PYRAN DERVATIVES AS CYP11A1 (CYTOCHROME P450 MONOOXYGENASE 11A1) INHIBITORS

Technical field

The present invention relates to therapeutically active compounds useful in the treatment of a steroid receptor, in particular androgen receptor (AR), dependent conditions and diseases, and to pharmaceutical compositions containing such compounds.

Background of the invention

Prostate cancer is worldwide the most common cancer in men. Even though the 5-year survival rate of patients with localized prostate cancer is high, the prognosis for those patients, who develop castration-resistant prostate cancer (CRPC) within that 5-year follow-up period, is poor.

The androgen receptor (AR) signalling axis is critical in all stages of prostate cancer. In the CPRC stage, disease is characterized by high AR expression, AR amplification and persistent activation of the AR signalling axis by residual tissue/tumor androgens and by other steroid hormones and intermediates of steroid biosynthesis. Thus, treatment of advanced prostate cancer involves androgen deprivation therapy (ADT) such as hormonal manipulation using gonadotropin-releasing hormone (GnRH) agonists/antagonists or surgical castration, AR antagonists or CYP17A1 inhibitors (such as abiraterone acetate in combination with prednisone).

Although therapies can initially lead to disease regression, eventually majority of the patients develop a disease that is refractory to currently available therapies. Increased progesterone levels in patients treated with abiraterone acetate has been hypothesized to be one of the resistance mechanisms. Several nonclinical and clinical studies have indicated upregulation of enzymes that catalyse steroid biosynthesis at the late stage of CRPC. Very recently it has been published that 11β-OH androstenedione can be

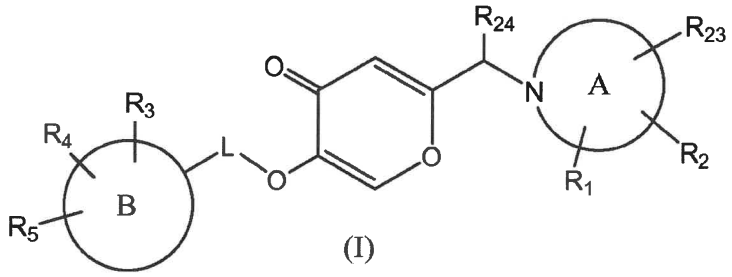
metabolized into 11-ketotestosterone (11-K-T) and 11-ketodehydrotestosterone (11-K-DHT) which can bind and activate AR as efficiently as testosterone and dihydrotestosterone. It has been shown that these steroids are found in high levels in plasma and tissue in prostate cancer patients, suggesting their role as AR agonists in CRPC. Furthermore, it has been addressed that prostate cancer resistance to CYP17A1 inhibition may still remain steroid dependent and responsive to therapies that can further suppress de novo intratumoral steroid synthesis upstream of CYP17A1, such as by CYP11A1 inhibition therapy (Cai, C. et al, Cancer Res., 71(20), 6503-6513, 2011).

Cytochrome P450 monooxygenase 11A1 (CYP11A1), also called cholesterol side chain cleavage enzyme, is a mitochondrial monooxygenase which catalyses the conversion of cholesterol to pregnenolone, the precursor of all steroid hormones. By inhibiting CYP11A1, the key enzyme of steroid biosynthesis upstream of CYP17A1, the total block of the whole steroid biosynthesis can be achieved. CYP11A1 inhibitors may therefore have a great potential for treating steroid hormone dependent cancers, such as prostate cancer, even in advanced stages of the disease, and especially in those patients who appear to be hormone refractory. It has been recently shown that a compound having CYP11A1 inhibitory effect significantly inhibited tumor growth in vivo in a murine CRPC xenograft model (Oksala, R. et al, Annals of Oncology, (2017) 28 (suppl. 5): Abstract/Poster 28P).

Summary of the invention

It has been found that compounds of formula (I) are potent CYP11A1 inhibitors. The compounds of the invention are therefore useful as medicaments in the treatment of steroid hormone dependent conditions and diseases where CYP11A1 inhibition is desired. Such conditions and diseases include, but are not limited to, endocrine cancers and diseases, such as prostate cancer and breast cancer. In particular, the compounds of the invention are useful in the treatment of AR dependent conditions and diseases including prostate cancer.

The present invention relates to a compound of formula (I)

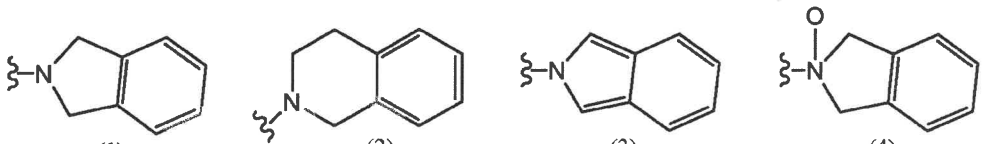


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups



(1) (2) (3) (4) ;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$, $-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, $-D-C(O)-NR_6R_7$, $-C(O)R_8$, $-D-NR_9R_{10}$, $-SO_2R_{11}$, an optionally substituted 3-10 membered carbocyclyl, an optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl,

an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl or an optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or an optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or -SO_2R_{21};

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2R_{17};

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound is not

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2,5-dimethylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(2,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(3-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-methylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(3,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(1-naphthalenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[3-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

5-[(2-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(2-Chloro-6-fluorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl) methyl]-4*H*-pyran-4-one;

5-[(4-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(4-Bromophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-methylphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(phenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[4-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

Methyl 4-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzoate;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3,5-dimethoxyphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-nitrophenyl)methoxy]- 4*H*-pyran-4-one;

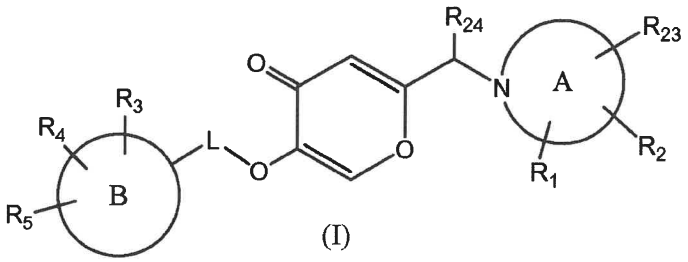
Methyl 5-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)furan-2-carboxylate;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(2-phenylethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-methylphenyl)methoxy]-4*H*-pyran-4-one; or

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-nitrophenyl)methoxy]-4*H*-pyran-4-one.

According to one embodiment, the invention provides a method for the treatment or prevention of a steroid receptor, particularly androgen receptor (AR), dependent conditions and diseases, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I)

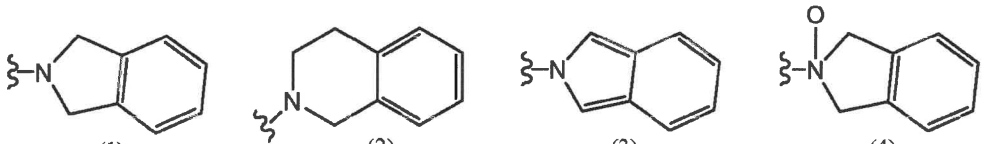


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups



(1) (2) (3) (4) ;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, ydroxyl C_{3-7} cycloalkyl, C_{1-7} alkoxy, ydroxyl C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$, $-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, $-D-C(O)-NR_6R_7$, $-C(O)R_8$, $-D-NR_9R_{10}$, $-SO_2R_{11}$, an optionally substituted 3-10 membered carbocyclyl, an optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl or an optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or an optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or -SO_2R_{21};

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2R_{17};

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

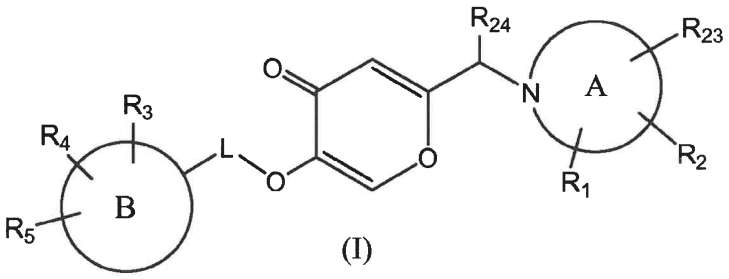
According to one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined in any of the above embodiments together with a pharmaceutically acceptable carrier.

According to one embodiment, the invention provides a method for the treatment or prevention of a steroid receptor, in particular androgen receptor (AR), dependent conditions and diseases. Such conditions and diseases include, but are not limited to, endocrine cancers and diseases, such as prostate cancer and breast cancer. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) as defined in any of the above embodiments.

Detailed description of the invention

The present application provides novel 4*H*-pyran-4-one derivatives of formula (I) or pharmaceutically acceptable salts thereof which are useful as CYP11A1 inhibitors.

One of the embodiments of the present invention provides a compound of formula (I)

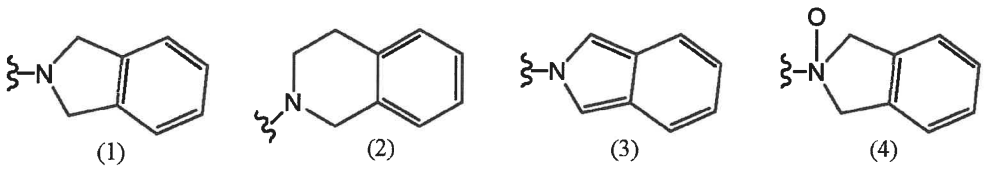


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups


(1) (2) (3) (4) ;

L is absent, -CH_2- , -CH_2-CH_2- or -CH_2-CH_2-CH_2-, or in case ring A is (1), L can also be -C(O)-CH_2-;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, =NSO_2R_{20},-S(O)-C_{1-7} alkyl, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), -C(S)$NR_{18}R_{19}$, -D-C(O)-NR_6R_7, -C(O)R_8, -D-NR_9R_{10}, -SO_2R_{11}, an optionally substituted 3-10 membered carbocyclyl, an optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl or an optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or an optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2(C_{1-7}$ alkyl) or $-SO_2(C_{3-7}$ cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or $-SO_2R_{21}$;

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2R_{17}$;

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound is not

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2,5-dimethylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(2,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(3-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-methylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(3,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(1-naphthalenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[3-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

5-[(2-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(2-Chloro-6-fluorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl) methyl]-4*H*-pyran-4-one;

5-[(4-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(4-Bromophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-methylphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(phenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[4-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

Methyl 4-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzoate;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3,5-dimethoxyphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-nitrophenyl)methoxy]- 4*H*-pyran-4-one;

Methyl 5-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)furan-2-carboxylate;

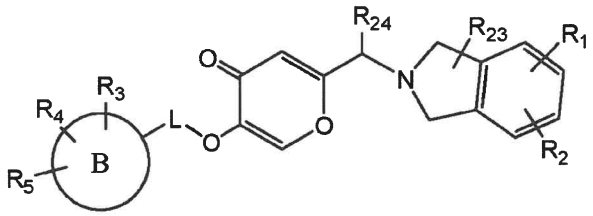
2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(2-phenylethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-methylphenyl)methoxy]-4*H*-pyran-4-one; or

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-nitrophenyl)methoxy]-4*H*-pyran-4-one.

It is to be understood that the left bond in linker L is attached to the ring B of formula (I).

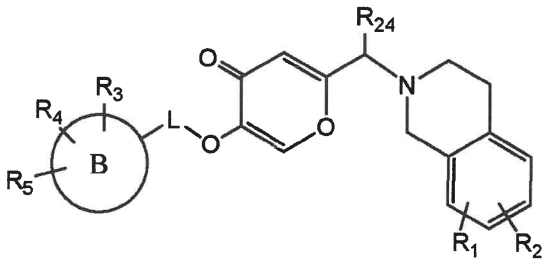
According to one embodiment, the compound according to the present invention is represented by formula (IA):



(IA),

wherein R_1, R_2, R_3, R_4, R_5, R_{23}, R_{24}, L and B are as defined in any of the above embodiments for formula (I), or a pharmaceutically acceptable salt thereof.

According to one embodiment, the compound according to the present invention is represented by formula (IB):

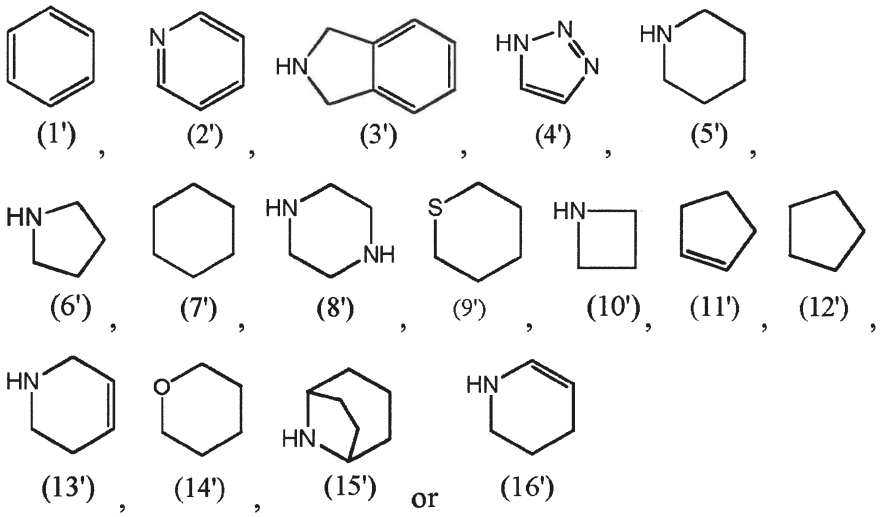


(IB),

wherein R_1, R_2, R_3, R_4, R_5, R_{24}, L and B are as defined in any of the above embodiments for formula (I), or a pharmaceutically acceptable salt thereof.

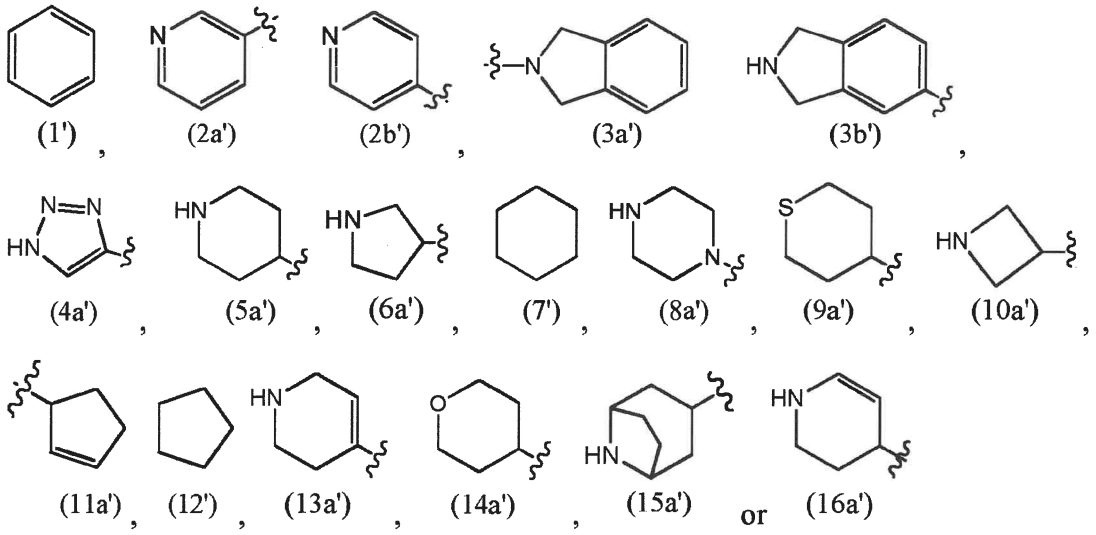
According to one embodiment, specifically provided is a compound of formula (I) wherein L is $-CH_2-$ or $-CH_2-CH_2-$, for example L is $-CH_2-$ or as another example L is $-CH_2-CH_2-$.

According to one embodiment, specifically provided is a compound of formula (I), wherein ring B is any one of the following groups



wherein R_3, R_4 and R_5, as defined in any of the above embodiments for formula (I), are attached to the above B-rings.

In a subclass of the above embodiment are compounds wherein ring B is any one of the following groups



and wherein R_3, R_4 and R_5, as defined in any of the above embodiments for formula (I), are attached to the above B-rings and wherein the wavy line denotes the site of attachment to L.

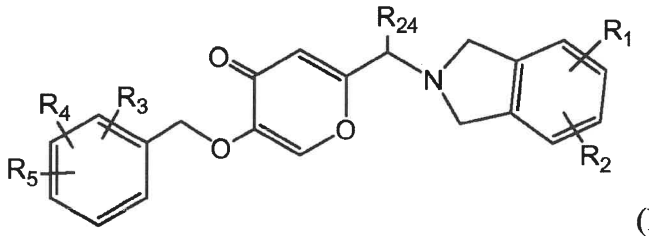
According to yet one embodiment, specifically provided are compounds wherein ring B is ring (1'), (5'), (7'), (9'), (13') or (14') as defined above.

In a subclass of the above embodiment are compounds wherein ring B is (1'), (5a'), (7'), (9a'), (13a') or (14a') as defined above.

According to one embodiment, specifically provided are compounds wherein R_3 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), -C(S)$NR_{18}R_{19}$, an optionally substituted 3-10 membered carbocyclyl, an optionally substituted 4-10 membered heterocyclyl, or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl; wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo, and wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S.

According to one embodiment, specifically provided are compounds wherein R_4 and R_5 are hydrogen.

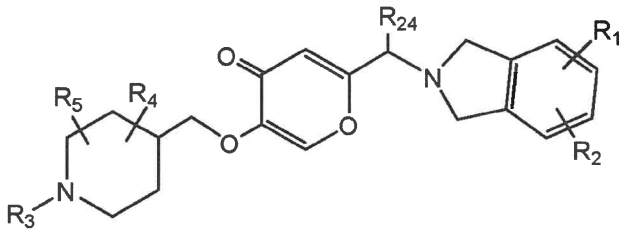
According to one embodiment, the compound according to the present invention is represented by formula (IC):



(IC)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in any of the above embodiments for formula (I), or a pharmaceutically acceptable salt thereof.

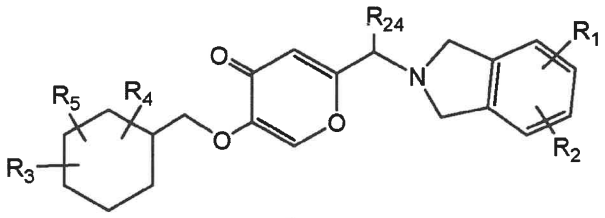
According to one embodiment, the compound according to the present invention is represented by formula (ID):



(ID)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in any of the above embodiments for formula (I), or a pharmaceutically acceptable salt thereof.

According to one embodiment, the compound according to the present invention is represented by formula (IE):



(IE)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in any of the above embodiments for formula (I), or a pharmaceutically acceptable salt thereof.

According to one embodiment, specifically provided are compounds as defined in any of the above embodiments wherein

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, thio, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -$C(O)R_8$, -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), -C(S)$NR_{18}R_{19}$, a 3-6 membered carbocyclyl which is optionally substituted with 1-2 hydroxyl substituents, a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen, hydroxyl, C_{1-7} alkoxycarbonyl or oxo, or a 4-6 membered heterocyclyl C_{1-7} alkyl optionally substituted with 1-2 oxo substituents;

R_4 is hydrogen, C_{1-7} alkyl, hydroxy or halogen;

R_5 is hydrogen or halogen;

R_6 is C_{1-7} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 halogen substituents;

R_9 is C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, a 3-6 membered carbocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl, or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or

C_{1-7} alkylcarbonyl;

R_{13} is hydrogen or C_{1-7} alkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or $-SO_2R_{21}$;

R_{15} is hydrogen, C_{1-7} alkyl, $-SO_2R_{17}$;

R_{17} is C_{1-7} alkyl or a 3-6 membered carbocyclyl which is optionally substituted by 1-2 C_{1-7} alkyl substituent;

R_{18}, and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

R_{21} is a 3-6 membered carbocyclyl optionally substituted with 1-2 C_{1-7} alkyl substituents;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

In one subclass are compounds represented by formula (IC) wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, $-C(O)R_8$, $-SO_2R_{11}$, -D-NR_9R_{10}, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), a 3-6 membered carbocyclyl which is optionally substituted with 1-2 hydroxy substituents, or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or hydroxy;

R_4 is hydrogen, hydroxy or halogen;

R_5 is hydrogen or halogen;

R_6 is C_{1-7} alkyl, hydroxy C_{1-7} alkyl or $-C_{1-7}$ alkyl-O-C(O)C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, halo C_{1-7} alkyl, $-N=S(O)(C_{1-7}$ alkyl)(C_{1-7} alkyl) or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 halogen substituents;

R_9 is C_{1-7} alkylcarbonyl or $-SO_2(C_{1-7}$ alkyl);

R_{10} is hydrogen or C_{1-7} alkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$ or a 4-6 membered heterocyclyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{13} is hydrogen or C_{1-7} alkyl;

R_{14} is hydrogen, C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is hydrogen or $-SO_2R_{17}$;

R_{17} is a 3-6 membered carbocyclyl which is optionally substituted by 1-2 C_{1-7} alkyl substituents;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

In a subclass of the above embodiment are compounds wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, nitro, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_{10} are hydrogen;

R_3 is C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $-D-C(O)-NR_6R_7$, $-C(O)R_8$, $-SO_2R_{11}$, $-D-NR_9R_{10}$, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), oxazolyl, cyclobutyl optionally substituted with a hydroxy substituent, or oxetanyl optionally substituted with a hydroxy substituent;

R_4 and R_5 are hydrogen or halogen;

R_6 is C_{1-7} alkyl or hydroxy C_{1-7} alkyl;

R_7, R_{13}, R_{14} and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, pyrrolidinyl, oxetanyl, or azetidinyl optionally substituted with 1-2 halogen substituents,$-N=S(O)(C_{1-7}$ alkyl)(C_{1-7} alkyl);

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, pyrrolidinyl, piperidinyl, azetidinyl or morpholinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is hydrogen or $-SO_2R_{17}$;

R_{17} is phenyl optionally substituted by a C_{1-7} alkyl substituent;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

In still another subclass of the above embodiment are compounds wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_{10} are hydrogen;

R_3 is hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, $-C(O)R_8$, $-SO_2R_{11}$, -D-NR_9R_{10}, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), oxazolyl, cyclobutyl optionally substituted with a hydroxy substituent, or oxetanyl optionally substituted with a hydroxy substituent;

R_4 and R_5 are hydrogen or halogen;

R_6 is C_{1-7} alkyl;

R_7, R_{13}, R_{14} and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is pyrrolidinyl, azetidinyl or $-N=S(O)(C_{1-7}$ alkyl)(C_{1-7} alkyl);

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{11} is C_{1-7} alkyl, halo C_{1-7} alkyl, $-NR_{12}R_{13}$ or pyrrolidinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is $-SO_2R_{17}$;

R_{17} is phenyl optionally substituted by a C_{1-7} alkyl substituent;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

In still another subclass of the above embodiment are compounds wherein R_1 is hydrogen, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_4, R_5 and R_{10} are hydrogen;

R_3 is hydroxy C_{1-7} alkyl, -D-C(O)-NR_6R_7, -C(O)R_8, -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}) or oxetanyl optionally substituted with a hydroxy substituent;

R_6 and R_7 is C_{1-7} alkyl;

R_8 is pyrrolidinyl, or -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl);

R_9 is -SO_2(C_{1-7} alkyl);

R_{11} is C_{1-7} alkyl, -$NR_{12}R_{13}$ or pyrrolidinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, or C_{1-7} alkoxy C_{1-7} alkyl;

R_{13} and R_{14} is hydrogen or C_{1-7} alkyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

In one subclass are compounds represented by formula (ID) wherein

R_1 is hydrogen, C_{1-7} alkyl, cyano, halogen, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11} or -C(S)$NR_{18}R_{19}$;

R_4 is hydrogen, C_{1-7} alkyl, hydroxy or halogen;

R_5 is hydrogen;

R_6 is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_7 and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, C_{1-7} alkoxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl) or a 4-10 membered heterocyclyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, a 3-6 membered carbocyclyl which is optionally substituted with 1-2 halogen substituents, or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{18}, and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

D is absent;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S.

or a pharmaceutically acceptable salt thereof.

In a subclass of the above embodiment are compounds wherein

R_1 is hydrogen, C_{1-7} alkyl, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_5 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, or -C(S)$NR_{18}R_{19}$, or oxetanyl optionally substituted by a hydroxy substituent;

R_4 is hydrogen, C_{1-7} alkyl or halogen;

R_6 is C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, C_{1-7} alkoxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), azetidinyl, morpholinyl, furanyl or pyrrolidinyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, pyrrolidinyl, phenyl optionally substituted with a halogen substituent, oxetanyl, or pyrazolyl optionally substituted with a C_{1-7} alkyl substituent;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{18} and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent;

or a pharmaceutically acceptable salt thereof.

In still another subclass of the above embodiment are compounds wherein

R_1 is hydrogen, C_{1-7} alkyl, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_5 and R_7 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 or -SO_2R_{11};

R_4 is hydrogen or C_{1-7} alkyl;

R_6 is C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), morpholinyl or pyrrolidinyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, oxetanyl, or pyrazolyl optionally substituted with a C_{1-7} alkyl substituent;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent;

or a pharmaceutically acceptable salt thereof.

In still another subclass of the above embodiment are compounds wherein

R_1 is hydrogen, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_4, R_5 and R_7 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 or -SO_2R_{11};

R_6 , R_{12} and R_{13} are C_{1-7} alkyl;

R_8 is C_{1-7} alkyl or halo C_{1-7} alkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$ or oxetanyl;

R_{24} is hydrogen;

D is absent;

or a pharmaceutically acceptable salt thereof.

In one subclass are compounds represented by formula (IE) wherein

R_1, R_2, R_4, R_5 and R_{24} are hydrogen;

R_3 is hydrogen, -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), a 4-6 membered heterocyclyl which is optionally substituted with 1-2 oxo substituents, or a 4-6 membered heterocyclyl C_{1-7} alkyl optionally substituted with 1-2 oxo substituents;

R_6, R_{11} and R_{22} are C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{1-7} alkoxy, or a 4-6 membered heterocyclyl;

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen or $-SO_2R_{21}$;

R_{21} is 3-6 membered carbocyclyl optionally substituted with 1-2 C_{1-7} alkyl;

D is absent or C_{1-7} alkyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

In still another subclass of the above embodiment are compounds wherein

R_1, R_2, R_4, R_5 and R_{24} are hydrogen;

R_3 is -D-C(O)-NR_6R_7, $-C(O)R_8$, $-SO_2R_{11}$, -D-NR_9R_{10}, $-S(O)(NR_{14})(R_{22})$, 1,1-dioxidoisothiazolidinyl or 1,1-dioxidoisothiazolidinyl C_{1-7} alkyl;

R_6, R_{11} and R_{22} are C_{1-7} alkyl;

R_7 is C_{1-7} alkyl;

R_8 is C_{1-7} alkyl or azetidinyl;

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is $-SO_2R_{21}$;

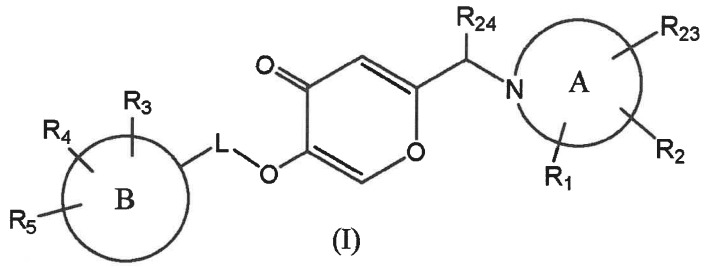
R_{21} is phenyl optionally substituted with a C_{1-7} alkyl substituent;

D is absent or C_{1-7} alkyl;

or a pharmaceutically acceptable salt thereof.

According to one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined in any of the above embodiments together with a pharmaceutically acceptable carrier.

According to still one embodiment, the present invention provides a method for the treatment of a steroid receptor, in particular androgen receptor (AR), dependent conditions and diseases, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I)

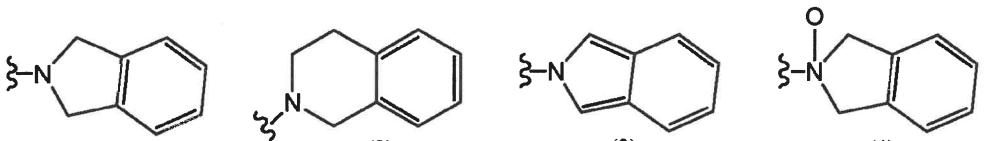


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S;

ring A is any of the following groups



(1) (2) (3) (4) ;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$,$-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, $-D-C(O)NR_6R_7$, $-C(O)R_8$, $-D-NR_9R_{10}$, $-SO_2R_{11}$, an optionally substituted 3-10 membered carbocyclyl, an optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, an optionally substituted 4-10 membered heterocyclyl or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl or an optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or an optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, an optionally substituted 3-10 membered carbocyclyl or an optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or -SO_2R_{21};

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2R_{17};

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

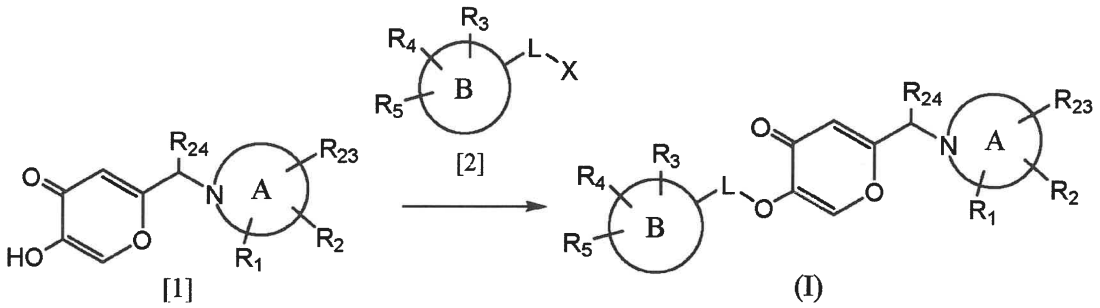
or a pharmaceutically acceptable salt thereof.

According to one embodiment, the steroid receptor dependent disease or condition is androgen receptor dependent disease or condition including endocrine cancers and diseases, for example prostate cancer or breast cancer, particularly castration-resistant prostate cancer (CRPC). According to one embodiment of the invention, the CRPC to be treated is refractory to CYP17A1 inhibitor treatment. According to another embodiment, the androgen receptor dependent disease or condition is endocrine cancer which is dependent upon CYP11A1 activation.

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The compounds according to formula (I) can be prepared e.g. analogously or according to the following reaction Schemes. Some compounds included in the formula (I) can be obtained by converting the functional groups of the other compounds of formula (I) obtained in accordance with the following Schemes, by well known reaction steps such as oxidation, reduction, hydrolysis, acylation, alkylation, amidation, amination, sulfonation and others. It should be noted that any appropriate leaving groups, e.g. N-protecting groups, such as a t-butoxycarbonyl (t-BOC) group or a phenylsulfonyl group, can be used in well known manner during the syntheses in order to improve the selectivity of the reaction steps.

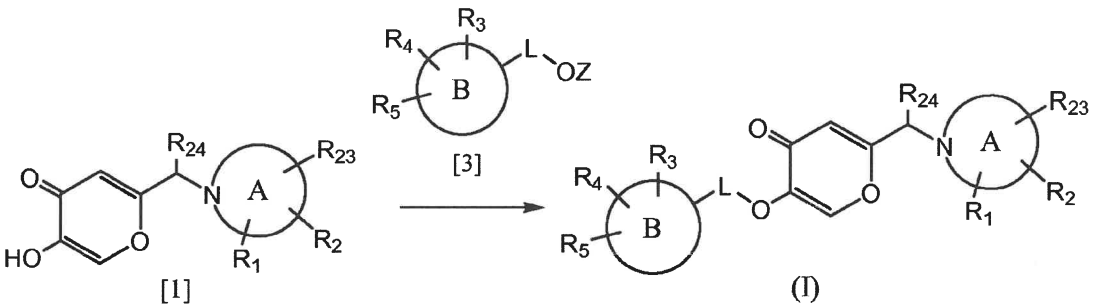
Compounds of formula (I) can be prepared, for example, according to Scheme 1, wherein R_1, R_2, R_3, R_4, R_5, R_{23}, R_{24}, L, A and B, are as defined above, and X is a halogen. In the method of Scheme 1, the 5-hydroxy-4H-pyran-4-one derivative [1] is coupled with ring B derivative [2] where halogen is acting as the leaving group in a suitable solvent in the presence of a base at elevated temperature, for example using K_2CO_3 in DMF, K_2CO_3 in DMSO, NaOH/KOH in MeOH/EtOH, NaH in DMF or K_2CO_3 in THF/1,4-dioxane, to produce a compound of formula (I).

SCHEME 1.



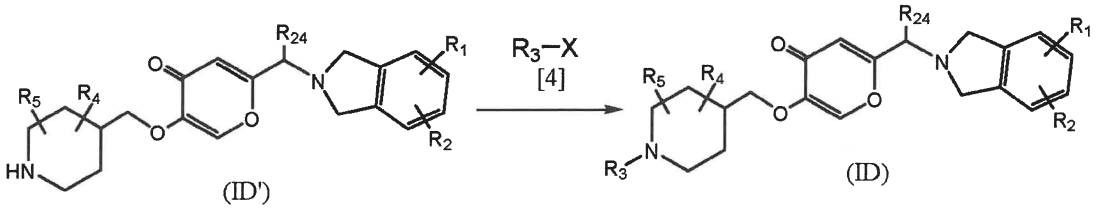
Alternatively, compounds of formula (I) can be prepared according to Scheme 2, wherein R_1, R_2, R_3, R_4, R_5, R_{23}, R_{24}, L, A and B, are as defined above, and Z is mesyl or tosyl group. In the method of Scheme 2, the 5-hydroxy-4H-pyran-4-one derivative [1] is coupled with ring B derivative [3], where mesylate or tosylate is acting as the leaving group, in a suitable solvent in the presence of a base at elevated temperature, for example using K_2CO_3 in DMF, K_2CO_3 in DMSO, NaOH/KOH in MeOH/EtOH, NaH in DMF or K_2CO_3 in THF/1,4-dioxane, to produce a compound of formula (I).

SCHEME 2.



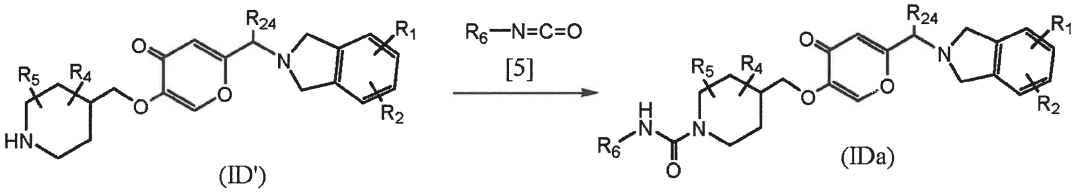
Compounds of formula (ID) where R_3 is coupled to the piperidine ring via acyl or sulfonyl group, can be prepared, for example, according to Scheme 3, wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined above, and X is a halogen. In the method of Scheme 3, the compound of formula (ID') is coupled with a halogen compound [4] in a suitable solvent such as CH_2Cl_2 in the presence of suitable base such as triethylamine to produce a compound of formula (ID).

SCHEME 3.



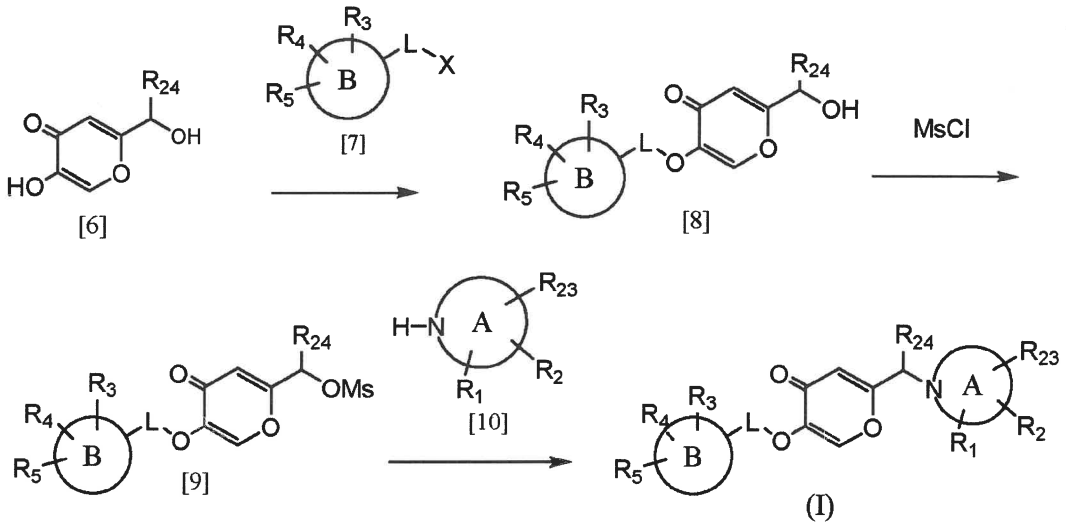
Compounds of formula (ID) where R_3 is -C(O)-NHR_6, can be prepared, for example, according to Scheme 4, wherein R_1, R_2, R_4, R_5, R_7 and R_{24} are as defined above. In the method of Scheme 4, the compound of formula (ID') is coupled with a isocyanate compound [5] in a suitable solvent such as CH_2Cl_2 or DMF in the presence of suitable base such as triethylamine or DIPEA to produce a compound of formula (IDa). Compounds of formula (ID) where R_3 is -C(S)NHR_{19} can be prepared in similar manner using R_{19}-N=C=S as a reagent.

SCHEME 4.



Compounds of formula (I) can also be prepared according to Scheme 5, wherein R_1, R_2, R_3, R_4, R_5, R_{23}, R_{24}, L, A and B, are as defined above, and X is a halogen. In the method of Scheme 5, the compound of formula [6] is coupled with a compound of formula [7] in a suitable solvent such as DMF in the presence of a base such as K_2CO_3 at elevated temperature to produce a compound of formula [8]. The compound of formula [8] can be then reacted with methanesulfonyl chloride in a suitable solvent such as DCM under cooling in the presence of suitable base such as triethylamine to produce a compound of formula [9]. Compounds of formula (I) can be obtained by coupling the compound of formula [9] with a compound of formula [10] in a suitable solvent such as DMSO or DMF in the presence of a base such as K_2CO_3 at elevated temperature.

SCHEME 5.



Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

The term "subject", as employed herein, refers to humans and animals.

The term "steroid receptor" refers to receptor which binds to and is activated by a steroid hormone. Examples of steroid receptors include, but are not limited to, androgen, glucocorticoid, and progesterone receptors.

The term "endocrine cancer" refers to partially or completely unregulated growth of one or more cellular components of the endocrine system, including, but not limited to, cancers of one or more of the adrenal glands.

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

The term "C_{1-7} alkyl", as employed herein as such or as part of another group, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4, 5, 6 or 7 carbon atom(s). Representative examples of C_{1-7} alkyl include, but are not limited to,

methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl and *n*-hexyl. One preferred embodiment of "C_{1-7} alkyl" is C_{1-3} alkyl. The term "C_{1-3} alkyl" refers to a preferred embodiment of "C_{1-7} alkyl" having 1, 2 or 3 carbon atoms.

The term "C_{2-7} alkenyl", as employed herein as such or as part of another group, refers to an aliphatic hydrocarbon group having 2, 3, 4, 5, 6 or 7 carbon atoms and containing one or several double bonds. Representative examples include, but are not limited to, ethenyl, propenyl and cyclohexenyl.

The term "C_{3-7} cycloalkyl", as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3, 4, 5, 6 or 7 carbon atoms. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C_{3-7} cycloalkyl C_{1-7} alkyl", as employed herein refers to a C_{3-7} cycloalkyl group, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein.

The term "hydroxy", as employed herein as such or as part of another group, refers to an –OH group.

The term "cyano", as employed herein as such or as part of another group, refers to a –CN group.

The term "carboxy", as employed herein as such or as part of another group, refers to –COOH group.

The term "carbonyl", as employed herein as such or as part of another group, refers to a carbon atom double-bonded to an oxygen atom (C=O).

The term "oxo", as employed herein as such or as part of another group, refers to oxygen atom linked to another atom by a double bond (=O).

The term "C_{1-7} alkoxy", as employed herein as such or as part of another group, refers to C_{1-7} alkyl, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of C_{1-7} alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

The term "hydroxy C_{1-7} alkyl", as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein. Representative examples of hydroxy C_{1-7} alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl and 1-methyl-1-hydroxypropyl.

The term "halo C_{1-7} alkyl", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein. Representative examples of halo C_{1-7} alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl and 3-bromopropyl.

The term "cyano C_{1-7} alkyl", as employed herein, refers to a cyano group, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein. Representative examples of cyano C_{1-7} alkyl include, but are not limited to, cyanomethyl, 1-cyanoethyl, 1-cyanopropyl and 2-cyanopropyl.

The term "halo C_{1-7} alkoxy", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkoxy group, as defined herein.

The term "phenyl C_{1-7} alkyl", as employed herein, refers to at least one phenyl group appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein.

The term "C_{1-7} alkyl carbonyl", as employed herein as such or as part of another group, refers to a C_{1-7} alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

The term "C_{1-7} alkoxy C_{1-7} alkyl", as employed herein as such or as part of another group, refers to at least one C_{1-7} alkoxy group, as defined herein, appended to the parent molecular moiety through an C_{1-7} alkyl group, as defined herein.

The term "hydroxy C_{1-7} alkoxy", as employed herein such or as part of another group, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through an C_{1-7} alkoxy group, as defined herein.

The term "hydroxy C_{1-7} alkoxy C_{1-7} alkyl", as employed herein, refers to a hydroxy C_{1-7} alkoxy group, as defined herein, appended to the parent molecular moiety through an C_{1-7} alkyl group, as defined herein.

The term "4-10 membered heterocyclyl" as employed herein, refers to a saturated, partially saturated or aromatic ring with 4-10 ring atoms, of which 1-4 atoms are heteroatoms selected from a group consisting of N, O and S. One embodiment of a "4-10 membered heterocyclyl" is a "4-6 membered heterocyclyl" which refers to a saturated, partially saturated or aromatic ring with 4-6 ring atoms, of which 1-4 atoms are heteroatoms selected from a group consisting of N, O and S. Representative examples of a 4-10 membered heterocyclic ring include, but are not limited to, oxetanyl, azetidinyl, pyrazolyl, 1,2,4-triazol-1-yl, 1,2,3-triazol-1-yl, pyrimidinyl, pyridinyl, piperidinyl, tetrazolyl, piperazinyl, furanyl, morpholinyl, piperidinyl, pyrrolidinyl, thiazolyl, isoxazolyl, pyrazinyl tetrahydropyranyl, 1,2,4-oxadiazolyl, oxazolyl, imidazolyl, indolyl and 4,5-dihydroimidazolyl rings.

The term "3-10 membered carbocyclyl" as employed herein, refers to a saturated, partially saturated or aromatic ring with 3 to10 ring atoms consisting of carbon atoms

only. One embodiment of a "3-10 membered carbocyclyl" is a "3-6 membered carbocyclyl" which refers to a saturated, partially saturated or aromatic ring with 3 to6 ring atoms consisting of carbon atoms only. Representative examples of a 3-10 membered carbocyclic ring include, but are not limited to, phenyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl and cyclobutyl rings.

The term "4-10 membered heterocyclyl C_{1-7} alkyl" as employed herein, refers to a "4-10 membered heterocyclyl" group, as defined herein, appended to the parent molecular moiety through an C_{1-7} alkyl group, as defined herein.

The term "3-10 membered carbocyclyl C_{1-7} alkyl " as employed herein, refers to a "3-10 membered carbocyclyl" group, as defined herein, appended to the parent molecular moiety through an C_{1-7} alkyl group, as defined herein.

The term "substituted" as used herein in connection with various residues refers to, if not otherwise defined, to halogen substituents, such as fluorine, chlorine, bromine, iodine, or C_{1-7} alkyl, C_{3-7} cycloalkyl, hydroxy, amino, nitro, cyano, thiol C_{1-7} alkyl, methylsulfonyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, hydroxy C_{1-7} alkyl or amino C_{1-7} alkyl substituents. Preferred are halogen, C_{1-7} alkyl, hydroxy, amino, halo C_{1-7} alkyl, C_{1-7} alkoxy and methylsulfonyl substituents. In one group of preferred substituents are 1-2 substituents selected from C_{1-7} alkyl or halogen substituents, particularly C_{1-3} alkyl or halogen substituents, particularly methyl, ethyl, chloro, fluoro or bromo substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, of the above mentioned substituents, if not otherwise defined.

Optically active enantiomers or diastereomers of compounds of formula (I) can be prepared e.g. by resolution of the racemic end product by known methods or by using suitable optically active starting materials. Similarly, racemic compounds of formula (I) can be prepared by using racemic starting materials. Resolution of racemic compounds of formula (I) or a racemic starting material thereof can be carried out, for example, by

converting the racemic compound into its diastereromeric salt mixture by reaction with an optically active acid and subsequent separation of the diastereomers by crystallization. Representative examples of said optically active acids include, but are not limited to, D-tartaric acid and dibenzoyl-D-tartaric acid. Alternatively, preparative chiral chromatography may be used for resolution of the racemic mixture.

Pharmaceutically acceptable salts are well known in the field of pharmaceuticals. Non-limiting examples of suitable salts include metal salts, ammonium salts, salts with an organic base, salts with an inorganic acid, salts with organic acid, and salts with basic or acidic amino acid. Non-limiting examples of metal salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt, and magnesium salt. Non-limiting examples of salts with inorganic or organic acids include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates, acetates, oxalates, fumarates, hemifumarates, and succinates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

The definition of formula (I) above is inclusive of all the possible isotopes and isomers, such as stereoisomers, of the compounds, including geometric isomers, for example *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers, and prodrug esters, e.g. phosphate esters and carbonate esters.

It will be appreciated by those skilled in the art that the present compounds may contain at least one chiral center. Accordingly, the compounds may exist in optically active or racemic forms. It is to be understood that the formula (I) includes any racemic or optically active form, or mixtures thereof. In one embodiment, the compounds are the

pure (R)-isomers. In another embodiment, the compounds are the pure (S)-isomers. In another embodiment, the compounds are a mixture of the (R) and the (S) isomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. The compounds may contain two chiral centers. In such case, according to one embodiment, the compounds are a mixture of diasteromers. According to another embodiment, the compounds of the invention are a mixture of enantiomers. According to still another embodiment, the compounds are pure enantiomers. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers or diastereomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

The present compounds may also exist as tautomers or equilibrium mixtures thereof wherein a proton of a compound shifts from one atom to another. Examples of tautomerism include, but are not limited to, amido-imido, keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine, annular tautomerism of heterocyclic rings, and the like. Tautomeric forms are intended to be encompassed by compounds of formula (I), even though only one tautomeric form may be depicted.

Examples of preferred compounds of one group of formula (I) include

Methyl (E)-3-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)phenyl)acrylate (Compound 2);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidin-1-ylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 5);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methyl-benzenesulfonamide (Compound 8);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-di-methylbenzenesulfonamide (Compound 10);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-(2-methoxyethyl)benzenesulfonamide (Compound 11);

N-(2-Hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)-oxy)methyl)-N-methylbenzenesulfonamide (Compound 12);

N-(2-Hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)-oxy)methyl)benzenesulfonamide (Compound 15);

N-Ethyl-N-(2-hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzenesulfonamide (Compound 21);

5-((4-((Difluoromethyl)sulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 22);

N-(2-Cyanoethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N-methylbenzenesulfonamide (Compound 23);

2-(Isoindolin-2-ylmethyl)-5-((1-(oxetan-3-ylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 36);

5-((4-(Methylsulfonyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)-methyl)-4H-pyran-4-one (Compound 37);

2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(2-hydroxypropan-2-yl)-benzyl)oxy)-4H-pyran-4-one (Compound 44);

2-Isoindolin-2-ylmethyl)-5-((4-(prop-1-en-2-yl)benzyl)oxy)-4H-pyran-4-one (Compound 47);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 49);

5-(Cyclohexylmethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 65);

5-((1-(Oxetan-3-ylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)-isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 69a);

N-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-sulfonyl)-N-methylacetamide (Compound 70);

5-((4-(Cyclobutanesulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 71);

5-((4-(Cyclopropylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 72);

5-((4-(Isobutylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 73);

5-((4-(S-methylsulfinimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 74);

4-({[6-(1,3-Dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}methyl)-*N*-[dimethyl(oxido)-λ^6-sulfanylidene]benzamide (Compound 83);

N-[Dimethyl(oxido)- λ^6-sulfanylidene]-4-[({6-[(5-fluoro-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-4-oxo-4*H*-pyran-3-yl}oxy)methyl]benzamide (Compound 84);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 89);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 90);

2-(1-(Isoindolin-2-yl)ethyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 91);

5-((4-(N,S-Dimethylsulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 92);

N-{[4-({[6-(1,3-dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}-methyl)phenyl](methyl)-λ^4-sulfanylidene}-4-methylbenzenesulfonamide (Compound 93);

5-((4-(Azetidine-1-carbonyl)-2-fluorobenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 95);

2-(Isoindolin-2-ylmethyl)-5-((4-(propan-2-ylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 103);

5-((5-Fluoro-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 104);

2-(Isoindolin-2-ylmethyl)-5-((4-(oxazol-2-yl)benzyl)oxy)-4*H*-pyran-4-one (Compound 109);

5-((4-(1-Hydroxycyclobutyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 111);

N-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)benzyl)-methanesulfonamide (Compound 113);

5-((4-(3-Hydroxyoxetan-3-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 114);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((4-(3-hydroxyoxetan-3-yl)benzyl)oxy)-4*H*-pyran-4-one (Compound 115);

5-((4-(3-Hydroxyoxetan-3-yl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 116);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 122);

5-((4-(Azetidine-1-carbonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 129);

2-((5-Bromoisoindolin-2-yl)methyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 130);

N-(tert-Butyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 131);

4-(((6-Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-diiso-propylbenzamide (Compound 134);

4-(((6-((5-Chloroisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 137);

4-(((6-((5-Methoxyisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 138);

N,N-Dimethyl-4-(((4-oxo-6-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 139);

(E)-3-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-N,N-dimethylacrylamide (Compound 146);

5-((4-(3,3-Difluoroazetidine-1-carbonyl)benzyl)oxy)-2-((5-methoxyisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 162);

3,5-Difluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 172);

N-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclohexyl)-methyl)methanesulfonamide (Compound 173);

5-((4-((1,1-Dioxidoisothiazolidin-2-yl)methyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 176);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 184);

2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 185);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 186);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 187);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 188);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 189);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 190);

5-((1-(Ethylsulfonyl)-4-methylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 192);

2-(1-Isoindolin-2-yl)ethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 195);

2-(Isoindolin-2-ylmethyl)-5-((tetrahydro-2H-thiopyran-4-yl)methoxy)-4H-pyran-4-one (Compound 196);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethoxy)-isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 205);

2-((5-Methylisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 211);

2-(Isoindolin-2-ylmethyl)-5-(3-(1-(methylsulfonyl)piperidin-4-yl)propoxy)-4H-pyran-4-one (Compound 213);

2-(Isoindolin-2-ylmethyl)-5-((1-(pyrrolidine-1-carbonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 215);

5-(((1r,4r)-4-(1,1-Dioxidoisothiazolidin-2-yl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 216);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylcyclohexane-1-carboxamide (Compound 217);

N-Cyclopropyl-N-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)cyclohexyl)methanesulfonamide (Compound 219);

5-((1-Butyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 221);

5-((1-(2,2-Difluoropropanoyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 222);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 224);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-sulfonamide (Compound 225);

5-((1-(Cyclopropanecarbonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 226);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*-isopropyl-piperidine-1-carboxamide (Compound 229);

4-(((6-((5-Fluoroisoindolin-2-yl)methyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-sulfonamide (Compound 230);

2-(Isoindolin-2-ylmethyl)-5-((1-(morpholine-4-carbonyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 232);

5-((4-(Azetidine-1-carbonyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 234);

2-(Isoindolin-2-ylmethyl)-5-((1-(2-(methylsulfonyl)acetyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 238);

5-(((1r,4r)-4-Acetylcyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 244);

5-((1-Propionylpiperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)-methyl)-4H-pyran-4-one (Compound 244a);

2-((5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)methyl)-isoindoline-5-carbonitrile (Compound 245a);

1-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)-4-methylpentane-1,2-dione (Compound 249);

2-(Isoindolin-2-ylmethyl)-5-((1-pivaloylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 251);

2-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)sulfonyl)acetonitrile (Compound 254);

2-(Isoindolin-2-ylmethyl)-5-((1-((1-methyl-1H-pyrazol-5-yl)sulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 255);

2-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)-2-oxoethyl acetate (Compound 257);

2-(Isoindolin-2-ylmethyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 261);

2-(Isoindolin-2-ylmethyl)-5-((1-((2-methoxyethyl)sulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 262);

5-((1-(Isobutylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 271);

5-((1-Isobutyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 272);

4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzo-nitrile (Compound 278);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 285);

5-((4-(R-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 286);

and tautomers and pharmaceutically acceptable salts thereof.

Examples of preferred compounds of another group of formula (I) include

2-(Isoindolin-2-ylmethyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 1);

N,N-Diethyl-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzenesulfonamide (Compound 4);

2-(Isoindolin-2-ylmethyl)-5-((4-(morpholinosulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 6);

2-(Isoindolin-2-ylmethyl)-5-((4-(piperidin-1-ylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 7);

5-((4-(Azetidin-1-ylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 9);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-(2-methoxyethyl)-N-methylbenzenesulfonamide (Compound 20);

5-((4-(Ethylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 24);

2-(Isoindolin-2-ylmethyl)-5-((4-(isopropylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 25);

2-((5,6-Difluoroisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 26);

2-(Isoindolin-2-ylmethyl)-5-((4-((2-methoxyethyl)sulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 28);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((4-((2-methoxyethyl)sulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 29);

5-((1-((5-Chlorothiophen-3-yl)sulfonyl)azetidin-3-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 30);

5-((4-Acetylbenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 31);

5-((2-Fluoro-4-(methylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 34);

5-((4-(4-Bromo-1*H*-pyrazol-1-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 39);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(2-hydroxy-2-methyl-propyl)benzyl)oxy)-4H-pyran-4-one (Compound 46);

4-(((6-((6-Methoxy-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzonitrile (Compound 53);

3-Fluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 56);

3-Fluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 61);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 63);

2-((5-Chloroisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 64);

2-(Isoindolin-2-ylmethyl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-4H-pyran-4-one (Compound 67);

5-((4-(Methylsulfonyl)benzyl)oxy)-2-((5-nitroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 68);

N-(2-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-propan-2-yl)acetamide (Compound 69);

2-(Isoindolin-2-ylmethyl)-5-((4-(methylsulfinyl)benzyl)oxy)-4H-pyran-4-one (Compound 81);

2-(Isoindolin-2-ylmethyl)-5-((4-(methylthio)benzyl)oxy)-4H-pyran-4-one (Compound 82);

4-(((6-((5,6-Difluoroisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 82a);

2-(Isoindolin-2-ylmethyl)-5-((4-(S-methylsulfinimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 85);

2-(Isoindolin-2-ylmethyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 86);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 88);

N-{[4-({[6-(1,3-dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}-methyl)phenyl](methyl)oxido-λ^6-sulfanylidene} (Compound 94);

5-((4-(N-Ethyl-S-methylsulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 97);

2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-4H-pyran-4-one (Compound 98);

5-((1-(Ethylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 99);

2-(Isoindolin-2-ylmethyl)-5-((1-(isopropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-4H-pyran-4-one (Compound 100);

5-((4-(Ethylsulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 101);

5-((4-(Ethylsulfonimidoyl)benzyl)oxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 102);

5-((4-(1*H*-1,2,3-triazol-1-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 107);

5-((4-(1*H*-Pyrazol-1-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 108);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 120);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-methoxybenzyl)oxy)-4H-pyran-4-one (Compound 121);

4-(((6-((6-Fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 124);

N,N-Diethyl-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 126);

4-(((6-((5-Fluoroisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 127);

2-(Isoindolin-2-ylmethyl)-5-((4-(piperidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 128);

N-(tert-Butyl)-4-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 135);

2-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-N,N-dimethylacetamide (Compound 136);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-isopropyl-benzamide (Compound 140);

N-Hexyl-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 142);

2-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamido)-2-methylpropyl acetate (Compound 143);

N-(2-Hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N-methylbenzamide (Compound 147);

5-((4-(3,3-Difluoroazetidine-1-carbonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 158);

5-((4-(3,3-Difluoroazetidine-1-carbonyl)benzyl)oxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 161);

2-((5-Chloroisoindolin-2-yl)methyl)-5-((4-(3,3-difluoroazetidine-1-carbonyl)-benzyl)oxy)-4H-pyran-4-one (Compound 163);

5-([1,1'-Biphenyl]-4-ylmethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 164);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyridin-2-yl)benzyl)oxy)-4H-pyran-4-one (Compound 165);

5-((4-(Ethylsulfonimidoyl)benzyl)oxy)-2-((5-nitroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 168);

N-Butyl-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 169);

2,6-Difluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 174);

2-(Isoindolin-2-ylmethyl)-5-(((1R,5S)-8-(methylsulfonyl)-8-azabicyclo[3.2.1]-octan-3-yl)methoxy)-4H-pyran-4-one (Compound 177);

5-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)isoindolin-1-one (Compound 180);

4-(((6-((5-Fluoroisoindolin-2-yl)methyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-carboxamide (Compound 181);

2-(Isoindolin-2-ylmethyl)-5-((4-methyl-1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 191);

N-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-1-oxido-tetrahydro-2H-thiopyran-1-ylidene)-4-methylbenzenesulfonamide (Compound 194);

2-(Isoindolin-2-ylmethyl)-5-(2-(1-(methylsulfonyl)piperidin-4-yl)ethoxy)-4*H*-pyran-4-one (Compound 198);

(*R*)-*tert*-Butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-pyrrolidine-1-carboxylate (Compound 199);

(*S*)-*tert*-Butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-pyrrolidine-1-carboxylate (Compound 200);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(methylthio)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 208);

2-((5,7-Dihydro-6H-[1,3]dioxolo[4,5-f]isoindol-6-yl)methyl)-5-((1-(methyl-sulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 209);

2-((5,6-Difluoroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 210);

2-(Isoindolin-2-ylmethyl)-5-(3-(pyridin-4-yl)propoxy)-4H-pyran-4-one (Compound 214);

N-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclohexyl)-N-methylmethanesulfonamide (Compound 218);

2-(Isoindolin-2-ylmethyl)-5-((4-(methylsulfonyl)cyclohexyl)methoxy)-4H-pyran-4-one (Compound 220);

5-((1-(2,2-Difluoropropanoyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 223);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*-methylcyclo-hexanecarboxamide (Compound 227);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*-methyl-piperidine-1-carboxamide (Compound 228);

5-((1-(Azetidine-1-carbonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 231);

2-(Isoindolin-2-ylmethyl)-5-((4-(oxetan-3-ylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 233);

5-((4-Fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 235);

5-((4-Fluoro-1-(isopropylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 236);

5-((4-Fluoro-1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 237);

N-{[4-({[6-(1,3-Dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}-methyl)cyclohexyl](methyl)oxido-λ^6-sulfanylidene}-4-methylbenzenesulfonamide (Compound 239);

2-((5-Chloroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 241);

N-Cyclopropyl-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)piperidine-1-carboxamide (Compound 247);

N-(tert-Butyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)piperidine-1-carboxamide (Compound 248);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methyl-piperidine-1-carbothioamide (Compound 250);

5-((1-Acetylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 252);

5-((1-((4-Fluorophenyl)sulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 256);

5-((1-Acryloylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 258);

5-((1-(Furan-2-carbonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 260);

2-(Isoindolin-2-ylmethyl)-5-((1-(pyrrolidin-1-ylsulfonyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 267);

5-((1-(Azetidin-1-ylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 268);

Ethyl 2-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-piperidin-1-yl)-2-oxoacetate (Compound 269);

2-(Isoindolin-2-ylmethyl)-5-((1-(isopropylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 270);

2-(Isoindolin-2-ylmethyl)-5-((1-(2,2,2-trifluoroacetyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 273);

Cis-*N*-(3-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-cyclopentyl)-methanesulfonamide (Compound 276);

2-((5-Methylisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 279);

5-((4-(Methylsulfonyl)benzyl)oxy)-2-((5-(methylthio)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 280);

N-(1-Hydroxy-2-methylpropan-2-yl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 283);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidine-1-carbaldehyde (Compound 284);

5-((1-(Methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 291);

and tautomers and pharmaceutically acceptable salts thereof.

Examples of preferred compounds of still another group of formula (I) include

2-(Isoindolin-2-ylmethyl)-5-((4-((trifluoromethyl)thio)benzyl)oxy)-4H-pyran-4-one (Compound 3);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzenesulfonamide (Compound 13);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 14);

5-((2-Chloro-4-(methylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 16);

5-((3-Fluoro-4-(methylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 17);

5-((2-Chloro-4-(methylsulfonyl)benzyl)oxy)-2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one (Compound 18);

2-(Isoindolin-2-ylmethyl)-5-((4-(methylsulfonyl)-2-(trifluoromethyl)benzyl)oxy)-4H-pyran-4-one (Compound 19);

2-((4-Fluoroisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 27);

4-(((6-((4-Fluoroisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 32);

2-((4-Fluoroisoindolin-2-yl)methyl)-5-((4-(2-hydroxypropan-2-yl)benzyl)oxy)-4H-pyran-4-one (Compound 33);

5-((1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 35);

2-(Isoindolin-2-ylmethyl)-5-((4-nitrobenzyl)oxy)-4*H*-pyran-4-one (Compound 38);

Ethyl 1-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)phenyl)-1*H*-pyrazole-4-carboxylate (Compound 40);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzonitrile (Compound 41);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-methylbenzyl)oxy)-4H-pyran-4-one (Compound 42);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzamide (Compound 43);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzonitrile (Compound 45);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N-methylbenzamide (Compound 48);

3-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzonitrile (Compound 50);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-3-fluorobenzonitrile (Compound 51);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-((6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one (Compound 52);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-3-fluorobenzamide (Compound 55);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 57);

5-((4-Bromobenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 58);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-((1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one (Compound 59);

Methyl 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzoate (Compound 60);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methyl-benzamide (Compound 62);

2-((5,7-Dihydro-6H-[1,3]dioxolo[4,5-f]isoindol-6-yl)methyl)-5-((4-(methyl-sulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 66);

2-(Isoindolin-2-ylmethyl)-5-((6-(trifluoromethyl)pyridin-3-yl)methoxy)-4H-pyran-4-one (Compound 75);

2-(Isoindolin-2-ylmethyl)-5-((6-methoxypyridin-3-yl)methoxy)-4H-pyran-4-one (Compound 76);

N,N-Dimethyl-4-(((6-((1-methylisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 77);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-2-fluoro-N,N-dimethylbenzamide (Compound 78);

2-Fluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methylbenzamide (Compound 79);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-2-fluoro-N-methylbenzamide (Compound 80);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(S-methylsulfonimidoyl)-benzyl)oxy)-4H-pyran-4-one (Compound 87);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-(2-oxotetrahydrothiophen-3-yl)benzamide (Compound 96);

2-(Isoindolin-2-ylmethyl)-5-((3-nitrobenzyl)oxy)-4*H*-pyran-4-one (Compound 105);

5-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-2-methylisoindolin-1-one (Compound 106);

2-(Isoindolin-2-ylmethyl)-5-((2-methoxypyridin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 110);

4-(2-((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)ethyl)-*N,N*-dimethylbenzamide (Compound 112);

2-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-5-((4-(3-hydroxyoxetan-3-yl)-benzyl)oxy)-4*H*-pyran-4-one (Compound 117);

2-Chloro-4-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzonitrile (Compound 118);

4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N,N-dimethylbenzamide (Compound 119);

5-((4-(Hydroxymethyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 123);

2-((1-Methyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 125);

(S)-N,N-Dimethyl-4-(((6-((1-methylisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 132);

(R)-N,N-Dimethyl-4-(((6-((1-methylisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 133);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-(prop-2-yn-1-yl)benzamide (Compound 141);

2-(Isoindolin-2-ylmethyl)-5-((4-vinylbenzyl)oxy)-4H-pyran-4-one (Compound 144);

N-(4-Hydroxybutyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzamide (Compound 145);

(E)-3-(4-(((6-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-N-methylacrylamide (Compound 148);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(3-hydroxypiperidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 149);

5-((4-(Azetidine-1-carbonyl)benzyl)oxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 150);

N-(3-Hydroxy-2,2-dimethylpropyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 151);

5-((4-(4-Hydroxypiperidine-1-carbonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 152);

5-(2-(4-Benzylpiperazin-1-yl)-2-oxoethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 153);

5-(2-(4-(4-Chlorophenyl)piperazin-1-yl)-2-oxoethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 154);

5-(2-(4-Benzylpiperidin-1-yl)-2-oxoethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 155);

2-(Isoindolin-2-ylmethyl)-5-(2-oxo-2-(4-(phenylsulfonyl)piperazin-1-yl)ethoxy)-4H-pyran-4-one (Compound 156);

2-(Isoindolin-2-ylmethyl)-5-(2-oxo-2-(4-tosylpiperazin-1-yl)ethoxy)-4H-pyran-4-one (Compound 157);

2-(Isoindolin-2-ylmethyl)-5-(2-(4-(3-(methoxymethyl)pyridin-2-yl)piperazin-1-yl)-2-oxoethoxy)-4H-pyran-4-one (Compound 159);

5-((4-(3-Hydroxypiperidine-1-carbonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 160);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(ethylsulfonimidoyl)-benzyl)oxy)-4H-pyran-4-one (Compound 166);

6-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethyl-nicotinamide (Compound 170);

2-Fluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 171);

Methyl (1r,4r)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-cyclohexane-1-carboxylate (Compound 178);

2-((3,4-Dihydroisoquinolin-2(1H)-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 179);

tert-Butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-pyrrolidine-1-carboxylate (Compound 182);

3-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-pyrrolidine-1-carboxamide (Compound 183);

5-((3-Hydroxy-1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-yl-methyl)-4H-pyran-4-one (Compound 193);

tert-Butyl 4-(2-((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)ethyl)-piperidine-1-carboxylate (Compound 197);

(*S*)-*tert*-Butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-piperidine-1-carboxylate (Compound 201);

(*R*)-*tert*-Butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-piperidine-1-carboxylate (Compound 202);

tert-Butyl 4-((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)piperidine-1-carboxylate (Compound 203);

5-(2-(1-Acetylpiperidin-4-yl)ethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 206);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-nitroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 207);

2-((1,1-Dimethylisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 212);

2-(Isoindolin-2-ylmethyl)-5-((4-(S-methylsulfonimidoyl)cyclohexyl)methoxy)-4H-pyran-4-one (Compound 240);

5-((1-Imino-1-oxidohexahydro-1 λ^6-thiopyran-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 242);

N-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-1-oxido-tetrahydro-2H-1 λ^6-thiopyran-1-ylidene)acetamide (Compound 243);

2-((4,5-Difluoroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 245);

2-Isoindolin-2-ylmethyl)-5-((1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 253);

5-((3-Aminobenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 263);

4/5-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 264);

4/5-(((6-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-4-oxo-4*H*-pyran-3-yl)-oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 265);

Cis-*N*-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclo-pent-2-en-1-yl)cyclopropanesulfonamide (Compound 274);

Cis-*N*-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclo-pent-2-en-1-yl)-3-methylbutanamide (Compound 275);

(*R*)-2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-4H-pyran-4-one (Compound 277);

2-((4-Chloroisoindolin-2-yl)methyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 281);

N-(3-Hydroxypropyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzamide (Compound 282);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)-2H-isoindol-2-yl)methyl)-4H-pyran-4-one (Compound 287);

2-((5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)-methyl)isoindoline 2-oxide (Compound 289);

2-((5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindoline 2-oxide (Compound 290);

and tautomers and pharmaceutically acceptable salts thereof.

