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(54) Title:

**DI - SUBSTITUTED PYRIDINE DERIVATIVES AS
ANTICANCERS**

(57) Abstract:

The present invention provides a novel compound having an excellent antitumor effect. The compound of the present invention is represented by the following general formula (1) wherein R1 and R2 are aryl or the like; A is lower alkylene; Ring X is optionally substituted arylene; E is bond or lower alkenylene; Ring Y is optionally substituted heterocycloalkylene containing one or more nitrogen atoms, one of which is attached to the adjacent carbonyl group; G is -NH-G2-, -N(lower alkyl)-

G2-, -NH-CH₂-G2-, -N(lower alkyl)-CH₂-G2- or -CH₂-G2-, [wherein G2 binds to R₂, G2-R₂ is bond-R₂, phenylene-G3-R₂, phenylene-G4-O-R₂, phenylene-G5-NH-R₂, phenylene-G6-N(lower alkyl)-R₂ or quinolinediyl-O-R₂, the phenylene of said phenylene-containing groups being optionally substituted with one or more substituents; G3-R₂ is -O-lower alkylene-R₂ or the like; G4-O- is lower alkylene-O- or the like; G5 is lower alkylene; G6 is lower alkylene].



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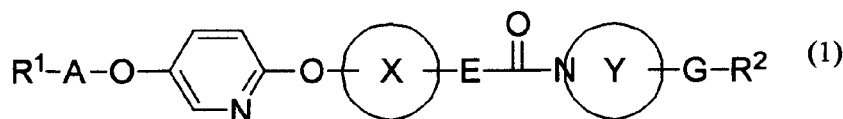
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[Continued on next page]

(54) Title: DI - SUBSTITUTED PYRIDINE DERIVATIVES AS ANTICANCERS



(57) Abstract: The present invention provides a novel compound having an excellent antitumor effect. The compound of the present invention is represented by the following general formula (1) wherein R¹ and R² are aryl or the like; A is lower alkylene; Ring X is optionally substituted arylene; E is bond or lower alkenylene; Ring Y is optionally substituted heterocycloalkylene containing one or more nitrogen atoms, one of which is attached to the adjacent carbonyl group; G is -NH-G₂-, -N(lower alkyl)-G₂-, -NH-CH₂-G₂-, -N(lower alkyl)-CH₂-G₂- or -CH₂-G₂-, [wherein G₂ binds to R², G₂-R² is bond-R², phenylene-G₃-R², phenylene-G₄-O-R², phenylene-G₅-NH-R², phenylene-G₆-N(lower alkyl)-R² or quinolinediyl-O-R², the phenylene of said phenylene-containing groups being optionally substituted with one or more substituents; G₃-R² is -O-lower alkylene-R² or the like; G₄-O- is lower alkylene-O- or the like; G₅ is lower alkylene; G₆ is lower alkylene].

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DESCRIPTION

DI - SUBSTITUTED PYRIDINE DERIVATIVES AS ANTICANCERS

TECHNICAL FIELD

[0001]

The present invention relates to a heterocyclic compound.

BACKGROUND ART

5 [0002]

Since the clinical use of nitrogen mustard as an anticancer agent in the 1940s for the first time in the world, numerous anticancer drugs have ever been developed. Actually, for example, antimetabolites such as 5-fluorouracil, antitumor antibiotics such as adriamycin, platinum complex such as cisplatin, and plant-derived carcinostatics such as vindesine have been

10 subjected to clinical use.

[0003]

However, most of these carcinostatics have significant side effects such as digestive disorders, myelosuppression and alopecia since they are cytotoxic also to normal cells. Due to the side effects, their range of application is limited. In addition, the therapeutic effects

15 themselves are partial and short, in most cases.

[0004]

Developments of new carcinostatics in place of these has been made; however, satisfactory results have not yet been obtained. Patent Documents 1, 2, 3 and 4 disclose that certain kinds of compounds have fibrosing inhibitory actions, antitumor actions and STAT3/5

20 activation inhibitory actions, respectively. However, it is not known whether the specific compounds of the present invention have an antitumor effect.

CITATION LIST

PATENT LITERATURE

[0005]

25 [Patent Document 1] WO/2006/014012

[Patent Document 2] WO/2007/066784

[Patent Document 3] WO/2008/044667

[Patent Document 4] WO/2009/057811

SUMMARY OF INVENTION

30 TECHNICAL PROBLEM

[0006]

An object of the present invention is therefore to provide a compound which has an antitumor effect with less side effects, and excellent safety.

SOLUTION TO PROBLEM

5 [0007]

The present inventors intensively conducted studies with the view to attaining the aforementioned object. As a result, they found that a compound represented by the general formula (1) below and a salt thereof have an excellent anti-proliferative activity with less side effects, and excellent safety, and therefore they are useful as a medical drug for treating or

10 preventing various cancer types. Examples of the cancer include sex-steroid hormone related cancer (for example, prostate cancer, breast cancer, ovarian cancer, uterine cancer, testicular cancer) and solid cancer (for example, lung cancer, colon cancer, bladder cancer, thyroid cancer, esophageal cancer, liver cancer). The present invention has been achieved based on the finding.

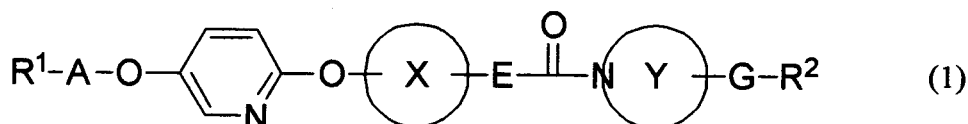
[0008]

15 More specifically, the present invention provides a heterocyclic compound shown in the following items:

[0009]

Item 1. A compound represented by the following general formula (1) or a salt thereof;

[Formula 1]



20 wherein

R^1 and R^2 are each independently aryl or unsaturated heterocyclic ring, each of which is optionally substituted with one or more substituents,

A is lower alkylene,

Ring X is optionally substituted arylene,

25 E is bond or lower alkenylene,

the partial structural formula:



is optionally substituted heterocycloalkylene containing one or more nitrogen atoms, one of which is attached to the adjacent carbonyl group,

G is -NH-G₂-, -N(lower alkyl)-G₂-, -NH-CH₂-G₂-, -N(lower alkyl)-CH₂-G₂- or -CH₂-G₂-,

wherein G₂ of said G binds to R²,

5 G₂-R² is bond-R², phenylene-G₃-R², phenylene-G₄-O-R², phenylene-G₅-NH-R², phenylene-G₆-N(lower alkyl)-R² or quinolinediyl-O-R², wherein the phenylene of said phenylene-G₃-R², phenylene-G₄-O-R², phenylene-G₅-NH-R² and phenylene-G₆-N(lower alkyl)-R² is optionally substituted with one or more substituents selected from the group consisting of halogen and lower alkyl,

10 G₃-R² is bond-R², -O-lower alkylene-R², lower alkylene-O-lower alkylene-R² or -O-lower alkylene-CO-R²,

G₄-O- is bond-O-, lower alkylene-O-, lower alkenylene-O-, -O-lower alkylene-O- or -CO-lower alkylene-O-,

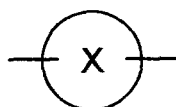
G₅ and G₆ are each lower alkylene.

[0010]

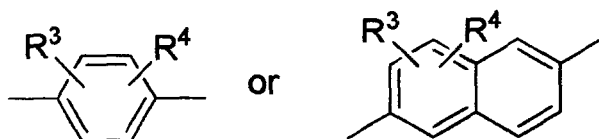
15 Item 2. The compound according to Item 1 or a salt thereof, wherein

R¹ is phenyl, pyridyl, benzothiazolyl or thiazolyl, each of which is optionally substituted with one or more substituents,

the partial structural formula:



20 is the following formula:



wherein R³ and R⁴ are the same or different, and are each independently hydrogen, halogen, lower alkyl or lower alkoxy,

the partial structural formula:



25 is piperazinediyl, piperidinediyl, pyrrolidinediyl, diazepanediyl or oxadiazepanediyl, each of which is optionally substituted with one or more substituents, and

R^2 is:

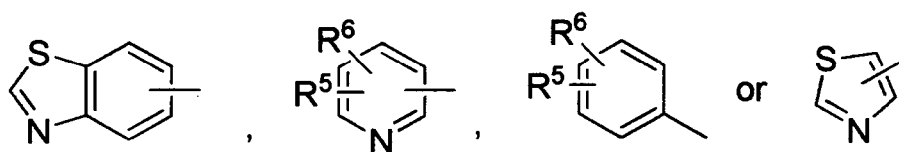
(i) aryl which may be substituted with one or more substituents selected from the group consisting of halogen, cyano, nitro, methylenedioxy, trimethylene, tetramethylene, pyrrolyl, lower alkyl carbonyl, lower alkyl sulfonyl, lower alkyl which may be substituted with one or more halogen, lower alkoxy which may be substituted with one or more halogen, cyclo lower alkyl, lower alkoxy lower alkyl, lower alkenyl, hydroxy lower alkenyl, lower alkoxy lower alkenyl, hydroxy lower alkyl, amino which may be substituted with one or more lower alkyl, and hydroxy lower alkoxy,

(ii) unsaturated heterocyclic ring which may be substituted with one or more substituents selected from the group consisting of halogen, lower alkyl which may be substituted with one or more halogen, and lower alkoxy.

[0011]

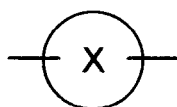
Item 3. The compound according to Item 2 or a salt thereof;
wherein

R^1 is the following formula:

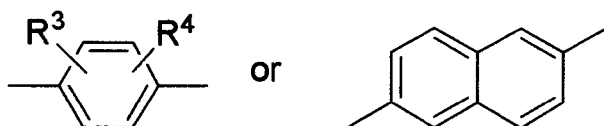


wherein R^5 and R^6 are the same or different, and are each independently hydrogen, halogen, cyano, nitro, lower alkoxy which may be substituted with one or more halogen, or lower alkyl which may be substituted with one or more halogen,

the partial structural formula:

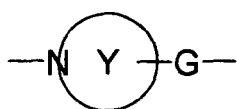


is the following formula:

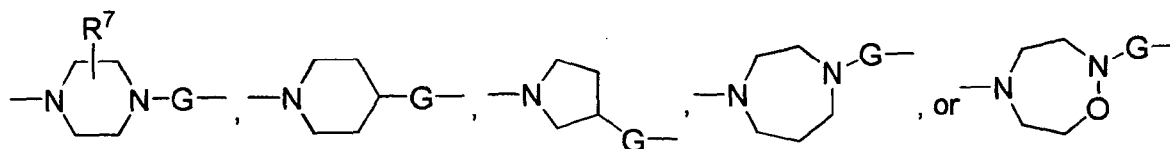


and,

the partial structural formula:



is the following formula:



wherein R^7 is hydrogen or lower alkyl.

[0012]

Item 4. The compound according to Item 3 or a salt thereof;

5 wherein

R^2 is:

(i) phenyl which may be substituted with one or more substituents selected from the group consisting of halogen, cyano, nitro, methylenedioxy, trimethylene, tetramethylene, pyrrolyl, lower alkyl carbonyl, lower alkyl sulfonyl, lower alkyl which may be substituted with one or more halogen, lower alkoxy which may be substituted with one or more halogen, cyclo lower alkyl, lower alkoxy lower alkyl, lower alkenyl, hydroxy lower alkenyl, lower alkoxy lower alkenyl, hydroxy lower alkyl, amino which may be substituted with one or more lower alkyl, and hydroxy lower alkoxy,

(ii) naphthyl,

(iii) pyridyl which may be substituted with one or more substituents selected from the group consisting of halogen, lower alkyl which may be substituted with one or more halogen, and lower alkoxy,

(iv) benzoxazolyl which may be substituted with one or more halogen,

(v) benzothiazolyl which may be substituted with one or more lower alkyl, or

(vi) quinolyl.

[0013]

Item 5. The compound according to Item 4 or a salt thereof;

wherein

G is $-NH-G_2-$, $-N(\text{lower alkyl})-CH_2-G_2-$ or $-CH_2-G_2-$,

wherein G_2 of said G binds to R^2 ,

G_2-R^2 is phenylene- G_3-R^2 , phenylene- G_4-O-R^2 , phenylene- G_5-NH-R^2 , phenylene- $G_6-N(\text{lower alkyl})-R^2$ or quinolinediyl- $O-R^2$, wherein the phenylene of said phenylene- G_3-R^2 ,

phenylene-G₄-O-R², phenylene-G₅-NH-R² and phenylene-G₆-N(lower alkyl)-R² is optionally substituted with one or more substituents selected from the group consisting of halogen and lower alkyl.

[0014]

- 5 Item 6. The compound according to Item 4 or a salt thereof, wherein G is methylene.

[0015]

Item 7. The compound according to Item 1 or a salt thereof, which is selected from the group consisting of:

- (2E)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-
 10 (4-{4-[(1E)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one,
 4-{2-[4-({4-[(E)-3-{3-chloro-5-methyl-4-[(5-{[4-
 (trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoyl]piperazin-1-
 15 yl}{methyl}phenyl]ethoxy}benzonitrile,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
 20 (E)-3-{3-chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-
 yl)oxy]phenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-1-[4-(4-{2-[4-(4-chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-
 25 dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one,
 (E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[(3S)-4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}-3-methylpiperazin-1-yl]prop-2-en-1-one,
 30 4-[(6-{4-[(E)-3-(2-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-
 5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile,
 (2E)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-
 {3-methyl-4-[(1E)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-

- 1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
5 methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
10 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
15 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
20 (*E*)-3-[3-chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-
one,
(*E*)-3-(3-chloro-5-methyl-4-{{5-(pyridin-3-yl)methoxy}pyridin-2-yl}oxy)phenyl)-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
25 (*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
30 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

5 (E)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[3-chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

10 (E)-3-[3-chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

15 [6-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone,

4-({6-({4-[(E)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,

20 4-({6-(2-fluoro-4-({(E)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl)oxy)methyl}benzonitrile,

(E)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

25 (E)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

30 (E)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-

(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 4-[[6-{2-chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy]methyl}benzonitrile,

5 4-[[6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]-3-fluorobenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy]methyl}benzonitrile,

4-([6-(4-{(*E*)-3-[4-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile,

10 4-[[6-{2-chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl]oxy]methyl}benzonitrile,

4-[[6-{2-chloro-6-methyl-4-[(*E*)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy]methyl}benzonitrile,

15 4-([6-(2-chloro-4-{(*E*)-3-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile,

4-[[6-{2-chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl]oxy]methyl}benzonitrile

20 4-([6-(2,6-dimethyl-4-{(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl]phenoxy)pyridin-3-yl]oxy}methyl}benzonitrile,

(*E*)-3-(3,5-dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

25 4-([6-(4-{(1*E*)-3-[4-(4-{(1*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2-chloro-6-methylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile,

4-([6-(2-chloro-4-{(*E*)-3-[4-(4-{2-[4-methoxyphenyl]amino}ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]phenoxy)pyridin-3-yl]oxy}methyl}benzonitrile,

30 (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-

yl)oxy]phenyl}-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,
 4-{{(6-{4-[(*E*)-3-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 5 2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one,
 10 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-
 15 (3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-1-[4-(4-chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 20 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one, and
 (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one.

[0016]

- 25 Item 8. The compound according to Item 1, which is selected from the group consisting of:

(2*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 30 1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one,
 4-{2-[4-({4-[(*E*)-3-{3-chloro-5-methyl-4-[(5-{4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoyl]piperazin-1-yl}methyl)phenyl]ethoxy}benzonitrile,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-

1-(4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
 (*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-
 5 yl)oxy]phenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (*E*)-1-[4-(4-{2-[(4-chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-
 dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-[(3*S*)-4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}-3-methylpiperazin-1-yl]prop-2-en-1-one,
 4-[(6-{4-[(*E*)-3-(2-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-
 5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile,
 (2*E*)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-
 {3-methyl-4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
 hydrochloride,
 (*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
 methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
 hydrochloride,
 (*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
 methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
 hydrochloride,
 (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
 1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

5 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-
one hydrochloride,

10 (E)-3-(3-chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

15 (E)-3-[3-chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

20 (E)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

25 (E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(E)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-
[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

30 (E)-3-[3-chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
hydrochloride,

(E)-3-[3-chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
hydrochloride,

(E)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-

- {2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
[6-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-
5 (propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone hydrochloride,
4-{{(6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-
oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,
4-{{(6-(2-fluoro-4-{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-
yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-
10 yl)oxy)methyl}benzonitrile hydrochloride,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-
(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-
[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,
15 (*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-
(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-
[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-
20 (4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,
(*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-
(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
25 hydrochloride,
4-{{(6-{2-chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{{5-(trifluoromethyl)pyridin-
2-yl}oxy}ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-
yl)oxy)methyl}benzonitrile hydrochloride,
4-{{(6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]-3-fluorobenzyl}piperazin-1-
30 yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile
hydrochloride,
4-{{(6-(4-{(*E*)-3-[4-(2-fluoro-4-{2-[4-
(trifluoromethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl)-2,6-
dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

4-{{(6-{2-chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

5 4-{{(6-{2-chloro-6-methyl-4-[(*E*)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

4-{{(6-{2-chloro-4-[(*E*)-3-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

10 4-{{(6-{2-chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

4-{{(6-{2,6-dimethyl-4-[(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

15 (*E*)-3-(3,5-dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

4-{{(6-{4-[(1*E*)-3-[4-(4-{(1*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2-chloro-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

20 4-{{(6-{2-chloro-4-[(*E*)-3-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile dihydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

30 4-{{(6-{4-[(*E*)-3-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide,

(*E*)-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one hydrobromide,

5 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one ethanedioate,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one ethanedioate,

10 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-1-[4-(4-chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

15 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride, and

(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride.

[0017]

20 Item 9. A pharmaceutical composition comprising a compound represented by the general formula (1) or a salt thereof according to Item 1, and a pharmacologically acceptable carrier.

[0018]

Item 10. A pharmaceutical composition according to Item 9 for preventing and/or treating cancer.

25 [0019]

Item 11. A compound represented by the general formula (1) or a salt thereof according to Item 1 for use in the pharmaceutical composition.

[0020]

30 Item 12. Use of a compound represented by the general formula (1) or a salt thereof according to Item 1 as a pharmaceutical composition.

[0021]

Item 13. Use of a compound represented by the general formula (1) or a salt thereof according to Item 1 for the production of a pharmaceutical composition.

[0022]

Item 14. A method of preventing and/or treating cancer, comprising administering to a patient a compound represented by the general formula (1) or a salt thereof according to Item 1. [0023]

Specific examples of individual groups shown in the general formula (1) are as follows. [0024]

Examples of the "lower alkoxy" include linear or branched alkoxy groups having 1 to 6 carbon atoms and cycloalkylalkoxy groups having 4 to 7 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, cyclopropylmethoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy groups. [0025]

Examples of the "lower alkyl" include linear or branched alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, 2,2-dimethylpropyl, 1-ethylpropyl, butyl, isobutyl, *tert*-butyl, isopentyl, pentyl, cyclopropylmethyl, and hexyl groups. [0026]

Examples of the "cyclo lower alkyl" include cyclo alkyl groups having 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. [0027]

Examples of the "halogen" are fluorine, chlorine, bromine, and iodine. [0028]

Examples of the "lower alkylene" include linear or branched alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, 1-methylethylene, 2-methylethylene, trimethylene, 2-methyltrimethylene, 2,2 dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, dimethylmethylene, tetramethylene, pentamethylene, and hexamethylene. [0029]

Examples of the "lower alkenylene" include linear or branched alkenylene group having 1 to 3 double bonds and 2 to 6 carbon atoms such as vinylene, 1-methylvinylene, 2-methylvinylene, 1,2-dimethylvinylene, 1-propenylene, 1-methyl-1-propenylene, 2-methyl-1-propenylene, 2-propenylene, 2-butenylene, 1-butenylene, 3-butenylene, 2-pentenylene, 1-pentenylene, 3-pentenylene, 4-pentenylene, 1,3-butadienylene, 1,3-pentadienylene, 2-penten-4-ynylene, 2-hexenylene, 1-hexenylene, 5-hexenylene, 3-hexenylene, 4-hexenylene, 3,3-dimethyl-1-propenylene, 2-ethyl-1-propenylene, 1,3,5-hexatrienylene, 1,3-hexadienylene, and 1,4-hexadienylene.

[0030]

Examples of the “unsaturated heterocyclic ring” include unsaturated monocyclic or bicyclic heterocyclic ring containing at least one hetero atom selected from among oxygen, sulfur and nitrogen. Examples of preferable unsaturated heterocyclic ring include the following

5 (a) to (i):

(a) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic ring containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, and its N-oxide, tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4*H*-1,2,4-triazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1*H*-tetrazolyl, 2*H*-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5- dihydro-1,2,4-triazinyl, etc.), etc.;

(b) unsaturated condensed 7 to 12-membered heterocyclic rings containing 1 to 3 oxygen atoms, for example, benzofuranyl, dihydrobenzofuranyl(e.g. 2,3-dihydrobenzo[*b*]furanyl, etc.), chromanyl, benzodioxanyl (e.g., 1,4-benzodioxanyl, etc.), benzodioxolyl (benzo[1,3]dioxolyl, etc.), etc.;

(c) unsaturated condensed 7 to 12-membered heterocyclic rings containing 1 to 5 nitrogen atoms, for example, decahydroquinolyl, indolyl, dihydroindolyl (e.g., 2,3-dihydroindolyl, etc.), isoindolyl, indolizinyl, benzimidazolyl, dihydrobenzimidazolyl (e.g., 2,3-dihydro-1*H*-benzo[*d*]imidazolyl, etc.), quinolyl, dihydroquinolyl (e.g. 1,4-dihydroquinolyl, 1,2-dihydroquinolyl, etc.), tetrahydroquinolyl (1,2,3,4-tetrahydroquinolyl, etc.), isoquinolyl, dihydroisoquinolyl (e.g., 3,4-dihydro-1*H*-isoquinolyl, 1,2-dihydroisoquinolyl, etc.), tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1*H*-isoquinolyl, 5,6,7,8-tetrahydroisoquinolyl, etc.), carbostyryl, dihydrocarbostyryl (e.g., 3,4- dihydrocarbostyryl, etc.), indazolyl, benzotriazolyl (e.g. benzo[*d*][1,2,3]triazolyl, etc.), tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-*b*]pyridazinyl, etc.), dihydrotriazolopyridazinyl, imidazopyridyl (e.g., imidazo[1,2-*a*]pyridyl, imidazo[4,5-*c*]pyridyl, imidazo[1,5-*a*]pyridyl, etc.), naphthyridinyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolopyridyl (e.g., pyrazolo[2,3-*a*]pyridyl, etc.), tetrahydropyridoindolyl (e.g., 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indolyl, etc.), etc.;

(d) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4- oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

(e) unsaturated condensed 7 to 12-membered heterocyclic rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzisoxazolyl, dihydrobenzoxazinyl (e.g., 2,3-dihydrobenz-1,4-oxazinyl, etc.), furopyridyl

(e.g., furo[2,3-*c*]pyridyl, 6,7-dihydrofuro[2,3-*c*]pyridyl, furo[3,2-*c*]pyridyl, 4,5-dihydrofuro[3,2-*c*]pyridyl, furo[2,3-*b*]pyridyl, 6,7-dihydrofuro[2,3-*b*]pyridyl, etc.), furopyrryl (e.g., furo[3,2-*b*]pyrrolyl etc.), etc.;

(f) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5- thiadiazolyl, 1,2,3-thiadiazolyl, etc.), isothiazolyl , etc.;

(g) unsaturated 3 to 8-membered, preferably 5 or 6- membered heteromonocyclic rings containing a sulfur atom, for example, thienyl, etc.;

(h) unsaturated condensed 7 to 12-membered heterocyclic rings containing 1 to 3 sulfur atoms, for example, benzothienyl (e.g. benzo[*b*]thienyl, etc.);

(i) unsaturated condensed 7 to 12-membered heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, benzothiazolyl, benzothiadiazolyl, thienopyridyl (e.g., thieno[2,3-*c*]pyridyl, 6,7-dihydrothieno[2,3-*c*]pyridyl, thieno[3,2-*c*]pyridyl, 4,5-dihydrothieno[3,2-*c*]pyridyl, thieno[2,3-*b*]pyridyl, 6,7-dihydrothieno[2,3-*b*]pyridyl, 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridyl, etc.), imidazothiazolyl (e.g., imidazo[2,1-*b*]thiazolyl, etc.), dihydroimidazothiazolyl (e.g., 2,3-dihydroimidazo[2,1-*b*]thiazolyl, etc.), thienopyrazinyl (e.g., thieno[2,3-*b*]pyrazinyl, etc.), etc.; and the like.

[0031]

The term "heterocycloalkylene" refers to the bivalent group derived from heterocyclyl (including substituted heterocyclyl).

[0032]

Examples of heterocycloalkylene which contains one or more nitrogen atoms and optionally contains another hetero atom include the following (j) to (m):

(j) 3 to 8-membered, preferably 5 to 7- membered, heterocycloalkylene containing 1 to 4 nitrogen atoms, for example, azetidinediyl, pyrrolidinediyl, imidazolidinediyl, piperidinediyl, pyrazolidinediyl, piperazinediyl, azepanediyl, 1,4-diazepandiyl, etc.;

(k) 3 to 8-membered, preferably 5 or 6- membered heterocycloalkylene containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, morpholinediyl, oxadiazepanediyl, etc

(l) 3 to 8-membered, preferably 5 or 6- heterocycloalkylene containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolidinediyl, etc.; and the like.

[0033]

Examples of "aryl" include monocyclic or polycyclic aryl, such as phenyl and

naphthyl.

[0034]

Examples of the "arylene" include monocyclic or polycyclic arylene such as phenylene, naphthalenediyl, anthracenediyl, indenediyl, phenanthrenediyl, azulenediyl, 5 heptalenediyl etc., in which preferred are (C₆₋₁₄)arylene such as phenylene, naphthalenediyl, etc.

[0035]

Table 1 lists abbreviations used throughout the specification.

[0036]

Table 1 List of Abbreviation

Abbreviation	Description
AcOEt	ethyl acetate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DBU	1,8-diazabicyclo[5.4.0]undecene-7
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DEPC	diethyl pyrocarbonate
DIBAH	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
ELISA	enzyme-linked immunosorbent assay
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtOH	ethyl alcohol
HOBT	1-hydroxybenzotriazole
MeOH	methyl alcohol
MS-3A	molecular sieve 3A
MS-4A	molecular sieve 4A
NaBH(OAc) ₃	sodium triacetoxyborohydride
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMP	<i>N</i> -methylpyrrolidone
Pd(OAc) ₂	palladium(II) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
Pd/C	palladium on carbon
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
PPTS	pyridinium <i>p</i> -toluenesulfonate
PSA	prostatic specific antigen
Pt/C	platinum on carbon
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
WSC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

[0037]

Methods for producing compounds according to the present invention will be described below.

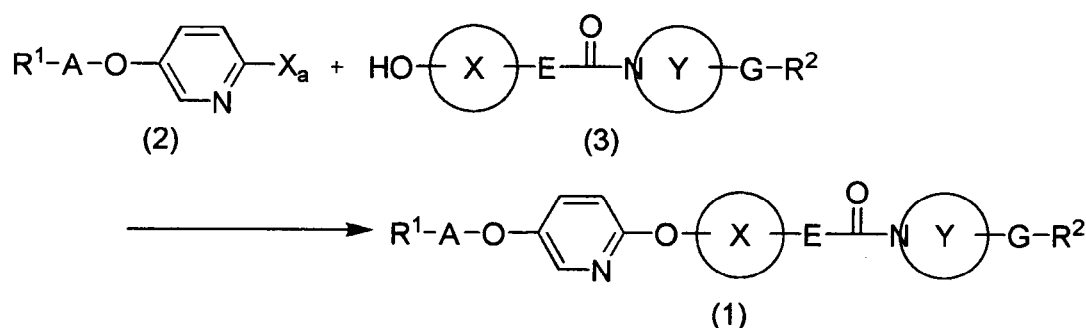
[0038]

The compound of the present invention represented by the general formula (1) or its salt can be readily produced by persons skilled in the art using technical knowledge, based on the EXAMPLES of the present specification. For example, the compound (1) or its salt can be produced according to the processes shown in the following reaction formulae.

[0039]

[Reaction formula 1]

10 [Formula 2]



wherein R¹, R², Ring X, Ring Y, A, E and G are the same as described above, and X_a is a leaving group.

[0040]

- Examples of the leaving group for X_a include halogen (e.g., fluorine, chlorine, bromine, iodine), optionally halogenated C1-6 alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), arylsulfonyloxy (e.g., C6-10 arylsulfonyloxy (e.g., phenylsulfonyloxy, naphthylsulfonyloxy) optionally substituted by 1 to 3 substituents selected from the group of C1-6 alkyl group (e.g., methyl, ethyl, etc.), C1-6 alkoxy (e.g., methoxy, ethoxy, etc.) and a nitro group), and the like.
- 20 Specific examples include phenylsulfonyloxy, *m*-nitrophenylsulfonyloxy, *p*-toluenesulfonyloxy and the like, acyloxy (e.g., trichloroacetoxy, trifluoroacetoxy and the like) and the like.

[0041]

- The reaction of the compound (2) with the compound (3) is carried out by the known palladium- and copper-catalyzed cross-coupling, etc. For example, the reaction can be carried out in a solvent (e.g., toluene, THF, DMF, NMP and DMSO), in the presence of transition metal compound (e.g., Pd(OAc)₂, Pd₂(dba)₃ and copper iodide), a basic compound (e.g., sodium tert-butoxide, K₃PO₄ and Cs₂CO₃), and if necessary a phosphine (e.g., xantphos,
- 25

BINAP, tetrafluoroborate, N,N'-dimethylethylenediamine, and L-proline).

[0042]

The reaction is carried out typically at -30 to 200°C, and preferably at about 0 to 180°C, and is generally completed in about 5 minutes to 80 hours.

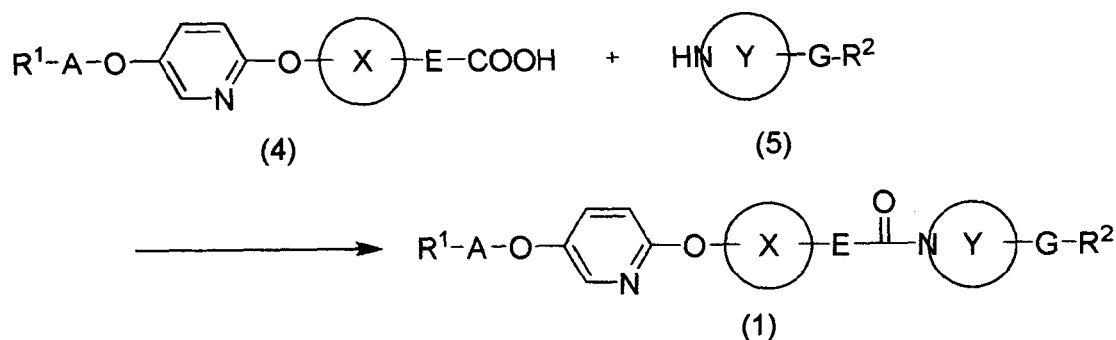
5 [0043]

The compound (2) and the compound (3) can be easily obtained as a commercial product, and also can be produced according to a method known per se or similar manner to EXAMPLES as mentioned below.

[0044]

10 [Reaction Formula 2]

[Formula 3]



wherein R^1 , R^2 , Ring X, Ring Y, A, E and G are the same as described above.

