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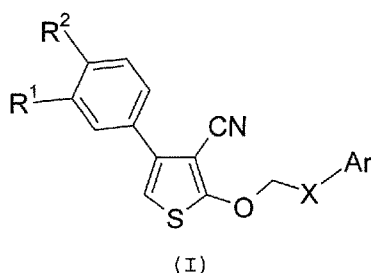
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(54) Title: 3-CYANOTHIOPHENE DERIVATIVES AS INHIBITORS OF THE PD-1/PD-L1 PROTEIN/PROTEIN INTERACTION

(57) Abstract: The present invention provides novel compounds of formula (I) that are useful as inhibitors of the PD-1/PD-L1 protein/protein interaction. The compounds may be used in the treatment of cancer, infectious diseases and neurodegenerative diseases such as schizophrenia, Alzheimer, multiple sclerosis or Parkinson.



3-CYANOTHIOPHENE DERIVATIVES AS INHIBITORS OF THE PD-1/PD-L1 PROTEIN/PROTEIN INTERACTION

The present invention provides novel compounds that are useful as inhibitors of the PD-1/PD-L1 protein/protein interaction.

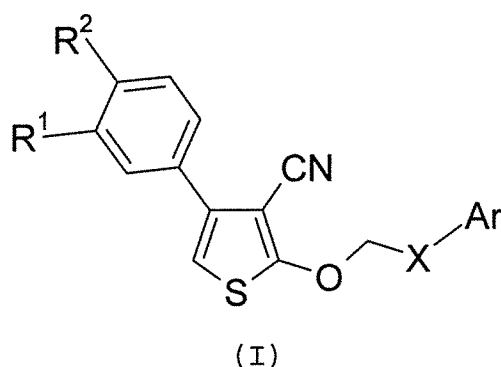
The PD-1/PD-L1 axis is hijacked by viruses, bacteria and uncontrolled fast growing cells to suppress the immune surveillance. In cancer for example, the malignant cells express PD-L1 which bind to the PD1 receptor expressed on immune T-cells. Binding of PD-1 to PD-L1 determines a downregulation of T-cell effector functions in cancer patients inhibiting the antitumor immune response and leading to T-cell exhaustion. In viral and infectious diseases a similar mechanism is used by viruses and bacteria to undermine the effective immune recognitions and answer.

Current medication directed towards the PD-1/PD-L1 axis includes monoclonal antibodies. These have shown impressive clinical results in the treatment of several types of tumours. Therapeutic antibodies however exhibit several disadvantages such as limited tissue and tumour penetration, very long half life time, lacking oral bioavailability, immunogenicity, and difficult and expensive production. The current PD-1/PD-L1 axis directed monoclonal antibodies lead to a tumour response only in a fraction of cases and tumour types. Recently small molecules have been described to bind to PD-L1 in WO 2015/160641 and WO 2015/034820. The compounds described therein, however, display a high lipophilicity (cLogP).

A high cLogP is often associated with extensive metabolism, poor water solubility, fast excretion and toxicity and reduced target selectivity.

Therefore PD-1/PD-L1 axis targeted drugs are needed which overcome the above disadvantages and which further lead to a high tumour response, are fast and efficient to produce and can penetrate tumour tissue and have favourable half-life times to be able to adequately react on drug induced immunological adverse side effects. These objects are solved by the compounds of the present invention.

The present invention provides compounds of formula (I):



wherein

R^1 is a hydrogen atom or a halogen atom; and

R^2 is a hydrogen atom or a halogen atom; or

R^1 and R^2 together are a group of formula $-O-CH_2-CH_2-O-$, $-O-CH_2-CH_2-N(Me)-$, $-N(Me)-CH_2-CH_2-O-$, $-O-CF_2-O-$ or $-O-CH_2-O-$;

X is a bond, an oxygen atom or a group of formula $-C(=O)-$, or $-(CH_2)_n-$ wherein n is 1, 2 or 3 or a group of formula $-(CH_2)_m-O-$ wherein m is 2, 3 or 4; and

Ar is a phenyl group, a naphthyl group or a heteroaryl group containing 1 or 2 rings and from 5 to 10 ring atoms selected from C, O, N and S, wherein Ar may be substituted by 1, 2, 3, 4 or 5 groups R³ and/or wherein Ar may be substituted by a group of formula -CH₂-N(R⁴)-R⁵;

the groups R³ are independently from each other halogen, NO₂, N₃, OH, SH, NH₂ or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted;

R⁴ is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted; and

R⁵ is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted; or

R⁴ and R⁵ together with the nitrogen atom to which they are bound are part of an optionally substituted heterocycloalkyl group containing 5, 6 or 7 ring atoms;

or a pharmaceutically acceptable salt, ester, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

In the following, preferred embodiments of the present invention are disclosed. It is preferred that the preferred embodiments may be combined in any manner:

Preferably, R^1 and R^2 together are a group of formula $-O-CH_2-CH_2-O-$ or $-O-CH_2-O-$.

Further preferably, R^1 and R^2 are both hydrogen atoms.

Moreover preferably, R^1 and R^2 are both chlorine atoms.

Further preferably, X is a bond, an oxygen atom or a group of formula $-(CH_2)_n-$ wherein n is 1, 2 or 3 or a group of formula $-(CH_2)_3-O-$.

Especially preferably, X is a bond.

Moreover preferably, Ar is a phenyl group or a heteroaryl group containing one ring and 5 or 6 ring atoms selected from C, O, N and S, wherein Ar may be substituted by 1, 2, 3, 4 or 5 groups R^3 and/or wherein Ar may be substituted by a group of formula $-CH_2-N(R^4)-R^5$.

Further preferably, Ar is substituted by one or two groups R^3 .

Moreover preferably, the groups R^3 are independently halogen, NO_2 , N_3 , OH, SH, NH_2 or a C_1-C_6 alkyl group; a C_1-C_6 heteroalkyl group; a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N; an alkylcycloalkyl group containing a C_1-C_6 alkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heteroalkylcycloalkyl group containing a C_1-C_6 alkyl group or a C_1-C_6 heteroalkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring

atoms or a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N with the proviso that a heteroalkylcycloalkyl group contains at least one heteroatom; a phenyl group; a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N; an aralkyl group containing a C₁-C₆ alkyl group and a phenyl group; or a heteroaralkyl group containing a C₁-C₆ alkyl group or a C₁-C₆ heteroalkyl group and a phenyl group or a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N with the proviso that a heteroaralkyl group contains at least one heteroatom; all of which groups may optionally be substituted.

Especially preferably, Ar is substituted by a group of formula -CH₂-N(R⁴)-R⁵.

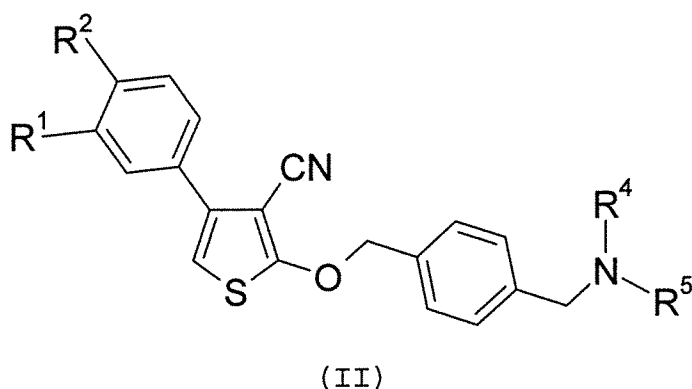
Further preferably, Ar is substituted by a group of formula -CH₂-N(R⁴)-R⁵ and further by one group R³, which is preferably selected from F, Cl, -OMe and -CHO.

Moreover preferably, R⁴ is a hydrogen atom and R⁵ is a hydrogen atom or a C₁-C₆ alkyl group; a C₁-C₆ heteroalkyl group; a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N; an alkylcycloalkyl group containing a C₁-C₆ alkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heteroalkylcycloalkyl group containing a C₁-C₆ alkyl group or a C₁-C₆ heteroalkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms or a heterocycloalkyl group containing one ring having

from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N with the proviso that a heteroalkylcycloalkyl group contains at least one heteroatom; a phenyl group; a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N; an aralkyl group containing a C₁-C₆ alkyl group and a phenyl group; or a heteroaralkyl group containing a C₁-C₆ alkyl group or a C₁-C₆ heteroalkyl group and a phenyl group or a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N with the proviso that a heteroaralkyl group contains at least one heteroatom; all of which groups may optionally be substituted.

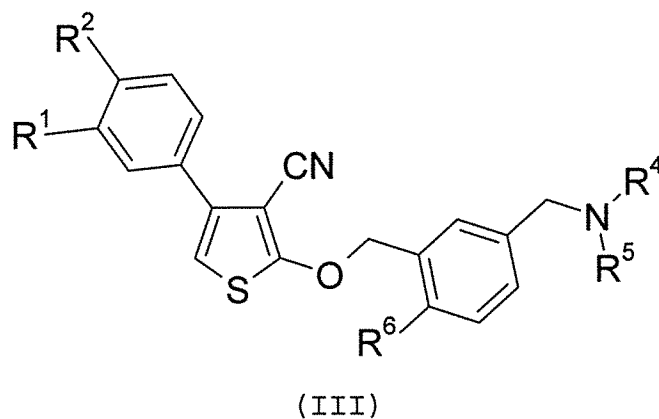
Further preferably, R⁴ and R⁵ together with the nitrogen atom to which they are bound are part of a heterocycloalkyl group containing 5, 6 or 7 ring atoms and optionally one further heteroatom selected from O and N, which heterocycloalkyl group may be substituted (preferably by a C₁-C₄ alkyl group or a group of formula -C(=O)-CH₃ or -CH₂OH).

Especially preferred are compounds of formula (II):



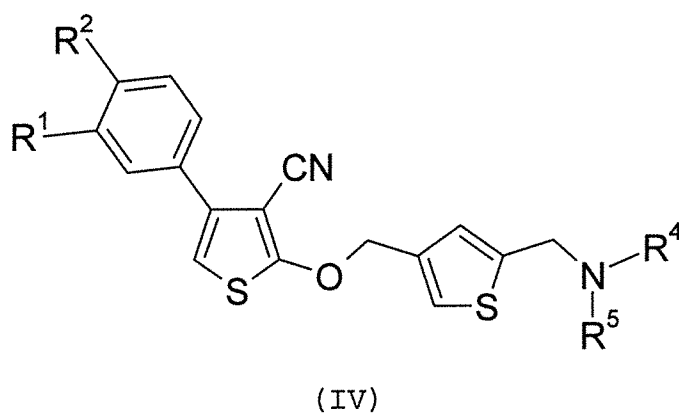
wherein R¹, R², R⁴ and R⁵ are as defined above.

Further especially preferred are compounds of formula (III):



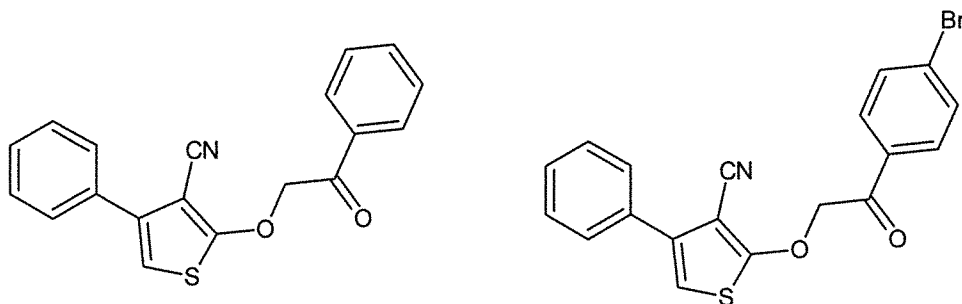
wherein R¹, R², R⁴ and R⁵ are as defined above and R⁶ is H or OMe.

Moreover especially preferred are compounds of formula (IV):



wherein R¹, R², R⁴ and R⁵ are as defined above.

According to a preferred embodiment, the following compounds are excluded from the scope of the present application:



The most preferred compounds of formula (I) of the present invention are the compounds disclosed in the examples.

The expression alkyl refers to a saturated, straight-chain or branched hydrocarbon group that contains from 1 to 20 carbon atoms, preferably from 1 to 12 carbon atoms, especially from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms, for example a methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, 2,2-dimethylbutyl or n-octyl group. Furthermore, the term alkyl refers to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl) such as, for example, a 2,2,2-trichloroethyl or a trifluoromethyl group.

The expressions alkenyl and alkynyl refer to at least partially unsaturated, straight-chain or branched hydrocarbon groups that contain from 2 to 20 carbon atoms, preferably from 2 to 12 carbon atoms, especially from 2 to 6 (e.g. 2, 3 or 4) carbon atoms, for example an ethenyl (vinyl), propenyl (allyl), iso-propenyl, butenyl, ethinyl, propinyl, butinyl, acetylenyl, propargyl, isoprenyl or hex-2-enyl group. Preferably, alkenyl groups have one or two (especially preferably one) double bond(s), and alkynyl groups have one or two (especially preferably one) triple bond(s). Furthermore, the terms alkenyl and alkynyl refer to groups in which one or more

hydrogen atoms have been replaced by a halogen atom (preferably F or Cl).

The expression heteroalkyl refers to an alkyl, alkenyl or alkynyl group in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus, boron, selenium, silicon or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a group of formula SO or SO₂. The expression heteroalkyl furthermore refers to a carboxylic acid or to a group derived from a carboxylic acid, such as, for example, acyl, acylalkyl, alkoxy carbonyl, acyloxy, acyloxyalkyl, carboxyalkylamide or alkoxy carbonyloxy.

Preferably, a heteroalkyl group contains from 1 to 12 carbon atoms and from 1 to 4 hetero atoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). Especially preferably, a heteroalkyl group contains from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms and 1, 2 or 3 (especially 1 or 2) hetero atoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). The term C₁-C₆ heteroalkyl refers to a heteroalkyl group containing from 1 to 6 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially O and/or N). The term C₁-C₄ heteroalkyl refers to a heteroalkyl group containing from 1 to 4 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially O and/or N). Furthermore, the term heteroalkyl refers to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl).

Examples of heteroalkyl groups are groups of formulae:
R^a-O-Y^a-, R^a-S-Y^a-, R^a-N(R^b)-Y^a-, R^a-CO-Y^a-, R^a-O-CO-Y^a-,

R^a -CO-O- Y^a -, R^a -CO-N(R^b)- Y^a -, R^a -N(R^b)-CO- Y^a -, R^a -O-CO-N(R^b)- Y^a -,
 R^a -N(R^b)-CO-O- Y^a -, R^a -N(R^b)-CO-N(R^c)- Y^a -, R^a -O-CO-O- Y^a -,
 R^a -N(R^b)-C(=NR^d)-N(R^c)- Y^a -, R^a -CS- Y^a -, R^a -O-CS- Y^a -, R^a -CS-O- Y^a -,
 R^a -CS-N(R^b)- Y^a -, R^a -N(R^b)-CS- Y^a -, R^a -O-CS-N(R^b)- Y^a -,
 R^a -N(R^b)-CS-O- Y^a -, R^a -N(R^b)-CS-N(R^c)- Y^a -, R^a -O-CS-O- Y^a -,
 R^a -S-CO- Y^a -, R^a -CO-S- Y^a -, R^a -S-CO-N(R^b)- Y^a -, R^a -N(R^b)-CO-S- Y^a -,
 R^a -S-CO-O- Y^a -, R^a -O-CO-S- Y^a -, R^a -S-CO-S- Y^a -, R^a -S-CS- Y^a -,
 R^a -CS-S- Y^a -, R^a -S-CS-N(R^b)- Y^a -, R^a -N(R^b)-CS-S- Y^a -, R^a -S-CS-O- Y^a -,
 R^a -O-CS-S- Y^a -, wherein R^a being a hydrogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl or a C₂-C₆ alkynyl group; R^b being a hydrogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl or a C₂-C₆ alkynyl group; R^c being a hydrogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl or a C₂-C₆ alkynyl group; R^d being a hydrogen atom, a C₁-C₆ alkyl, a C₂-C₆ alkenyl or a C₂-C₆ alkynyl group and Y^a being a direct bond, a C₁-C₆ alkylene, a C₂-C₆ alkenylene or a C₂-C₆ alkynylene group, wherein each heteroalkyl group contains at least one carbon atom and one or more hydrogen atoms may be replaced by fluorine or chlorine atoms.

Specific examples of heteroalkyl groups are methoxy, trifluoromethoxy, ethoxy, n-propyloxy, isopropyloxy, butoxy, tert-butyloxy, methoxymethyl, ethoxymethyl, -CH₂CH₂OH, -CH₂OH, methoxyethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino, isopropyl-ethylamino, methylamino methyl, ethylamino methyl, diisopropylamino ethyl, methylthio, ethylthio, isopropylthio, enol ether, dimethylamino methyl, dimethylamino ethyl, acetyl, propionyl, butyryloxy, acetyloxy, methoxycarbonyl, ethoxycarbonyl, propionyloxy, acetyl amino or propionyl amino, carboxymethyl, carboxyethyl or carboxypropyl, N-ethyl-N-methylcarbamoyl or N-methylcarbamoyl. Further examples of

heteroalkyl groups are nitrile, isonitrile, cyanate, thiocyanate, isocyanate, isothiocyanate and alkyl nitrile groups.

The expression cycloalkyl refers to a saturated or partially unsaturated (for example, a cycloalkenyl group) cyclic group that contains one or more rings (preferably 1 or 2), and contains from 3 to 14 ring carbon atoms, preferably from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms. The expression cycloalkyl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH₂, =NH, N₃ or NO₂ groups, thus, for example, cyclic ketones such as, for example, cyclohexanone, 2-cyclohexenone or cyclopentanone. Further specific examples of cycloalkyl groups are a cyclopropyl, cyclobutyl, cyclopentyl, spiro[4,5]decanyl, norbornyl, cyclohexyl, cyclopentenyl, cyclohexadienyl, decaliny, bicyclo[4.3.0]nonyl, tetraline, cyclopentylcyclohexyl, fluorocyclohexyl or cyclohex-2-enyl group.

The expression heterocycloalkyl refers to a cycloalkyl group as defined above in which one or more (preferably 1, 2, 3 or 4) ring carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom). A heterocycloalkyl group has preferably 1 or 2 ring(s) containing from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms (preferably selected from C, O, N and S). The expression heterocycloalkyl refers furthermore to groups that may be substituted by one or more fluorine, chlorine, bromine or iodine atoms or by one or more OH, =O, SH, =S, NH₂, =NH, N₃ or NO₂ groups. Examples are a piperidyl, prolinyl, imidazolidinyl, piperazinyl, morpholinyl,

urotropinyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrofuryl or 2-pyrazolinyl group and also lactames, lactones, cyclic imides and cyclic anhydrides.

The expression alkylcycloalkyl refers to groups that contain both cycloalkyl and also alkyl, alkenyl or alkynyl groups in accordance with the above definitions, for example alkylcycloalkyl, cycloalkylalkyl, alkylcycloalkenyl, alkenylcycloalkyl and alkynylcycloalkyl groups. An alkylcycloalkyl group preferably contains a cycloalkyl group that contains one or two rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms, and one or two alkyl, alkenyl or alkynyl groups (especially alkyl groups) having 1 or 2 to 6 carbon atoms.

The expression heteroalkylcycloalkyl refers to alkylcycloalkyl groups as defined above in which one or more (preferably 1, 2, 3, 4 or 5) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom). A heteroalkylcycloalkyl group preferably contains 1 or 2 rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms, and one or two alkyl, alkenyl, alkynyl or heteroalkyl groups (especially alkyl or heteroalkyl groups) having from 1 or 2 to 6 carbon atoms (the heteroalkyl groups having preferably 1, 2 or 3 heteroatoms selected from O, S and N). Examples of such groups are alkylheterocycloalkyl, alkylheterocycloalkenyl, alkenylheterocycloalkyl, alkynylheterocycloalkyl, heteroalkylcycloalkyl, heteroalkylheterocycloalkyl and heteroalkylheterocycloalkenyl, the cyclic groups being saturated or mono-, di- or tri-unsaturated.

The expression aryl refers to an aromatic group that contains one or more rings containing from 5 or 6 to 14 ring carbon atoms, preferably from 5 or 6 to 10 (especially 6) ring carbon atoms. The expression aryl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH₂, N₃ or NO₂ groups. Examples are the phenyl, naphthyl, biphenyl, 2-fluorophenyl, anilinyll, 3-nitrophenyl or 4-hydroxyphenyl group.

The expression heteroaryl refers to an aromatic group that contains one or more rings containing from 5 to 14 ring atoms, preferably from 5 to 10 (especially 5 or 6 or 9 or 10) ring atoms, and contains one or more (preferably 1, 2, 3, 4 or 5) oxygen, nitrogen, phosphorus or sulfur ring atoms (preferably O, S or N). The expression heteroaryl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, SH, N₃, NH₂ or NO₂ groups. Examples are pyridyl (e.g. 4-pyridyl), imidazolyl (e.g. 2-imidazolyl), phenylpyrrolyl (e.g. 3-phenylpyrrolyl), thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, isoxazolyl, indazolyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, pyridazinyl, quinolinyl, isoquinolinyl, pyrrolyl, purinyl, carbazolyl, acridinyl, pyrimidyl, 2,3'-bifuryl, pyrazolyl (e.g. 3-pyrazolyl) and isoquinolinyl groups.

The expression aralkyl refers to groups containing both aryl and also alkyl, alkenyl, alkynyl and/or cycloalkyl groups in

accordance with the above definitions, such as, for example, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, arylcycloalkenyl, alkylarylcycloalkyl and alkylarylcycloalkenyl groups. Specific examples of aralkyls are toluene, xylene, mesitylene, styrene, benzyl chloride, o-fluorotoluene, 1H-indene, tetraline, dihydronaphthalene, indanone, phenylcyclopentyl, cumene, cyclohexylphenyl, fluorene and indane. An aralkyl group preferably contains one or two aromatic ring systems (1 or 2 rings) containing from 6 to 10 carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing from 1 or 2 to 6 carbon atoms and/or one or two cycloalkyl groups containing 5 or 6 ring carbon atoms.

The expression heteroaralkyl refers to an aralkyl group as defined above in which one or more (preferably 1, 2, 3 or 4) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus, boron or sulfur atom (preferably oxygen, sulfur or nitrogen), that is to say to groups containing both aryl or heteroaryl, respectively, and also alkyl, alkenyl, alkynyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups in accordance with the above definitions. A heteroaralkyl group preferably contains one or two aromatic ring systems (1 or 2 rings) containing from 5 or 6 to 10 ring carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing 1 or 2 to 6 carbon atoms and/or one or two cycloalkyl groups containing 5 or 6 ring carbon atoms, wherein 1, 2, 3, 4, 5 or 6 of these carbon atoms have been replaced by oxygen, sulfur or nitrogen atoms.

Examples are arylheteroalkyl, arylheterocycloalkyl, arylheterocycloalkenyl, arylalkylheterocycloalkyl, arylalkenyl-

heterocycloalkyl, arylalkynylheterocycloalkyl, arylalkylheterocycloalkenyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroaryl-cycloalkyl, heteroarylcycloalkenyl, heteroarylhetero-cycloalkyl, heteroarylheterocycloalkenyl, heteroarylalkyl-cycloalkyl, heteroarylalkylheterocycloalkenyl, heteroaryl-heteroalkylcycloalkyl, heteroarylheteroalkylcycloalkenyl and heteroarylheteroalkylheterocycloalkyl groups, the cyclic groups being saturated or mono-, di- or tri-unsaturated. Specific examples are a tetrahydroisoquinoliny, benzoyl, 2- or 3-ethylindolyl, 4-methylpyridino, 2-, 3- or 4-methoxyphenyl, 4-ethoxyphenyl, 2-, 3- or 4-carboxy-phenylalkyl group.

The term halogen or halogen atom refers to F, Cl, Br or I.

The expression "optionally substituted" especially refers to groups in which one, two, three or more hydrogen atoms may have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH₂, =NH, N₃ or NO₂ groups. This expression refers furthermore to groups that may be substituted by one, two, three or more preferably unsubstituted C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ heteroalkyl, C₃-C₁₈ cycloalkyl, C₂-C₁₇ heterocycloalkyl, C₄-C₂₀ alkylcycloalkyl, C₂-C₁₉ heteroalkylcycloalkyl, C₆-C₁₈ aryl, C₁-C₁₇ heteroaryl, C₇-C₂₀ aralkyl or C₂-C₁₉ heteroaralkyl groups. This expression refers furthermore especially to groups that may be substituted by one, two, three or more preferably unsubstituted C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₁₀ cycloalkyl, C₂-C₉ heterocycloalkyl, C₇-C₁₂ alkylcycloalkyl, C₂-C₁₁ heteroalkylcycloalkyl, C₆-C₁₀ aryl, C₁-C₉ heteroaryl, C₇-C₁₂ aralkyl or C₂-C₁₁ heteroaralkyl groups.

If a substituent contains a ring, this ring may be bonded to the respective substituted group via a single or double bond (especially a single bond) or, if the substituted group also contains a ring, the ring of the substituent may also be annulated to the ring of the substituted group.

Preferred substituents are F, Cl, Br, I, OH, =O, NH₂, NO₂, C₁₋₄ alkyl (e.g. methyl, ethyl, t-butyl), NMe₂, NHMe, CONH₂, CH₂NMe₂, NHSO₂Me, C(CH₃)₂CN, COMe, OMe, SMe, COOMe, COOEt, CH₂COOH, OCH₂COOH, COOH, SOMe, SO₂Me, cyclopropyl, SO₂NH₂, SO₂NHMe, SO₂CH₂CH₂OH, SF₅, SO₂NMe₂, CHO, OCF₃, SO₂CF₃, COMe, CH₂OH, CN or CF₃.