Examples of compounds in one particularly preferred group of compounds of formula (I) include

N-Ethyl-N-(2-hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzenesulfonamide (Compound 21);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 49);

4-({[6-(1,3-Dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}methyl)-*N*-[dimethyl(oxido)-λ^6-sulfanylidene]benzamide (Compound 83);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 90);

2-(1-(Isoindolin-2-yl)ethyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 91);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 122);

5-((4-((1,1-Dioxidoisothiazolidin-2-yl)methyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 176);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 184);

2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 185);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 187);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 188);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 189);

2-(1-Isoindolin-2-yl)ethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 195);

2-(Isoindolin-2-ylmethyl)-5-(3-(1-(methylsulfonyl)piperidin-4-yl)propoxy)-4H-pyran-4-one (Compound 213);

5-(((1r,4r)-4-(1,1-Dioxidoisothiazolidin-2-yl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 216);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethyl-cyclohexane-1-carboxamide (Compound 217);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-piperidine-1-sulfonamide (Compound 225);

5-(((1r,4r)-4-Acetylcyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 244);

5-((1-Propionylpiperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 244a);

2-(Isoindolin-2-ylmethyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 261);

4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzo-nitrile (Compound 278);

and tautomers and pharmaceutically acceptable salts thereof.

Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 1 to about 2000 mg, more typically form about 10 to about 1500 mg, daily depending on the age, sex, weight, ethnic group, condition of the patient, condition to be treated, administration route and the active ingredient used. The compounds of the invention can be formulated into dosage forms using the principles known in the art. The compound can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. Suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may also be used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

The compounds of the invention can be given to the subject as the sole active ingredient or in combination with one of more other active ingredients for treatment of a particular disease.

In the treatment of a steroid receptor dependent disease or condition, such as endocrine cancers and disorders including prostate cancer and breast cancer, a combination of therapeutic agents and/or other treatments (e.g., radiation therapy) is often advantageous. The second (or third) agent to be administered may have the same or different mechanism of action than the primary therapeutic agent.

Accordingly, a compound of the invention may be administered in combination with other anti-cancer treatments useful in the treatment of cancers such as prostate cancer or breast cancer. For example, a compound of the invention can be packaged together with instructions that the compound is to be used in combination with other anti-cancer agents and treatments for the treatment of cancer. The present invention further comprises combinations of a compound of the invention and one or more additional agents in kit form, for example, where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) is co-administered with a glucocorticoid and/or a mineralocorticoid and, optionally, with one or more anti-cancer agents.

Examples of suitable glucocorticoids include, but are not limited to, hydrocortisone, prednisone, prednisolone, methylprednisolone and dexamethasone. Examples of suitable mineralocorticoids include, but are not limited to, fludrocortisone, deoxycorticosterone, 11-desoxycortisone and deoxycorticosterone acetate.

The optional other anti-cancer agents which can be administered in addition to a compound of formula (I) include, but are not limited to,

- non-steroidal androgen receptor antagonists (e.g. enzalutamide, apalutamide and darolutamide);
- steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel);
- chemotherapeutic agents (e.g. docetaxel and paclitaxel);
- antiestrogens (e.g. tamoxifen and fulvestrant);
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors);
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribocyclib).

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) is administered to a subject in need thereof in addition to a therapeutically effective amount of one or more anti-cancer agents selected from the list consisting of

- non-steroidal androgen receptor antagonists (e.g. enzalutamide, apalutamide and darolutamide);
- steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel);
- chemotherapeutic agents (e.g. docetaxel and paclitaxel);
- antiestrogens (e.g. tamoxifen and fulvestrant);
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors);
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);

- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribocyclib).

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) is administered to a subject in need thereof in addition to a therapeutically effective amount of a steroidogenesis inhibitor (e.g. a CYP17A1 inhibitor). Examples of suitable CYP17A1 inhibitors include, but are not limited to, abiraterone acetate and seviteronel.

According to another embodiment of the invention, the therapeutically effective amount of a compound of formula (I) is administered to a subject in need thereof in addition to a therapeutically effective amount of a non-steroidal androgen receptor antagonist. Examples of suitable non-steroidal androgen receptor (AR) antagonists include, but are not limited to, enzalutamide, apalutamide and darolutamide.

According to still another embodiment, the present invention provides a pharmaceutical combination comprising a compound of formula (I) and at least one additional active ingredient selected from the list consisting of

- a glucocorticoid,
- a mineralocorticoid,
- a steroidogenesis inhibitor (e.g. a CYP17A1 inhibitor),
- a non-steroidal androgen receptor antagonist,
- chemotherapeutic agents (e.g. docetaxel and paclitaxel),
- antiestrogens (e.g. tamoxifen and fulvestrant),
- epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors),
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaccuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribocyclib)

for simultaneous, separate or sequential administration.

The above other therapeutic agents, when employed in combination with a compound of the invention can be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The present invention will be explained in more detail by the following experiments and examples. The experiments and examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

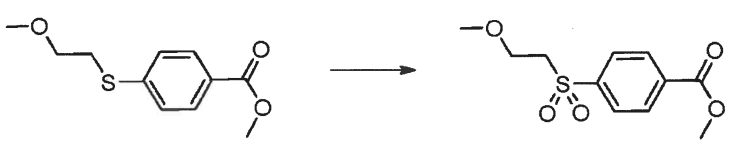
EXAMPLES:

Intermediate-1: Methyl 4-((2-methoxyethyl)thio)benzoate



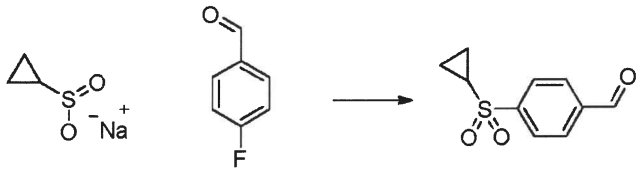
To a solution of methyl 4-mercaptobenzoate (2 g, 10.98 mmol) in MeOH (35 ml) was added K_2CO_3 (2.27 g, 16.48 mmol) followed by addition of 1-bromo-2-methoxy-ethane (1.54 g, 16.48 mmol) at RT. The mixture was refluxed for 16 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2.19 g of the title compound as colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.95 (d, 2H), 7.33 (d, 2H), 3.89 (s, 3H), 3.64 (t, 2H), 3.37 (s, 3H), 3.18 (t, 2H).

Intermediate-2: Methyl 4-((2-methoxyethyl)sulfonyl)benzoate



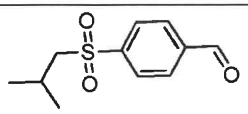
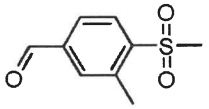
To a solution of methyl 4-((2-methoxyethyl)thio)benzoate (2.19 g, 9.15 mmol) in DCM (30 ml) was added *m*-CPBA (~ 70 % assay, 7.89 g, 32.1 mmol) at 0 °C followed by stirring at RT for 16 h. The reaction mixture was quenched with 10 % aqueous NaOH solution and extracted with DCM. The organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1.86 g of the title compound as a white solid. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.22 (d, 2H), 8.02 (d, 2H), 3.97 (s, 3H), 3.75 (t, 2H), 3.42 (t, 2H), 3.20 (t, 3H).

Intermediate-3: 4-(Cyclopropylsulfonyl)benzaldehyde

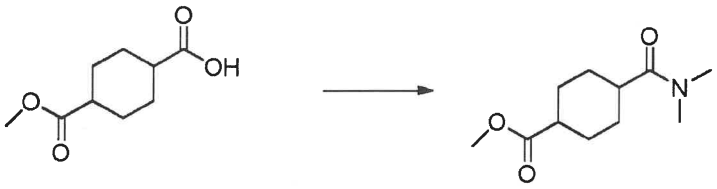


To a solution of 4-fluorobenzaldehyde (0.09 ml, 0.8 mmol) in DMSO (5 ml) was added cyclopropanesulfinic acid sodium salt (0.13 g, 1.0 mmol). The reaction mixture was heated in microwave oven at 140 °C for 1 h. Water was added to the mixture and the product was extracted with EtOAc. The organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 0.15 g of the title compound. LC-MS: *m/z* 211.1 $[M+H]^+$.

The following intermediates were prepared according to the procedure described for Intermediate-3 from the starting material indicated on the table.

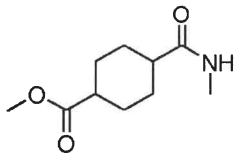
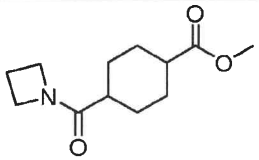
No	Structure	LC-MS	Starting material
4		LC-MS: *m/z* 227.2 $(M+H)^+$.	iso-Butylsulfinic acid sodium salt
5		LC-MS: *m/z* 199.2 $(M+H)^+$	Methanesulfinic acid sodium salt

Intermediate-6: Methyl 4-(dimethylcarbamoyl)cyclohexane-1-carboxylate

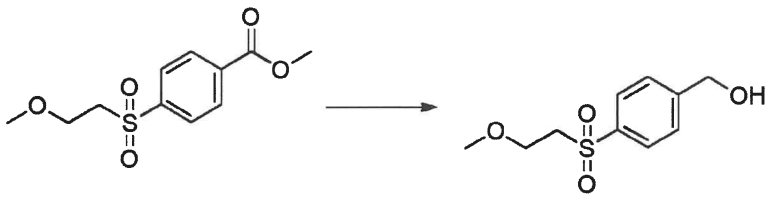


To a solution of 4-(methoxycarbonyl)cyclohexane-1-carboxylic acid (2.0 g, 10.7 mmol) in DCM (25 ml) were added DMF (1 drop) and oxalyl chloride (2.32 ml, 26.8 mmol) at 0 °C followed by stirring at RT for 3 h. The reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM (25 ml) and cooled to 0 °C. Dimethyl amine (30 ml) was added to the above solution followed by stirring at RT for 2 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound. MS: *m/z* 213 $[M+H]^+$.

The following intermediates were prepared according to the procedure described for Intermediate 6 from the starting material indicated on the table.

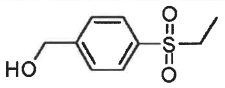
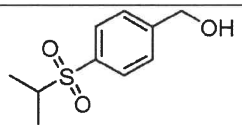
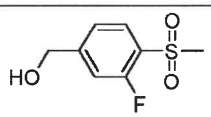
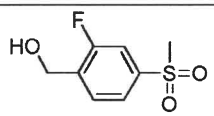
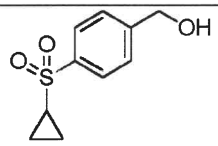
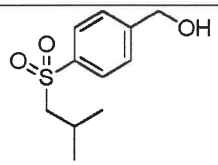
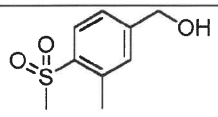
No	Structure	LC-MS	Starting material
7		LC-MS: *m/z* 200.1 $[M+H]^+$	4-(Methoxycarbonyl) cyclo-hexane-1-carboxylic acid and methylamine
8		LC-MS: *m/z* 226.1 $[M+H]^+$	4-(Methoxycarbonyl) cyclo-hexane-1-carboxylic acid and azetidine

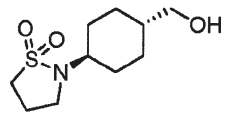
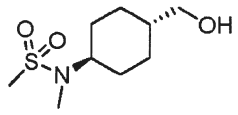
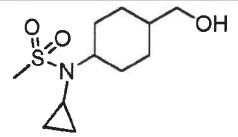
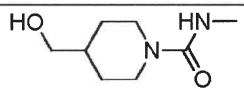
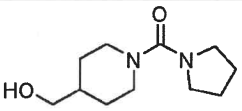
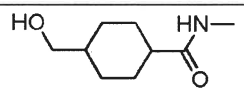
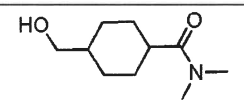
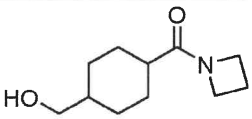
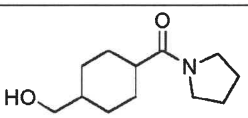
Intermediate-9: (4-((2-Methoxyethyl)sulfonyl)phenyl)methanol



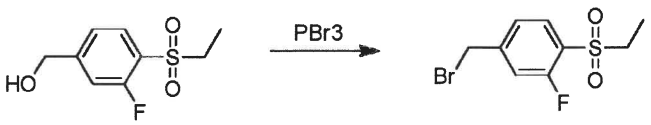
To a solution of methyl 4-((2-methoxyethyl)sulfonyl)benzoate (1.86 g, 6.84 mmol) in EtOH (20 ml) was added $NaBH_4$ (1.3 g, 34.24 mmol) at 0 °C followed by stirring at RT for 3 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1.18 g of the title compound as a colorless oil. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.91 (d, 2H), 8.55 (d, 2H), 5.0 (t, 1H), 4.82 (s, 2H), 3.74 (t, 2H), 3.38 (t, 2H), 3.24 (s, 3H).

The following intermediates were prepared according to the procedure described for Intermediate 9 from the starting material indicated on the table.

No	Structure	LC-MS	Starting material
10		LC-MS: *m/z* 201 $[M+H]^+$	4-(Ethylsulfonyl)benzaldehyde
11		LC-MS: *m/z* 215 $[M+H]^+$	4-(Isopropylsulfonyl)benzaldehyde
12		LC-MS: *m/z* 205.0 $(M+H)^+$	3-Fluoro-4-(methylsulfonyl)benz-aldehyde
13		LC-MS: *m/z* 205.2 $(M+H)^+$	2-Fluoro-4-(methylsulfonyl)benz-aldehyde
14		LC-MS: *m/z* 213.2 $(M+H)^+$	4-(Cyclopropylsulfonyl)benz-aldehyde
15		LC-MS: *m/z* 229.2 $(M+H)^+$	4-(Isobutylsulfonyl)benzaldehyde
16		LC-MS: *m/z* 201.2 $(M+H)^+$	3-Methyl-4-(methylsulfonyl)-benzaldehyde

17		LC-MS: *m/z* 234.3 $(M+H)^+$	(1r,4r)-Methyl 4-(1,1-dioxidoisothiazolidin-2-yl)cyclohexane-carboxylate
18		LC-MS: *m/z* 222.3 $(M+H)^+$	(1r,4r)-Methyl 4-(N-methyl-methylsulfonamido)cyclohexane carboxylate
19		LC-MS: *m/z* 248.3 $(M+H)^+$	Ethyl 4-(N-cyclopropylmethyl-sulfonamido)cyclohexane-carboxylate
20		LC-MS: *m/z* 173 $(M+H)^+$	Ethyl 1-(methylcarbamoyl) piperidine-4-carboxylate
21		MS: *m/z* 213	4-Piperidinecarboxylic acid, 1-(pyrrolidinylcarbonyl)-ethyl ester
22		MS: *m/z* 171	Methyl-4-(methylcarbamoyl)-cyclohexane-1-carboxylate
23		MS: *m/z* 185	Methyl-4-(dimethylcarbamoyl)-cyclohexane-1-carboxylate
24		MS: *m/z* 197	Methyl 4-(azetidine-1-carbonyl)-cyclohexane-1-carboxylate
25		MS: *m/z* 212.2	Methyl 4-(pyrrolidine-1-carbonyl)-cyclohexane-1-carboxylate

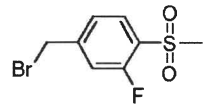
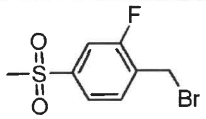
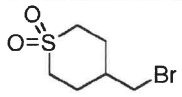
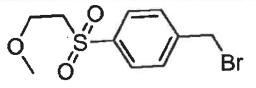
Intermediate-26: 4-(Bromomethyl)-2-fluoro-1-(ethylsulfonyl)benzene



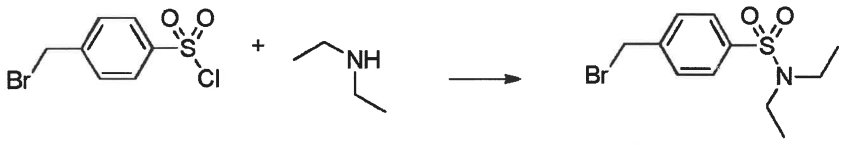
To a solution of (3-fluoro-4-(ethylsulfonyl)phenyl)methanol (3.90 g, 19.11 mmol) in dry DCM (50 ml) was added PBr_3 (3.63 ml, 38.23 mmol) at 0 °C followed by stirring at RT for 16 h. The reaction mixture was quenched with cold water, neutralized with

aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to give 1.72 g of the title compound as a white solid. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 7.84-7.88 (t, 1H), 7.62-7.65 (d, 1H), 7.53-7.55 (d, 1H), 4.77 (s, 2H), 3.32 (s, 3H). MS: *m/z* 268 $[M+H]^+$.

The following intermediates were prepared according to the procedure described for Intermediate 26 from the starting material indicated on the table.

No	Structure	LC-MS	Starting material
27		LC-MS: *m/z* 268.0 $[M+H]^+$	3-Fluoro-4-(methylsulfonyl)-phenyl)methanol
28		LC-MS: *m/z* 268.5 $[M+H]^+$	(2-Fluoro-4-(methylsulfonyl)-phenyl)methanol
29		LC-MS: *m/z* 226.3 $[M+H]^+$	4-(hydroxymethyl)tetrahydro-2H-thiopyran 1,1-dioxide
30		LC-MS: *m/z* 293 $[M+H]^+$	(4-((2-Methoxyethyl)-sulfonyl)phenyl)methanol

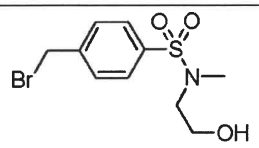
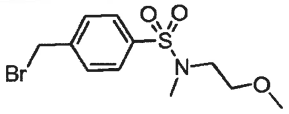
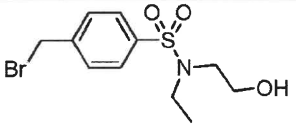
Intermediate-31: 4-(Bromomethyl)-N,N-diethylbenzenesulfonamide



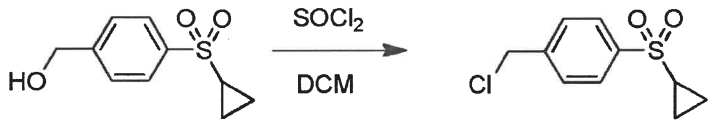
To a solution of diethylamine (0.05 g, 0.74 mmol) in DCM (5 ml) at 0 °C were added 4-(bromomethyl)benzenesulfonyl chloride (0.2 g, 0.74 mmol) and TEA (0.1 ml, 0.74 mmol) at RT followed by stirring for 1 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to give 0.10 g of the title compound.^{1}H NMR (400

MHz, DMSO-d_6) δ ppm 1.04 (t, J=7.12 Hz, 6 H) 3.16 (q, J=7.11 Hz, 4 H) 4.77 (s, 2 H) 7.57 - 7.68 (m, 2 H) 7.78 (d, J=8.60 Hz, 2 H).

The following intermediates were prepared according to the procedure described for Intermediate 31 from the starting material indicated on the table.

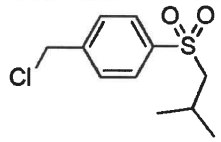
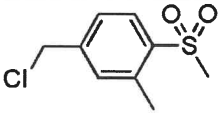
No	Structure	LC-MS	Starting material
32		LC-MS: *m/z* 320.1 $(M+H)^+$	2-(Methylamino)ethanol
33		LC-MS: *m/z* 322.3 $(M+H)^+$	N-(2-Methoxyethyl)methyl-amine
34		LC-MS: *m/z* 323.5 $(M+H)^+$	2-(Ethylamino)ethanol

Intermediate-35: 1-(Chloromethyl)-4-(cyclopropylsulfonyl)benzene

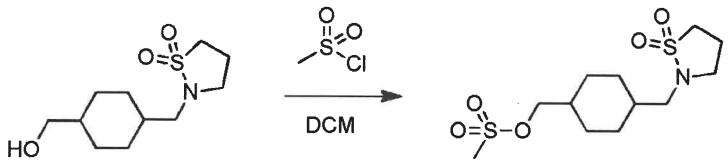


To a solution of (4-(cyclopropylsulfonyl) phenyl) methanol (0.18 g, 0.848 mmol) in DCM (5.0 ml) and DMF (0.1 ml) was added $SOCl_2$ (1.0 ml, 1.5mmol) dropwise at 0 °C followed by refluxing for 2 h. Water was added and the reaction mixture was extracted with DCM. The organic layer was washed with water and saturated $NaHCO_3$ solution. After drying with Na_2SO_4 the solvent was evaporated and the residue was purified by column chromatography to give 0.17 g of the title compound. LC-MS: *m/z* 213.2 $(M+H)^+$

The following intermediates were prepared according to the procedure described for Intermediate 35 from the starting material indicated on the table.

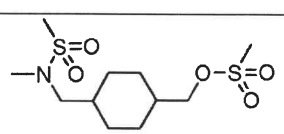
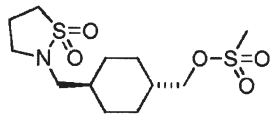
No	Structure	LC-MS	Starting material
36		LC-MS: *m/z* 247.2 $(M+H)^+$	(4-(Isobutylsulfonyl)phenyl) methanol
37		LC-MS: *m/z* 219.2 $(M+H)^+$	(3-Methyl-4-(methylsulfonyl) phenyl)methanol

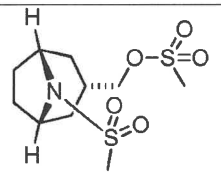
Intermediate-38: (4-((1,1-Dioxidoisothiazolidin-2-yl)methyl)cyclohexyl)methyl methanesulfonate



To a solution of 2-((4-(hydroxymethyl)cyclohexyl)methyl)isothiazolidine 1,1-dioxide (1.6 g, 6.47 mmol) in DCM (10 ml) at 0 °C were added Et_3N (3.0 ml, 19.0mmol), DMAP (0.07 g, 0.6 mmol) followed by MsCl (1.4 ml, 17.5 mmol). The mixture was stirred at RT for 16 h, quenched with water and extracted with DCM. The organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound. LC-MS: *m/z* 326.2 $(M+H)^+$

The following intermediates were prepared according to the procedure described for Intermediate 38 from the starting material indicated on the table.

No	Structure	LC-MS	Starting material
39		LC-MS: *m/z* 300.4 $(M+H)^+$	4-(Aminomethyl)cyclohexane methanol
40		LC-MS: *m/z* 292.1 $(M+H)^+$	2-(((1r,4r)-4-(Hydroxy-methyl)cyclohexyl)methyl)-isothiazolidine 1,1-dioxide

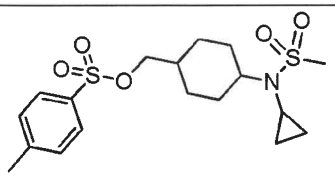
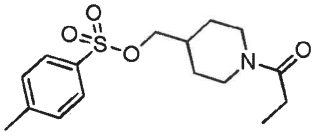
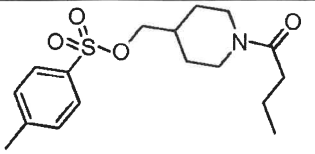
41		LC-MS: *m/z* 298.2 $(M+H)^+$	(1R,3r,5S)-8-Azabicyclo-[3.2.1]octan-3-ylmethanol hydrochloride

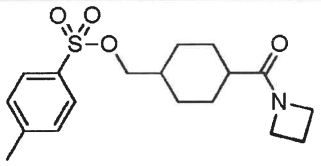
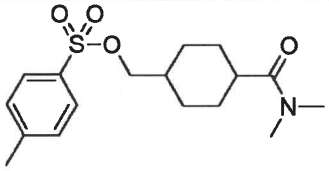
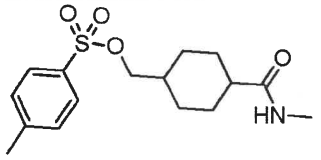
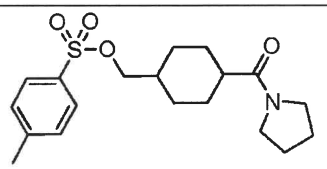
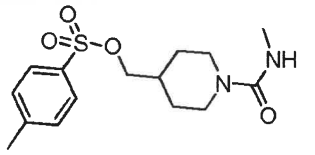
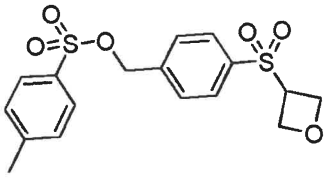
Intermediate-42: ((1r,4r)-4-(N-Methylmethylsulfonamido)cyclohexyl)methyl 4-methylbenzenesulfonate



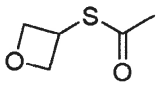
To a solution of N-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-N-methylmethane-sulfonamide (0.302 g, 1.365 mmol) in pyridine (3 ml) at 0 °C was added TsCl (0.31 g, 1.6 mmol). The reaction mixture was stirred at RT for 16 h then quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound. LC-MS: *m/z* 375.5 $(M+H)^+$

The following intermediates were prepared according to the procedure described for Intermediate 42 from the starting material indicated on the table.

No	Structure	LC-MS	Starting material
43		LC-MS: *m/z* 402.4 $(M+H)^+$	N-Cyclopropyl-N-(4-(hydroxymethyl)cyclohexyl)-methanesulfonamide
44		LC-MS: *m/z* 326.6 $(M+H)^+$	1-(4-(Hydroxymethyl)-piperidin-1-yl)propan-1-one
45		LC-MS: *m/z* 340.2 $(M+H)^+$	1-(4-(Hydroxymethyl)-piperidin-1-yl)butan-1-one

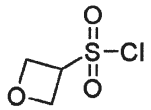
46		LC-MS: *m/z* 351	Azetidin-1-yl(hydroxyl-methyl)cyclohexyl)methanone
47		LC-MS: *m/z* 339	4-(Hydroxymethyl)-*N, N*-dimethylcyclohexane-carboxamide
48		LC-MS: *m/z* 325	4-(Hydroxymethyl)-*N*-methyl-cyclohexanecarboxamide
49		LC-MS: *m/z* 367	(4-(Hydroxymethyl)cyclo-hexyl) (pyrrolidinyl-1-yl)-methanone
50		LC-MS: *m/z* 327	4-(Hydroxymethyl)-N-methyl-piperidine-1-carboxamide
51		LC-MS: *m/z* 383.1	(4-(Oxetan-3-ylsulfonyl)-phenyl)methanol

Intermediate-52: *S*-(Oxetan-3-yl)ethanethioate



To a solution of ethanethioic S-acid (10.0 g, 54 mmol) in DMF (100 ml) was added 3-iodooxetane (6.82 g, 59 mmol) followed by stirring at RT for 16 h. The reaction was quenched with cold water and extracted with EtOAc. The organic layer was washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.52 g of the title compound as yellow oil. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 4.94 (t, 2H), 4.56 (m, 1H), 4.42 (t, 2H), 2.33 (s, 3H).

Intermediate-53: Oxetane-3-sulfonyl chloride



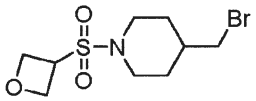
To a solution of N-chlorosuccinamide (10.0 g, 75 mmol) in MeCN (50 ml) at 0 °C were added 2 N HCl (5 ml) and S-(oxetan-3-yl)ethanethioate (2.5 g, 18 mmol) followed by stirring at RT for 16 h. The reaction was concentrated, quenched with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.8 g of crude title compound.

Intermediate-54: 4-(Bromomethyl)piperidine hydrobromide



A mixture of piperidin-4-ylmethanol (0.5 g, 4.3 mmol) and aqueous HBr (10 ml) was heated at 140 °C for 3 h. The reaction mixture was concentrated under reduced pressure to give 0.5 g of the title compound as a yellow solid. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 3.70 (s, 1H), 3.50 (d, 2H), 3.25 (d, 2H), 2.84-2.93 (m, 2H), 1.86-1.97 (m, 3H), 1.36-1.46 (m, 2H).

Intermediate-55: 4-(Bromomethyl)-1-(oxetan-3-ylsulfonyl)piperidine



To a solution of 4-(bromomethyl)piperidine hydrobromide (4.16 g, 16 mmol) in DCM (200 ml) were added Et_3N (3.23 ml, 44 mmol) and oxetane-3-sulfonyl chloride (2.3 g, 14 mmol) followed by stirring at RT for 16 h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel using 30 % EtOAc in hexane as an eluent to give 0.780 g of the title compound as a white solid. ^{1}H-NMR (400 MHz; DMSO): δ 4.76-4.80 (m, 1H), 4.67-4.74 (m, 3H), 3.6 (d, 2H), 3.46 (d, 2H), 2.75 (t, 1H), 1.72-1.81 (m, 3H), 1.08-1.23 (m, 2H).

Intermediate-56: 4-(Bromomethyl)-3-fluorobenzoic acid



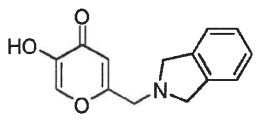
To a solution of 3-fluoro-4-methylbenzoic acid (5.0 g, 34.67 mmol) in benzene (50 ml) were added benzoyl peroxide (0.8 g, 3.46 mmol) and NBS (6.0 g, 34.6 mmol) followed by heating at 85 °C for 4 h. The reaction mixture was cooled to RT, the solid precipitated was filtered, washed with water followed by hexane and then dried to give 4.6 g of the title compound. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.8 (d, 1H), 7.76 (d, 1H), 7.51 (t, 1H), 1.79 (s, 2H). MS: *m/z* 231 $[M-H]^+$.

Intermediate 57: Azetidin-1-yl(4-(chloromethyl)-3-fluorophenyl)methanone



To a solution of 4-(bromomethyl)-3-fluorobenzoic acid (4.5 g, 19.4 mmol) in DCM (60 ml) at 0 °C were added azetidine hydrochloride (2.17 g, 23.3 mmol), DIPEA (17 ml, 97.4 mmol) and T_3P (17.5 ml, 58.4 mmol) at RT followed by stirring for 16 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using 30 % EtOAc in hexane as an eluent to give 1.2 g of the title compound as a white solid. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.49-7.35 (m, 4H), 4.64 (s, 2H), 4.29-4.24 (m, 4H), 2.09 (m, 2H). MS: *m/z* 228 $[M+H]^+$.

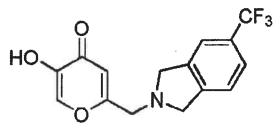
Intermediate 58: 5-Hydroxy-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one



To a stirred solution of 2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one (2.0 g, 12.5 mmol) in acetonitrile (50 mL) were added DIPEA (3.22 mL, 25.0 mmol) and isoindoline (1.78 g, 25.0 mmol) at RT. When the reaction was complete, the precipitated solid was

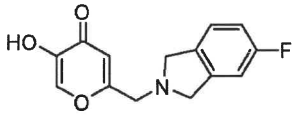
filtered and washed with EtOAc. The title compound was collected as pale brown solid (1.1 g). LC-MS: *m/z* 244.1 $(M+H)^+$.

Intermediate 59: 5-Hydroxy-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one



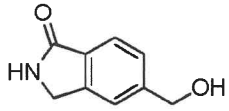
To a stirred solution of 2-(aminomethyl)-5-hydroxy-4*H*-pyran-4-one (5.6 g, 17.0 mmol) in acetonitrile (40 mL) were added 1,2-bis(bromomethyl)-4-(trifluoromethyl)-benzene (2.4 g, 17.0 mmol) and DIPEA (23.78 mL, 136.2 mmol) at RT. The reaction mixture was heated to 90 °C until the reaction was complete. The reaction mixture was concentrated under reduced pressure and the obtained residue was stirred in EtOAc. The mixture was filtered and the filtrate was concentrated. The crude compound was further purified by semipreparative HPLC to afford the title compound (0.85 g). LC-MS *m/z*: 312.1 $(M+H)^+$.

Intermediate 60: 2-((5-Fluoroisoindolin-2-yl) methyl)-5-hydroxy-4*H*-pyran-4-one



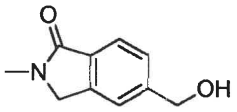
To a solution of 2-(amino methyl)-5-hydroxy-4*H*-pyran-4-one (14.2 g, 63.8 mmol) in toluene (100 mL) were added 1,2-bis-(bromomethyl)-4-fluorobenzene (19.7 g, 70.2 mmol) and Et_3N (35.8 mL, 255 mmol) at RT. The mixture was stirred at 100 °C until the reaction was complete. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography to give the title compound as a beige solid (4.60 g). LC-MS: *m/z* 262.2 $(M+H)^+$.

Intermediate 61: 5-(Hydroxymethyl)isoindolin-1-one



To a stirred solution of methyl 1-oxoisoindoline-5-carboxylate (4.0 g, 20.9 mmol) in THF (120 mL) was added DIBAL-H (1.2 M, 87.2 mL, 104.6 mmol) at -70 °C. After two hours at -70 °C the mixture was allowed to warm to 0 °C and stirred for 1 h. The reaction was quenched with MeOH and the emulsion was filtered through a pad of Celite®. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography to give the title compound as a pale brown solid (0.8 g). LC-MS: *m/z* 164.1 $(M+H)^+$

Intermediate 62: 5-(Hydroxymethyl)-2-methylisoindolin-1-one



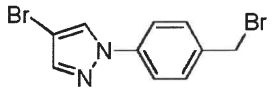
a) Methyl 2-methyl-1-oxoisoindoline-5-carboxylate

To a stirred solution of methyl 1-oxoisoindoline-5-carboxylate (5.0 g, 26.1 mmol) in DMF (100 mL) was added NaH (60 % dispersion, 1.5 g, 37.5 mmol) at 0 °C. After 30 min at 0 °C iodomethane (2.44 mL, 39.2 mmol) was added. The mixture was allowed to react at 0 °C. When the reaction was complete the mixture was poured into ice water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Crude compound was purified by washing with pentane/diethyl ether to give the title compound as a pale brown solid (2.0 g). LC-MS: *m/z* 206.1 $(M+H)^+$.

b) 5-(Hydroxymethyl)-2-methylisoindolin-1-one

To a stirred solution of methyl 2-methyl-1-oxoisoindoline-5-carboxylate (3.4 g, 16.6 mmol) in THF (150 mL) was added MeOH (0.53 mL,13.1 mmol) and $LiBH_4$ (2.0 M solution, 16.6 mL. 33.2 mmol) at 0 °C. After 3 h at 0 °C the solution was allowed to warm to RT and stirred until the reaction was complete. The reaction was quenched with MeOH:H_2O (1:1) and the mixture was concentrated under reduced pressure. Crude compound was purified by column chromatography to give the title compound as a pale brown solid (2.0 g). LC-MS *m/z* 178.1 $(M+H)^+$.

Intermediate 63: 4-Bromo-1-(4-(bromomethyl)phenyl)-1*H*-pyrazole



a) 1-(p-Tolyl)-1*H*-pyrazole

A microwave reactor was charged with copper(II) acetate monohydrate (0.02 g, 0.1 mmol), DMF (5 mL), pyrazole (0.177 g, 2.60 mmol), 4-iodotoluene (0.436 g, 2.0 mmol) and Cs_2CO_3 (1.30 g, 4 mmol). The solution was flushed with nitrogen gas before being heated under microwave irradiation at 120 °C. When the reaction was complete (LC-MS) the reaction mixture was diluted with H_2O and EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (0.26 g). LC-MS: *m/z* 159.1 $(M+H)^+$.

b) 4-Bromo-1-(p-tolyl)-1*H*-pyrazole

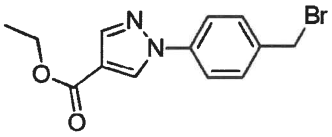
A round-bottomed flask was charged with 1-(p-tolyl)-1*H*-pyrazole (0.26 g, 1.64 mmol), chloroform (10 mL), *N*-bromosuccinimide (0.336 g, 1.89 mmol) and benzoyl peroxide (0.04 g, 0.16 mmol). The solution was flushed with nitrogen and heated to reflux. When the reaction was complete (LC-MS) it was quenched with water. The aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness to give the title compound (0.409 g, crude yield). LC-MS: *m/z* 237.1 $(M+H)^+$.

c) 4-Bromo-1-(4-(bromomethyl)phenyl)-1*H*-pyrazole

A round-bottomed-flask was charged with crude bromide compound from above (0.40 g), chloroform (10 mL), *N*-bromosuccinimide (0.345 g, 1.94 mmol) and benzoyl peroxide (0.041 g, 0.17 mmol). The solution was flushed with nitrogen and heated to reflux. When the reaction was complete (LC-MS) it was quenched with water. The

aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness to provide the title compound (0.569 g, crude yield). This material was used as such in the following step. LC-MS: *m/z* 315.1 $(M+H)^+$.

Intermediate 64: Ethyl 1-(4-(bromomethyl)phenyl)-1*H*-pyrazole-4-carboxylate



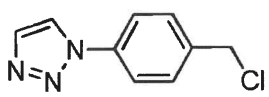
a) Ethyl 1-(p-tolyl)-1H-pyrazole-4-carboxylate

Title compound was prepared from 4-iodotoluene (0.436 g, 2.0 mmol), copper (II) acetate monohydrate (0.02 g, 0.1 mmol), 4-ethoxycarbonyl pyrazole (0.392 g, 2.80 mmol) and Cs_2CO_3 (1.30 g, 4 mmol) in DMF (5 mL) as described in step (a) of Intermediate 66. The title compound was purified by column chromatography (0.11 g). LC-MS: *m/z* 231.3 $(M+H)^+$.

b) Ethyl 1-(4-(bromomethyl)phenyl)-1*H*-pyrazole-4-carboxylate

A round-bottomed-flask was charged with ethyl 1-(p-tolyl)-1*H*-pyrazole-4-carboxylate (0.11 g, 0.48 mmol), acetonitrile (4 mL), N-bromosuccinimide (0.102 g, 0.57 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.016 g, 0.1 mmol). The solution was refluxed until the reaction was complete (LC-MS). Reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc. Combined organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum. Crude material was purified by column chromatography to give the title compound (0.12 g). LC-MS: *m/z* 309.3 $(M+H)^+$.

Intermediate 65: 1-(4-(Chloromethyl)phenyl)-1*H*-1,2,3-triazole



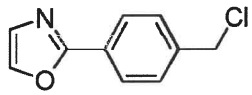
a) (4-(1*H*-1,2,3-Triazol-1-yl)phenyl)methanol

A vial was charged with p-iodobenzyl alcohol (0.234 g, 1 mmol), DMSO (4 mL), L-proline (0.023 g, 0.200 mmol), copper (I) iodide (0.019 g, 0.100 mmol), sodium L-ascorbate (0.040 g, 0.200 mmol), sodium azide (0.098 g, 1.500 mmol), trimethylsilyl-acetylene (0.285 mL, 2.000 mmol), H_2O (0.5 ml) and potassium carbonate (0.207 g, 1.500 mmol). Nitrogen gas was passed through the solution and the mixture was heated to 80 °C. When the reaction was complete (LC-MS) 10 % ammonia solution was added followed by EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Crude material was purified by column chromatography to give the title compound (0.055 g). LC-MS: *m/z* 176.2 $(M+H)^+$.

b) 1-(4-(Chloromethyl)phenyl)-1*H*-1,2,3-triazole

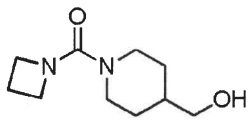
An oven dried round-bottomed-flask was charged with (4-(1*H*-1,2,3-triazol-1-yl)phenyl)methanol (0.11 g, 0.628 mmol) and CH_2Cl_2 (3 mL). A drop of DMF (~0.05 mL) followed by $SOCl_2$ (0.069 mL, 0.94 mmol) were added at 0 °C. The solution was kept at 0 °C for 10 min before it was allowed to warm to RT. When the reaction was complete (LC-MS), solvent was evaporated under vacuum. The residue was dissolved in saturated $NaHCO_3$ and EtOAc. Aqueous layer was extracted with EtOAc. Combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give the title compound (0.049 g) LC-MS: *m/z* 194.2 $(M+H)^+$.

Intermediate 66: 2-(4-(Chloromethyl)phenyl)oxazole



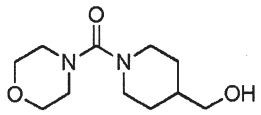
The title compound was prepared from (4-(oxazol-2-yl)phenyl)methanol (0.13 g, 0.74 mmol), $SOCl_2$ (0.081 mL, 1.11 mmol) and a drop of DMF (~0.05 mL) in CH_2Cl_2 (3 mL) according to the procedure described in step (b) of Intermediate 65 (0.122 g). LC-MS: *m/z* 194.2 $(M+H)^+$.

Intermediate 67: Azetidin-1-yl(4-(hydroxymethyl)piperidin-1-yl)methanone



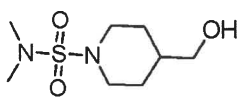
A round-bottomed flask was charged with piperidin-4-ylmethanol (0.230 g, 2 mmol), acetonitrile (10 mL) and *N*,*N*'-carbonyldiimidazole (0.357 g, 2.200 mmol). The mixture was allowed to react at RT for two hours. DIPEA (0.35 mL, 2.0 mmol) followed by azetidine (0.270 mL, 4.00 mmol) were added and the mixture was heated to 60 °C until the reaction was complete (LC-MS). A 1:1 mixture of saturated $NaHCO_3$, brine and EtOAc were added. The aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated to dryness to give the title compound (0.41 g). LC-MS: *m/z* 199.2 $(M+H)^+$.

Intermediate 68: (4-(Hydroxymethyl)piperidin-1-yl)(morpholino)methanone



A round-bottomed flask was charged with piperidin-4-ylmethanol (0.230 g, 2 mmol), dichloromethane (10 mL), Et_3N (0.5 mL, 3.6 mmol) and 4-morpholinecarbonyl chloride (0.257 mL, 2.20 mmol) and the mixture was allowed to react at RT until the reaction was complete (NMR). The mixture was evaporated to dryness followed by the addition of saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the title compound (0.2 g). LC-MS: *m/z* 229.3 $(M+H)^+$.

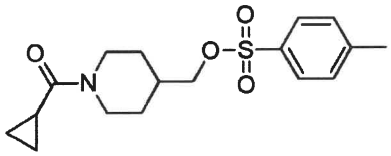
Intermediate 69: 4-(Hydroxymethyl)-N,N-dimethylpiperidine-1-sulfonamide



A round bottomed flask was charged with piperidin-4-ylmethanol (0.65 g, 5.6 mmol), CH_2Cl_2 (15 mL) and Et_3N (1 mL, 7.2 mmol). Dimethylsulfamoyl chloride (0.55

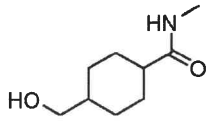
mL, 5.1 mmol) was added at 0 °C, after which the solution was allowed to warm to RT. When the reaction was complete (TCL), the solution was concentrated under vacuum. The residue was passed through a pad of silica to give the title compound as a yellow solid (0.81 g). LC-MS: *m/z* 223.2 $(M+H)^+$.

Intermediate 70: (1-(Cyclopropanecarbonyl)piperidin-4-yl)methyl 4-methyl-benzenesulfonate



An oven-dried round bottomed flask was charged with piperidin-4-ylmethanol (0.346 g, 3 mmol), CH_2Cl_2 (10 mL) and Et_3N (1.67 ml, 12 mmol). Cyclopropane-carbonyl chloride (0.28 mL, 3.9 mmol) was added at 0 °C. The solution was allowed to react at RT. When the amide formation was complete (TCL), p-toluenesulfonyl chloride (0.858 g, 4.50 mmol) was added at RT. When the reaction was complete (LC-MS) solvent was evaporated under vacuum. The residue was dissolved in saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography to give the title compound (0.548 g). LC-MS: *m/z* 338.4 $(M+H)^+$.

Intermediate 71: 4-(Hydroxymethyl)-*N*-methylcyclohexane-1-carboxamide



a) Methyl 4-(methylcarbamoyl)cyclohexane-1-carboxylate

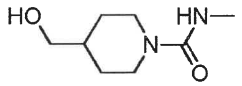
To a solution of 4-(methoxycarbonyl) cyclohexane-1-carboxylic acid (1.2 g, 6.4 mmol) in CH_2Cl_2 (25 mL) were added DMF (1 drop) followed by $(COCl)_2$ (1.4 mL, 16.1 mmol) at 0 °C after which the mixture was stirred at RT. The reaction mixture was concentrated under reduced pressure to remove excess $(COCl)_2$. The residue was dissolved in CH_2Cl_2 (25 ml) and cooled to 0 °C. $MeNH_2$ (17 ml) was added to the above

solution followed by stirring at RT until the reaction was complete. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound as colorless oil (0.5 g) LC-MS: *m/z* 200 $(M+H)^+$.

b) 4-(Hydroxymethyl)-*N*-methylcyclohexane-1-carboxamide

To the solution of methyl-4-(methylcarbamoyl)cyclohexane-1-carboxylate (0.4 g, 2.0 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.57 g, 20.1 mmol) at 0 °C followed by stirring at RT until the reaction was complete. The reaction mixture was concentrated under reduced pressure. The crude was purified by column chromatography to give the title compound as colorless liquid (0.3 g). LC-MS: *m/z* 172 $(M+H)^+$.

Intermediate 72: 4-(Hydroxymethyl)-*N*-methylpiperidine-1-carboxamide



a) Ethyl 1-(methylcarbamoyl) piperidine-4-carboxylate

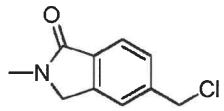
To a solution of ethyl piperidine-4-carboxylate (10.6 g, 68.0 mmol) in THF (25 mL) were added Et_3N (13.7 mL, 136.1 mmol) and phenyl methylcarbamate (10.4 g, 68.0 mmol) followed by heating at 80 °C. When the reaction was complete the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography to give the title compound as a yellow solid (9.8 g). LC-MS: *m/z* 215 $(M+H)^+$.

b) 4-(Hydroxymethyl)-*N*-methylpiperidine-1-carboxamide

To a solution of ethyl 1-(methylcarbamoyl) piperidine-4-carboxylate (3.0 g, 14.0 mmol) in MeOH (100 ml) at 0 °C was added $NaBH_4$ (4.2 g, 112.0 mmol) followed by stirring at RT until the reaction was complete. The reaction mixture was quenched with cold water and concentrated under reduced pressure. The crude product was purified by

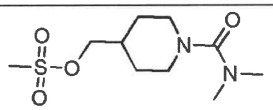
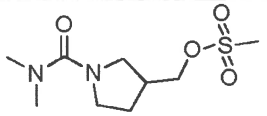
column chromatography to give the title compound as a sticky mass (1.21 g). MS: *m/z* 173 $(M+H)^+$.

Intermediate 73: 5-(Chloromethyl)-2-methylisoindolin-1-one

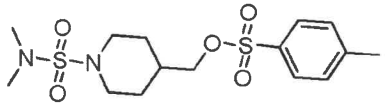


To a stirred solution of 5-(hydroxymethyl)-2-methylisoindolin-1-one (2.5 g, 14.1 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (8.86 mL, 63.5 mmol) at 0 °C. MsCl (1.64 mL , 21.2 mmol) was added and the solution was stirred at 0 °C for 2 h after which it was warmed to RT. The reaction mixture was quenched with water and extracted with CH_2Cl_2. Combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and reduced under vacuum. Crude compound was purified by column chromatography to give the title compound as an off white solid (500 mg). LC-MS: *m/z* 196.1 $(M+H)^+$.

The following intermediates were prepared as described for Intermediate 73 from the starting material indicated on the table.

No.	Structure	LC-MS	Starting material
74		LC-MS: *m/z* 265.3 $(M+H)^+$	4-(Hydroxymethyl)-*N*,*N*-dimethyl-piperidine-1-carboxamide
75		LC-MS: *m/z* 251.3 $(M+H)^+$	3-(Hydroxymethyl)-*N*,*N*-dimethyl-pyrrolidine-1-carboxamide

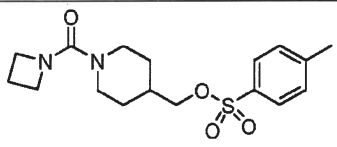
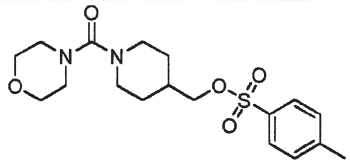
Intermediate 76: (1-(N,N-Dimethylsulfamoyl)piperidin-4-yl)methyl 4-methyl-benzenesulfonate



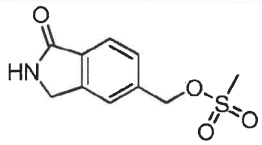
The title compound was prepared from 4-(hydroxymethyl)-*N*,*N*-dimethylpiperi-dine-1-sulfonamide (0.58 g, 2.6 mmol), p-toluenesulfonyl chloride (0.572 g, 3.0 mmol) and Et_3N (0.545 mL, 3.91 mmol) in CH_2Cl_2 (10 mL) according to the procedure

described for Intermediate 73. Crude material was purified by column chromatography to give the title compound as an off-white solid (0.44 g). LC-MS: *m/z* 377.5 $(M+H)^+$.

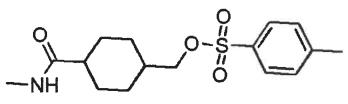
The following intermediates were prepared as described for Intermediate 76 from the starting material indicated on the table.

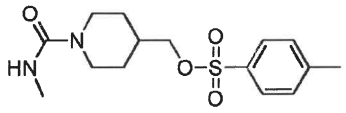
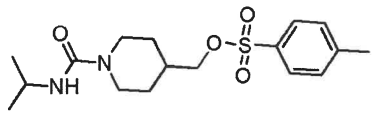
No.	Structure	LC-MS	Starting material
77		LC-MS: *m/z* 353.4 $(M+H)^+$	Azetidin-1-yl(4-(hydroxy-methyl)piperidin-1-yl)metha-none
78		LC-MS: *m/z* 383.4 $(M+H)^+$	(4-(Hydroxymethyl)piperi-din-1-yl)(morpholino)-methanone

The following intermediate was prepared according to the procedure described for Intermediate 38 from the starting material indicated on the table.

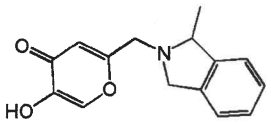
No.	Structure	LC-MS	Starting material
79		LC-MS: *m/z* 242.1 $(M+H)^+$	5-(Hydroxymethyl)iso-indolin-1-one

The following intermediates were prepared according to the procedure described for Intermediate 42 from the starting material indicated on the table.

No.	Structure	LC-MS	Starting material
80		LC-MS: *m/z* 326.3 $(M+H)^+$	4-(Hydroxymethyl)-*N*-methylcyclohexane-1-carboxamide

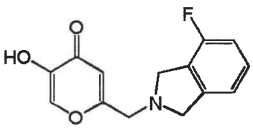
81		LC-MS: *m/z* 327.3 $(M+H)^+$	4-(Hydroxymethyl)-*N*-methylpiperidine-1-carboxamide
82		LC-MS: *m/z* 355.3 $(M+H)^+$	4-(hydroxymethyl)-N-isopropylpiperidine-1-carboxamide

Intermediate 83. 5-Hydroxy-2-((1-methylisoindolin-2-yl)methyl)-4*H*-pyran-4-one



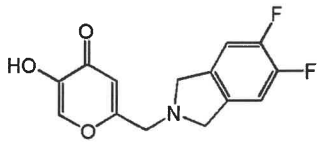
To a stirred solution of 2,3-dihydro-1-methyl-1*H*-isoindole hydrochloride (480 mg, 2.83 mmol) in CH_3CN (10 mL) were added DIPEA (1.77 mL, 9.91 mmol) and 2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one (453 mg, 2.83 mmol) at RT. When the reaction was complete, the solid was filtered and washed with chilled CH_3CN. The title compound was collected as a pink solid (235 mg). LC-MS: m/z: 258 (M+H)+.

Intermediate 84: 2-((4-Fluoroisoindolin-2-yl)methyl)-5-hydroxy-4*H*-pyran-4-one



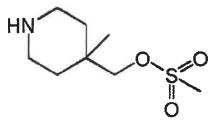
The compound was prepared using the method described for Intermediate 83 using 4-fluoro-2,3-dihydro-1*H*-isoindole hydrochloride (2.90 g, 16.8 mmol), 2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one (2.24 g, 14.0 mmol), DIPEA (5.2 ml, 29.4 mmol) and acetonitrile (50 mL). Yield 1.0 g. LC-MS: *m/z* 288.6 $(M+H)^+$.

Intermediate 85: 2-((5,6-Difluoroisoindolin-2-yl)methyl)-5-hydroxy-4*H*-pyran-4-one



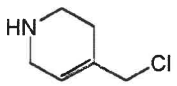
To a stirred solution of 2-(aminomethyl)-5-hydroxy-4*H*-pyran-4-one (2.35 g, 16.7 mmol) in CH_3CN (100 mL) were added DIPEA (23.8 mL, 136 mmol) and 1,2-bis(bromomethyl)-4,5-difluoro-benzene (5.0 g, 16.7 mmol) at RT. The reaction mixture was heated at 90 °C. When the reaction was complete, the reaction mixture was concentrated under reduced pressure and the residue was stirred in EtOAc (100 mL). White solid precipitated which was filtered to afford the title compound (1.10 g). LC-MS: m/z: 280 (M+H)+.

Intermediate 86: (4-Methylpiperidin-4-yl)methyl methanesulfonate trifluoro-acetate



To a solution of tert-butyl 4-methyl-4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (1.37 g, 4.46 mmol) in DCM (17 ml) at 0 °C trifluoroactic acid (17.2 ml, 0.22 mol) was added. The mixture was stirred for 30 min and then evaporated to dryness. The residue was triturated twice with Et_2O to afford the title compound as a white solid (1.2 g). LC-MS: *m/z* 208.2 $(M+H)^+$.

Intermediate 87: 4-(Chloromethyl)-1,2,3,6-tetrahydropyridine trifluoroacetate



a) tert-Butyl-4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (5 g, 25.1 mmol) in THF (50 ml) at -78 °C was added LiHMDS (1.0 M in THF, 27.5 ml, 27.5 mmol) followed by stirring for 30 min. A solution of 1,1,1-trifluoro-N-phenyl-N-((trifluoro-methyl)sulfonyl) methanesulfonamide (9.7 g, 27.6 mmol) in THF (15 ml) was added at -

78 °C and reaction mixture was stirred for 3 h at -78 °C. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was dried, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 6.6 g of the title compound as a pale liquid. 1H-NMR (400 MHz; DMSO-d6): δ 6.01 (d, 1H), 3.98 (t, 2H), 3.55 (d, 2H), 2.38 (t, 2H), 1.40 (s, 9H).

b) 1-(tert-Butyl)4-methyl 3,6-dihydropyridine-1,4(2*H*)-dicarboxylate

To a mixture of tert-butyl4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (5.6 g, 16.8 mmol), Et_3N (4.7 ml, 33.0 mmol) in DMF (69 ml) and MeOH (52 ml) was added PPh_3 (0.2 g, 1.0 mmol) and $Pd(OAc)_2$ (0.1 g, 0.5 mmol) at RT under nitrogen followed by stirring under CO atmosphere for 12 h. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography to give 2.0 g of the title compound as a greenish liquid. 1H-NMR (400 MHz; DMSO-d6): δ 6.85 (d, 1H), 4.00 (t, 2H), 3.67 (s, 3H), 3.42 (d, 2H), 2.25 (t, 2H), 1.41 (s, 9H).

c) tert-Butyl-4-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a solution of 1-(tert-butyl)4-methyl-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (1.7 g, 7.3 mmol) in DCM (20 ml) at -78 °C was added DIBAL-H (1.0 M in toluene, 10.5 ml, 10.5 mmol) followed by stirring at RT for 16 h. The reaction was cooled to 0 °C and quenched with water and extracted with DCM. The organic layer was dried, filtered and concentrated under reduced pressure to give 1.5 g of the title compound as greenish viscous liquid. LC-MS: m/z 214 (M+H) +.

d) tert-Butyl-4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

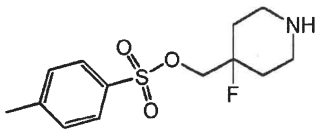
To the solution of tert-butyl-4-(hydroxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate (1.3 g, 6.3 mmol) in DCM (20 ml) at 0 °C were added Et_3N (1.9 ml, 18.0 mmol) and TsCl (1.8 g, 9.5 mmol). The reaction mixture was stirred at RT for 16 h. The

reaction mixture was poured over crushed ice and extracted with DCM. The organic layer was washed with brine, dried, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 1.1 g of the title compound. 1H-NMR (400 MHz; DMSO-d6): δ 5.85 (d, 1H), 4.19 (s, 2H), 3.79-3.81 (m, 2H), 3.42 (t, 2H), 2.05-2.15 (m, 2H), 1.40 (s, 9H).

e) 4-(Chloromethyl)-1,2,3,6-tetrahydropyridine trifluoroacetate

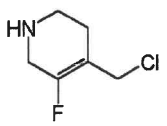
The title compound was prepared by the method described for Intermediate 86 using tert-butyl-4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (0.10 g, 0.43 mmol), TFA (1.7 ml, 22 mmol) and DCM (1.6 ml). Yield 0.076 g. LC-MS: *m/z* 132.0 $(M+H)^+$.

Intermediate 88: (4-Fluoropiperidin-4-yl)methyl 4-methylbenzenesulfonate, Trifluoroacetate



The title compound was prepared by the method described for Intermediate 86 using tert-butyl 4-fluoro-4-((tosyloxy)methyl)piperidine-1-carboxylate (0.30 g, 0.77 mmol), TFA (3 ml, 39 mmol) and DCM (4.5 ml). Yield 0.264 g. LC-MS: *m/z* 288.6 $(M+H)^+$.

Intermediate 89: 4-(Chloromethyl)-5-fluoro-1,2,3,6-tetrahydropyridine trifluoroacctate



a) Ethyl-1-benzyl-5-fluoro-1,2,3,6-tetrahydropyridine-4-carboxylate

To a solution of ethyl-1-benzyl-5-hydroxy-1,2,3,6-tetrahydropyridine-4-carboxylate (25.0 g, 84.0 mmol) in DCM (500 ml) at 0 °C was added DAST (33.3 ml,

252 mmol) followed by stirring at RT for 3 h. The reaction mixture was quenched with cold saturated $NaHCO_3$ solution and extracted with DCM. The organic layer was dried, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 9.8 g of the title compound as a yellow oil. LC-MS: m/z 264 (M+H)+.

b) Ethyl-5-fluoro-1,2,3,6-tetrahydropyridine-4-carboxylate

To a solution of ethyl-1-benzyl-5-fluoro-1,2,3,6-tetrahydropyridine-4-carboxylate (9.8 g, 37.0 mmol) in DCE (200 ml) at 0 °C was added 1-chloroethyl chloroformate (20.0 ml, 186 mmol). The reaction mixture was stirred at 60 °C for 4 h. The mixture was cooled to 0 °C and MeOH (200 ml) was added followed by refluxing for 1 h. The residue was neutralized with Et_3N to pH 7 and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 4.5 g of the title compound as a brown solid. LC-MS: m/z 174 (M+H)+.

c) 1-(tert-Butyl)-4-ethyl-5-fluoro-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate

To a solution of ethyl-5-fluoro-1,2,3,6-tetrahydropyridine-4-carboxylate (4.5 g, 26.0 mmol) in DCM (100 ml) were added Et_3N (10.8 ml, 78.0 mmol) and Boc_2O (11.3 ml, 52.0 mmol) at 0 °C and stirred at RT for 16 h. The reaction was quenched with water and extracted with DCM. The organic layer was washed with brine, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give 3.5 g of the title compound as a yellow liquid. 1H-NMR (400 MHz; CDCl3): δ 4.27 (q, 2H), 4.12 (d, 2H), 3.48 (d, 2H), 2.43 (s, 2H), 1.47 (s, 9H), 1.32 (t, 3H).

d) tert-Butyl 5-fluoro-4-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate

To a solution of 1-(tert-butyl)-4-ethyl-5-fluoro-3,6-dihydropyridine-1,4(2*H*)-dicarboxylate (3.5 g, 12.8 mmol) in THF (60 ml) was added LAH (1.0 M in THF, 12.8

ml, 12.8 mmol) at -20 °C followed by stirring at RT for 16 h. The reaction mixture was quenched with ice and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 1.2 g of the title compound as a colourless oil. 1H-NMR (400 MHz; DMSO-d6): δ 4.76 (t, 1H), 4.02 (d, 2H), 3.87 (s, 2H), 3.38 (d, 2H), 2.13 (d, 2H), 1.40 (s, 9H).

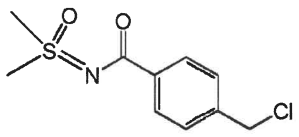
e) tert-Butyl 4-(chloromethyl)-5-fluoro-3,6-dihydropyridine-1(2*H*)-carboxylate

To a solution of tert-butyl-5-fluoro-4-(hydroxymethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.2 g, 5.1 mmol) in DCM (25 ml) at 0 °C were added Et_3N (2.1 ml, 15.0 mmol) and TsCl (1.4 g, 7.7 mmol). The reaction mixture was stirred at RT for 16 h. The reaction was quenched with water and extracted with DCM. The organic layer was washed with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give 0.4 g of the title compound as a white solid. 1H-NMR (400 MHz; CDCl3): δ 4.29 (s, 2H), 3.96 (s, 2H), 3.43 (t, 2H), 2.20 (d, 2H), 1.41 (s, 9H).

f) 4-(Chloromethyl)-5-fluoro-1,2,3,6-tetrahydropyridine trifluoroacetate

The title compound was prepared by the method described for Intermediate 86 using tert-butyl 4-(chloromethyl)-5-fluoro-3,6-dihydropyridine-1(2*H*)-carboxylate (0.15 g, 0.60 mmol), TFA (2.3 ml, 30 mmol) and DCM (2.5 ml). Yield 0.147 g. LC-MS: *m/z* 150.0 $(M+H)^+$.

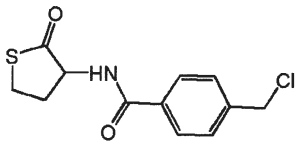
Intermediate 90: 4-(Chloromethyl)-*N*-(dimethyloxido-λ^4-sulfanylidene)-benzamide



To a mixture of NaH (60 % dispersion, 0.063 g, 1.6 mmol) in DCM (10 ml) under nitrogen atmosphere at RT was added S,S-dimethyl-sulfoximine, (0.15 g, 1.6

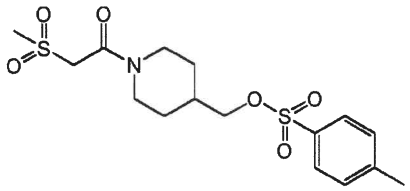
mmol) and the mixture was stirred for 1 h. The mixture was cooled to 0 °C and 4-(chloromethyl)benzoyl chloride (0.30 g, 1.6 mmol) was added and stirring continued for 1 h. Ice water was added and the product extracted with DCM. The organic phase was washed with NaOH and brine, dried and evaporated to give the title compound (0.236 g, crude yield). LC-MS: *m/z* 246.1 $(M+H)^+$.

Intermediate 91: 4-(Chloromethyl)-N-(2-oxotetrahydrothiophen-3-yl)benzamide



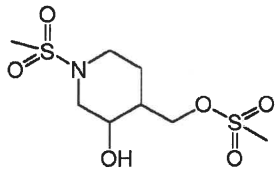
To a solution of 4-(chloromethyl)benzoyl chloride (0.60 g, 3.17 mmol) in THF (8 ml) DL-homocysteine thiolactone hydrochloride (0.49 g, 3.17 mmol) was added under nitrogen atmosphere and the mixture was cooled in ice water bath. Et_3N (1.1 ml, 7.9 mmol) was added and mixing was continued for 2 h. THF was evaporated, water added to the residue and the mixture extracted with EtOAc. The organic layer was washed with 1 M HCl, 1 M NaOH and brine, dried and evaporated to give the title compound (0.66 g, crude yield). LC-MS: *m/z* 270.2 $(M+H)^+$.

Intermediate 92: (1-(2-(Methylsulfonyl)acetyl)piperidin-4-yl)methyl 4-methyl-benzenesulfonate



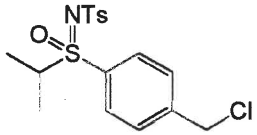
To a solution of phosphorus pentachloride (0.232 g, 1.11 mmol) in DCM (6 ml) methanesulfonylacetic acid (0.154 g, 1.11 mmol) was added and the mixture refluxed for 30 min. Piperidin-4-ylmethyl 4-methylbenzenesulfonate (0.200 g, 0.743 mmol) in DCM (2 ml) was added at RT and then the mixture refluxed for 1 h. Water was added and the product was extracted with EtOAc. The organic phase was washed with 0.5 M NaOH, 1 M HCl and brine, dried and evaporated to give the title compound (0.122 g, crude yield). LC-MS: *m/z* 390.4 $(M+H)^+$.