[0045]

Known reactions for producing an amide bond may be applied to the reaction of the compound (4) with the compound (5). Specific methods thereof include: (i) a mixed acid anhydride method, in which Carboxylic Acid (4) is reacted with an alkyl halocarboxylate to form a mixed acid anhydride, which is then reacted with Amine (5); (ii) an active ester method, in which Carboxylic Acid (4) is converted to an activated ester such as a phenyl ester, *p*-nitrophenyl ester, *N*-hydroxysuccinimide ester, or 1-hydroxybenzotriazole ester, or to an activated amide with benzoxazoline-2-thione, and the activated ester or amide is reacted with Amine (5); (iii) a carbodiimide method, in which Carboxylic Acid (4) is subjected to a condensation reaction with Amine (5) in the presence of an activating agent such as DCC, WSC, or carbonyldiimidazole; and (iv) other methods, for example, a method in which Carboxylic Acid (4) is converted to a carboxylic anhydride using a dehydrating agent such as acetic anhydride, and the carboxylic anhydride is reacted with Amine (5), a method in which an ester of Carboxylic Acid (4) with a lower (C1-6) alcohol is reacted with Amine (5) at a high pressure and a high temperature, and a method in which an acid halide of Carboxylic Acid (4), i.e., a

carboxylic acid halide, is reacted with Amine (5).

[0046]

Generally, the mixed acid anhydride method (i) is performed in a solvent, in the presence or absence of a basic compound. Any solvents used for conventional mixed acid anhydride methods are usable. Specific examples of usable solvents include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as Et₂O, diisopropyl ether, THF, and dimethoxyethane; esters such as methyl acetate, AcOEt, and isopropyl acetate; aprotic polar solvents such as DMF, DMSO, and hexamethylphosphoric triamide; and mixtures thereof.

[0047]

Examples of usable basic compounds include organic bases such as Et₃N, trimethylamine, pyridine, dimethylaniline, DIPEA, dimethylaminopyridine, *N*-methylmorpholine, DBN, DBU and DABCO; inorganic bases, for example, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide, and calcium hydroxide; potassium hydride; sodium hydride; potassium; sodium; sodium amide; and metal alcoholates such as sodium methoxide and sodium ethoxide.

[0048]

Examples of alkyl halocarboxylates usable in the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. In this method, Carboxylic Acid (4), an alkyl halocarboxylate, and Amine (5) are preferably used in equimolar amounts, but each of the alkyl halocarboxylate and Carboxylic Acid (4) can also be used in an amount of about 1 to about 1.5 moles per mole of Amine (5).

[0049]

The reaction is typically performed at about -20 to about 150°C, and preferably at about 10 to about 50°C, typically for about 5 minutes to about 30 hours.

[0050]

Method (iii), in which a condensation reaction is performed in the presence of an activating agent, can be performed in a suitable solvent in the presence or absence of a basic compound. Solvents and basic compounds usable in this method include those mentioned hereinafter as solvents and basic compounds usable in the method in which a carboxylic acid halide is reacted with Amine (5) mentioned above as one of the other methods (iv). A suitable

amount of activating agent is typically at least 1 mole, and preferably 1 to 5 moles per mole of Compound (5). When WSC is used as an activating agent, the addition of 1-hydroxybenzotriazol to the reaction system allows the reaction to proceed advantageously. The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is typically completed in about 5 minutes to about 90 hours.

[0051]

When the method in which a carboxylic acid halide is reacted with Amine (5), mentioned above as one of the other methods (iv), is employed, the reaction is performed in the presence of a basic compound in a suitable solvent.

[0052]

Examples of usable basic compounds include a wide variety of known basic compounds, such as those for use in the method (i).

[0053]

In addition to those usable in the mixed acid anhydride method, usable solvents include alcohols such as MeOH, EtOH, 2-propanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, and methyl cellosolve; acetonitrile; pyridine; acetone; and water.

[0054]

The ratio of the carboxylic acid halide to Amine (5) is not limited, and can be suitably selected from a wide range. It is typically suitable to use, for example, at least about 1 mole, and preferably about 1 to about 5 moles of the carboxylic acid halide per mole of Amine (5).

[0055]

The reaction is typically performed at about -20 to about 180°C, and preferably at about 0 to about 150°C, and is typically completed in about 5 minutes to about 30 hours.

[0056]

The amide bond formation reaction shown in Reaction Formula 2 can also be performed by reacting Carboxylic Acid (4) with Amine (5) in the presence of a phosphorus compound serving as a condensing agent, such as triphenylphosphine, diphenylphosphinyl chloride, phenyl-*N*-phenylphosphoramidate chloridate, diethyl chlorophosphate, diethyl cyanophosphate, diphenylphosphoric azide, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, or the like.

[0057]

The reaction is performed in the presence of a solvent and a basic compound usable for the method in which a carboxylic acid halide is reacted with Amine (5), typically at

about -20 to about 150°C, and preferably at about 0 to about 100°C, and is typically completed in about 5 minutes to about 30 hours. It is suitable to use each of the condensing agent and Carboxylic Acid (4) in amounts of at least about 1 mole, and preferably about 1 to about 2 moles, per mole of Amine (5).

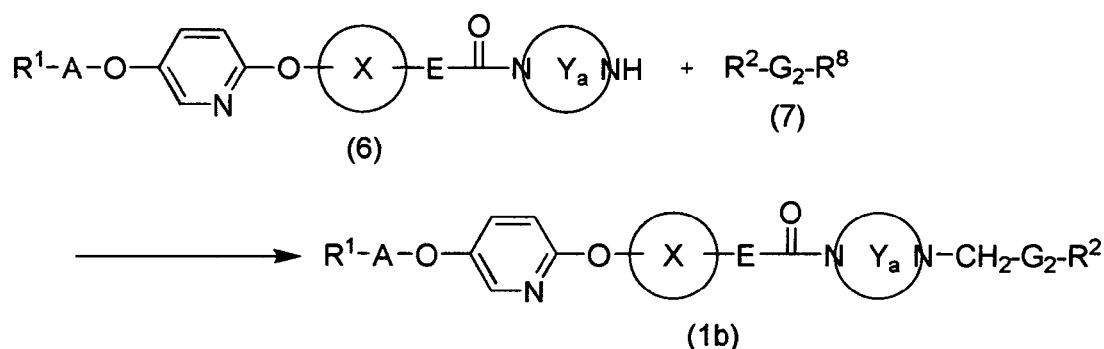
5 [0058]

The compound (4) and the compound (5) can be easily obtained as a commercial product, and also can be produced according to a method known per se or similar manner to EXAMPLES as mentioned below.

[0059]

10 [Reaction formula 3]

[Formula 4]



wherein R^1 , R^2 , Ring X, A, E and G^2 are the same as described above,

R^8 is $-\text{CH}_2\text{-Xb}$ or formyl,

Xb is a leaving group,

15 Ring Y_a is optionally substituted heterocycloalkylene containing at least two nitrogen atoms.

[0060]

Examples of the leaving group for Xb include those recited for a leaving group

Xa.

[0061]

20 Examples of the "optionally substituted heterocycloalkylene containing at least two nitrogen atoms" include imidazolidinediyl, pyrazolidinediyl, piperazinediyl, 1,4-diazepandiyl, oxadiazepanediy, each of which is optionally substituted with one or more lower alkyl, and the like.

(i) When R^8 is formyl, the reaction between the compound (6) and the compound
25 (7) is performed, for example, in a suitable solvent or without using any solvent, in the presence of a reducing agent.

[0062]

Examples of usable solvents include water; lower (C1-6) alcohols such as MeOH, EtOH, isopropanol, butanol, *tert*-butanol, and ethylene glycol; aliphatic acids such as formic acid, and acetic acid; ethers such as Et₂O, THF, dioxane, monoglyme, and diglyme; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; acetonitrile; and mixtures thereof.

[0063]

Examples of reducing agents include aliphatic acids such as formic acid; aliphatic acid alkali metal salts such as sodium formate; hydride reducing agents such as sodium borohydride, sodium cyanoborohydride, NaBH(OAc)₃, sodium trimethoxyborohydride, lithium aluminium hydride, and mixtures thereof, or mixtures of aliphatic acids or aliphatic acid alkali metal salts with hydride reducing agents; and catalytic hydrogenation reducing agents such as palladium black, palladium on carbon, platinum oxide, platinum black, and Raney nickel.

[0064]

When an aliphatic acid such as formic acid, or an aliphatic acid alkali metal salt such as sodium formate is used as a reducing agent, a suitable reaction temperature is typically about room temperature to about 200°C, and preferably about 50 to about 150°C. The reaction is typically completed in about 10 minutes to about 10 hours. Preferably, the aliphatic acid or aliphatic acid alkali metal salt is used in large excess relative to the compound (6).

[0065]

When a hydride reducing agent is used, a suitable reaction temperature is typically about -80 to about 100°C, and preferably about -80 to about 70°C. The reaction is typically completed in about 30 minutes to about 100 hours. The hydride reducing agent is typically used in an amount of about 1 to about 20 moles, and preferably about 1 to about 10 moles, per mole of the compound of (6). Particularly when lithium aluminium hydride is used as a hydride reducing agent, it is preferable to use as a solvent an ether such as Et₂O, THF, dioxane, monoglyme, or diglyme; or an aromatic hydrocarbon such as benzene, toluene, or xylene. To the reaction system may be added an amine such as trimethylamine, Et₃N, or DIPEA; or a molecular sieve such as MS-3A or MS-4A.

[0066]

When a catalytic hydrogenation reducing agent is used, the reaction is typically performed at about -30 to about 100°C, and preferably at about 0 to about 60°C, in a hydrogen atmosphere at typically about atmospheric pressure to about 20 atm, and preferably at about atmospheric pressure to about 10 atm, or in the presence of a hydrogen donor such as formic

acid, ammonium formate, cyclohexene, or hydrazine hydrate. The reaction is typically completed in about 1 to about 12 hours. The catalytic hydrogenation reducing agent is typically used in an amount of about 0.1 to about 40 wt%, and preferably about 1 to about 20 wt%, based on the compound (6).

5 [0067]

In the reaction of the compound of (6) and the compound (7), the compound (7) is typically used in an amount of at least 1 mole, and preferably 1 to 5 moles, per mole of the compound (7).

[0068]

10 The compound (6) may also be a hydrated compound wherein a water molecule is attached to a carbonyl group.

(ii) When R^8 is $-CH_2-Xb$, the reaction of the compound (6) with the compound (7) can be performed in a general inert solvent or without using any solvent, in the presence or absence of a basic compound and/or catalyst.

15 [0069]

Examples of inert solvents include water; ethers such as dioxane, THF, Et_2O , diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene, and xylene; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride; lower (C1-6) alcohols such as MeOH, EtOH, and isopropanol; ketones such as acetone and methyl ethyl ketone; polar solvents such as DMF, DMSO, hexamethylphosphoric triamide, and acetonitrile; and mixtures thereof.

[0070]

A wide variety of known basic compounds can be used as the basic compound. Examples of such basic compounds include inorganic bases, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; sodium amide; sodium hydride; and potassium hydride; and organic bases, for example, alkali metal alcoholates such as sodium methoxide, sodium ethoxide, potassium methoxide, and potassium ethoxide; Et_3N ; DIPEA; tripropylamine; pyridine; quinoline; DBN; DBU; and DABCO. These basic compounds can be used singly or in a combination of two or more.

30 [0071]

Examples of the catalyst include palladium compounds such as palladium acetate,

bis(tributyltin)/bis(dibenzylideneacetone) palladium, copper iodide/2,2'-bipyridyl, bis (dibenzylideneacetone) palladium, copper iodide/bis (triphenylphosphine) palladium dichloride, tris(dibenzylideneacetone) dipalladium, R-tris (dibenzylideneacetone)-dipalladium, S-tris (dibenzylideneacetone) dipalladium, palladium(II) acetate, [1,1'-bis(diphenylphosphino) -
5 ferrocene] dichloropalladium(II), and Pd(PPh₃)₄.

[0072]

Additives (ligands etc.) can be used together with the catalyst. Examples of the additive include compounds such as BINAP, and 2,2-bis(diphenylimidazolidinyliden), xanthene compounds such as 4,5-bis (diphenylphosphino)-9,9- dimethylxanthene, and borates such as tri-
10 *tert*-butylphosphine tetrafluoroborate, and a mixture thereof.

[0073]

The above reaction may be performed by adding to the reaction system, as required, an alkali metal iodide serving as a reaction accelerator, such as potassium iodide or sodium iodide.

15 [0074]

The compound (6) is typically used in an amount of at least 0.5 moles, and preferably about 0.5 to about 10 moles, per mole of the compound (6).

[0075]

The amount of basic compound is typically 0.5 to 10 moles, and preferably 0.5 to
20 6 moles, per mole of the compound (6).

[0076]

The catalyst is appropriately used in a typical catalytic amount, preferably 0.0001 to 1 moles, and more preferably 0.001 to 0.5 moles, per mole of the compound (6).

[0077]

25 The reaction is typically performed at a temperature of 0 to 250°C, and preferably 0 to 200°C, and is typically completed in about 1 to about 80 hours.

[0078]

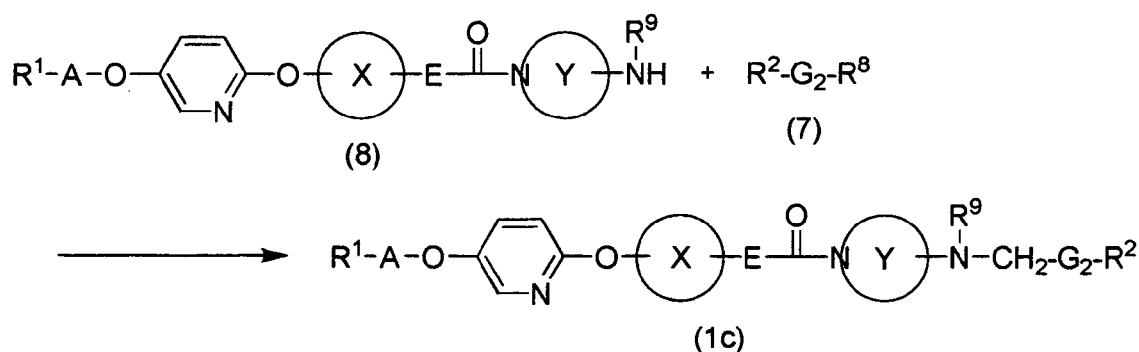
The compound (6) and the compound (7) can be easily obtained as a commercial product, and also can be produced according to a method known per se or similar manner to
30 EXAMPLES as mentioned below.

[0079]

[Reaction formula 4]

[Formula 5]

29



wherein R^1 , R^2 , R^8 , Ring X, Ring Y, A, E and G_2 are the same as described above,
 R^9 is hydrogen or lower alkyl.

[0080]

The reaction of the compound (8) with the compound (7) can be performed under
 5 the same reaction conditions as those for the reaction of the compound (6) with the compound
 (7) shown in Reaction Formula 3 above.

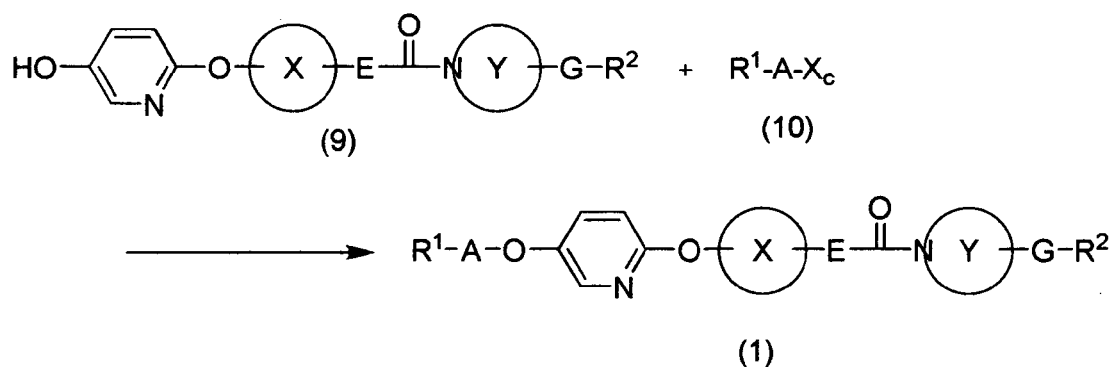
[0081]

The compound (8) can be easily obtained as a commercial product, and also can
 be produced according to a method known per se or similar manner to EXAMPLES as
 10 mentioned below.

[0082]

[Reaction Formula 5]

[Formula 6]



wherein R^1 , R^2 , Ring X, Ring Y, A, E and G are the same as described above,

15 X_c is hydroxy or a leaving group.

[0083]

Examples of the leaving group for X_c include those recited for leaving group X_a .

(i) When X_c is leaving group, the reaction of the compound (9) with the compound (10) is
 carried out in an appropriate solvent or with no solvent in the presence or absence of a basic

compound.

[0084]

Examples of the inert solvent used include aromatic hydrocarbons such as benzene, toluene, and xylene, ethers such as Et₂O, THF, dioxane, monoglyme, and diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride, lower alcohols such as MeOH, EtOH, 2-propanol, butanol, tert-butanol, and ethylene glycol, fatty acids such as acetic acid, esters such as AcOEt and methyl acetate, ketones such as acetone and methyl ethyl ketone, acetonitrile, pyridine, DMSO, DMF, NMP, and hexamethylphosphoric acid triamide, and a mixture thereof.

10 [0085]

Examples of the basic compound include carbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, and cesium carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide, and calcium hydroxide, sodium hydride, potassium hydride, potassium, sodium, sodium amide, metal alcoholates such as sodium methoxide, sodium ethoxide, and sodium n-butoxide, and organic bases such as pyridine, imidazole, DIPEA, dimethylaminopyridine, Et₃N, trimethylamine, dimethylaniline, N-methylmorpholine, DBN, DBU, and DABCO, and a mixture thereof.

15

[0086]

When the reaction is carried out in the presence of a basic compound, the basic compound is used in an amount typically equimolar to the compound (9), and preferably 1 to 10 times of the compound (9) on a molar basis

20

[0087]

The compound (10) is used in an amount typically at least equimolar to the compound (9), and preferably 1 to 10 times of the compound (9) on a molar basis.

25

[0088]

The reaction is carried out typically at -30 to 200°C, and preferably at about 0 to 180°C, and is generally completed in about 5 minutes to 80 hours.

[0089]

To this reaction system, an alkali metal halide such as sodium iodide or potassium iodide may be added, and a phase-transfer catalyst may be added.

30

[0090]

Examples of the phase-transfer catalyst include quaternary ammonium salts substituted with a group selected from the group consisting of a linear or branched alkyl group having 1 to 18 carbon atoms, a phenyl alkyl group of which alkyl moiety is a linear or branched

alkyl group having 1 to 6 carbon atoms and a phenyl group, such as tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogensulfite, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltriethylammonium chloride, benzyldimethyloctadecylammonium chloride, methyltridecylammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride; phosphonium salts substituted with a linear or branched alkyl group having 1 to 18 carbon atoms such as tetrabutylphosphonium chloride; and pyridinium salts substituted with a linear or branched alkyl group having 1 to 18 carbon atoms such as 1-dodecylpyridinium chloride. These phase-transfer catalysts are used singly or in a combination of two or more. [0091]

Typically the phase-transfer catalyst is used in an amount of 0.1 to 1 times of the compound (9), and preferably 0.1 to 0.5 times of the compound (9).

(ii) When Xc is hydroxy, the reaction of the compound (9) with the compound (10) is carried out in an appropriate solvent in the presence of a condensation agent.

[0092]

Specific examples of the solvent include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as Et₂O, diisopropyl ether, THF, and dimethoxyethane, esters such as methyl acetate, AcOEt, and isopropyl acetate, and aprotic polar solvents such as DMF, DMSO, and hexamethylphosphoric acid triamide, and a mixture thereof.

[0093]

Examples of the condensation agent used include a mixture of an azocarboxylate (such as diethyl azocarboxylate) with a phosphorus compound (such as triphenylphosphine).

[0094]

The condensation agent is appropriately used in an amount typically at least equimolar to the compound (9), and preferably 1 to 2 times of the compound (9) on a molar basis.

[0095]

The compound (9) is appropriately used in an amount typically at least equimolar to the compound (9), and preferably 1 to 2 times of the compound (9) on a molar basis.

[0096]

The above described reaction favorably proceeds typically at 0 to 200°C, preferably at around 0 to 150°C and is, in general, completed in around 1 to 10 hours.

[0097]

5 The compound (9) and the compound (10) can be easily obtained as a commercial product, and also can be produced according to a method known per se or similar manner to EXAMPLES as mentioned below.

[0098]

10 The compounds obtained by the above Processes 1 to 5 can be successively prepared by a conventional method within the scope of the compound (1).

[0099]

In addition, compounds in the form in which a solvate (for example, a hydrate, ethanolate, etc.) was added to the starting material compounds and object compounds shown in each of the reaction formulae are included in each of the formulae.

15 [0100]

The compound (1) according to the present invention includes stereoisomers and optical isomers.

[0101]

20 The starting material compounds and object compounds represented by each of the reaction formulae can be used in an appropriate salt form.

[0102]

25 Each of the object compounds obtained according to the above reaction formulae can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a general purification procedure such as column chromatography, recrystallization, etc.

[0103]

30 Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acids, methansulfonic acid, *p*-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acids, etc.

[0104]

Among the compounds of the present invention, those having an acidic group or

groups can easily form salts by reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

5 [0105]

In the compound of the present invention, one or more atoms can be substituted with one or more isotopic atoms. Examples of the isotopic atoms include deuterium (^2H), tritium (^3H), ^{13}C , ^{14}N , ^{18}O , etc.

[0106]

10

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient. Such pharmaceutical preparations are obtained by formulating the compound of the present invention into general pharmaceutical preparations, using typically employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

15 [0107]

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

20 [0108]

To form tablets, any of various known carriers can be used, including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, EtOH, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, 25 potassium phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, aliphatic acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; 30 glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

[0109]

Such tablets may be coated with general coating materials as required, to prepare,

for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc. To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, EtOH and
5 other binders; laminaran, agar and other disintegrants; etc.

[0110]

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

10 [0111]

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, EtOH, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol,
15 aliphatic acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare an isotonic solution, and may contain general solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

20 [0112]

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is typically preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion of 1 to 70 wt. %.

25 [0113]

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation can be administered by a route suitable for the form of the preparation, the patient's age and sex, the conditions of the disease, and other conditions.

30 [0114]

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally.

[0115]

Injectons are intravenously administered singly or as mixed with general

injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

[0116]

- 5 The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient's age and sex, the severity of the disease, and other conditions, and is typically about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

EXAMPLES

10 [0117]

Manufacturing examples of compounds used in the invention are shown below, being followed by the Pharmacological Test results of these compounds.

Reference Example 1

[0118]

- 15 To a 1,2-dichloroethane (15 mL) solution of 4-(2-{{*tert*-butyl(dimethyl)silyl}-oxy}ethyl)benzaldehyde (0.70 g) and *tert*-butyl piperazine-1-carboxylate (0.52 g) was added NaBH(OAc)₃ (0.83 g) at 0 °C. The resultant mixture was stirred at room temperature for 66 hours. To the reaction mixture was added saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous
20 MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 2/1) to afford *tert*-butyl 4-[4-(2-{{*tert*-butyl(dimethyl)silyl}oxy}ethyl)benzyl]piperazine-1-carboxylate (0.96 g) as a colorless oil.
¹H-NMR (CDCl₃) δ: -0.02 (6H, s), 0.86 (9H, s), 1.45 (9H, s), 2.36 (4H, t, *J* = 4.9 Hz), 2.80 (2H, t, *J* = 6.9 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 3.79 (2H, t, *J* = 6.9 Hz), 7.15 (2H, d, *J* = 7.9
25 Hz), 7.22 (2H, d, *J* = 7.9 Hz).

[0119]

The following compounds were produced in the same manner as in Reference Example 1 using appropriate starting materials.

30 Reference Example 2

tert-Butyl 4-(4-bromo-2-fluorobenzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.39-2.41 (4H, m), 3.41-3.43 (4H, m), 3.53 (2H, s), 7.20-7.28 (3H, m).

Reference Example 3

tert-Butyl 4-{{4-(2-hydroxyethyl)phenyl}amino}piperidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.30-1.45 (2H, m), 1.46 (9H, s), 1.80-1.90 (1H, m), 1.98-2.05 (2H, m), 2.92 (2H, t, *J* = 11.9 Hz), 2.95-3.08 (1H, m), 3.35-3.51 (2H, m), 3.75-3.91 (3H, m), 3.95-4.11 (2H, m), 6.52-6.60 (2H, m), 7.00-7.08 (2H, m).

Reference Example 4

tert-Butyl 4-[4-(3-hydroxypropyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.65 (1H, brs), 1.86-1.93 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.70 (2H, t, *J* = 7.7 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 3.68 (2H, t, *J* = 6.2 Hz), 7.15 (2H, d, *J* = 8.1 Hz), 7.23 (2H, d, *J* = 8.1 Hz).

Reference Example 5

tert-Butyl 4-(3-fluoro-4-hydroxybenzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38-2.40 (4H, m), 3.43-3.45 (6H, m), 6.85-6.92 (2H, m), 7.02 (1H, d, *J* = 11.7 Hz).

Reference Example 6

tert-Butyl 4-{4-[(*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 5.0 Hz), 3.39 (3H, s), 3.42 (4H, t, *J* = 5.0 Hz), 3.49 (2H, s), 4.09 (2H, dd, *J* = 6.1, 1.5 Hz), 6.27 (1H, dt, *J* = 16.1, 6.1 Hz), 6.60 (1H, d, *J* = 16.1 Hz), 7.26 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.3 Hz).

Reference Example 7

tert-Butyl 4-{4-[2-(4-methylphenyl)-2-oxoethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.35 (4H, t, *J* = 4.9 Hz), 2.43 (3H, s), 3.41 (4H, t, *J* = 4.9 Hz), 3.43 (2H, s), 5.24 (2H, s), 6.87-6.90 (2H, m), 7.19-7.23 (2H, m), 7.28-7.31 (2H, m), 7.89-7.92 (2H, m).

Reference Example 8

tert-Butyl 4-(biphenyl-4-ylmethyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.41-2.43 (4H, m), 3.44-3.45 (4H, m), 3.55 (2H, s), 7.31-7.47 (5H, m), 7.52-7.61 (4H, m).

Reference Example 9

tert-Butyl 4-[4-(4-chlorophenoxy)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.38-2.39 (4H, m), 3.42-3.43 (4H, m), 3.48 (2H, s), 6.92-6.95 (4H, m), 7.26-7.29 (4H, m).

5

Reference Example 10

tert-Butyl 4-{4-[4-(propan-2-yl)phenoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, *J* = 6.8 Hz), 1.46 (9H, s), 2.36-2.40 (4H, m), 2.87-2.93 (1H, m), 3.42-3.43 (4H, m), 3.47 (2H, s), 6.94 (4H, dd, *J* = 8.5, 2.2 Hz), 7.18 (2H, d, *J* = 8.5 Hz), 7.25 (2H, d, *J* = 9.3 Hz).

10

[0120]

Reference Example 11

To a solution of (4-bromobenzyloxy)(*tert*-butyl)dimethylsilane (3.080 g) in THF (20 mL) were added Mg (0.288 g) and I₂ (cat) at room temperature under an Ar atmosphere.

15

The mixture was heated at 50 °C for 1 hour, and then cooled to room temperature. To the mixture was added 1,2-epoxypropane (0.77 mL) at room temperature under an Ar atmosphere, and the mixture was stirred at room temperature for 14.5 hours, and then heated at 50 °C for 1 hour, and then cooled to room temperature. To the mixture was added saturated aqueous

20

NH₄Cl, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ AcOEt = 2/1) to afford 1-[4-({*tert*-butyl(dimethyl)silyl}oxy)methyl]phenyl]propan-2-ol (1.485 g) as a colorless oil.

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 1.25 (3H, d, *J* = 6.1 Hz), 1.48 (1H, d, *J* = 3.7 Hz), 2.67 (1H, dd, *J* = 13.6, 8.1 Hz), 2.79 (1H, dd, *J* = 13.6, 4.8 Hz), 3.99-4.03 (1H, m), 4.72 (2H, s), 7.18 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.3 Hz).

25

[0121]

The following compounds were produced in the same manner as in Reference Example 11 using appropriate starting materials.

30

Reference Example 12

2-[4-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-2-methylphenyl]ethanol

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 1.35 (1H, t, *J* = 6.0 Hz), 2.33 (3H, s), 2.88 (2H, t, *J* = 6.8 Hz), 3.80-3.85 (2H, m), 4.68 (2H, s), 7.09-7.14 (3H, m).

Reference Example 13

1-[4-(Diethoxymethyl)phenyl]propan-2-ol

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.0 Hz), 1.25 (3H, d, *J* = 6.1 Hz), 1.49 (1H, brs), 2.69 (1H, dd, *J* = 13.6, 7.9 Hz), 2.79 (1H, dd, *J* = 13.6, 4.6 Hz), 3.50-3.67 (4H, m), 4.02 (1H, brs), 5.48 (1H, s), 7.21 (2H, d, *J* = 8.3 Hz), 7.42 (2H, d, *J* = 8.3 Hz).

Reference Example 14

2-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-methylphenyl]ethanol

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 1.35 (1H, t, *J* = 6.1 Hz), 2.26 (3H, s), 2.83 (2H, t, *J* = 6.5 Hz), 3.82-3.87 (2H, m), 4.68 (2H, s), 7.00 (1H, d, *J* = 1.5 Hz), 7.05 (1H, dd, *J* = 7.6, 1.5 Hz), 7.35 (1H, d, *J* = 7.6 Hz).

[0122]

15 Reference Example 15

To a THF (8 mL) solution of *tert*-butyl 4-[4-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-ethyl)benzyl]piperazine-1-carboxylate (0.96 g) was added 1.0 M solution of TBAF in THF (2.32 mL) at 0 °C. The resultant mixture was stirred at room temperature for 2.5 hours. After cooling to 0 °C, the reaction mixture was diluted with AcOEt and water. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH = 40/1) to afford *tert*-butyl 4-[4-(2-hydroxyethyl)benzyl]piperazine-1-carboxylate (0.55 g) as a colorless oil.

¹H-NMR (DMSO-*d*₆) δ: 1.38 (9H, s), 2.28 (4H, t, *J* = 4.9 Hz), 2.69 (2H, t, *J* = 6.9 Hz), 3.29 (4H, t, *J* = 4.9 Hz), 3.42 (2H, s), 3.54-3.62 (2H, m), 4.60 (1H, t, *J* = 5.3 Hz), 7.13-7.20 (4H, m).

[0123]

The following compounds were produced in the same manner as in Reference Example 15 using appropriate starting materials.

30 Reference Example 16

{4-[2-(4-Methylphenoxy)propyl]phenyl}methanol

¹H-NMR (CDCl₃) δ: 1.28 (3H, d, *J* = 6.1 Hz), 1.56 (1H, t, *J* = 6.0 Hz), 2.27 (3H, s), 2.81 (1H, dd, *J* = 13.7, 6.6 Hz), 3.07 (1H, dd, *J* = 13.7, 6.0 Hz), 4.47-4.55 (1H, m), 4.66 (2H, d, *J* = 6.0 Hz), 6.79 (2H, dt, *J* = 9.0, 2.4 Hz), 7.06 (2H, d, *J* = 8.1 Hz), 7.23 (2H, d, *J* = 8.1 Hz), 7.29 (2H,

d, $J = 8.1$ Hz).

