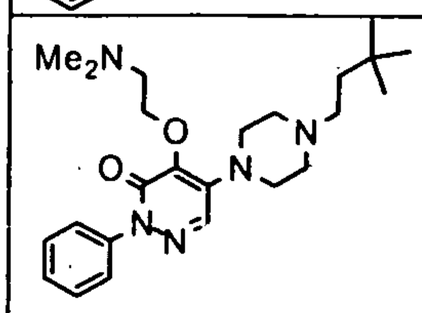
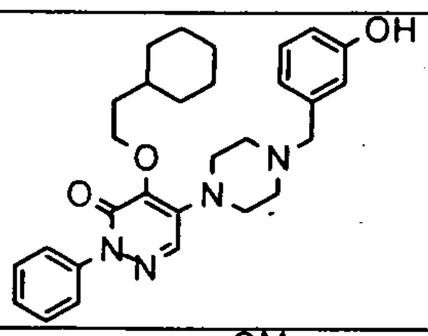
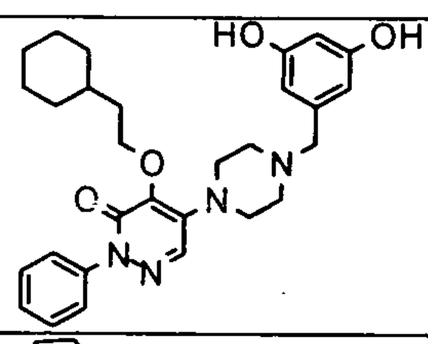
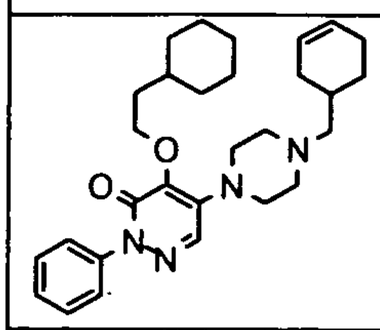
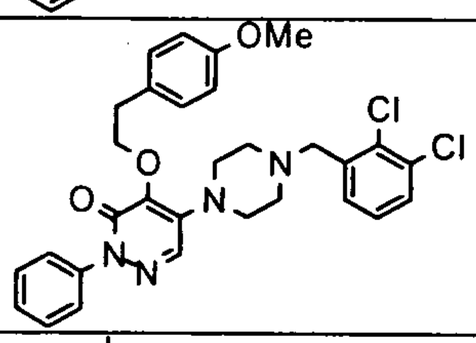
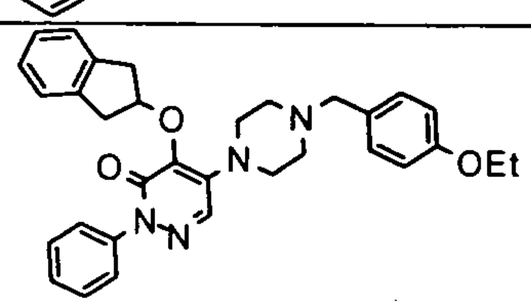
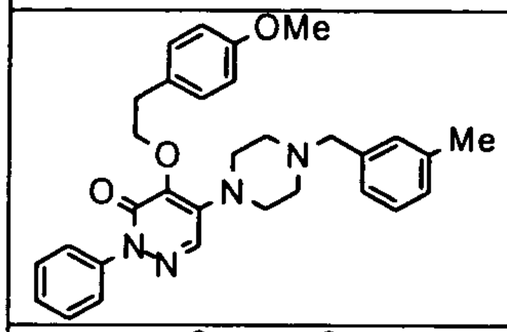
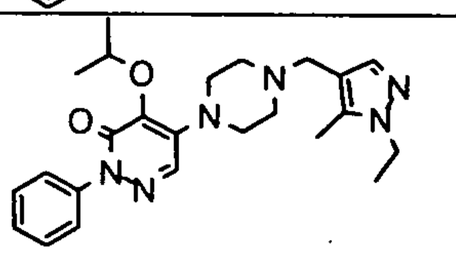
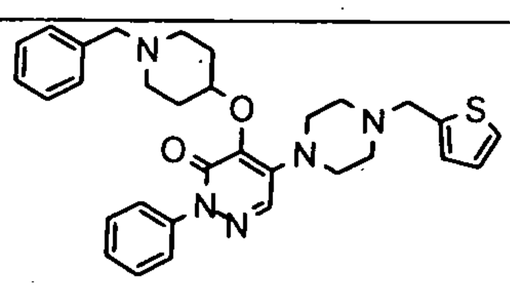
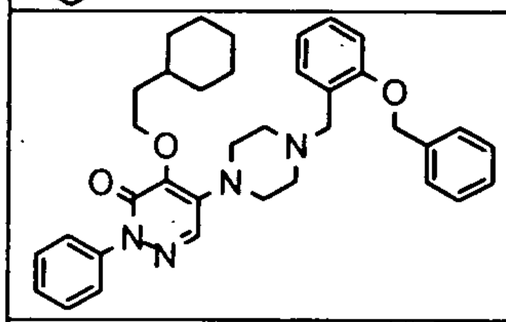
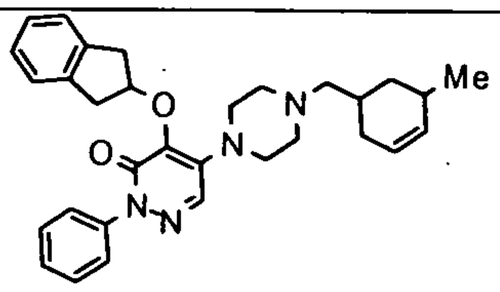
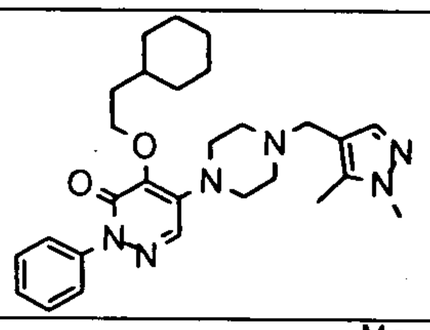
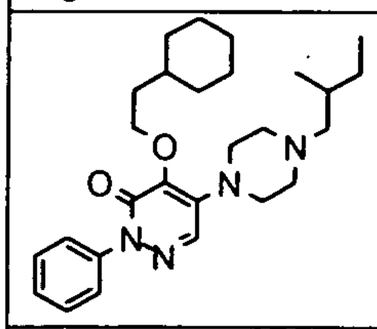
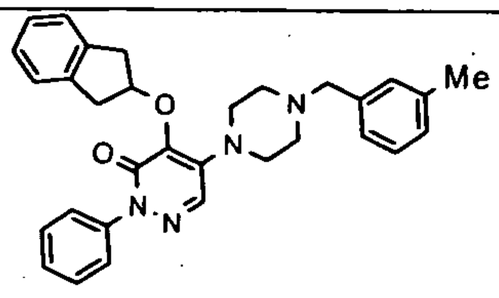
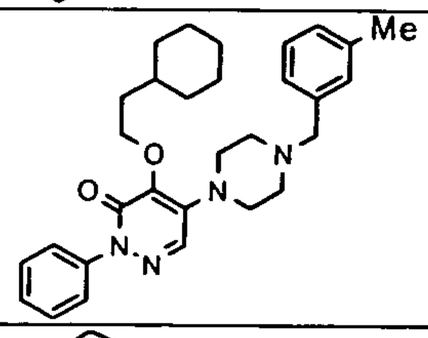
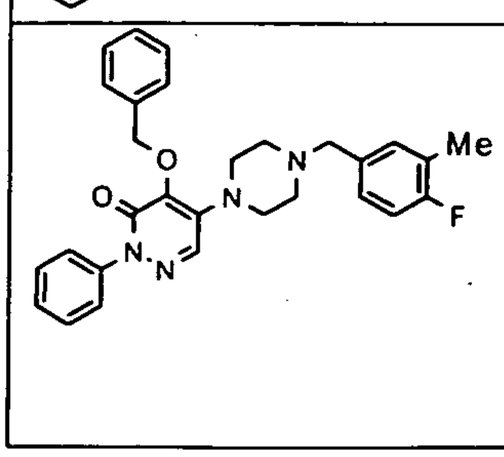
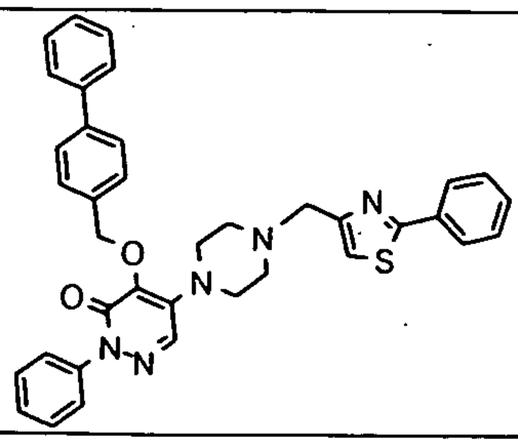
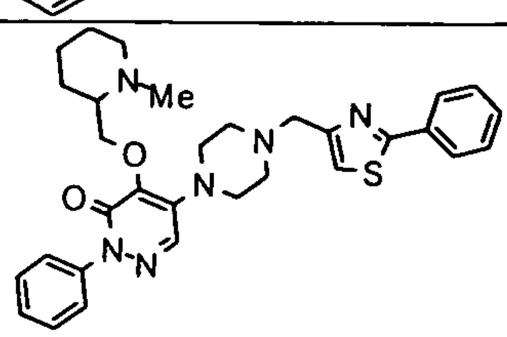
		
		
		
		
		
		
		

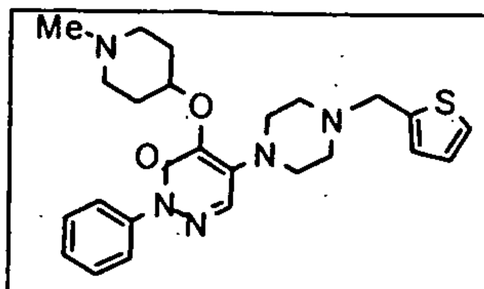
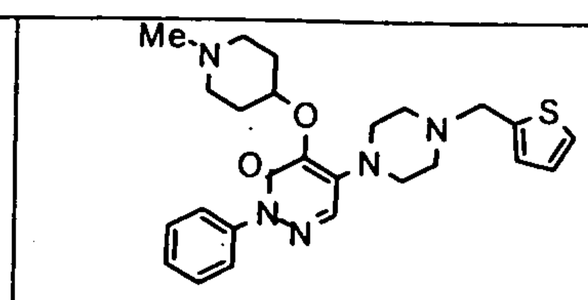
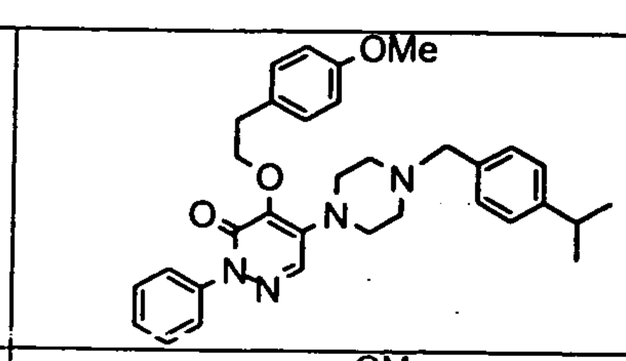
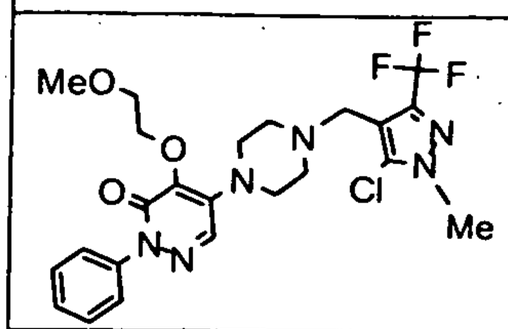
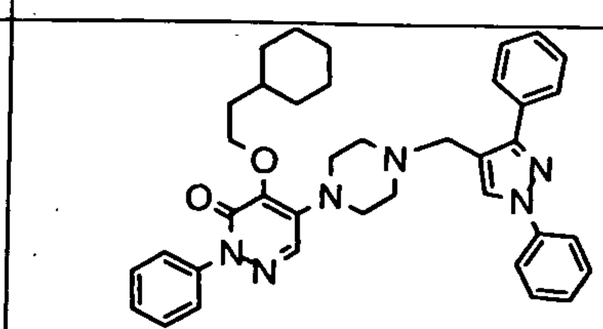
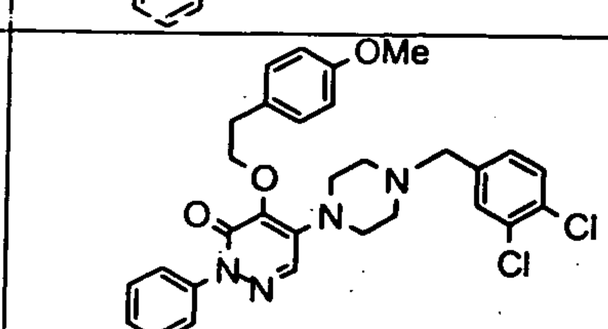
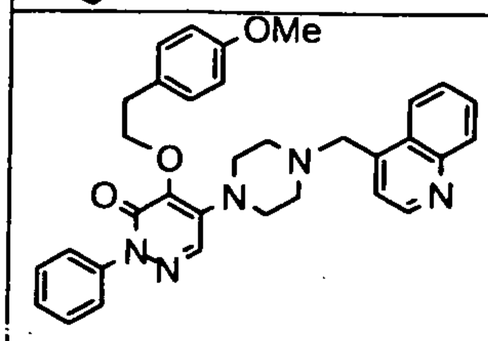
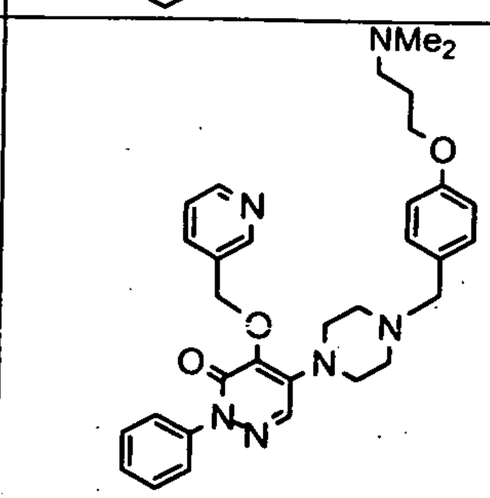
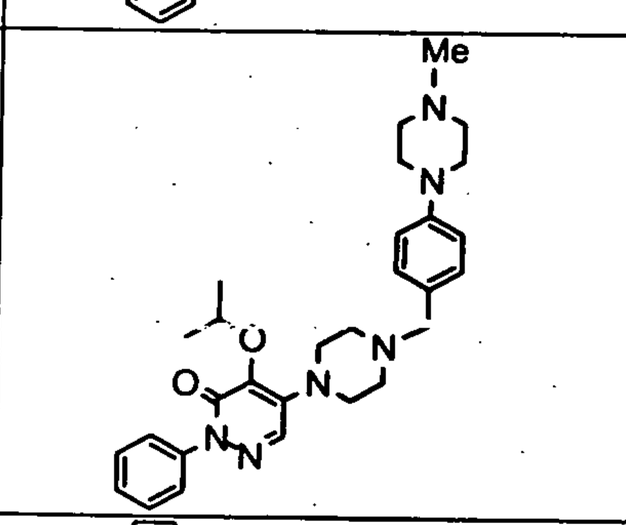
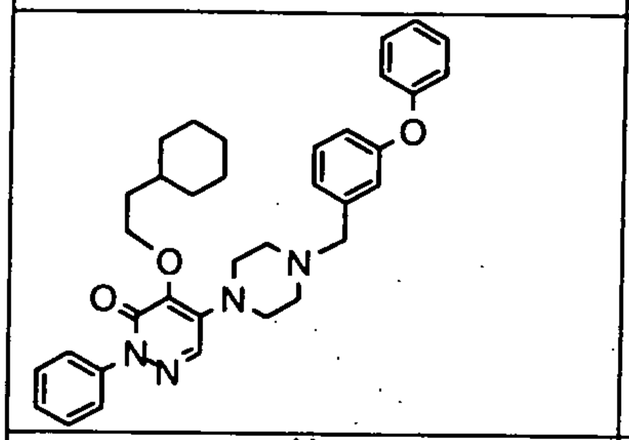
		
		
		
		
		
		
		

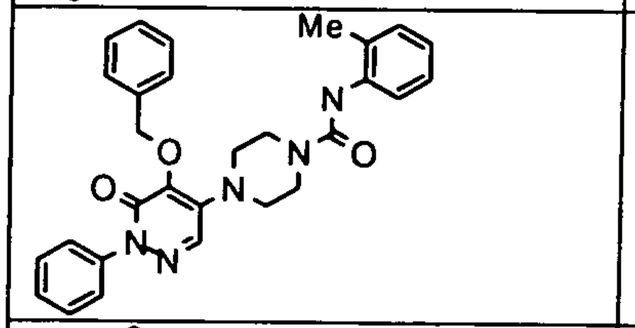
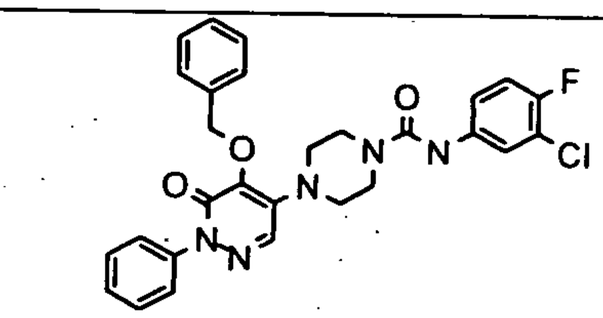
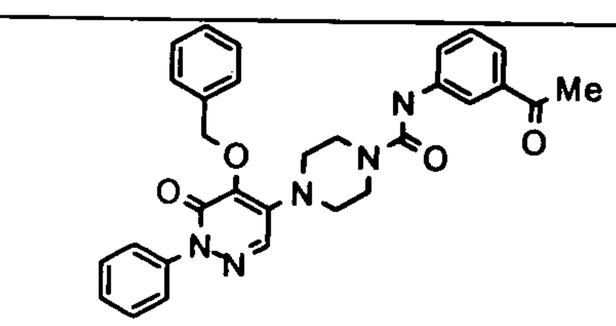
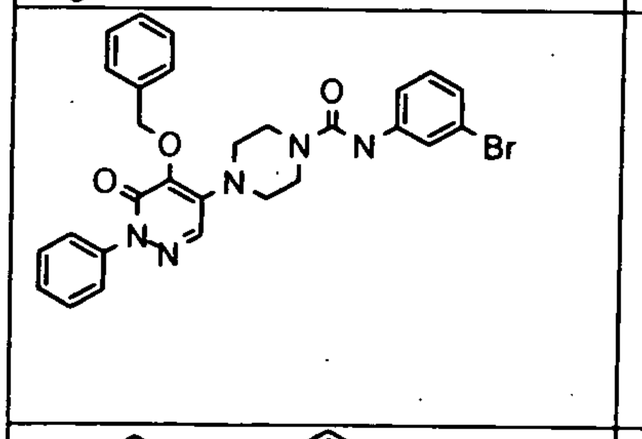
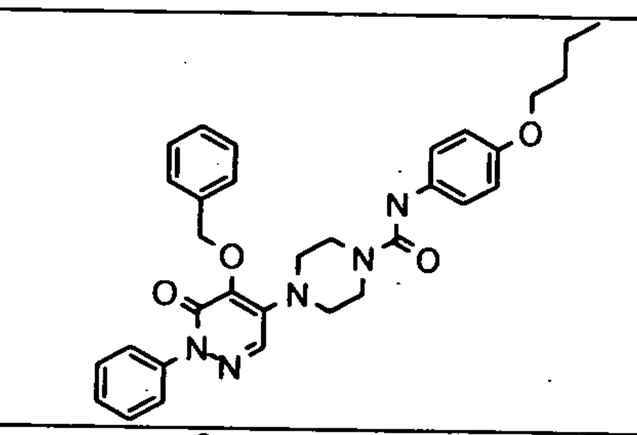
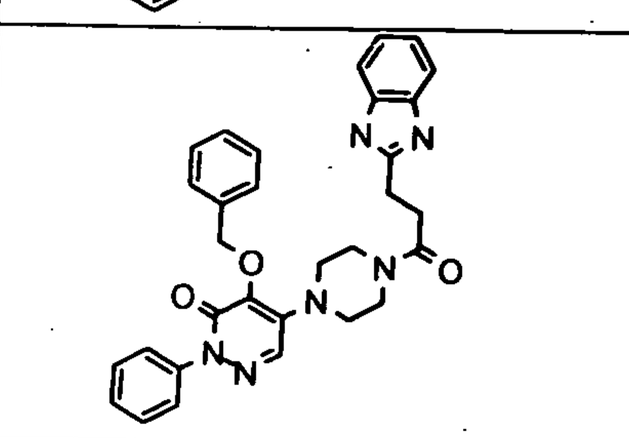
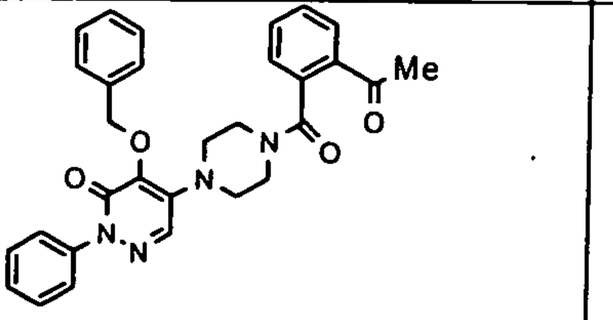
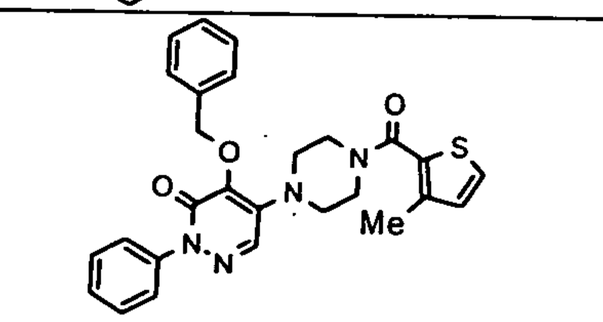
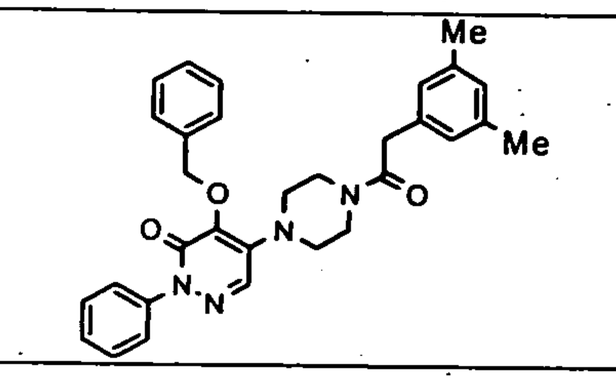
		
		
		
		
		
		
		
		

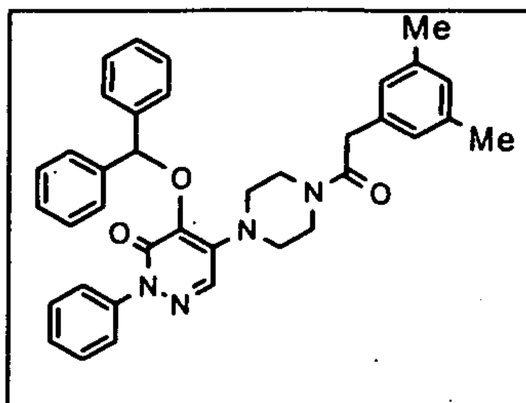
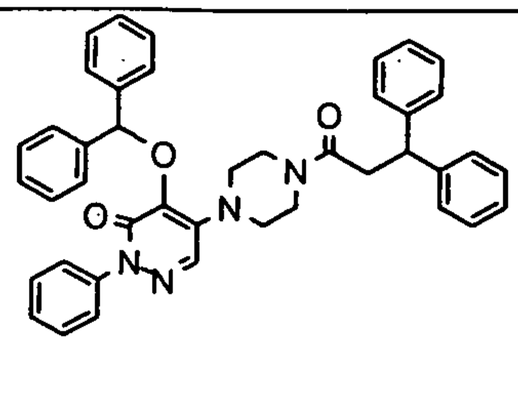
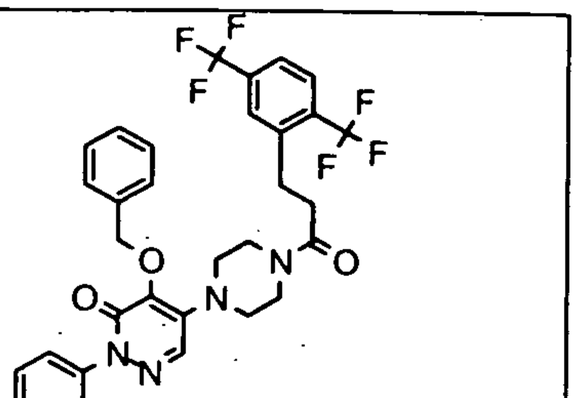
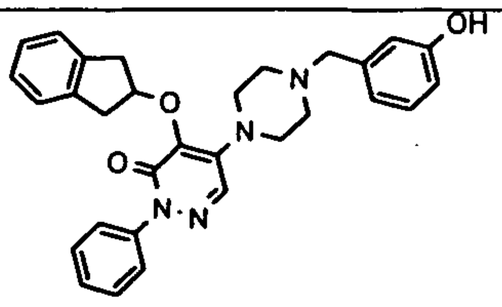
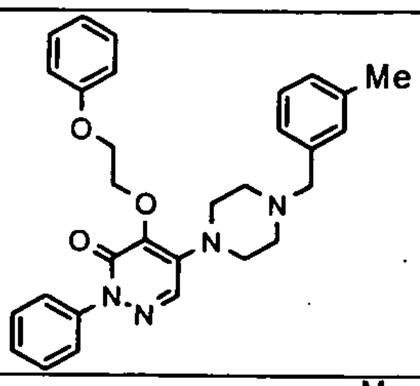
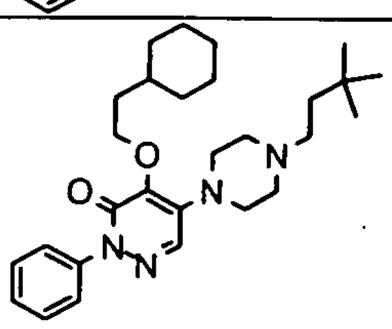
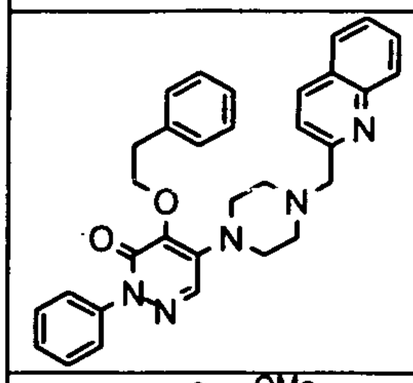
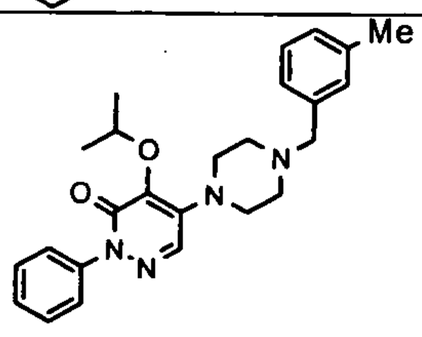
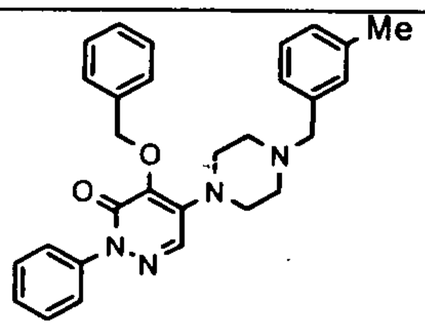
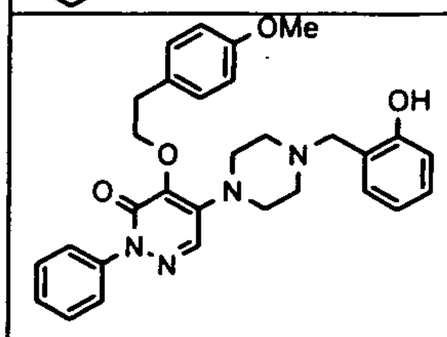
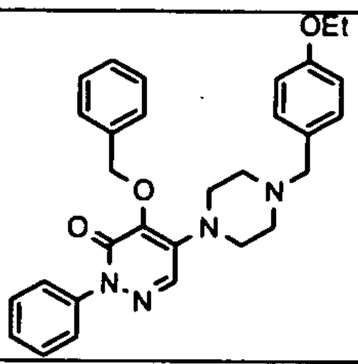
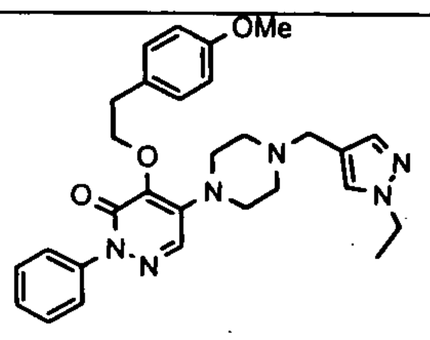
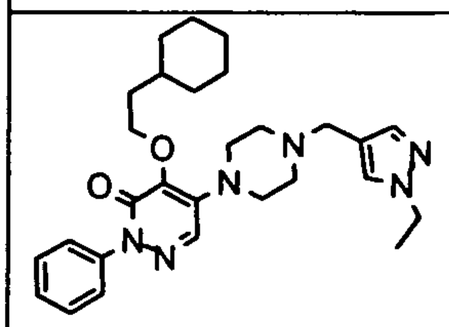
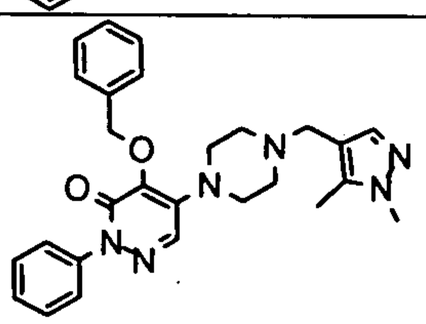
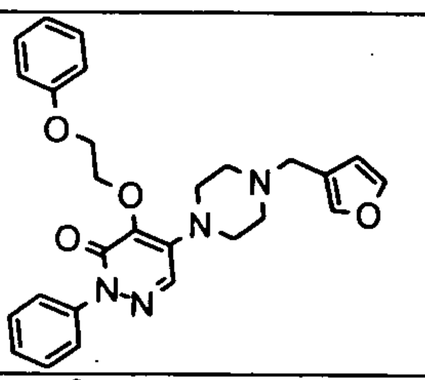
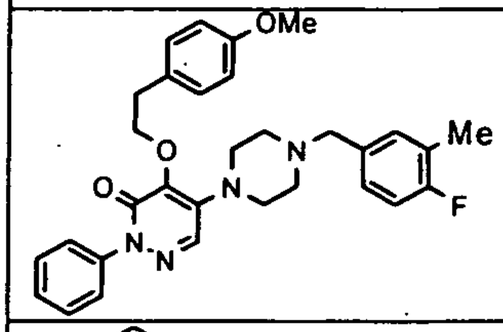
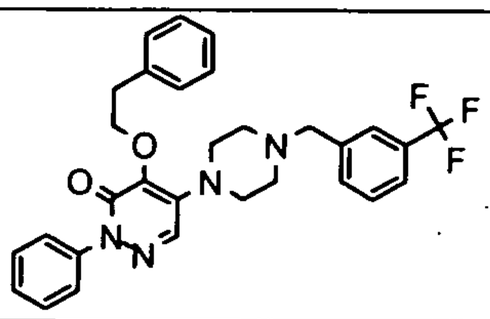
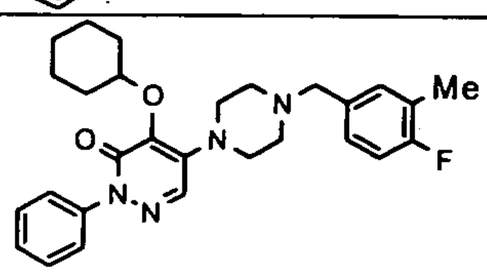
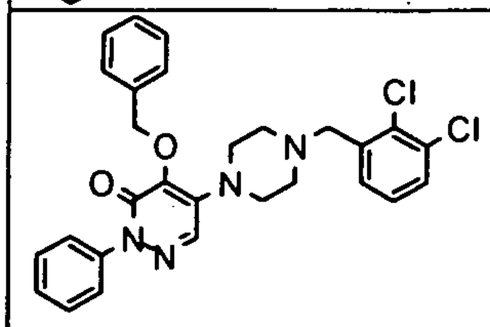
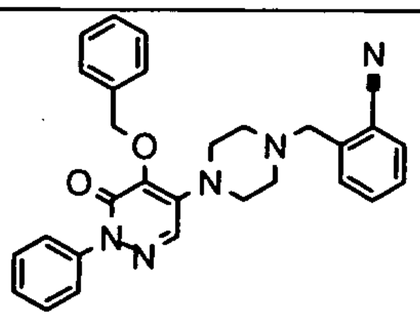
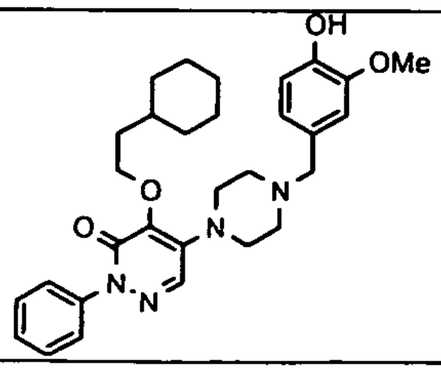
		
		
		
		
		
		
		
		

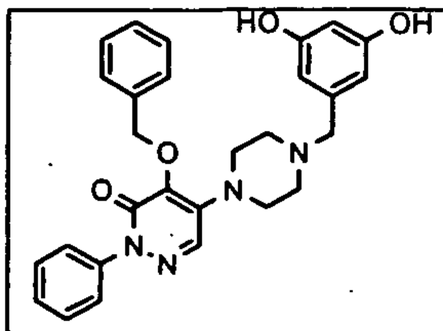
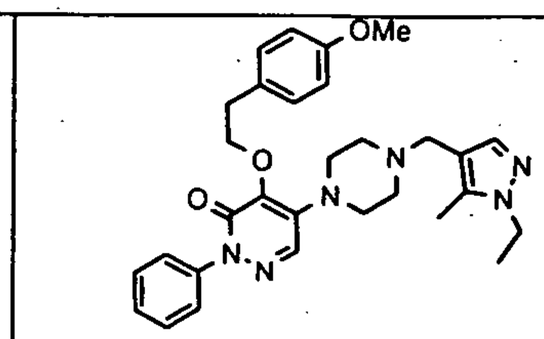
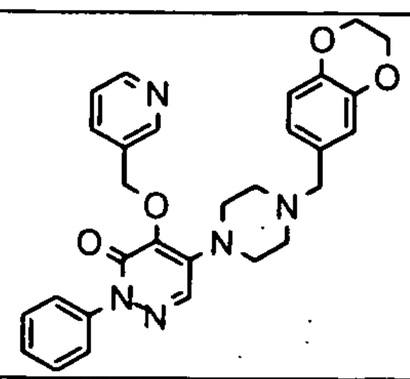
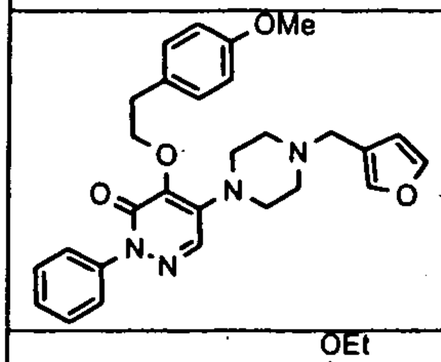
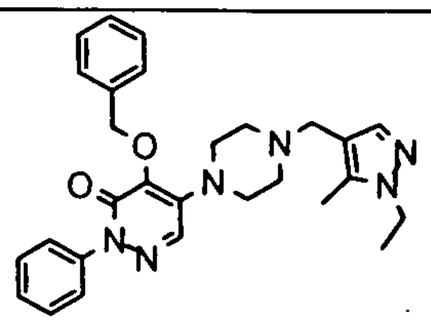
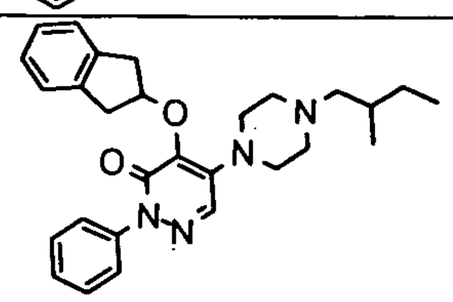
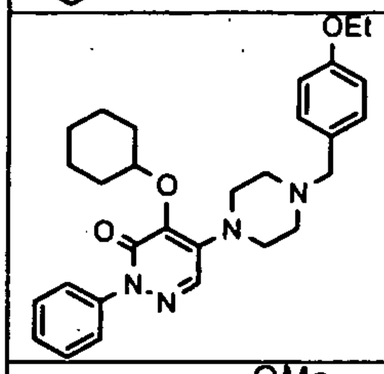
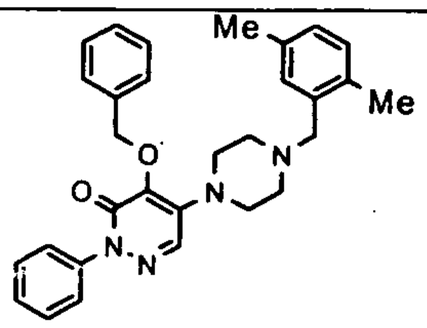
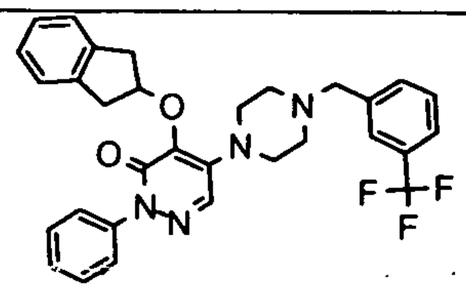
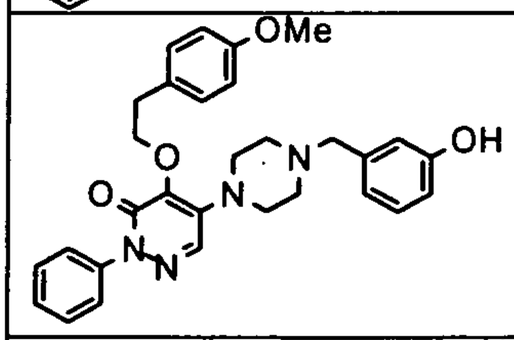
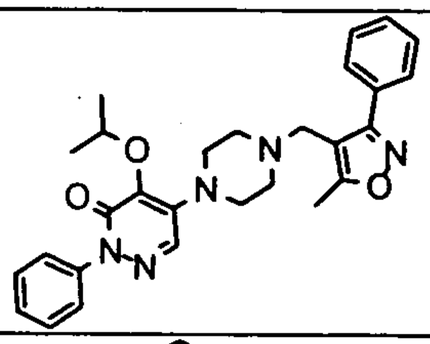
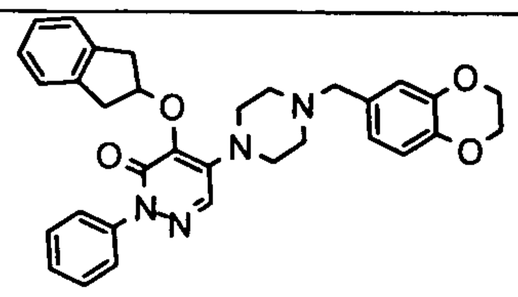
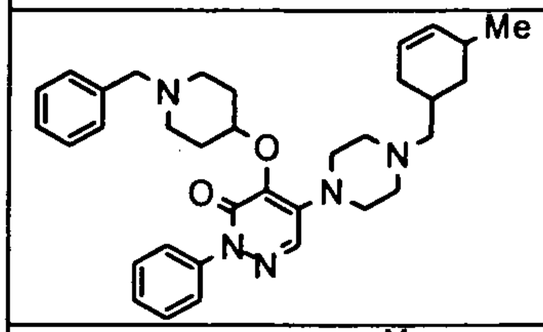
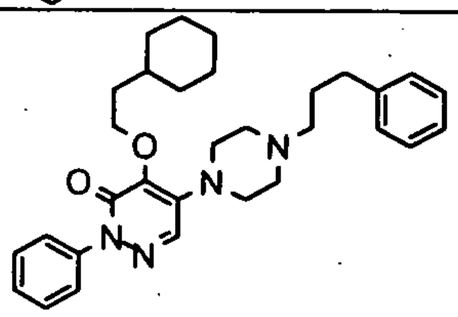
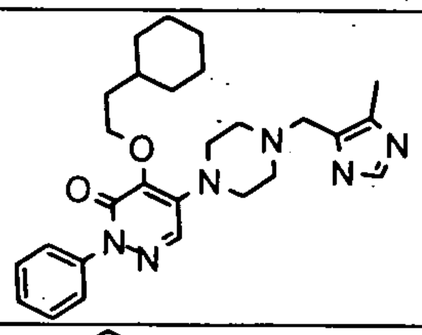
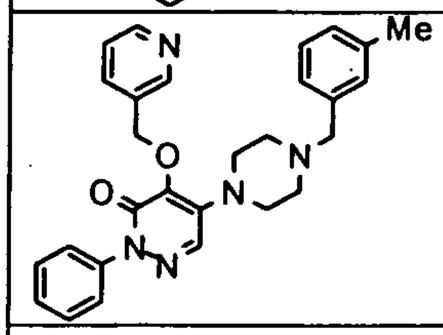
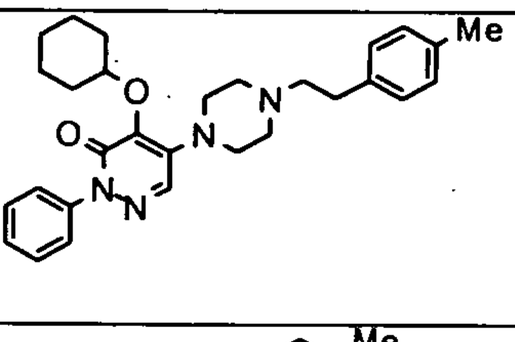
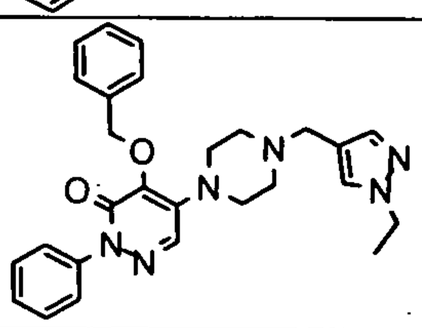
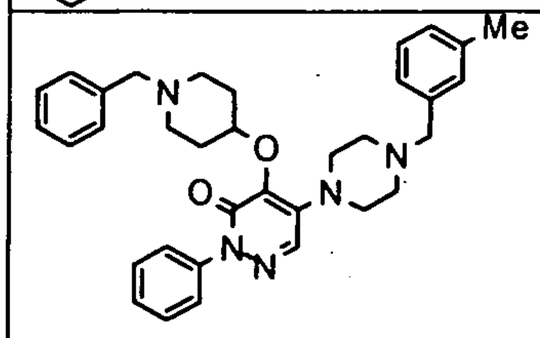
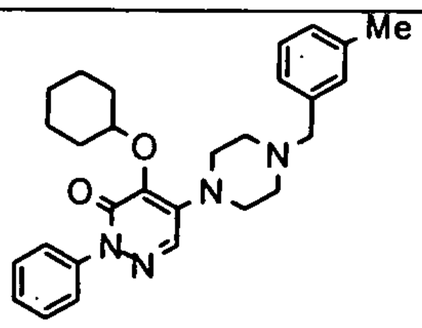
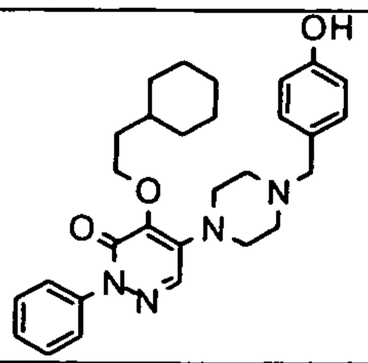
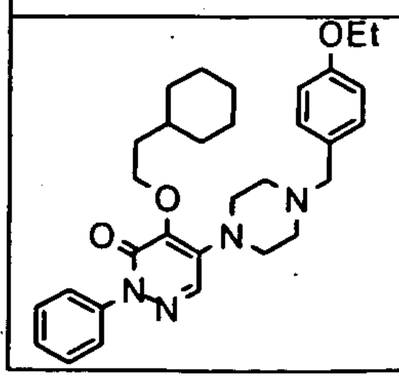
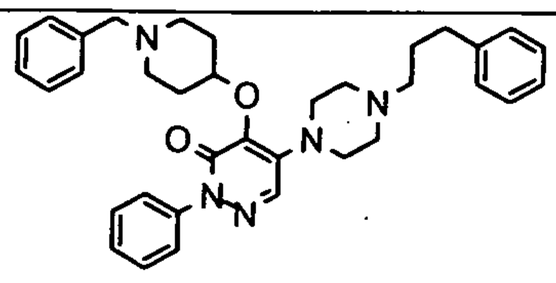
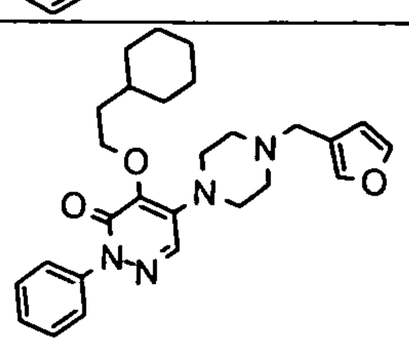
		
		
		
		
		
		
		
		
		

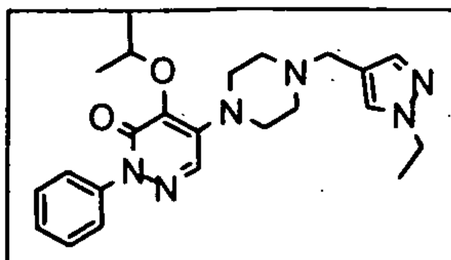
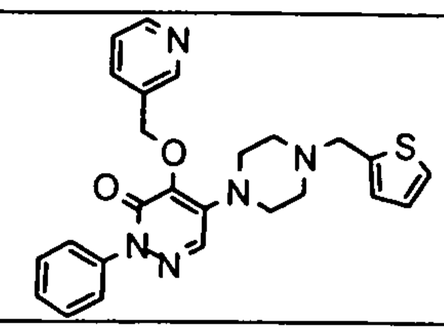
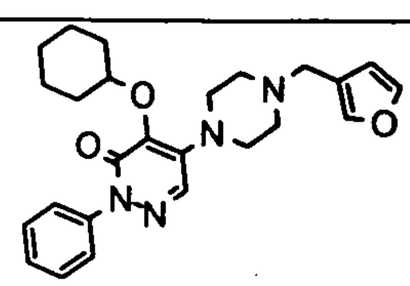
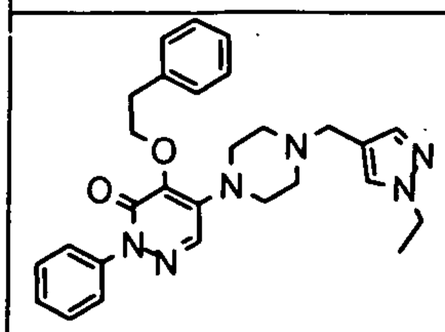
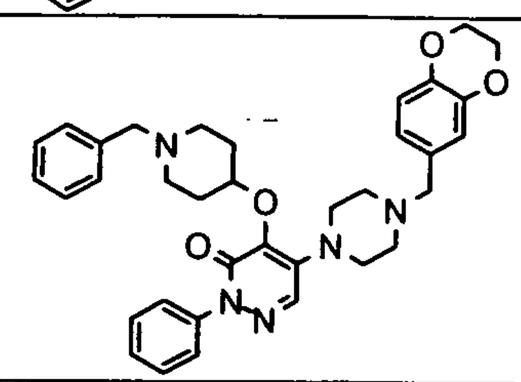
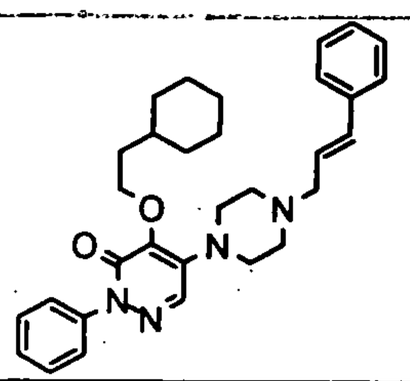
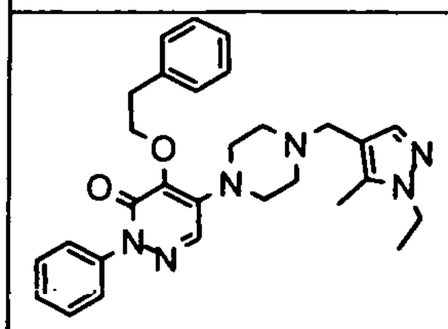
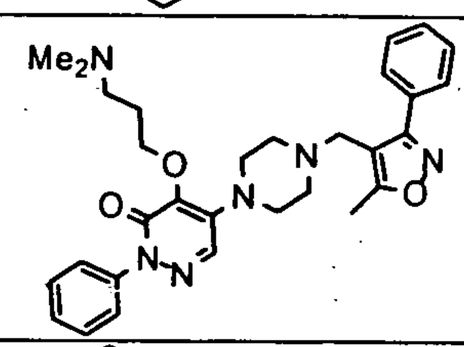
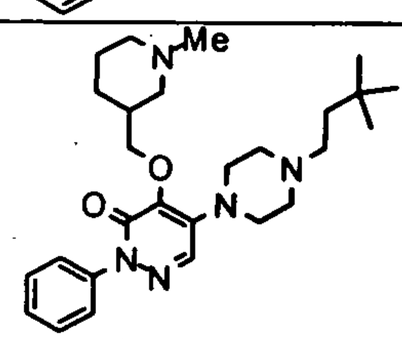
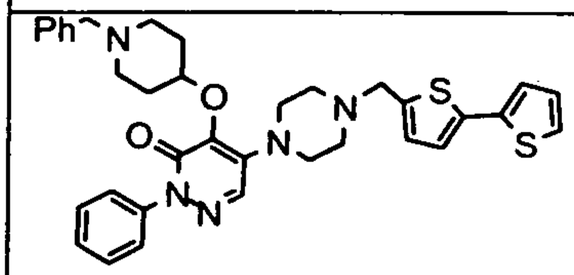
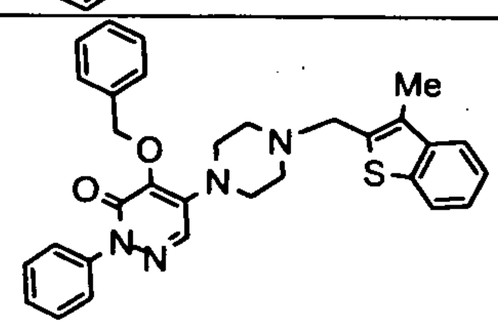
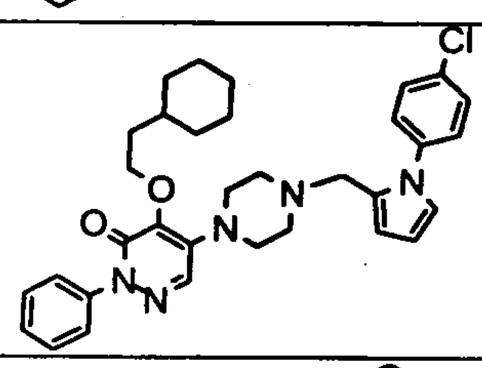
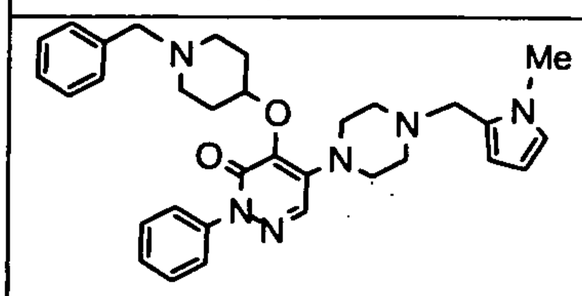
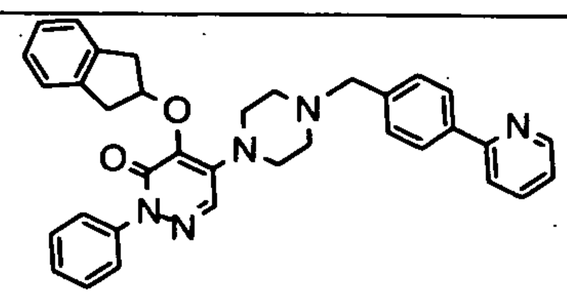
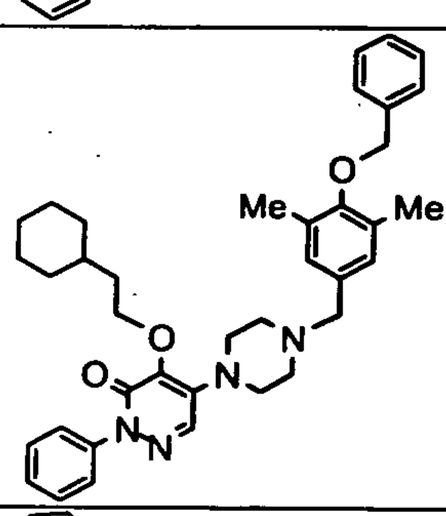
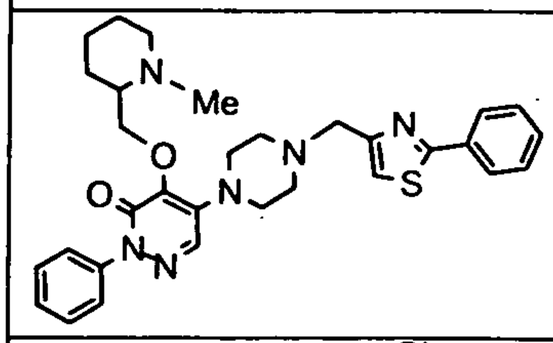
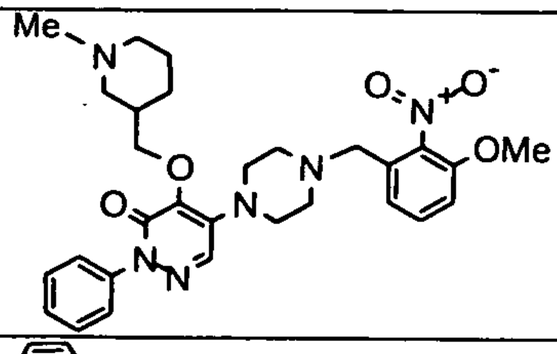
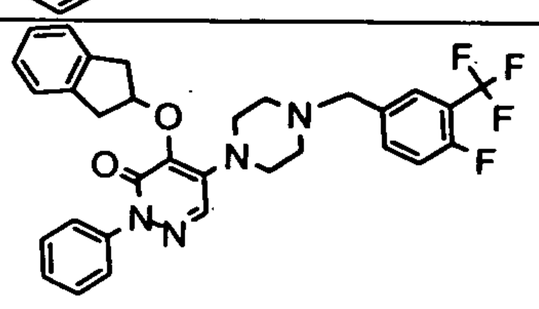
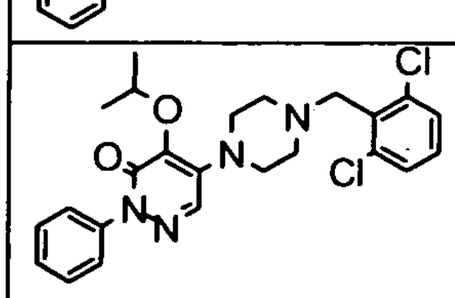
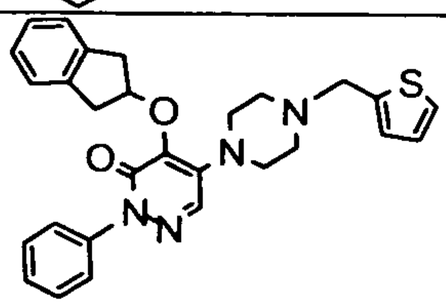
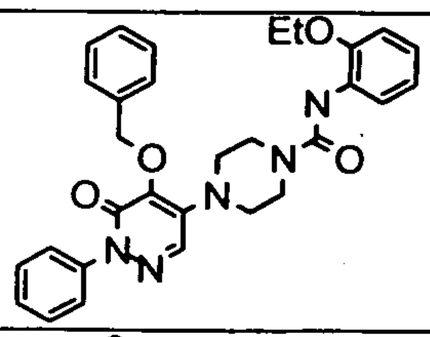
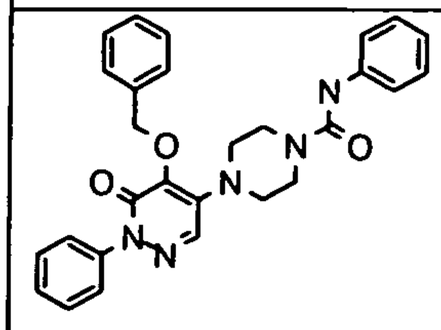
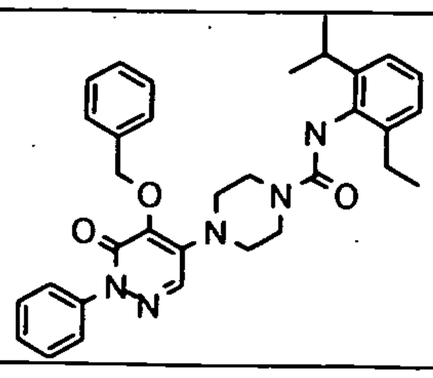
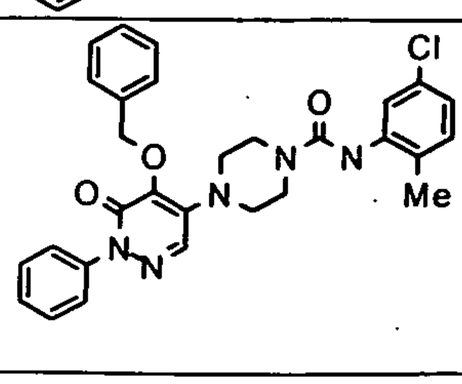
		
		
		
		
		
		
		
		

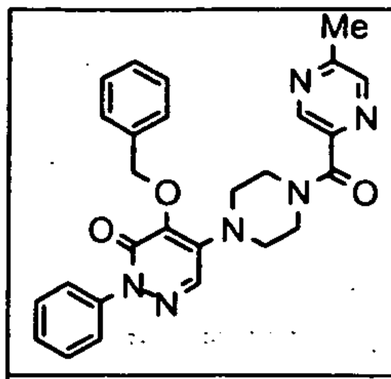
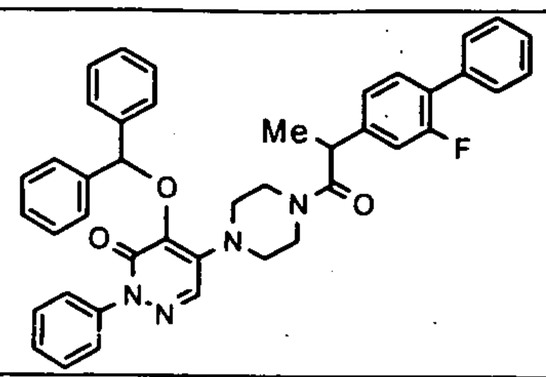
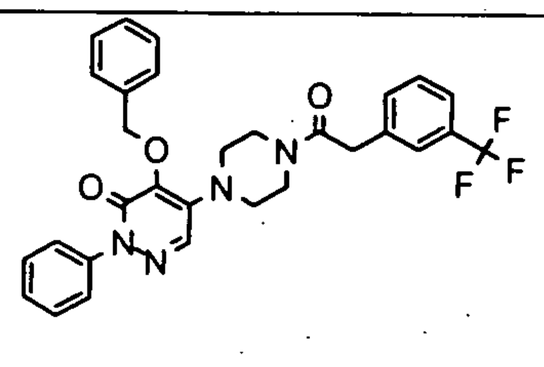
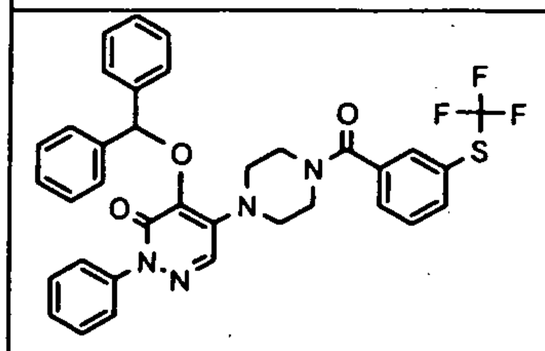
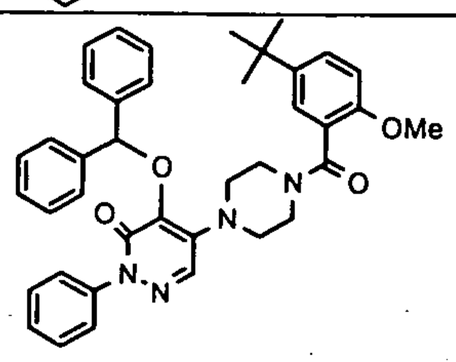
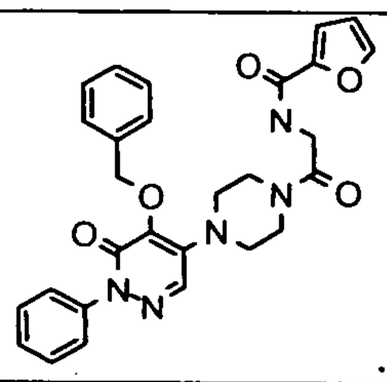











The invention also relates to a pharmaceutical composition for human or veterinary use comprising one or more compounds of Formula I and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for human or veterinary use comprising combination of one or more compounds of Formula I and one or more other antifungal agents with or without a pharmaceutically acceptable carrier.

The invention also relates to a method of treating or preventing growth of fungal pathogens in plants, and to a method of reducing or eliminating fungal growth on inanimate surfaces, comprising applying a compound of Formula I to said plant or surface.

The invention also relates to a method of treating or preventing growth of fungal pathogens on inanimate surface by applying one or more compounds of Formula I to said surface.

Further, the invention relates to a method of treating or preventing growth of fungal pathogens on inanimate surface by applying other antifungal agents along with the compounds of Formula I.

The invention also relates to a method of treating fungal pathogens by administering pharmaceutical compositions for human or veterinary use comprising one or more compounds of Formula I and a pharmaceutically acceptable carrier.

The invention also relates to the use of a glucan synthase inhibitor of Formula I for the preparation of a medicament for treating or preventing fungal infections.

The invention also relates to a method of treating or preventing fungal infections by administering a combination of one or more compounds of Formula I and one or more other antifungal agents.

Further, the invention relates to a method of treating or preventing fungal infections by administering a human or veterinary pharmaceutical composition comprising one or more compounds of Formula I and one or more other antifungal agents in a pharmaceutically acceptable carrier. Also contemplated the method of preparing a kit comprising in a single package, one container comprising one or more compounds of Formula I in a pharmaceutically acceptable carrier, and a separate container comprising one or more other antifungal agents in a pharmaceutically acceptable carrier, with the compounds of Formula I and the other antifungal agents being present in amounts such that the combination is therapeutically effective.

Also, the invention relates to a method of inhibiting one or more glucan synthase comprising administering at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof to a patient in need of such inhibition.

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment, the present invention provides novel compounds represented by structural Formula I, or pharmaceutically acceptable salts, solvates, esters or prodrugs thereof, wherein the various moieties are as described above, provided that the compounds of Formula I do not include the compounds of Table A listed above.

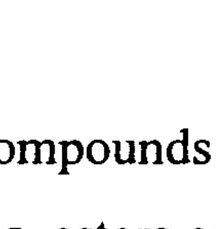
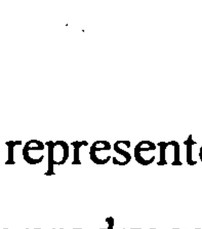
In another embodiment, in Formula I, A is O.

In another embodiment, in Formula I, D is N or C.

In another embodiment, in Formula I, D is N.

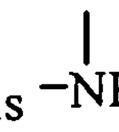
In another embodiment, in Formula I, D is C.

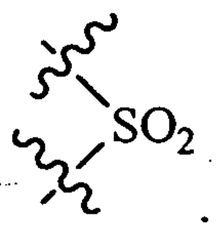
In another embodiment, in Formula I, E is C.

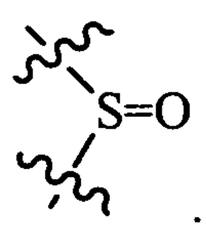
In another embodiment, in Formula I, Y is $-NR^9$, -O-, -S-,  ,  or absent.

In another embodiment, in Formula I, Y is S.

In another embodiment, in Formula I, Y is O.

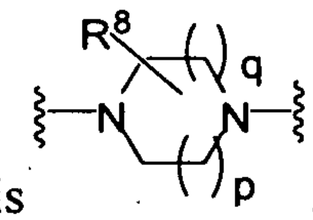
In another embodiment, in Formula I, Y is  .

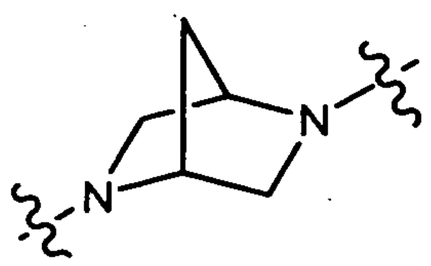
In another embodiment, in Formula I, Y is  .

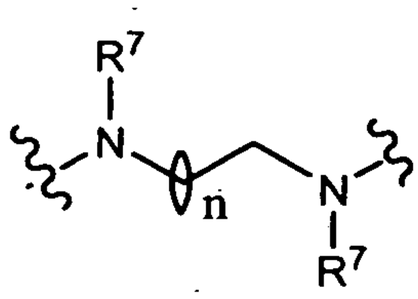
In another embodiment, in Formula I, Y is  .

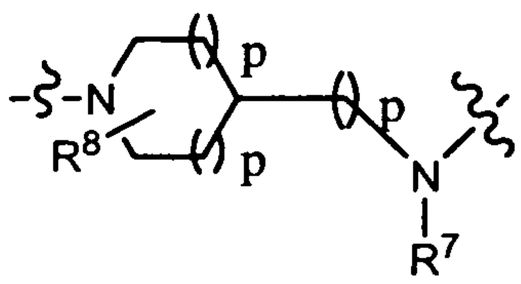
In another embodiment, in Formula I, Y is .

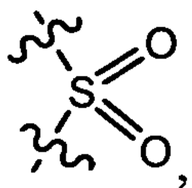
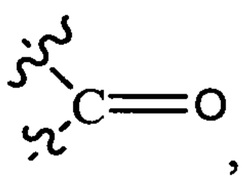
In another embodiment, in Formula I, Y is absent.

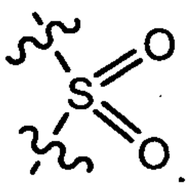
In another embodiment, in Formula I, Z is  .

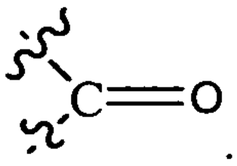
In another embodiment, in Formula I, Z is  .

In another embodiment, in Formula I, Z is  .

In another embodiment, in Formula I, Z is  .

In another embodiment, in Formula I, R^5 is  ,  , $-CR^9{}_2-$ or heteroaryl.

In another embodiment, in Formula I, R^5 is  .

In another embodiment, in Formula I, R^5 is  .

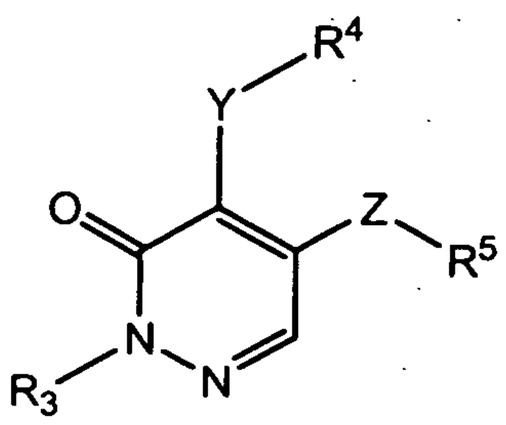
In another embodiment, in Formula I, R^5 is $-CR^9{}_2-$.

In another embodiment, in Formula I, R^5 is heteroaryl.

In another embodiment, in Formula I, E is C and R^6 is H.

In another embodiment, in Formula I, D is N, E is C, a double bond is present between D and E, and R^6 is H.

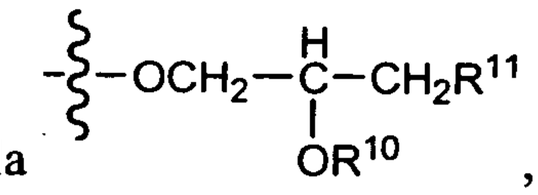
In another embodiment, this invention discloses a compound of Formula A:



Formula A

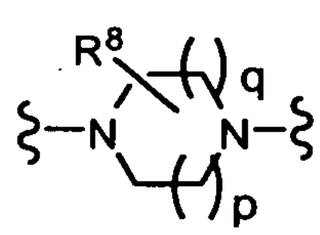
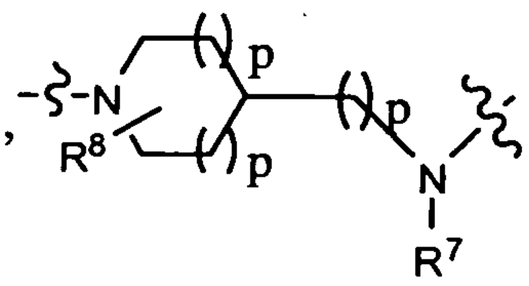
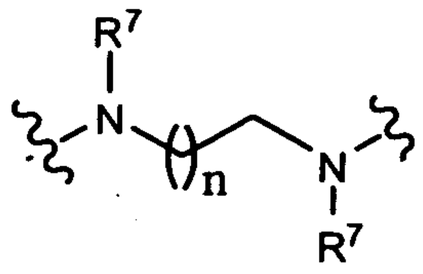
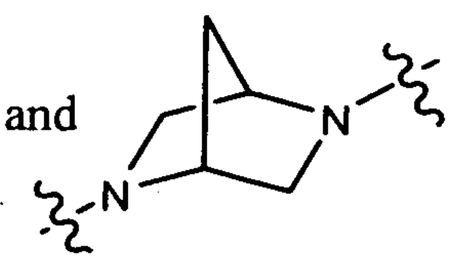
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y is -O-,

provided that Y-R^4 taken together is not alkoxyl of the formula  , wherein $-CH_2R^{11}$ and $-OR^{10}$ together with the CH to which they are attached, form a heterocyclyl that is substituted with one or more moieties, which can be the same or different , selected from the group consisting of alkyl and aryl, or

wherein R^{10} is H and R^{11} is hydroxyl or butylamine;

Z is a linker attached at either end of said linker to the parent ring of Formula A, wherein said linker is selected from the group consisting of :

 ,  ,  , and 

wherein

n is 1 to 4,

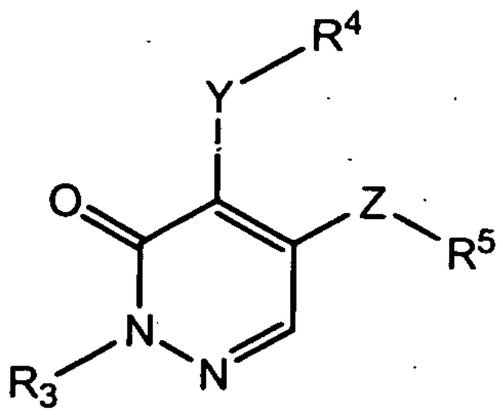
p is 0 to 2,

q is 1 to 3;

R^3, R^4, R^5, R^7, R^8, R^9 and R^{12} are as described in Formula I above;

provided that Formula A does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula B:



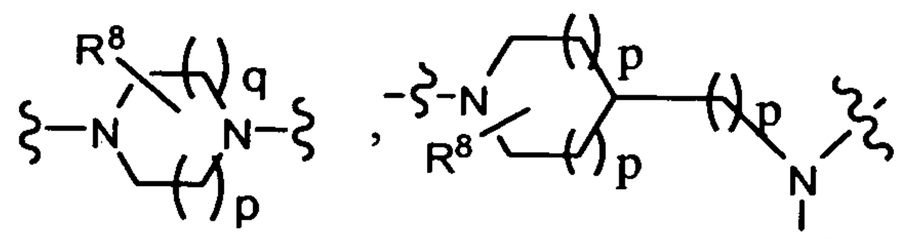
Formula B

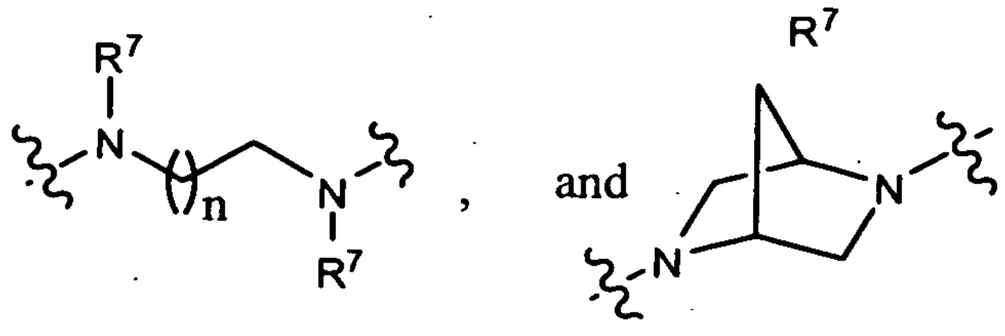
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y is absent;

R^3, R^4, R^5, R^7, R^8, R^9 and R^{12} are as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula B, wherein said linker is selected from the group consisting of :





wherein

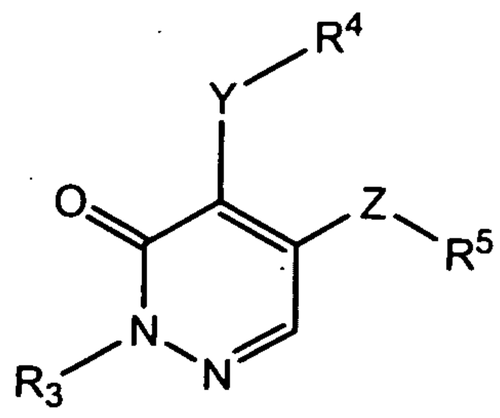
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

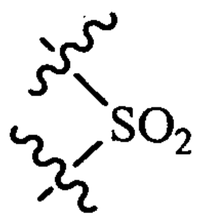
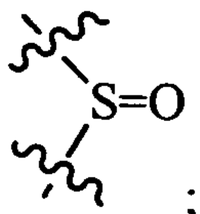
provided that Formula B does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula C:



Formula C

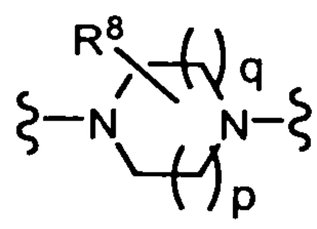
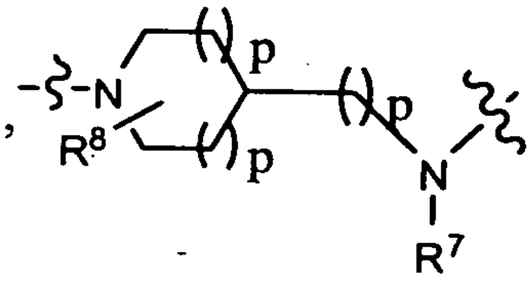
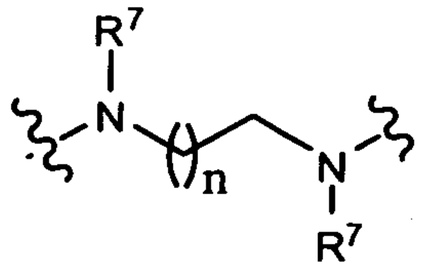
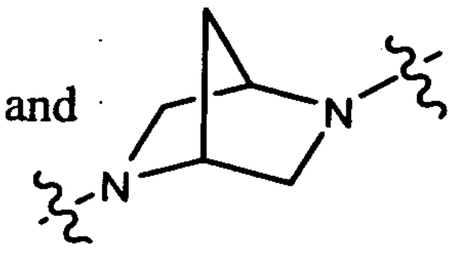
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y is S-,  or  ;

R^3, R^4, R^5, R^7, R^8 R^9 and R^{12} as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula C,

wherein said linker is selected from the group consisting of :




and


wherein

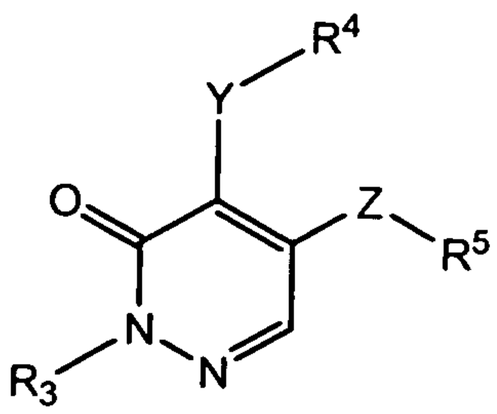
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

provided that Formula C does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses compounds of the Formula D:



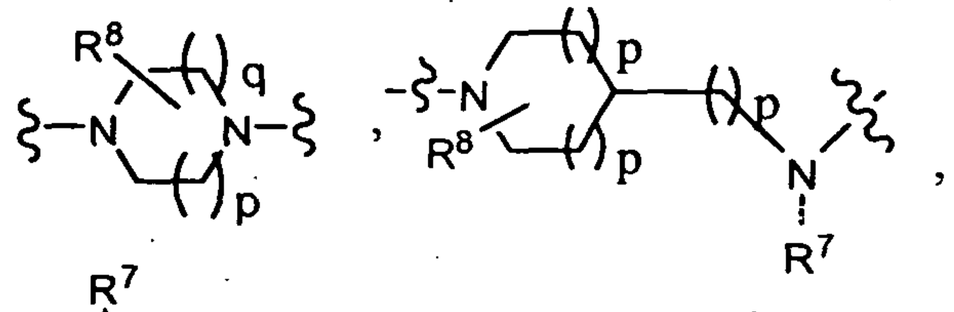
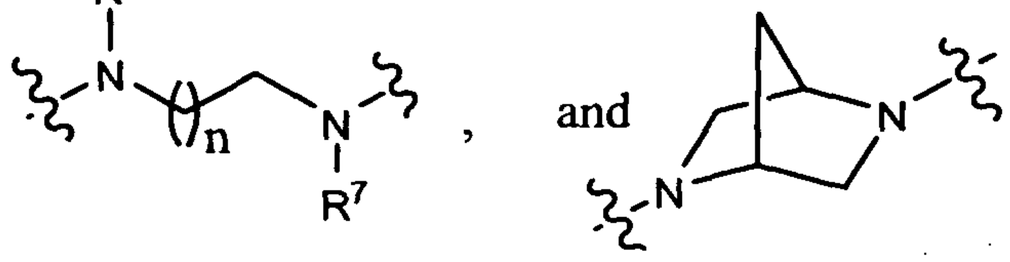
Formula D

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y is NR^9_2;

R^3, R^4, R^5, R^7, R^8 R^9 and R^{12} as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula D, wherein said linker is selected from the group consisting of:

wherein

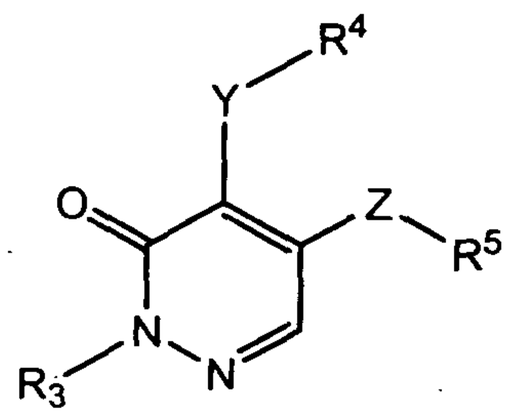
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

provided that Formula D does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses compounds of Formula E:

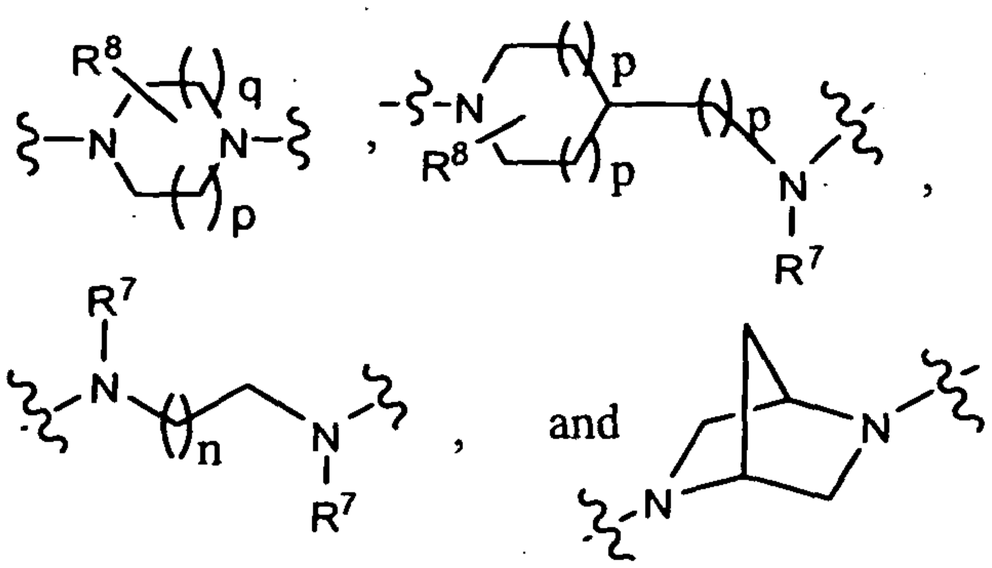


Formula E

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y, R^3, R^4, R^7, R^8, R^9 and R^{12} as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula E, wherein said linker is selected from the group consisting of :

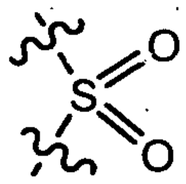
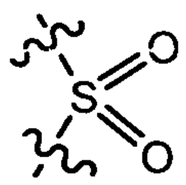


wherein

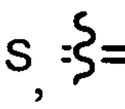
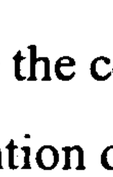
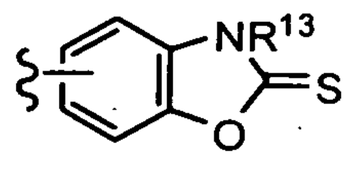
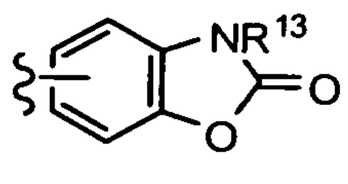
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

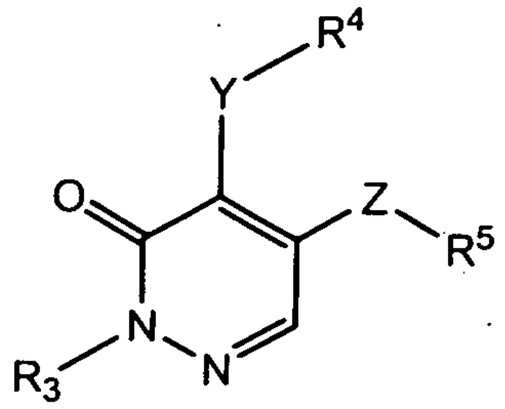
R^5 is  wherein each of said  is attached at one end to Z and at the second end substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, $-OR^9$ and $-NR^9_2$,

further, wherein each of said alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, or heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, alkenyl, cycloalkyl, $-OR^9$, alkylOR^9, alkylCO_2R^9, alkyl$NR^{16}COR^9$, alkyl$NR^{16}CONR^9$, alkylSO_2R^9, alkylCOR^9, alkyl$SO_2NR^9_2$, alkylNR^9_2, alkylaryl, alkylheteroaryl, alkylSR^9, alkylSOR^9, -CN, $-CO_2R^9$, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^{16}COR^9$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2-R^{13}$, $-SO_2R^9$, $-COR^9$, $-NO_2$, $-SO_2NR^9_2$, aryl, heteroaryl, $-NR^9_2$, $-SR^9$, $-SOR^9$,

$-C(=NOH)-NR^{13}$,  , ,  ,  and  ;

provided that Formula E does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses compounds of Formula F:

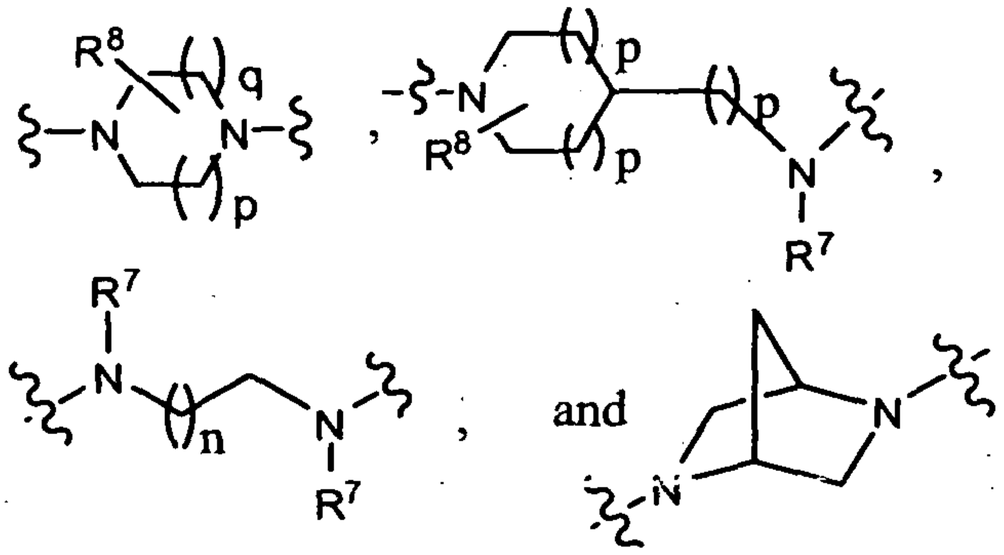


Formula F

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein

Y, R^3, R^4, R^7, R^8, R^9 and R^{12} are as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula F, wherein said linker is selected from the group consisting of:



wherein

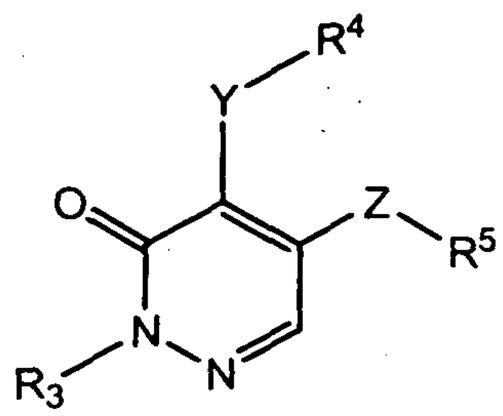
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

R^5 is heteroaryl, optionally substituted by 1 to 3 ring system substituents, provided that Formula F does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula G:

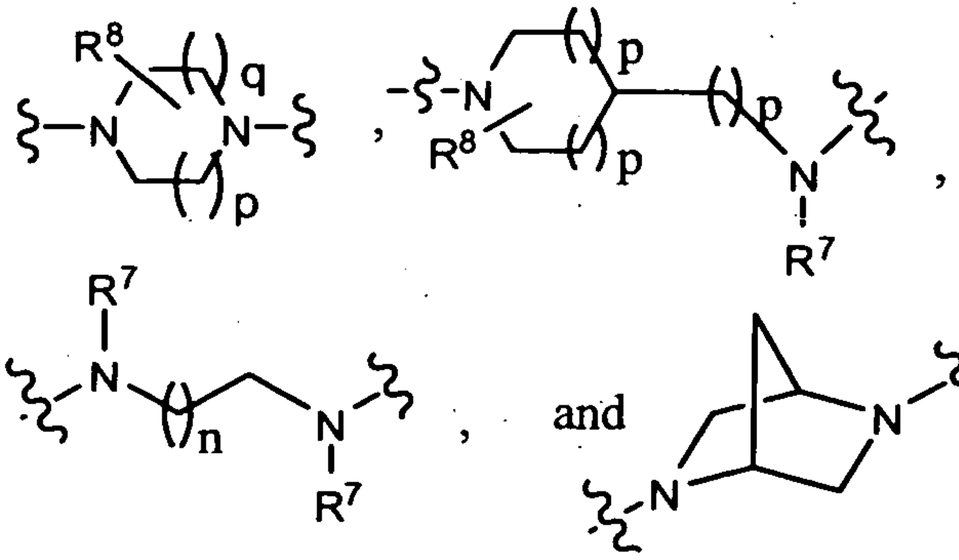


Formula G

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

Y, R^3, R^4, R^7, R^8, R^9 and R^{12} are as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula G, wherein said linker is selected from the group consisting of:

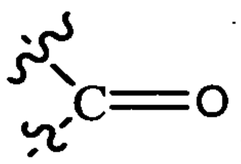
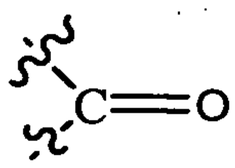


wherein

n is 1 to 4,

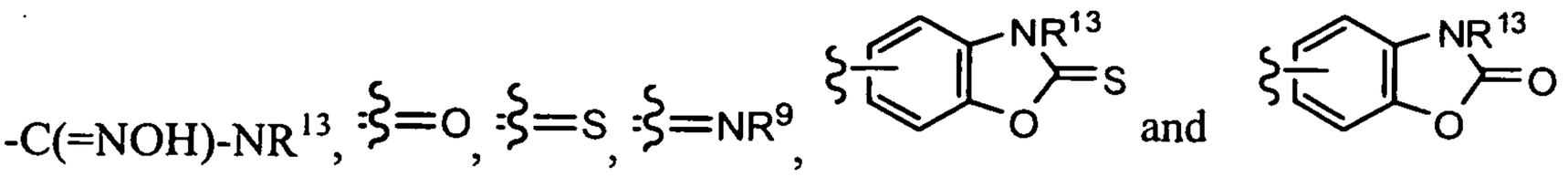
p is 0 to 2,

q is 1 to 3;

R^5 is  wherein said  is attached at one end to Z and at the second end substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, $-OR^9$ and $-NR^9_2$,

further, wherein each of said alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, or heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, alkenyl, cycloalkyl, $-OR^9$, $alkylOR^9$, $alkylCO_2R^9$, $alkylNR^{16}COR^9$, $alkylNR^{16}CONR^9$, $alkylSO_2R^9$, $alkylCOR^9$, $alkylSO_2NR^9_2$, $alkylNR^9_2$, alkylaryl, alkylheteroaryl, $alkylSR^9$, $alkylSOR^9$, -CN, $-CO_2R^9$, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^{16}COR^9$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2-R^{13}$, $-SO_2R^9$,

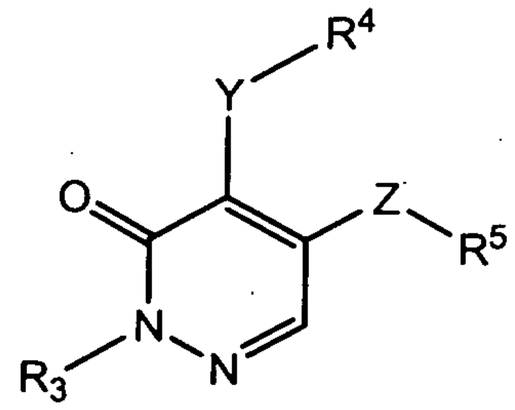
-COR^9, -NO_2, -$SO_2NR^9_2$, aryl, heteroaryl, -NR^9_2, -SR^9, -SOR^9,



-C(=NOH)-NR^{13}, and ;

provided that said Formula G does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula H:

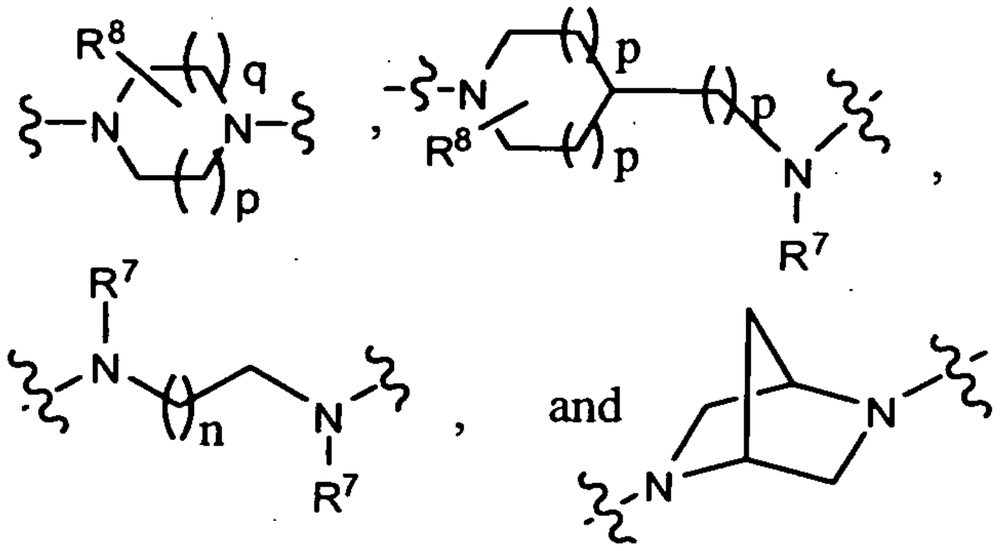


Formula H

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

Y, R^3, R^4, R^7, R^8, R^9 and R^{12} are as described in Formula I above;

Z is a linker attached at either end of said linker to the parent ring of Formula H, wherein said linker is selected from the group consisting of:



wherein

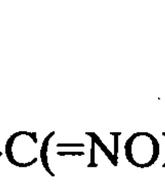
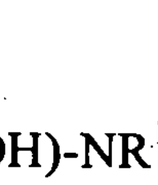
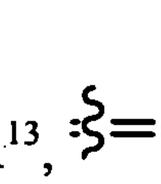
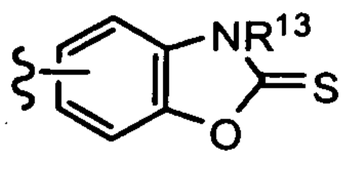
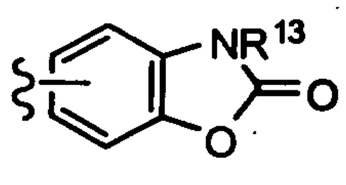
n is 1 to 4,

p is 0 to 2,

q is 1 to 3;

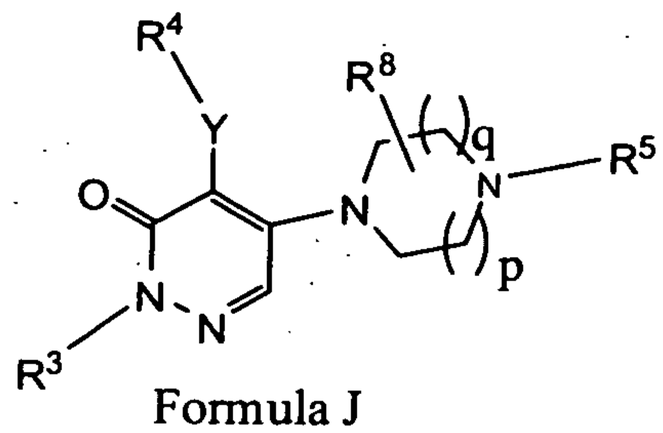
R^5 is -CR^9_2- wherein said -CR^9_2- is attached at one end to Z and at the second end substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl,

heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, $-OR^9$ and $-NR^9_2$, further, wherein each of said alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, or heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, alkenyl, cycloalkyl, $-OR^9$, $alkylOR^9$, $alkylCO_2R^9$, $alkylNR^{16}COR^9$, $alkylNR^{16}CONR^9$, $alkylSO_2R^9$, $alkylCOR^9$, $alkylSO_2NR^9_2$, $alkylNR^9_2$, alkylaryl, alkylheteroaryl, $alkylSR^9$, $alkylSOR^9$, -CN, $-CO_2R^9$, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^{16}COR^9$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2-R^{13}$, $-SO_2R^9$, $-COR^9$, $-NO_2$, $-SO_2NR^9_2$, aryl, heteroaryl, $-NR^9_2$, $-SR^9$, $-SOR^9$,

$-C(=NOH)-NR^{13}$,  ,  ,  ,  and  ;

provided that Formula H does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula J



Formula J

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

Y, R^3, R^4, R^5, R^8, R^9 and R^{12} are as described in Formula I above;

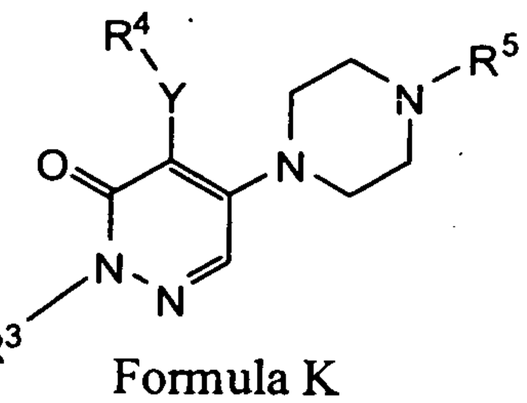
wherein

q is 1,

p is 0-1,

provided that Formula J does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula K



Formula K

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent on R^5 together are –alkyl-, -alkenyl-, -alkyl-NH-,or –alkenyl-NH-, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

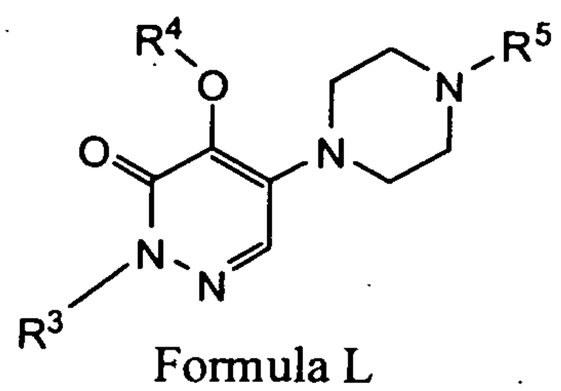
or Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent of R^5 together are an -alkyl-phenylene-alkyl-NR^{13}- group or a -alkyl-phenylene-alkyl- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent of R^5 together are an -alkyl-heteroarylene-alkyl- group or an -alkyl-heteroarylene-alkyl-NR^{13}- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached; and

R^3, R^7, R^8 and R^{13} are as described in Formula I above;

provided that Formula K does not include the compounds of Table A as defined above.

In another embodiment, this invention discloses a compound of Formula L



Formula L

wherein R^3 is mono- or dihalo-phenyl;

R^4 is alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted benzyl, or optionally substituted benzofused cycloalkyl;

R^5 is $–SO_2$-, wherein the second end substituent is alkyl, haloalkyl, optionally substituted

arylalkyl, or optionally substituted heteroarylalkyl; or $-N(R^9)_2$, wherein one R^9 is H and the other is optionally substituted arylalkyl or optionally substituted heteroarylalkyl;
or R^4 and the second end substituent on R^5 together are –alkenyl-;
provided that Formula L does not include the compounds of Table A as defined above.

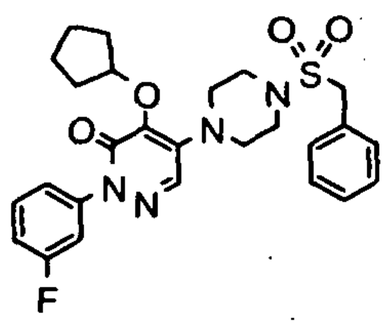
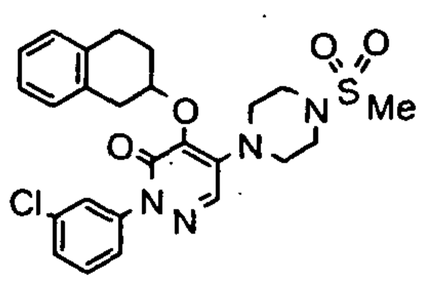
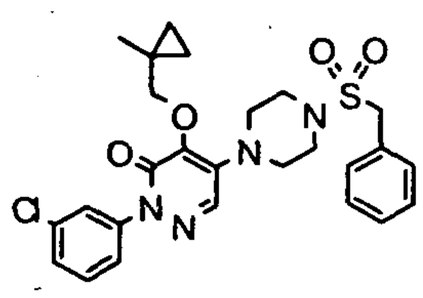
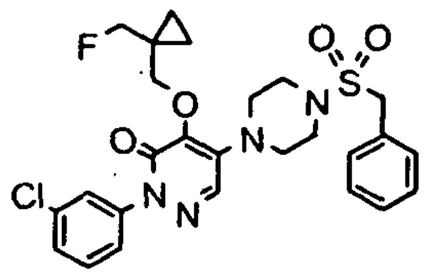
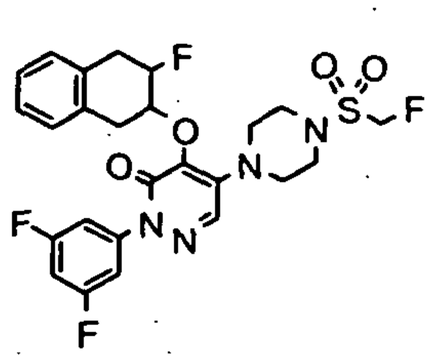
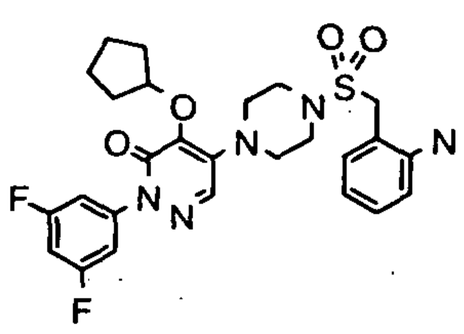
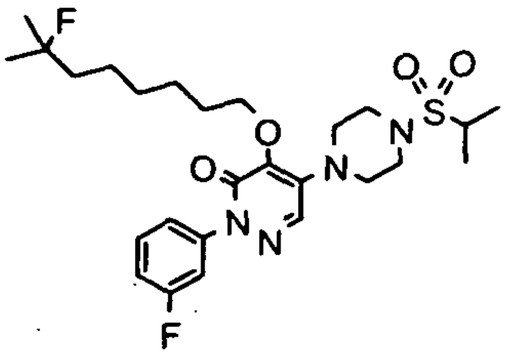
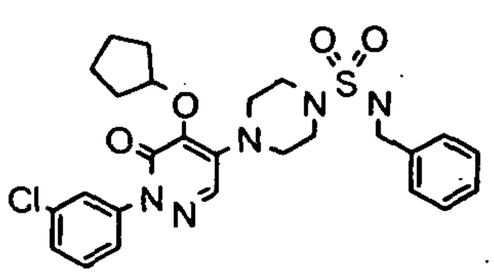
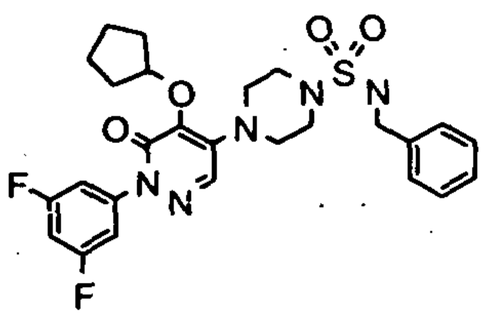
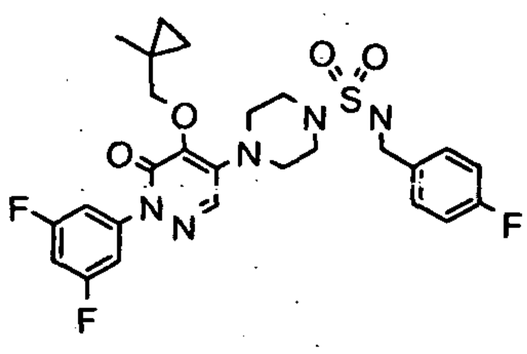
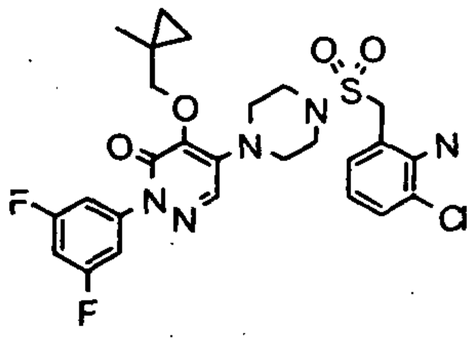
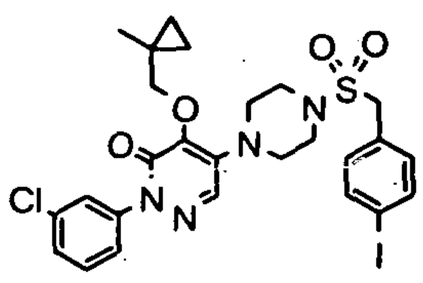
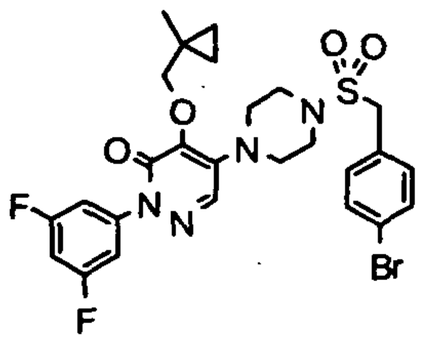
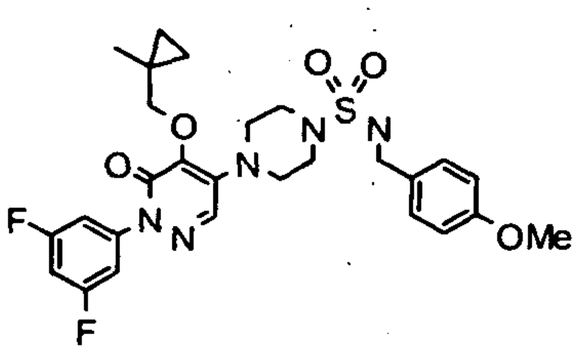
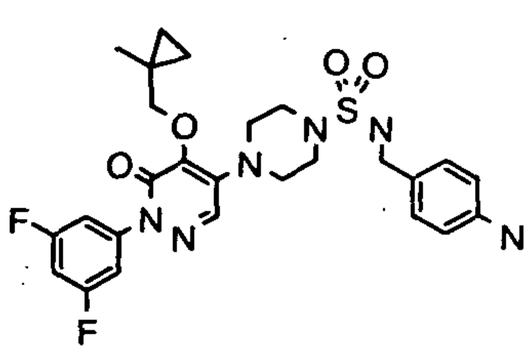
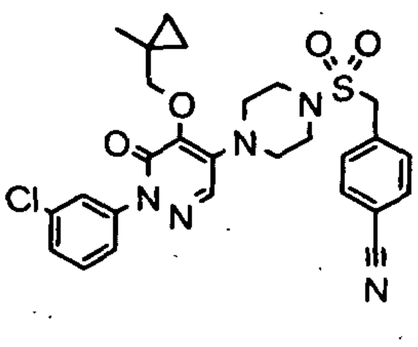
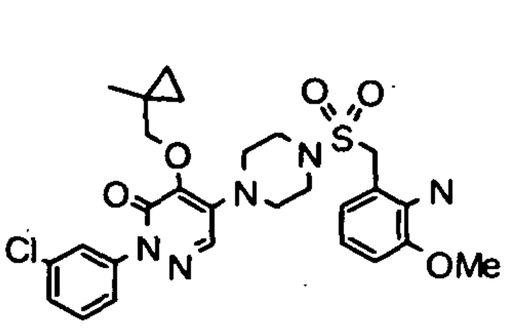
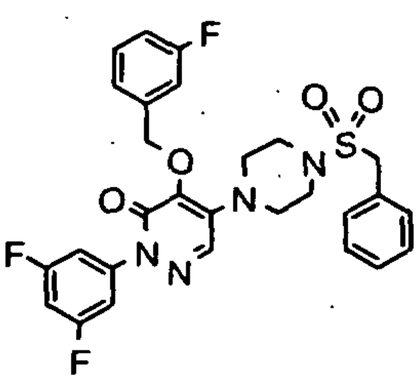
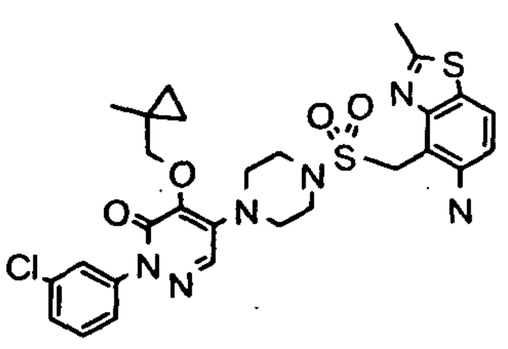
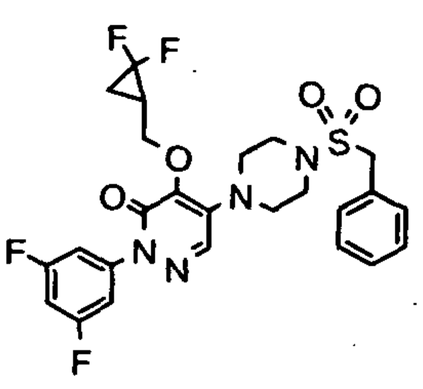
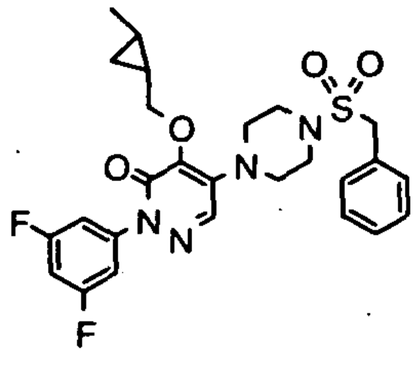
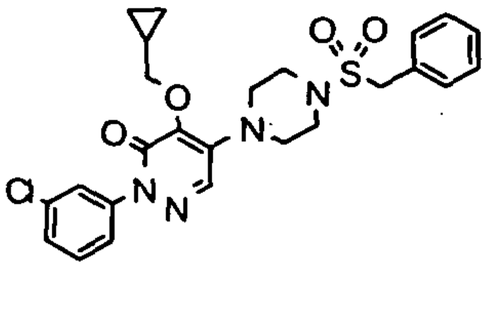
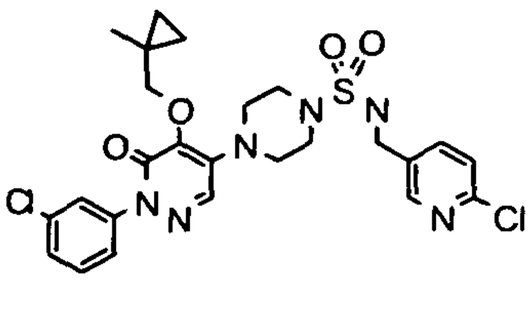
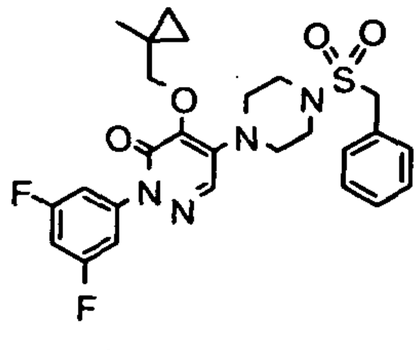
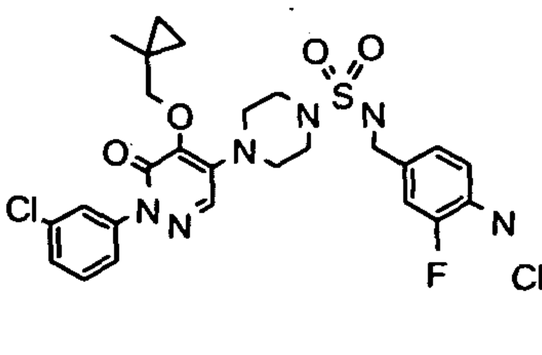
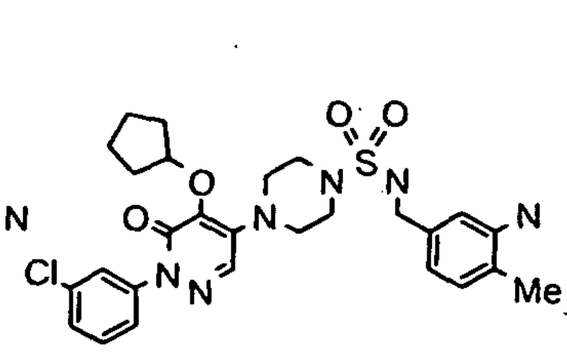
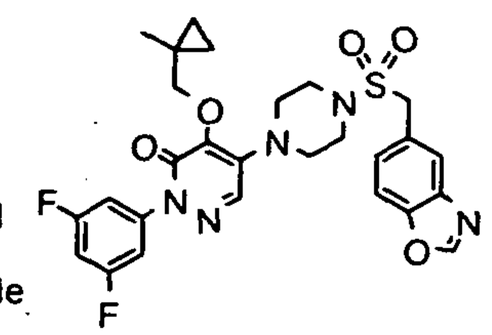
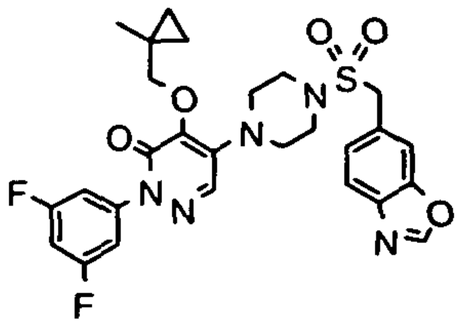
In each of Formulas I, A, B, C, D, E, F, G, H, J, K and L, R^3 is preferably optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroaryl alkyl. R^3 is more preferablyoptionally substituted phenyl, with the preferred optional substituents being 1 or 2 haolgens.

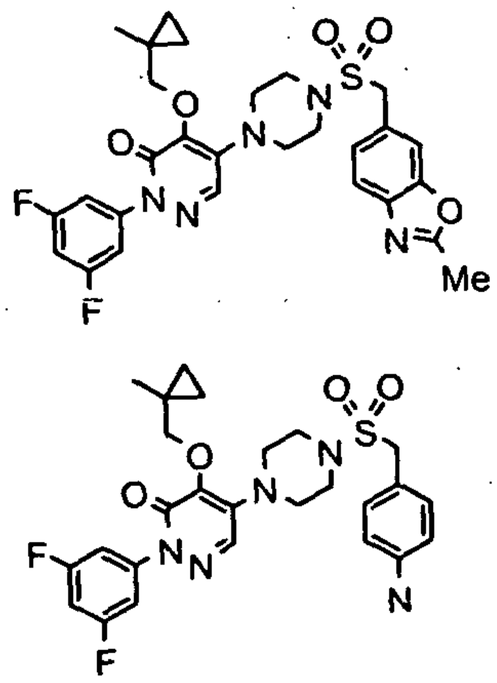
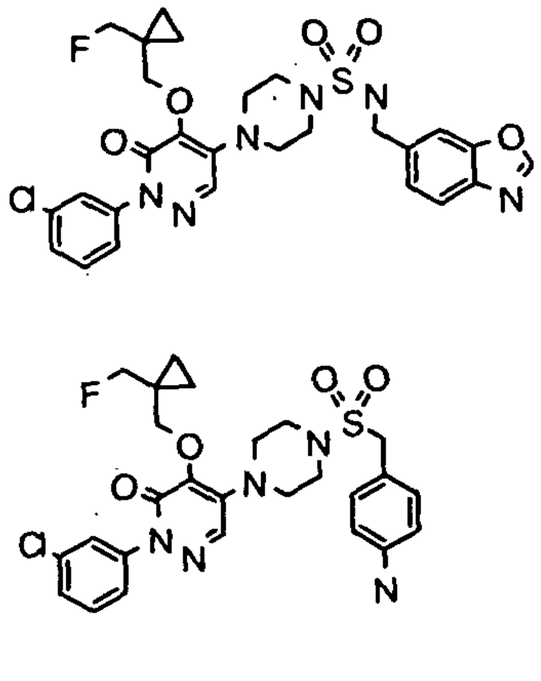
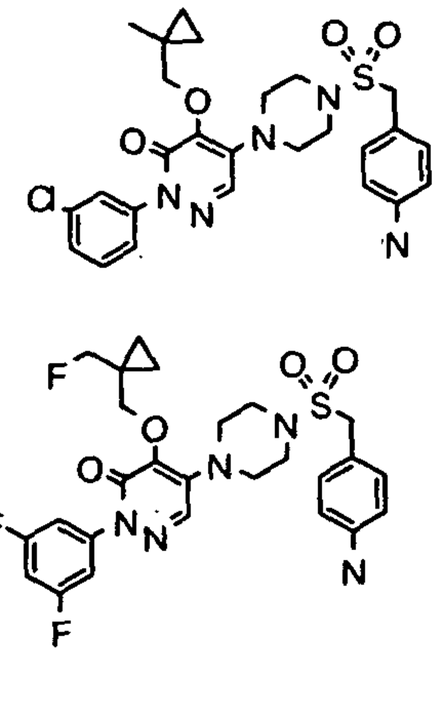
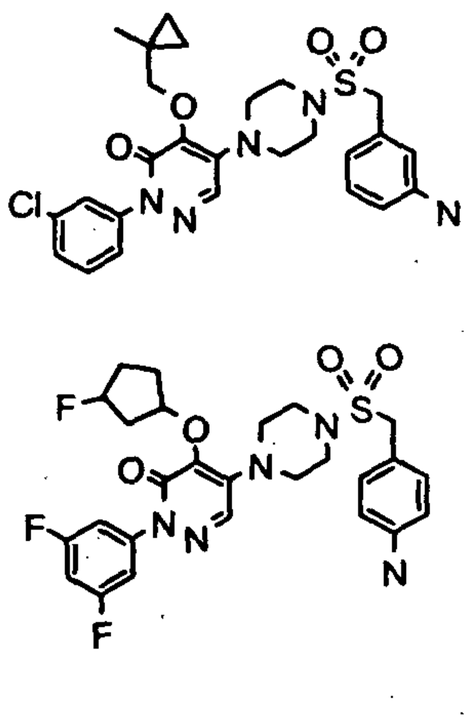
In each of Formulas I, A, B, C, D, E, F, G, H, J, K and L, when the R^4 group has a substituent that includes an R^9 group, R^9 is preferably H, alkyl, aryl or arylalkyl, more preferably H, alkyl, phenyl or benzyl.

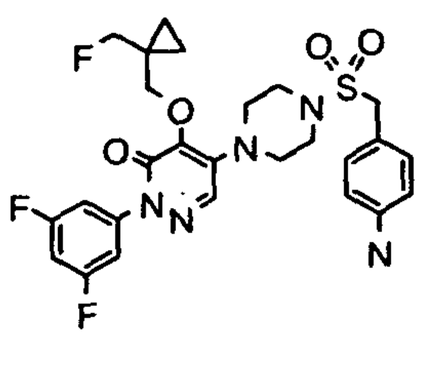
In each of Formulas I, A, B, C, D, E, F, G, H, J, K and L, R^6 is preferably H, alkyl or optionally substituted alkyl (e.g., -alkyl-OR^9) . When the R^6 group has a substituent that includes an R^9 group, R^9 is preferably H, alkyl, aryl or arylalkyl, more preferably H, alkyl, phenyl or benzyl.

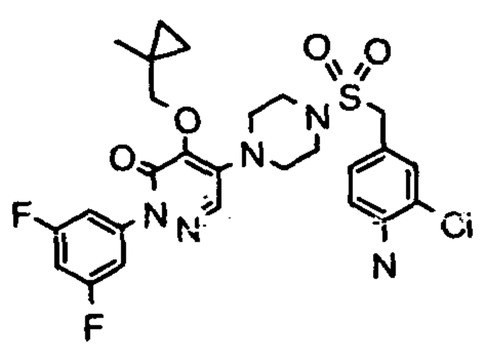
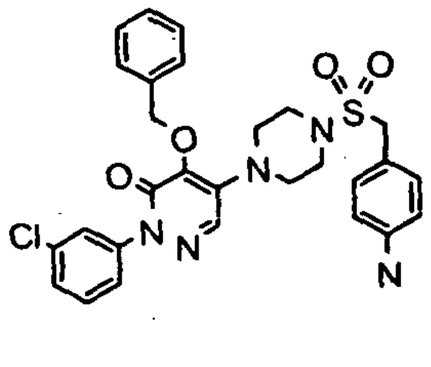
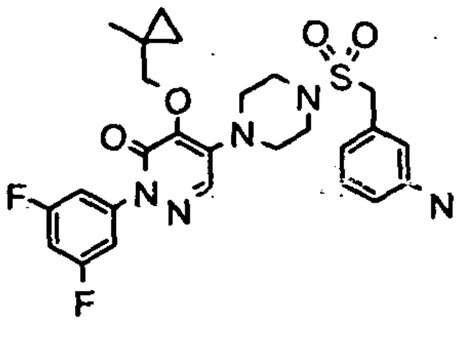
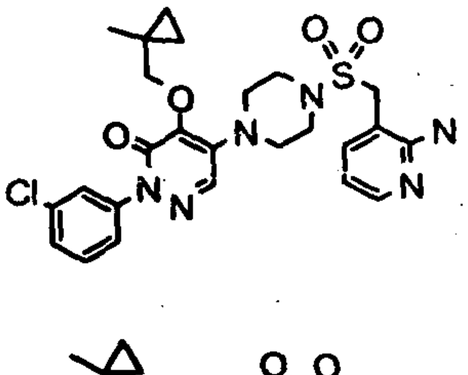
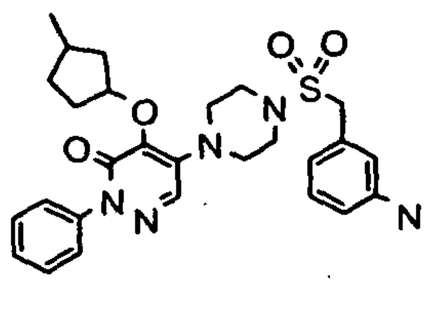
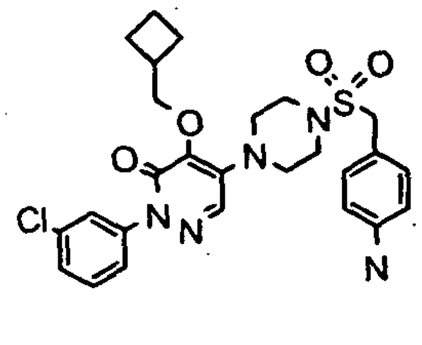
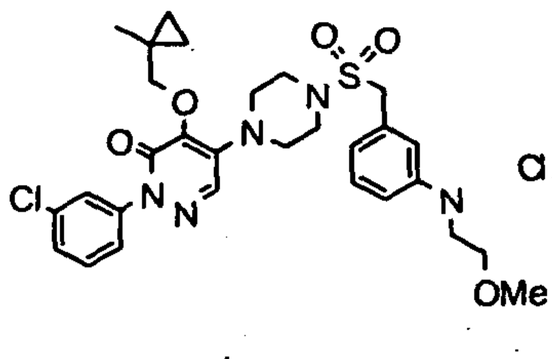
In each of Formulas I, A, B, C, D, E, F, G, H and J, R^8 is preferably H or alkyl. When the R^8 group has a substituent that includes an R^9 group, R^9 is preferably H, alkyl, aryl or arylalkyl, more preferably H, alkyl, phenyl or benzyl.

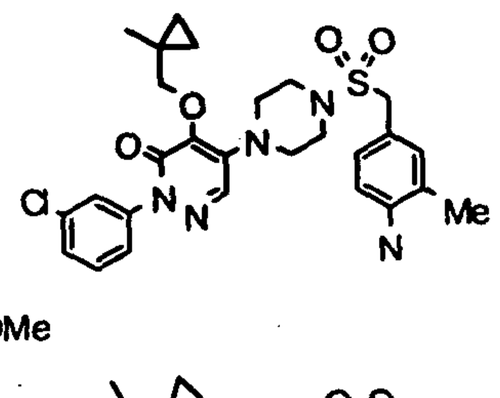
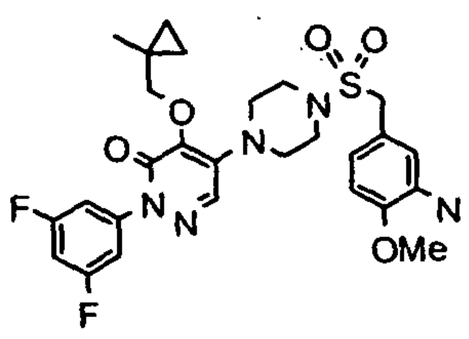
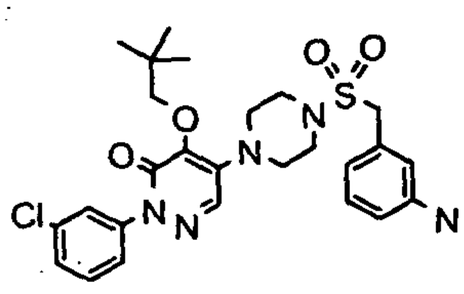
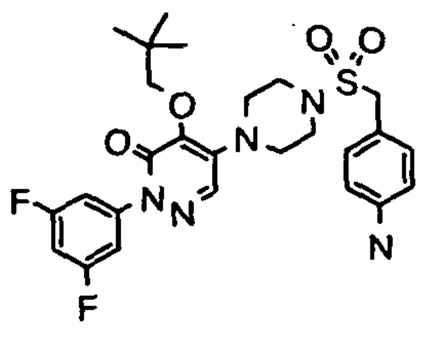
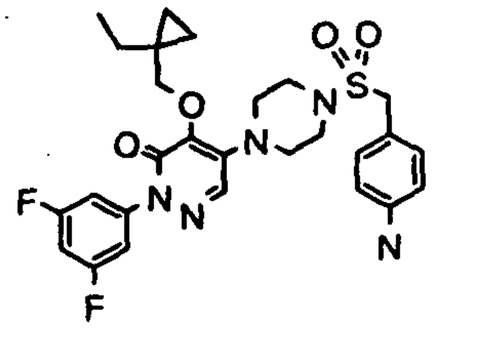
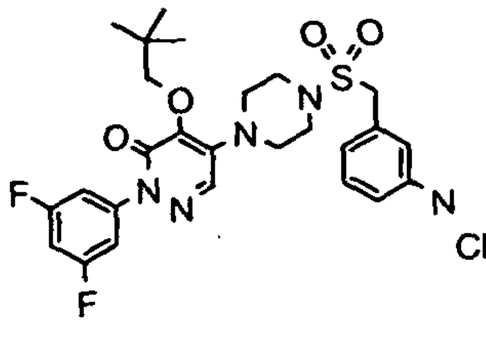
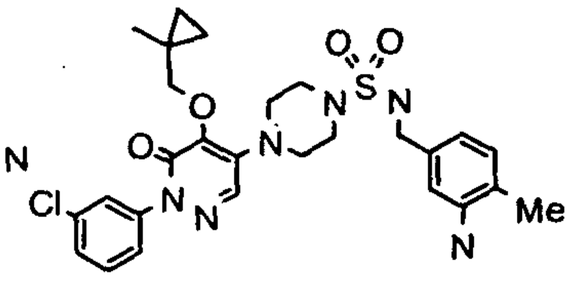
Preferred compounds of Formula I include:

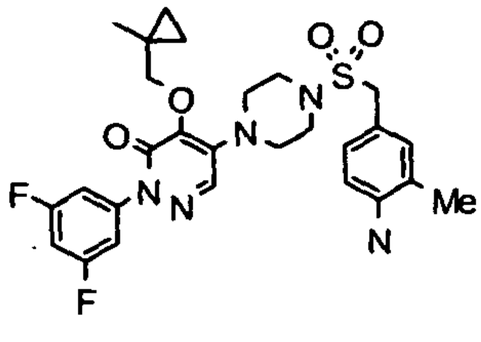
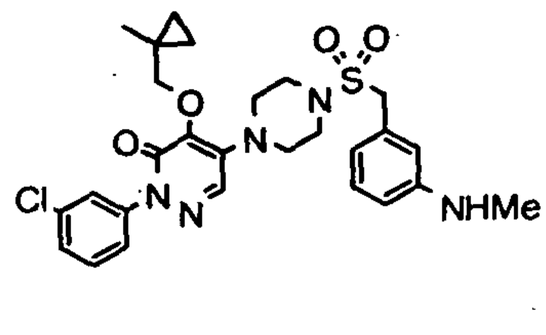





























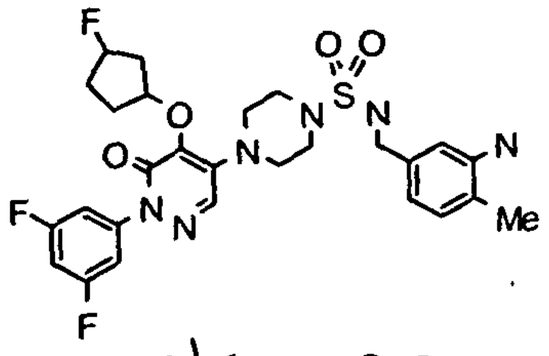
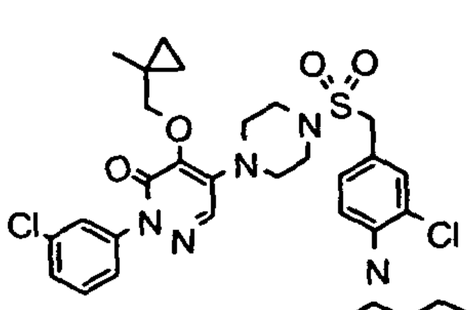
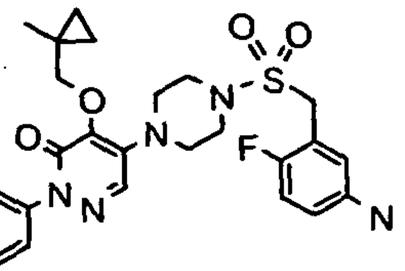
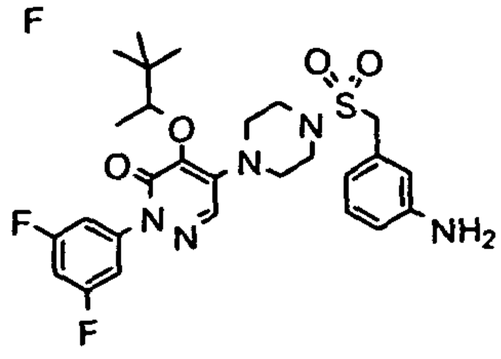





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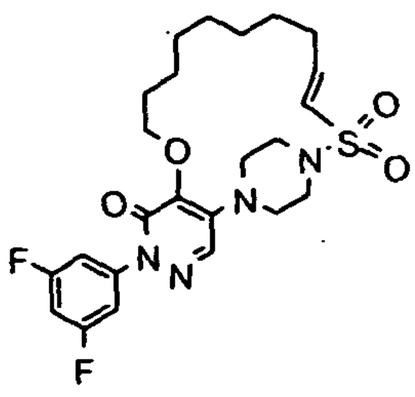
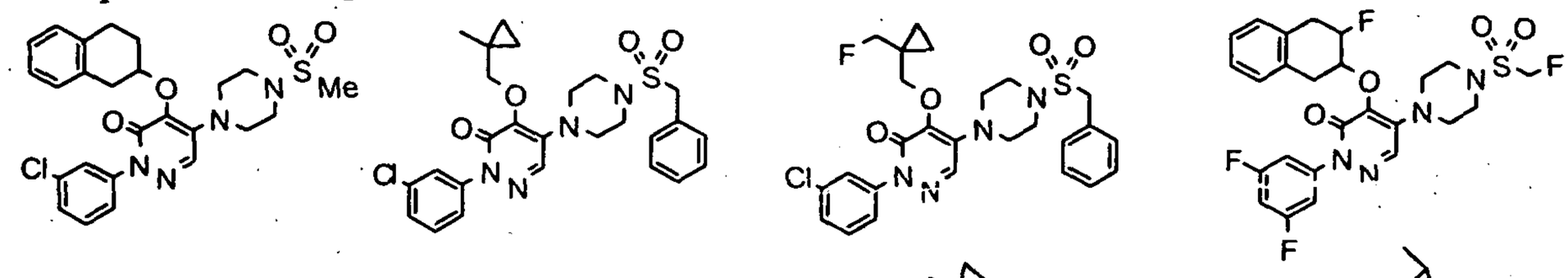


More preferred compounds of Formula I include:



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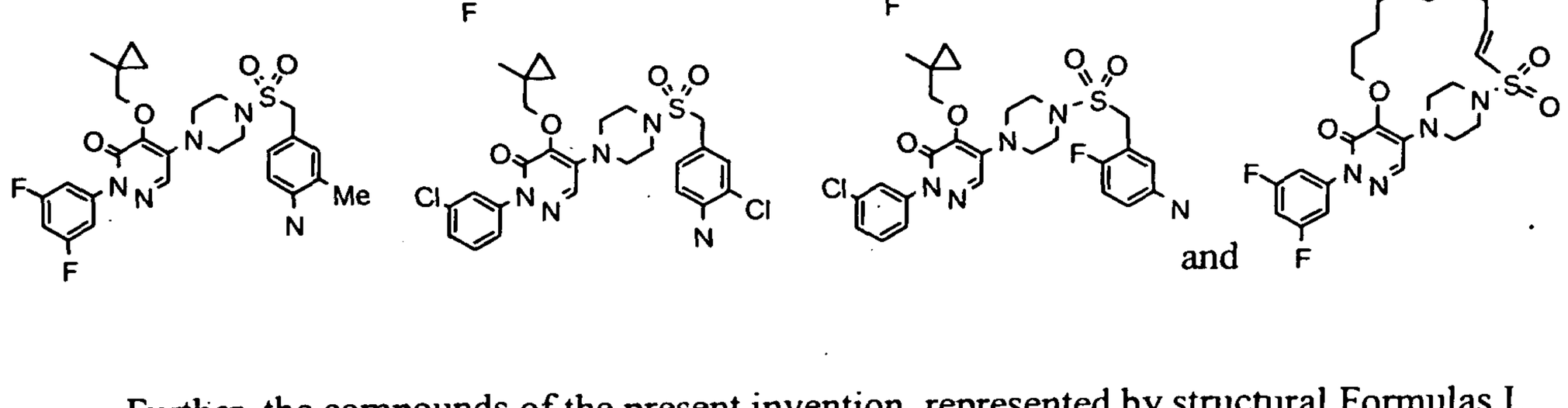


Further, the compounds of the present invention, represented by structural Formulas I, A, B, C, D, E, F, G, H, J, K and L are inhibitors of glucan synthase and therefore are useful in the treatment or prevention of fungal infections caused by pathogens such as *Candida,*

Cryptococcus, Pichia, Rhodotorula, Saccharomyces, Trichosporon, Absidia, Apophysomyces, Aspergillus, Bjerkandera, Blastomyces, Coccidioides, Cunninghamella, Exophiala, Fusarium, Histoplasma, Microsporum, Mucor, Paecilomyces, Penicillium, Pseudallescheria, Ramichloridium, Rhizomucor, Rhizopus, Saksenaea, Scedosporium, Sporothrix, Trichophyton, Wangiella, Alternaria, Aphanomyces, Ascophyta, Biploaris, Botrytis, Cercospora, Claviceps, Cochlioobolus, Colletotrichum, Erysiphe, Gibberella, Glomerella, Gomyces, Guignardia, Helminthosporium, Leptosphaeria, Magnaporthe, Microdochium, Monolinia, Mycosphaerella, Nectria, Penicillium, Plasmopara, Podosphaera, Puccinia, Pyrenophora, Pyricularia, Pythium, Phytophthora, Rhizoctonia, Sclerotina, Sclerotium, Septoria, Sphaerotheca, Thielaviopsis, Tilletia, Uncinula, Urocystis, Ustilago, Venturia, Verticillium, Microsporum, Malassezia, Paracoccidioides, Trichosporon, Aureobasidium, Etserophilum, and Geotrichum.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkoxyalkoxy, alkylthio, amine, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are

attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryi, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Amine" is a type of functional group that contains a nitrogen as the key atom. Structurally it resembles ammonia, wherein one or more hydrogen atoms are replaced by organic substituents such as alkyl, cycloalkyl, aryl or any of the other organic substituents defined herein. "Amino" is the amine, as defined above, as a functional group or substituent.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or

sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl, carbazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. Arylalkenyl an aryl-alkenyl group in which the aryl and alkenyl are as previously described. The bond to the parent moiety is through the alkyl or alkenyl respectively.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"Cycloalkylalkenyl" means a cycloalkyl moiety as defined above linked via an alkenyl moiety (defined above) to a parent core.

"Cycloalkenyl" or "cyclenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

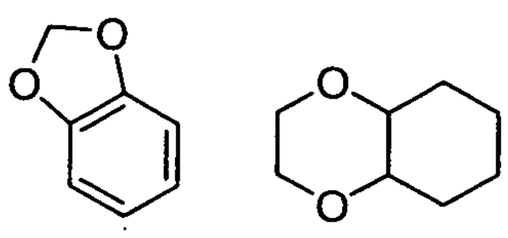
"Cycloalkenylalkyl" or "cyclenylalkyl" means a cycloalkenyl or cyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Cycloalkenylalkenyl" or "cyclenylalkenyl" means a cycloalkenyl or cyclenyl moiety as defined above linked via an alkenyl moiety (defined above) to a parent core.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, trihaloalkoxy, aryloxy, aralkoxy, alkoxyalkoxy, acyl, aroyl, halo, monohaloalkyl, dihaloalkyl, trihaloalkyl, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, $-NY_1Y_2$, $-aklkyl-NY_1Y_2$, $-C(O)NY_1Y_2$ and $-SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the

group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example: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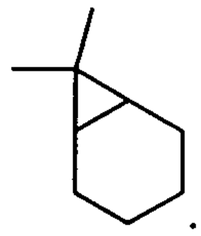


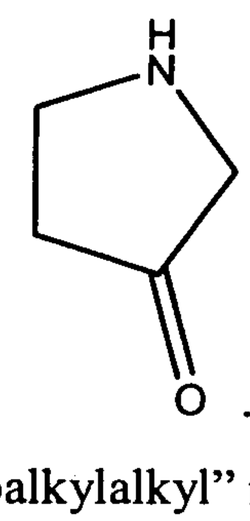
"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein one or more of the chain atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For example, alkoxy (i.e., --O-alkyl or --O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, aryloxy, heteroaryloxy, acyloxy, carboxy, monocyclic aryl, heteroaryl, cycloalkyl, heterocyclyl, spirocycle, amine, acylamino, amido, keto, thioketo, cyano, or any combination thereof.

"Heterocyclyl" or "Heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon; for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root

name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

"Heterocyclyl" may also mean heterocyclyl ring wherein a single moiety (e.g., carbonyl) simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:

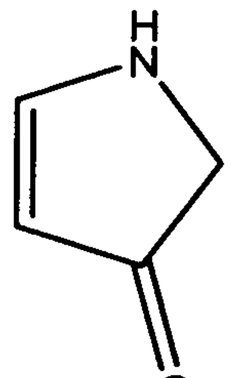


"Heterocyclylalkyl" or "Heterocycloalkylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclylalkenyl" or "Heterocycloalkylalkenyl" means a heterocyclyl moiety as defined above linked via an alkenyl moiety (defined above) to a parent core.

"Heterocyclenyl" or "Heterocycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 15 ring atoms, preferably about 5 to about 14 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 13 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring

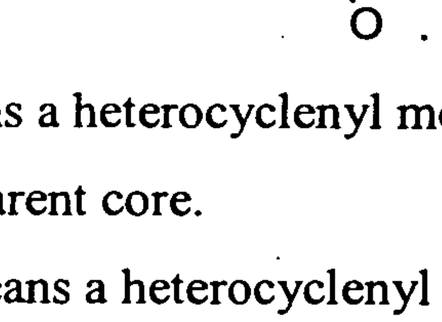
system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" may also mean a heterocyclenyl ring wherein a single moiety (e.g., carbonyl) simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:



"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

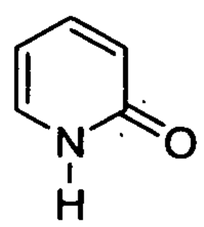
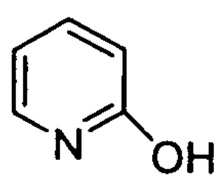
"Heterocyclenylalkenyl" means a heterocyclenyl moiety as defined above linked via an alkenyl moiety (defined above) to a parent core.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:


and


are considered equivalent in certain embodiments of this invention.

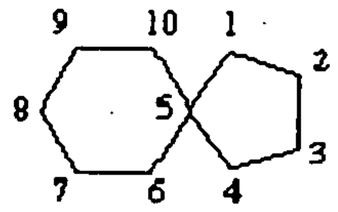
"Heterocyclenylalkenyl" means a heterocyclenyl moiety as defined above linked via an alkenyl moiety (defined above) to a parent core.

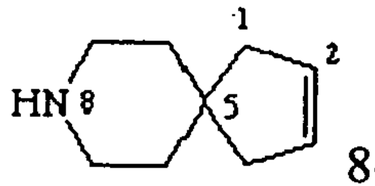
"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For example, alkoxy (i.e., --O-alkyl or --O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, aryloxy, heteroaryloxy, acyloxy, carboxy, monocyclic aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amine, acylamine, amido, keto, thioketo, cyano, or any combination thereof.

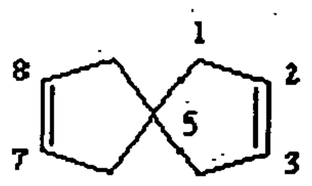
"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Spiro ring systems" have two or more rings linked by one common atom. Preferred spiro ring systems include spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spirocycloalkyl, spirocyclenyl, and spiroaryl. Non-limiting examples of suitable spiro ring systems include 

spiro[4.5]decane, 

8-azaspiro[4.5]dec-2-ene, and 

spiro[4.4]nona-2,7-diene.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen. An alkoxy linked directly to another alkoxy is an "alkoxyalkoxy".

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" or "thioalkoxy" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

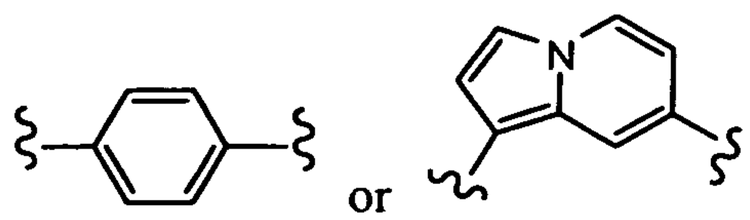
"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

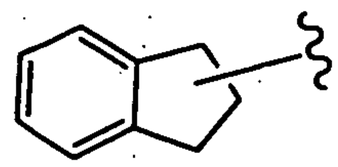
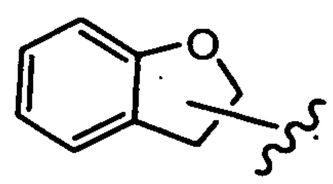
"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The terms "arylene" and heteroarylene" mean divalent aryl and heteroaryl groups, e.g.,



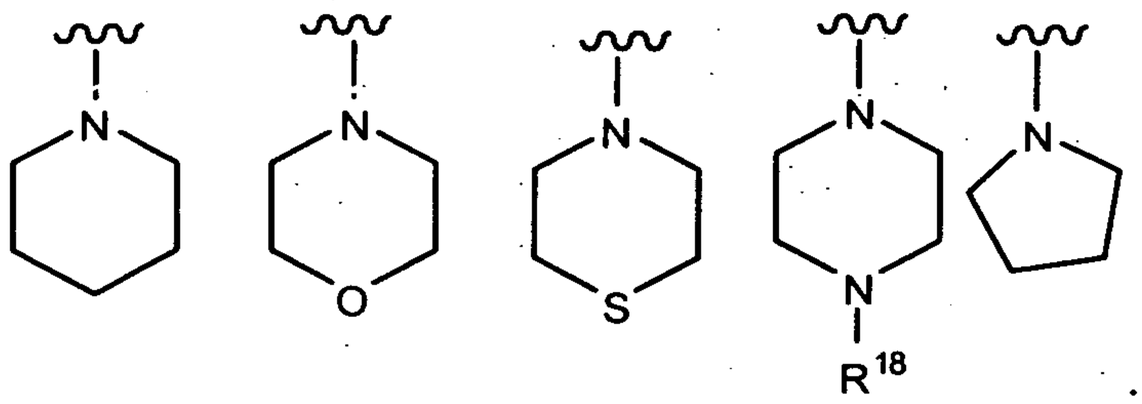
"Benzofused-cycloalkyl" and benzofused-heterocycloalkyl" mean that a benzene ring is fused to two adjacent carbon atoms of a cycloalkyl or heterocycloalkyl ring. The group is joind to the rest of the molecule through a carbon atom in the cycloalkyl or heterocycloalkyl ring. Both the aromatic and saturated ring moieties are optionally substituted by suitable ring system substituents as defined above. Examples of benzofused-cycloalkyl and benzofused-heterocycloalkyl groups are

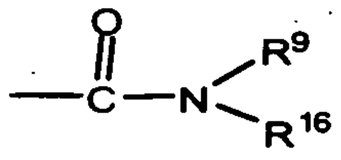
 and  .

In the terms above, "oxyl" means the same as "oxy", i.e., alkoxyl and alkoxy both refer to an alkyl-O- group.

In the terms above, where a nitrogen atom appears in a chain of atoms and a substituent on the third bond to the nitrogen is not identified, the third bond is understood to be hydrogen, e.g., -alkyl-N-alkyl- is –alkyl-NH-alkyl.

In the terms above, when two R^9 groups on a N form a ring, non-limiting examples of such rings are



In the terms above, when an nitrogen-containing radical is written as, for example,. –$CONR^9R^{16}$, the two "R" groups are each attached to the nitrogen, i.e.,  .

In the definitions above, notably in the "R" groups, where no hyphen is present to indicate the point of attachment and the term is not otherwise defined, the radical is attached to the rest of the molecule through the group on the right side of the term, e.g., "alkylalkenyl" is "alkylalkenyl-".

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The terms "one or more" and "at least one", when referring to the number of substituents on a group (e.g., alkyl, aryl or heteroaryl) means 1 to 6 substituents, preferably 1 to 3 substituents, unless otherwise specified.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formulas I, A, B, C, D, E, F, G, H, J, K and L, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is

transformed *in vivo* to yield a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula I, Formula A, Formula B, Formula C, Formula D, Formula E, Formula F, Formula G, Formula H, Formula J, Formula K or Formula L or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminemethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amine)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamine(C_2-C_3)alkyl (such as β-dimethylamineethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula I, Formula A, Formula B, Formula C, Formula D, Formula E, Formula F, Formula G, Formula H, Formula J, Formula K or Formula L contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula I, Formula A, Formula B, Formula C, Formula D, Formula E, Formula F, Formula G, Formula H, Formula J, Formula K or Formula L incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L can form salts which are also within the scope of this invention. Reference to a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formulas I, A, B, C, D, E, F, G, H, J, K and L may be formed, for example, by reacting a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L

incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formulas I, A, B, C, D, E, F, G, H, J, K and L incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.) Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is

intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L can generally be prepared by following procedures Analogsous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L and of the salts, solvates, esters and prodrugs of the compounds of Formulas I, A, B, C, D, E, F, G, H, J, K and L are intended to be included in the present invention.

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels- refer to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powders for constitution refer to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing

friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d,l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

The compounds listed above are inhibitors of glucan synthase and therefore are useful in the treatment or prevention of fungal infections caused by pathogens such as *Absidia corymbifera*; *Absidia spp*; *Acremonium spp*; *Ajellomyces capsulatus*; *Ajellomyces dermatitidis*; *Alternaria spp*; *Aphanoascus fulvescens*; *Apophysomyces spp*; *Arthroderma benhamiae*; *Arthroderma fulvum*; *Arthroderma gypseum*; *Arthroderma incurvatum*; *Arthroderma otae*; *Arthroderma vanbreuseghemii*; *Aspergillus flavus*; *Aspergillus fumigatus*; *Aspergillus glaucus*; *Aspergillus nidulans*; *Aspergillus niger*; *Aspergillus oryzae*; *Aspergillus*

spp; *Aspergillus sydowi*; *Aspergillus terreus*; *Aspergillus ustus*; *Aspergillus versicolor*; *Aureobasidium pullulans*; *Basidiomycetes*; *Beauveria spp*; *Bipolaris hawaiiensis*; *Bipolaris spicifera*; *Bipolaris spp*; *Bjerkandera adusta*; *Blastomyces dermatitidis*; *Blastoschizomyces capitatus*; *Candida albicans*; *Candida beigelii*; *Candida colliculosa*; *Candida dubliniensis*; *Candida dubliniensis*; *Candida famata*; *Candida glabrata*; *Candida guilliermondii*; *Candida haemulonii*; *Candida holmii*; *Candida inconspicua*; *Candida intermedia*; *Candida keyfyr*; *Candida krusei*; *Candida lambica*; *Candida lipolytica*; *Candida lusitaniae*; *Candida maris*; *Candida melibiosica*; *Candida norvegensis*; *Candida parapsilosis*; *Candida pelliculosa*; *Candida pseudotropicalis*; *Candida pulcherrima*; *Candida rugosa*; *Candida sake*; *Candida sphaerica*; *Candida spp*; *Candida stellatoidea*; *Candida tropicalis*; *Candida viswanathii*; *Candida zeylanoides*; *Chrysosporium spp*; *Cladophialophora bantiana*; *Cladophialophora carrionii*; *Cladosporium spp*; *Coccidioides immitis*; *Cokeromyces recurvatus*; *Coprinus spp*; *Cryptococcus albidus*; *Cryptococcus gattii*; *Cryptococcus laurentii*; *Cryptococcus neoformans*; *Cunninghamella bertholletiae*; *Cunninghamella spp*; *Curvularia lunata*; *Curvularia spp*; *Dekkera bruxellensis*; *Epidermophyton floccosum*; *Exophiala dermatitidis*; *Exophiala jeanselmei*; *Exophiala moniliae*; *Exserohilum rostratum*; *Filobasidiella neoformans*; *Fonsecaea pedrosoi*; *Fusarium dimerum*; *Fusarium moniliforme*; *Fusarium oxysporum*; *Fusarium proliferatum*; *Fusarium solani*; *Fusarium spp*; *Geotrichum candidum*; *Geotrichum spp*; *Histoplasma capsulatum*; *Hortaea werneckii*; *Issatschenkia orientalis*; *Kluveromyces lactis*; *Kluyveromyces marxianus*; *Madurella grisae*; *Malassezia furfur*; *Malassezia globosa*; *Malassezia obtusa*; *Malassezia pachydermatis*; *Malassezia restricta*; *Malassezia slooffiae*; *Malassezia sympodialis*; *Metarrhizium anisopliae*; *Microsporum audouinii*; *Microsporum canis*; *Microsporum fulvum*; *Microsporum gypseum*; *Microsporum persicolor*; *Mucor circinelloides*; *Mucor hiemalis*; *Mucor racemosus*; *Mucor rouxii*; *Mucor spp*; *Nattrassia mangiferae*; *Nectria haematococca*; *Onychocola canadensis*; *Paecilomyces lilacinus*; *Paecilomyces spp*; *Paecilomyces variotii*; *Paracoccidioides brasiliensis*; *Penicillium marneffei*; *Penicillium spp*; *Phialophora spp*; *Phialophora verrucosa*; *Phoma spp*; *Pichia anomala*; *Pichia etchellsii*; *Pichia guilliermondii*; *Pichia ohmeri*; *Pithomyces spp*; *Pneumocystis carinii*; *Pseudallescheria boydii*; *Ramichloridium obovoideum*; *Rhizomucor miehei*; *Rhizomucor pusillus*; *Rhizomucor spp*; *Rhizopus arrhizus*; *Rhizopus microsporus*; *Rhizopus oryzae*; *Rhizopus schipperae*; *Rhizopus spp*; *Rhodotorula mucilaginosa*; *Rhodotorula rubra*; *Rhodotorula spp*; *Saccharomyces cerevisiae*;

Saccharomyces spp; *Sagrahamala spp*; *Saksenaea vasiformis*; *Scedosporium apiospermum*; *Scedosporium prolificans*; *Schizophyllum commune*; *Schizosaccharomyces pombe*; *Scopulariopsis brevicaulis*; *Scytalidium dimidiatum Ulocladium spp*; *Sporobolomyces spp*; *Sporothrix schenckii*; *Trichoderma spp*; *Trichophyton krajdenii*; *Trichophyton mentagrophytes*; *Trichophyton raubitschekii*; *Trichophyton rubrum*; *Trichophyton soudanense*; *Trichophyton spp*; *Trichophyton terrestre*; *Trichophyton tonsurans*; *Trichophyton verrucosum*; *Trichophyton violaceum*; *Trichosporon asahii*; *Trichosporon beigelii*; *Trichosporon capitatum*; *Trichosporon cutaneum*; *Trichosporon inkin*; *Trichosporon mucoides*; *Trichosporon spp*; *Tritirachium spp*; *Wangiella dermatitidis* and *Yarrowia lipolytica*

For pharmaceutical use, treatment of yeasts (e.g., *Candida, Cryptococcus, Pichia, Rhodotorula, Saccharomyces*, and *Trichosporon*) or moulds (e.g., *Absidia, Alternaria, Apophysomyces, Aspergillus, Bjerkandera, Blastomyces, Coccidioides, Cunninghamella, Exophiala, Fusarium, Histoplasma, Microsporum, Mucor, Paecilomyces, Penicillium, Pseudallescheria, Ramichloridium, Rhizomucor, Rhizopus, Saksenaea, Scedosporium, Sporothrix, Trichophyton* and *Wangiella*) are preferred.

As used herein, the terms "treat" or "treating" mean eliminating the fungal infection, reducing the fungal burden, or stopping the progression of fungal growth.

The terms "prevent" or "preventing", as used herein, mean administering at least one compound listed above before exposure to a potential fungal pathogen. For example at least one compound listed above can be administered to an animal before organ transplant surgery, a procedure known to frequently result in fungal infections, or an animal known to be susceptible to fungal infections can be treated in advance of likely exposure. In the case of fungal plant pathogens, at least one compound listed above can be applied to a plant regularly throughout the growing season, before a potential pathogen can cause any harm to the plant.

When used to treat plant pathogens, at least one compound listed above can be applied to the leaves and stems of the plant using a method well known in the art, for example as a topical spray (e.g., an aqueous solution) or powder, or as a solution or powder added to the soil to allow systemic absorption. Topical application to plants is preferred. Similarly, when applied to the surfaces of inanimate objects to reduce or eliminate fungal growth, at least one compound listed above can be applied as a solution, a spray or a powder.

As indicated above, it is contemplated that more than one compound as listed above can be administered to treat fungal infections. When used herein, the terms "at least one" or "one or more" preferably mean one to three compounds, but more preferably one compound listed above is administered. When administered in combination with another antifungal agent, preferably one compound listed above and one other antifungal agent are administered.

Other antifungal agents for use in combination are: for example azoles (e.g. fluconazole, miconazole, itraconazole, voriconazole, posaconazole), echinocandins (e.g. caspofungin, micafungin, anidulafungin), polyenes (e.g. amphotericin B, including liposomal formulations of amphotericin B, and nystatin), allylamines (e.g. terbinafine), thiocarbamates (e.g. tolnaftate), nikkomycins, pradimicins, 5-fluorocytosines, oxaboroles, ciclopiroxolamine, griseofulvin and morpholines (e.g., fenpropimorph).

As used herein, "animal" means a mammalian or non-mammalian (e.g., birds, fish, crustaceans, reptiles) species, preferably a mammal and more preferably a human. As used herein, "patient" refers to an animal, more preferably a human.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:

It should also be noted that any carbon or heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any Tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual

dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

EXPERIMENTAL PROCEDURES

Compounds useful in the method of the invention will show utility as antifungal agents in the following assays.

β(1,3) GLUCAN SYNTHASE ASSAY:

1. Preparation of permeabilized *Saccharomyces cerevisiae* cells.

Permeabilization of yeast cells was performed according to Crotti *et al.* (Analytical Biochemistry, 292, 8-16, 2001) with some modifications. A 10 ml-starter culture of the *S. cerevisiae* strain in YPD medium (1% yeast extract, 2% bacto-peptone, 2% dextrose) with OD_{600}=3-4 was used to inoculate 1 liter of YPD. The culture was grown at 30°C until OD_{600}=0.8. Cells were collected by centrifugation (5,300 g for 15 min at 4°C) and resuspended in buffer (40 mM EDTA, 100 mM β-mercaptoethanol) at 1 g of cell pellet/3.5 ml buffer. The cell suspension was shaken for 30 min at 30°C, followed by centrifugation at 12,000 g for 10 min at 4°C. The cell pellet was washed with 5 ml 0.8 M sorbitol and resuspended in 6.8 ml of 2.9 mM citric acid, 11.3 mM dibasic sodium phosphate, 1 mM EDTA, 0.8 M sorbitol, with constant shaking at 30°C for 30 min. After centrifugation at 12,000 g for 10 min at 4°C, the pellet was resuspended in 31.3 ml 50 mM Tris-HCl, pH 7.0, and incubated on ice for 5 min. The mixture was then centrifuged at 12,000 g for 10 min at 4 °C, and the pellet was resuspended in 1 ml of 50 mM Tris-HCl and 33% glycerol, pH 7.5. The permeabilized cell preparation was stored at –80°C in aliquots.

2. Preparation of membrane fraction of yeast cells

The protocol was modified from Douglas *et al.* (Journal of Bacteriology, 176, 5686-5696, 1994). For the preparation of *S. cerevisiae* and *C. albicans* membrane fractions, 1 liter of YPD supplemented with 0.02 mg/mL adenine and 0.08 mg/mL uracil was inoculated with 10 mL starter culture of PM503 (OD_{600}=4) or the *C. albicans* strain BWP17 (OD_{600}=12) in

the same medium and grown at 30°C until OD_{600} reached about 1. *A. fumigatus* (strain ND158) membranes were prepared by first preparing a spore suspension from agar slants by adding 6 mL of sterile saline, 0.1% Tween-20 solution to each slant, and resuspending by pipetting and scraping. The spore suspensions were used to inoculate two 200 mL flasks containing Sabouraud dextrose broth media. Cultures were incubated at 37°C, 250 rpm for ~8 hrs. All cells, *S. cerevisiae*, *C. albicans* or *A. fumigatus* were harvested by centrifugation at 5,300 g at 4°C for 40 minutes. After washing with 100 mL of breakage buffer (0.1 M KPi, pH 7.0, 1 mM EDTA, 1 mM DTT), the cell pellet was resuspended in 50 ml ice-cold breakage buffer. The mixture was transferred to a bead-beater chamber packed in ice (BioSpec Products, Bartlesville, OK). To each 50 mL sample was added 50 g of acid-washed glass beads (0.45 μM, Sigma). Cells were disrupted using 12 x 20 second pulses with 2 min-cooling intervals. Cell debris was removed by centrifugation at 3,000 g for 20 minutes at 4°C, and the supernatant was collected and centrifuged at 100,000 g for 1 hour at 4°C to pellet the membrane fraction. The pellet was resuspended in 5 mL of ice-cold breakage buffer containing 25% glycerol, homogenized with a Dounce tissue homogenizer and stored at –80°C in small aliquots.

3. Glucan synthase assay and compound screening

The assay was performed according to Mo *et al.* (Journal of Biological Chemistry, 269, 31267-31274, 1994) and Taft *et al.* (The Journal of Antibiotics, 47, 1001-1009, 1994), in a 96-well Optiplate (PerkinElmer). To each well was added 3 μL 10xcompound stock (in 100% DMSO), or 3 μL of 30 μg/mL caspofungin in 100% DMSO (as positive control), or 3 μL 100% DMSO (as negative control), followed by the addition of appropriate amount of glucan synthase sources (2 μL permeabilized PM503 cells, or 3 μL membrane preparations from either PM503, BWP17, or ND158). The reaction was initiated by adding 25 μL reaction buffer (0.6 mM UDP-Glucose, 0.6 nCi [U-^{14}C]DUP-Glucose (327 mCi/mmol, Amersham Bioscience), 20 μM GTP-γ-S, 25 mM NaF, 7.5 mg/mL BSA, 8% glycerol in 75 mM Tris-HCl, pH 7.5). The plate was incubated on a shaker for 1.5 hour at room temperature before being quenched with 250 μL 1% TCA (Trichloroacetic Acid). The quenched reaction was mixed by pipetting, and immediately transferred to a 96-well filter plate (Glass fiber B on 0.65 μm hydrophilic durapore membrane, Millipore) pre-wetted with wash buffer (5% TCA, 60 mM NaPPi). The glucan product was retained on the filter

membrane by applying vacuum to the plate using a MutiScreen Resist Vacuum Manifold (Millipore). The filter plate was further washed 4 times with 200 µL wash buffer. The plate was dried at 50°C for 30 minutes. 100 µL of Microscint-0 (PerkinElmer) was added to each well, and plate was counted in a TopCount NXT plate reader (PerkinElmer).

IC_{50} DETERMINATIONS:

Dose-response curves were plotted from inhibition data generated. IC_{50} was determined by fitting the CPM versus the Concentration of the test compound plot with the following equation (4-parameter logistic model, ID Business Solutions XL_{fit} 4.2).

MICROBROTH SUSCEPTIBILITY TESTING METHODS

Yeast susceptibility testing procedure followed the NCCLS document M27-A2 (*Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Second Edition* (ISBN 1-56238-469-4). NCCLS, 940 West Valley Road, Suite 1400 Wayne, Pennsylvania 19087-1898 USA, 2002) with the following modifications:

1. The final test volume was 100 µl and not 200 µl as stipulated.
2. For testing *Saccharomyces cerevisiae* strain PM503 YPD was used in place of RPMI 1640 broth.

Filamentous fungi susceptibility testing procedure follows the NCCLS document M38-A (*Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard* (ISBN 1-56238-470-8). NCCLS, 940 West Valley Road, Suite 1400 Wayne, Pennsylvania 19087-1898 USA, 2002) with the following modifications:

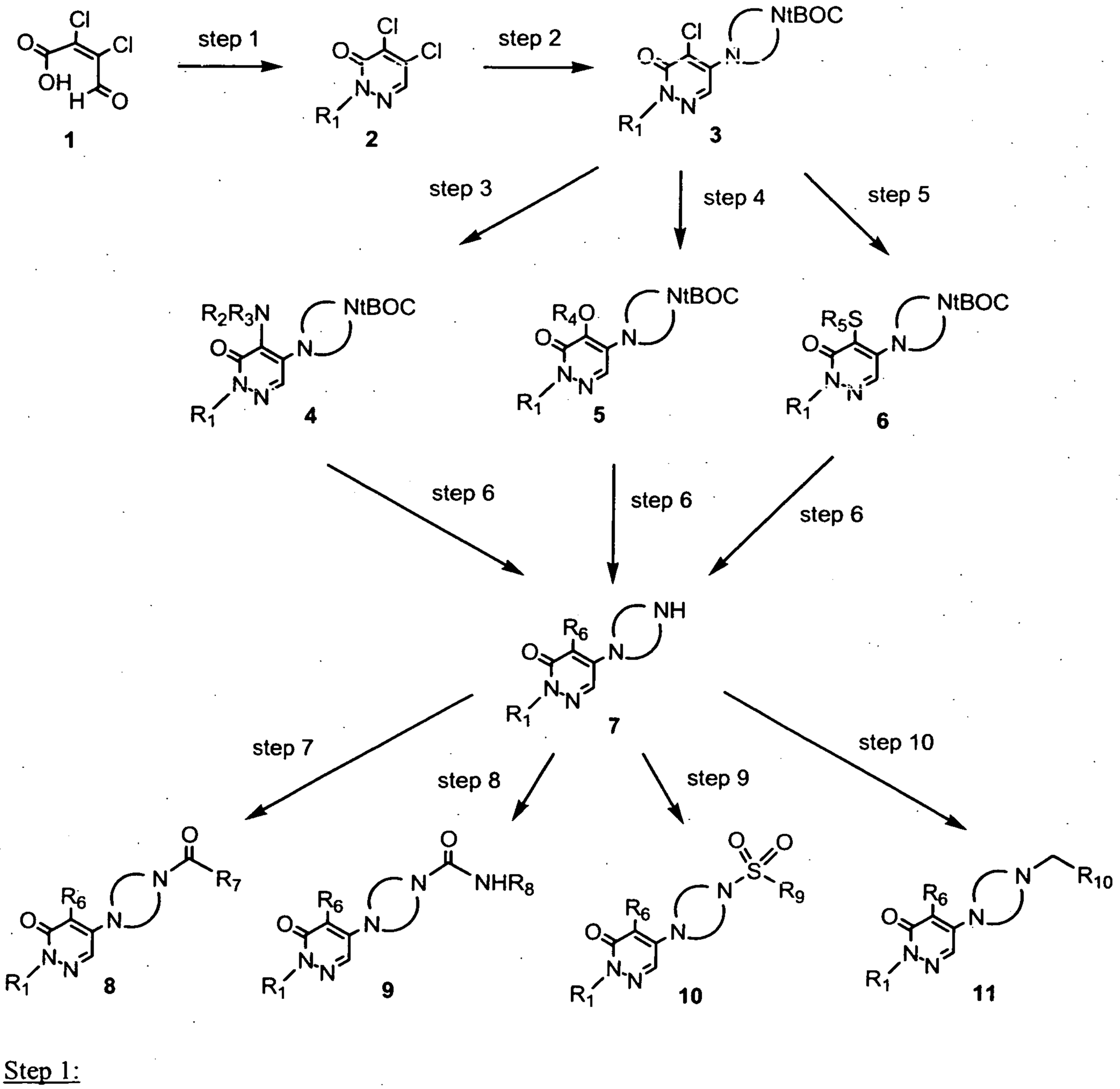
1. The final test volume was 100 µl and not 200 µl as stipulated.
2. The end point used to assess the in vitro activity of glucan synthase inhibitors may require microscopic evaluation of cell morphology in the test wells (Kurtz *et al.*, Antimicrobial Agents and Chemotherapy, 38, 1480-1489, 1994; Arikan *et al.*, Antimicrobial Agents and Chemotherapy, 45, 327-330, 2001). This endpoint, termed the minimum effective concentration (MEC), is characterized by changes in the fungal growth that resulted in truncated and highly branched hyphae.

The invention disclosed herein is exemplified by the following preparations of the inventive compounds and examples which should not be construed to limit the scope of the

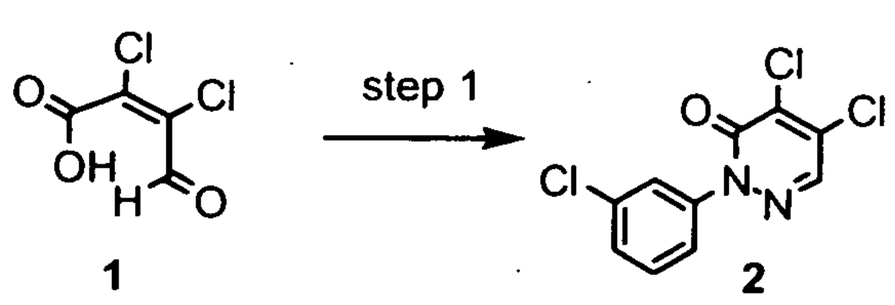
disclosure. Alternative mechanistic pathways and Analogous structures will be apparent to those skilled in the art.

SYNTHESIS

Scheme 1



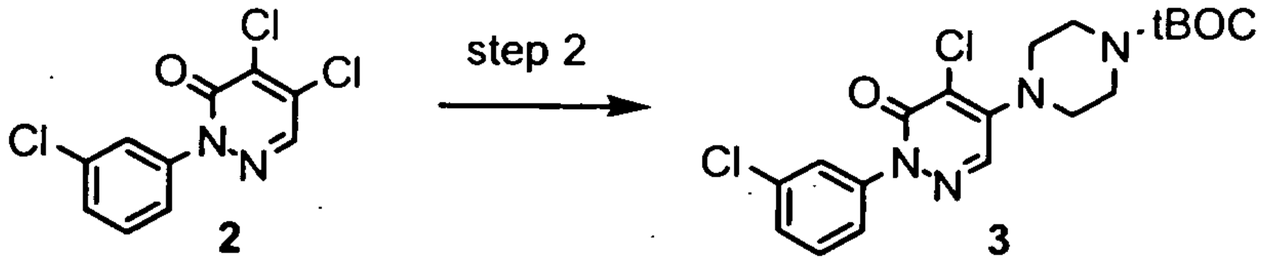
Step 1:



To a solution of sodium hydroxide (22.3 g, 0.559 mol) dissolved in water (50 mL) was added ethanol (300 mL) and 3-chlorophenylhydrazine hydrochloride (100 g, 0.559 mol). The reaction mixture was stirred at room temperature for 15 mins, and then mucochloric acid **1**

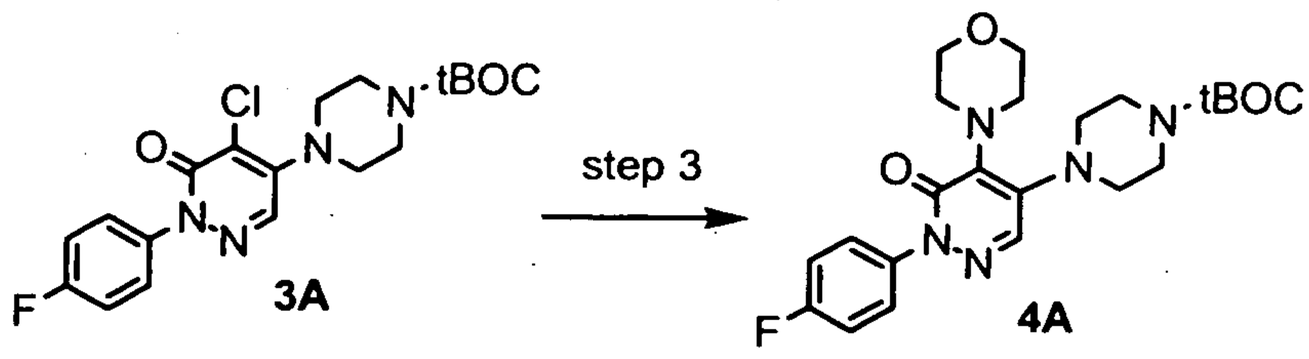
(94.4, 0.559 mol) was added. The resulting slurry was heated at 100 °C for 24 h then cooled to room temperature. Water (1500 mL) was added. The slurry was stirred and then filtered. The yellow solid was air-dried overnight to give 149.4 g (97%) of the product **2** as a yellow solid. MS (M+1): m/e 277.

Step 2:



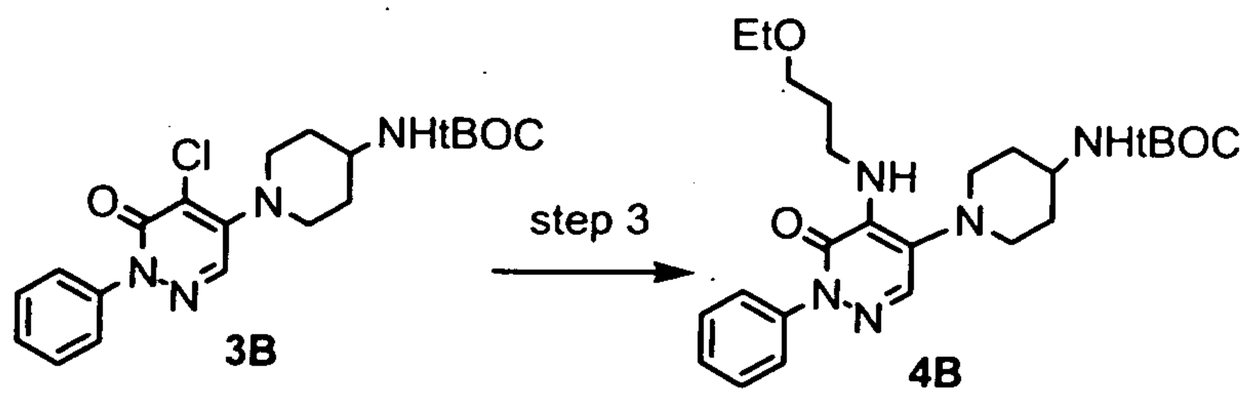
To a solution of compound **2** (50.2 g, 0.182 mol) dissolved in ethanol (300 mL) was added N-BOC-piperazine (36.3 g, 0.195 mol) and triethylamine (22.1 g, 30.5 mL, 0.218 mol). The reaction mixture was heated at reflux for 19 h and then cooled to room temperature. The solvent was evaporated, and the solid was triturated with 5% EtOH – Et_2O (800 mL). The product was filtered and air-dried to give 79.7 g (99%) of the product **3** as a beige solid. MS (M+1): m/e 425.

Step 3 (Method 1):



A solution of compound **3A** (484 mg, 1.18 mmol) and morpholine (1.04 mL, 11.9 mmol) in 5 mL toluene was heated in a sealed tube in a 138 °C oil bath for 28 h. The mixture was cooled to room temperature and filtered. The solvent was evaporated. Purification by silica gel chromatography (eluant: EtOAc - hexanes gradient) provided 60.7 mg (11% yield) of the product **4A** as a solid. MS (M+1): m/e 460.

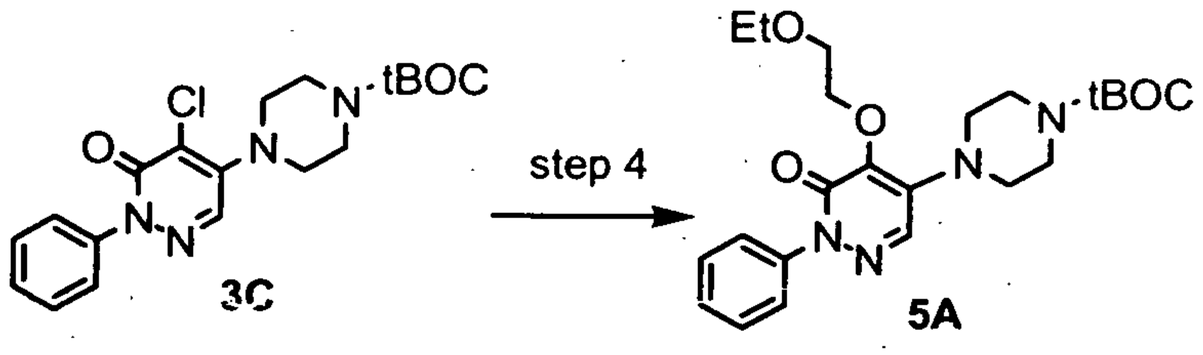
Step 3 (Method 2):



To a solution of compound **3B** (1.5 g, 3.70 mmol) dissolved in toluene (35 mL) was added 3-ethoxypropylamine (0.46 g, 4.45 mmol), potassium carbonate (2.6 g, 18.5 mmol), palladium

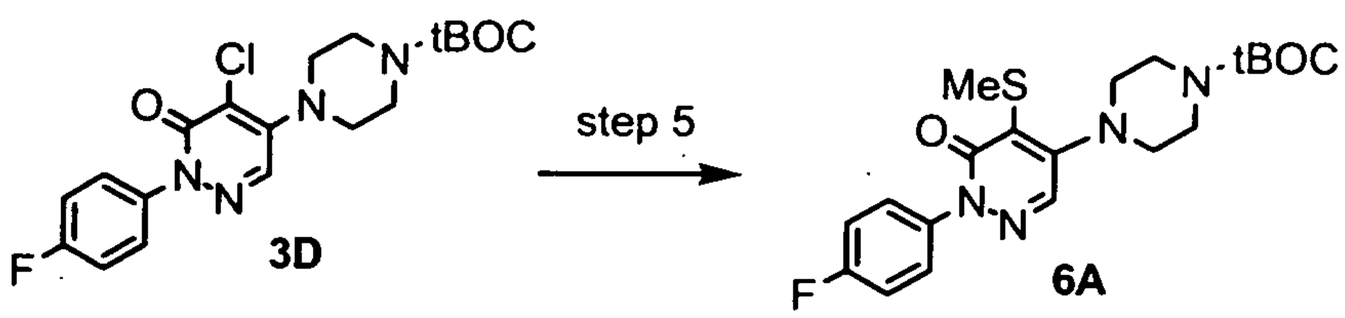
acetate (33 mg, 0.15 mmol), and racemic BINAP (93 mg, 0.15 mmol) under a nitrogen atmosphere. The reaction mixture was heated at 120 °C for 40 h then cooled to room temperature. EtOAc was added, and the organic solution was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 1 – 4% MeOH – CH_2Cl_2) gave 0.92 g (53%) of the product **4B** as a yellow foam. MS (M+1): m/e 472.

Step 4:



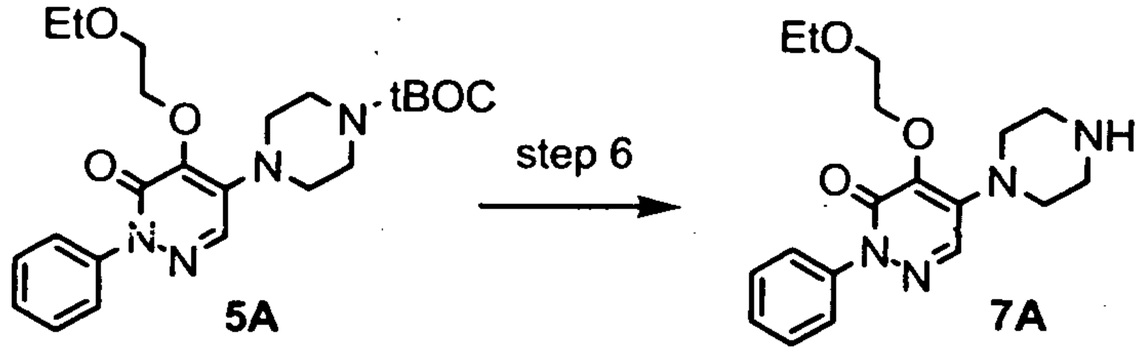
To a solution of 2-ethoxyethanol (0.24 g, 2.69 mmol) dissolved in dry THF (10 mL) under a nitrogen atmosphere was added sodium bis(trimethylsilyl)amide (1 M in THF, 2.3 mL, 2.30 mmol) via syringe. The reaction mixture was stirred at room temperature for 15 mins then compound **3C** (0.75 g, 1.92 mmol) was added in dry THF (5 mL). The resulting solution was stirred at room temperature for 16 h. The solvent was evaporated, water (30 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 15 – 40% EtOAc – CH_2Cl_2) gave 0.66 g (78%) of the product **5A** as a light yellow solid. MS (M+1): m/e 445.

Step 5:



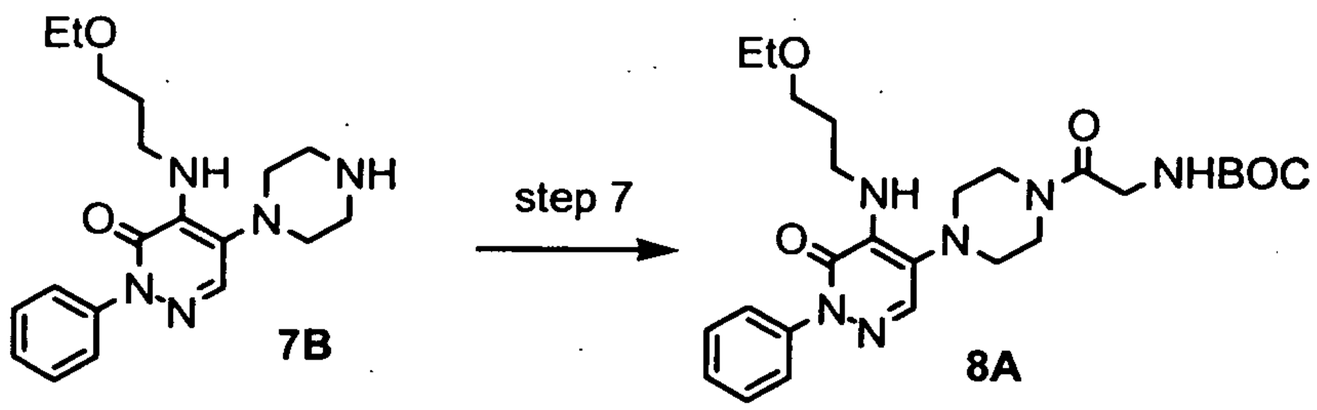
To a solution of compound **3D** (242 mg, 0.59 mmol) in methanol (3 mL) was added sodium thiomethoxide (124 mg , 1.77 mmol). The reaction mixture was stirred at reflux for 1 h. The solvent was evaporated. The residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give 248 mg (100%) of the product **6A** as an off-white solid. MS (M+1): m/e 421.

Step 6:



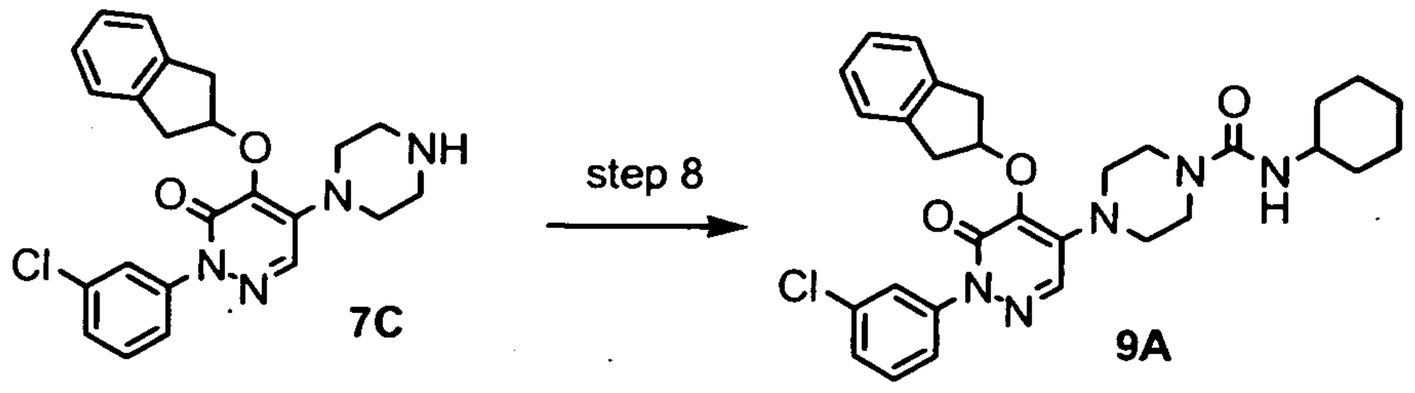
To a solution of compound **5A** (0.65 g, 1.46 mmol) dissolved in CH_2Cl_2 (10 mL) was added HCl-dioxane (4 N, 3.7 mL, 14.6 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the product was dried under high vacuum to give 0.56 g (100%) of the HCl salt of the product **7A** as a white solid. MS (M+1): m/e 345.

Step 7:



To a solution of compound **7B** (107 mg, 0.30 mmol) dissolved in 1:1 DMF:CH_2Cl_2 (10 mL) was added Hunig's base (116 mg, 0.16 mL, 0.90 mmol), HATU (171 mg, 0.45 mmol), and BOC-glycine (58 mg, 0.33 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated. Water was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 10 – 25% EtOAc – CH_2Cl_2 gradient) gave 125 mg (83%) of the product **8A**. MS (M+1): m/e 515.

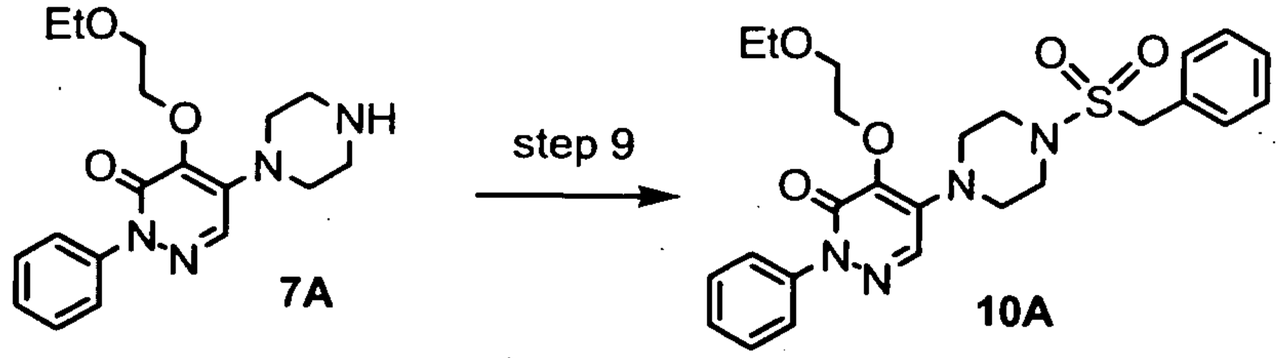
Step 8:



To a solution of compound **7C** (65 mg, 0.147 mmol) in dichloromethane (2.5 mL) was added diisopropylethylamine (100 uL) and cyclohexylisocyanate (28 uL , 0.22 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporataed. The residue

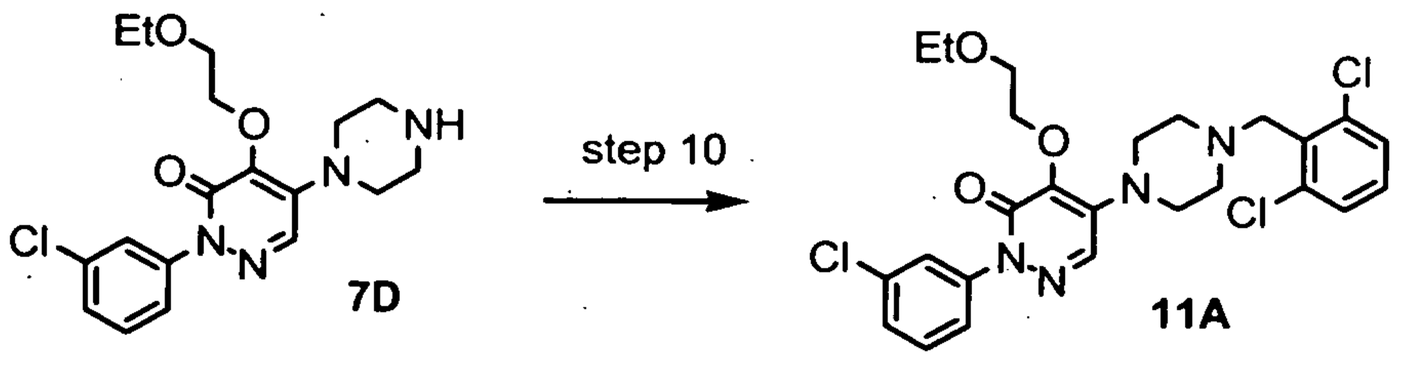
was dissolved in DMF (2 mL) and purified by chromatography on a C-18 reverse phase column (eluant: acetonitrile / water gradient with 0.1% formic acid). The appropriate fractions were combined and concentrated to give 61.7 mg (79%) of the product **9A** as a pale-yellow solid. MS (M+1): m/e 532.

Step 9:



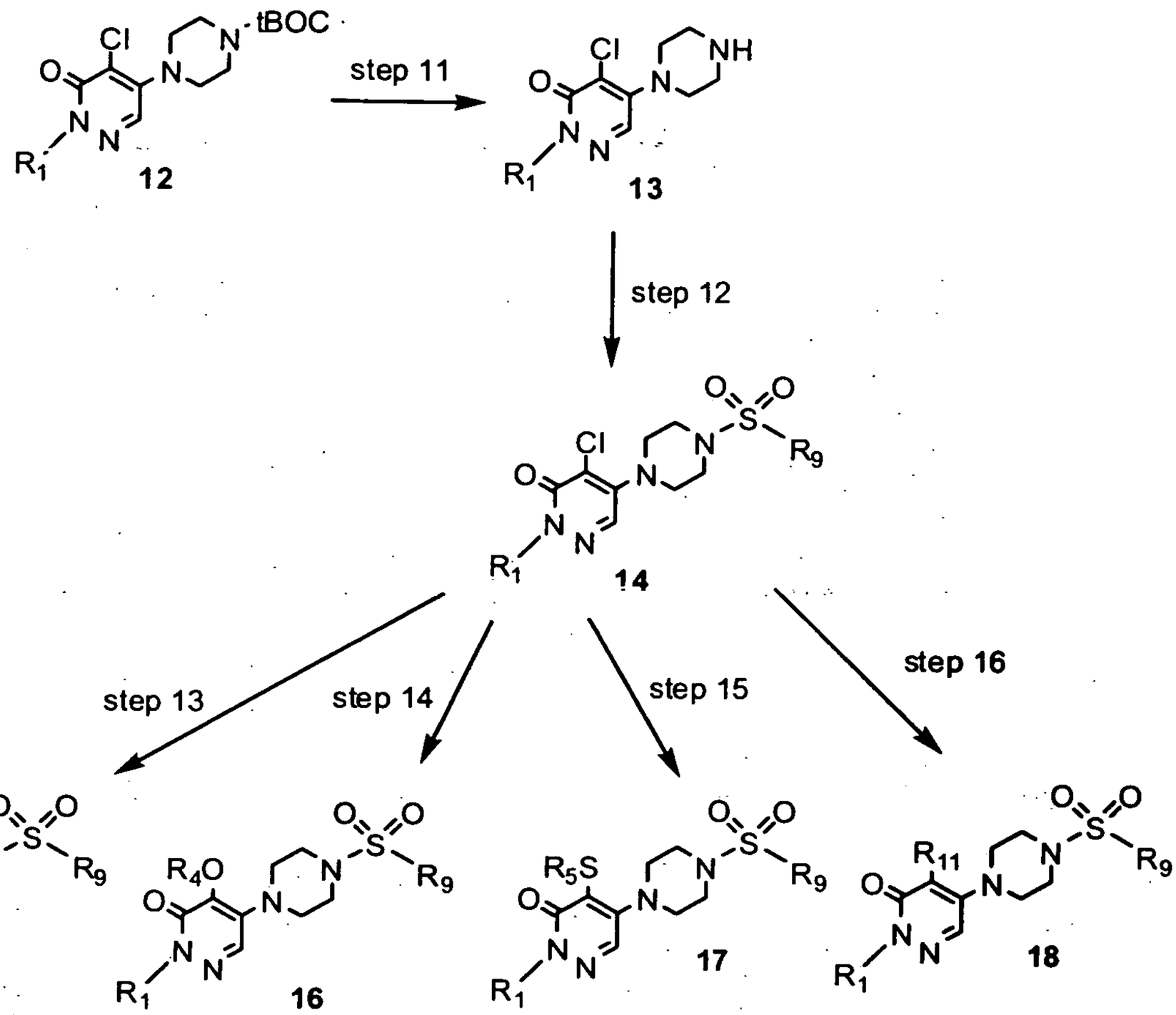
To a solution of the HCl salt of compound **7A** (75 mg, 0.197 mmol) dissolved in DMF (1.5 mL) was added Hunigs base (127 mg, 0.16 mL, 0.985 mmol) and α-toluenesulfonyl chloride (56 mg, 0.295 mmol). The reaction mixture was stirred at room temperature for 3 h. The product was purified by chromatography on a C-18 reverse phase column (eluant: acetonitrile / water gradient with 0.1% formic acid) to give 55 mg (56%) of the product **10A** as a cream solid. MS (M+1): m/e 499.

Step 10:



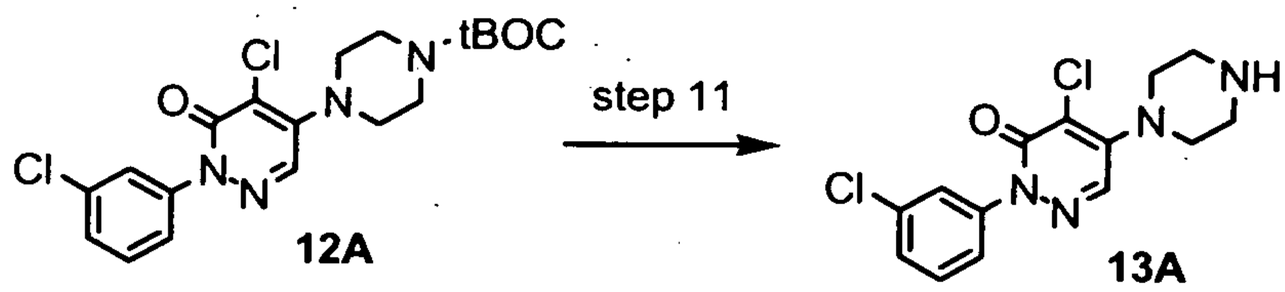
To a solution of compound **7D** TFA salt (130 mg, 0.26 mmol) dissolved in toluene (4 mL) was added 2,6-dichlorobenzylchloride (65 mg, 0.33 mmol) and Hunigs base (104 uL, 0.63 mmol). The reaction mixture was heated at reflux for 18 h. The solvent was evaporated. Purification by silica gel chromatography (eluant: 10% MeOH / NH3 – CH_2Cl_2) gave 50 mg (36%) of the product **11A**. MS (M+1): m/e 539.

Scheme 2



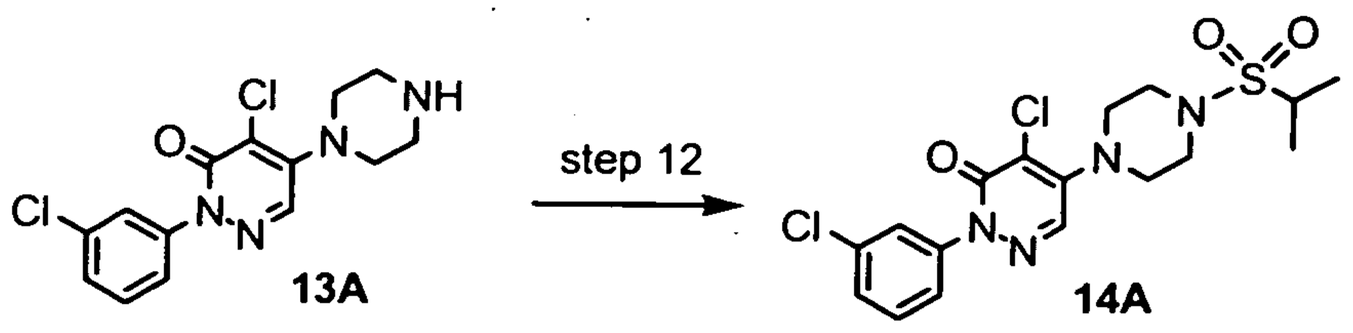
Compound **12** can be synthesized using steps 1 and 2 from Scheme 1.

Step 11:



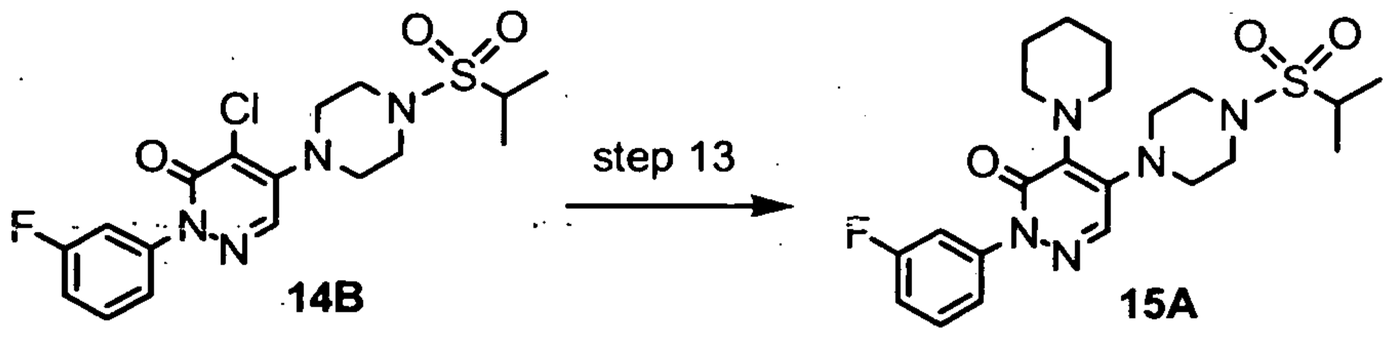
Suspended compound **12A** (4.00 g, 9.41 mmol) in CH_2Cl_2 (100 mL). Added HCl in dioxane (4 N, 23.5 mL, 94.1 mmol). The reaction mixture was stirred at room temperature for 5 h and precipitate formed. The solvent was evaporated, and the solid was dried under high vacuum to give 3.40 g (100%) of the product **13A** as a yellow solid. MS (M+1): m/e 327.

Step 12:



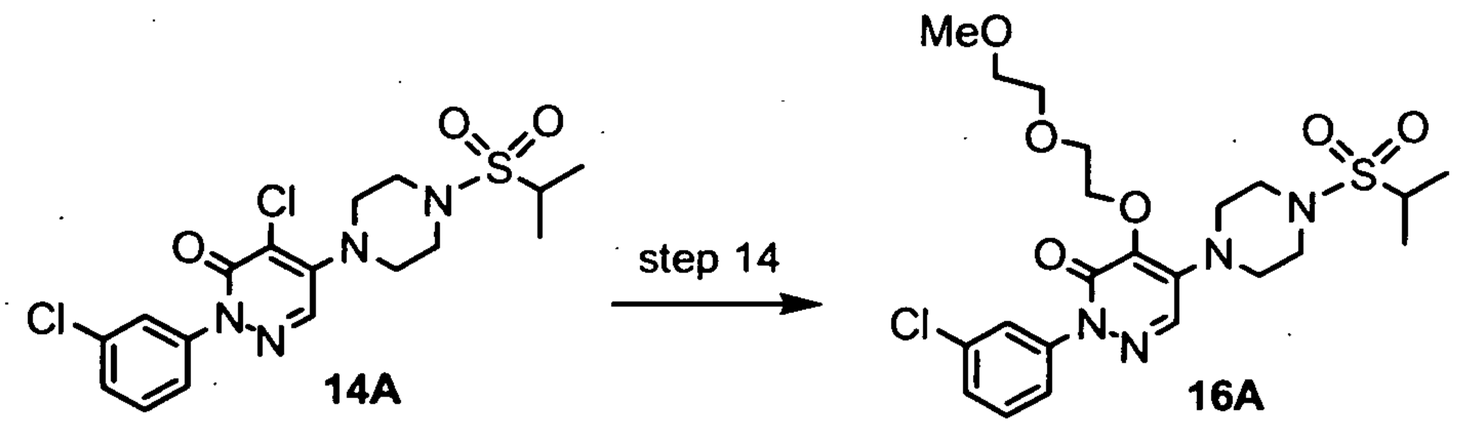
Suspended compound **13A** (3.40 g, 9.41 mmol) in CH_2Cl_2 (100 mL) and added triethylamine (2.86 g, 3.9 mL, 28.2 mmol). Cooled reaction mixture to 0 °C and added isopropylsulfonyl chloride (1.74 g, 1.4 mL, 12.2 mmol). The reaction mixture was stirred at 0 °C for 30 mins then at room temperature for 24 h. Water (100 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 10 – 20% EtOAc – CH_2Cl_2) gave 2.47 g (61% yield) of the product 14A as a yellow solid. MS (M+1): m/e 431.

Step 13:



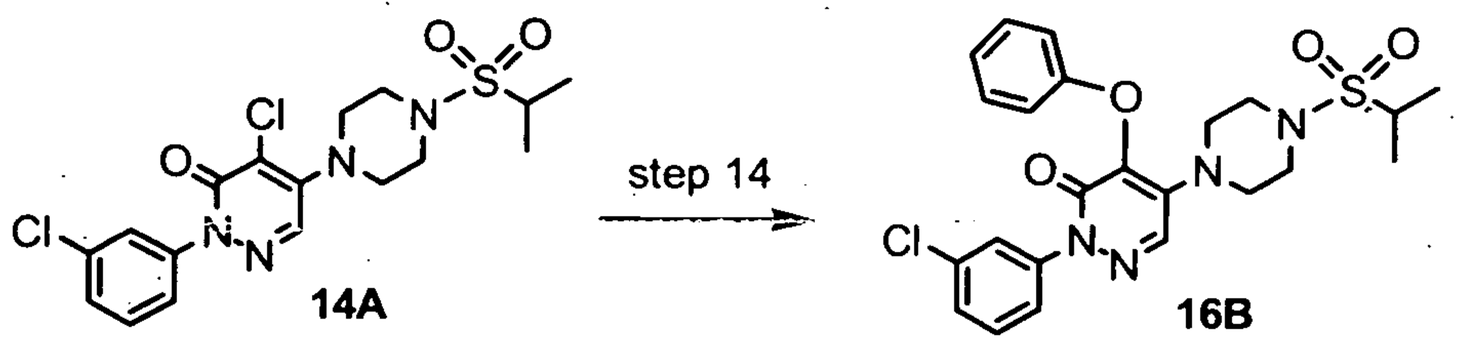
A solution of compound **14B** (207 mg, 0.50 mmol) and piperidine (170 mg, 2.0 mmol) dissolved in dichlorobenzene (5 mL) was heated at 250 °C for 60 mins. The reaction mixture was cooled to room temperature. Purification by silica gel chromatography (eluant: EtOAc – hexanes gradient) gave 112 mg (48%) of the product **15A**. MS (M+1): m/e 464.

Step 14 (Method 1):



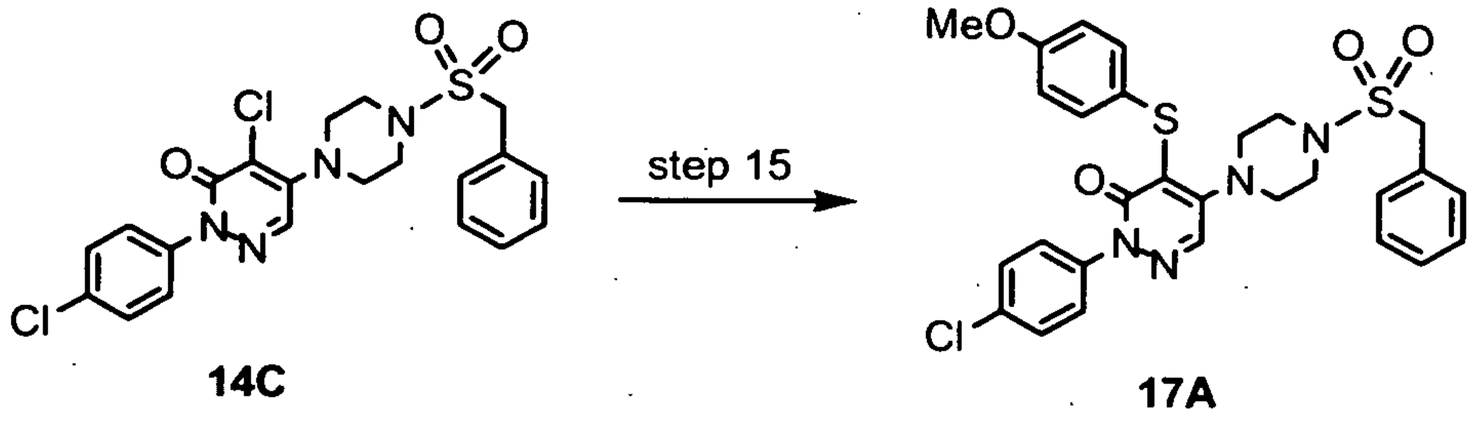
To a solution of 2-(2-methoxyethoxy)ethanol (244 mg, 0.24 mL, 2.03 mmol) dissolved in dry THF (5 mL) was added $NaNTMS_2$ (1 M in THF, 1.74 mL, 1.74 mmol). The reaction mixture was stirred at room temperature for 15 mins then compound **14A** (250 mg, 0.580 mmol) was added. The reaction mixture was heated at reflux for 5 h. The solvent was evaporated. Water (25 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 20 – 30% EtOAc – hexanes) gave 233 mg (78%) of the product **16A** as an orange solid. MS (M+1): m/e 515.

Step 14 (Method 2):



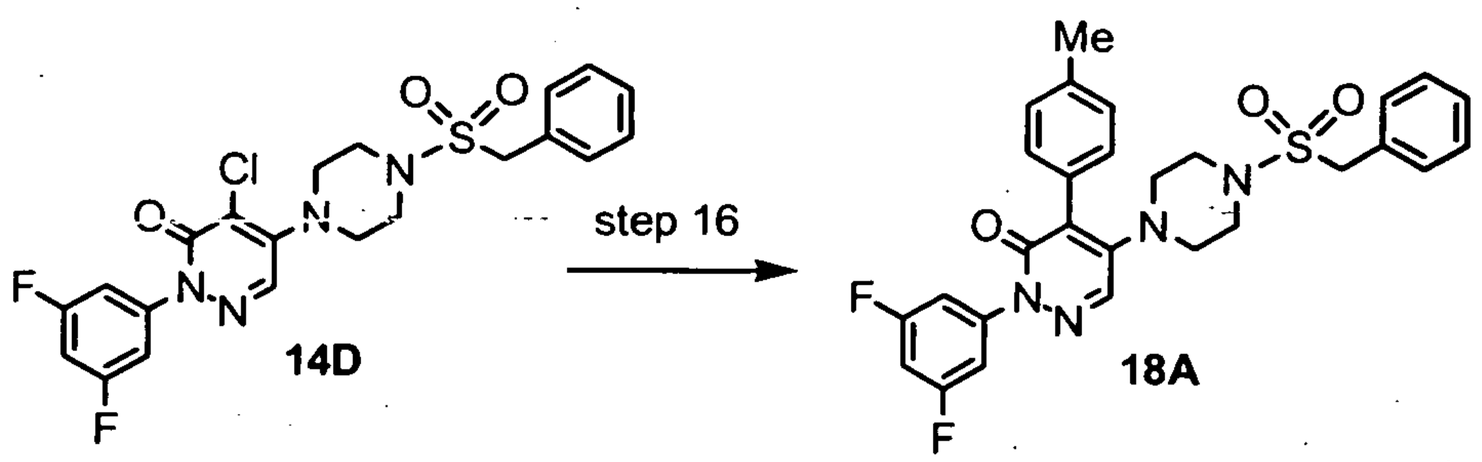
A mixture of anhydrous cesium carbonate (0.114 g, 3.5 mmol) and phenol (0.066 g, 7.0 mmol) in anhydrous methanol (5 mL) was stirred at room temperature for 30 mins. The solvent was evaporated. To the residue at room temperature was added dropwise a solution of compound **14A** (0.086 g, 2.0 mmol) in anhydrous DMF (5 mL). The resulting solution was stirred for at 110 °C for 8 h, and then the solvent was evaporated. The residue was quenched with aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was washed with H_2O (2 ×10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (1:20 EtOAc - hexanes) gave 42 mg (41%) of the product **16B** as a colorless oil. MS (M+1): m/e 489.

Step 15:



To a solution of compound **14C** (240 mg, 0.50 mmol) and potassium carbonate (70 mg, 0.5 mmol) in acetonitrile (2 mL) was added 4-methoxybenzenethiol (100 uL , 0.81 mmol). The reaction mixture was stirred at reflux for 6 h. The solvent was evaporated. The residue was partitioned between water and EtOAc. The organic phase was washed consecutively with water, 1 N sodium hydroxide, and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc – hexanes gradient) gave 272 mg (93% yield) of the product **17A** as a yellow solid. MS (M+1): m/e 583.

Step 16:



Compound **14D** (34 mg, 0.070 mmol), 4-methylphenylboronic acid (14 mg. 0.11 mmol), Na_2CO_3 (11 mg, 0.11 mmol), and $PdCl_2(PPh_3)_2$ catalyst (2.5 mg, 0.004 mmol) were combined in 5:1 acetonitrile:water (2 mL). The reaction mixture was heated in a microwave at 140 °C for 20 mins then filtered through a Si-carbonate column with CH_2Cl_2. Purification by chromatography on a C-18 reverse phase column (eluant: acetonitrile / water gradient with 0.1% formic acid) gave 22 mg (59%) of the product **18A**. MS (M+1): m/e 537.

Table 1: Sulfur Linked Analogs with Amide

The following compounds can be synthesized using steps 1, 2, 5, 6, and 7 of Scheme 1.

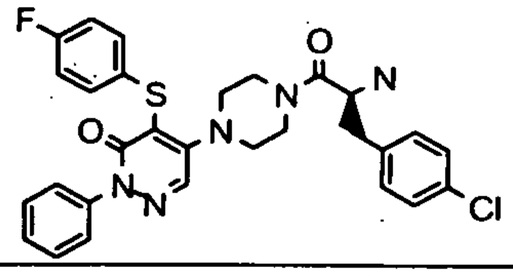
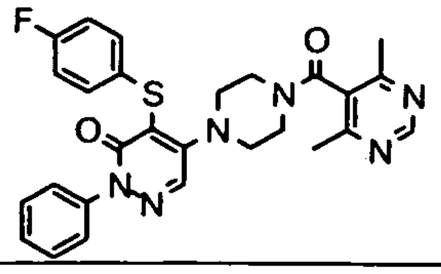
Compound No.	Structure	MS M+1
1Z		564
2Z		517

Table 2: Sulfur Linked Analogs with Sulfonamide

The following compounds can be synthesized using steps 1, 2, 5, 6, and 9 of Scheme 1 or steps 11, 12, and 15 of Scheme 2.

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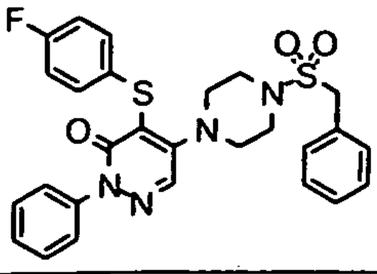
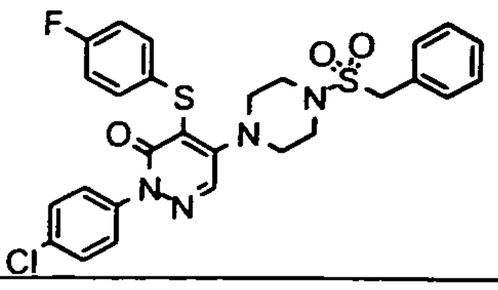
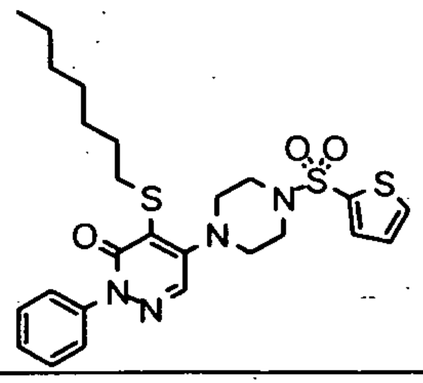
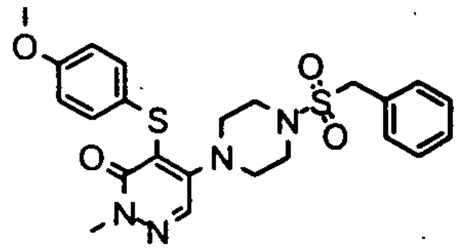
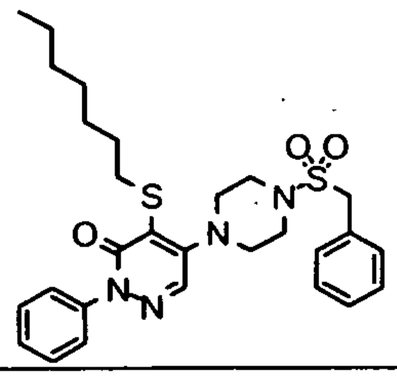
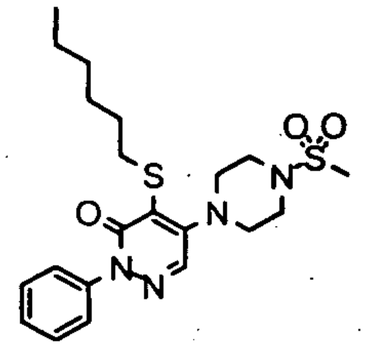
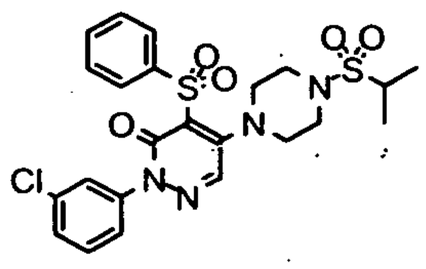
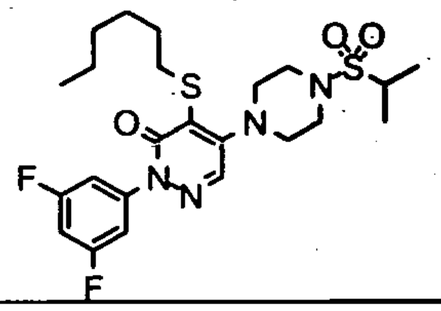
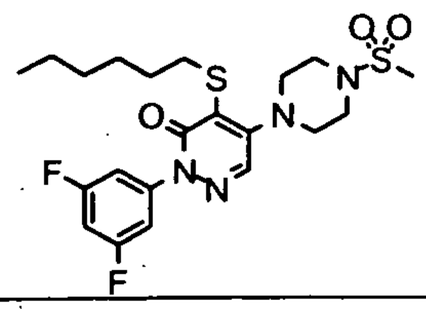
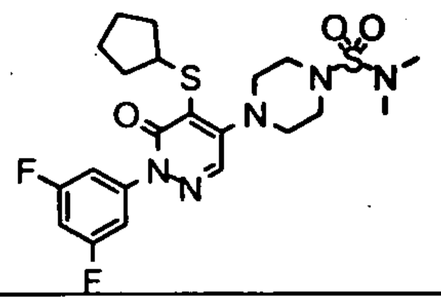
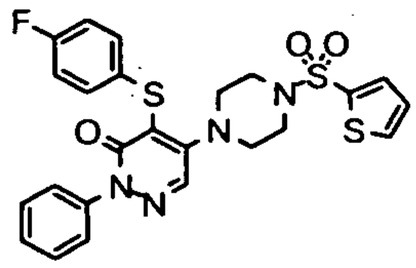
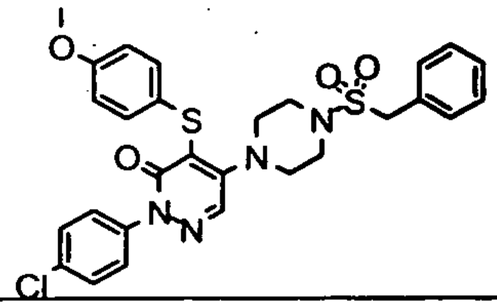
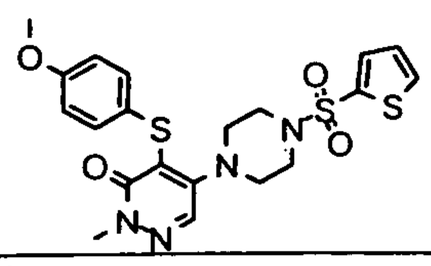
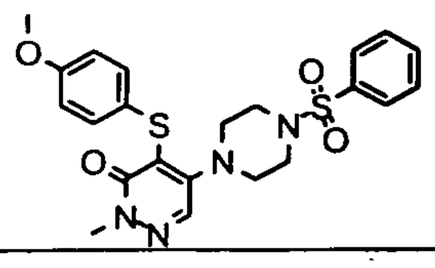
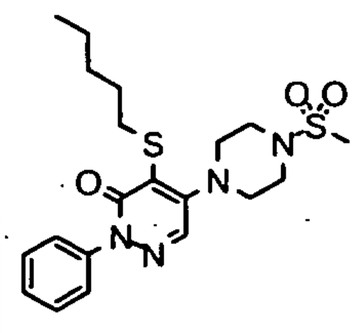
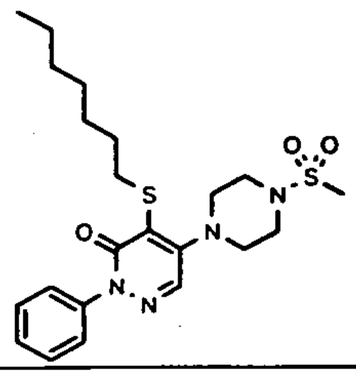
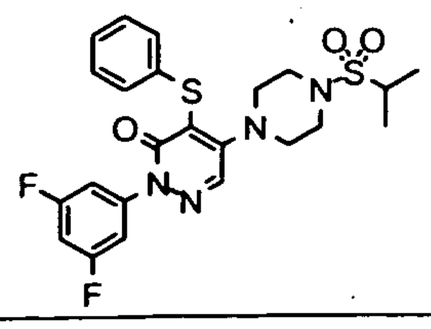
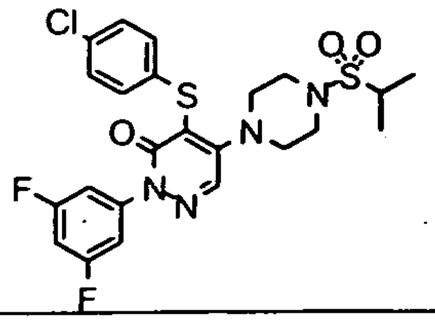
3Z		537

Comp. No.	Structure	MS M+1
4Z		571

5Z		533
6Z		487
7Z		541
8Z		451
9Z		537
10Z		515
11Z		487
12Z		500
13Z		529
14Z		583
15Z		479
16Z		473
17Z		437
18Z		465
19Z		507
20Z		541

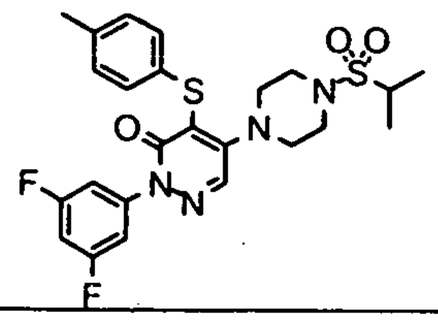
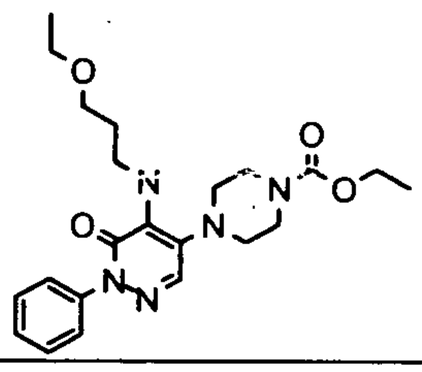
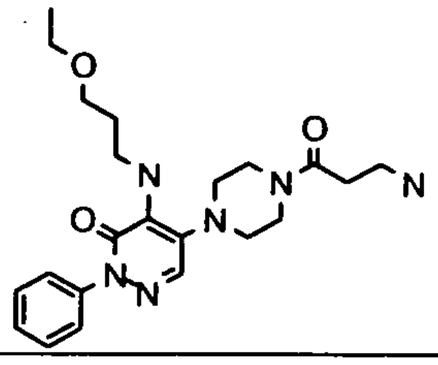
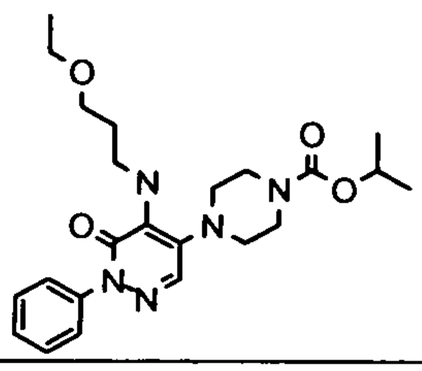
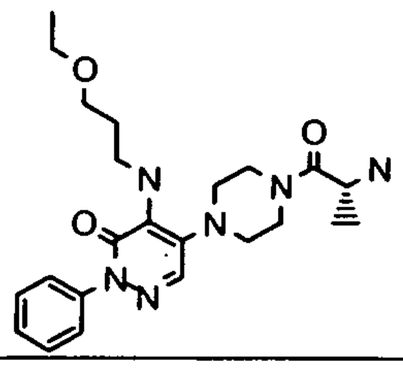
21Z		521

Table 3: Nitrogen Linked Analogs with Amide

The following compounds can be synthesized using steps 1, 2, 3, 6, and 7 of Scheme 1.

Comp. No.	Structure	MS M+1
22Z		403
24Z		429
26Z		444
28Z		429

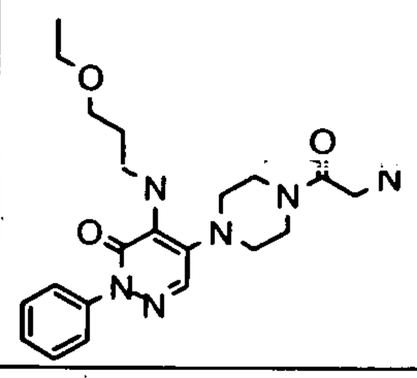
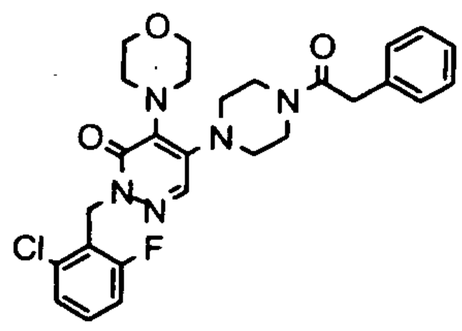
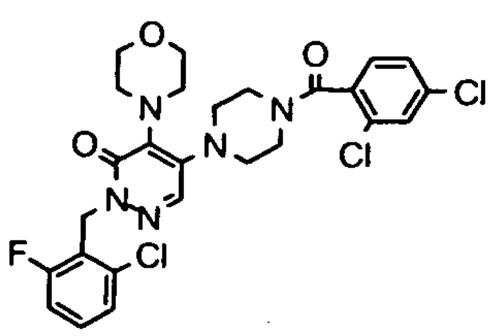
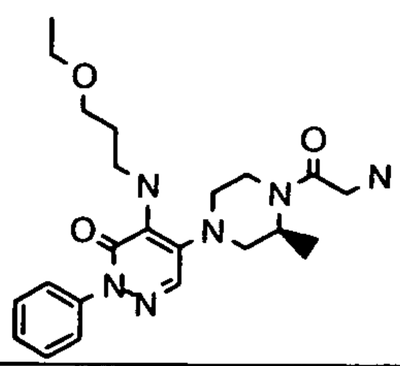
Comp. No.	Structure	MS M+1
23Z		415
25Z		529
27Z		472
29Z		429

Table 4: Nitrogen Linked Analogs with Sulfonamide

The following compounds can be synthesized using steps 1, 2, 3, 6, and 9 of Scheme 1 or steps 11, 12, and 13 of Scheme 2.

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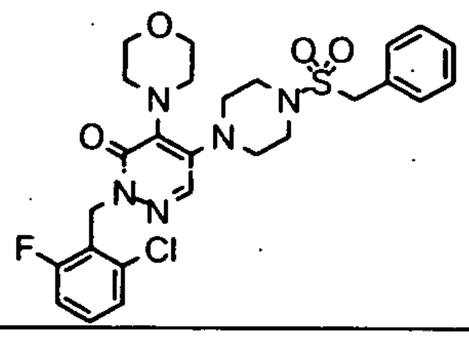
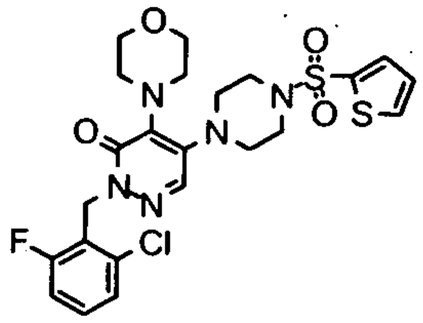
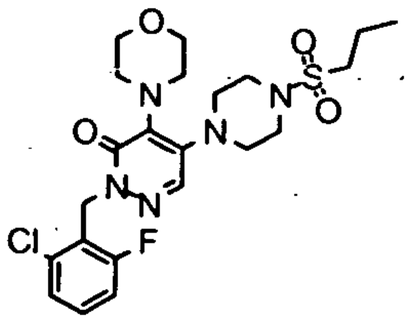
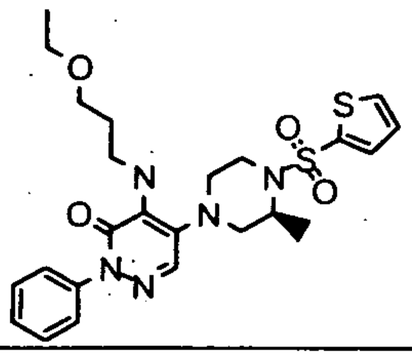
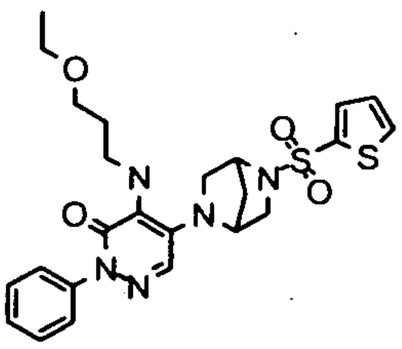
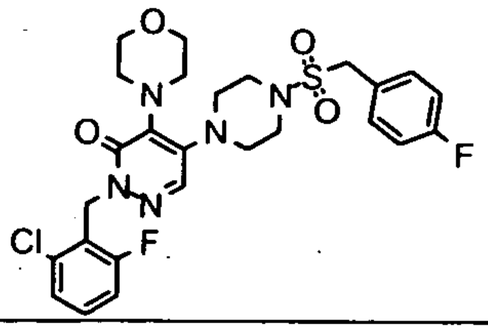
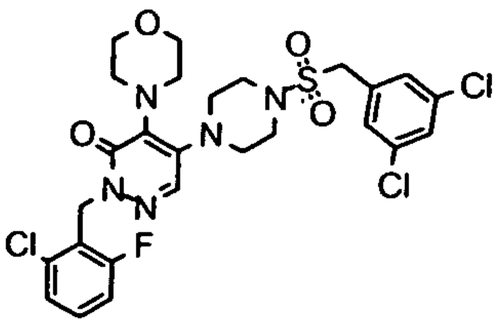
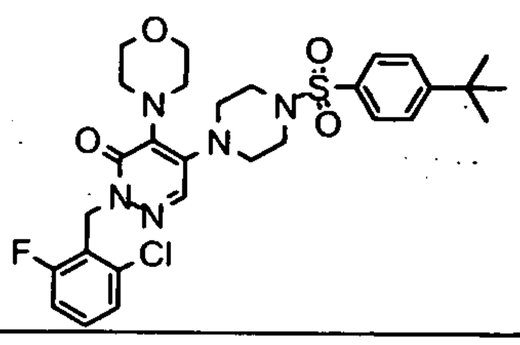
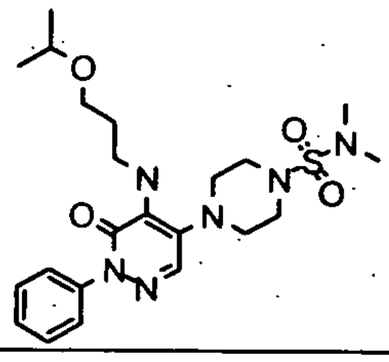
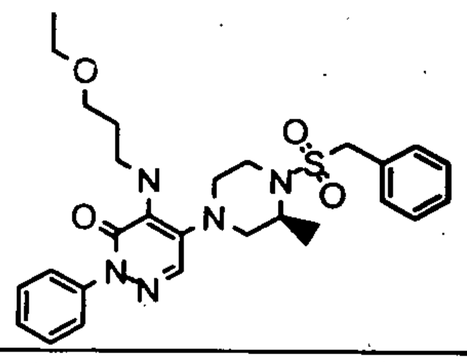
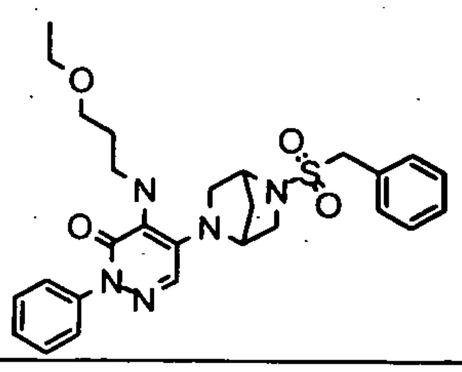
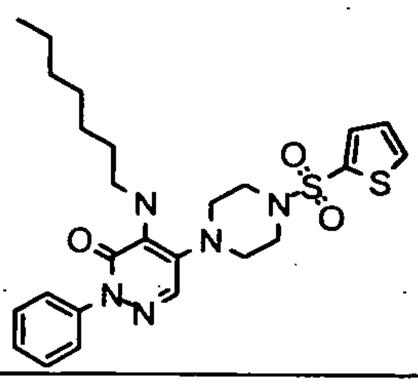
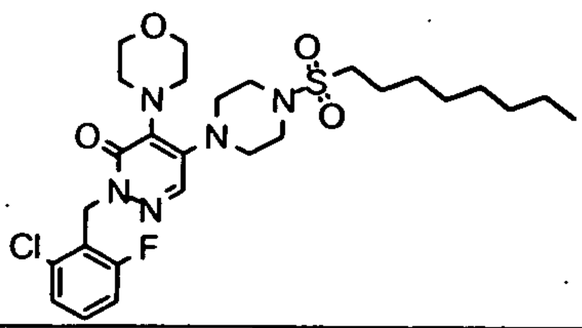
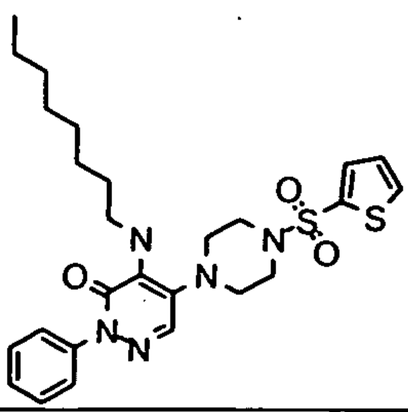
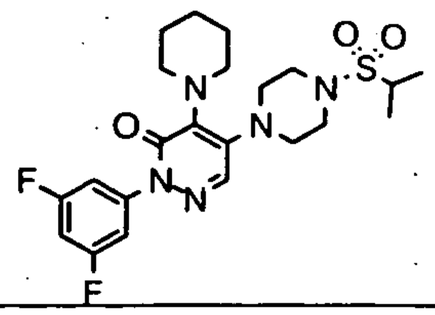
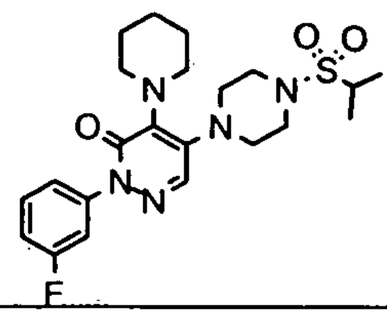
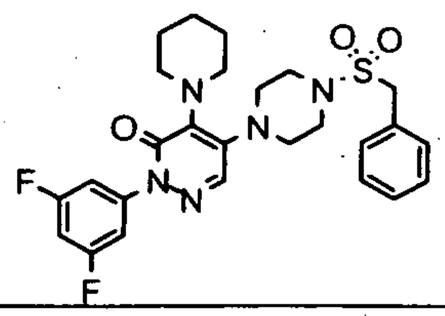
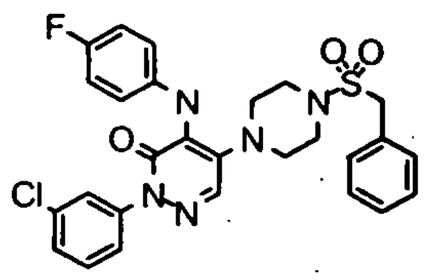
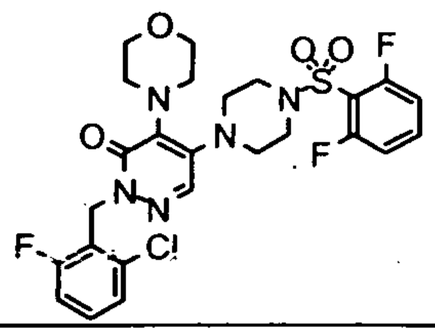
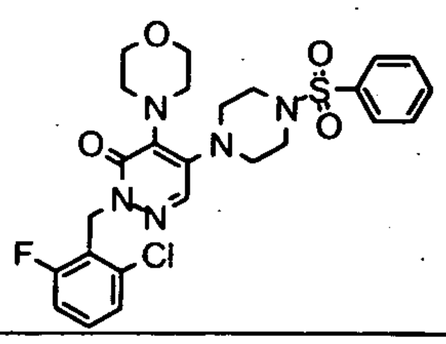
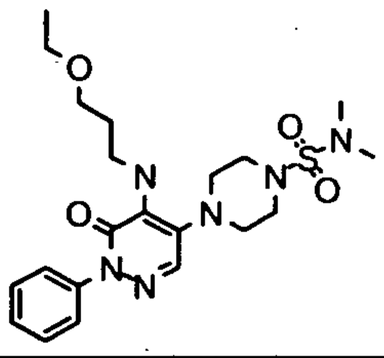
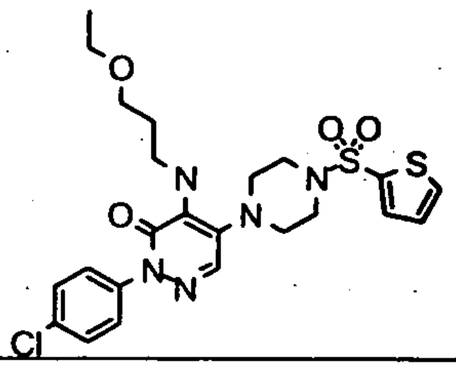
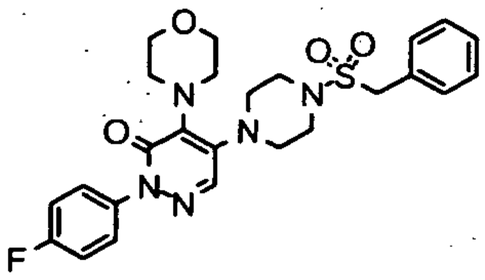
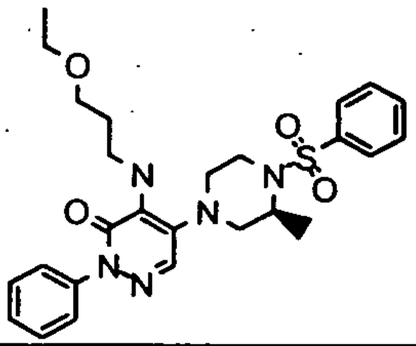
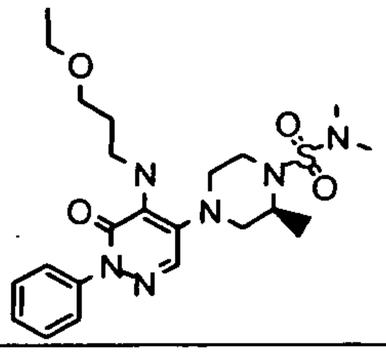
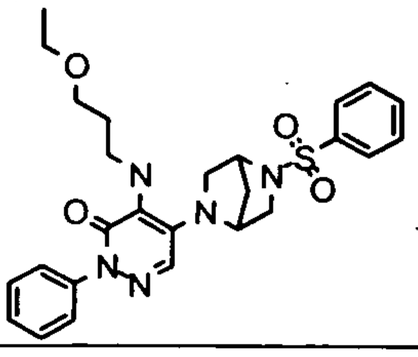
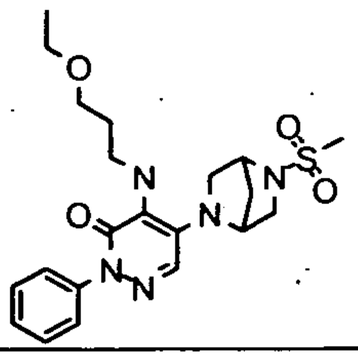
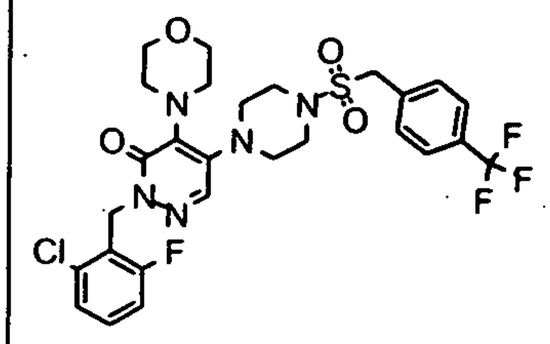
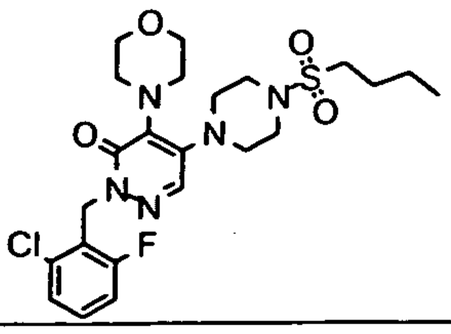
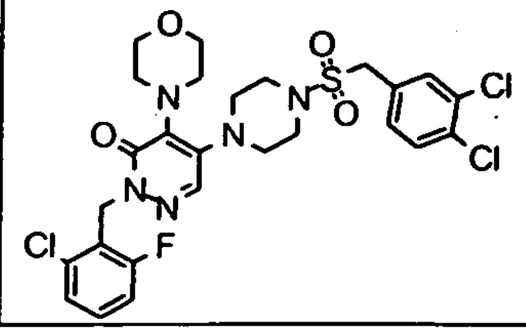
30Z		562
32Z		554
34Z		514
36Z		518
38Z		516
40Z		580
42Z		632

Comp. No.	Structure	MS M+1
31Z		604
33Z		479
35Z		526
37Z		524
39Z		516
41Z		584
43Z		530

44Z		482
45Z		464
46Z		530
47Z		554 556
48Z		584
49Z		548
50Z		465
51Z		538 540
52Z		514
53Z		512
54Z		479
55Z		510
56Z		448
57Z		630
58Z		528
59Z		632

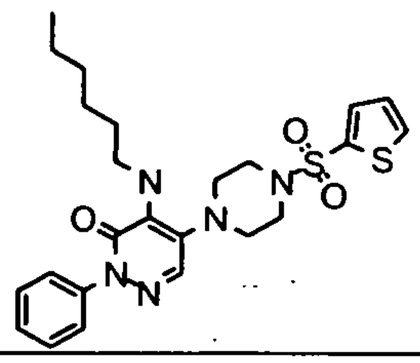
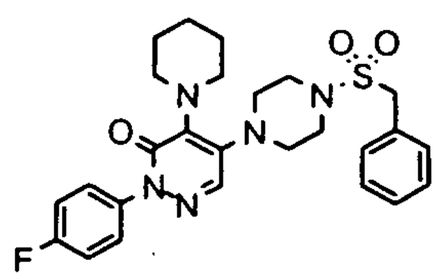
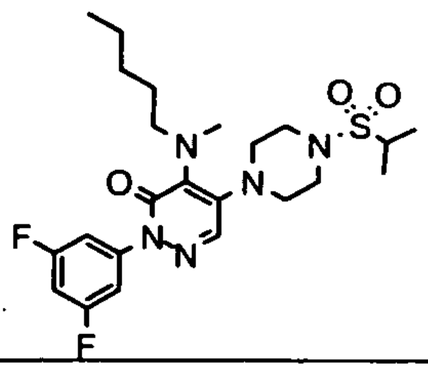
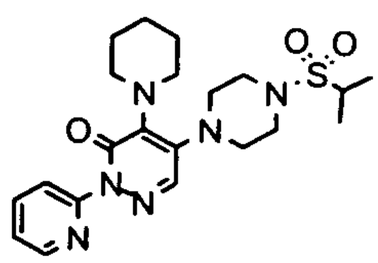
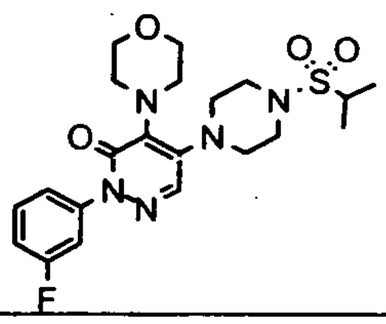
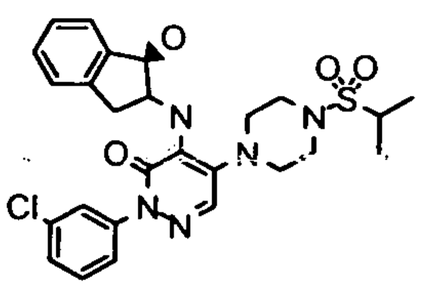
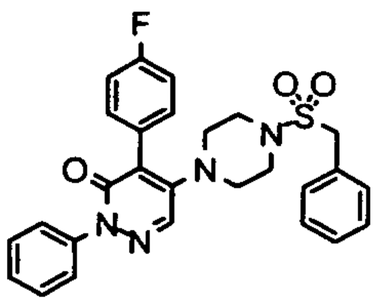
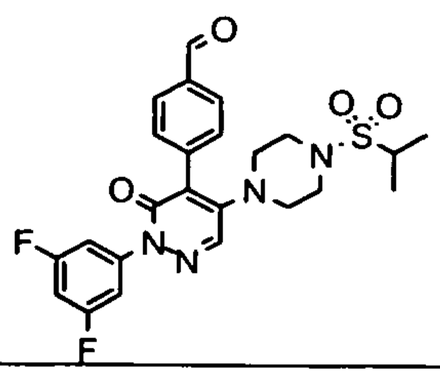
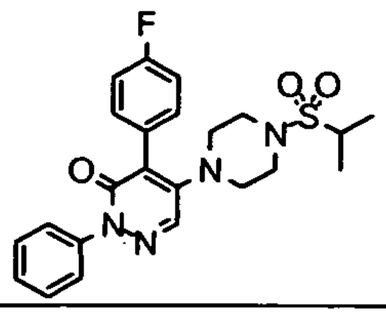
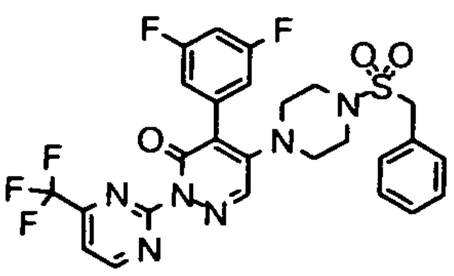
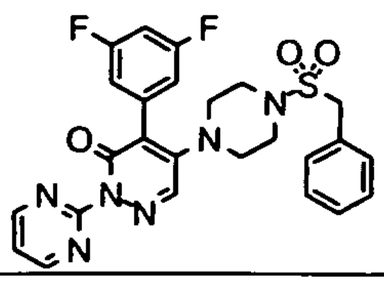
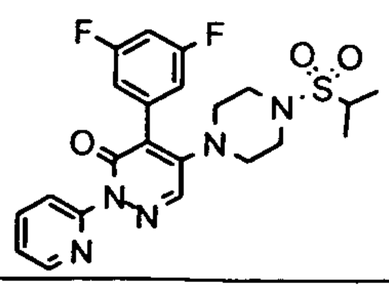
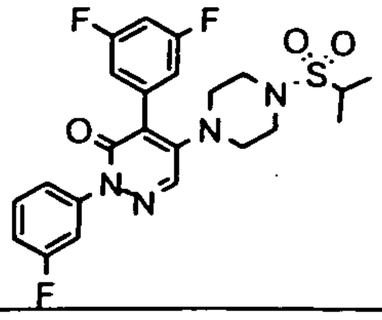
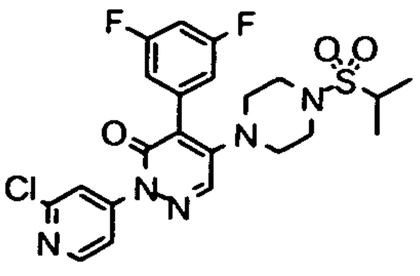
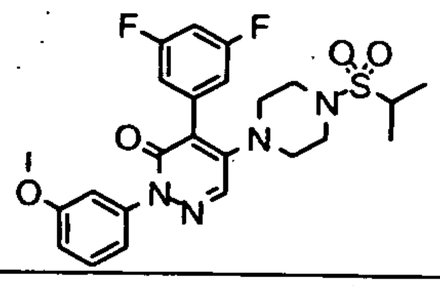
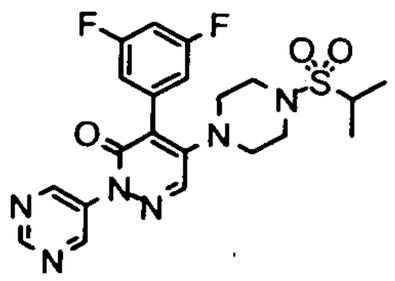
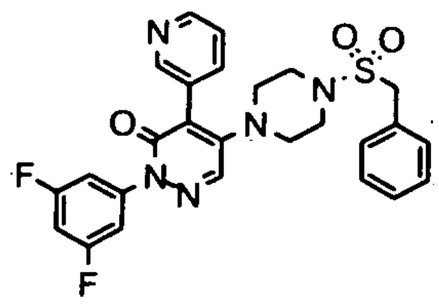
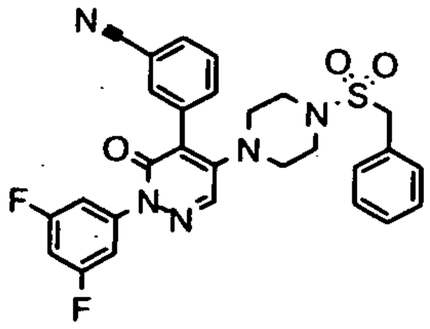
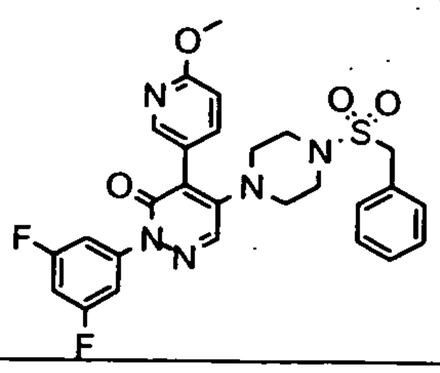
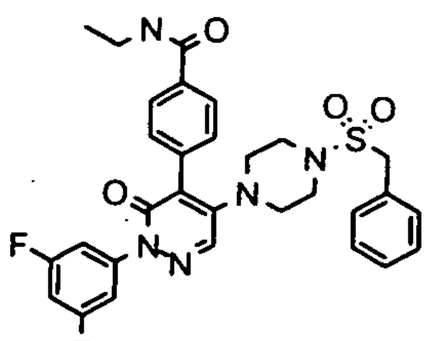
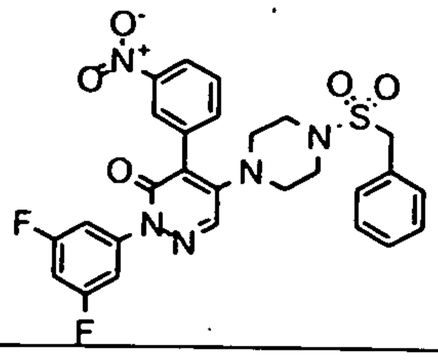
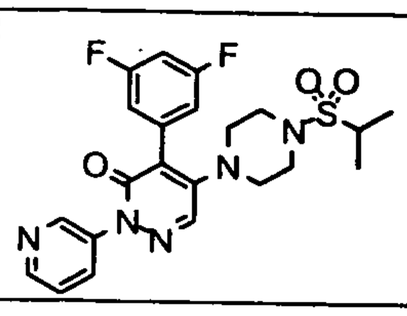
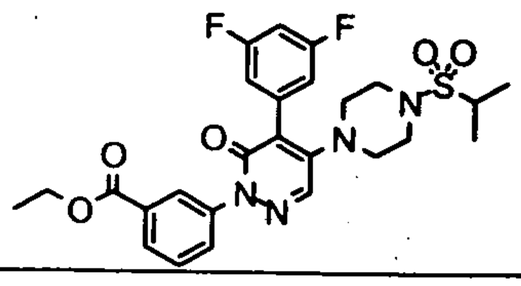
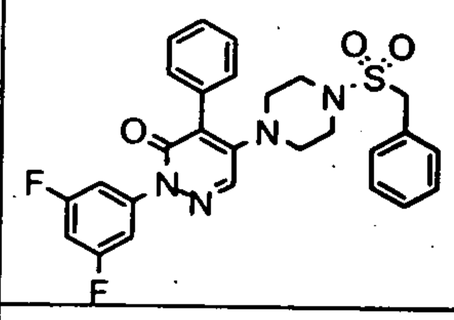
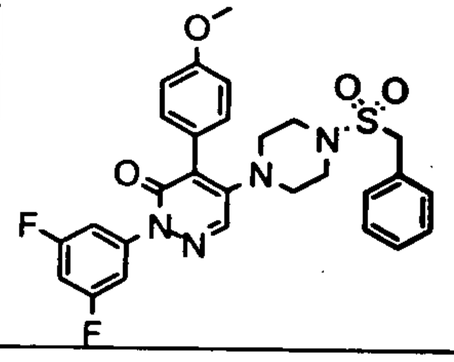
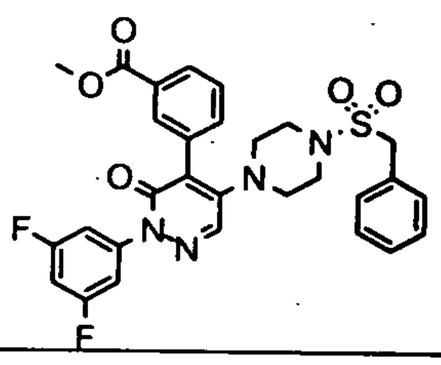
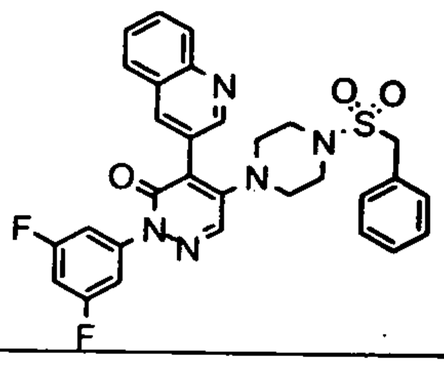
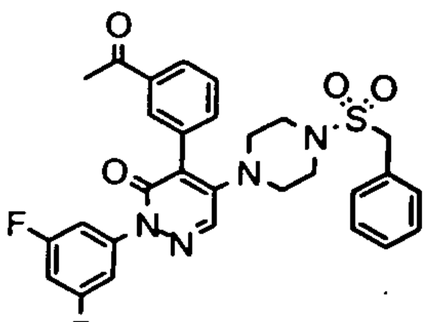
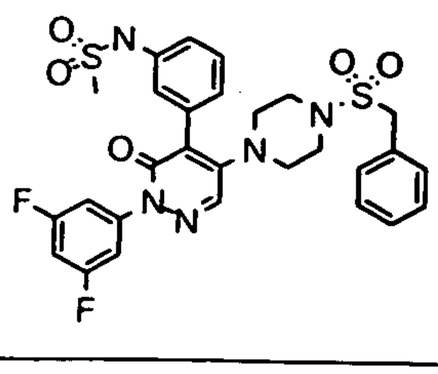
60Z		502
61Z		512
62Z		498
63Z		447
64Z		466
65Z		544

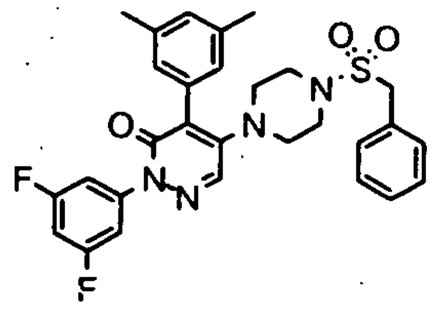
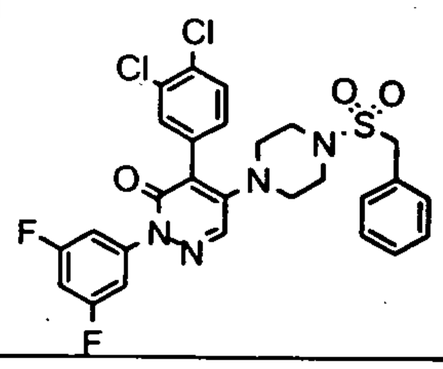
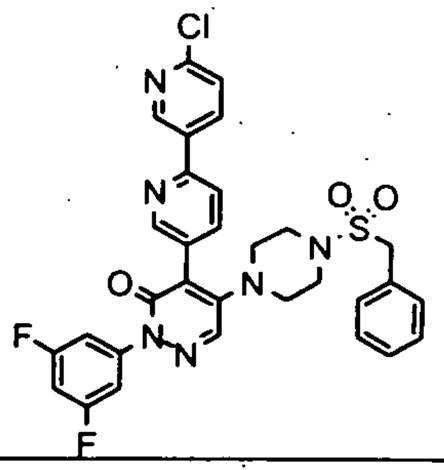
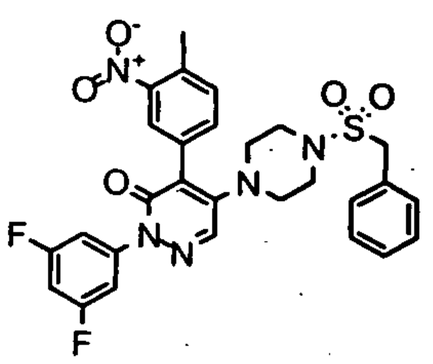
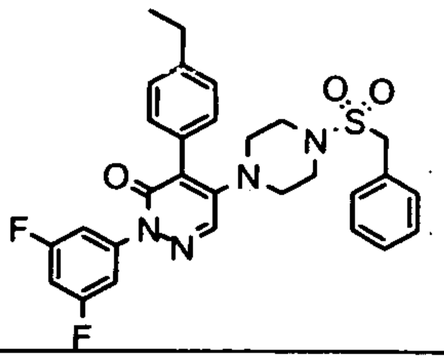
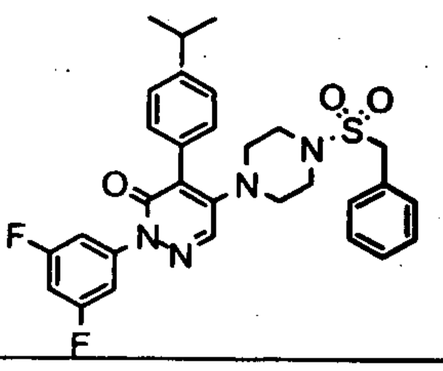
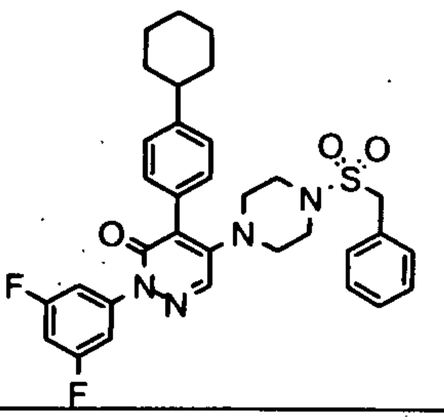
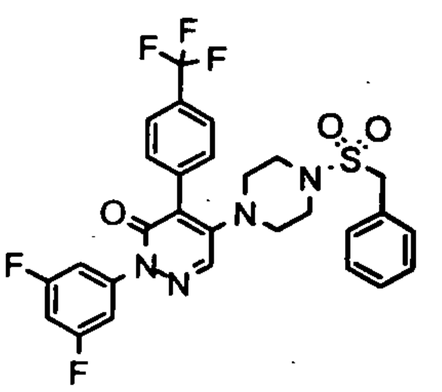
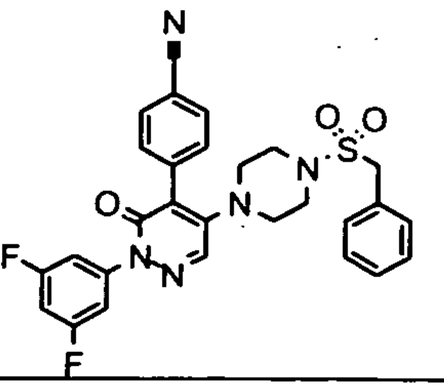
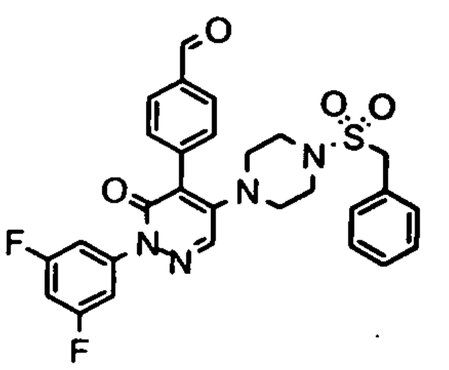
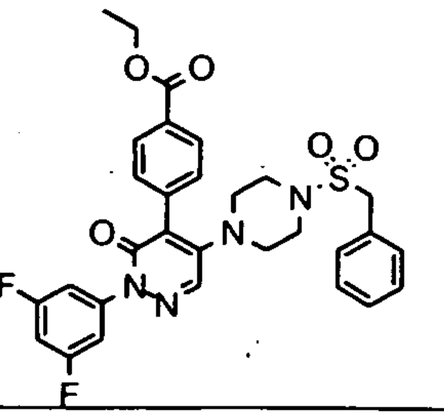
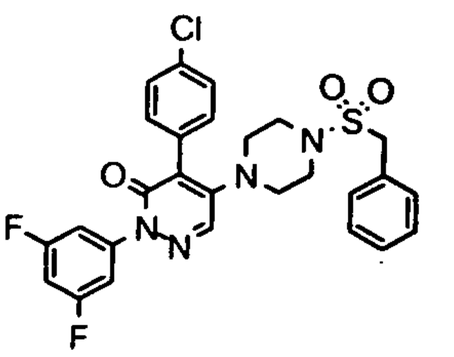
Table 5: Carbon Analogs with Sulfonamide

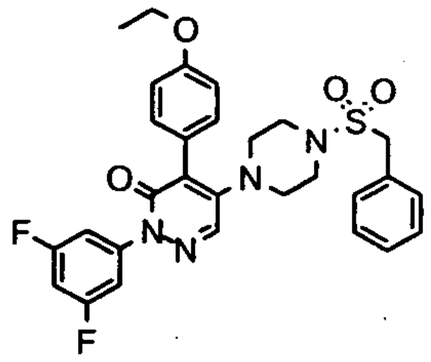
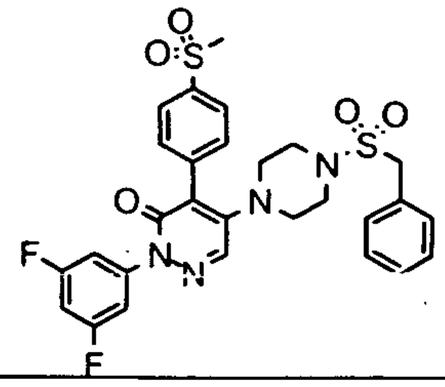
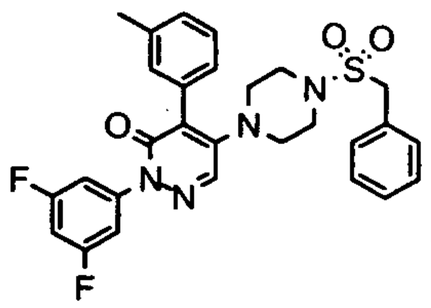
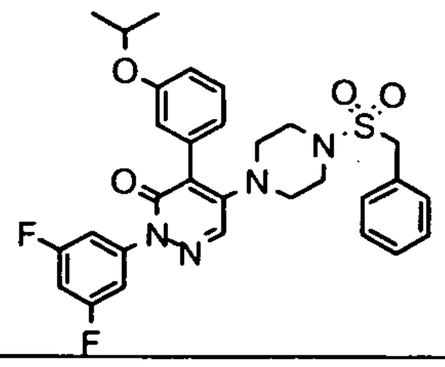
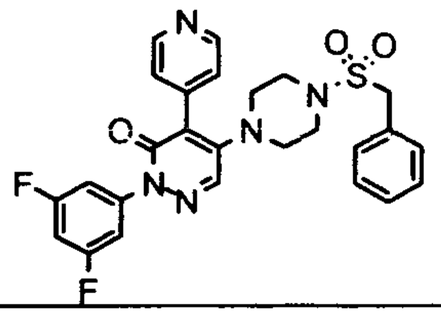
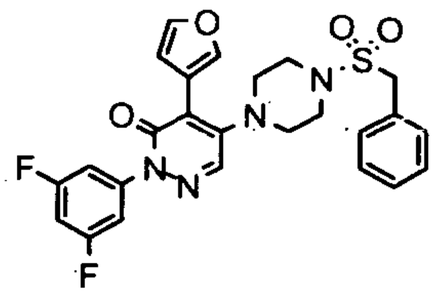
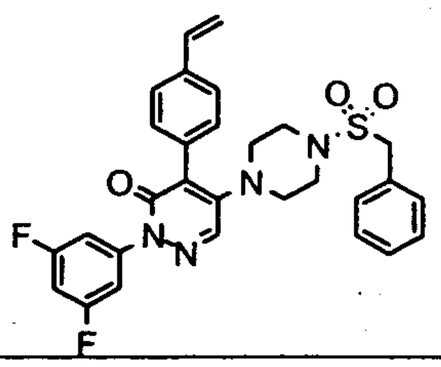
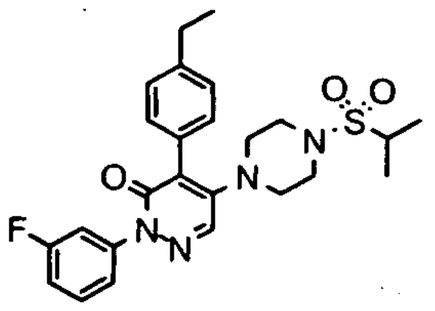
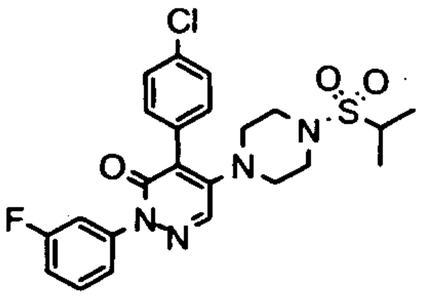
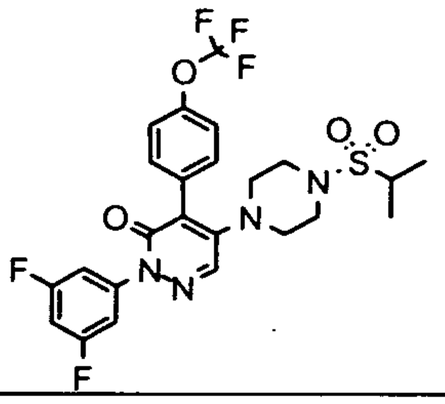
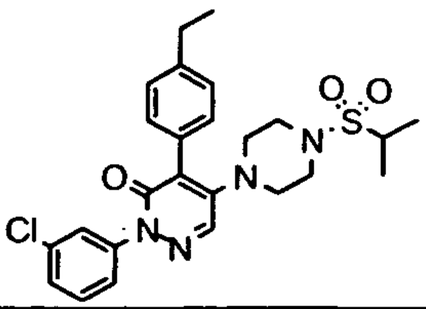
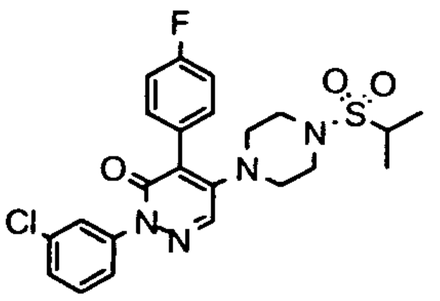
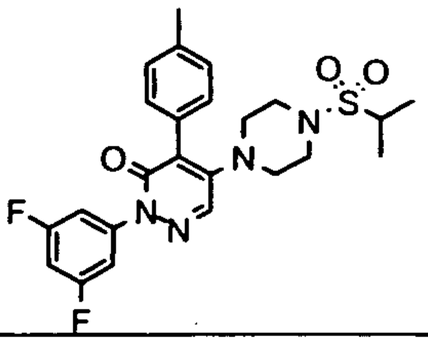
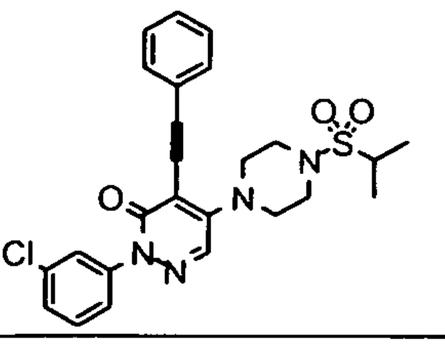
The following compounds can be synthesized by using steps 11, 12, and 16 in Scheme 2.

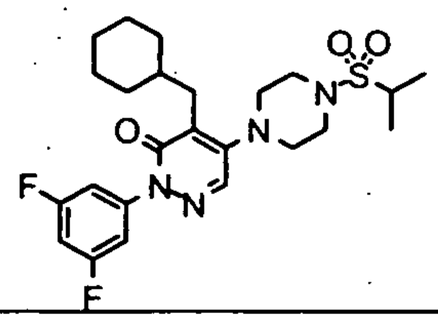
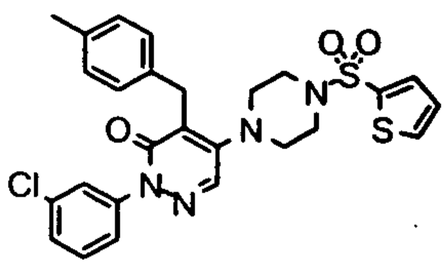
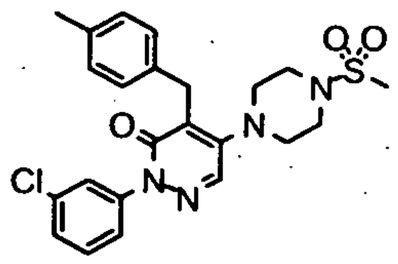
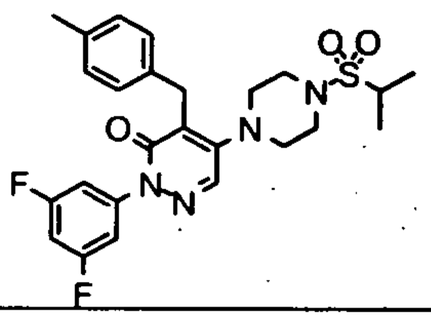
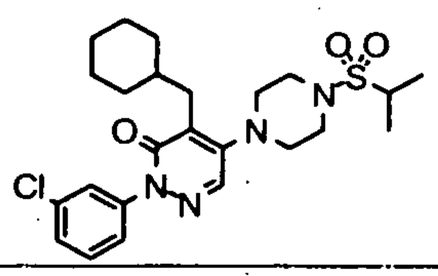
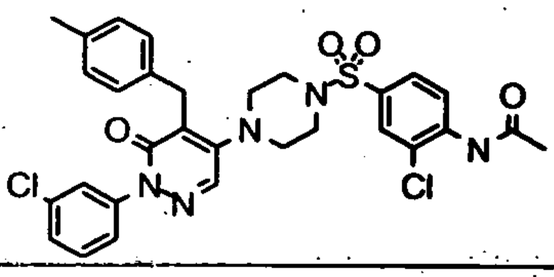
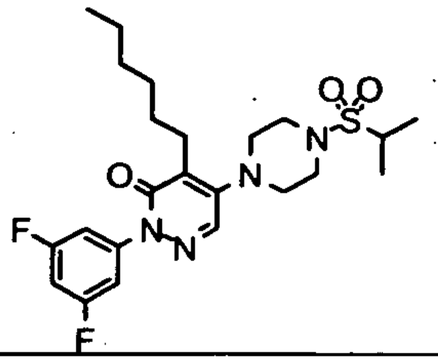
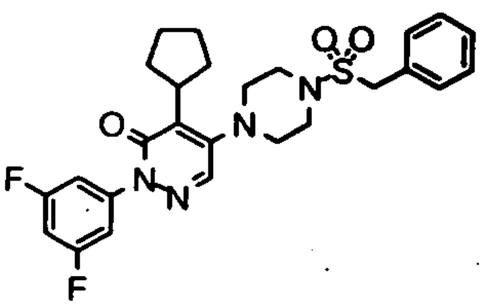
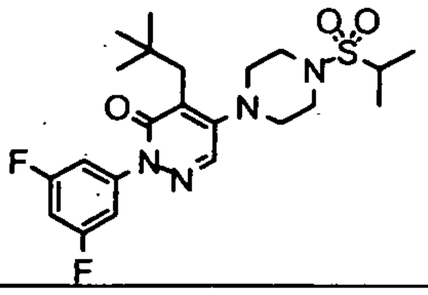
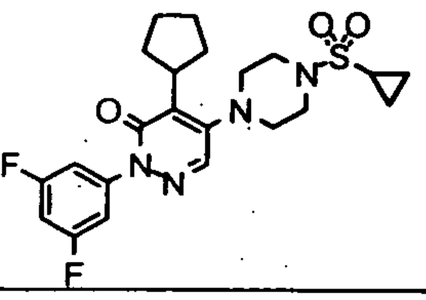
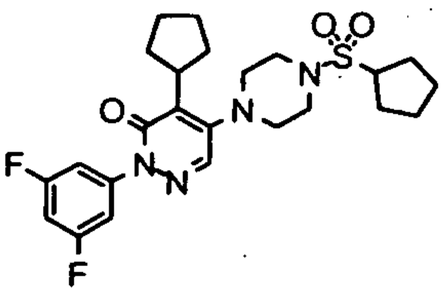
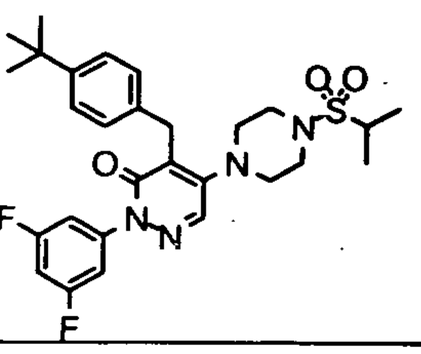
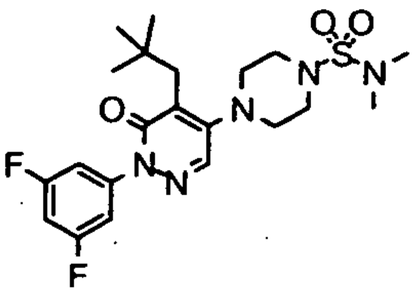
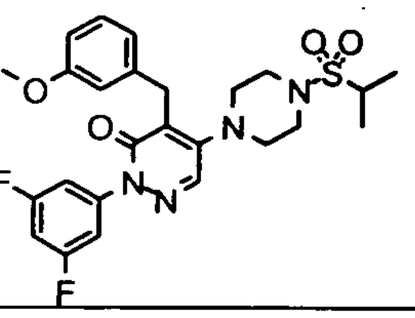
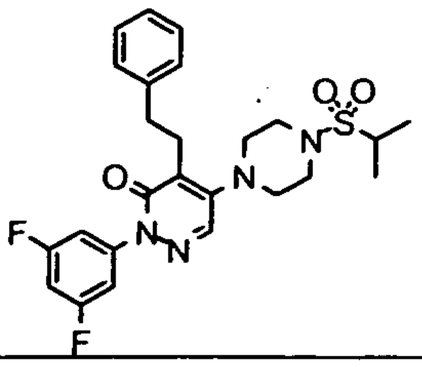
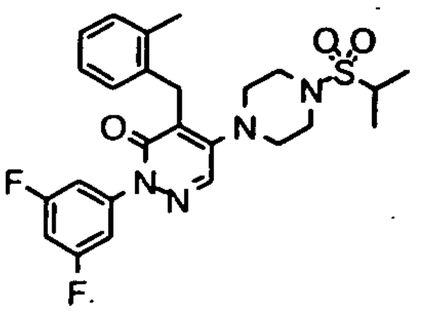
Comp. No.	Structure	MS M+1
66Z		505
67Z		503
68Z		457
69Z		593
70Z		525
71Z		476
72Z		493
73Z		510

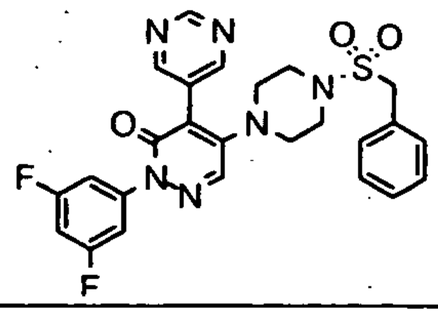
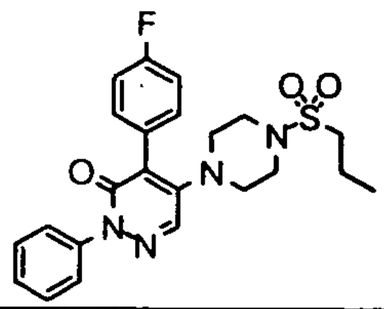
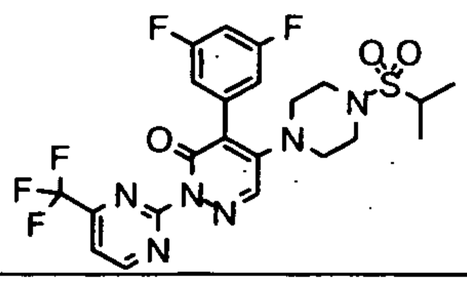
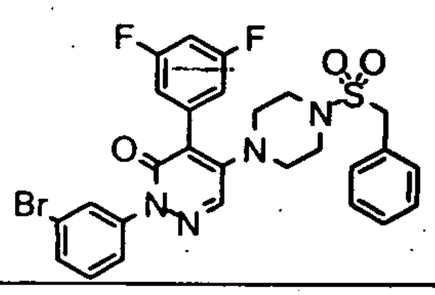
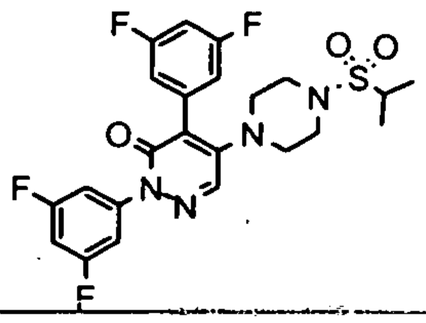
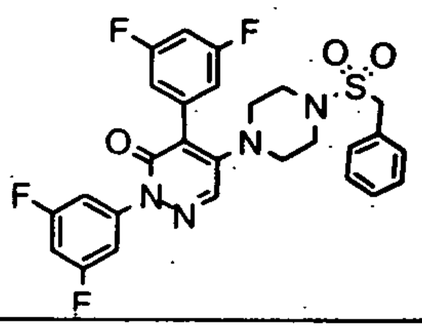
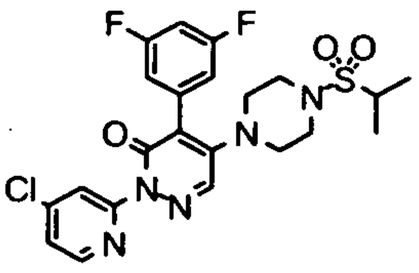
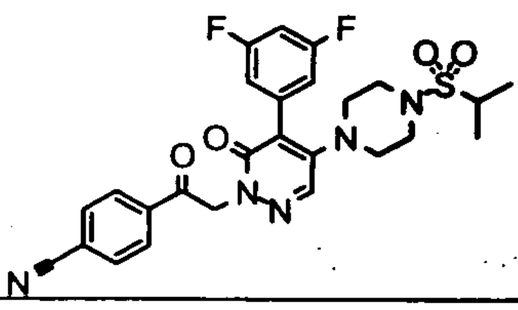
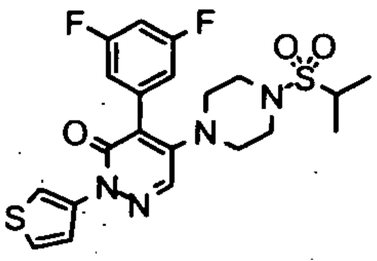
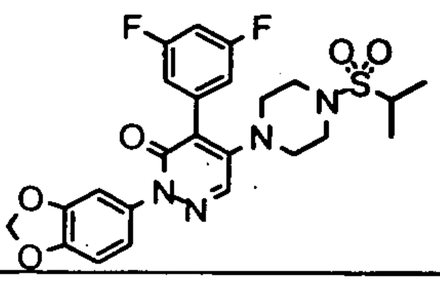
74Z		505
76Z	no compound	
78Z		477
80Z		524
82Z		548
84Z		554
86Z		594
88Z		568

75Z		476
77Z		547
79Z		523
81Z		553
83Z		581
85Z		574
87Z		565
89Z		616

90Z		551
91Z		591
92Z		635
93Z		582
94Z		551
95Z		565
96Z		605
97Z		591
98Z		548
99Z		551
100Z		595
101Z		557

102Z		567
103Z		601
104Z		537
105Z		581
106Z		524
107Z		513
108Z		549
109Z		485
110Z		491
111Z		559
112Z		501
113Z		491
114Z		489
115Z		497

116Z		495
117Z		541
118Z		473
119Z		503
120Z		493
121Z		626
122Z		483
123Z		515
124Z		469
125Z		465
126Z		493
127Z		545
128Z		470
129Z		519
130Z		503
131Z		503

132Z		525
133Z		457
134Z		545
135Z		603
136Z		511
137Z		559
138Z		510
139Z		542
140Z		481
141Z		519
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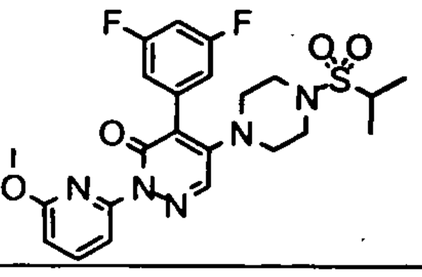
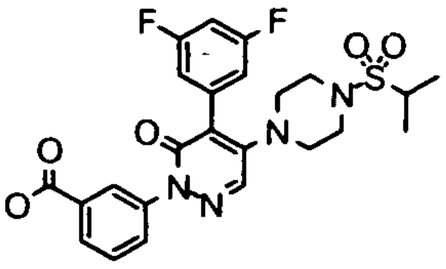
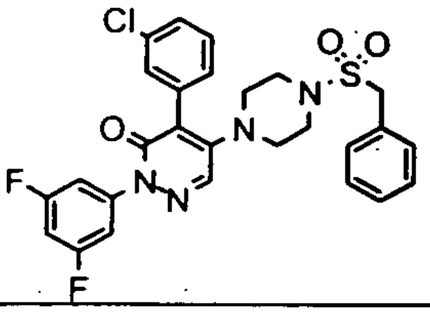
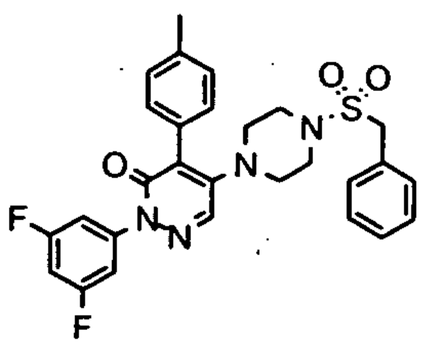
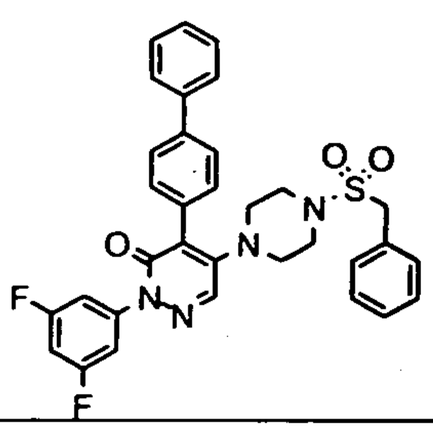
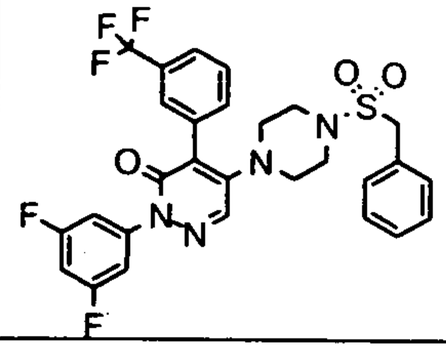
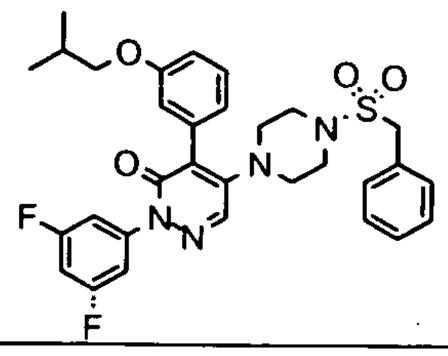
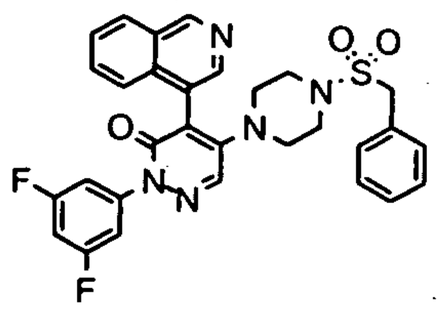
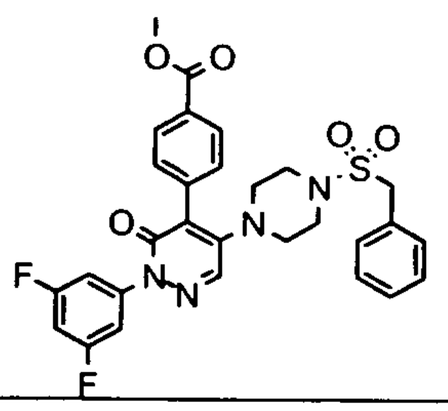
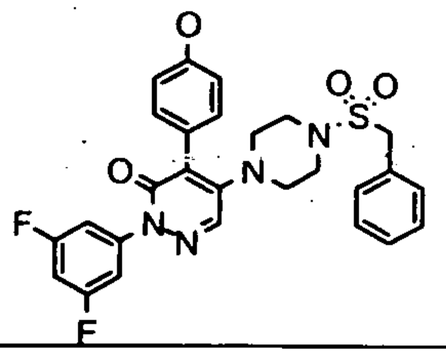
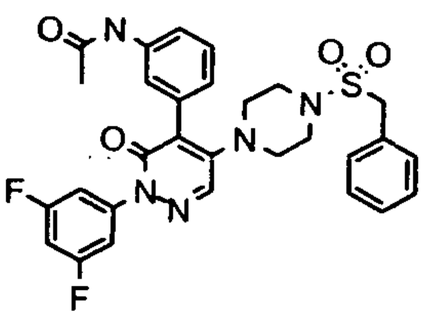
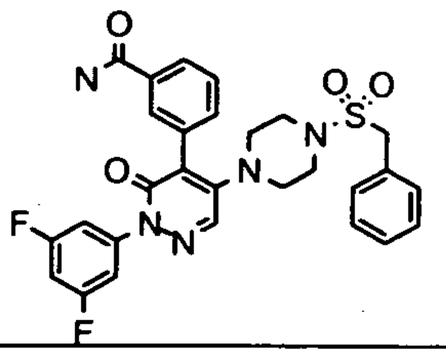
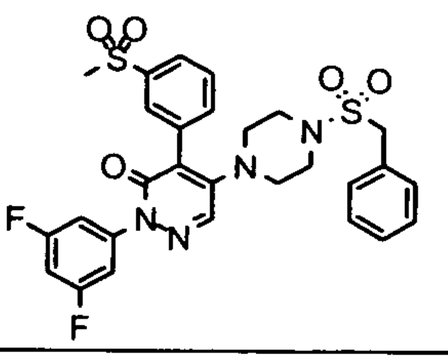
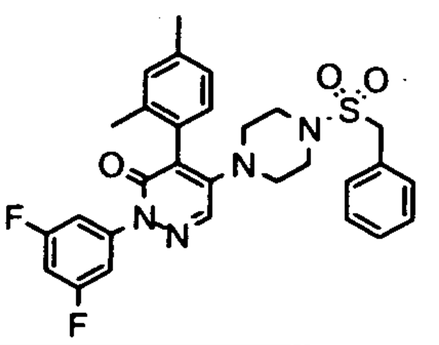
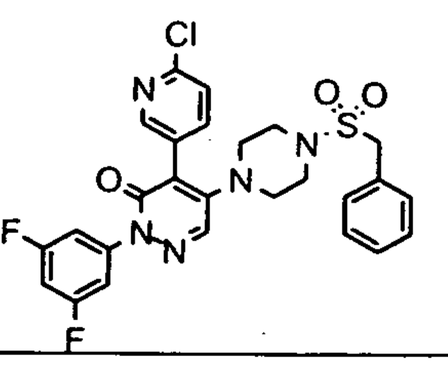
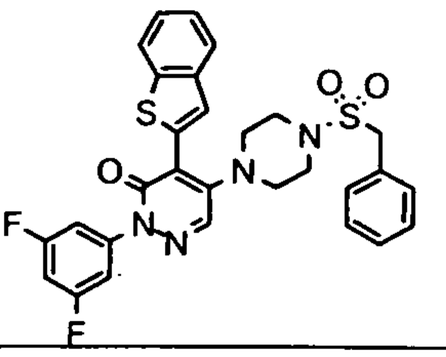
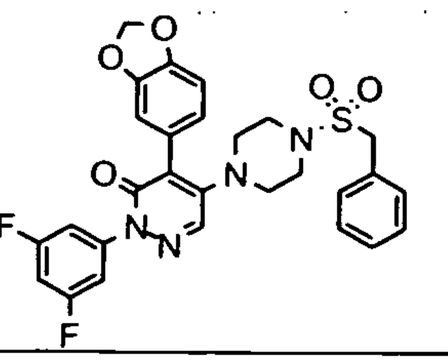
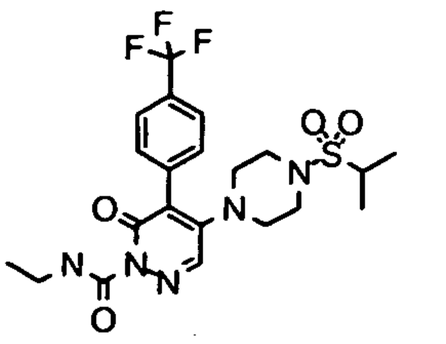
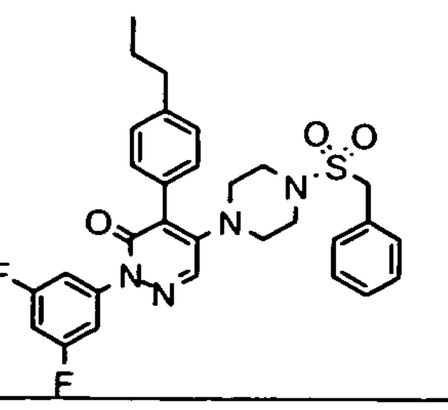
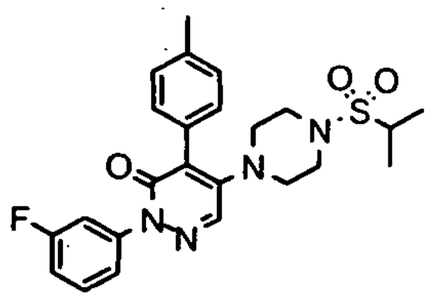
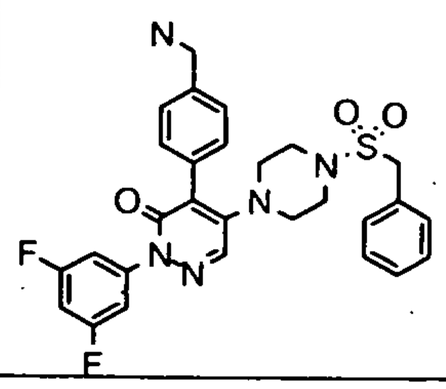
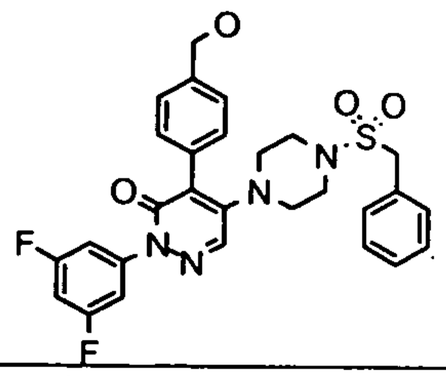
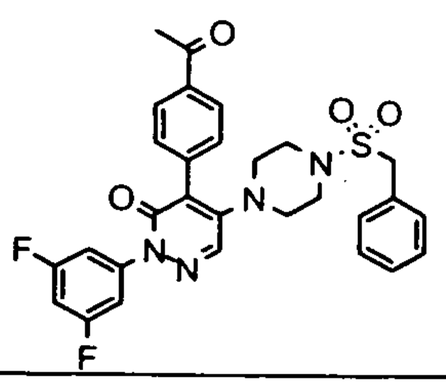
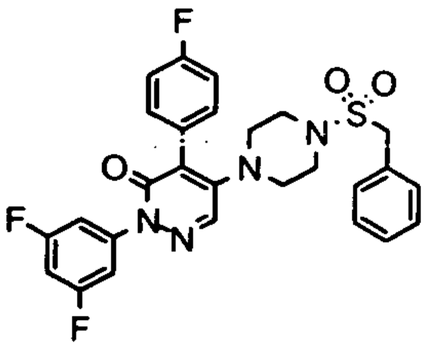
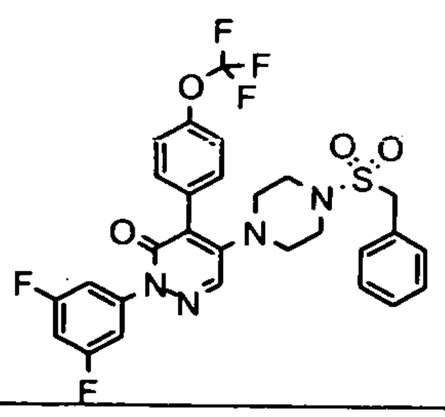
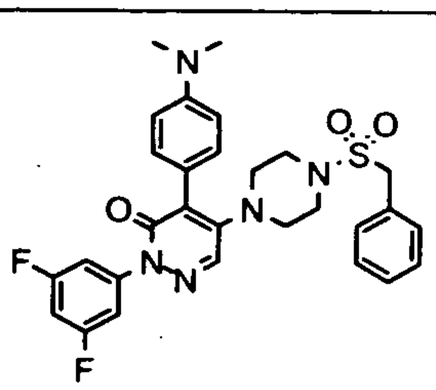
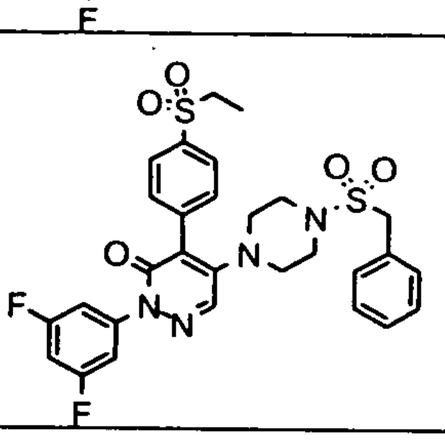
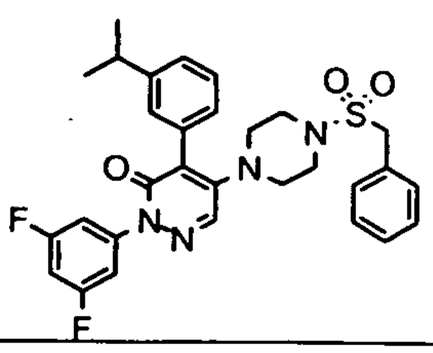
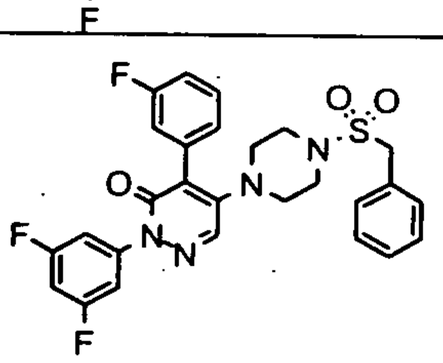
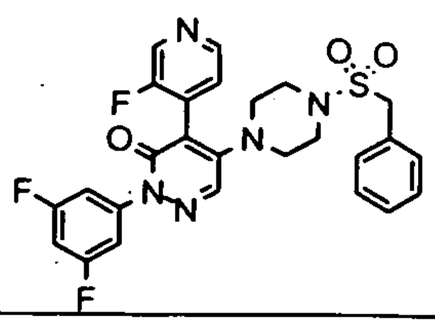
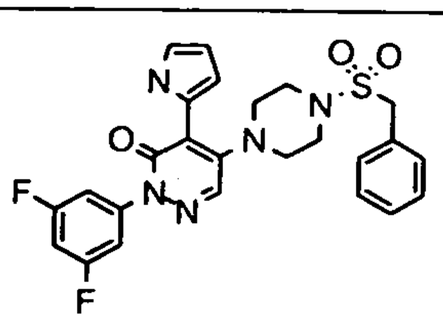
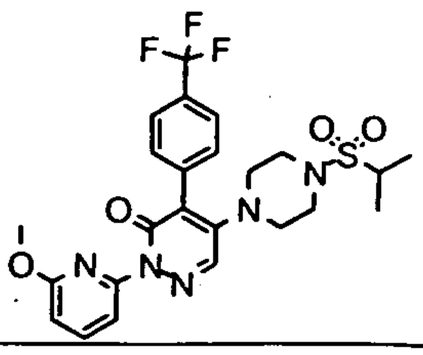
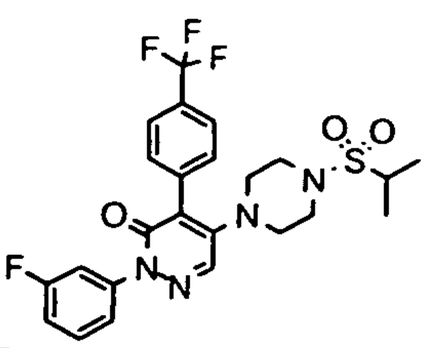
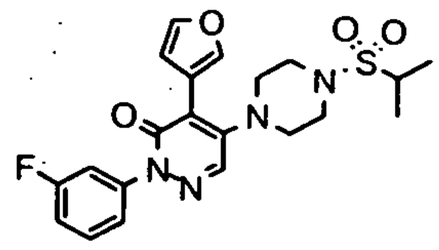
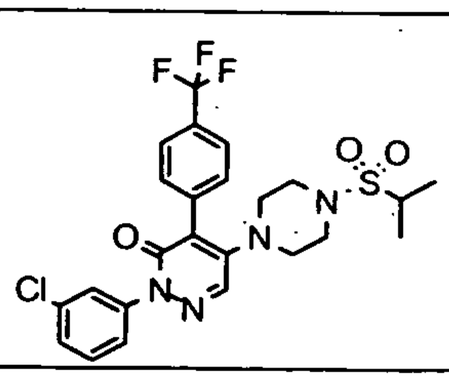
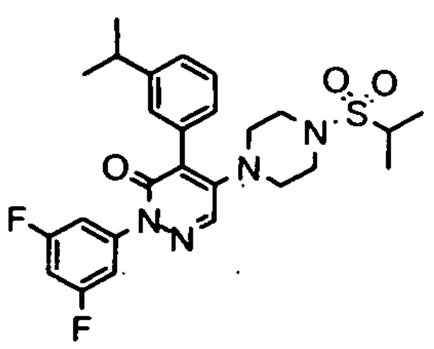
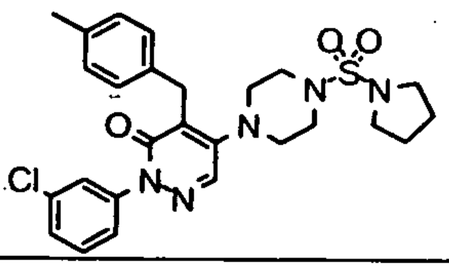
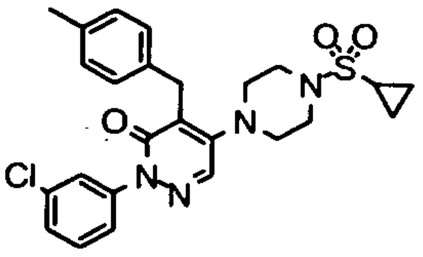
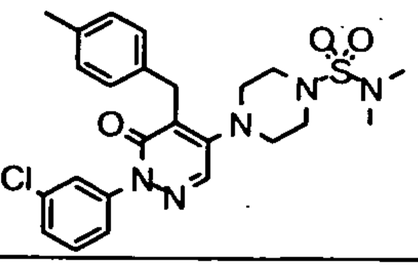
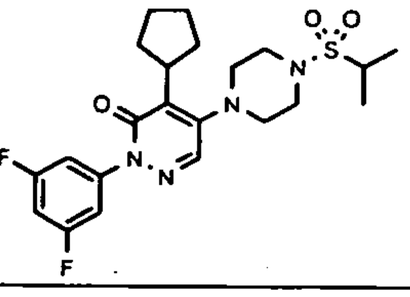
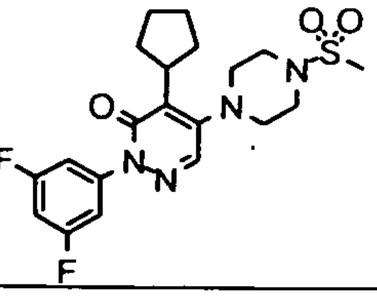
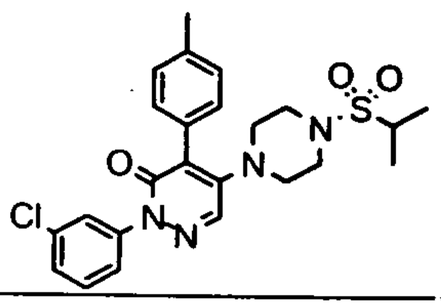
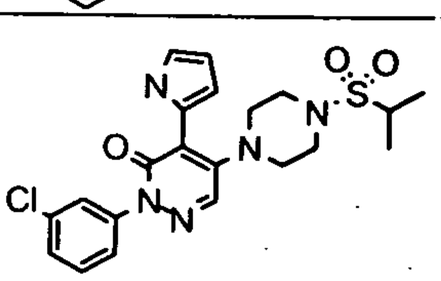
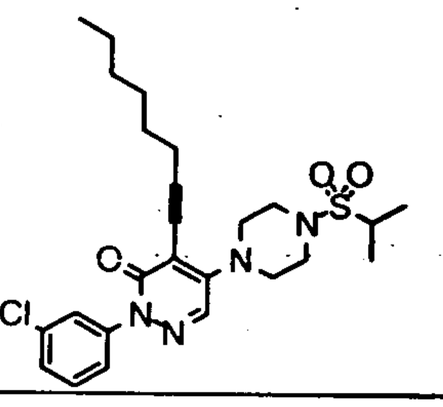
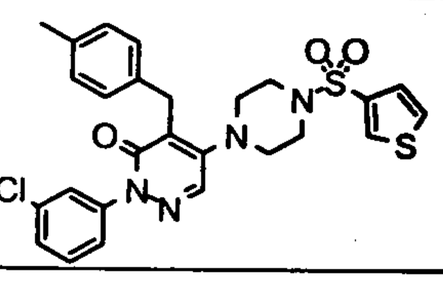
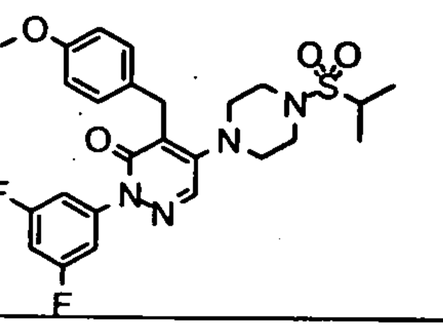
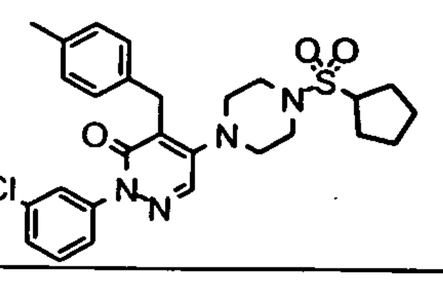
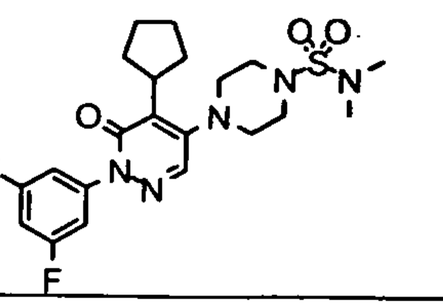
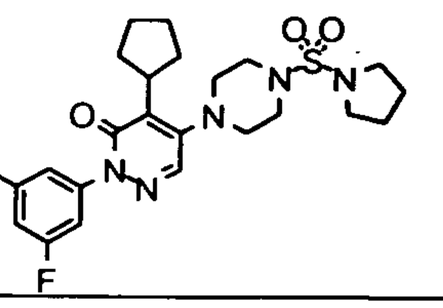
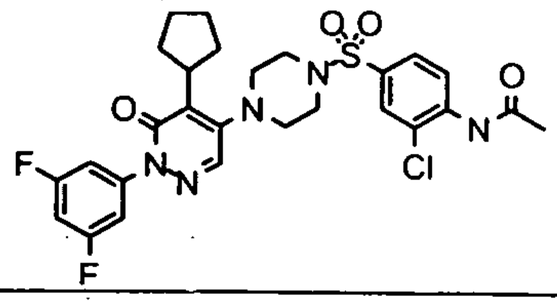
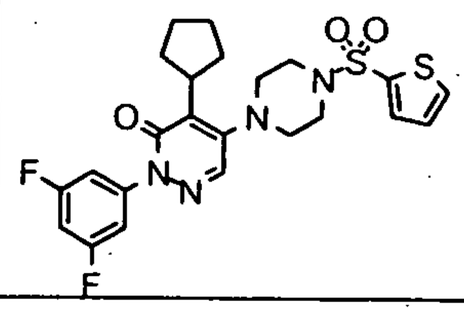
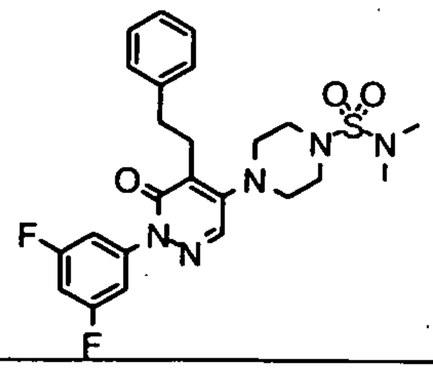
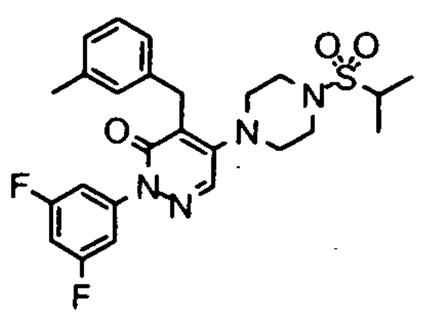
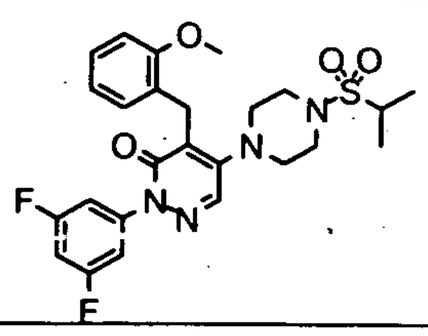
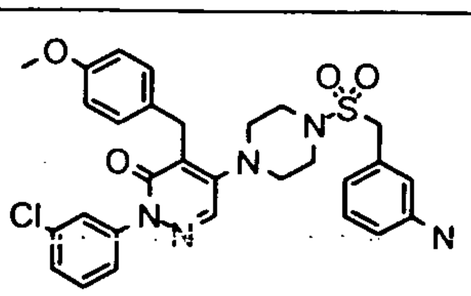
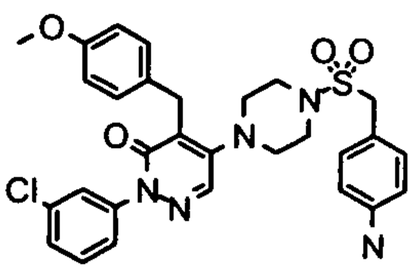
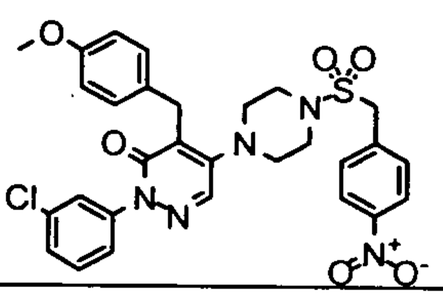
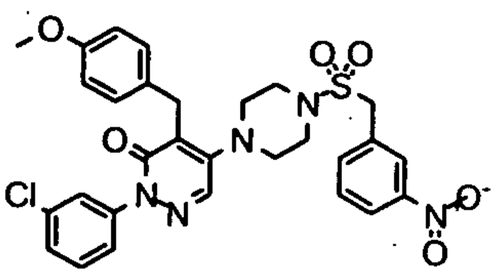
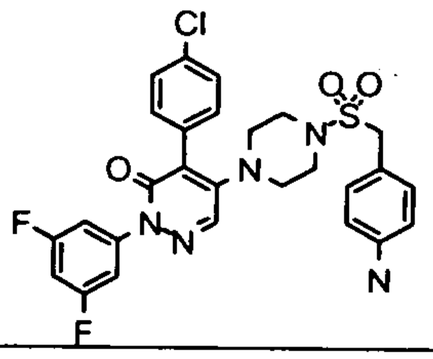
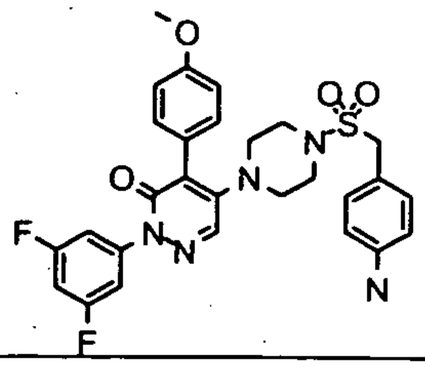
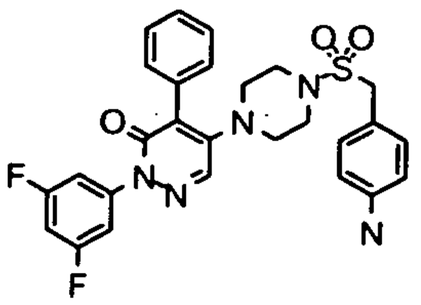
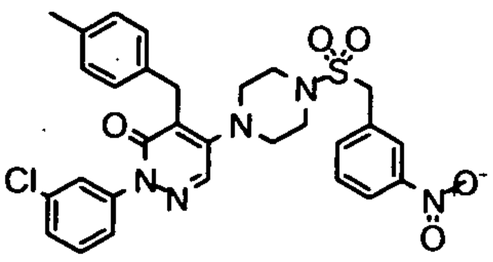
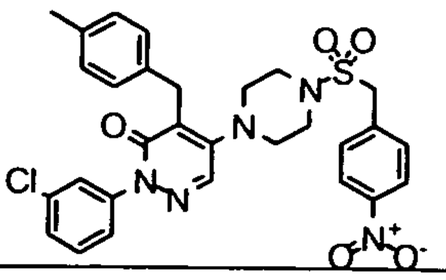
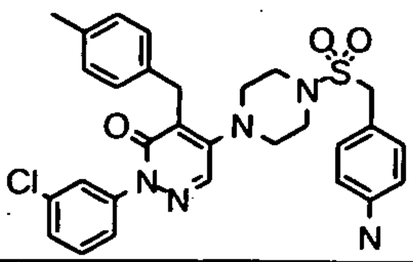
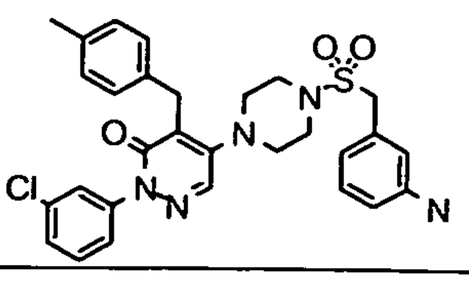
143Z		506
144Z		519
145Z		557
146Z		537
147Z		599

148Z		591
149Z		595
150Z		574
151Z		581
152Z		539
153Z		580
154Z		566
155Z		601
156Z		551
157Z		558
158Z		579
159Z		567
160Z		502
161Z		565

162Z		471
163Z		552
164Z		553
165Z		565
166Z		541
167Z		607
168Z		566
169Z		615
170Z		565
171Z		541
172Z		565
173Z		512
174Z		538
175Z		525

176Z		447
178Z		541
180Z		517
182Z		528
184Z		499
186Z		502
188Z		467
190Z		439

177Z		487
179Z		462
181Z		505
183Z		541
185Z		519
187Z		527
189Z		468
191Z		494

192Z		592
193Z		507
194Z		504
195Z		503
196Z		519
196ZA		580
196ZB		580
196ZC		610
196ZD		610
196ZE		572
196ZF		568
196ZG		538
196ZH		594
196ZI		594
196ZJ		564
196ZK		564

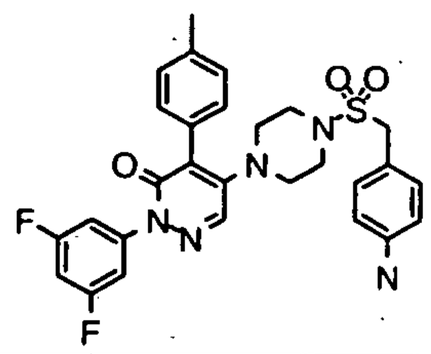
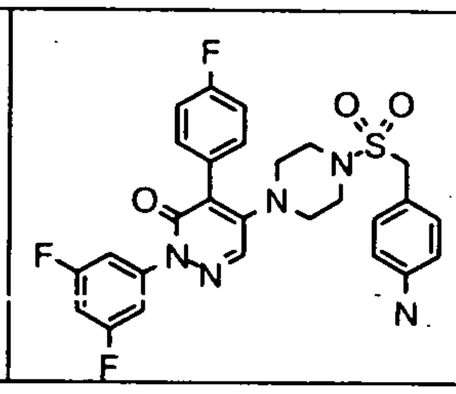
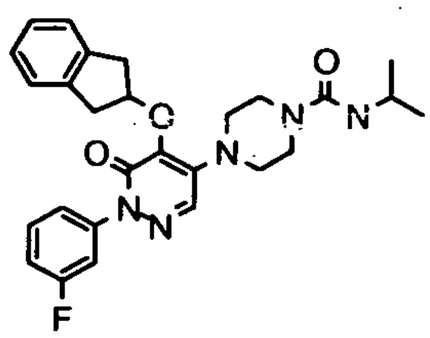
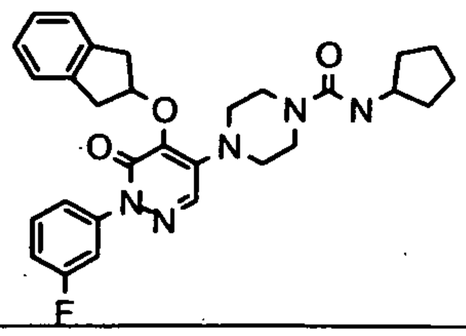
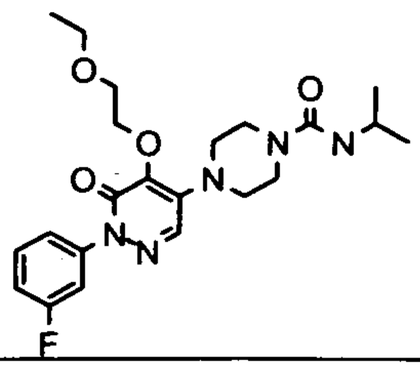
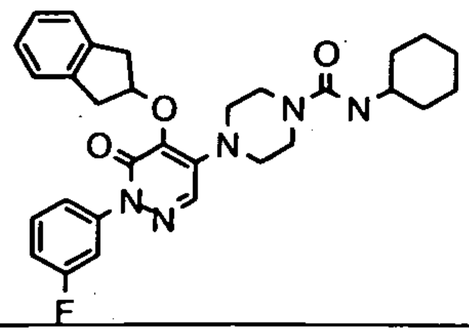
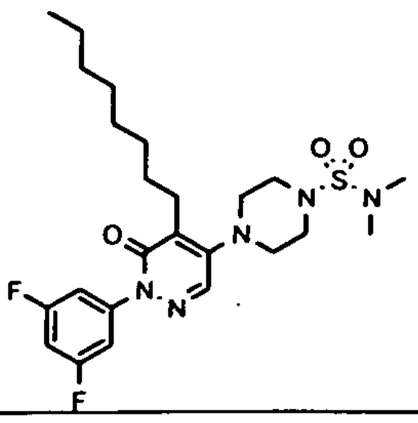
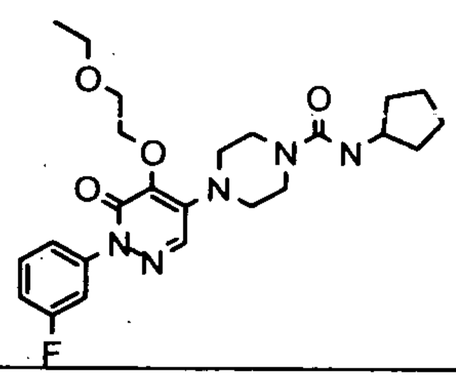
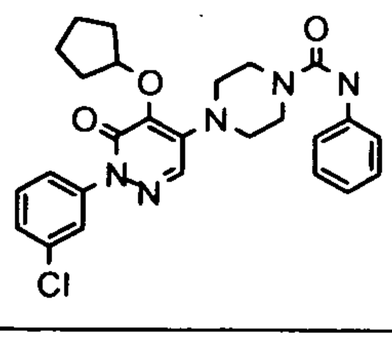
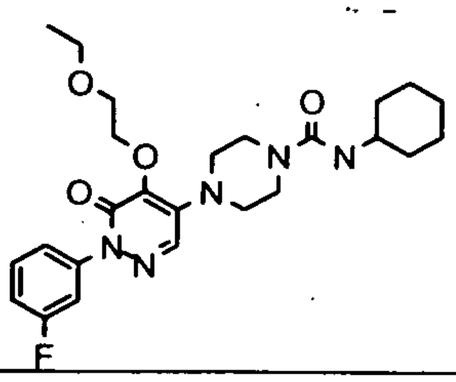
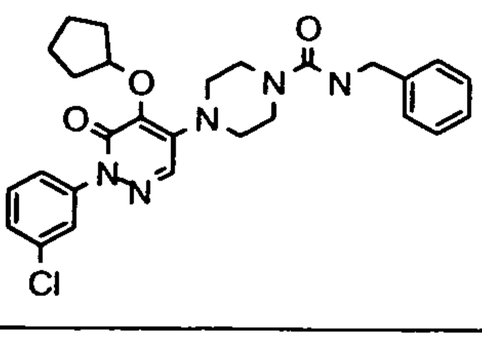
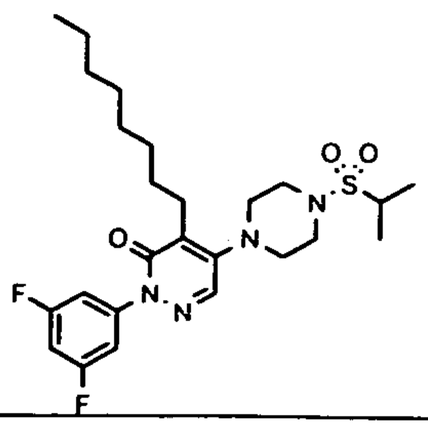
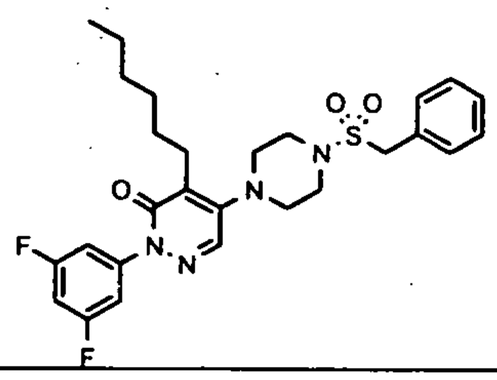
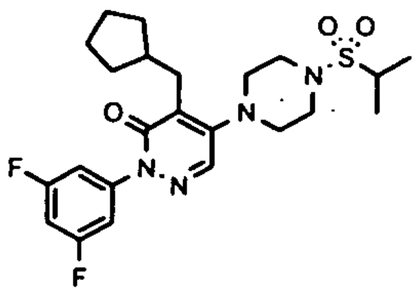
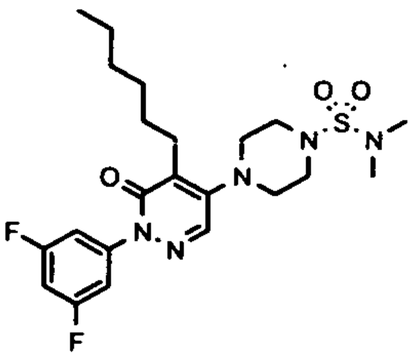
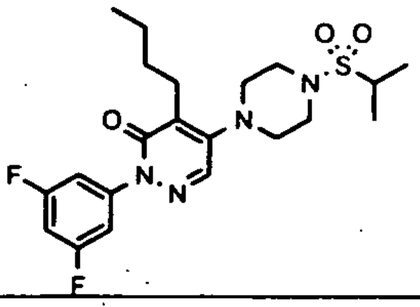
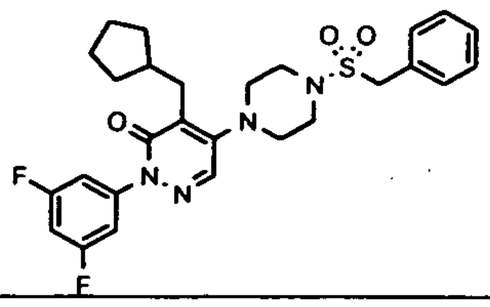
196ZL		552
196ZM		556

Table 6: Oxygen Linked Analogs with Urea

The following compounds can be synthesized by using steps 1, 2, 4, 6, and 8 in Scheme 1.

Comp. No.	Structure	MS M+1
197Z		492
199Z		518
201Z		448
203Z		532
204Za		512

Comp. No.	Structure	MS M+1
198Z		474
200Z		494
202Z		488
204Z		508
204Zb		511

204Zc		531
204Ze		481
204Zg		484
204Zi		455
204Zk		529

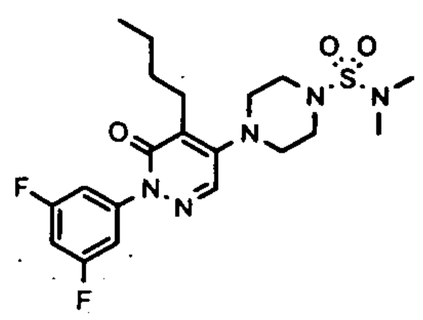
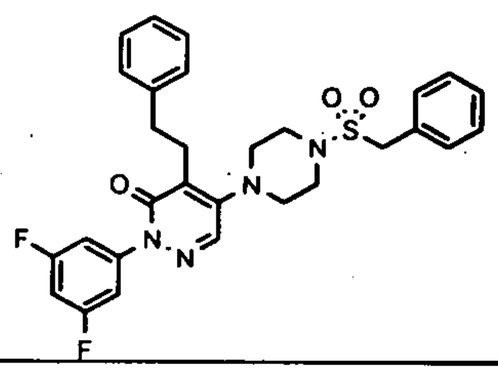
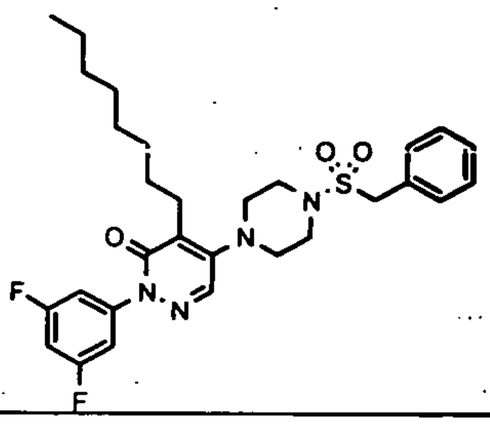
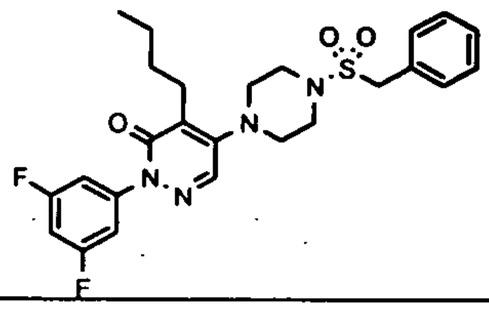
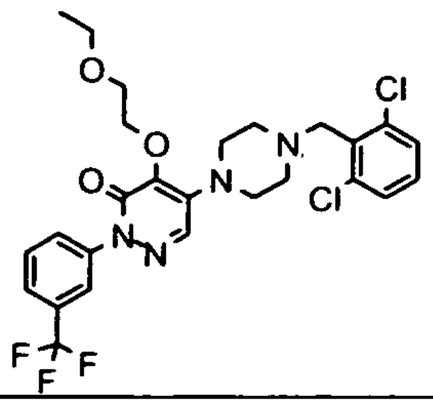
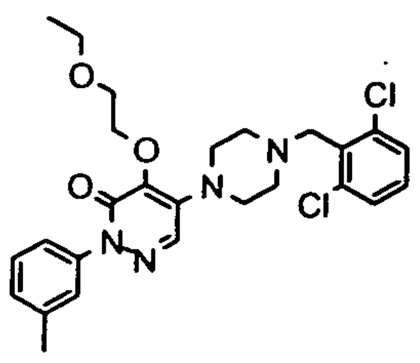
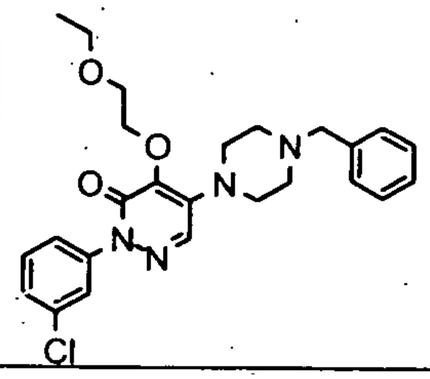
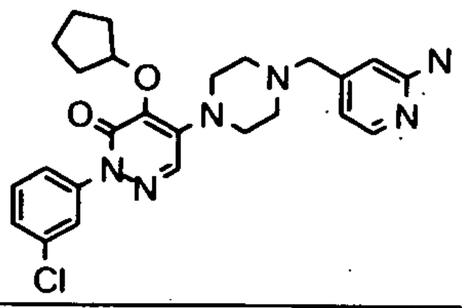
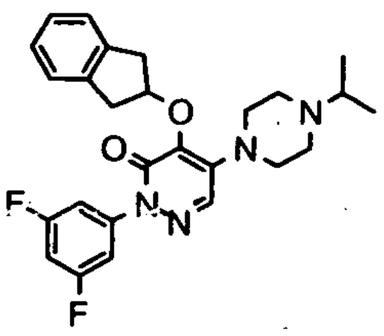
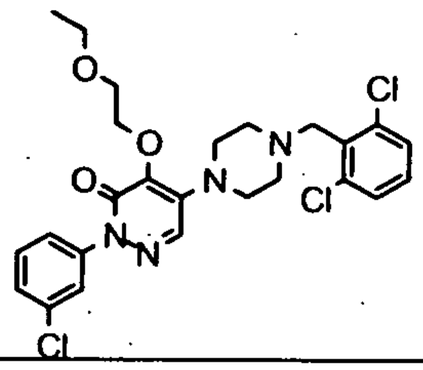
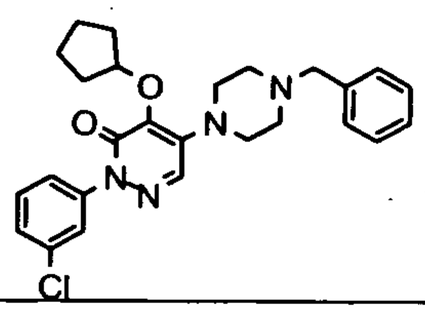
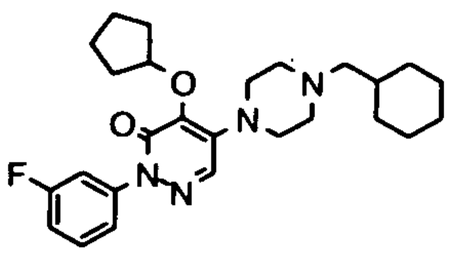
204Zd		456
204Zf		551
204Zh		559
204Zj		503

Table 7: Oxygen Analogs with Amine

The following compounds can be synthesized by using steps 1, 2, 4, 6, and 10 in Scheme 1.