Intermediate 93: (3-Hydroxy-1-(methylsulfonyl)piperidin-4-yl)methyl methanesulfonate



To a solution of 4-(hydroxymethyl)piperidin-3-ol (0.070 g, 0.53 mmol) in ACN (10 ml) at 0 °C were added K_2CO_3 (0.15 g, 1.07 mmol) and methanesulfonyl chloride (0.122 g, 1.07 mmol) in ACN (1ml) in two steps. 1 ml DMF was added to get better solubility. The reaction mixture was stirred at RT for 1 h and then evaporated to dryness to afford the title compound (0.10 g, crude yield). LC-MS: *m/z* 288.1 $(M+1)^+$.

Intermediate 94: 1-(Chloromethyl)-4-(propan-2-ylsulfonimidoyl)benzene tosyl



a) 4-(Isopropylthio)benzaldehyde

To a solution of propane-2-thiol (3.3 g, 44.9 mmol) in DMSO (100 ml) at 0 °C were added K_2CO3 (11.0 g, 80.0 mmol) and 4-fluorobenzaldehyde (5.0 g, 40.0 mmol) followed by heating at 100 °C for 16 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried and concentrated under reduced pressure to give the title compound (6.4 g). LC-MS: *m/z* 181 $(M+1)^+$.

b) (4-(Isopropylthio)phenyl)methanol

To a solution of 4-(isopropylthio)benzaldehyde (6.4 g, 35.0 mmol) in MeOH (120 ml) was added $NaBH_4$ (2.0 g, 53.0 mmol) at 0 °C followed by stirring at RT for 2 h. The reaction was quenched with ice cold water and extracted with EtOAc. The organic layer was dried and concentrated under reduced pressure to give the title compound (5.5 g). LC-MS: *m/z* 183 $(M+1)^+$.

c) (4-(Chloromethyl)phenyl)(isopropyl)sulfane

To a solution of (4-(isopropylthio)phenyl)metanol (5.5 g, 30.0 mmol) in dry DCM (100 ml) at 0 °C was added $SOCl_2$ (3.8 g, 33.0 mmol) followed by stirring at RT for 1 h. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water, dried and concentrated under reduced pressure to give the title compound (5.7 g). 1H-NMR (400 MHz; DMSO-d6): 7.36 (d, 2H), 7.30 (d, 2H), 4.56 (s, 2H), 3.38-3.41 (m, 1H), 1.30 (d, 6H).

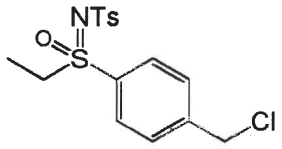
d) N-((4-(Chloromethyl)phenyl)isopropyl)-λ4-sulfanylidene)-4-methylbenzene-sulfonamide

To a solution of (4-(chloromethyl)phenyl)(isopropyl)sulfane (5.7 g, 28.0 mmol) in ACN (100 ml) was added 4-methylbenzenesulfonamide (4.8 g, 28.0 mmol), iodobenzene diacetate (14.4 g, 44.0 mmol) and Fe (III) acetylacetonate (0.7 g, 1.9 mmol) at RT followed by stirring for 16 h. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title compound (8.5 g). LC-MS: *m/z* 370 $(M+1)^+$.

e) 1-(Chloromethyl)-4-(propan-2-ylsulfonimidoyl)benzene tosyl

To a solution of N-((4-(chloromethyl)phenyl)isopropyl)-λ4-sulfanylidene)-4-methylbenzenesulfonamide (8.0 g, 21.0 mmol) in DCM (150 ml) were added *m*-CPBA (70 % in water, 11.1 g, 65.0 mmol), K_2CO_3 (11.5 g, 84.0 mmol) followed by stirring at RT for 2 days. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with water, dried and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title compound (1.1 g). LC-MS: *m/z* 384 $(M+1)^+$.

Intermediate 95: N-((4-(Chloromethyl)phenyl)(ethyl)(oxo)-λ4-sulfanylidene)-4-methylbenzenesulfonamide



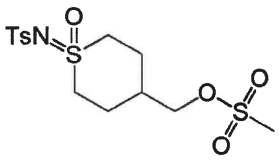
a) N-((4-(Chloromethyl)phenyl)(ethyl)-λ4-sulfanylidene)-4-methylbenzene-sulfonamide

The title compound was prepared by the method described in step (d) of Intermediate 94 starting from (4-(chloromethyl)phenyl)-(ethyl)sulfane (11.0 g, 59.1 mmol) and 4-methylbenzenesulfonamide (10.0 g, 59.1 mmol). Yield 14.8 g. LC-MS: *m/z* 356 $(M+1)^+$.

b) N-((4-(Chloromethyl)phenyl)(ethyl)(oxo)-λ4-sulfanylidene)-4-methylbenzene-sulfonamide

The title compound was prepared by the method described in step (e) of Intermediate 94 starting from N-((4-(chloromethyl)phenyl)(ethyl)-λ4-sulfanylidene)-4-methylbenzenesulfonamide (14.5 g, 40.0 mmol) and *m*-CPBA (70% in water, 14.0 g, 80.0 mmol). Yield: 7.1 g. LC-MS: m/z 372 (M+H)+.

Intermediate 96: 1-Oxido-1-(tosylimino)tetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate



a) [1-({[(4-Methylphenyl)sulfonyl]oxy}imino)hexahydro-1λ^4-thiopyran-4-yl]-methyl methanesulfonate

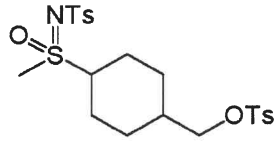
The title compound was prepared by the method described in step (d) of Intermediate 94 starting from (tetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate (2.1 g, 10.0 mmol), 4-methylbenzenesulfonamide (2.56 g, 15.0 mmol), iodobenzene

diacetate (5.12 g, 16.0 mmol) and Fe (III) acetylacetonate (0.25g, 0.7 mmol). Yield 0.94 g. LCMS: *m/z* 380.1 $(M+1)^+$.

b) (1-Oxido-1-(tosylimino)tetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate

The title compound was prepared by the method described in step (e) of Intermediate 94 starting from [1-({[(4-methylphenyl)sulfonyl]oxy}imino)hexahydro-1λ^4-thiopyran-4-yl]methyl methanesulfonate (0.86 g, 2.27 mmol), *m*-CPBA (77 % in water, 1.0 g, 4.5 mmol) and K_2CO_3 (0.94 g, 6.8 mmol). Yield: 0.31 g. LC-MS: m/z 396.1 [M+H]+.

Intermediate 97: (4-(S-methyl-N-tosylsulfonimidoyl)cyclohexyl)methyl-4-methylbenzenesulfonate



a) (4-(Methylthio)cyclohexyl)methanol

To a solution of methyl-4-(methylthio)cyclohexane-1-carboxylate (6.0 g, 31.9 mmol) in THF (100 ml) was added $LiBH_4$ (2.0 M in THF, 40 ml, 95.7 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title compound. Yield 4.0 g. MS: m/z 161 (M+H)+.

b) (4-(Methylthio)cyclohexyl)methyl-4-methylbenzenesulfonate

To a solution of (4-(methylthio)cyclohexyl)methanol (4.0 g, 29.3 mmol) in DCM (50 ml) was added Et_3N (12 ml, 87.9 mmol) and TsCl (8.4 g, 44.0 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. The reaction was quenched with ice water and extracted with DCM. The organic layer was dried, filtered and concentrated under

reduced pressure. The crude residue was purified by column chromatography to afford the title compound. Yield 7.5 g. 1H-NMR (400 MHz; DMSO-d6): δ 7.78 (d, 2H), 7.48 (d, 2H), 3.83 (d, 2H), 2.89-2.90 (m, 1H), 2.44 (s, 3H), 1.99 (s, 3H), 1.60 (q, 4H), 1.58 (s, 1H), 1.41 (q, 2H), 1.33 (q, 2H).

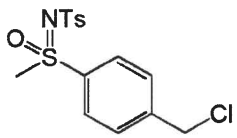
c) (4-(S-methyl-N-tosylsulfinimidoyl)cyclohexyl)methyl-4-methylbenzene-sulfonate

The title compound was prepared by the method described in step (d) of Intermediate 94 starting from (4-(methylthio)cyclohexyl)methyl-4-methylbenzenesulfonate (5.0 g, 15.9 mmol), 4-methylbenzenesulfonamide (4.0 g, 23.8 mmol), iodobenzene diacetate (8.2 g, 25.4 mmol) and Fe (III)acetylacetonate (0.36 g, 1.1 mmol). Yield 2.5 g. LC-MS: m/z 484 (M+H)+.

d) (4-(S-methyl-N-tosylsulfonimidoyl)cyclohexyl)methyl-4-methylbenzene-sulfonate

To a solution of (4-(S-methyl-N-tosylsulfinimidoyl)cyclohexyl)methyl-4-methyl-benzenesulfonate (1.5 g, 3.1 mmol) in ethanol : ACN (1:3) (20 ml) was added H_2O_2 (30 % in water, 0.8 ml, 6.8 mmol) and K_2CO_3 (2.5 g, 18.8 mmol) at 0 °C. The reaction mixture was stirred at RT for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title compound. LC-MS: m/z 498 (M+H)+.

Intermediate 98: N-((4-(Chloromethyl)phenyl)(methyl)(oxo)-λ4-sulfanylidene)-4-methylbenzenesulfonamide



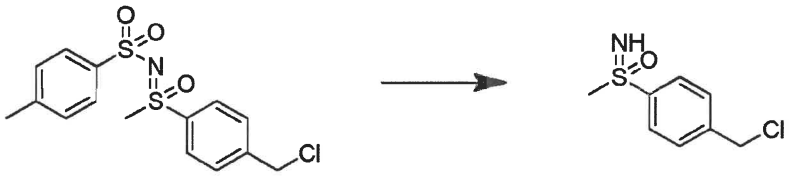
a) N-((4-(Chloromethyl)phenyl)methyl)-λ4-sulfanylidene)-4-methylbenzene-sulfonamide

The title compound was prepared by the method described in step (d) of Intermediate 94 starting from 4-(methylthio)benzyl chloride (2.5 g, 14.5 mmol), 4-methylbenzenesulfonamide (3.7 g, 21.7 mmol), iodobenzene diacetate (7.5 g, 23.1 mmol) and Fe (III) acetylacetonate (0.36g, 1.0 mmol). Yield 3.3 g. LC-MS: *m/z* 342.1 $(M+1)^+$.

b) N-((4-(Chloromethyl)phenyl)(methyl)(oxo)-λ4-sulfanylidene)-4-methylbenzenesulfonamide

The title compound was prepared by the method described in step (e) of Intermediate 94 starting from N-((4-(chloromethyl)phenyl)methyl)-λ4-sulfanylidene)-4-methylbenzenesulfonamide (3.3 g, 9.7 mmol), *m*-CPBA (77 % in water, 4.37 g, 19.5 mmol) and K_2CO_3 (4.0 g, 29 mmol). Yield 3.0 g (white solid). LC-MS: *m/z* 358.1 (M+H)+.

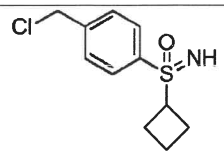
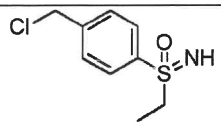
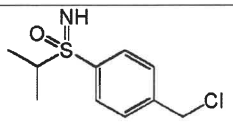
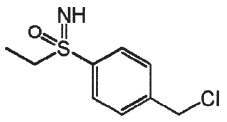
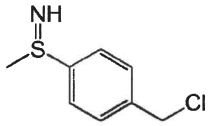
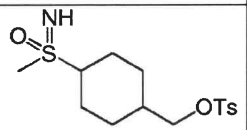
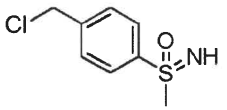
Intermediate-99: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene



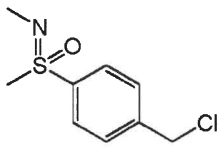
A solution of 1-(chloromethyl)-4-(methylsulfonimidoyl)benzene tosyl (0.70 g, 1.95 mmol) in sulfuric acid (3.0 ml) was stirred at RT for 1 h. The reaction mixture was poured into water, basified using 2 M NaOH solution and extracted with DCM. The organic layer was washed with water, dried with Na_2SO_4 and evaporated to give the titled compound. LC-MS: *m/z* 205.9 $(M+H)^+$

The following intermediates were prepared according to the procedure described for Intermediate 99 from the starting material indicated on the table.

No	Structure	LC-MS	Starting material

100		LC-MS: *m/z* 244.4 $(M+H)^+$	1-(Chloromethyl)-4-(S-cyclobutyl-N-(p-tolylsulfonyl)sulfoximine)benzene
101		LC-MS: *m/z* 218.7 $(M+H)^+$	1-(Chloromethyl)-4-(ethylsulfon-imidoyl)benzene tosyl
102		LC-MS: *m/z* 233.2 $(M+H)^+$	1-(Chloromethyl)-4-(propan-2-yl-sulfonimidoyl)benzene tosyl
103		LC-MS: m/z 219.1 $(M+H)^+$	N-((4-(Chloromethyl)phenyl)(ethyl)-(oxo)-λ4-sulfanylidene)-4-methyl-benzenesulfonamide
104		LC-MS: m/z 189.0 $(M+H)^+$	N-((4-(Chloromethyl)phenyl)methyl)-λ4-sulfanylidene)-4-methyl-benzenesulfonamide
105		LC-MS: m/z 346.7 $(M+H)^+$	(4-(S-methyl-N-tosylsulfonimidoyl)-cyclohexyl)methyl-4-methylbenzene-sulfonate
106		LC-MS: *m/z* 205.9 $(M+H)^+$	N-((4-(Chloromethyl)phenyl)-(methyl)(oxo)-λ4-sulfanylidene)-4-methylbenzenesulfonamide

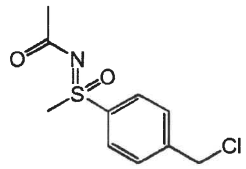
Intermediate 107: 1-(Chloromethyl)-4-(*N*,*S*-dimethylsulfonimidoyl)benzene



To a solution of 1-(chloromethyl)-4-(S-methylsulfonimidoyl)benzene (Intermediate 107) (0.038 g, 0.18 mmol) in DCM (4 ml) under nitrogen atmosphere was added trimethyloxonium tetrafluoroborate (0.041 g, 0.28 mmol). The mixture was stirred at RT for 5 h. The reaction was quenched with saturated $NaHCO_3$ solution and the

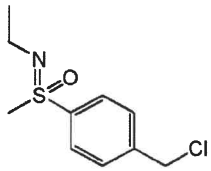
mixture was extracted with DCM. The organic phase was dried, filtered and evaporated to dryness to afford the title compound (yield 0.025 g). LC-MS: *m/z* 218.2 $(M+1)^+$.

Intermediate 108: 1-(Chloromethyl)-4-(*N*-acetyl-*S*-methylsulfonimidoyl)benzene



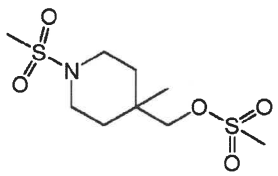
To a solution of 1-(chloromethyl)-4-(S-methylsulfonimidoyl)benzene (Intermediate 106) (0.097 g, 0.47 mmol) in DCM (5 ml) under nitrogen atmosphere was added Et_3N (0.072 g, 0.71 mmol) followed by cooling to 0 °C. Acetyl chloride (0.037 g, 0.047 mmol) was added followed by stirring at 0 °C for 3 h. The reaction was quenched with ice water and the aqueous layer extracted with EtOAc. The organic layer was washed with 0.5 M HCl, saturated $NaHCO_3$ and brine, dried, filtered and evaporated to dryness to afford the title compound (yield 0.162 g). LC-MS: *m/z* 246.1 $(M+1)^+$.

Intermediate 109: 1-(Chloromethyl)-4-(*N*-ethyl-*S*-methylsulfonimidoyl)benzene



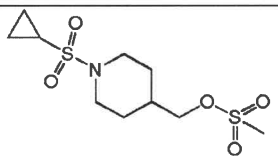
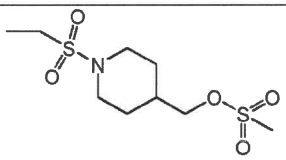
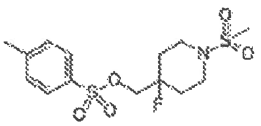
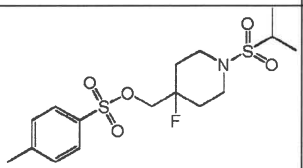
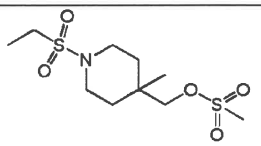
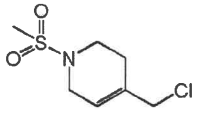
To a solution of Intermediate 108 (0.109 g, 0.44 mmol) in DCM (3 ml) under nitrogen atmosphere at 0 °C was added borane-methyl sulfide complex (0.067 g, 0.89 mmol) followed by stirring for 4 h. MeOH (1 ml) and water (2 ml) were added and the product was extracted with EtOAc. The organic phase was dried, filtered and evaporated to dryness to afford the title compound (yield 0.055 g). LC-MS: *m/z* 232.1 $(M+1)^+$.

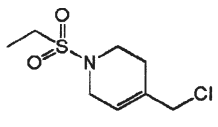
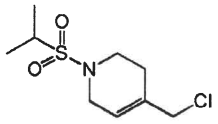
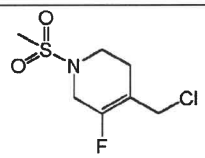
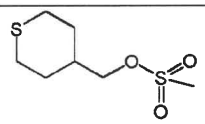
Intermediate 110: (4-Methyl-1-(methylsulfonyl)piperidin-4-yl)methyl methanesulfonate



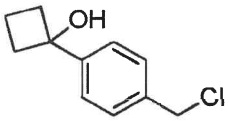
To a suspension of (4-methylpiperidin-4-yl)methyl methanesulfonate trifluoroacetate (Intermediate 86) (0.40 g, 1.24 mmol) in DCM (25 ml) were added Et_3N (0.52 ml, 3.73 mmol) and methanesulfonyl chloride (0.096 ml, 1.24 mmol). The reaction mixture was stirred at RT. When the reaction was complete, EtOAc was added and the mixture washed with saturated $NaHCO_3$, 0.5 M HCl and brine. The organic layer was dried and evaporated to dryness to afford the title compound (0.25 g). LC-MS: m/z 286.2 $(M+1)^+$.

The following intermediates were prepared according to the procedure described for Intermediate 110 from the starting material indicated on the table.

No	Structure	LC-MS	Starting materials
111		LC-MS: m/z 298.3 (M+H)+	Cyclopropanesulfonyl chloride; Piperidin-4-ylmethyl methanesulfonate, trifluoroacetate
112		LC-MS: m/z 286.3 (M+H)+.	Ethanesulfonyl chloride; Piperidin-4-ylmethyl methanesulfonate, trifluoroacetate
113		LC-MS: m/z 366.1 (M+H)+	Methanesulfonyl chloride, Intermediate 88
114		LC-MS: m/z 394.7 (M+1)+	Isopropylsulfonyl chloride, Intermediate 88
115		LC-MS: m/z 300.3 (M+1)+	Ethanesulfonyl chloride, Intermediate 86
116		LC-MS: m/z 210.1 (M+1)+	Methanesulfonyl chloride, tert-Butyl-4-(chloromethyl)-3,6-

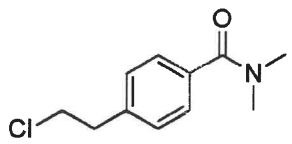
			dihydropyridine-1(2*H*)-carboxylate
117		LC-MS: m/z 224.2 (M+1)+	Ethanesulfonyl chloride, tert-Butyl-4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate
118		LC-MS: m/z 238.1 (M+1)+	Isopropylsulfonyl chloride, tert-Butyl-4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate
119		LC-MS: m/z 228.0 (M+1)+	Methanesulfonyl chloride, Intermediate 89
120		LC-MS: m/z 211.1 (M+1) +	(Tetrahydro-2H-thiopyran-4-yl)methanol

Intermediate 121: 1-(4-(Chloromethyl)phenyl)cyclobutanol



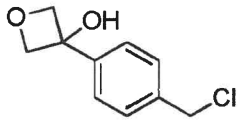
To a stirred solution of 4-bromobenzyl chloride (5.0 g, 24.3 mmol) in THF (50 mL) was added *n*-BuLi (18 ml, 29.2 mmol) and cyclobutanone (2.2 ml, 29.2 mmol) at -78 °C followed by stirring for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude compound. Purification by column chromatography afforded the title compound (1.2 g). ^{1}H NMR (Chloroform-d): δ 7.50 (d, 2H), 7.40 (d, 2H), 4.59 (s, 2H), 2.52-2.59 (m, 2H), 2.33-2.41 (m, 2H), 1.98-2.05 (m, 1H), 1.66-1.77 (m, 1H). LC-MS: *m/z* 179 $[(M-H_2O)+H]^+$

Intermediate 122: 4-(2-Chloroethyl)-*N,N*-dimethylbenzamide



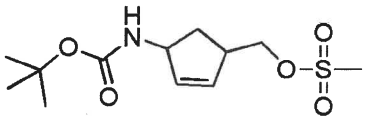
To an ice cooled mixture of *p*-(*beta*-chloroethyl)benzoic acid (0.554 g, 3 mmol), dimethylamine hydrochloride (0.306 g, 3.75 mmol) and triethylamine (2.4 ml, 17.22 mmol) in DMF (6 ml) was added dropwise 1-propanephosphonic acid cyclic anhydride (50 % in EtOAc, 2.4 mL, 4.07 mmol). The mixture was stirred at RT until the reaction reached completion (analysed by LC-MS). The mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford the title compound (0.583 g).^{1}HNMR (400 MHz, Chloroform-*d*): δ 7.36-7.41 (m, 2H), 7.23-7.27 (m, 2H), 3.72 (t, 2H), 3.11 (br s, 3H), 3.09 (t, 2H), 2.99 (br s, 3H); LC-MS: *m/z* 212.1 $(M+H)^+$.

Intermediate 123: 3-(4-(Chloromethyl)phenyl)oxetan-3-ol



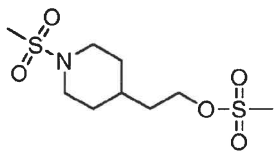
To a stirred solution of 4-bromobenzyl chloride (7 g, 34.06 mmol) in THF (110 mL) was added *n*-BuLi (2.2 M, 18.60 mL, 40.87 mmol) and 3-oxetanone (2.94 g, 40.87 mmol) at -78 °C followed by stirring for 1.5 h. The reaction mixture was quenched with ice water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude compound. Purification by column chromatography afforded the title compound (1.21 g). ^{1}H NMR (DMSO-d6): δ 7.68 (d, 2H), 7.45 (d, 2H), 6.36 (bs, 1H), 4.75-4.77 (m, 4H), 4.66 (d, 2H); LC-MS *m/z* 181 $[(M-H_2O)+H]^+$

Intermediate 124: *cis*-(4-((tert-Butoxycarbonyl)-amino)cyclopent-2-en-1-yl)-methyl methanesulfonate



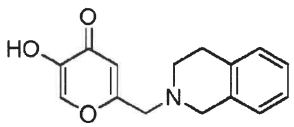
To an ice cooled solution of *cis-tert*-butyl (4-(hydroxymethyl)cyclopent-2-en-1-yl)carbamate (1.0 g, 4.69 mmol) and triethylamine (1.0 ml, 7.17 mmol) in DCM (20 ml) was added methanesulfonyl chloride (0.5 ml, 6.46 mmol) in DCM (2 ml). The mixture was stirred at 5-20 °C until the reaction reached completion (analysed by LC-MS). The mixture was diluted with water and saturated NH_4Cl solution, washed with water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford the title compound (1.36 g). ^{1}HNMR (400 MHz, Chloroform-*d*): δ 5.77-5.86 (m, 2H), 4.50-4.85 (m, 2H), 4.12-4.23 (m, 2H), 3.02 (s, 3H), 2.98-3.07 (m, 1H), 2.59 (dt, 1H), 1.45 (s, 9H), 1.35 (dt, 1H).

Intermediate 125: 2-(1-(methylsulfonyl)piperidin-4-yl)ethyl methanesulfonate



To a mixture of 4-piperidine ethanol (1.0 g, 7.74 mol) and potassium carbonate (3.53 g, 25.5 mmol) in dry ACN (20 ml) was added dropwise methanesulfonyl chloride (1.5 ml, 19.38 mmol). The mixture was stirred at RT until the reaction reached completion (analysed by LC-MS). The mixture was poured into water and stirred overnight. The precipitated product was filtered, washed with water and dried under vacuum to afford the title compound (1.06 g). ^{1}H NMR (Chloroform -d): δ 4.30 (t, 2H), 3.78-3.86 (m, 2H), 3.02 (s, 3H), 2.77 (s, 3H), 2.66 (td, 2H), 1.81-1.88 (m, 2H), 1.74 (q, 2H), 1.56-1.68 (m, 1H), 1.30-1.42 (m, 2H).

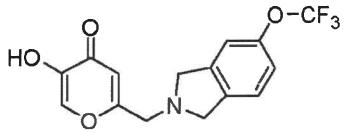
Intermediate 126: 2-{[3,4-Dihydroisoquinolin-2(1H)-yl]methyl}-5-hydroxy-4H-pyran-4-one



To a stirred solution of 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (5.0 g, 158.0 mmol) in acetonitrile (50 mL) were added DIPEA (15.0 mL, 94.92 mmol) and 1,2,3,4-tetrahydroisoquinolene (5.05 g, 37.96 mmol) at RT followed by stirring for 16 h. The precipitated solid was filtered, washed with EtOAc and dried under reduced

pressure to afford the title compound (2.6 g). ^{1}H NMR (DMSO-d6): δ 9.06 (s, 1H), 8.05 (s, 1H), 7.0-7.11 (m, 4H), 6.40 (s, 1H), 3.62 (s, 1H), 3.58 (s, 2H), 2.81-2.84 (m, 1H), 2.74-2.76 (m, 2H). LC-MS *m/z* 258.2 $(M+H)^+$

Intermediate 127: 5-Hydroxy-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4H-pyran-4-one



a) *tert*-Butyl-5-(((methylthio)carbonothioyl)oxy)isoindoline-2-carboxylate

To a solution of *tert*-butyl-5-hydroxyisoindoline-2-carboxylate (3.0 g, 12.7 mmol) in DMF (60 ml) was added NaH (60 % in mineral oil, 0.8 g, 19.1 mmol) at 0 °C followed by stirring for 30 min. To this reaction mixture was added CS_2 (1.0 ml, 16.5 mmol) followed by stirring for 1 h. MeI (1.1 ml, 16.5 mmol) was added to the mixture followed by stirring at RT for 16 h. The reaction was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried, filtered and concentrated under reduced pressure to afford the title compound (4.4 g). ^{1}H-NMR (400 MHz; $CDCl_3$): *δ* 7.39 (d, 1H), 7.16 (s, 1H), 7.08 (d, 1H), 4.5 (d, 4H), 2.68 (s, 3H), 1.45 (s, 9H); LC-MS: *m/z* 324 $(M-H)^+$.

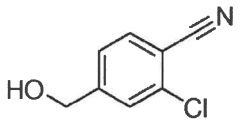
b) 5-(Trifluoromethoxy)isoindoline

To a solution of *tert*-butyl-5-(((methylthio)carbonothioyl)oxy)isoindoline-2-carboxylate (4.4 g, 13.5 mmol) in hydrogen-fluoride pyridine complex (31.0 ml, 108.0 mmol) was added 1,3-dibromo-5,5-dimethylhydantoin (11.6 g, 40.6 mmol) at 0 °C followed by stirring at RT for 16 h. The reaction was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried, filtered and concentrated under reduced pressure to obtain crude product. Purification by column chromatography afforded the title compound (1.3 g). ^{1}H-NMR (400 MHz; DMSO-d_6): *δ* 9.36 (s, 1H), 7.55 (d, 1H), 7.47 (s, 1H), 7.38 (d, 1H), 4.53 (d, 4H); LC-MS: *m/z* 204 $(M+H)^+$.

c) 5-Hydroxy-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4*H*-pyran-4-one

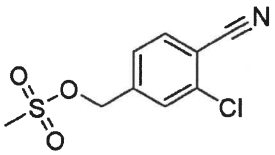
To a solution of 2-(chloromethyl)-5-hydroxy-4*H*-pyran-4-one (0.788 g, 4.9 mmol) in dioxane (20 ml) were added 5-(trifluoromethoxy)isoindoline (1.0 g, 4.9 mmol) and DIPEA (4.5 ml, 24.5 mmol) at RT followed by stirring at 80 °C for 16 h. The reaction was concentrated under reduced pressure to obtain crude product. Purification by column chromatography afforded the title compound (0.4 g). ^{1}H-NMR (400 MHz; DMSO-d_6): δ 9.11 (s, 1H), 8.05 (s, 1H), 7.35 (d, 1H), 7.20 (s, 1H), 7.18 (d, 1H), 6.41 (s, 1H), 3.96 (d, 4H), 3.7 (s, 2H); MS: *m/z* 328 $(M+H)^+$.

Intermediate 128: 2-Chloro-4-(hydroxymethyl)benzonitrile



To a solution of 2-chloro-4-formylbenzonitrile (0.25 g, 1.510 mmol) in THF (15 ml) was added sodium borohydride (0.228 g, 6.04 mmol) in 5 batches in 15 min. The reaction mixture was heated at reflux for 15 min. The mixture was cooled in an ice-bath, and saturated NH_4Cl solution (5 ml) was added to the solution followed by addition of EtOAc (10 ml). The resulting mixture was filtered through a 5 mm layer of Celite®. The Celite® was washed with EtOAc (10ml), and the combined organic layers were washed with NH_4Cl solution, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.12 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.66 (d, 1 H), 7.54 - 7.56 (m, 1 H), 7.36 (d, 1 H), 4.78 (s, 2 H).

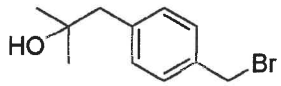
Intermediate 129: 3-Chloro-4-cyanobenzyl methanesulfonate



To a solution of 2-chloro-4-(hydroxymethyl)benzonitrile (0.119 g, 0.710 mmol) and triethylamine (0.109 ml, 0.781 mmol) in DCM (2 ml) at 0 – 5 °C was added dropwise methanesulfonyl chloride (0.060 ml, 0.781 mmol) in DCM (2 ml). The reaction

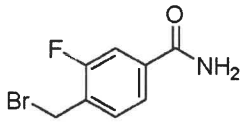
mixture was stirred at RT for 1 h. Water (15 ml) was added, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with saturated $NaHCO_3$ solution, water and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.12 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.72 (d, 1 H), 7.51 - 7.64 (m, 1 H), 7.33 - 7.49 (m, 1 H), 3.08 (s, 3 H).

Intermediate 130: 1-(4-(Bromomethyl)phenyl)-2-methylpropan-2-ol



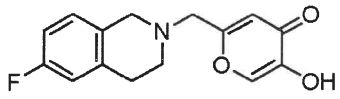
To a solution of methyl 2-(4-(bromomethyl)phenyl)acetate (1 g, 4.11 mmol) in THF (10 ml) at -78°C was added dropwise 3 M methylmagnesium bromide solution (3.93 ml, 11.79 mmol). The reaction mixture was stirred at -78 °C for 2 h, at 0 °C for 4 h and at RT for 16 h. Saturated NH_4Cl solution and water were added, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.81 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.29 - 7.35 (m, 2 H), 7.15 - 7.23 (m, 2 H), 4.67 - 4.75 (m, 2 H), 2.63 - 2.65 (m, 2 H), 1.05 (s, 6 H).

Intermediate 131: 4-(Bromomethyl)-3-fluorobenzamide



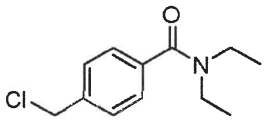
To a suspension of 4-(bromomethyl)-3-fluorobenzonitrile (1 g, 4.67 mmol) and water (0.185 ml, 10.28 mmol) was added sulfuric acid (4.58 ml, 93 mmol) followed by stirring at 100 °C for 1 h, cooling to 50 °C, and pouring on ice. The mixture was stirred, and the precipitated material was filtered, washed with water, and dried in a vacuum-oven at 40 °C for 16 h to afford the title compound (0.94 g). LC-MS: *m/z* 232.0 $(M+H)^+$.

Intermediate 132: 2-((6-Fluoro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-hydroxy-4H-pyran-4-one



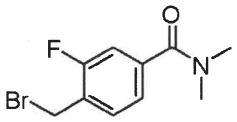
To a solution of 6-fluoro-1,2,3,4-tetrahydroisoquinoline (0.301 g, 1.993 mmol) and 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (0.32 g, 1.993 mmol) in 1,2-dichloroethane (5 ml) at 0°C was added dropwise TEA (0.972 ml, 6.98 mmol). The solution was stirred at 60°C for 3 h, and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM. the organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography to afford the title compound (70 mg). LC-MS: *m/z* 276.2 $(M+H)^+$.

Intermediate 133: 4-(Chloromethyl)-N,N-diethylbenzamide



To a suspension of sodium hydride (0.099 g, 2.476 mmol) and 4-(chloromethyl)-benzamide (0.14 g, 0.825 mmol) in DMF (3 ml) was added dropwise iodoethane (0.664 ml, 8.25 mmol) in DMF (2 ml) at 0 °C. The reaction mixture was stirred at 20 °C for 3 h and quenched with water to form a precipitate. The precipitate was filtered, washed with water and dried to afford the title compound (0.14g) ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.28 - 7.44 (m, 4 H), 4.42 - 4.64 (m, 2 H), 3.38 - 3.62 (m, 2 H), 3.15 - 3.38 (m, 2 H), 1.05 - 1.30 (m, 6 H).

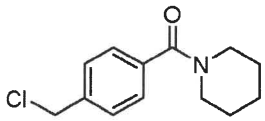
Intermediate 134: 4-(Bromomethyl)-3-fluoro-N,N-dimethylbenzamide



To a solution of 4-(bromomethyl)-3-fluorobenzamide (0.2 g, 0.862 mmol) and NaH (0.103 g, 2.59 mmol) in DMF (1 ml) at 0 °C was added iodomethane (0.537 ml, 8.62 mmol) in DMF (2 ml). The reaction mixture was stirred at 0 °C for 1 h and poured on ice. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated. The crude

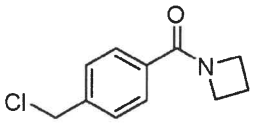
product was purified by column chromatography to afford the title compound (0.10 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.39 (t, 1 H), 7.08 - 7.17 (m, 2 H), 4.38 - 4.51 (m, 2 H), 3.10 (br s, 3 H), 2.99 (br s, 3 H).

Intermediate 135: (4-(Chloromethyl)phenyl)(piperidin-1-yl)methanone



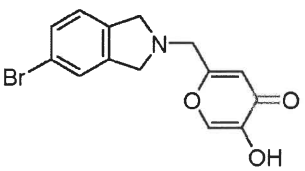
To a suspension of 4-(chloromethyl)benzoyl chloride (0.88 g, 4.66 mmol) and piperidine hydrochloride (0.566 g, 4.66 mmol) in DCM (10 ml) at 0°C was added dropwise triethylamine (1.363 ml, 9.78 mmol). The reaction mixture was stirred at 0 °C for 1 h and at 20 °C for 1 h, and washed with 1M NaOH, 1M HCl, brine and water. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.98 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 - 7.52 (m, 2 H), 7.35 - 7.41 (m, 2 H), 4.80 (s, 2 H), 3.25 (br s, 2 H), 1.37 - 1.65 (m, 8 H).

Intermediate 136: Azetidin-1-yl(4-(chloromethyl)phenyl)methanone



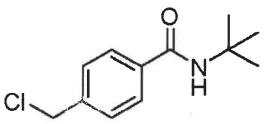
To a suspension of 4-(chloromethyl)benzoyl chloride (2.1 g, 9.22 mmol) and azetidine hydrochloride (0.863 g, 9.22 mmol) in DCM (20 ml) at 0°C was added dropwise triethylamine (2.70 ml, 19.36 mmol). The reaction mixture was stirred at 0 °C for 1 h, and washed with 1M NaOH, 1M HCl, brine and water. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.52g). LC-MS: *m/z* 210.1 $(M+H)^+$.

Intermediate 137: 2-((5-Bromoisoindolin-2-yl)methyl)-5-hydroxy-4H-pyran-4-one



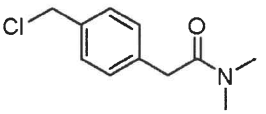
To a solution of 5-bromoisoindoline (1.21g, 6.11 mmol) and 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (0.981 g, 6.11 mmol) in DMF (10 ml) at 0°C was added DIPEA (2.66 ml, 15.27 mmol) dropwise. The reaction mixture was stirred at 50 °C for 2.5 h and poured on ice. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography to afford the title compound (0.22 g). LC-MS: *m/z* 322.2 $(M+H)^+$.

Intermediate 138: *N*-(*tert*-Butyl)-4-(chloromethyl)benzamide



To a suspension of 4-(bromomethyl)phenylacetic acid (0.82 g, 3.72 mmol) and oxalyl chloride (1.351 ml, 18.60 mmol) was added one drop of DMF. The reaction mixture was stirred at 20 °C for 16 h. The excess of oxalyl chloride was evaporated. DCM (15 ml) and 2-methylpropan-2-amine hydrochloride (0.408 g, 3.72 mmol) were added followed by addition of DIPEA (1.620 ml, 9.30 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Water was added, and the layers were separated. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 1M NaOH, 1M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.85 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.76 - 7.78 (m, 2 H), 7.47 - 7.50 (m, 2 H), 4.80 (s, 2 H), 1.37 (s, 9 H).

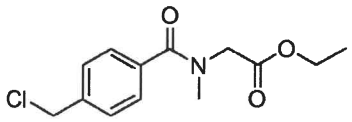
Intermediate 139: 2-(4-(Chloromethyl)phenyl)-N,N-dimethylacetamide



To a suspension of 4-(bromomethyl)phenylacetic acid (2 g, 8.73 mmol) and oxalyl chloride (3 ml, 34.9 mmol) was added one drop of DMF. The reaction mixture was stirred at 20 °C for 16 h. The excess of oxalyl chloride was evaporated. DCM (20 ml) and dimethylamine hydrochloride (0.783 g, 9.60 mmol) were added followed by addition of triethylamine (2.74 ml, 19.64 mmol) in DCM (5 ml) at 0 °C. The reaction

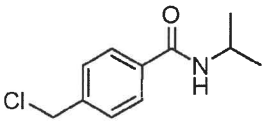
mixture was stirred at 0 °C for 3.5 h. Water (20 ml) was added, and the layers were separated. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 1M NaOH, 1M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.64 g). LC-MS: *m/z* 212.2 $(M+H)^+$.

Intermediate 140: Ethyl 2-(4-(chloromethyl)-N-methylbenzamido)acetate



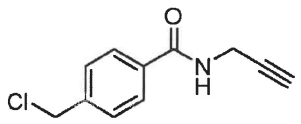
To a suspension of alpha-bromo-*p*-toluic acid (1 g, 4.65 mmol) and oxalyl chloride (1.35 ml, 18.60 mmol) was added one drop of DMF. The reaction mixture was stirred at 20 °C for 16 h. The excess of oxalyl chloride was evaporated. DCM (40 ml) and sarcosine ethyl ester hydrochloride (0.714 g, 4.65 mmol) were added. The mixture was cooled to 0 °C, and DIPEA (2.03 ml, 11.63 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h. The organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.14 g). LC-MS: *m/z* 270.2 $(M+H)^+$.

Intermediate 141: 4-(Chloromethyl)-N-isopropylbenzamide



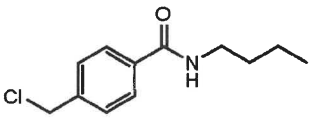
To a suspension of propan-2-amine hydrochloride (0.531 g, 5.55 mmol) and 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) in DCM (20 ml) was added drop-wise TEA (1.659 ml, 11.90 mmol) under 5 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1M NaOH, 1M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.05 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.23 (br d, *J*=7.5 Hz, 1 H), 7.81 - 7.87 (m, 2 H), 7.48 - 7.53 (m, 2 H), 4.80 (s, 2 H), 4.09 (dt, *J*=7.7, 6.6 Hz, 1 H), 1.16 (d, *J*=6.6 Hz, 6 H).

Intermediate 142: 4-(Chloromethyl)-N-(prop-2-yn-1-yl)benzamide



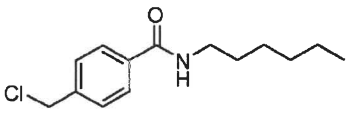
To a suspension of prop-2-yn-1-amine hydrochloride (0.508 g, 5.55 mmol) and 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) in DCM (20 ml) was added dropwise TEA (1.659 ml, 11.90 mmol) under 5 °C. The reaction mixture was stirred at 0 °C for 45 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1M NaOH, 1M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.82 g). LC-MS: *m/z* 208.1 $(M+H)^+$.

Intermediate 143: *N*-butyl-4-(chloromethyl)benzamide



To a suspension of butan-1-amine hydrochloride (0.609 g, 5.55 mmol) and 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) in DCM (20 ml) was added dropwise TEA (1.659 ml, 11.90 mmol) under 5 °C followed by stirring at 0 °C for 45 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was triturated with heptane:MTBE to afford the title compound (1.01g). LC-MS: m/z 226.2 (M+H) +.

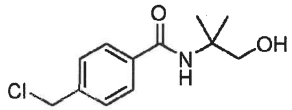
Intermediate 144: 4-(Chloromethyl)-N-hexylbenzamide



To a suspension of 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) and hexan-1-amine hydrochloride (0.765 g, 5.55 mmol) in DCM (20 ml) was added drop-wise TEA (1.659 ml, 11.90 mmol) under 5 °C. The reaction mixture was stirred at 0 °C for 45 min. Water was added to the mixture, the layers were separated, and the aqueous

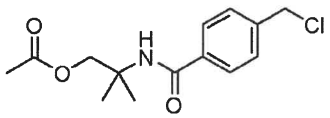
layer was extracted with DCM. The organic layers were combined, washed with 1M NaOH, 1M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.24 g). LC-MS: *m/z* 254.2 $(M+H)^+$.

Intermediate 145: 4-(Chloromethyl)-N-(1-hydroxy-2-methylpropan-2-yl)-benzamide



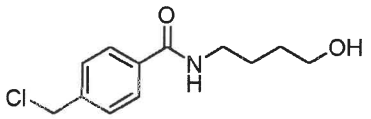
To a suspension of 4-(chloromethyl)benzoyl chloride (0.92 g, 4.87 mmol) and 2-amino-2-methylpropan-1-ol hydrochloride (0.64 g, 5.11 mmol) in DCM (20 ml) was added dropwise TEA (1.526 ml, 10.95 mmol) under 5 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.80 g). LC-MS: *m/z* 242.2 $(M+H)^+$.

Intermediate 146: 2-(4-(Chloromethyl)benzamido)-2-methylpropyl acetate



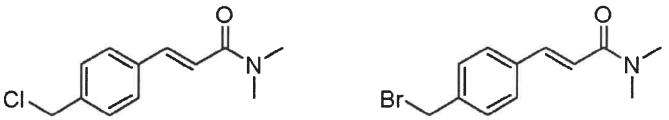
To a solution of 4-(chloromethyl)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide (0.367 g, 1.518 mmol) in pyridine (5 ml) at 0 °C was added acetic anhydride (0.215 ml, 2.277 mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 min and then at 20 °C for 2 h. The volatiles were removed *in vacuo*, and the residue was dissolved in DCM. The solution was washed with 1 M HCl, 5 % $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.26 g). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.84 (s, 1 H), 7.76 - 7.81 (m, 2 H), 7.47 - 7.53 (m, 2 H), 4.80 (s, 2 H), 4.25 (s, 2 H), 3.86 (s, 1 H), 2.02 (s, 3 H), 1.36 (s, 6 H).

Intermediate 147: 4-(Chloromethyl)-N-(4-hydroxybutyl)benzamide



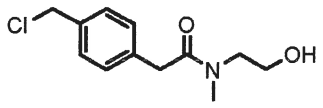
To a suspension of 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) and 4-aminobutan-1-ol hydrochloride (0.664 g, 5.29 mmol) in DCM (20 ml) was added dropwise TEA (1.659 ml, 11.90 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. Diethyl ether was added to the residue. The mixture was stirred, filtrated, and dried to afford the title compound (0.44 g). LC-MS: *m/z* 242.2 $(M+H)^+$.

Intermediates 148 and 149: (*E*)-3-(4-(chloromethyl)phenyl)-N,N-dimethyl-acrylamide and (*E*)-3-(4-(bromomethyl)phenyl)-N,N-dimethylacrylamide



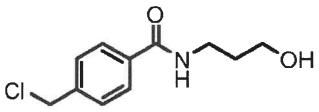
To a suspension of (E)-3-(4-(bromomethyl)phenyl)acrylic acid (0.76 g, 3.15 mmol) and oxalyl chloride (1.083 ml, 12.6 mmol) was added one drop of DMF. The mixture was stirred at 20 °C for 16 h. The excess of oxalyl chloride was evaporated. DCM (20 ml) and dimethylamine hydrochloride (0.27 g, 3.31 mmol) were added followed by addition of triethylamine (0.989 ml, 7.09 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Water (20 ml) was added, and the layers were separated. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound as mixture of (E)-3-(4-(chloromethyl)phenyl)-N,N-dimethyl-acrylamide and (E)-3-(4-(bromomethyl)phenyl)-N,N-dimethylacrylamide (0.33 g). LC-MS: *m/z* 224.2 $(M+H)^+$. LC-MS: *m/z* 270.1 $(M+H).^+$.

Intermediate 150: 2-(4-(Chloromethyl)phenyl)-N-(2-hydroxyethyl)-N-methyl-acetamide



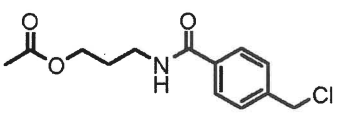
To a suspension of 4-(bromomethyl)phenylacetic acid (2 g, 8.73 mmol) and oxalyl chloride (3 ml, 34.9 mmol) was added one drop of DMF. The reaction mixture was stirred at 20 °C for 16 h. The excess of oxalyl chloride was evaporated. DCM (15 ml) and *N*-methyl ethanolamine HCl (0.974 g, 8.73 mmol), were added followed by addition of TEA (2.738 ml, 19.64 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Water was added, and the layers were separated. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.23 g). LC-MS: *m/z* 242.2 $(M+H)^+$.

Intermediate 151: 4-(Chloromethyl)-*N*-(3-hydroxypropyl)benzamide



To a solution of 4-(chloromethyl)benzoyl chloride (2.97 g, 15.71 mmol) in DCM (10 ml) was added 3-amino-1-propanol (1.180 g, 15.71 mmol) in DCM (20 ml) followed by dropwise addition of TEA (2.409 ml, 17.28 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography followed by trituration with diethyl ether to afford the title compound (1.79 g). LC-MS: *m/z* 228.2 $(M+H)^+$.

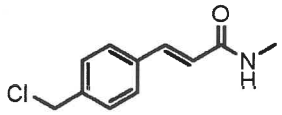
Intermediate 152: 3-(4-(Chloromethyl)benzamido)propyl acetate



To a solution of 4-(chloromethyl)-N-(3-hydroxypropyl)benzamide (1.79 g, 7.86 mmol) in pyridine (15 ml) was added acetic anhydride (1.115 ml, 11.79 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and at 20 °C for 30 min. The solvent

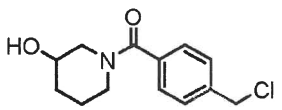
was evaporated, and water was added to the residue. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with 1 M HCl, water, 5 % $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.29 g). LC-MS: *m/z* 270.2 $(M+H)^+$.

Intermediate 155: (E)-3-(4-(chloromethyl)phenyl)-N-methylacrylamide



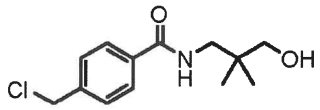
To a suspension of (E)-3-(4-(bromomethyl)phenyl)acrylic acid (1.0 g, 4.15 mmol) and oxalyl chloride (1.424 ml, 16.59 mmol) was added one drop of DMF followed by stirring at 20 °C for 16 h. The excess of oxalyl chloride was evaporated, and DCM (20 ml) and methylamine hydrochloride (0.28 g, 4.15 mmol) were added followed by addition of triethylamine (1.301 ml, 9.33 mmol) at 0 °C. The reaction mixture was stirred at 0°C for 1 h. Water (20 ml) was added, and the layers were separated. The aqueous layer was extracted with DCM. The organic layers were combined and washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, evaporated, and triturated with diethyl ether to afford the title compound (0.42 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 - 8.11 (m, 1 H), 7.51 - 7.58 (m, 2 H), 7.44 - 7.50 (m, 2 H), 7.37 - 7.44 (m, 1 H), 6.52 - 6.69 (m, 1 H), 4.71 - 4.79 (m, 2 H), 2.68 - 2.75 (m, 3 H).

Intermediate 156: (4-(Chloromethyl)phenyl)(3-hydroxypiperidin-1-yl)methanone



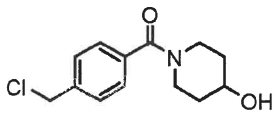
To a suspension of 4-(chloromethyl)benzoyl chloride (1 g, 5.29 mmol) and piperidin-3-ol hydrochloride (0.728 g, 5.29 mmol) in DCM (20 ml) was added drop-wise TEA (0.811 ml, 5.82 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. Heptane was added to the residue followed by stirring, filtration, and drying to afford the title compound (0.62 g). LC-MS: *m/z* 254.2 $(M+H)^+$.

Intermediate 157: 4-(Chloromethyl)-*N*-(3-hydroxy-2,2-dimethylpropyl)-benzamide



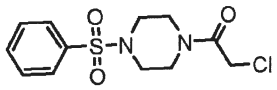
To a suspension of 4-(chloromethyl)benzoyl chloride (2.058 g, 10.89 mmol) and 3-amino-2,2-dimethylpropan-1-ol hydrochloride (1.520 g, 10.89 mmol) in DCM (25 ml) was added dropwise TEA (1.669 ml, 11.98 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to afford the title compound (0.67 g). LC-MS: *m/z* 256.2 $(M+H)^+$.

Intermediate 158: (4-(Chloromethyl)phenyl)(4-hydroxypiperidin-1-yl)methanone



To a suspension of 4-(chloromethyl)benzoyl chloride (3.3 g, 17.46 mmol) and piperidin-4-ol hydrochloride (2.376 g, 17.27 mmol) in DCM (35 ml) was added drop-wise TEA (5.41 ml, 38.9 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (3.62 g). LC-MS: *m/z* 254.3 $(M+H)^+$.

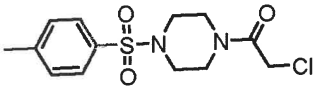
Intermediate 159: 2-Chloro-1-(4-(phenylsulfonyl)piperazin-1-yl)ethanone



To a solution of 1-(phenylsulfonyl)piperazine (1 g, 4.42 mmol) and TEA (1.355 ml, 9.72 mmol) in DCM (15 ml) was added chloroacetyl chloride (0.422 ml, 5.30 mmol) in DCM (5 ml) at 0 °C. The reaction mixture was stirred at 20°C for 50 min, washed

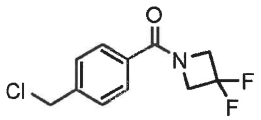
with water and brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.12 g). LC-MS: *m/z* 303.3 $(M+H)^+$.

Intermediate 160: 2-Chloro-1-(4-tosylpiperazin-1-yl)ethanone



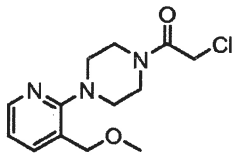
To a solution of 1-tosylpiperazine (1 g, 4.16 mmol) and TEA (0.696 ml, 4.99 mmol) in DCM (15 ml) was added chloroacetyl chloride (0.397 ml, 4.99 mmol) in DCM (5 ml) at 0 °C. The mixture was stirred at 20 °C for 50 min, washed with water and brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (1.30 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.59 - 7.66 (m, 2 H), 7.44 - 7.49 (m, 2 H), 4.34 (s, 2 H), 3.47 - 3.59 (m, 4 H), 2.80 - 3.00 (m, 4 H), 2.41 (s, 3 H).

Intermediate 161: (4-(Chloromethyl)phenyl)(3,3-difluoroazetidin-1-yl)-methanone



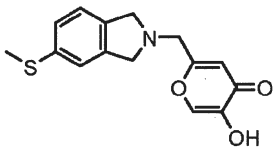
To a suspension of 4-(chloromethyl)benzoyl chloride (1.0 g, 5.29 mmol) and 3,3-difluoroazetidine hydrochloride (0.685 g, 5.29 mmol) in *tert*-butylmethyl ether (15 ml) at 0 °C was added dropwise triethylamine (1.659 ml, 11.90 mmol). The reaction mixture was stirred at 0 °C for 1 h. Water was added to the reaction mixture, and the organic phase was extracted with EtOAc. The organic layers were combined, washed with 1 M NaOH, 1 M HCl, brine and water. The organic layer was dried with Na_2SO_4, filtered, and the majority of the solvents were evaporated. Diethyl ether and heptane were added, and the precipitation was filtered, washed with heptane and dried to afford the title compound (0.9 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.67 - 7.73 (m, 2 H), 7.51 - 7.57 (m, 2 H), 4.82 (s, 2 H), 4.61 - 4.81 (m, 2 H), 4.38 - 4.58 (m, 2 H).

Intermediate 162: 2-Chloro-1-(4-(3-(methoxymethyl)pyridin-2-yl)piperazin-1-yl)ethanone



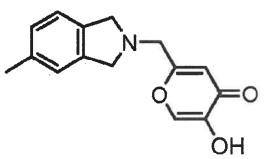
To a solution of 1-(3-(methoxymethyl)pyridin-2-yl)piperazine hydrochloride (0.75 g, 3.08 mmol) and TEA (0.944 ml, 6.77 mmol) in DCM (15 ml) was added chloroacetyl chloride (0.294 ml, 3.69 mmol) in DCM (5 ml) at 0 °C. The reaction mixture was stirred at 20 °C for 50 min, washed with water and brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.59 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 (dd, J=4.8, 1.9 Hz, 1 H), 7.72 (dd, J=7.4, 1.9 Hz, 1 H), 7.05 (dd, J=7.5, 4.8 Hz, 1 H), 4.43 (s, 2 H), 4.42 (s, 2 H), 4.27 (s, 2 H), 3.57 - 3.64 (m, 4 H), 3.11 - 3.18 (m, 2 H), 3.03 - 3.11 (m, 2 H)

Intermediate 163: 5-Hydroxy-2-((5-(methylthio)isoindolin-2-yl)methyl)-4H-pyran-4-one



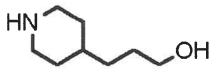
To a solution of 5-(methylthio)isoindoline HCl (0.1 g, 0.496 mmol) and 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (0.080 g, 0.496 mmol) in DMSO (1 ml) at 60 °C was added DIPEA (0.181 ml, 1.041 mmol) dropwise. The reaction mixture was stirred at 60 °C for 35min, and poured on ice. The aqueous layer was extracted with DCM. The organic layers were combined, dried with Na_2SO_4, filtered, and evaporated. The crude product was triturated with diethyl ether to afford the title compound (0.12 g). ^{1}H NMR (400 MHz, Chloroform-d) δ ppm 7.85 (s, 1 H), 7.11 - 7.18 (m, 3 H), 6.56 (s, 1 H), 4.17 - 4.24 (m, 1 H), 3.98 - 4.04 (m, 4 H), 3.79 (s, 2 H), 2.47 (s, 3 H).

Intermediate 164: 5-Hydroxy-2-((5-methylisoindolin-2-yl)methyl)-4H-pyran-4-one



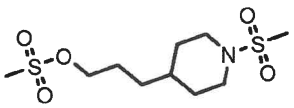
A solution of 5-methylisoindoline (0.207g, 1.557 mmol), 2-(chloromethyl)-5-hydroxy-4H-pyran-4-one (0.25 g, 1.557 mmol) and DIPEA (0.298 ml, 1.713 mmol) in DMSO (2 ml) was stirred at 75 °C for 1 h, and poured on water. The precipitation was filtered, washed with water, and dried to afford the title compound (0.28 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.98 - 9.12 (m, 1 H), 8.06 (s, 1 H), 7.10 - 7.13 (m, 1 H), 7.05 (s, 1 H), 6.97 - 7.02 (m, 1 H), 6.41 (s, 1 H), 3.90 (s, 4 H), 3.77 (s, 2 H), 2.28 (s, 3 H).

Intermediate 165: 3-(Piperidin-4-yl)propan-1-ol, HCl



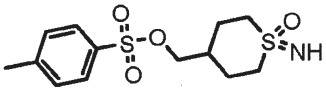
A suspension of 4-pyridinepropanol (3.29 g, 24 mmol), platinum (IV) oxide (0.545 g, 2.400 mmol), 37 % HCl (6.00 ml, 24 mmol) and ethanol (35 ml) was shaked in a Parr apparatus under 8 kPa hydrogen pressure for 3.5 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness to afford the title compound (5.80 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 - 9.32 (m, 1 H), 8.85 - 9.09 (m, 1 H), 3.35 - 3.40 (m, 2 H), 3.15 - 3.23 (m, 2 H), 2.73 - 2.84 (m, 2 H), 1.71 - 1.80 (m, 2 H), 1.27 - 1.51 (m, 5 H), 1.19 - 1.25 (m, 2 H).

Intermediate 166: 3-(1-(Methylsulfonyl)piperidin-4-yl)propyl methanesulfonate



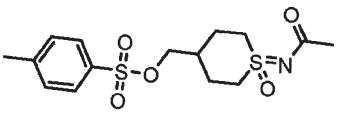
To a suspension of 3-(piperidin-4-yl)propan-1-ol-hydrochloride (1g, 5.57 mmol) and K_2CO_3 (3.31 g, 23.93 mmol) in ACN (10 ml) was added dropwise methanesylfonyl chloride (12.92 ml, 16.70 mmol) at 0 °C. The reaction mixture was stirred at 30 °C for 1.5 h. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was stirred in brine, filtered, washed with brine and water, and dried to afford the title compound (0.68 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 4.19 - 4.26 (m, 2 H), 3.76 - 3.83 (m, 2 H), 3.02 (s, 3 H), 2.77 (s, 3 H), 2.59 - 2.69 (m, 2 H), 1.74 - 1.85 (m, 4 H), 1.26 - 1.45 (m, 5 H).

Intermediate 167: (1-Imino-1-oxidotetrahydro-2H-thiopyran-4-yl)methyl 4-methylbenzenesulfonate



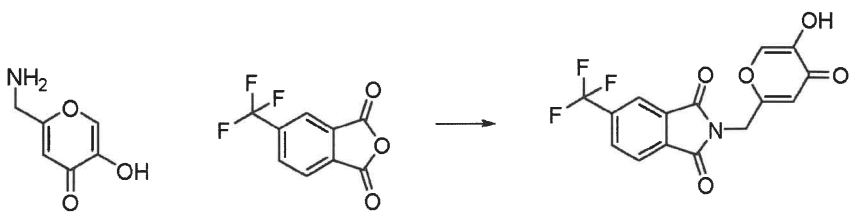
A mixture of (1-oxido-1-(tosylimino)tetrahydro-2H-thiopyran-4-yl)methyl 4-methylbenzenesulfonate (0.4 g, 0.848 mmol) and sulfuric acid (1.260 ml, 25.4 mmol) was stirred at 20 °C for 2 h. Ice was added to the reaction mixture followed by the adjustment of pH to 10 with NaOH. The aqueous layer was extracted with DCM, and the organic layer was washed with brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.23 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.77 - 7.81 (m, 2 H), 7.47 - 7.51 (m, 2 H), 3.90 - 3.97 (m, 2 H), 3.66 (s, 1 H), 2.87 - 3.05 (m, 4 H), 2.43 (s, 3 H), 1.80 - 1.99 (m, 3 H), 1.49 - 1.64 (m, 2 H).

Intermediate 168: (1-(Acetylimino)-1-oxidotetrahydro-2H-thiopyran-4-yl)-methyl 4-methylbenzenesulfonate



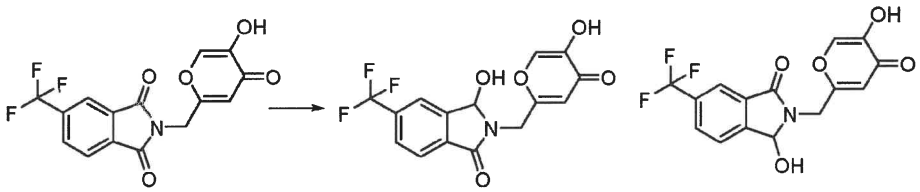
To a solution of (1-imino-1-oxidotetrahydro-2H-thiopyran-4-yl)methyl 4-methyl-benzenesulfonate (0.28 g, 0.882 mmol) and TEA (0.307 ml, 2.205 mmol) in DCM (10 ml) was added acetyl chloride (0.069 ml, 0.970 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, washed with 1 M HCl, 1 M NaOH and brine. The organic layer was dried with Na_2SO_4, filtered, and evaporated to afford the title compound (0.31g). LC-MS: *m/z* 360.2 $(M+H)^+$.

Intermediate 169: 2-((5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoro-methyl)isoindoline-1,3-dione



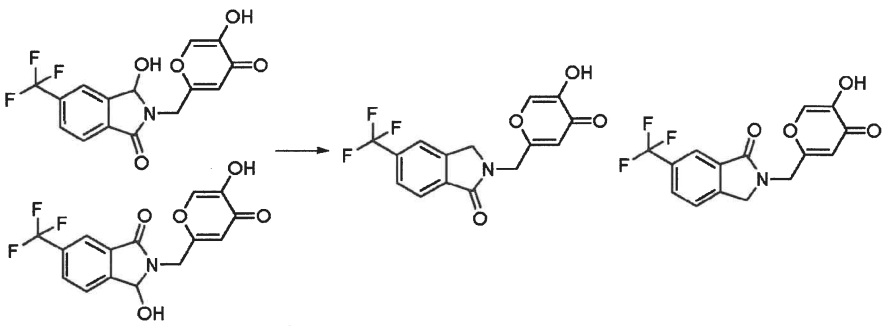
A solution of 2-(Aminomethyl)-5-hydroxy-4H-pyran-4-one (1.1 g, 7.91 mmol) and 5-(trifluoromethyl)isobenzofuran-1,3-dione (1.7 g, 7.91 mmol) in acetic acid (12 ml) was stirred by heating for 1 h. The reaction mixture was poured into water. The obtained precipitate was filtered and dried to afford 2.45 g of the title compound. LC-MS: *m/z* 340.1 $(M+H)^+$.

Intermediate 170: Mixture of 3-Hydroxy-2-((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindolin-1-one and 3-Hydroxy-2-((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl)-6-(trifluoromethyl)isoindolin-1-one



2-((5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindoline-1,3-dione 2.82 g, 8.31 mmol in methanol (50 ml) was treated with $NaBH_4$ (0.94 g, 24.94 mmol) at 0 °C for 1 h. After evaporation of solvent, water (20 ml) was added. The product was extracted EtOAc. The organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to afford 1.2 g of the title mixture. LC-MS: *m/z* 342.1 $(M+H)^+$.

Intermediate 171: Mixture of 2-((5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindolin-1-one and 2-((5-Hydroxy-4-oxo-4H-pyran-2-yl)methyl)-6-(trifluoromethyl)isoindolin-1-one



To a mixture of 3-hydroxy-2-((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindolin-1-one and 3-hydroxy-2-((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl)-6-(trifluoromethyl)isoindolin-1-one (230 mg, 0.67 mmol) was added TFAA (5 ml) and triethylsilane (0.60 ml, 3.81 mmol) at 0 °C. The mixture was stirred at RT for 2 h, then poured into water (10 ml) and basified with 2 M NaOH. The product was extracted with DCM. The organic layer was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to afford 0.20 g of the title mixture. LC-MS: *m/z* 326.1 $(M+H)^+$.

Example 1.

2-(Isoindolin-2-ylmethyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 1)



To a solution of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.20 g, 0.82 mmol) in DMF (5 ml) were added 4-methylsulfonylbenzyl bromide (0.20 g, 0.82 mmol) and K_2CO_3 (0.23 g, 1.6 mmol). The reaction mixture was heated at 60 °C for 1 h. The mixture was cooled to RT, water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4 filtered and evaporated. The crude product was purified by column chromatography to afford 0.21 g of the title compound. ^{1}H NMR (Chloroform-d) δ: 7.95-7.98 (m, 2H), 7.62-7.65 (m, 3H), 7.21 (d, 4H), 6.52 (s, 1H), 5.18 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.06 (s, 3H). LC-MS: *m/z* 413.4 $(M+H)^+$.

The following compounds were prepared according to the procedure described for Compound 1 of Example 1 starting from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one or 5-hydroxy-2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one or a derivative thereof and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, base,

reaction temperature, reaction time, purification method), if any, are indicated on the table.