Especially preferred substituents are F, Cl, Br, OH, NH₂, Me, Ethyl, NMe₂, CONH₂, OMe, CN or CF₃.

According to a preferred embodiment, all alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aralkyl and heteroaralkyl groups described herein may optionally be substituted.

When an aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroaralkyl group contains more than one ring, these rings may be bonded to each other via a single or double bond or these rings may be annulated.

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I), (II), (III) or (IV) as defined herein or a pharmaceutically

acceptable ester, prodrug, hydrate, solvate or salt thereof, optionally in combination with a pharmaceutically acceptable carrier.

It is a further object of the present invention to provide a compound of formula (I), (II), (III) or (IV) as defined herein or a pharmaceutical composition as defined herein for the preparation of a medicament for the treatment of one or more diseases mentioned herein.

Preferably the compounds of the present invention may be used for the treatment and/or prevention of cancer, viral diseases and infectious diseases.

Further preferably, the compounds of the present invention may be used for the treatment and/or prevention of neurodegenerative diseases such as: Schizophrenia, Alzheimer, Multiples Sclerosis, Parkinson, Corea Huntington, Spinocerebellar ataxia type 1 (SCA1), Amyotrophic lateral sclerosis, Batten disease.

A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage may be adjusted to the individual requirements in each

particular case including the specific compound being administered, the route of administration, the condition being treated, as well as the patient being treated.

Examples of pharmacologically acceptable salts of sufficiently basic compounds of formula (I), (II), (III) or (IV) are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound of formula (I), (II), (III) or (IV) may form alkali or earth alkali metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts; all of which are also further examples of salts of formula (I), (II), (III) or (IV). Compounds of formula (I), (II), (III) or (IV) may be solvated, especially hydrated. The hydratization/hydration may occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds of formula (I), (II), (III) or (IV). The solvates and/or hydrates may e.g. be present in solid or liquid form.

It should be appreciated that certain compounds of formula (I), (II), (III) or (IV) may have tautomeric forms from which only one might be specifically mentioned or depicted in the following description, different geometrical isomers (which are usually denoted as cis/trans isomers or more generally as (E) and (Z) isomers) or different optical isomers as a result

of one or more chiral carbon atoms (which are usually nomenclatured under the Cahn-Ingold-Prelog or R/S system). All these tautomeric forms, geometrical or optical isomers (as well as racemates and diastereomers) and polymorphous forms are included in the invention. Since the compounds of formula (I), (II), (III) or (IV) may contain asymmetric C-atoms, they may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds. The present invention comprises both all pure enantiomers and all pure diastereomers, and also the mixtures thereof in any mixing ratio.

The therapeutic use of compounds according to formula (I), (II), (III) or (IV), their pharmacologically acceptable salts, solvates and hydrates, respectively, as well as formulations and pharmaceutical compositions also lie within the scope of the present invention.

The pharmaceutical compositions according to the present invention comprise at least one compound of formula (I), (II), (III) or (IV) as an active ingredient and, optionally, carrier substances and/or adjuvants.

The present invention also relates to pro-drugs which are composed of a compound of formula (I), (II), (III) or (IV) and at least one pharmacologically acceptable protective group which will be cleaved off under physiological conditions, such as an alkoxy-, arylalkoxy-, acyl-, acyloxymethyl group (e.g. pivaloyloxymethyl), an 2-alkyl-, 2-aryl- or 2-arylalkyloxycarbonyl-2-alkylidene ethyl group or an acyloxy group as defined herein, e.g. ethoxy, benzyloxy, acetyl or acetyloxy or, especially for a compound of formula (I), (II), (III) or

(IV), carrying a hydroxy group (-OH): a sulfate, a phosphate (-OPO₃ or -OCH₂OPO₃) or an ester of an amino acid.

Preferably, the present invention also relates to a prodrug, a biohydrolyzable ester, a biohydrolyzable amide, a polymorph, tautomer, stereoisomer, metabolite, N-oxide, biohydrolyzable carbamate, biohydrolyzable ether, physiologically functional derivative, atropisomer, or in vivo-hydrolysable precursor, diastereomer or mixture of diastereomers, chemically protected form, affinity reagent, complex, chelate and a stereoisomer of the compounds of formula (I), (II), (III) or (IV).

As used herein, the term pharmaceutically acceptable ester especially refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

As mentioned above, therapeutically useful agents that contain compounds of formula (I), (II), (III) or (IV), their solvates, salts or formulations are also comprised in the scope of the present invention. In general, compounds of formula (I), (II), (III) or (IV) will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent.

For oral administration such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containing the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatine, malt, silica gel, starch or derivatives thereof, talc, stearinic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use as excipients e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, lipids, phospholipids, cyclodextrins, vegetable, petroleum, animal or synthetic oils. Especially preferred are lipids and more preferred are phospholipids (preferred of natural origin; especially preferred with a particle size between 300 to 350 nm) preferred in phosphate buffered saline (pH = 7 to 8, preferred 7.4). For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases

suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilization, e.g. UV stabilizers, emulsifiers, sweetener, aromatizers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

In general, in the case of oral or parenteral administration to adult humans weighing approximately 80 kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 20 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion or subcutaneous injection.

The present invention moreover provides a method of inhibiting growth, proliferation, or metastasis of cancer cells in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound of formula (I), (II), (III) or (IV), or a pharmaceutically acceptable salt. In one embodiment the cancer is selected from melanoma, renal cell carcinoma, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, colorectal cancer, castration-resistant prostate cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, gastrointestinal tract and breast, cancer of the genital organs, penis and vagina, and a hematological malignancy.

Further the present invention provides a method of treating an infectious disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I), (II), (III) or (IV), or a pharmaceutically acceptable salt thereof. In one embodiment the infectious disease is caused by a virus. In a further embodiment the virus is selected from HIV, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, herpes viruses, papillomaviruses and influenza.

In one embodiment, a method is provided for treating cancer comprising administering to a patient in need thereof, a therapeutically effective amount of a compound of formula (I), (II), (III) or (IV) or a salt thereof. Examples of cancers include those whose growth may be inhibited using compounds of the disclosure include cancers typically responsive to immunotherapy. Non-limiting examples of preferred cancers for treatment include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, colon cancer and lung cancer (e.g. non-small cell lung cancer). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the present invention.

Examples of other cancers that may be treated using the methods of the present invention include bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium,

carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The present invention is also useful for treatment of metastatic cancers, especially metastatic cancers that express PD-L1.

Some examples of pathogenic viruses causing infections treatable by methods of the present invention include HIV, hepatitis (A, B, C, or D), herpes viruses (e.g., VZV, HSV-1, HAV-6, HHV-7, HHV-8, HSV-2, CMV, and Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, coronavirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rabella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Some examples of pathogenic bacteria causing infections treatable by methods of the present invention include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumococci, meningococci and gonococci, leishmania, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme disease bacteria.

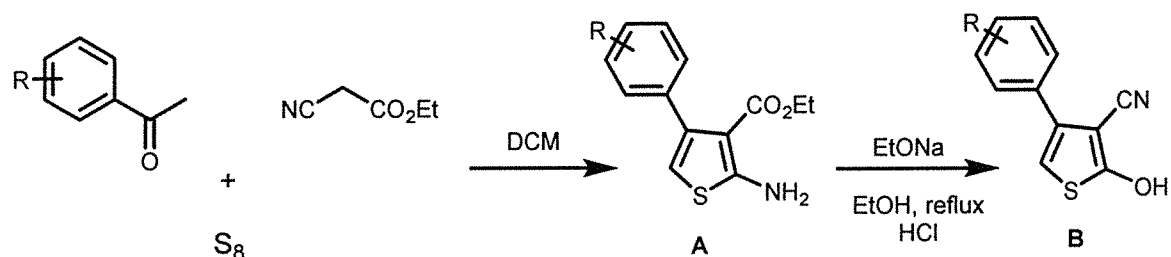
Some examples of pathogenic fungi causing infections treatable by methods of the present invention include Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizopus), Sporothrix schenckii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Some examples of pathogenic parasites causing infections treatable by methods of the present invention include Entamoeba histolytica, Balantidium coli, Naegleria fowleri, Acanthamoeba sp., Giardia lamblia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nippostrongylus brasiliensis.

Examples

I. Intermediates A and B:

(In the following Scheme, R represents R¹ and R²)

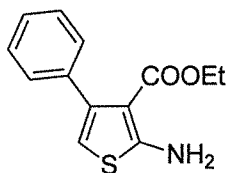


General procedure for the preparation of substituted 2-amino-4-phenylthiophene-3-carbonitrile (Building block A):

To a stirred solution of dry dichloromethane (DCM) (200 mL), the corresponding acetophenone (50.2 mmol), and ethyl cyanoacetate (6.42 mL, 60.3 mmol) were added. The reaction mixture was cooled to 0°C and neat TiCl₄ (11.02 mL, 100.5 mmol) was added dropwise. After completion of the addition at 0°C, the reaction mixture was stirred for 0.5 h. Then dry pyridine (3.4 mL) was added dropwise and stirred at room temperature (rt) for 1 h. Additional dry pyridine (10 mL) was added dropwise and the mixture was allowed to stir overnight. The mixture was poured into 3 M HCl (200 mL) and the organic layer was separated. The aqueous layer was further extracted with DCM (2 x 50 mL), and the combined organic phases were washed with water and brine, dried with MgSO₄, filtered and concentrated yielding a viscous amber oil. The oil is dissolved in THF (40 mL) and elemental sulfur (2.0 g, 62.38 mmol) was added followed by Et₂NH (10 mL) dropwise, and the solution was stirred at room temperature for 2 h. The mixture was diluted with ether (200 mL) and washed with water (2 x 100 mL) and finally with brine. The organic layer was separated, dried (MgSO₄), filtered, and evaporated in vacuo.

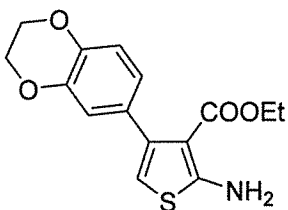
The following specific intermediates A have been prepared according to the above procedure:

Example 1: ethyl 2-amino-4-phenylthiophene-3-carboxylate



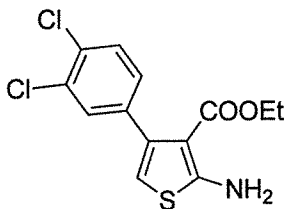
^1H NMR (500 MHz, CDCl_3): δ 4.91 (br s, 2H), 6.35 (s, 1H), 7.36-7.37 (m, 1H), 7.40-7.43 (m, 2H), 7.57-7.59 (m, 2H) ppm. MS (ESI) m/z: *calc.* for $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{S}$, $[\text{M}+\text{H}]^+$: 248.31; *found*: 248.32.

Example 2: ethyl 2-amino-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carboxylate



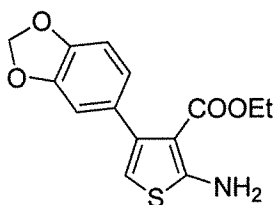
^1H NMR (500 MHz, CDCl_3): δ 1.04 (t, J = 10 Hz, 3H), 4.09 (q, J = 10 Hz, 2H), 6.02 (s, 1H), 6.06 br s, 2H), 6.77-6.83 (m, 3H) ppm. MS (ESI) m/z: *calc.* for $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$, $[\text{M}+\text{H}]^+$: 248.31; *found*: 248.37.

Example 3: ethyl 2-amino-4-(3,4-dichlorophenyl)thiophene-3-carboxylate



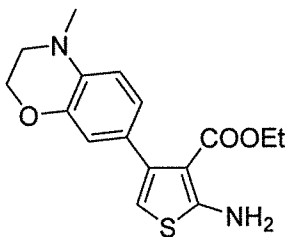
^1H NMR (500 MHz, CDCl_3): δ 1.02 (t, J = 10 Hz, 3H), 4.08 (q, J = 10 Hz, 2H), 6.07 (s, 1H), 6.15 (br s, 2H), 7.14 (dd, J = 5, 0.5 Hz, 1H), 7.38 (d, J = 10 Hz, 1H), 7.40 (d, J = 5 Hz, 1H) ppm. MS (ESI) m/z : *calc.* for $\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{NO}_2\text{S}$, $[\text{M}+\text{H}]^+$: 317.20; *found*: 317.28.

Example 4: ethyl 2-amino-4-(benzo[d][1,3]dioxol-5-yl)thiophene-3-carboxylate



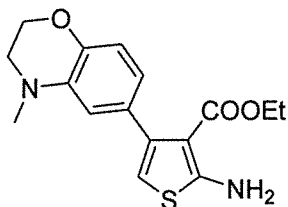
^1H NMR (500 MHz, CDCl_3): δ 1.04 (t, J = 10 Hz, 3H), 4.08 (q, J = 10 Hz, 2H), 5.96 (s, 2H), 6.02 (s, 1H), 6.08 (br s, 2H), 6.77 (s, 2H), 6.79 (s, 1H) ppm. MS (ESI) m/z : *calc.* for $\text{C}_{14}\text{H}_{13}\text{NO}_4\text{S}$, $[\text{M}+\text{H}]^+$: 292.32; *found*: 292.39.

Example 5a: ethyl 2-amino-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)thiophene-3-carboxylate



MS (ESI) m/z : *calc.* for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$, $[\text{M}+\text{H}]^+$: 319.10; *found*: 319.48.

Example 5b: ethyl 2-amino-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carboxylate



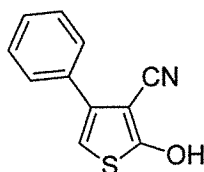
MS (ESI) m/z : *calc.* for $C_{16}H_{18}N_2O_3S$, $[M+H]^+$: 319.10; *found*: 319.21.

General procedure for the preparation of substituted 2-hydroxy-4-phenylthiophene-3-carbonitrile (Building block B):

To a boiling mixture of the corresponding building block A (40 mmol) in absolute ethanol (40 ml), a solution of Na (1.8 g) in EtOH (40 ml) was added dropwise. Then, the reaction mixture was refluxed for 4 h. Afterwards, 50 to 90 ml of the solvent were evaporated, the mixture was cooled, water (150 ml) was added and stirred for 1 h at rt. The residue was filtered off and the extract was acidified with HCl (37%). The solid was filtered and dried, providing the desired building blocks B.

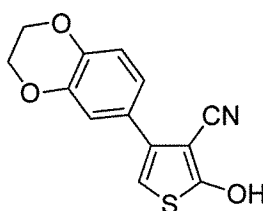
The following specific intermediates B have been prepared according to the above procedure:

Example 6: 2-hydroxy-4-phenylthiophene-3-carbonitrile



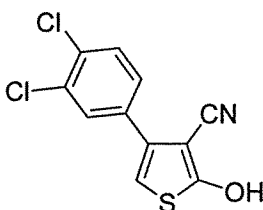
^1H NMR (500 MHz, $CDCl_3$): (*equilibrium with the keto form*) δ 4.59 (br s, 2H), 7.56-7.59 (m, 2H), 7.62-7.63 (m, 1H), 7.89-7.91 (m, 2H) ppm. MS (ESI) m/z : *calc.* for $C_{11}H_7NOS$, $[M+H]^+$: 202.24; *found*: 202.35.

Example 7: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-hydroxythiophene-3-carbonitrile



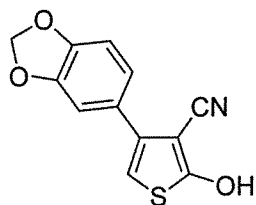
^1H NMR (500 MHz, CDCl_3): (equilibrium with the keto form) δ 4.32 (t, J = 0.5 Hz, 2H), 4.36 (t, J = 0.5 Hz, 2H), 4.51 (s, 2H), 7.01 (d, J = 10 Hz, 1H), 7.47 (s, 1H), 7.55 (d, J = 10 Hz, 1H) ppm. MS (ESI) m/z : calc. for $\text{C}_{13}\text{H}_9\text{NO}_3\text{S}$, $[\text{M}+\text{H}]^+$: 260.28; found: 260.32.

Example 8: 4-(3,4-dichlorophenyl)-2-hydroxythiophene-3-carbonitrile

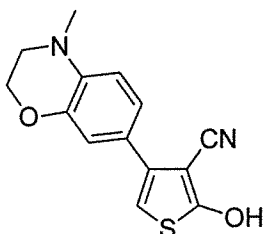


^1H NMR (500 MHz, CDCl_3): (equilibrium with the keto form) δ 4.54 (s, 2H), 7.66 (d, J = 10 Hz, 1H), 7.80 (dd, J = 10, 0.5 Hz, 1H), 7.92 (d, J = 0.5 Hz, 1H) ppm. MS (ESI) m/z : calc. for $\text{C}_{11}\text{H}_5\text{Cl}_2\text{NOS}$, $[\text{M}+\text{H}]^+$: 271.13; found: 271.19.

Example 9: 4-(benzo[d][1,3]dioxol-5-yl)-2-hydroxythiophene-3-carbonitrile

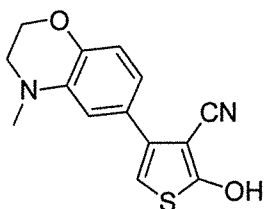


Example 10: 2-hydroxy-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)thiophene-3-carbonitrile



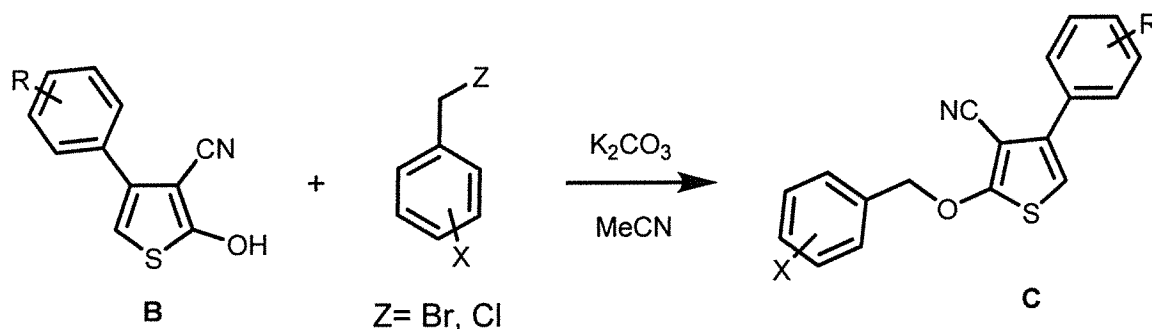
MS (ESI) m/z : *calc.* for $C_{14}H_{12}N_2O_2S$, $[M+H]^+$: 273.06; *found*: 273.12.

Example 11: 2-hydroxy-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{14}H_{12}N_2O_2S$, $[M+H]^+$: 273.06; *found*: 273.12.

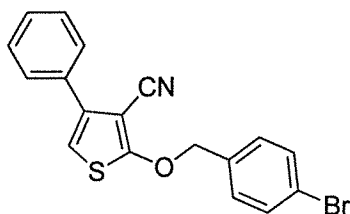
II. General procedure for the O-alkylation of building block C: (In the following scheme, R represents R^1 and R^2 and X represents one or more groups R^3 or $-CH_2-N(R^4)-R^5$)



In a microwave vial (4 ml), the corresponding building block B (0.5 mmol) was mixed with K_2CO_3 (2.0 mmol) and the corresponding benzyl bromide (1.1 mmol) in MeCN (1 ml). The reaction mixture was irradiated at 130 °C for 20 min and purified by column chromatography.

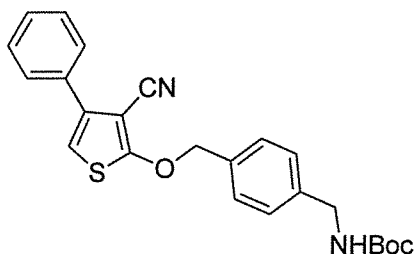
The following compounds have been prepared according to the above procedure:

Example 12: 2-((4-bromobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



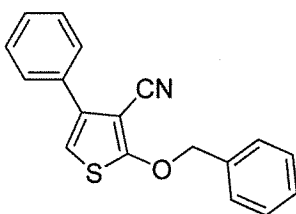
^1H NMR (500 MHz, CDCl_3): δ 5.29 (s, 2H), 6.59 (s, 1H), 7.34-7.43 (m, 5H), 7.44-7.58 (m, 4H) ppm. MS (ESI) m/z : calc. for $\text{C}_{18}\text{H}_{12}\text{BrNOS}$, $[\text{M}+\text{H}]^+$: 371.26; found: 371.32.

Example 13: tert-butyl 4-(((3-cyano-4-phenylthiophen-2-yl)oxy)methyl)benzylcarbamate



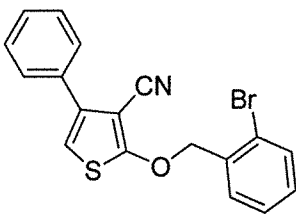
MS (ESI) *m/z*: *calc.* for C₂₄H₂₄N₂O₃S, [M+H]⁺: 421.15; *found*: 421.17

Example 14: 2-(benzyloxy)-4-phenylthiophene-3-carbonitrile



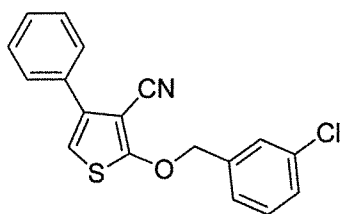
MS (ESI) *m/z*: *calc.* for C₁₈H₁₃NOS, [M+H]⁺: 292.07; *found*: 292.08

Example 15: 2-((2-bromobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



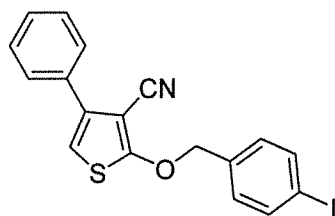
MS (ESI) *m/z*: *calc.* for C₁₈H₁₂BrNOS, [M+H]⁺: 369.98; *found*: 369.99

Example 16: 2-((3-chlorobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



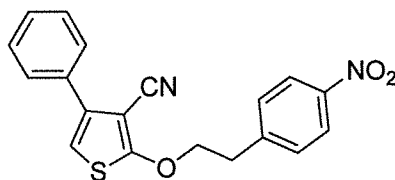
MS (ESI) m/z : *calc.* for $C_{18}H_{12}ClNOS$, $[M+H]^+$: 326.03; *found*: 327.10

Example 17: 2-((4-iodobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}INOS$, $[M+H]^+$: 417.97; *found*: 417.99

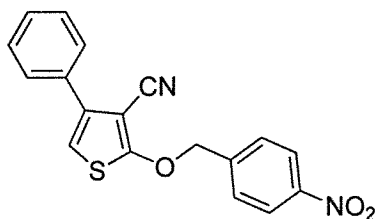
Example 18: 2-(4-nitrophenethoxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{14}N_2O_3S$, $[M+H]^+$: 351.07; *found*: 351.17

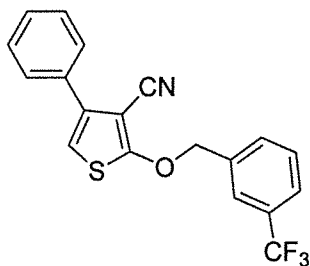
Example 19: 2-((4-nitrobenzyl)oxy)-4-phenylthiophene-3-carbonitrile

35



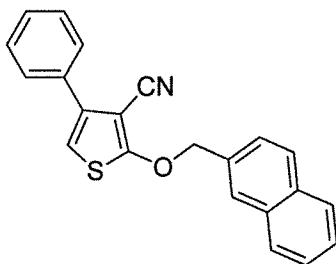
MS (ESI) m/z : *calc.* for $C_{18}H_{12}N_2O_3S$, $[M+H]^+$: 337.06; *found*: 337.08

Example 20: 4-phenyl-2-((3-(trifluoromethyl)benzyl)oxy)-thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{12}F_3NOS$, $[M+H]^+$: 360.06; *found*: 360.12

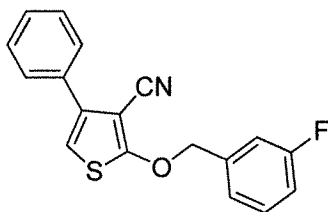
Example 21: 2-(naphthalen-2-ylmethoxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{22}H_{15}NOS$, $[M+H]^+$: 342.09; *found*: 342.13

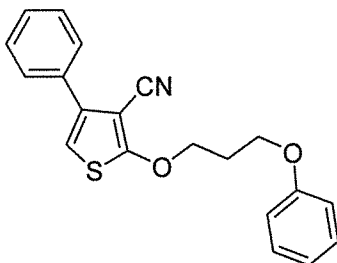
Example 22: 2-((3-fluorobenzyl)oxy)-4-phenylthiophene-3-carbonitrile

36



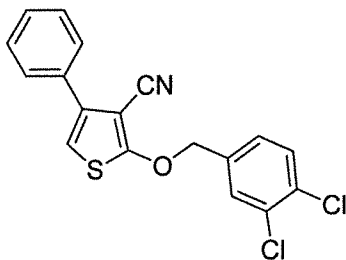
MS (ESI) m/z : *calc.* for $C_{18}H_{12}FNOS$, $[M+H]^+$: 310.06; *found*: 310.16

Example 23: 2-(3-phenoxypropoxy)-4-phenylthiophene-3-carbonitrile



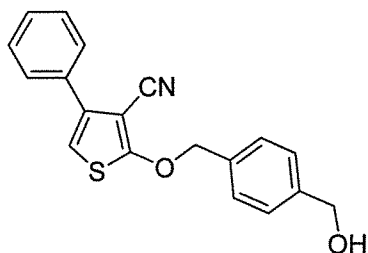
MS (ESI) m/z : *calc.* for $C_{20}H_{17}NO_2S$, $[M+H]^+$: 336.10; *found*: 336.20