Comp. No.	Structure	MS M+1
205Z		571
206Z		517

207Z		469
209Z		481
211Z		467
213Z		539
215Z		465
217Z		455

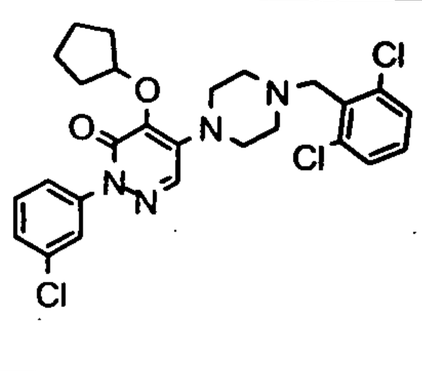
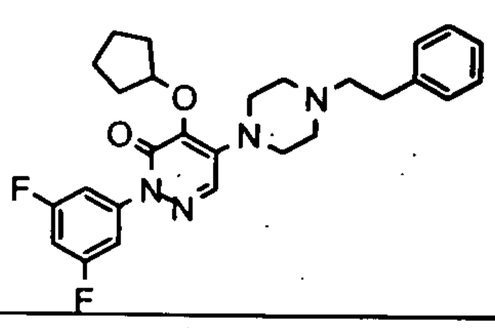
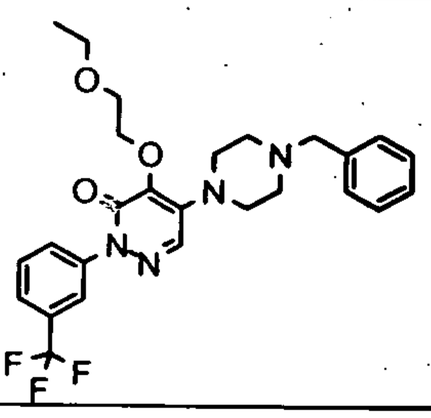
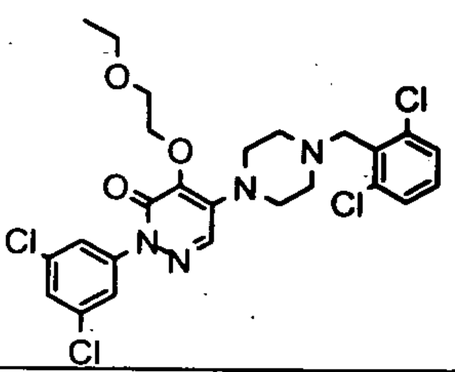
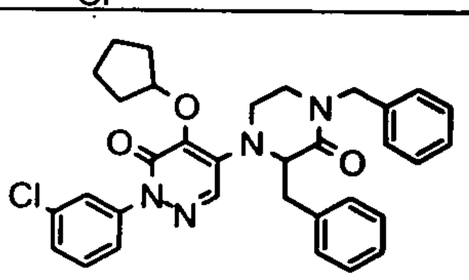
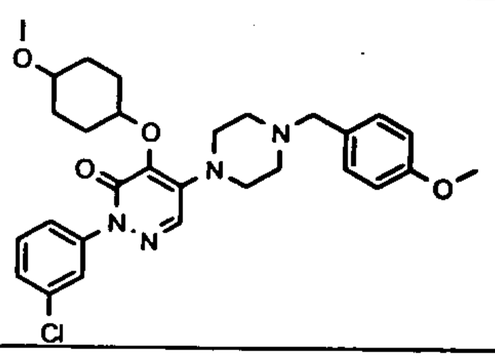
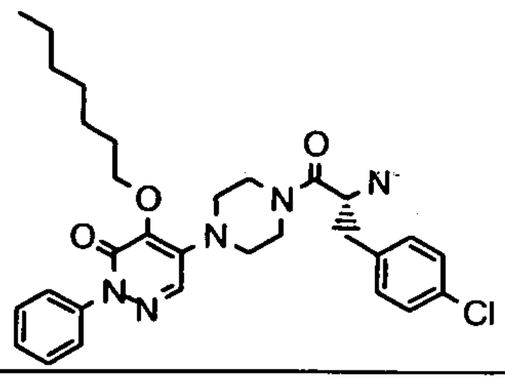
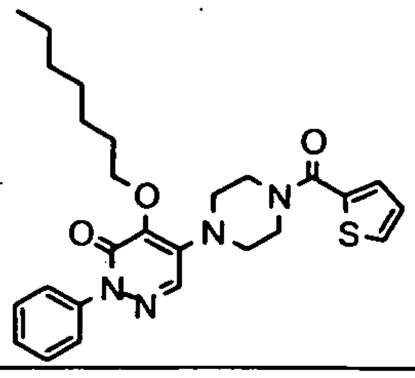
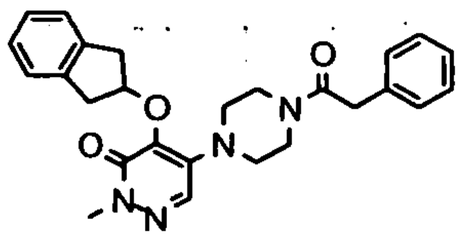
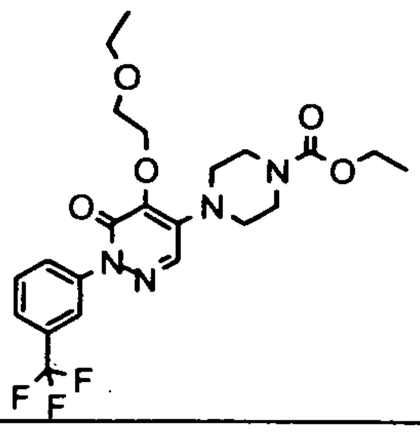
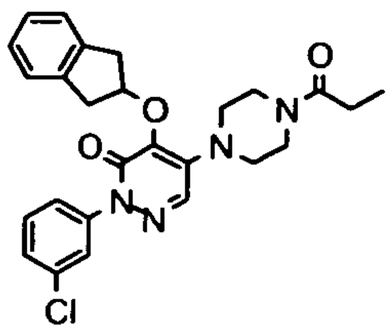
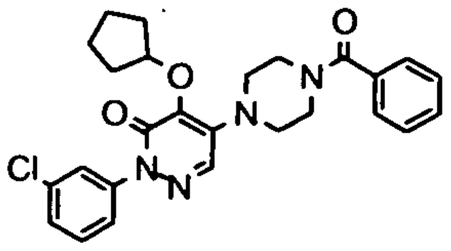
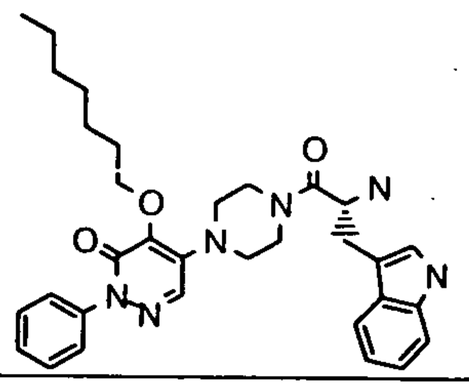
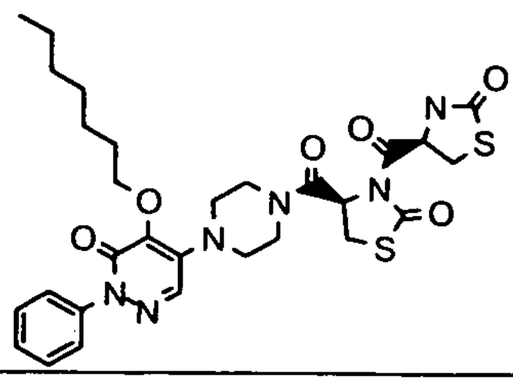
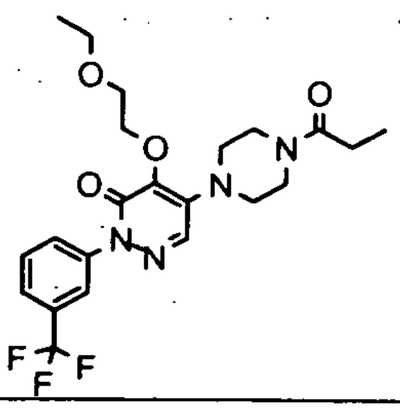
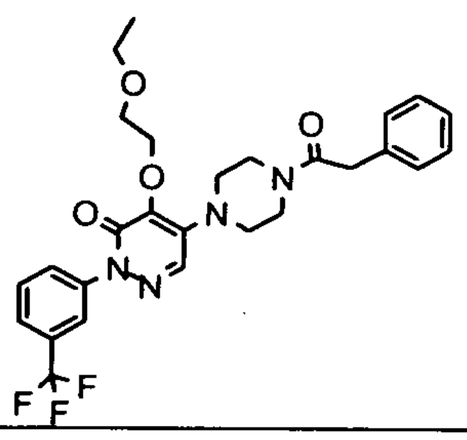
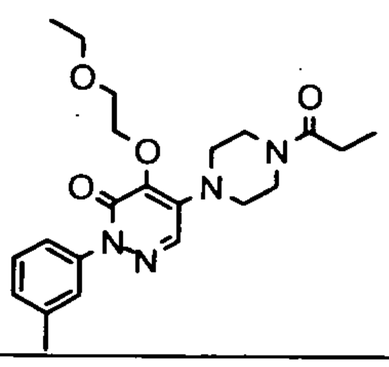
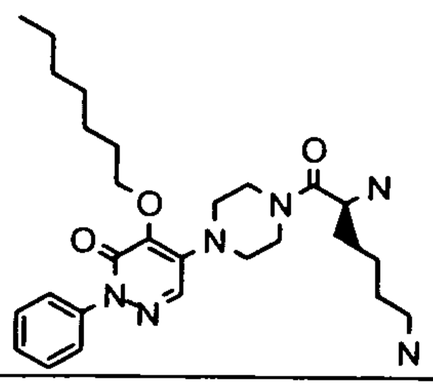
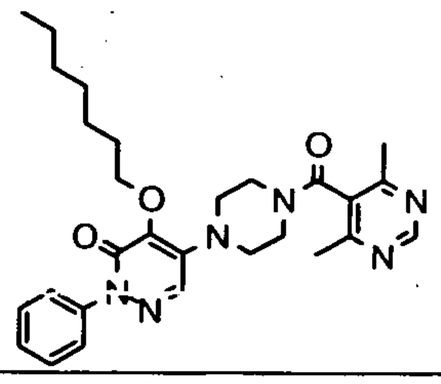
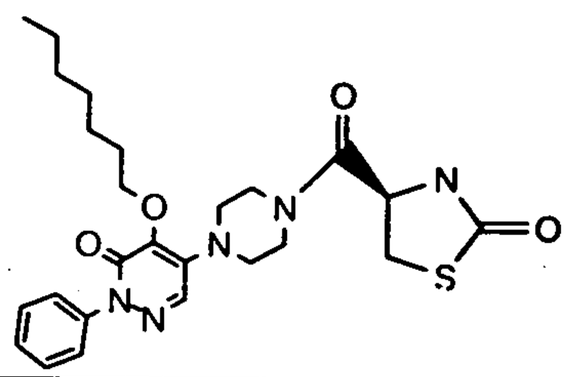
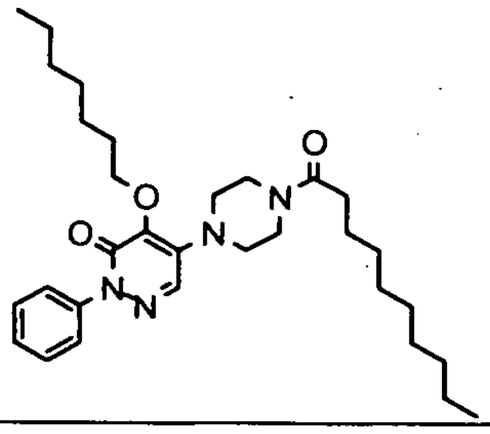
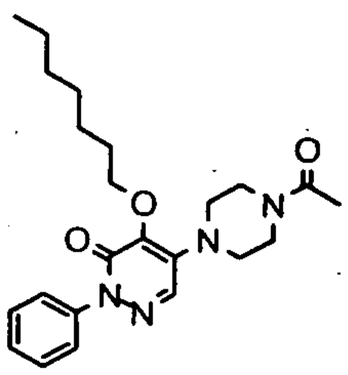
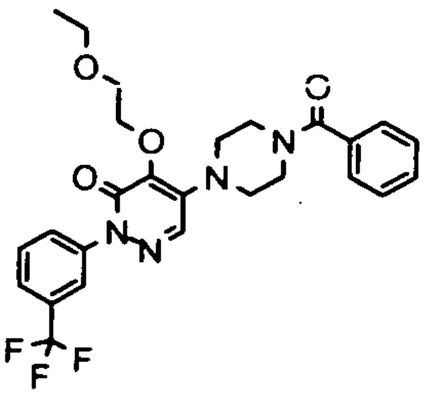
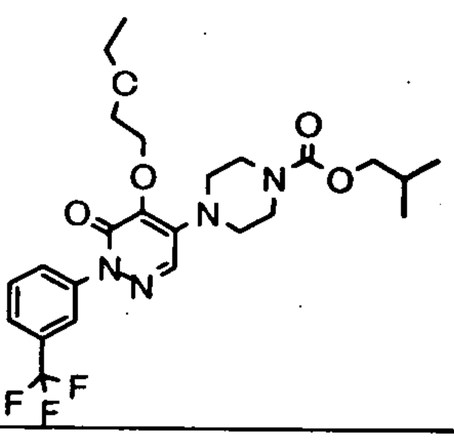
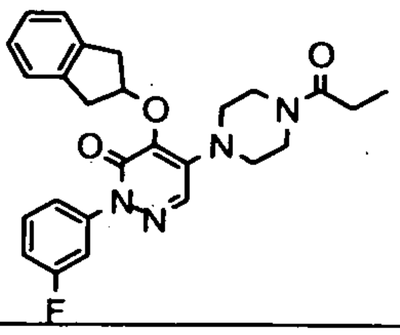
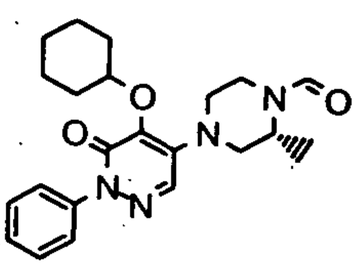
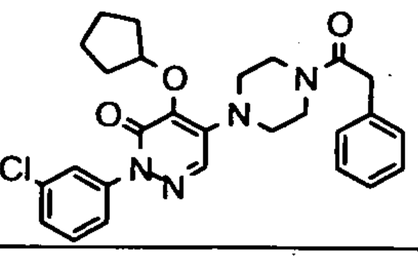
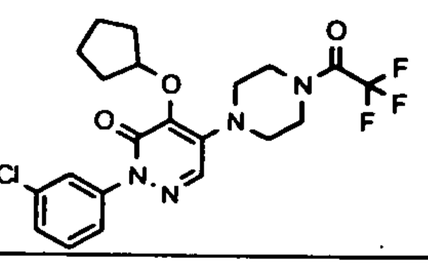
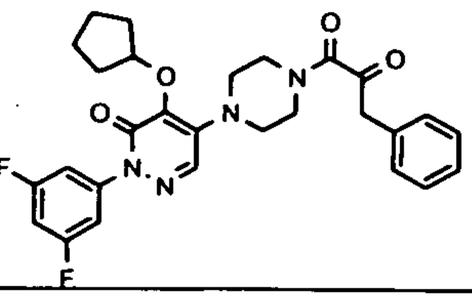
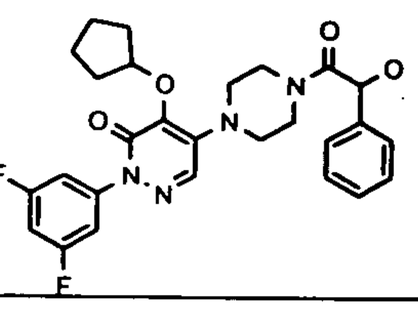
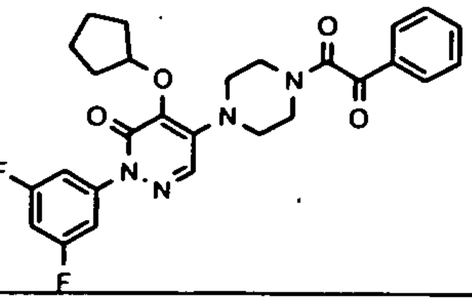
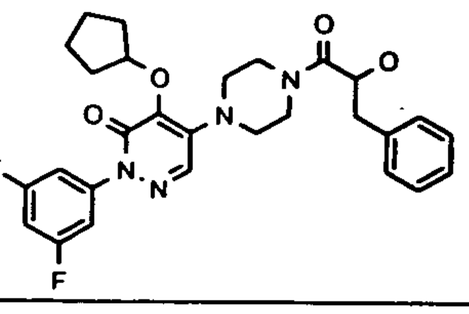
208Z		533
210Z		481
212Z		503
214Z		573
216Z		570
217ZA		539

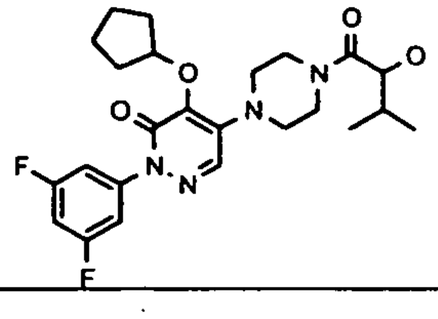
Table 8: Oxygen Linked Analogs with Amide

The following compounds can be synthesized by using steps 1, 2, 4, 6, and 7 in Scheme 1.

Comp. No.	Structure	MS M+1
218Z		552
220Z		481
222Z		445
224Z		485
226Z		479
228Z		479

Comp. No.	Structure	MS M+1
219Z		557
221Z		629
223Z		469
225Z		531
227Z		415
229Z		499

230Z		505
231Z		500
232Z		525
233Z		413
234Z		517
235Z		513
236Z		463
237Z		524
238Z		493
238A		471
238B		523
238C		511
238D		509
238E		525

238F		477

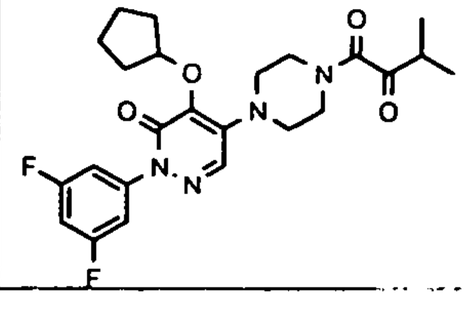
238G		475

Table 9: Oxygen Linked Analogs with Heterocycle

The following compounds can be synthesized by using steps 1, 2, and 4 in Scheme 1.

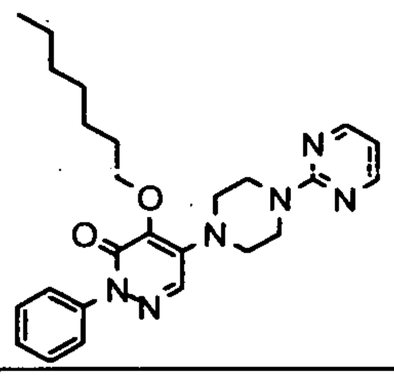
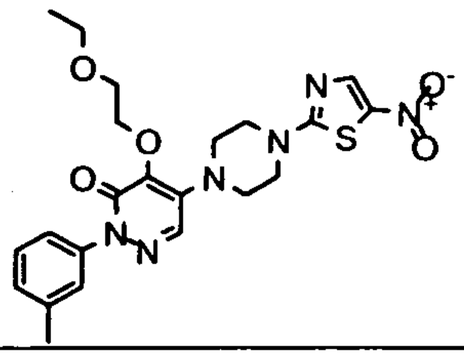
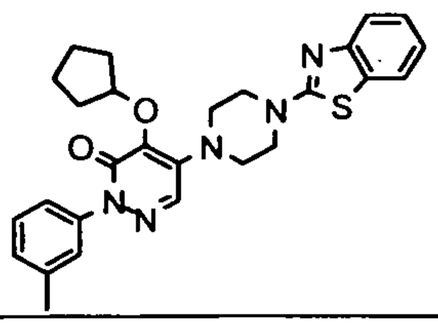
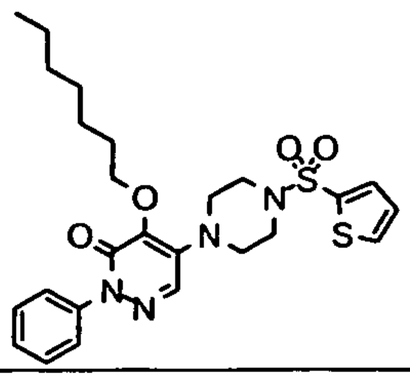
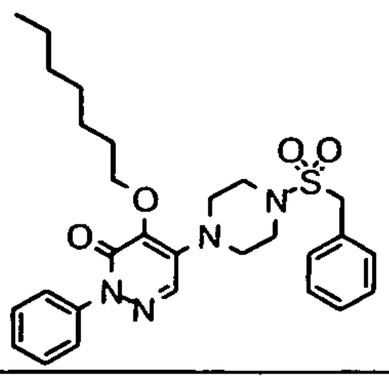
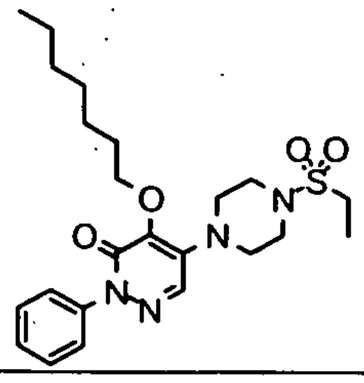
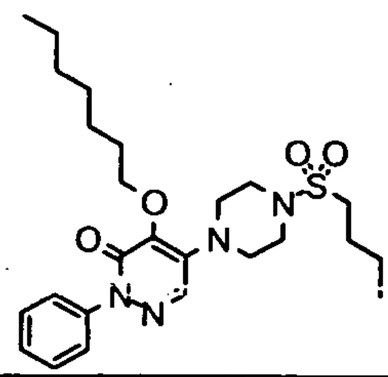
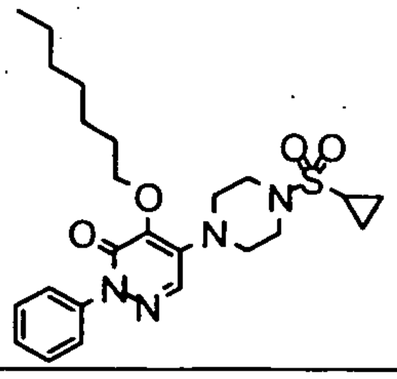
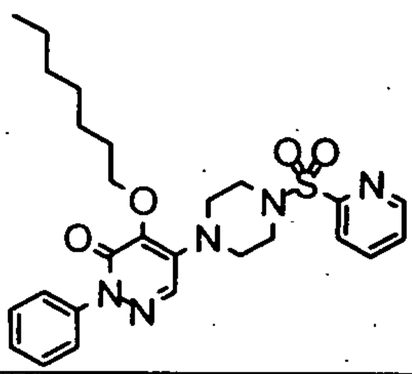
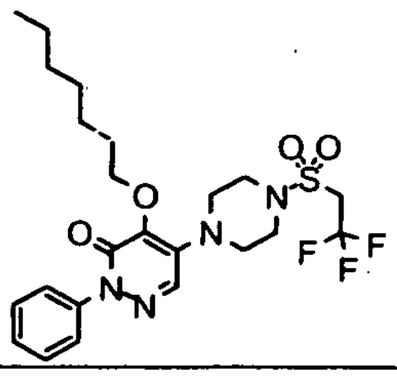
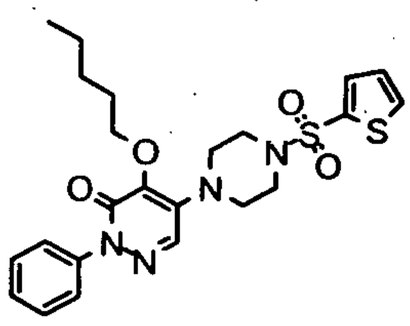
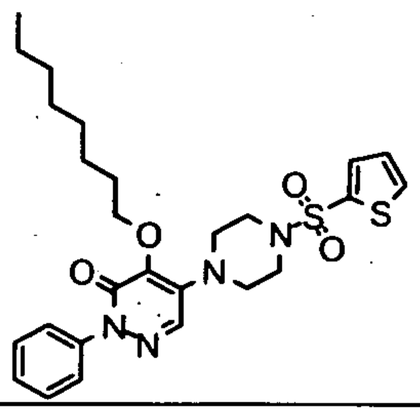
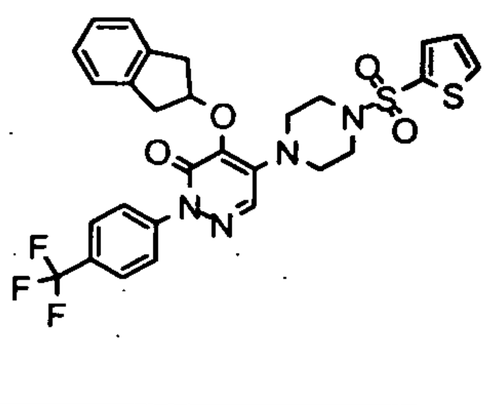
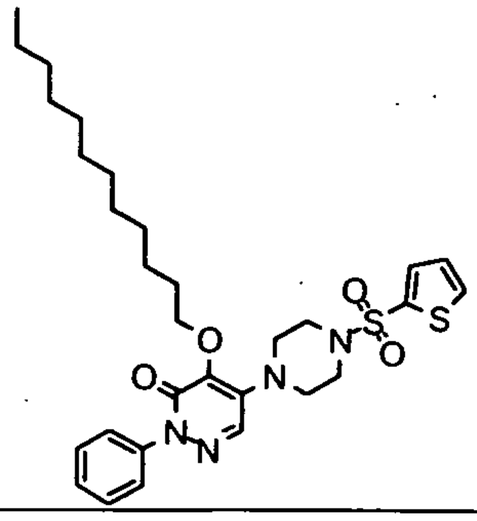
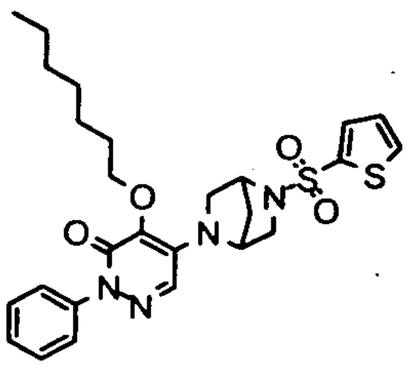
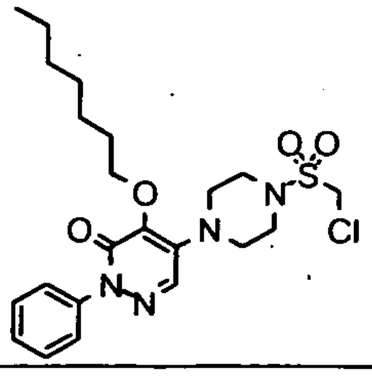
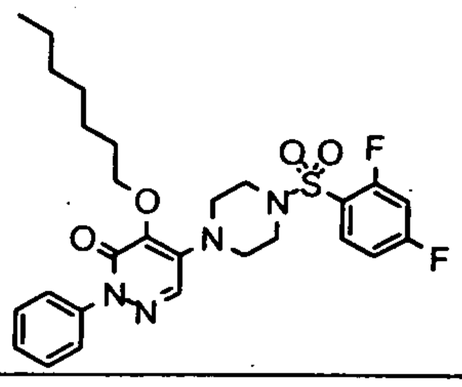
Compound No.	Structure	MS M+1
239Z		449
240Z		487
241Z		488

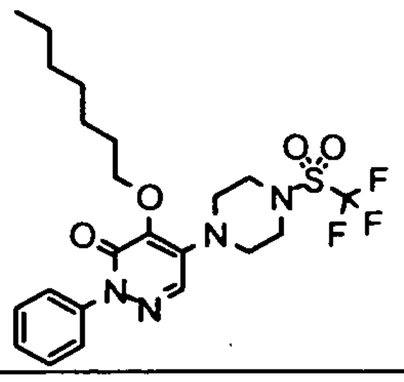
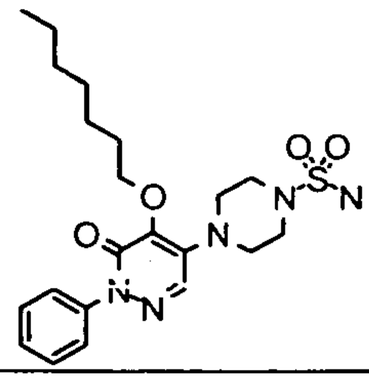
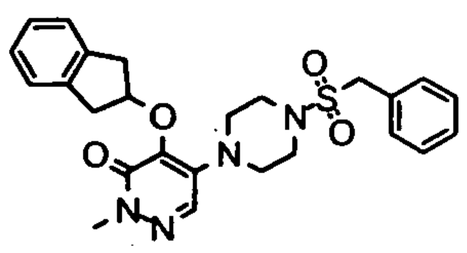
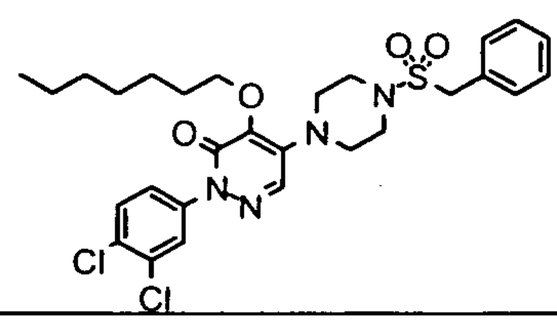
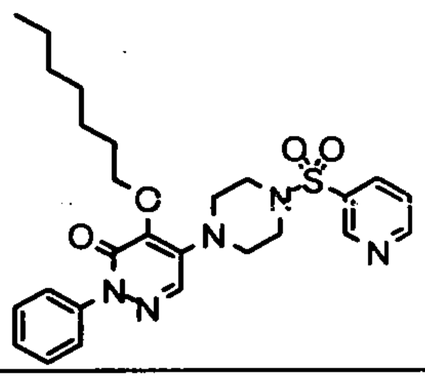
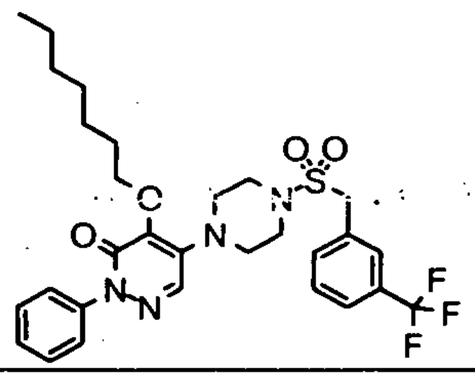
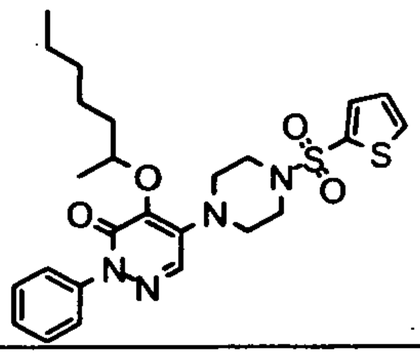
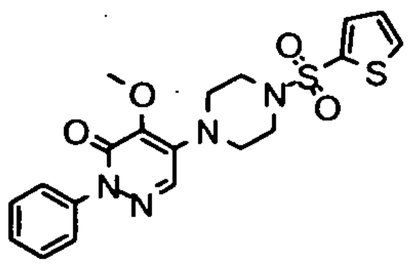
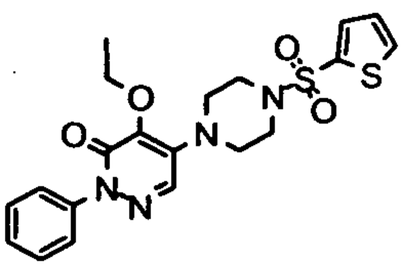
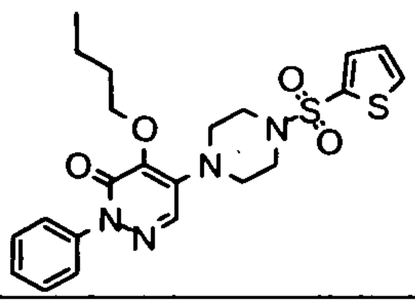
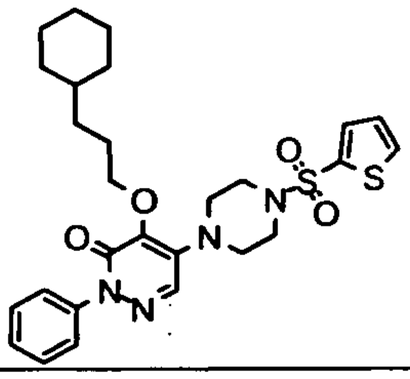
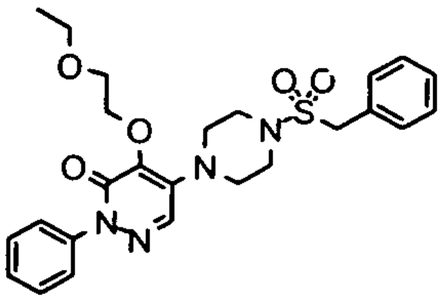
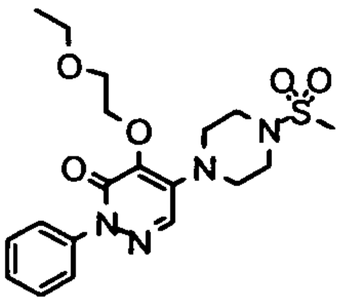
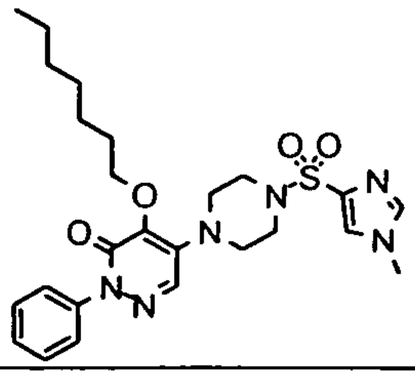
Table 10: Oxygen Linked Analogs with Sulfonamide

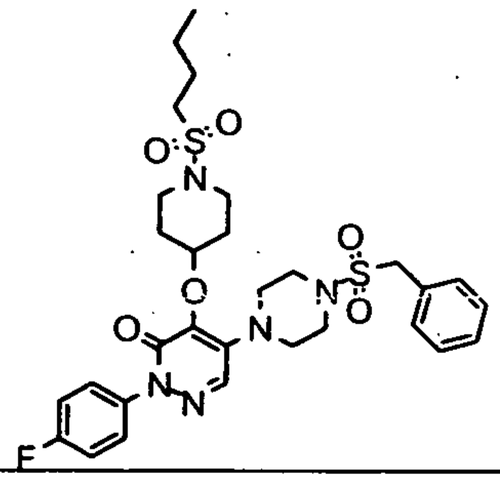
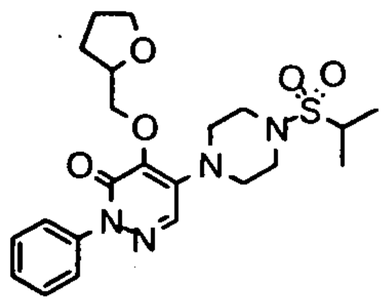
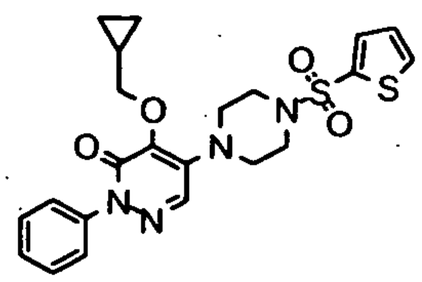
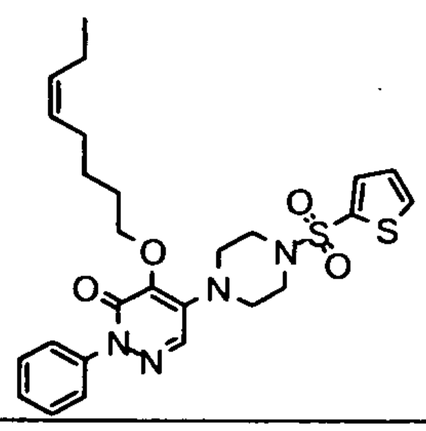
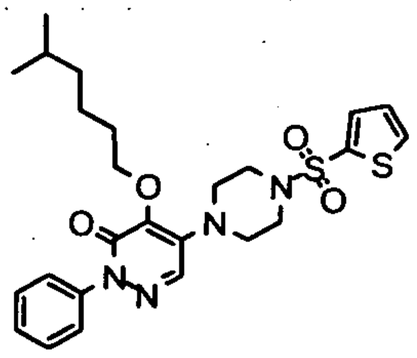
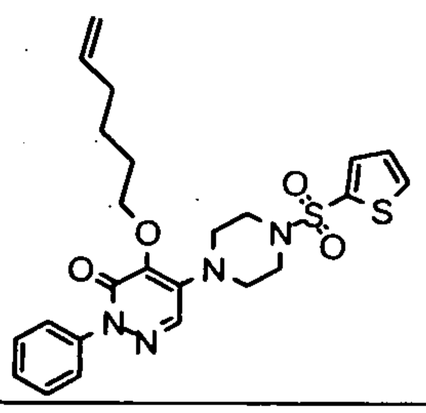
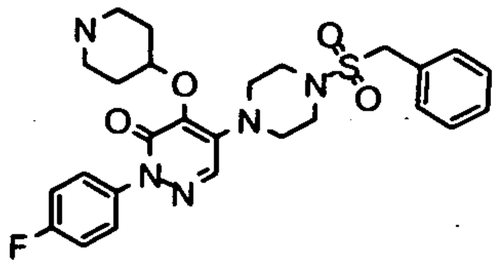
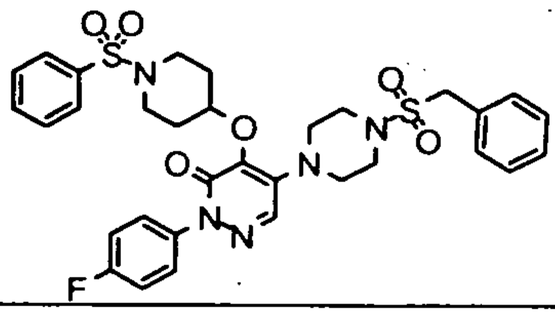
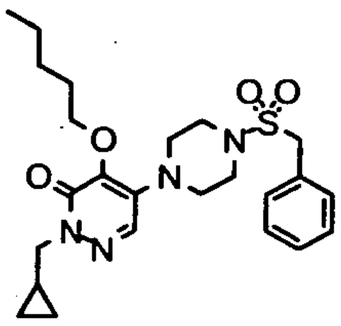
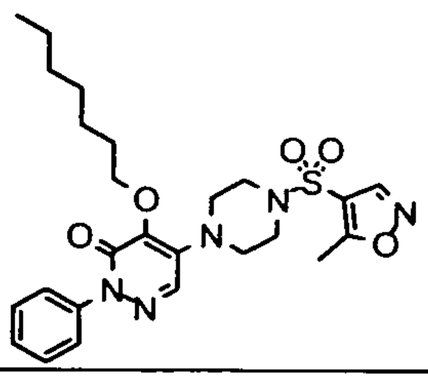
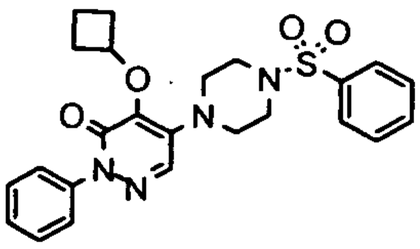
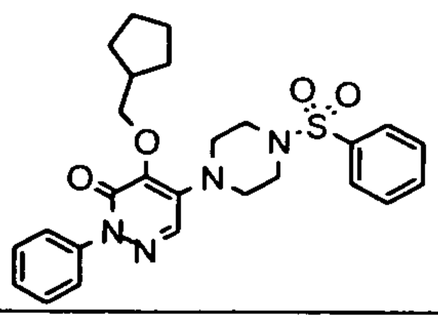
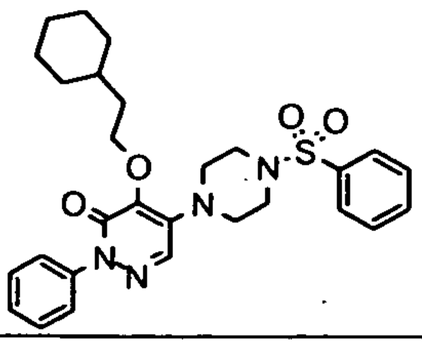
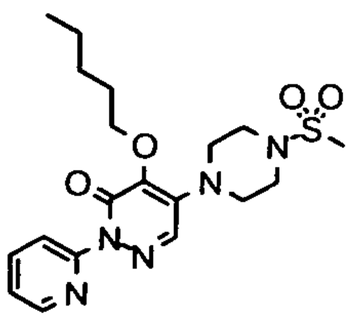
The following compounds can be synthesized using steps 1, 2, 4, 6, and 9 of Scheme 1 or steps 11, 12, and 14 of Scheme 2.

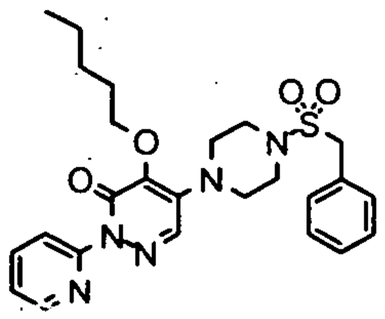
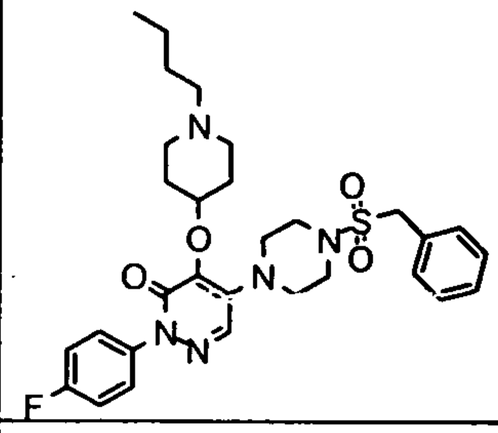
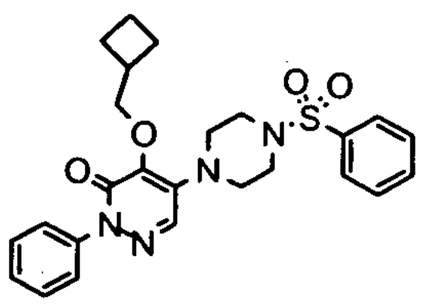
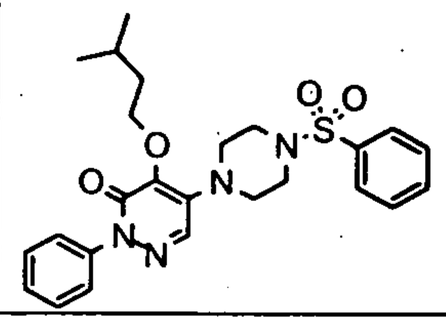
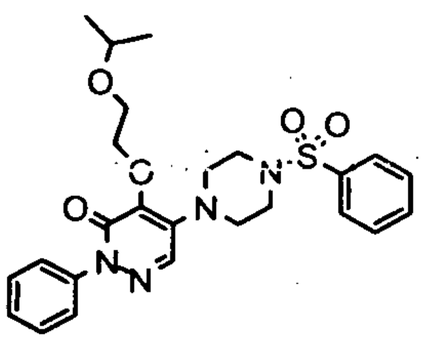
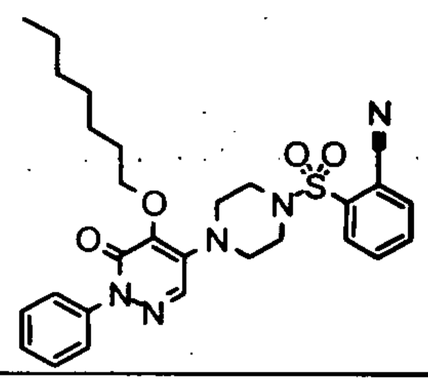
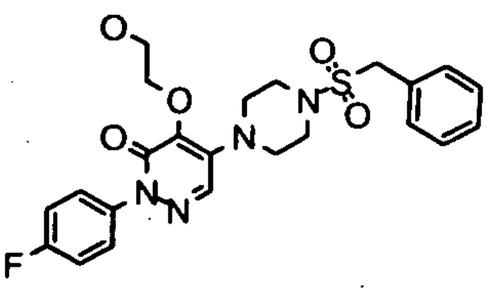
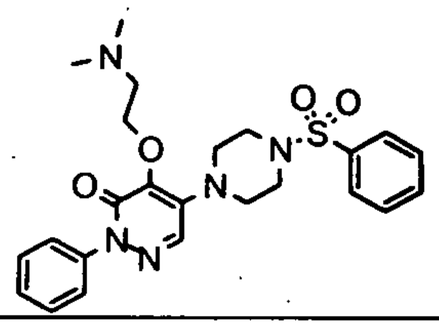
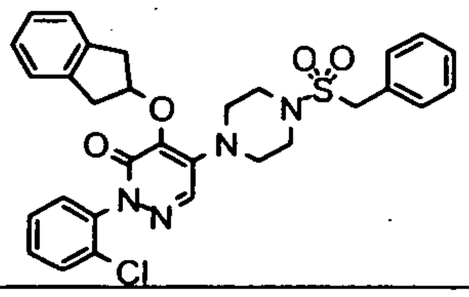
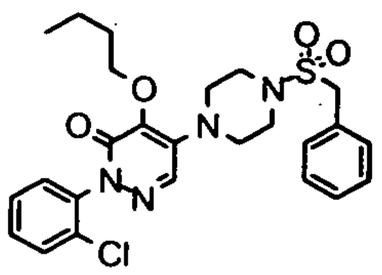
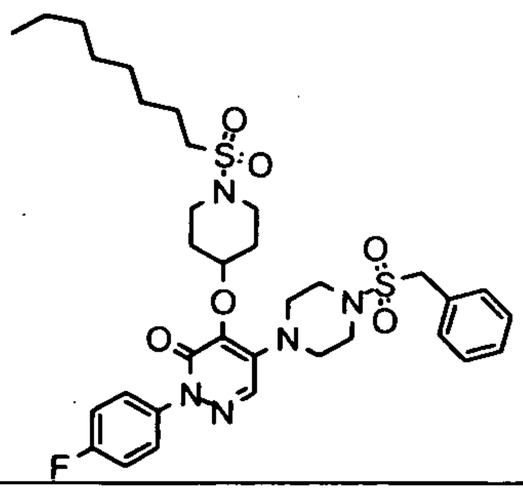
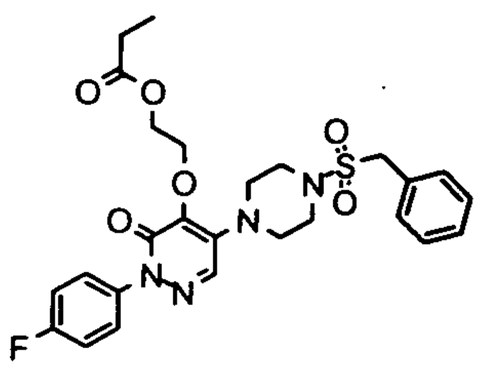
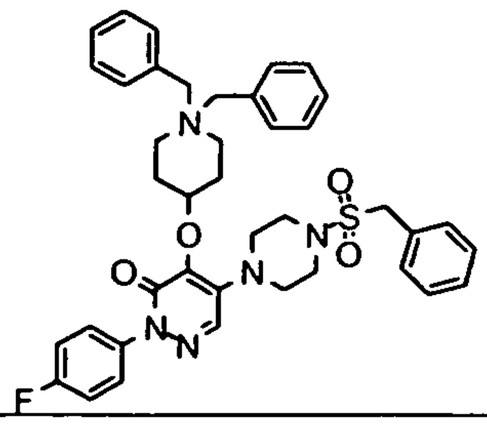
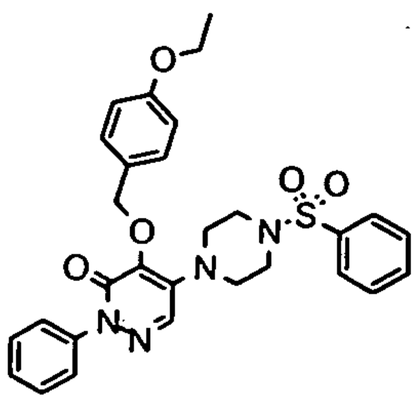
Comp. No.	Structure	MS M+1
242Z		517

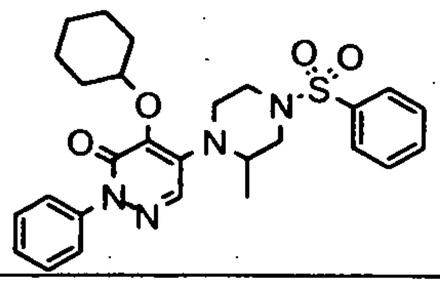
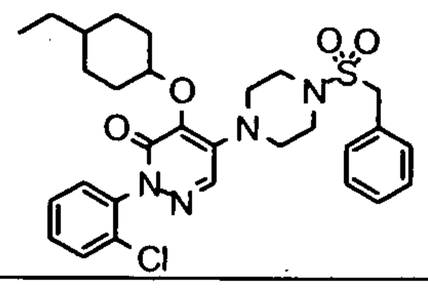
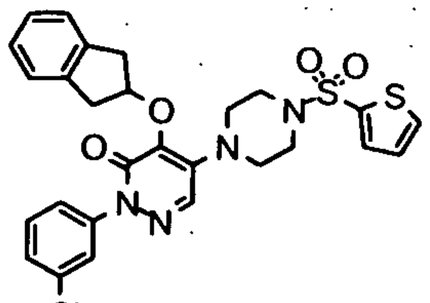
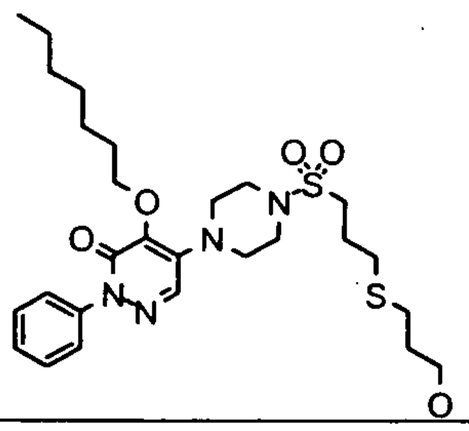
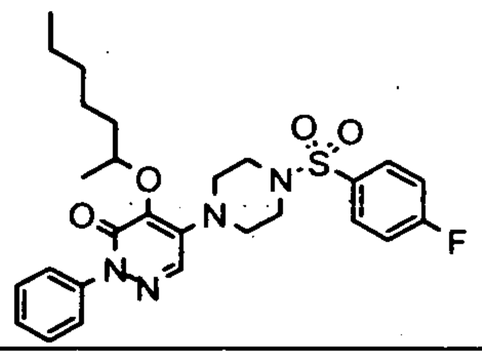
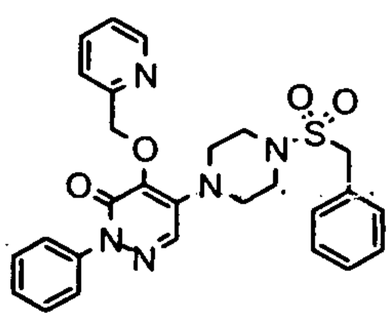
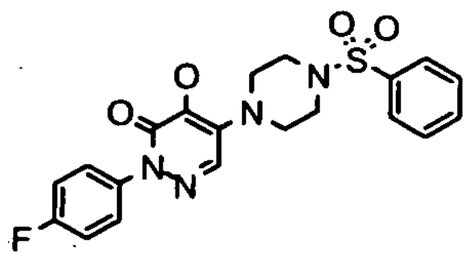
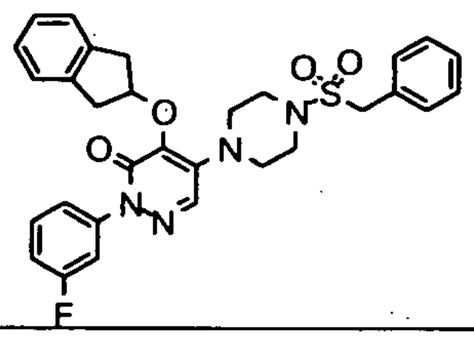
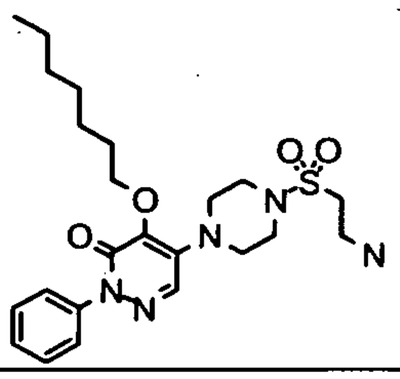
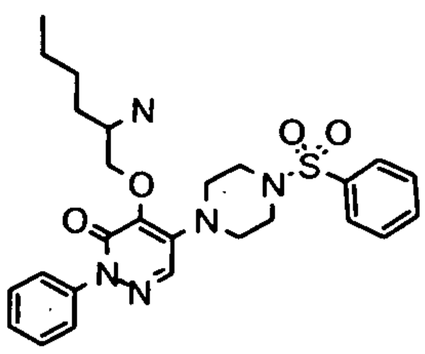
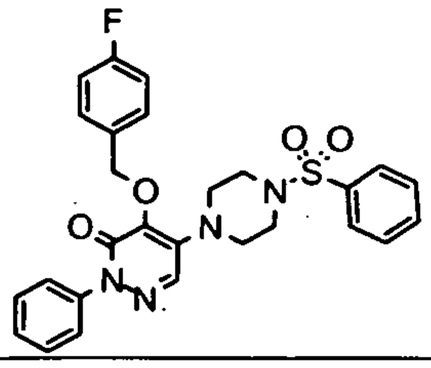
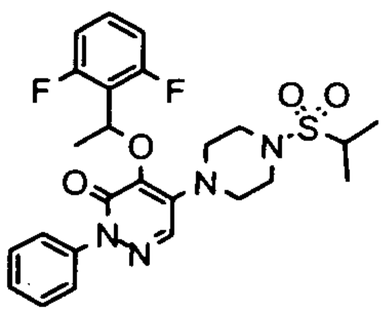
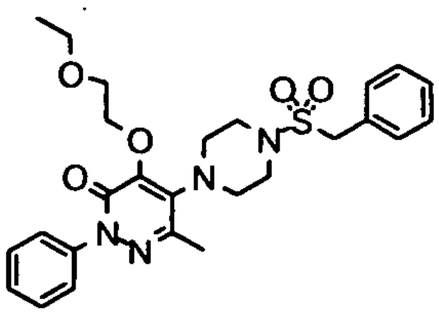
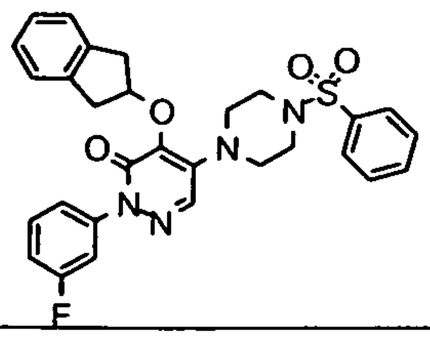
Comp. No.	Structure	MS M+1
243Z		525

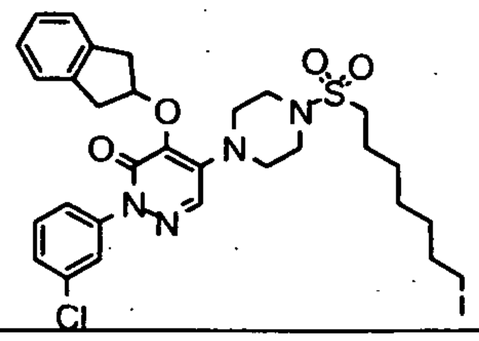
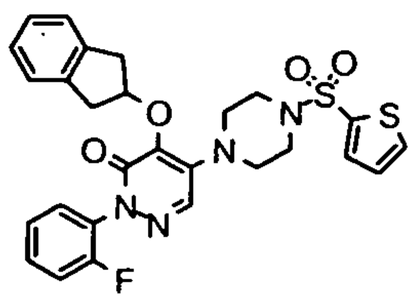
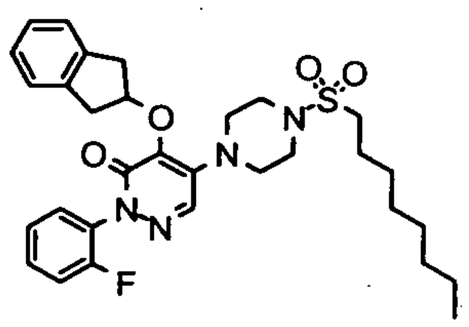
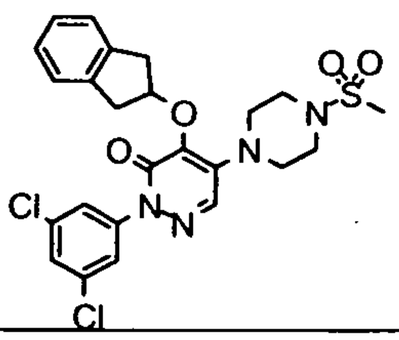
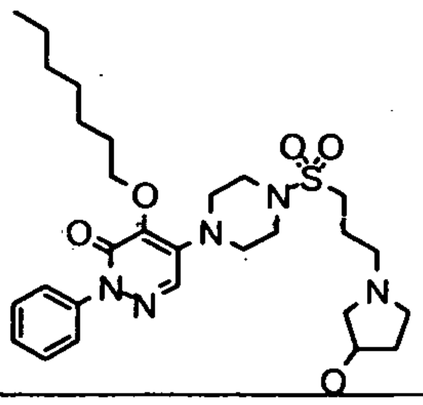
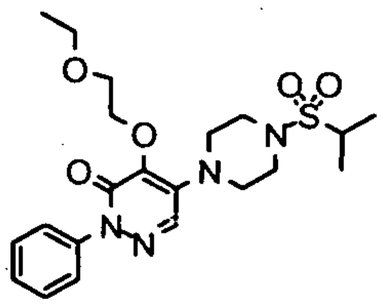
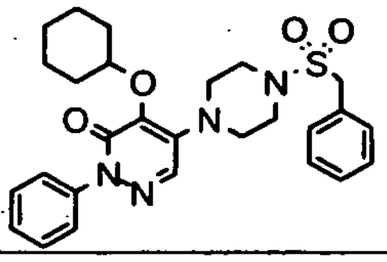
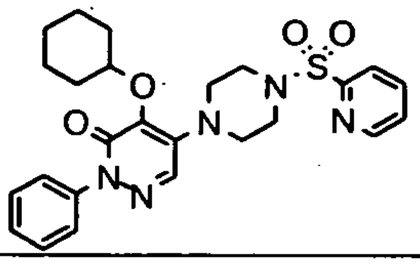
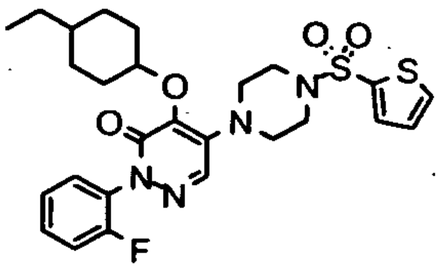
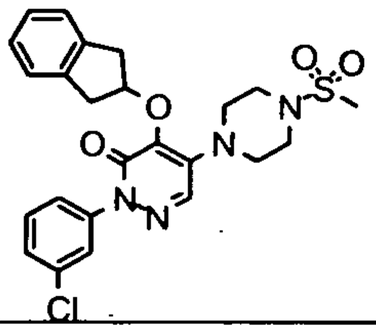
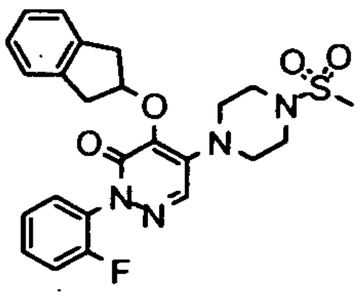
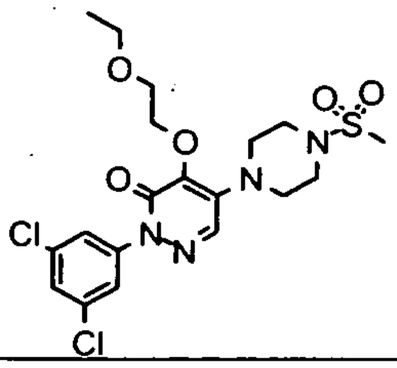
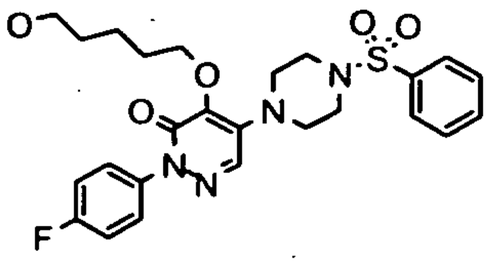
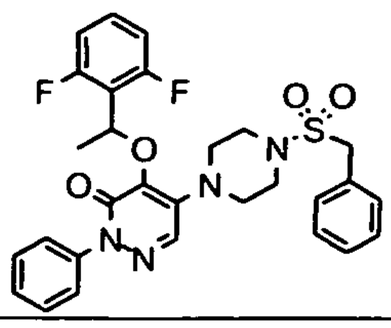
244Z		463
245Z		491
246Z		475
247Z		512
248Z		517
249Z		489
250Z		531
251Z		603
252Z		587
253Z		529
254Z		483
255Z		547

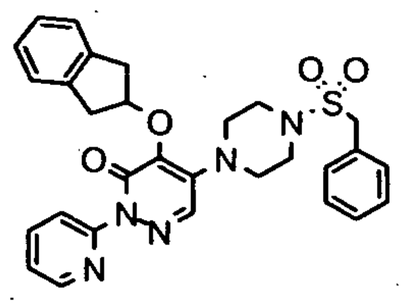
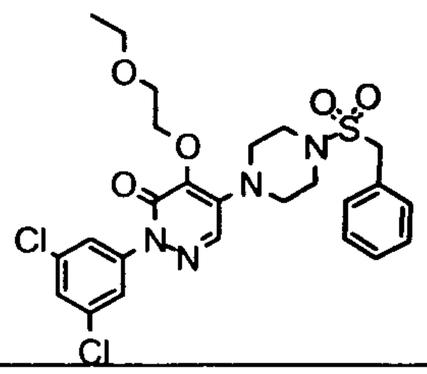
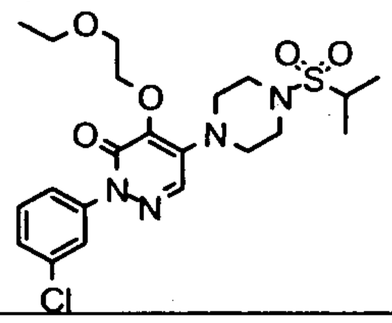
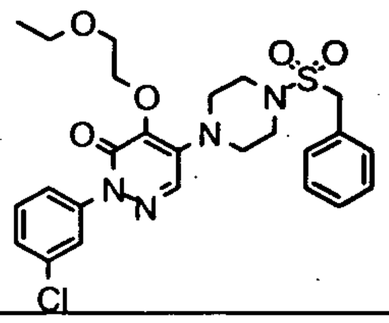
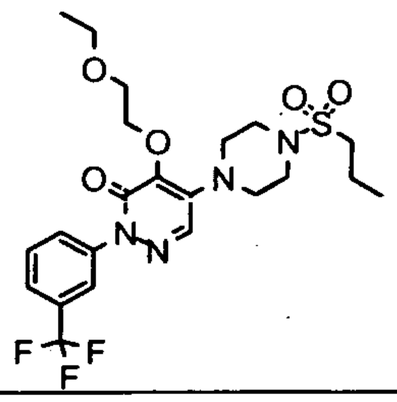
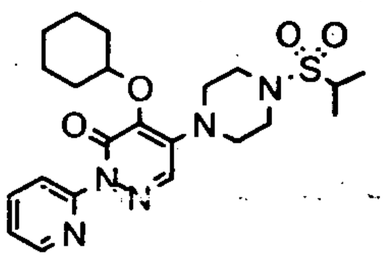
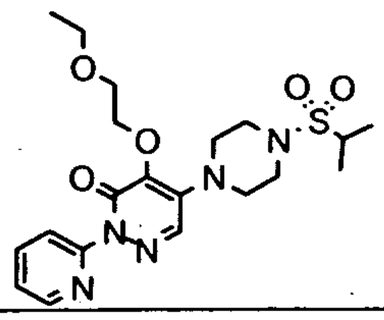
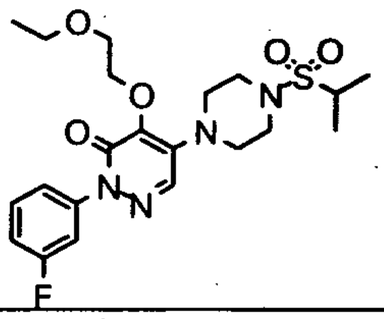
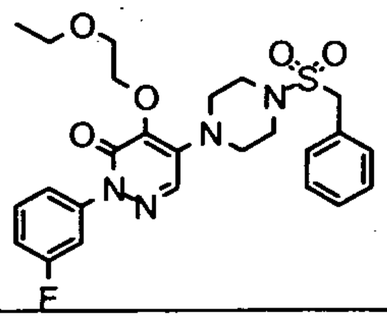
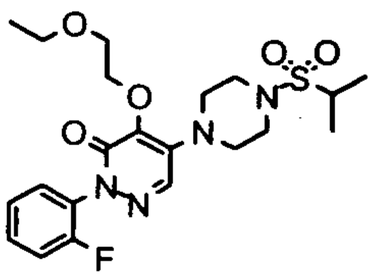
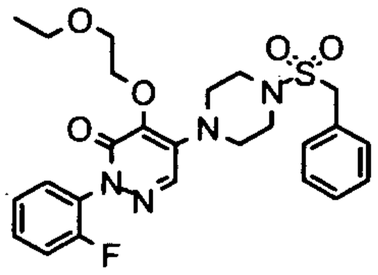
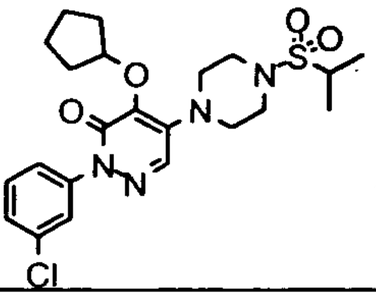
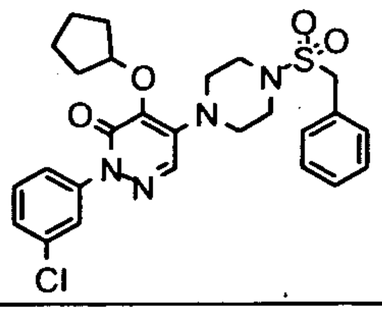
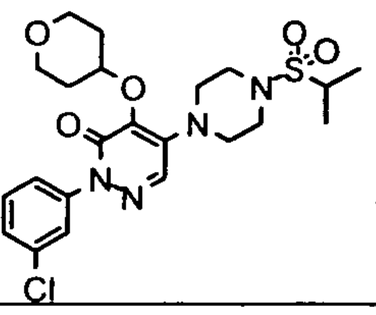
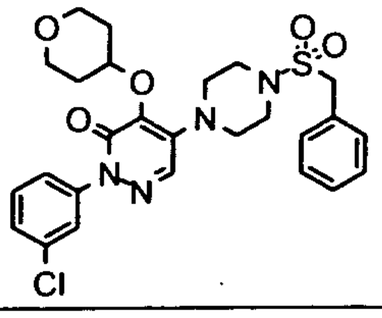
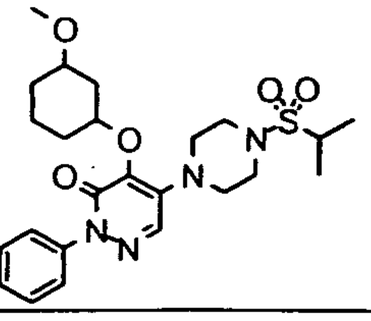
256Z		503	257Z		450
258Z		481	259Z		593
260Z		512	261Z		593
262Z		517	263Z		433
264Z		447	265Z		475
266Z		557	267Z		499
268Z		423	269Z		515

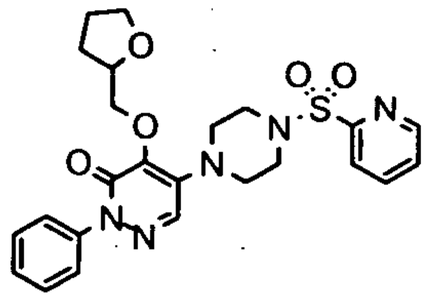
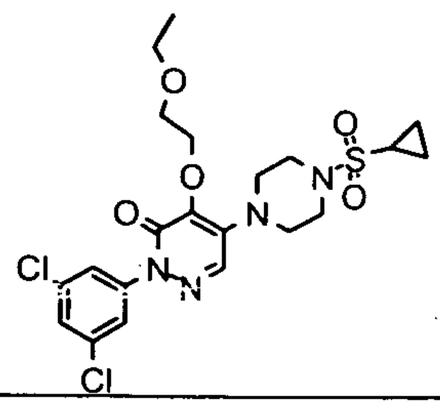
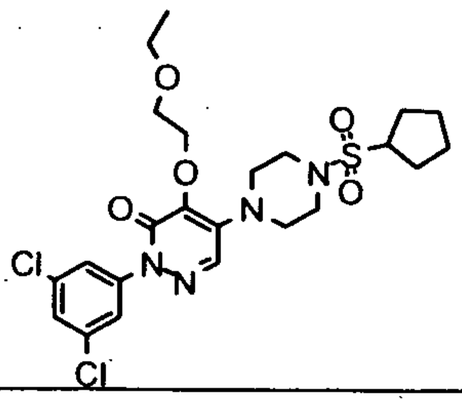
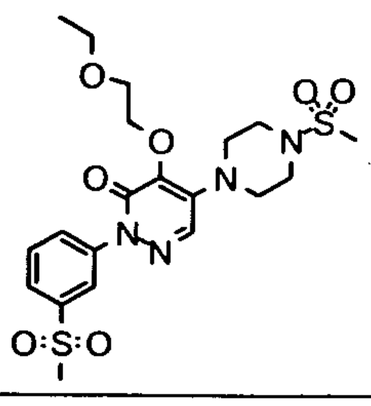
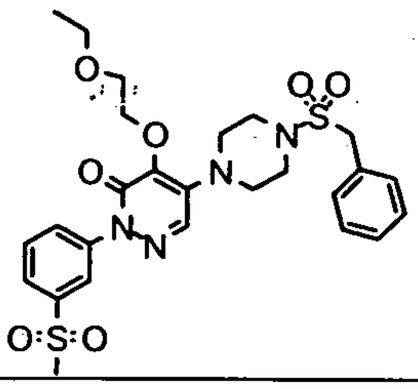
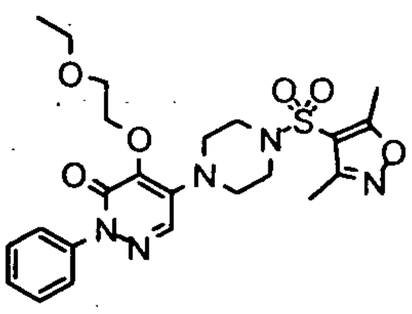
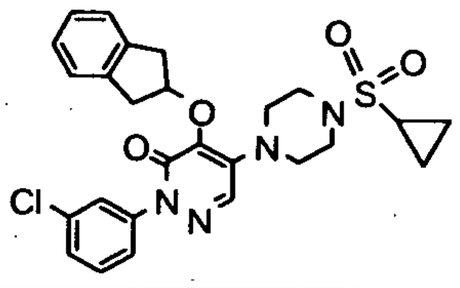
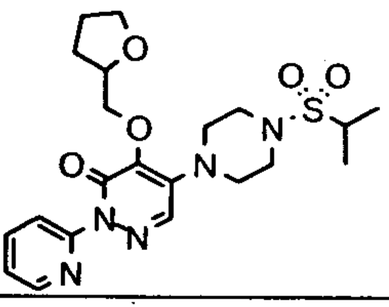
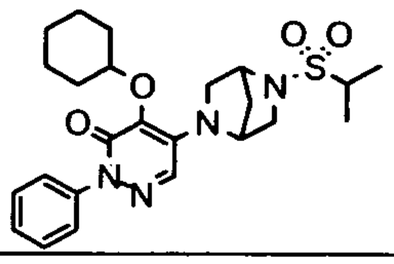
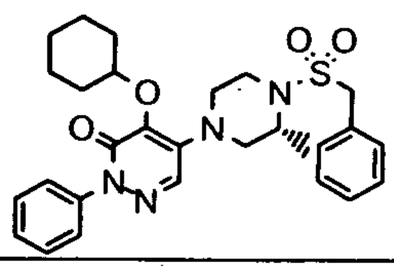
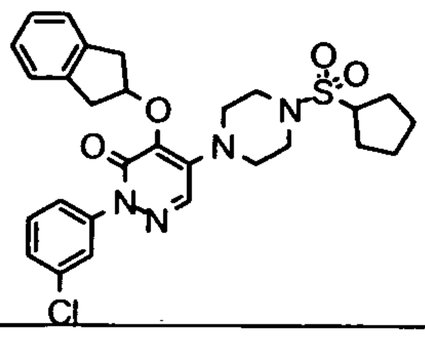
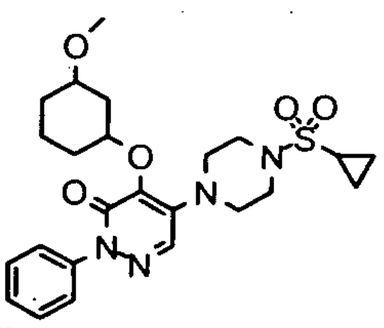
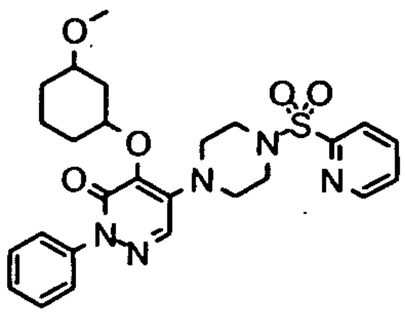
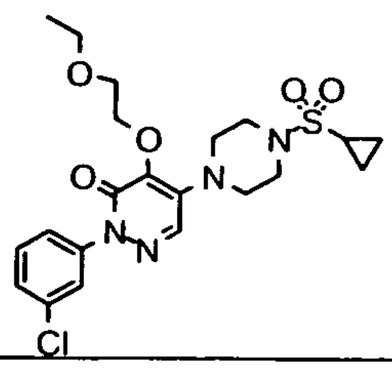
270Z		648
271Z		463
272Z		473
273Z		529
274Z		517
275Z		501
276Z		528
277Z		668
278Z		475
279Z		516
280Z		467
281Z		495
282Z		509
283Z		422

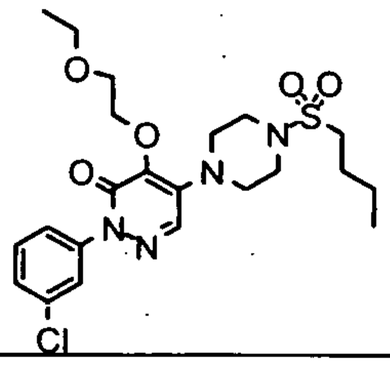
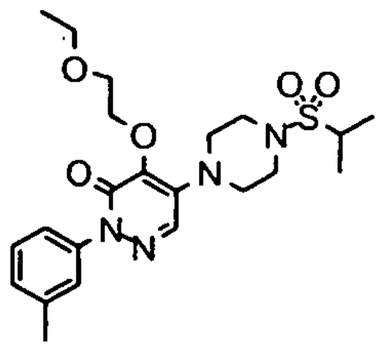
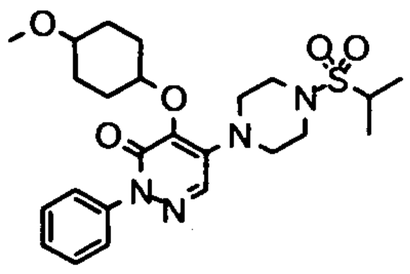
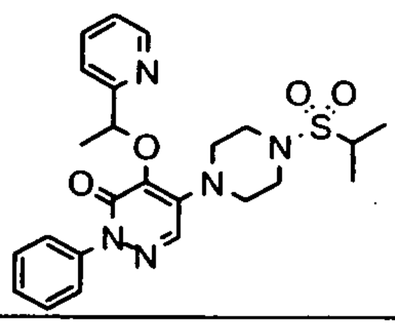
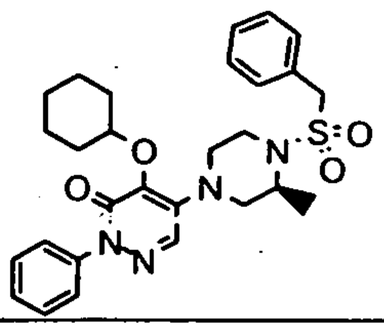
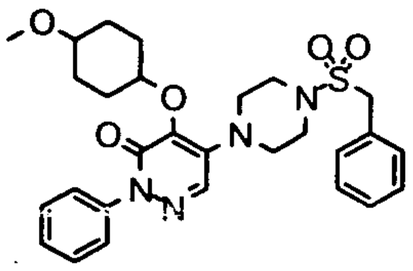
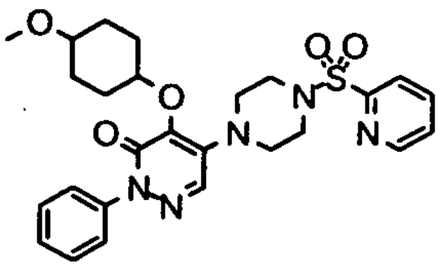
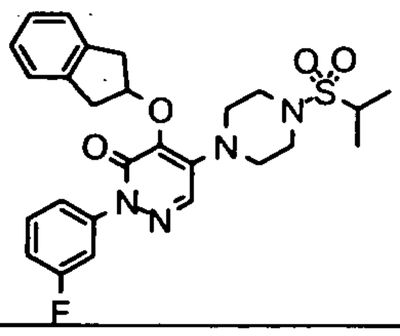
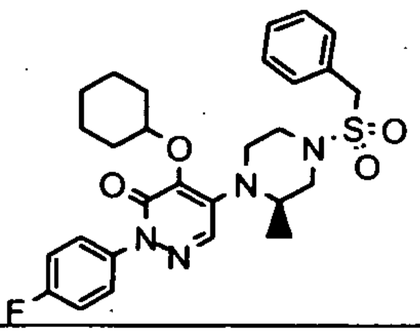
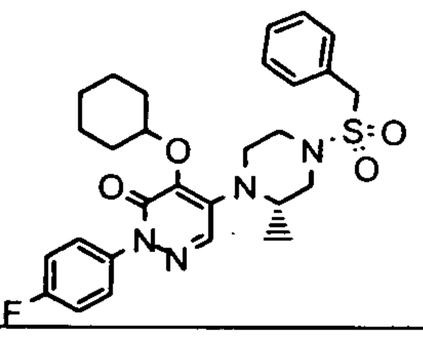
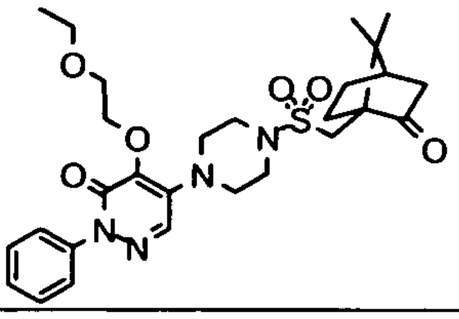
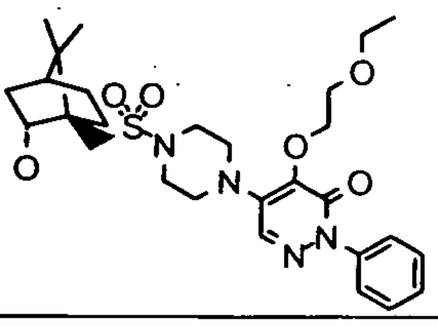
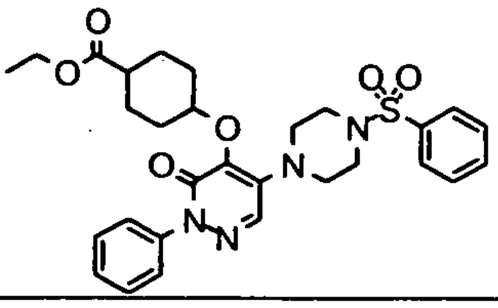
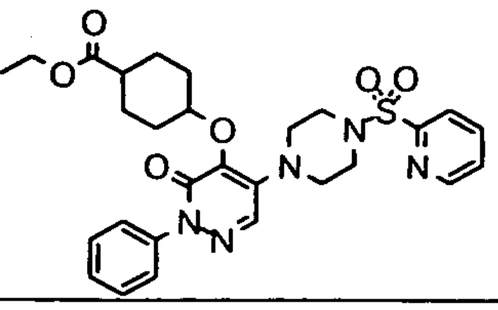
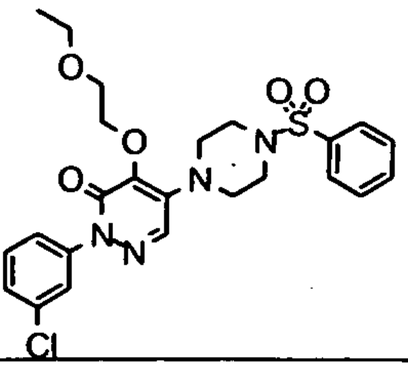
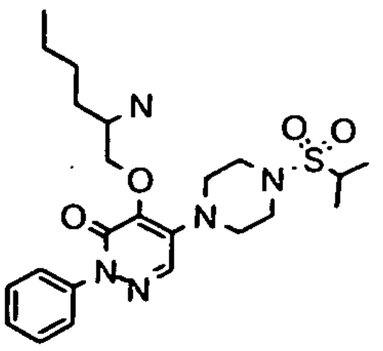
284Z		498
285Z		584
286Z		481
287Z		483
288Z		499
289Z		536
290Z		489
291Z		484
292Z		577
293Z		517
294Z		704
295Z		545
296Z		708
297Z		547

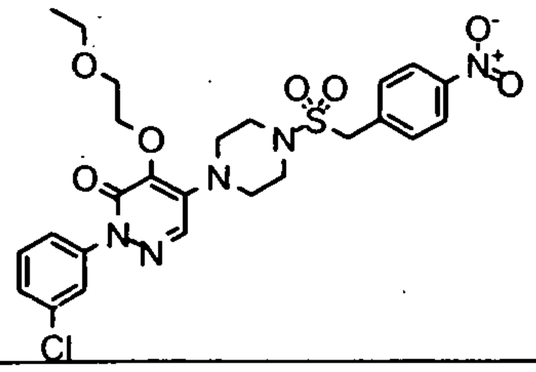
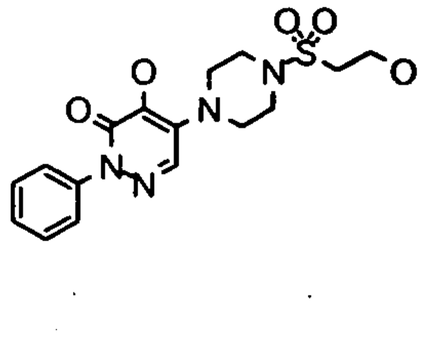
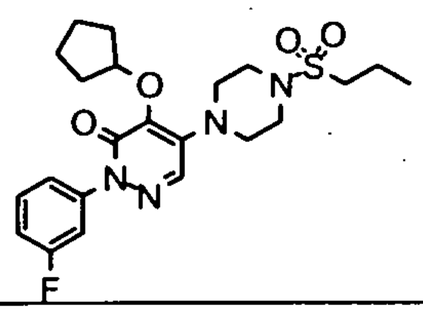
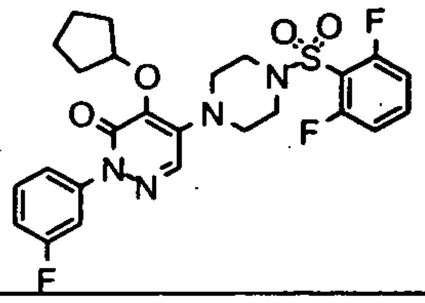
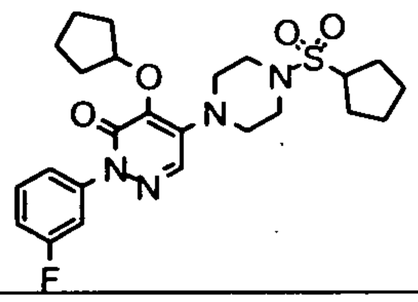
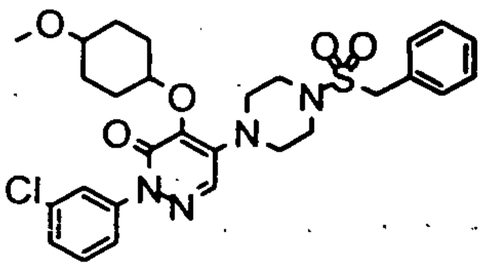
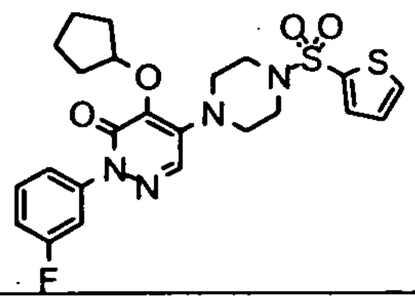
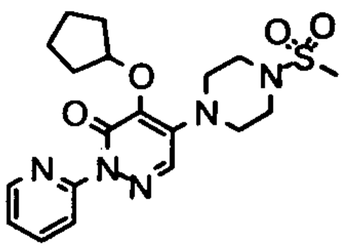
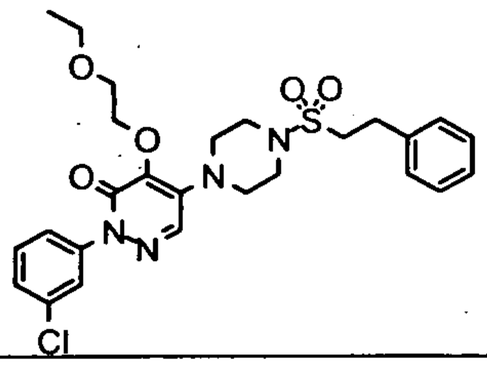
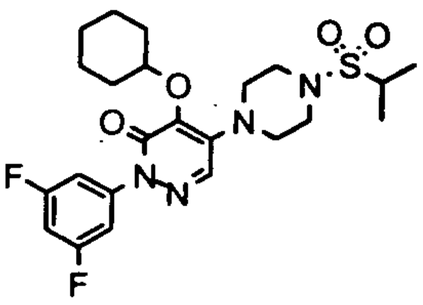
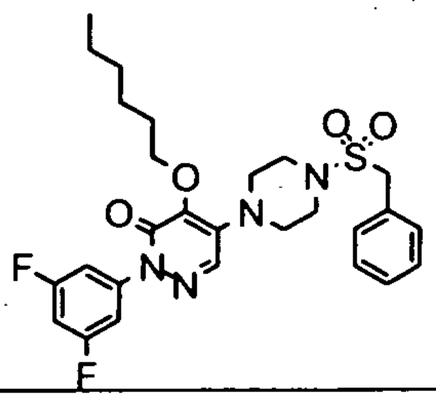
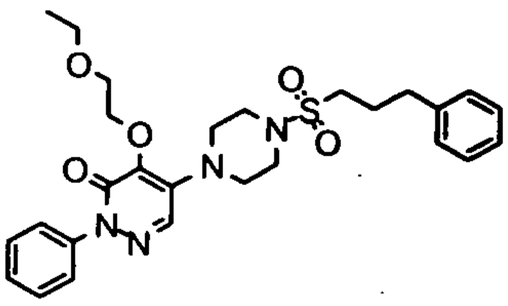
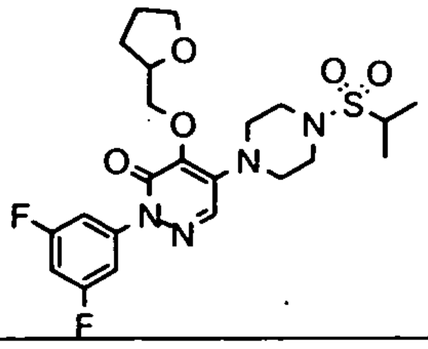
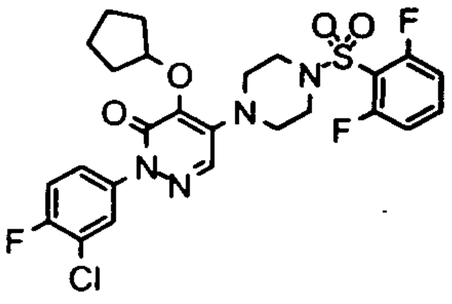
298Z		509
299Z		571
300Z		569
301Z		567
302Z		529
303Z		518
304Z		431
305Z		561
306Z		478
307Z		512
308Z		521
309Z		519
310Z		535
311Z		547

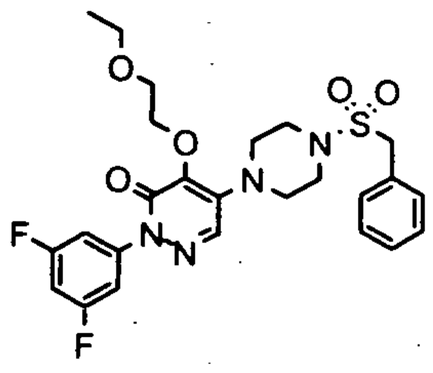
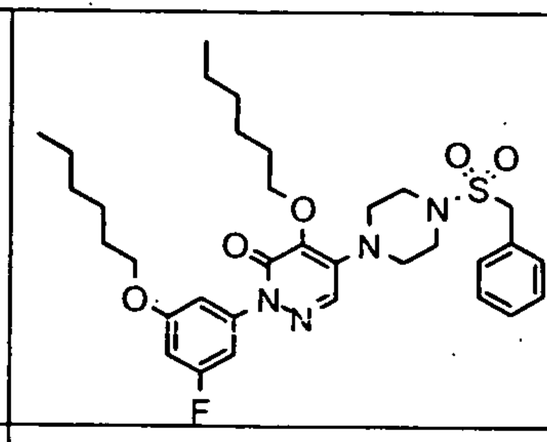
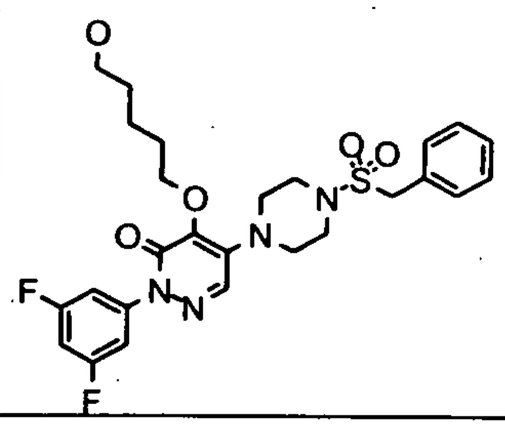
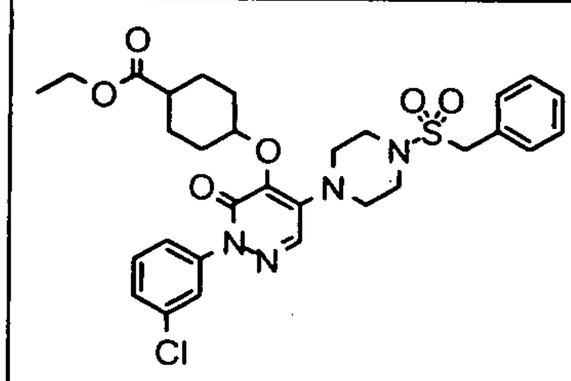
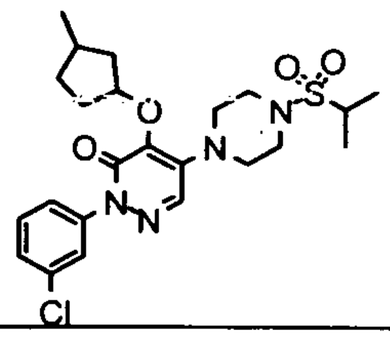
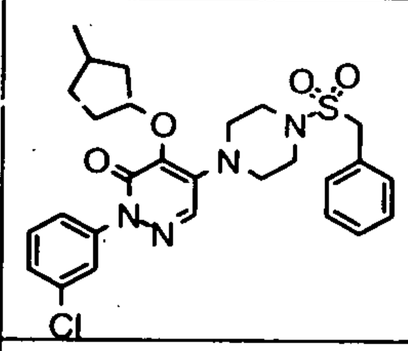
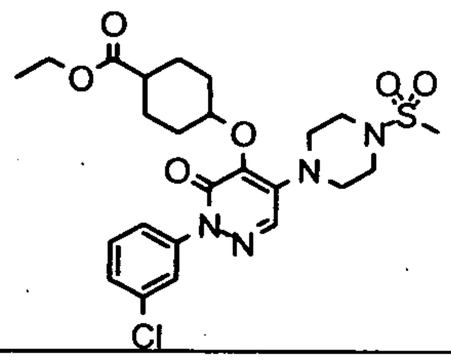
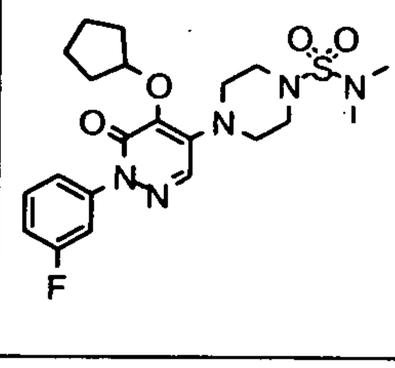
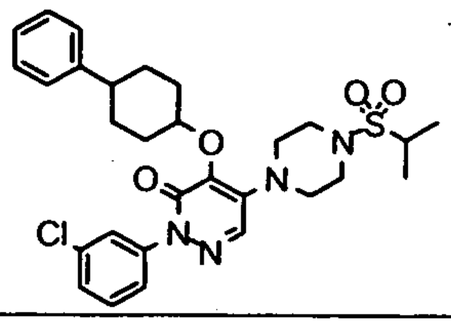
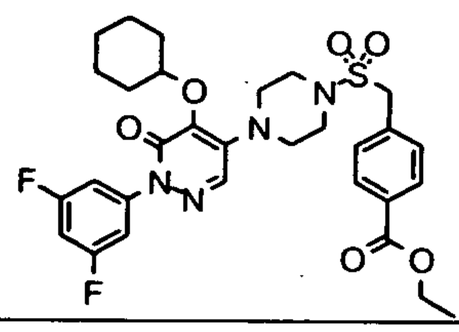
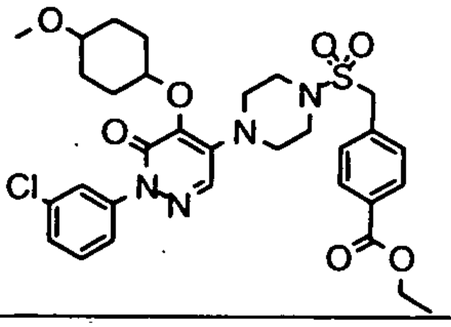
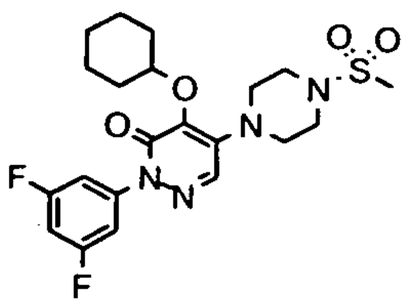
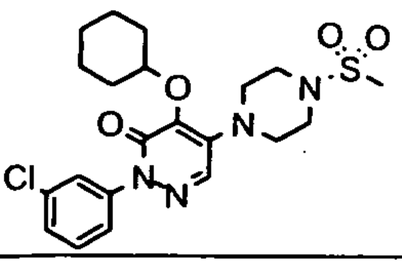
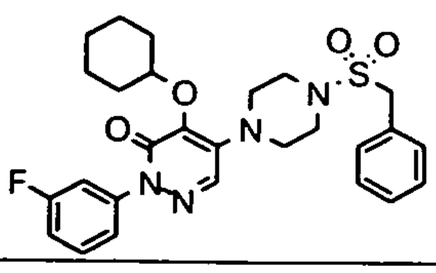
312Z		599 601
313Z		553
314Z		583
315Z		535
316Z		562
317Z		451
318Z		509
319Z		496
320Z		547
321Z		501
322Z		485
323Z		491
324Z		517
325Z		567

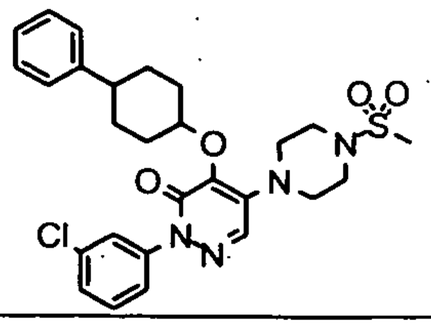
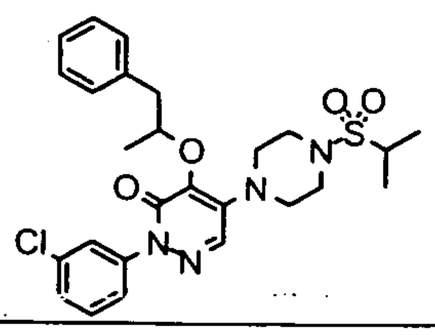
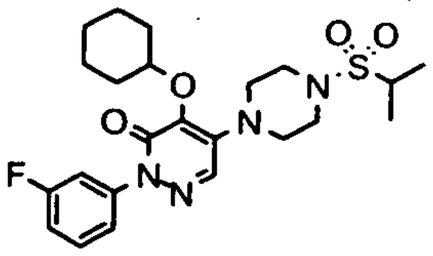
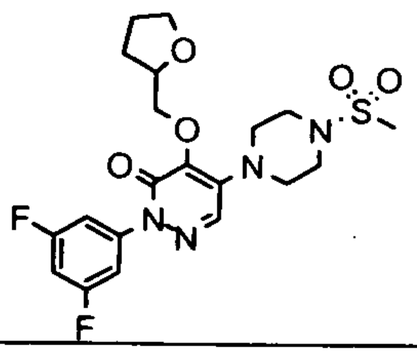
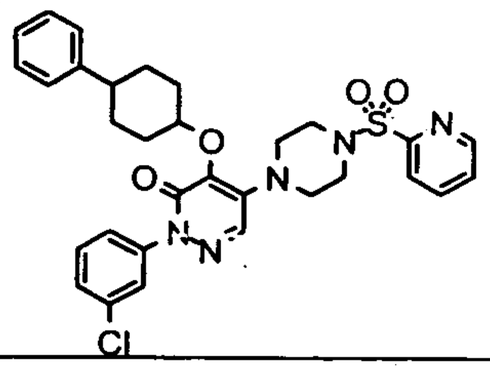
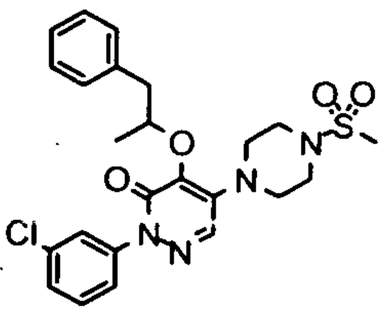
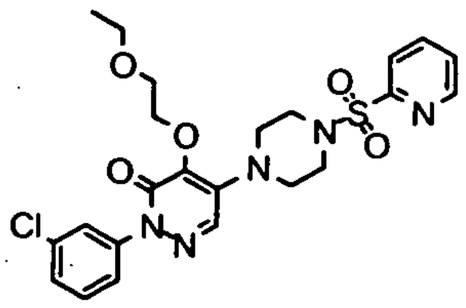
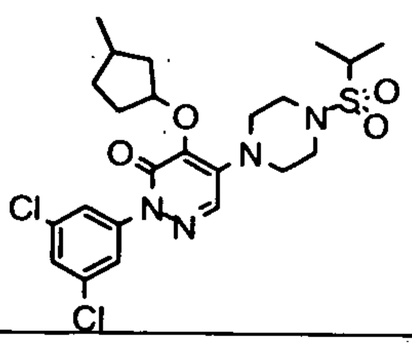
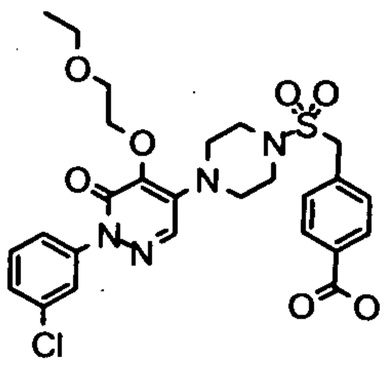
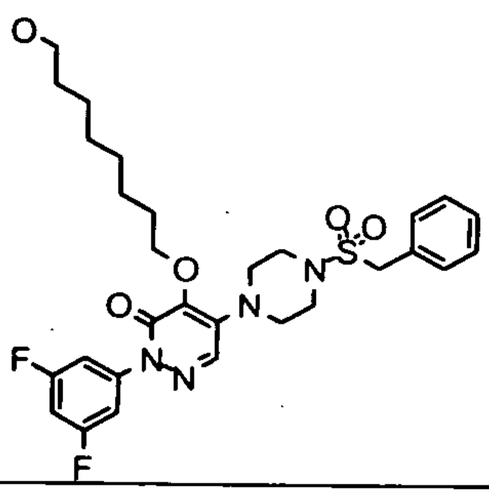
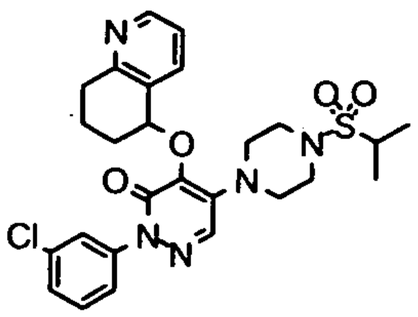
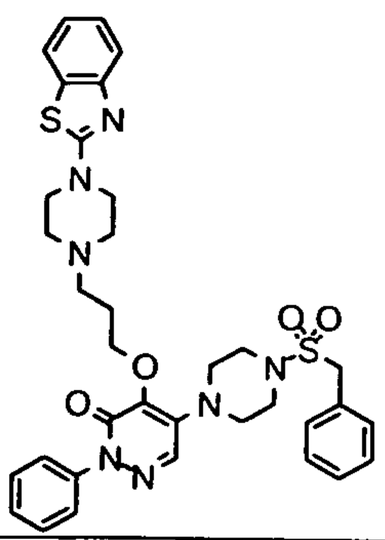
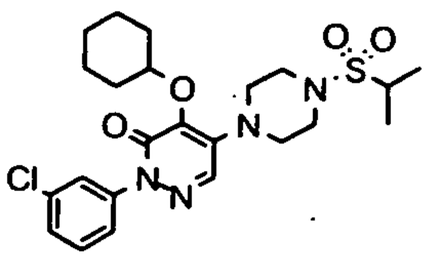
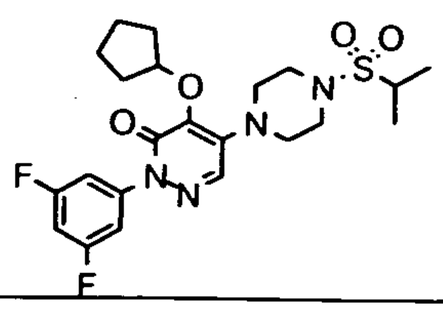
326Z		544	327Z		567
328Z		485	329Z		533
330Z		519	331Z		462
332Z		452	333Z		469
334Z		517	335Z		469
336Z		517	337Z		481
338Z		529	339Z		497
340Z		545	341Z		491

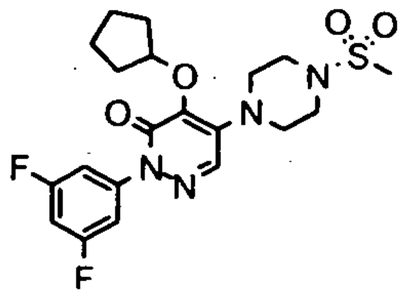
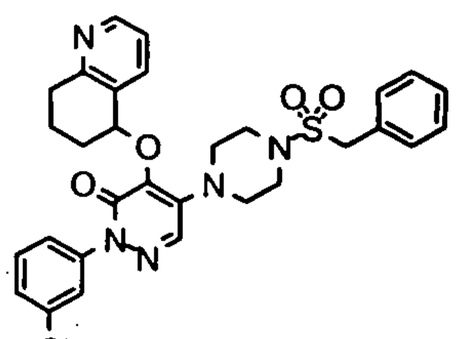
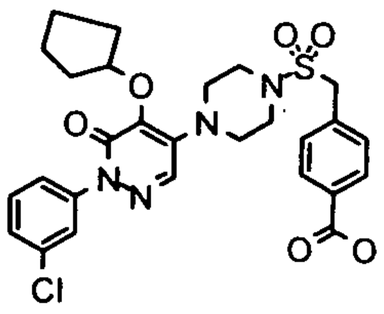
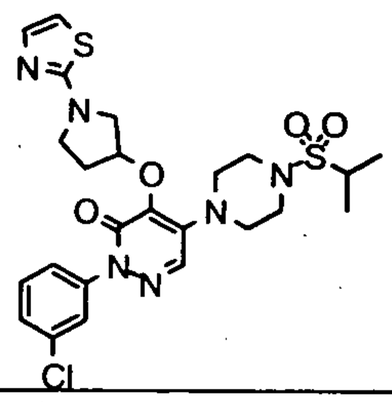
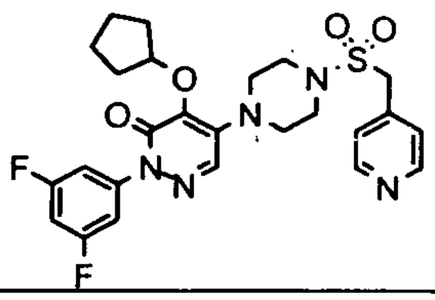
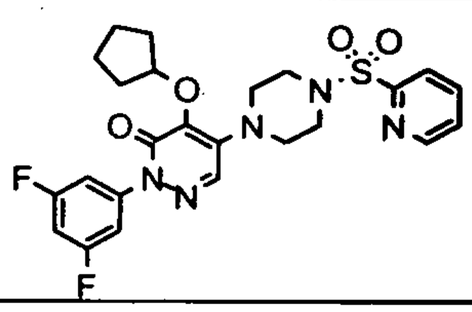
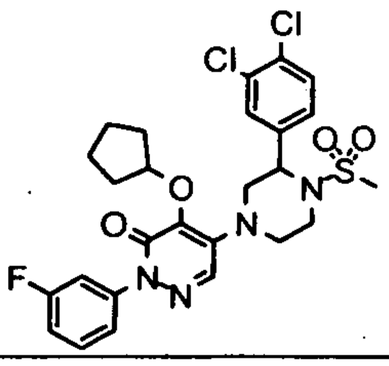
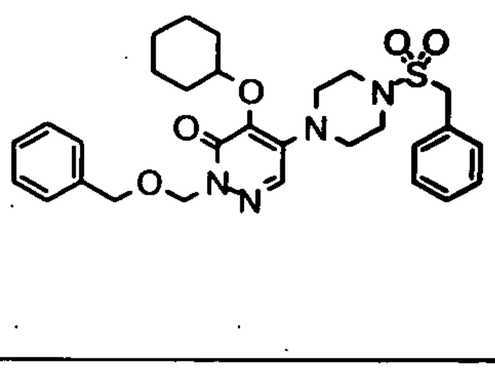
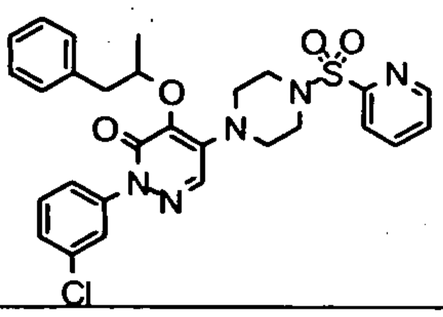
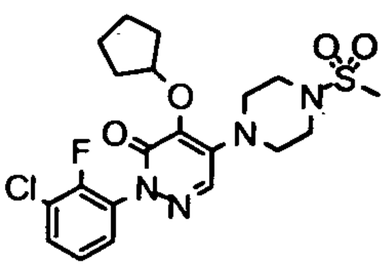
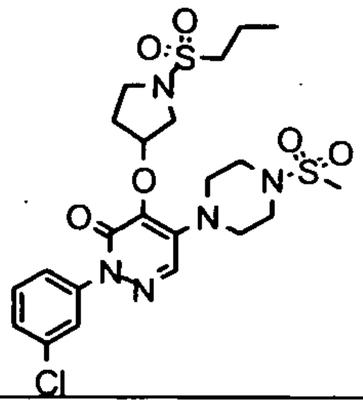
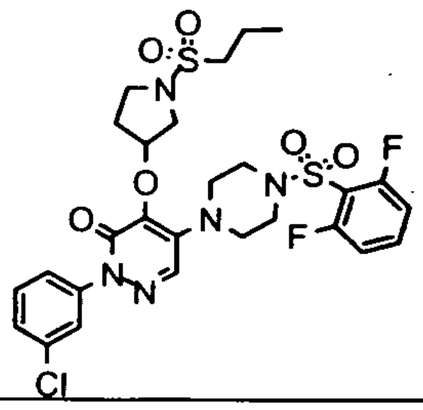
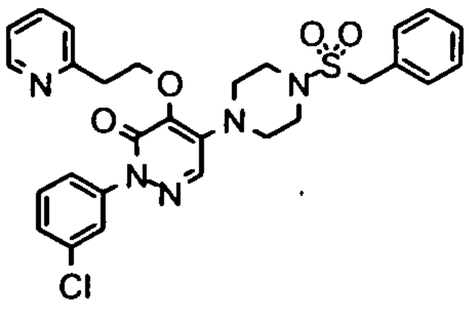
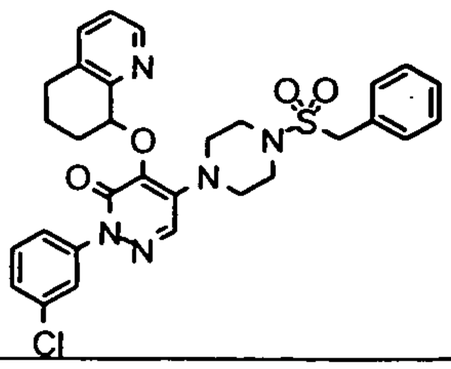
342Z		498
343Z		517
344Z		545
345Z		501
346Z		577
347Z		504
348Z		527
349Z		464
350Z		473
351Z		523
352Z		555
353Z		489
354Z		526
355Z		483

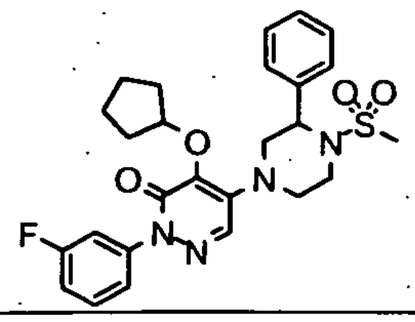
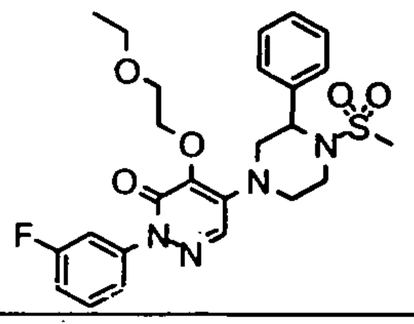
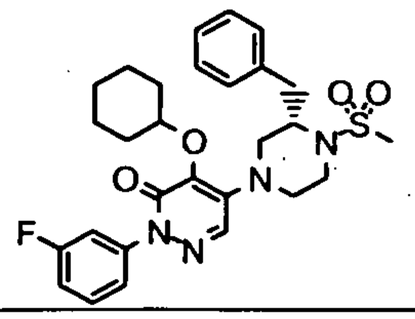
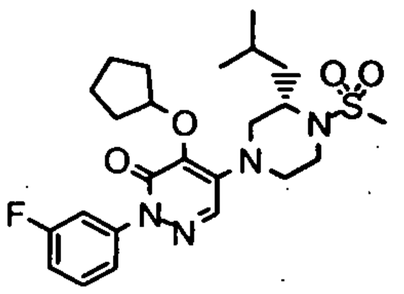
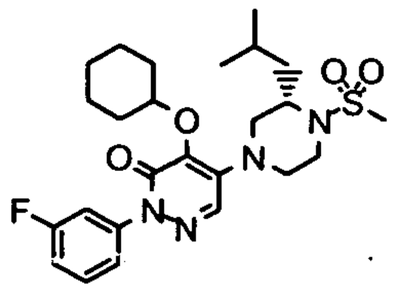
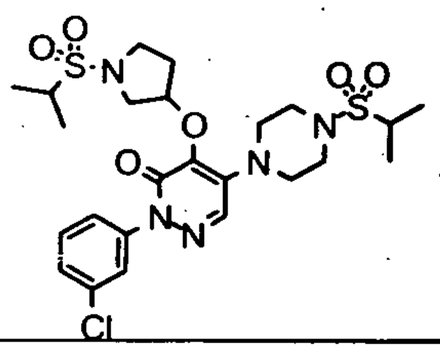
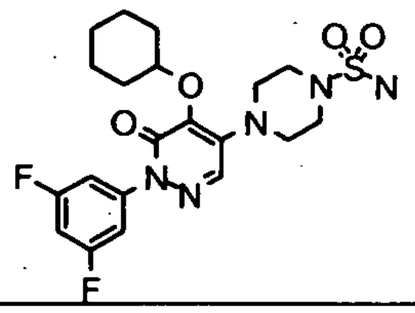
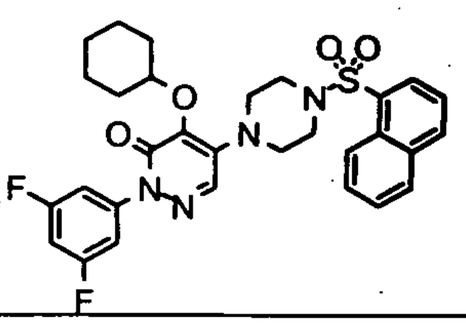
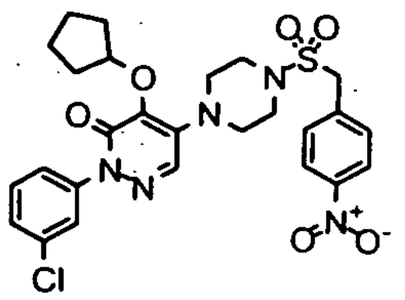
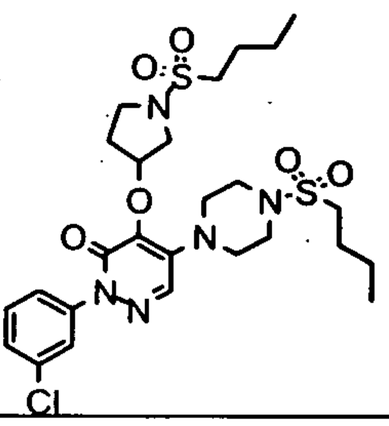
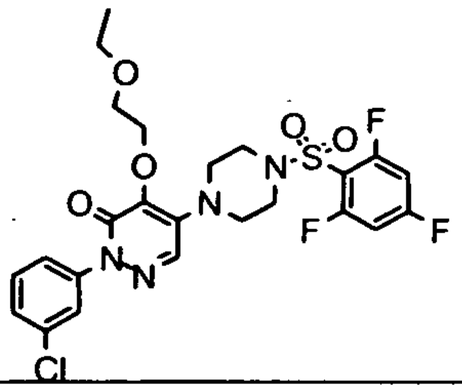
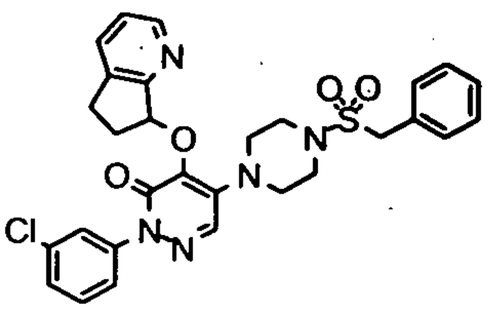
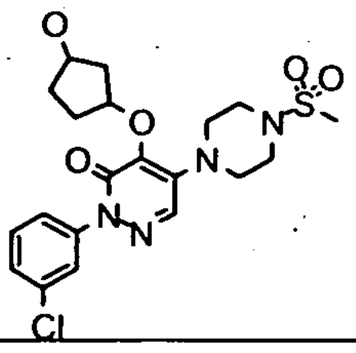
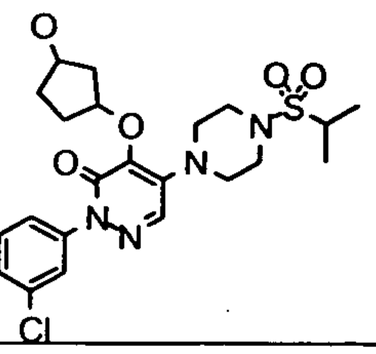
356Z		499
357Z		465
358Z		491
359Z		484
360Z		523
361Z		539
362Z		526
363Z		513
364Z		541
365Z		541
366Z		559
367Z		561
368Z		567
369Z		568
370Z		519
371Z		478

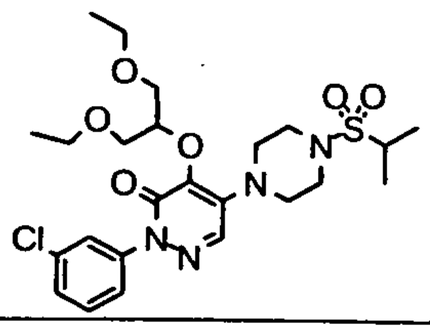
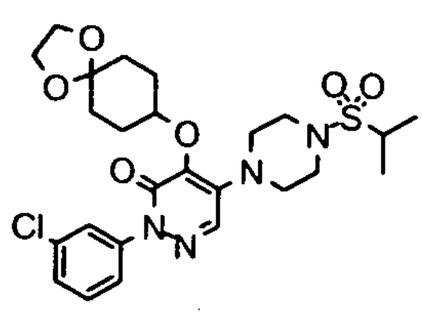
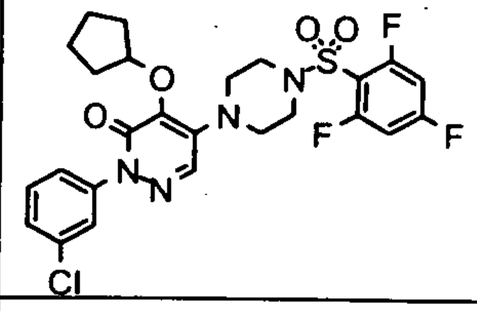
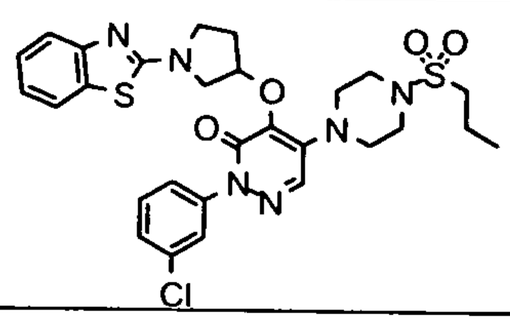
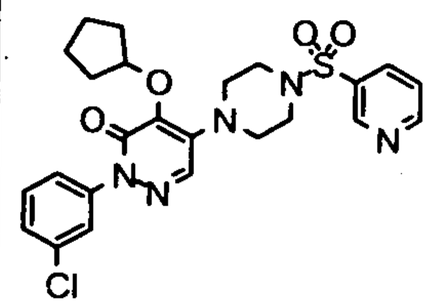
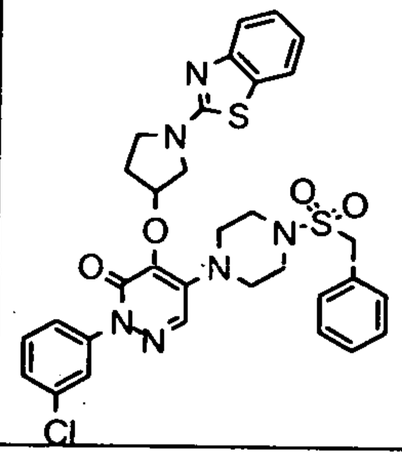
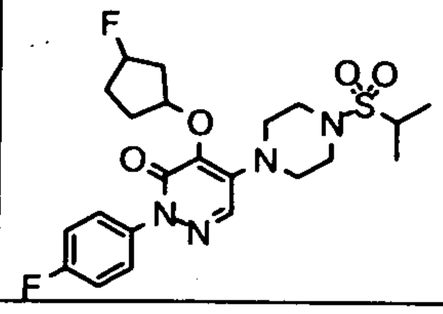
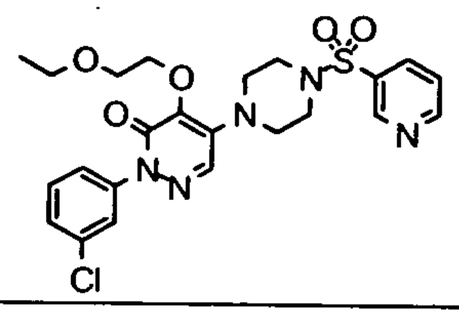
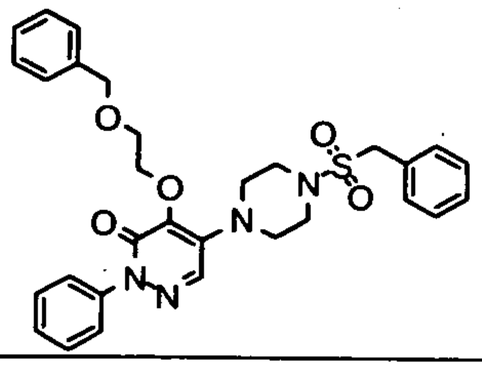
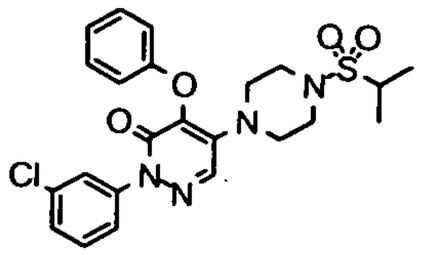
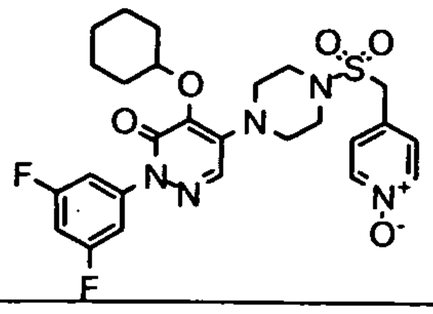
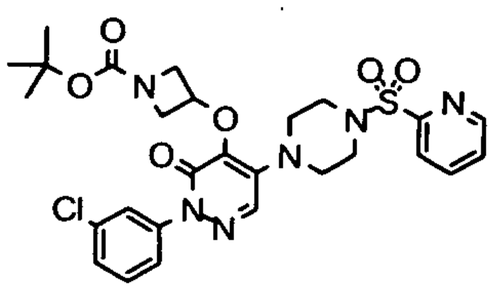
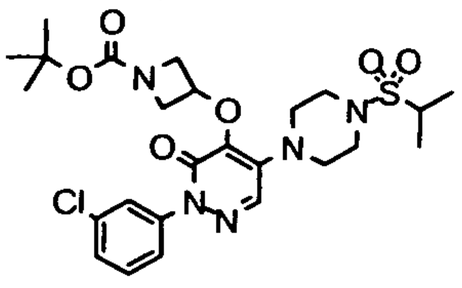
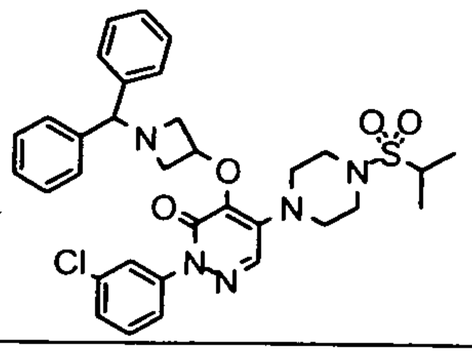
372Z		578	373Z		381
374Z		465	375Z		535
376Z		491	377Z		573
378Z		505	379Z		442 for M+1-methyl
380Z		547	381Z		497
382Z		547	383Z		527
384Z		499	385Z		569

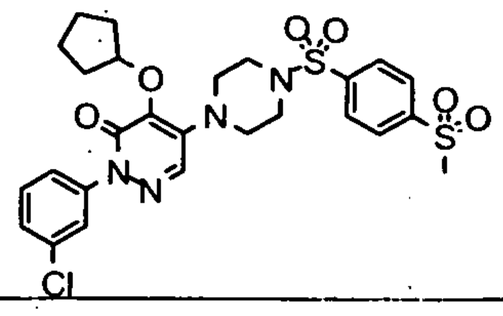
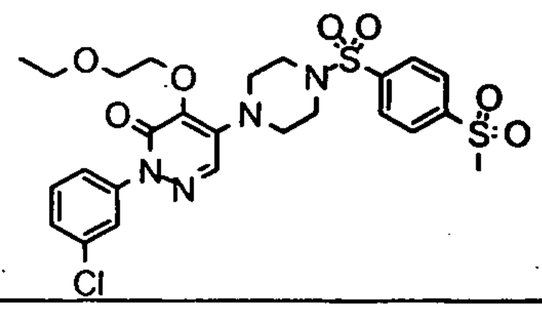
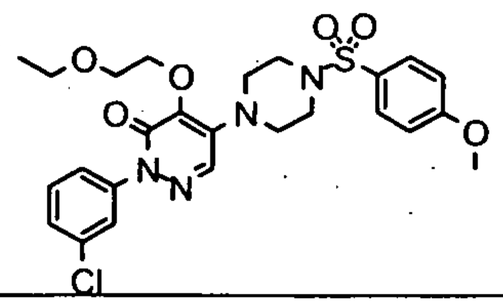
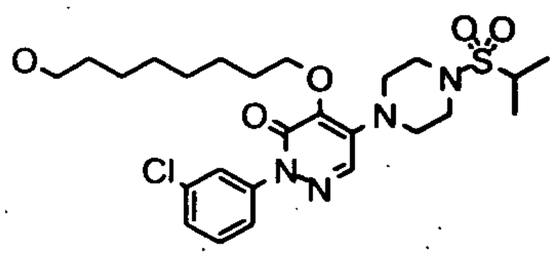
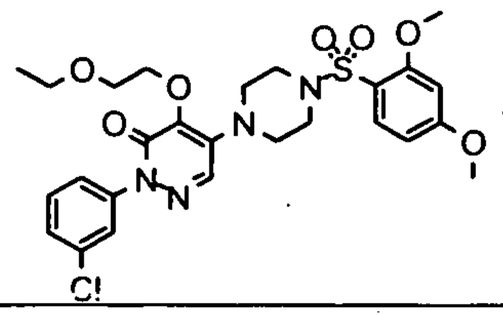
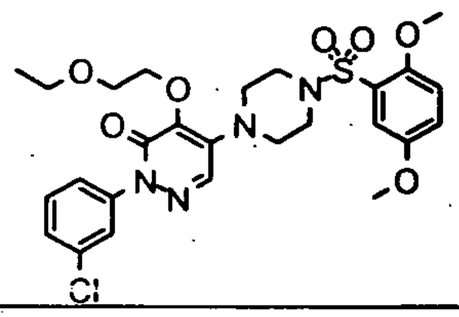
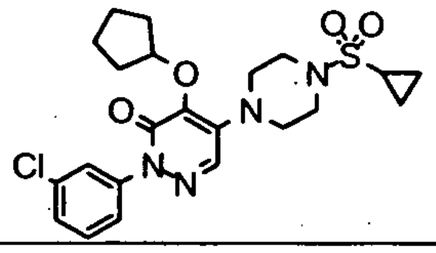
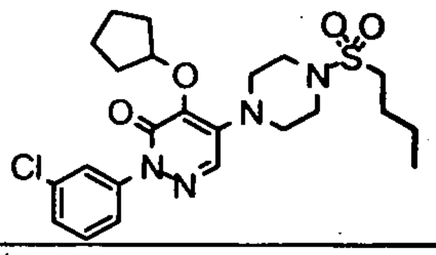
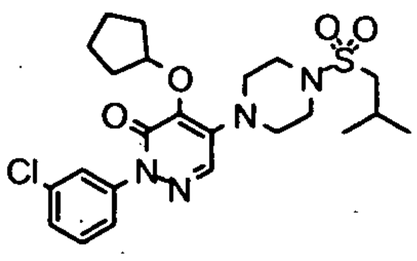
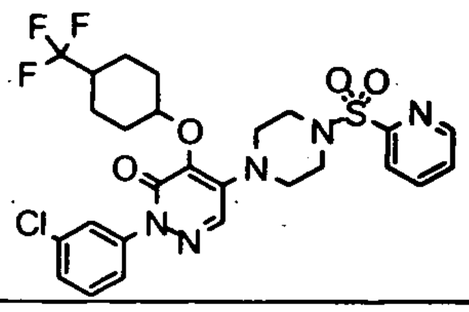
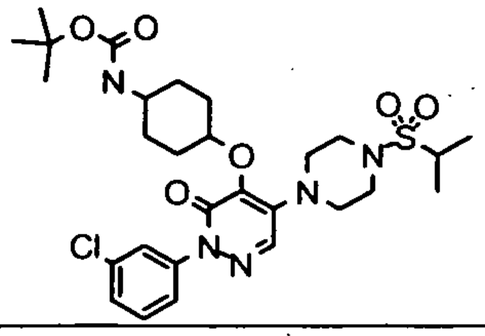
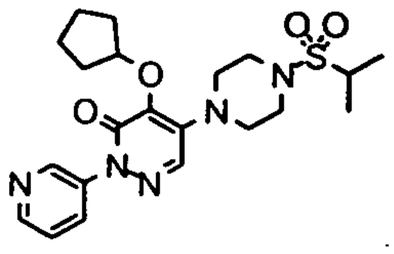
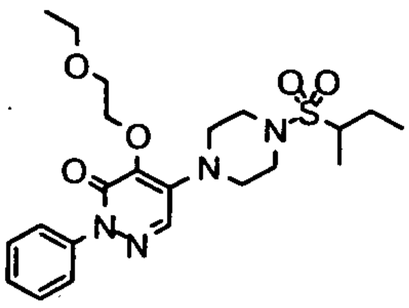
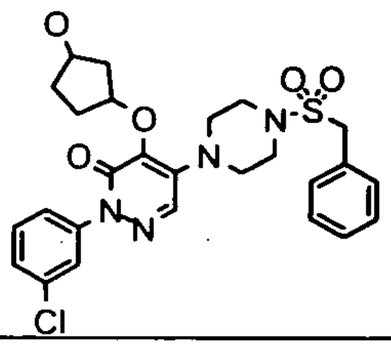
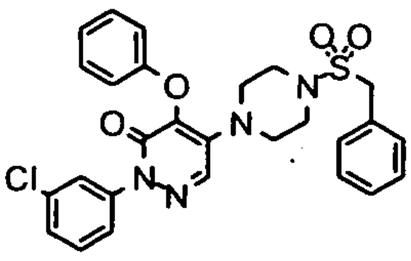
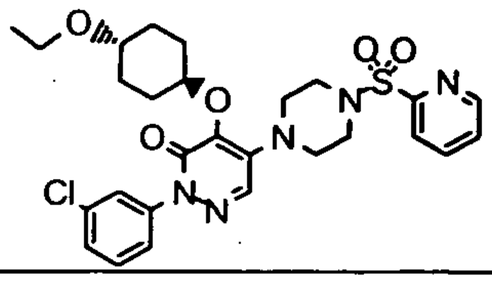
386Z		535
387Z		629
388Z		549
389Z		615
390Z		495
391Z		543 545
392Z		539
393Z		466
394Z		571
395Z		617
396Z		645
397Z		469
398Z		467
399Z		527

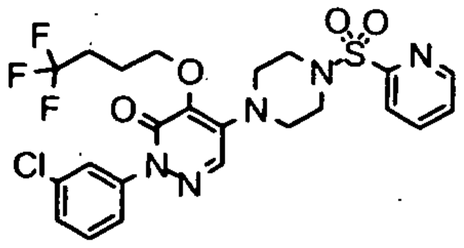
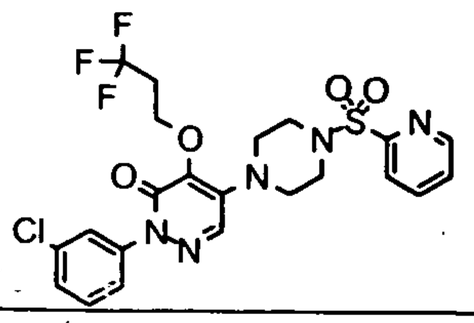
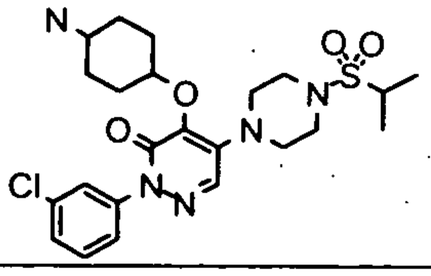
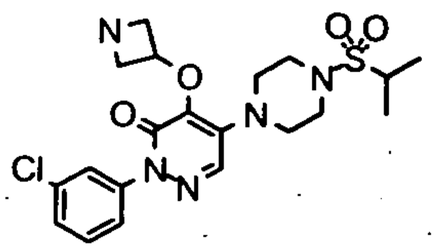
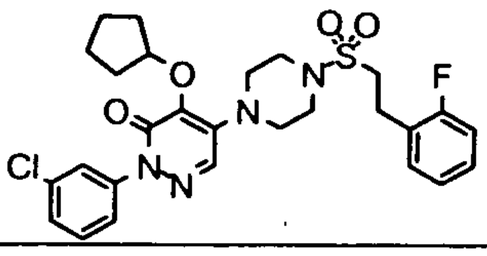
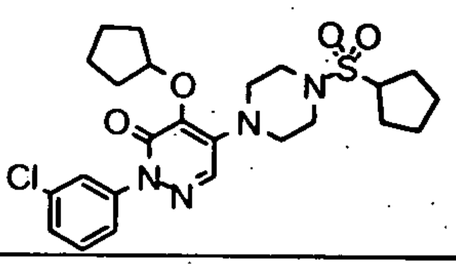
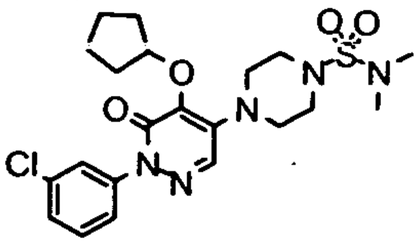
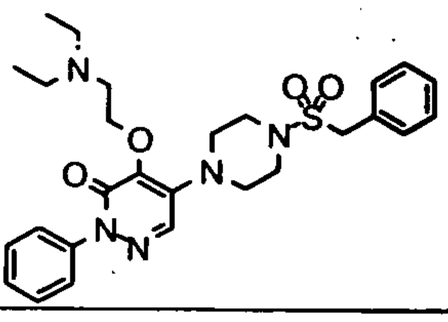
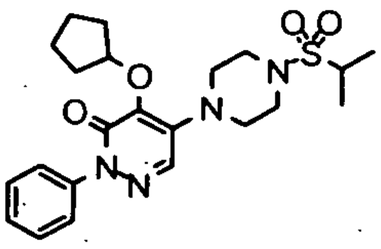
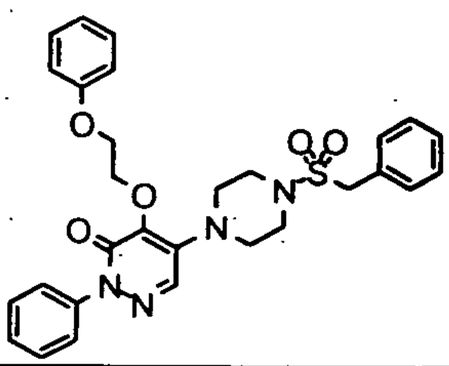
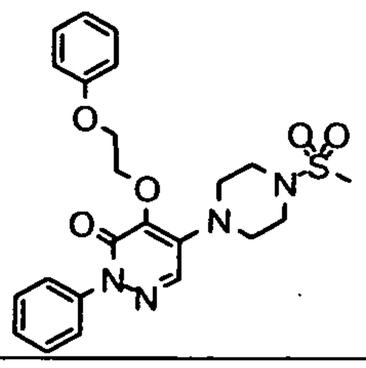
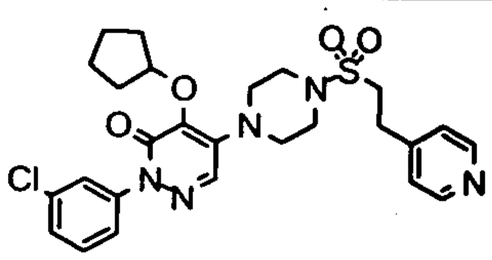
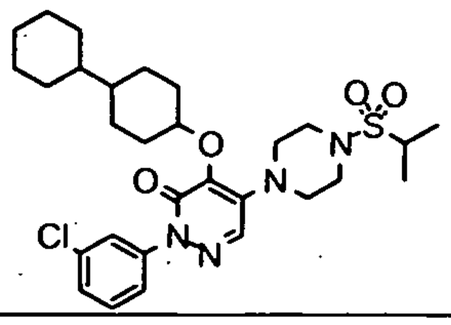
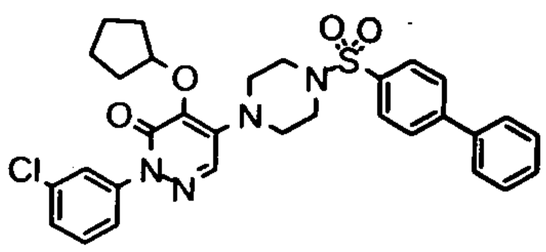
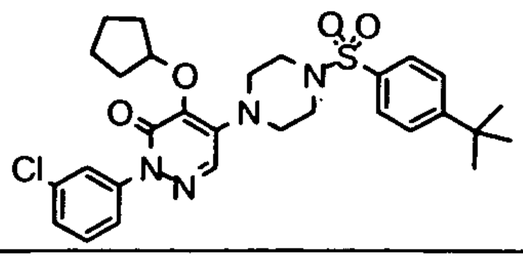
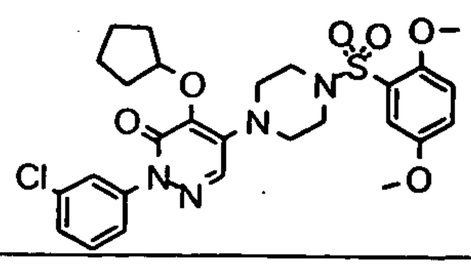
400Z		543
401Z		531
402Z		479
403Z		471
404Z		606
405Z		503
406Z		520
407Z		529
408Z		577
409Z		591
410Z		544
411Z		686
412Z		495
413Z		531

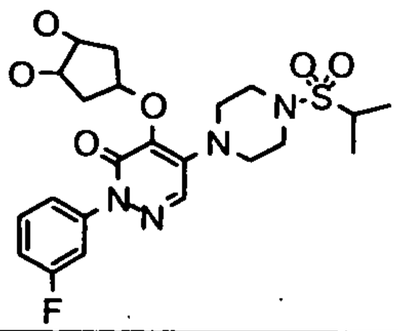
414Z		455
415Z		592
416Z		573
417Z		565
418Z		532
419Z		518
420Z		581
421Z		553
422Z		566
423Z		471
424Z		560
425Z		658
426Z		566
427Z		592

428Z		513
429Z		517
430Z		541
431Z		493
432Z		507
433Z		588
434Z		470
435Z		581
436Z		574
437Z		616
438Z		573
439Z		578
440Z		469
441Z		497

442Z		543
443Z		553
444Z		569
445Z		615
446Z		516
447Z		663
448Z		483
449Z		520
450Z		561
451Z		489
452Z		562
453Z		603
454Z		568
455Z		636

456Z		593
457Z		570
458Z		549
459Z		541
460Z		579
461Z		579
462Z		479
463Z		495
464Z		495
465Z		598
466Z		610
467Z		448
468Z		465
469Z		545
470Z		537
471Z		574

472Z		558
473Z		544
474Z		525
475Z		466 (M-H)
476Z		561
477Z		507
478Z		482
479Z		526
480Z		447
481Z		547
482Z		471
483Z		544
484Z		577
485Z		591
486Z		571
487Z		575

488Z		497
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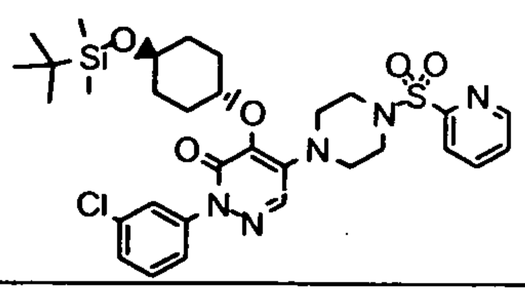
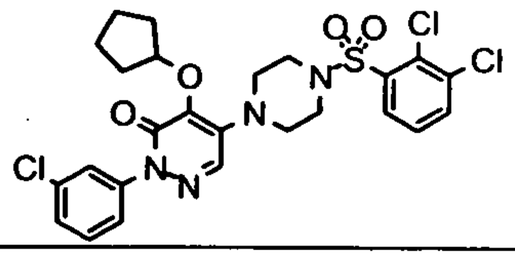
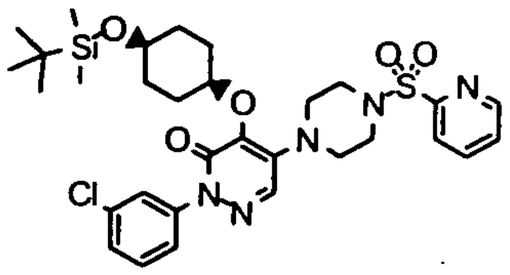
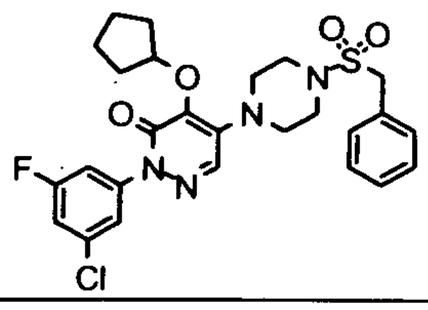
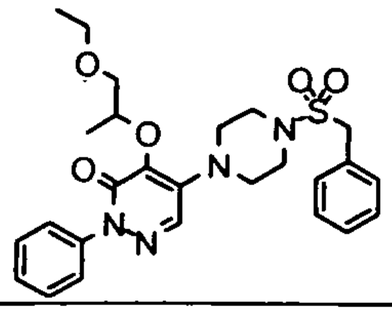
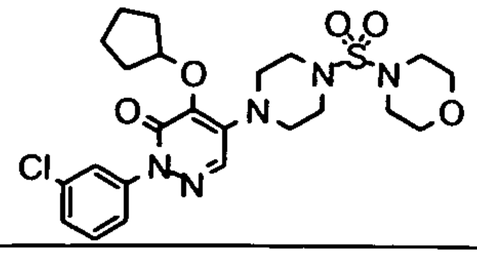
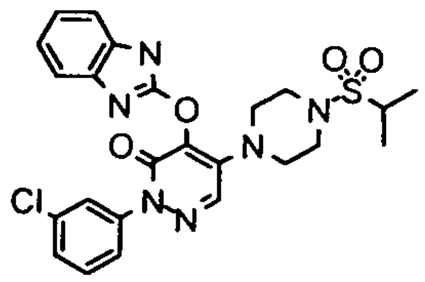
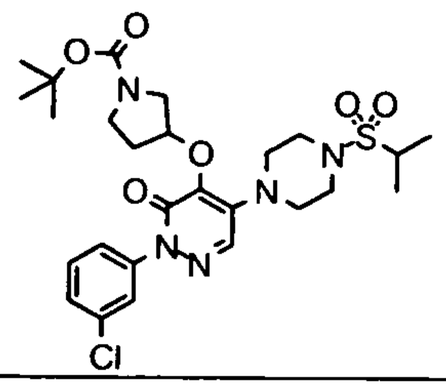
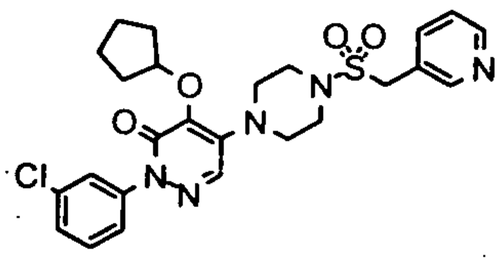
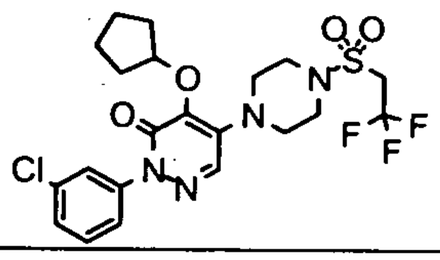
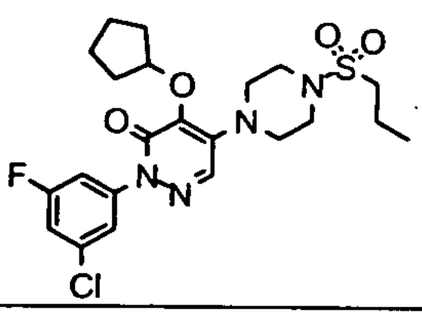
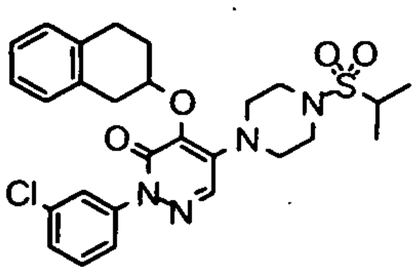
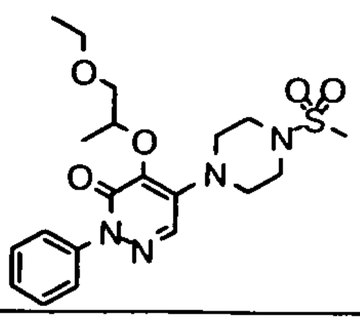
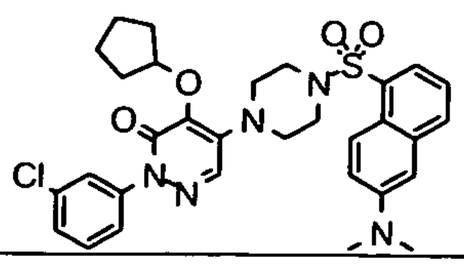
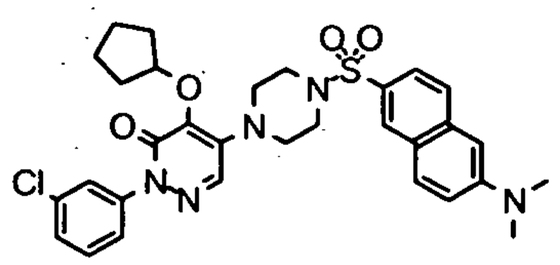
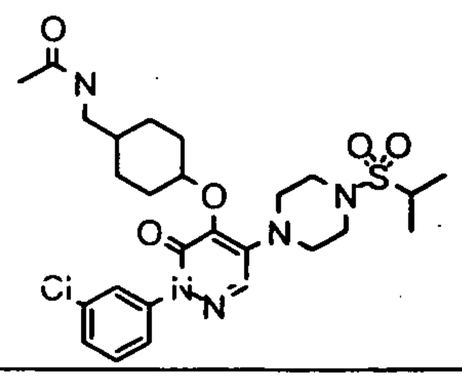
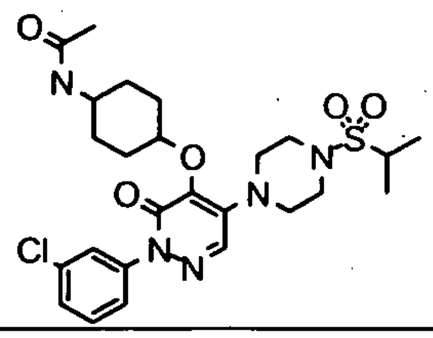
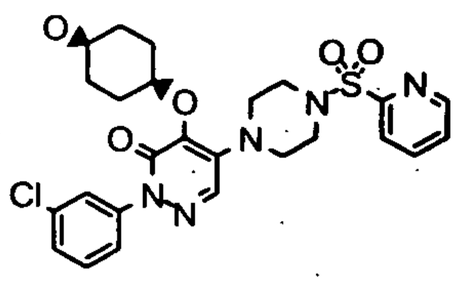
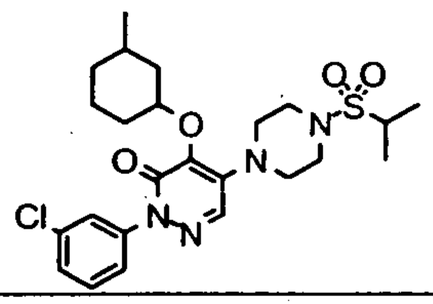
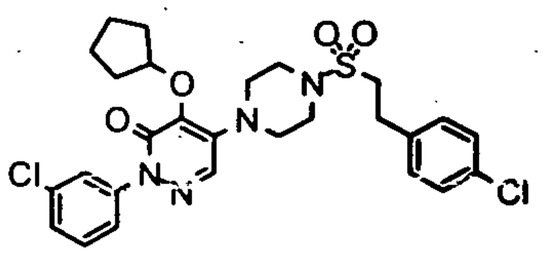
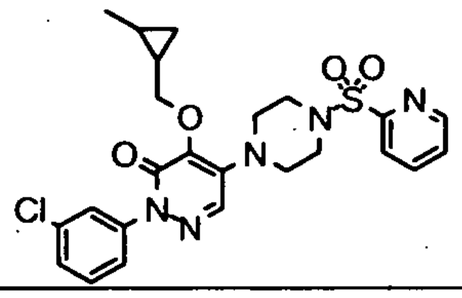
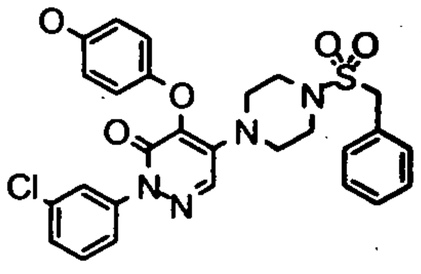
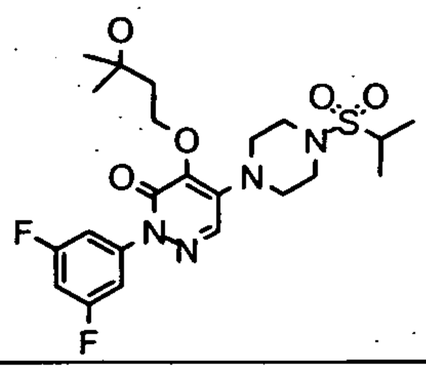
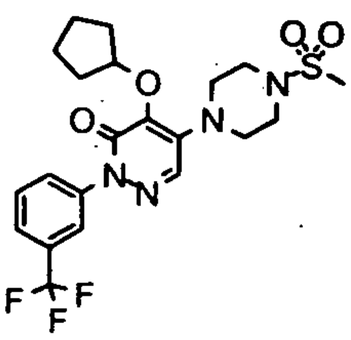
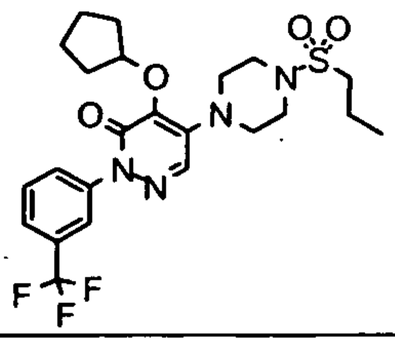
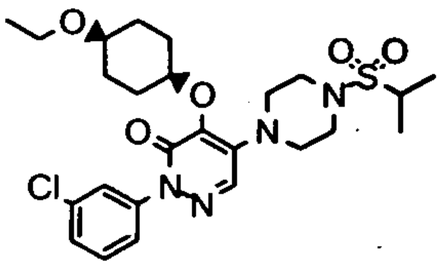
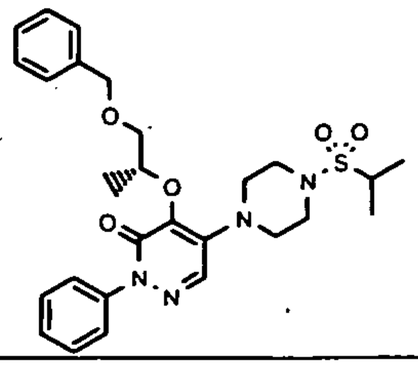
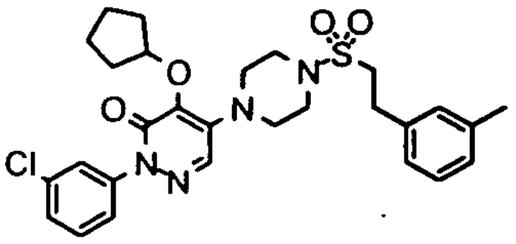
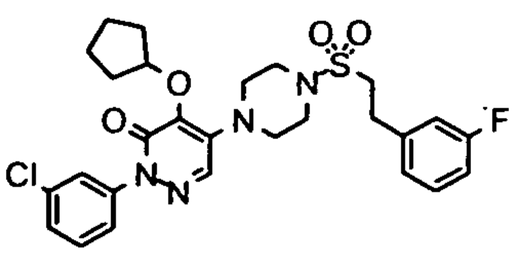
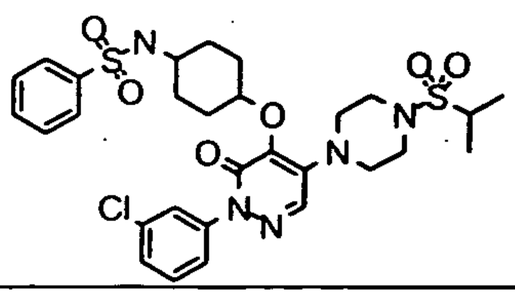
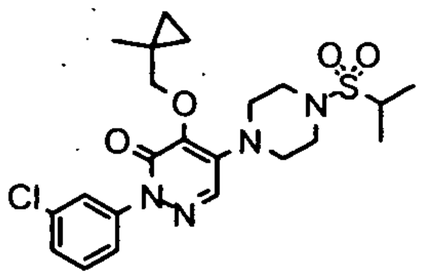
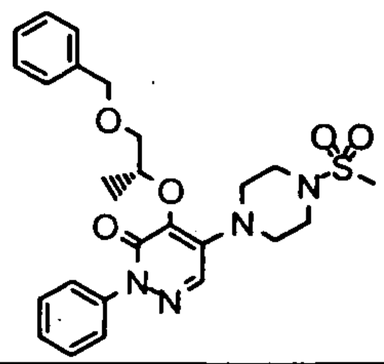
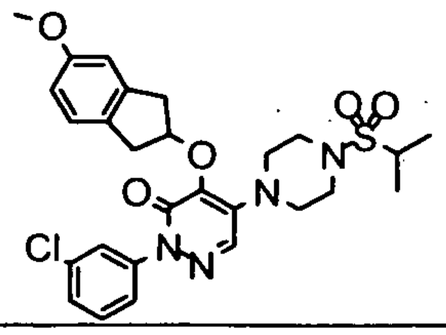
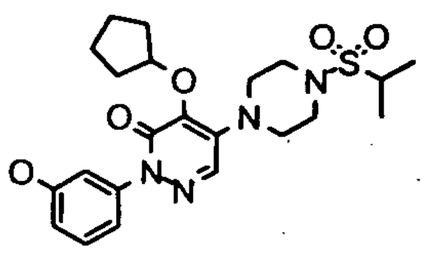
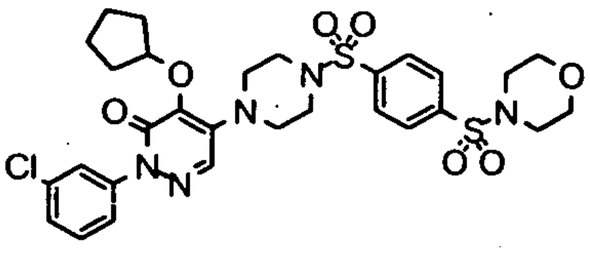
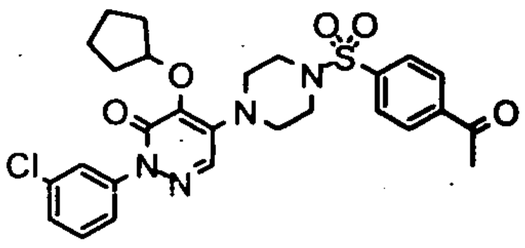
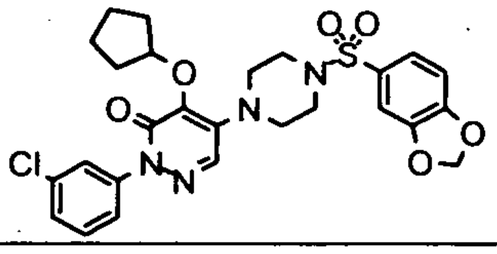
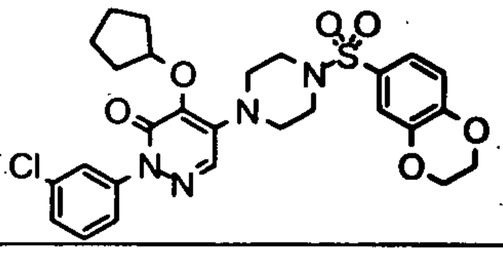
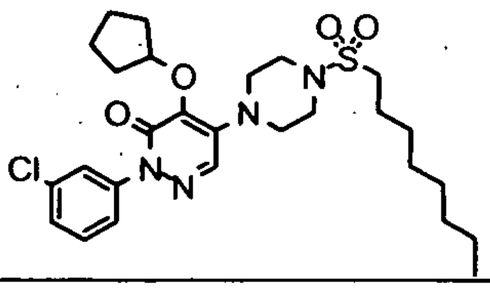
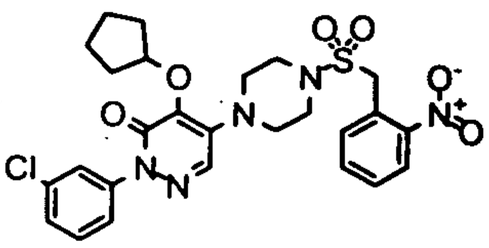
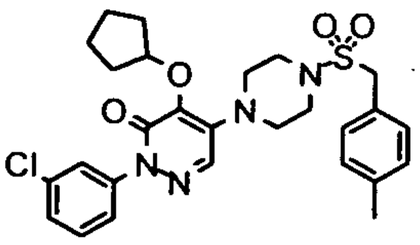
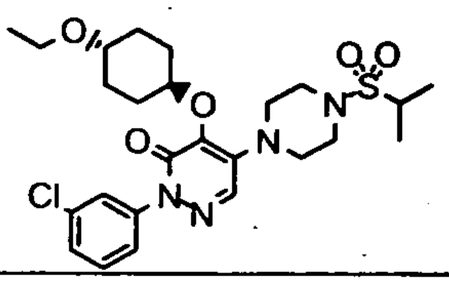
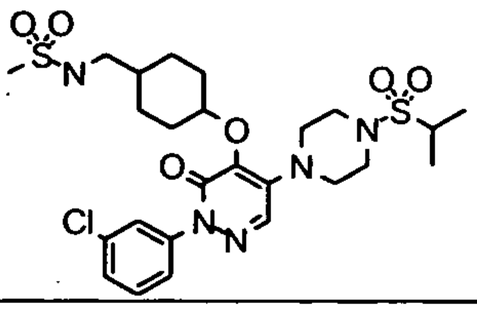
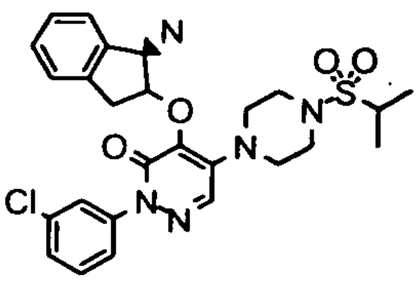
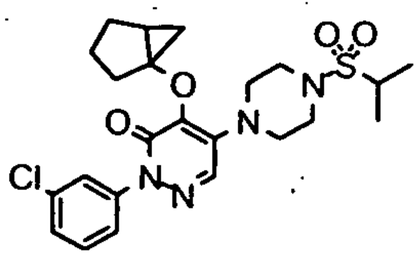
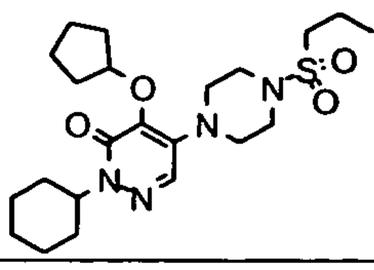
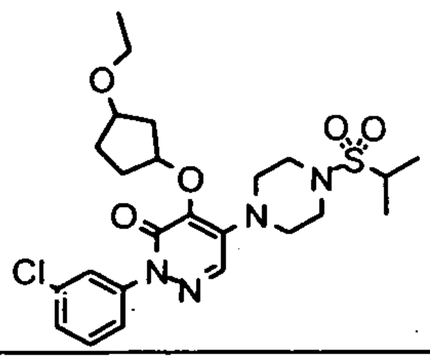
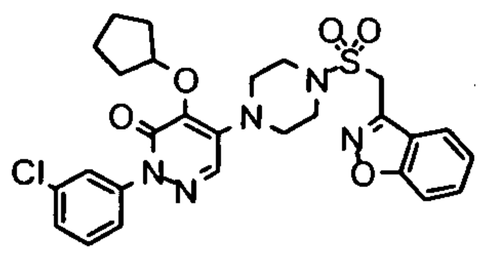
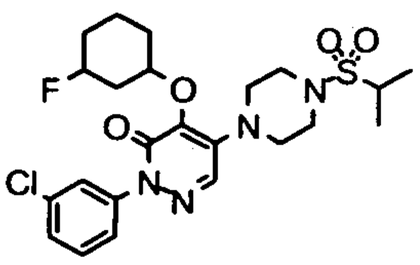
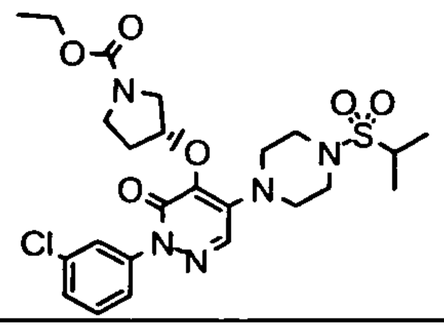
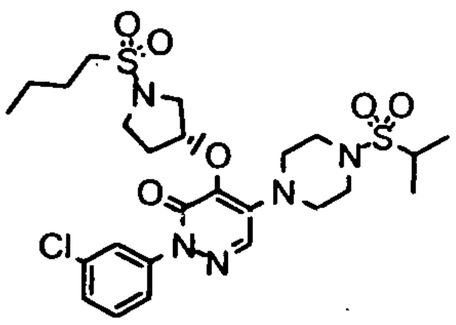
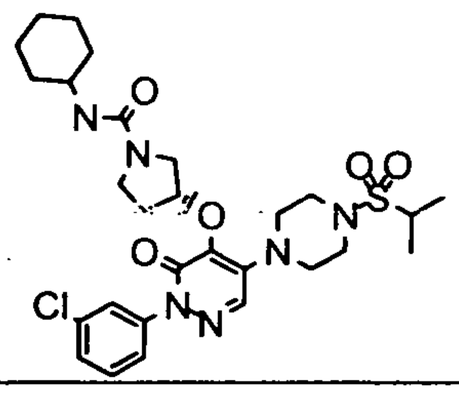
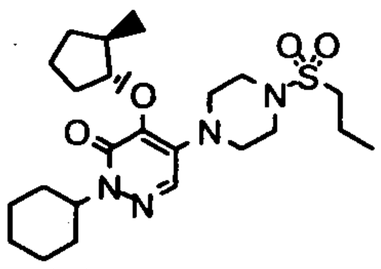
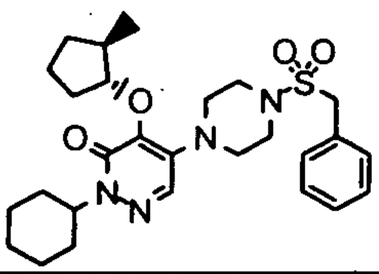
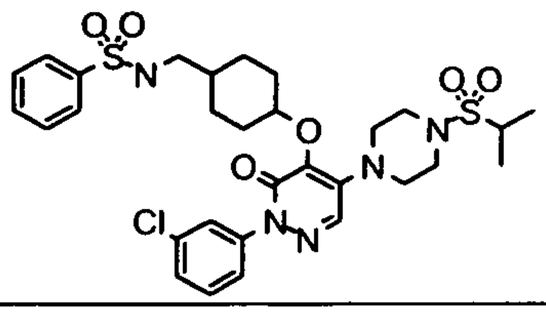
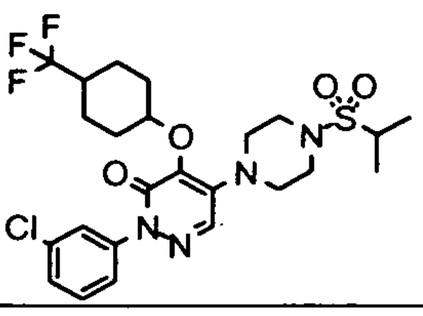
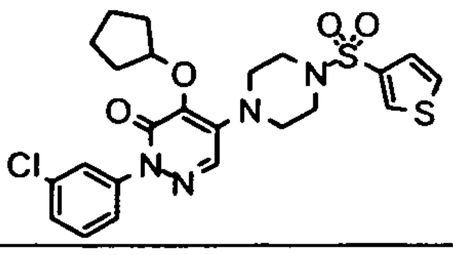
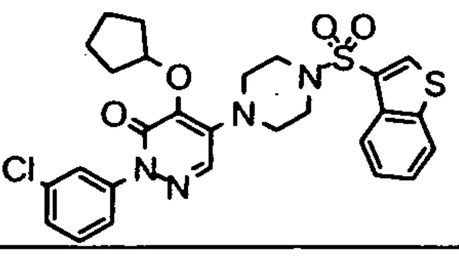
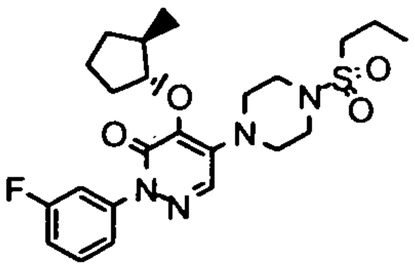
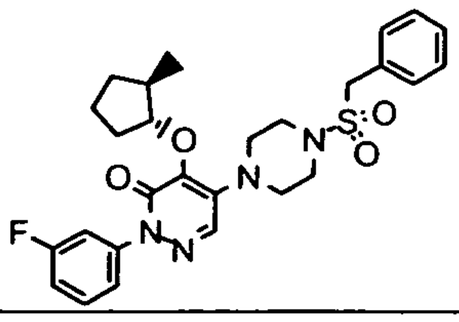
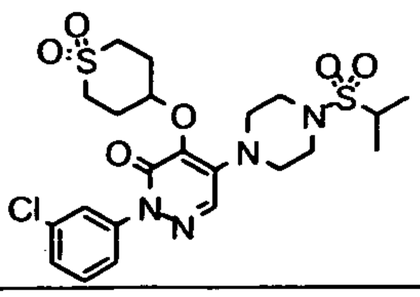
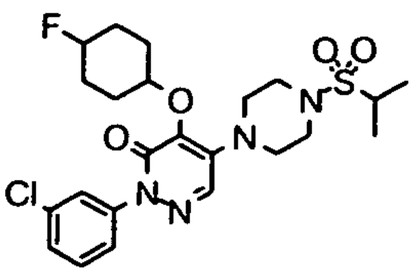
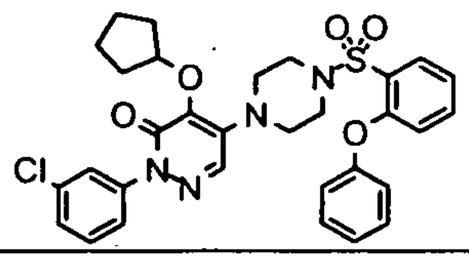
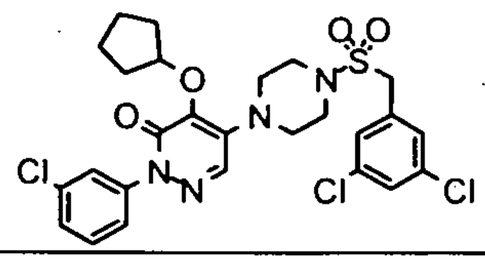
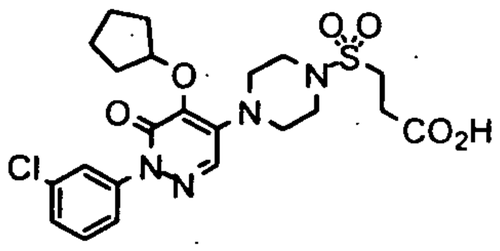
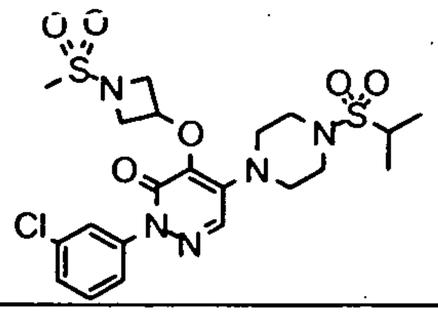
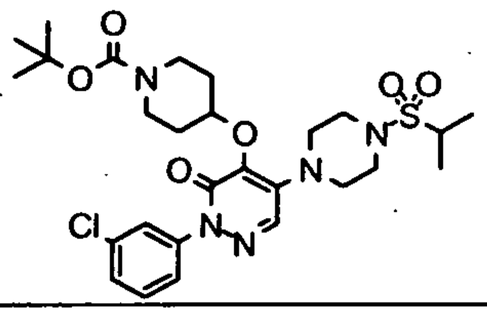
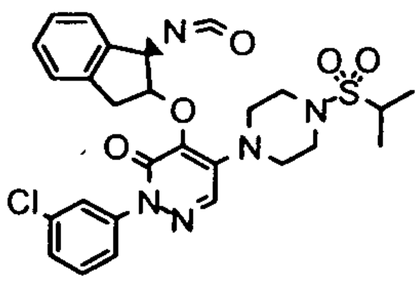
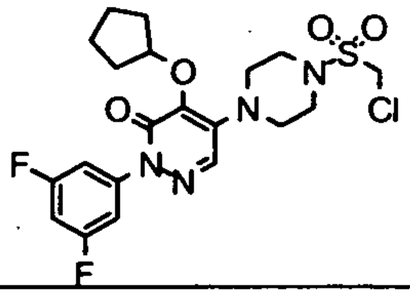
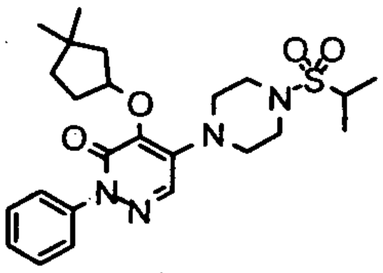
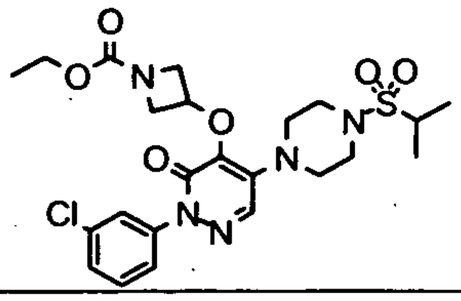
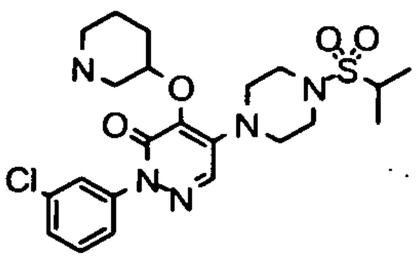
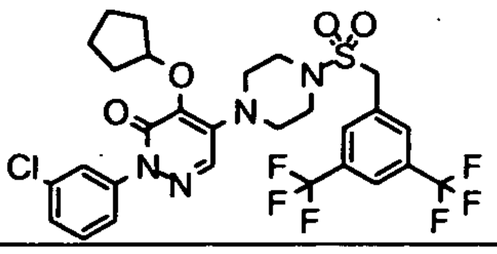
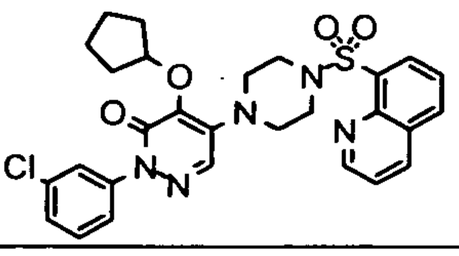
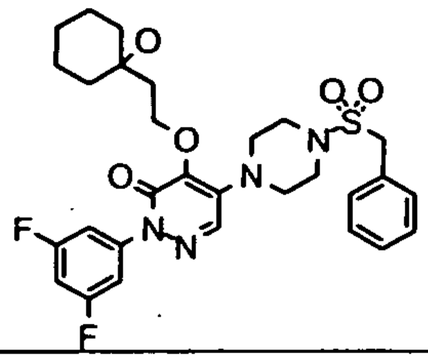
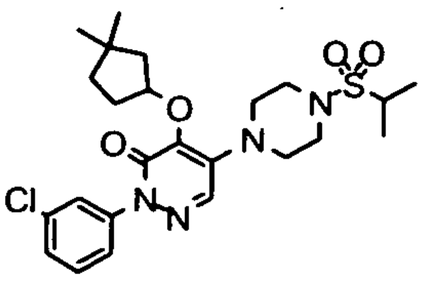
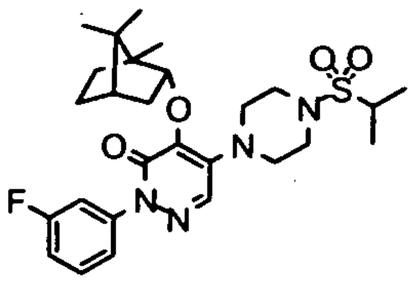
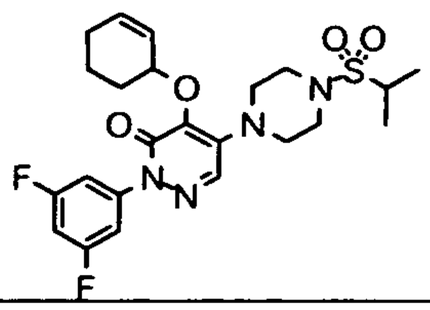
492Z		661
494Z		583
496Z		660
498Z		547
500Z		513
502Z		524

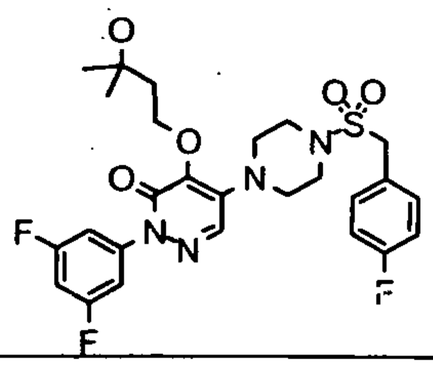
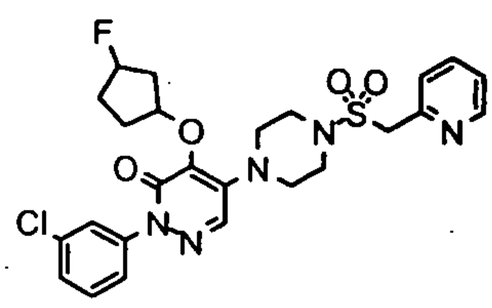
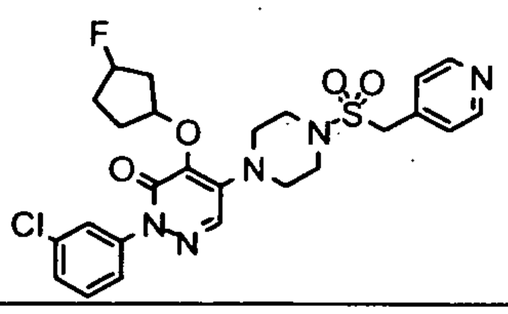
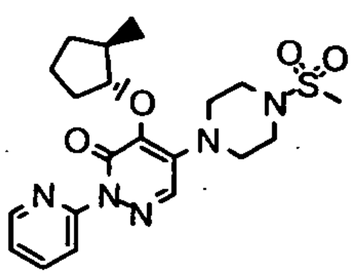
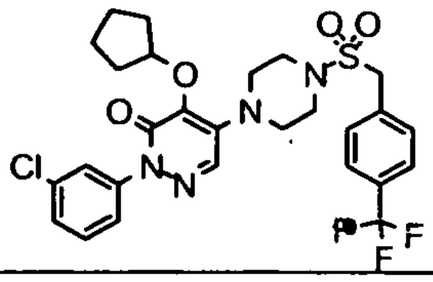
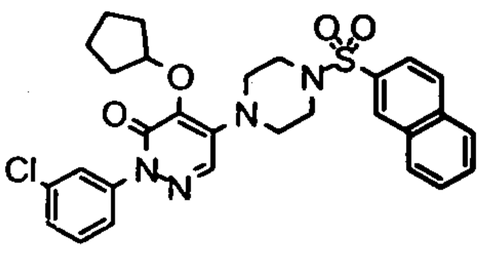
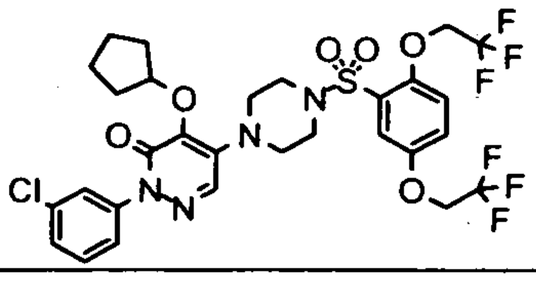
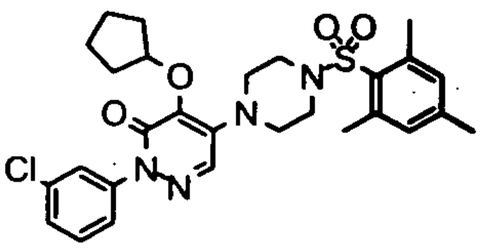
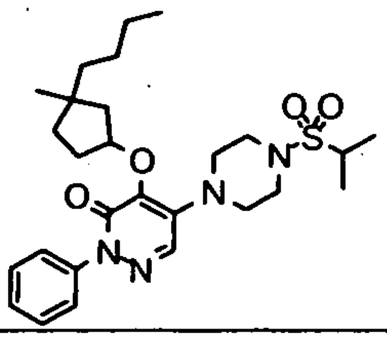
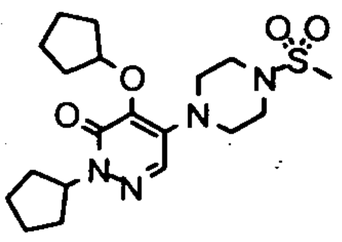
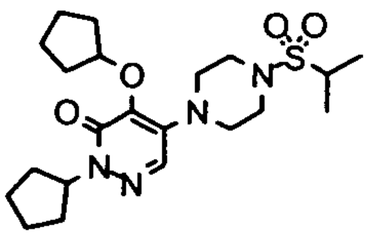
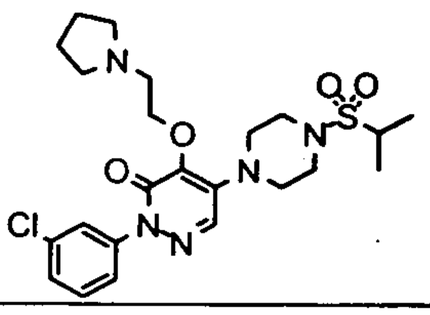
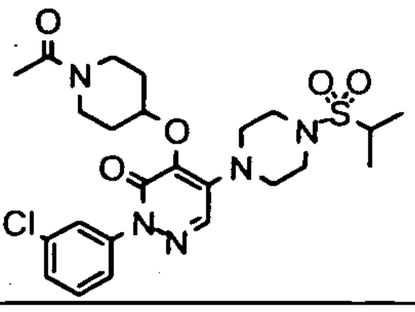
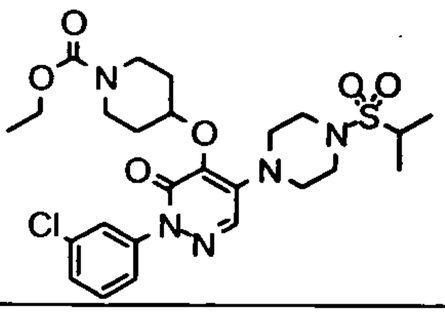
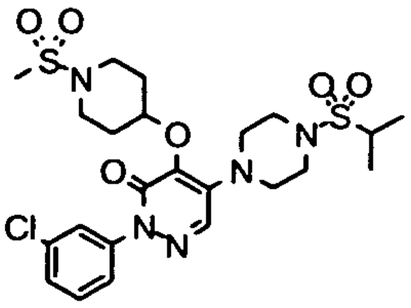
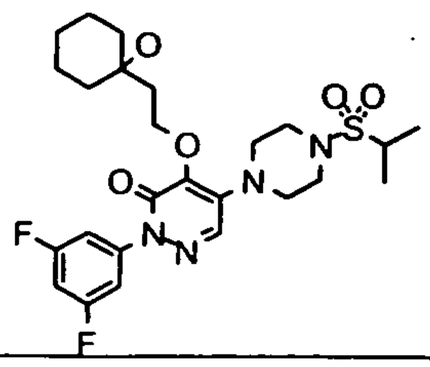
489Z		529
491Z		482 (M-BOC)
493Z		530
495Z		521
497Z		499
499Z		543
501Z		437
503Z		608

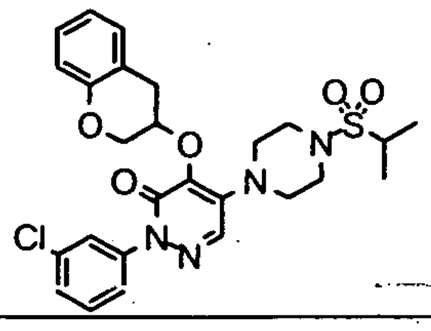
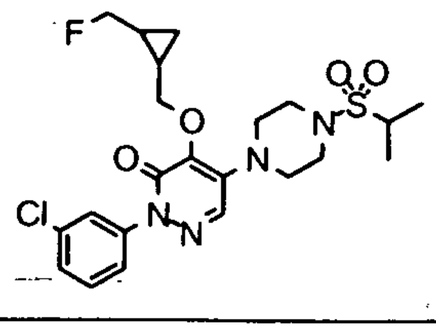
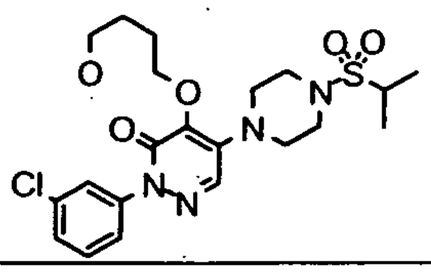
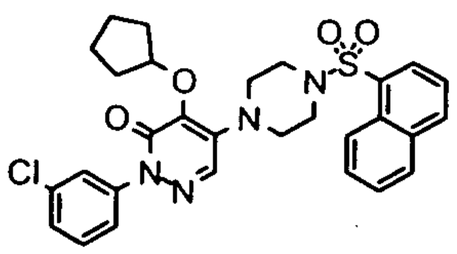
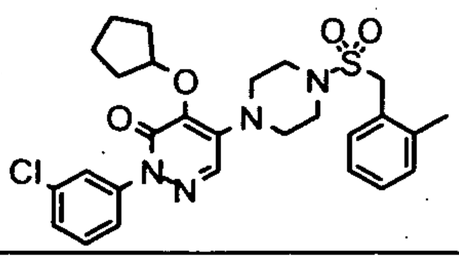
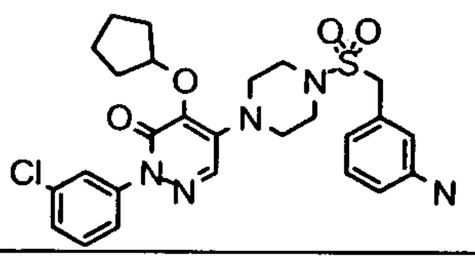
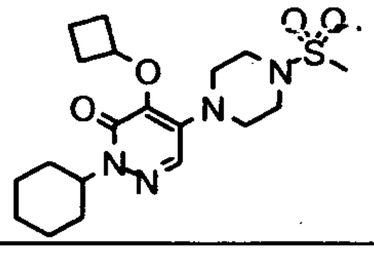
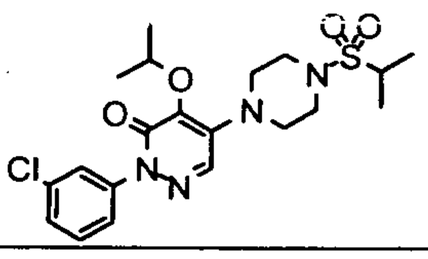
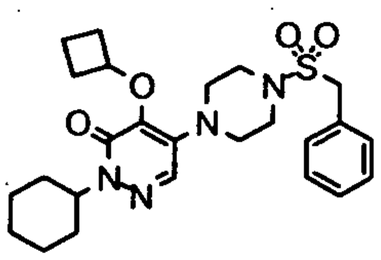
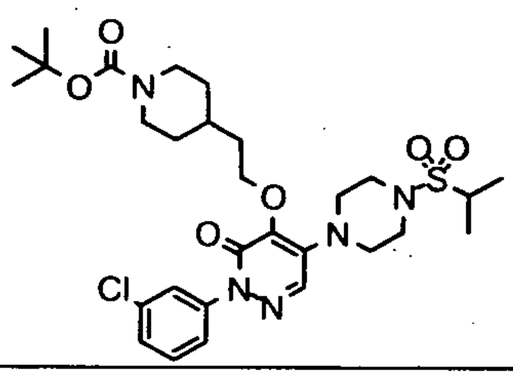
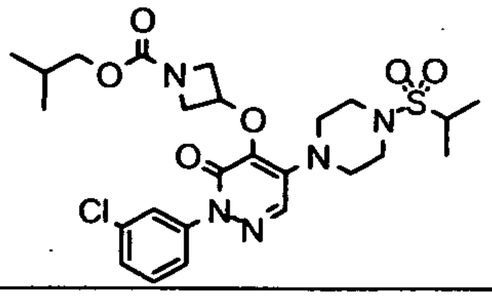
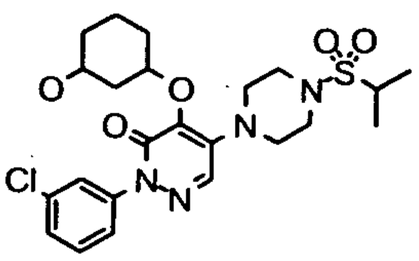
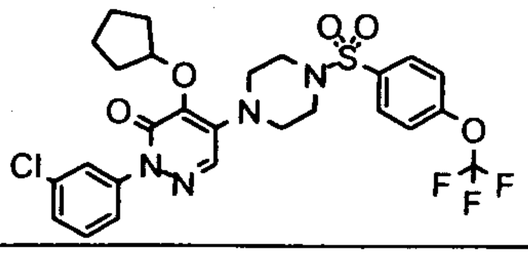
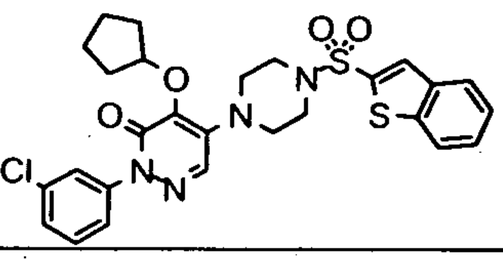
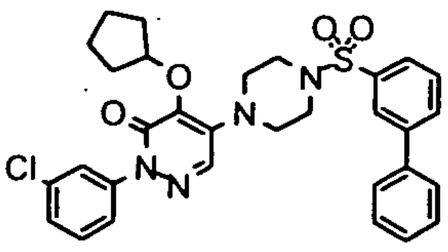
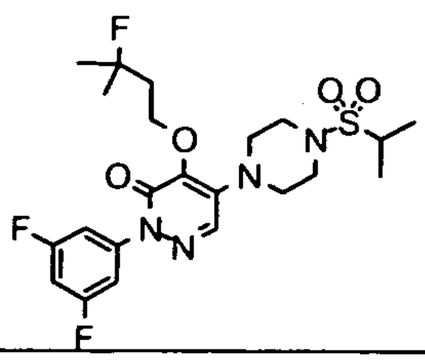
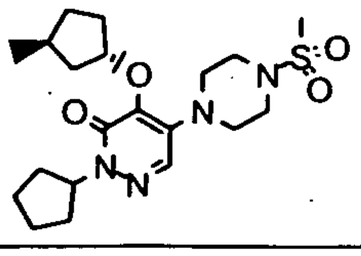
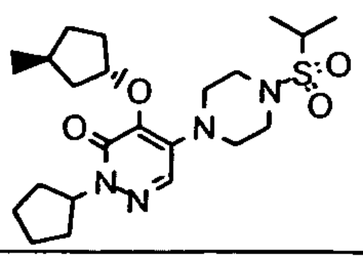
504Z		608
505Z		568 (M+2)
506Z		552
507Z		546
508Z		510
509Z		577
510Z		516
511Z		553
512Z		501
513Z		487
514Z		515
515Z		539
516Z		527
517Z		557
518Z		561
519Z		650

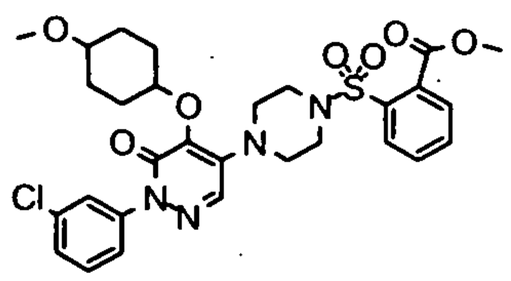
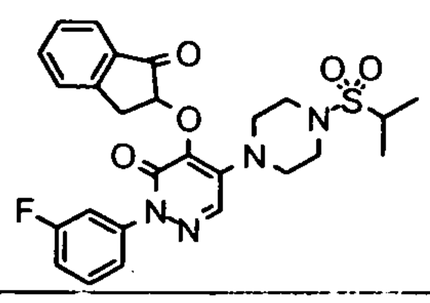
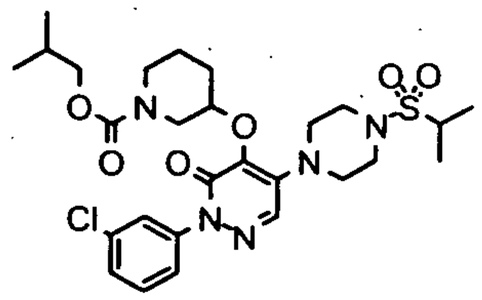
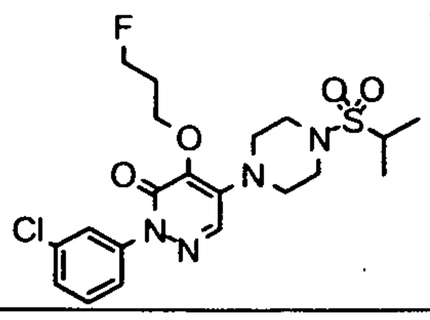
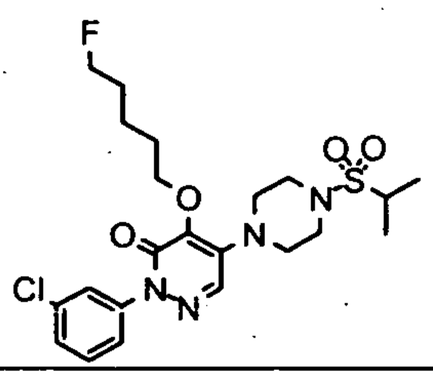
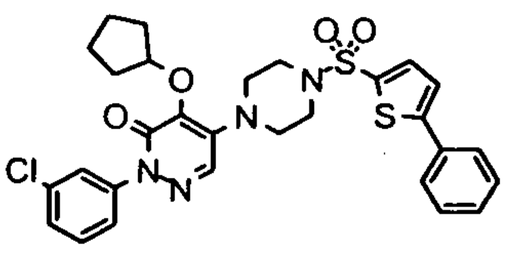
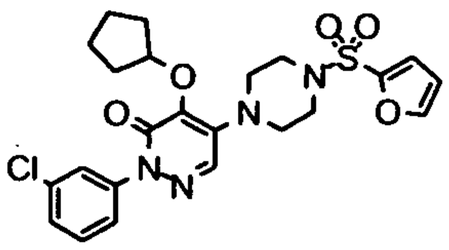
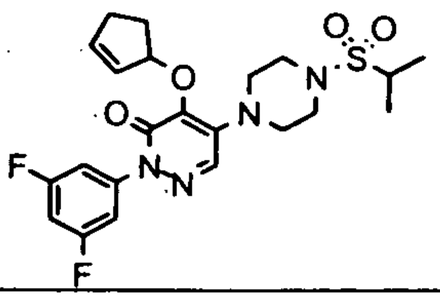
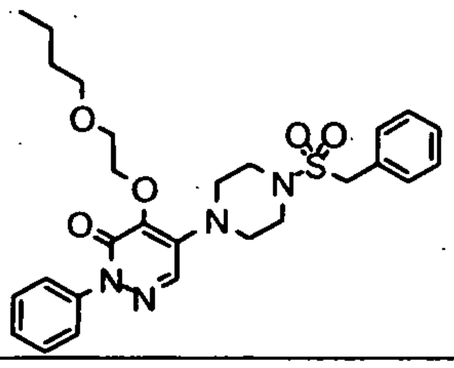
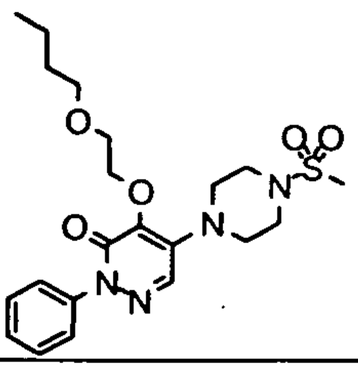
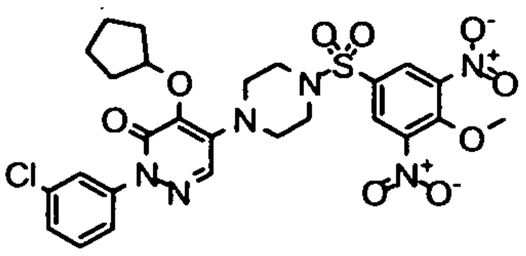
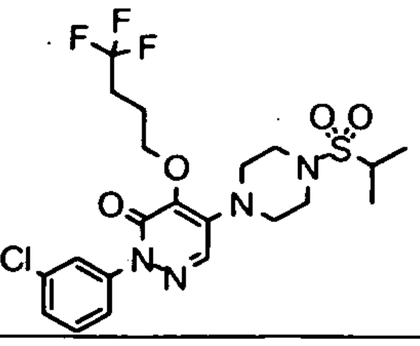
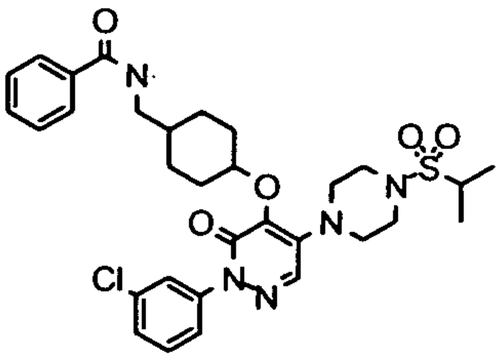
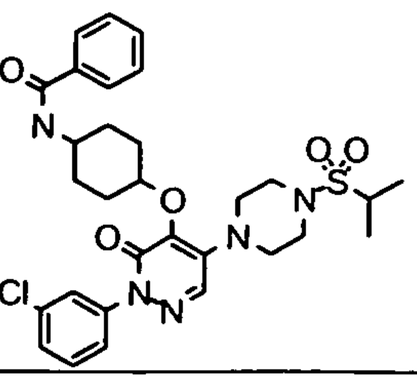
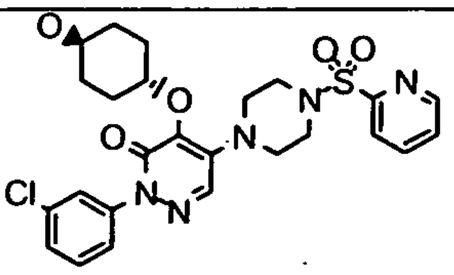
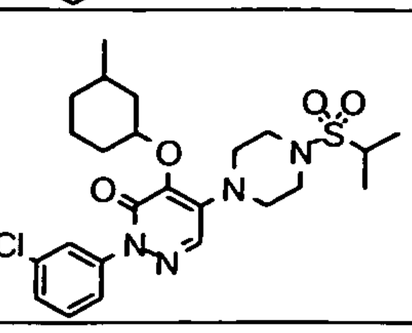
520Z		481	521Z		499
522Z		559	523Z		463
524Z		664	525Z		557
526Z		559	527Z		573
528Z		551	529Z		574
530Z		543	531Z		539
532Z		603	533Z		544
534Z		493	535Z		425 (M+1-ethylene)

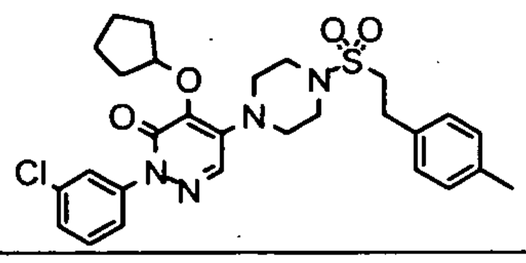
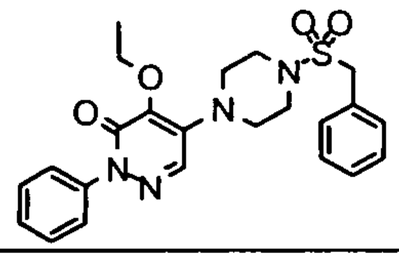
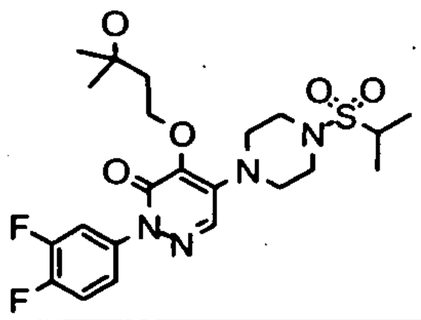
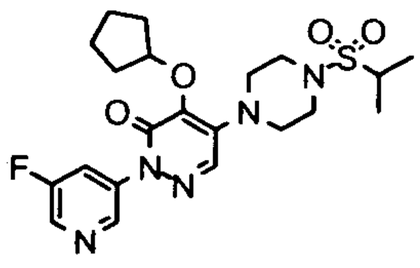
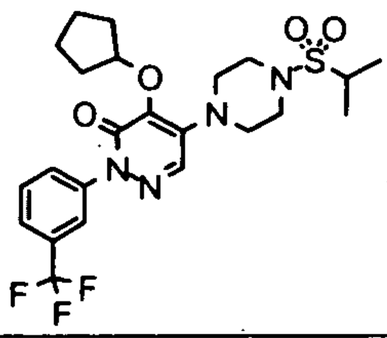
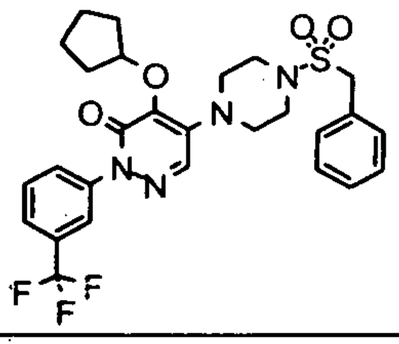
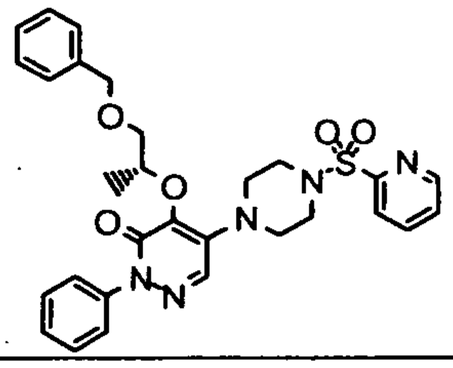
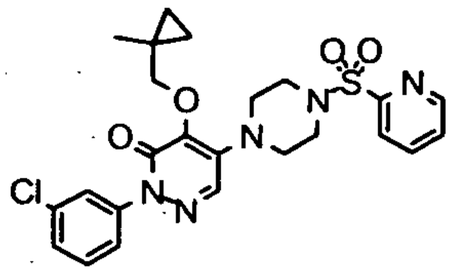
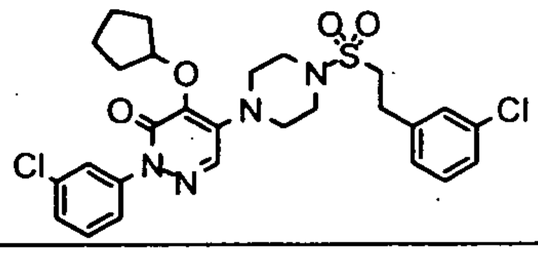
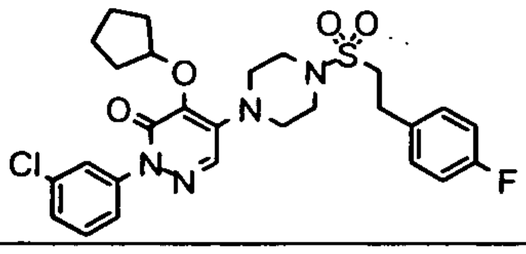
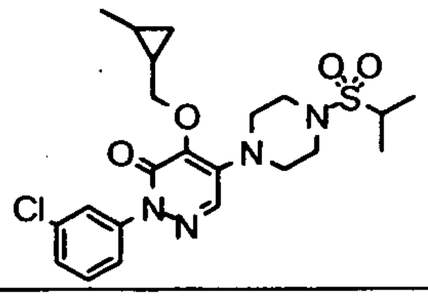
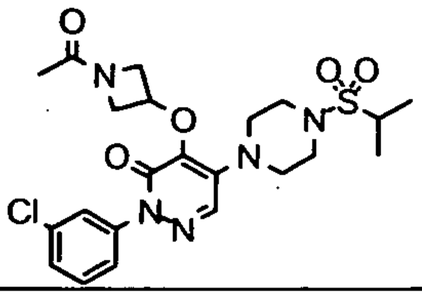
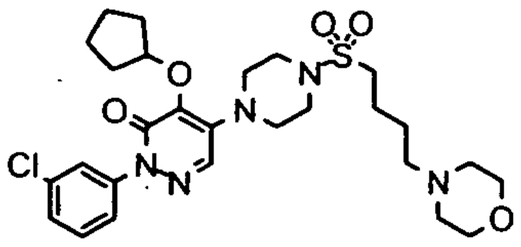
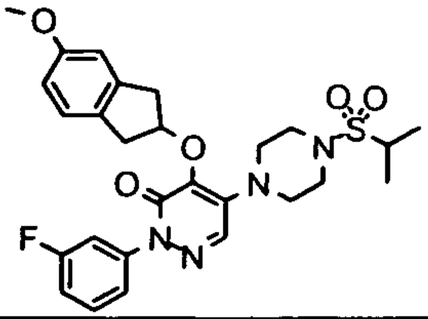
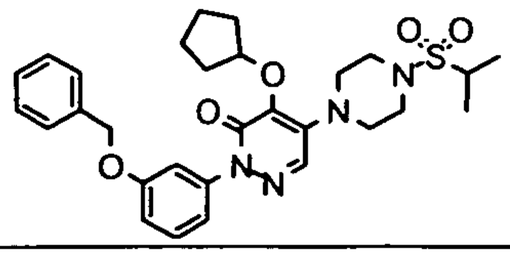
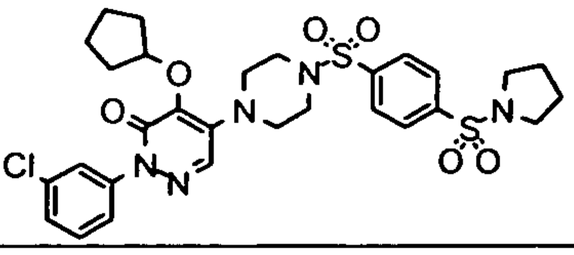
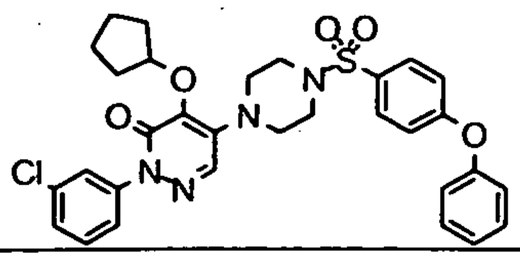
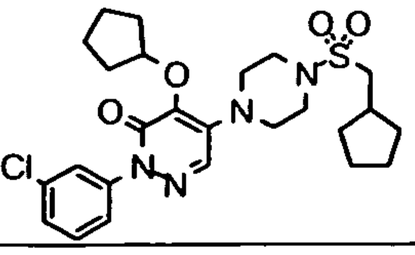
536Z		525	537Z		570
538Z		513	539Z		554
540Z		602	541Z		607
542Z		467	543Z		515
544Z		664	545Z		563
546Z		521	547Z		571
548Z		479	549Z		527
550Z		545	551Z		513

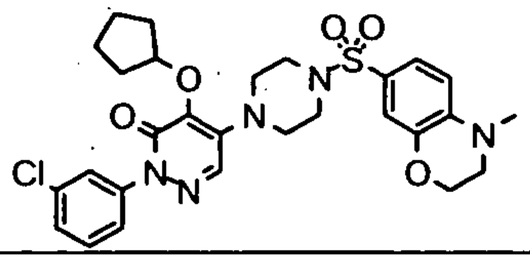
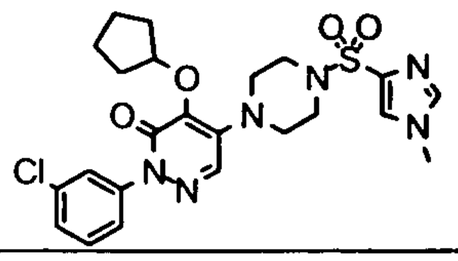
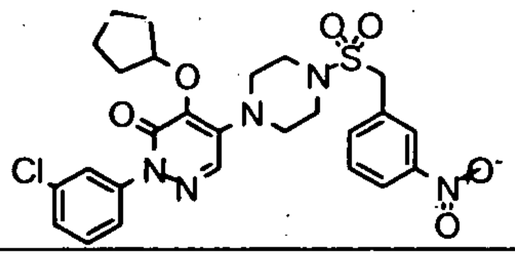
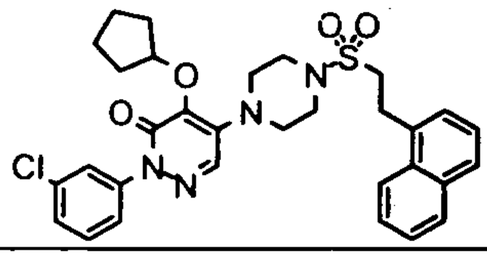
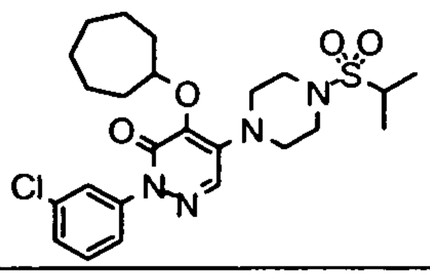
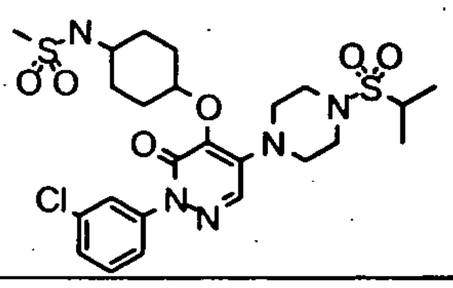
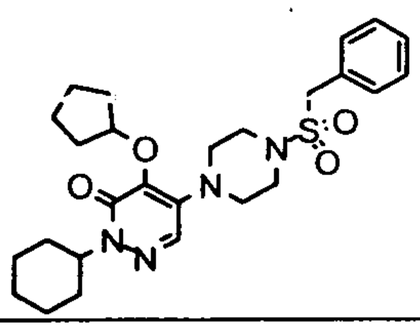
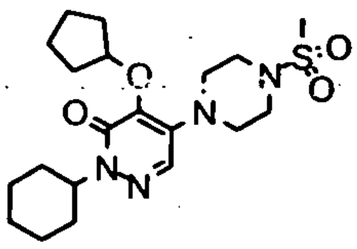
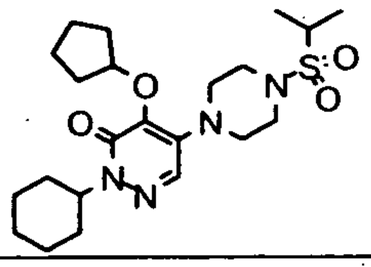
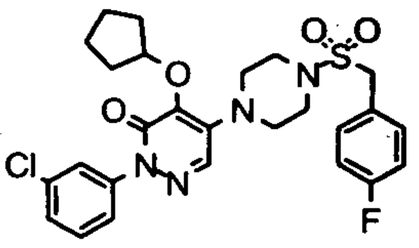
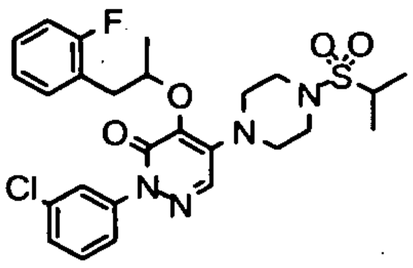
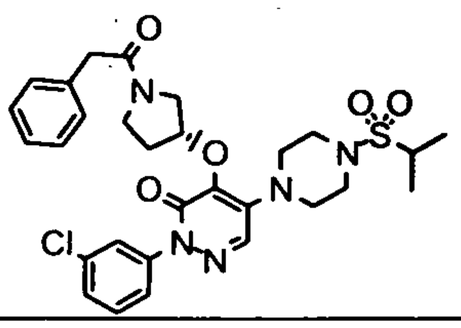
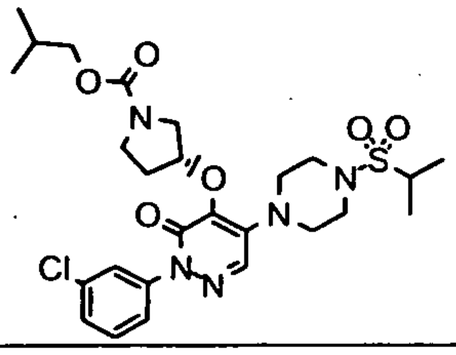
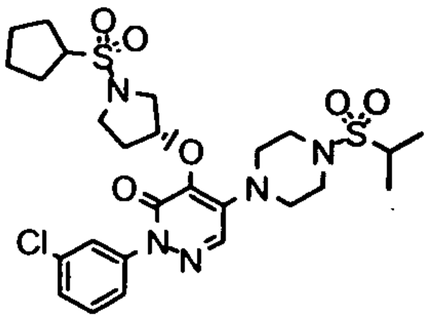
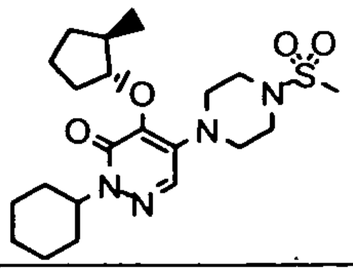
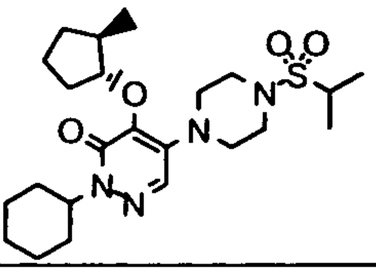
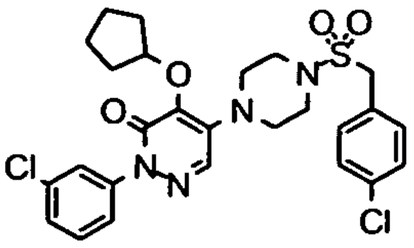
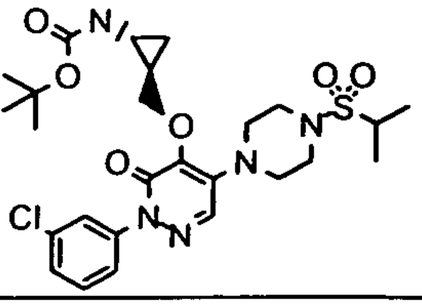
552Z		607	553Z		597
554Z		509 (M-1)	555Z		547
556Z		596	557Z		570
558Z		489	559Z		475
560Z		540	561Z		496
562Z		665	563Z		566
564Z		589	565Z		509
566Z		533	567Z		495

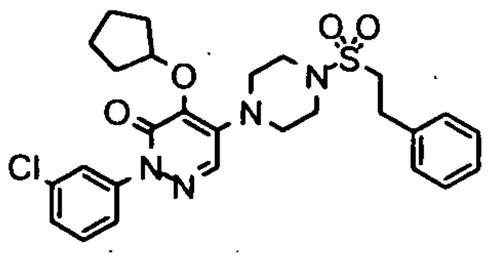
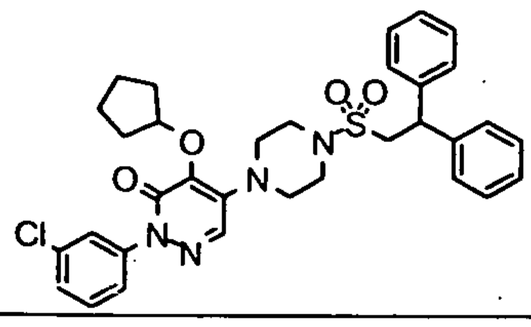
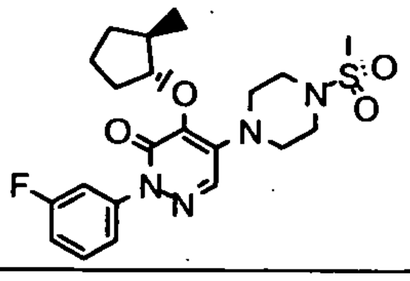
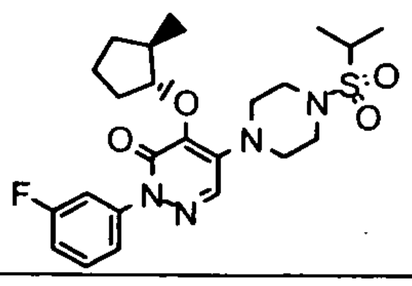
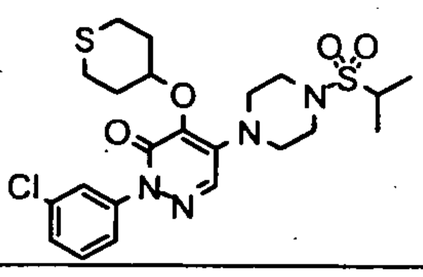
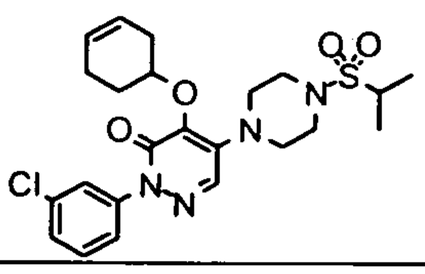
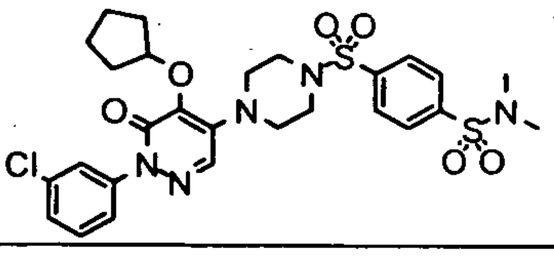
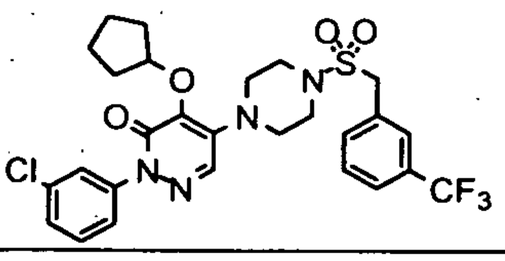
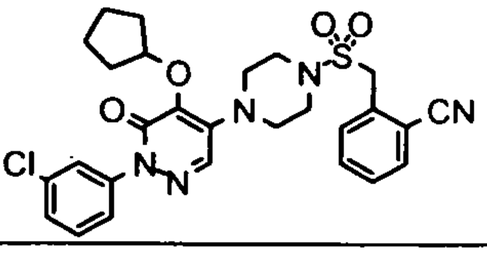
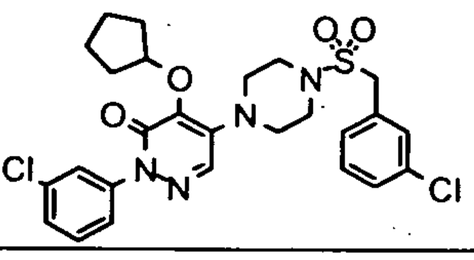
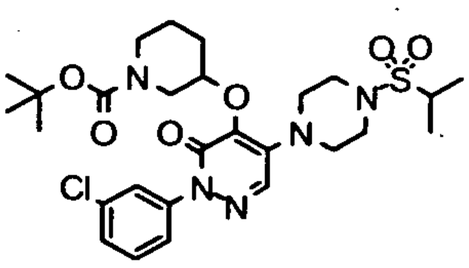
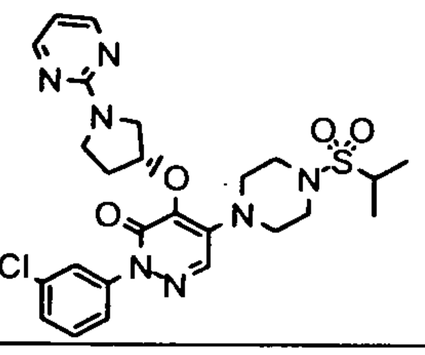
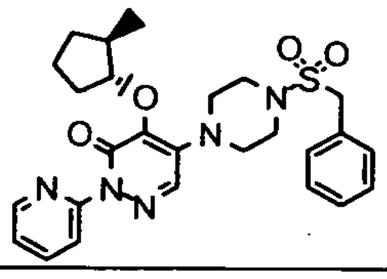
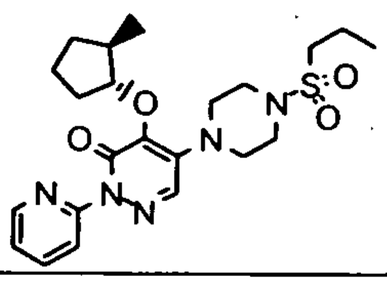
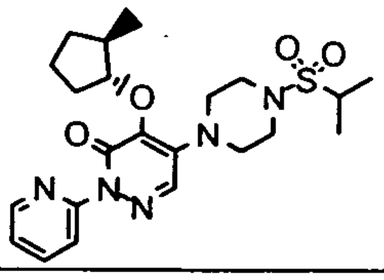
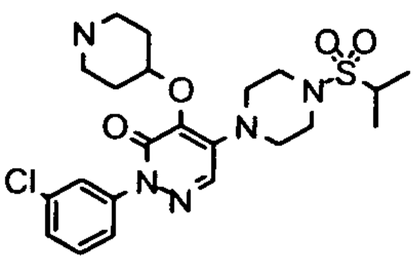
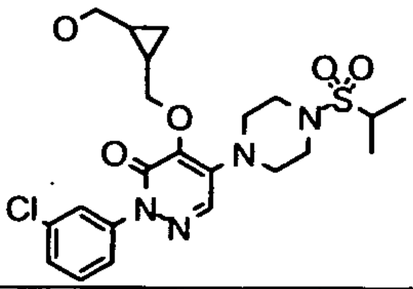
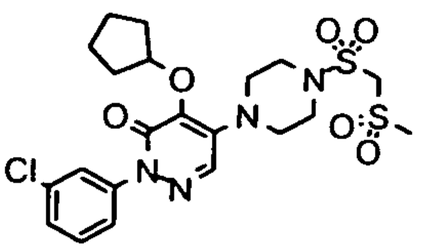
568Z		567	569Z		584
570Z		548	571Z		434
572Z		597	573Z		565
574Z		711	575Z		557
576Z		517	577Z		411
578Z		439	579Z		510
580Z		538	581Z		568
582Z		574	583Z		541

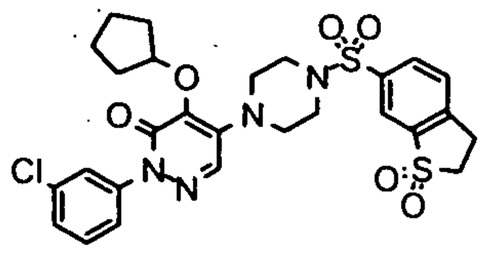
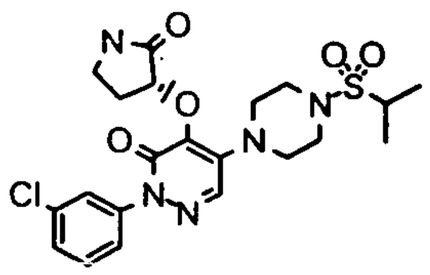
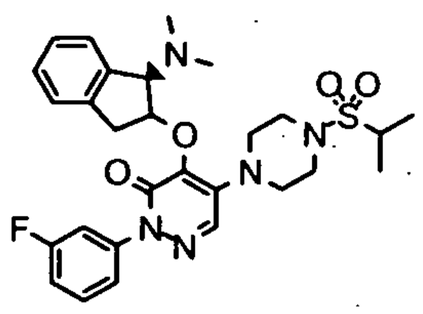
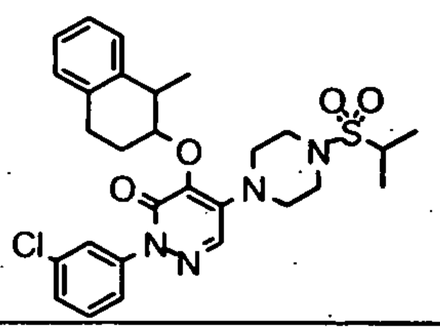
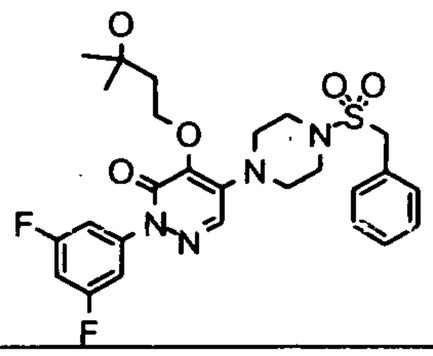
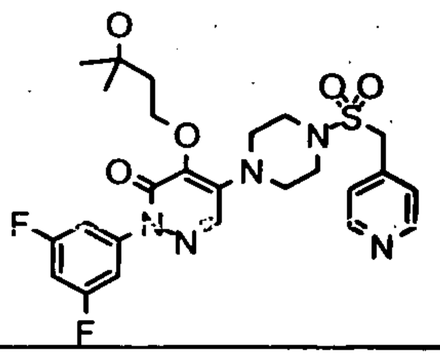
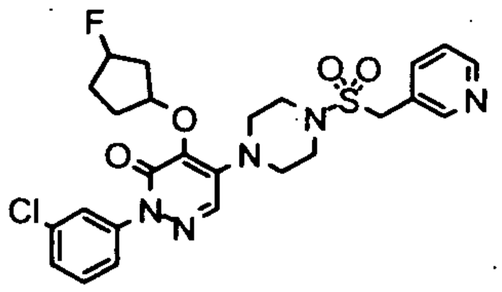
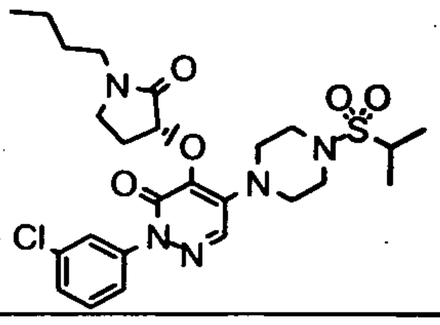
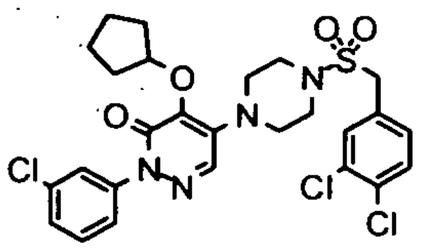
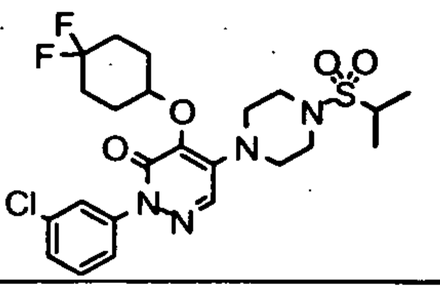
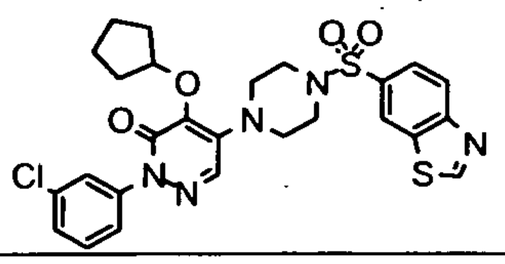
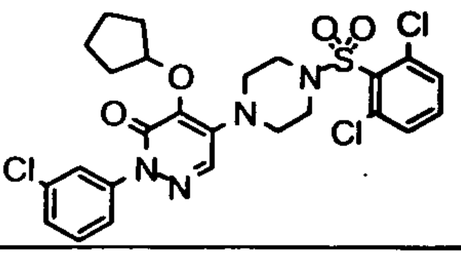
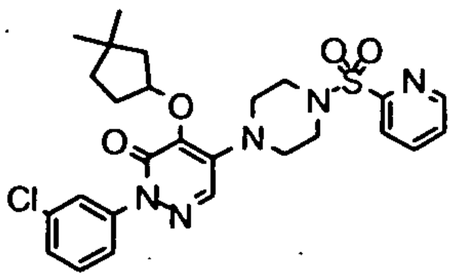
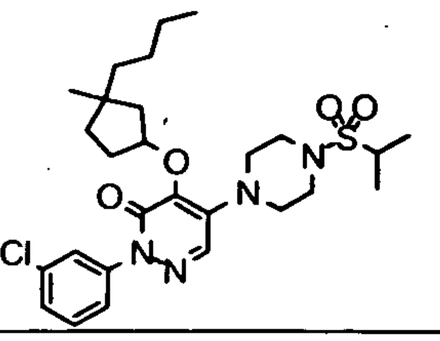
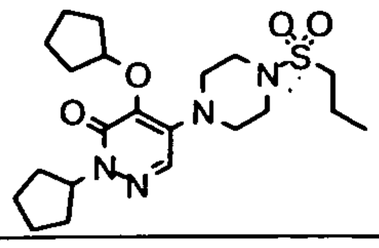
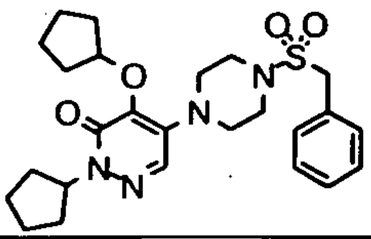
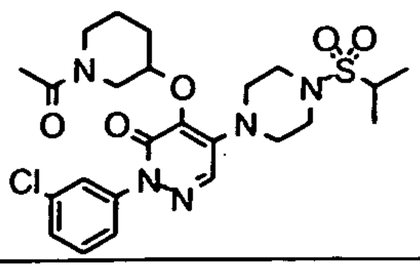
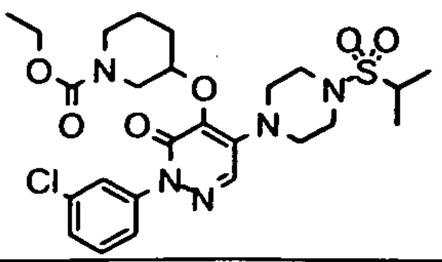
584Z		545
585Z		499
586Z		485
587Z		565
588Z		543
589Z		544
590Z		411
591Z		455
592Z		487
593Z		624
594Z		568
595Z		511
596Z		599
597Z		571
598Z		591
599Z		503
600Z		425
601Z		453

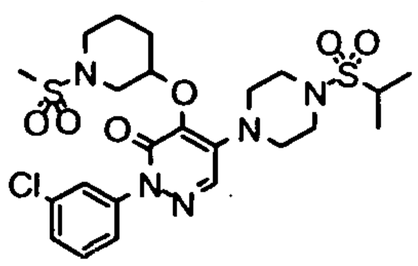
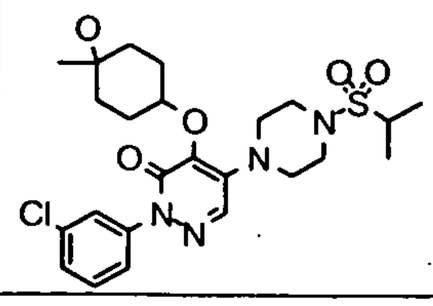
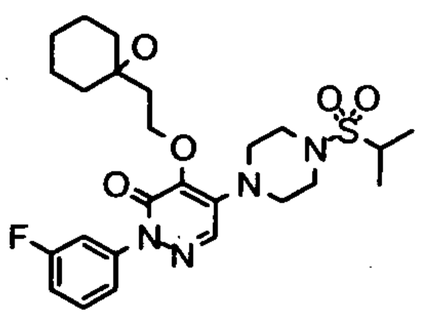
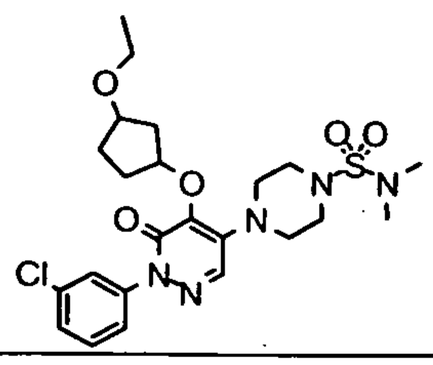
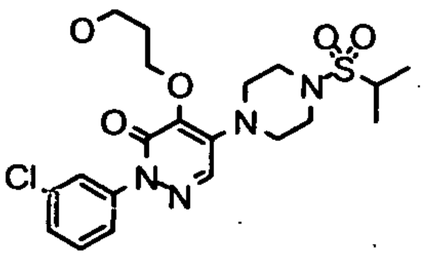
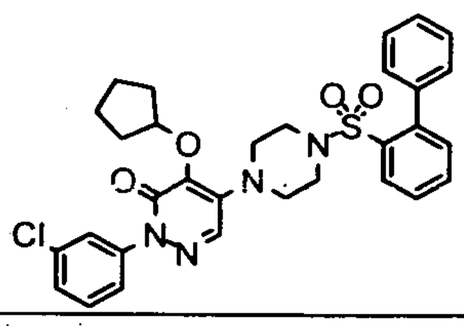
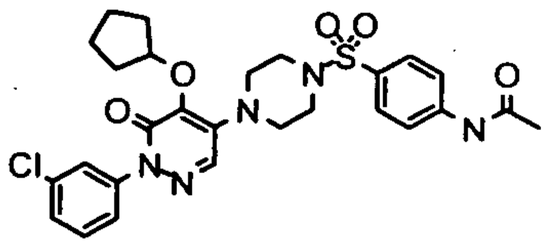
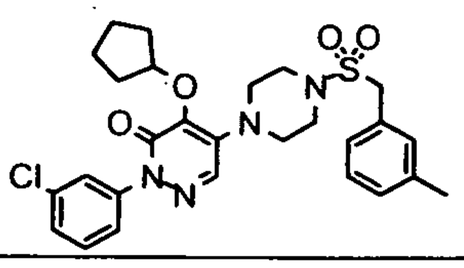
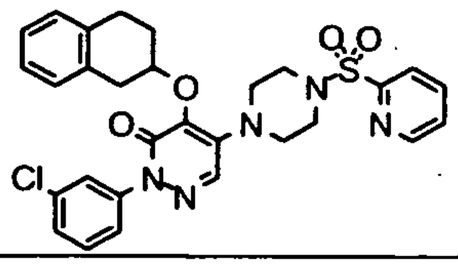
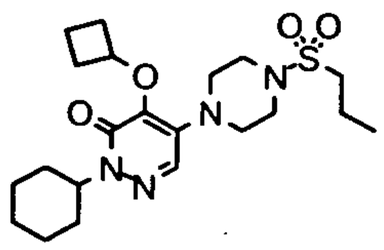
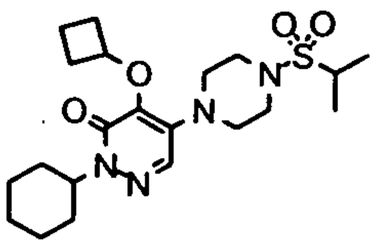
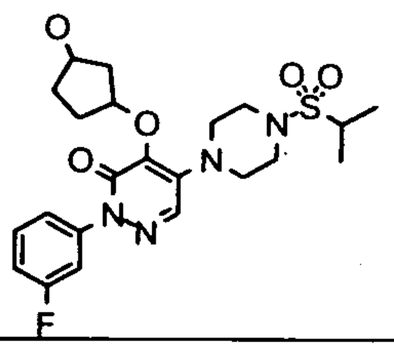
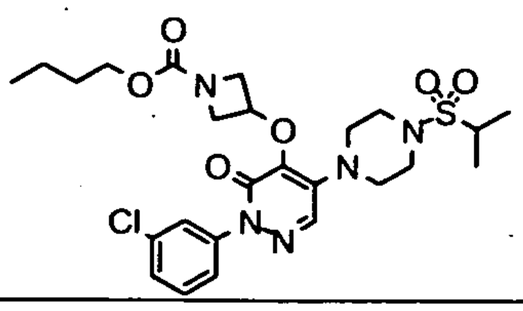
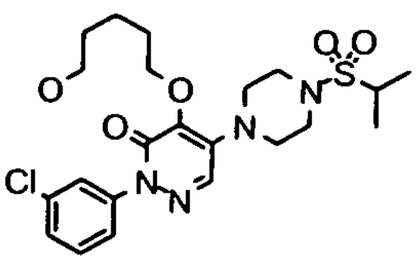
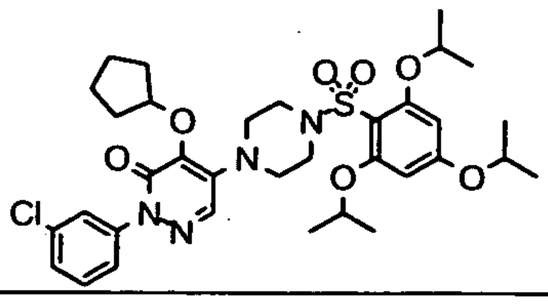
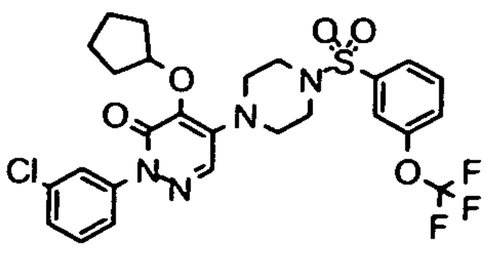
602Z		617	603Z		527
604Z		596	605Z		473
606Z		501	607Z		597
608Z		505	609Z		481
610Z		527	611Z		451
612Z		635	613Z		523
614Z		628	615Z		614
616Z		546	617Z		510

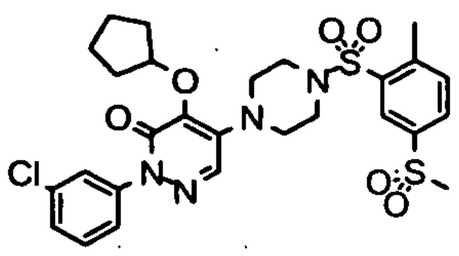
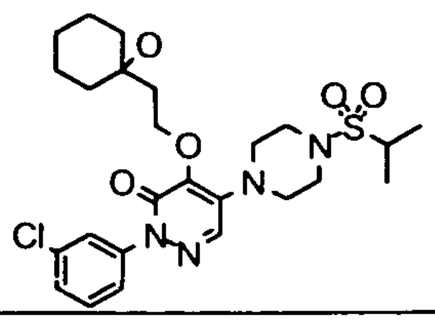
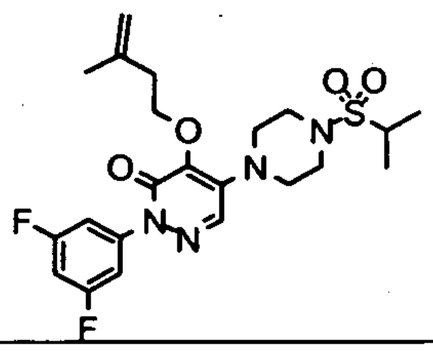
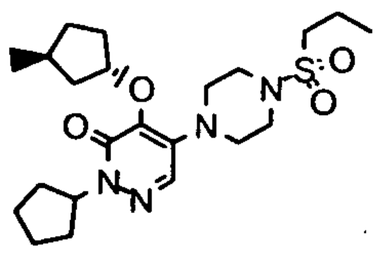
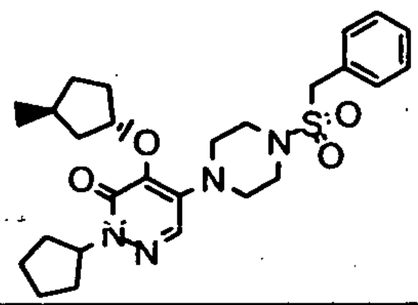
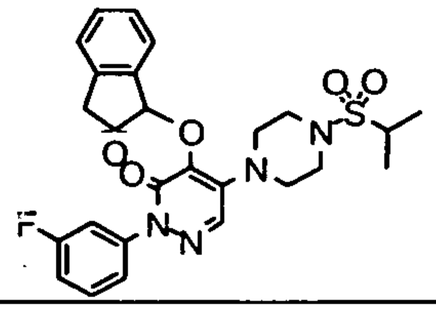
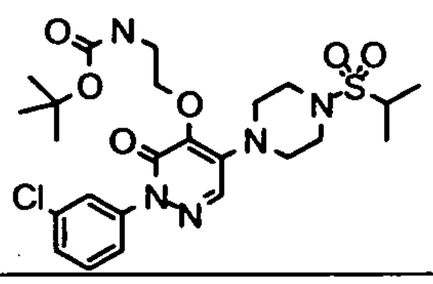
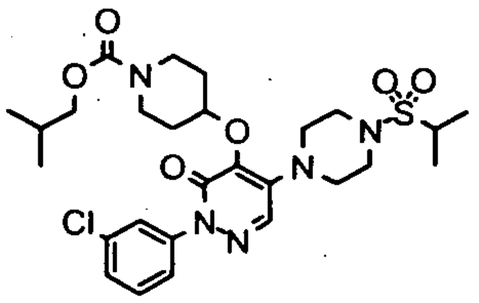
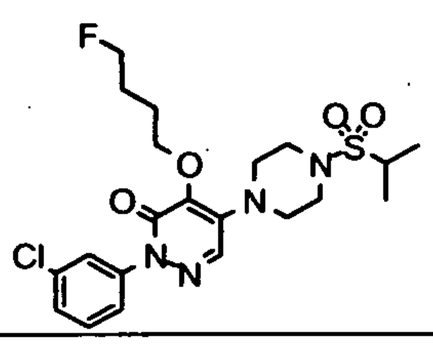
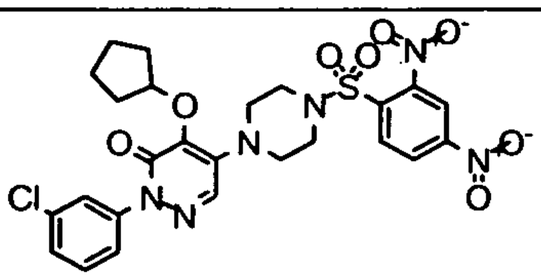
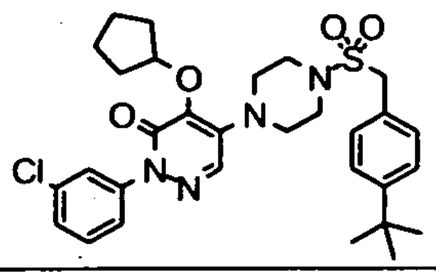
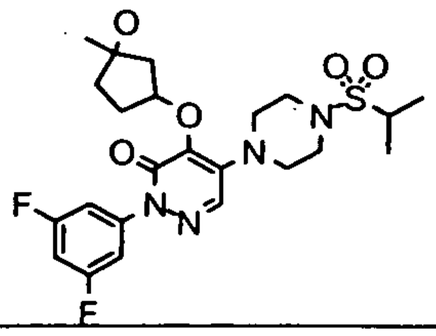
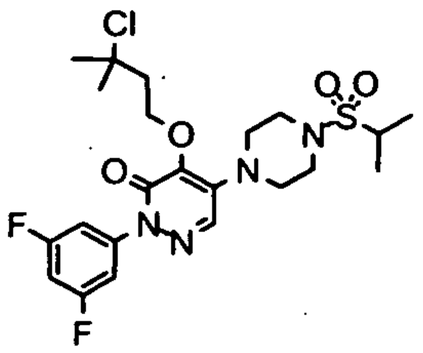
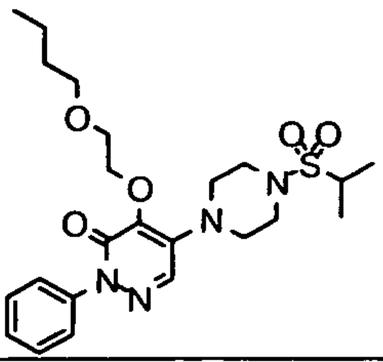
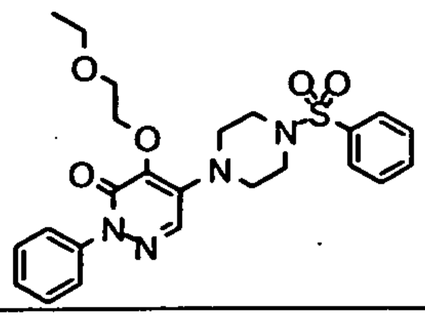
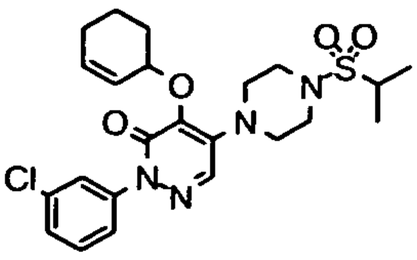
618Z		557	619Z		455
620Z		501	621Z		466
622Z		515	623Z		563
624Z		562	625Z		516
626Z		577	627Z		561
628Z		481	629Z		512 (M+2)
630Z		580	631Z		543
632Z		553	633Z		648
634Z		607	635Z		521

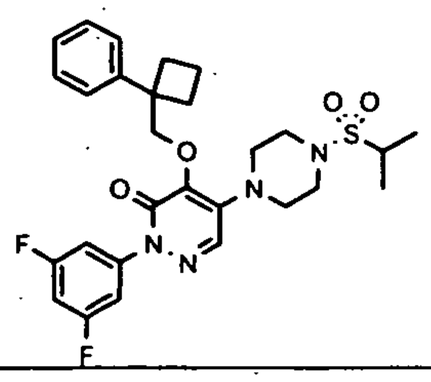
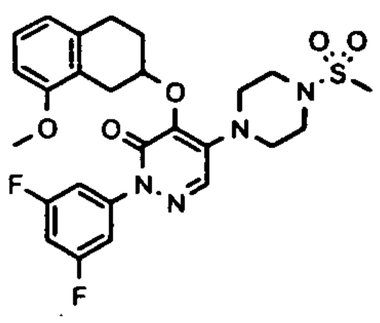
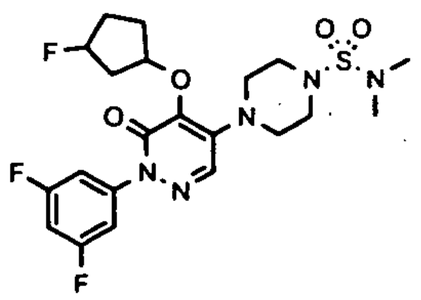
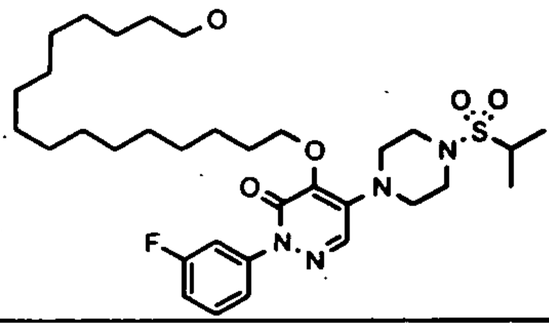
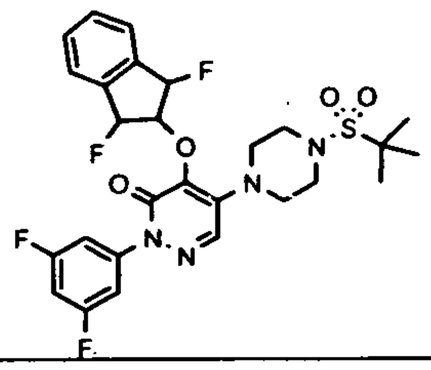
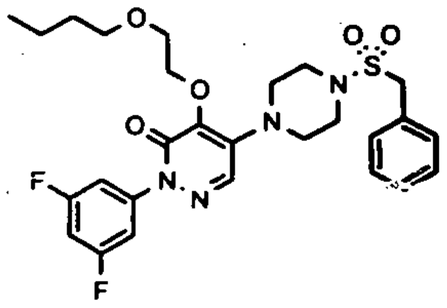
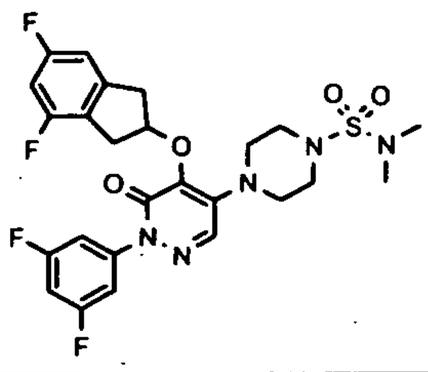
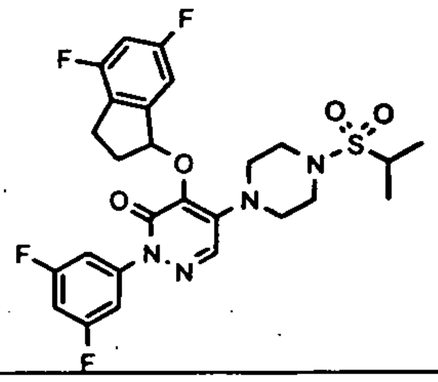
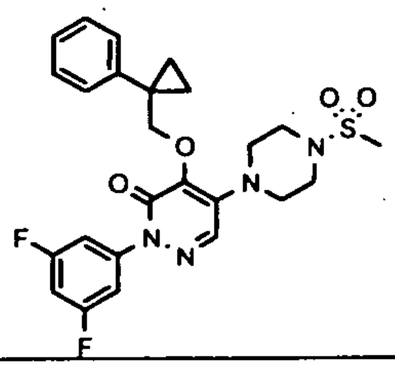
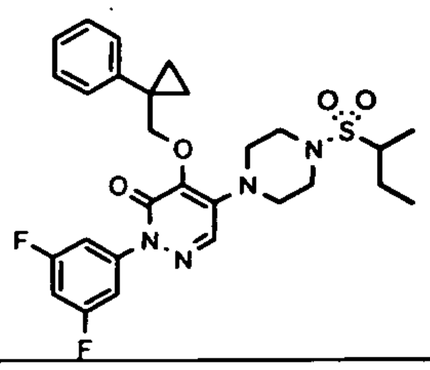
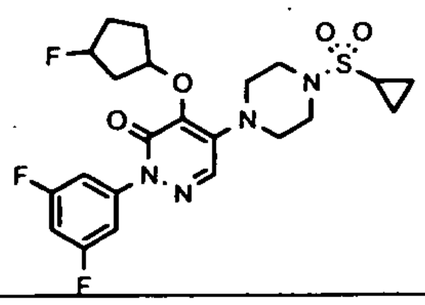
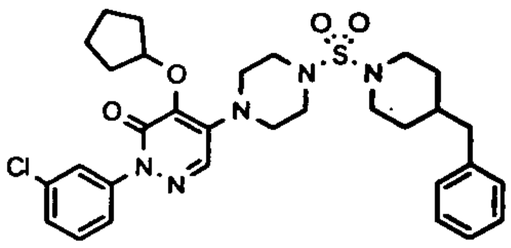
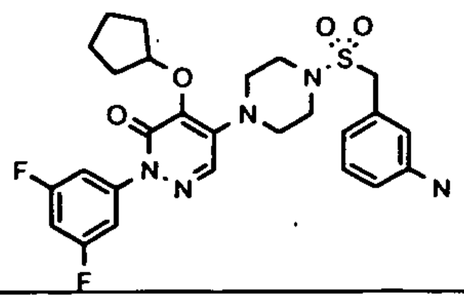
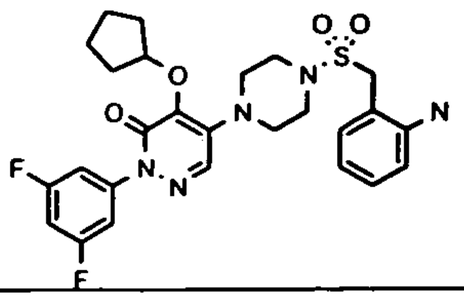
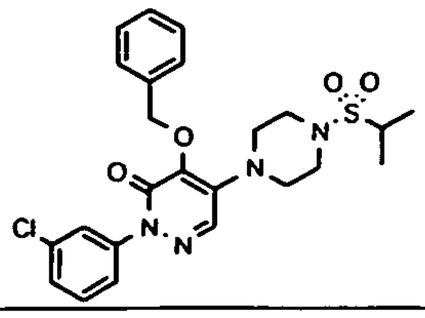
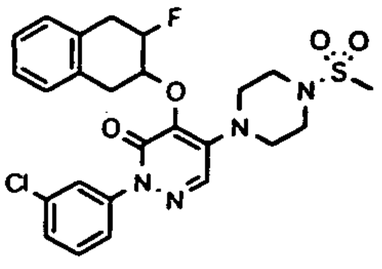
636Z		586	637Z		519
638Z		574	639Z		593
640Z		509	641Z		588
642Z		501	643Z		467 (M+ Na)
644Z		453	645Z		547
646Z		549	647Z		600
648Z		582	649Z		614
650Z		439	651Z		467
652Z		563	653Z		582

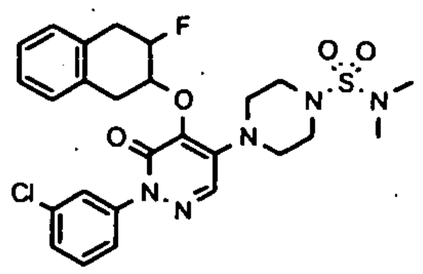
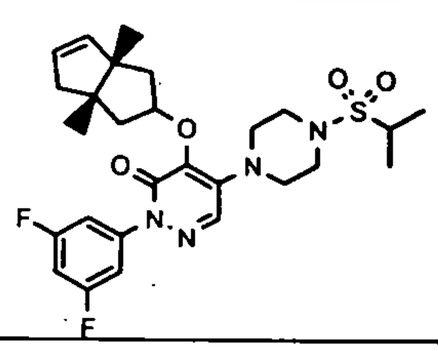
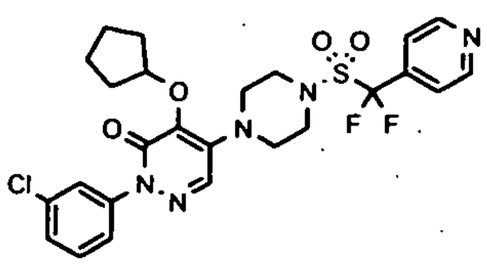
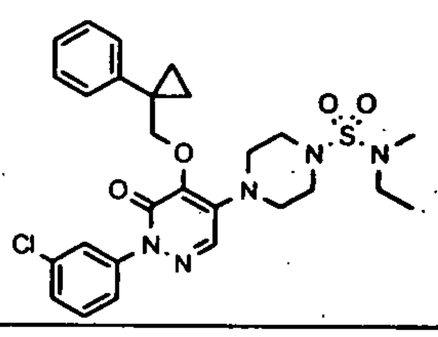
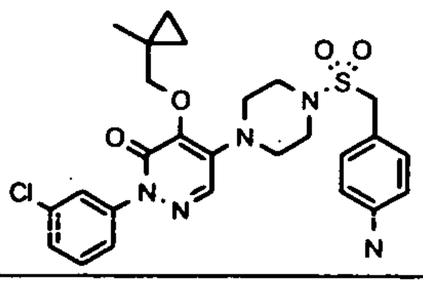
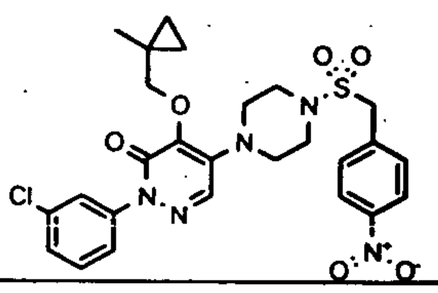
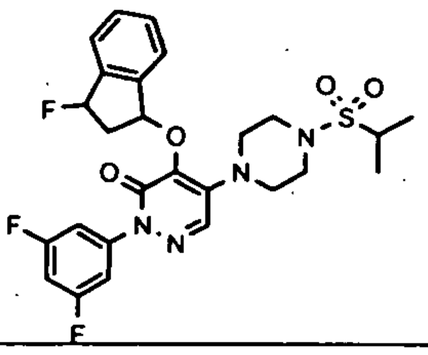
654Z		543	655Z		619
656Z		451	657Z		479
658		513	659Z		493
660Z		622	661Z		597
662Z		554	663Z		565
664Z		497 (M+1-BOC)	665Z		560
666Z		510	667Z		462
668Z		462	669Z		496
670Z		497	671Z		531

672Z		606	673Z		496
674Z		556	675Z		557
676Z		550	677Z		550
678Z		548	679Z		552
680Z		597	681Z		531
682Z		572	683Z		583
684Z		544	685Z		551
686Z		439	687Z		487
688Z		538	689Z		568

690Z		574
691Z		525
692Z		523
693Z		526
694Z		471
695Z		591
696Z		572
697Z		543
698Z		578
699Z		439
700Z		439
701Z		481
702Z		568
703Z		499
704Z		688 (M-1)
705Z		599

706Z		607
707Z		539
708Z		483
709Z		453
710Z		501
711Z		529
712Z		456 (M+1-BOC)
713Z		596
714Z		487
715Z		605
716Z		585
717Z		513
718Z		519
719Z		479
720Z		485
721Z		493

723Z		559	724Z		547
725Z		502	726Z		637
727Z		581	728Z		563
729Z		568	730Z		567
731Z		517	732Z		559
733Z		499	734Z		612
735Z		546	738Z		546
739Z		503	740Z		533

741Z		562
742Z		549
743Z		567
744Z		559
745Z		545
746Z		574
747Z		549
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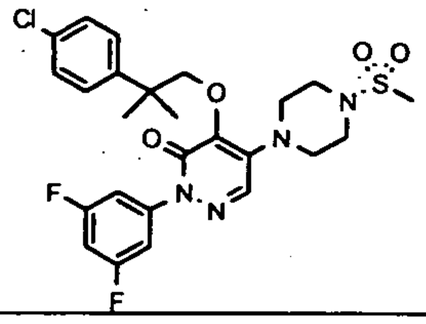
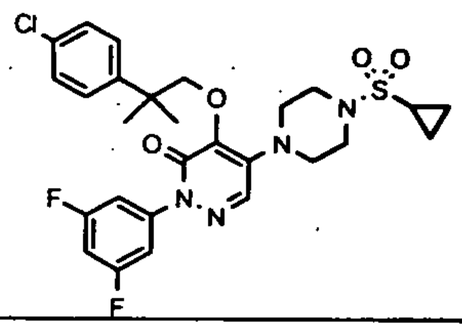
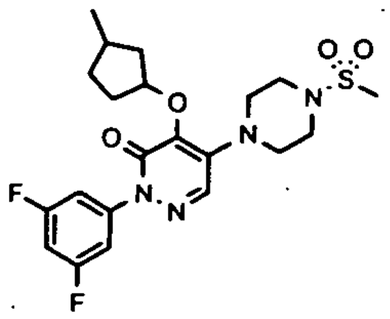
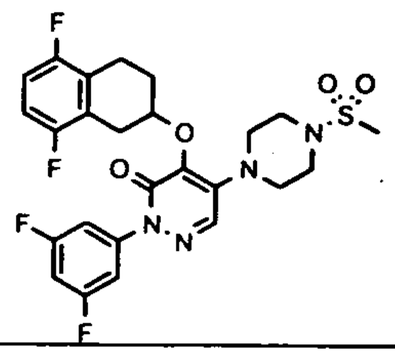
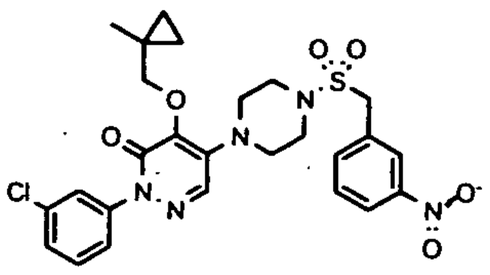
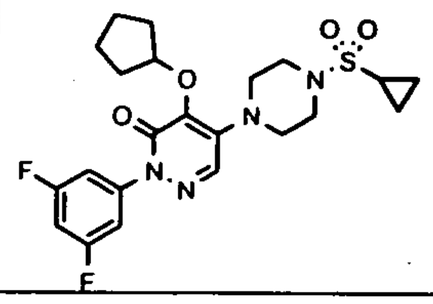
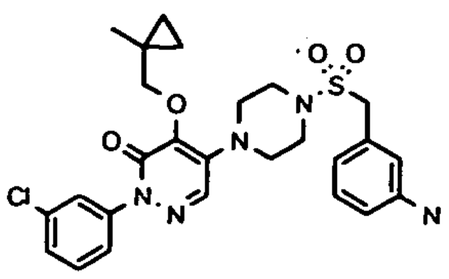
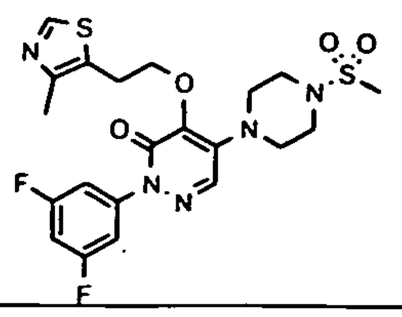
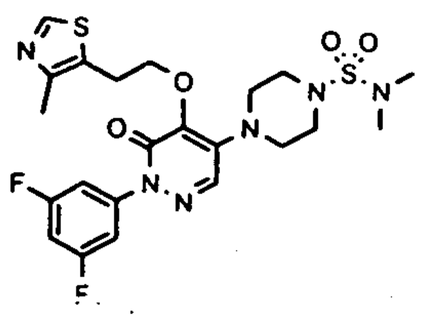
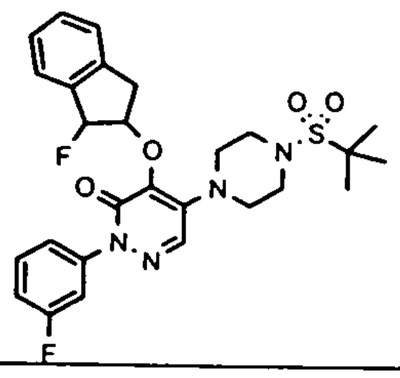
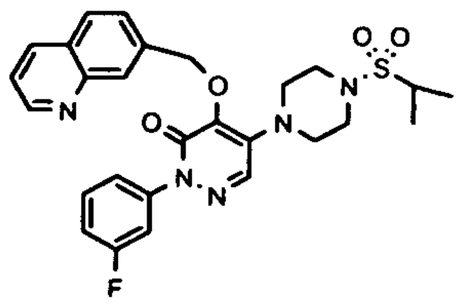
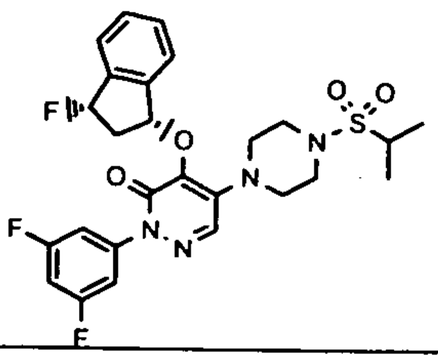
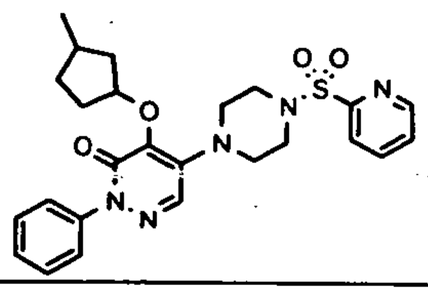
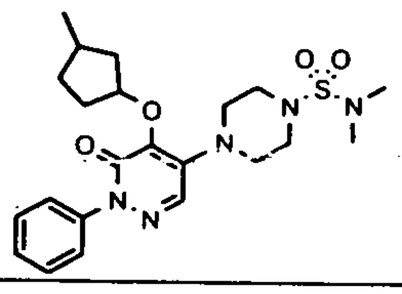
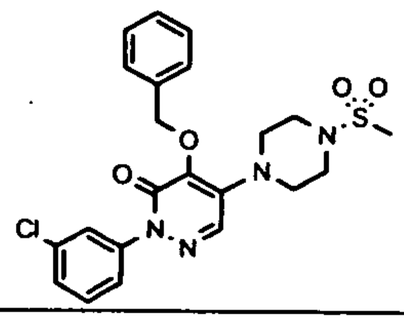
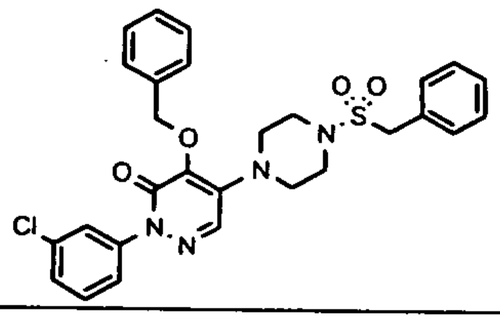
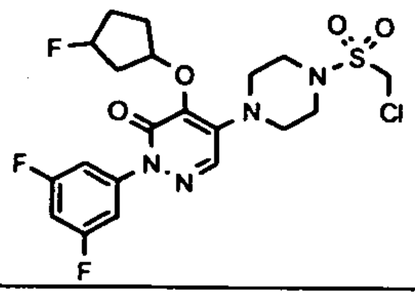
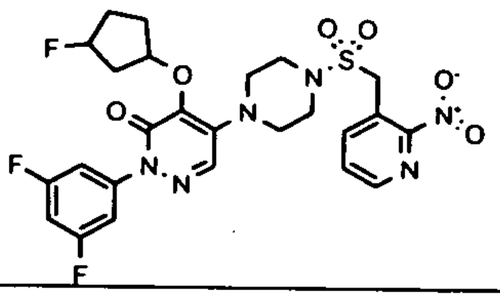
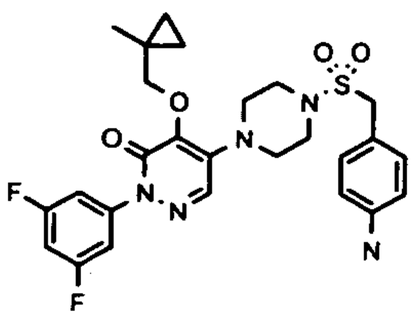
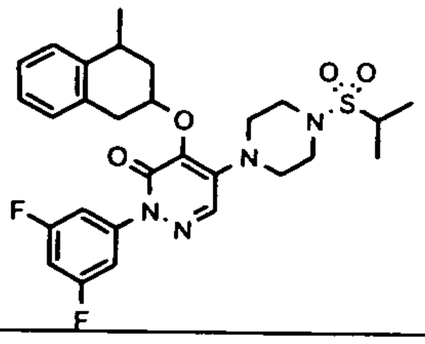
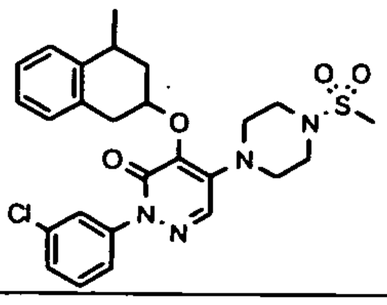
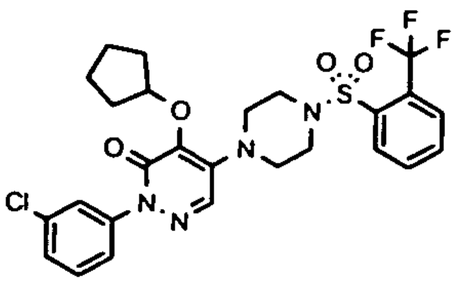
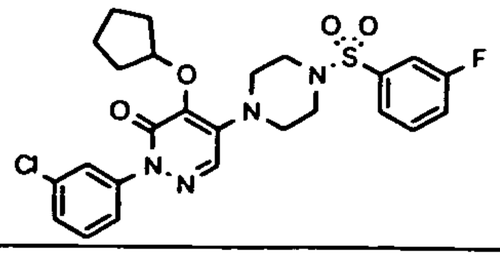
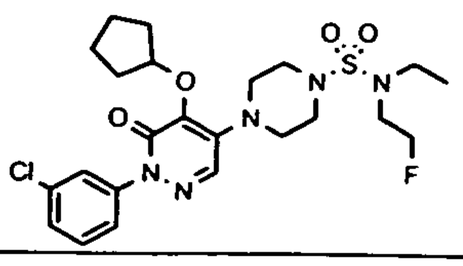
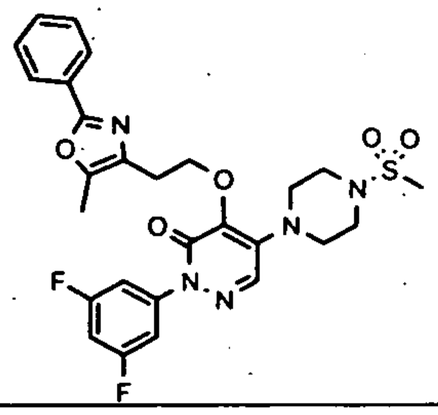
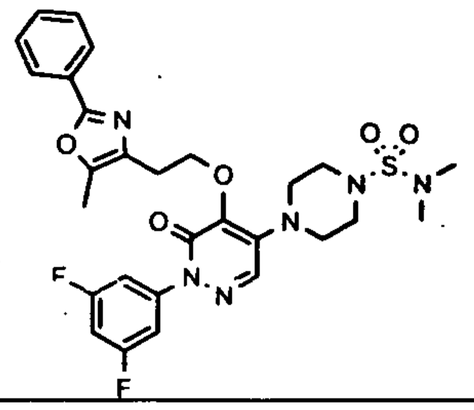
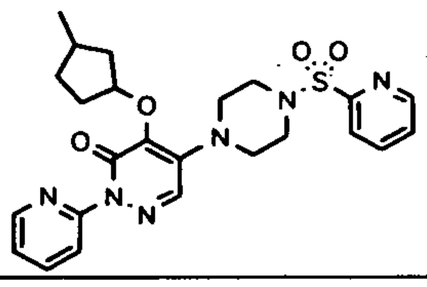
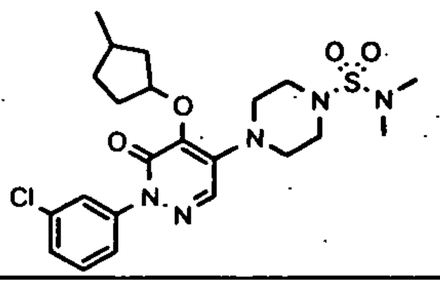
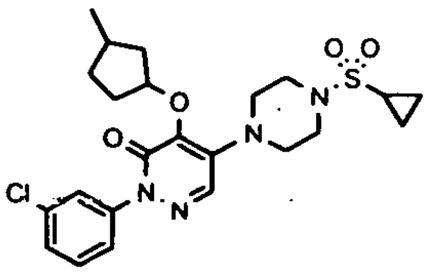
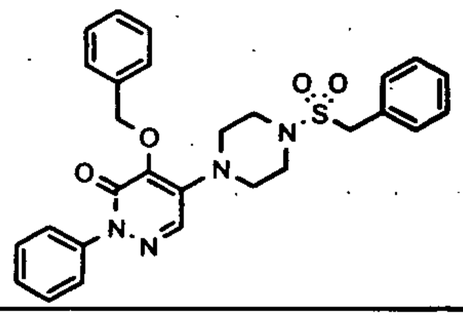
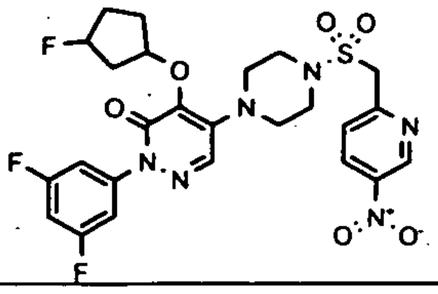
749Z		553
750Z		579
751Z		469
752Z		553
753Z		574
754Z		481
755Z		545
756Z		512

757Z		541
758Z		525
759Z		538
760Z		549
761Z		496
762Z		462
763Z		475
764Z		551
765Z		507
766Z		595
767Z		546
768Z		559
769Z		529
770Z		583
771Z		533
772Z		528

773Z		572
774Z		601
775Z		497
776Z		496
777Z		493
778Z		517
779Z		595
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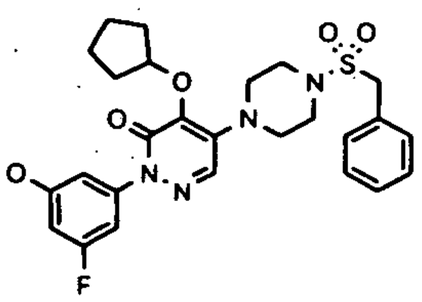
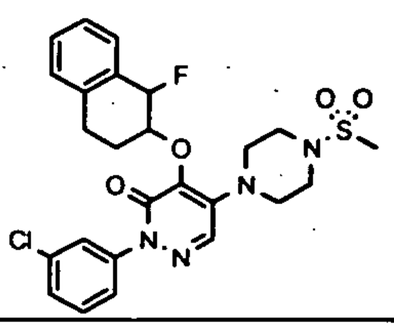
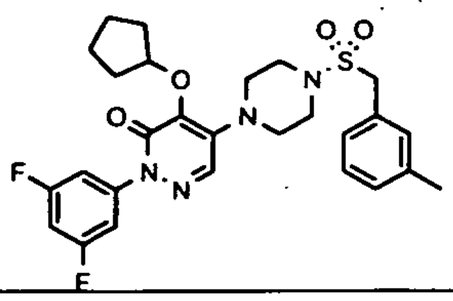
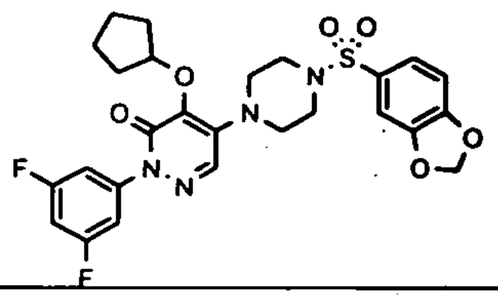
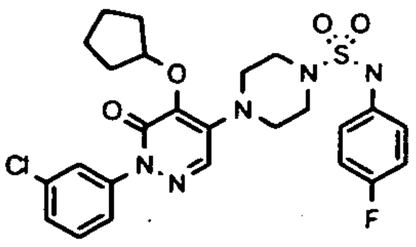
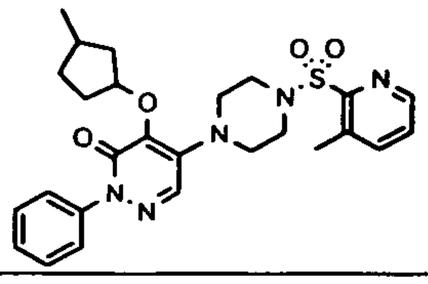
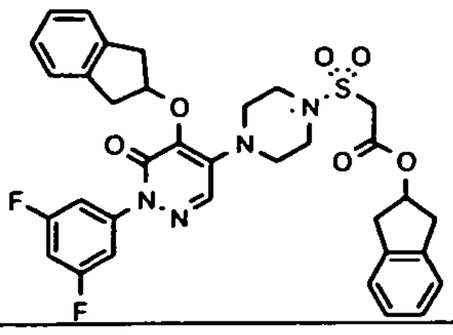
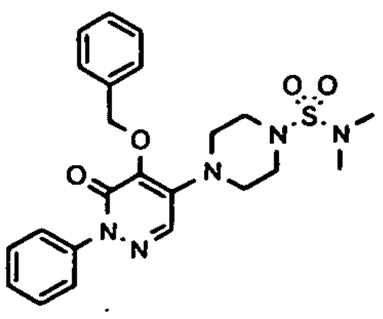
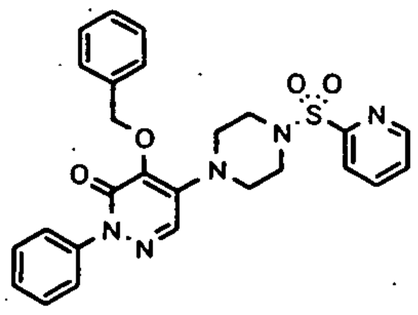
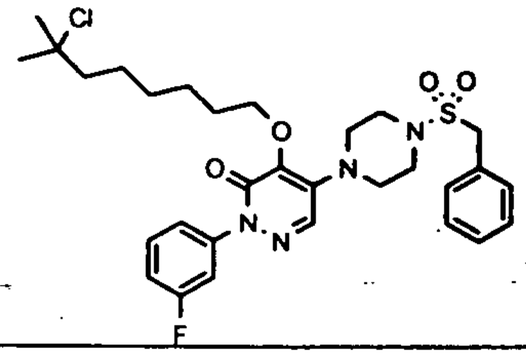
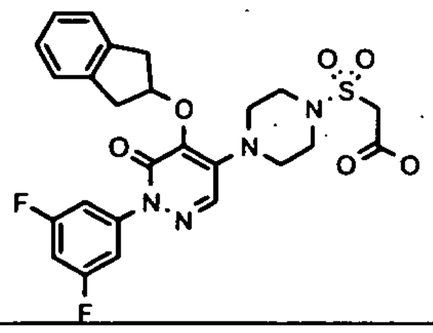
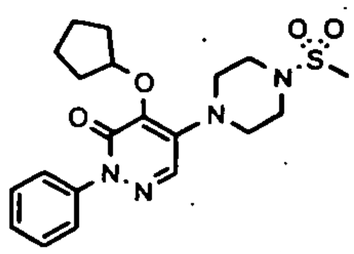
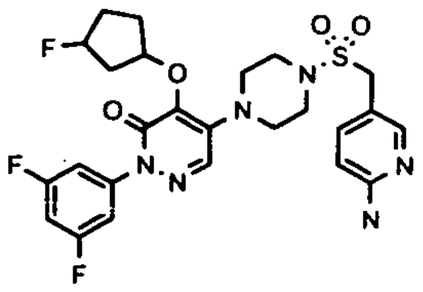
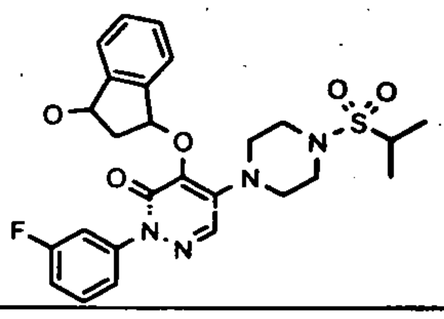
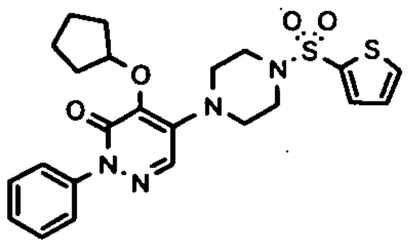
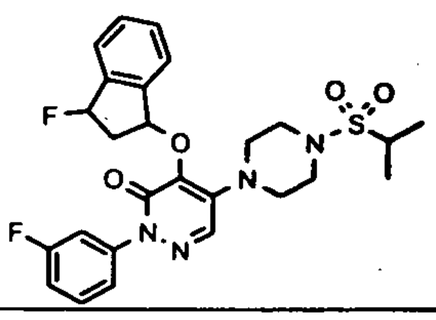
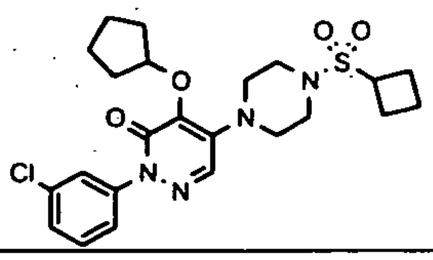
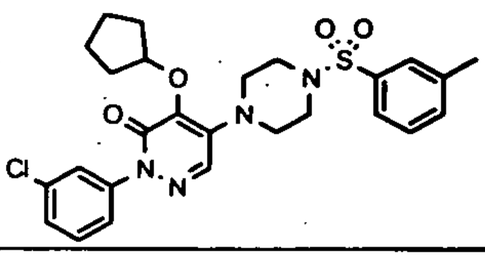
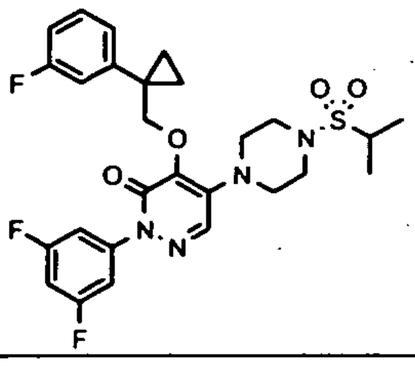
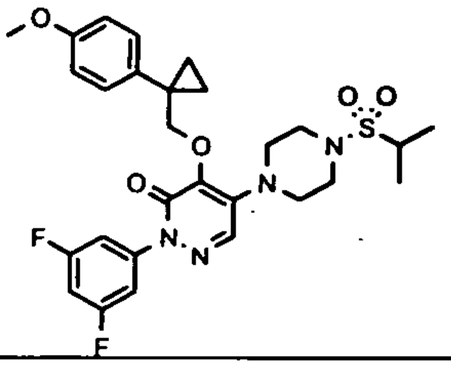
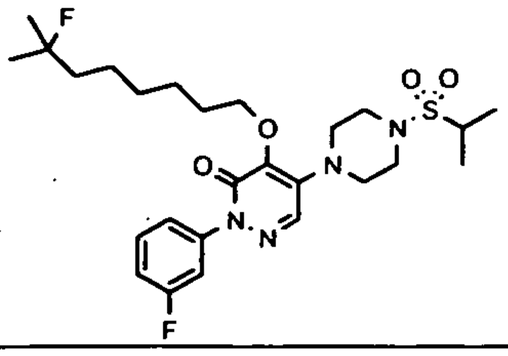
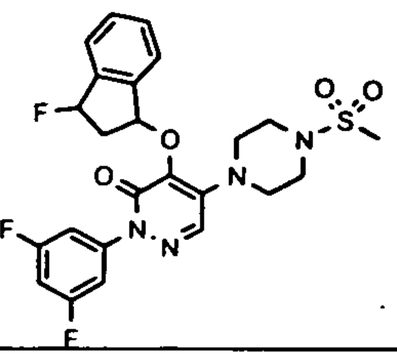
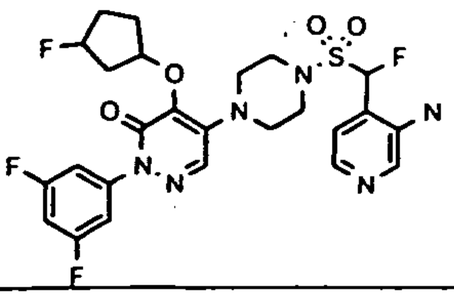
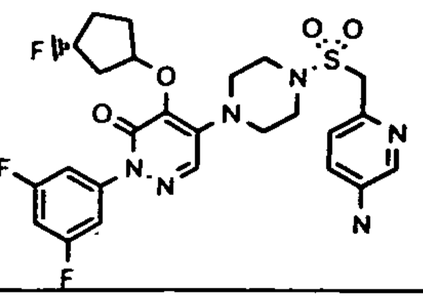
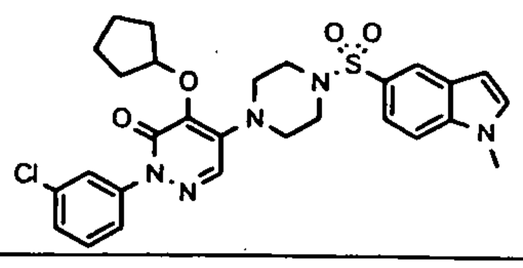
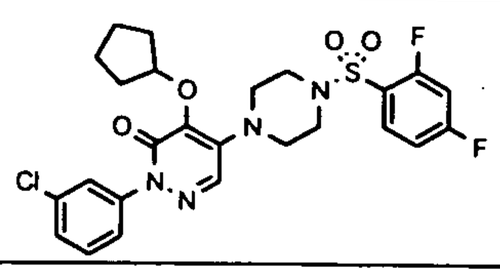
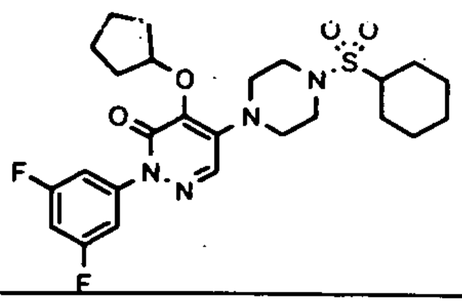
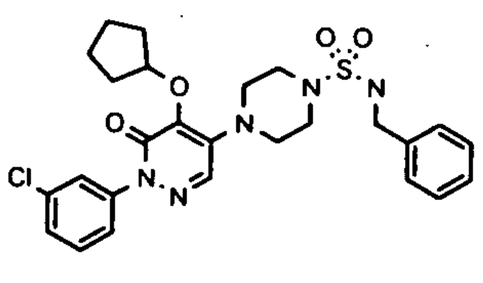
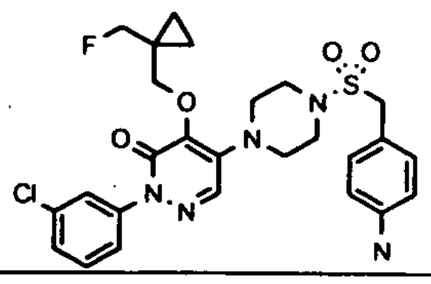
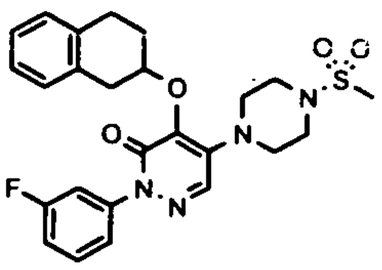
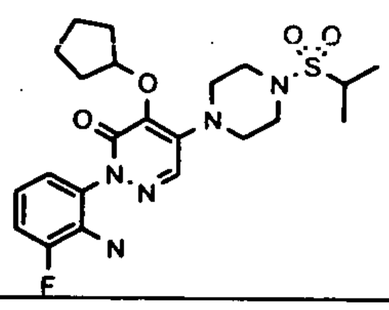
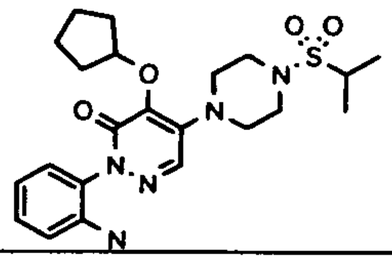
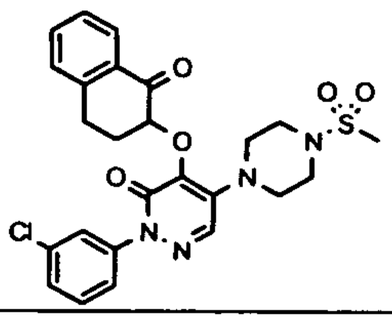
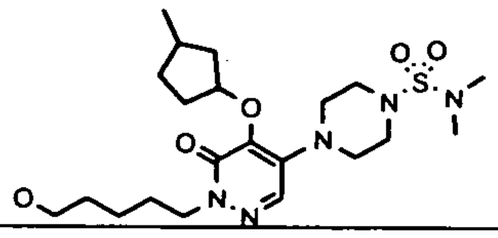
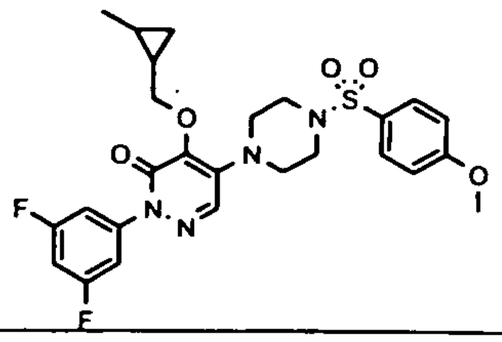
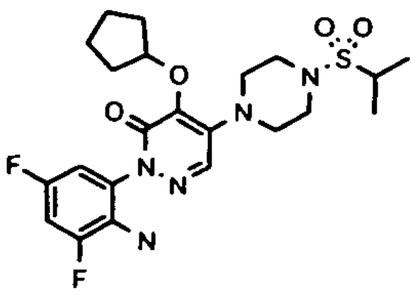
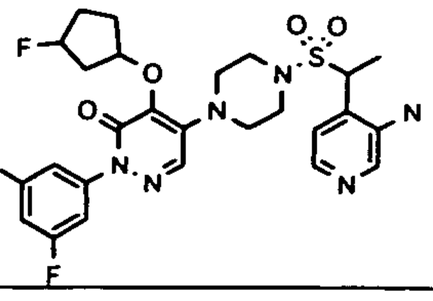
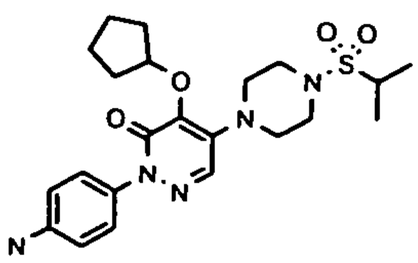
781Z		529
782Z		533
783Z		545
784Z		561
785Z		548
786Z		510
787Z		663
788Z		470

789Z		504	790Z		605
791Z		547	792Z		419
793Z		565	794Z		529
795Z		487	796Z		531
797Z		493	798Z		529
799Z		563	800Z		575
801Z		541	802Z		521
803Z		583	804Z		565

805Z		568	806Z		551
807Z		523	808Z		544
809Z		562	810Z	no compound	
811Z		499	812Z		480
813Z		462	814Z	no compound	
815Z		529	816Z	no compound	
817Z		472	818Z	no compound	
819Z		547	820Z		498
821Z		579	822Z		462

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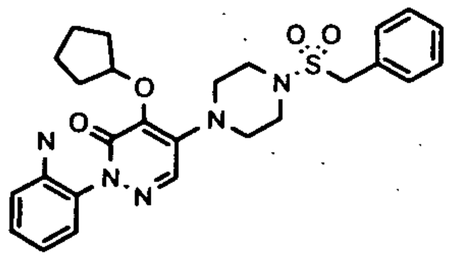
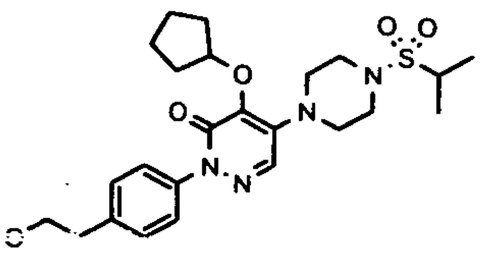
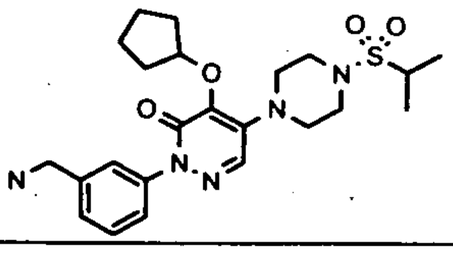
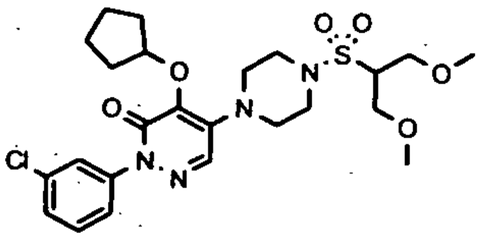
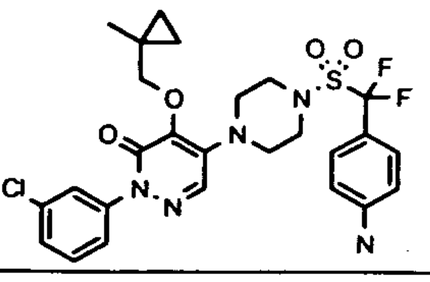
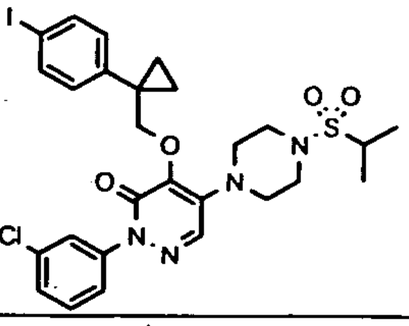
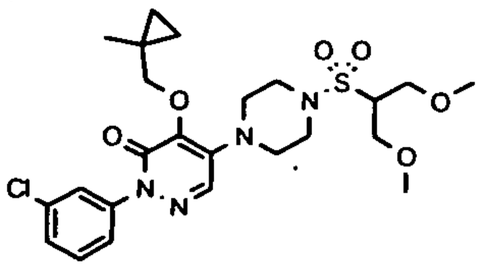
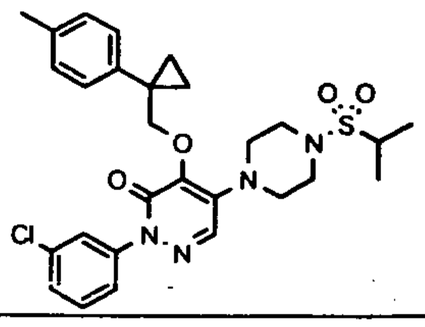
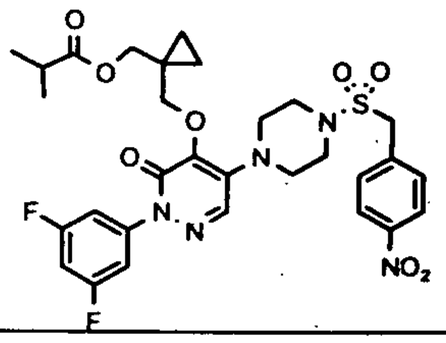
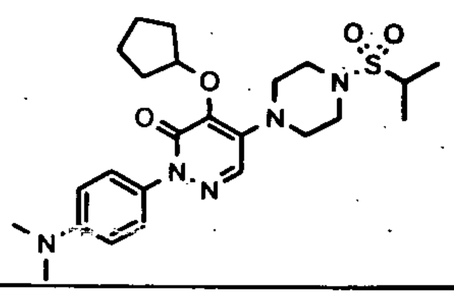
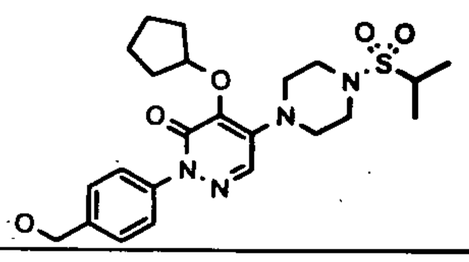
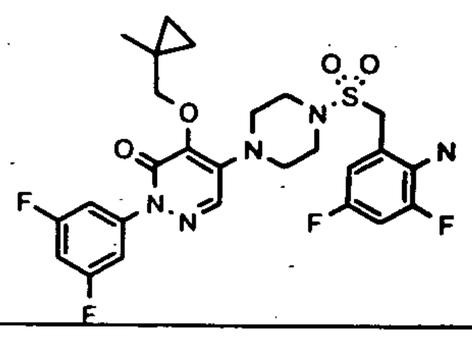
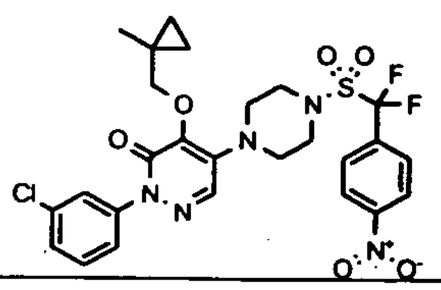
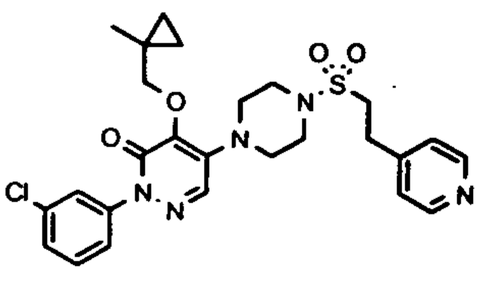
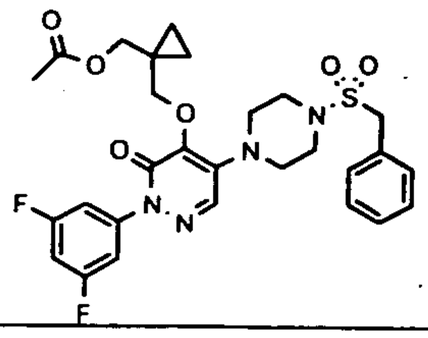
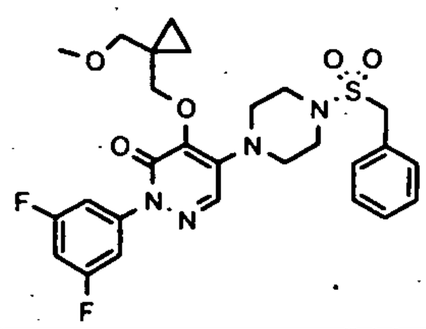
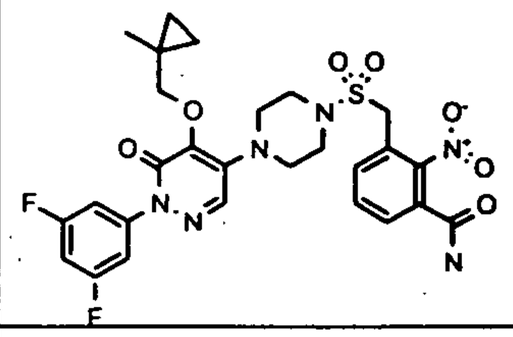
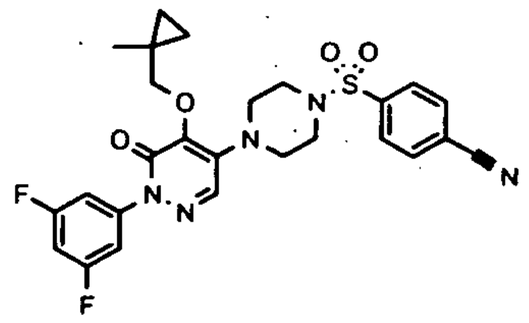
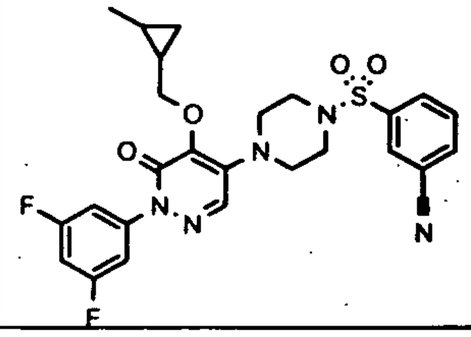
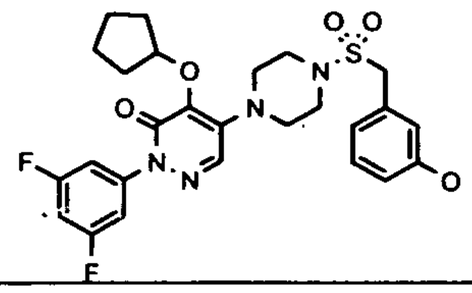
825Z		510
827Z		491
829Z		476
831Z		541
833Z		580
835Z		669
837Z		541

824Z		558
826Z		662
828Z		490
830Z		477
832Z		582
834Z		610
836Z		544
838Z		589

839Z		561
840Z		619
841Z		542
842Z		542
843Z		547
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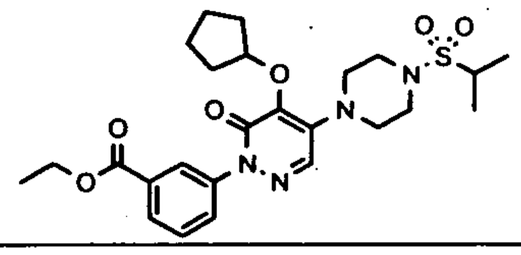
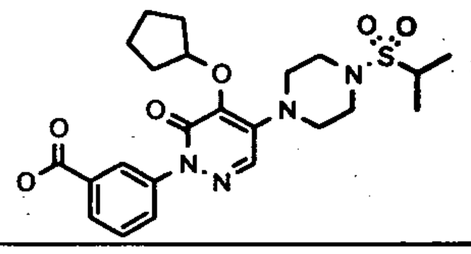
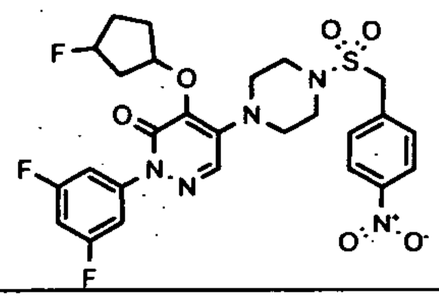
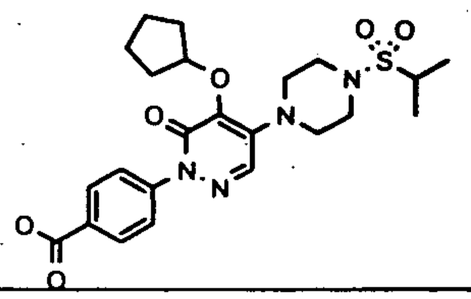
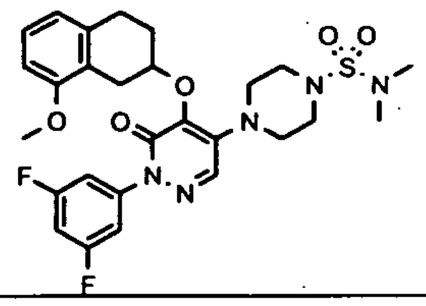
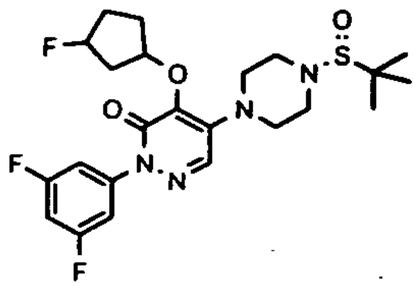
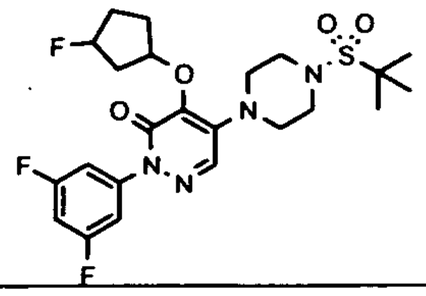
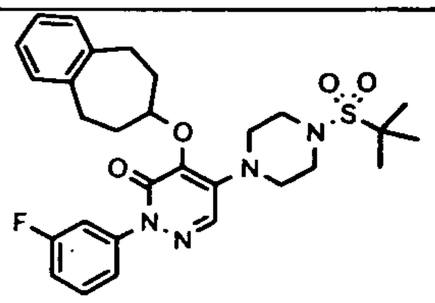
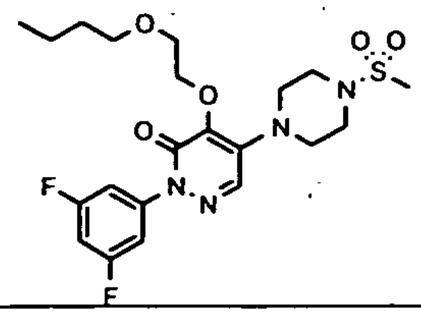
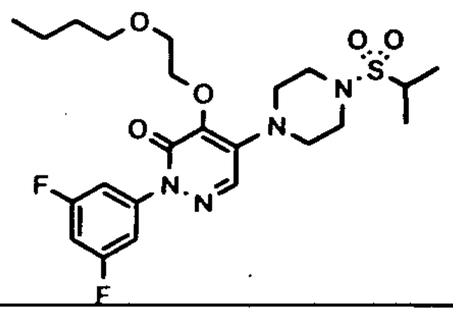
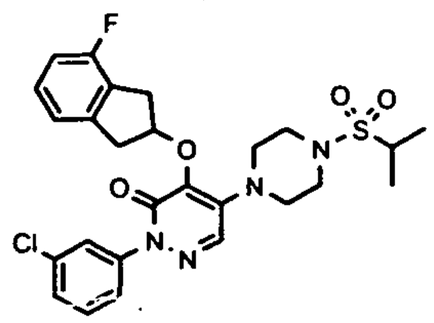
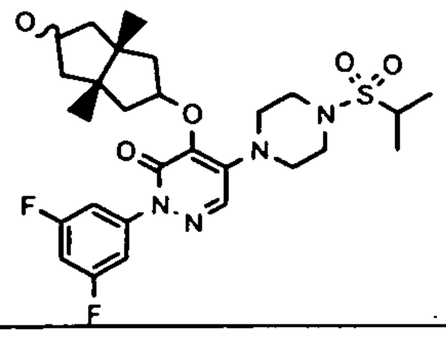
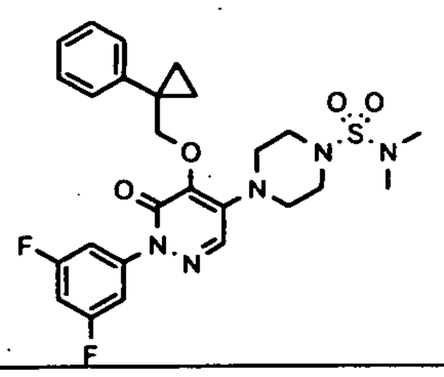
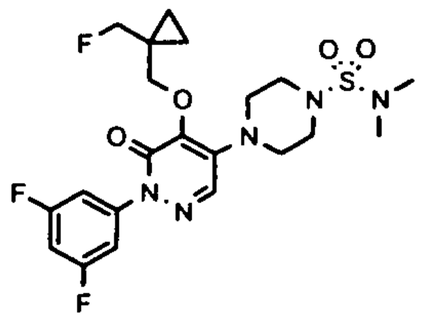
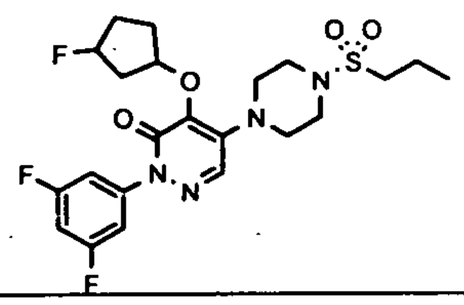
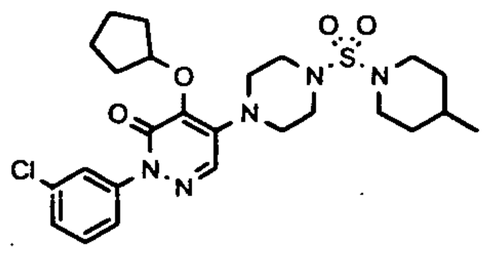
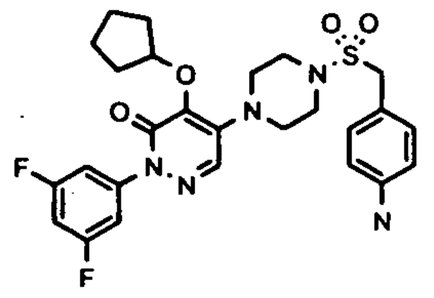
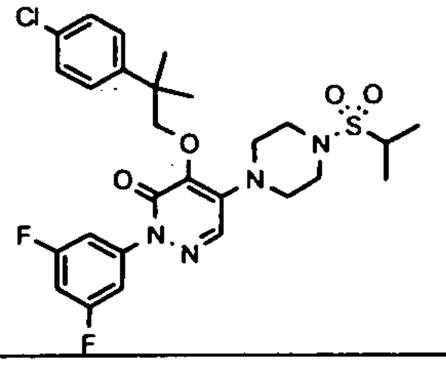
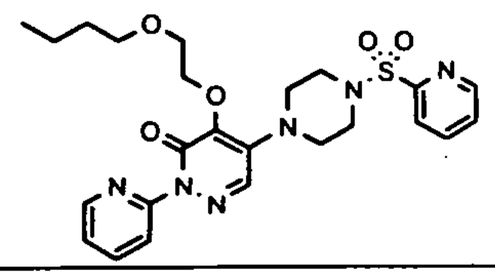
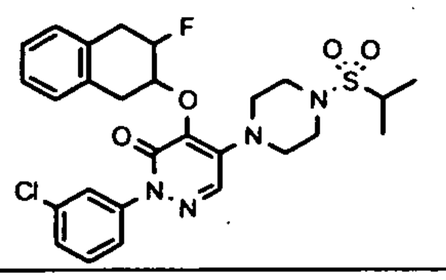
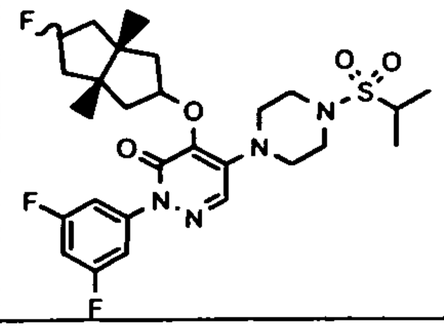
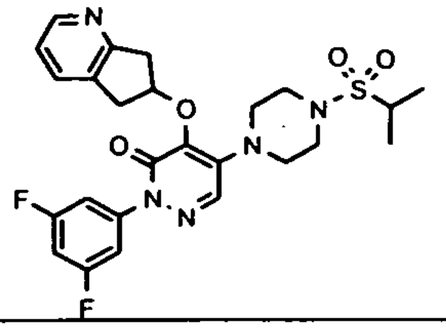
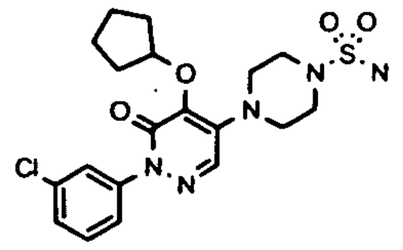
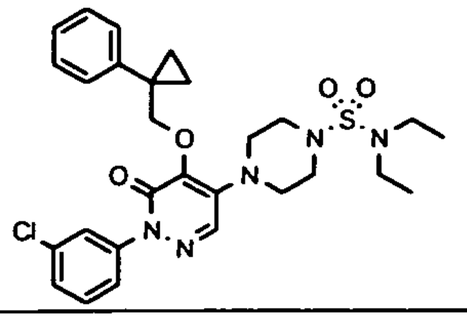
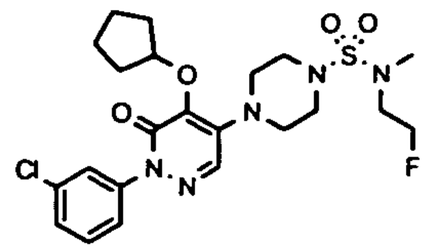
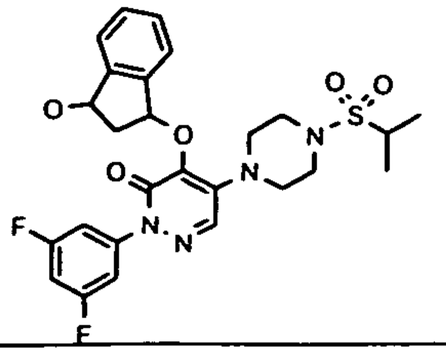
845Z		519
846Z		491
847Z		594
848Z		491
849Z		576
850Z		499
851Z		515
852		555
853Z		487
854Z		515

855Z		547
856Z		567
857Z		546
858Z		502
859Z		501
860Z		537
861Z		546
862Z		581
863Z		515
864Z		561
865Z		569
866Z		532
867Z		454
868Z		572
869Z		514
870Z		529