Reference Example 17

{3-Methyl-4-[2-(4-methylphenoxy)ethyl]phenyl}methanol

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.55 (1H, t, $J = 5.9$ Hz), 2.28 (3H, s), 2.38 (3H, s), 3.09 (2H, t, $J = 7.3$ Hz), 4.11 (2H, t, $J = 7.3$ Hz), 4.64 (2H, d, $J = 5.9$ Hz), 6.79 (2H, dt, $J = 9.2, 2.6$ Hz), 7.07 (2H, dt, $J = 9.2, 2.6$ Hz), 7.15-7.23 (3H, m).

Reference Example 18

- 10 {3-Methyl-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]phenyl}methanol

$^1\text{H-NMR}$ (CDCl_3) δ : 1.61 (1H, brs), 2.29 (3H, s), 2.35 (3H, s), 4.65 (2H, d, $J = 5.6$ Hz), 4.69 (2H, dd, $J = 5.8, 1.6$ Hz), 6.30 (1H, dt, $J = 15.9, 5.8$ Hz), 6.87 (2H, dt, $J = 9.2, 2.6$ Hz), 6.92 (1H, d, $J = 15.9$ Hz), 7.09 (2H, d, $J = 8.1$ Hz), 7.16-7.17 (2H, m), 7.47 (1H, d, $J = 8.5$ Hz).

- 15 Reference Example 19

{2-Methyl-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]phenyl}methanol

- $^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (1H, t, $J = 5.7$ Hz), 2.29 (3H, s), 2.35 (3H, s), 4.67 (2H, dd, $J = 5.8, 1.5$ Hz), 4.69 (2H, d, $J = 5.7$ Hz), 6.41 (1H, dt, $J = 16.1, 5.8$ Hz), 6.69 (1H, dt, $J = 16.1, 1.5$ Hz), 6.86 (2H, dt, $J = 9.3, 2.6$ Hz), 7.09 (2H, dd, $J = 8.7, 0.6$ Hz), 7.23-7.25 (2H, m), 7.31 (1H, d, $J =$
20 7.6 Hz).

[0124]

Reference Example 20

- To a THF (40 mL) solution of *tert*-butyl 4-[4-(2-hydroxyethyl)benzyl]piperazine-
25 1-carboxylate (4.74 g) and *p*-cresol (1.76 g) were added triphenylphosphine (4.27 g) and 2.2 M solution of DEAD in toluene (7.40 mL) at 0 °C. After stirring at room temperature for 85 hours, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 1/2), then the concentrated eluate was diluted with CH_2Cl_2 , and washed with 5 M NaOH and saturated aqueous NaCl, dried over anhydrous
30 MgSO_4 , and concentrated under reduced pressure to give *tert*-butyl 4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate as a yellow solid (3.87 g).
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 2.26 (3H, s), 2.37 (4H, t, $J = 4.9$ Hz), 3.07 (2H, t, $J = 6.9$ Hz), 3.42 (4H, t, $J = 4.9$ Hz), 3.48 (2H, s), 4.14 (2H, t, $J = 6.9$ Hz), 6.79 (2H, d, $J = 8.2$ Hz), 7.06 (2H, d, $J = 8.2$ Hz), 7.20-7.27 (4H, m).

[0125]

The following compounds were produced in the same manner as in Reference Example 20 using appropriate starting materials.

5 Reference Example 21

tert-Butyl 4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.76 (3H, s), 4.11 (2H, t, *J* = 6.9 Hz), 6.79-6.86 (4H, m), 7.20-7.27 (4H, m).

10

Reference Example 22

tert-Butyl 4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.9 Hz), 3.06 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 6.9 Hz), 3.48 (2H, s), 4.14 (2H, t, *J* = 6.9 Hz), 6.81-6.85 (2H, m), 7.11-7.14 (2H, m), 7.20-7.26 (4H, m).

15

Reference Example 23

tert-Butyl 4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.29 (6H, d, *J* = 5.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.14 (2H, t, *J* = 6.9 Hz), 4.41 (1H, septet, *J* = 5.9 Hz), 6.81 (4H, s), 7.19-7.30 (4H, m).

20

Reference Example 24

tert-Butyl 4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36-2.39 (4H, m), 3.04-3.09 (2H, m), 3.40-3.44 (4H, m), 3.48 (2H, s), 4.10-4.16 (2H, m), 6.81 (2H, d, *J* = 9.2 Hz), 7.18-7.28 (6H, m).

25

Reference Example 25

tert-Butyl 4-{4-[2-(4-bromophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.40-3.44 (4H, m), 3.48 (2H, s), 4.13 (2H, t, *J* = 6.9 Hz), 6.77 (2H, d, *J* = 8.9 Hz), 7.22 (2H, d, *J* = 8.2 Hz), 7.26 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.9 Hz).

30

Reference Example 26

tert-Butyl 4-{4-[2-(4-ethoxyphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 6.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.96 (2H, q, *J* = 6.9 Hz), 4.14 (2H, t, *J* = 6.9 Hz), 6.81 (4H, s), 7.20-7.30 (4H, m).

5

Reference Example 27

tert-Butyl 4-{4-[2-(3-chlorophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.14 (2H, t, *J* = 6.9 Hz), 6.73-6.83 (1H, m), 6.85-6.95 (2H, m), 7.12-7.32 (5H, m).

10

Reference Example 28

tert-Butyl 4-{4-[2-(4-cyanophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.10 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.50 (2H, s), 4.21 (2H, t, *J* = 6.9 Hz), 6.94 (2H, d, *J* = 8.9 Hz), 7.20-7.29 (4H, m), 7.57 (2H, d, *J* = 8.9 Hz).

15

Reference Example 29

tert-Butyl 4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J* = 6.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.6 Hz), 3.48 (2H, s), 4.00 (2H, q, *J* = 6.9 Hz), 4.14 (2H, t, *J* = 6.9 Hz), 6.43-6.54 (3H, m), 7.15 (1H, t, *J* = 8.2 Hz), 7.20-7.30 (4H, m).

20

Reference Example 30

tert-Butyl 4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.31 (3H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.44 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.15 (2H, t, *J* = 6.9 Hz), 6.69-6.76 (3H, m), 7.15 (1H, t, *J* = 7.6 Hz), 7.22-7.27 (4H, m).

25

Reference Example 31

tert-Butyl 4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.9 Hz), 3.08 (2H, t, *J* = 7.3 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.16 (2H, t, *J* = 7.3 Hz), 6.67-6.85 (3H, m), 7.19 (1H, d, *J* = 7.6 Hz), 7.23-7.30 (4H, m).

30

Reference Example 32

tert-Butyl 4-{4-[2-(3,4-dimethylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.18 (3H, s), 2.22 (3H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.3 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.13 (2H, t, *J* = 7.3 Hz), 6.63 (1H, dd, *J* = 8.2, 2.6 Hz), 6.71 (1H, d, *J* = 2.6 Hz), 7.01 (1H, d, *J* = 8.2 Hz), 7.20-7.30 (4H, m).

Reference Example 33

tert-Butyl 4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.3 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.78 (3H, s), 4.15 (2H, t, *J* = 7.3 Hz), 6.43-6.55 (3H, m), 7.16 (1H, t, *J* = 8.2 Hz), 7.20-7.30 (4H, m).

Reference Example 34

- 15 *tert*-Butyl 4-{4-[2-(4-*tert*-butylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.29 (9H, s), 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.15 (2H, t, *J* = 6.9 Hz), 6.86-6.80 (2H, m), 7.31-7.24 (6H, m).

- 20 Reference Example 35

tert-Butyl 4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.12 (2H, t, *J* = 7.1 Hz), 6.66 (2H, d, *J* = 6.9 Hz), 7.20-7.27 (4H, m), 7.53 (2H, d, *J* = 6.9 Hz).

25

Reference Example 36

tert-Butyl 4-{4-[2-(4-butylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 0.91 (3H, t, *J* = 7.3 Hz), 1.26-1.40 (2H, m), 1.45 (9H, s), 1.50-1.61 (2H, m), 2.38 (4H, t, *J* = 5.1 Hz), 2.54 (2H, t, *J* = 7.6 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.1 Hz), 3.48 (2H, s), 4.14 (2H, t, *J* = 7.1 Hz), 6.78-6.84 (2H, m), 7.04-7.10 (2H, m), 7.21-7.27 (4H, m).
- 30

Reference Example 37

tert-Butyl 4-(4-{2-[4-(methylsulfonyl)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.01 (3H, s), 3.11 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.23 (2H, t, *J* = 7.1 Hz), 7.01 (2H, d, *J* = 8.9 Hz), 7.21-7.29 (4H, m), 7.84 (2H, d, *J* = 8.9 Hz).

5 Reference Example 38

tert-Butyl 4-{4-[2-(2-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.19 (3H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.10 (2H, t, *J* = 6.8 Hz), 3.42 (4H, t, *J* = 5.1 Hz), 3.48 (2H, s), 4.16 (2H, t, *J* = 6.8 Hz), 6.77-6.86 (2H, m), 7.08-7.15 (2H, m), 7.25 (4H, s).

10

Reference Example 39

tert-Butyl 4-{4-[2-(1,3-benzodioxol-5-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.04 (2H, t, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.08 (2H, t, *J* = 6.9 Hz), 5.90 (2H, s), 6.31 (1H, dd, *J* = 8.6, 2.3 Hz), 6.47 (1H, d, *J* = 2.3 Hz), 6.68 (1H, d, *J* = 8.6 Hz), 7.20-7.27 (4H, m).

15

Reference Example 40

tert-Butyl 4-{4-[2-(2-chlorophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37-2.38 (4H, m), 3.14 (2H, t, *J* = 6.9 Hz), 3.41-3.43 (4H, m), 3.49 (2H, s), 4.21 (2H, t, *J* = 6.9 Hz), 6.85-6.91 (2H, m), 7.15-7.36 (6H, m).

20

Reference Example 41

tert-Butyl 4-{4-[2-(2,3-dimethylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.11 (3H, s), 2.25 (3H, s), 2.37-2.38 (4H, m), 3.09 (2H, t, *J* = 6.8 Hz), 3.41-3.42 (4H, m), 3.48 (2H, s), 4.14 (2H, t, *J* = 6.8 Hz), 6.68 (1H, d, *J* = 8.3 Hz), 6.76 (1H, d, *J* = 7.8 Hz), 7.02 (1H, t, *J* = 7.8 Hz), 7.21-7.27 (4H, m).

25

Reference Example 42

tert-Butyl 4-{4-[2-(3,5-dimethylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.27 (6H, s), 2.36-2.40 (4H, m), 3.06 (2H, t, *J* = 7.1 Hz), 3.40-3.45 (4H, m), 3.48 (2H, s), 4.13 (2H, t, *J* = 7.1 Hz), 6.53 (2H, s), 6.59 (1H, s), 7.23-7.28 (4H, m).

30

Reference Example 43

tert-Butyl 4-{4-[2-(quinolin-6-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37-2.38 (4H, m), 3.14 (2H, t, *J* = 6.8 Hz), 3.41-3.44 (4H, m), 3.48 (2H, s), 4.26 (2H, t, *J* = 6.8 Hz), 7.03 (1H, d, *J* = 2.4 Hz), 7.25-7.32 (5H, m), 7.36 (1H, dd, *J* = 9.3, 2.4 Hz), 7.94-8.01 (2H, m), 8.73 (1H, d, *J* = 3.4 Hz).

5 Reference Example 44

tert-Butyl 4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37-2.39 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.42-3.43 (4H, m), 3.49 (2H, s), 4.12 (2H, t, *J* = 7.0 Hz), 6.74 (1H, dd, *J* = 8.9, 2.8 Hz), 6.98 (1H, d, *J* = 2.9 Hz), 7.21-7.31 (5H, m).

10

Reference Example 45

tert-Butyl 4-{4-[2-(4-fluoro-3-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.21 (3H, d, *J* = 1.7 Hz), 2.37 (4H, t, *J* = 4.9 Hz), 3.04 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 4.08 (2H, t, *J* = 7.1 Hz), 6.61-6.69 (2H, m), 6.86 (1H, t, *J* = 9.0 Hz), 7.20-7.26 (4H, m).

15

Reference Example 46

tert-Butyl 4-{4-[2-(2,3-dihydro-1*H*-inden-5-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.01-2.08 (2H, m), 2.36 (4H, t, *J* = 4.9 Hz), 2.80-2.86 (4H, m), 3.05 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.46 (2H, s), 4.12 (2H, t, *J* = 7.1 Hz), 6.67 (1H, dd, *J* = 8.1, 2.4 Hz), 6.77 (1H, s), 7.08 (1H, d, *J* = 8.1 Hz), 7.22-7.25 (4H, m).

20

Reference Example 47

tert-Butyl 4-{4-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.74-1.77 (4H, m), 2.37 (4H, t, *J* = 4.9 Hz), 2.68-2.71 (4H, m), 3.05 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 4.12 (2H, t, *J* = 7.1 Hz), 6.59-6.61 (1H, m), 6.66 (1H, dd, *J* = 8.3, 2.7 Hz), 6.95 (1H, d, *J* = 8.3 Hz), 7.22-7.25 (4H, m).

25

Reference Example 48

tert-Butyl 4-{4-[2-(naphthalen-2-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36 (4H, brs), 3.12 (2H, t, *J* = 7.1 Hz), 3.42 (4H, brs), 3.46 (2H, s), 4.24 (2H, t, *J* = 7.1 Hz), 7.10-7.15 (2H, m), 7.25-7.32 (5H, m), 7.40 (1H, t, *J* = 7.0 Hz), 7.66-7.74 (3H, m).

30

Reference Example 49

tert-Butyl 4-{4-[2-(4-acetylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.55 (3H, s), 3.11 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.22 (2H, t, *J* = 7.1 Hz), 6.92 (2H, d, *J* = 8.3 Hz), 7.22-7.28 (4H, m), 7.92 (2H, d, *J* = 8.3 Hz).

Reference Example 50

tert-Butyl 4-(4-{2-[(6-bromopyridin-3-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.09 (2H, t, *J* = 6.8 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.19 (2H, t, *J* = 6.8 Hz), 7.08 (1H, dd, *J* = 8.5, 3.2 Hz), 7.22 (2H, d, *J* = 7.8 Hz), 7.27 (2H, d, *J* = 7.8 Hz), 7.34 (1H, d, *J* = 8.5 Hz), 8.04 (1H, d, *J* = 3.2 Hz).

Reference Example 51

tert-Butyl 4-{4-[2-(pyridin-2-yloxy)ethyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 4.51 (2H, t, *J* = 7.1 Hz), 6.71 (1H, d, *J* = 8.5 Hz), 6.81-6.85 (1H, m), 7.24 (4H, s), 7.51-7.55 (1H, m), 8.13 (1H, dd, *J* = 5.1, 1.2 Hz).

Reference Example 52

- 20 *tert*-Butyl 4-(4-{2-[(5-chloropyridin-2-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 4.47 (2H, t, *J* = 7.1 Hz), 6.66 (1H, d, *J* = 8.8 Hz), 7.20-7.27 (4H, m), 7.48 (1H, dd, *J* = 8.8, 2.7 Hz), 8.07 (1H, d, *J* = 2.7 Hz).

- 25 Reference Example 53

tert-Butyl 4-(4-{2-[(6-chloropyridin-3-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 5.0 Hz), 3.09 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.49 (2H, s), 4.20 (2H, t, *J* = 7.1 Hz), 7.14-7.28 (6H, m), 8.03 (1H, d, *J* = 2.4 Hz).

- 30 Reference Example 54

tert-Butyl 4-(4-{2-[(5-bromopyridin-2-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 5.0 Hz), 3.05 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 4.47 (2H, t, *J* = 7.1 Hz), 6.63 (1H, dd, *J* = 8.8, 0.7 Hz), 7.20-7.26 (4H, m), 7.61 (1H, dd, *J* = 8.8, 2.7 Hz), 8.16 (1H, t, *J* = 1.2 Hz).

Reference Example 55

tert-Butyl 4-(4-{2-[(6-methoxypyridin-3-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, brs), 3.06 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.48 (2H, s), 3.87 (3H, s), 4.19 (2H, t, *J* = 7.1 Hz), 6.66 (1H, d, *J* = 9.0 Hz), 7.17-7.27 (5H, m), 7.79 (1H, d, *J* = 2.7 Hz).

Reference Example 56

tert-Butyl 4-(4-{2-[(6-chloro-1,3-benzoxazol-2-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.32 (4H, brs), 3.04 (2H, t, *J* = 7.1 Hz), 3.41-3.44 (6H, m), 4.02 (2H, t, *J* = 7.1 Hz), 6.56 (1H, d, *J* = 8.3 Hz), 7.00 (1H, dd, *J* = 8.3, 2.0 Hz), 7.08-7.12 (2H, m), 7.16-7.21 (3H, m).

Reference Example 57

- 15 *tert*-Butyl 4-{4-[2-(1,3-benzothiazol-2-yloxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.32 (4H, t, *J* = 5.0 Hz), 2.99 (2H, t, *J* = 7.6 Hz), 3.41 (4H, t, *J* = 5.0 Hz), 3.44 (2H, s), 4.12 (2H, t, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 7.8 Hz), 7.08-7.15 (3H, m), 7.19-7.23 (3H, m), 7.36-7.38 (1H, m).

- 20 Reference Example 58

tert-Butyl 4-(4-{2-[(2-methyl-1,3-benzothiazol-5-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.79 (3H, s), 3.11 (2H, t, *J* = 7.0 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 4.23 (2H, t, *J* = 7.0 Hz), 6.97 (1H, dd, *J* = 8.8, 2.4 Hz), 7.23-7.28 (4H, m), 7.45 (1H, d, *J* = 2.4 Hz), 7.63 (1H, d, *J* = 8.8 Hz).

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Reference Example 59

tert-Butyl 4-(4-{2-[4-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: -0.01 (6H, s), 0.87 (9H, s), 1.45 (9H, s), 2.38-2.39 (4H, m), 2.75 (2H, t, *J* = 7.2 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.41-3.43 (4H, m), 3.48 (2H, s), 3.75 (2H, t, *J* = 7.2 Hz), 4.14 (2H, t, *J* = 7.1 Hz), 6.81 (2H, d, *J* = 8.5 Hz), 7.10 (2H, d, *J* = 8.5 Hz), 7.23-7.25 (4H, m).

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Reference Example 60

tert-Butyl 4-{2-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.41-2.44 (4H, m), 3.42-3.43 (4H, m), 3.59 (2H, s), 5.00 (2H, s), 6.87-7.00 (4H, m), 7.12 (1H, d, *J* = 10.5 Hz), 7.15 (1H, d, *J* = 8.1 Hz), 7.36-7.40 (1H, m).

Reference Example 61

- 5 *tert*-Butyl 4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 5.9 Hz), 1.46 (9H, s), 2.36-2.40 (4H, m), 3.42-3.43 (4H, m), 3.49 (2H, s), 4.40-4.45 (1H, m), 5.05 (2H, s), 6.83 (2H, d, *J* = 9.3 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 7.08 (1H, d, *J* = 1.7 Hz), 7.11 (1H, s), 7.43 (1H, t, *J* = 7.7 Hz).

- 10 Reference Example 62

tert-Butyl 4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.38-2.39 (4H, m), 3.42-3.44 (4H, m), 3.50 (2H, s), 5.06 (2H, s), 6.90-7.00 (4H, m), 7.11 (2H, d, *J* = 9.0 Hz), 7.42 (1H, t, *J* = 7.6 Hz).

- 15 Reference Example 63

tert-Butyl 4-{3-fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 0.93 (3H, t, *J* = 7.3 Hz), 1.46 (9H, s), 1.57-1.64 (2H, m), 2.36-2.40 (4H, m), 2.52-2.54 (2H, m), 3.42-3.43 (4H, m), 3.49 (2H, s), 5.08 (2H, s), 6.90 (2H, d, *J* = 8.3 Hz), 7.10 (4H, d, *J* = 8.5 Hz), 7.44 (1H, t, *J* = 7.6 Hz).

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Reference Example 64

tert-Butyl 4-[4-(2-{[(2-nitrophenyl)sulfonyl][4-(propan-2-yl)phenyl]amino}ethyl)benzyl]-piperazine-1-carboxylate

- 25 ¹H-NMR (CDCl₃) δ: 1.24 (6H, d, *J* = 6.8 Hz), 2.36 (4H, t, *J* = 4.9 Hz), 2.77-2.86 (2H, m), 2.91 (1H, septet, *J* = 6.8 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.46 (2H, s), 3.93-4.03 (2H, m), 7.07-7.12 (4H, m), 7.12-7.24 (4H, m), 7.40-7.52 (2H, m), 7.55-7.65 (2H, m).

Reference Example 65

- 30 *tert*-Butyl 4-[4-(2-{(4-fluorophenyl)[(2-nitrophenyl)sulfonyl]amino}ethyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36 (4H, t, *J* = 4.9 Hz), 2.77-2.86 (2H, m), 3.42 (4H, t, *J* = 4.9 Hz), 3.46 (2H, s), 3.96-4.04 (2H, m), 6.06-7.05 (2H, m), 7.08 (2H, d, *J* = 8.1 Hz), 7.01-7.18 (2H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.43-7.54 (2H, m), 7.58-7.72 (2H, m).

Reference Example 66

tert-Butyl 4-[4-(2-((4-methoxyphenyl)((2-nitrophenyl)sulfonyl)amino)ethyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36 (4H, t, *J* = 4.9 Hz), 2.77-2.86 (2H, m), 3.42 (4H, t, *J* = 4.9 Hz), 3.46 (2H, s), 3.81 (3H, s), 3.93-4.00 (2H, m), 6.79-6.86 (2H, m), 7.06-7.12 (4H, m), 7.20 (2H, d, *J* = 8.1 Hz), 7.43-7.52 (2H, m), 7.56-7.66 (2H, m).

Reference Example 67

tert-Butyl 4-[[4-(2-((2-nitrophenyl)sulfonyl)[4-(propan-2-yl)phenyl]amino)ethyl]phenyl]-amino]piperidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, *J* = 6.8 Hz), 1.27-1.38 (2H, m), 1.46 (9H, s), 1.96-2.07 (2H, m), 2.67-2.75 (2H, m), 2.83-2.98 (3H, m), 3.33-3.47 (2H, m), 3.87-3.95 (2H, m), 3.96-4.12 (2H, m), 6.48-6.55 (2H, m), 6.92-6.98 (2H, m), 7.07-7.12 (2H, m), 7.14-7.19 (2H, m), 7.41-7.53 (2H, m), 7.54-7.66 (2H, m).

Reference Example 68

tert-Butyl 4-((4-[2-(4-methylphenoxy)ethyl]phenyl)amino)piperidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.26-1.38 (2H, m), 1.46 (9H, s), 1.98-2.07 (2H, m), 2.27 (3H, s), 2.86-3.00 (4H, m), 3.35-3.45 (2H, m), 3.95-4.12 (4H, m), 6.53-6.59 (2H, m), 6.75-6.83 (2H, m), 7.00-7.11 (4H, m).

Reference Example 69

tert-Butyl 4-((4-[2-(4-fluorophenoxy)ethyl]phenyl)amino)piperidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.25-1.39 (2H, m), 1.46 (9H, s), 1.98-2.08 (2H, m), 2.86-3.00 (4H, m), 3.35-3.53 (2H, m), 3.95-4.15 (4H, m), 6.54-6.60 (2H, m), 6.79-6.85 (2H, m), 6.90-7.00 (2H, m), 7.04-7.11 (2H, m).

Reference Example 70

4-[2-(4-Methoxyphenyl)ethoxy]benzaldehyde

¹H-NMR (CDCl₃) δ: 3.04-3.09 (2H, m), 3.80 (3H, s), 4.19-4.24 (2H, m), 6.87 (2H, d, *J* = 8.6 Hz), 6.99 (2H, d, *J* = 8.6 Hz), 7.20 (2H, d, *J* = 8.6 Hz), 7.82 (2H, d, *J* = 8.6 Hz), 9.87 (1H, brs).

Reference Example 71

4-[2-(4-Methylphenyl)ethoxy]benzaldehyde

¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 3.09 (2H, t, *J* = 7.3 Hz), 4.23 (2H, t, *J* = 7.3 Hz), 6.95-7.04 (2H, m), 7.10-7.22 (4H, m), 7.77-7.88 (2H, m), 9.87 (1H, s).

Reference Example 72

5 4-{2-[4-(Propan-2-yl)phenyl]ethoxy}benzaldehyde

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, *J* = 6.9 Hz), 2.89 (1H, septet, *J* = 6.9 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 4.23 (2H, t, *J* = 7.3 Hz), 6.95-7.04 (2H, m), 7.13-7.27 (4H, m), 7.77-7.86 (2H, m), 9.87 (1H, s).

10 Reference Example 73

4-[3-(4-Fluorophenoxy)propyl]benzaldehyde

¹H-NMR (CDCl₃) δ: 2.04-2.17 (2H, m), 2.90 (2H, t, *J* = 7.7 Hz), 3.92 (2H, t, *J* = 6.1 Hz), 6.79-6.86 (2H, m), 6.92-7.01 (2H, m), 7.38 (2H, d, *J* = 8.1 Hz), 7.81 (2H, d, *J* = 8.2 Hz), 9.98 (1H, s).

15 Reference Example 74

4-{3-[4-(Propan-2-yl)phenoxy]propyl}benzaldehyde

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.06-2.17 (2H, m), 2.81-2.93 (3H, m), 3.95 (2H, t, *J* = 6.1 Hz), 6.82 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.1 Hz), 7.81 (2H, d, *J* = 8.2 Hz), 9.98 (1H, s).

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Reference Example 75

4-{{(*E*)-3-(4-Formylphenyl)prop-2-en-1-yl}oxy}benzonitrile

¹H-NMR (CDCl₃) δ: 4.79 (2H, dd, *J* = 5.5, 1.6 Hz), 6.55 (1H, dt, *J* = 15.8, 5.5 Hz), 6.80 (1H, d, *J* = 15.8), 7.00-7.03 (2H, m), 7.55-7.63 (4H, m), 7.85-7.87 (2H, m), 10.00 (1H, s).

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Reference Example 76

1-Bromo-4-[2-(4-fluorophenoxy)ethyl]benzene

¹H-NMR (CDCl₃) δ: 3.02 (2H, t, *J* = 6.6 Hz), 4.10 (2H, t, *J* = 6.6 Hz), 6.76-6.84 (2H, m), 6.90-7.00 (2H, m), 7.13-7.16 (2H, m), 7.40-7.44 (2H, m).

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Reference Example 77

1-Bromo-4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzene

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.9 Hz), 2.85 (1H, septet, *J* = 6.9 Hz), 3.03 (2H, t, *J* = 6.9 Hz), 4.13 (2H, t, *J* = 6.9 Hz), 6.77-6.85 (2H, m), 7.09-7.20 (4H, m), 7.38-7.47 (2H, m).

Reference Example 78

1-Bromo-4-[2-(4-methoxyphenoxy)ethyl]benzene

¹H-NMR (CDCl₃) δ: 3.02 (2H, t, *J* = 6.9 Hz), 3.76 (3H, s), 4.10 (2H, t, *J* = 6.8 Hz), 6.82 (4H, s),
5 7.14-7.17 (2H, m), 7.41-7.44 (2H, m).

Reference Example 79

1-Bromo-4-[2-(4-methylphenoxy)ethyl]benzene

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 3.03 (2H, t, *J* = 6.9 Hz), 4.12 (2H, t, *J* = 6.9 Hz), 6.73-6.83
10 (2H, m), 7.07 (2H, d, *J* = 8.2 Hz), 7.15 (2H, d, *J* = 8.6 Hz), 7.43 (2H, d, *J* = 8.9 Hz).

Reference Example 80

1-Bromo-4-[2-(4-ethoxyphenoxy)ethyl]benzene

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 6.9 Hz), 3.01 (2H, t, *J* = 6.9 Hz), 3.97 (2H, q, *J* = 6.9 Hz),
15 4.09 (2H, t, *J* = 6.9 Hz), 6.81 (4H, s), 7.15 (2H, d, *J* = 8.2 Hz), 7.42 (2H, d, *J* = 8.2 Hz).

Reference Example 81

1-Bromo-4-[1-(4-methylphenoxy)propan-2-yl]benzene

¹H-NMR (CDCl₃) δ: 1.37 (3H, d, *J* = 7.1 Hz), 2.27 (3H, s), 3.14-3.23 (1H, m), 3.92 (1H, dd, *J* =
20 9.2, 7.2 Hz), 4.00 (1H, dd, *J* = 9.2, 6.3 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 7.05 (2H, d, *J* = 8.5 Hz),
7.16 (2H, d, *J* = 8.5 Hz), 7.44 (2H, d, *J* = 8.5 Hz).

Reference Example 82

(E)-3-(4-Bromophenyl)but-2-en-1-yl 4-methylphenyl ether

¹H-NMR (CDCl₃) δ: 2.10 (3H, d, *J* = 1.2 Hz), 2.29 (3H, s), 4.68-4.70 (2H, m), 6.02-6.06 (1H,
25 m), 6.84 (2H, dt, *J* = 9.3, 2.5 Hz), 7.09 (2H, d, *J* = 8.7 Hz), 7.29 (2H, dt, *J* = 9.0, 2.3 Hz), 7.44
(2H, dt, *J* = 9.0, 2.3 Hz).

Reference Example 83

2-(4-Bromo-2-fluorophenyl)ethyl 4-chlorophenyl ether

¹H-NMR (CDCl₃) δ: 3.07 (2H, t, *J* = 6.7 Hz), 4.12 (2H, t, *J* = 6.7 Hz), 6.79 (2H, d, *J* = 9.0 Hz),
30 7.17-7.21 (5H, m).

Reference Example 84

tert-Butyl(dimethyl)({4-[2-(4-methylphenoxy)propyl]benzyl}oxy)silane

¹H-NMR (CDCl₃) δ: 0.09 (6H, s), 0.93 (9H, s), 1.26 (3H, d, *J* = 6.1 Hz), 2.27 (3H, s), 2.77 (1H, dd, *J* = 13.6, 6.8 Hz), 3.08 (1H, dd, *J* = 13.6, 5.7 Hz), 4.46-4.54 (1H, m), 4.71 (2H, s), 6.79 (2H, d, *J* = 8.3 Hz), 7.06 (2H, d, *J* = 8.3 Hz), 7.19 (2H, d, *J* = 8.1 Hz), 7.24 (2H, d, *J* = 8.1 Hz).

5

Reference Example 85

tert-Butyl(dimethyl)({3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}oxy)silane

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 2.28 (3H, s), 2.36 (3H, s), 3.08 (2H, t, *J* = 7.6 Hz), 4.09 (2H, t, *J* = 7.6 Hz), 4.69 (2H, s), 6.79 (2H, dt, *J* = 9.3, 2.6 Hz), 7.05-7.12 (4H, m), 7.18 (1H, d, *J* = 8.5 Hz).

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Reference Example 86

tert-Butyl(dimethyl)({3-methyl-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}oxy)silane

¹H-NMR (CDCl₃) δ: 0.09 (6H, s), 0.94 (9H, s), 2.29 (3H, s), 2.34 (3H, s), 4.67-4.69 (4H, m), 6.28 (1H, dt, *J* = 15.9, 5.7 Hz), 6.87 (2H, dt, *J* = 9.1, 2.5 Hz), 6.92 (1H, d, *J* = 15.9 Hz), 7.08-7.13 (4H, m), 7.44 (1H, d, *J* = 7.8 Hz).

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Reference Example 87

tert-Butyl(dimethyl)({2-methyl-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}oxy)silane

¹H-NMR (CDCl₃) δ: 0.09 (6H, s), 0.93 (9H, s), 2.25 (3H, s), 2.28 (3H, s), 4.65 (2H, dd, *J* = 6.1, 1.2 Hz), 4.68 (2H, s), 6.38 (1H, dt, *J* = 16.1, 6.1 Hz), 6.67 (1H, d, *J* = 16.1 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 7.08 (2H, d, *J* = 8.8 Hz), 7.17 (1H, brs), 7.22 (1H, dd, *J* = 7.9, 1.3 Hz), 7.35 (1H, d, *J* = 7.9 Hz).