Example 24: 2-((3,4-dichlorobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



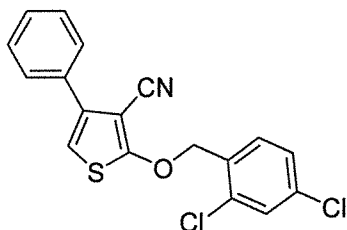
MS (ESI) m/z : *calc.* for $C_{18}H_{11}Cl_2NOS$, $[M+H]^+$: 359.99; *found*: 360.05

Example 25: 2-((4-(hydroxymethyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile



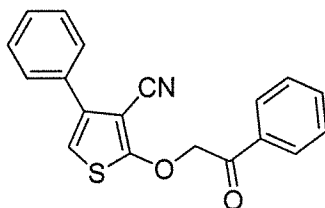
MS (ESI) m/z: *calc.* for $C_{19}H_{15}NO_2S$, $[M+H]^+$: 322.08; *found*: 322.12

Example 26: 2-((2,4-dichlorobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



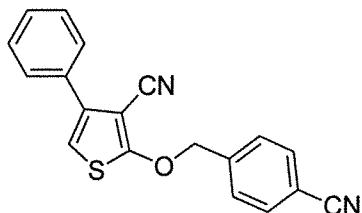
MS (ESI) m/z: *calc.* for $C_{18}H_{11}Cl_2NOS$, $[M+H]^+$: 359.99; *found*: 360.04

Example 27: 2-(2-oxo-2-phenylethoxy)-4-phenylthiophene-3-carbonitrile



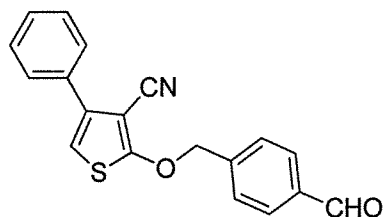
MS (ESI) m/z: *calc.* for $C_{19}H_{13}NO_2S$, $[M+H]^+$: 320.07; *found*: 320.27

Example 28: 2-((4-cyanobenzyl)oxy)-4-phenylthiophene-3-carbonitrile



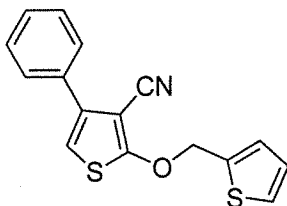
MS (ESI) m/z : *calc.* for $C_{19}H_{12}N_2OS$, $[M+H]^+$: 317.07; *found*: 317.09

Example 29: 2-((4-formylbenzyl)oxy)-4-phenylthiophene-3-carbonitrile



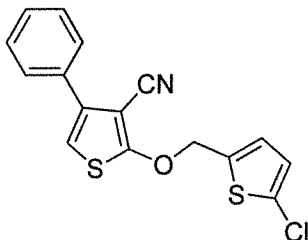
MS (ESI) m/z : *calc.* for $C_{19}H_{13}NO_2S$, $[M+H]^+$: 320.07; *found*: 320.12

Example 30: 4-phenyl-2-(thiophen-2-ylmethoxy)thiophene-3-carbonitrile



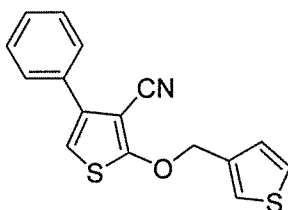
MS (ESI) m/z : *calc.* for $C_{16}H_{11}NOS_2$, $[M+H]^+$: 298.03; *found*: 298.08

Example 31: 2-((5-chlorothiophen-2-yl)methoxy)-4-phenylthiophene-3-carbonitrile



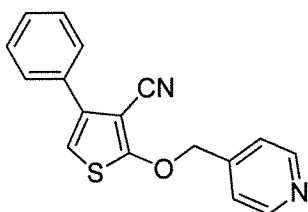
MS (ESI) m/z: *calc.* for $C_{16}H_{10}ClNOS_2$, $[M+H]^+$: 331.99; *found*: 332.02

Example 32: 4-phenyl-2-(thiophen-3-ylmethoxy)thiophene-3-carbonitrile



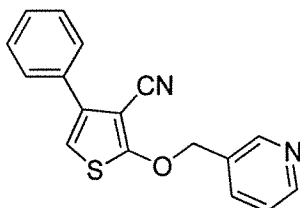
MS (ESI) m/z: *calc.* for $C_{16}H_{11}NOS_2$, $[M+H]^+$: 298.03; *found*: 298.09

Example 33: 4-phenyl-2-(pyridin-4-ylmethoxy)thiophene-3-carbonitrile



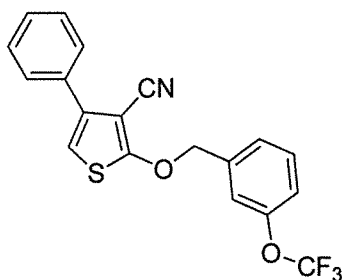
MS (ESI) m/z: *calc.* for $C_{17}H_{12}N_2OS$, $[M+H]^+$: 293.07; *found*: 293.14

Example 34: 4-phenyl-2-(pyridin-3-ylmethoxy)thiophene-3-carbonitrile



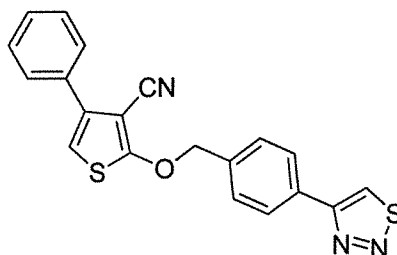
MS (ESI) m/z: *calc.* for $C_{17}H_{12}N_2OS$, $[M+H]^+$: 293.07; *found*: 293.12

Example 35: 4-phenyl-2-((3-(trifluoromethoxy)benzyl)oxy)-thiophene-3-carbonitrile



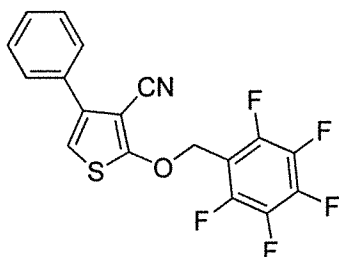
MS (ESI) m/z: *calc.* for $C_{19}H_{12}F_3NO_2S$, $[M+H]^+$: 376.05; *found*: 376.09

Example 36: 2-((4-(1,2,3-thiadiazol-4-yl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile



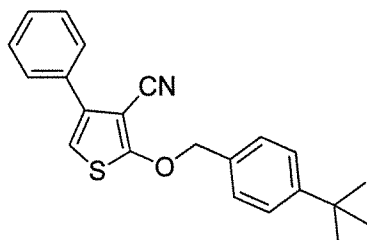
MS (ESI) m/z: *calc.* for $C_{20}H_{13}N_3OS_2$, $[M+H]^+$: 376.05; *found*: 376.12

Example 37: 2-((perfluorophenyl)methoxy)-4-phenylthiophene-3-carbonitrile



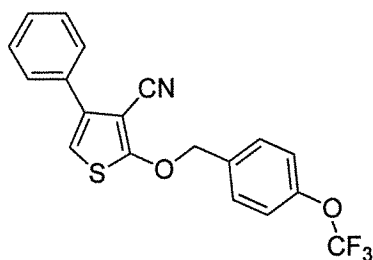
MS (ESI) m/z: *calc.* for $C_{18}H_8F_5NOS$, $[M+H]^+$: 382.02; *found*: 382.08

Example 38: 2-((4-(tert-butyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile



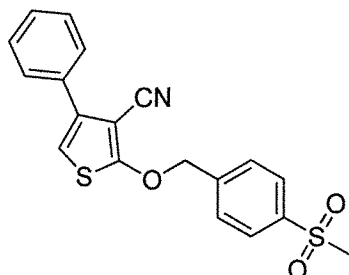
MS (ESI) m/z: *calc.* for $C_{22}H_{21}NOS$, $[M+H]^+$: 348.13; *found*: 348.16

Example 39: 4-phenyl-2-((4-(trifluoromethoxy)benzyl)oxy)-thiophene-3-carbonitrile



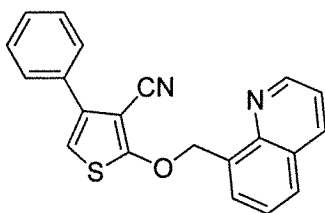
MS (ESI) m/z: *calc.* for $C_{19}H_{12}F_3NO_2S$, $[M+H]^+$: 376.05; *found*: 376.07

Example 40: 2-((4-(methylsulfonyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile



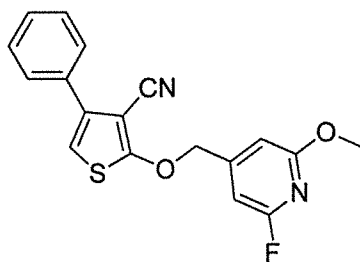
MS (ESI) m/z : *calc.* for $C_{19}H_{15}NO_3S_2$, $[M+H]^+$: 370.05; *found*: 370.12

Example 41: 4-phenyl-2-(quinolin-8-ylmethoxy)thiophene-3-carbonitrile



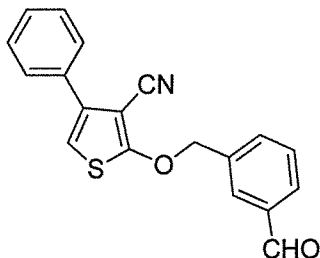
MS (ESI) m/z : *calc.* for $C_{21}H_{14}N_2OS$, $[M+H]^+$: 343.08; *found*: 343.09

Example 42: 2-((2-fluoropyridin-4-yl)methoxy)-4-phenylthiophene-3-carbonitrile



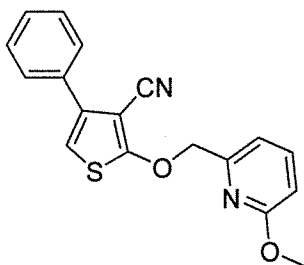
MS (ESI) m/z : *calc.* for $C_{18}H_{13}FN_2O_2S$, $[M+H]^+$: 341.07; *found*: 341.12

Example 43: 2-((3-formylbenzyl)oxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{13}NO_2S$, $[M+H]^+$: 320.07; *found*: 320.11

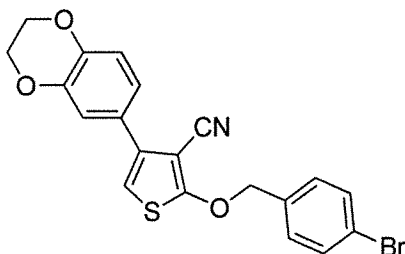
Example 44: 2-((6-methoxypyridin-2-yl)methoxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{14}N_2O_2S$, $[M+H]^+$: 323.08; *found*: 323.09

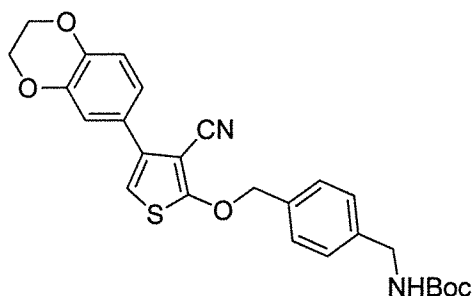
Example 45: 2-((4-bromobenzyl)oxy)-4-(2,3-dihydrobenzo-[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile

44



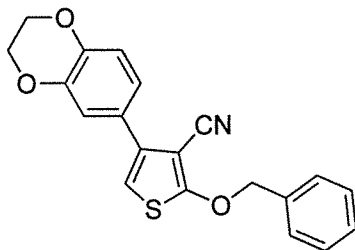
^1H NMR (500 MHz, CDCl_3): δ 4.26 (s, 4H), 5.20 (s, 2H), 6.47 (s, 1H), 6.90 (d, $J = 10$ Hz, 1H), 7.05-7.08 (m, 2H), 7.33 (d, $J = 5$ Hz, 2H), 7.54 (d, $J = 5$ Hz, 2H) ppm. MS (ESI) m/z : *calc.* for $\text{C}_{20}\text{H}_{14}\text{BrNO}_3\text{S}$, $[\text{M}+\text{H}]^+$: 429.30; *found*: 429.36

Example 46: tert-butyl 4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzylcarbamate



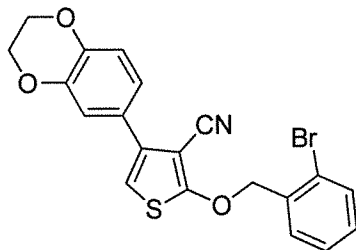
MS (ESI) m/z : *calc.* for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$, $[\text{M}+\text{H}]^+$: 479.16; *found*: 479.17

Example 47: 2-(benzyloxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



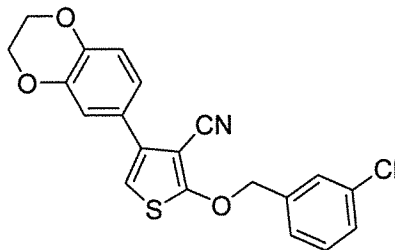
MS (ESI) m/z: *calc.* for $C_{20}H_{15}NO_3S$, $[M+H]^+$: 350.08; *found*: 350.12

Example 48: 2-((2-bromobenzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{20}H_{14}BrNO_3S$, $[M+H]^+$: 427.99; *found*: 428.01

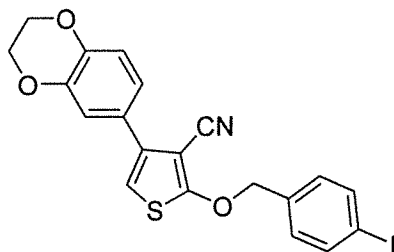
Example 49: 2-((3-chlorobenzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{20}H_{14}ClNO_3S$, $[M+H]^+$: 384.04; *found*: 384.12

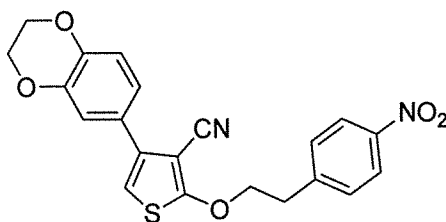
Example 50: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-iodobenzyl)oxy)thiophene-3-carbonitrile

46



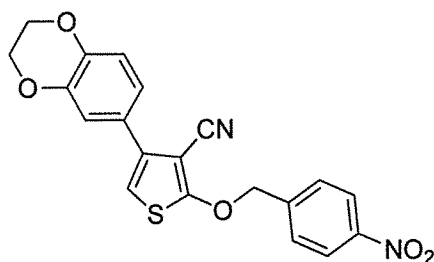
MS (ESI) m/z : *calc.* for $C_{20}H_{14}INO_3S$, $[M+H]^+$: 475.97; *found*: 475.99

Example 51: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(4-nitrophenethoxy)thiophene-3-carbonitrile



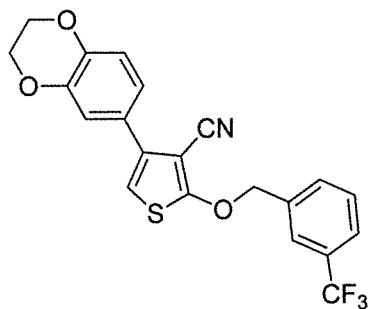
MS (ESI) m/z : *calc.* for $C_{21}H_{16}N_2O_5S$, $[M+H]^+$: 409.08; *found*: 409.11

Example 52: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-nitrobenzyl)oxy)thiophene-3-carbonitrile



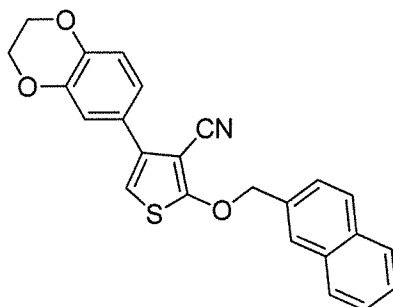
MS (ESI) m/z : *calc.* for $C_{20}H_{14}N_2O_5S$, $[M+H]^+$: 395.06; *found*: 395.13

Example 53: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((3-(trifluoromethyl)benzyl)oxy)thiophene-3-carbonitrile



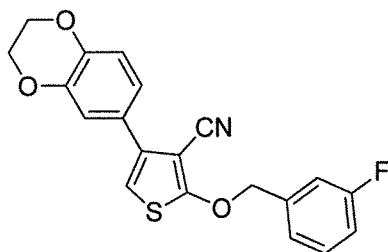
MS (ESI) m/z: *calc.* for $C_{21}H_{14}F_3NO_3S$, $[M+H]^+$: 418.06; *found*: 418.16

Example 54: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(naphthalen-2-ylmethoxy)thiophene-3-carbonitrile



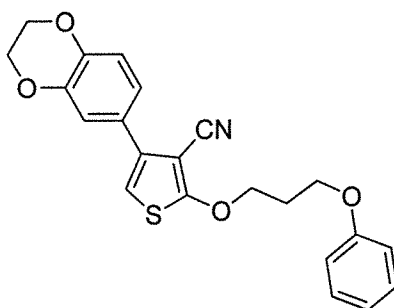
MS (ESI) m/z: *calc.* for $C_{24}H_{17}NO_3S$, $[M+H]^+$: 400.09; *found*: 400.11

Example 55: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((3-fluorobenzyl)oxy)thiophene-3-carbonitrile



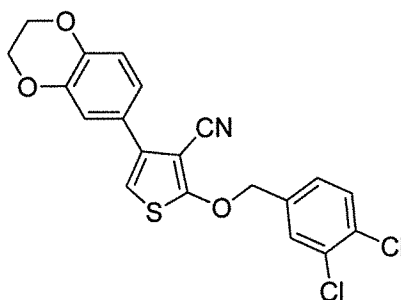
MS (ESI) m/z: *calc.* for C₂₀H₁₄FNO₃S, [M+H]⁺: 368.07; *found*: 368.13

Example 56: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(3-phenoxypropoxy)thiophene-3-carbonitrile



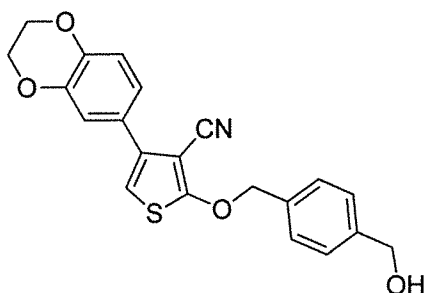
MS (ESI) m/z: *calc.* for C₂₂H₁₉NO₄S, [M+H]⁺: 394.10; *found*: 394.17

Example 57: 2-((3,4-dichlorobenzyl)oxy)-4-(2,3-dihydrobenzo-
[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



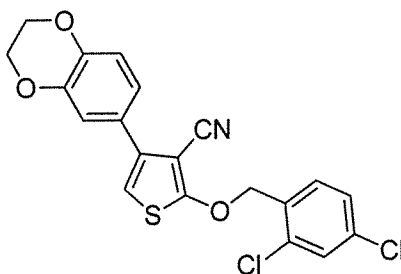
MS (ESI) m/z : *calc.* for $C_{20}H_{13}Cl_2NO_3S$, $[M+H]^+$: 418.00; *found*: 418.02

Example 58: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(hydroxymethyl)benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{21}H_{17}NO_4S$, $[M+H]^+$: 380.09; *found*: 380.11

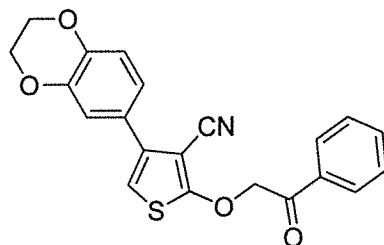
Example 59: 2-((2,4-dichlorobenzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{20}H_{13}Cl_2NO_3S$, $[M+H]^+$: 418.00; *found*: 418.02

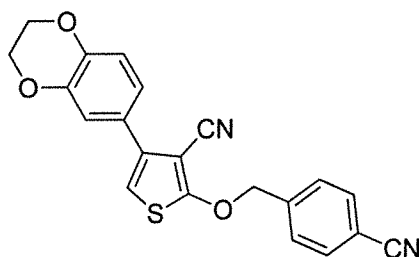
Example 60: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(2-oxo-2-phenylethoxy)thiophene-3-carbonitrile

50



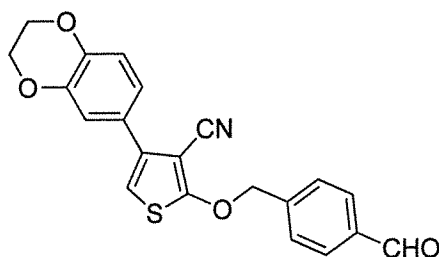
MS (ESI) m/z : *calc.* for $C_{21}H_{15}NO_4S$, $[M+H]^+$: 378.07; *found*: 378.11

Example 61: 2-((4-cyanobenzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



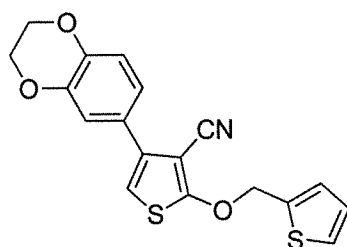
MS (ESI) m/z : *calc.* for $C_{21}H_{14}N_2O_3S$, $[M+H]^+$: 375.07; *found*: 375.08

Example 62: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-formylbenzyl)oxy)thiophene-3-carbonitrile



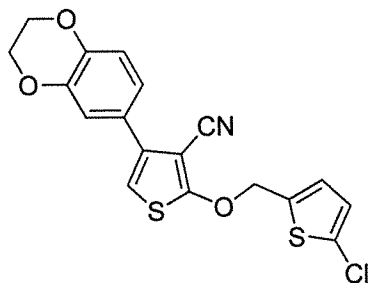
MS (ESI) m/z : *calc.* for $C_{21}H_{15}NO_4S$, $[M+H]^+$: 378.07; *found*: 378.10

Example 63: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(thiophen-2-ylmethoxy)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{13}NO_3S_2$, $[M+H]^+$: 356.03; *found*: 356.12

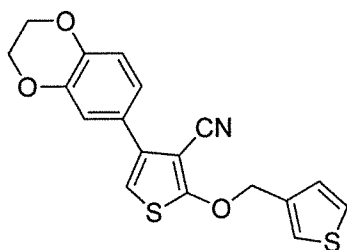
Example 64: 2-((5-chlorothiophen-2-yl)methoxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{12}ClNO_3S_2$, $[M+H]^+$: 389.99; *found*: 390.05

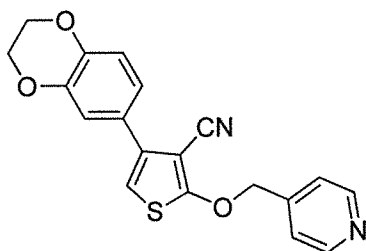
Example 65: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(thiophen-3-ylmethoxy)thiophene-3-carbonitrile

52



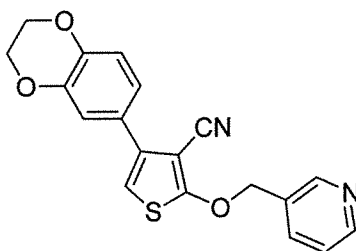
MS (ESI) m/z : *calc.* for $C_{18}H_{13}NO_3S_2$, $[M+H]^+$: 356.03; *found*: 356.08

Example 66: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(pyridin-4-ylmethoxy)thiophene-3-carbonitrile



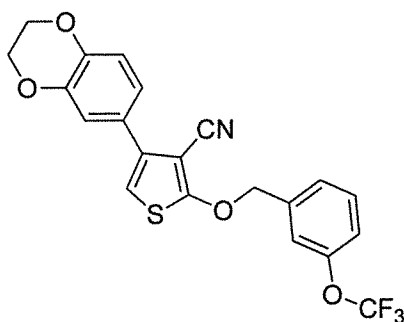
MS (ESI) m/z : *calc.* for $C_{19}H_{14}N_2O_3S$, $[M+H]^+$: 351.07; *found*: 351.11

Example 67: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(pyridin-3-ylmethoxy)thiophene-3-carbonitrile



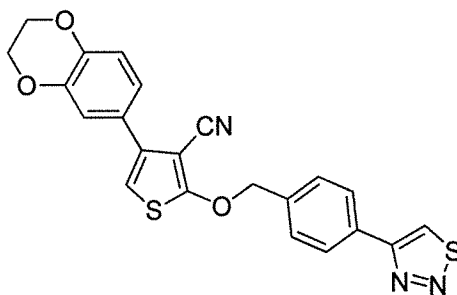
MS (ESI) m/z : *calc.* for $C_{19}H_{14}N_2O_3S$, $[M+H]^+$: 351.07; *found*: 351.10

Example 68: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((3-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile



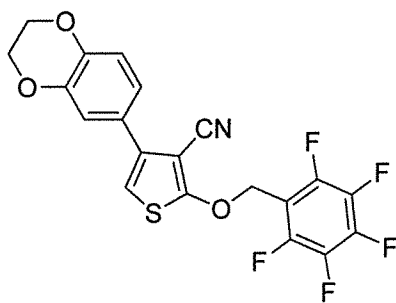
MS (ESI) m/z: *calc.* for $C_{21}H_{14}F_3NO_4S$, $[M+H]^+$: 434.06; *found*: 434.12

Example 69: 2-((4-(1,2,3-thiadiazol-4-yl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