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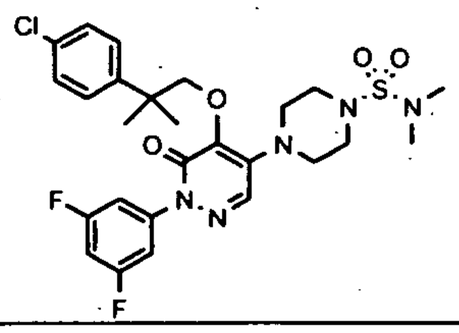
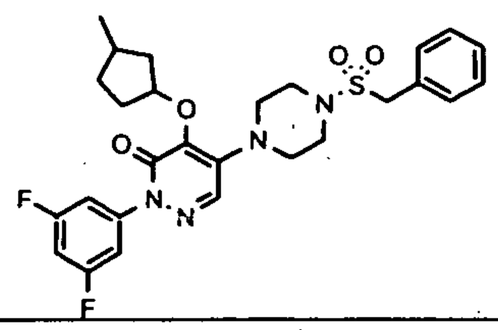
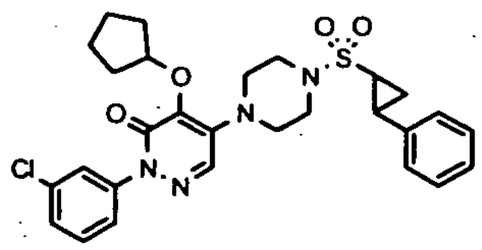
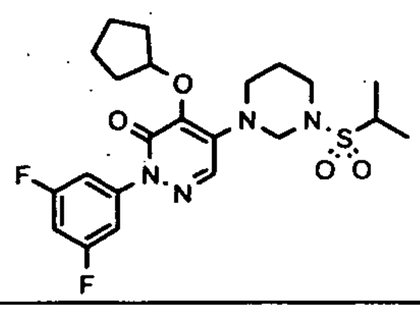
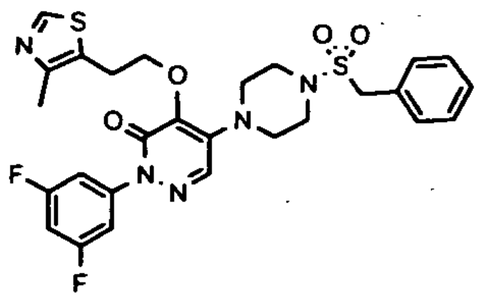
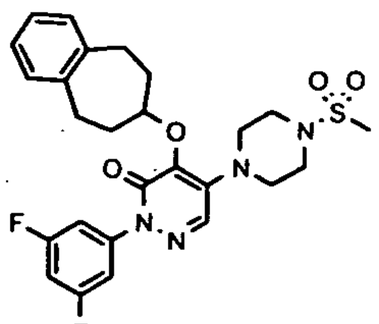
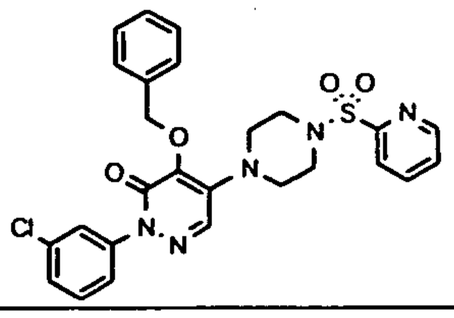
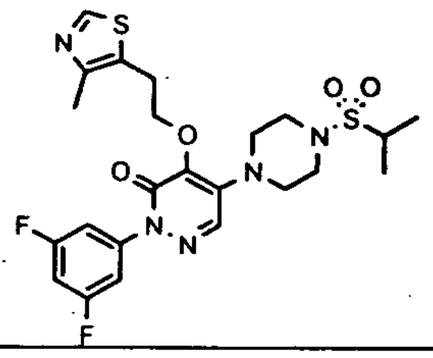
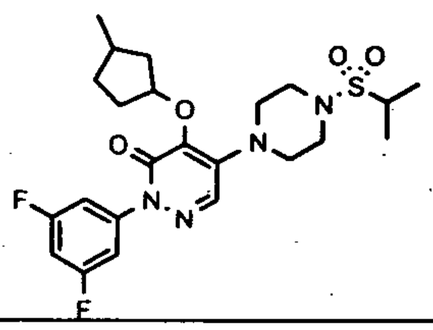
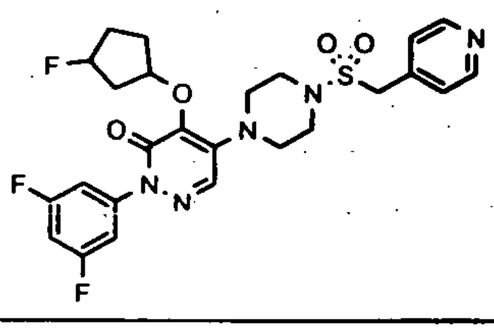
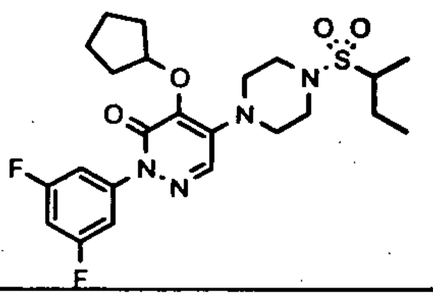
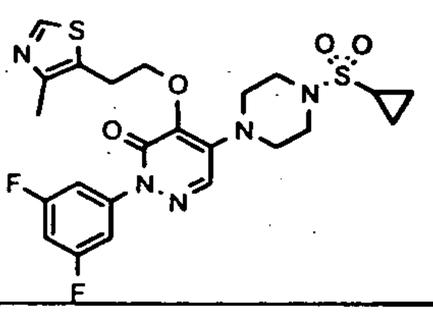
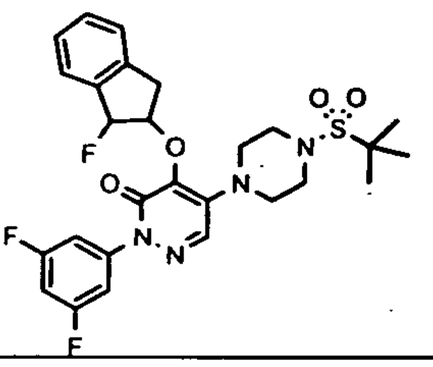
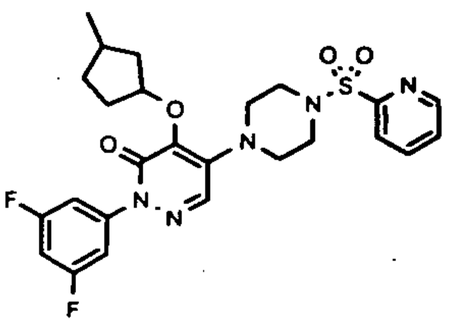
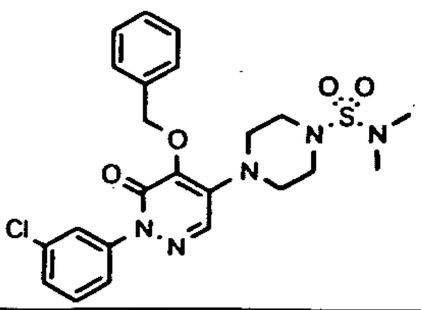
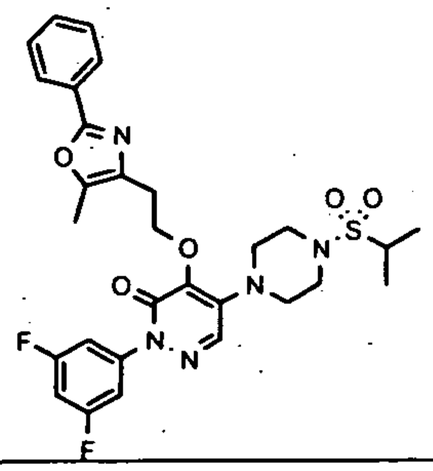
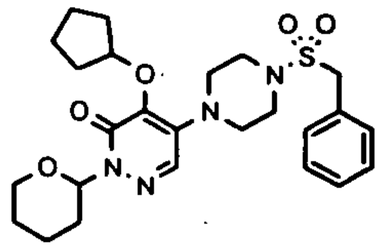
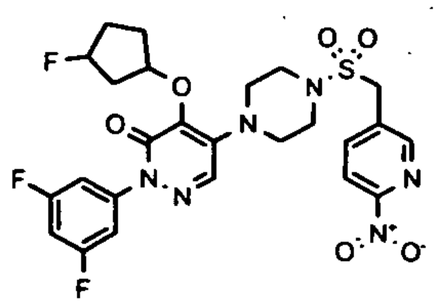
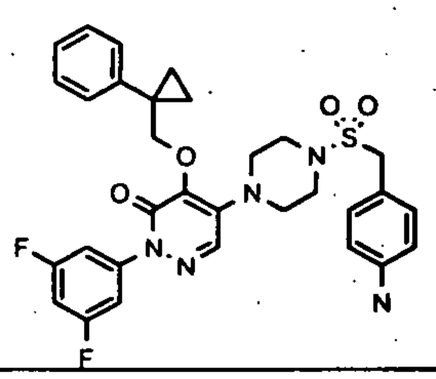
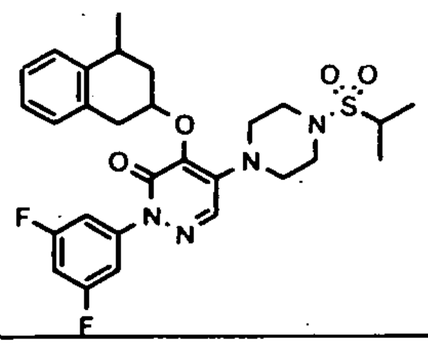
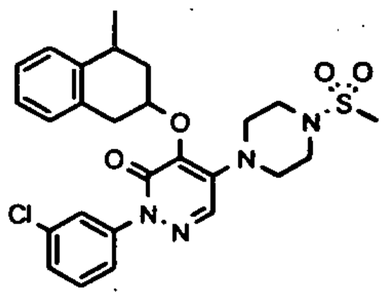
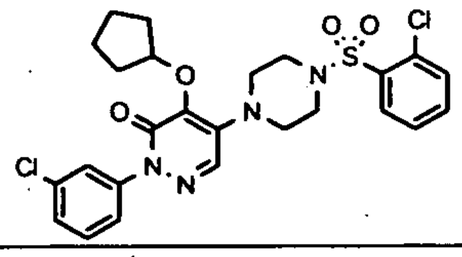
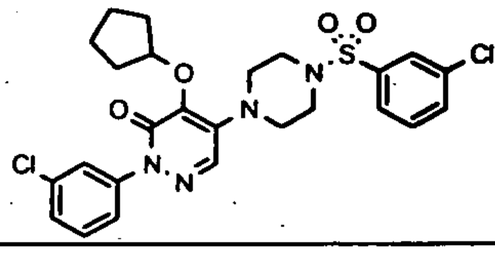
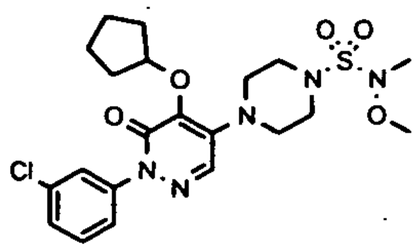
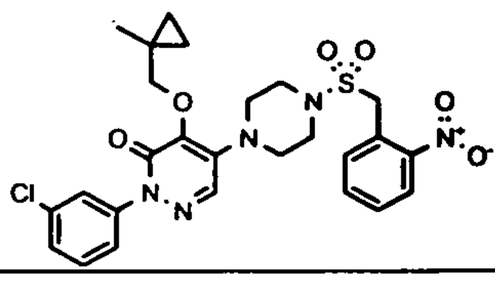
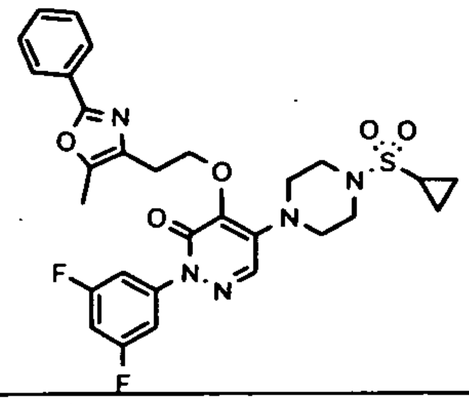
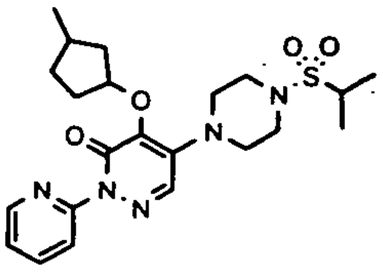
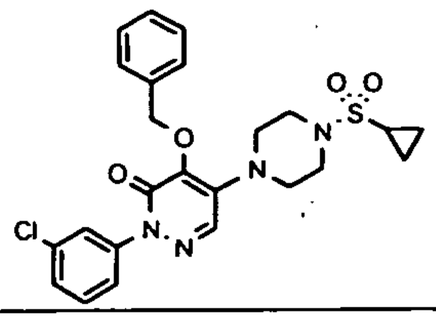
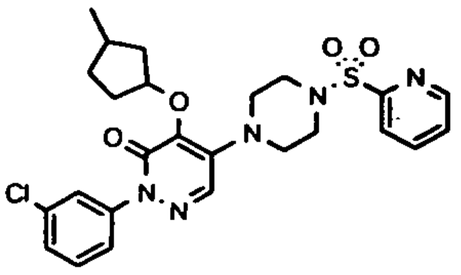
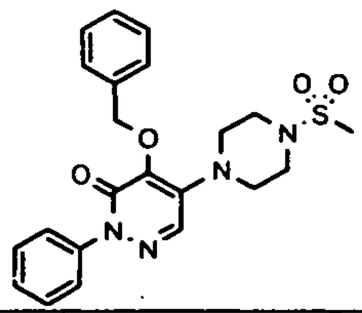
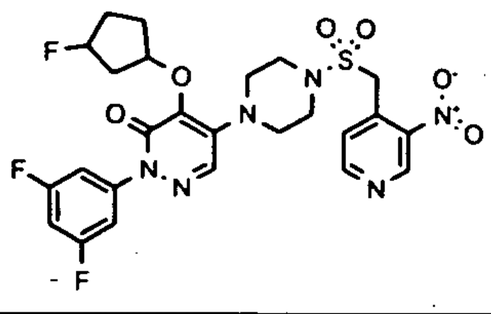
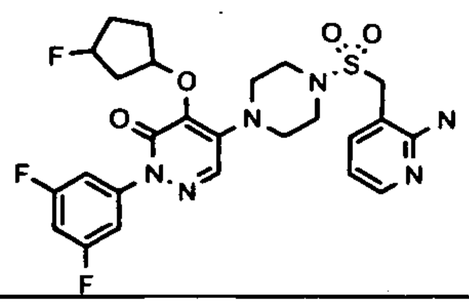
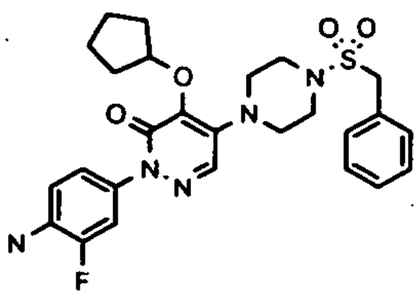
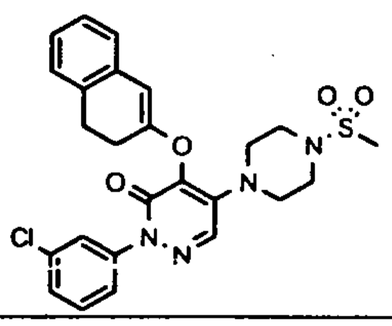
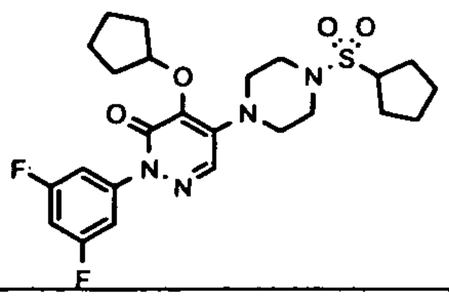
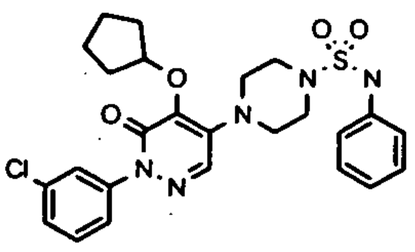
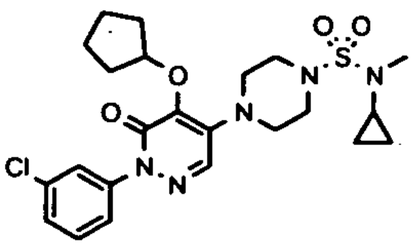
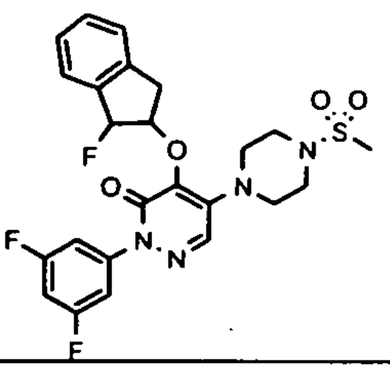
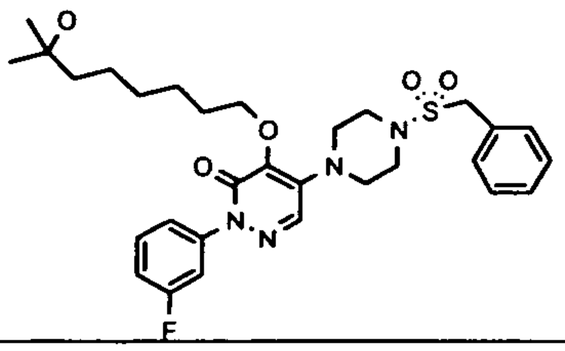
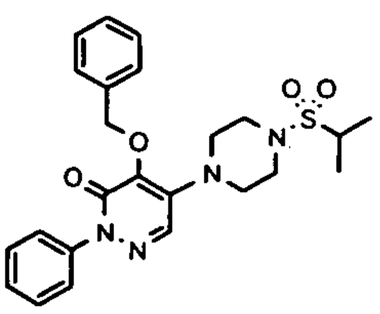
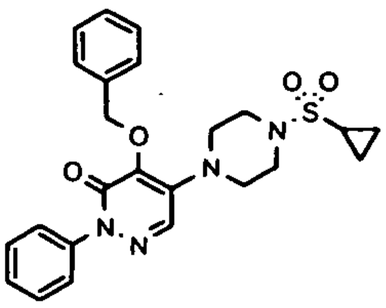
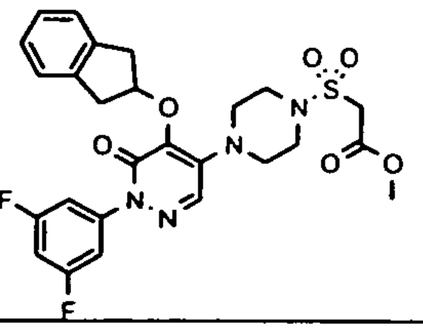
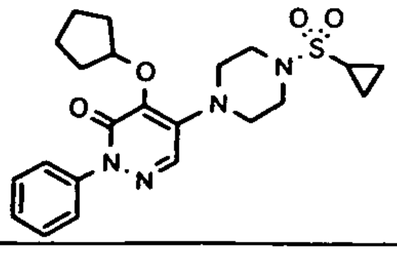
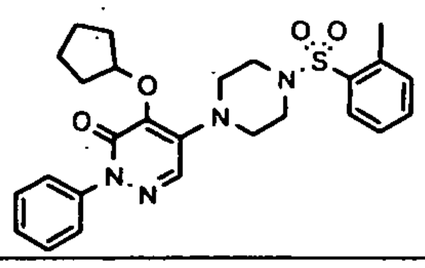
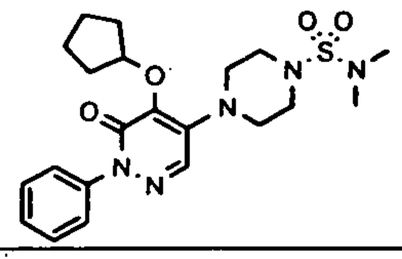
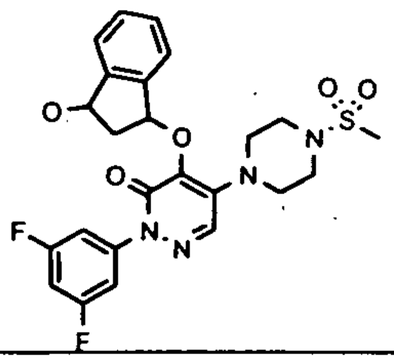
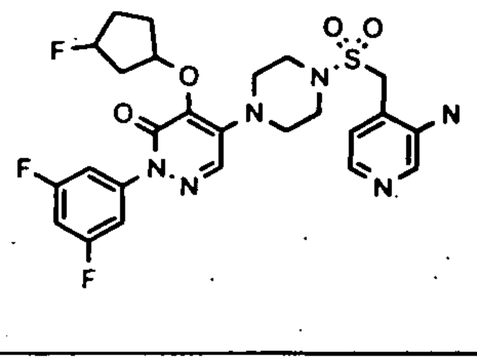
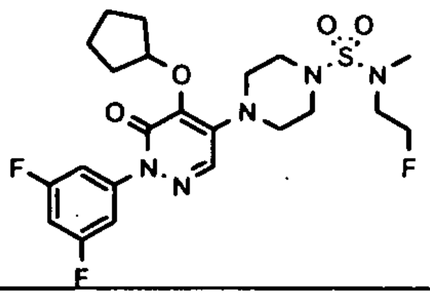
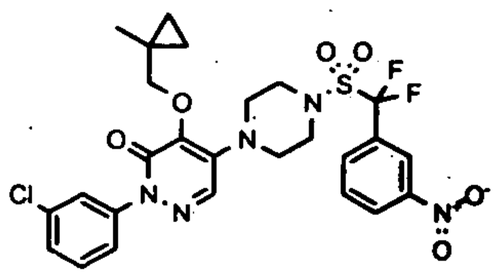
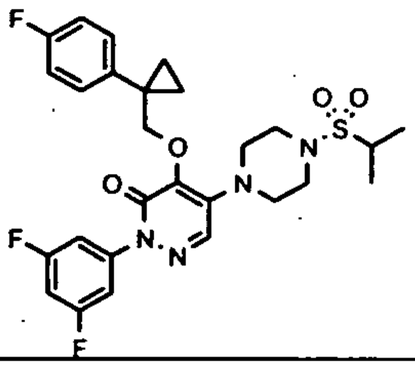
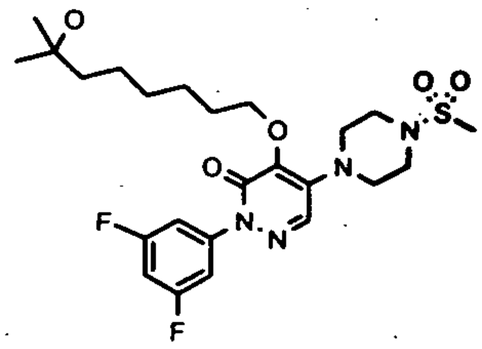
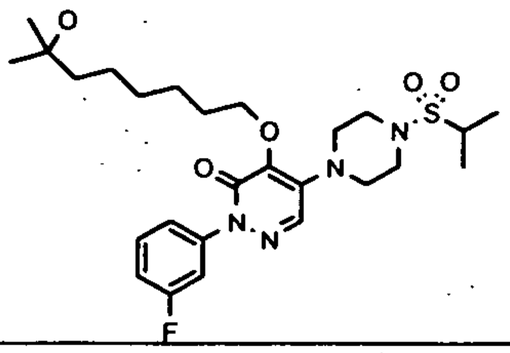
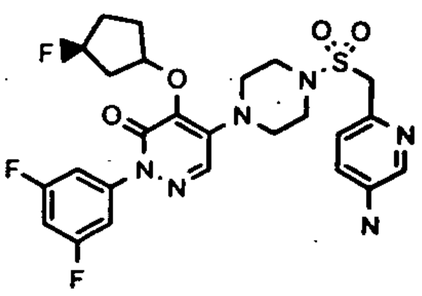
872Z		582
874Z		545
876Z		555
878Z		483
880Z		588
882Z		531
884Z		538
871Z		540
873Z		497
875Z		550
877Z		497
879Z		538
881Z		542
883Z		532
885Z		504

886Z		600
887Z		503
888Z		595
889Z		608
890Z		559
891Z		529
892Z		549
893Z		549
894Z		498
895Z		574
896Z		598
897Z		462
898Z		501
899Z		530

900Z		441	901Z		595
902Z		565	903Z	no compound	
904Z		528	905Z		513
906Z		509	907Z		530
908Z		508	909Z		501
910Z		(M-98) = 489	911Z		469
912Z		467	913Z		561
914Z	no compound		915Z		445

916Z		495	917Z		448
918Z		519	919Z		565
920Z		516	921Z		610
922Z		563	923Z		529
924Z		539	925Z		565
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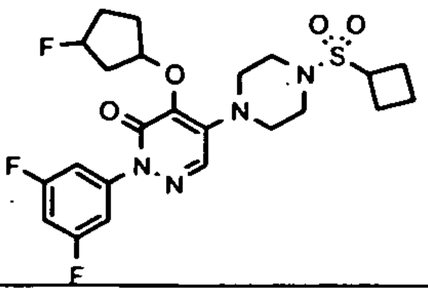
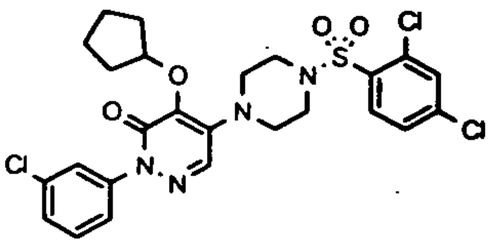
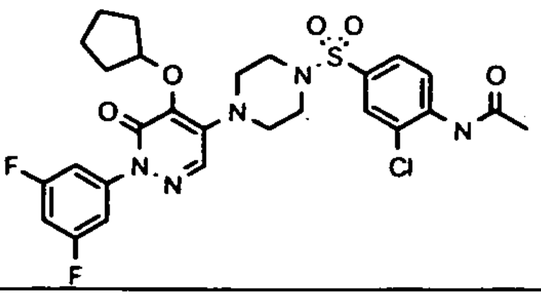
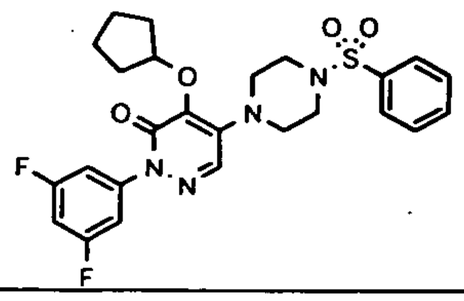
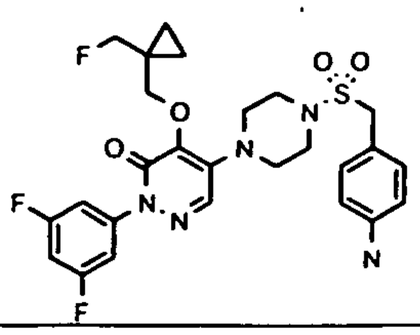
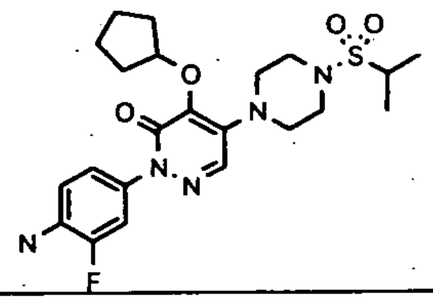
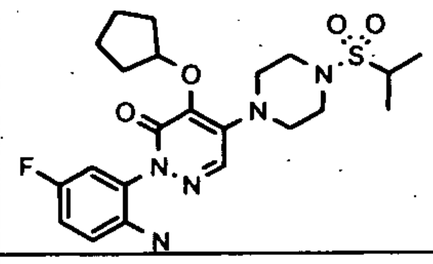
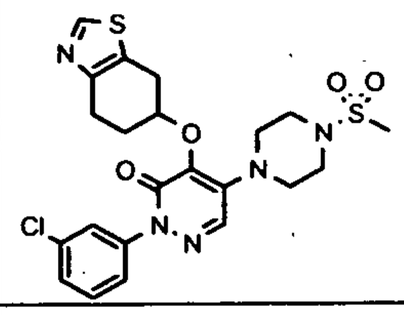
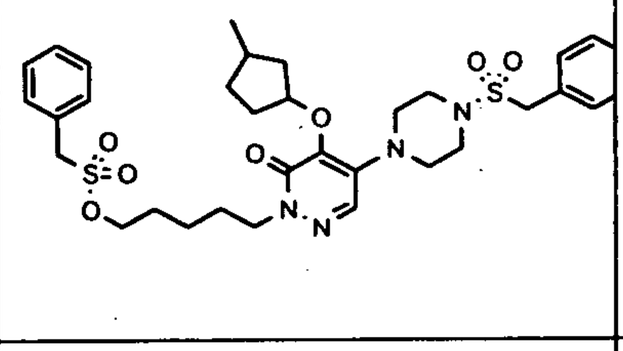
928Z		513	929Z		583
930Z		606	931Z		517
932Z		564	933Z	no compound	

934Z		480
936Z		480
938Z		522
940Z		673
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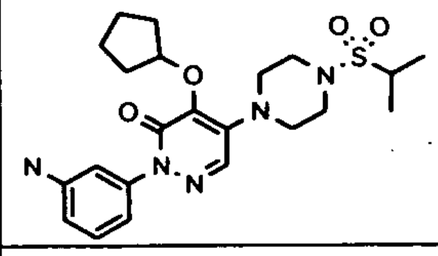
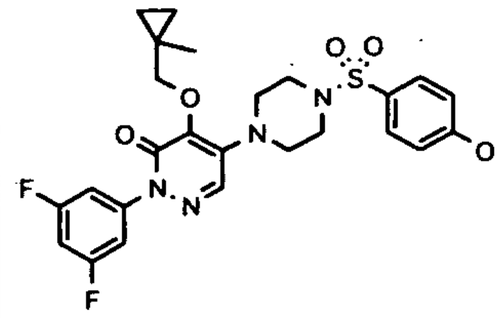
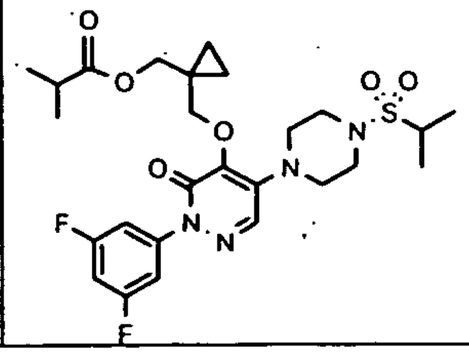
944Z		462
946Z		533
948Z		569
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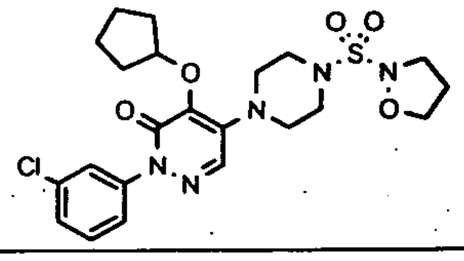
937Z		510
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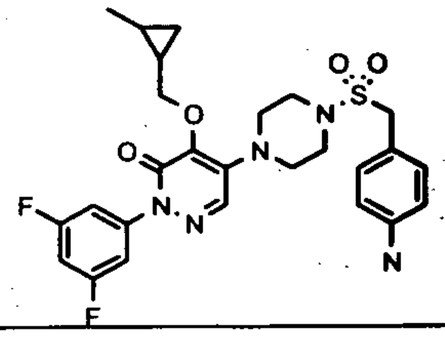
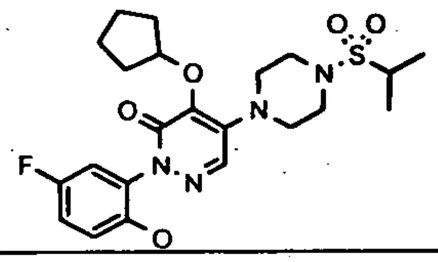
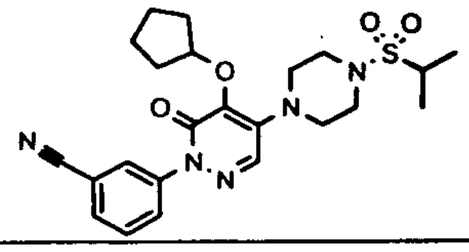
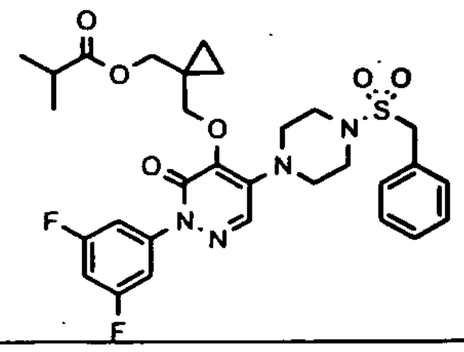
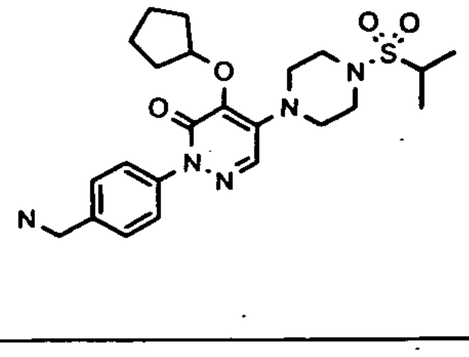
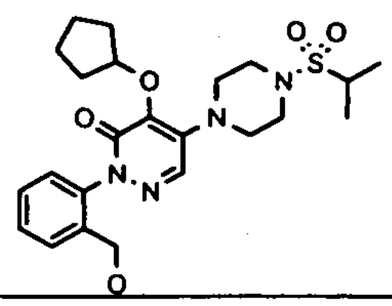
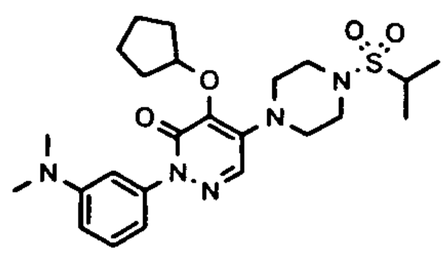
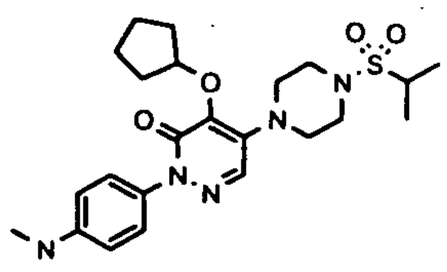
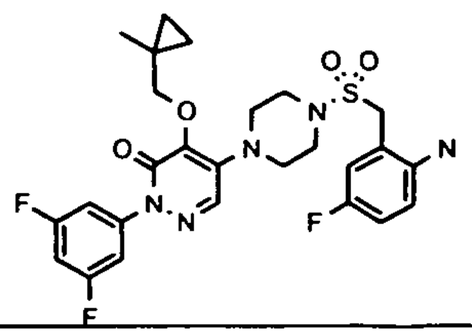
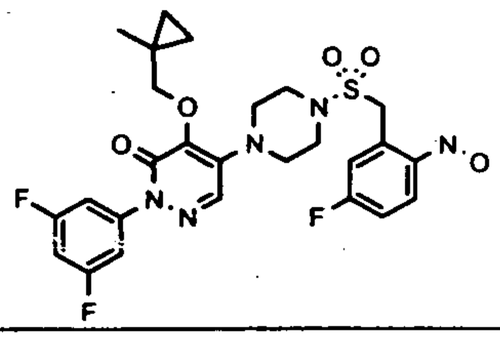
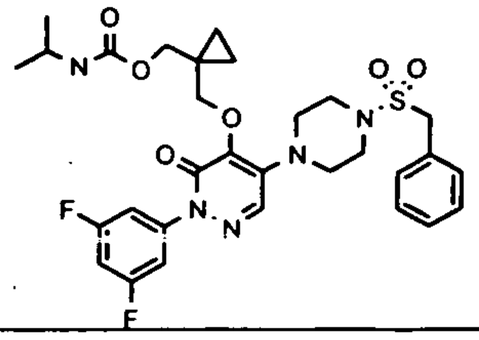
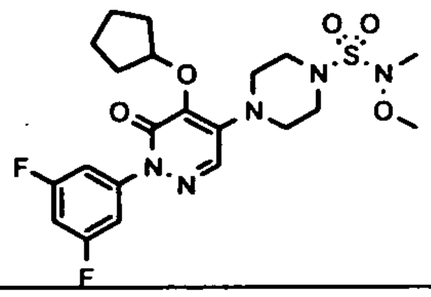
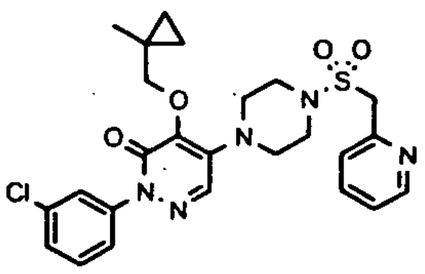
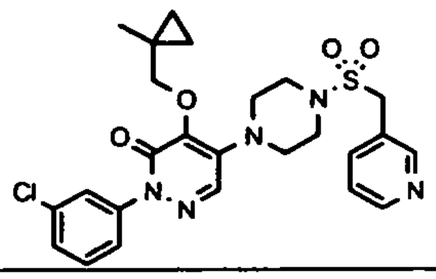
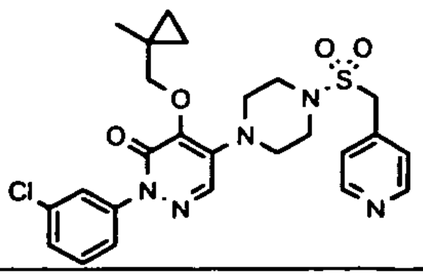
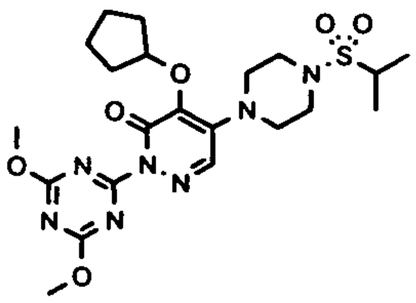
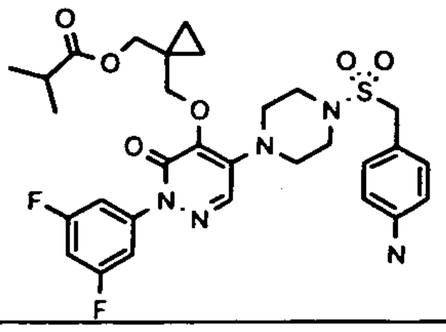
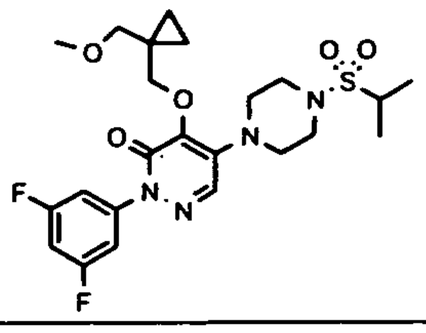
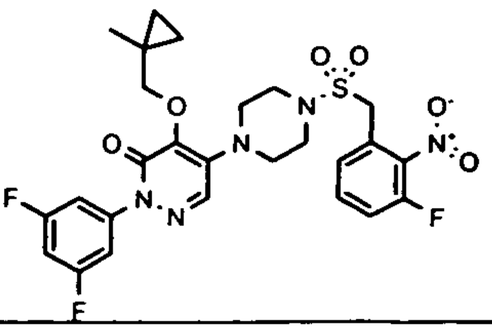
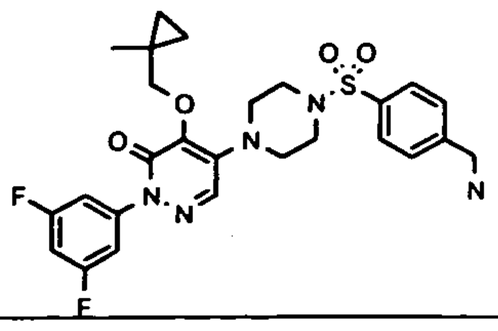
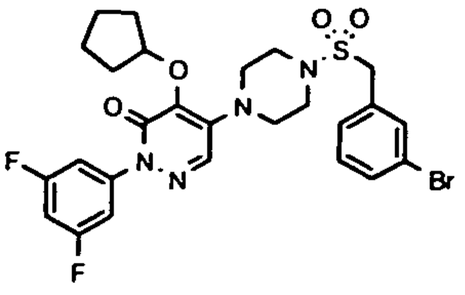
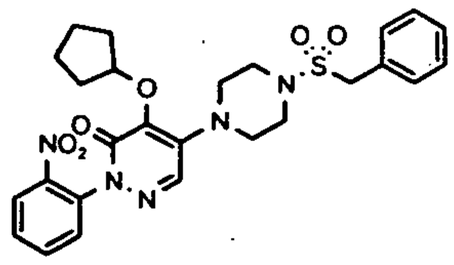
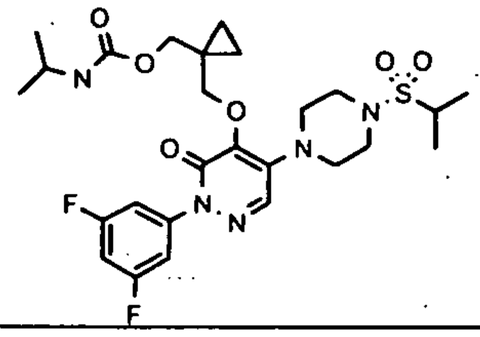
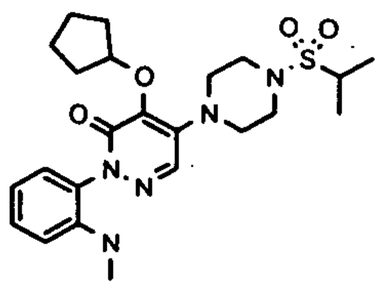
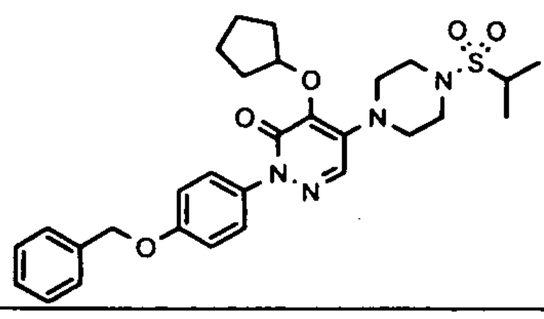
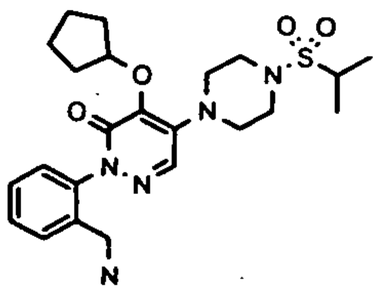
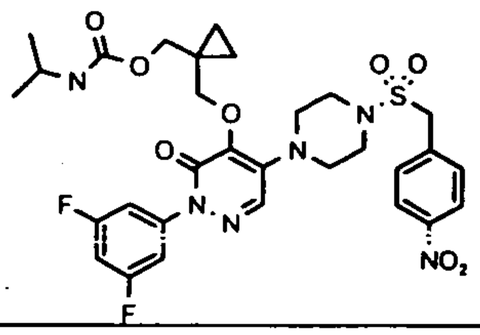
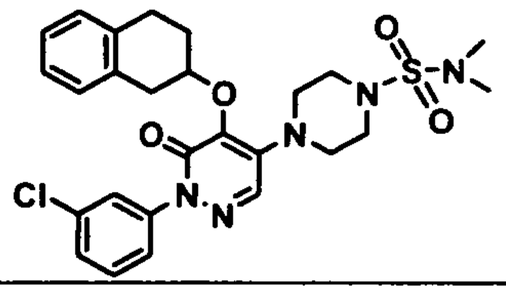
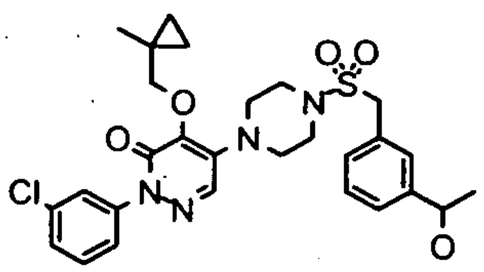
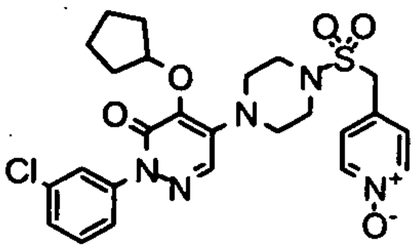
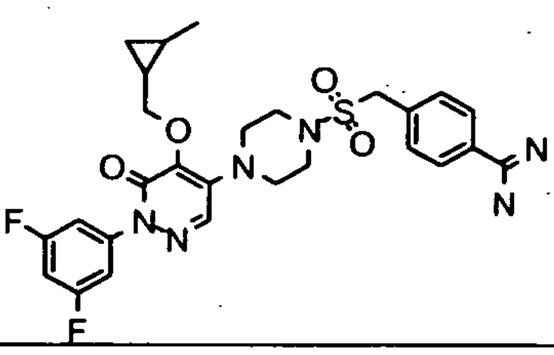
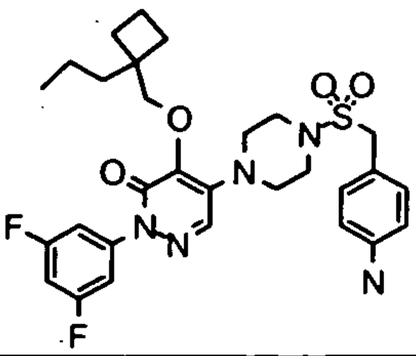
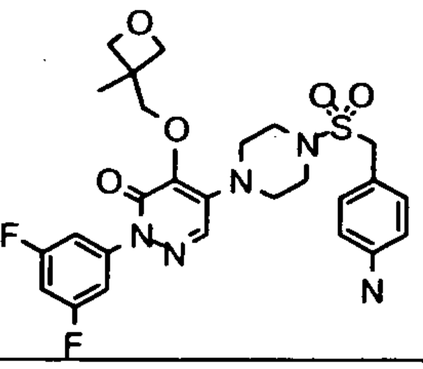
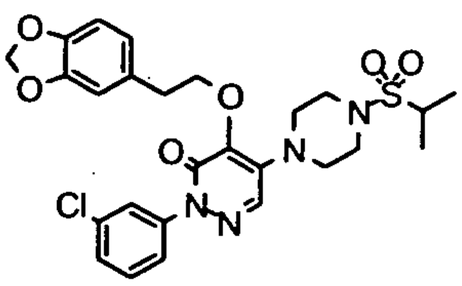
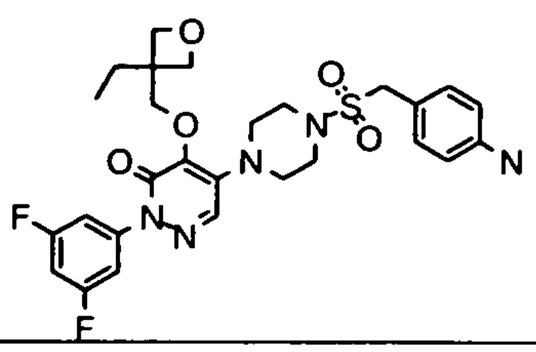
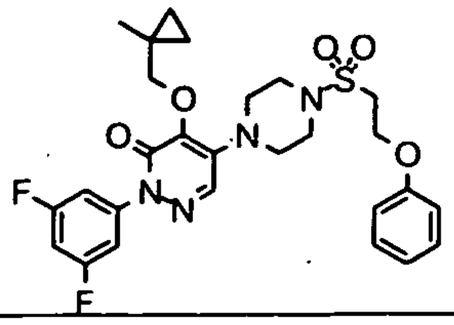
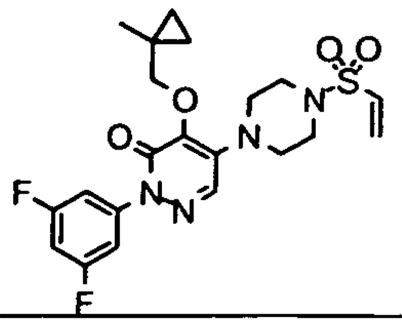
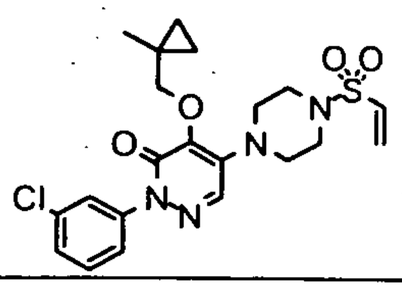
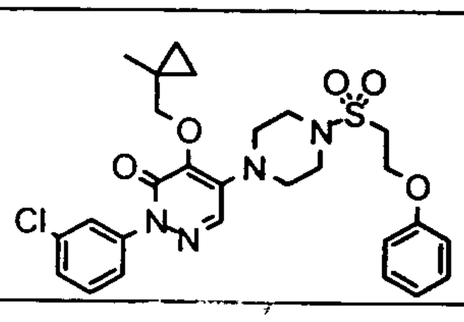
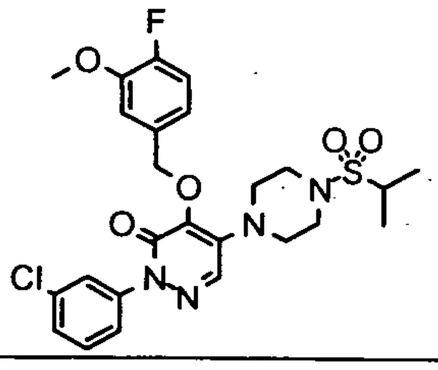
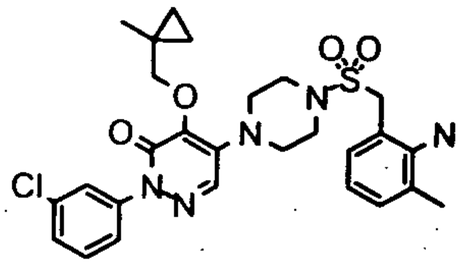
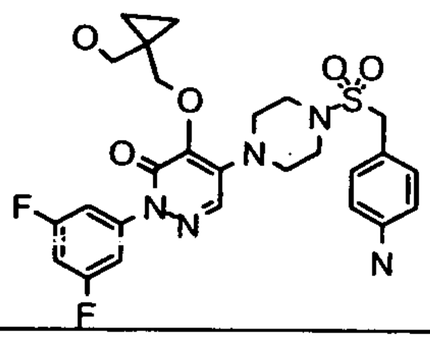
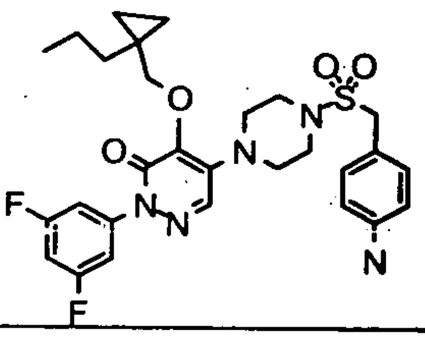
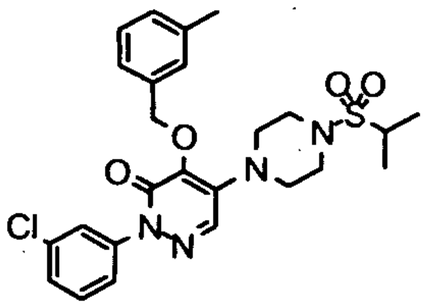
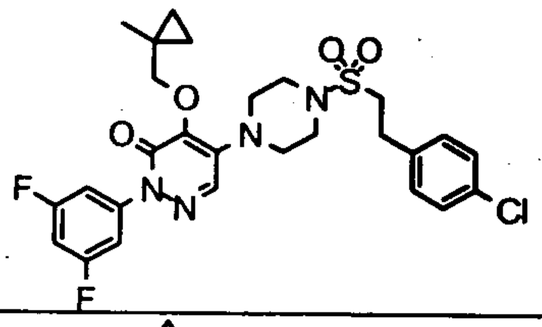
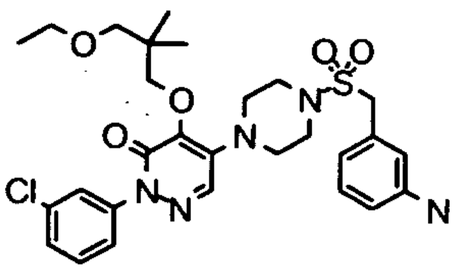
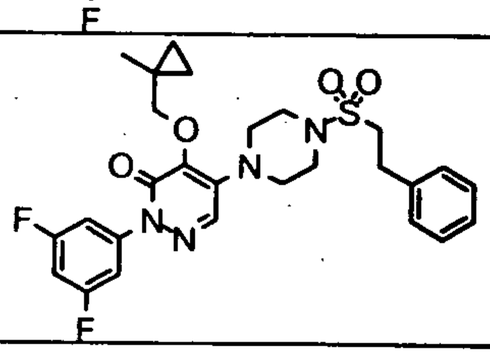
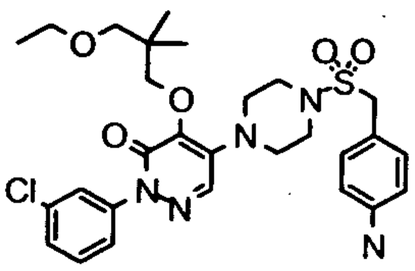
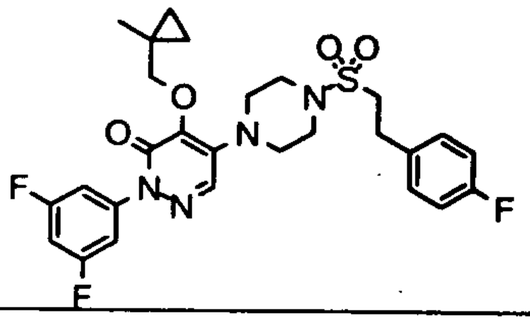
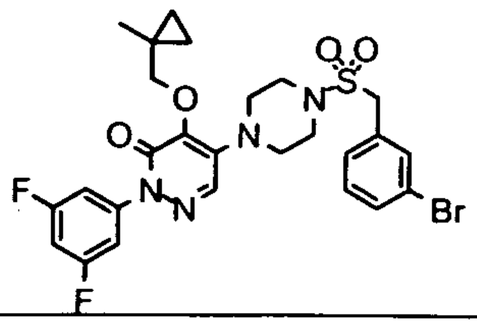
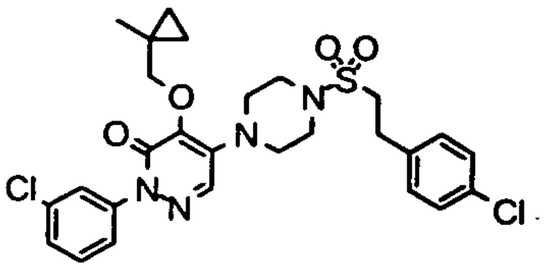
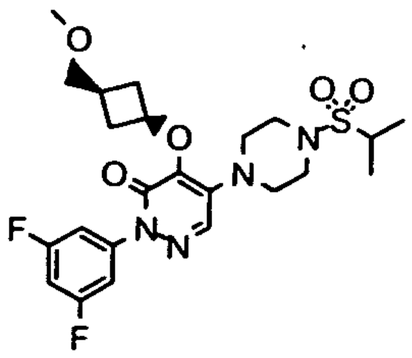
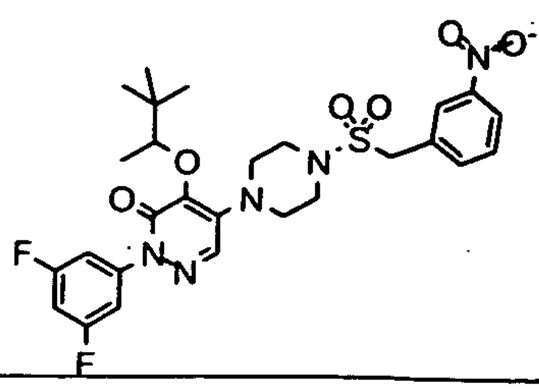
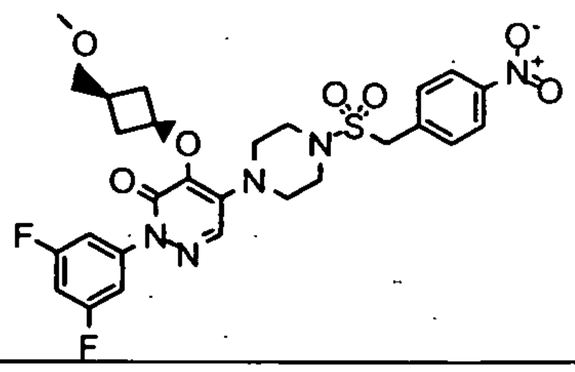
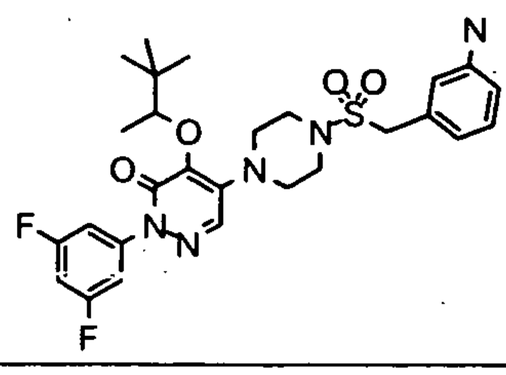
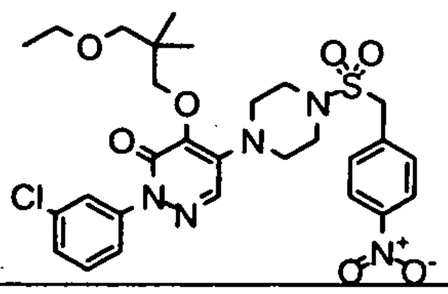
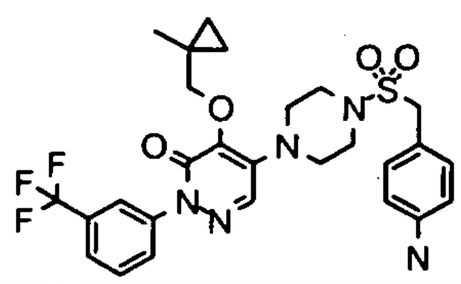
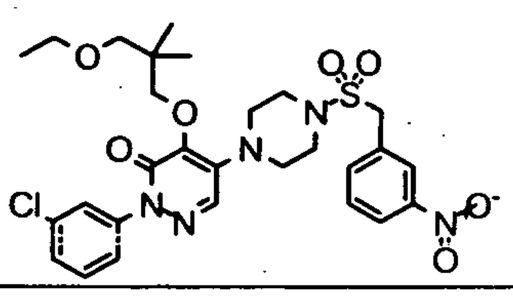
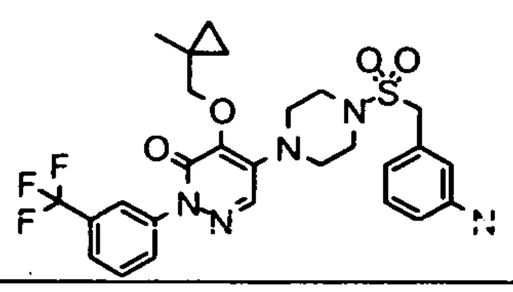
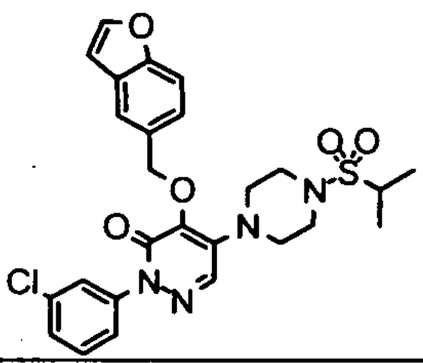
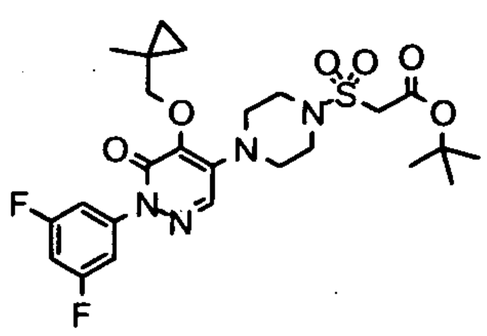
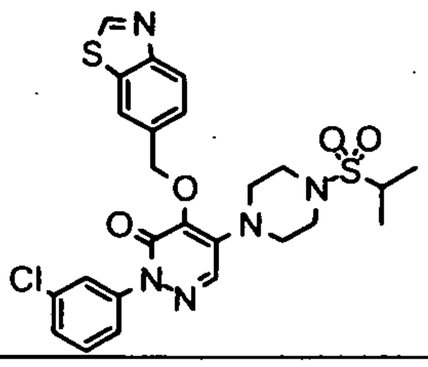
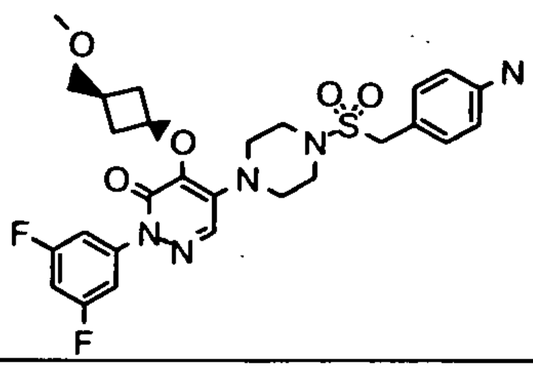
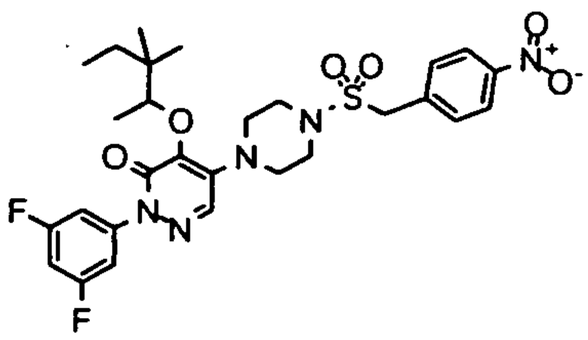
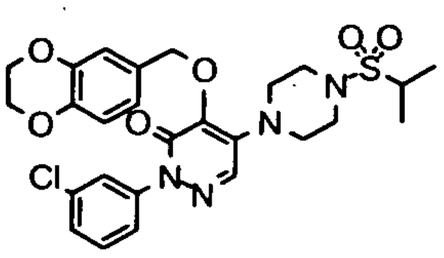
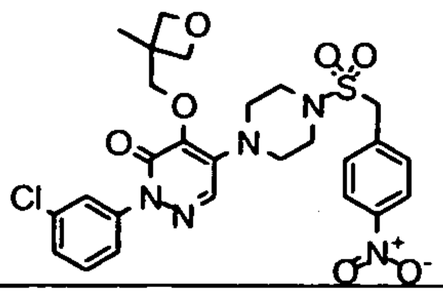
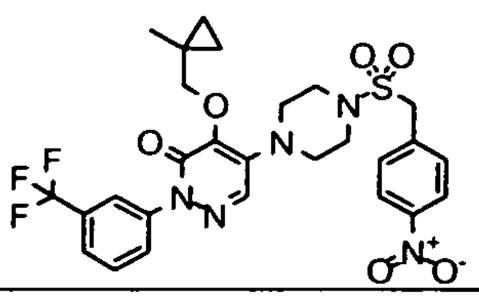
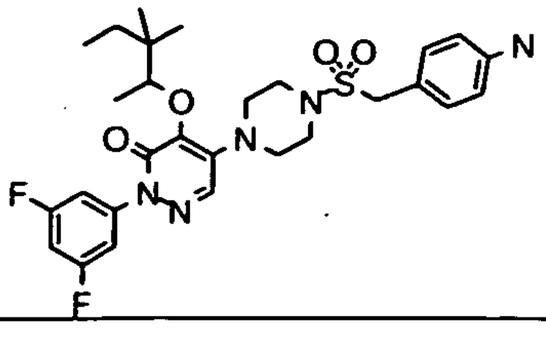
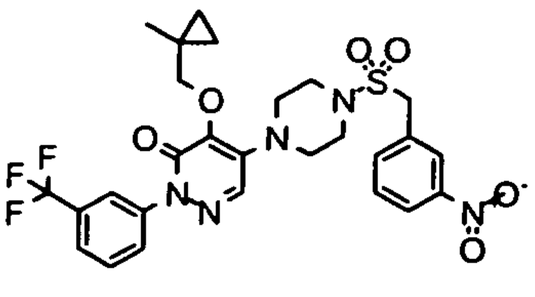
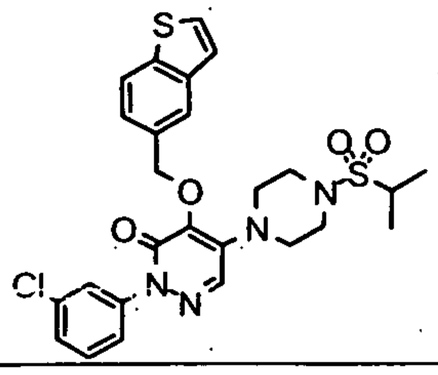
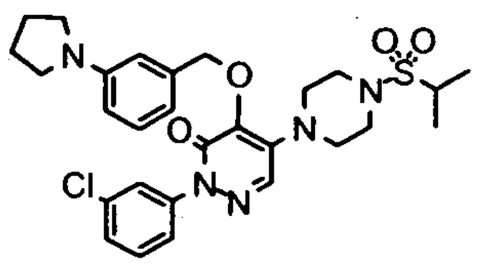
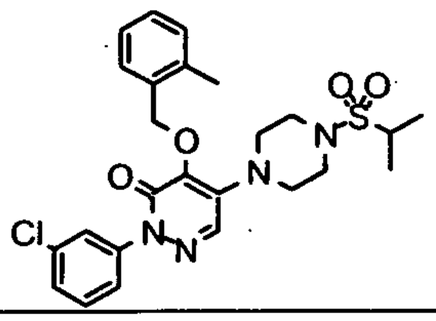
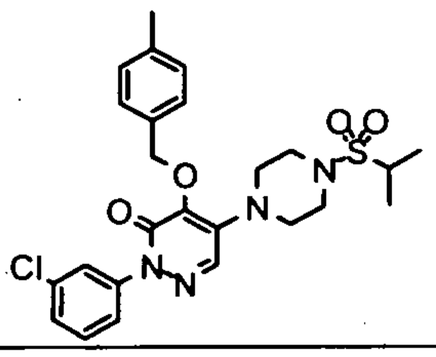
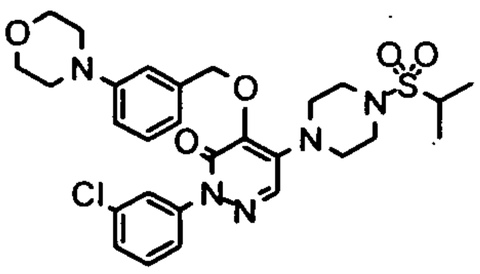
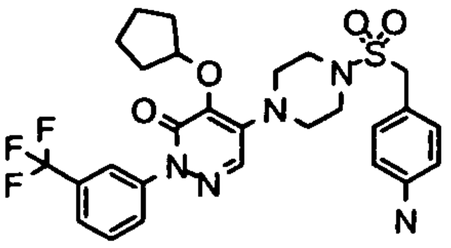
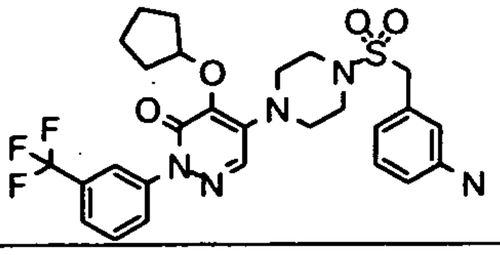
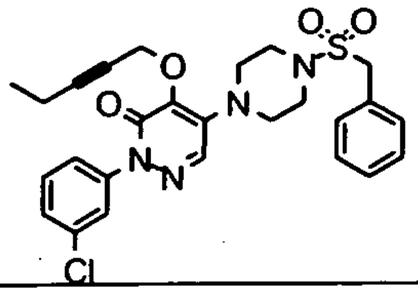
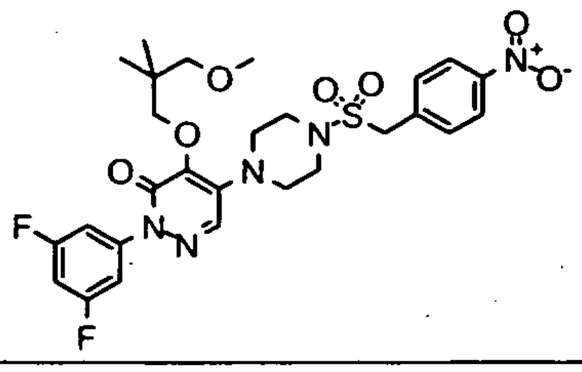
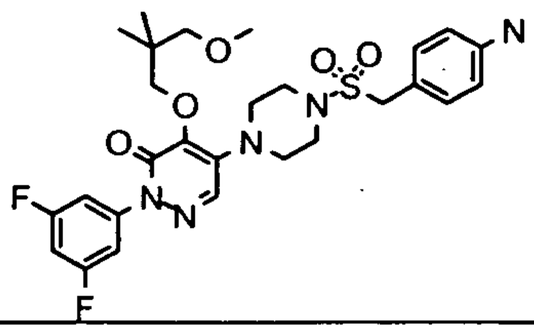
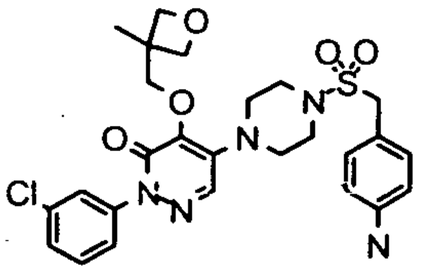
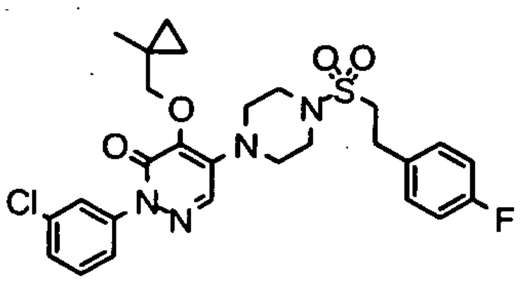
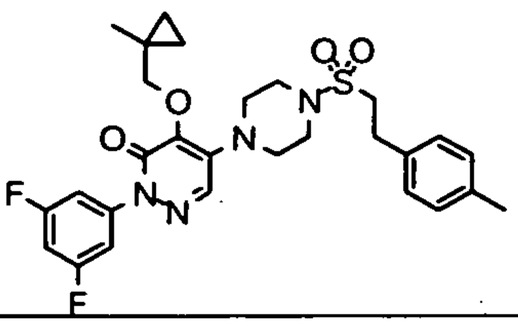
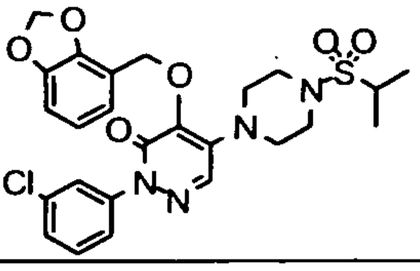
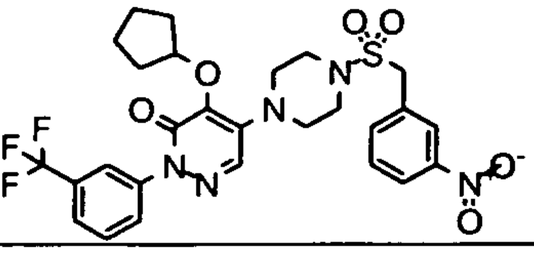
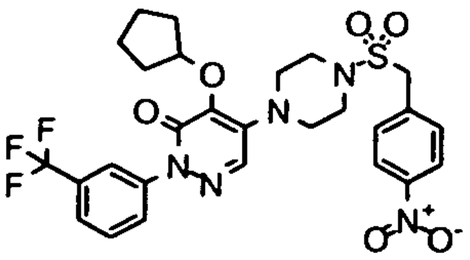
941Z		546
943Z		481
945Z		493
947Z		617
949Z		476

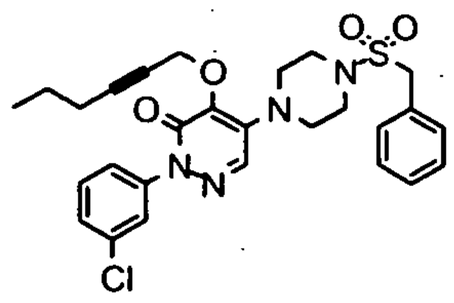
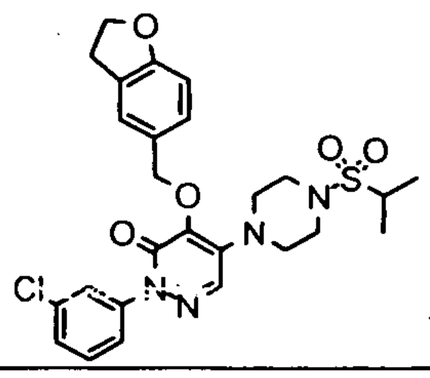
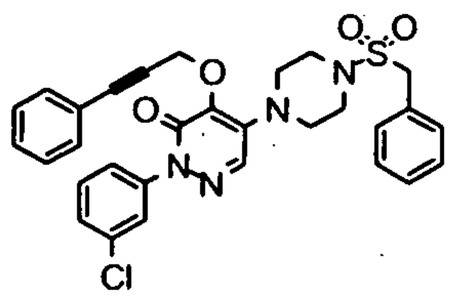
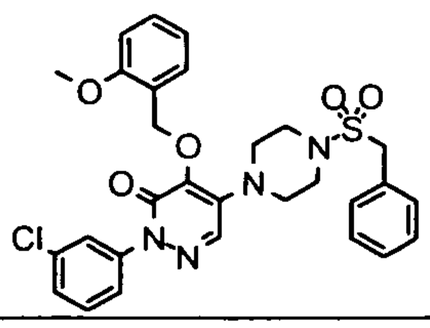
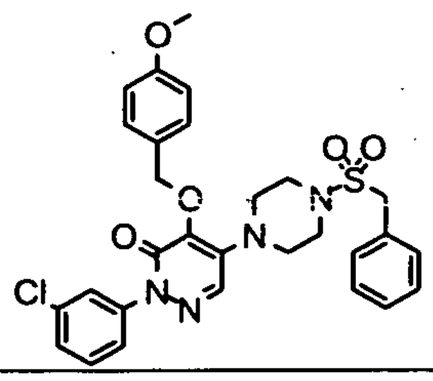
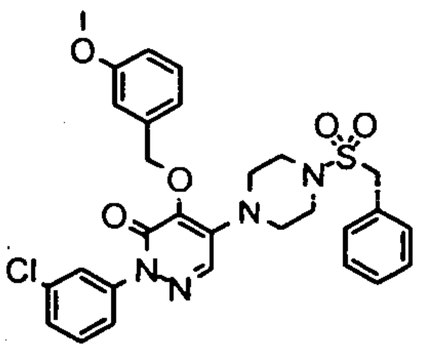
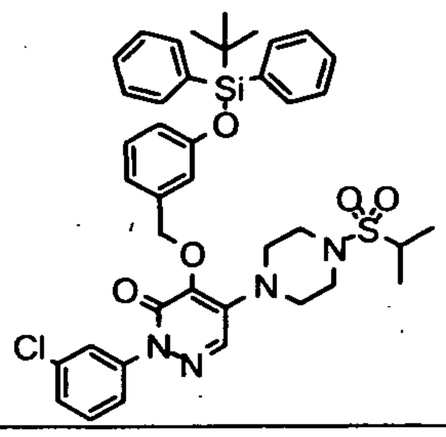
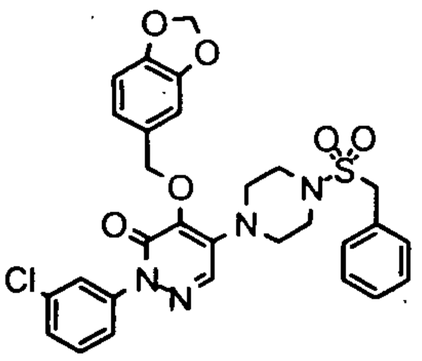
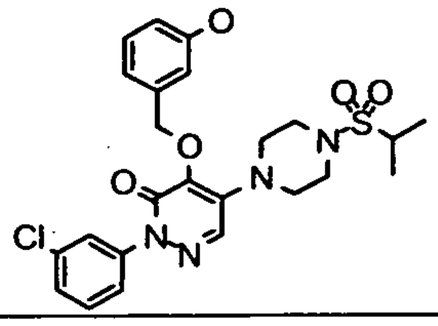
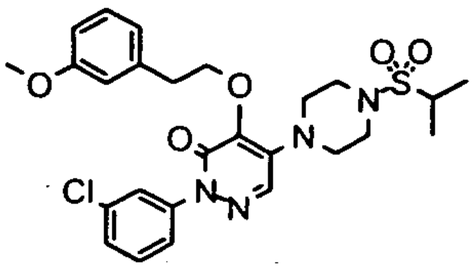
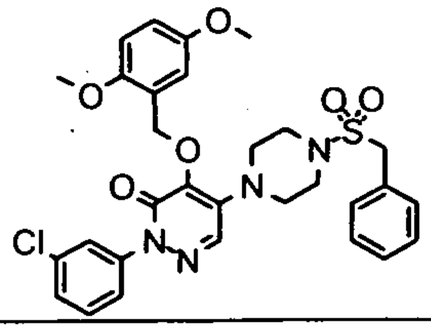
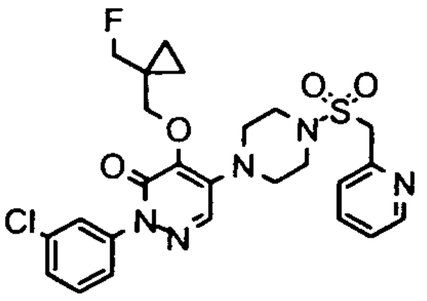
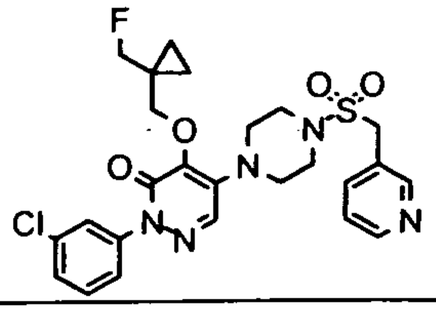
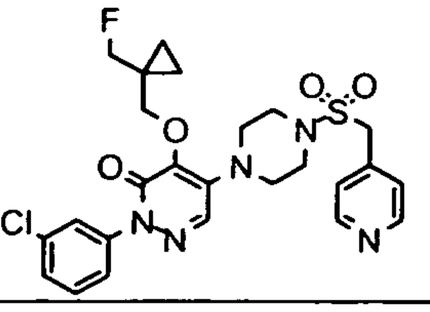
950Z		477	951Z		490
952Z		476	953Z		564
954Z		580	955Z		632
956Z		500	957Z		530
958Z		530	959Z		530
960Z		510	961Z		632
962Z		513	963Z		594
964Z		546	965Z		609

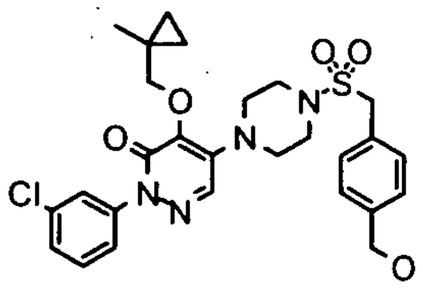
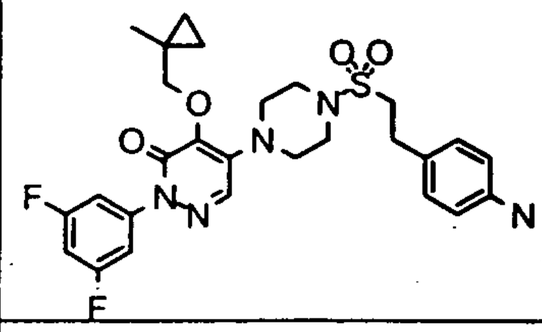
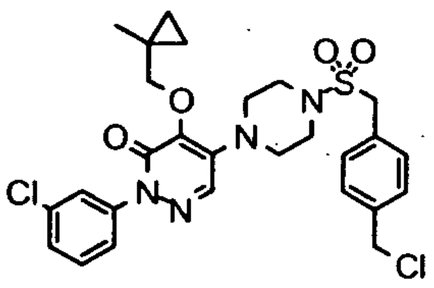
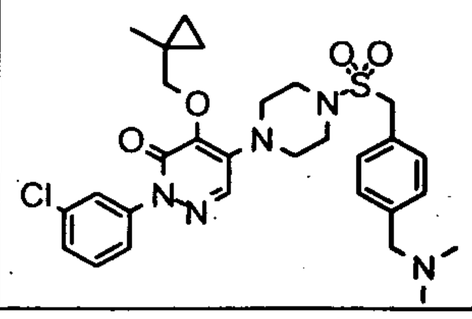
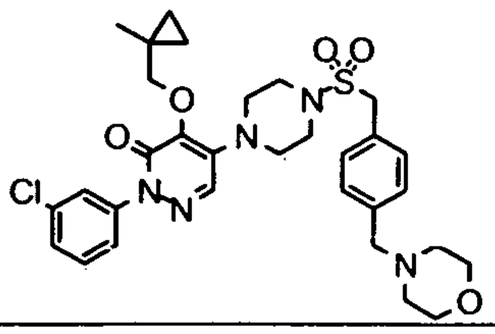
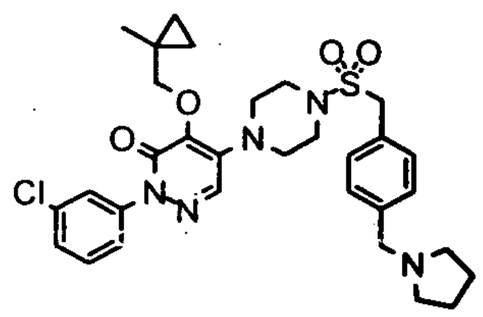
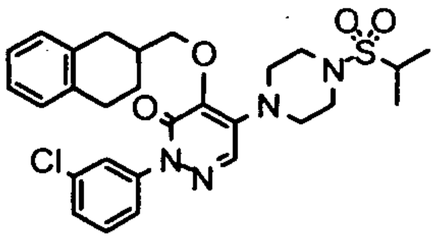
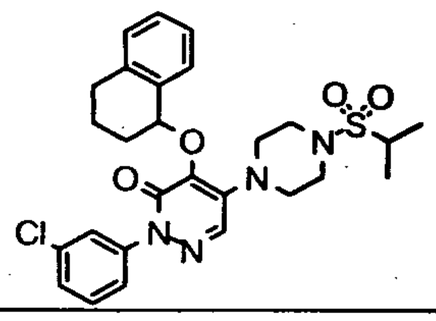
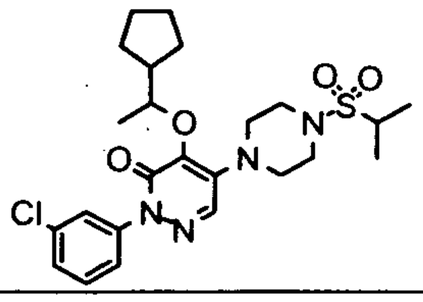
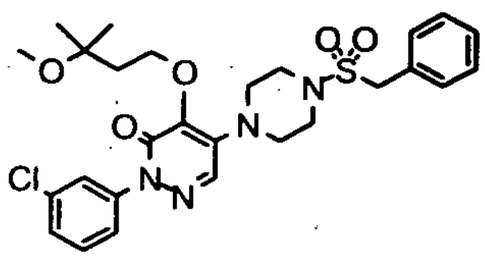
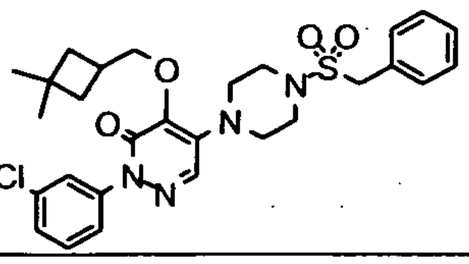
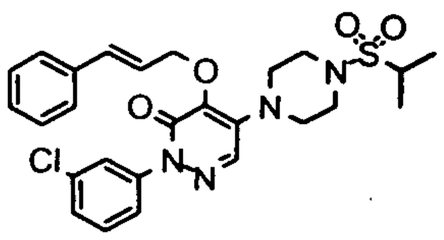
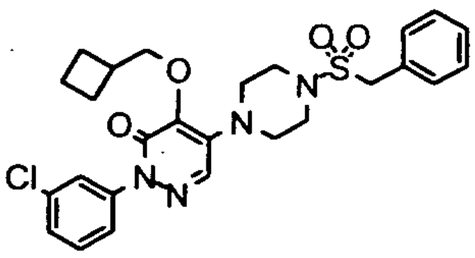
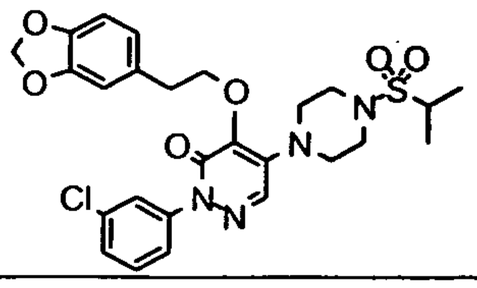
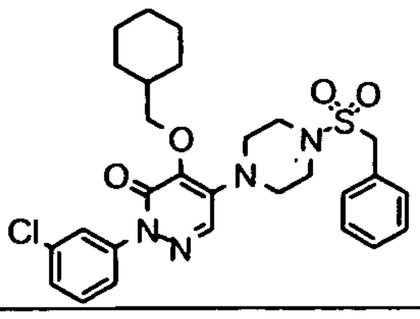
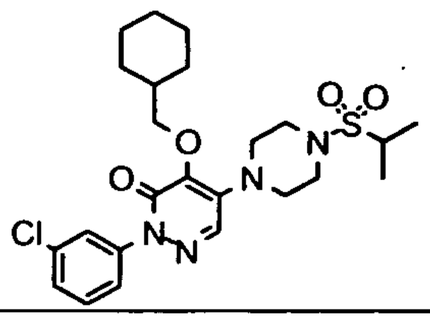
966Z		540
967Z		584
968Z		476
969Z		553
970Z		476
971Z		677
971Za		545
971Zb		573
971Zc		546
971Zd		573
971Ze		588
971Zf		562
971Zg		561
971Zh		576
971Zi		561
971Zj		467

971Zk		465
971Zl		559
971Zm		551
971Zn		558
971Zo		563
971Zp		574
971Zq		517
971Zr		579
971Zs		590
971Zt		545
971Zu		590
971Zv		563
971Zw		609
971Zx		577
971Zy		513
971Zz		592

971Zaa		606
971Zbb		562
971Zcc		620
971Zdd		578
971Zee		620
971Zff		578
971Zgg		543
971Zhh		555
971Zii		560
971Zjj		576
971Zkk		606
971Zll		561
971Zmm		590
971Znn		608
971Zoo		576
971Zpp		608

971Zqq		559
971Zss		572
971Zuu		517
971Zww		517
971Zyy		588
971ZA		578
971ZC		578
971ZE		527
971Zrr		608
971Ztt		578
971Zvv		560
971Zxx		561
971Zzz		559
971ZB		547
971ZD		608
971ZF		608

971ZG		541
971ZH		475
971ZI		575
971ZJ		581
971ZK		581
971ZL		581
971ZM		757
971ZN		595
971ZO		519
971ZP		547
971ZQ		611
971ZR		548
971ZS		548
971ZT		548

971ZU		559	971ZV		560
971ZW		577	971ZX		586
971ZY		628	971ZZ		612
971Za1		557	971Zb1		543
971Zc1		509	971Zd1		561
971Ze1		557	971Zf1		529
971Zg1		529	971Zh1		561
971Zi1		557	971Zj1		509

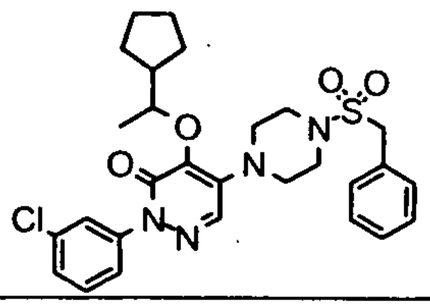
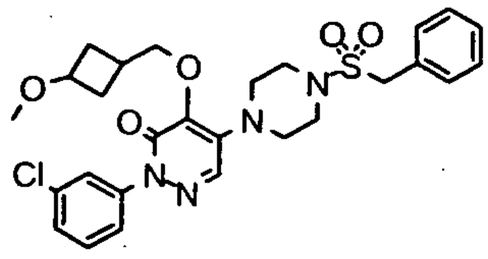
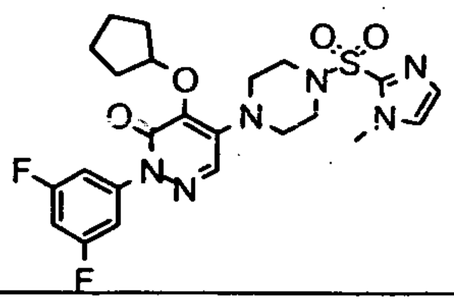
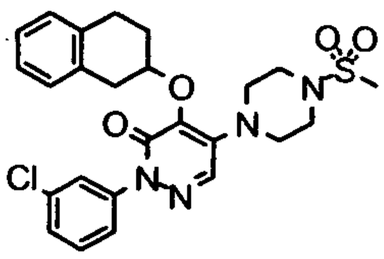
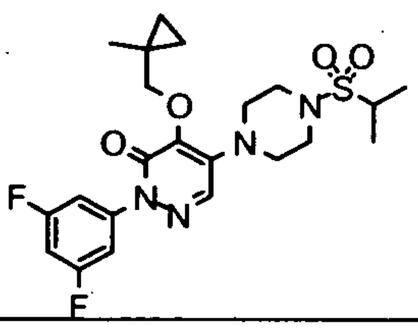
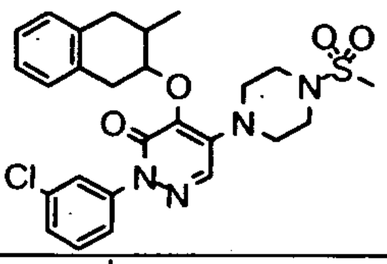
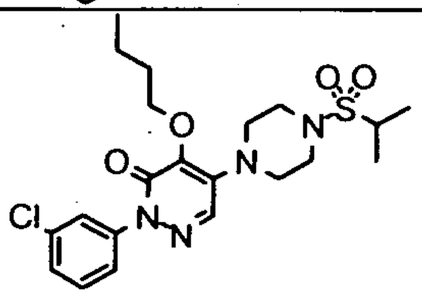
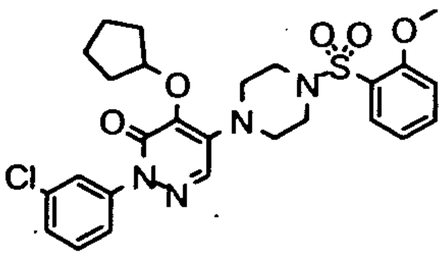
971Zk1		557
971Zl1		559

Table 11: Oxygen Linked Analogs with Sulfonamide

The following compounds can be synthesized using steps 1, 2, 4, 6, and 9 of Scheme 1 or steps 11, 12, and 14 of Scheme 2.

Comp. No.	Structure	MS M+1
972Z		521
974Z		515
976Z		483
978Z		529
980Z		469
982Z		545

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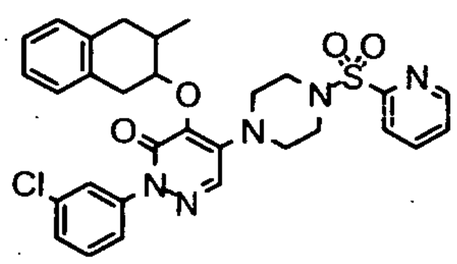
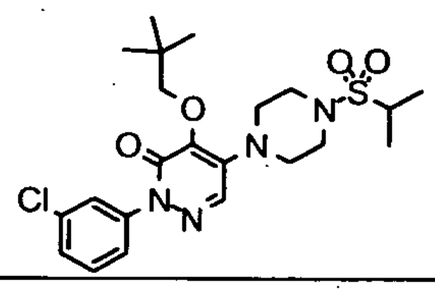
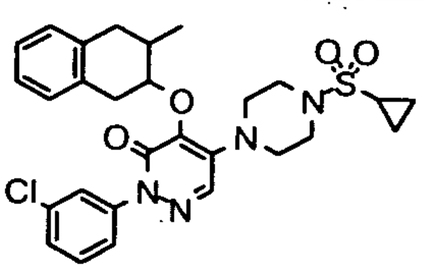
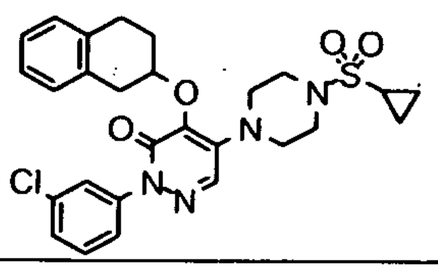
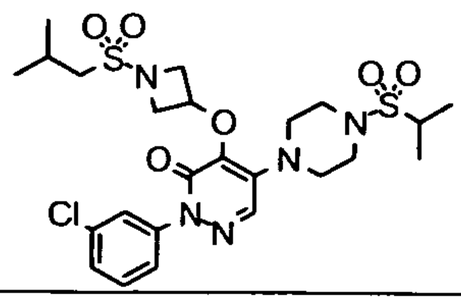
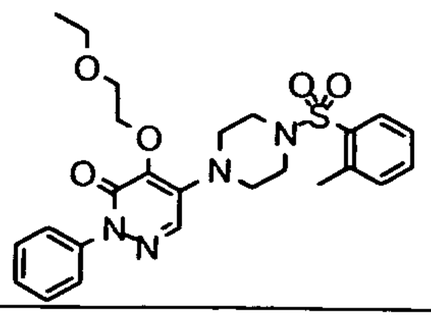
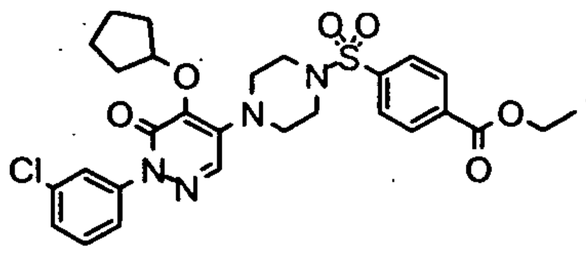
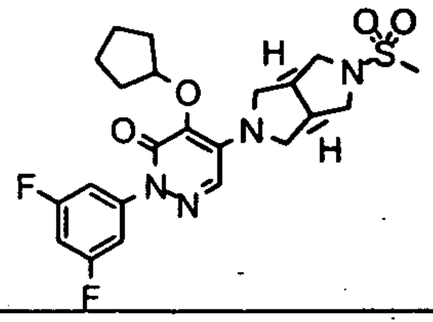
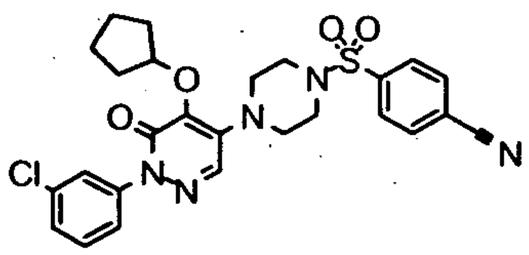
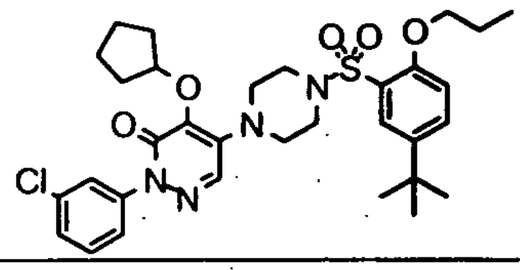
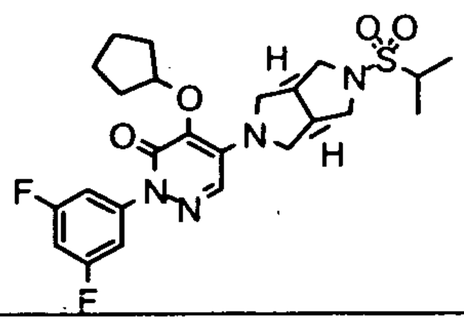
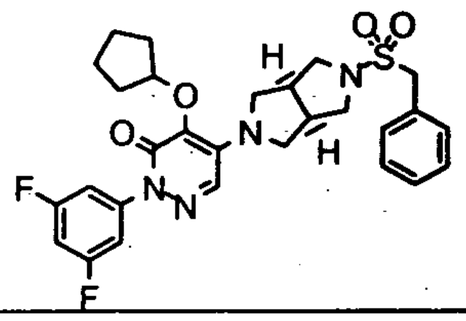
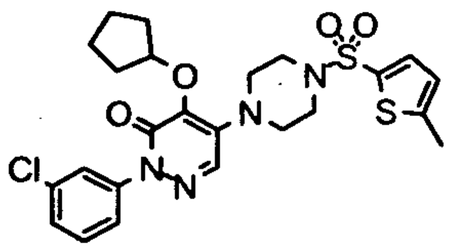
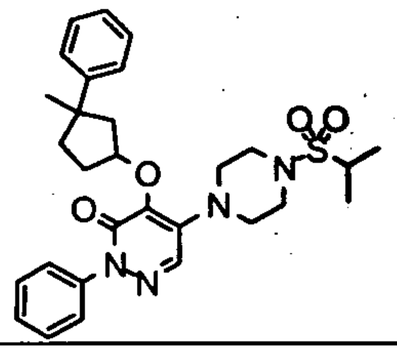
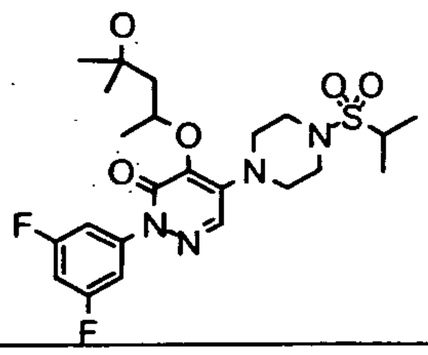
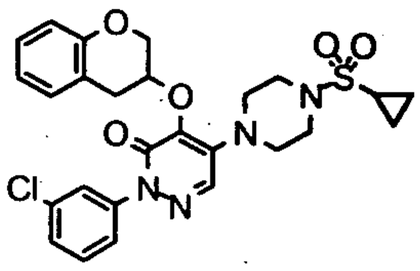
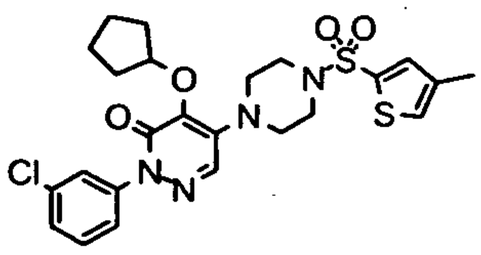
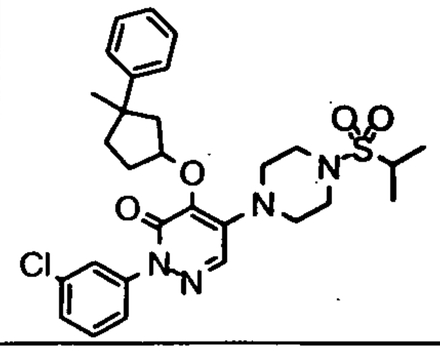
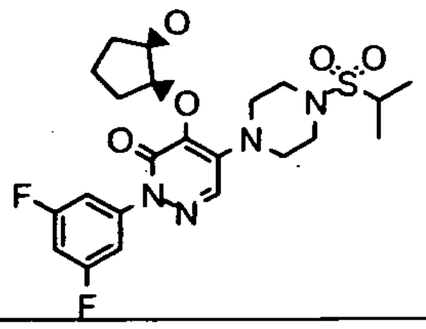
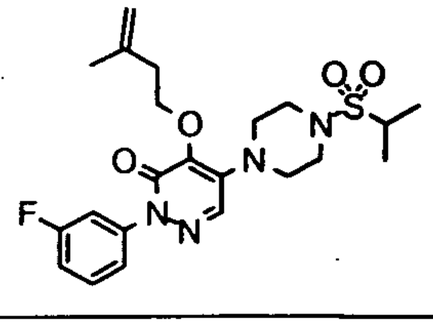
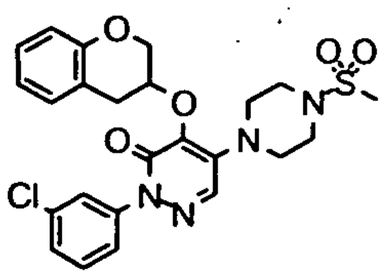
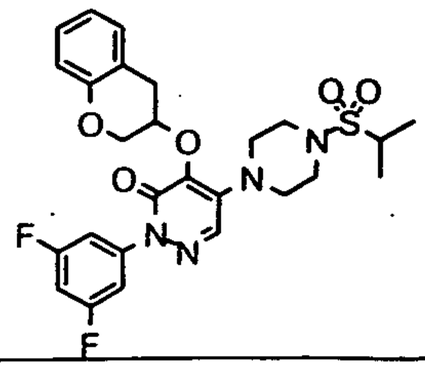
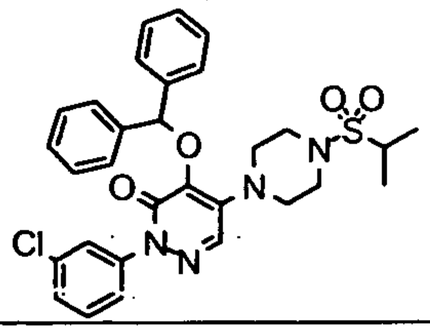
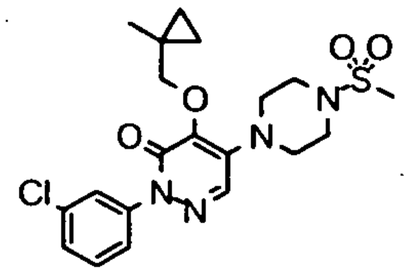
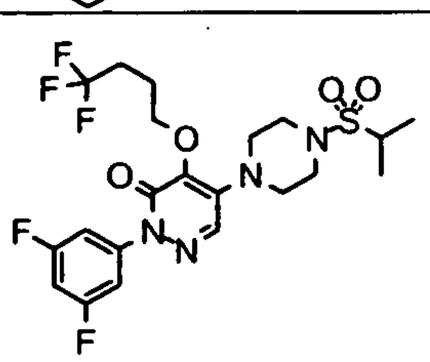
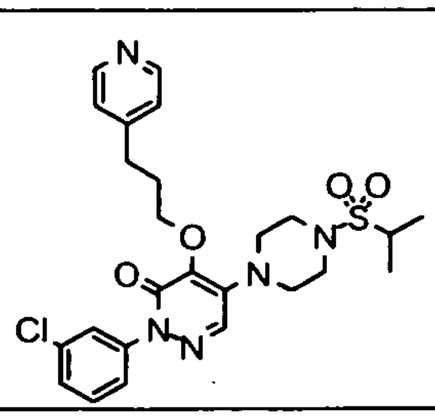
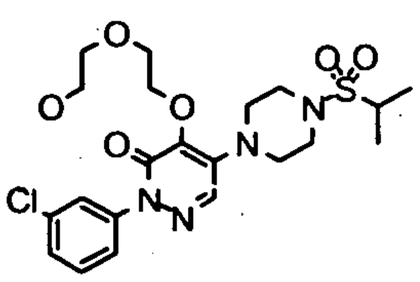
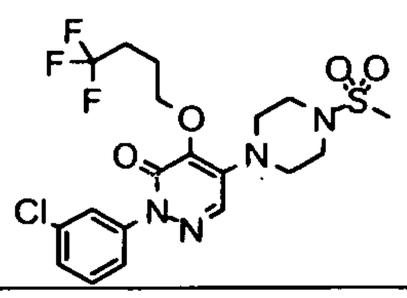
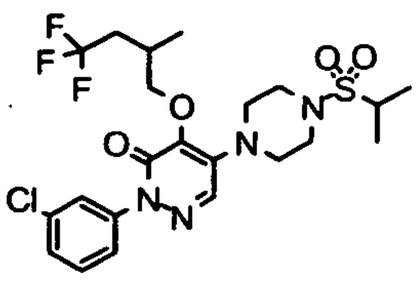
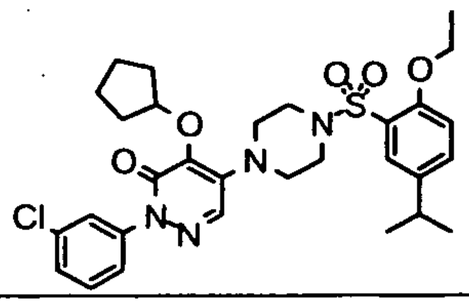
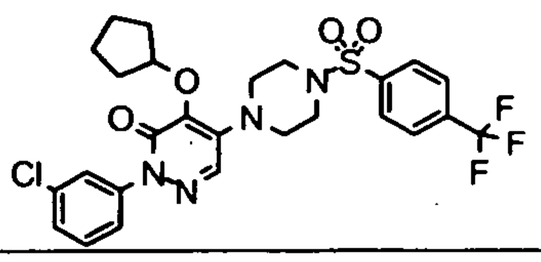
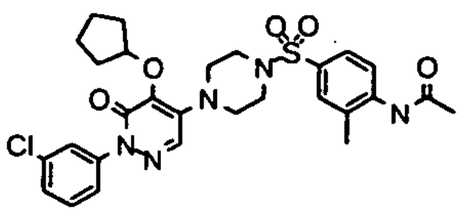
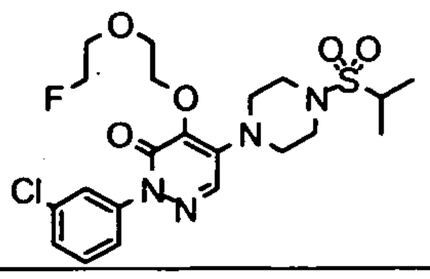
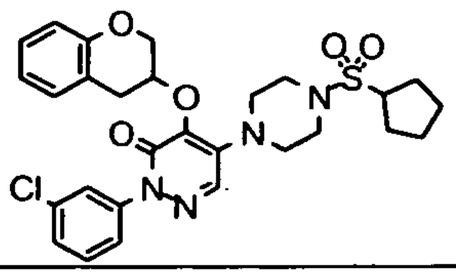
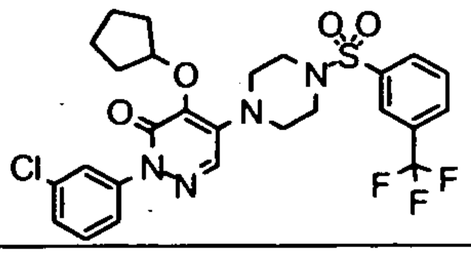
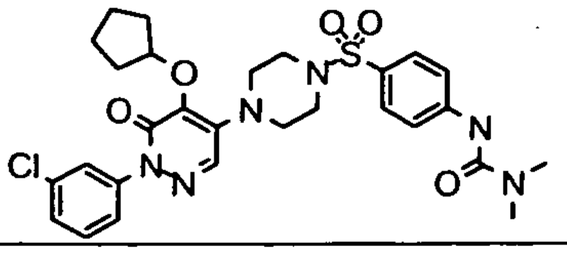
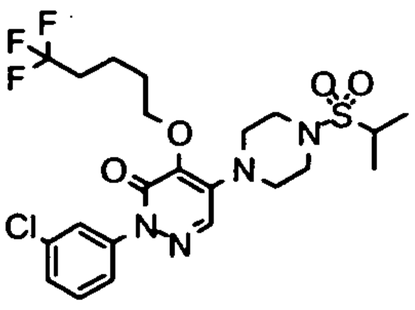
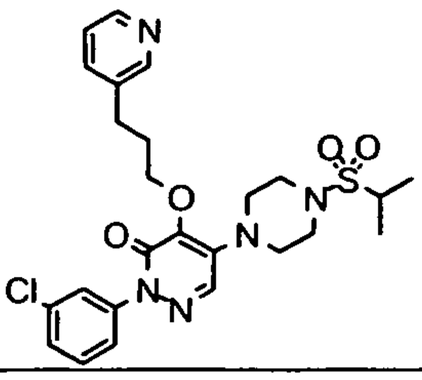
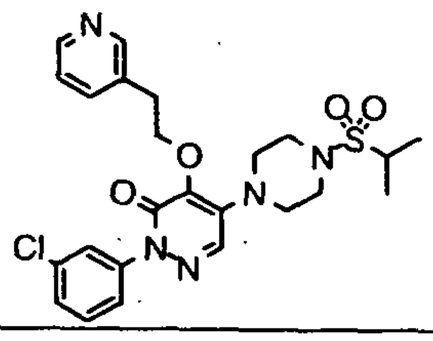
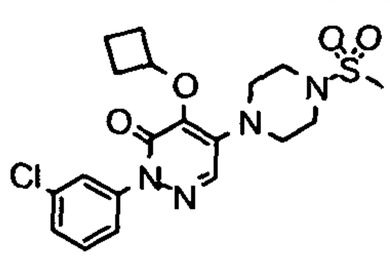
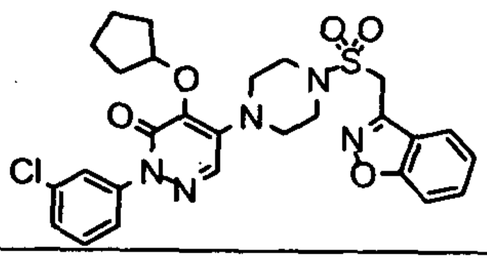
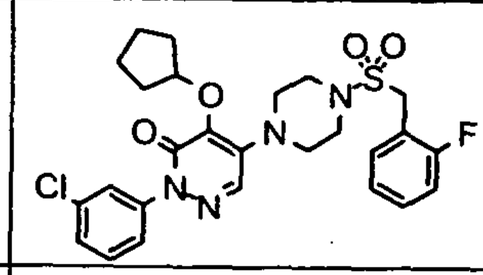
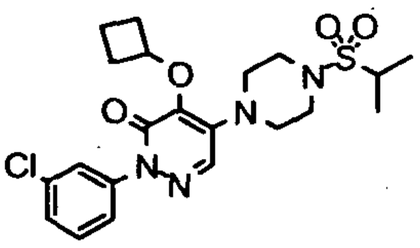
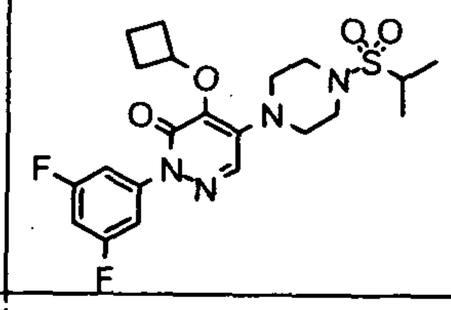
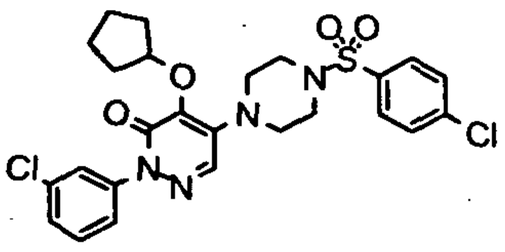
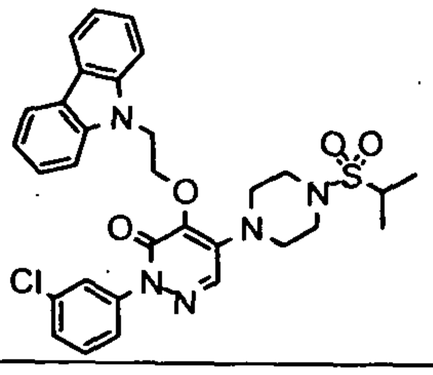
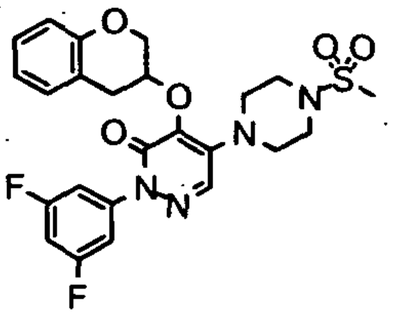
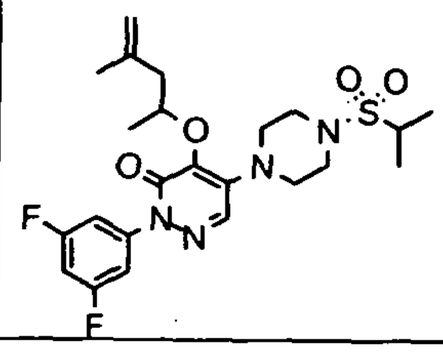
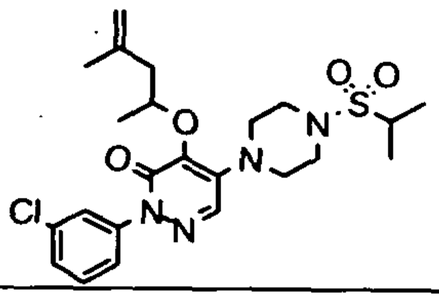
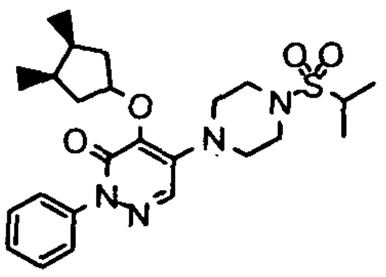
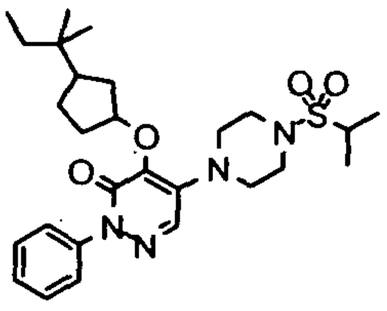
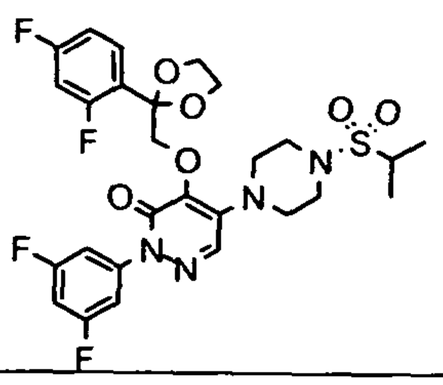
973Z		592
975Z		483
977Z		555
979Z		541
981Z		589
983Z		499

984Z		587
985Z		481
986Z		540
987Z		629
988Z		509
989Z		557
990Z		535
991Z		537
992Z		515
993Z		543
994Z		535
995Z		571
996Z		499
997Z		465
998Z		517
999Z		547

1000Z		580
1001Z		453
1002Z		525
1003Z		533
1004Z		501
1005Z		495
1006Z		537
1007Z		601
1008Z		583
1009Z		586
1010Z		503
1011Z		571
1012Z		583
1013Z		601
1014Z		537
1015Z		532

1016Z		518
1017Z		439
1018Z		570
1019Z		547
1020Z		467
1021Z		469.5
1022Z		549
1023Z		606
1024Z		519
1025Z		497
1026Z		495
1027Z		475
1028Z		517
1029Z		613
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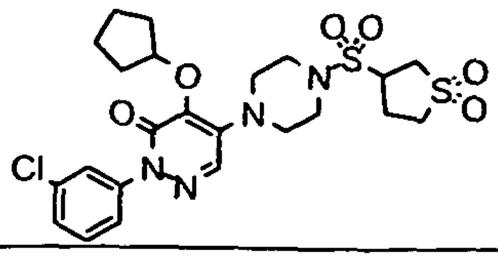
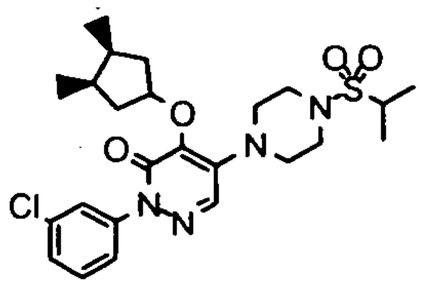
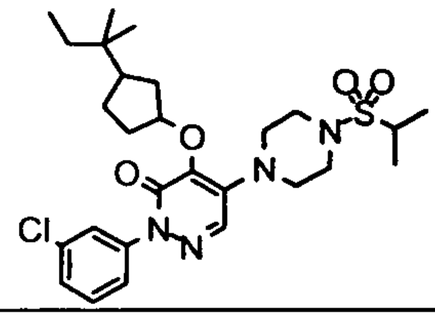
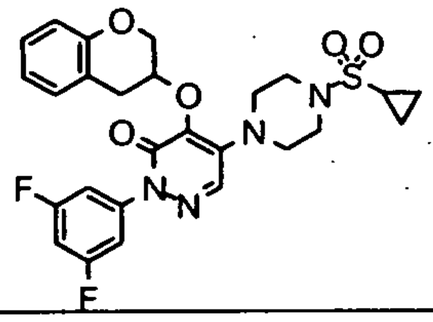
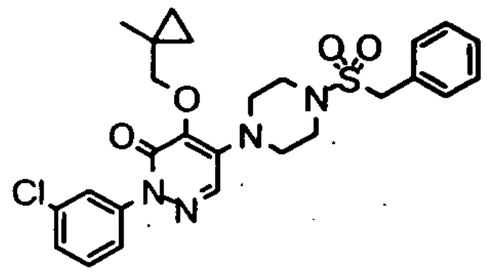
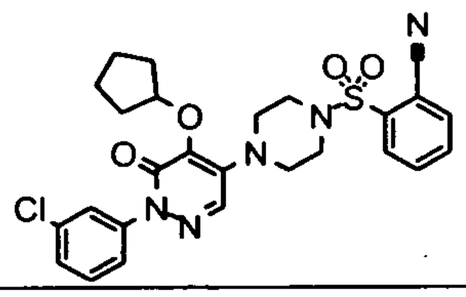
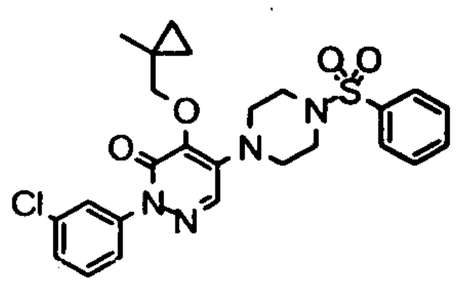
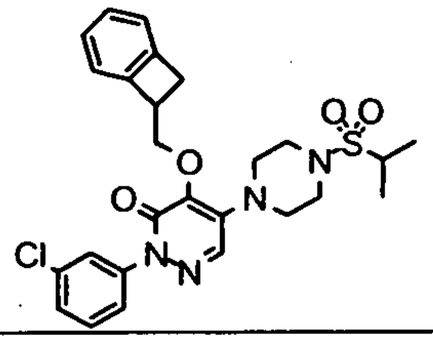
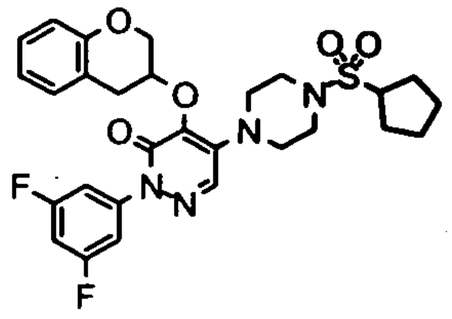
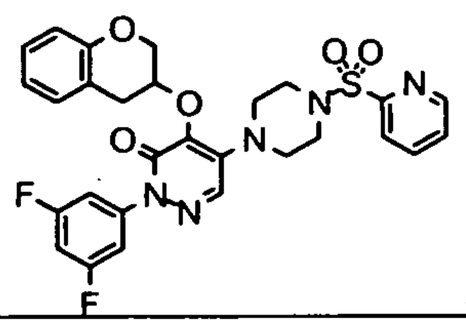
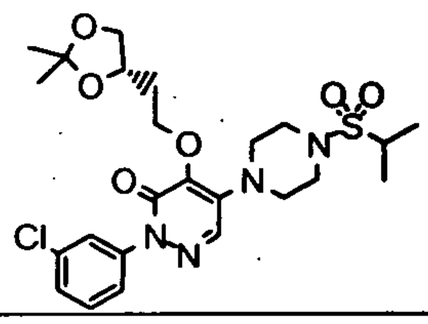
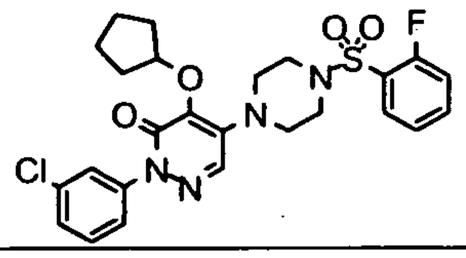
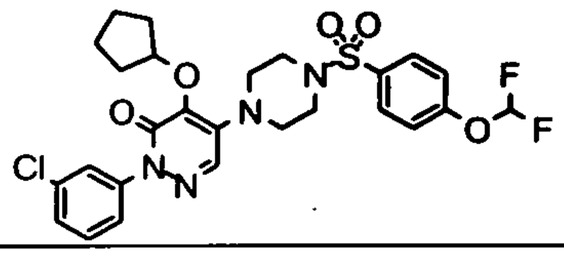
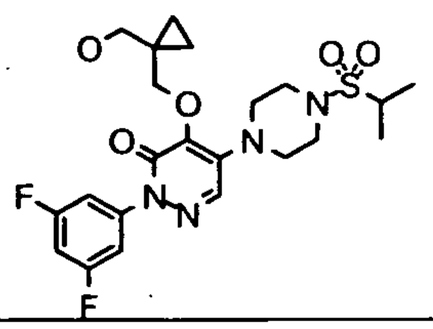
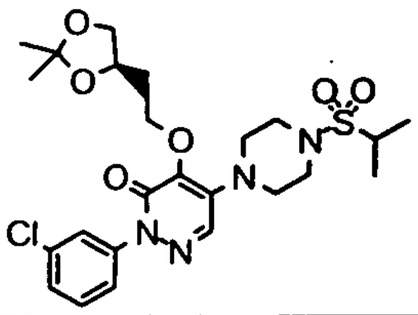
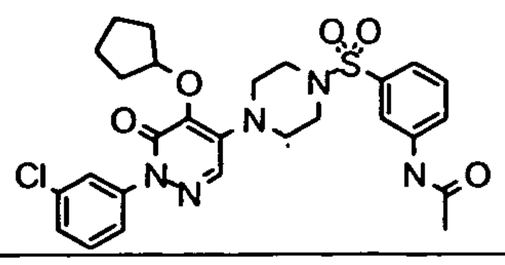
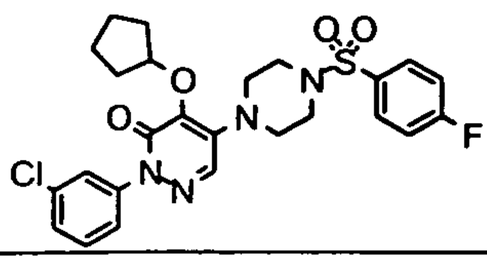
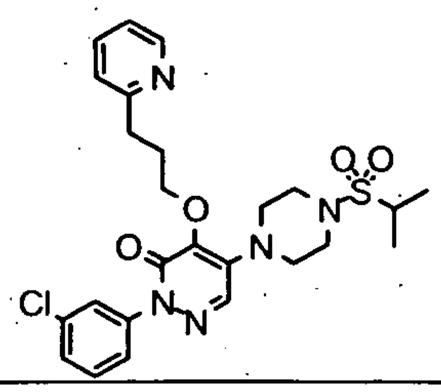
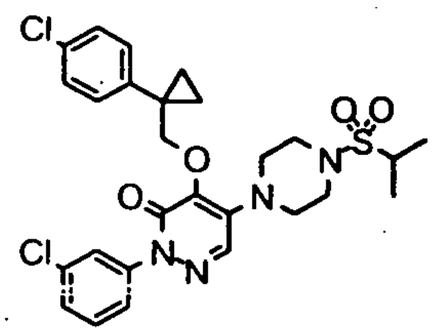
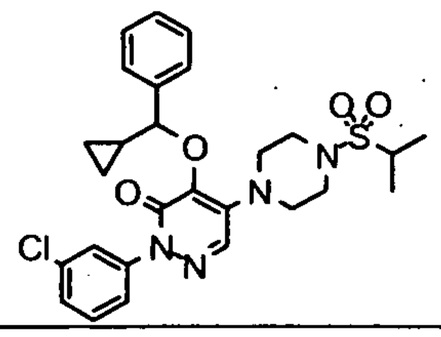
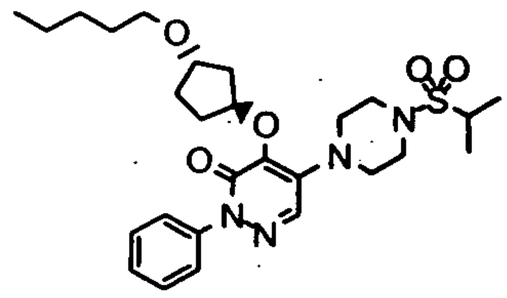
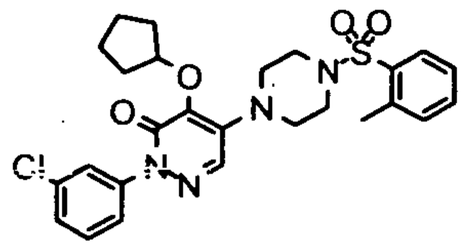
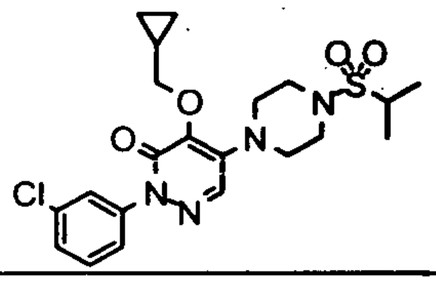
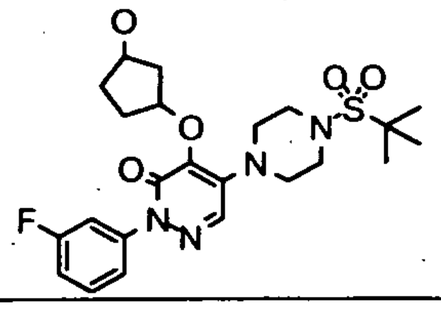
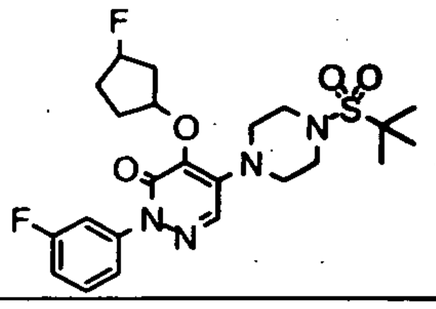
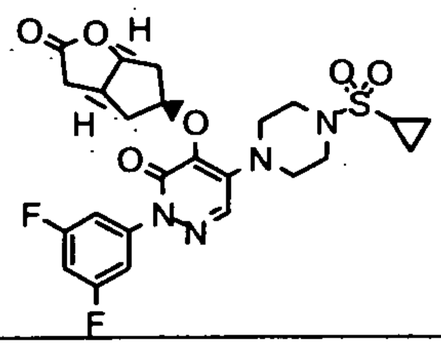
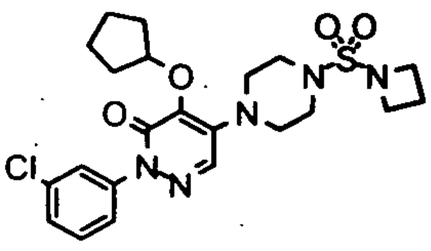
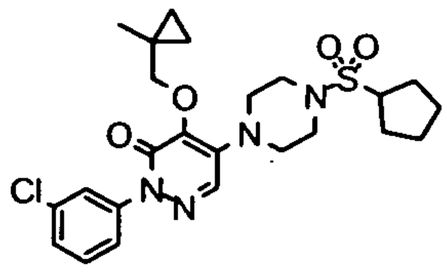
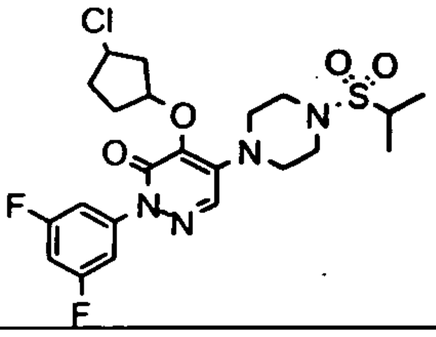
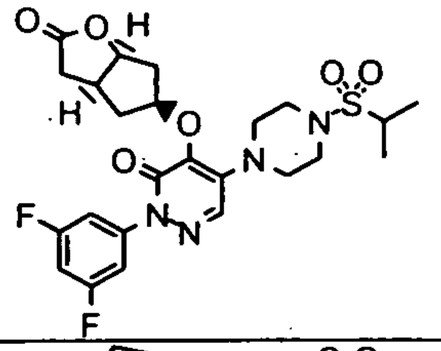
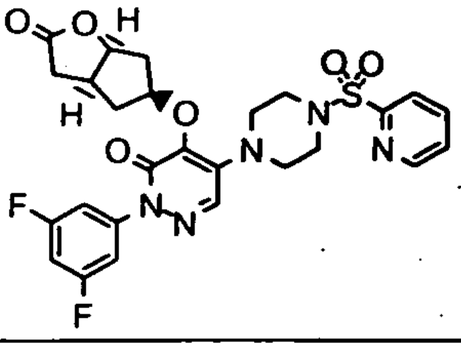
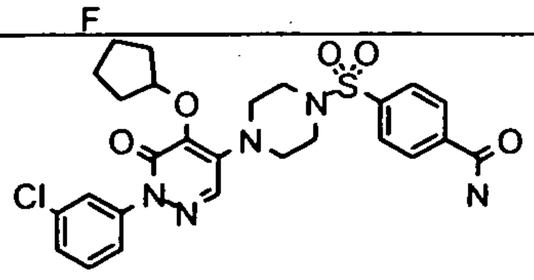
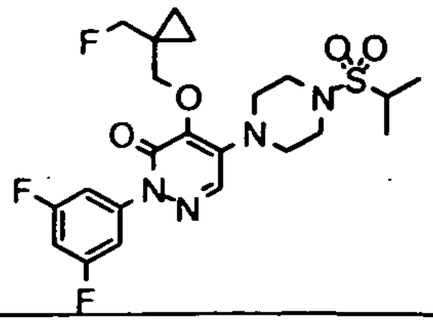
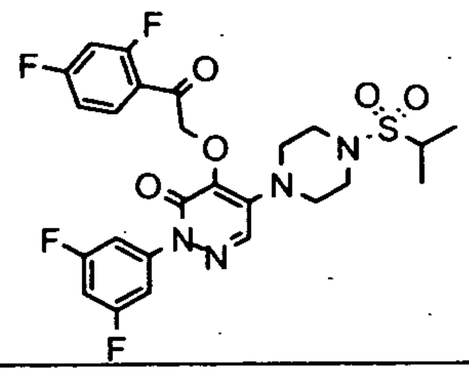
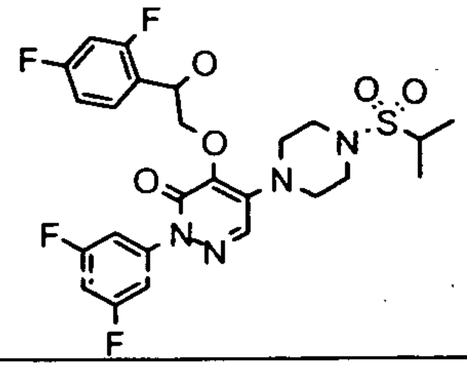
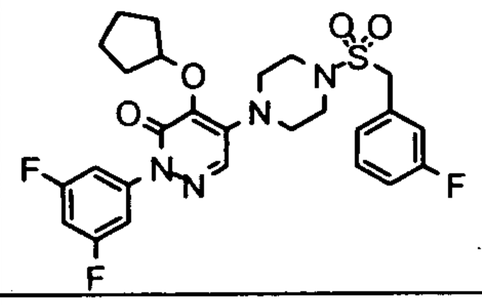
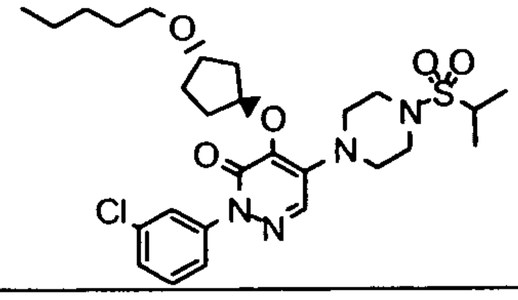
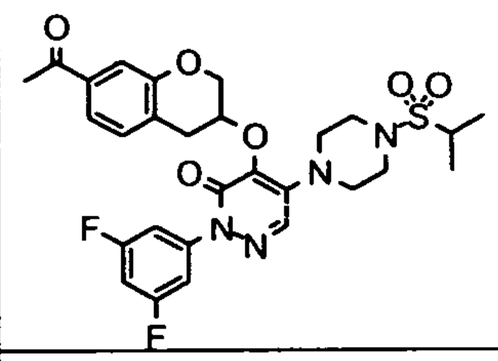
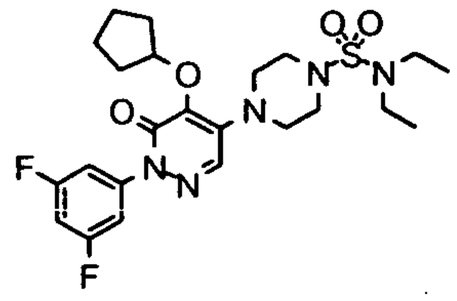
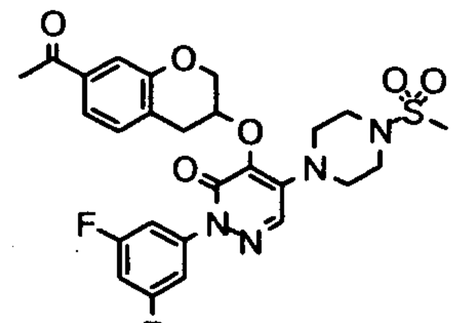
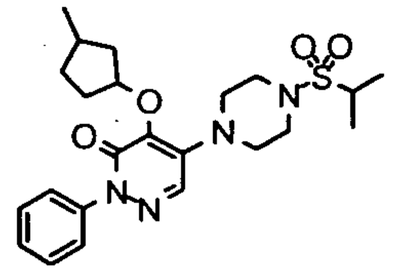
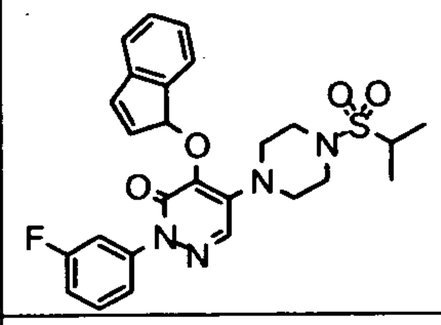
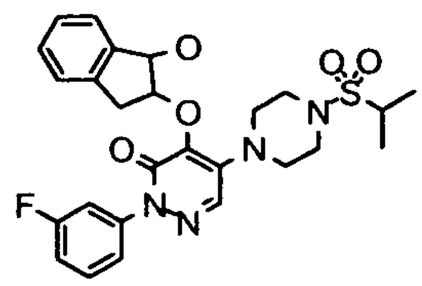
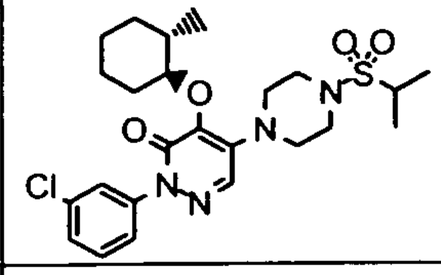
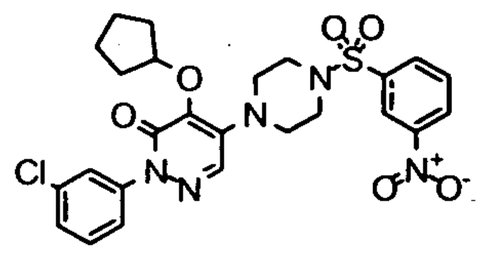
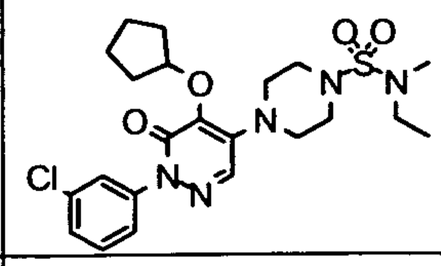
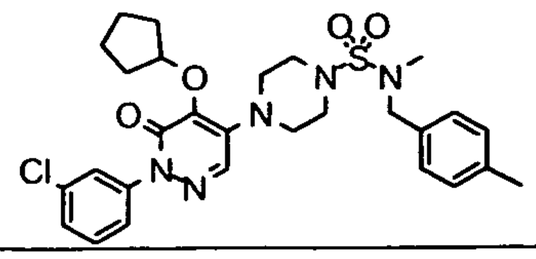
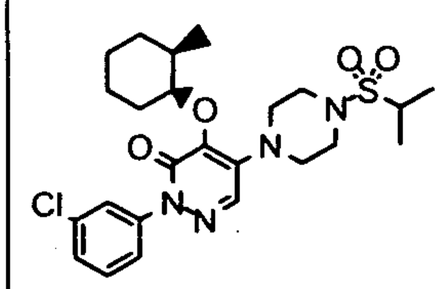
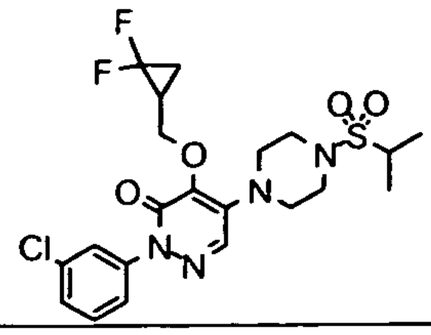
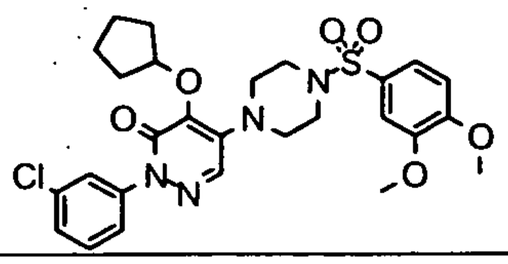
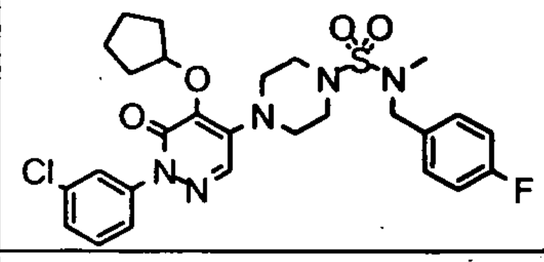
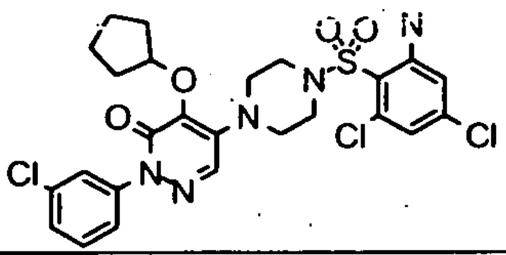
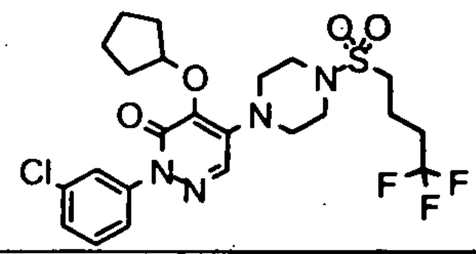
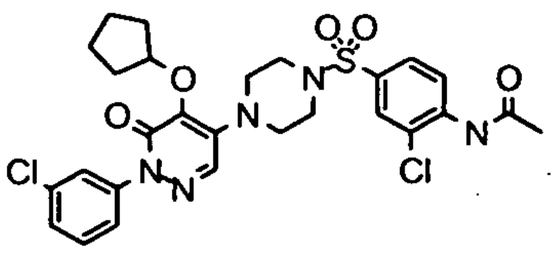
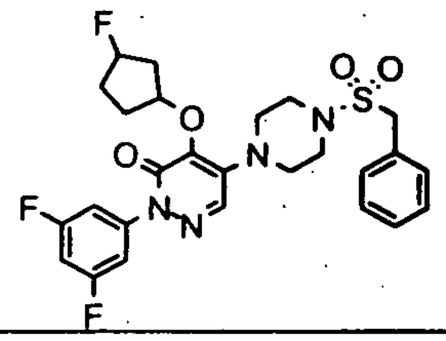
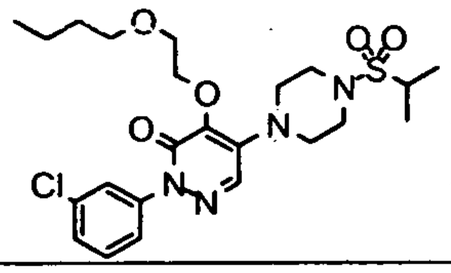
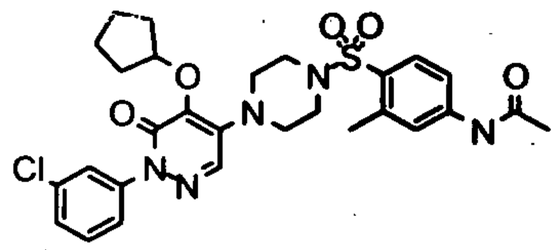
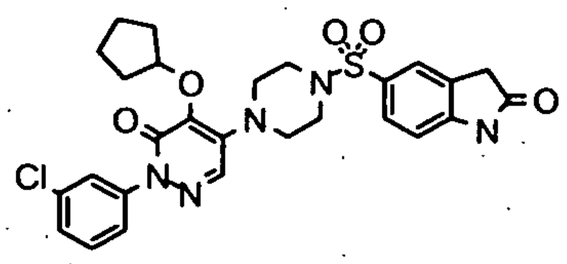
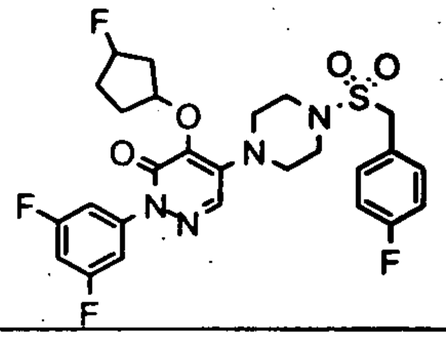
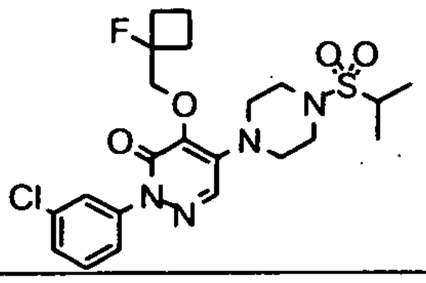
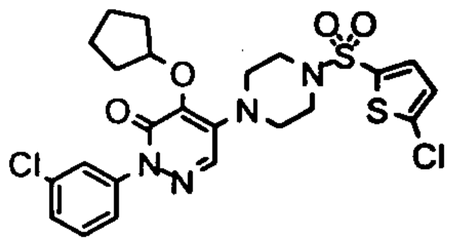
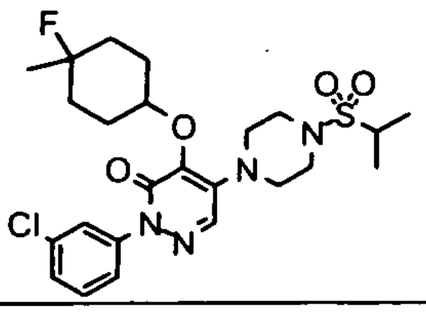
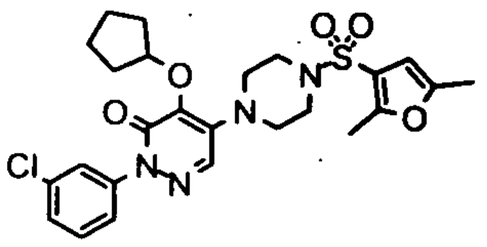
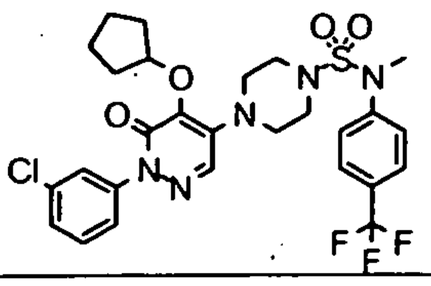
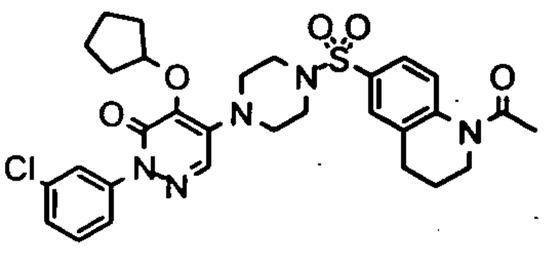
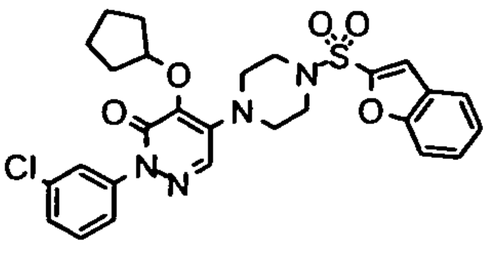
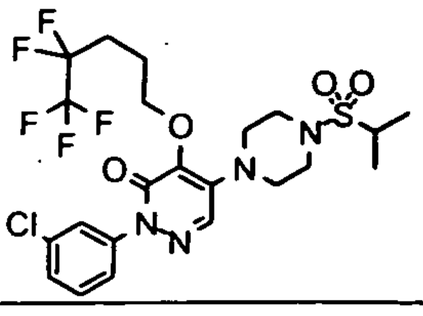
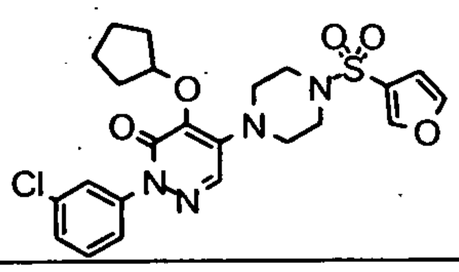
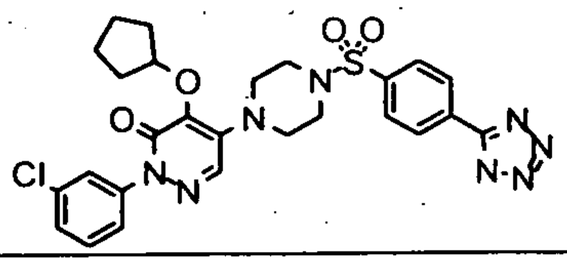
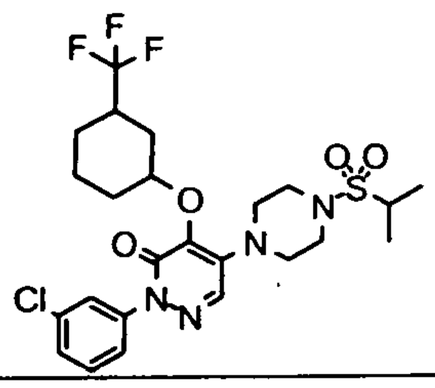
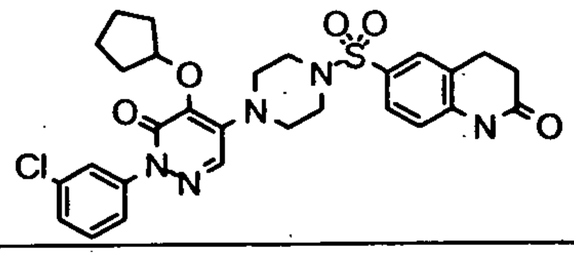
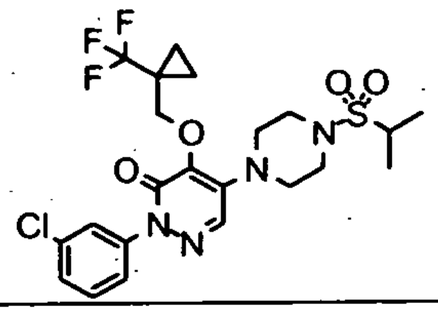
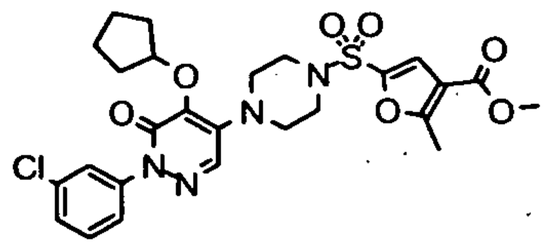
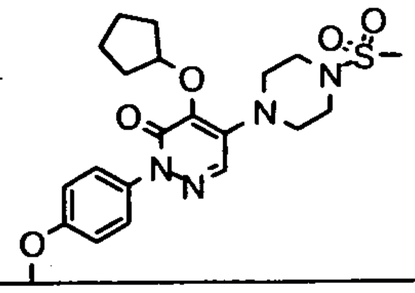
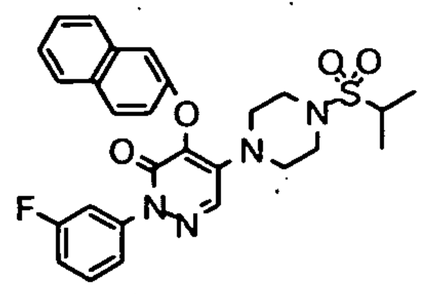
1031Z		557

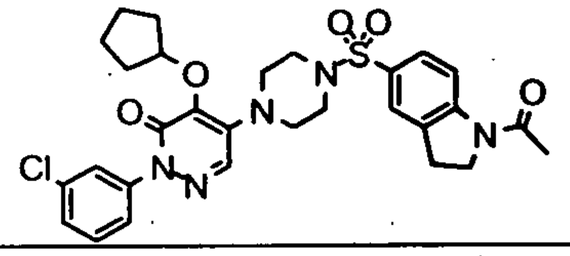
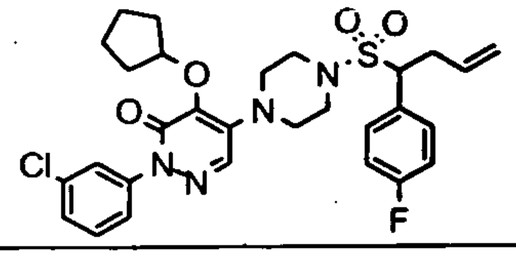
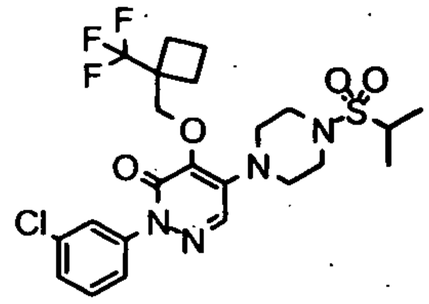
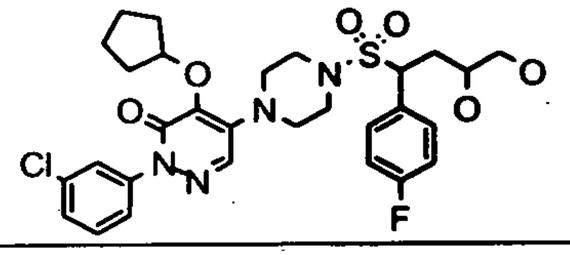
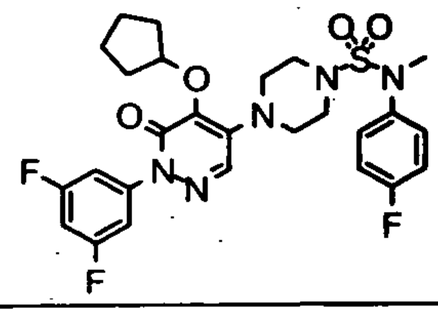
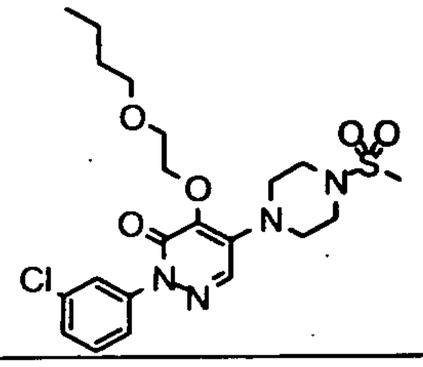
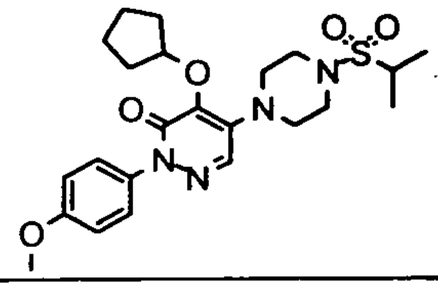
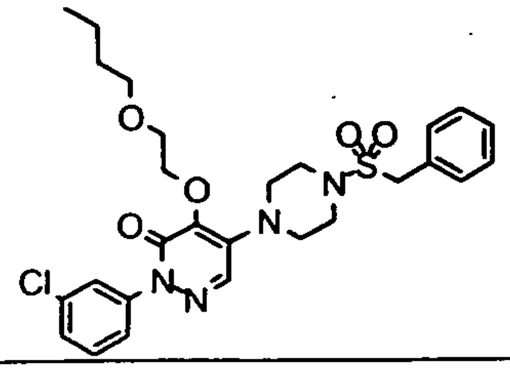
1032Z		509
1033Z		551
1034Z		545
1035Z		529
1036Z		540
1037Z		515
1038Z		529
1039Z		573
1040Z		582
1041Z		541
1042Z		533
1043Z		581
1044Z		481 (M-OH)
1045Z		541
1046Z		572
1047Z		533

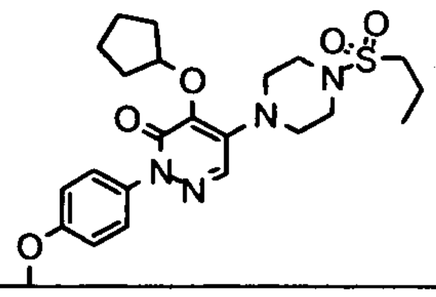
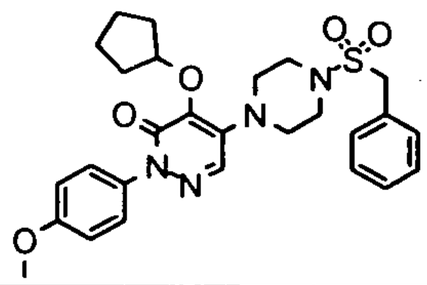
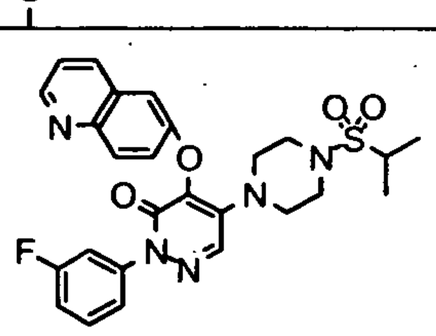
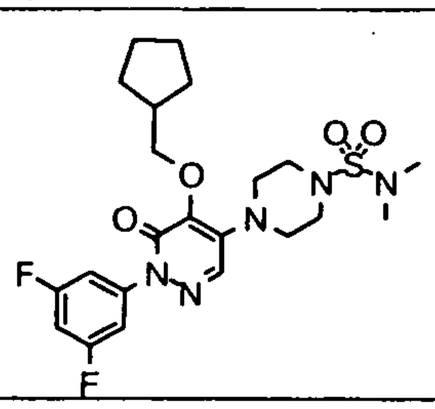
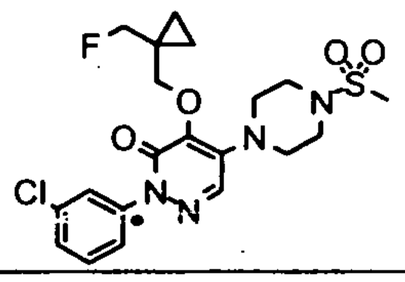
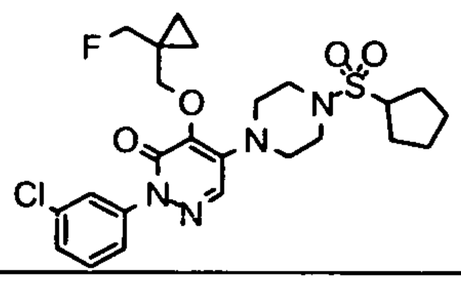
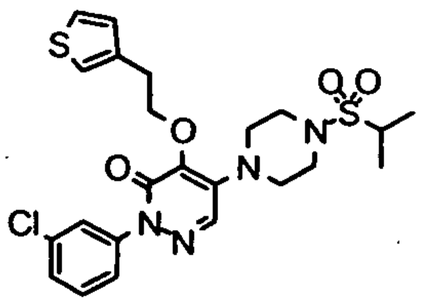
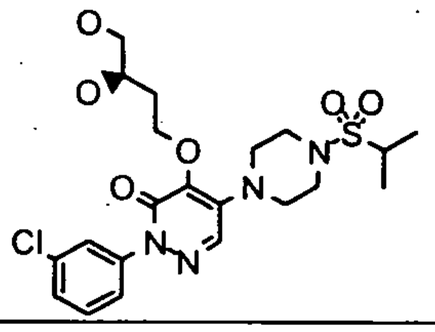
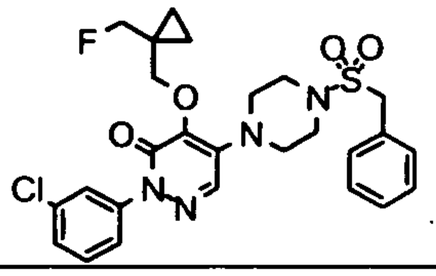
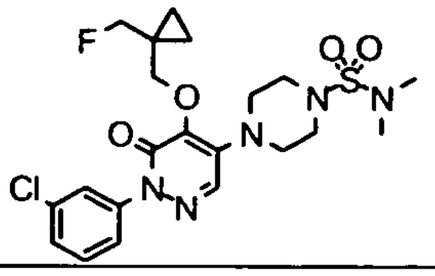
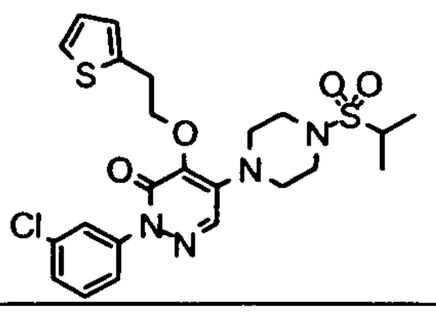
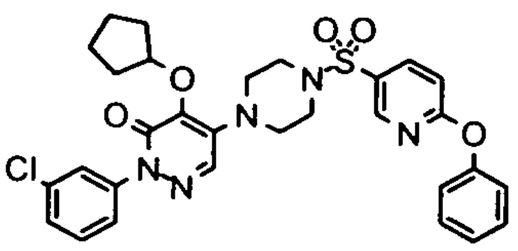
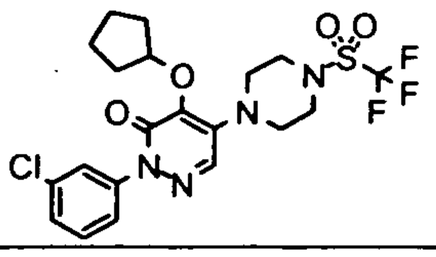
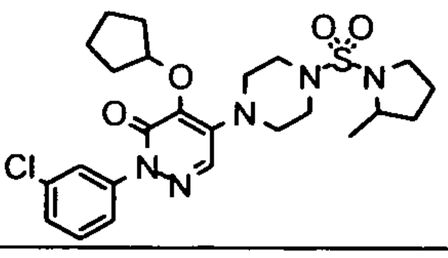
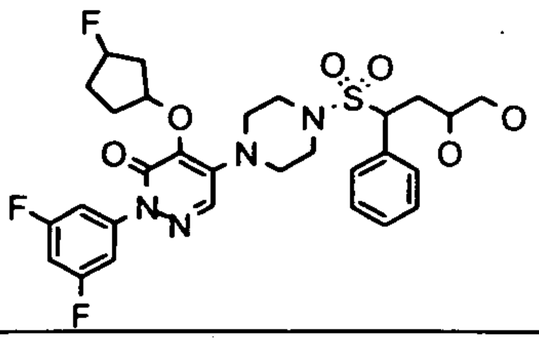
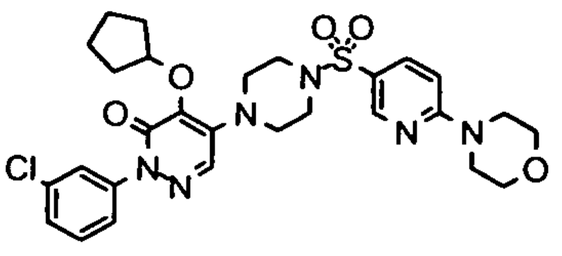
1048Z		532	1049Z		577
1050Z		543	1051Z		533
1052Z		529	1053Z		467
1054Z		495	1055Z		497
1056Z		537	1057Z		494
1058Z		507	1059Z		517
1060Z		539	1061Z		574
1062Z		558	1063Z		501

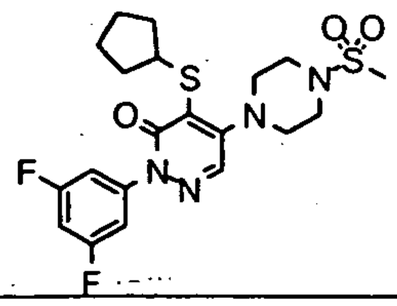
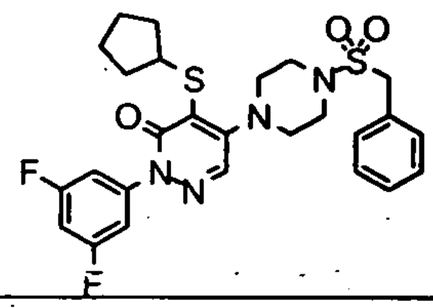
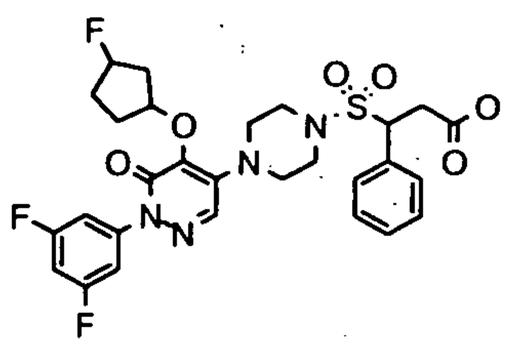
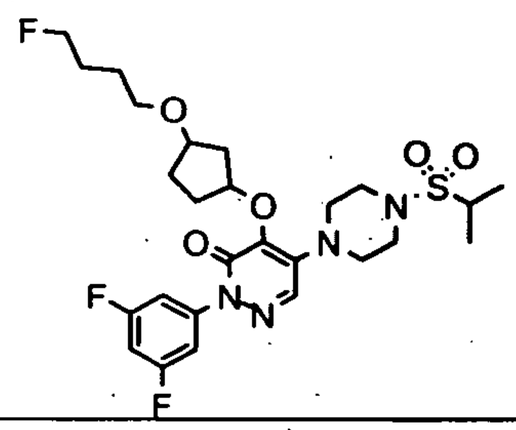
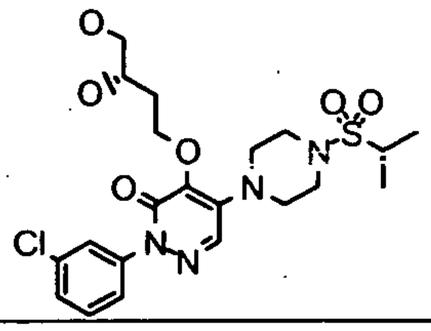
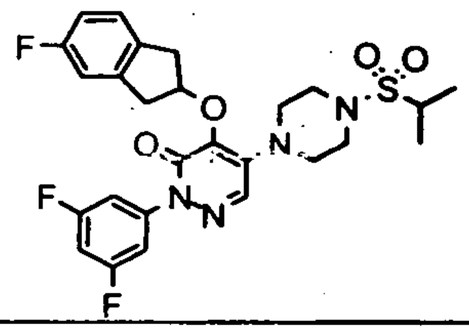
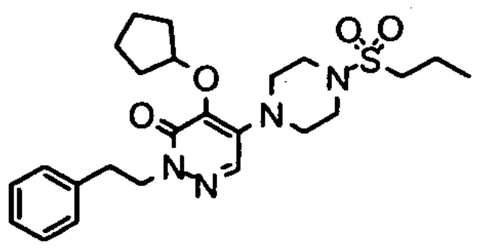
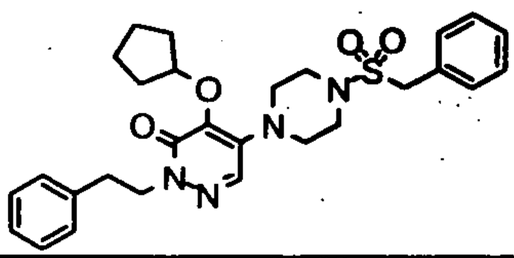
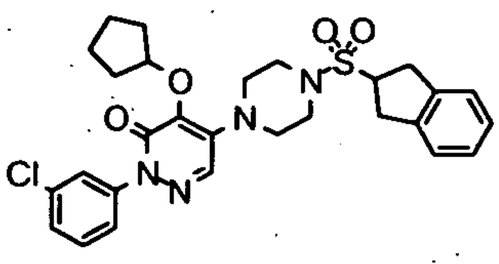
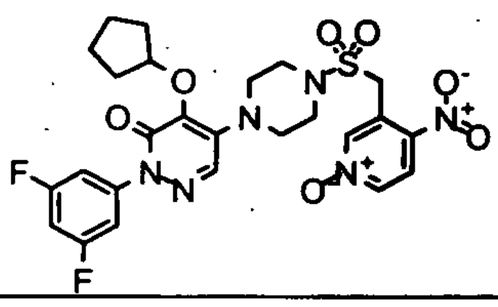
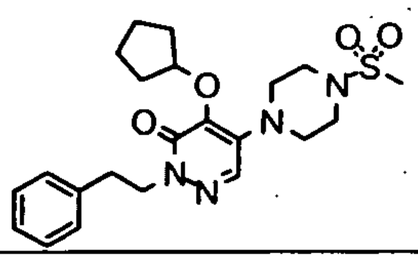
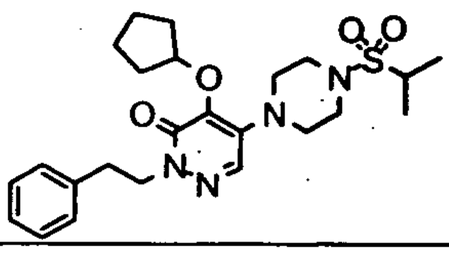
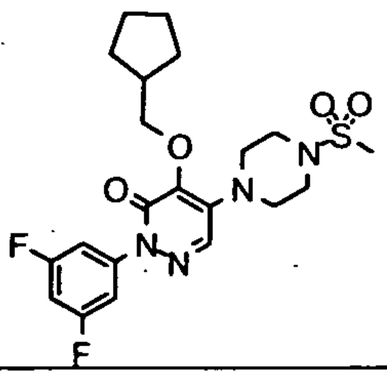
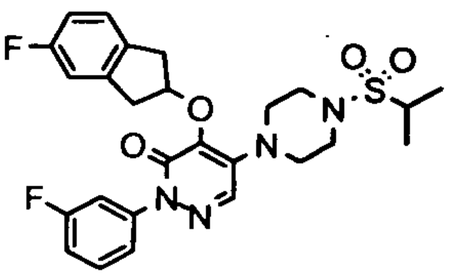
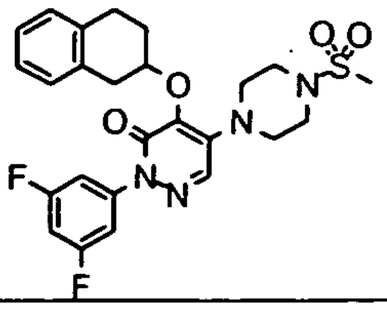
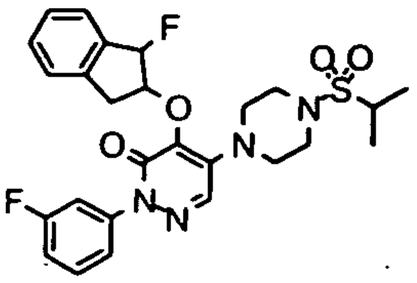
1064Z		569
1065Z		571
1066Z		549
1067Z		567
1068Z		589
1069Z		512
1070Z		561
1071Z		461
1072Z		511
1073Z		529
1074Z		509
1075Z		560
1076Z		496
1077Z		572
1078Z		509
1079Z		503

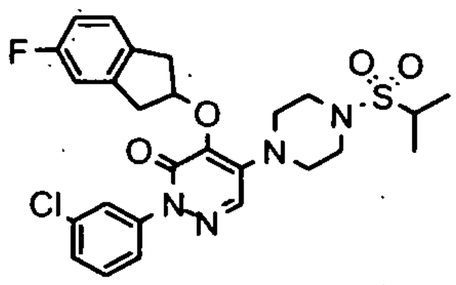
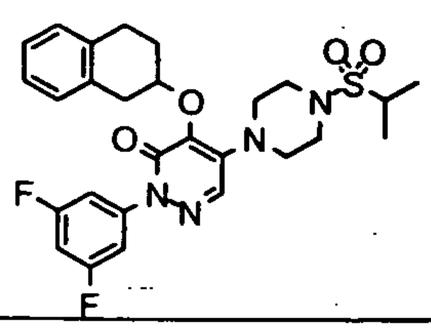
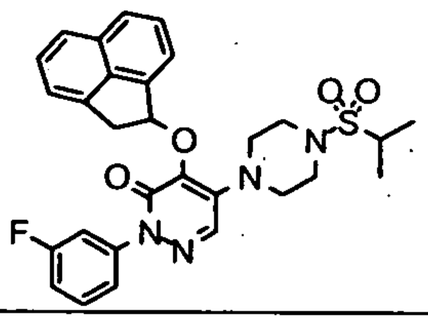
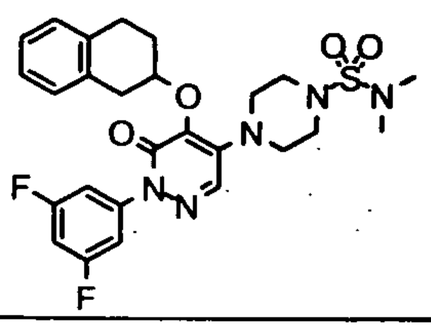
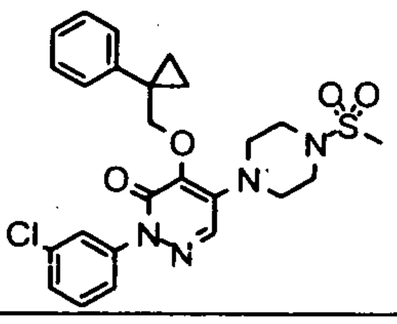
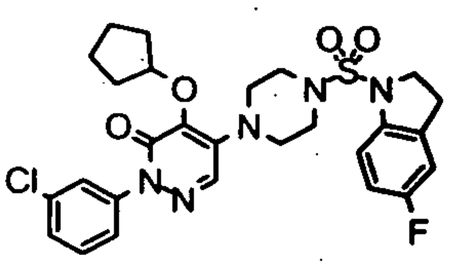
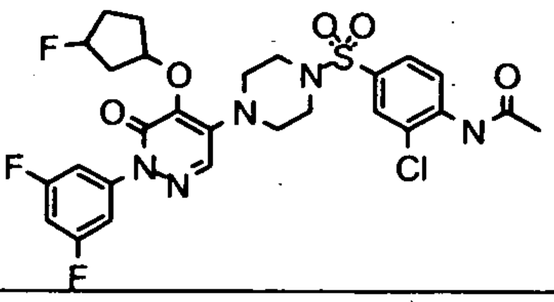
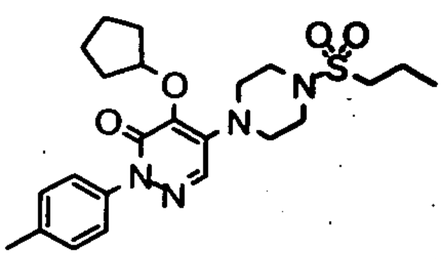
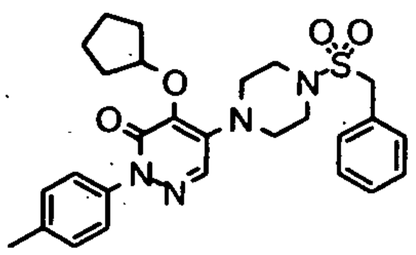
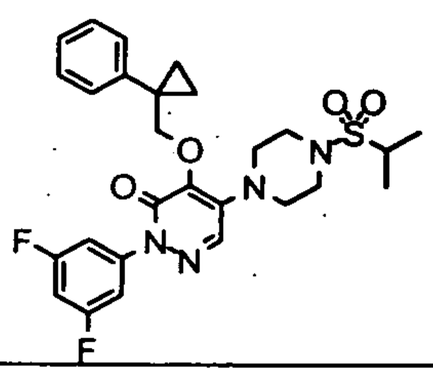
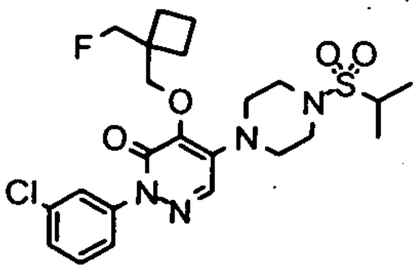
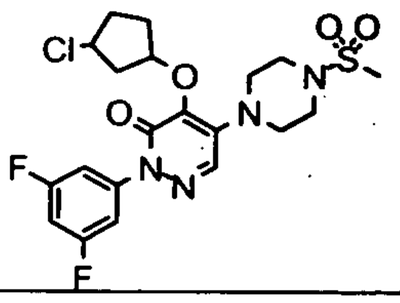
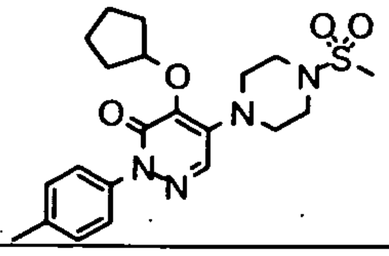
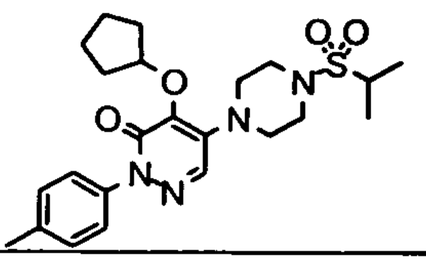
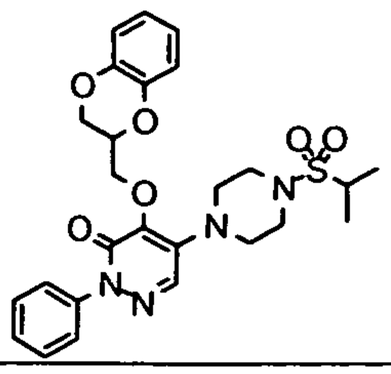
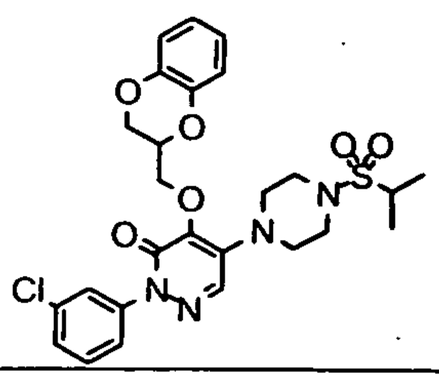
1080Z		575
1081Z		576
1082Z		598
1083Z		549
1084Z		606
1085Z		549
1086Z		513
1087Z		586
1088Z		570
1089Z		567
1090Z		499
1091Z		555
1092Z		527
1093Z		533
1094Z		612
1095Z		612
1096Z		555
1097Z		573

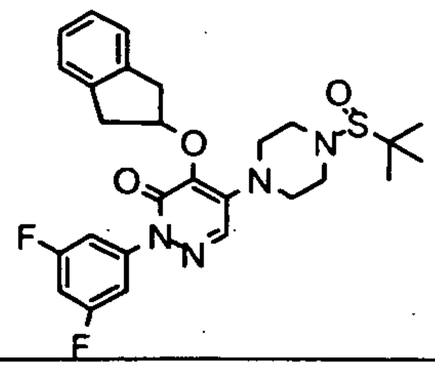
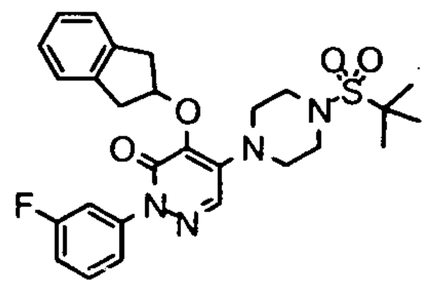
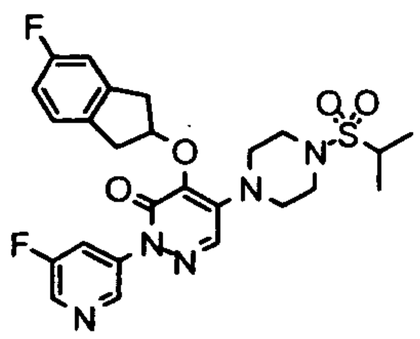
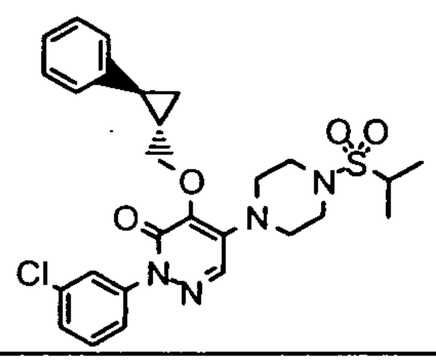
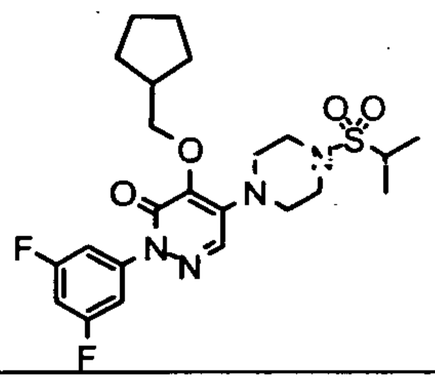
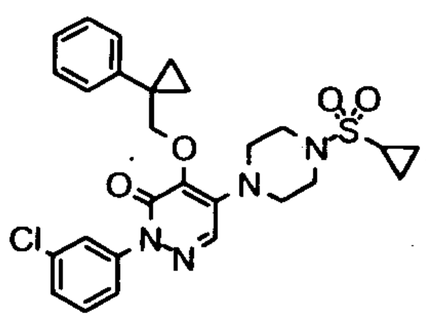
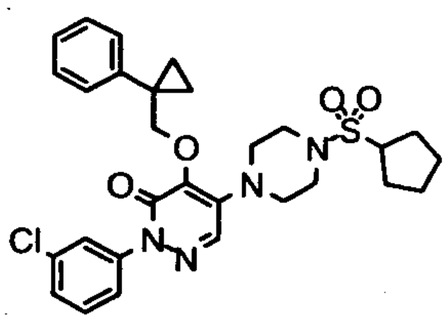
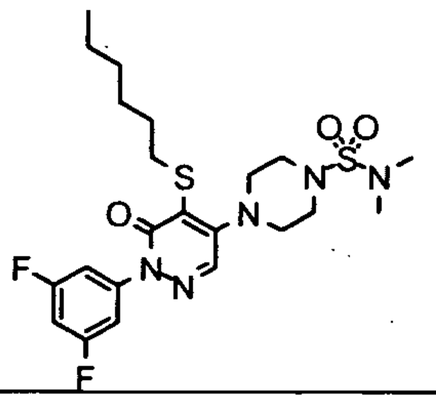
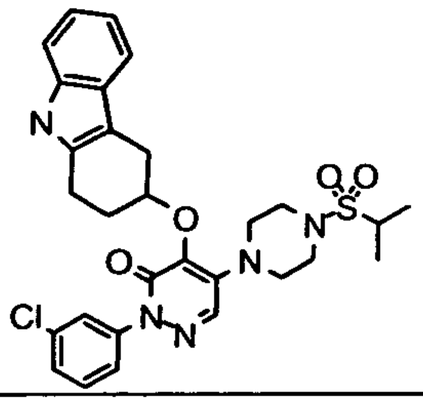
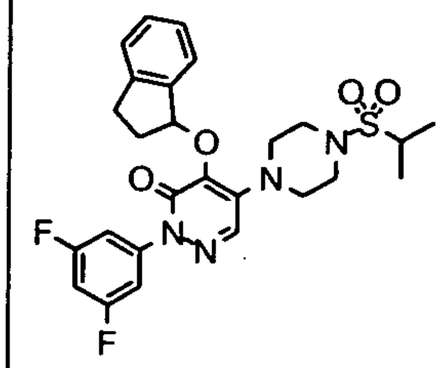
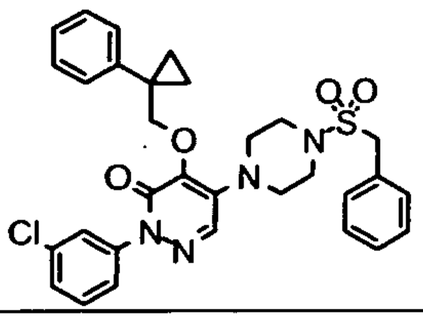
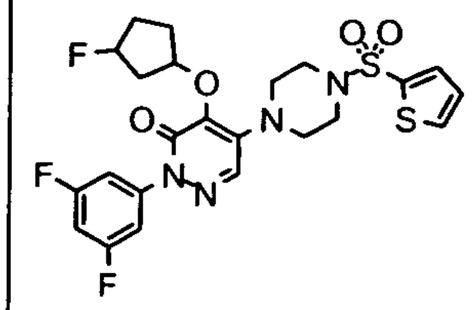
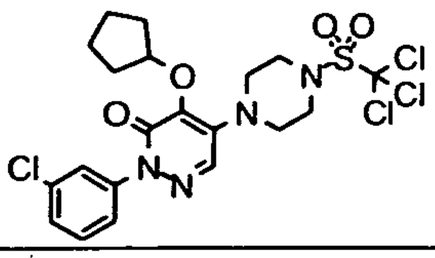
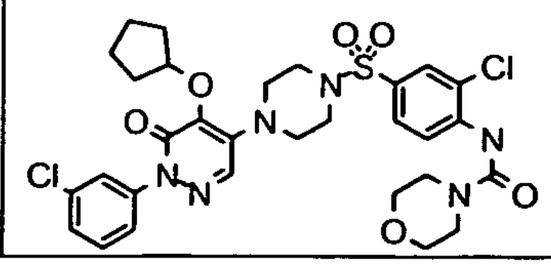
1098Z		505
1100Z		583
1102Z		563
1104Z		584
1106Z		535
1108Z		577
1110Z		449
1112Z		523

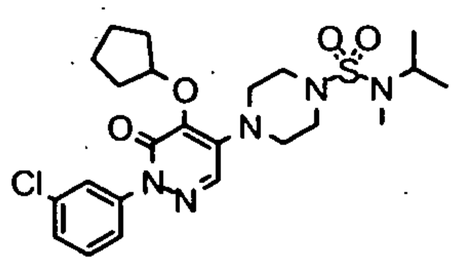
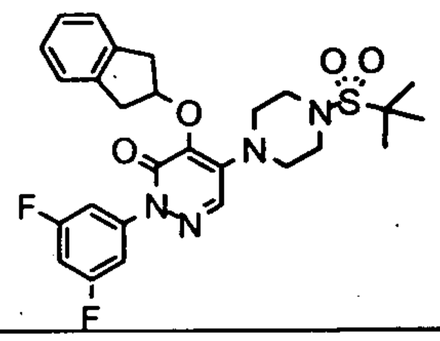
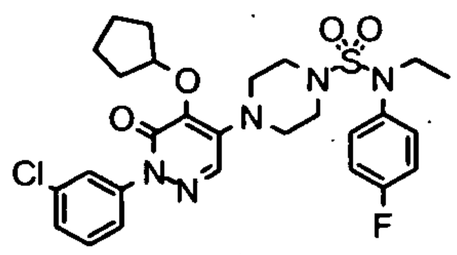
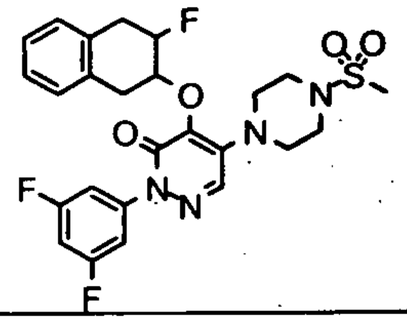
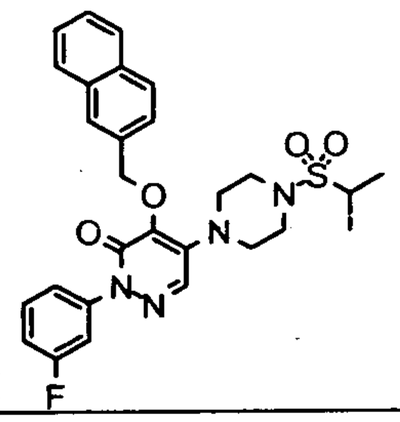
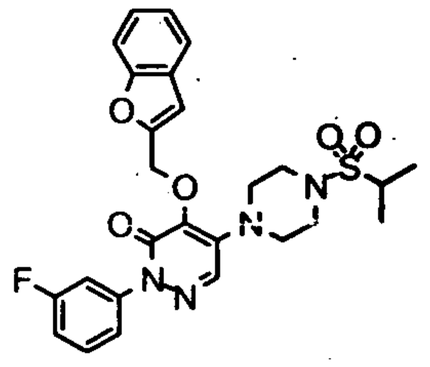
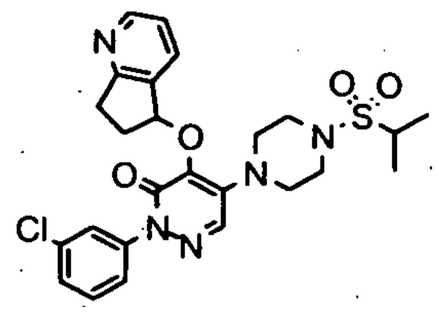
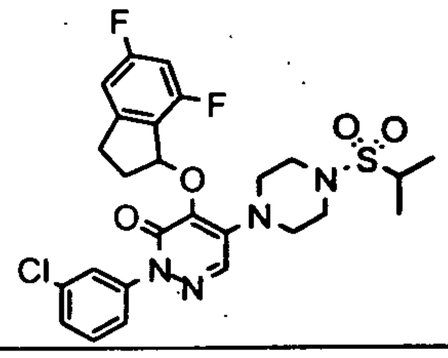
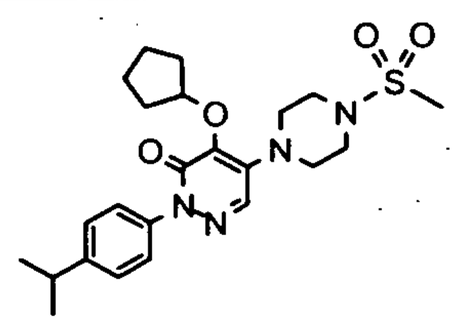
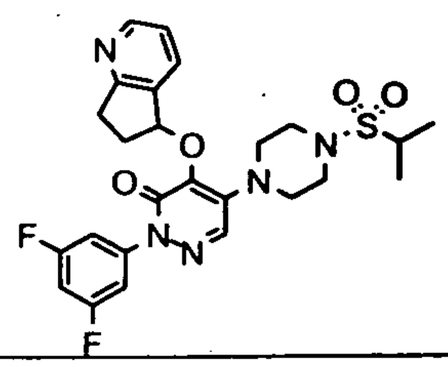
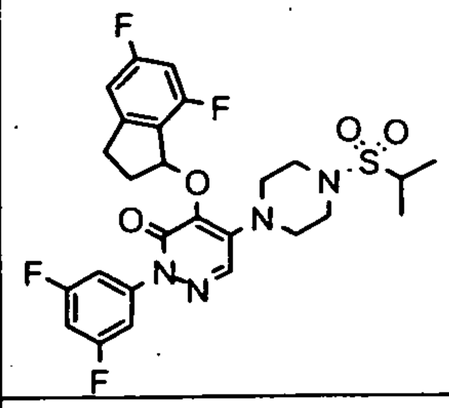
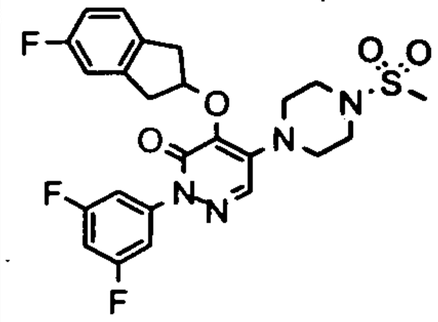
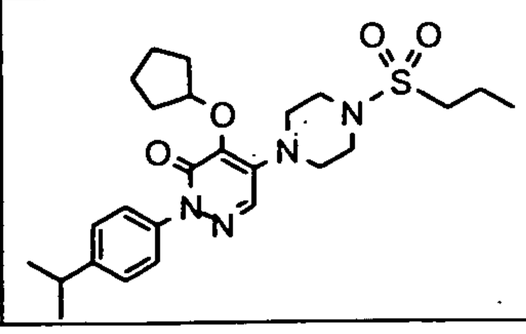
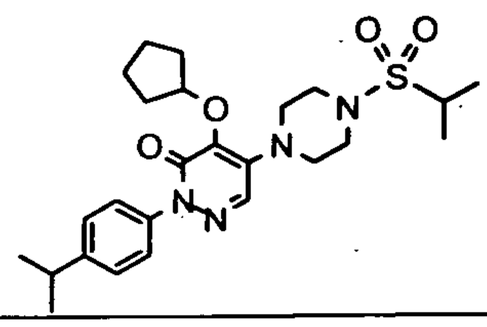
1099Z		598
1101Z		587
1103Z		549
1105Z		621
1107Z		564
1109Z		485
1111Z		477
1113Z		561

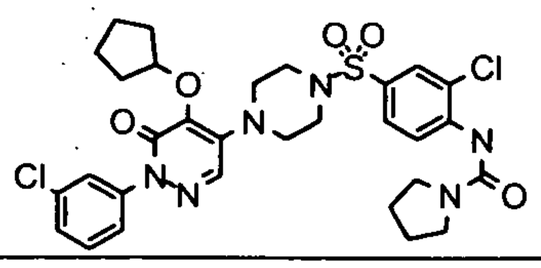
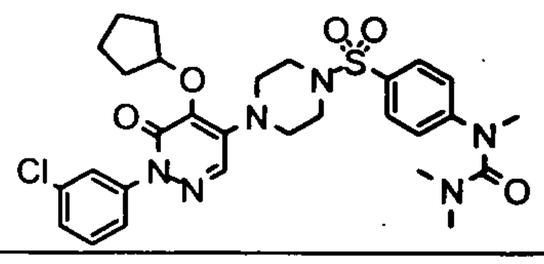
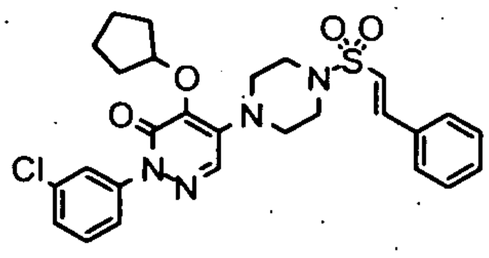
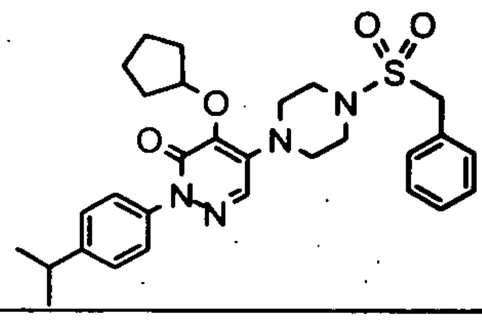
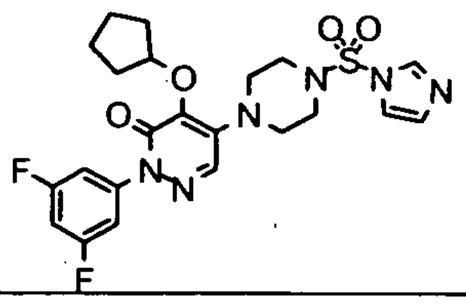
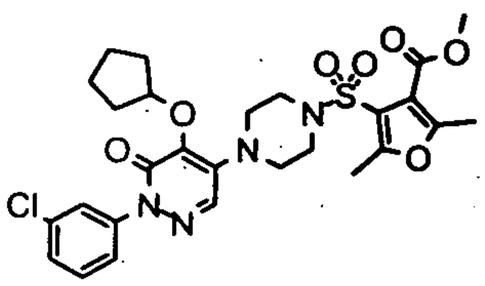
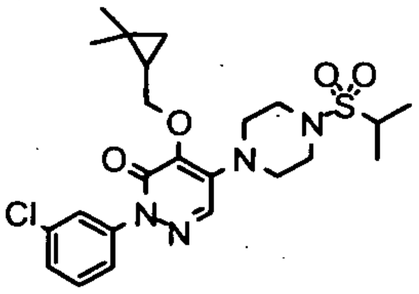
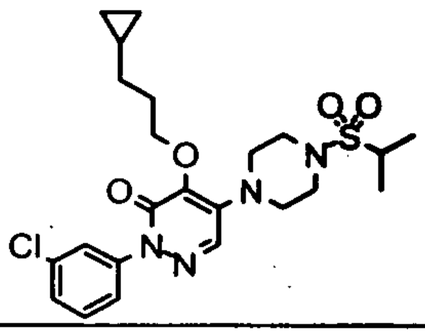
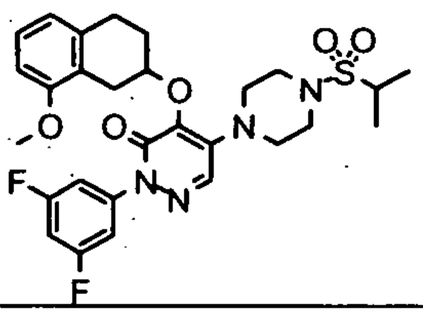
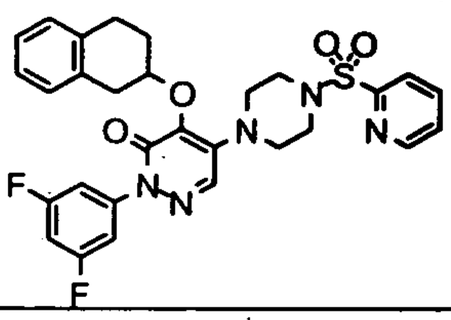
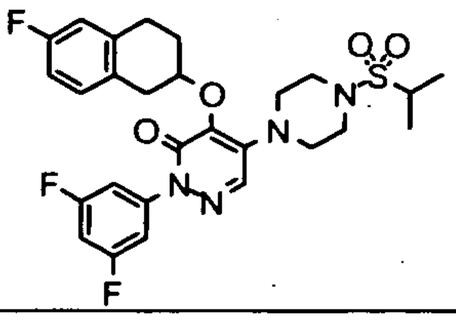
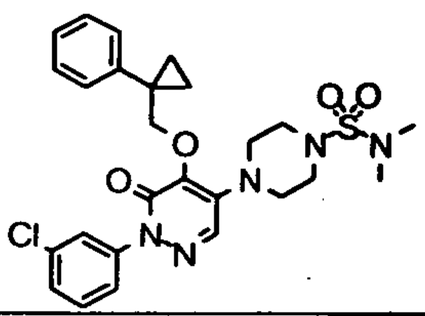
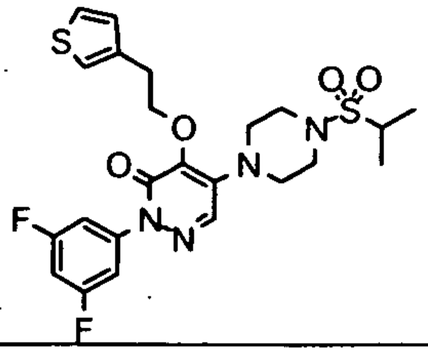
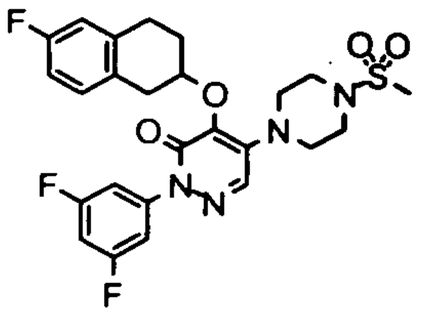
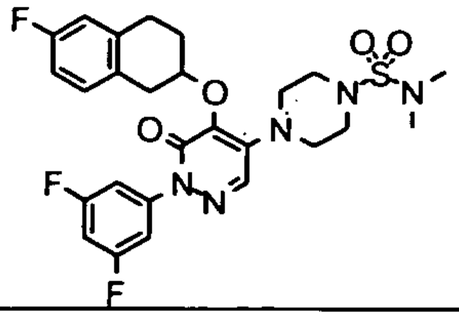
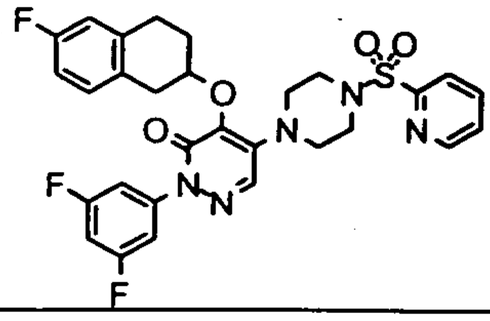
1114Z		477
1115Z		525
1116Z		524
1117Z		498
1118Z		471
1119Z		525
1120Z		523
1121Z		501
1122Z		547
1123Z		500
1124Z		523
1125Z		608
1126Z		507
1127Z		522
1128Z		623
1129Z		601

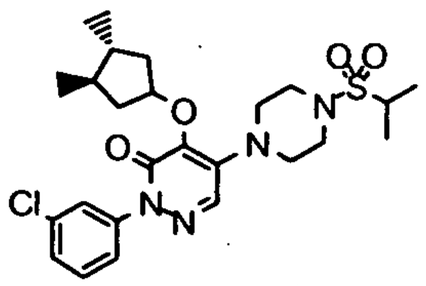
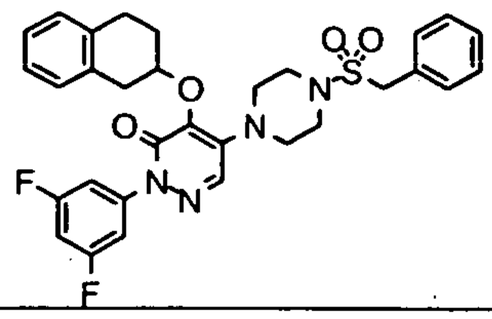
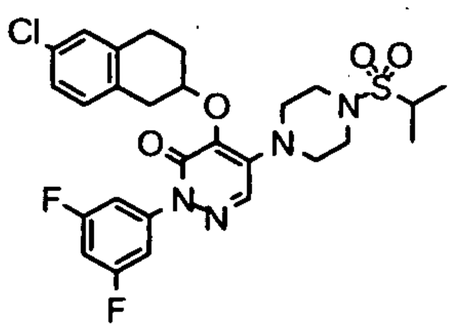
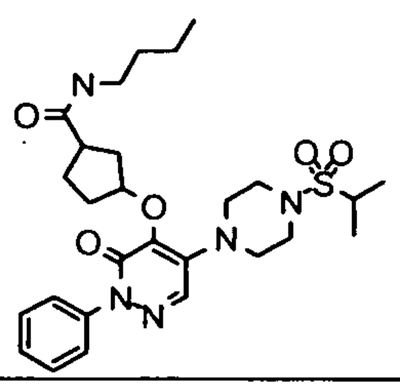
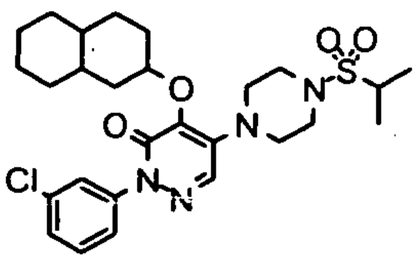
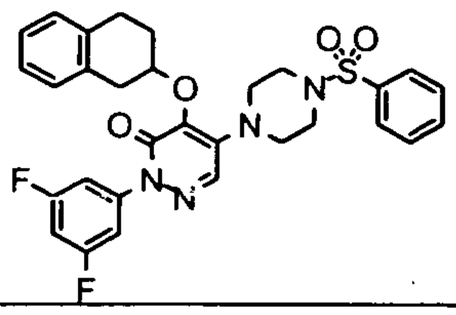
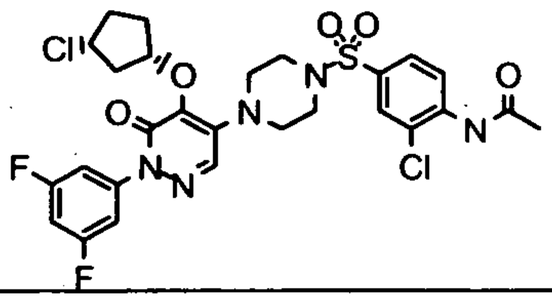
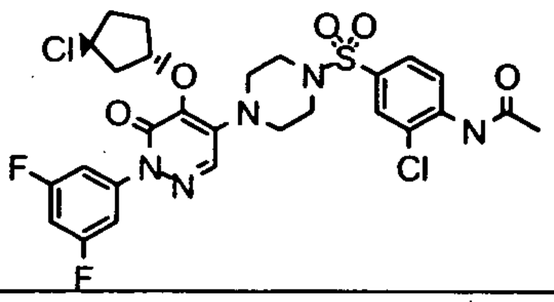
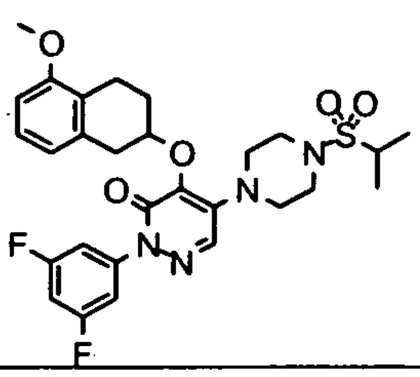
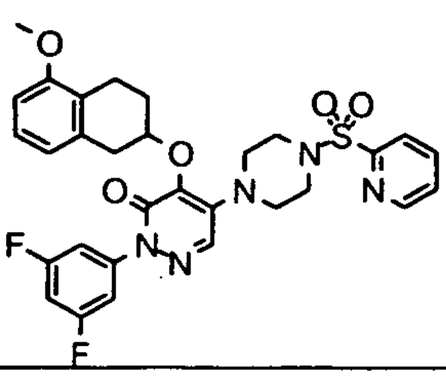
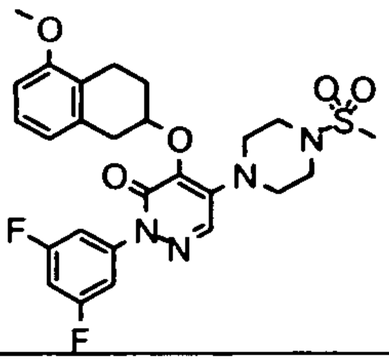
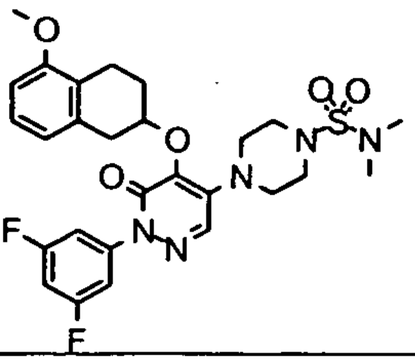
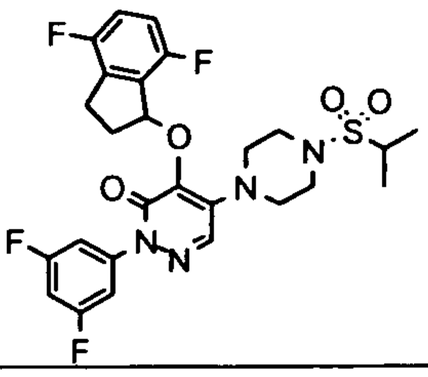
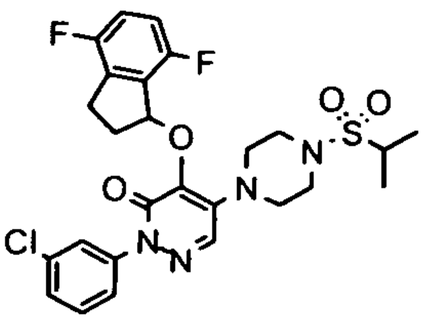
1130Z		471
1131Z		547
1132Z		607
1133Z		501
1134Z		501
1135Z		549
1136Z		475
1137Z		523
1138Z		555
1139Z		593
1140Z		447
1141Z		475
1142Z		469
1143Z		531
1144Z		517
1145Z		511

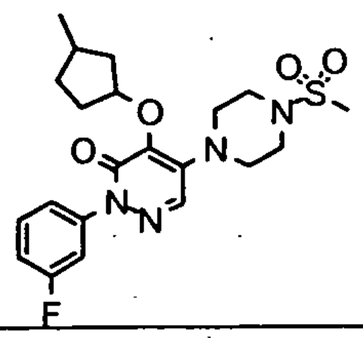
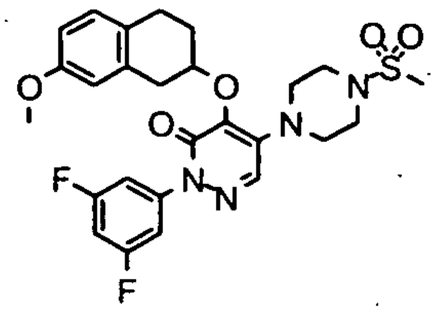
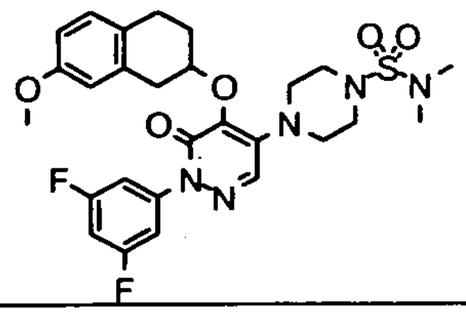
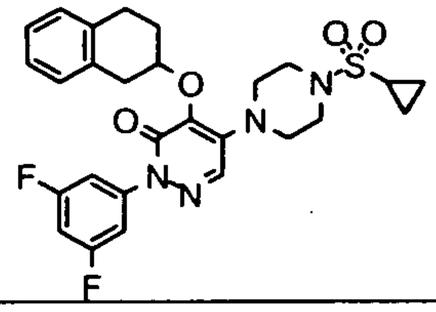
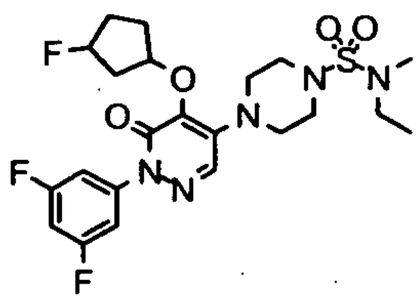
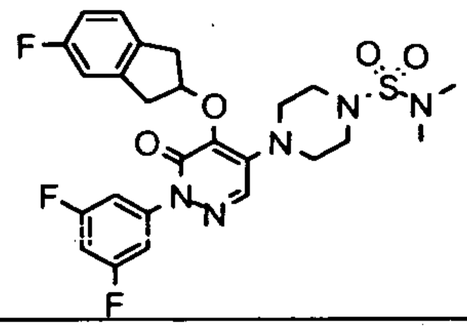
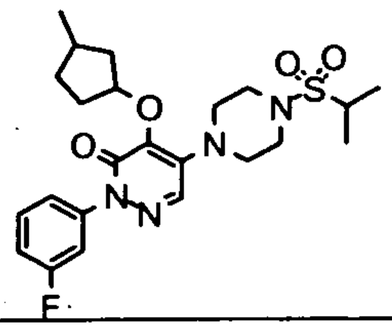
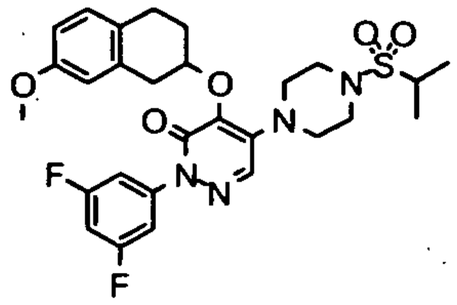
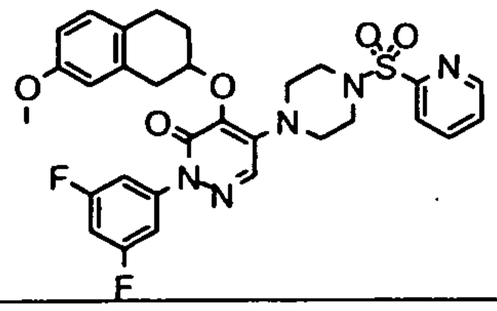
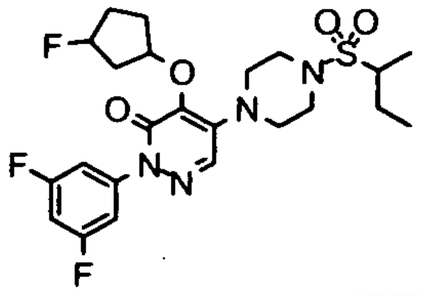
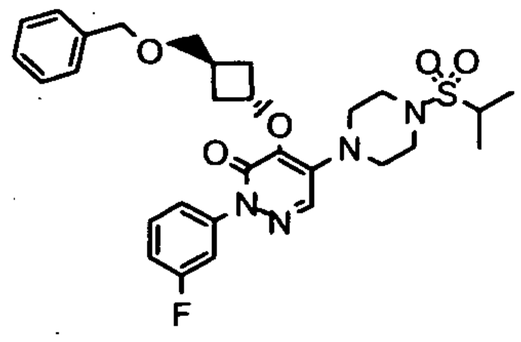
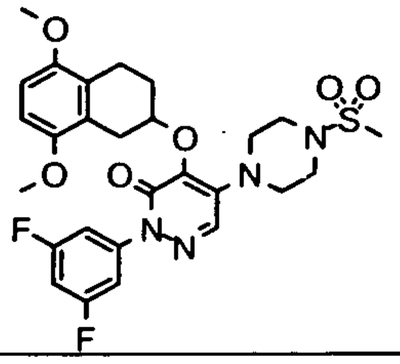
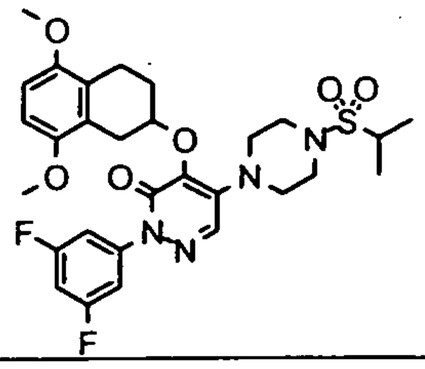
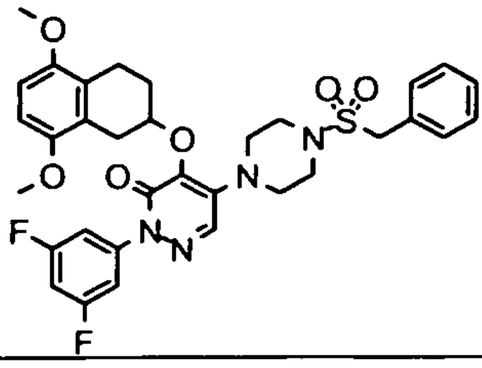
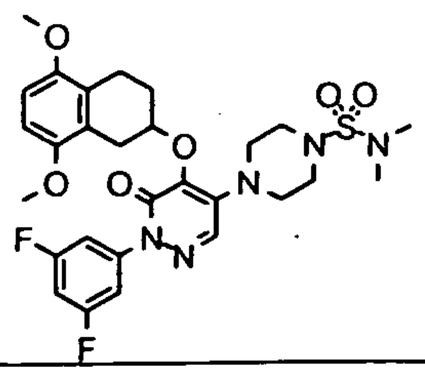
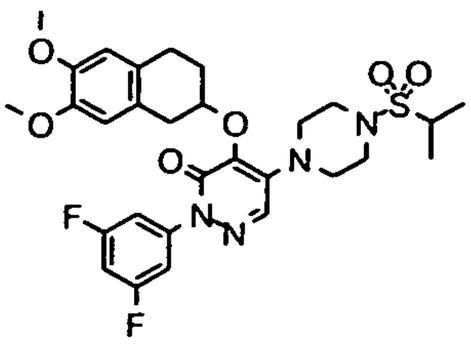
1146Z		547
1147Z		545
1148Z		549
1149Z		546
1150Z		515
1151Z		574
1152Z		626
1153Z		461
1154Z		509
1155Z		545
1156Z		513
1157Z		489
1158Z		433
1159Z		461
1160Z		527
1161Z		561

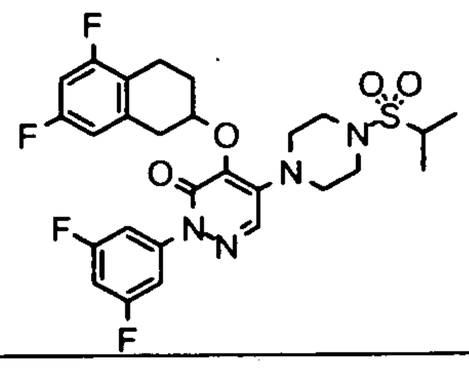
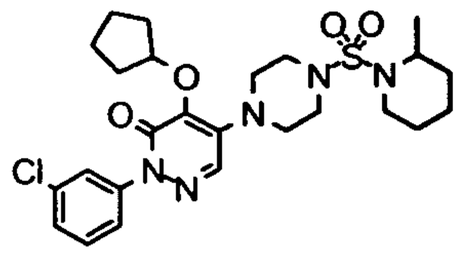
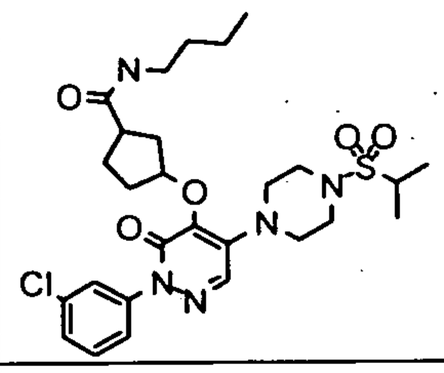
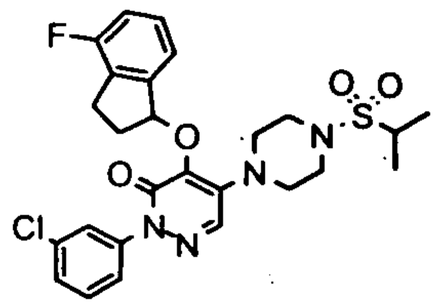
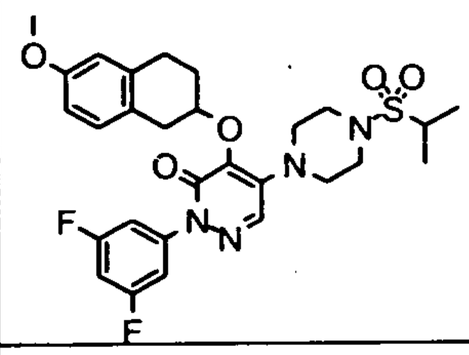
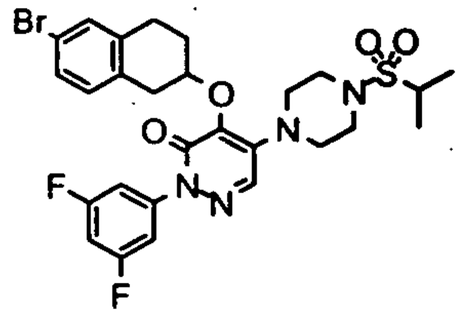
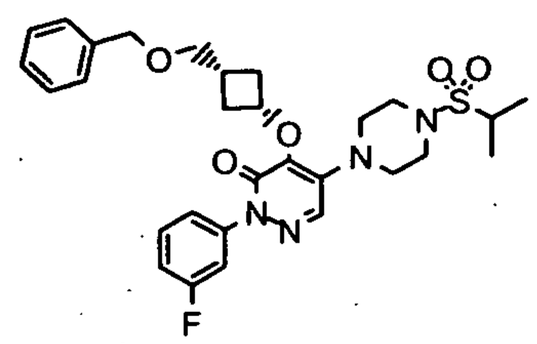
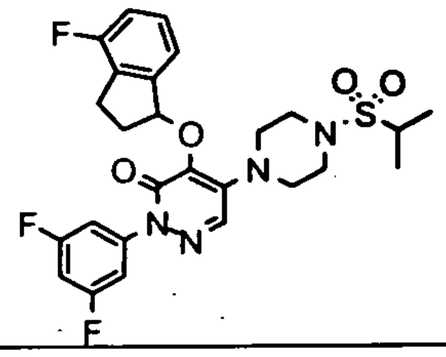
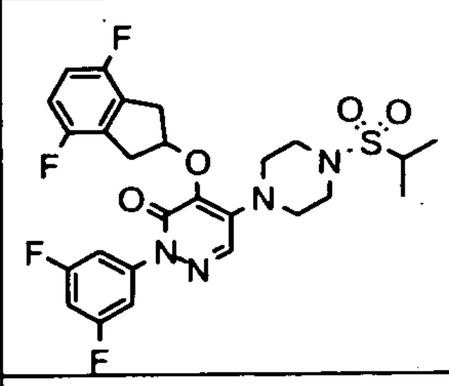
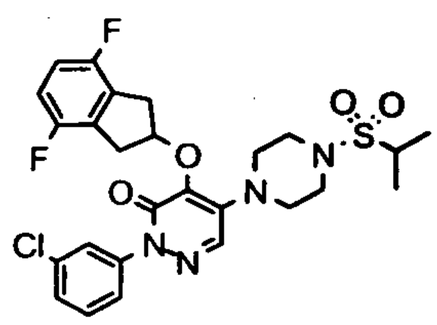
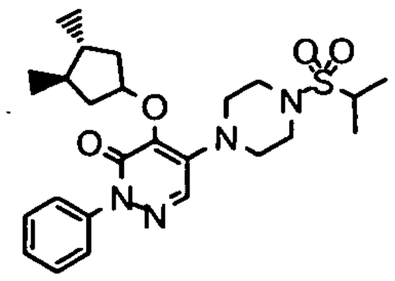
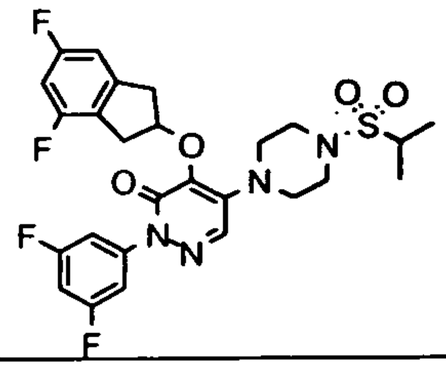
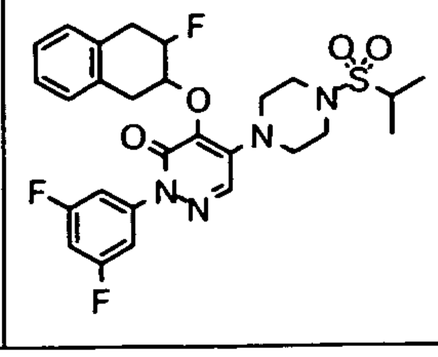
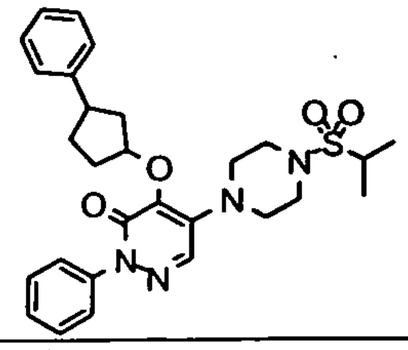
1162Z		529
1163Z		527
1164Z		532
1165Z		543
1166Z		497
1167Z		541
1168Z		569
1169Z		516
1170Z		582
1171Z		529 (M-H)
1172Z		591
1173Z		541
1174Z		555
1175Z		677

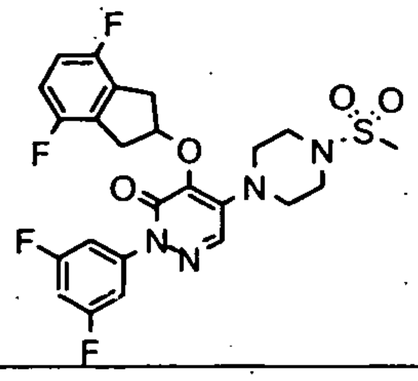
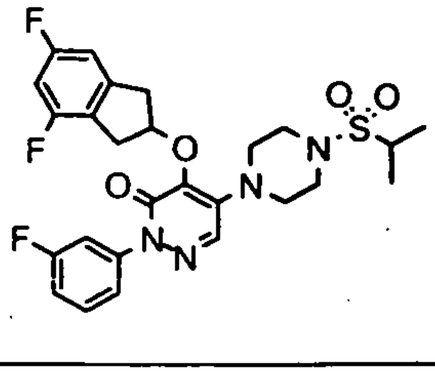
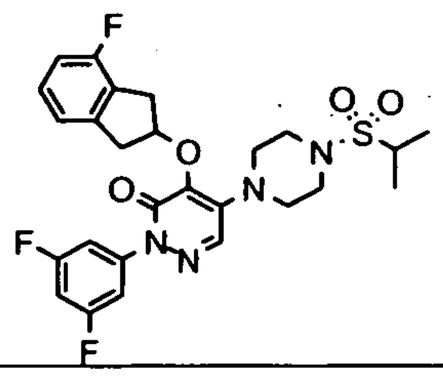
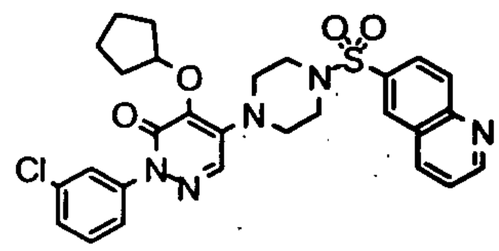
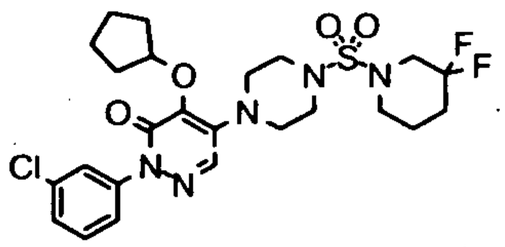
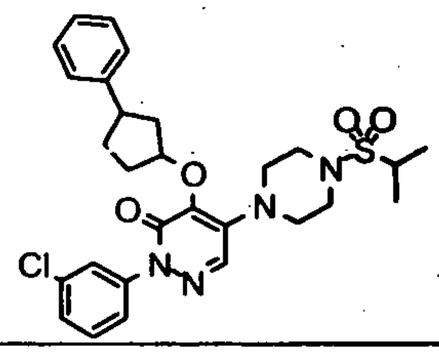
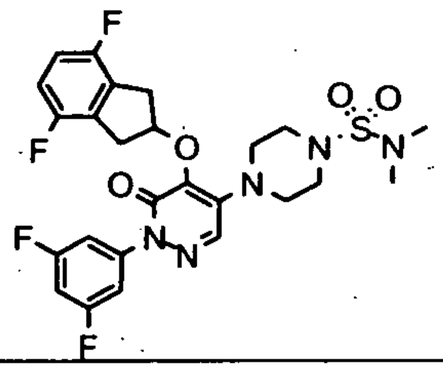
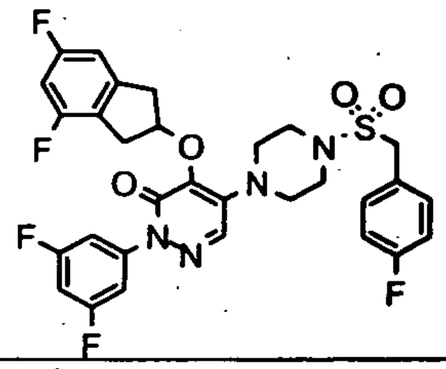
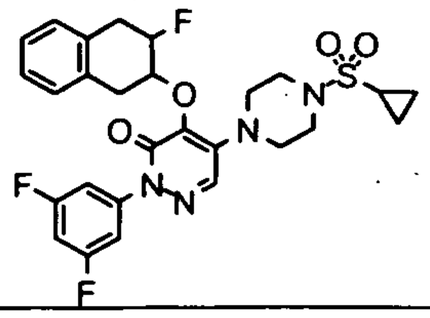
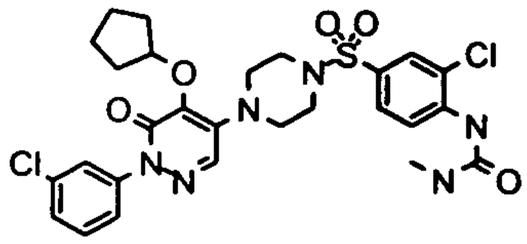
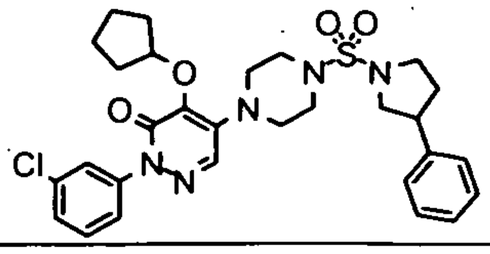
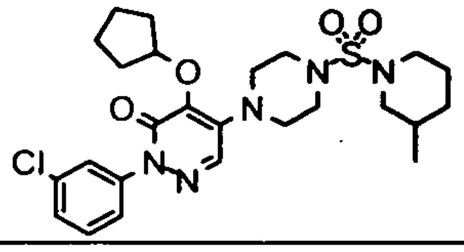
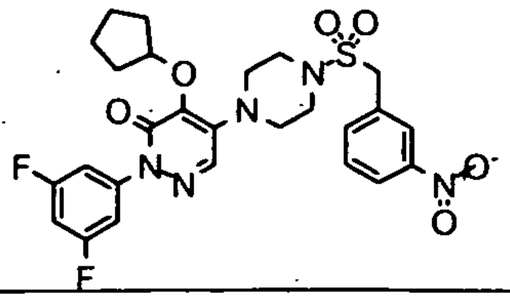
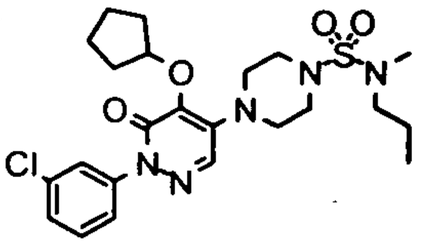
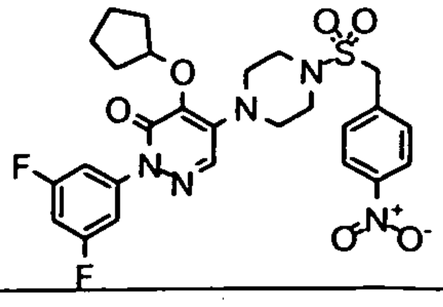
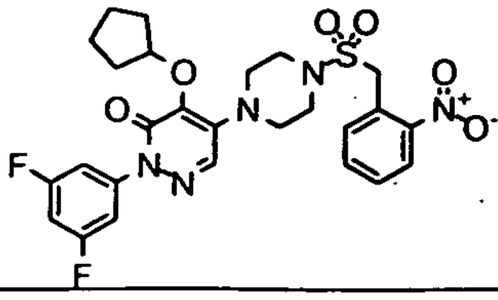
1176Z		510
1177Z		545
1178Z		576
1179Z		535
1180Z		537
1181Z		527
1182Z		530
1183Z		565
1184Z		461
1185Z		532
1186Z		567
1187Z		521
1188Z		489
1189Z		489

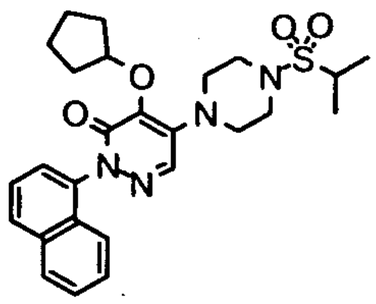
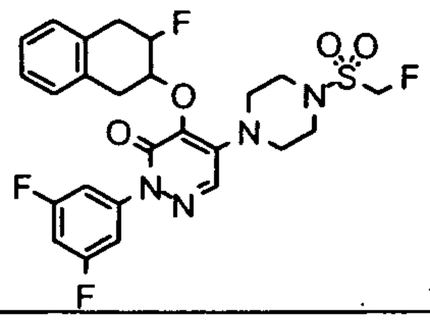
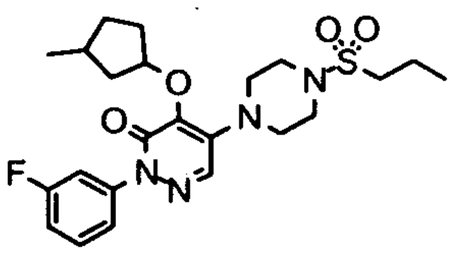
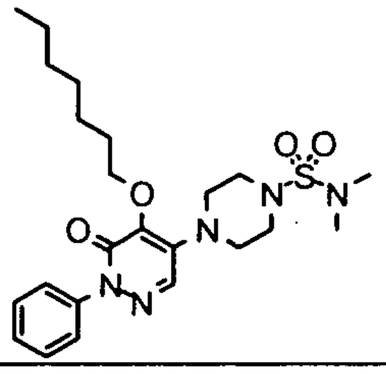
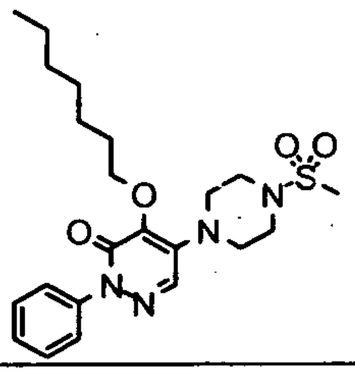
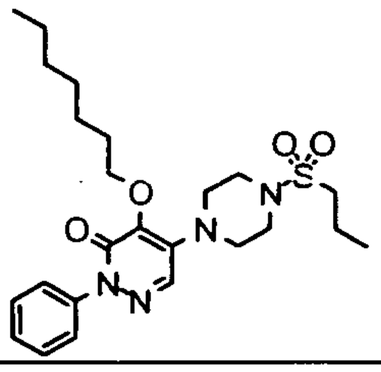
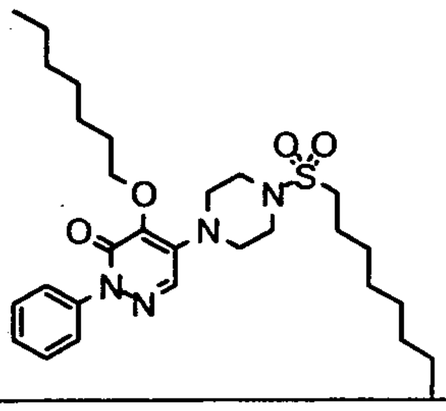
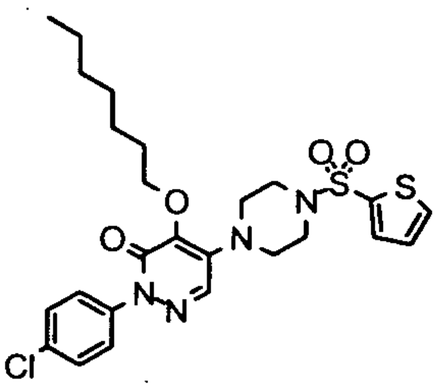
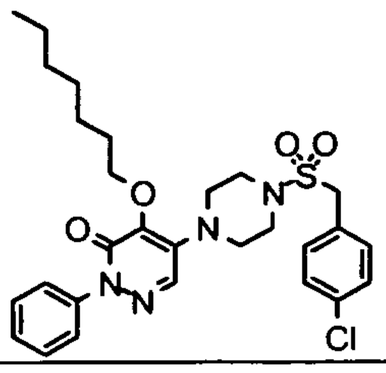
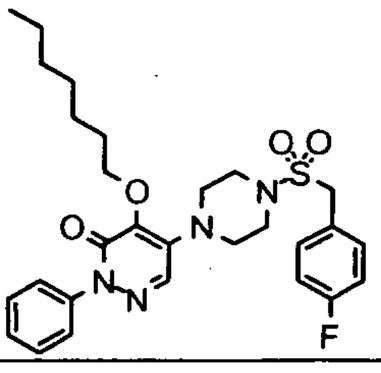
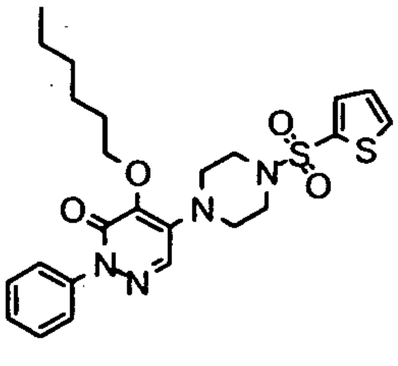
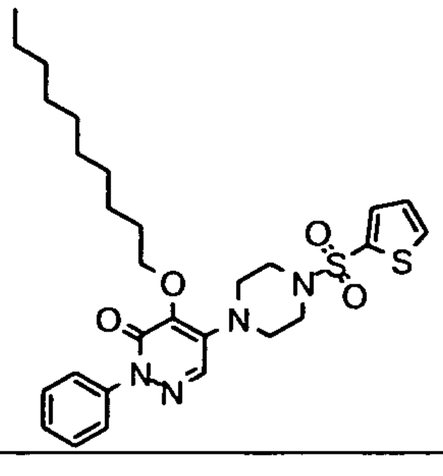
1190Z		677 (M+OH)
1191Z		616
1192Z		541
1193Z		537
1194Z		507
1195Z		592
1196Z		495
1197Z		495
1198Z		575
1199Z		580
1200Z		563
1201Z		544
1202Z		525
1203Z		535
1204Z		564
1205Z		598

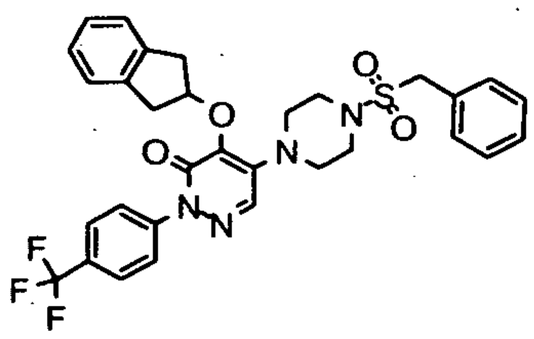
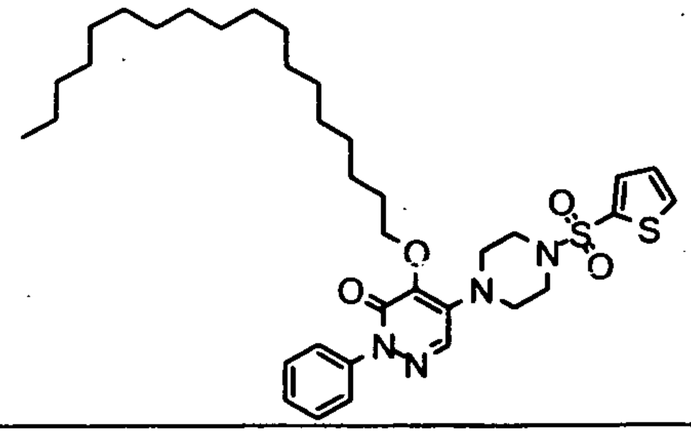
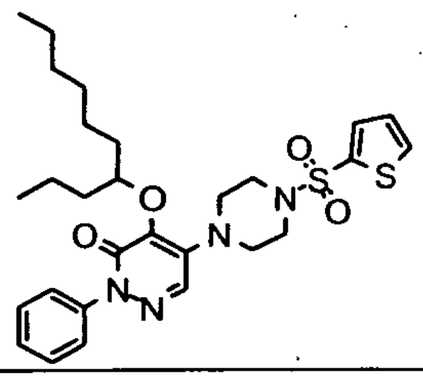
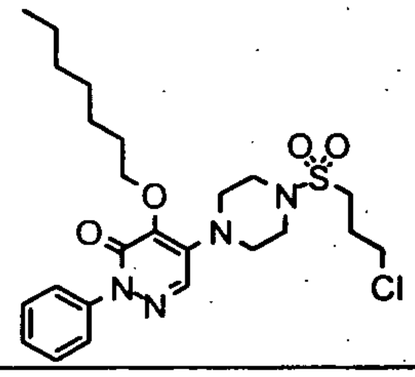
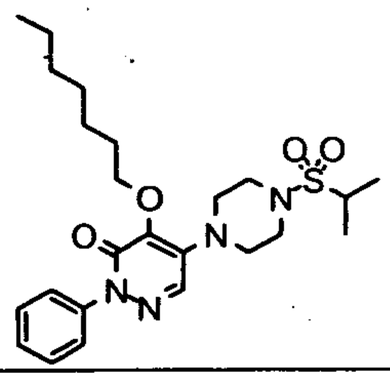
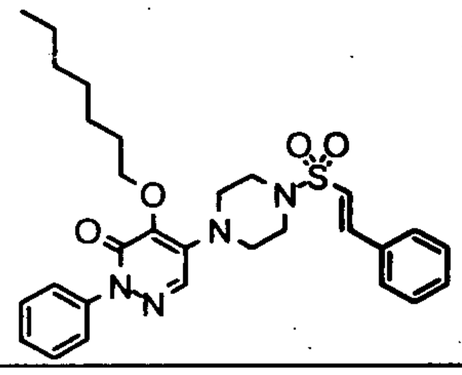
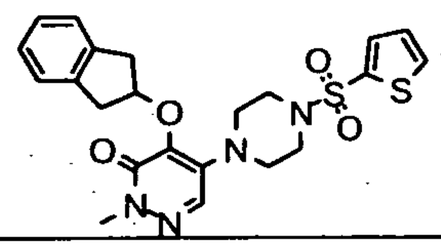
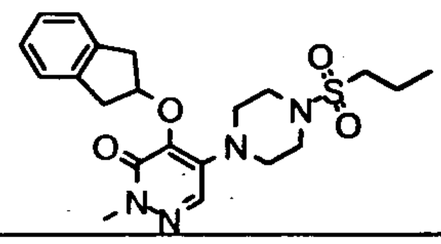
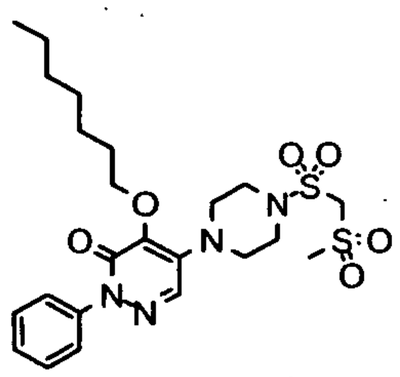
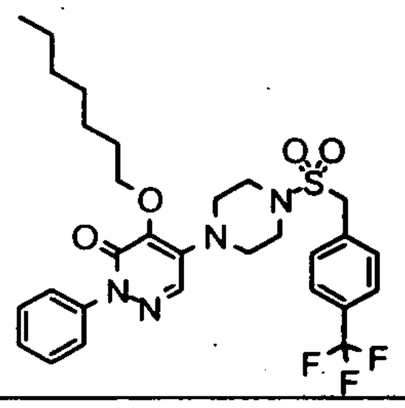
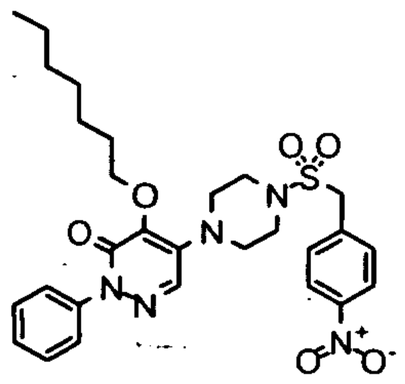
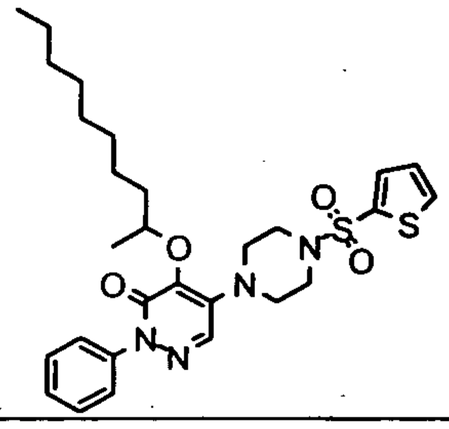
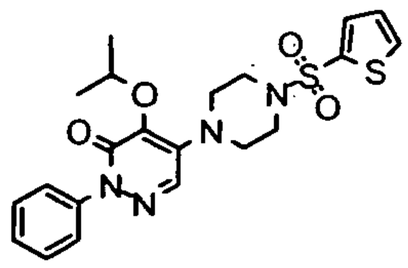
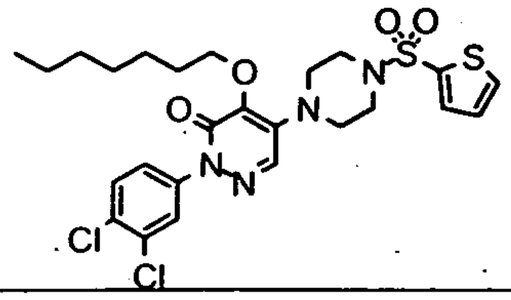
1206Z		509
1207Z		593
1208Z		579
1209Z		546
1210Z		549
1211Z		579
1212Z		642
1213Z		642
1214Z		575
1215Z		610
1216Z		547
1217Z		576
1218Z		567
1219Z		565

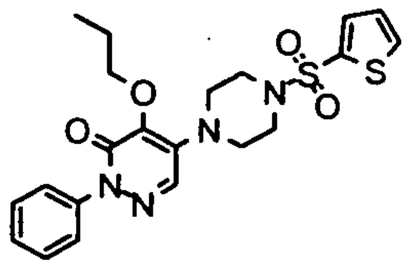
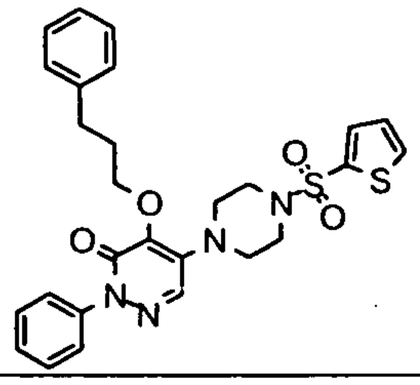
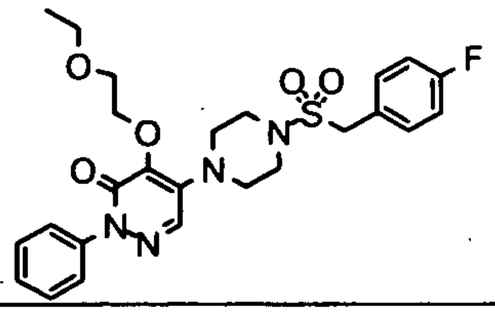
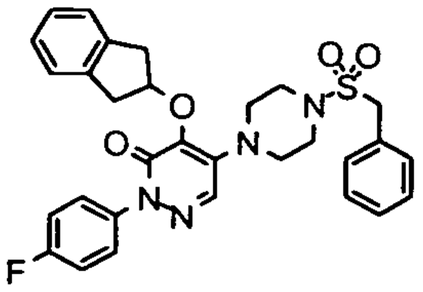
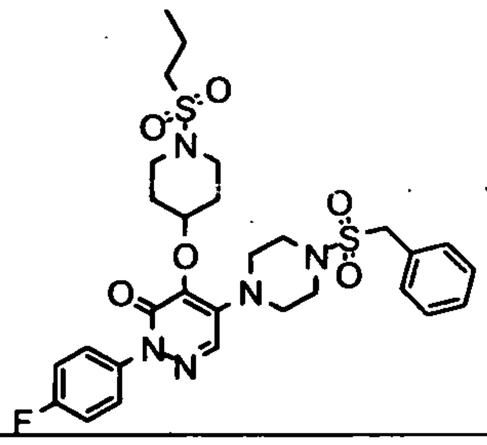
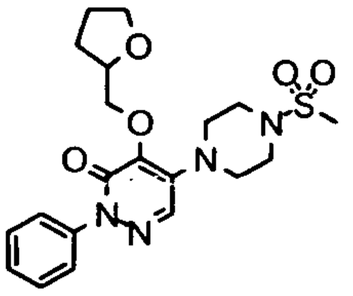
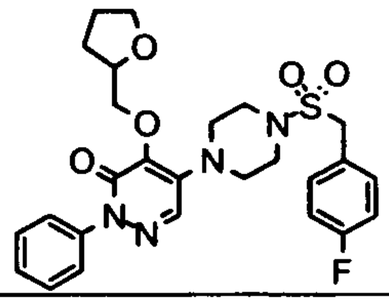
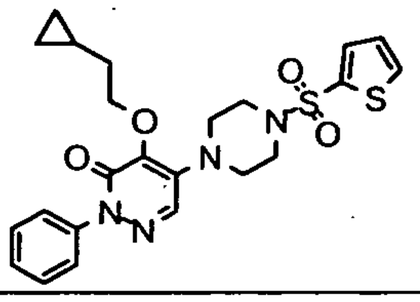
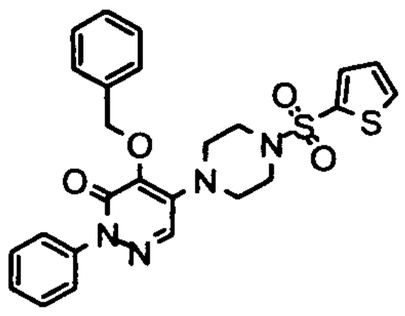
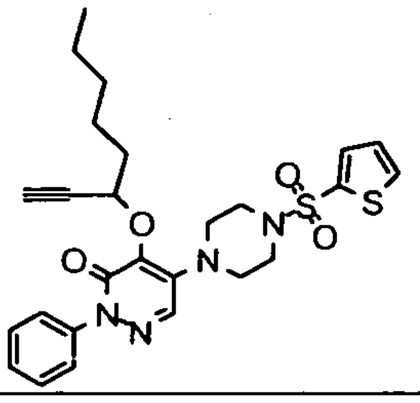
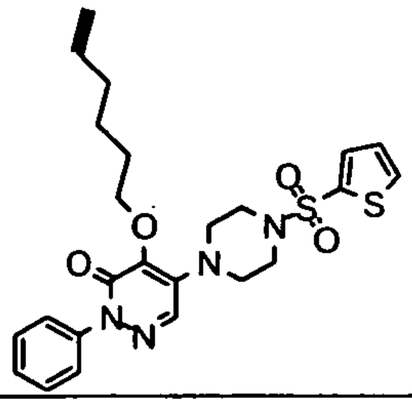
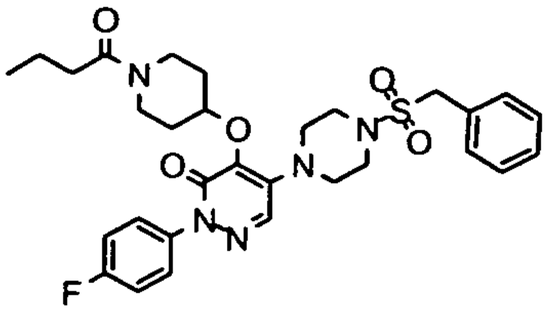
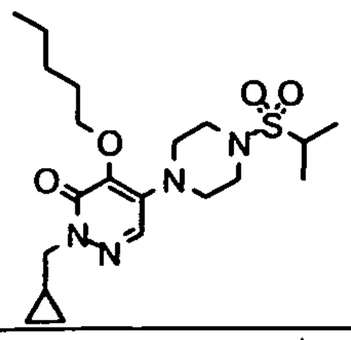
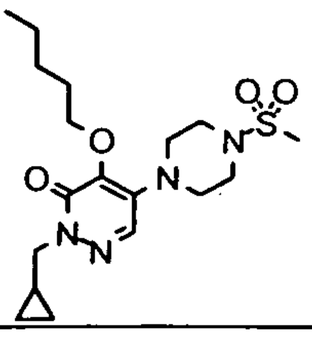
1220Z		451
1221Z		547
1222Z		576
1223Z		543
1224Z		516
1225Z		550
1226Z		479
1227Z		575
1228Z		610
1229Z		515
1230Z		571
1231Z		577
1232Z		605
1233Z		653
1234Z		606
1235Z		605

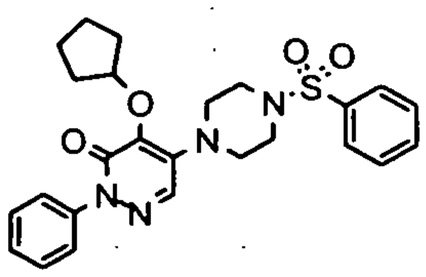
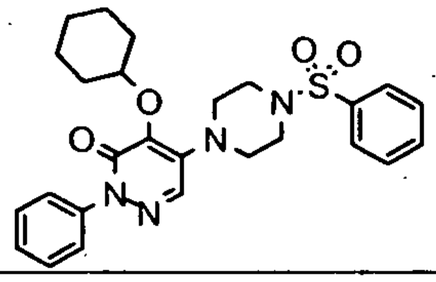
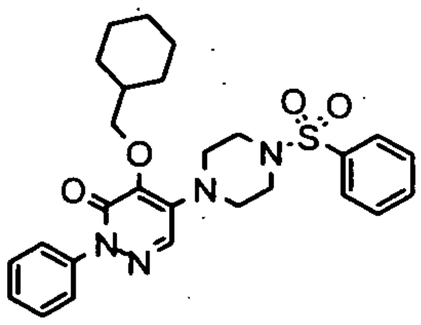
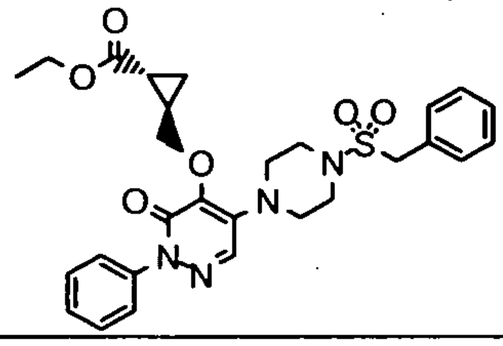
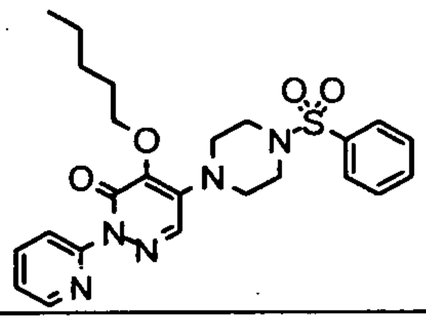
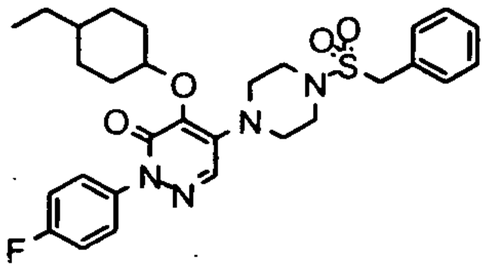
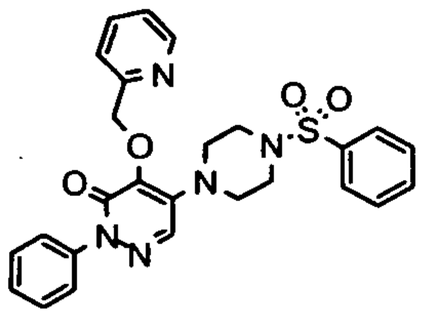
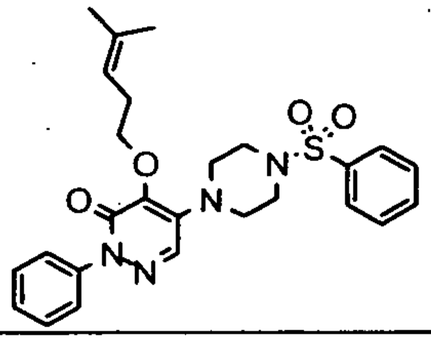
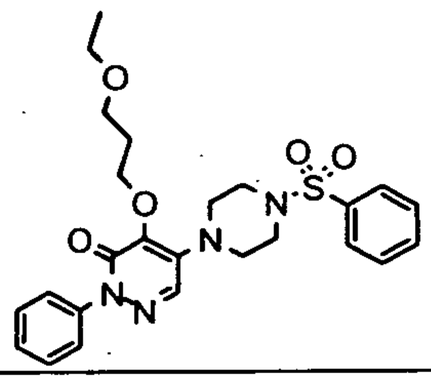
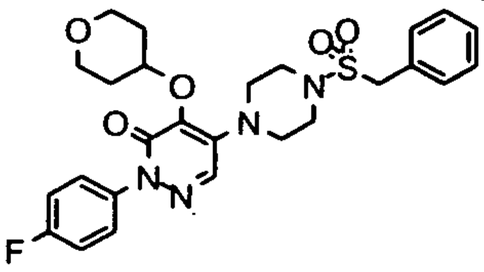
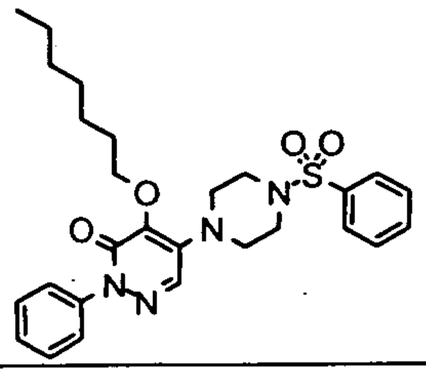
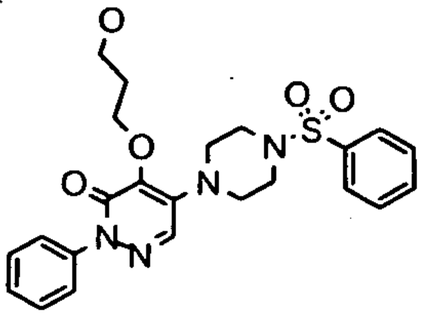
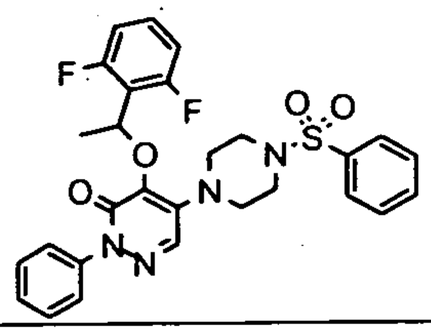
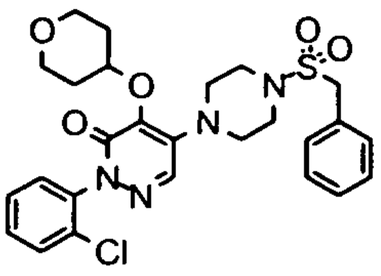
1236Z		581
1237Z		536
1238Z		580
1239Z		547
1240Z		575
1241Z		623
1242Z		571
1243Z		549
1244Z		567
1245Z		565
1246Z		475
1247Z		567
1248Z		563
1249Z		523

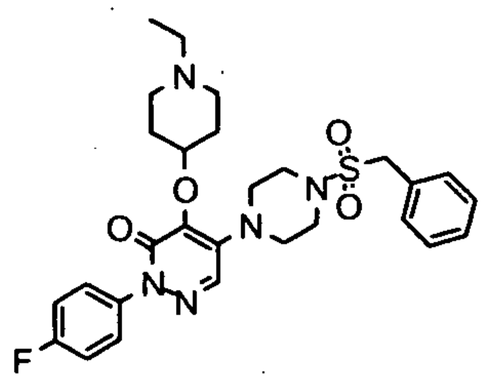
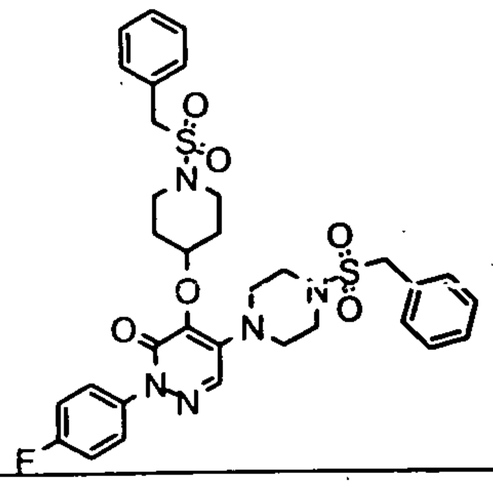
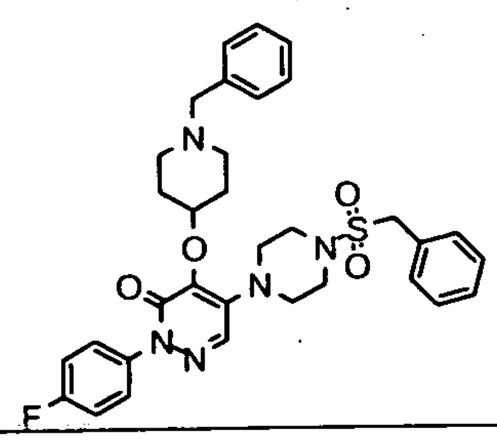
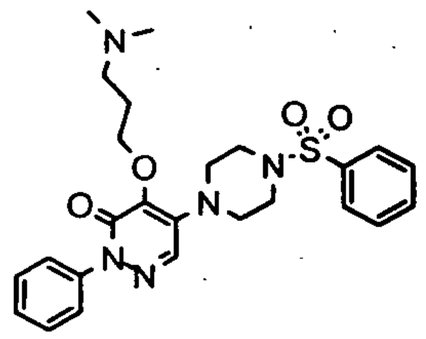
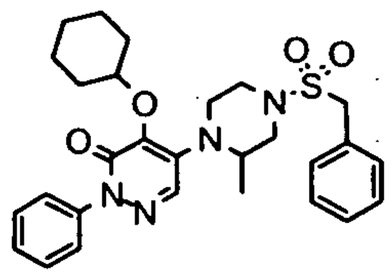
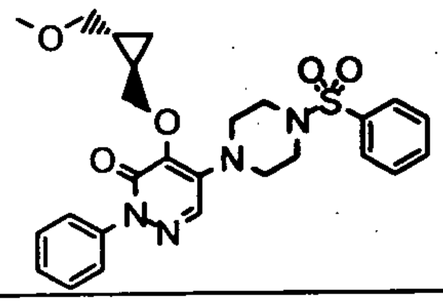
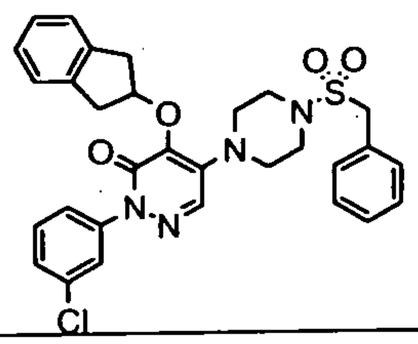
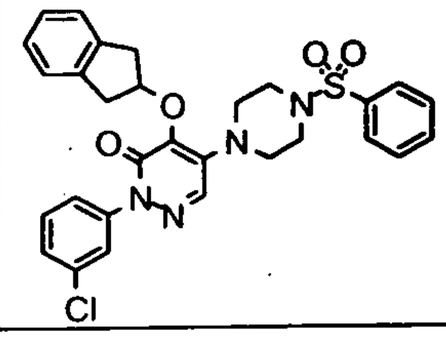
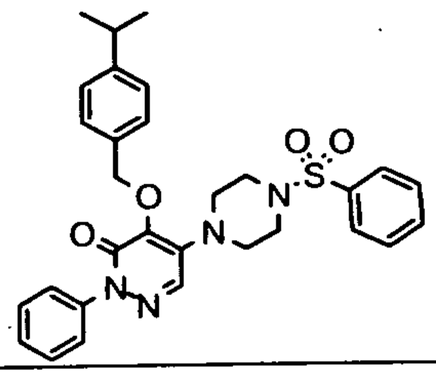
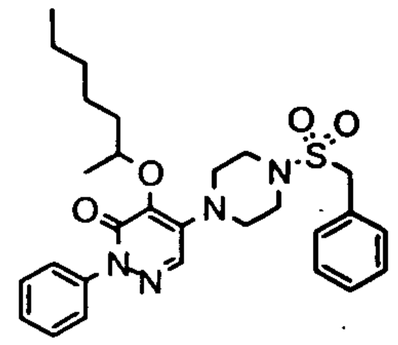
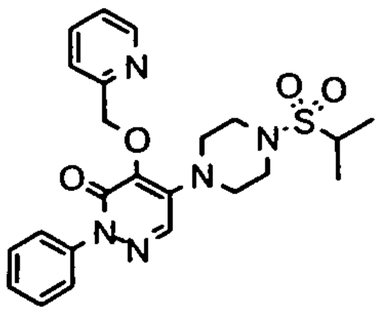
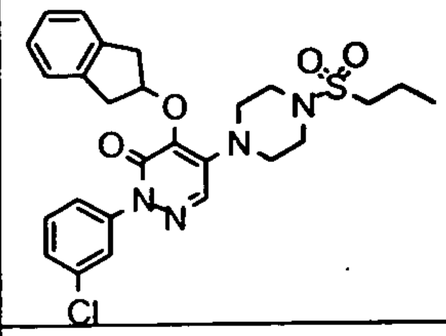
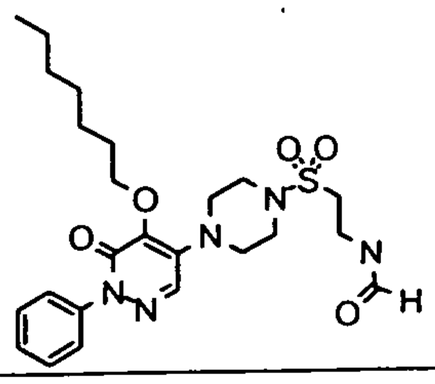
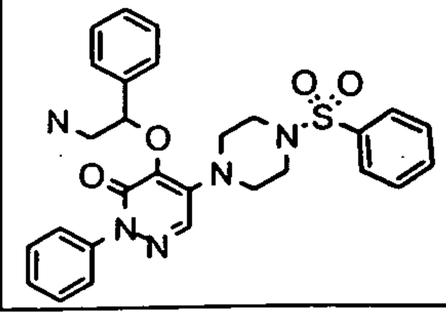
1250Z		539
1251Z		549
1252Z		549
1253Z		566
1254Z		559
1255Z		557
1256Z		568
1257Z		633
1258Z		561
1259Z		621
1260Z		584
1261Z		536
1262Z		576
1263Z		510
1264Z		576
1265Z		576

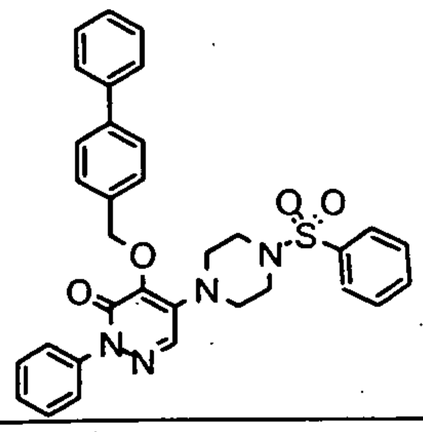
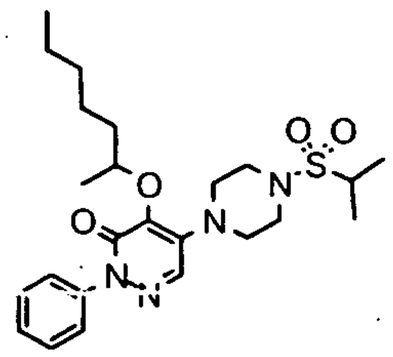
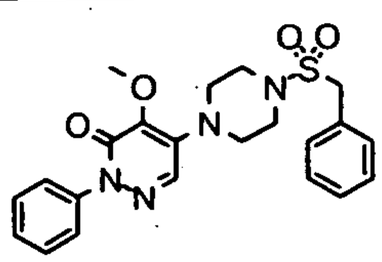
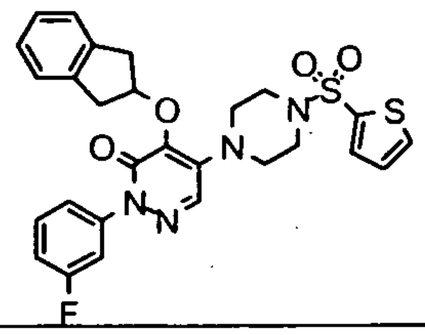
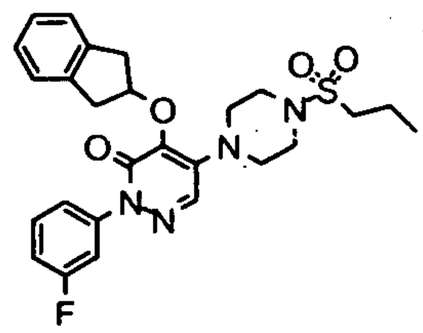
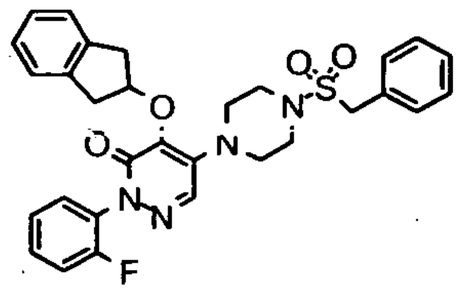
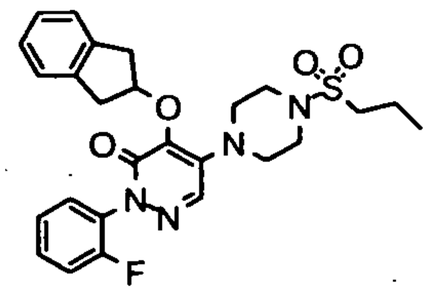
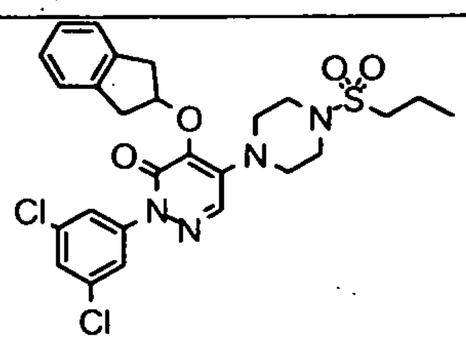
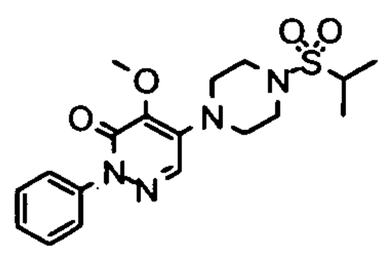
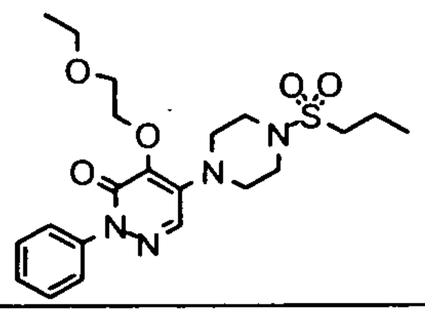
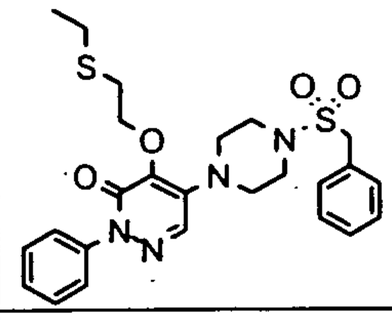
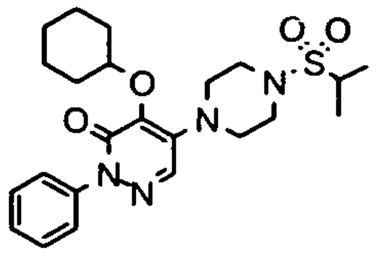
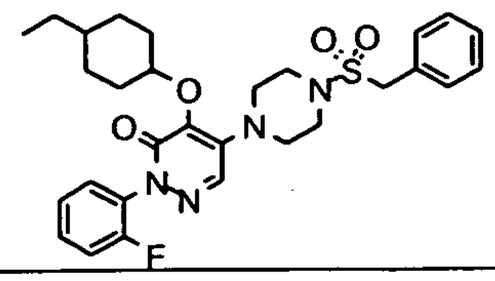
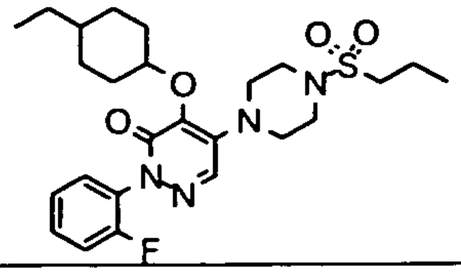
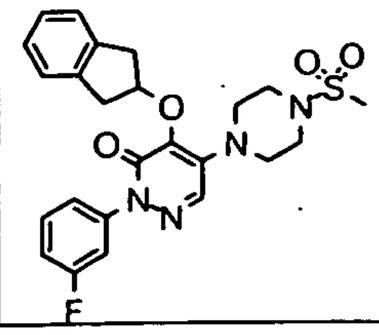
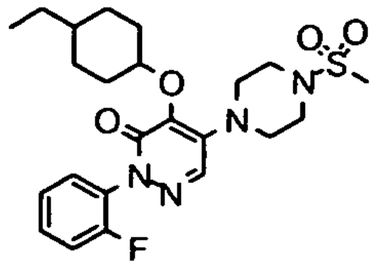
1266Z		497
1267Z		553
1268Z		479
1269Z		478
1270Z		449
1271Z		477
1272Z		547
1273Z		551
1274Z		559
1275Z		543
1276Z		503
1277Z		559

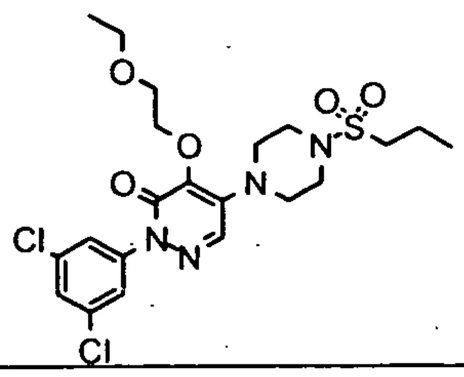
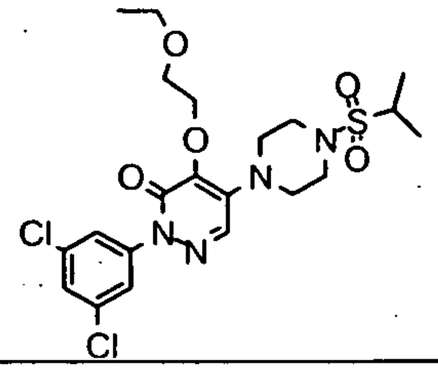
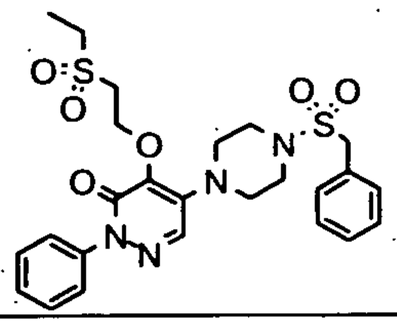
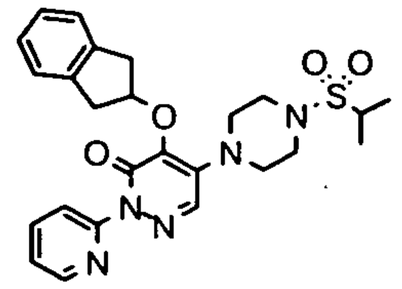
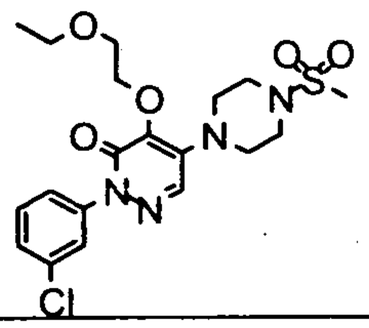
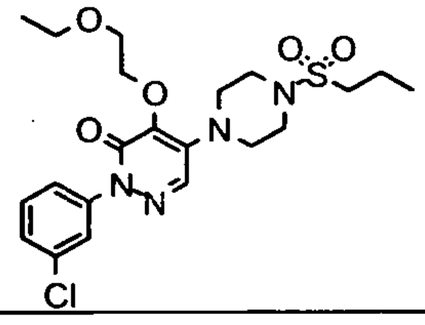
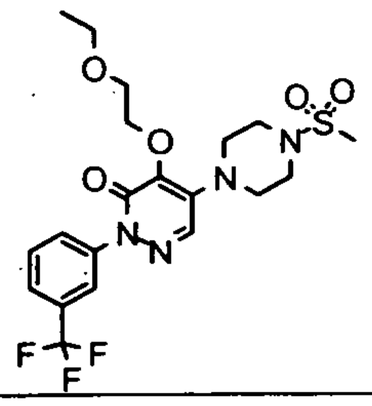
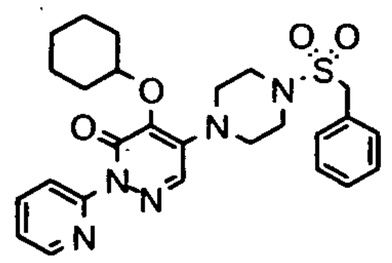
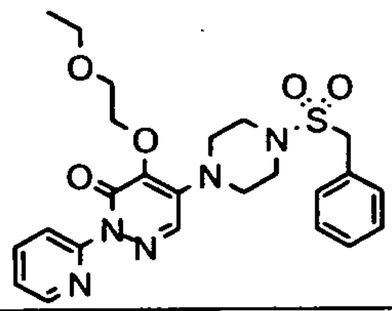
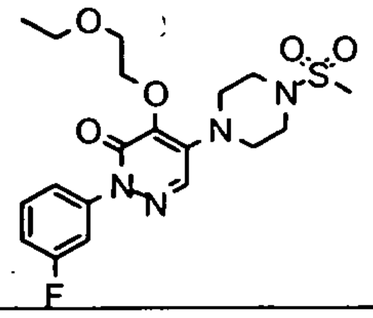
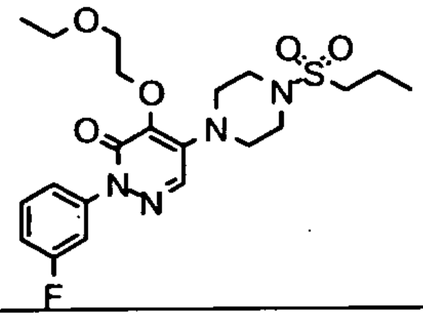
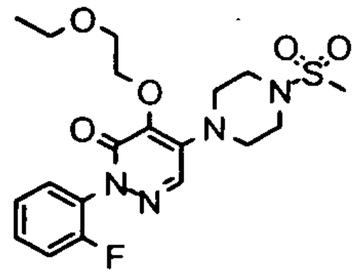
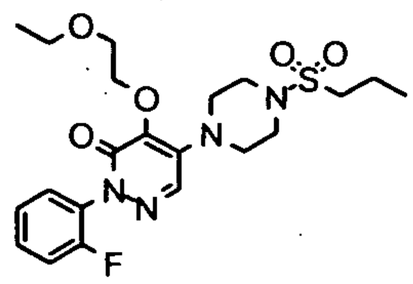
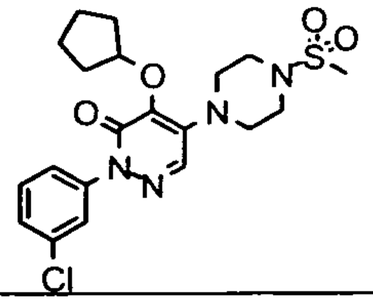
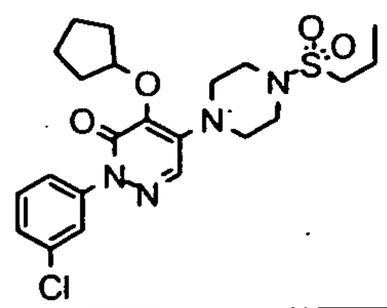
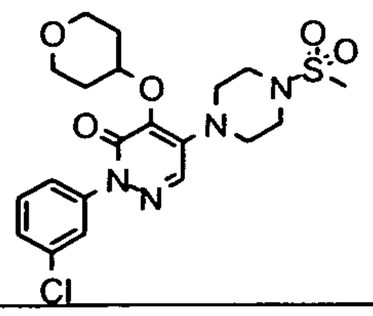
1278Z		611
1279Z		671
1280Z		559
1281Z		511
1282Z		477
1283Z		537
1284Z		473
1285Z		432
1286Z		527
1287Z		593
1288Z		570
1289Z		531
1290Z		461
1291Z		585

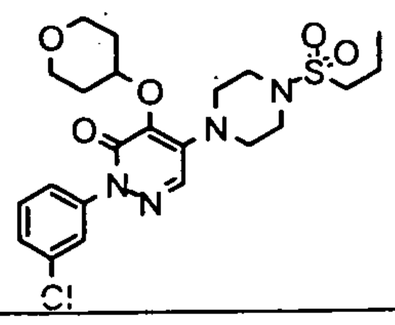
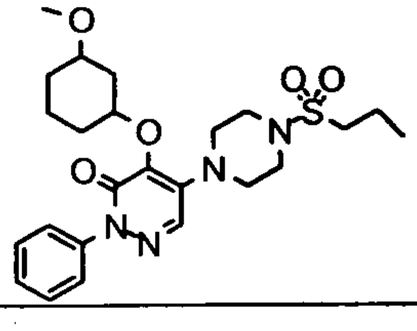
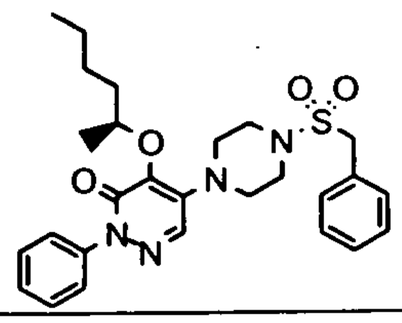
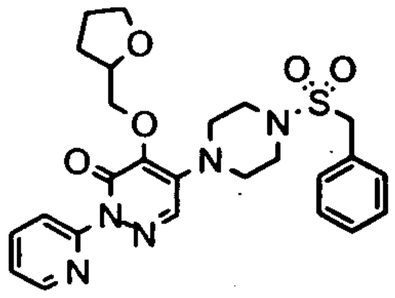
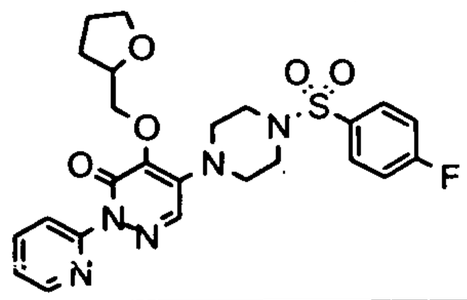
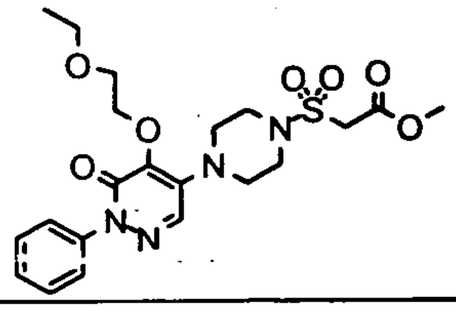
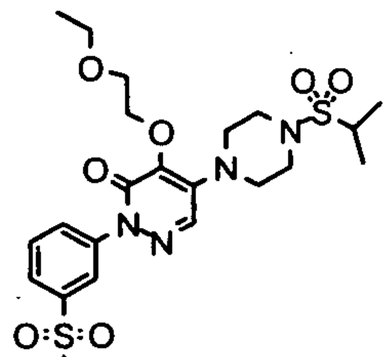
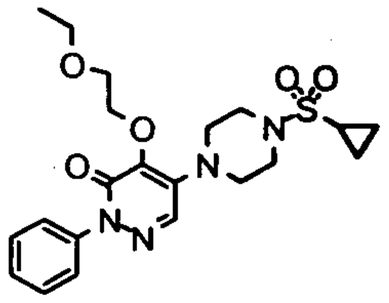
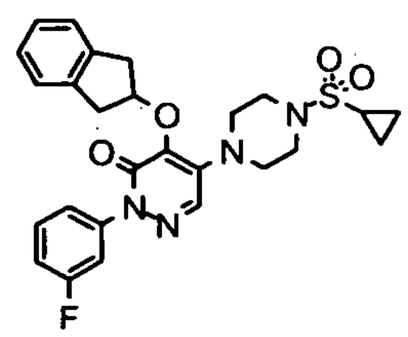
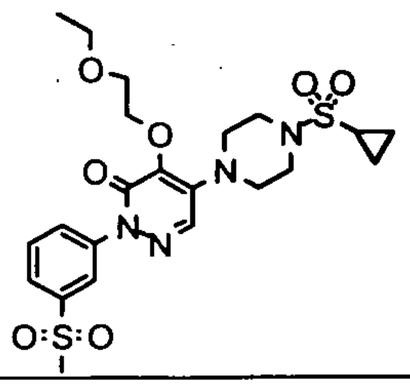
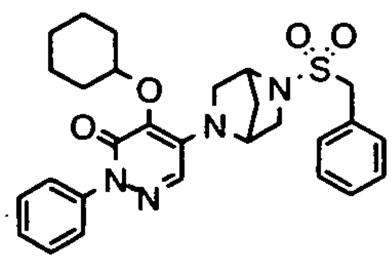
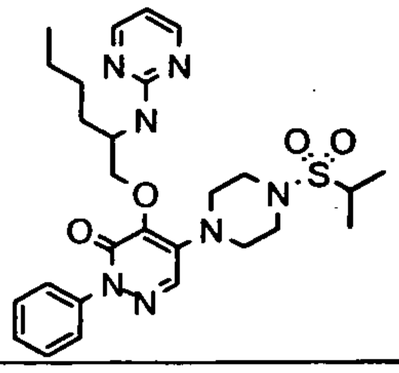
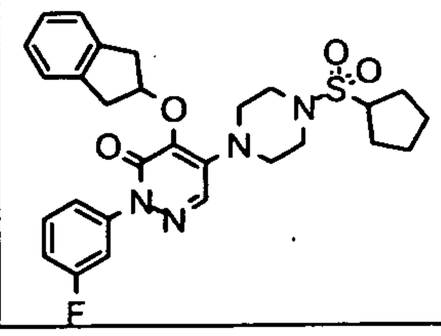
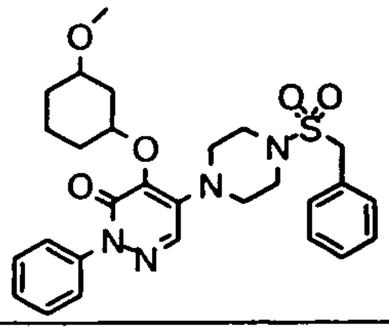
1292Z		461
1293Z		551
1294Z		517
1295Z		561
1296Z		634
1297Z		435
1298Z		529
1299Z		487
1300Z		509
1301Z		527
1302Z		499
1303Z		598
1304Z		427
1305Z		399

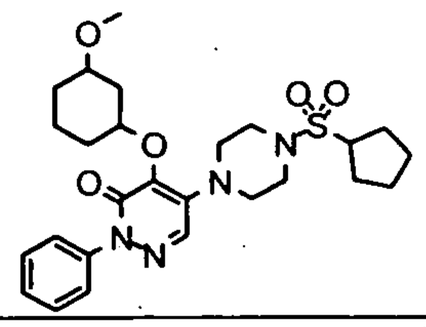
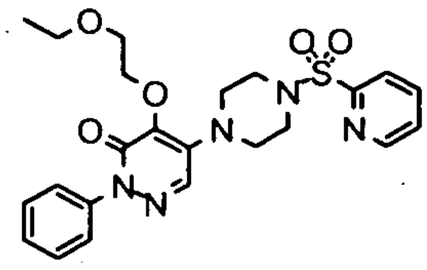
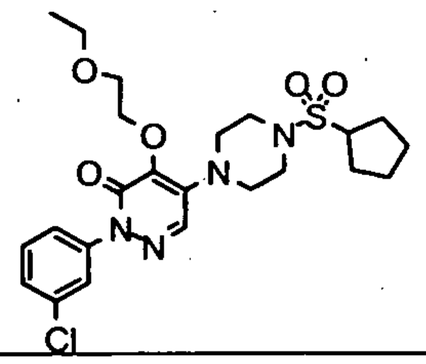
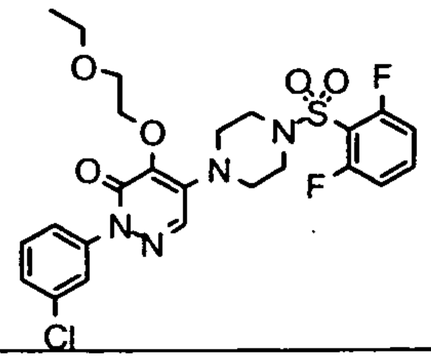
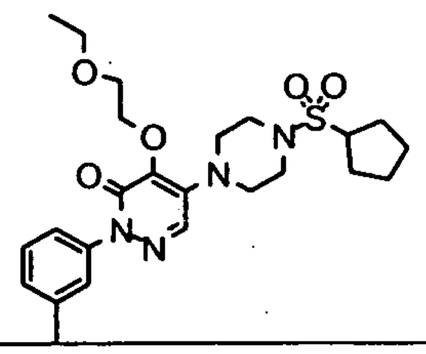
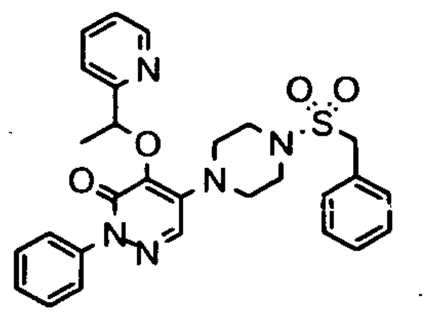
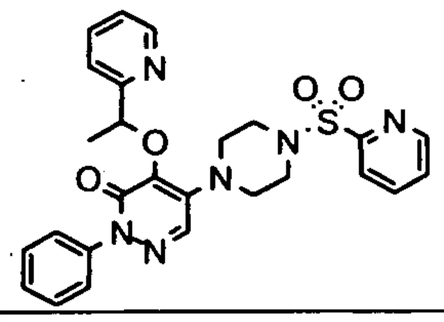
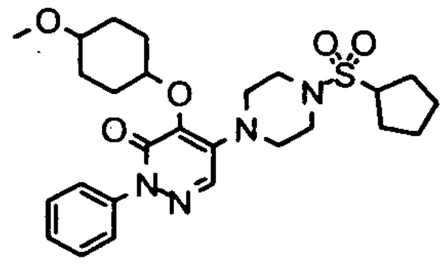
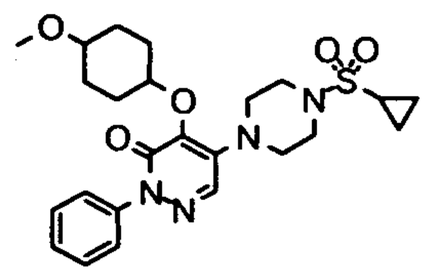
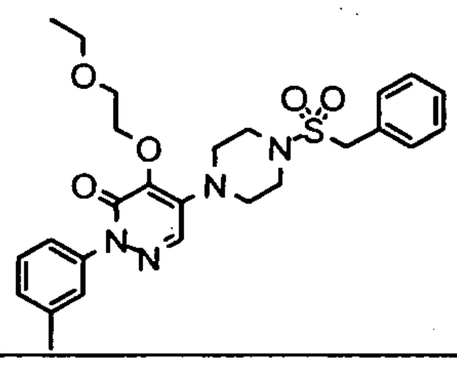
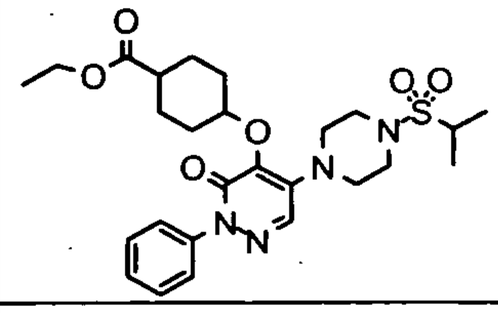
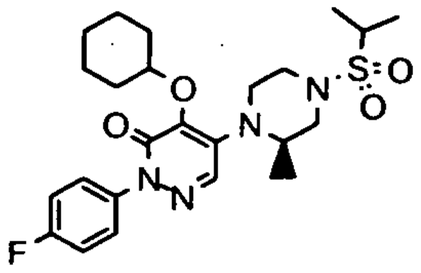
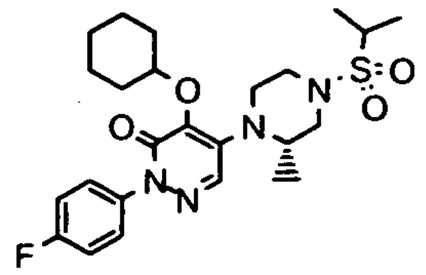
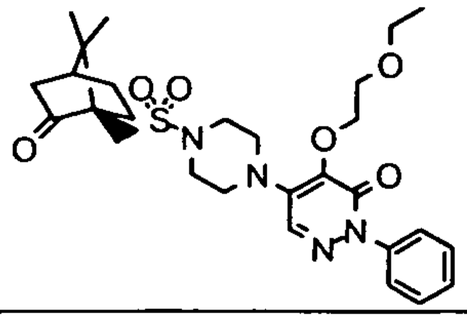
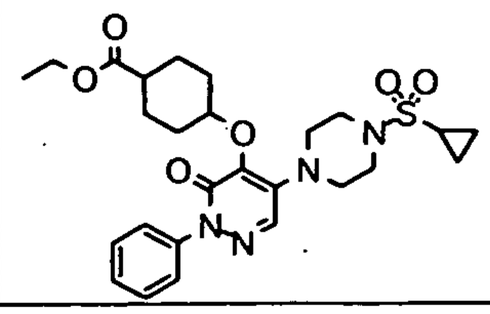
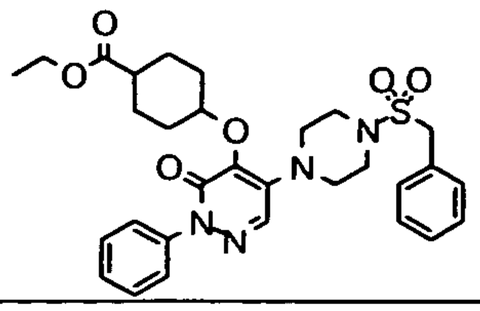
1306Z		481
1307Z		495
1308Z		509
1309Z		553
1310Z		484
1311Z		555
1312Z		504
1313Z		495
1314Z		499
1315Z		529
1316Z		511
1317Z		471
1318Z		553
1319Z		545

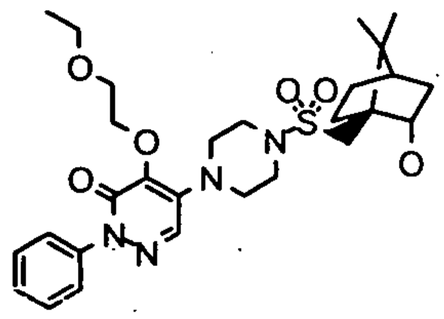
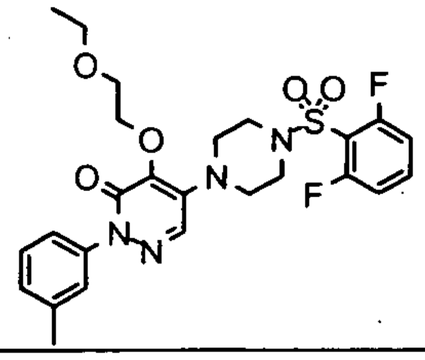
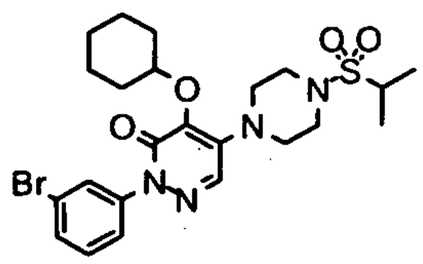
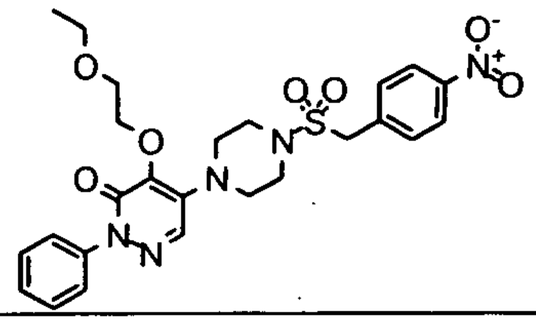
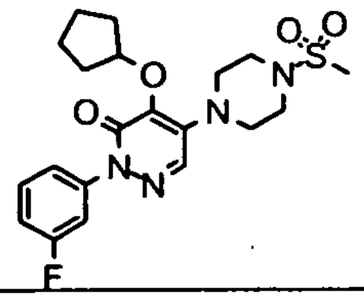
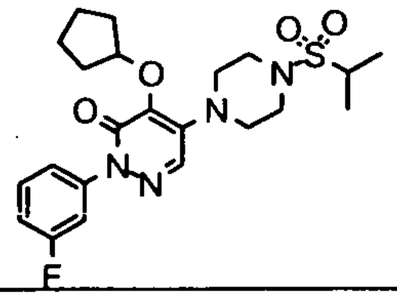
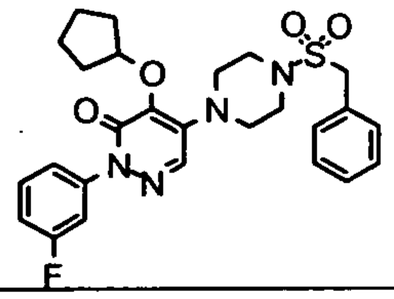
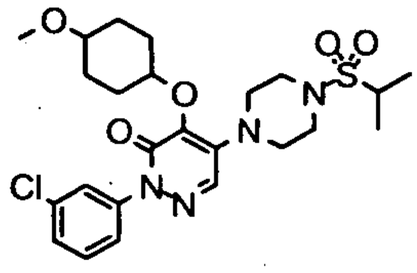
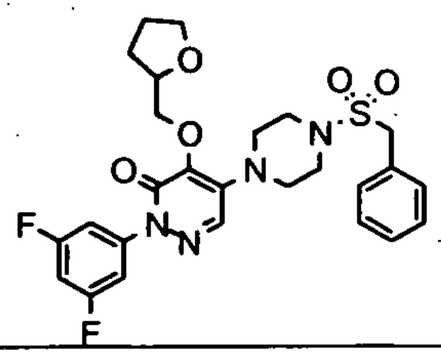
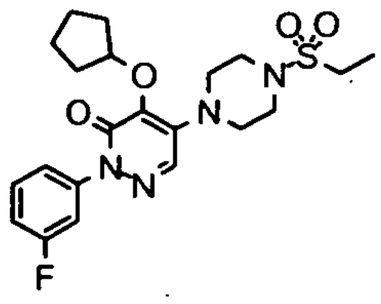
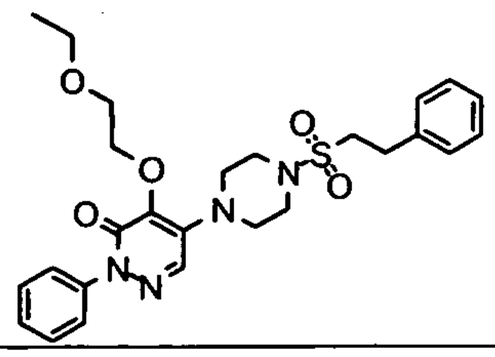
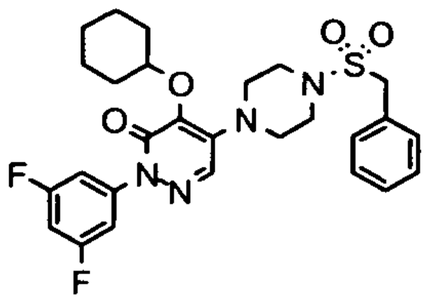
1320Z		556
1321Z		682
1322Z		618
1323Z		498
1324Z		523
1325Z		511
1326Z		577 579
1327Z		563
1328Z		545
1329Z		525
1330Z		470
1331Z		529
1332Z		506
1333Z		532

1334Z		579
1335Z		477
1336Z		441
1337Z		553
1338Z		513
1339Z		561
1340Z		513
1341Z		563
1342Z		393
1343Z		451
1344Z		515
1345Z		461
1346Z		555
1347Z		507
1348Z		485
1349Z		479

1350Z		519
1351Z		519
1352Z		547
1353Z		496
1354Z		457
1355Z		485
1356Z		491
1357Z		510
1358Z		500
1359Z		441
1360Z		469
1361Z		441
1362Z		469
1363Z		453
1364Z		481
1365Z		469

1366Z		497
1367Z		491
1368Z		511
1369Z		512
1370Z		516
1371Z		481
1372Z		529
1373Z		449
1374Z		511
1375Z		527
1376Z		521
1377Z		556
1378Z		539
1379Z		539

1380Z		517
1381Z		486
1382Z		511
1383Z		555
1384Z		491
1385Z		532
1386Z		519
1387Z		517
1388Z		489
1389Z		513
1390Z		533
1391Z		493
1392Z		493
1393Z		559
1394Z		531
1395Z		581

1396Z		561
1397Z		535
1398Z		541
1399Z		544
1400Z		437
1401Z		465
1402Z		513
1403Z		525
1404Z		547
1405Z		451
1406Z		513
1407Z		545
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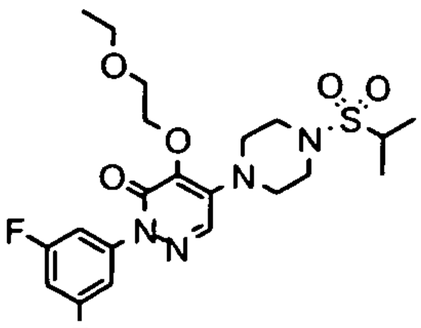
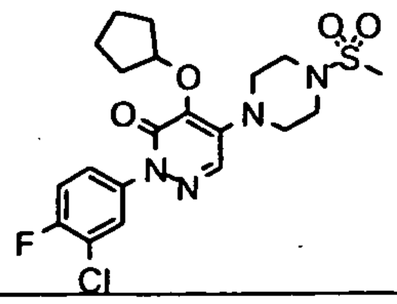
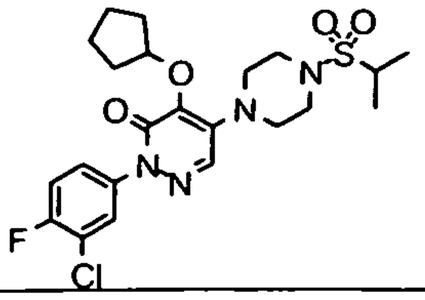
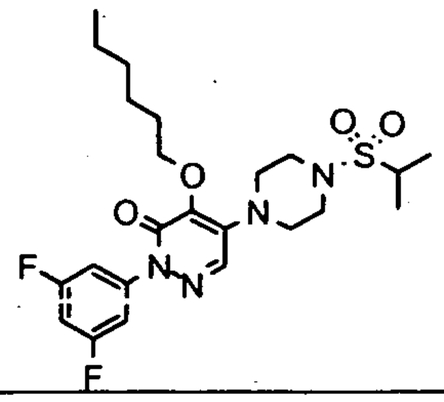
1409Z		557
1410Z		471
1411Z		499

1412Z		499
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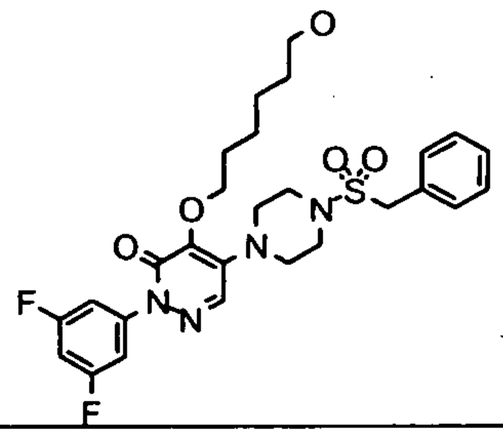
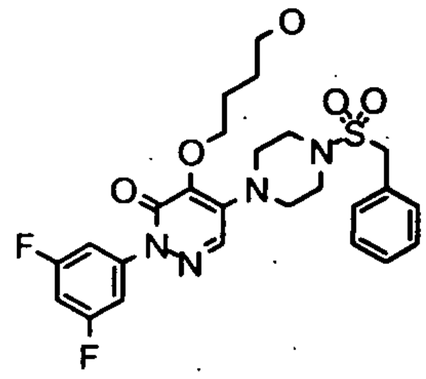
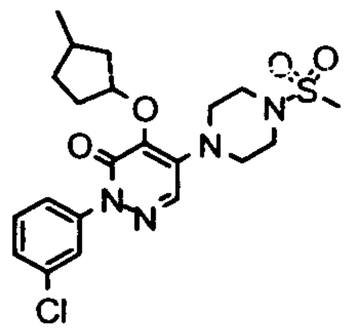
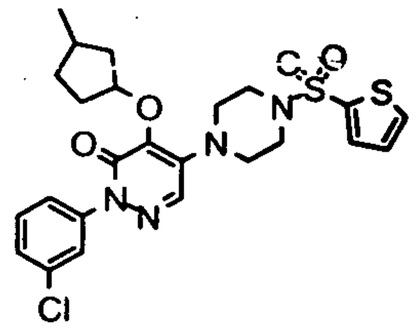
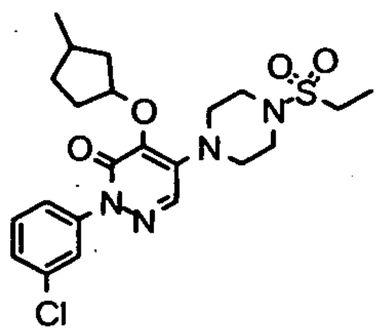
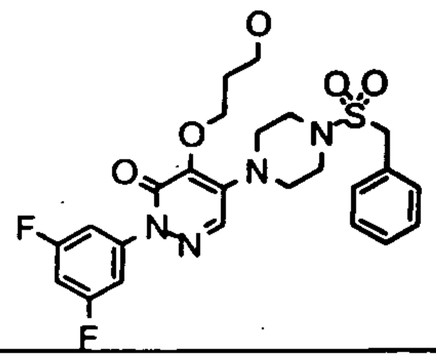
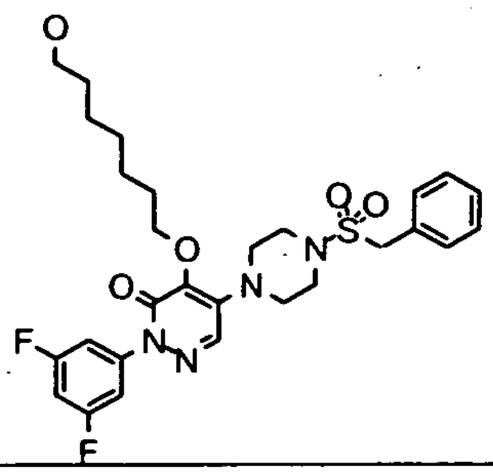
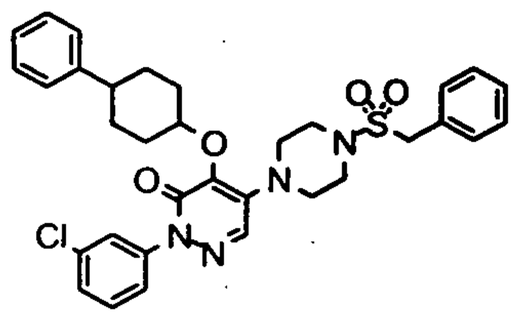
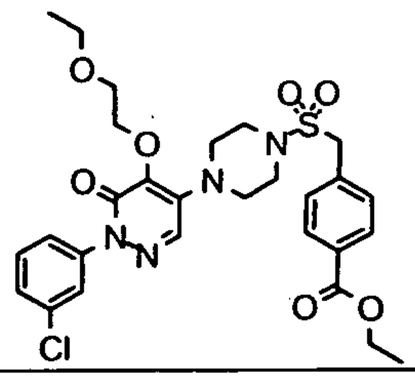
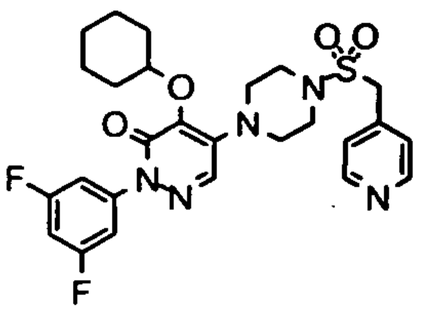
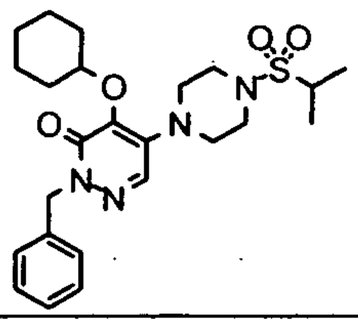
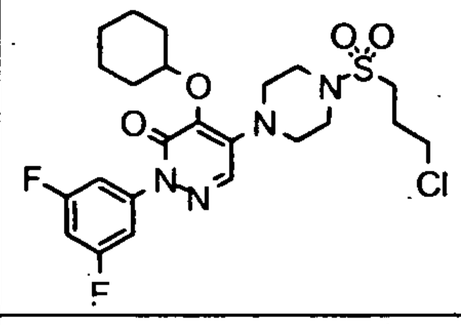
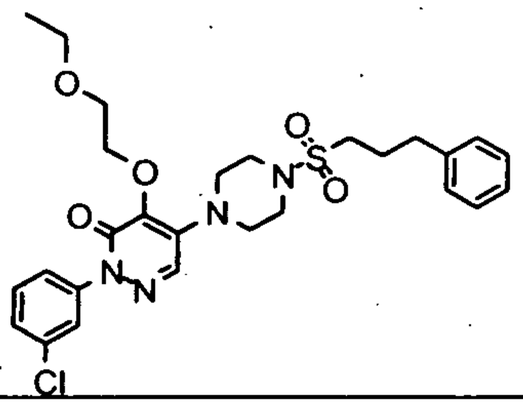
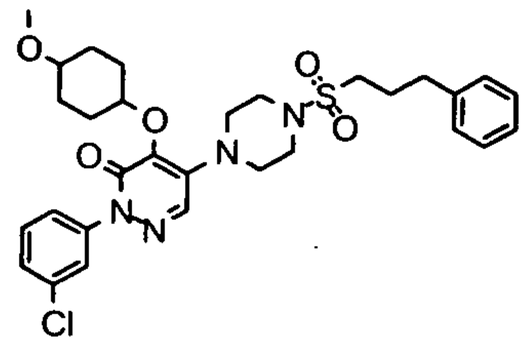
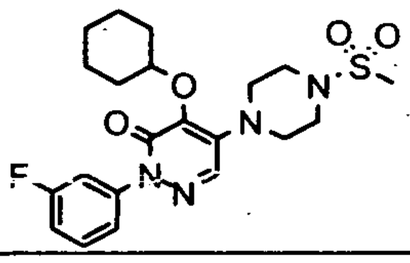
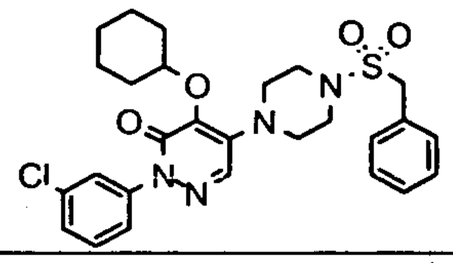
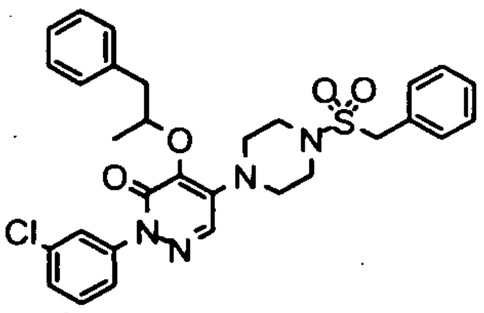
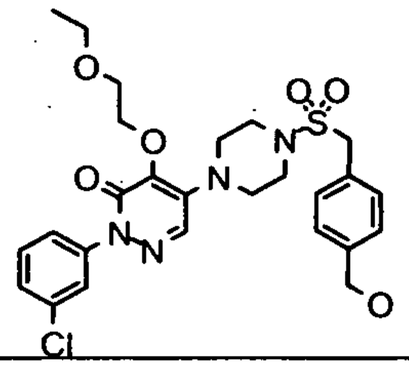
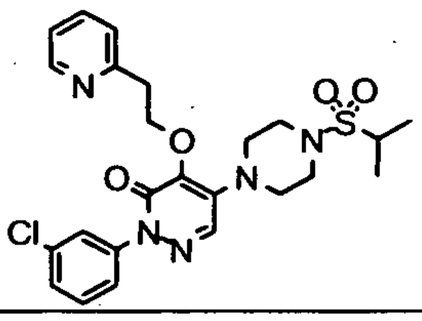
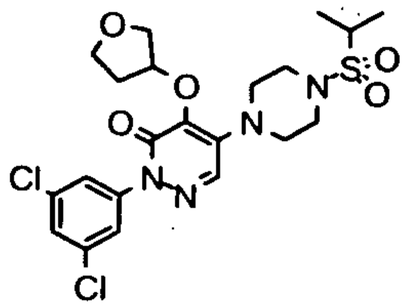
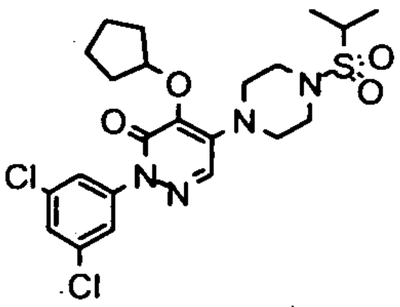
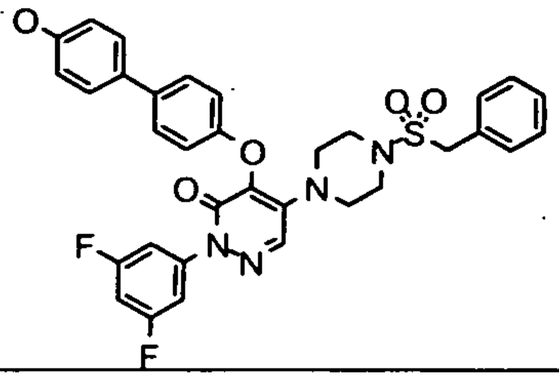
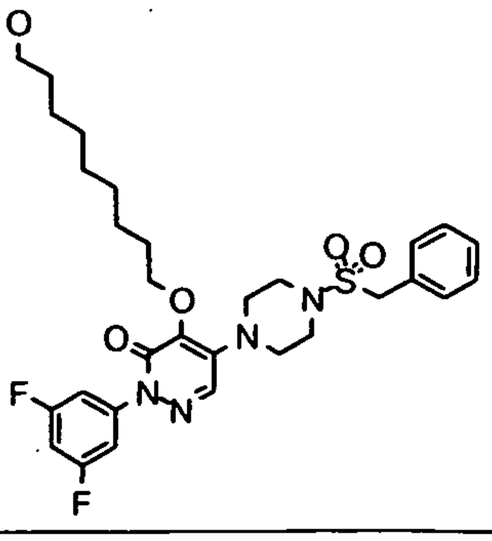
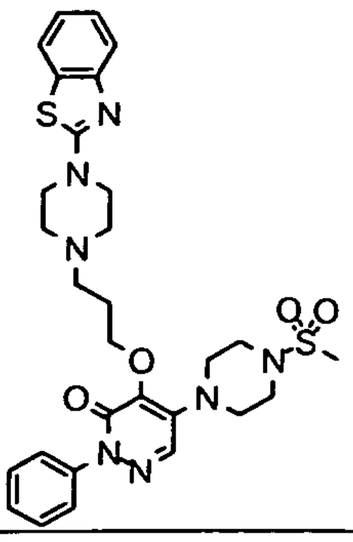
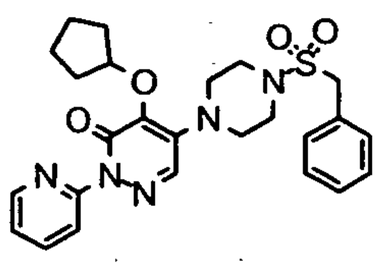
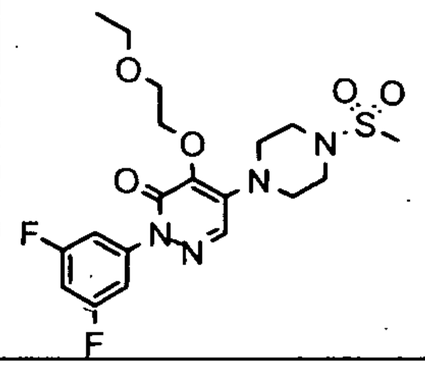
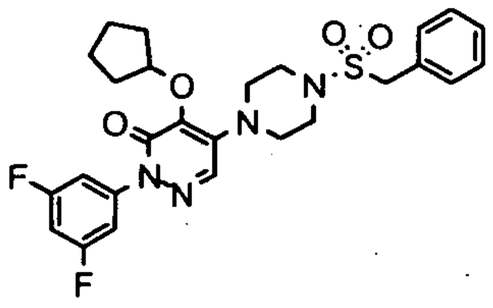
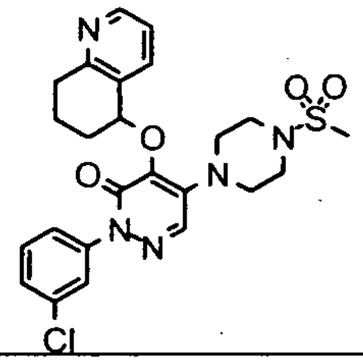
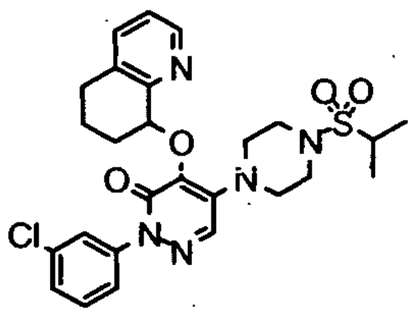
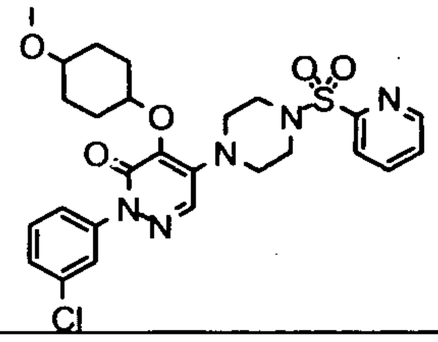
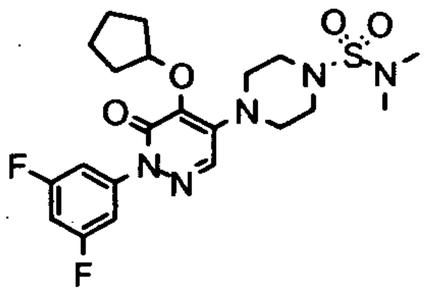
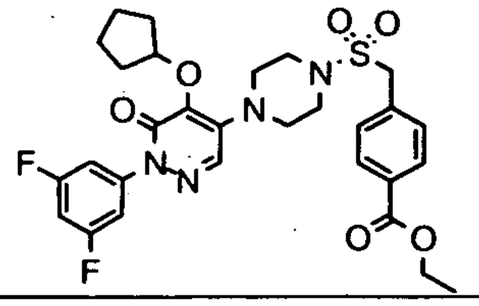
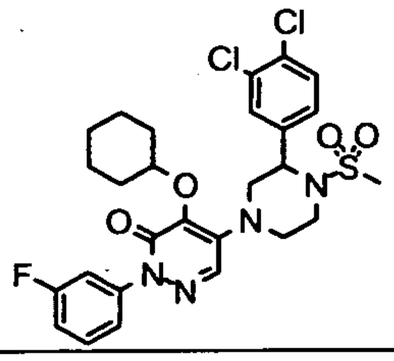
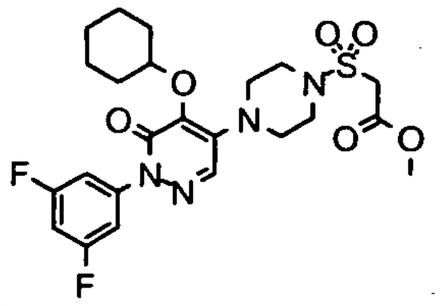
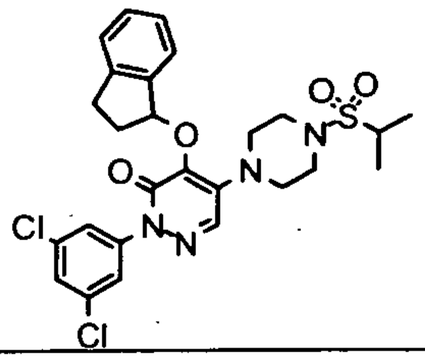
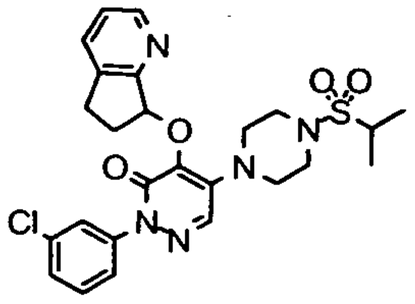
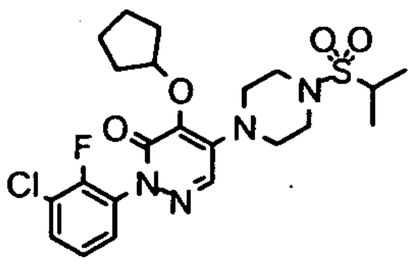
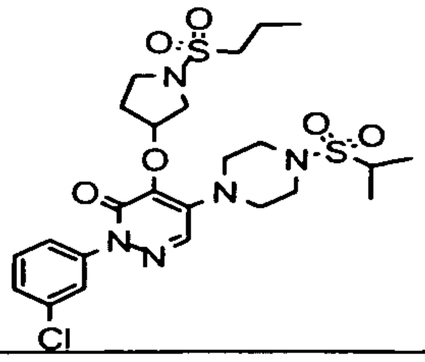
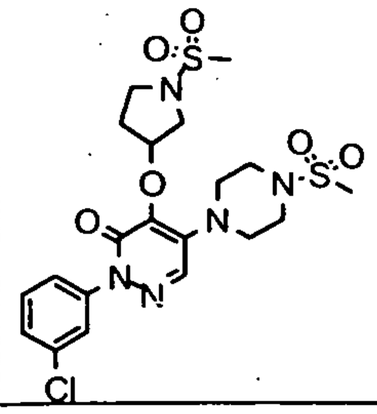
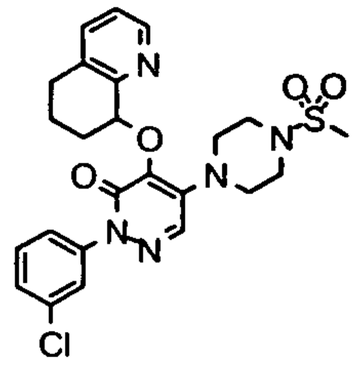
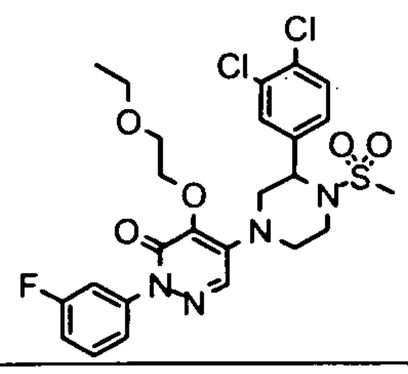
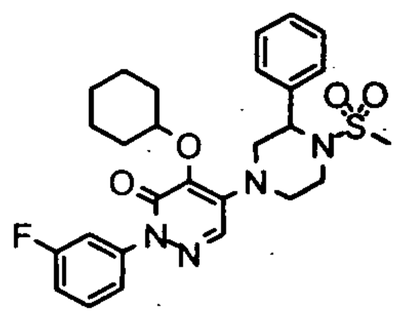
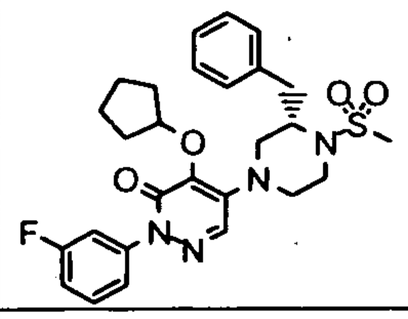
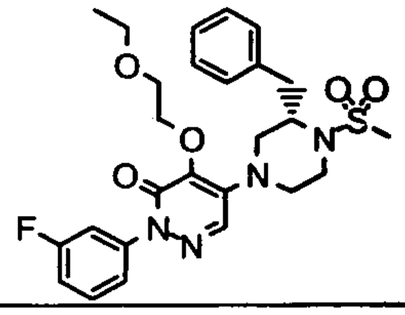
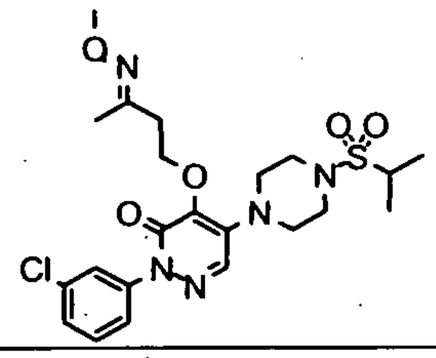
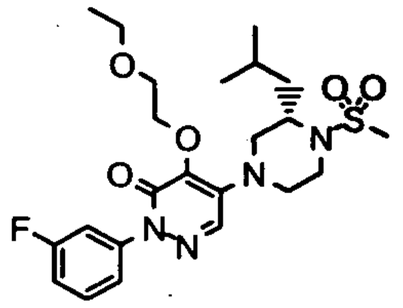
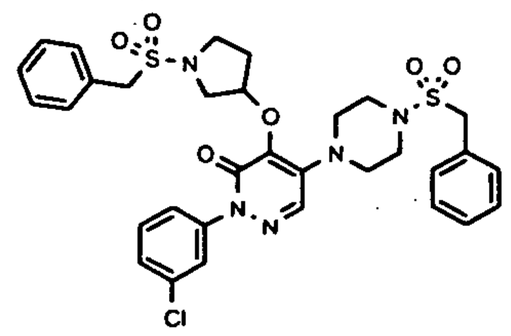
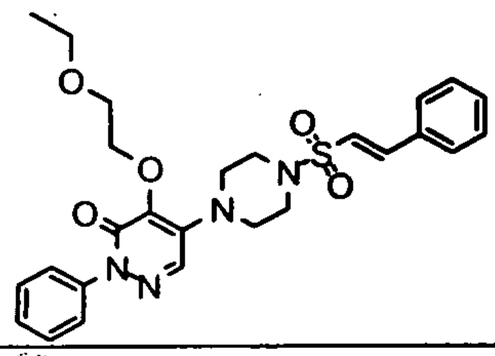
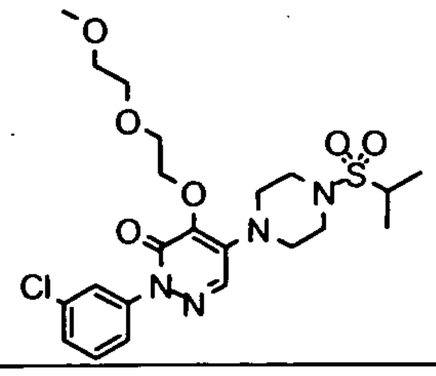
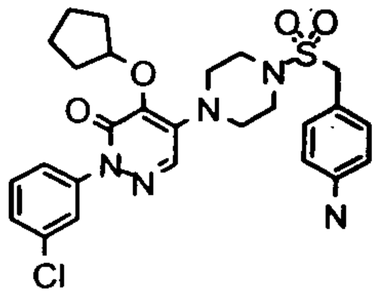
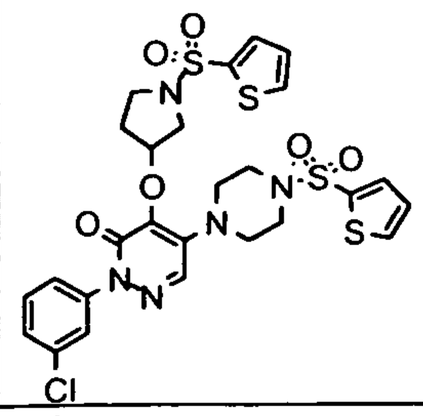
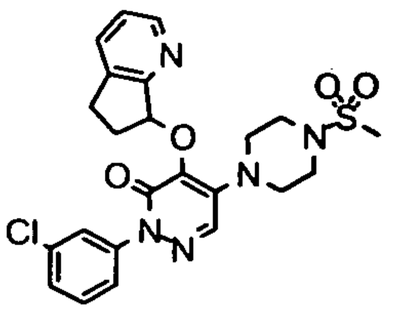
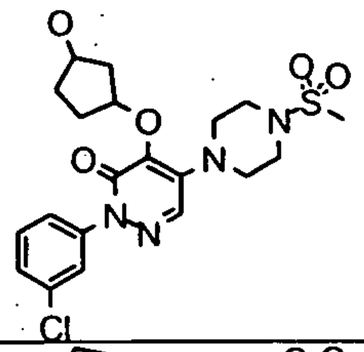
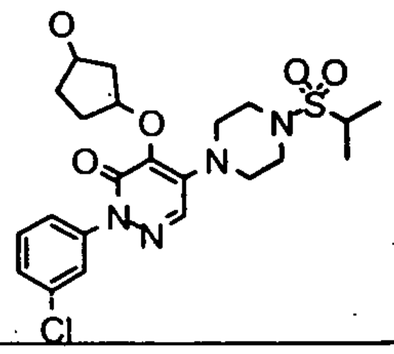
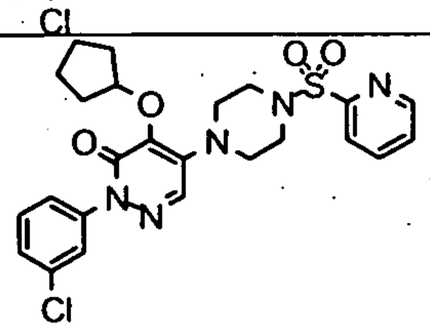
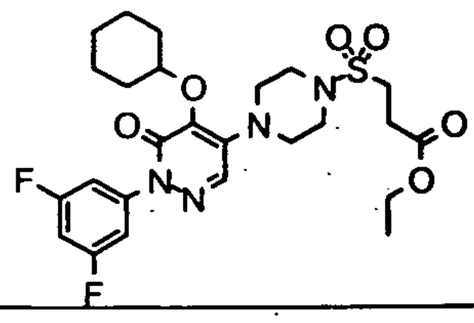
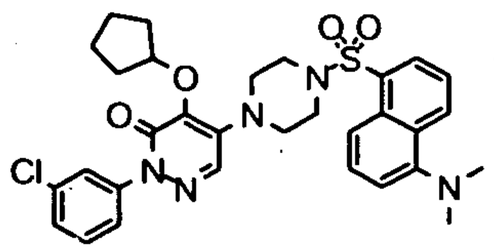
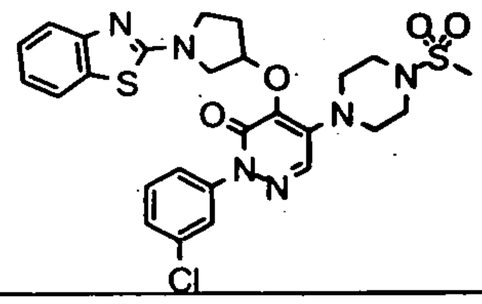
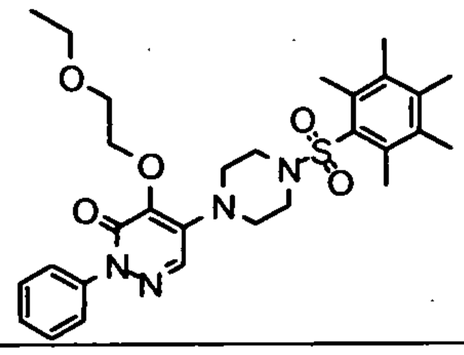
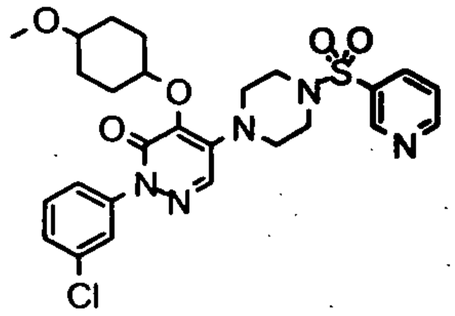
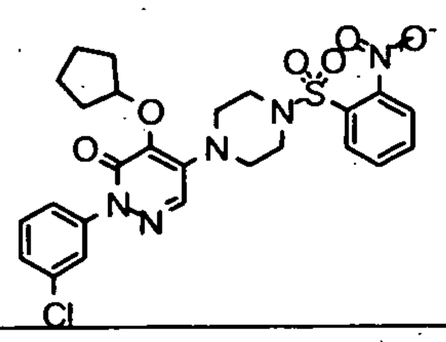
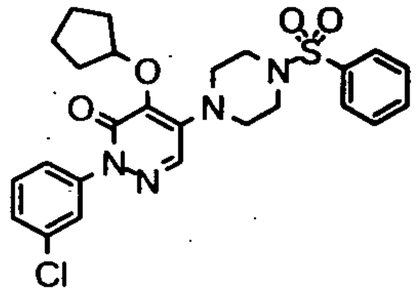
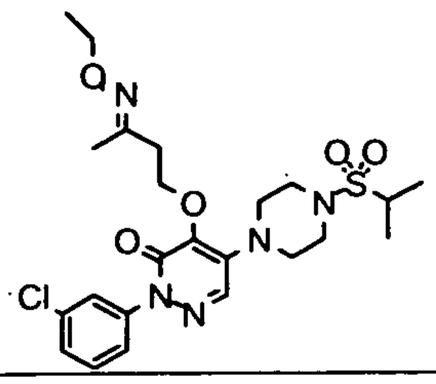
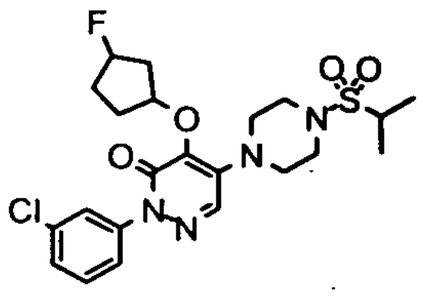
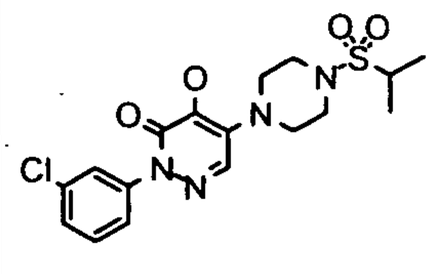
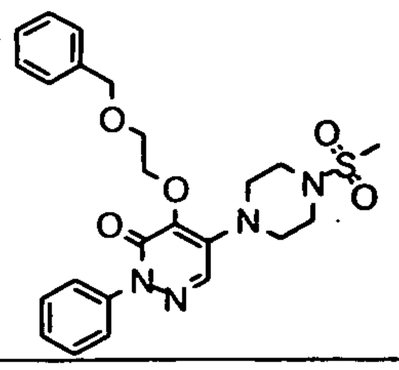
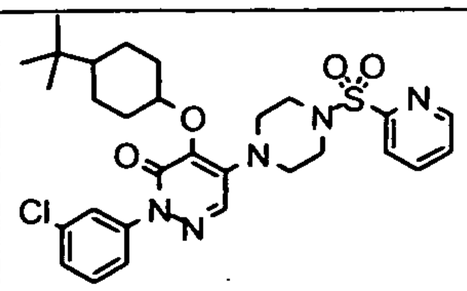
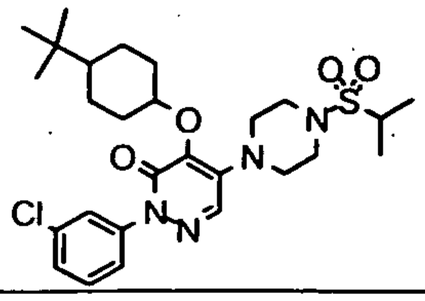
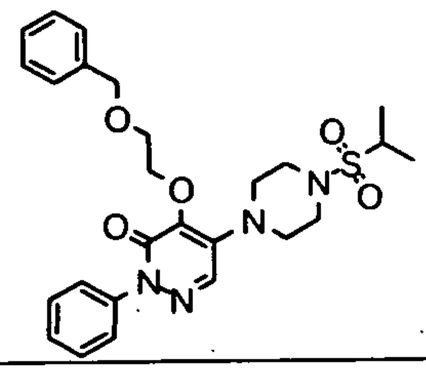
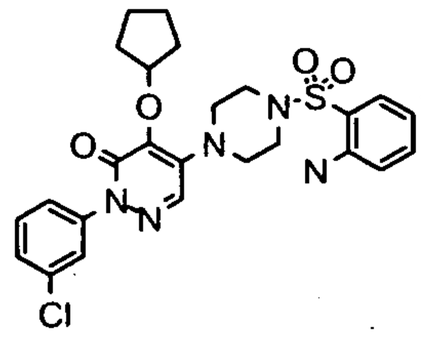
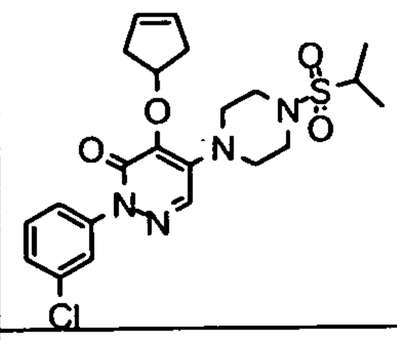
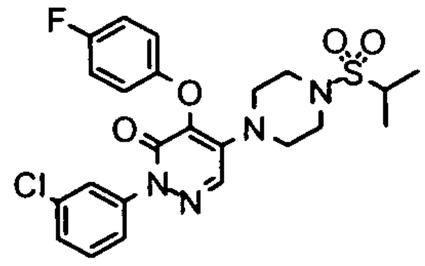
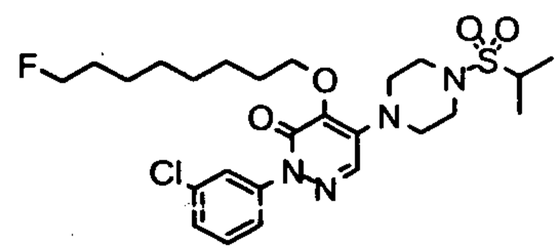
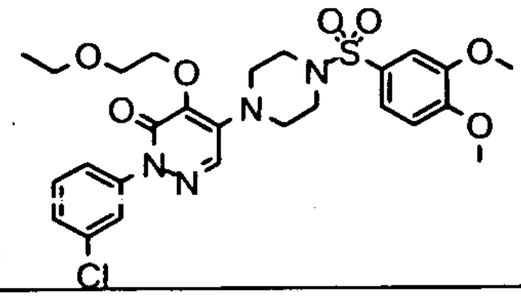
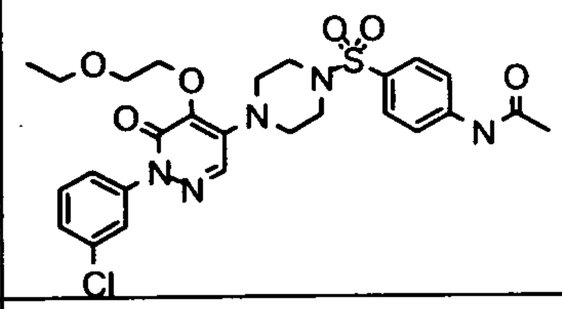
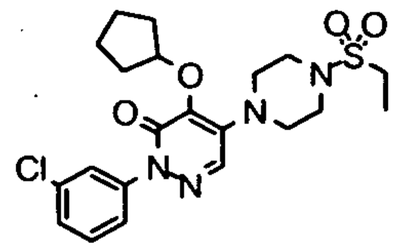
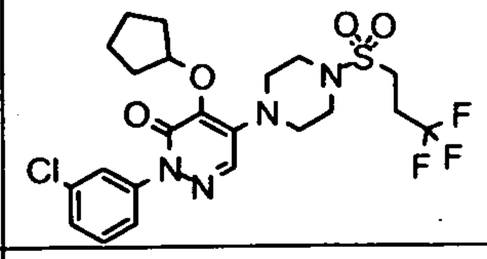
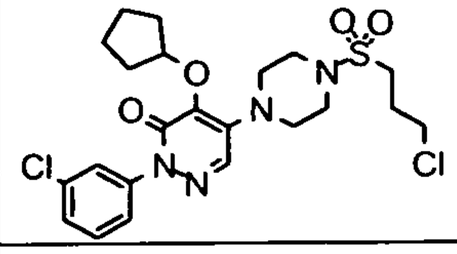
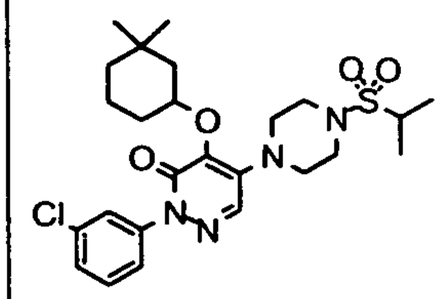
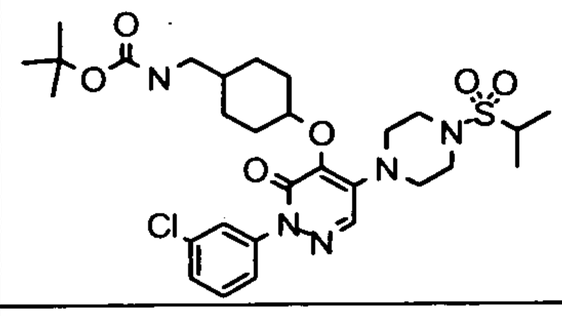
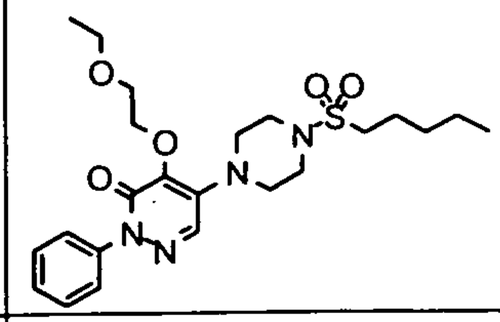
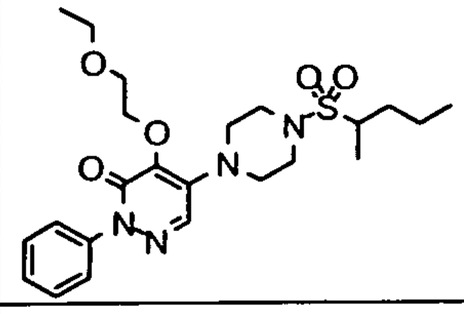
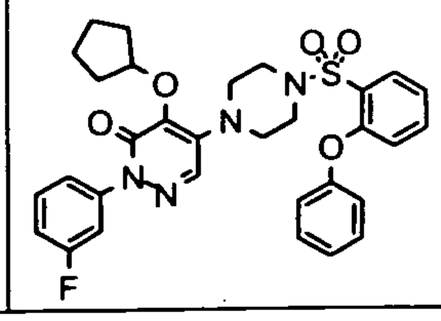
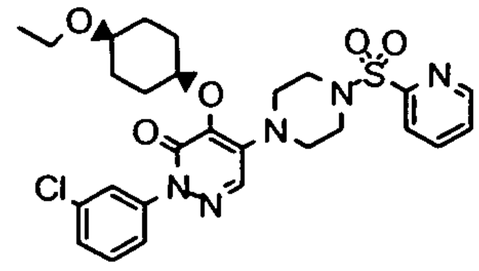
1414Z		563
1415Z		535
1416Z		467
1417Z		535
1418Z		481
1419Z		521
1420Z		577
1421Z		619
1422Z		605
1423Z		546