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Reference Example 88

1-(Diethoxymethyl)-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzene

¹H-NMR (CDCl₃) δ: 1.23 (6H, t, *J* = 7.1 Hz), 2.29 (3H, s), 3.49-3.65 (4H, m), 4.67 (2H, dd, *J* = 5.9, 1.5 Hz), 5.49 (1H, s), 6.42 (1H, dt, *J* = 16.0, 5.9 Hz), 6.72 (1H, dt, *J* = 16.0, 1.5 Hz), 6.86 (2H, dt, *J* = 9.3, 2.5 Hz), 7.09 (2H, d, *J* = 8.3 Hz), 7.39 (2H, d, *J* = 8.5 Hz), 7.43 (2H, d, *J* = 8.5 Hz).

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Reference Example 89

1-(Diethoxymethyl)-4-[(*E*)-3-(4-fluorophenoxy)prop-1-en-1-yl]benzene

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.1 Hz), 3.49-3.65 (4H, m), 4.66 (2H, dd, *J* = 5.9, 1.5 Hz),

5.49 (1H, s), 6.40 (1H, dt, $J = 16.1, 5.9$ Hz), 6.72 (1H, d, $J = 16.1$ Hz), 6.87-6.92 (2H, m), 6.95-7.00 (2H, m), 7.40 (2H, d, $J = 8.3$ Hz), 7.44 (2H, d, $J = 8.3$ Hz).

Reference Example 90

5 1-(Diethoxymethyl)-4-[(*E*)-3-phenoxyprop-1-en-1-yl]benzene

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, t, $J = 7.1$ Hz), 3.49-3.65 (4H, m), 4.70 (2H, dd, $J = 5.8, 1.5$ Hz), 5.49 (1H, s), 6.43 (1H, dt, $J = 16.0, 5.8$ Hz), 6.73 (1H, d, $J = 16.0$ Hz), 6.94-6.98 (3H, m), 7.27 (2H, m), 7.39-7.45 (4H, m).

10 Reference Example 91

1-(Diethoxymethyl)-4-[(*E*)-3-(4-methoxyphenoxy)prop-1-en-1-yl]benzene

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, t, $J = 7.1$ Hz), 3.49-3.65 (4H, m), 3.77 (3H, s), 4.65 (2H, dd, $J = 5.9, 1.3$ Hz), 5.49 (1H, s), 6.41 (1H, dt, $J = 15.9, 5.9$ Hz), 6.72 (1H, d, $J = 15.9$ Hz), 6.82-6.92 (4H, m), 7.38-7.44 (4H, m).

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Reference Example 92

5-({(*E*)-3-[4-(Diethoxymethyl)phenyl]prop-2-en-1-yl}oxy)-2-methylpyridine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, t, $J = 7.1$ Hz), 2.25 (3H, s), 3.49-3.64 (4H, m), 4.97 (2H, dd, $J = 6.1, 1.5$ Hz), 5.49 (1H, s), 6.47 (1H, dt, $J = 16.0, 6.0$ Hz), 6.69-6.75 (2H, m), 7.38-7.44 (5H, m),
20 7.96-7.97 (1H, m).

Reference Example 93

2-Chloro-5-({(*E*)-3-[4-(diethoxymethyl)phenyl]prop-2-en-1-yl}oxy)pyridine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, t, $J = 7.1$ Hz), 3.50-3.65 (4H, m), 4.73 (2H, dd, $J = 5.9, 1.5$ Hz),
25 5.50 (1H, s), 6.37 (1H, dt, $J = 16.0, 5.9$ Hz), 6.74 (1H, d, $J = 16.0$ Hz), 7.24 (2H, d, $J = 1.9$ Hz),
7.40 (2H, d, $J = 8.3$ Hz), 7.45 (2H, d, $J = 8.3$ Hz), 8.12 (1H, t, $J = 1.9$ Hz).

Reference Example 94

5-Bromo-2-({(*E*)-3-[4-(diethoxymethyl)phenyl]prop-2-en-1-yl}oxy)pyridine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (6H, t, $J = 7.1$ Hz), 3.48-3.64 (4H, m), 4.96 (2H, d, $J = 6.1$ Hz), 5.49 (1H, s), 6.43 (1H, dt, $J = 15.9, 6.1$ Hz), 6.69-6.74 (2H, m), 7.38-7.44 (4H, m), 7.65 (1H, ddd, $J = 8.8, 2.4, 0.7$ Hz), 8.20 (1H, d, $J = 2.4$ Hz).

Reference Example 95

1-(Diethoxymethyl)-4-[(*E*)-3-[4-(propan-2-yl)phenoxy]prop-1-en-1-yl]benzene

¹H-NMR (CDCl₃) δ: 1.22-1.25 (12H, m), 2.81-2.92 (1H, m), 3.49-3.65 (4H, m), 4.68 (2H, dd, *J* = 5.7, 1.2 Hz), 5.49 (1H, s), 6.42 (1H, dt, *J* = 16.0, 5.7 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.89 (2H, dt, *J* = 9.4, 2.5 Hz), 7.15 (2H, dt, *J* = 9.4, 2.5 Hz), 7.39-7.44 (4H, m).

5

Reference Example 96

2-[(*E*)-3-[4-(Diethoxymethyl)phenyl]prop-2-en-1-yl]oxy-5-methylpyridine

¹H-NMR (CDCl₃) δ: 1.23 (6H, t, *J* = 7.1 Hz), 2.25 (3H, s), 3.49-3.64 (4H, m), 4.97 (2H, dd, *J* = 6.1, 1.5 Hz), 5.49 (1H, s), 6.47 (1H, dt, *J* = 16.0, 6.0 Hz), 6.69-6.75 (2H, m), 7.38-7.44 (5H, m),
10 7.96-7.97 (1H, m).

Reference Example 97

1-(Diethoxymethyl)-4-(3-phenoxypropyl)benzene

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.1 Hz), 2.07-2.14 (2H, m), 2.82 (2H, t, *J* = 7.7 Hz), 3.50-
15 3.66 (4H, m), 3.96 (2H, t, *J* = 6.3 Hz), 5.48 (1H, s), 6.88-6.96 (3H, m), 7.21 (2H, d, *J* = 8.1 Hz),
7.25-7.31 (2H, m), 7.39 (2H, d, *J* = 8.1 Hz).

Reference Example 98

2-Chloro-5-{3-[4-(diethoxymethyl)phenyl]propoxy}pyridine

20 ¹H-NMR (CDCl₃) δ: 1.27 (6H, t, *J* = 7.1 Hz), 2.10-2.17 (2H, m), 2.84 (2H, t, *J* = 7.6 Hz), 3.52-
3.69 (4H, m), 4.00 (2H, t, *J* = 6.2 Hz), 5.50 (1H, s), 7.17-7.26 (4H, m), 7.43 (2H, d, *J* = 8.1 Hz),
8.07 (1H, dd, *J* = 3.1, 0.6 Hz).

Reference Example 99

25 1-(Diethoxymethyl)-4-[(*E*)-2-methyl-3-(4-methylphenoxy)prop-1-en-1-yl]benzene

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.1 Hz), 1.96 (3H, d, *J* = 1.2 Hz), 2.29 (3H, s), 3.50-3.67
(4H, m), 4.54 (2H, s), 5.50 (1H, s), 6.62 (1H, brs), 6.87 (2H, dt, *J* = 9.1, 2.4 Hz), 7.09 (2H, d, *J* =
8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 7.44 (2H, d, *J* = 8.3 Hz).

30 [0126]

Reference Example 100

tert-Butyl 4-[4-(2-hydroxyethyl)benzyl]piperazine-1-carboxylate (1.44 g), 2-hydroxy-5-methylpyridine (0.737 g), tri-*n*-butylphosphine (1.76 mL), 1,1'-(azodicarbonyl)-dipiperidine (1.70 g), and THF (16.5 mL) were mixed in a 20 mL process vial. The vial was

sealed, and the reaction mixture was heated with microwaves to 55 °C for 10 minutes. The reaction mixture was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 10/1 to 3/10) to give *tert*-butyl 4-(4-{2-[(5-methylpyridin-2-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate as a pale yellow amorphous (1.01 g).

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.22 (3H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 4.46 (2H, t, *J* = 7.1 Hz), 6.63 (1H, d, *J* = 8.3 Hz), 7.22-7.24 (4H, m), 7.36 (1H, dd, *J* = 8.5, 2.4 Hz), 7.93 (1H, s).

[0127]

The following compound was produced in the same manner as in Reference Example 100 using appropriate starting materials.

Reference Example 101

tert-Butyl 4-(4-{2-[(6-methylpyridin-3-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.39 (4H, t, *J* = 4.9 Hz), 2.48 (3H, s), 3.08 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.18 (2H, t, *J* = 7.1 Hz), 7.05-7.11 (2H, m), 7.20-7.22 (2H, m), 7.24-7.26 (2H, m), 8.16 (1H, d, *J* = 2.7 Hz).

[0128]

Reference Example 102

To a toluene (99 mL) solution of 4-bromo-2-fluorobenzaldehyde (10.00 g) was added ethylene glycol (3.30 mL) and toluenesulfonic acid (849 mg), then the resultant mixture was refluxed for 8 hours. The mixture was poured into saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 99/1 to 95/5) to afford 2-(4-bromo-2-fluorophenyl)-1,3-dioxolane as a colorless oil (11.046 g).

¹H-NMR (CDCl₃) δ: 4.02-4.06 (2H, m), 4.11-4.15 (2H, m), 6.03 (1H, s), 7.25-7.32 (2H, m), 7.40-7.42 (1H, m).

[0129]

Reference Example 103

To a THF (40 mL) solution of 2-(4-bromo-2-fluorophenyl)-1,3-dioxolane (3.29 g) was added Mg (406 mg) and I₂ (135 mg), then the resultant mixture was refluxed for 5 hours. After cooling to 0 °C, the reaction mixture was added ethylene oxide (12.5 mL, 1.1 M in THF),

then the resultant mixture was stirred at 50 °C for 3 hours. The reaction mixture was added ethylene oxide (12.5 mL, 1.1 M in THF), the resultant mixture was stirred at 50 °C over night. The mixture was poured into saturated aqueous NH₄Cl, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and
5 evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 99/1 to 4/1) to afford a colorless oil. To a THF (10 mL) solution of that colorless oil and PPh₃ (857 mg) and alpha,alpha,alpha-trifluoro-*p*-cresol (530 mg) were added DEAD (1.486 mL, 2.2 M in toluene) at 0 °C, then the resultant mixture was stirred at room temperature over night. The reaction mixture was evaporated, to the residue was added *n*-hexane/AcOEt (4/1), then the
10 mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/0 to 9/1) to afford 2-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}phenyl)-1,3-dioxolane as a colorless oil (0.552 g).
¹H-NMR (CDCl₃) δ: 3.11 (2H, t, *J* = 6.7 Hz), 4.03-4.21 (6H, m), 6.07 (1H, s), 6.93 (2H, d, *J* = 8.5 Hz), 7.01 (1H, d, *J* = 11.0 Hz), 7.08 (1H, d, *J* = 7.8 Hz), 7.46-7.54 (3H, m).

15 [0130]

Reference Example 104

tert-Butyl 4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazine-1-carboxylate (209 mg), potassium cyclopropyltrifluoroborate (86 mg), Pd(OAc)₂ (6 mg), di(1-adamantyl)-*n*-butylphosphine (13 mg), Cs₂CO₃ (391 mg), and toluene/water (10:1) (3.3 mL) were mixed in a 5 mL
20 process vial. The vial was sealed, and the reaction mixture was heated with microwaves to 130 °C for 1 hour. After filtration through a Celite pad, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/0 to 0/1) to give *tert*-butyl 4-{4-[2-(4-cyclopropylphenoxy)ethyl]benzyl}piperazine-1-carboxylate as a pale yellow solid (40 mg).

25 ¹H-NMR (CDCl₃) δ: 0.57-0.62 (2H, m), 0.85-0.90 (2H, m), 1.45 (9H, s), 1.81-1.86 (1H, m), 2.37 (4H, t, *J* = 5.0 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 4.13 (2H, t, *J* = 7.1 Hz), 6.78-6.81 (2H, m), 6.97-7.00 (2H, m), 7.21-7.26 (4H, m).

[0131]

Reference Example 105

30 To a THF (100 mL) solution of 1-bromo-4-[2-(4-fluorophenoxy)ethyl]benzene (3.05 g) was added 1.6 M solution of *n*-BuLi in *n*-hexane (6.80 mL) dropwise at -70 °C under an argon atmosphere. After stirring for 30 minutes, DMF (1.20 mL) was slowly added at -70 °C. The resultant mixture was stirred and slowly warmed to -40 °C for 3 hours. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl, and extracted with AcOEt. The

organic layer was washed with water, saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 1/1) to afford 4-[2-(4-fluorophenoxy)ethyl]benzaldehyde as a light yellow solid (1.63 g).

- 5 ¹H-NMR (DMSO-*d*₆) δ: 3.13 (2H, t, *J* = 6.6 Hz), 4.22 (2H, t, *J* = 6.6 Hz), 6.90-6.98 (2H, m), 7.05-7.15 (2H, m), 7.56 (2H, d, *J* = 8.2 Hz), 7.86 (2H, d, *J* = 8.2 Hz), 9.98 (1H, s).
[0132]

The following compounds were produced in the same manner as in Reference Example 105 using appropriate starting materials.

10

Reference Example 106

4-{2-[4-(Propan-2-yl)phenoxy]ethyl}benzaldehyde

- ¹H-NMR (CDCl₃) δ: 1.24 (6H, d, *J* = 6.9 Hz), 2.85 (1H, septet, *J* = 6.9 Hz), 3.16 (2H, t, *J* = 6.6 Hz), 4.20 (2H, t, *J* = 6.6 Hz), 6.77-6.88 (2H, m), 7.08-7.17 (2H, m), 7.42-7.49 (2H, m), 7.79-7.87
15 (2H, m), 9.99 (1H, s).

Reference Example 107

4-[2-(4-Methoxyphenoxy)ethyl]benzaldehyde

- ¹H-NMR (CDCl₃) δ: 3.15 (2H, t, *J* = 6.8 Hz), 3.76 (3H, s), 4.17 (2H, t, *J* = 6.8 Hz), 6.81 (4H, s),
20 7.45 (2H, d, *J* = 7.9 Hz), 7.82-7.84 (2H, m), 9.99 (1H, s).

Reference Example 108

4-[2-(4-Methylphenoxy)ethyl]benzaldehyde

- ¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 3.16 (2H, t, *J* = 6.6 Hz), 4.19 (2H, t, *J* = 6.9 Hz), 6.78 (2H, d, *J* = 8.6 Hz), 7.07 (2H, d, *J* = 8.2 Hz), 7.45 (2H, d, *J* = 7.9 Hz), 7.83 (2H, d, *J* = 8.2 Hz), 9.99 (1H, s).
25

Reference Example 109

4-[2-(4-Ethoxyphenoxy)ethyl]benzaldehyde

- ¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 6.9 Hz), 3.15 (2H, t, *J* = 6.9 Hz), 3.97 (2H, q, *J* = 6.9 Hz), 4.17 (2H, t, *J* = 6.9 Hz), 6.81 (4H, s), 7.45 (2H, d, *J* = 8.2 Hz), 7.83 (2H, d, *J* = 8.2 Hz), 9.99 (1H, s).
30

Reference Example 110

4-[1-(4-Methylphenoxy)propan-2-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 1.42 (3H, d, *J* = 7.1 Hz), 2.27 (3H, s), 3.27-3.36 (1H, m), 4.01 (1H, dd, *J* = 9.2, 6.7 Hz), 4.07 (1H, dd, *J* = 9.2, 6.7 Hz), 6.76 (2H, d, *J* = 8.5 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 7.45 (2H, d, *J* = 8.2 Hz), 7.84 (2H, dt, *J* = 8.2, 1.7 Hz), 9.99 (1H, s).

5

Reference Example 111

4-[(*E*)-4-(4-Methylphenoxy)but-2-en-2-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 2.16 (3H, d, *J* = 1.0 Hz), 2.30 (3H, s), 4.73-4.75 (2H, m), 6.17-6.21 (1H, m), 6.85 (2H, dt, *J* = 9.1, 2.4 Hz), 7.10 (2H, d, *J* = 8.3 Hz), 7.58 (2H, dt, *J* = 8.5, 1.8 Hz), 7.84 (2H, dt, *J* = 8.5, 1.8 Hz), 10.00 (1H, s).

10

Reference Example 112

4-[2-(4-Chlorophenoxy)ethyl]-3-fluorobenzaldehyde

¹H-NMR (CDCl₃) δ: 3.20 (2H, t, *J* = 6.6 Hz), 4.19 (2H, t, *J* = 6.6 Hz), 6.80 (2H, d, *J* = 8.8 Hz), 7.22 (2H, d, *J* = 8.8 Hz), 7.48-7.49 (1H, m), 7.56 (1H, d, *J* = 9.8 Hz), 7.63 (1H, d, *J* = 7.6 Hz), 9.96 (1H, d, *J* = 1.5 Hz).

15

[0133]

Reference Example 113

To a THF (44 mL) solution of *tert*-butyl 4-(4-bromo-2-fluorobenzyl)piperazine-1-carboxylate (8.445 g) was added slowly *n*-BuLi (11.31 mL, 2.6 M in hexane) at -78 °C, then the resultant mixture was stirred for 0.5 hour. To the mixture was added slowly DMF (1.927 mL) at -78 °C. After stirring for 1 hour at -78 °C, then the mixture was stirred at room temperature over night. The mixture was poured into saturated aqueous NH₄Cl, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 2/1) to afford a colorless oil. To a MeOH (13 mL) solution of that colorless oil was added NaBH₄ (0.200 g) at 0 °C, then the resultant mixture was stirred for 5 hours. To the reaction mixture was added saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 1/1) to afford *tert*-butyl 4-[2-fluoro-4-(hydroxymethyl)benzyl]piperazine-1-carboxylate as a colorless oil (0.500 g).

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¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.70-1.80 (1H, m), 2.41-2.42 (4H, m), 3.42-3.43 (4H, m), 3.58

(2H, s), 4.69 (2H, s), 7.06-7.12 (2H, m), 7.33-7.37 (1H, m).

[0134]

Reference Example 114

To a THF (53 mL) solution of *tert*-butyl 4-(4-bromo-2-fluorobenzyl)piperazine-1-carboxylate (5.331 g) was added slowly *n*-BuLi (11.48 mL, 2.6 M in hexane) at -78 °C, then the resultant mixture was stirred for 0.5 hour. To the mixture was added slowly DMF (1.681 mL) at -78 °C, then the resultant mixture was stirred for 2 hours. The mixture was poured into saturated aqueous NH₄Cl, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 95/5 to 67/33) to afford a colorless oil. To a CH₂Cl₂ (25 mL) solution of that colorless oil and *tert*-butyl 1-piperazinecarboxylate (3.42 g) were added NaBH(OAc)₃ (5.310 g) at 0 °C. The resultant mixture was stirred at room temperature over night. To the reaction mixture was added saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 67/33 to 33/67) to afford a colorless oil. To a THF (25 mL) solution of that colorless oil was added TBAF (25.05 mL, 1.0 M in THF) at 0 °C. The resultant mixture was stirred at room temperature for 1 hour. After cooling to 0 °C, the reaction mixture was diluted with AcOEt and water. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 67/33 to 1/4) to afford *tert*-butyl 4-[3-fluoro-4-(hydroxymethyl)benzyl]piperazine-1-carboxylate as a colorless oil (2.303 g).

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.78-1.80 (1H, m), 2.37-2.38 (4H, m), 3.42-3.43 (4H, m), 3.49 (2H, s), 4.74 (2H, s), 7.05-7.10 (2H, m), 7.33-7.38 (1H, m).

[0135]

Reference Example 115

To a solution of {4-[2-(4-methylphenoxy)propyl]phenyl}methanol (0.725 g) in THF (20 mL) were added CCl₄ (2.3 mL) and PPh₃ (1.640 g) at room temperature under an Ar atmosphere. The mixture was heated at reflux for 6.5 hours, and then cooled to room temperature, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ AcOEt = 5/1) to afford 1-[4-(chloromethyl)phenyl]propan-2-yl 4-methylphenyl ether (0.696 g) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.28 (3H, d, *J* = 6.1 Hz), 2.27 (3H, s), 2.81 (1H, dd, *J* = 13.7, 6.6 Hz), 3.07

(1H, dd, $J = 13.7, 6.1$ Hz), 4.47-4.55 (1H, m), 4.57 (2H, s), 6.78 (2H, dt, $J = 9.1, 2.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.23 (2H, d, $J = 8.3$ Hz), 7.31 (2H, d, $J = 8.3$ Hz).

[0136]

The following compounds were produced in the same manner as in Reference

5 Example 115 using appropriate starting materials.

Reference Example 116

2-[4-(Chloromethyl)-2-methylphenyl]ethyl 4-methylphenyl ether

$^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.37 (3H, s), 3.09 (2H, t, $J = 7.3$ Hz), 4.11 (2H, t, $J = 7.3$ Hz),
10 4.55 (2H, s), 6.79 (2H, dt, $J = 9.2, 2.6$ Hz), 7.07 (2H, dd, $J = 8.8, 0.5$ Hz), 7.16-7.23 (3H, m).

Reference Example 117

2-[4-(Chloromethyl)-2-methylphenyl]ethyl 4-fluorophenyl ether

$^1\text{H-NMR}$ (CDCl_3) δ : 2.37 (3H, s), 3.09 (2H, t, $J = 7.2$ Hz), 4.09 (2H, t, $J = 7.2$ Hz), 4.55 (2H, s),
15 6.79-6.84 (2H, m), 6.92-6.99 (2H, m), 7.17-7.22 (3H, m).

Reference Example 118

(*E*)-3-[4-(Chloromethyl)-2-methylphenyl]prop-2-en-1-yl 4-methylphenyl ether

$^1\text{H-NMR}$ (CDCl_3) δ : 2.29 (3H, s), 2.34 (3H, s), 4.55 (2H, s), 4.69 (2H, dd, $J = 5.9, 1.5$ Hz), 6.30
20 (1H, dt, $J = 15.9, 5.9$ Hz), 6.86 (2H, dt, $J = 9.3, 2.5$ Hz), 6.91 (1H, d, $J = 15.9$ Hz), 7.09 (2H, d, $J = 8.8$ Hz), 7.17-7.20 (2H, m), 7.46 (1H, d, $J = 7.8$ Hz).

Reference Example 119

(*E*)-3-[4-(Chloromethyl)-3-methylphenyl]prop-2-en-1-yl 4-methylphenyl ether

$^1\text{H-NMR}$ (CDCl_3) δ : 2.29 (3H, s), 2.42 (3H, s), 4.60 (2H, s), 4.67 (2H, dd, $J = 5.7, 1.6$ Hz), 6.41
25 (1H, dt, $J = 16.0, 5.7$ Hz), 6.68 (1H, d, $J = 16.0$ Hz), 6.85 (2H, dt, $J = 9.2, 2.4$ Hz), 7.09 (2H, d, $J = 8.8$ Hz), 7.21-7.35 (3H, m).

Reference Example 120

30 1-(Chloromethyl)-2-methyl-4-[2-(4-methylphenoxy)ethyl]benzene

$^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.42 (3H, s), 3.04 (2H, t, $J = 7.2$ Hz), 4.13 (2H, t, $J = 7.2$ Hz),
4.60 (2H, s), 6.79 (2H, dt, $J = 9.3, 2.6$ Hz), 7.06-7.12 (4H, m), 7.24 (1H, brs).

[0137]

Reference Example 121

To a CH₃CN (250 mL) solution of piperazine-1-carboxylic acid *tert*-butyl ester (19.8 g) and alpha,alpha-dichloro-*p*-xylene (18.6 g) was added DIPEA (18.5 mL) under a N₂ atmosphere, then the resultant mixture was stirred at room temperature for 3 days. The reaction mixture was poured into saturated aqueous NaHCO₃ (600 mL) and extracted with AcOEt (900 mL). The organic layer was washed with saturated aqueous NaCl (300 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1) to afford *tert*-butyl 4-[4-(chloromethyl)benzyl]piperazine-1-carboxylate (16.3 g) as a white powder.

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36-2.39 (4H, m), 3.40-3.44 (4H, m), 3.50 (2H, s), 4.58 (2H, s), 7.26-7.36 (4H, m).

[0138]

The following compounds were produced in the same manner as in Reference Example 121 using appropriate starting materials.

15 Reference Example 122

tert-Butyl 4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.28 (3H, d, *J* = 6.1 Hz), 1.45 (9H, s), 2.27 (3H, s), 2.36 (4H, t, *J* = 4.9 Hz), 2.78 (1H, dd, *J* = 13.7, 6.7 Hz), 3.06 (1H, dd, *J* = 13.7, 6.1 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 4.47-4.54 (1H, m), 6.77 (2H, dt, *J* = 9.4, 2.6 Hz), 7.05 (2H, dd, *J* = 8.7, 0.6 Hz), 7.18 (2H, d, *J* = 8.3 Hz), 7.22 (2H, d, *J* = 8.3 Hz).

Reference Example 123

tert-Butyl 4-{3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.28 (3H, s), 2.35 (3H, s), 2.38 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.4 Hz), 3.41-3.46 (6H, m), 4.10 (2H, t, *J* = 7.4 Hz), 6.79 (2H, dt, *J* = 9.1, 2.4 Hz), 7.05-7.11 (4H, m), 7.16 (1H, d, *J* = 7.6 Hz).

Reference Example 124

tert-Butyl 4-{4-[2-(4-fluorophenoxy)ethyl]-3-methylbenzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.35 (3H, s), 2.37 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.3 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.45 (2H, s), 4.09 (2H, t, *J* = 7.3 Hz), 6.79-6.85 (2H, m), 6.92-6.99 (2H, m), 7.09-7.17 (3H, m).

Reference Example 125

tert-Butyl 4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.28 (3H, s), 2.34 (3H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.03 (2H, t, *J* = 7.2 Hz), 3.39 (4H, t, *J* = 4.9 Hz), 3.43 (2H, s), 4.13 (2H, t, *J* = 7.2 Hz), 6.80 (2H, dt, *J* = 9.2, 2.5 Hz), 6.98-7.07 (4H, m), 7.17 (1H, d, *J* = 7.6 Hz).

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[0139]

Reference Example 126

To a solution of *tert*-butyl 4-[4-(chloromethyl)benzyl]piperazine-1-carboxylate (4.00 g) in DMF (25 mL) were added 4-isopropoxyphenol (2.81 g) and K₂CO₃ (3.40 g) at room temperature, then the reaction mixture was stirred for 2 days. The reaction mixture was diluted with H₂O, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 1/1) to afford *tert*-butyl 4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazine-1-carboxylate as a colorless solid (5.42 g).

15

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 5.9 Hz), 1.45 (9H, s), 2.39 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 4.42 (1H, septet, *J* = 5.9 Hz), 4.99 (2H, s), 6.80-6.96 (4H, m), 7.29-7.43 (4H, m).

[0140]

The following compounds were produced in the same manner as in Reference Example 126 using appropriate starting materials.

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Reference Example 127

tert-Butyl 4-{4-[(4-chlorophenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 5.01 (2H, s), 6.86-6.93 (2H, m), 7.20-7.26 (2H, m), 7.31-7.39 (4H, m).

25

Reference Example 128

tert-Butyl 4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 5.01 (2H, s), 6.89-6.94 (2H, m), 7.13-7.17 (2H, m), 7.32 (2H, d, *J* = 8.2 Hz), 7.38 (2H, d, *J* = 8.2 Hz).

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Reference Example 129

tert-Butyl 4-(4-{[4-(1*H*-pyrrol-1-yl)phenoxy]methyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.39 (4H, t, *J* = 5.0 Hz), 3.43 (4H, t, *J* = 5.0 Hz), 3.52 (2H, s), 5.06 (2H, s), 6.31-6.33 (2H, m), 6.99-7.04 (4H, m), 7.31 (2H, d, *J* = 8.9 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 7.40 (2H, d, *J* = 8.2 Hz).

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Reference Example 130

tert-Butyl 4-{4-[(4-fluorophenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (DMSO-*d*₆) δ: 1.39 (9H, s), 2.29 (4H, t, *J* = 4.9 Hz), 3.28-3.31 (4H, m), 3.47 (2H, s), 5.05 (2H, s), 6.98-7.05 (2H, m), 7.07-7.15 (2H, m), 7.31 (2H, d, *J* = 7.9 Hz), 7.39 (2H, d, *J* = 7.9 Hz).

10

Reference Example 131

tert-Butyl 4-{4-[(4-methoxyphenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 3.77 (3H, s), 4.99 (2H, s), 6.75-6.96 (4H, m), 7.29-7.43 (4H, m).

15

Reference Example 132

tert-Butyl 4-{4-[(4-ethoxyphenoxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 6.9 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 3.97 (2H, q, *J* = 6.9 Hz), 4.99 (2H, s), 6.70-6.95 (4H, m), 7.28-7.43 (4H, m).

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Reference Example 133

tert-Butyl 4-{4-[(1,3-benzodioxol-5-yloxy)methyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 4.96 (2H, s), 5.91 (2H, s), 6.39 (1H, dd, *J* = 8.6, 2.3 Hz), 6.56 (1H, d, *J* = 2.3 Hz), 6.70 (1H, d, *J* = 8.6 Hz), 7.30-7.38 (4H, m).

25

Reference Example 134

tert-Butyl 4-{4-[2-(4-fluorophenyl)-2-oxoethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.35 (4H, t, *J* = 5.3 Hz), 3.35-3.48 (6H, m), 5.20 (2H, s), 6.83-6.93 (2H, m), 7.12-7.27 (4H, m), 8.00-8.10 (2H, m).

30

Reference Example 135

tert-Butyl 4-{4-[2-(4-chlorophenoxy)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.36 (4H, t, *J* = 4.9 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.44 (2H, s), 4.25-4.30 (4H, m), 6.84-6.90 (4H, m), 7.21-7.26 (4H, m).

5 Reference Example 136

tert-Butyl 4-{4-[2-(4-methylphenoxy)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.29 (3H, s), 2.36 (4H, brs), 3.41 (4H, t, *J* = 4.9 Hz), 3.45 (2H, s), 4.30 (4H, s), 6.85 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 7.22 (2H, d, *J* = 8.5 Hz).

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Reference Example 137

tert-Butyl 4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 7.0 Hz), 1.45 (9H, s), 2.35 (4H, t, *J* = 4.9 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.43 (2H, s), 3.97 (2H, q, *J* = 7.0 Hz), 4.24-4.28 (4H, m), 6.81-6.90 (6H, m), 7.20-

15 7.22 (2H, m).

Reference Example 138

tert-Butyl 4-{4-[2-(4-methoxyphenoxy)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.35 (4H, t, *J* = 4.9 Hz), 3.40-3.43 (6H, m), 3.74 (3H, s), 4.23-
20 4.27 (4H, m), 6.81-6.84 (2H, m), 6.86-6.90 (4H, m), 7.21 (2H, d, *J* = 8.8 Hz).

Reference Example 139

tert-Butyl 4-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3-fluorobenzyl}piperazine-1-carboxylate

25 ¹H-NMR (CDCl₃) δ: 1.29 (3H, t, *J* = 7.2 Hz), 1.45 (9H, s), 1.57 (6H, s), 2.34-2.37 (4H, m), 3.41-3.43 (6H, m), 4.25 (2H, q, *J* = 7.2 Hz), 6.91-6.92 (2H, m), 7.07 (1H, d, *J* = 12.2 Hz).