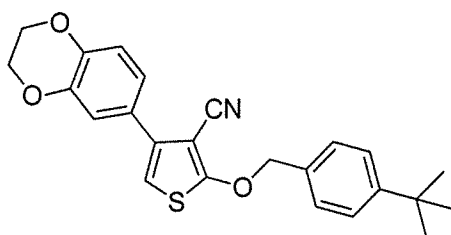
MS (ESI) m/z: *calc.* for $C_{22}H_{15}N_3O_3S_2$, $[M+H]^+$: 434.06; *found*: 434.08

Example 70: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((perfluorophenyl)methoxy)thiophene-3-carbonitrile



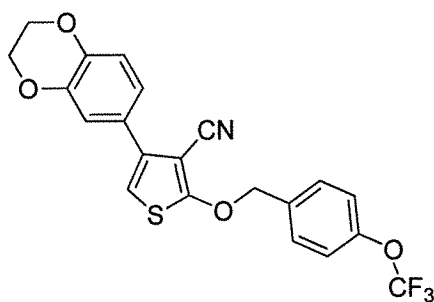
MS (ESI) m/z : *calc.* for $C_{20}H_{10}F_5NO_3S$, $[M+H]^+$: 440.03; *found*: 440.03

Example 71: 2-((4-(tert-butyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile



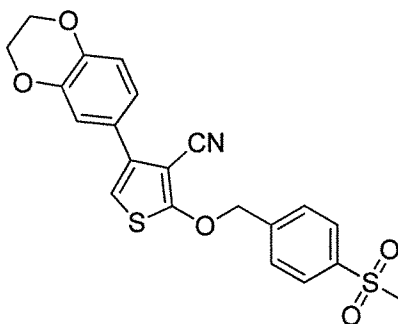
MS (ESI) m/z : *calc.* for $C_{24}H_{23}NO_3S$, $[M+H]^+$: 406.14; *found*: 406.13

Example 72: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile



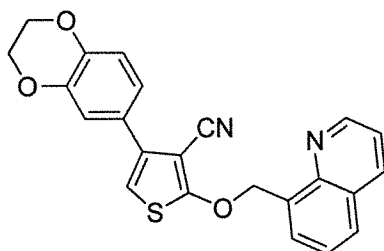
MS (ESI). m/z : *calc.* for $C_{21}H_{14}F_3NO_4S$, $[M+H]^+$: 434.06; *found*: 434.10

Example 73: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(methylsulfonyl)benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{21}H_{17}NO_5S_2$, $[M+H]^+$: 428.05; *found*: 428.11

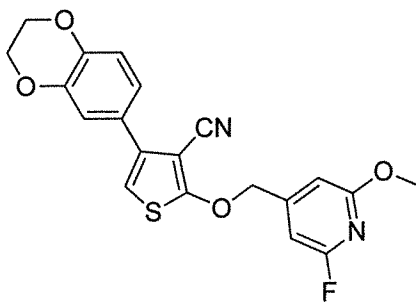
Example 74: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(quinolin-8-ylmethoxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{23}H_{16}N_2O_3S$, $[M+H]^+$: 401.09; *found*: 401.11

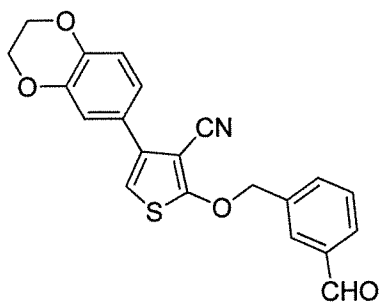
Example 75: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((2-fluoropyridin-4-yl)methoxy)thiophene-3-carbonitrile

56



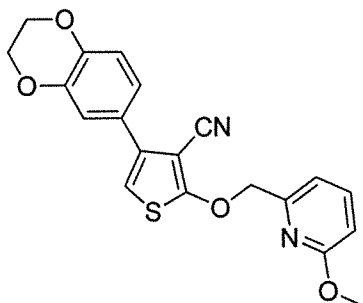
MS (ESI) m/z : *calc.* for $C_{20}H_{15}FN_2O_4S$, $[M+H]^+$: 399.07; *found*: 400.02

Example 76: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((3-formylbenzyl)oxy)thiophene-3-carbonitrile



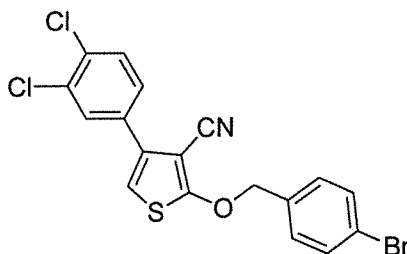
MS (ESI) m/z : *calc.* for $C_{21}H_{15}NO_4S$, $[M+H]^+$: 378.07; *found*: 378.09

Example 77: 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((6-methoxypyridin-2-yl)methoxy)thiophene-3-carbonitrile



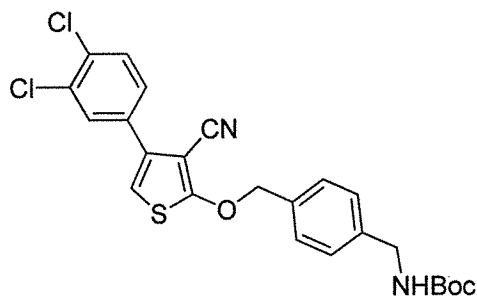
MS (ESI) m/z : *calc.* for $C_{20}H_{16}N_2O_4S$, $[M+H]^+$: 381.08; *found*: 381.14

Example 78: 2-((4-bromobenzyl)oxy)-4-(3,4-dichlorophenyl)-thiophene-3-carbonitrile



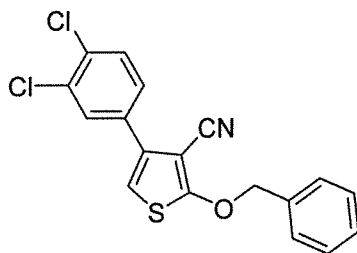
^1H NMR (500 MHz, $CDCl_3$): δ 5.24 (s, 1H), 6.62 (s, 1H), 7.35 (d, J = 10 Hz, 2H), 7.45 (dd, J = 5, 0.5 Hz, 1H), 7.50 (dd, J = 5, 0.5 Hz, 1H), 7.55 (d, J = 10 Hz, 2H), 7.44 (d, J = 5 Hz, 1H) ppm. MS (ESI) m/z : *calc.* for $C_{18}H_{10}BrCl_2NOS$, $[M+H]^+$: 440.15; *found*: 440.35

Example 79: tert-butyl 4-(((3-cyano-4-(3,4-dichlorophenyl)-thiophen-2-yl)oxy)methyl)benzylcarbamate



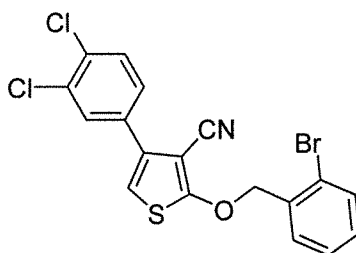
MS (ESI) m/z : *calc.* for $C_{24}H_{22}Cl_2N_2O_3S$, $[M+H]^+$: 489.07; *found*: 489.12

Example 80: 2-(benzyloxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



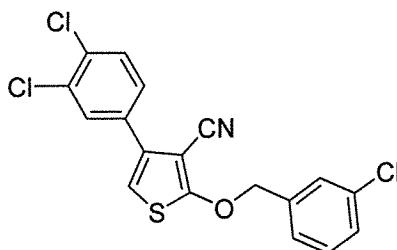
MS (ESI) m/z: *calc.* for $C_{18}H_{11}Cl_2NOS$, $[M+H]^+$: 359.99; *found*: 360.04

Example 81: 2-((2-bromobenzyl)oxy)-4-(3,4-dichlorophenyl)-thiophene-3-carbonitrile



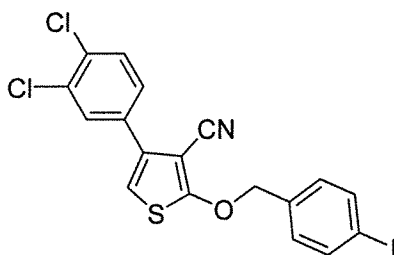
MS (ESI) m/z: *calc.* for $C_{18}H_{10}BrCl_2NOS$, $[M+H]^+$: 437.90; *found*: 437.99

Example 82: 2-((3-chlorobenzyl)oxy)-4-(3,4-dichlorophenyl)-thiophene-3-carbonitrile



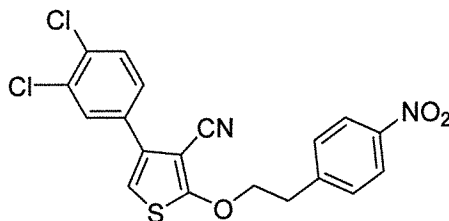
MS (ESI) m/z: *calc.* for $C_{18}H_{10}Cl_3NOS$, $[M+H]^+$: 393.95; *found*: 393.99

Example 83: 4-(3,4-dichlorophenyl)-2-((4-iodobenzyl)oxy)-thiophene-3-carbonitrile



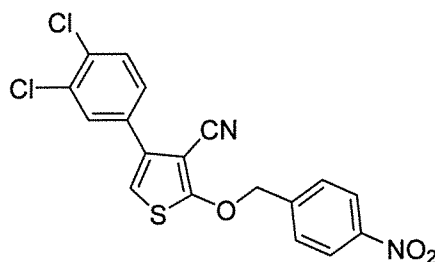
MS (ESI) m/z : *calc.* for $C_{18}H_{10}Cl_2INOS$, $[M+H]^+$: 485.89; *found*: 485.99

Example 84: 4-(3,4-dichlorophenyl)-2-(4-nitrophenethoxy)-thiophene-3-carbonitrile



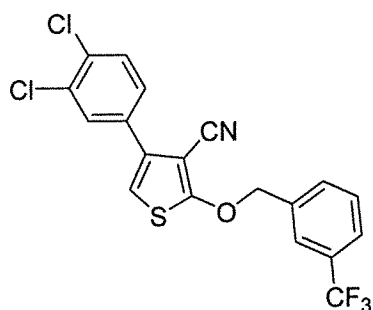
MS (ESI) m/z : *calc.* for $C_{19}H_{12}Cl_2NO_3S$, $[M+H]^+$: 418.99; *found*: 419.06

Example 85: 4-(3,4-dichlorophenyl)-2-((4-nitrobenzyl)oxy)-thiophene-3-carbonitrile



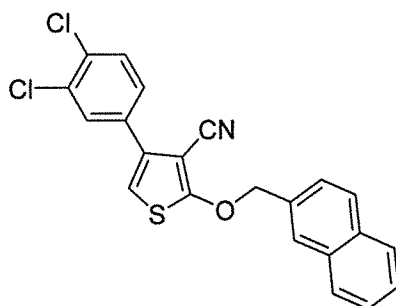
MS (ESI) m/z : *calc.* for $C_{18}H_{10}Cl_2N_2O_3S$, $[M+H]^+$: 404.98; *found*: 405.02

Example 86: 4-(3,4-dichlorophenyl)-2-((3-(trifluoromethyl)-benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{10}Cl_2F_3NOS$, $[M+H]^+$: 427.98; *found*: 428.03

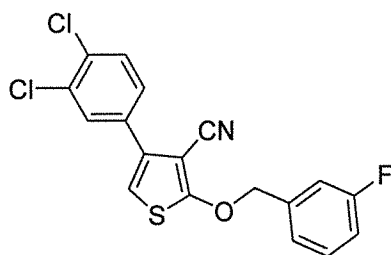
Example 87: 4-(3,4-dichlorophenyl)-2-(naphthalen-2-ylmethoxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{22}H_{13}Cl_2NOS$, $[M+H]^+$: 410.01; *found*: 410.12

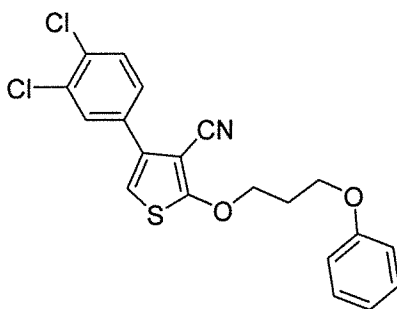
Example 88: 4-(3,4-dichlorophenyl)-2-((3-fluorobenzyl)oxy)thiophene-3-carbonitrile

61



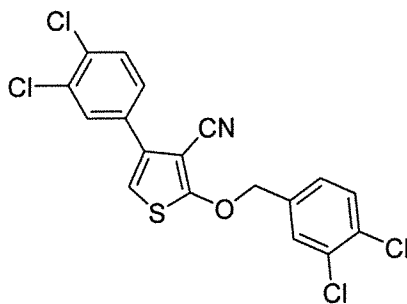
MS (ESI) *m/z*: *calc.* for C₁₈H₁₀Cl₂FNOS, [M+H]⁺: 377.98; *found*: 378.06

Example 89: 4-(3,4-dichlorophenyl)-2-(3-phenoxypropoxy)thiophene-3-carbonitrile



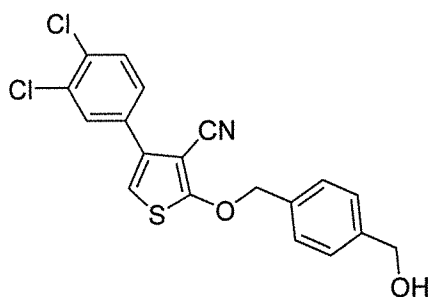
MS (ESI) *m/z*: *calc.* for C₂₀H₁₅Cl₂NO₂S, [M+H]⁺: 404.02; *found*: 404.09

Example 90: 2-((3,4-dichlorobenzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



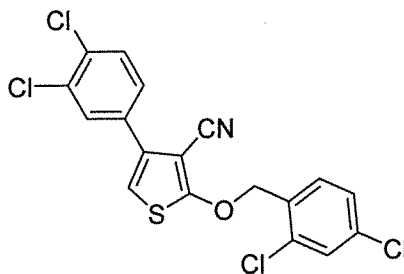
MS (ESI) m/z : *calc.* for $C_{18}H_9Cl_4NOS$, $[M+H]^+$: 427.92; *found*: 427.99

Example 91: 4-(3,4-dichlorophenyl)-2-((4-(hydroxymethyl)-benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{13}Cl_2NO_2S$, $[M+H]^+$: 389.00; *found*: 389.11

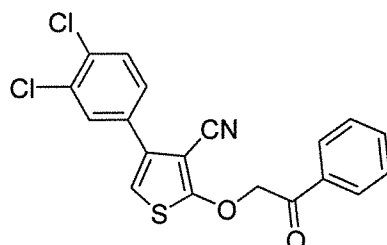
Example 92: 2-((2,4-dichlorobenzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_9Cl_4NOS$, $[M+H]^+$: 427.92; *found*: 427.99

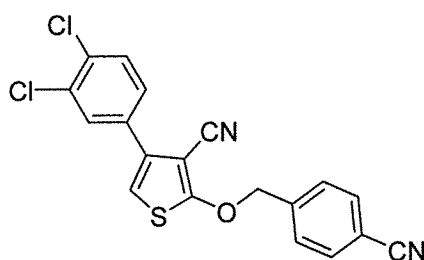
Example 93: 4-(3,4-dichlorophenyl)-2-(2-oxo-2-phenylethoxy)thiophene-3-carbonitrile

63



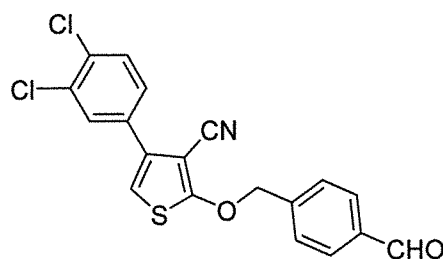
MS (ESI) m/z : *calc.* for $C_{19}H_{11}Cl_2NO_2S$, $[M+H]^+$: 387.99; *found*: 388.05

Example 94: 2-((4-cyanobenzyl)oxy)-4-(3,4-dichlorophenyl)-thiophene-3-carbonitrile



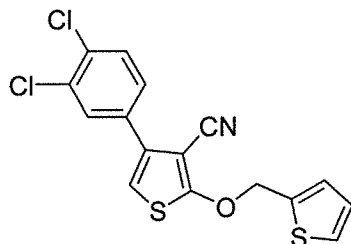
MS (ESI) m/z : *calc.* for $C_{19}H_{10}Cl_2N_2OS$, $[M+H]^+$: 384.99; *found*: 385.03

Example 95: 4-(3,4-dichlorophenyl)-2-((4-formylbenzyl)oxy)-thiophene-3-carbonitrile



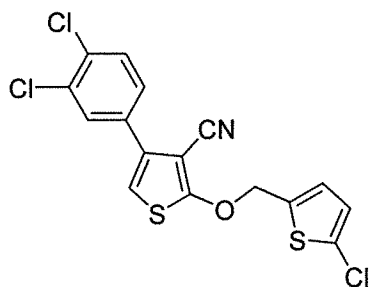
MS (ESI) m/z : *calc.* for $C_{19}H_{11}Cl_2NO_2S$, $[M+H]^+$: 387.99; *found*: 387.03

Example 96: 4-(3,4-dichlorophenyl)-2-(thiophen-2-ylmethoxy)-thiophene-3-carbonitrile



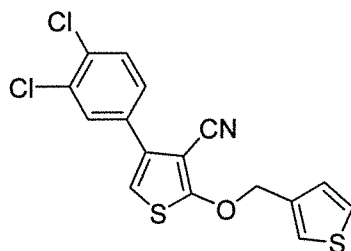
MS (ESI) m/z : *calc.* for $C_{16}H_9Cl_2NOS_2$, $[M+H]^+$: 365.95; *found*: 365.99

Example 97: 2-((5-chlorothiophen-2-yl)methoxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



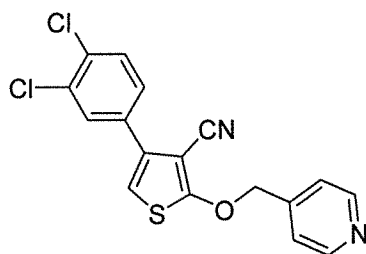
MS (ESI) m/z : *calc.* for $C_{16}H_8Cl_3NOS_2$, $[M+H]^+$: 399.91; *found*: 399.99

Example 98: 4-(3,4-dichlorophenyl)-2-(thiophen-3-ylmethoxy)-thiophene-3-carbonitrile



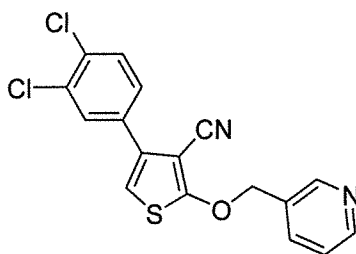
MS (ESI) m/z : *calc.* for $C_{16}H_9Cl_2NOS_2$, $[M+H]^+$: 365.95; *found*: 365.99

Example 99: 4-(3,4-dichlorophenyl)-2-(pyridin-4-ylmethoxy)-thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{17}H_{10}Cl_2N_2OS$, $[M+H]^+$: 359.99; *found*: 360.02

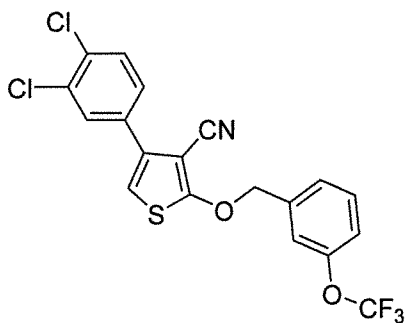
Example 100: 4-(3,4-dichlorophenyl)-2-(pyridin-3-ylmethoxy)-thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{17}H_{10}Cl_2N_2OS$, $[M+H]^+$: 360.99; *found*: 361.02

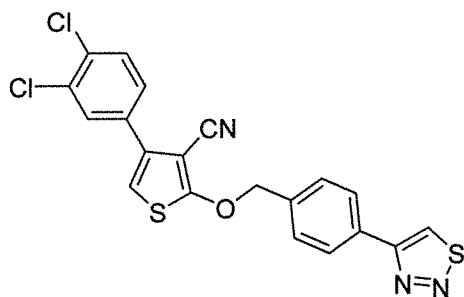
Example 101: 4-(3,4-dichlorophenyl)-2-((3-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile

66



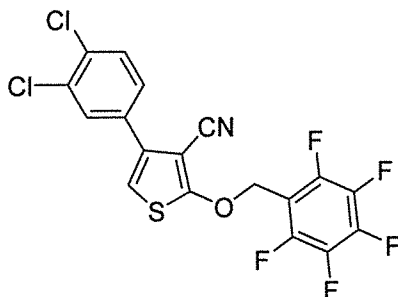
MS (ESI) m/z : *calc.* for $C_{19}H_{10}Cl_2F_3NO_2S$, $[M+H]^+$: 443.98; *found*: 444.09

Example 102: 2-((4-(1,2,3-thiadiazol-4-yl)benzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



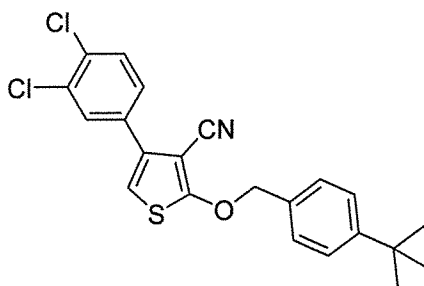
MS (ESI) m/z : *calc.* for $C_{20}H_{11}Cl_2N_3OS_2$, $[M+H]^+$: 443.97; *found*: 443.99

Example 103: 4-(3,4-dichlorophenyl)-2-((perfluorophenyl)methoxy)thiophene-3-carbonitrile



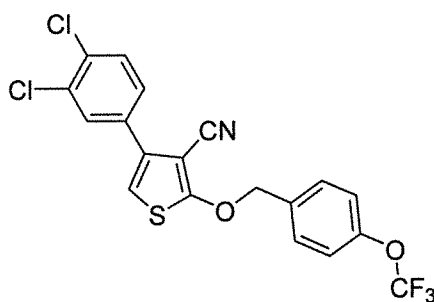
MS (ESI) m/z : *calc.* for $C_{18}H_6Cl_2F_5NOS$, $[M+H]^+$: 449.95; *found*: 450.08

Example 104: 2-((4-(tert-butyl)benzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{22}H_{19}Cl_2NOS$, $[M+H]^+$: 415.06; *found*: 415.12

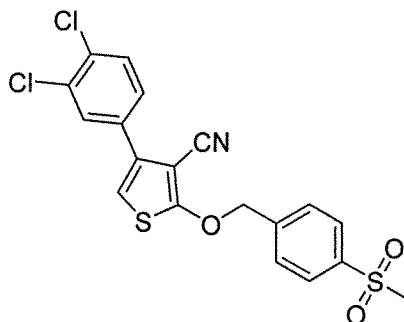
Example 105: 4-(3,4-dichlorophenyl)-2-((4-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{19}H_{10}Cl_2F_3NO_2S$, $[M+H]^+$: 443.98; *found*: 444.05

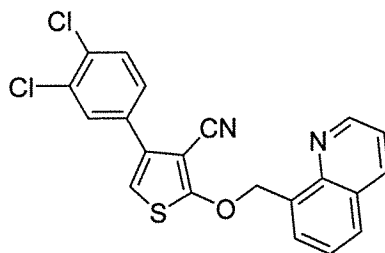
Example 106: 4-(3,4-dichlorophenyl)-2-((4-(methylsulfonyl)benzyl)oxy)thiophene-3-carbonitrile

68



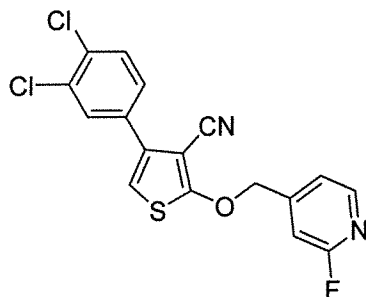
MS (ESI) m/z : *calc.* for $C_{19}H_{13}Cl_2NO_3S_2$, $[M+H]^+$: 437.97; *found*: 438.05

Example 107: 4-(3,4-dichlorophenyl)-2-(quinolin-8-ylmethoxy)thiophene-3-carbonitrile



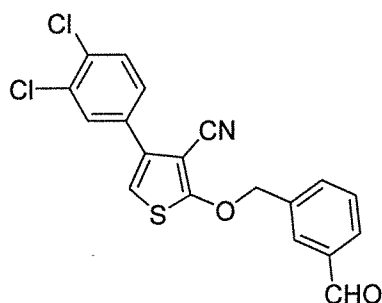
MS (ESI) m/z : *calc.* for $C_{21}H_{12}Cl_2N_2OS$, $[M+H]^+$: 411.00; *found*: 411.05

Example 108: 4-(3,4-dichlorophenyl)-2-((2-fluoropyridin-4-yl)methoxy)thiophene-3-carbonitrile



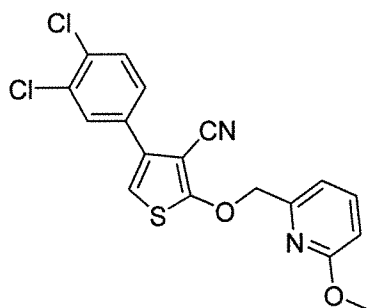
MS (ESI) m/z : *calc.* for $C_{17}H_{13}Cl_2NOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 109: 4-(3,4-dichlorophenyl)-2-((3-formylbenzyl)oxy)-thiophene-3-carbonitrile



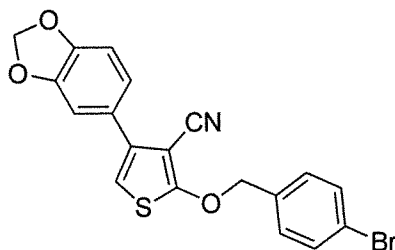
MS (ESI) m/z : *calc.* for $C_{19}H_{11}Cl_2NO_2S$, $[M+H]^+$: 387.99; *found*: 388.05