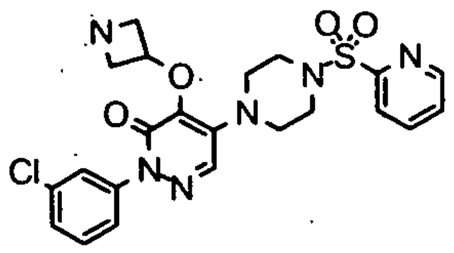
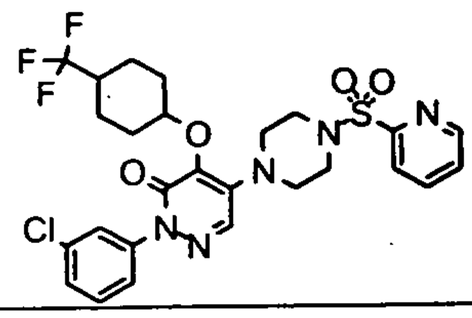
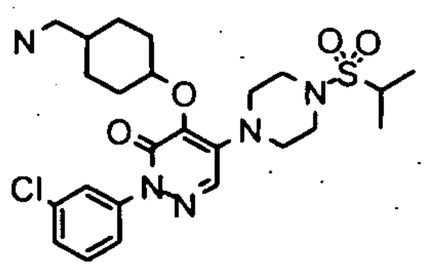
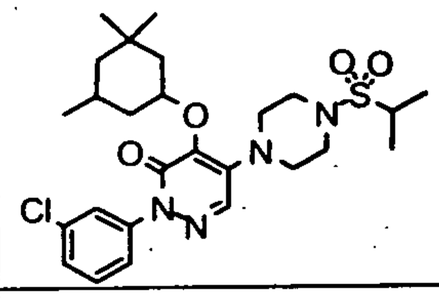
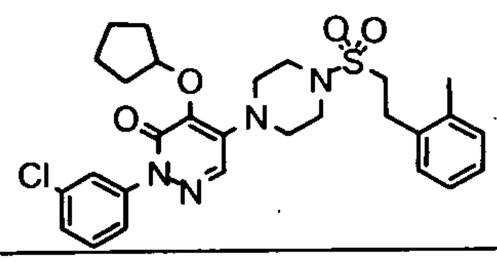
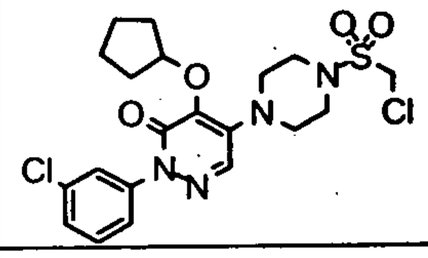
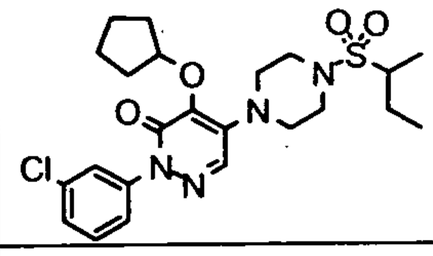
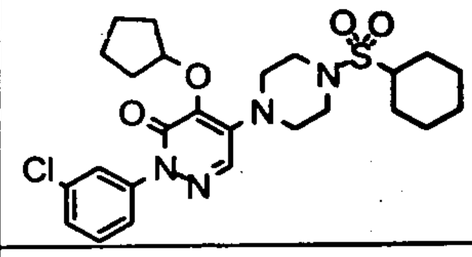
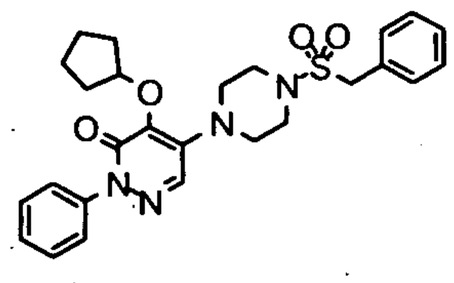
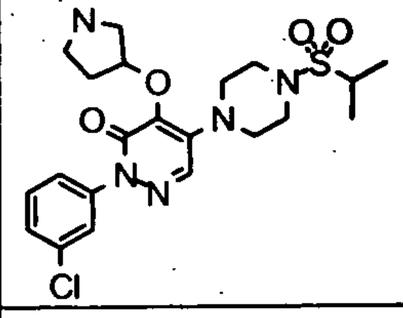
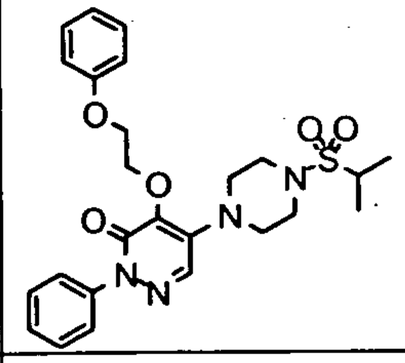
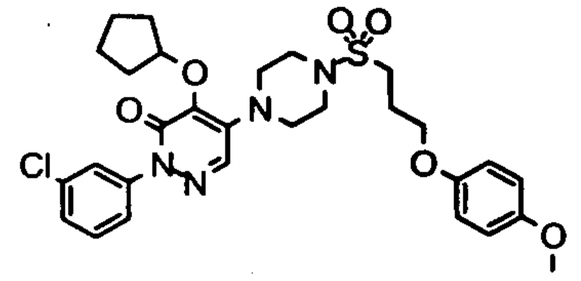
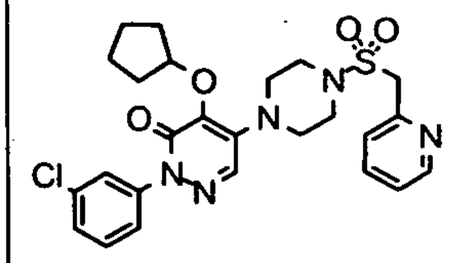
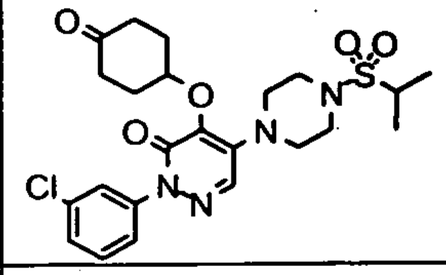
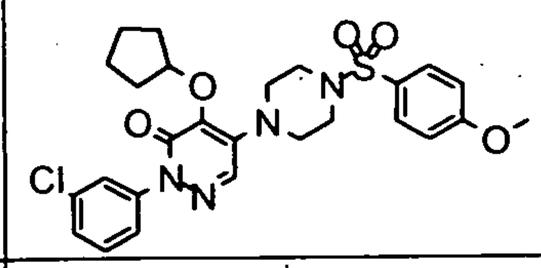
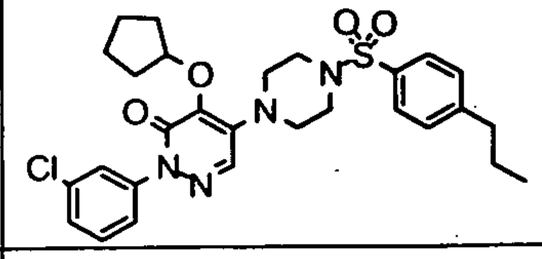
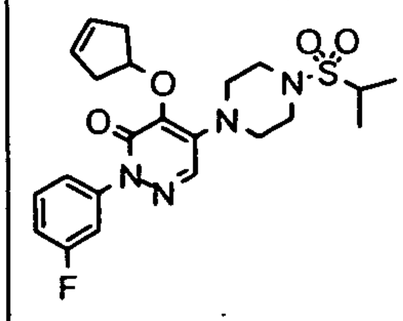
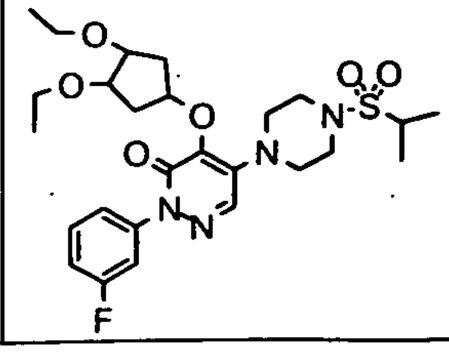
1424Z		475
1425Z		531
1426Z		561
1427Z		601
1428Z		451
1429Z		543
1430Z		579
1431Z		563
1432Z		518
1433Z		517
1434Z		515
1435Z		631
1436Z		605
1437Z		610

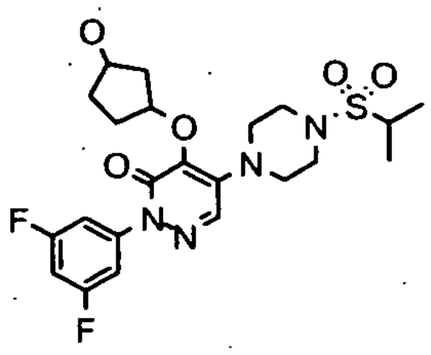
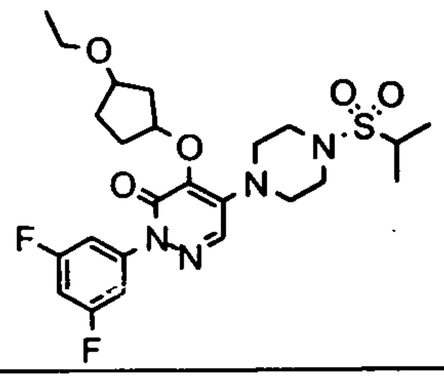
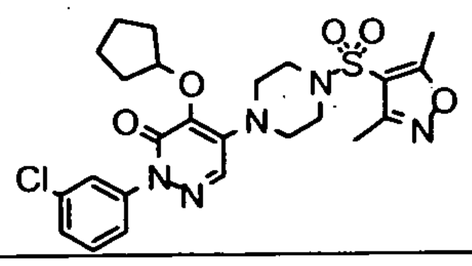
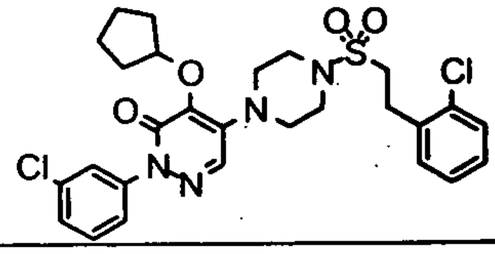
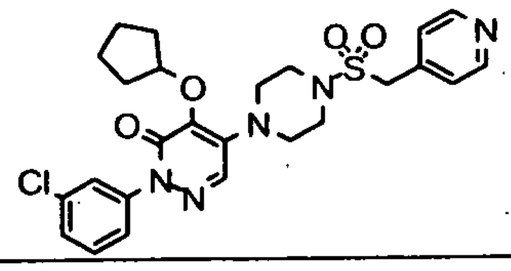
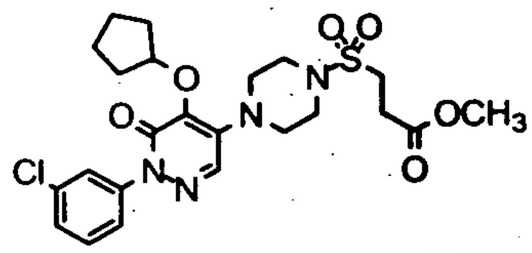
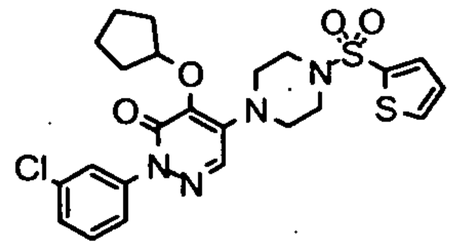
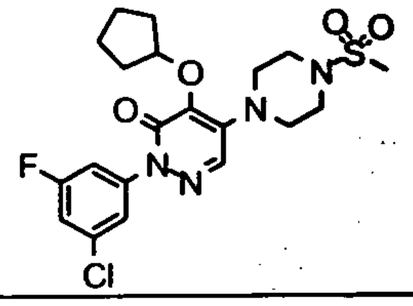
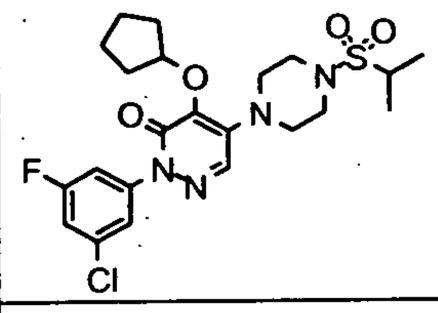
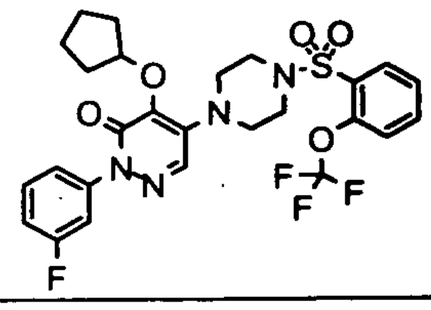
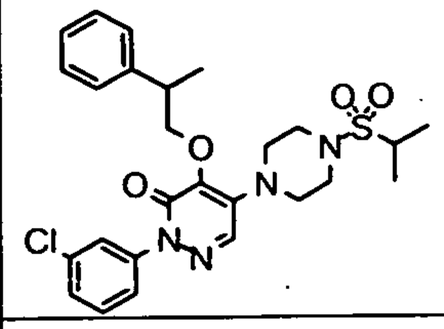
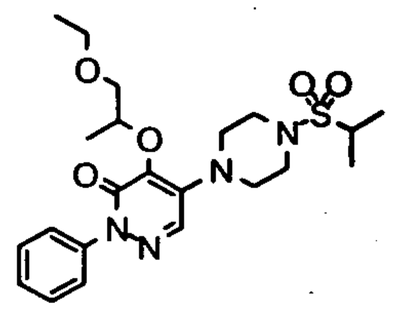
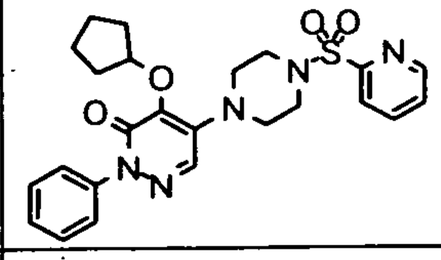
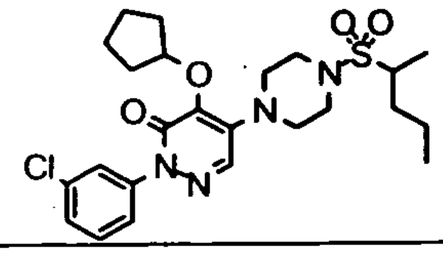
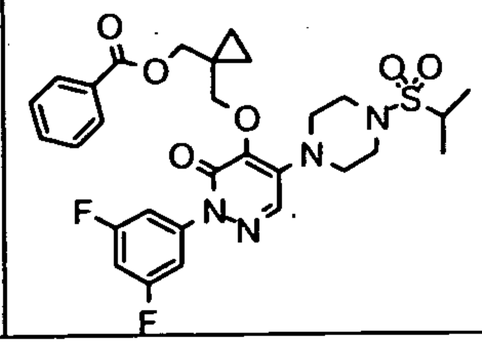
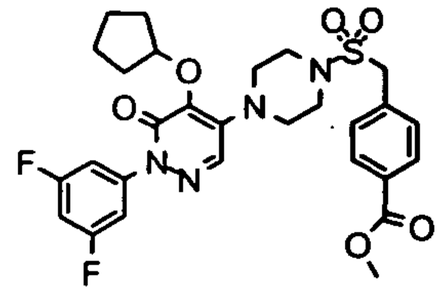
1438Z		496
1439Z		459
1440Z		483
1441Z		516
1442Z		544
1443Z		560
1444Z		484
1445Z		603
1446Z		595
1447Z		527
1448Z		563
1449Z		530
1450Z		499
1451Z		588

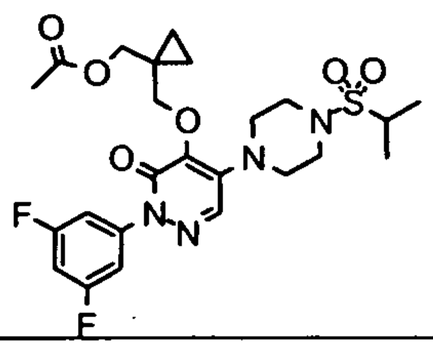
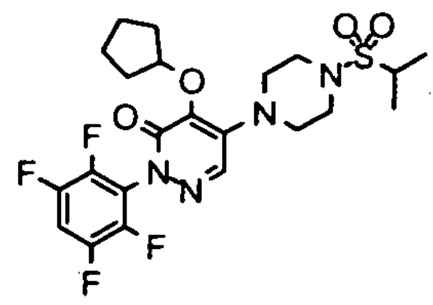
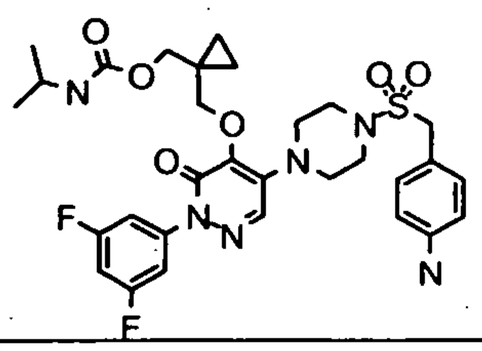
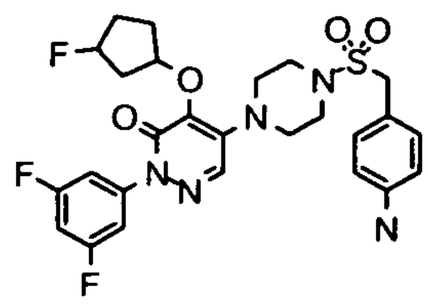
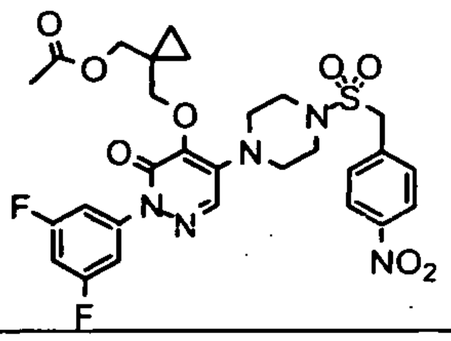
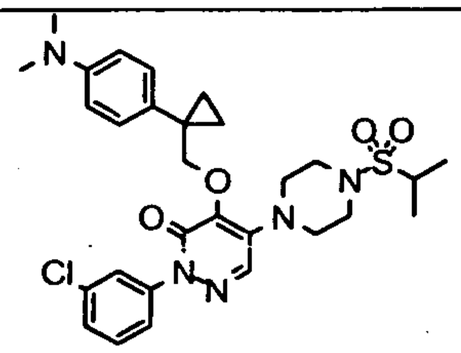
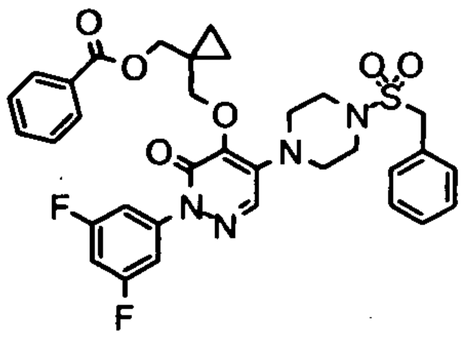
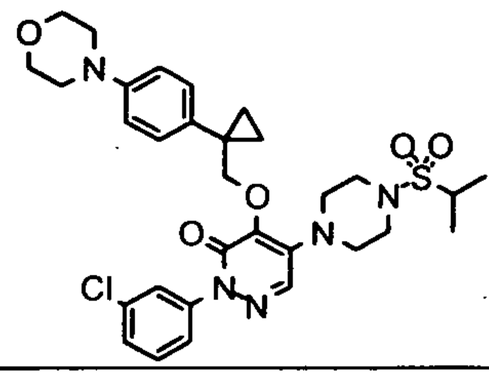
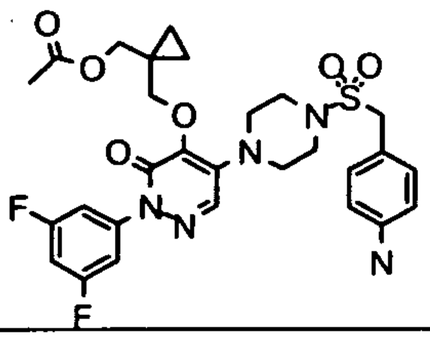
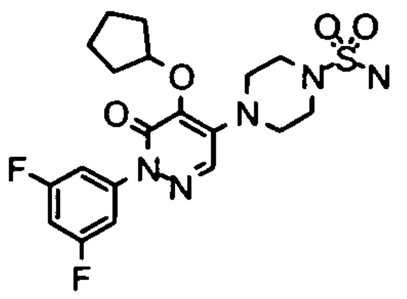
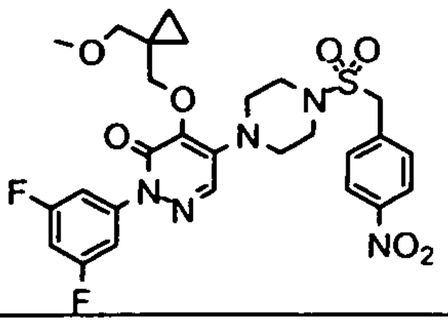
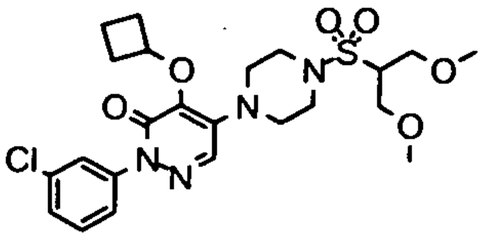
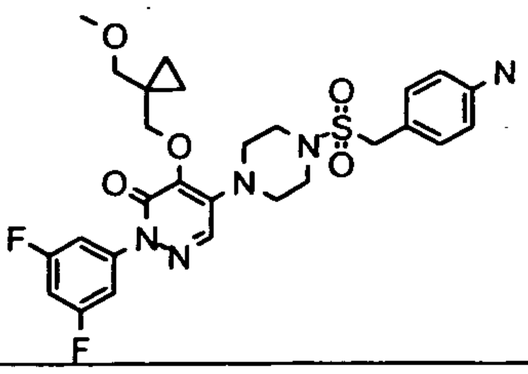
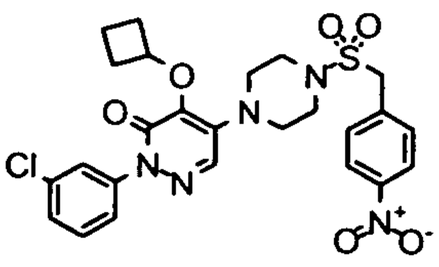
1452Z		532
1453Z		516
1454Z		585
1455Z		527
1456Z		527
1457Z		531
1458Z		512
1459Z		497
1460Z		684
1461Z		511
1462Z		515
1463Z		544
1464Z		668
1465Z		502

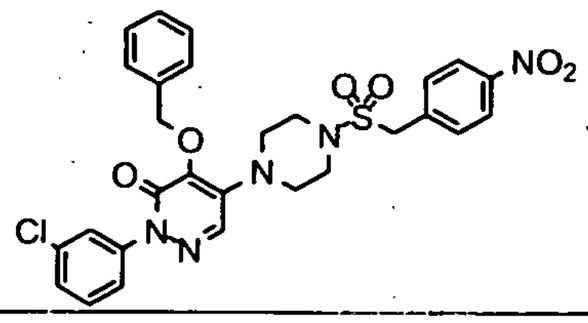
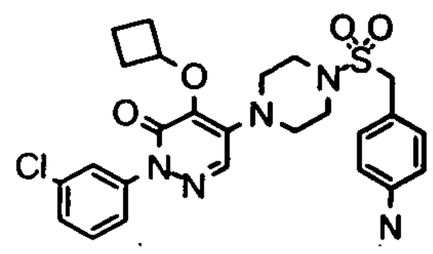
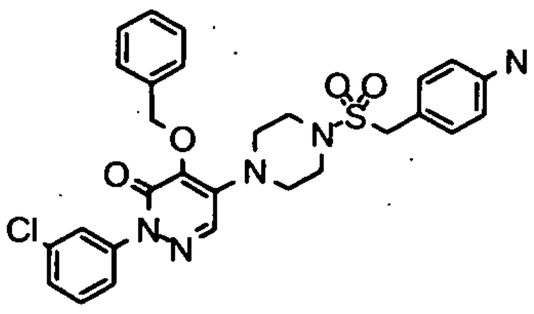
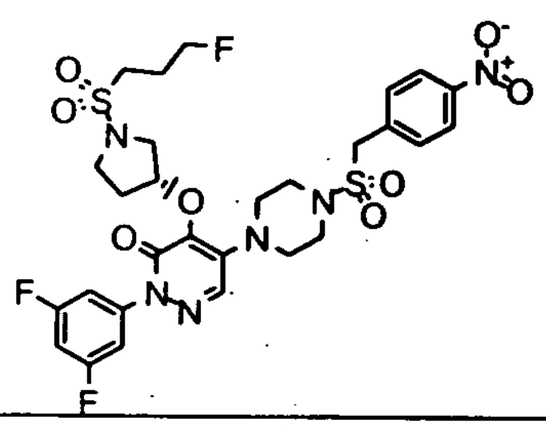
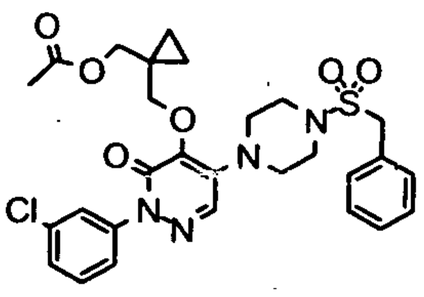
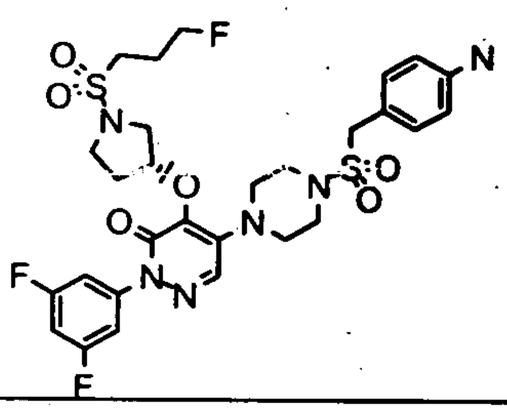
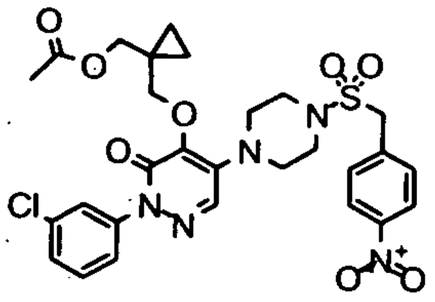
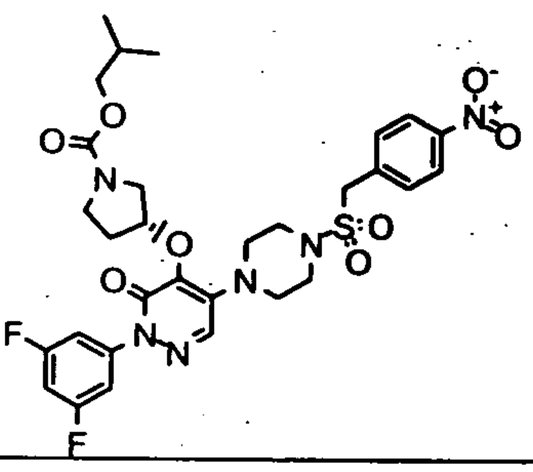
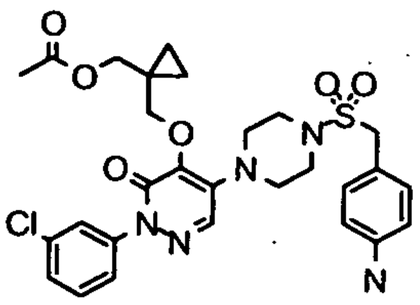
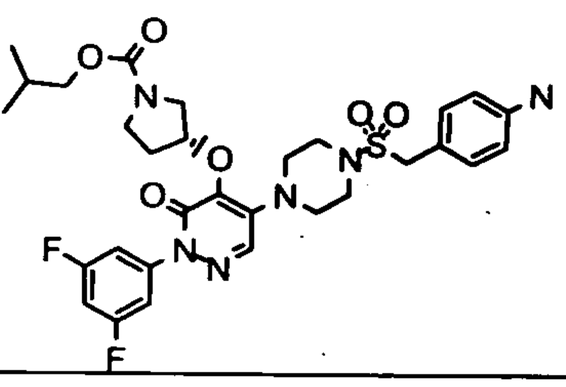
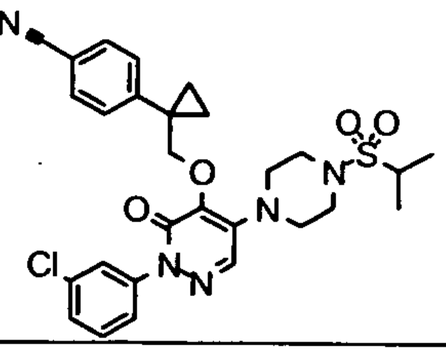
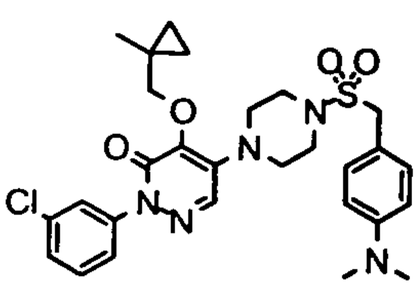
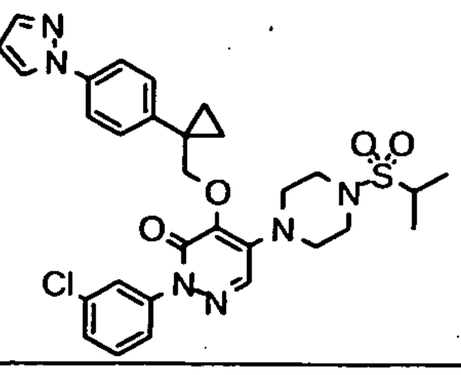
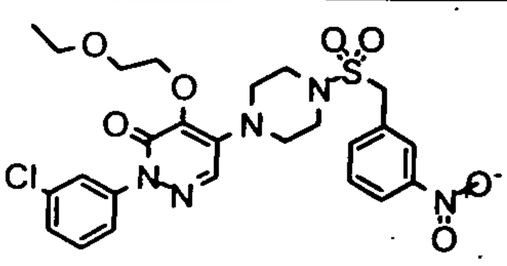
1466Z		469
1467Z		497
1468Z		516
1469Z		555
1470Z		608
1471Z		587
1472Z		555
1473Z		560
1474Z		560
1475Z		515
1476Z		526
1477Z		499
1478Z		413
1479Z		485
1480Z		586
1481Z		551

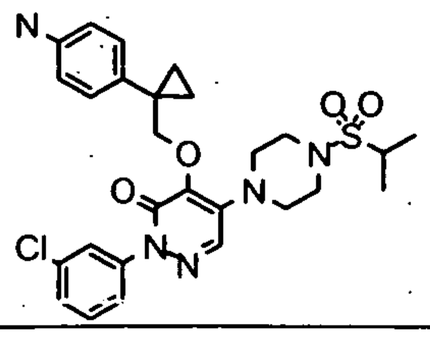
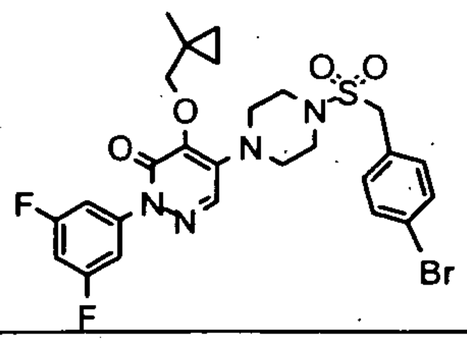
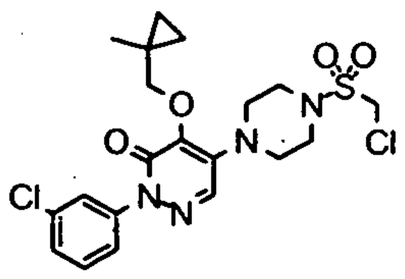
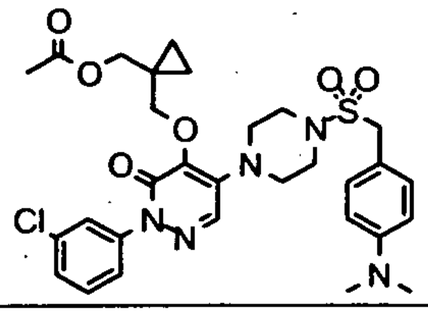
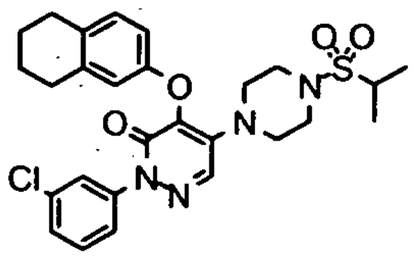
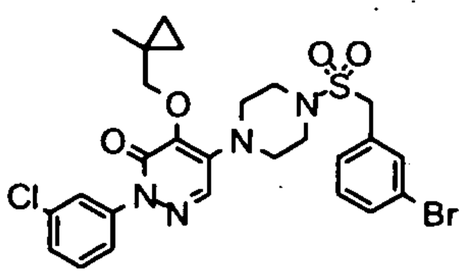
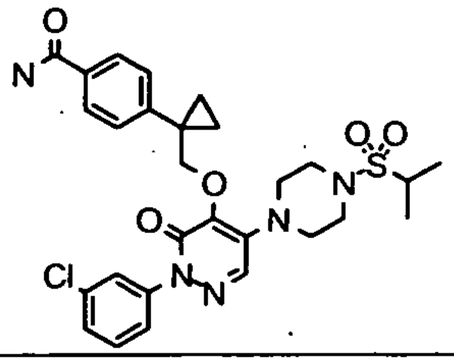
1482Z		513
1483Z		530
1484Z		479
1485Z		507
1486Z		543
1487Z		579
1488Z		576
1489Z		467
1490Z		535
1491Z		515
1492Z		523
1493Z		624
1494Z		479
1495Z		479
1496Z		591
1497Z		574

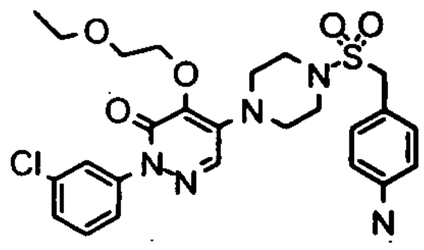
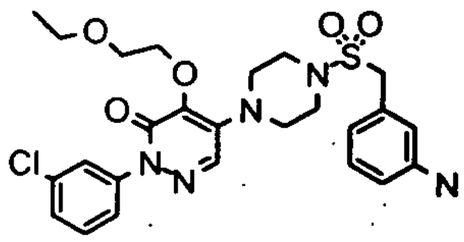
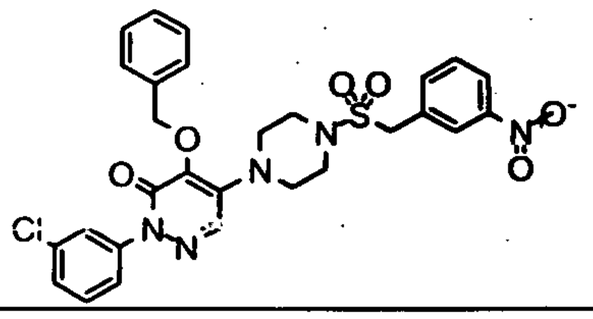
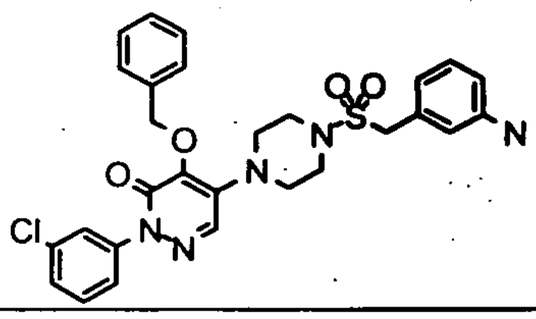
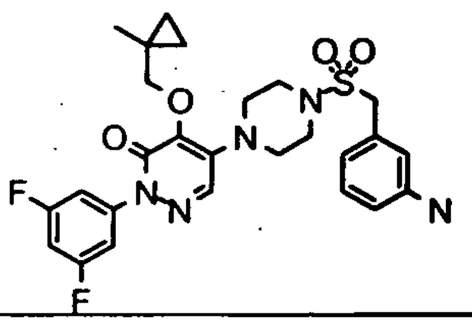
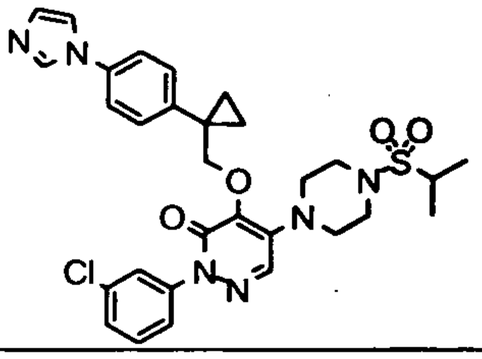
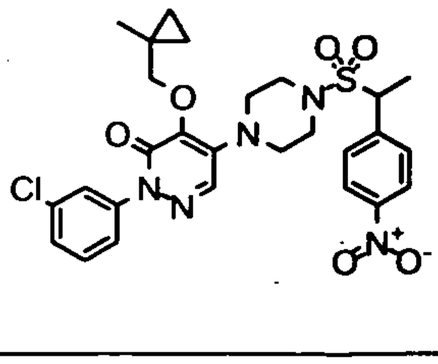
1498Z		503
1499Z		598
1500Z		524
1501Z		537
1502Z		557
1503Z		487
1504Z		495
1505Z		521
1506Z		495
1507Z		482
1508Z		499
1509Z		603
1510Z		530
1511Z		509
1512Z		545
1513Z		557
1514Z		463
1515Z		553

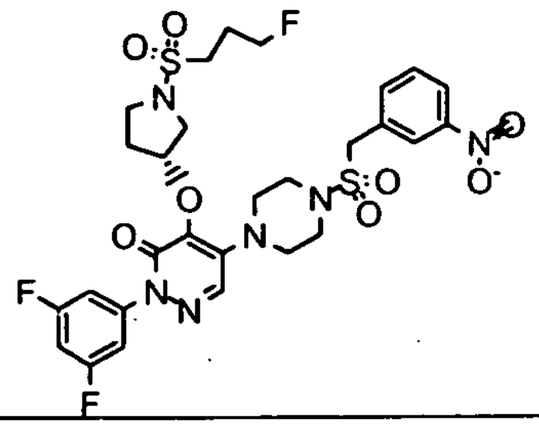
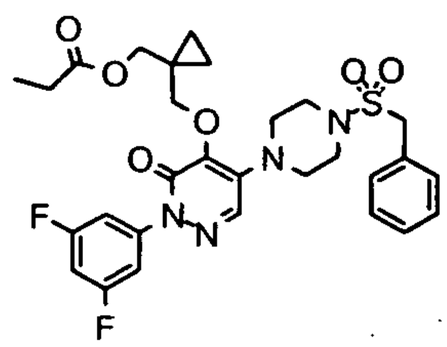
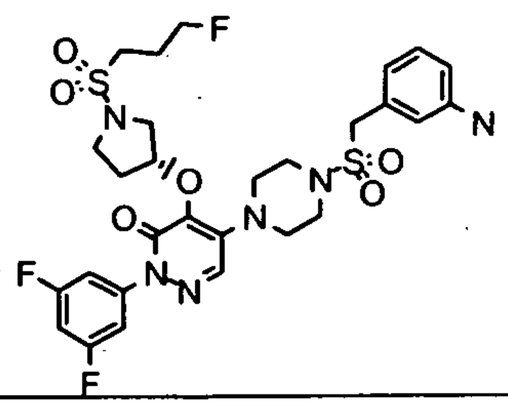
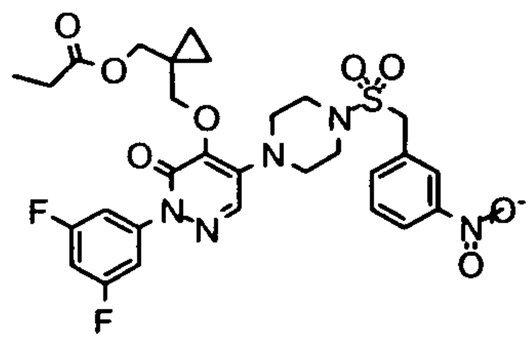
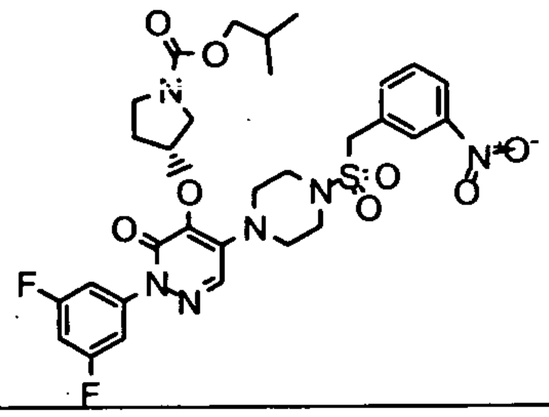
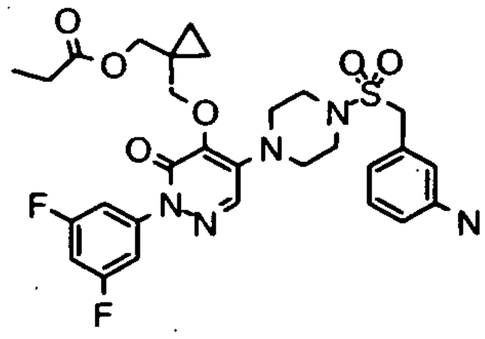
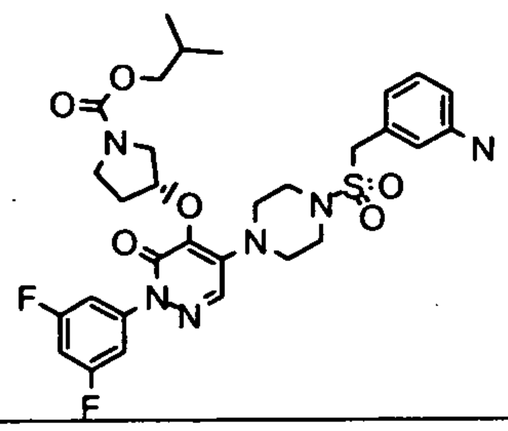
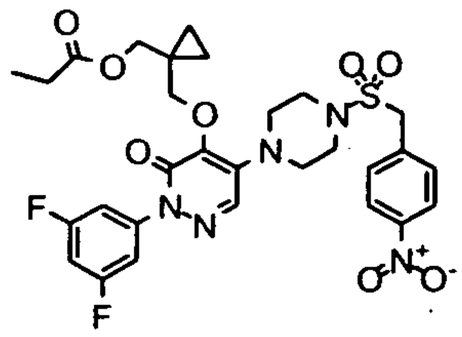
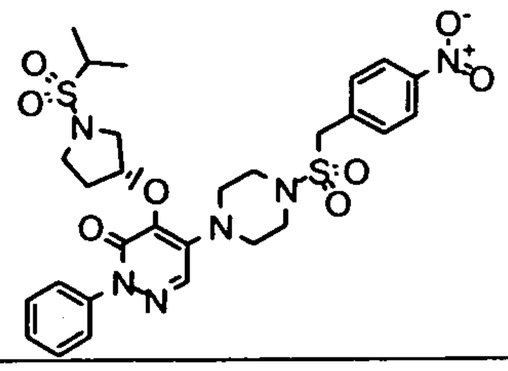
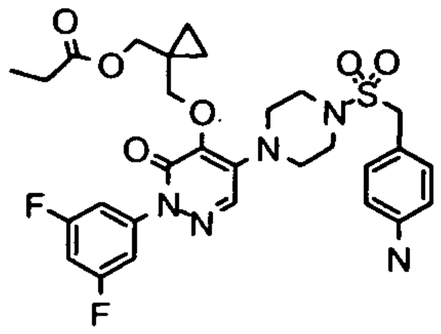
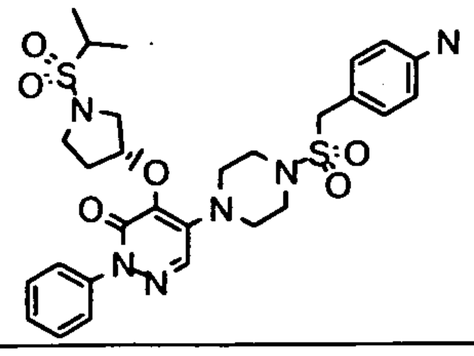
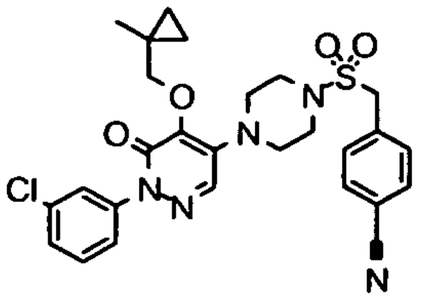
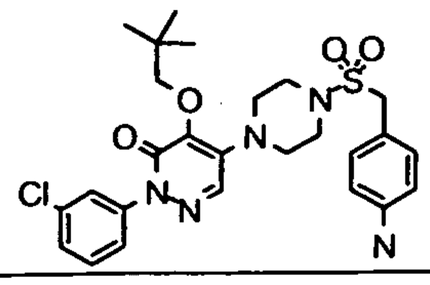
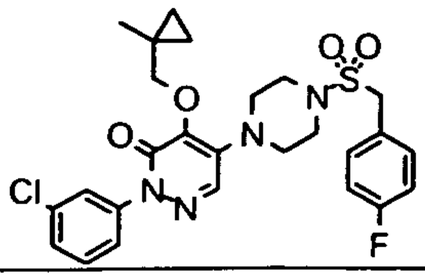
1516Z		481
1517Z		527
1518Z		534
1519Z		577
1520Z		530
1521Z		525
1522Z		521
1523Z		471
1524Z		499
1525Z		583
1526Z		531
1527Z		465
1528Z		482
1529Z		509
1529Z-1		603
1529Z-2		589

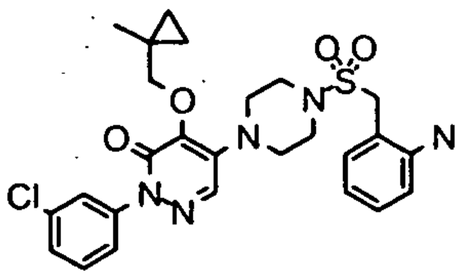
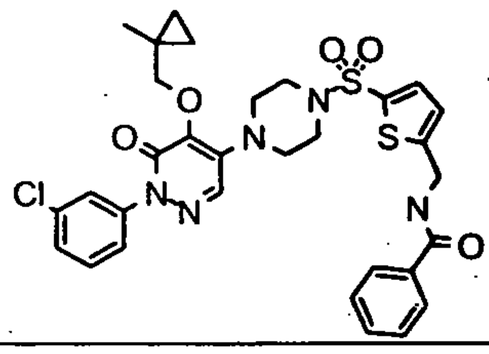
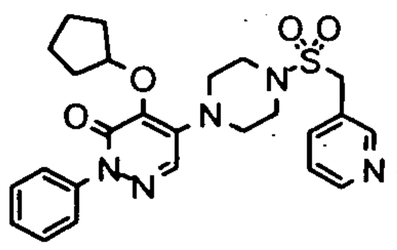
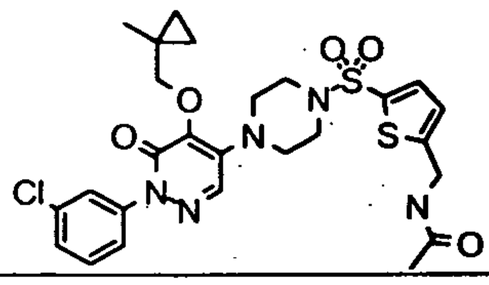
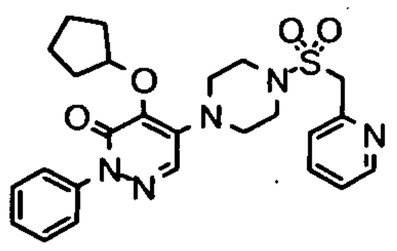
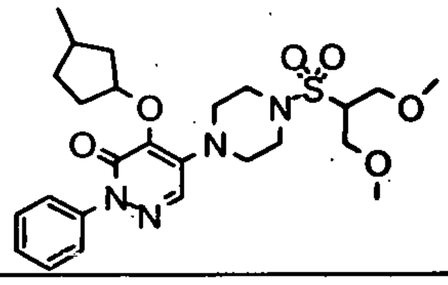
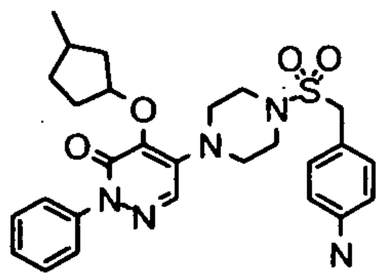
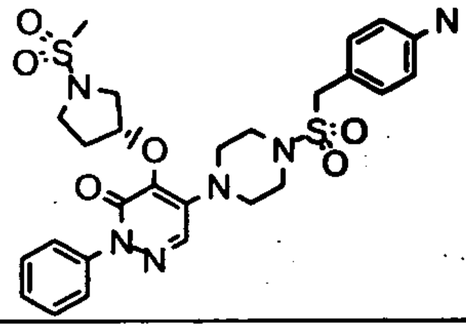
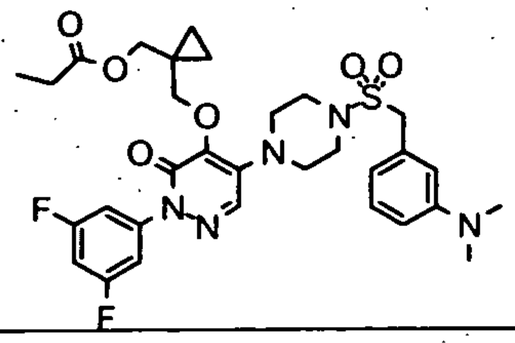
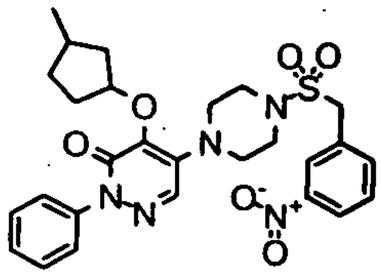
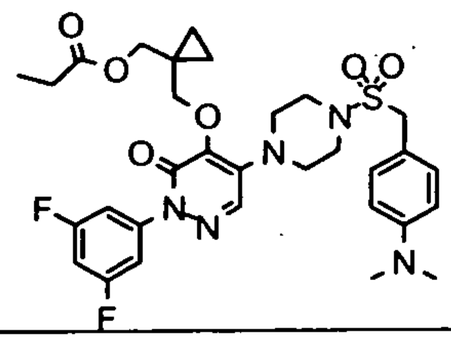
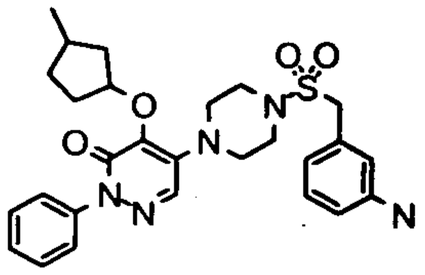
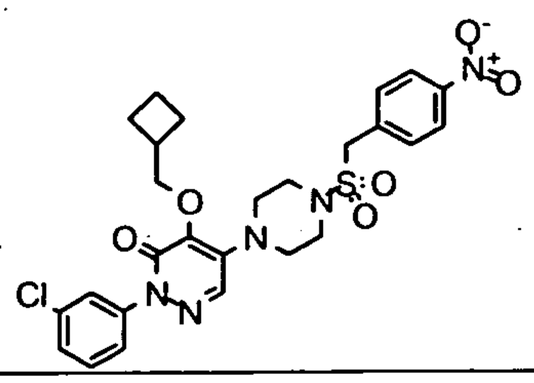
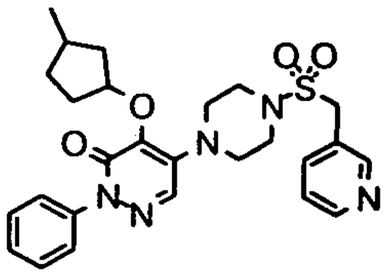
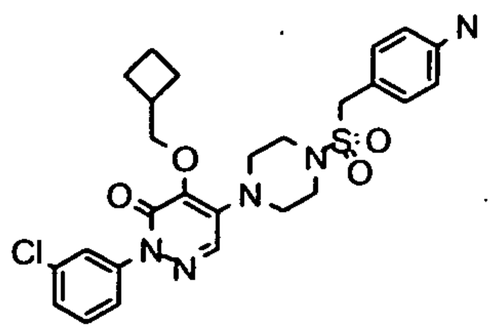
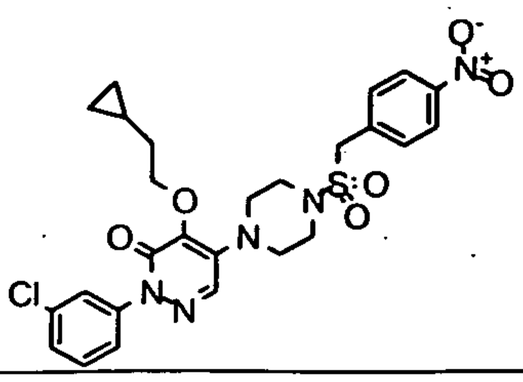
1529Z-3		541	1529Z-4		519
1529Z-5		647	1529Z-6		564
1529Z-7		634	1529Z-8		586
1529Z-9		651	1529Z-10		628
1529Z-11		604	1529Z-12		454 (M-1)
1529Z-13		606	1529Z-14		527
1529Z-15		576	1529Z-16		550

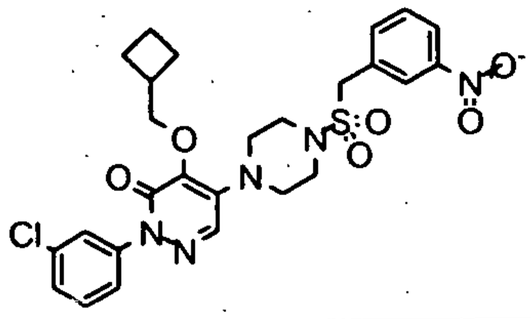
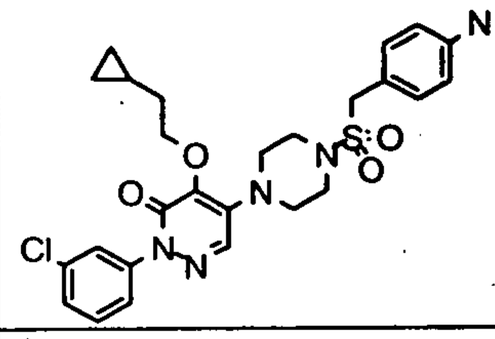
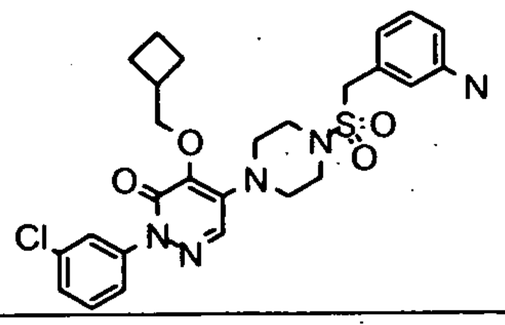
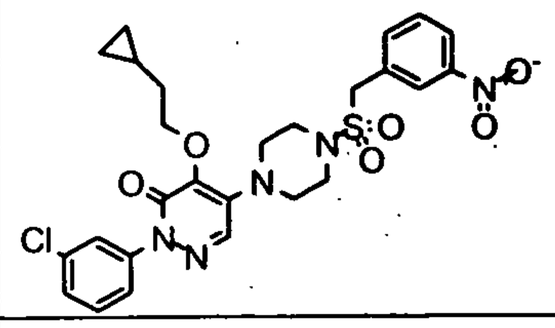
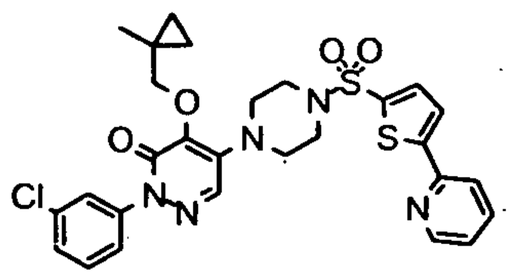
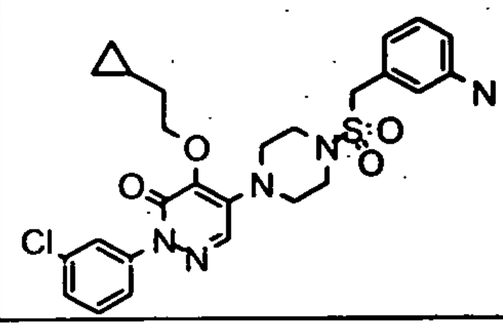
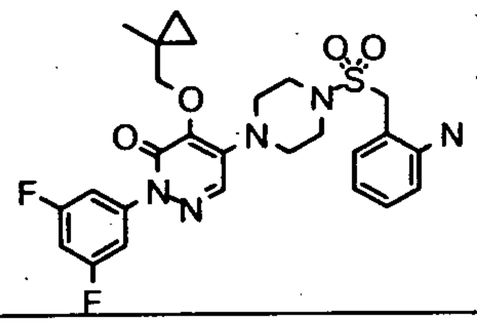
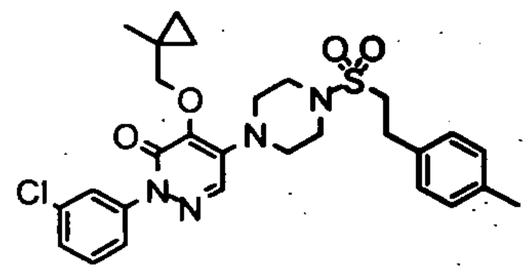
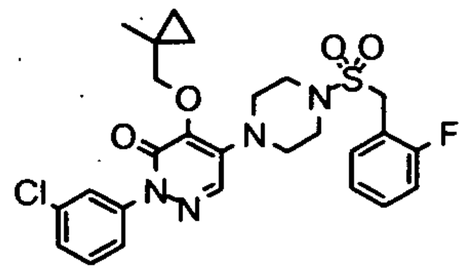
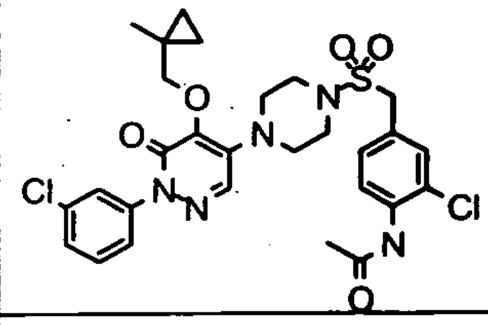
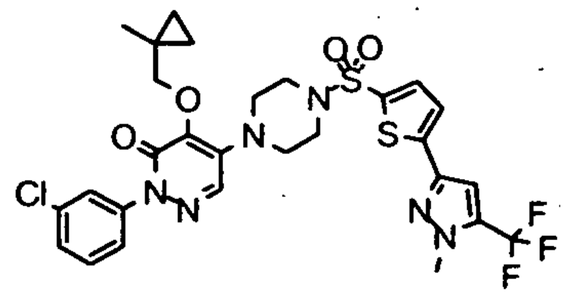
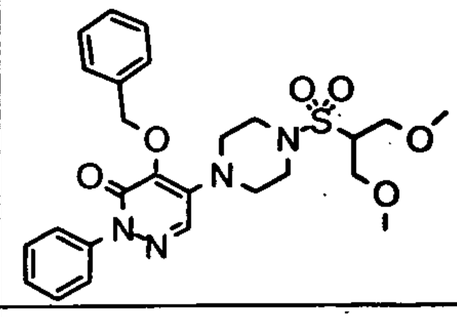
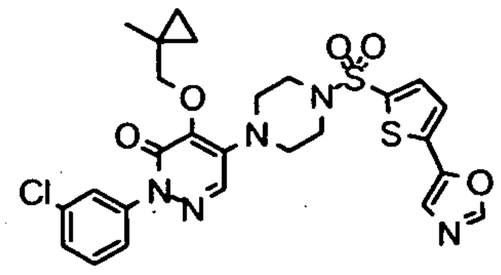
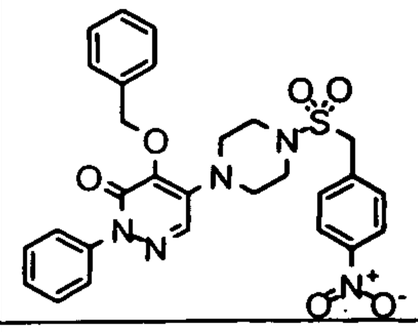
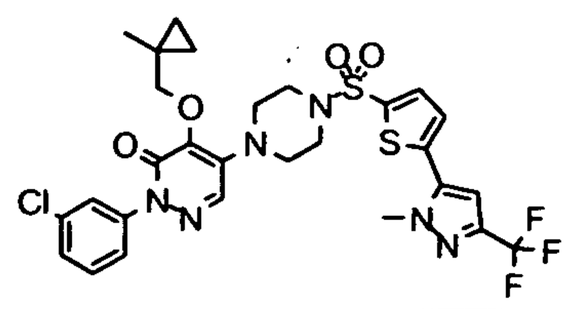
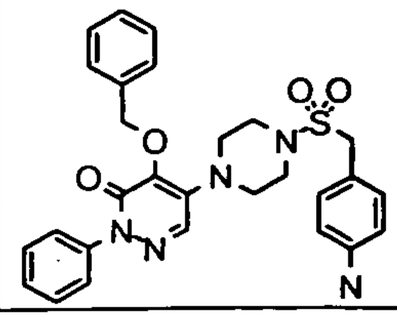
1529Z-17		596
1529Z-18		530
1529Z-19		566
1529Z-20		701
1529Z-21		587
1529Z-22		671
1529Z-23		632
1529Z-24		677
1529Z-25		602
1529Z-26		647
1529Z-27		568
1529Z-28		572
1529Z-29		609
1529Z-30		578

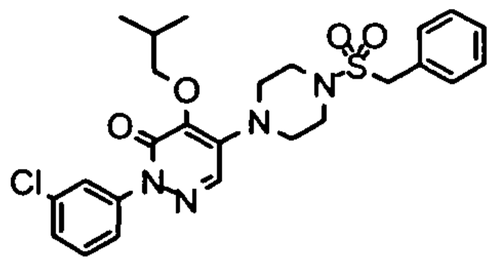
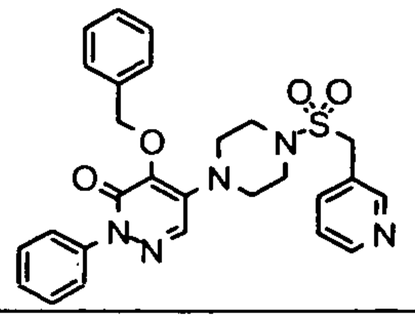
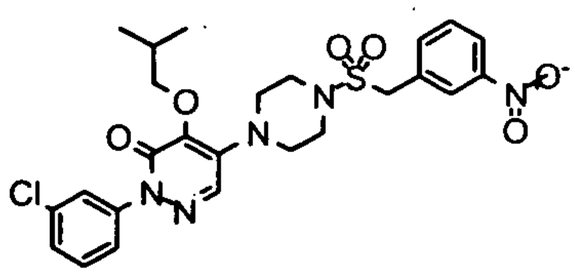
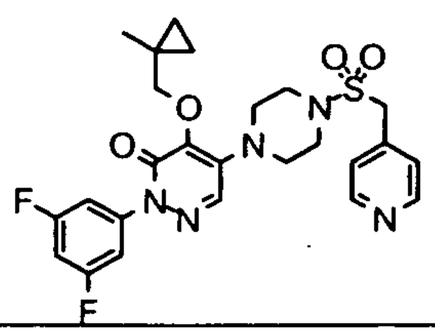
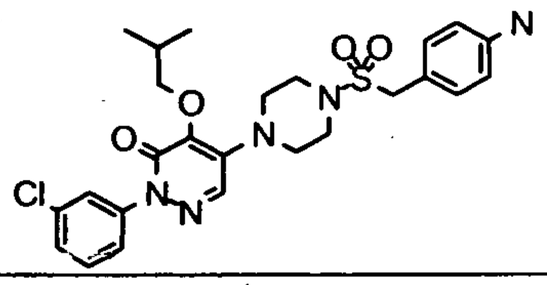
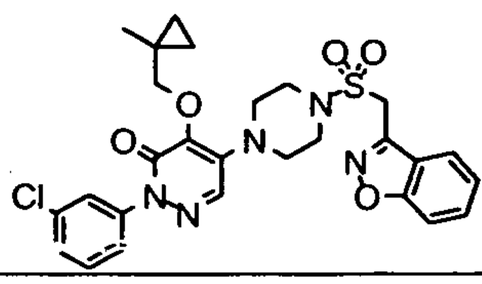
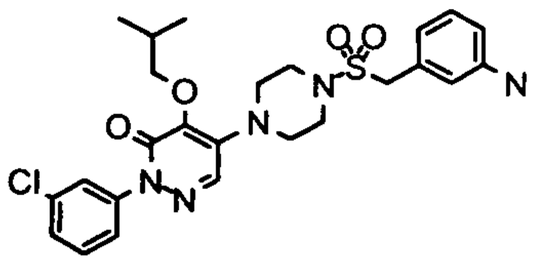
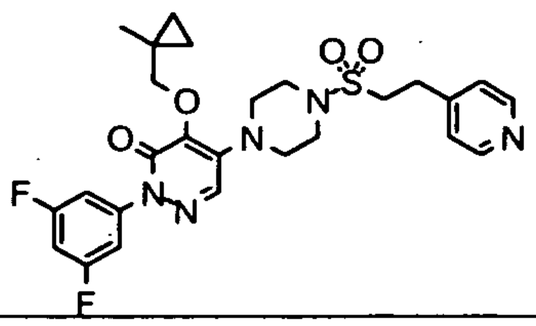
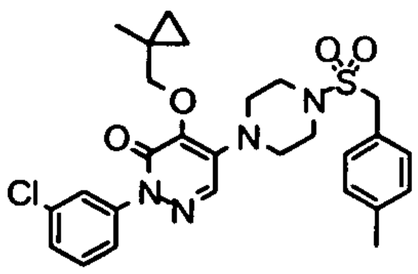
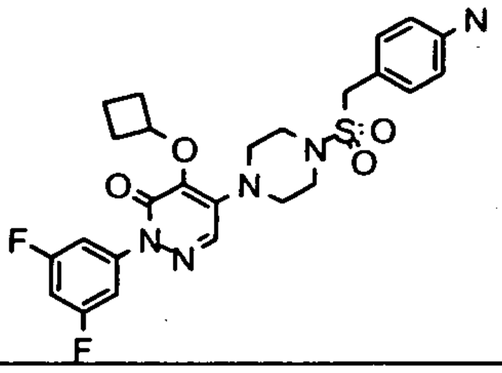
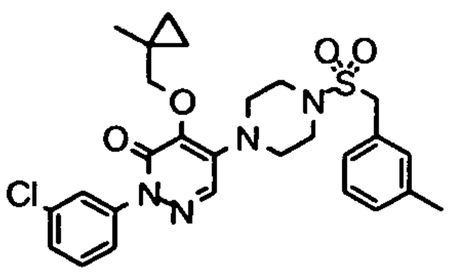
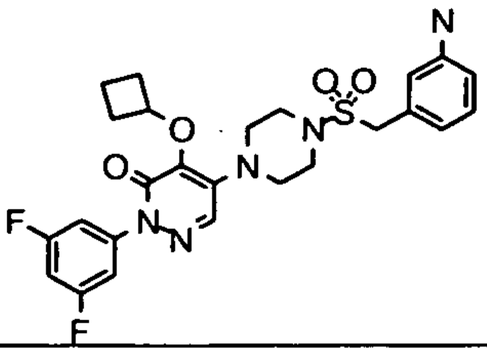
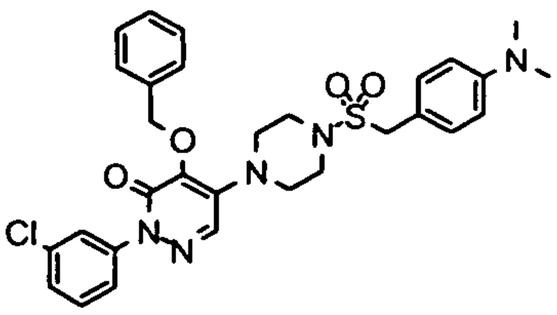
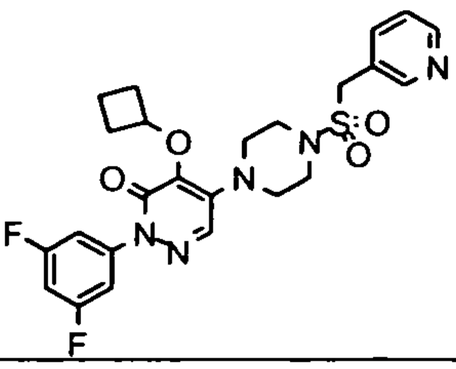
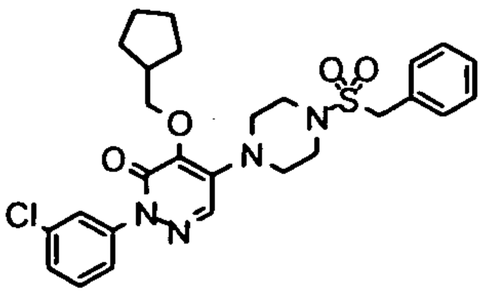
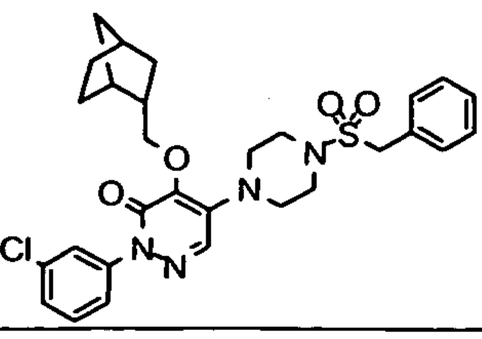
1529Z-31		558
1529Z-33		611
1529Z-35		487
1529Z-37		630
1529Z-39		543
1529Z-41		605 (M-1)
1529Z-43		586

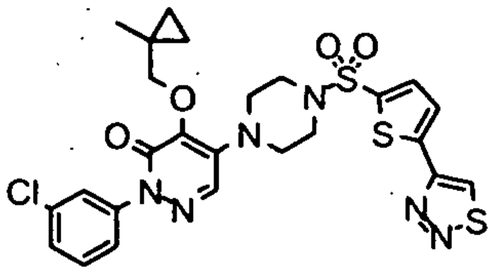
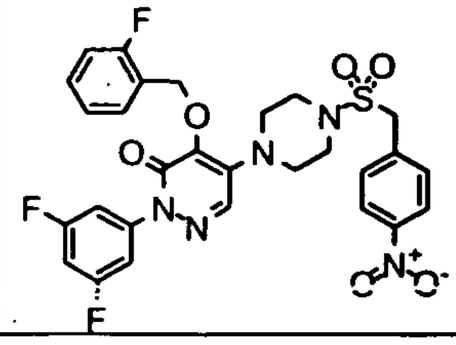
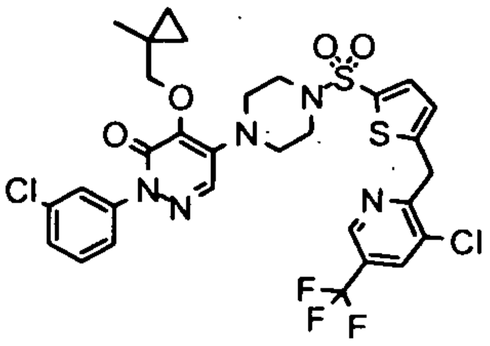
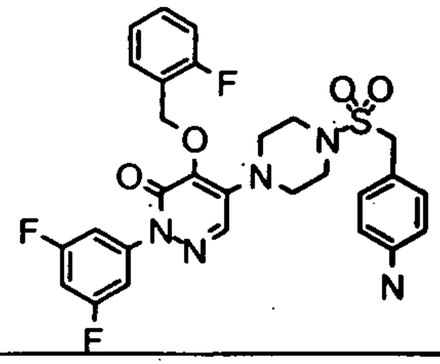
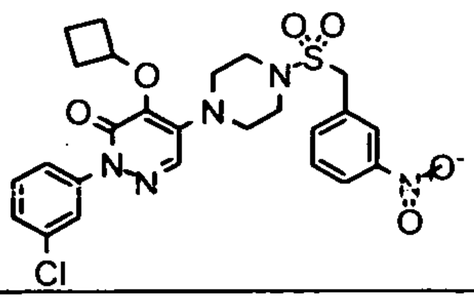
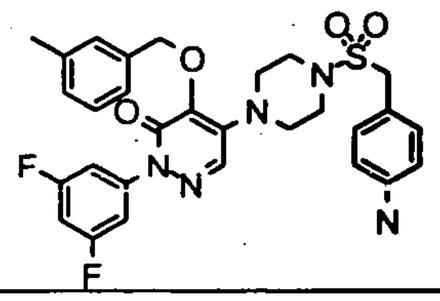
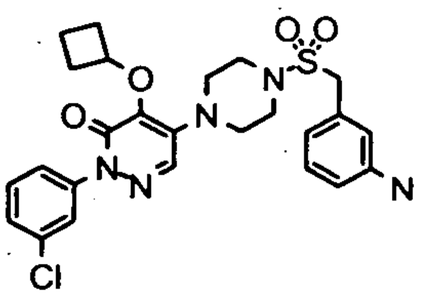
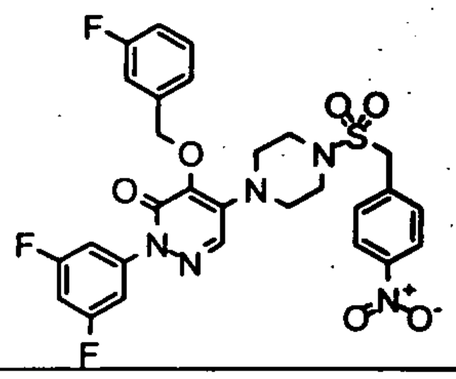
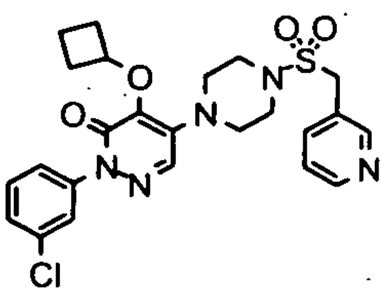
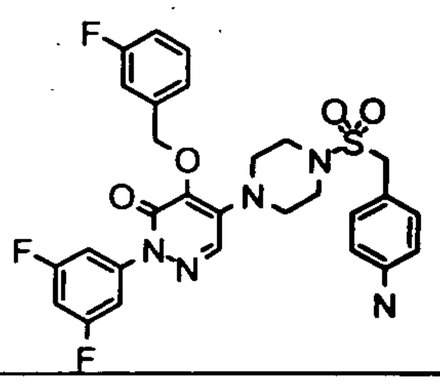
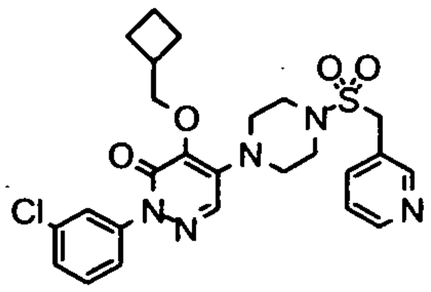
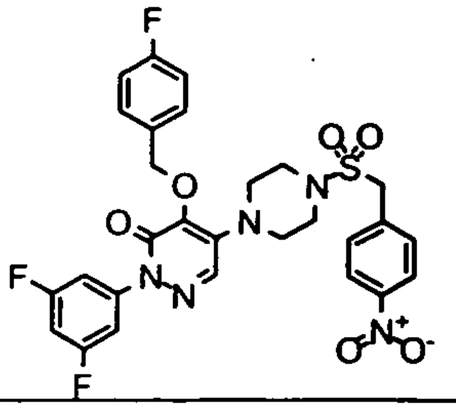
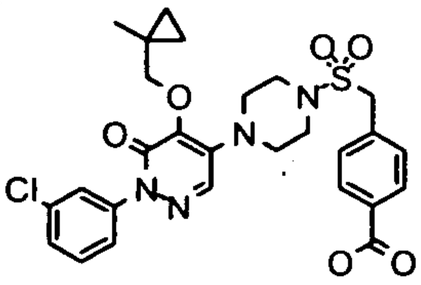
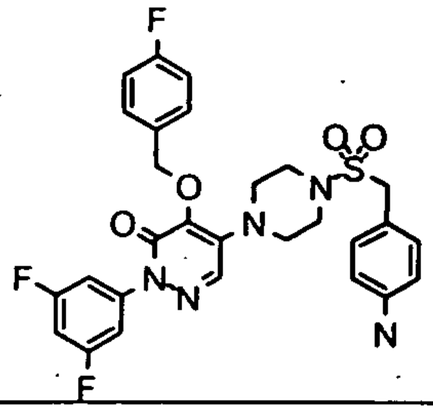
1529Z-32		548
1529Z-34		548
1529Z-36		596
1529Z-38		566
1529Z-40		546
1529Z-42		609
1529Z-44		588

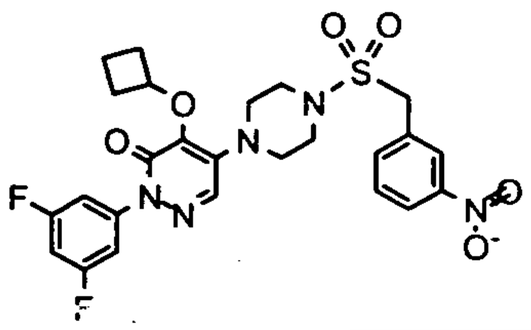
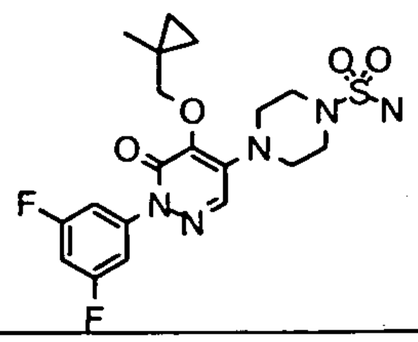
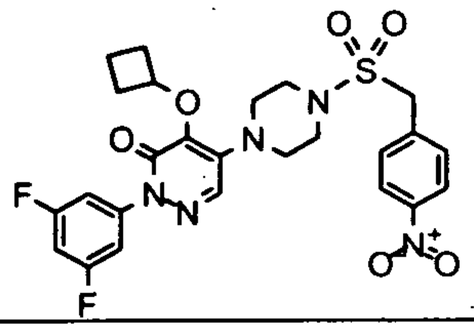
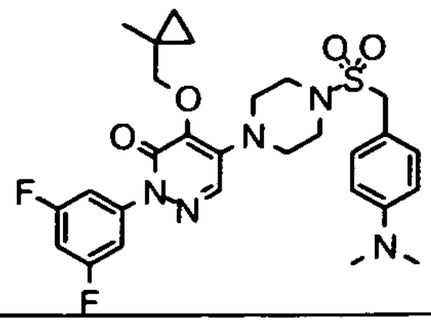
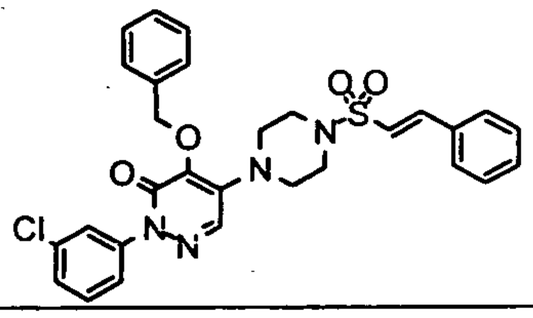
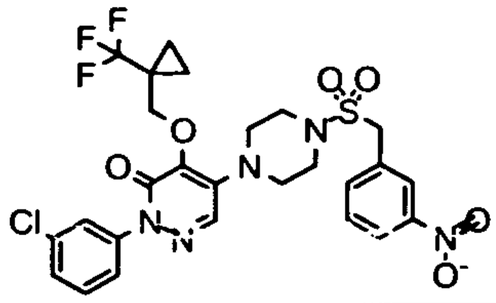
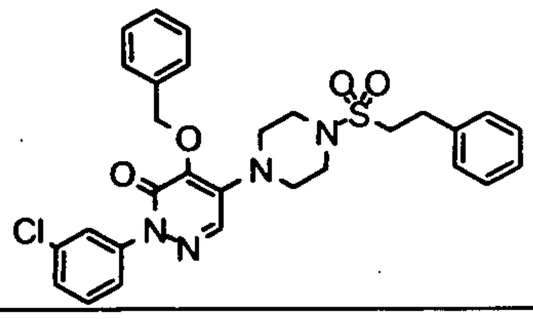
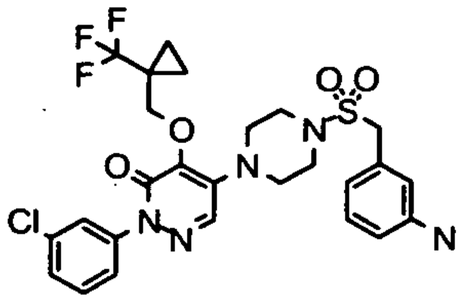
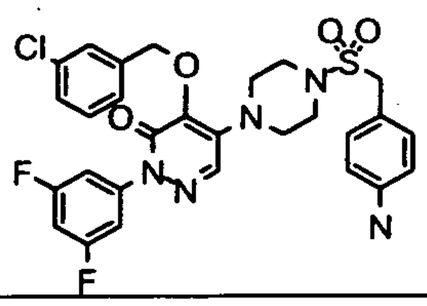
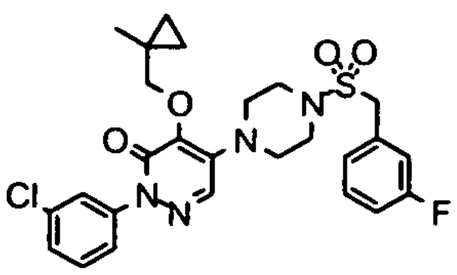
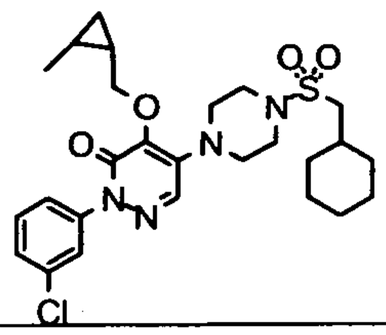
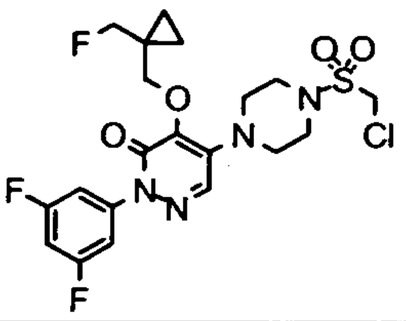
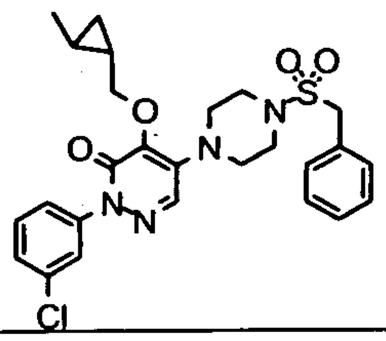
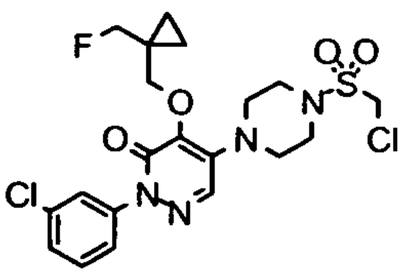
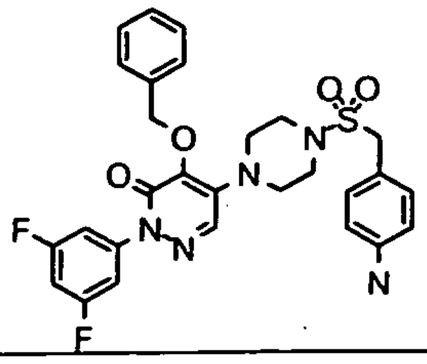
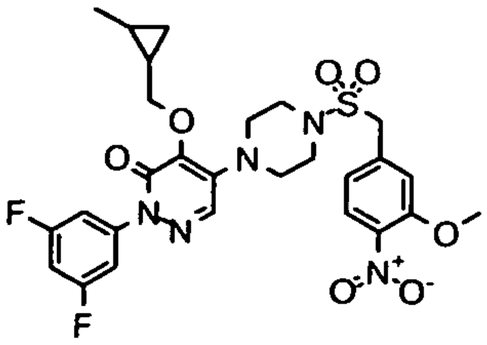
1529Z-45		701
1529Z-46		603
1529Z-47		671
1529Z-48		648
1529Z-49		677
1529Z-50		618
1529Z-51		647
1529Z-52		648
1529Z-53		647
1529Z-54		618
1529Z-55		617
1529Z-56		554
1529Z-57		546
1529Z-58		547

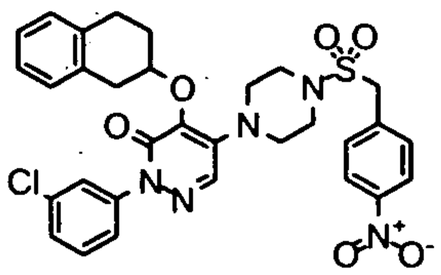
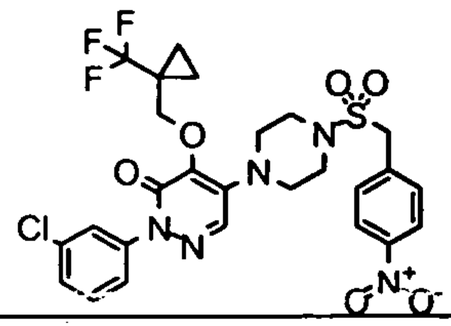
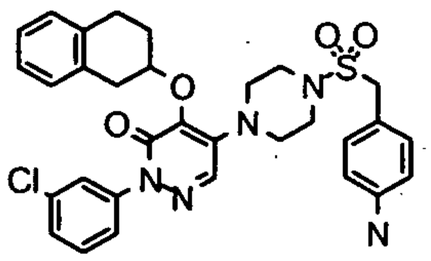
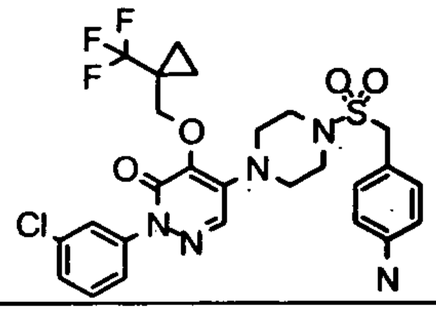
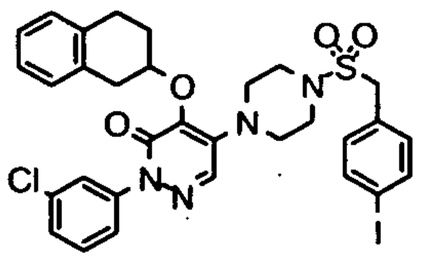
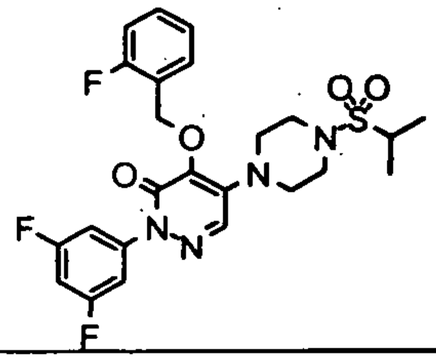
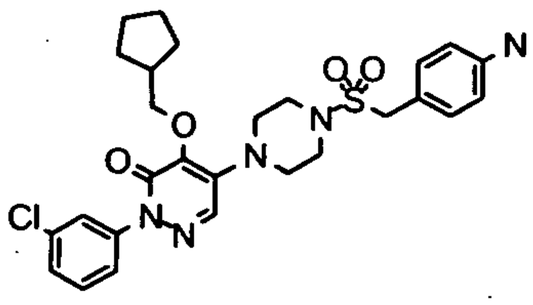
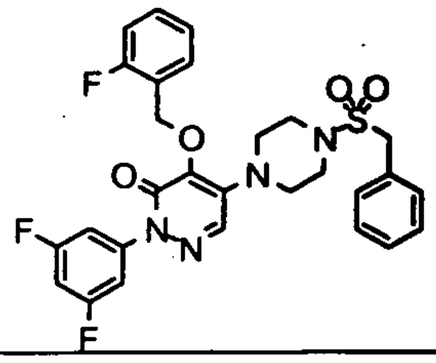
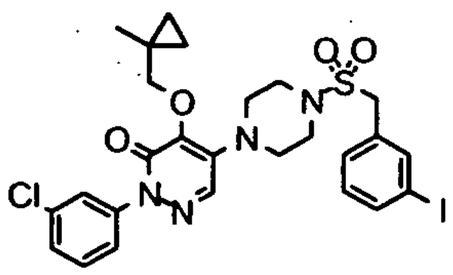
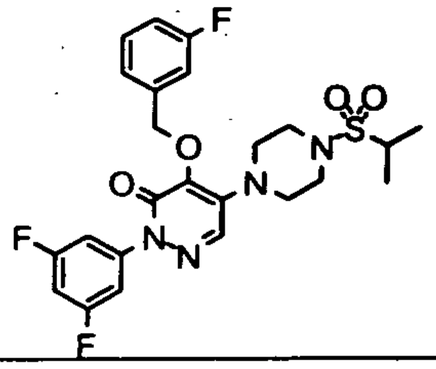
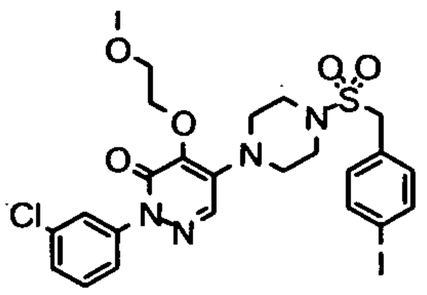
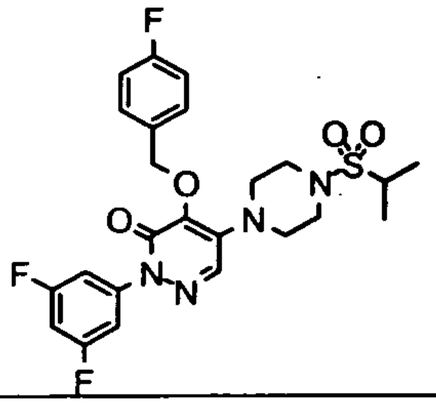
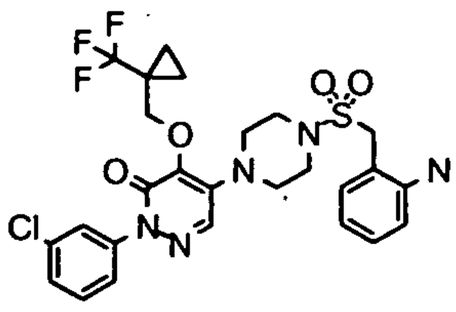
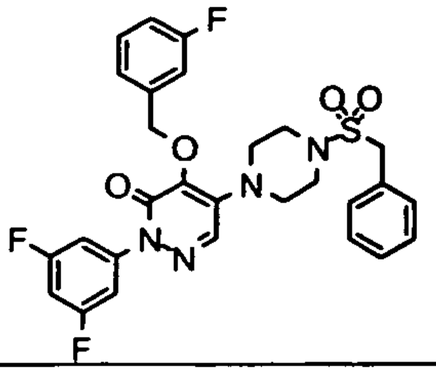
1529Z-59		544
1529Z-60		654
1529Z-61		496
1529Z-62		592
1529Z-63		496
1529Z-64		521
1529Z-65		524
1529Z-66		589
1529Z-67		646
1529Z-68		554
1529Z-69		646
1529Z-70		524
1529Z-71		574
1529Z-72		510
1529Z-73		544
1529Z-74		574

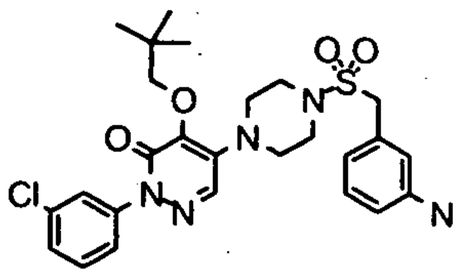
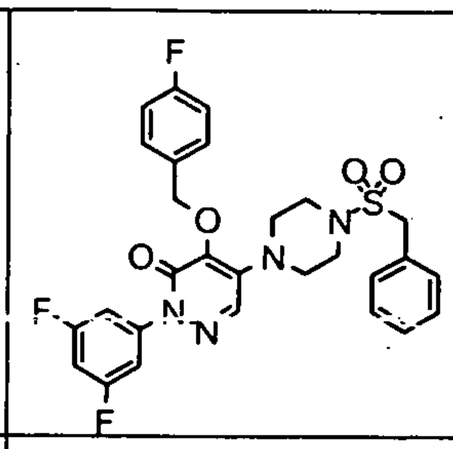
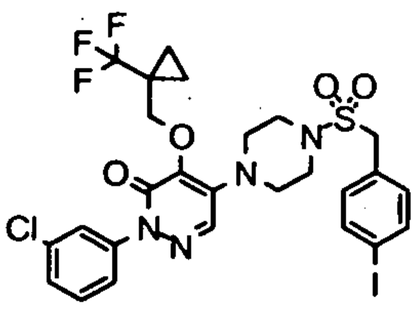
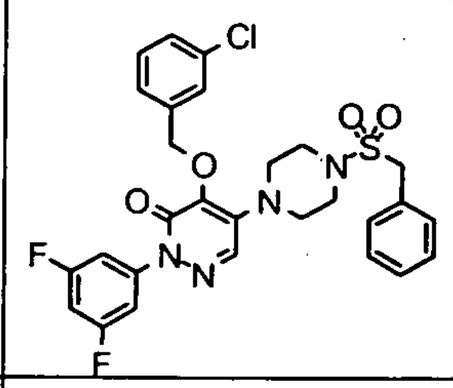
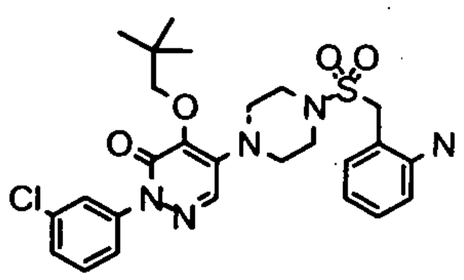
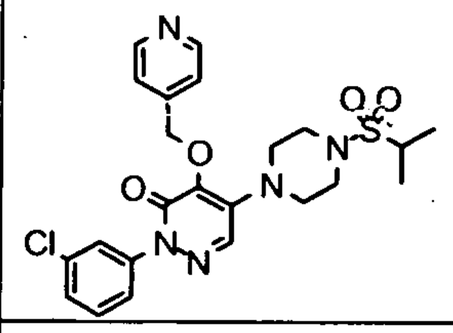
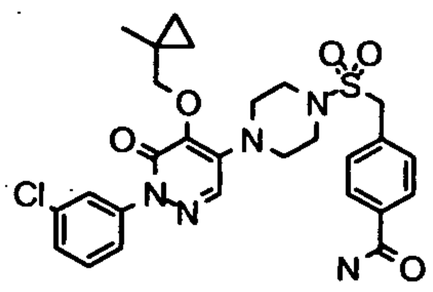
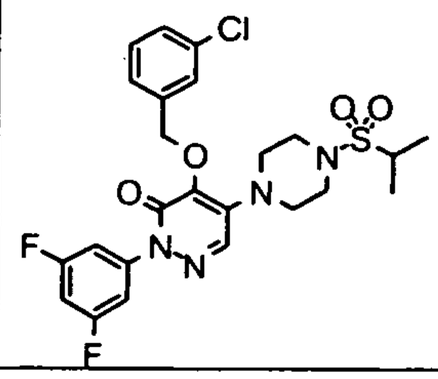
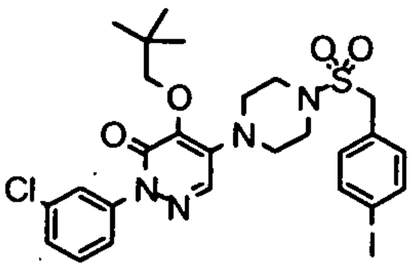
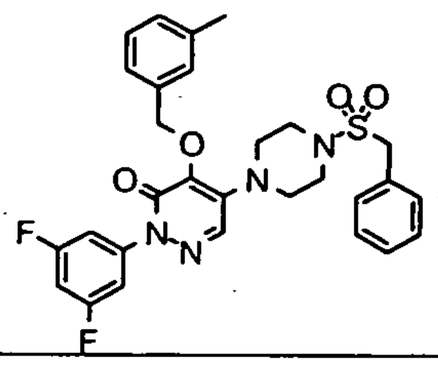
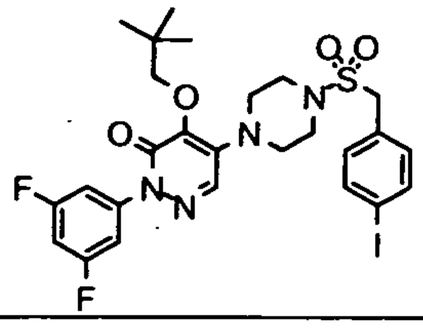
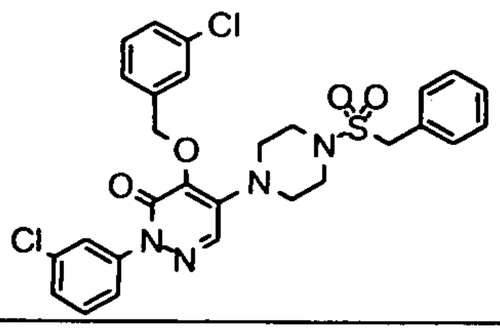
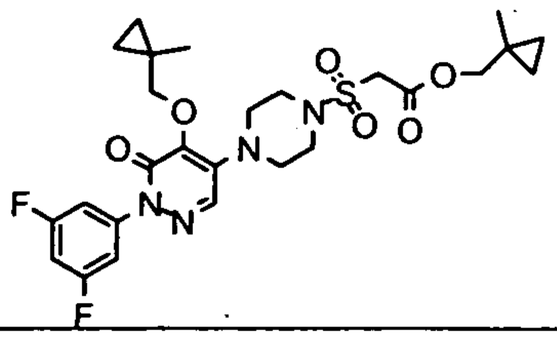
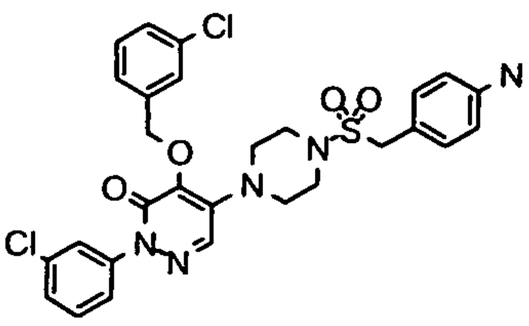
1529Z-75		574
1529Z-76		544
1529Z-77		544
1529Z-78		574
1529Z-79		598
1529Z-80		544
1529Z-81		546
1529Z-82		557
1529Z-83		547
1529Z-84		618 (M-1)
1529Z-85		669
1529Z-86		529
1529Z-87		588
1529Z-88		562
1529Z-89		669
1529Z-90		532

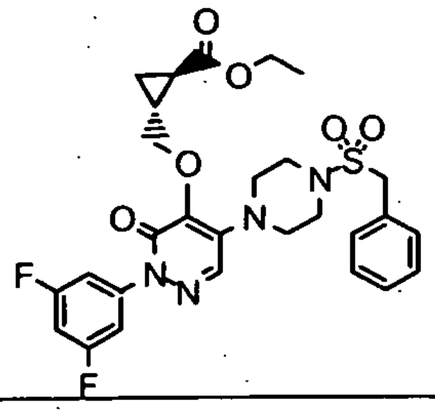
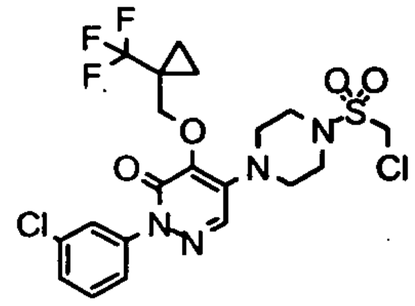
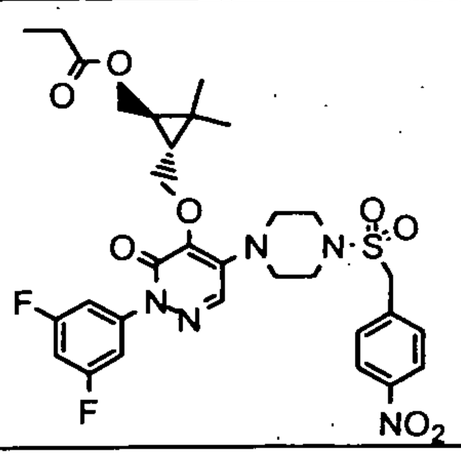
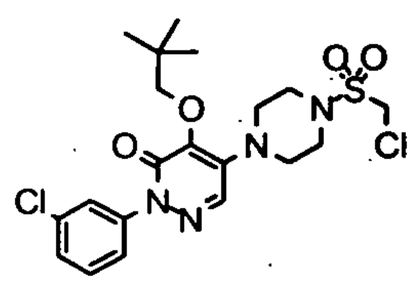
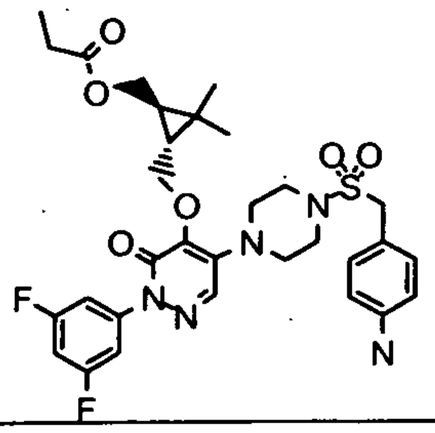
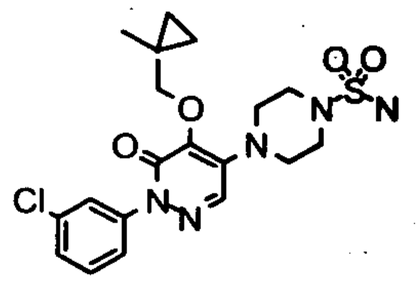
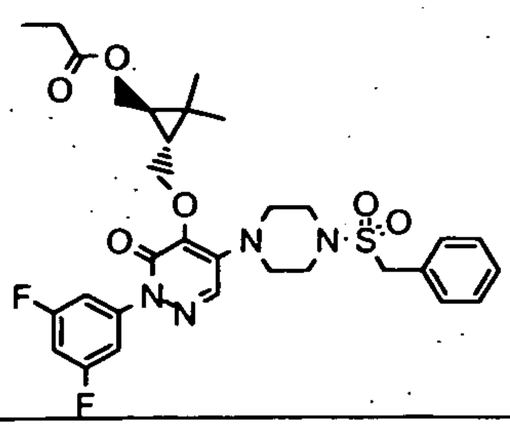
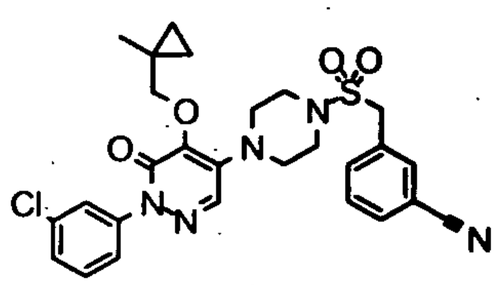
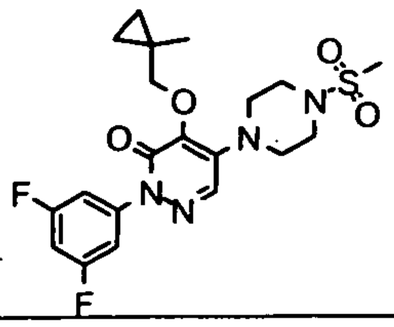
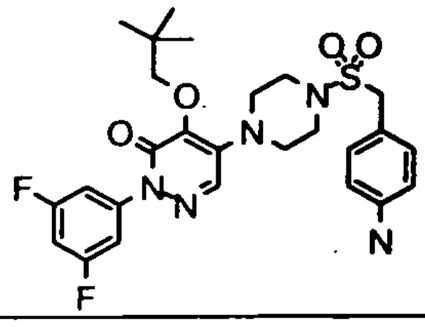
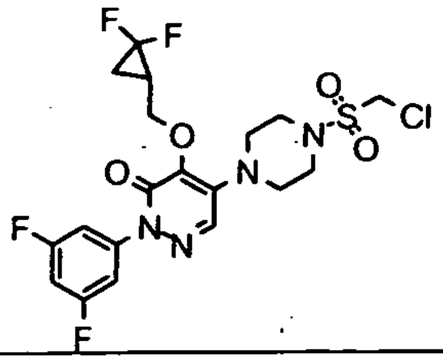
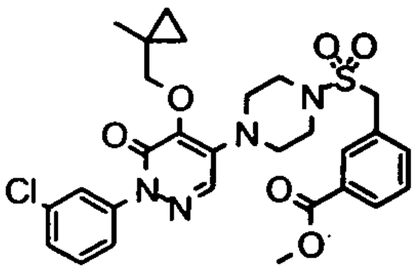
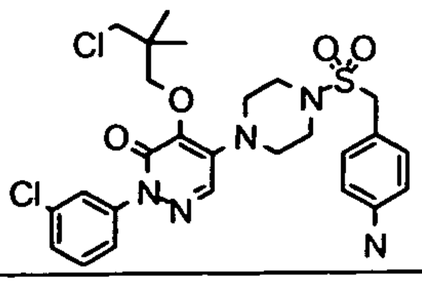
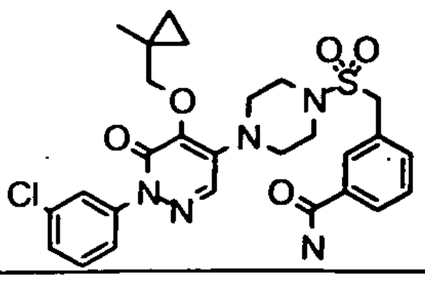
1529Z-91		517
1529Z-92		518
1529Z-93		562
1529Z-94		532
1529Z-95		532
1529Z-96		570
1529Z-97		532
1529Z-98		547
1529Z-99		543
1529Z-100		532
1529Z-101		543
1529Z-102		532
1529Z-103		594
1529Z-104		518
1529Z-105		543
1529Z-106		569

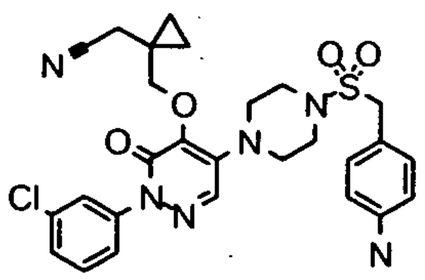
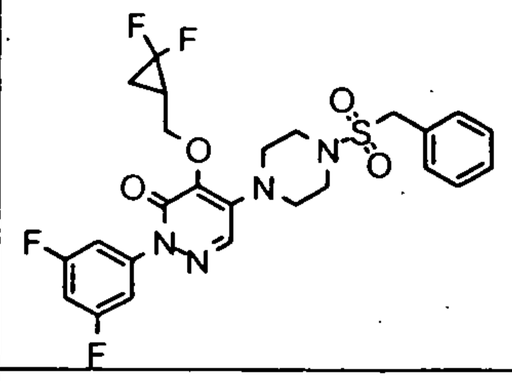
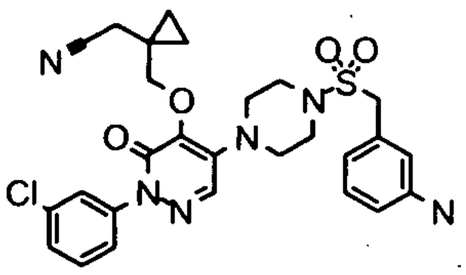
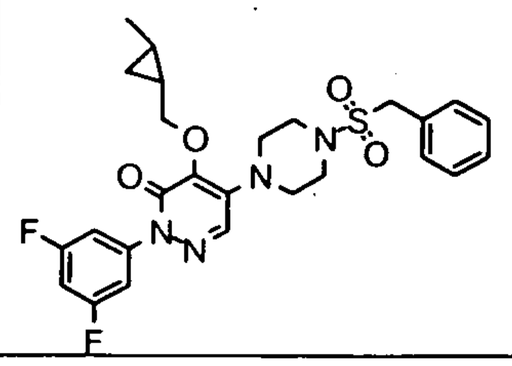
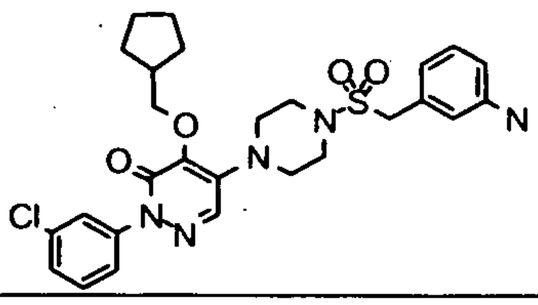
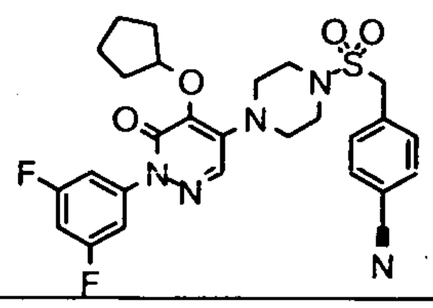
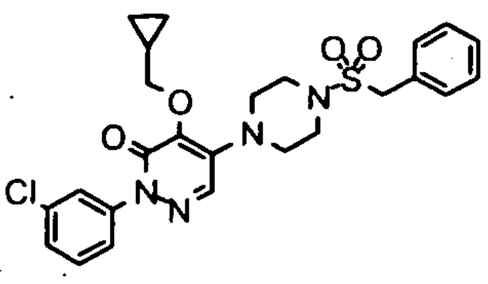
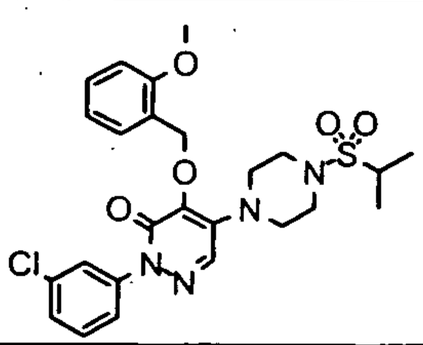
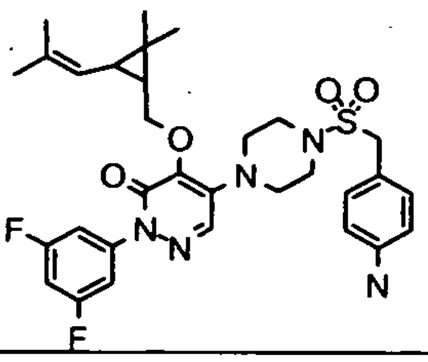
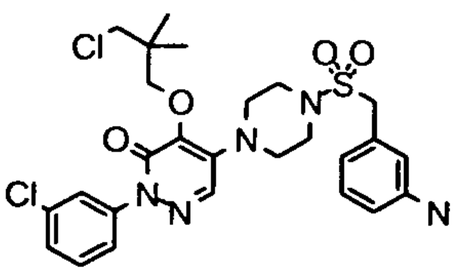
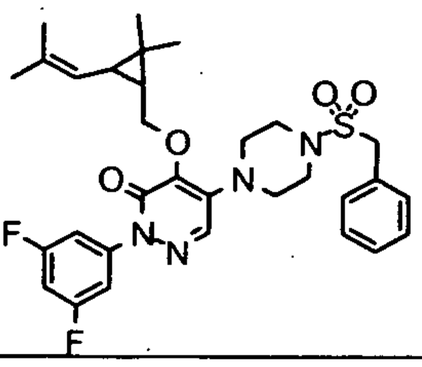
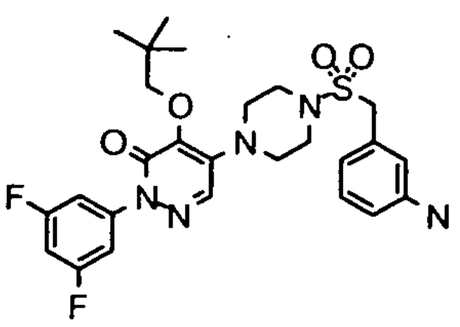
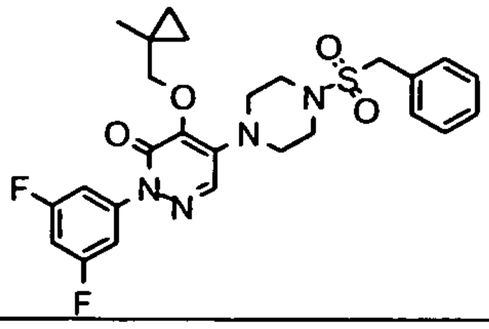
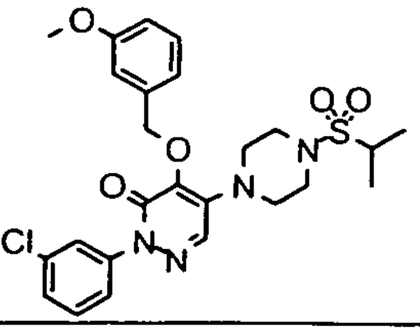
1529Z-107		605
1529Z-108		616
1529Z-109		714
1529Z-110		586
1529Z-111		560
1529Z-112		582
1529Z-113		530
1529Z-114		616
1529Z-115		516
1529Z-116		586
1529Z-117		530
1529Z-118		616
1529Z-119		571 (M-1)
1529Z-120		586

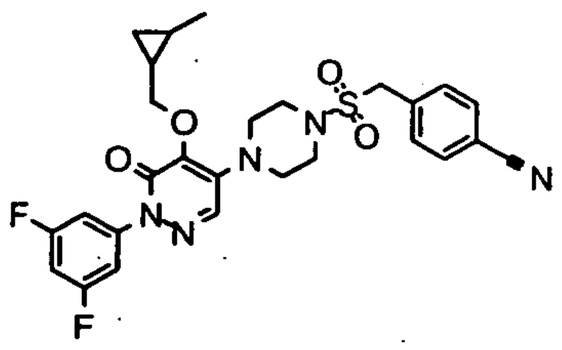
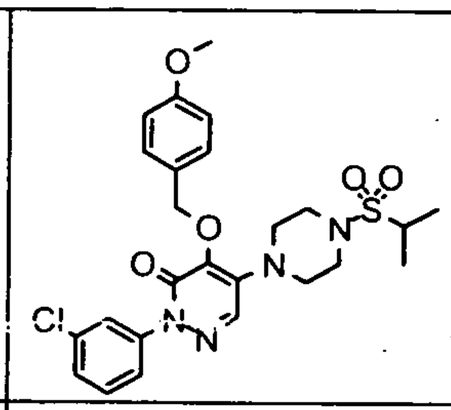
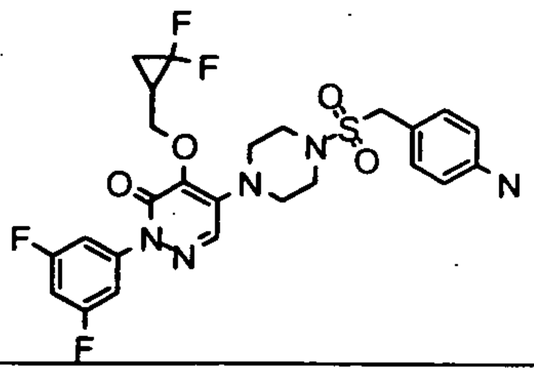
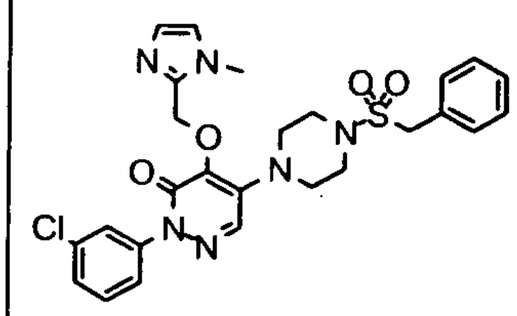
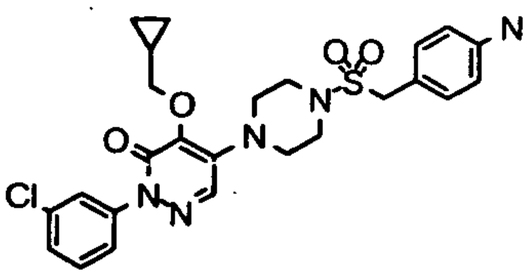
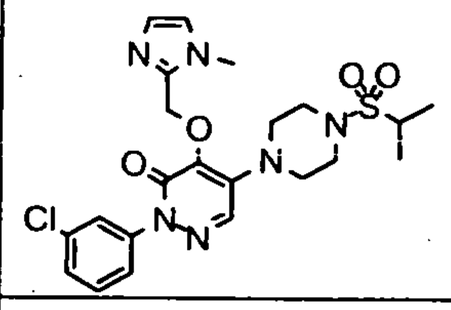
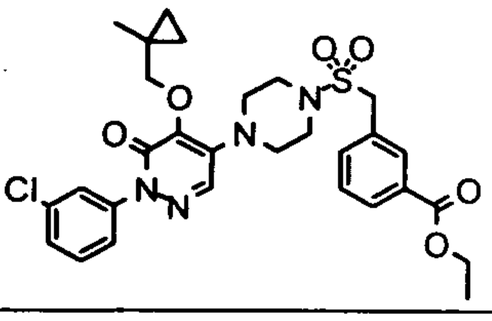
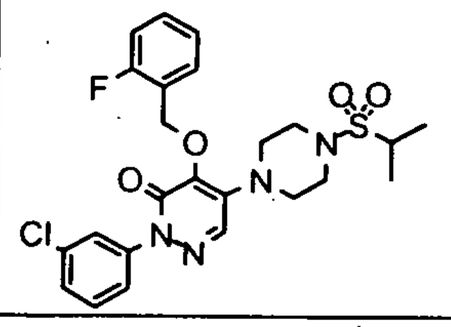
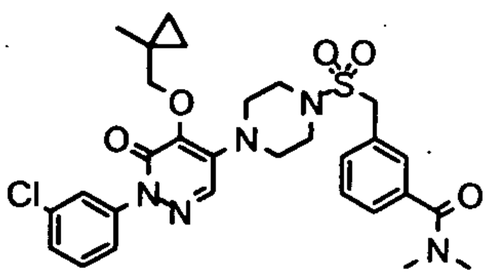
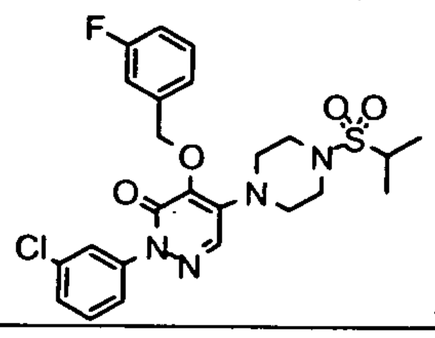
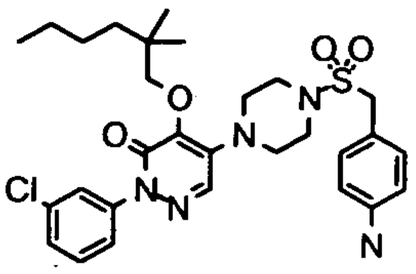
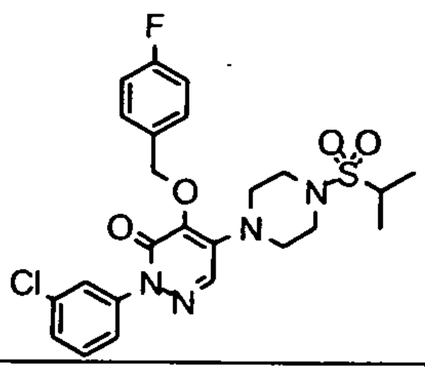
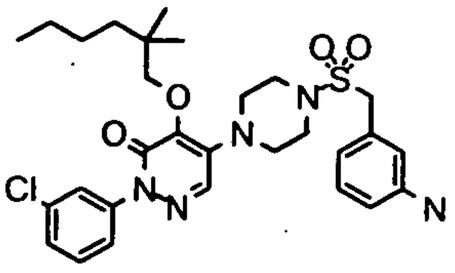
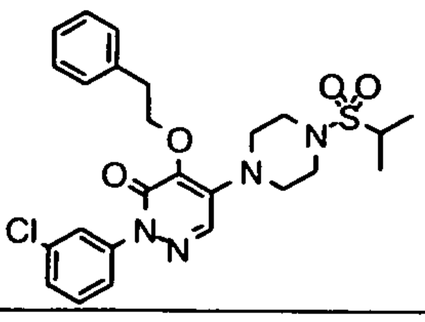
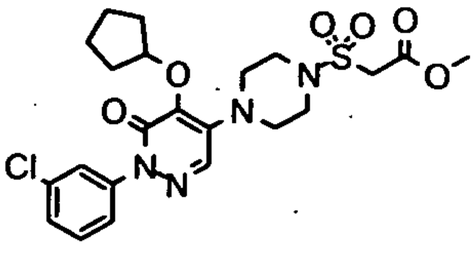
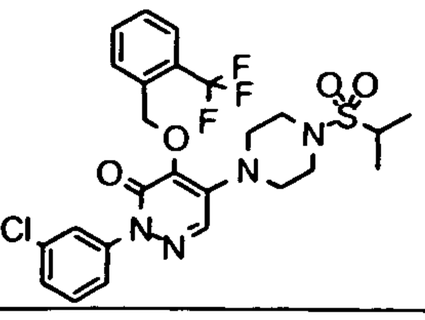
1529Z-121		562
1529Z-122		456
1529Z-123		562
1529Z-124		574
1529Z-125		563
1529Z-126		628
1529Z-127		565
1529Z-128		598
1529Z-129		602
1529Z-130		547
1529Z-131		535
1529Z-132		507
1529Z-133		530
1529Z-134		505
1529Z-135		568
1529Z-136		607

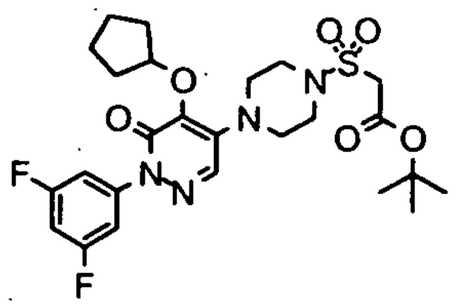
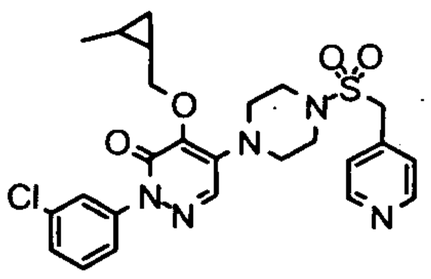
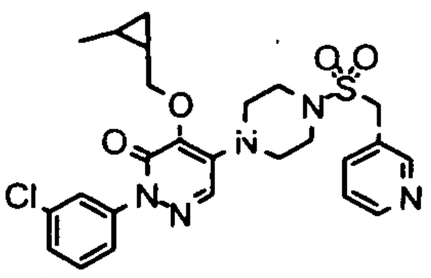
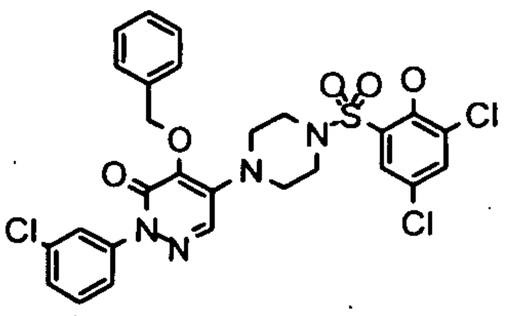
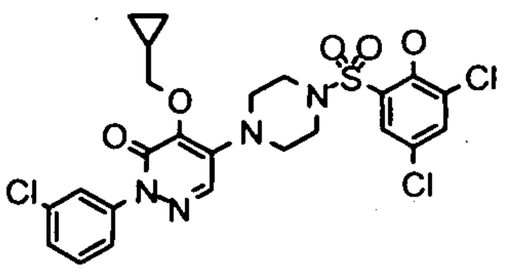
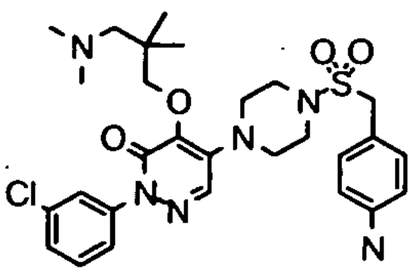
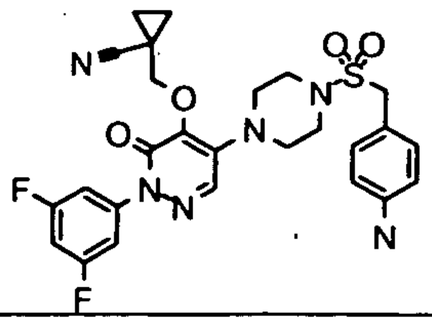
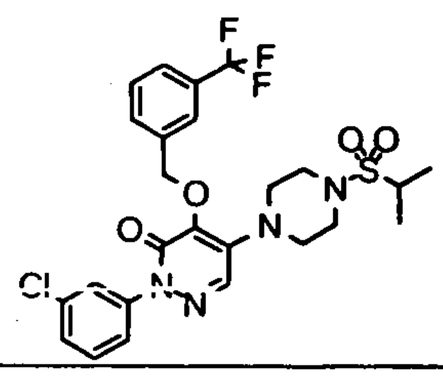
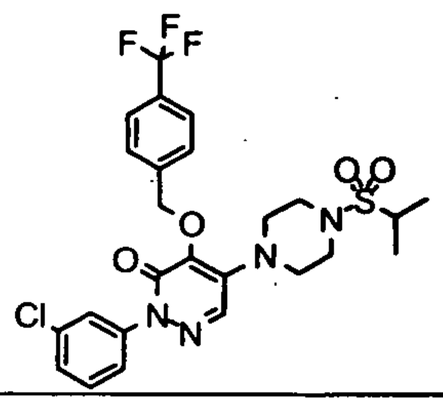
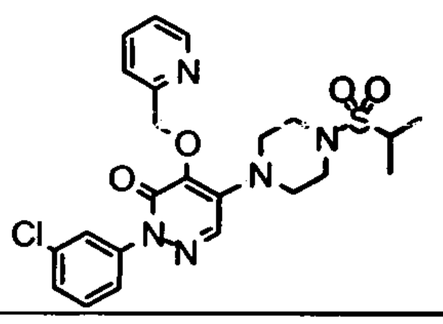
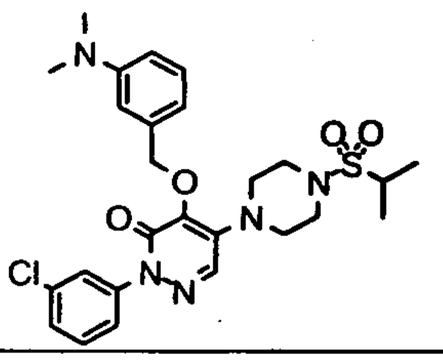
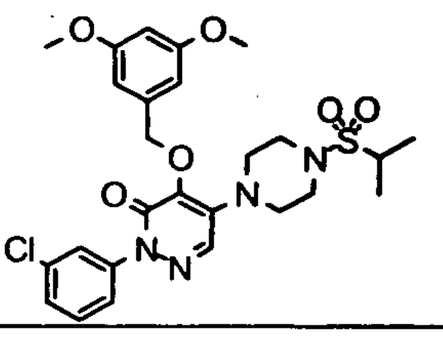
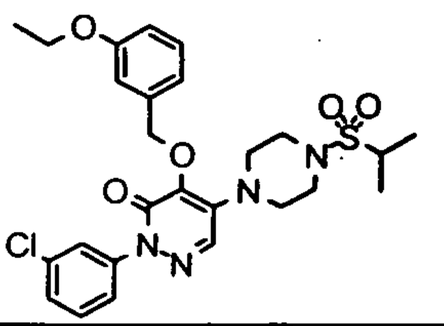
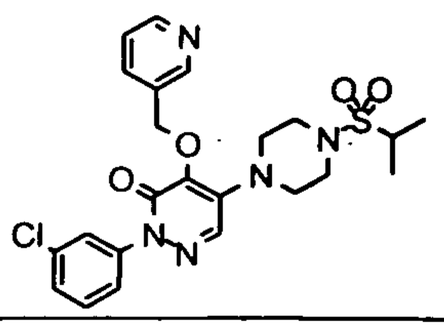
1529Z-137		636
1529Z-138		628
1529Z-139		606
1529Z-140		598
1529Z-141		717
1529Z-142		523
1529Z-143		558
1529Z-144		571
1529Z-145		653 (M-1)
1529Z-146		523
1529Z-147		645
1529Z-148		523
1529Z-149		599
1529Z-150		571

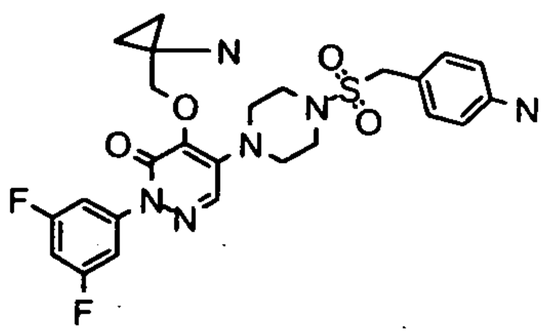
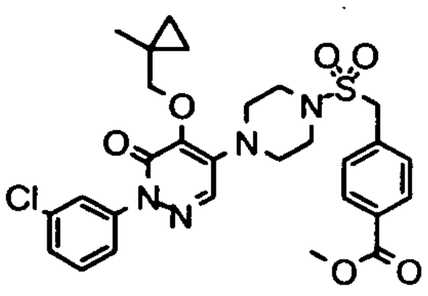
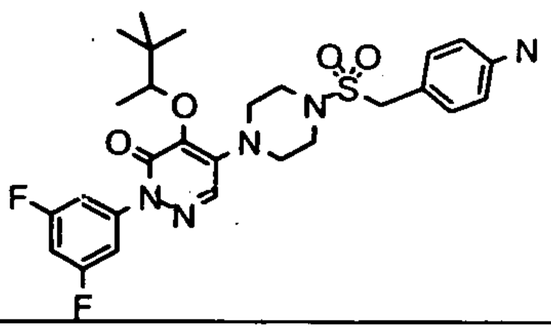
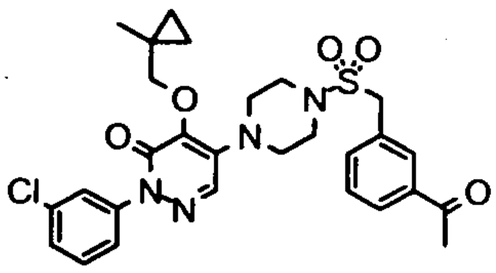
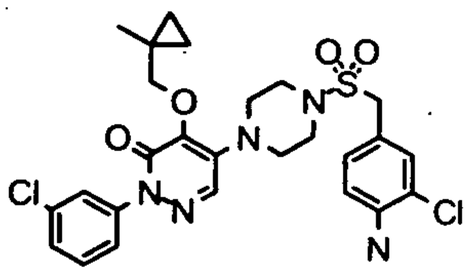
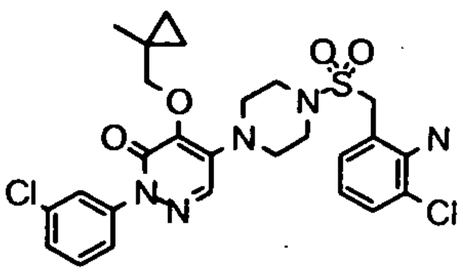
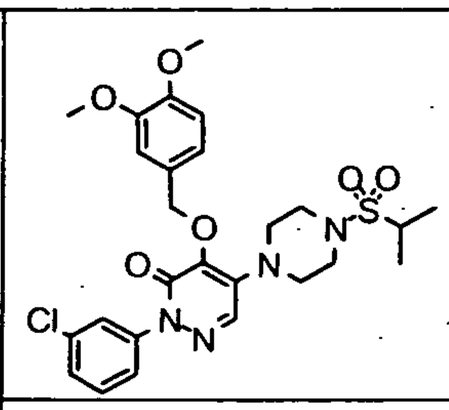
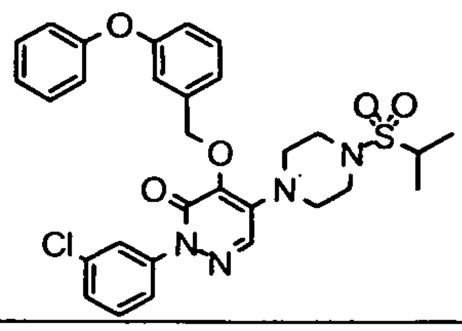
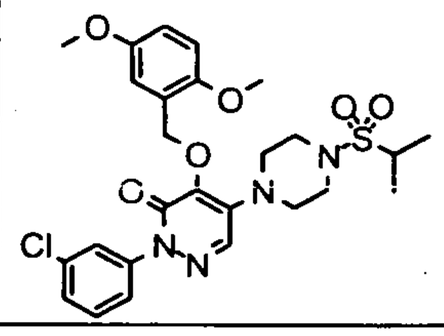
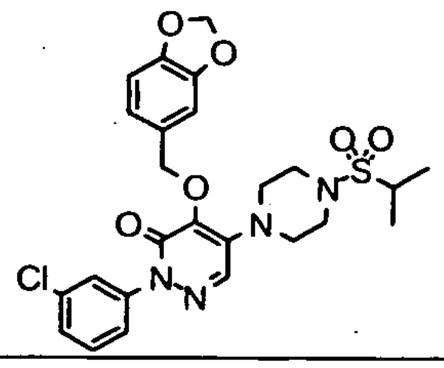
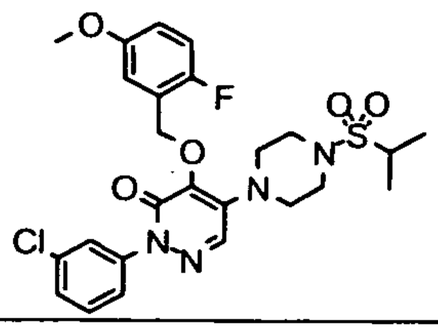
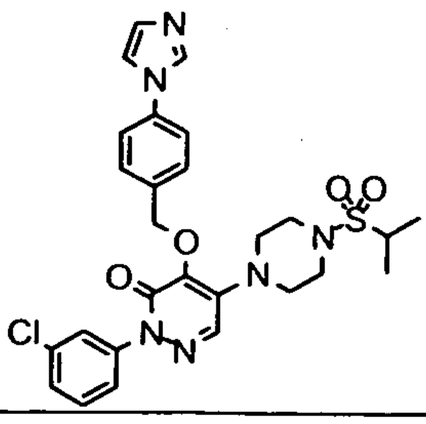
1529Z-151		546
1529Z-152		571
1529Z-153		709
1529Z-154		587
1529Z-155		546
1529Z-156		504
1529Z-157		572
1529Z-158		539
1529Z-159		657
1529Z-160		567
1529Z-161		659
1529Z-162		585
1529Z-163		567
1529Z-164		600

1529Z-165		589
1529Z-166		541
1529Z-167		676
1529Z-1689		489
1529Z-169		646
1529Z-170		454
1529Z-171		631
1529Z-172		554
1529Z-173		455
1529Z-174		548
1529Z-175		511
1529Z-176		587
1529Z-177		580
1529Z-178		572

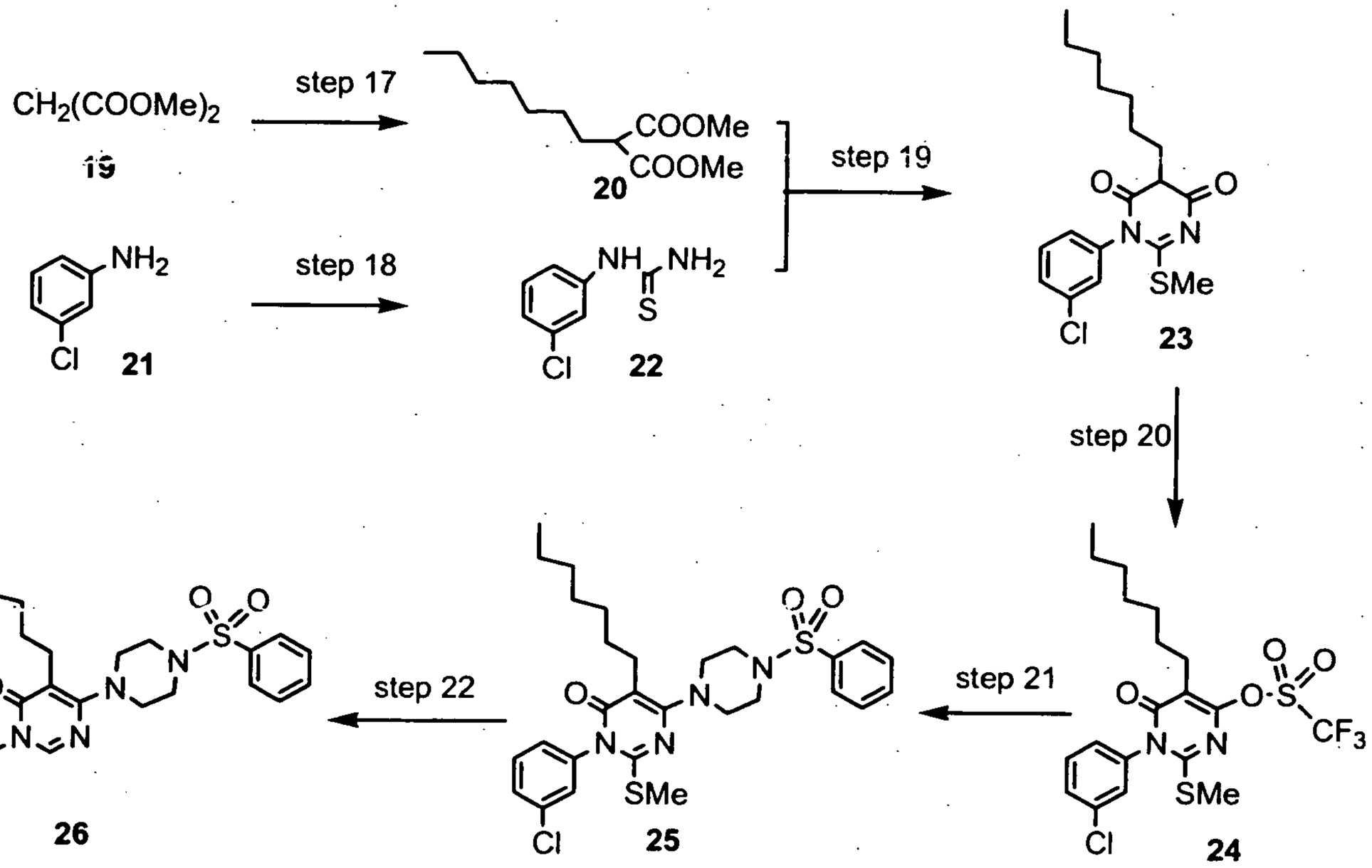
1529Z-179		569
1529Z-180		553
1529Z-181		569
1529Z-182		531
1529Z-183		558
1529Z-184		556
1529Z-185		515
1529Z-186		533
1529Z-187		614
1529Z-188		580
1529Z-189		599
1529Z-190		548
1529Z-191		531
1529Z-192		533

1529Z-193		556
1529Z-194		533
1529Z-195		568
1529Z-196		555
1529Z-197		530
1529Z-198		507
1529Z-199		601
15129Z-200		521
1529Z-201		600
1529Z-202		521
1529Z-203		588
1529Z-104		521
1529Z-105		588
1529Z-106		517
1529Z-107		511
1529Z-108		571

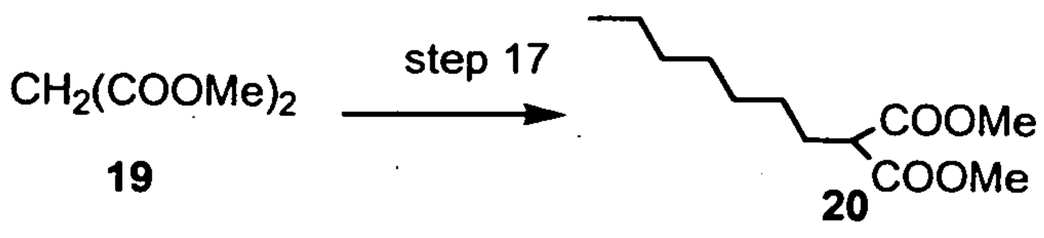
1529Z-109		555
1529Z-111		530
1529Z-113		530
1529Z-115		621
1529Z-117		585
1529Z-119		589
1529Z-121		558
1529Z-110		571
1529Z-112		571
1529Z-114		504
1529Z-116		546
1529Z-118		563
1529Z-120		547
1529Z-122		504

1529Z-123		561
1529Z-125		585 (M-1)
1529Z-127		562
1529Z-129		571
1529Z-131		578
1529Z-133		578
1529Z-124		563
1529Z-126		595
1529Z-128		563
1529Z-130		547
1529Z-132		551
1529Z-134		569

Scheme 3

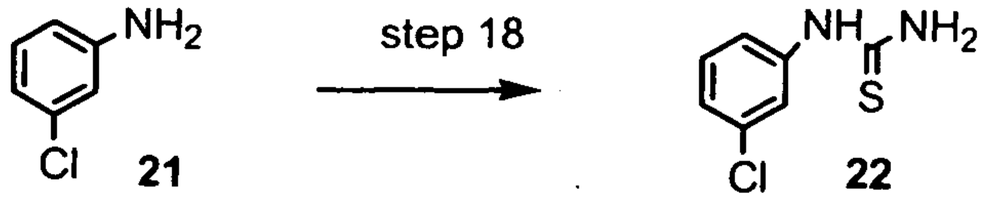


Step 17:



To a stirred solution of dimethyl malonate **19** (13.20 g, 0.10 mol) in MeOH (100 mL) was added dropwise sodium methoxide (220 mL, 0.5 M in MeOH, 0.11 mol) and then heptylbromide (16.90 g, 0.09 mol) in MeOH (30 mL). The reaction mixture was heated evaporated and $CHCl_3$ (50 mL) was added to the mixture, the resulting precipitate was removed by filtration. The concentrated filtrate was distilled under vaccum (140°C/ 14 mmHg) to give the product **20** as a colorless oil (21.0 g, 90.9%). MS (M+1): m/e 231.

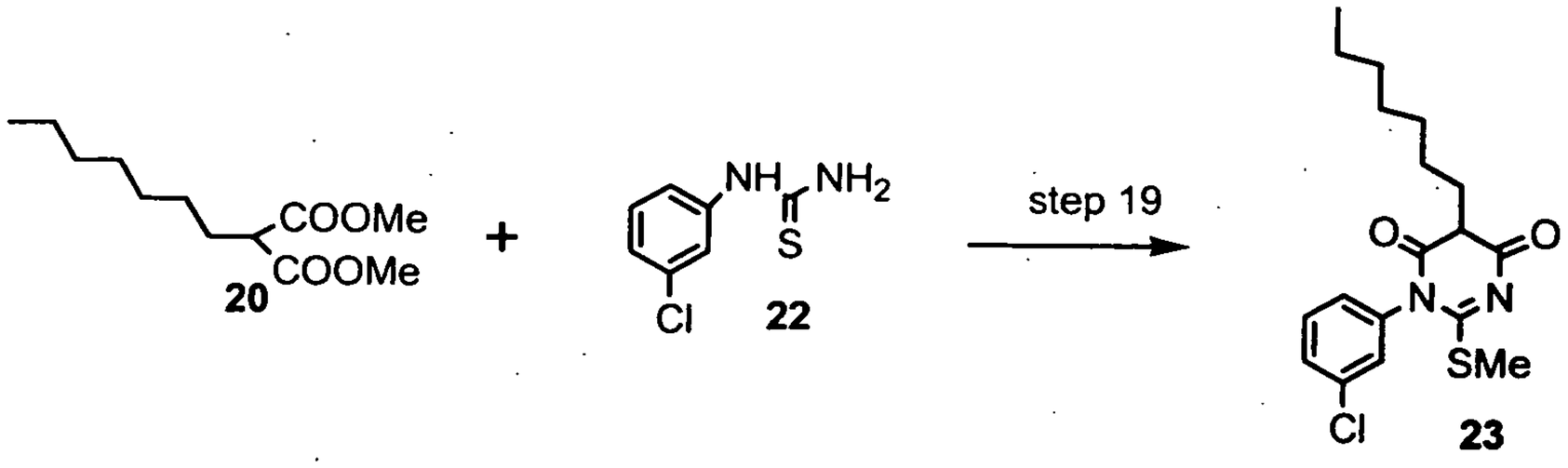
Step 18:



To a mixture of chloroaniline **21** (25.0 g, 0.20 mol) and KSCN (30.0 g, 0.30 mol) in anhydrous THF (50 mL) cooled to 0 °C was added dropwise 4N HCl in dioxane (50 mL, 0.20 mol). After the reaction mixture was heated at 80 °C for 20 h, the solvent was evaporated,

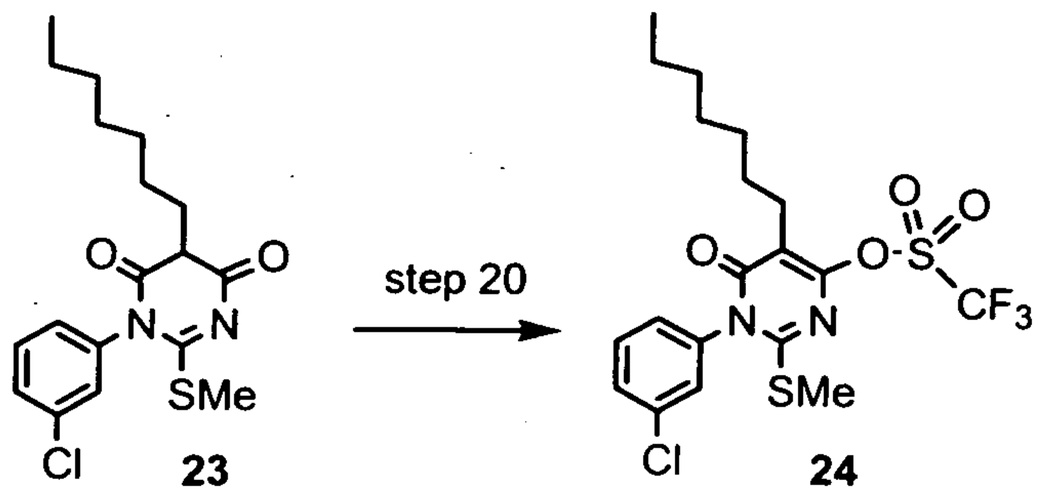
and water (20 mL) was added to the residue. After filtration, the precipitate was washed with water (20 mL) and dried to give a yellow solid. This solid was further washed with hot ethyl acetate and dried to give the product **22** (20.5 g, 55%) as a white solid.

Step 19:



To a solution of thiourea **22** (1.86 g, 0.010 mol) dissolved in anhydrous MeOH (20 mL), was added sodium methoxide (1.08 g, 0.020 mol) and compound **20** (2.30 g, 0.010 mol) at once. After the reaction mixture was heated at 65 °C for 3 h, methyl iodide (1.42 g, 0.010 mol) was added to the reaction mixture slowly over 10 min at 50 °C. The reaction mixture was further stirred at 50 °C for 30 min. The solvent was evaporated, and water (20 mL) was added. After neutralization with cold acetic acid, the white precipitate was filtered and dried under vacuum to give the desired compound **23** (3.12 g, 85%) as a white solid. MS (M+1): m/e 367.

Step 20:

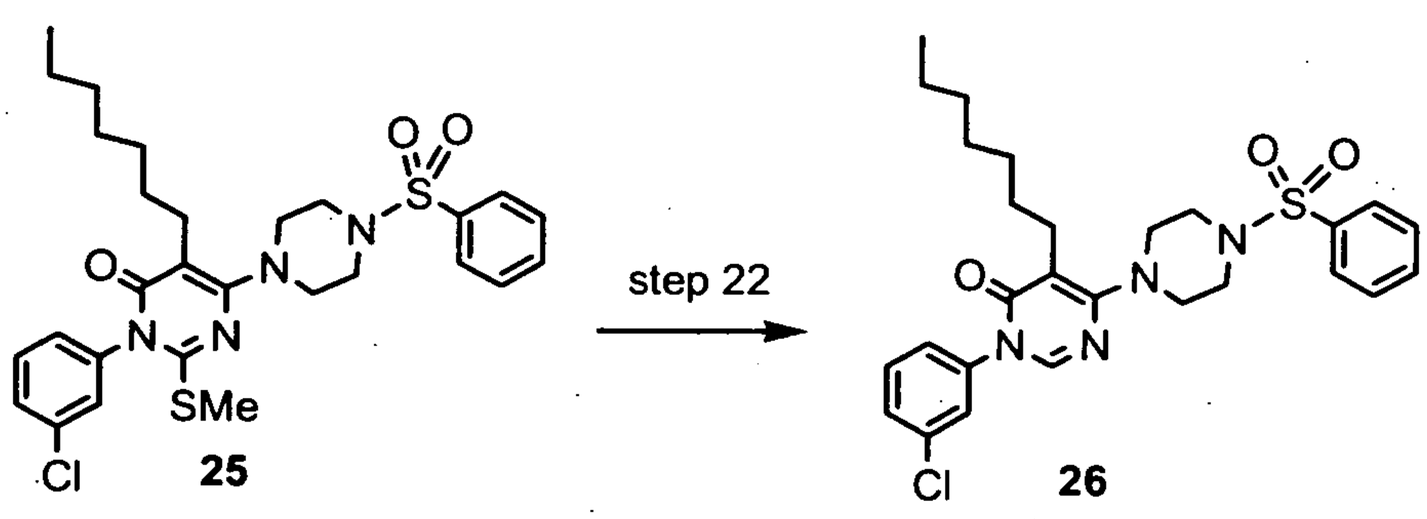


To a solution of compound **23** (1.46 g, 4.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise triflic acid (0.7 mL, 4.2 mmol) and 2, 6-lutidine (0.93 mL, 8.0 mmol) at -78 °C. The resulting solution was stirred for 2 h at –78 °C, and then allowed to warm to room temperature for 12 h. The reaction was quenched with aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was washed with 1 N HCl (10 mL), H_2O (10 mL), brine (10 mL), dried (MgSO4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 1:10 EtOAc:hexanes) gave the desired product **24** as a white solid (1.5 g, 75%). MS (M+1): m/e 499.

Step 21:

To a solution of compound **24** (0.498 g, 0.001 mol) in anhydrous chlorobenzene (10 mL) in a microwave tube was added diisopropylethyl amine (1.29 g, 0.010 mol) and benzenesulfonylpiperizine (2.26 g, 0.010 mol). After the reaction mixture was stirred at 160 °C for 2 h under microwave irradiation, the chlorobenzene was removed under vacuum. Purification by silica gel chromatography (1:5 EtOAc:hexanes) gave the desired compound **25** (0.345 g, 60%) as a light yellow oil. MS (M+1): m/e 575.

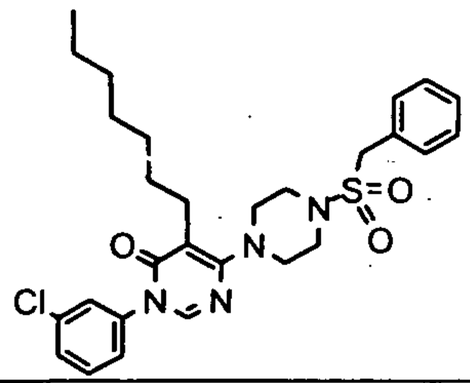
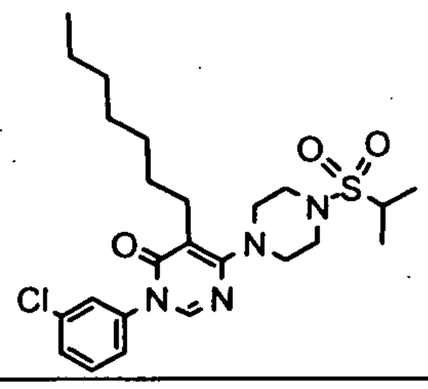
Step 22:

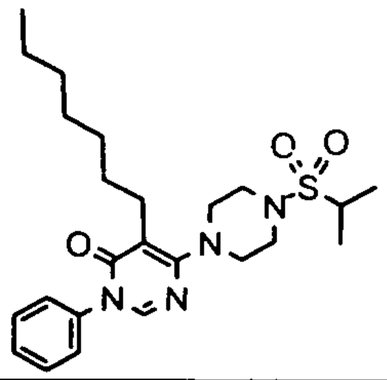
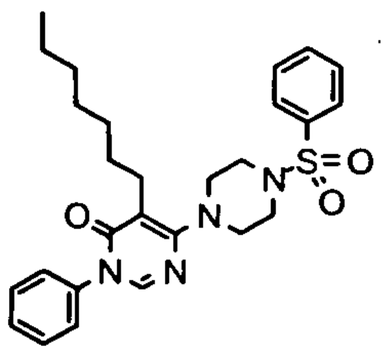


To a solution of compound **25** (0.058 g, 0.1 mmol) in anhydrous 3:1 MeOH:THF (10 mL) was added slowly $NiCl_2.6H_2O$ (0.237 g, 1.0 mmol) and $NaBH_4$(0.038 g, 1.0 mmol). After the reaction mixture was stirred at 0 °C for 1 h, the reaction mixture was filtered through celite and washed with1:1 MeOH:THF (100 mL). The solvent was evaporated, and the resulting residue was purified by silica gel chromatography (1:5 EtOAc:hexanes) to give the desired compound **26** (0.030 g, 52%) as a light yellow oil. MS (M+1): m/e 529.

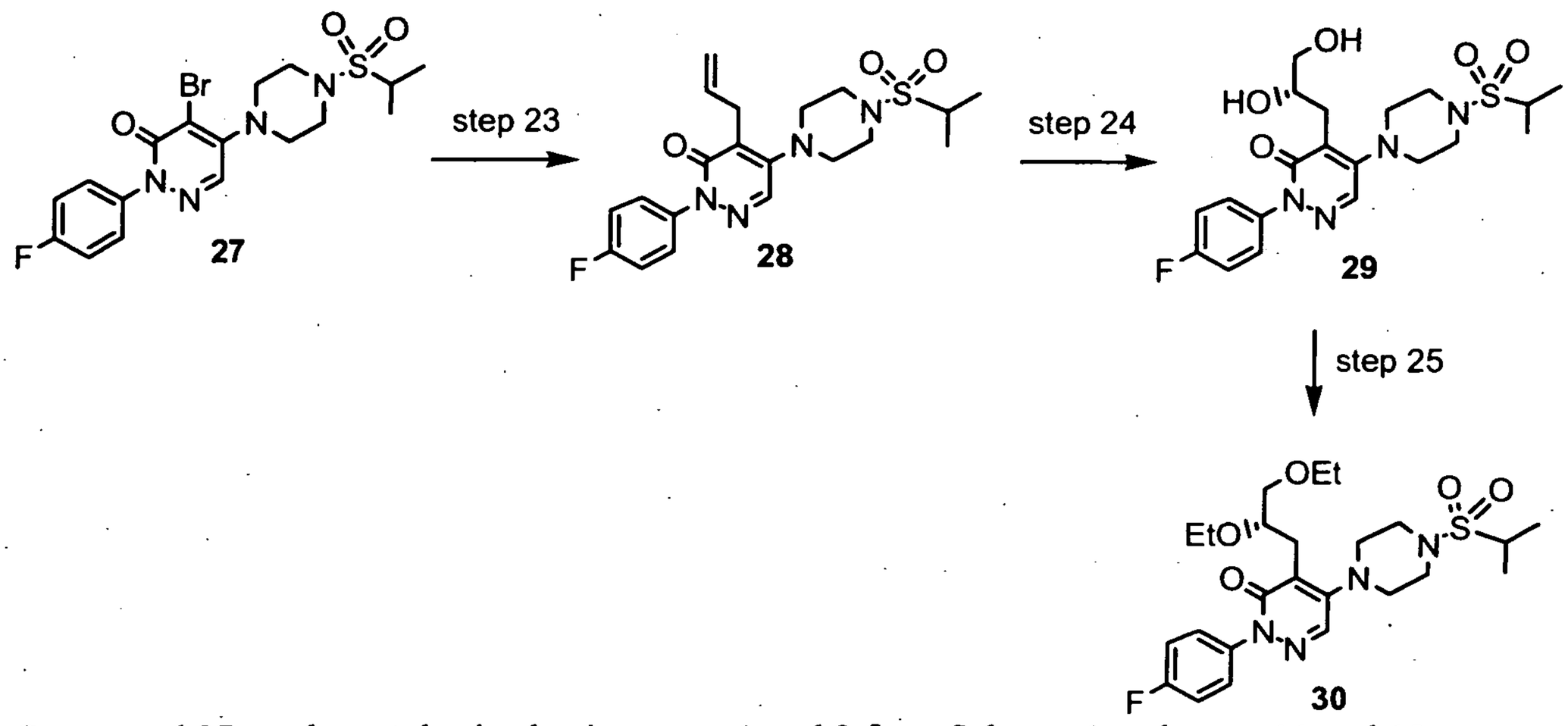
Table 12: Carbon Linked Analogs with Sulfonamide

The following compounds can be synthesized using the steps of Scheme 3.

Comp. No.	Structure	MS M+1
1530Z		543
1532Z		495

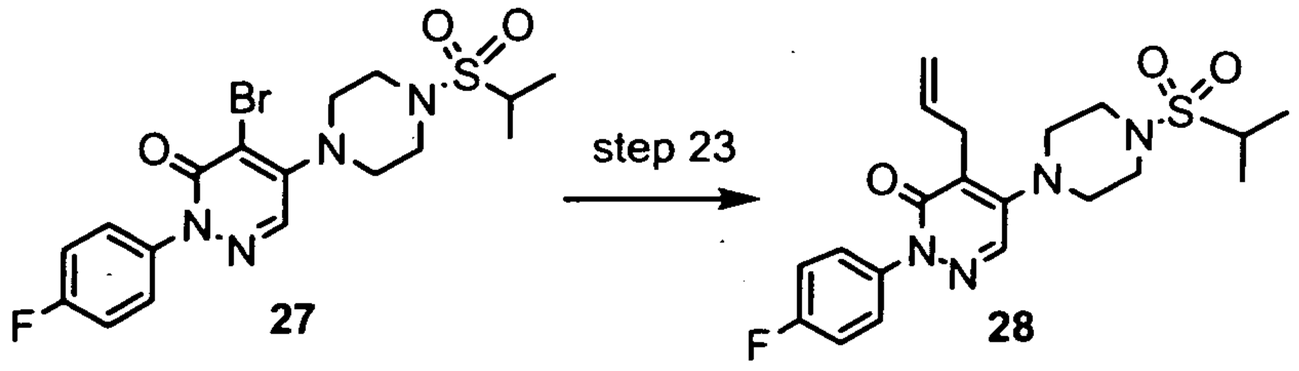
Comp. No.	Structure	MS M+1
1531Z		461
1533Z		495

Scheme 4



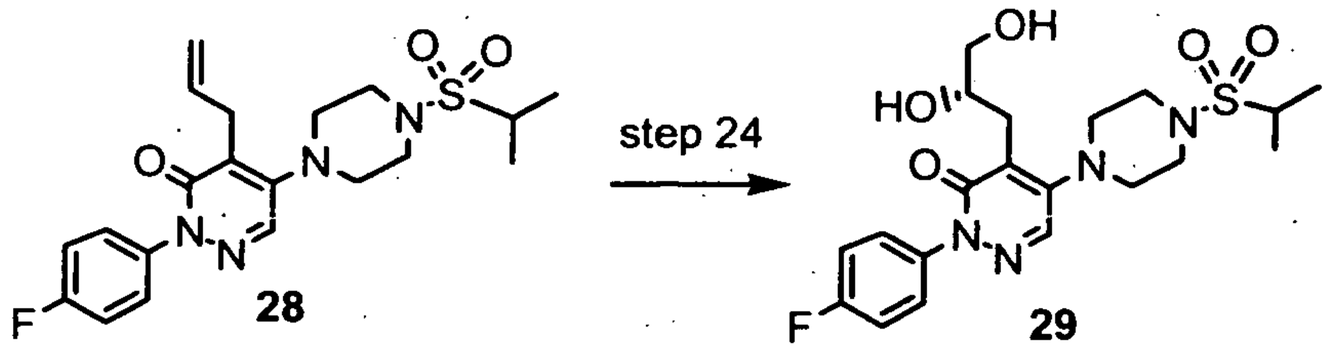
Compound 27 can be synthesized using steps 1 and 2 from Scheme 1 and steps 11 and 12 from Scheme 2.

Step 23:



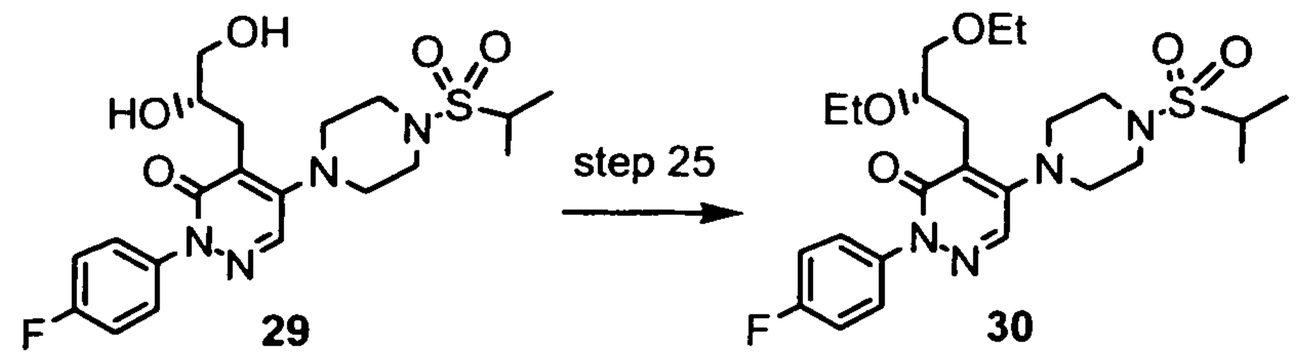
To a solution of compound **27** (0.290 g, 0.60 mmol), diisopropylethyl amine (0.154 g, 1.2 mmol) in 4:1 α,α,αtrifluorotoluene:toluene (10 mL) in a microwave tube, allyl tributyltin (0.397 g, 1.2 mmol) and $Pd(PPh_3)_4$ (0.080 g, 0.07 mmol) was added successively under an argon atmosphere. After the reaction mixture was stirred at 165 °C for 40 min under microwave irradiation, the reaction mixture was filtered through short path of silica gel, and the solvent was evaporated. Purification by silica gel chromatography (1:5 EtOAc:hexanes) gave the desired compound **28** (0.220 g, 87%) as a yellow oil. MS (M+1): m/e 421.

Step 24:



To a solution of the pyridazinone **28** (0.210 g, 0.50 mmol) in 10:1 acetone:H_2O (5 mL) was added NMO (0.073 g, 1.5 mmol) and OsO_4 (0.025 g, 0.1 mmol) at 20 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2h at -20 °C to 0 °C then treated with saturated aqueous Na_2SO_3 solution (10 mL) and extracted with EtOAc (6 × 50 mL). The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc) gave the product **29** (0.182 g, mg, 80%) as a white solid. (M+1): m/e 456.

Step 25:

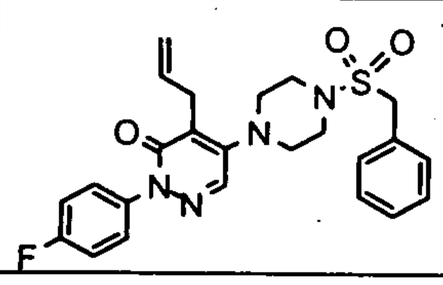
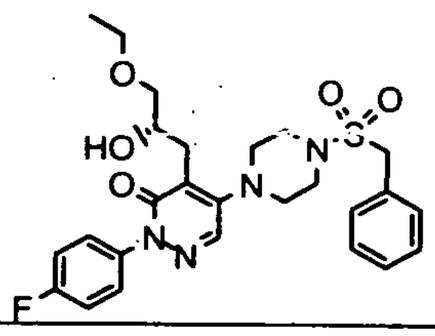
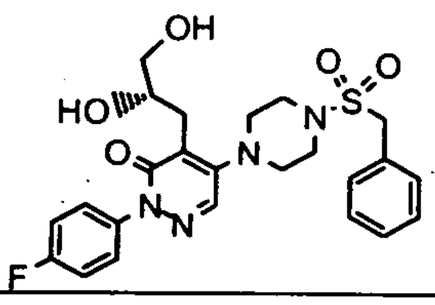
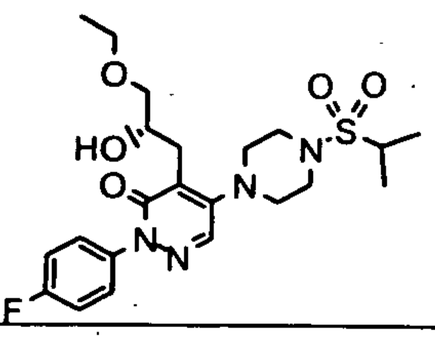


To a solution of compound **29** (0.090 g, 0.20 mmol), diisopropylethyl amine (0.077 g, 0.60 mmol) in CH_2Cl_2 (10mL), triethyloxonium tetrafluoroborate (0.114 g, 0.60 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 24 h then treated with saturated aqueous $NaHCO_3$ solution (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic extract was washed with H_2O (2 ×10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography

(1:10 EtOAc:hexanes) gave the desired compound **30** (0.220 g, 87%) as a colorless oil. MS (M+1): m/e 511.

Table 13: Carbon Linked Analogs with Sulfonamide

The following compounds can be synthesized using the steps of Scheme 4.

Compound No.	Structure	MS M+1
1534Z		429
1535Z		531
1536Z		503
1537Z		483

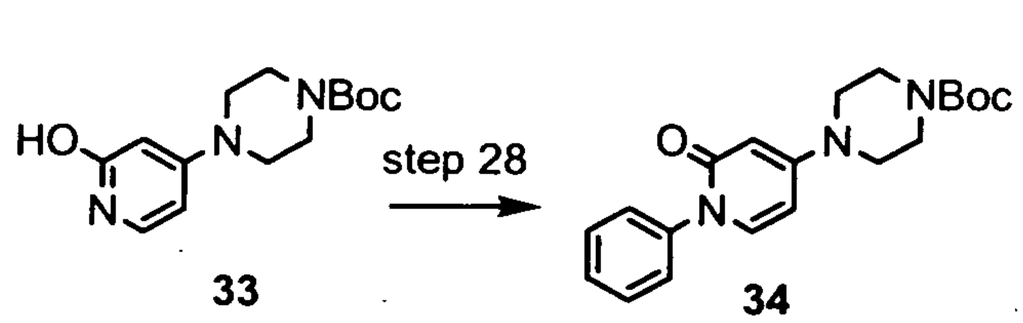
Scheme 5

Steps 26 and 27:

31 32

To a solution of 2,4-dihydroxypyridine **31** (10 g, 0.090 mol) and DMF (120 mL) was added in 4 portions NaH (60%, 4.32 g, 0.108 mol) at room temperature. The reaction mixture was cooled to 0 °C. *N*-Phenyltrifluoromethanesulfonimide (35.4 g, 0.099 mol) was then added in four separate portions. The reaction was warmed to room temperature and stirred for 5 h then quenched with saturated NH_4Cl (50 mL). EtOAc (200 mL) was added, and the organic layer was washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. To the crude was added DMF (120 mL) and BOCpiperazine (21.1 g, 0.113 mol). The reaction mixture was heated to 80 °C for 6 h then cooled to room temperature. EtOAc (200 mL) was added, and the organic layer was washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 10-30%% MeOH-EtOAc) to gave compound **32** (21.3 g) as a orange-white solid. MS (M + 1): m/e 280.

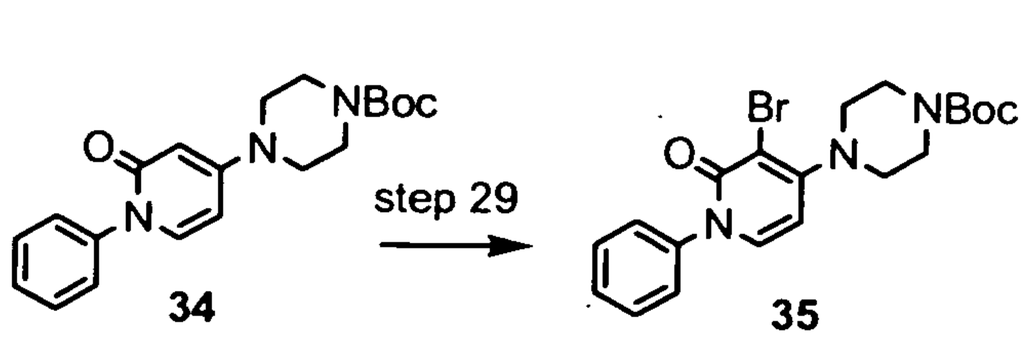
Step 28:



33 34

To a solution of compound **33** (2.74 g, 9.81 mmol) in CH_2Cl_2 (120 mL) was added phenyl boronic acid (2.40 g, 19.68 mmol), $Cu(OAc)_2$ (3.56 g, 19.560 mmol), 4Å MS (11 g), pyridine (1.6 mL, 19.78 mmol), and triethylamine (2.7 mL, 19.37 mmol). The reaction mixture was stirred at room temperature for 72 h then filtered through celite, concentrated, and purified by silica gel chromatography (1:1 hexanes:EtOAc to 5% MeOH in EtOAc) to give compound **34** (1.65 g) as a brown oil. MS (M + 1): m/e 356.

Step 29:

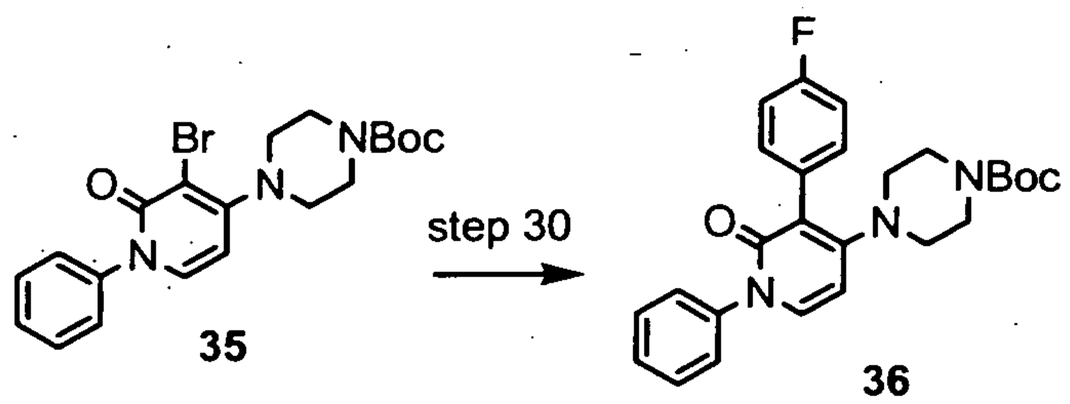


34 35

To a solution of compound **34** (186.5 mg, 0.525 mmol) in AcOH (8 mL) was added NBS (121.4 mg, 0.682 mmol) and stirred at room temperature for 3 h. The reaction mixture was

evaporated and purified by silica gel chromatography (3:1 to 1:1 hexanes:EtOAc) to give compound **35** (149.9 mg) as a light yellow solid. MS (M + 1): m/e 434.

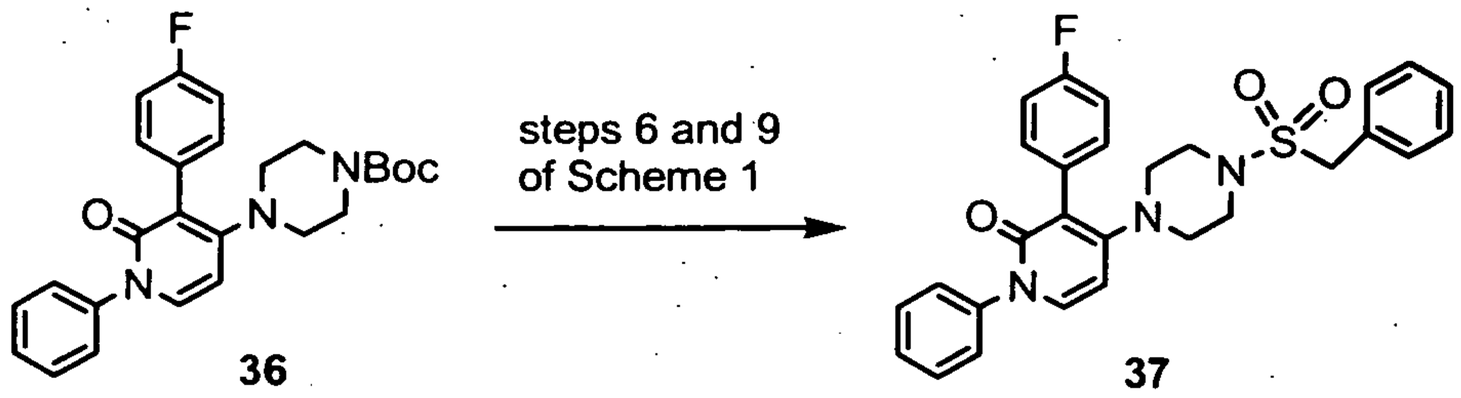
Step 30:



35 **36**

To a solution of compound **35** (144.6 mg) in degassed THF (10 mL) was added LiCl (28 mg, 0.661 mmol), tributyl(4-fluorophenyl)stannane (640 mg, 1.66 mmol), and tetrakis(triphenylphosphine)palladium(0) (42 mg, 0.036 mmol). The reaction mixture was heated at reflux for 42 h. The reaction was then cooled to room temperature, quenched with 1 N HCl (3 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by preparative TLC (eluted twice with 5% acetone in CH_2Cl_2) gave compound **36** (24.3 mg) as a white solid. MS (M+1): m/e 450.

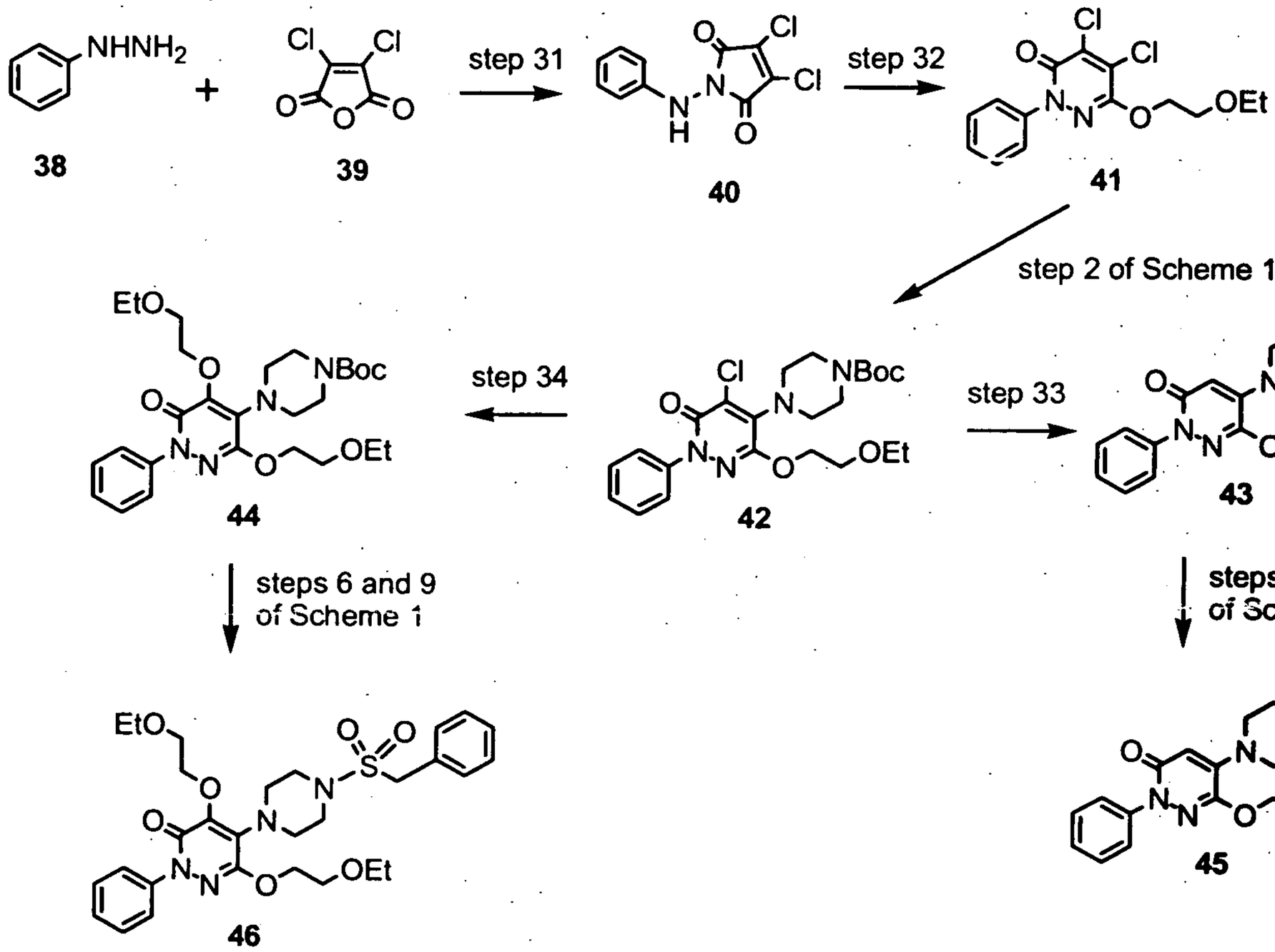
Steps 6 and 9 of Scheme 1:



36 **37**

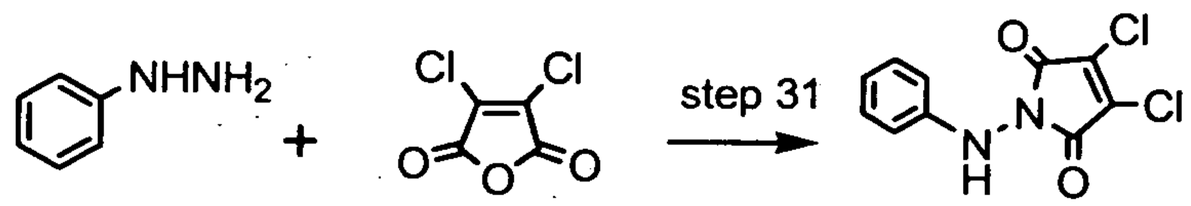
Using the procedures described above, compound **37** was synthesized. MS (M+1): m/e 504.

Scheme 6



38 39 40 41 42 43 44 45 46

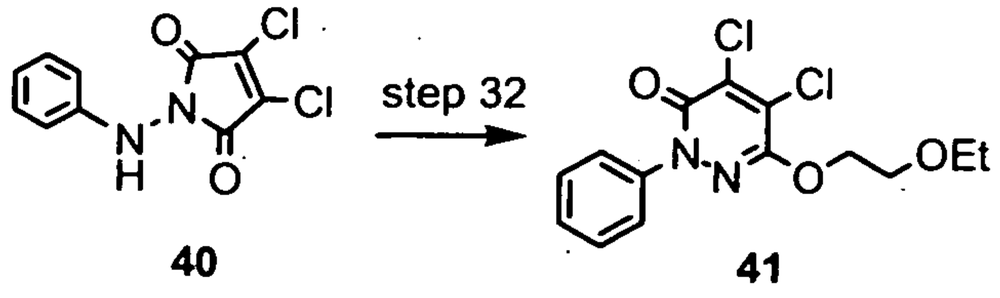
Step 31:



38 39 40

A solution of compound **39** (5.0 g, 0.030 mol) in AcOH (20 mL) was heated at 60 °C for 30 min then cooled to room temperature. Compound **38** (4.33 g, 0.030 mol) was then added, and the reaction mixture was heated at 120 °C for 1 h. The reaction mixture was cooled to room temperature, and the resulting solid was filtered and washed with AcOH to give compound **40** (6.47 g) as a white solid. MS (M + 1): m/e 257.

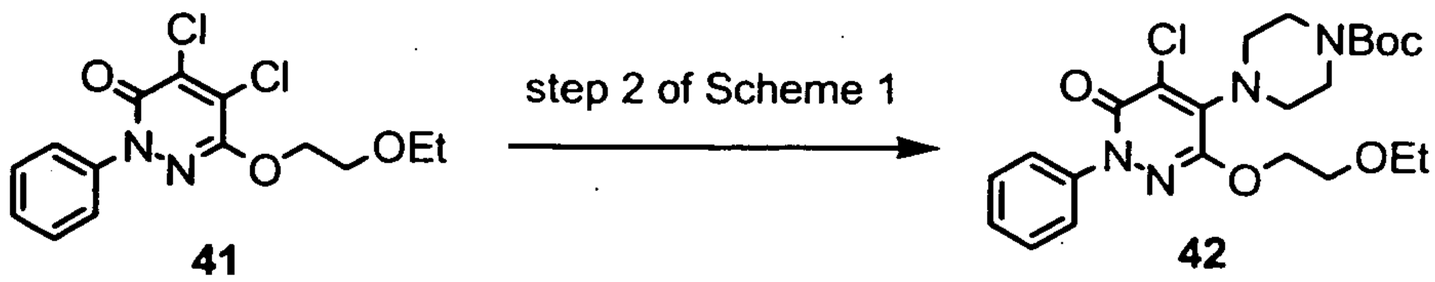
Step 32:



40 41

To a solution of compound **40** (1.0 g, 3.89 mmol) in DMF (30 mL) was added NaH (60%, 233 mg, 5.83 mmol) and stirred at room temperature for 15 h. The reaction was then quenched with saturated NH_4Cl (10 mL). EtOAc (250 mL) was added, and the organic layer was washed with brine (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (8:1 hexanes:EtOAc) gave compound **41** (177.4 mg) as a light yellow solid. MS (M + 1): m/e 533.

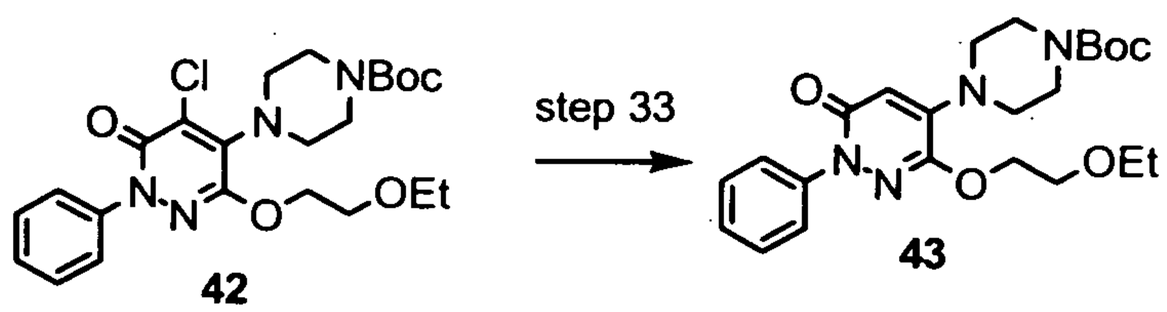
Step 2 of Scheme 1:



41 **42**

Using the procedure described above, compound **42** was synthesized. MS (M+1): m/e 480.

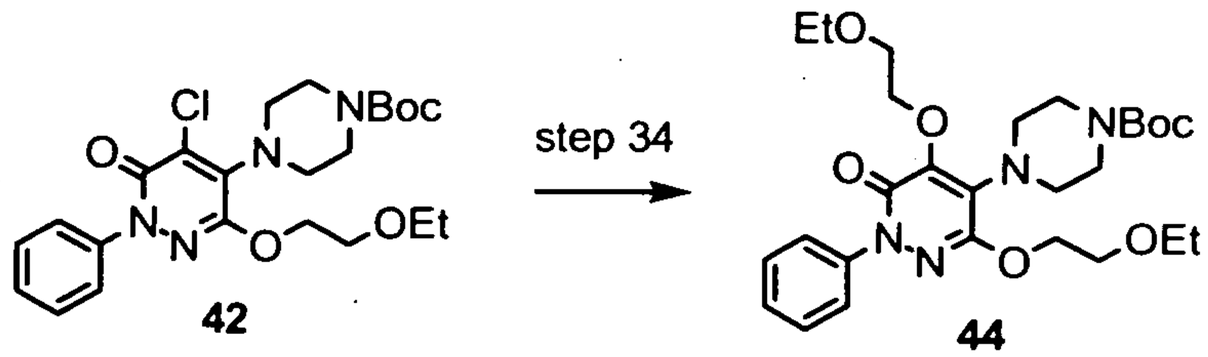
Step 33:



42 **43**

To a solution of compound **42** (94.3 mg, 0.197 mmol) in EtOH (10 mL) was added $Pd(OH)_2/C$ (20%, 70 mg) and stirred under H_2 (50 psi) at room temperature for 6 h, then filtered through celite. The solvent was evaporated, and purification by silica gel chromatography (2:1 to 1:1 hexanes:EtOAc) gave compound **43** (65.5 mg) as a colorless oil. MS (M + 1): m/e 445.

Step 34:



42 **44**

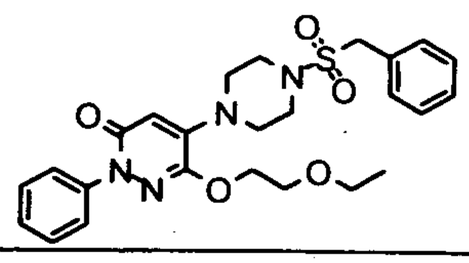
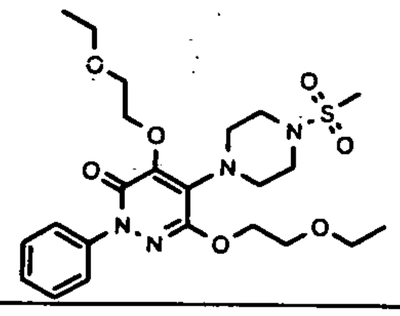
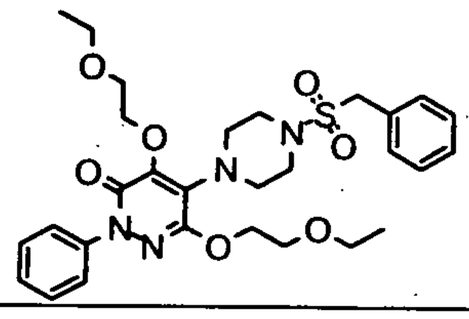
To a solution of compound **42** (102.3 mg, 0.214 mmol) and 2-ethoxyethanol (111.5 uL, 0.779 mmol) in THF (20 mL) was added NaH (60%, 37 mg, 0.925 mmol) and stirred at room temperature for 17 h. The reaction was then quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography

(3:1 to 2:1 hexanes:EtOAc) gave compound **44** (98.2 mg) as a colorless oil. MS (M + 1): m/e 533.

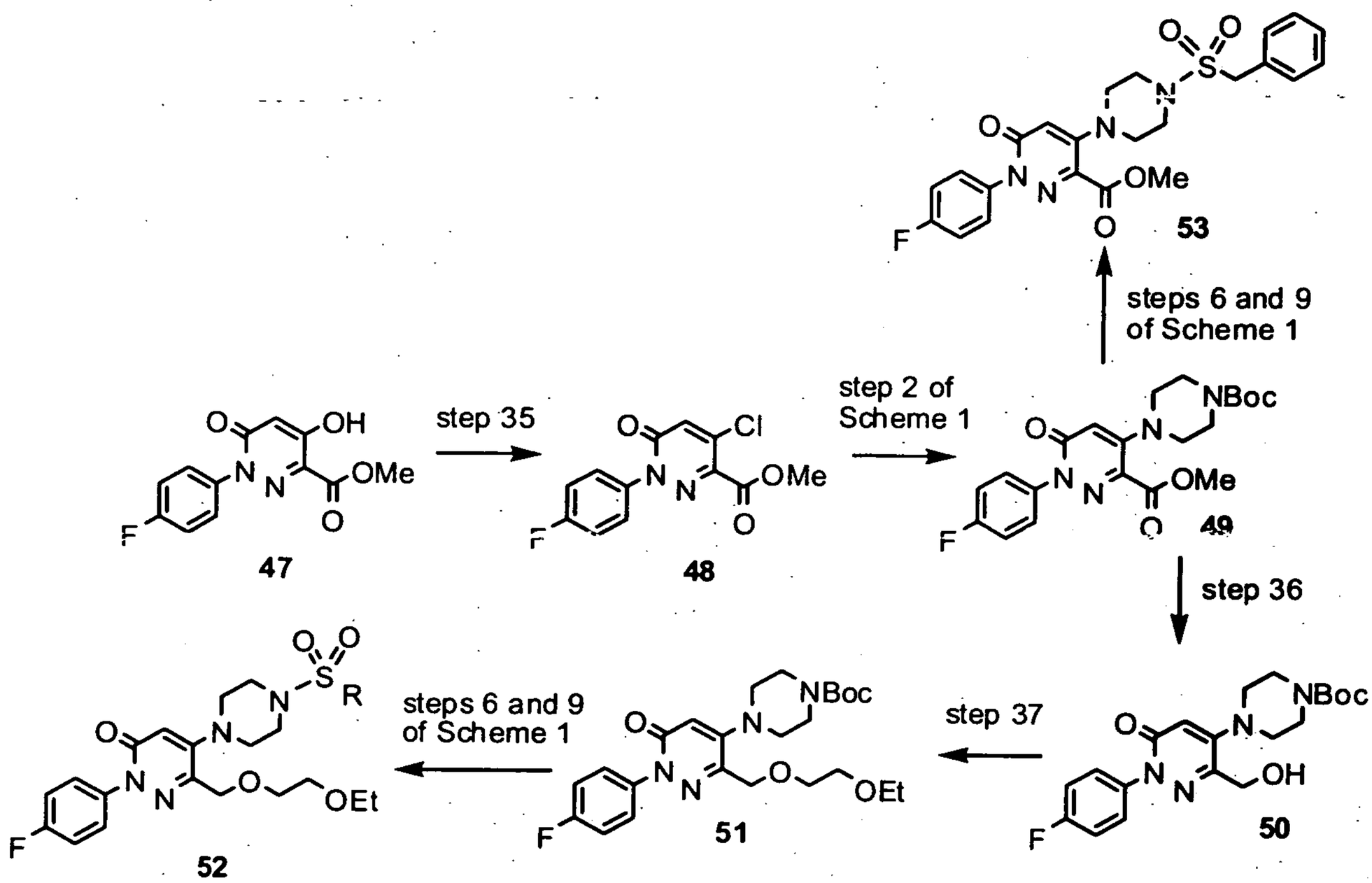
Steps 6 and 9 of Scheme 1:

Table 13A: Sulfonamide analogs

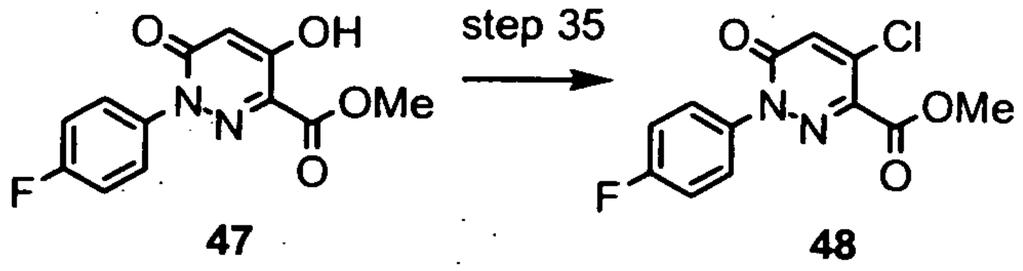
The following compounds can be synthesized using the steps of Scheme 6.

Compound No.	Structure	MS M+1
1537Za		499
1537Zb		511
1537Zc		587

Scheme 7

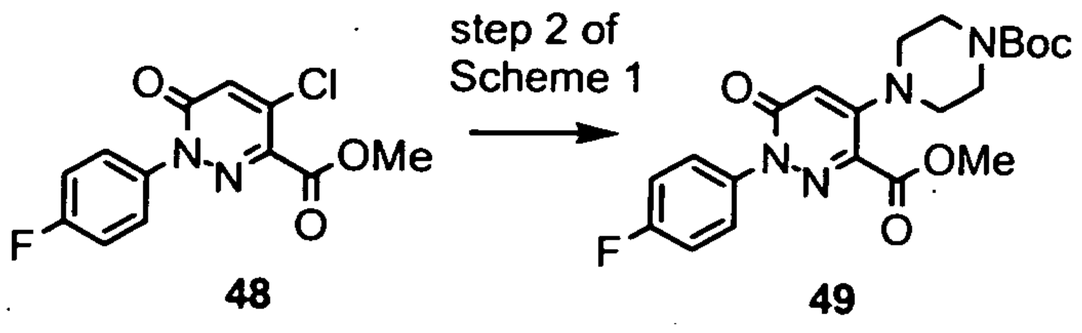


Step 35:



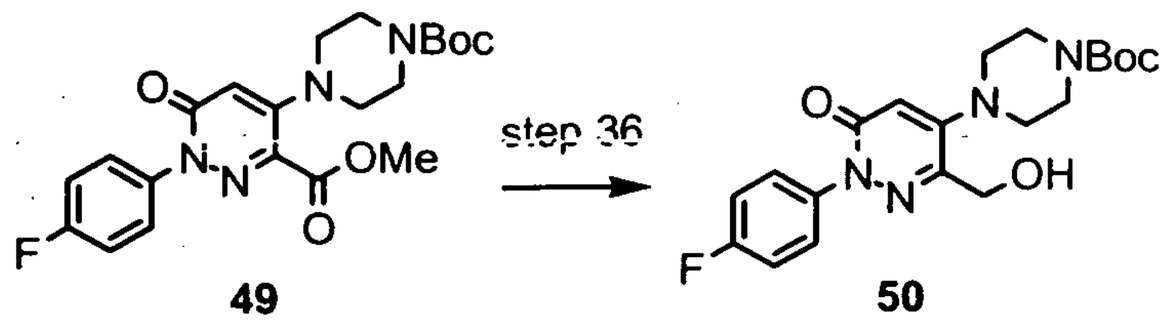
A solution of compound **47** (3.46 g, 0.013 mol) in $POCl_3$ (25 mL) was heated at 100 °C for 2 h. The reaction mixture was cooled to room temperature then concentrated. Saturated $NaHCO_3$ (150 mL) was added,and the aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (8:1 to 1:1 gradient of hexanes:EtOAc) gave compound **48** (2.82 g) as an orange solid. MS (M+1): m/e 283.

Step 2 of Scheme 1:



Using the procedure described above, compound **49** was synthesized. MS (M+1): m/e 433.

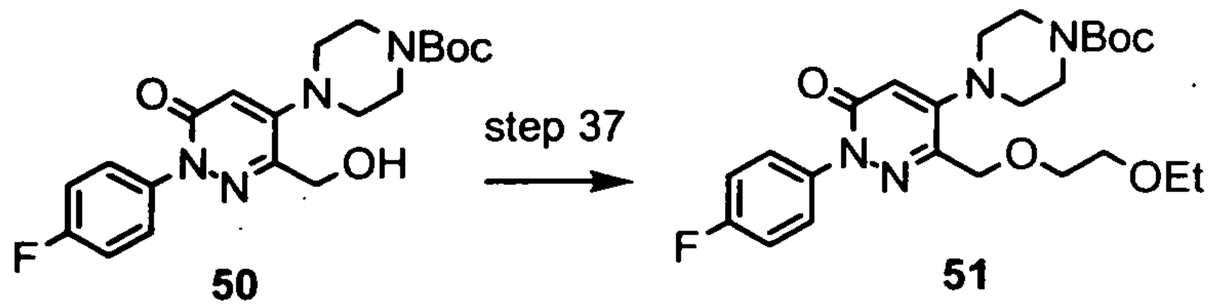
Step 36:



49 **50**

To a solution of compound **49** (100 mg, 0.231 mmol) in EtOH (10 mL) at 0 °C was added $NaBH_4$ (88 mg, 2.33 mmol). The reaction mixture was slowly warmed to room temperature and then stirred for 17 h. The reaction was quenched with saturated Rochelle's salt at 0 °C and extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (2:1 to 1:2 hexanes:EtOAc) gave compound **50** as a white foam. MS (M + 1): m/e 405.

Step 37:



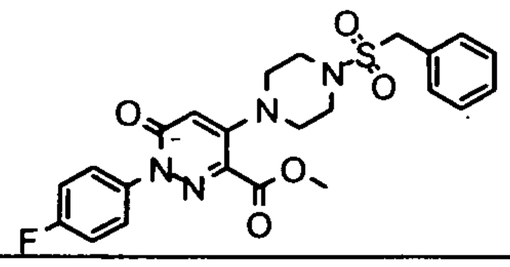
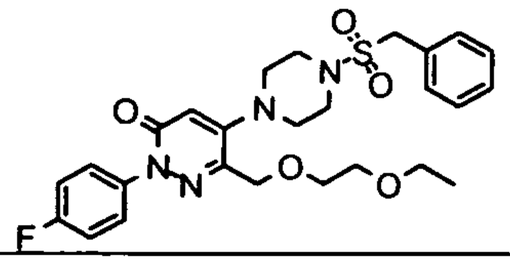
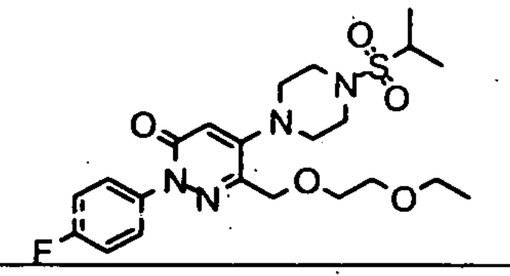
50 **51**

To a solution of compound **50** (80.3 mg, 0.199 mmol) in DMF (7 mL) at 0 °C was added NaH (60%, 24 mg, 0.600 mmol). Bromoethylether (134 uL, 1.19 mmol) was then added and the reaction mixture stirred at room temperature for 17 h. The reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extract was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (3:1 to 1:1 hexanes:EtOAc) gave compound **51** (93.9 mg) as a light yellow oil. MS (M + 1): m/e 477.

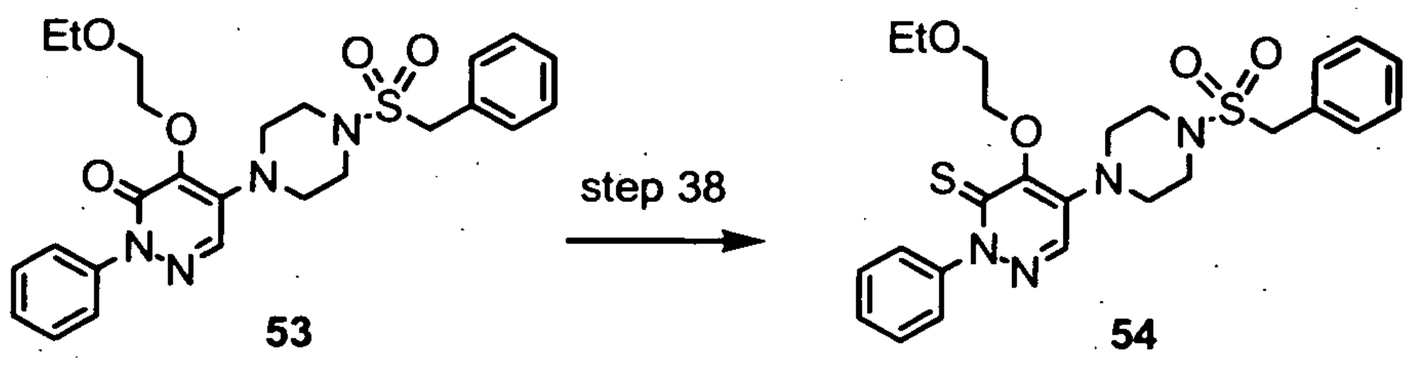
Steps 6 and 9 of Scheme 1:

Table 14: Sulfonamide Analogs

The following compouns can be synthesized using the steps of Scheme 7.

Compound No.	Structure	MS M+1
1538Z		487
1539Z		531
1540Z		483

Scheme 8



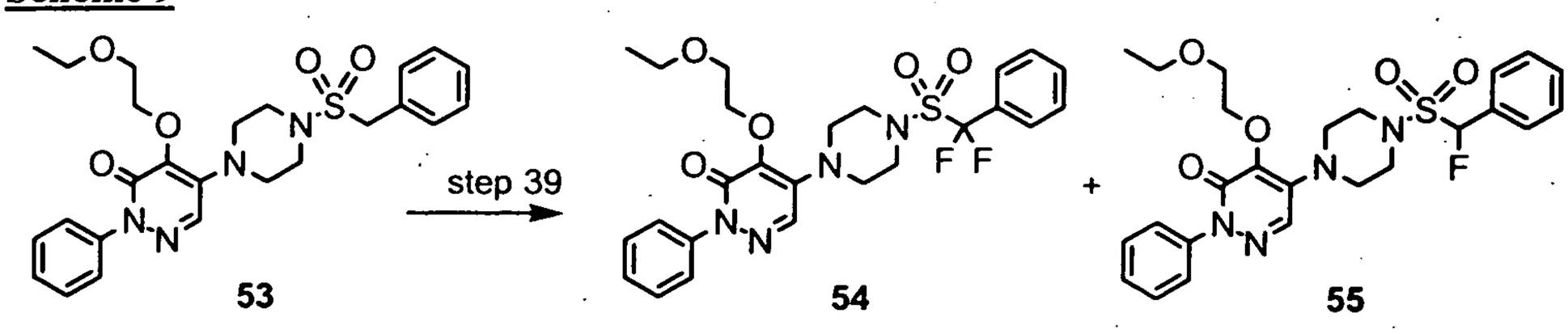
53 54

Compound **53** can be synthesized using steps 1, 2, 4, 6, and 9 of Scheme 1.

Step 38:

To a solution of compound **53** (31.5 mg, 0.063 mmol) in toluene (5 mL) was added Lawesson's reagent (26.0 mg, 0.064 mmol). The reaction mixture was heated to reflux (120 °C) for 48 h then cooled to room temperature and concentrated. Purification by Gilson reverse phase HPLC gave compound **54** (10.0 mg) as a light yellow oil. MS (M + 1): m/e 515.

Scheme 9



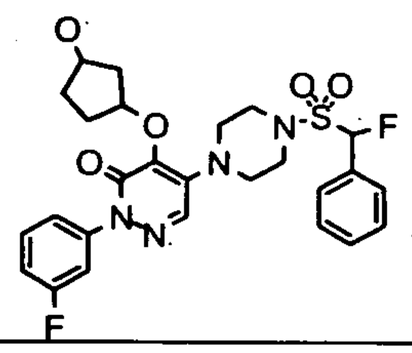
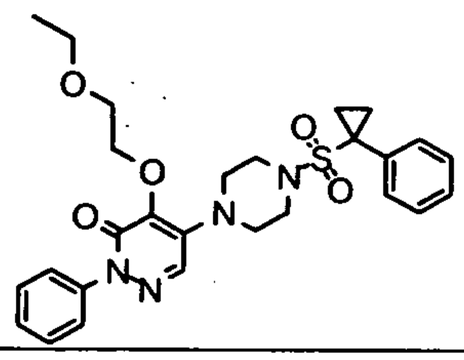
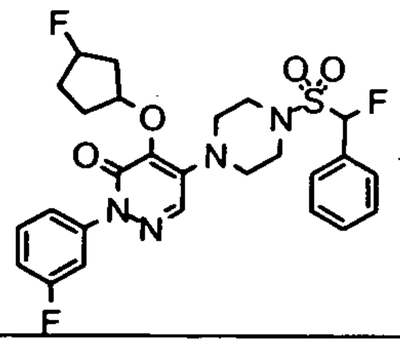
53 54 55

Step 39:

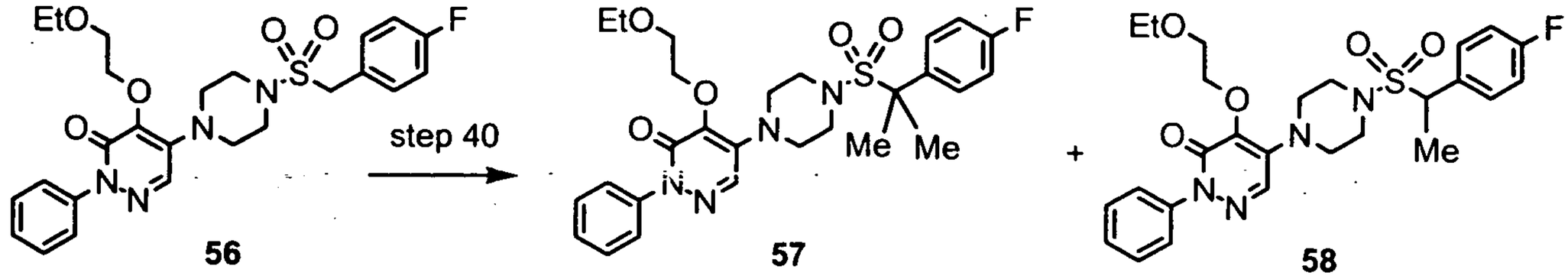
To a solution of compound **53**(100 mg, 0.201 mmol) in THF (20 mL) was added *N*-fluorobenzenesulfonimide (189.7 mg, 0.602 mmol), and the reaction mixture was cooled to –78 °C. NaHMDS (1 M, 421.2 uL, 0.421 mmol) was added slowly over 30 min to the reaction mixture then gradually warmed to room temperature and stirred overnight for 15 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine (25 mL), ($MgSO_4$), filtered, and concentrated. Purification by prep TLC (1:2 hexanes:ethyl acetate) gave compound **54** (20.2 mg) as a yellow solid and compound **55** (8.2 mg) as yellow oils. MS (M+1): m/e 535, m/e 517.

Table 15: Oxygen Linked Analogs with Sulfonamide

Using similar procedures described above, the following compounds were synthesized.

Compound No.	Structure	MS M+1
1541Z		547
1542Z		525
1543Z		549

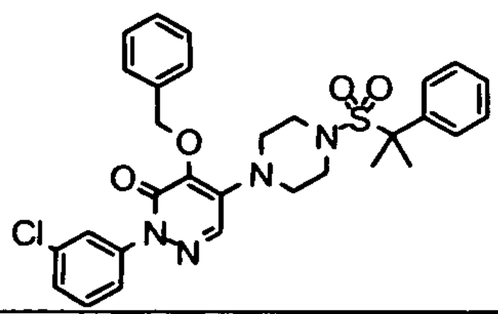
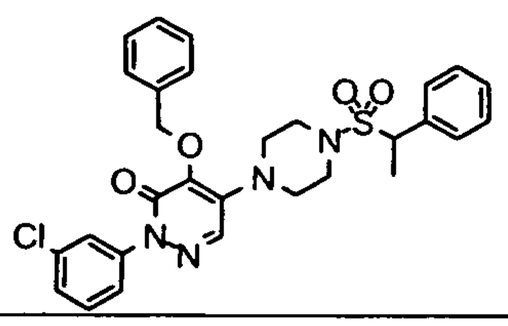
Scheme 10



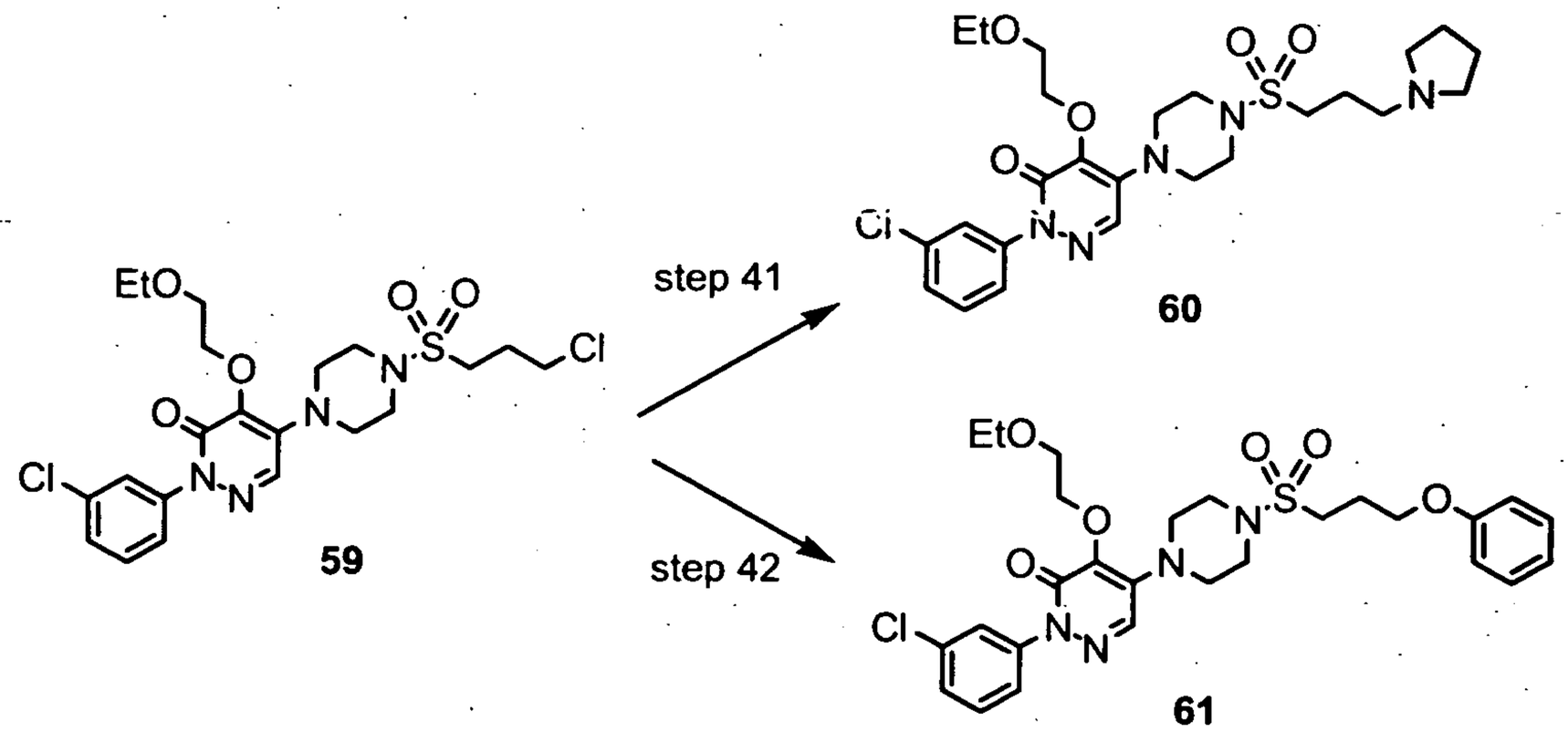
Step 40:

To a solution of compound **56** (150 mg, 0.290 mmol) dissolved in dry DMF (4 mL) was added methyl iodide (124 mg, 0.054 mL, 0.871 mmol) and potassium t-butoxide (1 M in THF, 0.87 mL, 0.87 mmol) under a nitrogen atmosphere. The reaction was stirred at room temperature for 24 h. The solvent was evaporated, water (25 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by reverse phase chromatography (eluant: acetonitrile:water gradient with 0.1% formic acid) gave 90 mg (57%) of compound **57** and 37 mg (24%) of compound **58** as colorless oils. MS (M+1): m/e 545 for compound **57** and 531 for compound **58**.

Using similar procedures described above, the following compounds were synthesized.

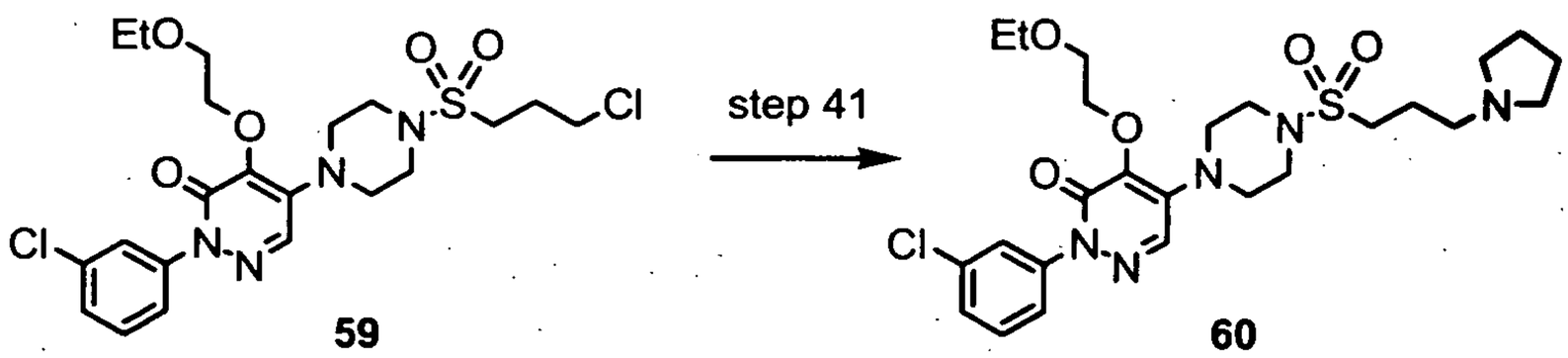
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1543Za		579	1543Zb		565

Scheme 11



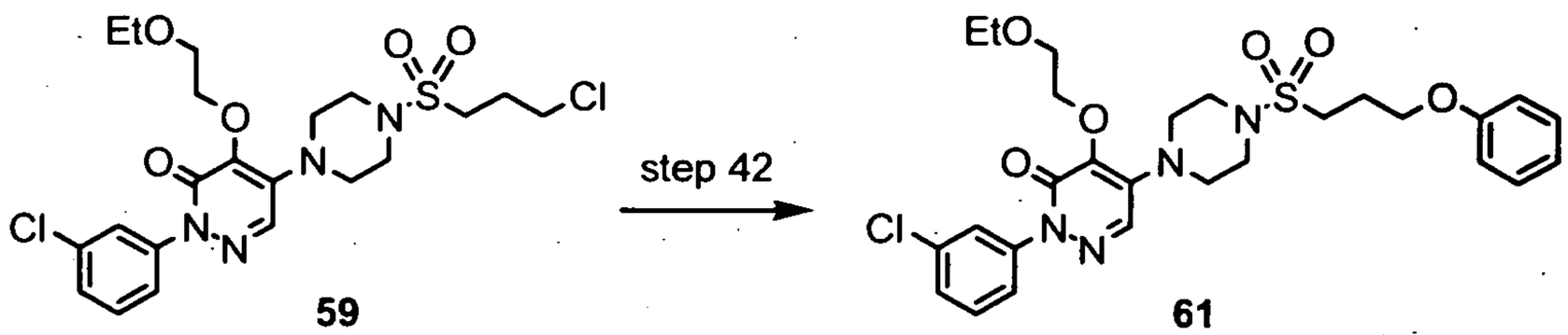
Compound **59** can be synthesized using steps 1, 2, 4, 6, and 9 of Scheme 1.

Step 41:



To a solution of compound **59** (150 mg, 0.289 mmol) dissolved in dry THF (4 mL) was added pyrrolidine (103 mg, 0.12 mL, 1.44 mmol). The reaction mixture was heated at reflux for 18 h. The solvent was evaporated, and purification by silica gel chromatography (eluant: 5 - 10% $MeOH/NH_3 – CH_2Cl_2$) gave 133 mg (83%) of the product **60** as a colorless oil. MS (M+1): m/e 554.

Step 42:

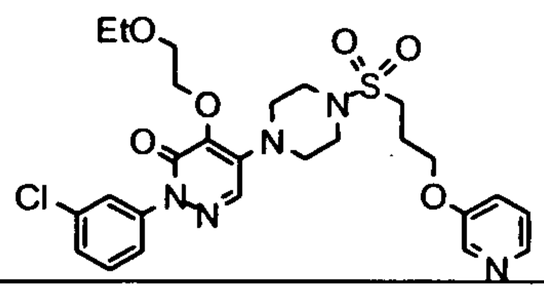


To a solution of compound **59** (250 mg, 0.481 mmol) dissolved in dry DMF (5 mL) was added potassium carbonate (200 mg, 1.44 mmol), potassium iodide (20 mg, 0.120 mmol), and phenol (136 mg, 1.44 mmol). The reaction mixture was heated at 100 °C for 16 h. The solvent was evaporated, water (25 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated.

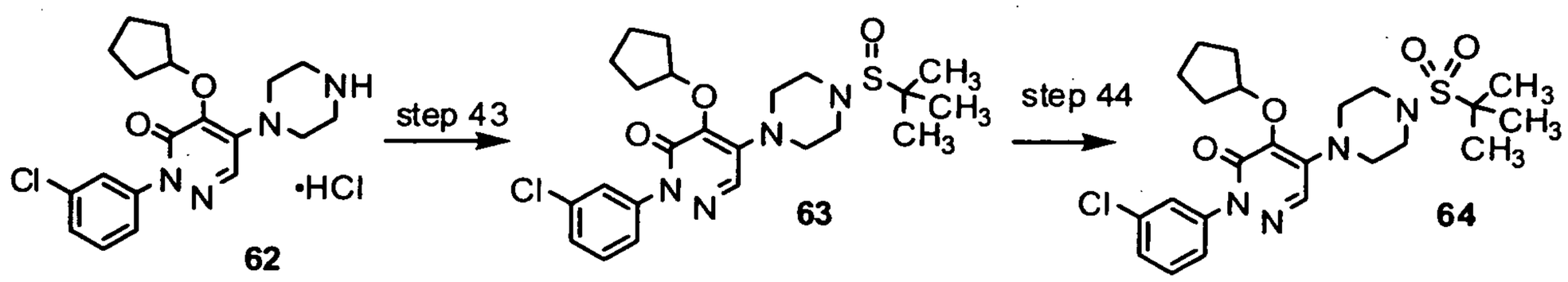
Purification by silica gel chromatography (eluant: 20 – 30% EtOAc-hexanes) gave 212 mg (76%) of the product **61** as a yellow solid. MS (M+1): m/e 599.

Table 16: Oxygen Linked Analogs with Sulfonamide

Using similar procedures described above, the following compound was synthesized.

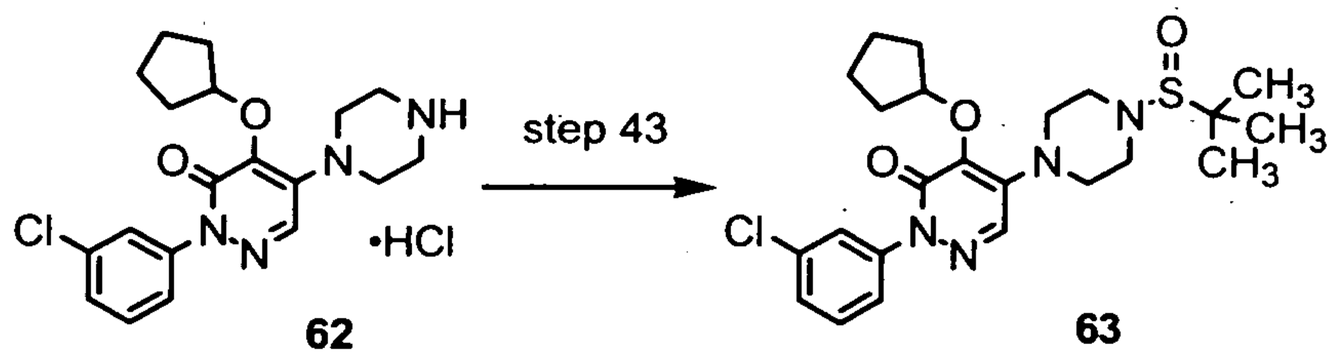
Compound No.	Structure	MS M+1
1544Z		578

Scheme 12



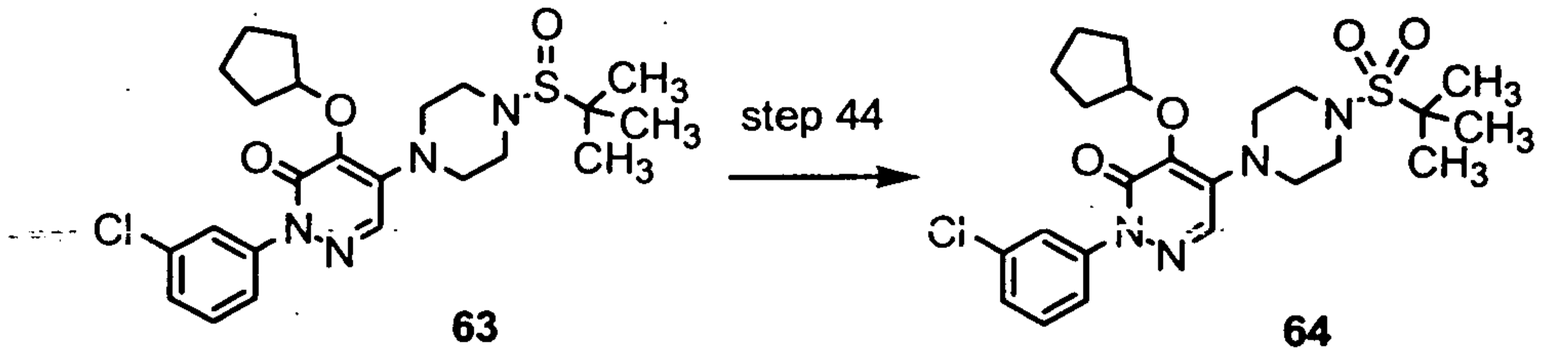
Compound **62** can be synthesized using steps 1, 2, 4, and 6 of Scheme 1.

Step 43:



Diisopropylethylamine (0.17 mL, 1.0 mmol) was added to a suspension of *tert*-butylsulfinyl chloride (0.04 mL, 0.30 mmol) and compound **62** (150 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (5 mL) at room temperature under nitrogen. The mixture was stirred for 22 h after which it was directly purified by CombiFlash Companion (40-g silica gel cartridge, eluant: 2:8 to 7:3 gradient ethyl acetate/hexanes), to provide sulfinamide **63** (120 mg, 82%) as a white solid: APCI MS *m/z* 479 $[M + H]^+$.

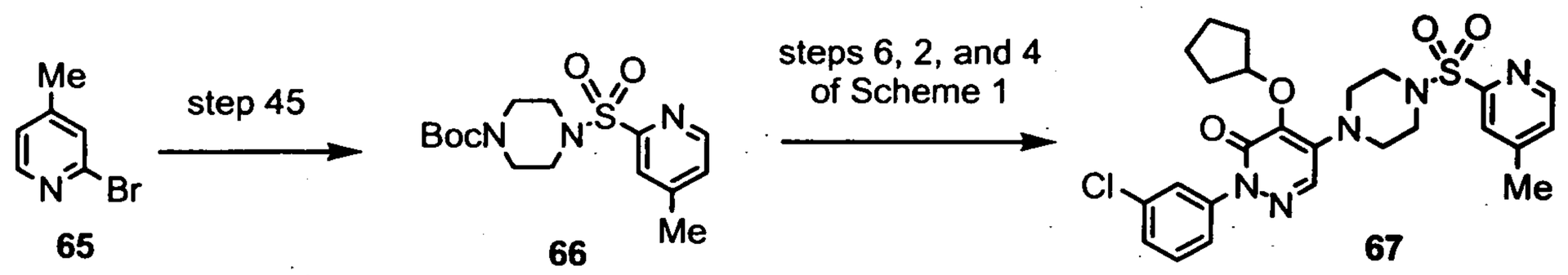
Step 44:



63 64

meta-Chloroperoxylbenzoic acid (190 mg, 0.78 mmol) was added to a solution of compound **63** (310 mg, 0.65 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature under nitrogen. The mixture was stirred for 2.5 h after which it was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous sodium bisulfite solution (50 mL) and the solvents were evaporated. The residue was purified by CombiFlash Companion (80-g silica gel cartridge, eluant 1:9 to 7:3 gradient ethyl acetate/hexanes) to provide product **64** (290 mg, 91%) as a white solid: APCI MS *m/z* 495 $[M + H]^+$.

Scheme 13

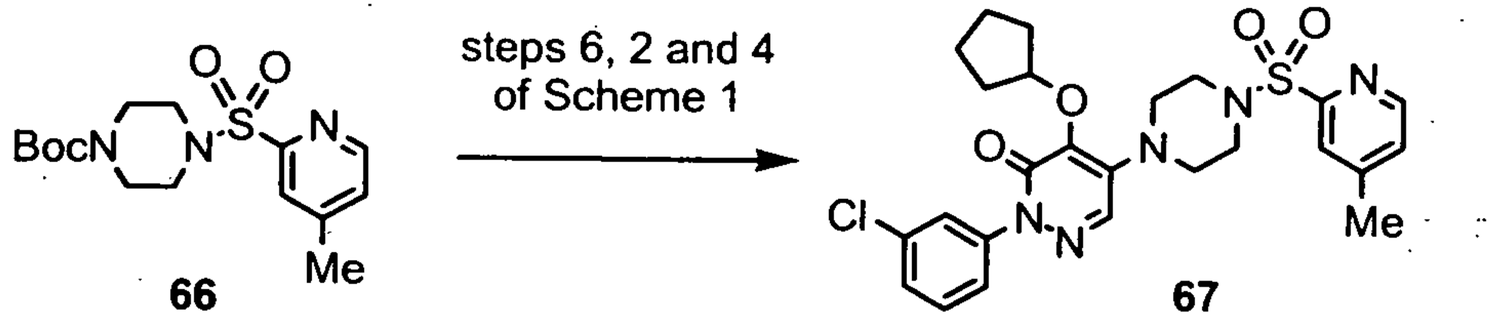


65 66 67

Step 45:

To a solution of 2-bromo-4-methylpyridine **65** (1.0 g, 5.81 mmol) in THF (20 mL) was added at room temperature isopropyl magnesium chloride (2 M, 3.2 mL, 6.40 mmol). The reaction mixture was heated to reflux for 3 h then cooled to –40 °C. SO_2(g) was bubbled through the reaction mixture for 5 min then stirred at –40 °C for 1 h. SO_2Cl_2 (607 uL, 7.49 mmol) was added, and the reaction mixture was stirred for 30 min. BOCpiperazine (3.2 g, 17.2 mmol) was then added, and the reaction mixture was slowly warmed to room temperature and stirred for 17 h. Water was added, and the aqueous solution was extracted with EtOAc (3 × 30 mL). The combined organic extract was washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (3:1 to 1:1 hexanes:EtOAc) gave compound **67** (1.41g) as a colorless oil. MS (M + 1): m/e 342.

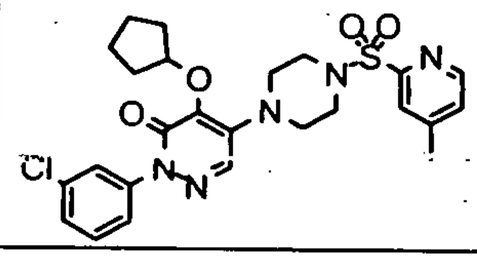
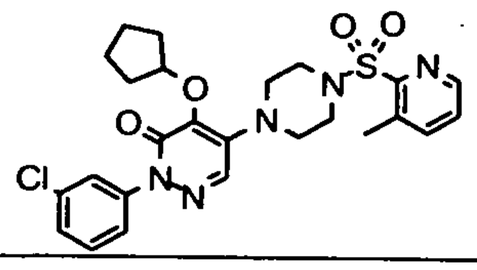
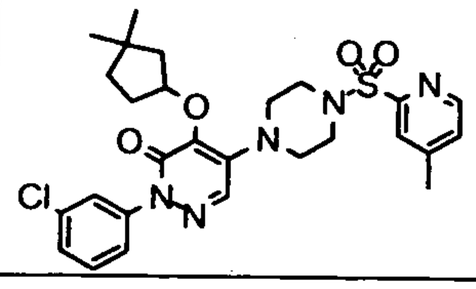
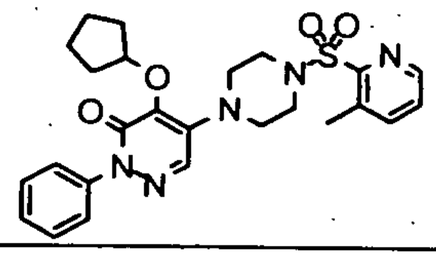
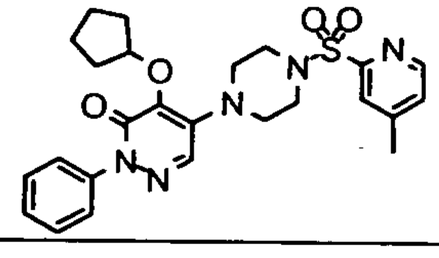
Steps 6, 2, and 4 of Scheme 1:



66 67

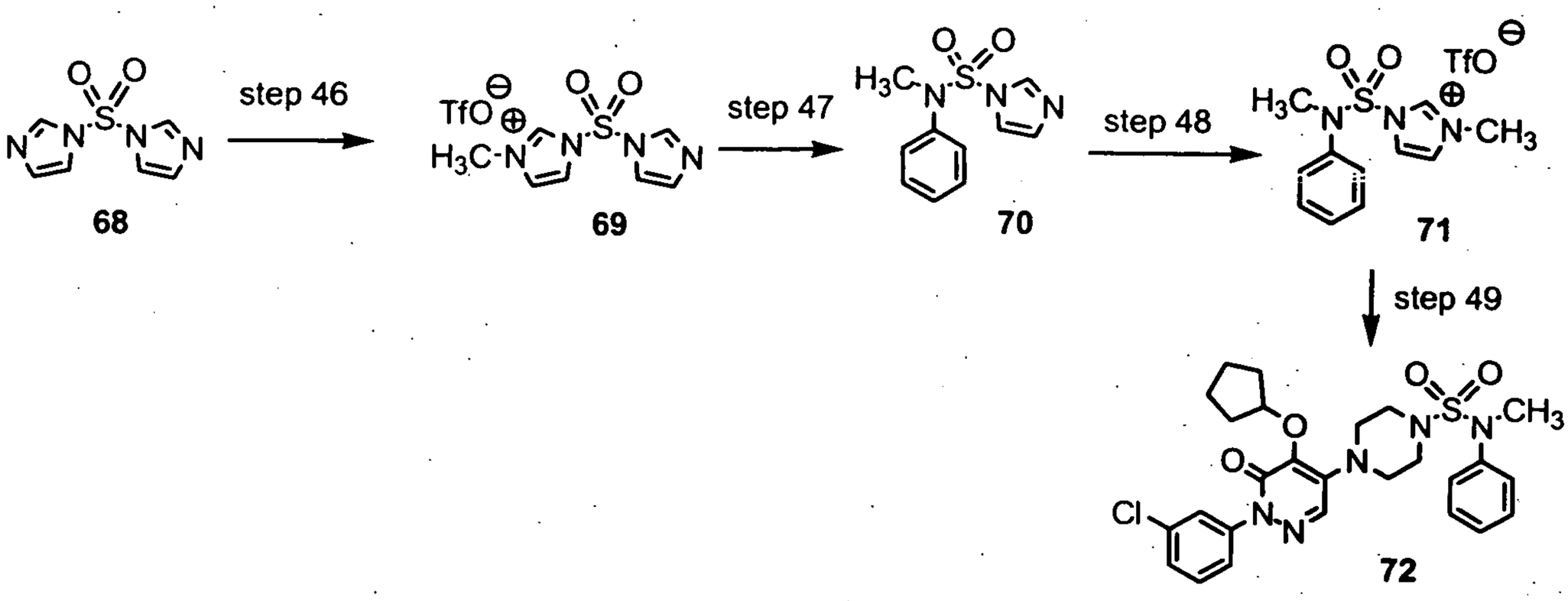
Table 17: Oxygen Linked Analogs with Sulfonamide

Using the procedures described above, the following compounds were synthesized.

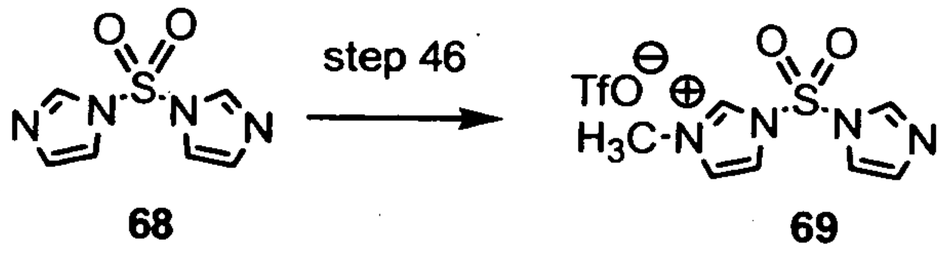
Compound No.	Structure	MS M+1
1545Z		530
1546Z		530
1547Z		558
1548Z		496
1549Z		496

5

Scheme 14

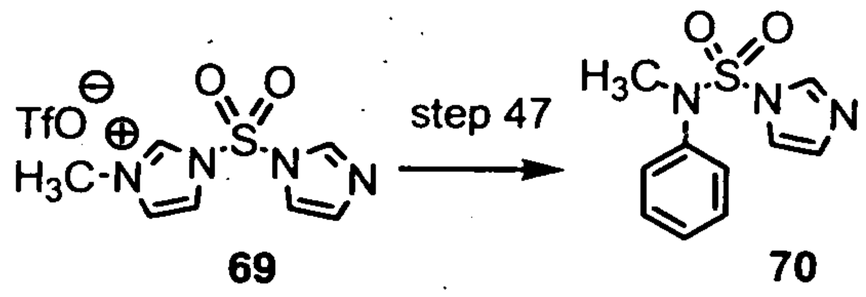


Step 46:



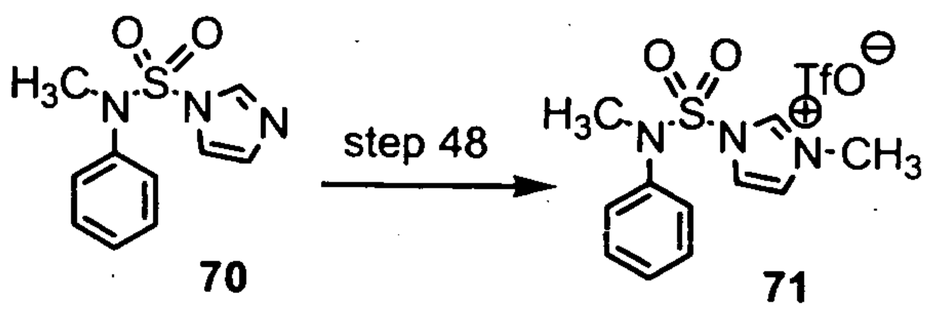
To a solution of *N,N'*-sulfuryldiimidazole **68** (2.00 g, 10.1 mmol) in anhydrous methylene chloride (40 mL) at 0 °C under nitrogen was added dropwise methyl triflate (1.4 mL, 12.4 mmol). The mixture was stirred at 0 °C for 3 h after which the solid was collected by vacuum filtration to provide product **69** (3.33 g, 91%) as a white solid.

Step 47:



To a solution of compound **69** (2.09 g, 5.77 mmol) in anhydrous acetonitrile (15 mL) at room temperature under nitrogen was added *N*-methylaniline (414 mg, 3.86 mmol). The mixture was stirred for 2.5 h after which the solvent was evaporated. The residue was purified by CombiFlash Companion (40-g silica gel cartridge, eluant 9:1 to 1:1 gradient hexanes/ethyl acetate) to provide product **70** (372 mg, 47%) as a viscous orange oil.

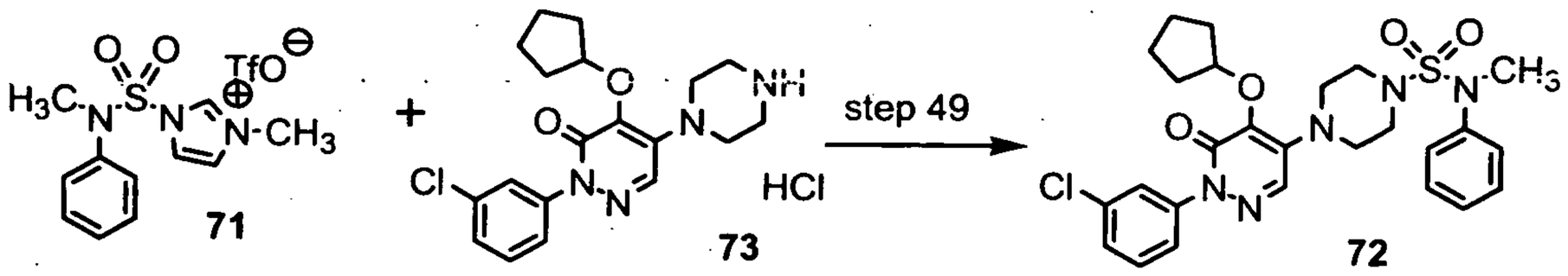
Step 48:



70 71

To a solution of compound **70** (372 mg, 1.57 mmol) in anhydrous methylene chloride (7 mL) at 0 °C under nitrogen was added methyl triflate (0.25 mL, 2.21 mmol). The mixture was stirred at 0 °C for 2 h after which the solvent was removed under reduced pressure to provide product **71** (373 mg, 59%) as a light-brown solid.

Step 49:

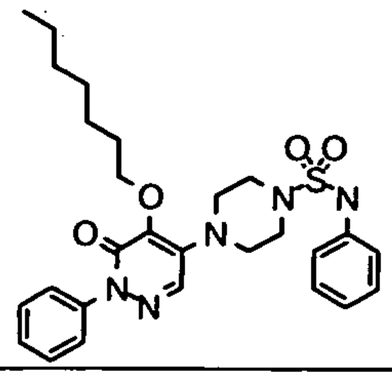


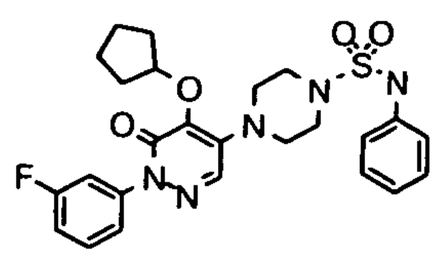
71 73 72

To a solution of compound **71** (373 mg, 0.93 mmol) in anhydrous methylene chloride (3 mL) at room temperature under nitrogen was added a solution of compound **73** (255 mg, 0.62 mmol) and *N*, *N*-diisopropylethylamine (0.11 mL, 0.631 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 6 h after which the solvent was removed under reduced pressure. The residue was purified by CombiFlash Companion (40-g silica gel cartridge, eluant 9:1 to 3:1 gradient hexanes/ethyl acetate) to provide product **72** (249 mg, 74%) as a white solid: APCI MS *m/z* 544 $[M + H]^+$.

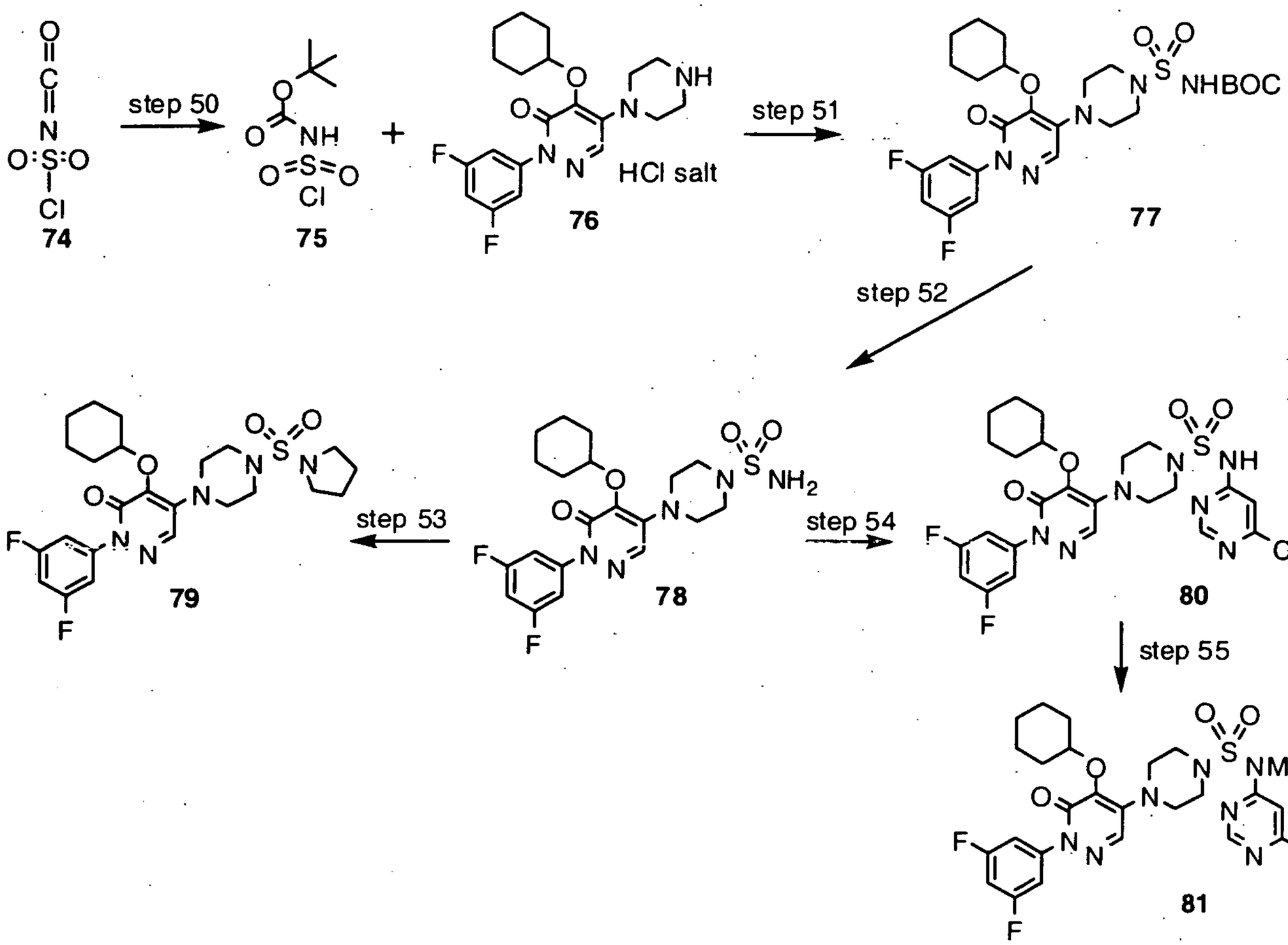
Table 18: Oxygen Linked Analogs with Sulfonamide

Using the procedures described above, the following compounds were synthesized.

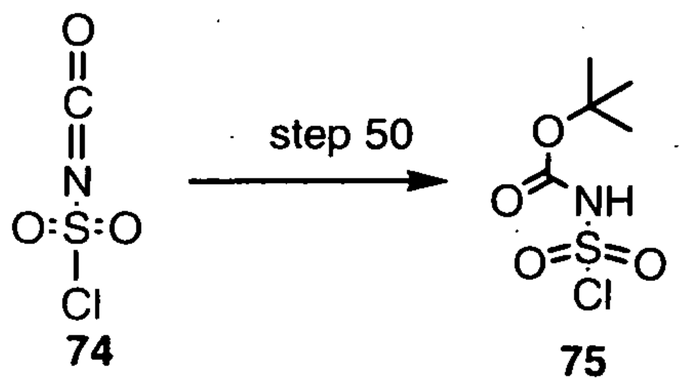
Comp. No.	Structure	MS M+1
1550Z		526

Comp. No.	Structure	MS M+1
1551Z		514

Scheme 15

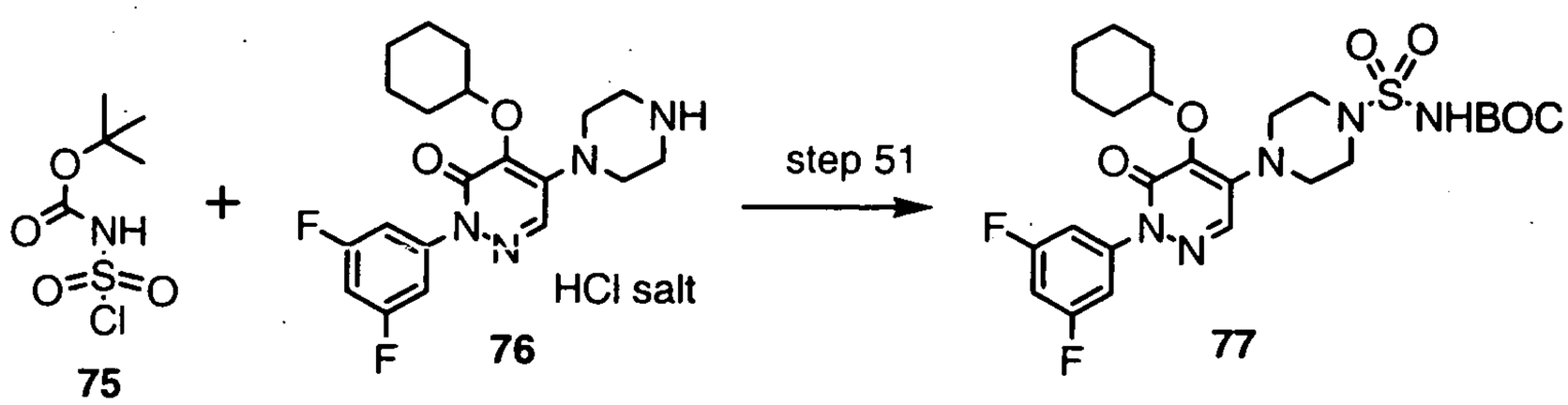


Step 50:



Dry t-butanol (0.96 mL, 10 mmol) in 20 mL of dry methylene chloride was cooled to 0 °C. Chlorosulfonyl isocyanate **74** (0.9 mL, 10 mmol) was then added dropwise. The resulting solution was stirred at 0 °C for 30 min, then at room temperature for 1 h. This 0.5 M solution of compound **75** was used directly in the next step.

Step 51:

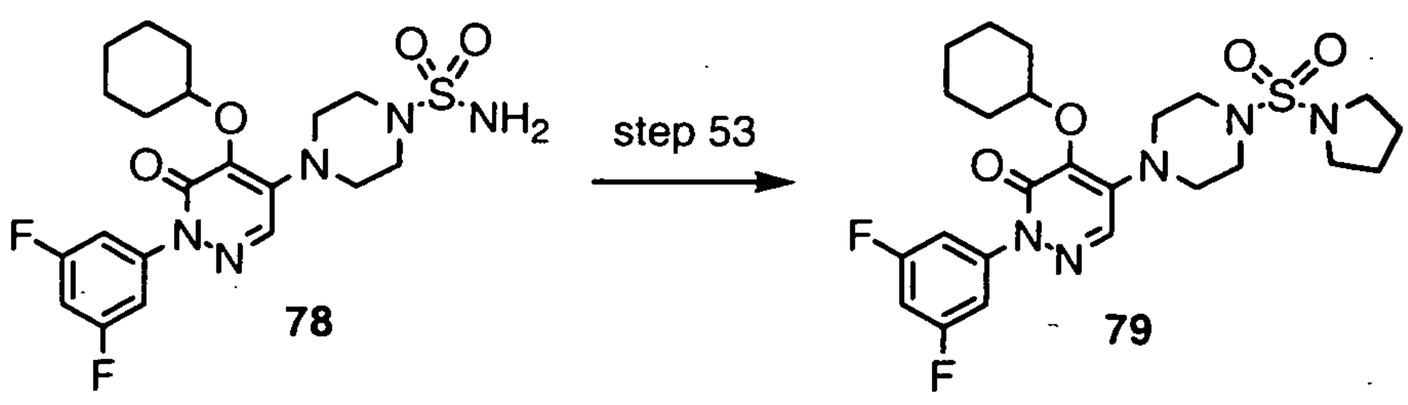


Compound **76** (0.43 g, 1.0 mmol) in 10 mL of dry methylene chloride was mixed with diisopropylethylamine (0.52 mL, 3.0 mmol). A 0.5 M solution of compound **75** in methylene chloride (2.4 mL, 1.2 mmol) was added dropwise. The resulting mixture was then stirred at room temperature for 16 h. EtOAc was added, and the organic solution was washed with 1 N HCl, then dried (Na_2SO_4), filtered, and concentrated to give quantitative yield of product **77** as a white solid.

Step 52:

To compound **77** (1.0 mmol) dissolved in methylene chloride was added 4 N HCl in dioxane at room temperature and stirred overnight. The solvent was evaporated, and purification by silica gel chromatography gave 0.45 g (96% from **76**) of product **78** as a white solid. MS (M+1): m/e 470.

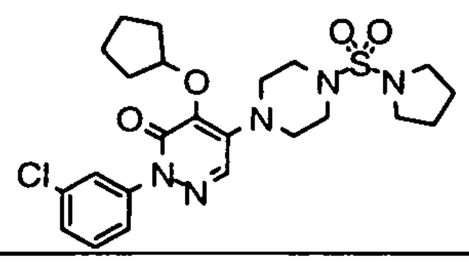
Step 53:



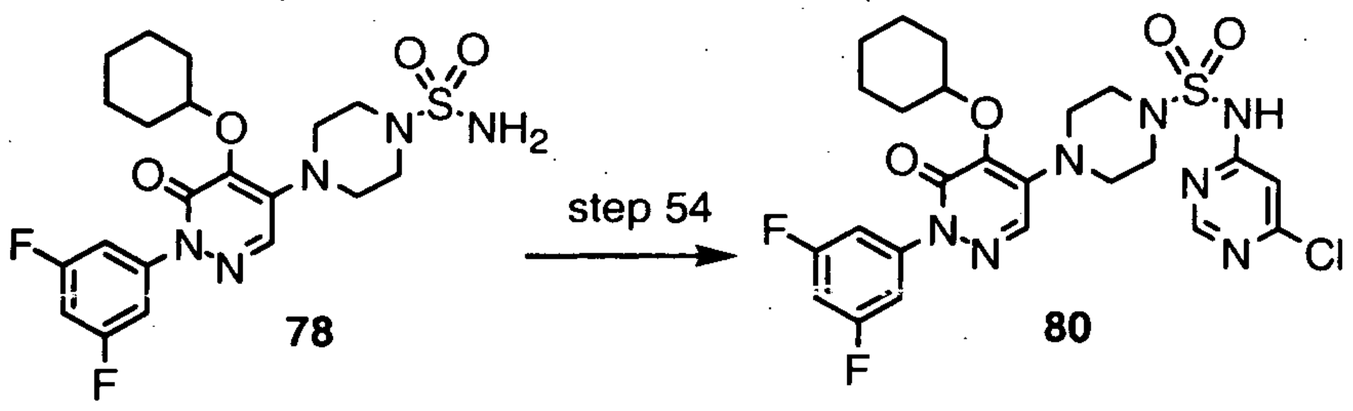
To compound **78** (52 mg, 0.11 mmol) dissolved in DMF (1 mL) was added 1, 4-diiodobutane (0.015 mL, 0.11 mmol) and NaH (60%, 10 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 16 h. EtOA was added, and the organic solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography gave 48 mg (83%) of product **79** as a white solid. MS (M+1): m/e 524.

Table 19: Oxygen Linked Analog with Sulfonamide

Using the procedures described above, the following compound was synthesized.

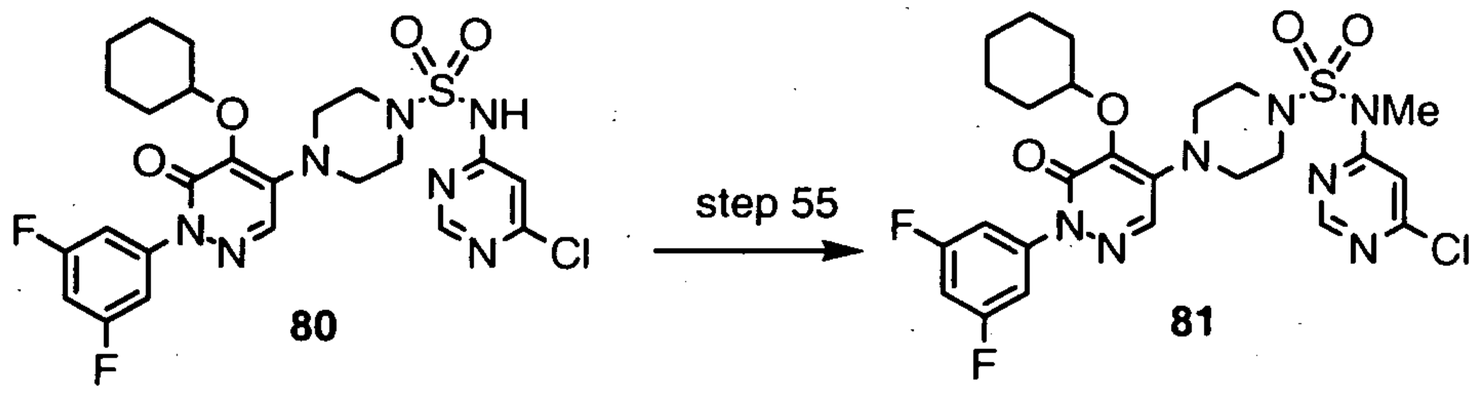
Compound No.	Structure	MS M+1
1552Z		508

Step 54:



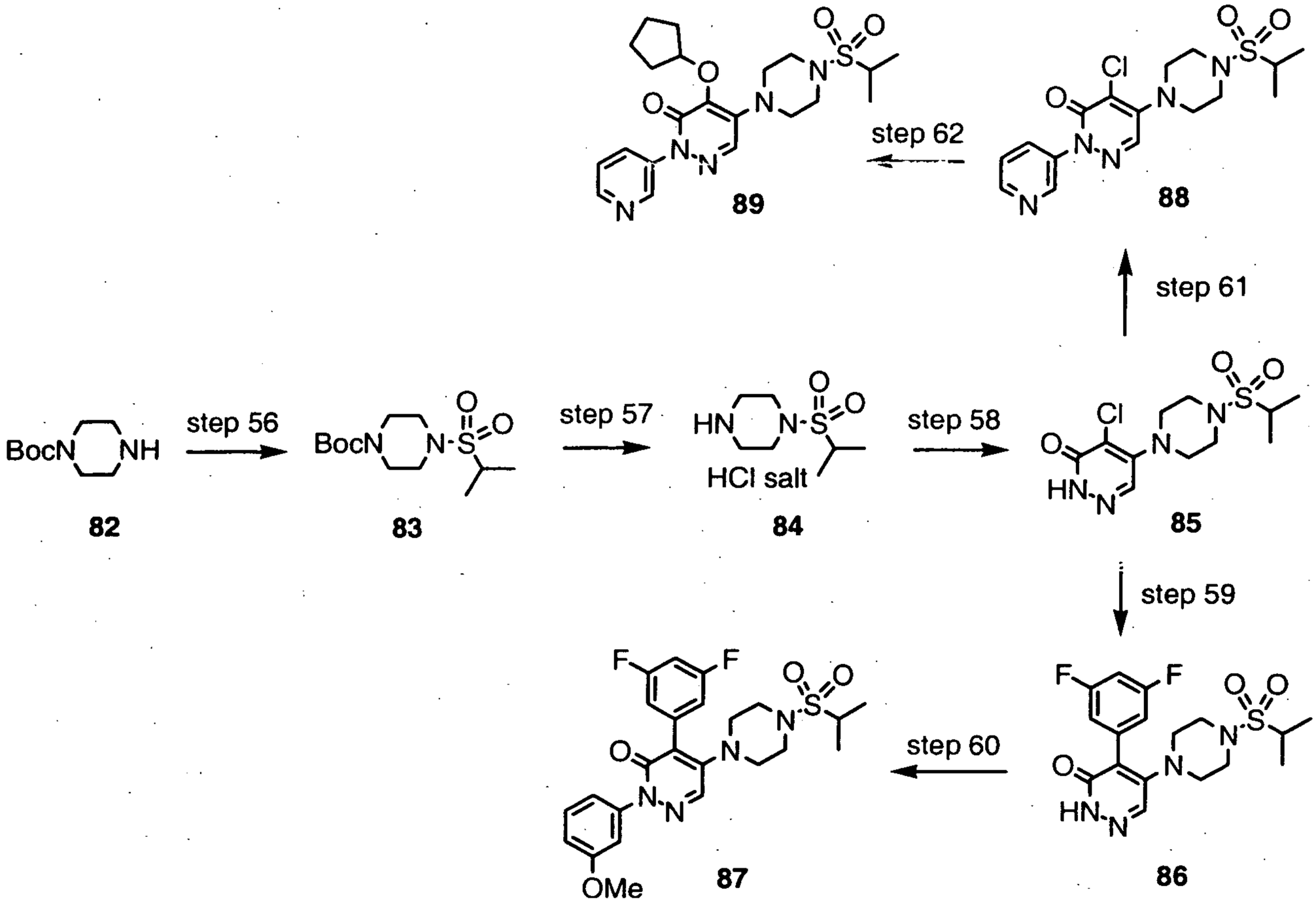
Compound **78** (50 mg, 0.1 mmol) was mixed with 4,6-dichloropyrimidine (20 mg, 0.13 mmol) in 1 mL of dry DMF. Phosphazene base P1-t-Bu (0.038 mL, 0.15 mmol) was added. The mixture was stirred at room temperature for 16 h. The crude mixture was purified by prep HPLC to give 0.033 g of product **80** as a white solid. MS (M+1): m/e 582.

Step 55:



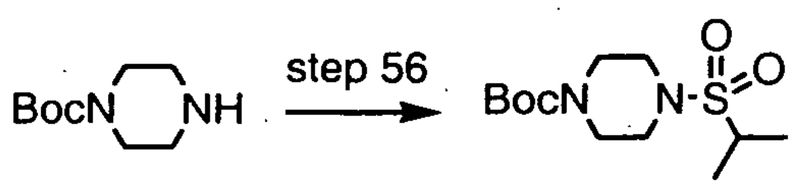
To compound **80** in dry DMF was added methyl iodide (0.1 mL), and the resulting mixture was stirred at room temperature for 3 days. The crude mixture was purified by prep HPLC to give 0.035 g of product **81** as a white solid. MS (M+1): m/e 596.

Scheme 16



82 83 84 85 86 87 88 89

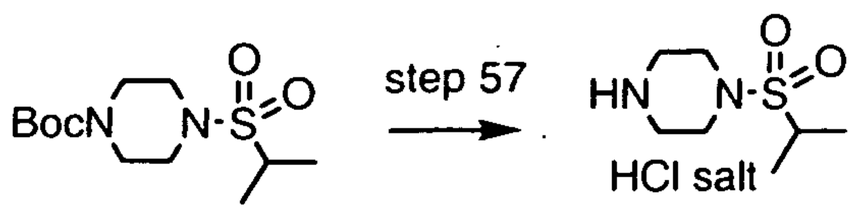
Step 56:



82 83

1-Boc-piperazine **82** (25.0 g, 0.13 mol) was mixed with diisopropylethylamine (28 mL, 0.16 mol) in dry methylene chloride (40 mL), and the mixture was cooled to -25 °C. 2-Isopropanesulfonyl chloride (16.5 mL, 0.15 mol) was added dropwise. The resulting mixture was slowly warmed up to room temperature, and stirred for 16 h. The solvent was evaporated, and EtOAc was added. The organic solution was washed with 1 N HCl, brine, dried (Na_2SO_4), filtered, and concentrated to give 39 g of product **83** as white solid. MS (M+1): m/e 293.

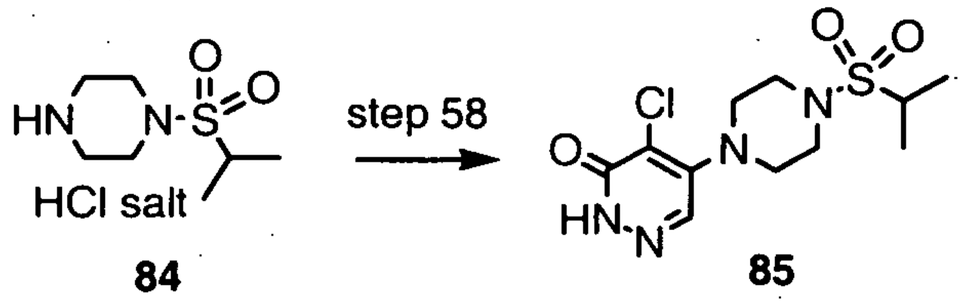
Step 57:



83 84

To compound **83** dissolved in methylene chloride (30 mL) was added of 4 N HCl in dioxane (100 mL). The resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated, and diethyl ether was added. The precipitate was collected by filtration and dried in a vacuum oven at 50 °C for two days to give 28.6 g of product **84** as the HCl salt. MS (M+1): m/e 193.

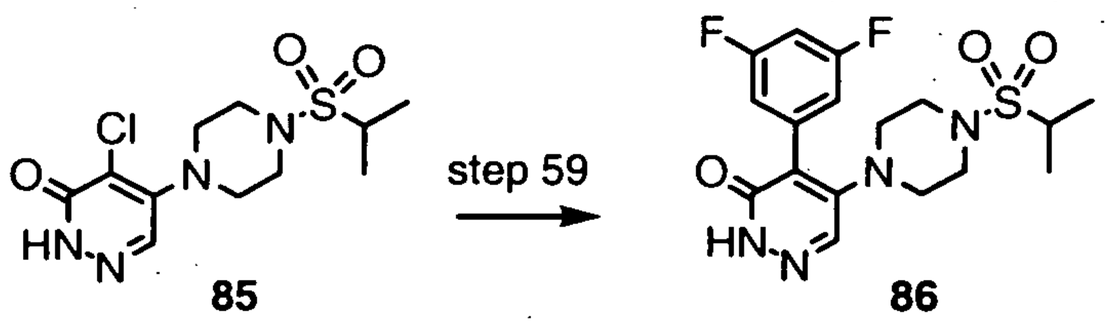
Step 58:



84 **85**

Compound **84** (9.6 g, 42 mmol) was mixed with 4,5-dichloro-3-hydroxy pyridazine (6.6 g, 40 mmol) and TEA (11.4 mL, 82 mmol) in ethanol (80 mL). The resulting mixture was stirred at 70 °C for 2 days then cooled to room temperature and diluted with water (160 mL). The precipitate was collected by filtration, washed with water/ethanol (1:1), and dried in a vacuum oven at 50 °C for 2 days to give 7.8 g of product **85** as a white solid. MS (M+1): m/e 321.

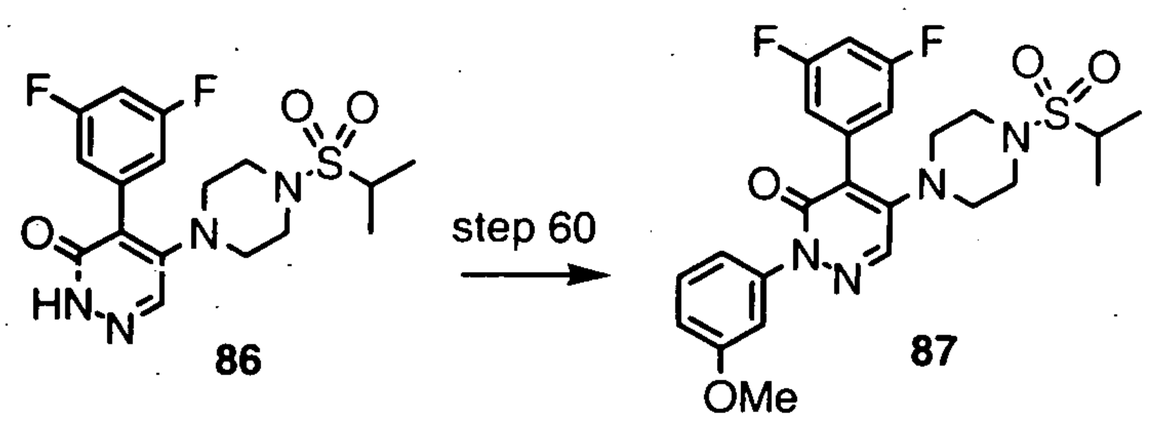
Step 59:



85 **86**

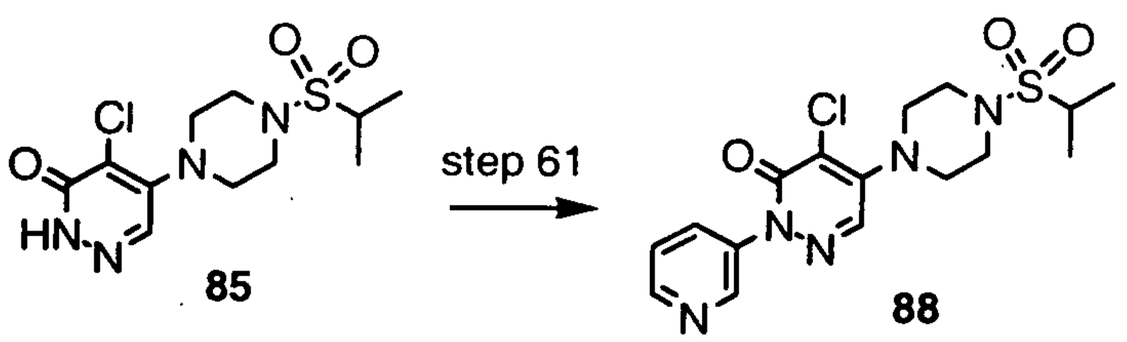
A 20-mL microwave reaction vial was charged with compound **85** (1.92 g, 6.0 mmol), 3, 5-difluorophenyl boronic acid (1.04 g, 6.6 mmol), sodium carbonate (1.33 g, 12.6 mmol), and $Pd(PPh_3)_2Cl_2$ (0.21 g, 0.3 mmol) in 1:1 CH_3CN:H_2O (16 mL). The reaction mixture was heated in the microwave with stirring at 150 °C for 12 mins. After cooling to room temperature, EtOAc was added. The organic solution was washed with 1 N HCl then brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography gave 1.35 g of the product **86** as a white solid. MS (M+1): m/e 399.

Step 60:



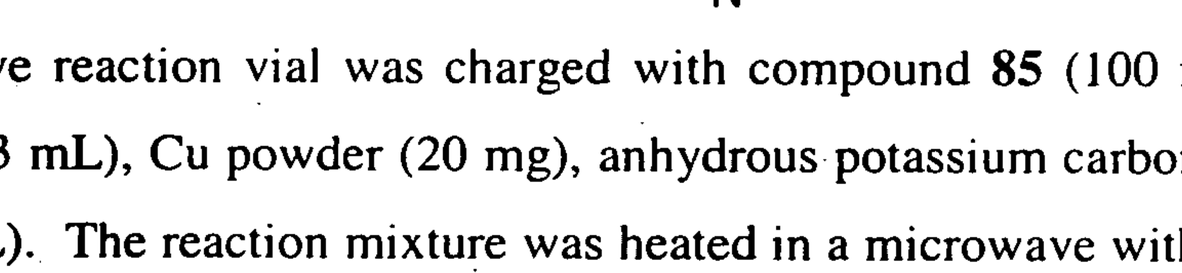
A 5-mL microwave reaction vial was charged with compound **86** (50 mg, 0.125 mmol), 3-methoxybromobenzene (0.12 mL), Cu powder (10 mg), anhydrous potassium carbonate (40 mg), and dry pyridine (3 mL). The reaction mixture was heated in the microwave with stirring at 190 °C for 15 min. After cooling to room temperature, the mixture was filtered, and the solution was concentrated. The residue was dissolved in DMF and purification by reverse phase chromatography on a Gilson prep HPLC gave 50.5 mg of product **87** as light-yellow solid. MS (M+1): m/e 505.

Step 61:



A 5-mL microwave reaction vial was charged with compound **85** (100 mg, 0.3 mmol), 3-bromopyridine (0.3 mL), Cu powder (20 mg), anhydrous potassium carbonate (100 mg), and dry pyridine (4 mL). The reaction mixture was heated in a microwave with stirring at 200 °C for 30 min. After cooling to room temperature, the mixture was filtered, and the solution was concentrated. Purification by silica gel chromatography gave 103 mg of product **88** as light-yellow solid. MS (M+1): m/e 398.

Step 62:

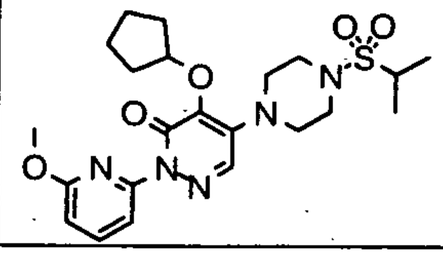


Compound **88** (85 mg, 0.21 mmol) and was mixed with cyclopentanol (55 mg, 0.63 mmol) in dry THF (2 mL). Sodium hydride (60 wt% in oil, 20 mg) was added. The reaction mixture was stirred at room temperature for 16 h. EtOAc was added, and the organic solution was

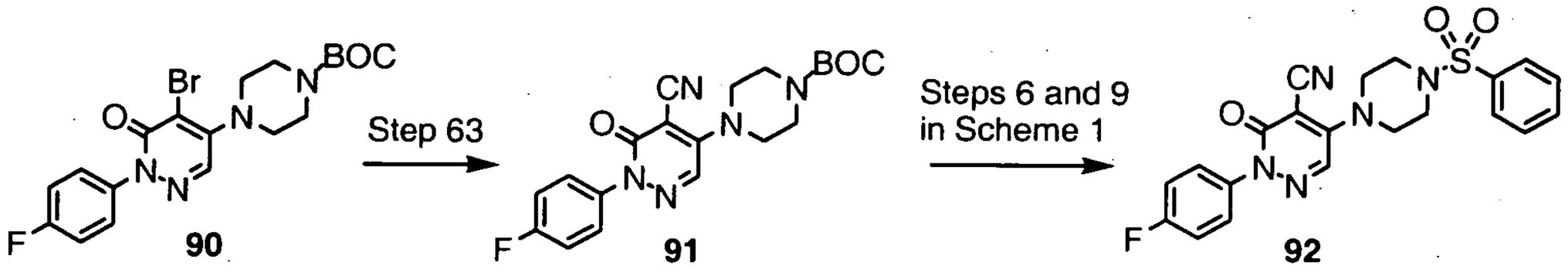
washed with water and brine, dried (Na_2SO4), filtered, and concentrated. Purification by silica gel chromatography gave 83 mg of product **89** as a light-yellow solid. MS (M+1): m/e 448.

Table 20: Oxygen Linked Analog with Sulfonamide

Using the procedures described above, the follow compound was synthesized.

Compound No.	Structure	MS M+1
1553Z		478

Scheme 17

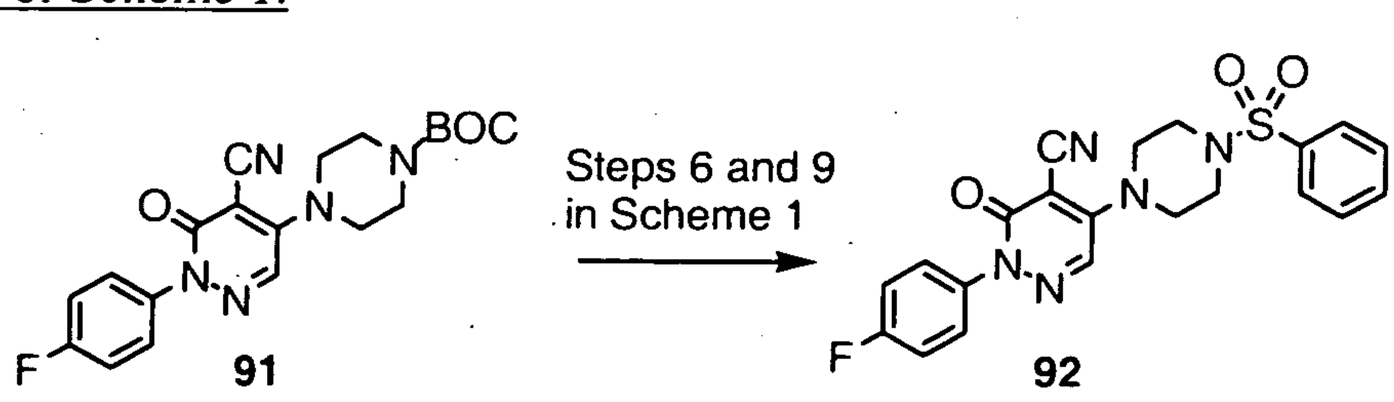


Compound **90** can be synthesized using steps 1 and 2 of Scheme 1.

Step 63:

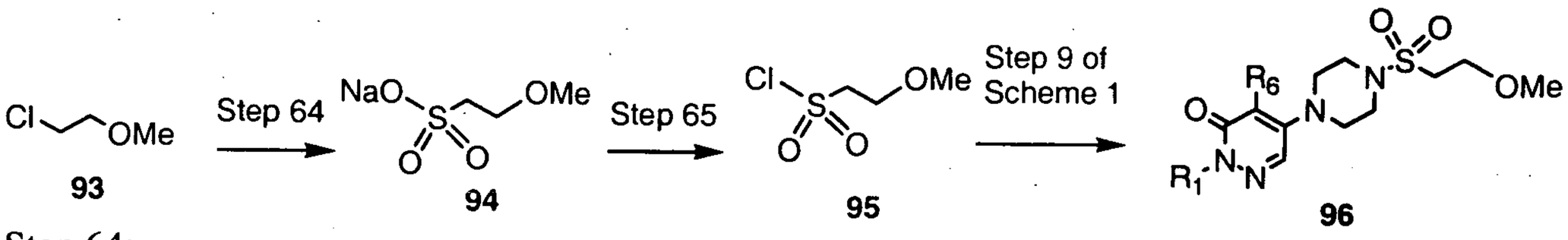
A mixture of anhydrous KCN (0.065 g, 1.0 mmol) and compound **90** (0.451 g, 1.0 mmol) in DMSO (5 mL) was stirred at room temperature for 24 h. The resulting solution was poured into ice H_2O (10 mL), and a white precipitate formed. The solid was filtered and dried under vacuum. Purification by silica gel chromatography (1:10 EtOAc:hexanes) gave the product **91** as a white solid (0.320 g, 80%). MS (M+1): m/e 400.

Steps 6 and 9 of Scheme 1:

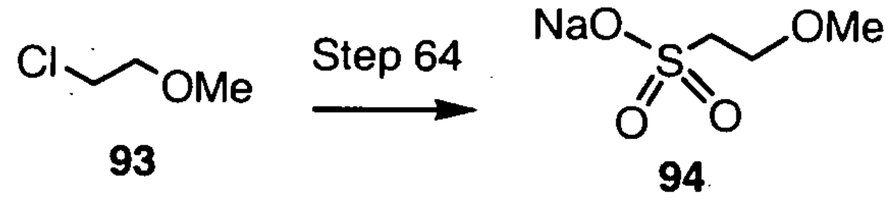


Using the procedure described above, compound **92** was synthesized. MS (M+1): m/e 440.

Scheme 18

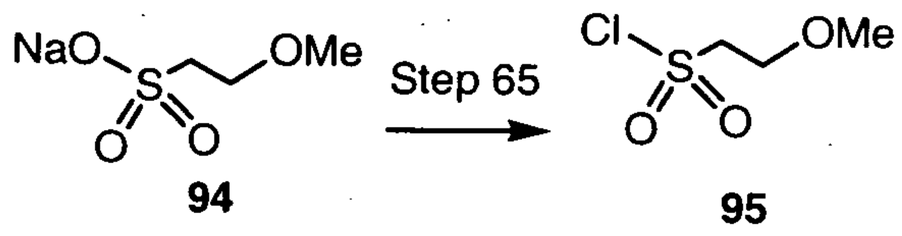


Step 64:



A mixture of 2-chloroethyl methyl ether **93** (25 g) and Na_2SO_3 (33 g) dissoved in H_2O (100 mL) was heated at reflux for 24 h. After cooling to room temperature, the solid was filtered, washed with ether/toluene (5:1), and dried under vacuum to give product **94.**

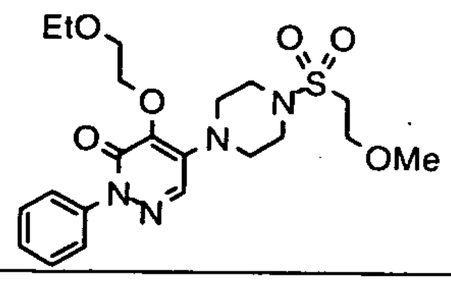
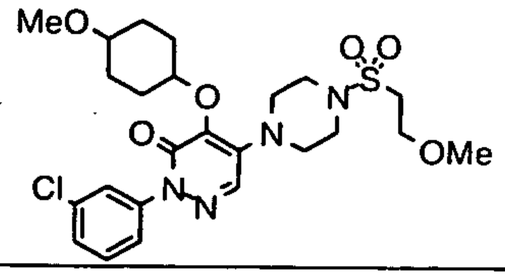
Step 65:

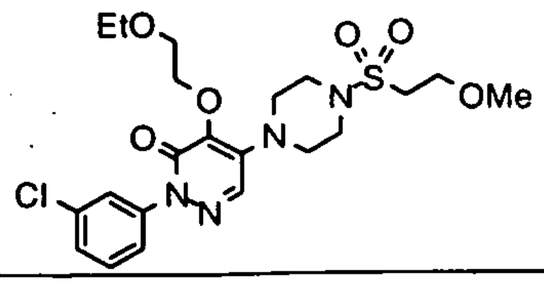
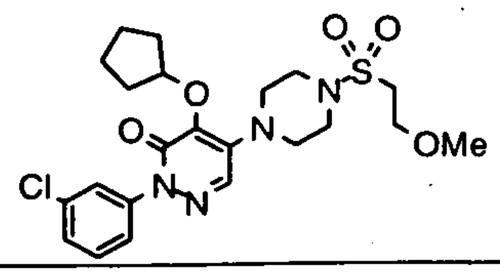


Compound **94** was added in small portions to $POCl_3$ (60 mL). The resulting heterogeneous mixture was stirred at room temperature for 16 h and then heated at reflux for 12 h. CH_2Cl_2 (100 mL) was added to the reaction mixture. After filtration, ethyl acetate was added to the residue and then poured into crushed ice. The organic phase was separated and washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to give product **95.**

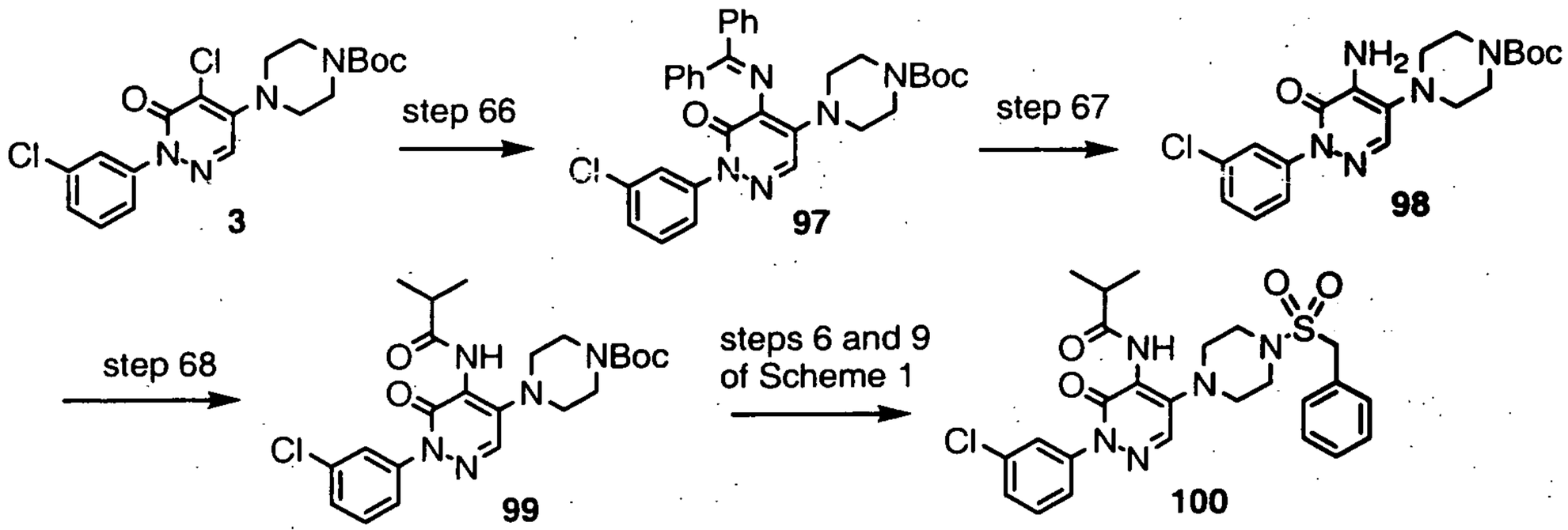
Table 21: Oxygen Linked Analogs with Sulfonamide

The following compounds can be synthesized by using compound **95** in step 9 of Scheme 1.

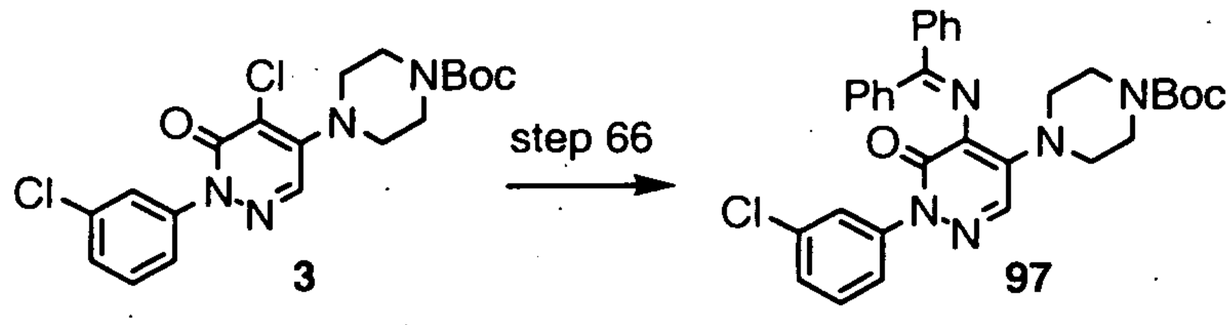
Compound No.	Structure	MS M+1
1554Z		467
1555Z		541

1556Z		501
1557Z		497

Scheme 19

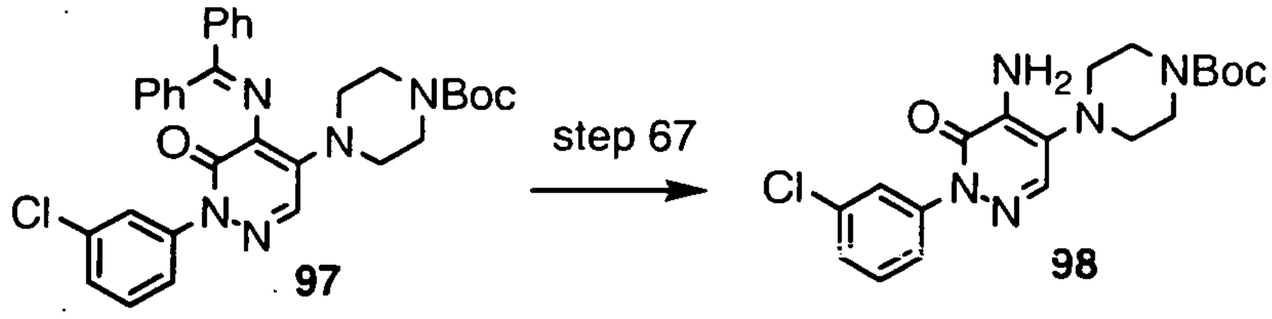


Step 66:



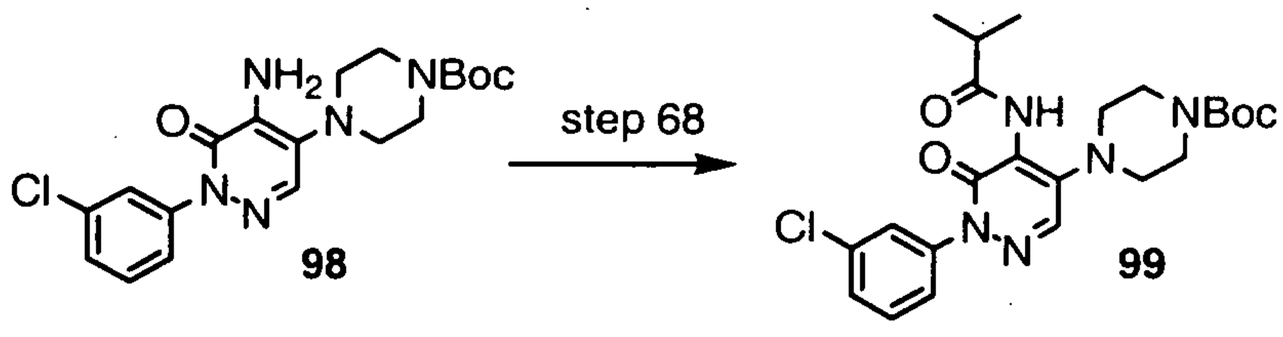
Compound **3** (0.43 g, 1 mmol) was mixed with $Pd(OAc)_2$ (4.5 mg), (±) BINAP (12.5 mg), $Ph_2C{=}NH$ (0.2 mL, 1.2 mmol), and potassium carbonate (0.7 g, 5 mmol) in dry toluene (9 mL). The reaction mixture was heated at 110 °C under nitrogen for 2 days. After cooling to room temperature, the mixture was filtered, and the solid was washed with methylene chloride. The combined filtrate was concentrated, and purification by silica gel chromatography gave 0.21 g of product **97** and 0.15 g of product **98**. For compound **97**: MS (M+1): m/e 570 and for compound **98**: MS (M+1): m/e 406.

Step 67:



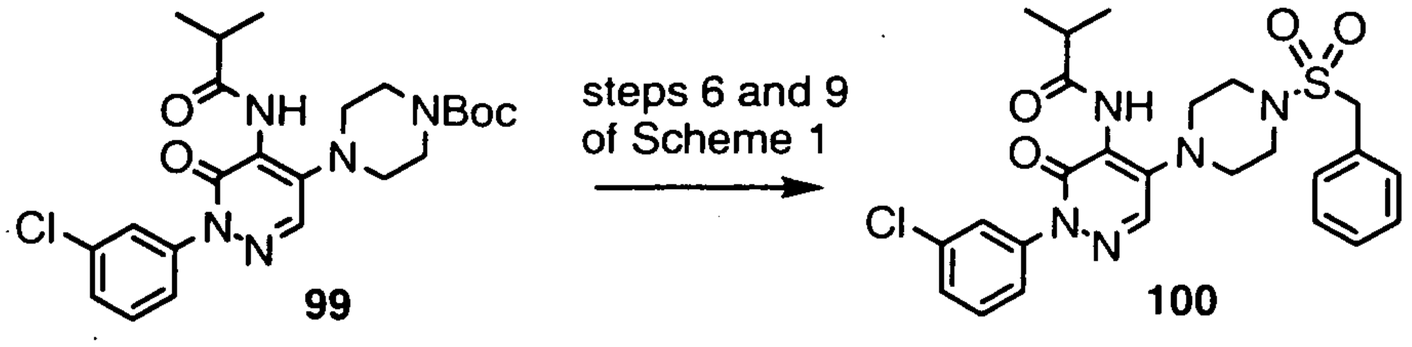
Compound **97** (0.15 mg) dissolved in methanol (2 mL) was treated with 2 N HCl (4 mL), and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with ethyl acetate and washed with brine. The organic extract was evaporated, and purification by silica gel chromatography gave the product **3** (100%).

Step 68:



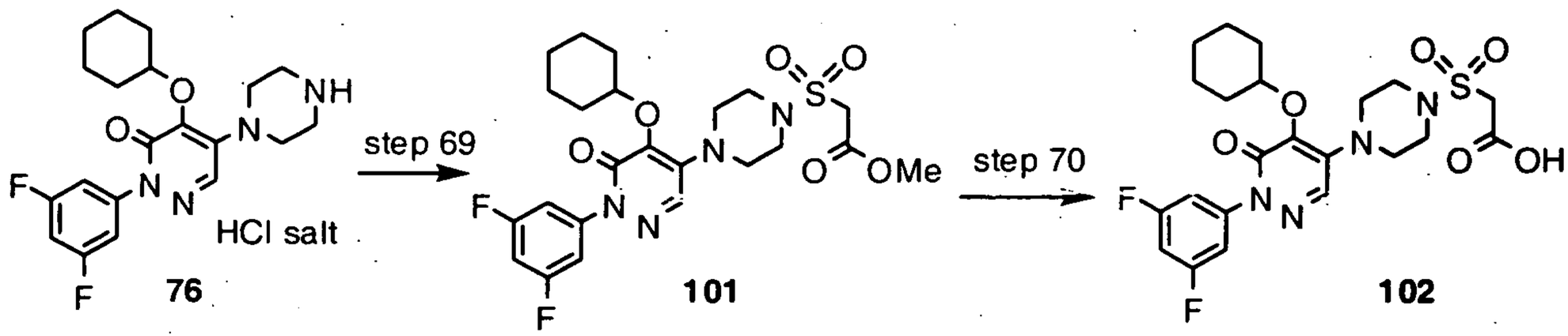
To a solution of compound **98** (0.13 g, 0.3 mmol) in dry DMF (2 mL) was added diisopropylethylamine (0.2 mL) and isobutyryl chloride (0.035 mL, 0.33 mmol). The reaction mixture was stirred at room temperature for 3 days. The mixture was diluted with ethyl acetate, and washed with saturated sodium bicarbonate solution, water, 1 N HCl, and brine. The organic solution was evaporated to give the product **99** which was used in the next step without further purification.

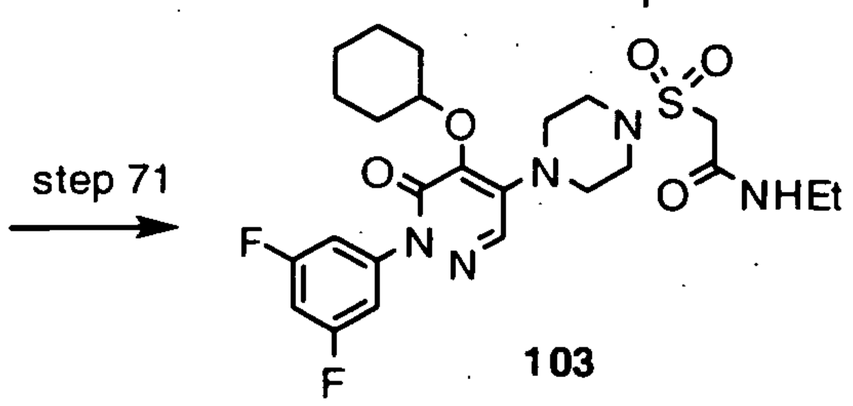
Steps 6 and 9 of Scheme 1:



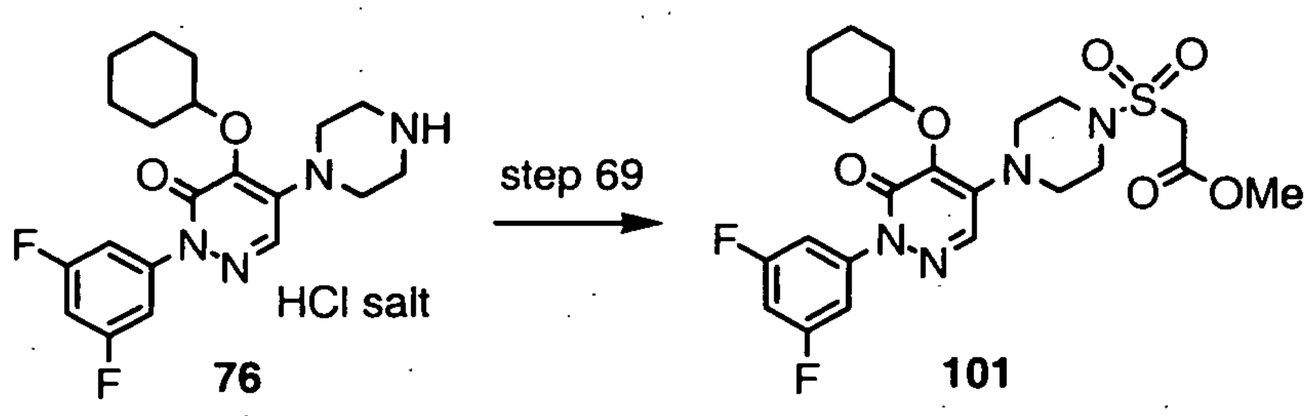
Using the procedures described above, compound 100 was synthesized. MS (M+1): m/e 530.

Scheme 20



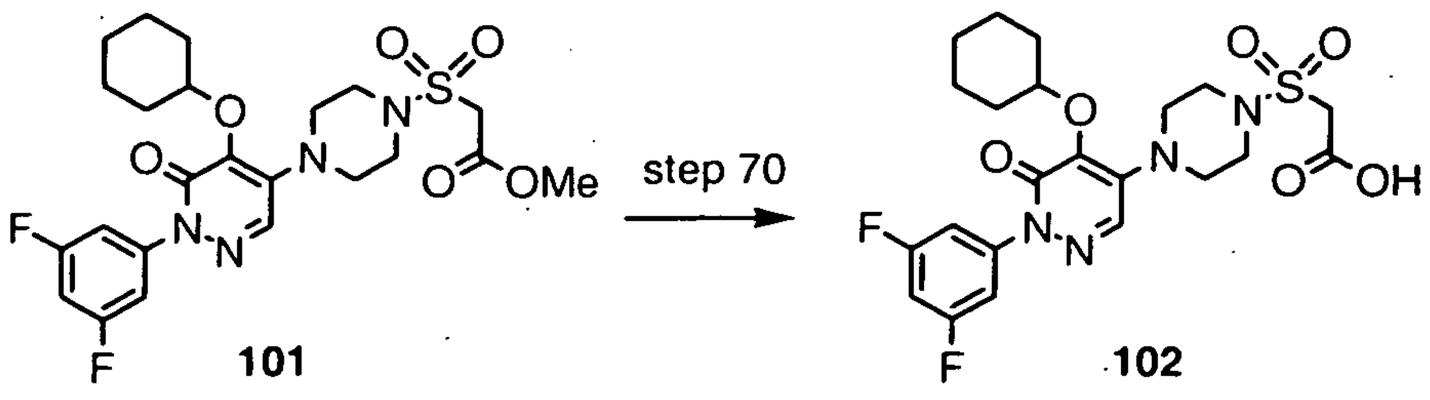


Step 69:



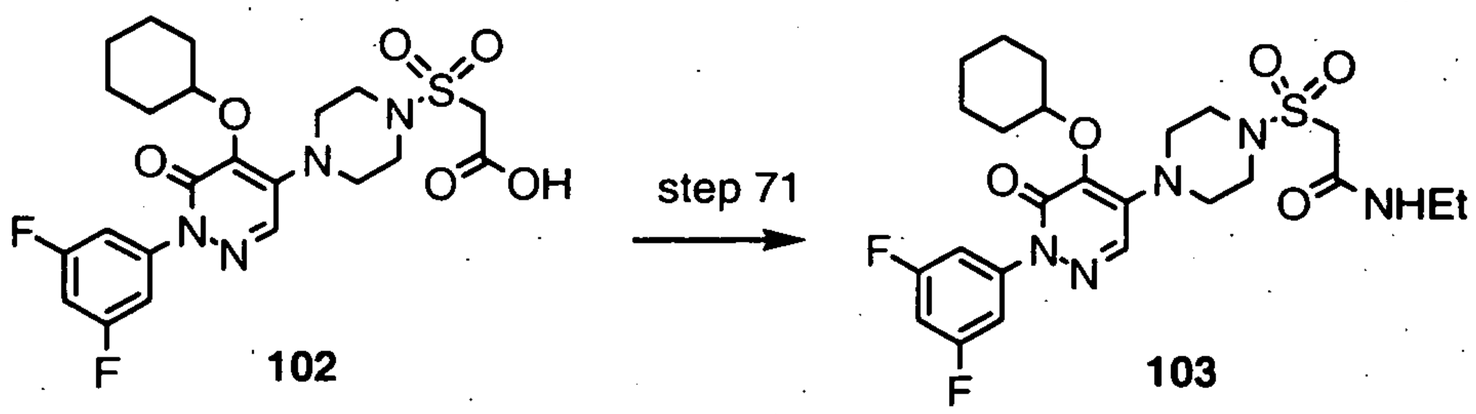
Chlorosulfonylacetyl chloride (0.16 mL, 1.5 mmol) in dry diethyl ether (2 mL) was cooled to -78 °C, and methanol (1.5 mmol) in dry ether (1 mL) was added. After warming to room temperature, the mixture was stirred at room temperature for 1 h, then added to a solution of compound **76** and diisopropylethylamine (0.88 mL, 5 mmol) in DMF (3 mL). The resulting mixture was stirred at room temperature for 16 h. EtOAc was added, and the organic solution was washed with 1 N HCl and brine, dried (Na_2SO_4), filtered and concentrated. Purification by silica gel chromatography gave 0.2 g of product **101** as a white solid. MS (M+1): m/e 527.

Step 70:



To compound **101** (0.17 g) dissolved in THF (3.8 mL) and water (1.5 mL) was added lithium hydroxide (0.019 g). The resulting mixture was stirred at room temperature for 3 h. 1 N HCl (5 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was dried (Na_2SO_4), filtered, and concentrated to give the product **102**. MS (M+1): m/e 513.

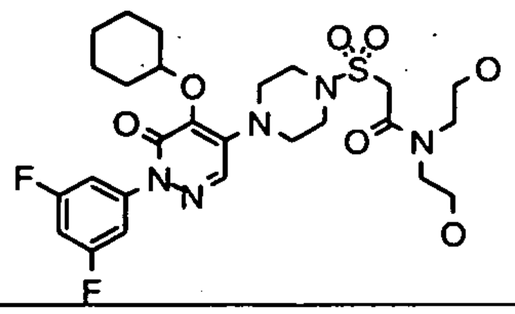
Step 71:



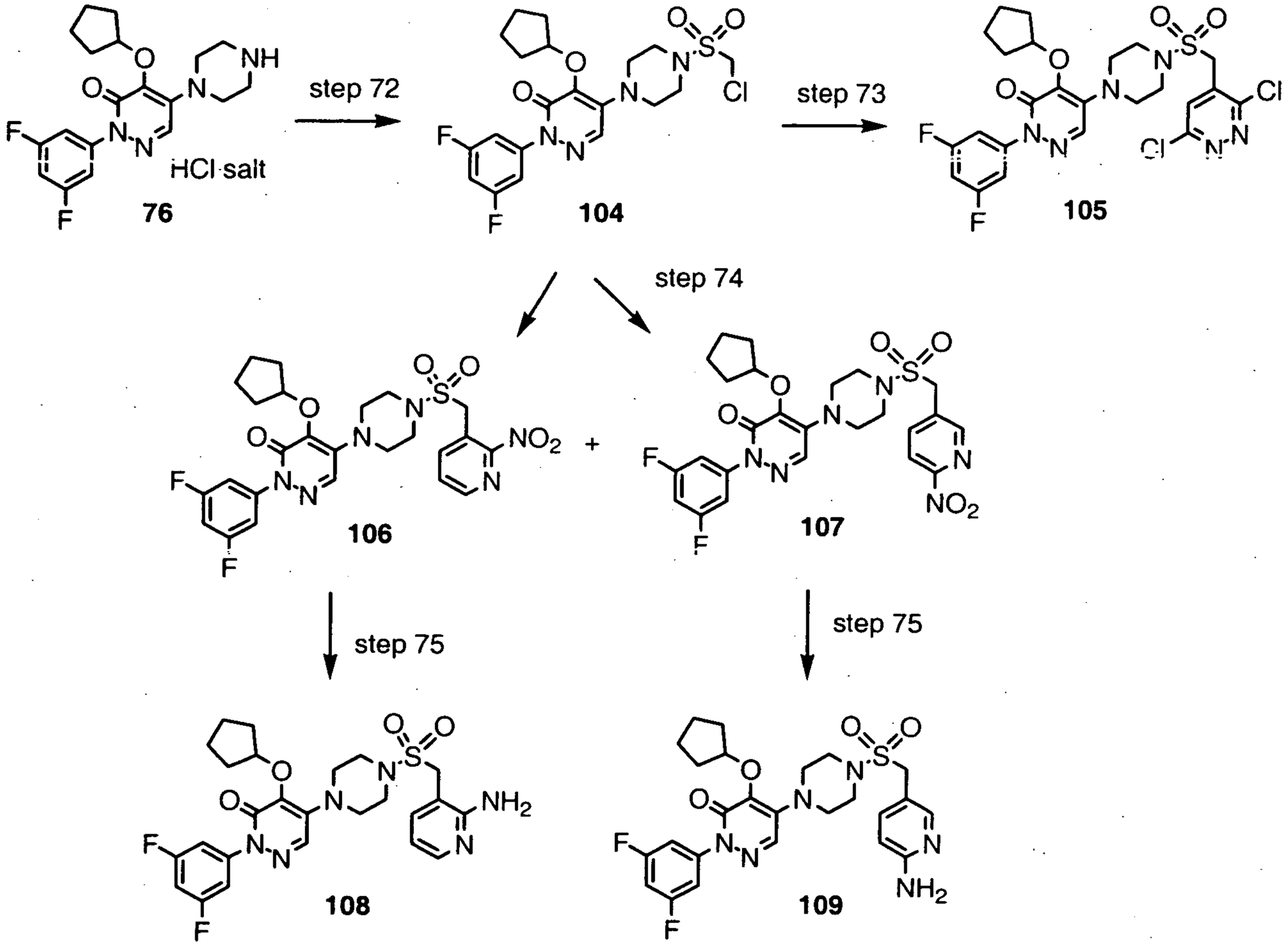
Compound **102** (40 mg) was mixed with ethylamine (0.5 mmol), diisopropylethylamine (0.1 mL), and HATU (0.3 g) in DMF (1 mL). The mixture was stirred at room temperature for 16 h, then purified directly with the Gilson reverse phase prep HPLC (acetonitrile – water gradient with 0.1% formic acid) to give 21 mg of the product **103** as light-yellow solid. MS (M+1): m/e 640.

Table 22: Oxygen Linked Analog with Sulfonamide

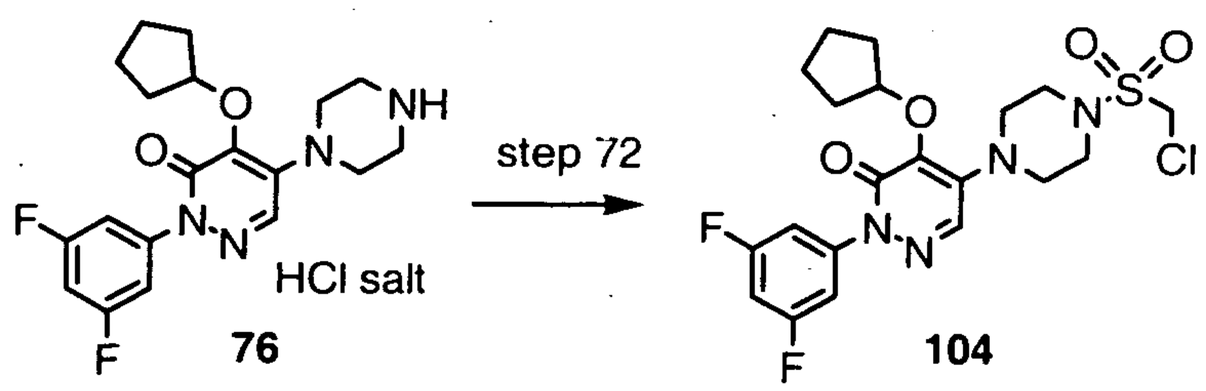
Using the procedures described above, the follow compound was synthesized.

Compound No.	Structure	MS M+1
1558Z		600

Scheme 21

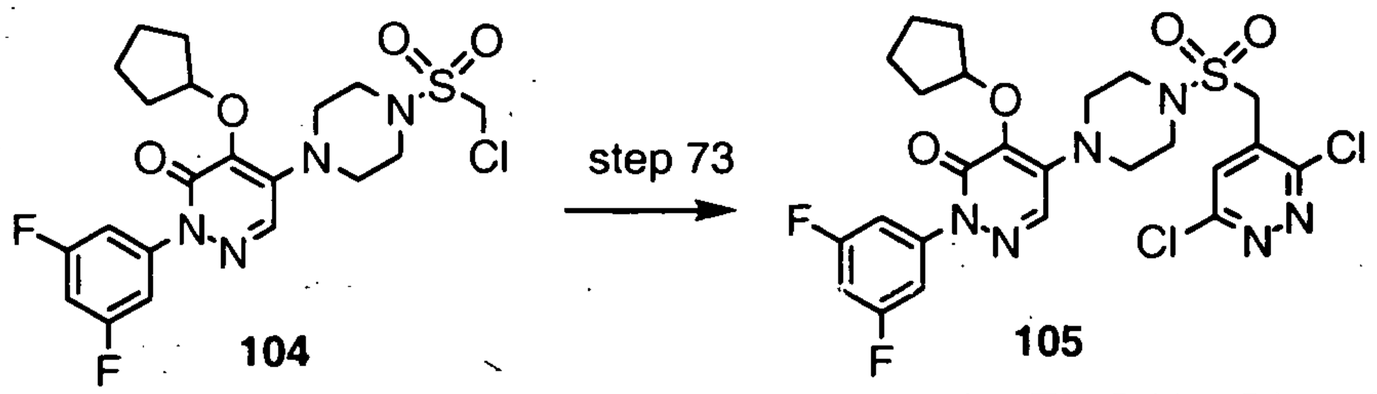


Step 72:



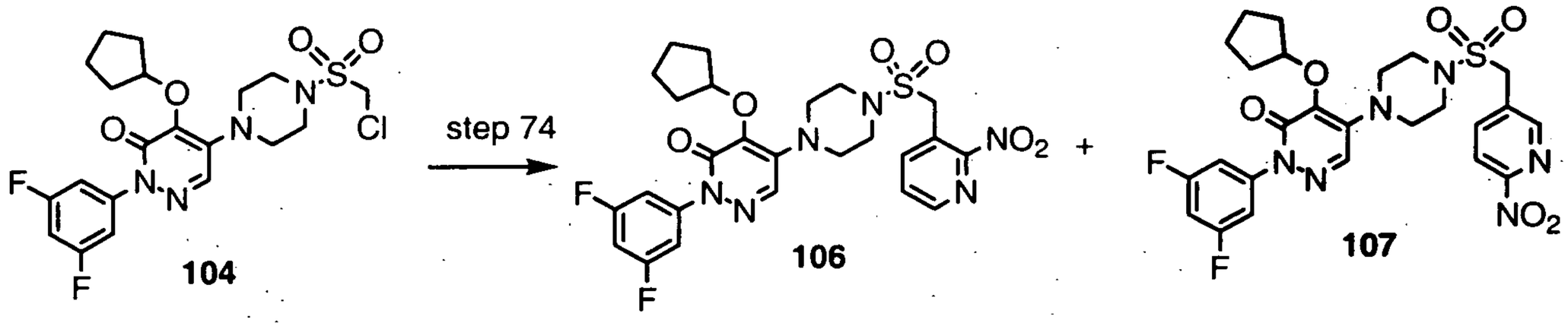
Compound **76** (2.1 g, 5.1 mmol) was mixed with diisopropylethylamine (2.1 mL, 12.7 mmol) in 1:1 DMF:CH_2Cl_2 (20 mL) and cooled to - 30 °C. Chloromethanesulfonyl chloride (0.91 g, 6.11 mmol) was added, and the resulting mixture was slowly warmed up to room temperature and stirred for 16 h. EtOAc was added, and the organic solution was washed with 1 N HCl, water, and brine, dried (Na_2SO_4), and concentrated. Purification by silica gel chromatography gave 2.3 g of the product **104** as a white solid MS (M+1): m/e 489.

Step 73:



Potassium *tert*-butoxide (0.22 g, 2 mmol) was dissolved in dry THF (4 mL) and cooled to -78 °C. A solution of compound **104** (0.24 g, 0.5 mmol) and 3, 6-dichloropyridazine (0.10 g, 0.65 mmol) dissolved in dry THF (2 mL) was added. The reaction mixture was stirred at - 78 °C for 1 h, and then 1 N aqueous HCl (4 mL) was added. EtOAc was added, and the organic solution was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography gave 0.25 g of the product **105** as white solid. MS (M+1): m/e 601.

Step 74:

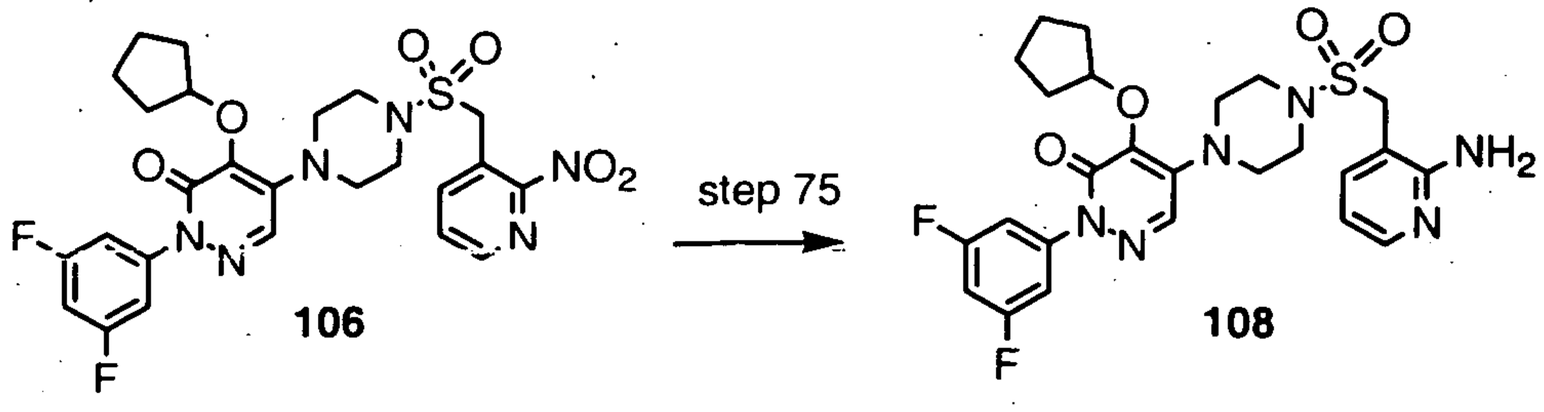


To compound **104** (0.24 g, 0.5 mmol) and 2-nitropyridine (0.12 g, 1.0 mmol) dissolved in DMSO (3 mL) was added potassium *tert*-butoxide (0.22 g, 2 mmol) was added portionwise at room temperature. After stirring for 5 mins, 1 N aqueous HCl (5 mL) was added. EtOAc was added, and the organic solution was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (10% hexane/CH_2CH_2 to 10% EtOAc/ CH_2CH_2) gave 0.12 g of the product **106** as a white solid and 0.065 g of the product **107** as a white solid.

The structure of each isomer was assigned by its ^1H NMR spectrum.

MS (M+1): m/e 577 (compound **106**) and 577 (compound **107**).