Purification methods used:

A = Crystallization

B = Column chromatography

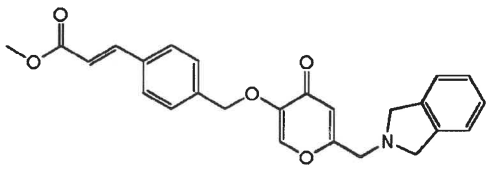
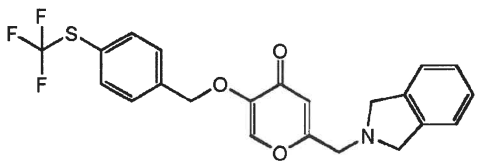
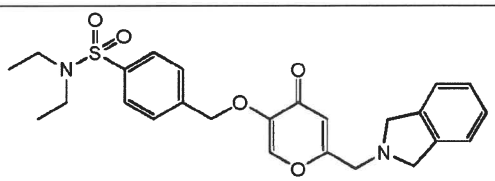
C = Precipitation in aqueous media

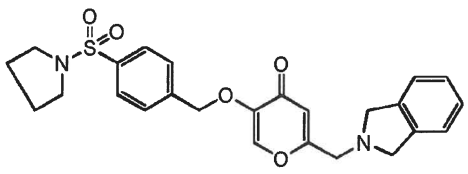
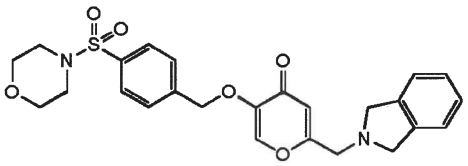
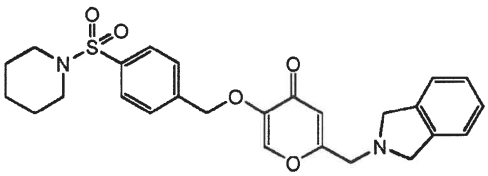
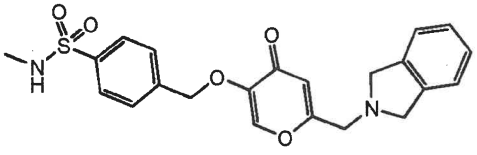
D = Semipreparative HPLC

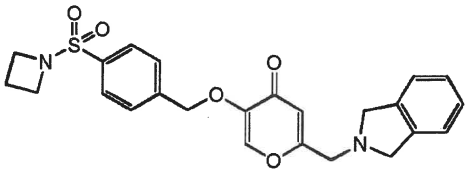
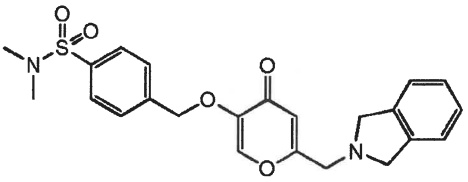
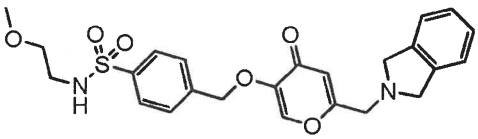
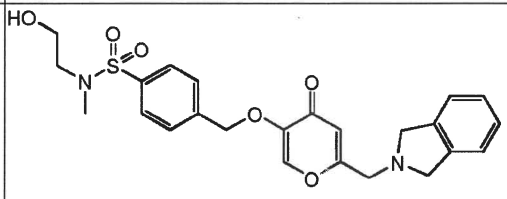
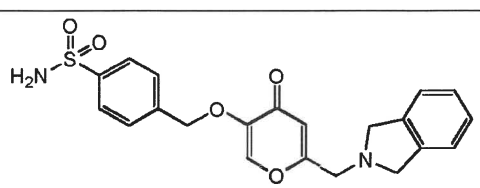
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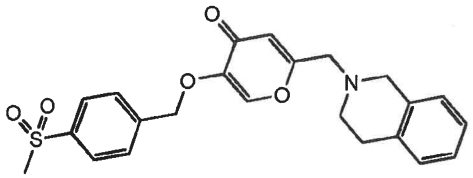
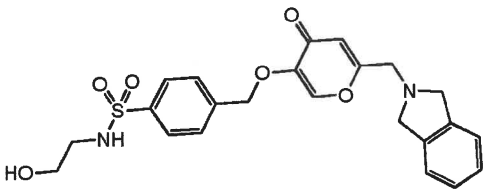
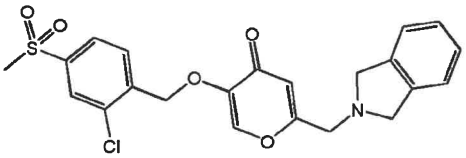
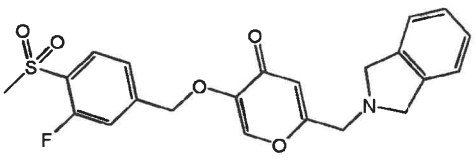
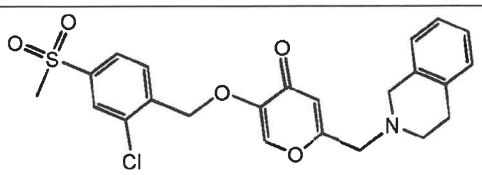
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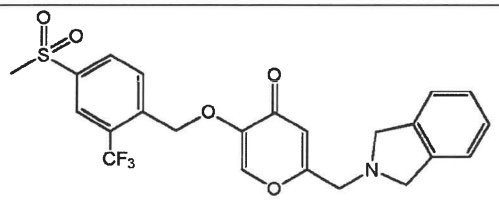
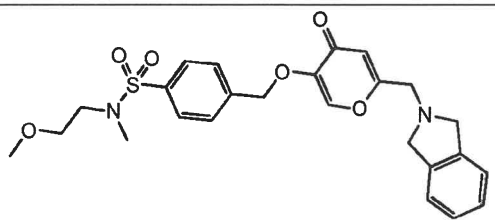
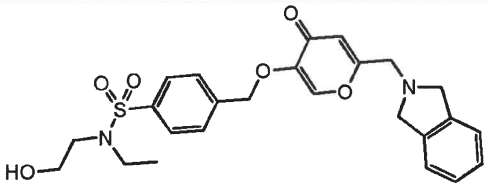
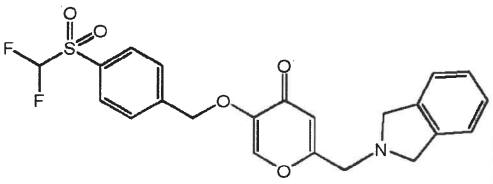
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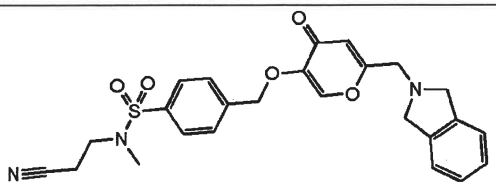
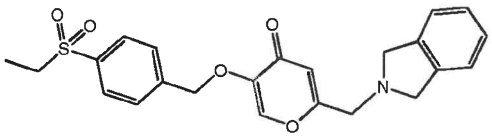
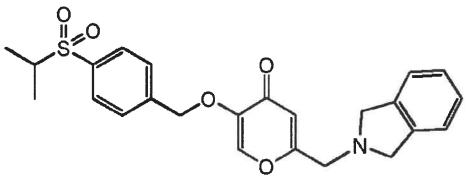
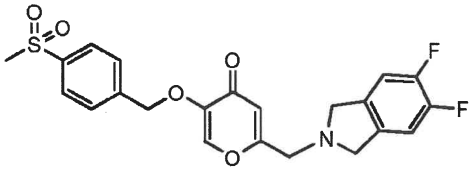
No	Structure and starting material	Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS
2	 Starting material: Methyl-p-bromo-methylcinnamate	^{1}H NMR (Chloroform-d) δ: 7.68 (d, 1H), 7.57 (s, 1H), 7.51-7.55 (m, 2H), 7.43 (d, 2H), 7.17-7.22 (m, 4H), 6.50 (s, 1H), 6.45 (d, 1H), 5.11 (s, 2H), 4.03 (s, 4H), 3.81 (s, 3H), 3.75 (s, 2H). LC-MS: *m/z* 419.6 $(M+H)^+$.
3	 Starting material:4-(Trifluoromethyl-thio)benzyl bromide	^{1}H NMR (Chloroform-d) δ: 7.66 (d, 2H), 7.59-7.62 (m, 1H), 7.59-7.62 (m, 1H), 7.48 (d, 2H), 7.18-7.26 (m, 4H), 6.51 (s, 1H), 5.12 (s, 2H), 4.04 (s, 4H). LC-MS: *m/z* 434.3 $(M+H)^+$.
4		Conditions: THF, 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.79-7.83 (m, 2H), 7.62-7.64 (m, 1H), 7.53-7.57 (m, 2H), 7.19-7.22 (m, 4H), 6.52 (s,

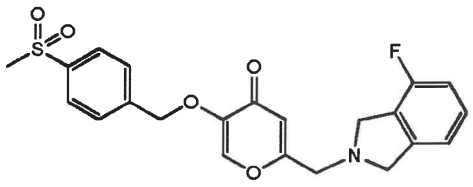
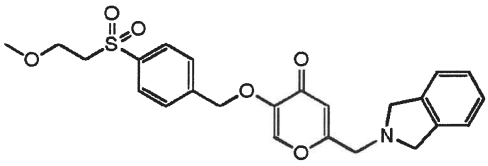
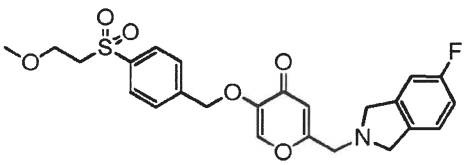
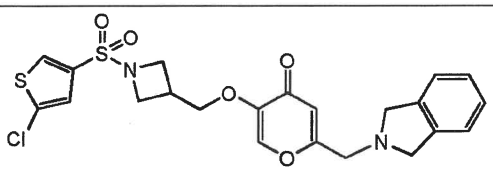
	Starting material: 4-(Bromomethyl)-N,N-diethylbenzenesulfonamide	1H), 5.13 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.20-3.27 (m, 4H), 1.11-1.16 (m, 6H). LCMS: *m/z* 469.4 $(M+H)^+$.
5	 Starting material:1-((4-(Bromo-methyl)phenyl)sulfonyl)pyrrolidine	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.84 (d, 2H), 7.64 (s, 1H), 7.59 (d, 2H), 7.19-7.25 (m, 4H), 6.53 (s, 1H), 5.14 (s, 2H), 4.05 (s, 4H), 3.78 (s, 2H), 3.21-3.29 (m, 4H), 1.72-1.82 (m, 4H). LC-MS: *m/z* 467.4 $(M+H)^+$.
6	 Starting material:4-((4-(Bromo-methyl)phenyl)sulfonyl)morpholine	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.77 (br d, 2H), 7.60-7.67 (m, 3H), 7.18-7.25 (m, 4H), 6.53 (s, 1H), 5.17 (s, 2H), 4.05 (s, 4H), 3.76 (br d, 6H), 3.01 (br s, 4H). LC-MS: *m/z* 483.4 $(M+H)^+$.
7	 Starting material:1-((4-(Bromo-methyl)phenyl)sulfonyl)piperidine	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.77 (d, 2H), 7.71 (s, 1H), 7.56 (d, 2H), 7.29-7.38 (m, 4H), 6.67 (s, 1H), 5.10 (s, 2H), 4.47-4.68 (m, 4H), 4.18 (br s, 2H), 2.95-3.03 (m, 4H), 1.65 (m, 4H), 1.44 (br d, 2H). LC-MS: *m/z* 481.4 $(M+H)^+$.
8	 Starting material: 4-(Bromomethyl)-N-methylbenzenesulfonamide	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.85-7.88 (m, 2H), 7.63-7.65 (m, 1H), 7.56-7.60 (m, 2H), 7.18-7.22 (m, 4H), 6.53 (s, 1H), 5.14 (s, 2H), 4.71 (m, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 2.66 (d, 3H). LCMS: *m/z* 427.3 $(M+H)^+$.

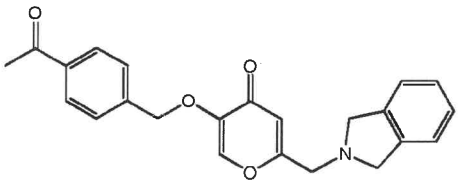
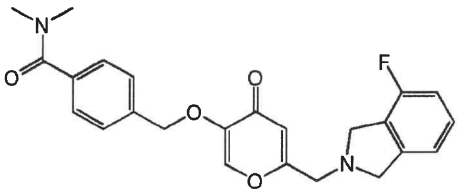
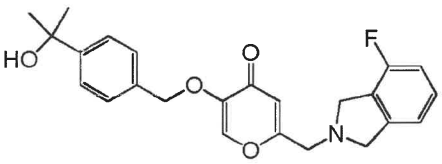
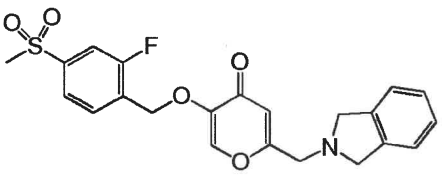
9	 Starting material:1-((4-(Bromo-methyl)phenyl)sulfonyl)azetidine	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.84-7.88 (m, 2H), 7.62-7.67 (m, 3H), 7.20-7.22 (m, 4H), 6.54 (s, 1H), 5.16 (s, 2H), 4.05 (s, 4H), 3.74-3.85 (m, 6H), 2.09 (m, 2H). LCMS: *m/z* 453.4 $(M+H)^+$.
10	 Starting material: 4-(Bromomethyl)-N,N-dimethylbenzenesulfonamide	Conditions: 80 °C. ^{1}H NMR (DMSO-d_6) δ: 8.27 (s, 1H), 7.77-7.81 (m, 2H), 7.69 (d, 2H), 7.18-7.26 (m, 4H), 6.44 (s, 1H), 5.08 (s, 2H), 3.96 (s, 4H), 3.81 (s, 2H), 2.61 (s, 6H). LCMS: *m/z* 441.3 $(M+H)^+$.
11	 Starting material: 4-(Bromomethyl)-N-(2-methoxyethyl) benzenesulfonamide	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.85-7.88 (m, 2H), 7.64 (s, 1H), 7.57 (d, 2H), 7.19-7.22 (m, 4H), 6.53 (s, 1H), 5.08-5.15 (m, 3H), 4.04 (s, 4H), 3.77 (s, 2H), 3.40 (m, 2H), 3.26 (s, 3H), 3.07-3.15 (m, 2H). LCMS: *m/z* 471.3 $(M+H)^+$.
12	 Starting material: 4-(Bromomethyl)-N-(2-hydroxyethyl)-N-methylbenzene-sulfonamide	Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.80-7.83 (m, 2H), 7.64 (s, 1H), 7.58 - 7.62 (m, 2H), 7.20-7.22 (m, 4H), 6.53 (s, 1H), 5.14 (s, 2H), 4.04 (s, 4H), 3.74-3.79 (m, 5H), 3.15-3.20 (m, 3H), 2.85 (s, 3H). LCMS: *m/z* 371.3 $(M+H)^+$.
13		Conditions: 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.93-7.96 (m, 2H), 7.61 (s, 1H), 7.58 (d, 2H),

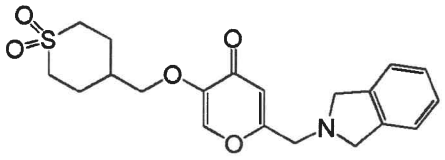
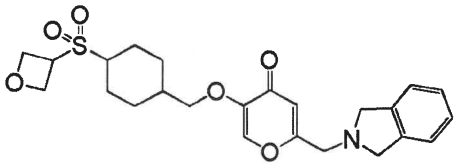
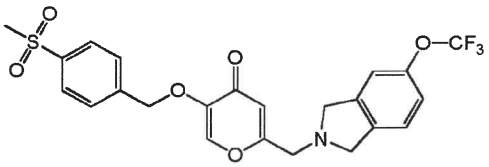
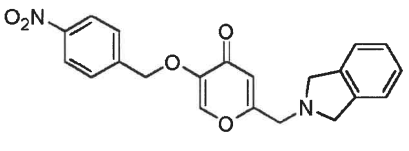
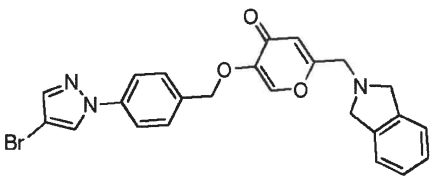
	Starting material:4-(Bromomethyl)-benzenesulfonamide	7.21 (d, 4H), 6.52 (s, 1H), 5.17 (s, 2H), 4.76 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H). LCMS: *m/z* 413.3 $(M+H)^+$.
14	 Starting material: 4-Methylsulfonyl-benzyl bromide	^{1}H NMR (Chloroform-d) δ: 7.96 (d, 2H), 7.61-7.66 (m, 3H), 6.97-7.17 (m, 4H), 6.53 (s, 1H), 5.18 (s, 2H), 3.71 (s, 2H), 3.55 (s, 2H), 3.05 (s, 3H), 2.80-2.97 (m, 4H). LCMS: *m/z* 426.4 $(M+H)^+$.
15	 Starting material: 4-(Bromomethyl)-N-(2-hydroxyethyl)benzenesulfonamide	^{1}H NMR (Chloroform-d) δ: 7.85-7.94 (m, 2H), 7.75 (br d, 1H), 7.60 (br d, 2H), 7.23 (br s, 4H), 6.55 (br d, 1H), 5.12 (br d, 2H), 4.06 (br d, 4H), 3.81 (br d, 2H), 3.60 (br d, 2H), 3.38 (br d, 1H), 2.97-3.12 (m, 2H). LCMS: *m/z* 457.4 $(M+H)^+$.
16	 Starting material: 1-(Bromomethyl)-2-chloro-4-(methylsulfonyl)benzene	^{1}H NMR (Chloroform-d) δ: 7.96-8.00 (m, 1H), 7.88 (d, 2H), 7.71 (s, 1H), 7.19-7.23 (m, 4H), 6.54 (s, 1H), 5.24 (s, 2H), 4.05 (s, 4H), 3.79 (s, 2H), 3.07 (s, 3H). LCMS: *m/z* 446.4 $(M+H)^+$.
17	 Starting material: 4-(Bromomethyl)-2-fluoro-1-(methylsulfonyl)benzene	^{1}H NMR (Chloroform-d) δ: 7.97 (m, 1H), 7.67 (s, 1H), 7.33-7.41 (m, 2H), 7.20-7.22 (m, 4H), 6.53 (s, 1H), 5.18 (s, 2H), 4.05 (s, 4H), 3.78 (s, 2H), 3.22 (s, 3H). LC-MS: *m/z* 430.4 $(M+H)^+$.
18		^{1}H NMR (Chloroform-d) δ: 7.97 (m, 1H), 7.87 (d, 2H), 7.70 (s, 1H), 6.96-7.18 (m, 4H), 6.55 (s, 1H), 5.24 (s,

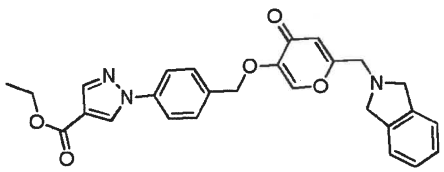
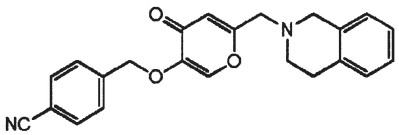
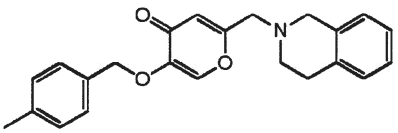
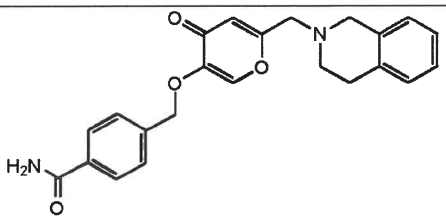
	Starting material: 1-(Bromomethyl)-2-chloro-4-(methylsulfonyl)benzene	2H), 3.72 (s, 2H), 3.57 (s, 2H), 3.07 (s, 3H), 2.81-3.06 (m, 4H). LCMS: *m/z* 460.4 $(M+H)^+$.
19	 Starting material: 4-(Methylsulfonyl)-2-(trifluoromethyl)benzyl bromide	^{1}H NMR (Chloroform-d) δ: 8.25 (s, 1H), 8.10-8.20 (m, 2H), 7.69 (s, 1H), 7.19-7.22 (m, 4H), 6.55 (s, 1H), 5.33 (s, 2H), 4.05 (s, 4H), 3.79 (s, 2H), 3.10 (s, 3H). LCMS: *m/z* 380.4 $(M+H)^+$.
20	 Starting material: 4-(Bromomethyl)-N-(2-methoxyethyl)-N-methylbenzene-sulfonamide	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.80 (d, 2H), 7.63 (s, 1H), 7.58 (d, 2H), 7.18-7.24 (m, 4H), 6.53 (s, 1H), 5.14 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.55 (m, 2H), 3.32 (s, 3H), 3.23 (m, 2H), 2.85 (s, 3H). LCMS: *m/z* 485.6 $(M+H)^+$.
21	 Starting material: 4-(Bromomethyl)-N-ethyl-N-(2-hydroxyethyl)benzene-sulfonamide	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.82 (d, 2H), 7.66 (s, 1H), 7.57 (d, 2H), 7.17-7.23 (m, 4H), 6.52 (s, 1H), 5.11 (s, 2H), 4.03 (s, 4H), 3.77 (s, 2H), 3.73 (m, 2H), 3.23-3.31 (m, 4H), 1.13 (m, 3H). LC-MS: *m/z* 485.6 $(M+H)^+$.
22	 Starting material: 1-(Bromomethyl)-4-	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 8.00 (d, 2H), 7.72 (d, 2H), 7.68 (s, 1H), 7.18-7.24 (m, 4H), 6.54 (s, 1H), 6.05-6.36 (m, 1H), 5.23 (s, 2H), 4.05 (s, 4H), 3.78 (s, 2H). LCMS: *m/z* 448.5

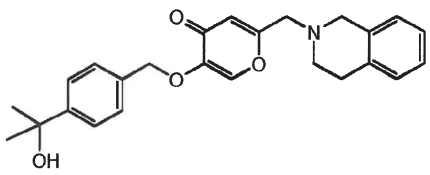
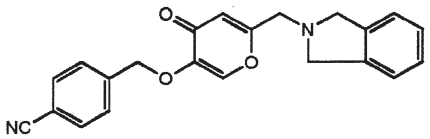
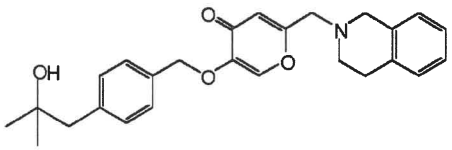
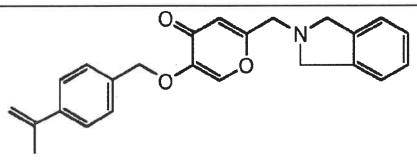
	[(difluoromethyl)sulfonyl]benzene	$(M+H)^+$.
23	 Starting material:4-(Bromomethyl)-N-(2-cyanoethyl)-N-methylbenzene-sulfonamide	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.80 (d, 2H), 7.68 (s, 1H), 7.62 (d, 2H), 7.17-7.24 (m, 4H), 6.52 (s, 1H), 5.13 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.33 (m, 2H), 2.88 (s, 3H), 2.67 (m, 2H). LCMS: *m/z* 480.5 $(M+H)^+$.
24	 Starting material: 1-(Bromomethyl)-4-(ethylsulfonyl)benzene	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.90-7.94 (m, 2H), 7.60-7.67 (m, 3H), 7.18-7.24 (m, 4H), 6.53 (s, 1H), 5.18 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.12 (m, 2H), 1.28 (m, 3H). LCMS: *m/z* 426.5 $(M+H)^+$.
25	 Starting material: 1-(Bromomethyl)-4-(propane-2-sulfonyl)benzene	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.87-7.92 (m, 2H), 7.60-7.65 (m, 3H), 7.18-7.22 (m, 4H), 6.53 (s, 1H), 5.17 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.14-3.24 (m, 1H), 1.30 (d, 6H). LC-MS: *m/z* 440.5 $(M+H)^+$.
26	 Starting material: 4-Methylsulfonyl-benzyl bromide	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.96 (d, 2H), 7.61-7.66 (m, 3H), 7.00 (m, 2H), 6.50 (s, 1H), 5.18 (s, 2H), 3.99 (s, 4H), 3.75 (s, 2H), 3.06 (s, 3H). LC-MS: *m/z* 448.4 $(M+H)^+$.

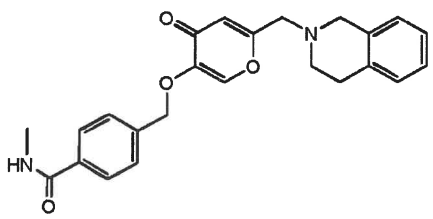
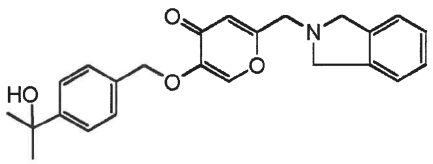
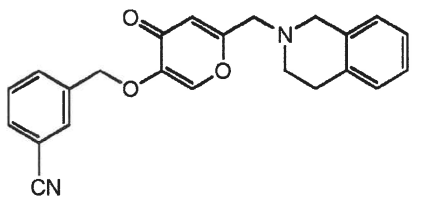
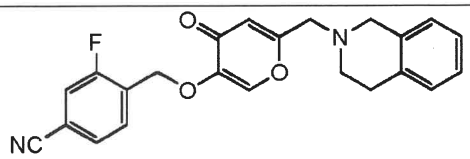
27	 Starting material: 4-Methylsulfonylbenzyl bromide	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.94-7.99 (m, 2H), 7.62-7.66 (m, 3H), 7.17-7.26 (m, 1H), 6.87-7.01 (m, 2H), 6.52 (s, 1H), 5.18 (s, 2H), 4.09 (d, 4H), 3.78 (s, 2H), 3.06 (s, 3H). LCMS: *m/z* 430.4 $(M+H)^+$.
28	 Starting material: 1-(Bromomethyl)-4-((2-methoxyethyl)sulfonyl)benzene	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.91-7.95 (m, 2H), 7.60-7.65 (m, 3H), 7.19-7.23 (m, 4H), 6.53 (s, 1H), 5.18 (s, 2H), 4.04 (s, 4H), 3.71-3.79 (m, 4H), 3.39 (m, 2H), 3.24 (s, 3H). LC-MS: *m/z* 456.5 $(M+H)^+$.
29	 Starting material: 1-(Bromomethyl)-4-((2-methoxyethyl)sulfonyl)benzene	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.93 (d, 2H), 7.60-7.65 (m, 3H), 7.10-7.17 (m, 1H), 6.87-6.94 (m, 2H), 6.52 (s, 1H), 5.18 (s, 2H), 4.01 (br d, 4H), 3.72-3.78 (m, 4H), 3.39 (m, 2H), 3.24 (s, 3H). LC-MS: *m/z* 474.5 $(M+H)^+$.
30	 Starting material: 3-(Bromomethyl)-1-((5-chlorothiophen-3-yl)sulfonyl)-azetidine	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.43 (d, 1H), 7.20-7.22 (m, 4H), 7.02 (d, 1H), 6.48 (s, 1H), 4.05 (s, 4H), 3.98-4.01 (m, 2H), 3.97 (s, 2H), 3.81 (m, 2H), 3.78 (s, 2H), 2.81-2.97 (m, 1H). LCMS: *m/z* 493.4 $(M+H)^+$.

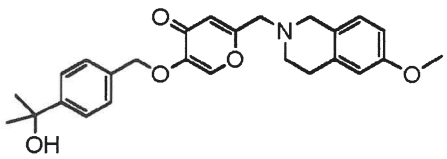
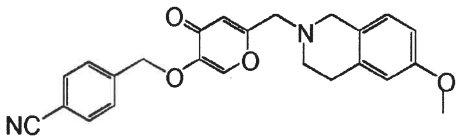
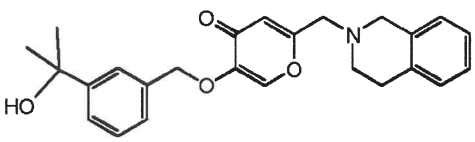
31	 Starting material: 1-[4-(Bromomethyl)-phenyl]ethanone	Conditions: DMSO, 80 °C. ^{1}H NMR (Chloroform-d) δ: 7.94-7.99 (m, 2H), 7.58 (s, 1H), 7.51 (d, 2H), 7.14-7.23 (m, 4H), 6.51 (s, 1H), 5.15 (s, 2H), 4.03 (s, 4H), 3.75 (s, 2H), 2.61 (d, 3H). LCMS: *m/z* 376.46 $(M+H)^+$.
32	 Starting material: 4-(Bromomethyl)-N, N-dimethyl-benzamide	Conditions: 50 °C. 1H NMR (Chloroform-d) δ: 7.57 (s, 1H), 7.46-7.41 (m, 4H), 7.22-7.17 (m, 1H), 6.68 (d, J=7.4 Hz, 1H), 6.92-6.88 m, 1H), 6.50 (s, 1H), 5.11 (s, 2H), 4.11-4.05 (m, 4H), 3.76 (d, J=0.52 Hz, 2H), 3.11 (s, 3H), 2.97 (s, 3H); LC-MS: m/z 423.1 (M+1)+.
33	 Starting materials: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: 50 °C. 1H NMR (Chloroform-d) δ: 7.57 (s, 1H), 7.51-7.48 (m, 2H), 7.39-7.36 (m, 2H), 7.27-7.17 (m, 1H), 6.98 (d, J=7.4 Hz,1H), 6.92-6.87 (m, 1H), 6.49 (s, 1H), 5.07 (s, 2H), 4.11-4.05 (m, 4H), 3.76 (s, 2H), 1.70 (s, 1H), 1.54 (s, 6H); LC-MS: m/z 410.1 (M+1)+.
34	 Starting material: 1-(Bromomethyl)-2-fluoro-4-(methylsulfonyl)benzene	Conditions: B and E (EtOH) 1H NMR (Chloroform-d) δ: 7.79 (m, 2 H), 7.70 (s, 1 H), 7.67 (m, 1 H), 7.21 (m, 4 H), 6.53 (s, 1 H), 5.23 (s, 2 H), 4.05 (s, 4 H), 3.78 (s, 2 H), 3.07 (s, 3 H); LC-MS: m/z 430.2 (M+1)+.

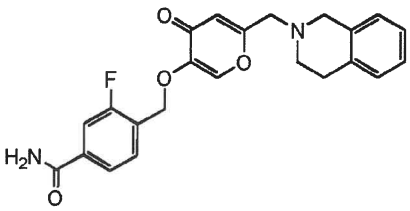
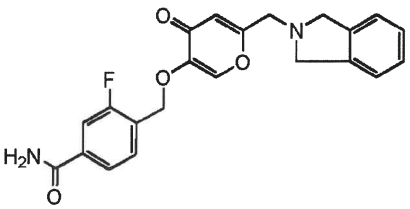
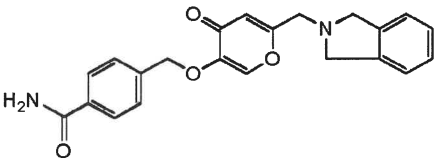
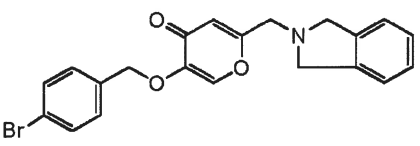
35	 Starting material: 4-(Bromomethyl)-tetrahydro-2H-thiopyran 1,1-dioxide	1H NMR (Chloroform-d) δ: 7.63 (s, 1 H), 7.21 (m, 4 H), 6.50 (s, 1 H), 4.05 (s, 4 H), 3.80 (d, 2 H), 3.78 (s, 2 H), 3.11 (m, 2 H), 3.02 (m, 2 H), 2.31 (m, 2 H), 2.12 (m, 1 H), 1.97 (m, 2 H); LC-MS: m/z 390.3 (M+1)+.
36	 Starting material: 4-(Bromomethyl)-1-(oxetan-3-ylsulfonyl)piperidine	1H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.94 (m, 2 H), 4.87 (m, 2 H), 4.42 (tt, 1 H), 4.04 (s, 4 H), 3.88 (br d, 2 H), 3.77 (s, 2 H), 3.74 (d, 2 H), 2.82 (td, 2 H), 2.00 (m, 3 H), 1.38 (br dd, 2 H); LC-MS: m/z 461.3 (M+1)+.
37	 Starting material: 4-Methylsulfonyl-benzyl bromide	Conditions: DMSO, C and A (EtOH). 1H NMR (Chloroform-d) δ: 7.96 (d, 2H), 7.64 (d, 2H), 7.63 (s, 1H), 7.21 (d, 1H), 7.10-7.06 (m, 2H), 6.52 (s, 1H), 5.18 (s, 2H), 4.05 (s, 2H), 4.03 (s, 2H), 3.77 (s, 2H), 3.06 (s, 3H); LC-MS: m/z 496.4 (M+1)+.
38	 Starting material: 1-(Bromomethyl)-4-nitrobenzene	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) *δ*: 8.21-8.27 (m, 2H), 7.65 (s, 1H), 7.61 (m, 2H), 7.17-7.24 (m, 4H), 6.53 (s, 1H), 5.21 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H). LC-MS: *m/z* 379.5 $(M+H)^+$.
39	 Starting material: 4-Bromo-1-(4-	^{1}H NMR (Chloroform-d) *δ*: 7.94 (d, 1H), 7.62-7.68 (m, 3H), 7.59 (s, 1H), 7.48-7.54 (m, 2H), 7.15-7.25 (m, 4H), 6.51 (s, 1H), 5.12 (s, 2H), 4.03 (s, 4H), 3.75 (s, 2H). LC-MS: *m/z* 478.9

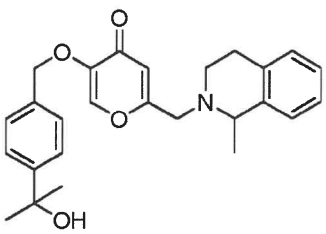
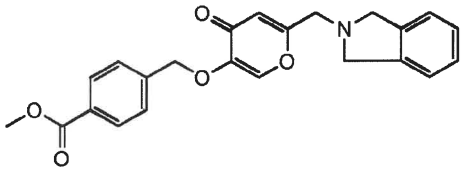
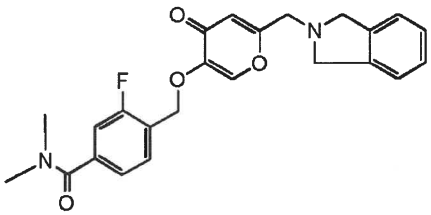
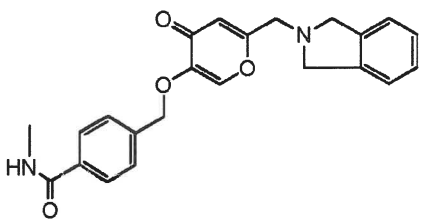
	(bromomethyl)phenyl)-1*H*-pyrazole	$(M+H)^+$.
40	 Starting material: Ethyl 1-(4-(bromo-methyl)phenyl)-1*H*-pyrazole-4-carboxylate	^{1}H NMR (Chloroform-d) δ: 8.41 (s, 1H), 8.10 (s, 1H), 7.68-7.77 (m, 2H), 7.60 (s, 1H), 7.49-7.57 (m, 2H), 7.15-7.24 (m, 4H), 6.51 (s, 1H), 5.14 (s, 2H), 4.34 (q, 2H), 4.03 (s, 4H), 3.76 (s, 2H), 1.38 (t, 3H). LC-MS: *m/z* 472.6 $(M+H)^+$.
41	 Starting material: 4-(Bromomethyl) benzonitrile	Conditions: MeOH:water, NaOH, reflux, B and E. 1H NMR (Chloro-form-d) δ: 7.65-7.70 (m, 2 H), 7.63 (s, 1 H), 7.52-7.56 (m, 2 H), 7.09-7.18 (m, 3 H), 6.96-7.02 (m, 1 H), 6.53 (s, 1 H), 5.14 (s, 2 H), 3.71 (s, 2 H), 3.54-3.56 (m, 2 H), 2.89-2.96 (m, 2 H), 2.80- 2.86 (m, 2 H), 1.57 (s, 3 H); LC-MS: m/z 373.4 (M+H) +.
42	 Starting material: 1-(Bromomethyl)-4-methylbenzene	Conditions: THF, reflux, B and A . 1H NMR (DMSO-d6) δ: 8.19 (s, 1 H), 7.30 (m, J=7.7 Hz, 2 H), 7.20 (m, J=7.6 Hz, 2 H), 7.07-7.14 (m, 3 H), 6.98-7.07 (m, 1 H), 6.40 (s, 1 H), 4.89 (s, 2 H), 3.60 (br d, 4 H), 2.66-2.87 (m, 4 H), 2.31 (s, 3 H); LC-MS: m/z 362.4 (M+H) +.
43	 Starting material: 4-(Bromomethyl) benzamide	Conditions: THF, reflux, A. 1H NMR (Chloroform-d) δ: 7.82 (m, 2 H), 7.58 (s, 1 H), 7.49 (m, 2 H), 7.08-7.17 (m, 3 H), 6.94-7.04 (m, 1 H), 6.52 (s, 1 H), 5.98-6.32 (m, 1 H), 5.54-5.86 (m, 1 H), 5.13 (s, 2 H), 3.70

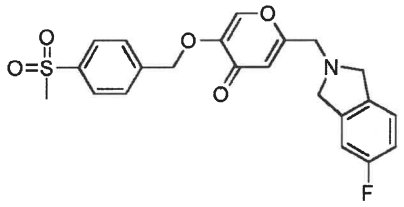
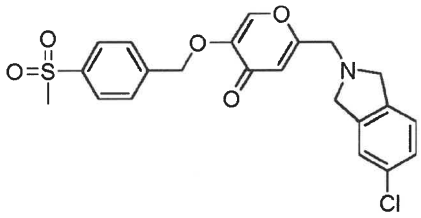
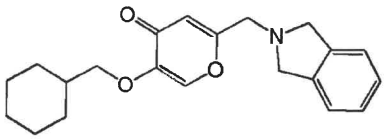
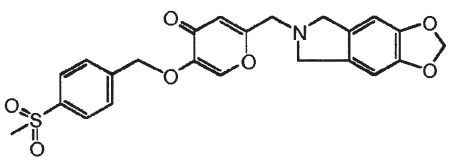
		(s, 2 H), 3.53 (s, 2 H), 2.88-2.96 (m, 2 H), 2.77-2.87 (m, 2 H); LC-MS: m/z 391.3 (M+H) +.
44	 Starting material: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: THF, reflux, B and E. 1H NMR (Chloroform-d) δ: 7.56 (s, 1 H), 7.47-7.51 (m, 2 H), 7.35-7.40 (m, 2 H), 7.04-7.17 (m, 4 H), 6.99 (d, J=6.6 Hz, 1 H), 6.50 (s, 1 H), 5.06 (s, 2 H), 3.69 (s, 2 H), 3.52 (s, 2 H), 2.87-2.97 (m, 2 H), 2.77-2.86 (m, 2 H); LC-MS: m/z 406.4 (M+H) +.
45	 Starting material: 4-(Bromomethyl) benzonitrile	Conditions: THF, reflux. 1H NMR (Chloroform-d) δ ppm 7.64-7.69 (m, 2 H), 7.63 (s, 1 H), 7.52-7.56 (m, 2 H), 7.11-7.23 (m, 4 H), 6.52 (s, 1 H), 5.14 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H); LC-MS: m/z 359.2 (M+H) +.
46	 Starting material: 1-(4-(Bromomethyl)-phenyl)-2-methylpropan-2-ol	Conditions: THF, reflux. 1H NMR (Chloroform-d) δ: 7.58 (s, 1 H), 7.31-7.38 (m, 2 H), 7.20-7.25 (m, 1 H), 7.07-7.17 (m, 3 H), 6.99 (d, J=6.6 Hz, 1 H), 6.50 (s, 1 H), 5.04 (s, 2 H), 3.69 (s, 2 H), 3.53 (s, 2 H), 2.87- 2.96 (m, 2 H), 2.78- 2.86 (m, 2 H), 2.76 (s, 2 H), 1.39 (s, 1 H), 1.19-1.23 (m, 6 H); LC-MS: m/z 420.4 (M+H) +.
47	 Starting material: 2-(4-(Bromomethyl)-phenyl)propan-2-ol	Conditions: THF, reflux, D. 1H NMR (Chloroform-d) δ: 7.55 (s, 1 H), 7.41-7.49 (m, 1 H), 7.33-7.40 (m, 1 H), 7.16-7.24 (m, 4 H), 6.49 (s, 1 H), 5.37 (s, 1 H), 5.05-5.12 (m, 3 H),

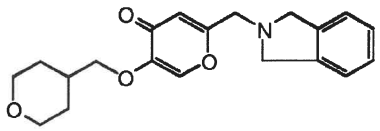
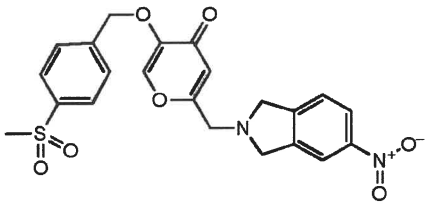
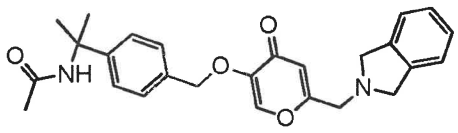
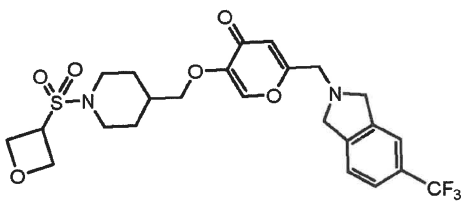
		4.02 (s, 4 H), 3.74 (s, 2 H), 2.14 (s, 3 H), 1.51-1.68 (m, 2 H); LC-MS: m/z 374.8 (M+H) +.
48	 Starting material: 4-(Bromomethyl)-*N*-methylbenzamide	Conditions: THF/DMF, reflux, C. 1H NMR (Chloroform-d) δ: 7.69-7.82 (m, 2 H), 7.57 (s, 1 H), 7.41-7.52 (m, 2 H), 7.07-7.18 (m, 3 H), 6.93-7.02 (m, 1 H), 6.51 (s, 1 H), 6.09-6.24 (m, 1 H), 5.12 (s, 2 H), 3.70 (s, 2 H), 3.53 (s, 2 H), 3.01 (d, J=4.9 Hz, 3 H), 2.88-2.96 (m, 2 H), 2.79-2.86 (m, 2 H); LC-MS: m/z 405.4 (M+H) +.
49	 Starting material: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: 70 °C. 1H NMR (Chloroform-d) δ: 7.56 (s, 1 H), 7.49 (m, J=8.4 Hz, 2 H), 7.37 (m, J=8.5 Hz, 2 H), 7.17-7.23 (m, 4 H), 6.49 (s, 1 H), 5.06 (s, 2 H), 4.02 (s, 4 H), 3.74 (s, 2 H), 1.57 (s, 6 H); LC-MS: m/z 392.5 (M+H) +.
50	 Starting material: 3-(Bromomethyl) benzonitrile	Conditions: THF, reflux, C. 1H NMR (Chloroform-d) δ: 7.71 - 7.75 (m, 1 H), 7.66-7.70 (m, 1 H), 7.59 - 7.66 (m, 2 H), 7.46-7.53 (m, 1 H), 7.09 - 7.25 (m, 3 H), 6.96 - 7.05 (m, 1 H), 6.53 (s, 1 H), 5.11 (s, 2 H), 3.71 (s, 2 H), 3.55 (s, 2 H), 2.90 - 2.96 (m, 2 H), 2.79 - 2.87 (m, 2 H); LC-MS: m/z 373.5 (M+H) +.
51		Conditions: THF, reflux, C, E and B. 1H NMR (Chloroform-d) δ: 7.70-7.75 (m, 1 H), 7.70 (s, 1 H), 7.47-7.52 (m,

	Starting material: 4-(Bromomethyl)-3-fluorobenzamide	1 H), 7.35-7.40 (m, 1 H), 7.09-7.18 (m, 3 H), 6.96-7.03 (m, 1 H), 6.53 (s, 1 H), 5.20 (s, 2 H), 3.71 (s, 2 H), 3.56 (s, 2 H), 2.90-2.96 (m, 2 H), 2.80-2.87 (m, 2 H); LC-MS: m/z 391.3 (M+H) +.
52	 Starting material: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: THF, reflux, C. 1H NMR (Chloroform-d) δ: 7.56 (s, 1 H), 7.26-7.52 (m, 5 H), 6.86-6.93 (m, 1 H), 6.68-6.72 (m, 1 H), 6.63 (s, 1 H), 6.49 (s, 1 H), 5.04-5.14 (m, 2 H), 3.72-3.83 (m, 3 H), 3.57-3.68 (m, 2 H), 3.51 (s, 2 H), 2.86-2.92 (m, 2 H), 2.73-2.84 (m, 2 H), 1.53-1.59 (m, 6 H); LC-MS: m/z 436.4 (M+H) +.
53	 Starting material: 4-(Bromomethyl) benzonitrile	Conditions: THF, reflux, C, E, B and D. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 7.89 (s, 1 H), 7.87 (s, 1 H), 7.60-7.64 (m, 2 H), 6.92-6.97 (m, 1 H), 6.66-6.71 (m, 2 H), 6.42 (s, 1 H), 5.07 (s, 2 H), 3.70 (s, 3 H), 3.57 (s, 2 H), 3.55 (s, 2 H), 2.65-2.86 (m, 4 H); LC-MS: m/z 403.3 (M+H) +.
54	 Starting material: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: 70 °C. 1H NMR (Chloro-form-d) δ: 7.55-7.61 (m, 1 H), 7.53 (s, 1 H), 7.40-7.48 (m, 1 H), 7.23-7.36 (m, 2 H), 7.08-7.17 (m, 3 H), 6.95-7.02 (m, 1 H), 6.50 (s, 1 H), 5.07 (s, 2 H), 3.69 (s, 2 H), 3.52 (s, 2 H), 2.87-2.97 (m, 2 H), 2.76-2.87 (m, 2 H), 1.96 (s, 1 H), 1.55-1.59 (m, 6 H); LC-

		MS: m/z 406.4 (M+H) +.
55	 Starting material: 4-(Bromomethyl)-3-fluorobenzamide	Conditions: 70°C, C, B and E. 1H NMR (Chloroform-d) δ: 7.65 (s, 1 H), 7.52-7.65 (m, 3 H), 7.09-7.17 (m, 3 H), 6.97-7.02 (m, 1 H), 6.53 (s, 1 H), 5.83-6.28 (m, 1 H), 5.32-5.77 (m, 1 H), 5.18 (s, 2 H), 3.71 (s, 2 H), 3.55 (s, 2 H), 2.90-2.97 (m, 2 H), 2.80-2.87 (m, 2 H); m/z 409.3 (M+H) +.
56	 Starting material: 4-(Bromomethyl)-3-fluorobenzamide	Conditions: 70 °C, C. 1H NMR (Chloroform-d) δ: 7.65 (s, 1 H), 7.61-7.64 (m, 1 H), 7.54-7.61 (m, 2 H), 7.18-7.26 (m, 4 H), 6.52 (s, 1 H), 6.04 (br s, 1 H), 5.60 (br s, 1 H), 5.20 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H); LC-MS: m/z 395.6 (M+H) +.
57	 Starting material: 4-(Bromomethyl) benzamide	1H NMR (DMSO-d6) δ: 8.23 (s, 1 H), 7.96-8.03 (m, 1 H), 7.85-7.94 (m, 2 H), 7.44-7.54 (m, 2 H), 7.34-7.40 (m, 1 H), 7.17-7.27 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H); LC-MS: m/z 377.6 (M+H) +.
58	 Starting material: 1-Bromo-4-(chloro-methyl)benzene	Conditions: 70°C, B and E. 1H NMR (Chloroform-d) δ: 7.56 (s, 1 H), 7.47-7.52 (m, 2 H), 7.27-7.30 (m, 2 H), 7.16-7.24 (m, 4 H), 6.48-6.51 (m, 1 H), 5.04 (s, 2 H), 4.03 (s, 4 H), 3.74-3.76 (m, 2 H); LC-MS: m/z 412.4 (M+H) +.

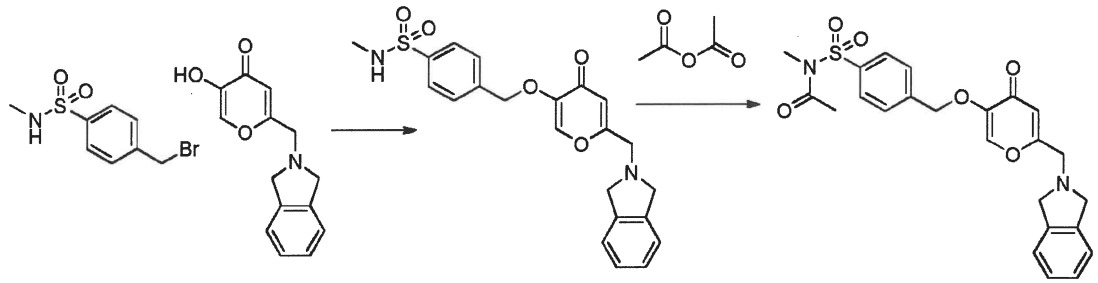
59	 Starting material: 4-(Bromomethyl)-α, α-dimethylbenzenemethanol	Conditions: 70 °C, E. 1H NMR (Chloroform-d) δ: 7.54 (s, 1 H), 7.46-7.52 (m, 2 H), 7.35-7.40 (m, 2 H), 7.03-7.18 (m, 4 H), 6.54 (s, 1 H), 5.06 (s, 2 H), 3.83-3.89 (m, 1 H), 3.57 (s, 2 H), 3.09-3.18 (m, 1 H), 2.84-2.96 (m, 1 H), 2.70-2.83 (m, 2 H), 1.71 (s, 1 H), 1.58 (s, 6 H), 1.35-1.40 (m, 3 H); LC-MS: m/z 420.5 (M+H) +.
60	 Starting material: 4-(Bromomethyl) benzoic acid, methyl ester	Conditions: 70 °C, D. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.98-8.02 (m, 2 H), 7.55-7.59 (m, 2 H), 7.16-7.26 (m, 4 H), 6.43 (s, 1 H), 5.06 (s, 2 H), 3.95 (s, 3 H), 3.89 (s, 1 H), 3.86 (s, 3 H), 3.77-3.83 (m, 2 H); LC-MS: m/z 392.3 (M+H) +.
61	 Starting material: 4-(Bromomethyl)-3-fluoro-*N,N*-dimethylbenzamide	Conditions: 70 °C, D. 1H NMR (Chloroform-d) δ: 7.65 (s, 1 H), 7.54-7.59 (m, 1 H), 7.21-7.23 (m, 4 H), 7.19-7.21 (m, 1 H), 7.14-7.17 (m, 1 H), 6.53 (s, 1 H), 5.15 (s, 2 H), 4.10 (s, 4 H), 3.82 (s, 2 H), 3.11 (br s, 3 H), 2.98 (br s, 3 H); LC-MS: m/z 423.4 (M+H) +.
62	 Starting material: 4-(Bromomethyl)-*N*-methylbenzamide	Conditions: 85 °C, C. 1H NMR (DMSO-d6) δ: 8.37-8.51 (m, 1 H), 8.23 (s, 1 H), 7.82-7.88 (m, 2 H), 7.46-7.52 (m, 2 H), 7.16-7.27 (m, 4 H), 6.42 (s, 1 H), 5.01 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 2.73-2.89 (m, 3 H); LC-MS: m/z 391.4 (M+H) +.

63	 Starting material: 1-(Bromomethyl)-4-(methylsulfonyl)benzene	Conditions: 85 °C, C. 1H NMR (DMSO-d6) δ: 8.32 (s, 1 H), 8.00-8.10 (m, 2 H), 7.71-7.81 (m, 2 H), 7.27-7.35 (m, 1 H), 7.12-7.20 (m, 1 H), 7.03-7.11 (m, 1 H), 6.49 (s, 1 H), 5.15 (s, 2 H), 3.99 (br d, J=13.3 Hz, 4 H), 3.85 (s, 2 H), 3.26 - 3.31 (m, 3 H); LC-MS: m/z 430.3 (M+H) +.
64	 Starting material: 1-(Bromomethyl)-4-(methylsulfonyl)benzene	Conditions: 80 °C, A. 1H NMR (DMSO-d6) δ: 8.26 (s, 1 H), 7.92-8.00 (m, 2 H), 7.65-7.73 (m, 2 H), 7.33 (s, 1 H), 7.26 (s, 2 H), 6.43 (s, 1 H), 5.09 (s, 2 H), 3.94 (br d, J=6.9 Hz, 4 H), 3.79 (s, 2 H), 3.22 (s, 3 H); LC-MS: m/z 446.3 (M+H) +.
65	 Starting material: (Bromomethyl)cyclohexane	Conditions: 65 °C, C. 1H NMR (DMSO-d6) δ: 8.12 (s, 1 H), 7.18-7.26 (m, 4 H), 6.37 (s, 1 H), 3.95 (s, 4 H), 3.78 (s, 2 H), 3.57-3.67 (m, 2 H), 1.61-1.81 (m, 6 H), 1.12-1.29 (m, 3 H), 0.94-1.07 (m, 2 H); LC-MS: m/z 340.7
66	 Starting material: 1-(Bromomethyl)-4-(methylsulfonyl)benzene	Conditions: 80°C, D. 1H NMR (DMSO-d6) δ: 8.26 (s, 1 H), 7.94-7.98 (m, 2 H), 7.67-7.71 (m, 2 H), 6.82 (s, 2 H), 6.42 (s, 1 H), 5.97 (s, 2 H), 5.09 (s, 2 H), 3.85 (s, 4 H), 3.76 (s, 2 H), 3.22-3.24 (m, 3 H); LC-MS: m/z 456.3 (M+H) +.

67	 Starting material: 2*H*- 4-(Bromo-methyl)tetrahydropyran	Conditions: 140 °C, D. 1H NMR (DMSO-d6) δ: 8.14-8.15 (m, 1 H), 7.18-7.26 (m, 4 H), 6.38 (s, 1 H), 3.95 (s, 4 H), 3.83-3.89 (m, 2 H), 3.78 (s, 2 H), 3.66-3.70 (m, 2 H), 3.28-3.36 (m, 3 H), 1.60-1.68 (m, 2 H), 1.22-1.33 (m, 2 H); LC-MS: m/z 342.7
68	 Starting material: 1-(Bromomethyl)-4-(methylsulfonyl)benzene	Conditions: E and A. 1H NMR (DMSO-d6) δ: 8.27 (s, 1 H), 8.15 (s, 1 H), 8.10-8.14 (m, 1 H), 7.93-7.99 (m, 2 H), 7.68-7.75 (m, 2 H), 7.51-7.55 (m, 1 H), 6.46 (s, 1 H), 5.10 (s, 2 H), 4.07 (s, 4 H), 3.84 (s, 2 H), 3.23 (s, 3 H); LC-MS: m/z 457.5
69	 Starting material: N-(2-(4-(Bromo-methyl)phenyl)propan-2-yl)acetamide	Conditions: 80 °C, D. 1H NMR (DMSO-d6) δ: 8.22 (s, 1 H), 8.15 (s, 1 H), 8.05 (s, 1 H), 7.31-7.33 (m, 4 H), 7.19-7.26 (m, 4 H), 6.40 (s, 1 H), 4.89 (s, 2 H), 3.95 (s, 4 H), 3.78-3.80 (m, 2 H), 1.82 (s, 2 H), 1.53 (s, 6 H); LC-MS: m/z 433.5 (M+H) +.
69a	 Starting material: 4-(Bromomethyl)-1-(oxetan-3-ylsulfonyl)piperidine	Conditions: DMSO, 80 °C, B. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.50 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 6.49 (s, 1H), 4.84-4.96 (m, 4H), 4.42 (m, 1H), 4.09 (s, 4H), 3.88 (br d, 2H), 3.79 (s, 2H), 3.74 (d, 2H), 2.82 (m, 2H), 2.00-2.09 (m, 1H), 1.97 (br d, 2H), 1.32-1.44 (m, 2H) LC-MS: *m/z* 529.2 $(M+H)^+$.

Example 2.

N-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-sulfonyl)-N-methylacetamide (Compound 70)

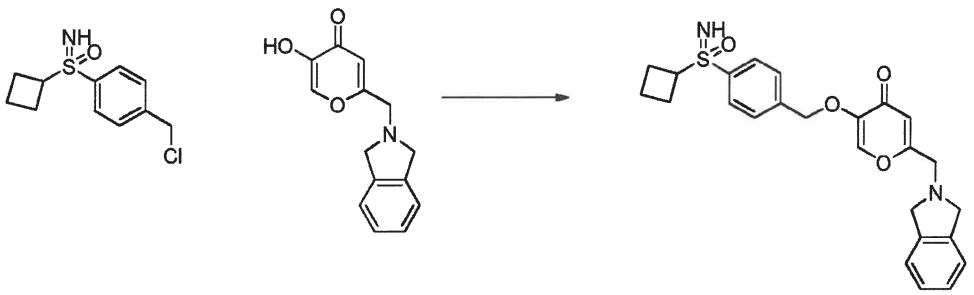


To a solution of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.36 g, 1.5 mmol) in DMF (5 ml) were added 4-methylsulfonylbenzyl bromide (0.40 g, 1.5 mmol) and K_2CO_3 (0.41 g, 2.9 mmol). The reaction mixture was heated at 60 °C for 1 h. The mixture was cooled to RT, water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated to afford 0.14 g of 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methylbenzenesulfonamide.

To a solution of 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N-methylbenzenesulfonamide (0.02 g, 0.05 mmol) in DCM (20 ml) were added acetic anhydride (0.24 g, 2,4 mmol) and zinc chloride (6.1 mg, 0.05 mmol). The reaction mixture was heated at 60 °C for 0.5 h. Water (5 ml) was added the product was extracted with DCM. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated to afford the crude product that was purified by column chromatography to afford 0.002 g of N-((4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)sulfonyl)-N-methylacetamide. ^{1}H NMR (Chloroform-d) δ: 7.88-7.92 (m, 2H), 7.66 (s, 1H), 7.63 (d, 2H), 7.20-7.23 (m, 4H), 6.54 (s, 1H), 5.17 (s, 2H), 4.05 (s, 4H), 3.78 (s, 2H), 3.30 (s, 3H), 2.39 (s, 3H). LC-MS: *m/z* 469.5 $(M+H)^+$.

Example 3.

5-((4-(Cyclobutanesulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 71)



To a solution of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.11 g, 0.46 mmol) in DMSO (4 ml) were added 1-(chloromethyl)-4-(cyclobutanesulfonimidoyl)benzene (0.14 g, 0.55 mmol) and K_2CO_3 (0.14 g, 1.0 mmol). The reaction mixture was heated at 80 °C for 2 h. The mixture was cooled to RT, water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography to afford (0.02 g) of 5-((4-(cyclobutanesulfonimidoyl)-benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one. ^{1}H NMR (Chloroform-d) δ: 7.94 (d, 2H), 7.64 (s, 1H), 7.59 (d, 2H), 7.18-7.24 (m, 4H), 6.54 (s, 1H), 5.14 (s, 2H), 4.07 (s, 4H), 3.87-3.95 (m, 1H), 3.80 (s, 2H), 2.58-2.68 (m, 1H), 2.39-2.51 (m, 1H), 2.21-2.33 (m, 1H), 1.89-2.07 (m, 3H)

The following compounds were prepared according to the procedure described for Compound 71 of Example 3 starting from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one or 5-hydroxy-2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one or a derivative thereof and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

Purification methods used:

A = Crystallization

B = Column chromatography

C = Precipitation in aqueous media

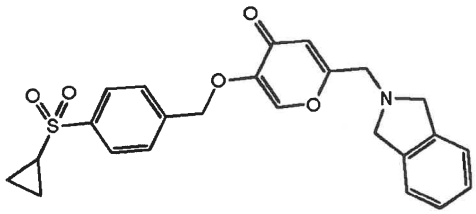
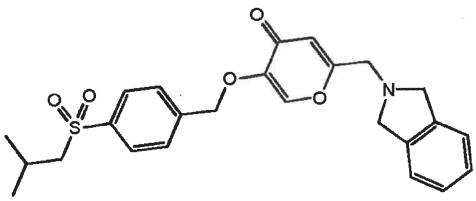
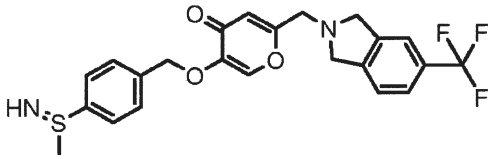
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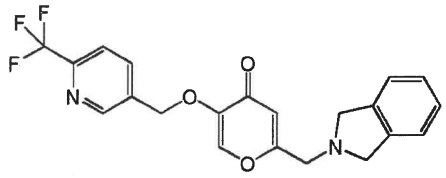
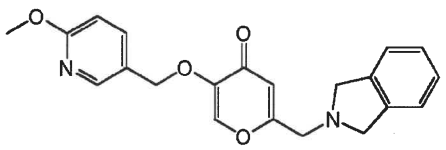
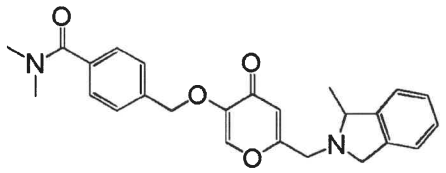
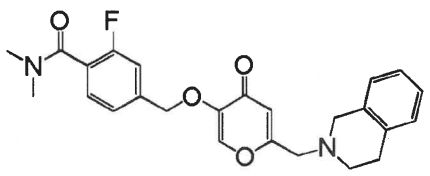
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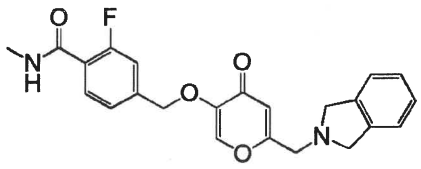
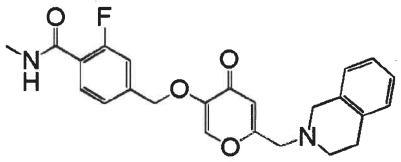
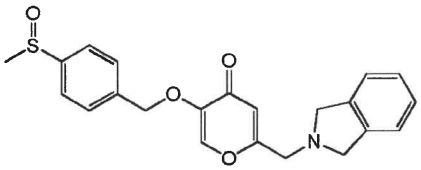
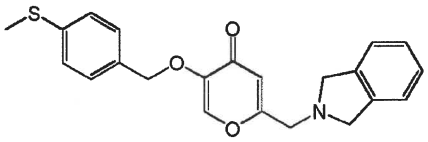
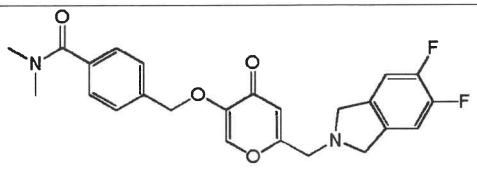
F = Salt formation

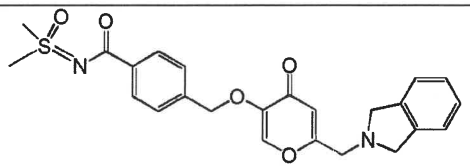
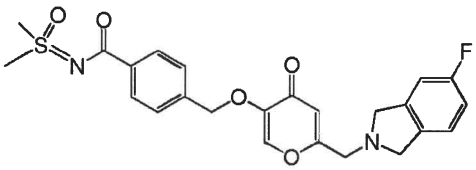
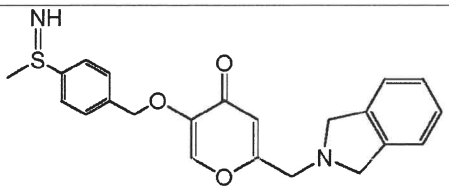
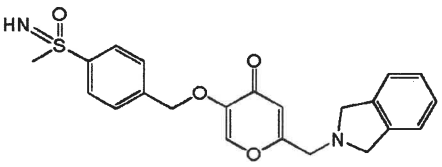
G = As such

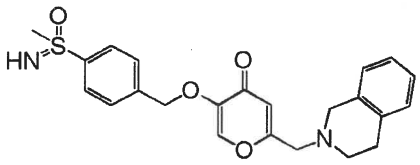
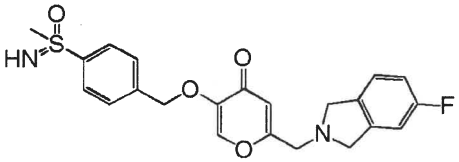
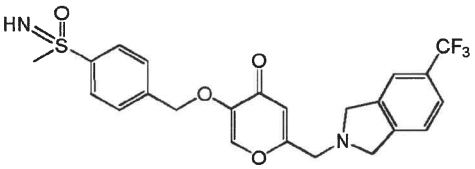
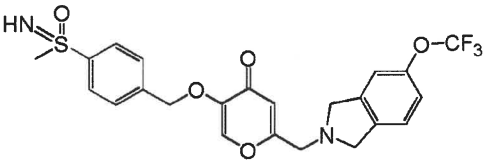
Alternative methods of preparation: NaOH/KOH in MeOH/EtOH, NaH in DMF, K_2CO_3 in THF/1,4-dioxane.