Example 110: 4-(3,4-dichlorophenyl)-2-((6-methoxypyridin-2-yl)-ethoxy)thiophene-3-carbonitrile

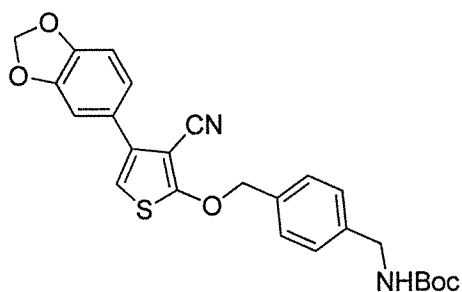


MS (ESI) m/z : *calc.* for $C_{18}H_{12}Cl_2N_2O_2S$, $[M+H]^+$: 391.00; *found*: 391.05

Example 111: Example 4: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-bromobenzyl)oxy)thiophene-3-carbonitrile

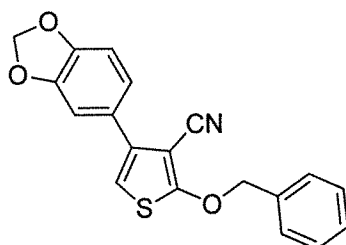


Example 112: tert-butyl 4-(((4-(benzo[d][1,3]dioxol-5-yl)-3-cyanothiophen-2-yl)oxy)methyl)benzylcarbamate



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

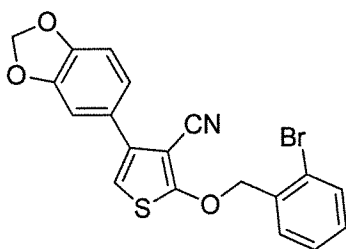
Example 113: 4-(benzo[d][1,3]dioxol-5-yl)-2-(benzyloxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

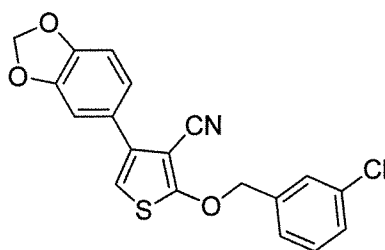
Example 114: 4-(benzo[d][1,3]dioxol-5-yl)-2-((2-bromobenzyl)oxy)thiophene-3-carbonitrile

71



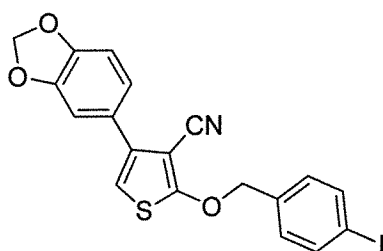
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 115: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3-chlorobenzyl)oxy)thiophene-3-carbonitrile



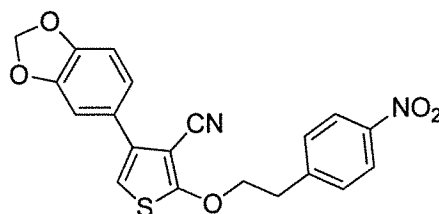
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 116: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-iodobenzyl)oxy)thiophene-3-carbonitrile



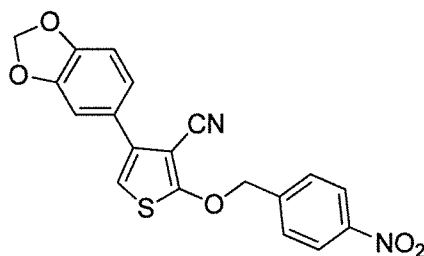
MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 117: 4-(benzo[d][1,3]dioxol-5-yl)-2-(4-nitrophenethoxy)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

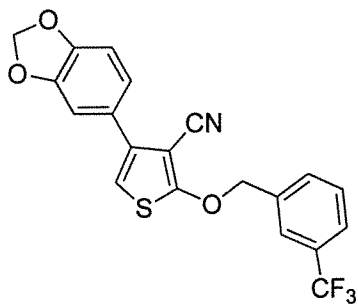
Example 118: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-nitrobenzyl)-oxy)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

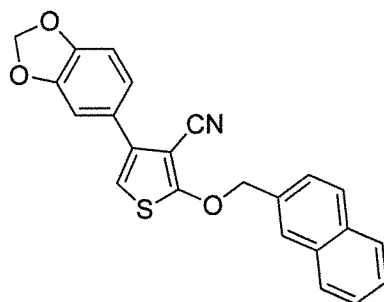
Example 119: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3-(trifluoromethyl)benzyl)oxy)thiophene-3-carbonitrile

73



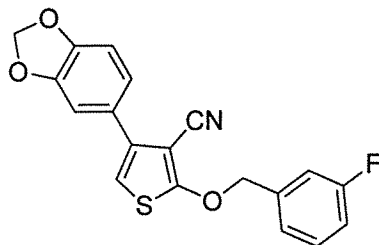
MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 120: 4-(benzo[d][1,3]dioxol-5-yl)-2-(naphthalen-2-yl-methoxy)thiophene-3-carbonitrile



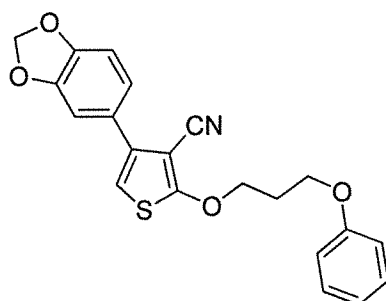
MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 121: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3-fluorobenzyl)-oxy)thiophene-3-carbonitrile



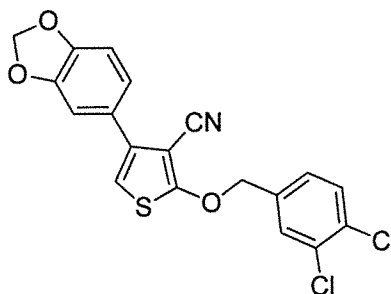
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 122: 4-(benzo[d][1,3]dioxol-5-yl)-2-(3-phenoxypropoxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

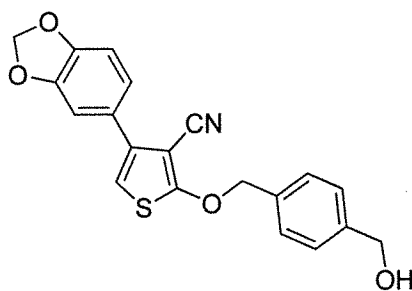
Example 123: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3,4-dichlorobenzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

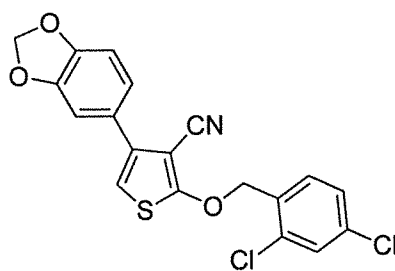
Example 124: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(hydroxymethyl)benzyl)oxy)thiophene-3-carbonitrile

75



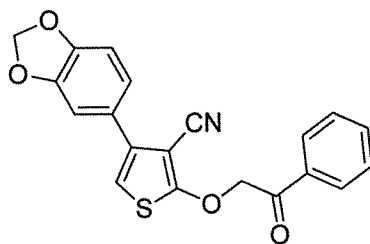
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 125: 4-(benzo[d][1,3]dioxol-5-yl)-2-((2,4-dichlorobenzyl)oxy)thiophene-3-carbonitrile



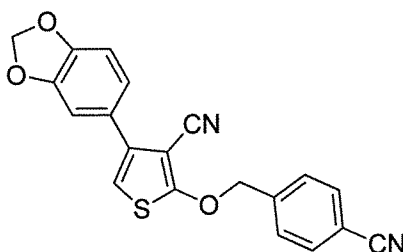
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 126: 4-(benzo[d][1,3]dioxol-5-yl)-2-(2-oxo-2-phenylethoxy)thiophene-3-carbonitrile



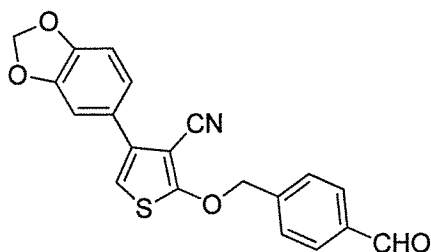
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 127: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-cyanobenzyl)-oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

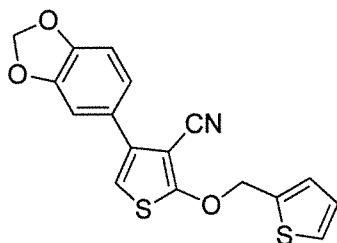
Example 128: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-formylbenzyl)-oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

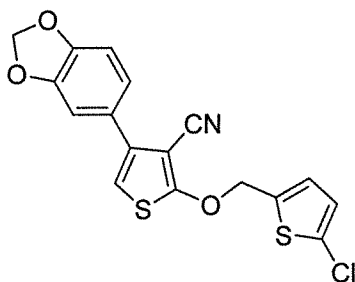
Example 129: 4-(benzo[d][1,3]dioxol-5-yl)-2-(thiophen-2-yl-methoxy)thiophene-3-carbonitrile

77



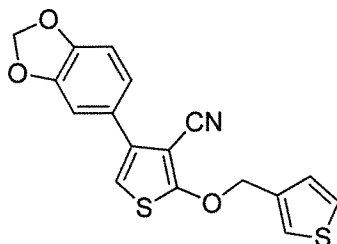
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 130: 4-(benzo[d][1,3]dioxol-5-yl)-2-((5-chlorothiophen-2-yl)methoxy)thiophene-3-carbonitrile



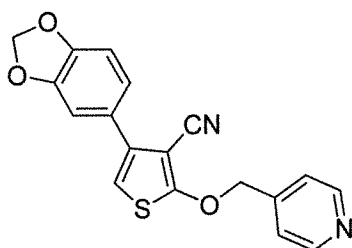
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 131: 4-(benzo[d][1,3]dioxol-5-yl)-2-(thiophen-3-ylmethoxy)thiophene-3-carbonitrile



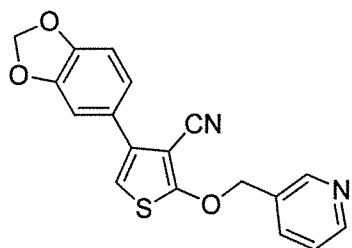
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 132: 4-(benzo[d][1,3]dioxol-5-yl)-2-(pyridin-4-yl-methoxy)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

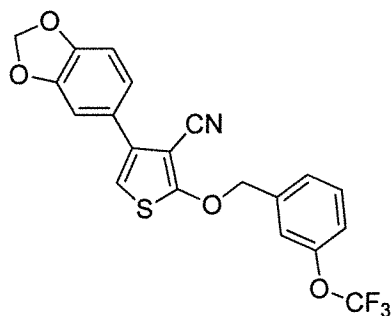
Example 133: 4-(benzo[d][1,3]dioxol-5-yl)-2-(pyridin-3-yl-methoxy)thiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

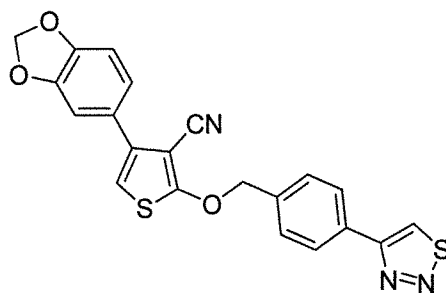
Example 134: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile

79



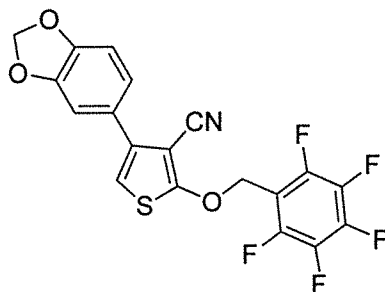
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 135: 2-((4-(1,2,3-thiadiazol-4-yl)benzyl)oxy)-4-(benzo[d][1,3]dioxol-5-yl)thiophene-3-carbonitrile



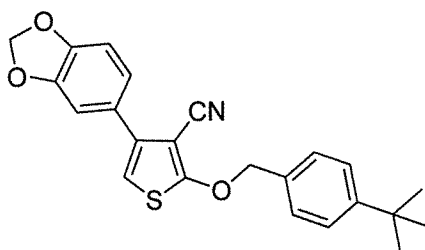
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 136: 4-(benzo[d][1,3]dioxol-5-yl)-2-((perfluorophenyl)methoxy)thiophene-3-carbonitrile



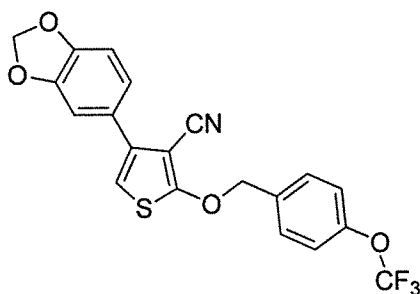
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 137: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(tert-butyl)-benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

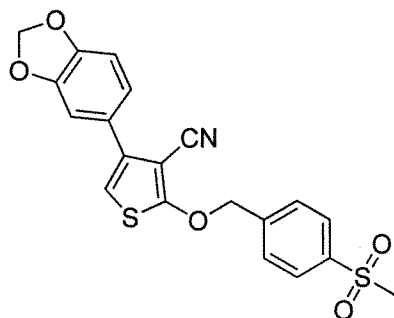
Example 138: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(trifluoromethoxy)benzyl)oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

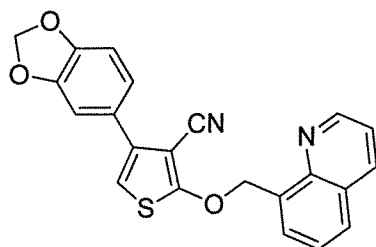
Example 139: 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(methylsulfonyl)benzyl)oxy)thiophene-3-carbonitrile

81



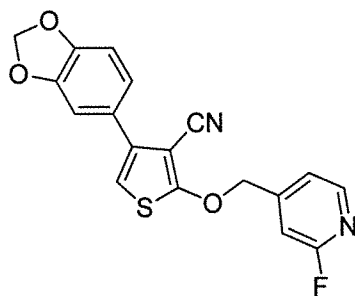
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 140: 4-(benzo[d][1,3]dioxol-5-yl)-2-(quinolin-8-yl-methoxy)thiophene-3-carbonitrile



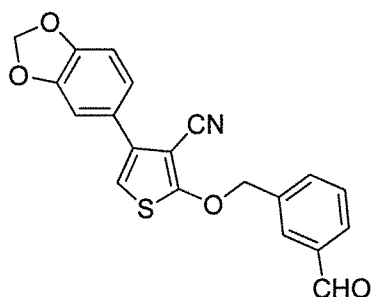
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 141: 4-(benzo[d][1,3]dioxol-5-yl)-2-((2-fluoropyridin-4-yl)methoxy)thiophene-3-carbonitrile



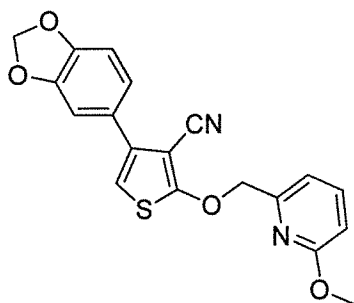
MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

Example 142: 4-(benzo[d][1,3]dioxol-5-yl)-2-((3-formylbenzyl)-oxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

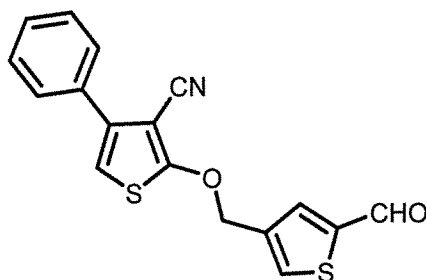
Example 143: 4-(benzo[d][1,3]dioxol-5-yl)-2-((6-methoxypyridin-2-yl)methoxy)thiophene-3-carbonitrile



MS (ESI) m/z : *calc.* for $C_{18}H_{12}BrNOS$, $[M+H]^+$: 371.26; *found*: 371.32

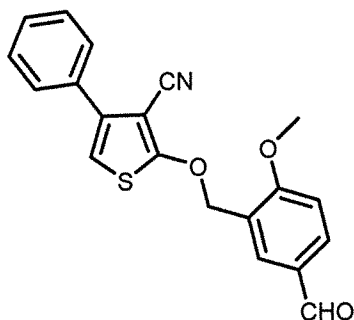
Example 144: 2-((5-formylthiophen-3-yl)methoxy)-4-phenylthiophene-3-carbonitrile

83



MS (ESI) m/z: *calc.* for $C_{17}H_{11}NO_2S_2$, $[M+H]^+$: 326.02; *found*: 326.10

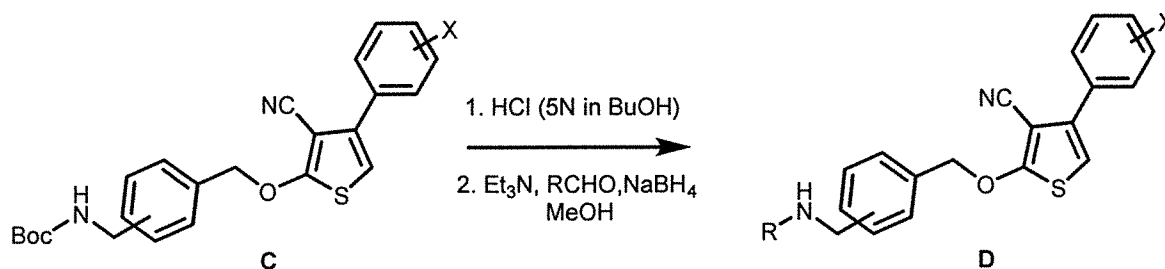
Example 145: 2-((5-formyl-2-methoxybenzyl)oxy)-4-phenylthiophene-3-carbonitrile



MS (ESI) m/z: *calc.* for $C_{20}H_{15}NO_3S$, $[M+H]^+$: 350.08; *found*: 350.09

III. General procedures for the reductive amination (In the following schemes, X represents R^1 and R^2 and R represents R^5)

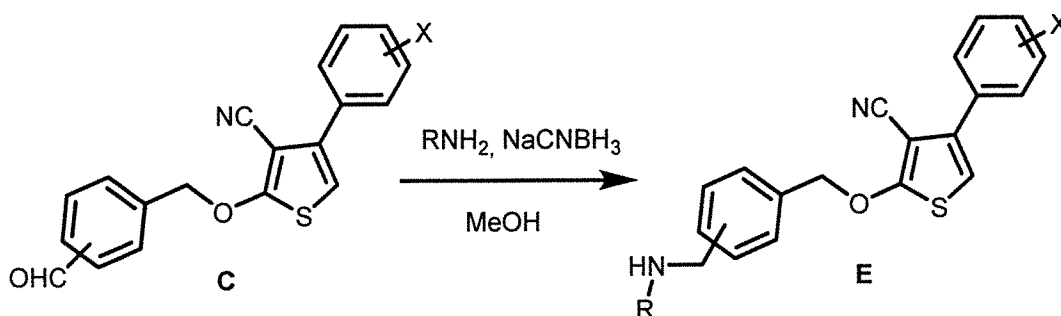
From the compounds produced from the general procedure of the O-alkylation specific scaffolds were selected for further functionalization (e.g. examples 13, 46, 79 and 112) towards compounds D.



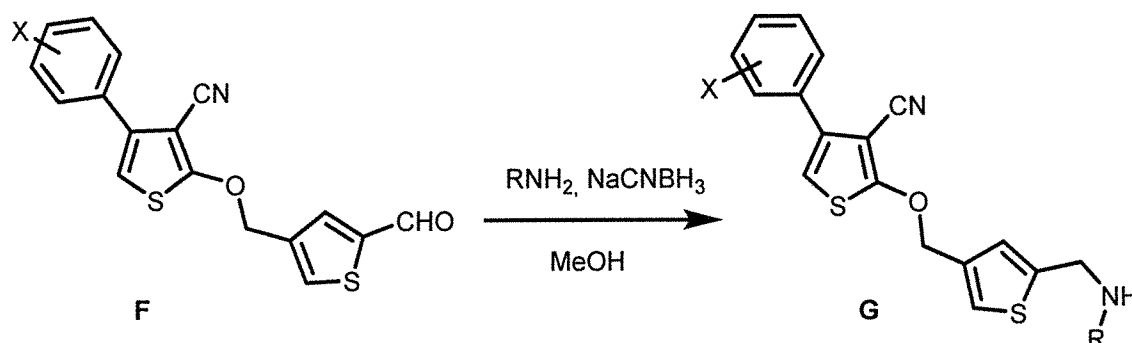
Compound C (1.0 mmol) was dissolved in a solution of HCl in butanol 5 N. After stirring at rt for 2 h, the solid that was obtained was filtered off and washed with ether.

The corresponding hydrochloric salt (0.5 mmol) was transferred into a round bottom flask and dissolved into MeOH (5 mL). Addition of Et₃N (1.1 eq) was followed and the reaction mixture was stirred at rt for 30 min. Afterwards, the corresponding carbonyl compound (1.1 eq) was added and after 1 h stirring at rt, NaBH₄ (1.1 eq) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water, extractions followed with DCM and finally purification by column chromatography.

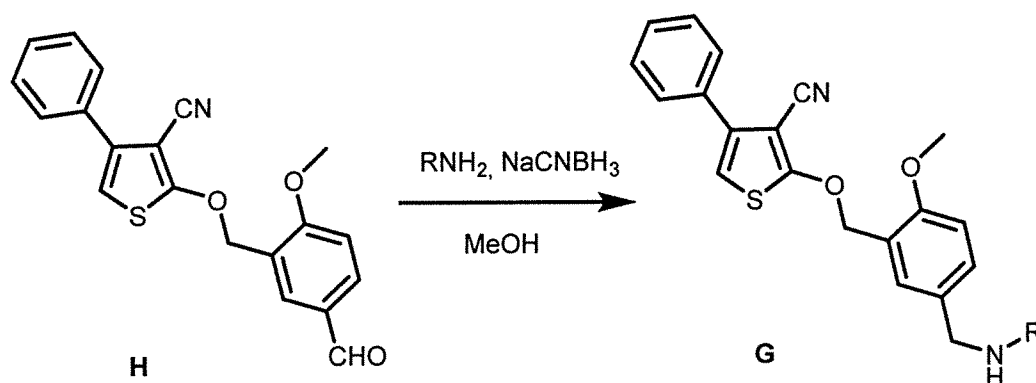
From the compounds produced from the general procedure of the O-alkylation specific scaffolds were selected for further functionalization (e.g. examples 29, 43, 62, 76, 95, 109, 128 and 142) towards compounds E.



To a stirred solution of compound **C** (0.5 mmol) in MeOH (5 mL), the corresponding carbonyl compound (1.1 eq) was added and after 1 h stirring at rt, NaCNBH₃ (1.1 eq) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water, extractions followed with DCM and finally purification by column chromatography.



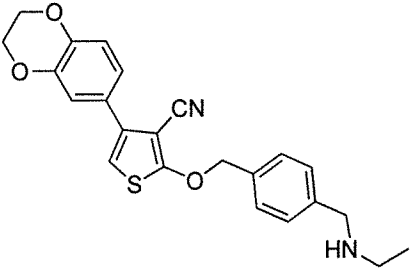
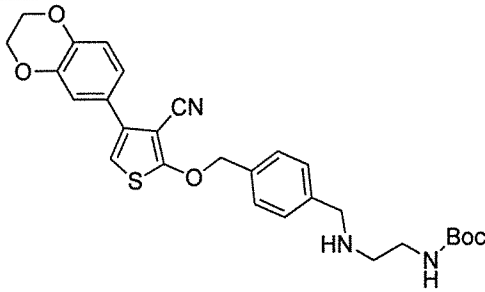
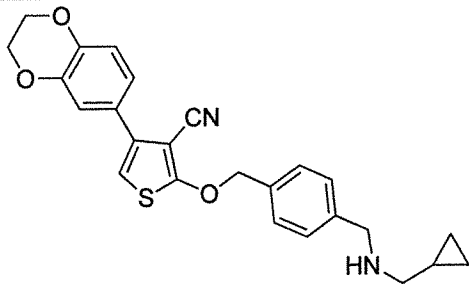
To a stirred solution of compound **F** (e.g. example 144) (0.5 mmol) in MeOH (5 mL), the corresponding carbonyl compound (1.1 eq) was added and after 1 h stirring at rt, NaCNBH₃ (1.1 eq) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water, extractions followed with DCM and finally purification by column chromatography.