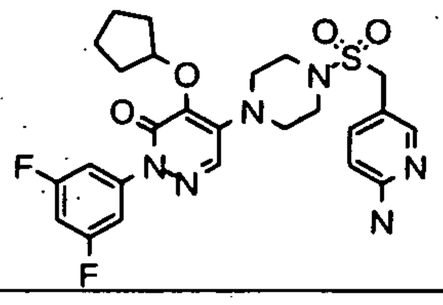
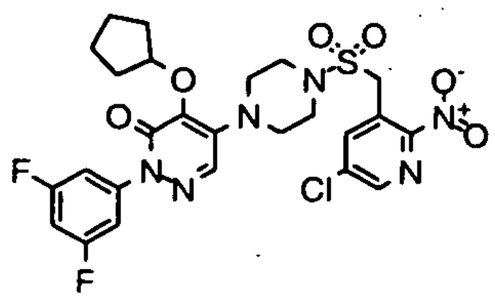
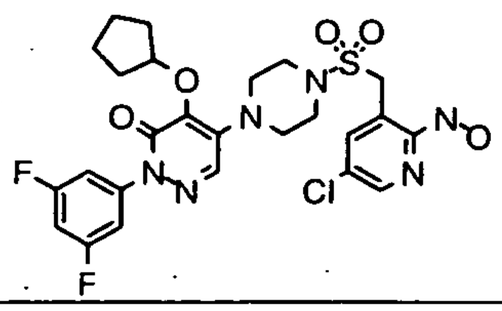
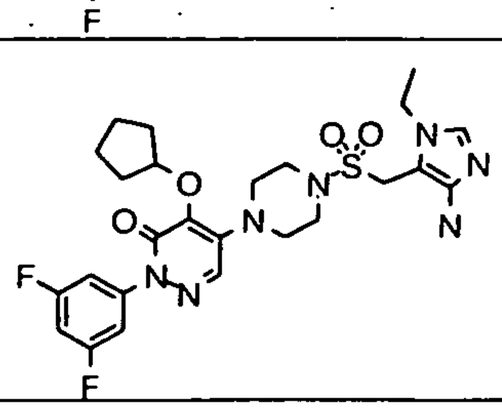
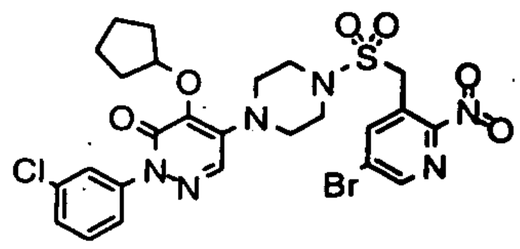
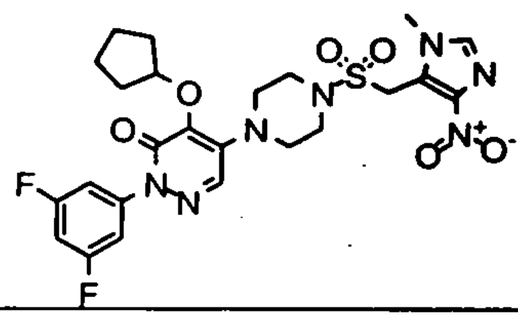
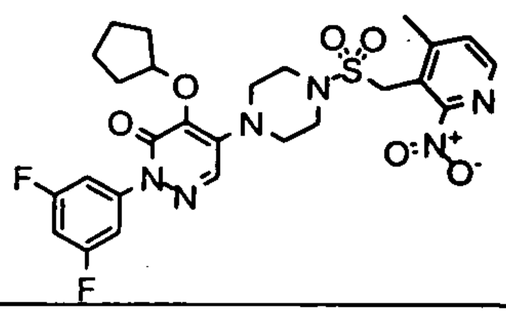
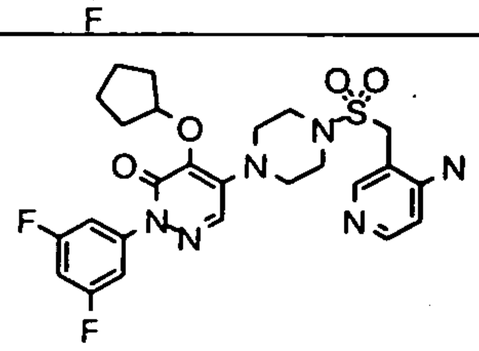
Step 75:

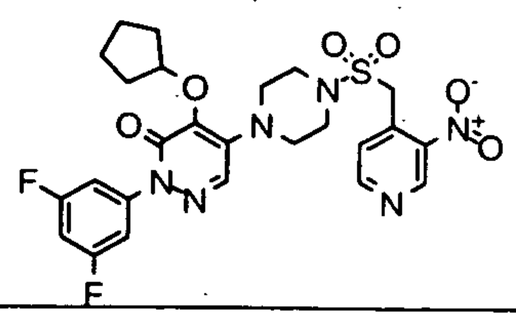
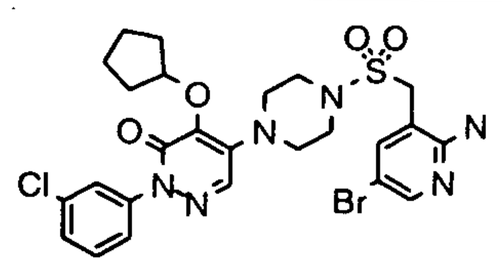
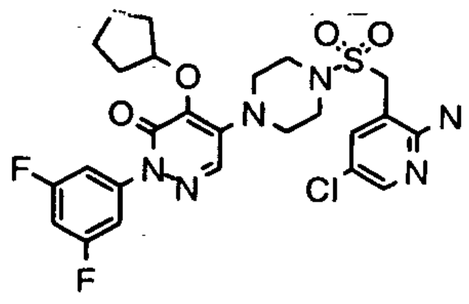
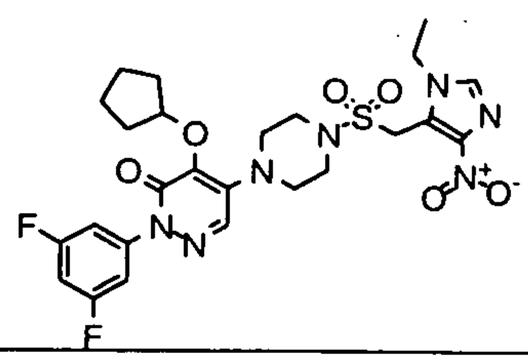
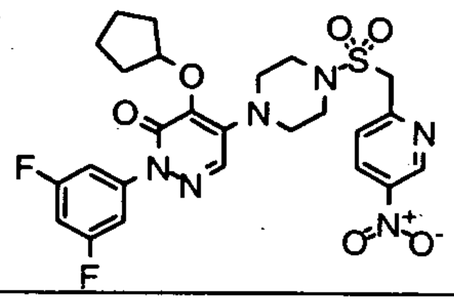
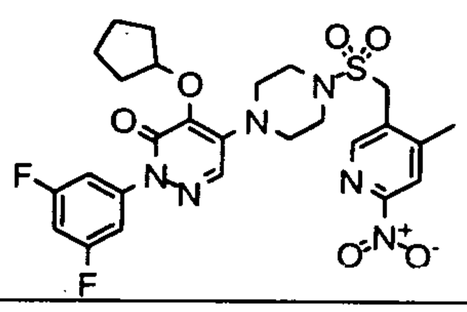
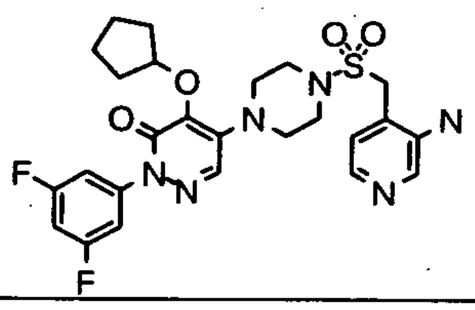
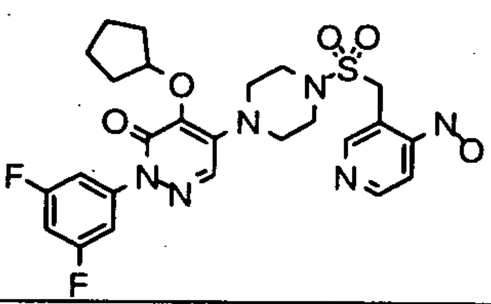
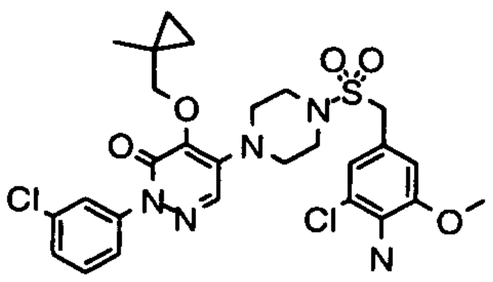
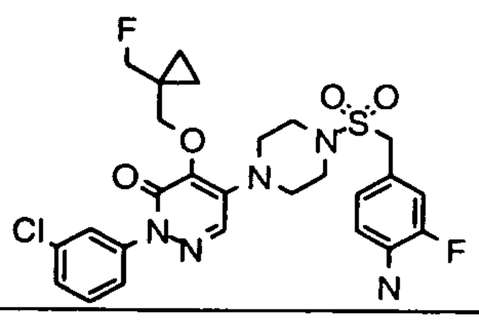
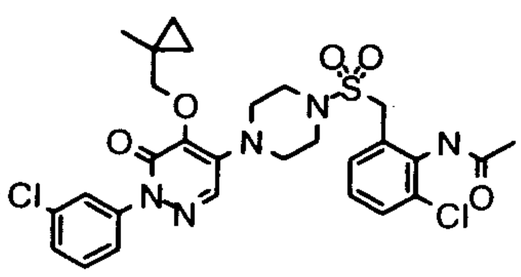
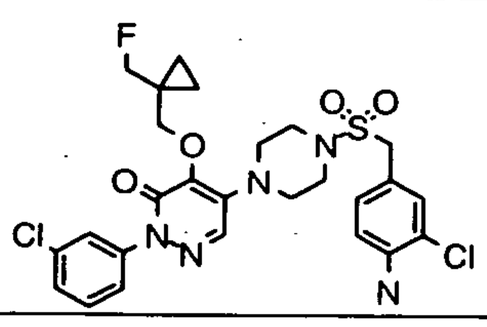
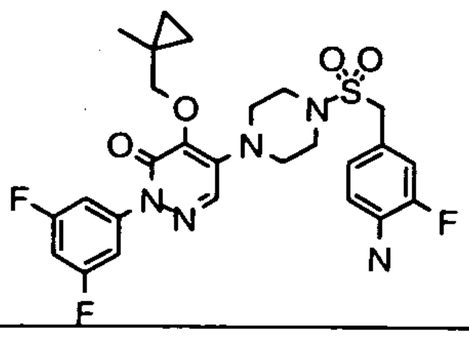
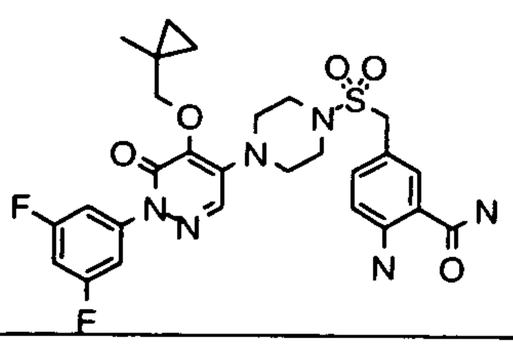
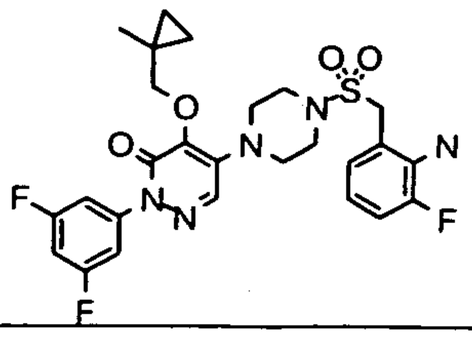
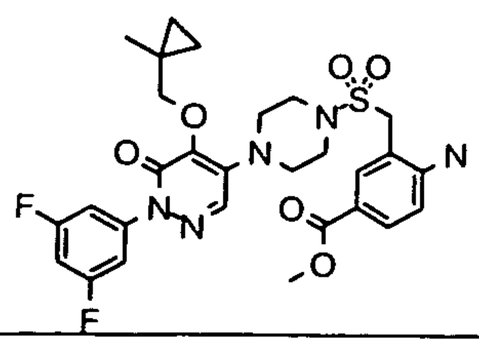


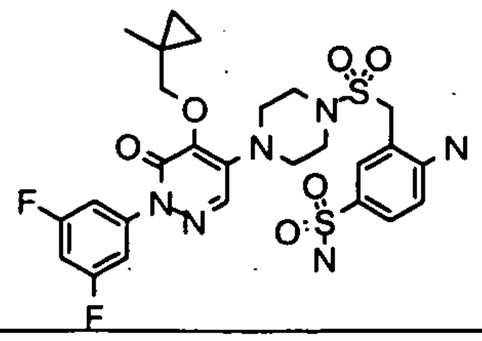
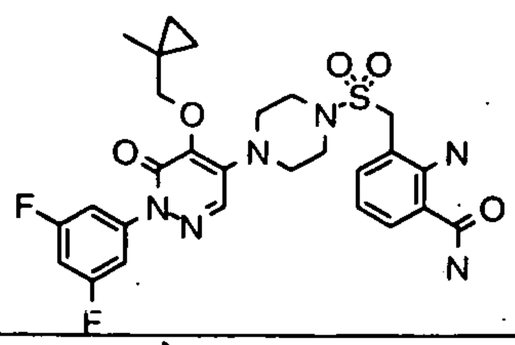
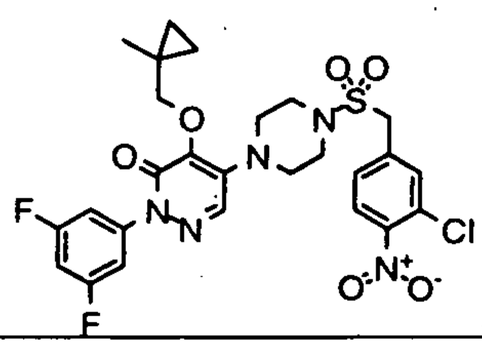
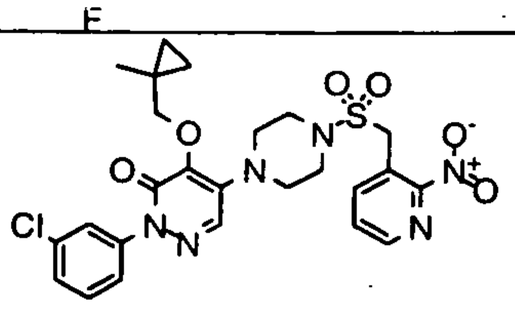
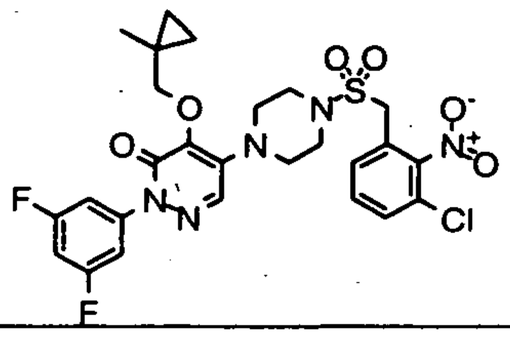
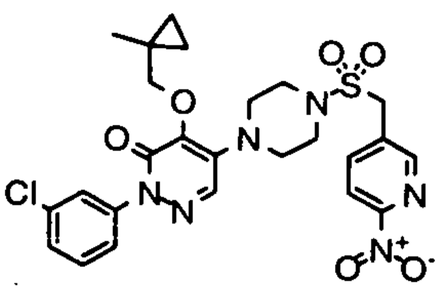
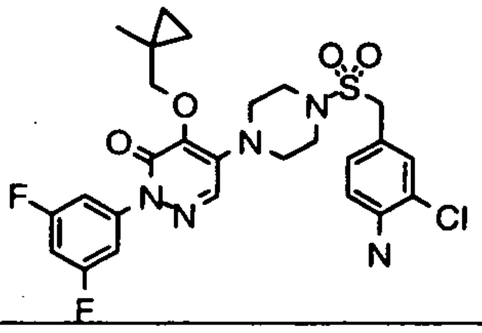
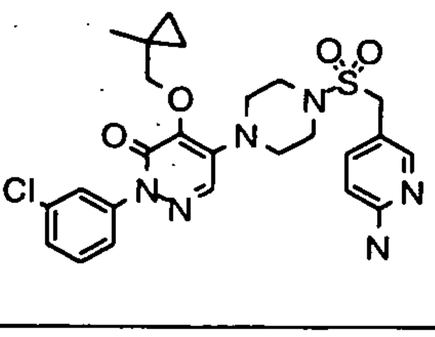
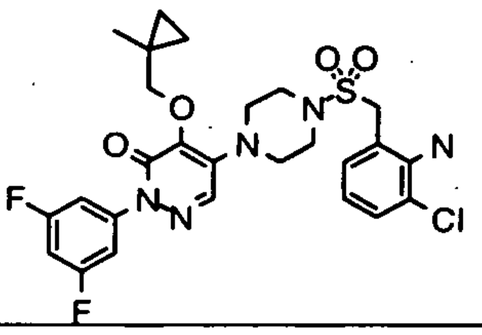
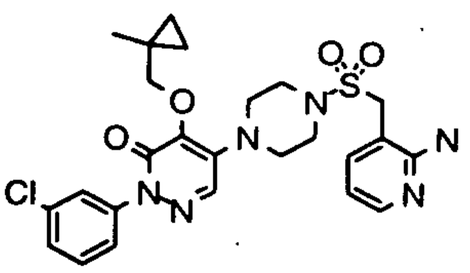
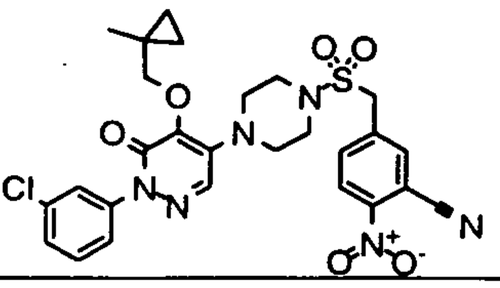
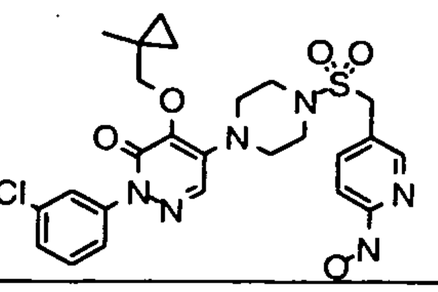
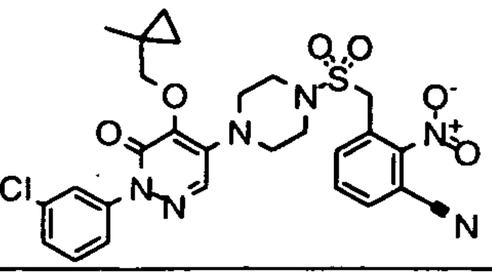
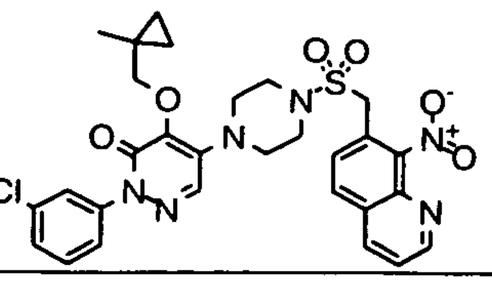
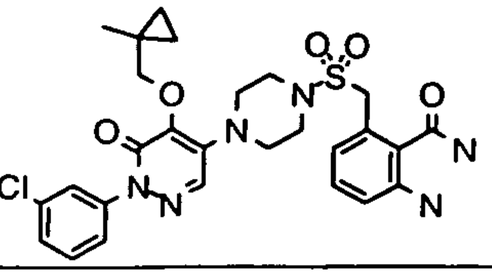
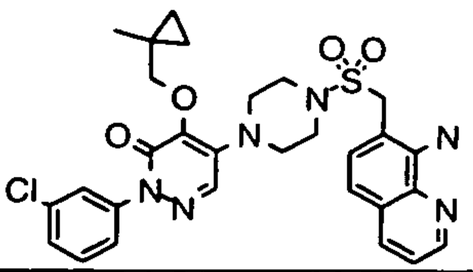
To compound **106** (100 mg) dissolved in THF (10 mL) was added 10% Pd/C (200 mg). The reaction mixture was stirred under a balloon of hydrogen gas at room temperature for 2 h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated, and purification by silica gel chromatography gave 0. 085 g of the product **108** as white solid. MS (M+1): m/e 547.

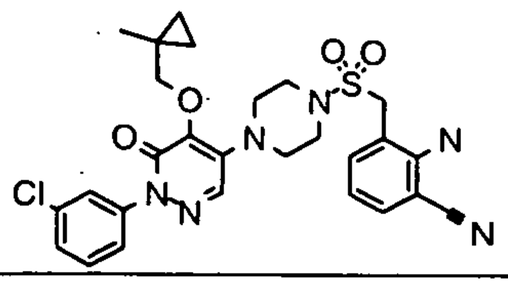
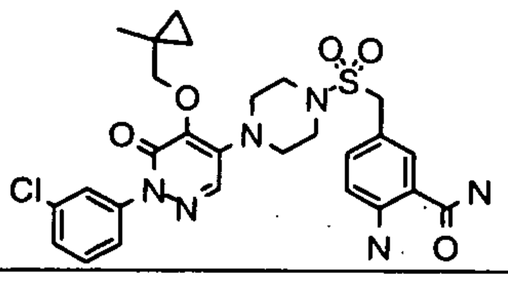
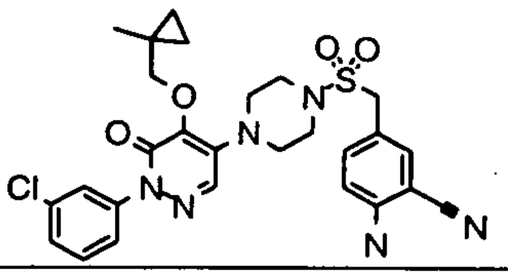
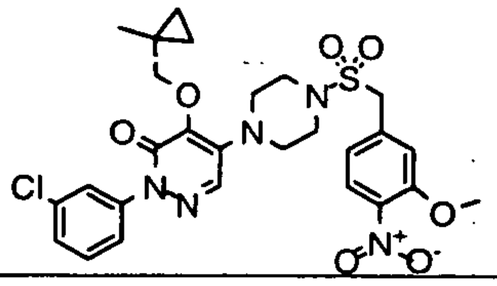
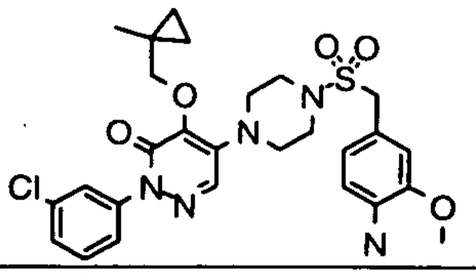
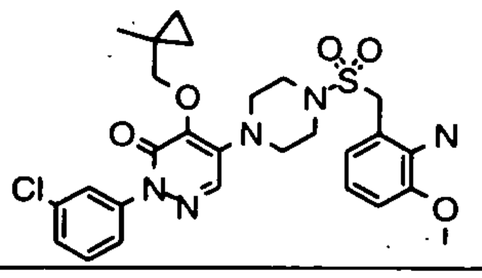
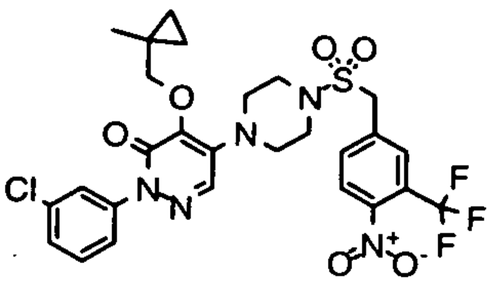
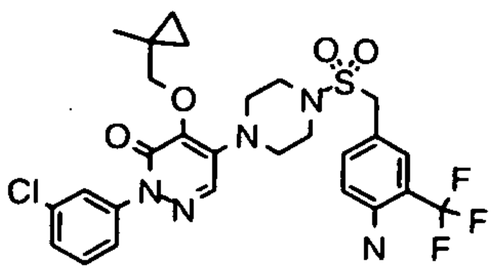
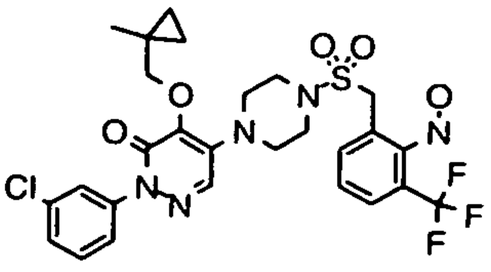
Table 23: Oxygen Linked Analogs with Sulfonamide

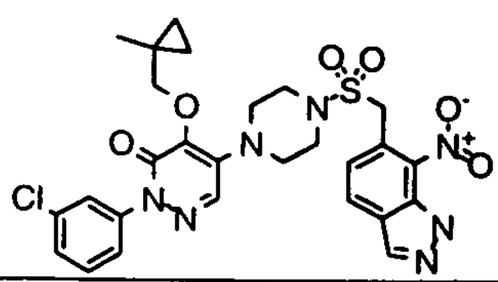
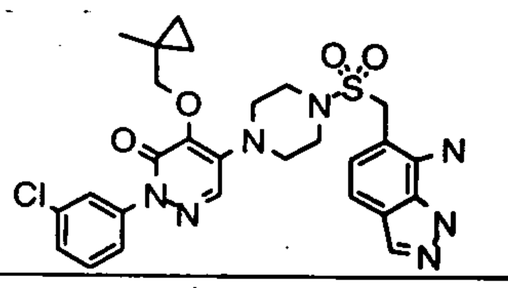
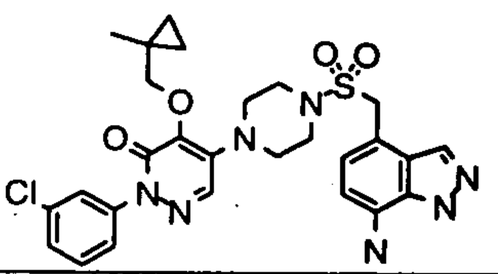
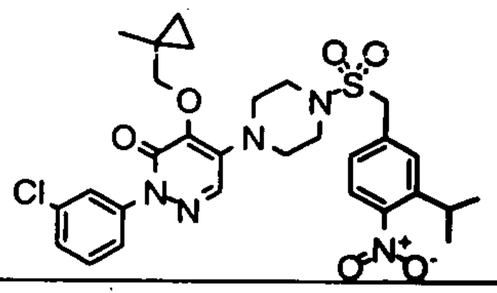
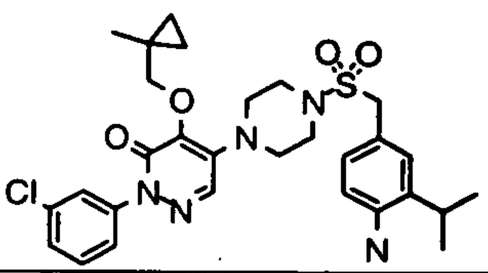
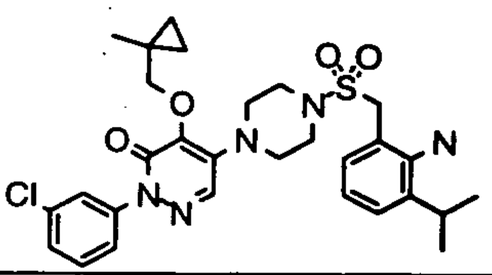
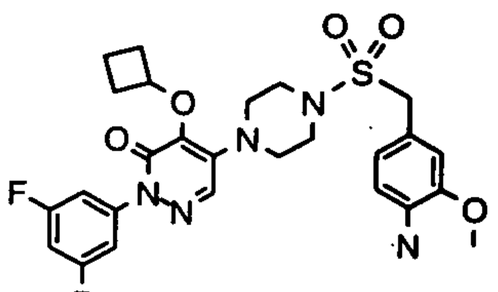
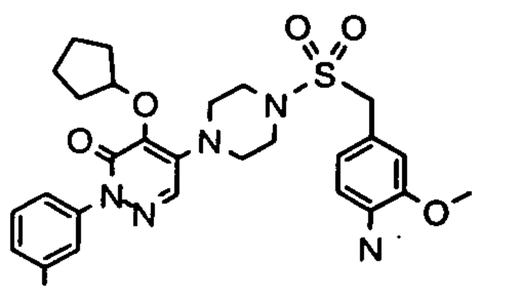
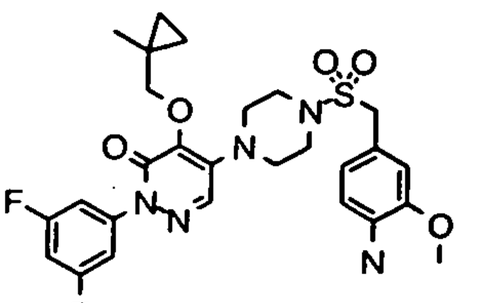
Using the procedures described above, the following compounds were synthesized.

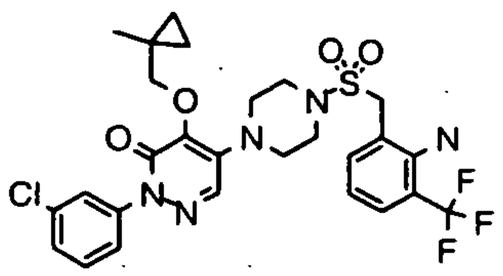
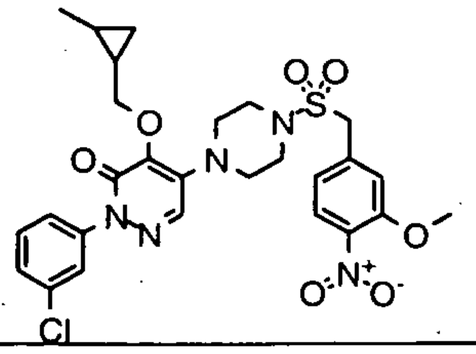
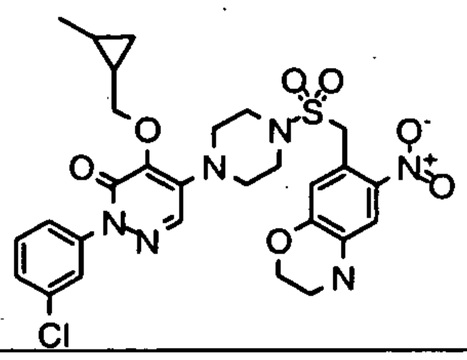
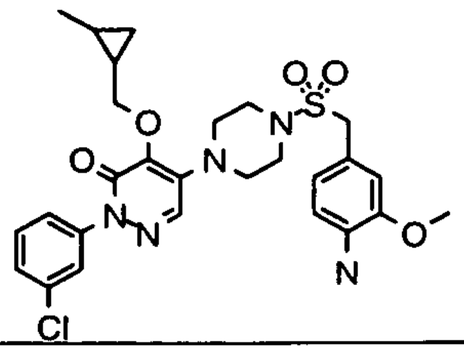
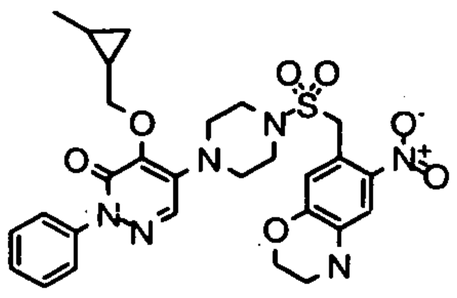
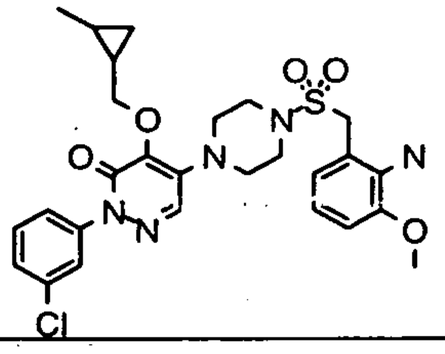
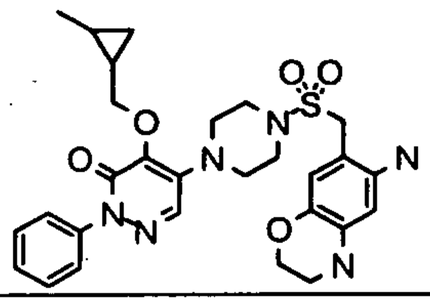
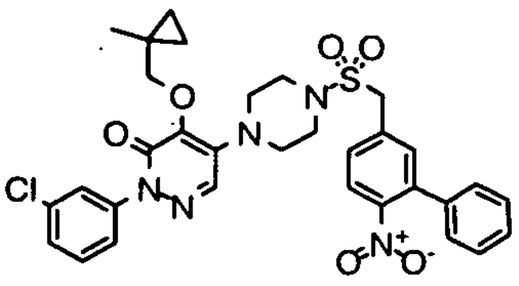
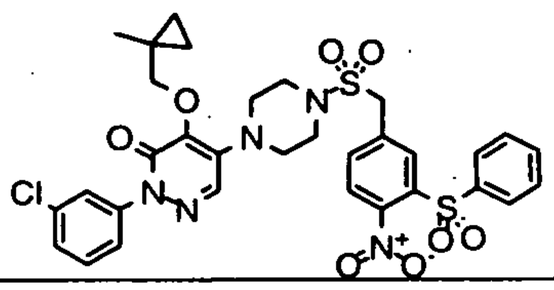
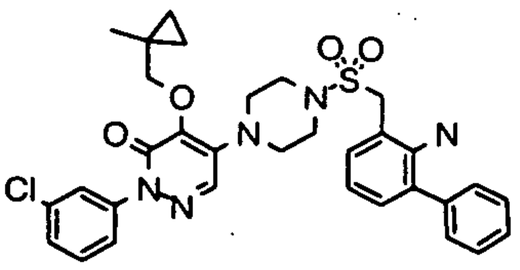
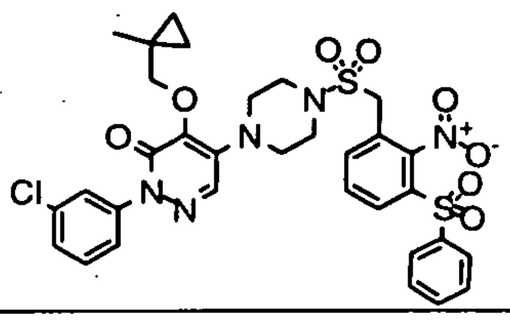
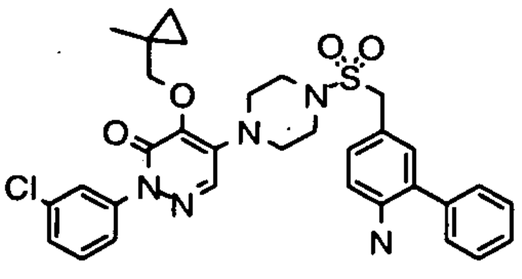
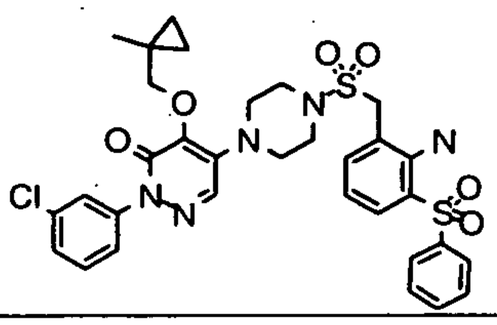
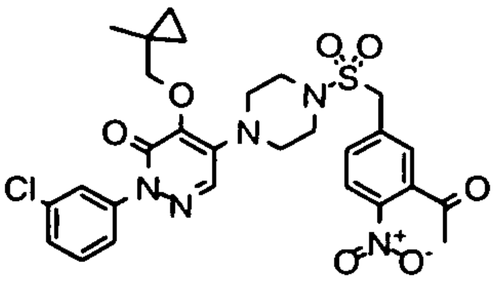
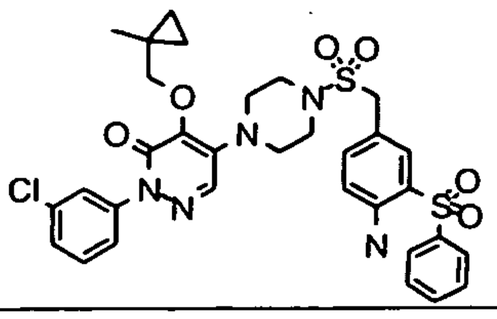
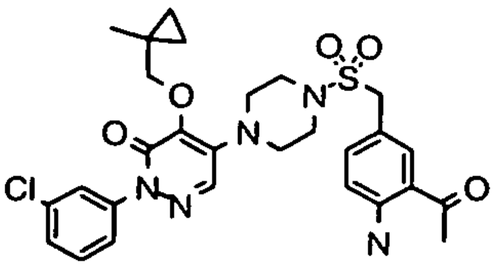
Comp. No.	Structure	MS M+1
1559Z		547
1561Z		612
1563Z		597
1565Z		564
1560Z		655
1562Z		580
1564Z		591
1566Z		547

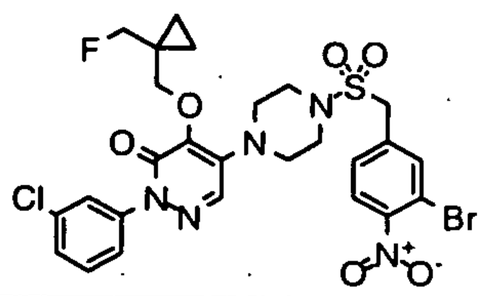
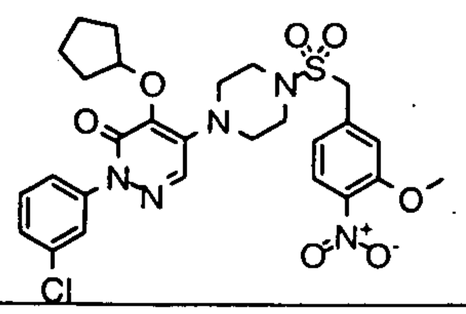
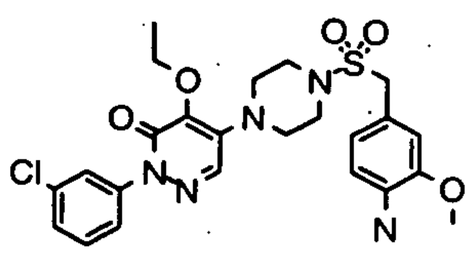
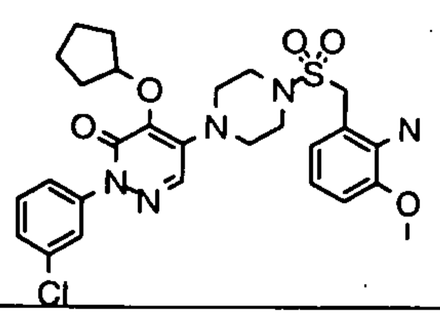
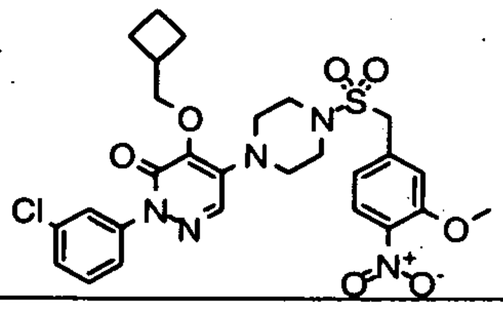
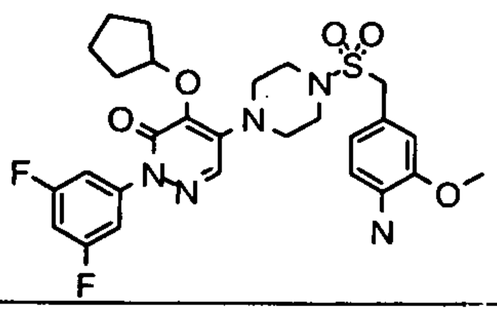
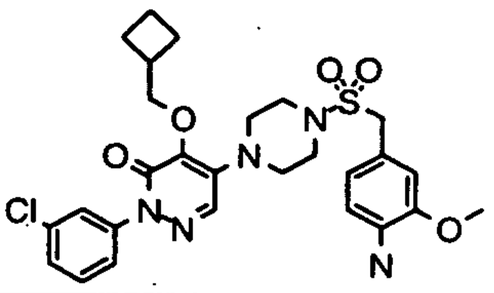
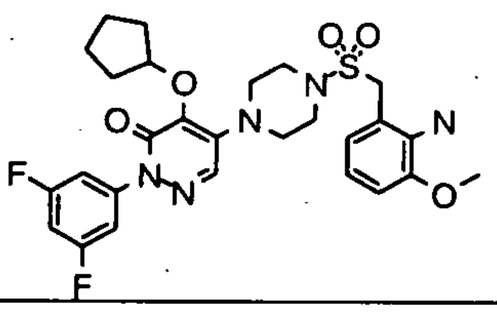
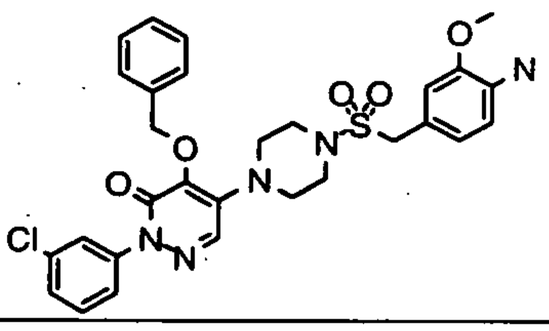
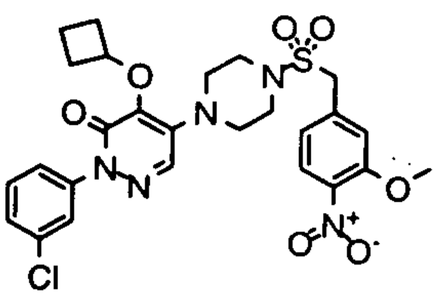
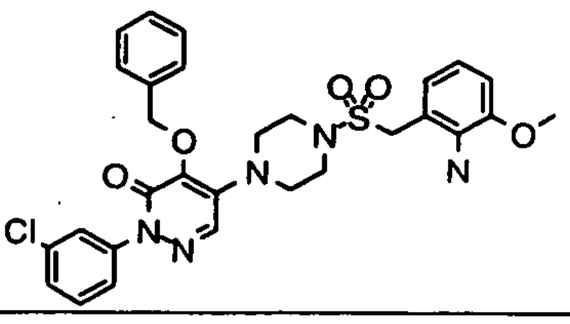
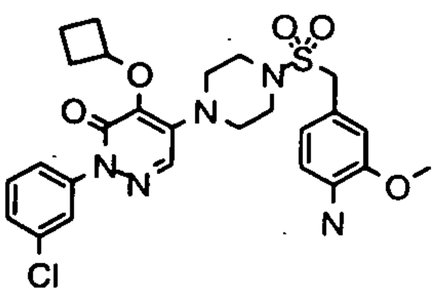
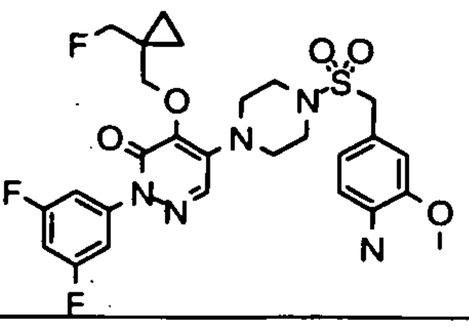
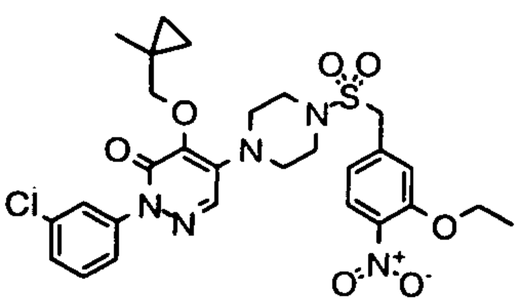
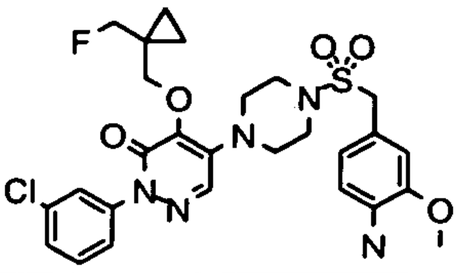
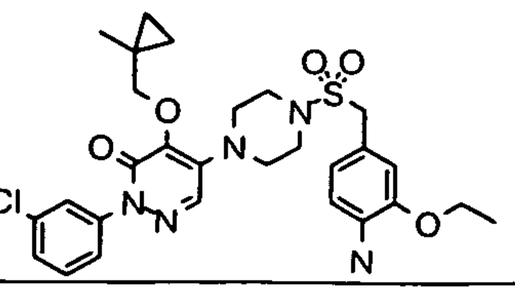
1567Z		577
1568Z		625
1569Z		582
1570Z		594
1571Z		577
1572Z		591
1573Z		547
1574Z		563
1574Za		608
1574Zb		580
1574Zc		618 (M-1)
1574Zd		596
1574Ze		564
1574Zf		589
1574Zg		564
1574Zh		604

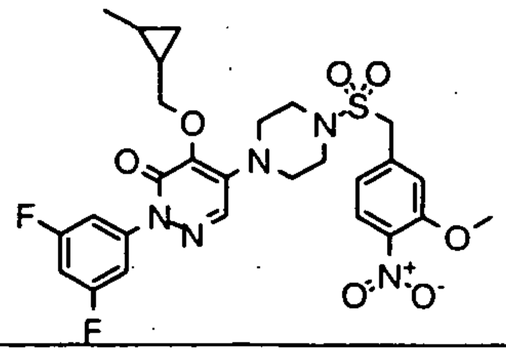
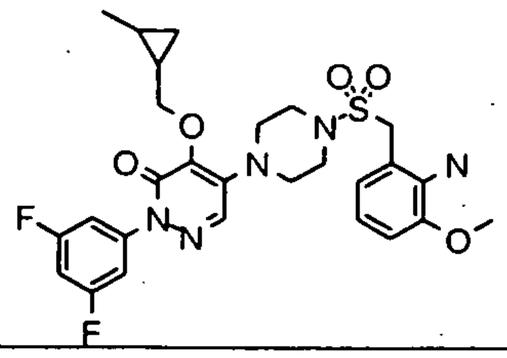
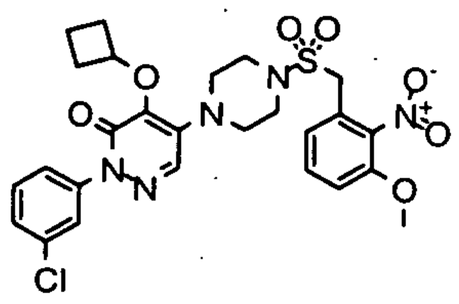
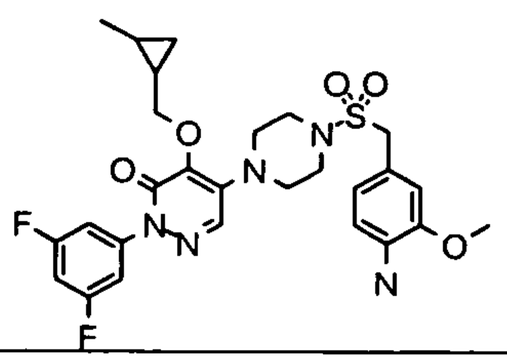
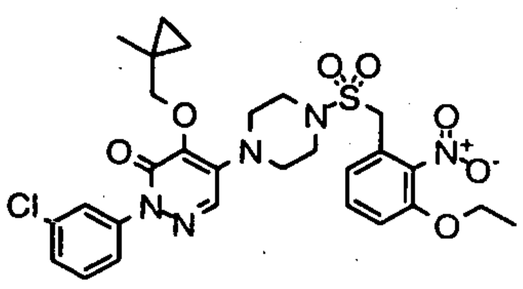
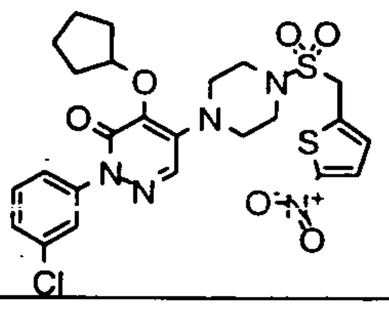
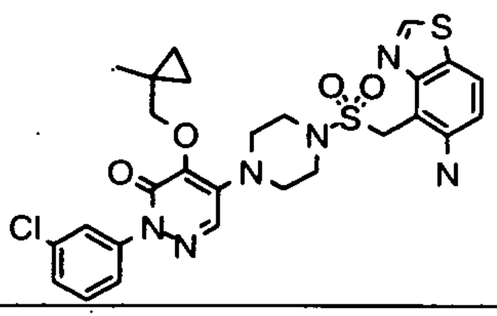
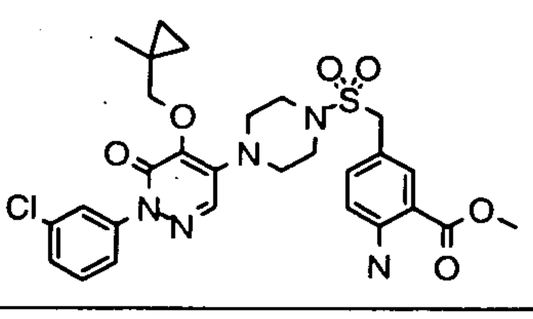
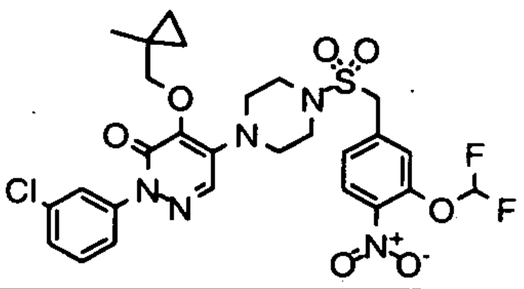
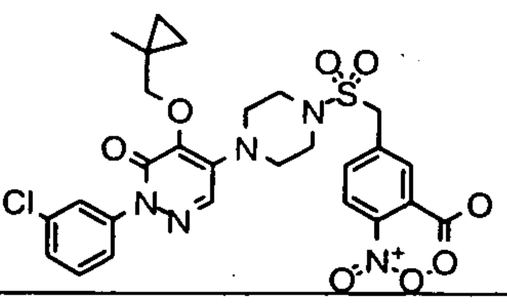
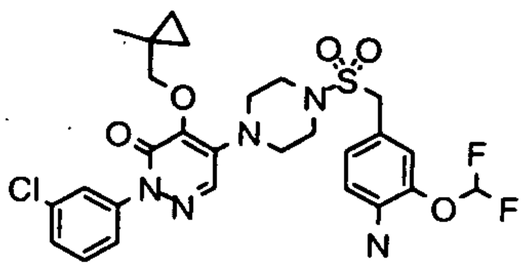
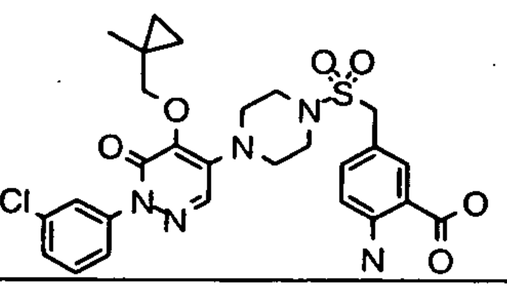
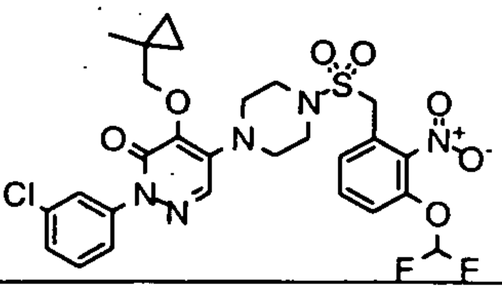
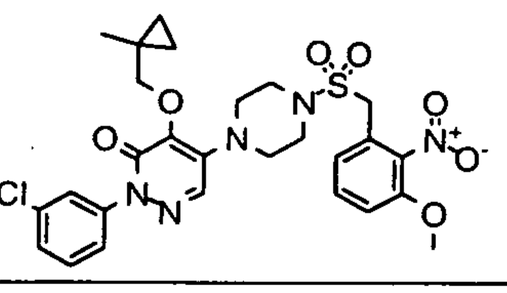
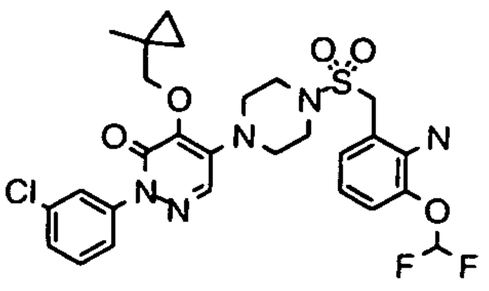
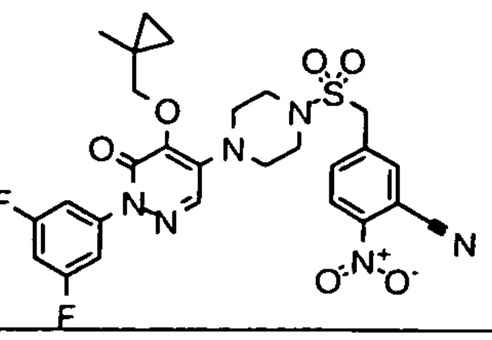
1574Zi		625
1574Zj		589
1574Zk		610
1574Zl		575
1574Zm		610
1574Zn		575
1574Zo		580
1574Zp		545
1574Zq		580
1574Zr		545
1574Zs		599
1574Zt		561
1574Zu		599
1574Zv		625
15784Zw		569
1574Zx		595

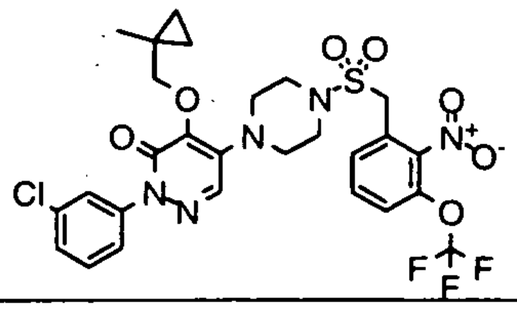
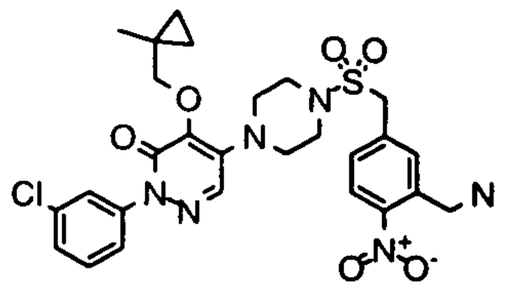
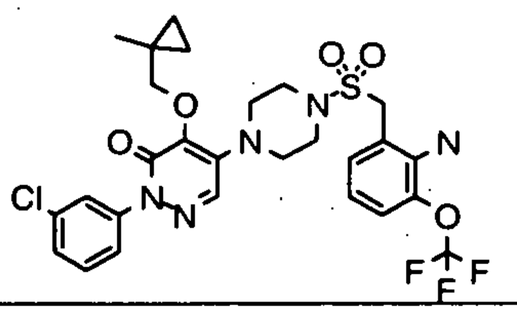
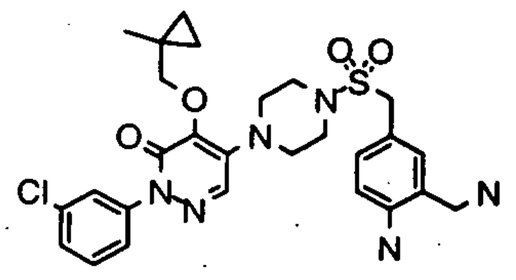
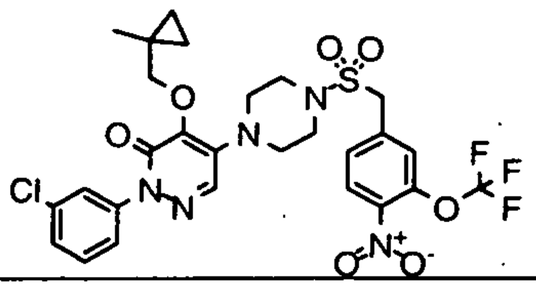
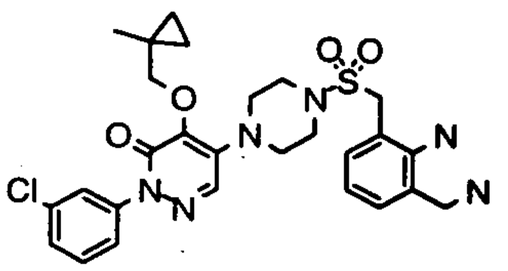
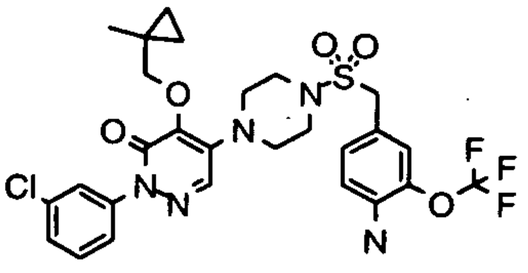
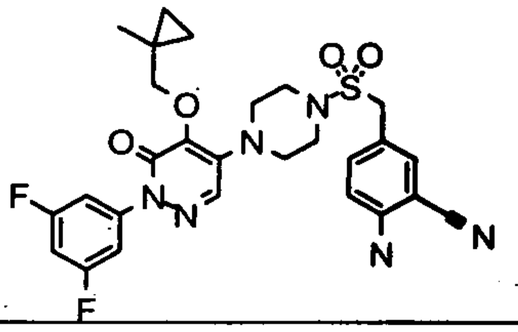
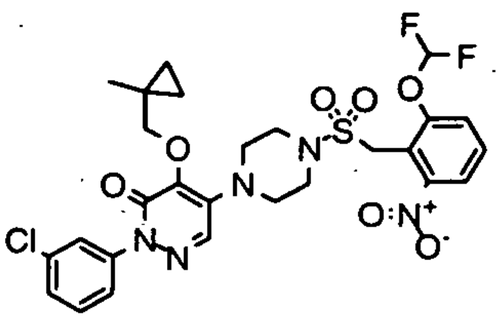
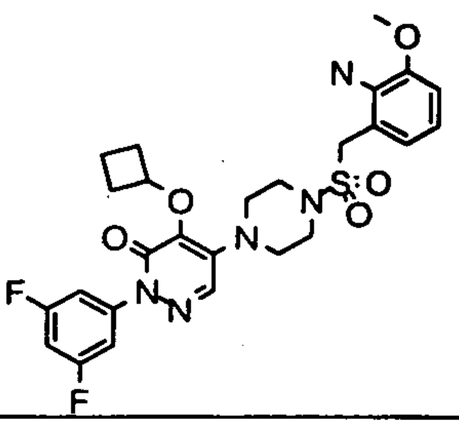
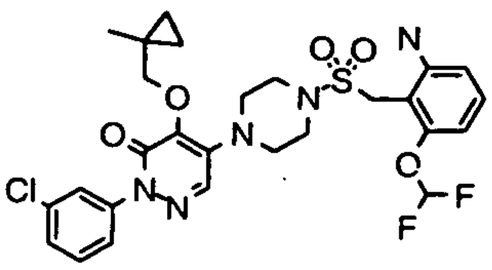
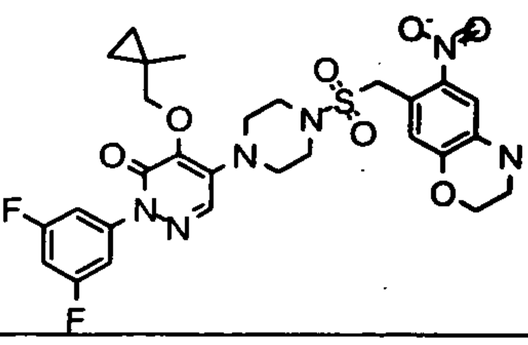
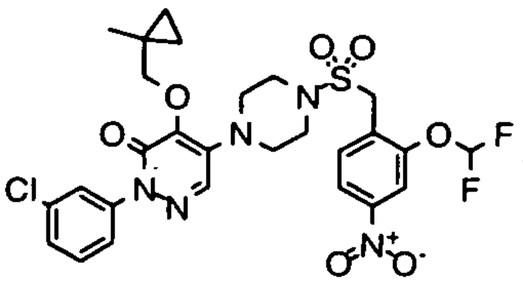
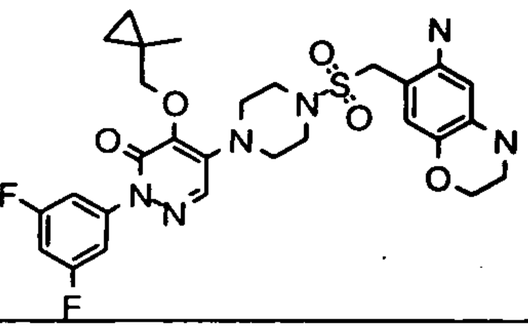
1574Zy		587
1574ZA		587
1574ZC		569
1574ZE		604
1574ZG		574
1574ZI		574
1574ZK		642
1574Z M		586
1574ZO		628

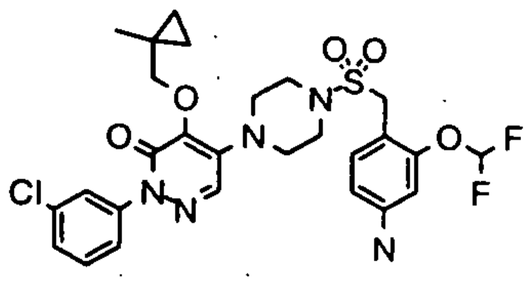
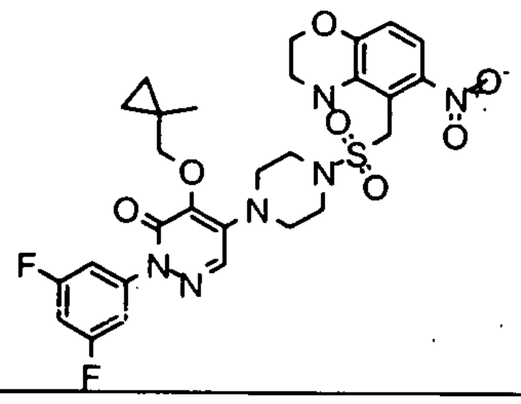
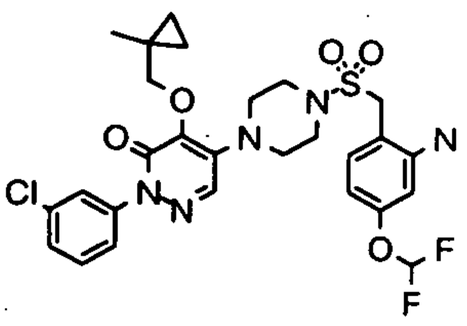
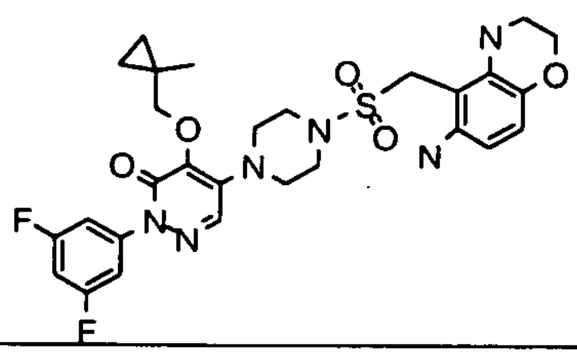
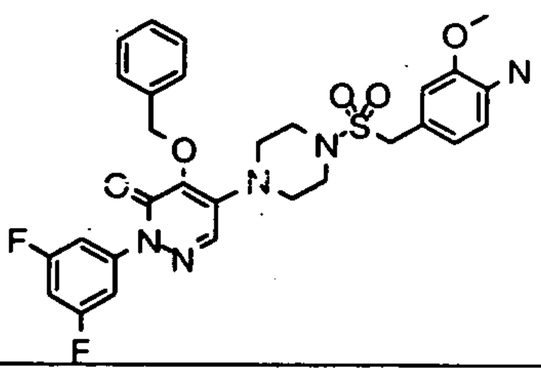
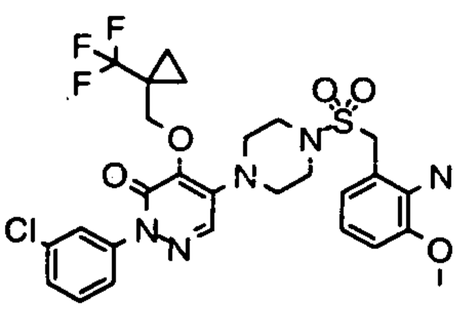
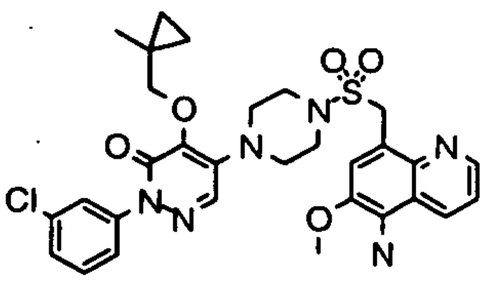
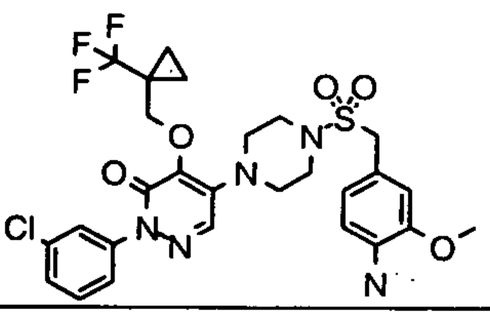
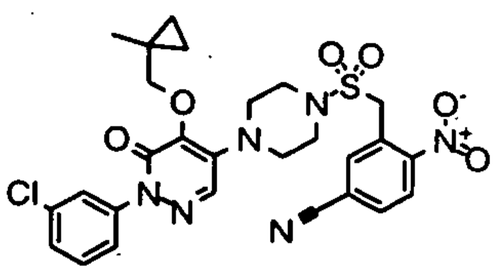
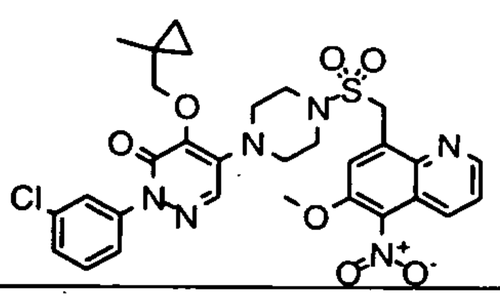
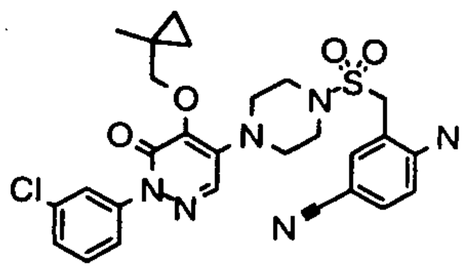
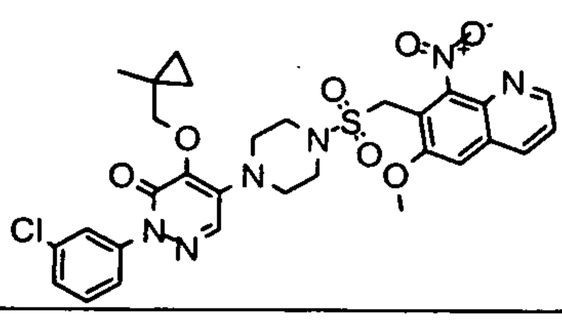
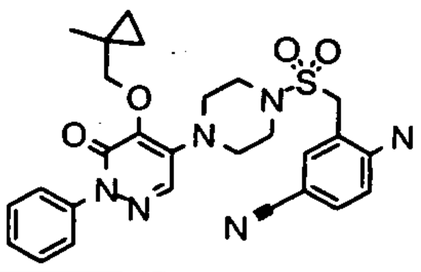
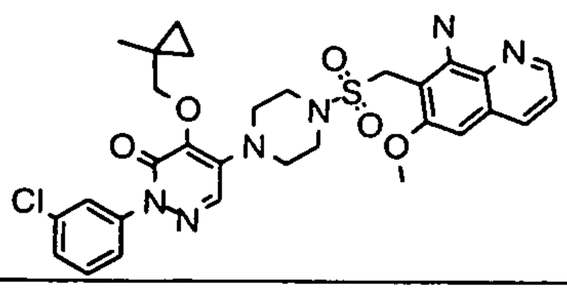
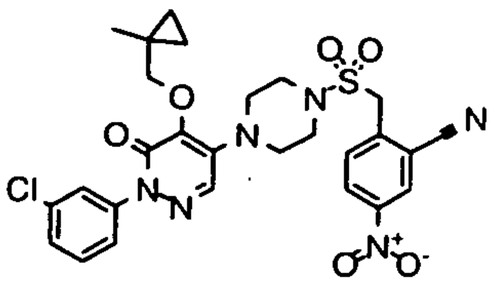
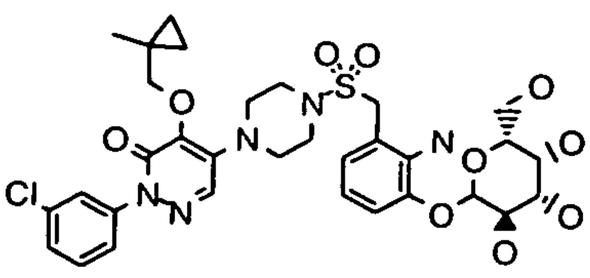
1574Zz		614
1574ZB		584
1574ZD		584
1574ZF		616
1574ZH		586
1574ZJ		586
1574ZL		562
1574ZN		574
1574ZP		576

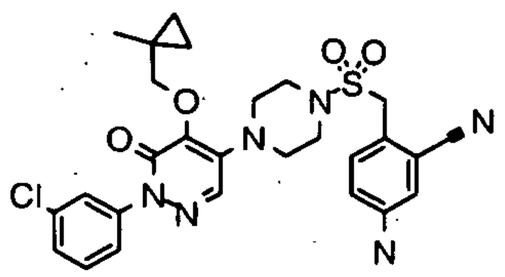
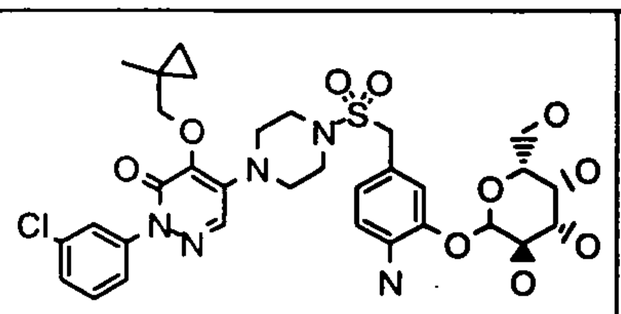
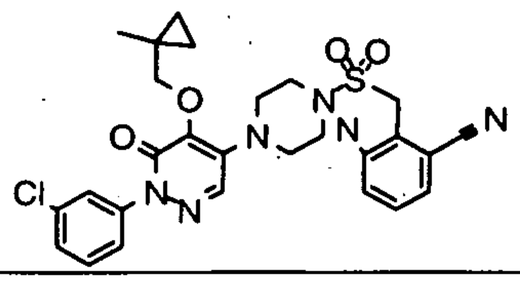
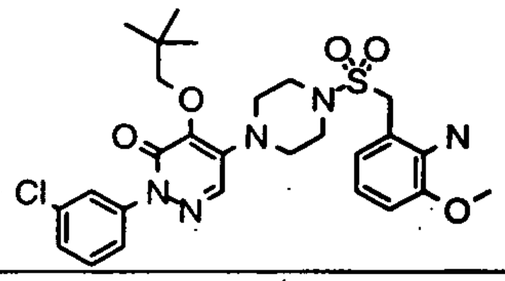
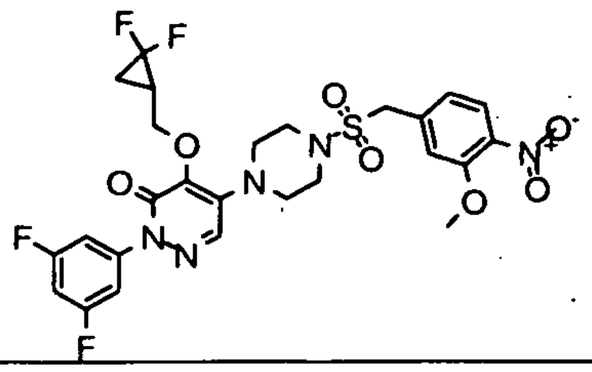
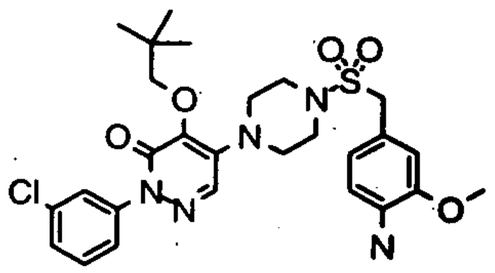
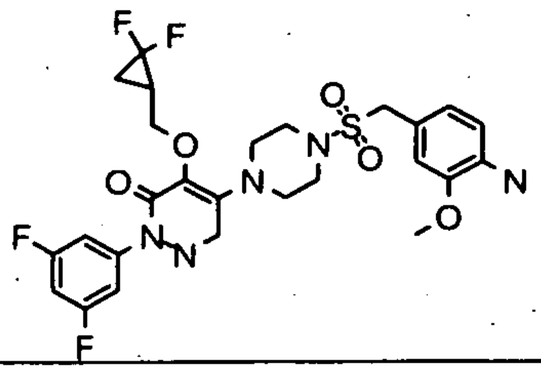
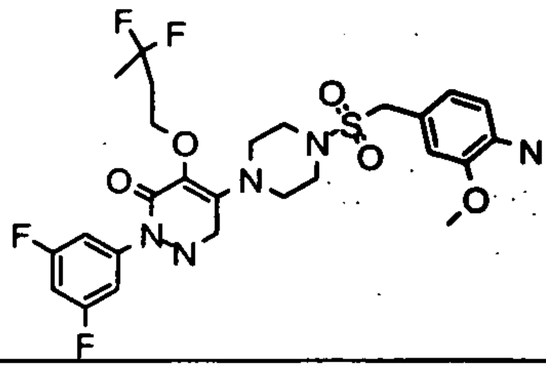
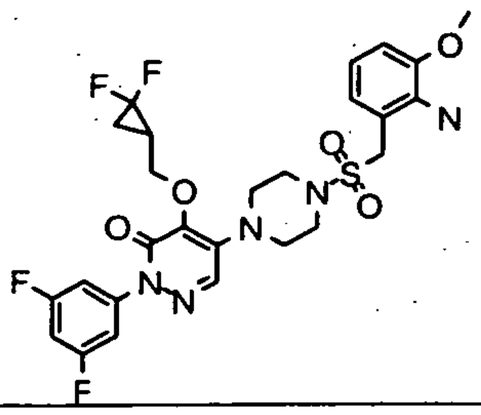
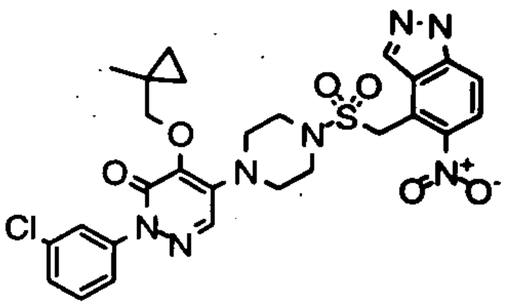
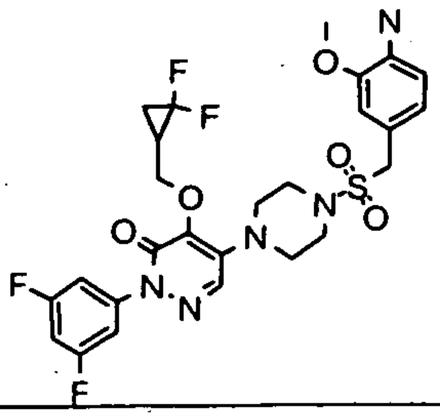
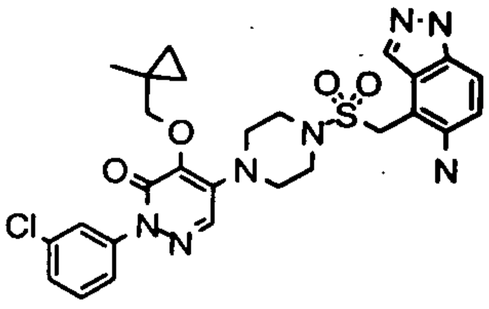
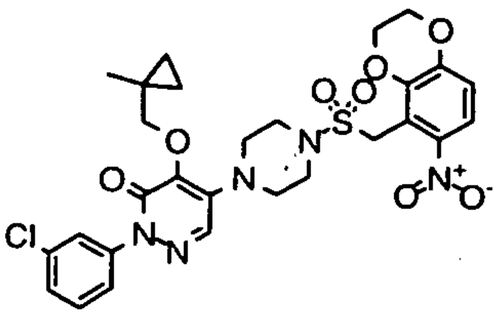
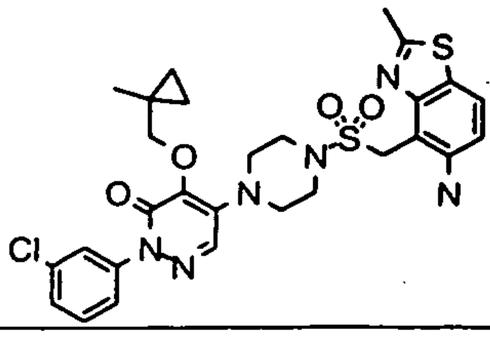
1574ZQ		586	1574ZR		604
1574ZS		629	1574ZT		574
1574ZU		597	1574ZV		574
1574ZW		567	1574ZX		650
1574ZY		714	1574ZZ		620
1574Z-1		714	1574Z-2		620
1574Z-3		684	1574Z-4		616
1574Z-5		684	1574Z-6		568

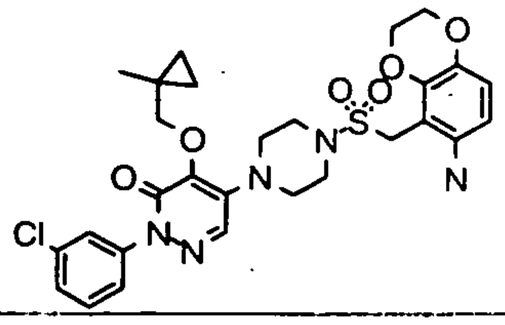
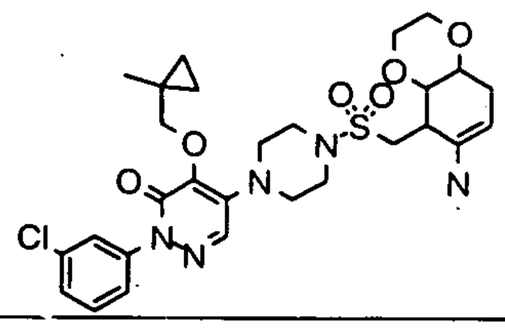
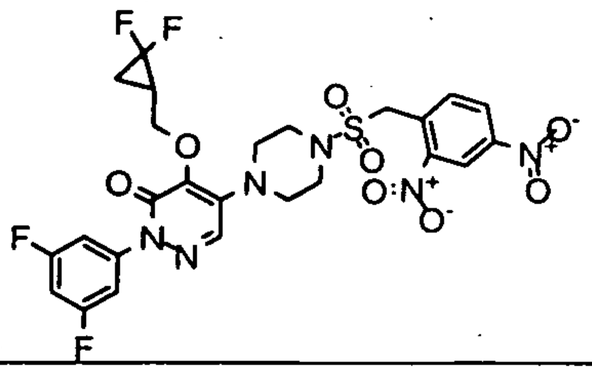
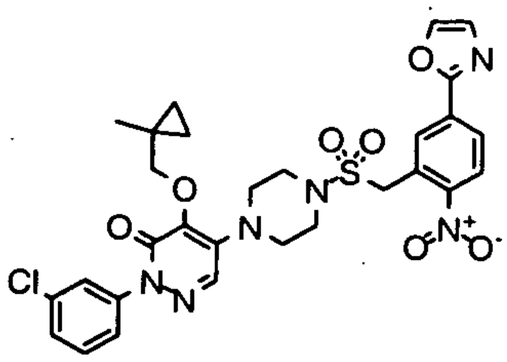
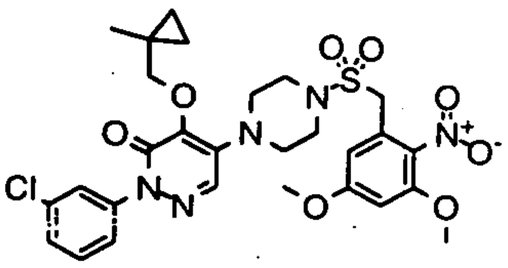
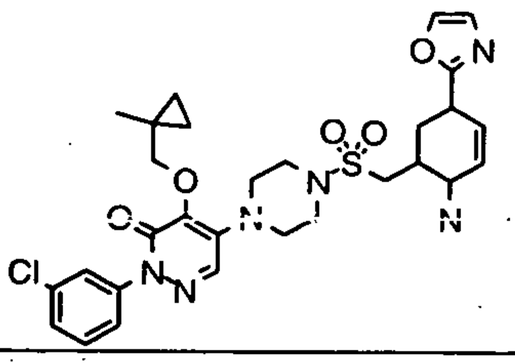
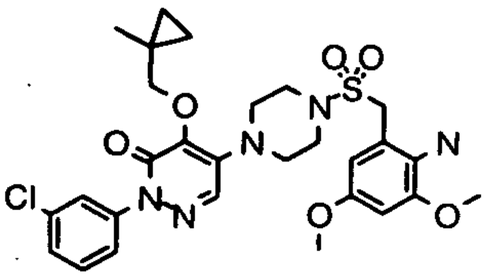
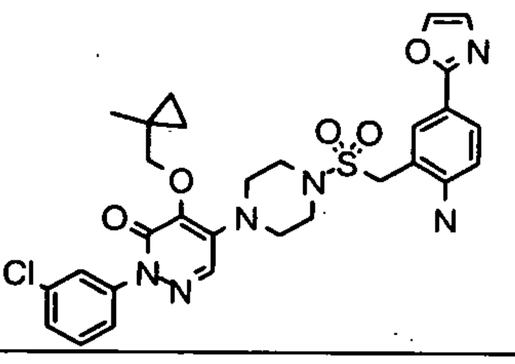
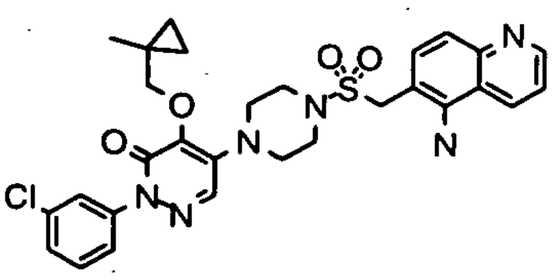
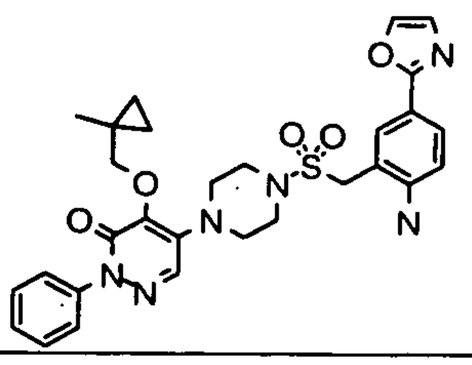
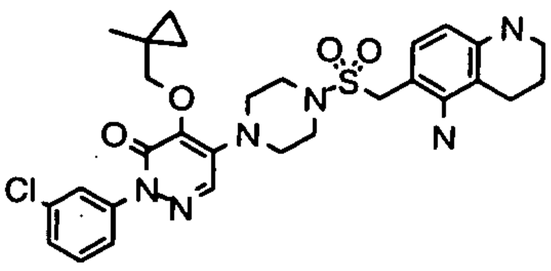
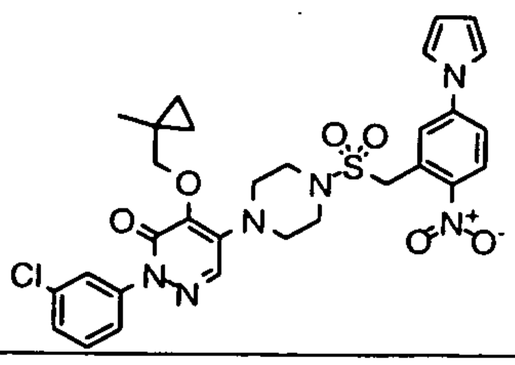
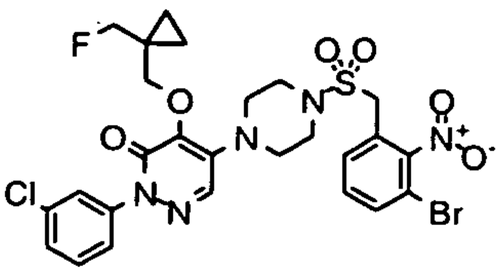
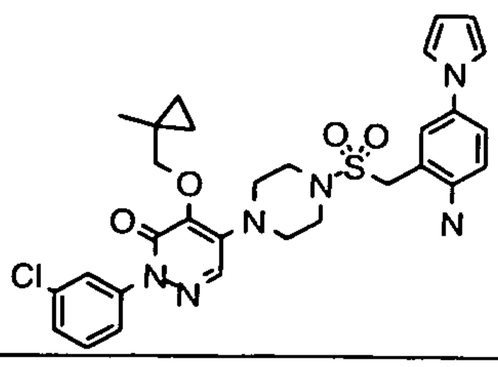
1574Z-7		672
1574Z-8		604
1574Z-9		534
1574Z-10 1401482		574
1574Z-11		604
1574Z-12		576
1574Z-13		574
1574Z-14		576
1574Z-15		596
1574Z-16		590
1574Z-17		596
1574Z-18		545
1574Z-19		594
1574Z-20		618
1574Z-21		592
1574Z-22		588

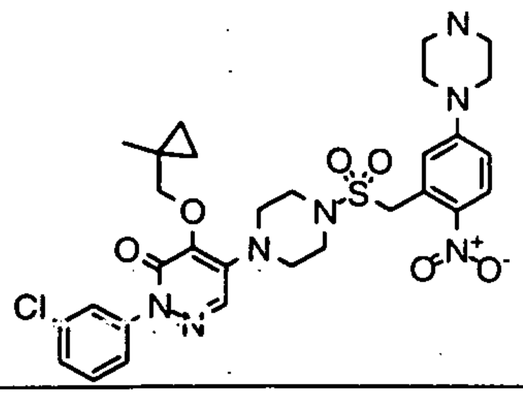
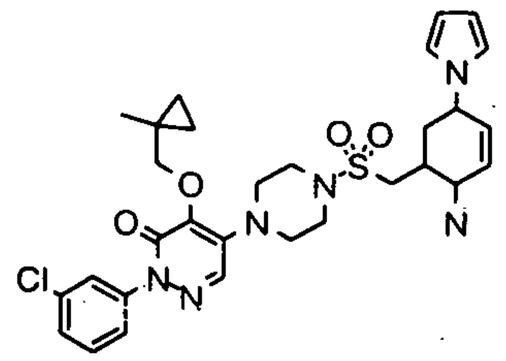
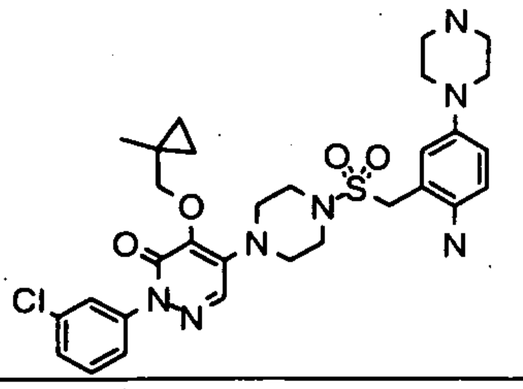
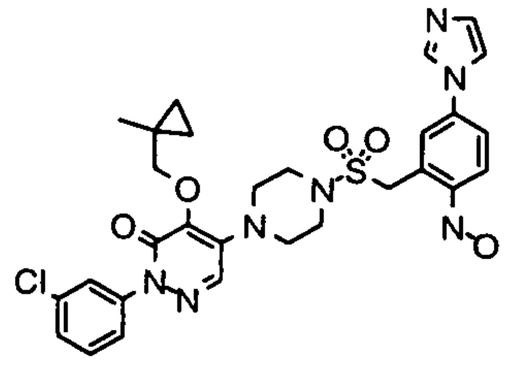
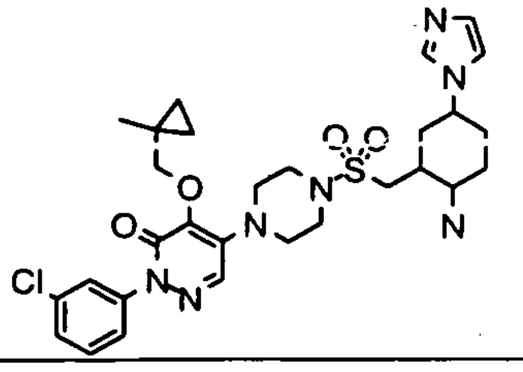
1574Z-23		607
1574Z-24		574
1574Z-25		590
1574Z-26		574
1574Z-27		618
1574Z-28		580
1574Z-29		601
1574Z-30		602
1574Z-31		640
1574Z-32		602
1574Z-33		610
1574Z-34		588
1574Z-35		640
1574Z-36		604
1574Z-37		610
1574Z-38		601

1574Z-39		658	1574Z-40		603
1574Z-41		628	1574Z-42		573
1574Z-43		658	1574Z-44		573
1574Z-45		628	1574Z-46		571
1574Z-47		640	1574Z-48		562
1574Z-49		610	1574Z-50		629
1574Z-51		640	1574Z-52		601

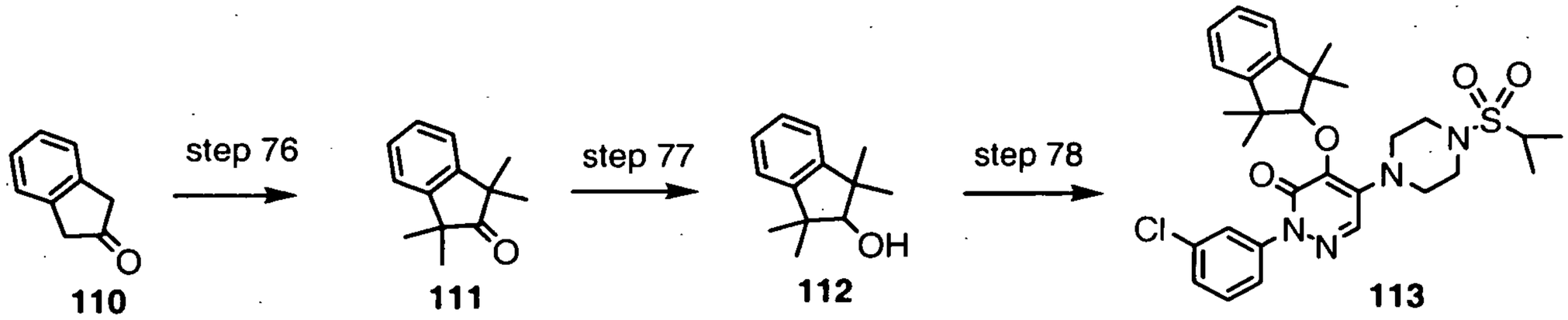
1574Z-53		610
1574Z-54		629
1574Z-55		610
1574Z-56		601
1574Z-57		598
1574Z-58		628
1574Z-59		625
1574Z-60		628
1574Z-61		599
1574Z-62		655
1574Z-63		569
1574Z-64		655
1574Z-65		535
1574Z-66		625
1574Z-67		599
1574Z-68		722

1574Z-69		569
1574Z-70		722
1574Z-71		569
1574Z-72		576
1574Z-73		626
1574Z-74		576
1574Z-75		600
1574Z-76		602
1574Z-77		598
1574Z-78		614
1574Z-79		598
1574Z-80		584
1574Z-81		632
1574Z-82		615

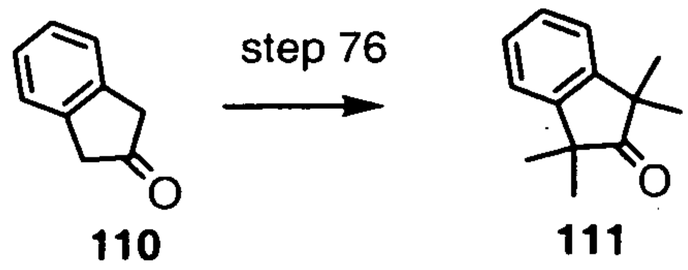
1574Z-83		602
1574Z-84		606
1574Z-85		643
1574Z-86		641
1574Z-87		634
1574Z-88		615
1574Z-89		604
1574Z-90		611
1574Z-91		595
1574Z-92		577
1574Z-93		599
1574Z-94		639
1574-95		672
1574Z-96		609

1574Z-97		658
1574Z-98		613
1574Z-99		628
1574Z-100		617
1574Z-101		610

Scheme 22



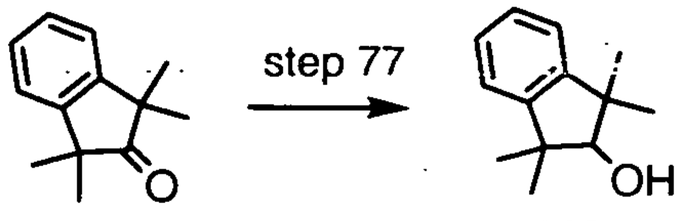
Step 76:



In a three necked flask containing a reflux condenser, dropping funnel, inner thermometer, a mixture of ketone **110** (2.64 g, 0.020 mol) and MeI (10 mL, 0.160 mol) was added to a suspension of KOH (22.40 g, 0.400 mol) in DMSO (30 mL) at 50-60 °C. The reaction mixture was stirred at this temperature for 1.5 h and then the slurry was poured into ice water. The mixture was extracted with pentane (3 × 50 mL). The combined organic extract was washed with H_2O (2 ×10 mL), brine (10 mL), dried (MgSO4), filtered, and concentrated.

Purification by silica gel chromatography (50:1 hexanes:EtOAc) gave the product **111** as a colorless oil (2.10 g, 56%). MS (M+1): m/e 187.

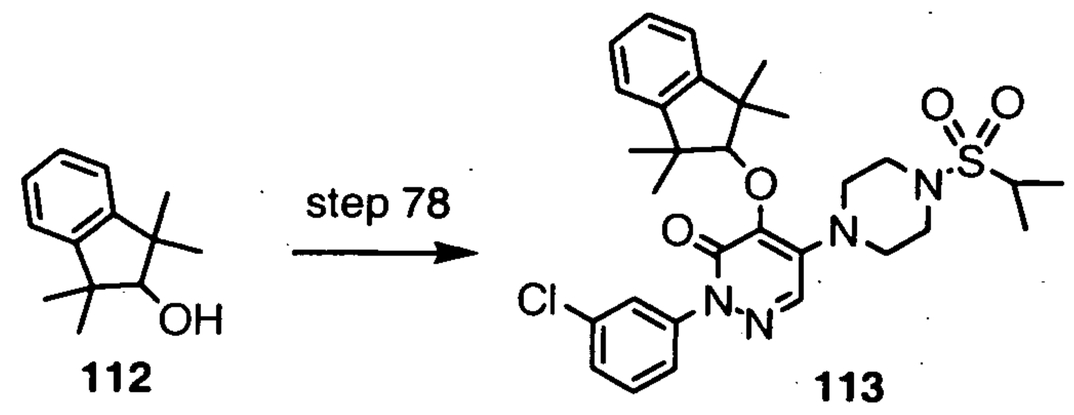
Step 77:



111 **112**

A solution of lithium aluminum hydride (5.0 mL, 1.0 M in THF, 5.0 mmol) was added to compound **111** (1.88 g, 10 mmol) dissolved in anhydrous ether (20 mL) and cooled to 0 °C. The reaction mixture was stirred for 4 h and then water (0.2 mL), 1 N NaOH (0.2 ml), and water (0.6 mL) were added sequentially. The mixture was filtered through celite and washed with ether. The filtrate was concentrated and purification by silica gel chromatography (20:1 hexanes:EtOAc) gave 1.0 g (53%) of the product **112** as a colorless oil.

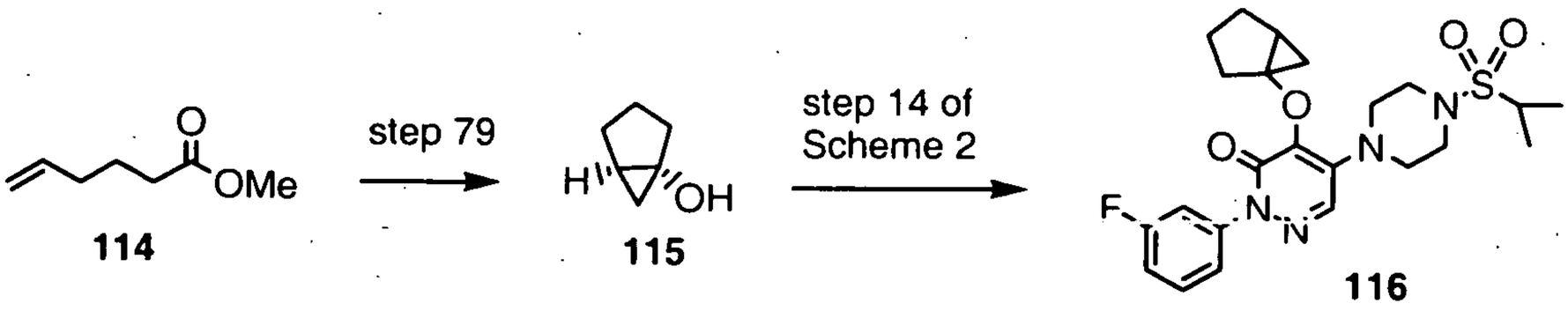
Step 78:



112 **113**

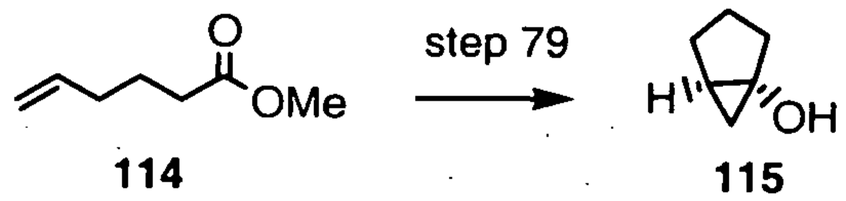
A mixture of anhydrous NaH (0.011 g, 0.30 mmol, 60%) and methoxylindanol **112** (0.062 g, 0.33 mmol) in anhydrous THF (5 mL) was stirred at room temperature for 10 mins. To this mixture, a solution of compound **14A** (0.070 g, 0.16 mmol) in anhydrous THF (5 mL) was added dropwise at room temperature. The resulting solution was refluxed for 8 h, and then the solvent was evaporated. Aqueous NH_4Cl (10 mL) was added and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was washed with H_2O (2 ×10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (10:1 hexanes:EtOAc) gave the product **113** as a colorless oil (0.042 g, 46%). MS (M+1): m/e 569.

Scheme 23



114 **115** **116**

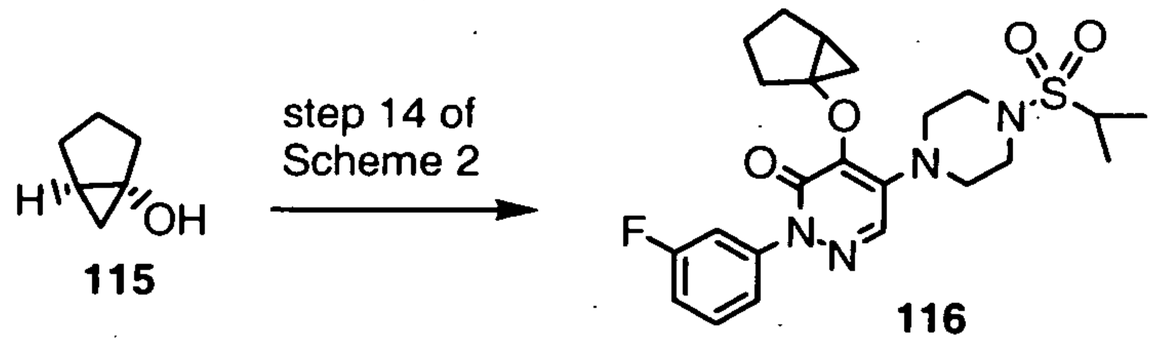
Step 79: *Organic Syntheses, Vol. 80, p.111 (2003).*



114 **115**

To compound **114** (2.0 g, 15.6 mmol) and chlorotitanium triisopropoxide (11.2 mL, 11.2 mmol of 1 M in hexane) dissolved in anhydrous ether (54 mL) under a nitrogen atmosphere was added n-butylmagnesium chloride in ether (1 M, 52 mL, 52 mmol) over 6.5 h via a syringe pump at room temperature. After the addition is complete, the resulting black reaction mixture is stirred for an additional 20 mins and then cooled to 0°C. Ether (50 mL) was added followed by the slow addition of water (14 mL). The resulting mixture was stirred for 3 h at room temperature. The organic phase was separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic extract was washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5 – 10% ether/pentane) gave 1.09 g (71%) of the product **115** as a colorless oil.

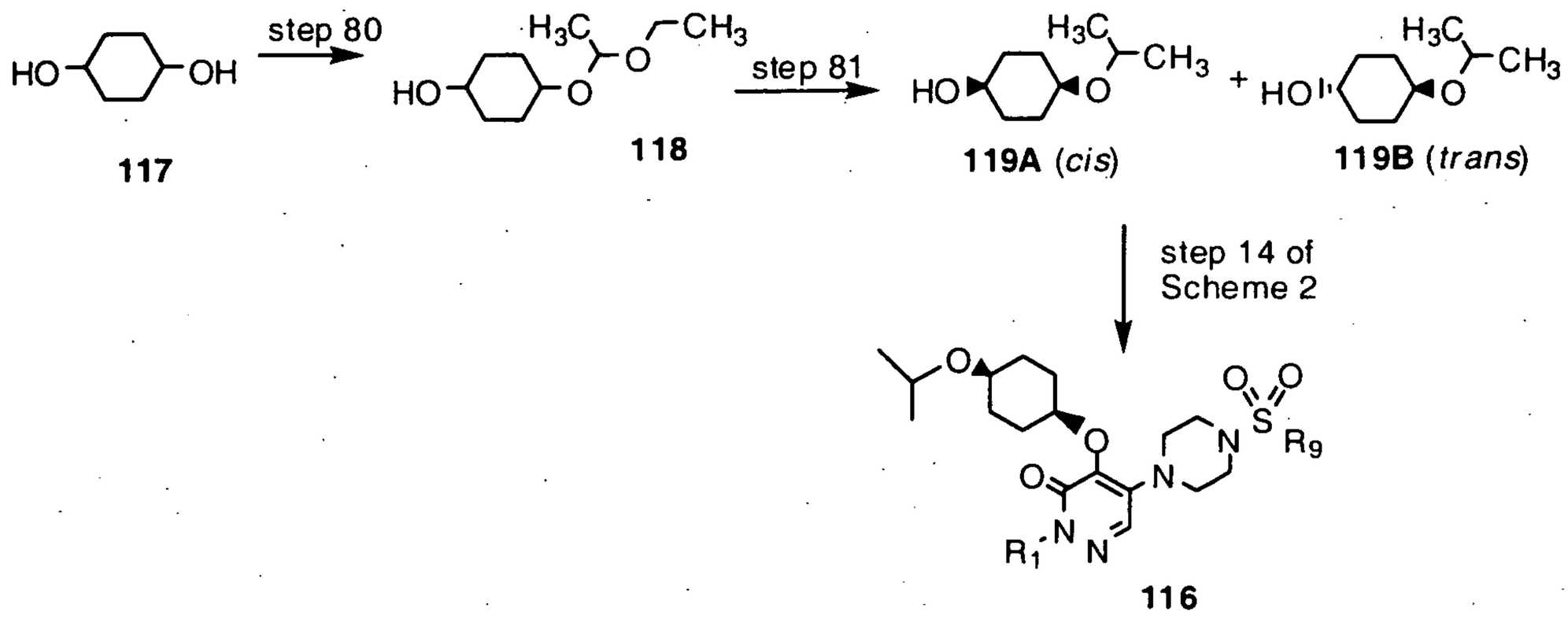
Step 14 of Scheme 2:



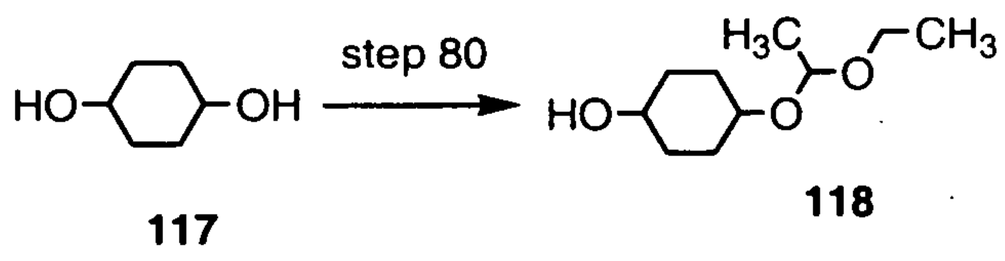
115 **116**

Using the procedure described above, compound **116** was synthesized. MS (M+1): m/e 477.

Scheme 24

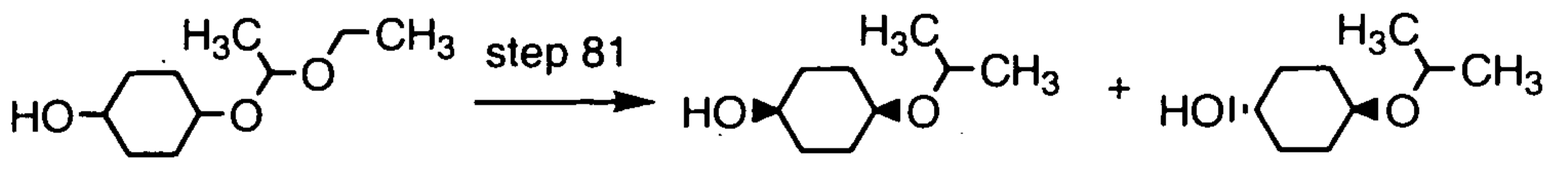


Step 80:



Ethyl vinyl ether (43 mL, 0.45 mol) was added to a suspension of cyclohexane-1,4-diol (**117**, 52 g, 0.45 mol, mixture of *cis* and *trans* isomers) in anhydrous tetrahydrofuran (300 mL) at 0 °C under nitrogen, after which 4-toluenesulfonic acid (15 mg, catalytic amount) was added. The mixture was warmed to room temperature and stirred for 1 h, after which sodium carbonate (30 g) was added to the clear solution. The solids were removed by filtration and the solvent was evaporated. Purification by flash column chromatography on silica gel (eluant: 1:1 ethyl acetate:hexanes) gave acetal **118** (19 g, 22%, mixture of *cis* and *trans* isomers) as a colorless oil.

Step 81:



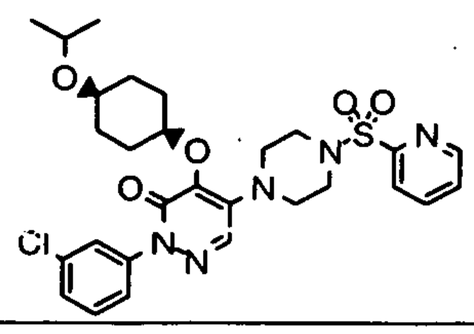
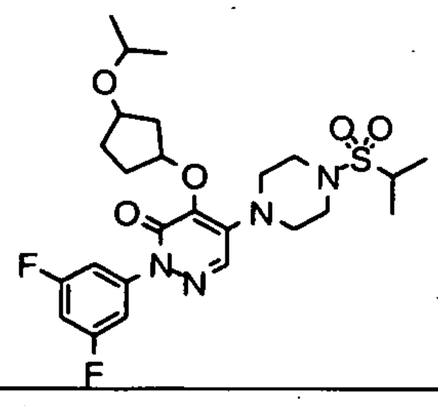
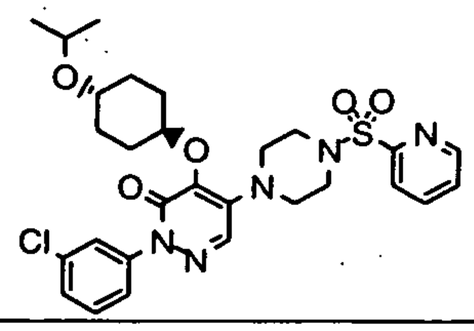
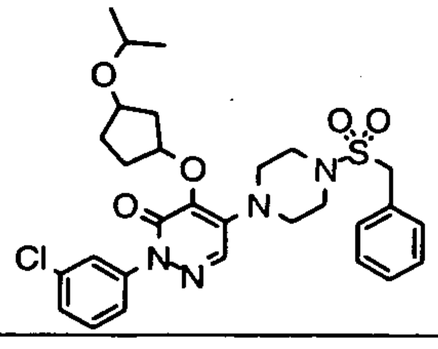
Methylmagnesium bromide (55 mL, 165 mmol, 3.0 M in tetrahydrofuran) was added to a solution of acetal **118** (7.8 g, 41.3 mmol, mixture of *cis* and *trans* isomers) in anhydrous toluene (500 mL) at room temperature under nitrogen, and the mixture was heated at 105 °C for 36 h. The mixture was cooled to 0 °C, diluted with water (100 mL) and the pH was adjusted to 4-5 with 2 N HCl. The mixture was extracted with diethyl ether (100 mL) and the

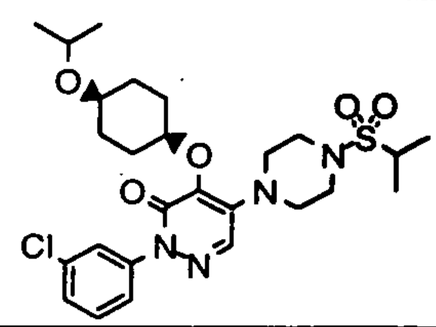
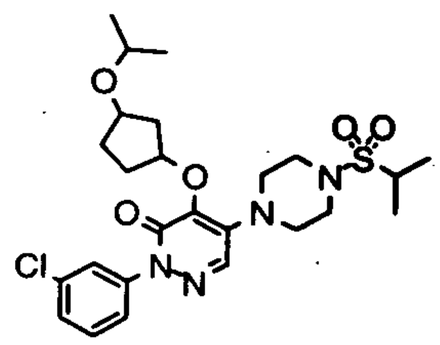
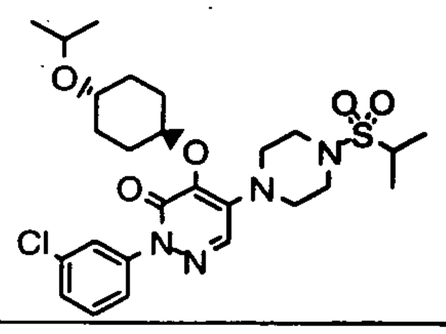
organic extract was washed with brine (3 x 200 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography on silica gel (eluant: 1:1 ethyl acetate:hexanes) to first produce cis compound **119a** (1.8 g, 28%) as a colorless oil. Additional elution produced the trans compound **119b** (0.9 g, 14%) as a colorless oil.

Table 24: Oxygen Linked Analogs with Sulfonamide

Step 14 of Scheme 2:

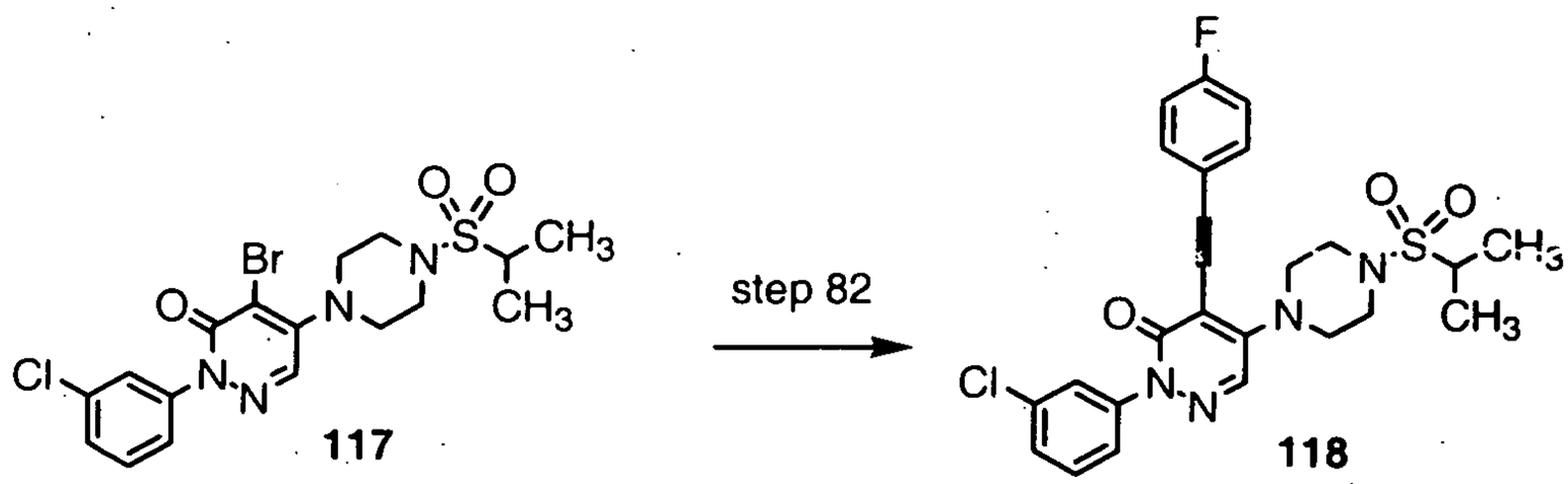
Using the procedure described above, the following compounds were synthesized.

Comp. No.	Structure	MS M+1
1575Z		588
1577Z		541
1579Z		588
1581Z		587

Comp. No.	Structure	MS M+1
1576Z		554
1578Z		539
1580Z		554

10

Scheme 25

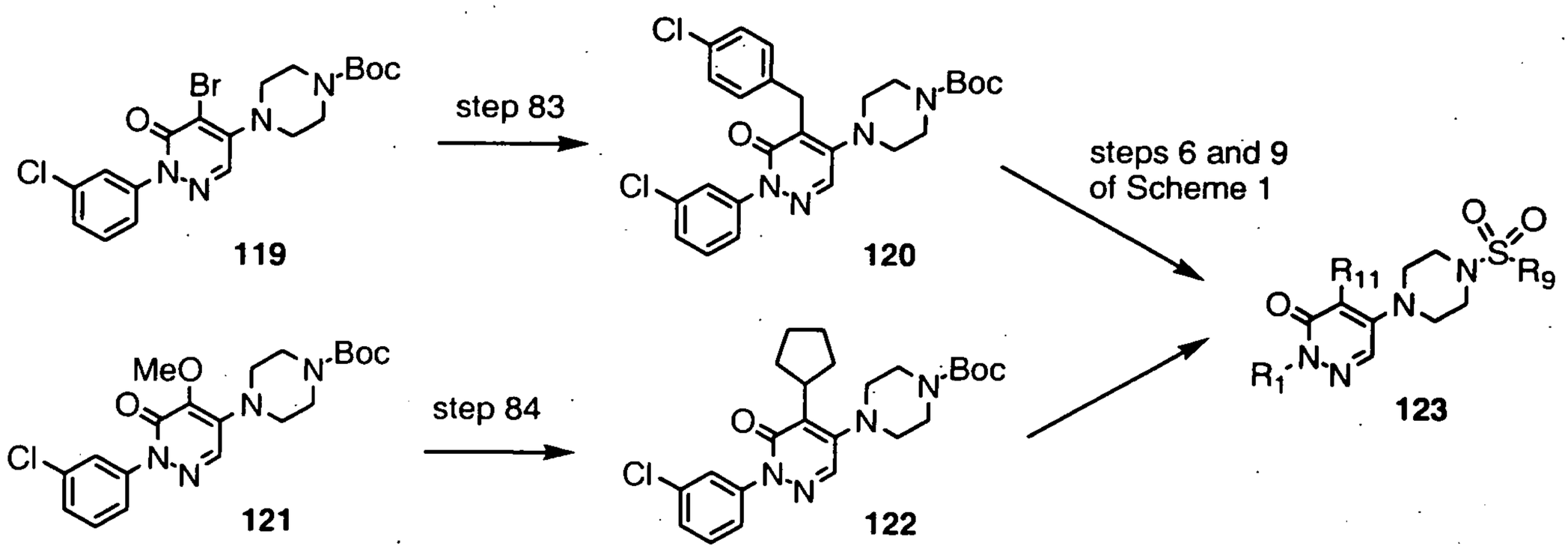


Compound **117** can be synthesized using steps 1 and 2 of Scheme 1 and steps 11 and 12 of Scheme 2.

Step 82:

A mixture of **117** (238 mg, 0.500 mmol), *p*-fluorophenylacetylene (0.10 mL, 0.10 g, 0.87 mmol), triethylamine (0.70 mL, 0.51 g, 5.0 mmol), bis(triphenylphosphine)palladium(II) dichloride (20 mg, 0.028 mmol) and copper(I) iodide (50 mg, 0.26 mmol) in anhydrous acetonitrile (3 mL) was sealed under nitrogen in a microwave tube. The mixture was heated to 130 °C over 5 mins and irradiated at 150 °C for 30 mins. The cooled mixture was poured into water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography on silica gel (eluant: 1:1 ethyl acetate:hexanes) gave the product **118** (50 mg, 19%) as a yellow solid: MS (M+1): m/e 515.

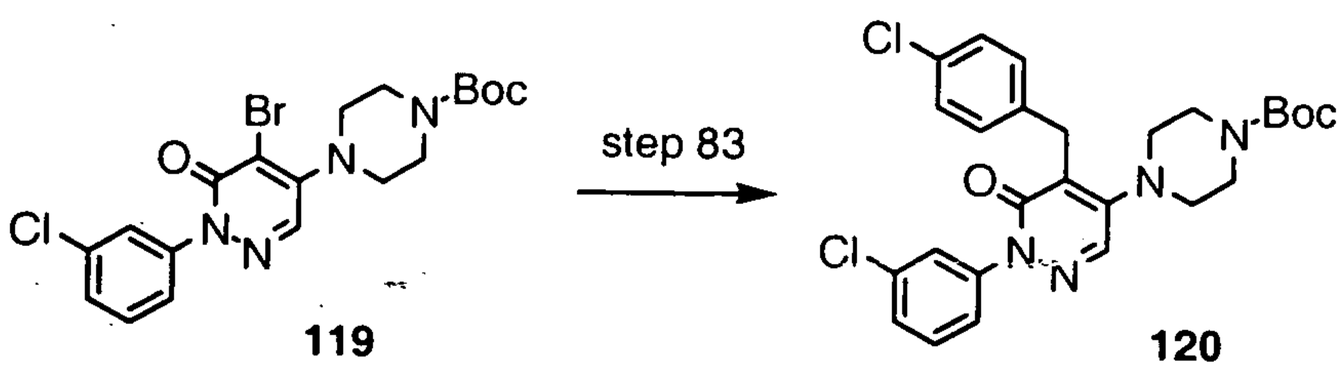
Scheme 26



Compound **119** can be synthesized using steps 1 and 2 of Scheme 1.

Compound **121** can be synthesized using steps 1, 2, and 4 of Scheme 1.

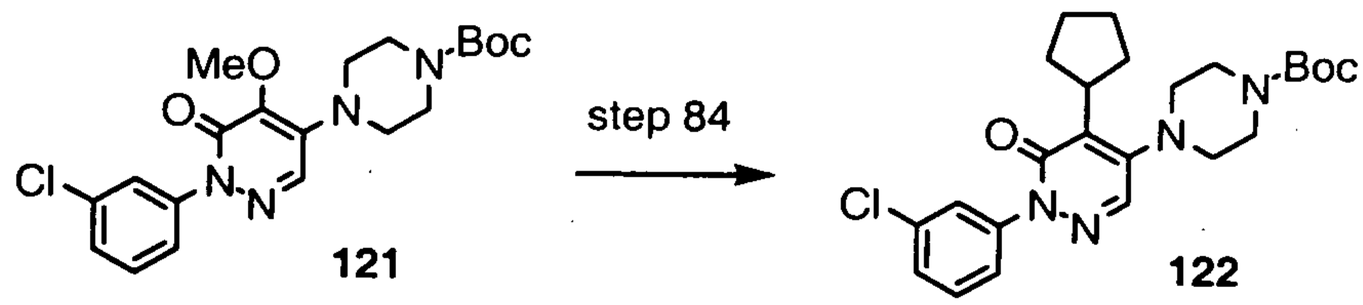
Step 83:



119 **120**

Argon was bubbled through a mixture of compound **119** (1.00 g, 2.13 mmol) and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (81 mg, 0.11 mmol) in anhydrous tetrahydrofuran (25 mL) at room temperature under nitrogen. The yellow solution was heated to reflux and *p*-chlorobenzylzinc chloride (5.0 mL, 2.5 mmol, 0.5 M in tetrahydrofuran) was added dropwise, after which the mixture was heated at reflux for 12 h. The cooled mixture was treated with saturated aqueous NH_4Cl solution (10 mL) followed by water (200 mL), and the mixture was extracted with ethyl acetate (3 X 100 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography on silica gel (eluant: 0:100 to 3:7 gradient of ethyl acetate:hexanes) gave the product **120** (807 mg, 74%) as a white solid: MS (M+1): m/e 515.

Step 84:



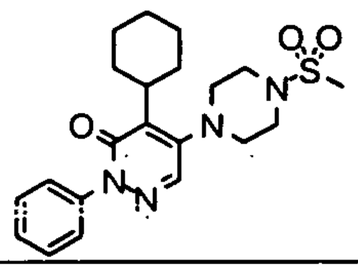
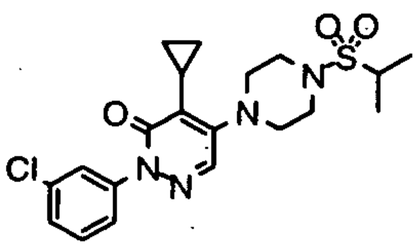
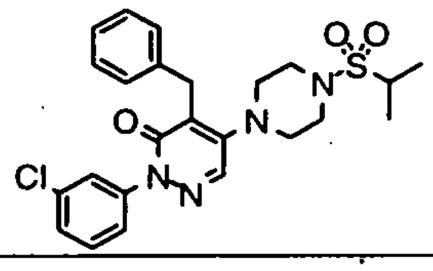
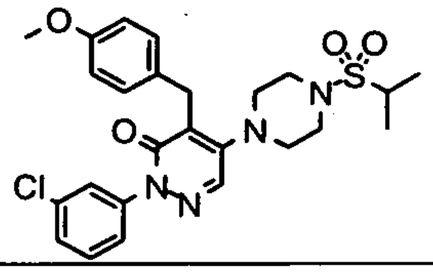
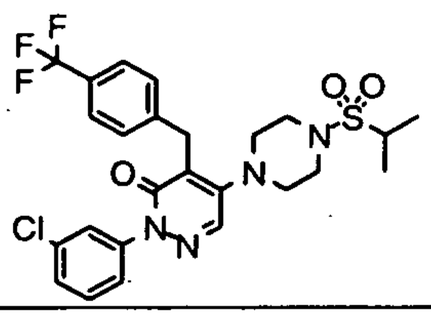
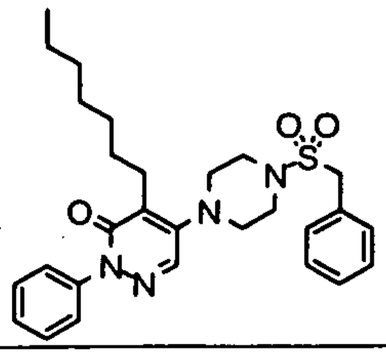
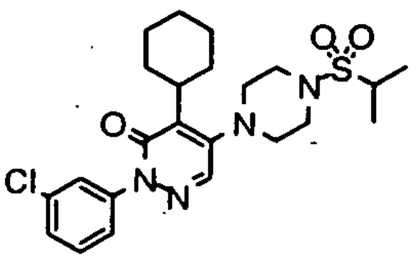
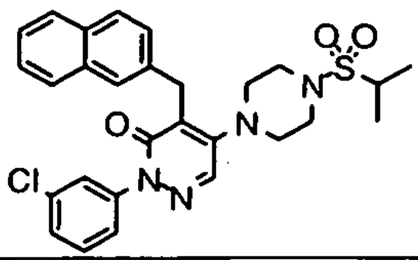
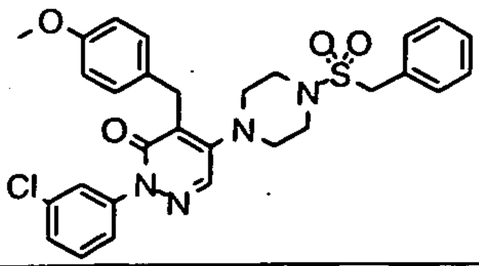
121 **122**

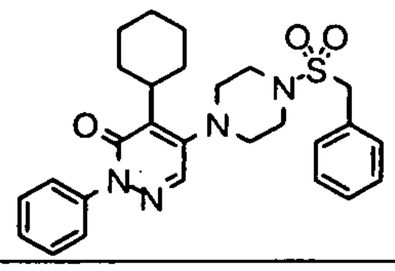
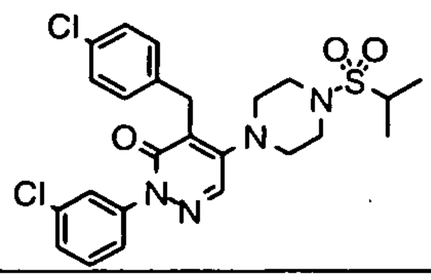
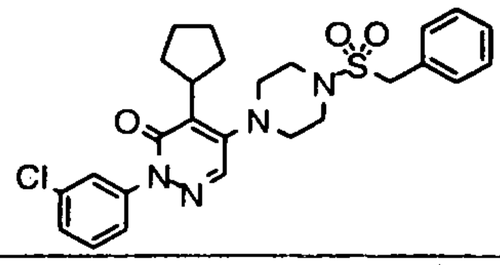
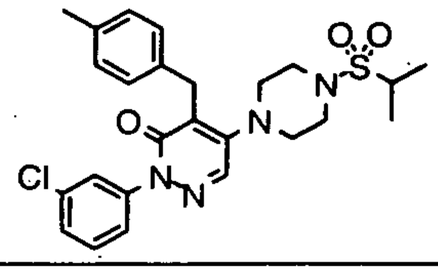
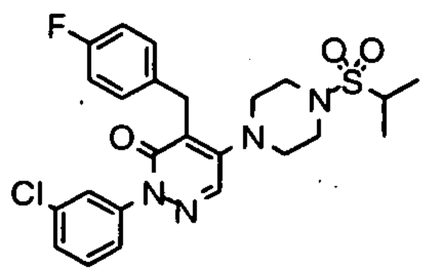
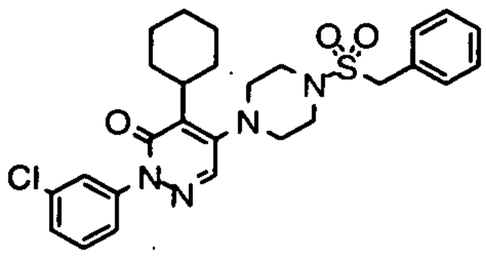
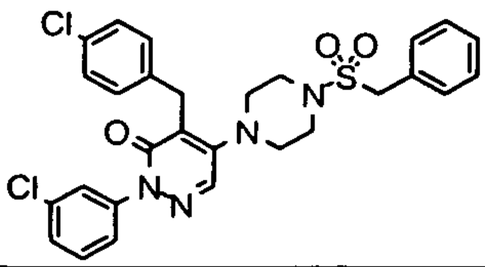
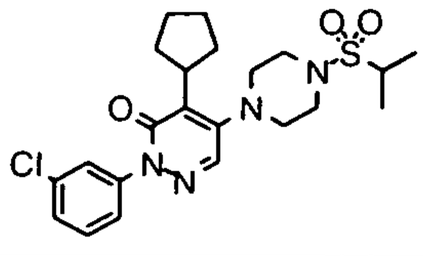
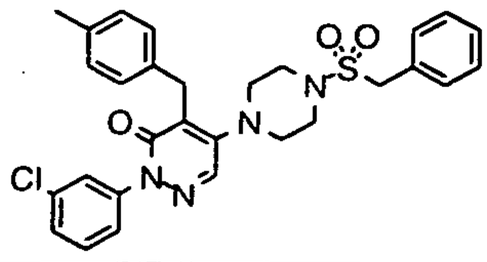
To a solution of **121** (350 mg, 0.832 mmol) in anhydrous tetrahydrofuran (20 mL) at -78 °C under nitrogen was added cyclopentylmagnesium chloride (0.85 mL, 1.7 mmol, 2.0 M in diethyl ether) at a rate which kept the internal reaction temperature below -70 °C. The mixture was slowly warmed to room temperature, stirring for a total of 18 h. The mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography on silica gel (eluant: 3:7 ethyl acetate:hexanes) gave the product **122** (351 mg, 92%) as a white solid: MS (M+1): m/e 459.

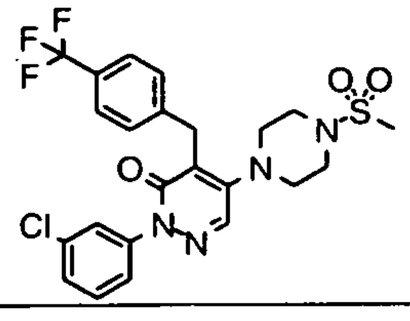
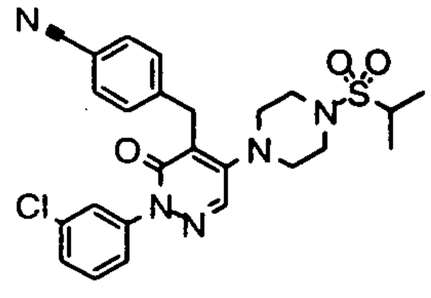
Table 25: Carbon Linked Analogs with Sulfonamide

Steps 6 and 9 of Scheme 1:

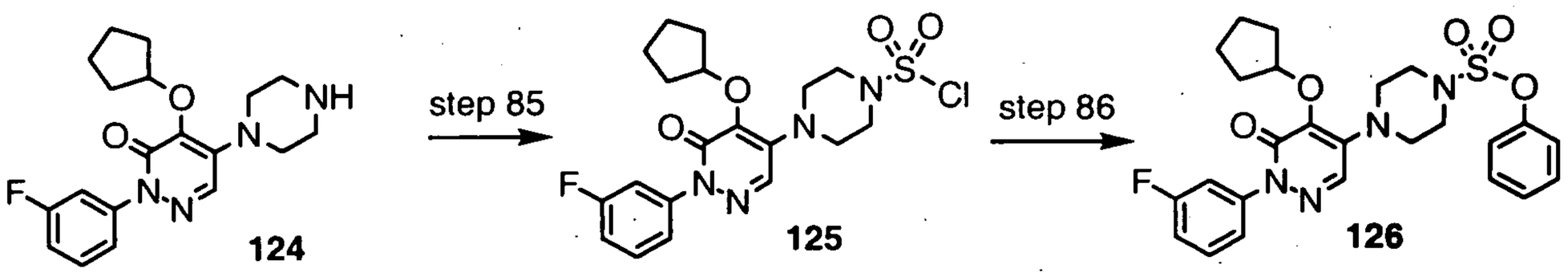
Using the procedures described above, the following compounds were synthesized.

Comp. No.	Structure	MS M+1
1582Z		417
1584Z		437
1586Z		487
1588Z		517
1590Z		555
1592Z		509
1594Z		479
1596Z		537
1598Z		565

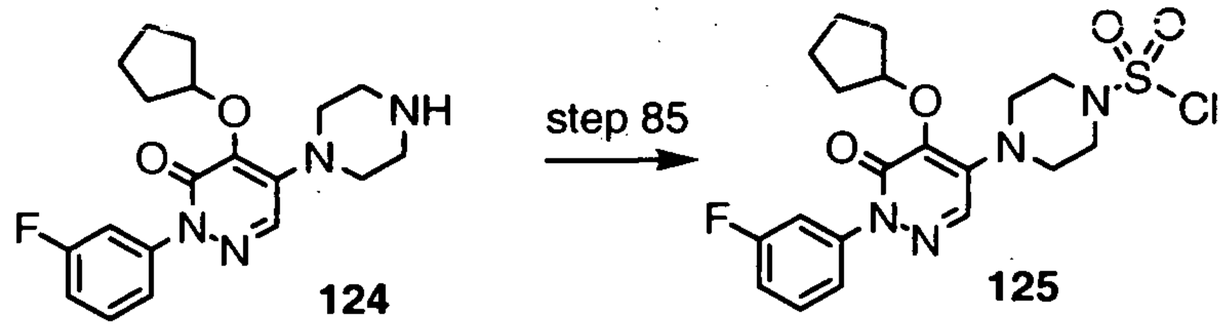
Comp. No.	Structure	MS M+1
1583Z		493
1585Z		521
1587Z		513
1589Z		501
1591Z		505
1593Z		527
1595Z		569
1597Z		465
1599Z		549

1600Z		527
1601Z		512

Scheme 27

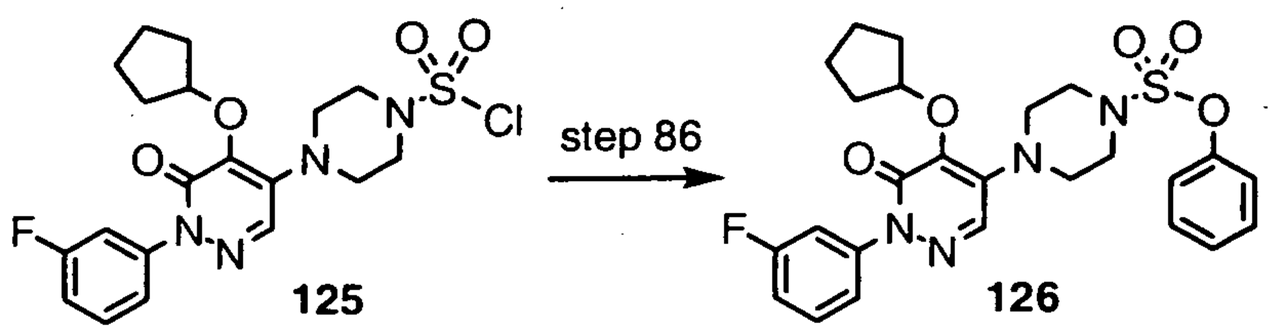


Step 85:



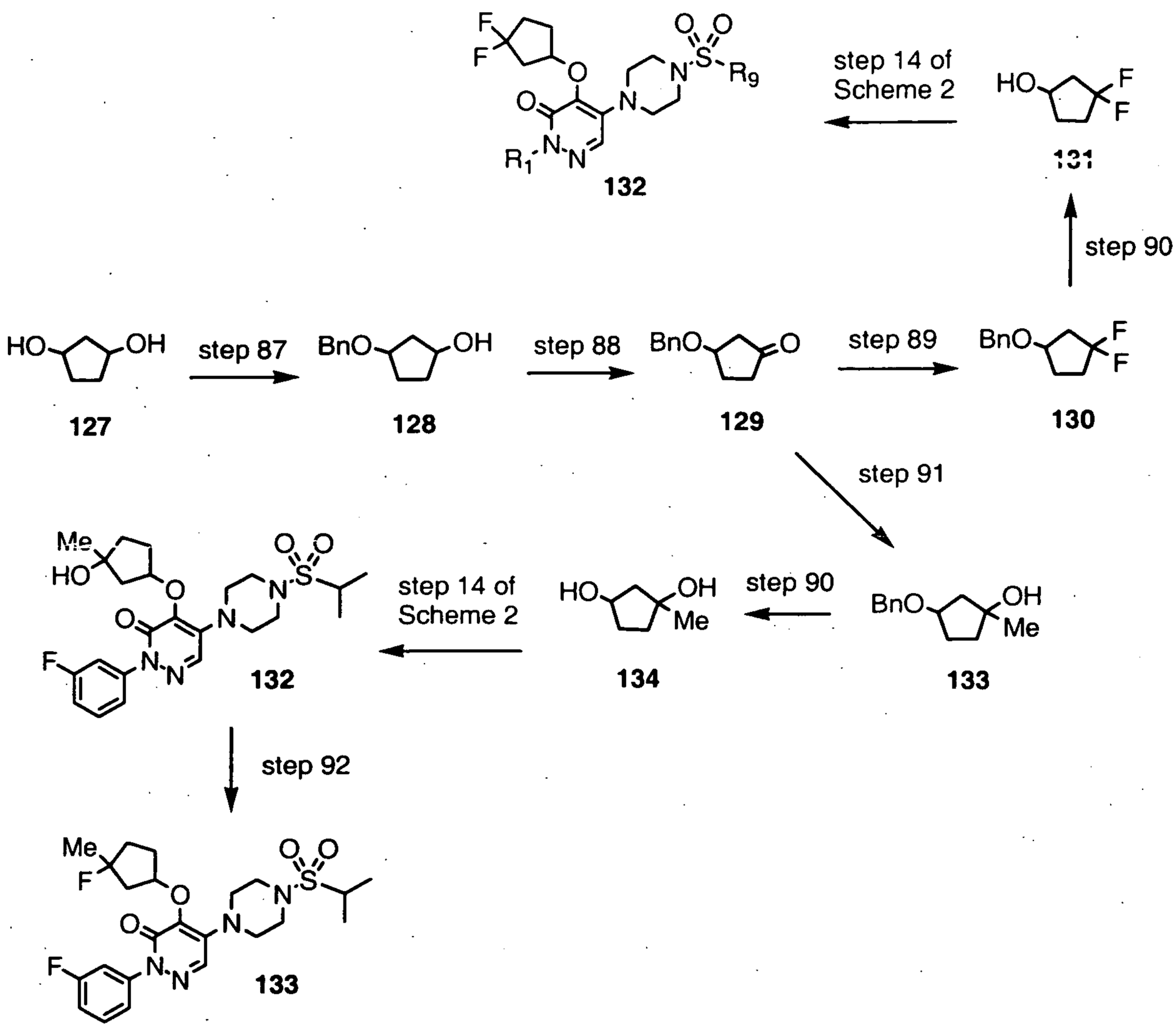
To a solution of SO_2Cl_2 (0.08 mL, 1.0 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added a solution of the compound **124** (0.36 g, 1.0 mmol) and Et_3N (0.16 mL, 1.1 mmol) in CH_2Cl_2 (5 mL). The reaction was slowly warmed up from -78 to - 20 °C over a period of 1 h. The solvent was evaporated and purification by silica gel chromatography (eluant 20:1 CH_2Cl_2:EtOAc) gave 82 mg (18%) of the product **125** as a white solid. MS (M+1): m/e 457.

Step 86:

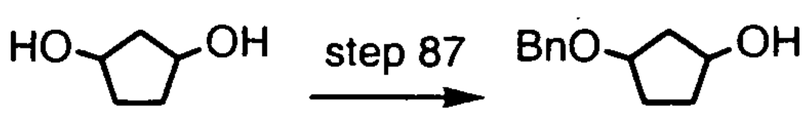


To a solution of phenol (47 mg, 0.50 mmol) in dry THF (3 mL), was added NaH (20 mg 60% by weight in oil, 0.50 mmol). The reaction mixture was stirred for 15 min at room temperature. A solution of the compound **125** (0.11 g, 0.25 mmol) in THF (2 mL) was added, and the reaction mixture was stirred for 1 h. The mixture was diluted with EtOAc (20 mL) and washed with 1 N HCl and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 0 - 25% EtOAc in hexanes) gave 40 mg (31%) of the product **126** as a pale yellow solid. MS (M+1): m/e 515.

Scheme 28

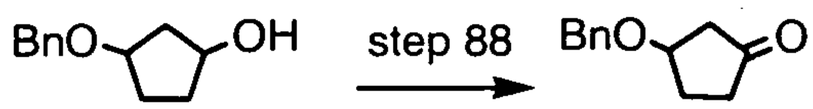


Step 87:



Sodium hydride (60%, 2.40 g, 60 mmol) was added to a solution of 1, 3-cyclopentadiol **127** (8.16 g, 80 mmol) in THF (200 mL) and the mixture was stirred for 15 mins at room temperature. Benzyl bromide (6.80 g, 40 mmol) was then added, and the resulting mixture was stirred at room temperature for 20 h. Solid sodium bicarbonate (10 g) was added, and stirring was continued for 30 mins. The reaction mixture was filtered, and the filtrate was concentrated. Purification by silica gel chromatography (eluant: 0-30% EtOAc in hexanes) gave 3.5 g (46%) of the product **128** as colorless oil.

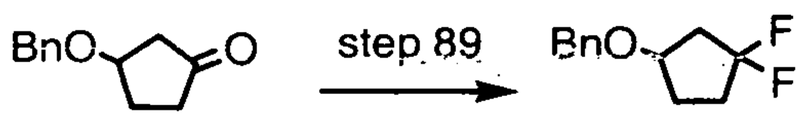
Step 88:



128 **129**

To a solution of the compound **128** (2.77 g, 14.4 mmol) in CH_2Cl_2 (50 mL) was added Dess-Martin periodinane (12.22 g, 28.8 mmol) followed by stirring for 2 h at room temperature. The reaction mixture was treated with 2.0 M NaOH (50 mL). The organic phase was separated, and the aqueous solution was extracted with 100 mL of EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 2.5 g (93%) of the product **129** as a colorless oil.

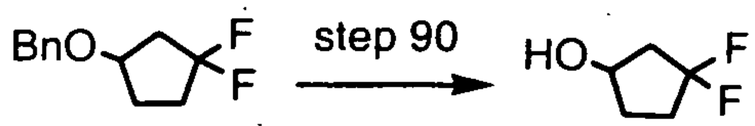
Step 89:



129 **130**

DAST (3.18 g, 19.7 mmol) was added dropwise to a solution of compound **129** (1.50 g, 7.9 mmol) in 1, 2-dichloroethane at room temperature. The reaction was heated at 90 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through a short silica gel plug and washed with CH_2Cl_2. The filtrate was concentrated and purification by silica gel chromatography (eluant: hexane) gave 0.99 g (59%) of the product **130** as colorless oil.

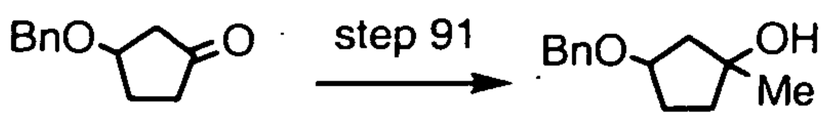
Step 90:



130 **131**

A flask was charged with Pd/C (10% wt, 1.00 g). Compound **130** (0.90 g, 4.3 mmol) dissolved in 5:1 MeOH:AcOH (30 mL) was added under nitrogen. The reaction mixture was shaken under hydrogen (50 psi) at room temperature for 48 h. The Pd/C catalyst was filtered and washed with CH_2Cl_2. The solvent was removed from the filtrate by distillation at 90 °C. The residue was diluted with Et_2O and treated with Na_2CO_3 (4.5 g) over 30 mins at room temperature. The solid was filtered off, and the filtrate was concentrated to give 0.37 g (71%) of the product **131** as a colorless oil.

Step 91:



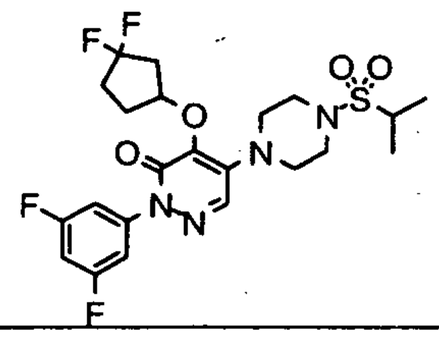
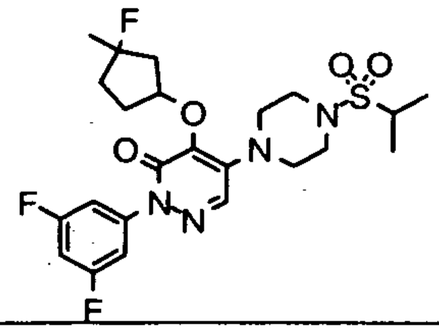
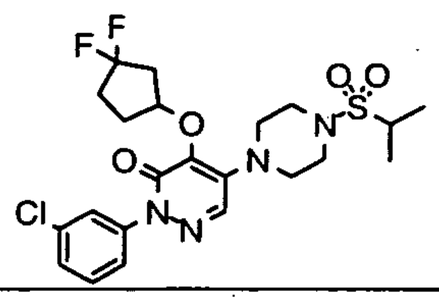
129 **133**

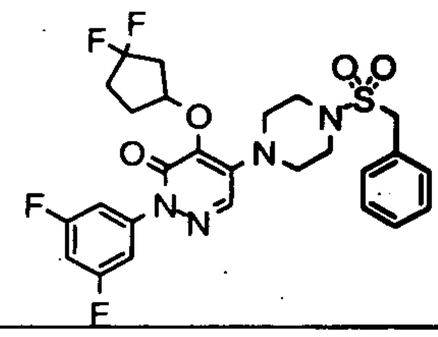
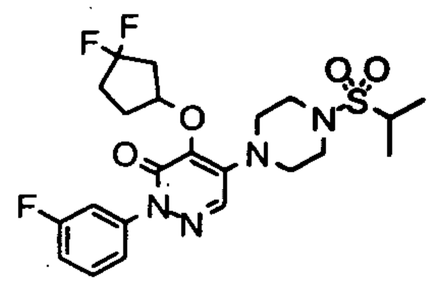
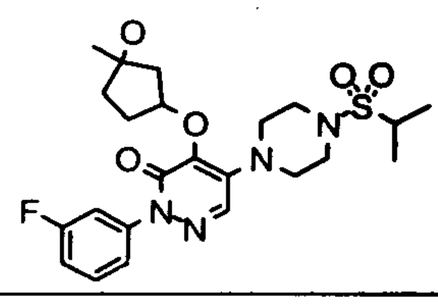
A solution of compound **129** (0.49 g, 2.6 mmol) in THF (10 mL) was cooled to -78 °C, and MeMgBr (1.4 M, 2.8 ml, 3.9 mmol) was added dropwise. The reaction mixture was warmed slowly from -78 to -10 °C over 1 h. Saturated NH_4Cl solution (5 mL) and then EtOAc were added. The organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 0-10% EtOAc in CH_2Cl_2) to give 0.20 g (37%) of the product **133** as a colorless oil.

Table 26: Oxygen Linked Analogs with Sulfonamide

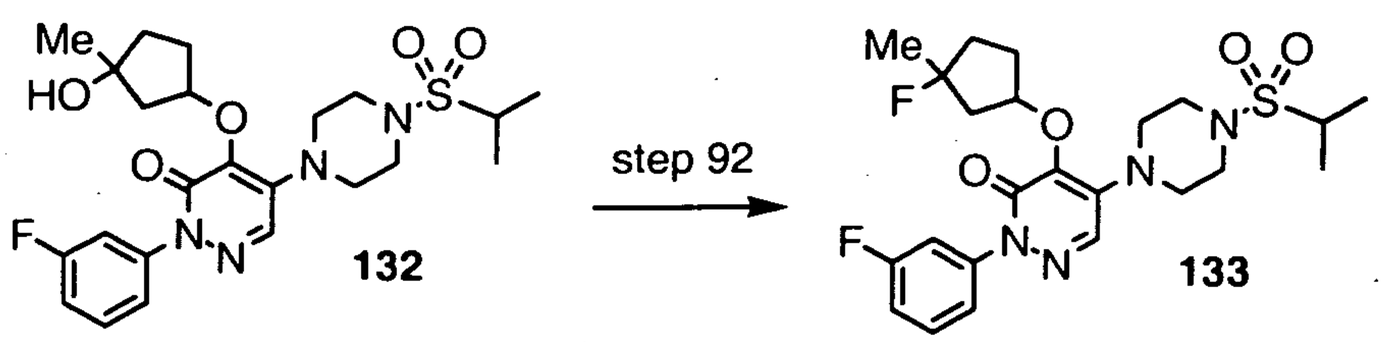
Step 14 of Scheme 2:

Using the procedures described above, the following compounds were synthesized.

Comp. No.	Structure	MS M+1
1601Z		519
1603Z		515
1605Z		517

Comp. No.	Structure	MS M+1
1602Z		567
1604Z		501
1606Z		495

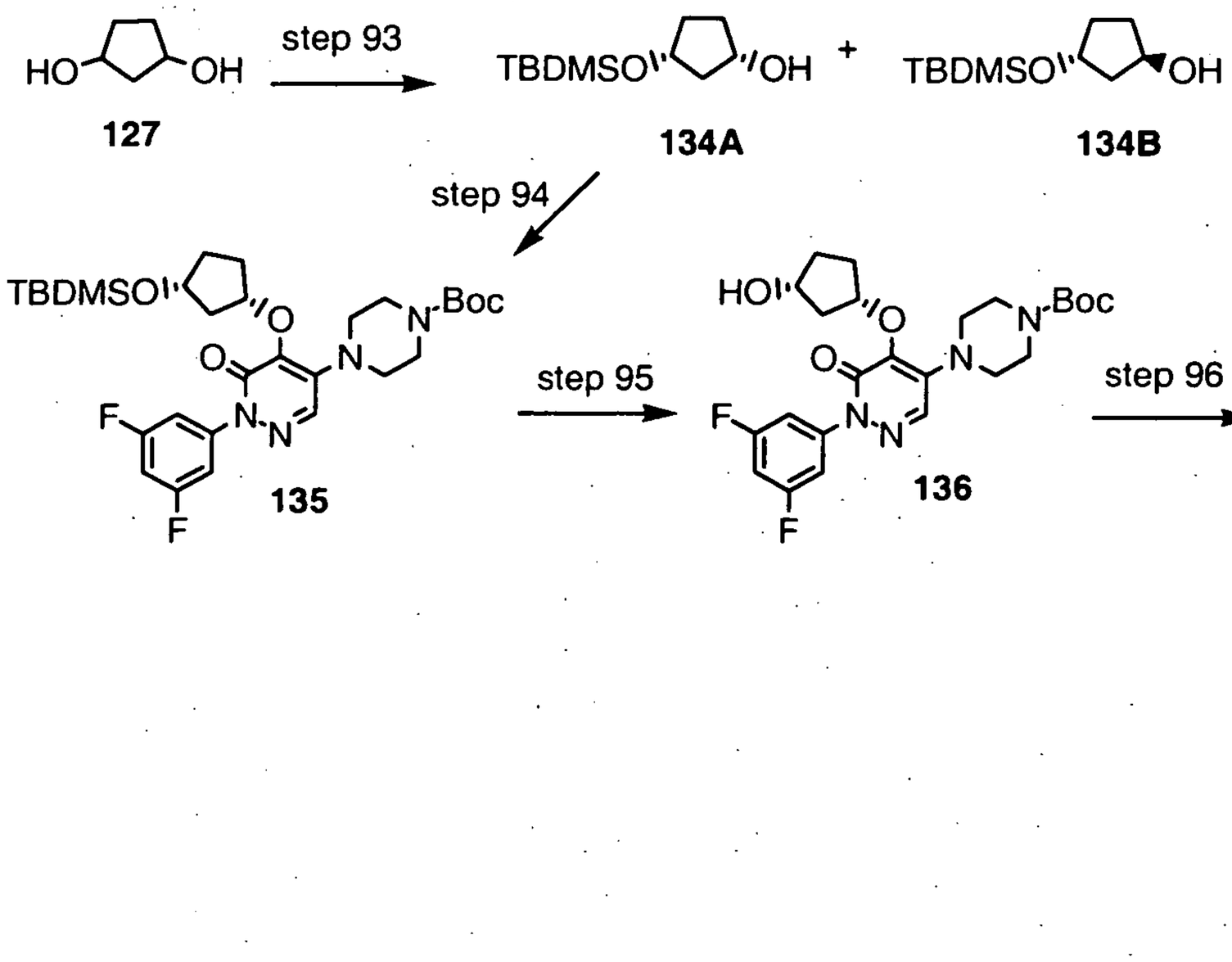
Step 92:



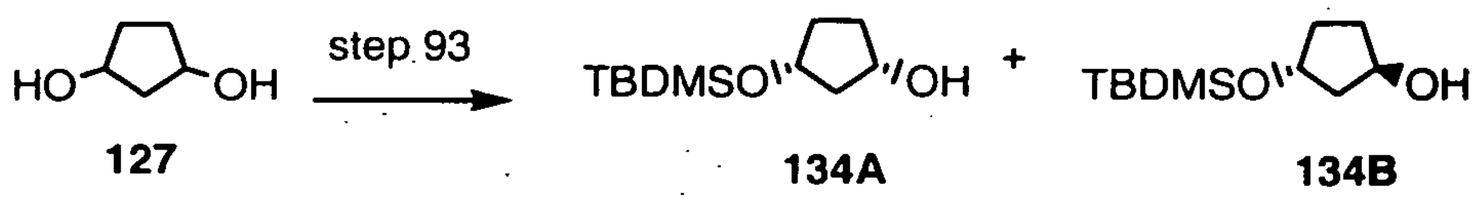
A solution of DAST (52 mg, 0.325 mmol) dissolved in CH_2Cl_2 (5 mL) and cooled to -78 °C was added dropwise a solution of the alcohol **132** (80 mg, 0.16 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. Saturated $NaHCO_3$ solution (0.1 mL) was added. Purification of the mixture by silica gel

chromatography (eluant: 0 - 35% EtOAc in hexanes) gave 68 mg (86%) of the product **133** as a pale yellow solid (86 %). MS (M+1): m/e 497.

Scheme 29

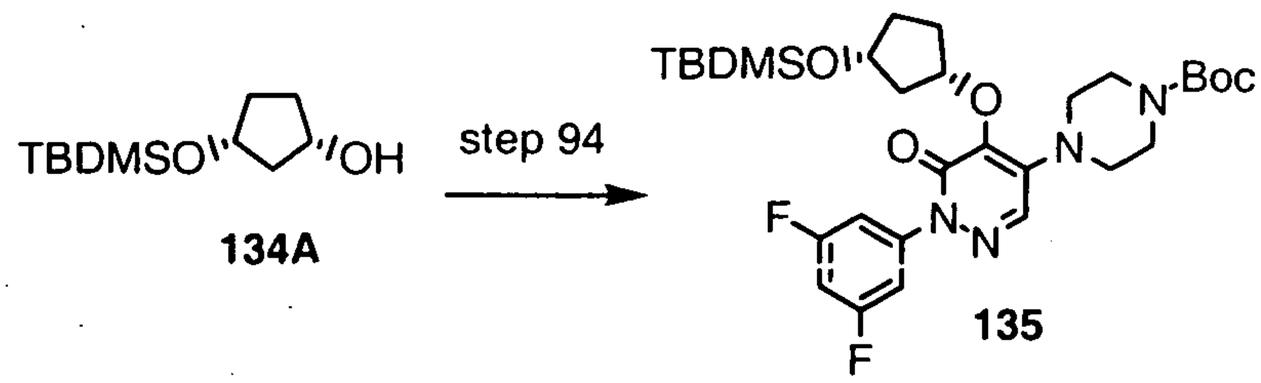


Step 93: Tetrahedron v. 53, p.1983 (1997) and Org. Process Res. Dev. v 2, p.357 (1998)



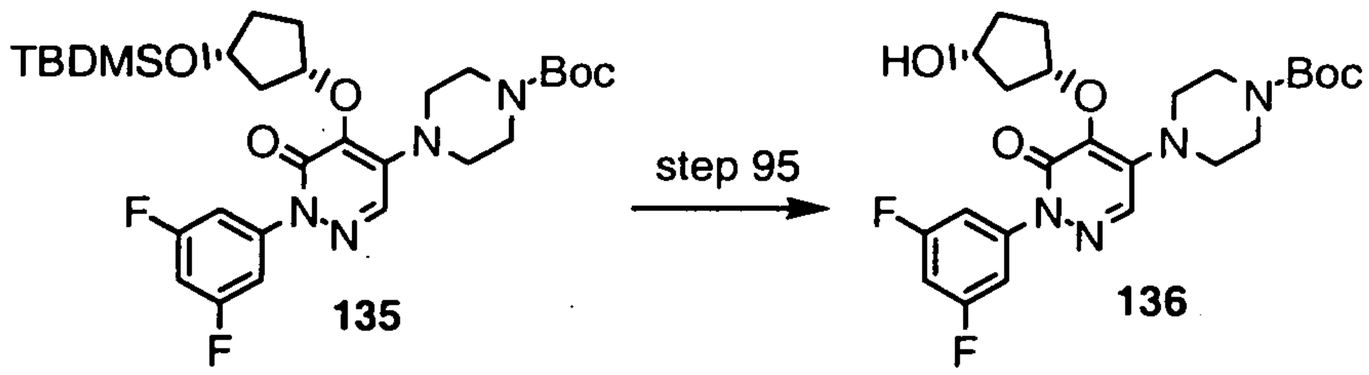
Sodium hydride (11.6 g, 289 mmol, 60% dispersion in mineral oil) was added to a solution of 1,3-cyclopentanediol **127** (28.1 g, 275 mmol, mixture of cis and trans isomers) in anhydrous tetrahydrofuran (500 mL) at 0 °C under nitrogen. The mixture was stirred for 1 h after which a solution of *tert*-butyldimethylchlorosilane (49.8 g, 330 mmol) in anhydrous tetrahydrofuran (200 mL) was added. The mixture was slowly warmed to room temperature and stirred for a total of 18 h after which the mixture was diluted with brine (500 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified in two batches by CombiFlash Companion (330-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 to 3:7), to provide the *cis* isomer **134A** (2.45 g, 4%) as a colorless oil. The later eluting *trans* isomer **134B** (15.18 g, 25%) was also isolated as a colorless oil.

Step 94:



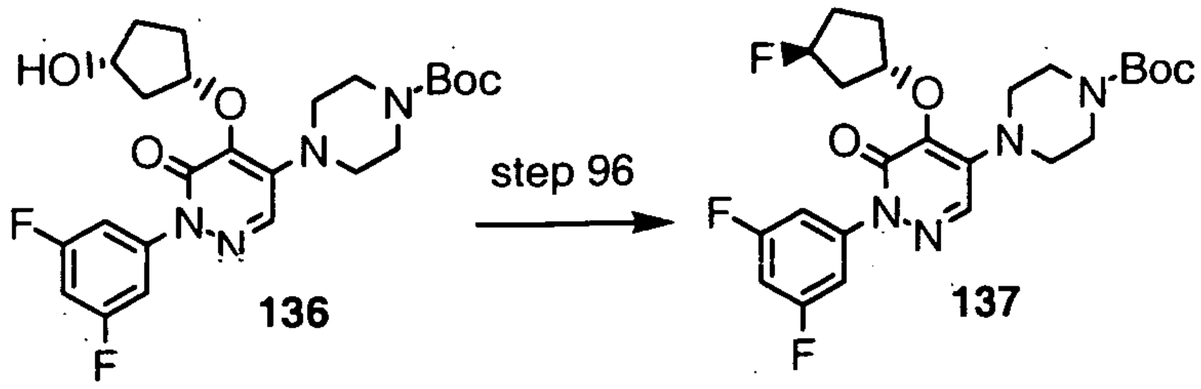
To a solution of compound **134A** (2.4 g, 11.1 mmol) in anhydrous THF (100 mL) at room temperature under nitrogen was added sodium bis(trimethylsilyl)amide (12 mL, 12.1 mmol, 1.0 M in THF). The mixture was stirred for 10 mins, after which chloropyridazinone (4.3 g, 10.1 mmol) was added portion wise. The mixture was stirred for 28 h after which the mixture was diluted with brine (100 mL) and extracted with ethyl acetate (300 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated. The residue was purified by CombiFlash Companion (120-g silica gel cartridge), eluting with ethyl acetate/hexanes (9:1 to 8:2), to give the product **135** (4.3 g, 71%) as an off-white solid. MS (M-H-SiMe$_2$tBu): m/e 491.

Step 95:



To a solution of compound **135** (4.3 g, 7.1 mmol) in anhydrous THF (50 mL) at 0 °C under nitrogen was added tetra-*n*-butylammonium fluoride (8.5 mL, 8.5 mmol, 1 M in THF), and the mixture was slowly warmed to room temperature and stirred for a total of 18 h. The mixture was diluted with ethyl acetate (200 mL), washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (2:8 to 8:2) gave the product **136** (2.88 g, 82%) as an off-white solid. MS (M-H): m/e 491.

Step 96:



Diethylaminosulfur trifluoride (DAST, 1.2 mL, 8.8 mmol) was added dropwise to a solution of compound **136** (2.88 g, 5.8 mmol) in anhydrous methylene chloride (100 mL) at -20 °C under nitrogen. The mixture was stirred for 3.5 h after which it was warmed to 0 °C and diluted with saturated aqueous sodium bicarbonate solution (50 mL) and extracted with methylene chloride (2 x 100 mL). The combined organic extract was washed with brine (100 mL) and then concentrated. Purification by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 to 4:6) gave the product **137** (2.16 g, 75%) as a white solid. MS (M+1): m/e 495.

Steps 6 and 9 of Scheme 1:

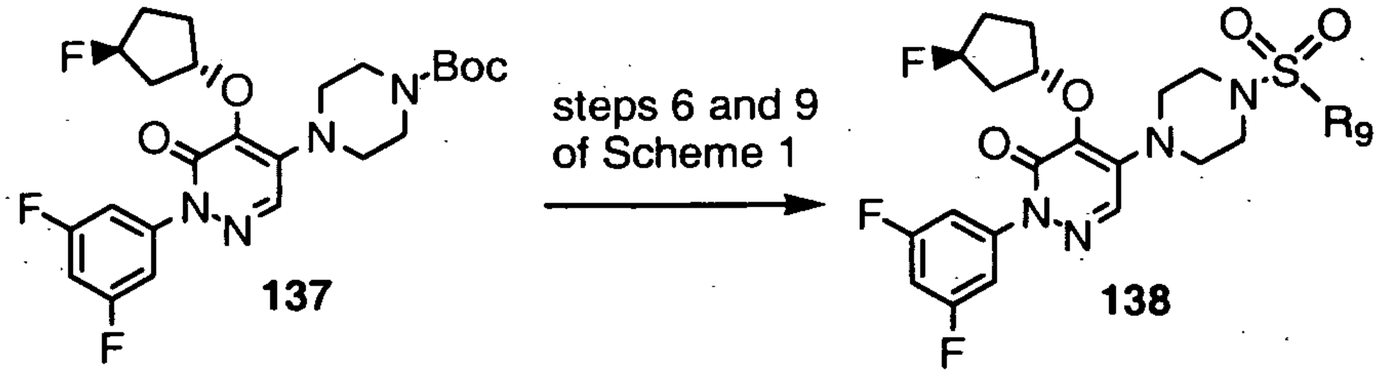
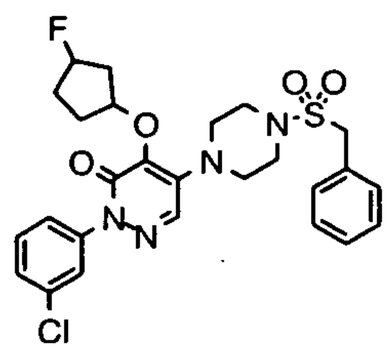
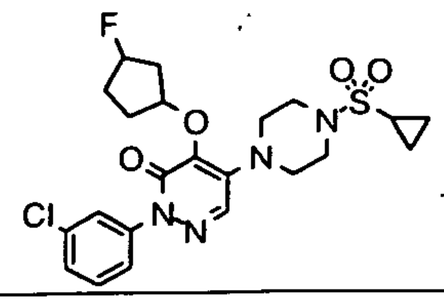
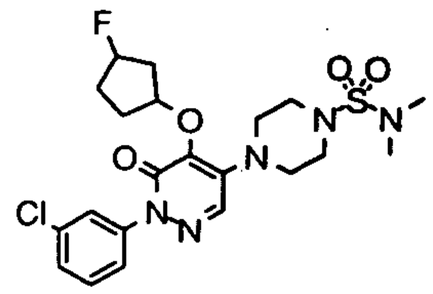
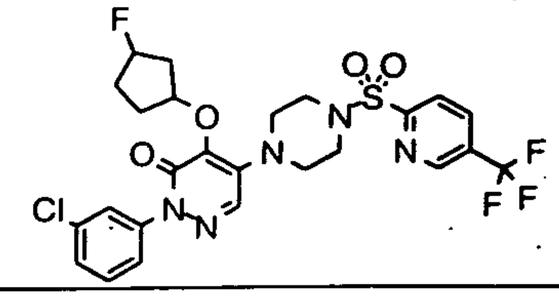
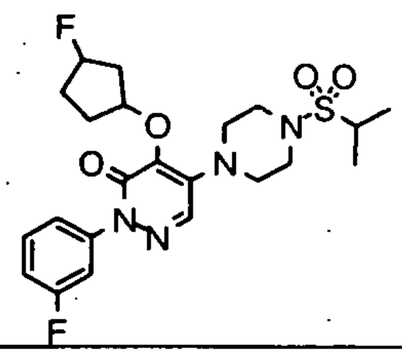
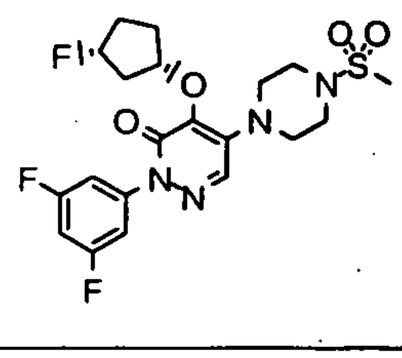
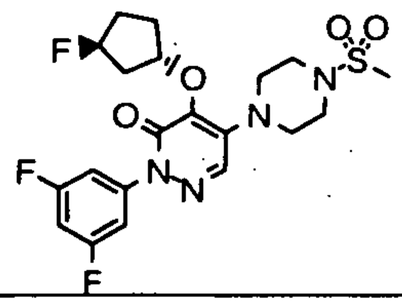
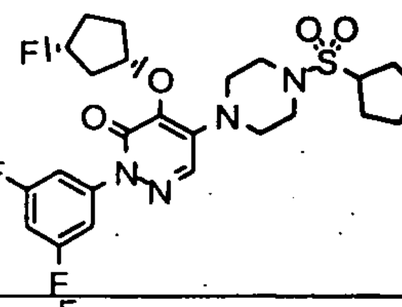
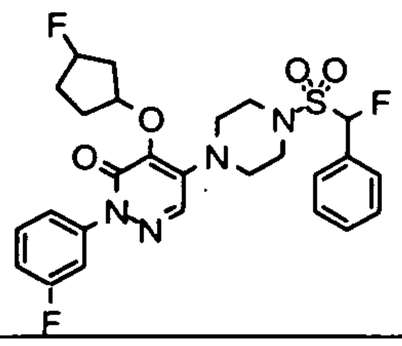
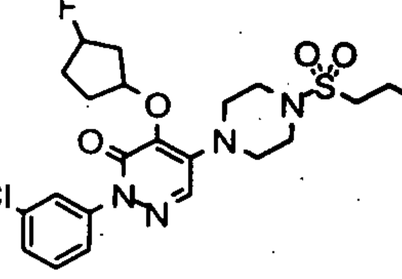
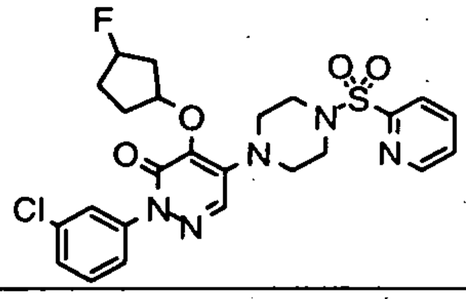
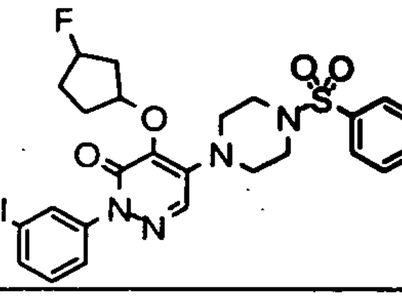
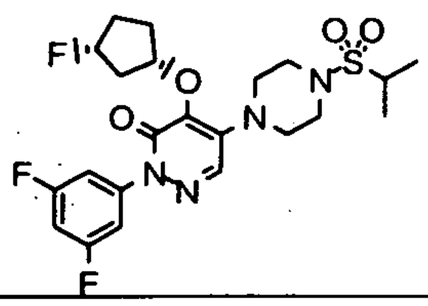
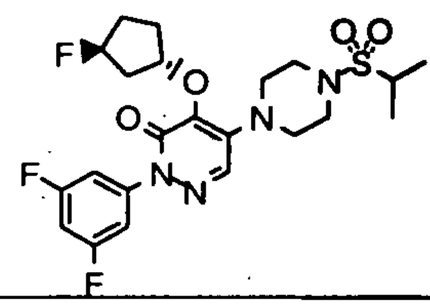
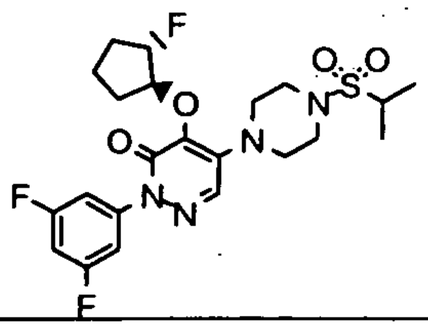
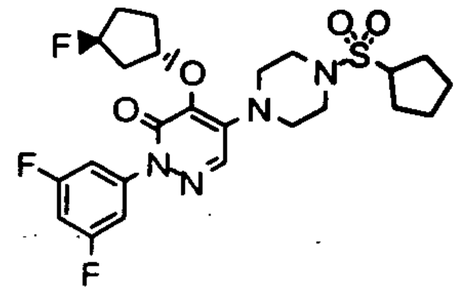


Table 27: Oxygen Linked Analogs with Sulfonamide

Using the procedures described above, the following compounds were synthesized.

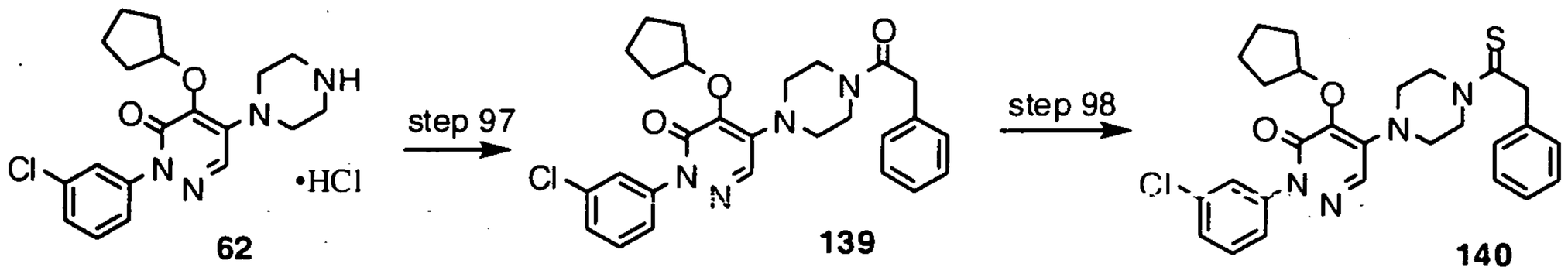
Comp. No.	Structure	MS M+1
1607Z		547
1609Z		497

Comp. No.	Structure	MS M+1
1608Z		500
1610Z		602

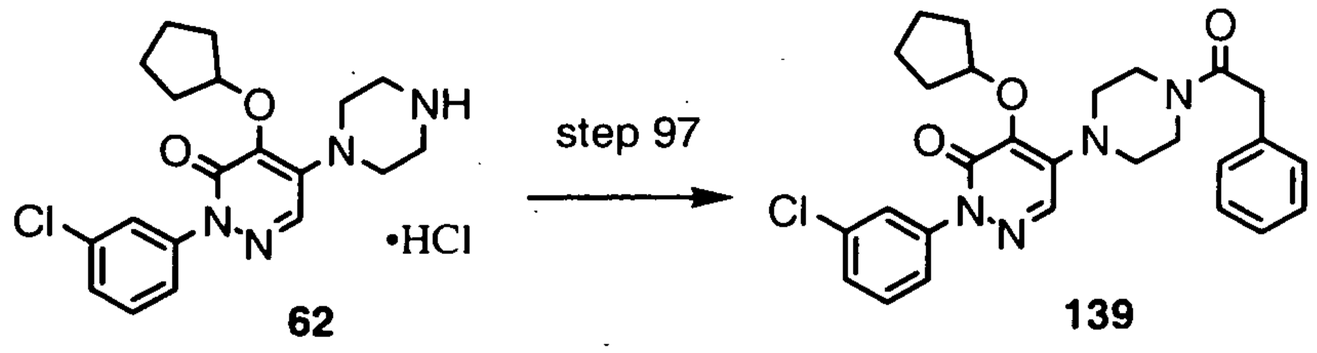
1611Z		483
1612Z		473
1613Z		473
1614Z		527
1615Z		549
1616Z		499
1617Z		534
1618Z		533
1619Z		501
1620Z		501
1621Z		501
1622Z		527

Using the procedure of Scheme 29, the following compounds listed above in Tables 10 and 11 are prepared: 448Z, 569Z, 570Z, 678Z, 733Z, 765Z, 766Z, 779Z, 793Z, 803Z, 804Z, 821Z, 847Z, 850Z, 851Z, 859Z, 875Z, 888Z, 902Z, 919Z, 925Z, 928Z, 1055Z, 1085Z, 1089Z, 1128Z, 1132Z, 1152Z, 1173Z, 1224Z and 1477Z.

Scheme 30

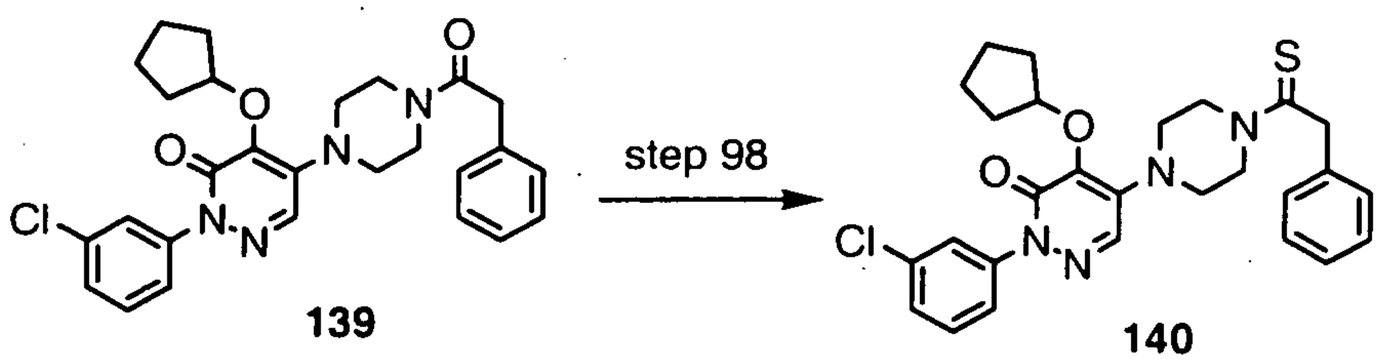


Step 97:



Diisopropylethylamine (0.50 mL, 3.0 mmol) was added to a suspension of phenylacetyl chloride (0.16 mL, 1.2 mmol) and amine hydrochloride salt **62** (500 mg, 1.2 mmol) in anhydrous methylene chloride (10 mL) at room temperature under nitrogen. The mixture was stirred for 4 h after which it was directly purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (2:8 to 100% ethyl acetate), to provide the product **139** (460 mg, 77%) as an off-white solid: MS (M+1): m/e 493.

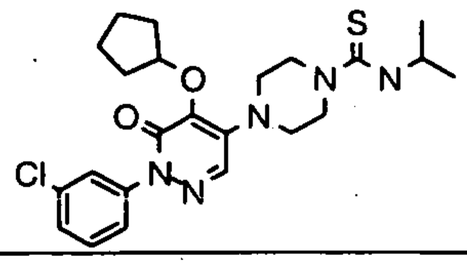
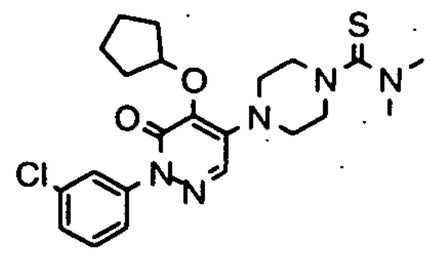
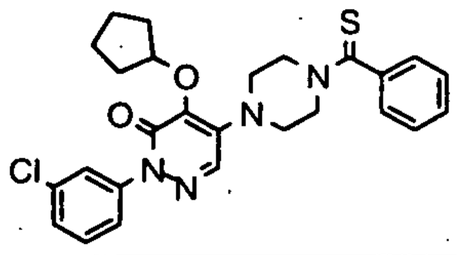
Step 98:

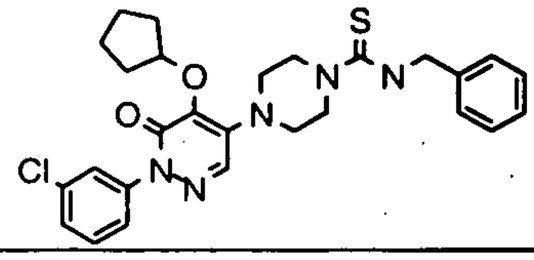
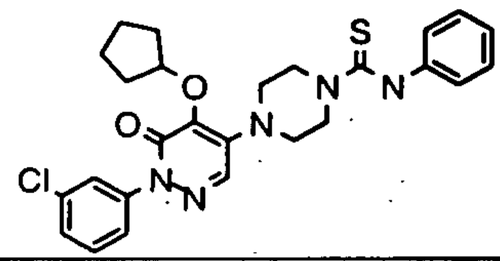
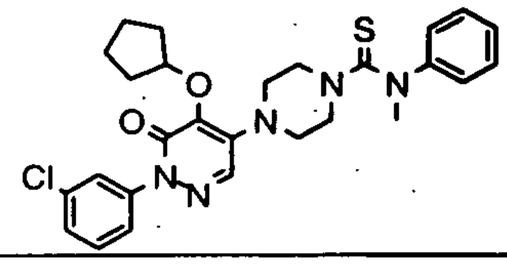


A mixture of benzamide **139** (400 mg, 0.81 mmol) and *p*-methoxyphenyl-thionophosphine sulfide dimer (Lawesson's reagent, 164 mg, 0.41 mmol) in anhydrous toluene (10 mL) was heated at reflux under nitrogen for 3 h. The solvent was removed from the cooled mixture under reduced pressure, and the residue was purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (2:8 to 4:6), to provide the product **140** (420 mg, 99%) as a light yellow solid: MS (M+1): m/e 509.

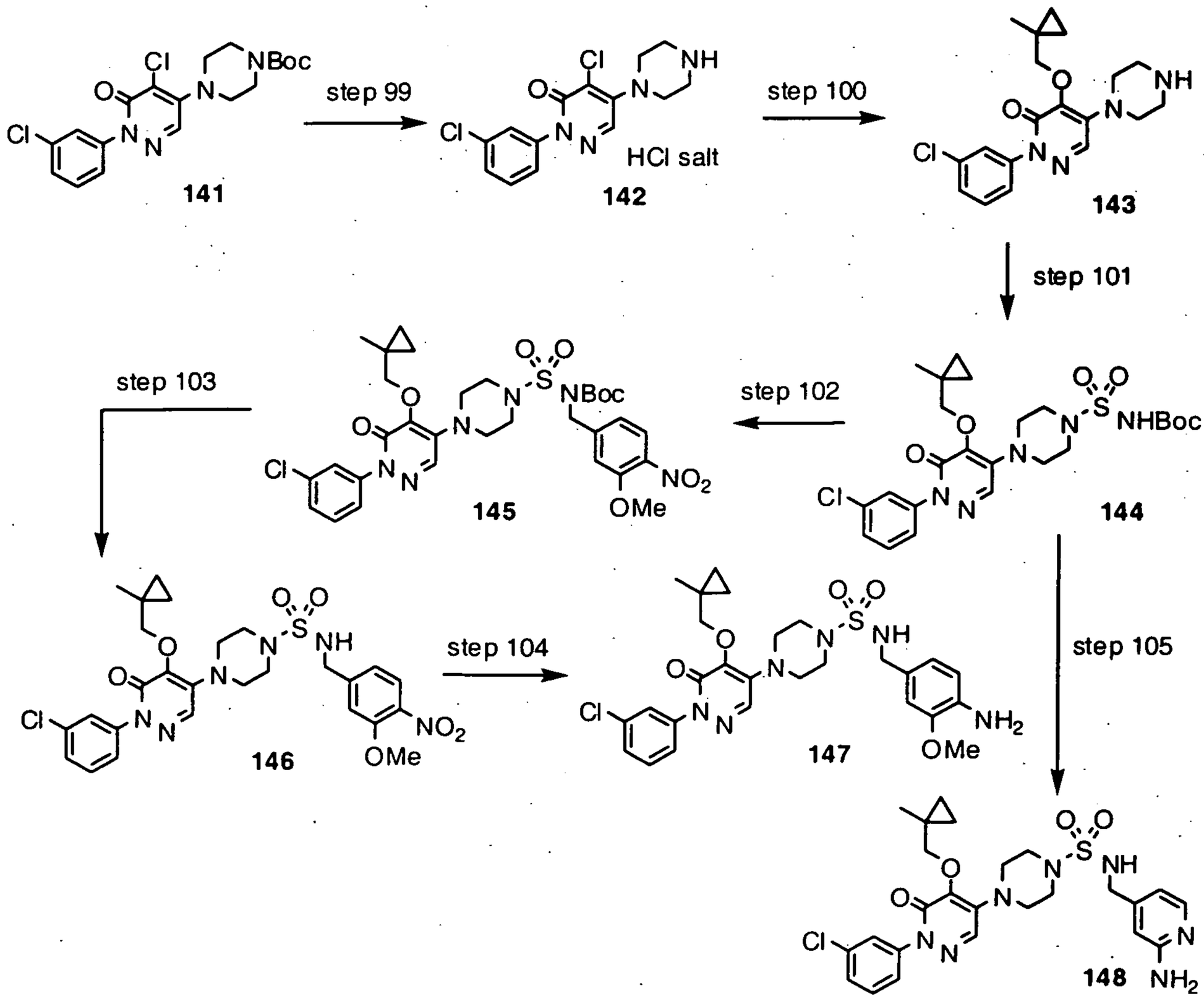
Table 28: Oxygen Linked Analogs with Sulfamide

Using the procedures described above, the following compounds were synthesized.

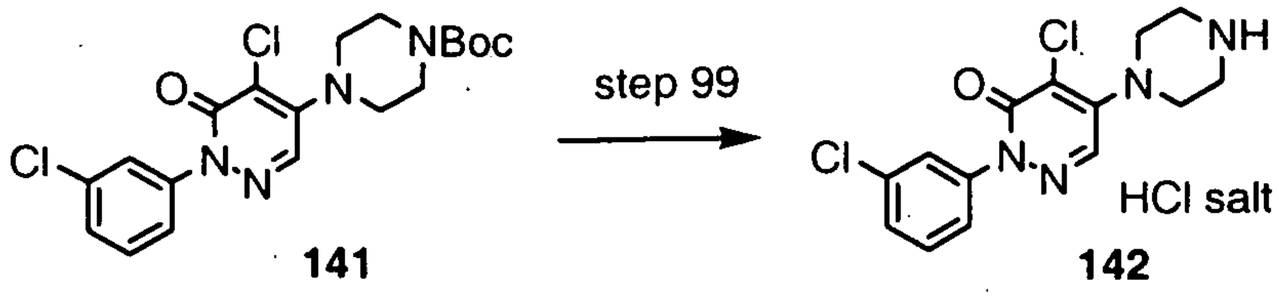
Comp. No.	Structure	MS M+1
1623Z		476
1625Z		462
1627Z		495

Comp. No.	Structure	MS M+1
1624Z		524
1626Z		510
1628Z		524

Scheme 31

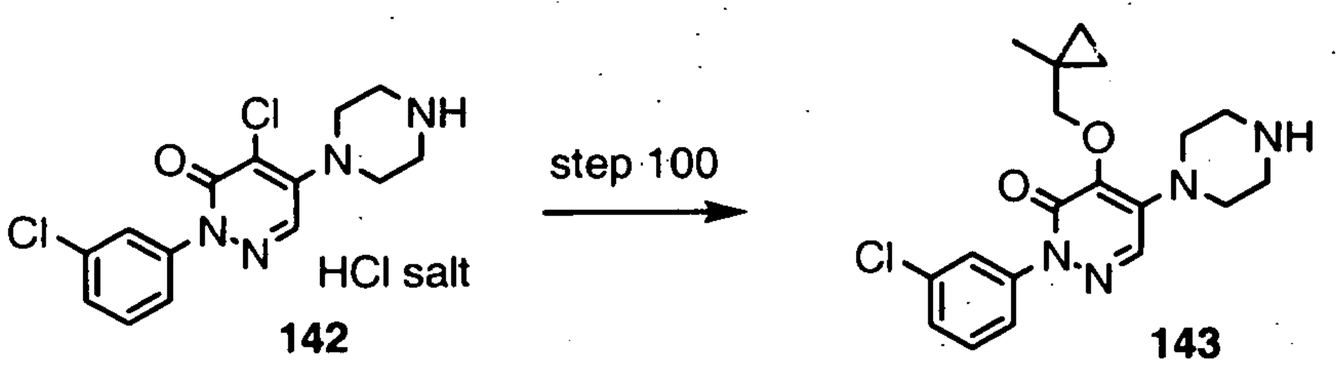


Step 99:



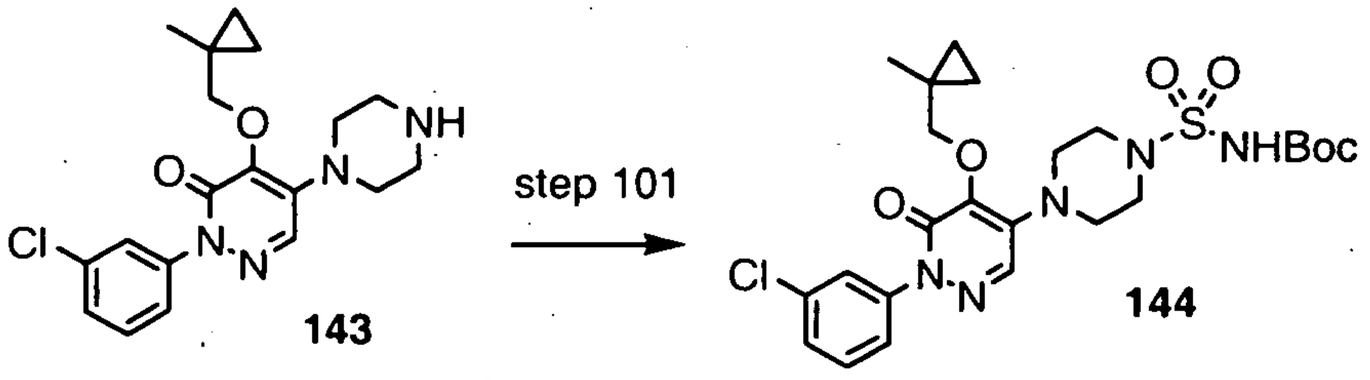
Compound **141** (20 g) in 50 mL of CH_2Cl_2 was treated with 150 mL of 4N HCl/dioxane solution at room temperature for 2 days. Ether (300 mL) was added, and the precipitate was collected by filtration and further washed with ether. The white solid was dried in a vacuum oven at 50 °C overnight to give 16.2 g of the product **142** as the HCl salt. MS (M+1): m/e 325.

Step 100:



Compound **142** (7.2 g, 20 mmol) was mixed with methylcyclopropanemethanol (2.6 g, 30 mmol) in 100 mL of dry THF. NaH (60%, 2.0 g, 50 mmol) was added. The resulting mixture was stirred at room temperature for one hour, then heated to 70 °C for 30 mins. The reaction mixture was cooled to room temperature, and water (100 mL) was added. The aqueous solution was extracted with ethyl ether (3 X 100 mL). The combined organic solutions were washed with brine, concentrated, and further dried by co-evaporation with toluene to give the product **143** as the free amine, which is used in the next step without further purification.

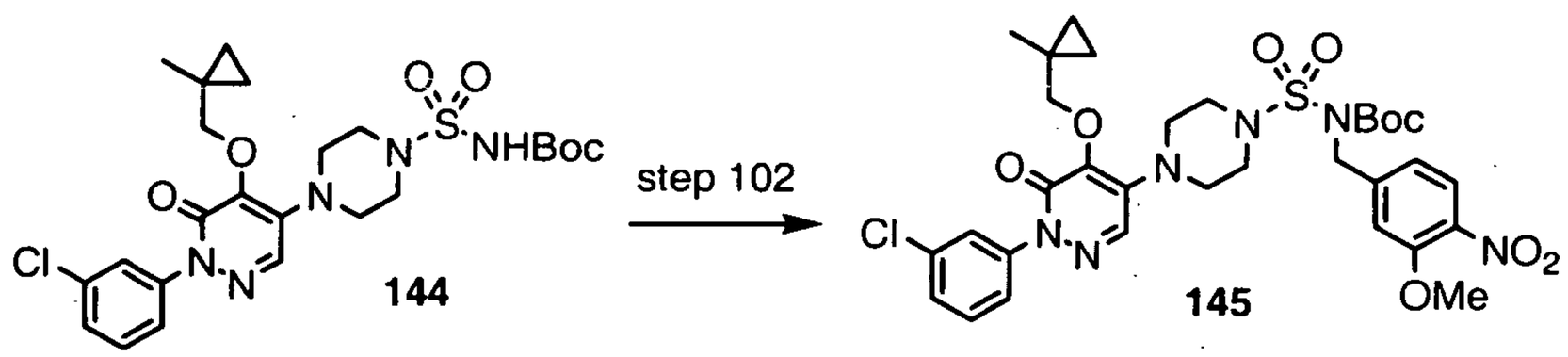
Step 101:



Dry t-butanol (4.0 mL, 42 mmol) in 80 mL of dry CH_2Cl_2 was cooled to 0°C. Chlorosulfonyl isocyanate (3.5 mL, 40 mmol) was then added dropwise. The resulting solution was stirred at 0 °C for 3 h. This 0.5 M solution of $BocNHSO_2Cl$ was used directly in the next step.

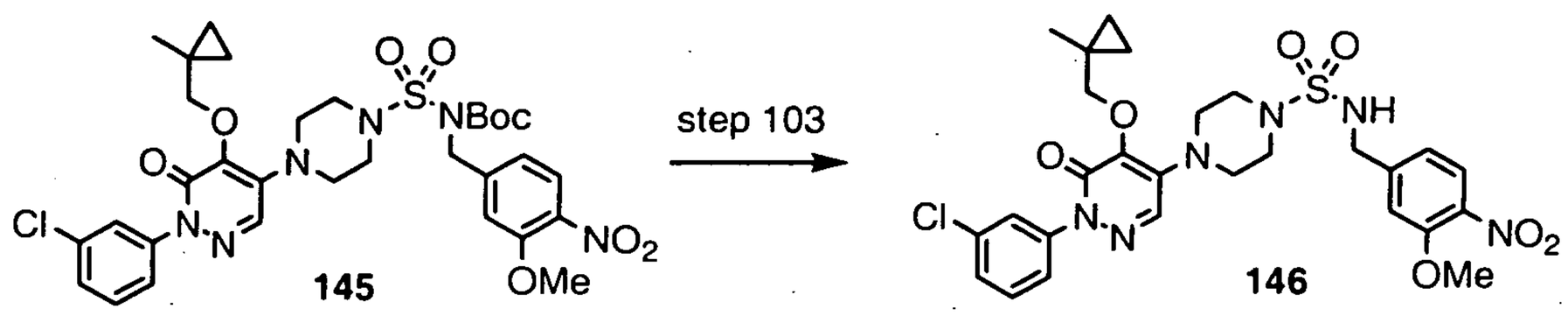
Compound **143** (20 mmol) in 100 mL of dry CH_2Cl_2 was mixed with isopropyldiethylamine (7 mL, 40 mmol), and cooled to 0 °C in an ice-water bath. A 0.5 M solution of $BocNHSO_2Cl$ (50 mL, 25 mmol) was added dropwise. The resulting mixture was then stirred at room temperature overnight. The mixture was diluted with 500 mL of CH_2Cl_2, and washed with 0.5 N HCl solution and water. The organic layer was separated and dried over anhydrous Na_2SO_4. The solution was concentrated to about 70 mL, and the precipitate was collected by filtration to give the first batch of product **144** (9.1 g after drying). Further concentration of the solution affords another 1.5 g of the product **144**. The product was dried in vacuum over at 50 °C for 2 days before use in the next step.

Step 102:



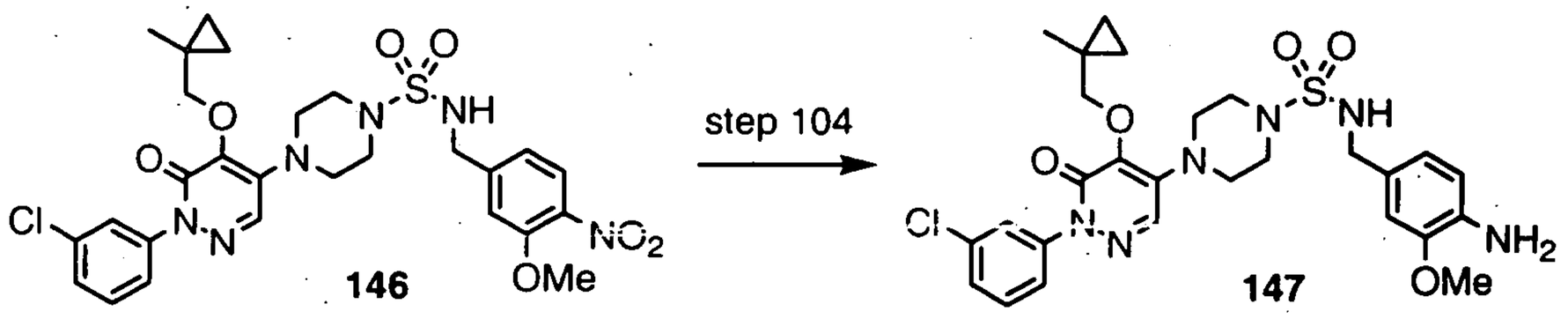
Compound **144** (0.11 g, 0.2 mmol) was mixed with (4-bromomethyl)-2-methoxy-1-nitrobenzene (0.054 g, 0.22 mmol) and phosphazene base P1-t-Bu (60 □L, 0.24 mmol) in 2 mL of dry THF. The resulting mixture was stirred at room temperature overnight, and the whole mixture was used directly in the next step.

Step 103:



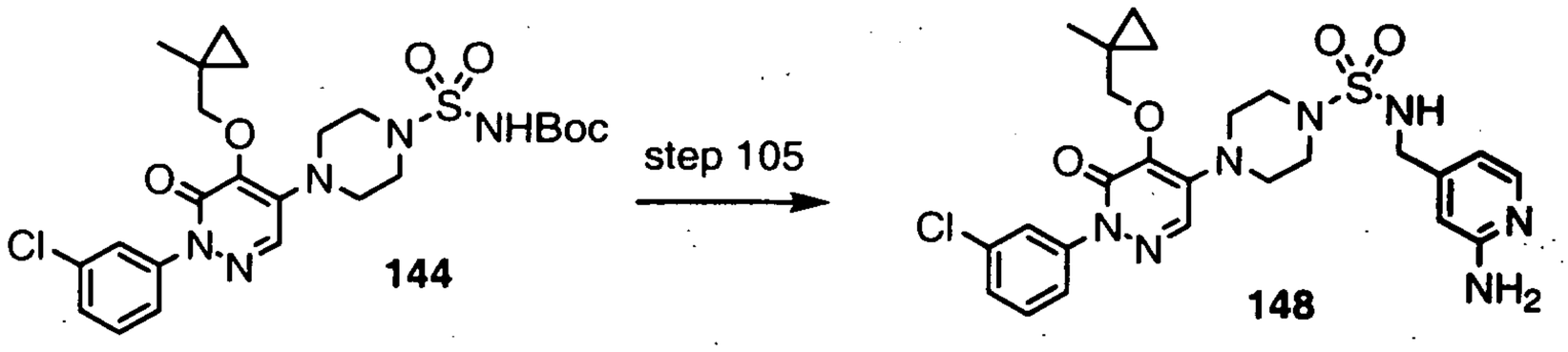
Water (0.5 mL) was added to the reaction mixture from step 104. The resulting mixture was heated to 155 °C for 5 mins in the microwave reactor. After cooling to room temperature, the mixture was concentrated and purified by flash chromatography (eluant: 0% - 10% EtOAc - CH_2Cl_2 gradient) to give 98 mg of compound **146** as a yellow solid. MS (M+1): m/e 619.

Step 104:



Compound **146** (93 mg) was dissolved in 8 mL of EtOAc/MeOH (3:1) mixed solvent system. PtO_2 (20 mg) was added. The mixture was stirred under atmospheric H_2 for one h. The reaction mixture was concentrated, and the crude product was purified by flash chromatography (eluant: 0% - 20% EtOAc - CH_2Cl_2 gradient) to give 75 mg of compound **147** as a yellow solid. MS (M+1): m/e 589.

Step 105:



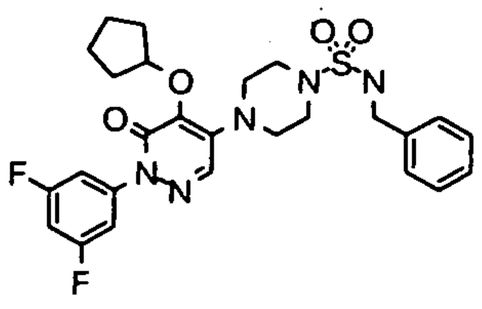
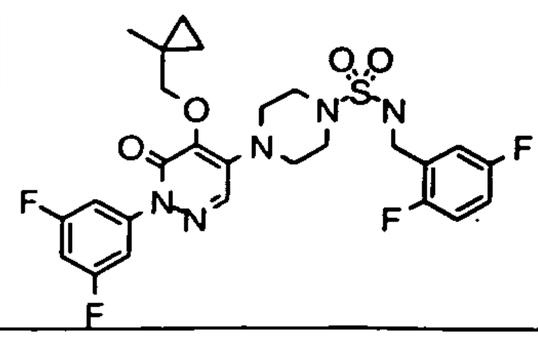
Compound **144** (0.11 g, 0.2 mmol) was mixed with (4-hydroxymethyl)-2-amino-pyridine (37 mg, 0.3 mmol), triphenylphosphine (0.12g, 0.44 mmol), and DEAD (88 mg, 0.48 mmol) in 2 mL of dry THF. The mixture was stirred at room temperature for 3 days.

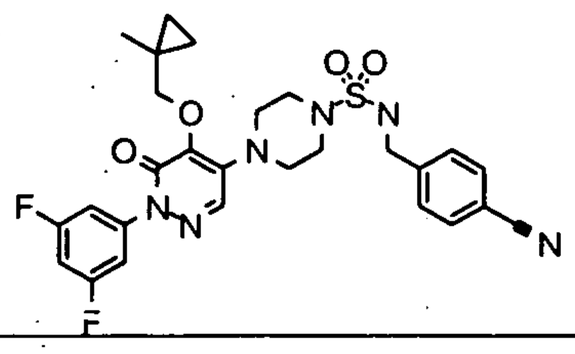
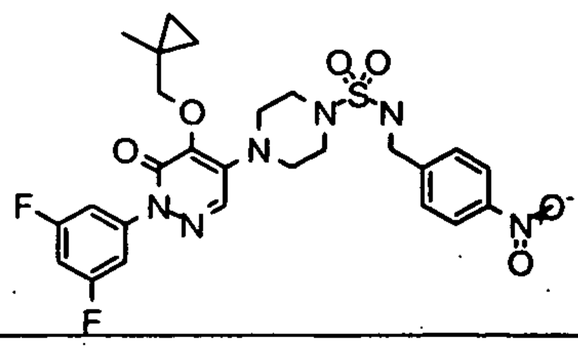
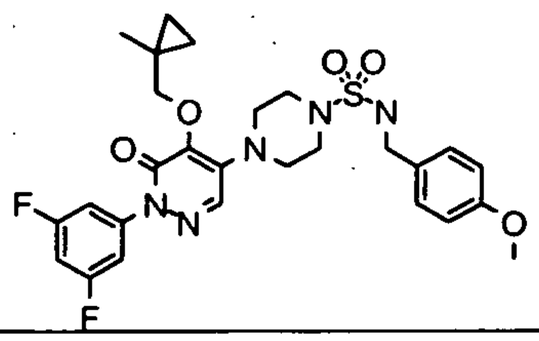
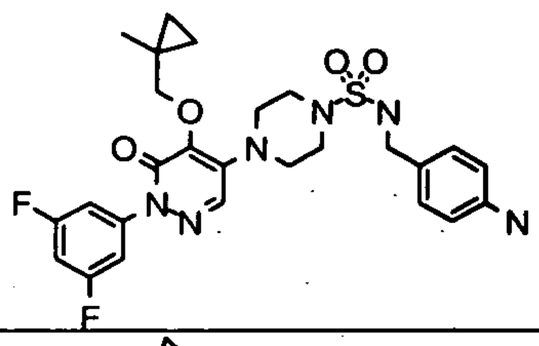
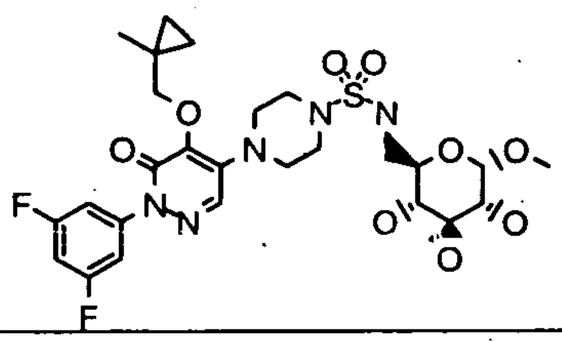
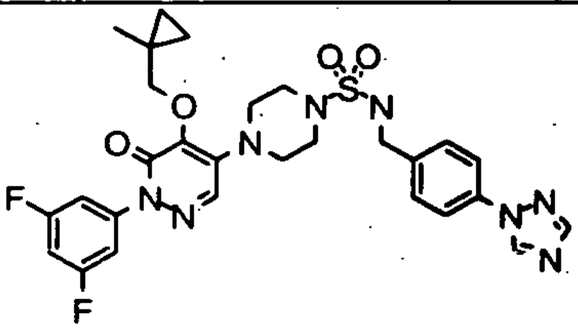
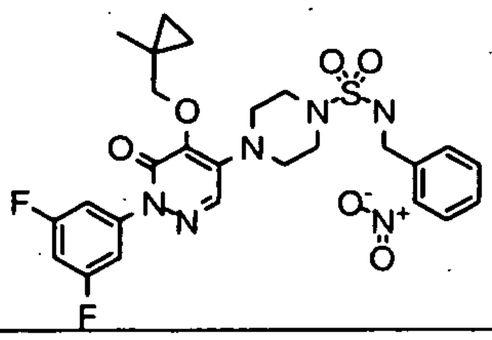
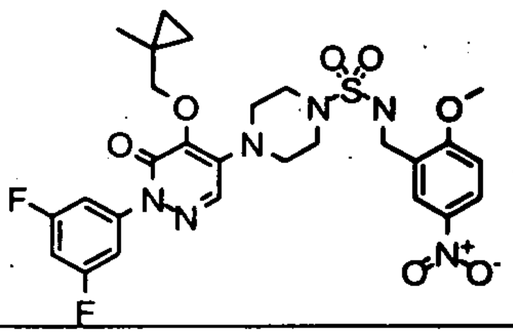
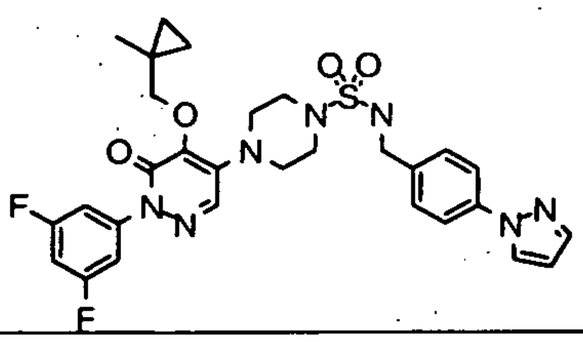
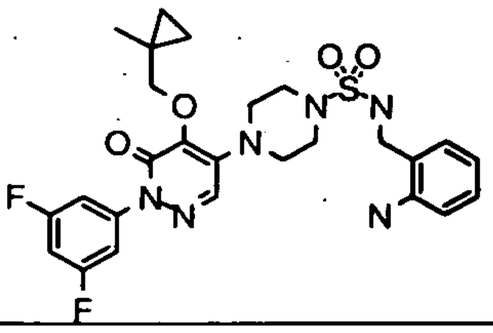
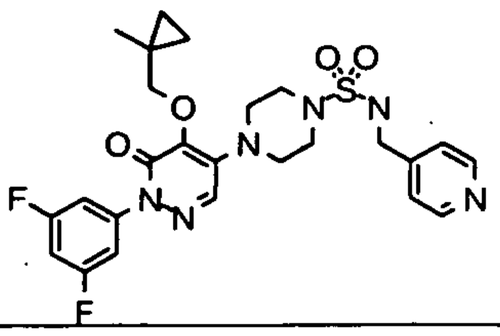
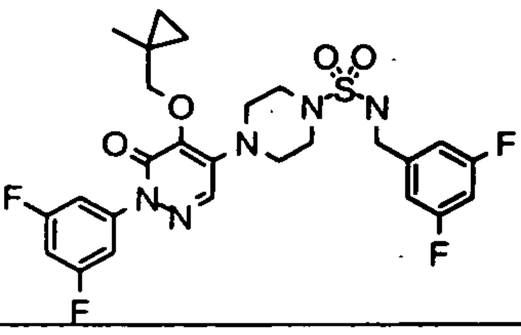
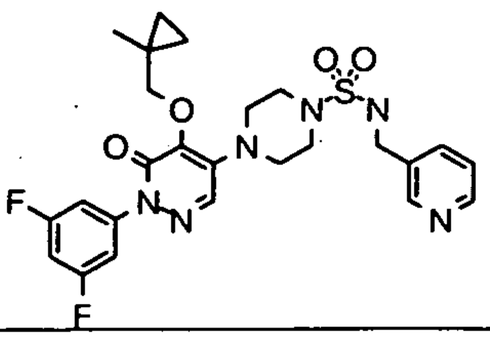
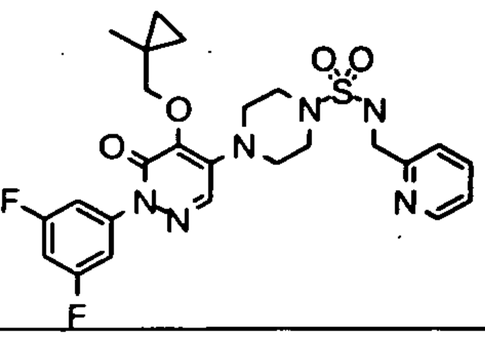
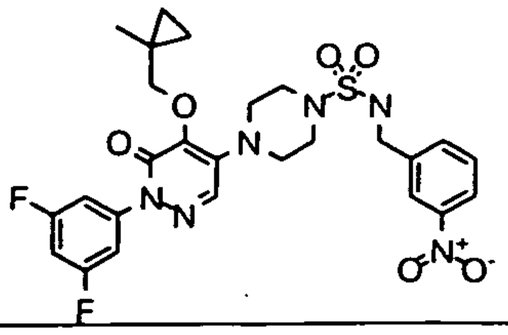
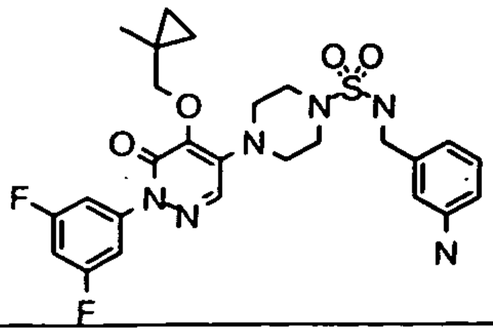
Water (0.5 mL) was added, and the mixture was heated to 155 °C for 5 mins in the microwave reactor. After cooling to room temperature, the mixture was concentrated and purified by Gilson prep HPLC to give 65 mg (56%) of compound **148** as a white solid. MS (M+1): m/e 560.

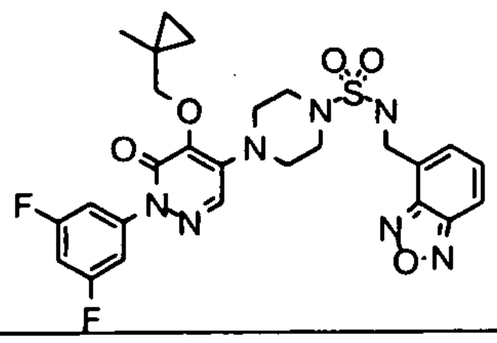
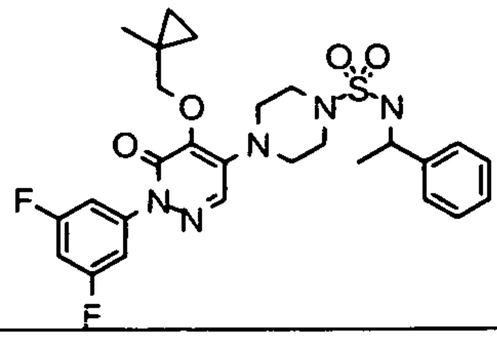
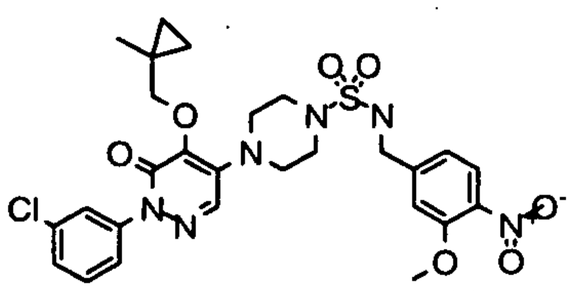
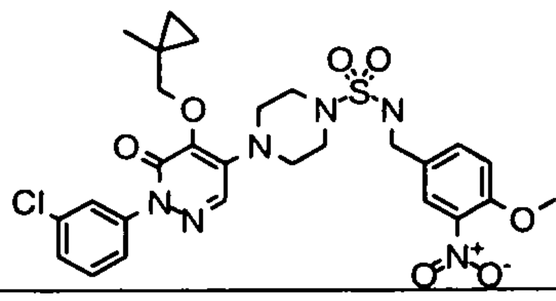
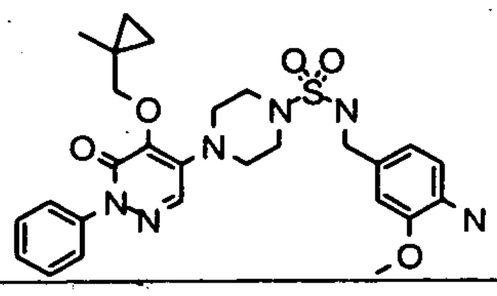
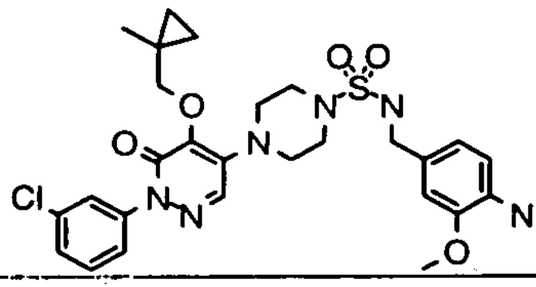
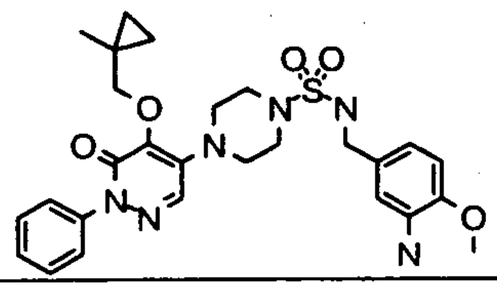
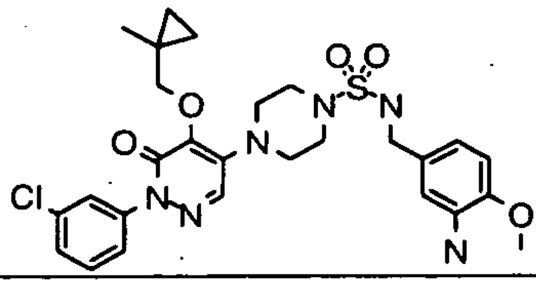
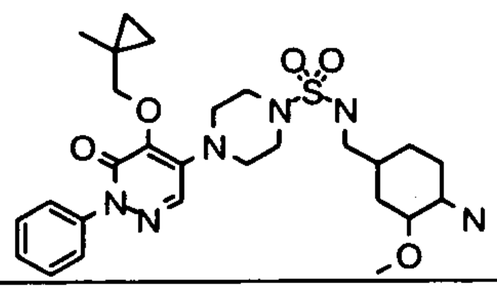
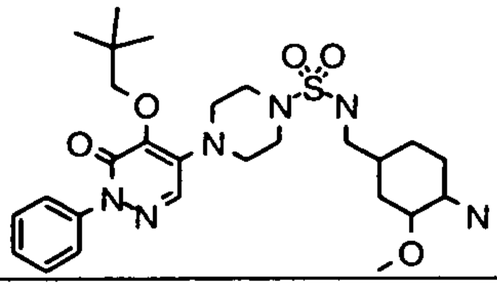
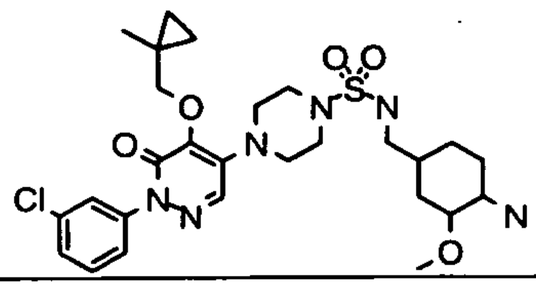
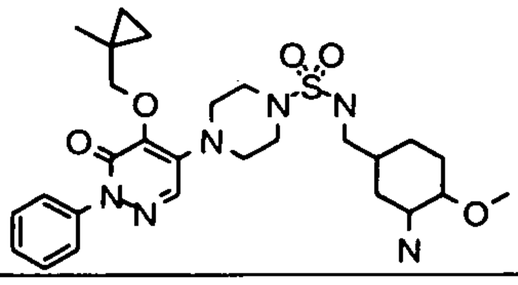
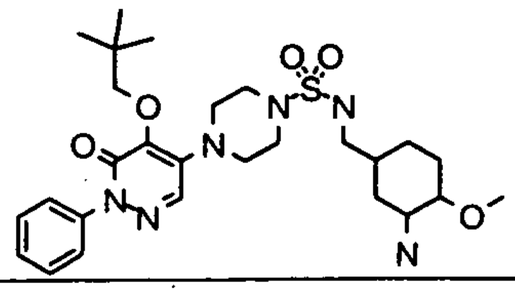
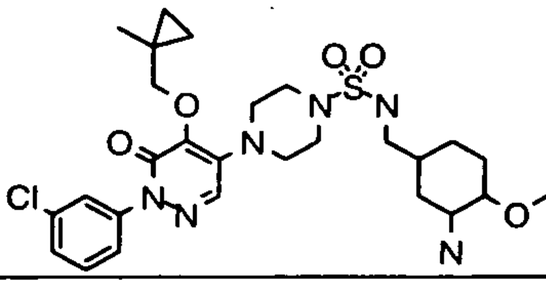
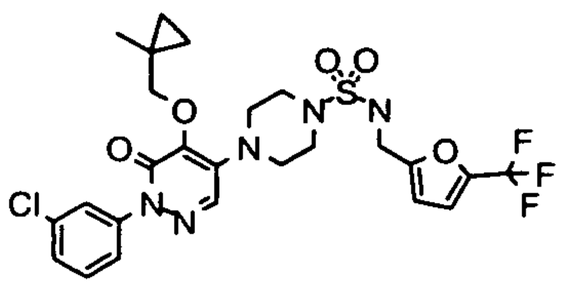
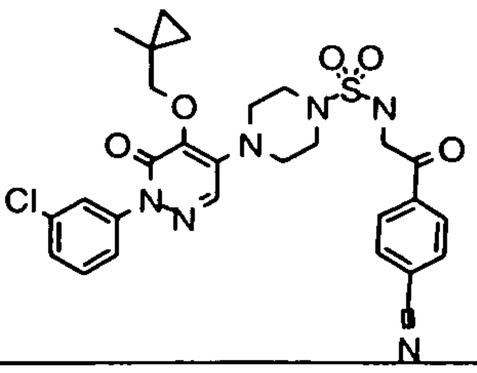
Using the procedures described above, the following compounds were synthesized.

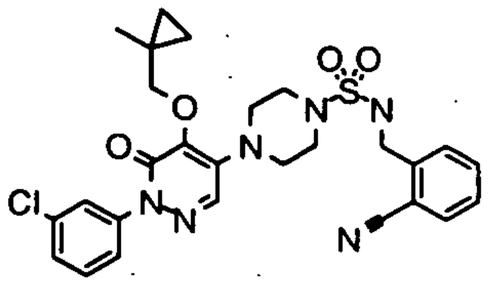
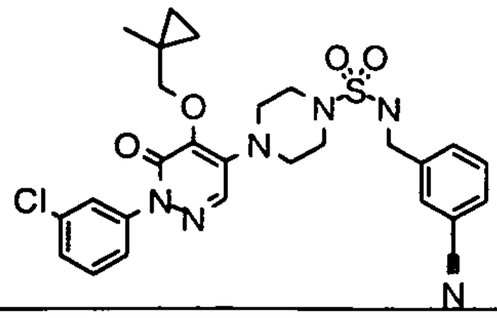
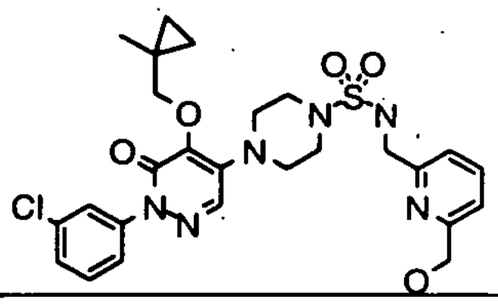
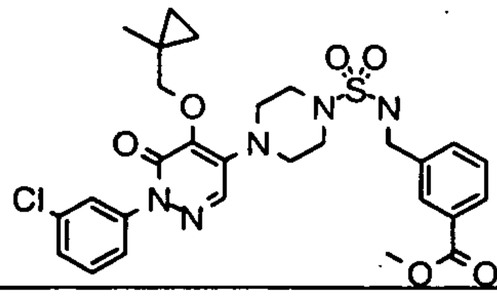
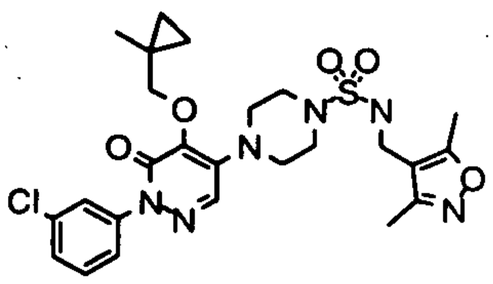
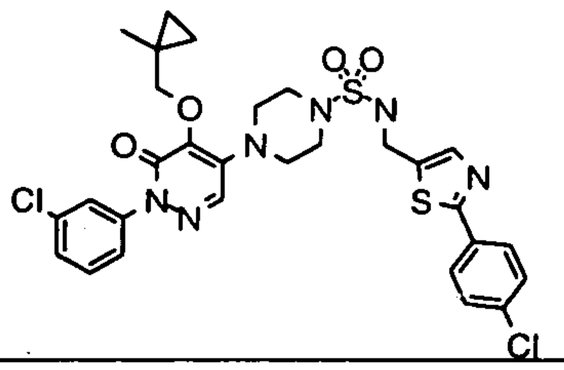
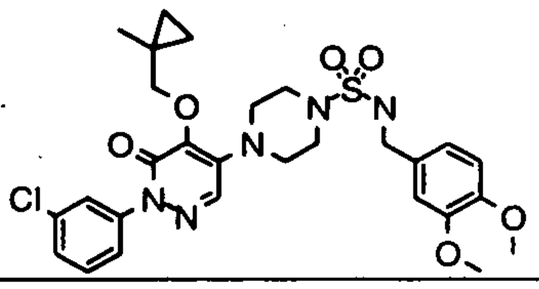
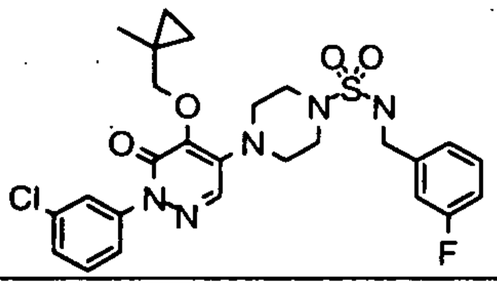
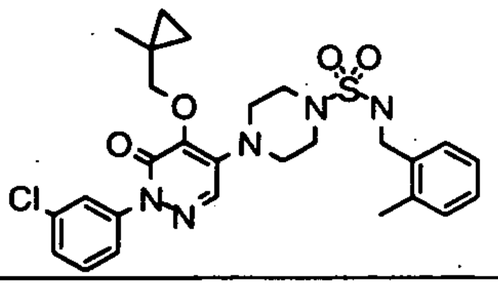
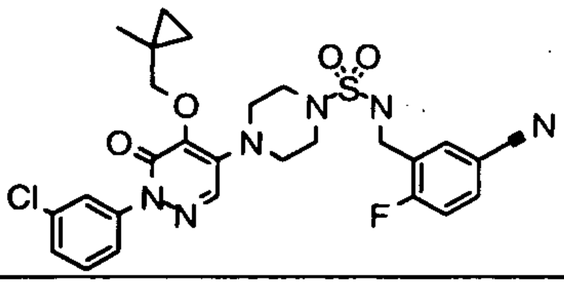
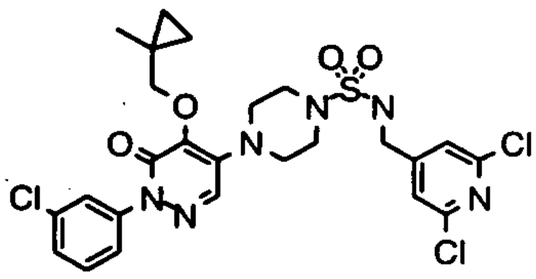
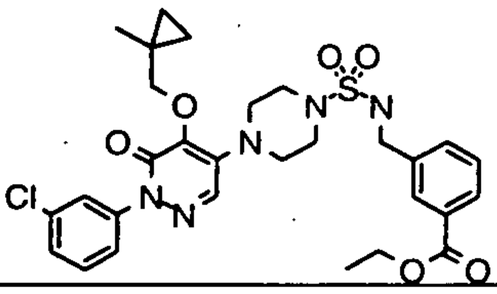
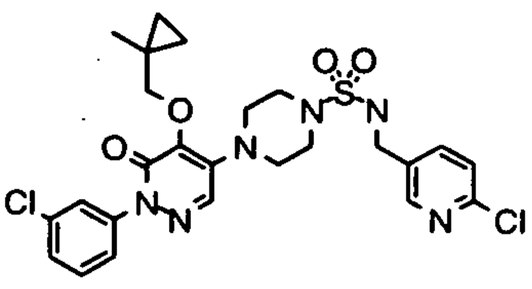
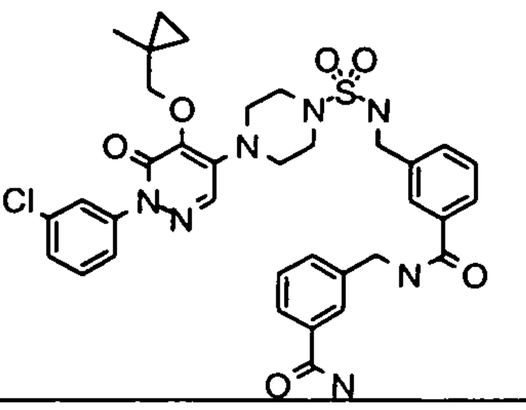
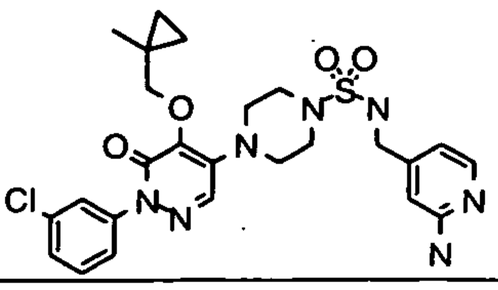
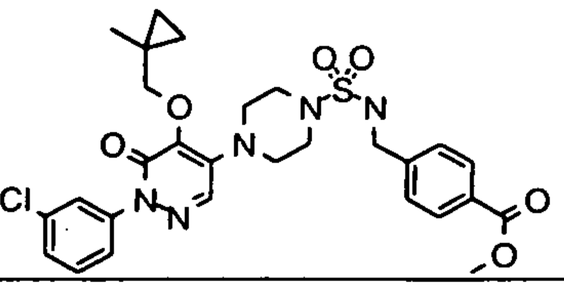
Table 29: Oxygen Analogues with Sulfamide Tails

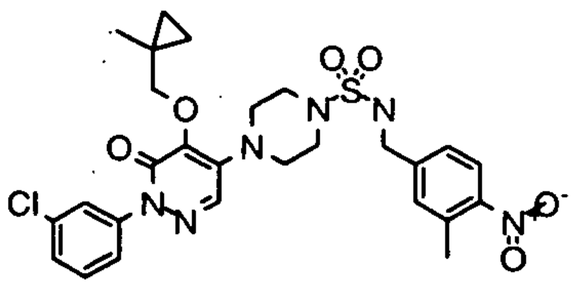
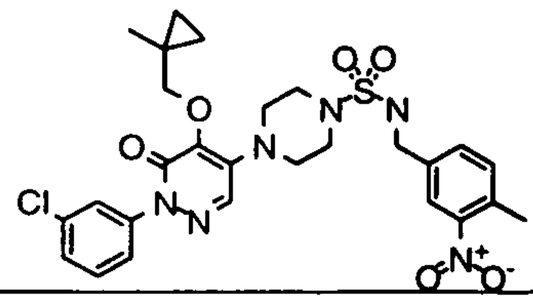
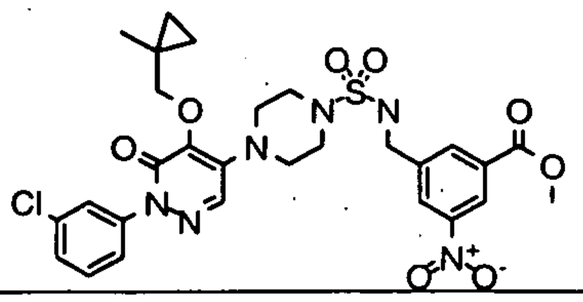
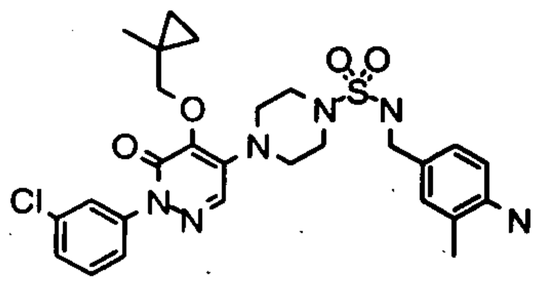
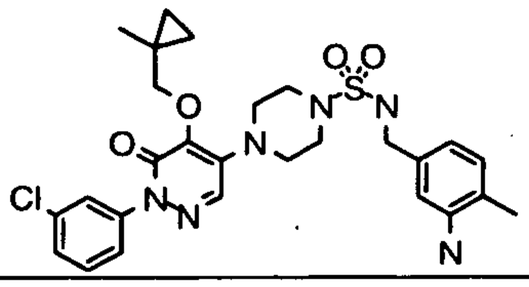
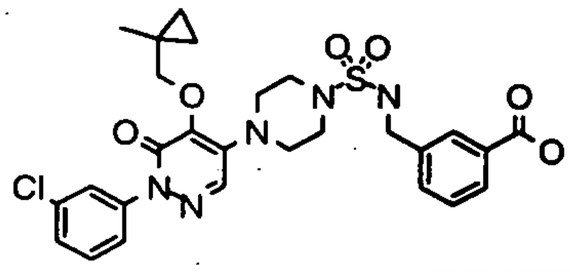
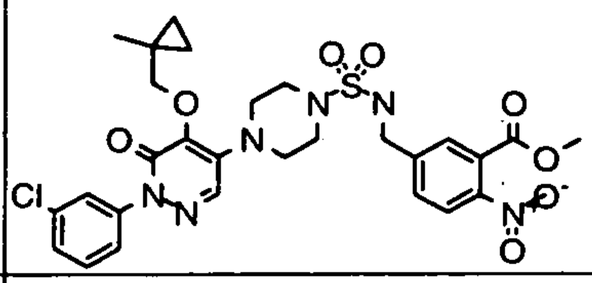
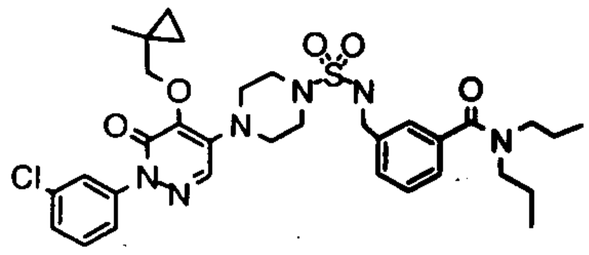
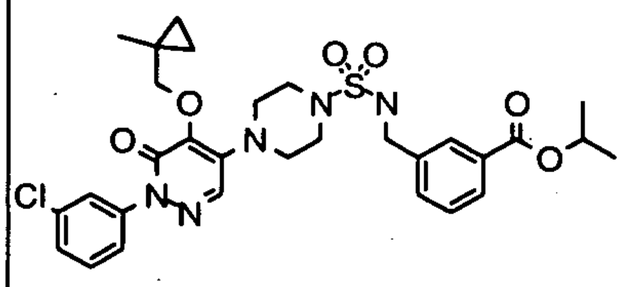
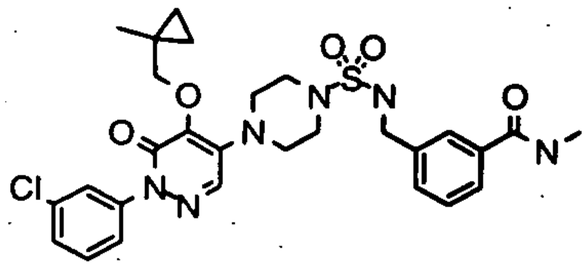
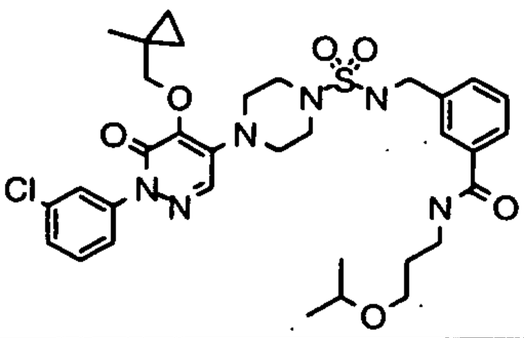
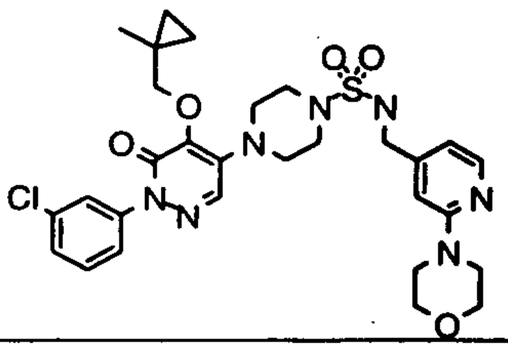
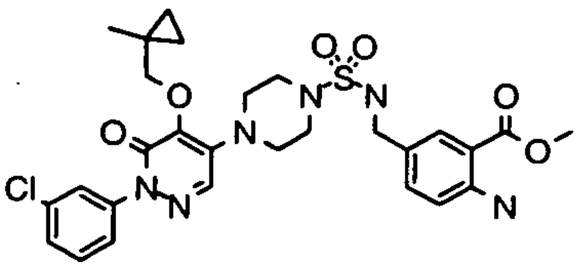
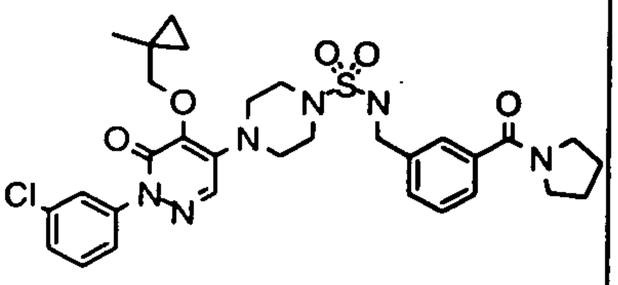
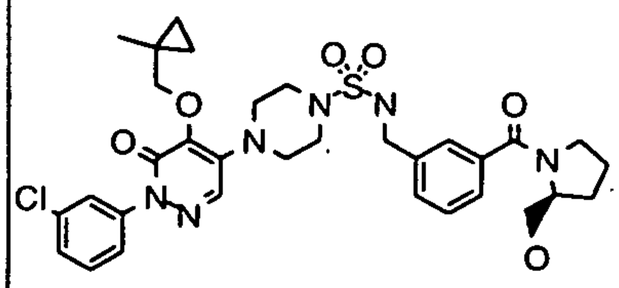
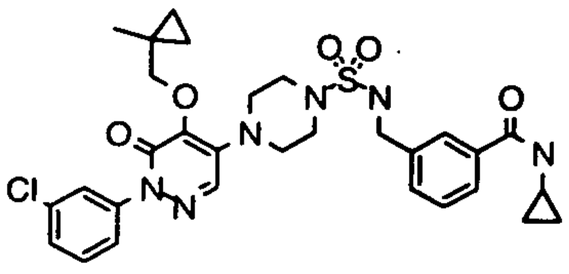
Using the procedures described above, the following compounds were synthesized.

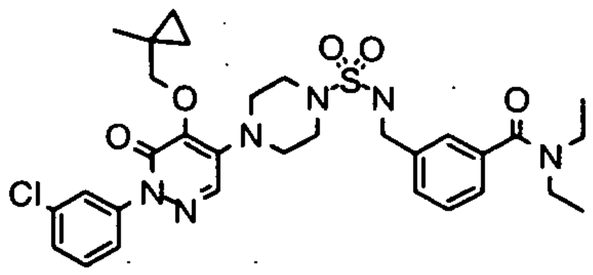
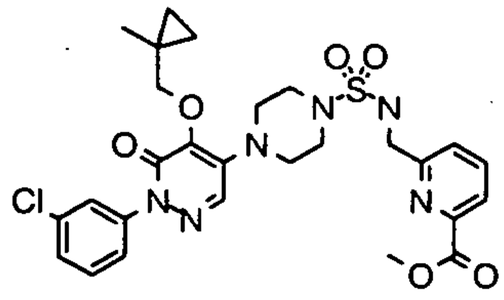
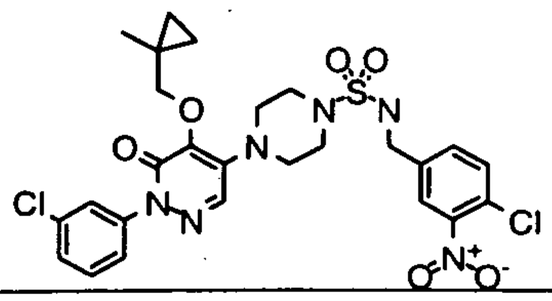
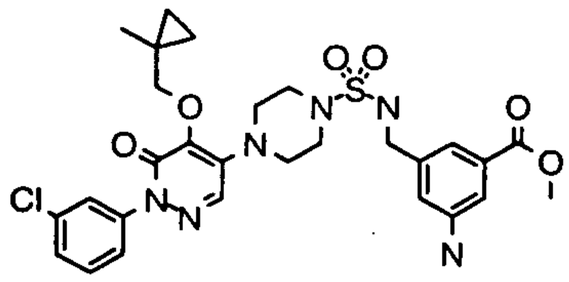
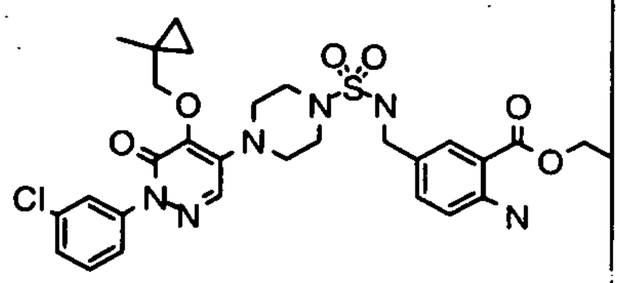
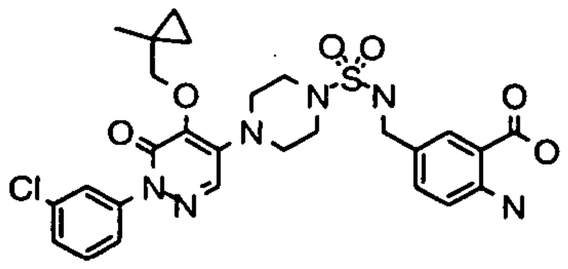
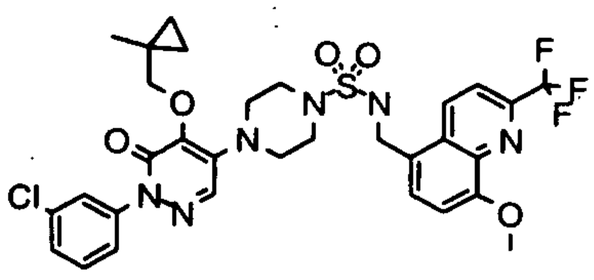
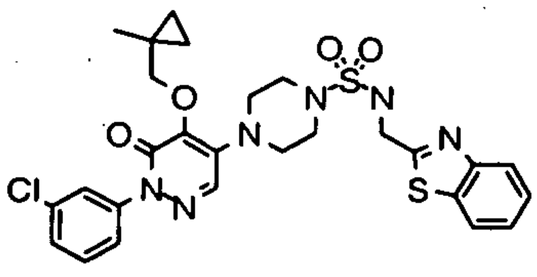
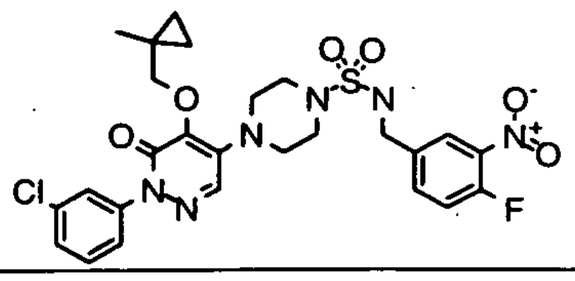
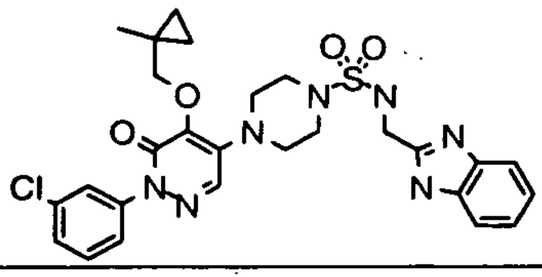
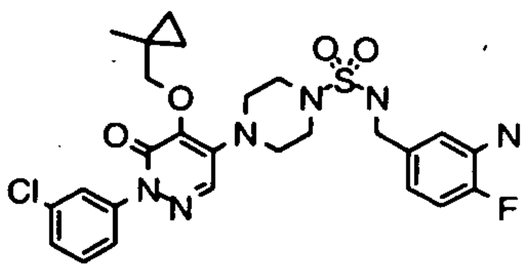
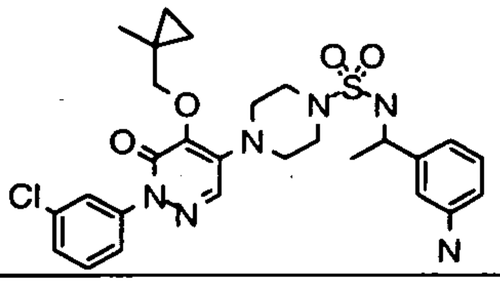
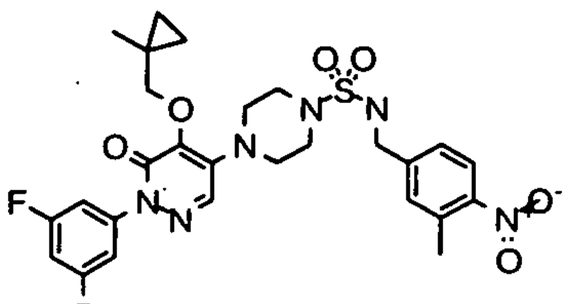
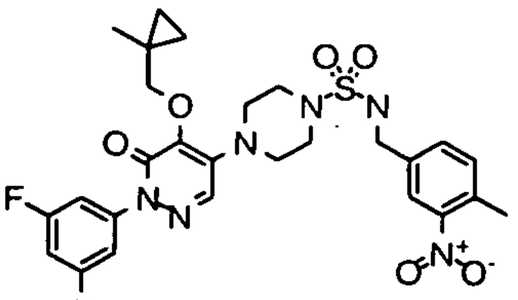
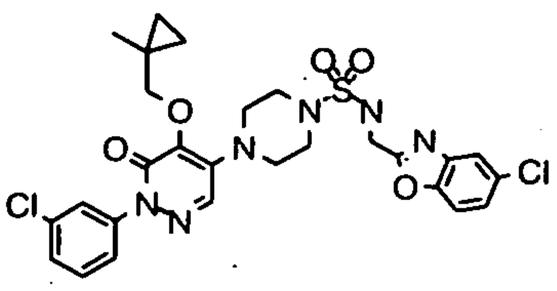
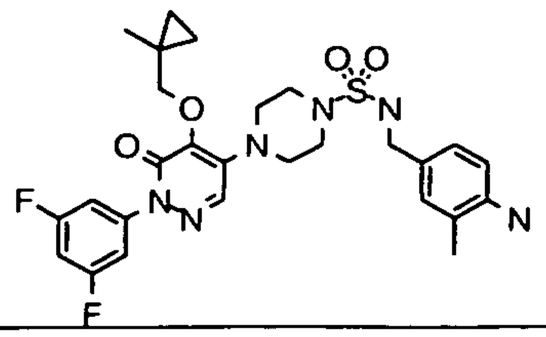
Comp. No.	Structure	MS M+1
1629Z		544 (M-1)
1630Z		582

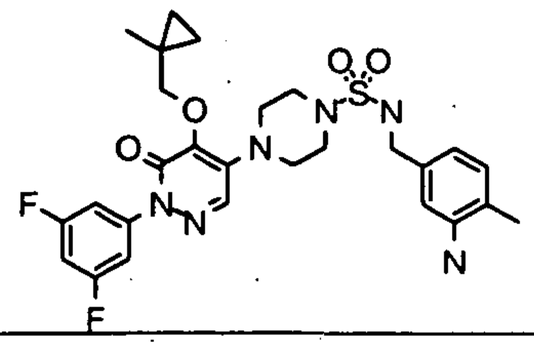
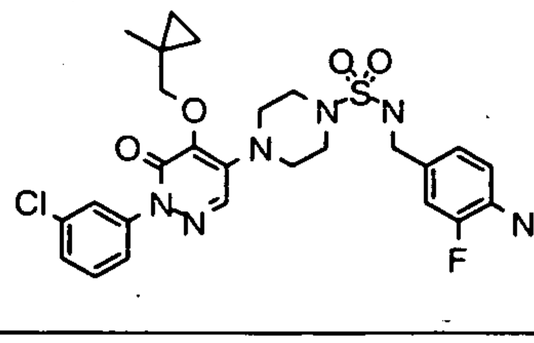
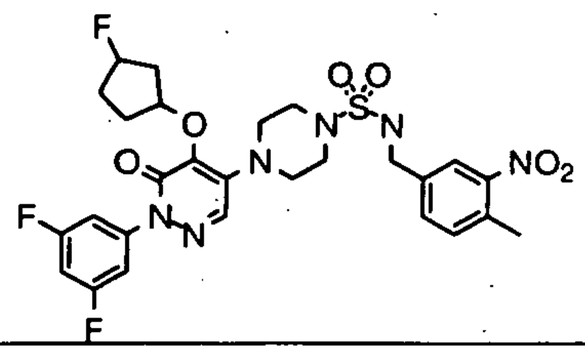
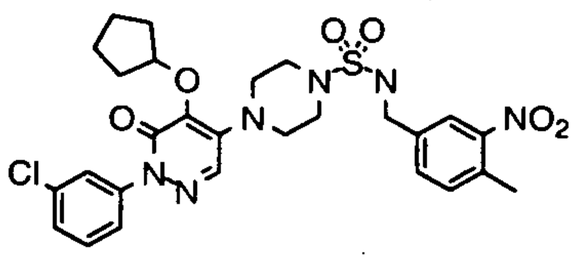
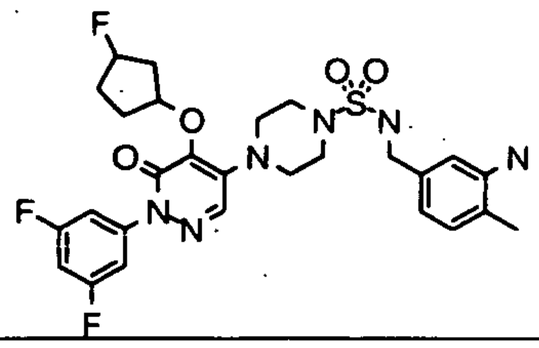
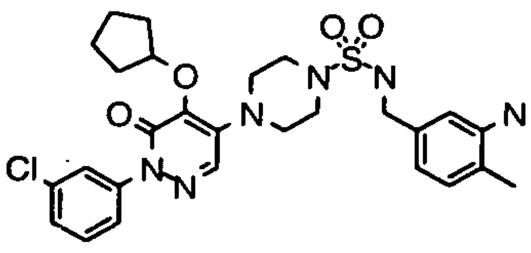
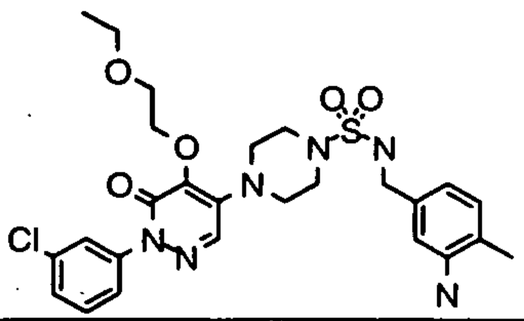
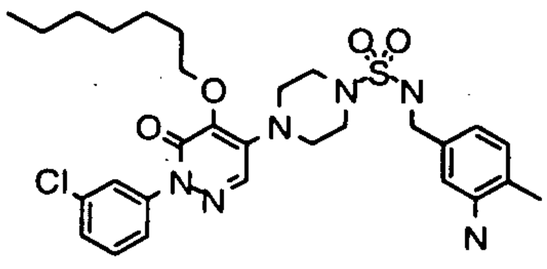
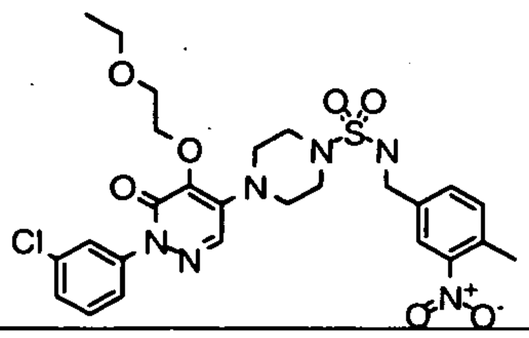
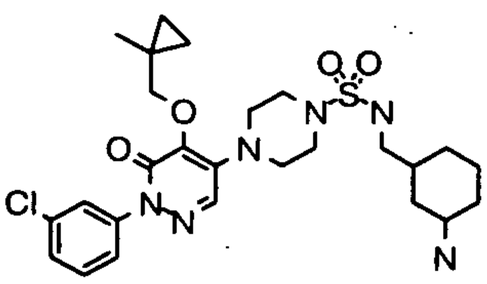
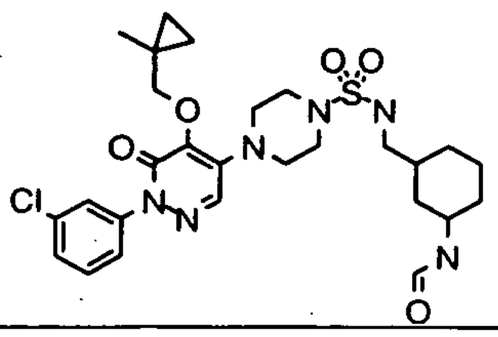
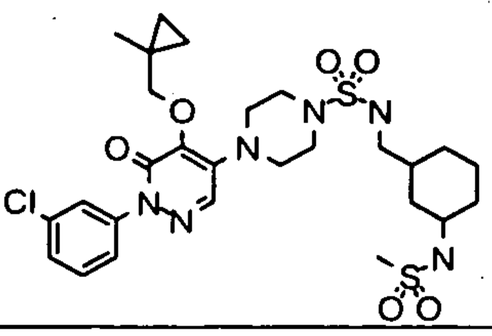
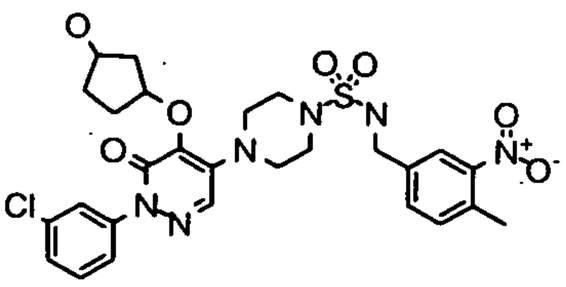
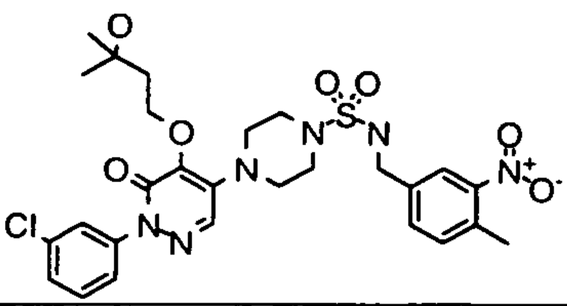
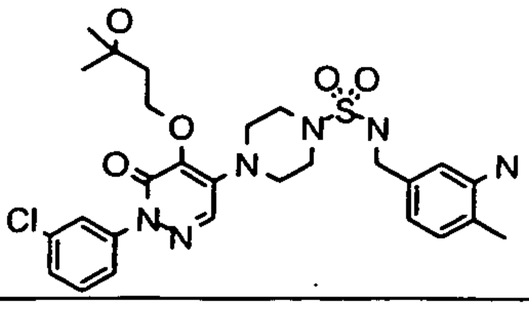
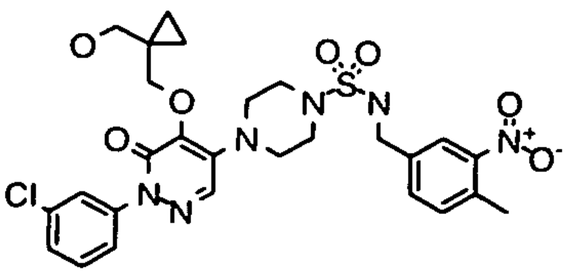
1631Z		571	1632Z		591
1633Z		576	1634Z		561
1635Z		632	1636Z		613
1637Z		591	1638Z		621
1639Z		612	1640Z		561
1641Z		547	1642Z		582
1643Z		547	1644Z		547
1645Z		591	1646Z		561

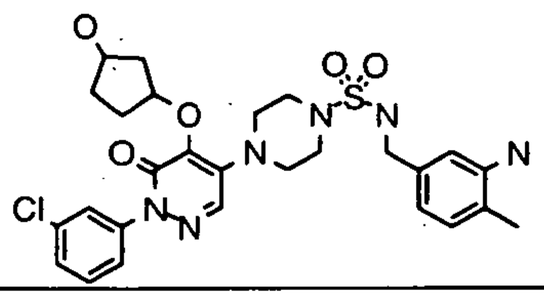
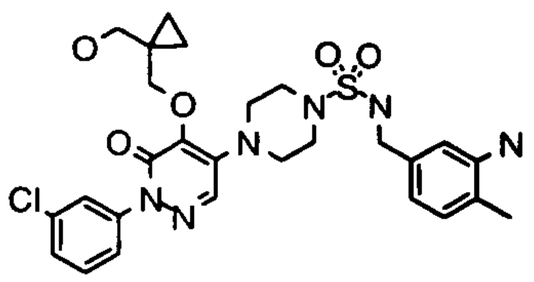
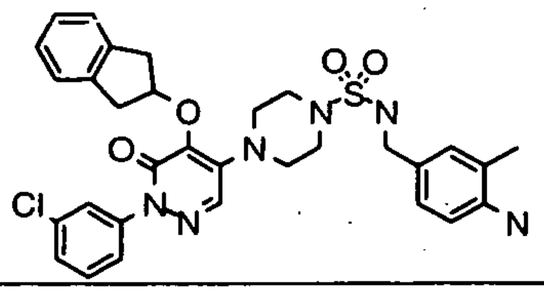
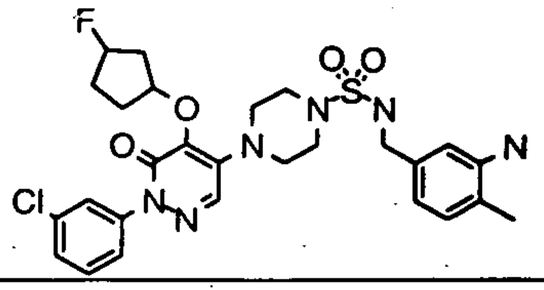
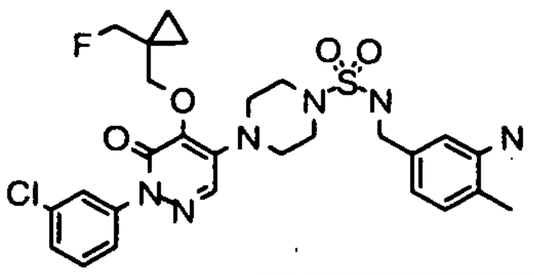
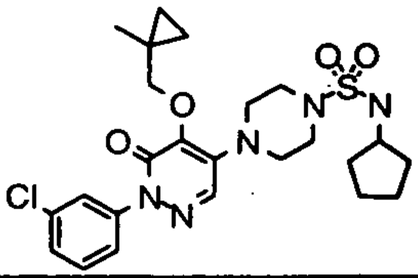
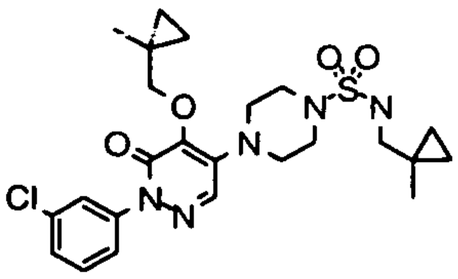
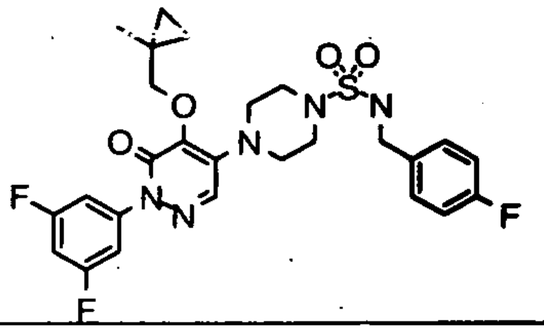
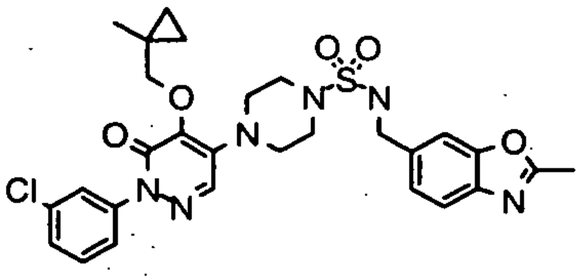
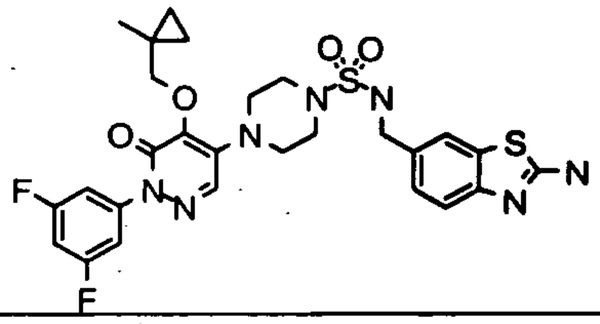
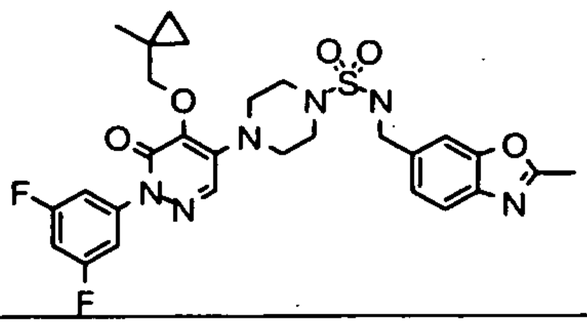
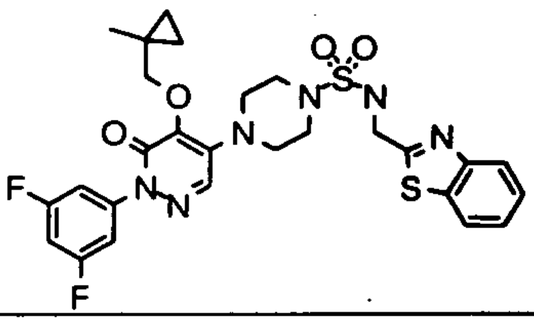
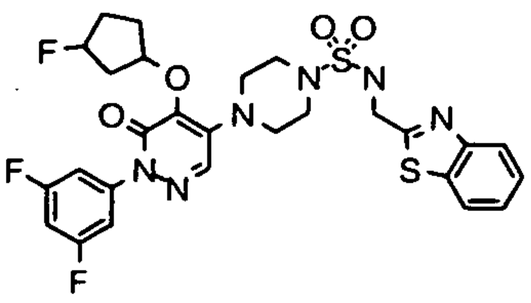
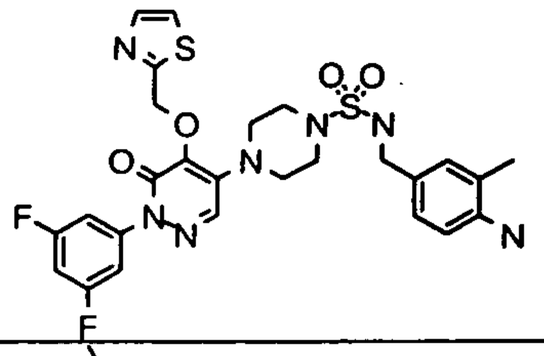
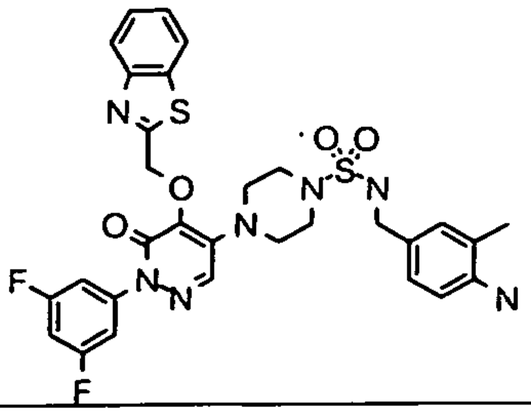
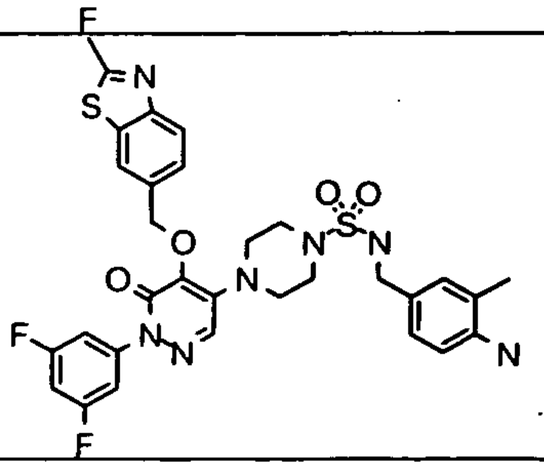
1647Z		588
1648Z		560
1649Z		619
1650Z		619
1651Z		555
1652Z		589
1653Z		555
1654Z		589
1655Z		561
1656Z		563
1657Z		595
1658Z		561
1659Z		563
1660Z		595
1661Z		602
1662Z		597

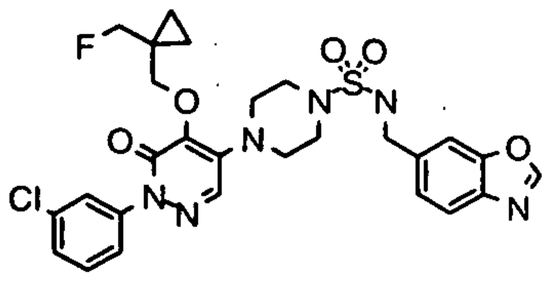
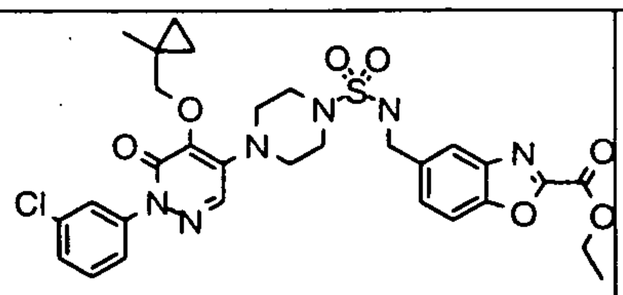
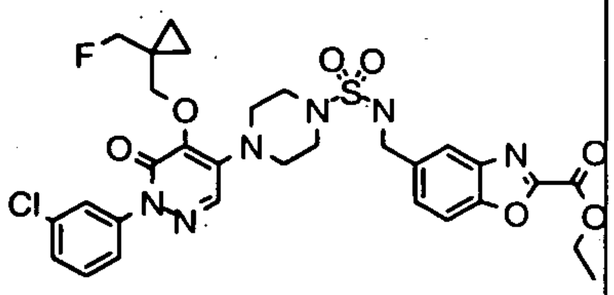
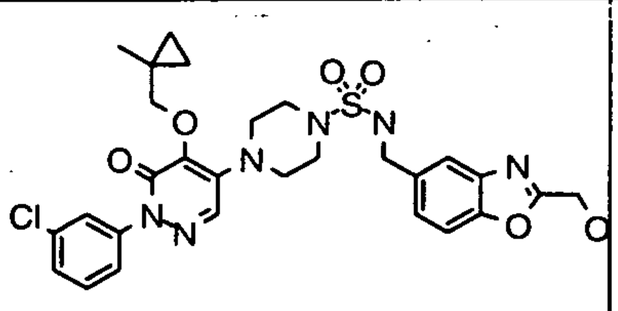
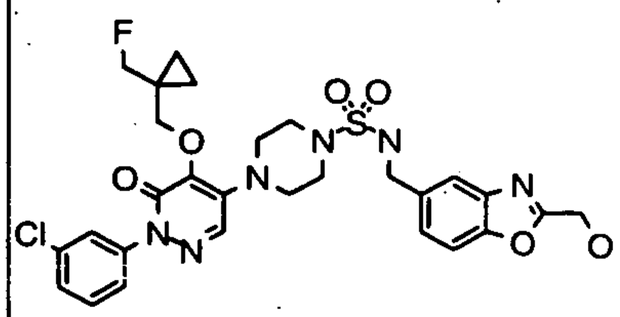
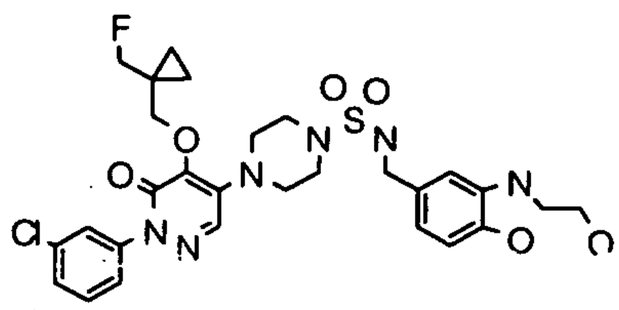
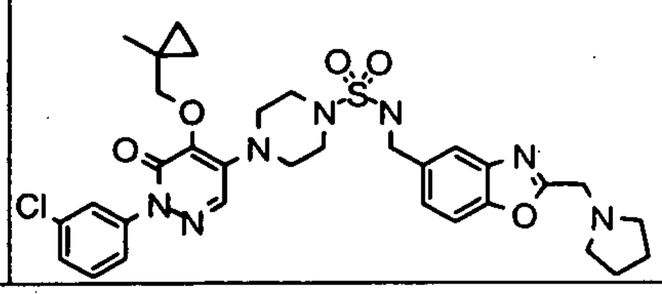
1663Z		569
1664Z		569
1665Z		575
1666Z		602
1667Z		563
1668Z		661
1669Z		604
1670Z		562
1671Z		558
1672Z		587
1673Z		615
1674Z		616
1675Z		579
1676Z		720
1677Z		560
1678Z		602

1679Z		603
1680Z		603
1681Z		647
1682Z		573
1683Z		573
1684Z		588
1685Z		647
1686Z		671
1687Z		630
1688Z		601
1689Z		687
1690Z		630
1691Z		617
1692Z		641
1693Z		671
1694Z		627

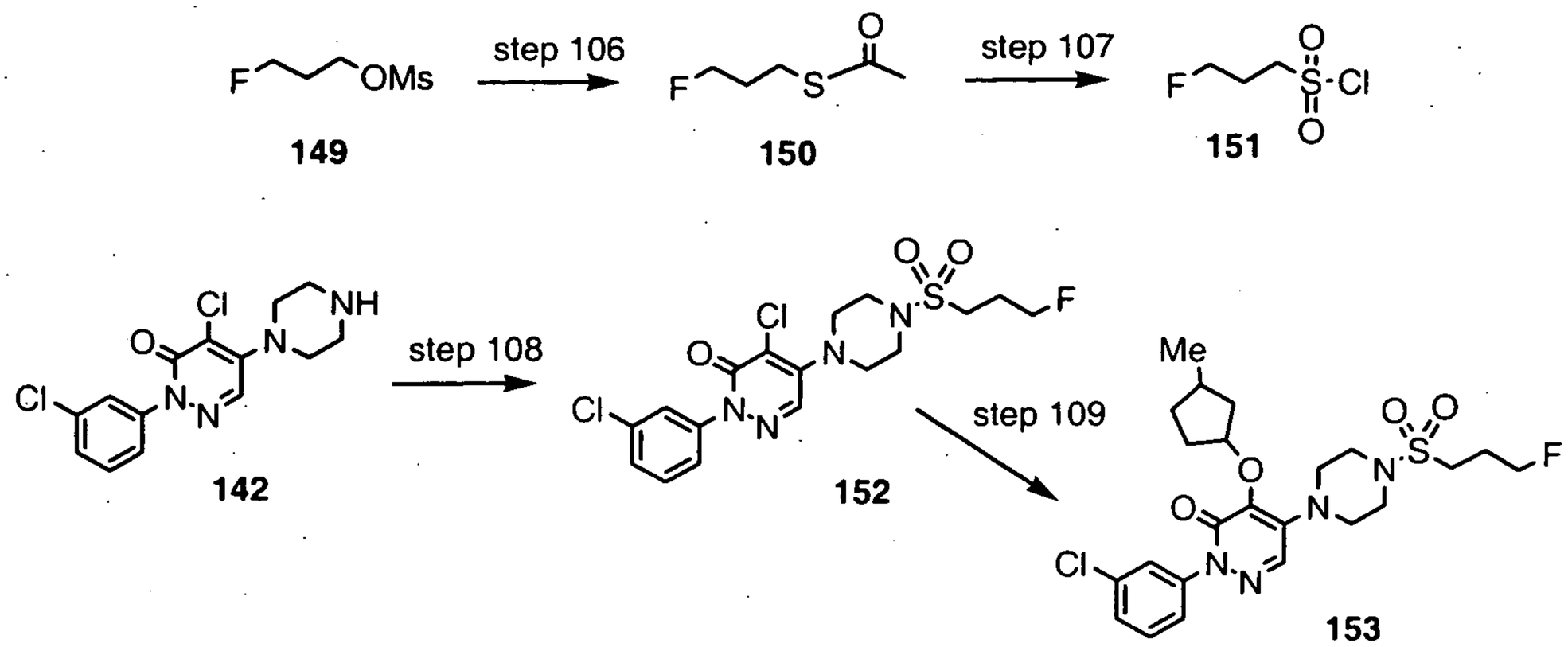
1695Z		643
1696Z		603
1697Z		623
1698Z		617
1699Z		631
1700Z		603
1701Z		693
1702Z		601
1703Z		607
1704Z		584
1705Z		577
1706Z		573
1707Z		605
1708Z		605
1709Z		621
1710Z		575

1711Z		575
1712Z		577
1713Z		623
1714Z		603
1715Z		593
1716Z		573
1717Z		577
1718Z		603
1719Z		607
1720Z		565
1721Z		593
1722Z		643
1723Z		619
1724Z		621
1725Z		591
1726Z		619

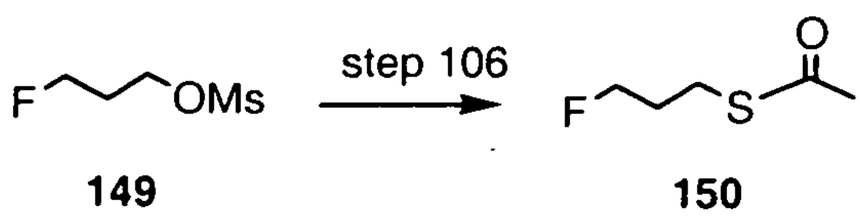
1727Z		589
1728Z		589
1729Z		621
1730Z		591
1731Z		591
1732Z		522
1733Z		522
1734Z		564
1735Z		599
1736Z		618
1737Z		601
1738Z		603
1739Z		621
1740Z		604
1741Z		654
1742Z		668

1743Z		603
1744Z		657
1745Z		675
1745Za		615
1745Zb		633
1745c		637
1745d		668

Scheme 32

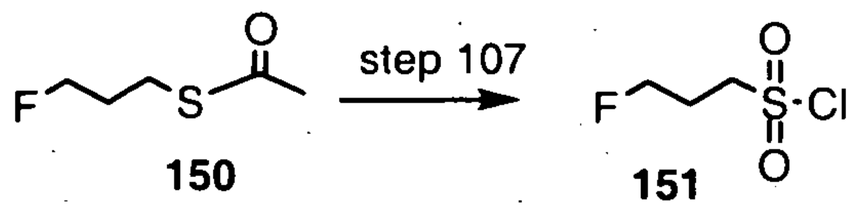


Step 106:



To a solution of fluoropropyl methylsulfonate **149** (4.7g, 30 mmol) in DMF (40 mL) was added potassium thioacetate (7 g, 60 mmol) at room temperature. The reaction mixture was warmed to 70 °C for 12 h. After cooling to room temperature, saturated aqueous NH_4Cl solution was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (eluant: 25% EtOAc -hexane) gave 5.2 g (100% yield) of the product **150** as a colorless liquid.

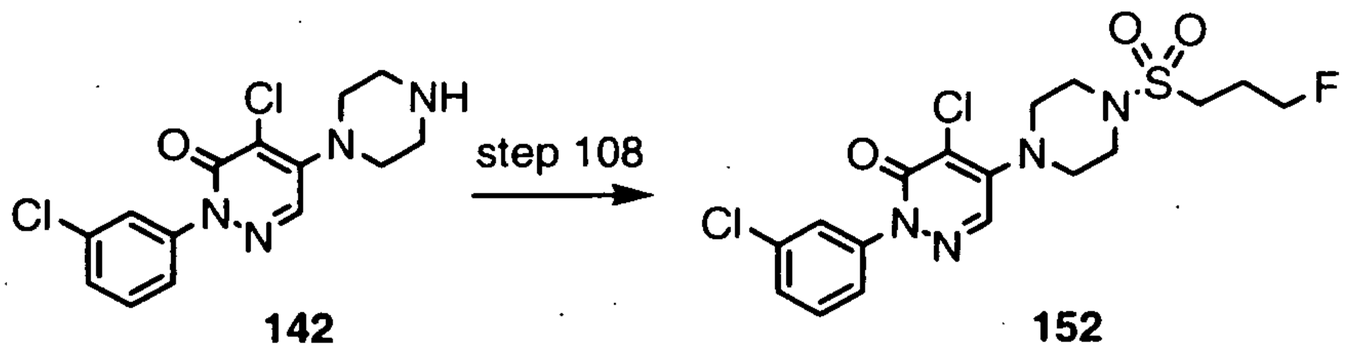
Step 107:



150 **151**

Chlorine gas was bubbled through a stirred solution of fluoropropyl thioacetate **150** (2 g, 14.7 mmol) in CH_2Cl_2 (30 mL) and H_2O (6 mL) at 6 °C to 9 °C. After compound **150** was completely consumed, water and CH_2Cl_2 were added, and the CH_2Cl_2 layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give 2.3 g (100% yield) of the product **151** as a colorless liquid.

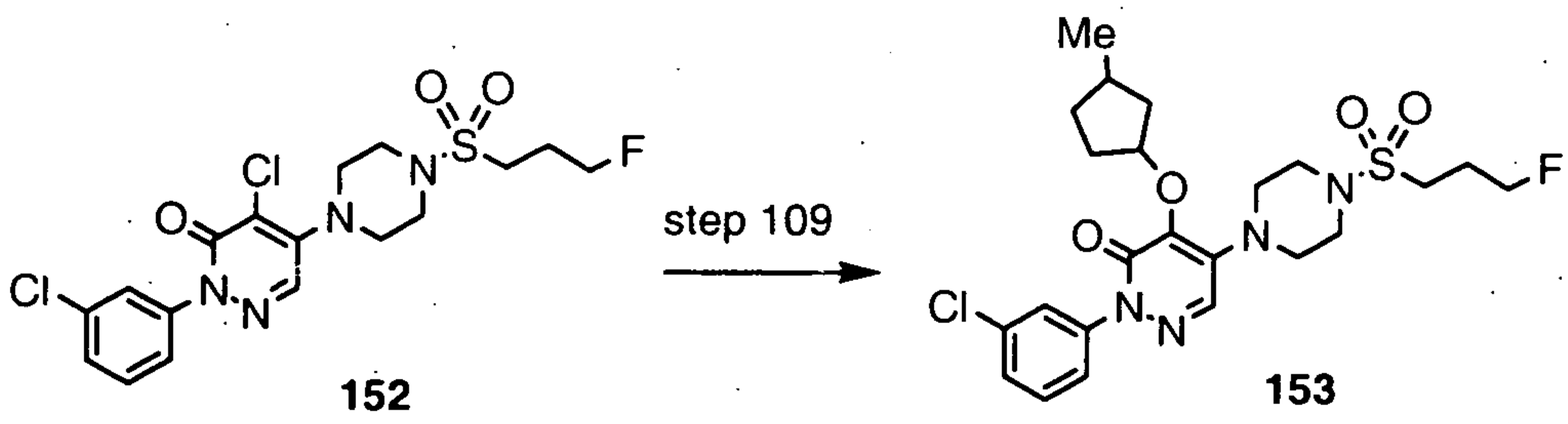
Step 108:



142 **152**

To a suspension of chloropyridazinone **142** (468 mg, 1.29 mmol, HCl salt) in CH_2Cl_2 (5 mL) at 0 °C was added iPr_2NEt (673 uL, 3.87 mmol) followed by the addition of fluoropropylsulfonyl chloride **151** (250 mg, 1.55 mmol) in CH_2Cl_2 (2.5 mL) over 2 mins. After 2 h at 0 °C and 1.5 h at room temperature, water was added to the reaction mixture, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide 560 mg (96% yield) of the product **152** as a white solid. MS (M+1): 449.

Step 109:

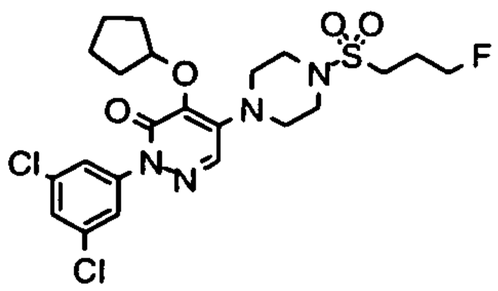
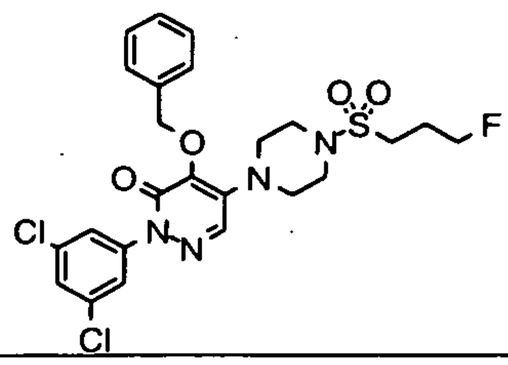
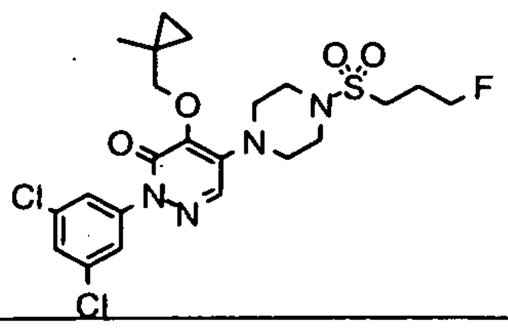
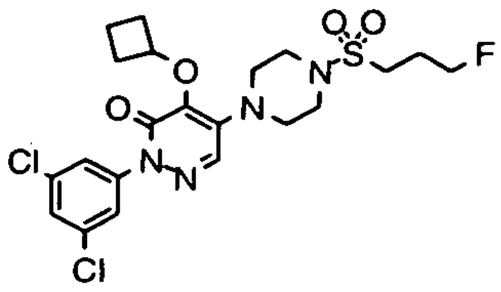
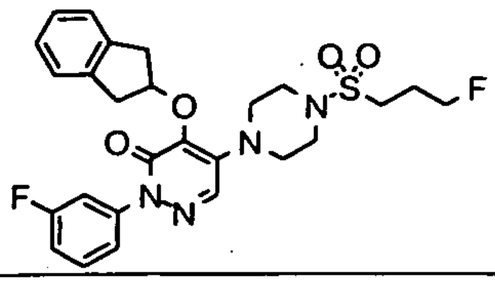
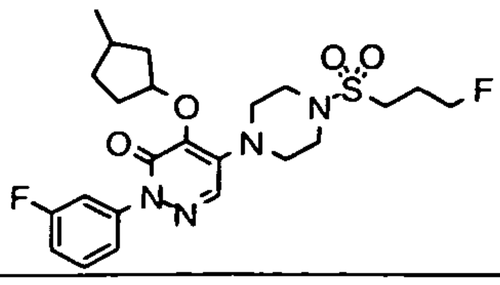


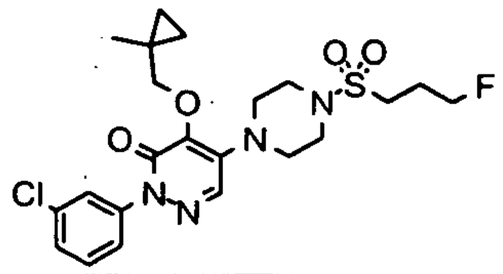
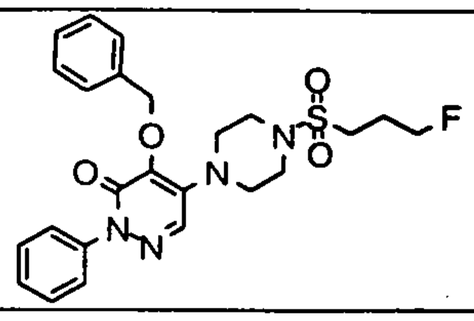
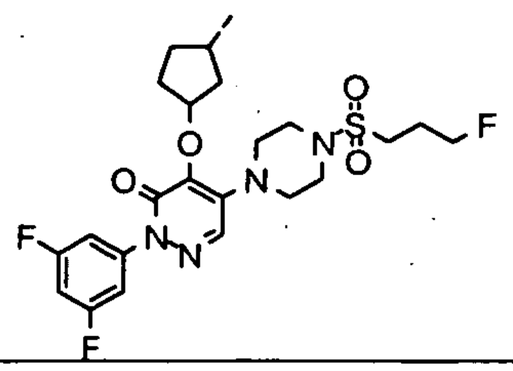
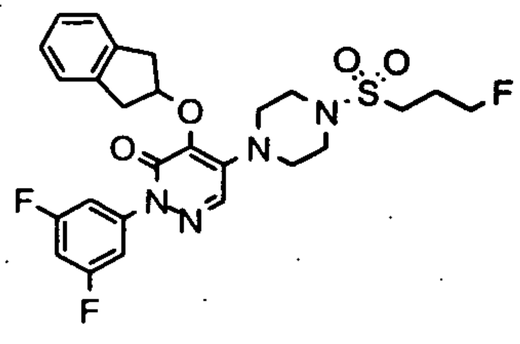
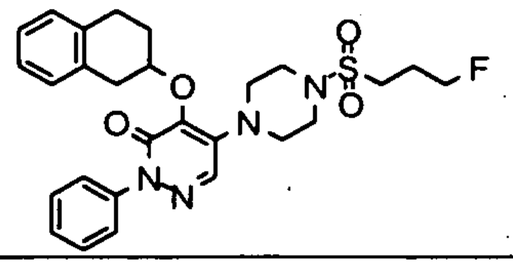
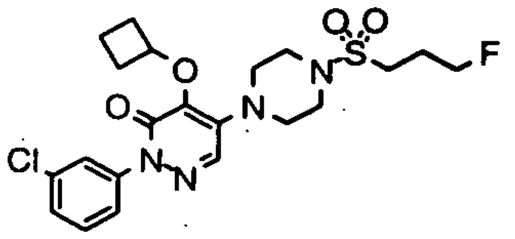
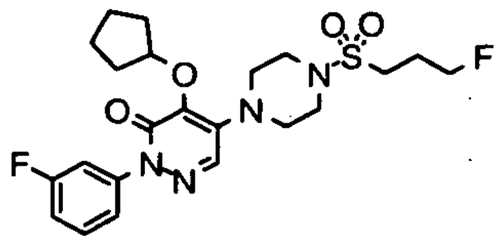
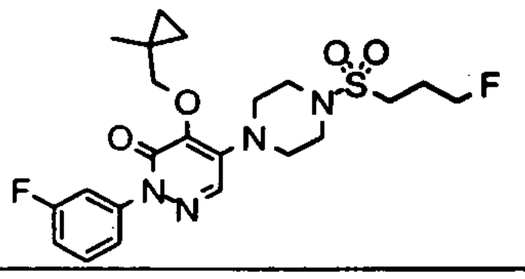
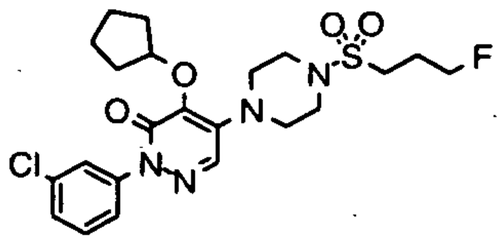
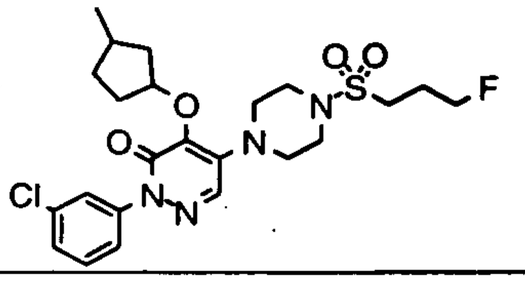
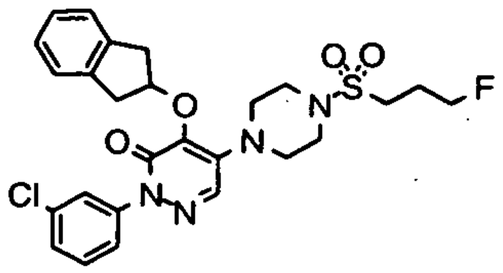
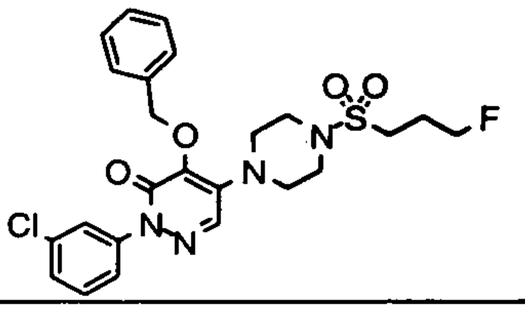
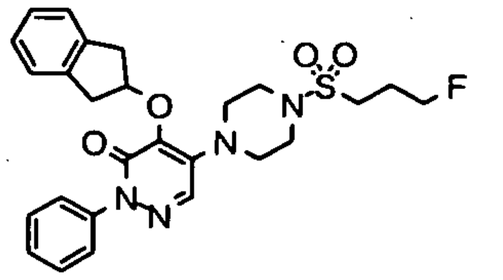
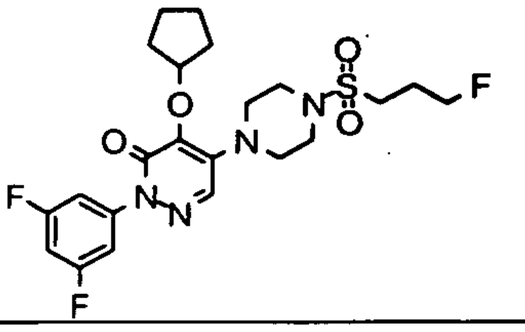
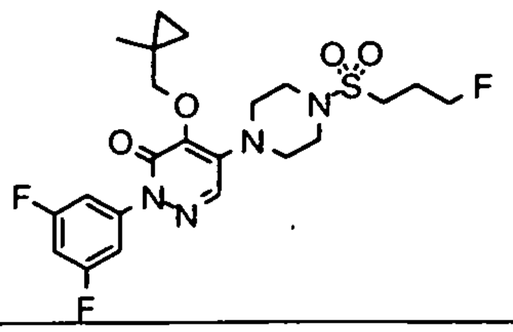
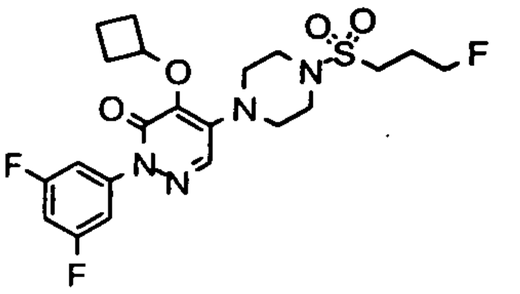
152 153

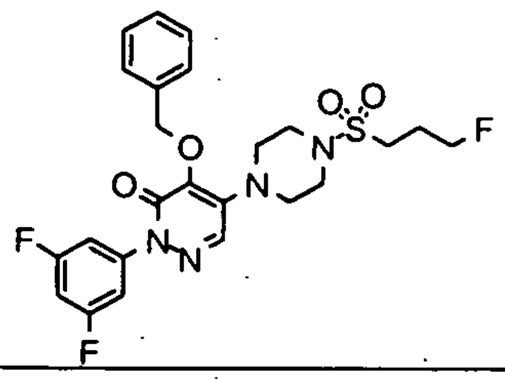
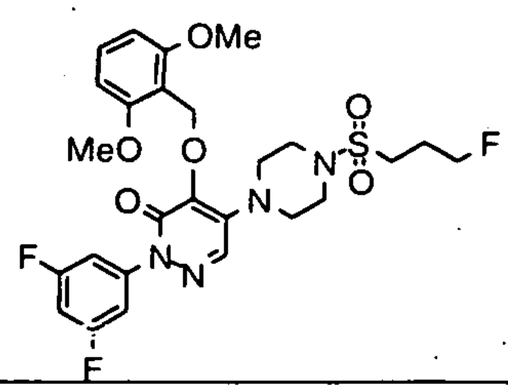
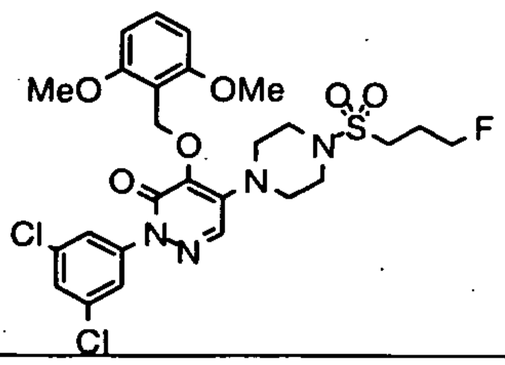
To a solution of 3-methylcyclopentanol (95 mg, 0.21 mmol) in THF (3 mL) at room temperature was added $NaN(TMS)_2$ (0.63 mL, 0.63 mmol) over 2 mins. After 15 mins, dichloropyridazinone **152** was added as a solid in one portion. The reaction mixture was stirred for 1 h and quenched with saturated aqueous NH_4Cl solution, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 82 mg (80% yield) of the product **153** as a white solid. MS (M+1): 513.

Using the procedures described above, the following compounds were synthesized.

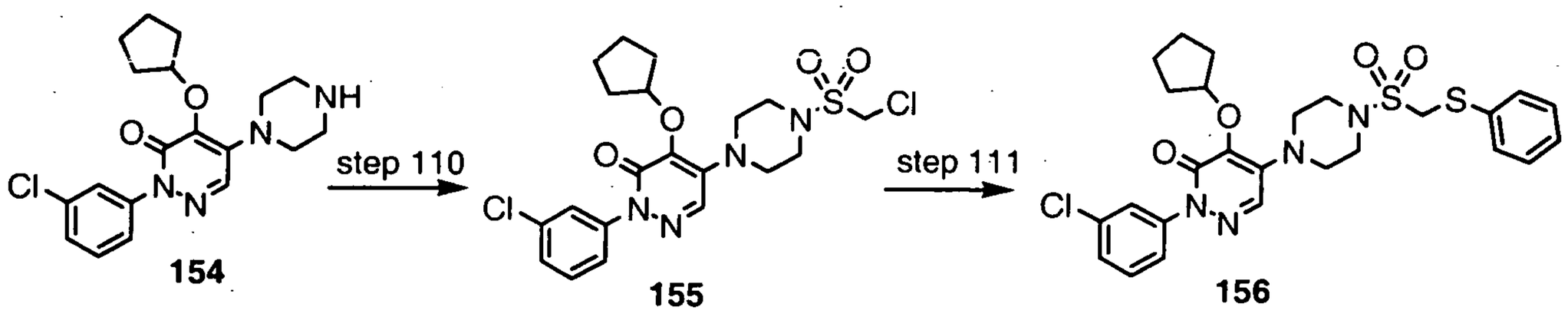
Table 30: Oxygen Analogues with Fluoropropyl Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1746Z		533	1747Z		555
1748Z		533	1749Z		519
1750Z		531	1751Z		497

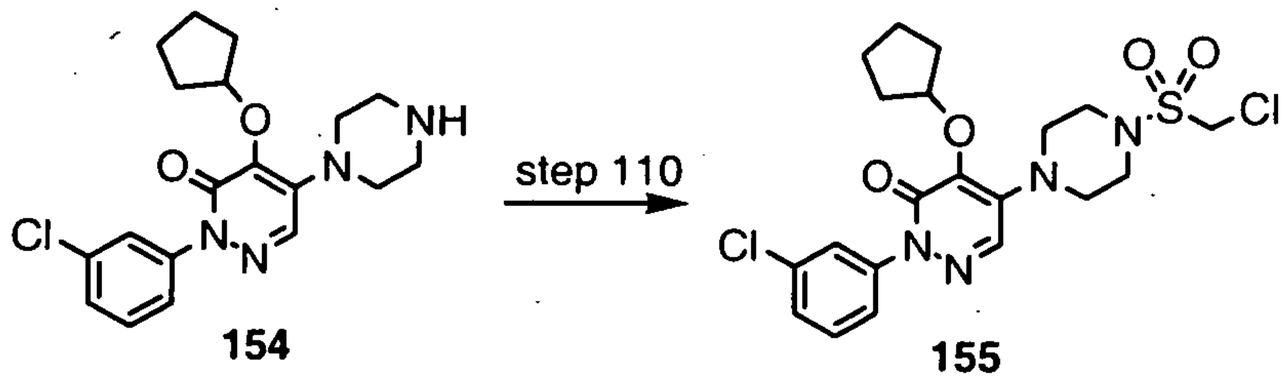
1752Z		499		1753Z		487
1754Z		515		1755Z		549
1756Z		527		1757Z		485
1758Z		483		1759Z		483
1760Z		499		1761Z		513
1762Z		547		1763Z		521
1764Z		513		1765Z		501
1766Z		501		1767Z		487

1768Z		523		1769Z		583
1770Z		614				

Scheme 33

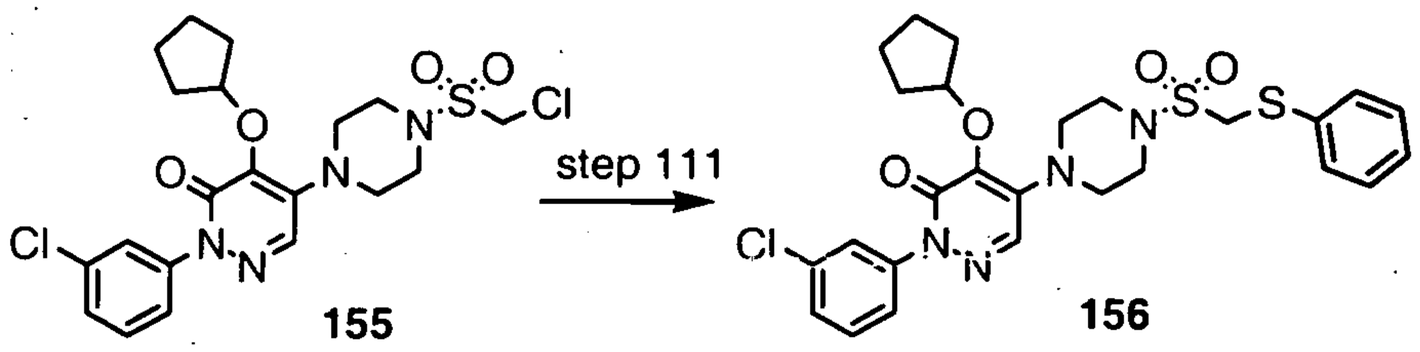


Step 110:



To a suspension of chloropyridazinone **154** (1.95 g, 4.74 mmol, HCl salt) in CH_2Cl_2 (30 mL) at -35 °C was added iPr_2NEt (2.06 mL, 11.85 mmol) followed by the addition of chloromethylsulfonyl chloride (918 mg, 6.16 mmol) in CH_2Cl_2 (20 mL) over 20 mins. After 2h at -35 °C to -10 °C, water was added to the reaction mixture and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was washed with 1 N HCl, brine, dried (Na_2SO_4), filtered, and concentrated. Purification by ISCO silica gel chromatography (eluant: EtOAc -hexane) gave 1.5 g (65% yield) of the product **155** as a white foam. MS (M+1): 487.

Step 111:

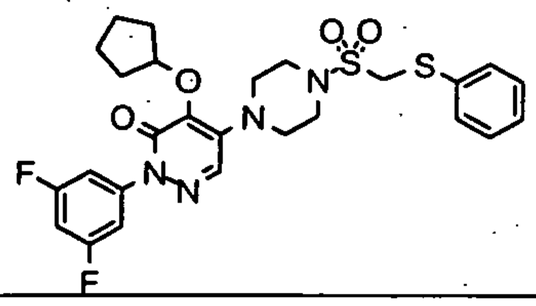
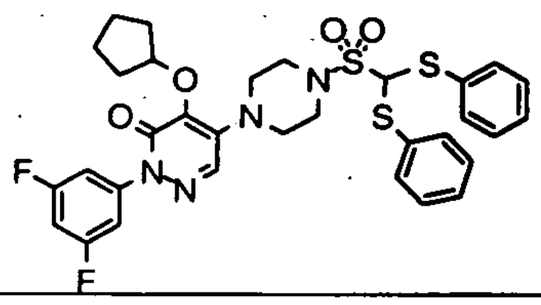
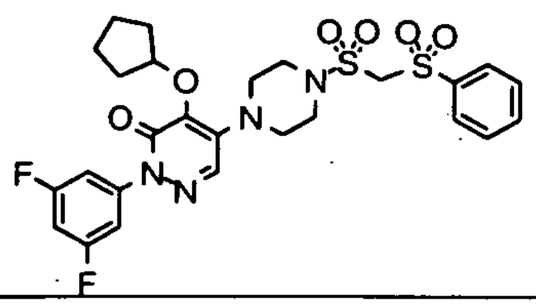
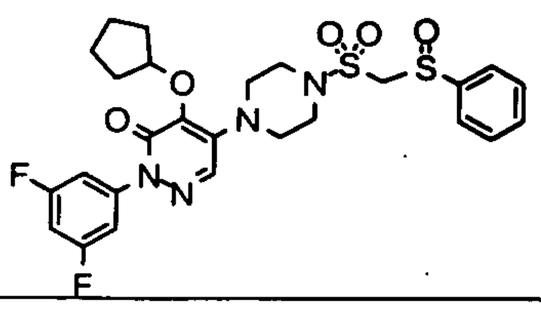
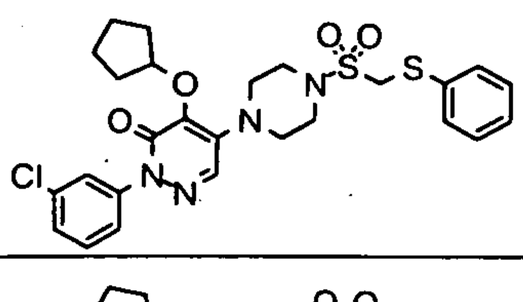
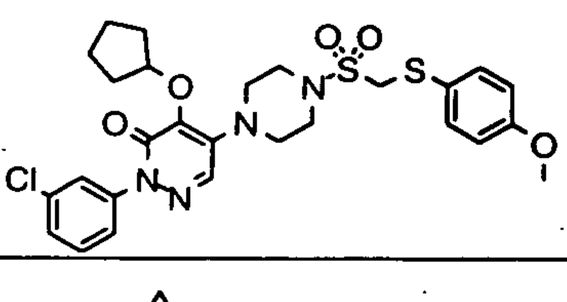
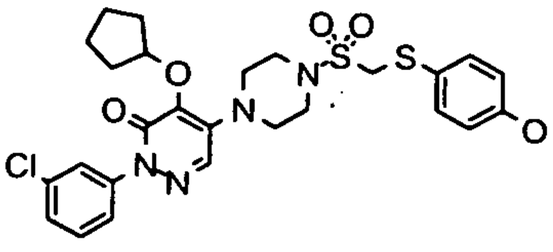
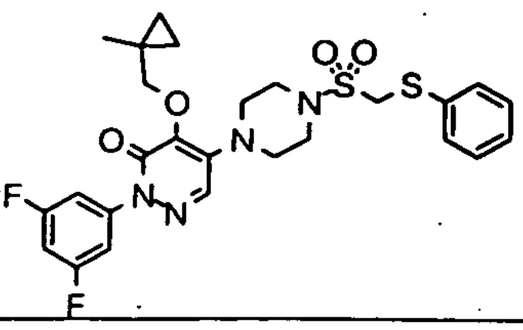


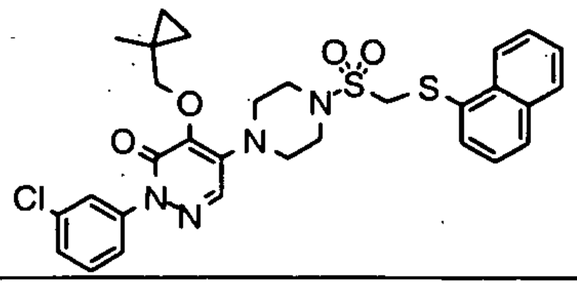
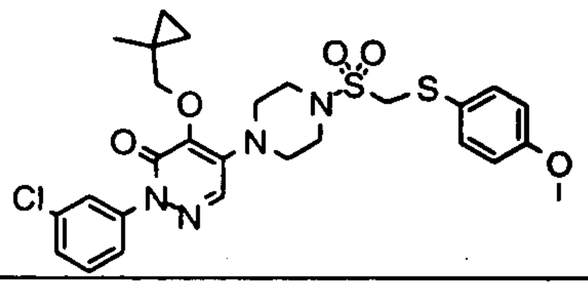
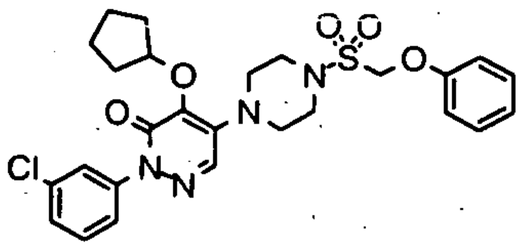
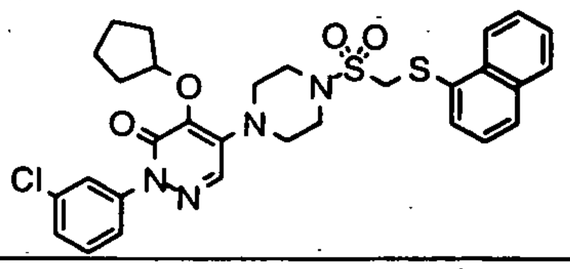
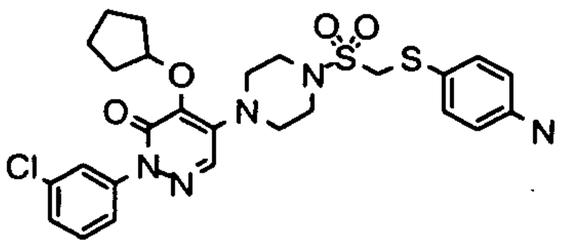
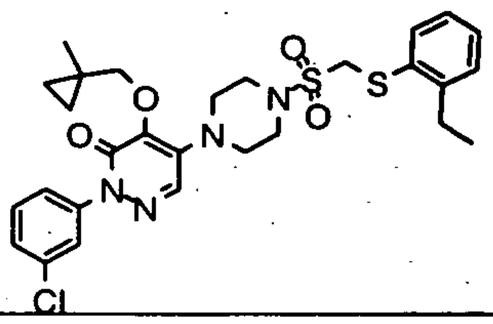
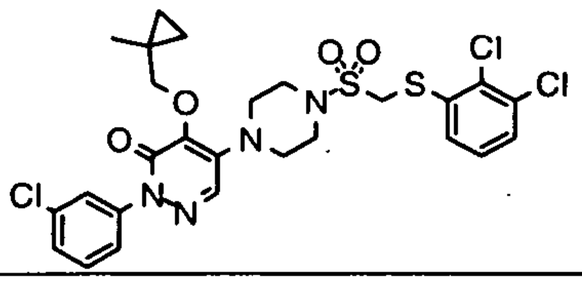
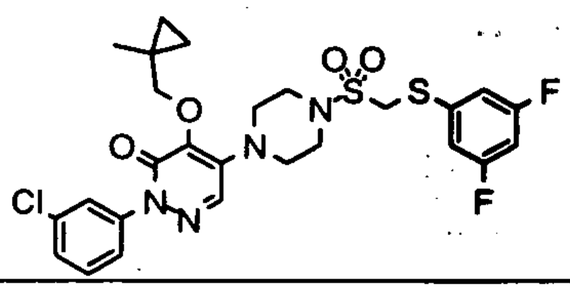
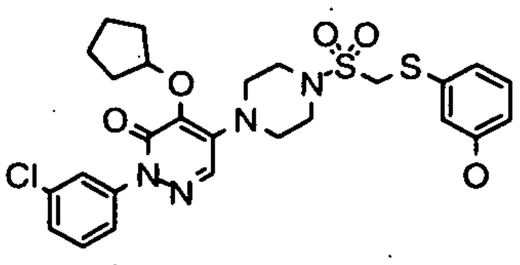
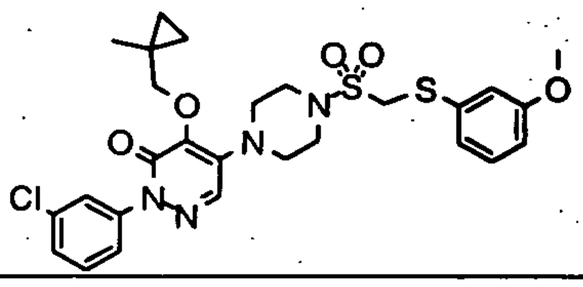
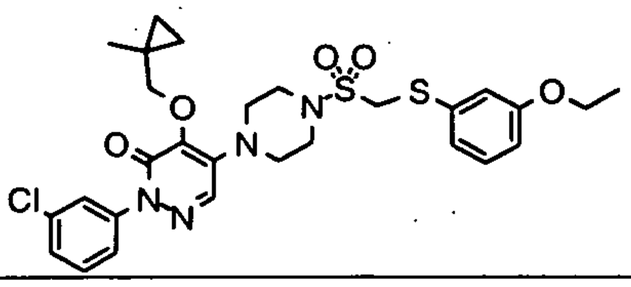
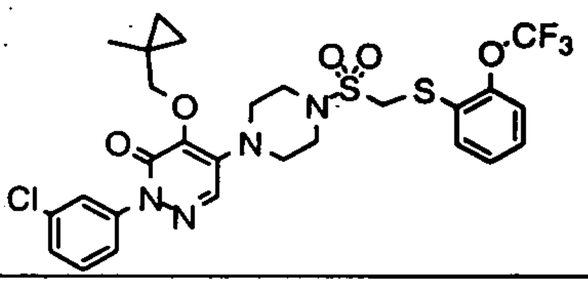
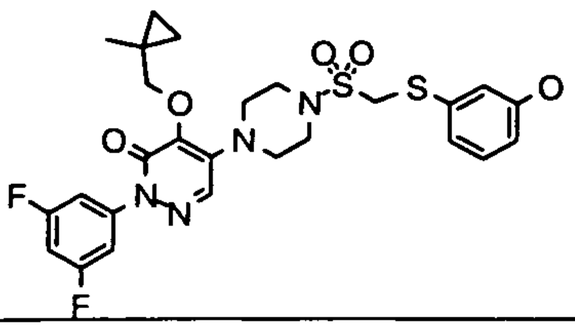
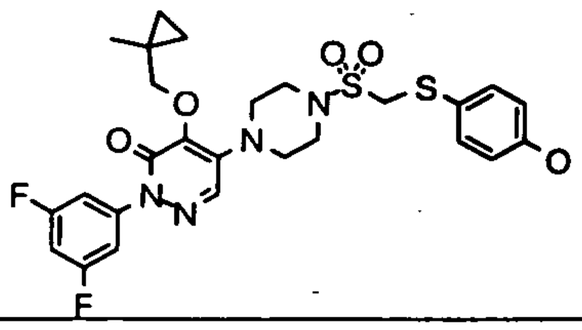
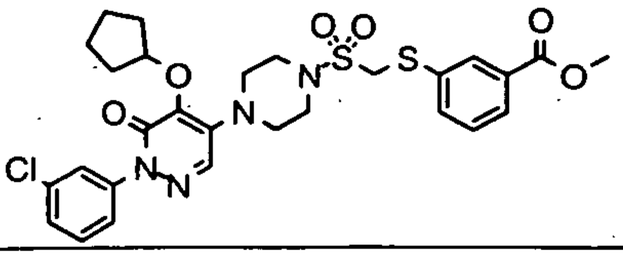
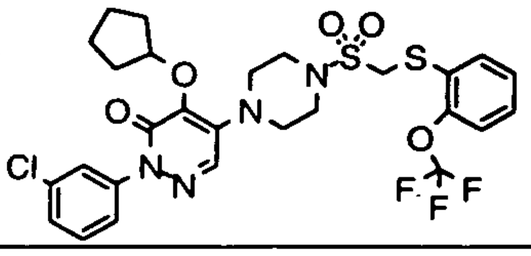
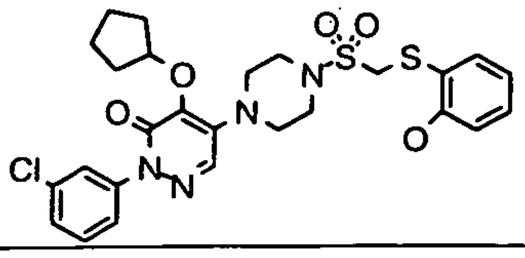
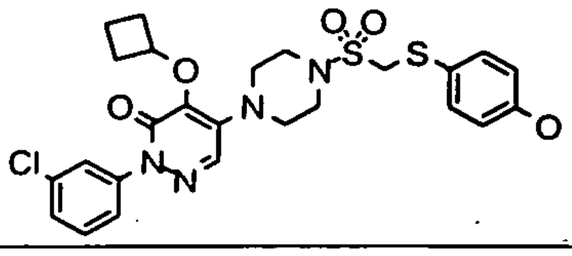
155 156

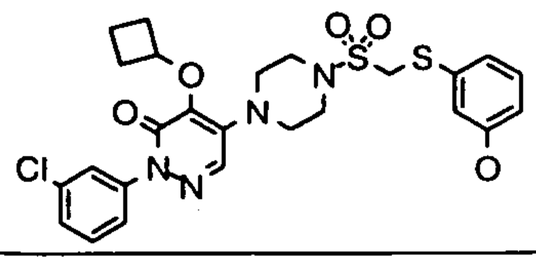
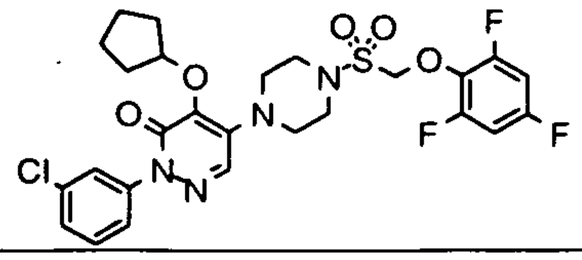
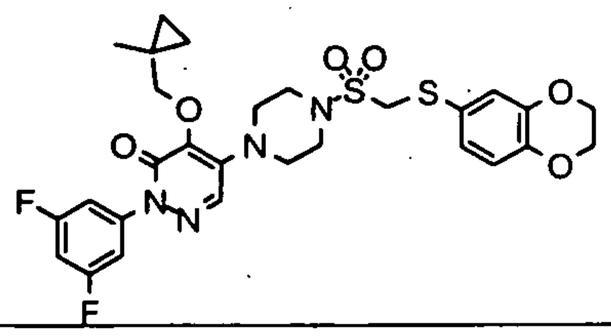
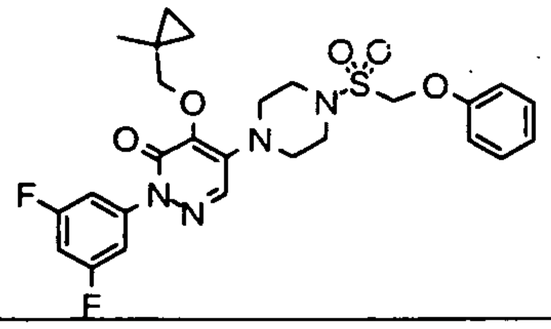
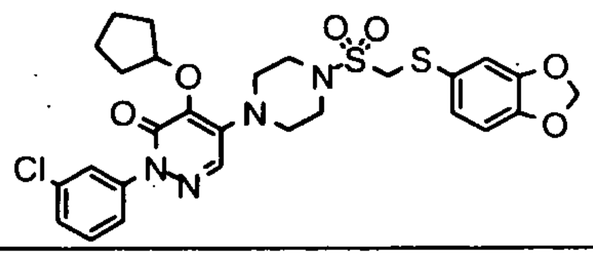
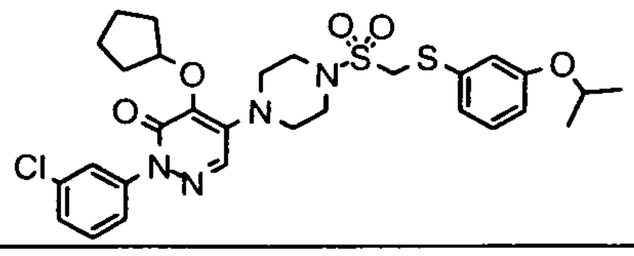
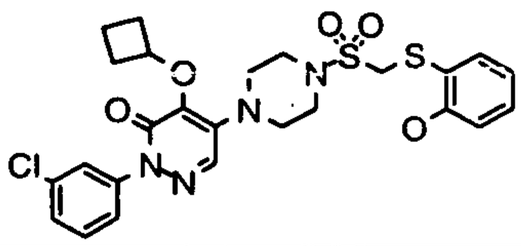
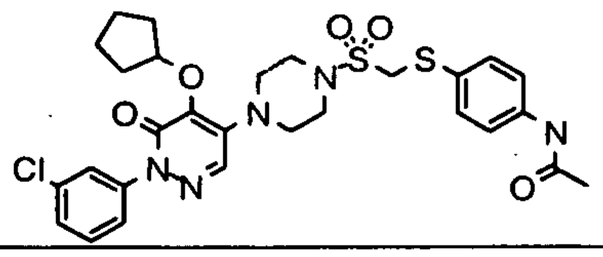
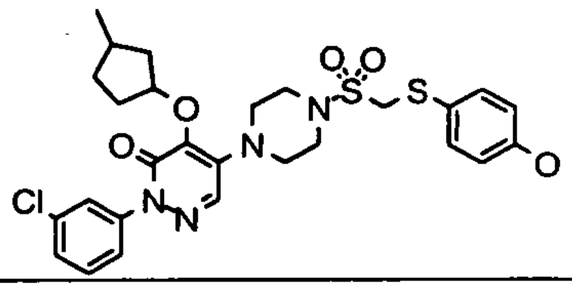
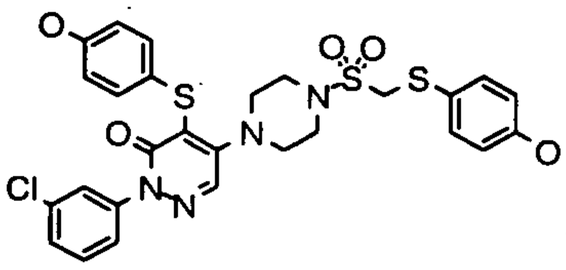
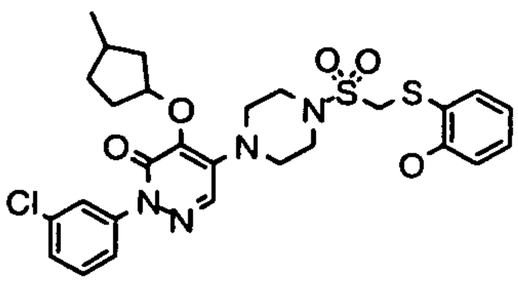
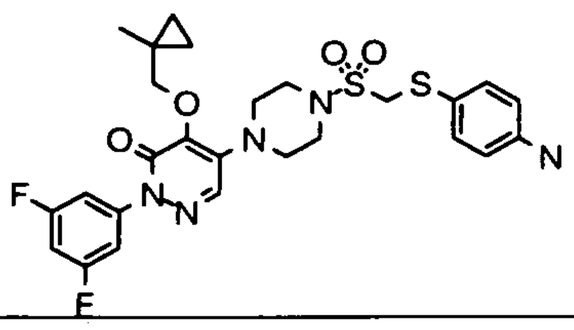
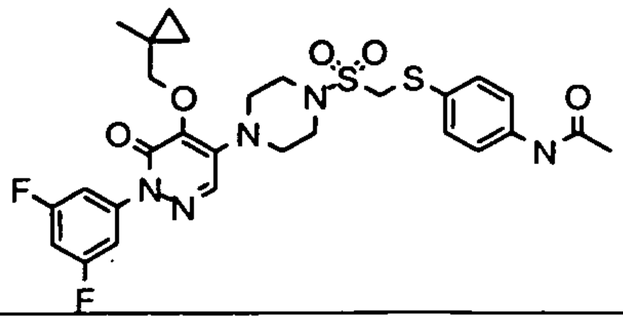
A reaction mixture of chloropyridazinone **155** (292 mg, 0.6 mmol), thiophenol (79 mg, 0.72 mmol) and K_2CO_3 (124 mg, 0.9 mmol) in DMF (3 mL) was heated to 80 °C for 30 mins via microwave irradiation. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 242 mg (72% yield) of the product **156** as a white solid. MS (M+1): 561.

Using the procedures described above, the following compounds were synthesized.

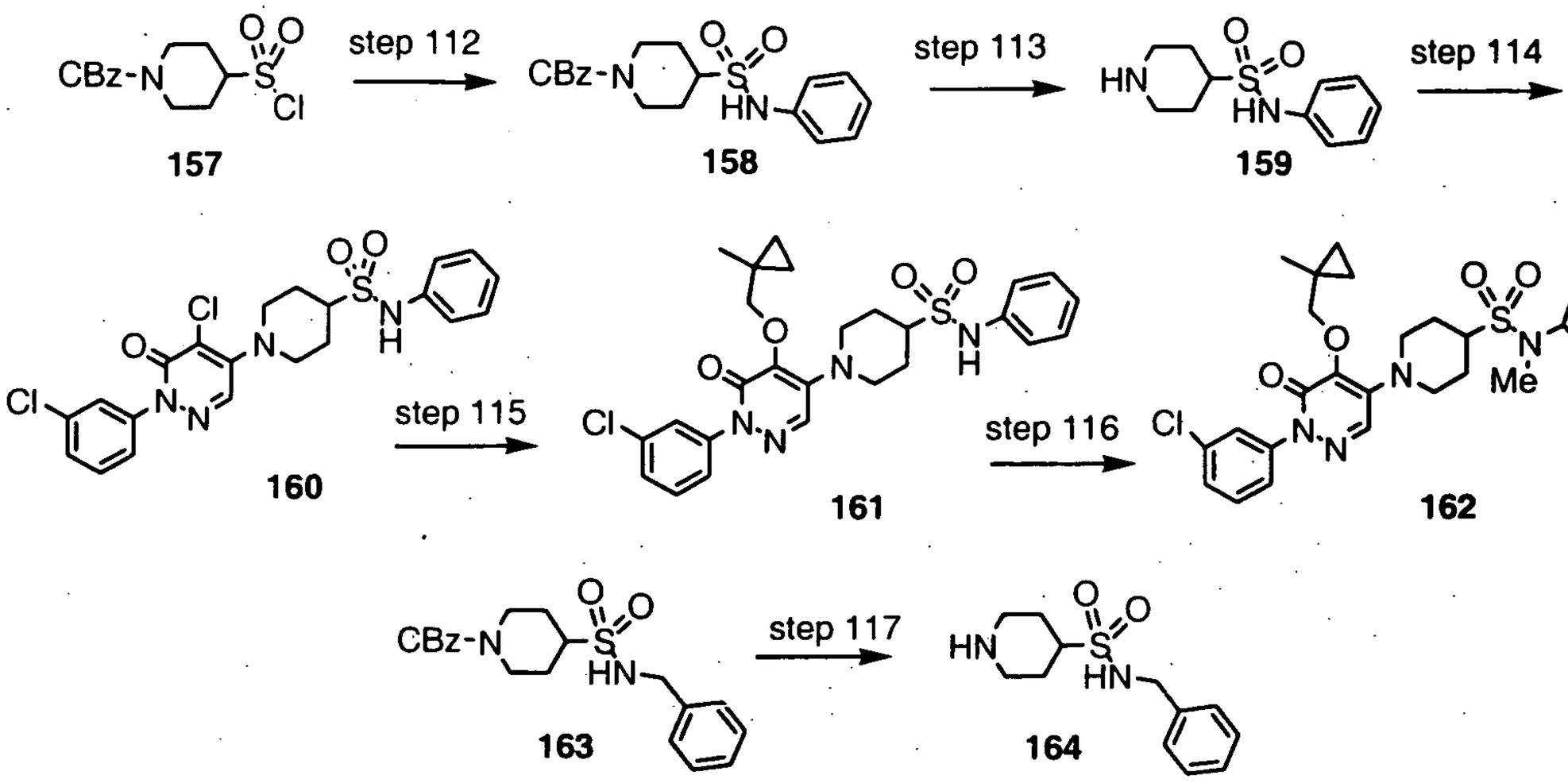
Table 31: Oxygen Analogues with Thioether / Ether Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1771Z		563	1772Z		671
1773Z		595	1774Z		579
1775Z		561	1776Z		591
1777Z		577	1778Z		563

1779Z		611	1780Z		591
1781Z		545	1782Z		611
1783Z		576	1784Z		589
1785Z		633	1786Z		597
1787Z		577	1788Z		591
1789Z		605	1790Z		645
1791Z		579	1792Z		579
1793Z		619	1794Z		645
1795Z		577	1796Z		563

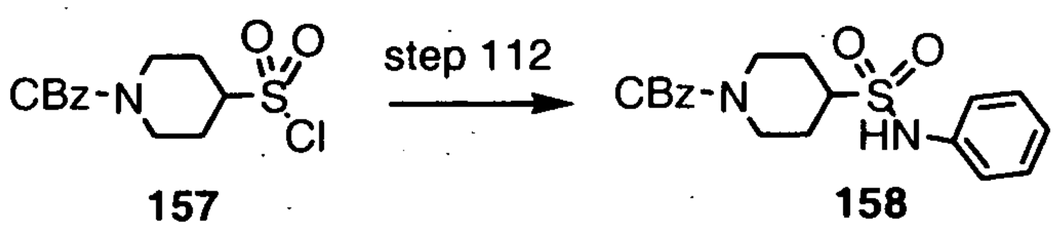
1797Z		563		1798Z		599
1799Z		621		1800Z		547
1801Z		605		1802Z		619
1803Z		563		1804Z		618
1805Z		591		1806Z		617
1807Z		591		1808Z		578
1809Z		620				

Scheme 34



157 158 159 160 161 162 163 164

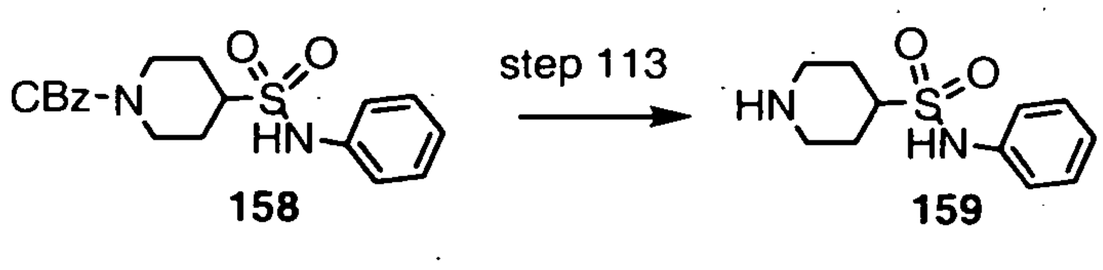
Step 112:



157 158

To a solution of aniline (2.3 g, 25.12 mmol) and iPr_2NEt (3.3 mL, 18.84 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added a solution of Cbz-piperidinylsulfonyl chloride **157** (4.0 g, 12.56 mmol) in CH_2Cl_2 (20 mL) over 10 mins. After 1 h at 0 °C and 2.5 h at room temperature, water was added to the reaction mixture, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was washed with 1 N HCl, brine, dried (Na_2SO_4), filtered, and concentrated. Purification by ISCO silica gel chromatography (eluant: EtOAc - hexane) gave 3.7 g (79% yield) of the product **158** as a white solid. MS (M+1): 375.