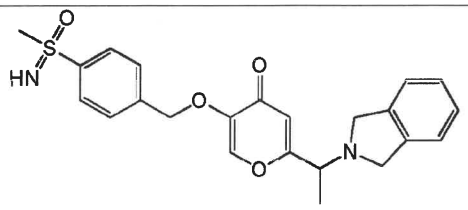
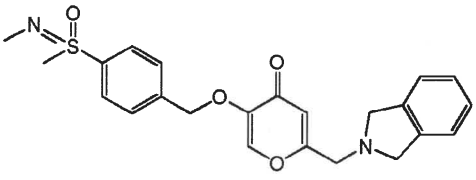
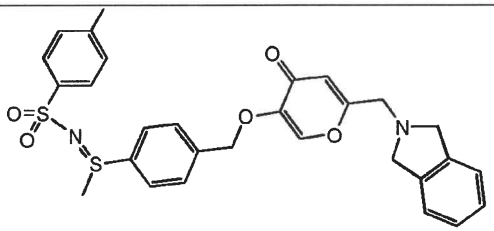
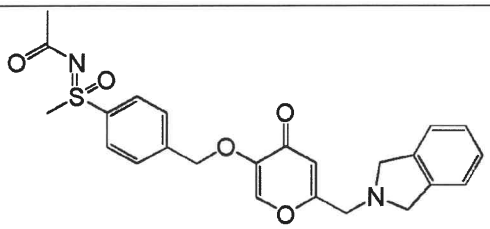
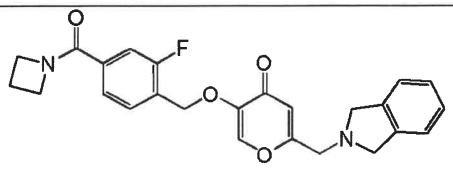
No	Structure and starting material	Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS
72	 Starting material:1-(Chloromethyl)-4-(cyclopropylsulfonyl)benzene	Conditions: DMF, 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.89-7.94 (m, 2H), 7.60-7.65 (m, 3H), 7.19-7.23 (m, 4H), 6.53 (s, 1H), 5.17 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 2.46 (m, 1H), 1.32-1.41 (m, 2H), 1.00-1.09 (m, 2H). LCMS: *m/z* 438.5 $(M+H)^+$.
73	 Starting material: 1-(Chloromethyl)-4-(isobutylsulfonyl)benzene	Conditions: DMF, 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.90-7.95 (m, 2H), 7.61-7.64 (m, 3H), 7.19-7.23 (m, 3H), 7.19-7.23 (m, 1H), 6.53 (s, 1H), 5.18 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 2.99 (d, 2H), 2.23 (dm, 1H), 1.06 (d, 6H). LC-MS: *m/z* 434.5 $(M+H)^+$.
74	 Starting material: (4-(Chloromethyl)-phenyl)(methyl)-λ4-sulfanimine	Conditions: DMSO, 80 °C, B. ^{1}H NMR (Chloroform-d) δ: 7.57-7.69 (m, 6H), 7.49 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 6.51 (s, 1H), 5.14 (s, 2H), 4.08 (s, 4H), 3.78 (s, 2H), 2.73 (s, 3H)

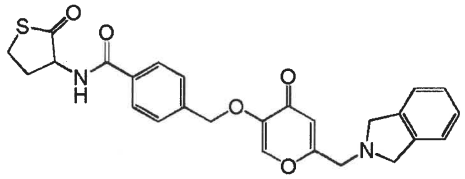
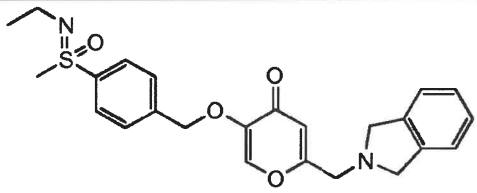
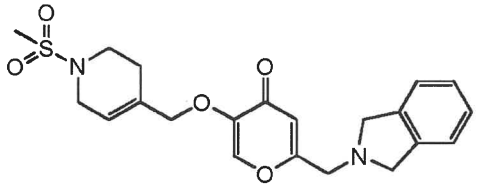
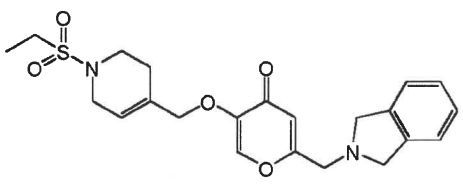
75	 Starting material: 5-(Chloromethyl)-2-(trifluoromethyl)pyridine	Conditions: 50 °C, C. ^{1}H NMR (Chloroform-d) δ: 8.75-8.74 (m, 1H), 8.04-8.01 (m, 1H), 7.71 (d, *J*=7.9 Hz, 1H), 7.10 (s, 1H), 7.24-7.19 (m, 4H), 6.54 (s, 1H), 5.22 (s, 2H), 4.05 (s, 4H), 3.79 (s, 2H); LC-MS: *m/z* 404.4 $(M+2)^+$.
76	 Starting material: 5-(Chloromethyl)-2-methoxypyridine	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 8.14 (d, 1H), 7.81-7.56 (m, 2H), 7.60 (s, 1H), 7.23-7.19 (m, 4H), 6.80-6.75 (m, 1H), 6.50 (s, 1H), 5.02 (s, 2H), 4.03 (s, 4H), 3.94 (s, 3H), 3.75 (s, 2H); LC-MS: *m/z* 365.3 $(M+1)^+$.
77	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: 50 °C, E (Et_2O). ^{1}H NMR (Methanol-d_4) δ: 8.11 (s, 1 H), 7.57 (d, 2 H), 7.46 (d, 2 H), 7.23 (m, 4 H), 6.60 (s, 1 H), 5.10 (s, 2 H), 4.22 (d, 1 H), 4.06 (m, 2 H), 3.79 (dd, 1 H), 3.69 (d, 1 H), 3.11 (s, 3 H), 3.00 (s, 3 H), 1.44 (d, 3 H); LC-MS: *m/z* 419.4 $(M+1)^+$.
78	 Starting material: 4-(Chloromethyl)-2-fluoro-N-methylbenzamide	Conditions: 60 °C, C and E (Et_2O). ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.37-7.42 (m, 1H), 7.16-7.25 (m, 2H), 7.08-7.16 (m, 3H), 6.97-7.02 (m, 1H), 6.47-6.57 (m, 1H), 5.09 (s, 2H), 3.71 (s, 2H), 3.55 (s, 2H), 3.13 (s, 3H), 2.90-2.97 (m, 5H), 2.81-2.86 (m, 2H); LC-MS: *m/z* 437.3 $(M+1)^+$.

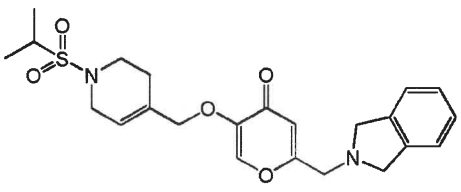
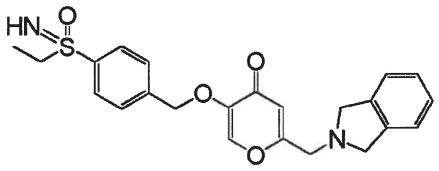
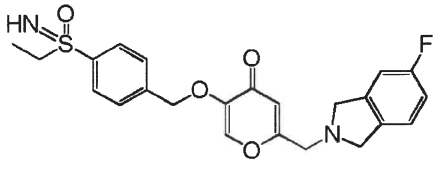
79	 Starting material: 4-(Chloromethyl)-2-fluoro-N-methylbenzamide	Conditions: 60 °C, C and E (Et_2O) ^{1}H NMR (Chloroform-d) δ: 8.11 (m, 1 H), 7.61 (m, 1 H), 7.26 (m, 2 H), 7.21 (m, 4 H), 6.72 (br d, 1 H), 6.52 (s, 1 H), 5.12 (s, 2 H), 4.04 (s, 4 H), 3.76 (s, 2 H), 3.04 (dd, 3 H); LC-MS: *m/z* 409.3 $(M+1)^+$.
80	 Starting material: 4-(Chloromethyl)-2-fluoro-N-methylbenzamide	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 8.11 (m, 1 H), 7.61 (s, 1 H), 7.26 (m, 2 H), 7.13 (m, 3 H), 6.99 (dd, 1 H), 6.72 (br d, 1 H), 6.53 (s, 1 H), 5.12 (s, 2 H), 3.71 (s, 2 H), 3.54 (s, 2 H), 3.04 (dd, 3 H), 2.93 (m, 2 H), 2.83 (m, 2 H); LC-MS: *m/z* 423.3 $(M+1)^+$.
81	 Starting material: 1-(Chloromethyl)-4-(methylsulfinyl)benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d δ: 7.66 (m, 2 H), 7.60 (m, 3 H), 7.21 (m, 4 H), 6.52 (s, 1 H), 5.14 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 2.73 (s, 3 H); LC-MS: *m/z* 396.3 $(M+1)^+$.
82	 Starting material: p-(Methylthio)benzyl chloride	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.55 (s, 1 H), 7.26 (m, 4 H), 7.20 (m, 4 H), 6.49 (s, 1 H), 5.04 (s, 2 H), 4.03 (s, 4 H), 3.74 (s, 2 H), 2.48 (s, 3 H); LC-MS: *m/z* 380.3 $(M+1)^+$.
82a	 Starting material: 4-Bromo-N,N-	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.56 (s, 1 H), 7.43 (m, 4 H), 7.00 (t, 2 H), 6.48 (s, 1 H), 5.11 (s, 2 H), 3.98 (s, 4 H),

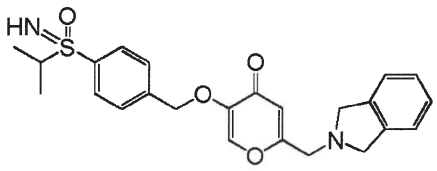
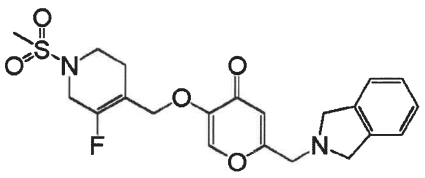
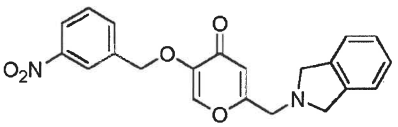
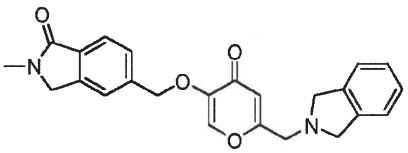
	dimethylbenzamide	3.74 (s, 2 H), 3.11 (s, 3 H), 2.97 (s, 3 H); LC-MS: *m/z* 441.4 $(M+1)^+$.
83	 Starting material: 4-(Chloromethyl)-*N*-(dimethyloxido-λ^4-sulfanylidene) benzamide	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 8.12 (d, 2 H), 7.54 (s, 1 H), 7.44 (d, 2 H), 7.22 (m, 4 H), 6.51 (s, 1 H), 5.14 (s, 2 H), 4.10 (br s, 4 H), 3.79 (s, 2 H), 3.39 (s, 6 H); LC-MS: *m/z* 453.2 $(M+1)^+$.
84	 Starting material: 4-(Chloromethyl)-*N*-(dimethyloxido-λ^4-sulfanylidene) benzamide	Conditions: 60 °C, B and E (EtOH). ^{1}H NMR (Chloroform-d) δ: 8.12 (m, 2 H), 7.53 (s, 1 H), 7.44 (m, 2 H), 7.13 (dd, 1 H), 6.90 (m, 2 H), 6.49 (s, 1 H), 5.15 (s, 2 H), 4.00 (s, 2 H), 3.97 (s, 2 H), 3.73 (m, 2 H), 3.39 (s, 6 H); LC-MS: *m/z* 471.3 $(M+1)^+$.
85	 Starting material: 4-Methyl-*N*-[(*S*)-methyl(4-chloromethylphenyl)-λ^4-sulfanylidene]benzenesulfonamide	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.66 (m, 2 H), 7.60 (m, 3 H), 7.21 (m, 4 H), 6.52 (s, 1 H), 5.14 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 2.73 (s, 3 H), 1.66 (s, 1H); LC-MS: *m/z* 396.4 $(M+2)^+$.
86	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 8.02 (m, 2 H), 7.62 (m, 3 H), 7.21 (m, 4 H), 6.52 (s, 1 H), 5.17 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 3.11 (s, 3 H), 2.69 (br s, 1 H); LC-MS: *m/z* 411.3 $(M+1)^+$.

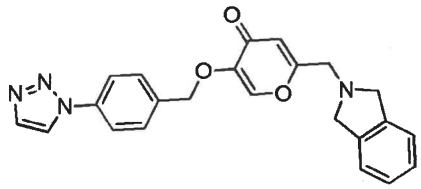
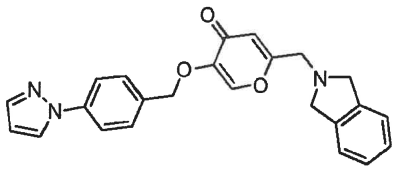
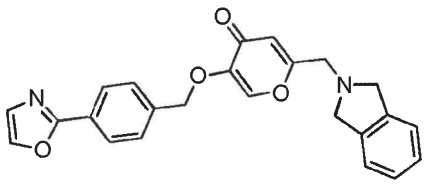
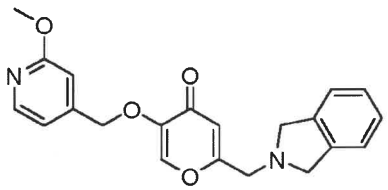
87	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 8.02 (m, 2 H), 7.62 (m, 3 H), 7.13 (m, 3 H), 6.99 (dd, 1 H), 6.53 (s, 1 H), 5.17 (s, 2 H), 3.71 (s, 2 H), 3.55 (s, 2 H), 3.11 (s, 3 H), 2.93 (m, 2 H), 2.84 (m, 2 H), 2.69 (br s, 1 H); LC-MS: *m/z* 425.4 $(M+1)^+$.
88	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	Conditions: 60 °C, C and A (IPA). ^{1}H NMR (Chloroform-d) δ: 8.02 (d, 2 H), 7.62 (m, 3 H), 7.13 (dd, 1 H), 6.91 (m, 2 H), 6.51 (s, 1 H), 5.17 (s, 2 H), 4.02 (br s, 2 H), 3.99 (br s, 2 H), 3.76 (s, 2 H), 3.11 (s, 3 H), 2.70 (br s, 1 H); LC-MS: *m/z* 429.2 $(M+1)^+$.
89	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 8.04-8.01 (m, 2H), 7.64 (s, 1H), 7.63-7.60 (m, 2H), 7.48-7.51 (m, 1H), 7.46 (s, 1H) 7.33-7.30 (m, 1H), 6.52 (s, 1H), 5.12 (s, 2H), 4.09 (s, 4H), 3.79 (s, 2H), 3.11 (s, 3H), 2.69 (s, 1H); LC-MS: *m/z* 479.3 $(M+1)^+$.
90	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	Conditions: C. ^{1}H NMR (Chloroform-d) δ: 8.03 (d, 2H), 7.58-7.65 (m, 3H), 7.21 (d, 1H), 7.05-7.11 (m, 2H), 6.51 (s, 1H), 5.17 (s, 2H), 4.04 (br d, 4H), 3.77 (s, 2H), 3.11 (d, 3H), 2.70 (s, 1H); LC-MS: *m/z* 495.3 $(M+1)^+$.

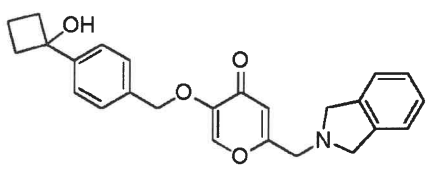
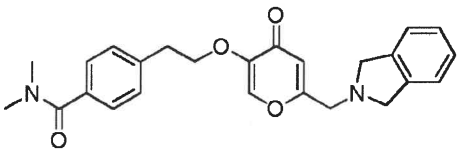
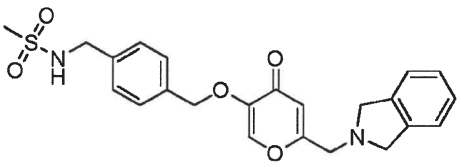
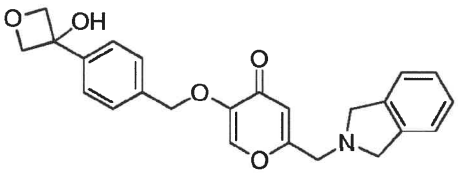
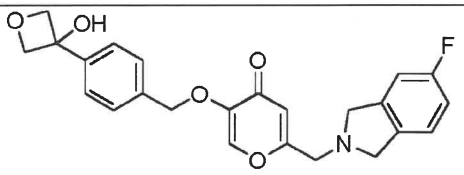
91	 Starting material: 1-(Chloromethyl)-4-(S-methylsulfonimidoyl)benzene	^{1}H NMR (Chloroform-d) δ: 8.03 (m, 2 H), 7.66 (d, 1 H), 7.62 (d, 2 H), 7.20 (m, 4 H), 6.49 (s, 1 H), 5.17 (s, 2 H), 3.98 (m, 4 H), 3.64 (q, 1 H), 3.11 (s, 3 H), 2.7 (br, 1H), 1.51 (d, 3 H); LC-MS: *m/z* 425.3 $(M+1)^+$.
92	 (formate) Starting material: *N,S*-dimethyl-*S*-(4-chloromethylphenyl)sulfoximine	Conditions: 60 °C, D. ^{1}H NMR (Chloroform-d) δ: 8.08 (s, 1 H), 7.93 (m, 2 H), 7.68 (s, 1 H), 7.65 (m, 2 H), 7.22 (m, 4 H), 6.56 (s, 1 H), 5.16 (s, 2 H), 4.09 (s, 4 H), 3.82 (s, 2 H), 3.16 (s, 3 H), 2.63 (s, 3 H); LC-MS: *m/z* 425.4 $(M+1)^+$.
93	 Starting material: N-((4-(Chloro-methyl)phenyl)methyl)-λ4-sulfanyli-dene)-4-methylbenzenesulfonamide	Conditions: 60 °C, C and E (EtOH). ^{1}H NMR (Chloroform-d) δ: 7.73 (m, 4 H), 7.63 (s, 1 H), 7.57 (m, 2 H), 7.20 (m, 6 H), 6.52 (s, 1 H), 5.11 (s, 2 H), 4.04 (s, 4 H), 3.78 (s, 2 H), 2.83 (m, 3 H), 2.36 (s, 3 H); LC-MS: *m/z* 549.5 $(M+1)^+$.
94	 Starting material: 1-(Chloromethyl)-4-(*N*-acetyl-*S*-methylsulfonimidoyl)-benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.99 (m, 2 H), 7.65 (m, 3 H), 7.21 (m, 4 H), 6.53 (s, 1 H), 5.18 (s, 2 H), 4.05 (s, 4 H), 3.78 (s, 2 H), 3.33 (s, 3 H), 2.16 (s, 3 H); LC-MS: *m/z* 453.5 $(M+1)^+$.
95		Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.64 (s, 1 H), 7.57 (m, 1 H), 7.39 (m, 2 H), 7.21

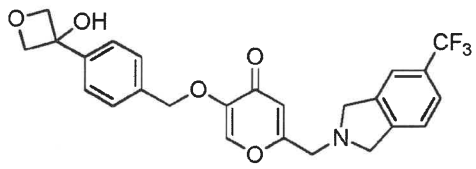
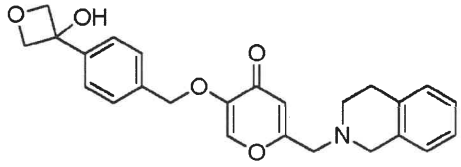
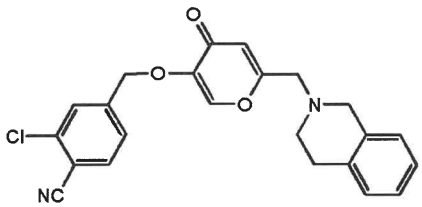
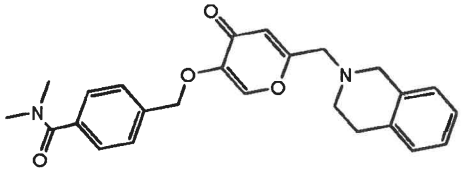
	Starting material: Azetidin-1-yl(4-(chloromethyl)-3-fluorophenyl)-methanone	(m, 4 H), 6.51 (s, 1 H), 5.16 (s, 2 H), 4.26 (m, 4 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 2.36 (m, 2 H); LC-MS: *m/z* 435.5 $(M+1)^+$.
96	 Starting material: 4-(Chloromethyl)-N-(2-oxotetrahydrothiophen-3-yl)-benzamide	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.81 (d, 2 H), 7.56 (s, 1 H), 7.49 (d, 2 H), 7.21 (s, 4 H), 6.61 (br d, 1 H), 6.51 (s, 1 H), 5.15 (s, 2 H), 4.67 (dt, 1 H), 4.03 (s, 4 H), 3.75 (s, 2 H), 3.43 (m, 1 H), 3.32 (m, 1 H), 3.11 (m, 1 H), 2.03 (qd, 1 H); LC-MS: *m/z* 477.4 $(M+1)^+$.
97	 Starting material: 1-(Chloromethyl)-4-(*N*-ethyl-*S*-methylsulfonimidoyl)-benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.92 (m, 2 H), 7.65 (s, 1 H), 7.62 (m, 2 H), 7.21 (m, 4 H), 6.53 (s, 1 H), 5.16 (s, 2 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 3.08 (m, 3 H), 3.02 (m, 1 H), 2.85 (dq, 1 H), 1.18 (t, 3 H); LC-MS: *m/z* 439.1 $(M+1)^+$.
98	 Starting material: 4-(Chloromethyl)-1-(methylsulfonyl)-1,2,3,6-tetrahydro-pyridine	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.65 (s, 1 H), 7.21 (m, 4 H), 6.50 (s, 1 H), 5.83 (m, 1 H), 4.45 (s, 2 H), 4.05 (s, 4 H), 3.82 (m, 2 H), 3.78 (s, 2 H), 3.42 (t, 2 H), 2.82 (s, 3 H), 2.36 (br d, 2 H); LC-MS: *m/z* 417.8 $(M+1)^+$.
99	 Starting material: 4-(Chloromethyl)-1-	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.65 (s, 1H), 7.24-7.18 (m, 4H), 6.49 (s, 1H), 5.83-5.80 (m, 1H), 4.43 (s, 2H), 4.05 (s, 4H), 3.88-3.85 (m, 2H), 3.77 (s,

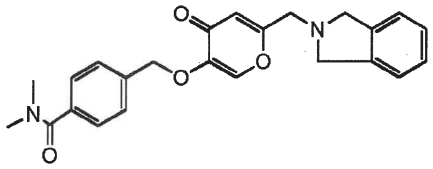
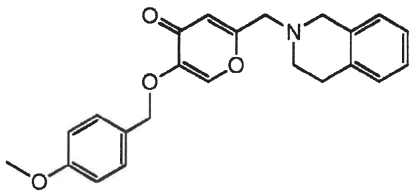
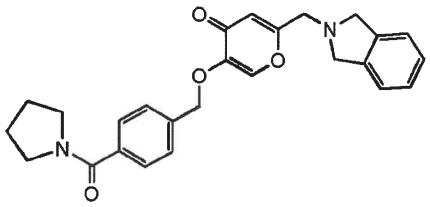
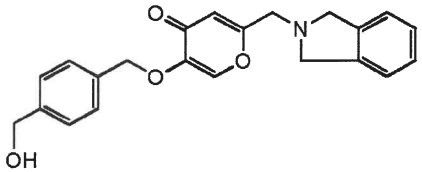
	(ethylsulfonyl)-1,2,3,6-tetrahydro-pyridine	2H), 3.47 (t, 2H, J = 5.7 Hz), 2.98 (q, 2H, J = 7.3 Hz), 2.35-2.30 (m, 2H), 1.36 (t, 3H, J=7.4 Hz); LC-MS: *m/z* 431.9 $(M+1)^+$.
100	 Starting material: 4-(Chloromethyl)-1-(isopropylsulfonyl)-1,2,3,6-tetrahydro-pyridine	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.64 (s, 1H), 7.23.7.18 (m, 4H), 6.49 (s, 1H), 5.83-5.80 (m, 1H), 4.43 (s, 2H), 4.04 (s, 4H), 3.92-3.89 (m, 2H), 3.78 (s, 2H), 3.50 (t, 2H, J=5.7 Hz), 3.23-3.16 (m, 1H), 2.39-2.29 (m, 2H), 1.34 (d, 6H, J=6.8 Hz); LC-MS: *m/z* 446.0 $(M+1)^+$.
101	 Starting material: 1-(Chloromethyl)-4-(ethylsulfonimidoyl)benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.99-7.96 (m, 2H), 7.63 (s, 1H), 7.62-7.59 (m, 2H), 7.23-7.19 (m, 4H), 6.52 (s, 1H), 5.17 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.20-3.14 (m, 2H), 2.4 (br, 1H) 1.28-1.24 (m, 3H); LC-MS: *m/z* 425.3 $(M+1)^+$.
102	 Starting material: 1-(Chloromethyl)-4-(ethylsulfonimidoyl)benzene	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.99-7.96 (m, 2H), 7.63 (s, 1H), 7.62-7.59 (m, 2H), 7.15-7.11 (m, 1H), 6.94-6.88 (m, 2H), 6.51 (s, 1H), 5.17 (s, 2H), 4.03-3.98 (m, 4H), 3.76 (s, 2H), 3.30-3.14 (m, 2H), 2.7 (br, 1H), 1.28-1,24 (m, 3H); LC-MS: *m/z* 443.3 $(M+1)^+$.

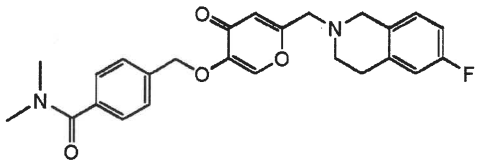
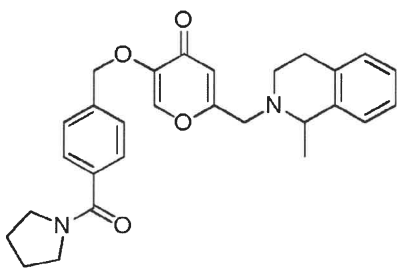
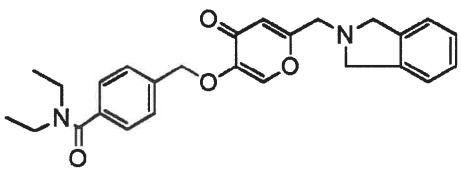
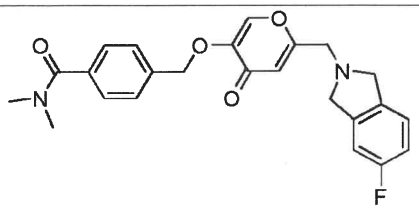
103	 Starting material: 1-(Chloromethyl)-4-(propan-2-ylsulfonimidoyl)benzene	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.97-7.93 (m, 2H), 7.63 (s, 1H), 7.61-7.58 (m, 2H), 7.23-7.18 (m, 4H), 6.62 (s, 1H), 5.17 (s, 2H), 4.06-4.03 (m, 4H), 3.77 (d, 2H, J= 0.52 Hz), 3.29-3.18 (m, 1H), 1.33-1.25 (m, 7H); LC-MS: *m/z* 439.2 $(M+1)^+$.
104	 Starting material: 4-(Chloromethyl)-5-fluoro-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.66 (s, 1H), 7.24-7.18 (m, 4H), 6.50 (s, 1H), 4.62 (s, 2H), 4.05 (s, 4H), 3.88 (s, 2H), 3.78 (s, 2H), 3.40 (m, 2H), 2.86 (s, 3H), 2.40-2.53 (m, 2H); LC-MS: *m/z* 435.8 $(M+1)^+$.
105	 Starting material: 1-(Chloromethyl)-3-nitrobenzene	Conditions: DMF, 60 °C, C. ^{1}H NMR (Chloroform-d) *δ*: 8.24-8.32 (m, 1H), 8.20 (br d, 1H), 7.72-7.87 (m, 1H), 7.68 (s, 1H), 7.57 (m, 1H), 7.21 (s, 4H), 6.53 (s, 1H), 5.19 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H). LC-MS: *m/z* 379.3 $(M+H)^+$.
106	 Starting material: 5-(Chloromethyl)-2-methylisoindolin-1-one	Conditions: DMF, RT, C. ^{1}H NMR (Chloroform-d) *δ*: 7.83 (d, 1H), 7.61 (s, 1H), 7.57 (m, 1H), 7.45 (m, 1H), 7.16-7.24 (m, 4H), 6.52 (s, 1H), 5.16 (s, 2H), 4.38 (s, 2H), 4.04 (s, 4H), 3.76 (s, 2H), 3.20 (s, 3H). LC-MS: *m/z* 403.4 $(M+H)^+$.

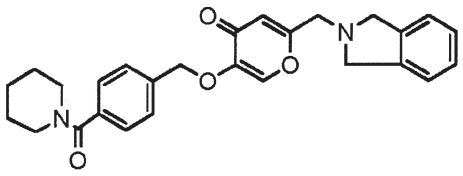
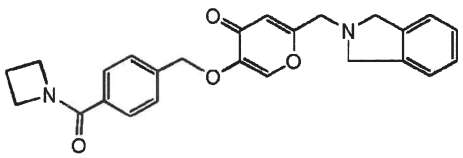
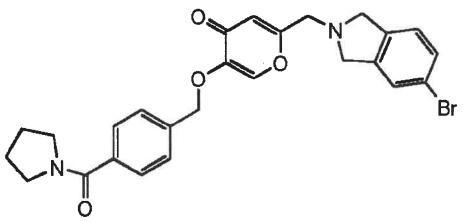
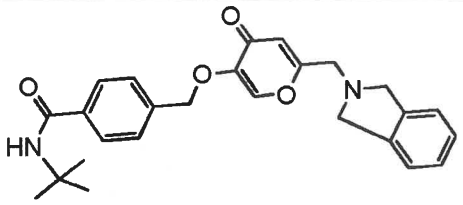
107	 Starting material: 1-(4-(Chloromethyl)-phenyl)-1H-1,2,3-triazole	Conditions: DMF, 60 °C. ^{1}H NMR (Chloroform-d) δ: 8.00 (d, 1H), 7.86 (d, 1H), 7.74-7.79 (m, 2H), 7.63 (s, 1H), 7.60 (d, 2H), 7.17-7.24 (m, 4H), 6.52 (s, 1H), 5.17 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H). LC-MS: *m/z* 401.5 $(M+H)^+$.
108	 Starting material: 1-(4-(Chloromethyl)-phenyl)-1*H*-pyrazole	Conditions: DMF, 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.93 (d, 1H), 7.67-7.75 (m, 3H), 7.58 (s, 1H), 7.50 (d, 2H), 7.16-7.23 (m, 4H), 6.51 (s, 1H), 6.45-6.49 (m, 1H), 5.13 (s, 2H), 4.03 (s, 4H), 3.75 (s, 2H). LC-MS: *m/z* 400.5 $(M+H)^+$.
109	 Starting material: 2-(4-(Chloromethyl)-phenyl)oxazole	Conditions: DMF, 60 °C. ^{1}H NMR (Chloroform-d) δ: 8.06 (d, 2H), 7.72 (s, 1H), 7.59 (s, 1H), 7.51 (d, 2H), 7.24 (s, 1H), 7.20 (d, 4H), 6.51 (s, 1H), 5.09-5.17 (m, 2H), 4.03 (s, 4H), 3.75 (s, 2H). LC-MS: *m/z* 401.5 $(M+H)^+$.
110	 Starting material: 4-(Chloromethyl)-2-methoxypyridine	Conditions: C. ^{1}H NMR (Chloroform-d) δ: 8.16 (dd, 1H), 7.58 (s, 1H), 7.18-7.24 (m, 4H), 6.89-6.92 (m, 1H), 6.76-6.78 (m, 1H), 6.51 (m, 1H), 5.07 (s, 2H), 4.04 (s, 4H), 3.94 (s, 3H), 3.76 (d, 2H). LC-MS: *m/z* 365.3 $(M+H)^+$

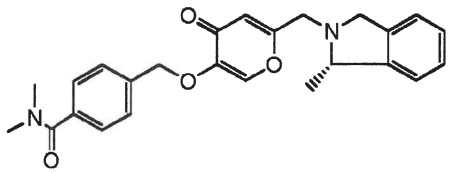
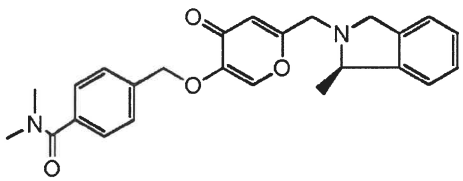
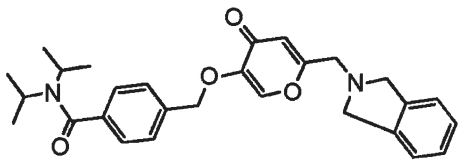
111	 Starting material: 1-(4-(Chloromethyl)-phenyl)cyclobutanol	^{1}H NMR (Chloroform-d) δ: 7.56 (s, 1H), 7.48-7.52 (m, 2H), 7.38-7.42 (m, 2H), 7.16-7.23 (m, 4H), 6.48 (m, 1H), 5.07 (s, 2H), 4.01 (s, 4H), 3.73 (d, 2H), 2.49-2.58 (m, 2H), 2.31-2.41 (m, 2H), 1.96-2.06 (m, 1H), 1.62-1.74 (m, 1H). LC-MS: *m/z* 404.4 $(M+H)^+$
112	 Starting material: 4-(2-Chloroethyl)-*N,N*-dimethylbenzamide	^{1}H NMR (Chloroform-d) δ: 7.56 (s, 1H), 7.35-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.17-7.24 (m, 4H), 6.49 (m, 1H), 4.11 (t, 2H), 4.04 (s, 4H), 3.76 (d, 2H), 3.15 (t, 2H), 3.10 (br s, 3H), 2.98 (s, 3H). LC-MS: *m/z* 419.4 $(M+H)^+$
113	 Starting material: N-(4-(Chloro-methyl)benzyl)methanesulfonamide	Conditions: 60 °C, B. 1H NMR (DMSO-d6) δ: 8.21 (s, 1H), 7.58 (t, 1H), 7.35-7.44 (m, 4H), 7.17-7.28 (m, 4H), 6.42 (s, 1H), 4.95 (s, 2H), 4.17 (d, 2H), 3.96 (s, 4H), 3.80 (s, 2H), 2.86 (s, 3H). LC-MS: m/z 441.8 (M+H)+
114	 Starting material: 3-(4-(Chloromethyl)-phenyl)oxetan-3-ol	^{1}H NMR (Chloroform-d) δ: 7.59-7.64 (m, 2H), 7.58 (s, 1H), 7.45-7.49 (m, 2H), 7.18-7.23 (m, 4H), 6.50 (s, 1H), 5.10 (s, 2H), 4.88-4.94 (m, 4H), 4.03 (s, 4H), 3.75 (s, 2H), 2.52 (s, 1H). LC-MS: *m/z* 406.5 $(M+H)^+$
115	 Starting material: 3-(4-(Chloromethyl)-phenyl)oxetan-3-ol	^{1}H NMR (Chloroform-d) δ: 7.60-7.63 (m, 2H), 7.58 (s, 1H), 7.45-7.49 (m, 2H), 7.10-7.15 (m, 1H), 6.87-6.94 (m, 2H), 6.49 (m, 1H), 5.10 (s, 2H), 4.88-4.94 (m, 4H), 4.01 (m, 2H), 3.98 (m,

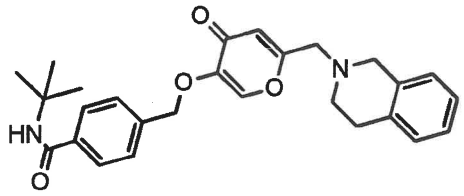
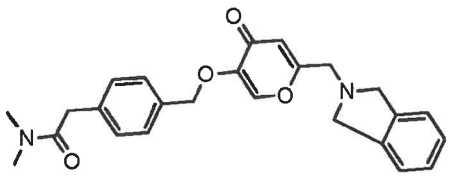
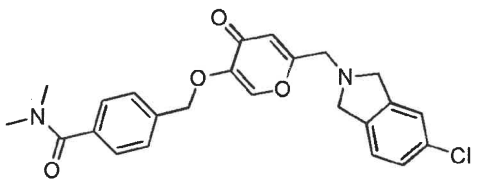
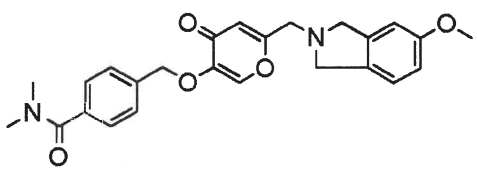
		2H), 3.74 (d, 2H), 2.52 (s, 1H). LC-MS: *m/z* 424.5 $(M+H)^+$
116	 Starting material:3-(4-(Chloromethyl)-phenyl)oxetan-3-ol	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.60-7.64 (m, 2H), 7.58 (s, 1H), 7.44-7.52 (m, 4H), 7.31 (d, 1H), 6.50 (s, 1H), 5.10 (s, 2H), 4.87-4.95 (m, 4H), 4.07 (s, 4H), 3.77 (s, 2H). LC-MS: *m/z* 474.8 $(M+H)^+$
117	 Starting material:3-(4-(Chloromethyl)-phenyl)oxetan-3-ol	Conditions: 60 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.59-7.64 (m, 2H), 7.57 (s, 1H), 7.45-7.49 (m, 2H), 7.08-7.16 (m, 3H), 6.97-7.01 (m, 1H), 6.51 (s, 1H), 5.10 (s, 2H), 4.88-4.94 (m, 4H), 3.70 (s, 2H), 3.53 (s, 2H), 2.92 (t, 2H), 2.82 (t, 2H), 2.49 (s, 1H). LC-MS: *m/z* 420.8 $(M+H)^+$
118	 Starting material: 3-Chloro-4-cyano-benzyl methanesulfonate	Conditions: THF, reflux, C. 1H NMR (DMSO-d6) δ: 8.27 (s, 1 H), 8.02 (m, J=7.9 Hz, 1 H), 7.80 (s, 1 H), 7.59 (m, J=7.9 Hz, 1 H), 7.11 (br s, 3 H), 6.98-7.08 (m, 1 H), 6.45 (s, 1 H), 5.08 (s, 2 H), 3.63 (s, 2 H), 3.60 (br s, 2 H), 2.72-2.92 (m, 4 H); LC-MS: m/z 407.7 (M+H) +.
119	 Starting material: 4-(Chloromethyl)-*N*,	Conditions: THF, reflux. 1H NMR (Chloroform-d) δ: 7.57 (s, 1 H), 7.39-7.47 (m, 1 H), 7.39-7.47 (m, 3 H), 7.09-7.18 (m, 3 H), 6.96-7.01 (m, 1 H), 6.51 (s, 1 H), 5.10 (s, 2 H), 3.70

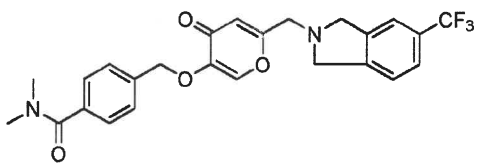
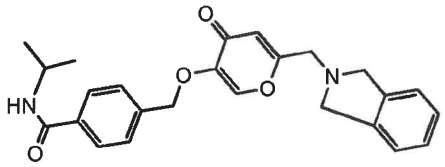
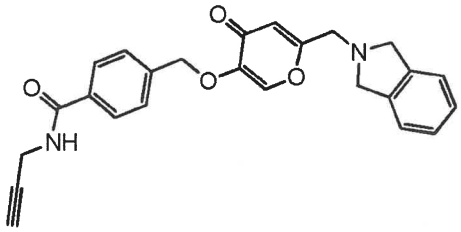
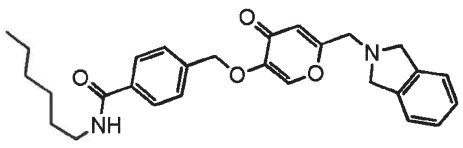
	N-dimethylbenzamide	(s, 2 H), 3.53 (s, 2 H), 3.11 (br s, 3 H), 2.95-3.03 (m, 3 H), 2.90-2.95 (m, 2 H), 2.79-2.86 (m, 2 H); LC-MS: m/z 419.4 (M+H) +.
120	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: THF/DMF, reflux, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.46-7.51 (m, 2 H), 7.44 (s, 2 H), 7.18-7.26 (m, 4 H), 6.43 (s, 1 H), 4.99 (s, 2 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 2.98 (br s, 3 H), 2.91 (br s, 3 H). LC-MS: m/z 405.3 (M+H) +.
121	 Starting material: 1-(Chloromethyl)-4-methoxybenzene	Conditions: DMF, 70 °C. 1H NMR (Chloroform-d) δ ppm 7.54 (s, 1 H), 7.30-7.36 (m, 2 H), 7.13 (s, 3 H), 6.95-7.01 (m, 1 H), 6.89 (m, J=8.7 Hz, 2 H), 6.49 (s, 1 H), 5.02 (s, 2 H), 3.80 (s, 3 H), 3.69 (s, 2 H), 3.52 (s, 2 H), 2.87-2.96 (m, 2 H), 2.81 (s, 2 H); LC-MS: m/z 378.8 (M+H) +.
122	 Starting material: [4-(Chloromethyl) phenyl]-1-pyrrolidinylethanone	Conditions: DMF, 70°C, C and E. 1H NMR (400 MHz, DMSO-d6) δ: 8.23 (s, 1 H), 7.41-7.59 (m, 4 H), 7.13 - 7.31 (m, 4 H), 6.42 (s, 1 H), 4.99 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.36 - 3.53 (m, 4 H), 1.72 - 1.94 (m, 4 H); LC-MS: m/z 431.4 (M+H) +.
123	 Starting material: 4-(Chloromethyl)	Conditions: B and E. 1H NMR (DMSO-d6) δ: 8.19 (s, 1 H), 7.32-7.42 (m, 4 H), 7.18-7.26 (m, 4 H), 6.41 (s, 1 H), 5.16-5.28 (m, 1 H), 4.86-4.96 (m, 2 H), 4.47-4.55 (m, 2

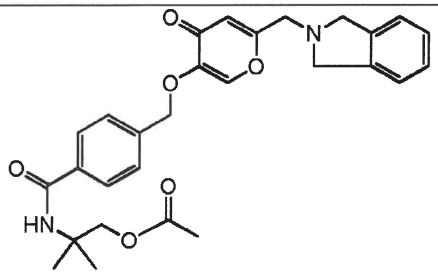
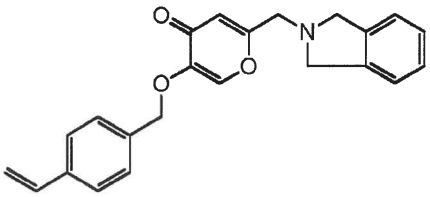
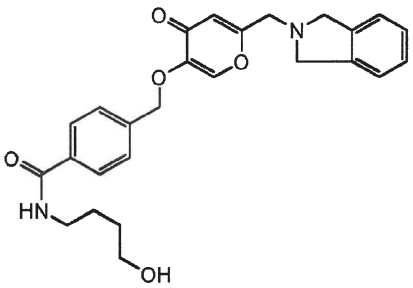
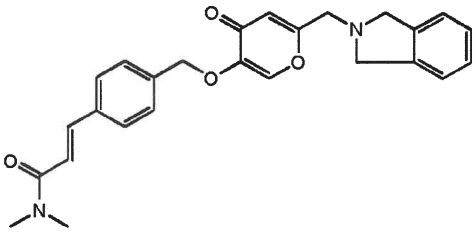
	benzenemethanol	H), 3.95 (s, 4 H), 3.78 (s, 2 H); LC-MS: m/z 364.2 (M+H) +.
124	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 70 °C, D. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.41-7.49 (m, 4 H), 7.03-7.13 (m, 1 H), 6.91-6.97 (m, 2 H), 6.42 (s, 1 H), 4.98 (s, 2 H), 3.59 (s, 4 H), 2.98 (br s, 3 H), 2.90 (br s, 3 H), 2.80-2.87 (m, 2 H), 2.71-2.78 (m, 2 H); LC-MS: m/z 437.5 (M+H) +.
125	 Starting material: [4-(Chloromethyl) phenyl]-1-pyrrolidinylmethanone	Conditions: DMF, 70 °C, G. 1H NMR (Chloroform-d) δ ppm 7.51-7.54 (m, 3 H), 7.41-7.46 (m, 2 H), 7.03-7.26 (m, 4 H), 6.55 (s, 1 H), 5.10 (s, 2 H), 3.61-3.67 (m, 2 H), 3.58 (s, 2 H), 3.37-3.45 (m, 2 H), 2.76 (s, 2 H), 1.93-2.00 (m, 2 H), 1.84-1.92 (m, 2 H), 1.56 (s, 3 H), 1.38 (d, J=6.7 Hz, 3 H); LC-MS: m/z 459.7 (M+H) +.
126	 Starting material: 4-(Chloromethyl)-*N,N*-diethylbenzamide	Conditions: DMF, 70°C. 1H NMR (Chloroform-d) δ: 7.58 (s, 1 H), 7.42-7.46 (m, 2 H), 7.36-7.39 (m, 2 H), 7.17-7.23 (m, 4 H), 6.51 (s, 1 H), 5.09 (s, 2 H), 4.04 (s, 4 H), 3.76 (s, 2 H), 3.54 (br s, 2 H), 3.25 (br s, 2 H), 1.20-1.30 (m, 3 H), 1.06-1.15 (m, 3 H); LC-MS: m/z 433.4 (M+H) +.
127		Conditions: DMF, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.41-7.50 (m, 4 H), 7.21-7.29 (m, 1 H), 6.95-7.15 (m, 2 H), 6.42 (s, 1 H),

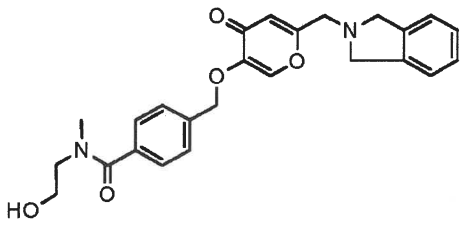
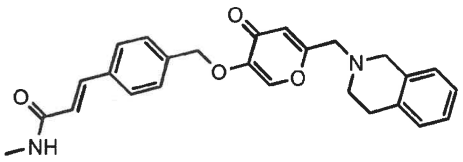
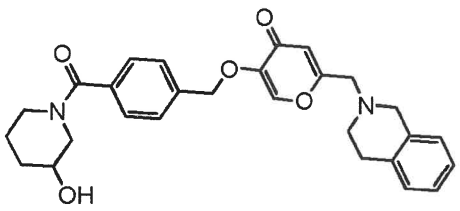
	Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	4.99 (s, 2 H), 3.87-4.00 (m, 4 H), 3.79 (s, 2 H), 2.98 (br s, 3 H), 2.91 (br s, 3 H); LC-MS: m/z 423.4 (M+H) +.
128	 Starting material: (4-(Chloromethyl)-phenyl)(piperidin-1-yl)methanone	Conditions: DMF, E and B. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.45-7.51 (m, 2 H), 7.37-7.41 (m, 2 H), 7.18-7.26 (m, 4 H), 6.43 (s, 1 H), 4.98 (s, 2 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 3.46-3.67 (m, 2 H), 3.19-3.31 (m, 2 H), 1.38-1.65 (m, 6 H); LC-MS: m/z 445.4 (M+H) +.
129	 Starting material: Azetidin-1-yl(4-(chloromethyl)phenyl)methanone	Conditions: DMF, 70 °C, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.61-7.68 (m, 2 H), 7.43-7.55 (m, 2 H), 7.17-7.27 (m, 4 H), 6.43 (s, 1 H), 5.00 (s, 2 H), 4.23-4.35 (m, 2 H), 3.99-4.10 (m, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 2.20-2.30 (m, 2 H); LC-MS: m/z 417.4 (M+H) +.
130	 Starting material: [4-(Chloromethyl) phenyl]-1-pyrrolidinylmethanone	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.23 (s, 1 H), 7.43-7.57 (m, 5 H), 7.35-7.42 (m, 1 H), 7.18-7.25 (m, 1 H), 6.42 (s, 1 H), 4.99 (s, 2 H), 3.90-3.98 (m, 4 H), 3.42-3.51 (m, 2 H), 3.36-3.41 (m, 2 H), 3.35 (s, 2 H), 1.76-1.92 (m, 4 H); LC-MS: m/z 510.4 (M+H) +.
131		Conditions: DMF, 85 °C, B and E. 1H NMR (DMSO-d6) δ: 8.21 (s, 1 H), 7.79-7.84 (m, 2 H), 7.76 (s, 1 H), 7.43-7.58 (m, 2 H), 7.18-7.26 (m, 4

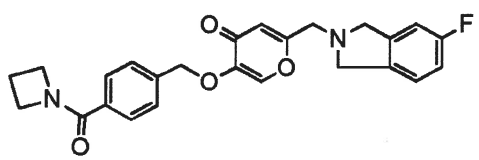
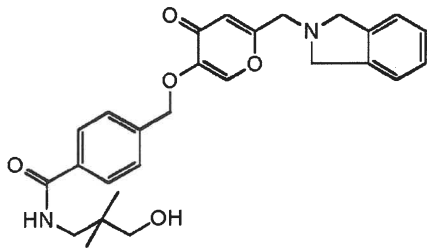
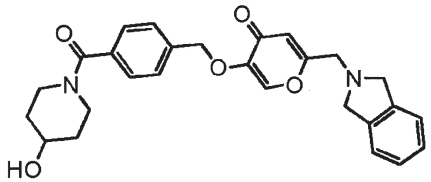
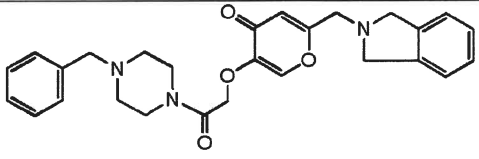
	Starting material: *N*-(tert-Butyl)-4-(chloromethyl)benzamide	H), 6.42 (s, 1 H), 5.01 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 1.38 (s, 9 H); LC-MS: m/z 433.4 (M+H) +.
132	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.39-7.51 (m, 4 H), 7.17-7.26 (m, 4 H), 6.44 (s, 1 H), 4.99 (s, 2 H), 4.08-4.16 (m, 1 H), 3.94-4.04 (m, 2 H), 3.70-3.77 (m, 1 H), 3.58-3.68 (m, 1 H), 2.98 (br s, 3 H), 2.90 (br s, 3 H), 1.32-1.38 (m, 3 H); LC-MS: m/z 463.3 (M+H) +.
133	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.40-7.50 (m, 4 H), 7.17-7.26 (m, 4 H), 6.44 (s, 1 H), 4.99 (s, 2 H), 4.09-4.16 (m, 1 H), 3.93-4.05 (m, 2 H), 3.69-3.78 (m, 1 H), 3.56-3.64 (m, 1 H), 2.98 (br s, 3 H), 2.90 (br s, 3 H), 1.32-1.37 (m, 3 H); LC-MS: m/z 419.4 (M+H) +.
134	 Starting material: 4-(Chloromethyl)-*N*, *N*-bis(1-methylethyl)benzamide	Conditions: DMF, 85 °C, D. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 8.13 (s, 1 H), 7.43-7.49 (m, 2 H), 7.28-7.32 (m, 2 H), 7.18-7.26 (m, 4 H), 6.42 (s, 1 H), 4.96 (s, 1 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 3.61 (br s, 1 H), 0.92-1.62 (m, 1 H); LC-MS: m/z 461.2 (M+H) +.

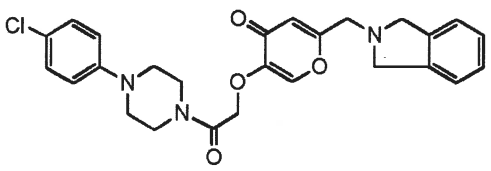
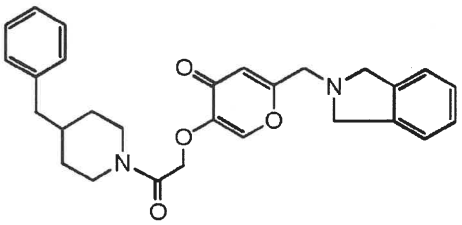
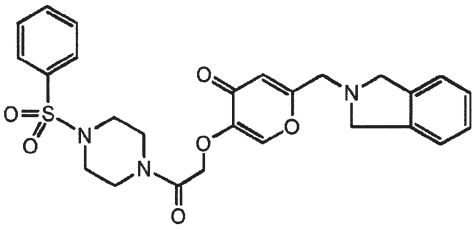
135	 Starting material: *N*-(tert-Butyl)-4-(chloromethyl)benzamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.21 (s, 1 H), 7.78-7.89 (m, 2 H), 7.73-7.77 (m, 1 H), 7.44-7.49 (m, 2 H), 7.06-7.17 (m, 3 H), 7.01-7.05 (m, 1 H), 6.42 (s, 1 H), 5.01 (s, 2 H), 3.53-3.68 (m, 4 H), 2.76 (s, 4 H), 1.38 (s, 9 H); LC-MS: m/z 447.4 (M+H) +.
136	 Starting material: 2-(4-(Chloromethyl)-phenyl)-*N,N*-dimethylacetamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.21 (s, 1 H), 7.30-7.41 (m, 2 H), 7.18-7.26 (m, 6 H), 6.41 (s, 1 H), 4.91 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.69 (s, 2 H), 2.97-3.01 (m, 3 H), 2.83 (s, 3 H); LC-MS: m/z 419.4 (M+H) +.
137	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.45-7.49 (m, 2 H), 7.41-7.45 (m, 2 H), 7.34 (s, 1 H), 7.22-7.28 (m, 2 H), 6.42 (s, 1 H), 4.99 (s, 2 H), 3.91-3.97 (m, 4 H), 3.79 (s, 2 H), 2.98 (br s, 3 H), 2.90 (br s, 3 H); LC-MS: m/z 439.3 (M+H) +.
138	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 85 °C, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.41-7.50 (m, 4 H), 7.10-7.16 (m, 1 H), 6.81-6.86 (m, 1 H), 6.73-6.78 (m, 1 H), 6.41 (s, 1 H), 4.99 (s, 2 H), 3.84-3.95 (m, 4 H), 3.78 (s, 2 H), 3.72 (s, 3 H), 2.98 (br s, 3 H), 2.91 (br s, 3 H); LC-MS: m/z 435.4 (M+H) +.

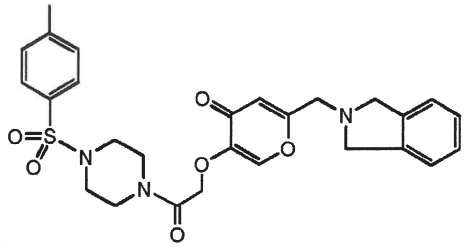
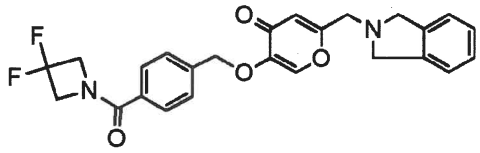
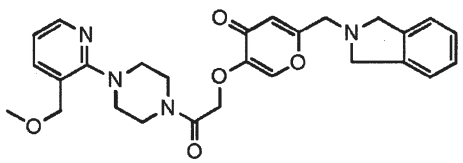
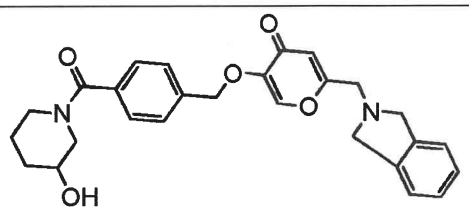
139	 Starting material: 4-(Chloromethyl)-*N*, *N*-dimethylbenzamide	Conditions: DMF, 85 °C, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.64 (s, 1 H), 7.55-7.60 (m, 1 H), 7.41-7.50 (m, 5 H), 6.44 (s, 1 H), 4.99 (s, 2 H), 4.03 (s, 4 H), 3.82 (s, 2 H), 2.98 (br s, 3 H), 2.91 (br s, 3 H); LC-MS: m/z 473.5 (M+H) +.
140	 Starting material: 4-(Chloromethyl)-*N*-(1-methylethyl)benzamide	Conditions: DMF, 85 °C, C. 1H NMR (DMSO-d6) δ: 8.18-8.27 (m, 2 H), 7.81-7.92 (m, 2 H), 7.43-7.54 (m, 2 H), 7.13-7.30 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 4.03-4.15 (m, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 1.17 (d, J=6.6 Hz, 6 H); LC-MS: m/z 419.3 (M+H) +.
141	 Starting material: 4-(Chloromethyl)-N-(prop-2-yn-1-yl)benzamide	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.96 (t, J=5.8 Hz, 1 H), 8.23 (s, 1 H), 7.85-7.94 (m, 2 H), 7.43-7.60 (m, 2 H), 7.15-7.29 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 4.00-4.12 (m, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.13 (t, J=2.5 Hz, 1 H); LC-MS: m/z 415.4 (M+H) +.
142	 Starting material: 4-(Chloromethyl)-N-hexylbenzamide	Conditions: DMF. 1H NMR (Chloroform-d) δ: 7.73-7.78 (m, 2 H), 7.56 (s, 1 H), 7.43-7.51 (m, 2 H), 7.18-7.24 (m, 4 H), 6.50 (s, 1 H), 6.07-6.18 (m, 1 H), 5.13 (s, 2 H), 4.03 (s, 4 H), 3.75 (s, 2 H), 3.41-3.48 (m, 2 H), 1.57-1.65 (m, 3 H), 1.29-1.38 (m, 5 H), 0.86-0.93 (m, 3 H); LC-

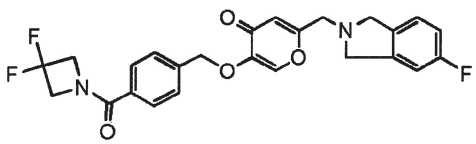
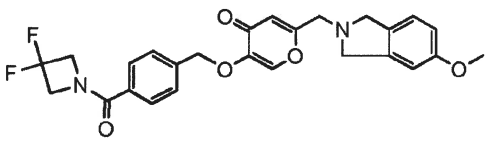
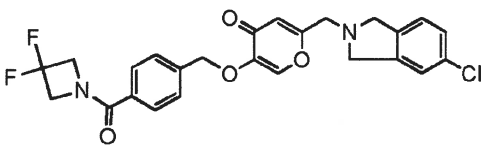
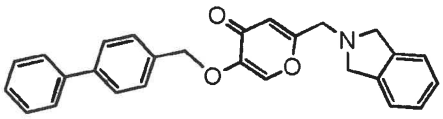
		MS: m/z 461.5 (M+H) +.
143	 Starting material: 2-(4-(Chloromethyl)-benzamido)-2-methylpropyl acetate	Conditions: DMF, G. 1H NMR (DMSO-d6) δ: 8.21 (s, 1 H), 7.80-7.84 (m, 3 H), 7.49 (s, 2 H), 7.18-7.28 (m, 4 H), 6.42 (s, 1 H), 5.02 (s, 2 H), 4.25 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 2.02 (s, 3 H), 1.36 (s, 6 H); LC-MS: m/z 491.5 (M+H) +.
144	 Starting material: 1-(Chloromethyl)-4-ethenylbenzene	Conditions: DMF, C. 1H NMR (DMSO-d6) δ: 8.21 (s, 1 H), 7.45-7.55 (m, 2 H), 7.36-7.43 (m, 2 H), 7.14-7.29 (m, 4 H), 6.69-6.80 (m, 1 H), 6.42 (s, 1 H), 5.82-5.89 (m, 1 H), 5.25-5.31 (m, 1 H), 4.94 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H); LC-MS: m/z 360.4 (M+H) +.
145	 Starting material: 4-(Chloromethyl)-N-(4-hydroxybutyl)benzamide	Conditions: DMF, E. 1H NMR (DMSO-d6) δ: 8.38-8.57 (m, 1 H), 8.23 (s, 1 H), 7.81-7.92 (m, 2 H), 7.40-7.59 (m, 2 H), 7.16-7.28 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 4.41 (t, J=5.1 Hz, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.35-3.47 (m, 2 H), 3.21-3.31 (m, 2 H), 1.50-1.60 (m, 2 H), 1.41-1.50 (m, 2 H); LC-MS: m/z 449.5 (M+H) +.
146		Conditions: DMF, 85°C, C. 1H NMR (DMSO-d6) δ: 8.22 (s, 1 H), 7.71-7.76 (m, 2 H), 7.43-7.50 (m, 3 H), 7.17-7.27 (m, 5 H), 6.42 (s, 1 H), 4.98 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2

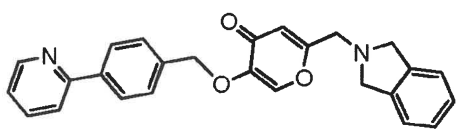
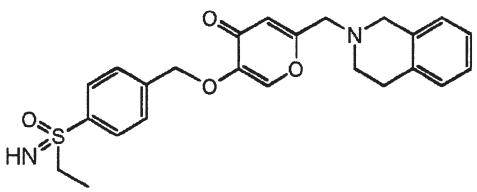
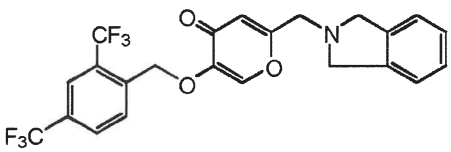
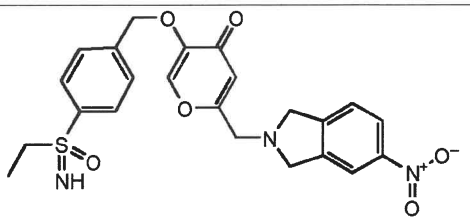
	Starting material: (E)-3-(4-(chloro-methyl)phenyl)-*N,N*-dimethylacryl-amide and (E)-3-(4-(bromomethyl)-phenyl)-*N,N*-dimethylacrylamide	H), 3.16 (s, 3 H), 2.93 (s, 3 H); LC-MS: m/z 431.6 (M+H) +.
147	 Starting material: 2-(4-(Chloromethyl)-phenyl)-N-(2-hydroxyethyl)-N-methyl-acetamide	Conditions: DMF, 85 °C, D. 1H NMR (DMSO-d6) δ: 8.19-8.25 (m, 1 H), 7.33-7.37 (m, 2 H), 7.18-7.26 (m, 6 H), 6.41 (s, 1 H), 4.91 (s, 2 H), 3.95 (s, 4 H), 3.74 (s, 1 H), 3.69 (s, 1 H), 3.51-3.55 (m, 2 H), 3.45-3.49 (m, 2 H), 3.38-3.42 (m, 3 H), 3.32-3.37 (m, 3 H); LC-MS: m/z 449.5 (M+H)+.
148	 Starting material: (E)-3-(4-(chloro-methyl)phenyl)-*N*-methylacrylamide	Conditions: DMF, E. 1H NMR (Chloroform-d) δ: 8.08 (s, 1 H), 7.57-7.63 (m, 2 H), 7.49 (m, J=8.2 Hz, 2 H), 7.36-7.43 (m, 2 H), 7.09-7.18 (m, 3 H), 6.96-7.02 (m, 1 H), 6.53 (s, 1 H), 6.40 (d, J=15.6 Hz, 1 H), 5.80-5.90 (m, 1 H), 5.07 (s, 2 H), 3.72 (s, 2 H), 3.56 (s, 2 H), 2.90-2.97 (m, 5 H), 2.80-2.89 (m, 2 H); LC-MS: m/z 431.6 (M+H) +.
149	 Starting material: (4-(Chloromethyl)-phenyl)(3-hydroxypiperidin-1-yl)-methanone	Conditions: DMF, D. 1H NMR (Chloroform-d) δ: 7.58 (s, 1 H), 7.40-7.47 (m, 4 H), 7.09-7.17 (m, 3 H), 6.97-7.02 (m, 1 H), 6.52 (s, 1 H), 5.09 (s, 2 H), 3.78-4.02 (m, 1 H), 3.70 (s, 2 H), 3.54 (s, 2 H), 2.89-2.96 (m, 2 H), 2.80-2.86 (m, 2 H), 1.80-1.97 (m, 2 H), 1.66 (s, 5 H); LC-MS: m/z 475.6 (M+H) +.

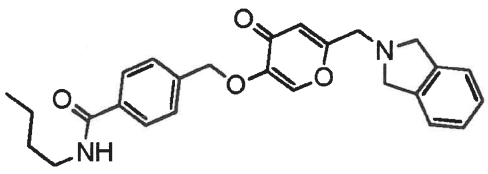
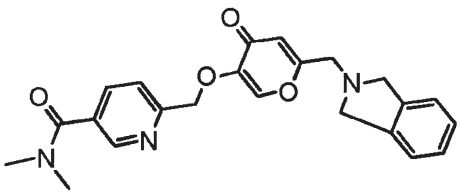
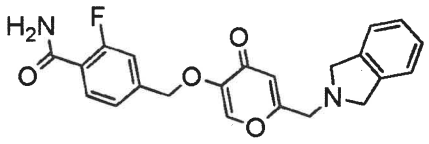
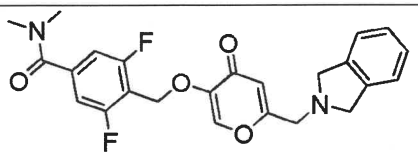
150	 Starting material: Azetidin-1-yl(4-(chloromethyl)phenyl)methanone	Conditions: DMF, G. 1H NMR (Chloroform-d) δ: 7.64 (s, 1 H), 7.62-7.63 (m, 1 H), 7.57 (s, 1 H), 7.42-7.47 (m, 2 H), 6.82-7.00 (m, 2 H), 6.50 (s, 1 H), 5.11 (s, 2 H), 4.20-4.33 (m, 5 H), 4.00 (br d, J=12.4 Hz, 4 H), 3.75 (s, 2 H), 2.31-2.39 (m, 2 H); LC-MS: m/z 435.6 (M+H) +.
151	 Starting material: 4-(Chloromethyl)-*N*-(3-hydroxy-2,2-dimethylpropyl)-benzamide	Conditions: DMF, D. 1H NMR (DMSO-d6) δ: 8.35-8.45 (m, 1 H), 8.23 (s, 1 H), 8.15 (s, 1 H), 7.84-7.88 (m, 2 H), 7.49-7.53 (m, 2 H), 7.18-7.26 (m, 4 H), 6.43 (s, 1 H), 5.03 (s, 2 H), 3.95 (s, 4 H), 3.78-3.81 (m, 2 H), 3.15-3.17 (m, 2 H), 3.13 (s, 2 H), 0.82-0.97 (m, 6 H); LC-MS: m/z 463.6 (M+H) +.
152	 Starting material: (4-(Chloromethyl)-phenyl)(4-hydroxypiperidin-1-yl)-methanone	Conditions: DMF, B and E. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 7.46-7.51 (m, 2 H), 7.36-7.44 (m, 2 H), 7.18-7.27 (m, 4 H), 6.43 (s, 1 H), 4.98 (s, 2 H), 4.78 (d, J=4.0 Hz, 1 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 3.71-3.79 (m, 1 H), 3.33-3.57 (m, 1 H), 3.06-3.31 (m, 2 H), 1.78 (br s, 1 H), 1.70 (br s, 1 H), 1.35 (br s, 2 H); LC-MS: m/z 461.6 (M+H) +.
153	 Starting material: 2-Chloro-1-[4-	Conditions: DMF, A. 1H NMR (Chloroform-d) δ: 7.98 (s, 1 H), 7.26-7.35 (m, 5 H), 7.17-7.25 (m, 4 H), 6.50 (s, 1 H), 4.78 (s, 2 H), 4.05

	(phenylmethyl)-1-piperazinyl]ethanone	(s, 4 H), 3.77 (s, 2 H), 3.52-3.64 (m, 4 H), 3.51 (s, 2 H), 2.38-2.48 (m, 4 H); LC-MS: m/z 460.4 (M+H) +.
154	 Starting material: 2-Chloro-1-[4-(4-chlorophenyl)-1-piperazinyl]ethanone	Conditions: DMF, C. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 7.20-7.26 (m, 6 H), 6.96-6.99 (m, 2 H), 6.41 (s, 1 H), 4.77 (s, 2 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 3.59 (br s, 4 H), 3.12-3.21 (m, 4 H); LC-MS: m/z 480.3 (M+H) +.
155	 Starting material: 2-Chloro-1-[4-(phenylmethyl)-1-piperidinyl]ethanone	Conditions: DMF, A. 1H NMR (DMSO-d6) δ: 8.10 (s, 1 H), 7.15-7.31 (m, 9 H), 6.40 (s, 1 H), 4.62-4.79 (m, 2 H), 4.21-4.35 (m, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.70-3.77 (m, 1 H), 2.93 (br s, 1 H), 2.51-2.57 (m, 2 H), 1.68-1.82 (m, 1 H), 1.48-1.67 (m, 2 H), 0.95-1.22 (m, 2 H); LC-MS: m/z 459.7 (M+H) +.
156	 Starting material: 2-Chloro-1-(4-(phenylsulfonyl)piperazin-1-yl)-ethanone	Conditions: DMF, A. 1H NMR (Chloroform-d) δ: 7.88 (s, 1 H), 7.71-7.78 (m, 2 H), 7.59-7.65 (m, 1 H), 7.52-7.59 (m, 2 H), 7.18-7.24 (m, 4 H), 6.46 (s, 1 H), 4.71 (s, 2 H), 4.03 (s, 4 H), 3.76 (s, 2 H), 3.70 (s, 2 H), 3.67-3.70 (m, 2 H), 2.98-3.11 (m, 4 H); LC-MS: m/z 510.5 (M+H) +.