Reference Example 140

Ethyl 4-[(4-methylphenoxy)acetyl]benzoate

30 ¹H-NMR (CDCl₃) δ: 1.42 (3H, t, *J* = 7.1 Hz), 2.28 (3H, s), 4.42 (2H, q, *J* = 7.1 Hz), 5.23 (2H, s), 6.82-6.86 (2H, m), 7.06-7.10 (2H, m), 8.04-8.06 (2H, m), 8.14-8.16 (2H, m).

[0141]

Reference Example 141

To a DMF (10 mL) solution of *tert*-butyl 4-[4-(2-hydroxyethyl)benzyl]piperazine-1-carboxylate (1.000 g) was added NaH (112 mg, 60% in mineral oil) at 0 °C, then the resultant mixture was stirred for 1 hour. To the mixture was added 2-fluoro-6-methylpyridine (0.419 mL), then the resultant mixture was stirred at 70 °C over night. The mixture was poured into
5 water, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 4/1 to 1/1) to afford *tert*-butyl 4-(4-{2-[(6-methylpyridin-2-yl)oxy]ethyl}benzyl)piperazine-1-carboxylate as a pale yellow amorphous powder (350 mg).

10 ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37-2.38 (4H, m), 2.42 (3H, s), 3.06 (2H, t, *J* = 7.2 Hz), 3.41-3.42 (4H, m), 3.48 (2H, s), 4.48 (2H, t, *J* = 7.2 Hz), 6.50 (1H, d, *J* = 8.1 Hz), 6.69 (1H, d, *J* = 7.1 Hz), 7.24-7.26 (4H, m), 7.42-7.44 (1H, m).

[0142]

The following compounds were produced in the same manner as in Reference

15 Example 141 using appropriate starting materials.

Reference Example 142

tert-Butyl 4-(4-{[(4-fluorobenzyl)oxy]methyl}benzyl)piperazine-1-carboxylate

20 ¹H-NMR (DMSO-*d*₆) δ: 1.38 (9H, s), 2.29 (4H, t, *J* = 4.9 Hz), 3.30 (4H, t, *J* = 4.9 Hz), 3.46 (2H, s), 4.50 (2H, s), 4.50 (2H, s), 7.14-7.22 (2H, m), 7.25-7.33 (4H, m), 7.36-7.42 (2H, m).

Reference Example 143

tert-Butyl 4-[4-({[4-(propan-2-yl)benzyl]oxy}methyl)benzyl]piperazine-1-carboxylate

25 ¹H-NMR (CDCl₃) δ: 1.25 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 2.91 (1H, septet, *J* = 6.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.50 (2H, s), 4.53 (2H, s), 4.53 (2H, s), 7.20-7.34 (8H, m).

Reference Example 144

tert-Butyl 4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)benzyl]piperazine-1-carboxylate

30 ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 5.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 5.1 Hz), 3.48 (2H, s), 4.57 (2H, t, *J* = 7.1 Hz), 6.80 (1H, d, *J* = 8.9 Hz), 7.21-7.27 (4H, m), 7.75 (1H, dd, *J* = 8.9, 2.5 Hz), 8.42 (1H, brs).

Reference Example 145

tert-Butyl 4-{4-[2-(4-nitrophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.11-3.14 (2H, m), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, brs), 4.24-4.27 (2H, m), 6.94 (2H, d, *J* = 9.3 Hz), 7.23 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.8 Hz), 8.19 (2H, d, *J* = 9.3 Hz).

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[0143]

Reference Example 146

To a dioxane (10 mL) solution of 4-bromo-2-chlorophenol (207 mg) were added *n*-butyl acrylate (0.158 mL), *N*-methyldicyclohexylamine (0.236 mL), tri-*tert*-butylphosphonium tetrafluoroborate (12 mg), and tris(dibenzylideneacetone)dipalladium (0) (18 mg) under a N₂ atmosphere. The resultant mixture was refluxed over night. After cooling, the reaction mixture was filtered off on Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 4/1 to 2/1) to afford butyl (*E*)-3-(3-chloro-4-hydroxyphenyl)prop-2-enoate (244 mg) as a colorless oil.

10 ¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.8 Hz), 1.36-1.49 (2H, m), 1.62-1.74 (2H, m), 4.20 (2H, t, *J* = 6.9 Hz), 5.84 (1H, s), 6.31 (1H, d, *J* = 15.6 Hz), 7.02 (1H, d, *J* = 8.2 Hz), 7.36 (1H, dd, *J* = 8.7, 2.3 Hz), 7.52 (1H, d, *J* = 1.8 Hz), 7.55 (1H, d, *J* = 16.0 Hz).

[0144]

The following compounds were produced in the same manner as in Reference
20 Example 146 using appropriate starting materials.

Reference Example 147

Butyl (*E*)-3-(4-hydroxy-3-methylphenyl)prop-2-enoate

10 ¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.42-1.46 (2H, m), 1.63-1.73 (2H, m), 2.26 (3H, s), 4.20 (2H, t, *J* = 6.6 Hz), 5.01 (1H, s), 6.29 (1H, d, *J* = 16.2 Hz), 6.77 (1H, d, *J* = 8.2 Hz), 7.25-7.32 (2H, m), 7.60 (1H, d, *J* = 16.2 Hz).

Reference Example 148

Butyl (*E*)-3-(4-hydroxy-2-methylphenyl)prop-2-enoate

30 ¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.37-1.50 (2H, m), 1.64-1.74 (2H, m), 2.38 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.41-5.44 (1H, m), 6.26 (1H, d, *J* = 15.8 Hz), 6.67-6.71 (2H, m), 7.47-7.50 (1H, m), 7.91 (1H, d, *J* = 15.8 Hz).

Reference Example 149

Butyl (*E*)-3-(3-fluoro-4-hydroxyphenyl)prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.39-1.48 (2H, m), 1.65-1.72 (2H, m), 4.20 (2H, t, *J* = 6.6 Hz), 5.51 (1H, s), 6.30 (1H, d, *J* = 16.1 Hz), 6.99-7.03 (1H, m), 7.21-7.29 (2H, m), 7.57 (1H, d, *J* = 16.1 Hz).

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Reference Example 150

Butyl (*E*)-3-[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-methylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.95 (9H, s), 0.97 (3H, t, *J* = 8.1 Hz), 1.40-1.49 (2H, m), 1.66-1.73 (2H, m), 2.43 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 4.71 (2H, s), 6.35 (1H, d, *J* = 15.9 Hz), 7.15-7.18 (2H, m), 7.53 (1H, d, *J* = 7.8 Hz), 7.96 (1H, d, *J* = 15.9 Hz).

10

Reference Example 151

Butyl (*E*)-3-[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-methylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.11 (6H, s), 0.95 (9H, s), 0.97 (3H, t, *J* = 7.2 Hz), 1.39-1.49 (2H, m), 1.65-1.72 (2H, m), 2.27 (3H, s), 4.20 (2H, t, *J* = 6.7 Hz), 4.70 (2H, s), 6.41 (1H, d, *J* = 16.1 Hz), 7.29 (1H, brs), 7.37 (1H, dd, *J* = 7.9, 1.6 Hz), 7.45 (1H, d, *J* = 7.9 Hz), 7.65 (1H, d, *J* = 16.1 Hz).

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[0145]

Reference Example 152

To a DMF (30 mL) solution of 2-chloro-4-bromo-6-methylphenol (4.90 g) were added 2-chloro-5-nitropyridine (3.58 g) and K₂CO₃ (3.12 g) at room temperature. After stirring at 50 °C for 3 hours, the solvent was removed under reduced pressure. To the residue was added water, and extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give 2-(4-bromo-2-chloro-6-methylphenoxy)-5-nitropyridine as a brown solid (7.59 g).

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¹H-NMR (CDCl₃) δ: 2.17 (3H, s), 7.16 (1H, d, *J* = 8.8 Hz), 7.36-7.37 (1H, m), 7.48-7.49 (1H, m), 8.53 (1H, dd, *J* = 8.8, 2.8 Hz), 8.98 (1H, d, *J* = 2.8 Hz).

[0146]

The following compounds were produced in the same manner as in Reference Example 152 using appropriate starting materials.

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Reference Example 153

Butyl (*E*)-3-{3-methyl-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97(3H, t, *J* = 7.3 Hz), 1.38-1.52 (2H, m), 1.65-1.75 (2H, m), 2.18 (3H, s),

4.22 (2H, q, $J = 6.6$ Hz), 6.42 (1H, d, $J = 15.8$ Hz), 7.07-7.11 (2H, m), 7.43-7.48 (2H, m), 7.67 (1H, d, $J = 16.2$ Hz), 8.48-8.53 (1H, m), 9.02 (1H, d, $J = 3.0$ Hz).

Reference Example 154

5 Ethyl (*E*)-3-{3-methoxy-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.36 (3H, t, $J = 7.1$ Hz), 3.78 (3H, s), 4.28 (2H, q, $J = 7.2$ Hz), 6.42 (1H, d, $J = 16.1$ Hz), 7.09 (1H, d, $J = 9.3$ Hz), 7.16-7.22 (3H, m), 7.68 (1H, d, $J = 16.1$ Hz), 8.49 (1H, dd, $J = 9.0, 2.7$ Hz), 9.00 (1H, d, $J = 2.9$ Hz).

10 Reference Example 155

3,5-Dimethoxy-4-[(5-nitropyridin-2-yl)oxy]benzaldehyde

$^1\text{H-NMR}$ (CDCl_3) δ : 3.87 (6H, s), 7.17 (1H, d, $J = 9.0$ Hz), 7.24 (2H, s), 8.50 (1H, dd, $J = 9.0, 2.7$ Hz), 8.96 (1H, d, $J = 2.7$ Hz), 9.96 (1H, brs).

15 Reference Example 156

Butyl (*E*)-3-{2-methyl-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

$^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.38-1.51 (2H, m), 1.63-1.76 (2H, m), 2.46 (3H, s), 4.22 (2H, t, $J = 6.9$ Hz), 6.36 (1H, d, $J = 15.8$ Hz), 7.00-7.08 (3H, m), 7.62-7.66 (1H, m), 7.94 (1H, d, $J = 15.8$ Hz), 8.50 (1H, dd, $J = 8.9, 2.6$ Hz), 9.05 (1H, d, $J = 2.6$ Hz).

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Reference Example 157

Methyl 2-[4-(propan-2-yl)phenoxy]quinoline-6-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (6H, d, $J = 6.9$ Hz), 2.97 (1H, septet, $J = 6.9$ Hz), 3.97 (3H, s), 7.10-7.22 (3H, m), 7.24-7.34 (2H, m), 7.81 (1H, d, $J = 8.9$ Hz), 8.19 (1H, d, $J = 8.9$ Hz), 8.20 (1H, dd, $J = 8.9, 2.0$ Hz), 8.51 (1H, d, $J = 2.0$ Hz).

25

Reference Example 158

Methyl 2-(4-methoxyphenoxy)quinoline-6-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 3.85 (3H, s), 3.97 (3H, s), 6.92-7.01 (2H, m), 7.12 (1H, d, $J = 8.6$ Hz), 7.15-7.22 (2H, m), 7.79 (1H, d, $J = 8.9$ Hz), 8.18 (1H, d, $J = 8.9$ Hz), 8.21 (1H, dd, $J = 8.9, 2.0$ Hz), 8.50 (1H, d, $J = 1.6$ Hz).

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Reference Example 159

Butyl (*E*)-3-{3-chloro-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.38-1.51 (2H, m), 1.66-1.76 (2H, m), 4.23 (2H, t, *J* = 6.8 Hz), 6.44 (1H, d, *J* = 16.1 Hz), 7.17 (1H, d, *J* = 9.8 Hz), 7.26 (1H, d, *J* = 8.3 Hz), 7.51 (1H, dd, *J* = 8.3, 2.0 Hz), 7.64 (1H, d, *J* = 16.1 Hz), 7.67 (1H, d, *J* = 2.0 Hz), 8.54 (1H, dd, *J* = 8.8, 2.4 Hz), 9.00 (1H, d, *J* = 2.9 Hz).

5

Reference Example 160

Butyl (*E*)-3-{3-fluoro-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.40-1.49 (2H, m), 1.67-1.74 (2H, m), 4.23 (2H, t, *J* = 6.8 Hz), 6.42 (1H, d, *J* = 15.6 Hz), 7.17 (1H, d, *J* = 9.3 Hz), 7.27 (1H, t, *J* = 8.1 Hz), 7.37-

10 7.41 (2H, m), 7.64 (1H, d, *J* = 16.1 Hz), 8.54 (1H, dd, *J* = 9.0, 2.7 Hz), 9.01 (1H, d, *J* = 2.9 Hz).

Reference Example 161

Ethyl 6-[(5-nitropyridin-2-yl)oxy]naphthalene-2-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (3H, t, *J* = 7.1 Hz), 4.46 (2H, q, *J* = 7.2 Hz), 7.14 (1H, dd, *J* = 9.0, 0.5 Hz), 7.36 (1H, dd, *J* = 8.9, 2.3 Hz), 7.67 (1H, d, *J* = 2.4 Hz), 7.86 (1H, d, *J* = 8.8 Hz), 8.04 (1H, d, *J* = 9.0 Hz), 8.11 (1H, dd, *J* = 8.7, 1.6 Hz), 8.53 (1H, dd, *J* = 9.0, 2.7 Hz), 8.65 (1H, d, *J* = 0.5 Hz), 9.05 (1H, dd, *J* = 2.9, 0.5 Hz).

Reference Example 162

20 3,5-Dimethyl-4-[(5-nitropyridin-2-yl)oxy]benzaldehyde

¹H-NMR (CDCl₃) δ: 2.18 (6H, s), 7.15 (1H, d, *J* = 9.0 Hz), 7.69 (2H, s), 8.54 (1H, dd, *J* = 9.0, 2.7 Hz), 8.98 (1H, d, *J* = 2.7 Hz), 9.98 (1H, brs).

Reference Example 163

25 2-(4-Bromo-5-chloro-2-methylphenoxy)-5-nitropyridine

¹H-NMR (CDCl₃) δ: 2.11 (3H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (1H, s), 7.56 (1H, s), 8.51 (1H, dd, *J* = 9.0, 2.9 Hz), 9.01 (1H, d, *J* = 2.9 Hz).

Reference Example 164

30 2-(4-Bromo-2-chloro-5-methylphenoxy)-5-nitropyridine

¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 7.11-7.14 (2H, m), 7.67 (1H, s), 8.52 (1H, dd, *J* = 9.0, 2.7 Hz), 9.00 (1H, d, *J* = 2.7 Hz).

[0147]

Reference Example 165

To a THF (39 mL) suspension of LiAlH_4 (0.15 g) was slowly added methyl 2-(4-methoxyphenoxy)quinoline-6-carboxylate (1.22 g) at 0 °C, then the resultant mixture was stirred over night at room temperature. The reaction mixture was acidified with 6 M aqueous HCl, and
5 extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford [2-(4-methoxyphenoxy)quinolin-6-yl]methanol (1.11 g) as a pale yellow amorphous powder.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.89 (1H, brs), 3.84 (3H, s), 4.84 (2H, s), 6.91-6.99 (2H, m), 7.05 (1H, d, J = 8.6 Hz), 7.13-7.22 (2H, m), 7.59 (1H, dd, J = 8.6, 2.0 Hz), 7.73 (1H, brs), 7.78 (1H, d, J = 8.6
10 Hz), 8.08 (1H, d, J = 8.6 Hz).

[0148]

The following compounds were produced in the same manner as in Reference Example 165 using appropriate starting materials.

15 Reference Example 166

{2-[4-(Propan-2-yl)phenoxy]quinolin-6-yl}methanol

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (6H, d, J = 6.9 Hz), 1.65 (1H, brs), 2.96 (1H, septet, J = 6.9 Hz), 4.84 (2H, s), 7.05 (1H, d, J = 8.9 Hz), 7.13-7.20 (2H, m), 7.24-7.31 (2H, m), 7.60 (1H, dd, J = 8.6, 2.0
20 Hz), 7.71-7.75 (1H, m), 7.80 (1H, d, J = 8.9 Hz), 8.08 (1H, d, J = 8.9 Hz).

Reference Example 167

1-[4-(Hydroxymethyl)phenyl]-2-(4-methylphenoxy)ethanol

$^1\text{H-NMR}$ (CDCl_3) δ : 1.63 (1H, t, J = 5.4 Hz), 2.29 (3H, s), 2.77 (1H, d, J = 2.6 Hz), 3.97 (1H, dd, J = 9.8, 9.0 Hz), 4.08 (1H, dd, J = 9.8, 3.2 Hz), 4.72 (2H, d, J = 5.4 Hz), 5.12 (1H, dt, J = 9.0,
25 2.6 Hz), 6.80-6.83 (2H, m), 7.06-7.10 (2H, m), 7.40 (2H, d, J = 8.1 Hz), 7.46 (2H, d, J = 8.1 Hz).

Reference Example 168

tert-Butyl 4-{3-fluoro-4-[(1-hydroxy-2-methylpropan-2-yl)oxy]benzyl}piperazine-1-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (6H, s), 1.46 (9H, s), 2.33-2.37 (5H, m), 3.43-3.44 (6H, m), 3.58-3.60
30 (2H, m), 6.99-7.01 (2H, m), 7.10 (1H, d, J = 11.2 Hz).

[0149]

Reference Example 169

To a solution of (*E*)-ethyl 3-(4-(diethoxymethyl)phenyl)acrylate (1.400 g) in

toluene (10 mL) was added DIBAH(1 M solution in toluene) (10 mL) at -20 °C under an Ar atmosphere. The mixture was stirred at -20 °C for 1 hour. To the mixture was added MeOH, and then the mixture was heated to room temperature. To the mixture was added water, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ AcOEt = 1/1) to afford (*E*)-3-[4-(diethoxymethyl)phenyl]prop-2-en-1-ol (1.120 g) as a colorless oil.

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.1 Hz), 1.42 (1H, t, *J* = 6.0 Hz), 3.49-3.65 (4H, m), 4.33 (2H, td, *J* = 6.0, 1.5 Hz), 5.49 (1H, s), 6.38 (1H, dt, *J* = 16.1, 6.0 Hz), 6.62 (1H, dt, *J* = 16.1, 1.5 Hz), 7.38 (2H, dd, *J* = 6.6, 1.8 Hz), 7.43 (2H, dd, *J* = 6.6, 1.8 Hz).

[0150]

The following compounds were produced in the same manner as in Reference Example 169 using appropriate starting materials.

15 Reference Example 170

(*E*)-3-[4-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-2-methylphenyl]prop-2-en-1-ol

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 1.42 (1H, t, *J* = 6.0 Hz), 2.35 (3H, s), 4.32-4.36 (2H, m), 4.69 (2H, s), 6.25 (1H, dt, *J* = 15.9, 5.8 Hz), 6.81 (1H, d, *J* = 15.9 Hz), 7.10-7.13 (2H, m), 7.42 (1H, d, *J* = 8.1 Hz).

20

Reference Example 171

(*E*)-3-[4-({*tert*-Butyl(dimethyl)silyl}oxy)methyl]-3-methylphenyl]prop-2-en-1-ol

¹H-NMR (CDCl₃) δ: 0.10 (6H, s), 0.94 (9H, s), 1.40-1.43 (1H, m), 2.26 (3H, s), 4.30-4.33 (2H, m), 4.69 (2H, s), 6.34 (1H, dt, *J* = 15.9, 5.9 Hz), 6.58 (1H, dt, *J* = 15.9, 1.3 Hz), 7.16 (1H, d, *J* = 1.7 Hz), 7.22 (1H, dd, *J* = 8.1, 1.7 Hz), 7.36 (1H, d, *J* = 8.1 Hz).

25

Reference Example 172

(*E*)-3-[4-(Diethoxymethyl)phenyl]-2-methylprop-2-en-1-ol

¹H-NMR (CDCl₃) δ: 1.24 (6H, t, *J* = 7.0 Hz), 1.50 (1H, t, *J* = 6.1 Hz), 1.90 (3H, d, *J* = 1.0 Hz), 3.51-3.67 (4H, m), 4.19 (2H, d, *J* = 6.1 Hz), 5.50 (1H, s), 6.52 (1H, brs), 7.28 (2H, d, *J* = 8.3 Hz), 7.44 (2H, d, *J* = 8.3 Hz).

30

[0151]

Reference Example 173

To a CH₂Cl₂ (38 mL) solution of [2-(4-methoxyphenoxy)quinolin-6-yl]methanol (1.11 g) and iodobenzene diacetate (1.33 g) was added 2,2,6,6-tetramethyl-1-piperidinyloxy radical (61.0 mg), then the resultant mixture was stirred over night at room temperature. The reaction mixture was quenched by addition of saturated aqueous Na₂S₂O₃ and NaHCO₃, and
5 extracted with CH₂Cl₂. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 10/1 to 5/1) to afford 2-(4-methoxyphenoxy)quinoline-6-carbaldehyde (1.08 g) as a colorless solid.

¹H-NMR (CDCl₃) δ: 3.86 (3H, s), 6.92-7.02 (2H, m), 7.13-7.23 (3H, m), 7.85 (1H, d, *J* = 8.6

10 Hz), 8.08 (1H, dd, *J* = 8.6, 1.6 Hz), 8.23 (1H, d, *J* = 8.9 Hz), 8.26 (1H, d, *J* = 2.0 Hz), 10.13 (1H, s).

[0152]

The following compounds were produced in the same manner as in Reference Example 173 using appropriate starting materials.

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Reference Example 174

2-[4-(Propan-2-yl)phenoxy]quinoline-6-carbaldehyde

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.9 Hz), 2.98 (1H, septet, *J* = 6.9 Hz), 7.14-7.22 (3H, m),
20 7.27-7.34 (2H, m), 7.88 (1H, d, *J* = 8.6 Hz), 8.09 (1H, dd, *J* = 8.6, 2.0 Hz), 8.24 (1H, d, *J* = 8.9 Hz), 8.27 (1H, d, *J* = 2.0 Hz), 10.13 (1H, s).

Reference Example 175

4-[(4-Methylphenoxy)acetyl]benzaldehyde

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 5.23 (2H, s), 6.82-6.85 (2H, m), 7.07-7.10 (2H, m), 7.98-8.01
25 (2H, m), 8.13-8.16 (2H, m), 10.11 (1H, s).

[0153]

Reference Example 176

To a solution of 1-(diethoxymethyl)-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzene (1.270 g) in THF (20 mL) was added 6 M HCl (4 mL) at room temperature. The mixture was stirred at room temperature for 0.5 hour. To the mixture was added 5 M NaOH (4 mL), and the mixture was evaporated under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under
30

reduced pressure to afford 4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzaldehyde (0.942 g) as a colorless solid.

¹H-NMR (CDCl₃) δ: 2.30 (3H, s), 4.72 (2H, dd, *J* = 5.4, 1.8 Hz), 6.58 (1H, dt, *J* = 16.2, 5.4 Hz), 6.80 (1H, dt, *J* = 16.2, 1.8 Hz), 6.86 (2H, dt, *J* = 9.2, 2.4 Hz), 7.10 (2H, d, *J* = 8.3 Hz), 7.55 (2H, d, *J* = 8.3 Hz), 7.84 (2H, dt, *J* = 8.3, 1.7 Hz), 9.99 (1H, s).

[0154]

The following compounds were produced in the same manner as in Reference Example 176 using appropriate starting materials.

10 Reference Example 177

4-[(*E*)-3-(4-Fluorophenoxy)prop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 4.70 (2H, dd, *J* = 5.4, 1.7 Hz), 6.56 (1H, dt, *J* = 16.3, 5.4 Hz), 6.79 (1H, dt, *J* = 16.3, 1.7 Hz), 6.88-6.93 (2H, m), 6.97-7.03 (2H, m), 7.56 (2H, d, *J* = 8.3 Hz), 7.85 (2H, dt, *J* = 8.3, 1.7 Hz), 9.99 (1H, s).

15

Reference Example 178

4-[(*E*)-3-Phenoxyprop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 4.75 (2H, dd, *J* = 5.4, 1.7 Hz), 6.59 (1H, dt, *J* = 16.1, 5.4 Hz), 6.81 (1H, d, *J* = 16.1 Hz), 6.95-7.00 (3H, m), 7.29-7.39 (2H, m), 7.56 (2H, d, *J* = 8.3 Hz), 7.83-7.86 (2H, m), 9.99 (1H, s).

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Reference Example 179

4-[(*E*)-3-(4-Methoxyphenoxy)prop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 3.78 (3H, s), 4.69 (2H, dd, *J* = 5.4, 1.5 Hz), 6.59 (1H, dt, *J* = 16.1, 5.4 Hz), 6.79 (1H, d, *J* = 16.1 Hz), 6.83-6.93 (4H, m), 7.55 (2H, d, *J* = 8.3 Hz), 7.83-7.85 (2H, m), 9.99 (1H, s).

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Reference Example 180

4-[(*E*)-3-[4-(Propan-2-yl)phenoxy]prop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 7.1 Hz), 2.82-2.93 (1H, m), 4.72 (2H, dd, *J* = 5.3, 1.7 Hz), 6.58 (1H, dt, *J* = 16.1, 5.3 Hz), 6.80 (1H, d, *J* = 16.1 Hz), 6.88-6.92 (2H, m), 7.15-7.18 (2H, m), 7.56 (2H, d, *J* = 8.2 Hz), 7.84 (2H, d, *J* = 8.2 Hz), 9.99 (1H, s).

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Reference Example 181

4-{{(E)-3-[(6-Chloropyridin-3-yl)oxy]prop-1-en-1-yl}benzaldehyde

¹H-NMR (CDCl₃) δ: 4.78 (2H, dd, *J* = 5.3, 1.6 Hz), 6.53 (1H, dt, *J* = 16.1, 5.3 Hz), 6.80 (1H, d, *J* = 16.1 Hz), 7.25 (2H, d, *J* = 2.0 Hz), 7.56 (2H, d, *J* = 8.1 Hz), 7.85-7.87 (2H, m), 8.13 (1H, t, *J* = 1.8 Hz), 10.00 (1H, s).

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Reference Example 182

4-{{(E)-3-[(5-Bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzaldehyde

¹H-NMR (CDCl₃) δ: 5.01 (2H, dd, *J* = 5.7, 1.3 Hz), 6.60 (1H, dt, *J* = 15.9, 5.7 Hz), 6.72-6.79 (2H, m), 7.55 (2H, d, *J* = 8.2 Hz), 7.68 (1H, dd, *J* = 8.8, 2.4 Hz), 7.84 (2H, d, *J* = 8.2 Hz), 8.21 (1H, d, *J* = 2.4 Hz), 9.99 (1H, s).

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Reference Example 183

4-{{(E)-3-[(5-Methylpyridin-2-yl)oxy]prop-1-en-1-yl}benzaldehyde

¹H-NMR (CDCl₃) δ: 2.26 (3H, s), 5.02 (2H, dd, *J* = 5.6, 1.5 Hz), 6.63 (1H, dt, *J* = 16.0, 5.6 Hz), 6.72 (1H, d, *J* = 8.6 Hz), 6.78 (1H, d, *J* = 16.0 Hz), 7.42 (1H, ddd, *J* = 8.6, 2.5, 0.5 Hz), 7.55 (2H, d, *J* = 8.3 Hz), 7.83 (2H, dt, *J* = 8.3, 1.7 Hz), 7.96-7.97 (1H, m), 9.98 (1H, s).

15

Reference Example 184

4-[(E)-3-Hydroxyprop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 1.68 (1H, brs), 4.39 (2H, s), 6.53 (1H, dt, *J* = 15.9, 5.3 Hz), 6.70 (1H, dt, *J* = 15.9, 1.7 Hz), 7.53 (2H, d, *J* = 8.2 Hz), 7.83 (2H, dt, *J* = 8.2, 1.7 Hz), 9.98 (1H, s).

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Reference Example 185

4-(3-Phenoxypropyl)benzaldehyde

¹H-NMR (CDCl₃) δ: 1.56-1.58 (1H, m), 2.13-2.15 (2H, m), 2.91 (2H, t, *J* = 7.6 Hz), 3.97 (2H, t, *J* = 6.1 Hz), 6.87-6.91 (2H, m), 6.93-6.96 (1H, m), 7.26-7.31 (2H, m), 7.38 (2H, d, *J* = 8.2 Hz), 7.81 (2H, d, *J* = 8.2 Hz), 9.98 (1H, s).

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Reference Example 186

4-{3-[(6-Chloropyridin-3-yl)oxy]propyl}benzaldehyde

¹H-NMR (CDCl₃) δ: 2.12-2.19 (2H, m), 2.91 (2H, t, *J* = 7.6 Hz), 4.00 (2H, t, *J* = 6.1 Hz), 7.16 (1H, dd, *J* = 8.8, 3.0 Hz), 7.22 (1H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 8.0 Hz), 8.04 (1H, d, *J* = 3.0 Hz), 9.98 (1H, s).

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Reference Example 187

4-[(*E*)-2-Methyl-3-(4-methylphenoxy)prop-1-en-1-yl]benzaldehyde

¹H-NMR (CDCl₃) δ: 1.99 (3H, d, *J* = 1.2 Hz), 2.30 (3H, s), 4.56 (2H, s), 6.68 (1H, brs), 6.87 (2H, dt, *J* = 9.2, 2.6 Hz), 7.10 (2H, dd, *J* = 8.7, 0.6 Hz), 7.45 (2H, d, *J* = 8.3 Hz), 7.85 (2H, dt, *J* = 8.3, 1.7 Hz), 9.99 (1H, s).

[0155]

Reference Example 188

To a solution of 3-[4-(diethoxymethyl)phenyl]propan-1-ol (3.00 g), *p*-cresol (1.63 g), and triphenylphosphine (4.95 g) in THF (25 mL) was added 2.2 M solution of DEAD in toluene (8.58 mL). After stirring at room temperature for 2 hours, to the reaction mixture was added H₂O, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/0 to 9/1) to afford a colorless oil (0.751 g). To a solution of that colorless oil (0.751 g) in THF (30 mL) was added 6 M aqueous HCl (0.492 mL). After stirring at room temperature for 1 hour, to the reaction mixture was added 5 M aqueous NaOH, and the solvent was removed under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 4/1) to afford 4-[3-(4-methylphenoxy)propyl]benzaldehyde as a colorless oil (0.497 g).

¹H-NMR (CDCl₃) δ: 2.08-2.15 (2H, m), 2.29 (3H, s), 2.90 (2H, t, *J* = 7.6 Hz), 3.94 (2H, t, *J* = 6.1 Hz), 6.79 (2H, dt, *J* = 9.2, 2.4 Hz), 7.06-7.10 (2H, m), 7.38 (2H, d, *J* = 8.1 Hz), 7.81 (2H, dt, *J* = 8.1, 1.7 Hz), 9.98 (1H, s).

[0156]

The following compounds were produced in the same manner as in Reference Example 188 using appropriate starting materials.

30 Reference Example 189

{4-[2-(4-Fluorophenoxy)ethyl]-3-methylphenyl}methanol

¹H-NMR (CDCl₃) δ: 1.54 (1H, brs), 2.38 (3H, s), 3.09 (2H, t, *J* = 7.3 Hz), 4.09 (2H, t, *J* = 7.3 Hz), 4.65 (2H, s), 6.79-6.84 (2H, m), 6.92-6.99 (2H, m), 7.15-7.23 (3H, m).

Reference Example 190

4-[2-(4-Fluorophenoxy)propyl]benzaldehyde

¹H-NMR (CDCl₃) δ: 1.30 (3H, d, *J* = 6.1 Hz), 2.94 (1H, dd, *J* = 13.8, 5.6 Hz), 3.11 (1H, dd, *J* = 13.8, 6.7 Hz), 4.46-4.54 (1H, m), 6.76-6.81 (2H, m), 6.91-6.97 (2H, m), 7.41 (2H, d, *J* = 8.3 Hz),
5 7.82 (2H, d, *J* = 8.3 Hz), 9.98 (1H, s).