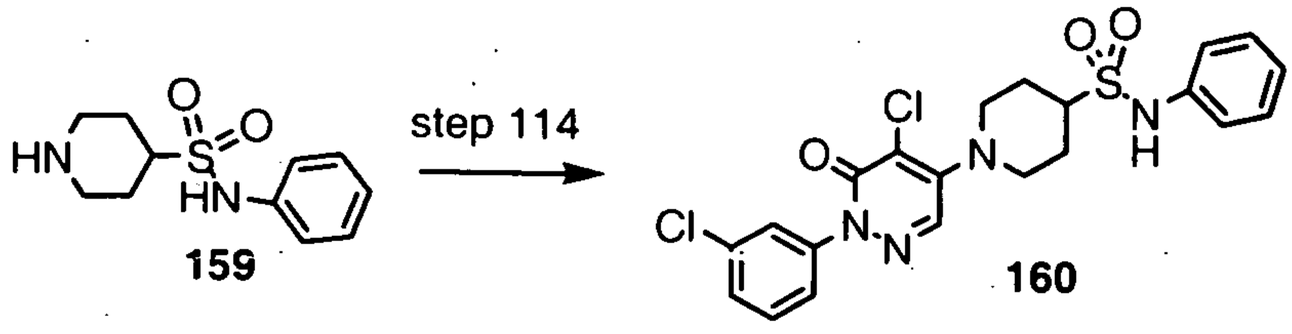
Step 113:



158 159

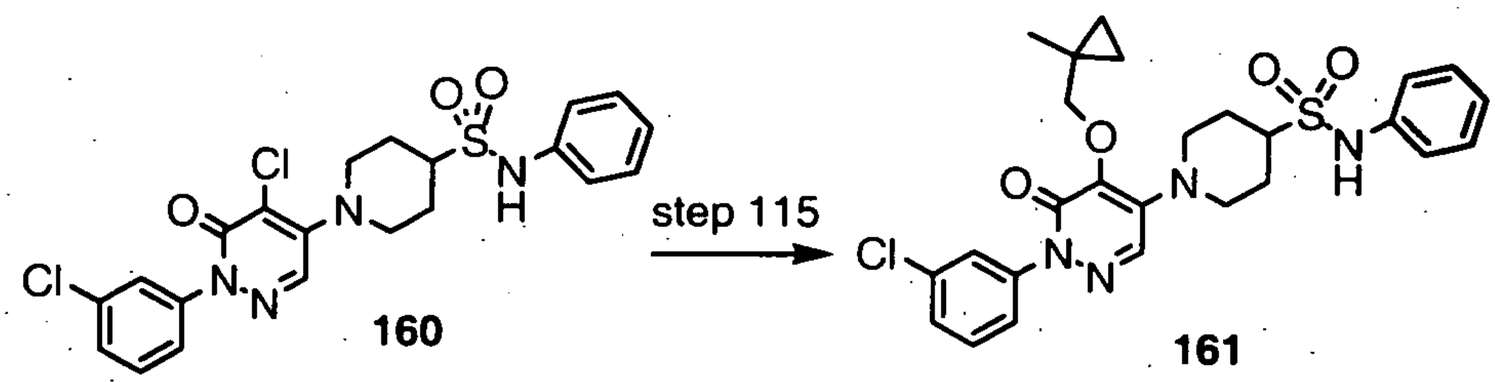
To a solution of sulfonamide **158** (810 mg, 2.16 mmol) in MeOH (50 mL) and EtOAc (15 mL) was added Pd/C (500 mg) and the reaction mixture was treated with H_2 (44 psi) for 18 h. The reaction mixture was filtered, and the filtrate was concentrated to give 440 mg (85% yield) of the product **159** as a white solid. MS (M+1): 241.

Step 114:



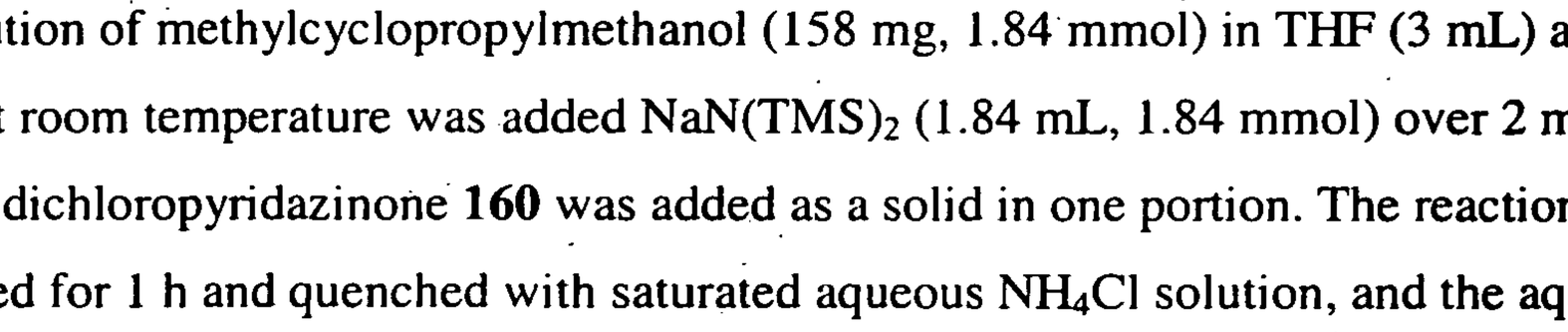
The reaction mixture of sulfonamide **159** (400 mg, 1.67 mmol), dichloropyridazinone (460 mg, 1.67 mmol) and iPr_2NEt (580 uL, 3.34 mmol) in EtOH (8 mL) was heated to 92 °C for 15 h, and then concentrated to provide a solid residue. To the above residue was added saturated aqueous NH_4Cl solution and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. ISCO silica gel chromatography (eluant: CH_2Cl_2 - MeOH) gave 551 mg (69% yield) of the product **160** as a white solid. MS (M+1): 480.

Step 115:



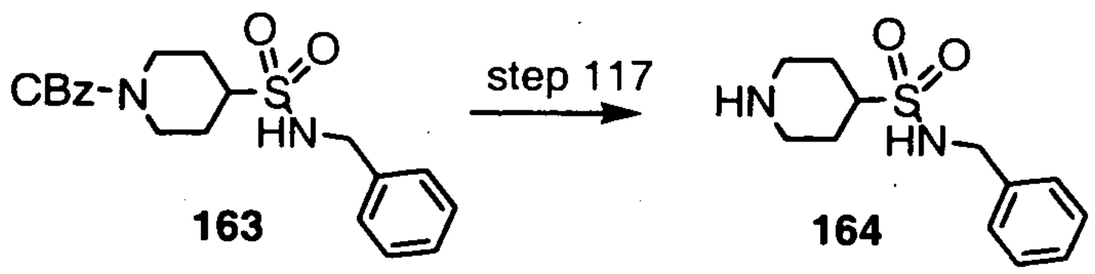
To a solution of methylcyclopropylmethanol (158 mg, 1.84 mmol) in THF (3 mL) and DMF (1 mL) at room temperature was added $NaN(TMS)_2$ (1.84 mL, 1.84 mmol) over 2 mins. After 20 mins, dichloropyridazinone **160** was added as a solid in one portion. The reaction mixture was stirred for 1 h and quenched with saturated aqueous NH_4Cl solution, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 148 mg (61% yield) of the product **161** as a white solid. MS (M+1): 529.

Step 116:



To a solution of sulfonamide **161** (110 mg, 0.21 mmol) in DMF (2 mL) at room temperature was added NaH (17 mg, 0.42 mmol, 60% in oil) in one portion. After 25 mins, methyl iodide (60 mg, 0.42 mmol) was added in one portion. After 1 h, the reaction mixture was added slowly to a saturated aqueous NH_4Cl solution, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 85 mg (79% yield) of the product **162** as a white solid. MS (M+1): 543.

Step 117:

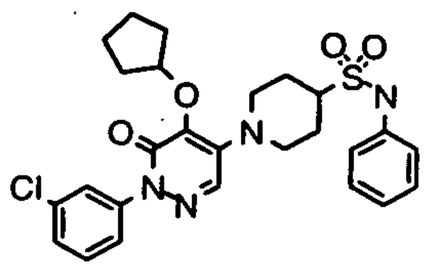
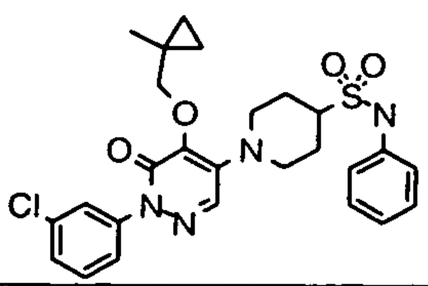
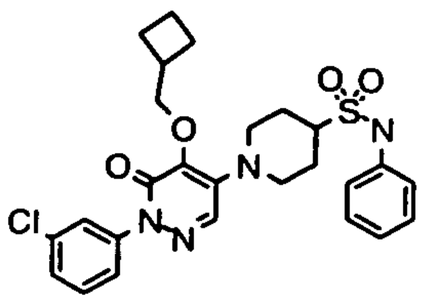
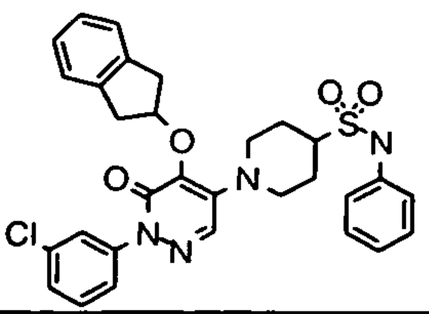


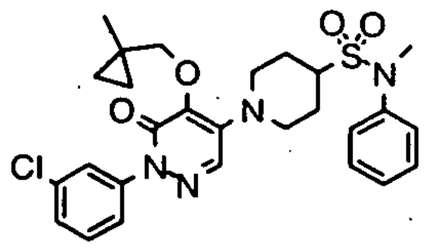
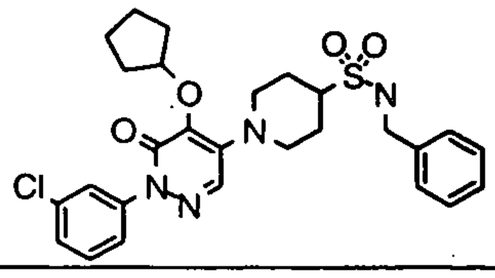
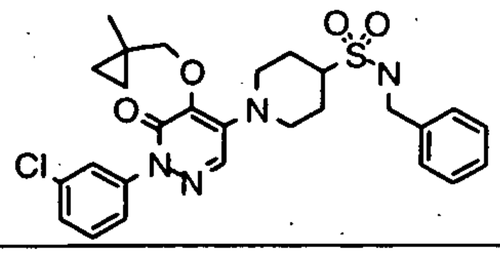
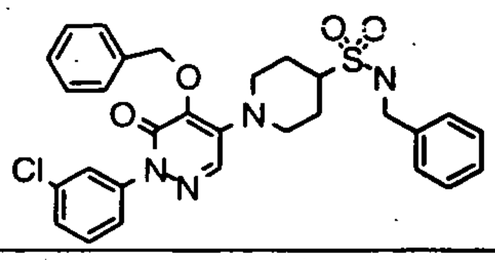
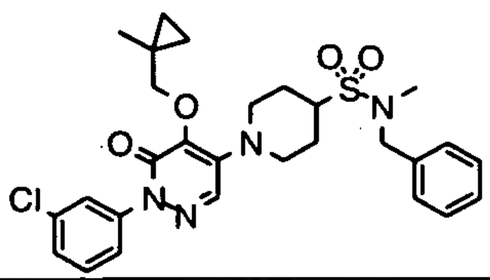
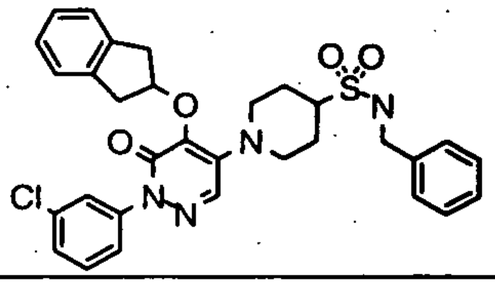
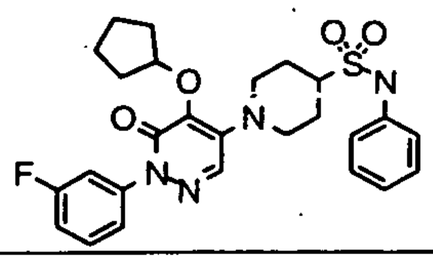
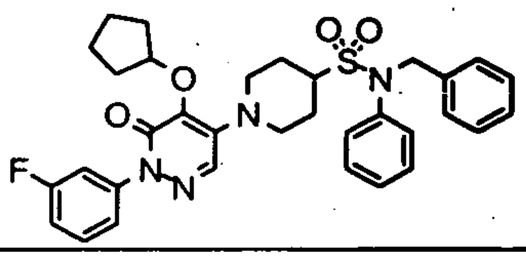
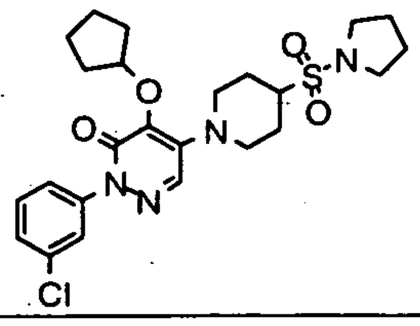
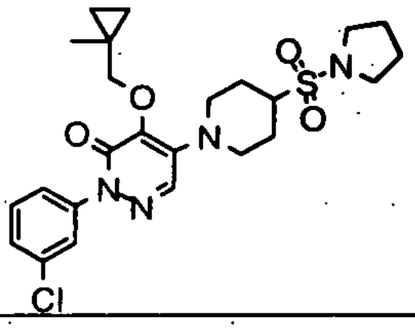
163 **164**

The reaction mixture of sulfonamide **163** (1.1 g, 2.83 mmol) in 33% HBr/HOAc (26 mL) was stirred at room temperature for 2 h, and then poured into ice water. To the aqueous reaction mixture was added NaOH solution until the pH = 12-13, then the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated to give a solid. The solid was washed with a mixture of Et_2O and hexane to remove the benzyl bromide impurity and dried to give 530 mg (68% yield) of the product **164** as a white solid. MS (M+1): 276.

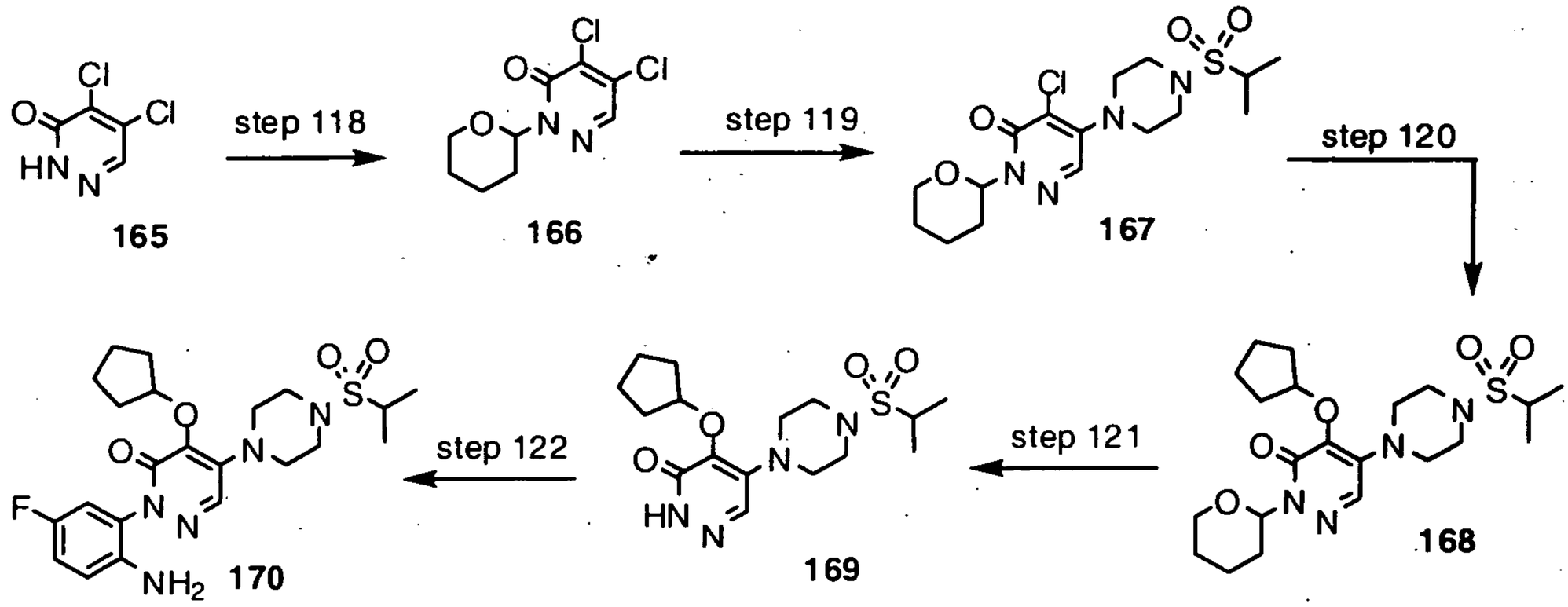
Using the procedures described above, the following compounds were synthesized.

Table 32: Oxygen Analogues with Reverse Sulfonamide

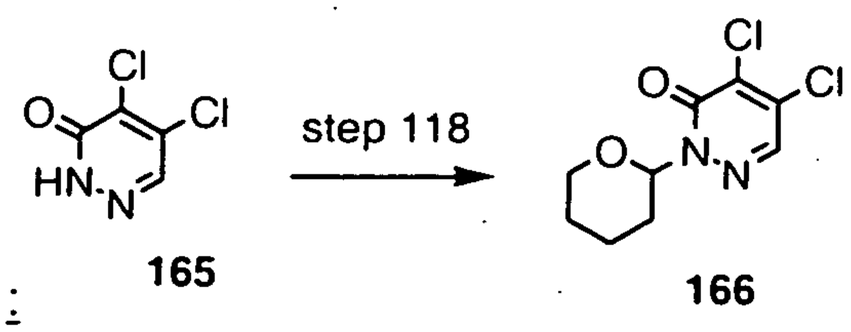
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1810Z		529	1811Z		529
1812Z		529	1813Z		577

1814Z		543		1815Z		543
1816Z		543		1817Z		565
1818Z		557		1819Z		591
1820Z		513		1821Z		603
1822Z		507		1823Z		507

Scheme 35

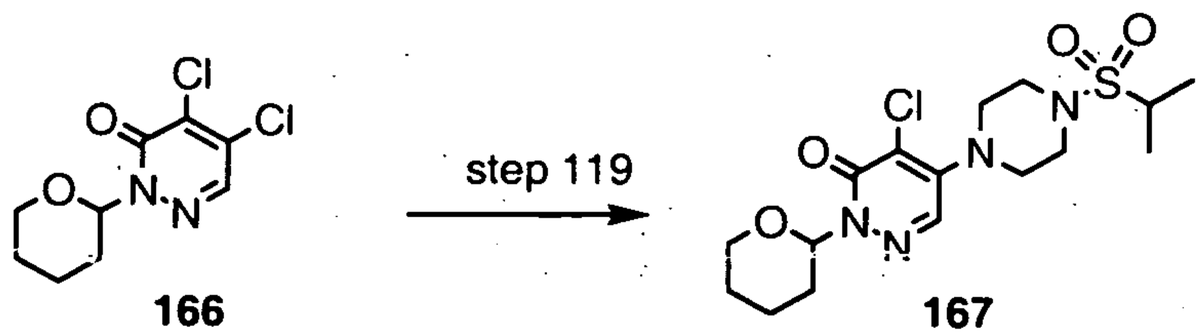


Step 118:



4,5-Dichloropyridazinone (25 g, 150 mmol) was mixed with dihydropyrane (41 mL, 450 mmol), and p-toluenesulfonic acid monohydrate (1.0 g) in a mixed solvent of toluene (120 mL) and THF (20 mL). The mixture was heated at reflux for 4 h. After cooling, the mixture was then diluted with 300 mL of EtOAc and 150 mL of water. The solid was removed by filtration. The organic layer was washed with diluted $NaHCO_3$ then brine, dried over anhydrous sodium sulfate, and concentrated. Purification by flash chromatography gave 24.4 g of the product **166** as an oil.

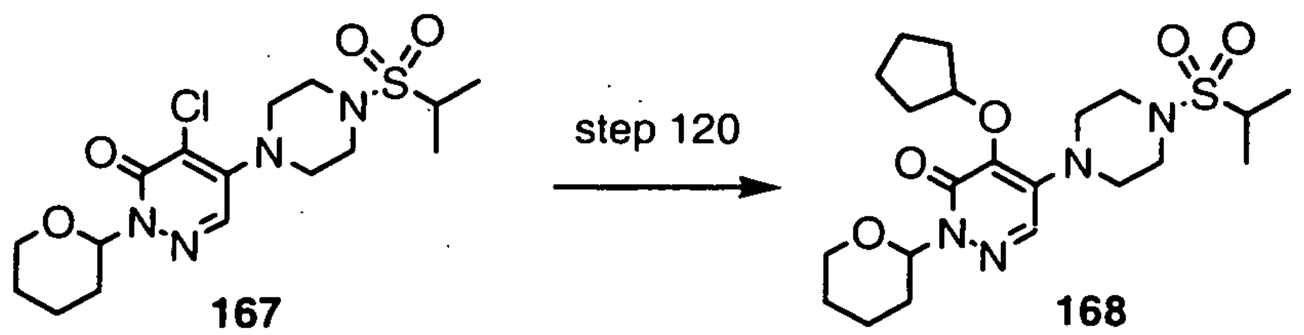
Step 119:



166 **167**

Compound **166** (12.5 g, 50 mmol) was mixed with 1-(isopropylsulfonyl)-piperazine HCl salt (16.8 g, 52.5 mmol) and triethylamine (14.6 mL, 105 mmol) in 180 mL of ethanol. The mixture was heated to 70 °C overnight. After cooling, the solvent was evaporated. The crude product was stirred in 200 mL of MeOH/water (1:1). The product was collected by filtration, washed with water and MeOH/water(1:1), and dried in a vacuum oven at 70 °C for 3 days to give 13.6 g of the product **167**. MS (M+1): m/e 405.

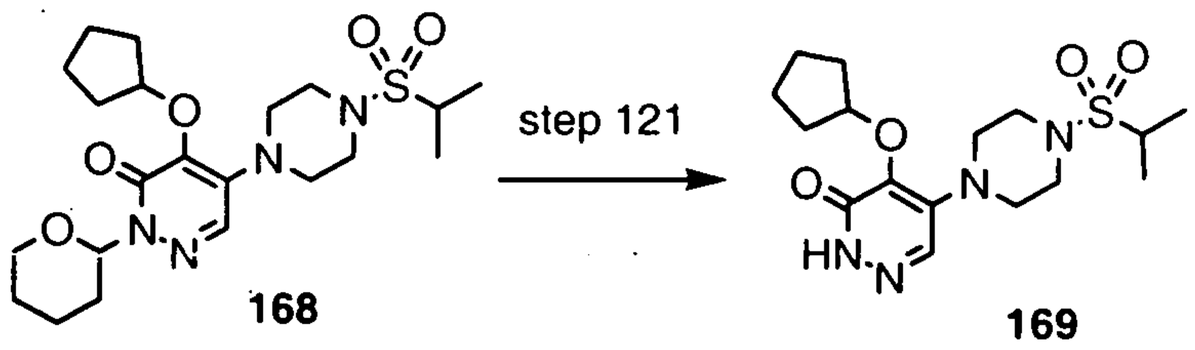
Step 120:



167 **168**

Compound **167** (6.1 g, 15 mmol) was mixed with cyclopentanol (2.1 mL, 23 mmol) in 80 mL of dry THF. NaH (60%, 0.72 g, 18 mmol) was added. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give the product **168** as an oil, which was dried under high vacuum overnight before use in the next step.

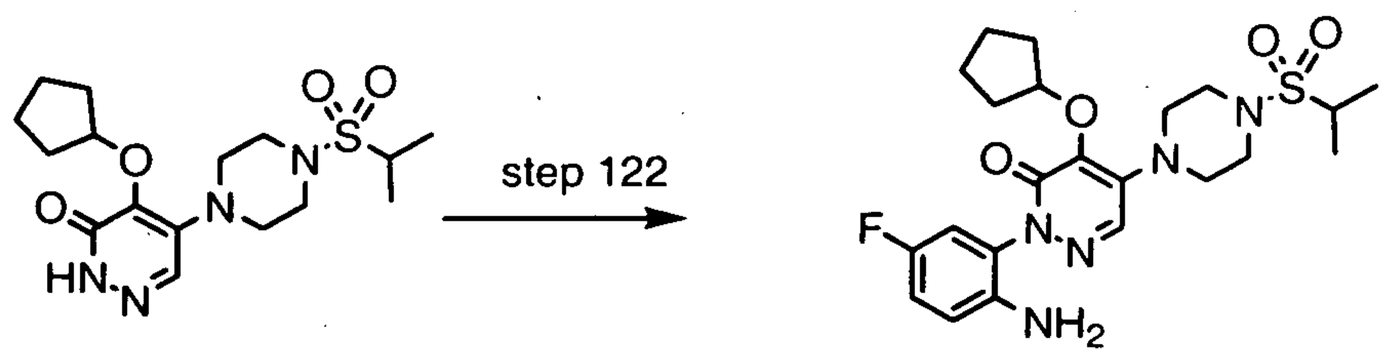
Step 121:



168 169

Compound **168** (~15 mmol) in 150 mL of dry methylene chloride was cooled to 0 °C. $BF_3.Et_2O$ (5.6 mL, 45 mmol) was added slowly. The mixture was then stirred at 0 °C for 1 h. Ice-water was added to quench the reaction. The mixture was diluted with methylene chloride then washed with water, diluted sodium bicarbonate, and brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The product was further dried in a vacuum oven to give 5.2 g of the product **169** as a pale yellow solid. MS (M+1): m/e 371.

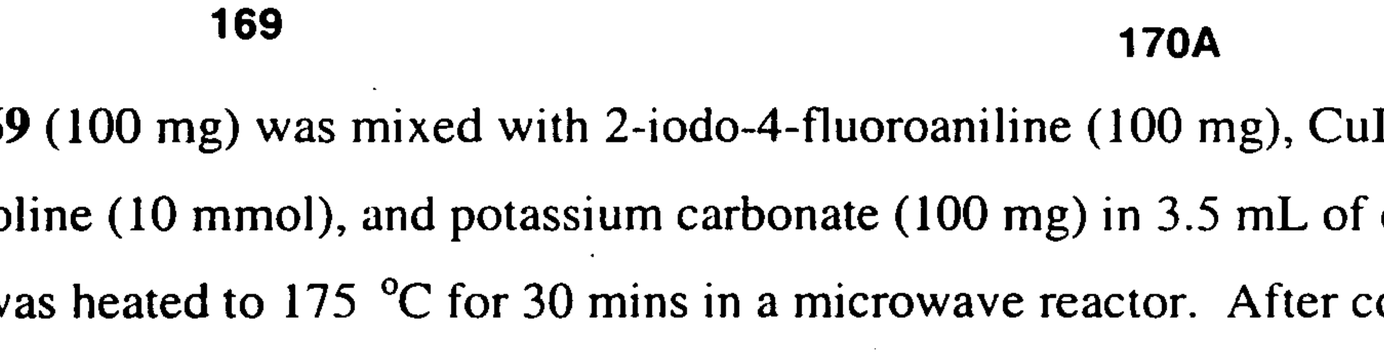
Step 122 (method A):



169 170A

Compound **169** (100 mg) was mixed with 2-iodo-4-fluoroaniline (100 mg), CuI (10 mg), 8-hydroxylquinoline (10 mmol), and potassium carbonate (100 mg) in 3.5 mL of dry pyridine. The mixture was heated to 175 °C for 30 mins in a microwave reactor. After cooling, the mixture was filtered through celite which was washed with EtOAc. The filtrate was concentrated, and the crude product was purified by Gilson prep HPLC (eluant: CH_3CN – water gradient with 0.1% HCOOH) to give 60 mg of pure product **170A** as pale solid. MS (M+1): m/e 480.

Step 122 (Method B):

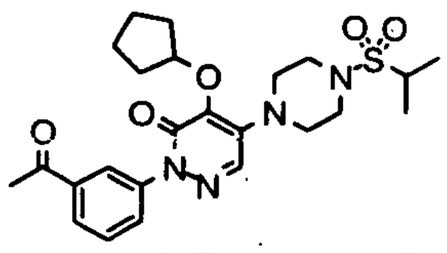
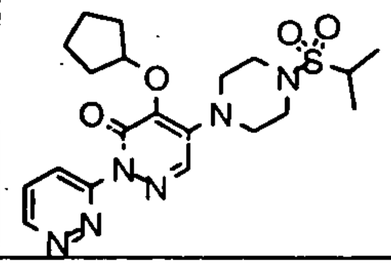
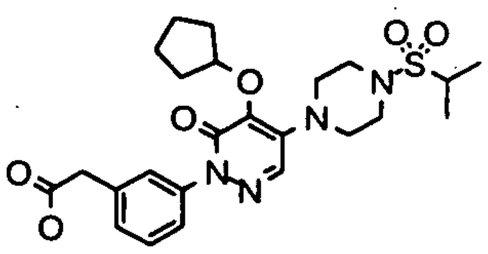
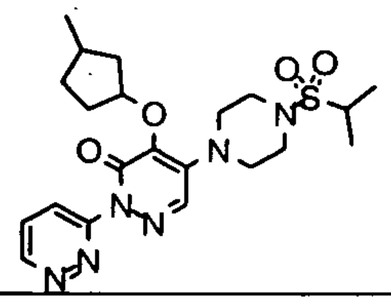
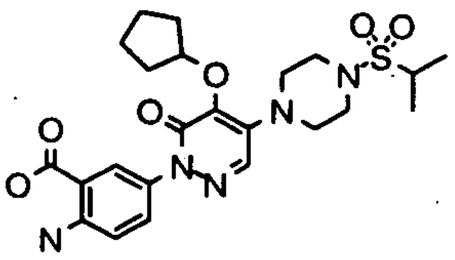
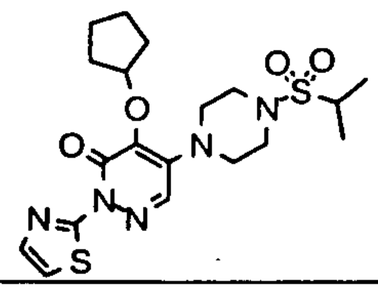
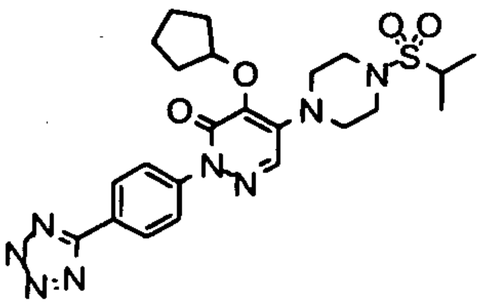
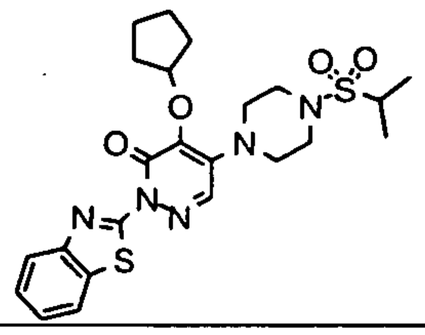
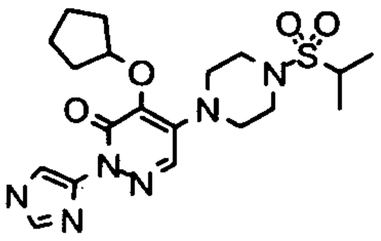
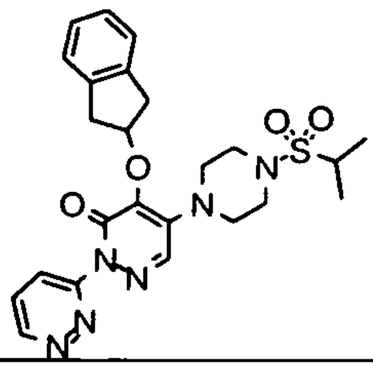
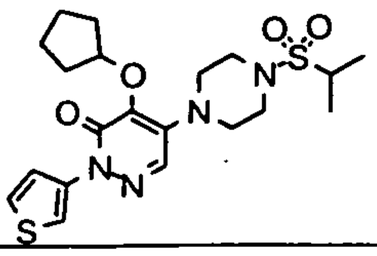


169 170B

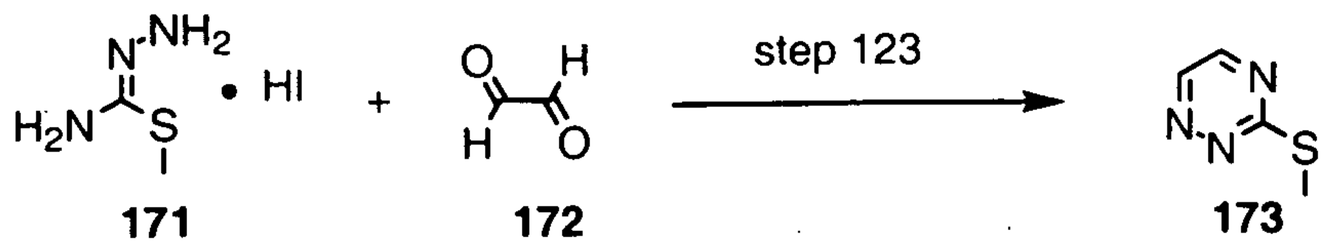
Compound **169** (100 mg, 0.27 mmol) was mixed with 2, 4, 6-trifluoropyridine (53 mg, 0.4 mmol), and phosphazene base P_1-t-Bu (0.13 mL, 0.5 mmol) in 0.7 mL of dry DMF. The mixture was stirred at room temperature overnight then diluted to 4 mL with DMF, and purified by Gilson prep HPLC (eluant: CH_3CN – water gradient with 0.1% HCOOH) to give 51 mg of compound **170B** as light-yellow solid. MS (M+1): m/e 484.

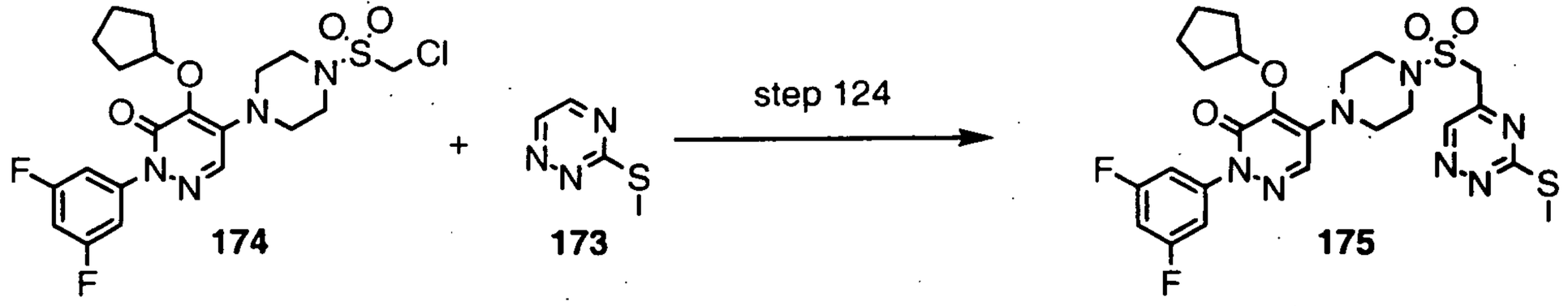
Using the procedures described above, the following compounds were synthesized.

Table 33: R^3 Substituent Analogs

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1824Z		489	1825Z		449
1826Z		505	1827Z		463
1828Z		506	1829Z		454
1830Z		515	1831Z		504
1832Z		437	1833Z		497
1834Z		453			

Scheme 36





Step 123:

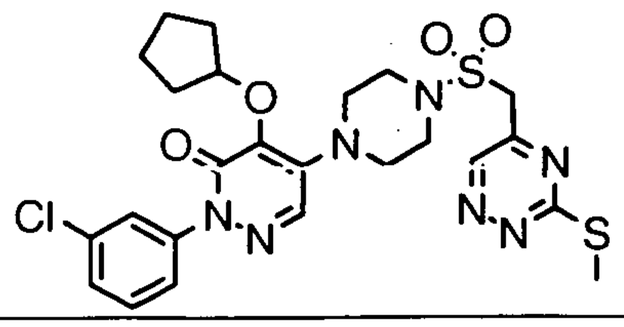
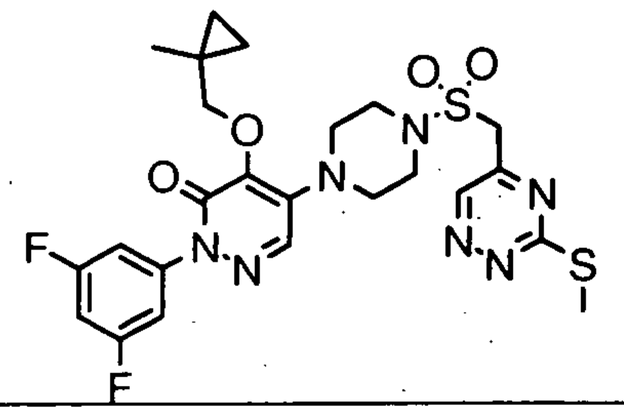
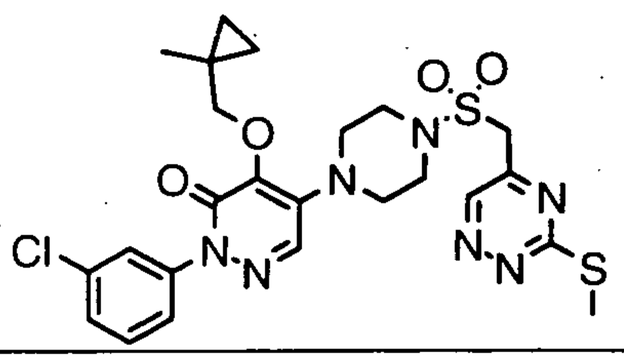
Compound **173** was prepared via the method of William W. Paudler and The-Kuei Chen, *J. Hetero. Chem. Vol.7 (1970) 767-771.*

A solution of sodium bicarbonate (3.7 g, 44 mmol) and 40% glyoxal **172** (7 g, **48 mmol**) in ice water (100 mL) was added to a solution of S-methylthiosemicarbazide hydroiodide **171** (9.32 g, 40 mmol) dissolved in ice water (60 mL) set in an ice bath. The resulting mixture was placed in the refrigerator (about -10 °C) for 5 h. The reaction mixture was extracted several times with CH_2Cl_2 . The combined organic extract was dried (Na_2SO_4), filtered, and concentrated to give an oil (4.37 g, 86% yield). ^{1}H-NMR : 9.0 ppm s (1H), 8.4 ppm s (1H),2.7 ppm s (3H).

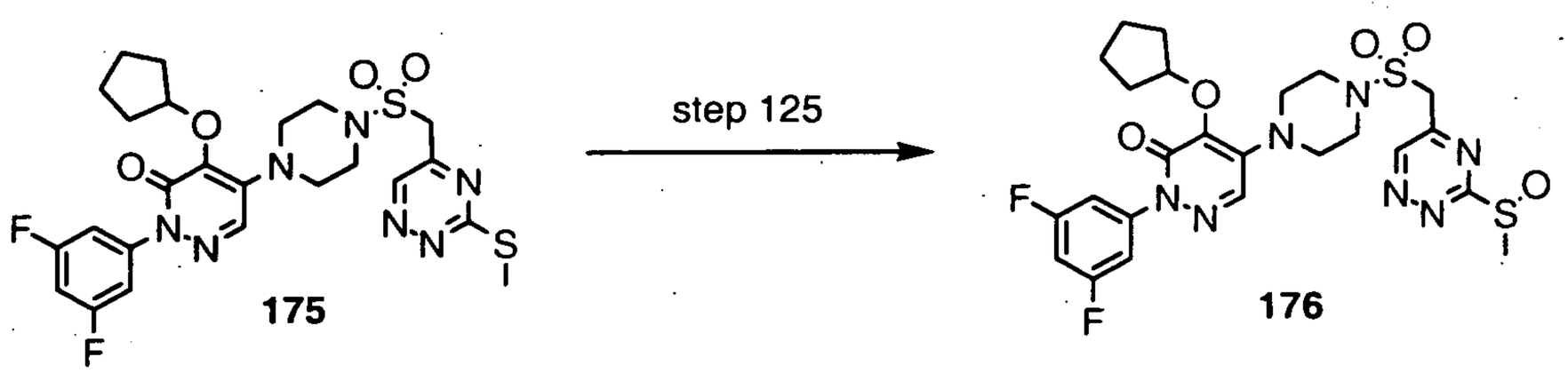
Step 124:

A solution of compound **174** (430 mg, 0.88 mmol) and compound **173** (102 mg, 0.8 mmol) in DMSO (1 mL) was added dropwise to a mixture of potassium hydroxide powder (320 mg, 5.7 mmol) in DMSO (1.5 mL) at room temperature. The darkened mixture was stirred for 1 h, then poured into a saturated ammonium chloride solution. The precipitate was collected by filtration. Purification by silica gel chromatography (eluant: 0% - 40% EtOAc - hexanes gradient) gave 300 mg (65% yield) of the product **175** as a pale-yellow foam. MS (M+1): m/e 580.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No	Structure	MS M+1
1835Z		578
1836Z		580
1837Z		578

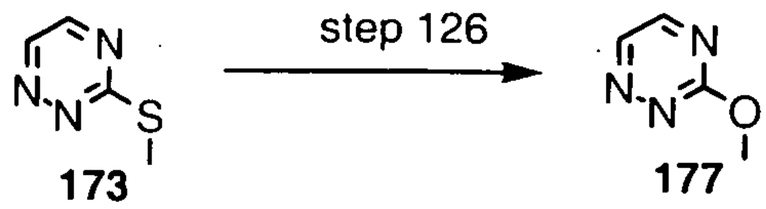
Scheme 37

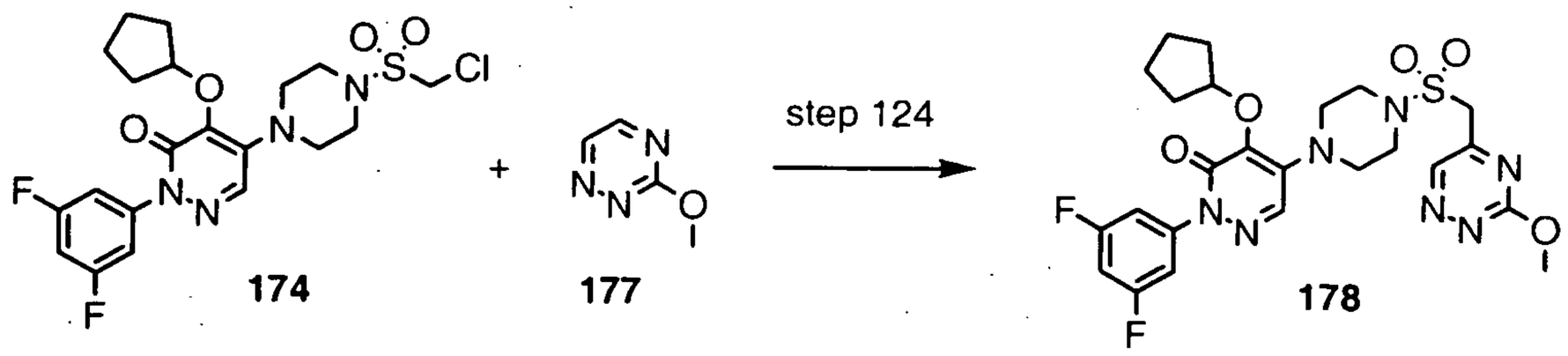


Step 125:

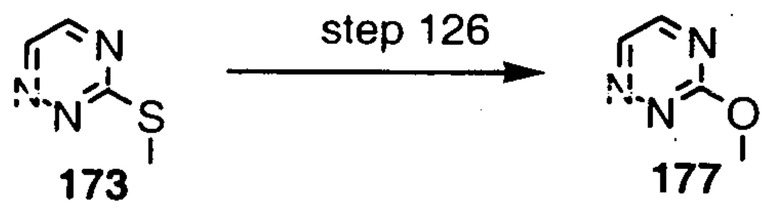
m-Chloroperbenzoic acid (77%, 23 mg, 0.1 mmol) was added to compound **175** (58 mg, 0.1 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The mixture was allowed to warm to 25 °C and stir for 15 h. A second dose of m-chloroperbenzoic acid (77%, 23 mg, 0.1 mmol) was added. After 5 h, additional CH_2Cl_2 was added, and the solution was washed with 10% sodium thiosulfate, saturated sodium bicarbonate, then brine. The dried (Na_2SO_4) organic layer was concentrated to a residue. Purification by silica gel chromatography (eluant: 0% - 100% EtOAc - hexanes gradient) gave 44 mg (74% yield) of the product **176** as a beige solid. MS (M+1): m/e 596.

Scheme 38





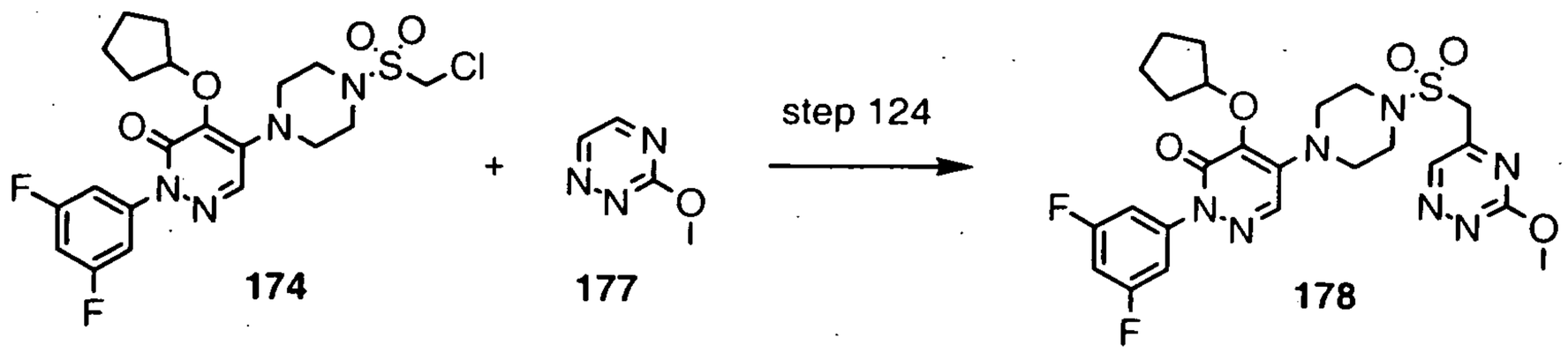
Step 126:



Compound **177** was prepared via the method of William W. Paudler and The-Kuei Chen, *J. Hetero. Chem. Vol.7 (1970) 767-771*

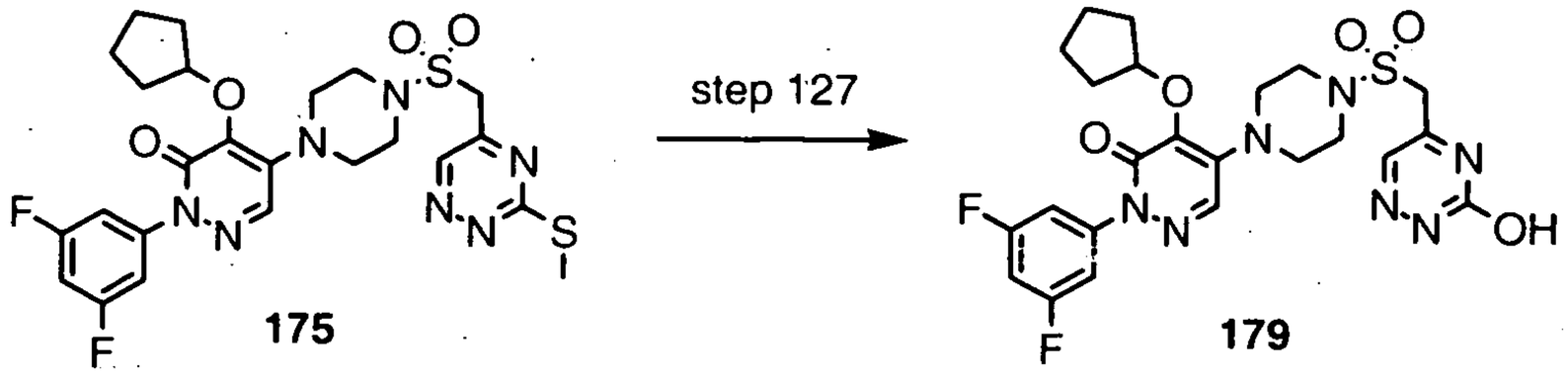
Sodium methoxide (1.18 g, 21.8 mmol) was added to compound **173** (2.54 g, 20 mmol) in absolute methanol (35 mL). The mixture was stirred for 15 h. Ground dry ice was added slowly, and the mixture was filtered with a methanol rinse. The filtrate was concentrated to a residue. Purification by silica gel chromatography (eluant: 0% - 40% EtOAc - hexanes gradient) gave 804 mg (36% yield) of the product **177** as a solid. MS (M+1): m/e 112.

Step 127:



Using the procedure described in step 124, with compounds **174** and **177**, compound **178** was prepared (53% yield) as a yellow solid. MS (M+1): m/e 564.

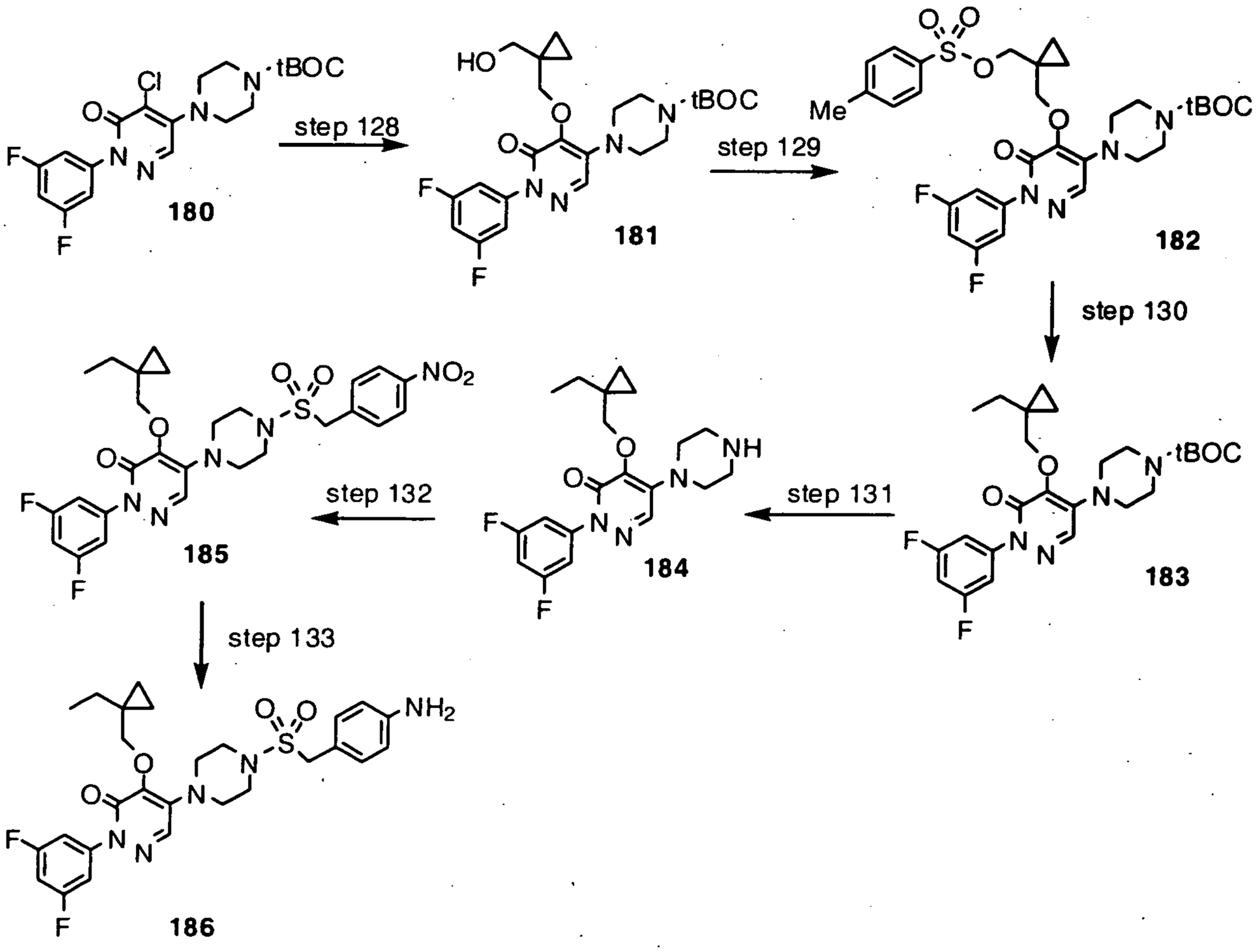
Scheme 39



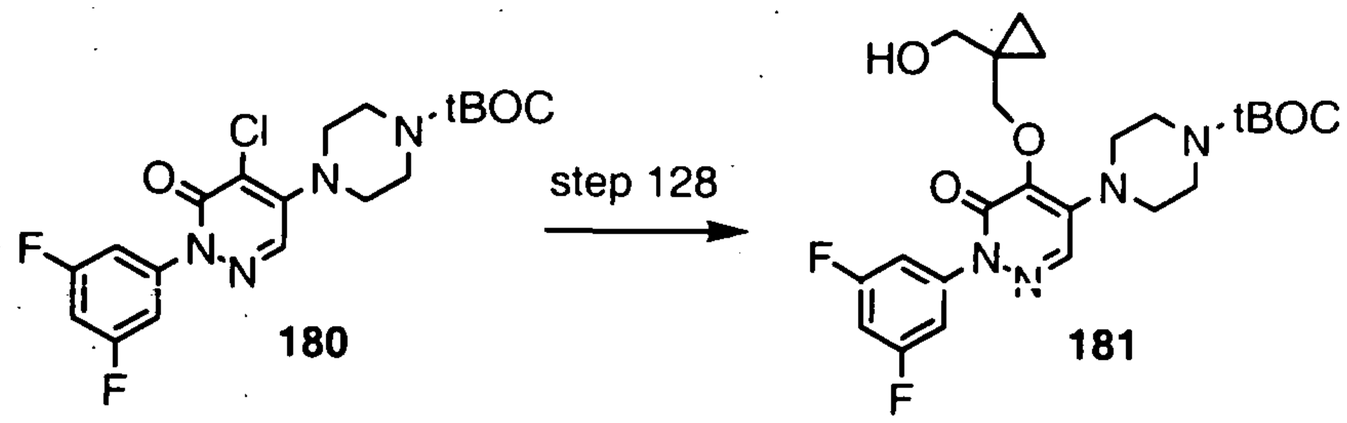
Step 127:

m-Chloroperbenzoic acid (77%, 48.6 mg, 0.22 mmol) was added to compound **175** (53 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) at 25 °C. The mixture was allowed to stir for 12 days. The solution was diluted with CH_2Cl_2, washed with 10% sodium thiosulfate, saturated sodium bicarbonate and brine. The dried (Na_2SO_4) organic layer was concentrated to a residue. Exposure to silica gel thin layer chromatography (60% EtOAc - hexanes) for 15 h gave 32 mg (65% yield) of the product **179** as a solid. MS (M+1): m/e 550.

Scheme 40

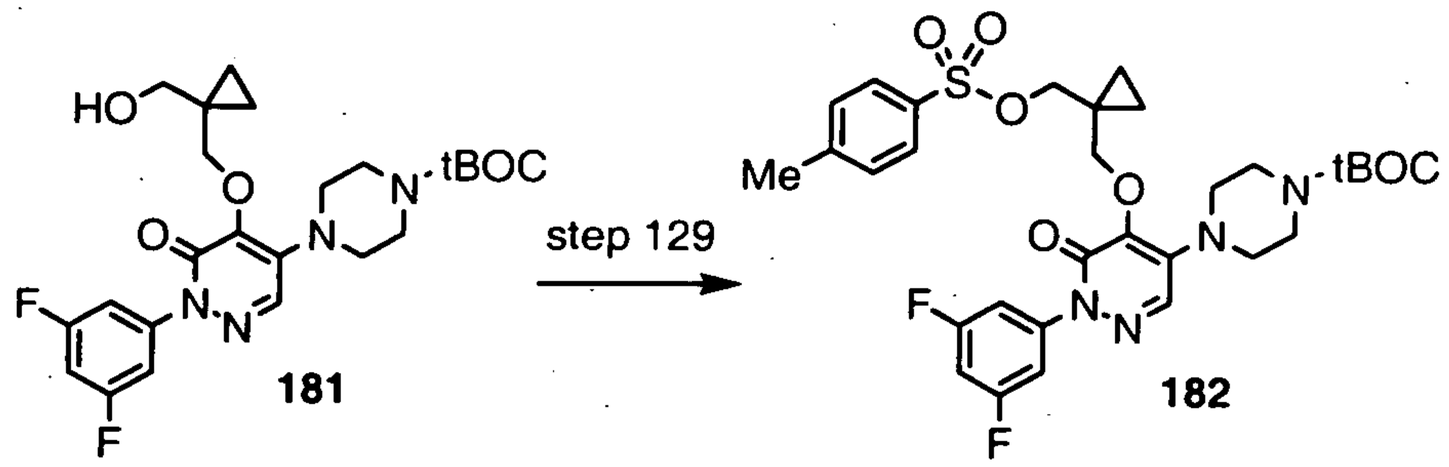


Step 128:



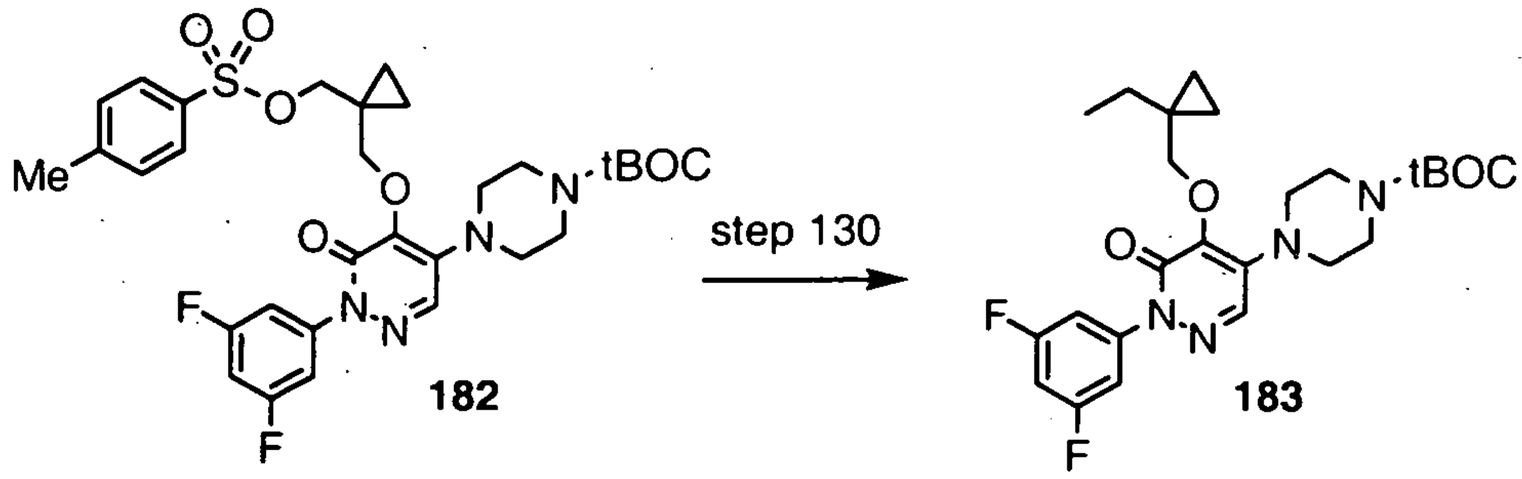
To cyclopropanedimethanol (11.2 g, 98.7 mmol) dissolved in dry THF (200 mL) under a nitrogen atmosphere was added sodium hexamethyldisilazane (1.0 M in THF, 49 mL, 49 mmol). The cloudy reaction mixture was stirred at room temperature for 20 mins then chloropyridazinone **180** (10.4 g, 24.4 mmol) was added. The reaction mixture was stirred at room temperature for 20 mins then heated at 80 °C for 10 h. The solvent was evaporated from the cooled mixture. Water (300 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 20% EtOAc - CH_2Cl_2) gave 8.8 g (73% yield) of the product **181** as a yellow solid. MS (M+1): m/e 493.

Step 129:



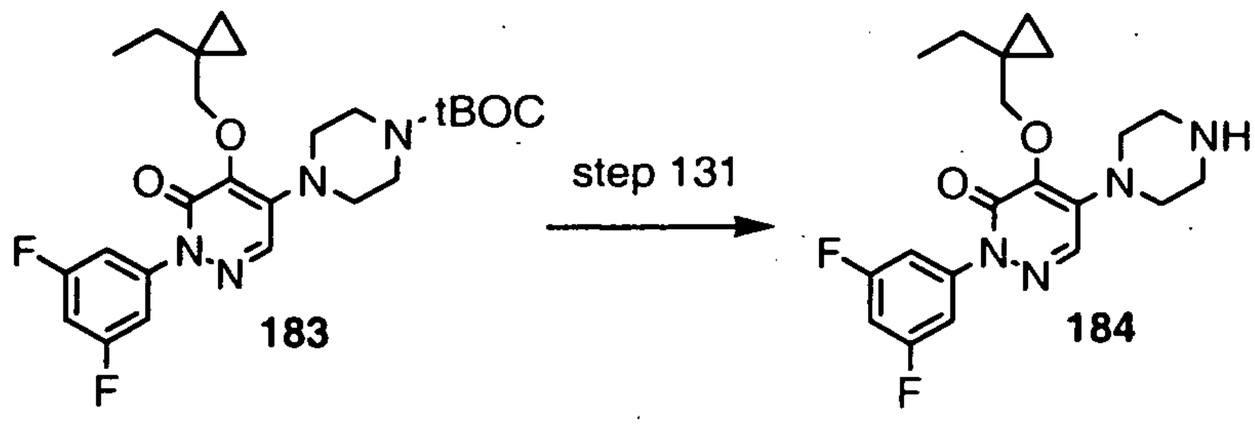
To compound **181** (2.00 g, 4.06 mmol) dissolved in CH_2Cl_2 (40 mL) was added dimethylaminopyridine (0.25 g, 2.03 mmol), triethylamine (1.23 g, 1.7 mL, 12.2 mmol), and then p-toluenesulfonyl chloride (1.93 g, 10.2 mmol). The reaction mixture was stirred at room temperature for 24 h. Water (50 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% - 10% EtOAc - CH_2Cl_2 gradient) gave 1.69 g (64% yield) of the product **182** as a yellow foam. MS (M+1): m/e 647.

Step 130:



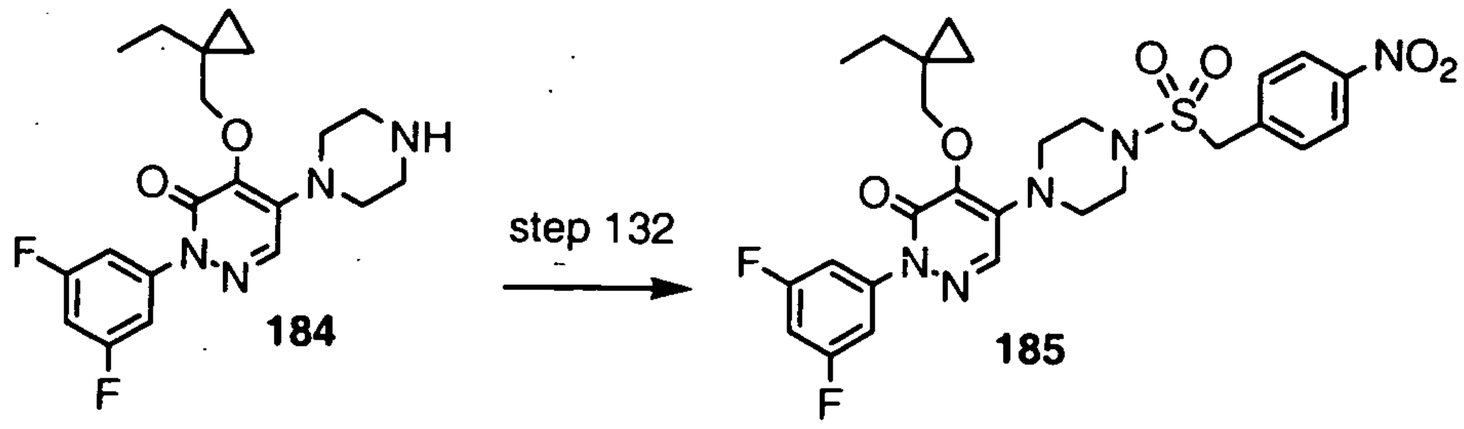
To copper iodide (1.48 g, 7.79 mmol) suspended in dry diethyl ether (20 mL) and cooled in -10 °C isopropanol bath (Neslab ethylene glycol circulator) under a nitrogen atomosphere was added methyl lithium (1.6 M in diethyl ether, 9.7 mL, 15.6 mmol) via syringe. The reaction mixture became cloudy yellow then colorless and was stirred for 30 mins in the -10 °C bath. The tosylate compound **182** (1.68 g, 2.60 mmol) was dissolved in diethyl ether (50 mL) and added via addition funnel. The reaction mixture was stirred in the -10 °C bath for 45 mins, then warmed slowly to room temperature, and stirred at room temperature for 16 h. Saturated NH_4Cl (50 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% EtOAc - CH_2Cl_2) gave 0.51 g (40% yield) of the product **183** as a yellow oil. MS (M+1): m/e 491.

Step 131:



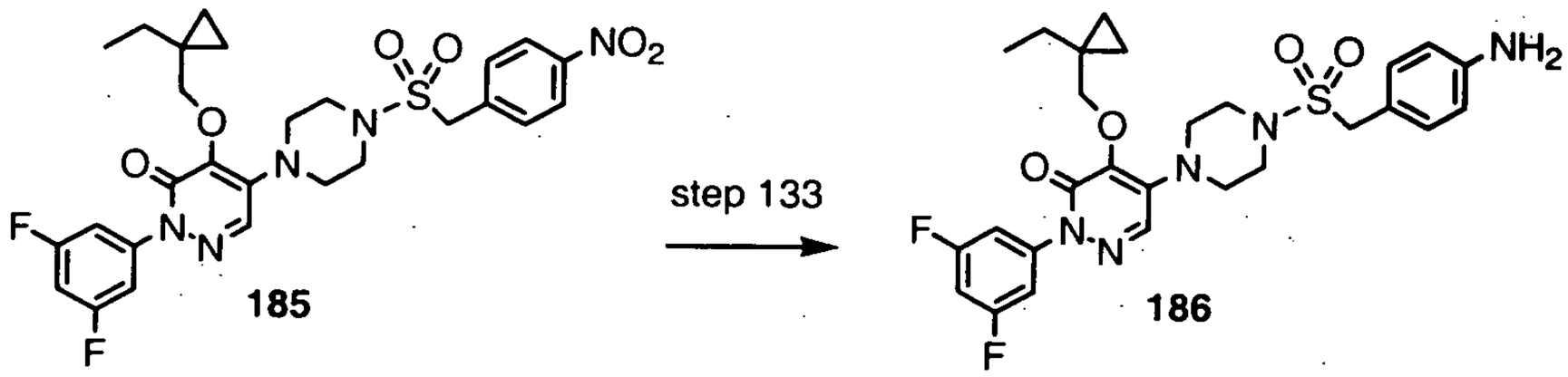
To compound **183** (0.50 g, 1.02 mmol) dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at 0 °C for 2 h then the solvent was evaporated. Aqueous 0.5 N NaOH (15 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to give 0.25 g (63% yield) of the product **184** as a yellow oil. MS (M+1): m/e 391.

Step 132:



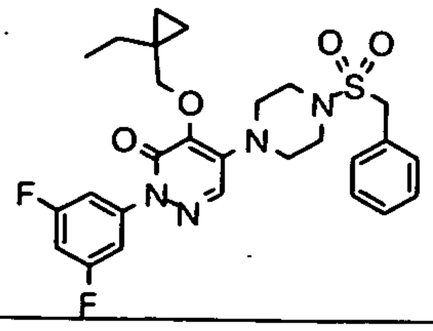
To compound **184** (185 mg, 0.474 mmol) dissolved in CH_2Cl_2 (8 mL) was added pyridine (0.11 mL, 1.4 mmol) then (4-nitrophenyl)methanesulfonyl chloride (160 mg, 0.62 mmol). The reaction mixture was stirred at room temperature for 4 h. Water was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 10% EtOAc - CH_2Cl_2) gave 110 mg (39% yield) of the product **185** as a yellow oil. MS (M+1): m/e 590.

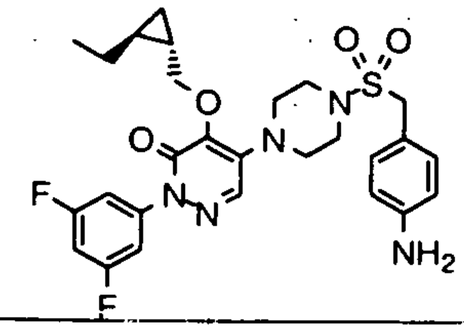
Step 133:



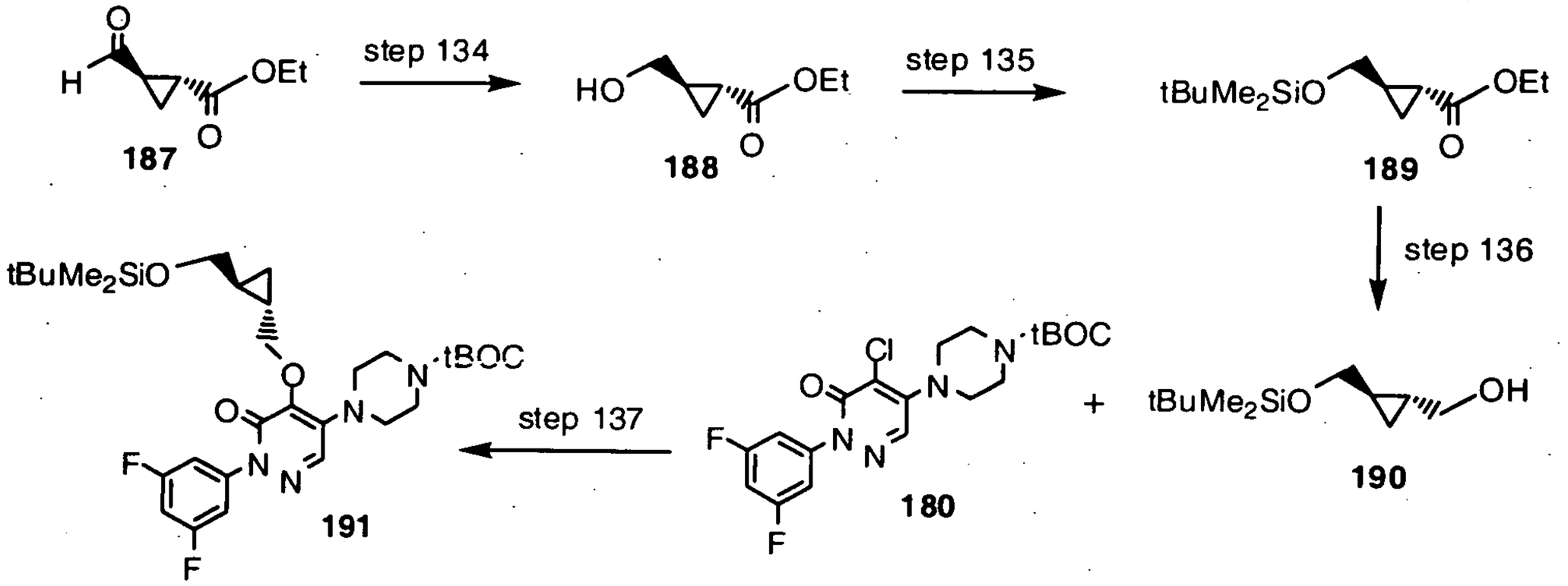
To compound **185** (116 mg, 0.197 mmol) suspended in EtOAc (20 mL) and iPrOH (10 mL) was added platinum oxide (26.7 mg, 0.098 mmol). The reaction mixture was stirred under a hydrogen balloon for 4 h. The platinum oxide catalyst was removed by filtration, washed with iPrOH, and the filtrate was evaporated. Purification by silica gel chromatography (eluant: 40% EtOAc - hexane) gave 65 mg (56% yield) of the product **186** as a yellow foam. MS (M+1): m/e 560.

Using the procedures described above, the following compounds were synthesized.

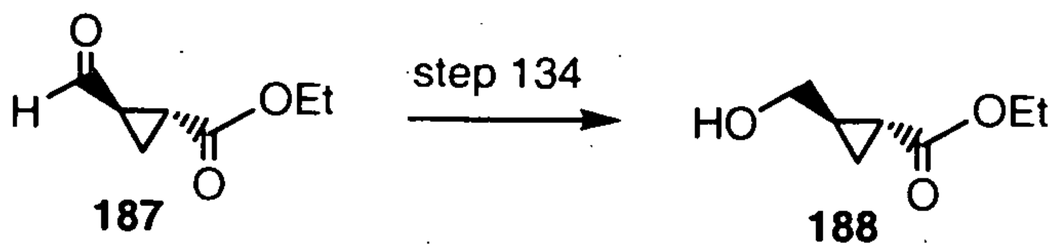
Cmpd. No.	Structure	MS M+1
1838Z		545

1839Z		560

Scheme 41

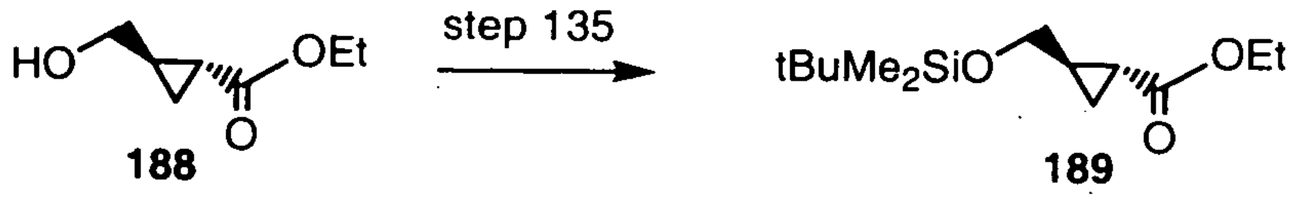


Step 134:



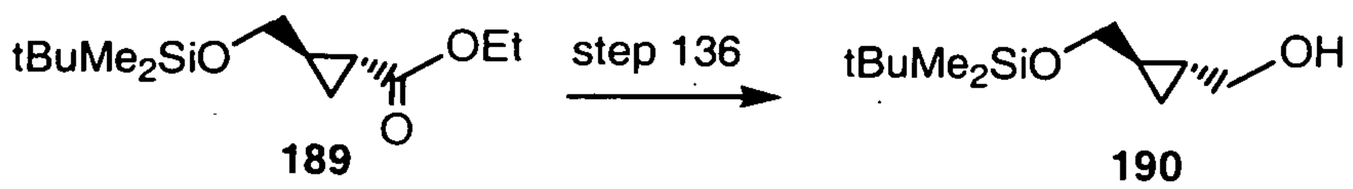
To ethyl 2-formyl-1-cyclopropane carboxylate **187** (10.00 g, 0.0703 mol) dissolved in ethanol (250 mL) was added sodium borohydride (3.99 g, 0.106 mol). The reaction mixture was stirred at room temperature for 5 h. The solvent was evaporated, and water (200 mL) was added. The aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5 - 8% MeOH - CH_2Cl_2) gave 9.19 g (91% yield) of the product **188** as a colorless oil. MS (M-17): m/e 127.

Step 135:



To compound **188** (2.00 g, 13.9 mmol) dissolved in CH_2Cl_2 (50 mL) was added dimethylaminopyridine (0.42 g, 3.47 mmol), triethylamine (2.11 g, 2.9 mL, 20.8 mmol), and t-butyldimethylsilyl chloride (2.72 g, 18.0 mmol). The reaction mixture was stirred at room temperature for 18 h. Water (50 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 3% EtOAc - CH_2Cl_2) gave 3.59 g (100% yield) of the product **189** as a colorless oil. MS (M+1): m/e 259.

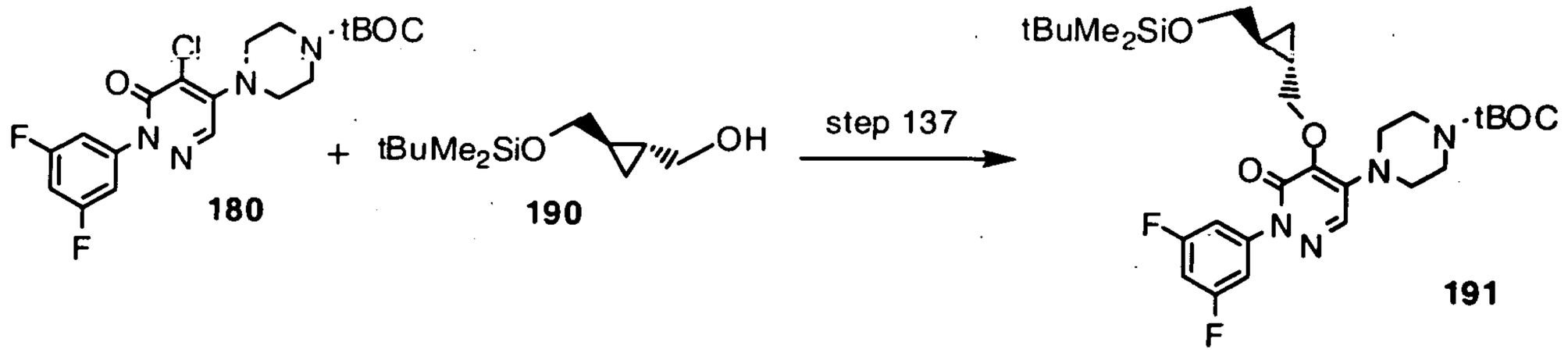
Step 136:



To compound **189** (3.59 g, 13.9 mmol) dissolved in dry THF (50 mL) was added solid lithium aluminum hydride (0.53 g, 13.9 mmol) portionwise. The reaction mixture was stirred at room temperature for 16 h under nitrogen. Carefully added water (0.5 mL), 1 N NaOH (0.5 mL) then water (1.5 mL) to precipitate the aluminum salts. Additional CH_2Cl_2 (50 mL) and $MgSO_4$ was added and stirred. The mixture was filtered, and the aluminum salts washed with CH_2Cl_2. The filtrate was evaporated. Purification by silica gel chromatography (eluant: 20%

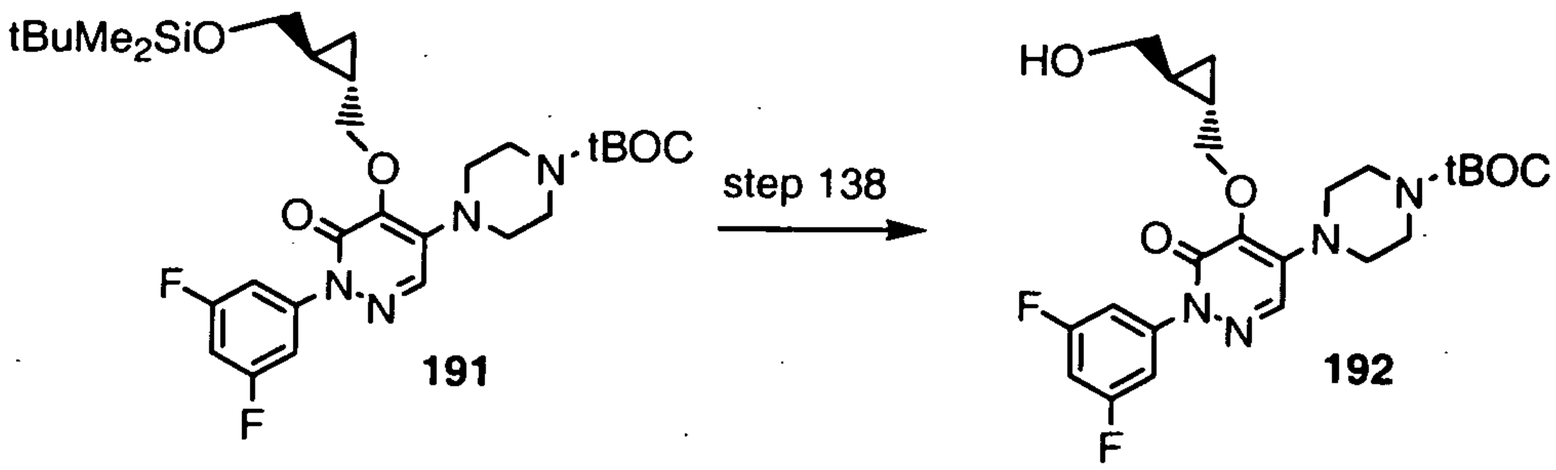
EtOAc - CH_2Cl_2) gave 2.15 g (71% yield) of the product **190** as a colorless oil. MS (M+1): m/e 217.

Step 137:



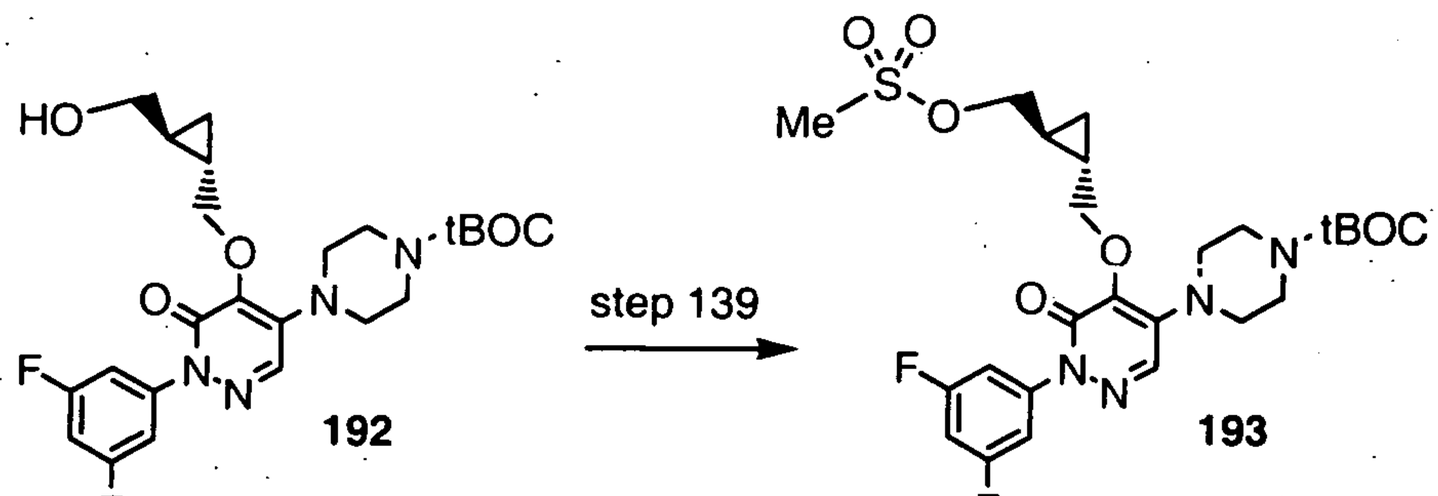
To compound **190** (2.14 g, 9.89 mmol) dissolved in dry THF (50 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 9.5 mL, 9.50 mmol) via syringe. The reaction mixture was stirred at room temperature for 15 mins under nitrogen. Chloropyridazinone **180** (3.52 g, 8.24 mmol) was added, and the reaction mixture was heated at 80 °C for 1 h then stirred at room temperature for 16 h. The solvent was evaporated. Water (75 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5 - 10% EtOAc - CH_2Cl_2) gave 4.94 g (99% yield) of the product **191** as a yellow oil. MS (M+1): m/e 607.8.

Step 138:



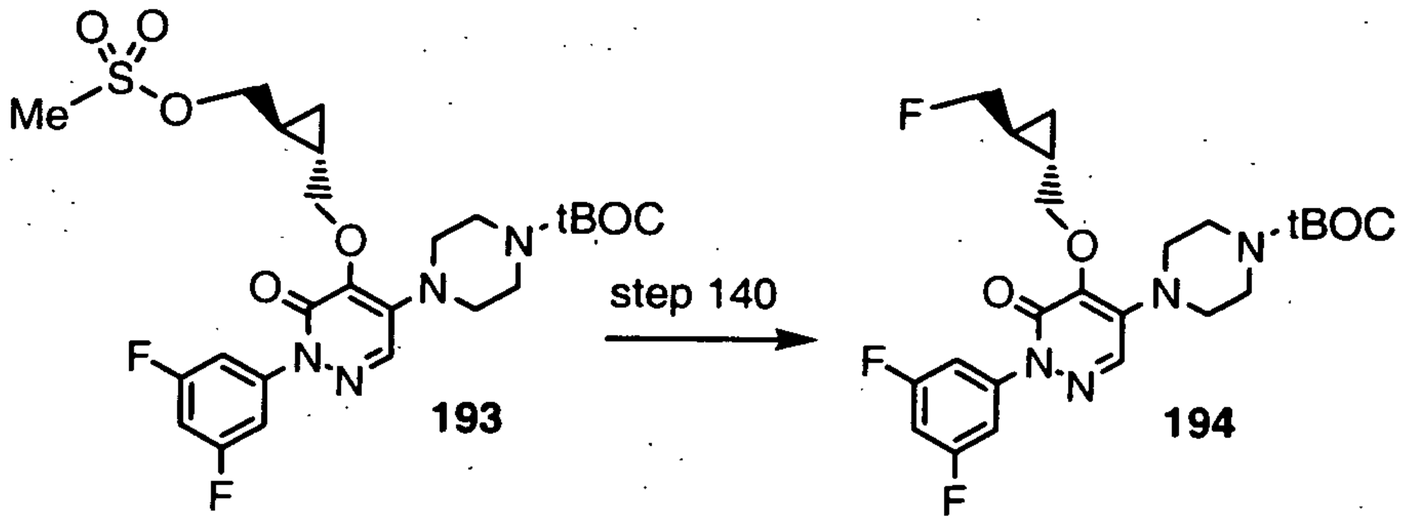
To compound **191** (4.93 g, 8.12 mmol) dissolved in dry THF (60 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 12.2 mL, 12.2 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated. Water (75 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% MeOH - CH_2Cl_2) gave 4.00 g (100% yield) of the product **192** as a yellow oil. MS (M+1): m/e 493.

Step 139:



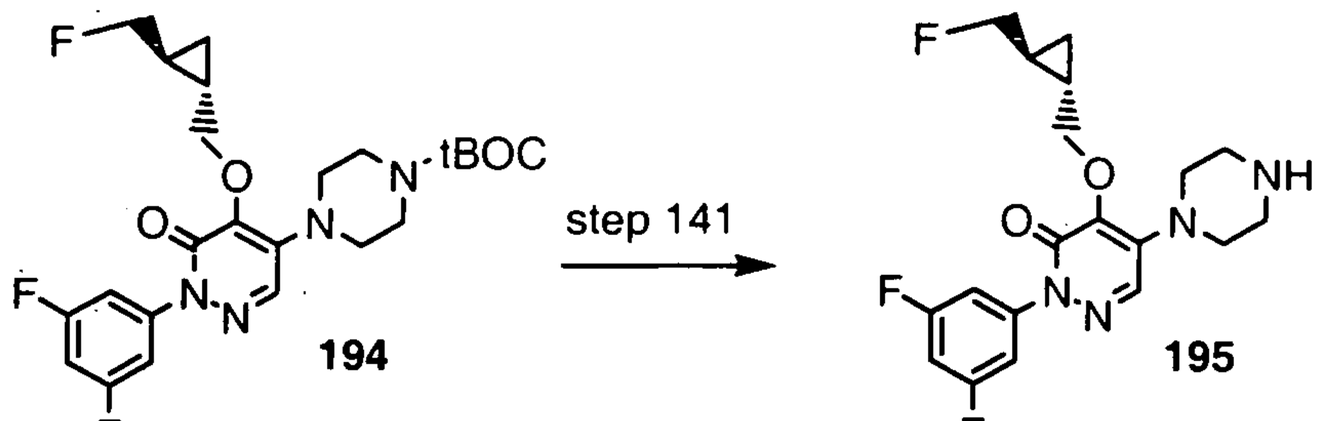
To compound **192** (1.07 g, 2.17 mmol) dissolved in CH_2Cl_2 (25 mL) was added dimethylaminopyridine (0.053 g, 0.434 mmol), triethylamine (0.33 g, 0.45 mL, 3.26 mmol), and methanesulfonic anhydride (0.45 g, 2.61 mmol). The reaction mixture was stirred at room temperature for 5 h. Saturated $NaHCO_3$ (30 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to give 1.24 g (100% yield) of the product **193** as a yellow oil. **MS (M+1)**: m/e 571.

Step 140:



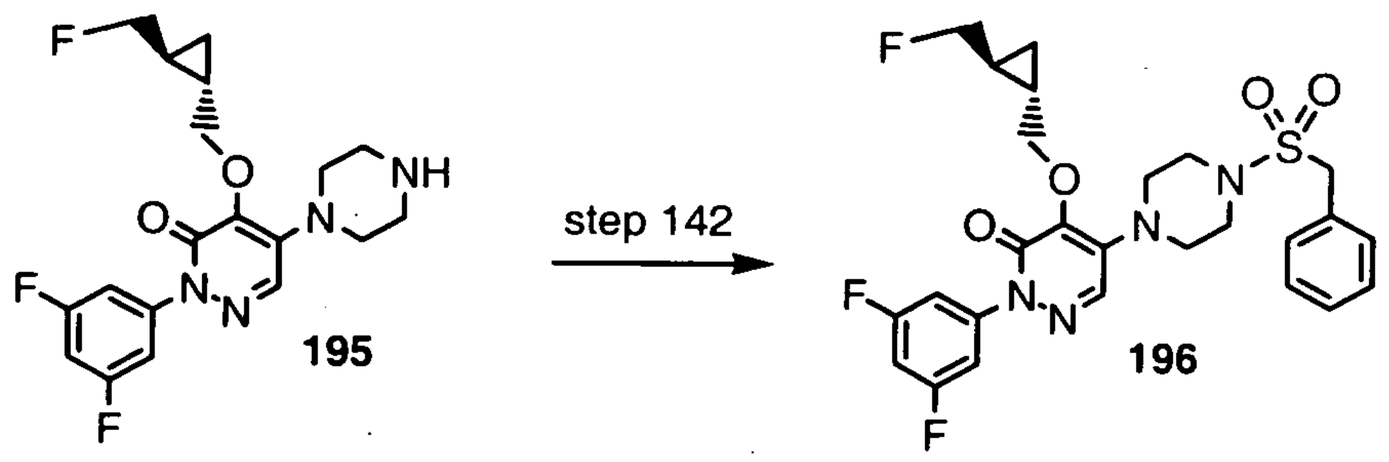
To compound **193** (1.24 g, 2.17 mmol) dissolved in dry THF (25 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 3.3 mL, 3.3 mmol). The reaction mixture was heated at 45 °C for 4.5 h. The solvent was evaporated. Water (30 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5 - 10% EtOAc - CH_2Cl_2) gave 0.67 g (63% yield) of the product **194** as a yellow oil. MS (M+1): m/e 495.

Step 141:



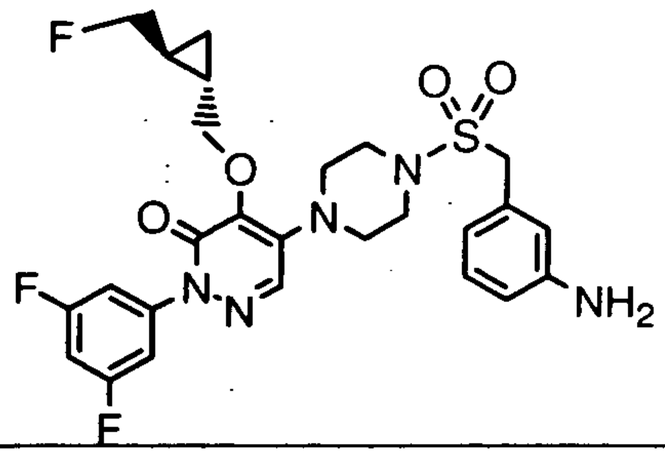
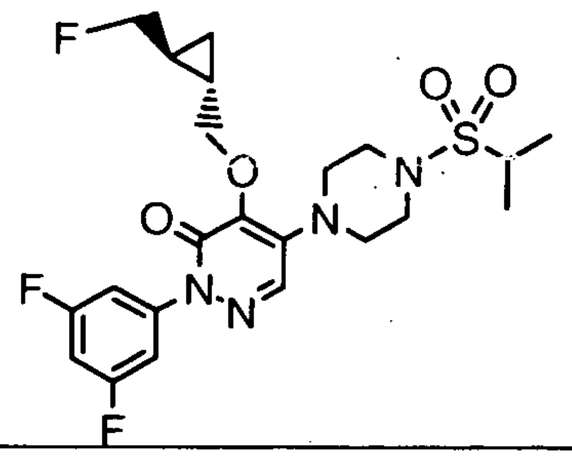
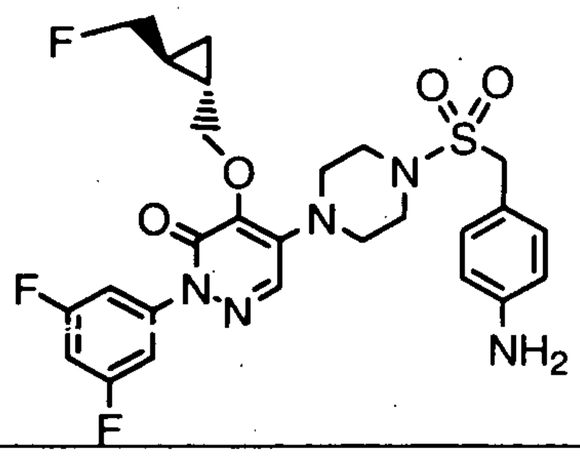
To compound **194** (0.66 g, 1.33 mmol) dissolved in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 3.5 h then the solvent was evaporated. Aqueous 0.5 N NaOH (20 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to give 0.52 g (100% yield) of the product **195** as a yellow oil. MS (M+1): m/e 395.7.

Step 142:

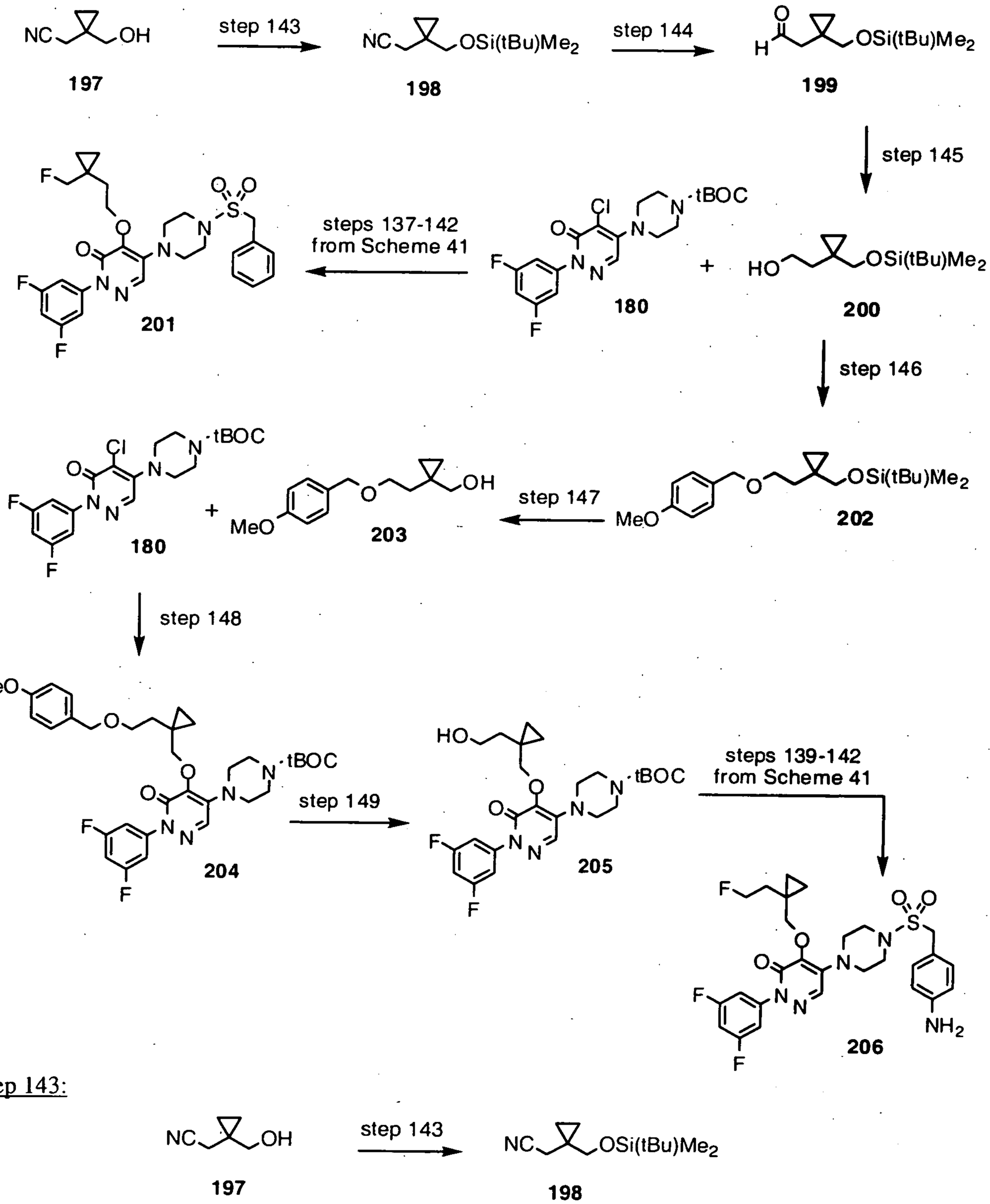


To compound **195** (100 mg, 0.254 mmol) dissolved in CH_2Cl_2 (5 mL) was added pyridine (0.062 mL, 0.762 mmol) then □-toluenesulfonyl chloride (63 mg, 0.33 mmol). The reaction mixture was stirred at room temperature for 7 h. Water was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% EtOAc - CH_2Cl_2) gave 74 mg (53% yield) of the product **196** as a yellow oil. MS (M+1): m/e 549.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1840Z		564	1841Z		501
1842Z		564			

Scheme 42

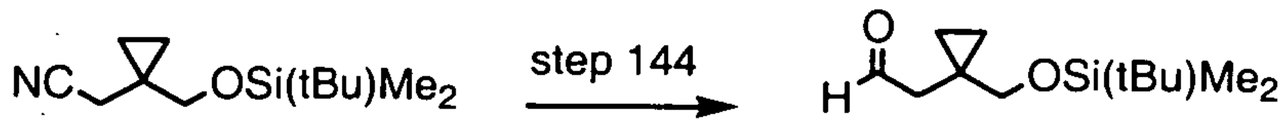


Step 143:

To compound **197** (5.00 g, 45.0 mmol) dissolved in CH_2Cl_2 (200 mL) was added dimethylaminopyridine (1.37 g, 11.2 mmol), triethylamine (6.83 g, 9.4 mL, 67.5 mmol), and

t-butyldimethylsilyl chloride (8.82 g, 58.5 mmol). The reaction mixture was stirred at room temperature for 5 h. Water (150 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 3% EtOAc - CH_2Cl_2) gave 9.57 g (94% yield) of the product **198** as a colorless oil. MS (M+1): m/e 226.

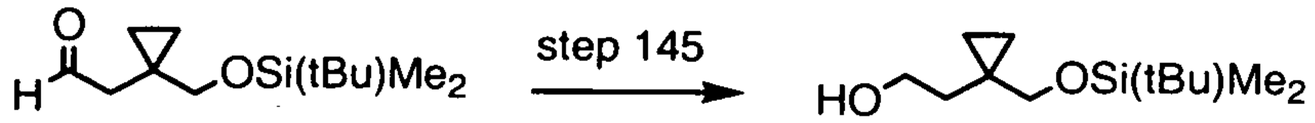
Step 144:



198 **199**

To compound **198** (9.56 g, 42.4 mmol) dissolved in CH_2Cl_2 (150 mL) and cooled to -78 °C under nitrogen was added diisobutylaluminum hydride (1 M in hexane, 46.7 mL, 46.7 mmol) via addition funnel over 10 mins. The reaction mixture was warmed slowly to 0 °C over 45 mins and stirred at 0 °C for 30 mins. Carefully added 1 N HCl (200 mL) and then extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to give 9.69 g (100% yield) of the product **199** as a yellow oil. MS (M+1): m/e 228.

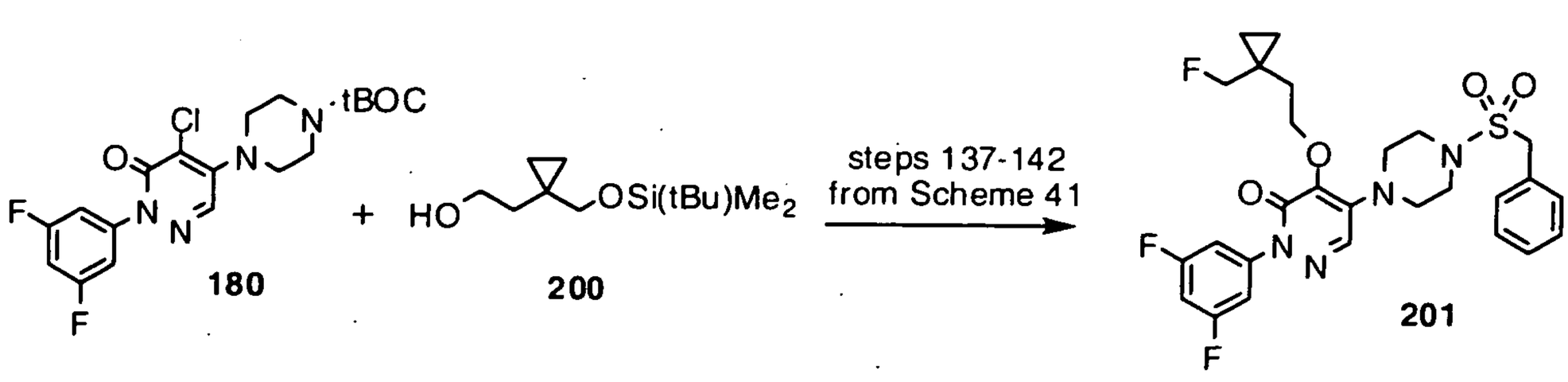
Step 145:



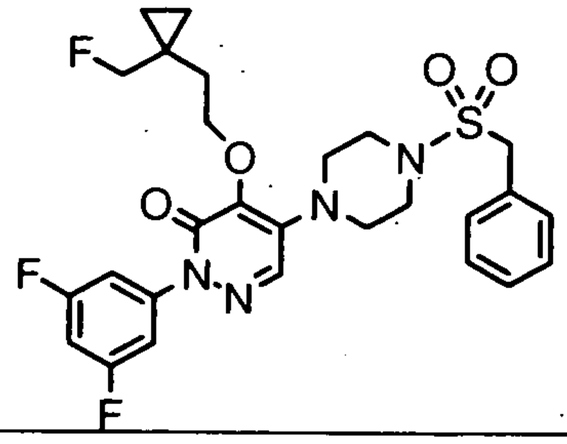
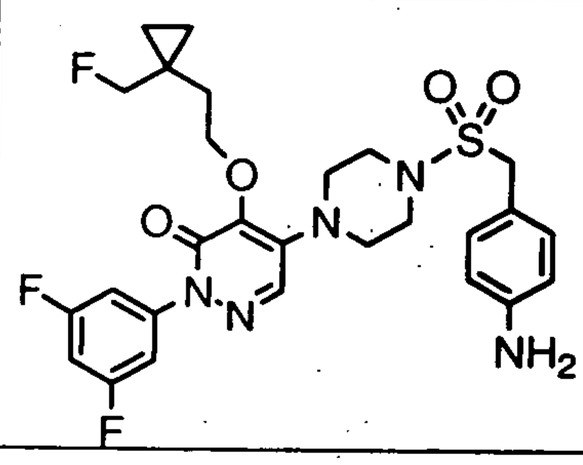
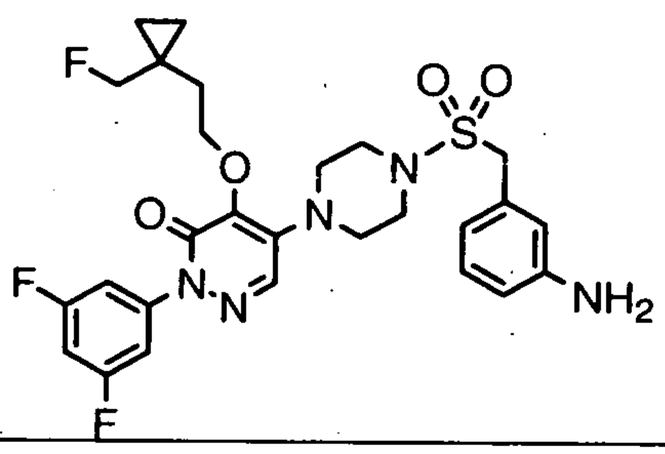
199 **200**

To compound **199** (9.69 g, 42.4 mmol) dissolved in ethanol (200 mL) was added sodium borohydride (2.41 g, 63.6 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated. Water (200 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 10% EtOAc - CH_2Cl_2) gave 6.86 g (70% yield) of the product **200** as a yellow oil. MS (M+1): m/e 231.

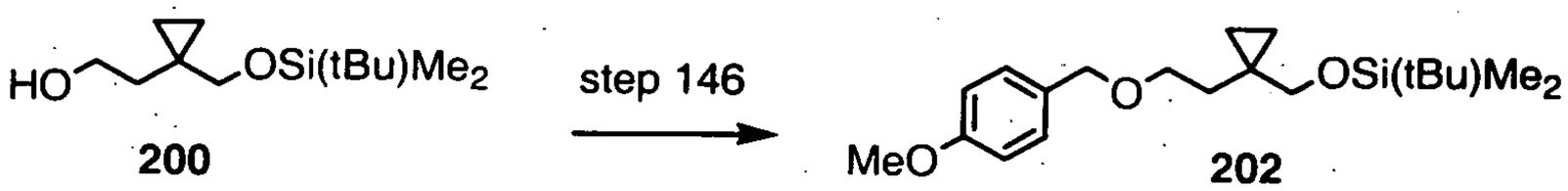
Steps 137-142 from Scheme 41:



Using the procedures from steps 137-142 from Scheme 41, the following compounds were synthesized.

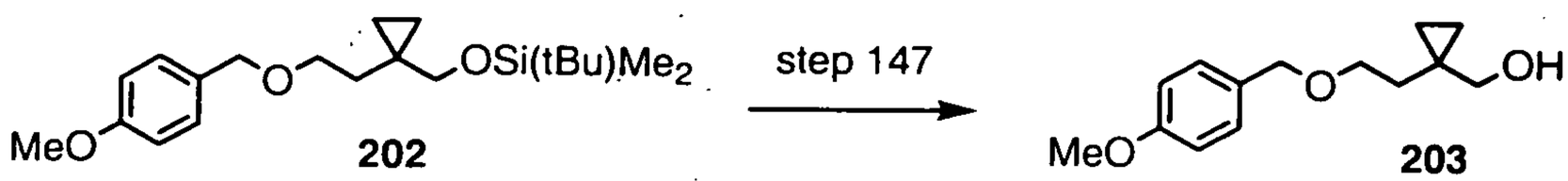
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1843Z		563	1844Z		578
1845Z		578			

Step 146:



To compound **200** (5.45 g, 23.7 mmol) dissolved in dry THF (100 mL) under nitrogen was added sodium bis(trimethylsilyl)amide via syringe. The reaction mixture was stirred at room temperature for 15 mins then p-methoxybenzylbromide (6.18 g, 30.8 mmol) was added. The resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated. Water (100 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 2% EtOAc - CH_2Cl_2) gave 7.59 g (92% yield) of the product **202** as a colorless oil. MS (M+1): m/e 351.

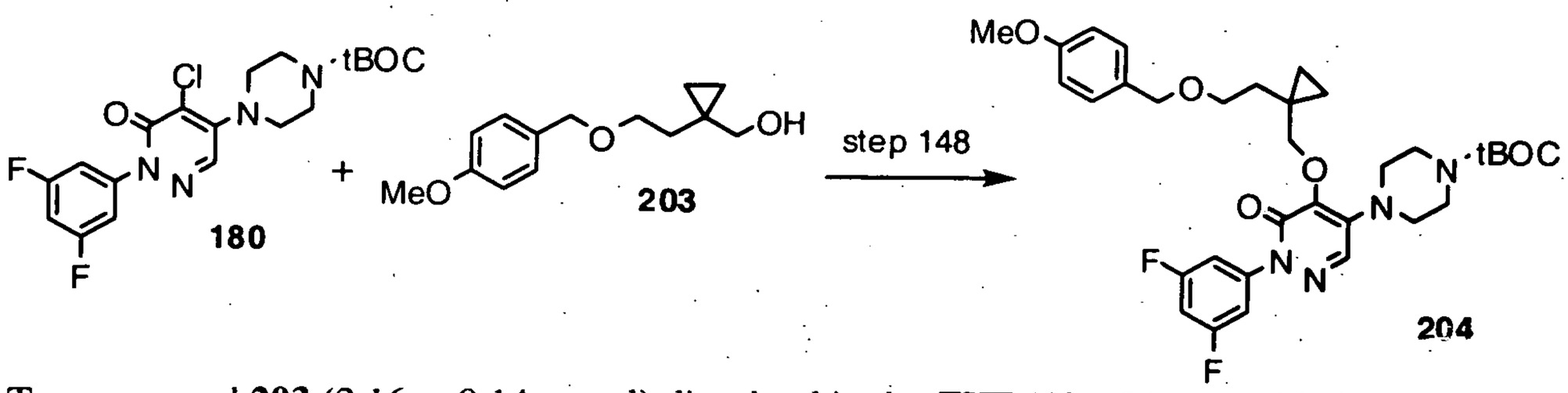
Step 147:



To compound **202** (7.58 g, 21.6 mmol) dissolved in dry THF (100 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 27.0 mL, 27.0 mmol). The reaction mixture

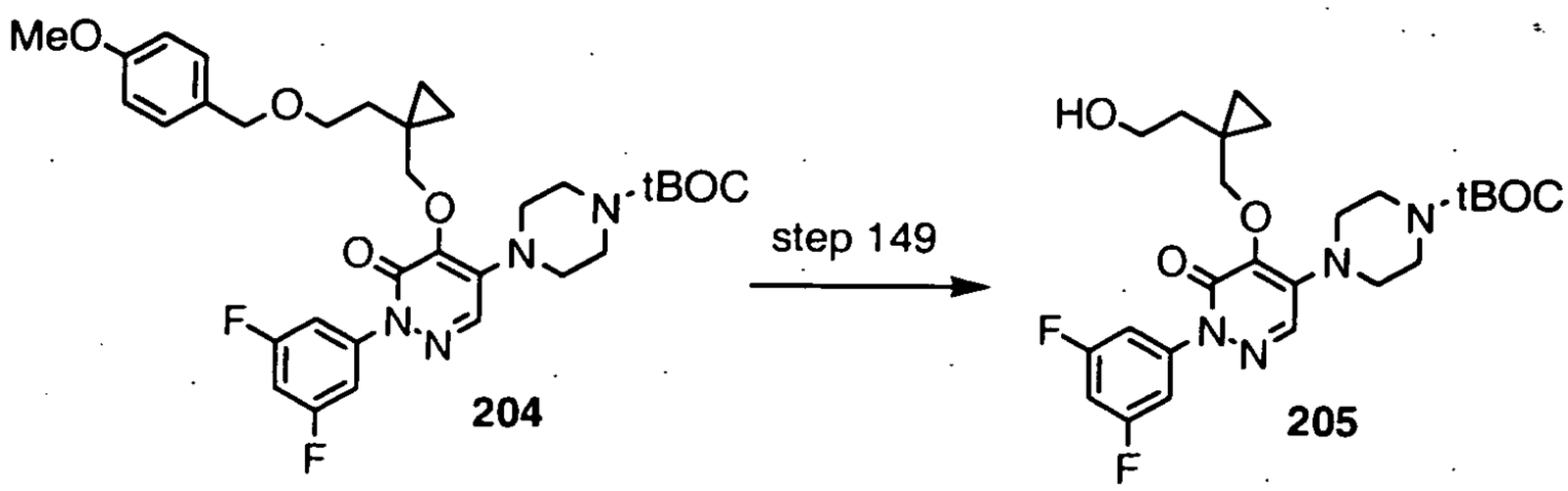
was stirred at room temperature for 16 h. The solvent was evaporated. Water (100 mL) was added, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 15% EtOAc - CH_2Cl_2) gave 5.03 g (98% yield) of the product **203** as a colorless oil. MS (M+1): m/e 237.

Step 148:



To compound **203** (2.16 g, 9.14 mmol) dissolved in dry THF (40 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 8.4 mL, 8.40 mmol) via syringe. The reaction mixture was stirred at room temperature for 15 mins under nitrogen. Chloropyridazinone **180** (3.00 g, 7.03 mmol) was added, and the reaction mixture was heated at 80 °C for 1 h then stirred at room temperature for 16 h. The solvent was evaporated. Water (50 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 5 - 15% EtOAc - CH_2Cl_2) gave 4.40 g (100% yield) of the product **204** as a yellow oil. MS (M+1): m/e 628.

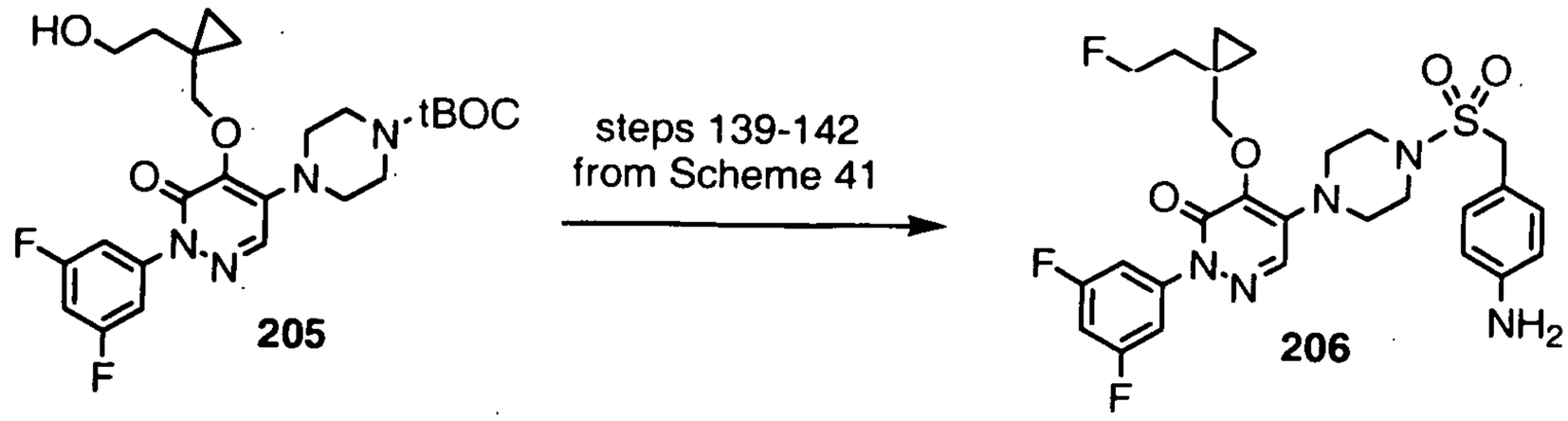
Step 149:



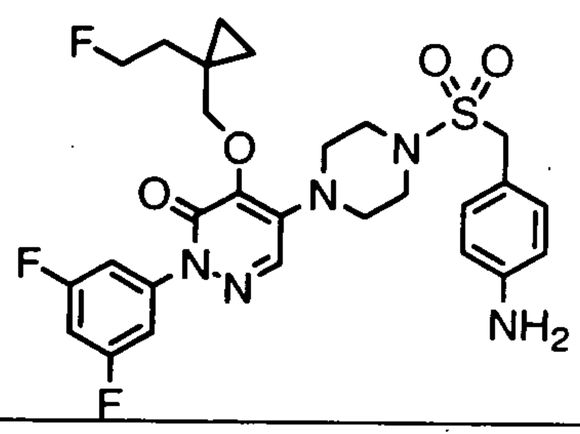
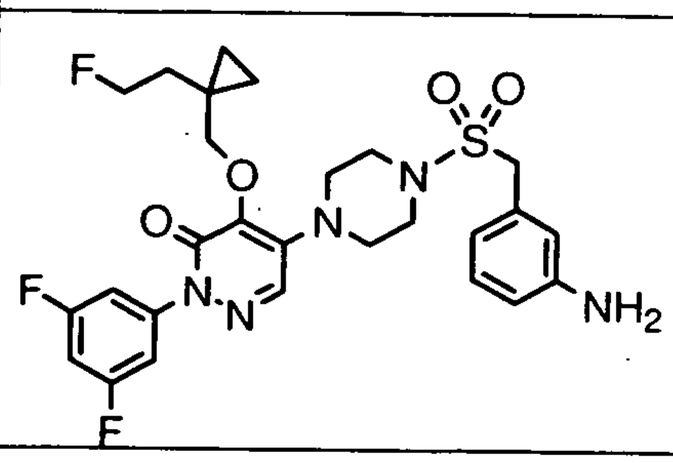
To compound **204** (4.40 g, 7.03 mmol) dissolved in CH_2Cl_2 (50 mL) and water (3 mL) was added 2,3-dichloro-5,6-dicyano-benzoquinone (1.92 g, 8.44 mmol). The reaction mixture was stirred at room temperature for 60 mins. Saturated $NaHCO_3$ (100 mL) was added and the aqueous solution was extracted with EtOAc. The combined organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 15%

EtOAc - CH_2Cl_2 then 5% MeOH – CH_2Cl_2) gave 2.90 g (81% yield) of the product **205** as a white foam. MS (M+1): m/e 508.

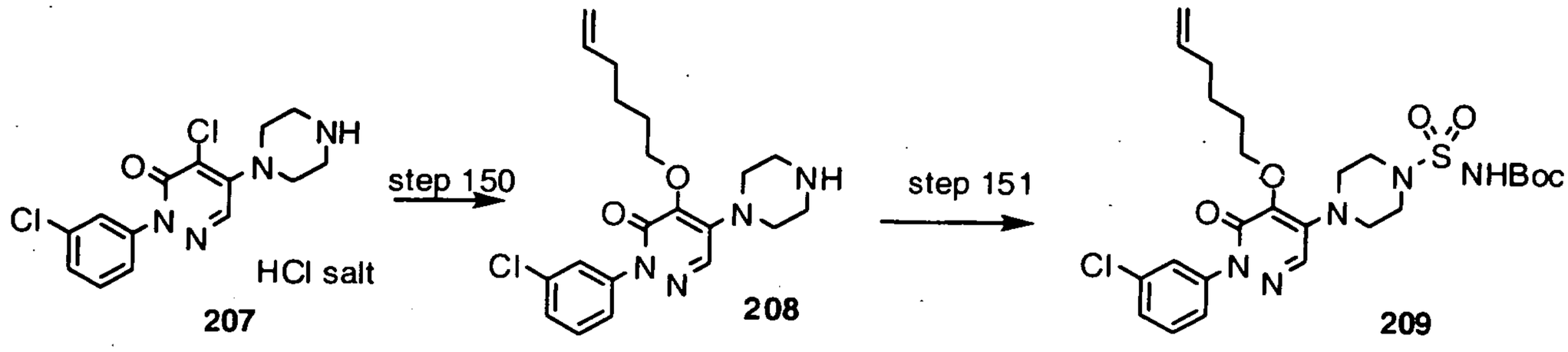
Steps 139-142 from Scheme 41:



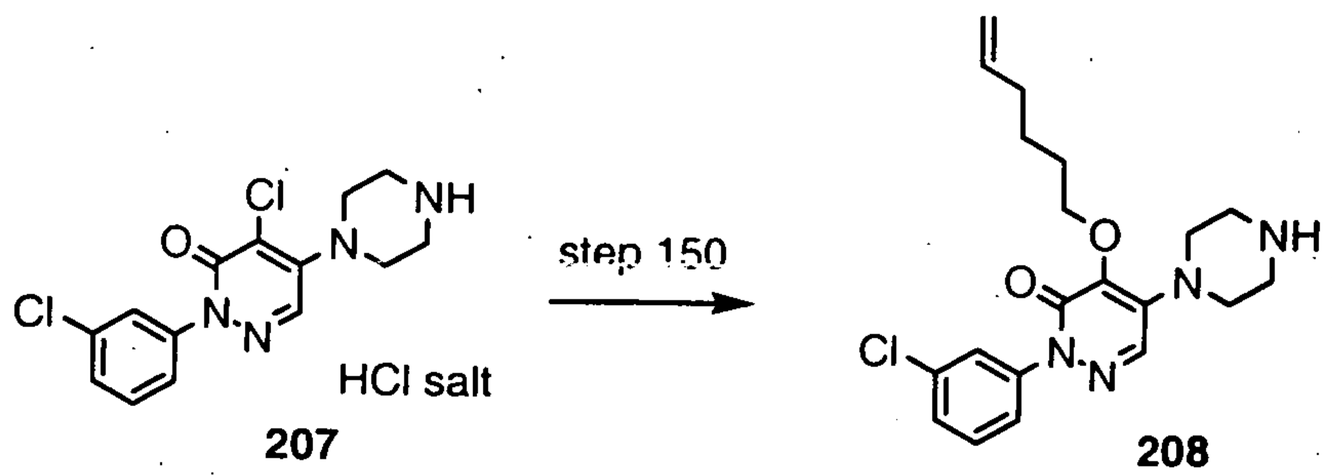
Using the procedures from steps 139-142 from Scheme 41, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1846Z		578	1847Z		578

Scheme 43



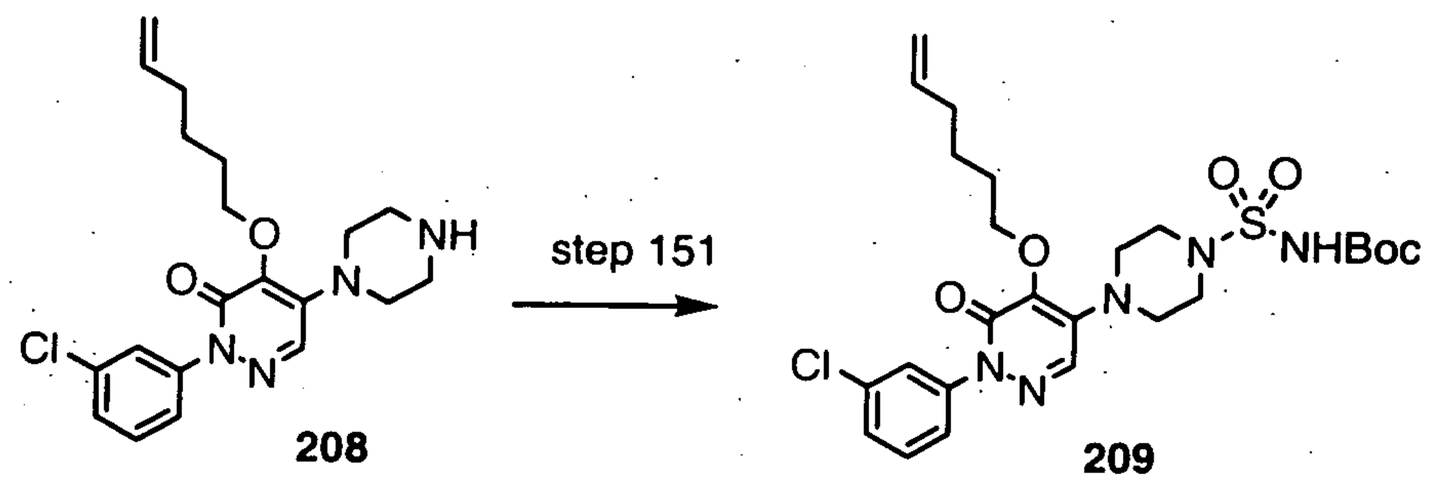
Step 150:



207 208

Compound **207** (1.0 g, 2.8 mmol) and 5-hexenol-1 (0.83 g, 8.3 mmol) were mixed in 15 mL of dry THF. NaH (60%, 0.28 g, 7 mmol) was added. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with 10 mL of water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by flash chromatography (eluant: 0-0.5% 7 M NH_3/MeOH in CH_2Cl_2 gradient) to give 1.1 g (100%) of compound **208** as a colorless oil. MS (M+1): m/e 389.

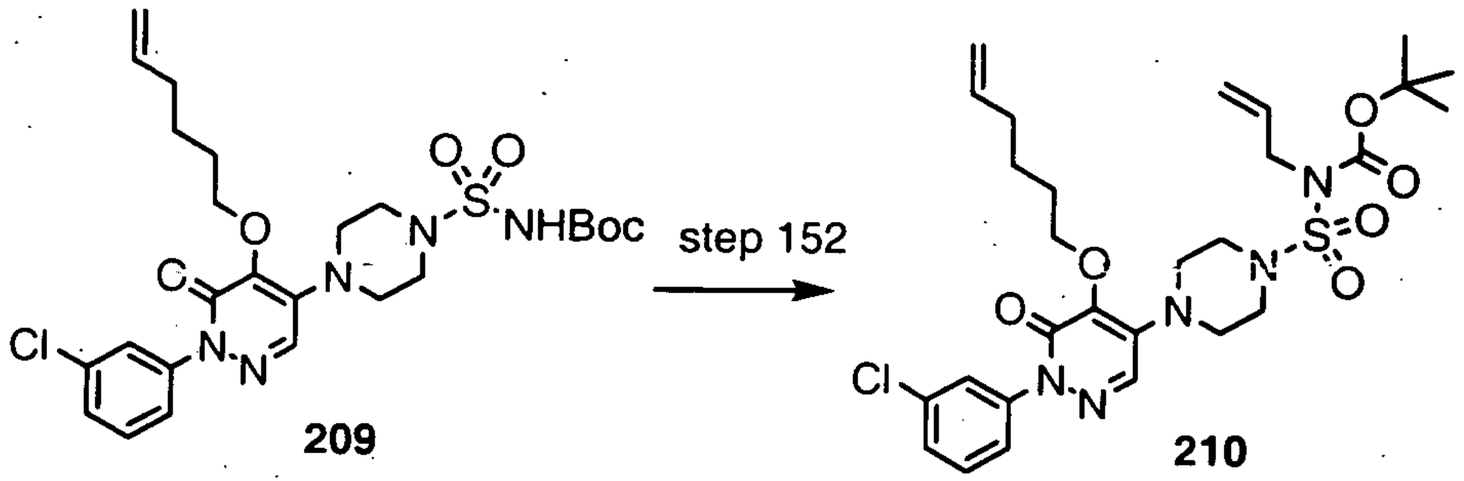
Step 151:



208 209

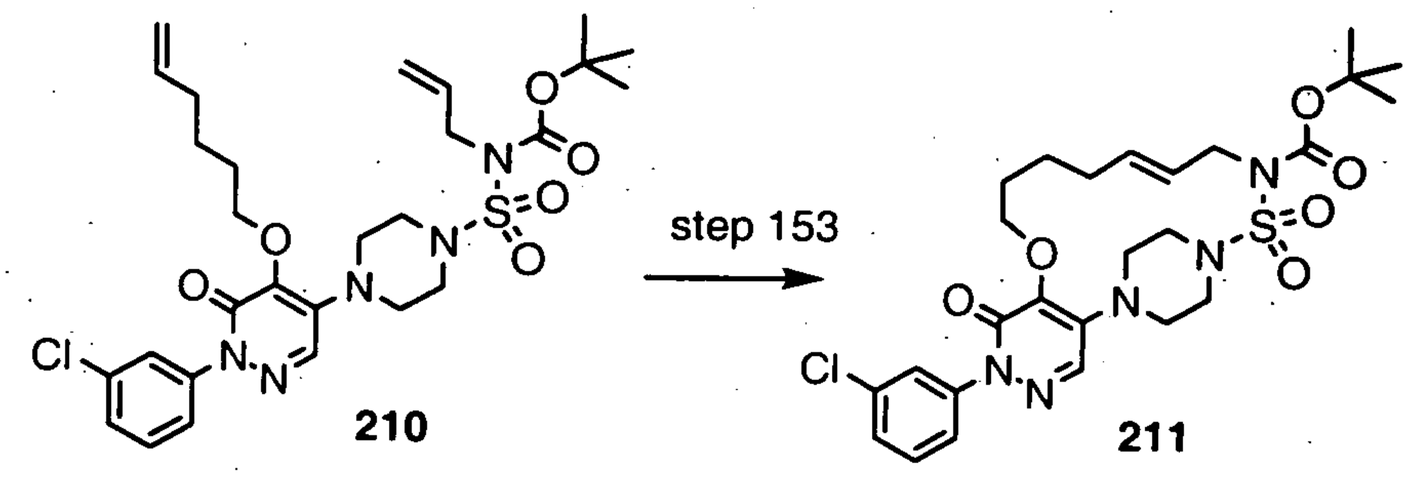
Compound **208** (2.7 mmol) dissolved in 10 mL of dry CH_2Cl_2 was mixed with isopropyldiethylamine (1.5 mL, 8.8 mmol), and cooled to 0 °C with an ice-water bath. A freshly prepared 0.5 M solution of $BocNHSO_2Cl$ in CH_2Cl_2 (8 mL, 4 mmol) was added dropwise. The resulting mixture was then stirred at room temperature overnight. The mixture was diluted with 500 mL of CH_2Cl_2, and washed with 1 N HCl solution then water. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography gave 1.4 g of compound **209** as a white solid. MS (M+1): m/e 568.

Step 152:



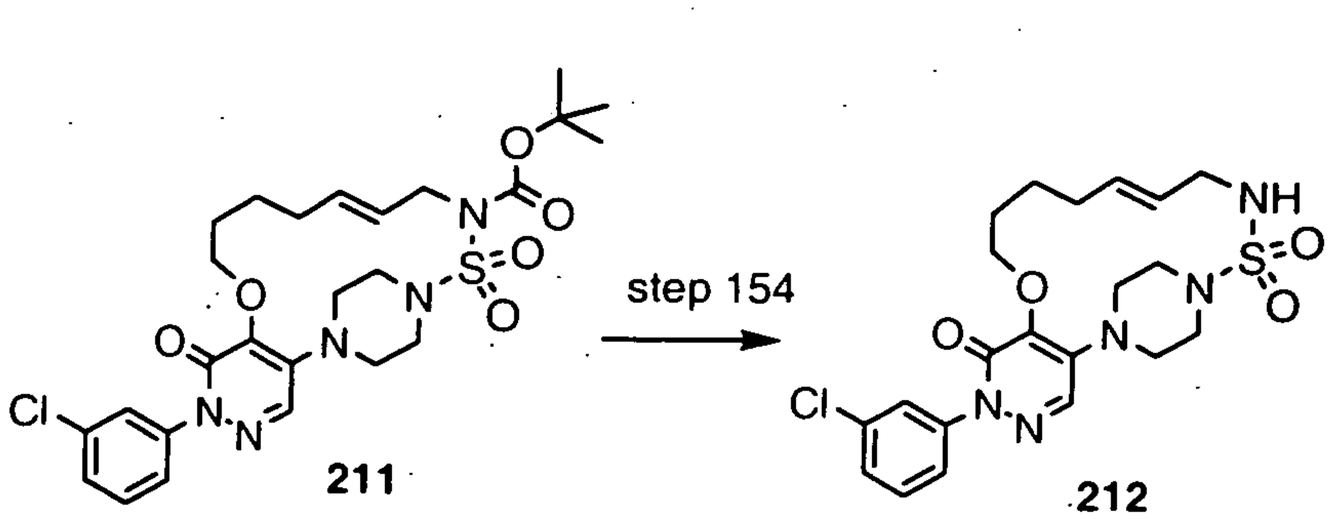
Compound **209** (0.38 g, 0.7 mmol) was mixed with allyl bromide (0.3 mL), and phosphazene base P1-t-Bu (0.25 mL, 1 mmol) in 5 mL of dry THF. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, and washed with water then brine. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated. Purification by flash chromatography gave 0.35 g of compound **210** as a white solid. MS (M+1): m/e 608.

Step 153:



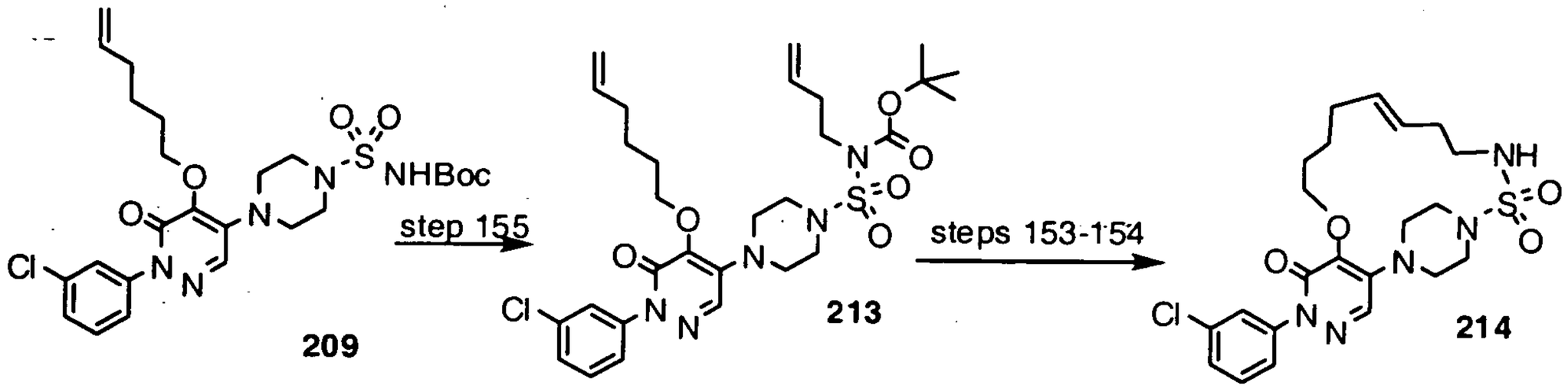
Compound **210** (92 mg, 0.15 mmol) in 60 mL of CH_2Cl_2 was mixed with 25 mg of 2nd generation Grubbs' catalyst under nitrogen. The mixture was then heated to 50 °C under nitrogen overnight. After cooling, the mixture was concentrated. Purification by flash chromatography (eluant: 10% - 30% EtOAc - hexane gradient) gave 81 mg of compound **211** as a white solid. MS (M+1): m/e 580.

Step 154:

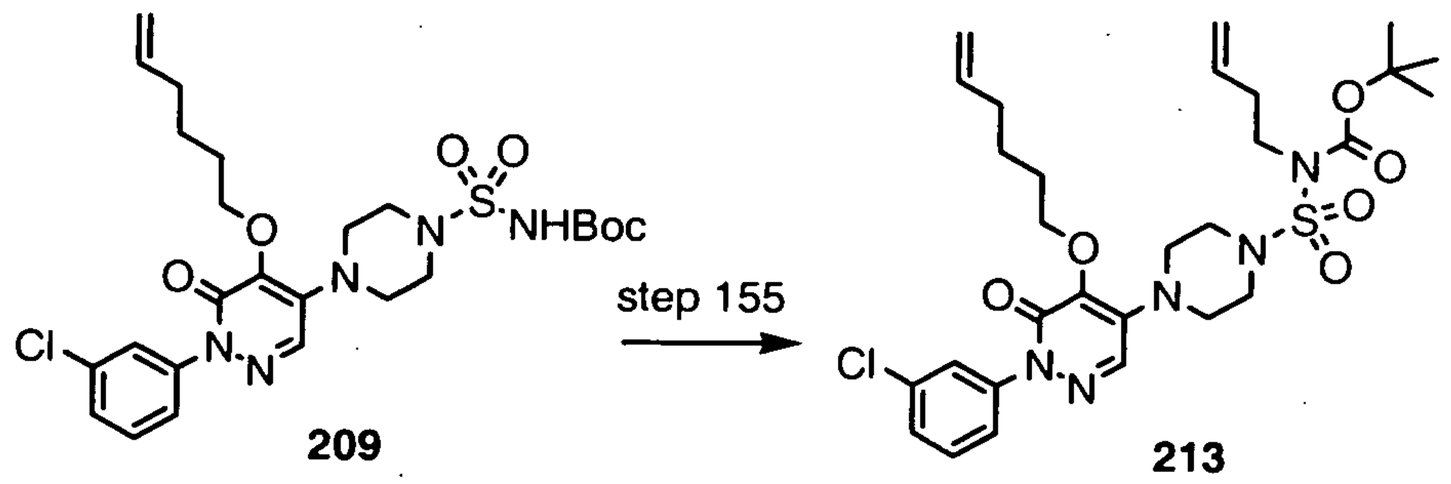


Compound **211** (70 mg) was treated with 10 mL of 4 N HCl in dioxane at room temperature overnight. The mixture was concentrated, and the crude product was purified by flash chromatography (eluant: 10% - 40% EtOAc - hexane gradient) to give 51 mg of compound **212** as a white solid. MS (M+1): m/e 480.

Scheme 44

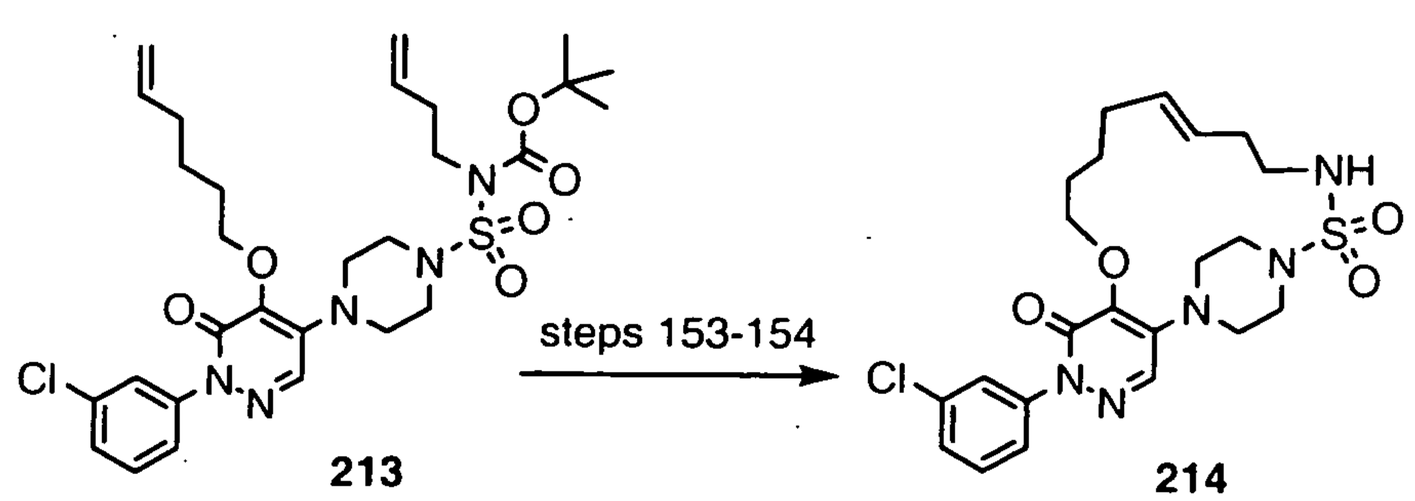


Step 155:

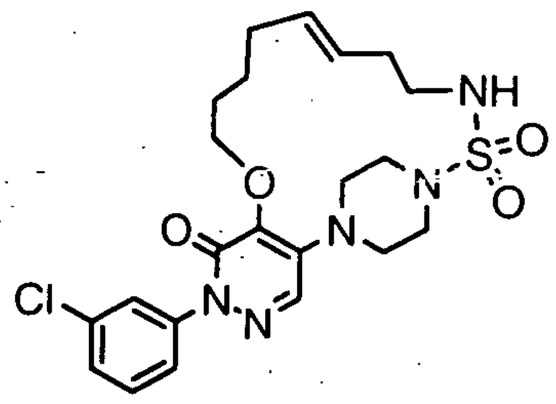
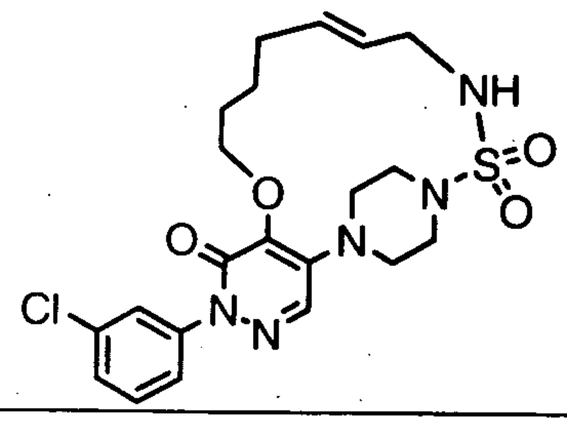
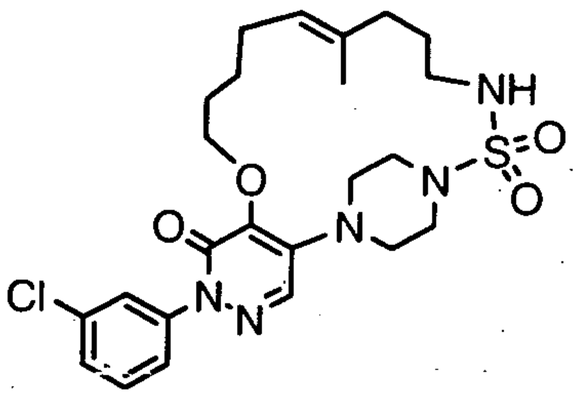
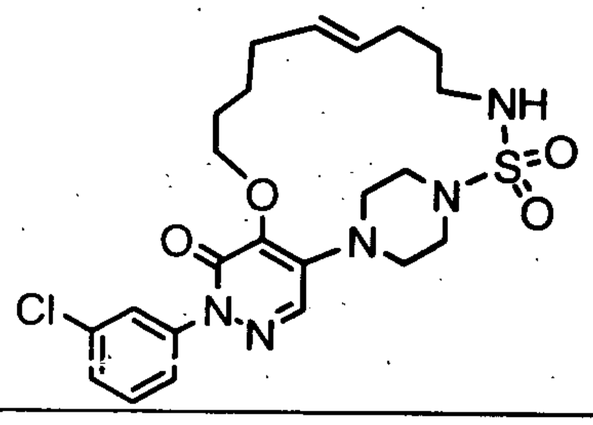


Compound **209** (0.20 g, 0.35 mmol) was mixed with 3-buten-1-ol (0.06 mL, 0.7 mmol), triphenylphosphine (0.18g, 0.7 mmol), and DIAD (0.14 mL, 0.7 mmol) in 3 mL of dry THF. The mixture was stirred at room temperature overnight then concentrated. Purification by flash chromatography (eluant: 10% - 30% EtOAc - hexane gradient) gave 0.21 g of compound **213** as a white solid. MS (M+1): m/e 622.

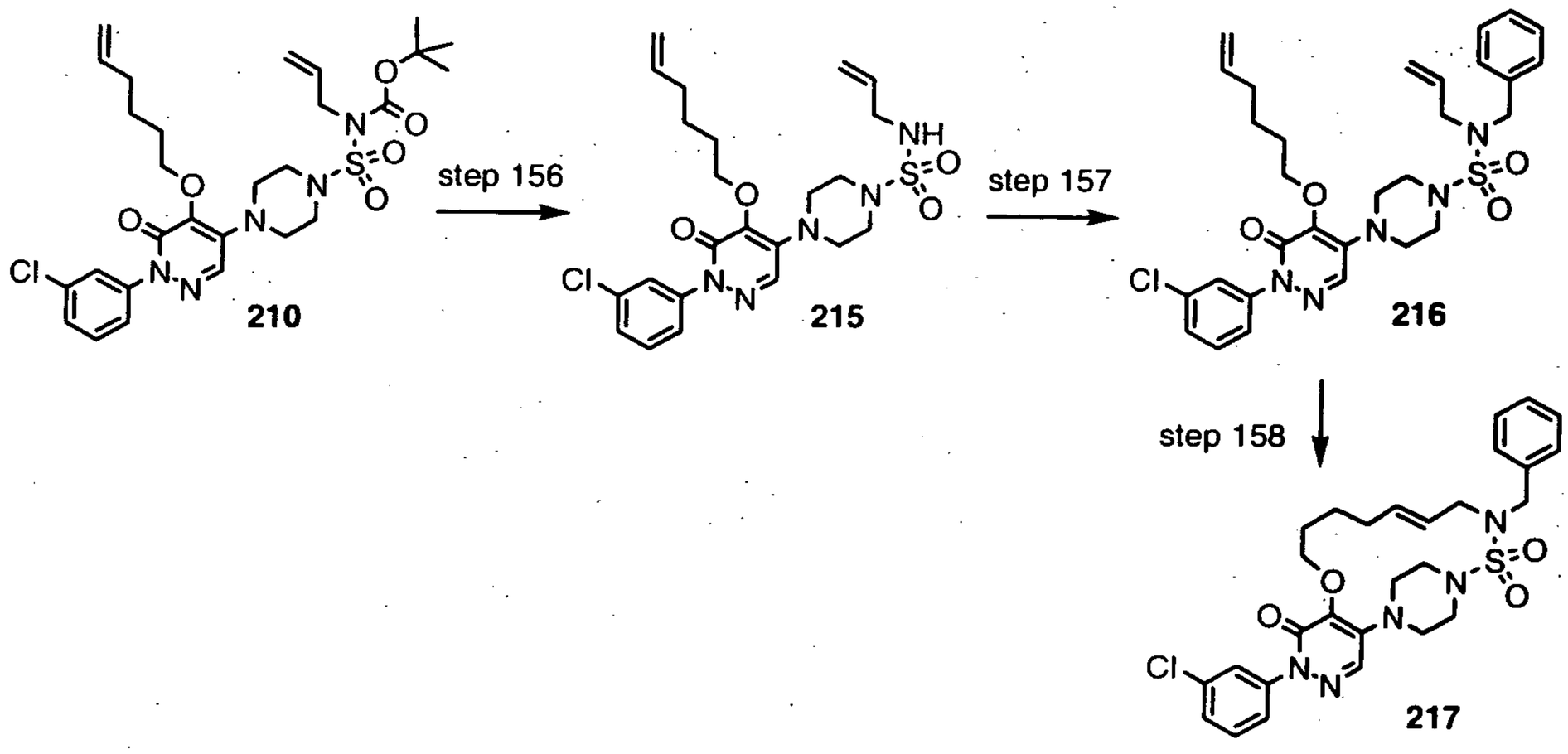
Steps 153-154:



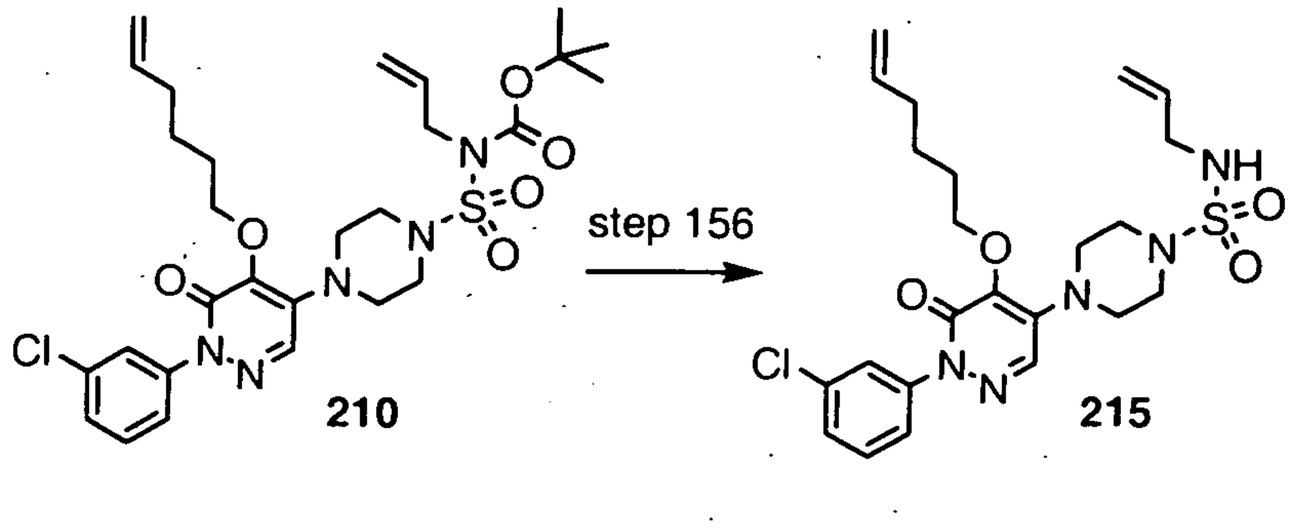
Using the procedures from step 153-154 from Scheme 43, the following compounds were synthesized.

Cmpd. No	Structure	MS M+1		Cmpd. No.	Structure	MS M+1
1848Z		493		1849Z		479
1850Z		521		1851Z		507

Scheme 45

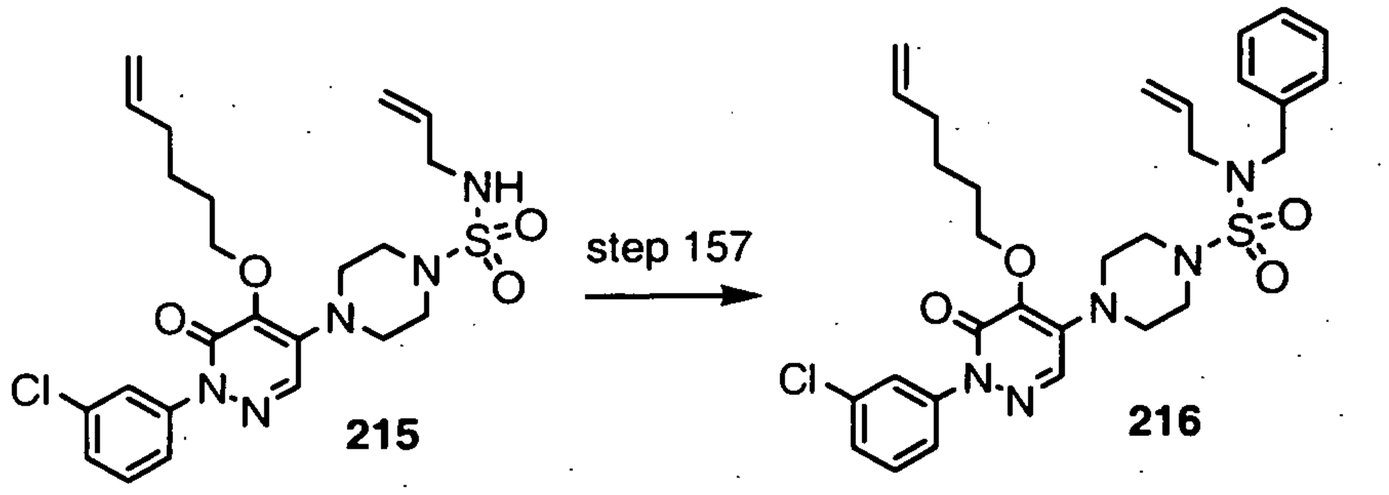


Step 156:



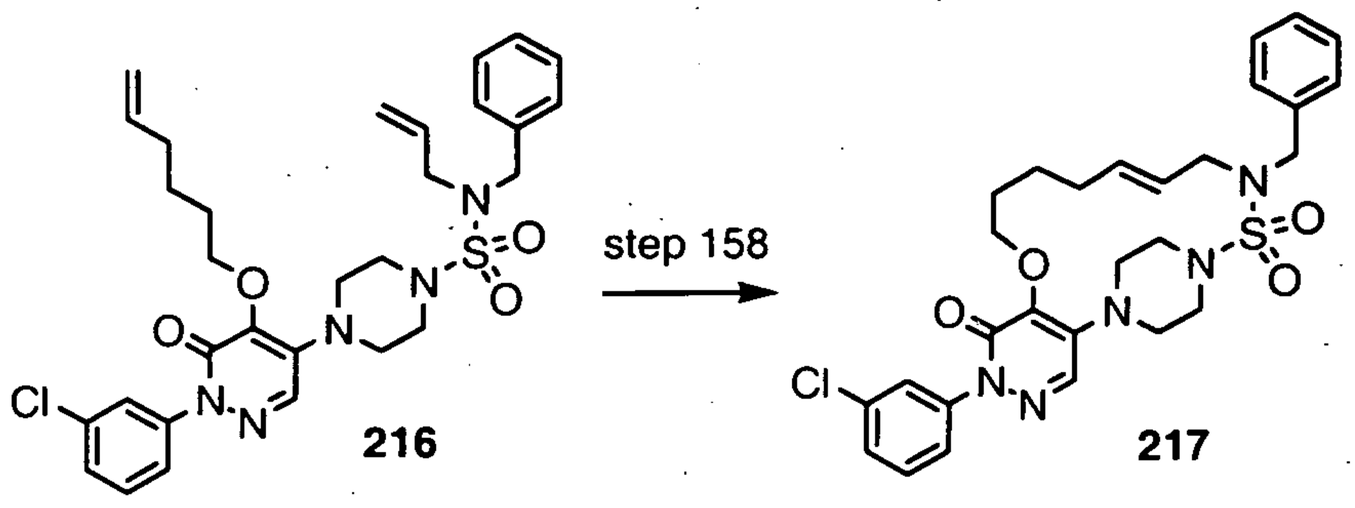
Compound **210** (220 mg) was treated with 10 mL of 4 N HCl in dioxane at room temperature overnight. Mixture was concentrated, and the crude was purified by flash chromatography (eluant: 10% - 40% EtOAc - hexane gradient) to give 180 mg of compound **215** as a white solid. MS (M+1): m/e 508.

Step 157:



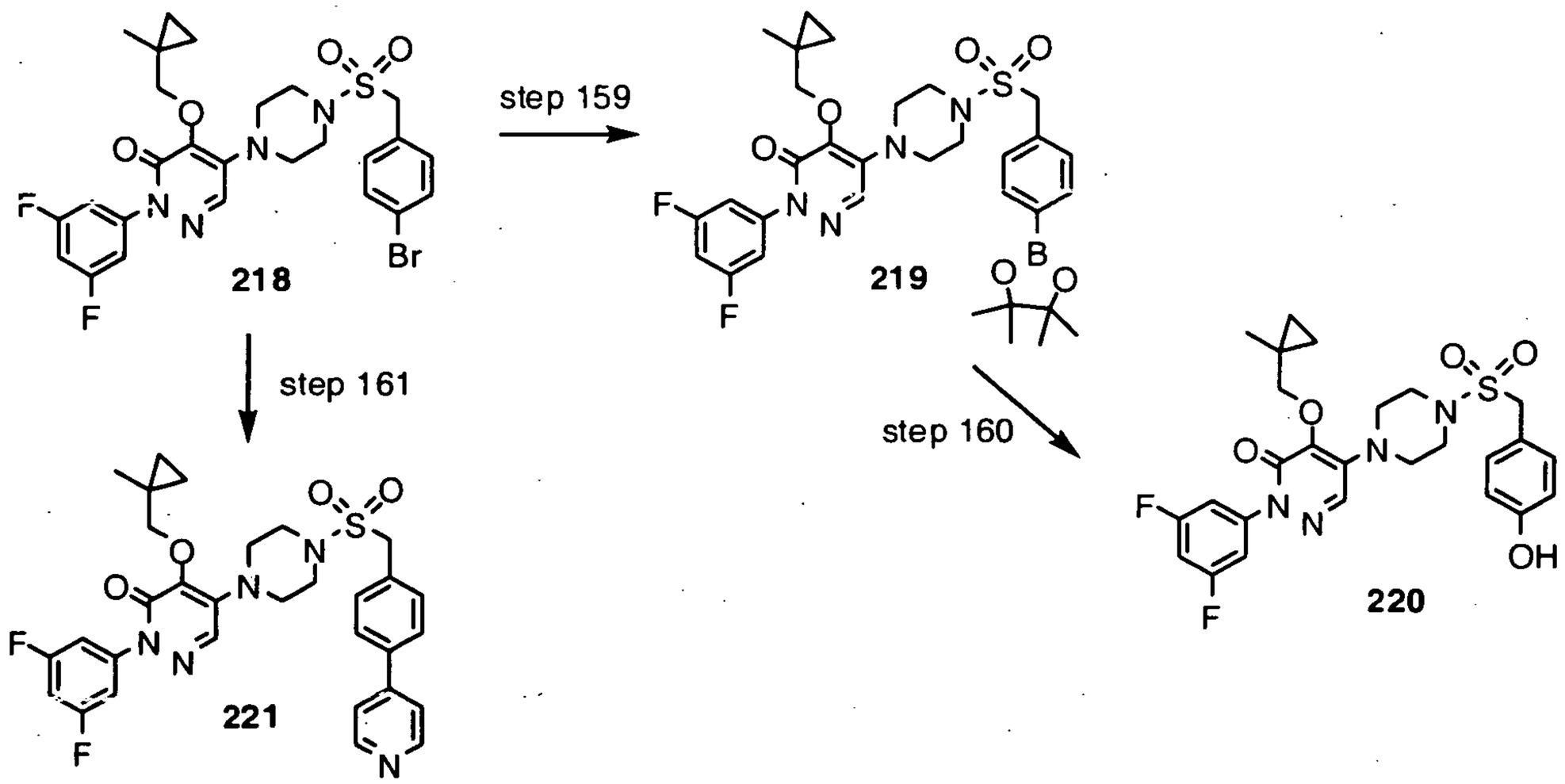
Compound **215** (0.11 g, 0.22 mmol) was mixed with benzyl bromide (40 mg, 0.23 mmol), and 60% NaH (10 mg, 0.24 mmol) in 2 mL of dry DMF at 0 °C . The resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, and washed with water then brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography gave 0.10 g of compound **216** as a white solid. MS (M+1): m/e 598.

Step 158:

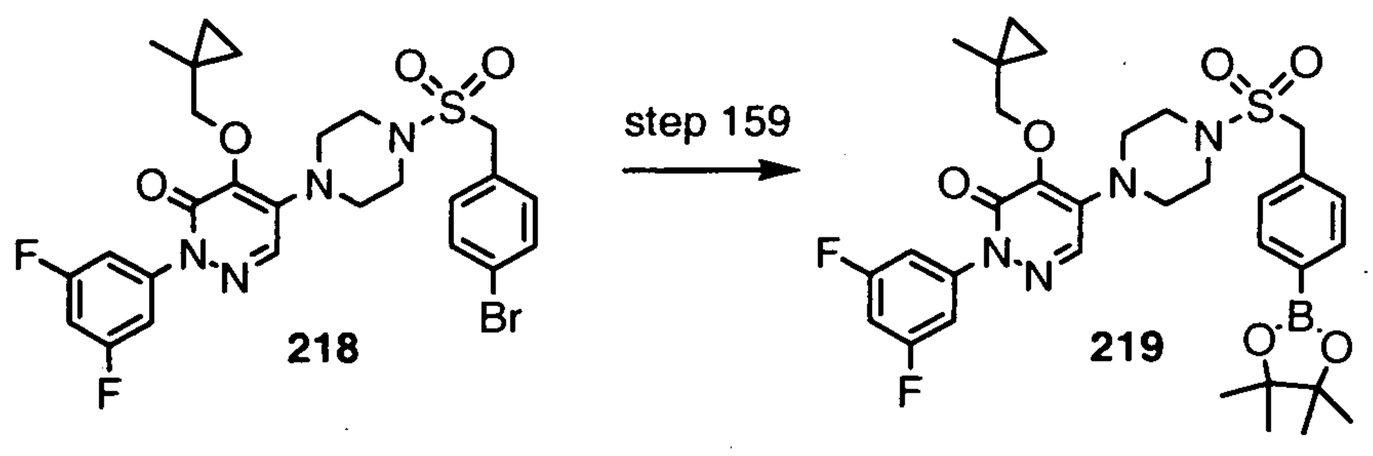


Compound **216** (90 mg, 0.15 mmol) in 50 mL of CH_2Cl_2 was mixed with 25 mg of 2nd generation Grubbs' catalyst under nitrogen. The mixture was then heated to 50 °C under nitrogen overnight. After cooling, the mixture was concentrated, and the crude product was purified by Gilson Prep HPLC (eluant: CH_3CN – water gradient) to give 69 mg of compound **217** as a white solid. MS (M+1): m/e 570.

Scheme 46

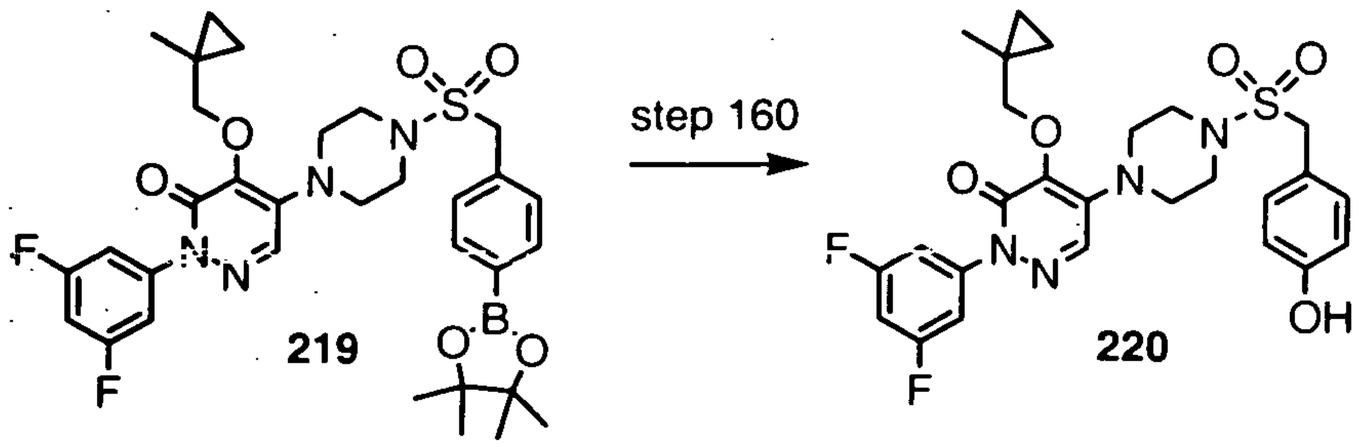


Step 159:



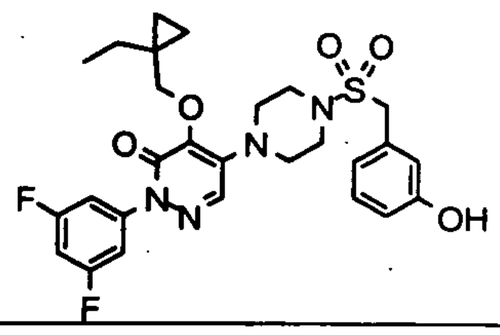
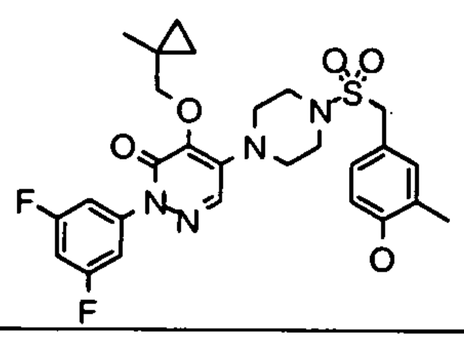
A round bottom flask was charged with [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II),complex with dichloromethane (1:1) (6.70 mg, 0.00820 mmol); compound 218 (100 mg, 0.164 mmol); bis(pinacolato)diboron (50.0 mg, 0.197 mmol); and potassium acetate (80.5 mg, 0.820 mmol) in 1,4-dioxane (20 mL) . The reaction mixture was placed under a nitrogen atmosphere and was degassed under vacuum three times. The reaction was stirred at 100 °C overnight. After cooling, the mixture was filtered through a short path silica column (eluant: ethyl acetate). The solvent was concentrated then purification by flash chromatography (eluant: 1:1 hexane:EtOAc) gave 75 mg (70% yield) of the product **219**. MS (M+1): m/e 657.

Step 160:

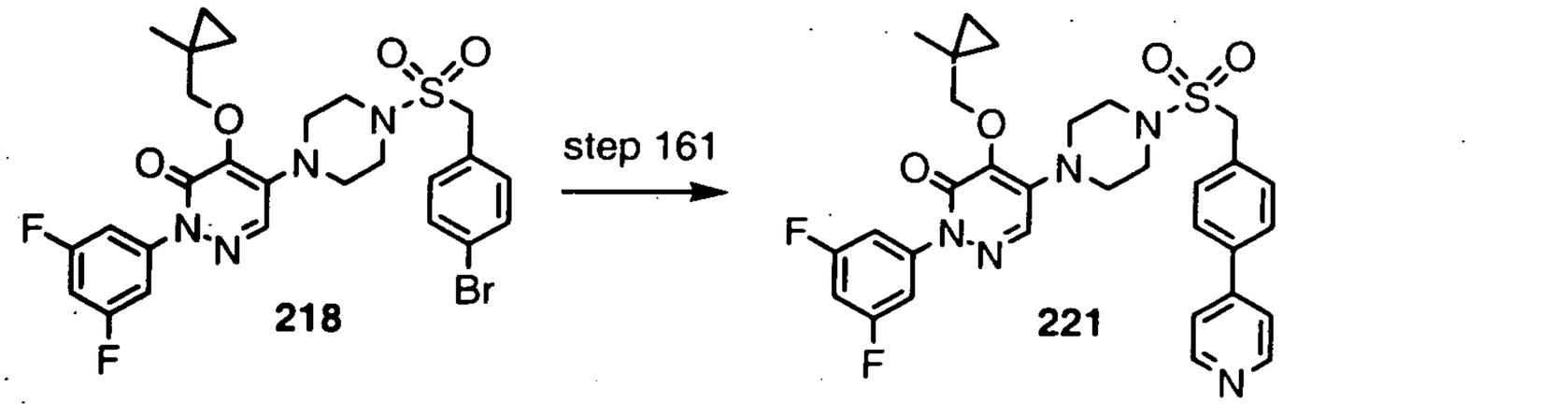


Compound **219** (80 mg, 0.1 mmol) was dissolved in ethanol, and 1 M of sodium bicarbonate (200 uL) and hydrogen peroxide (50 uL, 0.5 mmol) were added at 0 °C. The reaction was stirred at 0 °C overnight then concentrated. 1 M Hydrogen chloride in water (5 mL) was added, the mixture was extracted with ethyl acetate (150 mL), dried over sodium sulfate, and concentrated. Purification by silica gel chromatography (eluant: 1:1 hexane:EtOAc) gave 42 mg (63% yield) of the product **220**. MS (M+1): m/e 547.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No	Structure	MS M+1		Cmpd. No.	Structure	MS M+1
1852Z		547		1853Z		562

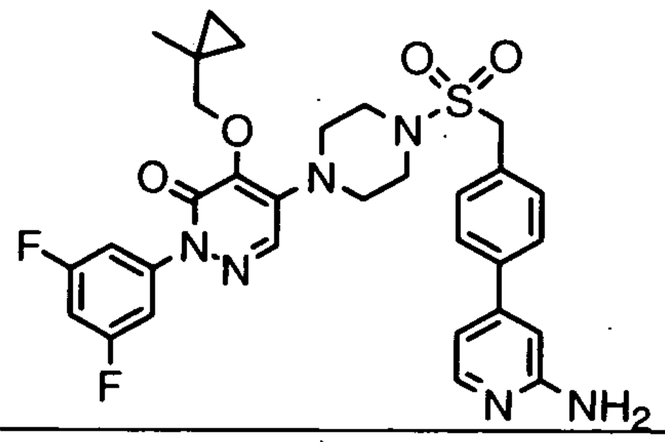
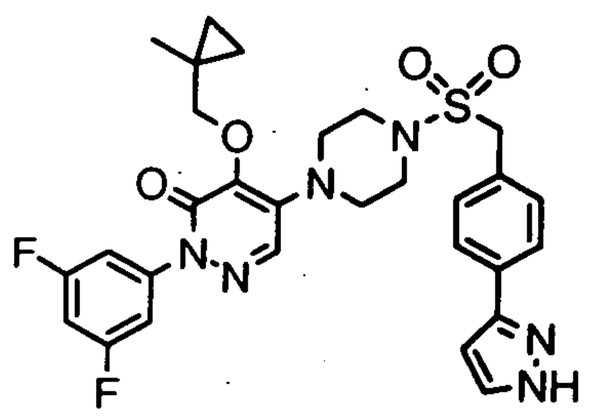
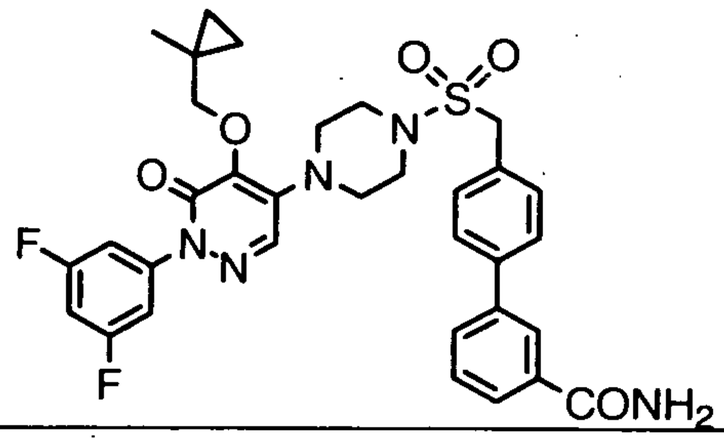
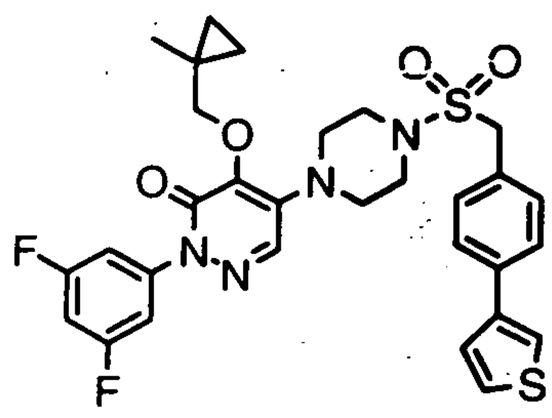
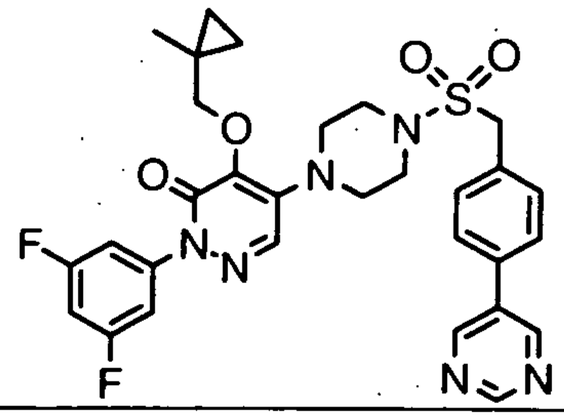
Step 161:



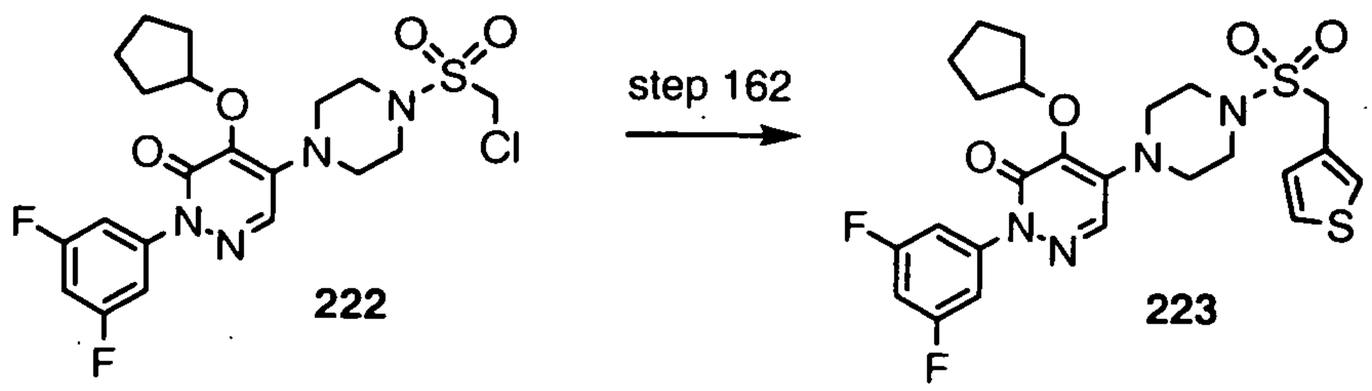
A round bottom flask was charged with compound **218** (70.0 mg, 0.115 mmol), tetrakis(triphenylphosphine)palladium(0) (5.69 mg, 0.00492 mmol), 4-pyridylboronic acid (20.0 mg, 0.163 mmol), and cesium carbonate (38.5 mg, 0.118 mmol) in 1,4-dioxane (20 mL) and water (2 mL). The reaction was placed under an atmosphere of nitrogen and degassed under vacuum three times. The reaction mixture was stirred at 100 °C overnight. After cooling, the mixture was filtered through a short path silica column (eluant: ethyl acetate).

The solvent was concentrated, and purification by silica gel chromatography (eluant: 1:2 hexane:EtOAc) gave 70 mg (100% yield) of the product **221**. MS (M+1): m/e 608.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1854Z		624	1855Z		598
1856Z		651	1857Z		614
1858Z		610			

Scheme 47

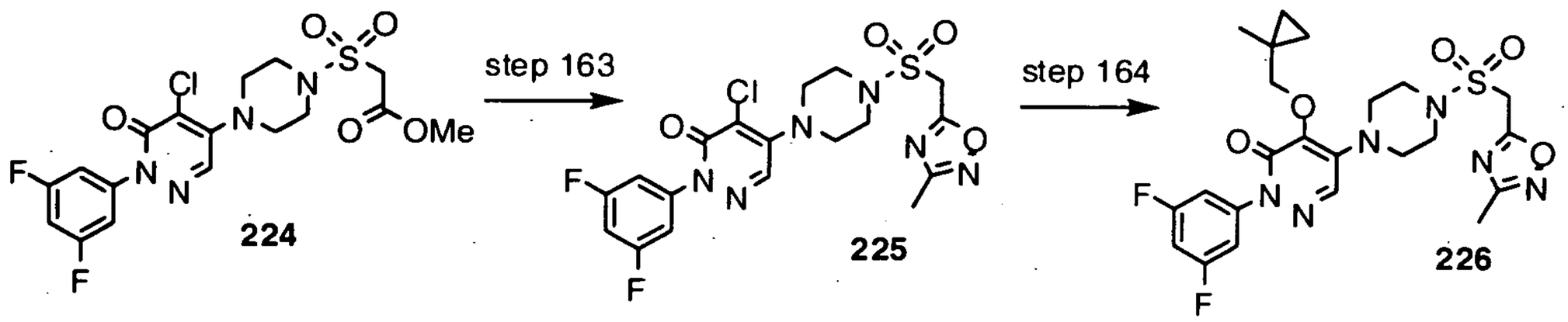


Step 162:

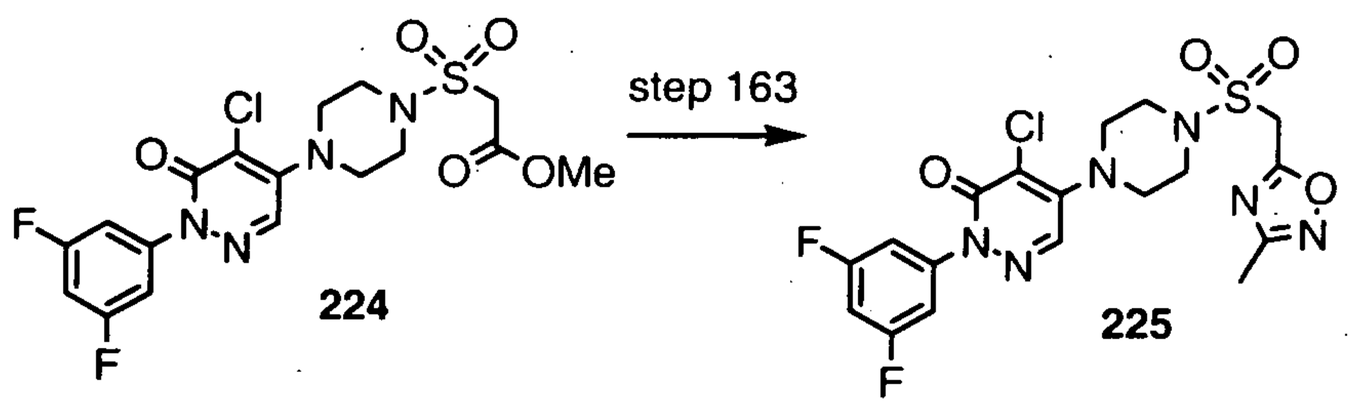
A round bottom flask was charged with compound **222** (50 mg, 0.102 mmol), 3-thienylboronic acid (26.2 mg, 0.204 mmol), L-proline (2.82 mg, 0.0245 mmol), potassium bis(trimethylsilyl)amide (40.8 mg, 0.204 mmol), isopropyl alcohol (0.5 mL, 6 mmol), and nickel chloride dimethoxyethane (2.70 mg, 0.0123 mmol). The reaction was placed under an

atmosphere of nitrogen and degassed under vacuum three times. The reaction was filtered through a short path silica gel column (eluant: ethyl acetate), and the solvent was concentrated. Purification by silica gel chromatography (eluant: 1:2 hexane:EtOAc) gave the product which was further purified on the Gilson reverse phase HPLC (eluant: water:CH_3CN gradient) to give 5 mg (9% yield) of the product **223**. MS (M+1): m/e 537.

Scheme 48

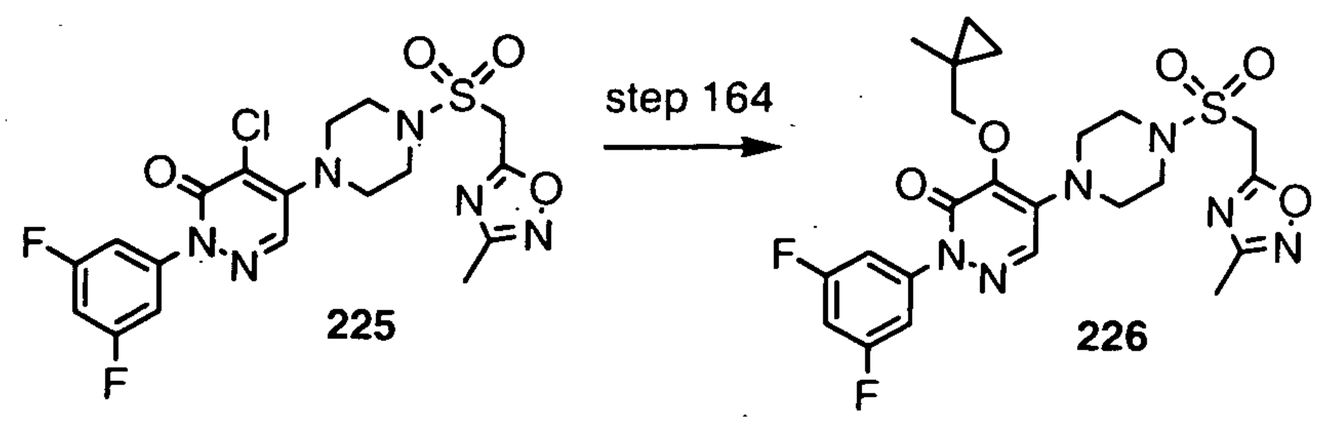


Step 163:



Compound **224** (100 mg, 0.216 mmol), potassium carbonate (60 mg, 0.432 mmol), and N-hydroxyacetimidamide (18 mg, 0.24 mmol) in toluene (10 mL) was heated at reflux for 48 h. After cooling, the reaction mixture was filtered through a short path silica gel column (eluant: ethyl acetate). The solvent was concentrated, and purification by silica gel chromatography (eluant: 1:2 hexane:ethyl acetate) gave 81 mg (77% yield) of the product **225**. MS (M+1): m/e 487.

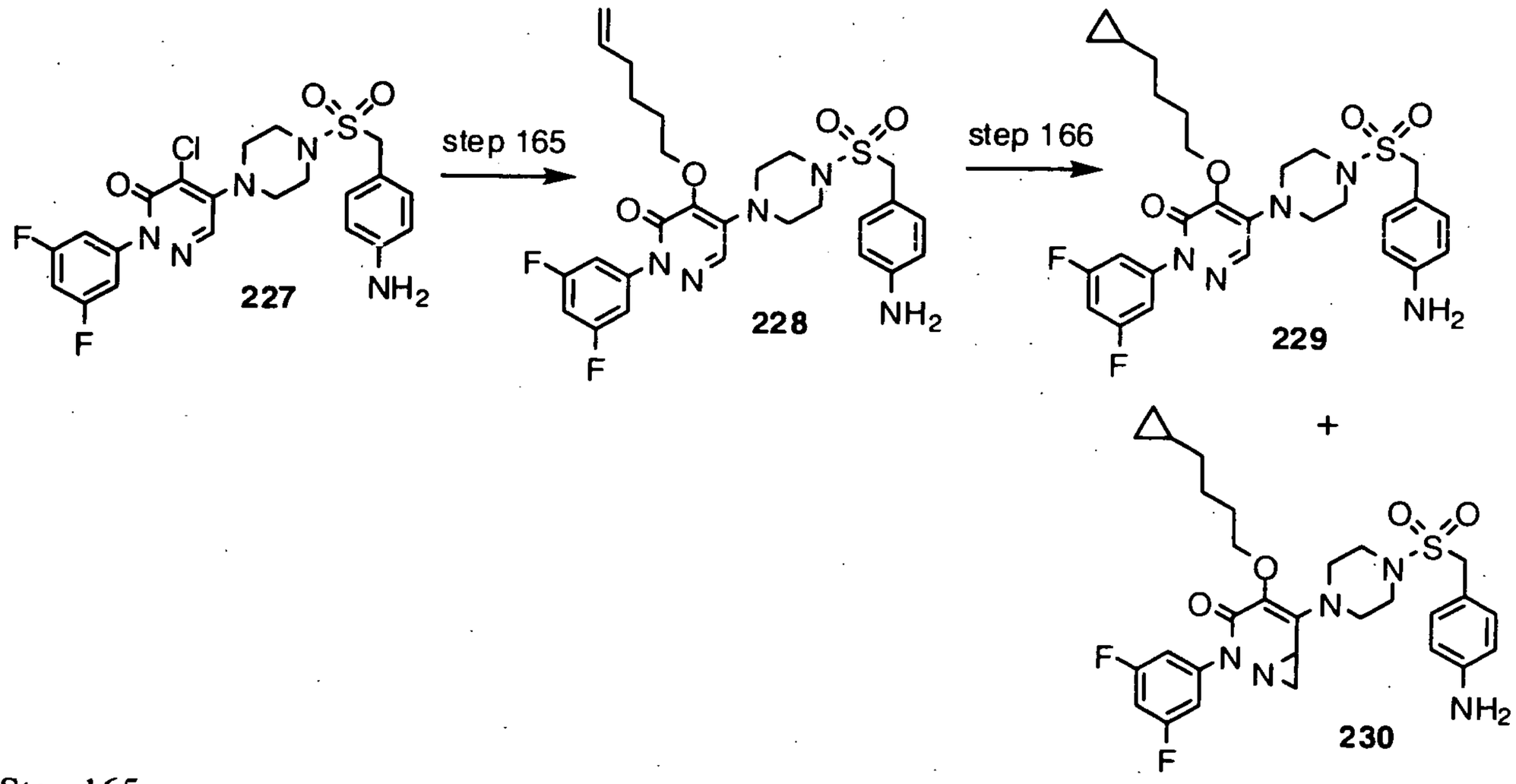
Step 164:



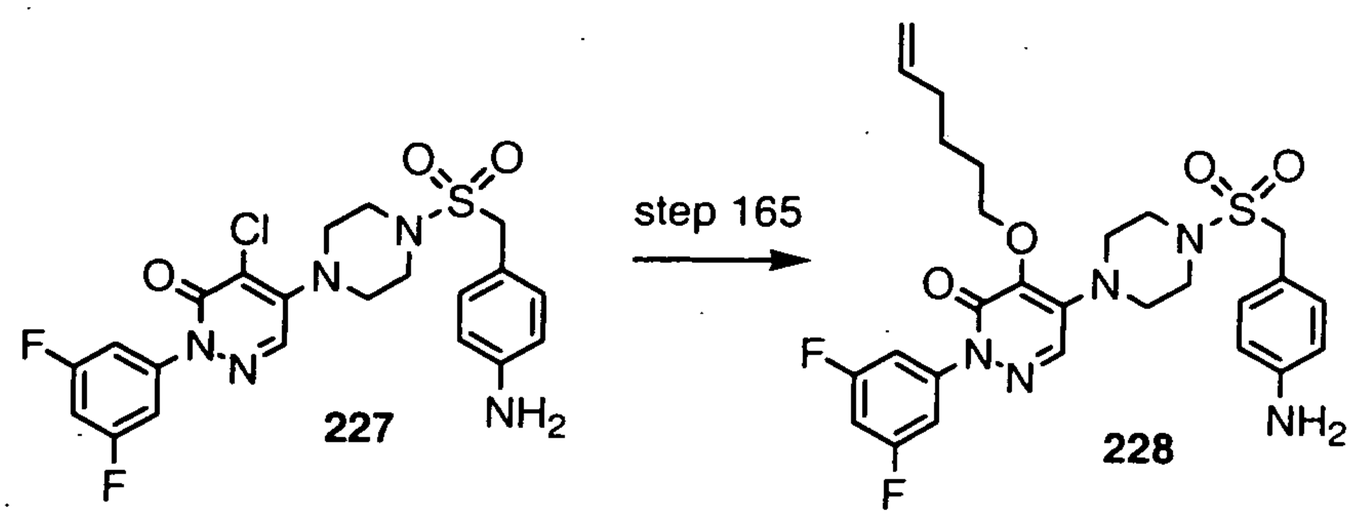
To methylcyclopropanemethanol (168 mg, 1.94 mmol) in dry THF (6 mL) was added sodium hydride (60.2 mg of 60 wt% in oil, 1.50 mmol). The reaction mixture was stirred at room

temperature for 10 mins, and then compound **225** (50 mg, 0.103 mmol) was added. The reaction mixture was stirred at room temperature overnight and then the solvent was concentrated. Water was added, and the aqueous solution was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography (eluant: 1:1 hexane:EtOAc) gave 30 mg (54% yield) of the product **226**. MS (M+1): m/e 537.

Scheme 49



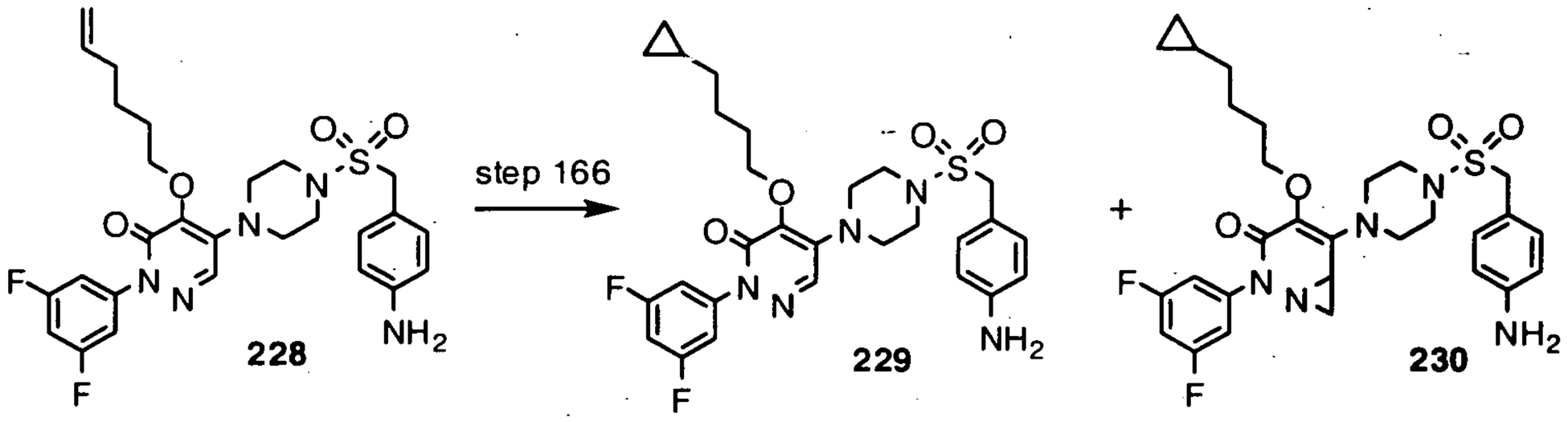
Step 165:



To 5-hexen-1-ol (48 mg, 0.483 mmol) dissolved in dry THF (5 mL) was added 1 M sodium hexamethyldisilazane in THF (0.323 mL, 0.323 mmol). The reaction was stirred at room temperature for 10 mins then compound **227** (80.0 mg, 0.161 mmol) was added. The reaction was stirred at room temperature overnight, and the solvent was evaporated. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel chromatography

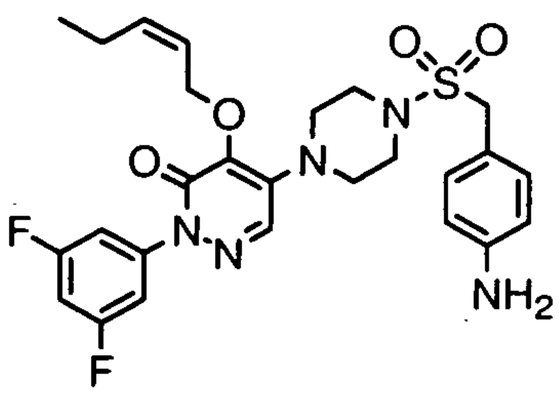
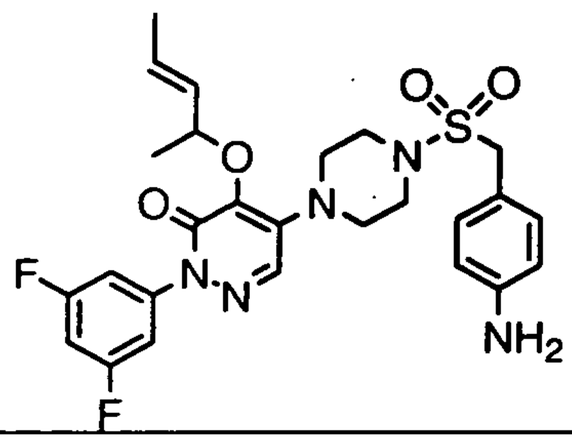
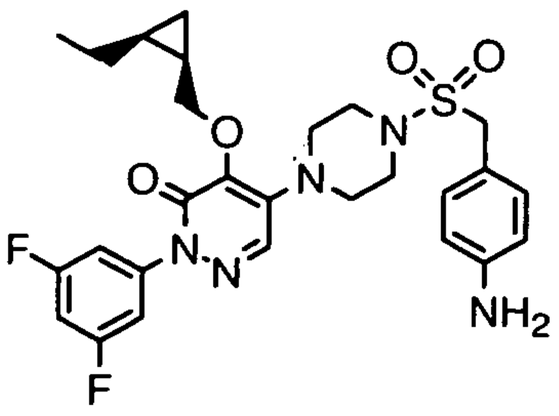
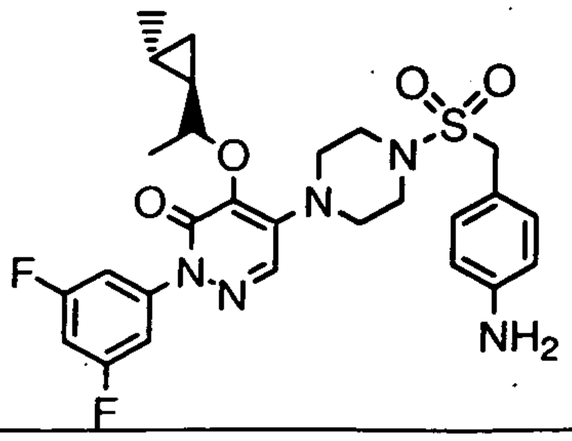
(eluant: 1:1 hexane:EtOAc) gave 80 mg (89% yield) of the product **228**. MS (M+1): m/e 560.

Step 166:

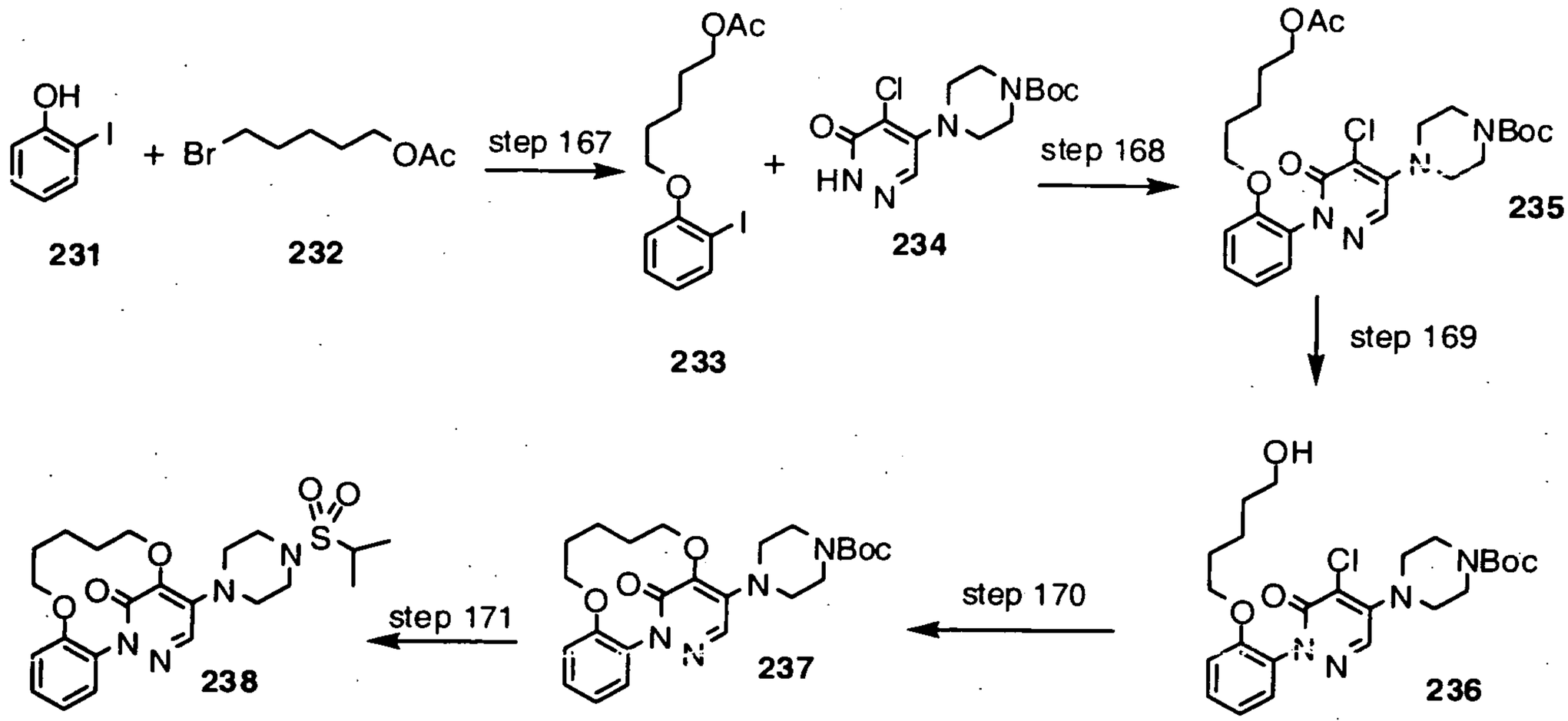


To a Schlenk flask charged with diiodomethane (0.034 mL, 0.43 mmol) in methylene chloride (10 mL) was slowly added trifluoroacetic acid (49 mg, 0.032 mL, 0.43 mmol) then 1.0 M of diethyl zinc in pentane (0.43 mL, 0.43 mmol). The reaction mixture was stirred for 30 mins at 0 °C. Compound **228** (80 mg, 0.143 mmol) in methylene chloride was added. The reaction mixture was warmed slowly to room temperature and stirred overnight. Saturated ammonium chloride was added, and the aqueous solution was extracted with methylene chloride, dried over MgSO4, filtered, and concentrated. Purification by silica gel chromatography (eluant: 1:1 hexane:EtOAc) gave 10 mg (12% yield) of the product **229** MS (M+1): m/e 574 and 30 mg (36% yield) of the product **230** MS (M+1): m/e 588.

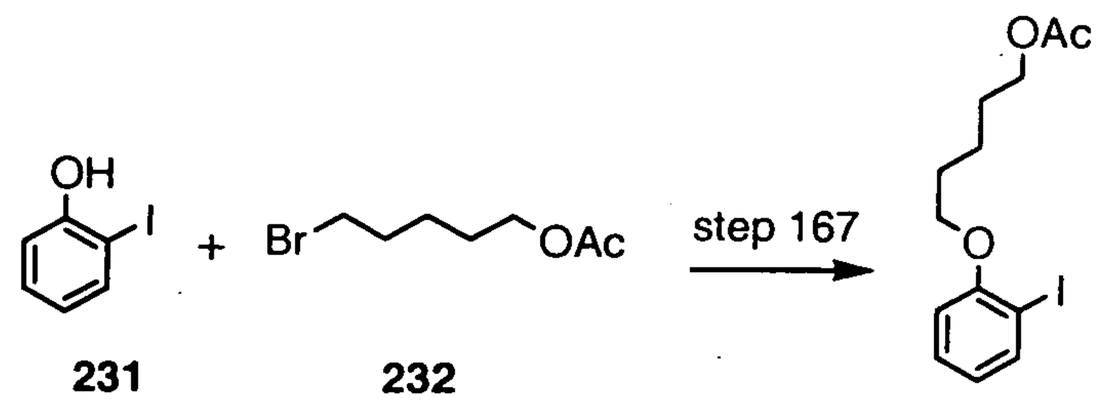
Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1		Cmpd. No.	Structure	MS M+1
1859Z		546		1860Z		546
1861Z		560		1862Z		560

Scheme 50

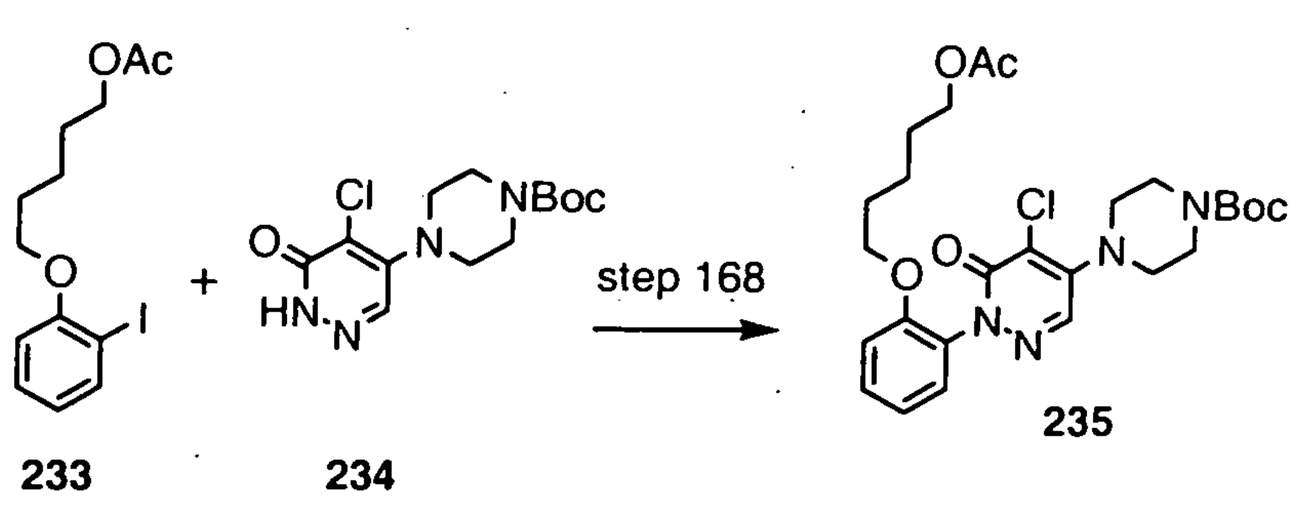


Step 167:



To a solution of 2-iodophenol **231** (2.0 g, 9.09 mmol) in dry DMF (40 mL) was added K_2CO_3 (4.93 g, 35.7 mmol) and 5-bromopentyl acetate (4.16 mL, 25.0 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 50° C and stirred for 17 h. The reaction mixture was diluted with ethyl acetate then washed with brine. The organic extract was dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 5% ethyl acetate in hexanes) yielded 1.81 g (57% yield) of the product **233** as a yellow liquid.

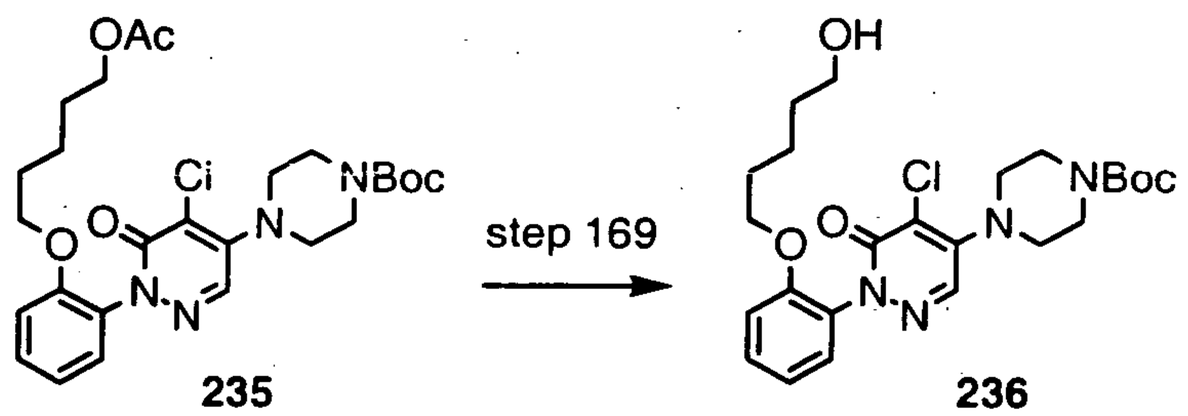
Step 168:



Reference: Pu, Y.M. *et.al. Tet. Lett.* **2006**, *47*, 149-153.

To a solution of iodide **233** (829.6 mg, 2.38 mmol) and pyridazinone **234** (500 mg, 1.59 mmol) in dry DMF (10 mL) in a sealed flask was added K_2CO_3 (329.3 mg, 2.38 mmol) and Cu catalyst (69.2 mg, 0.159 mmol) and flushed with nitrogen. The reaction mixture was heated to 120° C for 17 h. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl then brine. The organic extract was dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 50% ethyl acetate in hexanes) yielded 81 mg (10%) of the product **235** as a yellow oil. MS (M+1): m/e 535.

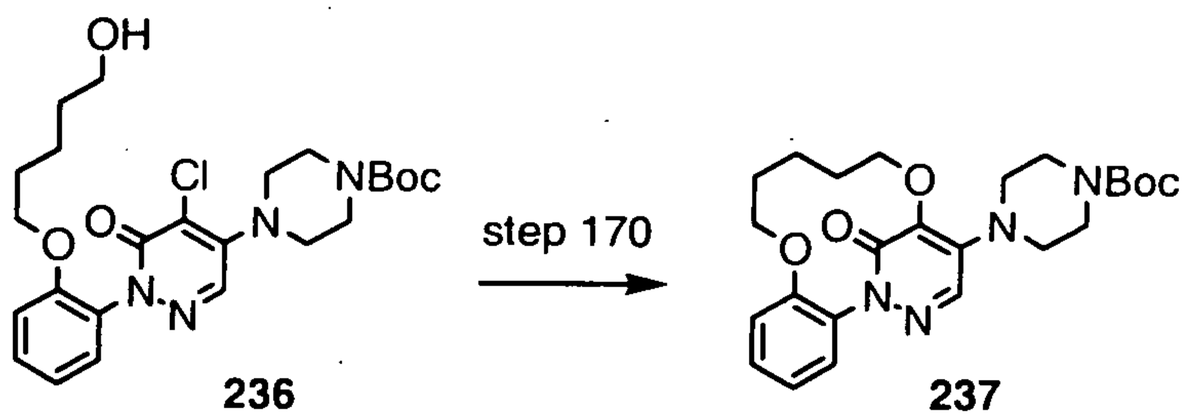
Step 169:



235 **236**

To a solution of acetate **235** (81 mg, 0.151 mmol) in MeOH (5 mL) was added water (3 drops) and K_2CO_3 (105 mg, 0.760 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated NH_4Cl, then extracted with ethyl acetate. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 65% ethyl acetate in hexanes) yielded 52.6 mg (71%) of the product **236** as a white foam. MS (M+1): m/e 493.

Step 170:

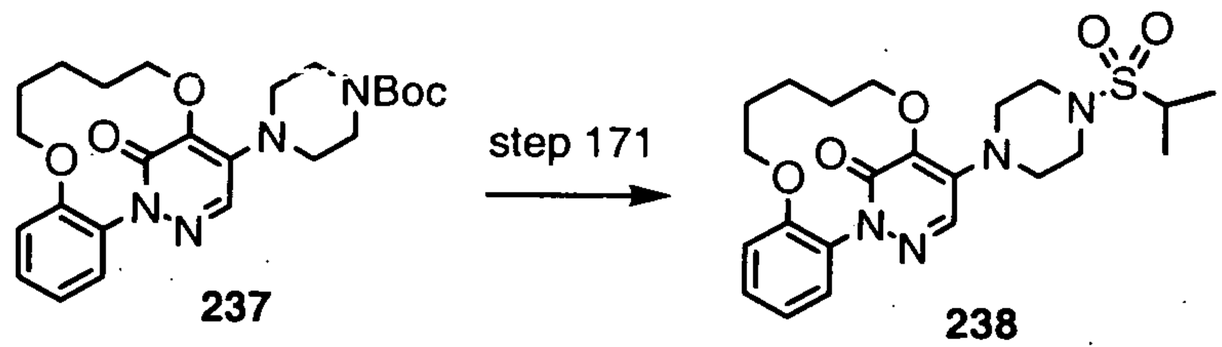


236 **237**

To a solution alcohol **236** (42.3 mg, 0.086 mmol) in THF (15 mL) was added NaH (60%, 6.9 mg, 0.479 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated NH_4Cl then extracted with ethyl acetate. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 35% ethyl

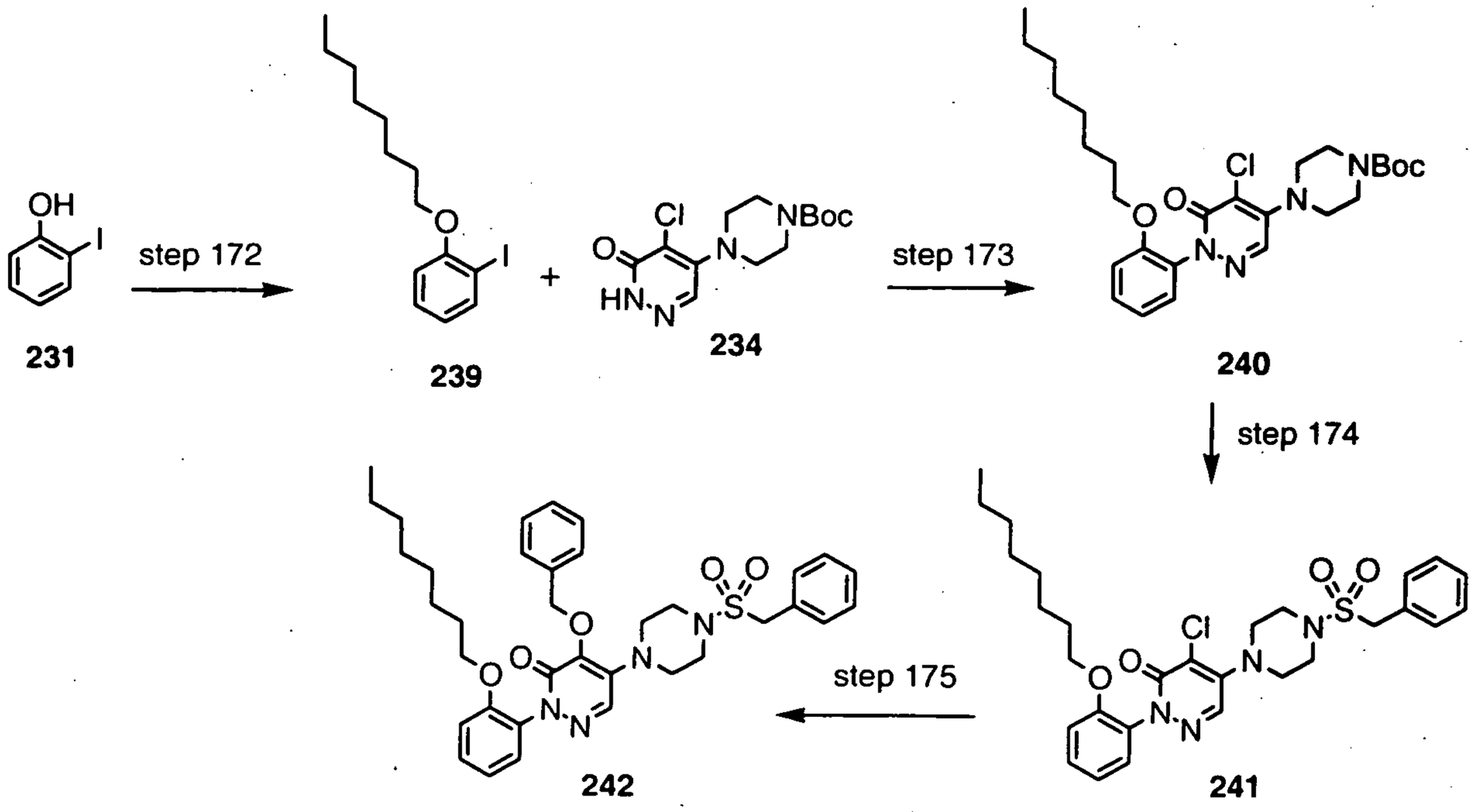
acetate in hexanes) yielded 12 mg (31%) of the product **237** as a white solid. MS (M+1): m/e 457.

Step 171:

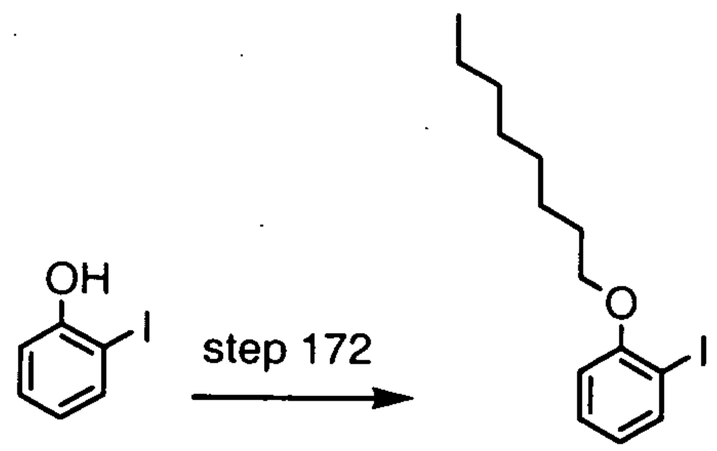


4 N HCl in dioxane (5 mL) was added to macrocycle **237** (52 mg, 0.114 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was then concentrated and dried under high vacuum. To a solution of this crude product in CH_2Cl_2 (10 mL) was added isopropyl sulfonyl chloride (51.2 uL, 0.456 mmol) and Hunig's base (119 uL, 0.683 mmol). The reaction was stirred at room temperature for 17 h then concentrated. Purification by silica gel chromatography yielded 16.3 mg (31%) of the product **238** as a brown solid. MS (M+1): m/e 463.

Scheme 51



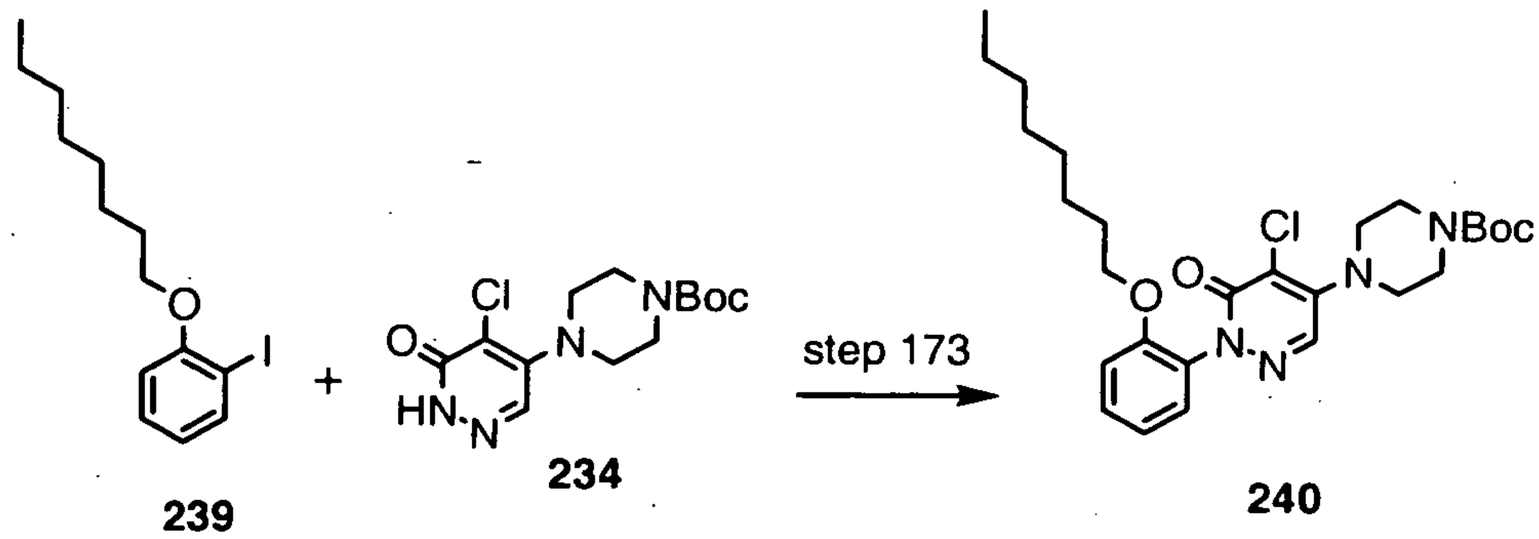
Step 172:



231 239

To a solution of 2-iodophenol **231** (2.0 g, 9.09 mmol) in dry DMF (40 mL) was added K_2CO_3 (3.77 g, 27.3 mmol) and 1-iodooctane (1.98 mL, 10.9 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 40° C and stirred for 17 h. The reaction mixture was diluted with ethyl acetate then washed with brine. The organic extract was dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 3% ethyl acetate in hexanes) yielded 3.02 g (99% yield) of the product **239** as a yellow liquid.

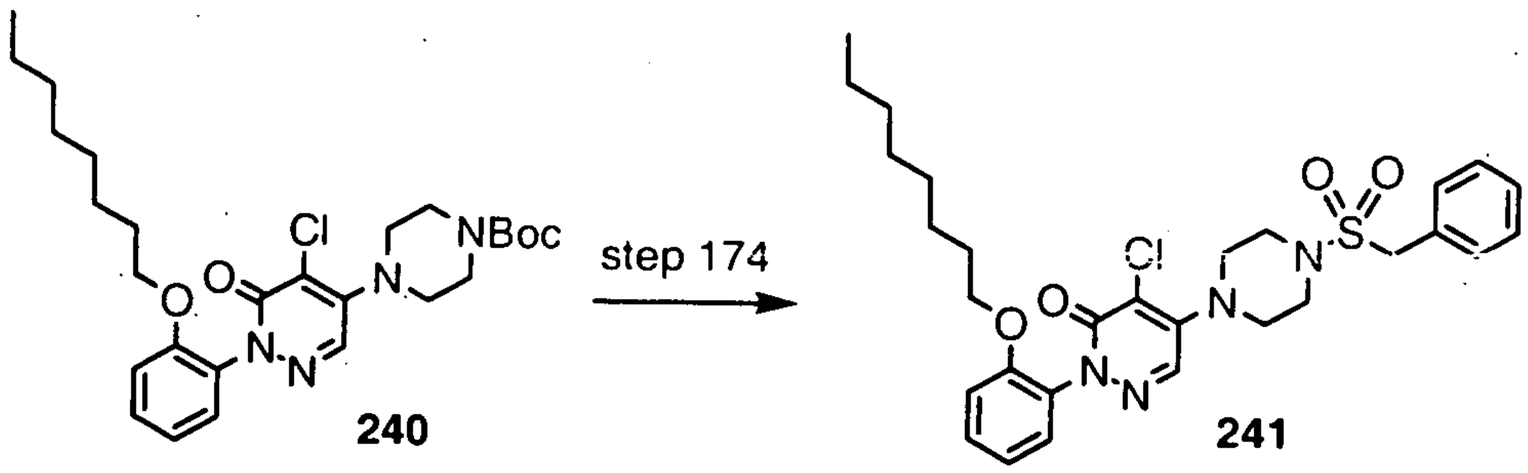
Step 173:



239 234 240

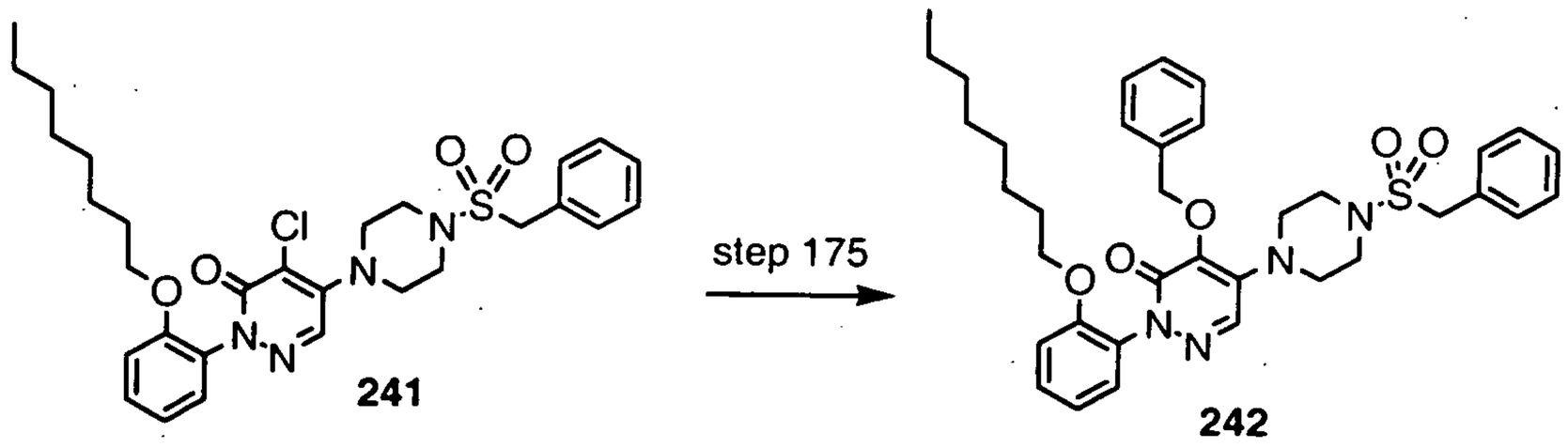
To a solution of iodide **239** (1.27 g, 3.82 mmol) and pyridazinone **234** (1 g, 3.18 mmol) in dry DMF (14 mL) in a sealed flask was added K_2CO_3 (483 mg, 3.50 mmol) and Cu catalyst (139 mg, 0.319 mmol) and flushed with nitrogen. The reaction mixture was heated to 120° C for 17 h. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl then brine. The organic extract was dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 50% ethyl acetate in hexanes) yielded 300 mg (15%) of the product **240** as a yellow oil. MS (M+1): m/e 519.

Step 174:



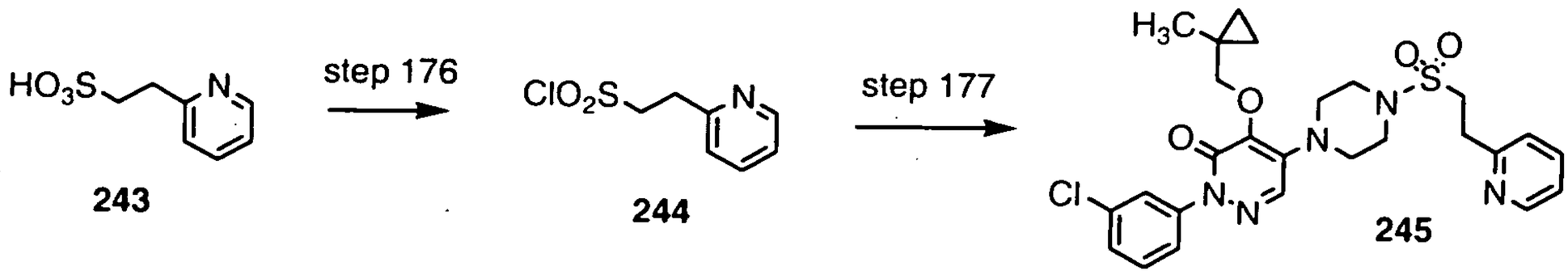
4 N HCl in dioxane (5 mL) was added to compound **240** (50 mg, 0.096 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was then concentrated and dried under high vacuum. To a solution of this crude product in CH_2Cl_2 (5 mL) was added □-toluenesulfonyl chloride (55.1 mg, 0.289 mmol) and Hunig's base (100 uL, 0.574 mmol). The reaction was stirred at room temperature for 17 h then concentrated. Purification by silica gel chromatography yielded 44.9 mg (81%) of the product **241** as a colorless oil. MS (M+1): m/e 573.

Step 175:



To a solution of benzyl alcohol (39.1 mg, 0.362 mmol) in THF (10 mL) was added NaH (60% in oil, 11.6 mg, 0.290 mmol) under a nitrogen atmosphere. To the reaction solution was added chloride **241** (41.4 mg, 0.072 mmol), and the reaction mixture was stirred at room temperature for 17 h. The reaction was quenched with saturatedNH_4Cl and extracted with ethyl acetate. The organic extract was then washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (eluant: 65% ethyl acetate in hexanes) yielded 34.6 mg (74%) of the product **242** as a brown oil. MS (M+1): m/e 645.

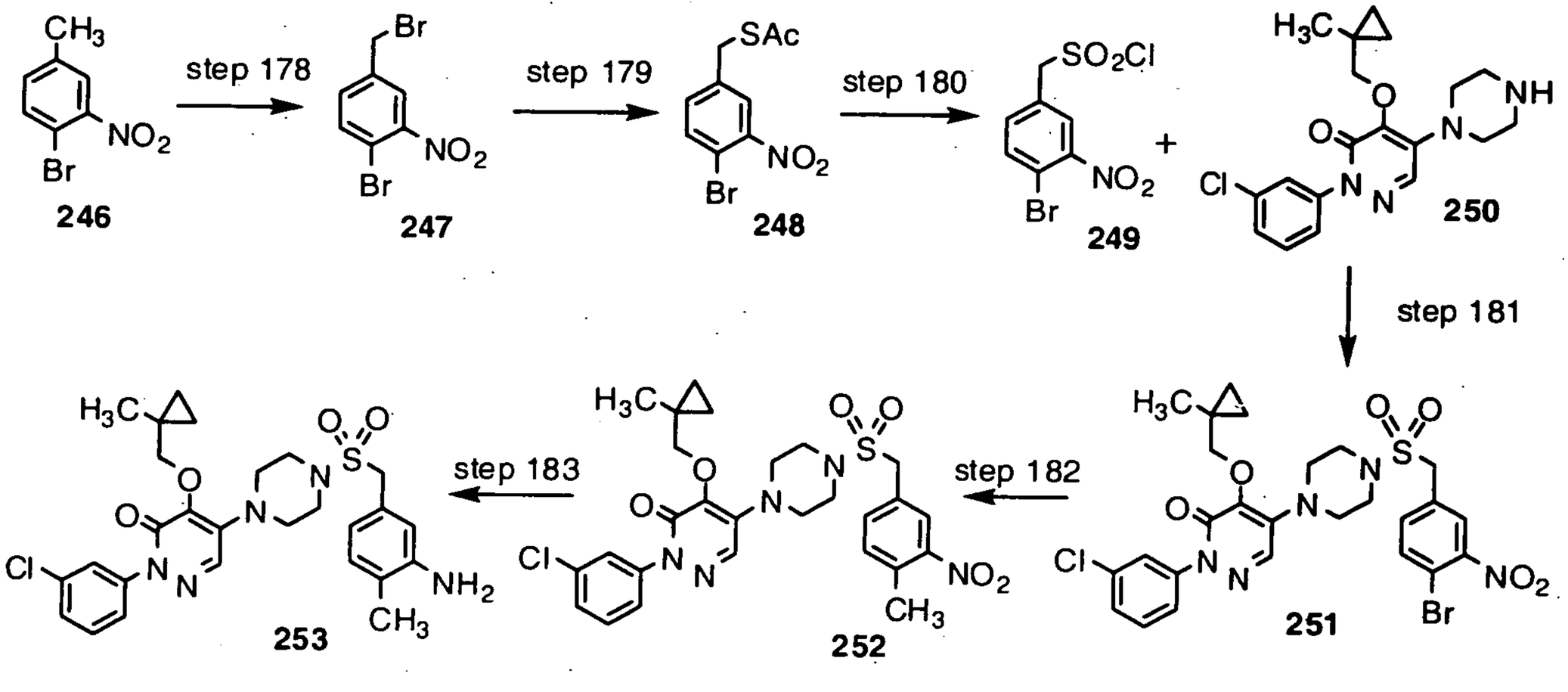
Scheme 52



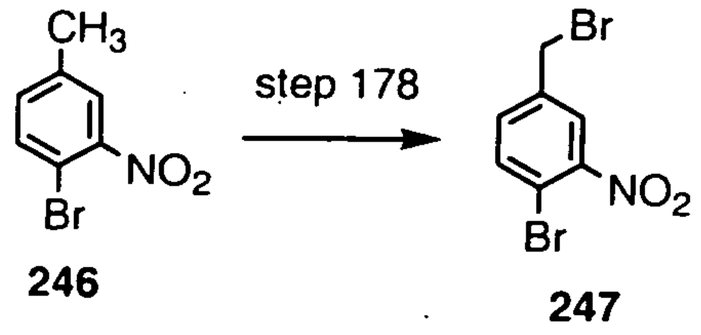
Steps 176 and 177:

A mixture of 2-(pyridin-2-yl)ethanesulfonic acid (**243**) (60 mg, 0.32 mmol) and thionyl chloride (2.3 mL, 31.6 mmol) under nitrogen was stirred at 55 °C for 5 h. The mixture was cooled to room temperature and concentrated to dryness under reduced pressure. The resulting residue was further diluted with toluene (5 mL), which was removed under reduced pressure to give crude 2-(pyridin-2-yl)ethanesulfonyl chloride (**244**) as a fine powder. Compound **244** was diluted with methylene chloride (2 mL) and the solution was cooled to 0 °C and a cold solution of 2-(3-chlorophenyl)-4-((1-methyl cyclopropyl)methoxy)-5-(piperazin-1-yl)pyridazin-3(2H)-one (120 mg, 0.32 mmol) and triethylamine (0.54 mL, 3,87 mmol) in methylene chloride (3 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature, stirring for a total of 18 h after which the solvents were removed under reduced pressure. The residue was purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 to 7:3), to provide the product **245** (66 mg, 38%) as a white solid. MS (M+1): m/e 544.

Scheme 53

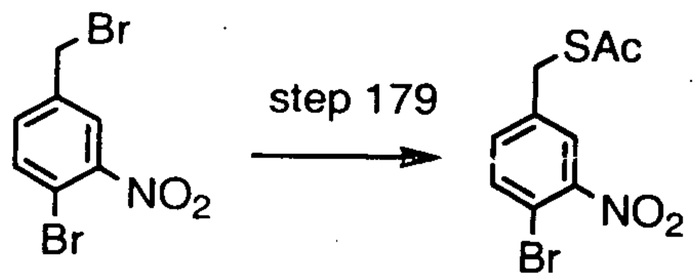


Step 178:



A mixture of 1-bromo-4-methyl-2-nitrobenzene **246** (10.0 g, 46.29 mmol), *N*-bromosuccinimide (9.06 g, 50.92 mmol) and AIBN (0.76 g, 4.63 mmol) in carbon tetrachloride (50 mL) at room temperature was purged with nitrogen (subsurface bubbling) for 10 mins after which the mixture was heated to reflux and stirred for 17 h. The cooled mixture was vacuum filtered, and the filtrate was concentrated. The resulting residue was purified by CombiFlash Companion (330-g silica gel cartridge), eluting with ethyl acetate/hexanes (3:97 to 1:9), to provide 6.88 g (50% yield) of the product **247** as a yellow solid.

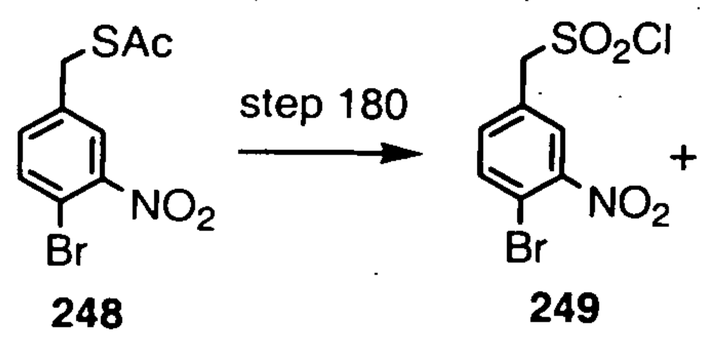
Step 179:



247 **248**

A solution of 1-bromo-4-(bromomethyl)-2-nitrobenzene **247** (6.88 g, 23.33 mmol) and potassium thioacetate (3.46 g, 30.33 mmol) in anhydrous DMF (100 mL) was heated at 55 °C under nitrogen for 17 h. The cooled mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water (3 x 50 mL), brine (100 mL) and then concentrated to afford the product **248** (6.73 g, 99% yield) as a dark-red oil that was used in the next step without further purification.

Step 180:

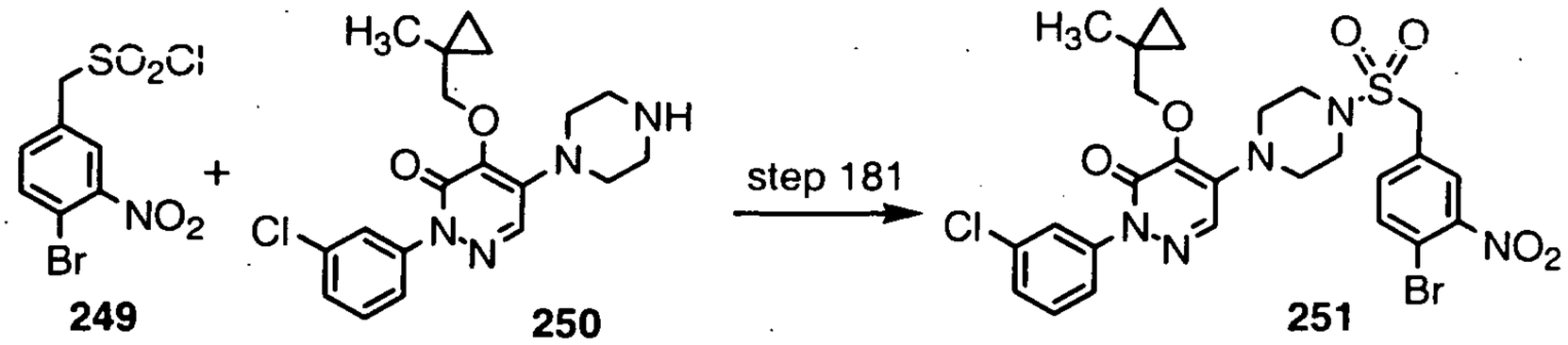


248 **249**

Chlorine gas was slowly bubbled through a biphasic mixture of *S*-4-bromo-3-nitrobenzyl ethanethioate **8** (6.73 g, 23.2 mmol) in methylene chloride (100 mL) and water (20 mL) at 0 °C for 45 mins, during which time the solution became a persistent yellow color. Nitrogen gas was slowly bubbled through the solution to displace the chlorine gas, and the reaction mixture was extracted with methylene chloride (100 mL). The aqueous layer was further extracted with methylene chloride (2 x 30 mL), and the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to afford (4-bromo-3-

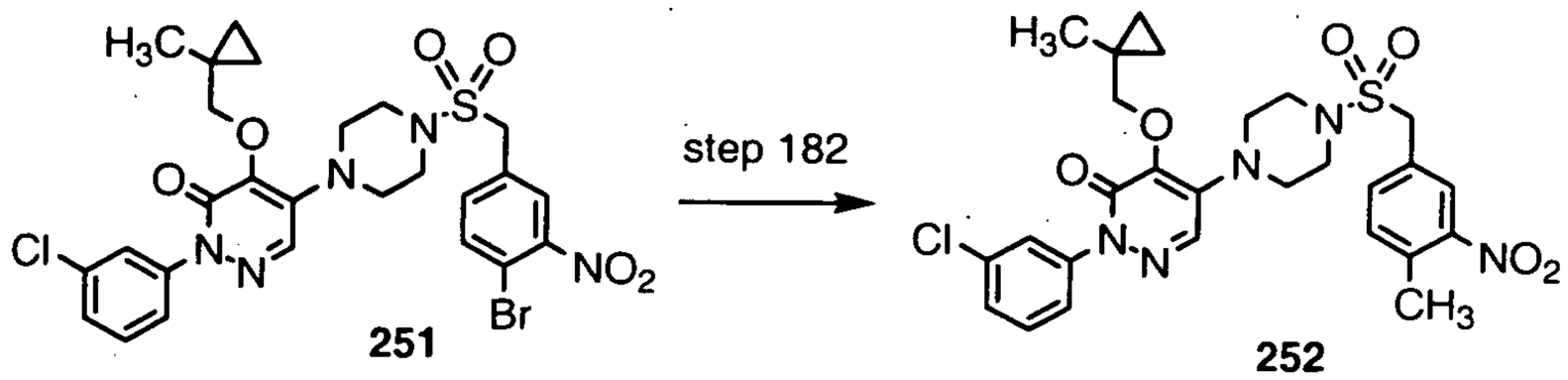
nitrophenyl)methanesulfonyl chloride **9** (7.00 g, 96% yield) as a yellow solid which was used in the next step without further purification.

Step 181:



Triethylamine (1.64 mL, 11.8 mmol) was added to a mixture of 2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)-5-(piperazin-1-yl)pyridazin-3(2*H*)-one **250** (2.21 g, 5.89 mmol) and (4-bromo-3-nitrophenyl)methanesulfonyl chloride **249** (1.86 g, 5.91 mmol) in anhydrous methylene chloride (25 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 1 h after which it was slowly warmed to room temperature, stirring for a total of 16 h. The mixture was diluted with methylene chloride (150 mL), washed with water (50 mL) then brine (50 mL), and the solvents were removed under reduced pressure. The residue was purified by CombiFlash Companion (120-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 4:6), to provide 980 mg (25% yield) of the product **251** as a yellow solid: MS (M+1): m/e 652.

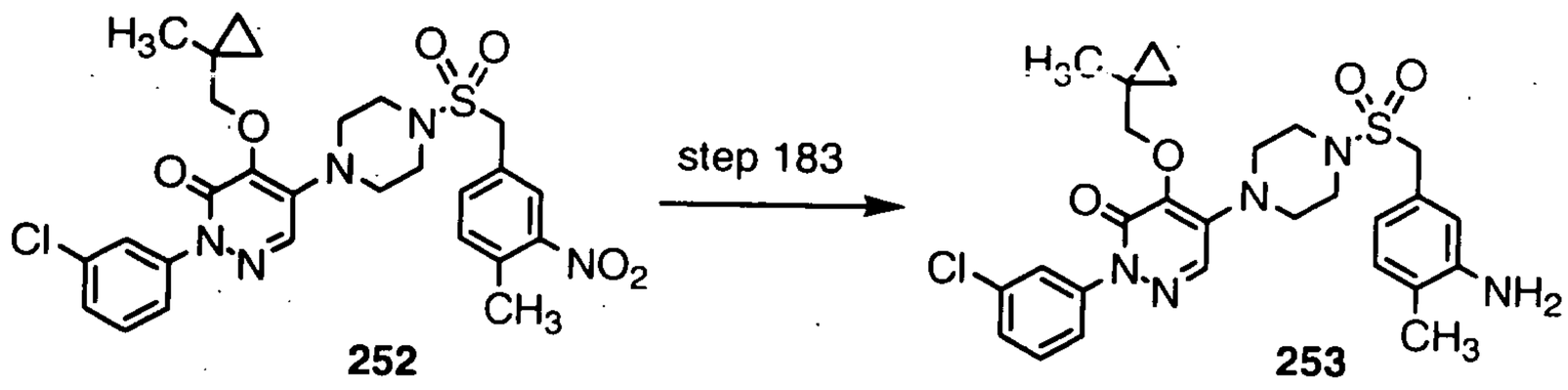
Step 182:



Cesium carbonate (46 mg, 0.14 mmol) and potassium carbonate (39 mg, 0.28 mmol) were added to a degassed solution of 5-(4-(4-bromo-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **10** (93 mg, 0.142 mmol) in 1,4-dioxane (5 mL) at room temperature under nitrogen after which $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and trimethylboroxine (44 uL, 0.315 mmol) were added. The reaction mixture was stirred at reflux for 16 h after which the cooled mixture was concentrated. The resulting residue was diluted with water (30 mL) and extracted with methylene chloride (2 x 30 mL). The combined organic extracts were washed with brine (50 mL) then concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl

acetate/hexanes (1:9 to 4:6), to provide 75 mg (90% yield) of the product **252** as a yellow solid. MS (M+1): m/e 588.

Step 183:

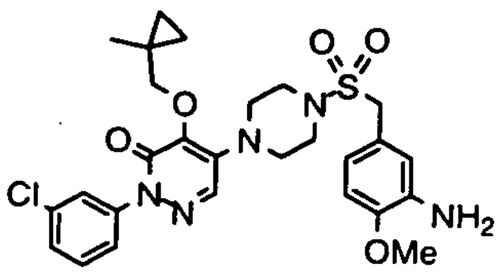
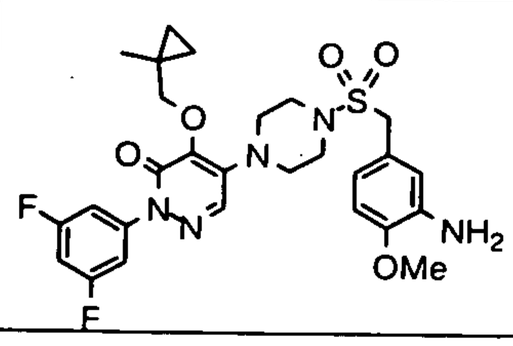
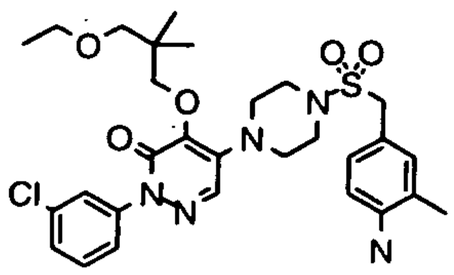
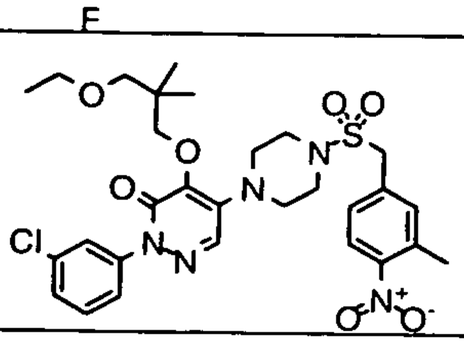
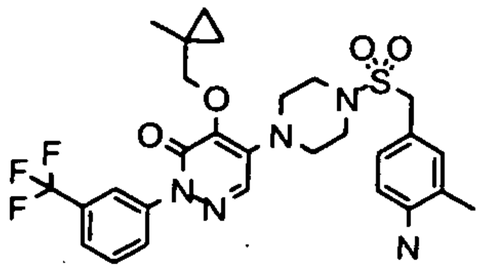
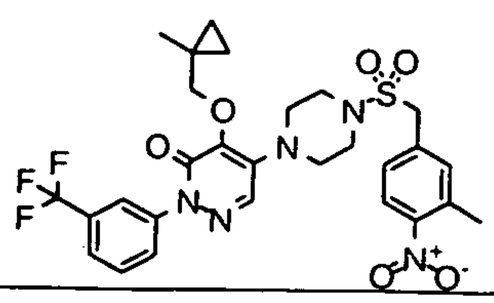


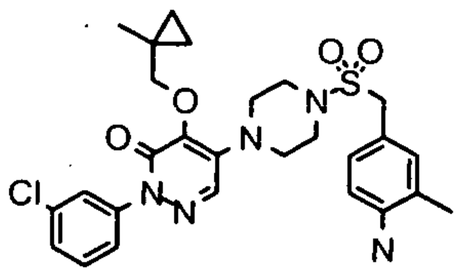
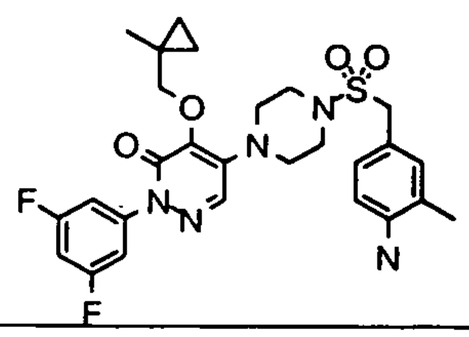
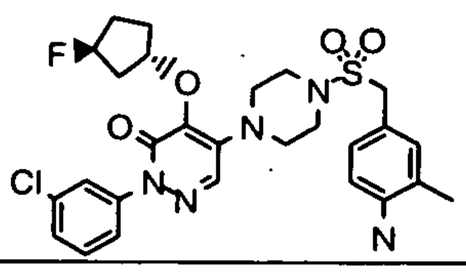
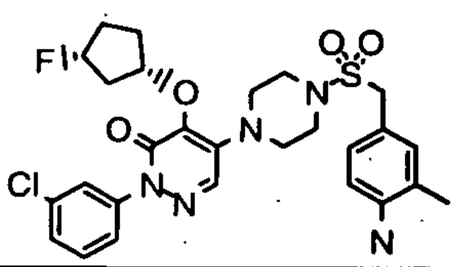
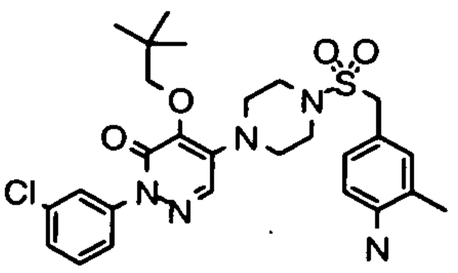
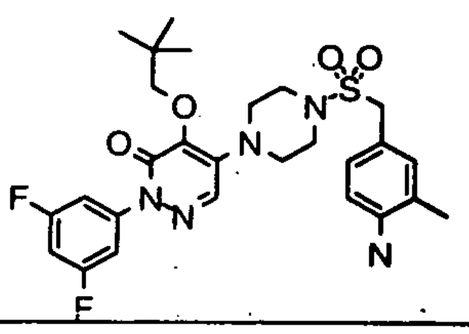
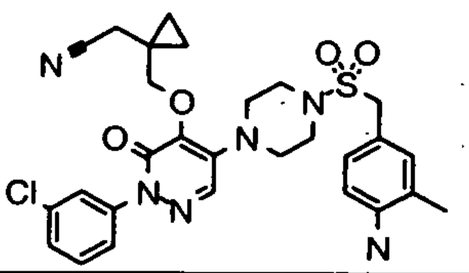
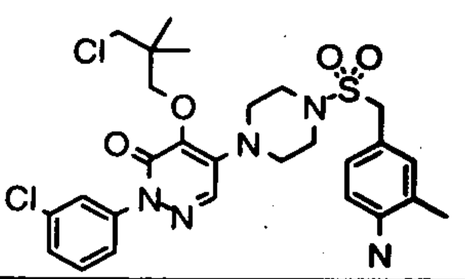
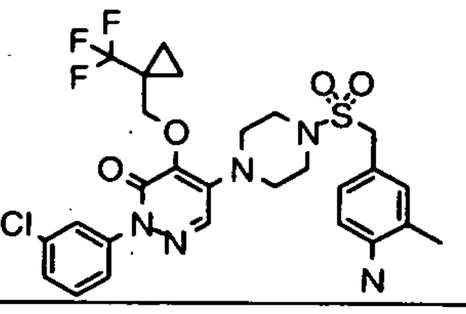
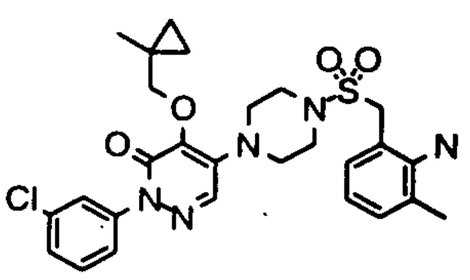
252 **253**

A mixture of 2-(3-chlorophenyl)-5-(4-(4-methyl-3-nitrobenzylsulfonyl) piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **252** (75 mg, 0.13 mmol) and platinum(II) oxide (11 mg, 0.048 mmol) in ethanol (5 mL) and THF (5 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 18 h. The mixture was filtered through a plug of celite under reduced pressure, and the filtrate was concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (15:85 to 8:2), to provide 36 mg (51% yield) of the product **253** as a white solid. MS (M+1): m/e 558.

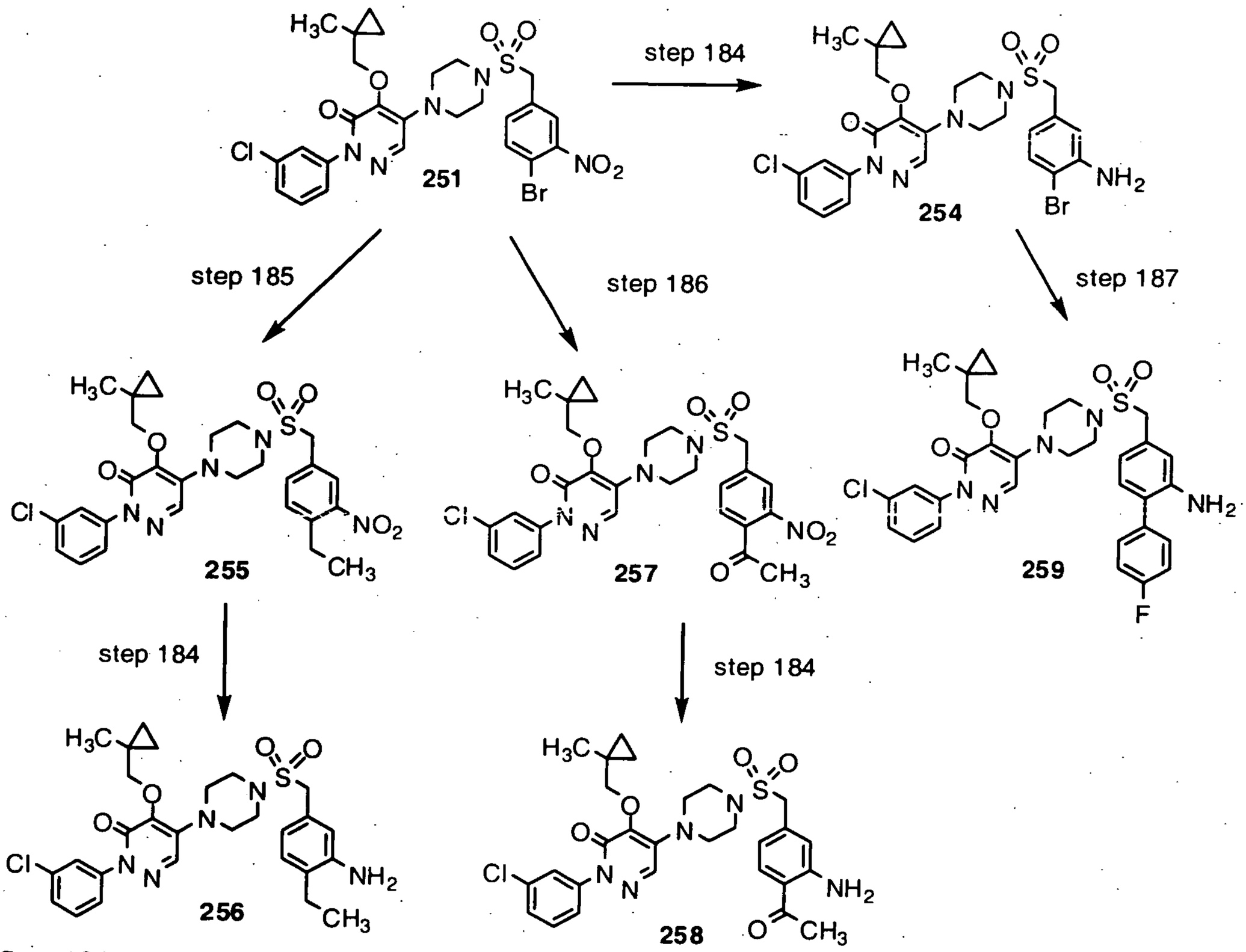
Using the procedures described above, the following compounds were synthesized.

Table 34: Oxygen Analogs with Methyl-or Methoxy-Substituted Sulfonamide

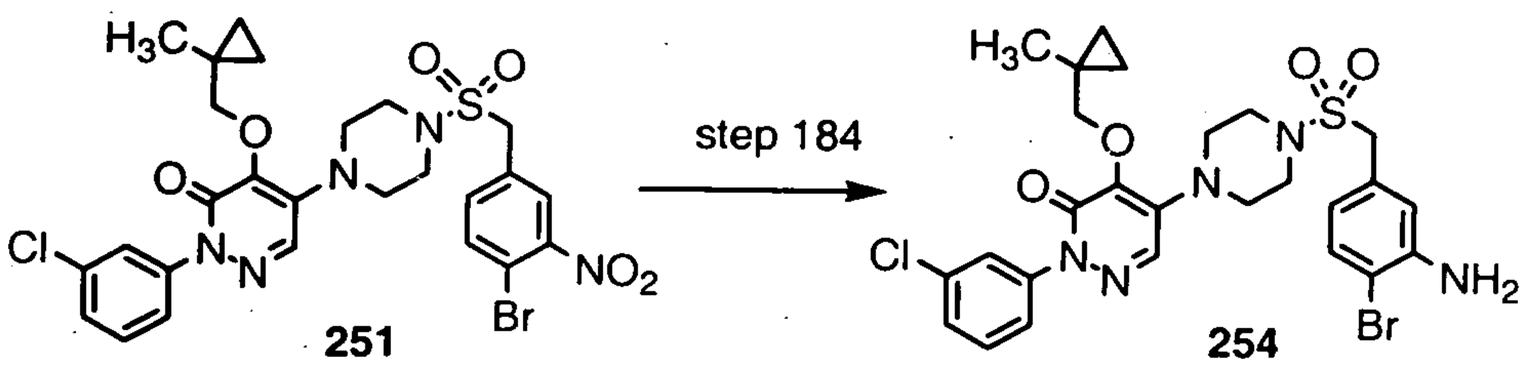
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1863Z		574	1864Z		576
1865Z		604	1866Z		634
1867Z		592	1868Z		622

1869Z		558		1870Z		560
1871Z		576		1872Z		576
1873Z		560		1874Z		562
1875Z		583		1876Z		594
1877Z		612		1878Z		558

Scheme 54

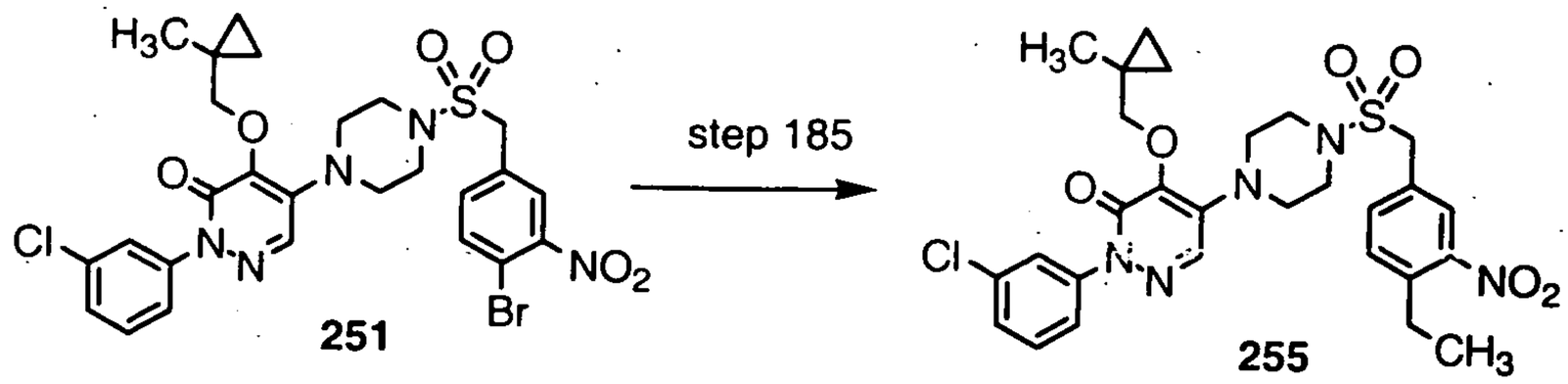


Step 184:



A mixture of 5-(4-(4-bromo-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **251** (49 mg, 0.075 mmol) and platinum(II) oxide (10 mg, 0.044 mmol) in ethanol (5 mL) and THF (2 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 16 h. The mixture was filtered through a plug of celite under reduced pressure, and the filtrate was concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 8:2), to provide 21 mg (45% yield) of the product **254** as a white solid. MS (M+1): m/e 622.

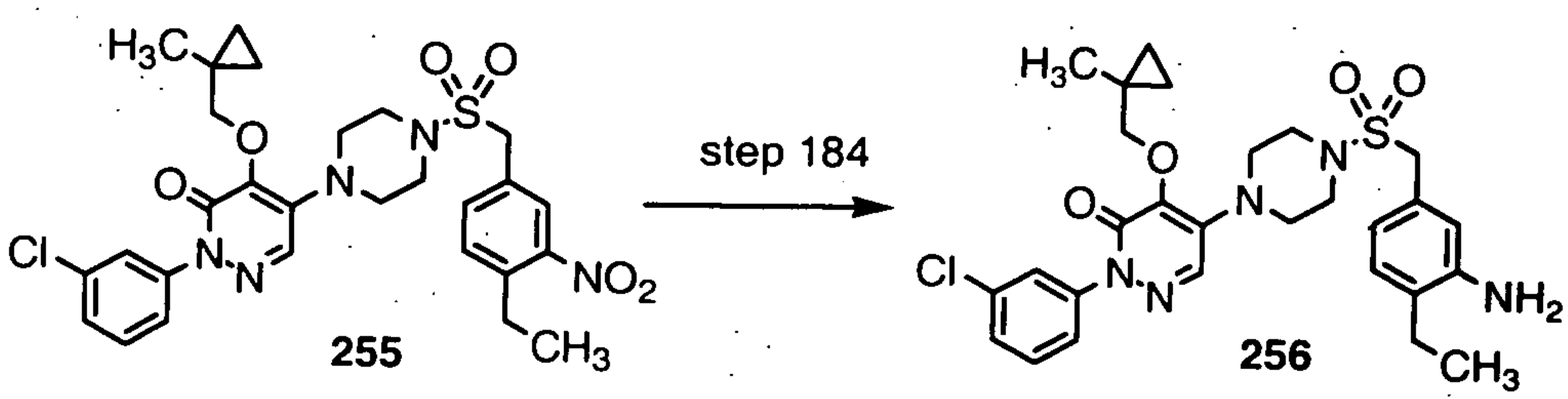
Step 185:



251 255

A solution of potassium phosphate (66 mg, 0.31 mmol) in water (2 mL) was added to a degassed solution of 5-(4-(4-bromo-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **251** (92 mg, 0.141 mmol) in THF (5 mL) after which $PdCl_2$(dppf) (8 mg, 0.01 mmol) and triethyl borane (1.0 M in THF, 0.17 mL, 0.17 mmol) were added, and the mixture was heated to reflux, stirring for a total of 18 h. The cooled mixture was diluted with water (30 mL) and extracted with methylene chloride (3 x 30 mL). The combined organic extracts were washed with brine (50 mL) then concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 4:6), to provide 34 mg (40% yield) of the product **255** as a yellow solid. MS (M+1): m/e 602.

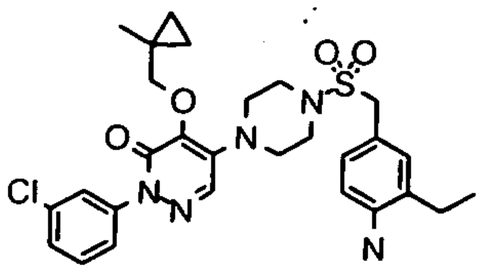
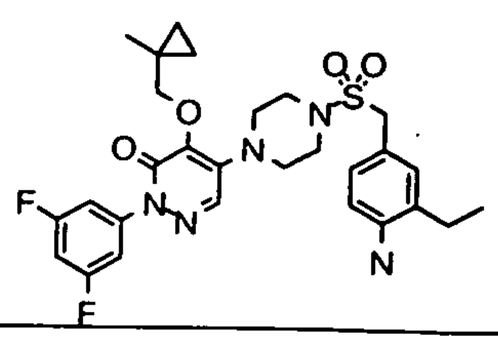
Step 184:



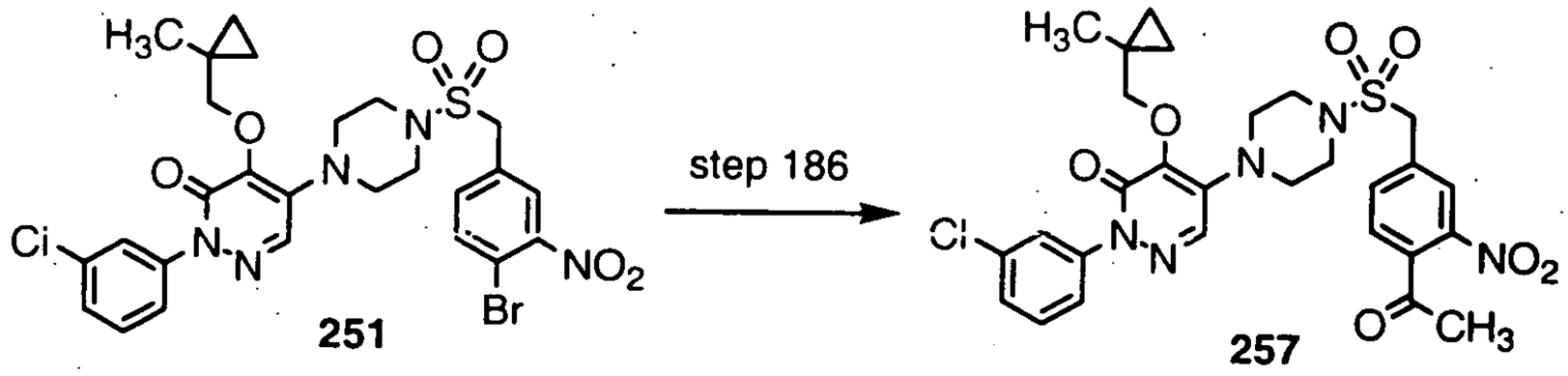
255 256

Hydrogenation of 2-(3-chlorophenyl)-5-(4-(4-ethyl-3-nitrobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2H)-one **255** (34 mg, 0.057 mmol) was performed as described above to provide 26 mg (80% yield) of the product **256** as a white solid. MS (M+1): m/e 572.

Using the procedures described above, the following compounds were synthesized.

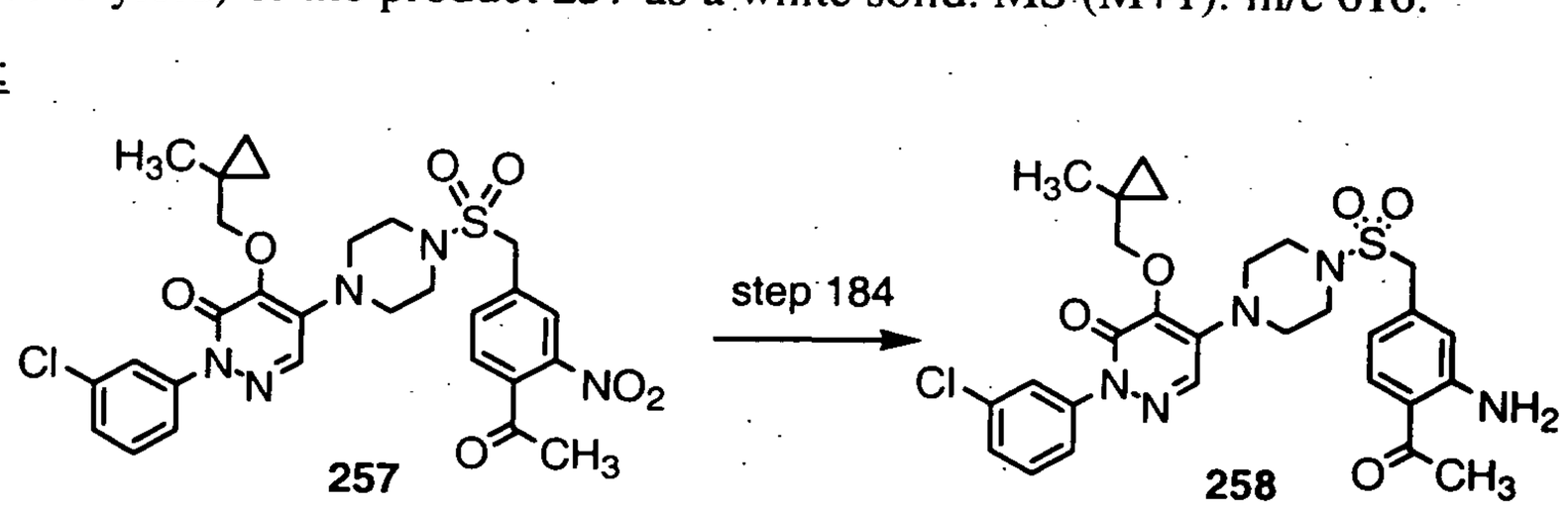
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1879Z		572	1880Z		574

Step 186:



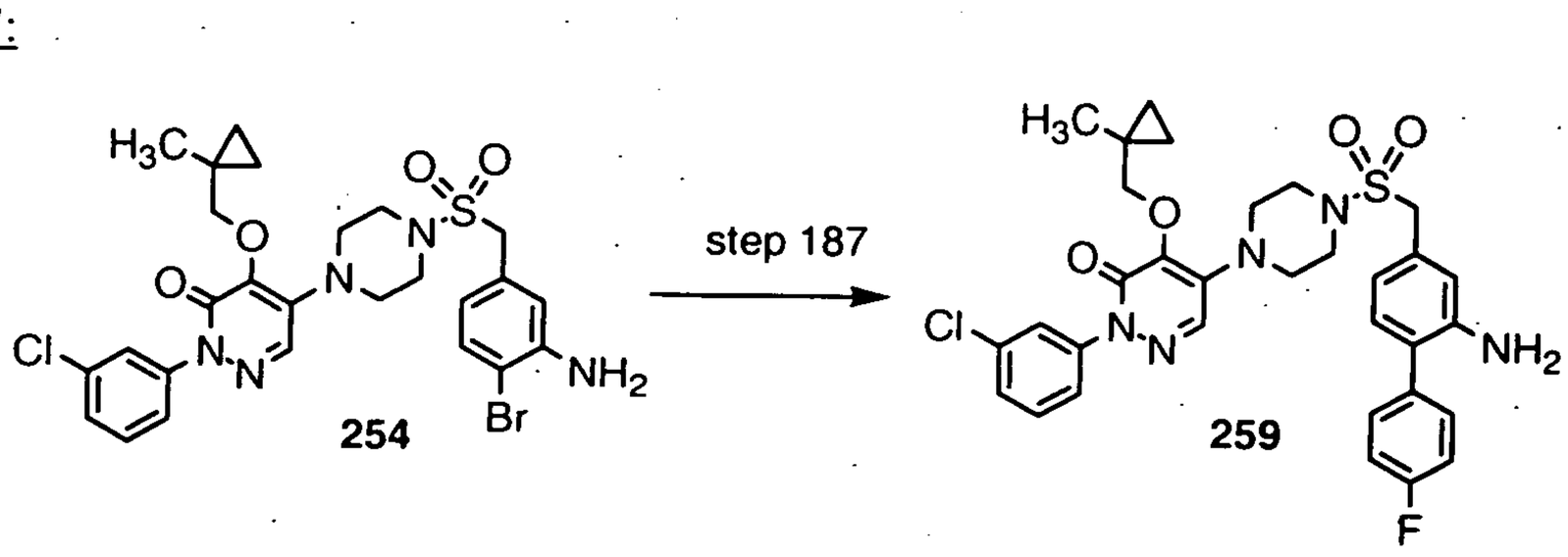
Tributylethoxyvinyltin (126 uL, 0.373 mmol) and $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol) were added to a degassed solution of 5-(4-(4-bromo-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2H)-one **251** (187 mg, 0.286 mmol) in 1,4-dioxane (6 mL) at room temperature under nitrogen after which the mixture was heated to reflux, stirring for a total of 18 h. The cooled mixture was diluted with 1 M HCl (4 mL) and stirred at room temperature for an additional 90 mins. Aqueous sodium hydroxice (1 M, 4.5 mL) was added, and the mixture was extracted with methylene chloride (60 mL x 2). The solvent was concentrated, and the residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 6:4), to provide 139 mg (79% yield) of the product **257** as a white solid. MS (M+1): m/e 616.

Step 184:



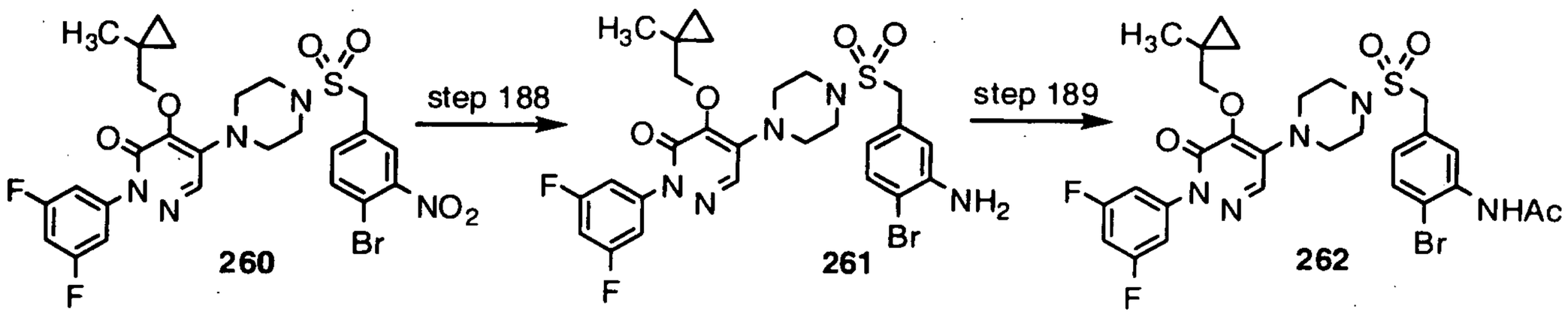
Hydrogenation of 5-(4-(4-acetyl-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3-chloro phenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **257** (139 mg, 0.226 mmol) was performed as described above to provide 99 mg (74% yield) of the product **258** as a yellow solid. MS (M+1): m/e 586.

Step 187:

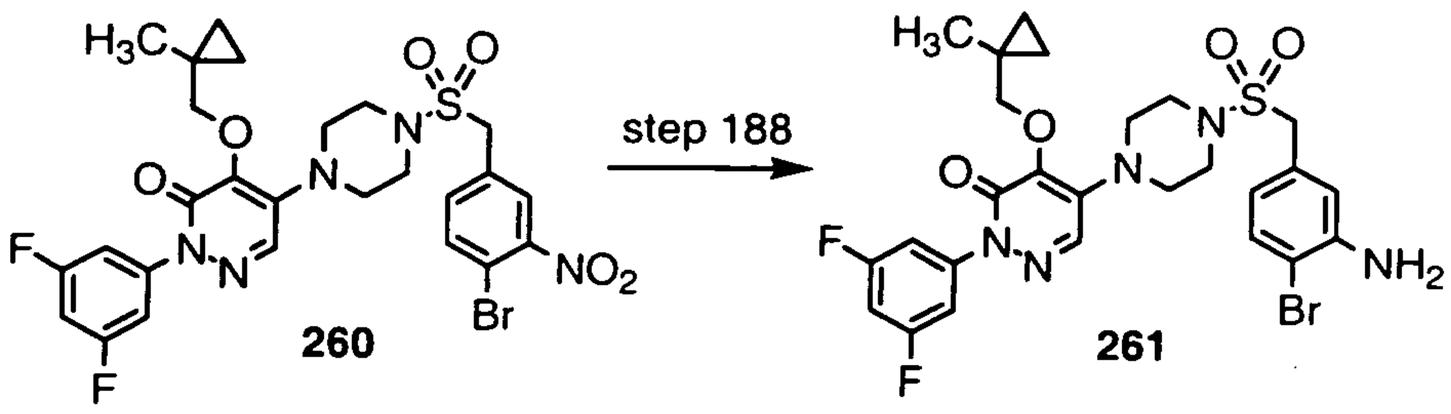


A solution of sodium carbonate (2 M, 0.4 mL, 0.8 mmol) and 4-fluorophenylboronic acid (34 mg, 0.24 mmol) was added to a degassed solution of 5-(4-(3-amino-4-bromobenzylsulfonyl)piperazin-1-yl)-2-(3-chloro phenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **254** (60 mg, 0.096 mmol) in 1,4-dioxane (4 mL) at room temperature under nitrogen, after which $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added, and the mixture was stirred at 95 °C 16 h. The cooled mixture was diluted with methylene chloride (150 mL), washed with brine (40 mL) and then concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 4:6), to provide 14 mg (23% yield) of the product **259** as a white solid. MS (M+1): m/e 638.

Scheme 55

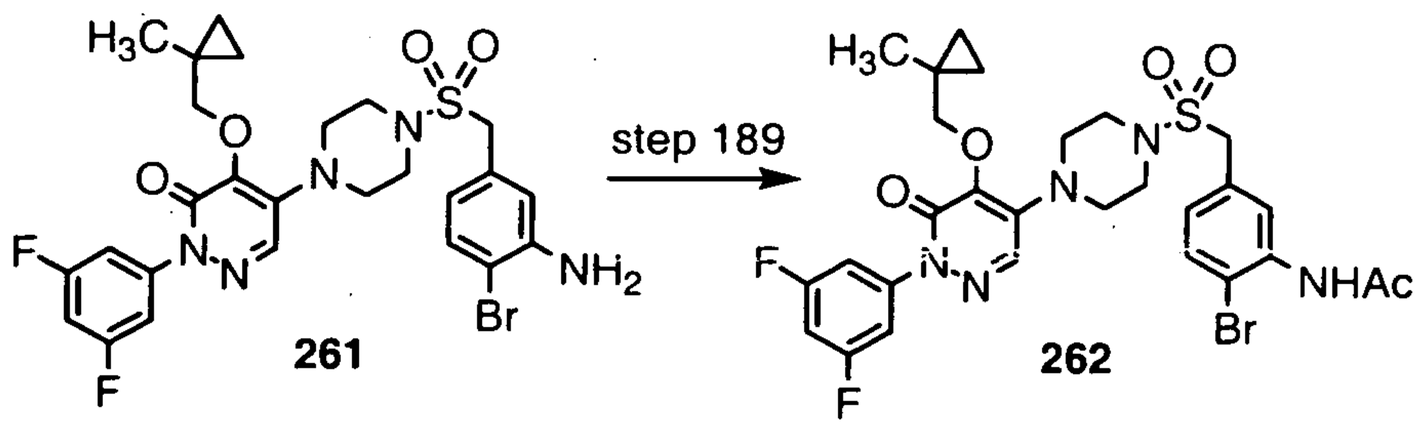


Step 188:



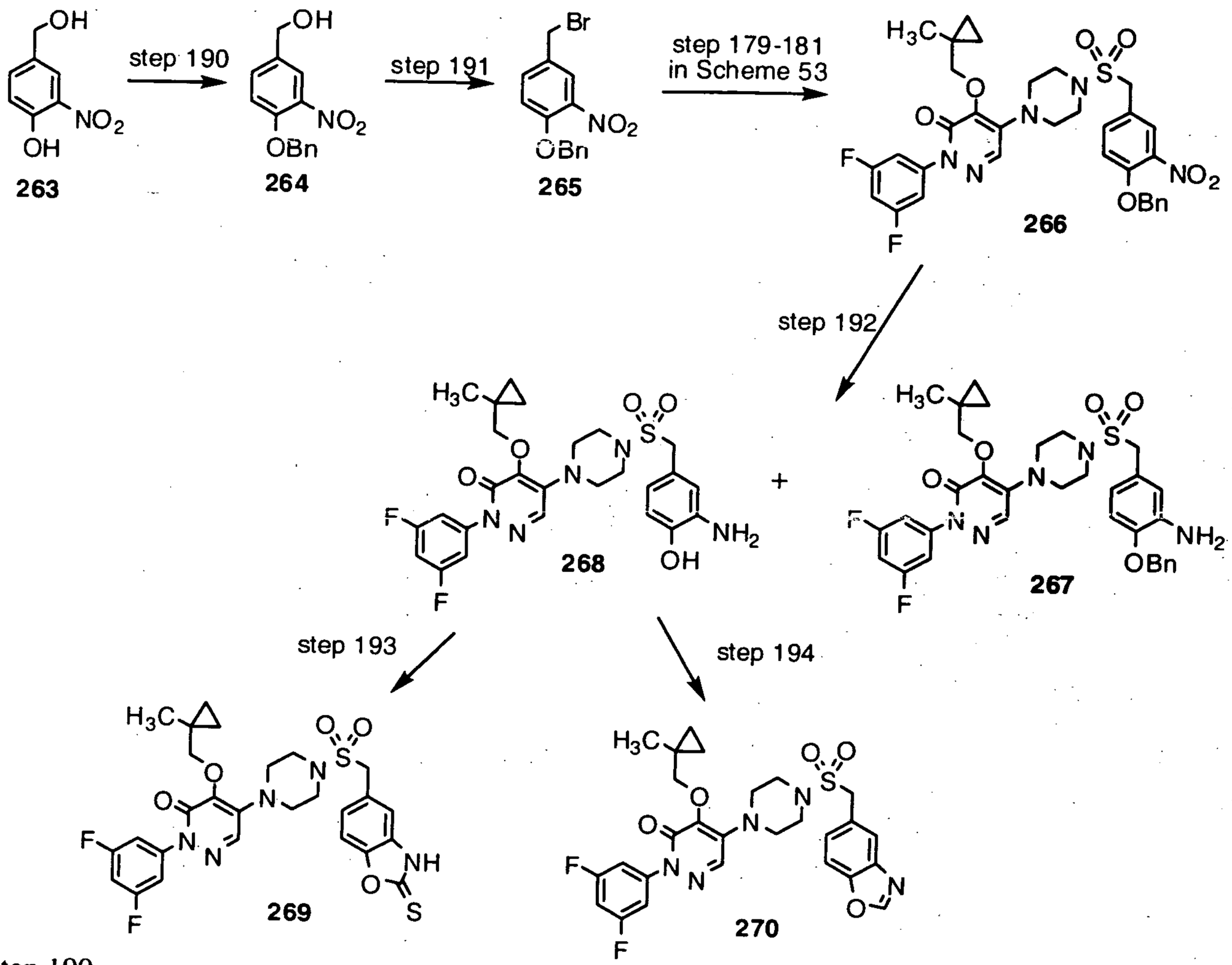
Iron powder (448 mg, 8.02 mmol) was added portionwise to a solution of 5-(4-(4-bromo-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3,5-difluoro phenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **260** (105 mg, 0.160 mmol) in THF (3mL) at room temperature under nitrogen, after which acetic acid (3.7 mL, 64 mmol) was added slowly. The reaction mixture was stirred at room temperature for 4 h then the solids were removed by vacuum filtration. The filtrate was concentrated, and the residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 1:1), to provide 82 mg (82% yield) of the product **261** as a white solid. MS (M+1): m/z 624.

Step 189:

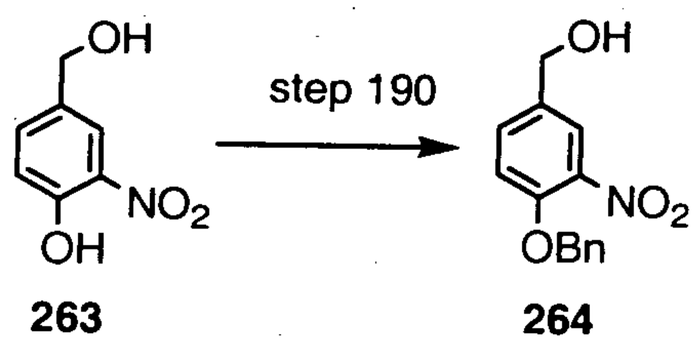


Acetyl chloride (28 uL, 0.394 mmol) was added to a solution of 5-(4-(3-amino-4-bromobenzyl sulfonyl)piperazin-1-yl)-2-(3,5-difluorophenyl)-4-((1-methylcyclopropyl)methoxy) pyridazin-3(2*H*)-one **261** (82 mg, 0.131 mmol) and triethylamine (110 uL, 0.79 mmol) in THF (3 mL) at room temperature under nitrogen, and the mixture was stirred for 18 h then concentrated. The crude product was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 6:4), to provide 57 mg (65% yield) of the product **262** as a yellow solid. MS (M+1): m/e 666.

Scheme 56

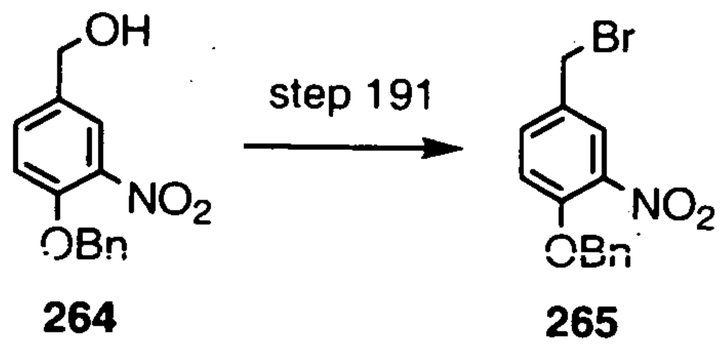


Step 190:



A mixture of 4-(hydroxymethyl)-2-nitrophenol **263** (3.27 g, 19.33 mmol), potassium carbonate (5.34 g, 38.64 mmol) and benzyl bromide (2.53 mL, 21.30 mmol) in acetone (200 mL) was stirred at reflux for 18 h. After cooling, the solvent was concentrated, and the residue was triturated with methylene chloride (300 mL) and vacuum filtered. The filtrate was concentrated, and the residue was purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:1), to provide 5.49 g (95% yield) of the product **264** as a yellow solid.

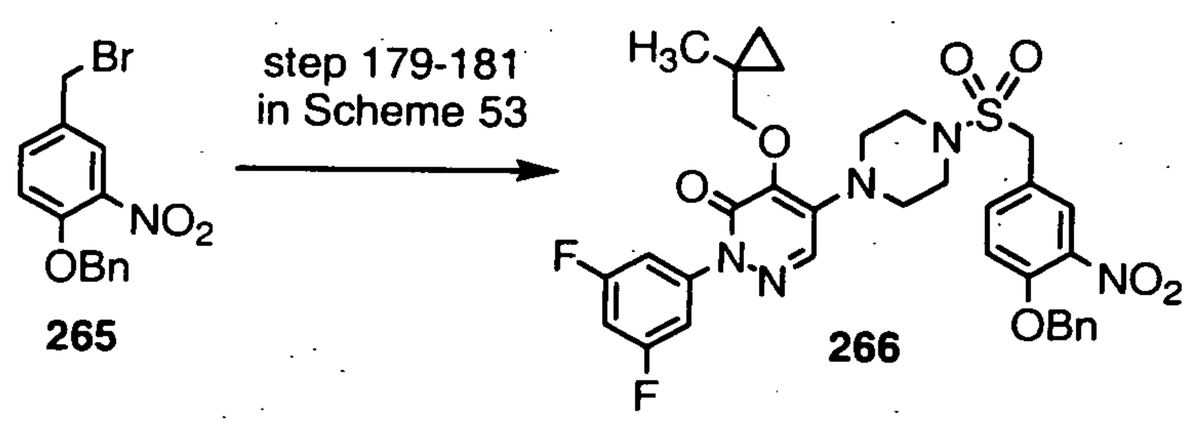
Step 191:



264 **265**

Triphenylphosphine (11.12 g, 42.39 mmol) was added to a solution of *N*-bromosaccharin (11.11 g, 42.39 mmol) in methylene chloride (180 mL) at 0 °C under nitrogen, and the mixture was stirred for 5 mins. The mixture was warmed to room temperature, and a solution of (4-(benzyloxy)-3-nitrophenyl)methanol **264** (5.49 g, 21.17 mmol) in methylene chloride (60 mL) was added dropwise. The mixture was stirred at room temperature for 1 h after which the white precipitate was removed by filtration under reduced pressure. The filtrate was concentrated, and the residue was purified by CombiFlash Companion (80-g silica gel cartridge), eluting with methylene chloride/hexanes (1:1), to provide 5.57 g (82% yield) of the product **265** as a yellow solid.

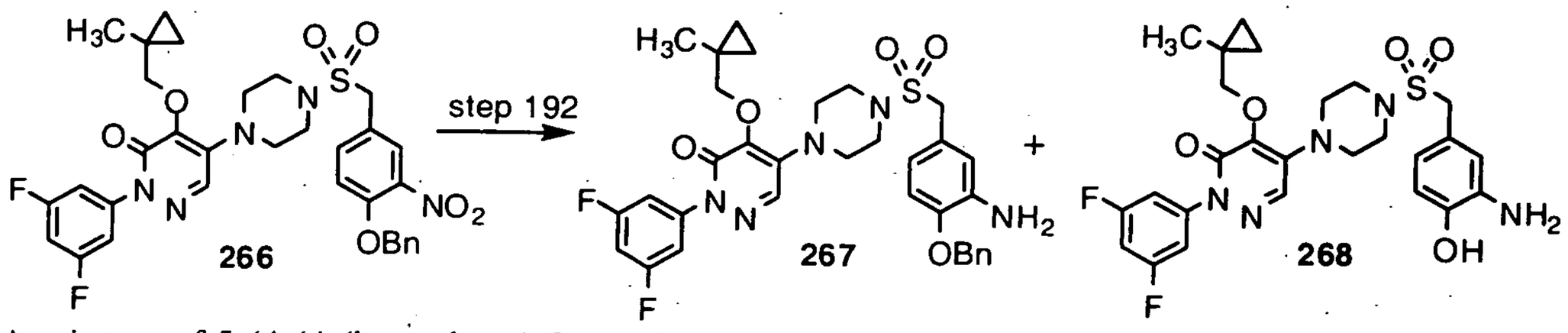
Steps 179-181 in Scheme 53:



265 **266**

Using the described procedures for step 179-181 in Scheme 53, compound **266** was synthesized. MS (M+1): m/e 682.

Step 192:

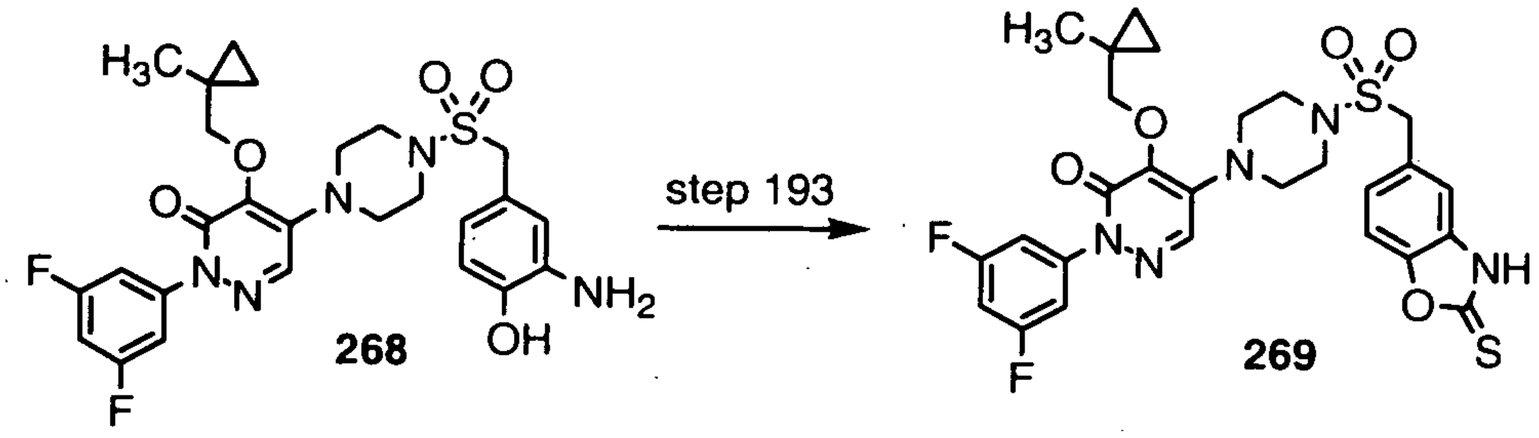


266 **267** **268**

A mixture of 5-(4-(4-(benzyloxy)-3-nitrobenzylsulfonyl)piperazin-1-yl)-2-(3,5-difluorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **266** (166 mg, 0.244 mmol) and platinum(II) oxide (24 mg, 0.098 mmol) in ethyl acetate (6 mL) and ethanol (6 mL) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 18 h.

The mixture was filtered through a plug of celite, and the filtrate was concentrated. The resulting residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 8:2), to provide 85 mg (54% yield) of the product **267** as a white solid: MS (M+1): m/e 652 and 10 mg (7% yield) of the product **268**: MS (M+1): m/e 562.

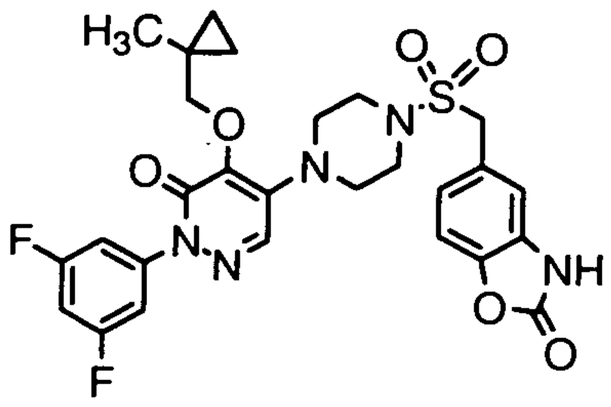
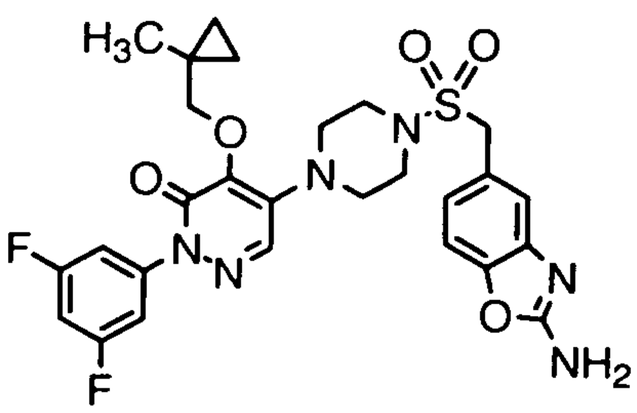
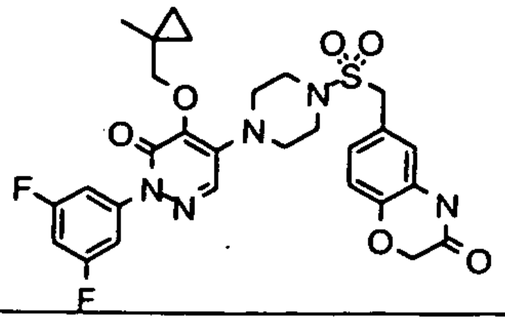
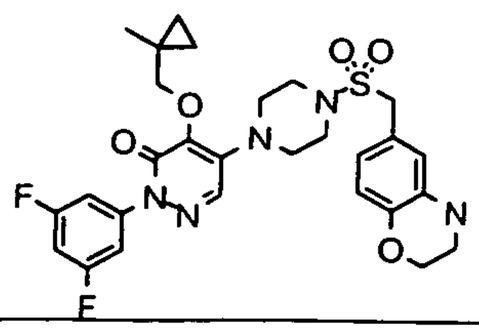
Step 193:

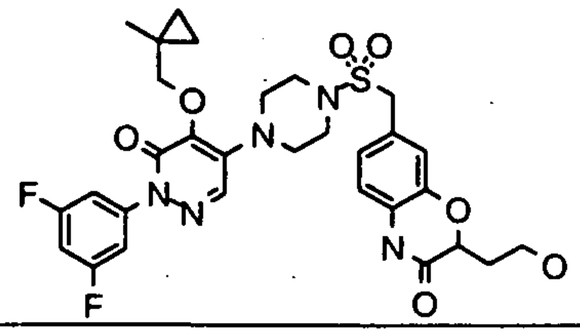
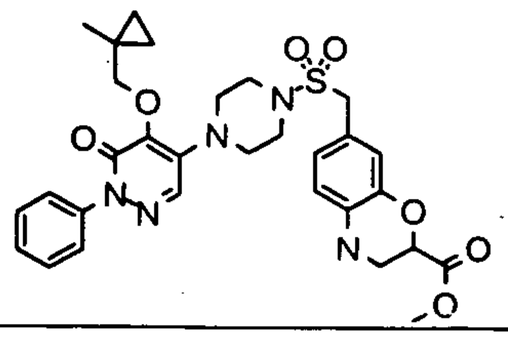
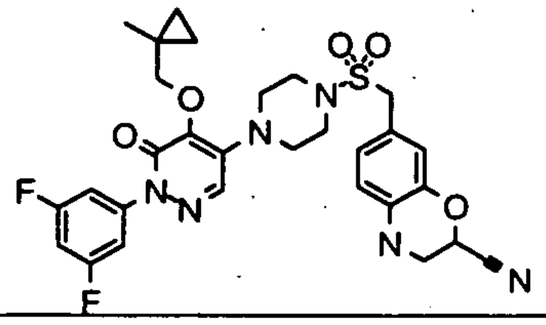


A mixture of 5-(4-(3-amino-4-hydroxybenzylsulfonyl)piperazin-1-yl)-2-(3,5-difluorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **268** (66 mg, 0.12 mmol) and 1,1'-thiocarbonyldiimidazole (42 mg, 0.24 mmol) in DMF (3 mL) at room temperature under nitrogen was stirred for 24 h, after which the mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with water (30 mL x 3) then brine (70 mL), and the solvent was concentrated. The resulting residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 to 6:4), to provide 56 mg (79% yield) of the product **269** as a white solid. MS (M+1): m/e 604.

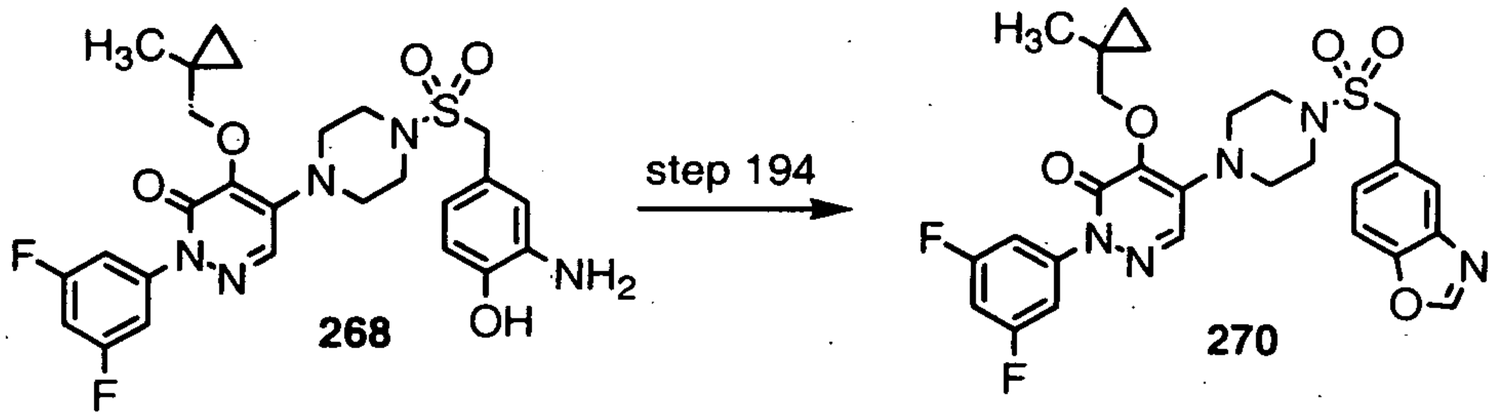
Using the procedures described above, the following compounds were synthesized.

Table 35: Oxygen Analogs with Cyclized Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1881Z		588	1882Z		587
1883Z		602	1884Z		588

1885Z		646		1886Z		610
1887Z		613				

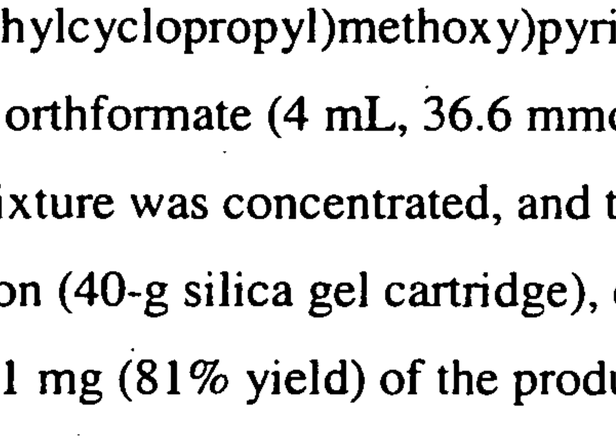
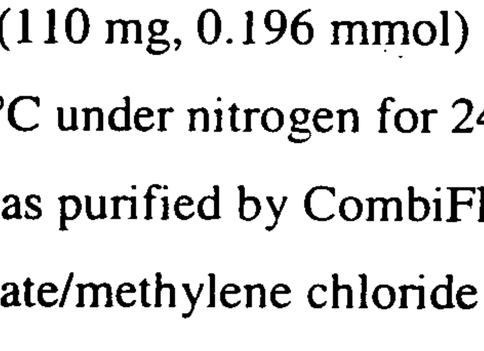
Step 194:

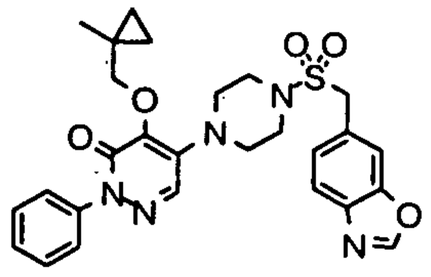
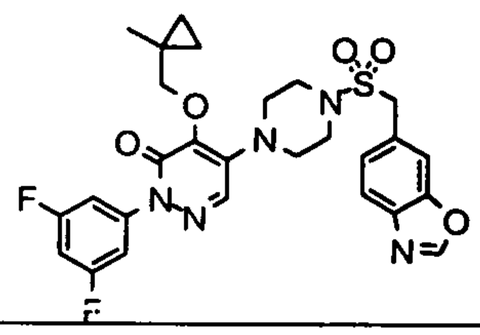
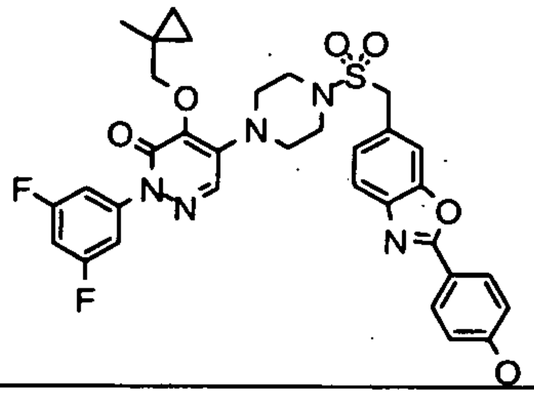
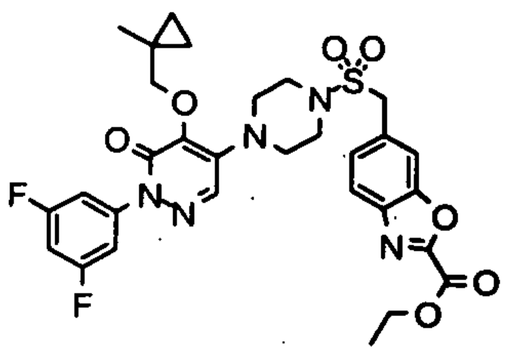
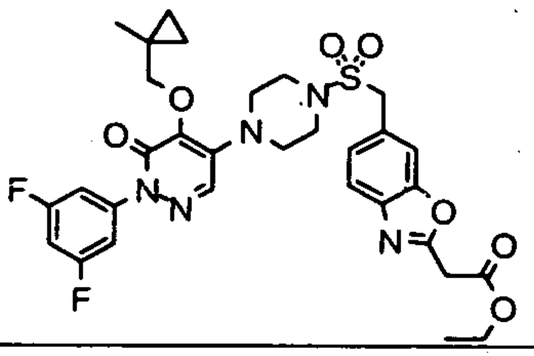
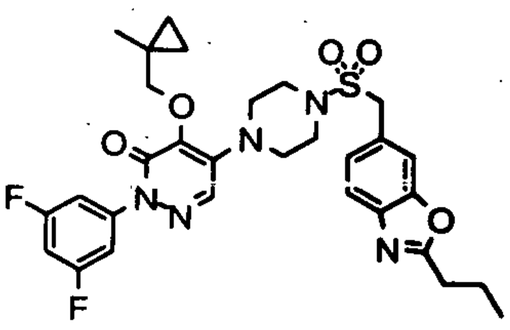
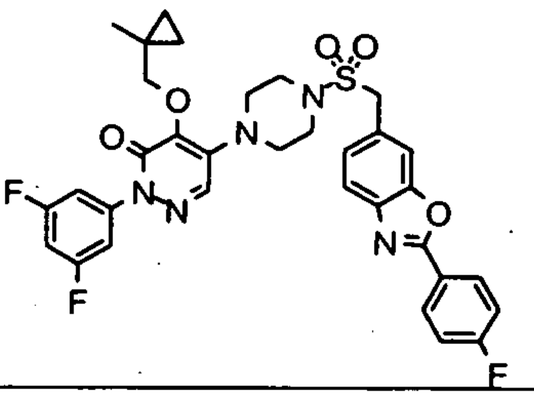
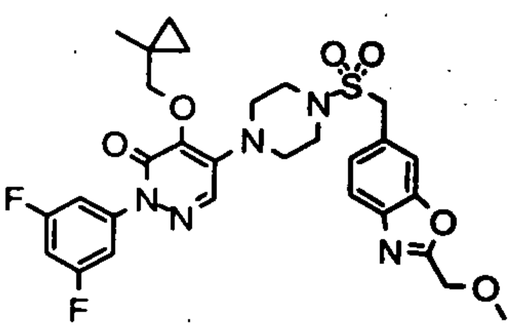
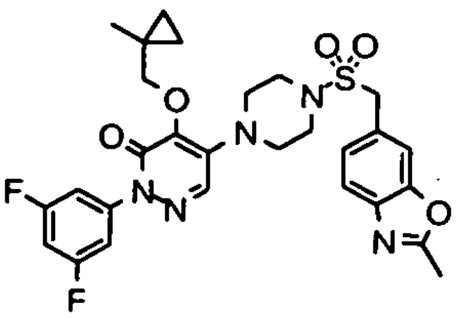
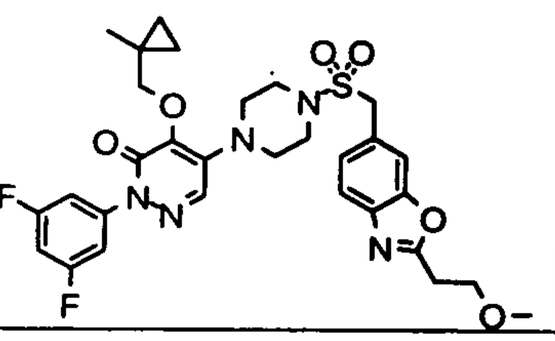
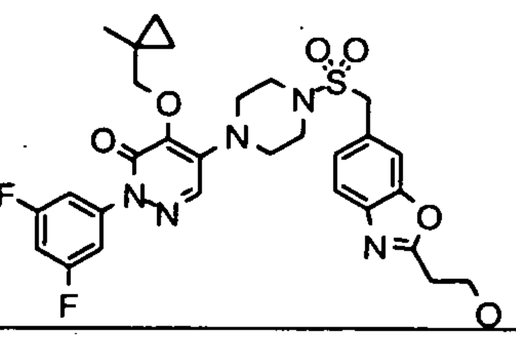
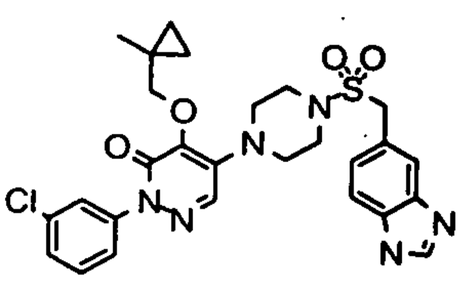
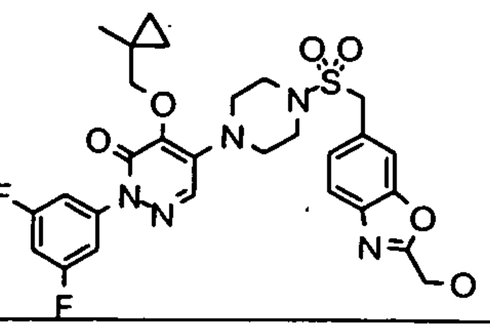
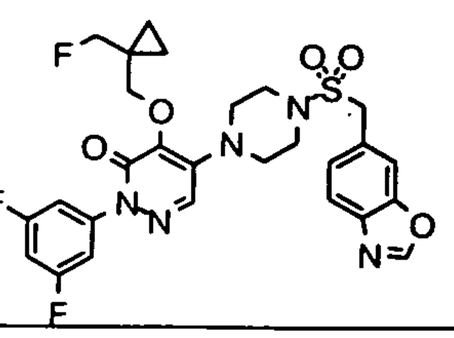


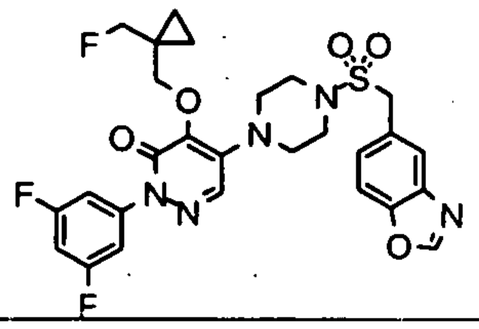
A mixture of 5-(4-(3-amino-4-hydroxybenzylsulfonyl)piperazin-1-yl)-2-(3,5-difluorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **268** (110 mg, 0.196 mmol) and trimethyl orthformate (4 mL, 36.6 mmol) was heated at 100 °C under nitrogen for 24 h. The cooled mixture was concentrated, and the resulting residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/methylene chloride (3:7), to provide 91 mg (81% yield) of the product **270** as a white solid. MS (M+1): m/e 572.

Using the procedures described above, the following compound was synthesized.

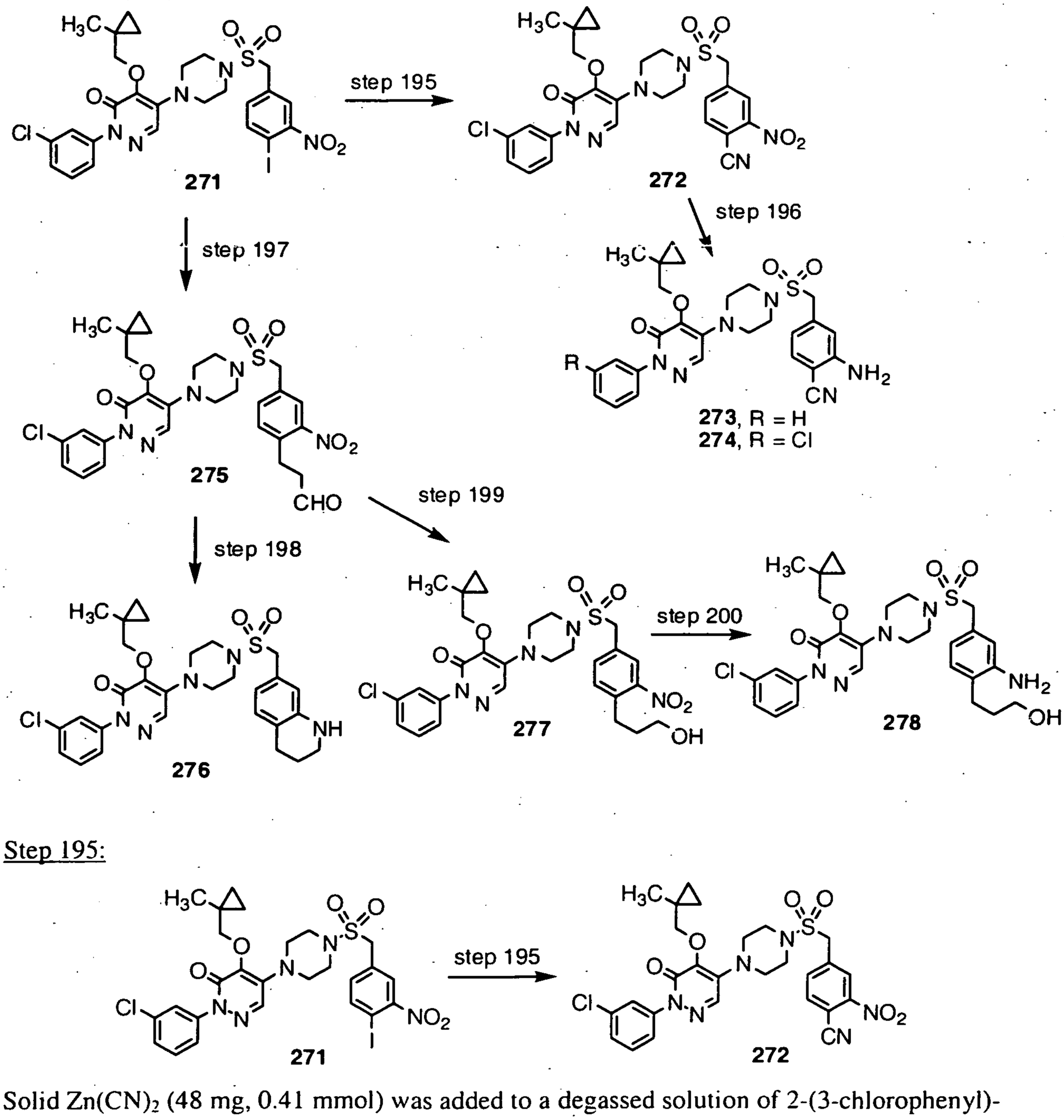
Table 36: Oxygen Analogs with Cyclized Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1888Z		586	1889Z		600

1890Z		536		1891Z		572	
1892Z		664		1893Z		644	
1894Z		658		1895Z		614	
1896Z		666		1897Z		616	
1898Z		586		1899Z		630	
1900Z		616		1901Z		569	
1902Z		602		1902ZA		590	

1902ZB		590

Scheme 57

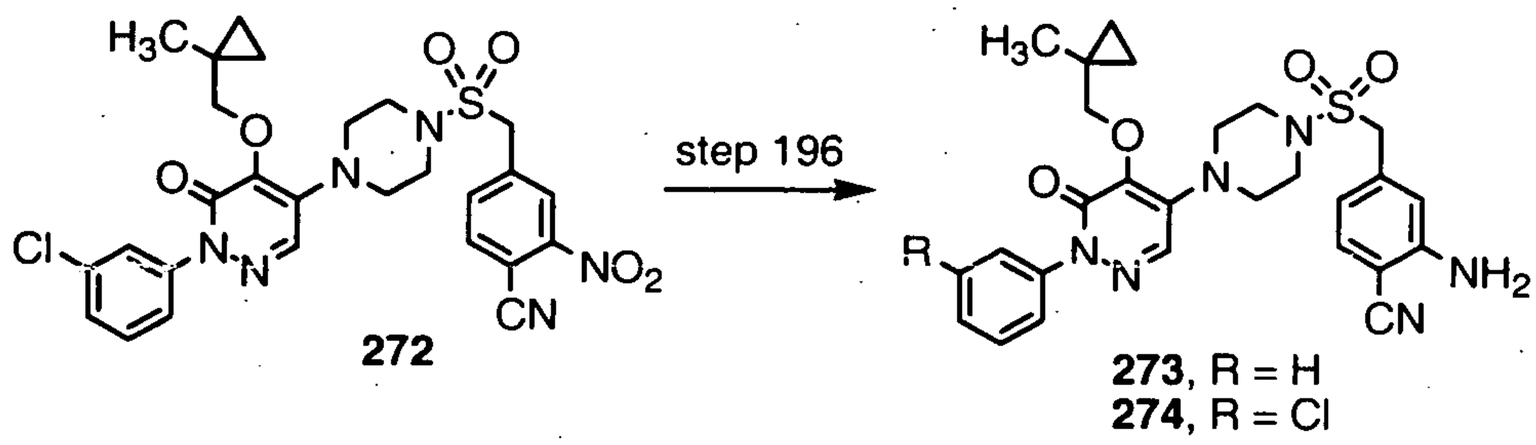


Step 195:

Solid $Zn(CN)_2$ (48 mg, 0.41 mmol) was added to a degassed solution of 2-(3-chlorophenyl)-5-(4-(4-iodo-3-nitrobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)-

pyridazin-3(2*H*)-one **271** (260 mg, 0.371 mmol) in DMF (5 mL) at room temperature under nitrogen, after which $Pd(PPh_3)_4$ (64 mg, 0.056 mmol) was added and the mixture was stirred at 85 °C under nitrogen for 18 h. The cooled mixture was diluted with ethyl acetate (150 mL), washed with water (15 mL x 3) and brine (75 mL), and the solvent was concentrated. The resulting residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 1:1), to provide 196 mg (88% yield) of the product **272** as a yellow solid. MS (M+1): m/e 599.

Step 196:

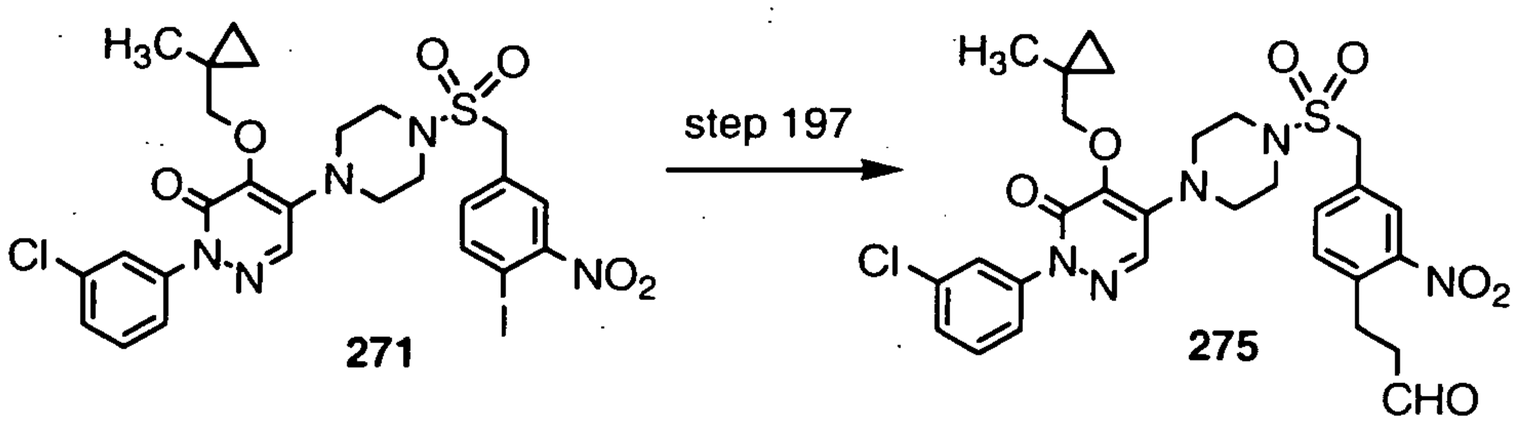


272

273, R = H
274, R = Cl

A mixture of 4-((4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl)-2-nitrobenzonitrile **272** (172 mg, 0.287 mmol) and palladium on carbon (100 mg) in methylene chloride (6 mL) and methanol (12 mL) at room temperature was stirred under an atmosphere of hydrogen (45 psi) for 3 h. The mixture was filtered through a plug of celite under reduced pressure, after which the filtrate was concentrated. The resulting residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 1:1), to provide first 95 mg (58% yield) of the product **274** as an off-white solid: MS (M+1): m/e 569 and second 27 mg (18% yield) of the product **273** as a white solid: MS (M+1): m/e 535.

Step 197:

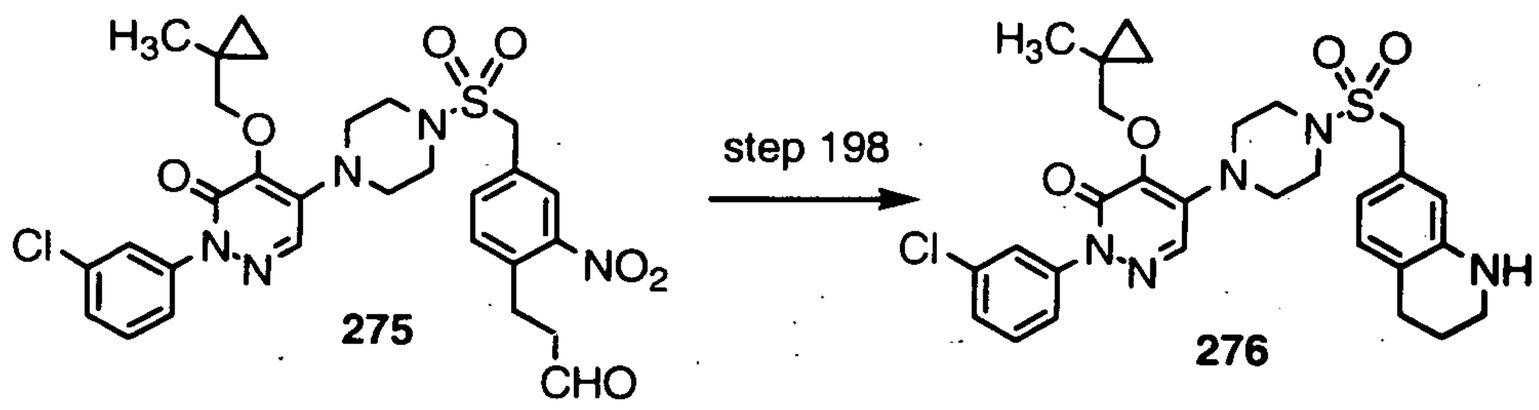


271 **275**

Sodium bicarbonate (89 mg, 1.06 mmol), Bu_4NBr (151 mg, 0.468 mmol), allyl alcohol (102 uL, 1.50 mmol) and $Pd(OAc)_2$ (8 mg, 0.03 mmol) were sequentially added to a degassed solution of 2-(3-chlorophenyl)-5-(4-(4-iodo-3-nitrobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **271** (298 mg, 0.426 mmol) in DMF (8 mL)

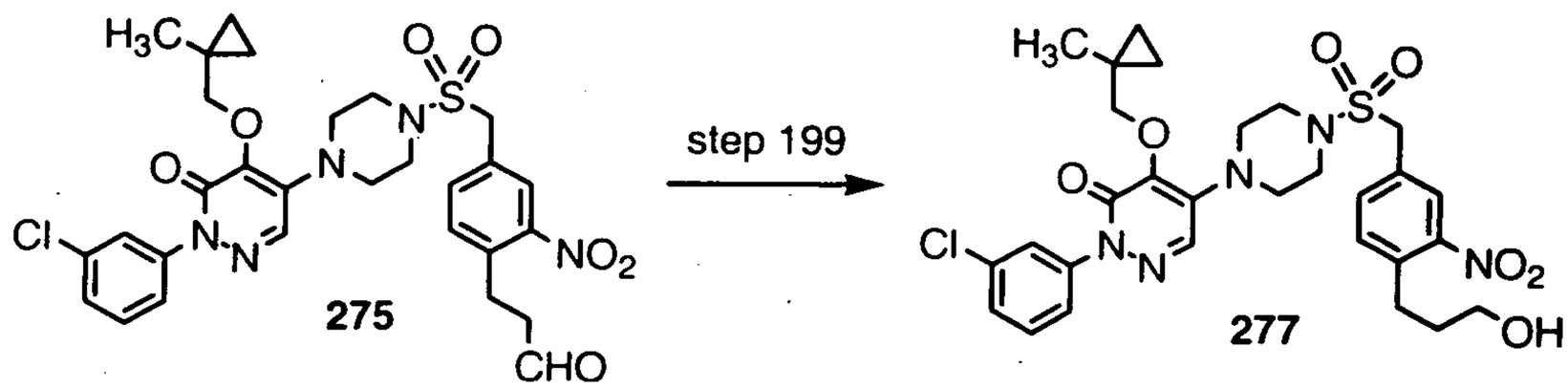
at room temperature under nitrogen, after which the mixture was stirred at 50 °C for 24 h. The cooled mixture was diluted with water (80 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic extracts were washed with water (30 mL x 3) and brine (80 mL), and the solvents was concentrated. The resulting residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/methylene chloride (5:95 to 3:7), to provide 177 mg (66% yield) of the product **275** as a yellow solid. MS (M+1): m/e 630.

Step 198:



A mixture of 3-(4-((4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl)-2-nitrophenyl)propanal **275** (100 mg, 0.159 mmol) and platinum(IV) oxide (14 mg, 0.062 mmol) in ethyl acetate (8 mL) and methanol (8 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 18 h. The mixture was filtered through a plug of celite under reduced pressure and the filtrate was concentrated. The resulting residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/methylene chloride (1:99 to 15:85) to provide 47 mg (51% yield) of the product **276**. MS (M+1): m/e 584.

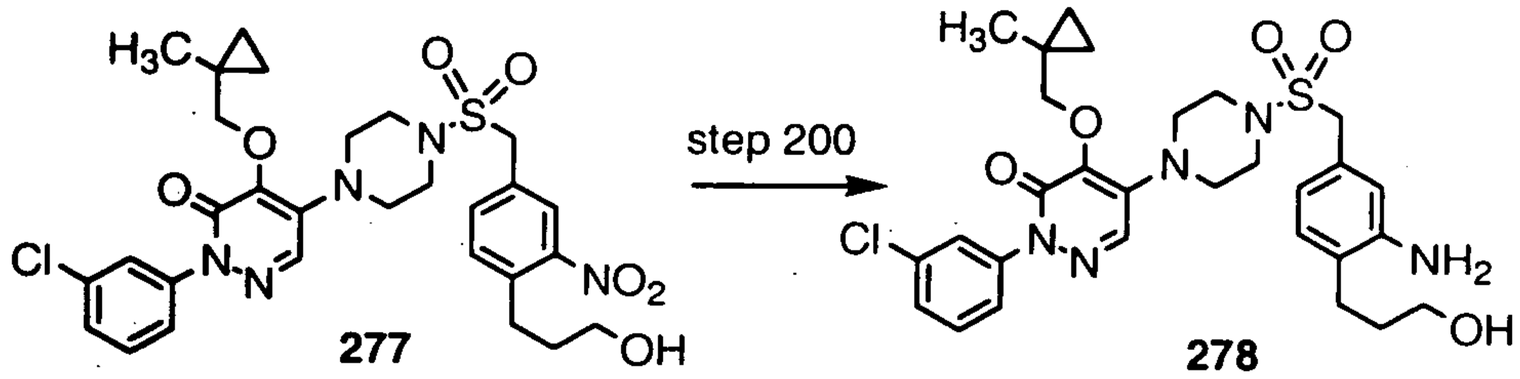
Step 199:



Sodium borohydride (14 mg, 0.37 mmol) was added to a solution of 3-(4-((4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl)-2-nitrophenyl)propanal **275** (77 mg, 0.122 mmol) in methanol (8 mL) at 0 °C under nitrogen and the mixture was stirred for 90 mins. Water (0.5 mL) was added, and the mixture was concentrated. The residue was diluted with water (15 mL) and adjusted to pH ~ 7 with 1 M HCl and then extracted with ethyl acetate (30 mL x 2).

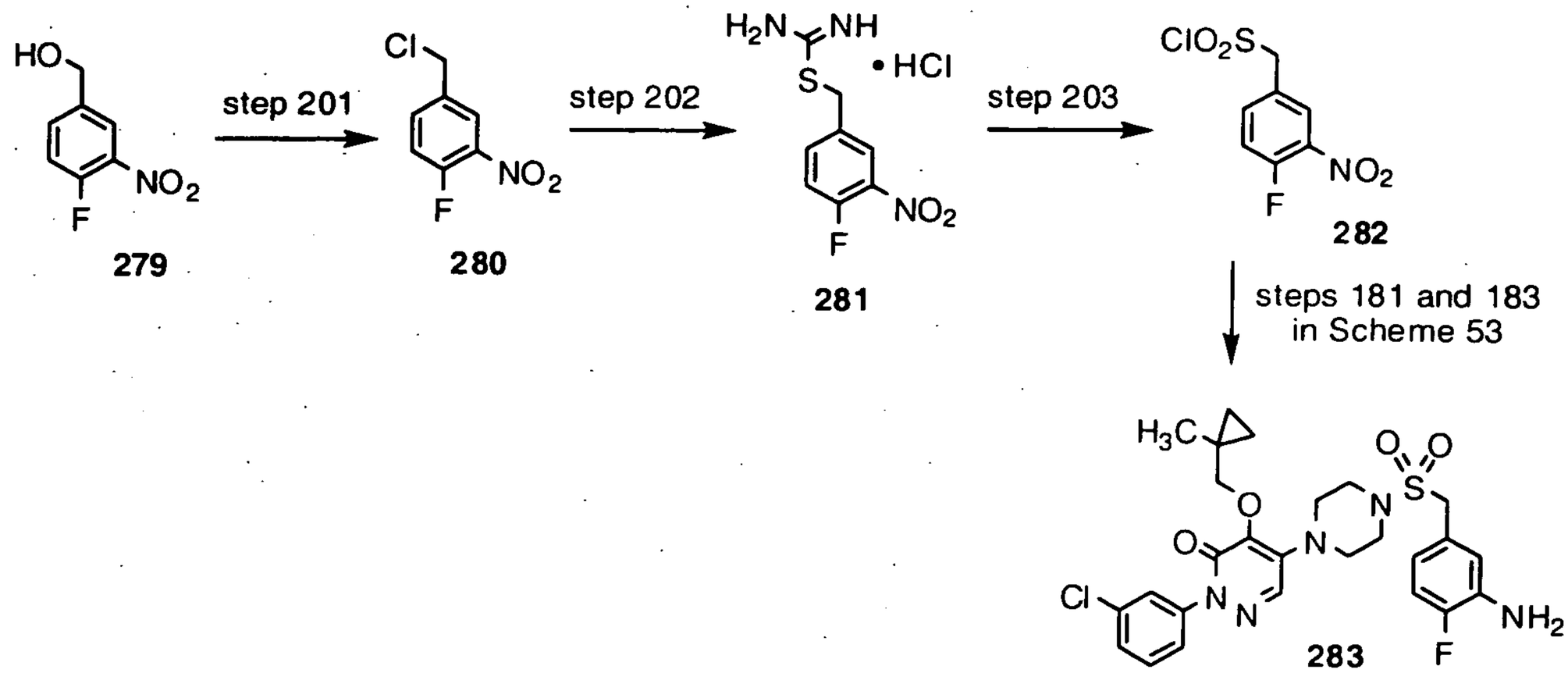
The combined organic extracts were washed with brine (30 mL) and the solvent was concentrated. The resulting residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/methylene chloride (5:95 to 3:7), to provide 56 mg (72% yield) of the product **277** as a white solid. MS (M+1): m/e 632.