157	 Starting material: 2-Chloro-1-(4-tosyl-piperazin-1-yl)ethanone	Conditions: DMF, A. 1H NMR (DMSO-d6) δ: 8.07 (s, 1 H), 7.59-7.65 (m, 2 H), 7.43-7.49 (m, 2 H), 7.17-7.27 (m, 4 H), 6.38 (s, 1 H), 4.66 (s, 2 H), 3.94 (s, 4 H), 3.77 (s, 2 H), 3.53 (br s, 2 H), 3.47 (br s, 2 H), 2.93 (br s, 2 H), 2.87 (br s, 2 H), 2.41 (s, 3 H); LC-MS: m/z 524.6 (M+H) +.
158	 Starting material: (4-(Chloromethyl)-phenyl)(3,3-difluoroazetidin-1-yl)-methanone	Conditions: DMF, 85°C, E. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 7.69-7.76 (m, 2 H), 7.46-7.60 (m, 2 H), 7.14-7.29 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 4.82 (s, 2 H), 4.38-4.58 (m, 2 H), 3.96 (s, 4 H), 3.80 (s, 2 H); LC-MS: m/z 453.4 (M+H) +.
159	 Starting material: 2-Chloro-1-(4-(3-(methoxymethyl)pyridin-2-yl)-piperazin-1-yl)ethanone	Conditions: DMF, 80 °C, D. 1H NMR (Chloroform-d) δ: 8.24-8.27 (m, 1 H), 8.06 (s, 1 H), 8.02 (s, 1 H), 7.71-7.74 (m, 1 H), 7.19-7.25 (m, 4 H), 6.99-7.03 (m, 1 H), 6.54 (s, 1 H), 4.84 (s, 2 H), 4.43 (s, 2 H), 4.10 (s, 4 H), 3.83 (s, 2 H), 3.66-3.78 (m, 4 H), 3.43 (s, 3 H), 3.14-3.25 (m, 4 H); LC-MS: m/z 491.6 (M+H) +.
160	 Starting material: (4-(Chloromethyl)-phenyl)(3-hydroxypiperidin-1-yl)-methanone	Conditions: DMF, 85 °C, D. 1H NMR (Chloroform-d) δ ppm 7.59 (s, 1 H), 7.38-7.49 (m, 4 H), 7.16-7.25 (m, 4 H), 6.52 (s, 1 H), 5.09 (s, 2 H), 4.05 (s, 4 H), 3.77 (s, 2 H), 3.13-3.64 (m, 3 H), 2.45-2.83 (m, 3 H), 1.76-2.02 (m, 2 H), 1.34-1.74 (m, 2 H); LC-

		MS: m/z 461.5 (M+H) +.
161	 Starting material: (4-(Chloromethyl)-phenyl)(3,3-difluoroazetidin-1-yl)-methanone	Conditions: DMF, 85 °C, C. 1H NMR (Chloroform-d) δ: 7.62-7.68 (m, 2 H), 7.60 (s, 1 H), 7.47-7.54 (m, 2 H), 7.10-7.17 (m, 1 H), 6.88-6.94 (m, 2 H), 6.50 (s, 1 H), 5.12 (s, 2 H), 4.48-4.59 (m, 4 H), 3.96-4.04 (m, 4 H), 3.75 (s, 2 H); LC-MS: m/z 471.5 (M+H)
162	 Starting material: (4-(Chloromethyl)-phenyl)(3,3-difluoroazetidin-1-yl)-methanone	Conditions: DMF, 85 °C, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.68-7.78 (m, 2 H), 7.49-7.57 (m, 2 H), 7.07-7.19 (m, 1 H), 6.80-6.87 (m, 1 H), 6.73-6.78 (m, 1 H), 6.42 (s, 1 H), 5.02 (s, 2 H), 4.66-4.91 (m, 2 H), 4.38-4.60 (m, 2 H), 3.83-3.97 (m, 4 H), 3.78 (s, 2 H), 3.72 (s, 3 H); LC-MS: m/z 483.5 (M+H) +.
163	 Starting material: (4-(Chloromethyl)-phenyl)(3,3-difluoroazetidin-1-yl)-methanone	Conditions: DMF, 85 °C, C. 1H NMR (DMSO-d6) δ: 8.24 (s, 1 H), 7.69-7.79 (m, 2 H), 7.50-7.56 (m, 2 H), 7.34 (s, 1 H), 7.27 (s, 2 H), 6.43 (s, 1 H), 5.03 (s, 2 H), 4.69-4.91 (m, 2 H), 4.51 (br s, 2 H), 3.90-3.99 (m, 4 H), 3.77-3.85 (m, 2 H); LC-MS: m/z 487.4 (M+H) +.
164	 Starting material: 4-(Chloromethyl)-1, 1'-biphenyl	Conditions: DMF, 85 °C, E and A. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 7.64-7.75 (m, 4 H), 7.43-7.54 (m, 4 H), 7.33-7.41 (m, 1 H), 7.18-7.27 (m, 4 H), 6.43 (s, 1 H), 5.00 (s, 2 H), 3.96

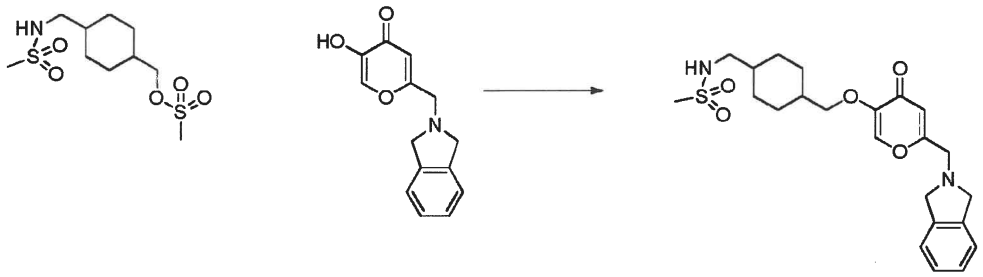
		(s, 4 H), 3.80 (s, 2 H); LC-MS: m/z 410.7
165	 Starting material: 2-[4-(Chloromethyl) phenyl]pyridine	Conditions: DMF, 85 °C, E. 1H NMR (DMSO-d6) δ: 8.64-8.76 (m, 1 H), 8.20-8.37 (m, 1 H), 8.06-8.19 (m, 2 H), 7.95-8.06 (m, 2 H), 7.87-7.95 (m, 1 H), 7.50-7.70 (m, 2 H), 7.34-7.41 (m, 1 H), 7.17-7.26 (m, 3 H), 6.44 (br s, 1 H), 5.03 (br s, 2 H), 3.96 (br s, 4 H), 3.80 (br s, 2 H); LC-MS: m/z 411.3
166	 Starting material: 1-(Chloromethyl)-4-(ethylsulfonimidoyl)benzene	Conditions: DMF, 80 °C, C. 1H NMR (Chloroform-d) δ: 7.95-7.99 (m, 2 H), 7.63 (s, 1 H), 7.58-7.62 (m, 2 H), 7.09-7.17 (m, 3 H), 6.98-7.02 (m, 1 H), 6.53 (s, 1 H), 5.16 (s, 2 H), 3.71 (s, 2 H), 3.55 (s, 2 H), 3.12-3.22 (m, 2 H), 2.91-2.96 (m, 2 H), 2.80-2.87 (m, 2 H), 2.68 (s, 1 H), 1.23-1.29 (m, 3 H); LC-MS: m/z 439.3
167	 Starting material: 1-(Chloromethyl)-2, 4-bis(trifluoromethyl)benzene	Conditions: $CsCO_3$, 1,4-dioxane, reflux. 1H NMR (Methanol-d4) δ: 8.17-8.18 (m, 1 H), 8.11-8.14 (m, 1 H), 7.99-8.04 (m, 2 H), 7.20-7.25 (m, 4 H), 6.61 (s, 1 H), 5.30 (s, 2 H), 4.04 (s, 4 H), 3.88 (s, 2 H); LC-MS: m/z 470.7
168		Conditions: E. 1H NMR (DMSO-d6) δ: 8.26 (s, 1 H), 8.15 (s, 2 H), 8.10-8.14 (m, 1 H), 7.86-7.99 (m, 2 H), 7.62-7.66 (m, 2

	Starting material: 1-(Chloromethyl)-4-(ethylsulfonimidoyl)benzene	H), 7.50-7.56 (m, 1 H), 6.45 (s, 1 H), 5.07 (s, 2 H), 4.06 (s, 4 H), 3.84 (s, 2 H), 3.10-3.16 (m, 2 H), 1.06 (t, J=7.4 Hz, 3 H); LC-MS: m/z 470.4
169	 Starting material: *N*-Butyl-4-(chloro-methyl)benzamide	Conditions: DMF, 85°C, E. 1H NMR (DMSO-d6) δ: 8.39-8.49 (m, 1 H), 8.23 (s, 1 H), 7.81-7.90 (m, 2 H), 7.46-7.52 (m, 2 H), 7.14-7.29 (m, 4 H), 6.43 (s, 1 H), 5.02 (s, 2 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.21-3.30 (m, 2 H), 1.46-1.55 (m, 2 H), 1.28-1.38 (m, 2 H), 0.90 (t, J=7.3 Hz, 3 H); LC-MS: m/z 433.4 (M+H) +.
170	 Starting material: 6-(Chloromethyl)-N,N-dimethylnicotinamide	Conditions: DMF, B and E. 1H NMR (DMSO-d6) δ: 8.60 - 8.63 (m, 1 H), 8.30 (s, 1 H), 7.91 - 7.95 (m, 1 H), 7.60 - 7.64 (m, 1 H), 7.18 - 7.27 (m, 4 H), 6.44 (s, 1 H), 5.08 (s, 2 H), 3.96 (s, 4 H), 3.81 (s, 2 H), 3.01 (s, 3 H), 2.94 (s, 3 H); LC-MS: m/z 406.4 (M+H) +.
171	 Starting material: 4-(Chloromethyl)-2-fluorobenzamide	Condition: DMF, C. 1H NMR (DMSO-d6) δ: 8.25 (s, 1 H), 7.62-7.75 (m, 3 H), 7.29-7.38 (m, 2 H), 7.17-7.29 (m, 3 H), 7.04-7.17 (m, 1 H), 6.44 (s, 1 H), 4.96-5.05 (m, 2 H), 3.85-3.97 (m, 4 H), 3.80 (s, 2 H); LC-MS: m/z 395.4 (M+H) +.
172		Condition: DMF, C. 1H NMR (DMSO-d6) δ: 8.26 (s, 1 H), 7.17-7.30 (m, 6 H), 6.44 (s, 1 H), 5.05

	Starting material: 4-(Chloromethyl)-3,5-difluoro-N,N-dimethylbenzamide	(s, 2 H), 3.96 (s, 4 H), 3.80 (s, 2 H), 2.98 (s, 3 H), 2.90 (s, 3 H); LC-MS: m/z 441.4 (M+H) +.

Example 4.

N-((4-((((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclohexyl)-methyl)methanesulfonamide (Compound 173)



To a solution of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.10 g, 0.41 mmol) in DMF (2 ml) were added (4-(methylsulfonamidomethyl)cyclohexyl)methyl methanesulfonate (0.14 g, 0.45 mmol) and K_2CO_3 (0.12 g, 0.8 mmol). The reaction mixture was heated at 80 °C for 2 h. The mixture was cooled to RT, water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography to afford the title compound (0.06 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 0.92 - 1.11 (m, 4 H) 1.40 - 1.63 (m, 2 H) 1.78 - 2.00 (m, 4 H) 2.91 - 2.99 (m, 5 H) 3.65 (d, *J*=6.46 Hz, 2 H) 3.77 (s, 2 H) 4.03 (s, 4 H) 5.04 (br t, *J*=6.31 Hz, 1 H) 6.49 (s, 1 H) 7.20 (s, 4 H) 7.59 (s, 1 H).

The following compounds were prepared according to the procedure described for Compound 173 of Example 4 starting from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one or 5-hydroxy-2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one or a derivative thereof and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

Purification methods used:

A = Crystallization

B = Column chromatography

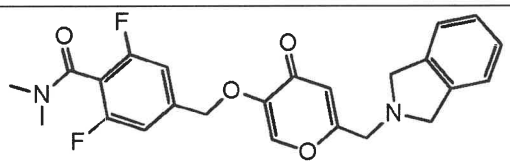
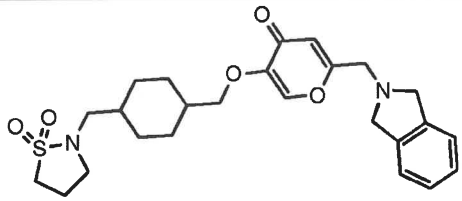
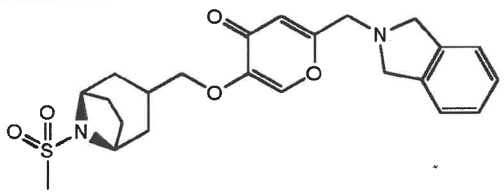
C = Precipitation in aqueous media

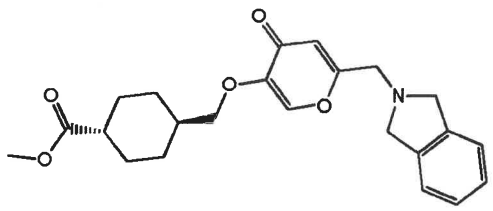
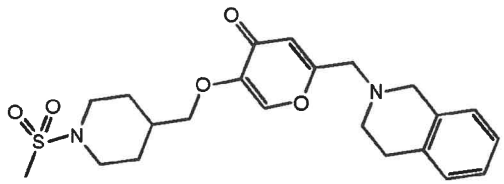
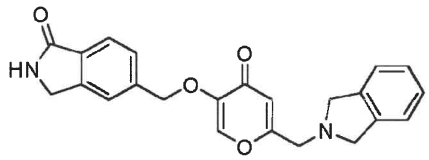
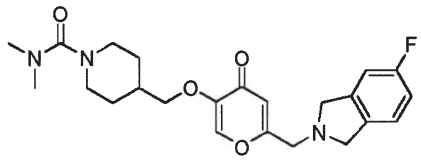
D = Semipreparative HPLC

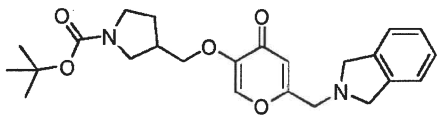
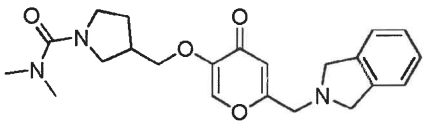
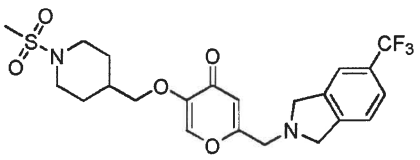
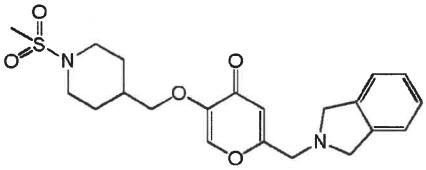
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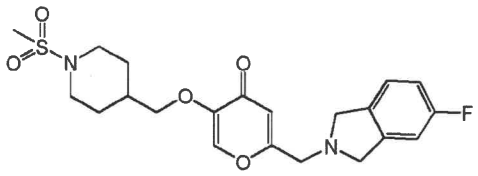
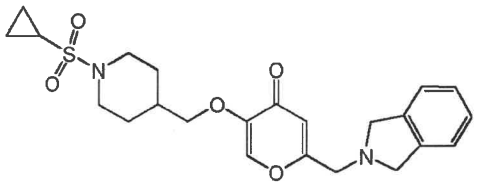
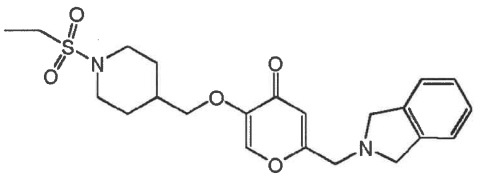
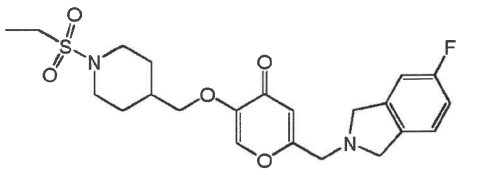
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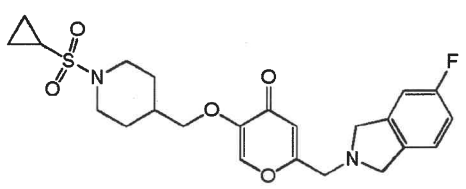
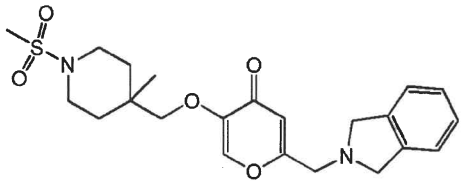
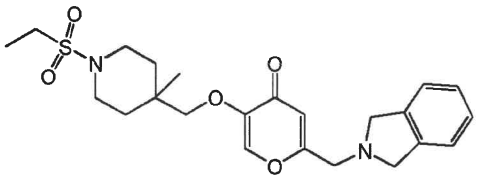
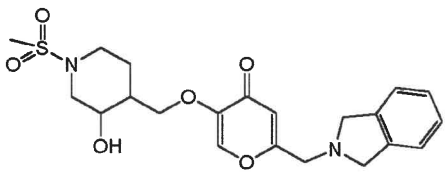
G = As such

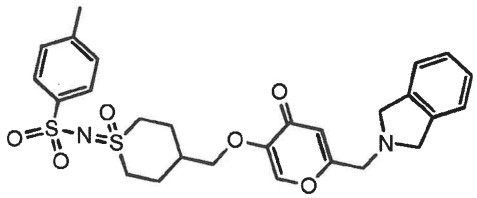
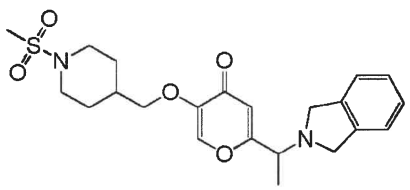
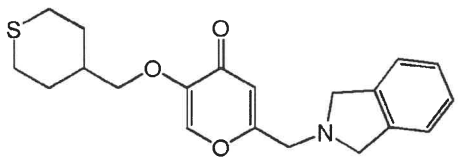
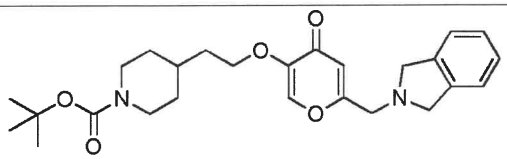
No	Structure and starting material	Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS
174	 Starting material: 4-(Dimethyl-carbamoyl)-3,5-difluorobenzyl methane-sulfonate	Conditions: 50 °C. ^{1}H NMR (Chloroform-d) δ: 7.64 (s, 1H), 7.21 (s, 4H), 7.03 (d, 2H), 6.53 (s, 1H), 5.09 (s, 2H), 4.05 (s, 4H), 3.78 (s, 1H), 3.77-3.79 (m, 1H), 2.94 (s, 3H). LCMS: *m/z* 44.5 $(M+H)^+$.
176	 Starting material: (4-((1,1-Dioxidoiso-thiazolidin-2-yl)methyl)cyclohexyl)-methyl methanesulfonate	Conditions: 90 °C. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.20 (s, 4H), 6.47 (s, 1H), 4.03 (s, 4H), 3.77 (s, 2H), 3.67 (d, 2H), 3.10-3.27 (m, 2H), 2.83-2.86 (m, 2H), 2.27-2.39 (m, 2H), 0.88-2.01 (m, 10H). LCMS: *m/z* 473.6 $(M+H)^+$.
177	 Starting material: ((1R,3r,5S)-8-(Methylsulfonyl)-8-azabicyclo[3.2.1]-octan-3-yl)methyl methanesulfonate	Conditions: DMSO, 100 °C. ^{1}H NMR (Chloroform-d) δ: 7.66 (s, 1H), 7.17-7.25 (m, 4H), 6.52 (s, 1H), 4.25 (br s, 2H), 4.09 (s, 4H), 3.90 (d, 2H), 3.82 (s, 2H), 2.91 (s, 3H), 2.05-2.37 (m, 5H), 1.66-1.82 (m, 4H) LC-MS: *m/z* 445.6$(M+H)^+$.

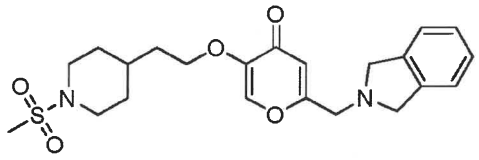
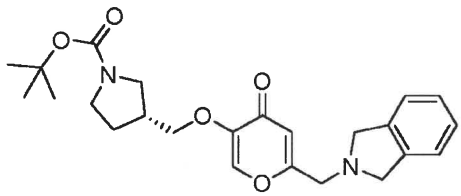
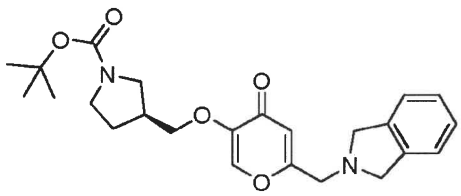
178	 Starting material: (1r,4r)-Methyl 4-(((methylsulfonyl)oxy)methyl)cyclo-hexanecarboxylate	Conditions: DMSO, 100 °C. 1H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.23 (br d, 4H), 6.54 (s, 1H), 4.15 (s, 4H), 3.87 (s, 2H), 3.64-3.71 (m, 4H), 2.20-2.35 (m, 1H), 2.01 (br m, 5H), 1.79-1.92 (m, 1H), 1.38-1.56 (m, 2H), 0.98-1.17 (m, 2H). LCMS: m/z 398.1 (M+H)+.
179	 Starting material: 4-(Methanesulphonyl-oxymethyl)-1-methanesulphonyl-piperidine	Conditions: DMSO. 1H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.09-7.17 (m, 3H), 6.98-7.01 (m, 1H), 6.50 (s, 1H), 3.85 (br d, 2H), 3.74 (d, 2H), 3.71 (s, 2H), 3.56 (s, 2H), 2.91-2.96 (m, 2H), 2.81-2.86 (m, 2H), 2.79 (s, 3H), 2.69 (m, 2H), 2.00 (br d, 3H), 1.43 (br m, 2H). LCMS: m/z 433.4 (M+H)+.
180	 Starting material: (1-Oxoisoindolin-5-yl)methyl methanesulfonate	Conditions: RT, E (in 2-propanol) and B. ^{1}H NMR (Chloroform-d) δ: 7.88 (d, 1H), 7.59-7.64 (m, 2H), 7.49 (d, 1H), 7.16-7.24 (m, 4H), 6.52 (s, 1H), 6.15 (br s, 1H), 5.18 (s, 2H), 4.46 (s, 2H), 4.04 (s, 4H), 3.76 (s, 2H). LC-MS: *m/z* 389.4 $(M+H)^+$.
181	 Starting material: (1-(Dimethyl-carbamoyl)piperidin-4-yl)methyl methanesulfonate	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.13 (m, 1H), 6.85-6.95 (m, 2H), 6.48 (s, 1H), 4.02 (s, 2H), 3.99 (s, 2H), 3.76 (s, 2H), 3.66-3.74 (m, 4H), 2.82 (s, 6H), 2.78 (br d, 2H), 2.01-2.13 (m, 1H), 1.83-1.90 (m,

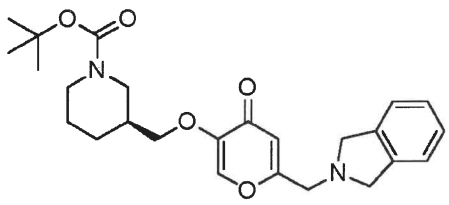
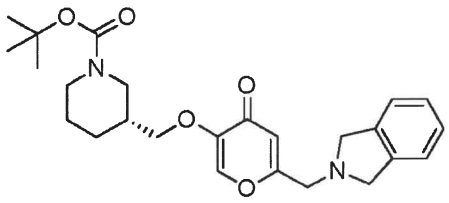
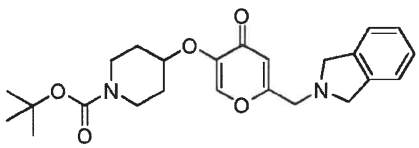
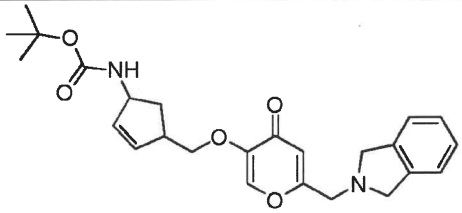
		2H), 1.23-1.36 (m, 2H). LC-MS: *m/z* 430.5 $(M+H)^+$.
182	 Starting material: *tert*-butyl 3-(((methyl-sulfonyl)oxy)methyl)pyrrolidine-1-carboxylate	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.60-7.67 (m, 1H), 7.21 (d, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.80-3.92 (m, 2H), 3.77 (s, 2H), 3.58 (br m, 1H), 3.27-3.52 (m, 2H), 3.18 (br m, 1H), 2.65-2.77 (m, 1H), 2.00-2.14 (m, 1H), 1.65-1.88 (m, 1H), 1.44-1.51 (m, 9H). LC-MS: *m/z* 427.5 $(M+H)^+$.
183	 Starting material: (1-(Dimethyl-carbamoyl)pyrrolidin-3-yl)methyl methanesulfonate	Conditions: 60 °C. ^{1}H NMR (Chloroform -d) δ: 7.61-7.65 (m, 1H), 7.15-7.25 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.81-3.94 (m, 2H), 3.77 (s, 2H), 3.56 (m, 1H), 3.36-3.50 (m, 2H), 3.29 (m, 1H), 2.84 (s, 6H), 2.62-2.74 (m, 1H), 2.01-2.12 (m, 1H), 1.74 (m, 1H). LC-MS: *m/z* 398.5 $(M+H)^+$.
184	 Starting material: (1-(Methylsulfonyl)-piperidin-4-yl)methyl methanesulfonate	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.50 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 6.49 (s, 1H), 4.09 (s, 4H), 3.82-3.90 (m, 2H), 3.79 (s, 2H), 3.74 (d, 2H), 2.79 (s, 3H), 2.69 (m, 2H), 1.96-2.08 (m, 3H), 1.36-1.49 (m, 2H). LC-MS: *m/z* 487.5 $(M+H)^+$.
185		Conditions: 50-80 °C, C. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.85 (m, 2 H), 3.78 (s, 2 H),

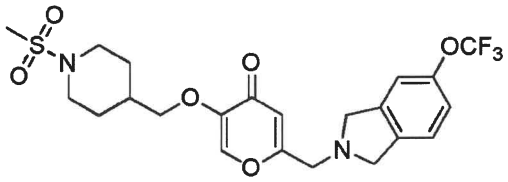
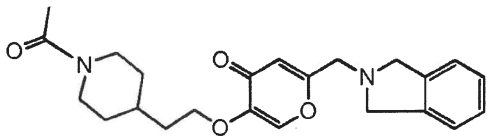
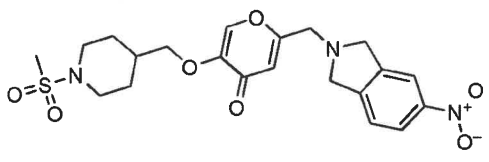
	Starting material: (1-(Methylsulfonyl)-piperidin-4-yl)methyl methanesulfonate	3.75 (d, 2 H), 2.79 (s, 3 H), 2.69 (td, 2 H), 2.00 (m, 3 H), 1.43 (m, 2 H); LC-MS: *m/z* 419.3 $(M+1)^+$.
186	 Starting material: (1-(Methylsulfonyl)-piperidin-4-yl)methyl methanesulfonate	Conditions: 60-80 °C. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.13 (m, 1 H), 6.91 (m, 2 H), 6.48 (s, 1 H), 4.02 (br s, 2 H), 3.99 (br s, 2 H), 3.86 (br d, 2 H), 3.75 (m, 4 H), 2.79 (s, 3 H), 2.69 (br t, 2 H), 2.00 (br d, 3 H), 1.43 (m, 2 H); LC-MS: *m/z* 437.3 $(M+1)^+$.
187	 Starting material: (1-(Cyclopropyl-sulfonyl)piperidin-4-yl)methyl methane-sulfonate	Conditions: C and E (Et_2O-EtOH). ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.86 (br d, 2 H), 3.77 (s, 2 H), 3.74 (d, 2 H), 2.84 (td, 2 H), 2.27 (tt, 1 H), 2.01 (m, 3 H), 1.42 (qd, 2 H), 1.18 (m, 2 H), 0.99 (m, 2 H); LC-MS: *m/z* 445.5 $(M+1)^+$.
188	 Starting material: (1-(Ethylsulfonyl)-piperidin-4-yl)methyl methanesulfonate	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.86 (br d, 2 H), 3.77 (s, 2 H), 3.74 (d, 2 H), 2.96 (q, 2 H), 2.81 (td, 2 H), 2.00 (m, 3 H), 1.37 (m, 5 H); LC-MS: *m/z* 433.3 $(M+1)^+$.
189	 Starting material: (1-(Ethylsulfonyl)-	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.13 (m, 1 H), 6.91 (m, 2 H), 6.48 (s, 1 H), 4.03 (s, 2 H), 4.00 (s, 2 H), 3.86 (br d, 2 H), 3.77 (s, 2 H), 3.73 (d, 2 H), 2.96 (q, 2 H), 2.81 (td, 2 H), 2.00 (m, 3 H), 1.37 (m, 5 H);

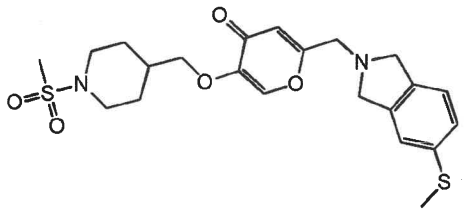
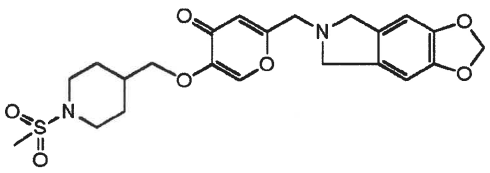
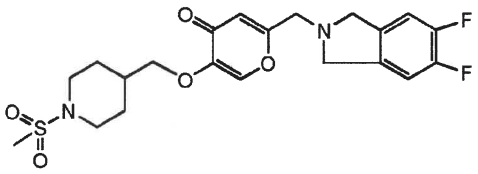
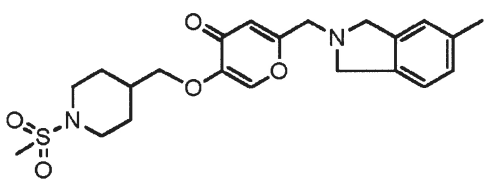
	piperidin-4-yl)methyl methanesulfonate	LC-MS: *m/z* 451.3 $(M+1)^+$.
190	 Starting material: (1-(Cyclopropyl-sulfonyl)piperidin-4-yl)methyl methane-sulfonate	Conditions: C. ^{1}H NMR (Chloro-form-d) δ: 7.60 (s, 1 H), 7.13 (dd, 1 H), 6.91 (m, 2 H), 6.48 (s, 1 H), 4.02 (s, 2 H), 3.99 (s, 2 H), 3.86 (br d, 2 H), 3.76 (s, 2 H), 3.74 (d, 2 H), 2.83 (td, 2 H), 2.27 (tt, 1 H), 2.00 (m, 3 H), 1.42 (m, 2 H), 1.17 (m, 2 H), 0.98 (m, 2 H); LC-MS: *m/z* 463.4 $(M+1)^+$.
191	 Starting material: (4-Methyl-1-(methyl-sulfonyl)piperidin-4-yl)methyl methane-sulfonate	Conditions: DMSO, 80 °C, micro-wave. ^{1}H NMR (Chloroform-d) δ: 7.63 (s, 1 H), 7.21 (m, 4 H), 6.48 (s, 1 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 3.69 (s, 2 H), 3.47 (m, 2 H), 3.15 (ddd, 2 H), 2.83 (s, 3 H), 1.78 (ddd, 2 H), 1.62 (ddd, 2 H), 1.12 (s, 3 H); LC-MS: *m/z* 433.4 $(M+1)^+$.
192	 Starting material: (1-(Ethylsulfonyl)-4-methylpiperidin-4-yl)methyl methane-sulfonate	Conditions: DMSO, 80 °C micro-wave. ^{1}H NMR (Chloroform-d) δ: 7.63 (s, 1 H), 7.21 (m, 4 H), 6.48 (s, 1 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 3.68 (s, 2 H), 3.50 (m, 2 H), 3.20 (m, 2 H), 2.98 (m, 2 H), 1.74 (ddd, 2 H), 1.59 (m, 2 H), 1.38 (m, 3 H), 1.12 (s, 3 H); LC-MS: *m/z* 447.4 $(M+1)^+$.
193	 Starting material: (3-Hydroxy-1-	^{1}H NMR (Chloroform-d) δ: 7.81 (d, 1 H), 7.21 (m, 4 H), 6.55 (d, 1 H), 4.22 (m, 1 H), 4.05 (d, 4 H), 3.70-3.93 (m, 5 H), 2.50- 2.98 (s, 5 H), 1.4- 2.1 (m, 4 H), 0.87 (m, 1 H); LC-

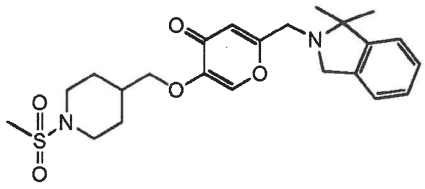
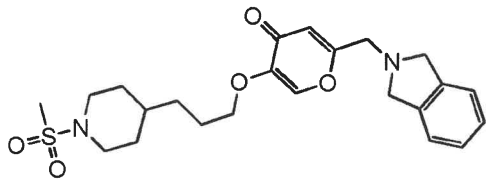
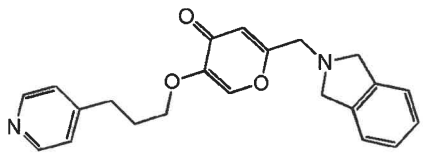
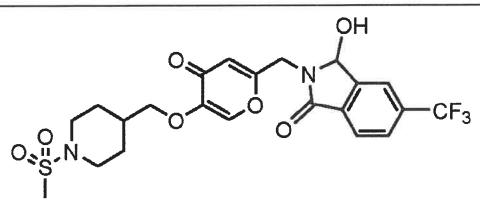
	(methylsulfonyl)piperidin-4-yl)methyl methanesulfonate	MS: *m/z* 435.3 $(M+1)^+$.
194	 (Formate) Starting material: (1-Oxido-1-(tosyl-imino)tetrahydro-2H-thiopyran-4-yl)-methyl methanesulfonate	Conditions: 70 °C. ^{1}H NMR (Chloro-form-d) δ: 8.09 (s, 1 H), 7.86 (dd, 2 H), 7.67 (d, 1 H), 7.28 (br d, 2 H), 7.23 (m, 4 H), 6.55 (d, 1 H), 4.13 (br d, 4 H), 3.91 (br d, 1 H), 3.87 (br d, 2 H), 3.80 (dd, 2 H), 3.72 (br d, 1 H), 3.36 (m, 1 H), 3.14 (m, 1 H), 2.40 (m, 5 H), 2.32 (m, 1 H), 2.09 (m, 1 H), 1.98 (m, 1 H); LC-MS: *m/z* 543.7 $(M+1)^+$.
195	 Starting material: 4-(Methanesulphonyl-oxymethyl)-1-methanesulphonyl-piperidine	Conditions: DMSO, 60 °C. ^{1}H NMR (Chloroform-d) δ: 7.62 (s, 1H), 7.26-7.17 (m, 4H), 6.47 (s, 1H), 4.06-3.95 (m, 4H), 3.90-3.83 (m, 2H), 3.74 (d, 2H), 3.65 (m, 1H), 2.79 (s, 3H), 2.73-2.66 (m, 2H), 2.04-1.98 (m, 3H), 1.52 (d, 3H), 1.45-1.40 (m, 2H); LC-MS: *m/z* 433.6 $(M+1)^+$.
196	 Starting material: (Tetrahydro-2H-thio-pyran-4-yl)methyl methanesulfonate	Conditions: DMSO, C. ^{1}H NMR (Chloroform-d) δ: 7.59 (m, 1 H), 7.21 (s, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.77 (s, 2 H), 3.67 (br d, 2 H), 2.67 (m, 4 H), 2.20 (br d, 2 H), 1.94 (m, 1 H), 1.46 (m, 2 H); LC-MS: *m/z* 358.8 $(M+1)^+$.
197	 Starting material: tert-Butyl 4-(2-	Conditions: DMSO, 60 °C, G. 1H NMR (DMSO-d6) δ: 8.14 (s, 1H), 7.17-7.26 (m, 4H), 6.38 (s, 1H), 3.95 (s, 4H), 3.88-3.96 (m, 2H), 3.86

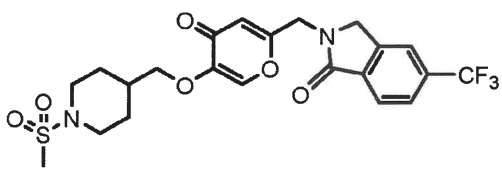
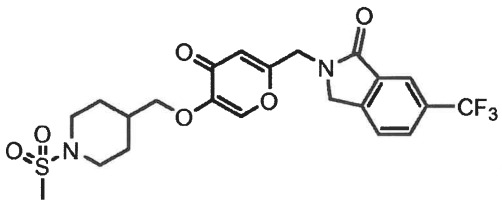
	((methylsulfonyl)oxy)ethyl)piperidine-1-carboxylate	(t, 2H), 3.78 (s, 2H), 2.56-2.82 (m, 2H), 1.53-1.72 (m, 5H), 1.39 (s, 9H), 0.95-1.09)m, 1H). LC-MS: m/z 455.8 (M+H)+
198	 Starting material: 2-(1-(Methylsulfonyl)-piperidin-4-yl)ethyl methanesulfonate	Conditions: DMSO, 60 °C, C. 1H NMR (Chloroform-d) δ: 7.61 (1H, s), 7.17-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.94 (s, 2H), 3.76-3.84 (m, 2H), 3.78 (d, 2H), 2.76 (s, 3H), 2.66 (td, 2H), 1.83-1.90 (m, 2H), 1.68-1.82 (m, 3H), 1.29-1.42 (m, 2H). LC-MS: m/z 433.8 (M+H)+
199	 Starting material: (R)-tert-Butyl 3-(((methylsulfonyl)oxy)methyl)-pyrrolidine-1-carboxylate	Conditions: DMSO, 60 °C. 1H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.17-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.80-3.92 (m, 2H), 3.77 (s, 2H), 3.58 (dd, 1H), 3.27-3.53 (m, 2H), 3.18 (dd, 1H), 2.63-2.80 (m, 1H), 2.01-2.17 (m, 1H), 1.68-1.92 (m, 1H), 1.46 (s, 9H). LC-MS: m/z 427.7 (M+H)+
200	 Starting material: (S)-tert-Butyl 3-(((methylsulfonyl)oxy)methyl)-pyrrolidine-1-carboxylate	Conditions: DMSO. 1H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.17-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.80-3.92 (m, 2H), 3.77 (s, 2H), 3.58 (dd, 1H), 3.27-3.53 (m, 2H), 3.18 (dd, 1H), 2.63-2.80 (m, 1H), 2.01-2.17 (m, 1H), 1.68-1.92 (m, 1H), 1.46 (s, 9H). LC-MS: m/z 427.7 (M+H)+

201	 Starting material: (S)-tert-Butyl 3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate	Conditions: DMSO. 1H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.17-7.24 (m, 4H), 6.48 (m, 1H), 4.04 (s, 4H), 3.90-4.02 (br, 1H), 3.75-3.85 (m, 3H), 3.77 (d, 2H), 2.67-3.02 (m, 2H), 1.98-2.11 (m, 1H), 1.82-1.96 (m, 1H), 1.59-1.77 (m, 2H), 1.45 (s, 9H), 1.31-1.42 (m, 1H). LC-MS: m/z 441.9 (M+H)+
202	 Starting material: (R)-tert-Butyl 3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate	Conditions: DMSO, C. 1H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.17-7.24 (m, 4H), 6.48 (m, 1H), 4.04 (s, 4H), 3.90-4.02 (br, 1H), 3.75-3.85 (m, 3H), 3.77 (d, 2H), 2.67 -3.02 (m, 2H), 1.98-2.10 (m, 1H), 1.82-1.96 (m, 1H), 1.6-1.76 (m, 2H), 1.45 (s, 9H), 1.31-1.42 (m, 1H). LC-MS: m/z 441.7 (M+H)+
203	 Starting material: tert-Butyl 4-((methyl-sulfonyl)oxy)piperidine-1-carboxylate	Conditions: DMSO. 1H NMR (Chloroform-d) δ: 7.71 (s, 1H), 7.18-7.24 (m, 4H), 6.49 (m, 1H), 4.48-4.56 (m, 1H), 4.05 (s, 4H), 3.77-3.85 (m, 2H), 3.78 (d, 2H), 3.15 (ddd, 2H), 1.87-1.96 (m, 2H), 1.61-1.72 (m, 2H), 1.46 (s, 9H). LC-MS: m/z 427.8 (M+H)+
204	 Starting material: cis-(4-((tert-Butoxy-	Conditions: 60 °C. 1H NMR (Chloroform-d): δ 7.54 (s, 1H), 7.17-7.24 (m, 4H), 6.48 (m, 1H), 6.02 (br d, 1H), 5.80-5.87 (m, 1H), 5.72-5.80 (m, 1H), 4.76-4.91

	carbonyl)amino)cyclopent-2-en-1-yl)-methyl methanesulfonate	(m, 1H), 4.03 (s, 4H), 3.73-3.85 (m, 2H), 3.76 (s, 2H), 2.99-3.08 (br, 1H), 2.5-2.62 (m, 1H), 1.50-1.58 (m, 1H), 1.48 (s, 9H). LC-MS: m/z 439.5 (M+H)+
205	 Starting material: (1-(Methylsulfonyl)-piperidin-4-yl)methyl methanesulfonate	Conditions: DMSO, G. ^{1}H NMR (Chloroform-d): δ 7.60 (s, 1H), 7.19-7.23 (m, 1H), 7.05-7.10 (m, 2H), 6.48 (s, 1H), 4.05 (br s, 2H), 4.03 (br s, 2H), 3.92-3.89 (m, 2H), 3.77 (s, 2H), 3.74 (d, 2H), 2.79 (s, 3H), 2.69 (td, 2H), 1.96-2.08 (m, 3H), 1.36-1.50 (m, 2H); LC-MS: *m/z* 504.0 $(M+H)^+$
206	 Starting material: 2-(1-Acetylpiperidin-4-yl)ethyl methanesulfonate	Conditions: D. 1H NMR (DMSO-d6) δ: 8.16-8.28 (m, 1 H), 8.14 (s, 1 H), 8.14 (s, 1 H), 7.18-7.26 (m, 4 H), 6.38 (s, 1 H), 3.95 (s, 4 H), 3.84-3.90 (m, 2 H), 3.78 (s, 2 H), 2.98 (s, 2 H), 1.97 (s, 3 H), 1.56 - 1.78 (m, 5 H), 0.82-1.22 (m, 2 H); LC-MS: m/z 397.5 (M+H) +.
207	 Starting material: 1-(Methanesulfonyl)piperidin-4-yl)-methyl methanesulfonate	Conditions: 85 °C, D. 1H NMR (DMSO-d6) δ: 8.16 (s, 1 H), 8.15 (s, 2 H), 8.10-8.14 (m, 1 H), 7.50-7.56 (m, 1 H), 6.41 (s, 1 H), 4.06 (s, 4 H), 3.82 (s, 2 H), 3.70-3.74 (m, 2 H), 3.54-3.63 (m, 4 H), 2.85 (s, 3 H), 2.66-2.78 (m, 3 H), 1.83-1.88 (m, 2 H); LC-MS: m/z 464.4 (M+H)+.

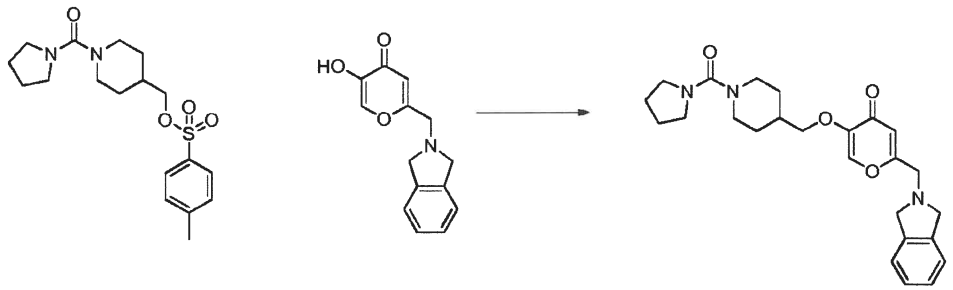
208	 Starting material: 1-(Methanesulfonyl)-piperidin-4-yl)methyl methanesulfonate	Condition: 85 °C. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 7.17 (s, 2 H), 7.07-7.13 (m, 1 H), 6.38 (s, 1 H), 3.88-3.95 (m, 4 H), 3.77 (s, 2 H), 3.69-3.75 (m, 2 H), 3.60-3.62 (m, 1 H), 3.56-3.62 (m, 1 H), 2.85 (s, 2 H), 2.64-2.77 (m, 3 H), 2.44-2.46 (m, 3 H), 1.81-1.90 (m, 3 H), 1.26-1.33 (m, 2 H); LC-MS: m/z 465.6
209	 Starting material: 1-(Methanesulfonyl)-piperidin-4-yl)methyl methanesulfonate	Conditions: D. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 6.81 (s, 2 H), 6.37 (s, 1 H), 5.97 (s, 2 H), 3.84 (s, 4 H), 3.75 (s, 2 H), 3.70-3.74 (m, 2 H), 3.55-3.61 (m, 3 H), 2.85 (s, 2 H), 2.68-2.76 (m, 2 H), 1.78-1.91 (m, 3 H), 1.18-1.36 (m, 2 H); LC-MS: m/z 463.3 (M+H) +.
210	 Starting material: 1-(Methanesulfonyl)-piperidin-4-yl)methyl methanesulfonate	Condition: E. 1H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 6.96-7.04 (m, 2 H), 6.47 (s, 1 H), 3.99 (s, 4 H), 3.80-3.91 (m, 2 H), 3.71-3.79 (m, 4 H), 2.79 (s, 3 H), 2.64-2.75 (m, 2 H), 1.95-2.07 (m, 3 H), 1.35-1.50 (m, 2 H); LC-MS: m/z 455.4 (M+H) +.
211	 Starting material: 1-(Methanesulfonyl)-piperidin-4-yl)methyl methanesulfonate	Conditions: E. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 7.10 (s, 1 H), 7.05 (s, 1 H), 6.99-7.03 (m, 1 H), 6.38 (s, 1 H), 3.90 (s, 4 H), 3.77 (s, 2 H), 3.70-3.74 (m, 2 H), 3.55-3.60 (m, 2 H), 2.85 (s, 3 H), 2.69-2.76 (m, 2 H),

		2.28 (s, 3 H), 1.80-1.88 (m, 3 H), 1.24-1.35 (m, 2 H); LC-MS: m/z 433.7
212	 Starting material: 1-(Methanesulfonyl)-piperidin-4-yl)methyl methanesulfonate	Condition: DMSO, 100°C, E. 1H NMR (DMSO-d6) δ: 8.16 (s, 1 H), 7.17-7.24 (m, 4 H), 6.39 (s, 1 H), 3.86 (s, 2 H), 3.68-3.76 (m, 4 H), 3.54-3.64 (m, 2 H), 2.85 (s, 3 H), 2.68-2.76 (m, 2 H), 1.81-1.88 (m, 3 H), 1.27-1.36 (m, 2 H), 1.26 (s, 6 H); LC-MS: m/z 447.3
213	 Starting material: 3-(1-(Methylsulfonyl)-piperidin-4-yl)propyl methanesulfonate	Condition: DMSO, E. 1H NMR (DMSO-d6) δ: 8.13 (s, 1 H), 7.18-7.27 (m, 4 H), 6.39 (s, 1 H), 3.95 (s, 4 H), 3.75-3.85 (m, 4 H), 3.51-3.57 (m, 2 H), 2.84 (s, 3 H), 2.62-2.69 (m, 2 H), 1.65-1.82 (m, 5 H), 1.33-1.37 (m, 2 H), 1.11-1.20 (m, 2 H); LC-MS: m/z 447.8
214	 Starting material: 4-Methanesulfonate-4-pyridinepropanol	Condition: DMSO, D. 1H NMR (DMSO-d6) δ: 8.45-8.48 (m, 2 H), 8.15-8.17 (m, 2 H), 7.19-7.29 (m, 7 H), 6.40 (s, 1 H), 3.94-3.97 (m, 5 H), 3.78-3.81 (m, 3 H), 2.71-2.76 (m, 2 H), 1.97-2.08 (m, 2 H); LC-MS: m/z 363.3
214a	 Starting material: 4-(Methanesulphonyl-	Conditions: DMSO, 100 °C, B. ^{1}H NMR (DMSO-d_6) δ: 8.12 (s, 1H), 7.90-8.01 (m, 3H), 6.99 (d, 1H), 6.35 (s, 1H), 5.97 (d, 1H), 4.39-4.72 (m, 2H), 3.70 (d, 2H), 3.52-3.57 (m,

	oxymethyl)-1-methanesulphonyl-piperidine	4H), 2.85 (s, 3H), 1.64-1.90 (m, 5H); LC-MS: *m/z* 517.2(M+H)$^+$.
214b	 Starting material: 4-(Methanesulphonyl-oxymethyl)-1-methanesulphonyl-piperidine	Conditions: DMF, 90 °C, D. ^{1}H NMR (DMSO-d_6) δ: 8.13 (s, 1H), 7.85-8.06 (m, 3H), 6.36 (s, 1H), 4.66-4.71 (m, 2H), 4.60-4.64 (m, 2H), 3.68 (d, 2H), 3.56 (br d, 2H), 2.84 (s, 3H), 2.67-2.73 (m, 2H), 1.81 (br d, 3H), 1.21-1.31 (m, 2H) LC-MS: *m/z* 501.2(M+H)$^+$.
214c	 Starting material: 4-(Methanesulphonyl-oxymethyl)-1-methanesulphonyl-piperidine	Conditions: DMF, 90 °C, D. ^{1}H NMR (DMSO-d_6) δ: 8.13 (s, 1H), 7.85-8.06 (m, 3H), 6.36 (s, 1H), 4.66-4.71 (m, 2H), 4.60-4.64 (m, 2H), 3.68 (d, 2H), 3.56 (br d, 2H), 2.84 (s, 3H), 2.67-2.73 (m, 2H), 1.81 (br d, 3H), 1.21-1.31 (m, 2H); LC-MS: *m/z* 501.2(M+H)$^+$.

Example 5.

2-(Isoindolin-2-ylmethyl)-5-((1-(pyrrolidine-1-carbonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 215)



To a solution of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.20 g, 0.82mmol) in DMF (4 ml) were added (1-(pyrrolidine-1-carbonyl)piperidin-4-yl)methyl

4-methylbenzenesulfonate (0.30 g, 0.82 mmol) and K_2CO_3 (0.25 g, 1.8 mmol). The reaction mixture was heated at 80 °C for 2 h. The mixture was cooled to RT. Water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography to afford the title compound (0.084 g). ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.17-7.22 (m, 4H), 6.48 (s, 1H), 4.04 (s, 4H), 3.75-3.84 (m, 4H), 3.72 (d, 2H), 3.32-3.38 (m, 4H), 2.76 (m, 2H), 2.00-2.11 (m, 1H), 1.77-1.90 (m, 6H), 1.22-1.36 (m, 2H). LCMS: *m/z* 438.5 $(M+H)^+$.

The following compounds were prepared according to the procedure described for Compound 215 of Example 5 starting from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

Purification methods used:

A = Crystallization

B = Column chromatography

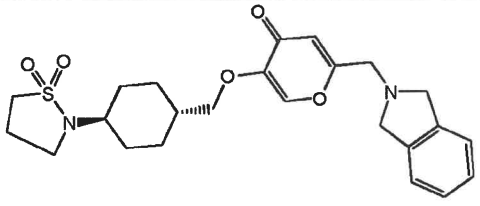
C = Precipitation in aqueous media

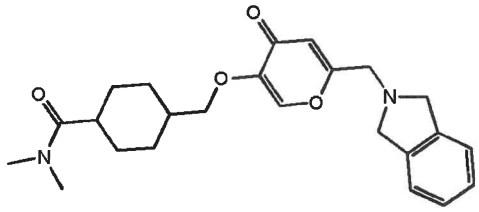
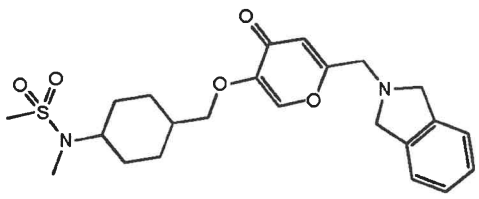
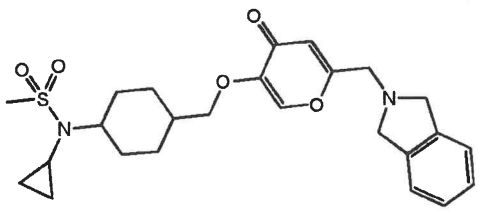
D = Semipreparative HPLC

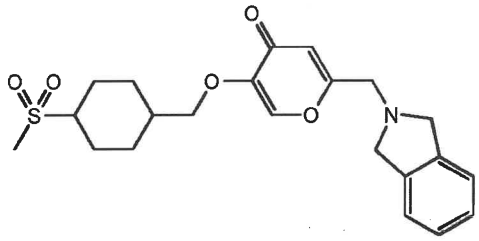
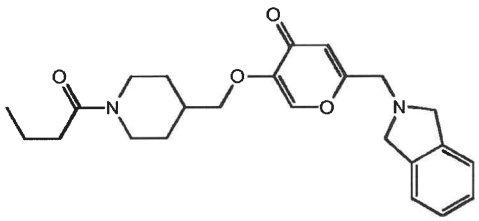
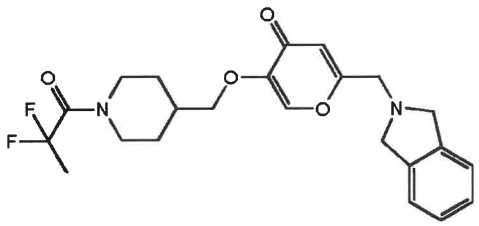
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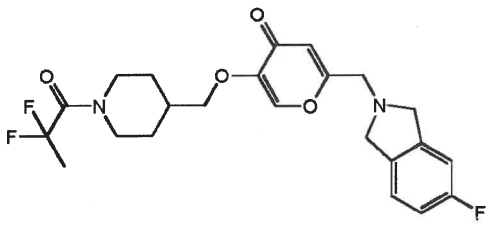
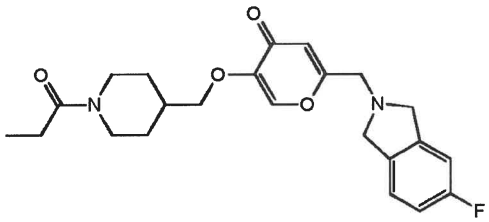
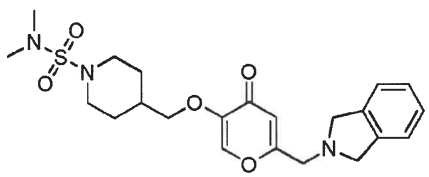
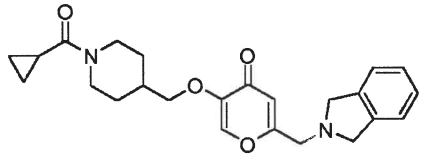
F = Salt formation

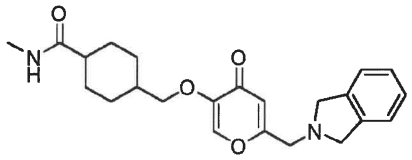
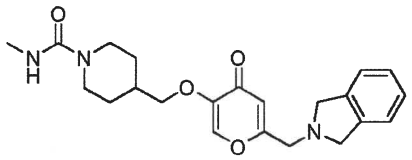
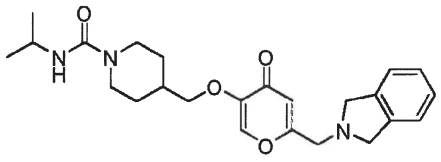
G = As such

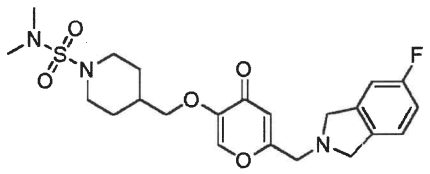
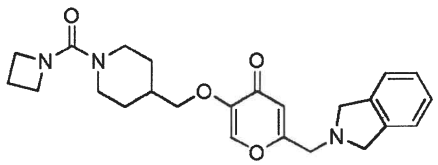
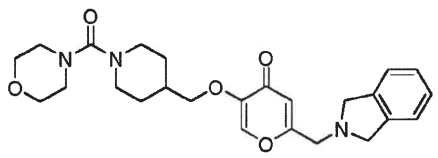
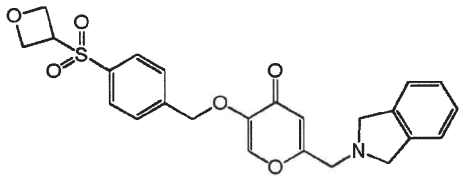
No	Structure and starting material	Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS
216	 Starting material: ((1r,4r)-4-(1,1-Di-	Conditions: 90 °C. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.17-7.22 (m, 4H), 6.48 (s, 1H), 4.03 (s, 4H), 3.76 (s, 2H), 3.65 (d, 2H), 3.36-3.47 (m, 1H), 3.24-3.33 (m,

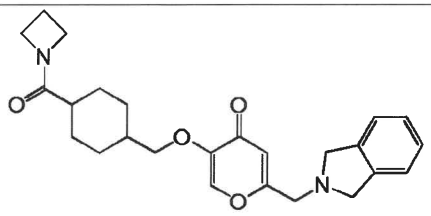
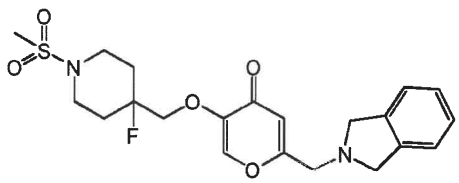
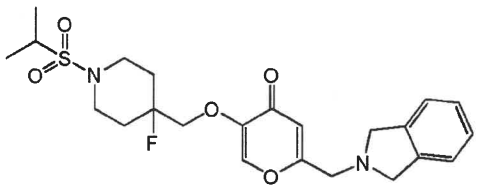
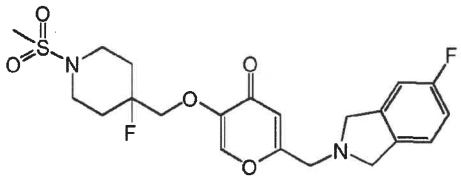
	oxidoisothiazolidin-2-yl)cyclohexyl)-methyl 4-methylbenzenesulfonate	2H), 3.07-3.15 (m, 2H), 2.28-2.40 (m, 2H), 1.90-2.08 (m, 4H), 1.76-1.91 (m, 1H), 1.41-1.58 (m, 2H), 1.00-1.25 (m, 2H). LC-MS: *m/z* 460.5 $(M+H)^+$.
217	 Starting material: (4-(Dimethylcarba-moyl)cyclohexyl)methyl 4-methyl-benzenesulfonate	Conditions: 90 °C. ^{1}H NMR (Chloroform-d) δ: 7.46-7.64 (m, 1H), 7.16-7.23 (m, 4H), 6.48 (s, 1H), 4.03 (s, 4H), 3.76 (s, 2H), 3.69 (d, 2H), 3.02-3.08 (m, 3H), 2.90-2.96 (m, 3H), 2.33-2.55 (m, 1H), 1.78-2.06 (m, 5H), 1.51-1.67 (m, 2H), 1.00-1.26 (m, 2H). LCMS: *m/z* 411.6 $(M+H)^+$.
218	 Starting material: ((1r,4r)-4-(N-methylmethylsulfonamido)cyclohexyl)-methyl 4-methylbenzenesulfonate	Conditions: 90 °C. ^{1}H NMR (Chloroform-d) δ: 7.57-7.70 (m, 1H), 7.19-7.22 (m, 4H), 6.48 (d, 1H), 4.04 (d, 4H), 3.77 (s, 2H), 3.66 (d, 2H), 2.82-2.85 (m, 3H), 2.77-2.80 (m, 3H), 1.93-2.13 (m, 3H), 1.76-1.90 (m, 2H), 1.65-1.75 (m, 1H), 1.47-1.61 (m, 2H), 1.08-1.29 (m, 2H). LCMS: *m/z* 447.5 $(M+H)^+$.
219	 Starting material: (4-(N-cyclopropyl-methylsulfonamido)cyclohexyl)methyl 4-methylbenzenesulfonate	Conditions: 90 °C. ^{1}H NMR (Chloroform-d) δ: 7.65 (s, 1H), 7.19-7.22 (m, 4H), 6.47 (s, 1H), 4.04 (s, 4H), 3.94 (d, 2H), 3.77 (s, 2H), 2.93 (s, 3H), 2.36 (m, 1H), 1.78-2.08 (m, 10H), 0.91-1.01 (m, 2H), 0.76-0.84 (m, 2H). LCMS: *m/z* 473.53 $(M+H)^+$.

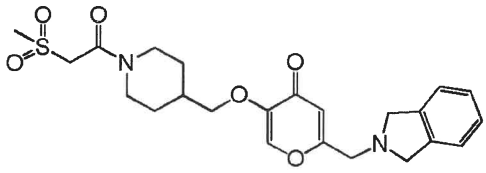
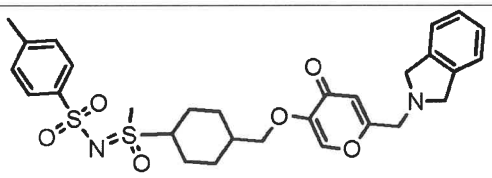
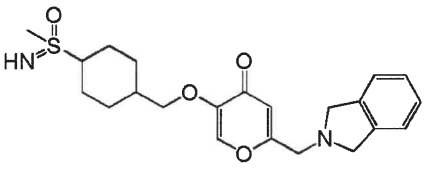
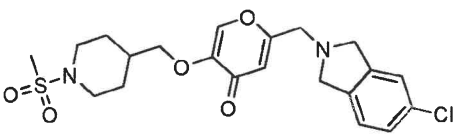
220	 Starting material: (4-(Methylsulfonyl)-cyclohexyl)methyl 4-methylbenzene-sulfonate	Conditions: DMSO. 1H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.19-7.24 (m, 4H), 6.49 (s, 1H), 4.03-4.07 (m, 4H), 3.84 (d, 2H), 3.76 - 3.79 (m, 2H), 2.90-3.01 (m, 1H), 2.88 (s, 3H), 2.82-2.84 (m, 1H), 2.48 - 2.54 (m, 1H), 2.20-2.35 (m, 2H), 1.92 - 2.03 (m, 3H), 1.63 - 1.76 (m, 2H). LC-MS: m/z 418.2 (M+H)+.
221	 Starting material: (1-butyrylpiperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: DMSO. ^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.22 (d, 4H), 6.52 (s, 1H), 4.68 (br d, 1H), 4.53 (s, 1H), 4.08 (s, 4H), 3.81 (s, 2H), 3.65-3.78 (m, 2H), 3.00 - 3.10 (m, 1H), 2.54-2.65 (m, 1H), 2.30 -2.35 (m, 2H), 2.06-2.14 (m, 1H), 2.01 (br d, 1H), 1.84 (br d, 1H), 1.61-1.70 (m, 2H), 1.16-1.30 (m, 2H), 0.97 (m, 3H). LC-MS: m/z 411.3 (M+H)+.
222	 Starting material: (1-(2,2-Difluoro-propanoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: DMSO. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.18-7.23 (m, 4H), 6.49 (s, 1H), 4.54-4.61 (m, 1H), 4.35 (br d, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.73 (m, 2H), 3.03-3.15 (m, 1H), 2.72 (br m, 1H), 2.11-2.23 (m, 1H), 1.97 (br m, 2H), 1.83 (m, 3H), 1.22-1.40 (m, 2H). LC-MS: *m/z* 433.3 $(M+H)^+$.