Reference Example 191

{2-Methyl-4-[2-(4-methylphenoxy)ethyl]phenyl}methanol

¹H-NMR (CDCl₃) δ: 1.46 (1H, brs), 2.28 (3H, s), 2.36 (3H, s), 3.04 (2H, t, *J* = 7.2 Hz), 4.13 (2H,
10 t, *J* = 7.2 Hz), 4.68 (2H, d, *J* = 4.9 Hz), 6.79 (2H, dt, *J* = 9.2, 2.6 Hz), 7.07 (2H, dd, *J* = 8.8, 0.7
Hz), 7.11-7.13 (2H, m), 7.29 (1H, d, *J* = 7.3 Hz).

[0157]

The following compounds were produced in the same manner as in Reference
Example 1 using appropriate starting materials.

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Reference Example 192

tert-Butyl 4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.35 (4H, t, *J* = 5.0 Hz), 3.00-3.05 (2H, m), 3.39-3.43 (4H, m),
3.48 (2H, s), 3.79 (3H, s), 4.09-4.14 (2H, m), 6.84 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.6 Hz),
20 7.20 (4H, d, *J* = 8.6 Hz).

Reference Example 193

tert-Butyl 4-{4-[2-(4-methylphenyl)ethoxy]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.44 (9H, s), 2.30-2.38 (7H, m), 3.04 (2H, t, *J* = 7.3 Hz), 3.36-3.45 (6H, m),
25 4.13 (2H, t, *J* = 7.3 Hz), 6.79-6.88 (2H, m), 7.08-7.25 (6H, m).

Reference Example 194

tert-Butyl 4-(4-{2-[4-(propan-2-yl)phenyl]ethoxy}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.35 (4H, t, *J* = 4.9 Hz), 2.89 (1H,
30 septet, *J* = 6.9 Hz), 3.06 (2H, t, *J* = 7.3 Hz), 3.36-3.47 (6H, m), 4.15 (2H, t, *J* = 7.3 Hz), 6.79-
6.88 (2H, m), 7.15-7.25 (6H, m).

Reference Example 195

tert-Butyl 4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.41 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.14 (2H, t, *J* = 6.9 Hz), 6.77-6.87 (2H, m), 6.90-7.00 (2H, m), 7.22 (2H, d, *J* = 8.2 Hz), 7.26 (2H, d, *J* = 8.2 Hz).

5 Reference Example 196

tert-Butyl 4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.03-2.13 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 3.42 (4H, t, *J* = 5.1 Hz), 3.48 (2H, s), 3.92 (2H, t, *J* = 6.3 Hz), 6.78-6.87 (2H, m), 6.91-7.01 (2H, m), 7.15 (2H, d, *J* = 8.2 Hz), 7.23 (2H, d, *J* = 8.1 Hz).

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Reference Example 197

tert-Butyl 4-(4-{3-[4-(propan-2-yl)phenoxy]propyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.03-2.13 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 2.80-2.93 (1H, m), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 3.94 (2H, t, *J* = 6.3 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 7.13 (2H, d, *J* = 8.4 Hz), 7.16 (2H, d, *J* = 8.2 Hz), 7.22 (2H, d, *J* = 8.2 Hz).

15

Reference Example 198

tert-Butyl 4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.41 (4H, t, *J* = 4.6 Hz), 3.44 (4H, t, *J* = 4.6 Hz), 3.63 (2H, s), 3.85 (3H, s), 6.91-6.99 (2H, m), 7.04 (1H, d, *J* = 8.6 Hz), 7.12-7.22 (2H, m), 7.60 (1H, dd, *J* = 8.6, 2.0 Hz), 7.63-7.68 (1H, m), 7.75 (1H, d, *J* = 8.2 Hz), 8.06 (1H, d, *J* = 8.9 Hz).

20

Reference Example 199

tert-Butyl 4-({2-[4-(propan-2-yl)phenoxy]quinolin-6-yl}methyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.29 (6H, d, *J* = 6.9 Hz), 1.45 (9H, s), 2.42 (4H, t, *J* = 4.9 Hz), 2.96 (1H, septet, *J* = 6.9 Hz), 3.44 (4H, t, *J* = 4.6 Hz), 3.64 (2H, s), 7.04 (1H, d, *J* = 8.6 Hz), 7.12-7.20 (2H, m), 7.22-7.31 (2H, m), 7.55-7.68 (2H, m), 7.78 (1H, d, *J* = 8.6 Hz), 8.07 (1H, d, *J* = 8.9 Hz).

25

30 Reference Example 200

tert-Butyl 4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepane-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 1.45-1.46 (9H, m), 1.75-1.88 (2H, m), 2.58-2.66 (4H, m), 2.85 (1H, septet, *J* = 6.8 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.42-3.51 (4H, m), 3.62 (2H, s), 4.14 (2H, t, *J* = 7.1 Hz), 6.81-6.85 (2H, m), 7.11-7.14 (2H, m), 7.21-7.27 (4H, m).

Reference Example 201

tert-Butyl 4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.39 (3H, d, *J* = 6.8 Hz), 1.45 (9H, s), 2.27 (3H, s), 2.38 (4H, t, *J* = 5.0 Hz),
5 3.16-3.25 (1H, m), 3.42 (4H, t, *J* = 5.0 Hz), 3.48 (2H, s), 3.91 (1H, dd, *J* = 9.3, 7.8 Hz), 4.05
(1H, dd, *J* = 9.3, 6.0 Hz), 6.78 (2H, dt, *J* = 9.2, 2.6 Hz), 7.05 (2H, dd, *J* = 8.7, 0.6 Hz), 7.23 (2H,
d, *J* = 8.3 Hz), 7.26 (2H, d, *J* = 8.3 Hz).

Reference Example 202

- 10 *tert*-Butyl 4-[4-(2-{methyl[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.77-2.89
(3H, m), 2.89 (3H, s), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.49-3.58 (2H, m), 6.66-6.71 (2H,
m), 7.08-7.14 (2H, m), 7.14-7.19 (2H, m), 7.21-7.26 (2H, m).

- 15 Reference Example 203

tert-Butyl 4-(4-{2-[(4-fluorophenyl)(methyl)amino]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 2.81 (2H, t, *J* = 7.8 Hz), 2.86 (3H, s),
3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.48-3.55 (2H, m), 6.60-6.69 (2H, m), 6.90-6.98 (2H, m),
7.13 (2H, d, *J* = 7.8 Hz), 7.23 (2H, d, *J* = 7.8 Hz).

20

Reference Example 204

tert-Butyl 4-{4-[(4-methylphenoxy)acetyl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.28 (3H, s), 2.39 (4H, t, *J* = 5.0 Hz), 3.44 (4H, t, *J* = 5.0 Hz),
3.56 (2H, s), 5.22 (2H, s), 6.83-6.86 (2H, m), 7.06-7.10 (2H, m), 7.46 (2H, d, *J* = 8.3 Hz), 7.95-
25 7.98 (2H, m).

Reference Example 205

tert-Butyl 4-{4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.29 (3H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz),
30 3.49 (2H, s), 4.67 (2H, dd, *J* = 5.8, 1.5 Hz), 6.40 (1H, dt, *J* = 16.0, 5.8 Hz), 6.71 (1H, d, *J* = 16.0
Hz), 6.86 (2H, dt, *J* = 9.3, 2.5 Hz), 7.09 (2H, d, *J* = 8.3 Hz), 7.27 (2H, d, *J* = 8.1 Hz), 7.36 (2H,
d, *J* = 8.1 Hz).

Reference Example 206

tert-Butyl 4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38-2.39 (4H, m), 2.86 (6H, s), 3.05 (2H, t, *J* = 7.1 Hz), 3.42-3.43 (4H, m), 3.48 (2H, s), 4.12 (2H, t, *J* = 7.1 Hz), 6.73 (2H, d, *J* = 9.0 Hz), 6.83 (2H, d, *J* = 9.0 Hz), 7.22-7.23 (4H, m).

5

Reference Example 207

tert-Butyl (3*S*)-3-[(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)amino]pyrrolidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 1.45 (9H, s), 1.67-1.72 (1H, m), 1.98-2.03 (1H, m), 2.80-2.87 (1H, m), 3.03-3.07 (2.5H, m), 3.12-3.16 (0.5H, m), 3.32-3.59 (5H, m), 3.73-3.76 (2H, m), 4.12 (2H, t, *J* = 7.1 Hz), 6.79-6.83 (2H, m), 7.09-7.13 (2H, m), 7.21-7.25 (4H, m).

10

Reference Example 208

tert-Butyl (3*S*)-3-[methyl(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)amino]pyrrolidine-1-carboxylate

15 ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 7.1 Hz), 1.46 (9H, s), 1.81-1.86 (1H, m), 2.04-2.10 (1H, m), 2.13 (3H, s), 2.80-2.87 (1H, m), 2.98-3.00 (1H, m), 3.06 (2H, t, *J* = 7.1 Hz), 3.18-3.23 (2H, m), 3.43-3.65 (3.5H, m), 3.69-3.72 (0.5H, m), 4.13 (2H, t, *J* = 7.1 Hz), 6.80-6.84 (2H, m), 7.09-7.12 (2H, m), 7.22-7.25 (4H, m).

20 Reference Example 209

tert-Butyl 4-{4-[(*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.70 (2H, dd, *J* = 5.8, 1.5 Hz), 6.41 (1H, dt, *J* = 15.9, 5.8 Hz), 6.72 (1H, d, *J* = 15.9 Hz), 6.94-6.97 (3H, m), 7.26-7.32 (4H, m), 7.36 (2H, d, *J* = 8.3 Hz).

25

Reference Example 210

tert-Butyl 4-{4-[(*E*)-3-(4-cyanophenoxy)prop-1-en-1-yl]benzyl}piperazine-1-carboxylate

30 ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 5.0 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.50 (2H, s), 4.75 (2H, dd, *J* = 5.9, 1.5 Hz), 6.36 (1H, dt, *J* = 16.1, 5.9 Hz), 6.72 (1H, d, *J* = 16.1 Hz), 6.98-7.02 (2H, m), 7.29 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.2 Hz), 7.58-7.61 (2H, m).

Reference Example 211

tert-Butyl 4-{4-[(*E*)-3-(4-methoxyphenoxy)prop-1-en-1-yl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37 (4H, t, *J* = 4.9 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s),

3.77 (3H, s), 4.65 (2H, dd, $J = 5.8, 1.2$ Hz), 6.39 (1H, dt, $J = 15.9, 5.8$ Hz), 6.70 (1H, d, $J = 15.9$ Hz), 6.82-6.92 (4H, m), 7.27 (2H, d, $J = 7.6$ Hz), 7.36 (2H, d, $J = 7.6$ Hz).

Reference Example 212

- 5 (2*E*)-1-(4-{4-[(1*E*)-3-(4-Fluorophenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.53 (2H, s), 3.65-3.75 (4H, m), 4.66 (2H, dd, $J = 5.9, 1.3$ Hz), 5.96 (1H, brs), 6.39 (1H, dt, $J = 15.9, 5.9$ Hz), 6.70-6.79 (3H, m), 6.88-6.92 (2H, m), 6.95-7.00 (2H, m), 7.22-7.26 (3H, m), 7.29 (2H, d, $J = 8.3$ Hz), 7.38 (2H, d, $J =$
- 10 8.3 Hz), 7.59 (1H, d, $J = 15.1$ Hz), 7.72 (1H, dd, $J = 3.1, 0.6$ Hz).

Reference Example 213

tert-Butyl 4-{4-[(*E*)-3-(4-fluorophenoxy)prop-1-en-1-yl]benzyl}piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, $J = 4.9$ Hz), 3.42 (4H, t, $J = 4.9$ Hz), 3.49 (2H, s),
- 15 4.66 (2H, dd, $J = 5.7, 1.5$ Hz), 6.38 (1H, dt, $J = 16.0, 5.7$ Hz), 6.71 (1H, d, $J = 16.0$ Hz), 6.87-6.92 (2H, m), 6.95-7.01 (2H, m), 7.28 (2H, d, $J = 8.2$ Hz), 7.36 (2H, d, $J = 8.2$ Hz).

Reference Example 214

tert-Butyl 4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazine-1-carboxylate

- 20 ¹H-NMR (CDCl₃) δ: 1.28 (3H, d, $J = 6.1$ Hz), 1.45 (9H, s), 2.37 (4H, t, $J = 5.0$ Hz), 2.80 (1H, dd, $J = 13.7, 6.6$ Hz), 3.04 (1H, dd, $J = 13.7, 6.1$ Hz), 3.42 (4H, t, $J = 5.0$ Hz), 3.47 (2H, s), 4.42-4.50 (1H, m), 6.77-6.82 (2H, m), 6.90-6.96 (2H, m), 7.18 (2H, d, $J = 8.1$ Hz), 7.23 (2H, d, $J =$
- 8.1 Hz).

25 Reference Example 215

tert-Butyl 4-(4-{(*E*)-3-[4-(propan-2-yl)phenoxy]prop-1-en-1-yl}benzyl)piperazine-1-carboxylate

- ¹H-NMR (CDCl₃) δ: 1.23 (6H, d, $J = 6.8$ Hz), 2.37 (4H, t, $J = 4.8$ Hz), 2.81-2.92 (1H, m), 3.42 (4H, t, $J = 4.9$ Hz), 3.49 (2H, s), 4.67 (2H, dd, $J = 5.7, 1.2$ Hz), 6.40 (1H, dt, $J = 16.0, 5.7$ Hz), 6.71 (1H, d, $J = 16.0$ Hz), 6.87-6.91 (2H, m), 7.13-7.16 (2H, m), 7.26-7.28 (2H, m), 7.36 (2H, d,
- 30 $J = 8.3$ Hz).

Reference Example 216

tert-Butyl 4-(4-{(*E*)-3-[(6-chloropyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.46 (9H, s), 2.38 (4H, t, *J* = 5.0 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.50 (2H, s), 4.73 (2H, dd, *J* = 5.9, 1.5 Hz), 6.35 (1H, dt, *J* = 16.0, 5.9 Hz), 6.73 (1H, d, *J* = 16.0 Hz), 7.24 (2H, d, *J* = 1.9 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 7.36 (2H, d, *J* = 8.1 Hz), 8.12 (1H, t, *J* = 1.9 Hz).

5 Reference Example 217

tert-Butyl 4-(4-{(*E*)-3-[(6-methylpyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 5.0 Hz), 2.49 (3H, s), 3.42 (4H, t, *J* = 5.0 Hz), 3.49 (2H, s), 4.72 (2H, dd, *J* = 5.9, 1.5 Hz), 6.38 (1H, dt, *J* = 15.9, 5.9 Hz), 6.72 (1H, d, *J* = 15.9 Hz), 7.07 (1H, d, *J* = 8.5 Hz), 7.16 (1H, dd, *J* = 8.5, 2.8 Hz), 7.28 (2H, d, *J* = 8.1 Hz), 7.36 (2H, d, *J* = 8.1 Hz), 8.25 (1H, d, *J* = 2.8 Hz).

Reference Example 218

9*H*-Fluoren-9-ylmethyl 4-(4-{(*E*)-3-[(5-methylpyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)-

15 piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.38 (4H, brs), 3.48-3.49 (6H, m), 4.24 (1H, t, *J* = 6.8 Hz), 4.42 (2H, d, *J* = 6.8 Hz), 4.97 (2H, dd, *J* = 6.1, 1.5 Hz), 6.46 (1H, dt, *J* = 16.0, 6.0 Hz), 6.70-6.74 (2H, m), 7.26-7.32 (4H, m), 7.37-7.42 (5H, m), 7.56 (2H, dd, *J* = 7.3, 0.7 Hz), 7.76 (2H, d, *J* = 7.6 Hz), 7.96-7.97 (1H, m).

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Reference Example 219

9*H*-Fluoren-9-ylmethyl 4-(4-{(*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)-piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 2.38 (4H, s), 3.49-3.50 (6H, m), 4.24 (1H, t, *J* = 6.7 Hz), 4.43 (2H, d, *J* = 6.7 Hz), 4.97 (2H, dd, *J* = 6.2, 1.5 Hz), 6.44 (1H, dt, *J* = 16.0, 6.2 Hz), 6.70-6.74 (2H, m), 7.28-7.32 (4H, m), 7.37-7.42 (4H, m), 7.57 (2H, dd, *J* = 7.3, 0.7 Hz), 7.66 (1H, dd, *J* = 8.8, 2.6 Hz), 7.76 (2H, d, *J* = 7.3 Hz), 8.21 (1H, dd, *J* = 2.6, 0.7 Hz).

Reference Example 220

30 *tert*-Butyl 4-{4-[(*E*)-3-hydroxyprop-1-en-1-yl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.63 (1H, brs), 2.38 (4H, t, *J* = 5.0 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.49 (2H, s), 4.32 (2H, d, *J* = 5.6 Hz), 6.36 (1H, dt, *J* = 15.9, 5.6 Hz), 6.61 (1H, d, *J* = 15.9 Hz), 7.25-7.27 (2H, m), 7.34 (2H, d, *J* = 8.1 Hz).

Reference Example 221

tert-Butyl 4-[4-(3-phenoxypropyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.06-2.13 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.80 (2H, t, *J* = 7.7 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 3.97 (2H, t, *J* = 6.3 Hz), 6.88-6.95 (3H, m), 7.16 (2H, d, *J* = 8.1 Hz), 7.22 (2H, d, *J* = 8.1 Hz), 7.25-7.30 (2H, m).

Reference Example 222

tert-Butyl 4-(4-{3-[(6-chloropyridin-3-yl)oxy]propyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.08-2.15 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.79 (2H, t, *J* = 7.6 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.48 (2H, s), 3.98 (2H, t, *J* = 6.2 Hz), 7.14-7.18 (3H, m), 7.21-7.25 (3H, m), 8.04 (1H, dd, *J* = 3.1, 0.6 Hz).

Reference Example 223

tert-Butyl 4-{4-[2-(4-chlorophenoxy)ethyl]-3-fluorobenzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.37-2.38 (4H, m), 3.10 (2H, t, *J* = 7.0 Hz), 3.42-3.43 (4H, m), 3.47 (2H, s), 4.14 (2H, t, *J* = 7.0 Hz), 6.81 (2H, d, *J* = 8.8 Hz), 7.03-7.05 (2H, m), 7.20-7.23 (3H, m).

Reference Example 224

tert-Butyl 4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.06-2.11 (2H, m), 2.28 (3H, s), 2.37 (4H, t, *J* = 5.0 Hz), 2.79 (2H, t, *J* = 7.7 Hz), 3.42 (4H, t, *J* = 5.0 Hz), 3.47 (2H, s), 3.93 (2H, t, *J* = 6.3 Hz), 6.79 (2H, dt, *J* = 9.2, 2.6 Hz), 7.05-7.08 (2H, m), 7.16 (2H, d, *J* = 8.2 Hz), 7.22 (2H, d, *J* = 8.2 Hz).

[0158]

Reference Example 225

To a THF (10 mL) solution of 2-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}phenyl)-1,3-dioxolane (0.552 g) was added 6 M HCl (0.775 mL) at 0 °C, then the resultant mixture was room temperature for 5 hours. The reaction mixture was evaporated to afford a pale yellow oil. To a CH₂Cl₂ (15 mL) solution of that pale yellow oil and *tert*-Butyl 1-piperazinecarboxylate (0.375 g) were added NaB(OAc)₃ (0.657 g) at 0 °C. The resultant mixture was stirred at room temperature for 3 days. To the reaction mixture was added saturated aqueous NaHCO₃, and extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 4/1) to afford *tert*-butyl 4-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazine-1-carboxylate as a colorless oil (0.511 g).

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.41-2.42 (4H, m), 3.09 (2H, t, *J* = 6.7 Hz), 3.42-3.43 (4H, m),
5 3.57 (2H, s), 4.20 (2H, t, *J* = 6.7 Hz), 6.93-7.04 (4H, m), 7.29-7.31 (1H, m), 7.53 (2H, d, *J* = 8.5 Hz).

[0159]

Reference Example 226

To a solution of *tert*-butyl 4-[4-(2-{(4-methoxyphenyl)[(2-nitrophenyl)sulfonyl]-
10 amino}ethyl)benzyl]piperazine-1-carboxylate in DMF (35 mL) was added mercaptoacetic acid (1.35 mL) and LiOH (1.63 g) at room temperature, then the reaction mixture was stirred over night. The reaction mixture was added mercaptoacetic acid (1.35 mL) and LiOH (1.63 g), and stirred for 5 hours. The reaction mixture was diluted with H₂O, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous
15 Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/2) to afford *tert*-butyl 4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazine-1-carboxylate as a pale yellow amorphous (5.96 g).

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.85-2.93 (2H, m), 3.45 (2H, t, *J* = 7.1
20 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.75 (3H, s), 6.55-6.61 (2H, m), 6.75-6.81 (2H, m), 7.16 (2H, d, *J* = 8.1 Hz), 7.23-7.30 (2H, m).

[0160]

The following compounds were produced in the same manner as in Reference Example 226 using appropriate starting materials.

Reference Example 227

tert-Butyl 4-[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.20 (6H, d, *J* = 6.8 Hz), 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.80 (1H, septet, *J* = 6.8 Hz), 2.90 (2H, t, *J* = 6.8 Hz), 3.37 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz),
30 3.48 (2H, s), 3.57 (1H, brs), 6.52-6.59 (2H, m), 7.01-7.08 (2H, m), 7.14-7.21 (2H, m), 7.22-7.28 (2H, m).

Reference Example 228

tert-Butyl 4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 2.88 (2H, t, *J* = 7.1 Hz), 3.34 (2H, t, *J* = 7.1 Hz), 3.42 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 6.49-6.57 (2H, m), 6.82-6.92 (2H, m), 7.13-7.20 (2H, m), 7.22-7.27 (2H, m).

5 Reference Example 229

tert-Butyl 4-{{[4-(2-{{[4-(propan-2-yl)phenyl]amino}ethyl)phenyl]amino}piperidine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.20 (6H, d, *J* = 6.8 Hz), 1.25-1.39 (2H, m), 1.47 (9H, s), 1.98-2.08 (2H, m), 2.75-2.84 (3H, m), 2.92 (2H, t, *J* = 11.5 Hz), 3.31 (2H, t, *J* = 6.8 Hz), 3.35-3.60 (3H, m),
10 3.95-4.10 (2H, m), 6.52-6.60 (4H, m), 7.00-7.09 (4H, m).

[0161]

Reference Example 230

To a solution of 3-[4-(diethoxymethyl)phenyl]propan-1-ol (2.27 g), 5-hydroxy-2-
15 methylpyridine (1.25 g), and triphenylphosphine (3.00 g) in THF (19 mL) was added 2.2 M solution of DEAD in toluene (5.20 mL). After stirring at room temperature for 1 hour, to the reaction mixture was added H₂O, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt =
20 17/3 to 13/7) to afford a colorless oil (3.86 g). To a solution of that colorless oil (3.86 g) in THF (50 mL) was added 6 M aqueous HCl (1.59 mL). After stirring at room temperature for 30 minutes, to the reaction mixture was added 5 M aqueous NaOH, and the solvent was removed under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous
25 Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 13/7) to afford a colorless oil (2.93 g). To a solution of that colorless oil (2.93 g) in (CH₂Cl)₂ (95 mL) was added *tert*-butyl piperazine-1-carboxylate (1.95 g) and NaBH(OAc)₃ (4.45 g). After stirring at room temperature for 37 hours, to the reaction mixture was added saturated aqueous NaHCO₃, and extracted with AcOEt. The
30 organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 1/1) to afford *tert*-butyl 4-(4-{3-[(6-methylpyridin-3-yl)oxy]propyl}benzyl)piperazine-1-carboxylate as a colorless oil (1.37 g).

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.06-2.13 (2H, m), 2.37 (4H, t, *J* = 5.0 Hz), 2.49 (3H, s), 2.79

(2H, t, $J = 7.7$ Hz), 3.42 (4H, t, $J = 5.0$ Hz), 3.47 (2H, s), 3.97 (2H, t, $J = 6.3$ Hz), 7.04 (1H, d, $J = 8.4$ Hz), 7.09 (1H, dd, $J = 8.4, 2.9$ Hz), 7.15 (2H, d, $J = 8.2$ Hz), 7.23 (2H, d, $J = 8.2$ Hz), 8.18 (1H, dd, $J = 2.9, 0.7$ Hz).

[0162]

5 Reference Example 231

To an EtOH (25 mL) solution of *tert*-butyl 4-{4-[2-(4-fluorophenoxy)ethyl]-benzyl}piperazine-1-carboxylate (2.36 g) was added 6 M HCl (9.49 mL) at room temperature. After stirring at 40 °C for 3 hours, the solvent was removed under reduced pressure. The

10 resulting precipitate was collected by filtration, and dissolved in water. The solution was alkalified with 5 M NaOH, and extracted with CH₂Cl₂. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford 1-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazine as a colorless oil (1.47 g).

¹H-NMR (CDCl₃) δ: 1.67 (1H, brs), 2.41 (4H, m), 2.88 (4H, t, $J = 4.6$ Hz), 3.06 (2H, t, $J = 6.9$ Hz), 3.47 (2H, s), 4.12 (2H, t, $J = 6.9$ Hz), 6.78-6.86 (2H, m), 6.90-7.00 (2H, m), 7.21 (2H, d, $J =$
15 7.9 Hz), 7.27 (2H, d, $J = 7.9$ Hz).

[0163]

The following compounds were produced in the same manner as in Reference Example 231 using appropriate starting materials.

20 Reference Example 232

1-{4-[2-(4-Methoxyphenyl)ethoxy]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.38 (4H, brs), 2.52 (1H, brs), 2.87 (4H, t, $J = 5.0$ Hz), 3.00-3.05 (2H, m), 3.41 (2H, s), 3.79 (3H, s), 4.12 (2H, t, $J = 7.3$ Hz), 6.84 (2H, d, $J = 8.6$ Hz), 6.85 (2H, d, $J = 8.6$ Hz), 7.18-7.21 (4H, m).

25

Reference Example 233

1-(4-{[4-(Propan-2-yl)phenoxy]methyl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.9$ Hz), 1.68 (1H, brs), 2.41 (4H, m), 2.81-2.90 (5H, m), 3.49 (2H, s), 5.01 (2H, s), 6.88-6.93 (2H, m), 7.13-7.17 (2H, m), 7.33 (2H, d, $J = 8.2$ Hz), 7.38
30 (2H, d, $J = 8.2$ Hz).

Reference Example 234

1-(4-{[4-(1*H*-Pyrrol-1-yl)phenoxy]methyl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 2.41 (4H, brs), 2.87-2.90 (4H, m), 3.50 (2H, s), 5.06 (2H, s), 6.31-6.32 (2H,

m), 6.99-7.03 (4H, m), 7.30 (2H, d, $J = 8.9$ Hz), 7.35 (2H, d, $J = 8.9$ Hz), 7.39 (2H, d, $J = 8.6$ Hz).

Reference Example 235

5 1-{4-[(4-Fluorophenoxy)methyl]benzyl}piperazine

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.26-2.28 (5H, m), 2.67 (4H, t, $J = 4.6$ Hz), 3.41 (2H, s), 5.04 (2H, s), 6.98-7.05 (2H, m), 7.07-7.15 (2H, m), 7.29 (2H, d, $J = 7.9$ Hz), 7.38 (2H, d, $J = 7.9$ Hz).

Reference Example 236

10 1-(4-{[(4-Fluorobenzyl)oxy]methyl}benzyl)piperazine

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.26-2.36 (5H, m), 2.67 (4H, t, $J = 4.9$ Hz), 3.40 (2H, s), 4.49 (2H, s), 4.49 (2H, s), 7.14-7.21 (2H, m), 7.24-7.31 (4H, m), 7.36-7.42 (2H, m).

Reference Example 237

15 1-[4-({[4-(Propan-2-yl)benzyl]oxy}methyl)benzyl]piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (6H, d, $J = 6.9$ Hz), 1.71-1.78 (1H, m), 2.41 (4H, brs), 2.86-2.96 (5H, m), 3.48 (2H, s), 4.53 (2H, s), 4.53 (2H, s), 7.20-7.31 (8H, m).

Reference Example 238

20 1-{4-[2-(4-Methoxyphenoxy)ethyl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.74 (1H, brs), 2.41 (4H, m), 2.89 (4H, t, $J = 4.9$ Hz), 3.05 (2H, t, $J = 7.3$ Hz), 3.47 (2H, s), 3.76 (3H, s), 4.11 (2H, t, $J = 7.3$ Hz), 6.79-6.85 (4H, m), 7.20-7.28 (4H, m).

Reference Example 239

25 1-(4-{2-[4-(Propan-2-yl)phenoxy]ethyl}benzyl)piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, $J = 6.9$ Hz), 1.68 (1H, brs), 2.41 (4H, m), 2.79-2.90 (5H, m), 3.06 (2H, t, $J = 6.9$ Hz), 3.46 (2H, s), 4.14 (2H, t, $J = 6.9$ Hz), 6.80-6.85 (2H, m), 7.10-7.14 (2H, m), 7.20-7.27 (4H, m).

30 Reference Example 240

1-{4-[2-(4-Methylphenoxy)ethyl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.67 (1H, brs), 2.28 (3H, s), 2.41 (4H, brs), 2.88 (4H, t, $J = 4.9$ Hz), 3.06 (2H, t, $J = 6.9$ Hz), 3.47 (2H, s), 4.13 (2H, t, $J = 6.9$ Hz), 6.79 (2H, d, $J = 8.6$ Hz), 7.06 (2H, d, $J = 8.6$ Hz), 7.20-7.28 (4H, m).

Reference Example 241

1-{4-[2-(4-Chlorophenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.42 (4H, brs), 2.52 (1H, brs), 2.90 (4H, t, *J* = 5.0 Hz), 3.03-3.08 (2H, m),
5 3.47 (2H, s), 4.09-4.14 (2H, m), 6.85 (2H, d, *J* = 9.2 Hz), 7.17-7.22 (4H, m), 7.26 (2H, d, *J* = 8.2 Hz).

Reference Example 242

1-{4-[2-(4-Bromophenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.44-2.45 (4H, m), 2.91 (4H, t, *J* = 5.0 Hz), 3.03-3.09 (2H, m), 3.47 (2H, s),
10 4.09-4.14 (2H, m), 6.74-6.78 (2H, m), 7.21 (2H, d, *J* = 7.9 Hz), 7.26 (2H, d, *J* = 7.9 Hz), 7.33-7.36 (2H, m).

Reference Example 243

15 1-[4-(2-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}ethyl)benzyl]piperazine

¹H-NMR (CDCl₃) δ: 2.41 (4H, brs), 2.89 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.47 (2H, s),
4.57 (2H, t, *J* = 7.1 Hz), 6.80 (1H, d, *J* = 8.6 Hz), 7.20-7.29 (4H, m), 7.75 (1H, dd, *J* = 9.2, 2.6 Hz), 8.41-8.43 (1H, m).

20 Reference Example 244

1-{4-[2-(3-Methylphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.59 (1H, brs), 2.31 (3H, s), 2.34-2.47 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz),
3.07 (2H, t, *J* = 7.3 Hz), 3.47 (2H, s), 4.14 (2H, t, *J* = 7.3 Hz), 6.66-6.79 (3H, m), 7.10-7.30 (5H, m).