Step 200:

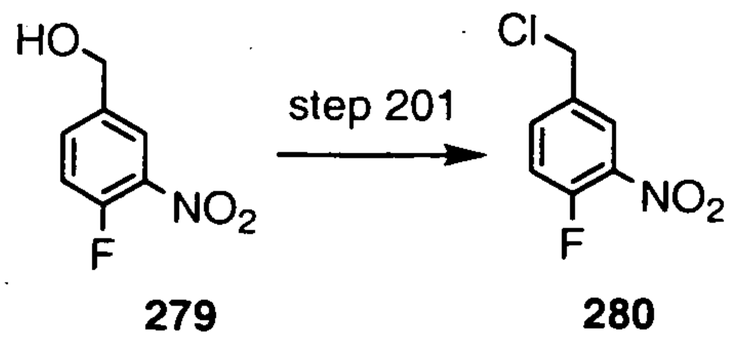


A mixture of 2-(3-chlorophenyl)-5-(4-(4-(3-hydroxypropyl)-3-nitrobenzylsulfonyl) piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **277** (42 mg, 0.066 mmol) and platinum(IV) oxide (8 mg, 0.033 mmol) in ethyl acetate (6 mL) and methanol (6 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 18 h. The mixture was filtered through a plug of celite under reduced pressure and the filtrate was concentrated. The resulting residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/methylene chloride (5:95 to 8:2), to provide 31 mg (77% yield) of the product **278** as a white solid. MS (M+1): m/e 602.

Scheme 58



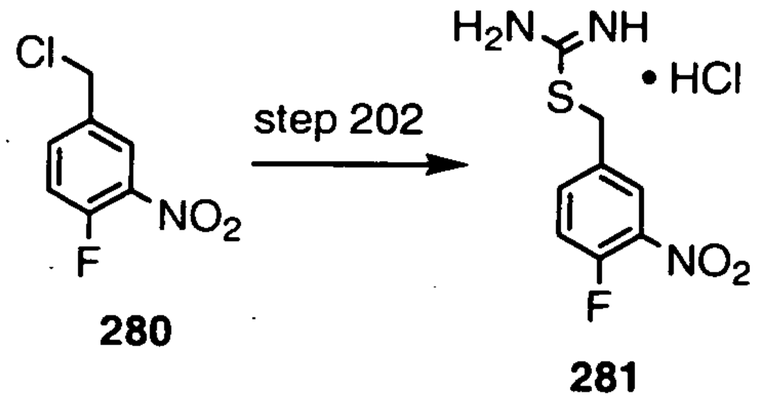
Step 201:



279 **280**

Methylene chloride (30 mL) was added to a solution of cyanuric chloride (1.84 g, 10.0 mmol) in dimethylformamide (1.90 g, 25.8 mmol) at room temperature under nitrogen, after which (4-fluoro-3-nitrophenyl)methanol **279** (2.22 g, 9.5 mmol) was added. The mixture was stirred for 3 h, diluted with methylene chloride, and washed sequentially with water (125 mL), saturated sodium carbonate solution (125 mL), 1 N hydrochloric acid (125 mL) and brine (150 mL). The organic solution was dried over sodium sulfate, filtered, and concentrated. The residue was purified by CombiFlash Companion (40-g silica cartridge), eluting with methylene chloride, to provide 1.62 g (90% yield) of the product **280** as a clear oil which solidified upon refrigeration, and was used without purification.

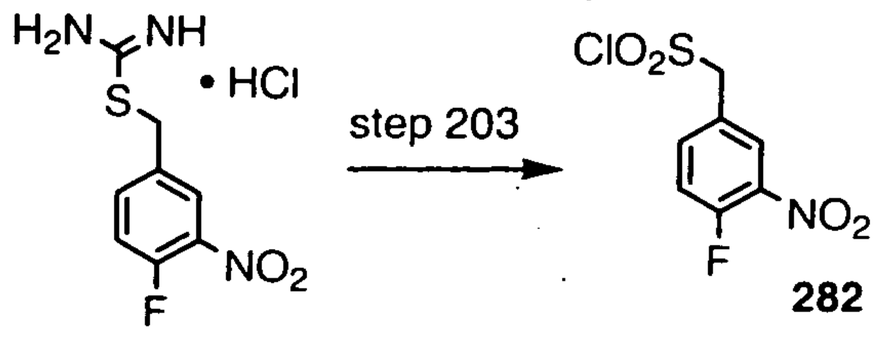
Step 202:



280 **281**

A mixture of 4-(chloromethyl)-1-fluoro-2-nitrobenzene **280** (1.62 g, 8.54 mmol) and thiourea (0.65 g, 8.54 mmol) in ethanol (10 mL) was heated at reflux under nitrogen for 15 h. The solvent was removed from the cooled mixture under reduced pressure, and the residue triturated with ethyl acetate (75 mL) for 30 mins at room temperature. The solids were collected by filtration, washed with ethyl acetate, and dried under reduced pressure to provide 1.32 g (58% yield) of the product **281** as a white solid that was used without purification.

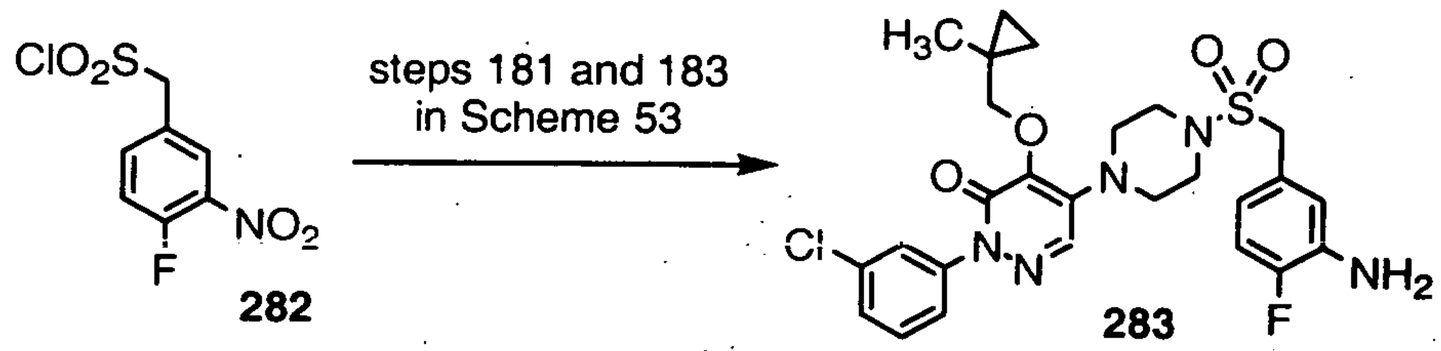
Step 203:



281 **282**

A stream of chlorine gas was introduced subsurface for 30 mins to a rapidly-stirred suspension of 4-fluoro-3-nitrobenzylcarbamimidothioate hydrochloride **281** (1.30 g, 4.96 mmol) in 1 N hydrochloric acid (40 mL) at 0 °C, after which the ice-bath was removed, and chlorine addition was continued for an additional 30 mins. The solids were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to provide 1.02 g (81% yield) of the product **282** as a white solid that was used without purification.

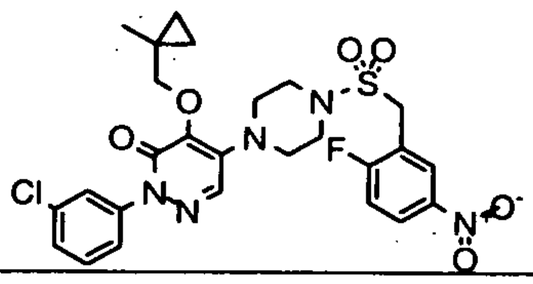
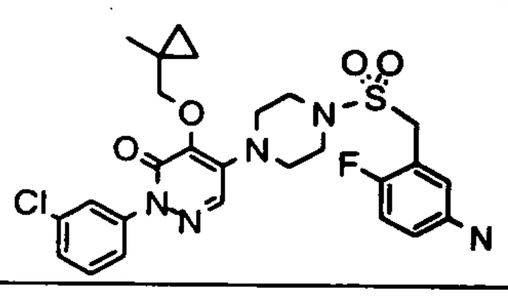
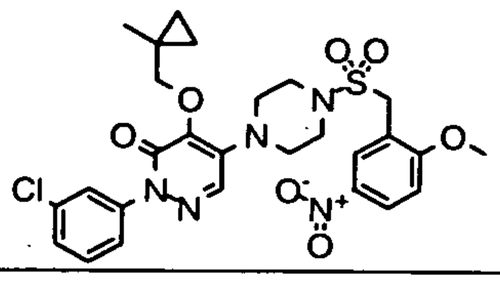
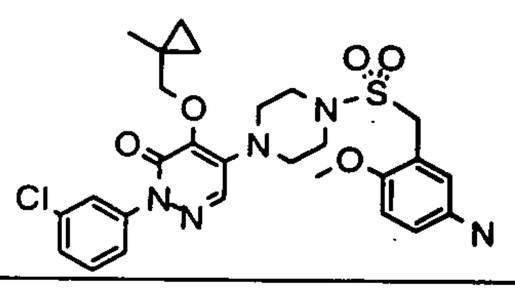
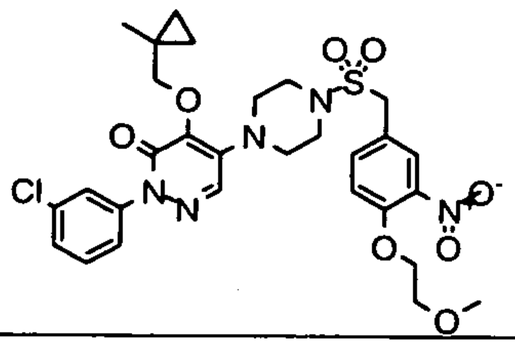
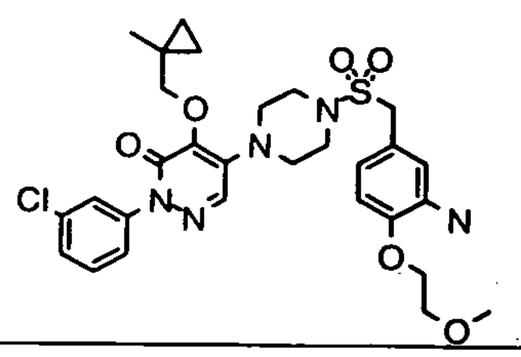
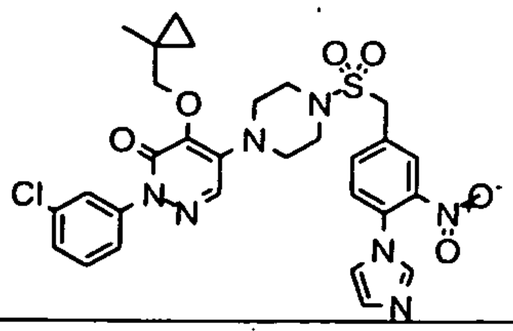
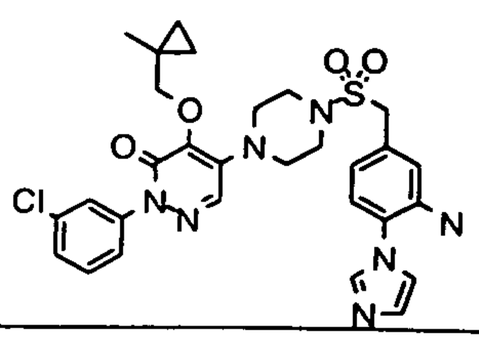
Steps 181 and 183 in Scheme 53:

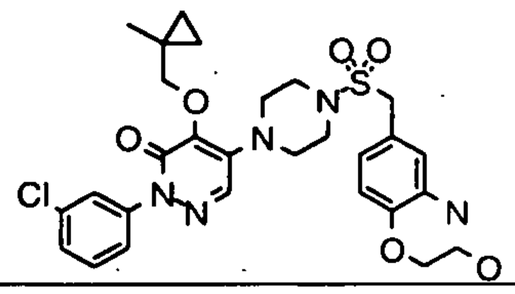


282 283

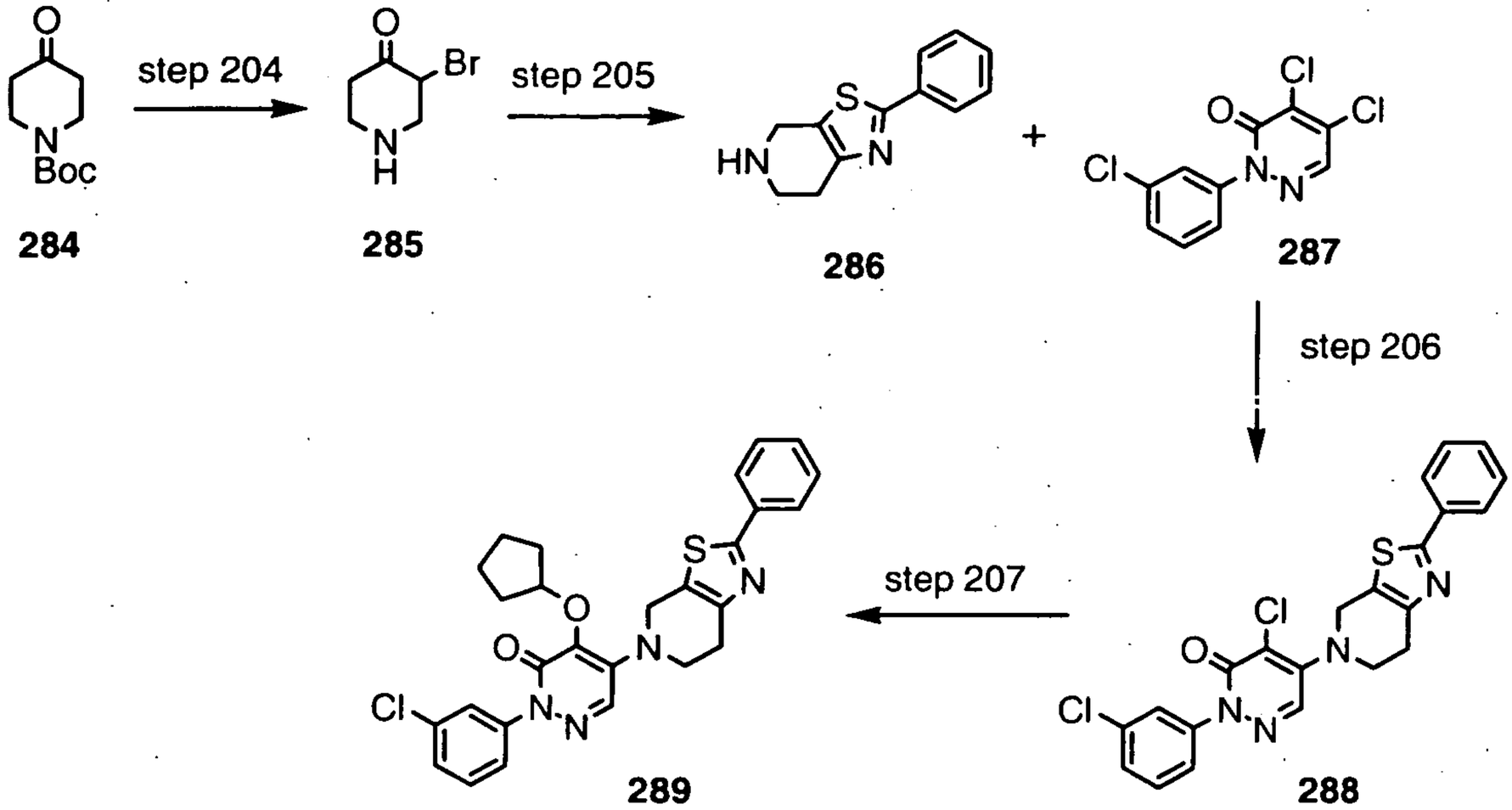
Using the described procedures for steps 181 and 183 in Scheme 53, compound **283** was synthesized. MS (M+1): m/e 562.

Using the procedures described above, the following compounds were synthesized.

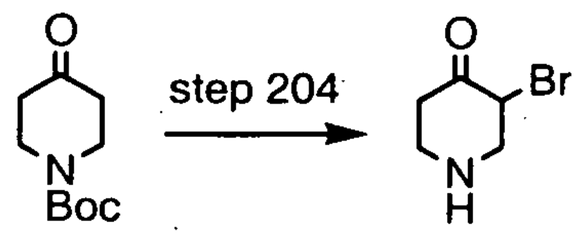
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1903Z		592	1904Z		562
1905Z		604	1906Z		574
1907Z		648	1908Z		618
1909Z		640	1910Z		610

1910ZA		604

Scheme 59



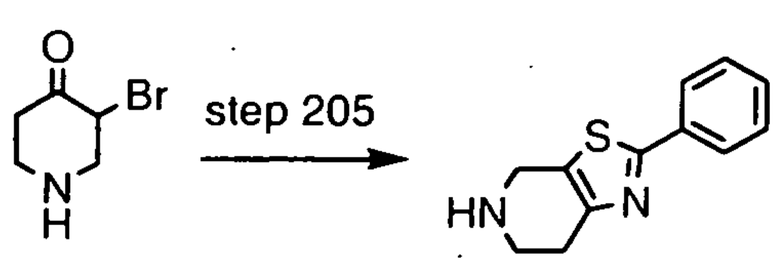
Step 204:



284 **285**

To a solution of 1-Boc-4-piperidone **284** (1 g, 5.01 mmol) in chloroform (20 mL) was slowly added bromine (0.26 mL, 5.02 mmol) over 30 mins under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The resulting solid was filtered and dried to give 684 mg (53% yield) of the product **285** as brown solid. MS (M+1): m/e 179.

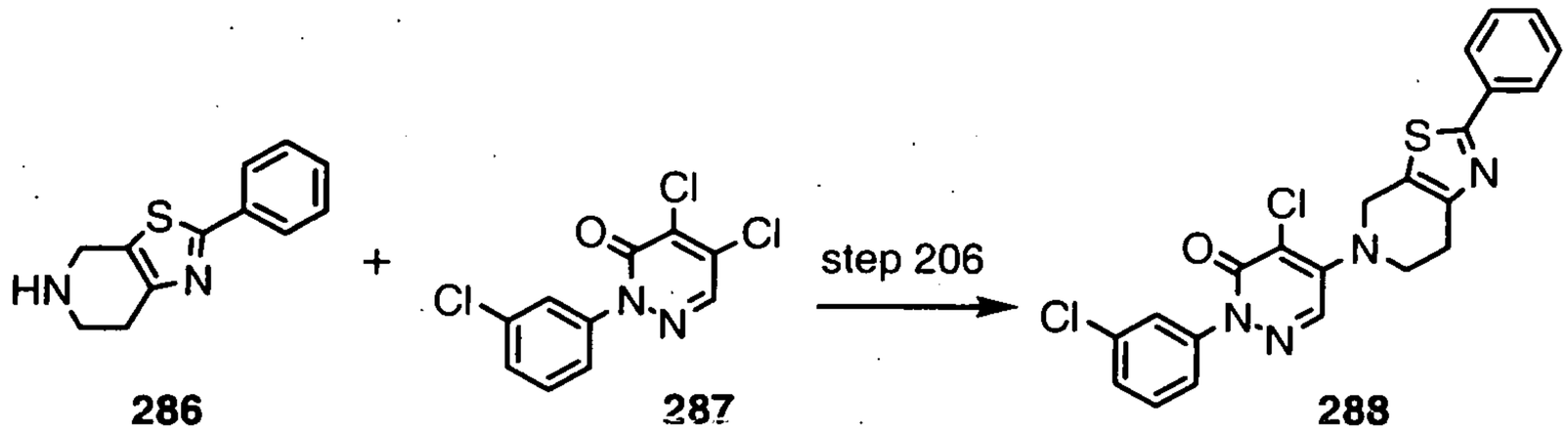
Step 205:



285 **286**

To a solution of bromine **285** (494 mg, 1.91 mmol), in DMF (10 mL) was added thiobenzamide (314 mg, 2.29 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C for 7 h then cooled to room temperature and stirred for 11 h. The reaction mixture was diluted with ethyl acetate and washed with water. The aqueous extract was concentrated to give 312 mg (59% yield) of thiazole **286** as brown oil. MS (M+1): m/e 217.

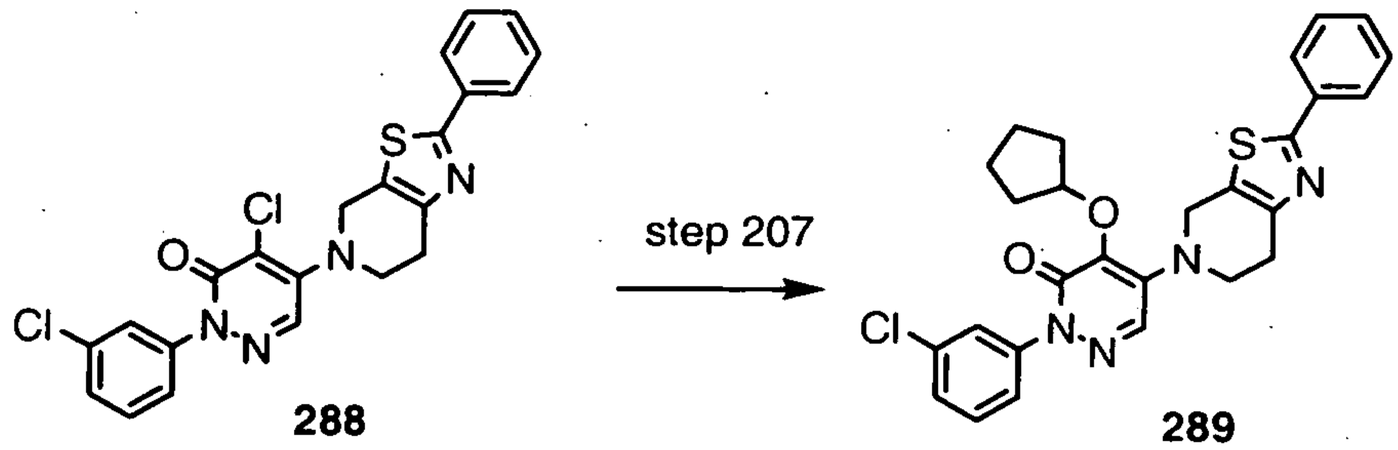
Step 206:



286 **287** **288**

To a solution of thiazole **286** (1.12 g, 5.18 mmol) in EtOH (20 mL) was added pyradizinone **287** (1.26 g, 4.57 mmol) and triethylamine (960 ul, 6.89 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 80 °C for 17 h. The reaction was concentrated and purification with silica gel chromatography (eluant: 25% ethyl acetate in hexanes) gave 816 mg (39% yield) of the product **288** as a brown oil. MS (M+1): m/e 455.

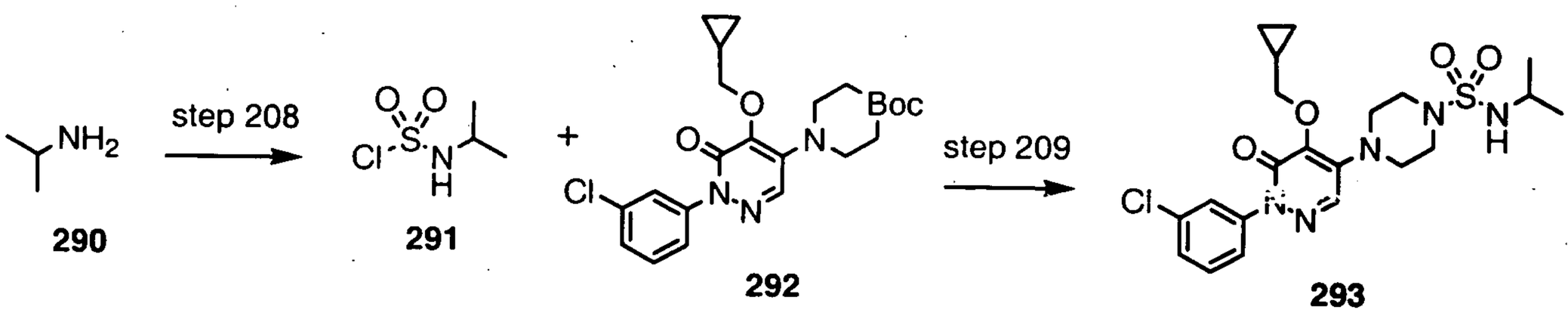
Step 207:



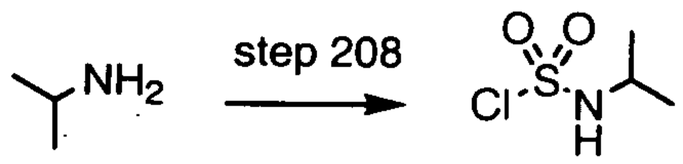
288 **289**

To a solution of cyclopentanol (47.3 mg, 0.549 mmol) in THF (10 mL) was added NaH (60%, 17.6 mg, 0.440 mmol) under a nitrogen atmosphere. To the solution was added compound **288** (50 mg, 0.110 mmol), and the reaction mixture was stirred at room temperature for 17 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic extract was then washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification with silica gel chromatography (eluant: 25% ethyl acetate in hexanes) gave 23.5 mg (42% yield) of the product **289** as brown oil. MS (M+1): m/e 505.

Scheme 60

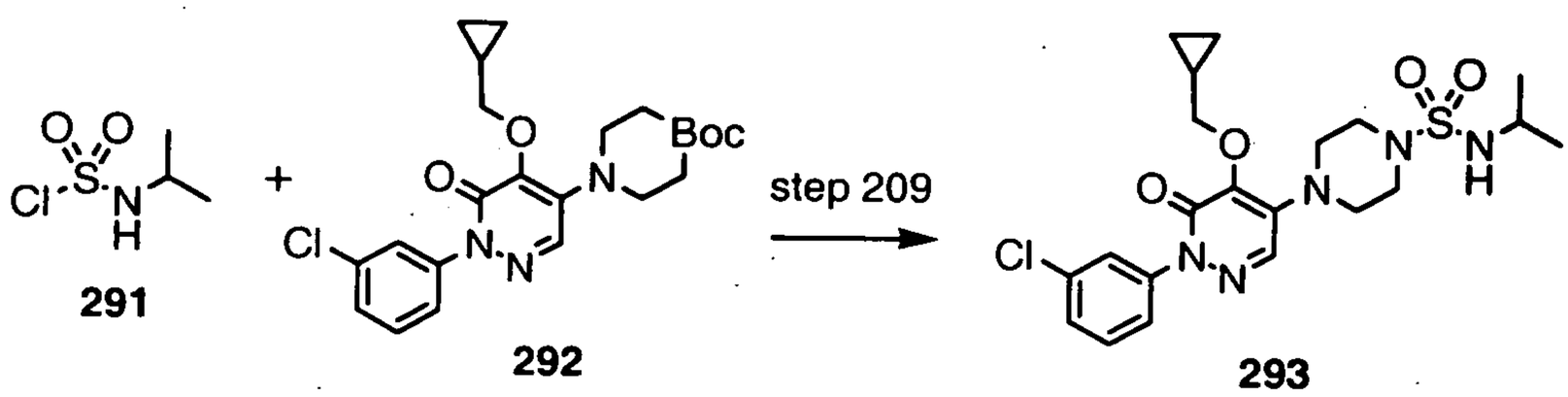


Step 208:



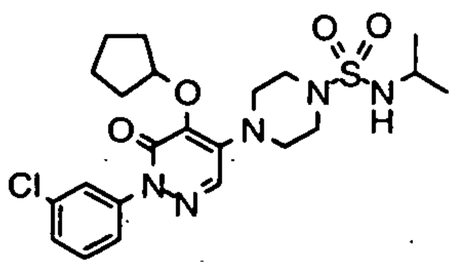
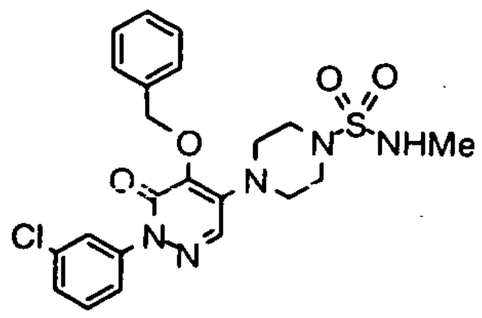
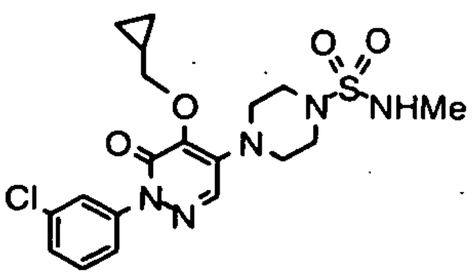
To a solution of sulfuryl chloride (4.57 mL, 56.38 mmol) in acetonitrile (9 mL) was added very slowly isopropylamine (1.44 mL, 16.91 mmol) under a nitrogen atmosphere. The reaction was then heated to 55 °C for 17 h. The reaction mixture was concentrated then diluted with water and extracted with ether. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated to give 683 mg (26% yield) of the product **291** as a white solid.

Step 209:

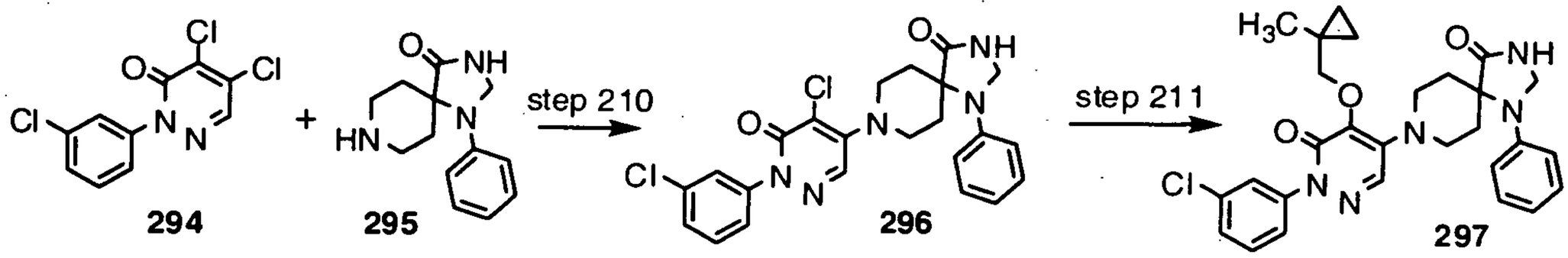


4N HCl in dioxane (5 mL) was added to ether **292** (50 mg, 0.145 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h. The reaction was then concentrated and dried under high vacuum. To a solution of the crude product in CH_2Cl_2 (5 mL) was added sulfamoyl chloride **291** (51.3 mg, 0.325 mmol) and Hunig's base (113.3 uL, 0.650 mmol). The reaction was stirred at room temperature for 17 h then concentrated. Purification with silica gel chromatography (eluant: 20% ethyl acetate in hexanes) gave 19.6 mg (38% yield) of the product **293** as a yellow oil. MS (M+1): m/e 482.

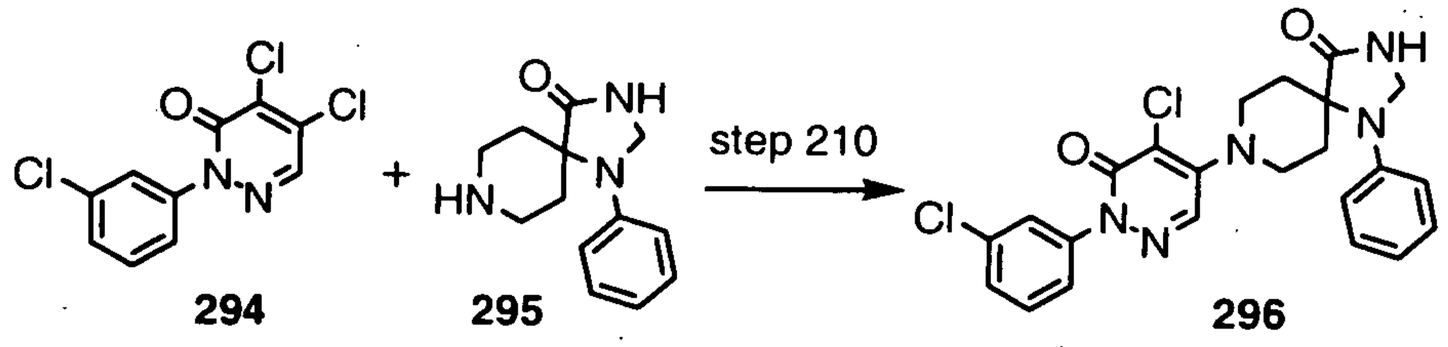
Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1
1911Z		496
1912Z		490
1913Z		454

Scheme 61

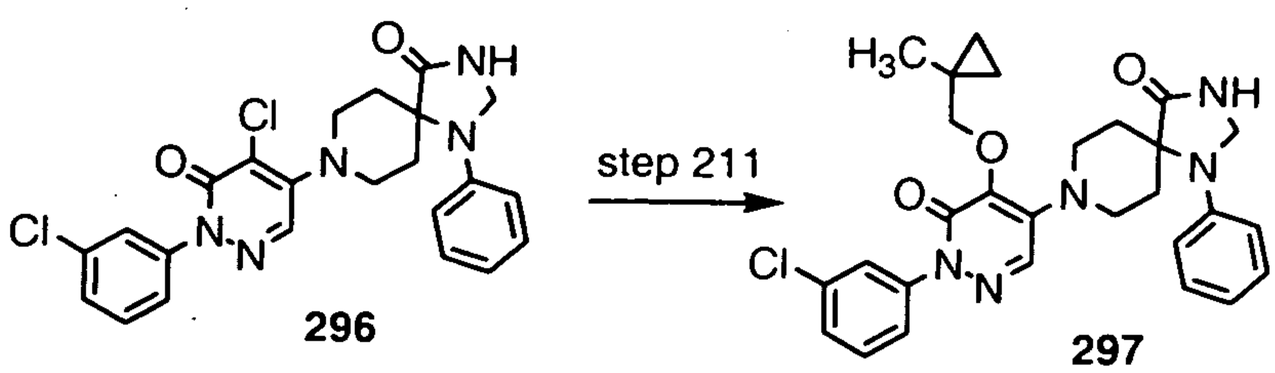


Step 210:



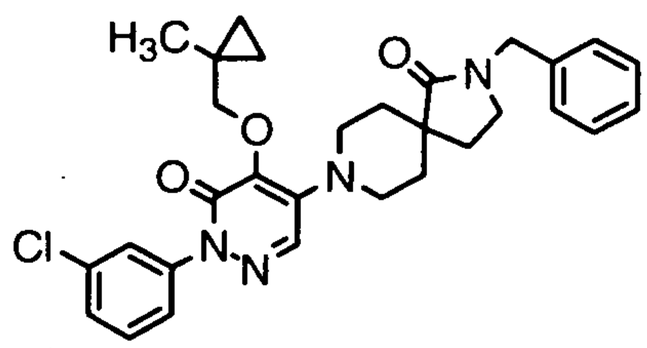
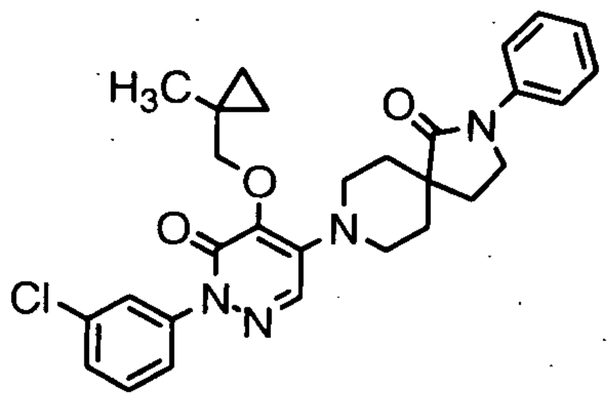
A mixture of 4,5-dichloro-2-(3-chlorophenyl)pyridazin-3(2*H*)-one **294** (1.0 g, 3.6 mmol), diisopropylethylamine (1.0 mL, 5.43 mmol) and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one **295** (1.0 g, 4.4 mmol) in absolute ethanol (15 mL) was heated at reflux under nitrogen for 16 h. The mixture was cooled to room temperature and purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate, to provide 1.1 g (64% yield) of the product **296** as an off-white solid. MS (M+1):m/e 470.

Step 211:

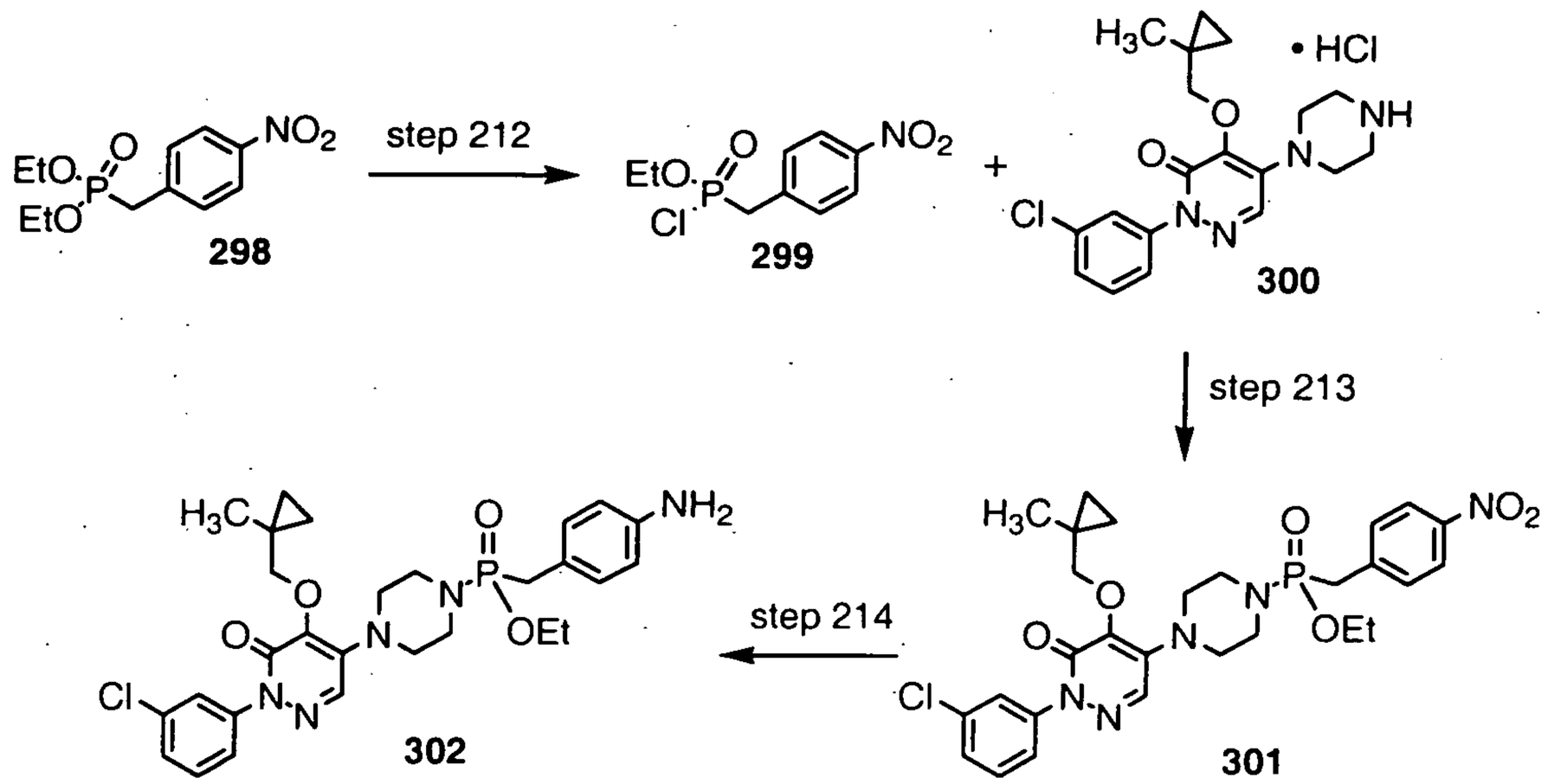


Sodium hydride (45 mg, 1.1 mmol, 60% suspension in mineral oil) was added to a solution of 1-methylcyclopropylmethanol (55 mg, 0.64 mmol) and 8-(5-chloro-1-(3-chlorophenyl)-6-oxo-1,6-dihydropyridazin-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one **296** (200 mg, 0.43 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature under nitrogen and the mixture was heated at reflux for 4 h. The cooled mixture was diluted with ethyl acetate (200 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and filtered. The solvent was concentrated, and the residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:1 to 100% ethyl acetate), to provide 60 mg (27% yield) of the product **297** as a yellow solid. MS (M+1): m/e 520.

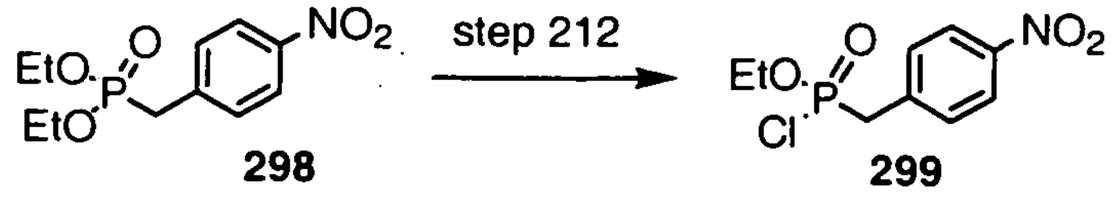
Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1914Z		533	1915Z		519

Scheme 62



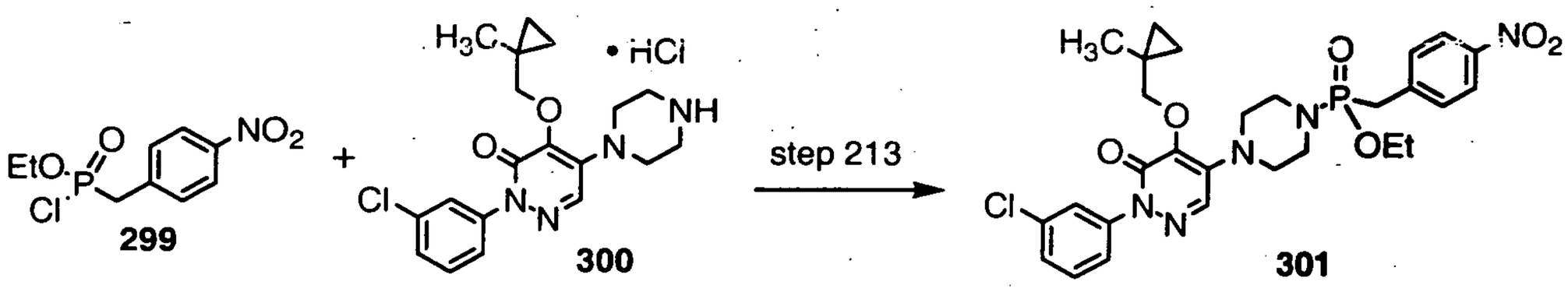
Step 212:



298 299

Oxalyl chloride (4.8 mL, 9.6 mmol, 2 M solution in methylene chloride) was added to a solution of diethyl 4-nitrobenzylphosphonate **298** (546 mg, 2.0 mmol) in methylene chloride (10 mL) at room temperature under nitrogen, and the mixture was stirred for 48 h. The mixture was diluted with chloroform (10 mL), and the solvent was concentrated to provide 520 mg (99% yield) of ethyl 4-nitrobenzylphosphonochloridate **299** as a thick yellow oil that was used in the next step without purification.

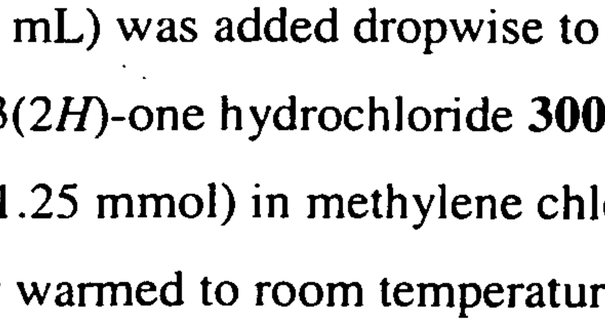
Step 213:



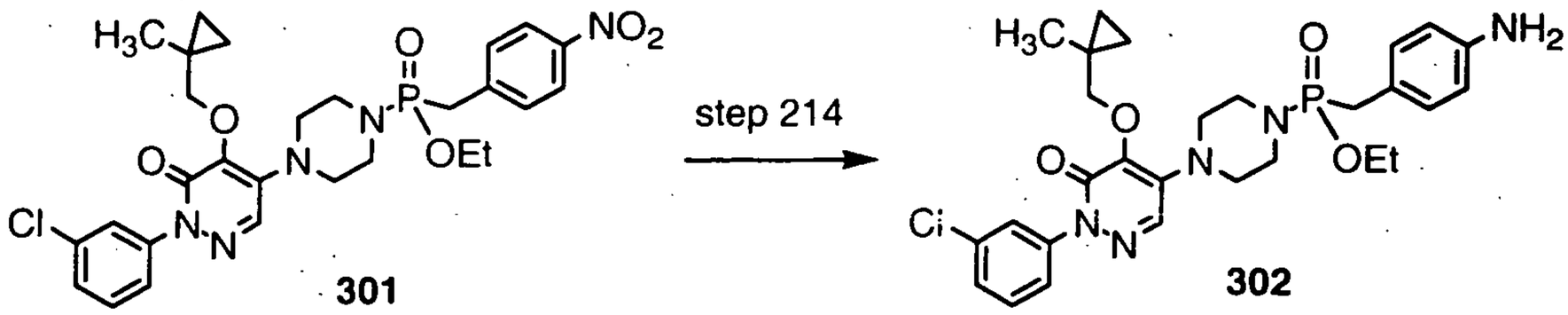
299 300 301

A solution of ethyl 4-nitrobenzylphosphonochloridate **299** (197 mg, 0.75 mmol) in methylene chloride (1 mL) was added dropwise to a mixture of 4,5-dichloro-2-(3-chlorophenyl)-pyridazin-3(2*H*)-one hydrochloride **300** (205 mg, 0.50 mmol) and diisopropylethylamine (0.22 mL, 1.25 mmol) in methylene chloride (5 mL) at 0 °C under nitrogen, and the mixture was slowly warmed to room temperature, stirring for a total of 16 h. The solvent was concentrated, and the residue was purified by CombiFlash Companion (12-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 to 100% ethyl acetate), to provide 96 mg (32% yield) of the product **301** as a light yellow solid. MS (M+1): m/e 600.

Using the procedures described above, the following compounds were synthesized.

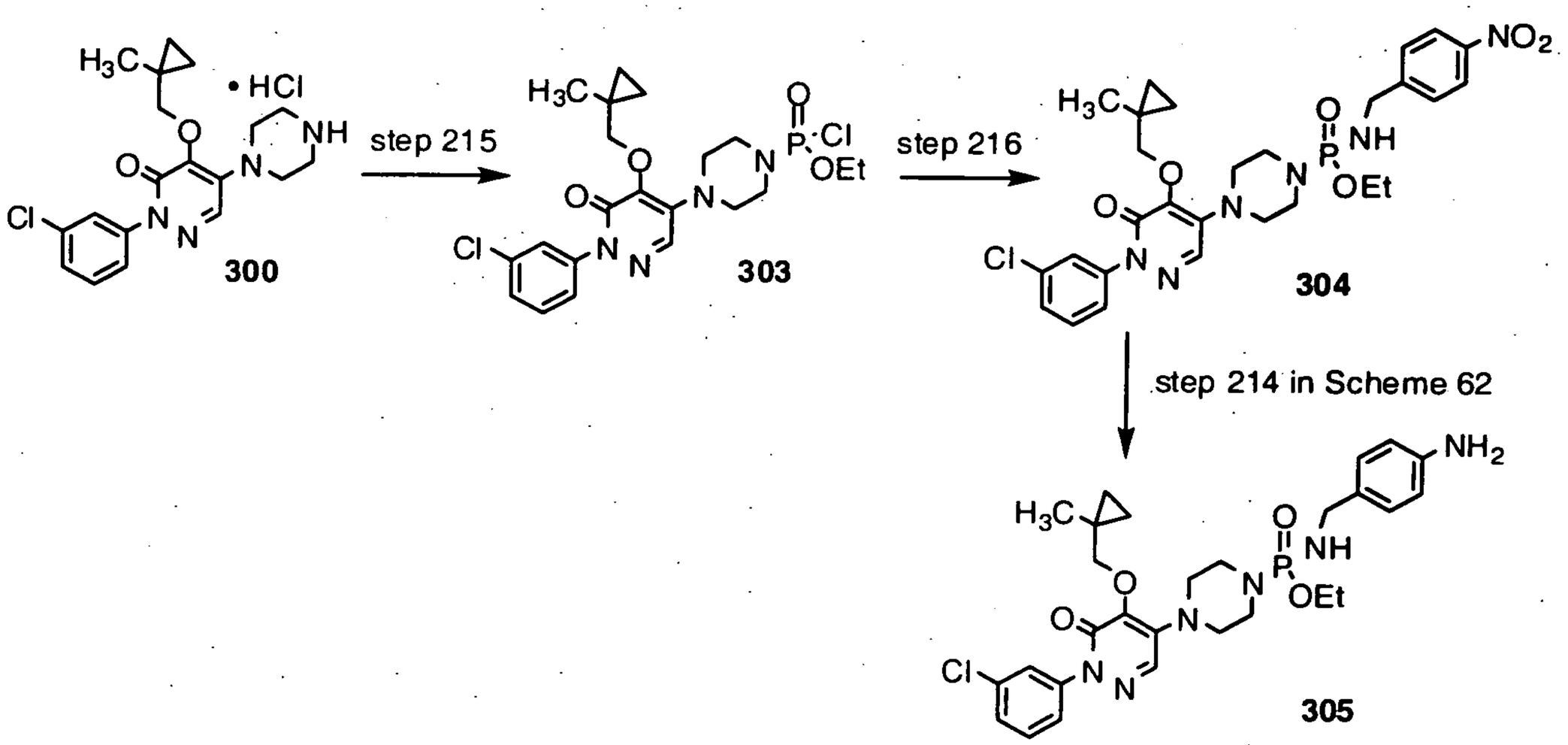
Cmpd. No.	Structure	MS M+1
1916Z		513

Step 214:

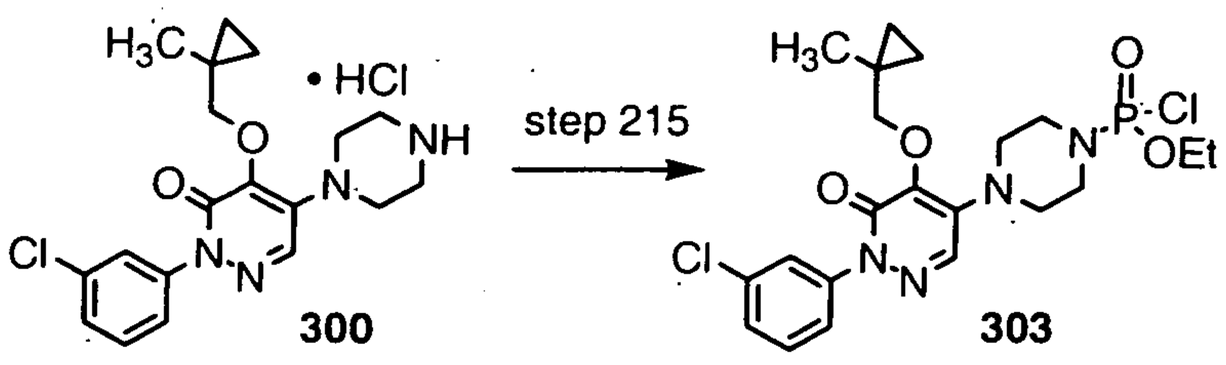


A mixture of ethyl 4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-yl(4-nitrobenzyl)phosphinate **301** (130 mg, 0.22 mmol) and platinum(II) oxide (24 mg, 0.11 mmol) in ethanol (4 mL) and ethyl acetate (4 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 90 mins. The mixture was filtered through a plug of celite under reduced pressure and the filtrate was concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with methanol/methylene chloride (1:99 to 1:9), to provide 88 mg (71% yield) of the product **302** as an off-white solid. MS (M+1): m/e 572.

Scheme 63

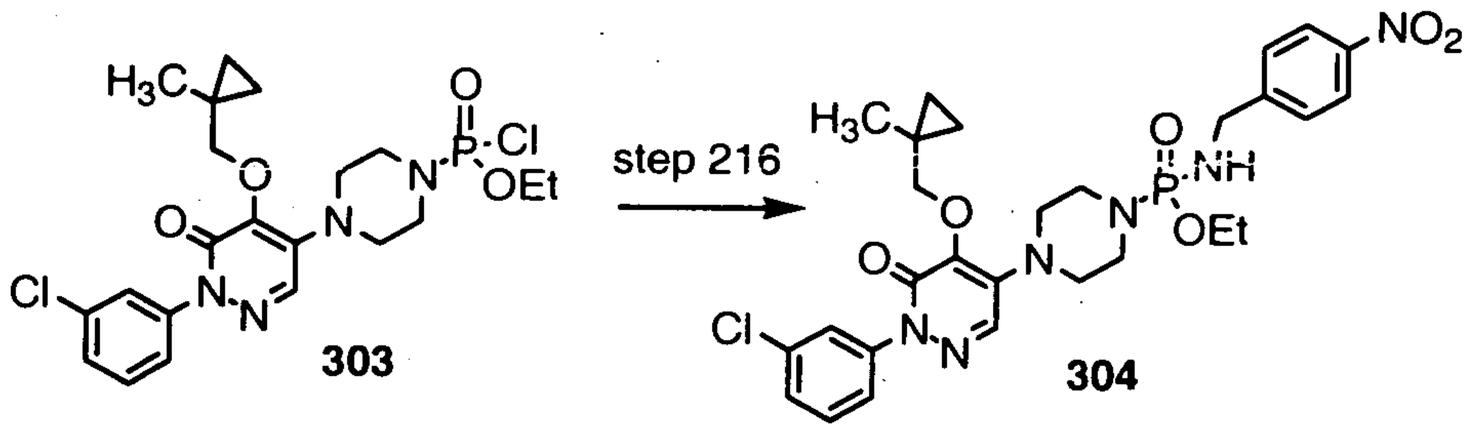


Step 215:



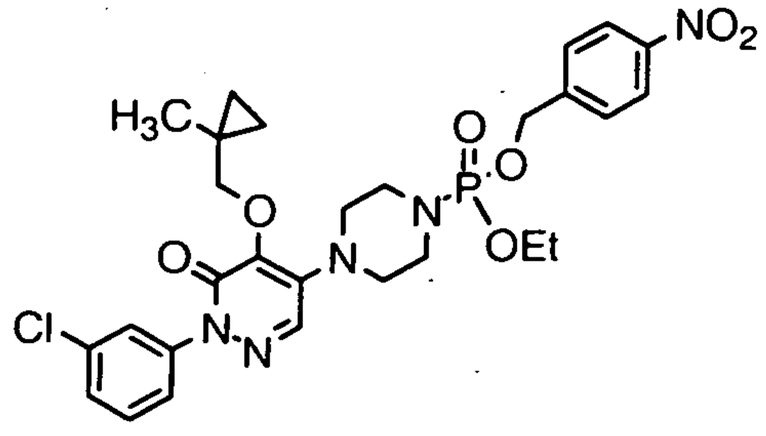
A solution of ethyl phosphorodichloridate (90 mg, 0.55 mmol) in methylene chloride (1 mL) was added dropwise to a solution of 4,5-dichloro-2-(3-chlorophenyl)pyridazin-3(2*H*)-one hydrochloride **300** (205 mg, 0.50 mmol) and diisopropylethylamine (0.26 mL, 1.50 mmol) in methylene chloride (5 mL) at room temperature under nitrogen, after which the mixture was slowly warmed to room temperature, stirring for a total of 16 h. The solvent was concentrated, and the residue was purified by CombiFlash Companion (12-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:9 to 2:3), to provide 121 mg (48% yield) of the product **303** as a viscous yellow oil that was used without purification.

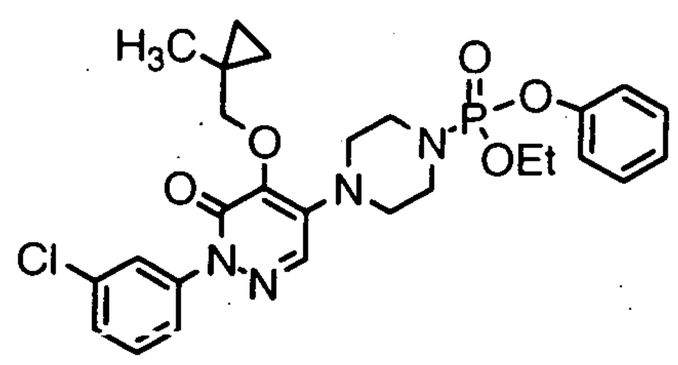
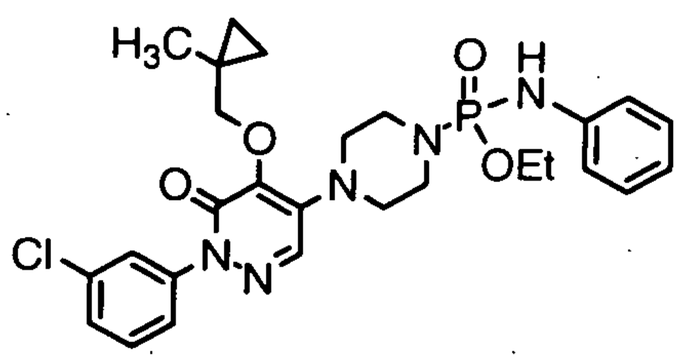
Step 216:



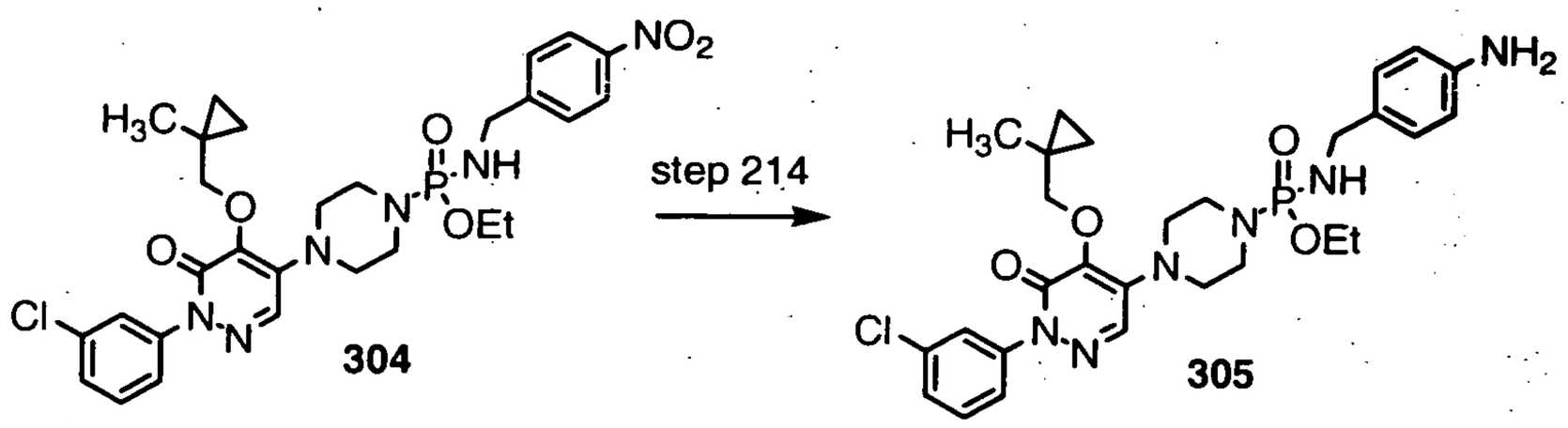
Diisopropylethylamine (84 uL, 0.48 mmol) was added over a period of 10 mins to a solution of ethyl 4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylphosphonochloridate **303** (110 mg, 0.22 mmol) and (4-nitrophenyl)methylamine hydrochloride (38 mg, 0.20 mmol) in methylene chloride (1 mL) at 0 °C under nitrogen, and the mixture was slowly warmed to room temperature, stirring for a total of 16 h. The solvent was concentrated, and the residue purified by CombiFlash Companion (12-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (2:3 to 100% ethyl acetate), to provide 96 mg (78% yield) of the product **304** as a light yellow foam. MS (M-1): m/e 615.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1
1917Z		618

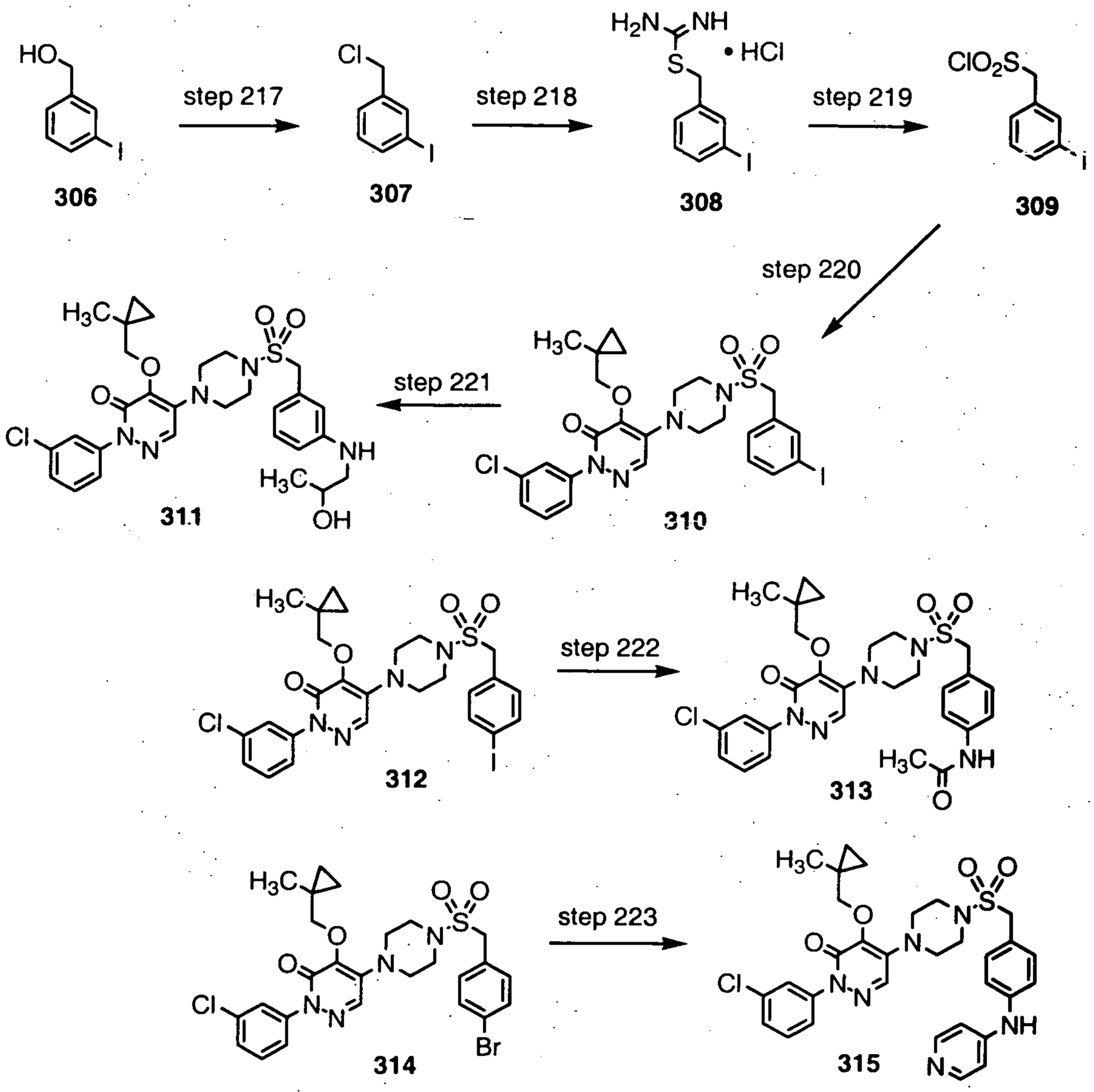
1918Z		559
1918ZA		558

Step 214:

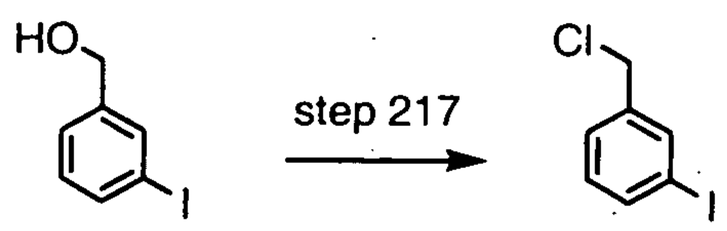


Using the procedure described above in step 214 in Scheme 62, compound **305** was synthesized. MS (M+1): m/e 587.

Scheme 64



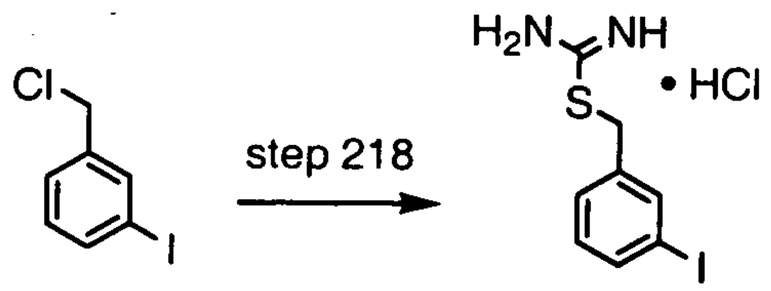
Step 217:



Methylene chloride (30 mL) was added to a mixture of cyanuric chloride (1.83 g, 10.0 mmol) in dimethylformamide (1.89 g, 25.8 mmol) at room temperature under nitrogen, after which (3-iodophenyl)methanol **306** (2.22 g, 9.5 mmol) was added, and the mixture was stirred for 1 h. The mixture was washed sequentially with water (25 mL), saturated sodium carbonate solution (125 mL), 1 N hydrochloric acid (125 mL) and brine (150 mL), dried over sodium

sulfate, filtered, and concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with hexanes, to provide 1.64 g (68% yield) of the product **307** as a clear, colorless oil.

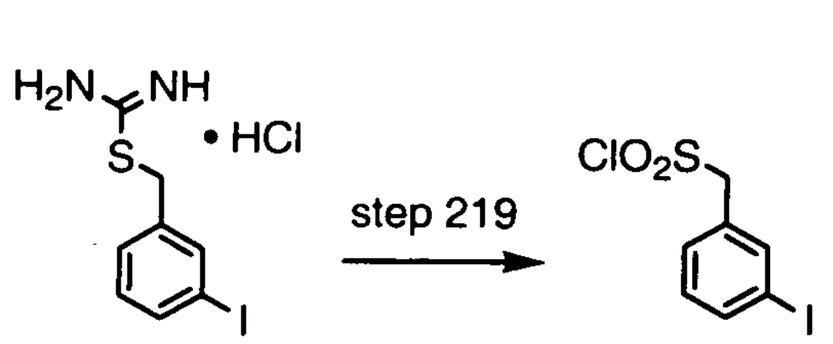
Step 218:



307 **308**

A mixture of 1-(chloromethyl)-3-iodobenzene **307** (1.64 g, 6.50 mmol) and thiourea (0.49 g, 6.50 mmol) in ethanol (10 mL) was heated at reflux under nitrogen for 20 h, after which the solvent was removed from the cooled mixture under reduced pressure. The residue was triturated with ethyl acetate (75 mL) for 30 mins, after which the solids were collected by filtration, washed with ethyl acetate (75 mL) and dried under reduced pressure to provide 2.02 g (94% yield) of the product **308** as a white solid that was used in the next step without purification.

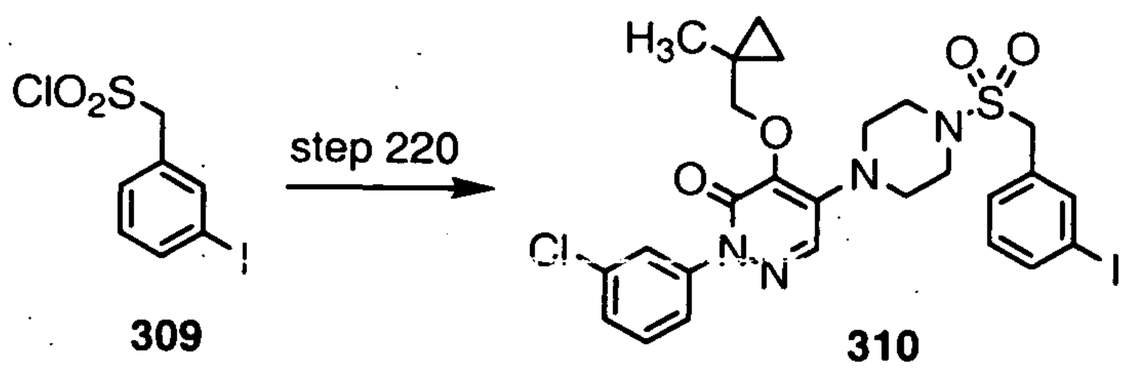
Step 219:



308 **309**

A stream of chlorine gas was introduced subsurface for 30 mins to a rapidly-stirred suspension of 3-iodobenzyl carbamimidothioate hydrochloride **308** (2.00 g, 6.09 mmol) in 1 N hydrochloric acid (100 mL) at 0 °C, after which the ice-bath was removed, and chlorine addition was continued for an additional 30 mins. The solids were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure. The dried solid was then suspended in hot toluene (45 mL), and the solids were removed by decantation. The filtrate was diluted with hexanes (15 mL), and the mixture was allowed to stand for 3 h at room temperature, and then placed into a freezer for 12 h. The resulting crystals were collected by filtration, washed with hexanes (75 mL), and dried under reduced pressure to give 1.02 g (53% yield) of the product chloride **309** as opaque crystals.

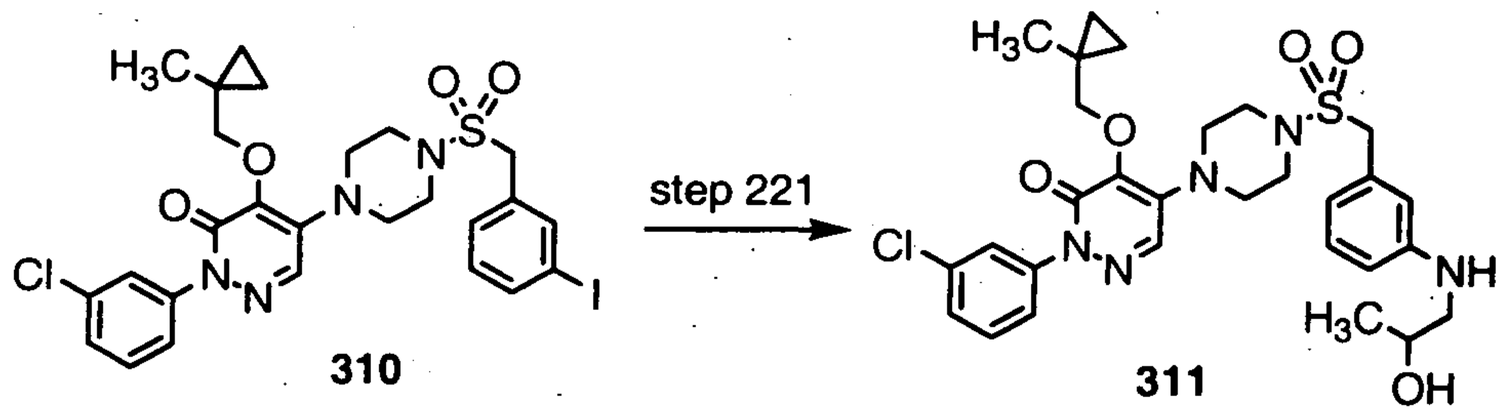
Step 220:



309 310

Diisopropylamine (2.80 mL, 16.60 mmol) was added dropwise to a mixture of 2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)-5-(piperazin-1-yl)pyridazin-3(2*H*)-one hydrochloride (3.00 g, 7.30 mmol) and (3-iodophenyl)methanesulfonyl chloride **309** (2.55 g, 8.03 mmol) in anhydrous dimethylformamide (5 mL) at 0 °C under nitrogen. The mixture was slowly warmed to room temperature and stirred for a total of 17 h. The mixture was poured into rapidly-stirred cold water (200 mL) and stirred for 30 mins. The precipitated solid was collected by filtration under reduced pressure, washed with water, and dried under reduced pressure at 45 °C. The crude product was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/methylene chloride (100% methylene chloride to 1:9), to provide 2.48 g (52% yield) of the product **310** as a light-yellow foam: MS (M+1): m/e 655.

Step 221:

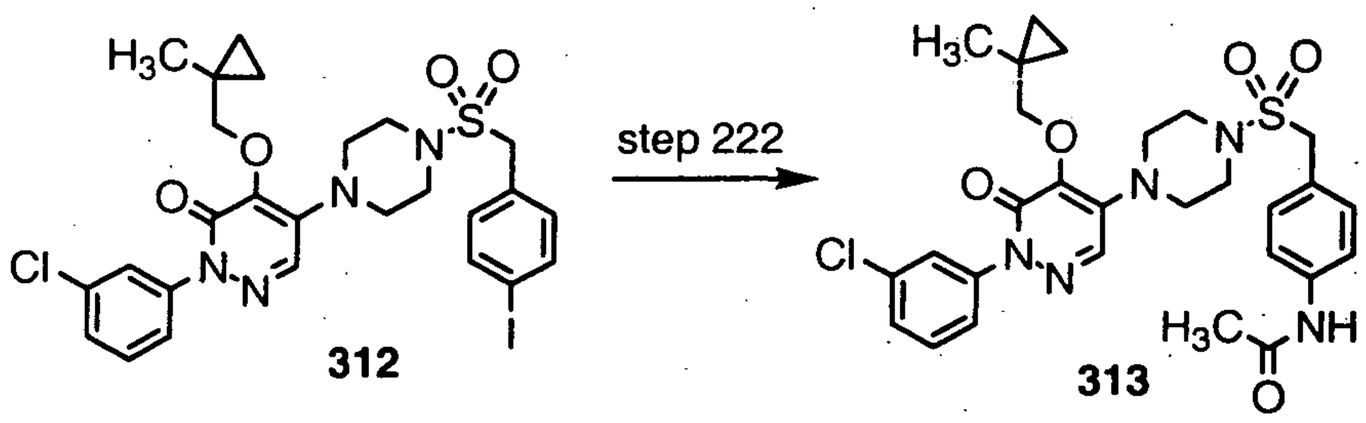


310 311

A degassed mixture of 2-(3-chlorophenyl)-5-(4-(3-iodobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **310** (150 mg, 0.23 mmol), (+/-)-1-aminopropan-2-ol (35 mg, 0.46 mmol), copper(I) iodide (11 mg, 0.06 mmol), L-proline (13 mg, 0.11 mmol), and potassium carbonate (63 mg, 0.46 mmol) in anhydrous dimethyl sulfoxide (1.0 mL) was heated at 95 °C under nitrogen for 16 h. The cooled mixture was diluted with dimethyl sulfoxide (3 mL), filtered through a pad of celite under reduced pressure, and washed with ethyl acetate (35 mL). The filtrate was washed with brine (3 x 15 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by

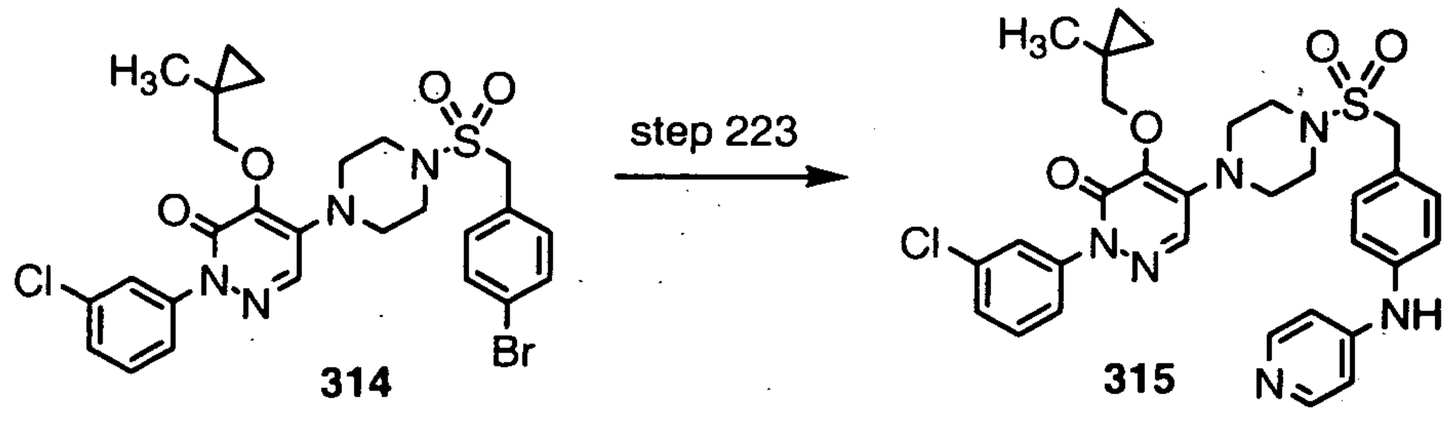
CombiFlash Companion (12-g SiO_2 cartridge), eluting with hexanes/ethyl acetate (1:4 to 1:1), to provide 88 mg (64% yield) of the product **311** as a white solid: MS (M+1): m/e 602.

Step 222:



A degassed mixture of 2-(3-chlorophenyl)-5-(4-(4-iodobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **312** (328 mg, 0.50 mmol), acetamide (36 mg, 0.61 mmol), copper(I) iodide (18 mg, 0.09 mmol), *N,N'*-dimethylethylene-diamine (12 mg, 0.14 mmol), and potassium carbonate (212 mg, 2.0 mmol) in dimethylformamide (3 mL) was heated in a resealable reaction vessel at 85 °C for 18 h. The cooled mixture was diluted with ethyl acetate (35 mL), washed with brine (35 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by CombiFlash Companion (40-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:1 to 100% ethyl acetate), to provide 165 mg (57% yield) of the product **313** as a white solid: MS (M+1): m/e 586.

Step 223:

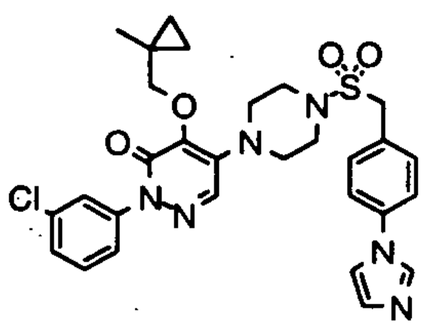
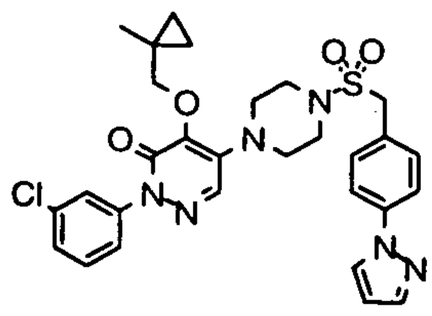
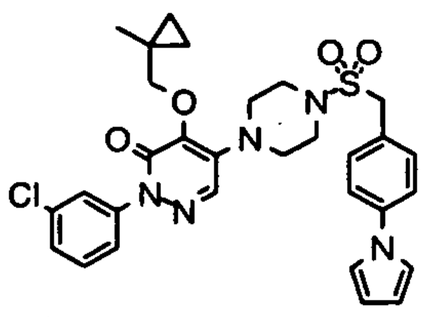
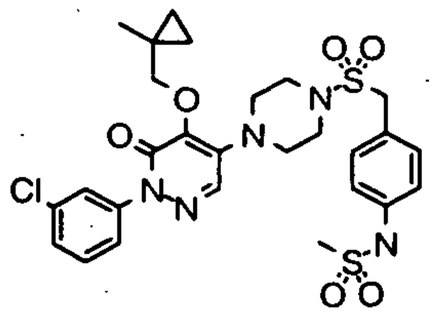
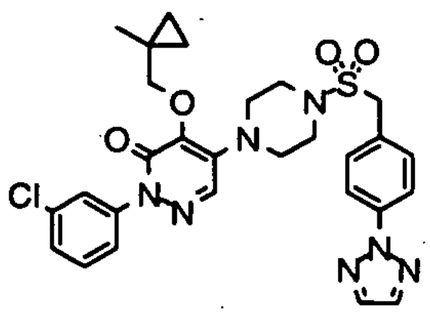
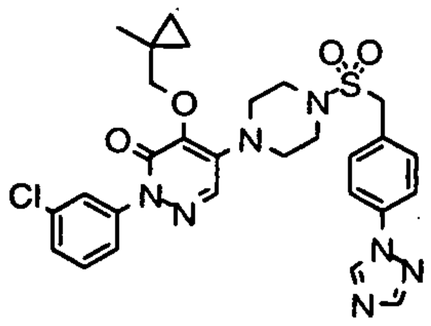
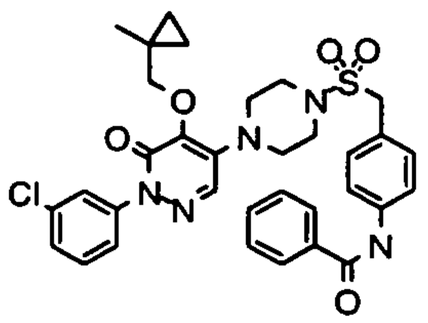
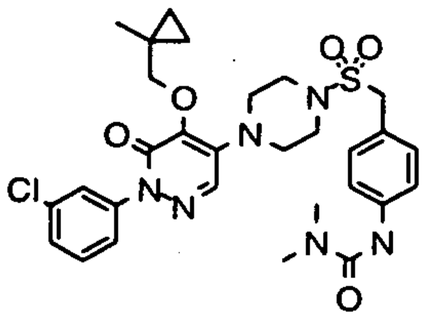
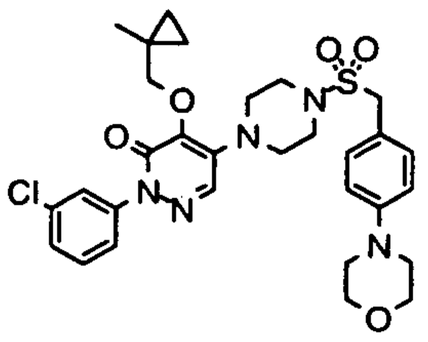
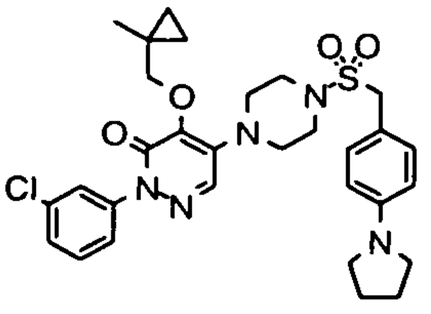
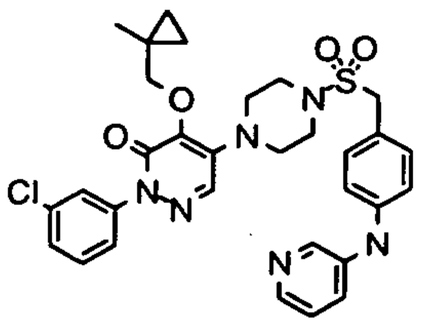
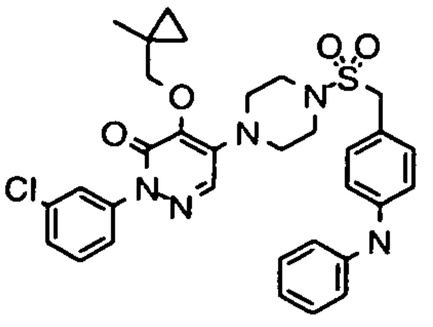


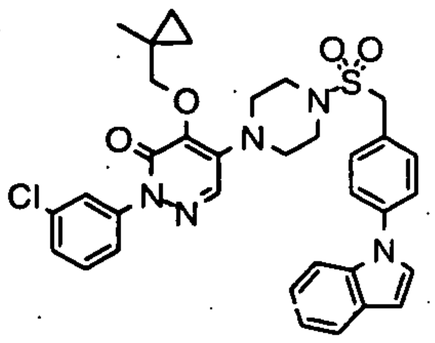
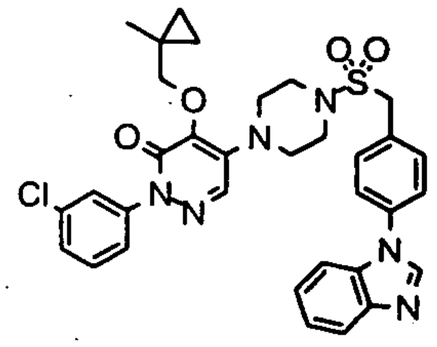
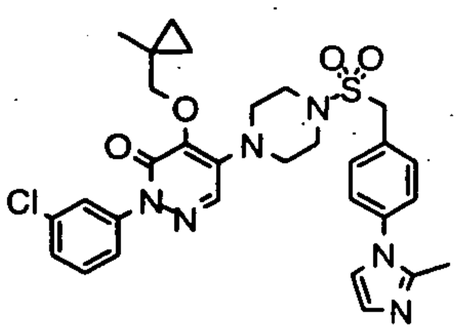
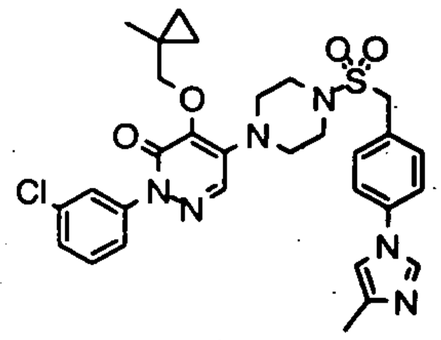
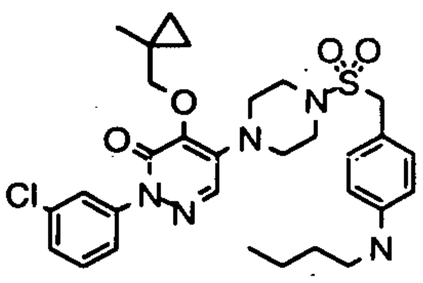
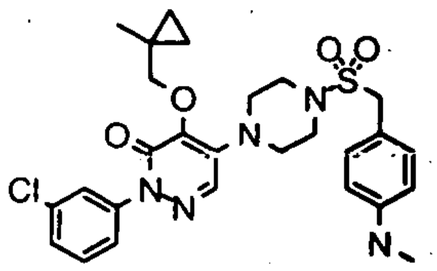
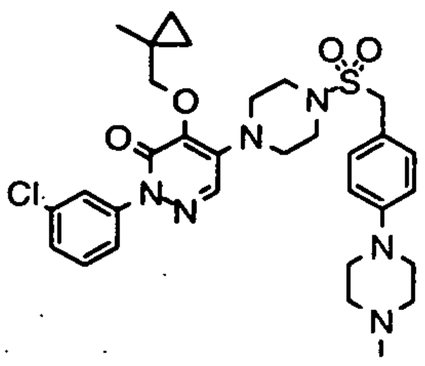
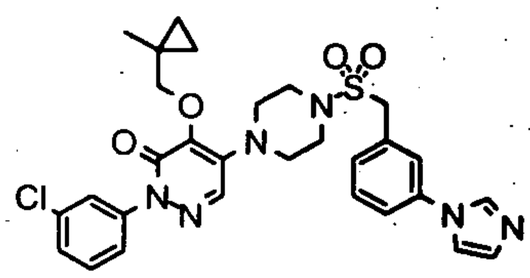
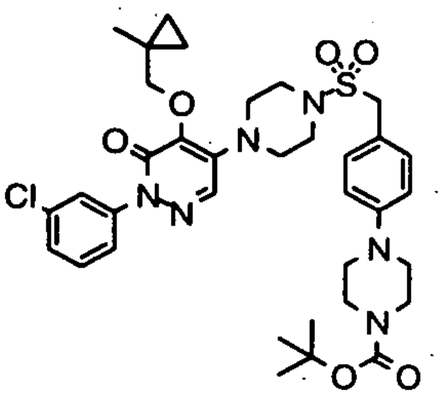
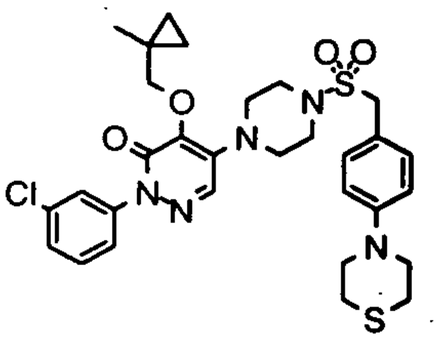
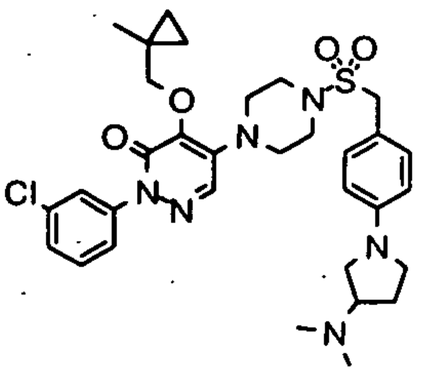
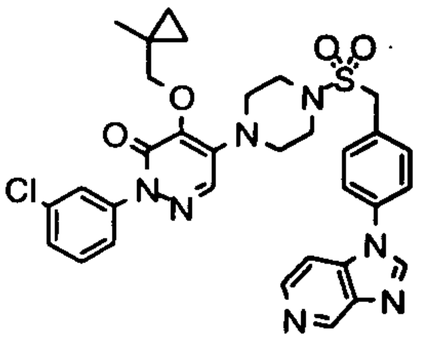
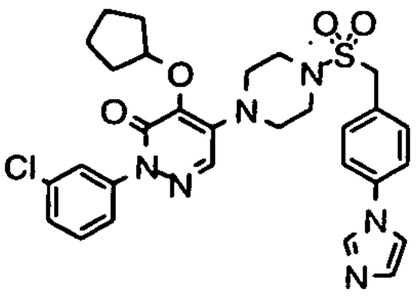
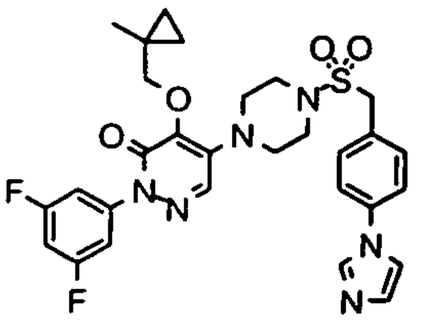
A degassed mixture of 5-(4-(4-bromobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **314** (152 mg, 0.25 mmol), 4-aminopyridine (26 mg, 0.28 mmol), tris(dibenzylideneacetone)dipalladium (4 mg, 0.008 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos, 12 mg, 0.012 mmol), and potassium phosphate (74 mg, 0.35 mmol) in anhydrous 1,4-dioxane (1.0 mL) was heated in a resealable reaction vessel at 105 °C for 18 h. The cooled mixture was diluted with ethyl acetate (2 mL), methylene chloride (2 mL) and methanol (2 mL), filtered through a plug of celite under reduced pressure, and the filtrate was concentrated. The residue was purified by CombiFlash Companion (12-g SiO_2 cartridge), eluting with methanol/methylene chloride

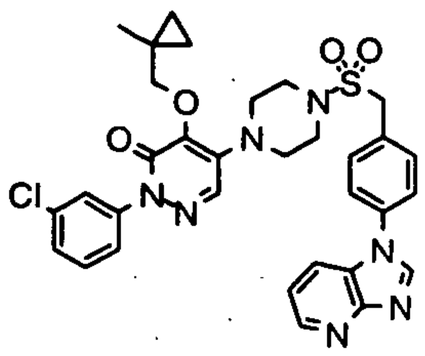
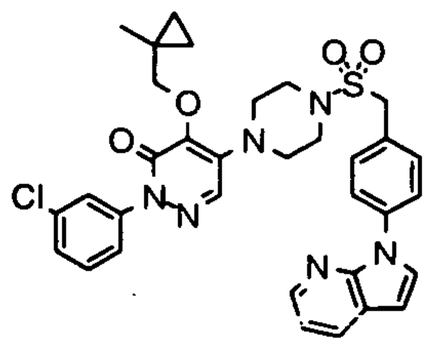
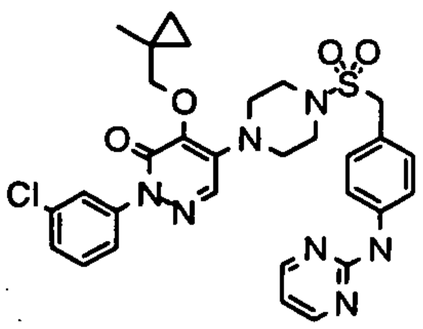
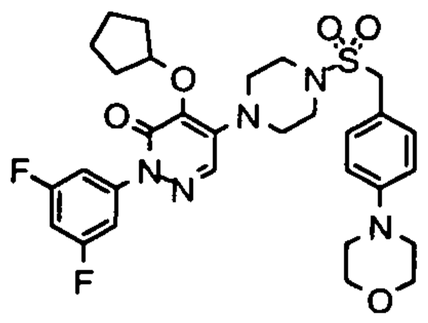
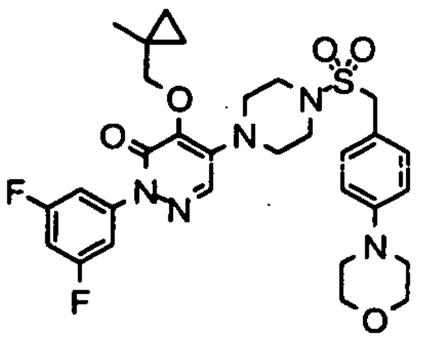
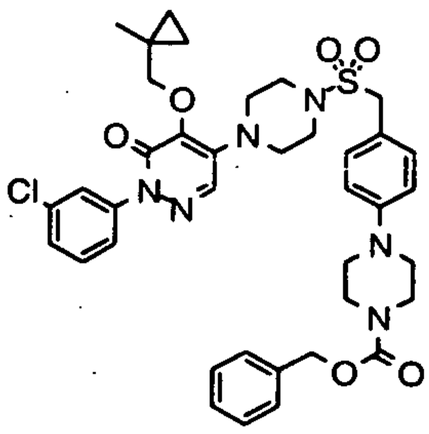
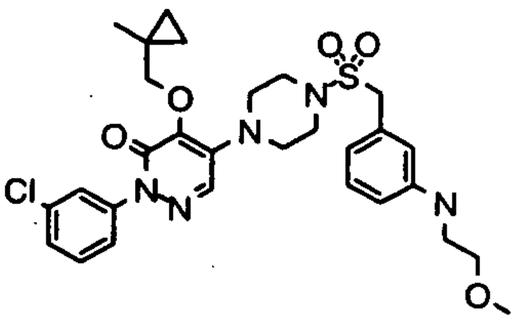
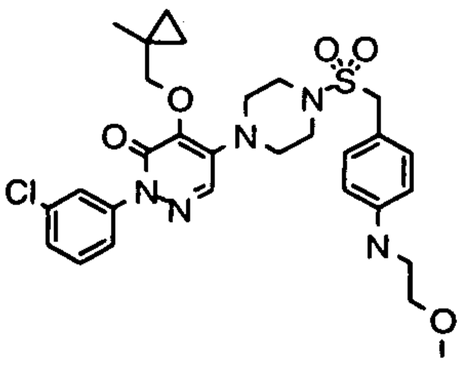
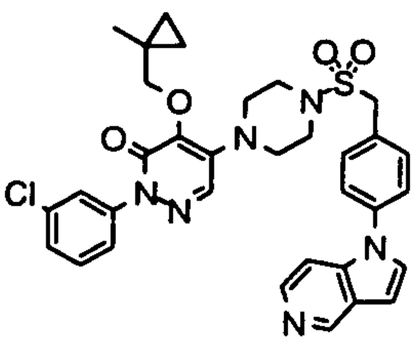
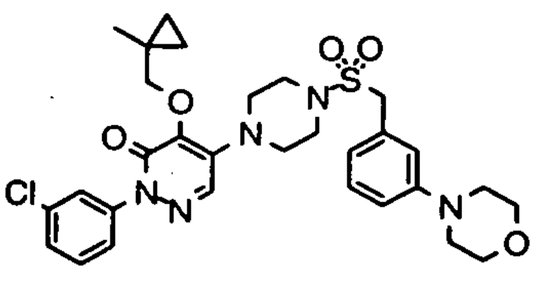
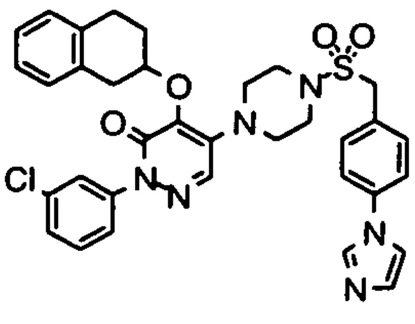
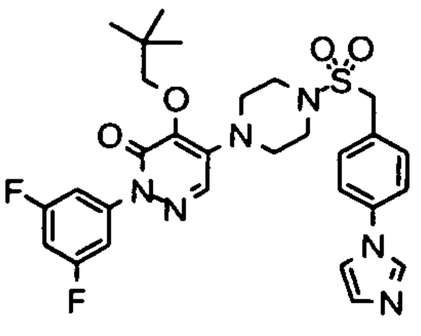
(1:99 to 1:9), to provide 35 mg (23% yield) of the product **315** as a light brown solid: MS (M+1): m/e 621.

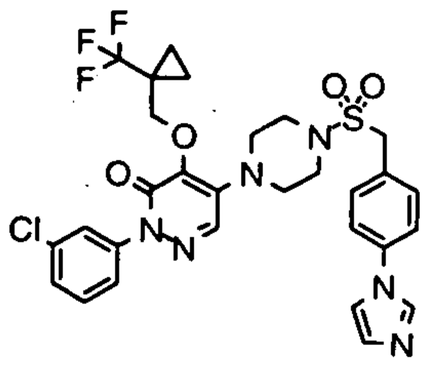
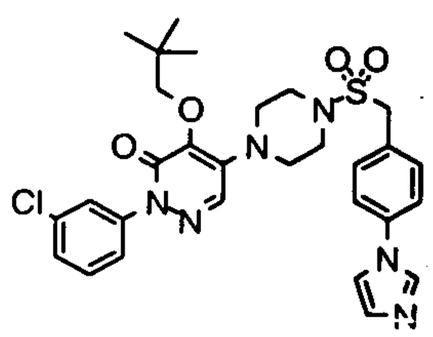
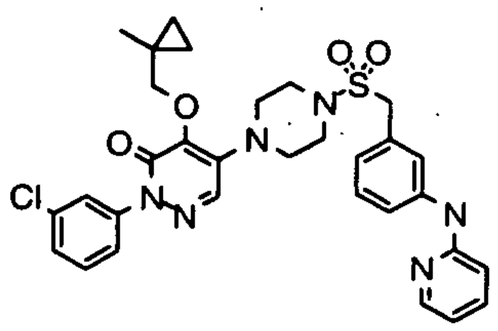
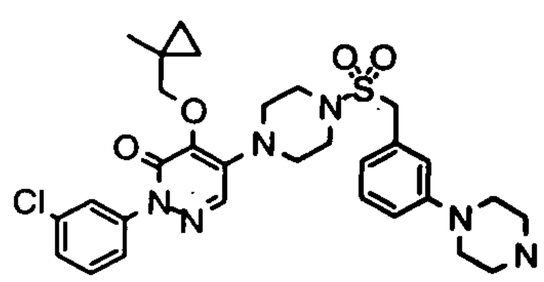
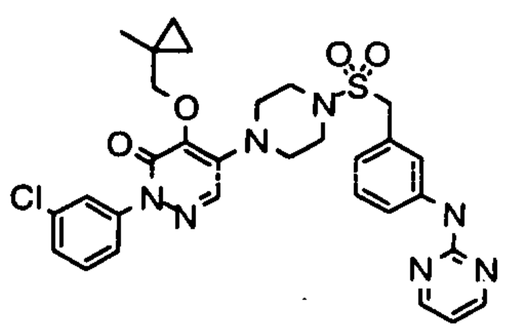
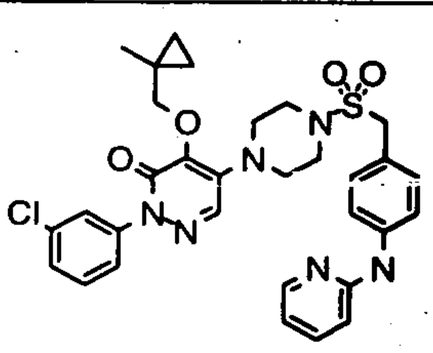
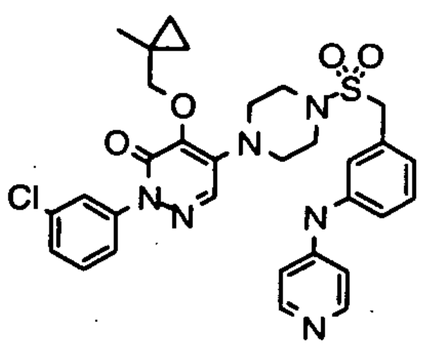
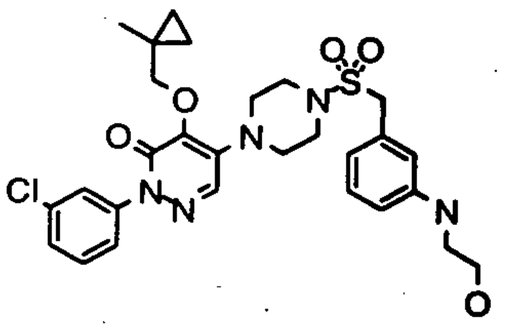
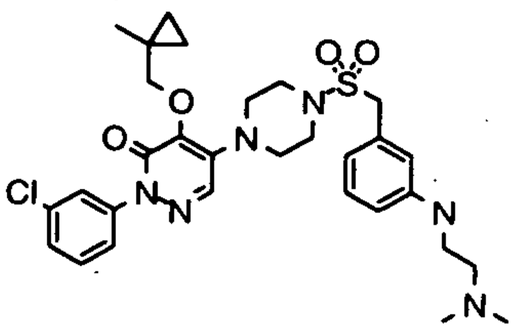
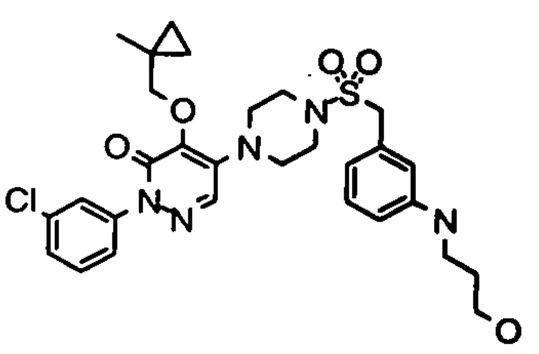
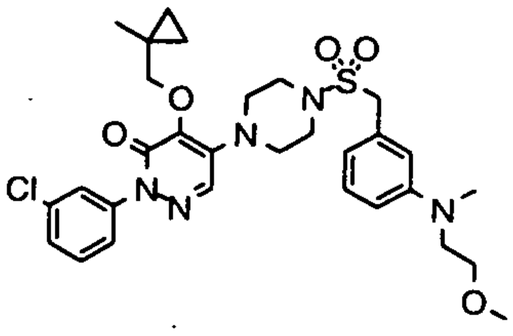
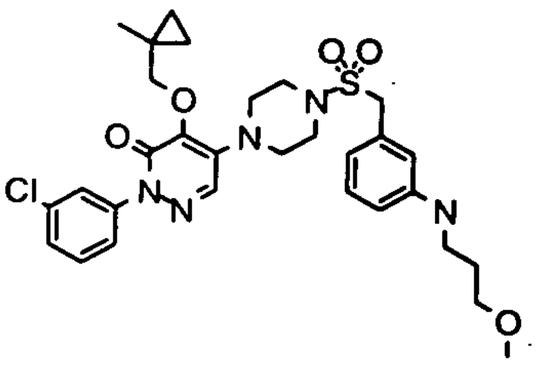
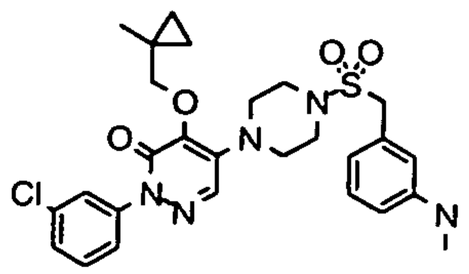
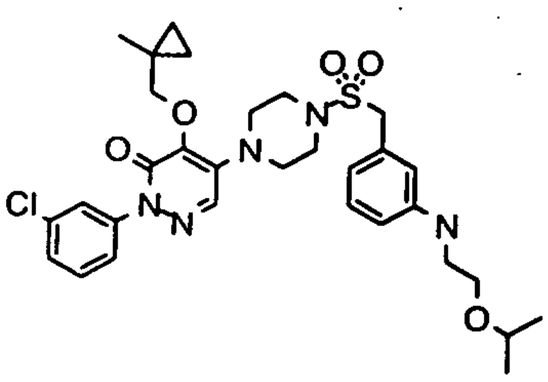
Using the procedures described above, the following compounds were synthesized.

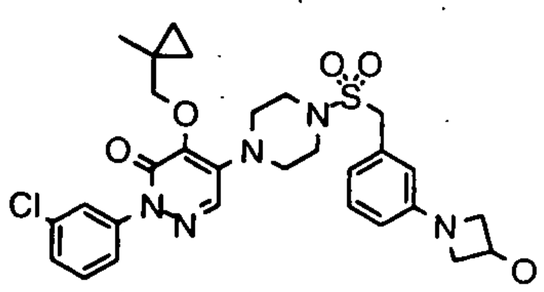
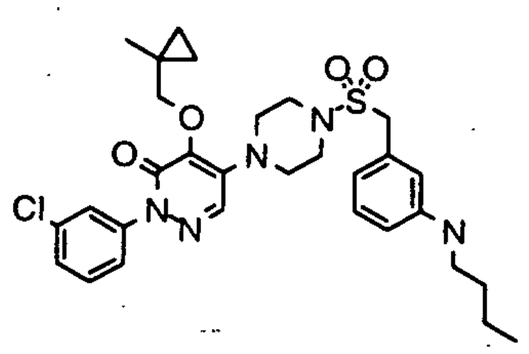
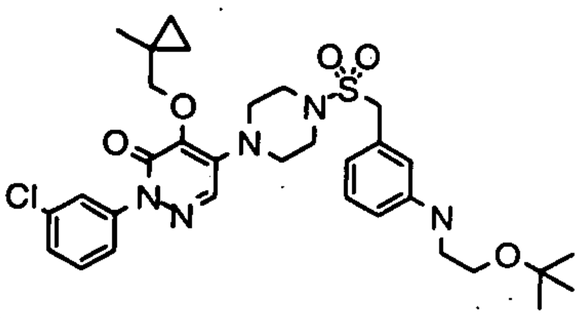
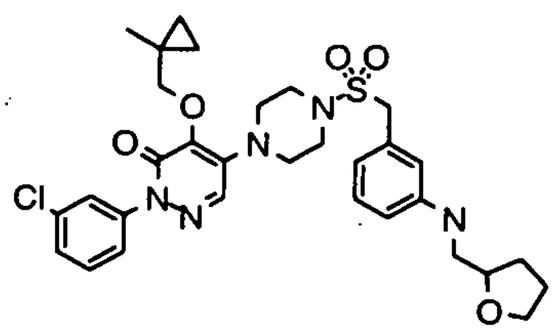
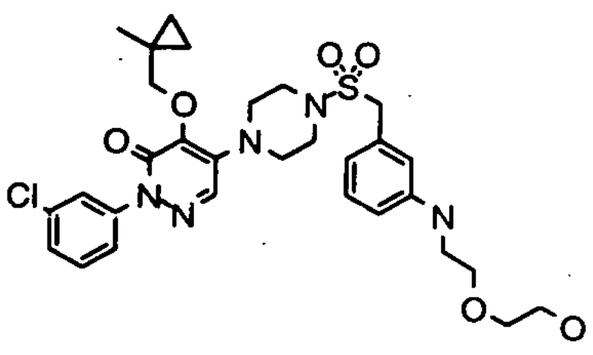
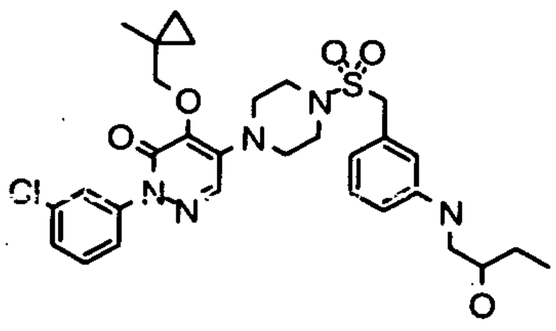
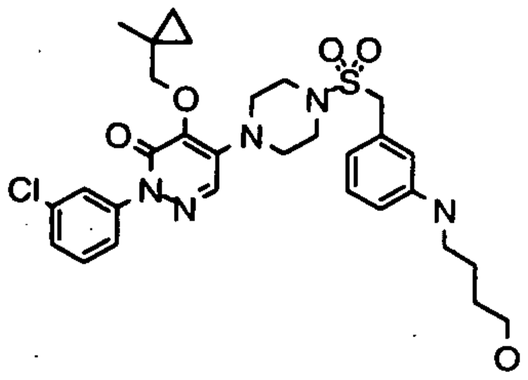
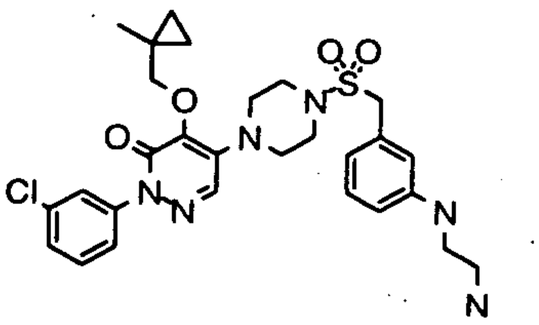
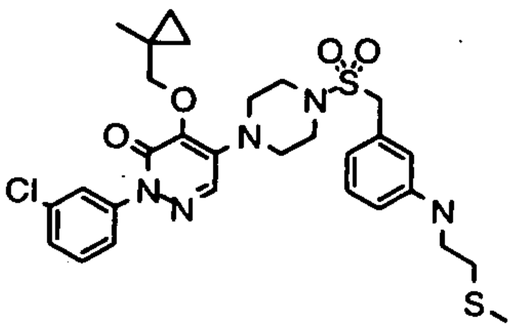
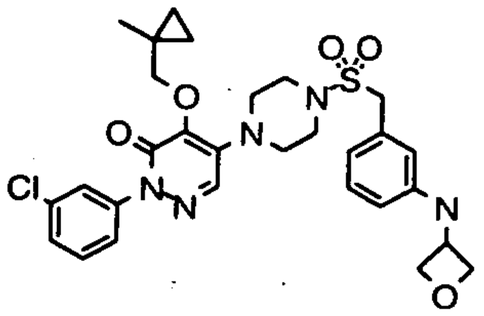
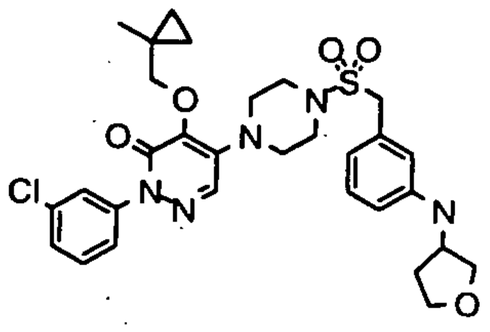
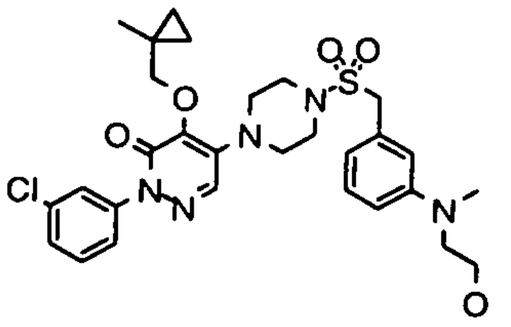
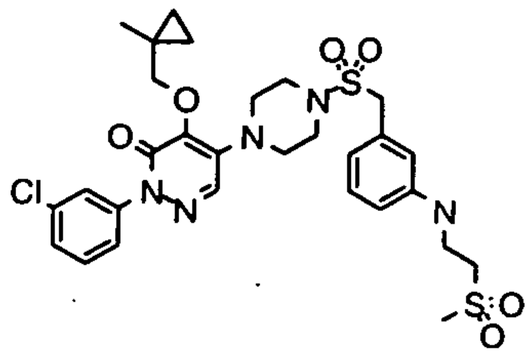
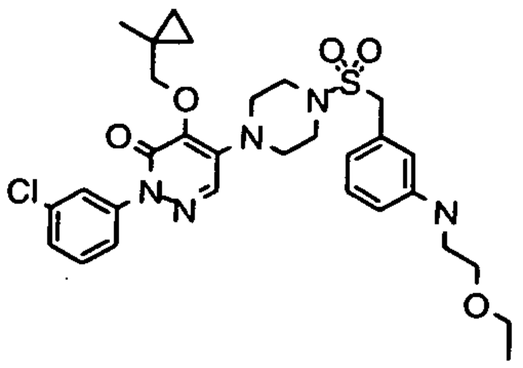
Table 37: Oxygen Analogs with Substituted Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1919Z		595	1920Z		593 (M-1)
1921Z		592 (M-1)	1922Z		620 (M-1)
1923Z		594 (M-1)	1924Z		594 (M-1)
1925Z		646 (M-1)	1926Z		613 (M-1)
1927Z		614	1928Z		598
1929Z		621	1930Z		620

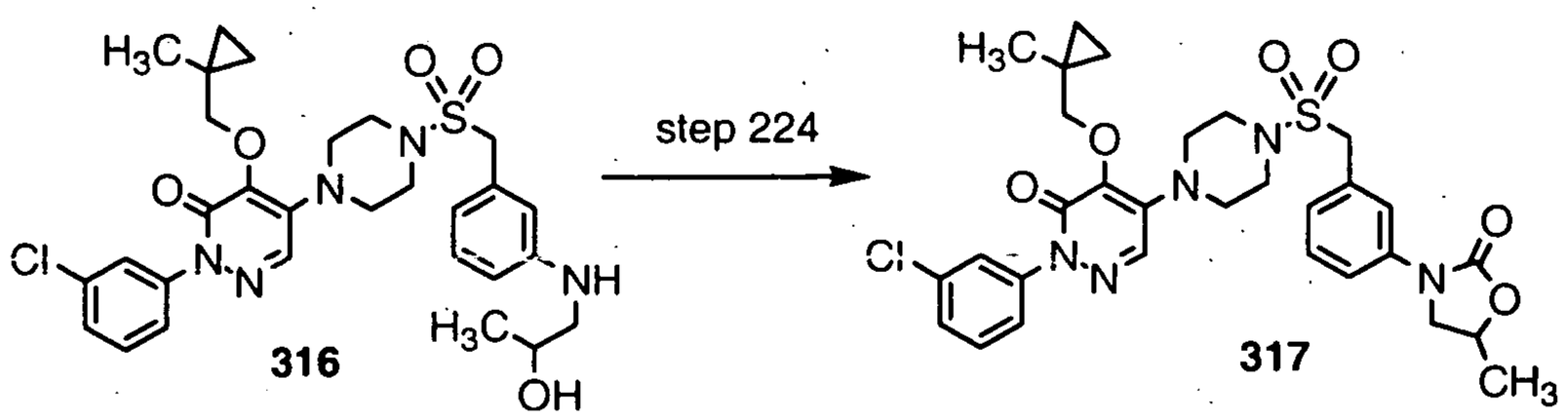
1931Z		642 (M-1)		1932Z		645
1933Z		609		1934Z		609
1935Z		600		1936Z		558
1937Z		627		1938Z		595
1939Z		713		1940Z		630
1941Z		641		1942Z		646
1943Z		595		1944Z		597

1945Z		646		1946Z		645	
1947Z		623		1948Z		614 (M-1)	
1949Z		616		1950Z		747	
1951Z		602		1952Z		602	
1953Z		645		1954Z		614	
1955Z		657		1956Z		599	

1957Z		649		1958Z		597
1959Z		621		1960Z		613
1961Z		622		1962Z		621
1963Z		621		1964Z		588
1965Z		615		1966Z		602
1967Z		616		1968Z		616
1969Z		558		1970Z		630

1971Z		600		1972Z		600
1973Z		644		1974Z		628
1975Z		632		1976Z		616
1977Z		616		1978Z		587
1979Z		618		1980Z		601
1981Z		615		1982Z		603
1983Z		651		1984Z		617

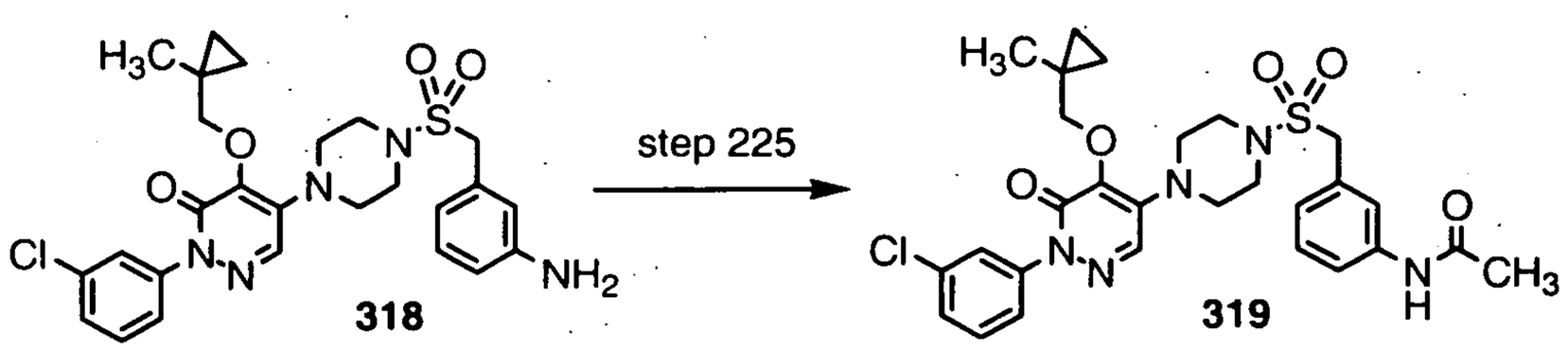
Scheme 65



Step 224:

A mixture of (+/-)-2-(3-chlorophenyl)-5-(4-(3-(2-hydroxypropylamino)-benzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **316** (43 mg, 0.071 mmol), carbonyl diimidazole (46 mg, 0.29 mmol), and 4-dimethylaminopyridine (2 mg, 0.016 mmol) in tetrahydrofuran (5 mL) was heated at 80 °C under nitrogen for 6 h. The solvent was removed from the cooled mixture under reduced pressure, and the residue was purified by CombiFlash Companion (4-g SiO_2 cartridge), eluting with hexanes/ethyl acetate (1:19 to 1:1), to provide 28 mg (62% yield) of the product **317** as a light yellow solid: MS (M+1): m/e 628.

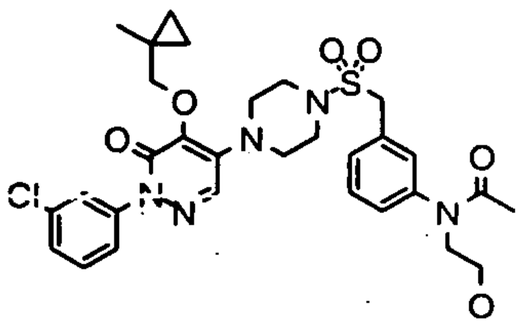
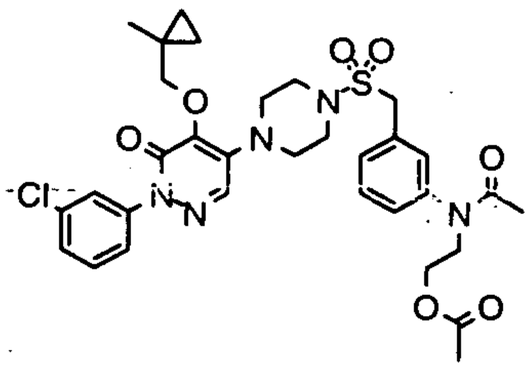
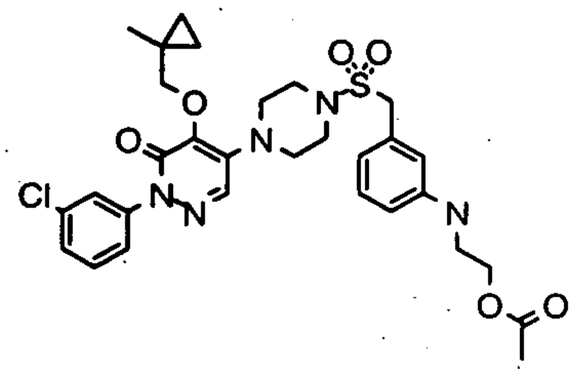
Scheme 66



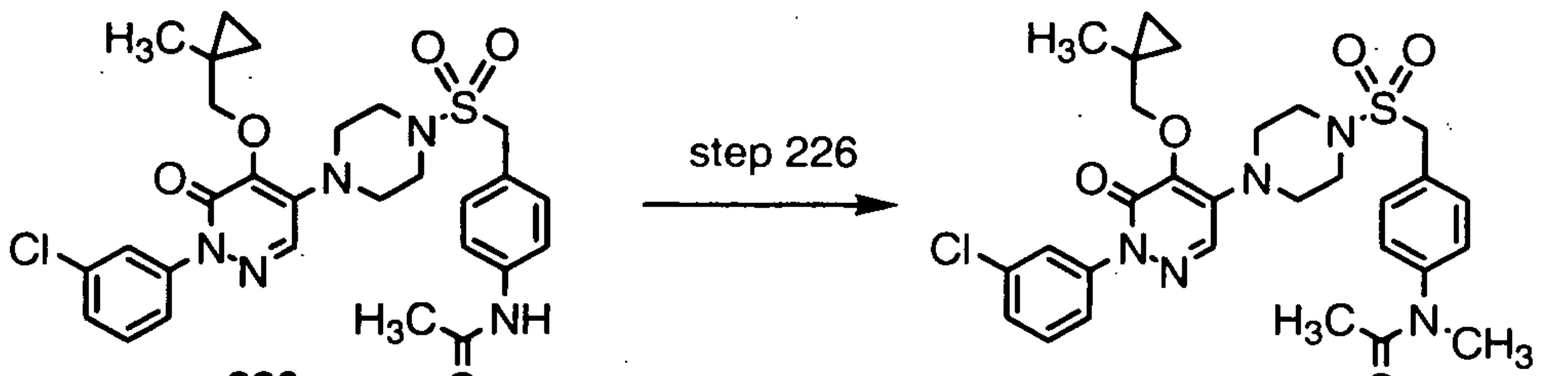
Step 225:

Acetyl chloride (22 mg, 0.28 mmol) was added dropwise to a mixture of 5-(4-(3-aminobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)-methoxy)pyridazin-3(2*H*)-one **318** (125 mg, 0.23 mmol) in pyridine (0.5 mL) at 0 °C under nitrogen. The mixture was slowly warmed to room temperature, stirring for a total of 22 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (25 mL). The combined organic extracts were washed with 0.2 N HCl (4 x 50 mL), water (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated to provide 112 mg (83% yield) of the product **319** as an off-white foam: MS (M+1): m/e 586.

Using the procedure described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1
1985Z		630
1986Z		673
1987Z		631

Scheme 67

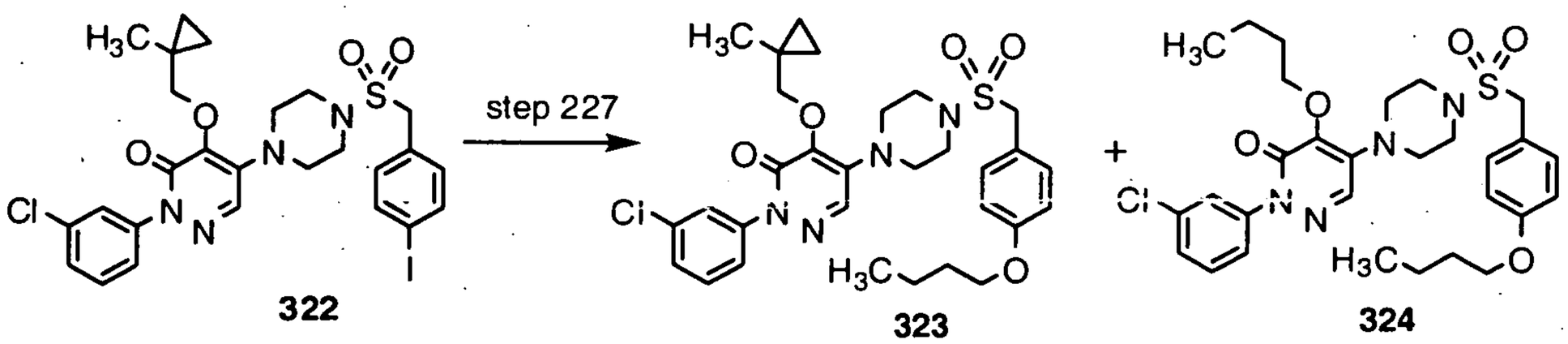


320 **321**

Step 226:

Dimethyl sulfate (26 mg, 0.22 mmol) was added to a mixture of *N*-(4-((4-(1-(3-chlorophenyl)-5-((1-methylcyclopropyl)methoxy)-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl)phenyl)acetamide **320** (100 mg, 0.17 mmol) and potassium hydroxide (14 mg, 0.26 mmol) in dimethylformamide (0.5 mL) at room temperature under nitrogen, and the mixture was stirred for 15 h. The mixture was poured into cold water (30 mL), and the solids were removed by filtration under reduced pressure. The filtrate was concentrated, and the residue was purified by preparative TLC on silica gel, eluting with ethyl acetate, to provide 10 mg (10% yield) of the product **321** as an off-white solid: MS (M+1): m/e 600.

Scheme 68

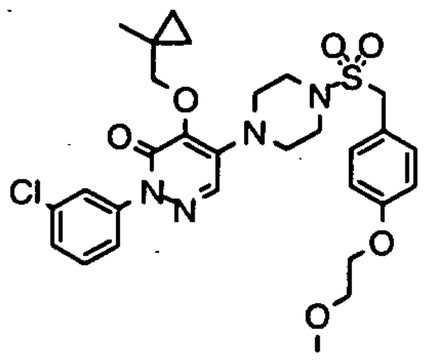
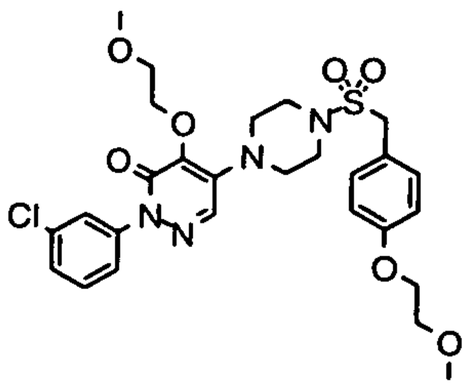
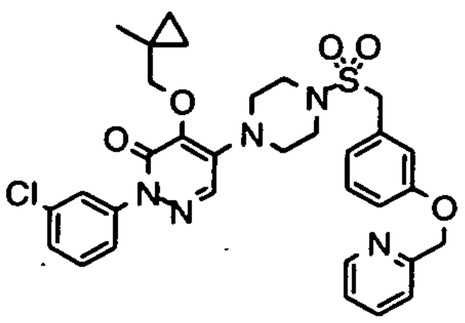
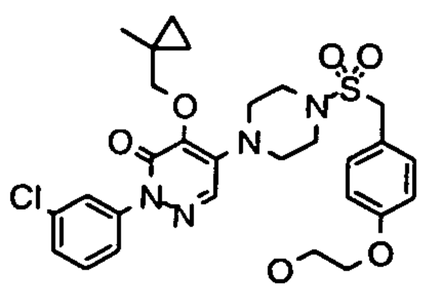


322 323 324

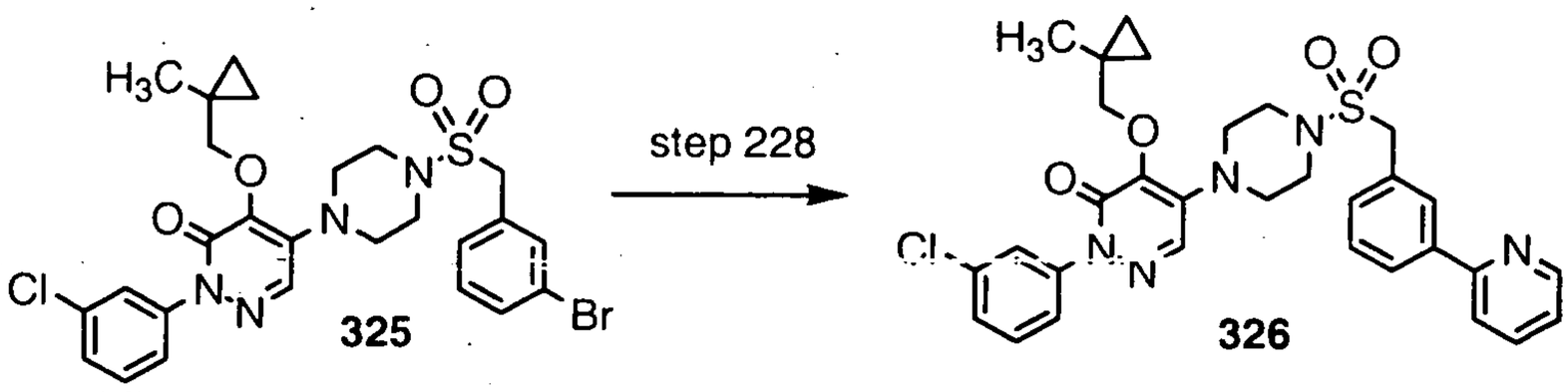
Step 227:

A mixture of 2-(3-chlorophenyl)-5-(4-(4-iodobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **322** (66 mg, 0.10 mmol), *n*-butanol (15 mg, 0.20 mmol), copper(I) iodide (2 mg, 0.01 mmol), cesium carbonate (65 mg, 0.20 mmol) and 1,10-phenanthroline (4 mg, 0.02 mmol) in toluene (0.5 mL) was heated at 105 °C under nitrogen for 16 h. Then additional 1,10-phenanthroline (8 mg, 0.04 mmol), cesium carbonate (130 mg, 0.40 mmol), *n*-butanol (30 mg, 0.40 mmol) and copper(I) iodide (4 mg, 0.02 mmol) were added, and the reaction was heated for an additional 16 h. The cooled mixture was triturated with methylene chloride (5 mL) and methanol (5 mL), and the solids were removed by filtration. The filtrate was concentrated, and the residue was purified by CombiFlash Companion (12-g SiO_2 cartridge), eluting with ethyl acetate/hexanes (1:19 to 2:3), to provide 10 mg (17% yield) of the product **323** as an off-white solid: MS (M+1): m/e 601. The byproduct **324** was also isolated as a white solid: MS (M+1): m/e 589.

Using the procedure described above, the following compounds were synthesized.

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1988Z		603	1989Z		594
1990Z		637	1991Z		590

Scheme 69

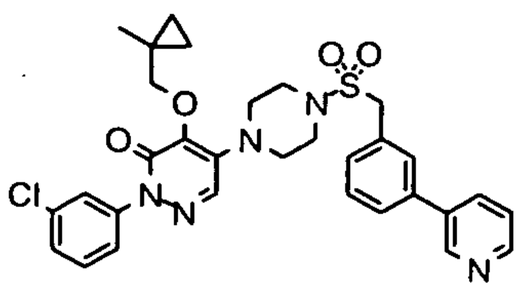
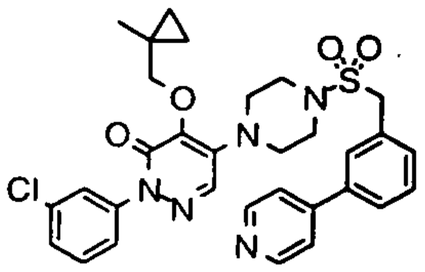
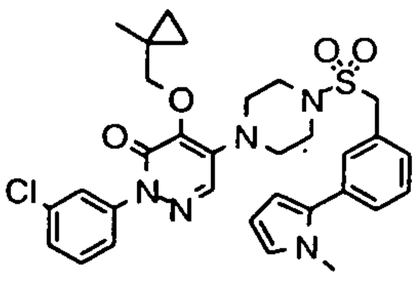
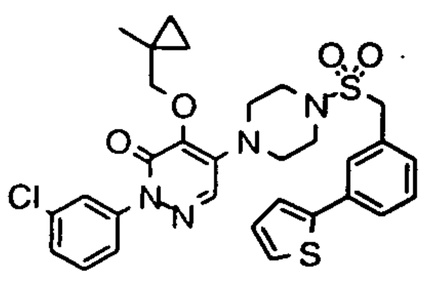


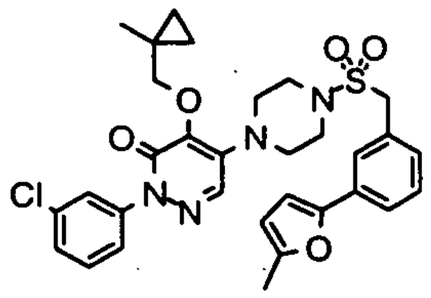
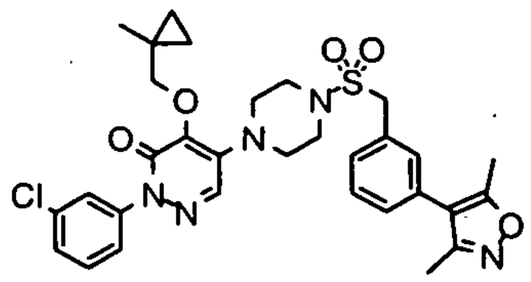
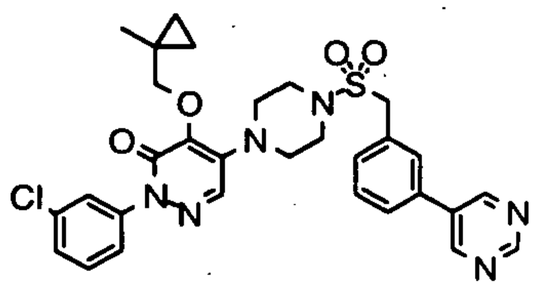
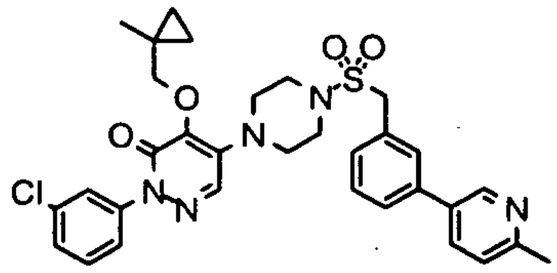
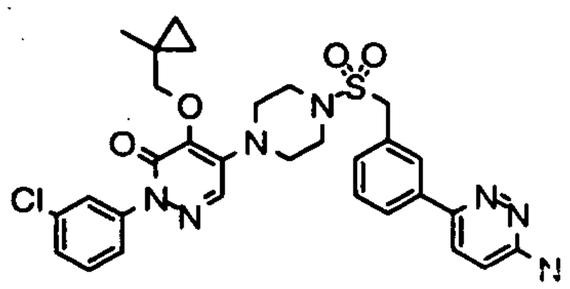
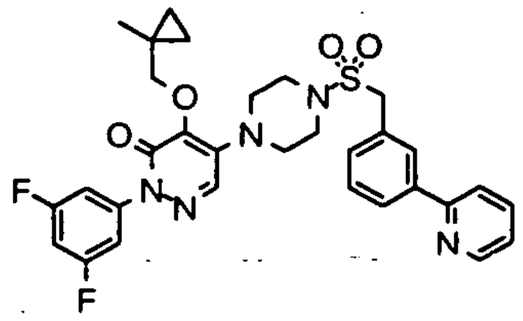
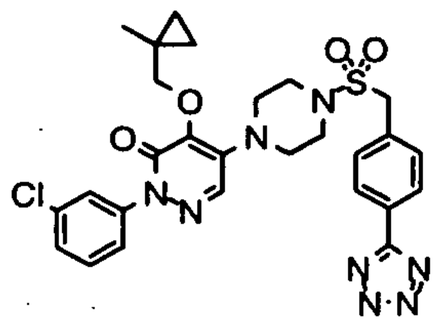
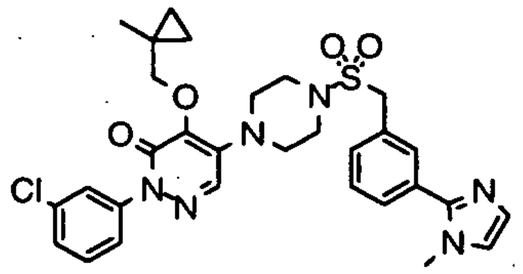
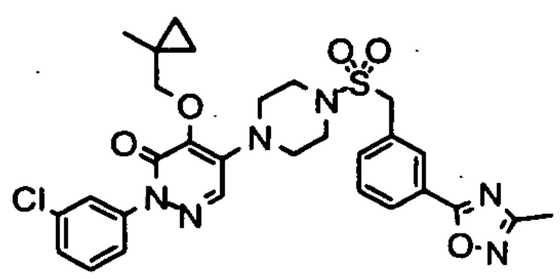
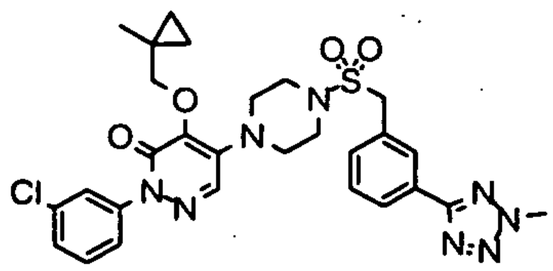
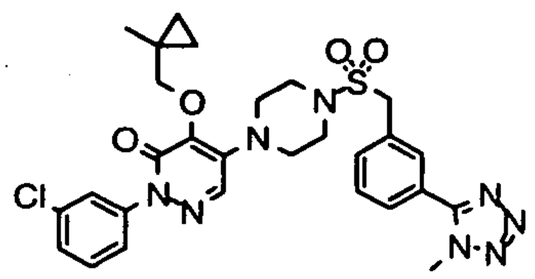
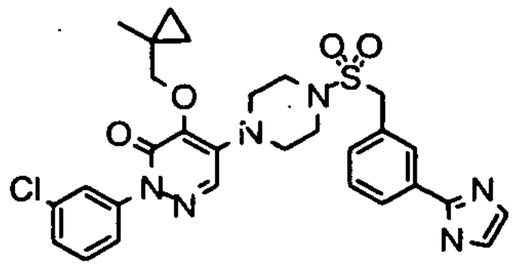
Step 228:

To a solution of 5-(4-(3-bromobenzylsulfonyl)piperazin-1-yl)-2-(3-chlorophenyl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2H)-one **325** (200 mg, 0.329 mmol) in anhydrous DMF (6.0 mL) was added $Pd(dppf)Cl_2$ (24.1 mg, 0.0329 mmol), bis(pinacolato)diboron (94.4 mg, 0.372 mmole), and potassium acetate (96.7 mg, 0.987 mmole), the reaction mixture was heated to 95 °C for a total of 18 h. LCMS confirmed the boron ester intermediate. Into the reaction mixture was added $Pd(dppf)Cl_2$ (24.1 mg, 0.0329 mmol), 2-chloropyridine (56.0 mg, 0.494 mmole), and sodium carbonate (0.5 mL, 2 N). The reaction mixture was heated to 95 °C for a total of 18 h. The mixture was diluted with ethyl acetate (100 mL), washed with water/brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparatory TLC (Analtech silica gel GF, 200 microns) eluting with hexanes/ethyl acetate (3:2), to provide 14 mg (7% yield) of the product **326** as a white solid: MS (M+1): m/e 606.

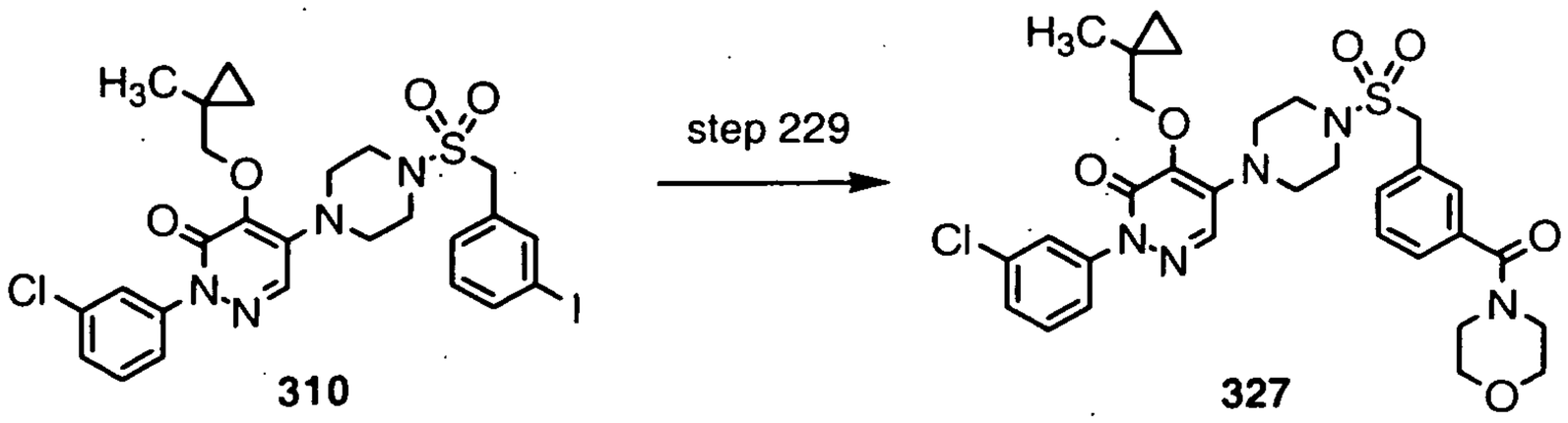
Using the procedure described above, the following compounds were synthesized.

Table 38: Oxygen Analogs with C-Linked Substituted Sulfonamide

Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
1992Z		606	1993Z		606
1994Z		608	1995Z		611

1996Z		609	1997Z		624
1998Z		607	1999Z		620
2000Z		622	2001Z		608
2002Z		597	2003Z		609
2004Z		611	2005Z		611
2006Z		611	2007Z		595

Scheme 70



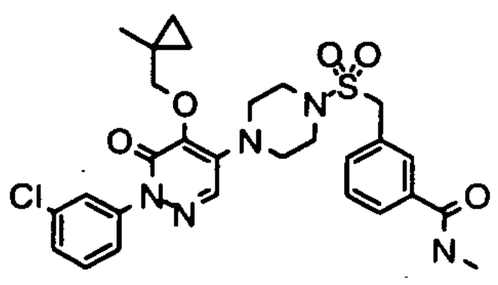
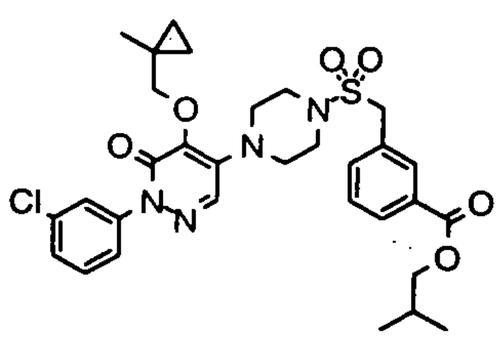
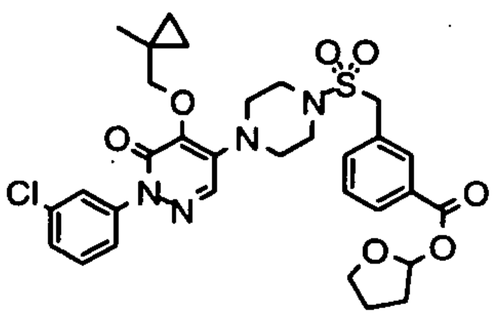
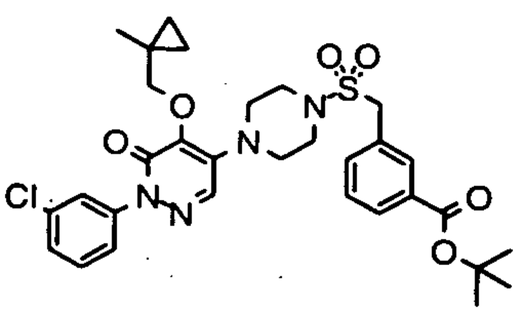
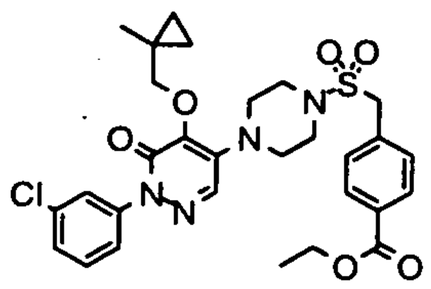
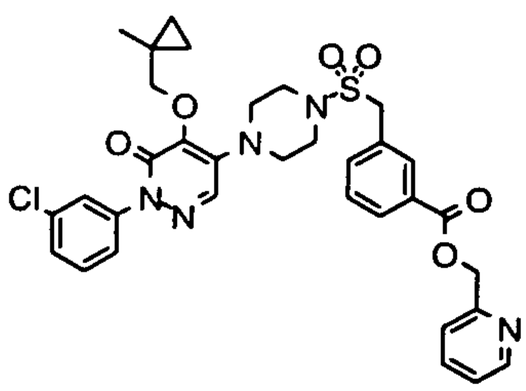
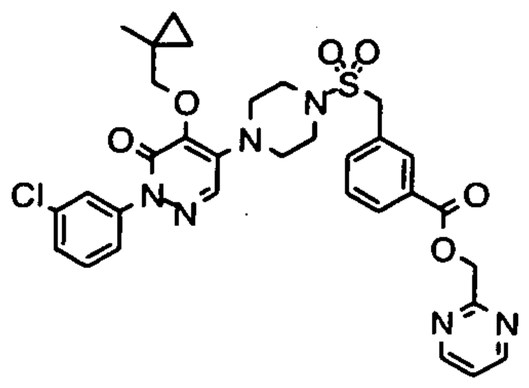
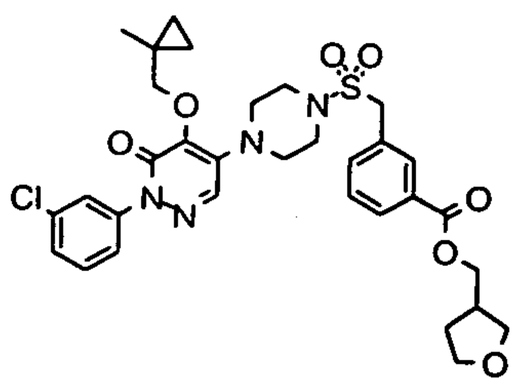
310 **327**

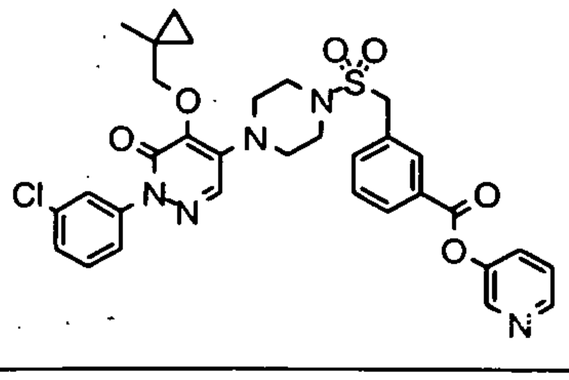
Step 229:

A mixture of 2-(3-chlorophenyl)-5-(4-(3-iodobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **310** (200 mg, 0.305 mmol), morpholine (39.9 mg, 0.458 mmol), and $Pd(dppf)Cl_2$ (22.3 mg, 0.03 mmole) in anhydrous DMSO (12 mL) at room temperature was charged with an atmosphere of carbon monoxide, after which the mixture was heated at 80 °C for 16 h. The cooled mixture was diluted with ethyl acetate (200 mL), washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative TLC on silica gel, eluting with ethyl acetate, to provide 79 mg (41% yield) of the product **327** as a light brown solid: MS (M+1): m/e 642.

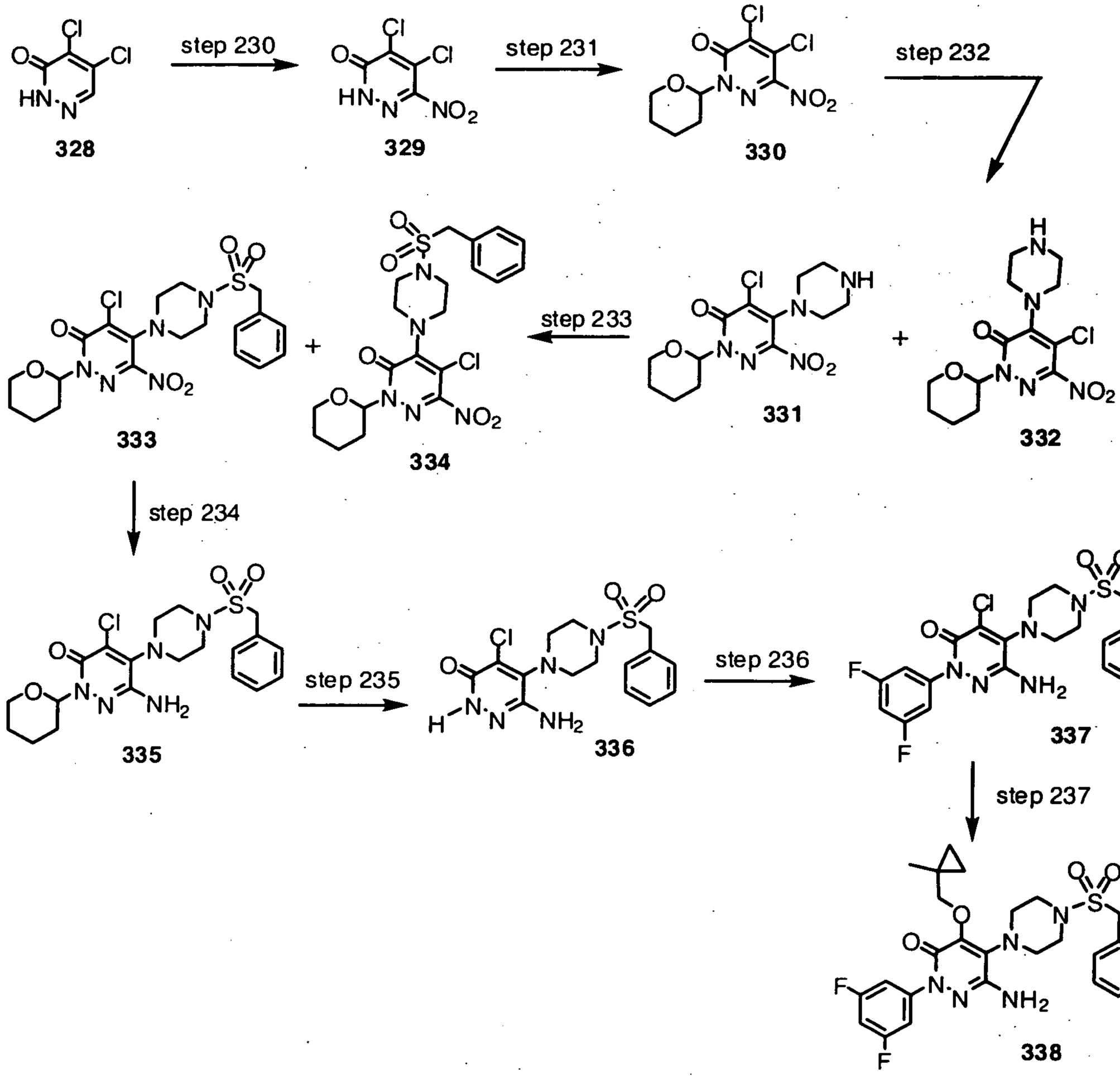
Using the procedure described above, the following compounds were synthesized.

Table 39: Oxygen Analogs with Carbonyl Substituted Sulfonamide

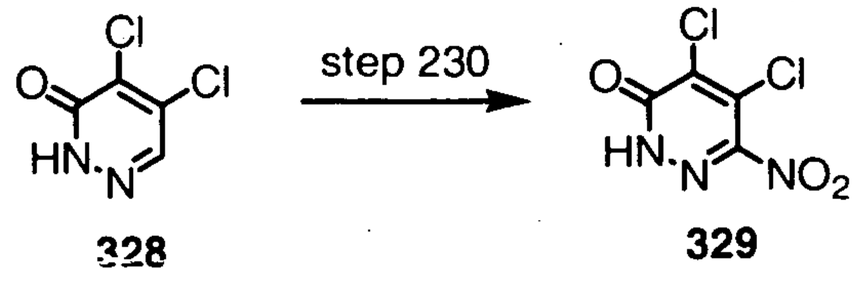
Cmpd. No.	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
2008Z		586	2009Z		629
2010Z		643	2011Z		629
2012Z		602	2013Z		665
2014Z		665	2015Z		658

2016Z		651

Scheme 71



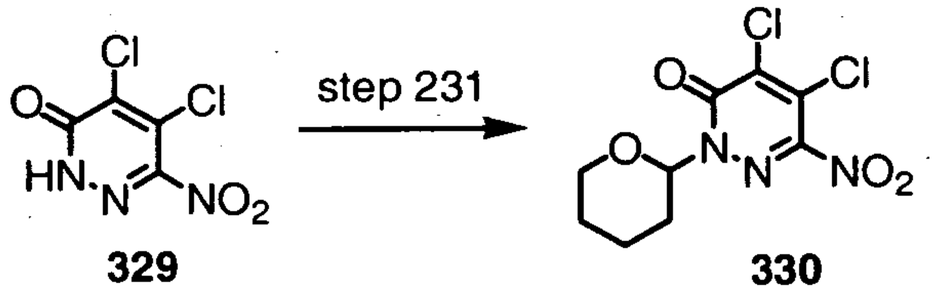
Step 230:



328 329

KNO_3 (20.0 g, mmol) was added portionwise to a mixture of fuming H_2SO_4 (30.0 mL) and 98% H_2SO_4 (16.0 mL) at 0 °C followed by stirring for 5 mins. Then 4,5-dichloropyridazinone **328** (1.0 g, 6.1 mmol) was added, and the reaction mixture was heated at 100 °C for 6 h. The reaction mixture was cooled to room temperature, poured into ice-water, and stirred for 5 mins to obtain a precipitate. The precipitate was collected by filtration, washed with H_2O (3 × 50 mL), and dried in a vacuum oven at 50 °C to afford 5.2 g (32% yield) of the crude product **329** as a white solid.

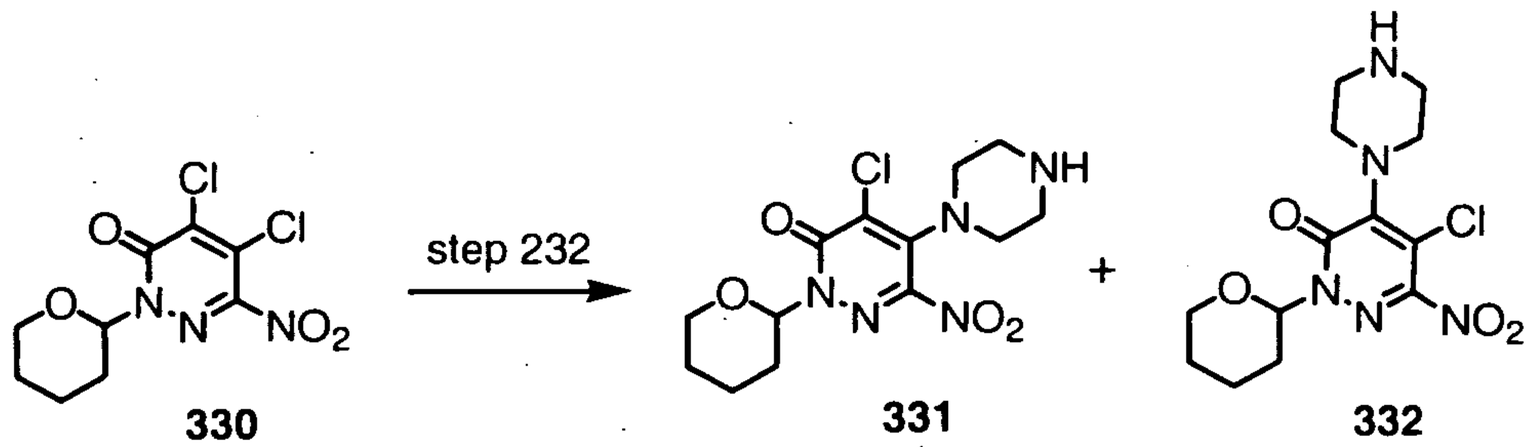
Step 231:



329 330

Compound **329** (6.16 g, 29.3 mmol) was added to a solution of 3,4-dihydropyran (24.7 g, 293 mmol) and p-toluene sulfuric acid monohydrate (0.56 g, 2.93 mmol) in THF (200 mL) The solution was refluxed for 29 h at 80 °C then cooled to room temperature, and the solvent was concentrated. The residue was purified by chromatography on a silica-gel column (eluant: 0-8% EtOAc/hexane gradient) to afford 6.5 g (75% yield) of the product **330** as pale yellow solid.

Step 232:



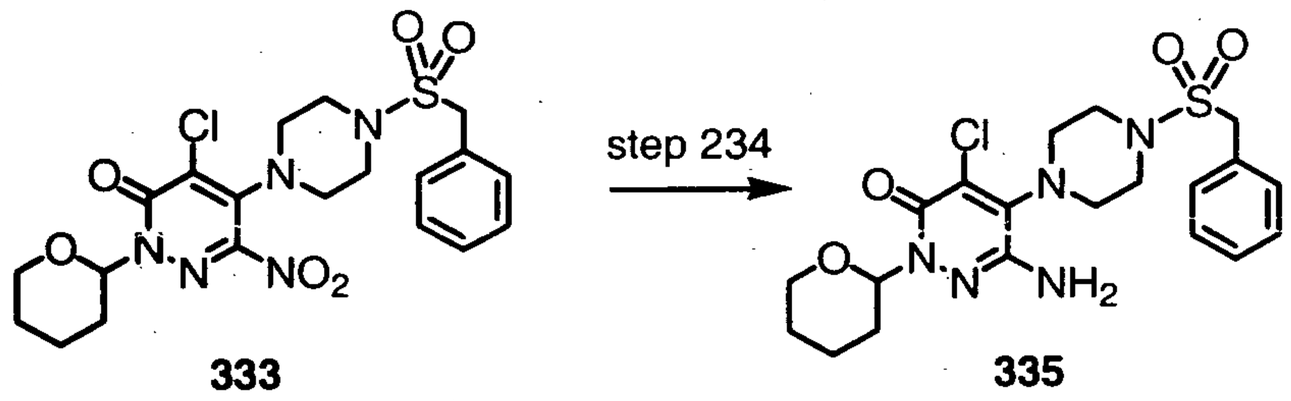
330 331 332

A solution of compound **330** (6.5 g, 22.1 mmol) and piperazine (3.8 g, 44.2 mmol) in EtOH (100 mL) was refluxed for 4 h at 80 °C then cooled to room temperature. The solvent was concentrated, and the residue was purified by chromatography on a silica-gel column (eluant: 4:1 to 1:2 EtOAc/MeOH gradient) to afford 5.1 g (67% yield) of a 1:1 mixture of products **331** and **332** as a yellow solid. MS (M+1): m/e 344.

Step 233:

α-Toluenesulfonyl chloride (0.81 g, 6.3 mmol) was added to a solution of the compounds **4** and **5** (1.8 g, 5.2 mmol) and *i*-Pr_2NEt (0.81 g, 6.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C followed by slowly warming to room temperature over 2 h. The solvent was concentrated. The residue was purified by chromatography on a silica-gel column (eluant: 0 – 40% EtOAc/hexane gradient) to afford 0.65 g (25% yield) of the first isomer **332** as pale yellow solid, MS (M+1): m/e 498; and 0.68 g (26% yield) of the second isomer **331** as pale yellow solid, MS (M + 1): m/e 498.

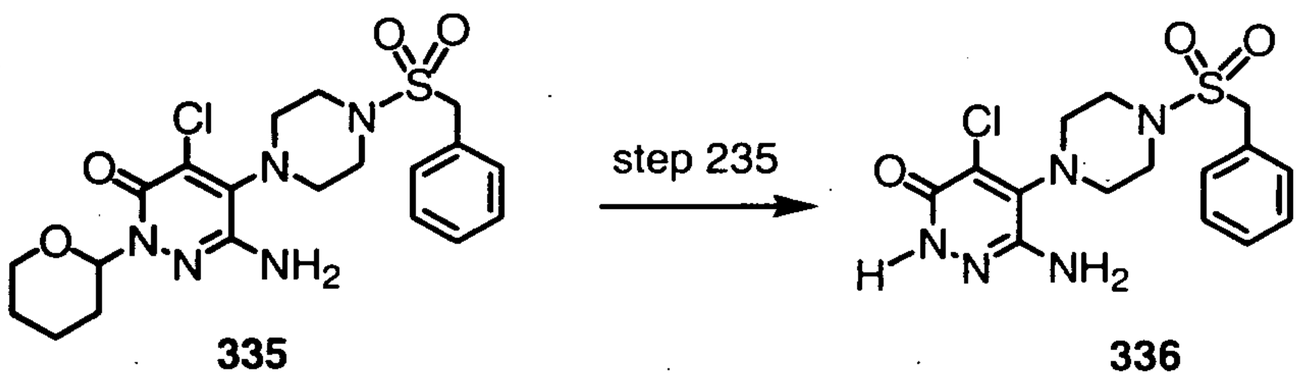
Step 234:



333 **335**

Compound **333** (0.68 g, 1.4 mmol) and PtO_2 (68 mg) dissolved in EtOAc/MeOH (15/30 mL) was stirred under a hydrogen atmosphere. The reaction was stirred overnight at room temperature under a hydrogen balloon. The solution was filtered through celite to remove the PtO_2. The filtrate was concentrated, and the product was purified by Prep Gilson HPLC to afford 0.48 g (75% yield) of the product **335** as a pale yellow solid. MS (M+1): m/e 468.

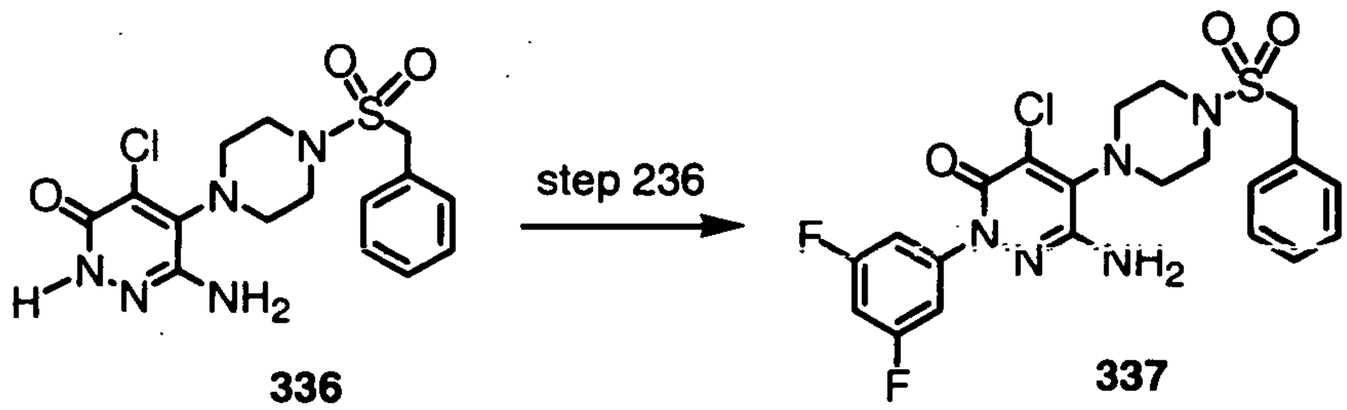
Step 235:



335 **336**

To compound **335** (0.24 g, 0.5 mmol) in MeOH (5 mL) was added a solution of 6 M aqueous HCl (2.5 mL) followed by stirring for 1 h at 75 °C. The reaction mixture was cooled to room temperature, and the solventl was concentrated. The residue was dissolved in EtOAc (25 mL) and washed with saturated $NaHCO_3$ (20 mL). The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated to afford 75 mg (39% yield) of the product **336** as a pale yellow solid. MS (M+1): m/e 384.

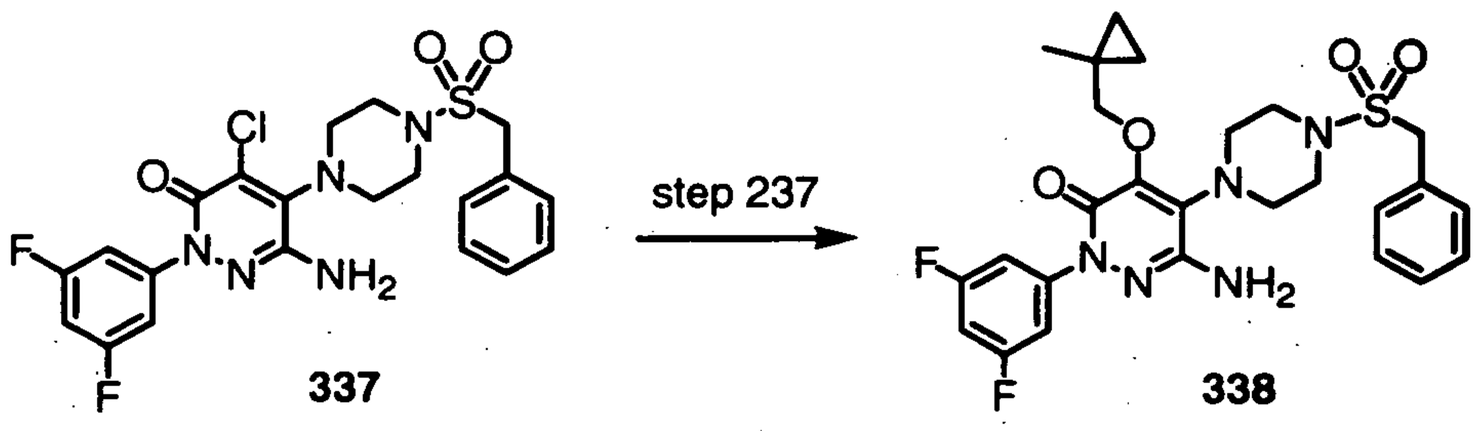
Step 236:



336 337

A suspension of compound **336** (75 mg, 0.20 mmol), 3,5-difluoroiodobenzene (72 mg, 0.30 mmol), 8-hydroxyquinoline (11 mg, 0.08 mmol), CuI (10 mg, 0.05 mmol), and K_2CO_3 (55 mg, 0.40 mmol) in pyridine (5 mL) was heated for 1.5 h at 170 °C in a microwave reactor. The reaction mixture was cooled to room temperature, and the solution was filtered to remove the solid. The filtrate was concentrated and purified by prep Gilson HPLC to afford **51 mg** (52% yield) of the product **337** as a pale yellow solid. MS (M+1): m/e 496.

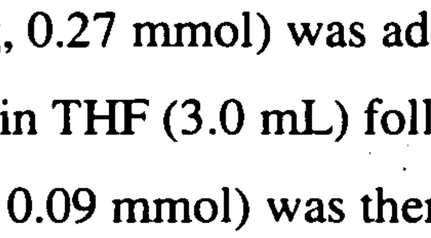
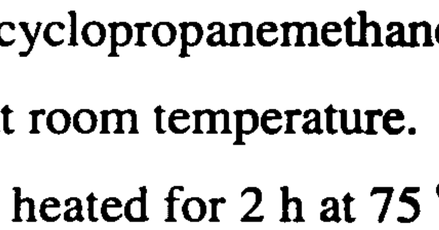
Step 237:

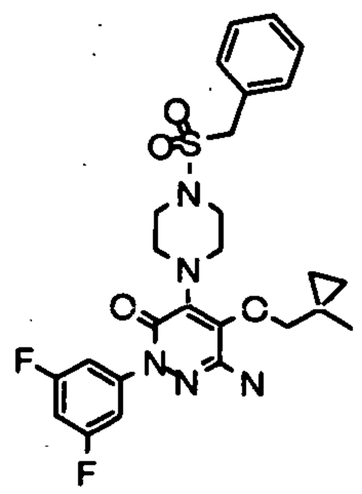


337 338

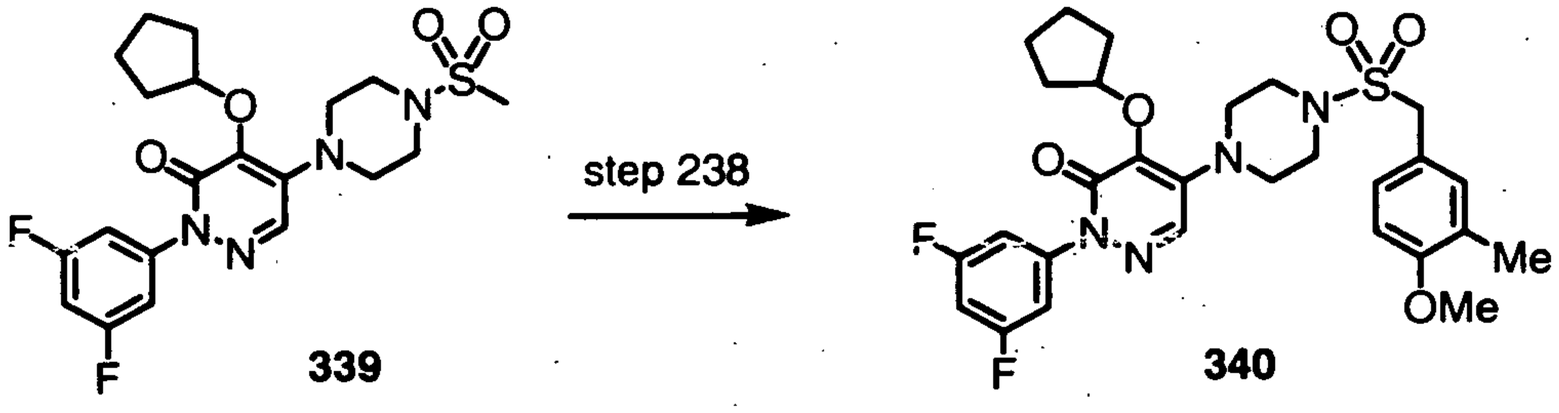
NaH (11 mg, 0.27 mmol) was added to a solution of 1-methylcyclopropanemethanol (26 µL, 0.27 mmol) in THF (3.0 mL) followed by stirring for 5 mins at room temperature. Compound **337** (45 mg, 0.09 mmol) was then added, and the reaction was heated for 2 h at 75 °C. The reaction mixture was cooled to room temperature, concentrated, and purified by chromatography on a silica-gel column (eluant: 0-35% EtOAc/hexane gradient) to afford 24 mg (49% yield) of the product **338** as a pale yellow solid. MS (M + 1): m/e 546.

Using the procedures described above, the following compounds were synthesized.

Cmpd. No	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
2017Z		546	2018Z		544

2019Z		546

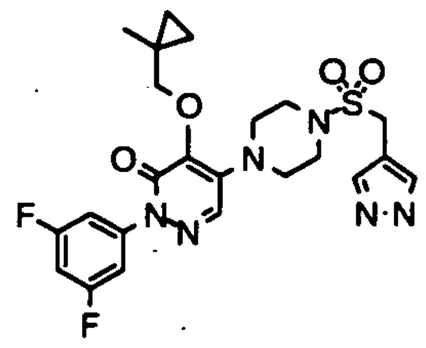
Scheme 72



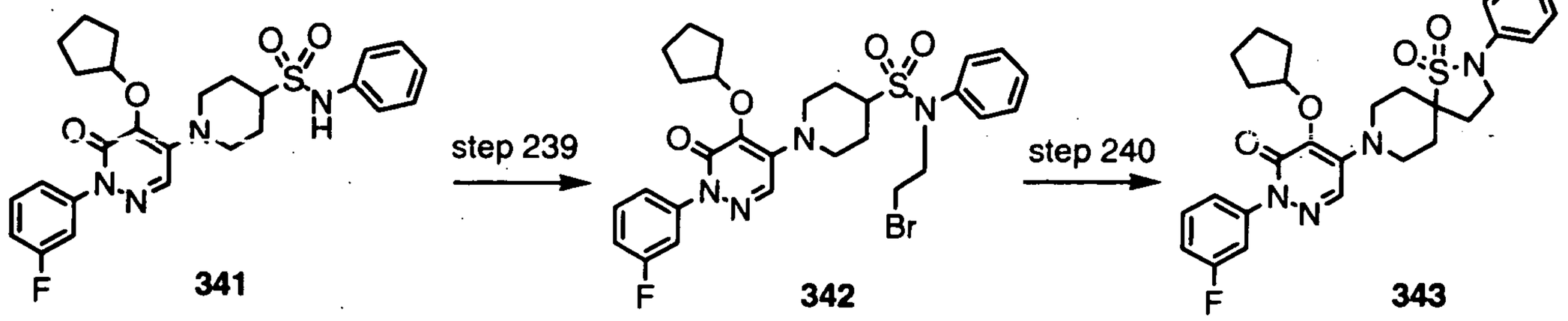
Step 238:

To compound **339** (45.4 mg, 0.0999 mmol) and 4-bromo-2-methylanisole (42.5 mg, 0.211 mmol) dissolved in anhydrous toluene (2 mL) at room temperature was added lithium hexamethyldisilazide in THF (0.200 mL, 1.0 M), palladium acetate (1.79 mg, 0.00799 mmol) and triphenylphosphine (6.55 mg, 0.0250 mmol). The reaction was degassed, placed under an atmosphere of nitrogen, and stirred at 100 °C overnight. The reaction mixture was filtered through a short path silica column and washed with ethyl acetate (150 mL). The solvent was concentrated, and the product was chromatographed on silica gel (eluant: 1:2 hexanes:EtOAc) to give 36 mg (63% yield) of the product **340**. MS (M+1): m/e 575.

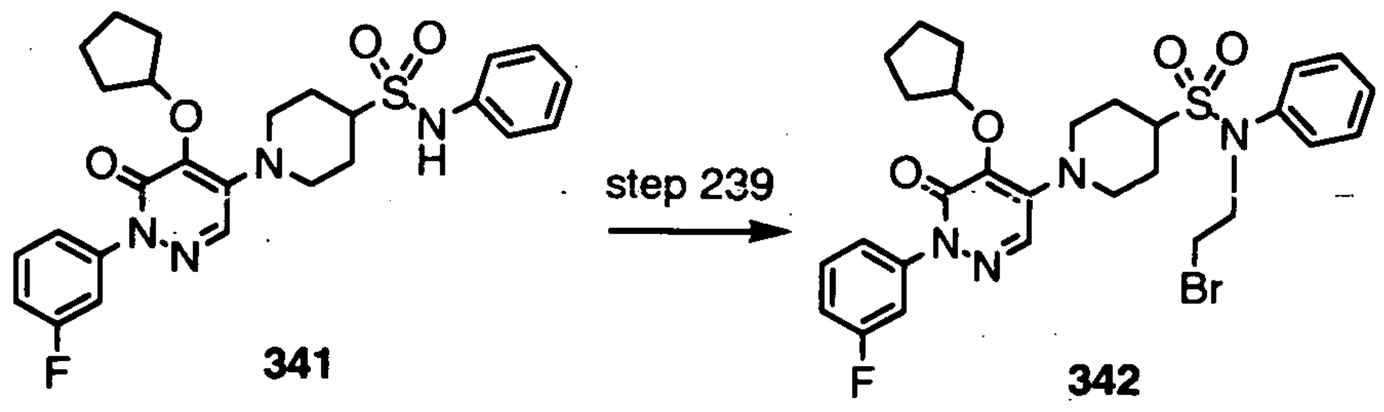
Using the procedure described above, the following compound was synthesized.

Cmpd. No.	Structure	MS M+1
2020Z		521

Scheme 73



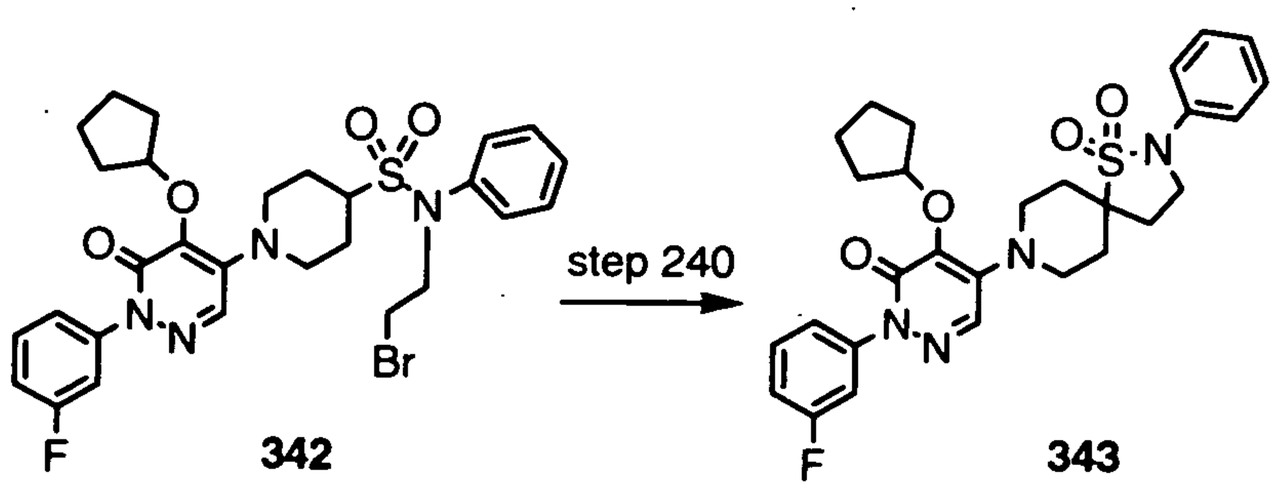
Step 239:



Compound **341** can be prepared according to Scheme 34.

To a solution of sulfonamide **341** (200 mg, 0.39 mmol) in DMF (4 mL) at room temperature was added NaH (39 mg, 0.98 mmol, 60% in oil) in one portion. After stirring for 20 mins, 1,2-dibromoethane (840 mg, 4.2 mmol) was added in one portion followed by the addition of K_2CO_3 (540 mg, 3.9 mmol). The reaction mixture was heated at 120 °C for 8h then cooled and slowly added to a saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 180 mg (74% yield) of the product **342** as a white solid. MS (M+1): 621.

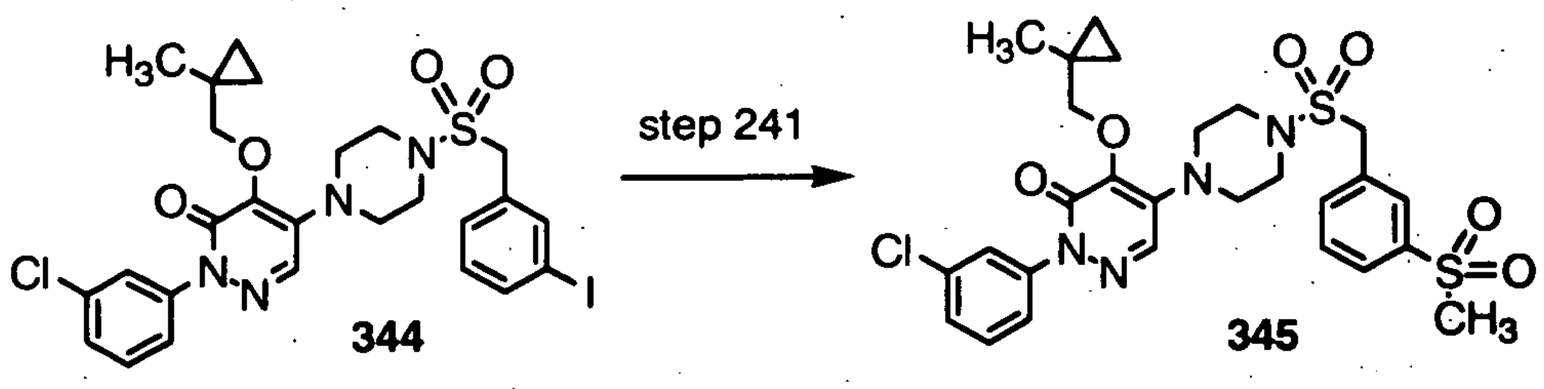
Step 240:



To a solution of bromosulfonamide **342** (160 mg, 0.26 mmol) in THF/HMPA (2 mL/0.4 mL) at -78 °C was added $KN(TMS)_2$ (1.55 mL, 0.77 mmol) over 2 mins. After stirring for 30 mins, the reaction mixture was raised to room temperature and stirred over night. Saturated aqueous

NH_4Cl solution was then added, and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by Gilson reverse phase chromatography (eluant: CH_3CN-H_2O) gave 10 mg (7.4% yield) of the product **343** as a solid. MS (M+1): 539.

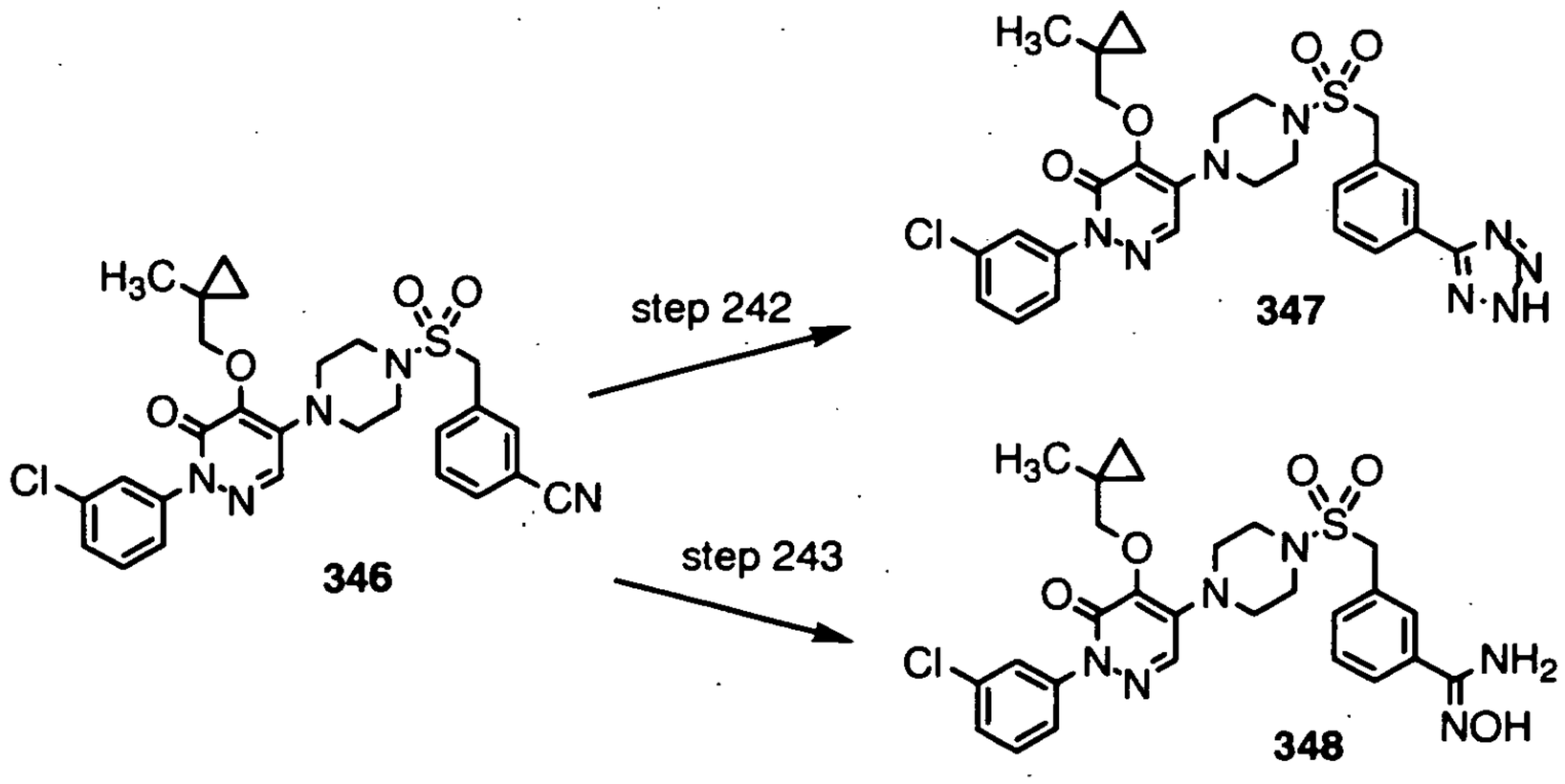
Scheme 74



Step 241:

A mixture of 2-(3-chlorophenyl)-5-(4-(3-iodobenzylsulfonyl)piperazin-1-yl)-4-((1-methylcyclopropyl)methoxy)pyridazin-3(2*H*)-one **344** (100 mg, 0.153 mmol), methylsulfonyl sodium (19 mg, 0.18 mmol), copper iodide (6 mg, 0.03 mmole), L-proline (7.0 mg, 0.06 mmole) and sodium hydroxide (3 mg, 0.06 mmole) in anhydrous DMSO (0.5 mL) was heated at 90 °C under nitrogen for 17 h. The cooled mixture was diluted with ethyl acetate (200 mL), washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparatory TLC (Analtech silica gel GF, 200 microns) eluting with methylene chloride/methanol (19:1), to provide 21.8 mg (24% yield) of the product **345** as a white solid: MS (M+1): m/e 607.

Scheme 75

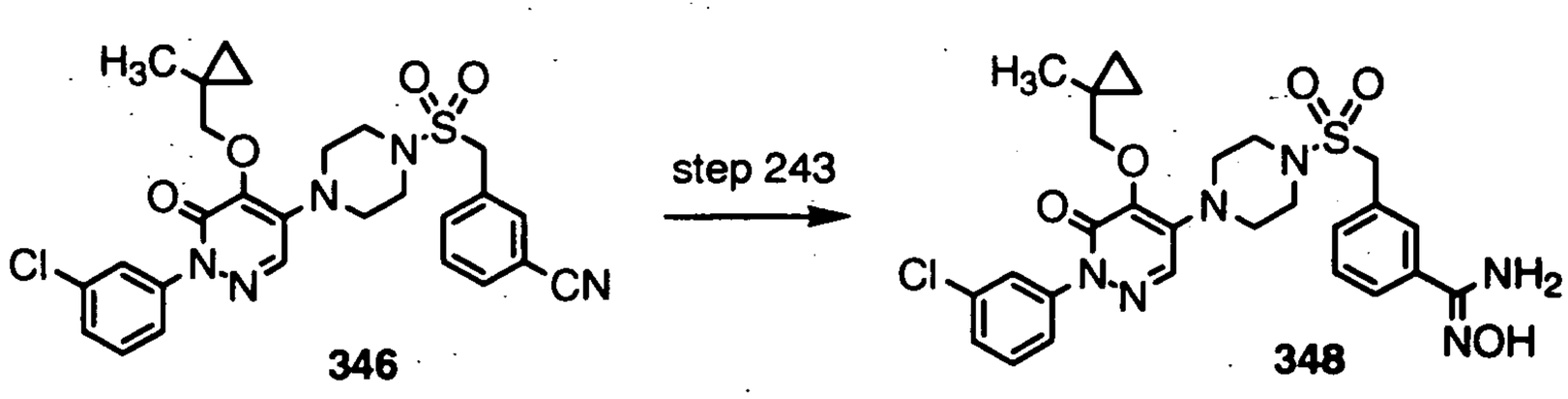


Step 242:

Compound **346** can be synthesized according to Scheme 64.

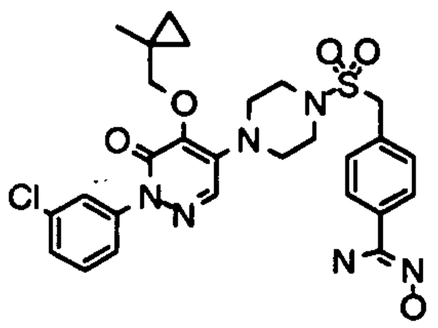
A mixture of 3-[(4-(1-(3-chlorophenyl]-5-[(1-methylcyclopropyl)methoxy-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl]benzonitrile **346** (100 mg, 0.180 mmol), sodium azide (36.6 mg, 0.564 mmol) and triethylamine hydrochloride (74.5 mg, 0.541 mmol) in anhydrous toluene (1 mL) was heated at 90 °C under nitrogen for 16 h. The cooled mixture was diluted with brine (100 mL), extracted with ethyl acetate (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with methylene chloride/methanol (19:1 to 3:1), to provide 44 mg (41 % yield) of the product **347** as a yellow solid: MS (M+1): m/e 597.

Step 243:

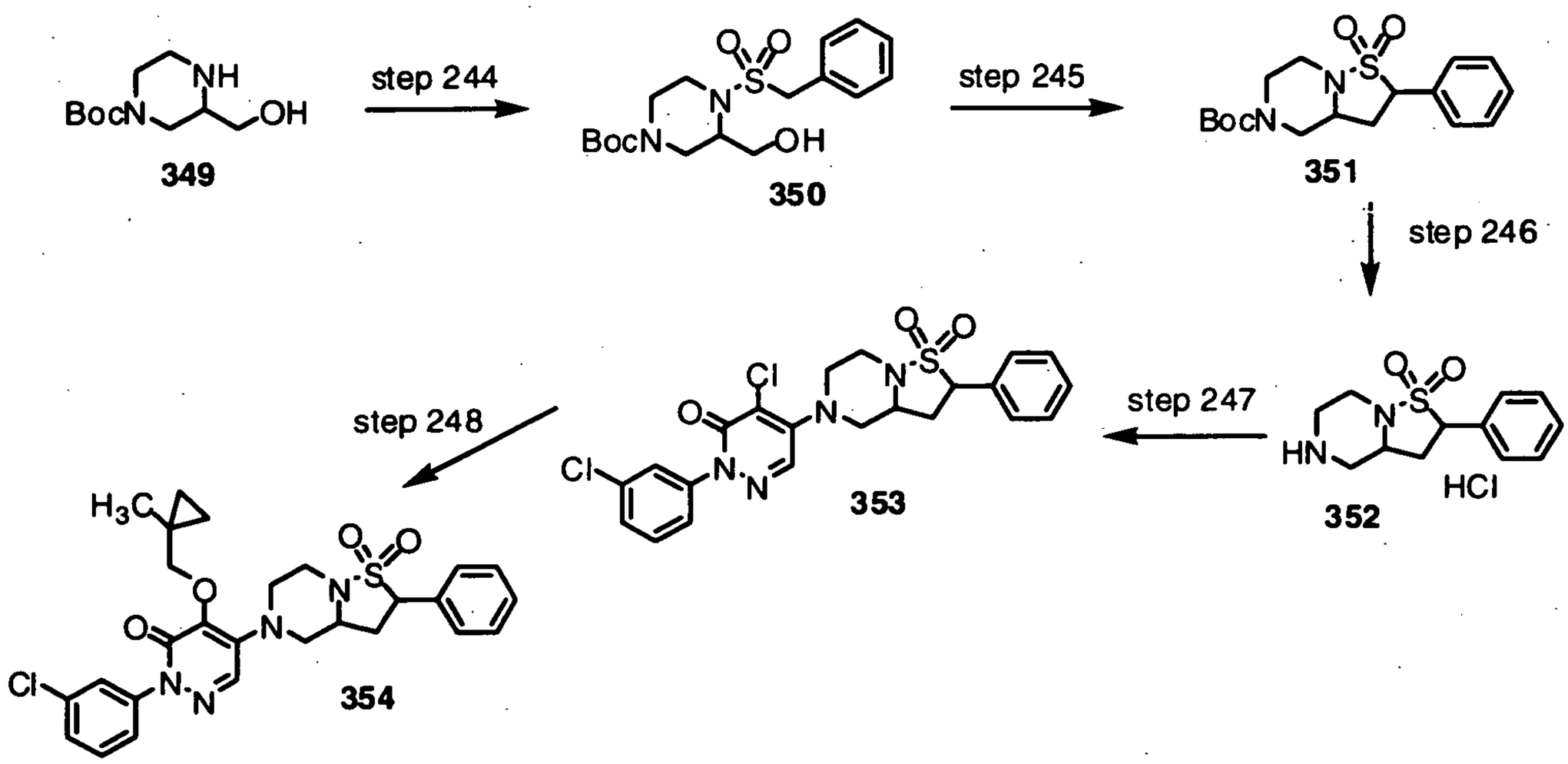


A mixture of 3-[(4-(1-(3-chlorophenyl]-5-[(1-methylcyclopropyl)methoxy-6-oxo-1,6-dihydropyridazin-4-yl)piperazin-1-ylsulfonyl)methyl]benzonitrile **346** (100 mg, 0.180 mmol), hydroxylamine hydrochloride (56.0 mg, 0.80 mmol), and sodium carbonate (84.0 mg, 1.01 mmol) in a biphasic mixture of water, (3 mL), methylene chloride (1 mL), and ethanol (9 mL) was heated at reflux under nitrogen for 19 h. The cooled suspension was diluted with water (100 mL), extracted with methylene chloride (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to provide a clear oil, which was triturated with diethyl ether (20 mL). The resulting solids were collected under reduced pressure to provide 130 mg (64% yield) of the product **348** as a yellow solid: MS (M+1): m/e 587.

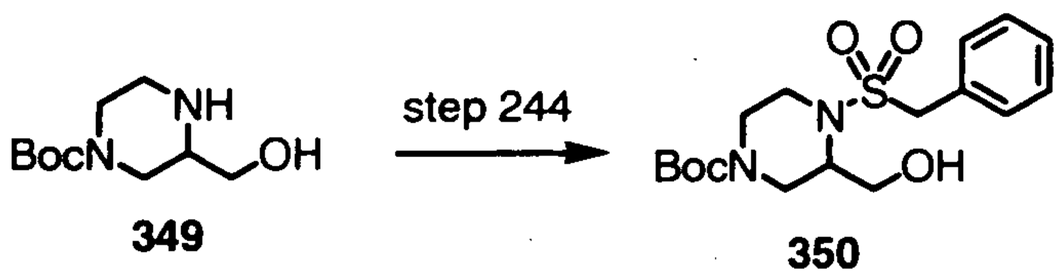
Using the procedures described above, the following compound was synthesized.

Cmpd. No	Structure	MS M+1
2021Z		587

Scheme 76

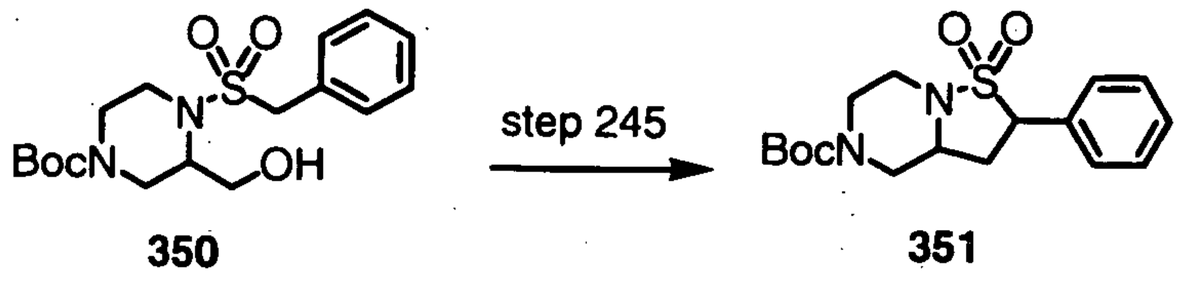


Step 244:



A solution of benzylsulfonyl chloride (210 mg, 1.1 mmol) in methylene chloride (0.5 mL) was added dropwise to a mixture of (+/-)-*tert*-butyl 3-(hydroxymethyl)piperazine-1-carboxylate **349** (216 mg, 1.0 mmol) and diisopropylethylamine (0.35 mL, 2.0 mmol) in methylene chloride (1.0 mL) at 0 °C under nitrogen, after which the mixture was slowly warmed to room temperature, stirring for a total of 2 h. The solvent was concentrated, and the residue was purified by CombiFlash Companion (12-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:19 to 1:1), to provide 102 mg (28% yield) of the product **350** as a white solid.

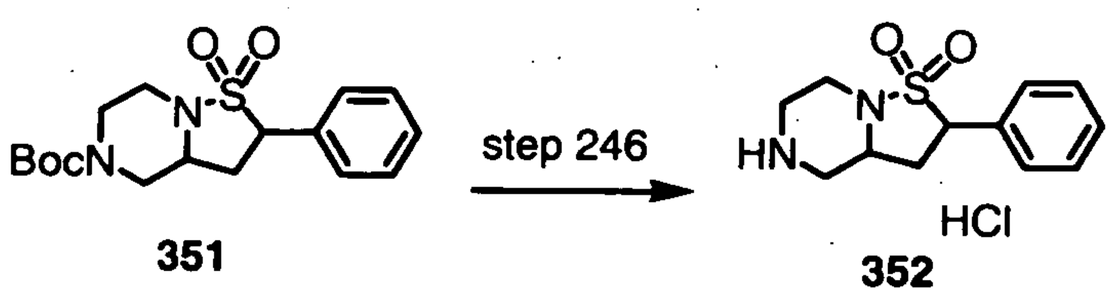
Step 245:



350 **351**

A solution of (+/-)-*tert*-butyl 4-(benzylsulfonyl)-3-(hydroxymethyl)piperazine-1-carboxylate **350** (222 mg, 0.60 mmol) and (cyanomethylene)tributylphosphorane (0.30 g, 1.24 mmol) in toluene (5 mL) was heated at 105 °C under nitrogen for 16 h. The solvents were removed from the cooled mixture under reduced pressure, and the residue was purified by CombiFlash Companion (12-g silica gel cartridge), eluting with ethyl acetate/hexanes (100% hexanes to 1:1), to provide 162 mg (77% yield) of the product **351** as a light brown oil.

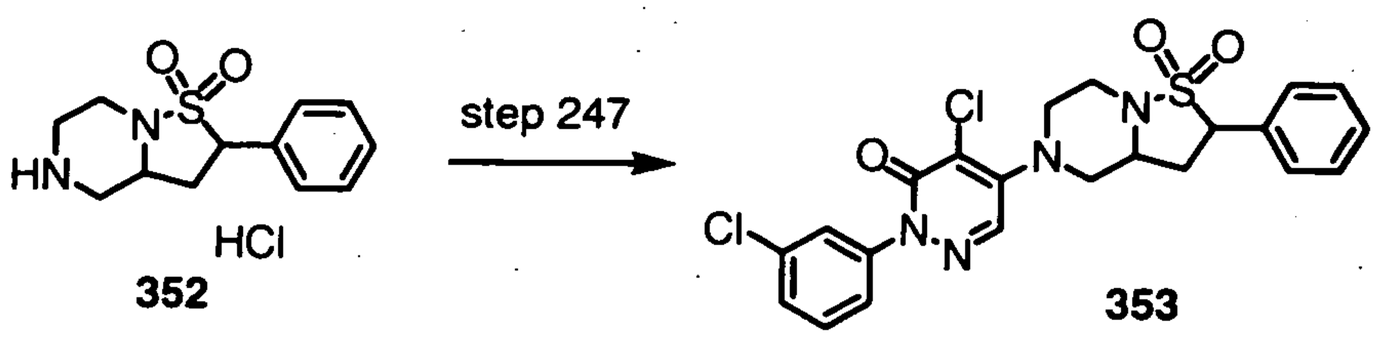
Step 246:



351 **352**

Solid (+/-)-bicyclic sulfonamide **351** (75 mg, 0.21 mmol) was treated with hydrochloric acid (2 mL, 8 mmol, 4 N in dioxane), and the mixture was stirred at room temperature for 2 h. The thick suspension was dissolved in methanol (25 mL), and the solvents were removed under reduced pressure to provide 63 mg (100% yield) of the product **352** as an off-white solid.

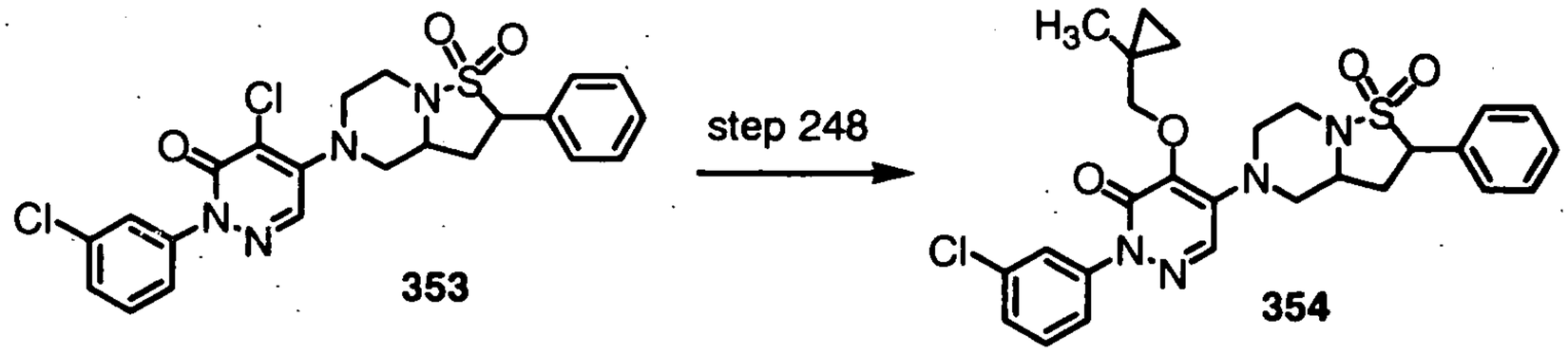
Step 247:



352 **353**

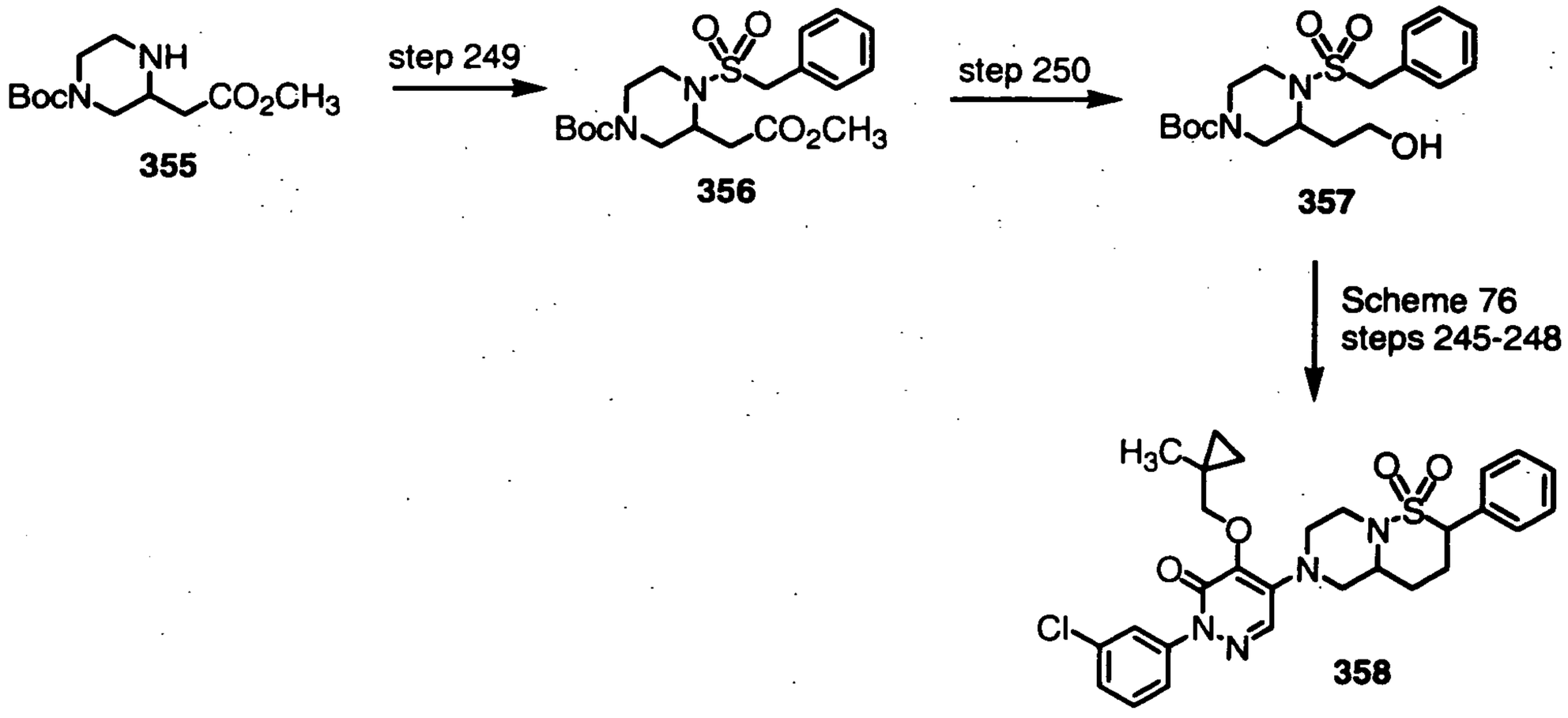
Diisopropylethylamine (0.11 mL, 0.63 mmol) was added to a mixture of 4,5-dichloro-2-(3-chlorophenyl)pyridazin-3(2*H*)-one (57 mg, 0.21 mmol) and (+/-)-bicyclic sulfonamide hydrochloride **352** (60 mg, 0.21 mmol) in DMF (0.5 mL) at room temperature under nitrogen, and the mixture was heated at 95 °C for 17 h. The cooled mixture was diluted with ethyl acetate (15 mL), washed with brine (3 x 15 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by CombiFlash Companion (4-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:19 to 1:1), to provide 61 mg (59% yield) of the product **353** as a tan solid: MS (M+1): m/e 491.

Step 248:



A solution of (1-methylcyclopropyl)methanol (20 mg, 0.23 mmol) and sodium hexamethyldisilazide (0.17 mL, 0.17 mmol, 1 N in THF) combined in THF (1 mL) was added dropwise to a solution of (+/-)-bicyclic sulfonamide pyridazinone **353** (55 mg, 0.11 mmol) dissolved in THF (1 mL) at room temperature under nitrogen. The mixture was heated at reflux for 6 h then cooled to room temperature and concentrated. The residue was purified by CombiFlash Companion (12-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:19 to 1:1), to provide 17 mg (28% yield) of the product **354** as an off-white solid: **MS (M+1) m/e** 541.

Scheme 77



Step 249:

A solution of benzylsulfonyl chloride (458 mg, 2.4 mmol) in methylene chloride (5 mL) was added dropwise to a mixture of (+/-)-*tert*-butyl 3-(2-methoxy-2-oxoethyl)piperazine-1-

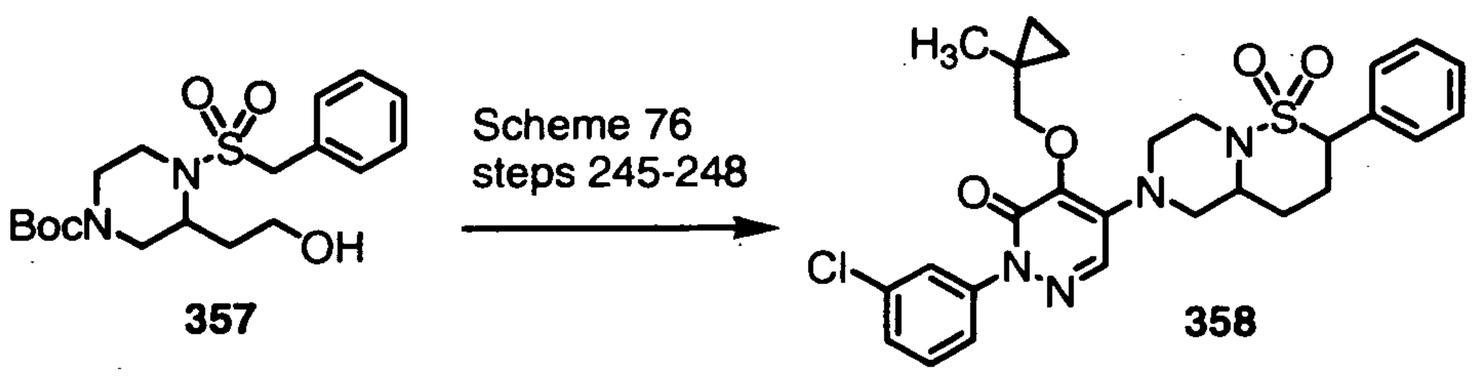
carboxylate **355** (517 mg, 2.0 mmol) and diisopropylethylamine (0.52 mL, 3.0 mmol) in methylene chloride (10.0 mL) at 0 °C under nitrogen, after which the mixture was slowly warmed to room temperature, stirring for a total of 5 days. The solvents were removed under reduced pressure, and the residue was purified by CombiFlash Companion (40-g silica gel cartridge), eluting with ethyl acetate/hexanes (100% hexanes to 2:3), to provide 450 mg (55% yield) of the product **356** as a white foam.

Step 250:

356 **357**

A mixture of (+/-)-*tert*-butyl 4-(benzylsulfonyl)-3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate **356** (1.29 g, 3.12 mmol) and sodium borohydride in THF (25 mL) was heated at reflux under nitrogen, after which methanol (0.75 mL) was added in small portions over 1 h. The resulting mixture was heated at reflux for an additional 4 h, after which the cooled mixture was diluted with brine (15 mL) and aqueous HCl (40 mL, 0.1 N). The mixture was extracted with ethyl acetate (10 mL), washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by CombiFlash Companion (80-g silica gel cartridge), eluting with ethyl acetate/hexanes (1:9 hexanes to 1:1), to provide 0.95 g (79% yield) of the product **357** as a colorless viscous oil.

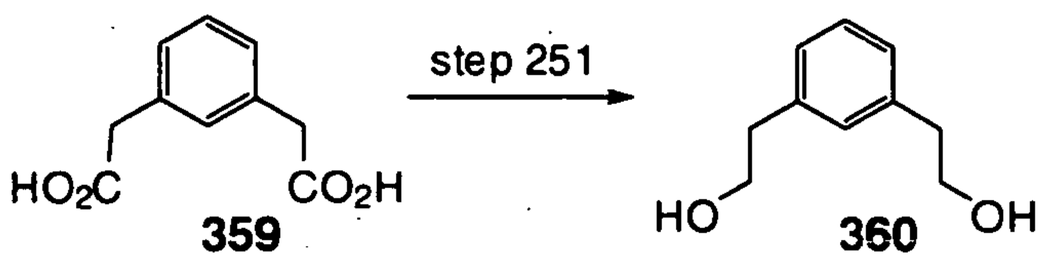
Steps 245-248 from Scheme 76:

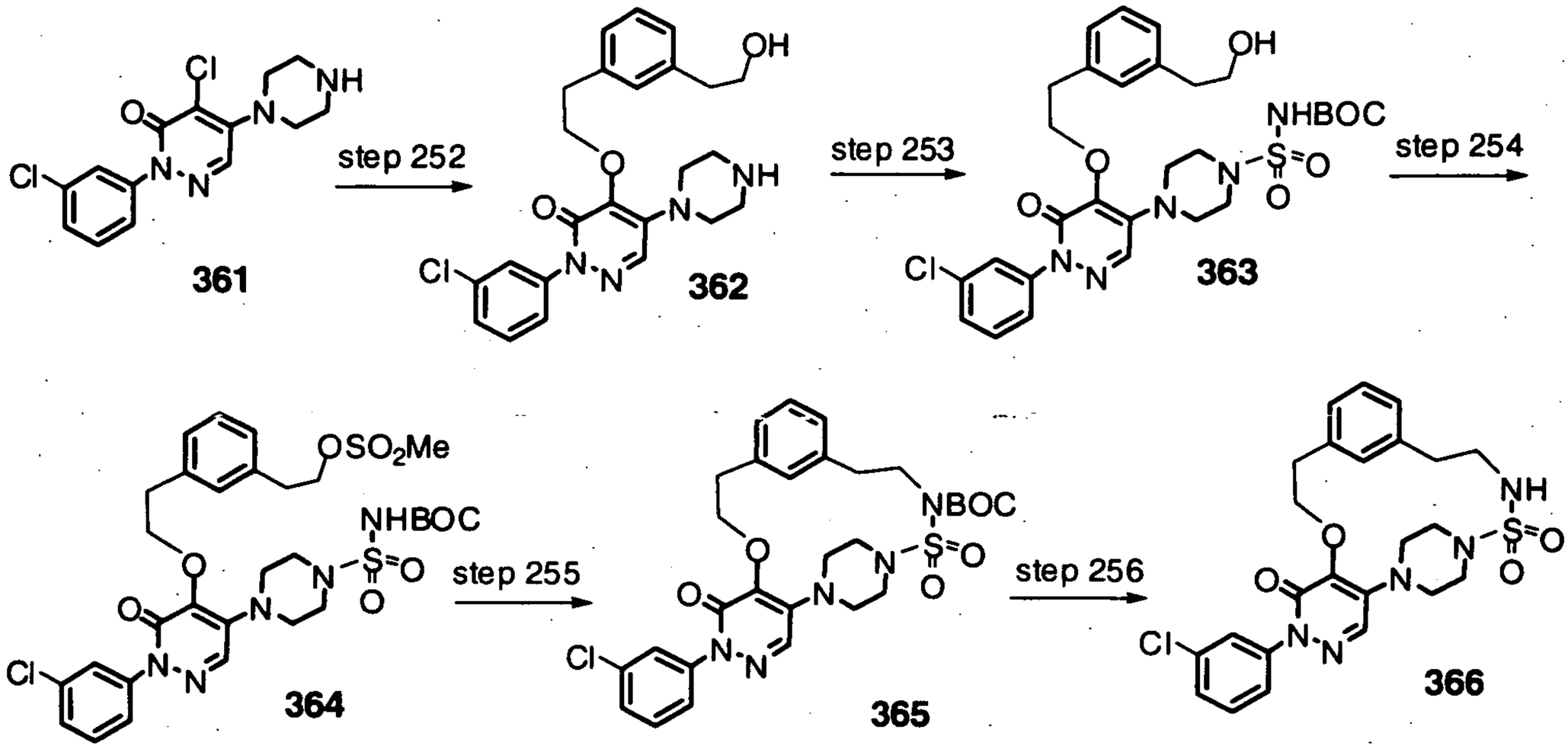


357 **358**

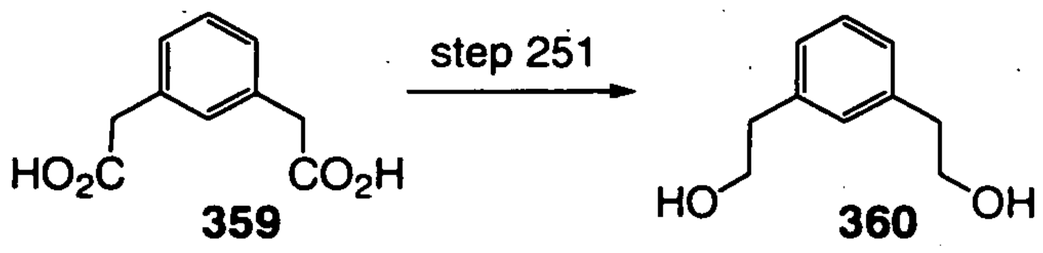
Using the procedures described above, compound **358** was synthesized. MS (M+1): m/e 555.

Scheme 78



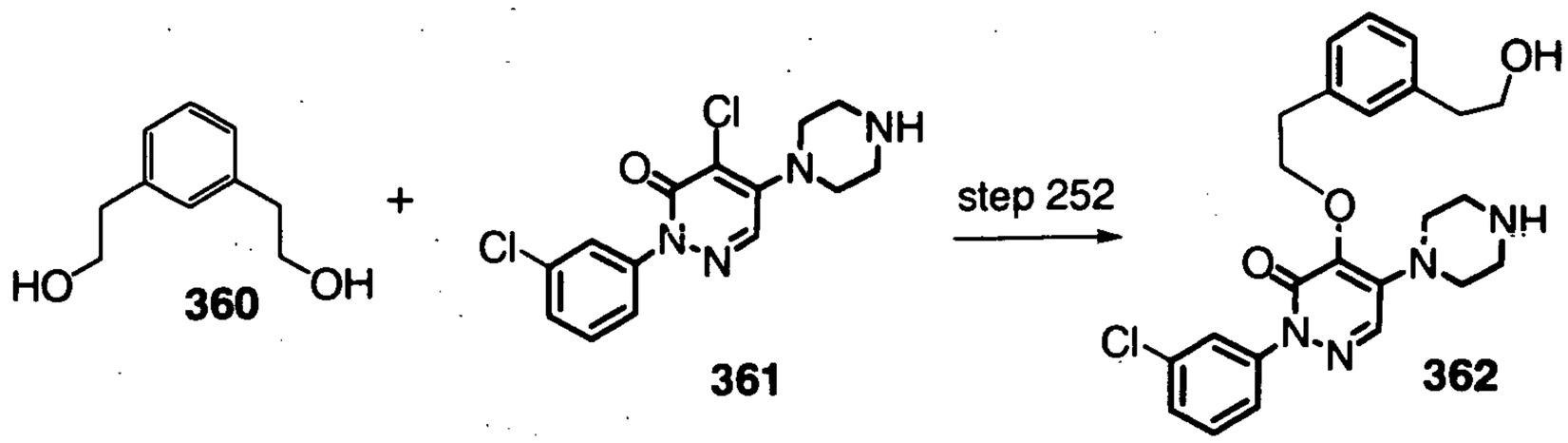


Step 251:



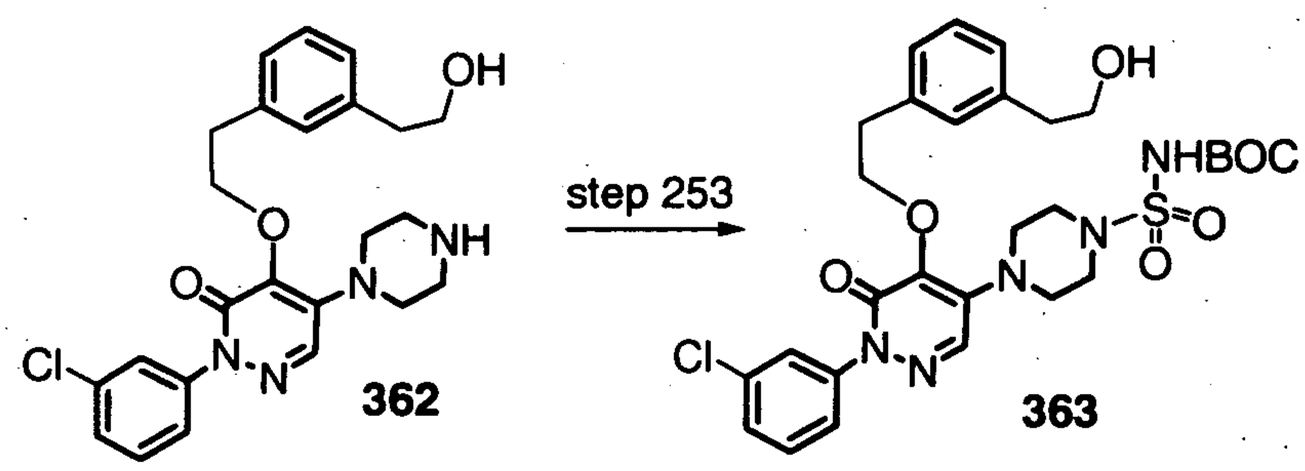
$BH_3 \cdot SMe_2$ (1.65 ml, 16.5 mmol) was added dropwise to a solution of 1,3-phenylenediacetic acid **359** (0.80 g, 4.12 mmol) in THF (20 mL) at room temperature followed by heating at 75 °C for 3. After cooling, the reaction mixture was diluted with EtOAc (20 mL) and treated with saturated aq. NH_4Cl. The organic phase was separated, and the aqueous solution was extracted with EtOAc (20 mL). The combined organic phase was washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified on a silica-gel column (eluant: 5:1 to 1:1 CH_2Cl_2/EtOAc gradient) to afford 0.53 g (78% yield) of the product **360** as a white solid.

Step 252:



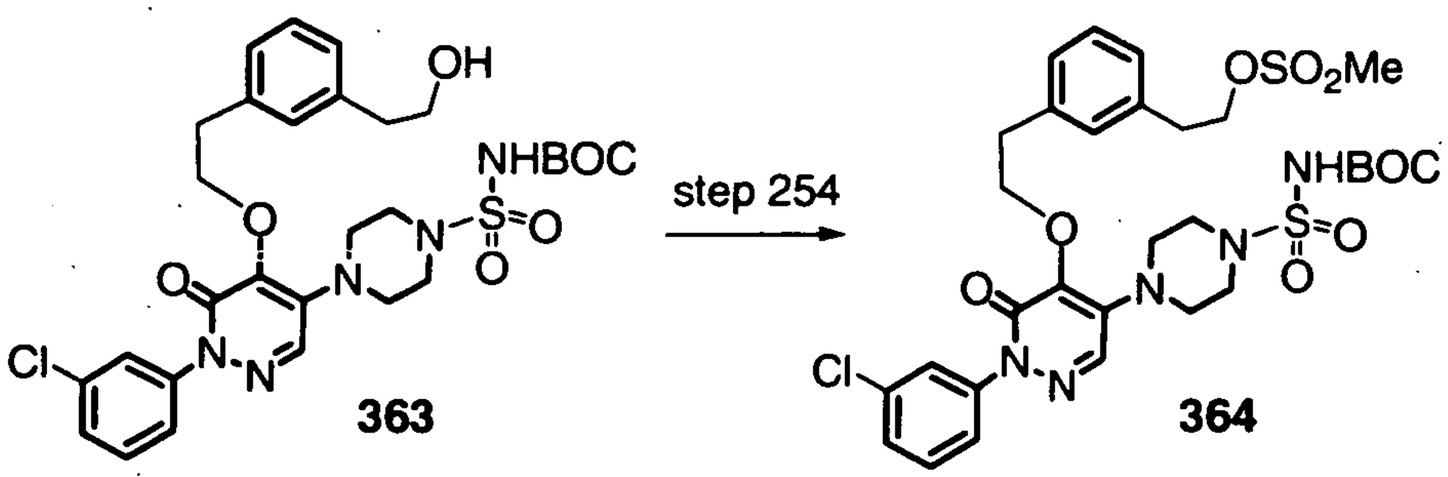
Sodium hydride (0.13 mg, 3.2 mmol) was added to a solution of 1,3-diphenylenediethanol **360** (0.53 g, 3.2 mmol) in THF at 0 °C followed by stirring for 15 mins. To the above mixture was added compound **361** (0.54 g, 1.5 mmol), and the reaction was heated for 1 h at 60 °C. The reaction mixture was cooled, concentrated, and purified by chromatography on a silica-gel column (eluant: 2:1 CH_2Cl_2/EtOAc mixed with 2 M ammonia in 5-20% CH_3OH gradient) to afford 0.41 g (60% yield) of the product **362** as a pale yellow solid. MS (M + 1): m/e 455.

Step 253:



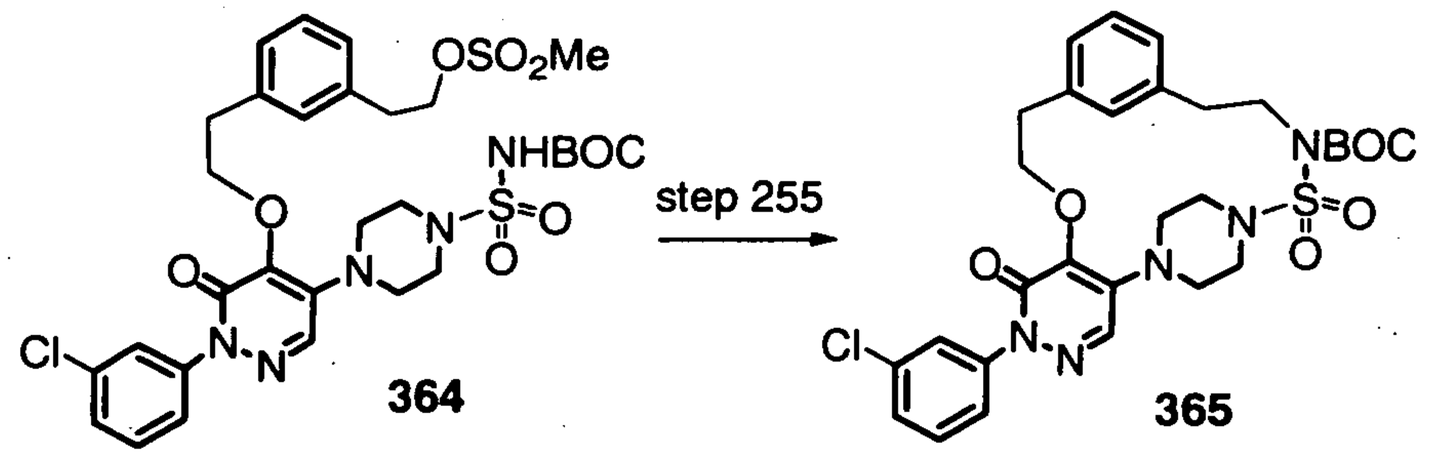
*t*BuOH (61 mg, 0.9 mml) was added dropwise to a solution of $ClSO_2NCO$ (127 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C followed by stirring for 30 mins. The resulting solution was then added to a solution of compound **362** (410 mg, 0.9 mmol) and *i*-Pr_2NEt (174 mg, 1.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C followed by stirring for 2 h, while temperature was slowly allowed to rise to room temperature. The mixture was concentrated, and the residue was purified by chromatography on a silica-gel column (eluant: 0 – 60% EtOAc/hexane gradient) to afford 0.30 g (53% yield) of the product **363** as a pale yellow solid. MS (M+1): m/e 634.

Step 254:



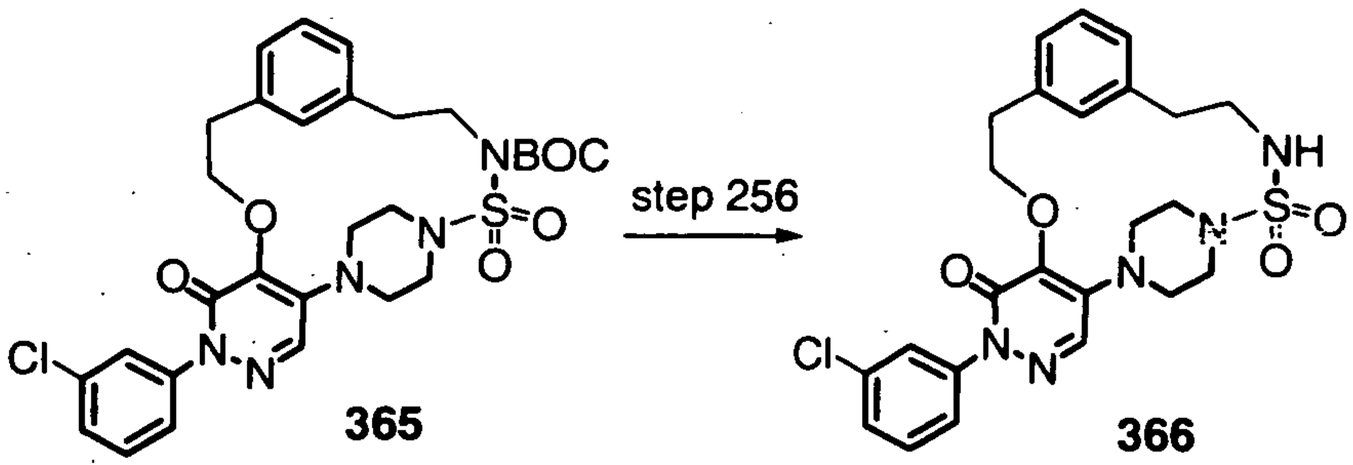
Methanesulfonic anhydride (42 mg, 0.24 mmol) was added to a solution of compound **363** (140 mg, 0.22 mmol), DMAP (54 mg, 0.44 mmol) and Et_3N in CH_2Cl_2 (5 mL) at 0 °C. After the reaction mixture was warmed to room temperature, the reaction was stirred for 2 h. The solvent was concentrated, and the crude product was purified by Prep Gilson HPLC to afford 0.12 g (92% yield) of the product **364** as a pale yellow soiid. MS (M+1): m/e 612.

Step 255:



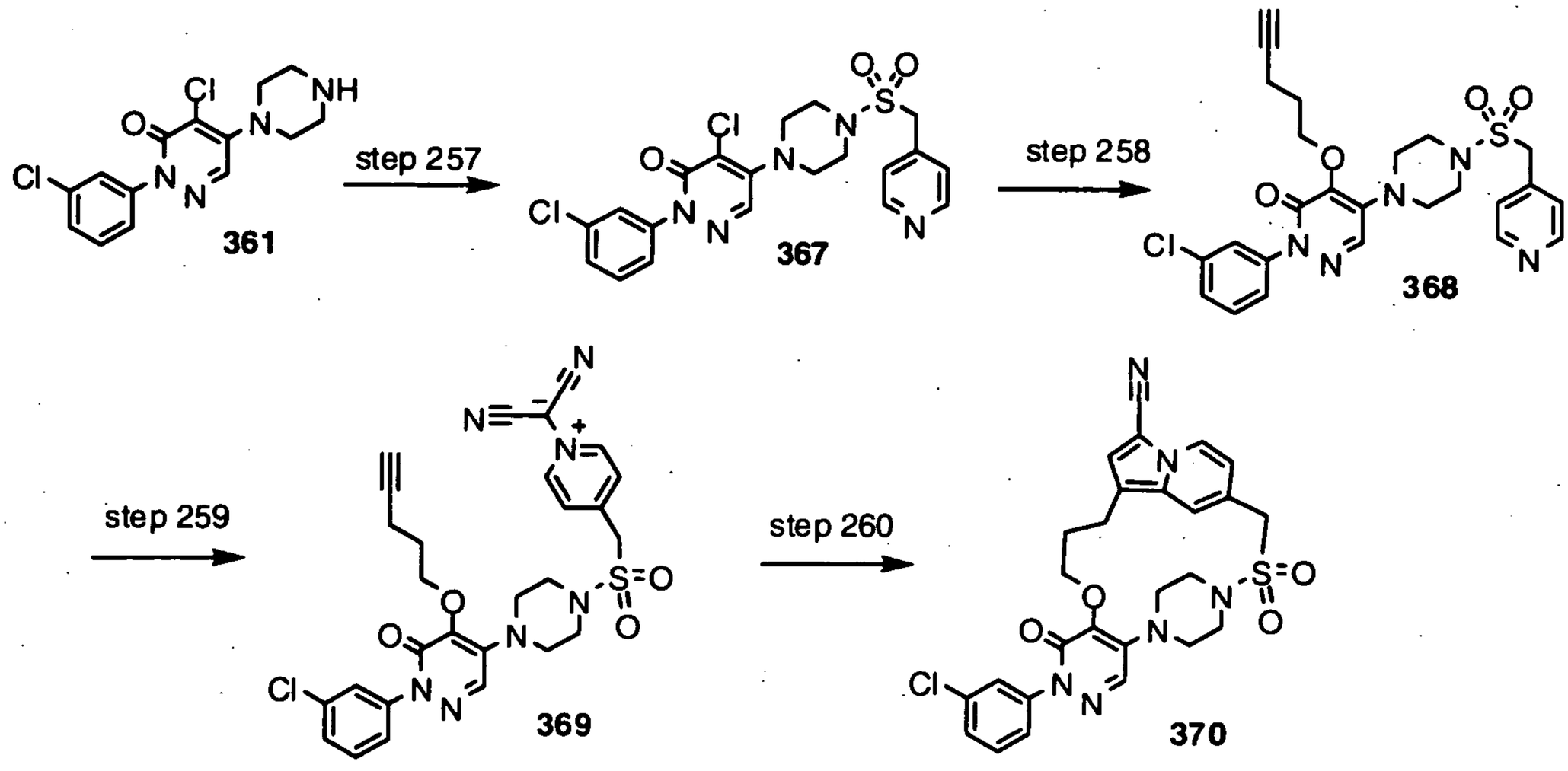
Compound **364** (52 mg, 0.07 mmol), K_2CO_3 (39 mg, 0.28 mmol) and DMF (5 mL) were mixed in a microwave reaction vial, which was then capped and heated to 90 °C for 1~2 h in a microwave reactor. The progress of the reaction was monitored by mass spectral data. After the reaction was complete, the mixture was diluted with EtOAc (25 mL) and washed with H_2O (20 mL). The organic phase was separated, and the aqueous solution was extracted with EtOAc (20 mL). The organic phase was combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by Prep Gilson HPLC to afford 18 mg (42% yield) of the product **365** as a pale yellow solid. MS (M+1): m/e 616.

Step 256:

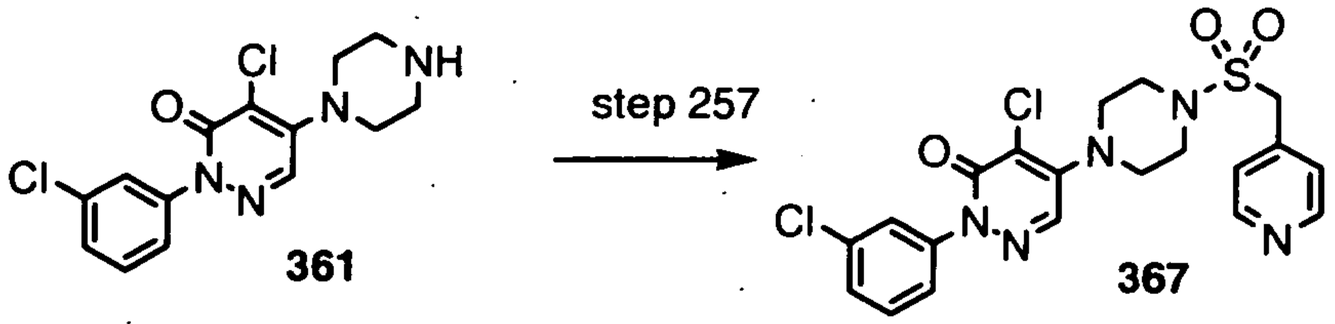


Compound **365** (18 mg, 0.03 mmol) and THF/H_2O (4 mL, 3:1) was mixed in a microwave reaction vial, which was then capped and heated at 145 °C for 20 mins in a microwave reactor. After cooling, the reaction mixture was concentrated and purified on a silica-gel column (eluant: 0 – 35% EtOAc/hexane gradient) to afford 12 mg (80% yield) of the product **366** as a pale yellow soiid. MS (M+1): m/e 516.

Scheme 79



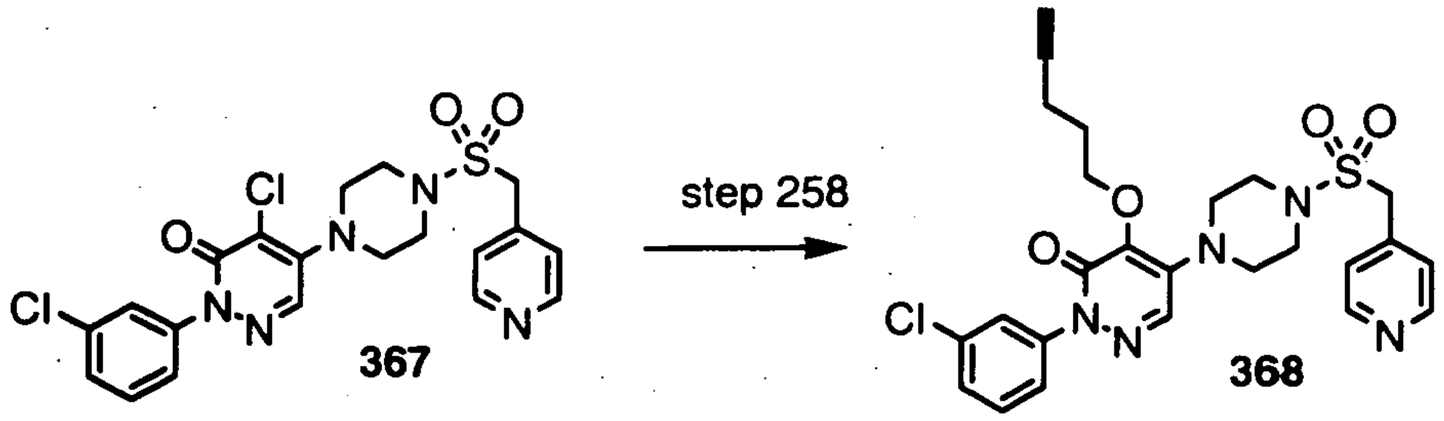
Step 257:



Compound **361** (1.06 g, 2.9 mmol) dissolved in CH_2Cl_2 (20 mL) was mixed with diisopropylethylamine (0.6 mL) at 0 °C. 4-Pyridylmethanesulfonyl chloride TfOH (1.0 g, 2.9

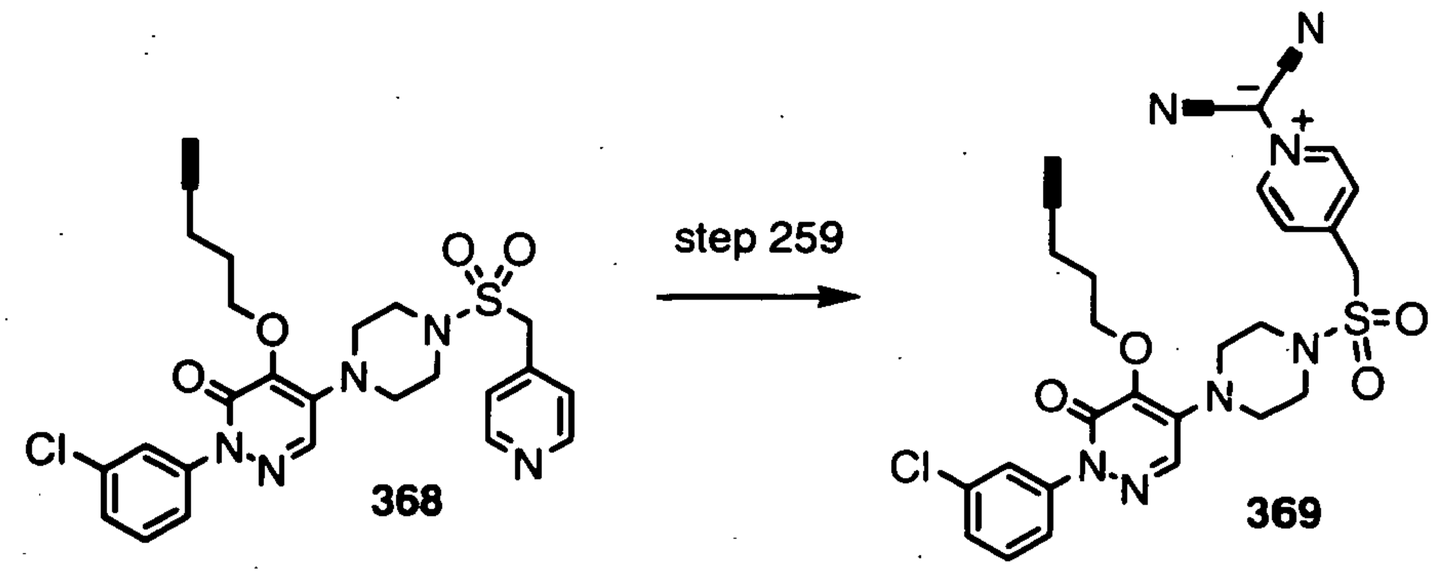
mmol) was added. The mixture was stirred at room temperature overnight then diluted with ethyl acetate (100 mL). The organic solution was washed with water then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography gave 0.81 g (59% yield) of the product **367** as a solid. MS (M+1): m/e 480.

Step 258:



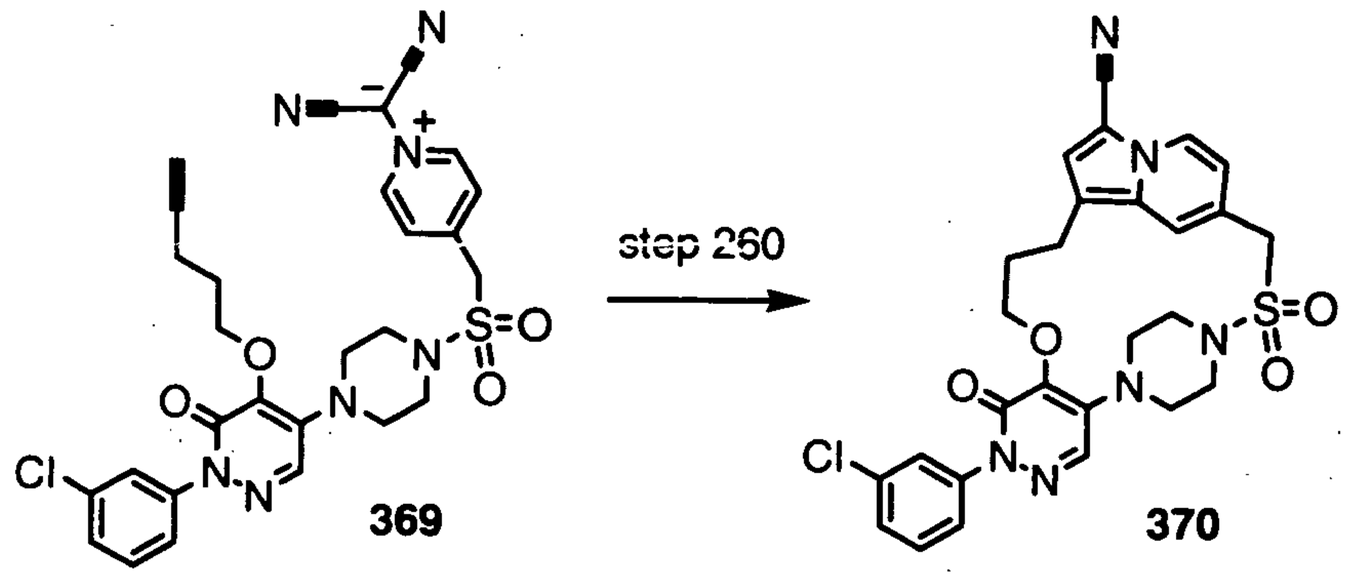
Compound **367** (0.1 g, 0.21 mmol) and 4-pentyn-1-ol (0.06 mL, 0.63 mmol) in dry THF (3 mL) were mixed with 60% NaH (12 mg, 0.3 mmol). The mixture was stirred at room temperature for 2 h then diluted with ethyl acetate. The organic solution washed with water then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography gave 0.081 g (73% yield) of the product **368** as a solid. MS (M+1): m/e 528.

Step 259:



Compound **368** (90 mg. 0.17 mmol) in dry THF (5 mL) was mixed with TCNEO (tetracyanoethylene oxide, 0.1 g). The resulting mixture was then stirred at room temperature overnight then concentrated. Purification by prep Gilson HPLC gave 62 mg (62% yield) of the product **369** as a bright yellow solid. MS (M+1): m/e 592.

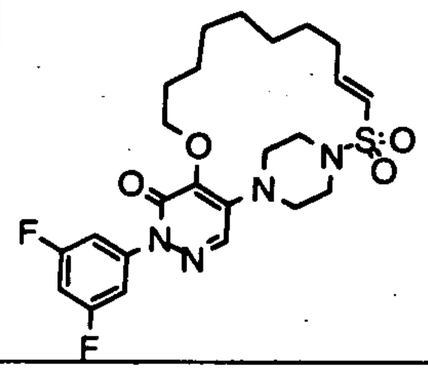
Step 260:



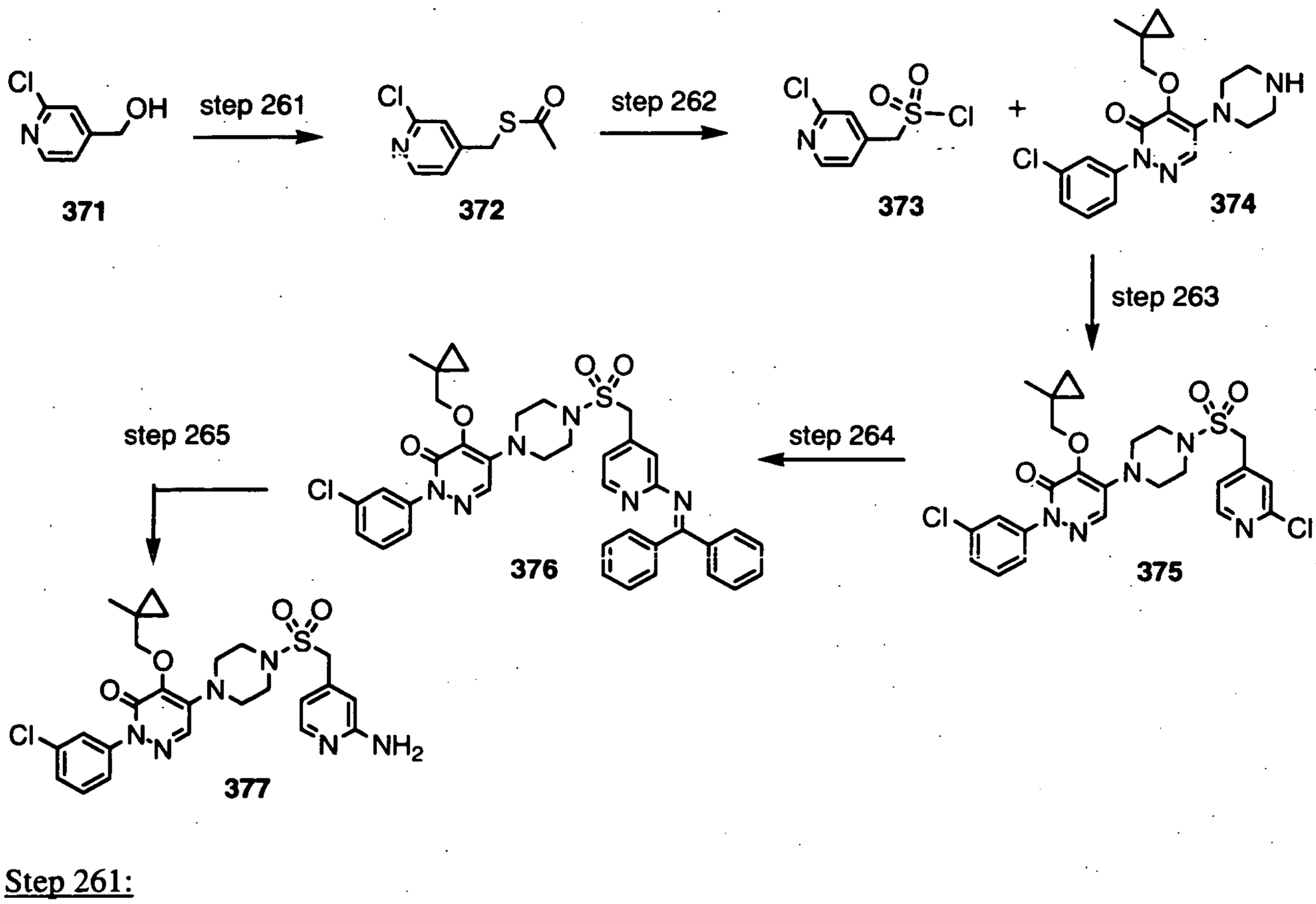
369 370

Compound **369** (20 mg, 0.034 mmol) in 3 mL of toluene and 0.5 mL of acetonitrile was heated to 180 °C for 15 mins in a microwave reactor. The mixture was concentrated and then purified by prep Gilson HPLC to give 9.5 mg (50% yield) of the product **370**. MS (M+1): m/e 565.

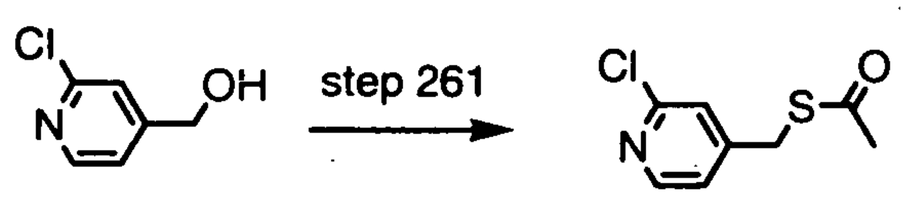
Using the procedure above, the following compound was synthesized.

Cmpd.	Structure	MS M+1
2022Z		509

Scheme 80

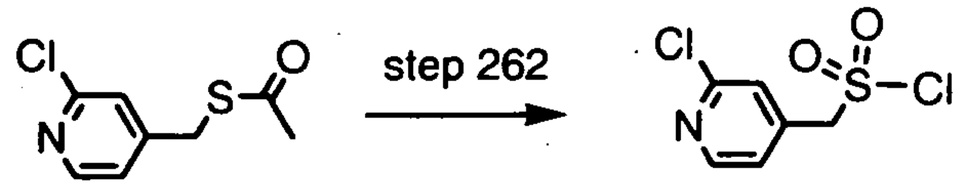


Step 261:



Compound **371** (2.15 g, 15 mmol) was mixed with triphenylphosphine (5.24 g, 20 mmol) and thioacetic acid (1.2 mL, 16 mmol) in dry THF (20 mL). DIAD (diisopropyl azodicarboxylate, 3.9 mL, 20 mmol) was added at 0 °C. The mixture was stirred at room temperature for 6 h and then concentrated. Purification by flash chromatography gave 1.9 g (63% yield) of the product **372** as a solid. MS (M+1): m/e 202.

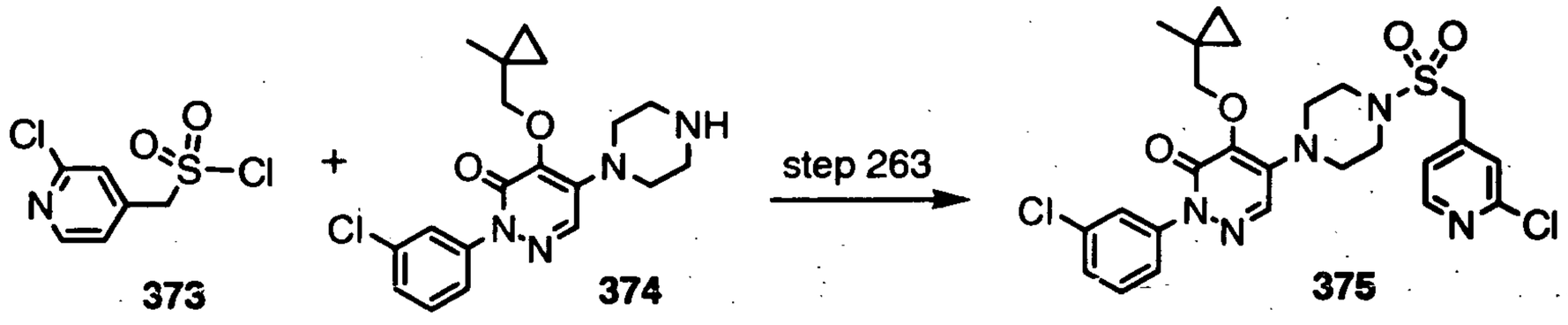
Step 262:



Compound **372** (0.35 g, 1.7 mmol) was mixed with water (0.09 mL, 5 mmol) and trifluoromethanesulfonic acid (0.3 mL, 3.4 mmol) in CH_2Cl_2 (15 mL) and cooled to 0 °C.

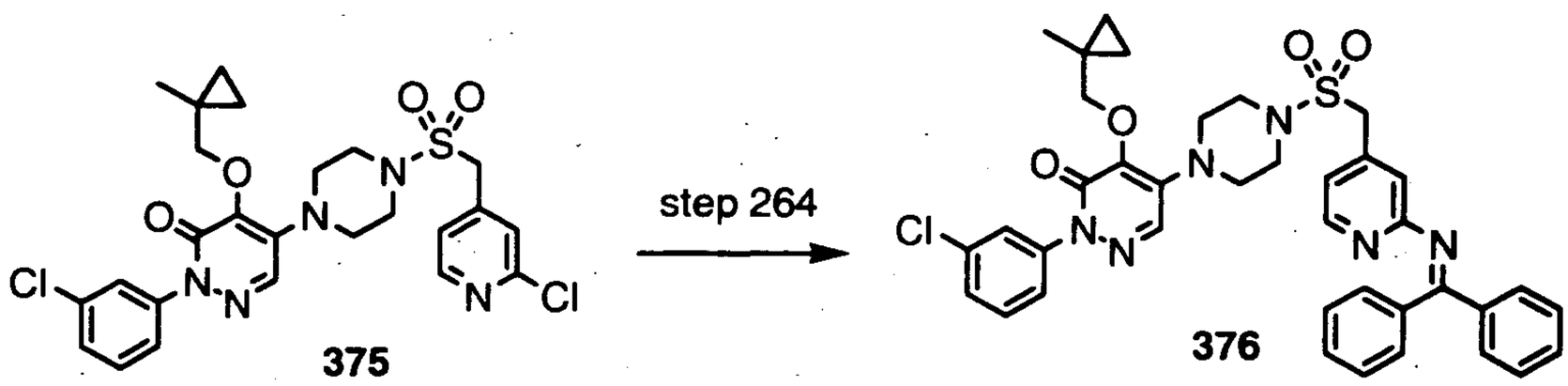
Chlorine gas was bubbled into the solution for 5 mins. The yellow solution was stirred at 0 °C for 1 h. Dry diethyl ether and hexane were added to the mixture, which was immediately cooled to -78 °C. A solid formed at the bottom of the solution, and the solvent was decanted. The solid was washed again with cold hexane, cooled to -78 °C, and the solvent was decanted to give the sulfonyl chloride product **373** as the triflate salt which was used in the next step immediately.

Step 263:



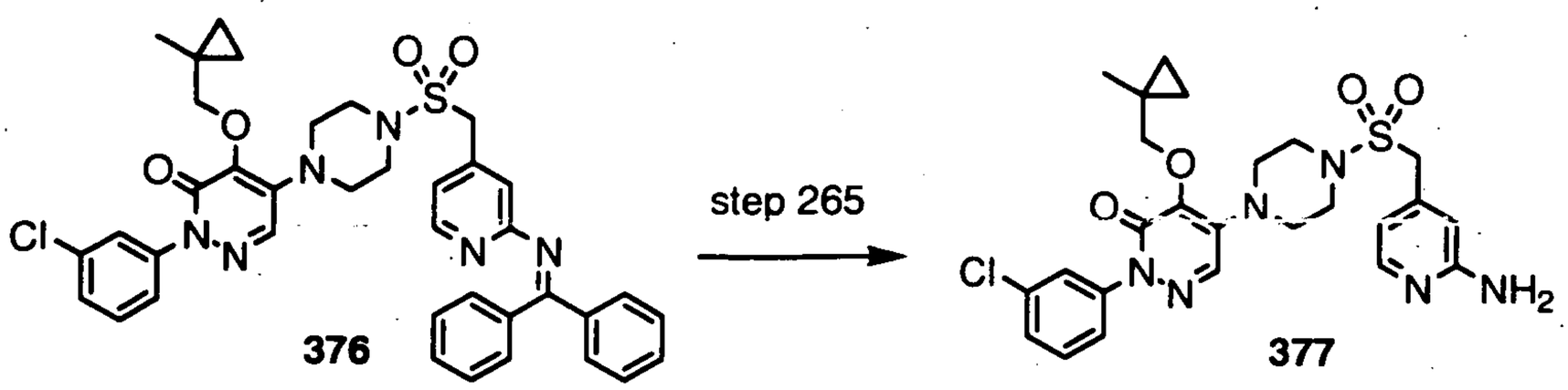
Compound **373** (~ 1.7 mmol) at -78 °C was mixed with compound **374** (750 mg, 2 mmol) and diisopropylethylamine (5 mmol) in CH_2Cl_2 (10 mL) The mixture was stirred at room temperature overnight then diluted with ethyl acetate (100 mL). The organic solution was washed with water then brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography gave 0.26 g (27% yield) of the product **375** as a solid. MS (M+1): m/e 564.

Step 264:



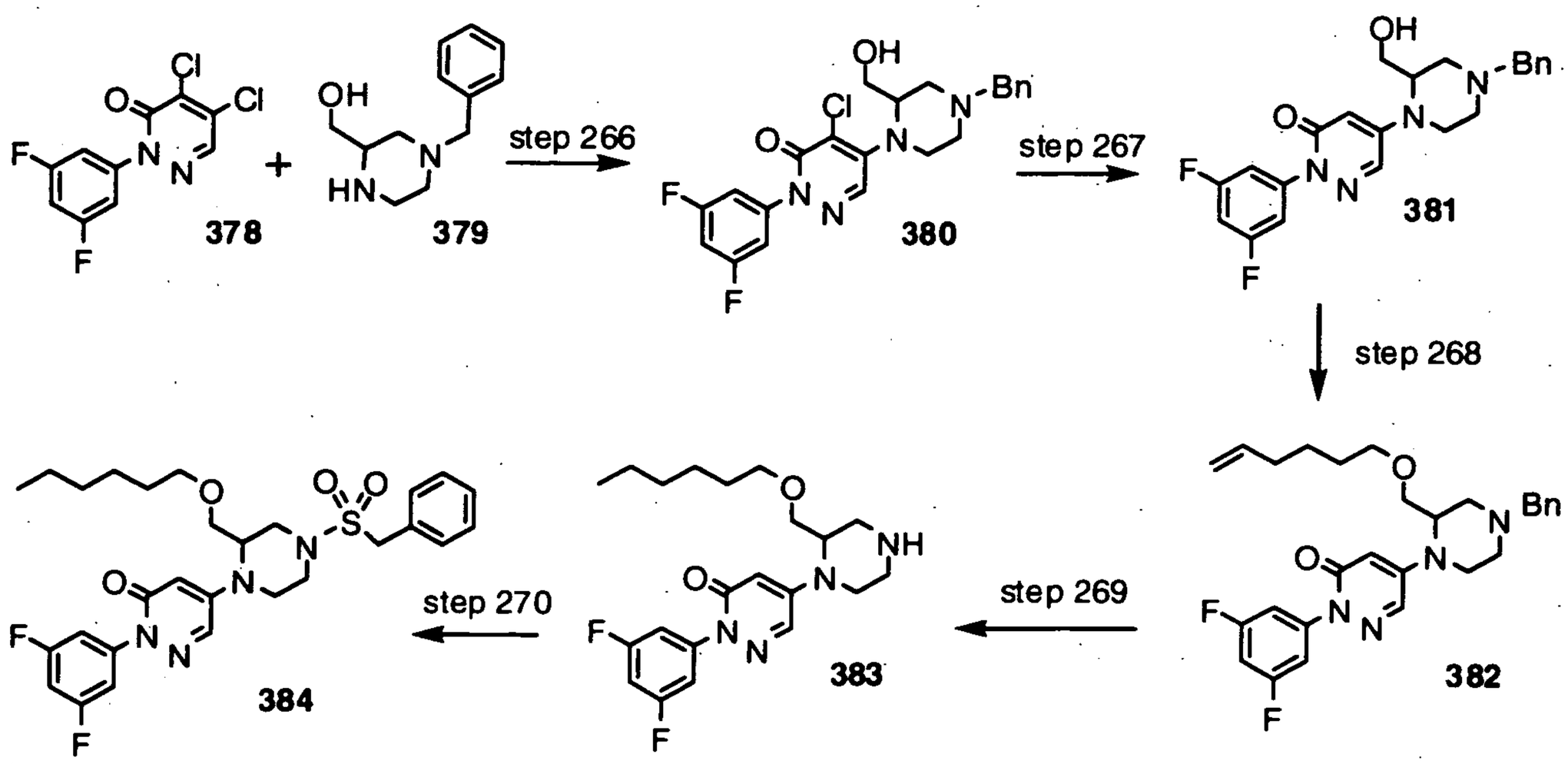
Compound **375** (35 mg) was mixed with palladium acetate (0.5 mg), BINAP (1.5 mg), benzophenone imine (20 mg), and cesium carbonate (100 mg). The mixture was heated to at 90 °C under nitrogen overnight then diluted with EtOAc (50 mL). The organic solution was washed with water then brine, dried, filtered, and concentrated. The crude product **376** was used in the next step without further purification.

Step 265:

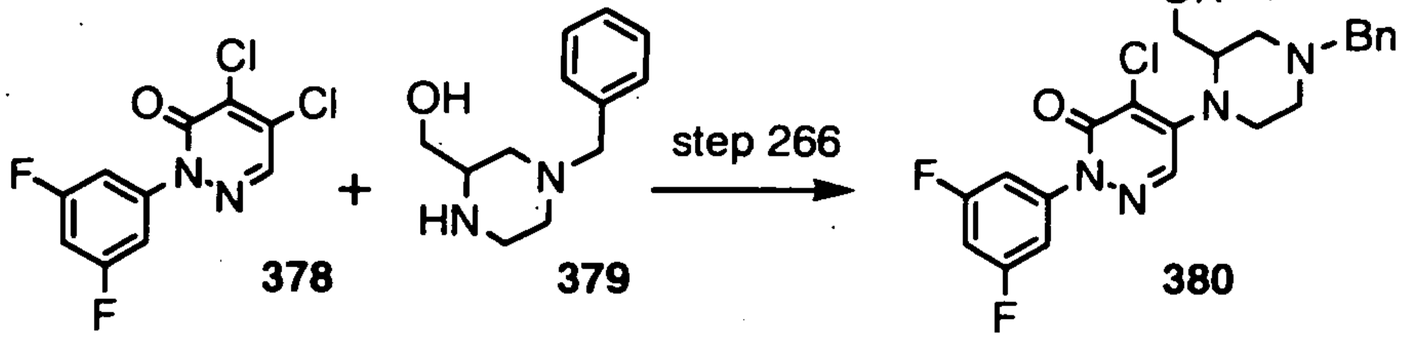


Compound **376** was treated with sodium acetate (0.1 g) and hydroxylamine hydrochloride (0.1 g) in methanol (3 mL) at room temperature for 1 h. The mixture was concentrated and then purified by prep Gilson HPLC to give 12 mg of the product **377** as the formate salt. MS (M+1): m/e 545.

Scheme 81



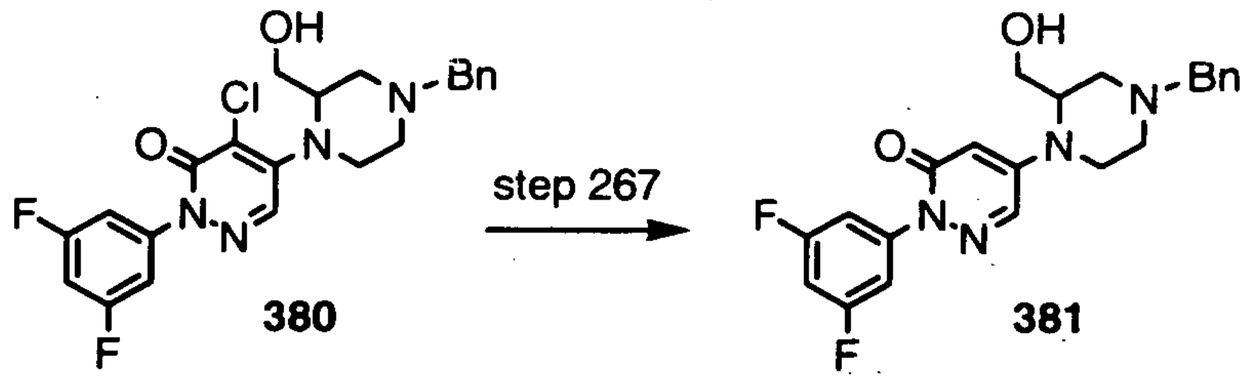
Step 266:



N-benzylhydroxymethylpiperazine was prepared according to the reported literature procedure: A. Naylor et al, *J. Med. Chem.* **1993**, *36*, 2075-2083. To compound **379** (2.48 g, 12.00 mmol), which was dried just before use by azeotropic distillation with toluene under reduced pressure, dissolved in anhydrous DMF (24 mL) under an argon atmosphere was

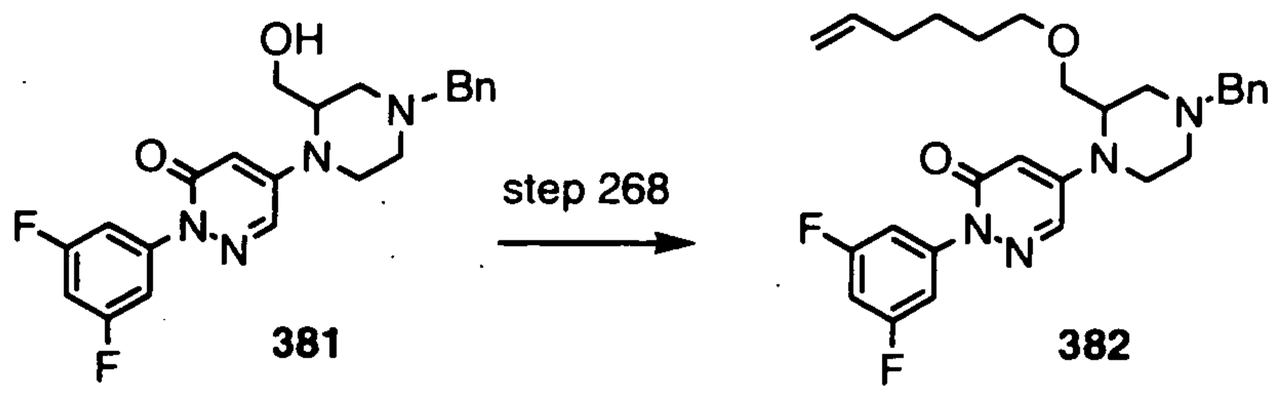
successively added *N*,*N*-diisopropylethylamine (3.15 mL, 17.95 mmol), 4 Å molecular sieves and dichloropyridazinone **378** (1.68 g, 5.98 mmol). The reaction mixture was heated at 100 °C for 23 h. Upon cooling to room temperature, the mixture was poured into an aqueous pH 7 phosphate buffer solution (400 mL) and diluted with ethyl acetate (300 mL). After decantation, the aqueous solution was extracted with ethyl acetate (3 x 350 mL). The combined organic extract was successively washed with water (400 mL) then brine (400 mL), dried ($MgSO_4$), filtered, and concentrated. The crude oil was recrystallized from boiling ethyl acetate (250 mL), filtered and rinsed with cold methylene chloride (70 mL) to give 1.08 g of the product **380** (41% yield) as an off-white solid. MS (M+1): m/e 447.

Step 267:



To chloropyridazinone **380** (100.0 mg, 0.224 mmol) dissolved in ethyl acetate (0.84 mL) and methanol (0.28 mL) at room temperature was added platinum oxide (20.4 mg, 0.090 mmol). A hydrogen atmosphere was introduced using a rubber balloon as the gas source, and the reaction mixture was stirred at room temperature for 6 h. The crude suspension was filtered over a ¼ inch celite pad under a positive pressure of nitrogen, thoroughly rinsed with methanol (50 mL) and concentrated. Purification by silica gel chromatography (eluant: 100% CH_2Cl_2 to 100% EtOAc gradient) gave 19.6 mg (20% yield) of the product **381** as a pale yellow oil. MS (M+1): m/e 413.

Step 268:



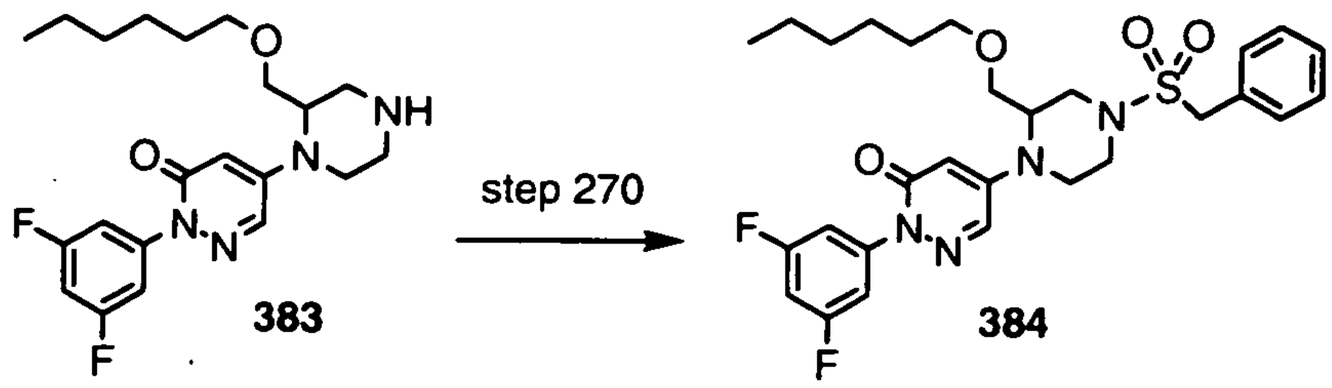
To compound **381** (19.0 mg, 0.045 mmol), dissolved in anhydrous THF (0.45 mL) under an argon atmosphere at 0 °C was added tetrabutylammonium iodide (16.6 mg, 0.045 mmol), followed by 6-bromo-1-hexene (30.1 µL, 0.225 mmol). Sodium hydride was then added (60% dispersion in oil, 3 mg, ca. 0.068 mmol). The milky reaction mixture was then

vigorously stirred at room temperature. Additional portions of 6-bromo-1-hexene (30.1 µL, 0.225 mmol) and NaH (60% dispersion in oil, 3 mg, ca. 0.068 mmol) were added until complete consumption of starting material was indicated by TLC and MS. The reaction mixture was diluted with Et_2O (30 mL) and carefully quenched with an aqueous pH 7 phosphate buffer solution (20 mL). The aqueous solution was extracted with Et_2O (3 x 30 mL). The combined organic extract was washed successively with an aqueous pH 7 phosphate buffer solution (30 mL) then brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give 23.7 mg (98% yield) of the product **382** as a light yellow oil which was used for the next step without purification. MS (M+1): m/e 495.

Step 269:

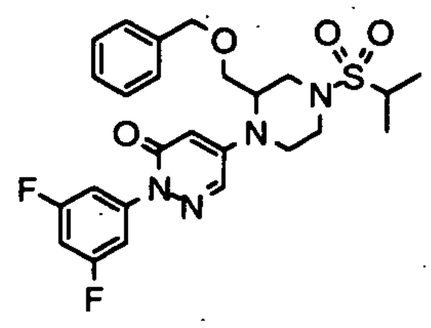
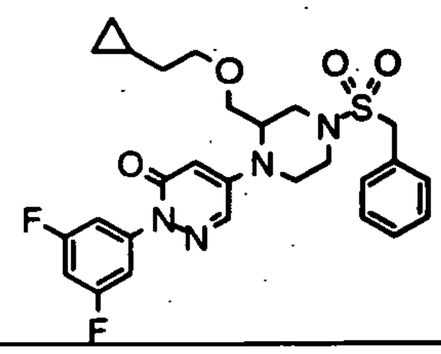
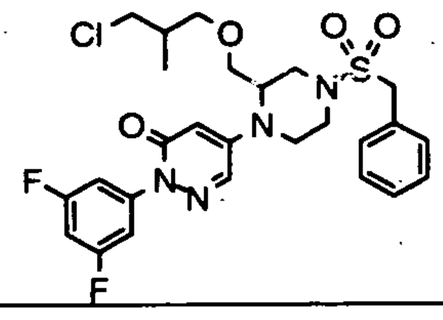
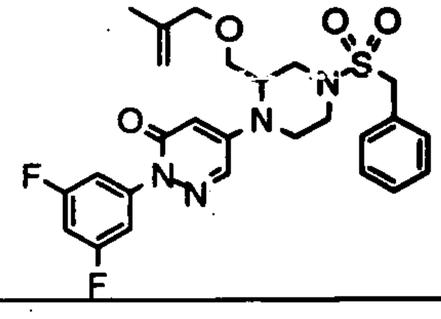
To compound **382** (23.7 mg, 0.045 mmol) dissolved in a methanolic solution of formic acid (v/v 5%, 0.45 mL) at room temperature was added 5% palladium over carbon (37.0 mg). The reaction mixture was vigorously stirred for 4 h, after which an additional portion of 5% Pd-C (20 mg) and methanolic solution of formic acid (v/v 5%, 0.10 mL) were added. After 3 h of additional stirring, the crude suspension was filtered over a celite pad under a positive pressure of nitrogen, thoroughly rinsed with methanol (50 mL) and concentrated to give 10.8 mg of crude oil containing the product **383**. MS (M+1): m/e 407. This material was used for the next step without purification.

Step 270:

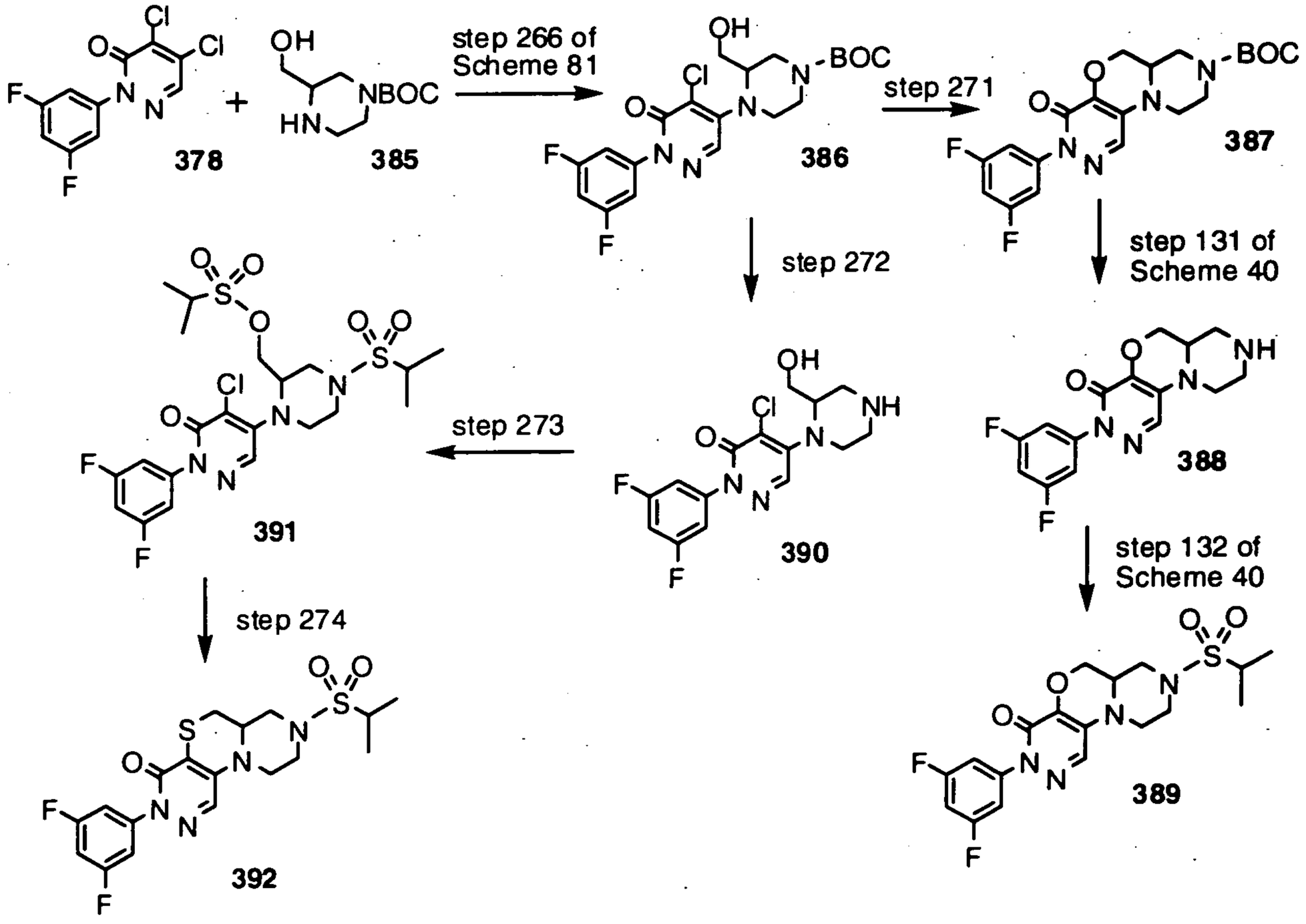


To compound **383** (10.8 mg of crude material from step 269, ca. 0.045 mmol) dissolved in CH_2Cl_2 (0.25 mL) was successively added triethylamine (10 µL, 0.062 mmol) and α-toluenesulfonyl chloride (7.1 mg, 0.037 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h and then concentrated to dryness. Purification by silica gel

chromatography (eluant: 100% hexanes to 100% EtOAc gradient) gave 2.8 mg (21% yield over steps 267 and 270 combined) of the product **384** as a white solid. MS (M+1): m/e 561. Using procedures similar to the ones described above, the following compounds were synthesized.

Cmpd. No	Structure	MS M+1	Cmpd. No.	Structure	MS M+1
2023Z		519	2024Z		545
2025Z		567	2026Z		531

Scheme 82

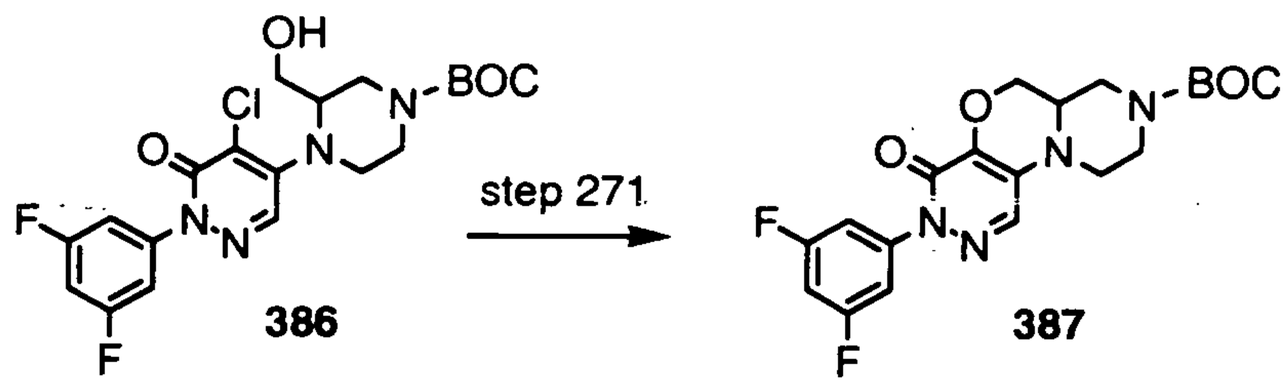


Step 266 from Scheme 81:

378 **385** **386**

Using the procedure of step 266 from Scheme 81, compound **386** was synthesized. MS (M+1): m/e 457.

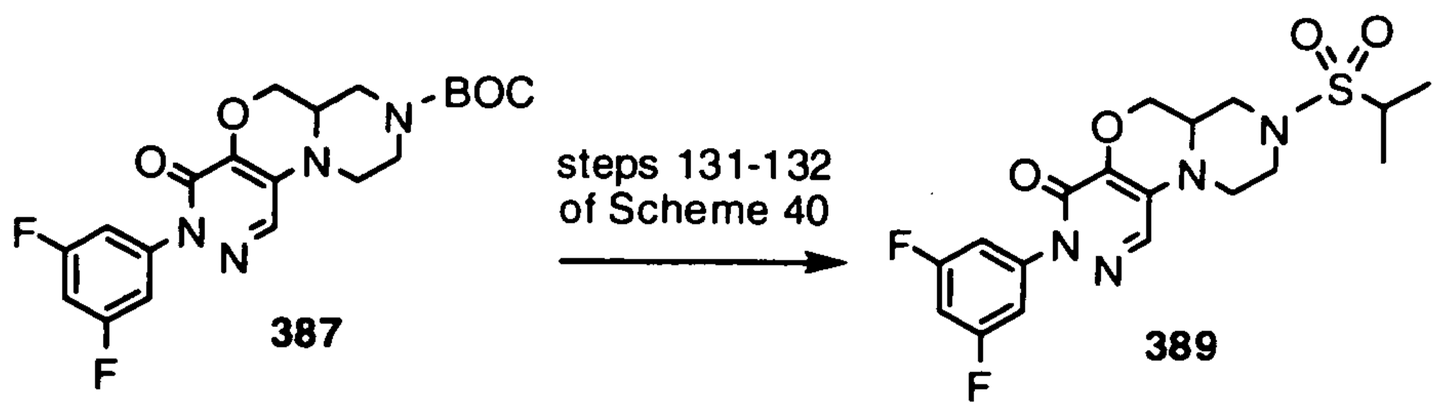
Step 271:



386 **387**

To chloropyridazinone **386** (176 mg, 0.385 mmol) dissolved in dry THF (10 mL) was added sodium hexamethyldisilazide (1.0 M in THF, 2.0 mL, 2.0 mmol). The reaction mixture was stirred at room temperature for 16 h. Saturated NH_4Cl (5 mL) and water were added, and the aqueous solution was extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc - hexanes gradient) gave 58 mg (36% yield) of the product **387** as a yellow solid. MS (M+1): m/e 421.

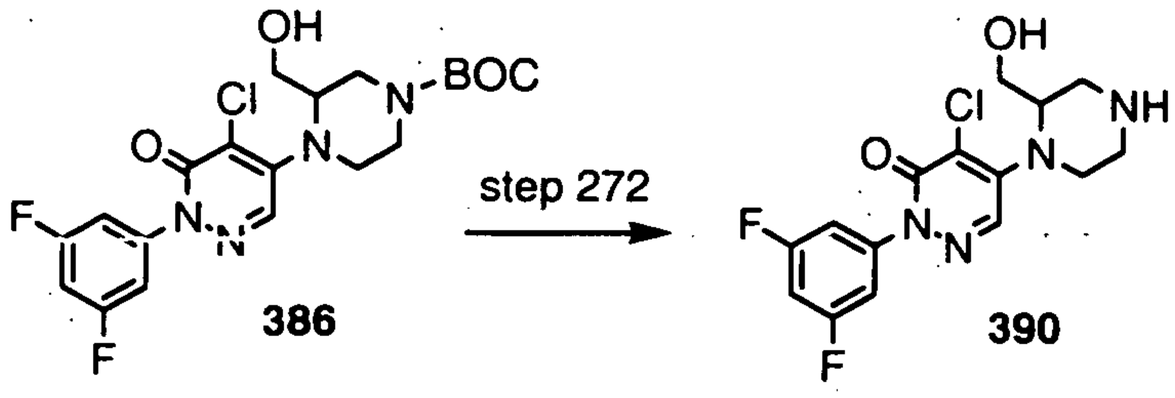
Steps 131-132 from Scheme 40:



387 **389**

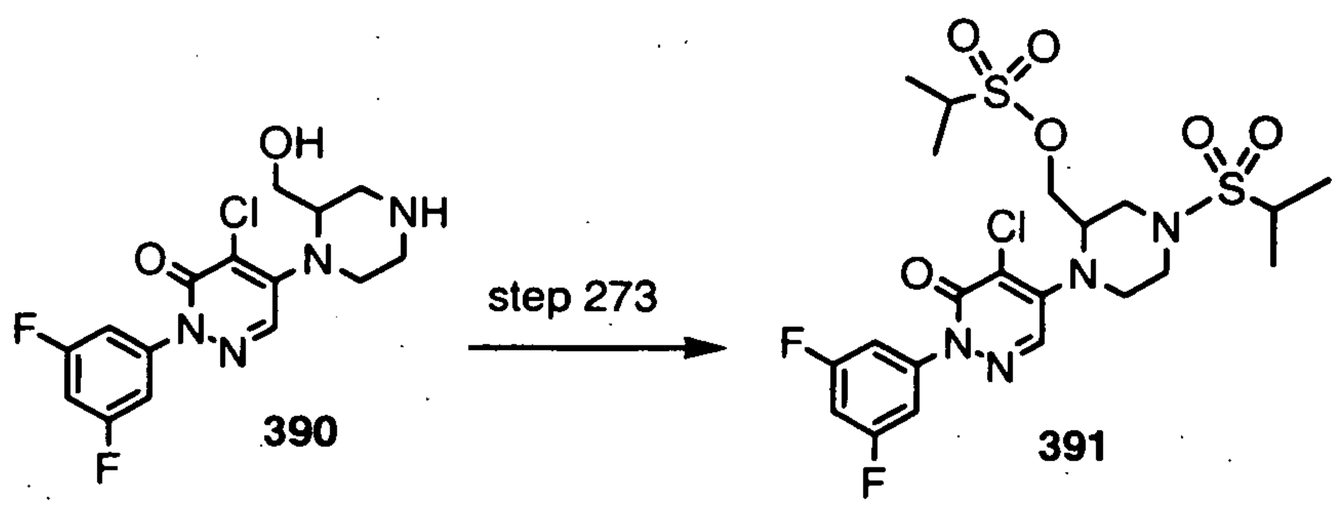
Using the procedures of steps 131-132 from Scheme 40, compound **389** was synthesized. MS (M+1): m/e 427.

Step 272:



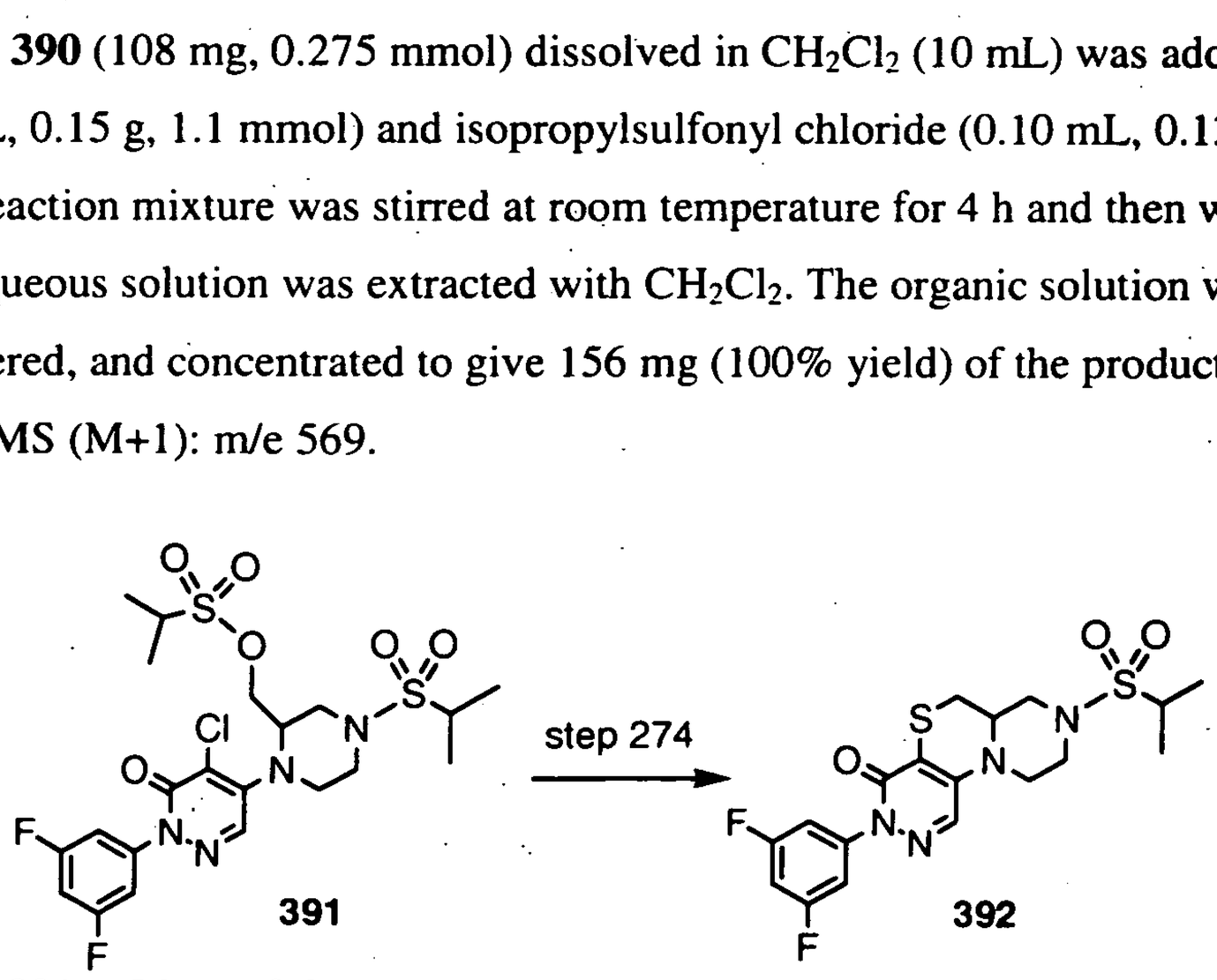
To compound **386** (250 mg, 0.547 mmol) dissolved in CH_2Cl_2 (20 mL) was added 4 N HCl in dioxane (2 mL, 8 mmol). The reaction mixture was stirred at room temperature for 4 h then concentrated. Additional MeOH and CH_2Cl_2 were added, and the solution was concentrated again to give 215 mg (100% yield) of the product **390** as the hydrochloride salt as a white solid. MS (M+1): m/e 357.

Step 273:



To compound **390** (108 mg, 0.275 mmol) dissolved in CH_2Cl_2 (10 mL) was added Hunig's base (0.20 mL, 0.15 g, 1.1 mmol) and isopropylsulfonyl chloride (0.10 mL, 0.13 g, 0.89 mmol). The reaction mixture was stirred at room temperature for 4 h and then water was added. The aqueous solution was extracted with CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered, and concentrated to give 156 mg (100% yield) of the product **391** as an orange solid. MS (M+1): m/e 569.

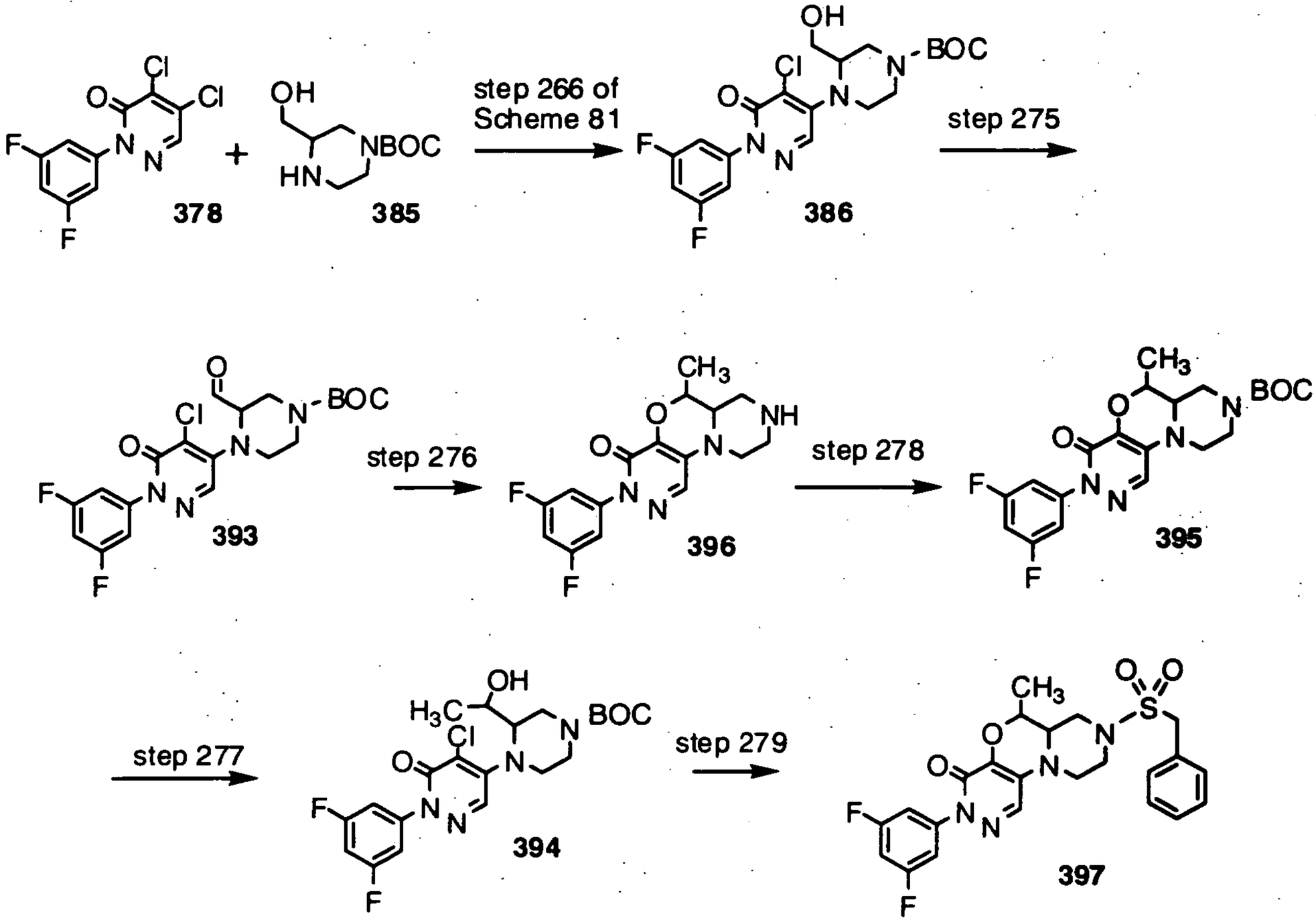
Step 274:



To compound **391** (156 mg, 0.275 mmol) dissolved in dry DMSO (3 mL) was added disodiumsulfide (108 mg, 0.450 mmol). The reaction mixture was stirred at room temperature

for 16 h and then water was added. The aqueous solution was extracted with EtOAc. The organic solution was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: 50% EtOAc in hexanes) gave 30 mg (25% yield) of the product **392** as an oil. MS (M+1): m/e 443.

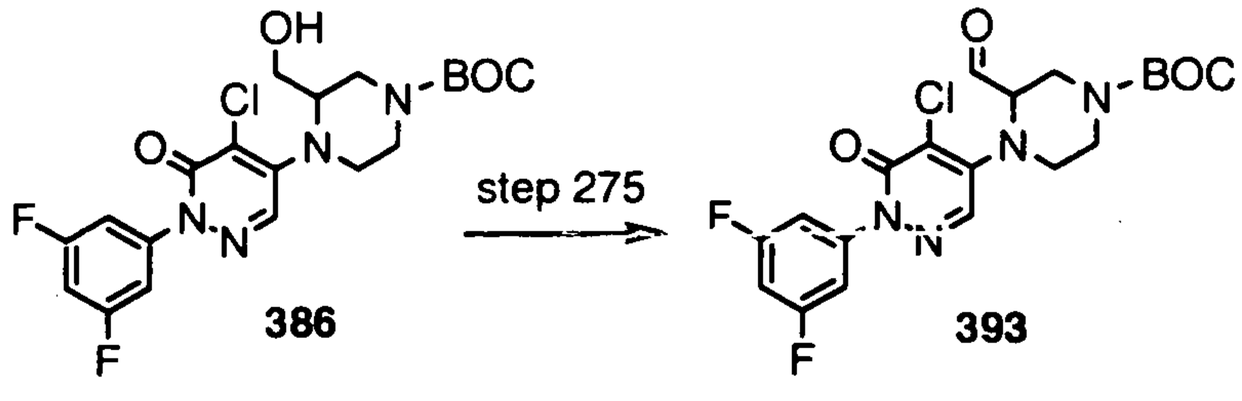
Scheme 83



Step 266 from Scheme 81:

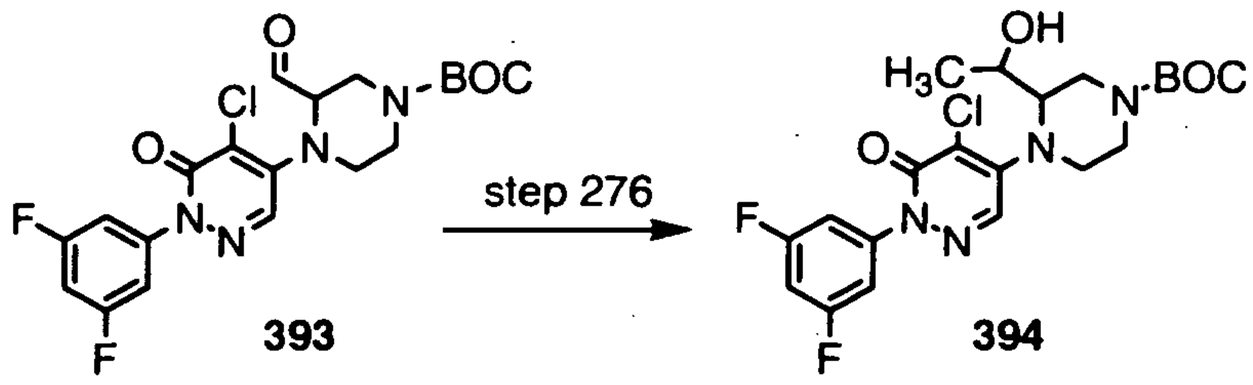
Using the procedure of step 266 from Scheme 81, compound **386** was synthesized. MS (M+1): m/e 457.

Step 275:



To oxalyl chloride (33.0 µL, 0.394 mmol) in anhydrous methylene chloride (0.20 mL) at –78 °C was added dropwise a solution of anhydrous DMSO (58.0 µL, 0.788 mmol) in anhydrous methylene chloride (0.20 mL). After stirring for 10 mins, chloropyridazinone **386** (100.0 mg, 0.197 mmol) suspended in anhydrous methylene chloride (1.00 mL) was added using a canula. After 40 mins additional stirring at –78 °C, anhydrous triethylamine (220.0 µL, 1.576 mmol) was added, and the reaction mixture was allowed to warm up to –10 °C over 1 h. The reaction mixture was then quenched with an aqueous pH 7 phosphate buffer solution (20 mL) and diluted with ethyl acetate (30 mL). After decantation, the aqueous solution was extracted with diethyl ether (2 x 30 mL) and finally once with ethyl acetate (30 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (40 mL), water (40 mL) and then brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc – methylene chloride gradient) gave 34.9 mg (39% yield) of the product **393** as a yellow solid. MS (M+1): m/e 455.

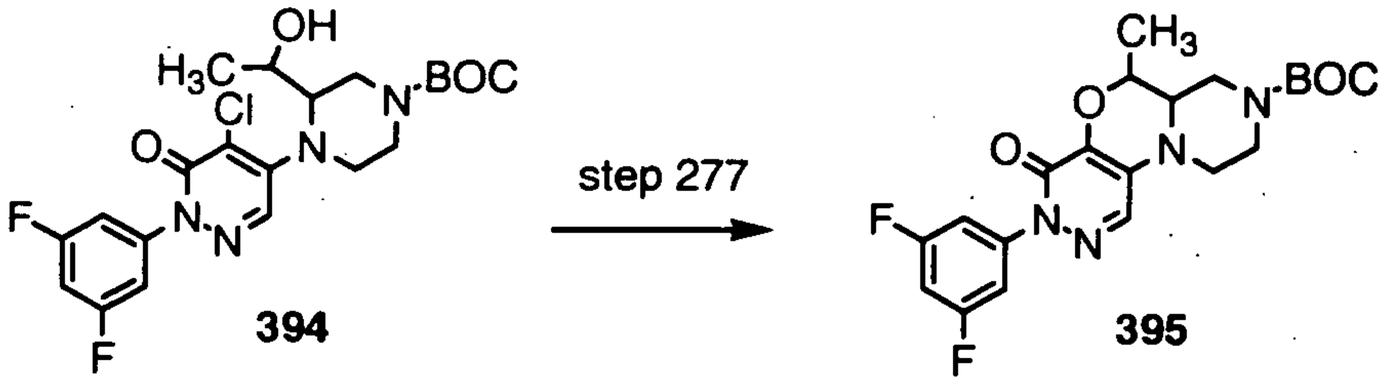
Step 276:



To chloropyridazinone **393** (63.5 mg, 0.138 mmol), which was dried just before use by azeotropic distillation with toluene under reduced pressure, dissolved in anhydrous THF (1.20 mL) at –40 °C was added dropwise a solution of methylmagnesium bromide (116.0 µL, 3.0 M in diethyl ether). After 40 mins, the reaction mixture was quenched at –40 °C with an aqueous pH 7 phosphate buffer solution (20 mL) and diluted with ethyl acetate (20 mL). After decantation, the aqueous solution was extracted with ethyl acetate (2 x 40 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (40 mL), and then brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. The

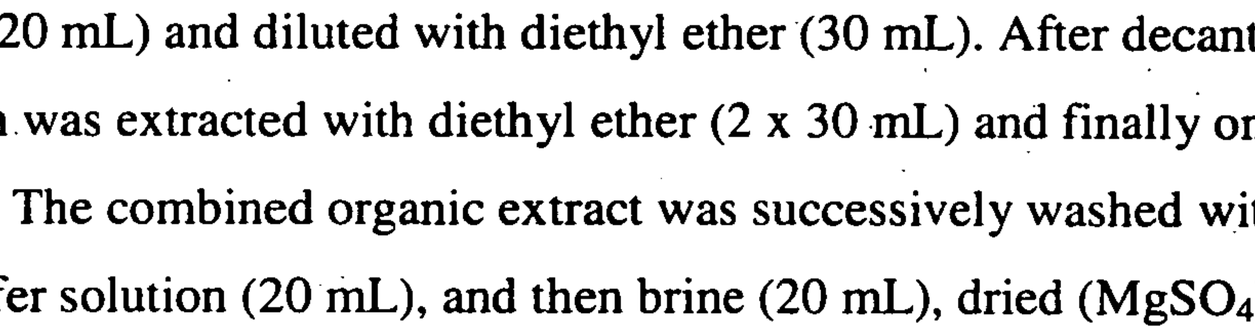
crude material (82.1 mg, obtained with trace-amount of residual solvents) showed exclusively the product **394** by MS and NMR and was used for the next step without additional purification. MS (M+1): m/e 471

Step 277:



To compound **394** (80.0 mg, ca 0.112 mmol crude), which was dried just before use by azeotropic distillation with toluene under reduced pressure, dissolved in anhydrous THF (11.20 mL) at room temperature was added sodium hydride (4.5 mg, 60% dispersion in oil, 0.112 mmol), followed by palladium acetate (1.3 mg, 0.0056 mmol) and *rac*-BINAP (3.5 mg, 0.0056 mmol). After stirring for 3 h at room temperature, sodium hydride (2.0 mg, 60% dispersion in oil, 0.050 mmol) was then added, and the mixture was heated to 35 °C for an additional 3 h period. The reaction mixture was quenched with an aqueous pH 7 phosphate buffer solution (20 mL) and diluted with diethyl ether (30 mL). After decantation, the aqueous solution was extracted with diethyl ether (2 x 30 mL) and finally once with ethyl acetate (40 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (20 mL), and then brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc – methylene chloride gradient) gave 49.2 mg of a mixture of alcohol **394** (31% yield based on **393**) and the product **395** (40% yield over two steps) as a yellow oil. MS for **395** (M+1): m/e 435. Further purification is possible but the mixture was used as such for the next step.

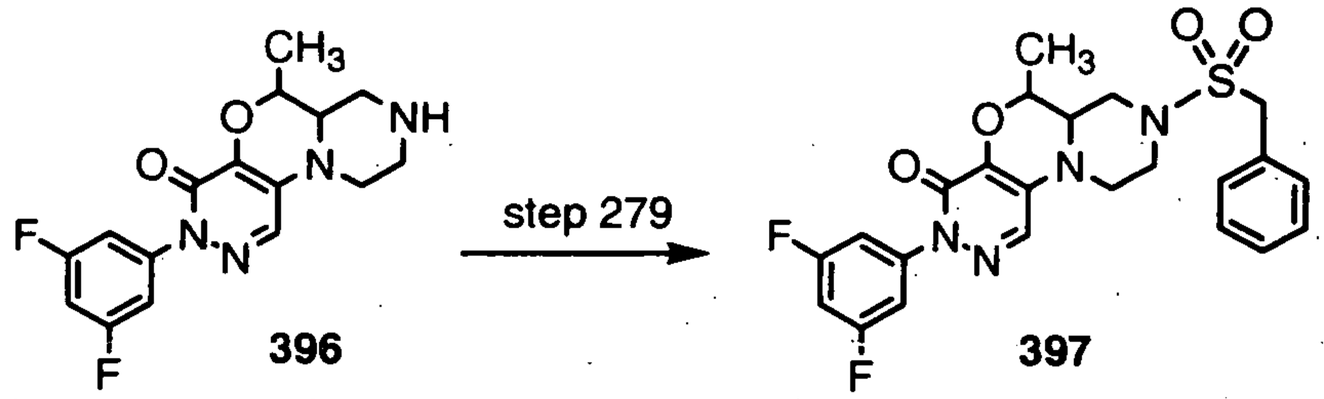
Step 278:



To compound **395** (48.0 mg of a mixture with **394**, 0.098 mmol total), dissolved in dry methylene chloride (0.80 mL) was added TFA (0.14 mL, 1.88 mmol). The reaction mixture was stirred at room temperature for 70 mins and then quenched with a saturated aqueous

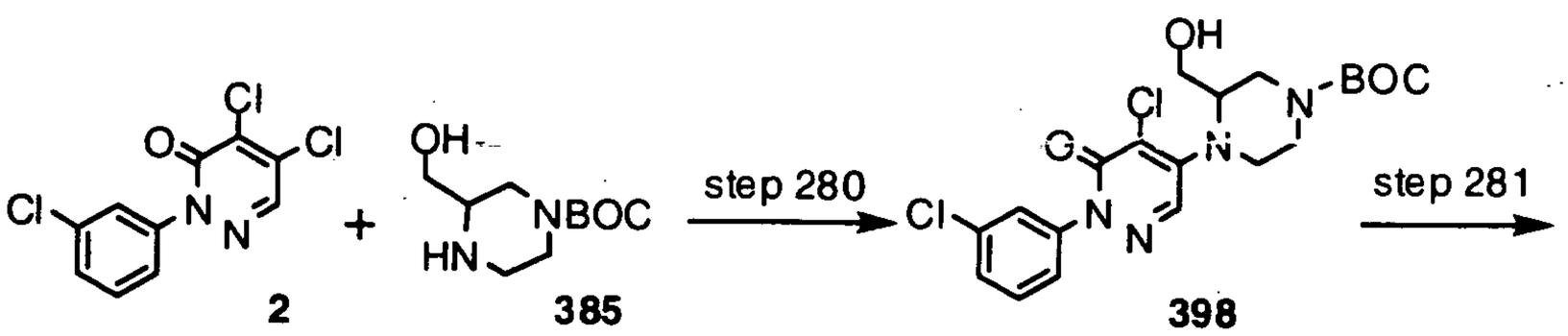
solution of Na_2CO_3 (30 mL) and diluted with ethyl acetate (30 mL). The aqueous solution was extracted with ethyl acetate (3 x 30 mL). The combined organic extract was successively washed with a saturated aqueous solution of Na_2CO_3 (30 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give 37.7 mg of yellow foam which was used for the next step without purification. MS analysis showed exclusively **396** and the amine corresponding to residual **394**. MS for **396** (M+1): m/e 335.

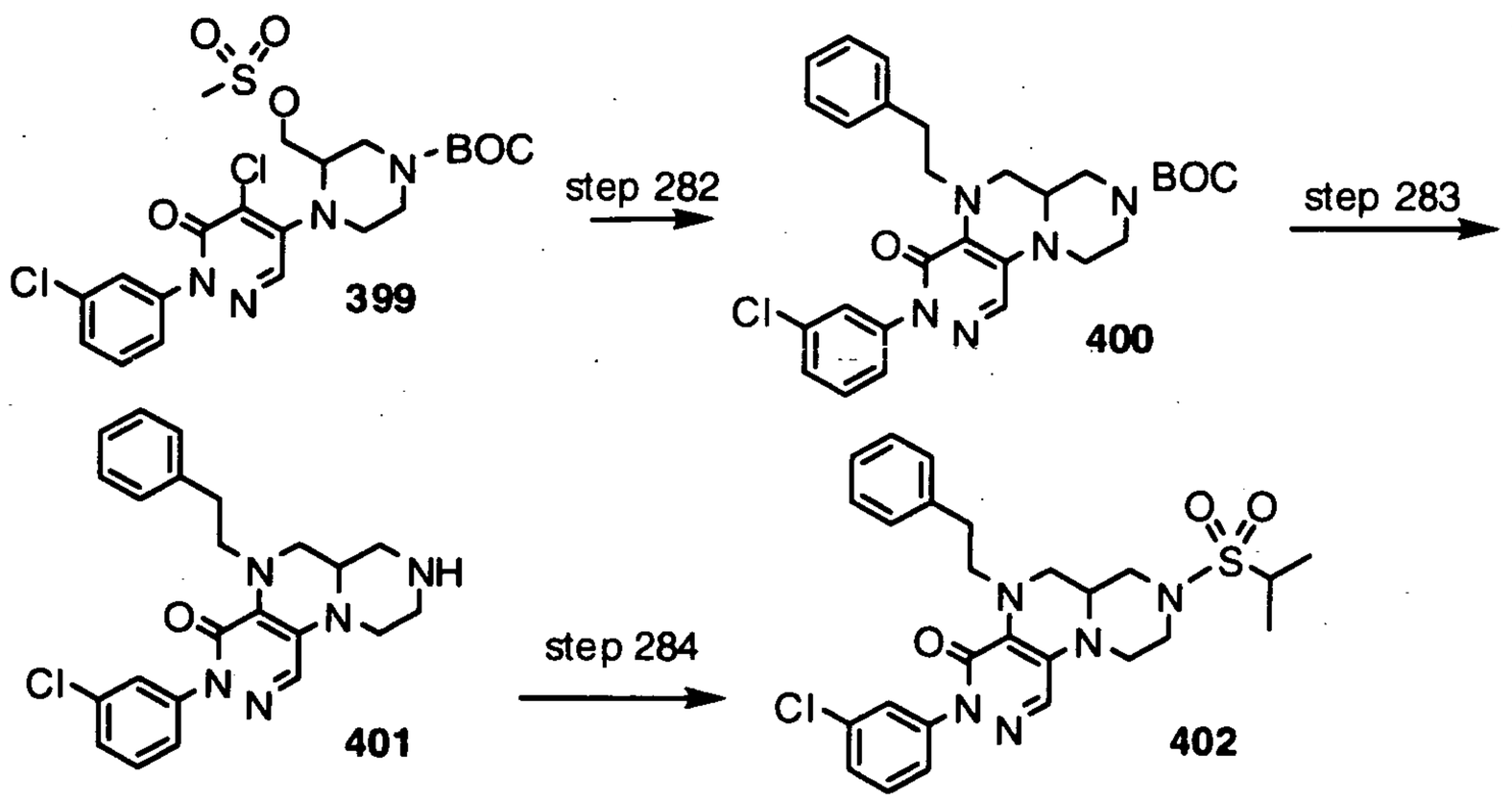
Step 279:



To compound **396** (37.7 mg of mixture, ca 0.090 mmol total), which was dried just before use by azeotropic distillation with toluene under reduced pressure, dissolved in anhydrous CH_2Cl_2 (0.30 mL) was added dry diisopropylethylamine (0.235 mL, 1.35 mmol), followed by α-tosyl chloride (120.0 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 48 h, then quenched with an aqueous pH 7 phosphate buffer solution (25 mL) and diluted with diethyl ether (30 mL). After decantation, the aqueous solution was extracted with ethyl acetate (2 x 35 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (30 mL), and then brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc – methylene chloride gradient) gave 7.8 mg (26% yield) of the product **397** as a yellow glass. MS (M+1): m/e 489.

Scheme 84

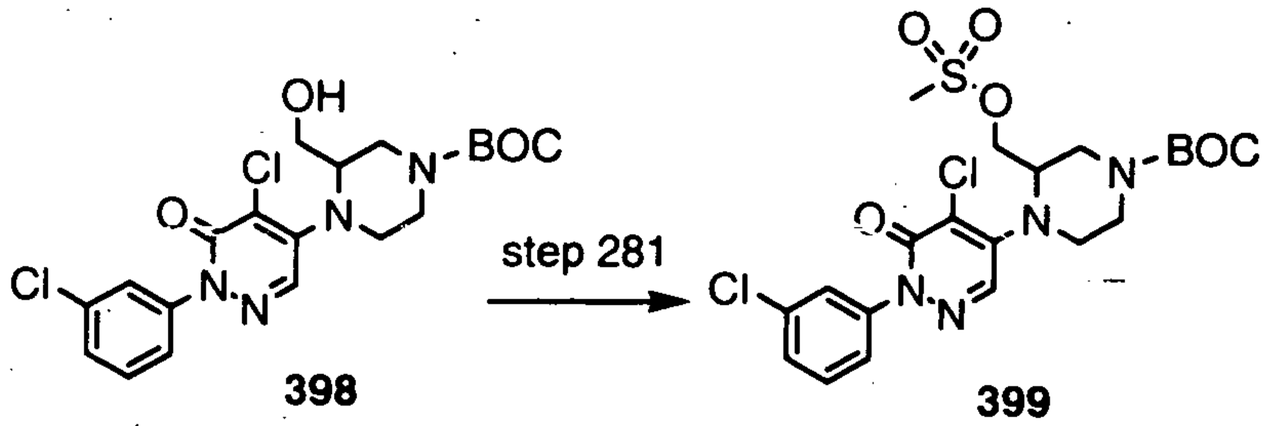




Step 280:

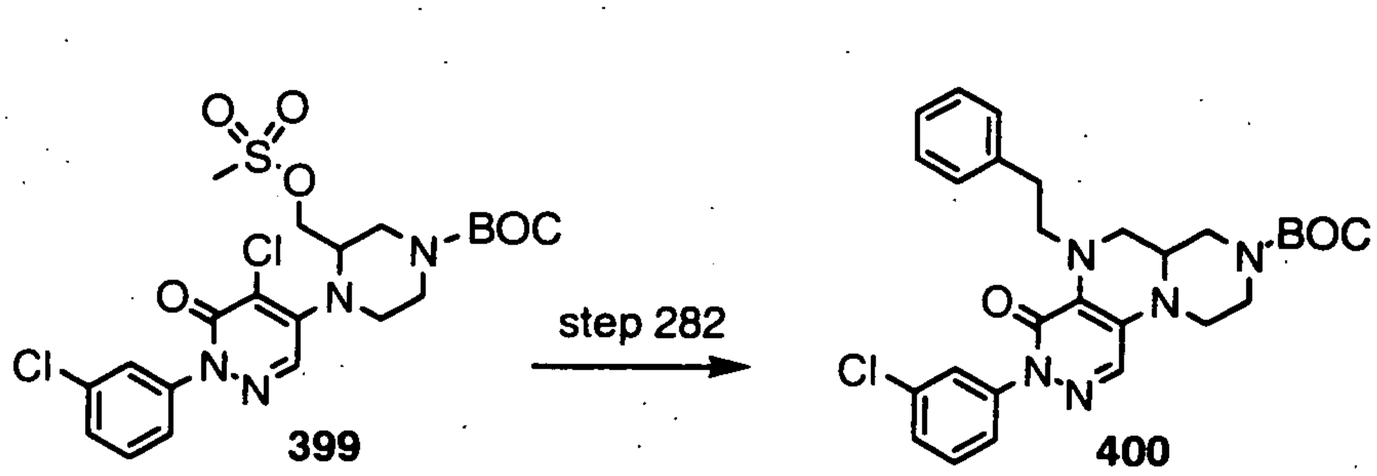
To chloropyridazinone **2** (955.4 mg, 3.47 mmol) and N-BOC hydroxypiperazine **385** (1.50 g, 6.936 mmol) dissolved in anhydrous DMF (13.90 mL) was added 4 Å molecular sieves and dry diisopropylethylamine (1.81 mL, 10.40 mmol). The reaction mixture was heated at 100 °C for 12 h, then cooled down to room temperature, poured onto water (60 mL) and diluted with ethyl acetate (100 mL). After decantation, the aqueous solution was extracted with ethyl acetate (3 x 120 mL). The combined organic extract was successively washed with water (100 mL), and then brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: EtOAc – methylene chloride gradient) gave 1.10 g (70% yield) of the product **398** as a light yellow solid. MS (M+1): m/e 455.

Step 281:



To chloropyridazinone **398** (100.0 mg, 0.210 mmol) dissolved in anhydrous methylene chloride (1.05 mL) at 0 °C was added dry triethylamine (117.0 µL, 0.840 mmol) and methanesulfonyl anhydride (54.9 mg, 0.315 mmol). The reaction mixture was stirred at 0 °C for 30 mins, then quenched with an aqueous pH 7 phosphate buffer solution (20 mL) and diluted with ethyl acetate (20 mL). After decantation, the aqueous solution was extracted with ethyl acetate (2 x 30 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (30 mL), and then brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude light tan solid obtained (123.0 mg, ca. 99% yield) showed exclusively the mesylate **399** by MS and NMR. MS (M+1): m/e 533.

Step 282:



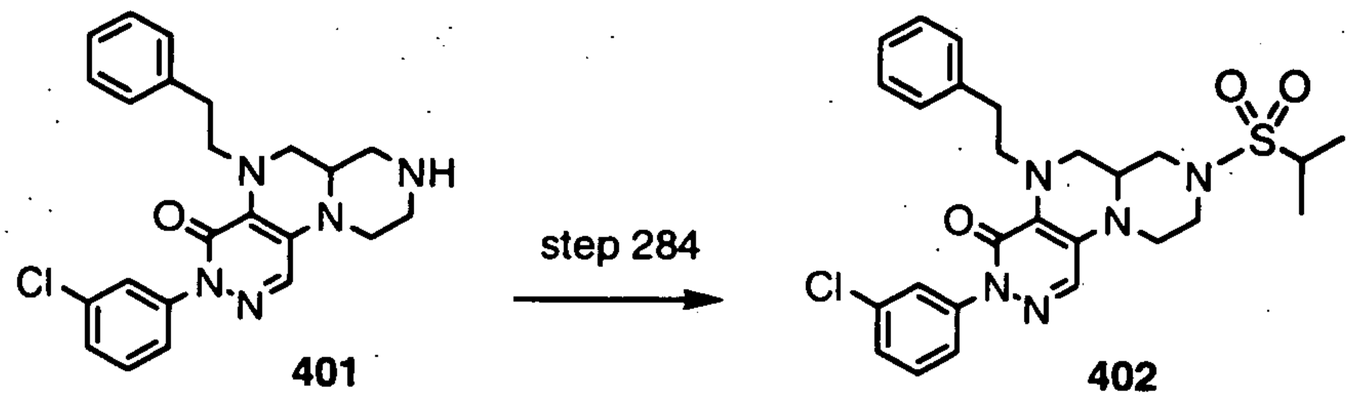
To chloropyridazinone **399** (115.0 mg, 0.210 mmol) dissolved in anhydrous toluene (1.50 mL) was added palladium acetate (2.4 mg, 0.011 mmol) and *rac*-BINAP (6.6 mg, 0.011 mmol), followed by K_2CO_3 (72.6 mg, 0.525 mmol) and phenethylamine (132 µL, 1.05 mmol). The reaction mixture was stirred at 110 °C for 16 h, then cooled to room temperature, quenched with an aqueous pH 7 phosphate buffer solution (20 mL) and diluted with ethyl acetate (20 mL). After decantation, the aqueous solution was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (30 mL), and then brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (eluant: hexanes – ethyl acetate gradient) gave 30.0 mg of the product **400** (25% yield) as a light tan solid. MS (M+1): m/e 522.

Step 283:

400 401

To compound **400** (28.0 mg, 0.051 mmol), dissolved in dry methylene chloride (0.80 mL) was added TFA (0.135 mL, 1.79 mmol). The reaction mixture was stirred at room temperature for 3.5 h, then quenched with a saturated aqueous solution of Na_2CO_3 (20 mL) and diluted with ethyl acetate (30 mL). The aqueous solution was extracted with ethyl acetate (2 x 30 mL). The combined organic extract was successively washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give 23.6 mg of yellow foam which was used for the next step without purification. MS and NMR analysis showed exclusively the product **401** (ca. 91% yield from crude). MS (M+1): m/e 422.

Step 284:



401 402

To compound **401** (23.5 mg, 0.045 mmol), which was dried just before use by azeotropic distillation with toluene under reduced pressure, dissolved in anhydrous methylene chloride (0.75 mL) was added dry diisopropylethylamine (0.118 mL, 0.675 mmol), followed by isopropylsulfonyl chloride (36.0 µL, 0.315 mmol). The reaction mixture was stirred at room temperature for 48 h, then quenched with an aqueous pH 7 phosphate buffer solution (40 mL) and diluted with diethyl ether (25 mL). After decantation, the aqueous solution was extracted with diethyl ether (3 x 30 mL) and finally with ethyl acetate (2 x 50 mL). The combined organic extract was successively washed with an aqueous pH 7 phosphate buffer solution (30 mL), and then brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by reverse phase HPLC (eluant: H_2O – acetonitrile gradient) gave 7.0 mg (28% yield) of the product **402** as a light yellow glass. MS (M+1): m/e 528.