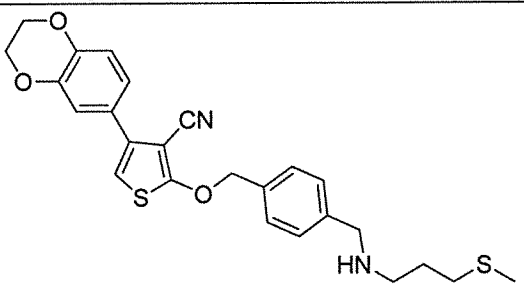
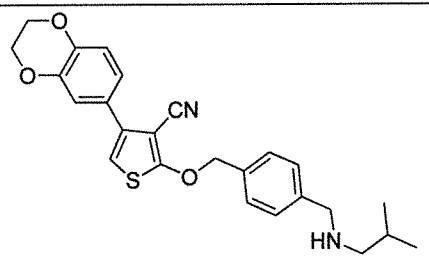
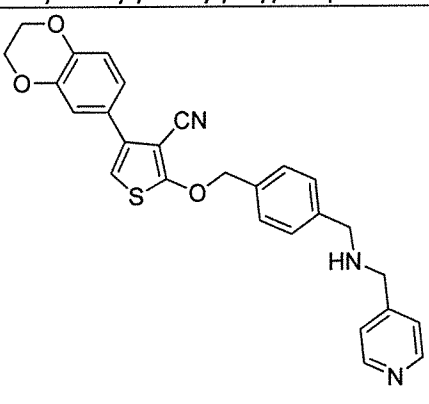
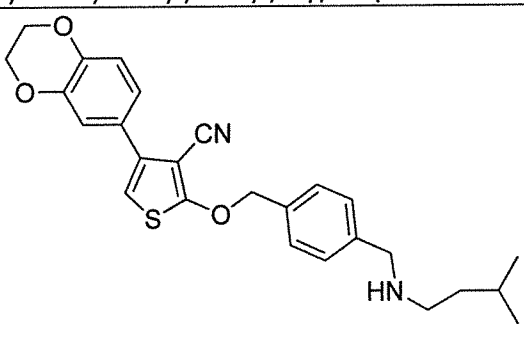


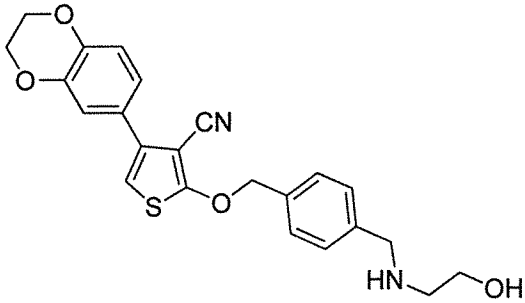
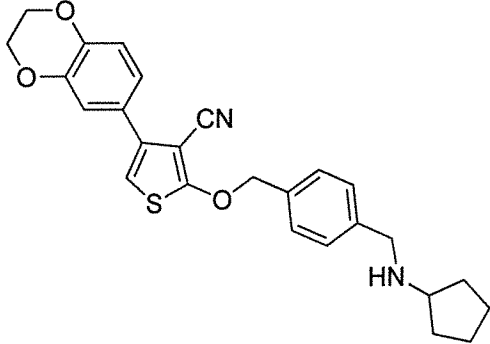
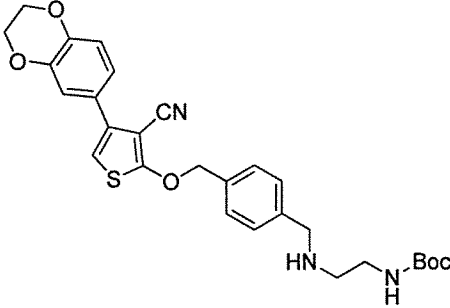
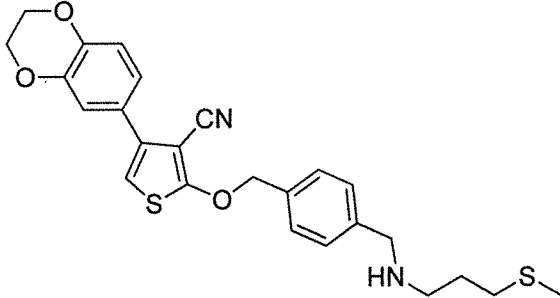
To a stirred solution of compound **H** (e.g. example 145) (0.5 mmol) in MeOH (5 mL), the corresponding carbonyl compound (1.1

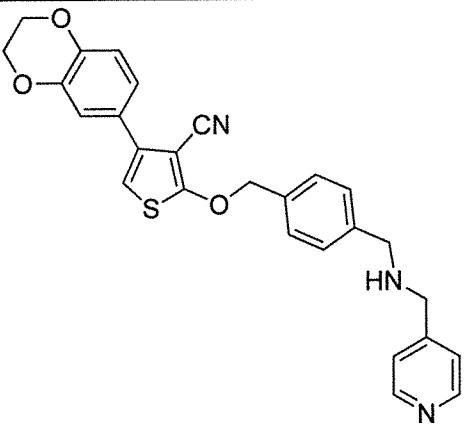
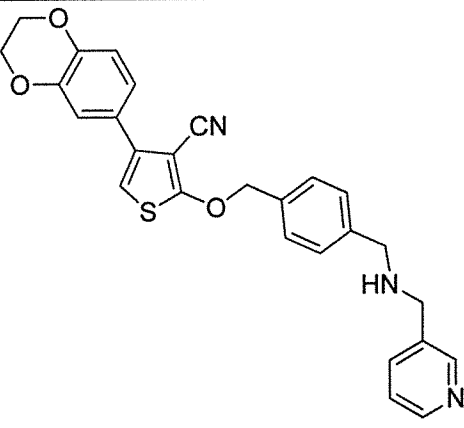
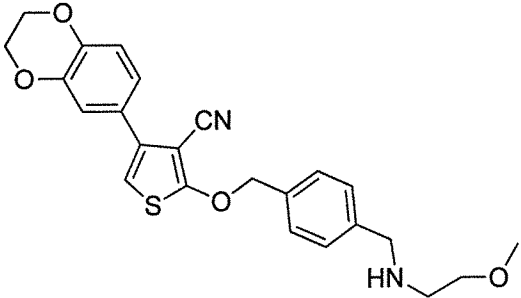
eq) was added and after 1 h stirring at rt, NaCNBH₃ (1.1 eq) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with water, extractions followed with DCM and finally purification by column chromatography.

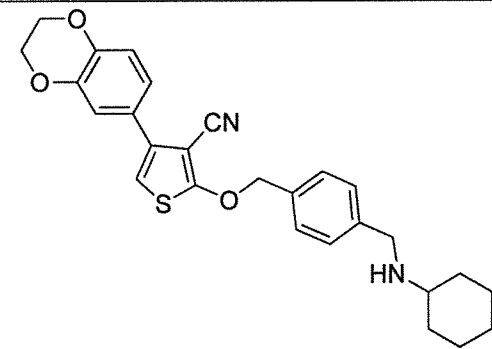
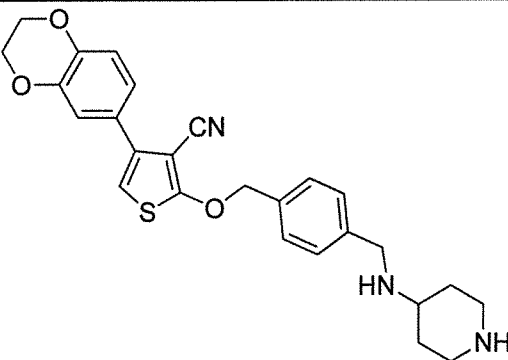
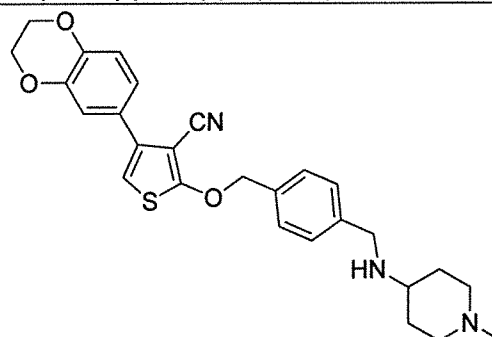
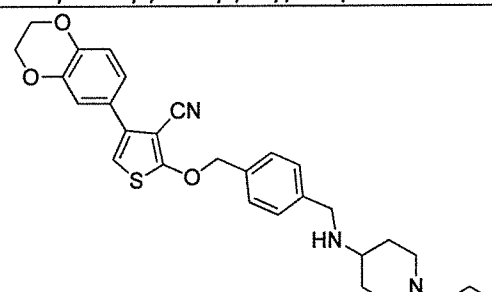
Further examples which have been prepared according to the general procedures described above:

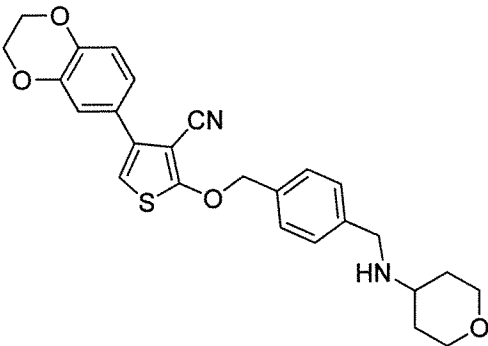
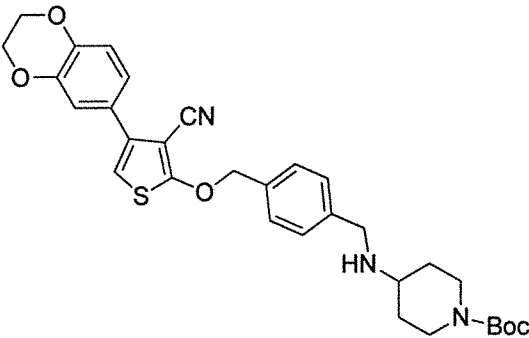
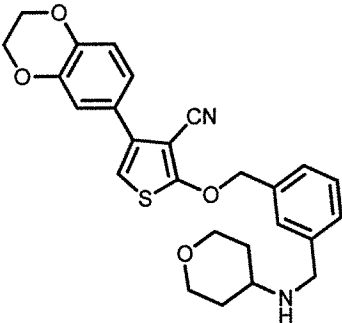
No.	Structure / Name	Molecular Weight	Found
146	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((ethylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	406.14	407.19
147	 tert-butyl (2-((4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	521.20	522.25
148	 2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,3-dihydrothiophene-3-carbonitrile	432.15	433.16

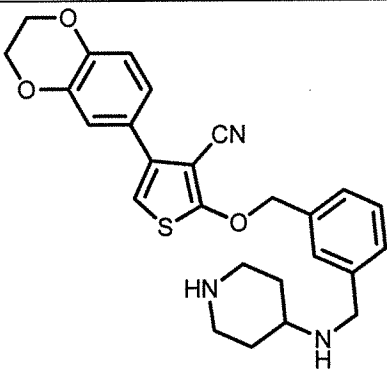
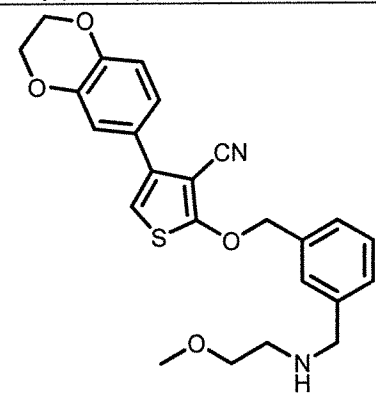
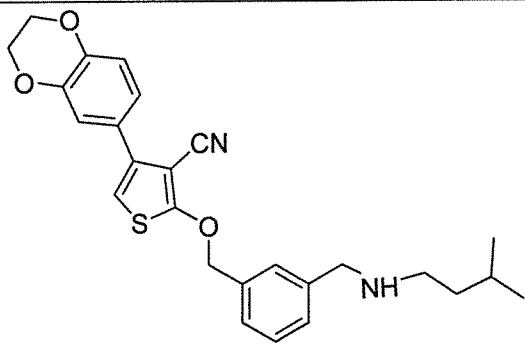
	4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile		
149	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((3-(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	466.14	567.16
150	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((isobutylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	434.17	435.18
151	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	469.15	470.02
152	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((3-methylbutyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	448.18	449.18

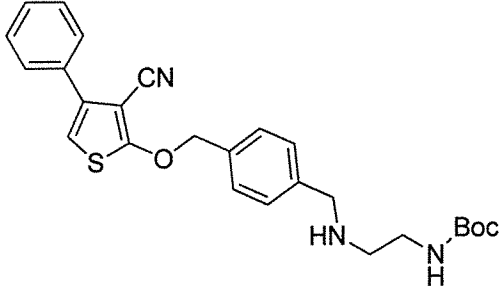
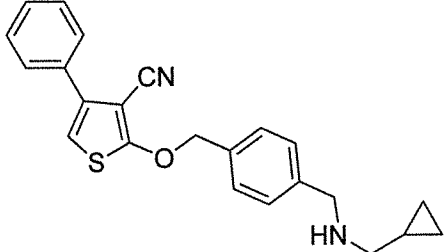
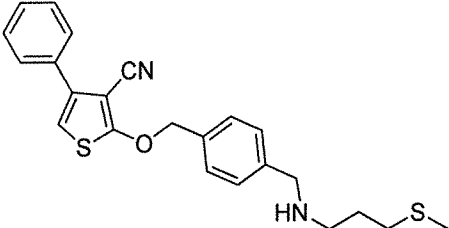
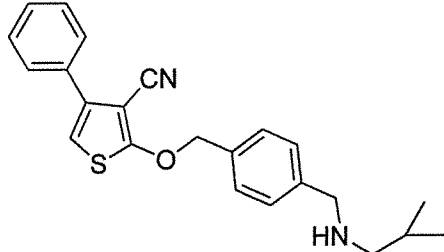
	((isopentylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile		
153	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((4-((2-hydroxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	422.13	423.22
154	 2-(((4-((cyclopentylamino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	446.17	447.20
155	 tert-butyl (2-(((4-((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	521.20	522.22
156	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((4-((3-(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	466.14	467.15

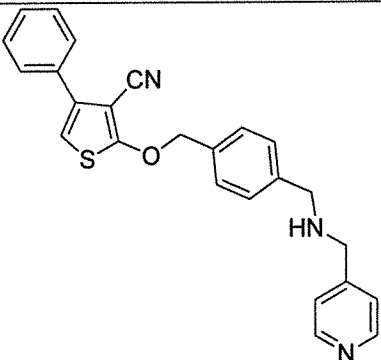
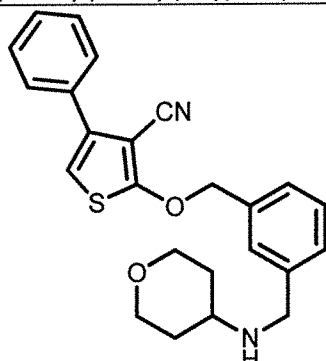
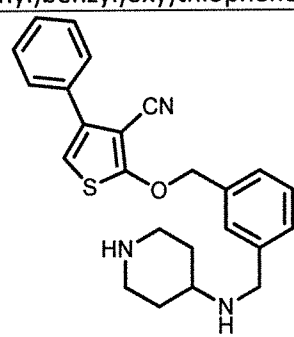
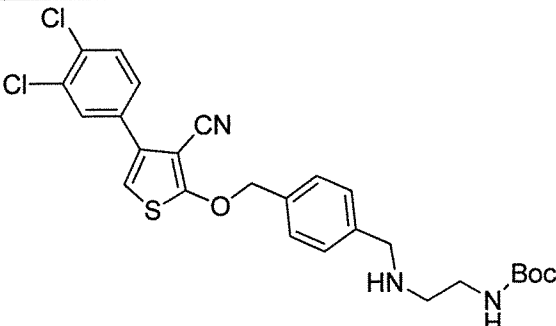
	(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile		
157	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((pyridin-4-yl)methyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	469.15	470.17
158	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((pyridin-3-yl)methyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	469.15	470.19
159	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((2-methoxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	436.15	437.16

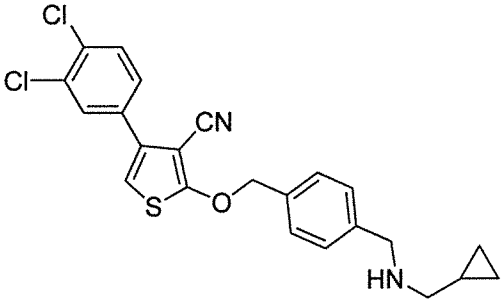
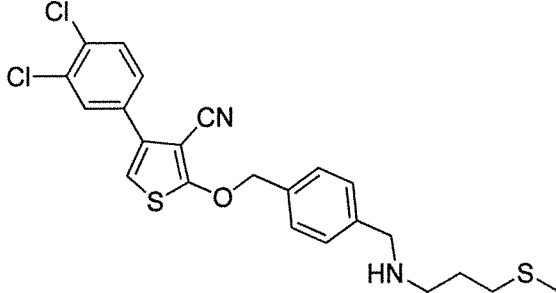
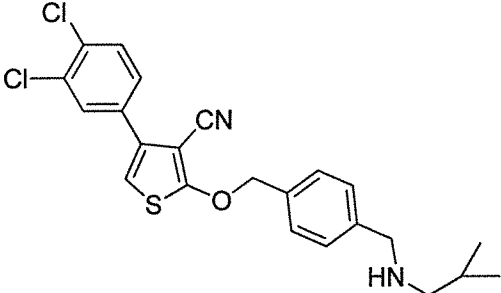
160	 2-((4-((cyclohexylamino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	460.18	461.19
161	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((piperidin-4-ylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	461.18	462.19
162	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((1-methylpiperidin-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	475.19	476.19
163		503.22	504.33

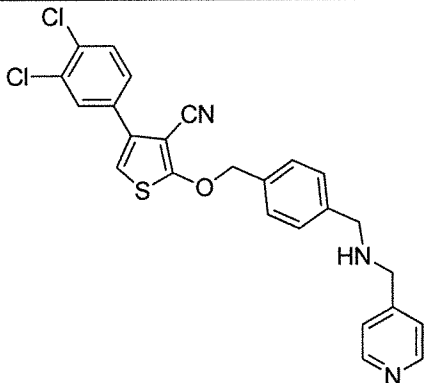
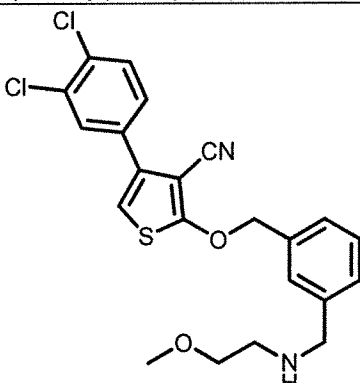
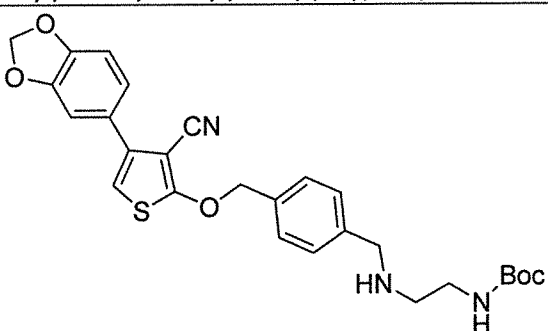
	4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((1-propylpiperidin-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile		
164	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((tetrahydro-2H-pyran-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	462.16	463.17
165	 tert-butyl 4-((4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)piperidine-1-carboxylate	561.23	562.28
166	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((3-(((tetrahydro-2H-pyran-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	462.16	463.20

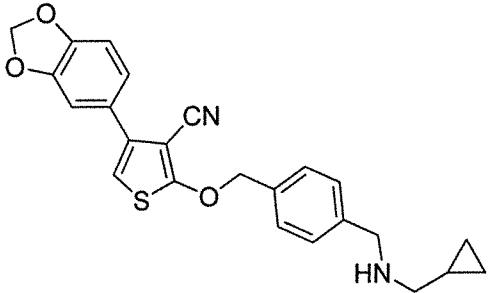
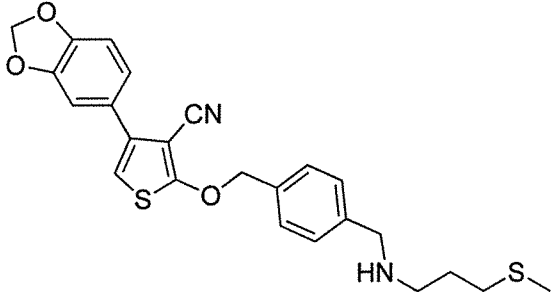
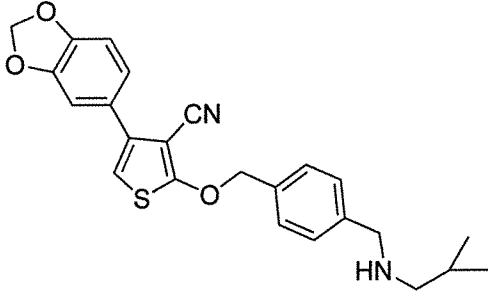
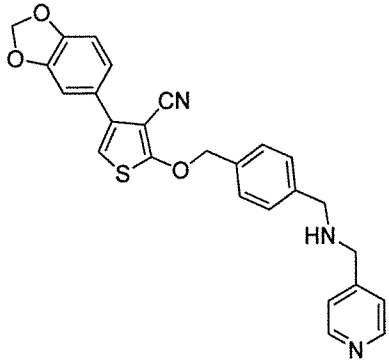
167	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((3-((piperidin-4-ylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	461.18	462.23
168	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((3-(((2-methoxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	436.15	437.20
169	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((3-(isopentylamino)benzyl)oxy)thiophene-3-carbonitrile	448.18	449.22

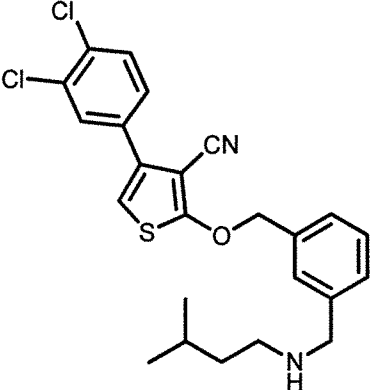
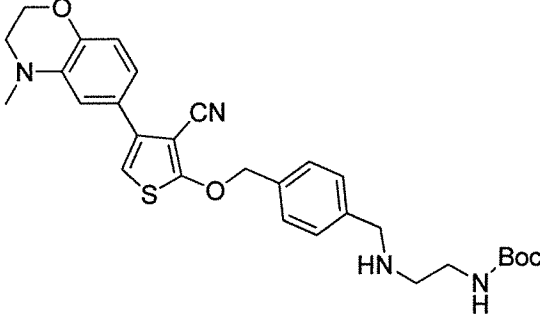
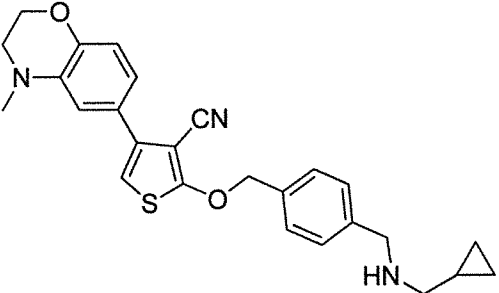
170	 tert-butyl (2-((4-(((3-cyano-4-phenylthiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	463.19	464.23
171	 2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	374.15	375.17
172	 2-((4-(((3-(methylthio)propyl)amino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	408.13	409.16
173	 2-((4-(((isobutylamino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	376.16	377.19

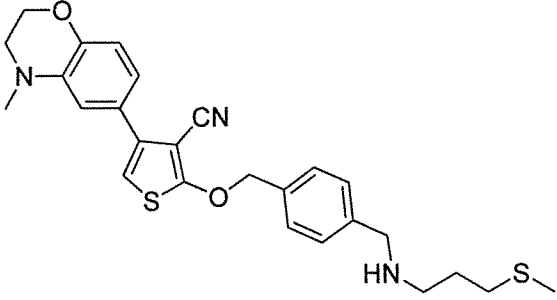
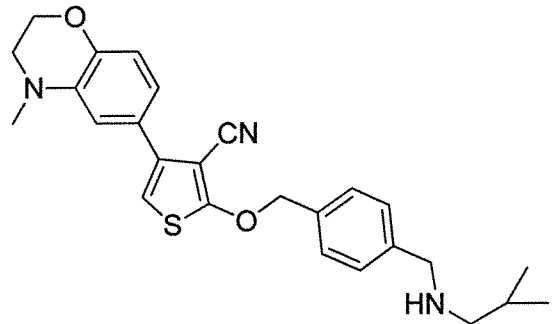
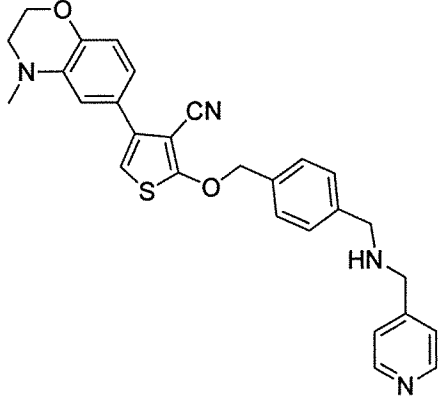
174	 4-phenyl-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	411.14	412.30
175	 4-phenyl-2-((3-(((tetrahydro-2H-pyran-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	404.16	405.16
176	 4-phenyl-2-((3-((piperidin-4-ylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	403.17	404.17
177		531.12	532.16