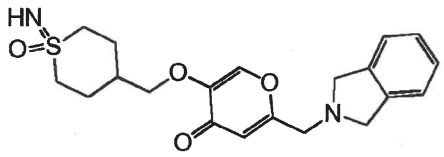
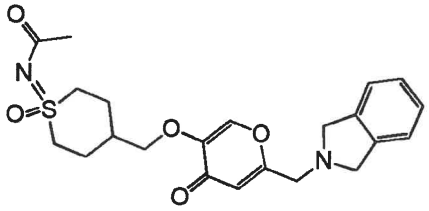
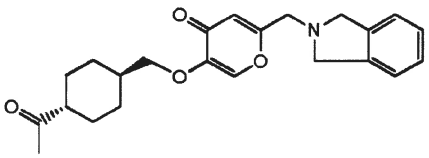
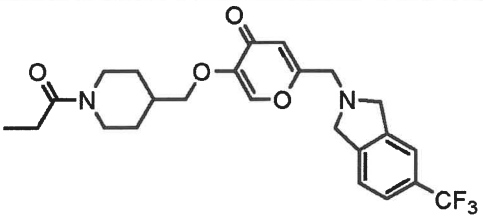
223	 Starting material: (1-(2,2-Difluoro-propanoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: DMSO. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.13 (m, 1H), 6.87-6.94 (m, 2H), 6.48 (s, 1H), 4.57 (br d, 1H), 4.35 (br d, 1H), 4.01 (br d, 4H), 3.76 (s, 2H), 3.73 (m, 2H), 2.99-3.14 (m, 1H), 2.72 (br m, 1H), 2.13-2.25 (m, 1H), 1.96 (br m, 2H), 1.83 (m, 3H), 1.30 (dqd, 2H). LC-MS: *m/z* 451.6 $(M+H)^+$.
224	 Starting material: (1-Propionylpiperi-din-4-yl)methyl 4-methylbenzene-sulfonate	Conditions: DMSO. ^{1}H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.15 (m, 1H), 6.87-6.96 (m, 2H), 6.53 (s, 1H), 4.67 (br d, 1H), 4.06 (d, 4H), 3.90 (br d, 1H), 3.83 (s, 2H), 3.64-3.78 (m, 2H), 3.06 (m, 1H), 2.60 (m, 1H), 2.38 (m, 2H), 2.07-2.19 (m, 1H), 1.97-2.05 (m, 1H), 1.84 (br d, 1H), 1.19-1.33 (m, 2H), 1.15 (m, 3H). LCMS: *m/z* 415.2 $(M+H)^+$.
225	 Starting material: (1-(*N*,*N*-dimethyl-sulfamoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) *δ*: 7.60 (s, 1H), 7.17-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.70-3.76 (m, 4H), 2.81 (s, 6H), 2.77-2.89 (m, 2H), 1.97-2.07 (m, 1H), 1.93 (m, 2H), 1.38 (m, 2H). LC-MS: *m/z* 448.6 $(M+H)^+$.
226	 Starting material: (1-(Cyclopropane-	Conditions: 60 °C. ^{1}H NMR (Chloroform-d) *δ*: 7.60 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.65 (m, 1H), 4.18-4.32 (m, 1H), 4.04

	carbonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	(s, 4H), 3.77 (s, 2H), 3.73 (br m, 2H), 3.12 (m, 1H), 2.63 (m, 1H), 2.08-2.22 (m, 1H), 2.01-2.08 (m, 1H), 1.84 (m, 1H), 1.75 (m, 1H), 1.16-1.37 (m, 2H), 0.92-1.01 (m, 2H), 0.74 (m, 2H). LC-MS: *m/z* 409.5 $(M+H)^+$.
227	 Starting material: (4-(Methylcarbamoyl)cyclohexyl)methyl 4-methylbenzenesulfonate	^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.18-7.23 (m, 4H), 6.49 (s, 1H), 4.39 (br s, 1H), 4.04 (s, 4H), 3.97 (m, 2H), 3.77 (s, 2H), 3.71 (m, 2H), 2.81 (d, 5H), 1.98-2.13 (m, 1H), 1.89 (m, 2H), 1.17-1.32 (m, 2H). LC-MS: *m/z* 397.5 $(M+H)^+$.
228	 Starting material: (1-(Methylcarbamoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.15-7.23 (m, 4H), 6.49 (s, 1H), 4.39 (br s, 1H), 4.04 (s, 4H), 3.97 (m, 2H), 3.77 (s, 2H), 3.71 (d, 2H), 2.75-2.86 (m, 5H), 1.99-2.11 (m, 1H), 1.89 (m, 2H), 1.25 (m, 2H). LC-MS: *m/z* 398.5 $(M+H)^+$.
229	 Starting material: (1-(Isopropylcarbamoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Condition: E (in Et_2O). ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.17-7.24 (m, 4H), 6.49 (s, 1H), 4.20 (br d, 1H), 4.04 (s, 4H), 3.91-3.99 (m, 3H), 3.77 (s, 2H), 3.72 (d, 2H), 2.72-2.85 (m, 2H), 1.98-2.11 (m, 1H), 1.88 (m, 2H), 1.20-1.33 (m, 2H), 1.15 (d, 6H). LC-MS: *m/z* 426.6 $(M+H)^+$.

230	 Starting material: (1-(*N*,*N*-Dimethyl-sulfamoyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: C. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.11-7.16 (m, 1H), 6.87-6.95 (m, 2H), 6.48 (s, 1H), 4.02 (s, 2H), 3.99 (s, 2H), 3.70-3.78 (m, 6H) 2.81 (s, 6H), 2.78-2.88 (m, 2H), 1.97-2.06 (m, 1H), 1.93 (m, 2H), 1.38 (m, 2H). LC-MS: *m/z* 466.5 $(M+H)^+$.
231	 Starting material: (1-(Azetidine-1-carbonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	^{1}H NMR (Chloroform-d) δ: 7.55-7.62 (s, 1H), 7.15-7.25 (m, 4H), 6.48 (s, 1H), 4.04 (s, 4H), 3.94-4.01 (m, 4H), 3.89 (m, 2H), 3.77 (s, 2H), 3.70 (d, 2H), 2.69-2.83 (m, 2H), 2.15-2.27 (m, 2H), 1.99-2.12 (m, 1H), 1.85 (m, 2H), 1.23 (m, 2H). LC-MS: *m/z* 424.5 $(M+H)^+$.
232	 Starting material: (1-(Morpholine-4-carbonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: C and E. ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.71-3.78 (m, 4H), 3.64-3.70 (m, 4H), 3.22-3.28 (m, 4H), 2.81 (m, 2H), 1.99-2.12 (m, 1H), 1.87 (m, 2H), 1.24-1.35 (m, 2H). LC-MS: *m/z* 454.5 $(M+H)^+$.
233	 Starting material: 4-(Oxetan-3yl-sulfonyl)benzyl 4-methylbenzene-sulfonate	Conditions: DMSO, C. ^{1}H NMR (Chloroform-d) δ: 7.92 (m, 2 H), 7.66 (m, 3 H), 7.21 (m, 4 H), 6.53 (s, 1 H), 5.17 (s, 2 H), 4.97 (dd, 2 H), 4.79 (t, 2 H), 4.45 (tt, 1 H), 4.04 (s, 4 H), 3.78 (s, 2 H); LC-MS: *m/z* 454.7 $(M+1)^+$.

234	 Starting material: (4-(Azetidine-1-carbonyl)cyclohexyl)methyl 4-methyl-benzenesulfonate	1H NMR (Chloroform-d) δ: 7.59 (s, 1 H), 7.23 (m, 4 H), 6.51 (s, 1 H), 3.97-4.17 (m, 8 H), 3.87 (s, 2 H), 3.67-3.78 (m, 2 H), 1.50-2.35 (m, 10 H), 1.11 (m, 2 H); LC-MS: m/z 423.6 (M+1)+.
235	 Starting material: (4-Fluoro-1-(methyl-sulfonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: DMSO, Cs_2CO_3. 1H NMR (Chloroform-d) δ: 7.77 (s, 1H), 7.26-7.18 (m, 4H), 6.50 (s, 1H), 4.09 (d, 2H, J = 19.5 Hz), 4.045 (br s, 4H) 3.779 (s, 2H), 3.75-3.71 (m, 2H), 3.06-2.99 (m, 2H), 2.81 (s, 3H), 2.16-2.08 (m, 2H), 1.99-1.83 (m, 2H); LC-MS: m/z 437.8 (M+1)+.
236	 Starting material: (4-Fluoro-1-(iso-propylsulfonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: DMSO, Cs_2CO_3. 1H NMR (Chloroform-d) δ: 7.77 (s, 1H), 7.21-7.19 (m, 4H), 6.50 (s, 1H), 4.07 (d, 2H, J=20 Hz), 4.05 (s, 4H), 3.80-3.72 (m, 4H), 3.29-3.16 (m, 3H), 2.09-2.00 (m, 2H), 1.95-1.76 (m, 2H), 1.35 (d, 6H, J=6.8 Hz); LC-MS: m/z 465.7 (M+1)+.
237	 Starting material: (4-Fluoro-1-(methyl-sulfonyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate;	Conditions: DMSO, Cs_2CO_3. 1H NMR (Chloroform-d) δ: 7.77 (s, 1H), 7.16-7.11 (m, 1H), 6.95-9.88 (m, 2H), 6.49 (s, 1H), 4.09 (d, 2H, 20 Hz), 4.04-3.98 (m, 4H), 3.78-3.71 (m, 4H), 3.07-2.99 (m, 2H), 2.82 (s, 3H), 2.17-2.07 (m, 2H), 2.00-1.82 (m, 2H); LC-MS: m/z 455.1 (M+1)+.

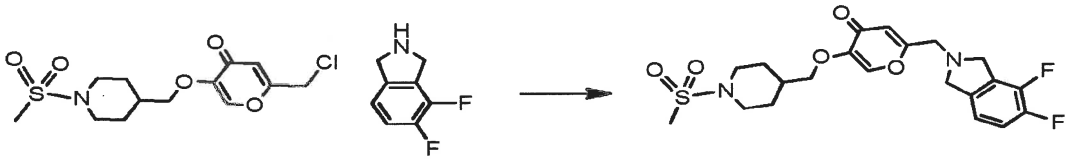
238	 (tosylate) Starting material: (1-(2-(Methyl-sulfonyl)acetyl)piperidin-4-yl)methyl 4-methylbenzenesulfonate	Conditions: 70 °C. 1H NMR (Methanol-d) δ: 8.10 (s, 1 H), 7.69 (d, 2 H), 7.34 (s, 4 H), 7.22 (d, 2 H), 6.65 (s, 1 H), 4.32-4.63 (m, 9 H), 4.10 (br d, 1 H), 3.78 (d, 2 H), 3.21 (m, 1 H), 3.12 (s, 3 H), 2.77 (td, 1 H), 2.36 (s, 3 H), 2.15 (br s, 1 H), 1.95 (m, 2 H), 1.45 (m, 1 H), 1.29 (m, 1 H); LC-MS: m/z 461.8 (M+1)+.
239	 (formate) Starting material: (4-(S-Methyl-N-tosylsulfonimidoyl)cyclohexyl)methyl-4-methylbenzenesulfonate	Conditions: 70 °C. 1H NMR (Chloroform-d) δ: 8.04 (s, 1 H), 7.85 (d, 2 H), 7.61 (m, 1 H), 7.27 (m, 2 H), 7.22 (m, 4 H), 6.50 (m, 1 H), 4.08 (m, 4 H), 3.83 (m, 4 H), 3.33 (m, 4 H), 2.40 (s, 3 H), 1.50-2.30 (m, 9 H); LC-MS: m/z 571.8 (M+1)+.
240	 (formate) Starting material: (4-(S-Methylsulfon-imidoyl)cyclohexyl)methyl 4-methyl-benzenesulfonate	Conditions: 70 °C. 1H NMR (Chloroform-d) δ: 8.12 (br, 1 H), 7.62 (d, 1 H), 7.22 (m, 4 H), 6.51 (s, 1 H), 4.07 (d, 4 H), 3.87 (d, 1 H), 3.81 (d, 2 H), 3.72 (d, 1 H), 2.95 (m, 4 H), 1.97-2.38 (m, 5 H), 1.54-1.96 (m, 4 H), 1.22 (m, 1 H); LC-MS: m/z 417.3 (M+1)+.
241	 Starting material: (1-(Methylsulfonyl)-piperidin-4-yl)methyl 4-methyl-benzenesulfonate	Conditions: 85°C, C. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 7.33 (s, 1 H), 7.26 (s, 2 H), 6.39 (s, 1 H), 3.94 (s, 2 H), 3.93 (br s, 2 H), 3.78 (s, 1 H), 3.69-3.75 (m, 2 H), 3.54-3.61 (m, 2 H), 2.85 (s, 3 H), 2.65-2.77 (m, 3 H), 1.78-1.90 (m, 3 H), 1.23-1.33

		(m, 2 H); LC-MS: m/z 453.3
242	 Starting material: (1-imino-1-oxidotetrahydro-2H-thiopyran-4-yl)methyl 4-methylbenzenesulfonate	Condition: 1,4-dioxane, reflux. 1H NMR (DMSO-d6) δ: 8.15 (s, 1 H), 7.17-7.27 (m, 4 H), 6.39 (s, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.71-3.77 (m, 2 H), 3.63-3.69 (m, 1 H), 2.96-3.08 (m, 4 H), 2.00-2.09 (m, 3 H), 1.64-1.73 (m, 2 H)); LC-MS: m/z 389.3
243	 Starting material: (1-(Acetylimino)-1-oxidotetrahydro-2H-thiopyran-4-yl)-methyl 4-methylbenzenesulfonate	Condition: D. 1H NMR (DMSO-d6) δ: 8.12-8.18 (m, 1 H), 7.17-7.27 (m, 4 H), 6.39-6.41 (m, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.71-3.77 (m, 2 H), 3.55-3.65 (m, 2 H), 3.39 (s, 2 H), 2.05-2.22 (m, 3 H), 1.97 (s, 1 H), 1.94 (s, 2 H), 1.55-1.84 (m, 2 H); LC-MS: m/z 431.3
244	 Starting material: ((1r,4r)-4-Acetyl-cyclohexyl)methyl 4-methylbenzene-sulfonate	Condition: F and E. 1H NMR (DMSO-d6) δ: 8.20 (s, 1 H), 7.33-7.42 (m, 4 H), 6.73 (s, 1 H), 4.58 (br s, 2 H), 3.63-3.68 (m, 1 H), 2.29-2.36 (m, 1 H), 2.06-2.12 (m, 3 H), 1.81-1.95 (m, 4 H), 1.62-1.75 (m, 1 H), 1.17-1.29 (m, 4 H), 1.07-1.11 (m, 2 H), 1.00-1.07 (m, 1 H), 0.83-0.89 (m, 1 H); LC-MS: m/z 382.7
244a	 Starting material: (1-Propionyl-piperidin-4-yl)methyl 4-methyl-	Conditions: DMSO, 80 °C, B. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.49 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 6.49 (s, 1H), 4.68 (br d, 1H), 4.09 (s, 3H), 3.89 (br d, 1H), 3.79 (s, 2H), 3.66-3.77 (m, 2H), 3.50-3.62 (m,

	benzenesulfonate	1H), 2.96-3.10 (m, 1H), 2.53-2.63 (m, 1H), 2.31-2.39 (m, 2H), 2.06-2.18 (m, 1H), 1.99 (br d, 1H), 1.79-1.89 (m, 1H), 1.18-1.30 (m, 2H), 1.14 (m, 3H); LC-MS: *m/z* 465.5 $(M+H)^+$.

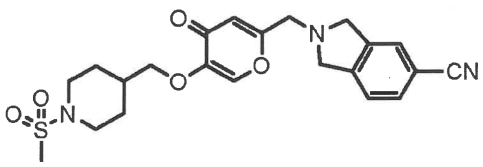
Example 6.

2-((4,5-Difluoroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 245)



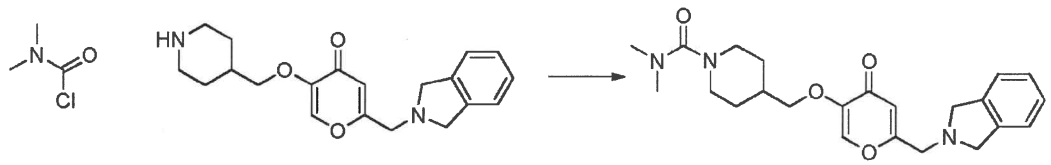
To a solution of 2-(chloromethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (0.15 g, 0.45 mmol) in ACN (10 ml) were added 4,5-di-fluoroisoindoline, HCl (0.08 g, 0.45 mmol), K_2CO_3 (0.15 g, 1.12 mmol) and KI (0.07 g, 0.45 mmol). The reaction mixture was heated at 90 °C for 2 h. The mixture was cooled to RT, water (10 ml) was added and the product was extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography to afford the title product. ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.00-7.07 (m, 1H), 6.87-6.92 (m, 1H), 6.48 (s, 1H), 4.11-4.15 (m, 4H), 4.02 (s, 2H), 3.86 (br d, 2H), 3.77 (s, 2H), 3.74 (d, 2H), 2.79 (s, 3H), 2.65-2.73 (m, 1H), 1.97-2.03 (m, 4H).

The following compounds were prepared according to the procedure described for Compound 245 of Example 6 starting from 2-(chloromethyl)-5-((1-(methylsulfonyl)-piperidin-4-yl)methoxy)-4H-pyran-4-one and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

245a	 Starting material: Isoindoline-5-carbo-nitrile hydrochloride	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.52-7.56 (m, 1H), 7.49 (s, 1H), 7.31 (d, 1H), 6.48 (s, 1H), 4.05-4.13 (br s, 4H), 3.82-3.90 (m, 2H), 3.79 (s, 2H), 3.74 (d, 2H), 2.79 (s, 3H), 2.64-2.74 (m, 2H), 1.96-2.07 (m, 3H), 1.33-1.51 (m, 2H); LC-MS: *m/z* 444.3 $(M+H)^+$.

Example 7.

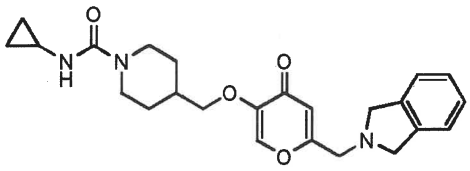
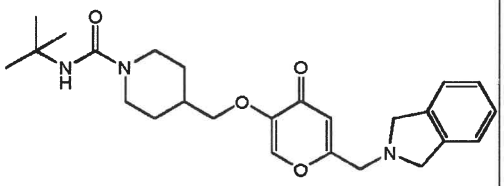
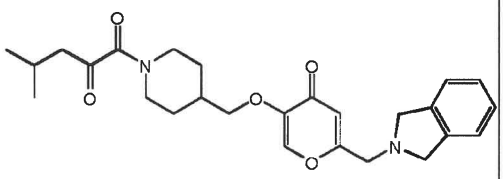
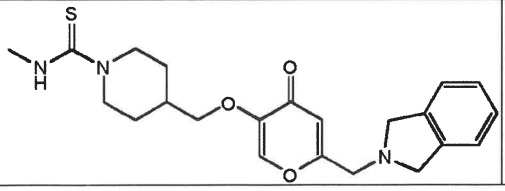
4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-carboxamide (Compound 246)

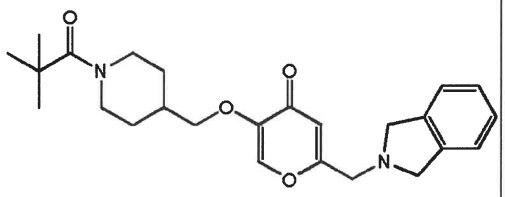
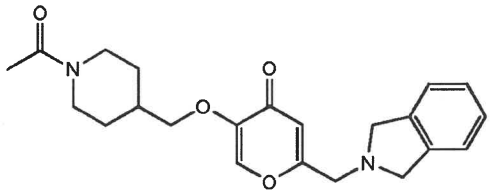
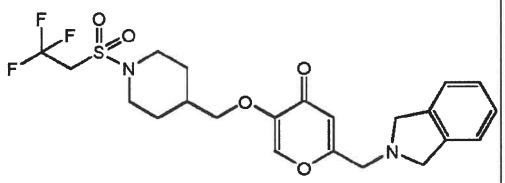
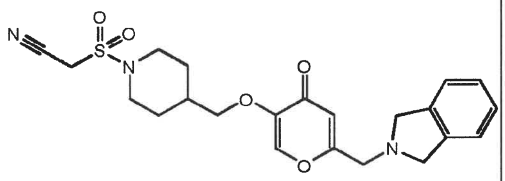


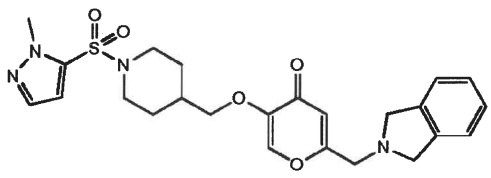
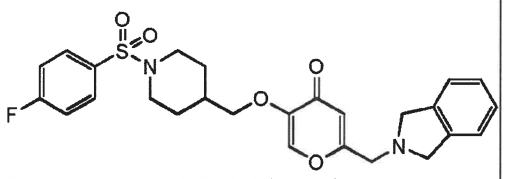
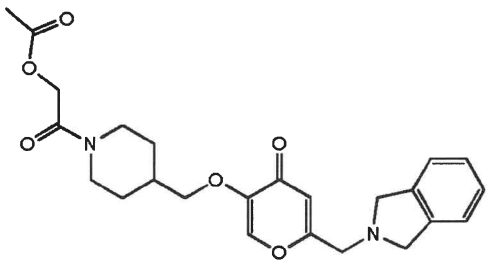
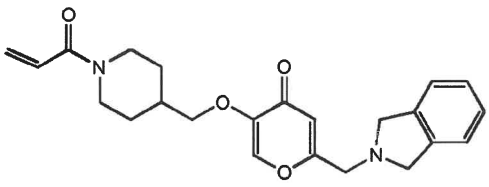
A round-bottomed-flask was charged with 2-(isoindolin-2-ylmethyl)-5-(piperidin-4-ylmethoxy)-4*H*-pyran-4-one trifluoroacetate (0.36 g), CH_2Cl_2 (3 mL), dimethylcarbamoyl chloride (0.10 mL, 1.1 mmol) and Et_3N (0.4 mL, 2.9 mmol). After 3 h at RT the reaction was not complete (LC-MS), so more of dimethylcarbamyl chloride (0.10 mL, 1.1 mmol) and Et_3N (0.4 mL, 2.9 mmol) were added. The solution was concentrated and then saturated $NaHCO_3$ was added. Aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography to give the title compound (0.07 g). ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.65-3.75 (m, 4H), 2.82 (s, 6H), 2.73-2.81 (m, 2H), 1.97-2.12 (m, 1H), 1.79-1.93 (m, 2H), 1.30 (m, 2H). LC-MS: *m/z* 412.6 $(M+H)^+$.

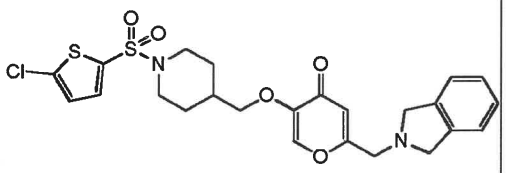
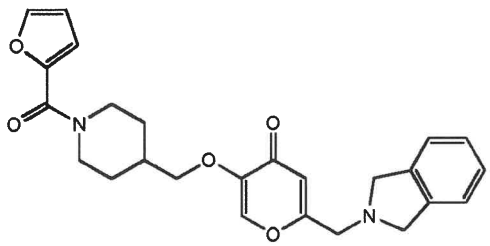
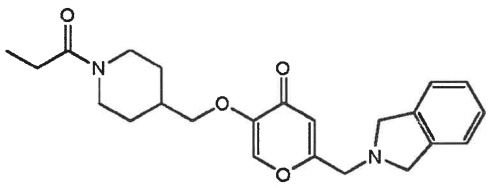
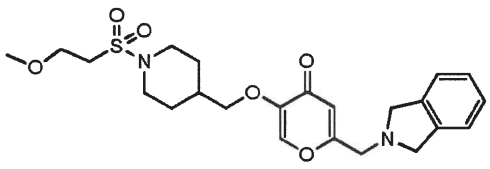
The following compounds were prepared according to the procedure described for Compound 246 of Example 7 starting from 2-(isoindolin-2-ylmethyl)-5-(piperidin-4-

ylmethoxy)-4*H*-pyran-4-one trifluoroacetate and another appropriate starting material. The characterization data and the starting material are indicated on the table.

No	Structure and starting material	^{1}H NMR (400 MHz) / LC-MS
247	 Starting material: Cyclopropyl iso-cyanate	^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.17-7.25 (m, 4H), 6.50 (s, 1H), 4.72 (br s, 1H), 4.05 (s, 4H), 3.94 (br d, 2H), 3.78 (s, 2H), 3.70 (d, 2H), 2.79 (br m, 2H), 2.60-2.68 (m, 1H), 1.96-2.17 (m, 1H), 1.87 (br d, 2H), 1.24 (qd, 2H), 0.68-0.75 (m, 2H), 0.42-0.49 (m, 2H). LC-MS: *m/z* 341.3 $(M+H)^+$.
248	 Starting material: tert-Butylisocyanate	^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.18-7.23 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.92 (br d, 2H), 3.77 (s, 2H), 3.71 (d, 2H), 2.76 (m, 2H), 1.97-2.10 (m, 1H), 1.87 (br m, 2H), 1.17-1.31 (m, 2H). LC-MS: *m/z* 440.3 $(M+H)^+$.
249	 Starting material: 4-Methyl-2-oxo-valeric acid	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.19-7.23 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.72-3.76 (m, 2H), 2.98-3.15 (m, 2H), 2.62-2.66 (m, 2H), 2.15-2.24 (m, 4H), 1.96 (br d, 2H), 1.23-1.38 (m, 2H), 0.97 (d, 6H) LCMS: *m/z* 453.4 $(M+H)^+$.
250		^{1}H NMR (Chloroform-d) δ: 7.63 (s, 1H), 7.14-7.31 (m, 4H), 6.55 (s, 1H), 5.80 (br s, 1H), 4.65 (br d, 2H), 4.09-

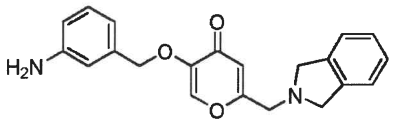
	Starting material: Methyl isothio-cyanate	4.20 (m, 4H), 3.87 (s, 2H), 3.71 (d, 2H), 3.16 (d, 3H), 2.98-3.12 (m, 2H), 2.05-2.23 (m, 1H), 1.79-2.01 (m, 2H), 1.25-1.42 (m, 2H). LCMS: *m/z* 414.7 $(M+H)^+$.
251	 Starting material: Trimethylacetyl chloride	^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.19-7.29 (m, 4H), 6.50-6.62 (m, 1H), 4.47 (br d, 2H), 4.20 (s, 4H), 3.92 (s, 2H), 3.70 (d, 2H), 2.83 (br m, 2H), 2.00-2.21 (m, 1H), 1.92 (br d, 2H), 1.28 (s, 9H), 1.12-1.27 (m, 2H). LCMS: *m/z* 425.8 $(M+H)^+$.
252	 Starting material: Acetyl chloride	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.18-7.23 (m, 4H), 6.49 (s, 1H), 4.61-4.70 (m, 2H), 4.04 (s, 4H), 3.85 (br d, 2H), 3.67-3.79 (m, 2H), 3.02-3.13 (m, 2H), 2.83-2.95 (m, 1H), 2.51-2.63 (m, 2H), 2.10 (s, 3H), 1.78-1.88 (m, 2H). LC-MS: *m/z* 383.2 $(M+H)^+$.
253	 Starting material: 2,2,2-Trifluoro-ethanesulfonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.21 (d, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.91 (br d, 2H), 3.66-3.79 (m, 7H), 2.89 (m, 2H), 1.93-2.11 (m, 3H), 1.41 (qd, 2H). LC-MS: *m/z* 487.5 $(M+H)^+$.
254	 Starting material: Cyanomethane-sulfonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.19-7.22 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 4.01 (br m, 2H), 3.93-3.95 (m, 2H), 3.75-3.79 (m, 4H), 3.06 (m, 2H), 1.96-2.14 (m, 3H), 1.39-1.52 (m, 2H). LC-MS: *m/z* 444.5 $(M+H)^+$.

255	 Starting material: 1-Methyl-1H-pyrazole-5-sulphonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.50 (d, 1H), 7.18-7.24 (m, 4H), 6.69 (d, 1H), 6.49 (s, 1H), 4.10 (s, 3H), 4.09 (s, 4H), 3.84-3.91 (m, 2H), 3.80 (s, 2H), 3.74 (d, 2H), 2.55-2.65 (m, 2H), 1.88-2.01 (m, 3H), 1.35-1.49 (m, 2H). LC-MS: *m/z* 485.5 $(M+H)^+$.
256	 Starting material: 4-Fluorobenzenesulfonyl chloride	^{1}H NMR (DMSO-d_6) δ: 8.19 (s, 1H), 7.79-7.87 (m, 2H), 7.45-7.55 (m, 2H), 7.32-7.43 (m, 4H), 6.68 (s, 1H), 4.43-4.84 (m, 6H), 3.63-3.71 (m, 4H), 2.23-2.34 (m, 2H), 1.65-1.86 (m, 3H), 1.20-1.39 (m, 2H). LCMS: *m/z* 499.5 $(M+H)^+$.
257	 Starting material: Acetoxyacetyl chloride	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.18-7.26 (m, 4H), 6.49 (s, 1H), 4.73 (d, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.65-3.77 (m, 2H), 3.08 (br m, 1H), 2.58-2.71 (m, 1H), 2.11-2.21 (m, 4H), 1.96-2.07 (m, 1H), 1.87 (br d, 1H), 1.17-1.37 (m, 2H). LC-MS: *m/z* 441.5 $(M+H)^+$.
258	 Starting material: Acryloyl chloride	^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.17-7.24 (m, 4H), 6.53-6.64 (m, 1H), 6.49 (s, 1H), 6.22-6.30 (m, 1H), 5.61-5.72 (m, 1H), 4.71 (br d, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.73 (br m, 2H), 3.09 (br m, 1H), 2.68 (br m, 1H), 2.08-2.24 (m, 1H), 1.82-2.05 (m, 2H), 1.14-1.37 (m, 2H). LC-MS: *m/z* 399.5 $(M+H)^+$.

259	 Starting material: 5-Chlorothiophene-2-sulfonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.31 (d, 1H), 7.18-7.22 (m, 4H), 6.98 (d, 1H), 6.49 (s, 1H), 4.05 (s, 4H), 3.82 (br d, 2H), 3.78 (s, 2H), 3.72 (d, 2H), 2.43 (m, 2H), 1.97 (br d, 2H), 1.83-1.93 (m, 1H), 1.44 (qd, 2H). LCMS: *m/z* 521.4 $(M+H)^+$.
260	 Starting material: 2-Furoyl chloride	^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.47 (s, 1H), 7.21 (s, 4H), 6.96 (d, 1H), 6.44-6.52 (m, 2H), 4.04 (s, 4H), 3.70-3.83 (m, 4H), 3.05 (br s, 2H), 2.20 (br d, 1H), 1.98 (br d, 2H), 1.35 (qd, 2H). LCMS: *m/z* 435.5 $(M+H)^+$.
261	 Starting material: Propanesulfonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.60 (br s, 1H), 7.21 (br s, 4H), 6.50 (br s, 1H), 4.68 (br d, 1H), 4.05 (br s, 4H), 3.62-3.94 (m, 5H), 3.04 (br m, 1H), 2.59 (br m, 1H), 2.35 (br d, 2H), 1.78-2.18 (m, 3H), 1.06-1.32 (m, 5H). LC-MS: *m/z* 397.6 $(M+H)^+$.
262	 Starting material: 2-Methoxyethane-sulfonyl chloride	^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.18-7.26 (m, 4H), 6.53 (s, 1H), 4.10 (s, 4H), 3.78-3.86 (m, 4H), 3.69-3.78 (m, 4H), 3.38 (s, 3H), 3.20 (m, 2H), 2.82 (m, 2H), 2.00-2.07 (m, 1H), 1.96 (br d, 2H), 1.32-1.45 (m, 2H). LC-MS: *m/z* 463.4 $(M+H)^+$.

Example 8.

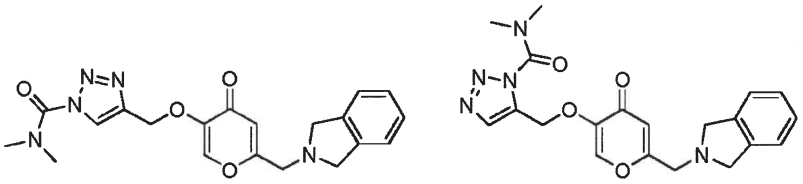
5-((3-Aminobenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 263)



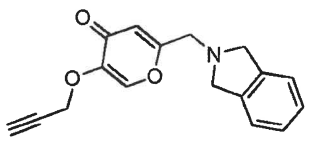
A round-bottomed flask was charged with 2-(isoindolin-2-ylmethyl)-5-((3-nitrobenzyl)oxy)-4*H*-pyran-4-one (0.640 g, 1.69 mmol), MeOH (17 mL), ammonium chloride (0.226 g, 4.23 mmol) and zinc dust (1.10 g, 16.9 mmol). The mixture was refluxed until the reaction was complete. Filtatration through a pad of Celite® was followed by concentration of the aliquots. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were dried (Na_2SO_4), filtered and concentrated to yield the title compound (0.48 g). ^{1}H NMR (DMSO-d6) δ: 8.14 (s, 1H), 7.17-7.27 (m, 4H), 7.01 (m, 1H), 6.60 (s, 1H), 6.52 (m, 2H), 6.40 (s, 1H), 5.13 (s, 2H), 4.78 (s, 2H), 3.95 (s, 4H), 3.79 (s, 2H). LC-MS: m/z 349.4 $(M+H)^+$.

Example 9.

4/5-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 264)



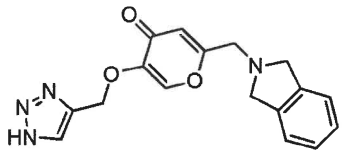
a) 2-(Isoindolin-2-ylmethyl)-5-(prop-2-yn-1-yloxy)-4*H*-pyran-4-one



The title compound was prepared from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (0.487 g, 2.0 mmol), propargyl chloride (0.6 mL, 8.3 mmol) and K_2CO_3 (0.553 g, 4.0 mmol) in DMF (5 mL) at 50 °C according to the procedure of Example 1, Compound 1. After quenching the reaction with water the aqueous layer was extracted with EtOAc. Combined organic layers were washed with water, dried over anhydrous

Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (350 mg). LC-MS: *m/z* 282.2 $(M+H)^+$.

b) 5-((1*H*-1,2,3-Triazol-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one



A flask was charged with 2-(isoindolin-2-ylmethyl)-5-(prop-2-yn-1-yloxy)-4*H*-pyran-4-one (0.35 g, 1.244 mmol) and DMSO (3 mL). Azidotrimethylsilane (0.165 mL, 1.244 mmol), H_2O (3 mL), sodium L-ascorbate (0.049 g, 0.249 mmol) and copper(II) sulfate pentahydrate (0.031 g, 0.124 mmol) were then added. The mixture was heated to 70 °C until the reaction was complete (LC-MS). Mixture was diluted with H_2O and solids were filtered off. The aqueous layer was extracted with EtOAc. Combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was treated first with EtOAc and then with EtOAc/Et_2O to afford the title compound as a precipitate (0.056 g). LC-MS: *m/z* 325.3.

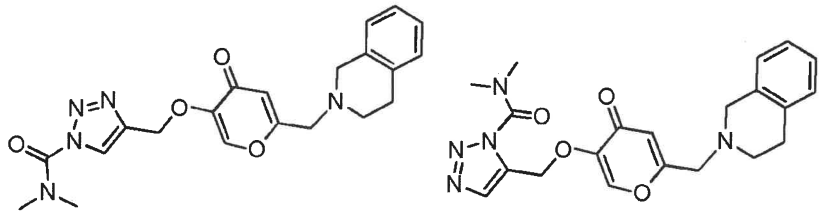
c) 4/5-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 264)

A round-bottomed flask was charged with 5-((1*H*-1,2,3-triazol-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (0.058 g, 0.179 mmol), acetonitrile (3 mL), Et_3N (0.087 ml, 0.626 mmol), dimethylcarbamyl chloride (0.028 ml, 0.304 mmol) and DMAP (4.37 mg, 0.036 mmol). The solution was allowed to react at RT until complete (LC-MS). Reaction was quenched with saturated $NaHCO_3$ solution and the aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography to afford the title compounds (40 mg).

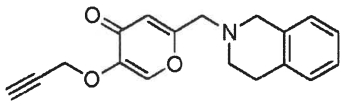
Isomer 1 (Compound 264a): ^1H NMR (Chloroform-d) δ: 7.93 (s, 1H), 7.77 (s, 1H), 7.16-7.24 (m, 4H), 6.51 (s, 1H), 5.27 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.22 (br s, 3H), 3.19 (br s, 3H). LC-MS: *m/z* 396.4 $(M+H)^+$.

Isomer 2 (Compound 264b): ^{1}H NMR (Chloroform-d) δ: 8.26 (s, 1H), 7.84 (s, 1H), 7.16-7.24 (m, 4H), 6.52 (s, 1H), 5.27 (s, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.34 (br s, 3H), 3.19 (br s, 3H). LC-MS: *m/z* 396.4 $(M+H)^+$.

Example 10. 4/5-(((6-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 265)

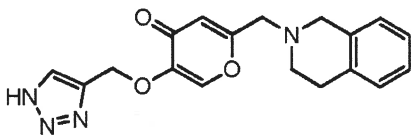


a) 2-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-5-(prop-2-yn-1-yloxy)-4*H*-pyran-4-one



Title compound was prepared from 2-{[3,4-dihydroisoquinolin-2(1*H*)-yl]-methyl}-5-hydroxy-4*H*-pyran-4-one (0.515 g, 2.0 mmol), propargyl chloride (0.15 mL, 2.07 mmol), K_2CO_3 (0.553 g, 4.0 mmol) in DMF (5 mL) at 50 °C according to the procedure of Example 1, Compound 1. After quenching the reaction with water, the aqueous layer was extracted with EtOAc. Combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the title compound (0.45 g). LC-MS: *m/z* 296.3 $(M+H)^+$.

b) 5-((1*H*-1,2,3-Triazol-4-yl)methoxy)-2-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-4*H*-pyran-4-one



Title compound was prepared from 2-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-5-(prop-2-yn-1-yloxy)-4*H*-pyran-4-one (0.15 g, 0.51 mmol), azidotrimethylsilane (0.067

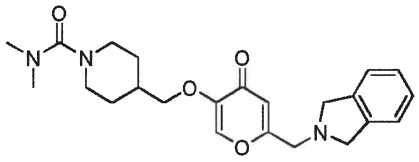
mL, 0.51 mmol), sodium L-ascorbate (0.020 g, 0.10 mmol) and copper (II) sulfate pentahydrate (0.013 g, 0.05 mmol) in DMSO/H_2O (1:1, 4 mL) as described in step (b) of Example 9. The reaction was quenched with water and extracted with EtOAc. The aqueous layer was adjusted to pH 7 and extracted with EtOAc. Combined second extracts were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the title compound. ^{1}H NMR (Chloroform-d) δ: 13.35 (br s, 1H), 7.81 (s, 1H), 7.58 (s, 1H), 7.10-7.18 (m, 3H), 7.01 (m, 1H), 6.59 (s, 1H), 5.12 (s, 2H), 3.73 (s, 2H), 3.59 (s, 2H), 2.91-2.97 (m, 2H), 2.80-2.91 (m, 2H). LC-MS: *m/z* 339.3 $(M+H)^+$.

c) 4-(((6-((3,4-Dihydroisoquinolin-2(1*H*)-yl)methyl)-4-oxo-4*H*-pyran-3-yl)-oxy)methyl)-*N*,*N*-dimethyl-1*H*-1,2,3-triazole-1-carboxamide (Compound 265)

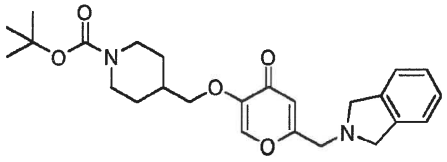
The title compound was prepared from 5-((1H-1,2,3-triazol-4-yl)methoxy)-2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4H-pyran-4-one (0.08 g, 0.236 mmol), triethylamine (0.1 mL, 0.72 mmol), dimethylcarbamyl chloride (0.033 mL, 0.36 mmol) and DMAP (5.8 mg, 0.05 mmol) in acetonitrile (3 mL) as described in step (c) of Example 9. Crude material was purified by column chromatography to afford the title compound (0.033 g). Major isomer (Compound 265a): ^{1}H NMR (Chloroform-d) δ: 7.91-7.94 (m, 1H), 7.77 (s, 1H), 7.08-7.17 (m, 3H), 6.99 (m, 1H), 6.52 (s, 1H), 5.26 (s, 2H), 3.71 (s, 2H), 3.55 (s, 2H), 3.33 (br s, 3H), 3.21 (br s, 3H), 2.90-2.97 (m, 2H), 2.80-2.86 (m, 2H). LC-MS: *m/z* 410.4 $(M+H)^+$.

Example 11.

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethyl-piperidine-1-carboxamide (Compound 266)

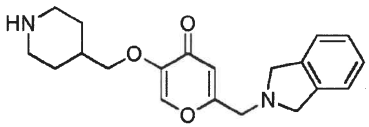


a) *tert*-Butyl 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-piperidine-1-carboxylate



The compound was prepared from 5-hydroxy-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (0.73 g, 3.0 mmol), *tert*-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (1.056 g, 3.6 mmol) and K_2CO_3 (0.871 g, 6.3 mmol) in DMF (6 mL) at 80 °C according to the procedure of Example 1. Crude material was purified by column chromatography to afford the title compound (0.28 g). LC-MS: *m/z* 441.5 $(M+H)^+$.

b) 2-(Isoindolin-2-ylmethyl)-5-(piperidin-4-ylmethoxy)-4*H*-pyran-4-one hydrogen chloride



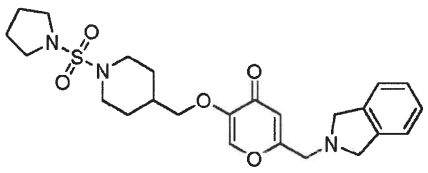
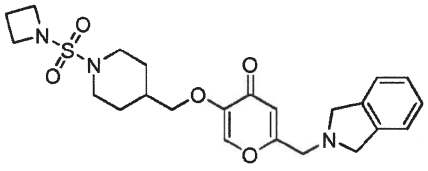
A round-bottomed-flask was charged with *tert*-butyl 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)piperidine-1-carboxylate (0.28 g, 0.64 mmol), CH_2Cl_2 (4 mL) and trifluoroacetic acid (0.5 mL, 6.7 mmol) at RT. When deprotection had occurred (LC-MS), the solution was concentrated to give the title compound as a TFA salt (0.36 g). LC-MS: *m/z* 341.4 $(M+H)^+$. The HCl salt of title compound can be prepared in a similar manner from *tert*-butyl 4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)piperidine-1-carboxylate in premixed solution of acetylchloride (6-7 equivalent) and methanol. Evaporation to dryness afforded the title compound as a HCl salt.

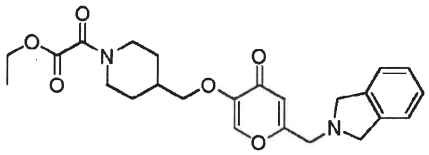
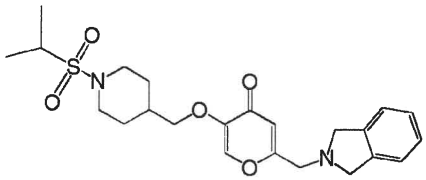
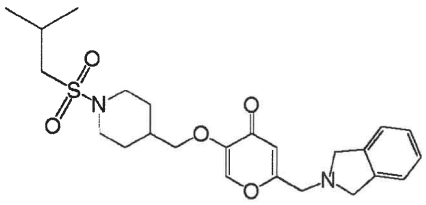
c) 4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-carboxamide (Compound 267)

A round-bottomed-flask was charged with 2-(isoindolin-2-ylmethyl)-5-(piperidin-4-ylmethoxy)-4*H*-pyran-4-one trifluoroacetate (0.36 g), DCM (3 mL), dimethylcarbamyl chloride (0.10 mL, 1.1 mmol) and Et_3N (0.4 mL, 2.9 mmol). After 3 h at RT the reaction was not complete (LC-MS), so more of dimethylcarbamyl chloride (0.10 mL, 1.1 mmol)

and Et_3N (0.4 mL, 2.9 mmol) were added. The solution was concentrated before saturated $NaHCO_3$ was added. Aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography to afford the title compound (0.07 g). ^{1}H NMR (Chloroform-d) δ: 7.59 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.77 (s, 2H), 3.65-3.75 (m, 4H), 2.82 (s, 6H), 2.73-2.81 (m, 2H), 1.97-2.12 (m, 1H), 1.79-1.93 (m, 2H), 1.30 (m, 2H). LC-MS: *m/z* 412.6 $(M+H)^+$.

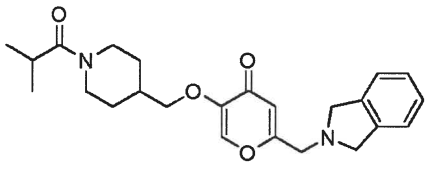
The following compounds were prepared according to the procedure of step (c) of Example 11 starting from 2-(isoindolin-2-ylmethyl)-5-(piperidin-4-ylmethoxy)-4*H*-pyran-4-one hydrogen chloride and another appropriate starting material. The characterization data, starting material and possible deviations in reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

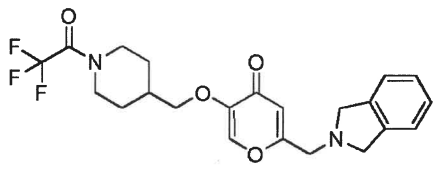
No	Structure and starting material	Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS
267	 Starting material: Pyrrolidine-1-sulfonyl chloride	Conditions: DMF. ^{1}H NMR (Chloroform-d) *δ*: 7.60 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.00-4.09 (m, 4H), 3.68-3.78 (m, 6H), 3.28-3.34 (m, 4H), 2.81 (m, 2H), 1.97-2.04 (m, 1H), 1.87-1.97 (m, 6H), 1.38 (m, 2H). LC-MS: *m/z* 474.5 $(M+H)^+$.
268	 Starting material: 1-Azetidine-sulfonyl chloride	Conditions: DMF. ^{1}H NMR (Chloroform-d) *δ*: 7.59 (s, 1H), 7.14-7.24 (m, 4H), 6.49 (s, 1H), 4.04 (s, 4H), 3.84-3.93 (m, 4H), 3.77 (s, 2H), 3.75-3.82 (m, 2H), 3.72 (d, 2H), 2.77 (m, 2H), 2.18-2.28 (m, 2H), 1.96-2.04 (m, 1H), 1.92 (m, 2H), 1.36 (m, 2H). LC-MS: *m/z* 460.5 $(M+H)^+$.

269	 Starting material: Ethyl chloro oxoacetate	Conditions: DIPEA. ^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.15-7.26 (m, 4H), 6.49 (s, 1H), 4.51-4.59 (m, 1H), 4.33 (q, 2H), 4.04 (s, 4H), 3.77 (s, 2H), 3.66-3.81 (m, 3H), 3.08-3.19 (m, 1H), 2.74 (m, 1H), 2.11-2.25 (m, 1H), 1.88-2.04 (m, 2H), 1.36 (t, 3H), 1.27-1.43 (m, 2H). LC-MS: *m/z* 441.8 $(M+H)^+$.
270	 Starting material: Isopropylsulfonyl chloride	Conditions: 4 h. 1H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.87 (m, 2 H), 3.77 (s, 2 H), 3.73 (d, 2 H), 3.18 (m, 1 H), 2.90 (td, 2 H), 2.05 (m, 1 H), 1.94 (br dd, 2 H), 1.34 (m, 8 H); LC-MS: m/z 447.2 (M+1)+.
271	 Starting material: Isobutanesulfonyl chloride	Conditions: 4 h. 1H NMR (Chloroform-d) δ: 7.60 (s, 1 H), 7.21 (m, 4 H), 6.49 (s, 1 H), 4.04 (s, 4 H), 3.84 (m, 2 H), 3.77 (s, 2 H), 3.73 (d, 2 H), 2.74 (m, 4 H), 2.29 (dt, 1 H), 2.00 (m, 3 H), 1.40 (m, 2 H), 1.11 (d, 6 H); LC-MS: m/z 461.2 (M+1)+.

Example 12.

5-((1-Isobutyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 272) and 2-(Isoindolin-2-ylmethyl)-5-((1-(2,2,2-trifluoroacetyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 273)





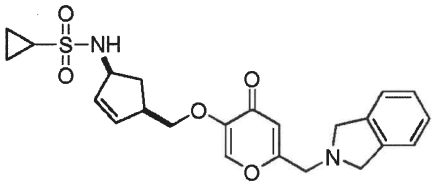
A round-bottomed-flask was charged with *tert*-butyl 4-(((6-(isoindolin-2-yl-methyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)piperidine-1-carboxylate (0.16 g, 0.36 mmol), CH_2Cl_2 (4 mL) and trifluoroacetic acid (0.32 mL, 4.3 mmol). The solution was allowed to react at RT. When the reaction was complete (LC-MS) the solvents were evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (4 mL) and Et_3N (0.25 mL, 4.9 mmol). Isobutyryl chloride (0.057 mL, 0.55 mmol) were then added at RT. When the reaction was complete (LC-MS) solvents were evaporated. The residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. Combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated to dryness. Crude material was purified by column chromatography followed by semipreparative HPLC to afford the title compounds.

5-((1-Isobutyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 272) (0.004 g): ^{1}H NMR (Chloroform-d) δ: 7.60 (s, 1H), 7.16-7.25 (m, 4H), 6.49 (s, 1H), 4.65-4.74 (m, 1H), 4.04 (s, 4H), 3.91-4.01 (m, 1H), 3.77 (s, 2H), 3.64-3.75 (m, 2H), 3.05 (br m, 1H), 2.75-2.85 (m, 1H), 2.50-2.64 (m, 1H), 1.79-1.89 (m, 2H), 1.17-1.25 (m, 2H), 1.08-1.15 (m, 6H). LC-MS: *m/z* 411.5 $(M+H)^+$.

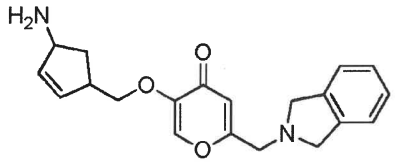
2-(Isoindolin-2-ylmethyl)-5-((1-(2,2,2-trifluoroacetyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 273) (0.079 g): ^{1}H NMR (Chloroform-d) δ: 7.61 (s, 1H), 7.16-7.24 (m, 4H), 6.49 (s, 1H), 4.54-4.63 (m, 1H), 4.01-4.11 (m, 1H), 4.04 (s, 4H), 3.71-3.81 (m, 4H), 3.09-3.23 (m, 1H), 2.74-2.87 (m, 1H), 2.14-2.30 (m, 1H), 1.95-2.11 (m, 2H), 1.26-1.49 (m, 2H). LC-MS: *m/z* 437.5 $(M+H)^+$.

Example 13.

Cis-N-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclopent-2-en-1-yl)cyclopropanesulfonamide, Formate (Compound 274)



a) *cis* 5-((4-Aminocyclopent-2-en-1-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one dihydrochloride



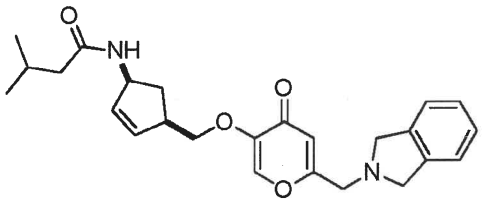
To a suspension of *cis*-tert-butyl (4-((((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclopent-2-en-1-yl)carbamate (0.250 g, 0.57 mmol) in 2-propanol (2.5 ml) was added hydrogen chloride (3 M in CPME, 0.653 ml, 1.96 mmol). The mixture was strirred at 50 °C until the reaction reached completion (analysed by LC-MS). The mixture was cooled and the precipitated product was isolated by suction filtration. Drying under vacuum afforded the title compound (0.128 g). ^{1}HNMR (400 MHz, DMSO-*d6*): δ 12.4 (br s, 1H), 8.34 (s, 1H), 8.07 (s, 3H), 7.37 (br, 4H), 6.80 (br s, 1H), 6.07-6.12 (m, 1H), 5.86-5.90 (m, 1H), 4.60 (br, 4H), 4.16-4.27 (br, 1H), 3.84-3.96 (m, 2H), 3.15-3.22 (m, 1H), 2.4-2.54 (m, 3H, partially overlapped by DMSO), 1.67-1.75 (m, 1H).

b) *Cis-N*-(4-((((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-cyclopent-2-en-1-yl)cyclopropanesulfonamide, Formate

To a suspension of *cis* 5-((4-aminocyclopent-2-en-1-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one dihydrochloride (0.128 g, 0.311 mmol) and triethylamine (0.167 ml, 1.195 mmol) in dry DCM (2 ml) was added cyclopropanesulfonyl chloride (35 µl, 0.341 mmol). The mixture was strirred at RT until the reaction reached completion (analysed by LC-MS). The mixture was diluted with DCM and saturated $NaHCO_3$ solution, washed with water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford crude product. Purification by column chromatography and semipreparative HPLC afforded the title compound (18.6 mg). ^{1}HNMR (400 MHz, Chloroform-*d*): δ 7.56 (s, 1H), 7.35-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.17-7.24 (m, 4H), 6.49 (m, 1H), 4.11 (t, 2H), 4.04 (s, 4H), 3.76 (d, 2H), 3.15 (t, 2H), 3.10 (br s, 3H), 2.98 (s, 3H); LC-MS: *m/z* 419.4 $(M+H)^+$

Example 14.

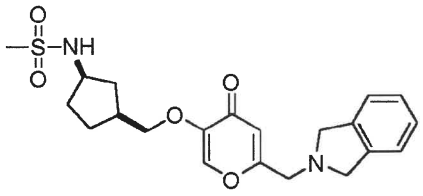
Cis-N-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclopent-2-en-1-yl)-3-methylbutanamide, Formate (Compound 275)



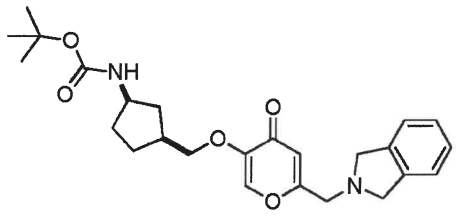
To a suspension of *cis* 5-((4-aminocyclopent-2-en-1-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one dihydrochloride (0.187 g, 0.455 mmol), triethylamine (0.209 ml, 1.50 mmol), and 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) in dry THF (1.5 ml) was added 3-methylbutyryl chloride (91 µl, 0.75 mmol) in dry THF (0.5 ml). The mixture was strirred at RT until the reaction reached completion (analysed by LC-MS). The mixture was diluted with EtOAc and 5 % aqueous Na_2CO_3 solution and stirred for 10 min. Phases were separated and the organic phase was washed with 5 % aqueous NaOH solution, water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford crude product. Purification by column chromatography and semipreparative HPLC afforded the title compound (39.5 mg). ^{1}H NMR (Chloroform-d): δ 8.11 (s, 1H), 7.92 (br d, 1H), 7.53 (s, 1H), 7.18-7.25 (m, 4H), 6.51 (s, 1H), 5.81-5.84 (m, 1H), 5.71-5.75 (m, 1H), 5.21-5.29 (m, 1H), 4.08 (s, 4H), 3.81 (s, 2H), 3.81 (dd, 1H), 3.72 (dd, 1H), 3.01-3.08 (m, 1H), 2.49-2.60 (m, 1H), 2.24-2.34 (m, 2H), 2.12 (sept, 1H), 1.55-1.63 (m, 1H), 0.96 (d, 3H), 0.92 (d, 3H); LC-MS: *m/z* 423.9 $(M+H)^+$

Example 15.

Cis-N-(3-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-cyclopentyl)-methanesulfonamide (Compound 276)

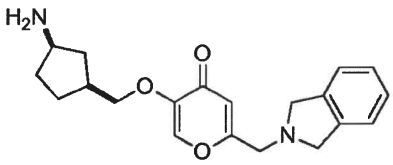


a) *cis-tert*-Butyl (3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)cyclopentyl)carbamate



To a mixture of Pd on activated charcoal (10 % Pd, 0.102 g, 0.096 mmol) in methanol (15 ml) was added a solution *cis-tert*-butyl (4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclopent-2-en-1-yl)carbamate (0.84 g, 1.916 mmol) in methanol (15 ml). The mixture was strirred under hydrogen at RT until the reaction reached completion (analysed by LC-MS). The reaction mixture was filtered through a plug of Celite®, and the filtrate was evaporated to afford crude product. Purification by column chromatography afforded the title compound (0.378 g). ^{1}H NMR (Chloroform-d): δ 7.59 (s, 1H), 7.17-7.24 (m, 4H), 6.48 (m, 1H), 5.07 (br, 1H), 3.98-4.08 (m, 1H), 4.04 (s, 4H), 3.82 (d, 2H), 3.77 (d, 2H), 2.36-2.48 (m, 1H), 2.22-2.32 (m, 1H), 1.90-1.99 (m, 1H), 1.78-1.89 (m, 1H), 1.49-1.65 (m, 3H), 1.45 (s, 9H).

b) *cis*-5-((3-Aminocyclopentyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one



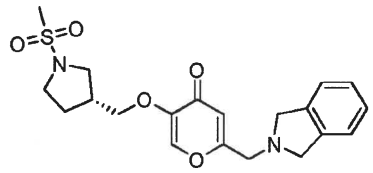
To a suspension of *cis-tert*-butyl (3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclopentyl)carbamate (0.350 g, 0.794 mmol) in 2-propanol (4 ml) was added hydrogen chloride (3 M in CPME, 0.927 ml, 2.78 mmol). The mixture was strirred at 60 °C until the reaction reached completion (analysed by LC-MS). The reaction mixture was diluted with water, basified with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. Organic phase was washed with brine, dried over sodium sulphate and concentrated under reduced pressure to afford the title compound (0.16 g) which was used as such in the next step. LC-MS: *m/z* 341.3 $(M+H)^+$

c) *Cis-N*-(3-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-cyclopentyl)-methanesulfonamide

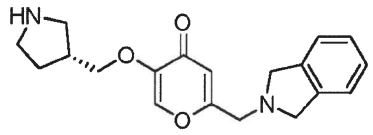
To a solution of *cis*-5-((3-aminocyclopentyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.16 g, 0.47 mmol) and triethylamine (0.131 ml, 0.94 mmol) in dry DCM (2.5 ml) was added methanesulfonyl chloride (36 µl, 0.47 mmol). The mixture was strirred at RT until the reaction reached completion (analysed by LC-MS). The mixture was diluted with DCM and saturated $NaHCO_3$ solution, washed with water and brine, dried over sodium sulphate and concentrated under reduced pressure to afford crude product. Purification by column chromatography afforded the title compound (39 mg). ^{1}H NMR (Chloroform-d): δ 7.56 (s, 1H), 7.18-7.24 (m, 4H), 6.53 (br d, 1H), 6.52 (s, 1H), 4.05-4.13 (m, 1H), 4.04 (s, 4H), 3.79-3.85 (m, 2H), 3.78 (d, 2H), 3.04 (s, 3H), 2.43-2.52 (m, 1H), 2.23-2.33 (m, 1H), 1.73-2.01 (m, 4H), 1.69 (td, 1H); LC-MS: *m/z* 463.2 $(M-H)^+$

Example 16.

(*R*)-2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-4H-pyran-4-one (Compound 277)



a) (*R*)-2-(Isoindolin-2-ylmethyl)-5-(pyrrolidin-3-ylmethoxy)-4H-pyran-4-one



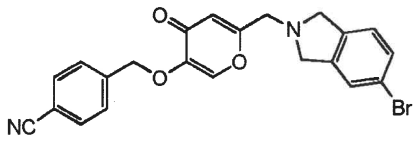
The compound was prepared according to the procedure described in step (b) of Example 15 starting from (*R*)-tert-butyl 3-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)pyrrolidine-1-carboxylate (0.834 g, 1.955 mmol) and hydrogen chloride (3 M in CPME, 2.28 ml, 6.84 mmol) in 2-propanol (10 ml). The title compound (0.175 g) was used as such in the next step. LC-MS: *m/z* 327.2 $(M+H)^+$

b) (*R*)-2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-4H-pyran-4-one

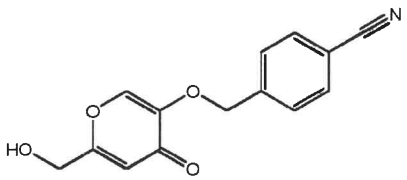
The compound was prepared according to the procedure described in step (c) of Example 15 starting from (*R*)-2-(isoindolin-2-ylmethyl)-5-(pyrrolidin-3-ylmethoxy)-4H-pyran-4-one (0.175 g, 0.536 mmol), triethylamine (0.149 ml, 1.072 mmol), and methanesulfonyl chloride (41 µl, 0.536 mmol) in dry DCM (3 ml). Purification by column chromatography afforded the title compound (50 mg). ^{1}H NMR (Chloroform-d): δ 7.66 (s,1H), 7.18-7.24 (m, 4H), 6.49 (m, 1H), 4.06 (s, 4H), 3.95 (dd, 1H), 3.88 (dd, 1H), 3.79 (d, 2H), 3.56 (dd, 1H), 3.45-3.53 (m, 1H), 3.34-3.40 (m, 1H), 3.31 (dd, 1H), 2.88 (s, 3H), 2.74-2.85 (m, 1H), 2.12-2.23 (m, 1H), 1.83-1.94 (m, 1H); LC-MS: *m/z* 405.2 $(M+H)^+$

Example 17.

4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzonitrile (Compound 278)

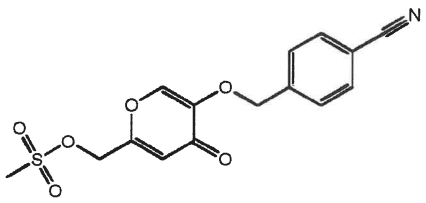


a) 4-((6-(hydroxymethyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzonitrile



A solution of 5-hydroxy-2-(hydroxymethyl)-4h-pyran-4-one (500 mg, 3.52 mmol), alpha-bromo-p-tolunitrile (690 mg, 3.52 mmol) and potassium carbonate (973 mg, 7.04 mmol) in DMF (10 ml) was heated at 80 °C in a micro-wave reactor for 15 min. The reaction mixture was poured into water. The precipitate was filtered, washed with water, and dried to afford the title compound (0.75 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 (s, 1 H), 7.89 (s, 1 H), 7.87 (s, 1 H), 7.60 - 7.64 (m, 2 H), 6.33 - 6.35 (m, 1 H), 5.07 (s, 2 H), 4.30 (s, 2 H).

b) (5-(4-Cyanobenzyloxy)-4-oxo-4H-pyran-2-yl)methyl methanesulfonate



To a solution of 4-((6-(hydroxymethyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzonitrile (0.2 g, 0.777 mmol) and TEA (0.325 ml, 2.332 mmol) in DCM (5 ml) at 0 °C was added dropwise methanesulfonyl chloride (0.075 ml, 0.972 mmol). The reaction mixture was stirred at 20°C for 3 h, and washed with satutared $NaHCO_3$, 0,1 M HCl and brine. The organic layer was dried with Na_2SO_4, filtered and evaporated to afford the title compound (0.14 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.66 - 7.70 (m, 2 H), 7.64 - 7.66 (m, 1 H), 7.51 - 7.56 (m, 2 H), 6.43 - 6.55 (m, 1 H), 5.14 (s, 2 H), 4.30 - 5.05 (m, 2 H), 3.11 - 3.15 (m, 3 H).

c) 4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)-benzonitrile

A solution of 5-bromoisoindoline (0.07 g, 0.353 mmol) and (5-(4-cyano-benzyloxy)-4-oxo-4H-pyran-2-yl)methyl methanesulfonate (0.119 g, 0.353 mmol) and potassium carbonate (0.098 g, 0.707 mmol) in DMSO (2 ml) was stirred at 60 °C for 30 min. Water was added, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, evaporated, and purified with semipreparative HPLC to afford the title compound (9 mg). 1H NMR (400 MHz, Chloroform-d) δ ppm 7.66 - 7.70 (m, 1 H), 7.63 (s, 1 H), 7.52 - 7.56 (m, 2 H), 7.33 - 7.37 (m, 2 H), 7.05 - 7.17 (m, 1 H), 6.50 (s, 1 H), 5.13 - 5.16 (m, 1 H), 3.95 - 4.04 (m, 4 H), 3.74 - 3.76 (m, 2 H), 1.54 - 1.83 (m, 2 H); LC-MS: m/z 437.3 (M+H) +.

The following compounds were prepared according to the procedure of step (c) of Example 17 starting from isoindoline or derivate thereof and another appropriate starting material. The characterization data, starting material and possible deviations in

reaction conditions (solvent, reaction temperature, reaction time, purification method), if any, are indicated on the table.