25

Reference Example 245

1-(4-{2-[3-(Propan-2-yl)phenoxy]ethyl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.9 Hz), 1.61 (1H, brs), 2.30-2.50 (4H, m), 2.77-2.96 (5H, m),
3.08 (2H, t, *J* = 7.3 Hz), 3.47 (2H, s), 4.16 (2H, t, *J* = 7.3 Hz), 6.71 (1H, dd, *J* = 8.2, 2.6 Hz),
30 6.75-6.85 (2H, m), 7.14-7.31 (5H, m).

Reference Example 246

1-{4-[2-(3-Methoxyphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.85 (1H, brs), 2.30-2.58 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* =

7.3 Hz), 3.47 (2H, s), 3.77 (3H, s), 4.14 (2H, t, $J = 7.3$ Hz), 6.44-6.54 (3H, m), 7.16 (1H, t, $J = 8.2$ Hz), 7.20-7.30 (4H, m).

Reference Example 247

5 1-{4-[2-(3,4-Dimethylphenoxy)ethyl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (3H, s), 2.22 (3H, s), 2.82-2.55 (4H, m), 2.90 (4H, t, $J = 4.9$ Hz), 3.06 (2H, t, $J = 7.3$ Hz), 3.47 (2H, s), 4.12 (2H, t, $J = 7.3$ Hz), 6.64 (1H, dd, $J = 8.2, 2.6$ Hz), 6.71 (1H, d, $J = 2.6$ Hz), 7.01 (1H, d, $J = 8.2$ Hz), 7.15-7.30 (4H, m).

10 Reference Example 248

1-{4-[2-(4-*tert*-Butylphenoxy)ethyl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (9H, s), 1.76 (1H, s), 2.40 (4H, brs), 2.88 (4H, t, $J = 4.9$ Hz), 3.06 (2H, t, $J = 6.9$ Hz), 3.46 (2H, s), 4.14 (2H, t, $J = 6.9$ Hz), 6.80-6.86 (2H, m), 7.20-7.31 (6H, m).

15 Reference Example 249

1-{4-[3-(4-Fluorophenoxy)propyl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (1H, s), 2.03-2.13 (2H, m), 2.41 (4H, brs), 2.78 (2H, t, $J = 7.6$ Hz), 2.88 (4H, t, $J = 4.9$ Hz), 3.46 (2H, s), 3.92 (2H, t, $J = 6.3$ Hz), 6.79-6.86 (2H, m), 6.91-7.00 (2H, m), 7.15 (2H, d, $J = 8.1$ Hz), 7.24 (2H, d, $J = 8.1$ Hz).

20

Reference Example 250

1-(4-{3-[4-(Propan-2-yl)phenoxy]propyl}benzyl)piperazine

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 1.45 (1H, s), 2.03-2.13 (2H, m), 2.41 (4H, brs), 2.78 (2H, t, $J = 7.6$ Hz), 2.80-2.90 (1H, m), 2.88 (4H, t, $J = 4.9$ Hz), 3.46 (2H, s), 3.94 (2H, t, $J = 6.3$ Hz), 6.83 (2H, d, $J = 8.7$ Hz), 7.13 (2H, d, $J = 8.7$ Hz), 7.15 (2H, d, $J = 8.2$ Hz), 7.23 (2H, d, $J = 8.1$ Hz).

25

Reference Example 251

1-{4-[2-(4-Methylphenoxy)ethyl]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.22 (3H, s), 3.04 (2H, t, $J = 6.6$ Hz), 3.01-3.80 (8H, m), 4.16 (2H, t, $J = 6.8$ Hz), 4.33 (2H, s), 6.82 (2H, d, $J = 8.6$ Hz), 7.07 (2H, d, $J = 8.6$ Hz), 7.40 (2H, d, $J = 7.9$ Hz), 7.57 (2H, d, $J = 7.6$ Hz), 9.67 (1H, s), 12.14 (1H, s).

30

Reference Example 252

1-{4-[2-(2-Methylphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47 (4H, s), 2.74 (1H, s), 2.94 (4H, t, *J* = 4.8 Hz), 3.09 (2H, t, *J* = 6.8 Hz), 3.48 (2H, s), 4.16 (2H, t, *J* = 6.4 Hz), 6.77-6.86 (2H, m), 7.09-7.15 (2H, m), 7.25 (4H, s).

5

Reference Example 253

1-{4-[2-(4-Butylphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 0.91 (3H, t, *J* = 7.3 Hz), 1.26-1.40 (2H, m), 1.50-1.61 (2H, m), 2.40 (4H, s), 2.54 (2H, t, *J* = 7.7 Hz), 2.88 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.46 (2H, s), 4.13 (2H, t, *J* = 7.1 Hz), 6.78-6.83 (2H, m), 7.04-7.10 (2H, m), 7.20-7.28 (4H, m).

10

Reference Example 254

1-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.05 (2H, t, *J* = 6.6 Hz), 3.12-3.60 (8H, m), 4.19 (2H, t, *J* = 6.6 Hz), 4.31 (2H, s), 6.90-6.98 (2H, m), 7.06-7.15 (2H, m), 7.41 (2H, d, *J* = 7.9 Hz), 7.56 (2H, d, *J* = 7.9 Hz), 9.56 (1H, brs), 12.01 (1H, brs).

15

Reference Example 255

1-{4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.59 (1H, brs), 2.40 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.04 (2H, t, *J* = 6.9 Hz), 3.46 (2H, s), 4.08 (2H, t, *J* = 6.9 Hz), 5.90 (2H, s), 6.31 (1H, dd, *J* = 8.6, 2.6 Hz), 6.48 (1H, d, *J* = 2.6 Hz), 6.68 (1H, d, *J* = 8.6 Hz), 7.20 (2H, d, *J* = 8.2 Hz), 7.27 (2H, d, *J* = 8.2 Hz).

20

Reference Example 256

1-{4-[2-(2-Chlorophenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.09 (2H, t, *J* = 6.3 Hz), 3.34-3.52 (10H, m), 4.22-4.34 (2H, m), 6.93 (1H, t, *J* = 7.6 Hz), 7.14 (1H, d, *J* = 7.9 Hz), 7.24-7.31 (1H, m), 7.38-7.46 (3H, m), 7.56 (2H, d, *J* = 6.9 Hz), 9.61 (2H, s).

25

30 Reference Example 257

2-[4-(Piperazin-1-ylmethyl)phenyl]ethanol dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.75 (2H, t, *J* = 6.9 Hz), 2.92-3.42 (7H, m), 3.62 (2H, t, *J* = 6.9 Hz), 4.11-4.45 (4H, m), 7.29 (2H, d, *J* = 7.3 Hz), 7.52 (2H, d, *J* = 5.0 Hz), 9.85 (2H, s), 12.20 (1H, s).

Reference Example 258

1-{4-[2-(2,3-Dimethylphenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.01 (3H, s), 2.18 (3H, s), 3.08 (2H, t, *J* = 6.3 Hz), 3.21-3.55 (8H, m),
4.15 (2H, t, *J* = 6.3 Hz), 4.33 (2H, s), 6.73 (1H, d, *J* = 7.3 Hz), 6.78 (1H, d, *J* = 8.3 Hz), 7.01
5 (1H, t, *J* = 7.8 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.57 (2H, d, *J* = 6.8 Hz), 9.65 (2H, s), 12.07 (1H, s).

Reference Example 259

1-{4-[2-(3,5-Dimethylphenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.21 (6H, s), 3.04 (2H, t, *J* = 6.3 Hz), 3.22-3.59 (8H, m), 4.15 (2H, t, *J* =
10 6.6 Hz), 4.35 (2H, s), 6.53-6.57 (3H, m), 7.40 (2H, d, *J* = 7.8 Hz), 7.59 (2H, d, *J* = 7.8 Hz), 9.80
(2H, s), 12.00-12.31 (1H, m).

Reference Example 260

1-{4-[2-(3-Ethoxyphenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.29 (3H, t, *J* = 6.8 Hz), 2.90-3.80 (10H, m), 3.98 (2H, q, *J* = 6.8 Hz),
15 4.19 (2H, t, *J* = 6.8 Hz), 4.35 (2H, brs), 6.44-6.54 (3H, m), 7.15 (1H, t, *J* = 8.1 Hz), 7.41 (2H, d,
J = 7.8 Hz), 7.57 (2H, d, *J* = 6.6 Hz), 9.65 (1H, brs), 12.11 (1H, brs).

Reference Example 261

20 6-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethoxy}quinoline dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.20 (2H, t, *J* = 6.6 Hz), 3.31-3.86 (8H, m), 4.38 (2H, s), 4.43 (2H, t, *J* =
6.6 Hz), 7.48 (2H, d, *J* = 8.3 Hz), 7.59 (2H, dd, *J* = 33.2, 7.8 Hz), 7.73-7.80 (2H, m), 7.97 (1H,
dd, *J* = 8.1, 5.1 Hz), 8.31 (1H, d, *J* = 9.3 Hz), 8.92 (1H, d, *J* = 7.8 Hz), 9.08 (1H, d, *J* = 4.4 Hz),
9.86 (2H, s), 12.27 (1H, s).

25

Reference Example 262

1-{4-[2-(4-Nitrophenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.75 (4H, t, *J* = 4.9 Hz), 3.12 (2H, t, *J* = 6.8 Hz), 3.20-3.22 (4H, m), 3.55
(2H, s), 4.26 (2H, t, *J* = 6.8 Hz), 6.94 (2H, d, *J* = 9.2 Hz), 7.24 (4H, brs), 8.18 (2H, d, *J* = 9.5
30 Hz).

Reference Example 263

1-{4-[(1,3-Benzodioxol-5-yloxy)methyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.68 (1H, brs), 2.41 (4H, brs), 2.88 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.96

(2H, s), 5.91 (2H, s), 6.39 (1H, dd, $J = 8.5, 2.4$ Hz), 6.56 (1H, d, $J = 2.4$ Hz), 6.70 (1H, d, $J = 8.5$ Hz), 7.30-7.39 (4H, m).

Reference Example 264

5 1-{4-[2-(3,4-Dichlorophenoxy)ethyl]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.07 (2H, t, $J = 6.5$ Hz), 3.23-3.56 (8H, m), 4.26 (2H, t, $J = 6.6$ Hz), 4.36 (2H, s), 6.97 (1H, dd, $J = 8.9, 2.6$ Hz), 7.25 (1H, d, $J = 2.4$ Hz), 7.41 (2H, d, $J = 7.8$ Hz), 7.51 (1H, d, $J = 9.0$ Hz), 7.61 (2H, d, $J = 7.6$ Hz), 9.92 (2H, s), 12.28 (1H, s).

10 Reference Example 265

1-{4-[2-(4-Fluoro-3-methylphenoxy)ethyl]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.19 (3H, d, $J = 2.0$ Hz), 3.04 (2H, t, $J = 6.9$ Hz), 3.11-3.61 (8H, m), 4.16 (2H, t, $J = 6.9$ Hz), 4.34 (2H, brs), 6.72-6.77 (1H, m), 6.85 (1H, dd, $J = 6.2, 3.1$ Hz), 7.00-7.04 (1H, m), 7.40 (2H, d, $J = 8.1$ Hz), 7.57 (2H, d, $J = 6.1$ Hz), 9.65 (2H, brs), 12.11 (1H, brs).

15

Reference Example 266

1-{4-[2-(3-Methylphenoxy)ethyl]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.26 (3H, s), 3.06 (2H, t, $J = 6.6$ Hz), 3.10-3.60 (8H, m), 4.18 (2H, t, $J = 6.8$ Hz), 4.34 (2H, s), 6.71-6.75 (3H, m), 7.15 (1H, t, $J = 7.6$ Hz), 7.41 (2H, d, $J = 7.8$ Hz), 7.57 (2H, d, $J = 7.3$ Hz), 9.63 (1H, s), 12.10 (1H, s).

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Reference Example 267

1-{4-[2-(4-Chlorophenoxy)ethoxy]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.95-3.61 (10H, m), 4.26-4.33 (4H, m), 7.00-7.07 (4H, m), 7.33-7.37 (2H, m), 7.54 (2H, brs), 9.53 (2H, brs), 11.87 (1H, brs).

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Reference Example 268

1-[4-(4-Chlorophenoxy)benzyl]piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.26-3.40 (8H, m), 4.35 (2H, s), 7.09 (4H, dd, $J = 8.4, 5.5$ Hz), 7.47 (2H, d, $J = 8.8$ Hz), 7.66 (2H, d, $J = 8.1$ Hz), 9.71 (2H, s), 12.12 (1H, s).

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Reference Example 269

1-{4-[2-(4-Methylphenoxy)ethoxy]benzyl}piperazine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.23 (3H, s), 2.93-3.60 (10H, m), 4.27-4.33 (4H, m), 6.85-6.88 (2H, m),

7.08-7.14 (4H, m), 7.54-7.56 (2H, m), 9.59 (2H, brs), 11.92 (1H, brs).

Reference Example 270

1-{4-[2-(5,6,7,8-Tetrahydronaphthalen-2-yloxy)ethyl]benzyl}piperazine dihydrochloride

- 5 ¹H-NMR (DMSO-*d*₆) δ: 1.67-1.70 (4H, m), 2.61-2.66 (4H, m), 3.03 (2H, t, *J* = 6.7 Hz), 3.29-3.45 (8H, m), 4.14 (2H, t, *J* = 6.7 Hz), 4.34 (2H, brs), 6.58-6.61 (1H, m), 6.65 (1H, dd, *J* = 8.3, 2.7 Hz), 6.93 (1H, d, *J* = 8.5 Hz), 7.40 (2H, d, *J* = 8.1 Hz), 7.56-7.58 (2H, m), 9.65 (2H, brs), 12.10 (1H, brs).

10 Reference Example 271

1-{4-[2-(2,3-Dihydro-1*H*-inden-5-yloxy)ethyl]benzyl}piperazine dihydrochloride

- ¹H-NMR (DMSO-*d*₆) δ: 1.94-1.99 (2H, m), 2.76-2.80 (4H, m), 3.04 (2H, t, *J* = 6.6 Hz), 3.29-3.44 (8H, m), 4.16 (2H, t, *J* = 6.6 Hz), 4.34 (2H, brs), 6.67 (1H, dd, *J* = 8.2, 2.3 Hz), 6.80 (1H, d, *J* = 2.0 Hz), 7.08 (1H, d, *J* = 8.1 Hz), 7.40 (2H, d, *J* = 7.3 Hz), 7.58 (2H, d, *J* = 7.8 Hz), 9.76
15 (2H, brs), 12.17 (1H, brs).

Reference Example 272

1-(4-{2-[4-(Propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepane

- ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 1.70-1.79 (3H, m), 2.63-2.69 (4H, m), 2.81-2.91
20 (3H, m), 2.96 (2H, t, *J* = 6.1 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.63 (2H, s), 4.14 (2H, t, *J* = 7.1 Hz), 6.81-6.85 (2H, m), 7.11-7.13 (2H, m), 7.22 (2H, d, *J* = 8.1 Hz), 7.28 (2H, d, *J* = 8.1 Hz).

Reference Example 273

1-(Biphenyl-4-ylmethyl)piperazine dihydrochloride

- 25 ¹H-NMR (DMSO-*d*₆) δ: 3.20-3.58 (8H, m), 4.40 (2H, s), 7.40 (1H, t, *J* = 7.2 Hz), 7.49 (2H, t, *J* = 7.6 Hz), 7.68-7.78 (6H, m), 9.78 (2H, s), 12.31 (1H, s).

Reference Example 274

1-{4-[4-(Propan-2-yl)phenoxy]benzyl}piperazine dihydrochloride

- 30 ¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.85-2.96 (1H, m), 3.16-3.48 (8H, m), 4.33 (2H, s), 6.98 (2H, d, *J* = 8.5 Hz), 7.02 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 7.61-7.62 (2H, m), 9.69 (2H, s), 12.07 (1H, s).

Reference Example 275

1-{4-[2-(Naphthalen-2-yloxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.13-3.71 (10H, m), 4.32-4.35 (4H, m), 7.15 (1H, dd, *J* = 8.9, 2.6 Hz), 7.32-7.36 (2H, m), 7.43-7.47 (3H, m), 7.61 (2H, d, *J* = 7.1 Hz), 7.79-7.83 (3H, m), 9.73 (2H, brs), 12.18 (1H, brs).

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Reference Example 276

1-(4-{2-[(6-Bromopyridin-3-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.08 (2H, t, *J* = 6.7 Hz), 3.17-3.47 (8H, m), 4.31 (2H, t, *J* = 6.7 Hz), 4.36 (2H, brs), 7.40-7.42 (3H, m), 7.54 (1H, d, *J* = 8.5 Hz), 7.59-7.61 (2H, m), 8.12 (1H, d, *J* = 3.2 Hz), 9.85 (2H, brs), 12.26 (1H, brs).

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Reference Example 277

1-(4-Fluorophenyl)-2-[4-(piperazin-1-ylmethyl)phenoxy]ethanone dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.90-3.70 (8H, m), 4.29 (2H, s), 5.62 (2H, s), 7.05 (2H, d, *J* = 8.5 Hz), 7.43 (2H, t, *J* = 8.8 Hz), 7.53 (2H, d, *J* = 7.6 Hz), 8.10-8.14 (2H, m), 9.52 (1H, s), 11.82 (1H, s).

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Reference Example 278

1-(4-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethoxy}phenyl)ethanone

¹H-NMR (CDCl₃) δ: 2.46 (4H, brs), 2.54 (3H, s), 2.93 (4H, t, *J* = 4.9 Hz), 2.99 (1H, brs), 3.10 (2H, t, *J* = 7.1 Hz), 3.48 (2H, s), 4.22 (2H, t, *J* = 7.1 Hz), 6.90-6.93 (2H, m), 7.22-7.28 (4H, m), 7.90-7.93 (2H, m).

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Reference Example 279

1-(4-{2-[(5-Chloropyridin-2-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.06 (2H, t, *J* = 6.8 Hz), 3.17-3.56 (8H, m), 4.35 (2H, s), 4.46 (2H, t, *J* = 6.8 Hz), 6.85 (1H, dd, *J* = 8.8, 0.5 Hz), 7.38 (2H, d, *J* = 8.1 Hz), 7.59 (2H, d, *J* = 7.8 Hz), 7.79 (1H, dd, *J* = 8.8, 2.7 Hz), 8.20 (1H, t, *J* = 1.5 Hz), 9.87 (2H, brs), 12.26 (1H, brs).

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Reference Example 280

1-{4-[2-(Pyridin-2-yloxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.08 (2H, t, *J* = 6.8 Hz), 3.28-3.66 (8H, m), 4.37 (2H, s), 4.50 (2H, t, *J* = 6.8 Hz), 6.86 (1H, dd, *J* = 5.0, 4.3 Hz), 7.00-7.02 (1H, m), 7.40 (2H, d, *J* = 8.1 Hz), 7.61 (2H, d, *J* = 8.1 Hz), 7.74-7.78 (1H, m), 8.15-8.19 (1H, m), 9.96 (2H, brs), 12.28 (1H, brs).

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Reference Example 281

1-{4-[2-(4-Cyclopropylphenoxy)ethyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 0.53-0.57 (2H, m), 0.82-0.88 (2H, m), 1.80-1.87 (1H, m), 3.04 (2H, t, *J* = 6.7 Hz), 3.17-3.50 (8H, m), 4.16 (2H, t, *J* = 6.7 Hz), 4.34 (2H, brs), 6.79-6.83 (2H, m), 6.97-
5 6.99 (2H, m), 7.40 (2H, d, *J* = 7.8 Hz), 7.55 (2H, brs), 9.55 (2H, brs), 12.03 (1H, brs).

Reference Example 282

1-{2-Fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.25-3.46 (8H, m), 4.31 (2H, s), 5.14 (2H, s), 7.02-7.07 (2H, m), 7.11-
10 7.18 (2H, m), 7.36-7.43 (2H, m), 7.73 (1H, s), 9.56 (2H, s).

Reference Example 283

N-Methyl-*N*-{2-[4-(piperazin-1-ylmethyl)phenyl]ethyl}-4-(propan-2-yl)aniline

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 1.69 (1H, brs), 2.32-2.57 (4H, m), 2.77-2.93 (10H,
15 m), 3.45-3.55 (4H, m), 6.66-6.72 (2H, m), 7.08-7.14 (2H, m), 7.14-7.19 (2H, m), 7.21-7.28 (2H, m).

Reference Example 284

1-{3-Fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 0.87 (3H, t, *J* = 7.3 Hz), 1.53-1.56 (2H, m), 2.67-3.35 (8H, m), 3.80-
20 3.87 (2H, m), 4.32-4.34 (2H, m), 5.10 (2H, s), 6.93 (2H, d, *J* = 8.5 Hz), 7.11 (2H, d, *J* = 8.5 Hz),
7.42-7.60 (3H, br m), 9.51 (2H, s), 12.27 (1H, s).

Reference Example 285

25 1-{3-Fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.13-3.48 (8H, m), 4.28-4.30 (2H, m), 5.13 (2H, s), 7.04-7.07 (2H, m),
7.13-7.16 (2H, m), 7.44-7.46 (1H, m), 7.61-7.64 (2H, m), 9.44-9.47 (2H, m), 12.17-12.20 (1H,
m).

30 Reference Example 286

1-(3-Fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.40-2.43 (4H, m), 2.89-2.90 (4H, m), 3.47 (2H,
s), 4.39-4.45 (1H, m), 5.05 (2H, s), 6.83 (2H, d, *J* = 9.0 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 7.10 (2H,
d, *J* = 9.5 Hz), 7.42 (1H, t, *J* = 7.6 Hz).

Reference Example 287

N-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethyl}-4-(propan-2-yl)aniline trihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.20 (6H, d, *J* = 6.8 Hz), 2.91 (1H, septet, *J* = 6.8 Hz), 3.00-4.20 (13H, m), 4.37 (2H, s), 7.36 (4H, t, *J* = 7.8 Hz), 7.43 (2H, d, *J* = 7.8 Hz), 7.61 (2H, d, *J* = 8.1 Hz), 9.89 (2H, brs), 12.27 (1H, brs).

Reference Example 288

4-Fluoro-*N*-methyl-*N*-{2-[4-(piperazin-1-ylmethyl)phenyl]ethyl}aniline trihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.60-4.60 (18H, m), 7.20-7.70 (8H, m), 9.88 (2H, brs), 12.27 (1H, brs).

Reference Example 289

4-Fluoro-*N*-{2-[4-(piperazin-1-ylmethyl)phenyl]ethyl}aniline trihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.98 (2H, t, *J* = 8.1 Hz), 3.10-3.60 (14H, m), 7.17 (4H, brs), 7.36 (2H, d, *J* = 8.3 Hz), 7.58 (2H, d, *J* = 8.1 Hz), 9.67 (2H, brs), 12.11 (1H, brs).

Reference Example 290

1-(4-{2-[(6-Chloropyridin-3-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.08 (2H, t, *J* = 6.6 Hz), 3.24-3.43 (8H, m), 4.30-4.33 (4H, m), 7.40-7.43 (3H, m), 7.47-7.51 (1H, m), 7.57-7.59 (2H, m), 8.12 (1H, dd, *J* = 3.2, 0.5 Hz), 9.72 (2H, brs), 12.18 (1H, brs).

Reference Example 291

1-(4-{2-[(5-Methylpyridin-2-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.21 (3H, s), 3.06 (2H, t, *J* = 6.8 Hz), 3.25 (2H, brs), 3.41-3.62 (4H, m), 4.36-4.47 (6H, m), 6.78 (1H, d, *J* = 8.5 Hz), 7.39 (2H, d, *J* = 8.3 Hz), 7.59-7.61 (3H, m), 7.99 (1H, dd, *J* = 1.6, 0.9 Hz), 9.83 (2H, brs), 12.23 (1H, brs).

Reference Example 292

1-(4-{2-[(6-Methylpyridin-3-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.61 (3H, s), 3.11 (2H, t, *J* = 6.7 Hz), 3.24-3.74 (8H, m), 4.33 (2H, brs), 4.42 (2H, t, *J* = 6.7 Hz), 7.42 (2H, d, *J* = 8.1 Hz), 7.58-7.60 (2H, m), 7.71 (1H, dd, *J* = 8.8, 2.9 Hz), 7.97-7.99 (1H, m), 8.46 (1H, d, *J* = 2.7 Hz), 9.65 (2H, brs), 11.53 (1H, brs).

Reference Example 293

1-(4-Methylphenyl)-2-[4-(piperazin-1-ylmethyl)phenoxy]ethanone dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.41 (3H, s), 2.90-3.65 (8H, m), 4.30 (2H, brs), 5.59 (2H, s), 7.03 (2H, d, *J* = 8.8 Hz), 7.39 (2H, d, *J* = 7.8 Hz), 7.53 (2H, d, *J* = 7.1 Hz), 7.92-7.95 (2H, m), 9.58 (1H, brs), 11.92 (1H, brs).

Reference Example 294

1-(4-{2-[(5-Bromopyridin-2-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.06 (2H, t, *J* = 6.8 Hz), 3.40-3.53 (8H, m), 4.33 (2H, brs), 4.46 (2H, t, *J* = 6.8 Hz), 6.81 (1H, dd, *J* = 8.8, 0.5 Hz), 7.38 (2H, d, *J* = 7.8 Hz), 7.54-7.56 (2H, m), 7.89 (1H, dd, *J* = 8.8, 2.7 Hz), 8.28 (1H, dd, *J* = 2.7, 0.5 Hz), 9.59 (2H, brs), 12.06 (1H, brs).

Reference Example 295

4-Methoxy-*N*-{2-[4-(piperazin-1-ylmethyl)phenyl]ethyl}aniline trihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.00-3.70 (15H, m), 3.77 (3H, s), 4.33 (2H, brs), 7.00-7.10 (2H, m), 7.35 (2H, d, *J* = 8.1 Hz), 7.40-7.51 (2H, m), 7.57 (2H, d, *J* = 7.6 Hz), 9.64 (2H, brs).

Reference Example 296

1-(4-{2-[(6-Methylpyridin-2-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.39 (3H, s), 3.07 (2H, t, *J* = 6.8 Hz), 3.24-3.27 (2H, m), 3.43-3.46 (6H, m), 4.37 (2H, s), 4.46 (2H, t, *J* = 6.8 Hz), 6.66 (1H, d, *J* = 8.1 Hz), 6.87 (1H, d, *J* = 7.3 Hz), 7.41 (2H, d, *J* = 7.8 Hz), 7.60-7.66 (3H, m), 9.85 (2H, s), 12.25 (1H, s).

Reference Example 297

1-(4-{2-[(6-Methoxypyridin-3-yl)oxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.05 (2H, t, *J* = 6.7 Hz), 3.32-3.57 (8H, m), 3.78 (3H, s), 4.22 (2H, t, *J* = 6.7 Hz), 4.35 (2H, brs), 6.75 (1H, dd, *J* = 9.0, 0.5 Hz), 7.39-7.41 (3H, m), 7.58-7.60 (2H, m), 7.85 (1H, d, *J* = 2.7 Hz), 9.76 (2H, brs), 12.20 (1H, brs).

Reference Example 298

6-Chloro-2-{2-[4-(piperazin-1-ylmethyl)phenyl]ethoxy}-1,3-benzoxazole dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.03 (2H, t, *J* = 7.1 Hz), 3.22-3.57 (8H, m), 4.07 (2H, t, *J* = 7.1 Hz), 4.32 (2H, brs), 7.19 (1H, d, *J* = 8.3 Hz), 7.24 (1H, dd, *J* = 8.3, 2.0 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 7.51-7.53 (3H, m), 9.75 (2H, brs), 12.14 (1H, brs).

Reference Example 299

2-(4-Methylphenoxy)-1-[4-(piperazin-1-ylmethyl)phenyl]ethanone dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.23 (3H, s), 2.85-3.70 (10H, m), 4.42 (1H, s), 5.52 (2H, s), 6.84-6.87
5 (2H, m), 7.08 (2H, dd, *J* = 8.8, 0.5 Hz), 7.80 (2H, d, *J* = 8.1 Hz), 8.08 (2H, d, *J* = 8.3 Hz), 9.51
(1H, brs), 12.32 (1H, brs).

Reference Example 300

1-{4-[2-(4-Ethoxyphenoxy)ethoxy]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.31 (3H, t, *J* = 6.9 Hz), 3.18-3.79 (8H, m), 3.96 (2H, q, *J* = 6.9 Hz),
10 4.25-4.34 (6H, m), 6.85-6.93 (4H, m), 7.07 (2H, d, *J* = 8.8 Hz), 7.57-7.59 (2H, m), 9.70 (2H,
brs), 12.05 (1H, brs).

Reference Example 301

15 1-{4-[2-(4-Methoxyphenoxy)ethoxy]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.23-3.50 (8H, m), 3.70 (3H, s), 4.24-4.26 (2H, m), 4.30-4.32 (4H, m),
6.87-6.92 (4H, m), 7.06 (2H, d, *J* = 8.8 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 9.93 (2H, brs), 12.20 (1H,
brs).

20 Reference Example 302

1-{4-[(*E*)-3-(4-Methylphenoxy)prop-1-en-1-yl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.23 (3H, s), 3.20-3.43 (8H, m), 4.35 (2H, brs), 4.70 (2H, dd, *J* = 5.6,
1.1 Hz), 6.58 (1H, dt, *J* = 16.1, 5.6 Hz), 6.77 (1H, d, *J* = 16.1 Hz), 6.88 (2H, dt, *J* = 9.1, 2.5 Hz),
7.09 (2H, d, *J* = 8.3 Hz), 7.55-7.58 (4H, m), 9.60 (2H, brs), 12.10 (1H, brs).

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Reference Example 303

2-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethoxy}-1,3-benzothiazole dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.99 (2H, t, *J* = 7.4 Hz), 3.22-3.43 (8H, m), 4.18 (2H, t, *J* = 7.4 Hz),
4.30 (2H, brs), 7.16-7.20 (1H, m), 7.31-7.37 (4H, m), 7.53 (2H, d, *J* = 6.8 Hz), 7.64 (1H, dd, *J* =
30 7.7, 0.9 Hz), 9.70 (2H, brs), 12.10 (1H, brs).

Reference Example 304

2-Methyl-5-{2-[4-(piperazin-1-ylmethyl)phenyl]ethoxy}-1,3-benzothiazole dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.77 (3H, s), 3.11 (2H, t, *J* = 6.6 Hz), 3.29-3.58 (8H, m), 4.30 (2H, t, *J* =

6.6 Hz), 4.38 (2H, brs), 7.03 (1H, dd, $J = 8.8, 2.4$ Hz), 7.44-7.46 (3H, m), 7.62-7.67 (2H, m), 7.89 (1H, d, $J = 8.8$ Hz), 9.81 (2H, brs), 12.18 (1H, s).

Reference Example 305

- 5 (3*S*)-*N*-Methyl-*N*-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)pyrrolidin-3-amine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.16 (6H, d, $J = 7.1$ Hz), 2.33-2.46 (2H, m), 2.60 (3H, s), 2.78-2.85 (1H, m), 3.06 (2H, t, $J = 6.7$ Hz), 3.20 (1H, brs), 3.47-3.66 (3H, m), 3.99-4.02 (1H, m), 4.16-4.19 (3H, m), 4.44-4.51 (1H, m), 6.83-6.86 (2H, m), 7.12-7.14 (2H, m), 7.41 (2H, d, $J = 8.1$ Hz), 7.56-7.58
10 (2H, m), 9.66 (1H, brs), 9.77 (1H, brs), 11.76 (1H, brs).

Reference Example 306

1-{4-[(*E*)-3-Phenoxyprop-1-en-1-yl]benzyl}piperazine

$^1\text{H-NMR}$ (CDCl₃) δ : 2.40 (4H, brs), 2.87 (4H, t, $J = 4.9$ Hz), 3.47 (2H, s), 4.69 (2H, dd, $J = 5.8,$
15 1.2 Hz), 6.40 (1H, dt, $J = 15.9, 5.8$ Hz), 6.72 (1H, d, $J = 15.9$ Hz), 6.93-6.97 (3H, m), 7.26-7.32 (4H, m), 7.35-7.37 (2H, m).