Results of the in vitro fungal enzyme activity assay for representative compounds of Formula I are listed in Table 40:

Table 40: Biological Data

Compound No.	IC_{50} (μg/mL) *Saccharomyces cerevisiae*	IC_{50} (μg/mL) *Candida albicans*
1Z	NT	10
7Z	0.34	1.1
11Z	1.2	6.2
19Z	0.081	1.7
25Z	NT	48
30Z	0.4	9
47Z	0.025	0.23
61Z	0.32	1.3
82Z	0.048	0.45
96Z	0.22	0.94
119Z	0.063	0.81
197Z	0.078	1.9
204Z	103	35
208Z	0.11	1.4
214Z	0.75	0.28
227Z	152	152
232Z	2	8.2
240Z	98	98
244Z	0.093	0.41
402Z	0.073	0.38
553Z	0.11	0.21
1402Z	0.02	0.06
974Z	0.13	0.33
1035Z	0.04	0.03
1122Z	0.03	0.03
1267Z	0.11	0.35
738Z	0.04	0.07
801Z	0.01	0.03
808Z	0.03	0.05
1629Z	0.02	0.05
1734Z	0.06	0.13
1574Zq	0.04	0.08
312*	0.06	0.07
1529Z-33	0.01	0.02
1633Z	0.08	0.05
1634Z	0.17	0.11
1529Z-56	0.17	0.06
1574ZI	0.05	0.05
1529Z-150	0.04	0.10

1574Z-82	0.16	0.29
1529Z-180	0.001	0.003
1529Z-182	0.001	0.01
1529Z-185	0.006	0.02
1675Z	0.08	0.20
1529Z-191	0.11	0.02
1712Z	0.08	0.06
1761Z	0.07	0.16
270*	0.03	0.02
1891Z	0.05	0.07
1898Z	0.05	0.06
1743Z	0.07	0.06
2022Z	0.04	0.08
745Z	0.04	0.06
755Z	0.05	0.04
767Z	0.05	0.13
809Z	0.04	0.11
932Z	0.04	0.13
1529Z-6	0.02	0.06
1574Zo	0.03	0.04
1529Z-19	0.04	0.13
1529Z-40	0.03	0.03
1574Zr	0.06	0.13
1529Z-70	0.07	0.08
1529Z-73	0.09	0.19
1951Z	0.06	0.05
1869Z	0.03	0.08
1864Z	0.06	0.05
1529Z-151	0.07	0.09
1529Z-174	0.07	0.10
186*	0.05	0.12
1529Z-190	0.05	0.12
1683Z	0.08	0.07
1870Z	0.03	0.07
1969Z	0.12	0.12
1715Z	0.10	0.31
1529Z-131	0.03	0.06
1904Z	0.06	0.08
971Zbb	0.33	1.6

NT = not tested; * numbers refer to structures in the reaction Schemes

The compounds listed above can be administered to an animal orally, intravenously, subcutaneously, intrathecally, by inhalation (e.g., to treat fungal infections in the lungs) or topically (e.g. to treat fungal infections of the skin or mucous membranes). Preferably the

compound(s) of the invention listed above is administered orally or intravenously, more preferably orally.

For preparing pharmaceutical compositions from the compounds useful in the method of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 0.1 to about 99 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds useful in the method of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of compound listed above in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compound listed above useful in the method of the invention will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for a compound listed above is oral administration of about 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to provide relief from the fungal infection.

When the invention comprises a combination of one or more compounds listed above and one or more other antifungal agents, the active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising one or more compounds listed above and one or more other antifungal agents in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosages of the other antifungal agents can be determined from published material, and may range from 1 to 1000 mg per dose. When used in combination, the dosage levels of the individual components are preferably lower than the recommended individual dosages because of the advantageous effect of the combination.

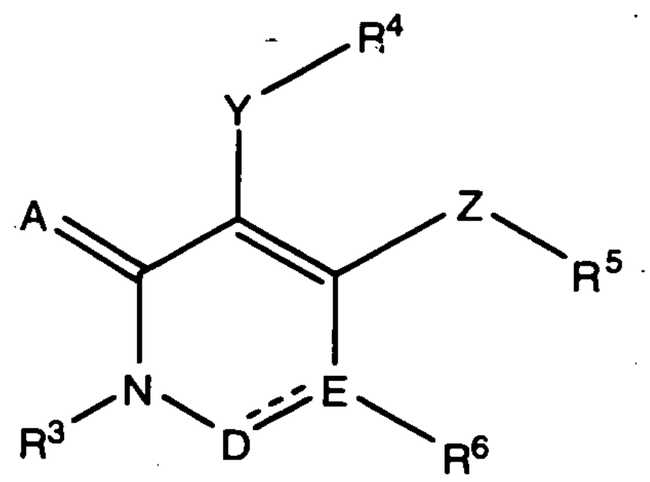
When separate pharmaceutical compositions of compounds listed above and other antifungal agents are to be administered, they can be provided in a kit comprising in a single package, one container comprising one or more compounds of the present invention listed above in a pharmaceutically acceptable carrier, and a separate container comprising one or

more other antifungal agents in a pharmaceutically acceptable carrier, with the compounds listed above and the other antifungal agents being present in amounts such that the combination is therapeutically effective. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

------ represents a double bond or a single bond, as permitted by the valency requirement, with the proviso that when E is N, the double bond is present and R^6 is absent;

A is O or S;

D and E are independently C or N,

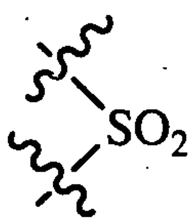
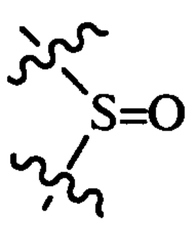
provided that when D is carbon, D is substituted with hydrogen, alkyl, -Oalkyl, -Nalkyl or –Salkyl;

R^3 is a moiety selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclenyl, heterocyclenylalkyl, heterocyclenylalkenyl , arylalkoxylalkyl, arylalkoxylalkenyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkenoxylalkyl, and cycloalkenyoxylalkenyl,

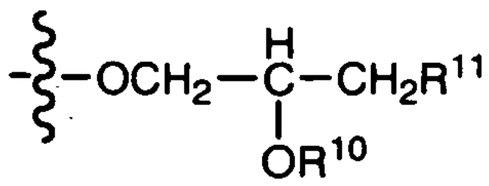
wherein each of said alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclenyl, heterocyclenylalkyl, heterocyclenylalkenyl , arylalkoxylalkyl, arylalkoxylalkenyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, halogen,

trihaloalkyl, dihaloalkyl, monohaloalkyl, -NR^9_2, -OR^9, -SR^9, -NO_2, -CN, -$NR^{16}COR^9$, -$NR^{16}SO_2R^9$, -COR^9, -CO_2R^9, -SO_2R^9, -$CONR^9R^{16}$, and -N=C=O;

Y can be present or absent; or

Y is $-\overset{|}{N}R^9$, -O-, -S-,  or 

provided that when Y is O, Y-R^4 taken together is not alkoxyl of the formula



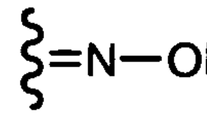
, wherein $-CH_2R^{11}$ and $-OR^{10}$ together with the CH to which they are attached, form a heterocyclyl that is substituted with one or more moieties, which can be the same or different , selected from the group consisting of alkyl and aryl, or

wherein R^{10} is H and R^{11} is hydroxyl or butylamine;

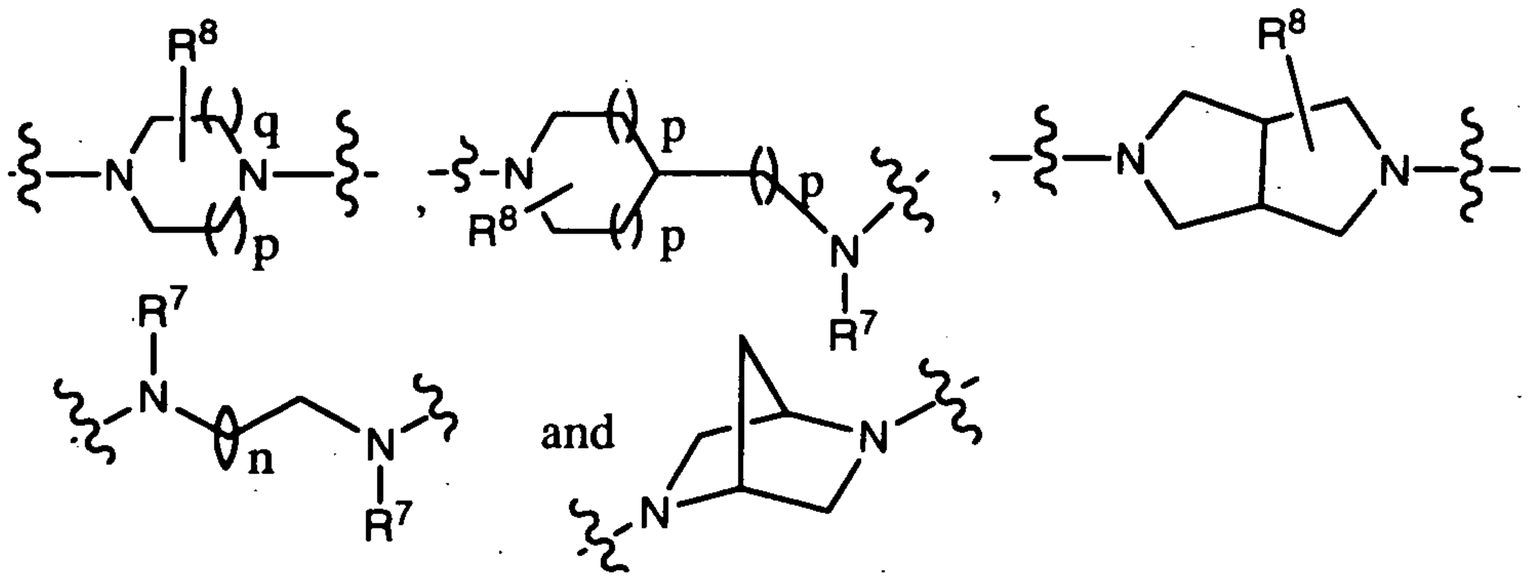
R^4 is alkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkenyl-O-alkyl, alkoxyalkenyl, alkenyl-O-alkenyl, alkynyl-O-alkyl, hydroxyalkyl, hydroxyalkenyl, alkyl-S-alkyl, alkenyl-S-alkyl, alkyl-S-alkenyl, alkenyl-S-alkenyl, alkyl-SO-alkyl, alkenyl-SO-alkyl, alkyl-SO-alkenyl, alkenyl-SO-alkenyl, alkyl-SO_2-alkyl, alkenyl-SO_2-alkyl, alkyl-SO_2-alkenyl, alkenyl-SO_2-alkenyl, alkyl-NR^9-alkyl, alkenyl-NR^9-alkyl, alkyl-NR^9-alkenyl, alkenyl-NR^9-alkenyl, alkyl-CO_2-alkyl, alkenyl-CO_2-alkyl, alkyl-CO_2-alkenyl, alkenyl-CO_2-alkenyl, alkyl-O_2C-alkyl, alkenyl-O_2C-alkyl, alkyl-O_2C-alkenyl, alkenyl-O_2C-alkenyl, alkyl-NCO-alkyl, alkenyl-NCO-alkyl, alkyl-NCO-alkenyl, alkenyl-NCO-alkenyl, alkyl-CON-alkyl, alkenyl-CON-alkyl, alkyl-CON-alkenyl, alkenyl-CON-alkenyl, alkyl-NCON-alkyl, alkenyl-NCON-alkyl, alkyl-NCON-alkenyl, alkenyl-NCON-alkenyl, alkyl-CO-alkyl, alkenyl-CO-alkyl, alkyl-CO-alkenyl, alkenyl-CO-alkenyl, cycloalkyl, cycloalkylalkyl, spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spiroheteroarylalkyl, spiroheteroarylalkenyl, spiroheterocyclenylalkyl, spiroheterocyclenylalkenyl, spiroheterocyclylalkyl, spiroheterocyclylalkenyl, spirocycloalkyl, spirocycloalkylalkyl, spirocycloalkylalkenyl, spirocyclenyl, spirocyclenylalkyl, spirocyclenylalkenyl, spiroaryl, spiroarylalkyl, spiroarylalkenyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylcycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, aryl, arylalkyl,

arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl, heterocyclenyl, heterocyclenylalkyl heterocyclenylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, benzofused-cycloalkyl, benzofused-heterocycloalkyl, benzofused-cycloalkylalkyl or benzofused-heterocycloalkylalkyl;

wherein said alkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkenyl-O-alkyl, alkoxyalkenyl, alkenyl-O-alkenyl, alkynyl-O-alkyl, hydroxyalkyl, hydroxyalkenyl, alkyl-S-alkyl, alkenyl-S-alkyl, alkyl-S-alkenyl, alkenyl-S-alkenyl, alkyl-SO-alkyl, alkenyl-SO-alkyl, alkyl-SO-alkenyl, alkenyl-SO-alkenyl, alkyl-SO_2-alkyl, alkenyl-SO_2-alkyl, alkyl-SO_2-alkenyl, alkenyl-SO_2-alkenyl, alkyl-NR^9-alkyl, alkenyl-NR^9-alkyl, alkyl-NR^9-alkenyl, alkenyl-NR^9-alkenyl, alkyl-CO_2-alkyl, alkenyl-CO_2-alkyl, alkyl-CO_2-alkenyl, alkenyl-CO_2-alkenyl, alkyl-O_2C-alkyl, alkenyl-O_2C-alkyl, alkyl-O_2C-alkenyl, alkenyl-O_2C-alkenyl, alkyl-NCO-alkyl, alkenyl-NCO-alkyl, alkyl-NCO-alkenyl, alkenyl-NCO-alkenyl, alkyl-CON-alkyl, alkenyl-CON-alkyl, alkyl-CON-alkenyl, alkenyl-CON-alkenyl, alkyl-NCON-alkyl, alkenyl-NCON-alkyl, alkyl-NCON-alkenyl, alkenyl-NCON-alkenyl, alkyl-CO-alkyl, alkenyl-CO-alkyl, alkyl-CO-alkenyl, alkenyl-CO-alkenyl, cycloalkyl, cycloalkylalkyl, spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spiroheteroarylalkyl, spiroheteroarylalkenyl, spiroheterocyclenylalkyl, spiroheterocyclenylalkenyl, spiroheterocyclylalkyl, spiroheterocyclylalkenyl, spirocycloalkyl, spirocycloalkylalkyl, spirocycloalkylalkenyl, spirocyclenyl, spirocyclenylalkyl, spirocyclenylalkenyl, spiroaryl, spiroarylalkyl, spiroarylalkenyl, alkylcycloalkyl, alkylcycloalkylalkyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heterocyclyl, heterocyclenyl, heterocyclenylalkyl heterocyclenylalkenyl, heterocyclylalkyl, heterocyclylalkenyl, benzofused-cycloalkyl, benzofused-heterocycloalkyl, benzofused-cycloalkylalkyl or benzofused-heterocycloalkylalkyl can be unsubstituted or substituted with at least one moiety independently selected from the group consisting of alkyl, alkenyl, aryl, OR^9, arylalkyl, arylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkyl, cycloalkylalkenyl, alkylCO_2alkyl-, halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, cycloalkyl, cyclenyl, hydroxyalkyl, hydroxyalkenyl, thiohydroxyalkyl, thiohydroxyalkenyl, hydroxyalkenyl, heteroaryl, heteroarylalkyl, heterocyclenyl, heterocyclenylalkyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, -CN, -NO_2,

$-OSiR^9_3$, $-NR^{16}COR^9$, $-OCONR^9_2$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2R^9$, $-NR^9_2$, -N=C=O,  , $-NR^{16}CO_2R^9$, $-COR^9$, $-CO_2R^9$, $-OCOR^9$, $-SO_2R^9$, $-SOR^9$, $-SR^9$, $-SO_2N(R^9)_2$ or $-CONR^9R^{16}$, wherein each of said alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkyl, cycloalkylalkenyl, halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, cycloalkyl, cyclenyl, hydroxyalkyl, hydroxyalkenyl, thiohydroxyalkyl, thiohydroxyalkenyl, hydroxyalkenyl, heteroaryl, heteroarylalkyl, heterocyclenyl, heterocyclenylalkyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl, can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from R^9;

Z is a linker attached at either end of said linker to the parent ring of Formula I, wherein said linker is selected from the group consisting of :

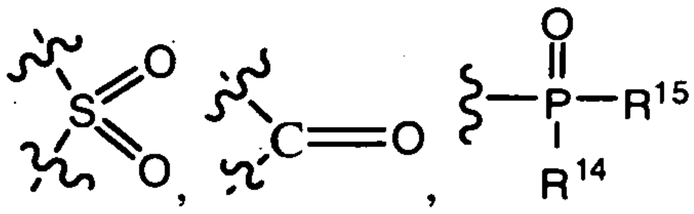


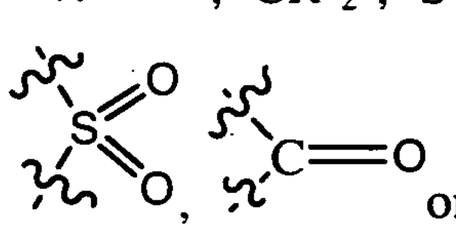
wherein

n is 1 to 4,

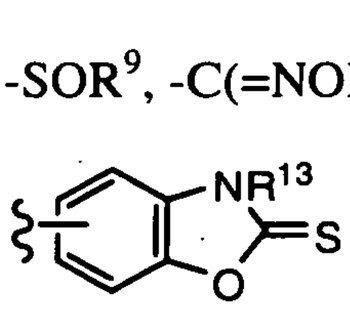
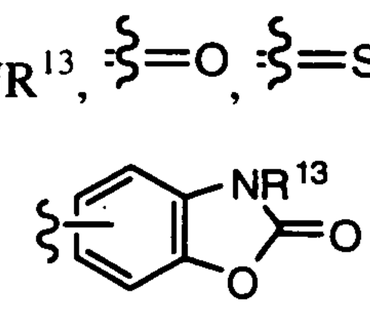
p is 0 to 2,

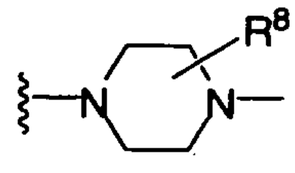
q is 1 to 3;

R^5 is  , $-CR^9_2-$, $-SO_2NR^{13}$-alkyl-C(O)-aryl, or heteroaryl,

wherein each of said  or $-CR^9_2-$ is attached at one end to Z and at the second end substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl,

heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, $-OR^9$ and $-NR^9_2$,

further, wherein each of said alkyl, alkenyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, or heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, alkenyl, cycloalkyl, $-OR^9$, alkylOR^9, alkylCO_2R^9, alkyl$NR^{16}COR^9$, alkyl$NR^{16}CONR^9$, alkylSO_2R^9, alkylCOR^9, alkyl$SO_2NR^9_2$, alkylNR^9_2, alkylaryl, alkylheteroaryl, alkylSR^9, alkylSOR^9, -CN, $-CO_2R^9$, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^{16}COR^9$, $-NR^{16}CONR^9_2$, $-NR^{16}SO_2-R^{13}$, $-SO_2R^9$, $-COR^9$, $-NO_2$, $-SO_2NR^9_2$, aryl, heteroaryl, $-NR^9_2$, $-SR^9$, $-SOR^9$, $-C(=NOH)-NR^{13}$,  ,  ;

or Y-R^4 taken together are H, provided that R^6 is not H; or Y-R^4 taken together are H and R^6 is H, provided that when Z is  , R^8 is not H;

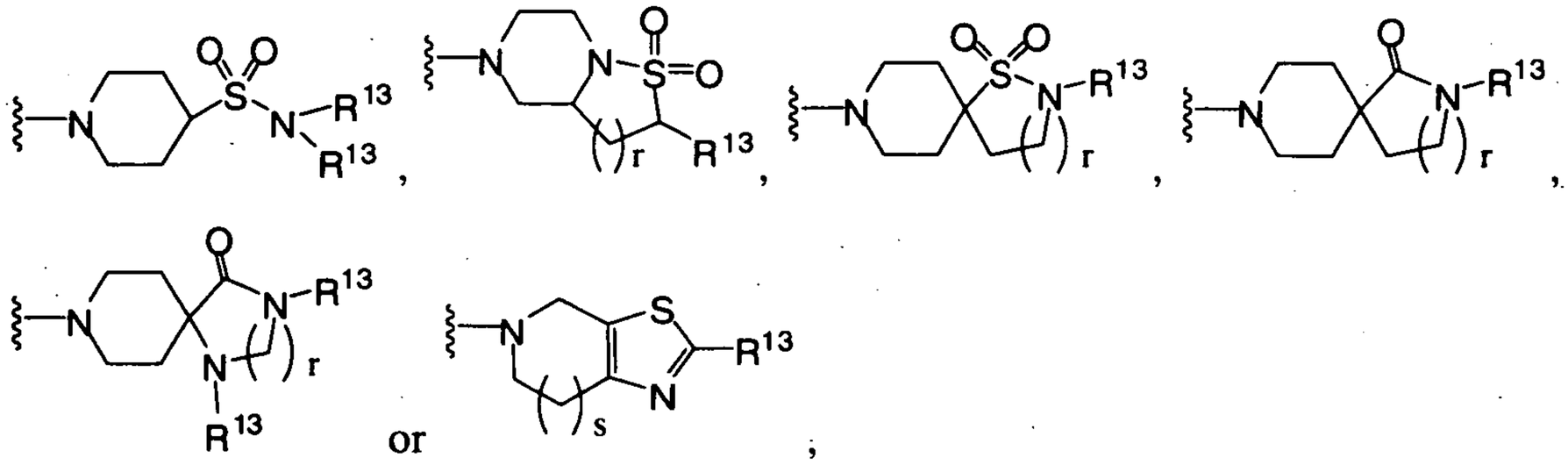
or when Y is –O- and R^5 is $–SO_2-$, R^4 and the second end substituent on R^5 together are –alkyl-, -alkenyl-, -alkyl-NH-,or –alkenyl-NH-, forming a ring with the –O- and $–SO_2-$ groups to which they are attached;

or when R^3 is a group having an $–OR^9$ substituent and Y is –O-, R^4 and the R^9 portion of the R^3 group together are a divalent alkyl group, forming a ring with the –O- atoms to which they are attached;

or when Y is –O- and R^5 is $–SO_2-$, R^4 and the second end substituent of R^5 together are an -alkyl-phenylene-alkyl-NR^{13}- group or a -alkyl-phenylene-alkyl- group, forming a ring with the –O- and $–SO_2-$ groups to which they are attached;

or when Y is –O- and R^5 is $–SO_2$-, R^4 and the second end substituent of R^5 together are an -alkyl-heteroarylene-alkyl- group or an -alkyl-heteroarylene-alkyl-NR^{13}- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or Z and R^5 taken together is

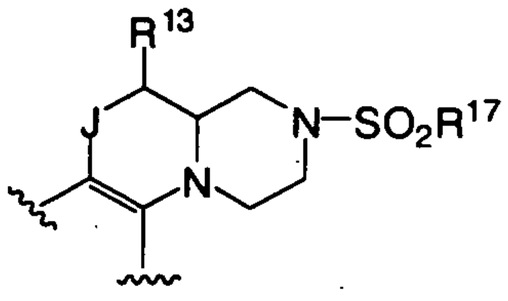


wherein

r is 1 or 2;

s is 0 or 1;

or -Y-R^4, -ZR^5 and the carbons to which they are attached form the group



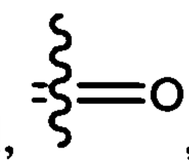
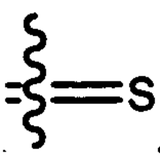
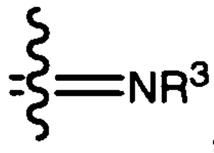
, wherein J is –O-, -S-, or –NR^{13}-;

R^6 is H, alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, arylalkoxylalkyl, arylalkoxylalkenyl, arylalkoxyl, cycloalkoxyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkylalkoxyl, cycloalkenoxyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl, -NR^9_2, -OR^9, -NO_2, -$NR^{16}COR^9$, -$NR^{16}CON(R^{17})_2$, -$NR^{16}SO_2R^9$, -COR^9, -CO_2R^9, or -$CONR^9R^{16}$;

wherein each of said alkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, arylalkoxylalkyl, arylalkoxylalkenyl, arylalkoxyl, cycloalkoxyl, cycloalkoxylalkyl, cycloalkoxylalkenyl, cycloalkylalkoxyl, cycloalkenoxyl, cycloalkenoxylalkyl, cycloalkenyoxylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, trihaloalkyl, dihaloalkyl,

monohaloalkyl, $-NR^9_2$, $-OR^9$, $-SR^9$, $-NO_2$, -CN, $-NR^{16}COR^9$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, $-CONR^9R^{16}$ and $-NR^{16}CON(R^{17})_2$;

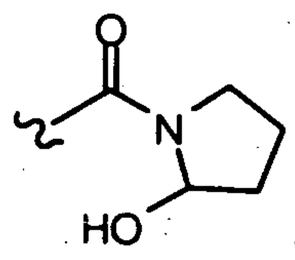
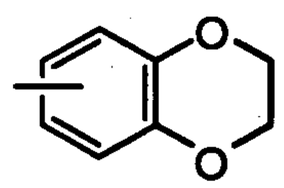
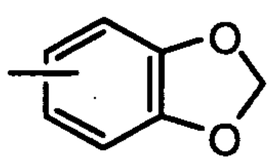
each R^7 is independently selected from the group consisting of H and alkyl;

R^8 is one or more moieties, which can be the same or different, each being independently selected from the group consisting of H, aryl, arylalkyl, alkyl,  ,  ,  , arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, alkenyl, alkynyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9_2$, $-OR^9$, $-SR^9$, $-NR^{16}COR^9$, $-NR^{16}CON(R^{17})_2$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, and $-CONR^9R^{16}$,

wherein each of said aryl, arylalkyl, alkyl, arylalkenyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cyclenyl, cyclenylalkyl, cyclenylalkenyl, alkenyl and alkynyl can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, trihaloalkyl, dihaloalkyl, monohaloalkyl, $-NR^9_2$, $-OR^9$, $-SR^9$, $-NO_2$, -CN, $-NR^{16}COR^9$, $-NR^{16}SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-SO_2R^9$, $-CONR^9R^{16}$ and $-NR^{16}CON(R^{17})_2$;

R^9 is one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heteroalkyl, heterocycloalkyl, heterocyclenyl, heteroaryl, hydroxyalkyl, hydroxyalkenyl, alkylthioalkyl, alkylthioalkenyl, alkenylthioalkyl, alkenylthioalkenyl, alkoxylalkyl, arylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, arylalkenyl, cycloalkyalkenyl, cyclenylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, alkoxyaryl, trihaloalkyl, trihaloalkenyl, dihaloalkyl, dihaloalkenyl, monohaloalkyl, and monohaloalkenyl,

wherein each of said alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heterocycloalkyl, heterocyclenyl, heteroaryl, hydroxyalkyl, hydroxyalkenyl, alkoxylalkyl, arylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, arylalkenyl, cycloalkyalkenyl, cyclenylalkenyl, heterocyclylalkenyl, heterocyclenylalkenyl, heteroarylalkenyl, and alkoxyaryl can be unsubstituted or

substituted with one or more moieties, which can be the same or different, each moiety being independently selected from the group consisting of halogen, trihaloalkyl, dihaloalkyl, monohaloalkyl, trihaloalkenyl, dihaloalkenyl, monohaloalkenyl, hydroxyl, alkoxy, hydroxyalkyl, $-N(R^{12})_2$, alkyl, alkynyl , cycloalkyl, alkenyl, cyclenyl, aryl, heteroaryl, heterocycloalkyl, heterocyclenyl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, heterocyclenylalkyl, cycloalkylalkenyl, cyclenylalkenyl, arylalkenyl, heteroarylalkenyl, heterocycloalkylalkenyl, heterocyclenylalkenyl, -CN, $-NO_2$, $-SO_2R^{17}$, $-C(O)N(R^{20})_2$, $-CO_2R^{19}$,  , $-NR^{16}-C(O)R^{19}$, $-NR^{16}CON(R^{17})_2$, $-NR^{16}SO_2R^{17}$, trihaloalkoxy, dihaloalkoxy, monohaloalkoxy,  and  ;

further wherein when two R^9 moieties are attached to a N, the two R^9 moieties, together with the N to which they are attached, can form a heterocyclyl or heterocyclenyl ring of 4 to 7 members, wherein 1 or 2 of said ring members can be –O-, -S- or $–NR^{18}$-, provided that there are no heteroatoms adjacent to each other; and wherein the heterocyclyl or heterocyclenyl ring is optionally substituted on 1 or 2 ring carbon atoms by a substituent independently selected from the group consisting of alkyl, alkoxy, -OH and $–NR^{16}$, or two hydrogen atoms on the same carbon are replaced by =O;

each R^{12} is independently selected from the group consisting of H, alkyl, aryl and arylalkyl;

each R^{13} is independently selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl;

R^{14} is alkyl or alkoxy;

R^{15} is aryl, arylalkyl, $-N(R^{13})$-aryl, $-N(R^{13})$-alkylaryl, -O-aryl or –O-alkylaryl;

R^{16} is independently selected from the group consisting of H and alkyl;

R^{17} is alkyl, aryl or arylalkyl;

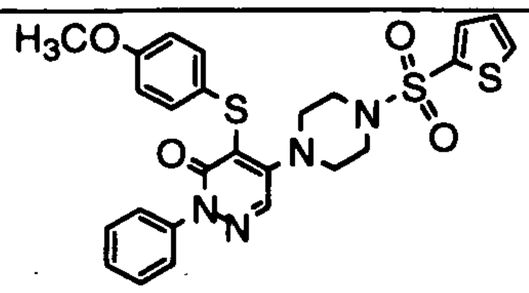
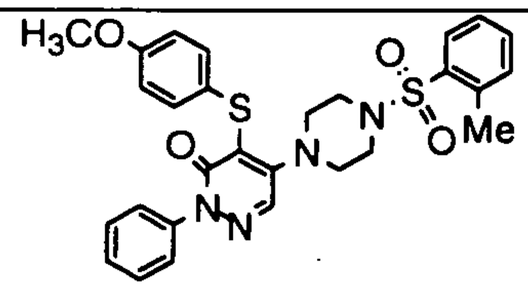
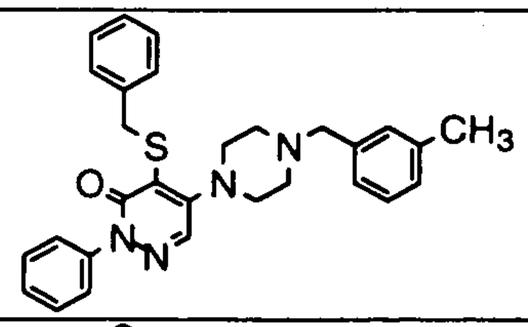
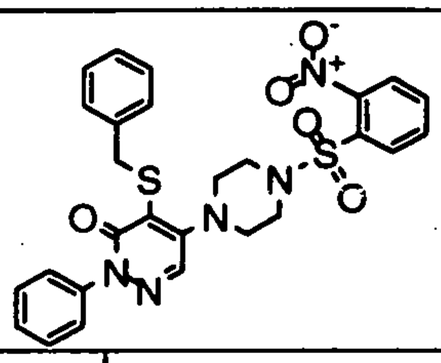
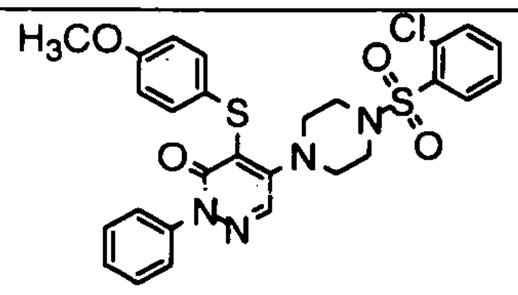
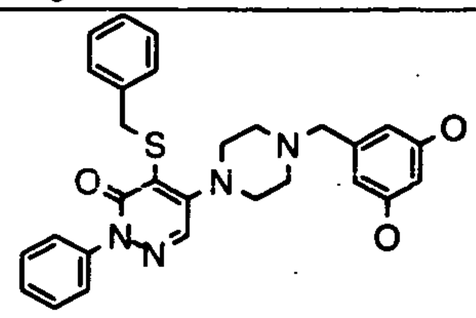
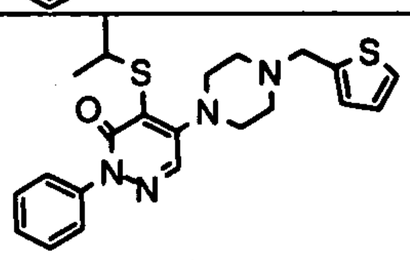
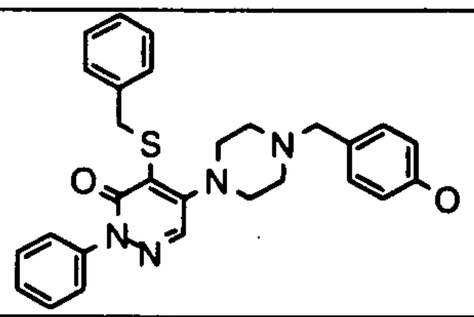
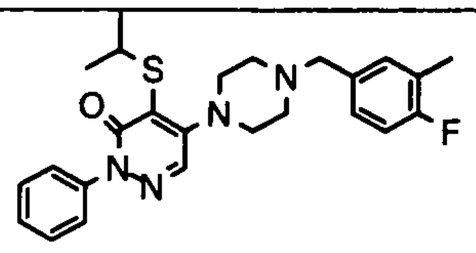
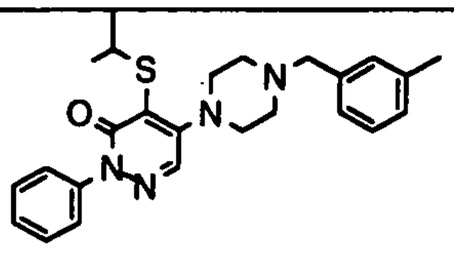
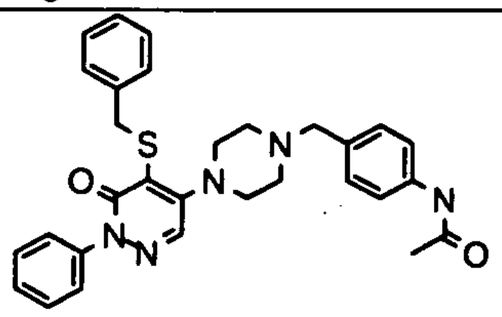
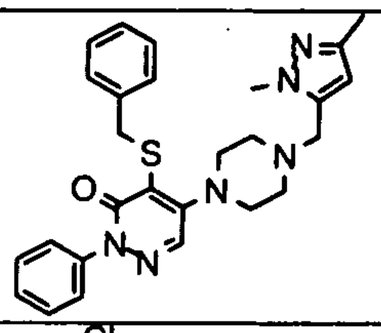
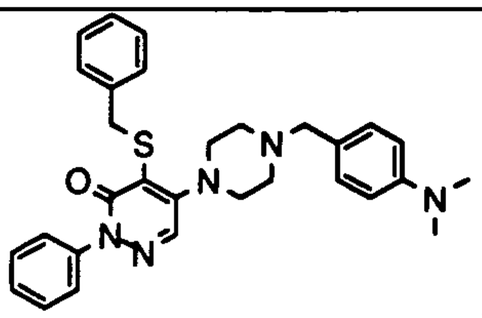
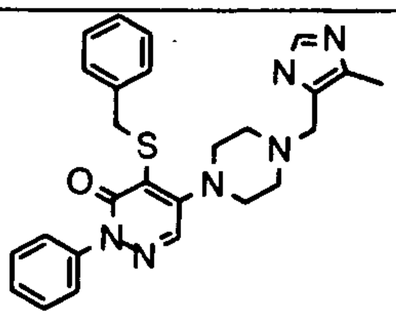
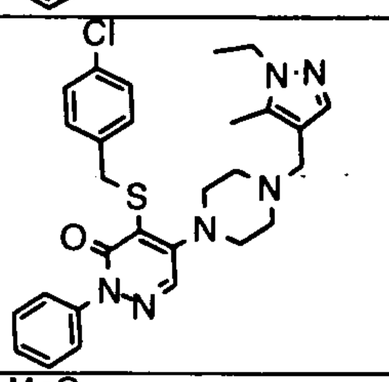
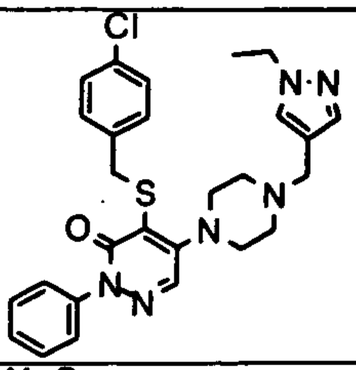
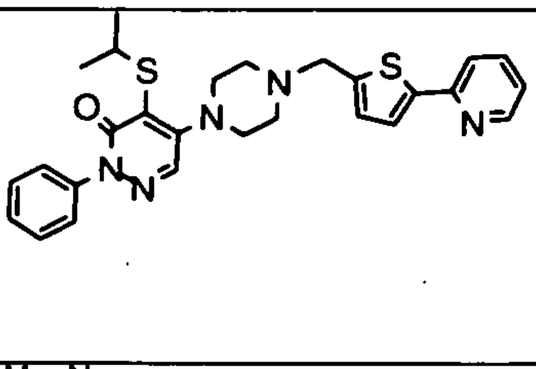
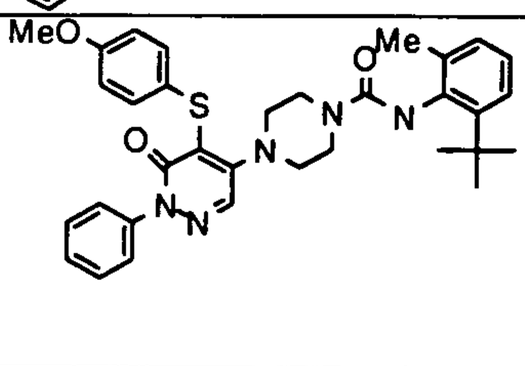
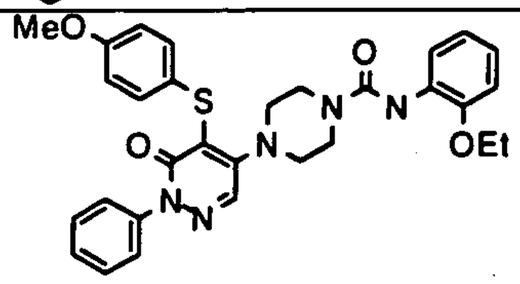
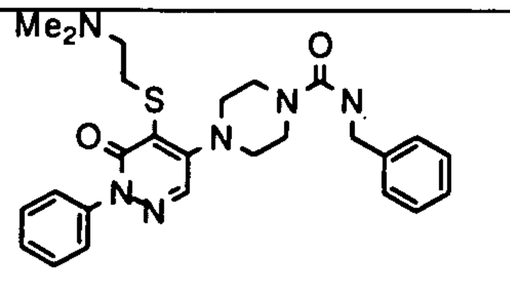
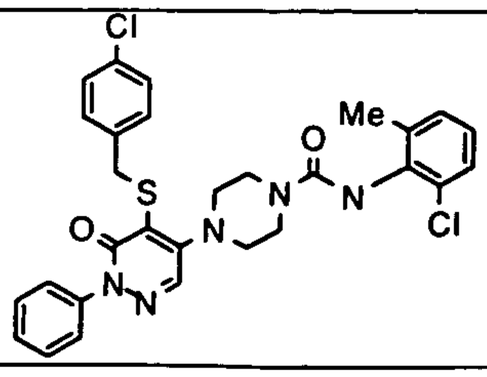
R^{18} is H, alkyl, $–COOR^{19}$, $-COR^{17}$ or $–CON(R^{17})_2$;

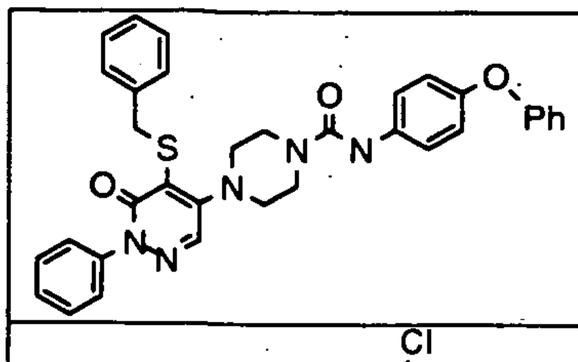
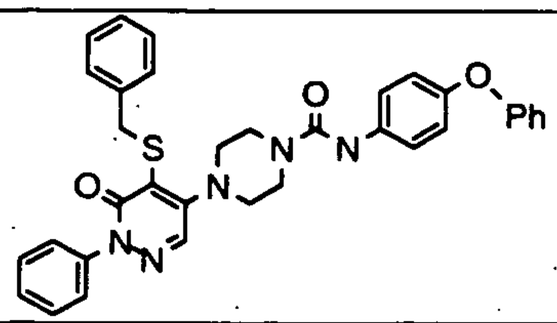
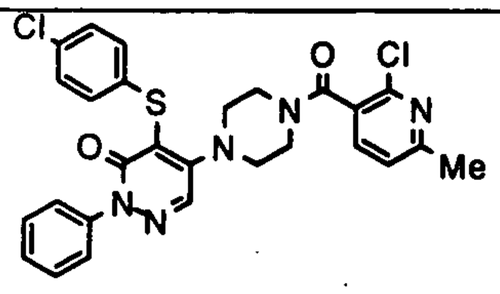
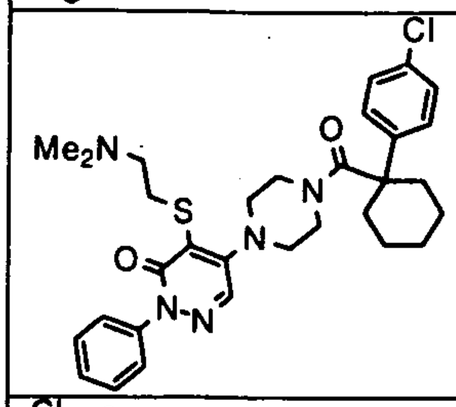
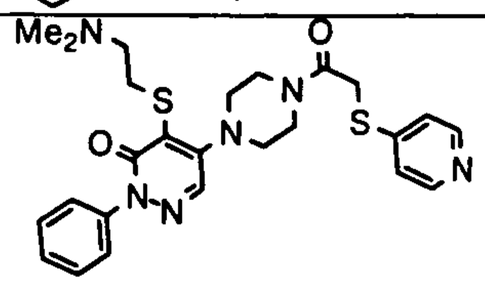
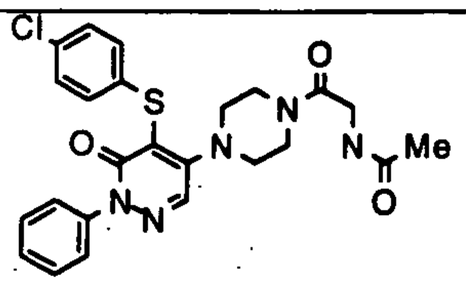
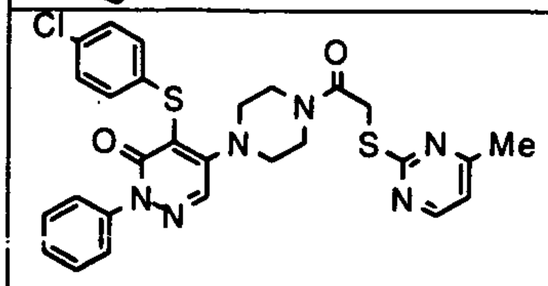
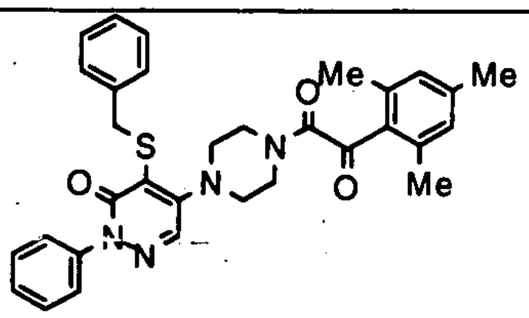
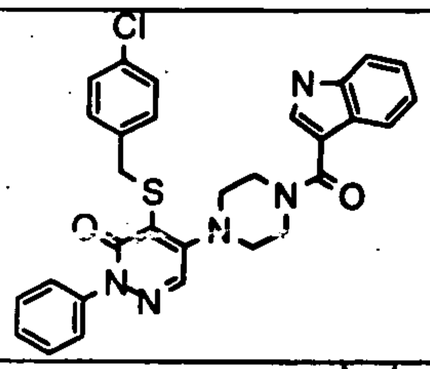
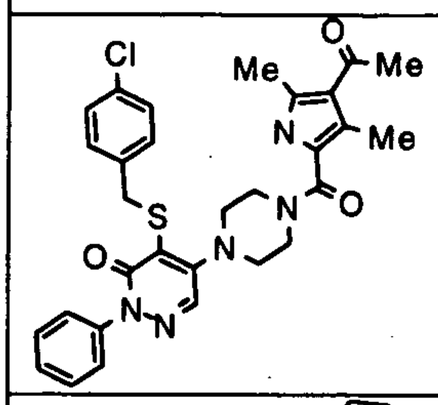
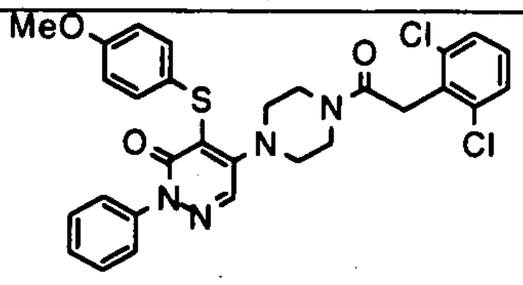
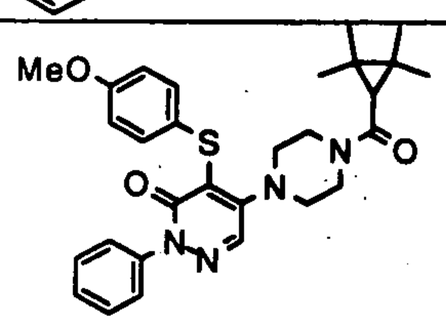
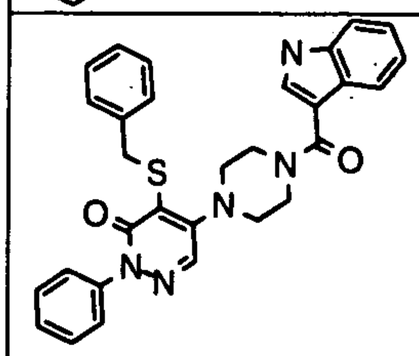
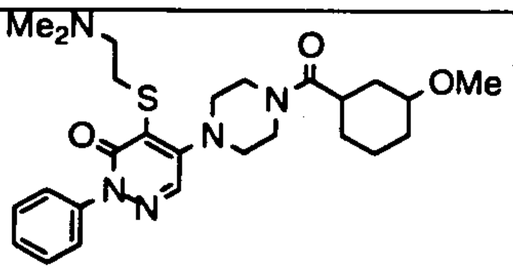
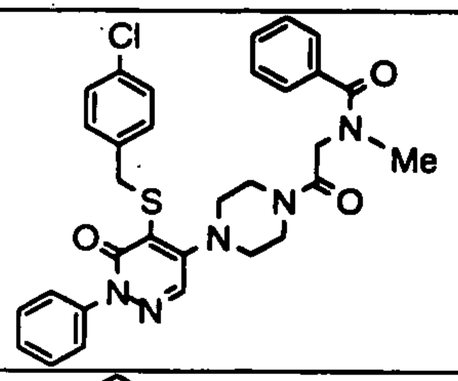
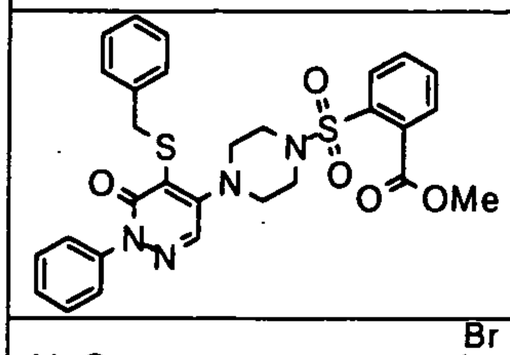
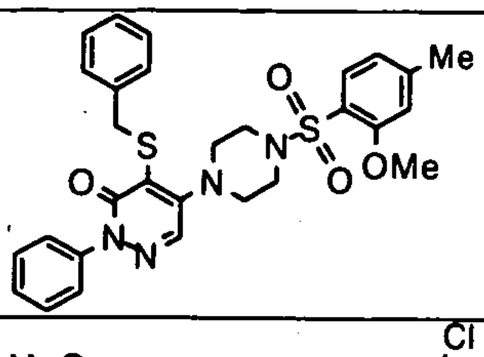
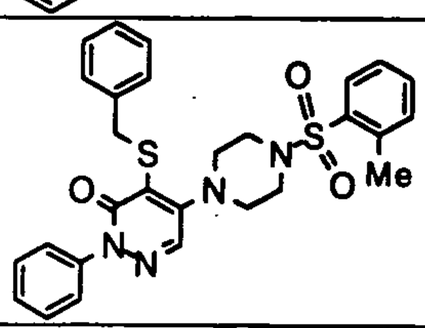
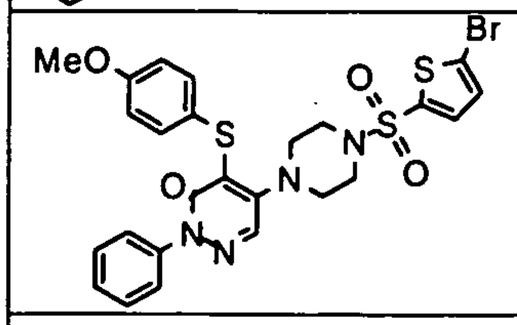
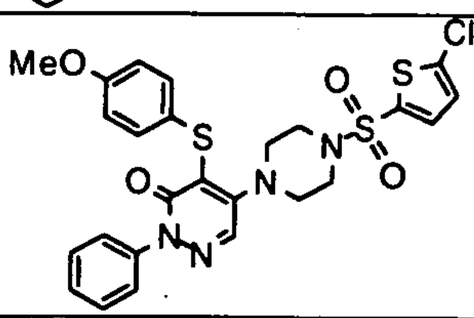
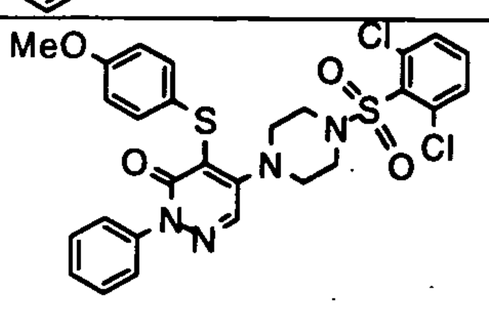
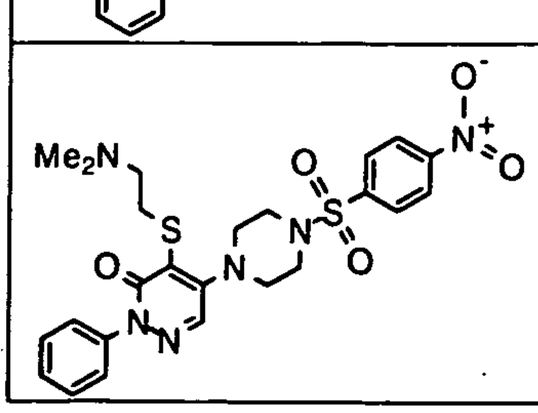
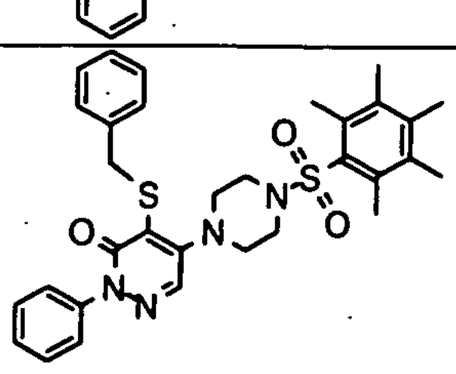
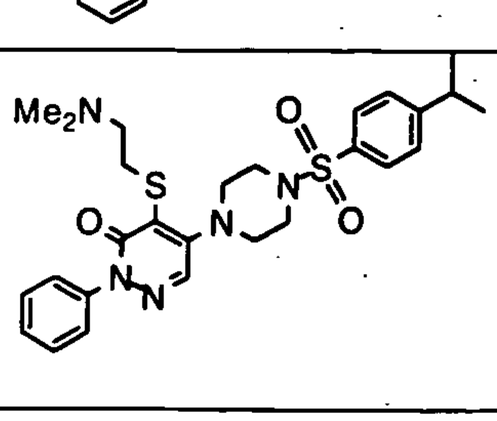
each R^{19} is independently selected from the group consisting of H, alkyl and benzyl;

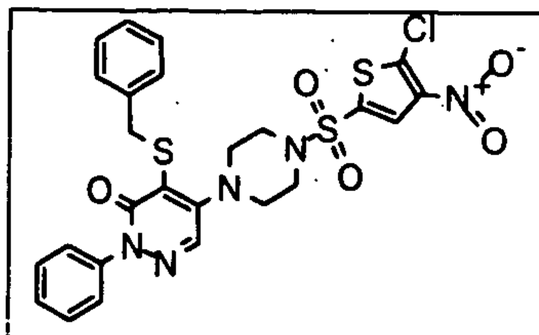
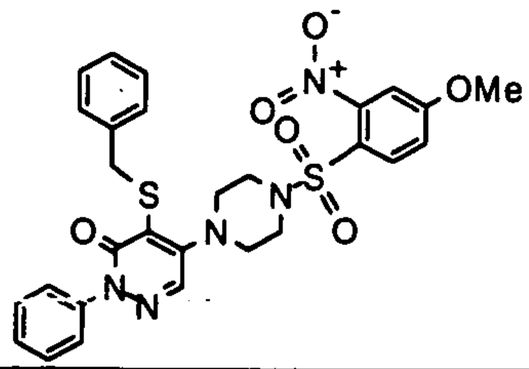
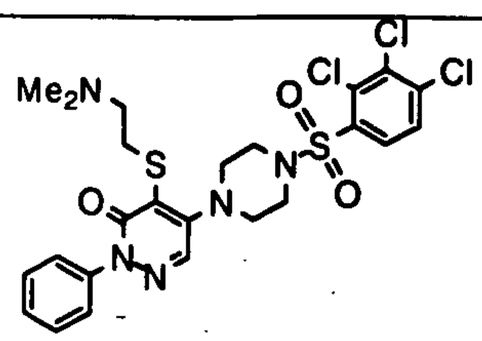
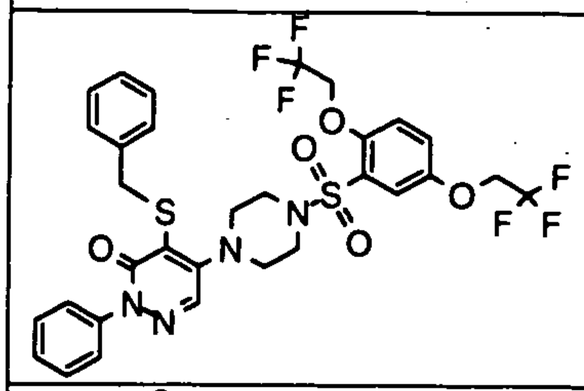
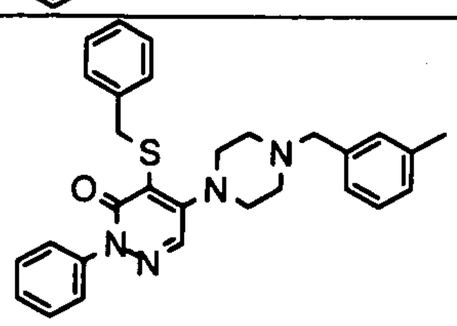
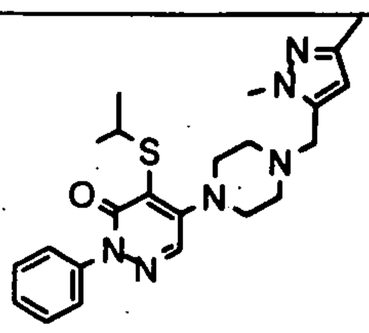
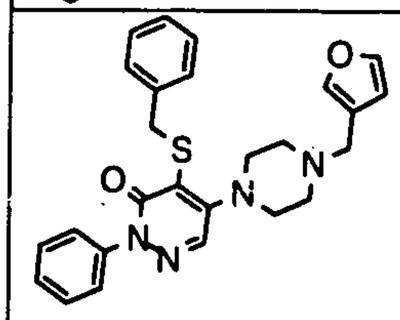
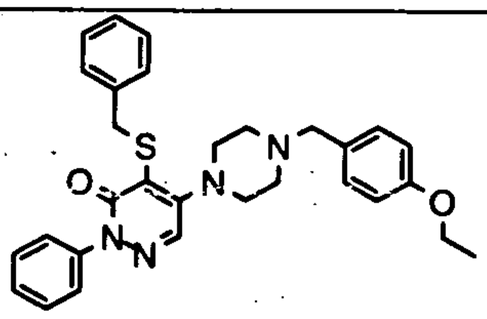
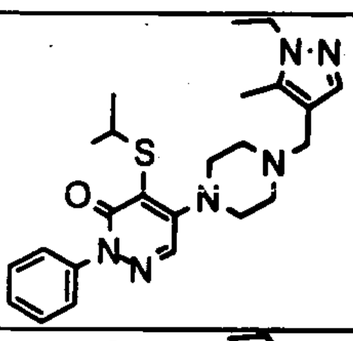
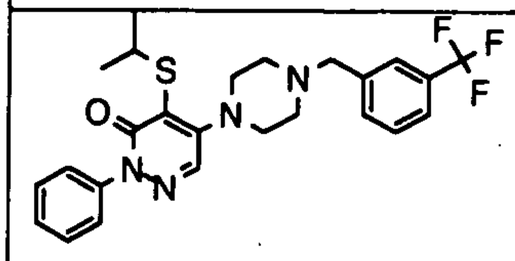
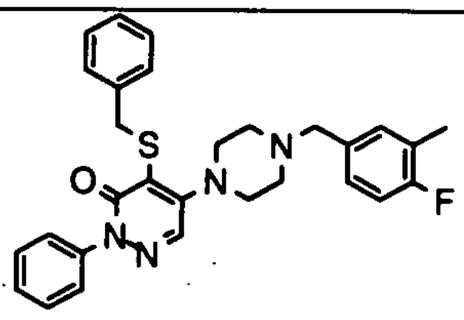
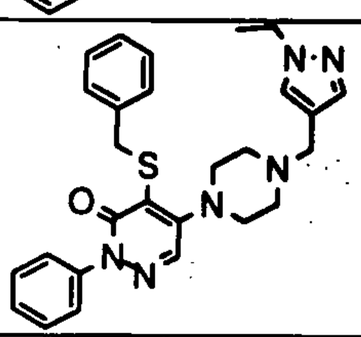
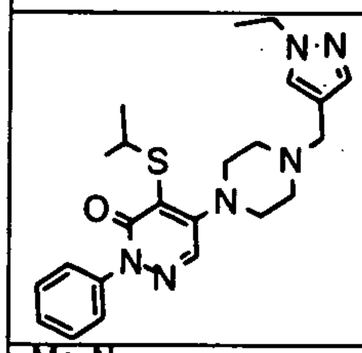
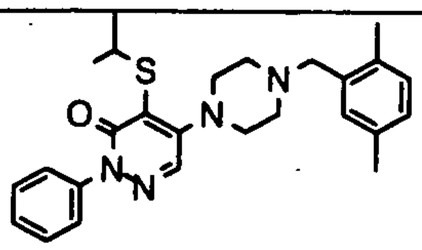
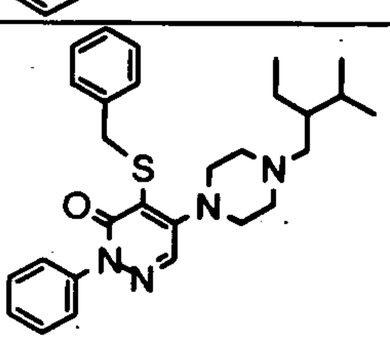
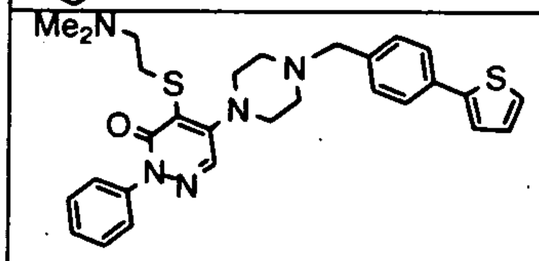
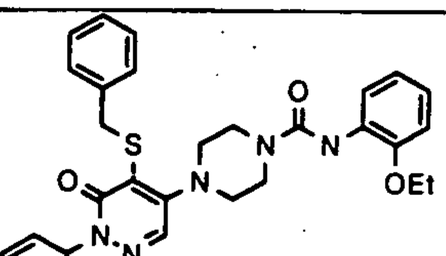
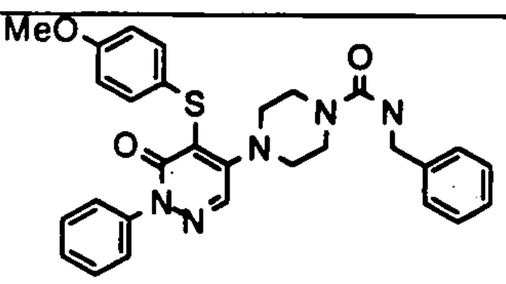
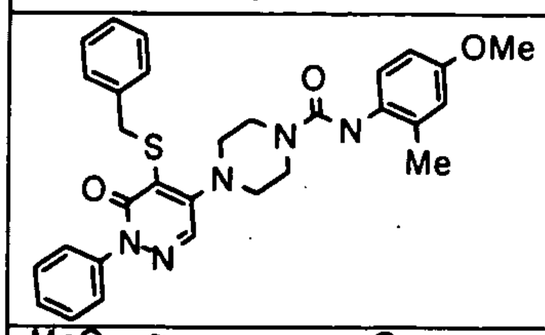
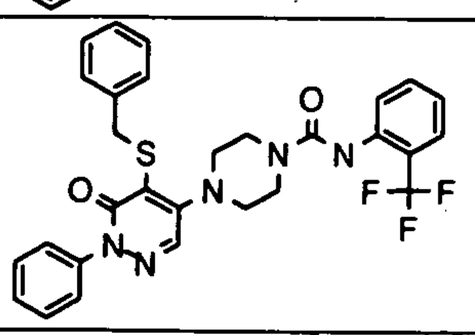
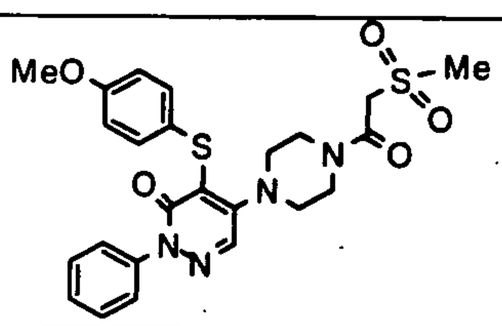
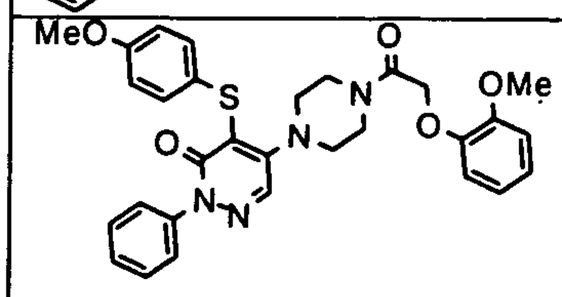
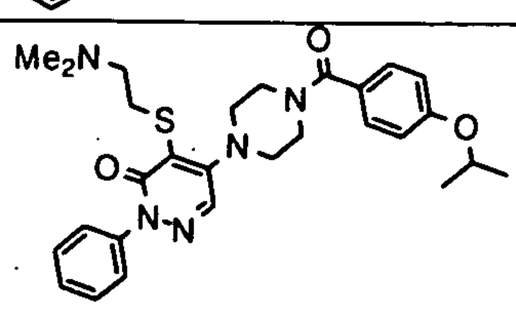
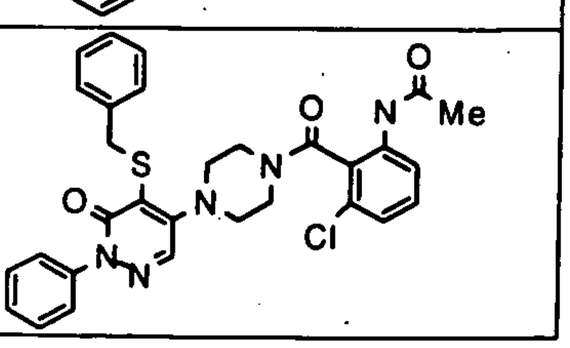
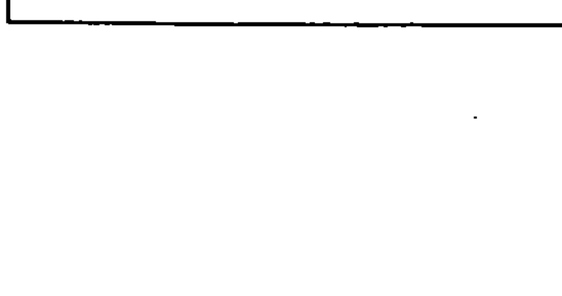
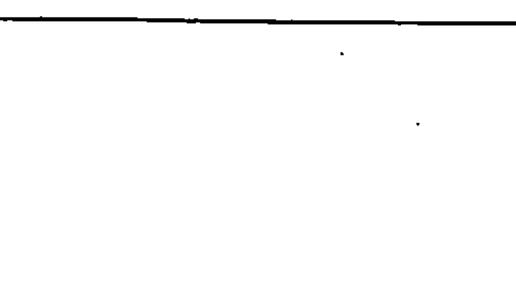
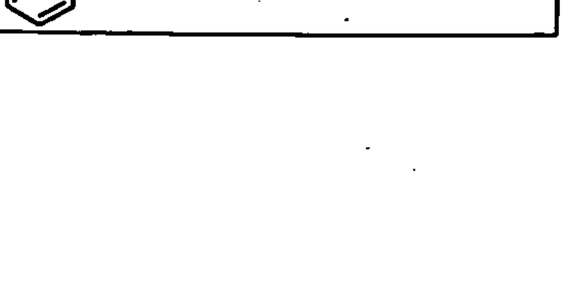
each R^{20} is independently selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, and alkoxyalkyl;

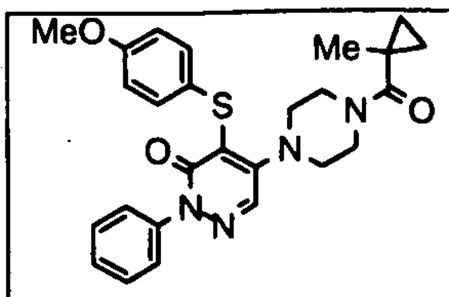
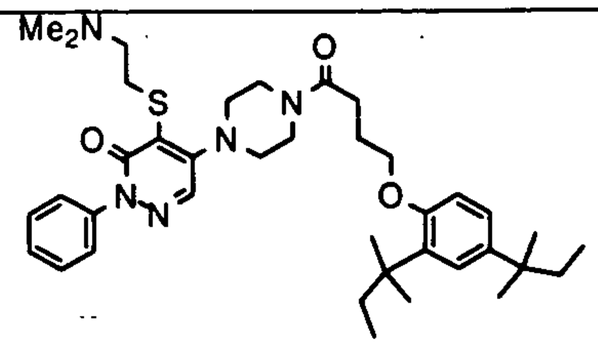
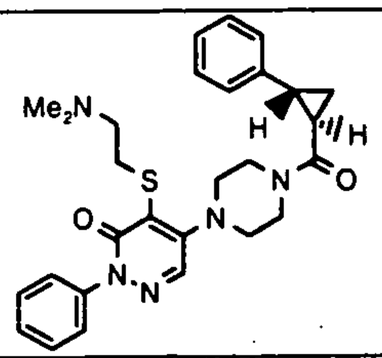
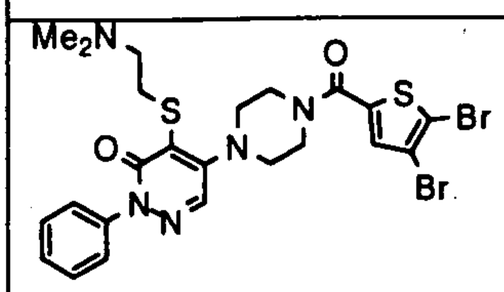
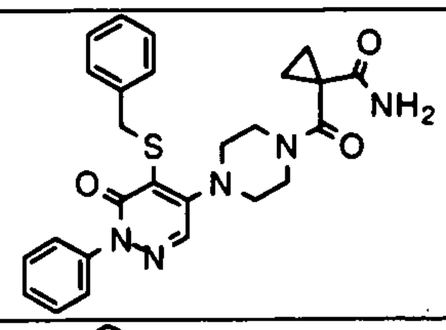
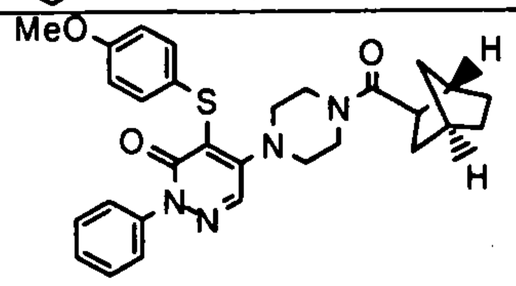
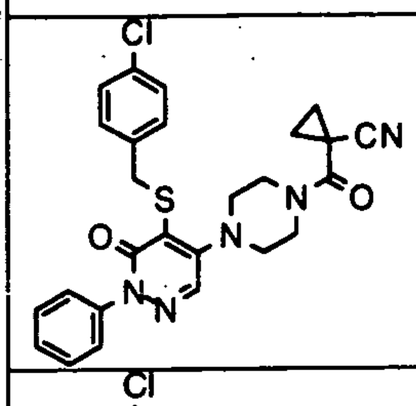
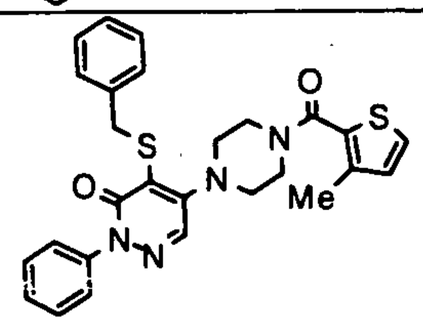
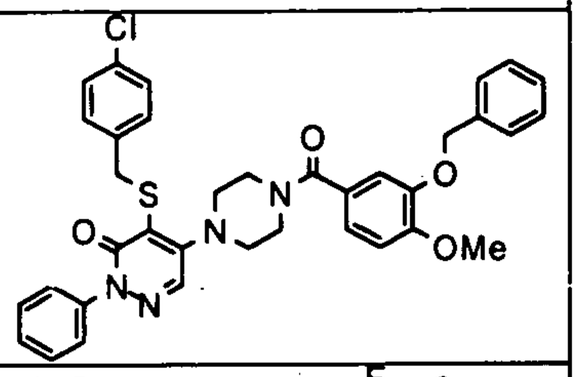
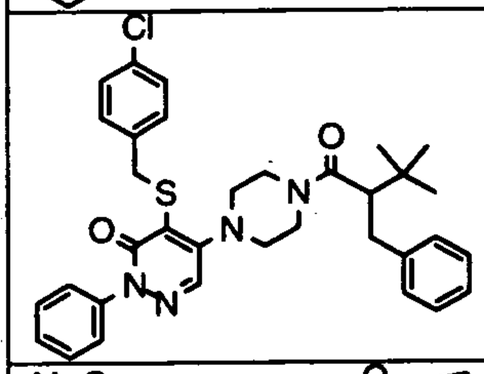
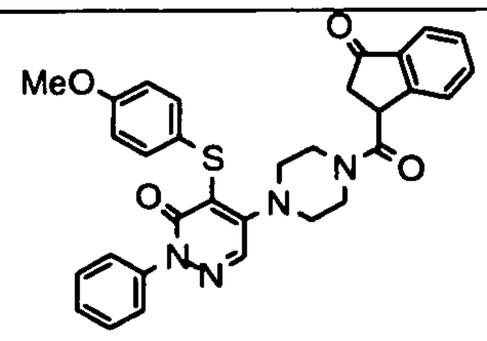
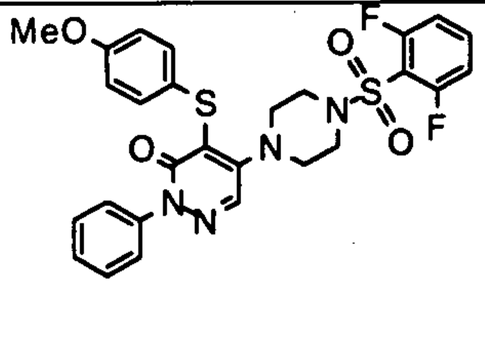
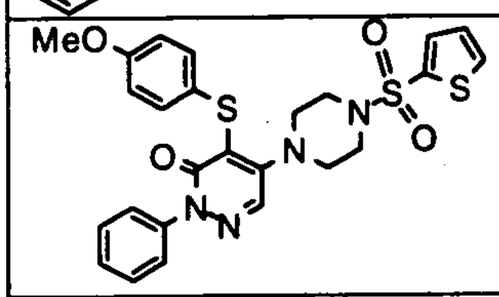
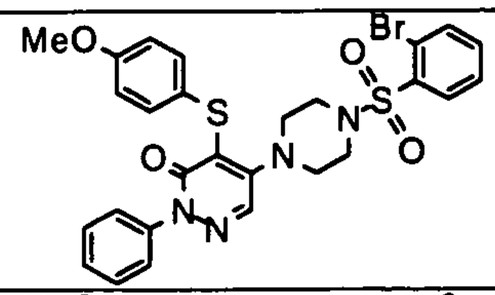
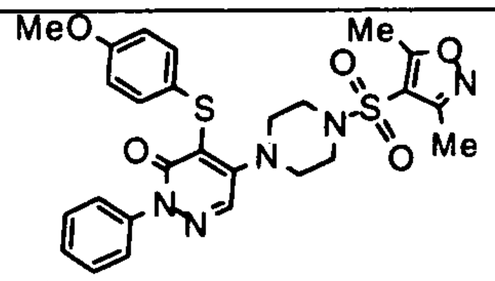
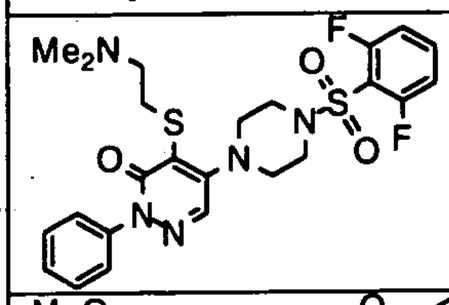
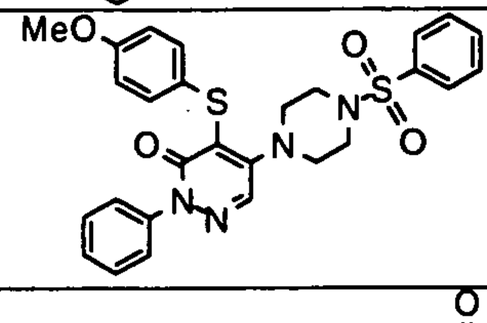
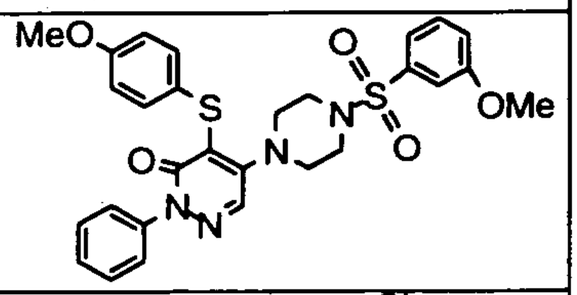
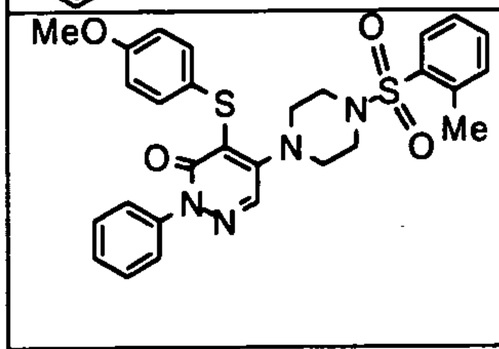
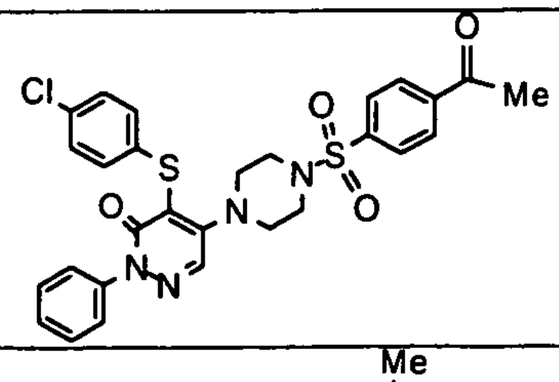
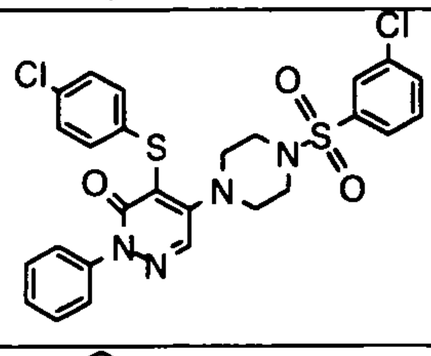
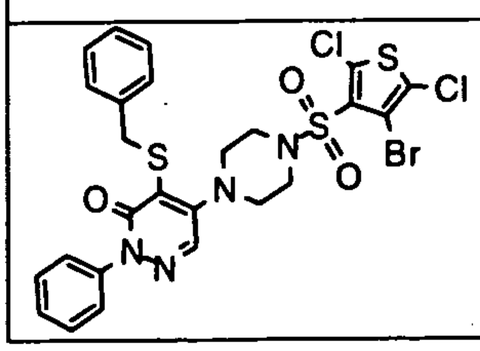
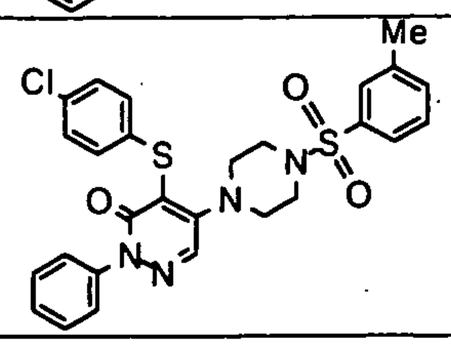
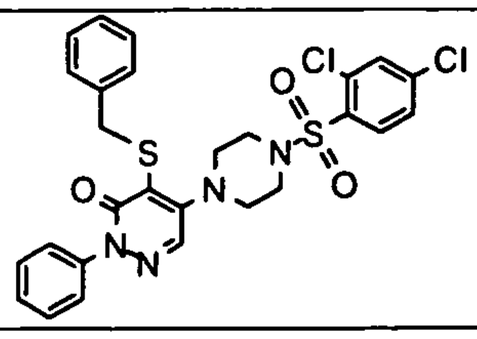
provided that Formula I does not include the compounds of Table A:

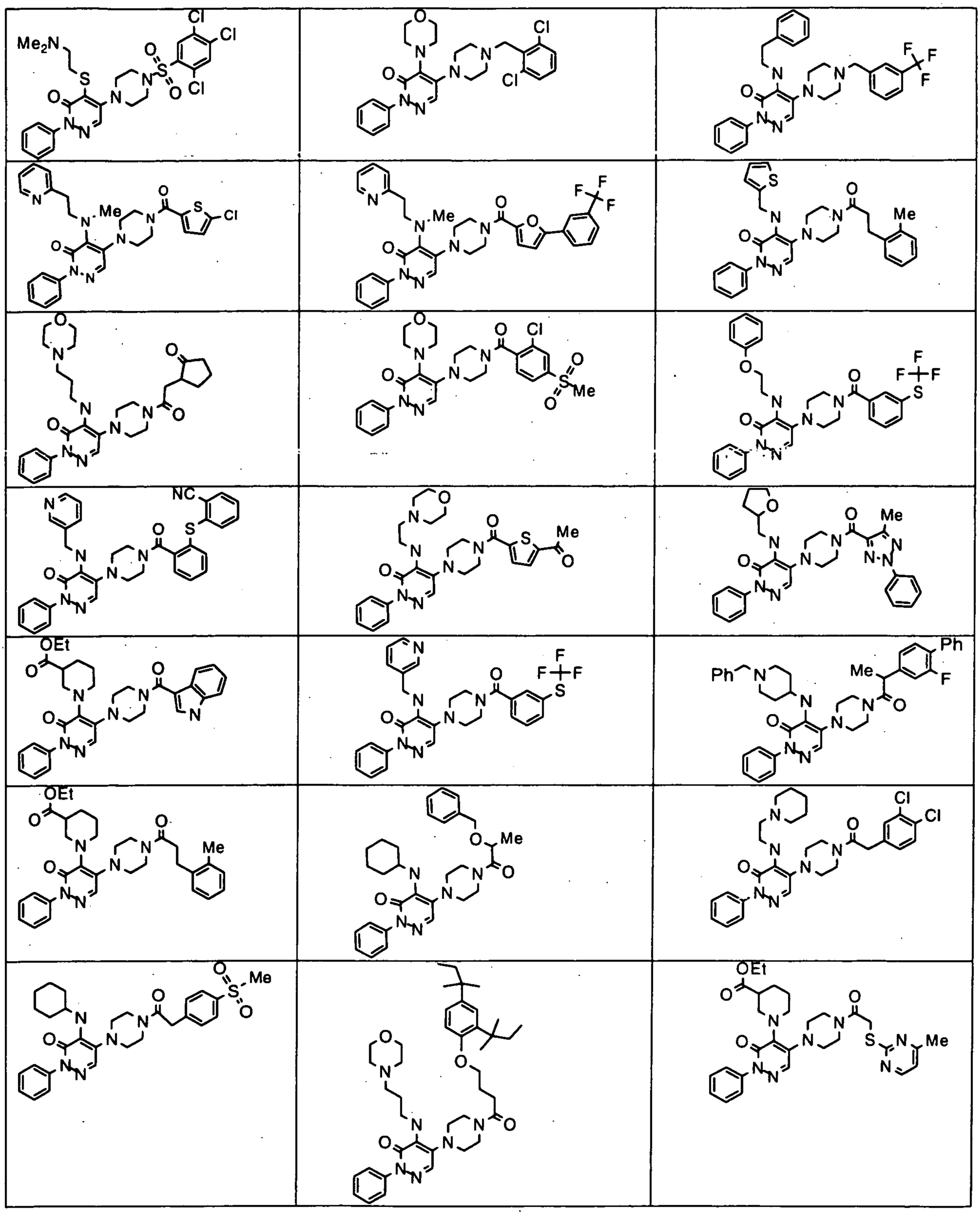
Table A:

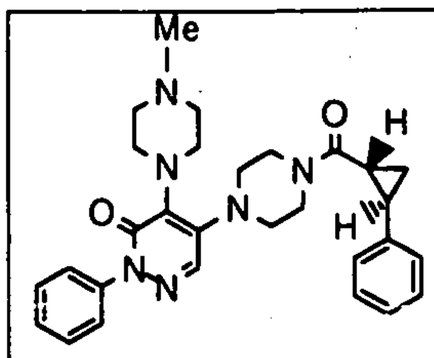
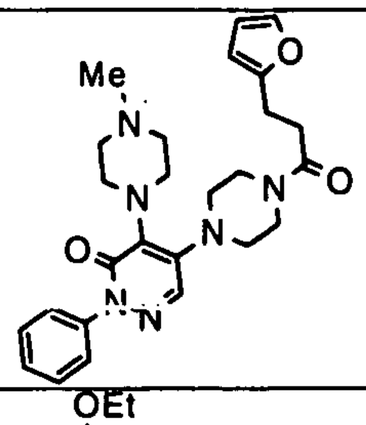
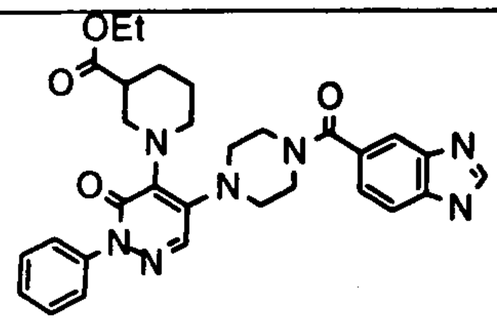
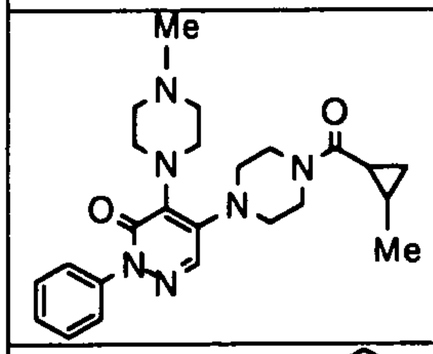
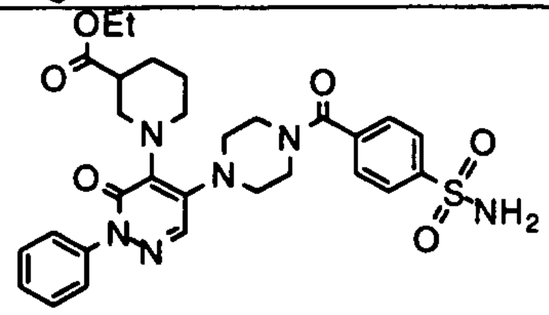
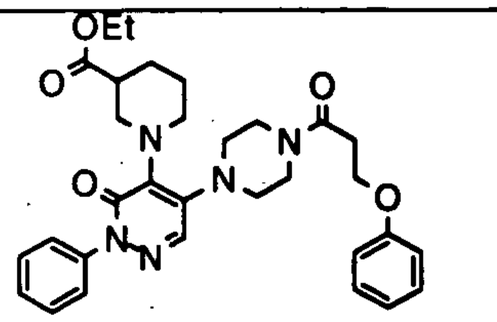
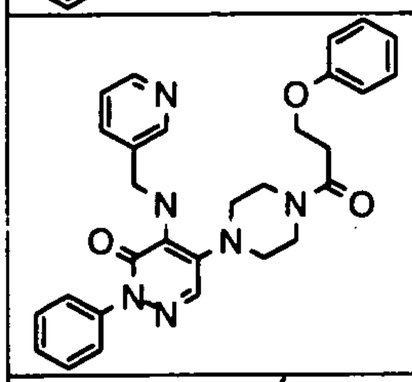
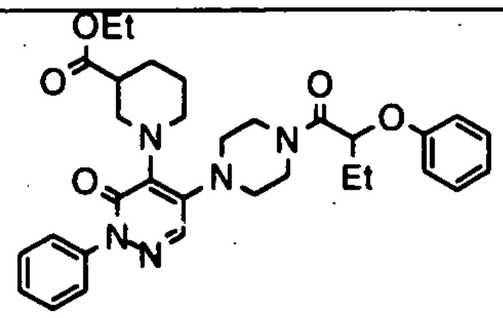
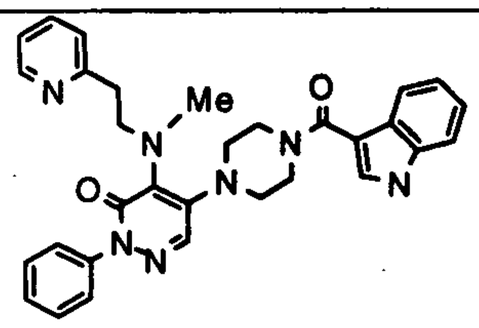
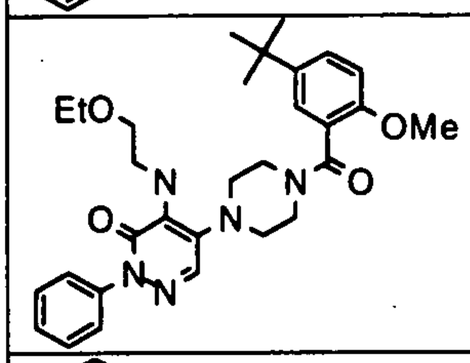
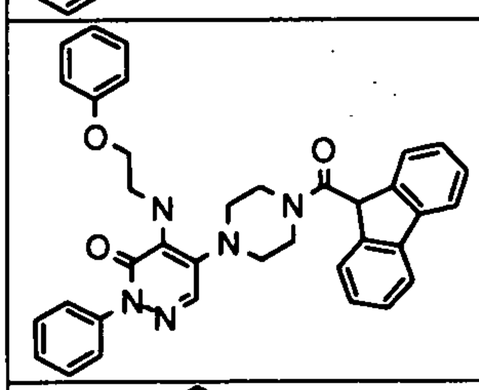
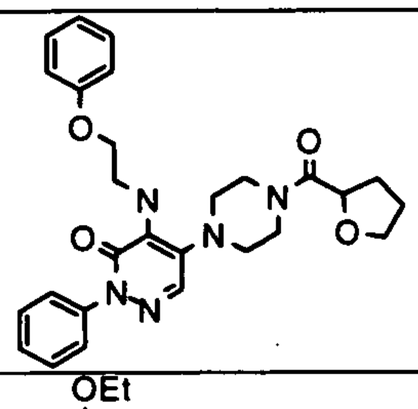
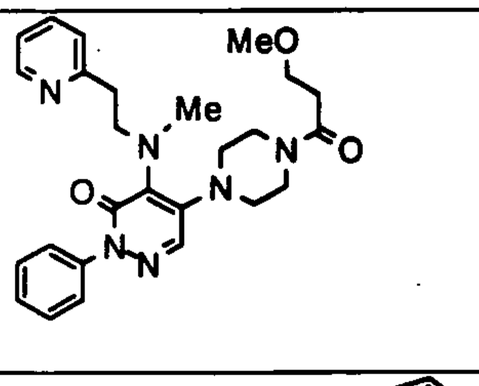
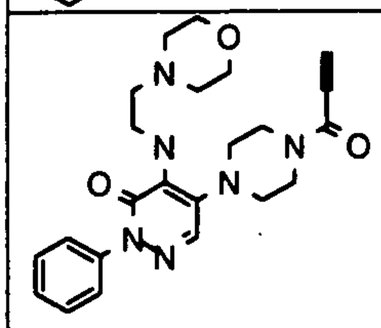
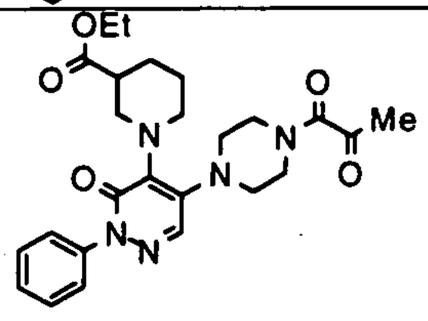
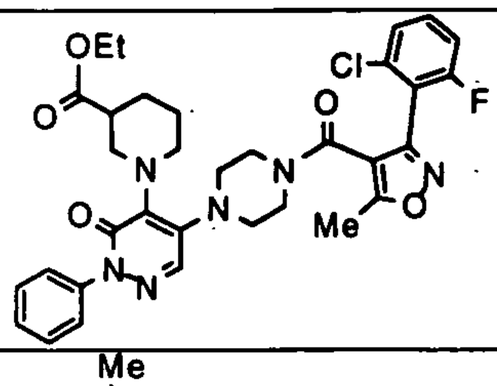
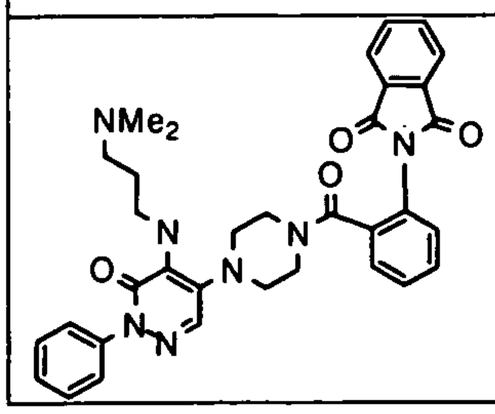
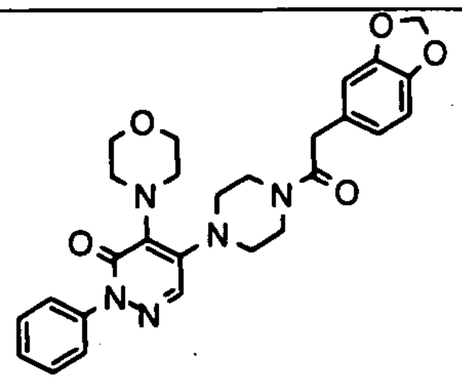
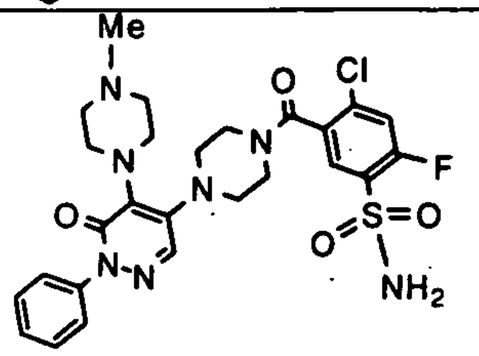
		
		
		
		
		
		
		

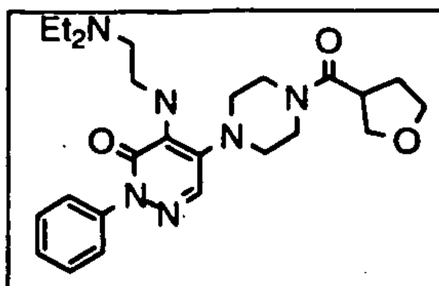
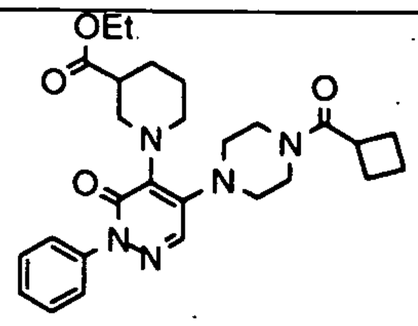
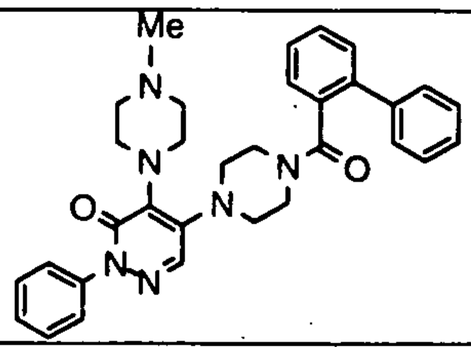
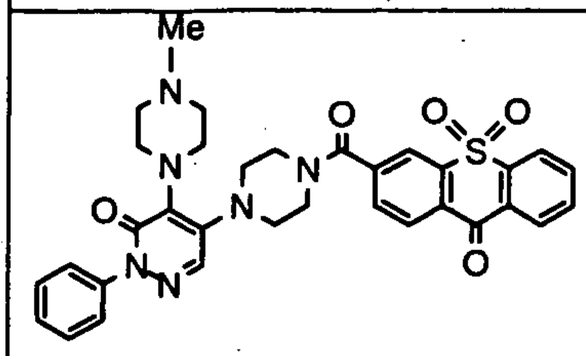
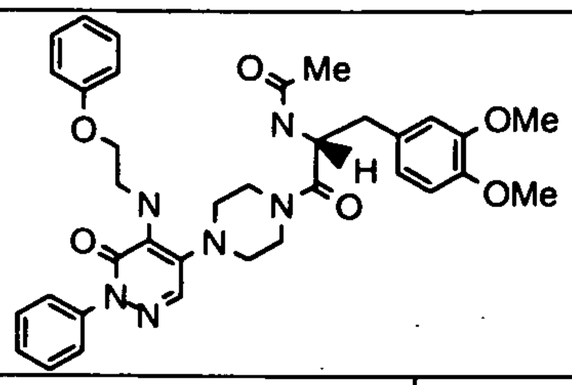
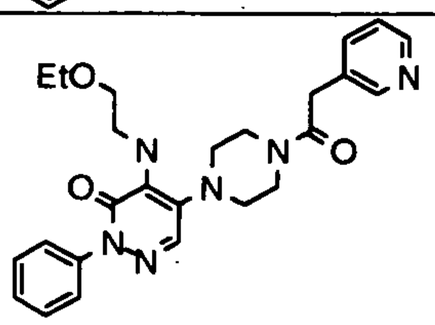
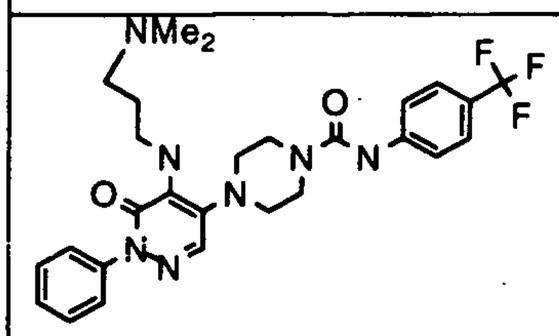
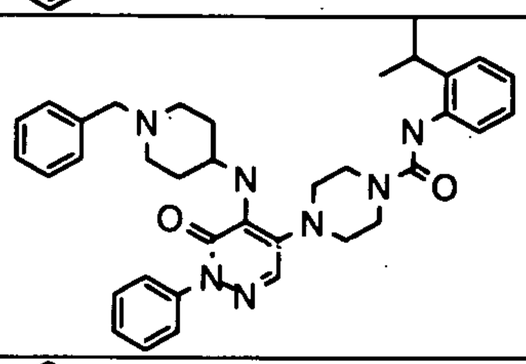
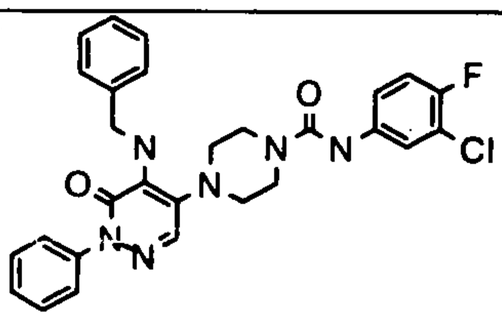
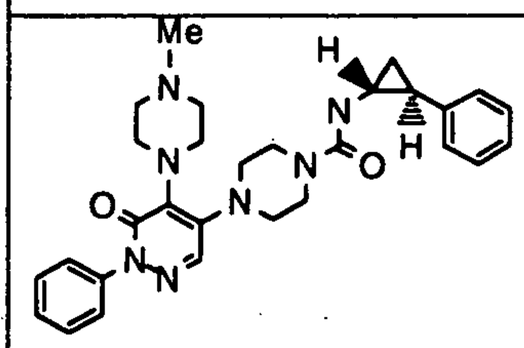
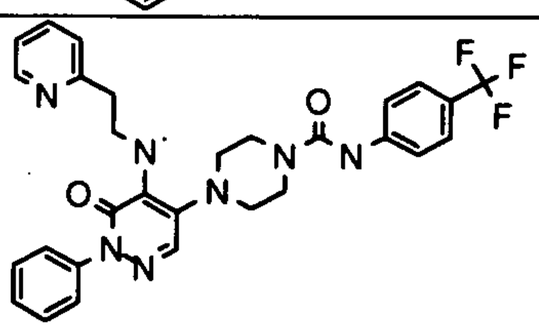
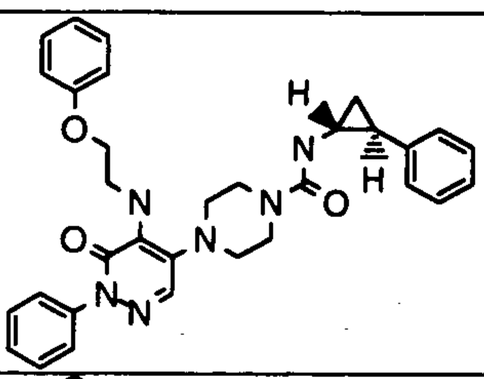
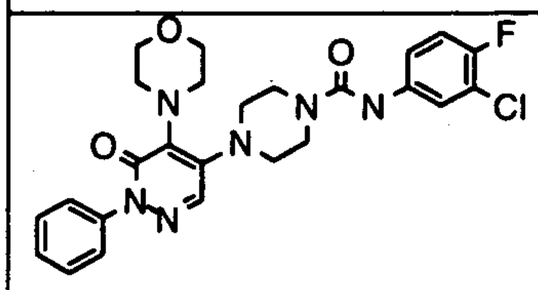
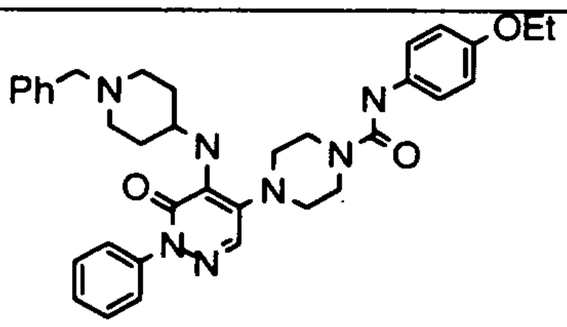
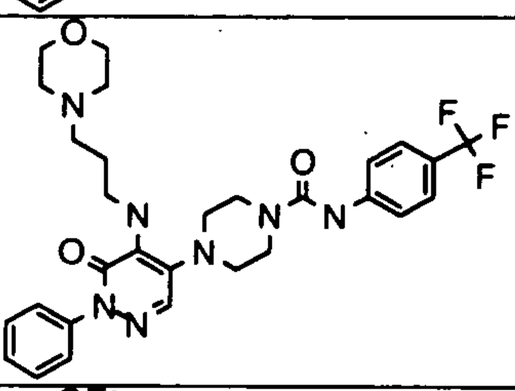
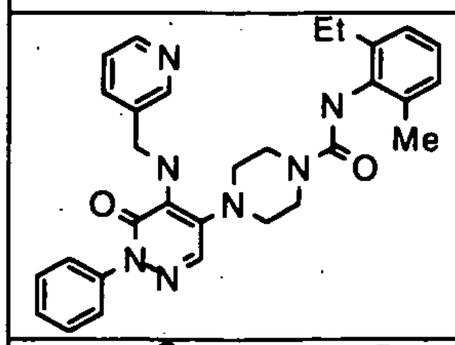
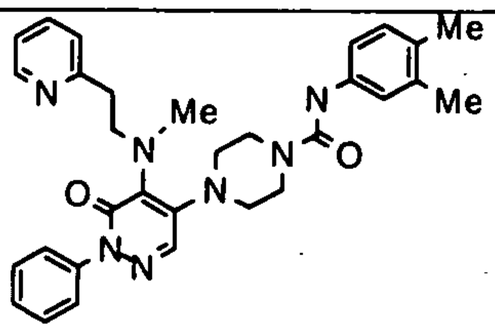
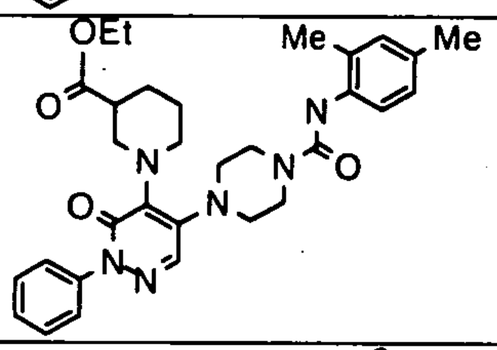
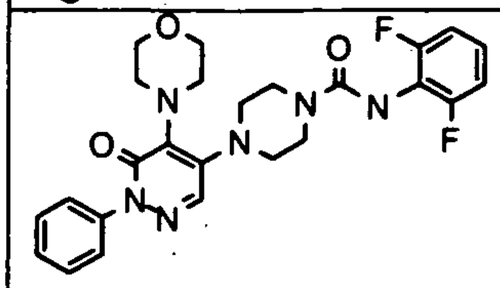
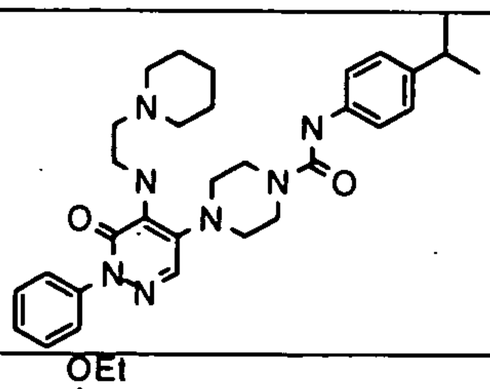
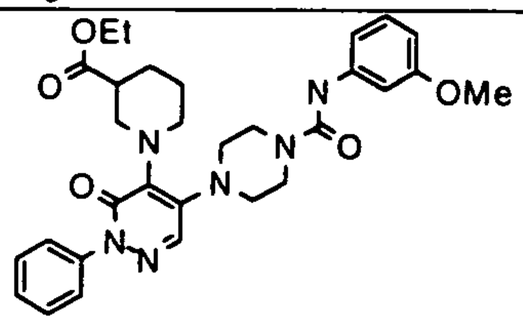
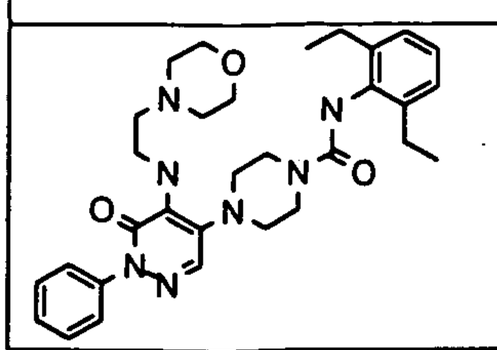
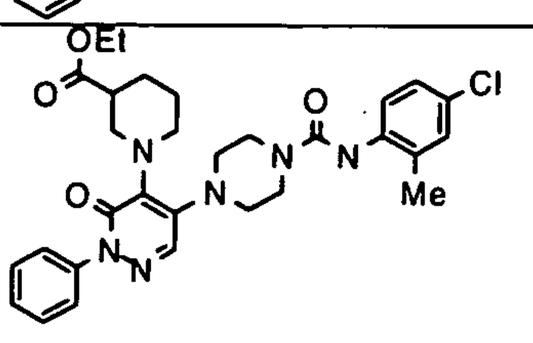
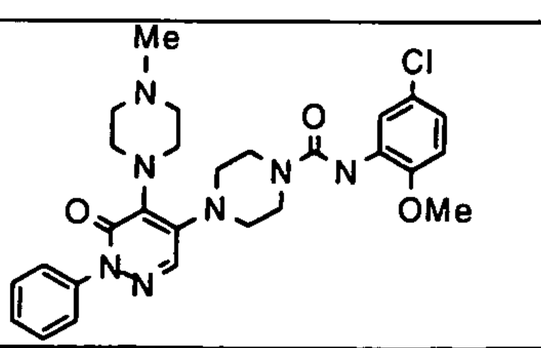
		
		
		
		
		
		
		
		

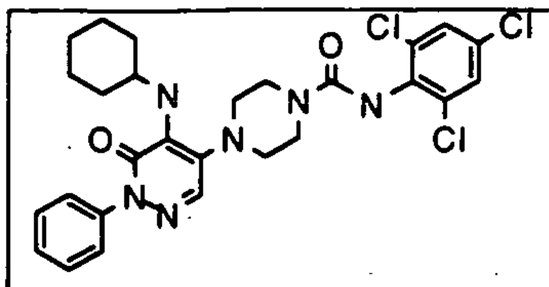
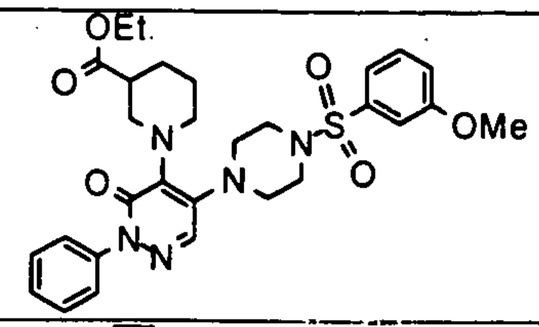
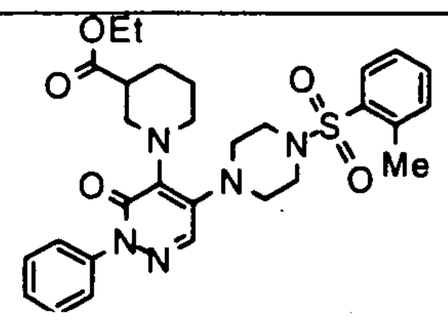
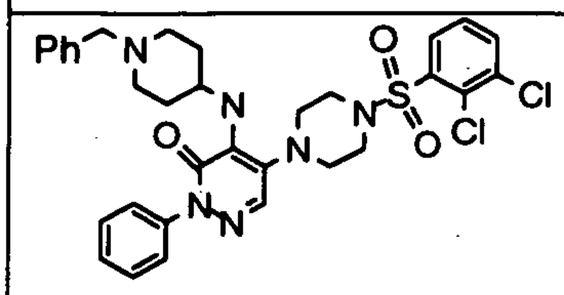
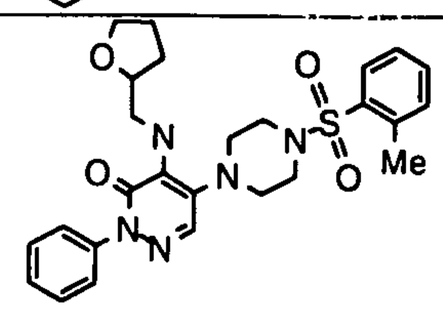
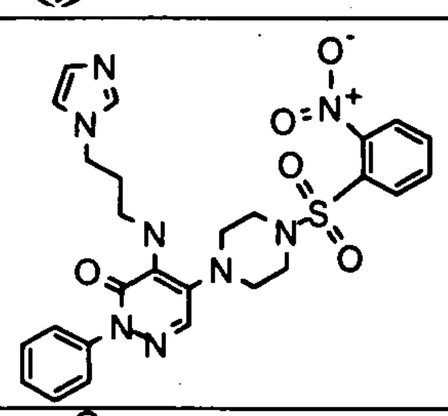
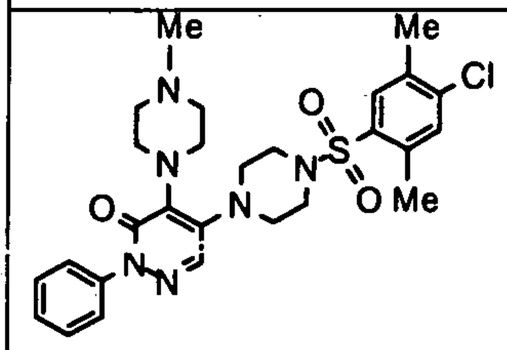
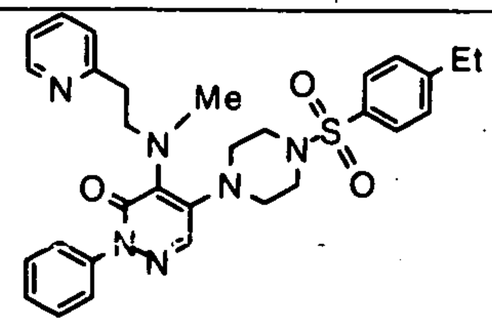
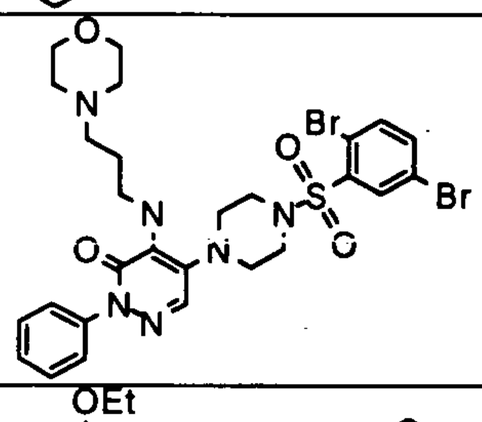
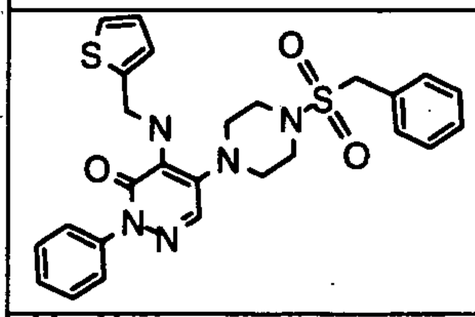
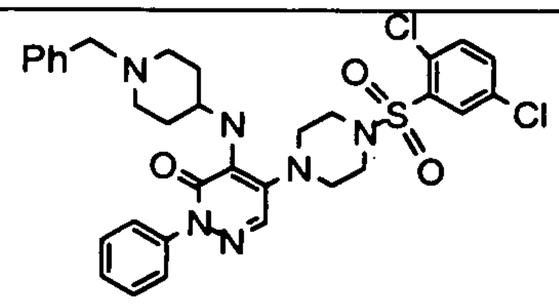
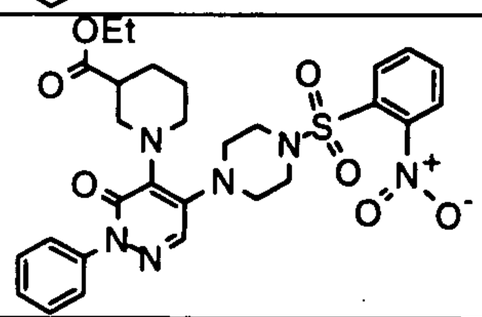
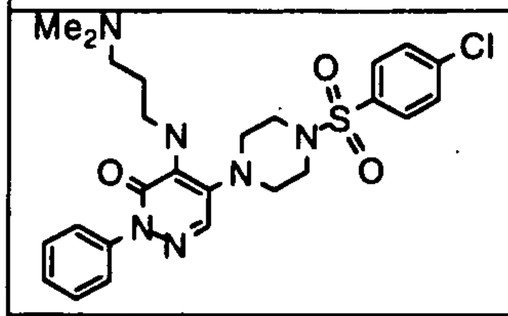
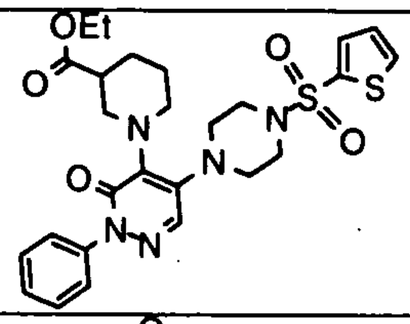
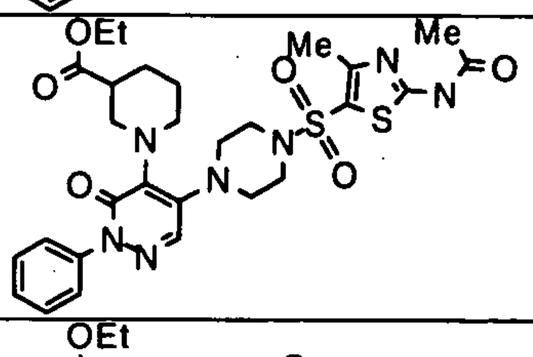
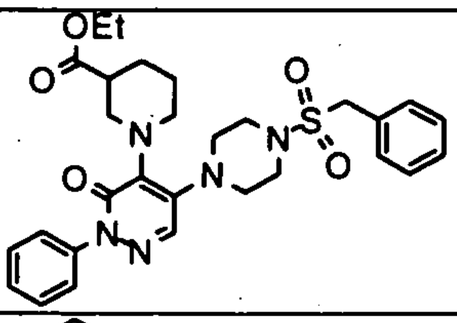
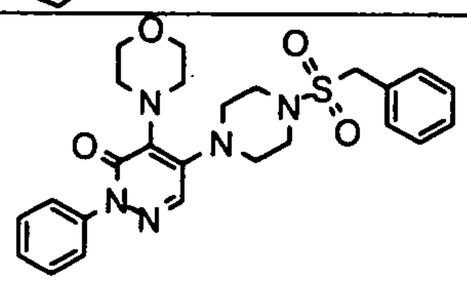
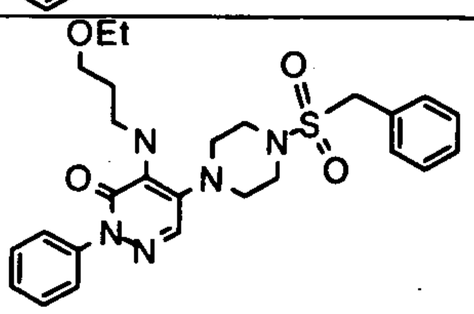
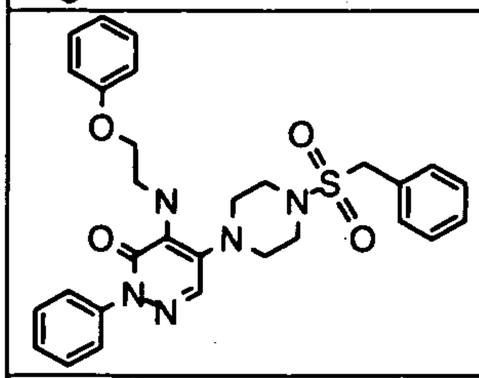
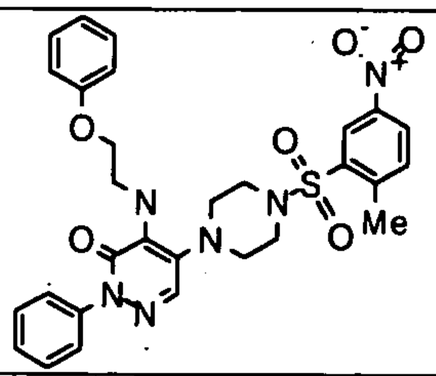
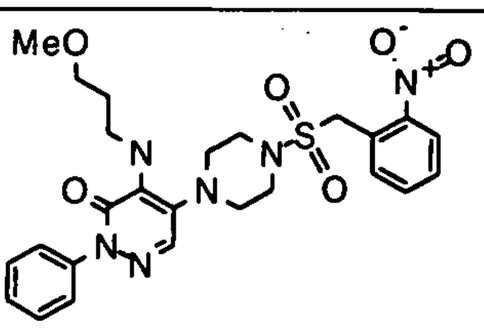
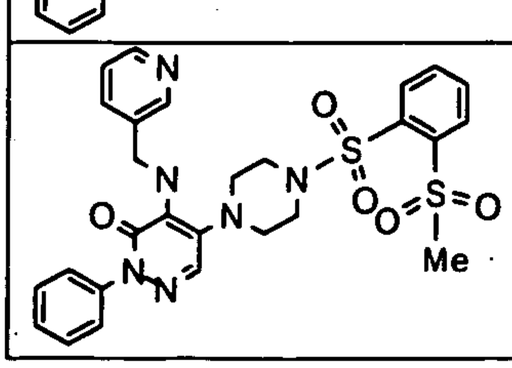
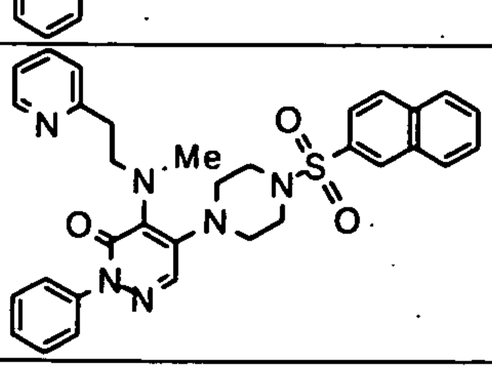
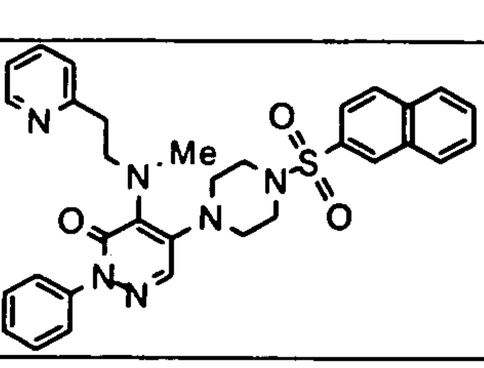
		
		
		
		
		
		
		
		
		

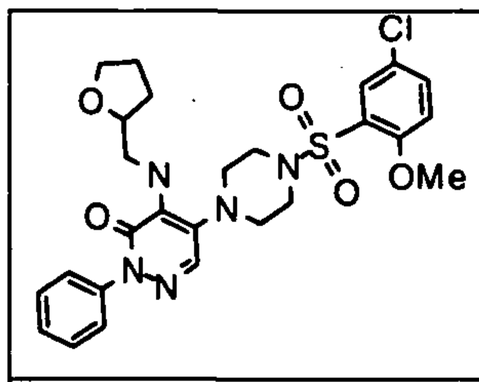
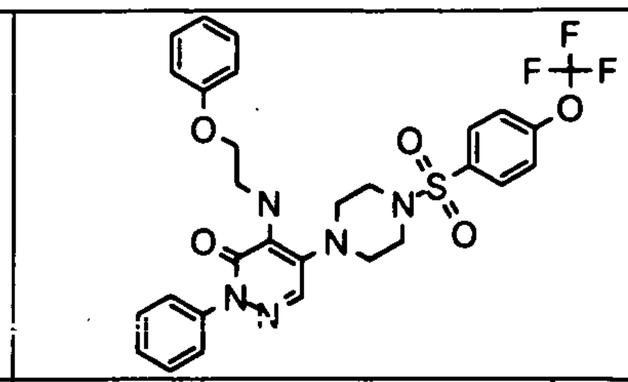
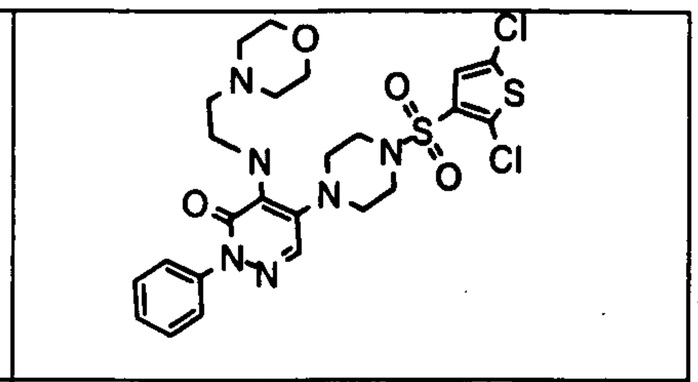
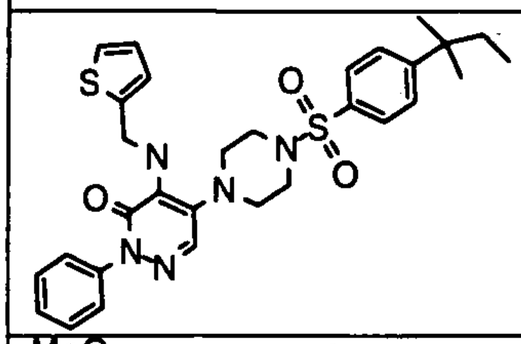
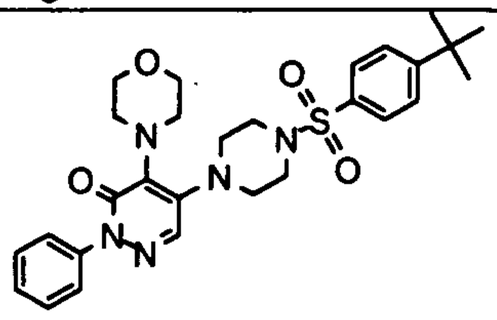
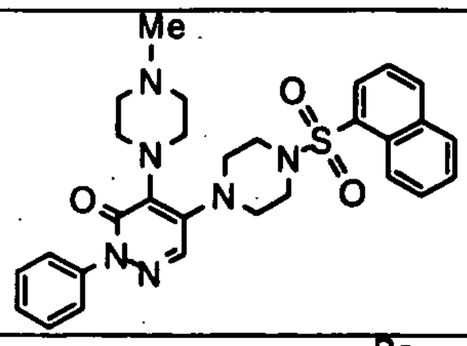
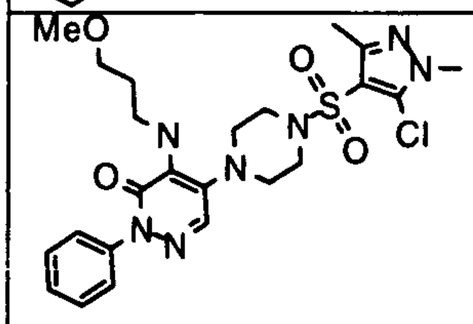
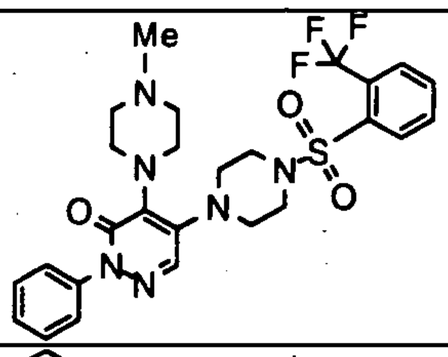
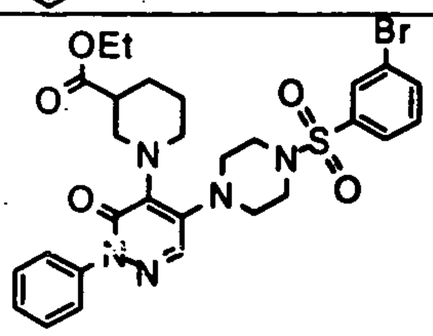
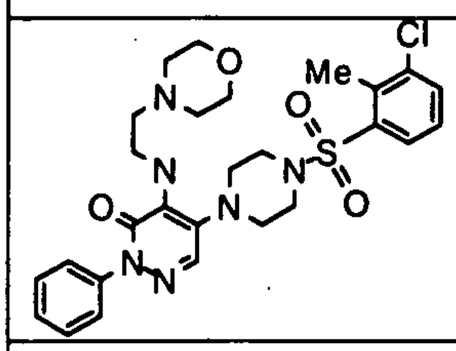
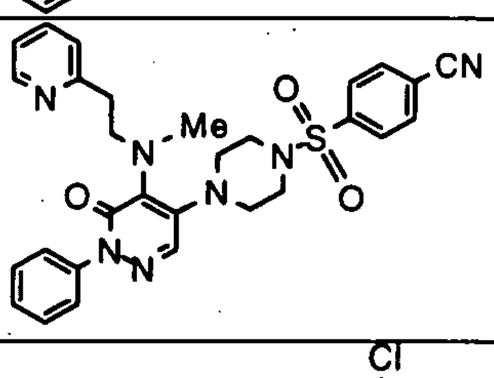
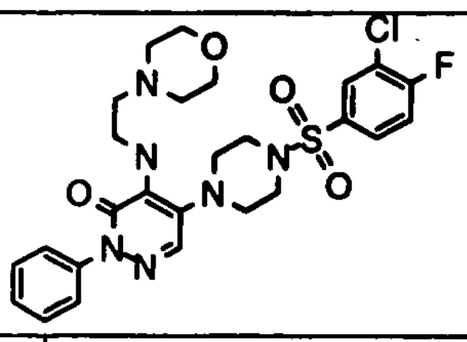
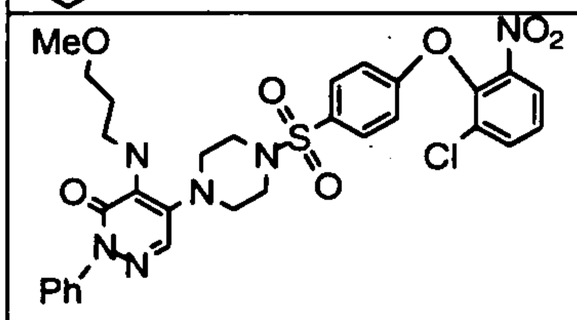
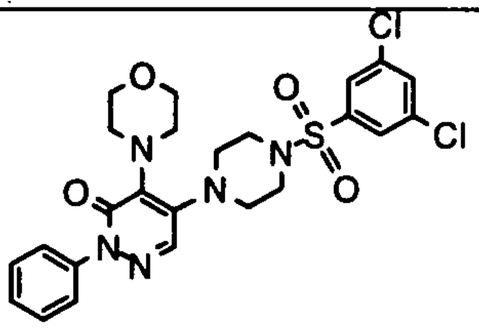
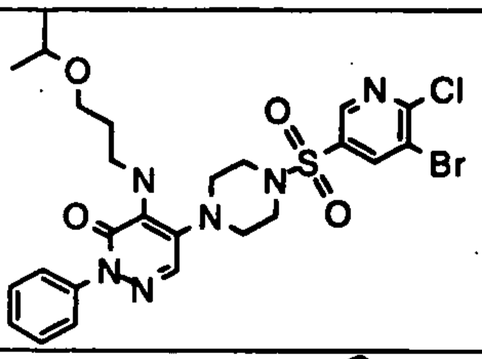
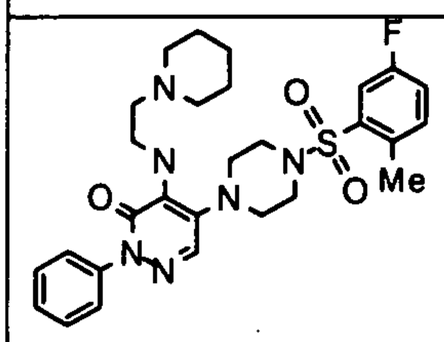
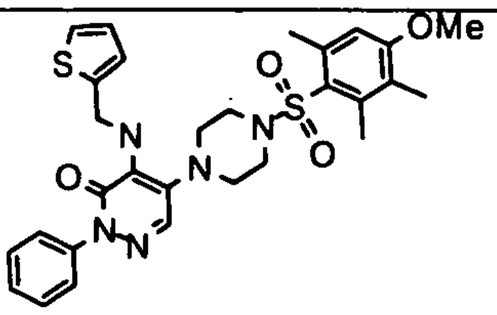
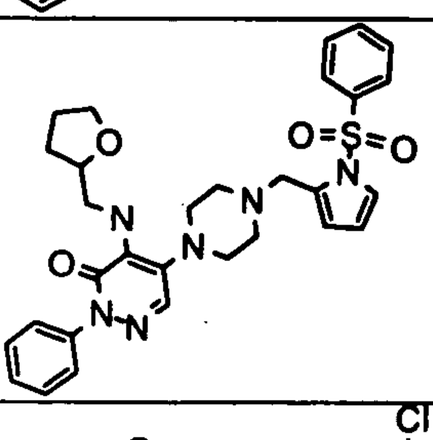
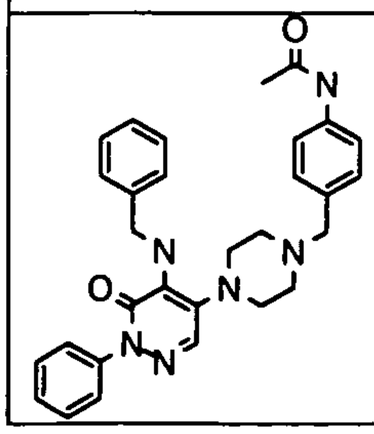
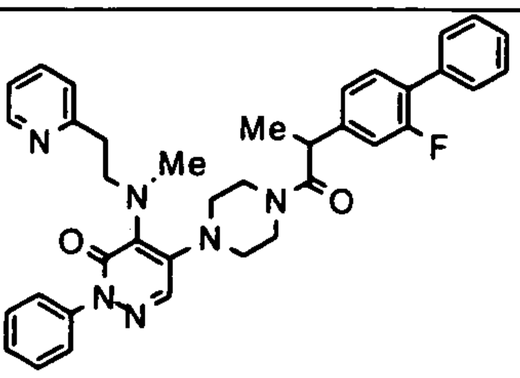
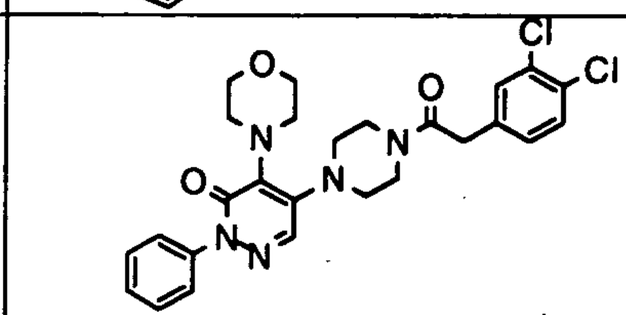
		
		
		
		
		
		
		
		

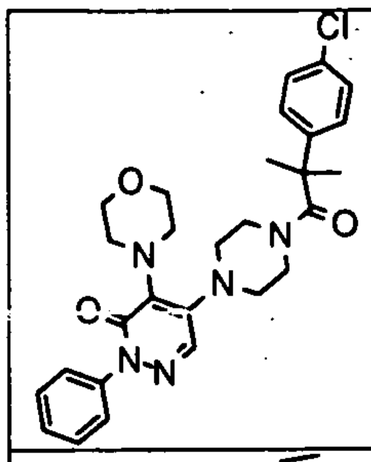
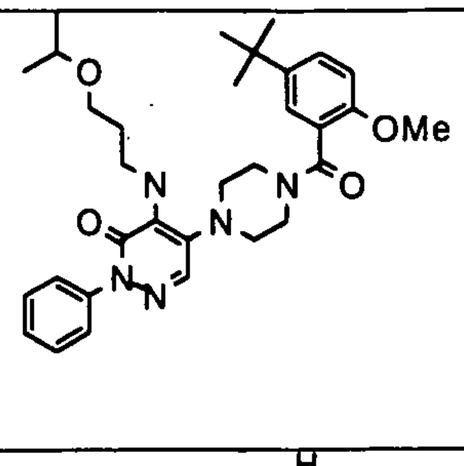
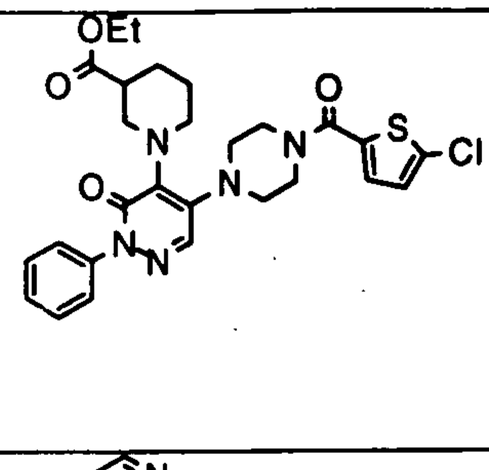
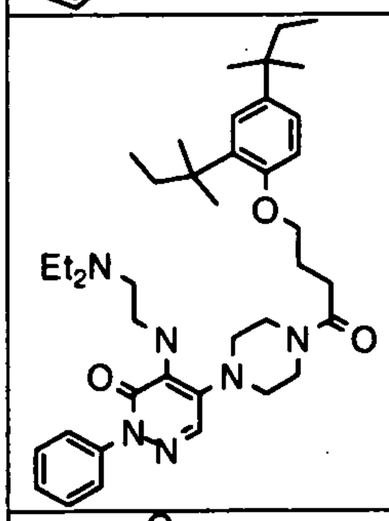
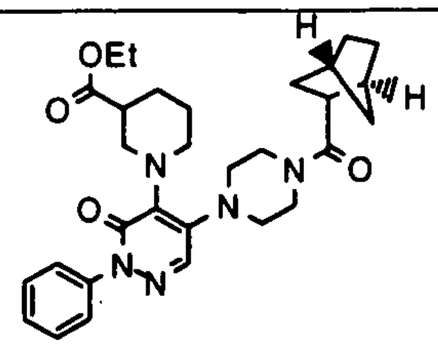
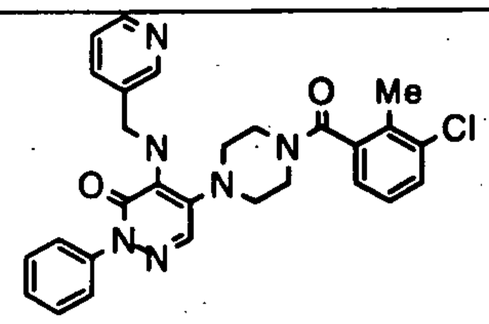
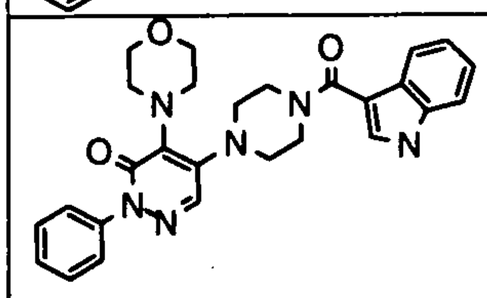
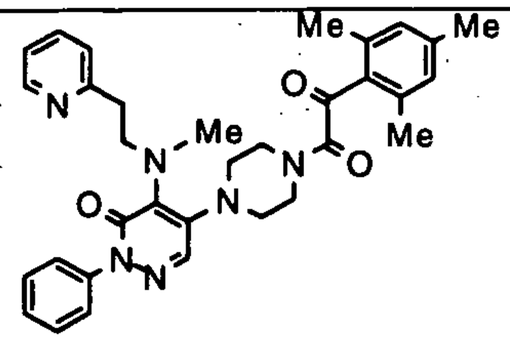
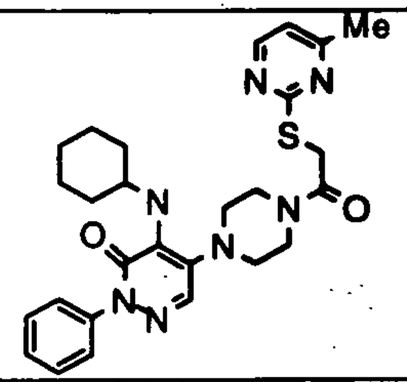
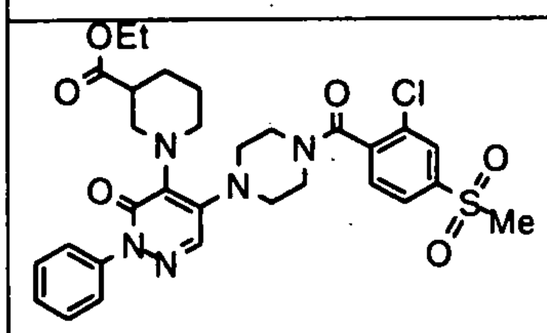
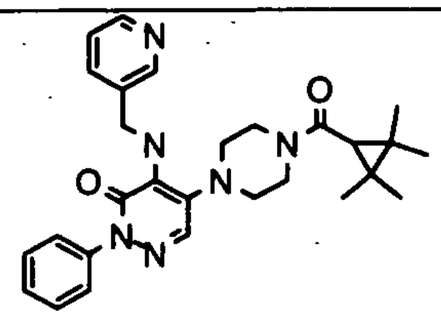
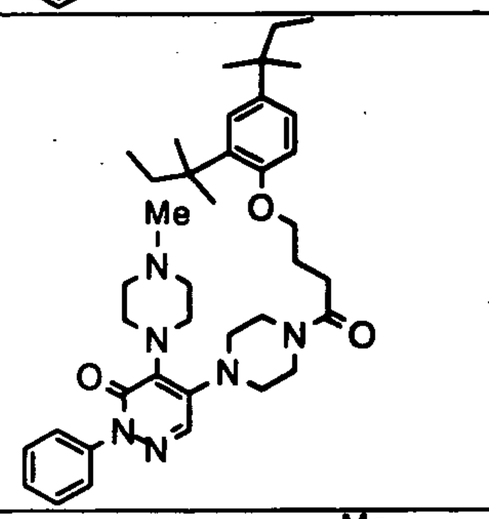
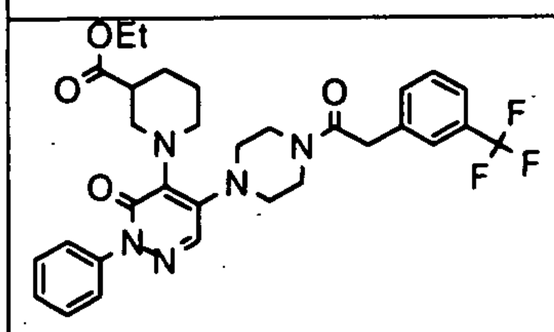
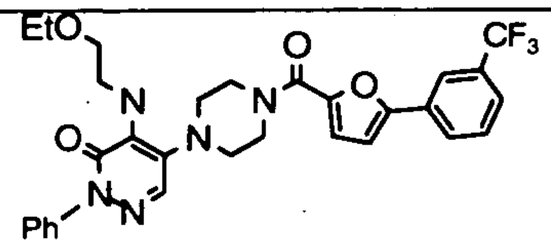
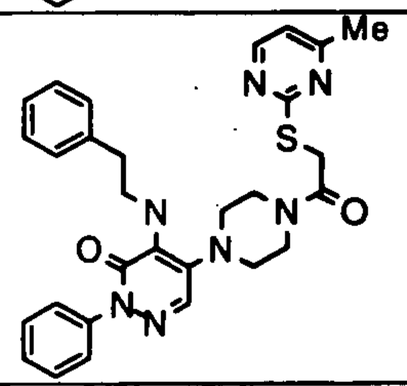
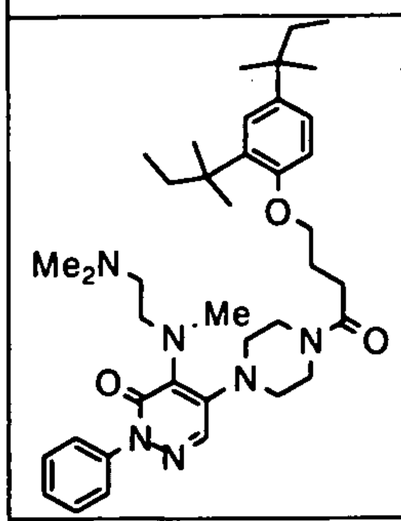
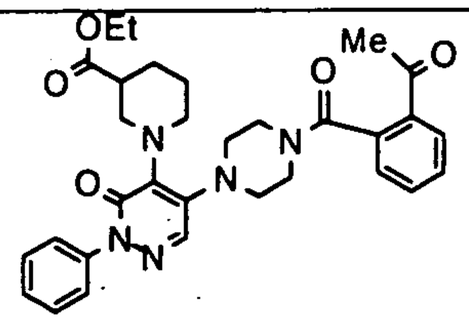
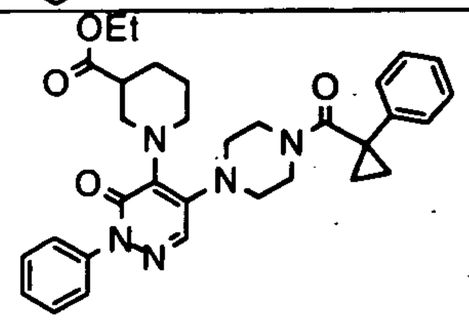


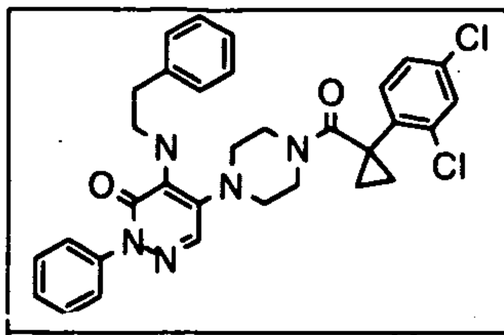
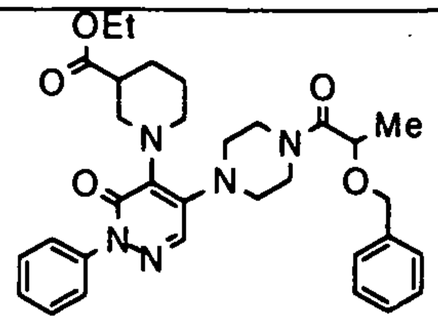
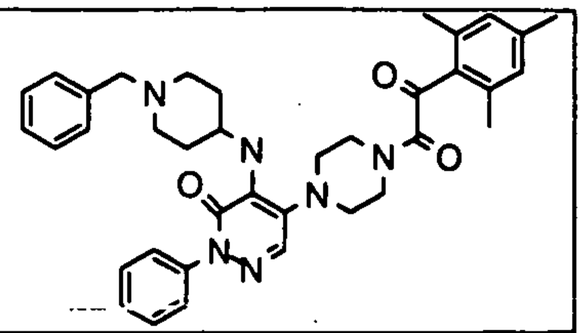
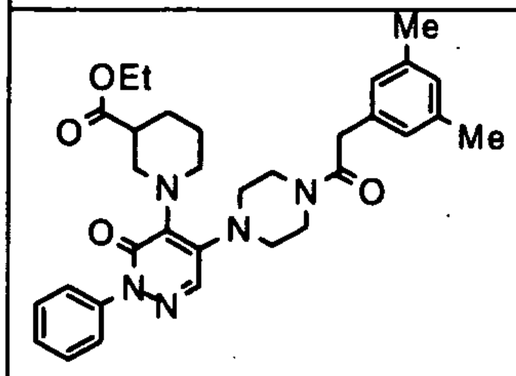
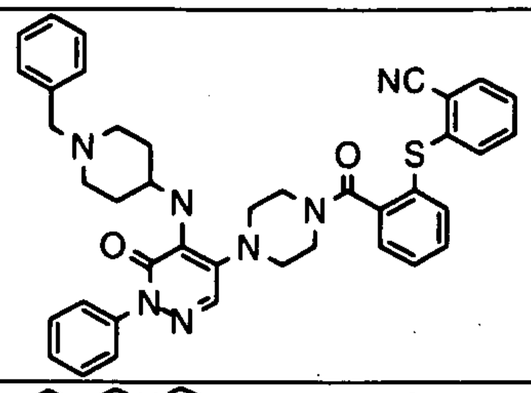
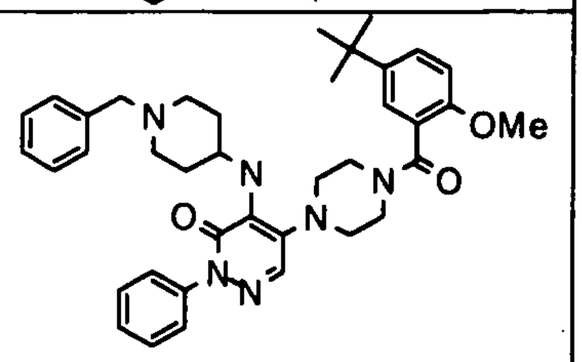
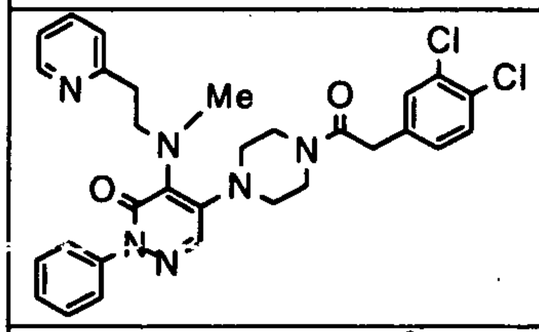
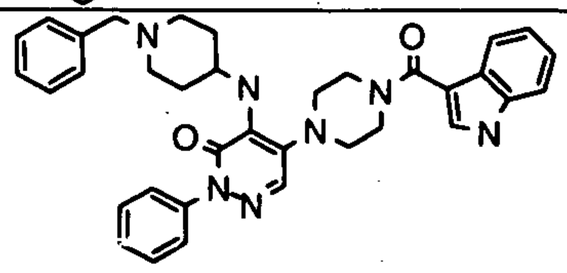
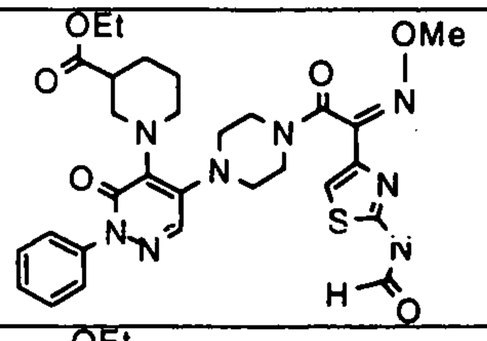
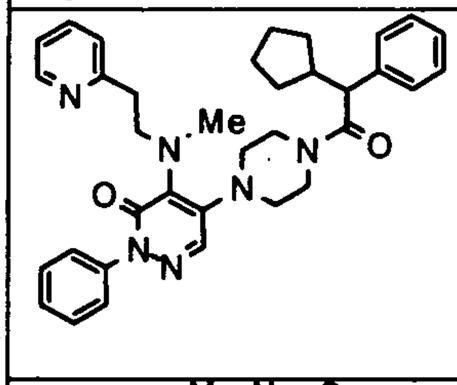
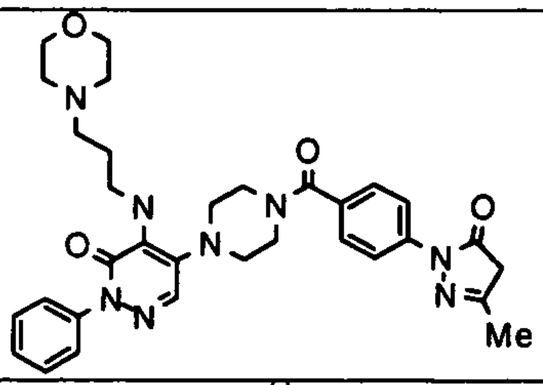
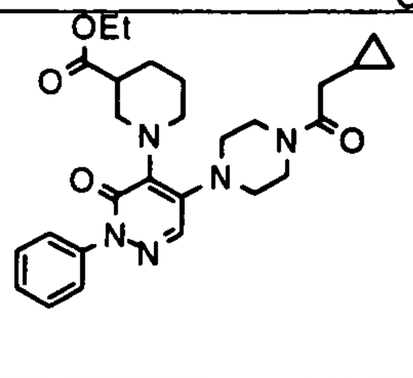
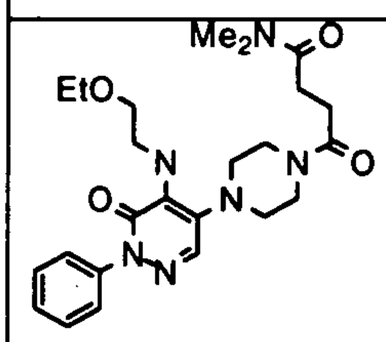
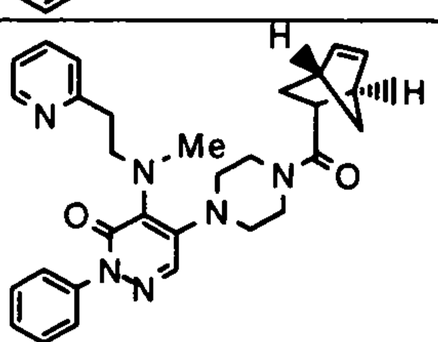
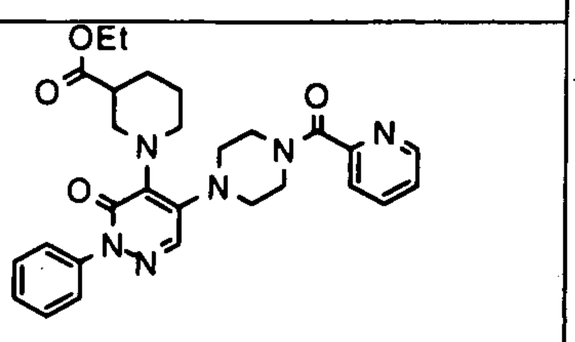
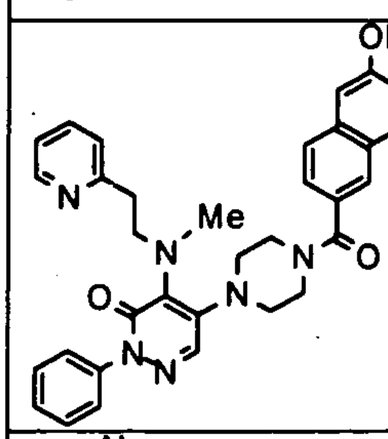
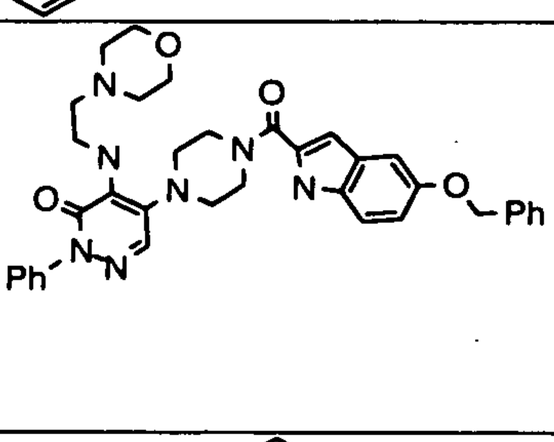
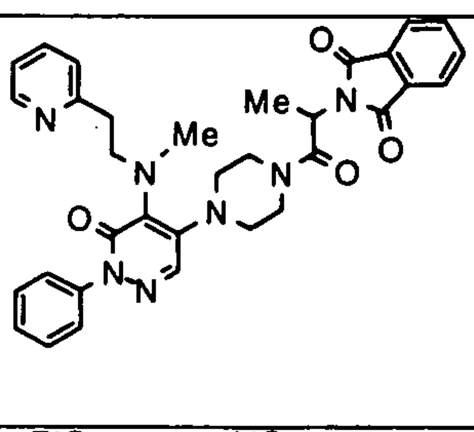
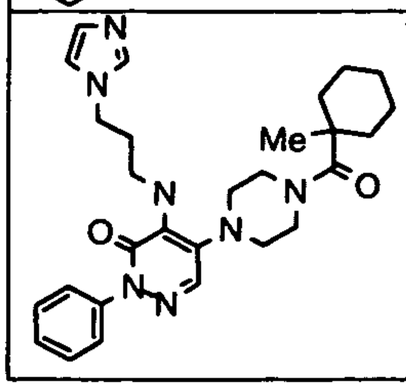
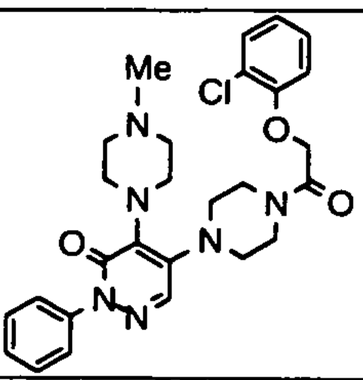
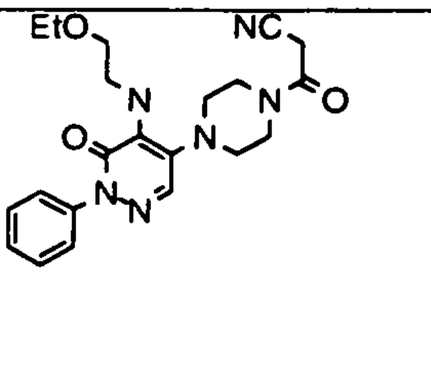
		
		
		
		
		
		
		

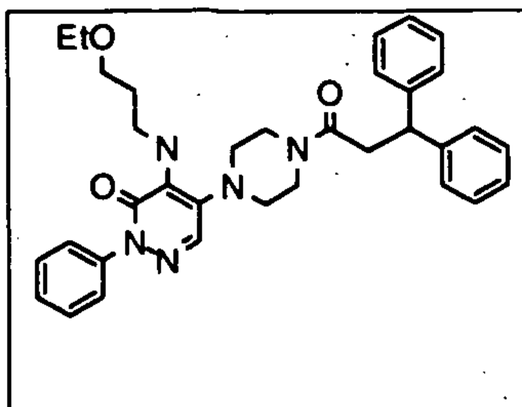
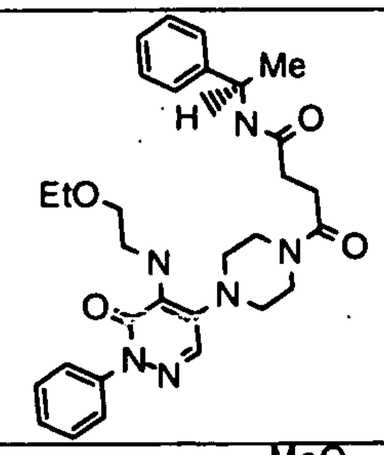
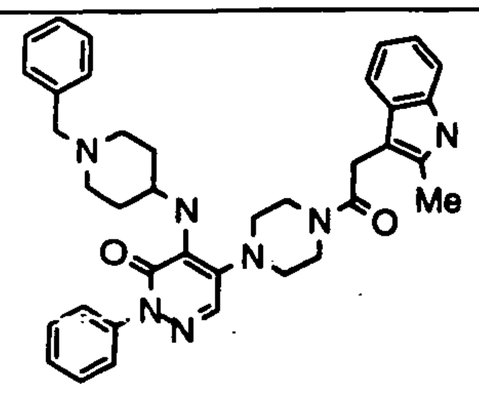
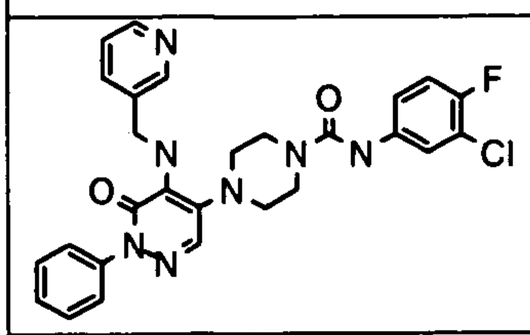
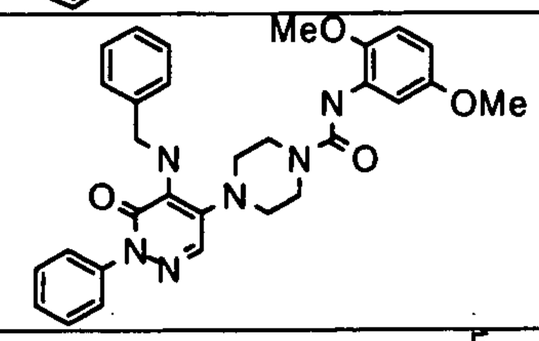
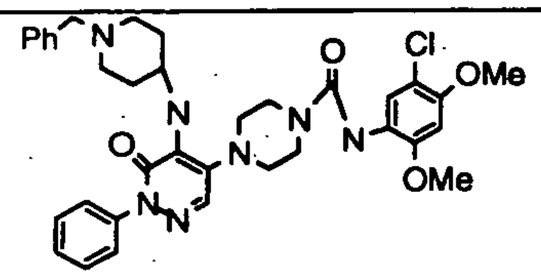
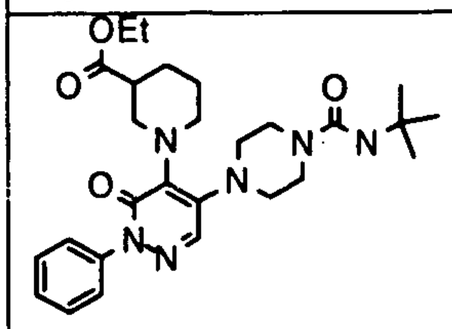
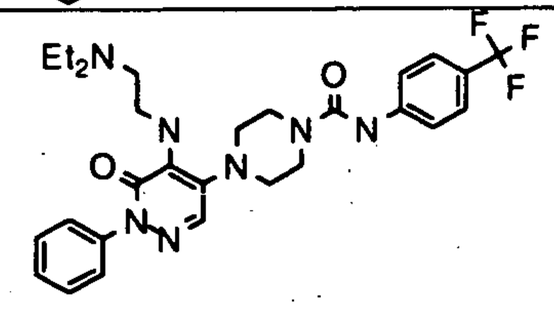
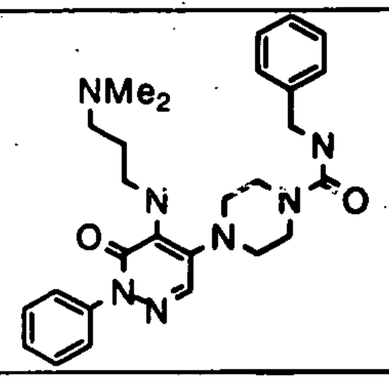
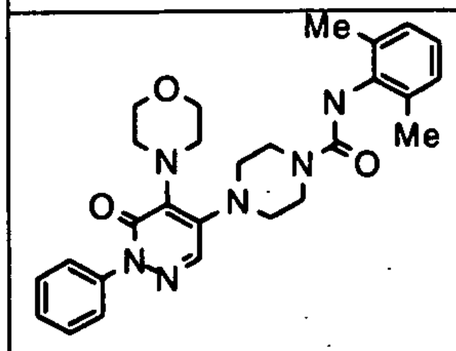
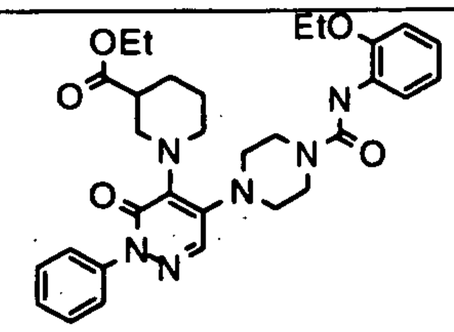
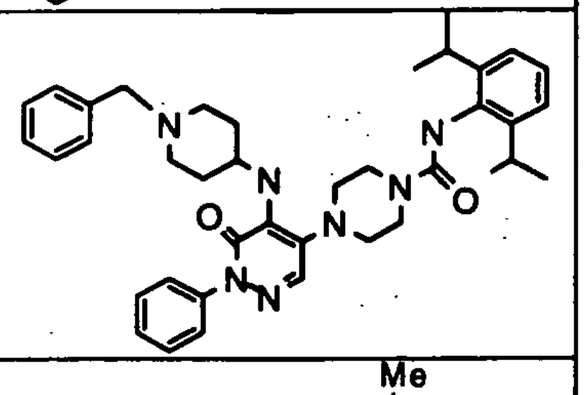
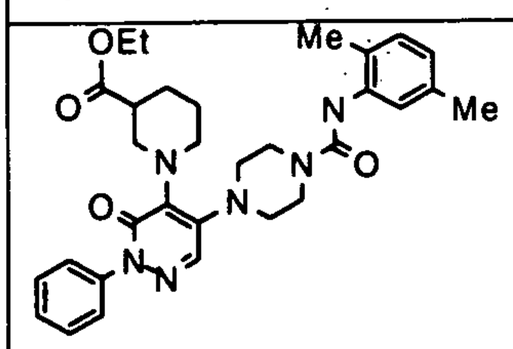
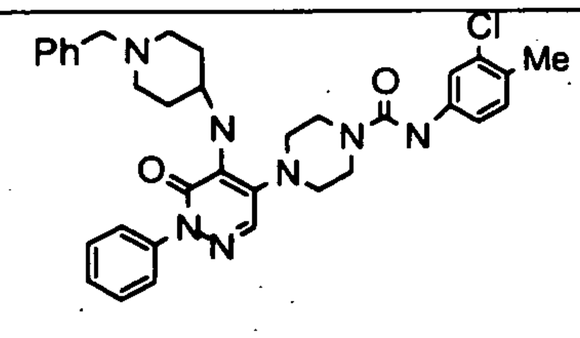
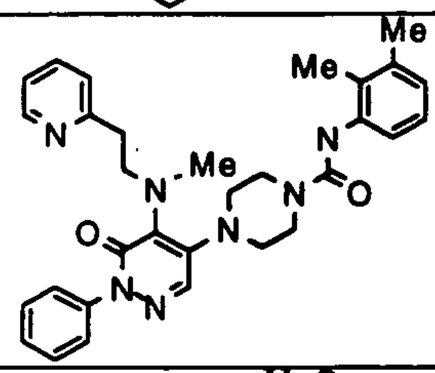
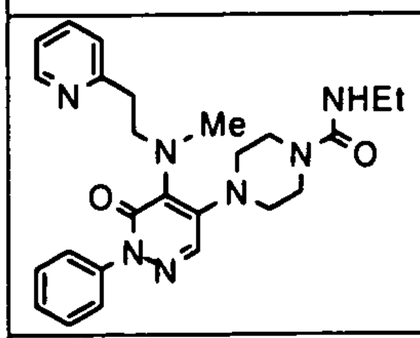
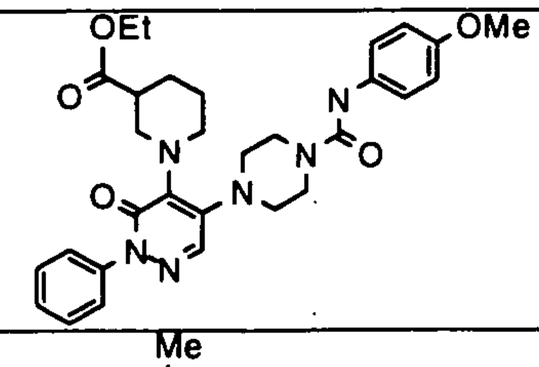
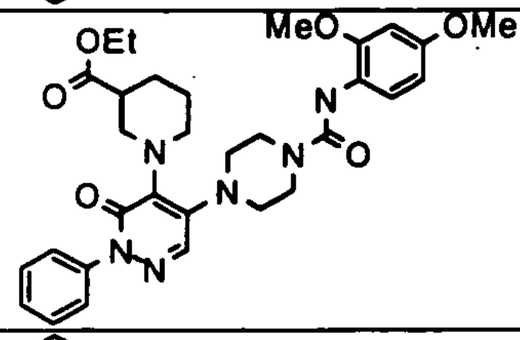
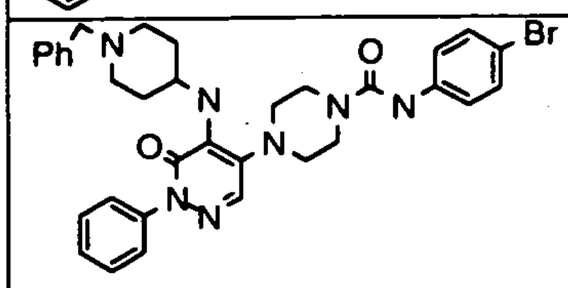
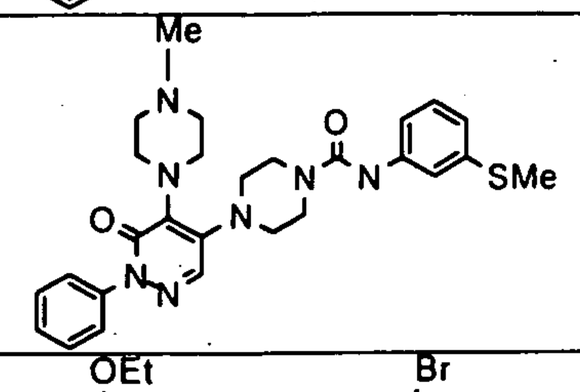
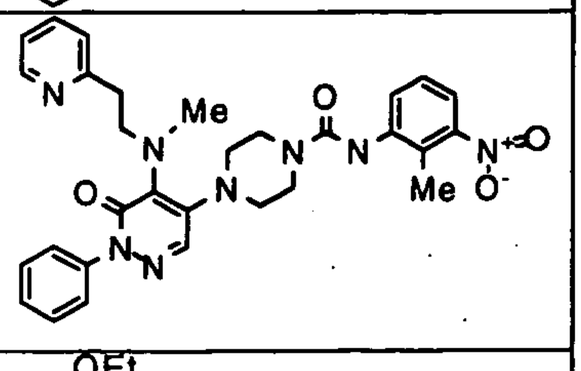
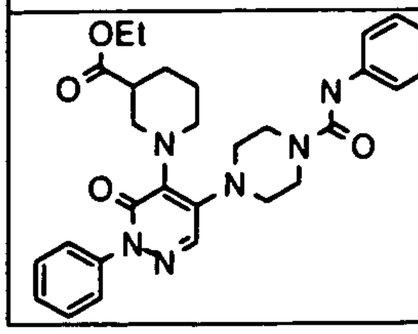
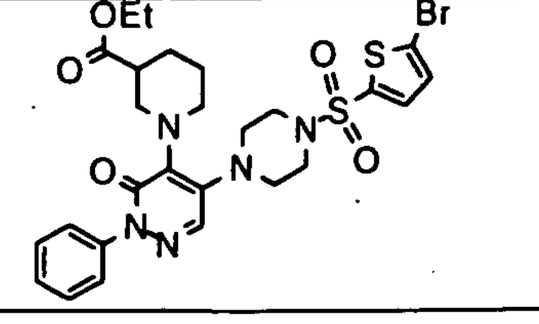
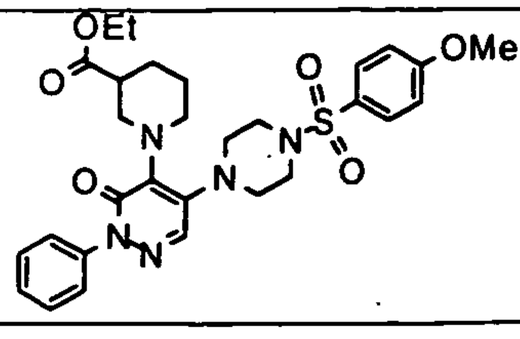
		
		
		
		
		
		
		
		

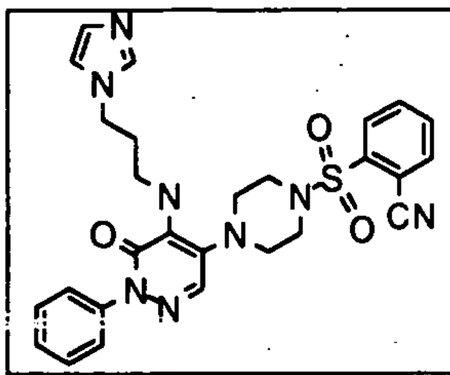
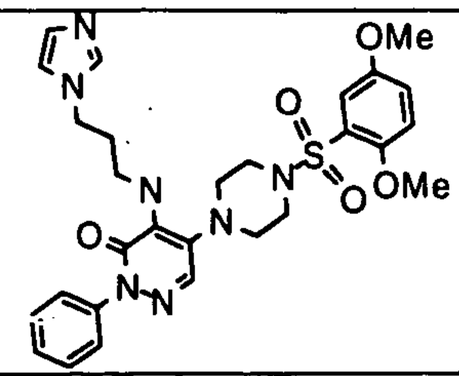
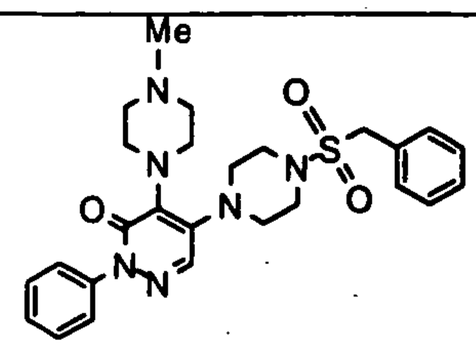
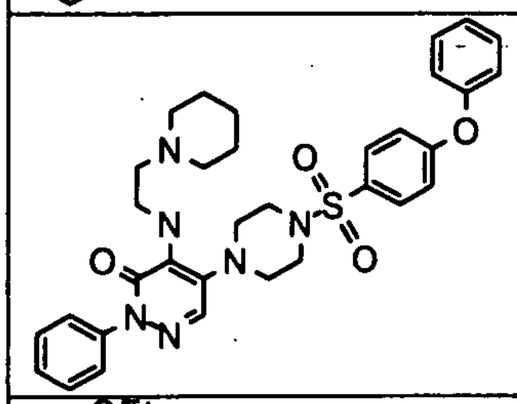
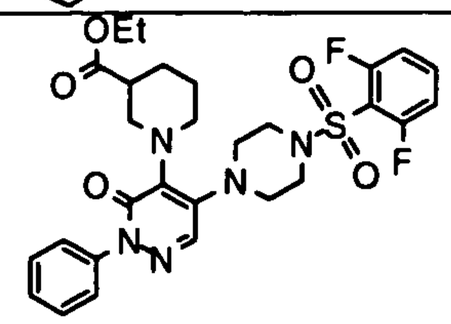
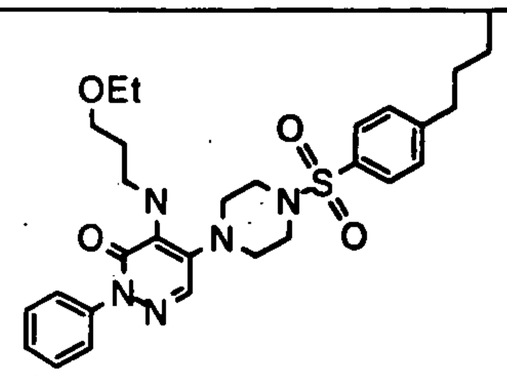
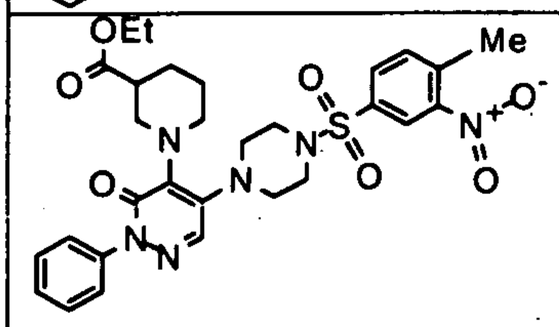
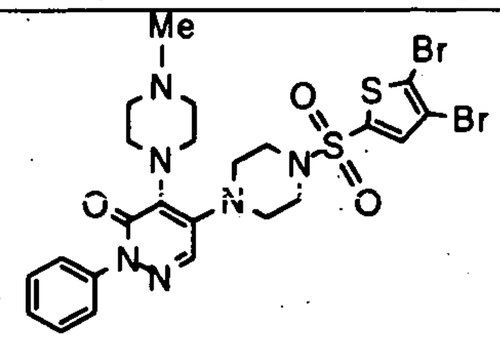
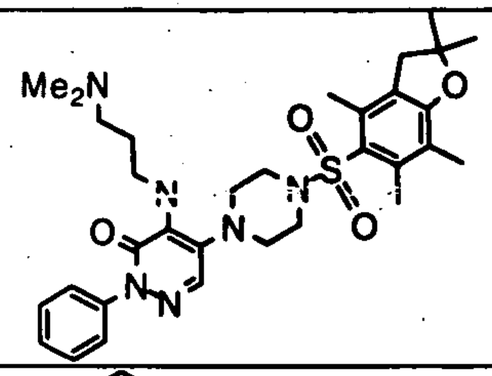
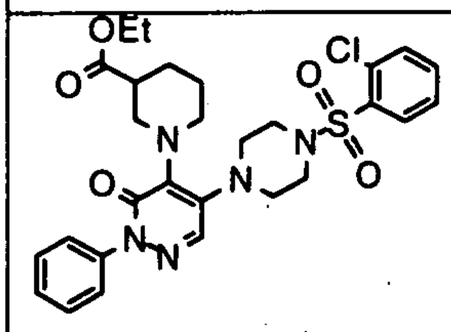
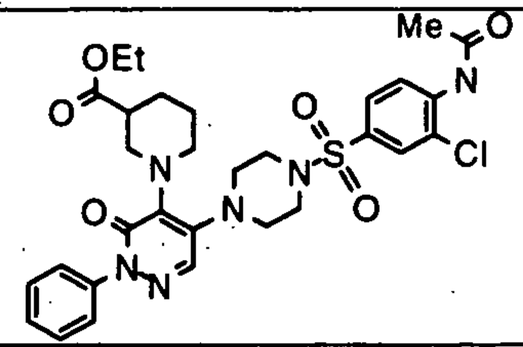
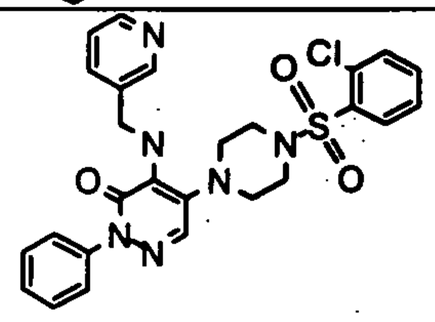
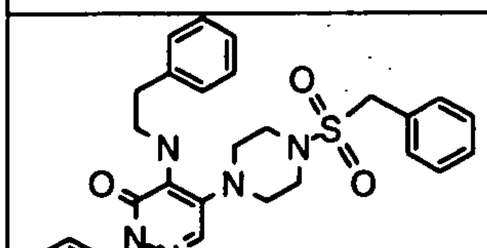
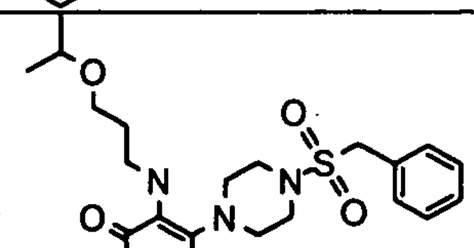
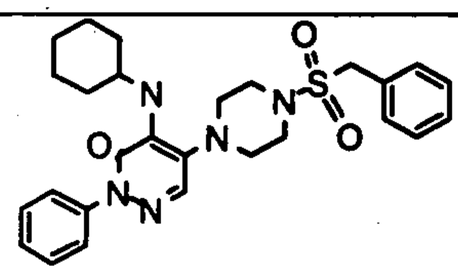
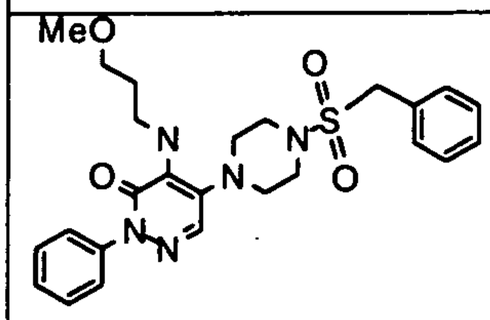
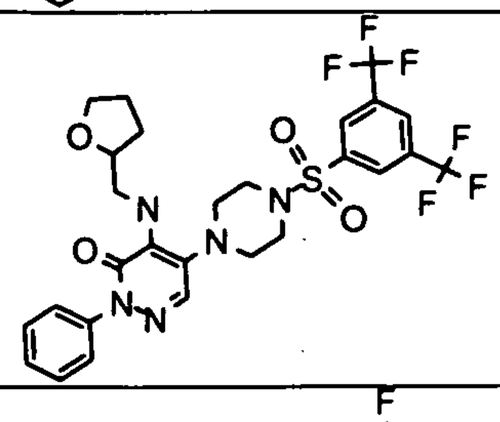
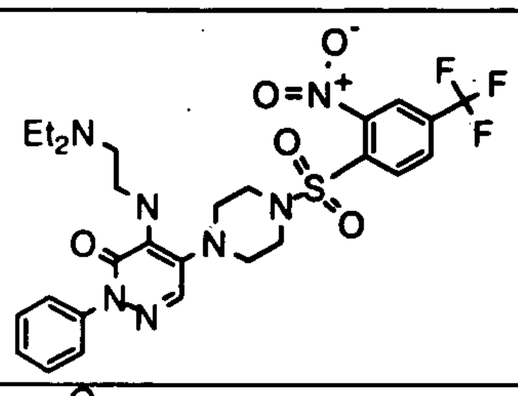
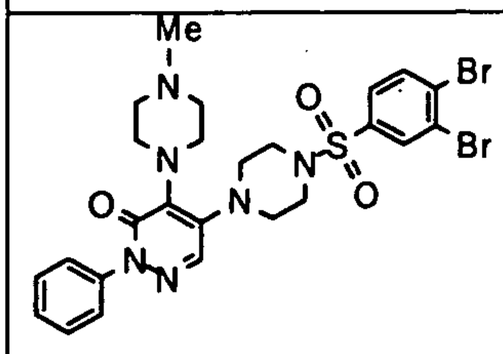
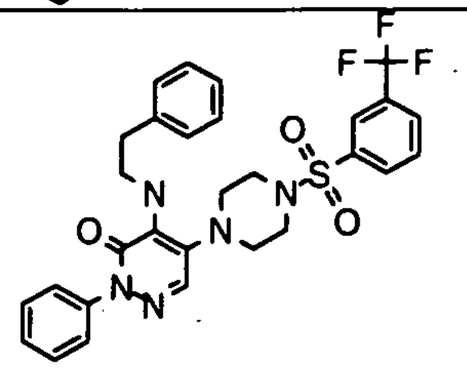
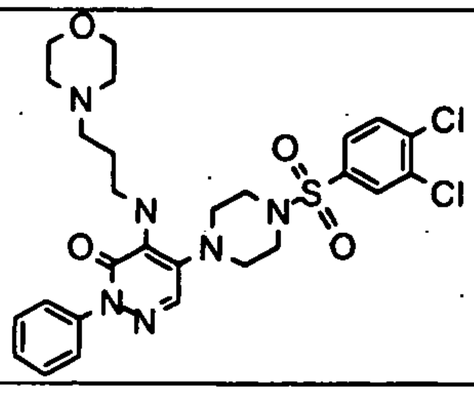
		
		
		
		
		
		
		
		

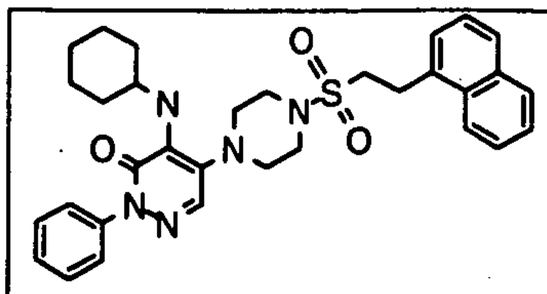
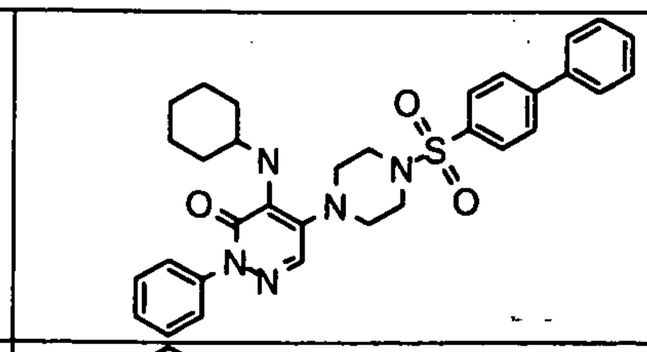
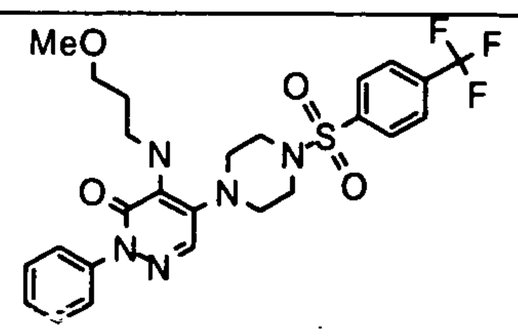
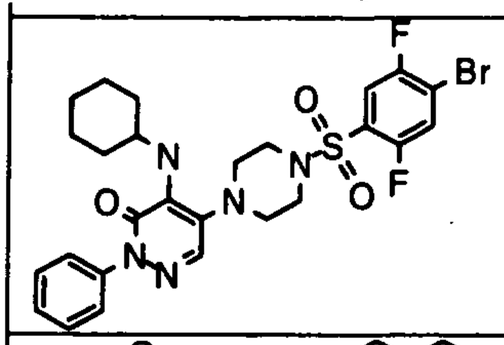
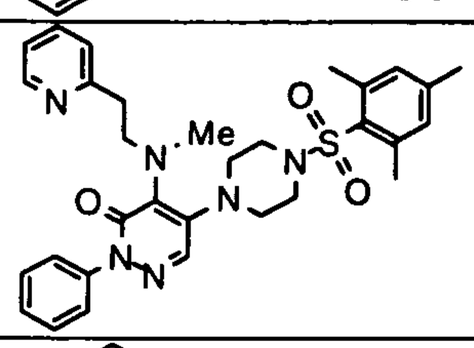
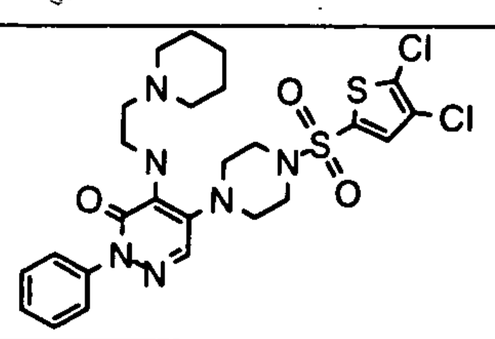
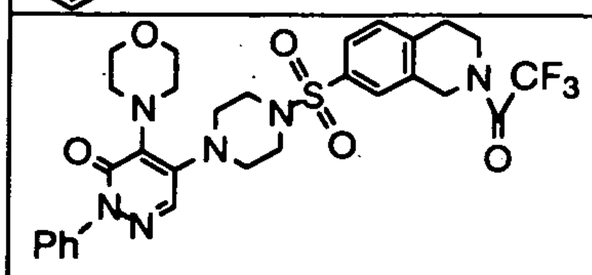
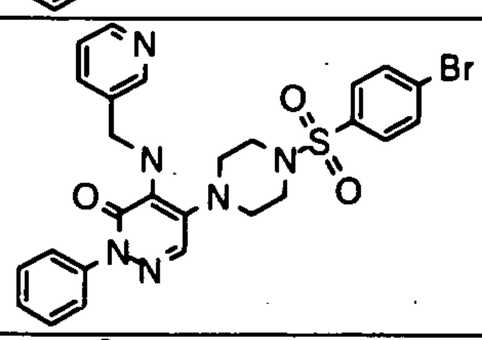
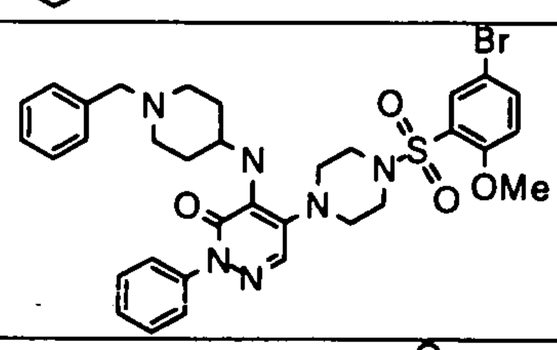
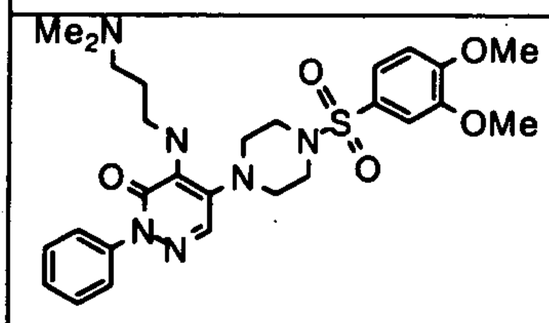
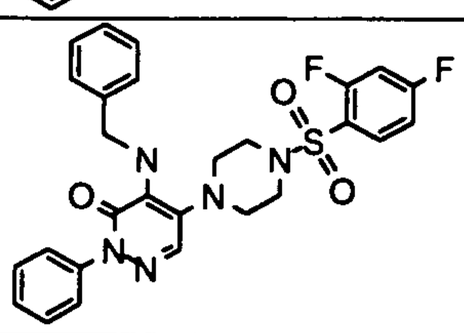
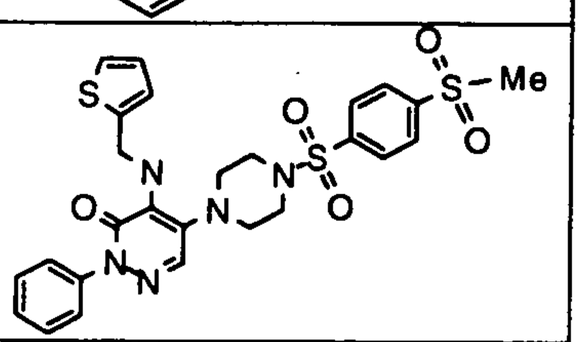
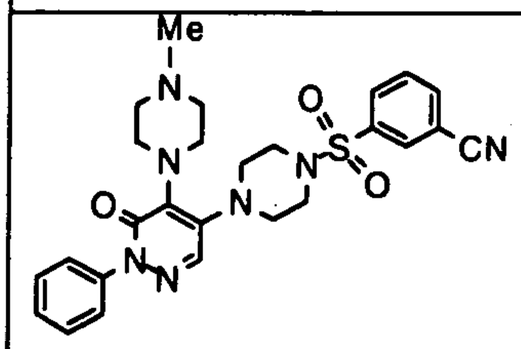
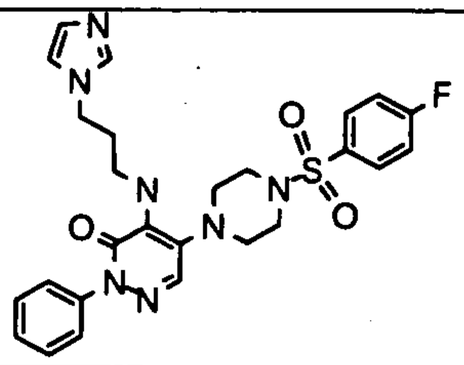
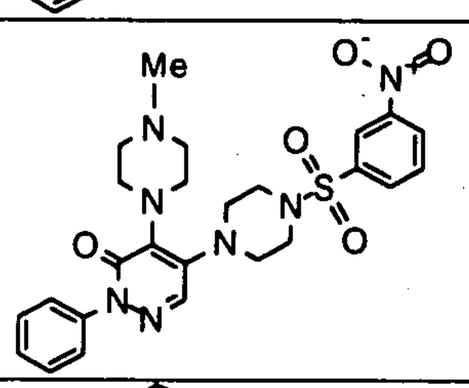
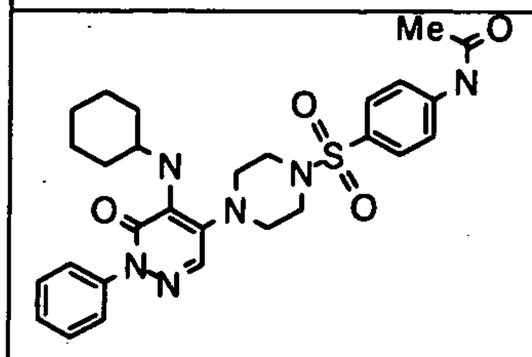
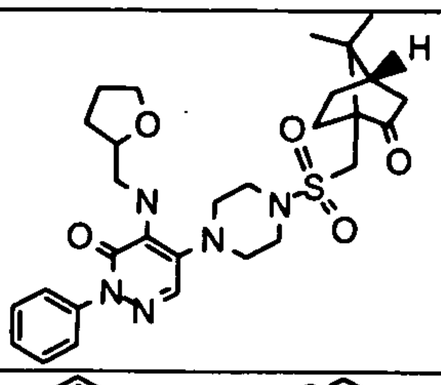
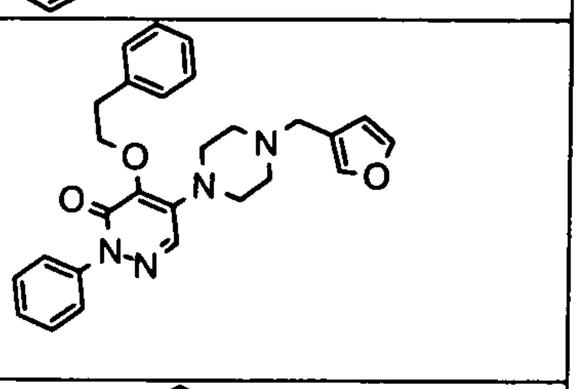
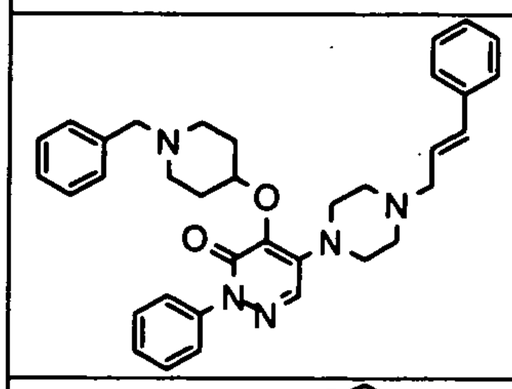
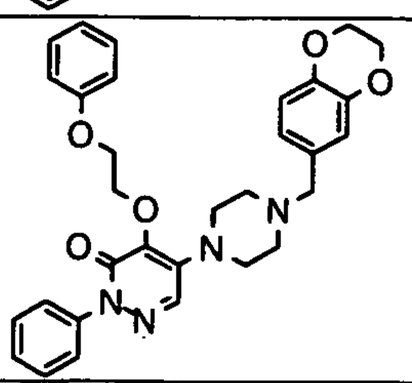
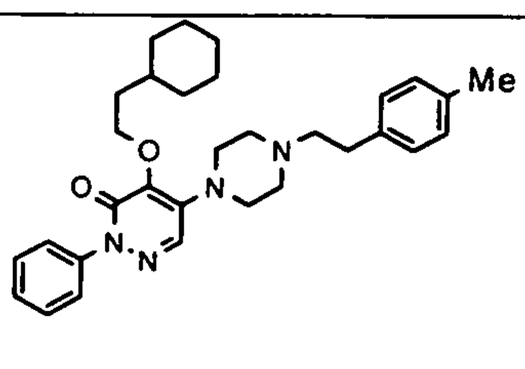
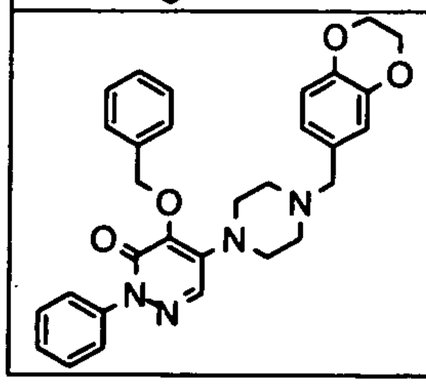
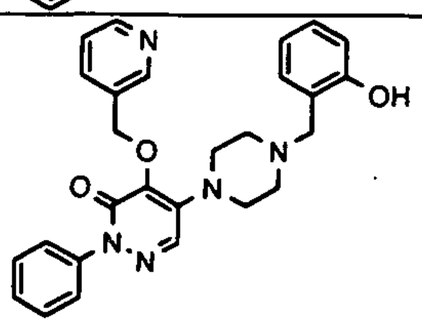
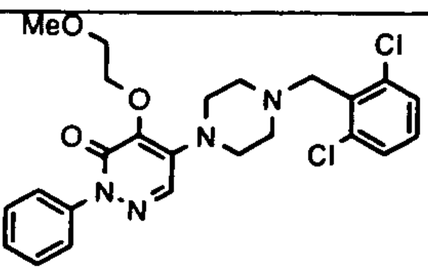






















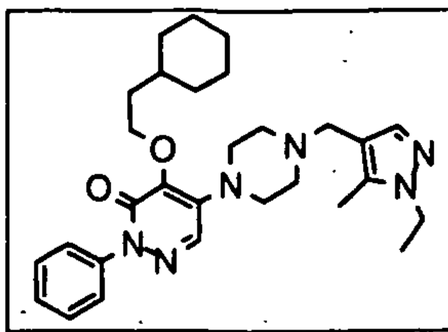
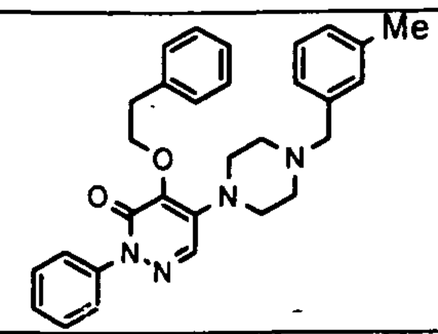
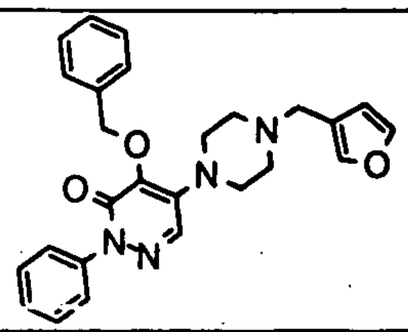
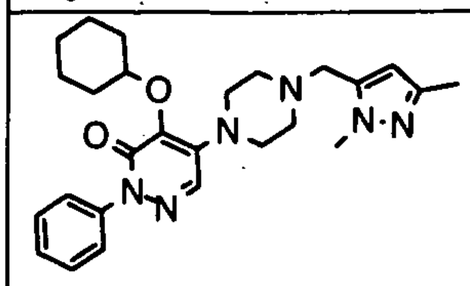
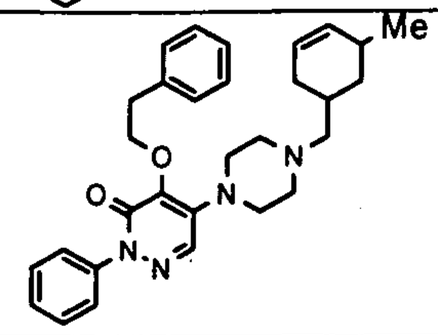
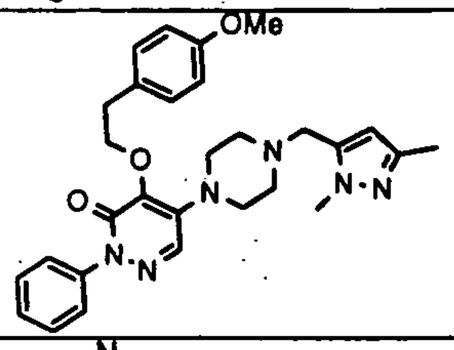
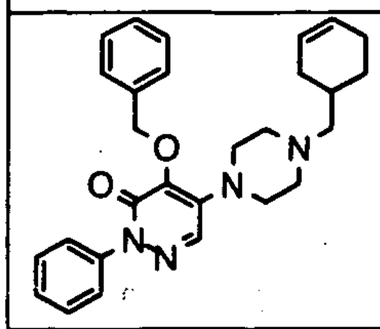
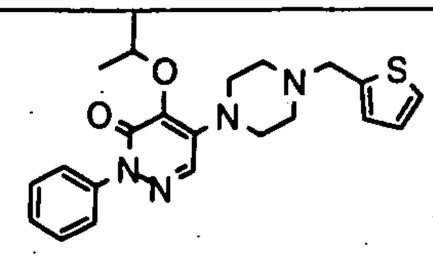
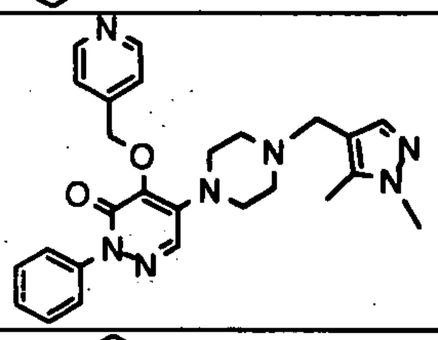
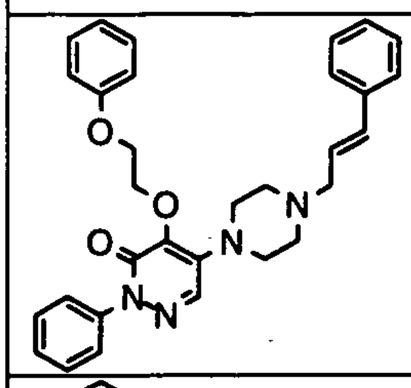
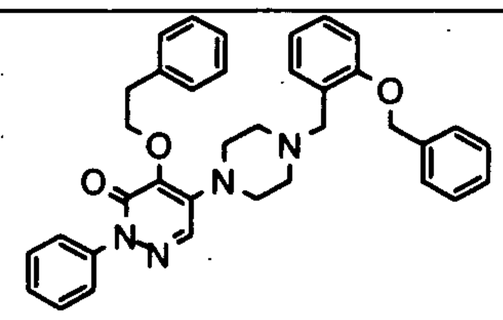
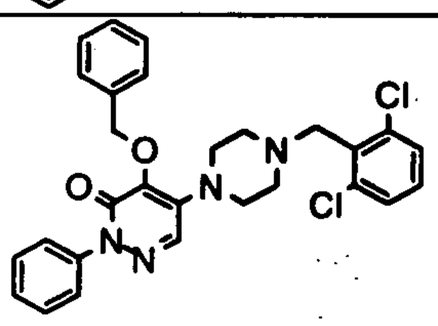
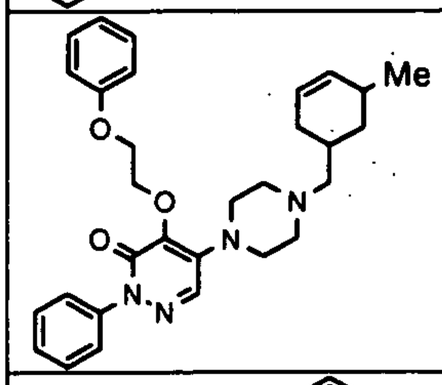
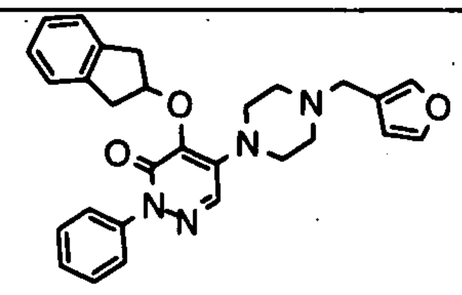
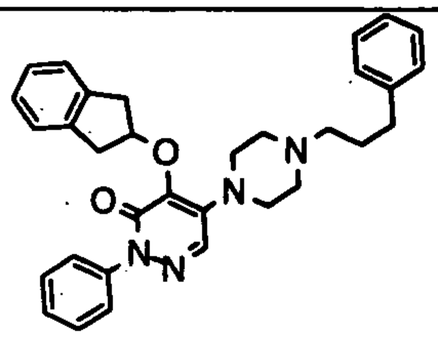
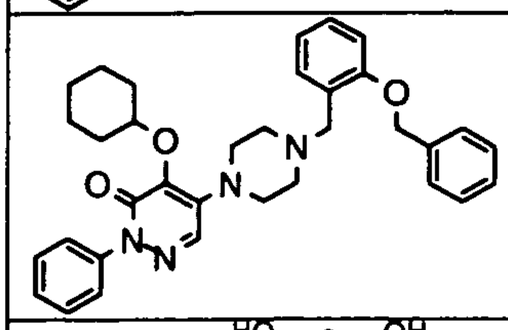
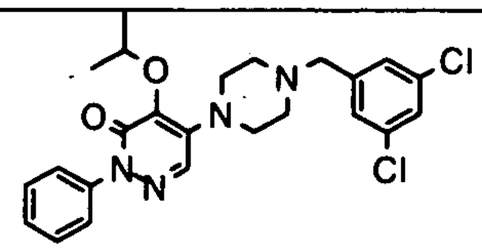
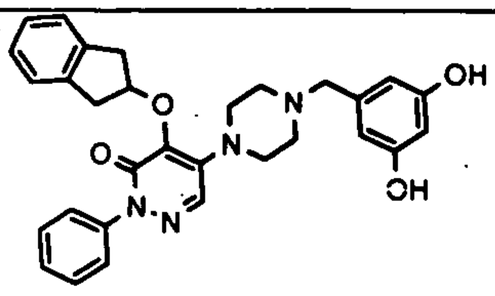
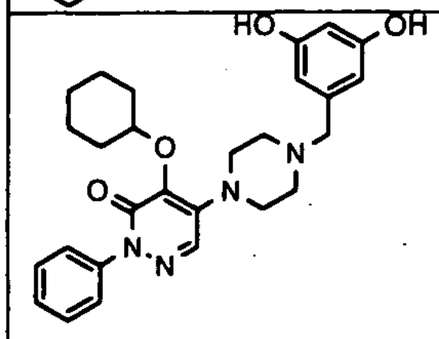
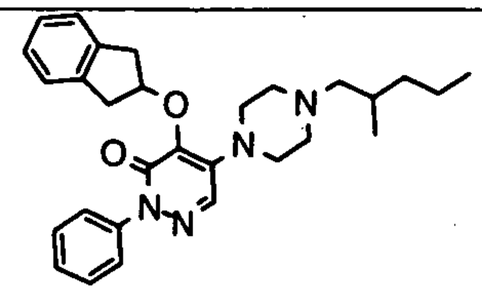
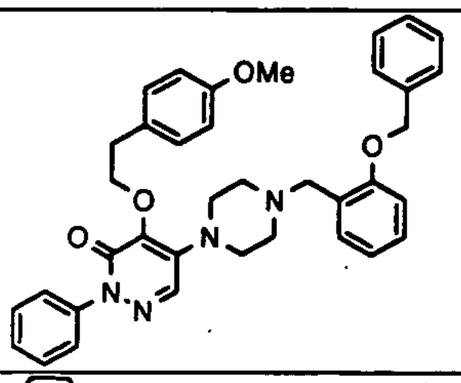
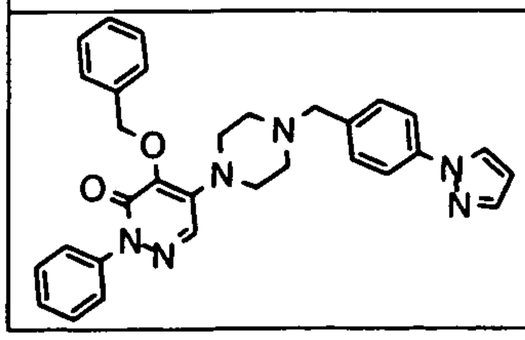
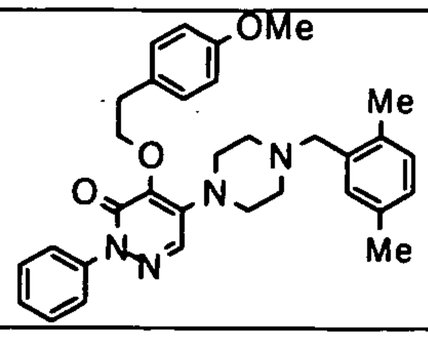
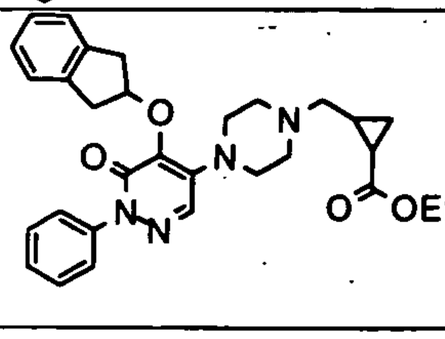
		
		
		
		
		
		

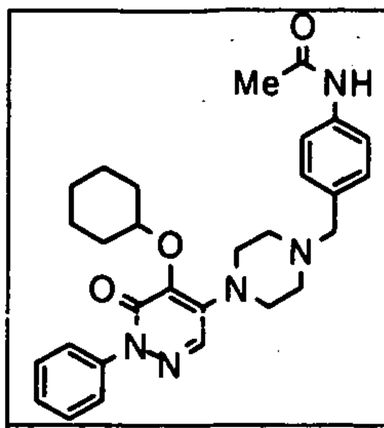
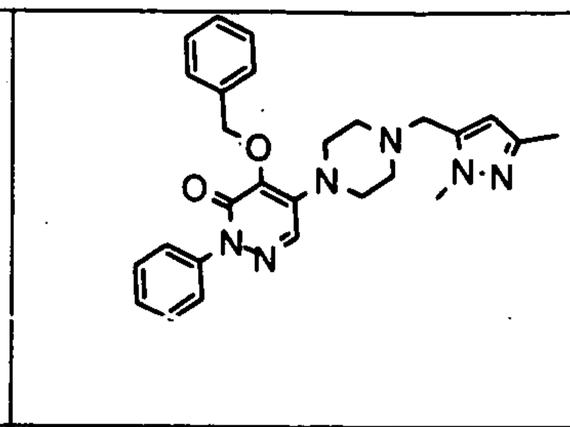
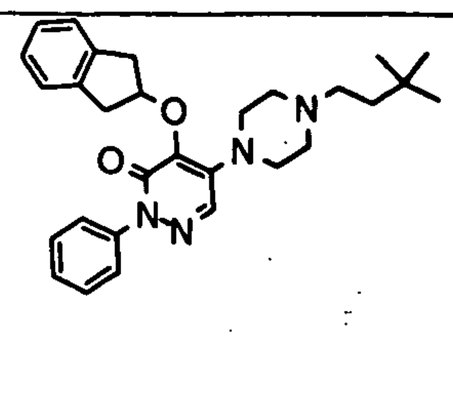
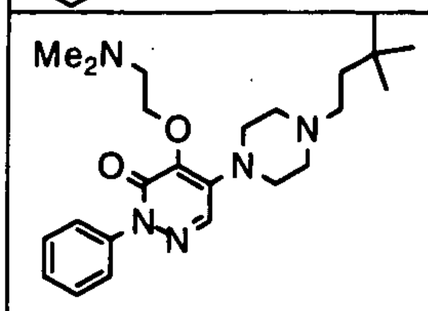
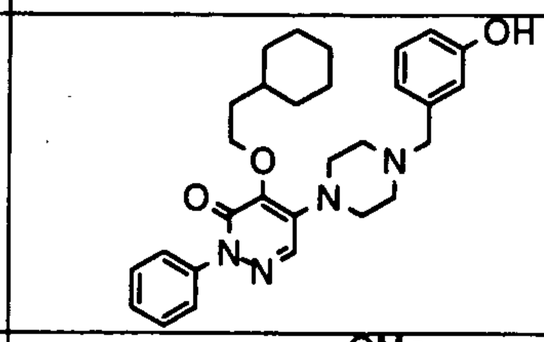
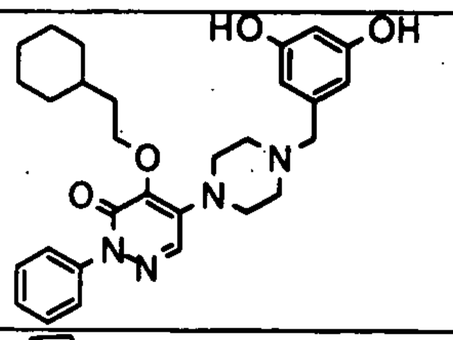
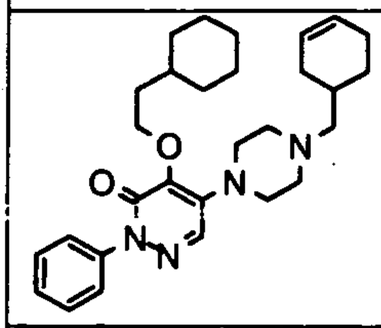
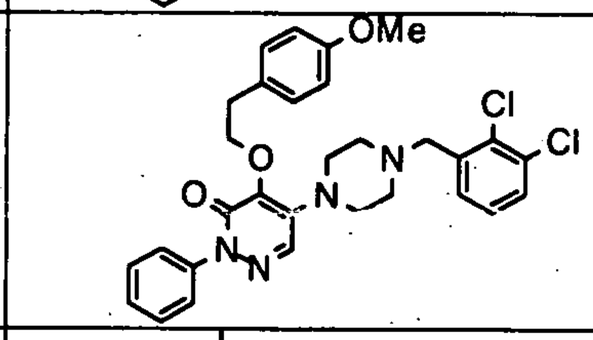
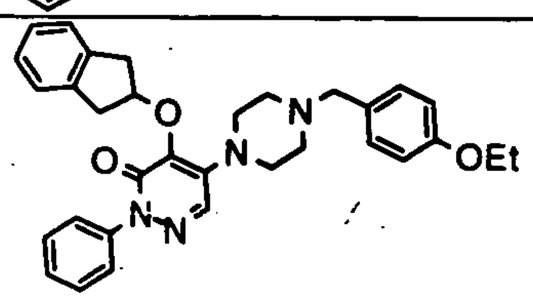
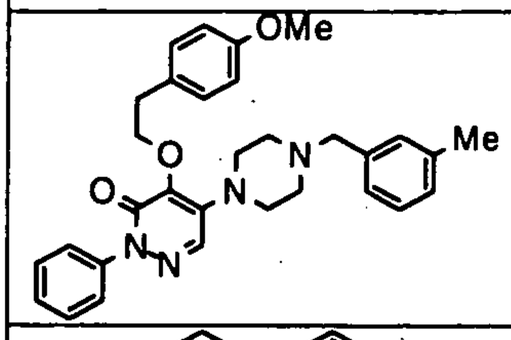
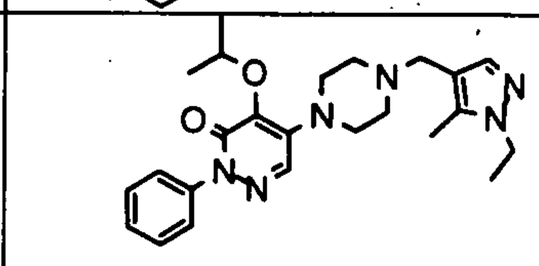
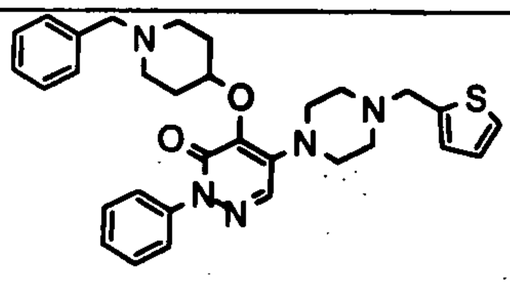
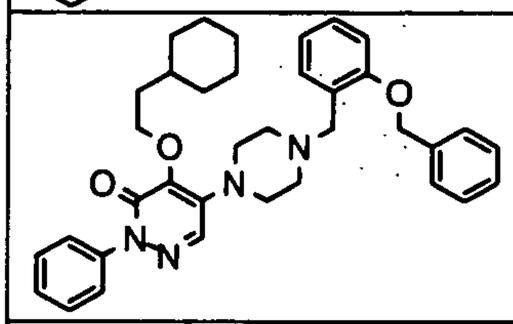
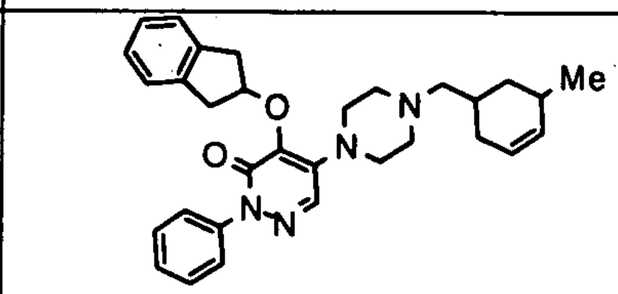
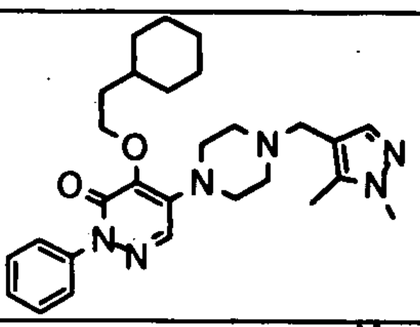
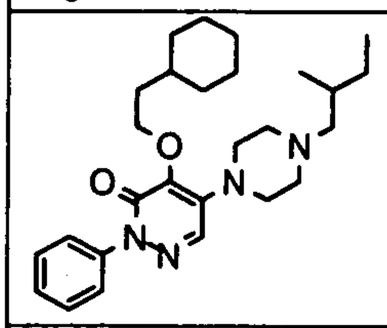
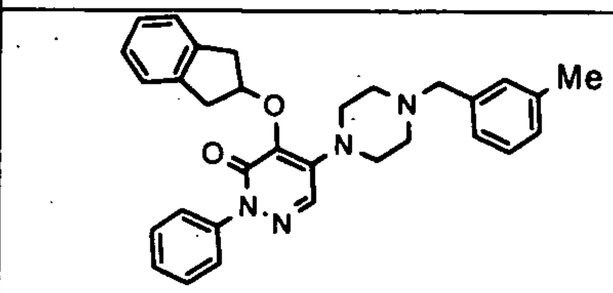
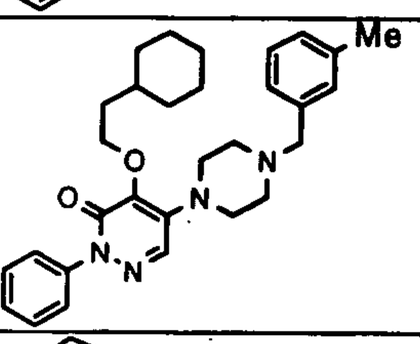
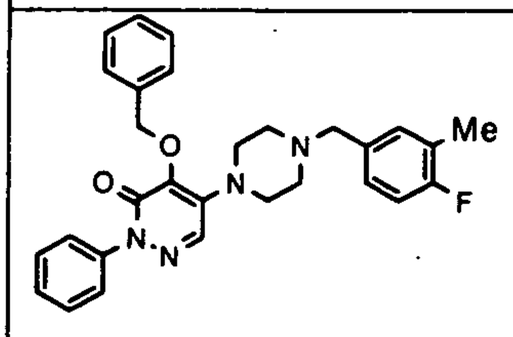
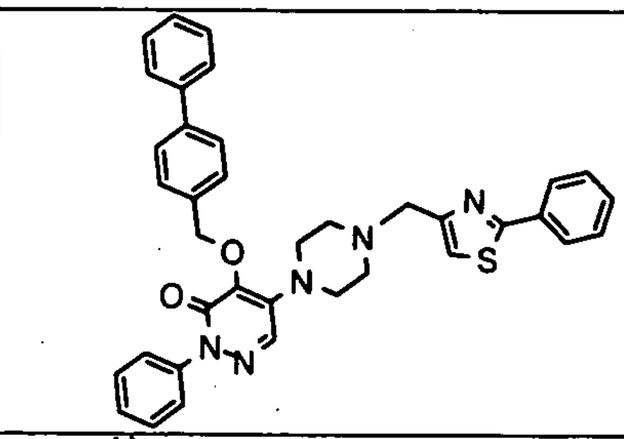
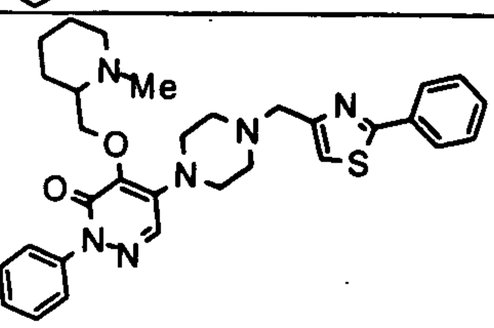
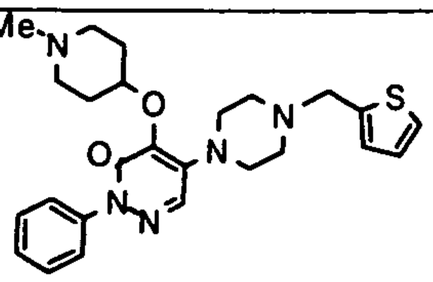
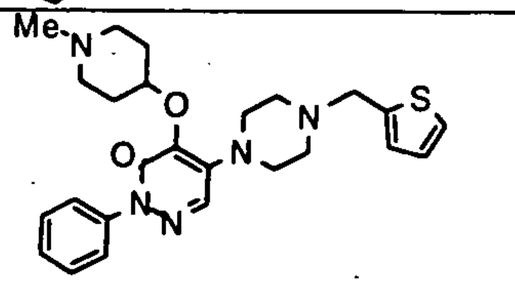
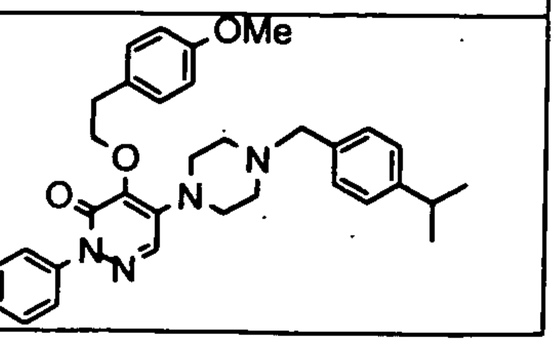
		
		
		
		
		
		
		

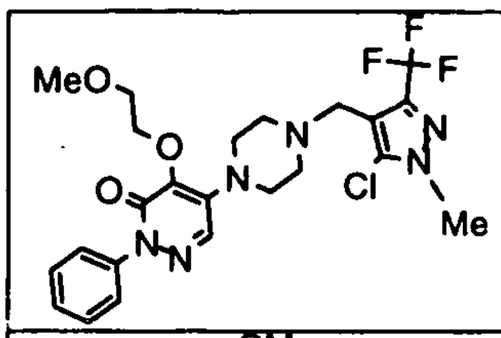
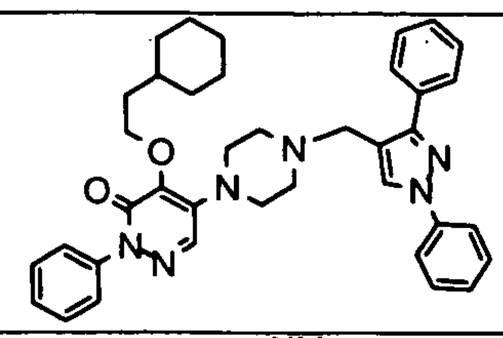
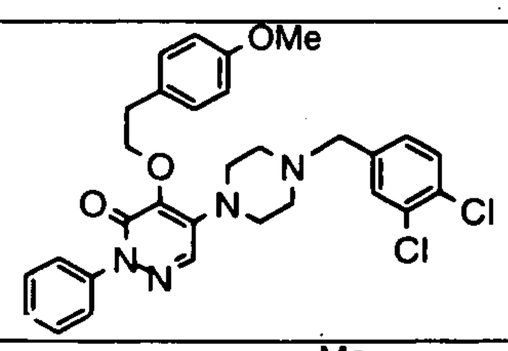
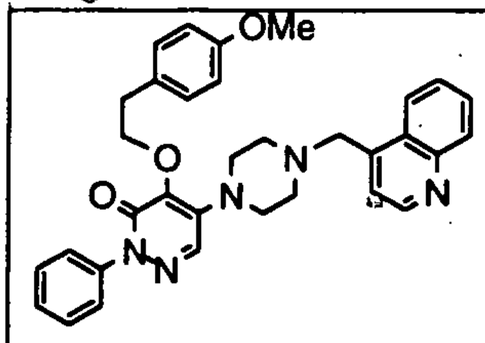
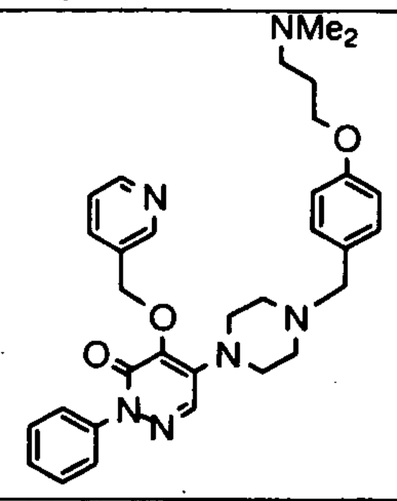
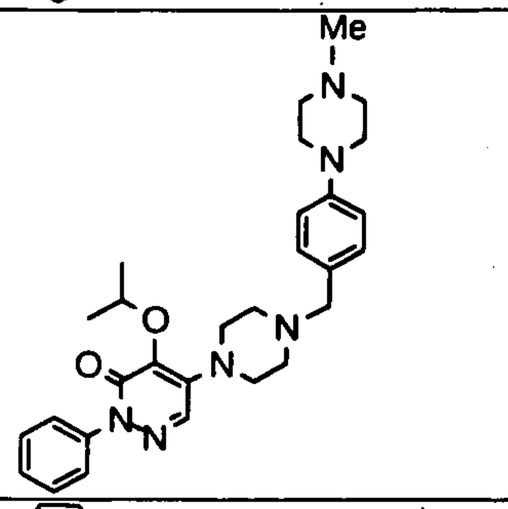
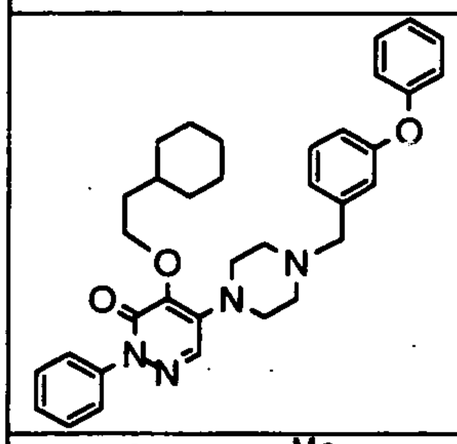
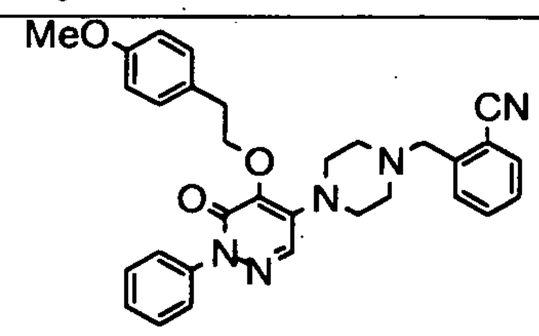
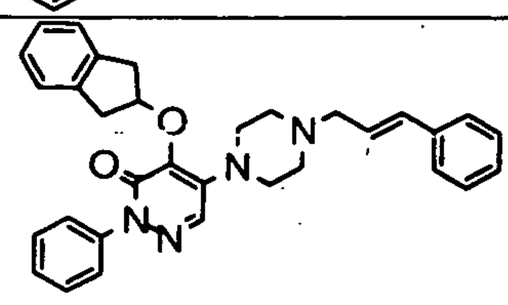
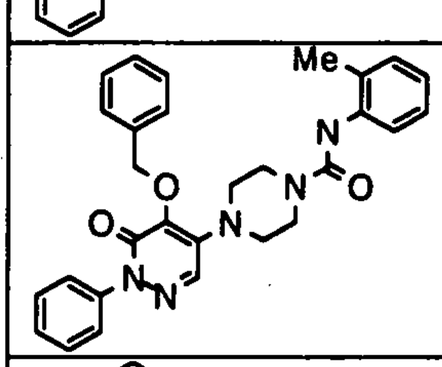
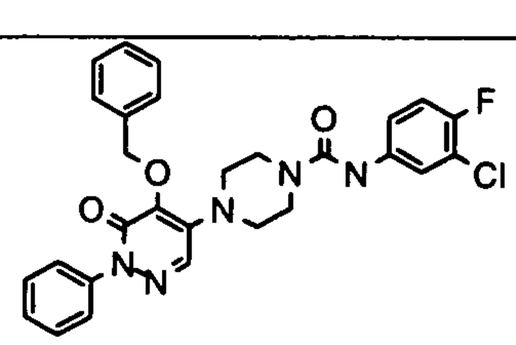
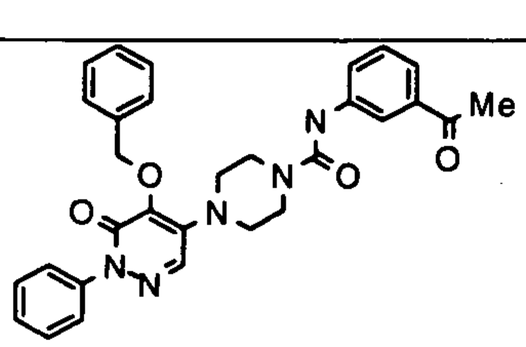
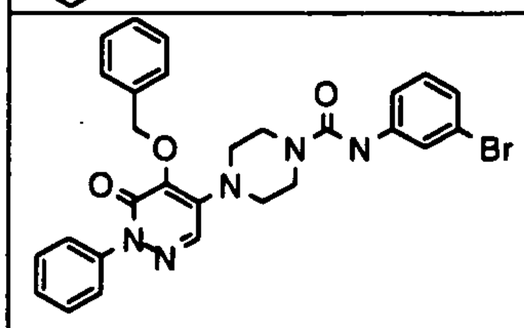
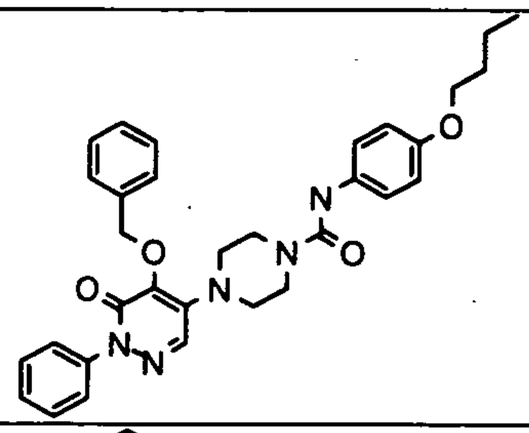
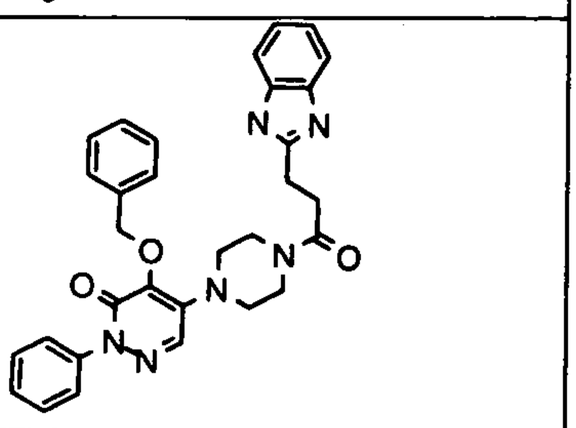
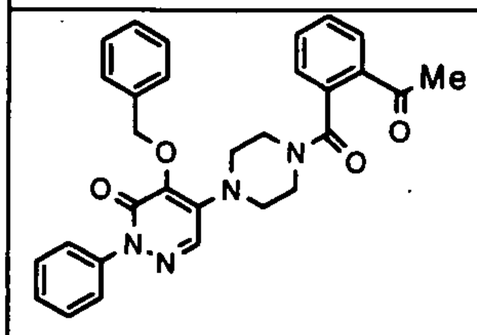
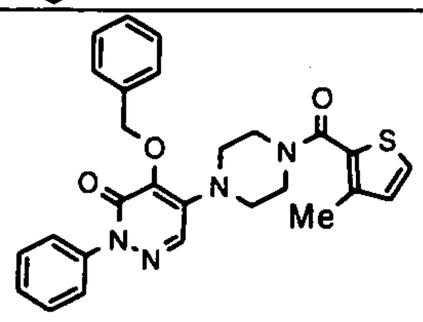
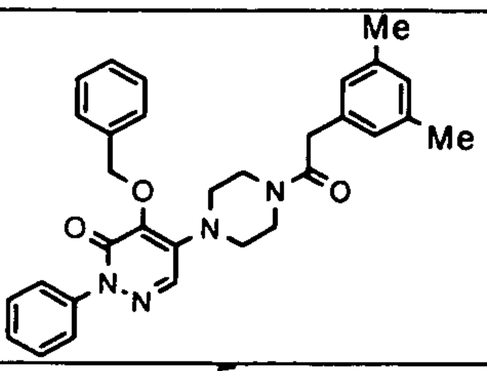
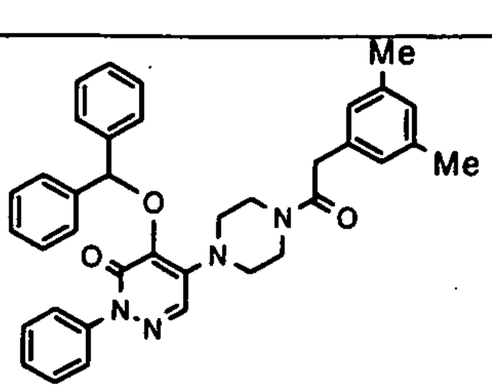
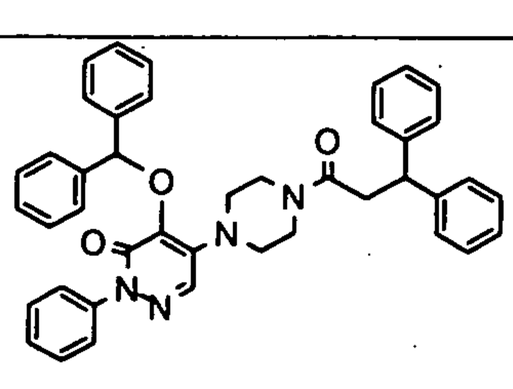
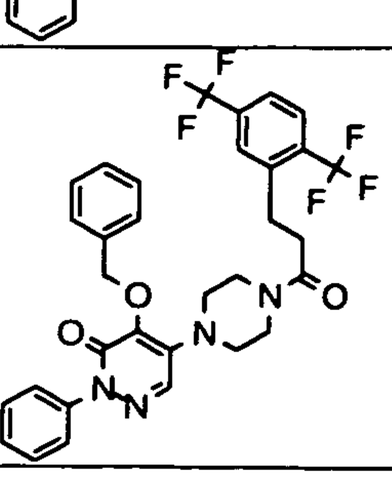
		
		
		
		
		
		
		
		

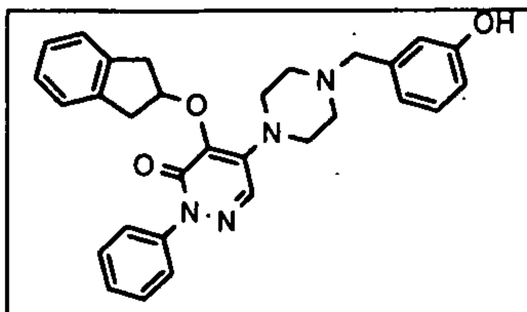
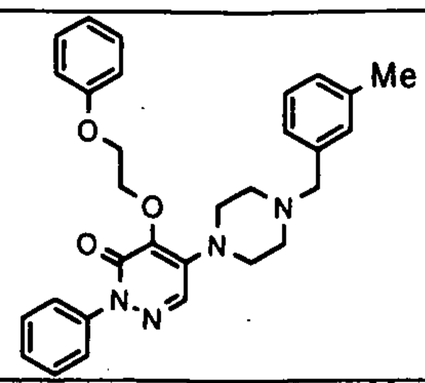
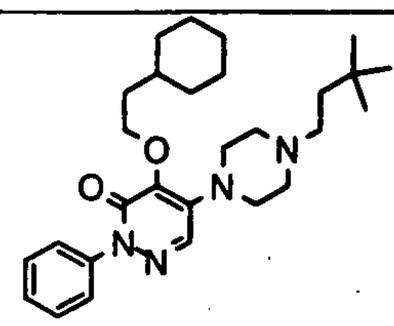
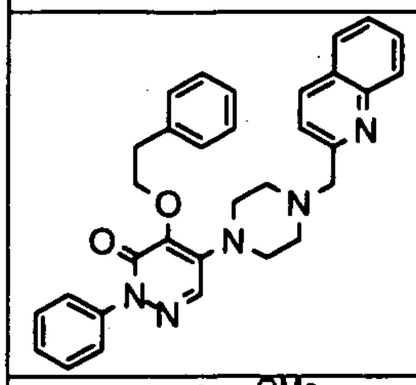
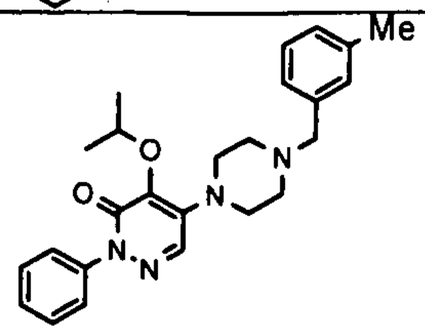
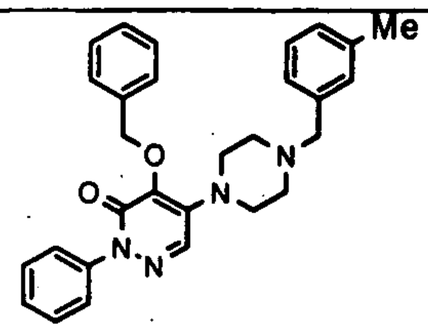
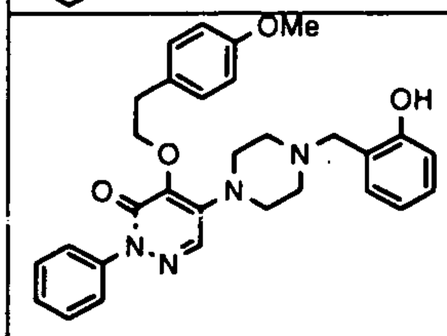
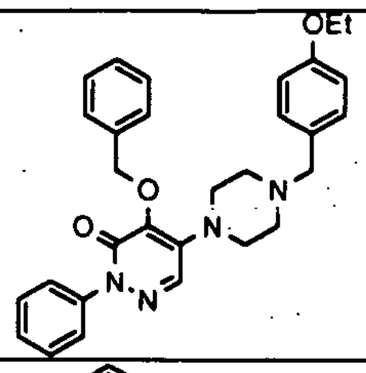
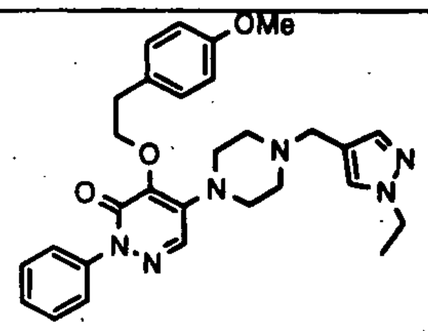
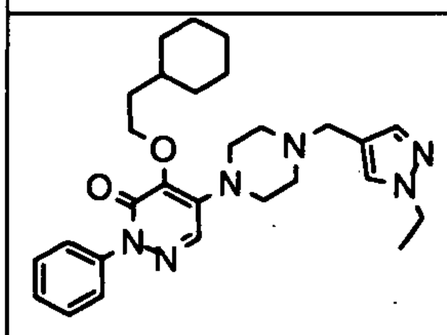
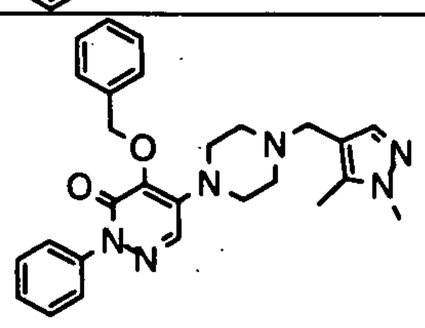
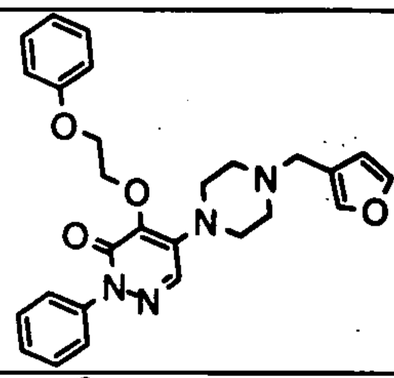
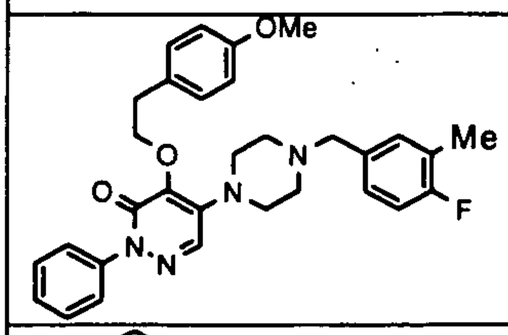
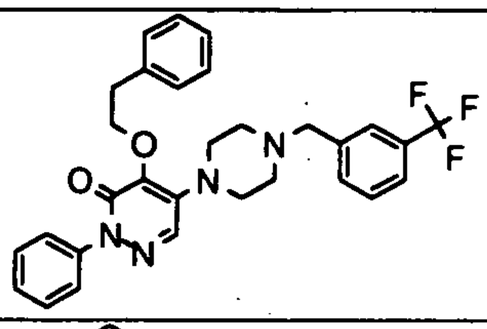
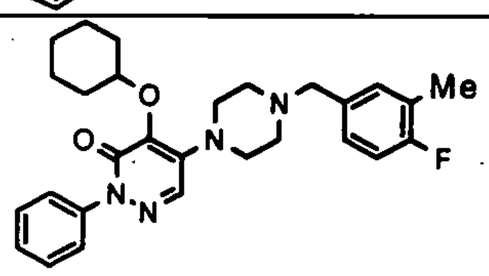
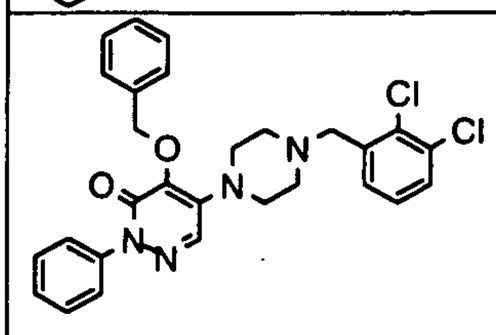
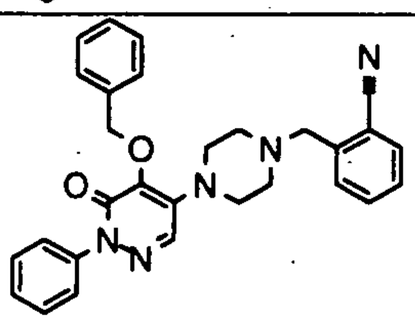
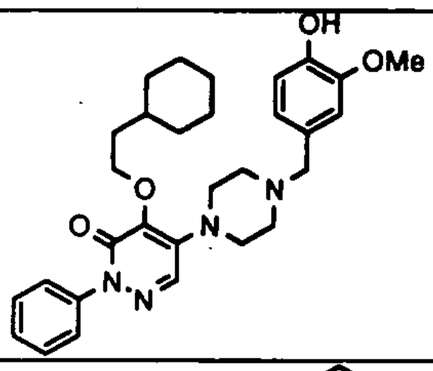
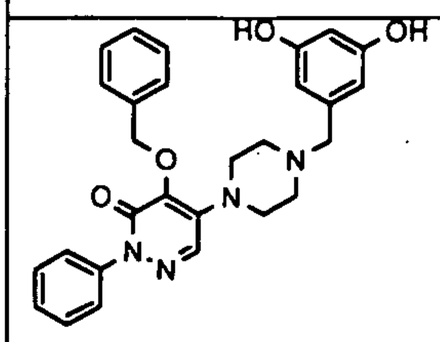
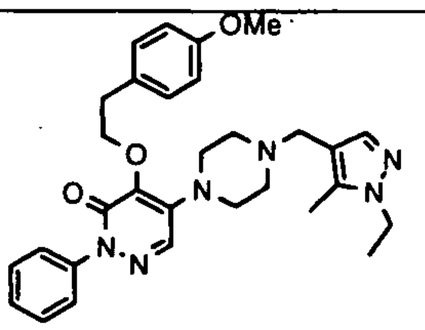
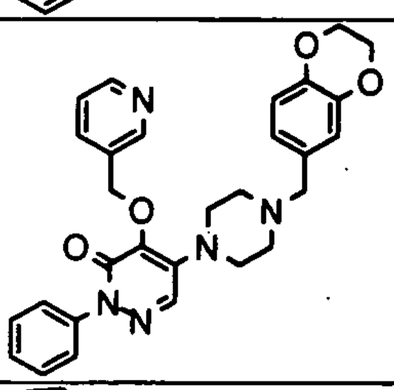
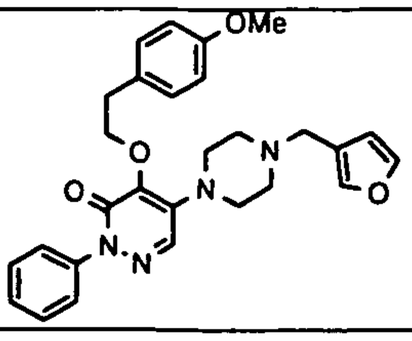
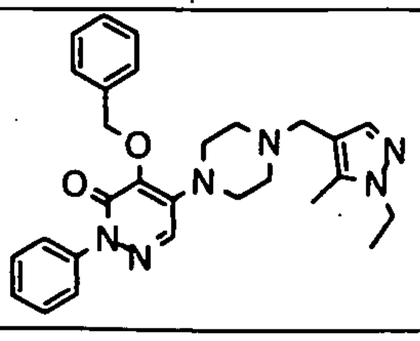
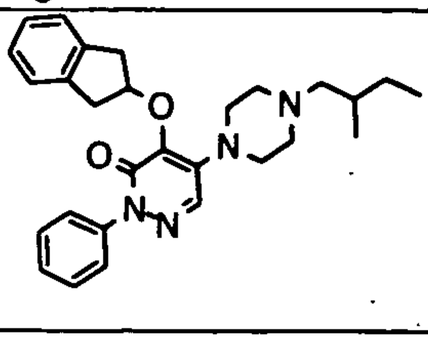
		
		
		
		
		
		
		

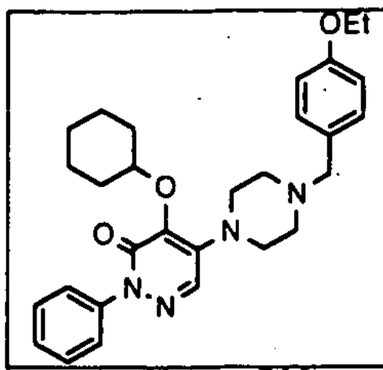
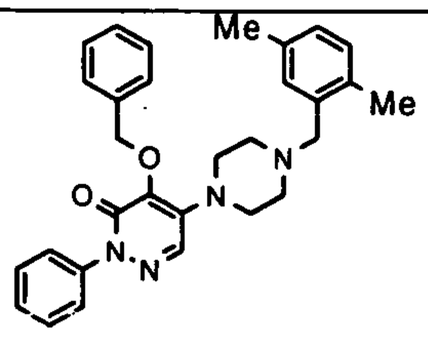
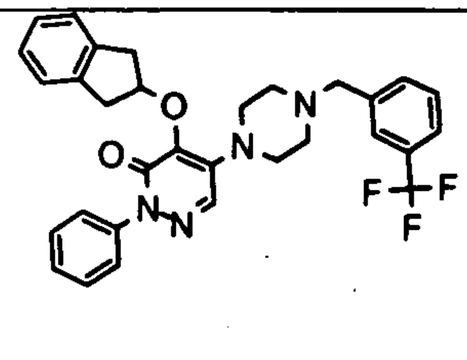
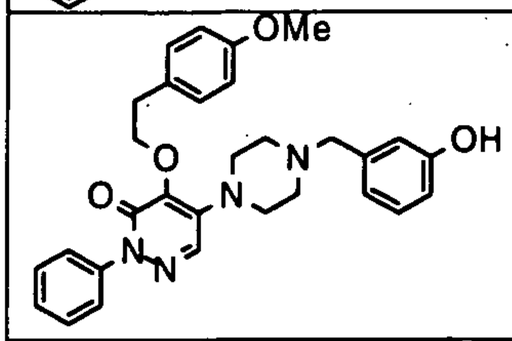
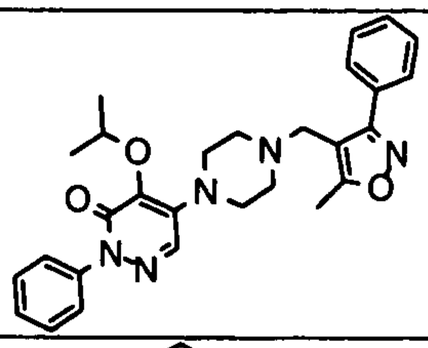
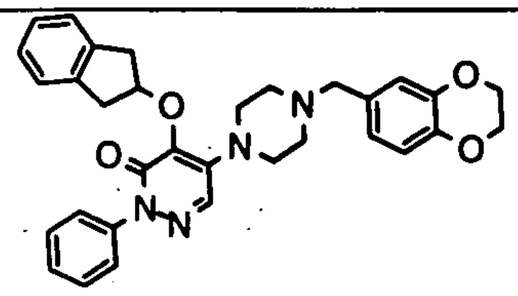
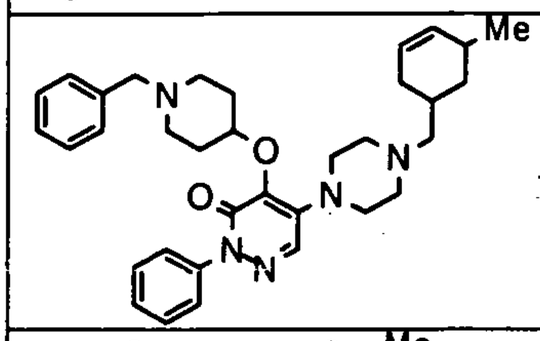
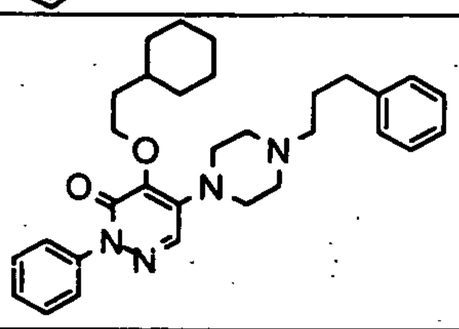
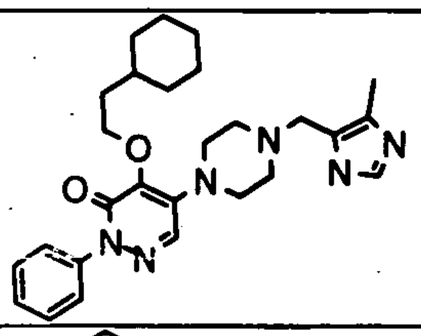
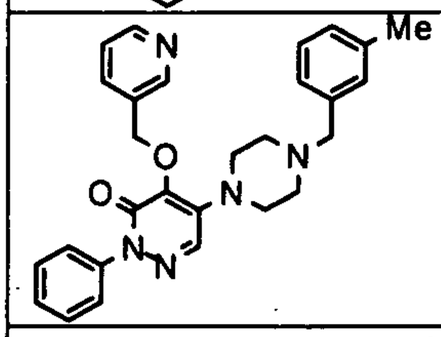
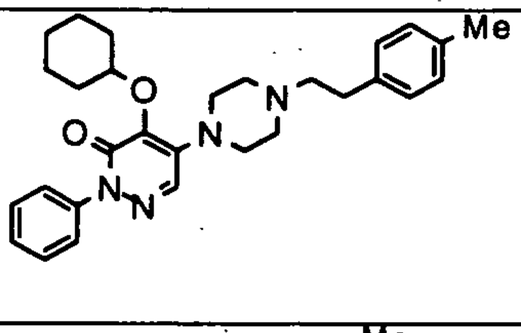
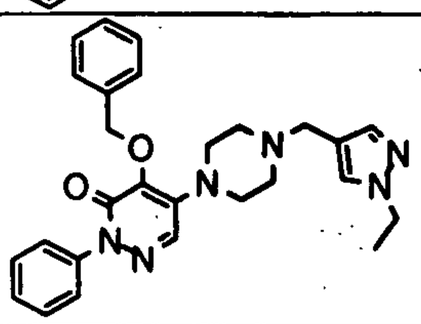
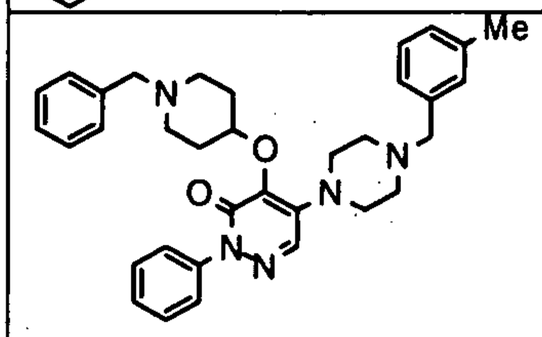
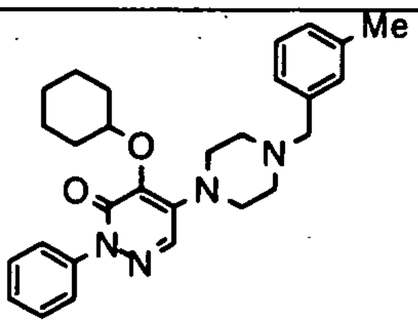
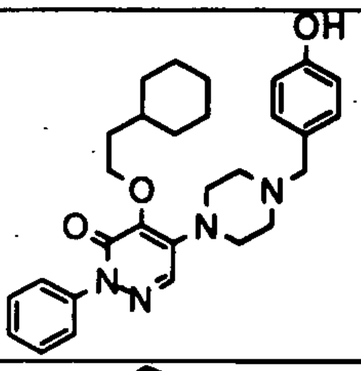
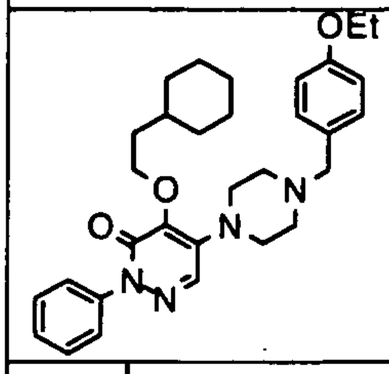
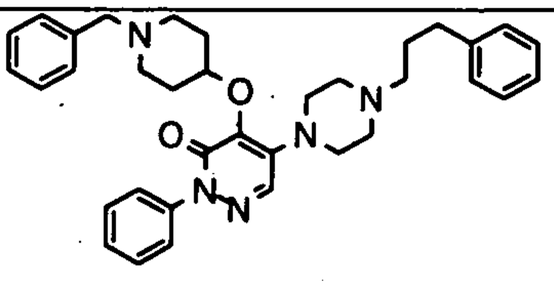
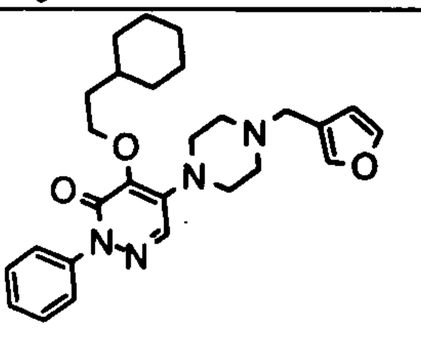
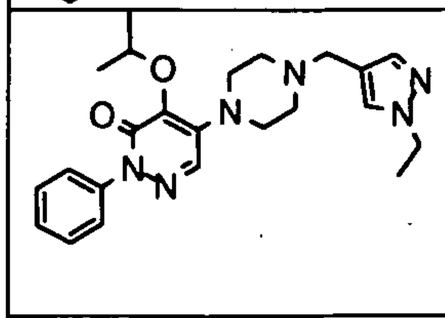
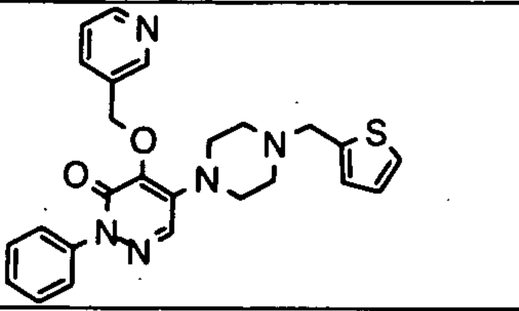
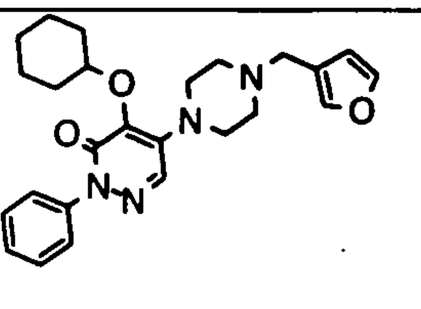
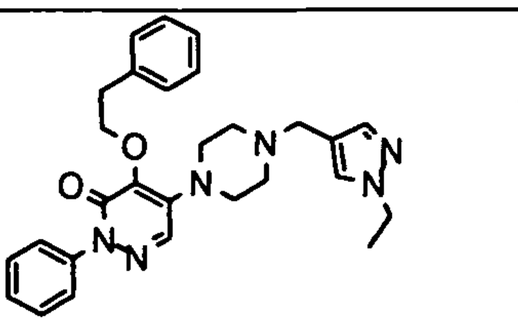
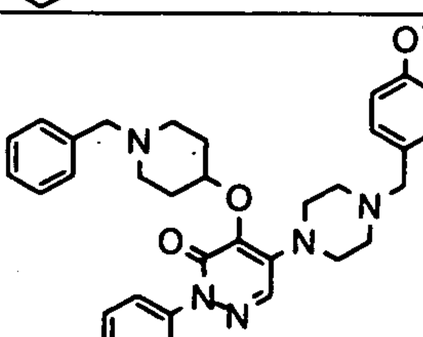
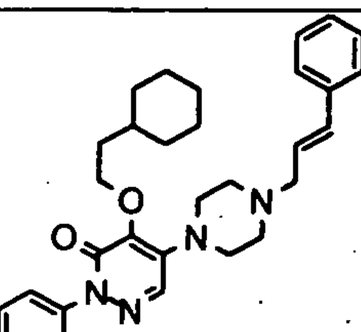
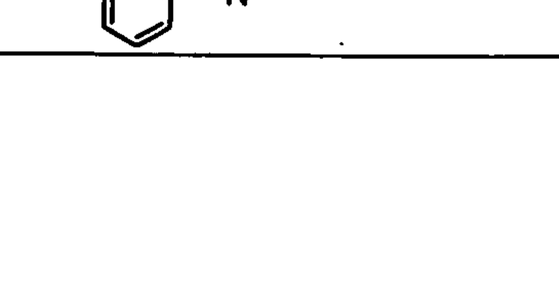
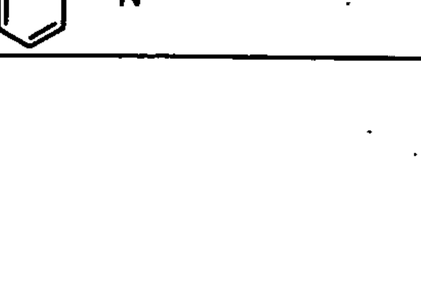
		
		
		
		
		
		
		
		

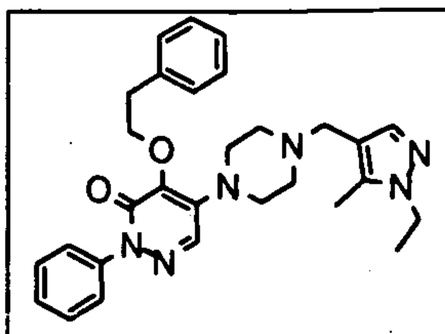
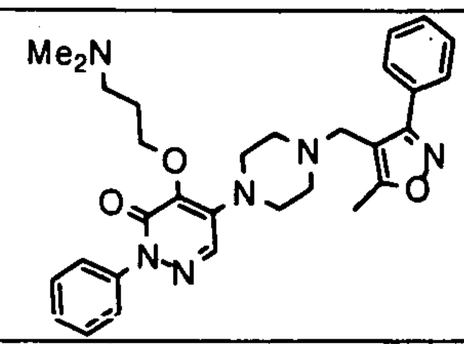
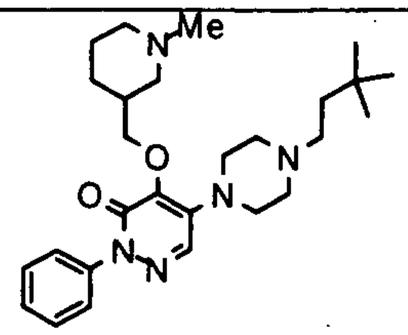
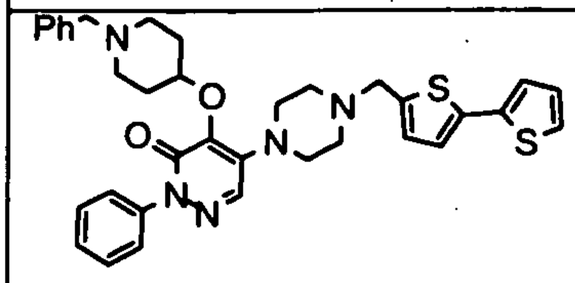
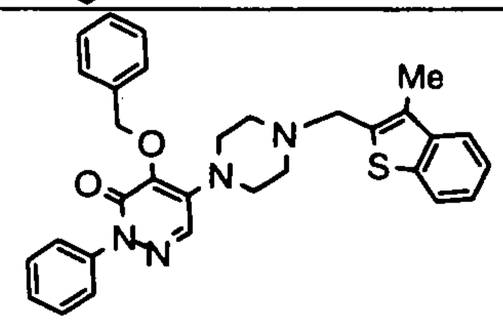
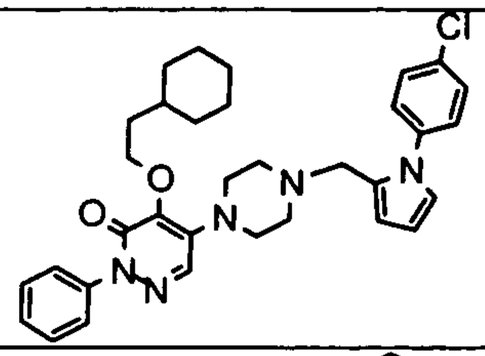
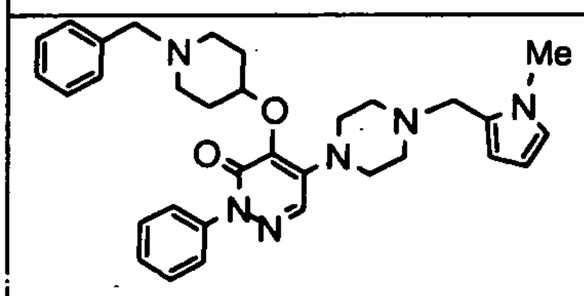
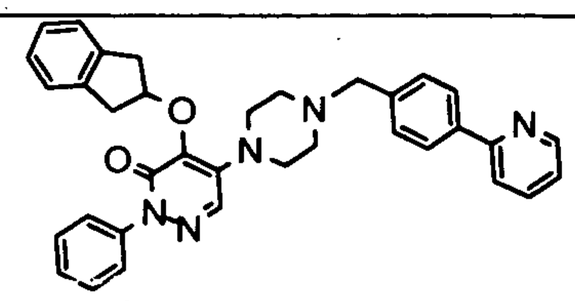
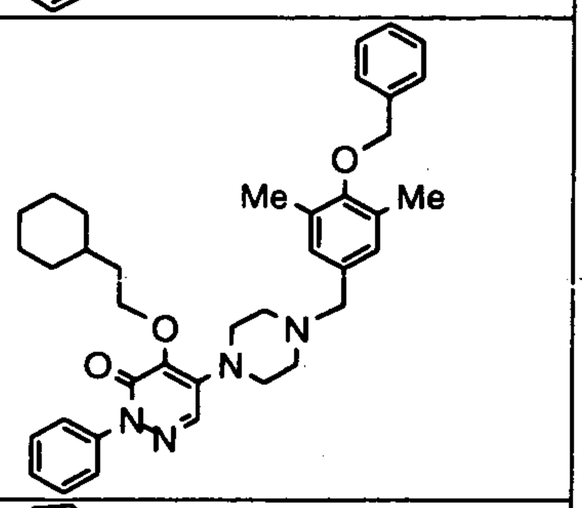
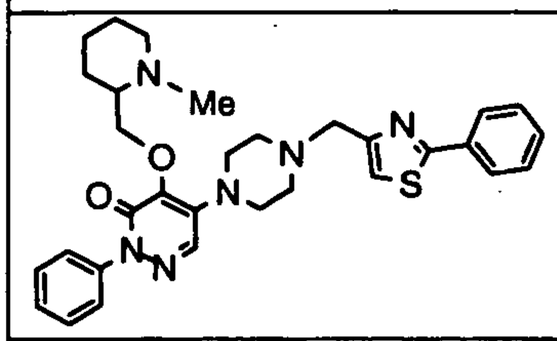
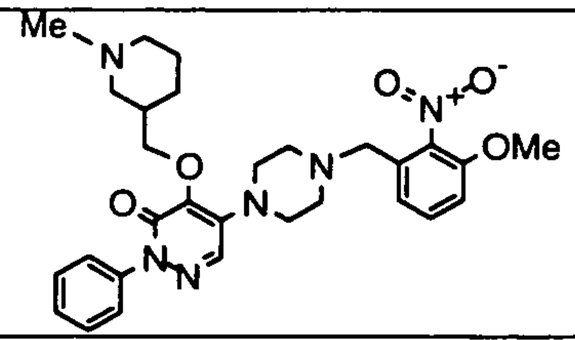
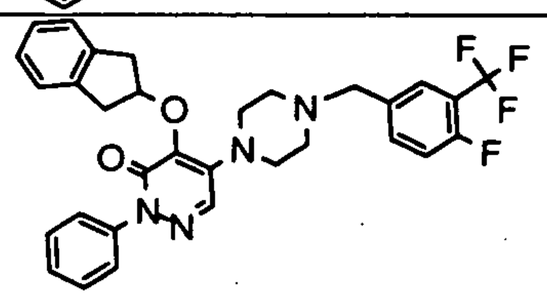
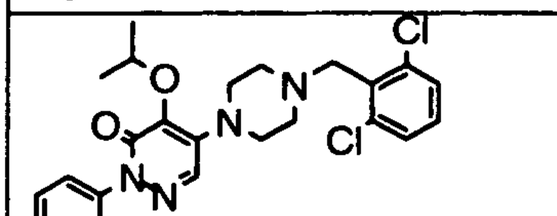
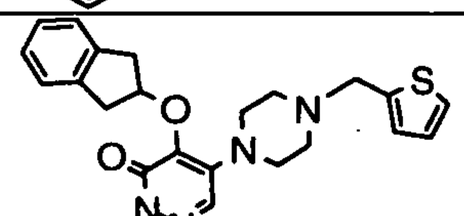
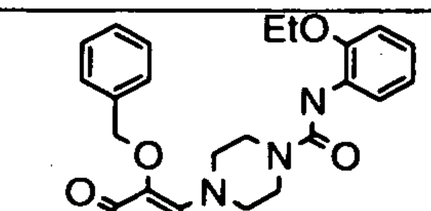
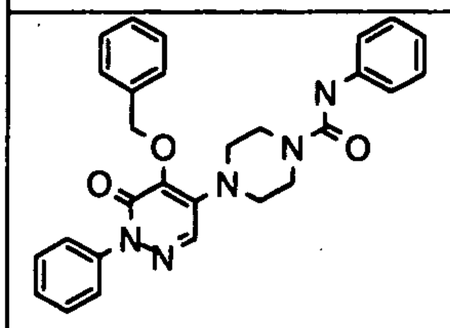
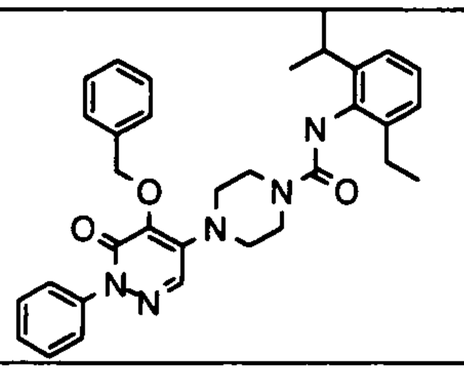
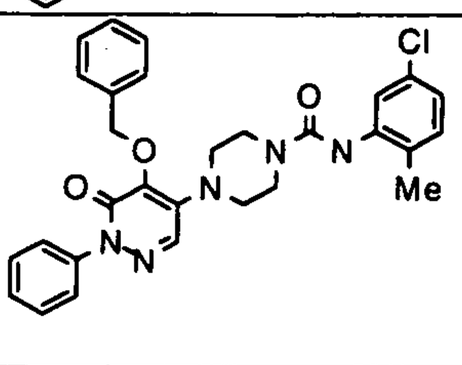
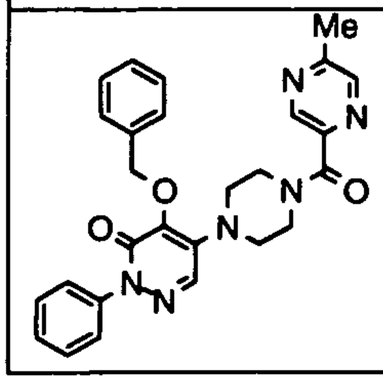
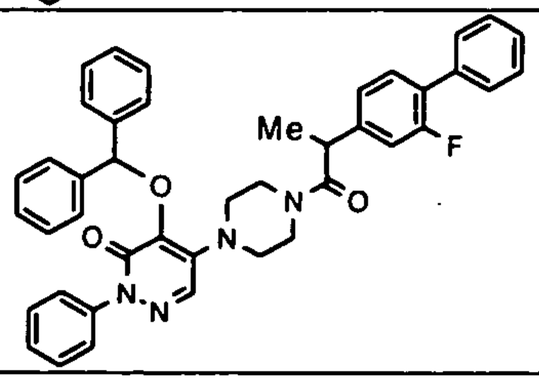
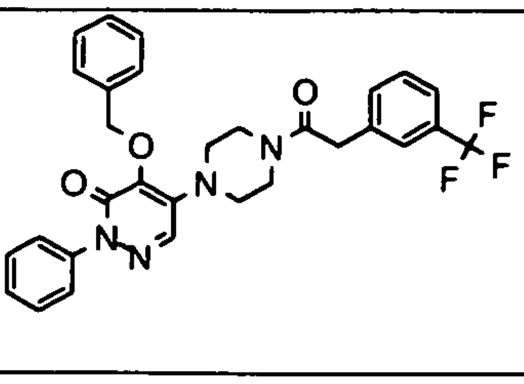
		
		
		
		
		
		
		
		

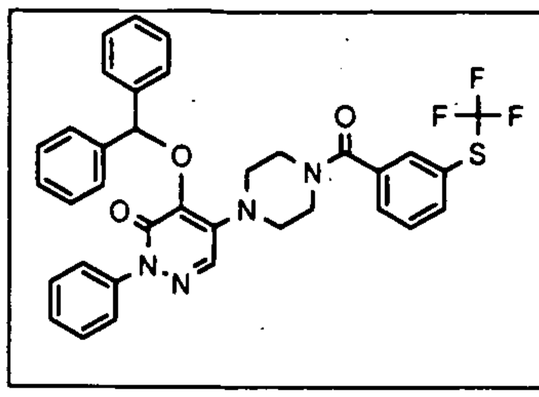
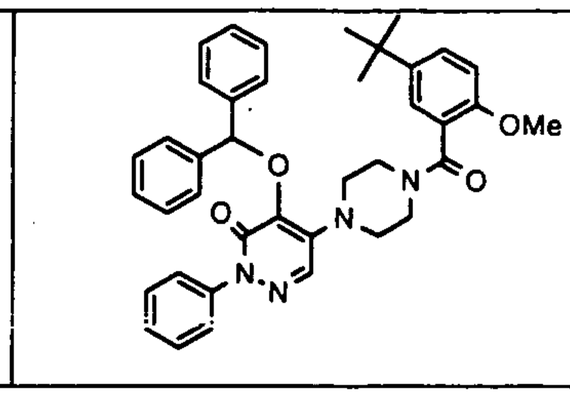
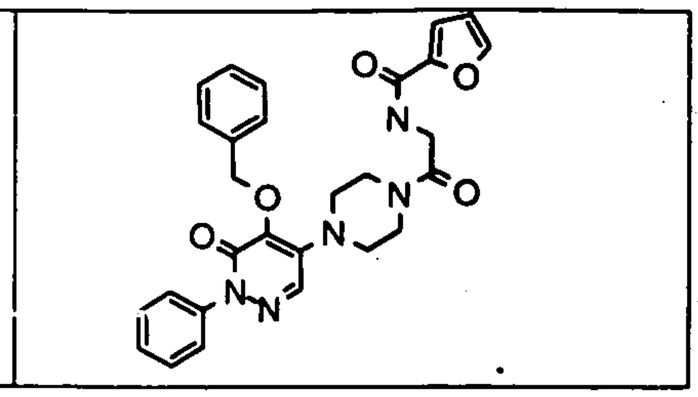
		
		
		
		
		
		
		
		

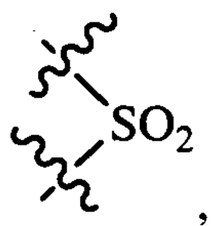
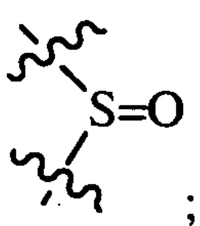
2. The compound of claim 1, wherein A is O.

3. The compound of claim 1, wherein D is N.

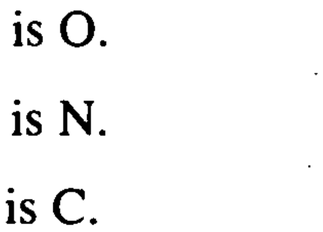
4. The compound of claim 1, wherein E is C.

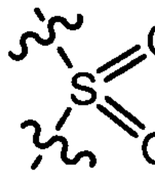
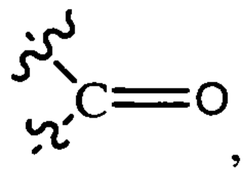
5. The compound of claim 1, wherein Y is O.

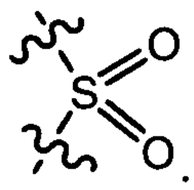
6. The compound of claim 1, wherein Y is $-NR^9-$.

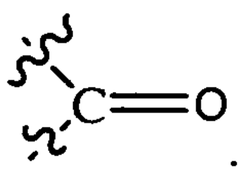
7. The compound of claim 1, wherein Y is –S-,  ,  ;

8. The compound of claim 1, wherein Y is absent.

9. The compound of claim 1, wherein Z is  .

10. The compound of claim 1, wherein R^5 is  ,  , $-CR^9{}_2-$, or heteroaryl.

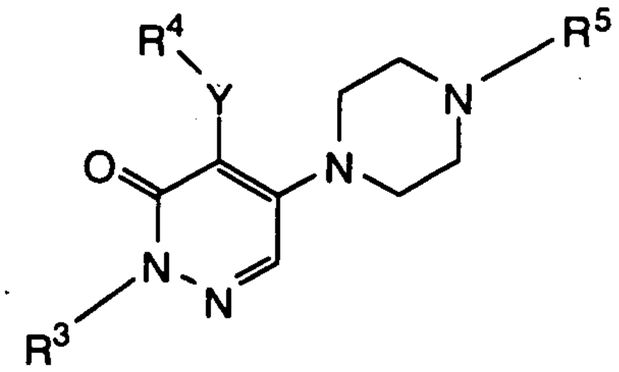
11. The compound of claim 1, wherein R^5 is  .

12. The compound of claim 1, wherein R^5 is  .

13. The compound of claim 1, wherein R^5 is $-CR^9{}_2-$.

14. The compound of claim 1, wherein E is C and R^6 is H.

15. The compound of claim 1 having the structure



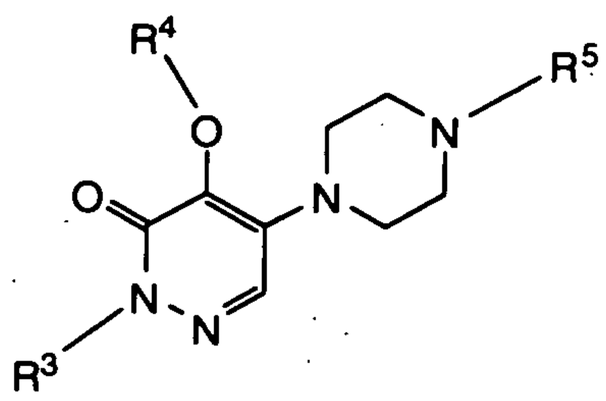
wherein

Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent on R^5 together are –alkyl-, -alkenyl-, -alkyl-NH-,or –alkenyl-NH-, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent of R^5 together are an -alkyl-phenylene-alkyl-NR^{13}- group or a -alkyl-phenylene-alkyl- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached;

or Y is –O- and R^5 is $–SO_2$-, and R^4 and the second end substituent of R^5 together are an -alkyl-heteroarylene-alkyl- group or an -alkyl-heteroarylene-alkyl-NR^{13}- group, forming a ring with the –O- and $–SO_2$- groups to which they are attached.

16. A compound of claim 1 having the structure



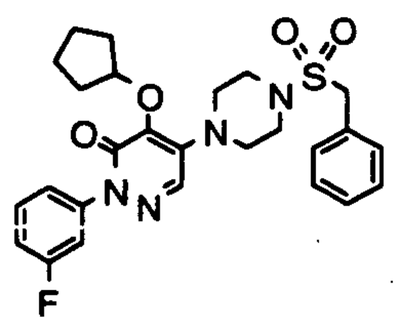
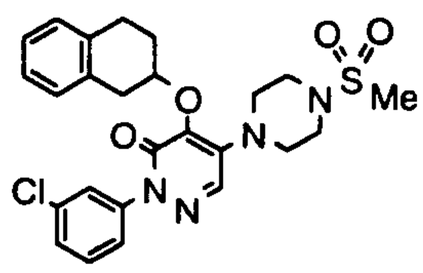
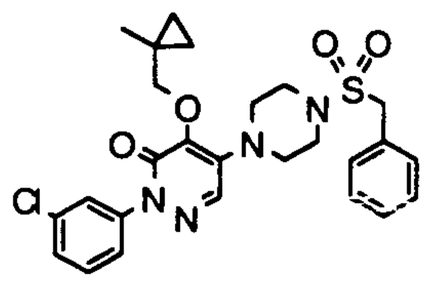
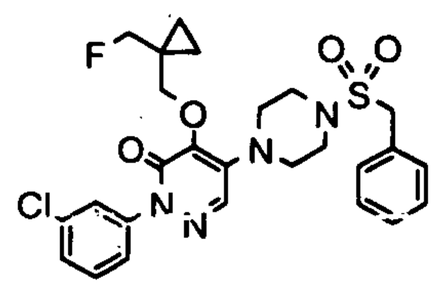
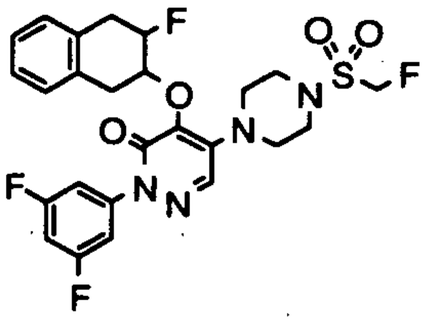
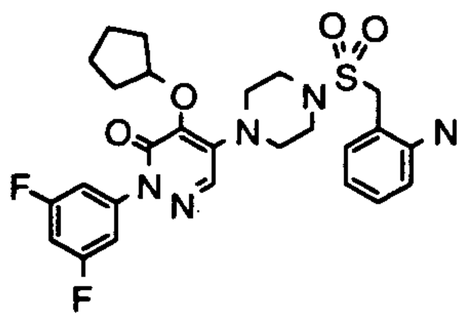
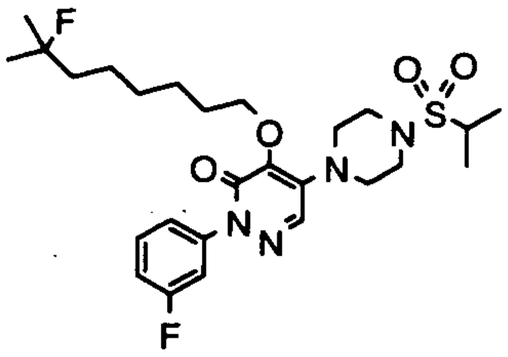
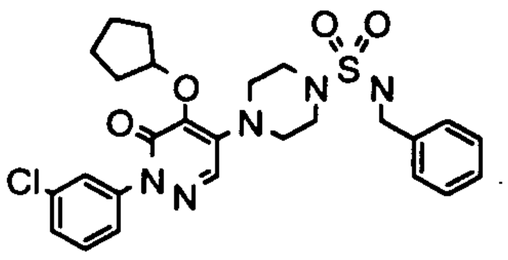
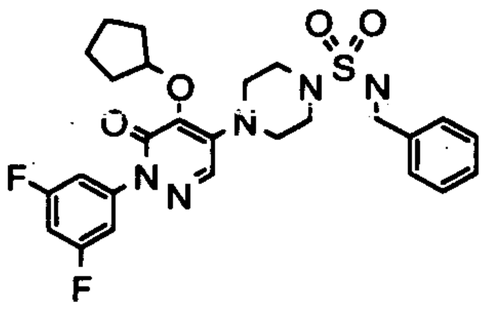
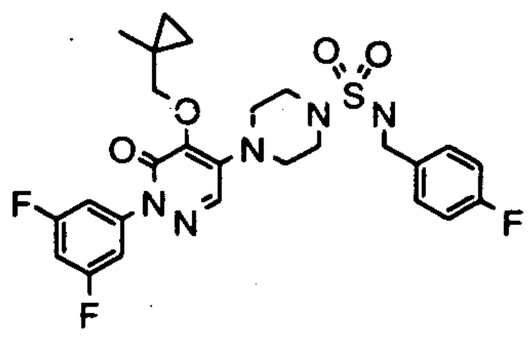
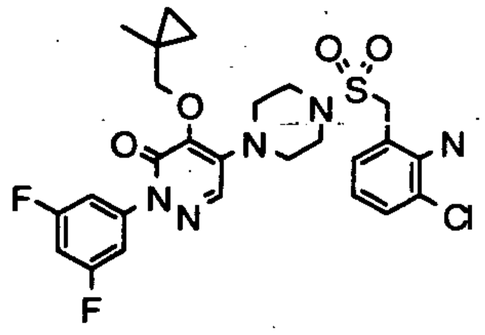
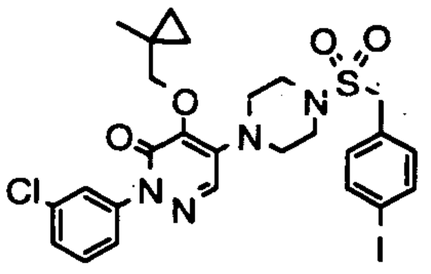
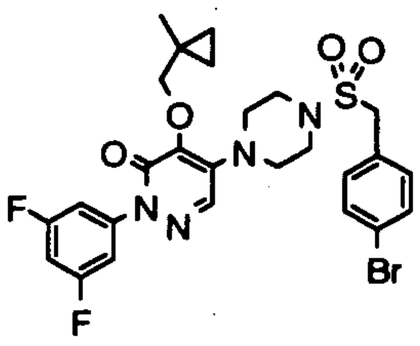
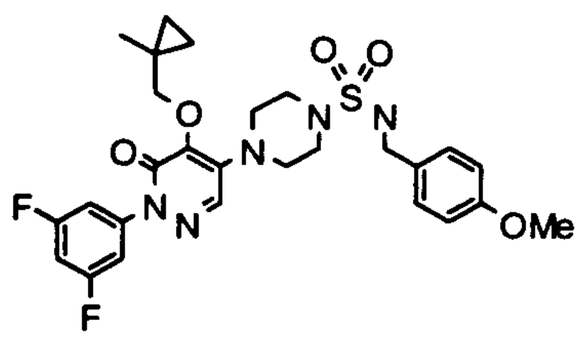
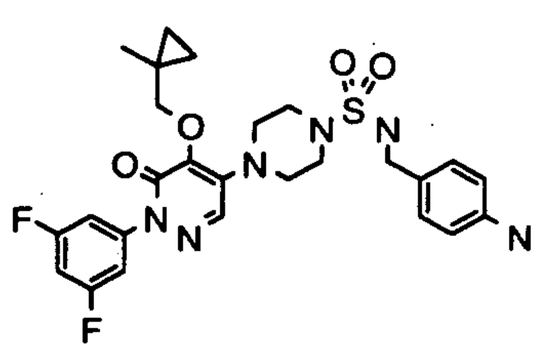
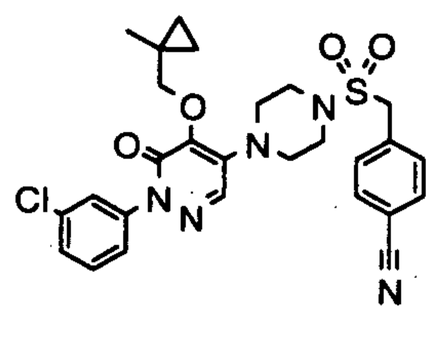
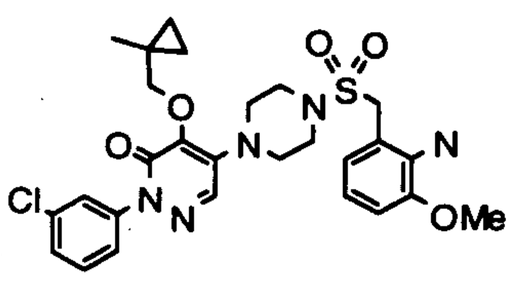
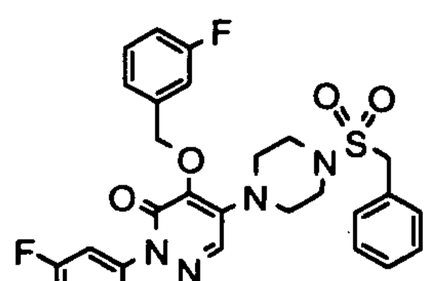
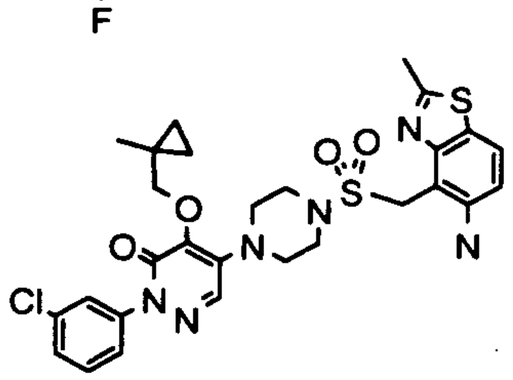
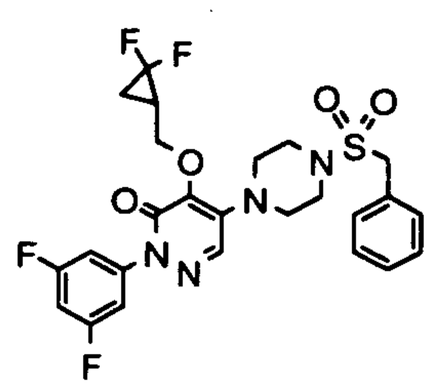
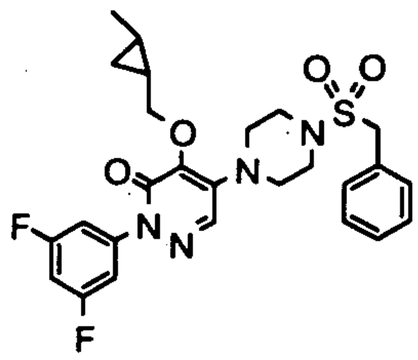
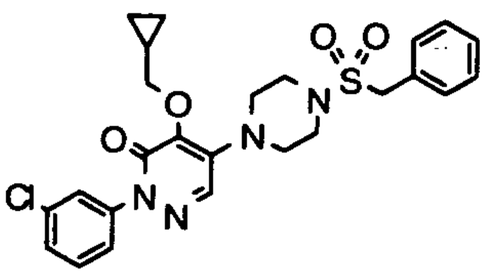
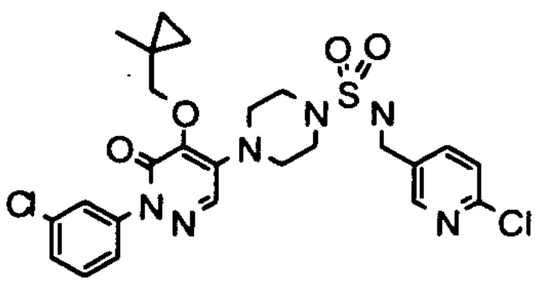
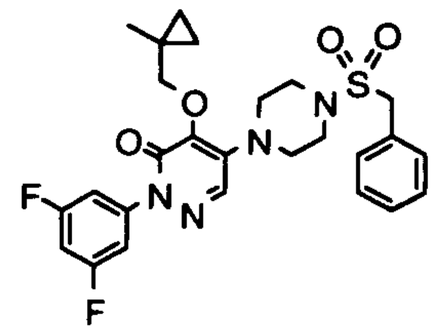
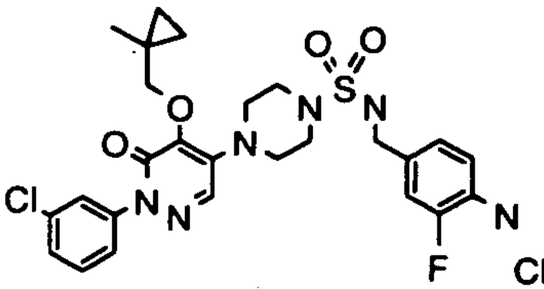
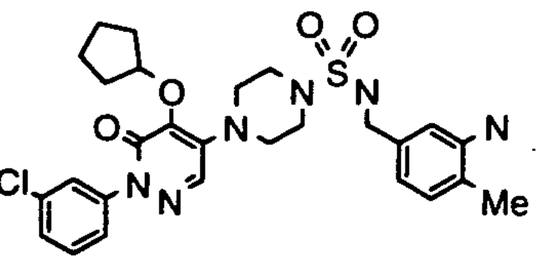
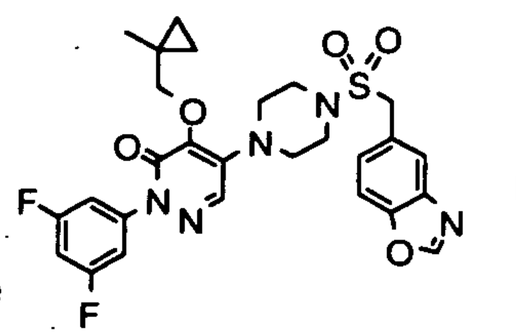
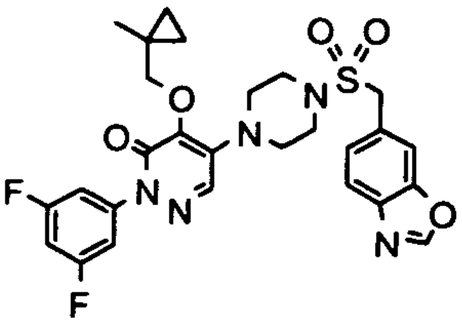
wherein R^3 is mono- or dihalo-phenyl;

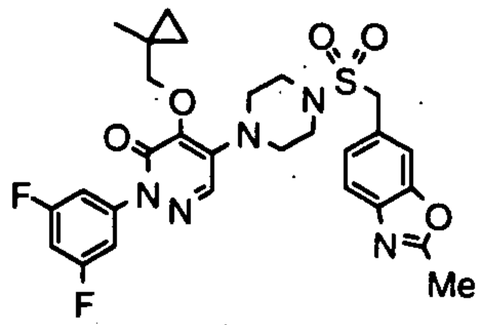
R^4 is alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted benzyl, or optionally substituted benzofused cycloalkyl;

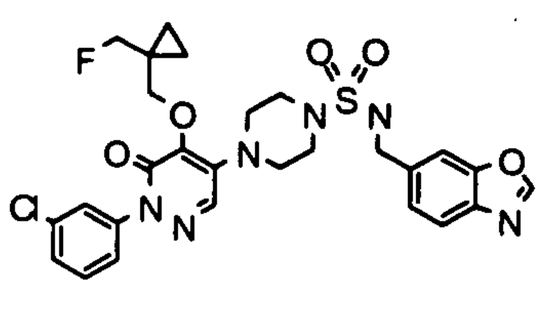
R^5 is $–SO_2$-, wherein the second end substituent is alkyl, haloalkyl, optionally substituted arylalkyl, or optionally substituted heteroarylalkyl; or $–N(R^9)_2$, wherein one R^9 is H and the other is optionally substituted arylalkyl or optionally substituted heteroarylalkyl;

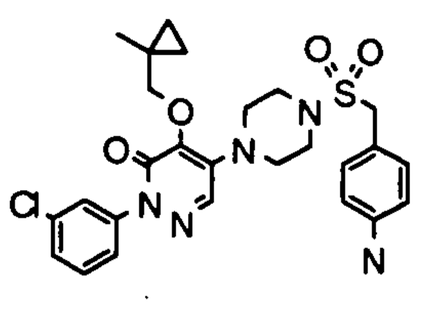
or R^4 and the second end substituent on R^5 together are –alkenyl-;

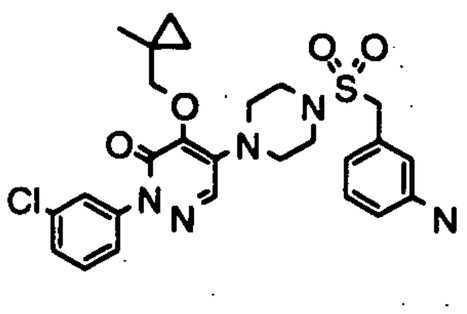
17. A compound of claim 1 selected from the group consisting of:

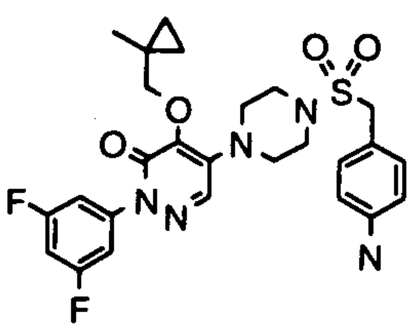





























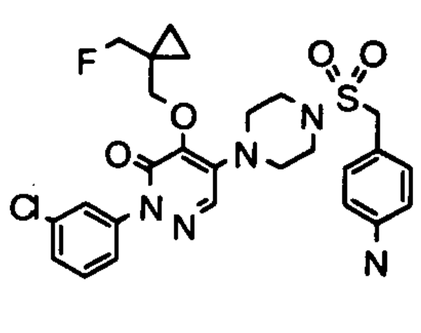


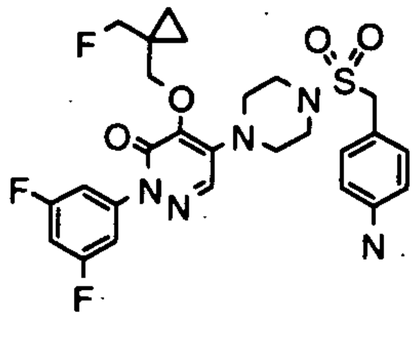


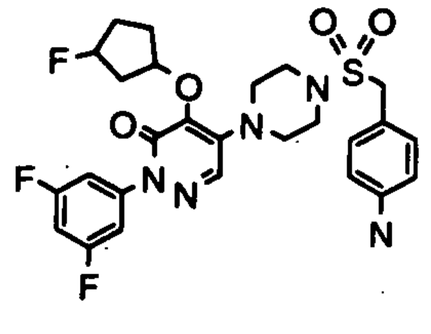


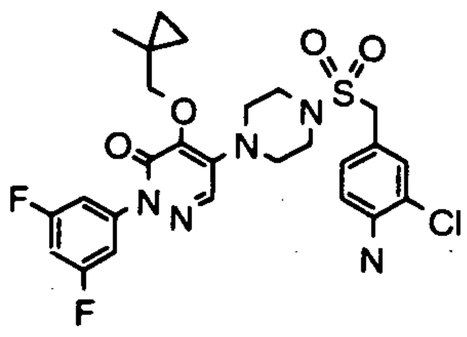


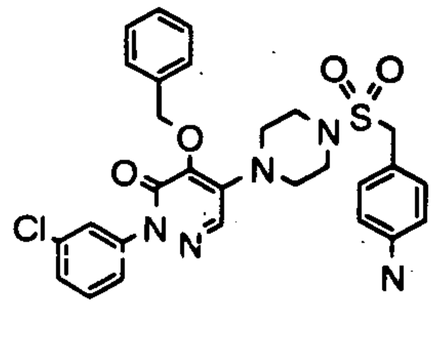


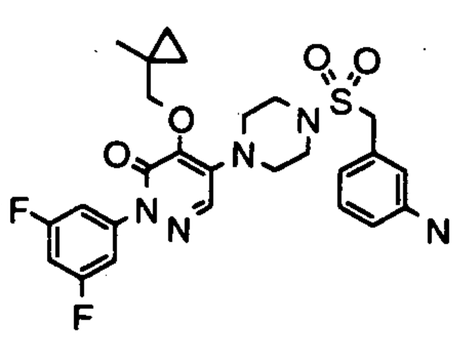


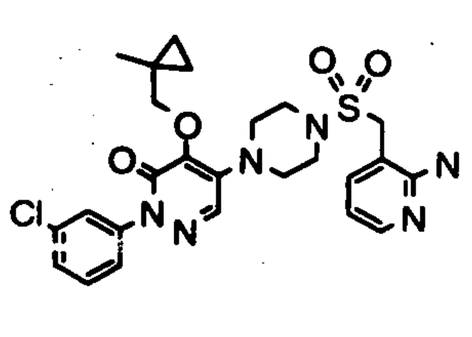


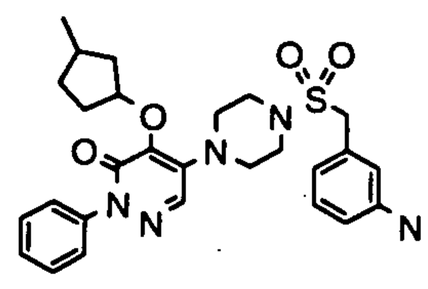


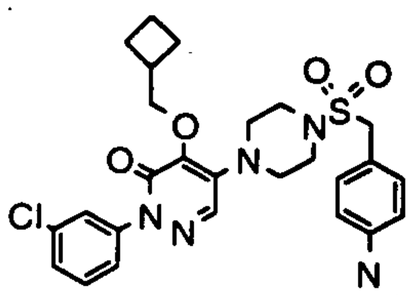


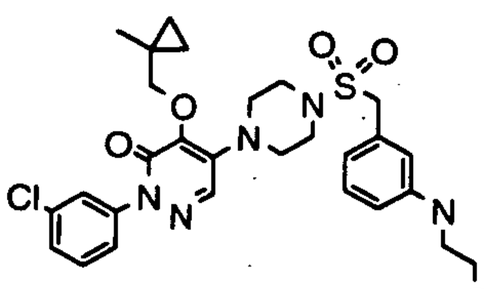


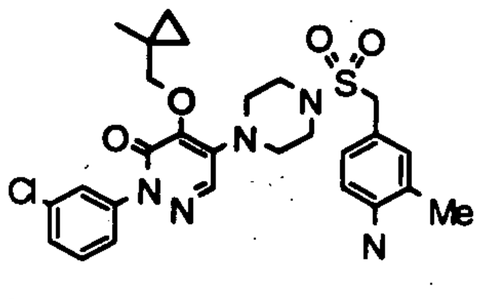


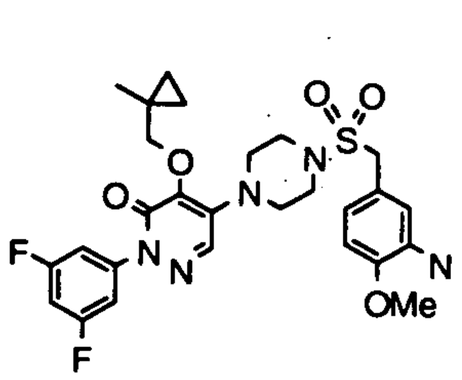


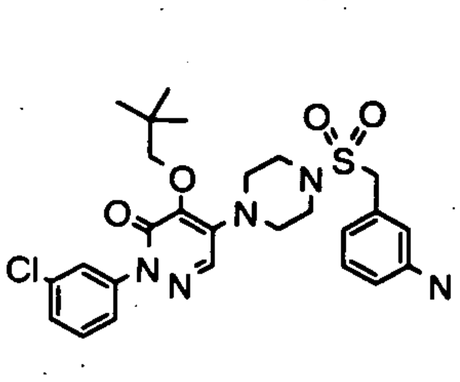


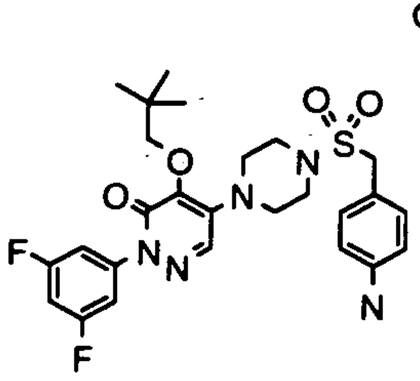


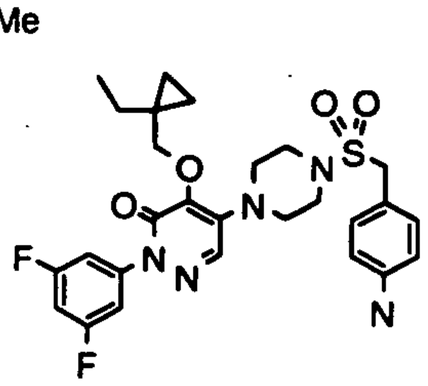


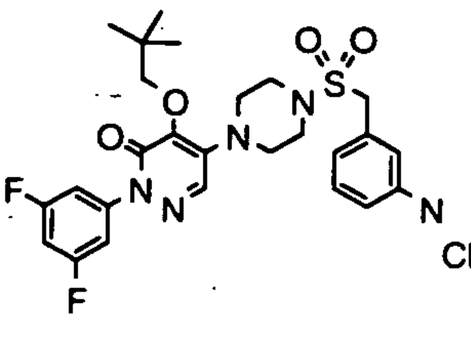


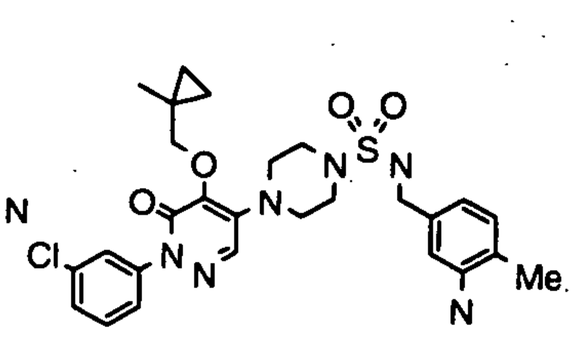


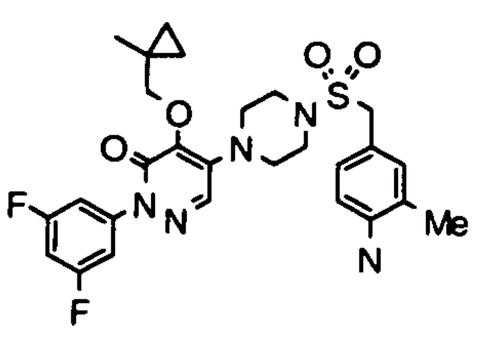


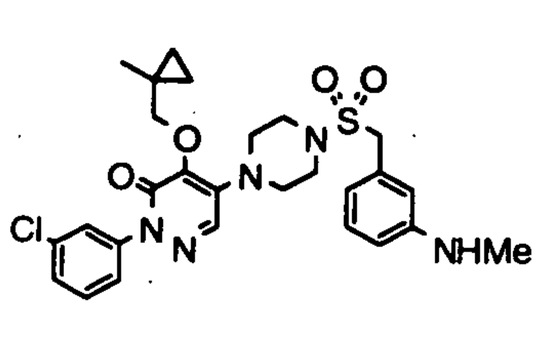


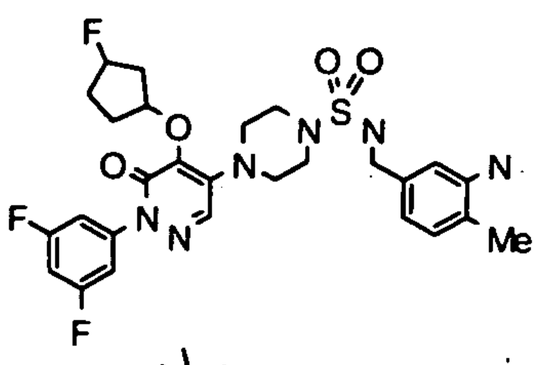


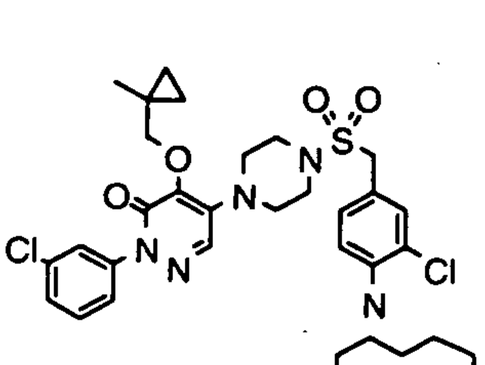


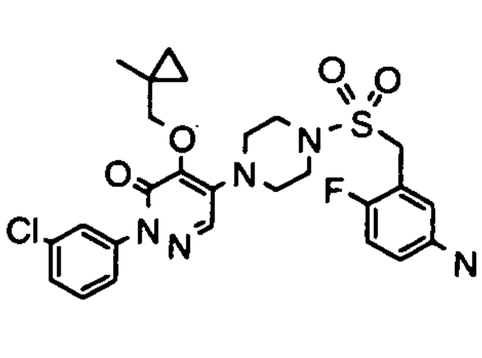


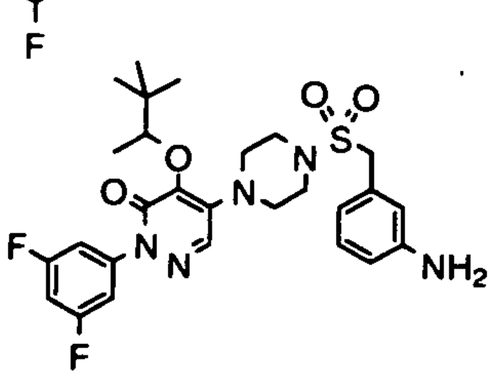




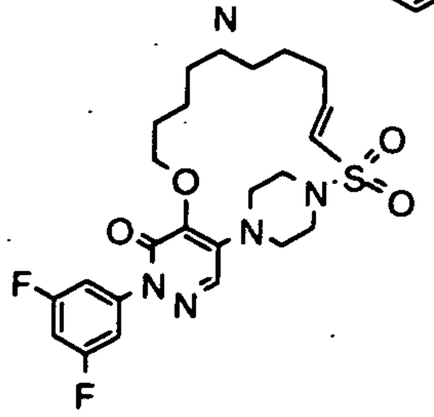




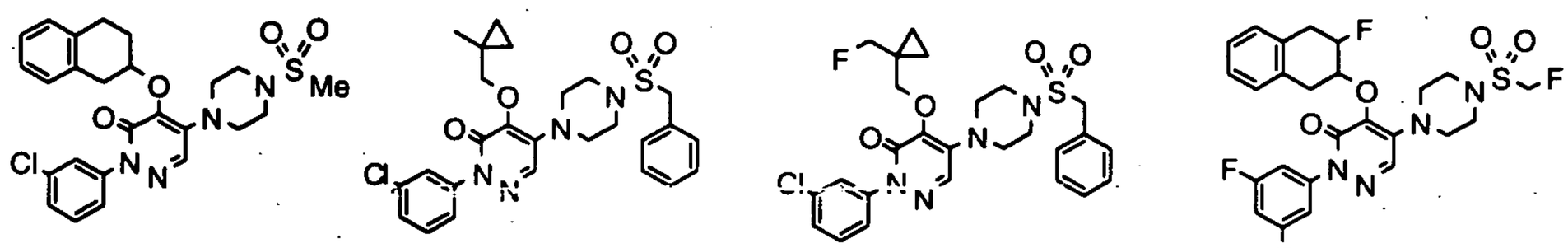
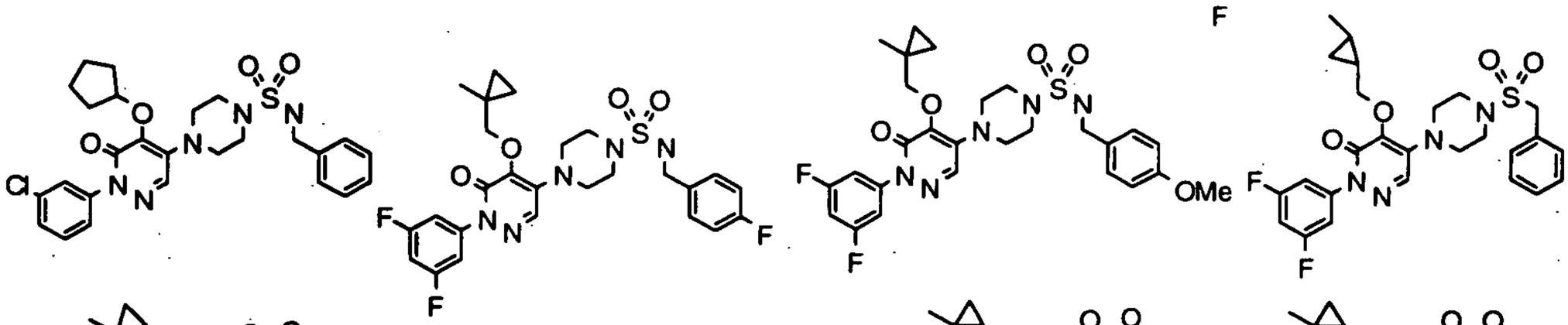
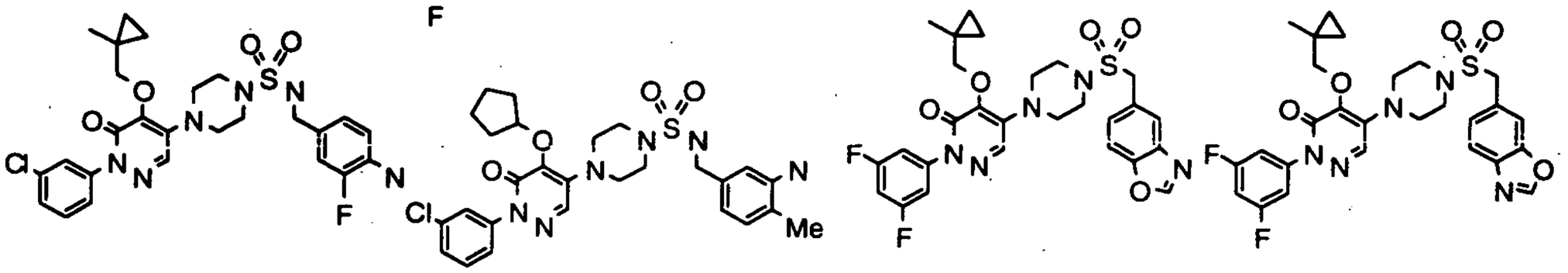
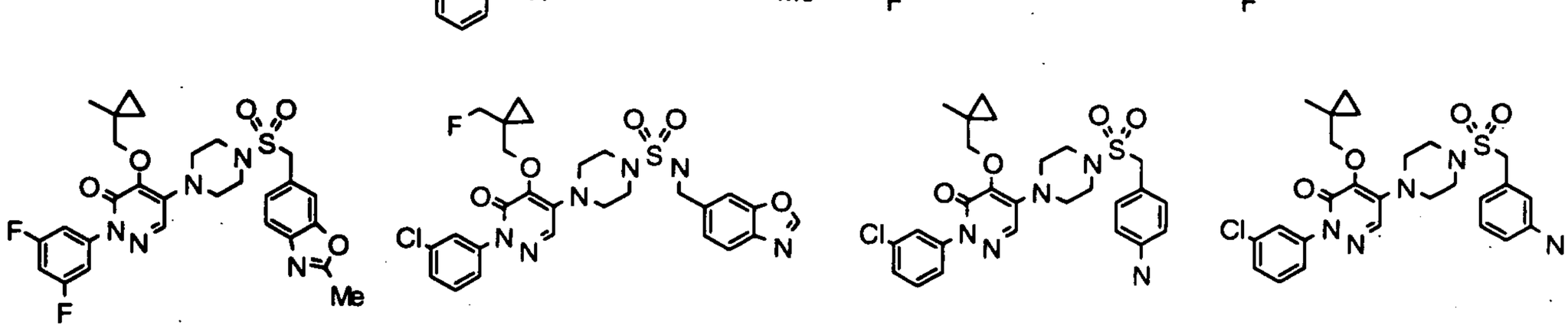
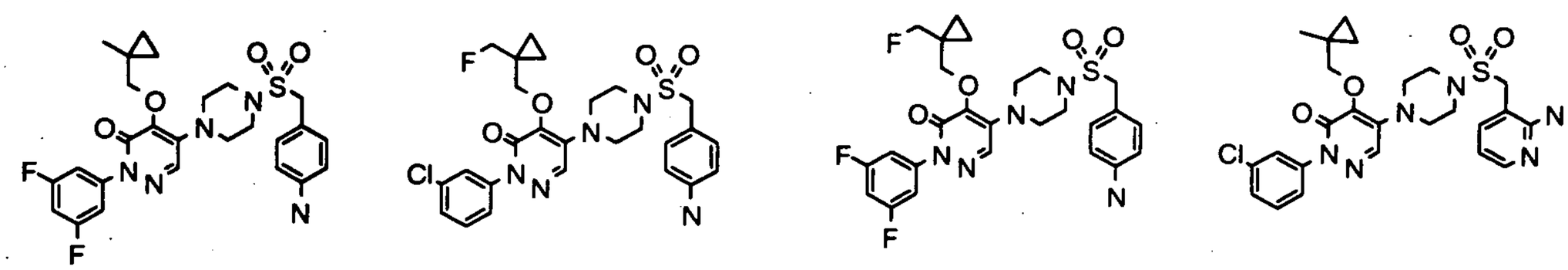
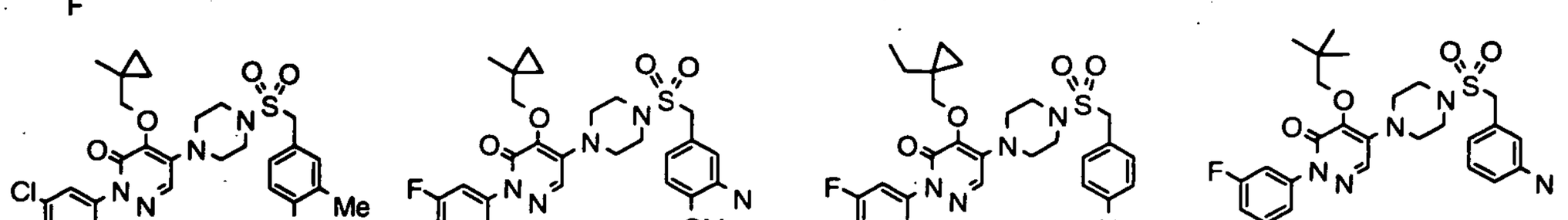
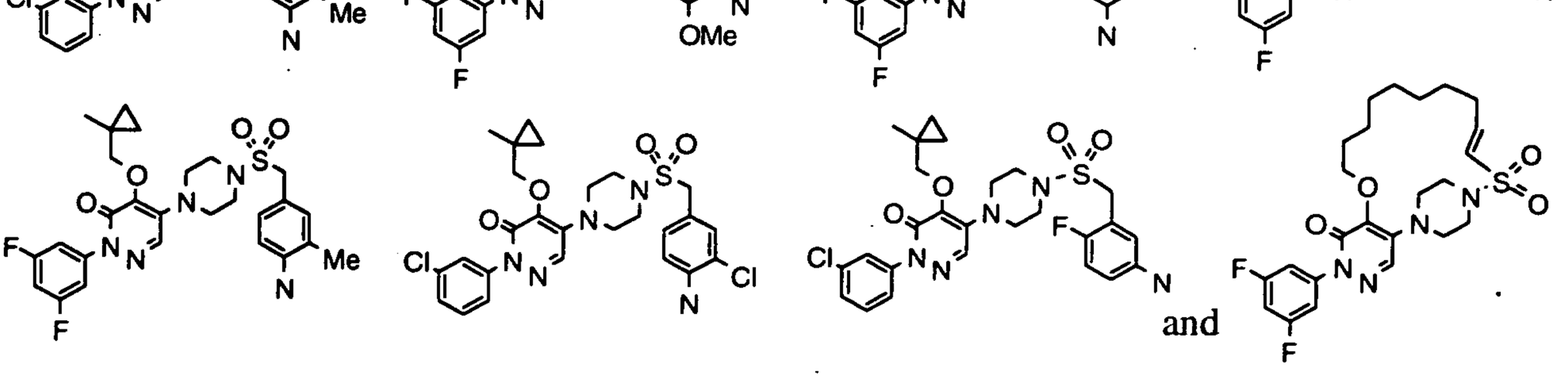




and



18. A compound of claim 1 selected from the group consisting of

and

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19. A method of treating or preventing fungal infections comprising administering to an animal or plant in need of such treatment an effective amount of a compound of claim 1.

20. A method of treating or preventing fungal infections comprising administering to an animal or plant in need of such treatment an effective amount of a compound of claim 17.

21. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, in combination with at least one pharmaceutically acceptable carrier.

22. The pharmaceutical composition according to claim 21, further comprising one or more anti-fungal agents different from the compound of claim 1.

23. The pharmaceutical composition according to claim 22, wherein the one or more anti-fungal agents are selected from the group consisting of azoles, echinocandins, polyenes, allylamines, thiocarbamates, nikkomycins, pradimicins, 5-fluorocytosines, oxaboroles, ciclopiroxolamine, griseofulvin and morpholines.

24. The pharmaceutical composition according to claim 22, wherein the one or more anti-fungal agents are selected from the group consisting of fluconazole, miconazole, itraconazole, voriconazole, posaconazole, caspofungin, micafungin, anidulafungin, amphotericin B, liposomal formulations of amphotericin B, nystatin, terbinafine, tolnaftate, ciclopiroxolamine, griseofulvin and fenpropimorph.

25. The method of claim 19 wherein at least one compound as defined in claim 1 is used to treat or prevent infections from yeasts or moulds.

26. The method of claim 25 wherein yeasts are selected from the group consisting of *Candida, Cryptococcus, Malassezia, Pichia, Rhodotorula, Saccharomyces* and *Trichosporon*, or moulds are selected from the group consisting of *Absidia, Alternaria, Apophysomyces, Aspergillus, Bjerkandera, Blastomyces, Coccidioides, Cunninghamella, Exophiala, Fusarium, Histoplasma, Microsporum, Mucor, Paecilomyces, Penicillium, Pseudallescheria, Ramichloridium, Rhizomucor, Rhizopus, Saksenaea, Scedosporium, Sporothrix, Trichophyton* and *Wangiella.*

27. The method of claim 19 wherein the animal is a mammal, a fish, a bird, a crustacean or a reptile.

28. The method of claim 19 wherein the animal is a human.

29. A method of treating or preventing growth of fungal pathogens in a plant comprising applying to said plant at least one compound as defined in claim 1.

30. The method of claim 19 wherein at least one compound as defined in claim 1 is used to treat or prevent the fungal infections, said fungal infections include *Absidia corymbifera*;

Absidia spp; *Acremonium spp*; *Ajellomyces capsulatus*; *Ajellomyces dermatitidis*; *Alternaria spp*; *Aphanoascus fulvescens*; *Apophysomyces spp*; *Arthroderma benhamiae*; *Arthroderma fulvum*; *Arthroderma gypseum*; *Arthroderma incurvatum*; *Arthroderma otae*; *Arthroderma vanbreuseghemii*; *Aspergillus flavus*; *Aspergillus fumigatus*; *Aspergillus glaucus*; *Aspergillus nidulans*; *Aspergillus niger*; *Aspergillus oryzae*; *Aspergillus spp*; *Aspergillus sydowi*; *Aspergillus terreus*; *Aspergillus ustus*; *Aspergillus versicolor*; *Aureobasidium pullulans*; *Basidiomycetes*; *Beauveria spp*; *Bipolaris hawaiiensis*; *Bipolaris spicifera*; *Bipolaris spp*; *Bjerkandera adusta*; *Blastomyces dermatitidis*; *Blastoschizomyces capitatus*; *Candida albicans*; *Candida beigelii*; *Candida colluculosa*; *Candida dubliniensis*; *Candida dubliniensis*; *Candida famata*; *Candida glabrata*; *Candida guilliermondii*; *Candida haemulonii*; *Candida holmii*; *Candida inconspicua*; *Candida intermedia*; *Candida keyfyr*; *Candida krusei*; *Candida lambica*; *Candida lipolytica*; *Candida lusitaniae*; *Candida maris*; *Candida melibiosica*; *Candida norvegensis*; *Candida parapsilosis*; *Candida pelliculosa*; *Candida pseudotropicalis*; *Candida pulcherrima*; *Candida rugosa*; *Candida sake*; *Candida sphaerica*; *Candida spp*; *Candida stellatoidea*; *Candida tropicalis*; *Candida viswanathii*; *Candida zeylanoides*; *Chrysosporium spp*; *Cladophialophora bantiana*; *Cladophialophora carrionii*; *Cladosporium spp*; *Coccidioides immitis*; *Cokeromyces recurvatus*; *Coprinus spp*; *Cryptococcus albidus*; *Cryptococcus gattii*; *Cryptococcus laurentii*; *Cryptococcus neoformans*; *Cunninghamella bertholletiae*; *Cunninghamella spp*; *Curvularia lunata*; *Curvularia spp*; *Dekkera bruxellensis*; *Epidermophyton floccosum*; *Exophiala dermatitidis*; *Exophiala jeanselmei*; *Exophiala moniliae*; *Exserohilum rostratum*; *Filobasidiella neoformans*; *Fonsecaea pedrosoi*; *Fusarium dimerum*; *Fusarium moniliforme*; *Fusarium oxysporum*; *Fusarium proliferatum*; *Fusarium solani*; *Fusarium spp*; *Geotrichum candidum*; *Geotrichum spp*; *Histoplasma capsulatum*; *Hortaea werneckii*; *Issatschenkia orientalis*; *Kluveromyces lactis*; *Kluyveromyces marxianus*; *Madurella grisae*; *Malassezia furfur*; *Malassezia globosa*; *Malassezia obtusa*; *Malassezia pachydermatis*; *Malassezia restricta*; *Malassezia slooffiae*; *Malassezia sympodialis*; *Metarrhizium anisopliae*; *Microsporum audouinii*; *Microsporum canis*; *Microsporum fulvum*; *Microsporum gypseum*; *Microsporum persicolor*; *Mucor circinelloides*; *Mucor hiemalis*; *Mucor racemosus*; *Mucor rouxii*; *Mucor spp*; *Nattrassia mangiferae*; *Nectria haematococca*; *Onychocola canadensis*; *Paecilomyces lilacinus*; *Paecilomyces spp*; *Paecilomyces variotii*; *Paracoccidioides brasiliensis*; *Penicillium marneffei*; *Penicillium spp*; *Phialophora spp*; *Phialophora verrucosa*; *Phoma*

spp; *Pichia anomala*; *Pichia etchellsii*; *Pichia guilliermondii*; *Pichia ohmeri*; *Pithomyces spp*; *Pneumocystis carinii*; *Pseudallescheria boydii*; *Ramichloridium obovoideum*; *Rhizomucor miehei*; *Rhizomucor pusillus*; *Rhizomucor spp*; *Rhizopus arrhizus*; *Rhizopus microsporus*; *Rhizopus oryzae*; *Rhizopus schipperae*; *Rhizopus spp*; *Rhodotorula mucilaginosa*; *Rhodotorula rubra*; *Rhodotorula spp*; *Saccharomyces cerevisiae*; *Saccharomyces spp*; *Sagrahamala spp*; *Saksenaea vasiformis*; *Scedosporium apiospermum*; *Scedosporium prolificans*; *Schizophyllum commune*; *Schizosaccharomyces pombe*; *Scopulariopsis brevicaulis*; *Scytalidium dimidiatum Ulocladium spp*; *Sporobolomyces spp*; *Sporothrix schenckii*; *Trichoderma spp*; *Trichophyton krajdenii*; *Trichophyton mentagrophytes*; *Trichophyton raubitschekii*; *Trichophyton rubrum*; *Trichophyton soudanense*; *Trichophyton spp*; *Trichophyton terrestre*; *Trichophyton tonsurans*; *Trichophyton verrucosum*; *Trichophyton violaceum*; *Trichosporon asahii*; *Trichosporon beigelii*; *Trichosporon capitatum*; *Trichosporon cutaneum*; *Trichosporon inkin*; *Trichosporon mucoides*; *Trichosporon spp*; *Tritirachium spp*; *Wangiella dermatitidis* and *Yarrowia lipolytica*.

31. A kit for treating or preventing fungal infections comprising in a single package, one container comprising one or more compounds as defined in claim 1 in a pharmaceutically acceptable carrier, and one or more separate containers, each comprising one or more additional antifungal agent in a pharmaceutically acceptable carrier.

32. A method of treating or preventing fungal infections comprising administering to an animal or plant in need of such treatment an effective amount the pharmaceutical composition as defined in claim 21.

33. A method of treating or preventing fungal infections comprising administering to an animal or plant in need of such treatment an effective amount the pharmaceutical composition as defined in claim 22.

34. A method of treating or preventing fungal infections comprising administering to an animal or plant in need of such treatment an effective amount the pharmaceutical composition as defined in claim 23.

35. A method of treating or preventing growth of fungal pathogens on inanimate surface, comprising applying one or more compounds of claim 1 to said surface.

36. The method of claim 35, further comprising other antifungal agents.

37. A method of inhibiting one or more glucan synthase comprising administering at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof to a patient in need of such inhibition.