Purification methods used:

A = Crystallization

B = Column chromatography

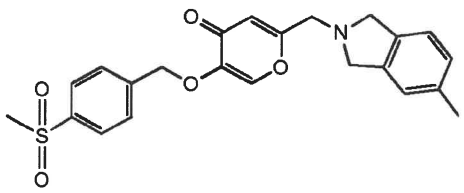
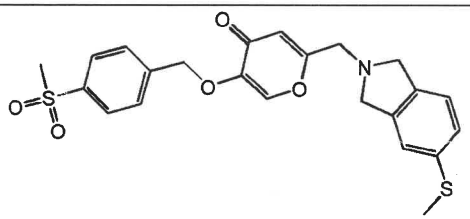
C = Precipitation in aqueous media

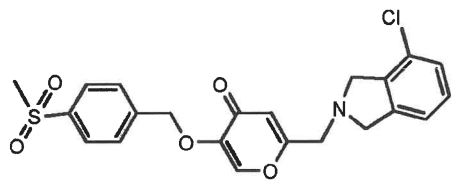
D = Semipreparative HPLC

E = Trituration

F = Salt formation

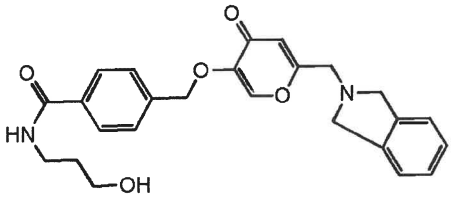
G = As such

No	**Structure and starting material**	**Deviating reaction conditions / ^{1}H NMR (400 MHz) / LC-MS**
279	 Starting material: (5-((4-(Methyl-sulfonyl)benzyl)oxy)-4-oxo-4H-pyran-2-yl)methyl methanesulfonate;	Conditions: DMF, 85 °C, B. 1H NMR (DMSO-d6) δ: 8.26 (s, 1 H), 7.94-7.99 (m, 2 H), 7.67-7.72 (m, 2 H), 7.09-7.15 (m, 1 H), 7.05 (s, 1 H), 6.99-7.03 (m, 1 H), 6.43 (s, 1 H), 5.10 (s, 2 H), 3.91 (s, 4 H), 3.78 (s, 2 H), 3.22 (s, 3 H), 2.28 (s, 3 H); LC-MS: m/z 426.3 (M+H) +.
280	 Starting material: (5-((4-(Methyl-sulfonyl)benzyl)oxy)-4-oxo-4H-pyran-2-yl)methyl methanesulfonate	Conditions: DMF, 80 °C. 1H NMR (Chloroform-d) δ: 7.94-7.98 (m, 2 H), 7.65 (s, 1 H), 7.61-7.64 (m, 2 H), 7.10-7.15 (m, 3 H), 6.51 (s, 1 H), 5.18 (s, 2 H), 3.98-4.02 (m, 4 H), 3.76 (s, 2 H), 3.06 (s, 3 H), 2.47 (s, 3 H); LC-MS: m/z 458.6

281	 Starting material: 2-(Chloromethyl)-5-((4-(methylsulfonyl)benzyl)oxy)-4H-pyran-4-one	Conditions: DMF, 70 °C, C and D. 1H NMR (DMSO-d6) δ: 8.28 (s, 1 H), 7.95-7.99 (m, 2 H), 7.68-7.72 (m, 2 H), 7.22-7.30 (m, 3 H), 6.46 (s, 1 H), 5.10 (s, 2 H), 3.99-4.10 (m, 4 H), 3.84 (s, 2 H), 3.23 (s, 3 H); LC-MS: m/z 446.6

Example 18.

N-(3-Hydroxypropyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 282)



a) 4-(Chloromethyl)-*N*-(3-hydroxypropyl)benzamide

To a solution of 4-(chloromethyl)benzoyl chloride (2.97 g, 15.71 mmol) in DCM (10 ml) was added 3-amino-1-propanol (1.180 g, 15.71 mmol) in DCM (20 ml) followed by dropwise addition of TEA (2.409 ml, 17.28 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min. Water was added to the mixture, the layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with 1 M NaOH, 1 M HCl and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography followed by trituration with diethyl ether to afford the title compound. LC-MS: *m/z* 228.2 $(M+H)^+$.

c) 3-(4-(Chloromethyl)benzamido)propyl acetate

To a solution of 4-(chloromethyl)-N-(3-hydroxypropyl)benzamide (1.79 g, 7.86 mmol) in pyridine (15 ml) was added acetic anhydride (1.115 ml, 11.79 mmol) at 0 °C.

The reaction mixture was stirred at 0 °C for 15 min and at 20 °C for 30 min. The solvent was evaporated, and water was added to the residue. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with 1 M HCl, water, 5 % $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and evaporated to afford the title compound. LC-MS: *m/z* 270.2 $(M+H)^+$.

c) 3-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamido)propyl acetate

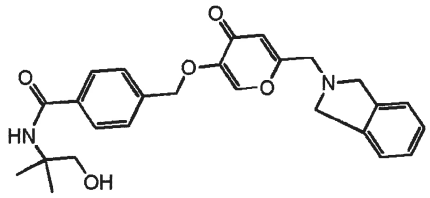
The suspension of 5-hydroxy-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (0.2 g, 0.822 mmol), 3-(4-(chloromethyl)benzamido)propyl acetate (0.222 g, 0.822 mmol) and K_2CO_3 (0.199 g, 1.439 mmol) in DMF (2 ml) was heated at 80 °C for 30 min. Water was added to the mixture, and the aqueous layer was extracted with DCM. The organic layers were combined, washed with water and brine, dried with Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography to afford the title compound. LC-MS: *m/z* 477.5 $(M+H)^+$.

d) *N*-(3-Hydroxypropyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)-oxy)methyl)benzamide

A suspension of 3-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzamido)propyl acetate (0.195 g, 0.409 mmol), K_2CO_3 (0.071 g, 0.512 mmol) and methanol (5 ml) in DCM (5 ml) was stirred at 20 °C for 1 h followed by filtration. The filtrate was evaporated to dryness, and the residue was purified by column chromatography followed by trituration with a mixture of heptane and diethyl ether to afford the title compound (0.04 g). 1H NMR (400 MHz, Chloroform-d) δ ppm 7.74-7.79 (m, 2 H), 7.58 (s, 1 H), 7.42 - 7.47 (m, 2 H), 7.18 - 7.24 (m, 4 H), 6.91 - 6.98 (m, 1 H), 6.51 (s, 1 H), 5.09 (s, 2 H), 4.03 (s, 4 H), 3.75 (s, 2 H), 3.70 - 3.73 (m, 2 H), 3.58 - 3.64 (m, 3 H), 1.75 - 1.83 (m, 3 H), 1.21 (t, J=7.0 Hz, 1 H); LC-MS: m/z 435.5 (M+H)+.

Example 19.

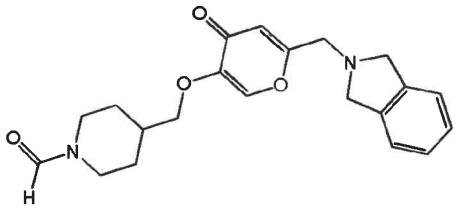
N-(1-hydroxy-2-methylpropan-2-yl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 283)



A suspension of 2-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)benzamido)-2-methylpropyl acetate (0.284 g, 0.579 mmol)] K_2CO_3 (0.100 g, 0.724 mmol) and methanol (5 ml) in DCM (5 ml) was stirred at 20 °C for 1 h followed by filtration. The filtrate was evaporated to dryness, and the residue was purified by column chromatography to afford the title compound (0.12 g). 1H NMR (400 MHz, DMSO-d6) δ ppm 8.21 (s, 1 H), 7.78 - 7.84 (m, 2 H), 7.51 - 7.58 (m, 1 H), 7.48 (s, 2 H), 7.17 - 7.26 (m, 4 H), 6.42 (s, 1 H), 5.02 (s, 2 H), 4.91 (t, J=6.0 Hz, 1 H), 3.95 (s, 4 H), 3.79 (s, 2 H), 3.50 (d, J=6.0 Hz, 2 H), 1.31 (s, 6 H); LC-MS: m/z 449.5 (M+H) +.

Example 20.

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidine-1-carbaldehyde, HCl (Compound 284)

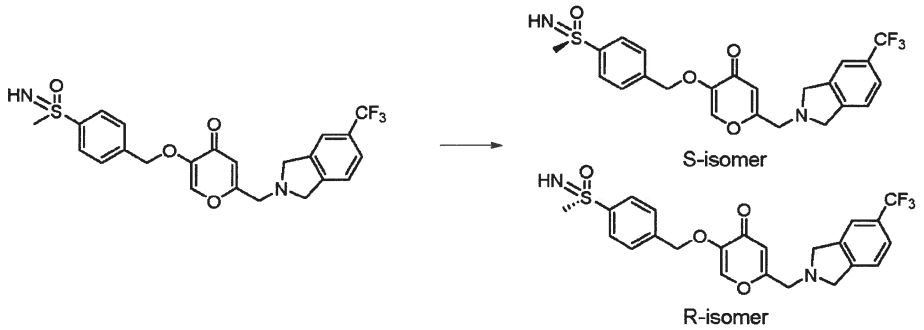


A solution of 2-(isoindolin-2-ylmethyl)-5-(piperidin-4-ylmethoxy)-4H-pyran-4-one (0.13 g, 0.382 mmol) and methyl formate (0.030 ml, 0.496 mmol) was stirred for 30 min 0 °C. Then the mixture was allowed to reach 20 °C and stirred for 90 min. Sodium hydroxide (0.04 g, 0.095 mmol) was added to the mixture. The mixture was stirred for 16 h. 10 ml of DCM was added, and the solids were removed by filtration. 1 M HCl in diethyl ether (1 ml) was added to the mixture. The mixture was filtered through Celite® and the solvent was removed under reduced pressure. The residue was treated with diethyl ether, filtered, and dried to afford the title compound (0.1 g). 1H NMR (400

MHz, DMSO-d6) δ ppm 8.22 (s, 1 H), 7.99 (s, 1 H), 7.34 - 7.44 (m, 5 H), 6.75 (s, 1 H), 6.75 (s, 1 H), 4.72 - 4.85 (m, 2 H), 4.61 (s, 2 H), 4.15 - 4.23 (m, 1 H), 3.70 - 3.74 (m, 3 H), 3.01 - 3.11 (m, 1 H), 2.59 - 2.72 (m, 1 H), 1.95 - 2.09 (m, 1 H), 1.72 - 1.85 (m, 2 H), 1.01 - 1.22 (m, 3 H); LC-MS: m/z 369.2.

Example 21.

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 285) and 5-((4-(R-Methylsulfonimidoyl)-benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 286)



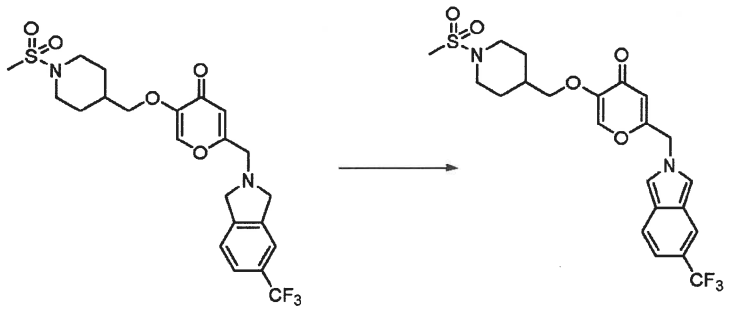
Racemic resolution of 5-((4-(R,S-methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (0.1 g, 0.21 mmol) was conducted using Chiralpak IF, 5 υm, 20 * 250 mm column and n-hexane, EtOH and DEA as eluent.

S-isomer (39.3 mg): ^{1}H NMR (Chloroform-d) δ: 8.02 (d, 2H), 7.64 (s, 1H), 7.61 (d, 2H), 7.50 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 6.52 (s, 1H), 5.17 (s, 2H), 4.09 (s, 4H), 3.79 (s, 2H), 3.11 (s, 3H).

R-isomer (43.9 mg) : ^{1}H NMR (Chloroform-d) δ: 7.99-8.08 (m, 1H), 7.99-8.08 (m, 1H), 7.64 (s, 1H), 7.61 (d, 2H), 7.50 (d, 1H), 7.46 (s, 1H), 7.31 (d, 1H), 7.27 (s, 1H), 7.26-7.27 (m, 1H), 6.52 (s, 1H), 5.17 (s, 2H), 4.09 (s, 4H), 3.79 (s, 2H), 3.11 (s, 3H).

Example 22.

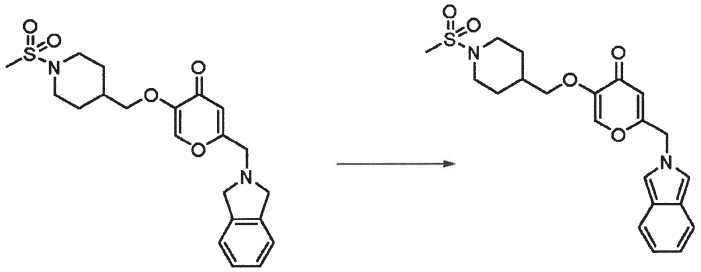
5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)-2H-isoindol-2-yl)methyl)-4H-pyran-4-one (Compound 287)



To a solution of 5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (0.40 g, 0.82 mmol) in dry dioxane (10 ml) were added palladium (II) acetate (0.18 g, 0.82 mmol) and cyclohexene (0.41 ml, 4.11 mmol). The reaction mixture was heated at 130 °C for 4 h. The catalyst was filtered off. The solvent was evaporated. The crude product was purified by column chromatography to afford 0.35 g of the title compound. ^{1}H NMR (Methanol-d_4) δ: 8.01 (s, 1H), 7.87 (s, 1H), 7.62 (m, 1H), 7.50 (d, 1H), 7.37-7.41 (m, 1H), 7.00 (m, 1H), 6.24 (s, 1H), 5.45 (s, 2H), 3.68-3.78 (m, 4H), 2.81 (s, 3H), 2.71-2.80 (m, 2H), 1.88-2.01 (m, 3H), 1.24-1.49 (m, 2H). LC-MS: *m/z* 487.3 $(M+H)^+$.

Example 23.

2-((2H-Isoindol-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 288)

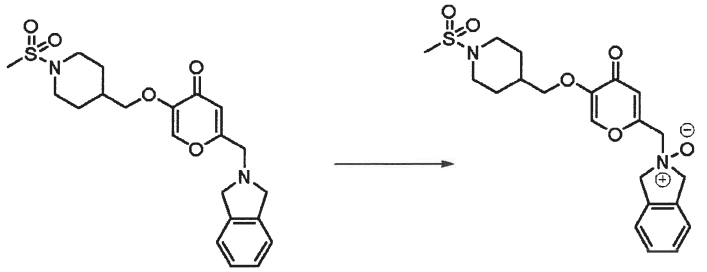


To a solution of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (0.20 g, 0.48 mmol) in dry dioxane (15 ml) were added palladium (II) acetate (107 mg, 0.48 mmol) and cyclohexene (0.48 ml, 4.78 mmol). The reaction mixture was heated at 130 °C for 4 h. The catalyst was filtered off. The solvent was evaporated. The crude product was purified by column chromatography to afford 24.7 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ: 8.12-8.17 (m, 1H), 7.47 (d, 2H),

6.84 (d, 2H), 6.22 (s, 1H), 5.42 (s, 2H), 3.68 (d, 2H), 3.55 (br d, 3H), 2.84 (s, 3H), 2.65-2.74 (m, 2H), 1.75-1.85 (m, 3H), 1.20-1.30 (m, 2H). LC-MS: *m/z* 416.5 $(M+H)^+$.

Example 24.

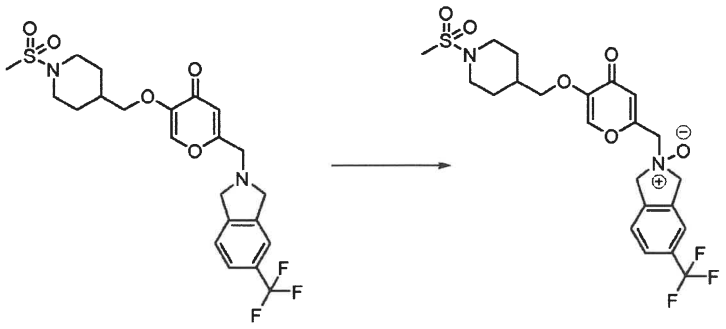
2-((5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)-methyl)isoindoline 2-oxide (Compound 289)



To a solution of 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (0.10 g, 0.24 mmol) in methanol (1 ml) were added formic acid (11.0 mg, 0.24 mmol) and hydrogen peroxide 35 % solution in water (8.13 mg, 0.24 mmol). The mixture was stirred at RT for 6 h. The solvent was evaporated. The crude product was purified by column chromatography to afford 70 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ: 10.44 (s, 1H), 7.96 (d, 1H), 7.85 (d, 2H), 7.61 (d, 2H), 7.41 (m, 1H), 7.20 (d, 1H), 6.95 (m, 1H), 6.84 (d, 1H), 6.59 (d, 1H), 3.36 (s, 1H), 3.27 (m, 2H), 2.77 (m, 1H), 2.14 (s, 3H), 1.05-1.13 (m, 8H). LC-MS: *m/z* 435.2 $(M+H)^+$.

Example 25.

2-((5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)methyl)-5-(trifluoromethyl)isoindoline 2-oxide (Compound 290)

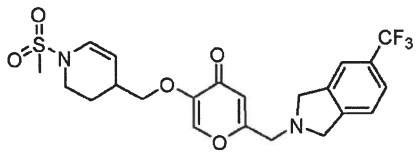


To a solution of 5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoro-methyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (0.10 g, 0.20 mmol) in methanol (2 ml)

were added formic acid (47.0 mg, 1.02 mmol) and hydrogen peroxide 35 % solution in water (0.20 g, 2.05 mmol). The mixture was stirred at RT for 6 h. The solvent was evaporated. The crude product was purified by column chromatography to afford 43 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ: 8.24 (br s, 1H), 7.77 (br s, 1H), 7.70 (br d, 1H), 7.59 (br d, 1H), 6.68 (s, 1H), 5.15-5.27 (m, 2H), 4.76 (br s, 2H), 4.62 (br d, 2H), 3.75 (br d, 2H), 3.38 (m, 2H), 2.86 (s, 3H), 2.73 (br m, 2H), 1.86 (br d, 3H), 1.24-1.36 (m, 2H). LC-MS: *m/z* 435.2 $(M+H)^+$.

Example 26.

5-((1-(Methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methoxy)-2-((5-(trifluoro-methyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 291)



a) Ethyl piperidine-4-carboxylate trifluoroacetate

To a solution of 1-(tert-butyl)-4-ethyl-piperidine-1,4-dicarboxylate (20 g, 77.8 mmol) in DCM (400 ml) was added TFA (200 ml) dropwise at 0 °C followed by stirring at RT for 2 h. The mixture was concentrated under reduced pressure to give 44 g of crude title compound as brown oil. This was used directly in the next reaction step without further purification.

b) Ethyl-1-(methylsulfonyl)piperidine-4-carboxylate

To a solution of ethyl piperidine-4-carboxylate trifluoroacetate (44 g, 162.3 mmol) in ACN (400 ml) was added DIPEA (106 ml, 649.4 mmol) and MsCl (25 ml, 327.4 mmol) at 0 °C followed by stirring at RT for 2-3 h. The reaction mixture was quenched with water (500 ml) and extracted with EtOAc (3 x 500 ml). The organic layer was washed with brine, dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica

gel using 25 % EtOAc in hexane as an eluent to give 5.6 g of the title compound as a white solid. MS: *m/z* 158 $[M+H]^+$.

c) Ethyl-1-(methylsulfonyl)-2-oxopiperidine-4-carboxylate

To a solution of ethyl-1-(methylsulfonyl)piperidine-4-carboxylate (3.6 g, 15.3 mmol) in ACN:H_2O (2:5) (14 mL) was added Ruthenium(IV) oxide hydrate (0.2 g, 1.5 mmol) under water bath. After 5 min, sodium periodate (6.8 g, 32.1 mmol) was added portionwise at temperature between 18 °C to 22 °C (temperature should not be more than 30 °C during addition). The mixture was stirred at RT for 7 h. The reaction mixture was quenched with water followed by addition of DCM (50 mL). The mixture was filtered through Celite® bed. The organic layer was seperated, dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel using 20-40 % EtOAc in hexane as an eluent to give 2.3 g of the title compound as a light yellow solid. MS: *m/z* 250 $[M+H]^+$.

d) Ethyl-2-hydroxy-1-(methylsulfonyl)piperidine-4-carboxylate

To a solution ethyl-1-(methylsulfonyl)-2-oxopiperidine-4-carboxylate (2.26 g, 9.0 mmol) in dry THF (100 ml) was added DIBAL-H in toluene (1.5 M in toluene, 15.1 ml, 22.6 mmol) dropwise at -78 °C followed by stirring for 5 h. The mixture was cooled to RT, quenched with saturated NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to give 2.1 g of crude title compound as pale yellow oil. This was used directly in the next reaction step without further purification.

e) Ethyl-1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate

To a solution of ethyl-2-hydroxy-1-(methylsulfonyl)piperidine-4-carboxylate (2.1 g, 8.3 mmol) in DCM (40 ml) was added TFAA (2.9 ml, 20.9 mmol) dropwise at -78 °C and followed by stirring for 6 h. Thereafter TEA (24 ml, 167.3 mmol) was added

at -78 °C followed by stirring at RT for 2.5 h. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted with DCM (3 x 50 mL). The organic layer was washed with water, dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography over silica gel using 10-20 % EtOAc in hexane as an eluent to give 1.1 g of the title compound as light yellow solid. MS: *m/z* 234 $[M+H]^+$.

f) (1-(Methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methanol

To a solution ethyl 1-(methylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate (0.95 g, 4.0 mmol) in dry THF (100 ml) was added $LiBH_4$ (3.0 M in THF, 2.7 ml, 8.1 mmol) dropwise at -40 °C followed by stirring at RT for 16 h. The reaction mixture was quenched with ice and extracted with EtOAc (3 x 50 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to give 0.77 g of the title compound as transparent oil. MS: *m/z* 192 $[M+H]^+$.

g) (1-(Methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methyl methanesulfonate

To a solution of (1-(methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methanol (0.76 g, 3.97 mmol) in ACN (10 ml) was added DIPEA (2.9 ml, 15.91 mmol) and MsCl (0.6 ml, 7.95 mmol) at 0 °C followed by stirring for 10 min. The reaction mixture was quenched with brine (50 ml) and extracted with EtOAc (3 x 25 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure to give 1.2 g of crude title compound. This was used directly in the next reaction step without further purification. MS: *m/z* 270 $[M+H]^+$.

h) 5-((1-(Methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one

To a solution of 5-hydroxy-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (0.5 g, 1.6 mmol) and (1-(methylsulfonyl)-1,2,3,4-tetrahydropyridin-4-

yl)methyl methanesulfonate (0.4 g, 1.6 mmol) in ACN (10 ml) was added Cs_2CO_3 (1.3 g, 4.0 mmol) followed by stirring at 70 °C for 16 h. The mixture was diluted with EtOAc (50 ml), filtered and concentrated under reduced pressure. The crude was purified by reverse phase preparative HPLC using Agilent, X Select Hexyl Phenyl (19 x 250) mm, 5 µm, gradient 30 % to 70% ACN in water containing 5 mM of Ammonium acetate in water, RT, 13.5 min to give 13.7 mg of the title compound as brown solid. ^{1}H-NMR (400 MHz; DMSO-d_6): δ 8.17 (s, 1H), 7.63 (s, 1H), 7.57 (d, 1H), 7.47 (d, 1H), 6.52 (d, 1H), 6.41 (s, 1H), 4.96 (q, 1H), 4.07 (s, 4H), 3.81 (s, 2H), 3.63-3.66 (m, 2H), 3.53-3.57 (m, 1H), 3.40-3.45 (m, 1H), 2.99 (s, 3H), 2.59-2.68 (m, 2H), 1.90-1.95 (m, 1H), 1.71-1.72 (m, 1H); MS: *m/z* 485 $[M+H]^+$.

EXPERIMENTS

CYP11A1 inhibition

The ability of the test compounds to inhibit conversion of cholesterole to pregnenolone and isocaproic acid was measured by modification of isocaproic acid release assay (IARA) described by Ruangwises et. al. (Biology of Reproduction 1991; 45(1):143-50) except that human H295R adrenocortical carcinoma cell line was used as source of enzyme and extraction was done with dextran-coated charcoal suspension (Isomaa, V. et al., Endocrinology 1982; 111(3):833-843). The H295R cell line has been shown to express all the key steroidogenic enzymes. To determine the half maximal inhibitory concentration (IC_{50}) of the test compounds on CYP11A1 inhibition, the cells were treated for three days with increasing concentrations of the test compounds in the presence of 3 nM [24,25-3H]-labelled cholesterol (American Radiolabelled Chemicals). The final DMSO concentration was 1 %. Cell culture medium was extracted with dextran-coated charcoal suspension and the radiolabelled isocaproic acid was determined by mixing 100 µl of supernatant fraction in 200 µl of scintillation fluid (OptiPhase SuperMix, Perkin Elmer). Radioactivity was measured using a Microbeta scintillation counter (1450 MicroBeta Trilux, Wallac). All the test compounds were studied at 10 concentrations in duplicates.

The compounds of the invention were screened in the above mentioned assay and the IC_{50} values of the compounds are set forth in Table 1 below wherein "A" refers to an IC_{50} value of less than 150 nM, "B" refers to IC_{50} value in range of 150 to 300 nM and "C" refers to IC_{50} value in range of 301 nM to 2000 nM.

Table 1.

Group	Compound No.
A	2, 5, 8, 10, 11, 12, 15, 21, 22, 23, 36, 37, 44, 47, 49, 65, 69a, 70, 71, 72, 73, 74, 83, 84, 89, 90, 91, 92, 93, 95, 103, 104, 109, 111, 113, 114, 115, 116, 122, 129, 130, 131, 134, 137, 138, 139, 146, 162, 172, 173, 176,

	184, 185, 186, 187, 188, 189, 190, 192, 195, 196, 205, 211, 213, 215, 216, 217, 219, 221, 222, 224, 225, 226, 229, 230, 232, 234, 238, 244, 244a, 249, 251, 254, 255, 257, 261, 262, 271, 272, 278, 285 and 286
B	1, 4, 6, 7, 9, 20, 24, 25, 26, 28, 29, 30, 31, 34, 39, 46, 53, 56, 61, 63, 64, 67, 68, 69, 81, 82, 82a, 85, 86, 88, 94, 97, 98, 99, 100, 101, 102, 107, 108, 120, 121, 124, 126, 127, 128, 135, 136, 140, 142, 143, 147, 158, 161, 163, 164, 165, 168, 169, 174, 177, 180, 181, 191, 194, 198, 199, 200, 208, 209, 210, 214, 218, 220, 223, 227, 228, 231, 233, 235, 236, 237, 239, 241, 247, 248, 250, 252, 256, 258, 260, 267, 268, 269, 270, 273, 276, 279, 280, 283, 284 and 291
C	3, 13, 14, 16, 17, 18, 19, 27, 32, 33, 35, 38, 40, 41, 42, 43, 45, 48, 50, 51, 52, 55, 57, 58, 59, 60, 62, 66, 75, 76, 77, 78, 79, 80, 87, 96, 105, 106, 110, 112, 117, 118, 119, 123, 125, 132, 133, 141, 144, 145, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 159, 160, 166, 170, 171, 178, 179, 182, 183, 193, 197, 201, 202, 203, 206, 207, 212, 240, 242, 243, 245, 245a, 253, 263, 264, 265, 274, 275, 277, 281, 282, 287, 289 and 290

Abbreviations

ACN - Acetonitrile

DAST - Diethylaminosulfur trifluoride

DCE - 1,2-Dichloroethane

DCM - Dichloromethane

DEA - Diethanolamine

DIBAL-H - Diisobutylaluminum hydride solution

DIPEA - N,N-diisopropylethylamine

DMF - N,N-Dimethylformamide

DMSO - Dimethylsulfoxide

DPPA - Diphenylphosphoryl azide

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

EtOAc - Ethyl acetate

EtOH – Ethanol

IPA - Isopropyl Alcohol

LAH - Lithium aluminium hydride

LiHMDS - Hexamethyldisilazane lithium salt TAI Lithium bis(trimethylsilyl)amide

m-CPBA - 3-Chloroperoxybenzoic acid

MeOH – Methanol

Ms - Methanesulfonyl

MTBE - Methyl Tertiary Butyl Ether

PPh_3 - Triphenylphosphine

$Pd_2(dba)_3$ -Tris(dibenzylideneacetone)dipalladium(0)

$Pd(PPh_3)_4$ – Tetrakis(triphenylphosphine)palladium(0)

PPTS - Pyridinium p-toluenesulfonate

rac-BINAP - *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

RT - Room temperature

rt – Retention time

TBABr - Tetrabutylammonium bromide

TBAF – Tetrabutylammonium fluoride

TBME - Mcthyl *tert*-butyl ether

TBSCl - tert-Butyldimethylsilyl chloride

TEA - Triethylamine

TFA – Trifluoroacetic acid

TFAA - Trifluoroacetic anhydride

THF – Tetrahydrofuran

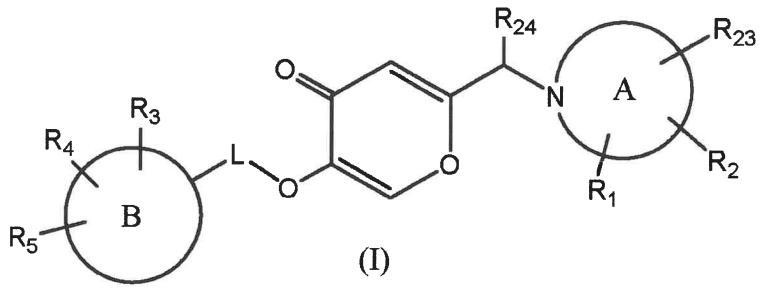
TMEDA – Tetramethylethylenediamine

Tf – trifluoromethanesulfonyl

Ts - *p*-Toluenesulfonyl

Claims

1. A compound of formula (I)

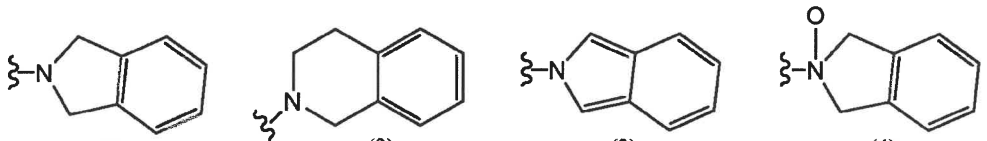


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups



;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$,$-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, -D-$C(O)-NR_6R_7$, $-C(O)R_8$, -D-NR_9R_{10}, $-SO_2R_{11}$, optionally substituted 3-10 membered carbocyclyl,

optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, optionally substituted 4-10 membered heterocyclyl or optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl or optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, optionally substituted 3-10 membered carbocyclyl or optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or -SO_2R_{21};

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, -SO_2R_{17};

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound is not

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2,5-dimethylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(2,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(3-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-methylphenyl)methoxy]-4*H*-pyran-4-one;

5-[(3,4-Dichlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(1-naphthalenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[3-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

5-[(2-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(2-Chloro-6-fluorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl) methyl]-4*H*-pyran-4-one;

5-[(4-Chlorophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

5-[(4-Bromophenyl)methoxy]-2-[(3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(2-methylphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(phenylmethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[[4-(trifluoromethyl)phenyl] methoxy]-4*H*-pyran-4-one;

Methyl 4-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzoate;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-fluorophenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3,5-dimethoxyphenyl)methoxy]-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-nitrophenyl)methoxy]- 4*H*-pyran-4-one;

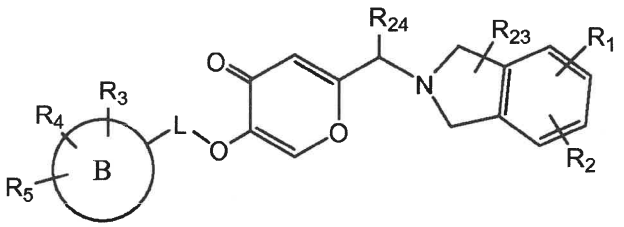
Methyl 5-(((6-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)furan-2-carboxylate;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-(2-phenylethoxy)-4*H*-pyran-4-one;

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(3-methylphenyl)methoxy]-4*H*-pyran-4-one; or

2-[(3,4-Dihydro-2(1*H*)-isoquinolinyl)methyl]-5-[(4-nitrophenyl)methoxy]-4*H*-pyran-4-one.

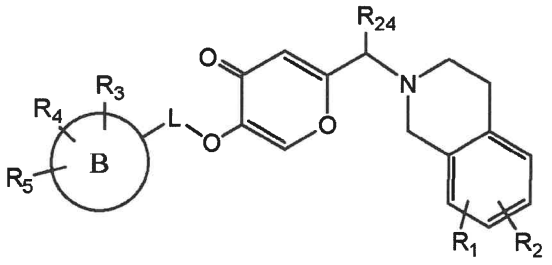
2. A compound according to claim 1, wherein the compound is represented by formula (IA):



(IA),

wherein R_1, R_2, R_3, R_4, R_5, R_{23}, R_{24}, L and B are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein the compound is represented by formula (IB):



(IB),

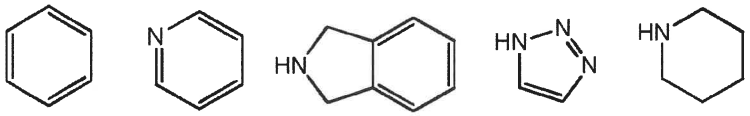
wherein R_1, R_2, R_3, R_4, R_5, R_{24}, L and B are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

4. A compound according to any of claims 1 to 3, wherein L is $-CH_2-$ or $-CH_2-CH_2-$.

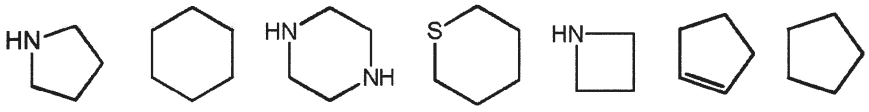
5. A compound according to claim 4, wherein L is $-CH_2-$.

6. A compound according to claim 5, wherein L is $-CH_2-CH_2-$.

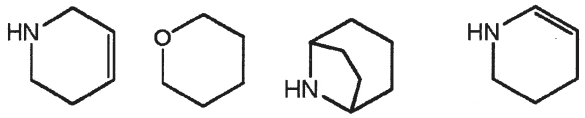
7. A compound according to any of the preceding claims, wherein ring B is any one of the following groups



(1'), (2'), (3'), (4'), (5'),



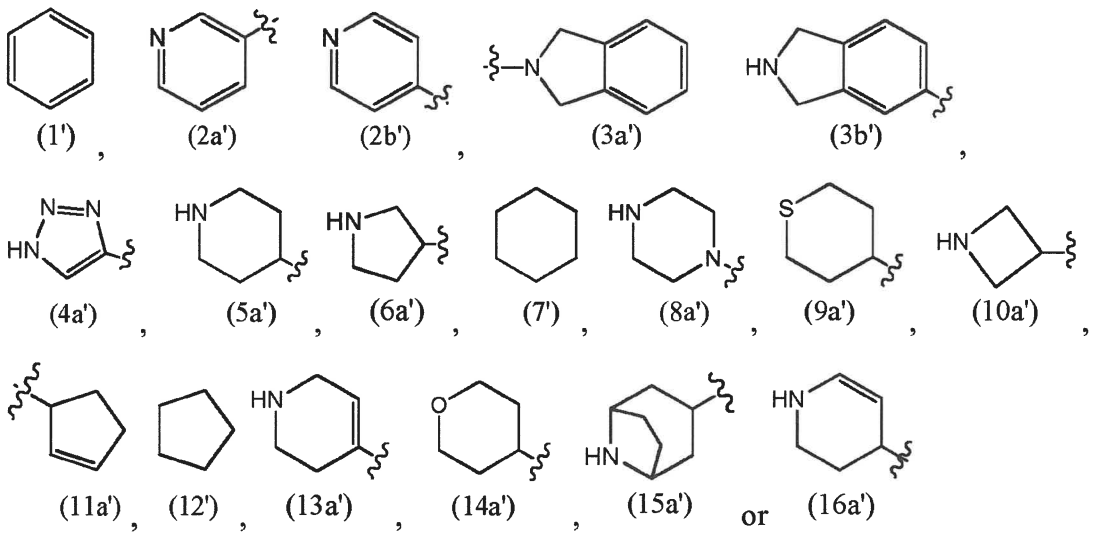
(6'), (7'), (8'), (9'), (10'), (11'), (12'),



(13') , (14') , (15') or (16')

R_3, R_4 and R_5 being attached to the above B-rings.

8. A compound according to claim 7, wherein ring B is any one of the following groups



(1') , (2a') (2b') , (3a') (3b') ,

(4a') , (5a') , (6a') , (7') , (8a') , (9a') , (10a') ,

(11a') , (12') , (13a') , (14a') , (15a') or (16a')

R_3, R_4 and R_5 being attached to the above B-rings and the wavy line denoting the site of attachment to L.

9. A compound according to claim 8, wherein ring B is (1'), (5'), (7'), (9'), (13') or (14').

10. A compound according to claim 8, wherein ring B is (1'), (5a'), (7'), (9a'), (13a') or (14a').

11. A compound according to any of the preceding claims, wherein R_3 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), -C(S)$NR_{18}R_{19}$, an optionally substituted 3-10

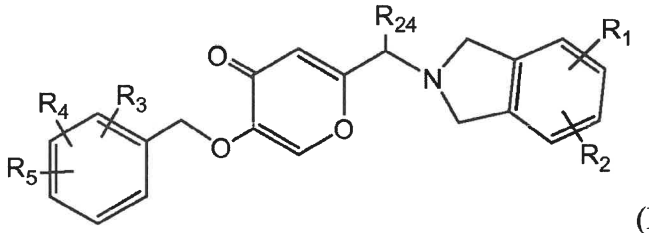
membered carbocyclyl, an optionally substituted 4-10 membered heterocyclyl, or an optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo, and

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S.

12. A compound according to any of the preceding claims, wherein R_4 and R_5 are hydrogen.

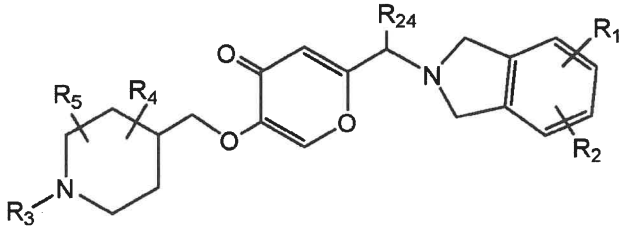
13. A compound according to claim 1 or 2, wherein the compound is represented by formula (IC):



(IC)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

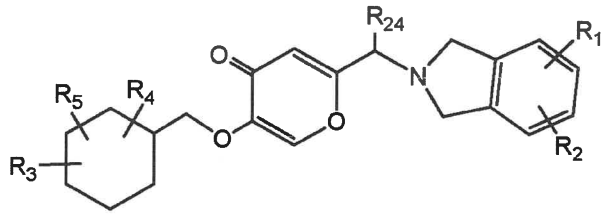
14. A compound according to claim 1 or 2, wherein the compound is represented by formula (ID):



(ID)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1 or 2, wherein the compound is represented by formula (IE):



(IE)

wherein R_1, R_2, R_3, R_4, R_5 and R_{24} are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

16. A compound according to any of claims 13-15, wherein

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), -C(S)$NR_{18}R_{19}$, 4-6 membered carbocyclyl which is optionally substituted with 1-2 hydroxyl substituents, 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen, hydroxyl, C_{1-7} alkoxycarbonyl or oxo, or 4-6 membered heterocyclyl C_{1-7} alkyl optionally substituted with 1-2 oxo substituents;

R_4 is hydrogen, C_{1-7} alkyl, hydroxy or halogen;

R_5 is hydrogen or halogen;

R_6 is C_{1-7} alkyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 halogen substituents;

R_9 is C_{1-7} alkylcarbonyl, -SO_2(C_{1-7} alkyl) or -SO_2(C_{3-7} cycloalkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, 3-6 membered carbocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl, or 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{13} is hydrogen or C_{1-7} alkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or $-SO_2R_{21}$;

R_{15} is hydrogen, C_{1-7} alkyl, $-SO_2R_{17}$;

R_{17} is C_{1-7} alkyl or 3-6 membered carbocyclyl which is optionally substituted by 1-2 C_{1-7} alkyl substituent;

R_{18}, and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

R_{21} is 3-6 membered carbocyclyl optionally substituted with 1-2 C_{1-7} alkyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 13, wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $-D-C(O)-NR_6R_7$, $-C(O)R_8$, $-SO_2R_{11}$, $-D-NR_9R_{10}$, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), a 3-6 membered carbocyclyl which is optionally substituted with 1-2 hydroxyl substituents, or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or hydroxyl;

R_4 is hydrogen, hydroxy or halogen;

R_5 is hydrogen or halogen;

R_6 is C_{1-7} alkyl, hydroxy C_{1-7} alkyl or -C_{1-7} alkyl-O-C(O)C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, halo C_{1-7} alkyl, -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl) or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 halogen substituents;

R_9 is C_{1-7} alkylcarbonyl or -SO_2(C_{1-7} alkyl);

R_{10} is hydrogen or C_{1-7} alkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$ or a 4-6 membered heterocyclyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{13} is hydrogen or C_{1-7} alkyl;

R_{14} is hydrogen, C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is hydrogen or -SO_2R_{17};

R_{17} is a 3-6 membered carbocyclyl which is optionally substituted by 1-2 C_{1-7} alkyl substituents;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 17, wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, nitro, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_{10} are hydrogen;

R_3 is C_{2-7} alkenyl, hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -C(O)R_8, -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), oxazolyl, cyclobutyl optionally substituted with a hydroxy substituent, or oxetanyl optionally substituted with a hydroxy substituent;

R_4 and R_5 are hydrogen or halogen;

R_6 is C_{1-7} alkyl or hydroxy C_{1-7} alkyl;

R_7, R_{13}, R_{14} and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, pyrrolidinyl, oxetanyl, or azetidinyl optionally substituted with 1-2 halogen substituents,-N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl);

R_9 is -SO_2(C_{1-7} alkyl);

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, pyrrolidinyl, piperidinyl, azetidinyl or morpholinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is hydrogen or -SO_2R_{17};

R_{17} is phenyl optionally substituted by a C_{1-7} alkyl substituent;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 18, wherein

R_1 is hydrogen, C_{1-7} alkoxy, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_{10} are hydrogen;

R_3 is hydroxy C_{1-7} alkyl, cyano, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, -D-C(O)-NR_6R_7, -C(O)R_8, -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), -S(NR_{15})(C_{1-7} alkyl), oxazolyl, cyclobutyl optionally substituted with a hydroxy substituent, or oxetanyl optionally substituted with a hydroxy substituent;

R_4 and R_5 are hydrogen or halogen;

R_6 is C_{1-7} alkyl;

R_7, R_{13}, R_{14} and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is pyrrolidinyl, azetidinyl or -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl);

R_9 is -SO_2(C_{1-7} alkyl);

R_{11} is C_{1-7} alkyl, halo C_{1-7} alkyl, -$NR_{12}R_{13}$ or pyrrolidinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_{15} is -SO_2R_{17};

R_{17} is phenyl optionally substituted by a C_{1-7} alkyl substituent;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 19, wherein

R_1 is hydrogen, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_4, R_5 and R_{10} are hydrogen;

R_3 is hydroxy C_{1-7} alkyl, -D-C(O)-NR_6R_7, -C(O)R_8, -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}) or oxetanyl optionally substituted with a hydroxy substituent;

R_6 and R_7 is C_{1-7} alkyl;

R_8 is pyrrolidinyl, or -N=S(O)(C_{1-7} alkyl)(C_{1-7} alkyl);

R_9 is -SO_2(C_{1-7} alkyl);

R_{11} is C_{1-7} alkyl, -$NR_{12}R_{13}$ or pyrrolidinyl;

R_{12} is C_{1-7} alkyl, hydroxy C_{1-7} alkyl, or C_{1-7} alkoxy C_{1-7} alkyl;

R_{13} and R_{14} is hydrogen or C_{1-7} alkyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

D is C_{1-7} alkyl or C_{2-7} alkenyl;

or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 14, wherein

R_1 is hydrogen, C_{1-7} alkyl, cyano, halogen, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen or halogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, or -C(S)$NR_{18}R_{19}$;

R_4 is hydrogen, C_{1-7} alkyl, hydroxy or halogen;

R_5 is hydrogen;

R_6 is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_7 and R_{24} are hydrogen or C_{1-7} alkyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, C_{1-7} alkoxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl) or a 4-10 membered heterocyclyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, a 3-6 membered carbocyclyl which is optionally substituted with 1-2 halogen substituents, or a 4-6 membered heterocyclyl which is optionally substituted with 1-2 substituents selected from halogen or C_{1-7} alkyl;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{18}, and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

D is absent;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S.

or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 21, wherein

R_1 is hydrogen, C_{1-7} alkyl, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2 and R_5 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, $-C(O)R_8$, $-SO_2R_{11}$, or $-C(S)NR_{18}R_{19}$, or oxetanyl optionally substituted by a hydroxy substituent;

R_4 is hydrogen, C_{1-7} alkyl or halogen;

R_6 is C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, C_{1-7} alkoxy C_{1-7} alkyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), azetidinyl, morpholinyl, furanyl or pyrrolidinyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, pyrrolidinyl, phenyl optionally substituted with a halogen substituent, oxetanyl, or pyrazolyl optionally substituted with a C_{1-7} alkyl substituent;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{18}, and R_{19} are, independently, hydrogen or C_{1-7} alkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent;

or a pharmaceutically acceptable salt thereof.

23. A compound according to claim 22, wherein

R_1 is hydrogen, C_{1-7} alkyl, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_5 and R_7 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 or -SO_2R_{11};

R_4 is hydrogen or C_{1-7} alkyl;

R_6 is C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, C_{1-7} alkylcarbonyl, -C_{1-7} alkyl-O-C(O)-C_{1-7} alkyl, -C_{1-7} alkyl-SO_2(C_{1-7} alkyl), morpholinyl or pyrrolidinyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$, oxetanyl, or pyrazolyl optionally substituted with a C_{1-7} alkyl substituent;

R_{12} and R_{13} are C_{1-7} alkyl;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent;

or a pharmaceutically acceptable salt thereof.

24. A compound according to claim 23, wherein

R_1 is hydrogen, halogen, halo C_{1-7} alkyl or halo C_{1-7} alkoxy;

R_2, R_4, R_5 and R_7 are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 or -SO_2R_{11};

R_6 , R_{12} and R_{13} are C_{1-7} alkyl;

R_8 is C_{1-7} alkyl or halo C_{1-7} alkyl;

R_{11} is C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy C_{1-7} alkyl, -$NR_{12}R_{13}$ or oxetanyl;

R_{24} is hydrogen;

D is absent;

or a pharmaceutically acceptable salt thereof.

25. A compound according to claim 15, wherein

R_1, R_2, R_4, R_5 and R_{24} are hydrogen;

R_3 is hydrogen, -D-C(O)-NR_6R_7, -C(O)R_8 , -SO_2R_{11}, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), a 4-6 membered heterocyclyl which is optionally substituted with 1-2

oxo substituents, or a 4-6 membered heterocyclyl C_{1-7} alkyl optionally substituted with 1-2 oxo substituents;

R_6, R_{11} and R_{22} are C_{1-7} alkyl;

R_7 is hydrogen or C_{1-7} alkyl;

R_8 is C_{1-7} alkyl, C_{1-7} alkoxy, or a 4-6 membered heterocyclyl;

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen or $-SO_2R_{21}$;

R_{21} is 3-6 membered carbocyclyl optionally substituted with 1-2 C_{1-7} alkyl;

D is absent or C_{1-7} alkyl;

wherein the heterocyclyl group in each occurrence has 1-3 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

26. A compound according to claim 25, wherein

R_1, R_2, R_4, R_5 and R_{24} are hydrogen;

R_3 is -D-C(O)-NR_6R_7, -C(O)R_8 , $-SO_2R_{11}$, -D-NR_9R_{10}, -S(O)(NR_{14})(R_{22}), 1,1-dioxidoisothiazolidinyl or 1,1-dioxidoisothiazolidinyl C_{1-7} alkyl;

R_6, R_{11} and R_{22} are C_{1-7} alkyl;

R_7 is C_{1-7} alkyl;

R_8 is C_{1-7} alkyl or azetidinyl;

R_9 is $-SO_2(C_{1-7}$ alkyl);

R_{10} is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is $-SO_2R_{21}$;

R_{21} is phenyl optionally substituted with a C_{1-7} alkyl substituent;

D is absent or C_{1-7} alkyl;

or a pharmaceutically acceptable salt thereof.

27. A compound according to claim 1, which is

Methyl (E)-3-(4-((((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)phenyl)acrylate (Compound 2);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidin-1-ylsulfonyl)benzyl)oxy)-4H-pyran-4-one (Compound 5);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-methylbenzenesulfonamide (Compound 8);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzenesulfonamide (Compound 10);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N-(2-methoxyethyl)benzenesulfonamide (Compound 11);

N-(2-Hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)-oxy)methyl)-N-methylbenzenesulfonamide (Compound 12);

N-(2-Hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)-oxy)methyl)benzenesulfonamide (Compound 15);

N-Ethyl-N-(2-hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzenesulfonamide (Compound 21);

5-((4-((Difluoromethyl)sulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 22);

N-(2-Cyanoethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)-N-methylbenzenesulfonamide (Compound 23);

2-(Isoindolin-2-ylmethyl)-5-((1-(oxetan-3-ylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 36);

5-((4-(Methylsulfonyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)-methyl)-4H-pyran-4-one (Compound 37);

2-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-5-((4-(2-hydroxypropan-2-yl)-benzyl)oxy)-4H-pyran-4-one (Compound 44);

2-Isoindolin-2-ylmethyl)-5-((4-(prop-1-en-2-yl)benzyl)oxy)-4H-pyran-4-one (Compound 47);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 49);

5-(Cyclohexylmethoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 65);

5-((1-(Oxetan-3-ylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)-isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 69a);

N-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-sulfonyl)-N-methylacetamide (Compound 70);

5-((4-(Cyclobutanesulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 71);

5-((4-(Cyclopropylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 72);

5-((4-(Isobutylsulfonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 73);

5-((4-(S-methylsulfinimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 74);

4-({[6-(1,3-Dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}methyl)-*N*-[dimethyl(oxido)-λ^6-sulfanylidene]benzamide (Compound 83);

N-[Dimethyl(oxido)- λ^6-sulfanylidene]-4-[({6-[(5-fluoro-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-4-oxo-4*H*-pyran-3-yl}oxy)methyl]benzamide (Compound 84);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 89);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 90);

2-(1-(Isoindolin-2-yl)ethyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 91);

5-((4-(N,S-Dimethylsulfonimidoyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 92);

N-{[4-({[6-(1,3-dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}-methyl)phenyl](methyl)-λ^4-sulfanylidene}-4-methylbenzenesulfonamide (Compound 93);

5-((4-(Azetidine-1-carbonyl)-2-fluorobenzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 95);

2-(Isoindolin-2-ylmethyl)-5-((4-(propan-2-ylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 103);

5-((5-Fluoro-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 104);

2-(Isoindolin-2-ylmethyl)-5-((4-(oxazol-2-yl)benzyl)oxy)-4*H*-pyran-4-one (Compound 109);

5-((4-(1-Hydroxycyclobutyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 111);

N-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)benzyl)-methanesulfonamide (Compound 113);

5-((4-(3-Hydroxyoxetan-3-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 114);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((4-(3-hydroxyoxetan-3-yl)benzyl)oxy)-4*H*-pyran-4-one (Compound 115);

5-((4-(3-Hydroxyoxetan-3-yl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 116);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 122);

5-((4-(Azetidine-1-carbonyl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 129);

2-((5-Bromoisoindolin-2-yl)methyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 130);

N-(tert-Butyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-benzamide (Compound 131);

4-(((6-Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-diiso-propylbenzamide (Compound 134);

4-(((6-((5-Chloroisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 137);

4-(((6-((5-Methoxyisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 138);

N,N-Dimethyl-4-(((4-oxo-6-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-3-yl)oxy)methyl)benzamide (Compound 139);

(E)-3-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)phenyl)-N,N-dimethylacrylamide (Compound 146);

5-((4-(3,3-Difluoroazetidine-1-carbonyl)benzyl)oxy)-2-((5-methoxyisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 162);

3,5-Difluoro-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylbenzamide (Compound 172);

N-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)cyclohexyl)-methyl)methanesulfonamide (Compound 173);

5-((4-((1,1-Dioxidoisothiazolidin-2-yl)methyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 176);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 184);

2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 185);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 186);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 187);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 188);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 189);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 190);

5-((1-(Ethylsulfonyl)-4-methylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 192);

2-(1-Isoindolin-2-yl)ethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 195);

2-(Isoindolin-2-ylmethyl)-5-((tetrahydro-2H-thiopyran-4-yl)methoxy)-4H-pyran-4-one (Compound 196);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethoxy)-isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 205);

2-((5-Methylisoindolin-2-yl)methyl)-5-((1-(methylsulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 211);

2-(Isoindolin-2-ylmethyl)-5-(3-(1-(methylsulfonyl)piperidin-4-yl)propoxy)-4H-pyran-4-one (Compound 213);

2-(Isoindolin-2-ylmethyl)-5-((1-(pyrrolidine-1-carbonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 215);

5-(((1r,4r)-4-(1,1-Dioxidoisothiazolidin-2-yl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 216);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylcyclohexane-1-carboxamide (Compound 217);

N-Cyclopropyl-N-(4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)-methyl)cyclohexyl)methanesulfonamide (Compound 219);

5-((1-Butyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 221);

5-((1-(2,2-Difluoropropanoyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 222);

2-((5-Fluoroisoindolin-2-yl)methyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 224);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-di-methylpiperidine-1-sulfonamide (Compound 225);

5-((1-(Cyclopropanecarbonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 226);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*-iso-propylpiperidine-1-carboxamide (Compound 229);

4-(((6-((5-Fluoroisoindolin-2-yl)methyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-sulfonamide (Compound 230);

2-(Isoindolin-2-ylmethyl)-5-((1-(morpholine-4-carbonyl)piperidin-4-yl)methoxy)-4*H*-pyran-4-one (Compound 232);

5-((4-(Azetidine-1-carbonyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 234);

2-(Isoindolin-2-ylmethyl)-5-((1-(2-(methylsulfonyl)acetyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 238);

5-(((1r,4r)-4-Acetylcyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 244);

5-((1-Propionylpiperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 244a);

2-((5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4-oxo-4H-pyran-2-yl)methyl)isoindoline-5-carbonitrile (Compound 245a);

1-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)-4-methylpentane-1,2-dione (Compound 249);

2-(Isoindolin-2-ylmethyl)-5-((1-pivaloylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 251);

2-((4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)sulfonyl)acetonitrile (Compound 254);

2-(Isoindolin-2-ylmethyl)-5-((1-((1-methyl-1H-pyrazol-5-yl)sulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 255);

2-(4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)piperidin-1-yl)-2-oxoethyl acetate (Compound 257);

2-(Isoindolin-2-ylmethyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 261);

2-(Isoindolin-2-ylmethyl)-5-((1-((2-methoxyethyl)sulfonyl)piperidin-4-yl)-methoxy)-4H-pyran-4-one (Compound 262);

5-((1-(Isobutylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 271);

5-((1-Isobutyrylpiperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4*H*-pyran-4-one (Compound 272);

4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzo-nitrile (Compound 278);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 285);

5-((4-(R-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 286);

and tautomers and pharmaceutically acceptable salts thereof.

28. A compound according to claim 27, which is

N-Ethyl-N-(2-hydroxyethyl)-4-(((6-(isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)benzenesulfonamide (Compound 21);

5-((4-(2-Hydroxypropan-2-yl)benzyl)oxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 49);

4-({[6-(1,3-Dihydro-2*H*-isoindol-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl]oxy}methyl)-*N*-[dimethyl(oxido)-λ^6-sulfanylidene]benzamide (Compound 83);

5-((4-(S-Methylsulfonimidoyl)benzyl)oxy)-2-((5-(trifluoromethoxy)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 90);

2-(1-(Isoindolin-2-yl)ethyl)-5-((4-(S-methylsulfonimidoyl)benzyl)oxy)-4H-pyran-4-one (Compound 91);

2-(Isoindolin-2-ylmethyl)-5-((4-(pyrrolidine-1-carbonyl)benzyl)oxy)-4H-pyran-4-one (Compound 122);

5-((4-((1,1-Dioxidoisothiazolidin-2-yl)methyl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 176);

5-((1-(Methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4*H*-pyran-4-one (Compound 184);

2-(Isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 185);

5-((1-(Cyclopropylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 187);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 188);

5-((1-(Ethylsulfonyl)piperidin-4-yl)methoxy)-2-((5-fluoroisoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 189);

2-(1-Isoindolin-2-yl)ethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 195);

2-(Isoindolin-2-ylmethyl)-5-(3-(1-(methylsulfonyl)piperidin-4-yl)propoxy)-4H-pyran-4-one (Compound 213);

5-(((1r,4r)-4-(1,1-Dioxidoisothiazolidin-2-yl)cyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 216);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4H-pyran-3-yl)oxy)methyl)-N,N-dimethylcyclohexane-1-carboxamide (Compound 217);

4-(((6-(Isoindolin-2-ylmethyl)-4-oxo-4*H*-pyran-3-yl)oxy)methyl)-*N*,*N*-dimethylpiperidine-1-sulfonamide (Compound 225);

5-(((1r,4r)-4-Acetylcyclohexyl)methoxy)-2-(isoindolin-2-ylmethyl)-4H-pyran-4-one (Compound 244);

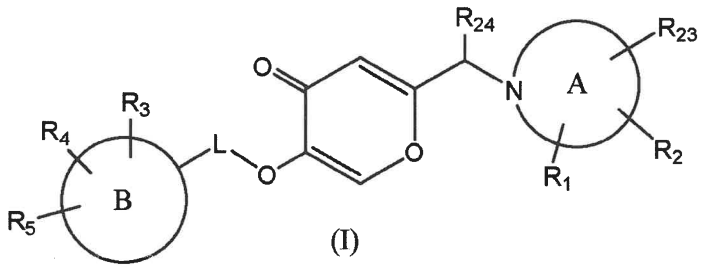
5-((1-Propionylpiperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (Compound 244a);

2-(Isoindolin-2-ylmethyl)-5-((1-propionylpiperidin-4-yl)methoxy)-4H-pyran-4-one (Compound 261);

4-((6-((5-Bromoisoindolin-2-yl)methyl)-4-oxo-4H-pyran-3-yloxy)methyl)benzonitrile (Compound 278);

and tautomers and pharmaceutically acceptable salts thereof.

29. A method for the treatment of a steroid receptor, particularly androgen receptor, dependent conditions and diseases comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I)

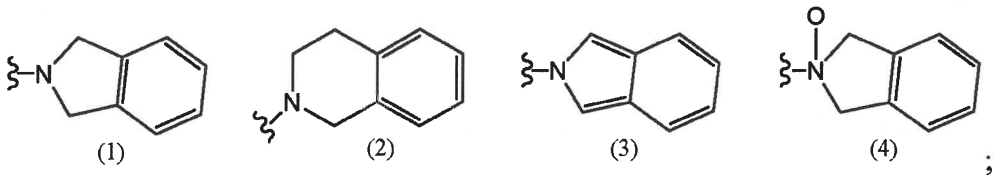


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups



(1) (2) (3) (4) ;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$,$-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, -D-$C(O)-NR_6R_7$, $-C(O)R_8$, -D-NR_9R_{10}, $-SO_2R_{11}$, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, optionally substituted 4-10 membered heterocyclyl or optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, $-C_{1-7}$ alkyl-O-$C(O)C_{1-7}$ alkyl or optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, $-C_{1-7}$ alkyl-O-$C(O)-C_{1-7}$ alkyl, $-C_{1-7}$ alkyl-$SO_2(C_{1-7}$ alkyl), $-N=S(O)(C_{1-7}$ alkyl)(C_{1-7} alkyl) or optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2(C_{1-7}$ alkyl) or $-SO_2(C_{3-7}$ cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, optionally substituted 3-10 membered carbocyclyl or optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or $-SO_2R_{21}$;

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2R_{17}$;

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

30. A method according to claim 29, wherein the steroid receptor dependent disease is cancer.

31. A method according to claim 30, wherein the cancer is prostate cancer.

32. A method according to claim 31, wherein the prostate cancer is castration-resistant prostate cancer (CRPC).

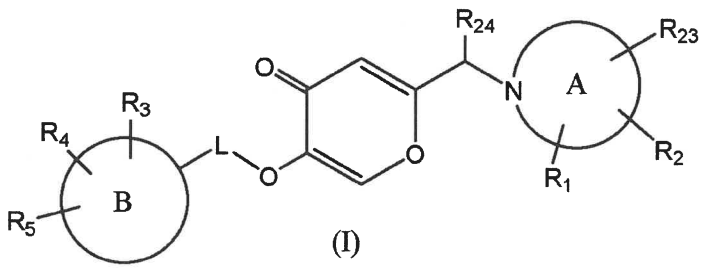
33. A method according to any of claims 29-32 wherein a therapeutically effective amount of a compound of formula (I) is administered in addition to a glucocorticoid and/or a mineralocorticoid and, optionally, one or more anti-cancer agent.

34. A method according to any of claims 29-33 wherein a therapeutically effective amount of a compound of formula (I) is administered in addition to one or more anti-cancer agents selected from the group consisting of

- non-steroidal androgen receptor antagonists;
- steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors; and
- CDK4/6 inhibitors.

35. A method according to any of claims 29-34 wherein a therapeutically effective amount of a compound of formula (I) and a therapeutically effective amount of a non-steroidal androgen receptor antagonist is administered.

36. A compound according to formula (I)

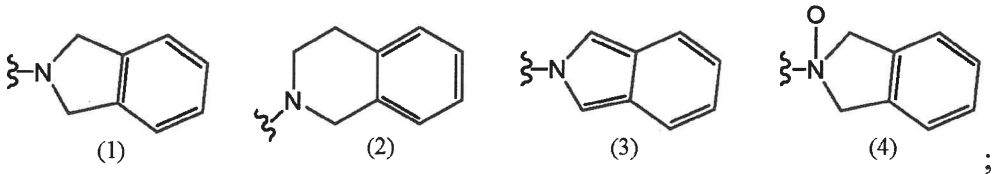


(I)

wherein

ring B is a 4-10 membered monocyclic or bicyclic ring containing 0-4 hetero-atoms independently selected form N, O or S

ring A is any of the following groups



(1) (2) (3) (4) ;

L is absent, $-CH_2-$, $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$, or in case ring A is (1), L can also be $-C(O)-CH_2-$;

R_1 is hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy, halogen, cyano, nitro, halo C_{1-7} alkyl, halo C_{1-7} alkoxy or C_{1-7} alkylthio;

R_2 is hydrogen, C_{1-7} alkyl, halogen, hydroxy, halo C_{1-7} alkyl, nitro, halo C_{1-7} alkoxy or thiol;

or R_1 and R_2 together with the carbon atoms to which they are attached form a fused 1,3 dioxole ring;

R_3 is hydrogen, halogen, nitro, cyano, oxo, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{3-7} cycloalkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylthio, aminocarbonyl C_{2-7} alkenyl, halo C_{1-7} alkylthio, C_{1-7} alkoxycarbonyl C_{1-7} alkyl, C_{1-7} alkoxycarbonyl C_{2-7} alkenyl, $=NSO_2R_{20}$,$-S(O)-C_{1-7}$ alkyl, $-S(O)(NR_{14})(R_{22})$, $-S(NR_{15})(C_{1-7}$ alkyl), $-C(S)NR_{18}R_{19}$, -D-$C(O)-NR_6R_7$, $-C(O)R_8$, -D-NR_9R_{10}, $-SO_2R_{11}$, optionally substituted 3-10 membered carbocyclyl, optionally substituted 3-10 membered carbocyclyl C_{1-7} alkyl, optionally substituted 4-10 membered heterocyclyl or optionally substituted 4-10 membered heterocyclyl C_{1-7} alkyl;

R_4 is hydrogen, halogen, hydroxy, C_{1-7} alkyl, halo C_{1-7} alkyl or oxo;

R_5 is hydrogen, halogen or C_{1-7} alkyl;

R_6 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, $-C_{1-7}$ alkyl-O-$C(O)C_{1-7}$ alkyl or optionally substituted 4-10 membered heterocyclyl;

R_8 is hydrogen, C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, C_{1-7} alkoxy, halo C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, $-C_{1-7}$ alkyl-O-$C(O)-C_{1-7}$ alkyl, $-C_{1-7}$ alkyl-$SO_2(C_{1-7}$ alkyl), $-N=S(O)(C_{1-7}$ alkyl)(C_{1-7} alkyl) or optionally substituted 4-10 membered heterocyclyl;

R_9 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2(C_{1-7}$ alkyl) or $-SO_2(C_{3-7}$ cycloalkyl);

R_{11} is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, halo C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy C_{1-7} alkyl, $-NR_{12}R_{13}$, optionally substituted 3-10 membered carbocyclyl or optionally substituted 4-10 membered heterocyclyl;

R_{12} is hydrogen, C_{1-7} alkyl, hydroxy C_{1-7} alkyl, cyano C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl or C_{1-7} alkylcarbonyl;

R_7, R_{10}, R_{13}, R_{18}, and R_{19} are, independently, hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{14} is hydrogen, C_{1-7} alkyl, C_{1-7} alkylcarbonyl or $-SO_2R_{21}$;

R_{15} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{1-7} alkylcarbonyl, $-SO_2R_{17}$;

R_{17} is C_{1-7} alkyl or an optionally substituted 3-10 membered carbocyclyl;

R_{20} and R_{21} are, independently, C_{1-7} alkyl, C_{3-7} cycloalkyl or optionally substituted 3-10 membered carbocyclyl;

R_{22} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{23} is hydrogen or oxo;

R_{24} is hydrogen or C_{1-7} alkyl;

D is absent, C_{1-7} alkyl or C_{2-7} alkenyl;

wherein the optional substitution in each occurrence is selected from 1-3 substituents independently selected from C_{1-7} alkyl, halogen, hydroxy, C_{1-7} alkoxy, C_{1-7} alkoxy C_{1-7} alkyl, C_{1-7} alkoxycarbonyl or oxo; and

wherein the heterocyclyl group in each occurrence has 1-4 heteroatoms independently selected from N, O and S;

or a pharmaceutically acceptable salt thereof,

for use in the treatment of steroid receptor, particularly androgen receptor, dependent diseases.

37. A compound according to claim 36 wherein the steroid receptor dependent disease is cancer.

38. A compound according to claim 37 wherein the cancer is prostate cancer.

39. A compound according to claim 38 wherein prostate cancer is castration-resistant prostate cancer (CRPC).

40. A compound according to any of claims 36-39 wherein the compound of formula (I) is administered in addition to a glucocorticoid and/or a mineralocorticoid and, optionally, one or more anti-cancer agent.

41. A compound according to any of claims 36-40 wherein a therapeutically effective amount of a compound of formula (I) is administered in addition to one or more anti-cancer agents selected from the group consisting of

- non-steroidal androgen receptor antagonists;
- steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors; and
- CDK4/6 inhibitors.

42. A compound according to any of claims 36-41 wherein the compound of formula (I) is administered in addition to a non-steroidal androgen receptor antagonist.

43. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically acceptable carrier.

44. Pharmaceutical combination comprising a compound according to claim 1 and at least one additional active ingredient selected from the list consisting of

- glucocorticoids;
- mineralocorticoids;
- non-steroidal androgen receptor antagonists;
- steroidogenesis inhibitors;
- chemotherapeutic agents;
- antiestrogens;
- epigenetic modulators;
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);
- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors; and
- CDK4/6 inhibitors;

for simultaneous, separate or sequential administration.