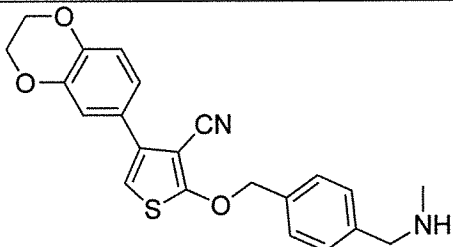
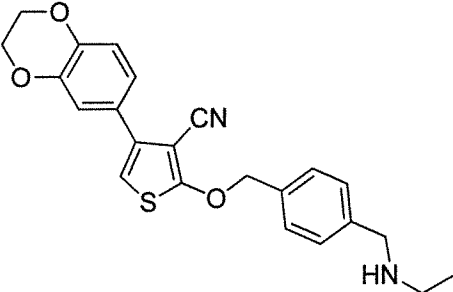
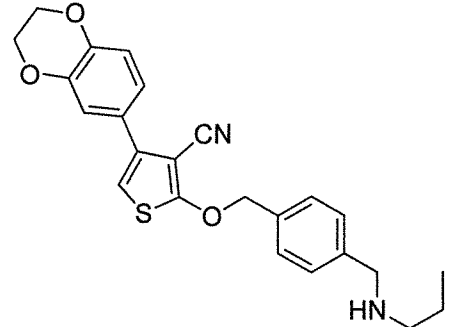
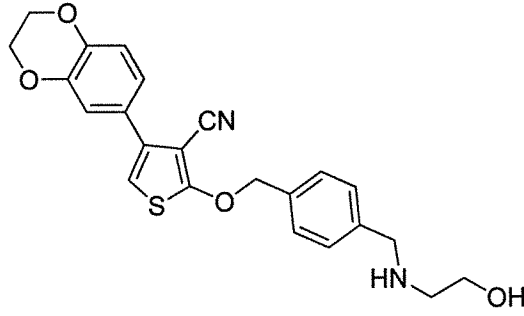
	tert-butyl (2-((4-(((3-cyano-4-(3,4-dichlorophenyl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate		
178	 2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile	442.07	443.12
179	 4-(3,4-dichlorophenyl)-2-((4-(((3-(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	476.06	477.16
180	 4-(3,4-dichlorophenyl)-2-((4-((isobutylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	444.08	445.11

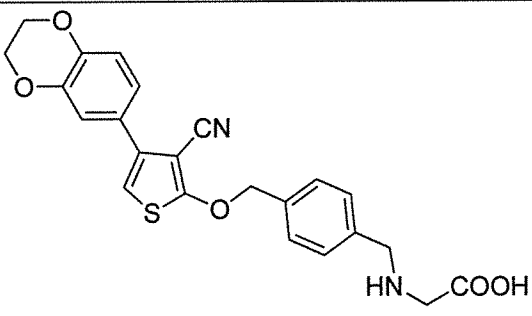
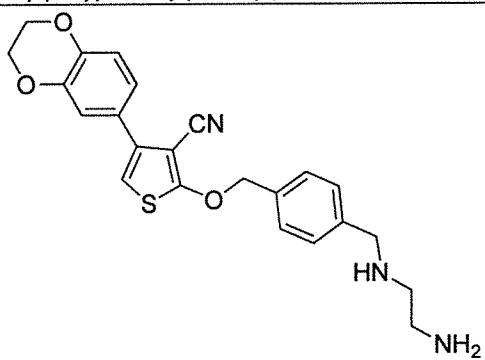
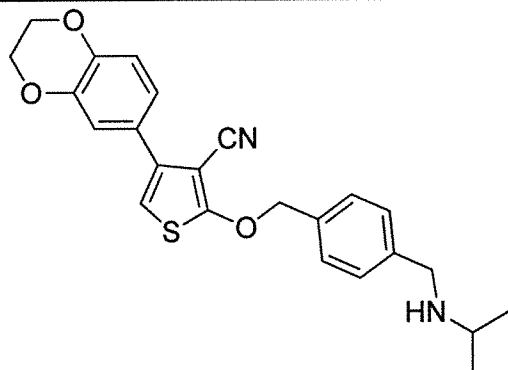
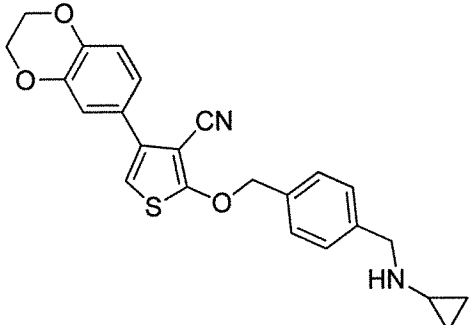
181	 4-(3,4-dichlorophenyl)-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	479.06	480.06
182	 4-(3,4-dichlorophenyl)-2-((3-((2-methoxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	446.06	447.07
183	 tert-butyl (2-((4-(((4-(benzo[d][1,3]dioxol-5-yl)-3-cyanothiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	507.18	508.18

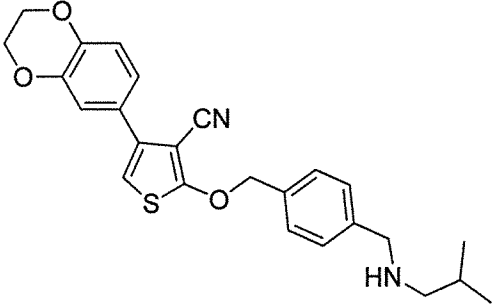
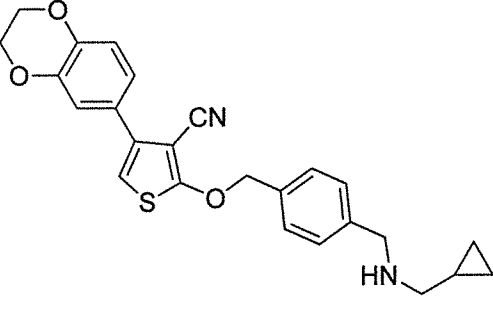
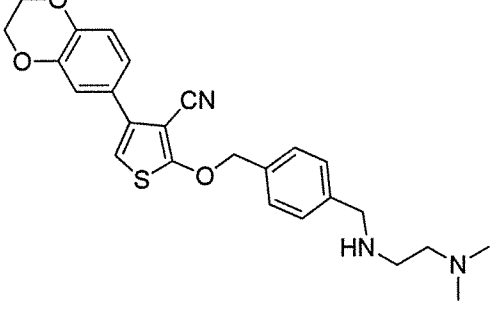
184	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	418.14	419.17
185	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(((3-(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	452.12	453.13
186	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(((isobutylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	420.15	421.16
187	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	455.13	456.14

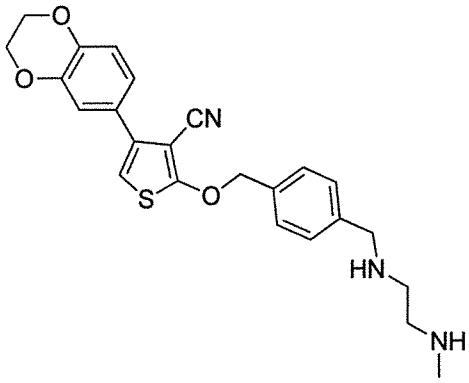
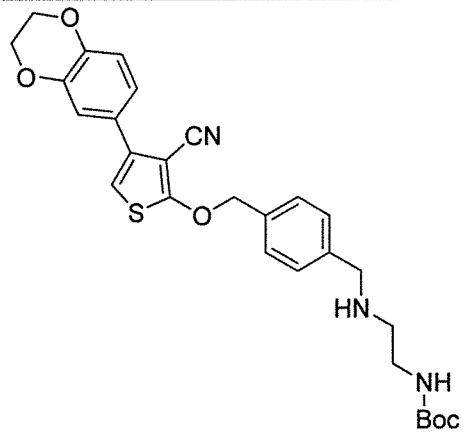
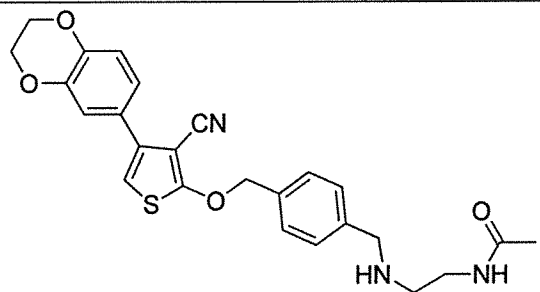
	ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile		
188	 4-(3,4-dichlorophenyl)-2-((3-((isopentylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	458.10	459.10
189	 tert-butyl (2-((4-(((3-cyano-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	534.23	535.29
190	 2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carbonitrile	445.18	446.19

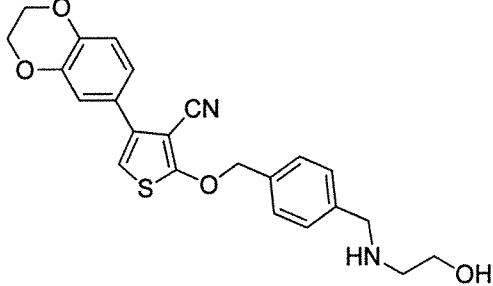
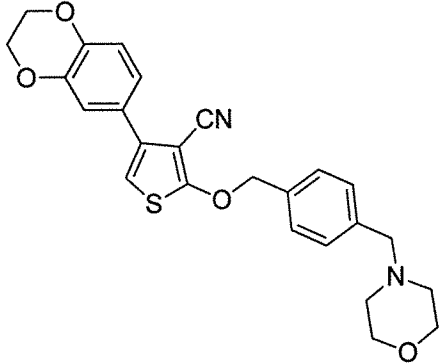
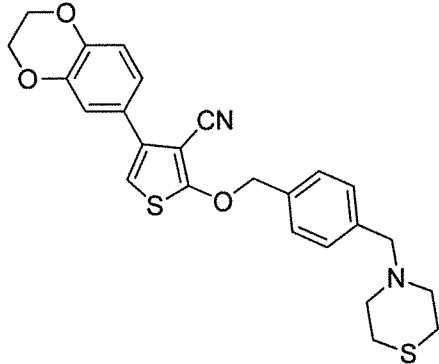
191	 4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-2-((4-(((3-(methylthio)propyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	479.17	480.18
192	 2-((4-((isobutylamino)methyl)benzyl)oxy)-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carbonitrile	447.20	448.29
193	 4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	482.18	483.16

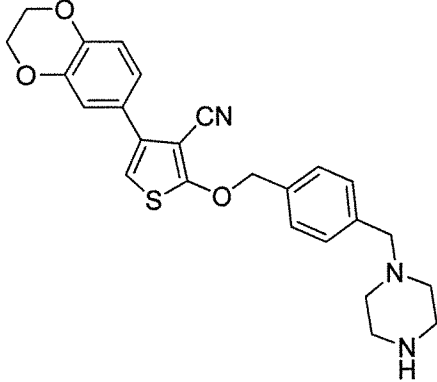
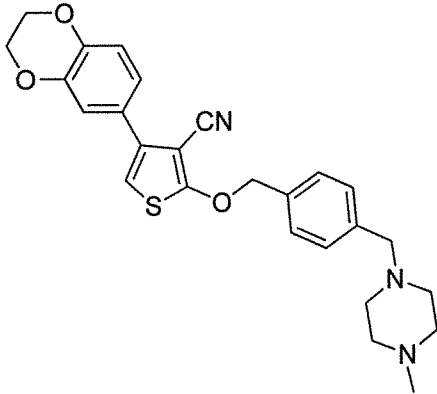
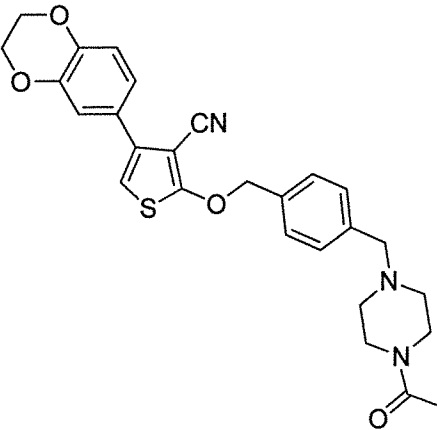
194	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((methylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	392.12	393.13
195	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((ethylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	406.14	407.20
196	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((propylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	420.15	421.16
197	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((2-hydroxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	422.13	423.19

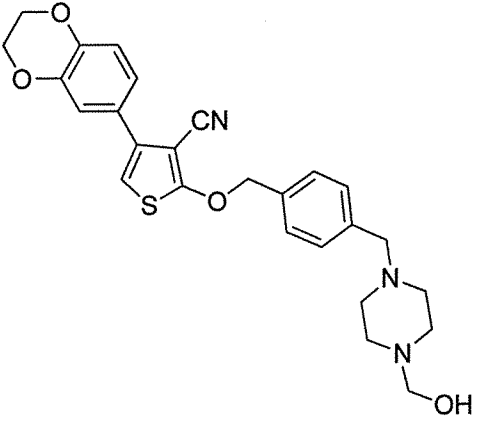
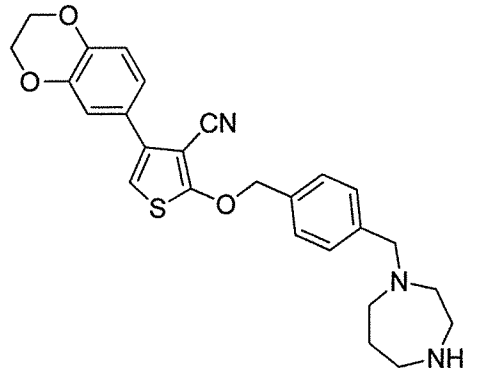
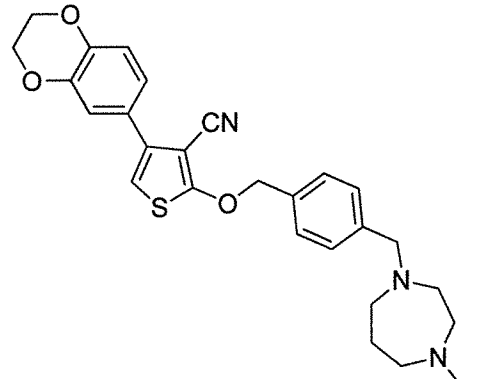
198	 2-((4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)acetic acid	436.11	437.15
199	 2-((4-(((2-aminoethyl)amino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	421.15	422.19
200	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((isopropylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	420.15	421.16
201		418.14	418.14

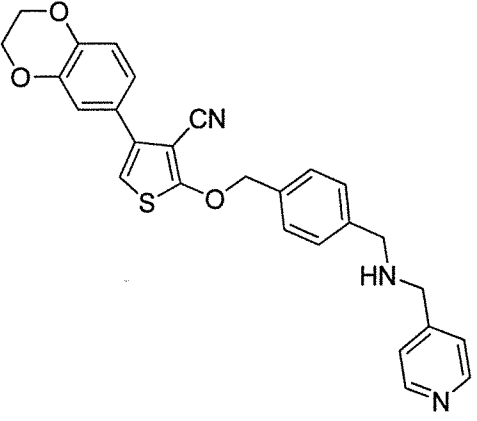
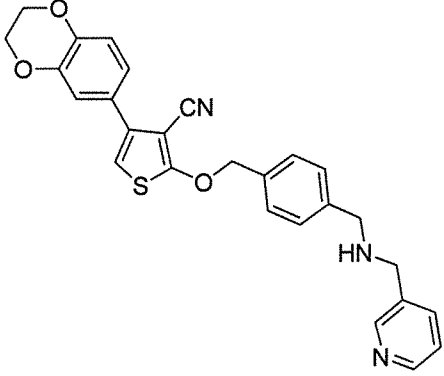
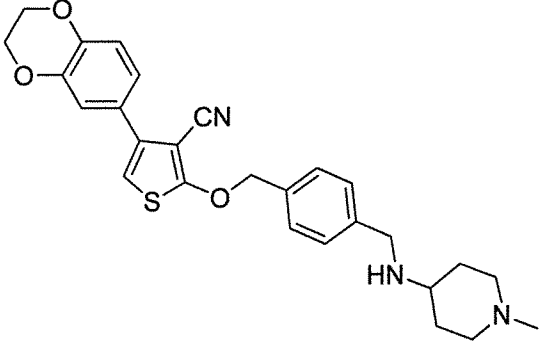
	2-((4-((cyclopropylamino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile		
202	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((isobutylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	434.17	435.17
203	 2-((4-(((cyclopropylmethyl)amino)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	432.15	433.31
204	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((2-(dimethylamino)ethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	449.18	450.19

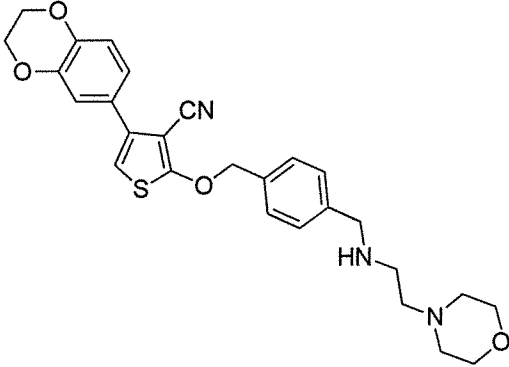
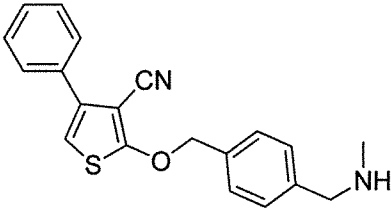
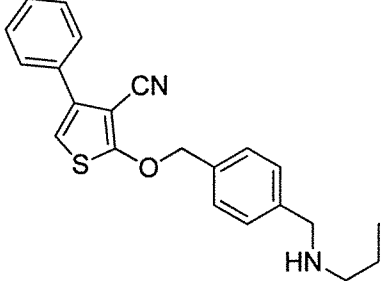
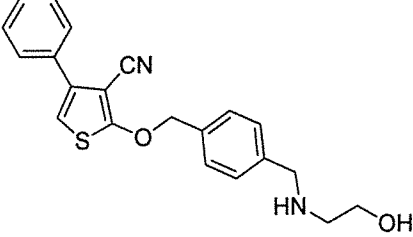
205	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((2-(methylamino)ethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	435.16	436.19
206	 tert-butyl (2-((4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)carbamate	521.20	522.22
207	 N-(2-((4-(((3-cyano-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)ethyl)acetamide	463.16	464.19

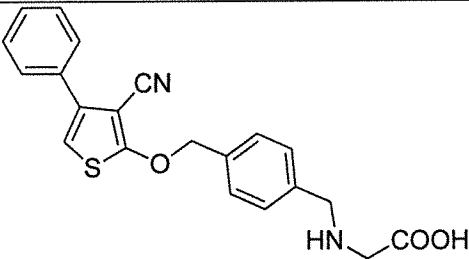
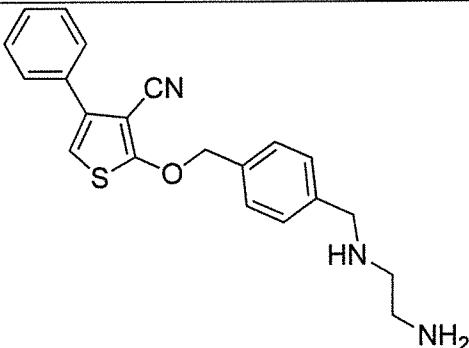
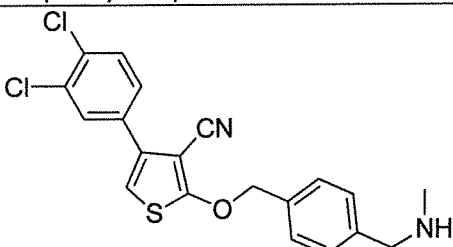
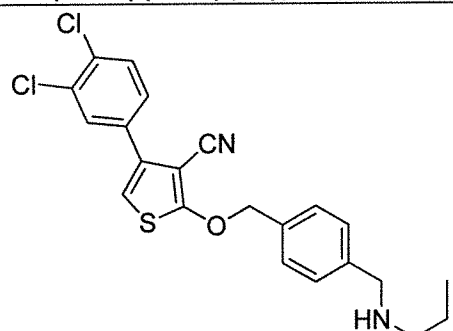
208	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(((2-hydroxyethyl)amino)methyl)benzyl oxythiophene-3-carbonitrile	422.13	423.16
209	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(morpholinomethyl)benzyl)oxy)thiophene-3-carbonitrile	448.15	449.16
210	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(thiomorpholinomethyl)benzyl)oxy)thiophene-3-carbonitrile	464.12	465.13

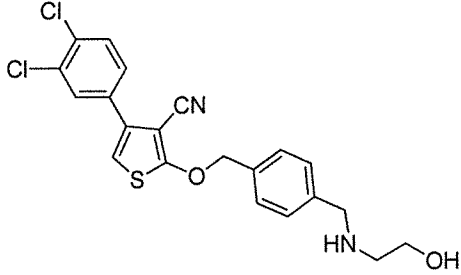
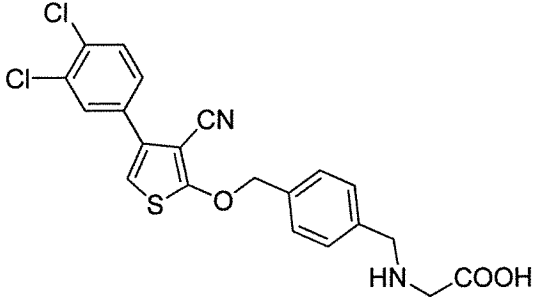
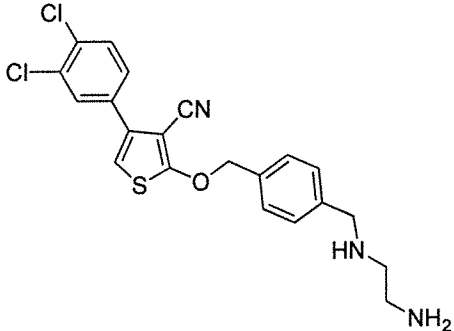
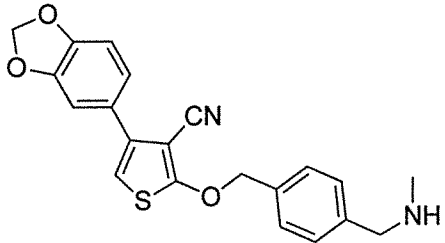
211	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(piperazin-1-ylmethyl)benzyl)oxy)thiophene-3-carbonitrile	447.16	448.18
212	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((4-methylpiperazin-1-yl)methyl)benzyl)oxy)thiophene-3-carbonitrile	461.18	462.19
213	 2-((4-((4-acetylpiperazin-1-yl)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	489.17	490.19

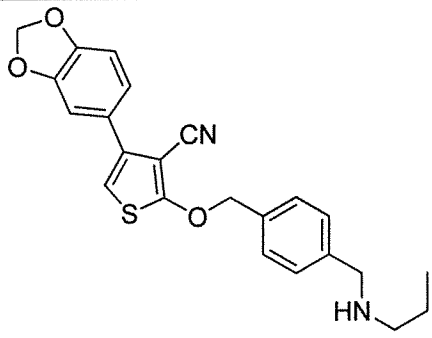
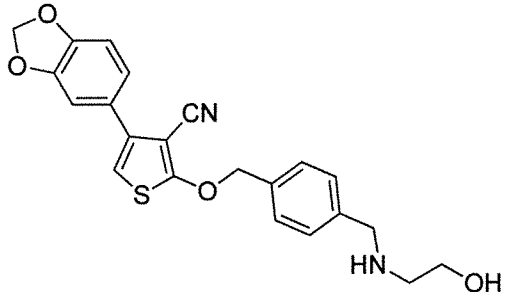
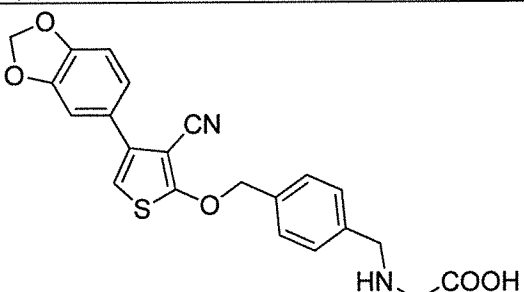
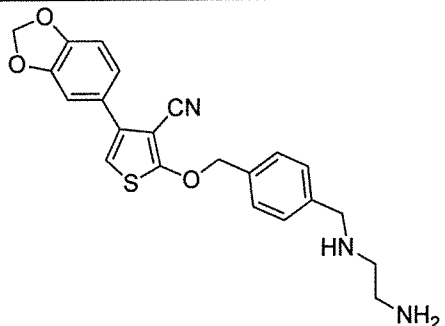
214	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((4-(hydroxymethyl)piperazin-1-yl)methyl)benzyl)oxy)thiophene-3-carbonitrile	477.17	478.19
215	 2-((4-((1,4-diazepan-1-yl)methyl)benzyl)oxy)-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophene-3-carbonitrile	461.18	462.19
216	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-((4-methyl-1,4-diazepan-1-yl)methyl)benzyl)oxy)thiophene-3-carbonitrile	475.19	476.19

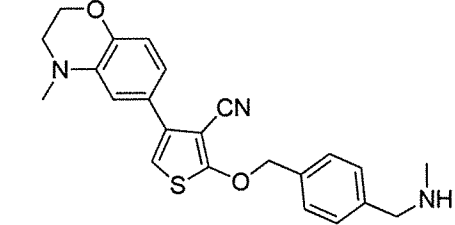
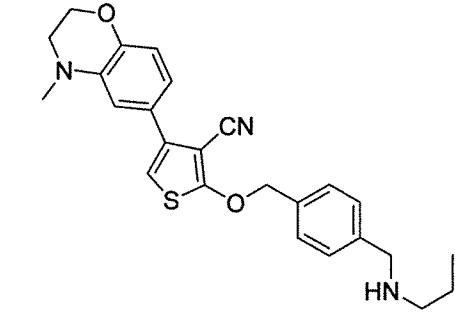
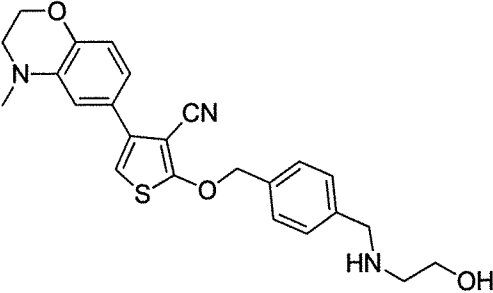
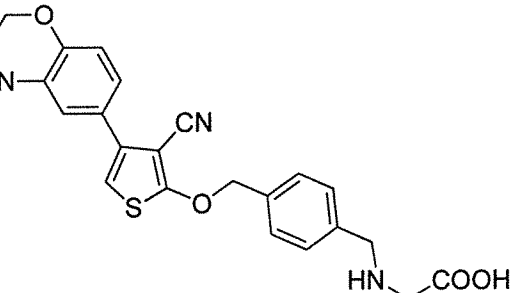
217	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	469.15	470.15
218	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((pyridin-3-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	469.15	470.16
219	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((1-methylpiperidin-4-yl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	475.19	476.22

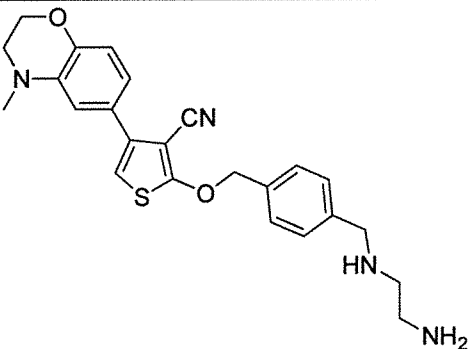
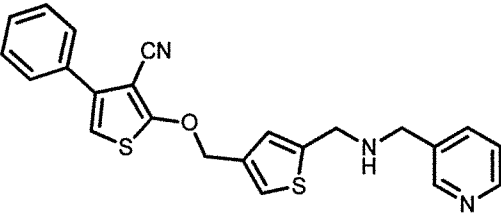
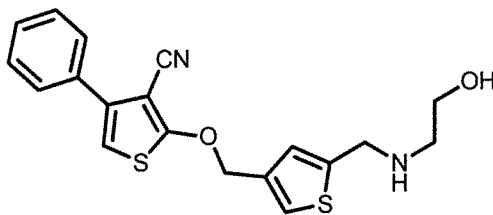
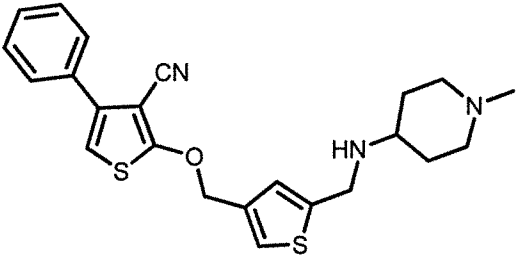
220	 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((4-(((2-morpholinoethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	491.19	492.22
221	 2-((4-((methylamino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	334.11	335.19
222	 4-phenyl-2-((4-((propylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	362.15	363.17
223	 2-((4-(((2-hydroxyethyl)amino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	364.12	365.12

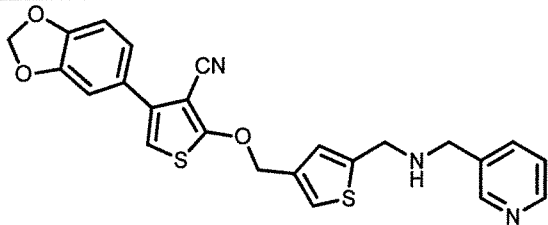
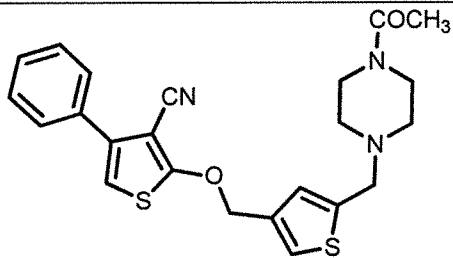
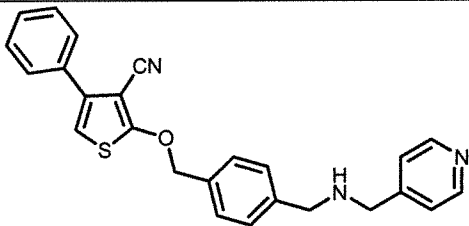
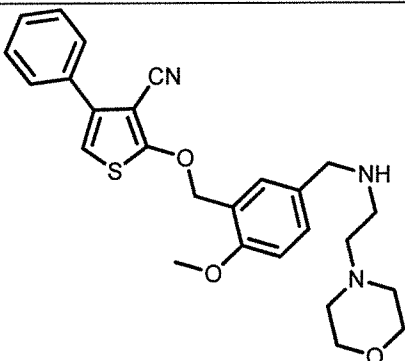
224	 2-((4-(((3-cyano-4-phenylthiophen-2-yl)oxy)methyl)benzyl)amino)acetic acid	378.10	379.11
225	 2-((4-(((2-aminoethyl)amino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	363.14	364.19
226	 4-(3,4-dichlorophenyl)-2-((4-((methylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	402.04	403.04
227	 4-(3,4-dichlorophenyl)-2-((4-((propylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	430.07	431.12

228	 4-(3,4-dichlorophenyl)-2-((4-(((2-hydroxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	432.05	433.20
229	 2-((4-(((3-cyano-4-(3,4-dichlorophenyl)thiophen-2-yl)oxy)methyl)benzyl)amino)acetic acid	446.03	447.06
230	 2-((4-(((2-aminoethyl)amino)methyl)benzyl)oxy)-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile	431.06	432.11
231	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-((methylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	378.10	379.12

232	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-((propylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	406.14	407.17
233	 4-(benzo[d][1,3]dioxol-5-yl)-2-((4-(((2-hydroxyethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	408.11	409.13
234	 2-(((4-(benzo[d][1,3]dioxol-5-yl)-3-cyanothiophen-2-yl)oxy)methyl)benzyl)amino)acetic acid	422.09	423.07
235	 2-(((4-(((2-aminoethyl)amino)methyl)benzyl)oxy)-4-(benzo[d][1,3]dioxol-5-yl)thiophene-3-carbonitrile	407.13	408.12

236	 4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-2-((4-((methylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	405.15	406.13
237	 4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-2-((4-((propylamino)methyl)benzyl)oxy)thiophene-3-carbonitrile	433.18	434.20
238	 2-((4-(((2-hydroxyethyl)amino)methyl)benzyl)oxy)-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carbonitrile	435.16	436.17
239	 2-((4-(((3-cyano-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophen-2-yl)oxy)methyl)benzyl)amino)acetic acid	449.14	450.11

240	 2-((4-(((2-aminoethyl)amino)methyl)benzyl)oxy)-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)thiophene-3-carbonitrile	434.18	435.20
241	 4-phenyl-2-((5-(((pyridin-3-ylmethyl)amino)methyl)thiophen-3-yl)methoxy)thiophene-3-carbonitrile	417.10	418.20
242	 2-((5-(((2-hydroxyethyl)amino)methyl)thiophen-3-yl)methoxy)-4-phenylthiophene-3-carbonitrile	370.08	371.11
243	 2-((5-(((1-methylpiperidin-4-yl)amino)methyl)thiophen-3-yl)methoxy)-4-phenylthiophene-3-carbonitrile	423.14	424.16

244	 4-(benzo[d][1,3]dioxol-5-yl)-2-((5-(((pyridin-3-ylmethyl)amino)methyl)thiophen-3-yl)methoxy)thiophene-3-carbonitrile	461.09	462.09
245	 2-((5-((4-acetylpiperazin-1-yl)methyl)thiophen-3-yl)methoxy)-4-phenylthiophene-3-carbonitrile	437.12	438.19
246	 4-phenyl-2-((4-(((pyridin-4-ylmethyl)amino)methyl)benzyl)oxy)thiophene-3-carbonitrile	411.14	412.19
247	 2-((2-methoxy-5-(((2-morpholinoethyl)amino)methyl)benzyl)oxy)-4-phenylthiophene-3-carbonitrile	463.19	464.19

Screening:

Expression and purification of recombinant PD-L1, PD-L2 and PD-1

The gene encoding human PD-L1 (amino acids 18-134) was cloned into the pET-21b, the gene encoding human PD-L2 (20-220) was cloned into pET28a and that of human PD-1 (33-150, Cys93 exchanged to serine) into pET-24d. Proteins were expressed in the E. coli BL21 (DE3). Cells were cultured in LB at 37°C. The protein production was induced with 1 mM IPTG at OD600 of 1.0 and the cells were cultured for additional 5h. For hPD-1, after induction the temperature was lowered to 30°C. Proteins were expressed as inclusion bodies which were collected by centrifugation, washed twice with 50 mM Tris-HCl pH 8.0 containing 200 mM NaCl, 0.5% Triton X-100, 10 mM EDTA and 10 mM 2-mercaptoethanol and once more with the same buffer with no detergent. The inclusion bodies were stirred overnight in 50 mM Tris pH 8.0 containing 6M GuHCl, 200 mM NaCl and 10 mM 2-mercaptoethanol. Solubilized fraction was clarified by high speed centrifugation. hPD-L1 and hPD-L2 were refolded by drop-wise dilution into 0.1 M Tris pH 8.0 containing 1 M L-Arg hydrochloride, 0.25 mM oxidized glutathione and 0.25 mM reduced glutathione for hPD-L1 and 0.1 M Tris pH 8.5 containing 1 M NDSB201, 0.2 M NaCl, 5 mM cysteamine and 0.5 mM cystamine for hPD-L2. hPD-1 was refolded in similar manner in 0.1 M Tris pH 8.0 containing 0.4 M L-Arg hydrochloride, 2 mM EDTA, 5 mM cystamine and 0.5 mM cysteamine. After refolding, the proteins were dialyzed 3 times against 10 mM Tris pH 8.0 containing 20 mM NaCl, and purified by size exclusion chromatography on Superdex 75 (GE Healthcare) in 10 mM Tris pH 8.0 containing 20 mM NaCl. The purity and protein folding were evaluated by SDS-PAGE and NMR, respectively.

Analytical size-exclusion chromatography

The oligomeric state of tested proteins was analyzed by size exclusion chromatography. Superdex 75 10/30 HR (GE Healthcare) was equilibrated with PBS pH 7.4 and calibrated using globular proteins of known molecular weight. Approximate molecular weight of apo-hPD-L1 and hPD-L1-small molecule complex (3:1 compound: protein molar ratio) were estimated using the calibration curve.

Differential scanning fluorimetry (DSF)

DSF analysis was performed according to Niesen and colleagues (24). In brief hPD-L1 and hPD-L2 (both 12.5 μ M) were incubated alone, with compound BMS-202 or compound 8 (both at 37.5 μ M) in the presence of SYPRO Orange Dye (Life Technologies, final concentration 20x). Constant temperature gradient of 0.2°C/min was applied and changes in fluorescence were monitored using real time thermocycler (BioRad). Melting temperature (T_m) was estimated from first derivative of fluorescence intensity as a function of temperature.

NMR methods

Uniform ^{15}N labeling was obtained by expressing the protein in the M9 minimal medium containing $^{15}\text{NH}_4\text{Cl}$ as the sole nitrogen source. Unlabeled proteins were prepared as for crystallization. For NMR measurements the buffer was exchanged by gel filtration to PBS pH 7.4 (hPD-L1) or 25 mM sodium phosphate containing 100 mM NaCl pH 6.4 (hPD-1). 10% (v/v) of D_2O was added to the samples to provide lock signal. All spectra were recorded at 300K using a Bruker Avance 600 MHz spectrometer.

Binding of the compounds was analyzed by titrating the ^{15}N -labeled PD-L1 (0.3 mM) and recording the ^1H - ^{15}N HMQC spectra prior and after addition of the compound (Supplementary Figs. S1, S2 and S3).

The ability of tested compounds to dissociate hPD-L1 / hPD-1 was evaluated using AIDA (27). ^{15}N -labeled hPD-1 (0.2 mM) was slightly overtitrated with unlabeled hPD-L1. Compound was aliquoted into the resulting mixture. During the experiment the ^1H - ^{15}N signals were monitored by HMQC experiment.

Changes in the oligomeric state of hPD-L1 in the presence of tested compounds were monitored by titration of unlabeled hPD-L1 (0.3 mM) while recording ^1H spectra prior and after addition of the compound. The approximate molecular weights of protein populations present in the sample were determined by analyzing the linewidth (relaxation time) of well separated NMR signals.

All compounds showed activity (IC_{50}) in the range of from 0.001 to 1000 μM .

Screening for PD-L1 binders using Microscale Thermophoresis

MST (Microscale Thermophoresis) using the Monolith NT.115 (NanoTemper technologies, München) is a technique that allows measuring of the interaction between biomolecules and the designed inhibitors. It can be used in several ways in the hit discovery and lead identification process. It can be used to determine if the designed compounds show binding to PD-L1 and determine their K_D for PD-L1. In addition, it allows measuring of the dissociation of the PD1/PD-L1 complex upon addition of

the compounds and it permits rapid screening of compounds using two point measurements.

Protein preparation, labeling and compound preparation:

Refolded PD-L1 and PD-1 proteins were used for all experiments. The PD-1 construct is a 13.2 kDa protein. While PD-L1 is 14.5 kDa containing a His6-tag. Labeling of PD-L1 can be performed in several ways, for example, by attaching a fluorescent label to free amine groups, cysteine's or by binding to the His6-tag. PD-L1 was labeled using the Monolith NTtm His-tag labeling kit RED-tris-NTA (Nano technologies, München). The RED-tris-NTA dye (100 nm) was mixing with PD-L1 (200 nM) in a 1:1 ratio and incubated for 30 min at room temperature followed by centrifugation at 13k rpm for 15 min. Binding of the dye to the PD-L1 His6-tag was confirmed by measuring the KD (~8 nm).

Compound stocks were prepared at 100 mM in 100% DMSO and were subsequently diluted in PBS-t buffer to a concentration of 2-0.25 mM, depending on their solubility, while keeping the DMSO concentration at 2%.

PD-L1 vs compounds:

For determining affinity of the test compounds to PD-L1 a 2-fold dilution series was made using the compound stocks and dilution with PBS-t buffer with 2% DMSO. The labeled PD-L1 was added to a final concentration of 50 nm and the samples were loaded into Monolith NT115 standard treated capillaries (NanoTemper technologies, München) and measured using the Monolith NT.115. The obtained binding curves were analyzed using the MO. Affinity analysis software (NanoTemper technologies, München).

Dissociation of the PD-1/ PD-L1 complex:

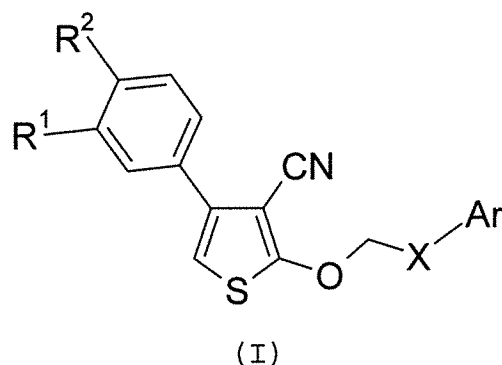
The PD-1/PD-L1 complex is prepared by mixing PD-L1 and PD-1 in a 1:10 ratio the complex was labeled as described above for PD-L1. The dissociation of the PD-1/ PD-L1 complex is measured by adding the labeled complex to a final PD-L1 concentration of 50 nM to a 2-fold dilution series of the compound and measuring using the Monolith NT.115.

Screening of compounds using two point measurements:

Rapid screening of PD-L1 binding without a full KD determination is also possible using MST. This requires preparation of two samples, one at low compound concentration and one at high compound concentration. If the MST measurements show a significant change in fluorescence signal between the two samples after the temperature jump it is a good indication if the compound is binding or not. Subsequently, a full KD determination as described above can be performed on the hits.

Claims

1. A compound of formula (I):



wherein

R^1 is a hydrogen atom or a halogen atom; and

R^2 is a hydrogen atom or a halogen atom; or

R^1 and R^2 together are a group of formula $-O-CH_2-CH_2-O-$, $-O-CH_2-CH_2-N(Me)-$, $-N(Me)-CH_2-CH_2-O-$, $-O-CF_2-O-$ or $-O-CH_2-O-$;

X is a bond, an oxygen atom or a group of formula $-C(=O)-$, or $-(CH_2)_n-$ wherein n is 1, 2 or 3 or a group of formula $-(CH_2)_m-O-$ wherein m is 2, 3 or 4; and

Ar is a phenyl group, a naphthyl group or a heteroaryl group containing 1 or 2 rings and from 5 to 10 ring atoms selected from C, O, N and S, wherein Ar may be substituted by 1, 2, 3, 4 or 5 groups R^3 and/or wherein Ar may be substituted by a group of formula $-CH_2-N(R^4)-R^5$;

the groups R^3 are independently from each other halogen, NO_2 , N_3 , OH , SH , NH_2 or an alkyl, alkenyl, alkynyl, hetero-

alkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted;

R⁴ is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted; and

R⁵ is a hydrogen atom or an alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl group; all of which groups may optionally be substituted; or

R⁴ and R⁵ together with the nitrogen atom to which they are bound are part of an optionally substituted heterocycloalkyl group containing 5, 6 or 7 ring atoms;

or a pharmaceutically acceptable salt, ester, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

2. A compound according to claim 1, wherein R¹ and R² together are a group of formula -O-CH₂-CH₂-O- or -O-CH₂-O-; or wherein R¹ and R² are both hydrogen atoms; or wherein R¹ and R² are both chlorine atoms.
3. A compound according to claim 1 or 2, wherein X is a bond.

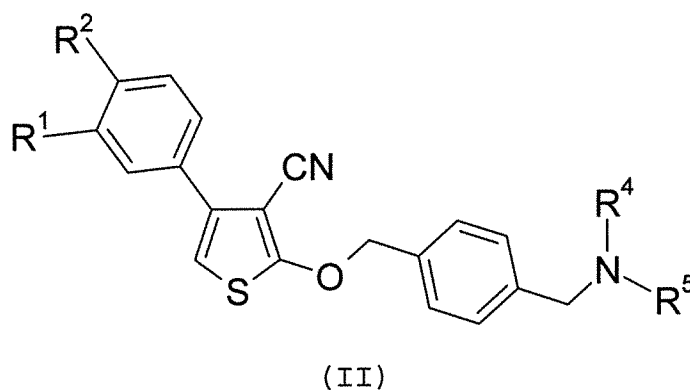
4. A compound according to any one of the preceeding claims, wherein Ar is a phenyl group or a heteroaryl group containing one ring and 5 or 6 ring atoms selected from C, O, N and S, wherein Ar may be substituted by 1, 2, 3, 4 or 5 groups R³ and/or wherein Ar may be substituted by a group of formula -CH₂-N(R⁴)-R⁵.
5. A compound according to any one of the preceeding claims, wherein, Ar is substituted by one or two groups R³.
6. A compound according to any one of the preceeding claims, wherein the groups R³ are independently halogen, NO₂, N₃, OH, SH, NH₂ or a C₁-C₆ alkyl group; a C₁-C₆ heteroalkyl group; a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N; an alkylcycloalkyl group containing a C₁-C₆ alkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heteroalkylcycloalkyl group containing a C₁-C₆ alkyl group or a C₁-C₆ heteroalkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms or a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N with the proviso that a heteroalkylcycloalkyl group contains at least one heteroatom; a phenyl group; a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N; an aralkyl group containing a C₁-C₆ alkyl group and a phenyl group; or a heteroaralkyl group containing a C₁-C₆ alkyl group or a C₁-C₆ heteroalkyl group and a phenyl group or a heteroaryl group containing

5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N with the proviso that a heteroaralkyl group contains at least one heteroatom; all of which groups may optionally be substituted.

7. A compound according to any one of the preceeding claims, wherein Ar is substituted by a group of formula $-\text{CH}_2-\text{N}(\text{R}^4)-\text{R}^5$.
8. A compound according to any one of the preceeding claims, wherein R^4 is a hydrogen atom and R^5 is a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl group; a $\text{C}_1\text{-C}_6$ heteroalkyl group; a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N; an alkylcycloalkyl group containing a $\text{C}_1\text{-C}_6$ alkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms; a heteroalkylcycloalkyl group containing a $\text{C}_1\text{-C}_6$ alkyl group or a $\text{C}_1\text{-C}_6$ heteroalkyl group and a cycloalkyl group containing one ring having from 3 to 7 ring atoms or a heterocycloalkyl group containing one ring having from 3 to 7 ring atoms comprising 1 or 2 heteroatoms selected from S, O and N with the proviso that a heteroalkylcycloalkyl group contains at least one heteroatom; a phenyl group; a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms selected from O, S and N; an aralkyl group containing a $\text{C}_1\text{-C}_6$ alkyl group and a phenyl group; or a heteroaralkyl group containing a $\text{C}_1\text{-C}_6$ alkyl group or a $\text{C}_1\text{-C}_6$ heteroalkyl group and a phenyl group or a heteroaryl group containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 heteroatoms

selected from O, S and N with the proviso that a heteroaralkyl group contains at least one heteroatom; all of which groups may optionally be substituted.

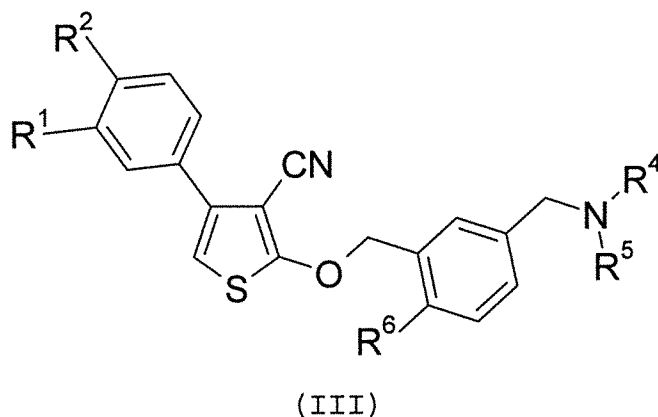
9. A compound according to any one of the preceeding claims, wherein R^4 and R^5 together with the nitrogen atom to which they are bound are part of a heterocycloalkyl group containing 5, 6 or 7 ring atoms and optionally one further heteroatom selected from O and N, which heterocycloalkyl group may be substituted.
10. A compound according to any one of claims 1, 2, 8 and 9 of formula (II):



wherein R^1 , R^2 , R^4 and R^5 are as defined above.

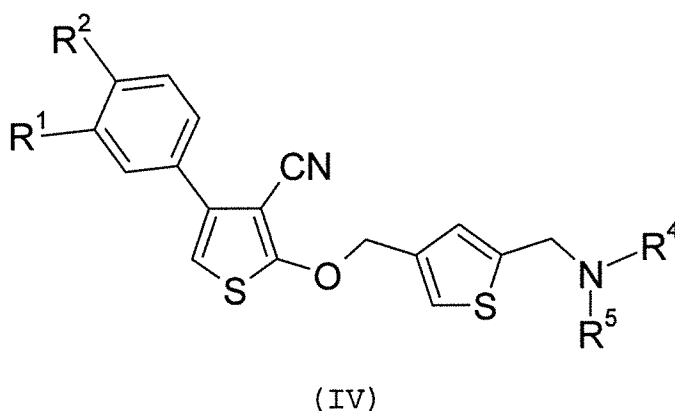
11. A compound according to any one of claims 1, 2, 8 and 9 of formula (III):

125



wherein R¹, R², R⁴ and R⁵ are as defined above and R⁶ is H or OMe.

12. A compound according to any one of claims 1, 2, 8 and 9 of formula (IV):



wherein R¹, R², R⁴ and R⁵ are as defined above.

13. A pharmaceutical composition comprising a compound according to anyone of the preceding claims or a pharmaceutically acceptable ester, prodrug, hydrate, solvate or salt thereof, optionally in combination with a pharmaceutically acceptable carrier.

14. Use of a compound or a pharmaceutical composition according to anyone of the preceding claims for the preparation of a medicament for the treatment of cancer, viral diseases and infectious diseases and neurodegenerative diseases such as: Schizophrenia, Alzheimer, Multiples Sclerosis, Parkinson, Corea Huntington, Spinocerebellar ataxia type 1 (SCA1), Amyotrophic lateral sclerosis, Batten disease.
15. A compound or a pharmaceutical composition according to anyone of claims 1 to 13 for use in the treatment of cancer, viral diseases and infectious diseases and neurodegenerative diseases such as Schizophrenia, Alzheimer, Multiples Sclerosis, Parkinson, Corea Huntington, Spinocerebellar ataxia type 1 (SCA1), Amyotrophic lateral sclerosis, Batten disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/068411

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D333/38 C07D409/04 C07D409/12 C07D409/14 C07D413/04
C07D413/14 C07D417/12 C07D417/14 A61K31/381 A61P35/00
A61P31/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. GEWALD ET AL: "3-Amino-thieno[2,3-b]furane und 3-Amino-thieno[3,2-b]furane", JOURNAL FÜR PRAKTISCHE CHEMIE, vol. 325, no. 3, 1983, pages 457-462, XP055399969, ISSN: 0021-8383, DOI: 10.1002/prac.19833250315 compounds 2a, 2b ----- -/-	1,2,4-6, 8,9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 August 2018

Date of mailing of the international search report

27/08/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/068411

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TRYFON ZARGANES-TZITZIKAS ET AL: "Inhibitors of programmed cell death 1 (PD-1): a patent review (2010-2015)", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 26, no. 9, 2016, pages 973-977, XP055394015, ISSN: 1354-3776, DOI: 10.1080/13543776.2016.1206527 the whole document figures 1, 2 -----	1-15
A	KRZYSZTOF M. ZAK ET AL: "Structural basis for small molecule targeting of the programmed death ligand 1 (PD-L1)", ONCOTARGET, vol. 7, no. 21, 2016, pages 30323-30335, XP055378141, DOI: 10.18632/oncotarget.8730 the whole document figure 1 -----	1-15