Reference Example 307

N-{4-[2-(4-Fluorophenoxy)ethyl]phenyl}piperidin-4-amine

20 $^1\text{H-NMR}$ (CDCl₃) δ : 1.24-1.37 (2H, m), 1.63 (1H, brs), 2.01-2.10 (2H, m), 2.66-2.76 (2H, m), 2.96 (2H, t, $J = 7.3$ Hz), 3.11 (2H, dt, $J = 13.2, 3.6$ Hz), 3.28-3.60 (2H, m), 4.06 (2H, t, $J = 7.3$ Hz), 6.51-6.61 (2H, m), 6.78-6.86 (2H, m), 6.90-7.00 (2H, m), 7.02-7.09 (2H, m).

Reference Example 308

- 25 *N*-[4-(2-{[4-(Propan-2-yl)phenyl]amino}ethyl)phenyl]piperidin-4-amine

$^1\text{H-NMR}$ (CDCl₃) δ : 1.20 (6H, d, $J = 6.8$ Hz), 1.27-1.39 (2H, m), 1.77 (1H, brs), 2.03-2.12 (2H, m), 2.67-2.85 (5H, m), 3.13 (2H, dt, $J = 12.9, 3.7$ Hz), 3.26-3.68 (5H, m), 6.51-6.61 (4H, m), 6.99-7.07 (4H, m).

- 30 Reference Example 309

N-{4-[2-(4-Methylphenoxy)ethyl]phenyl}piperidin-4-amine dihydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.78-1.96 (2H, m), 2.02-2.12 (2H, m), 2.22 (3H, s), 2.90 (2H, q, $J = 11.5$ Hz), 3.00 (2H, t, $J = 6.8$ Hz), 3.26-3.38 (2H, m), 3.40-4.10 (3H, m), 4.13 (2H, t, $J = 6.8$ Hz), 6.78-6.84 (2H, m), 7.04-7.10 (2H, m), 7.16-7.44 (4H, m), 8.86-8.99 (1H, m), 9.16-9.29 (1H, m).

Reference Example 310

3-[4-(Piperazin-1-ylmethyl)phenyl]propan-1-ol dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.69-1.76 (2H, m), 2.64 (2H, t, *J* = 7.7 Hz), 3.40-3.57 (10H, m), 4.35
5 (2H, s), 7.26-7.31 (2H, m), 7.55-7.59 (2H, m), 9.85 (2H, brs), 12.10 (1H, brs).

Reference Example 311

4-((*E*)-3-[4-(Piperazin-1-ylmethyl)phenyl]prop-2-en-1-yl}oxy)benzonitrile dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.41 (8H, brs), 4.36 (2H, s), 4.86 (2H, dd, *J* = 5.7, 1.1 Hz), 6.60 (1H, dt,
10 *J* = 16.0, 5.7 Hz), 6.82 (1H, d, *J* = 16.0 Hz), 7.16-7.20 (2H, m), 7.57 (2H, d, *J* = 8.2 Hz), 7.62
(2H, d, *J* = 8.2 Hz), 7.77-7.81 (2H, m), 9.73 (2H, brs).

Reference Example 312

1-{4-[(*E*)-3-(4-Methoxyphenoxy)prop-1-en-1-yl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.40 (8H, brs), 3.70 (3H, s), 4.34 (2H, brs), 4.68 (2H, dd, *J* = 5.6, 1.1
15 Hz), 6.58 (1H, dt, *J* = 16.1, 5.6 Hz), 6.78 (1H, d, *J* = 16.1 Hz), 6.85-6.89 (2H, m), 6.92-6.96 (2H,
m), 7.55-7.61 (4H, m), 9.62 (2H, brs).

Reference Example 313

20 1-{4-[(*E*)-3-(4-Fluorophenoxy)prop-1-en-1-yl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.38 (8H, brs), 4.32 (2H, s), 4.72 (2H, dd, *J* = 5.6, 1.0 Hz), 6.58 (1H, dt,
J = 16.1, 5.6 Hz), 6.79 (1H, d, *J* = 16.1 Hz), 7.04-7.99 (2H, m), 7.10-7.16 (2H, m), 7.56-7.59
(4H, m), 9.55 (2H, brs), 12.04 (1H, brs).

25 Reference Example 314

1-(4-{(*E*)-3-[4-(Propan-2-yl)phenoxy]prop-1-en-1-yl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.17 (6H, d, *J* = 7.1 Hz), 2.78-2.88 (1H, m), 3.38 (8H, brs), 4.32 (2H, s),
4.71 (2H, d, *J* = 5.2 Hz), 6.59 (1H, dt, *J* = 16.0, 5.2 Hz), 6.78 (1H, d, *J* = 16.0 Hz), 6.91 (2H, d, *J*
= 8.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 7.55-7.61 (4H, m), 9.58 (2H, brs), 12.03 (1H, brs).

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Reference Example 315

1-(4-{(*E*)-3-[(6-Chloropyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.41 (8H, brs), 4.36 (2H, s), 4.85 (2H, dd, *J* = 5.7, 1.2 Hz), 6.59 (1H, dt,
J = 16.0, 5.7 Hz), 6.82 (1H, d, *J* = 16.0 Hz), 7.45 (1H, dd, *J* = 8.8, 0.5 Hz), 7.54-7.64 (5H, m),

8.19 (1H, d, $J = 3.2$ Hz), 9.74 (2H, brs), 12.19 (1H, brs).

Reference Example 316

4-{(E)-3-[(6-Methylpyridin-3-yl)oxy]prop-1-en-1-yl}benzaldehyde

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.50 (3H, s), 4.76 (2H, dd, $J = 5.3, 1.6$ Hz), 6.55 (1H, dt, $J = 16.3, 5.3$ Hz), 6.80 (1H, d, $J = 16.3$ Hz), 7.08 (1H, d, $J = 8.5$ Hz), 7.17 (1H, dd, $J = 8.5, 2.9$ Hz), 7.56 (2H, d, $J = 8.3$ Hz), 7.85 (2H, dt, $J = 8.3, 1.7$ Hz), 8.26 (1H, d, $J = 2.9$ Hz), 10.00 (1H, s).

Reference Example 317

- 10 1-(4-{(E)-3-[(6-Methylpyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazine dihydrochloride

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.59-2.71 (3H, m), 3.46 (8H, brs), 4.37 (2H, s), 4.97 (2H, d, $J = 5.6$ Hz), 6.60 (1H, dt, $J = 16.0, 5.6$ Hz), 6.86 (1H, d, $J = 16.0$ Hz), 7.58 (2H, d, $J = 8.3$ Hz), 7.63 (2H, d, $J = 8.3$ Hz), 7.79 (1H, d, $J = 9.0$ Hz), 8.11 (1H, dd, $J = 9.0, 2.8$ Hz), 8.53 (1H, d, $J = 2.8$ Hz), 9.74 (2H, brs), 12.12 (1H, brs).

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Reference Example 318

(E)-3-[4-(Piperazin-1-ylmethyl)phenyl]prop-2-en-1-ol dihydrochloride

- $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.43 (8H, brs), 4.14 (2H, dd, $J = 4.8, 1.7$ Hz), 4.33 (2H, s), 6.47 (1H, dt, $J = 16.0, 4.8$ Hz), 6.59 (1H, d, $J = 16.0$ Hz), 7.50 (2H, d, $J = 8.2$ Hz), 7.57 (2H, d, $J = 8.2$ Hz),
20 9.61 (2H, brs), 11.98 (1H, brs).

Reference Example 319

1-[4-(3-Phenoxypropyl)benzyl]piperazine dihydrochloride

- $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.00-2.07 (2H, m), 2.78 (2H, t, $J = 7.8$ Hz), 3.41 (8H, brs), 3.98 (2H, t, $J = 6.3$ Hz), 4.31 (2H, s), 6.91-6.94 (3H, m), 7.26-7.34 (4H, m), 7.54 (2H, d, $J = 8.1$ Hz), 9.59 (2H, brs), 11.91 (1H, brs).

Reference Example 320

2-(4-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethoxy}phenyl)ethanol dihydrochloride

- 30 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.64 (2H, t, $J = 7.2$ Hz), 3.05 (2H, t, $J = 6.6$ Hz), 3.24-3.55 (9H, m), 4.19-4.30 (5H, m), 6.83 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.40 (2H, d, $J = 7.8$ Hz), 7.56-7.59 (2H, m), 9.82 (2H, s), 12.23 (1H, s).

Reference Example 321

1-(4-{3-[(6-Chloropyridin-3-yl)oxy]propyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.01-2.08 (2H, m), 2.77 (2H, t, *J* = 7.7 Hz), 3.40-3.45 (8H, m), 4.07 (2H, t, *J* = 6.2 Hz), 4.33 (2H, brs), 7.32 (2H, d, *J* = 8.0 Hz), 7.42 (1H, dd, *J* = 8.8, 0.6 Hz), 7.49 (1H, dd, *J* = 8.8, 3.2 Hz), 7.56 (2H, d, *J* = 8.0 Hz), 8.12 (1H, dd, *J* = 3.2, 0.6 Hz), 9.73 (2H, brs),
5 12.10 (1H, brs).

Reference Example 322

1-(4-{3-[(6-Methylpyridin-3-yl)oxy]propyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04-2.11 (2H, m), 2.66 (3H, s), 2.79 (2H, t, *J* = 7.6 Hz), 3.39-3.47 (8H, m), 4.19 (2H, t, *J* = 6.2 Hz), 4.35 (2H, s), 7.33 (2H, d, *J* = 8.2 Hz), 7.58 (2H, d, *J* = 8.2 Hz), 7.79 (1H, d, *J* = 8.8 Hz), 8.09 (1H, dd, *J* = 8.8, 2.9 Hz), 8.48 (1H, d, *J* = 2.9 Hz), 9.93 (2H, brs), 12.20 (1H, brs).

Reference Example 323

15 1-{4-[2-(4-Chlorophenoxy)ethyl]-3-fluorobenzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.07-3.43 (10H, m), 4.23-4.31 (4H, m), 6.96 (2H, d, *J* = 9.0 Hz), 7.31 (2H, d, *J* = 9.0 Hz), 7.44-7.49 (3H, m), 9.75 (2H, s), 12.33 (1H, s).

Reference Example 324

20 1-(2-Fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 3.12 (2H, t, *J* = 6.5 Hz), 3.21-3.49 (7H, m), 3.95-3.97 (1H, m), 4.32-4.34 (4H, m), 7.13 (2H, d, *J* = 8.5 Hz), 7.29-7.34 (2H, m), 7.64 (3H, d, *J* = 8.8 Hz), 9.60 (2H, s), 12.18-12.20 (1H, m).

25 Reference Example 325

1-{4-[3-(4-Methylphenoxy)propyl]benzyl}piperazine dihydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.97-2.04 (2H, m), 2.22 (3H, s), 2.76 (2H, t, *J* = 7.7 Hz), 3.40 (8H, brs), 3.93 (2H, t, *J* = 6.2 Hz), 4.32 (2H, brs), 6.82 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 7.8 Hz), 7.55 (2H, d, *J* = 7.8 Hz), 9.70 (2H, brs), 12.07 (1H, brs).

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[0164]

Reference Example 326

To a solution of *tert*-butyl 4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)-piperazine-1-carboxylate (5.42 g) in CH₂Cl₂ (41 mL) was added TFA (10 mL) at room

temperature, then the reaction mixture was stirred for 8 hours. The reaction mixture was basified with 5 M aqueous NaOH, and extracted with CH₂Cl₂. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford 1-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazine as a colorless solid (5.73 g).

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 5.9 Hz), 1.73 (1H, brs), 2.35-2.47 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 4.42 (1H, septet, *J* = 5.9 Hz), 4.98 (2H, s), 6.78-6.93 (4H, m), 7.29-7.43 (4H, m).

[0165]

The following compounds were produced in the same manner as in Reference Example 326 using appropriate starting materials.

Reference Example 327

1-{4-[(4-Chlorophenoxy)methyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.65 (1H, brs), 2.42 (4H, brs), 2.89 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 5.01 (2H, s), 6.86-6.93 (2H, m), 7.20-7.26 (2H, m), 7.31-7.39 (4H, m).

Reference Example 328

1-{4-[2-(4-Methylphenyl)ethoxy]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.80 (1H, brs), 2.33 (3H, s), 2.35-2.45 (4H, m), 2.87 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 7.3 Hz), 3.41 (2H, s), 4.13 (2H, t, *J* = 7.3 Hz), 6.79-6.88 (2H, m), 7.08-7.28 (6H, m).

Reference Example 329

1-(4-{2-[4-(Propan-2-yl)phenyl]ethoxy}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, *J* = 6.9 Hz), 1.94 (1H, brs), 2.33-2.43 (4H, m), 2.80-2.92 (5H, m), 3.06 (2H, t, *J* = 7.3 Hz), 3.41 (2H, s), 4.14 (2H, t, *J* = 7.3 Hz), 6.79-6.88 (2H, m), 7.15-7.28 (6H, m).

Reference Example 330

1-{4-[(4-Methoxyphenoxy)methyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.91 (1H, brs), 2.35-2.50 (4H, m), 2.89 (4H, t, *J* = 4.6 Hz), 3.50 (2H, s), 3.77 (3H, s), 4.99 (2H, s), 6.78-6.93 (4H, m), 7.30-7.43 (4H, m).

Reference Example 331

1-{4-[(4-Ethoxyphenoxy)methyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.39 (3H, t, *J* = 6.9 Hz), 2.18 (1H, brs), 2.38-2.50 (4H, m), 2.90 (4H, t, *J* = 4.9 Hz), 3.50 (2H, s), 3.98 (2H, q, *J* = 6.9 Hz), 4.99 (2H, s), 6.78-6.93 (4H, m), 7.30-7.43 (4H, m).

Reference Example 332

1-(4-{2-[4-(Propan-2-yloxy)phenoxy]ethyl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 1.29 (6H, d, *J* = 5.9 Hz), 1.86 (1H, brs), 2.33-2.52 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 7.3 Hz), 3.46 (2H, s), 4.11 (2H, t, *J* = 7.3 Hz), 4.40 (1H, septet, *J* = 5.9 Hz), 6.81 (4H, s), 7.18-7.34 (4H, m).

Reference Example 333

1-{4-[2-(4-Ethoxyphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 6.9 Hz), 1.69 (1H, brs), 2.34-2.50 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 6.9 Hz), 3.47 (2H, s), 3.97 (2H, q, *J* = 6.9 Hz), 4.11 (2H, t, *J* = 6.9 Hz), 6.81 (4H, s), 7.16-7.30 (4H, m).

Reference Example 334

1-{4-[2-(3-Chlorophenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.61 (1H, brs), 2.34-2.48 (4H, m), 2.88 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 6.9 Hz), 3.47 (2H, s), 4.14 (2H, t, *J* = 6.9 Hz), 6.72-6.83 (1H, m), 6.85-6.95 (2H, m), 7.10-7.30 (5H, m).

Reference Example 335

4-{2-[4-(Piperazin-1-ylmethyl)phenyl]ethoxy}benzonitrile trifluoroacetate

¹H-NMR (DMSO-*d*₆) δ: 2.92-3.14 (6H, m), 3.22-3.45 (4H, m), 4.01 (2H, brs), 4.31 (2H, t, *J* = 6.6 Hz), 7.11 (2H, d, *J* = 8.2 Hz), 7.38 (4H, s), 7.76 (2H, d, *J* = 8.2 Hz), 9.03 (1H, brs).

Reference Example 336

1-(4-{2-[4-(Methylsulfonyl)phenoxy]ethyl}benzyl)piperazine trifluoroacetate

¹H-NMR (DMSO-*d*₆) δ: 2.93-3.13 (6H, m), 3.15 (3H, s), 3.27 (4H, brs), 4.04 (2H, brs), 4.33 (2H, t, *J* = 6.9 Hz), 7.16 (2H, d, *J* = 8.9 Hz), 7.39 (4H, s), 7.83 (2H, d, *J* = 8.9 Hz), 9.09 (2H, brs).

Reference Example 337

1-{4-[2-(4-Iodophenoxy)ethyl]benzyl}piperazine trifluoroacetate

¹H-NMR (DMSO-*d*₆) δ: 2.93-3.11 (6H, m), 3.32 (4H, brs), 3.99 (2H, brs), 4.18 (2H, t, *J* = 6.9 Hz), 6.78 (2H, d, *J* = 8.9 Hz), 7.36 (4H, s), 7.58 (2H, d, *J* = 8.9 Hz), 8.99 (2H, brs), 11.12 (1H, brs).

Reference Example 338

6-(Piperazin-1-ylmethyl)-2-[4-(propan-2-yl)phenoxy]quinoline

¹H-NMR (CDCl₃) δ: 1.29 (6H, d, *J* = 6.9 Hz), 1.68 (1H, brs), 2.45 (4H, brs), 2.90 (4H, t, *J* = 4.6 Hz), 2.95 (1H, septet, *J* = 6.9 Hz), 3.62 (2H, s), 7.03 (1H, d, *J* = 8.7 Hz), 7.12-7.19 (2H, m), 7.24-7.30 (2H, m), 7.62 (1H, dd, *J* = 6.9, 1.8 Hz), 7.67 (1H, s), 7.77 (1H, d, *J* = 8.7 Hz), 8.07 (1H, d, *J* = 8.7 Hz).

Reference Example 339

2-(4-Methoxyphenoxy)-6-(piperazin-1-ylmethyl)quinoline

¹H-NMR (CDCl₃) δ: 1.58 (1H, brs), 2.44 (4H, brs), 2.89 (4H, t, *J* = 4.5 Hz), 3.61 (2H, s), 3.84 (3H, s), 6.91-6.99 (2H, m), 7.02 (1H, d, *J* = 9.2 Hz), 7.13-7.20 (2H, m), 7.61 (1H, dd, *J* = 8.2 Hz), 7.64-7.69 (1H, m), 7.74 (1H, d, *J* = 8.7 Hz), 8.06 (1H, d, *J* = 9.2 Hz).

Reference Example 340

1-{4-[2-(4-Methylphenoxy)propyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.27 (3H, d, *J* = 6.1 Hz), 2.27 (3H, s), 2.40 (4H, brs), 2.78 (1H, dd, *J* = 13.7, 6.6 Hz), 2.88 (4H, t, *J* = 4.9 Hz), 3.07 (1H, dd, *J* = 13.7, 5.9 Hz), 3.45 (2H, s), 4.47-4.54 (1H, m), 6.78 (2H, dt, *J* = 9.4, 2.6 Hz), 7.05 (2H, dd, *J* = 8.7, 0.6 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.23 (2H, d, *J* = 8.1 Hz).

Reference Example 341

1-{4-[1-(4-Methylphenoxy)propan-2-yl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.39 (3H, d, *J* = 7.1 Hz), 2.27 (3H, s), 2.41 (4H, brs), 2.88 (4H, t, *J* = 4.9 Hz), 3.17-3.25 (1H, m), 3.47 (2H, s), 3.91 (1H, dd, *J* = 9.2, 7.8 Hz), 4.05 (1H, dd, *J* = 9.2, 5.7 Hz), 6.78 (2H, d, *J* = 8.8 Hz), 7.05 (2H, d, *J* = 8.8 Hz), 7.22 (2H, d, *J* = 8.3 Hz), 7.27 (2H, d, *J* = 8.3 Hz).

Reference Example 342

1-{4-[(*E*)-3-Methoxyprop-1-en-1-yl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.42 (4H, brs), 2.89 (4H, t, *J* = 4.9 Hz), 3.39 (3H, s), 3.47 (2H, s), 4.09 (2H, dd, *J* = 6.1, 1.5 Hz), 6.26 (1H, dt, *J* = 16.1, 6.1 Hz), 6.60 (1H, d, *J* = 16.1 Hz), 7.27 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.3 Hz).

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Reference Example 343

1-{3-Methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.35 (3H, s), 2.40 (4H, brs), 2.88 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.4 Hz), 3.43 (2H, s), 4.10 (2H, t, *J* = 7.4 Hz), 6.79 (2H, dt, *J* = 9.3, 2.5 Hz), 7.05-7.12 (4H, m), 7.16 (1H, d, *J* = 7.8 Hz).

10

Reference Example 344

1-{4-[2-(4-Fluorophenoxy)ethyl]-3-methylbenzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.35 (3H, s), 2.41 (4H, brs), 2.89 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.3 Hz), 3.44 (2H, s), 4.09 (2H, t, *J* = 7.3 Hz), 6.79-6.85 (2H, m), 6.92-7.00 (2H, m), 7.09-7.16 (3H, m).

15

Reference Example 345

N,N-Dimethyl-4-{2-[4-(piperazin-1-ylmethyl)phenyl]ethoxy}aniline

¹H-NMR (CDCl₃) δ: 2.39-2.42 (4H, m), 2.86-2.88 (10H, m), 3.05 (2H, t, *J* = 7.2 Hz), 3.46 (2H, s), 4.11 (2H, t, *J* = 7.2 Hz), 6.72-6.73 (2H, m), 6.82-6.84 (2H, m), 7.21-7.27 (4H, m).

20

Reference Example 346

1-{4-[2-(4-Fluorophenoxy)propyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 1.28 (3H, d, *J* = 6.1 Hz), 2.39 (4H, brs), 2.79 (1H, dd, *J* = 13.7, 6.6 Hz), 2.88 (4H, t, *J* = 4.9 Hz), 3.04 (1H, dd, *J* = 13.7, 6.1 Hz), 3.46 (2H, s), 4.41-4.49 (1H, m), 6.77-6.82 (2H, m), 6.90-6.96 (2H, m), 7.17 (2H, d, *J* = 8.1 Hz), 7.24 (2H, d, *J* = 8.1 Hz).

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Reference Example 347

1-{2-Methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazine

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.35 (3H, s), 2.40 (4H, brs), 2.85 (4H, t, *J* = 4.9 Hz), 3.03 (2H, t, *J* = 7.2 Hz), 3.41 (2H, s), 4.12 (2H, t, *J* = 7.2 Hz), 6.80 (2H, dt, *J* = 9.3, 2.5 Hz), 7.00-7.08 (4H, m), 7.19 (1H, d, *J* = 7.6 Hz).

30

Reference Example 348

2-[2-Fluoro-4-(piperazin-1-ylmethyl)phenoxy]-2-methylpropan-1-ol

¹H-NMR (CDCl₃) δ: 1.28 (6H, s), 1.89-1.93 (2H, m), 2.39-2.42 (4H, m), 2.89-2.90 (4H, m), 3.43 (2H, s), 3.59 (2H, s), 6.98-7.00 (2H, m), 7.10 (1H, d, *J* = 12.0 Hz).

5

[0166]

Reference Example 349

To a solution of 9*H*-fluoren-9-ylmethyl 4-(4-{(*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazine-1-carboxylate (0.604 g) in CH₂Cl₂ (10 mL) was added piperidine (0.196 mL). After stirring at room temperature for 1 hour, to the reaction mixture was added piperidine (0.784 mL) and stirred at room temperature for 4 hours. Then to the reaction mixture was added saturated aqueous NH₄Cl and CH₂Cl₂. The organic layer was washed with saturated aqueous NH₄Cl and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was washed with Et₂O to afford 1-(4-{(*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazine as a white powder (0.282 g).

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15

¹H-NMR (CDCl₃) δ: 2.72 (4H, t, *J* = 4.8 Hz), 3.19 (4H, t, *J* = 4.8 Hz), 3.54 (2H, s), 4.96 (2H, d, *J* = 6.1 Hz), 6.42 (1H, dt, *J* = 15.9, 6.1 Hz), 6.68-6.72 (2H, m), 7.23-7.26 (2H, m), 7.36 (2H, d, *J* = 8.1 Hz), 7.65 (1H, dd, *J* = 8.7, 2.5 Hz), 8.20 (1H, d, *J* = 2.5 Hz).

20

[0167]

The following compound was produced in the same manner as in Reference Example 349 using appropriate starting materials.

Reference Example 350

1-(4-{(*E*)-3-[(5-Methylpyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazine

¹H-NMR (CDCl₃) δ: 2.25 (3H, s), 2.74 (4H, t, *J* = 4.8 Hz), 3.21 (4H, t, *J* = 4.9 Hz), 3.54 (2H, s), 4.96 (2H, dd, *J* = 6.0, 1.2 Hz), 6.45 (1H, dt, *J* = 15.9, 6.0 Hz), 6.69-6.72 (2H, m), 7.23 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.2 Hz), 7.40 (1H, ddd, *J* = 8.5, 2.4, 0.5 Hz), 7.96-7.97 (1H, m).

25

30

[0168]

Reference Example 351

To an EtOH (500 mL) solution of butyl (*E*)-3-{3-chloro-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate (45.4 g) and tin powder (57.3 g) was slowly added conc. HCl (36.6 mL) at 0 °C, then the resultant mixture was stirred at room temperature for 1 hour. The reaction

mixture was neutralized with 5 M aqueous NaOH, and the mixture was filtered off on Celite. The filtrate was evaporated and water was added to the residue, and the mixture was extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 2/1) to afford butyl (*E*)-3-{4-[(5-amino-
5 pyridin-2-yl)oxy]-3-chlorophenyl}prop-2-enoate (39.9 g) as a pale yellow solid.

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.38-1.50 (2H, m), 1.64-1.74 (2H, m), 3.58 (2H, brs), 4.21 (2H, t, *J* = 6.8 Hz), 6.37 (1H, d, *J* = 16.1 Hz), 6.85 (1H, d, *J* = 7.8 Hz), 7.08-7.15 (2H, m), 7.39 (1H, dd, *J* = 8.3, 2.0 Hz), 7.55-7.67 (3H, m).

10 [0169]

The following compounds were produced in the same manner as in Reference Example 351 using appropriate starting materials.

Reference Example 352

15 Ethyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-methoxyphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 3.50 (2H, s), 3.83 (3H, s), 4.27 (2H, q, *J* = 7.2 Hz), 6.36 (1H, d, *J* = 15.6 Hz), 6.82 (1H, d, *J* = 8.8 Hz), 7.03-7.14 (4H, m), 7.65 (2H, dd, *J* = 9.5, 6.6 Hz).

20 Reference Example 353

Butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.37-1.51 (2H, m), 1.64-1.74 (2H, m), 2.24 (3H, s), 3.55 (2H, brs), 4.20 (2H, q, *J* = 6.6 Hz), 6.35 (1H, d, *J* = 15.8 Hz), 6.76 (1H, d, *J* = 8.6 Hz), 6.93 (1H, d, *J* = 8.2 Hz), 7.09 (1H, dd, *J* = 8.6, 3.0 Hz), 7.31-7.35 (1H, m), 7.41 (1H, brs), 7.63 (1H, d, *J* = 15.8 Hz), 7.69 (1H, d, *J* = 3.0 Hz).

25

Reference Example 354

Butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-chloro-5-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.48 (2H, m), 1.65-1.72 (2H, m), 2.19 (3H, s), 3.47 (2H, brs), 4.20 (2H, t, *J* = 6.6 Hz), 6.37 (1H, d, *J* = 15.9 Hz), 6.82 (1H, d, *J* = 8.5 Hz), 7.10-7.13 (1H, m), 7.31-7.32 (1H, m), 7.46 (1H, d, *J* = 1.7 Hz), 7.56-7.60 (2H, m).

30

Reference Example 355

Ethyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3,5-dimethoxyphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.2 Hz), 3.41 (2H, brs), 3.79 (6H, s), 4.27 (2H, q, *J* = 7.2 Hz), 6.38 (1H, d, *J* = 15.9 Hz), 6.82 (2H, s), 6.85 (1H, d, *J* = 8.8 Hz), 7.08 (1H, dd, *J* = 8.5, 2.9 Hz), 7.58 (1H, d, *J* = 2.9 Hz), 7.64 (1H, d, *J* = 15.9 Hz).

5 Reference Example 356

Butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-2-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.37-1.50 (2H, m), 1.64-1.74 (2H, m), 2.40 (3H, s), 3.58 (2H, brs), 4.20 (2H, t, *J* = 6.6 Hz), 6.29 (1H, d, *J* = 15.8 Hz), 6.80 (1H, d, *J* = 8.9 Hz), 6.86-6.90 (2H, m), 7.10 (1H, dd, *J* = 8.6, 3.0 Hz), 7.53-7.56 (1H, m), 7.73 (1H, dd, *J* = 3.0 Hz), 7.92 (1H, d, *J* = 15.8 Hz).

Reference Example 357

6-(4-Bromo-2-chloro-6-methylphenoxy)pyridin-3-amine

¹H-NMR (CDCl₃) δ: 2.16 (3H, s), 3.46 (2H, brs), 6.80 (1H, dd, *J* = 8.6, 0.5 Hz), 7.10 (1H, dd, *J* = 8.8, 3.2 Hz), 7.25-7.33 (1H, m), 7.43 (1H, dd, *J* = 2.3, 0.5 Hz), 7.56 (1H, dd, *J* = 2.9, 0.5 Hz).

Reference Example 358

Butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-fluorophenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 3.54 (2H, s), 4.21 (2H, t, *J* = 6.6 Hz), 6.36 (1H, d, *J* = 16.1 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 7.12 (1H, dd, *J* = 9.0, 2.7 Hz), 7.17 (1H, t, *J* = 8.1 Hz), 7.26-7.35 (2H, m), 7.59-7.64 (2H, m).

Reference Example 359

Ethyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 2.12 (6H, s), 3.44 (2H, brs), 4.26 (2H, t, *J* = 7.1 Hz), 6.36 (1H, d, *J* = 16.1 Hz), 6.70 (1H, d, *J* = 8.8 Hz), 7.08 (1H, dd, *J* = 8.6, 2.9 Hz), 7.26 (2H, s), 7.61-7.65 (2H, m).

[0170]

30 Reference Example 360

To a solution of ethyl 6-[(5-nitropyridin-2-yl)oxy]naphthalene-2-carboxylate (23.3 g) in EtOH (460 mL) was added Pd/C (0.367 g) under a H₂ atmosphere. Then the reaction mixture was warmed to 50 °C, and stirred for 7.5 hours. The reaction mixture was filtered off on celite, and the filtrate was concentrated under reduced pressure. The residual

solid was dried under reduced pressure at 60 °C to afford ethyl 6-[(5-aminopyridin-2-yl)oxy]naphthalene-2-carboxylate as a pale brown powder (19.6 g).

¹H-NMR (CDCl₃) δ: 1.44 (3H, t, *J* = 7.2 Hz), 3.60 (2H, s), 4.43 (2H, q, *J* = 7.2 Hz), 6.87 (1H, dd, *J* = 8.5, 0.5 Hz), 7.14 (1H, dd, *J* = 8.5, 3.2 Hz), 7.32 (1H, dd, *J* = 8.9, 2.3 Hz), 7.41 (1H, d, *J* = 2.2 Hz), 7.74 (1H, d, *J* = 8.5 Hz), 7.76 (1H, dd, *J* = 2.9, 0.5 Hz), 7.93 (1H, d, *J* = 9.0 Hz), 8.03 (1H, dd, *J* = 8.5, 1.7 Hz), 8.57 (1H, s).

[0171]

Reference Example 361

To a solution of 2-(4-bromo-2-chloro-5-methylphenoxy)-5-nitropyridine (10.0 g) in AcOEt (150 mL) was added 5% Pt/C (1.00 g) at 0 °C. After stirring at room temperature for 5 hours under a hydrogen atmosphere, the reaction mixture was filtered off using celite, and the filtrate was concentrated under reduced pressure to give 6-(4-bromo-2-chloro-5-methylphenoxy)pyridin-3-amine as a pink solid (9.13 g).

¹H-NMR (CDCl₃) δ: 2.33 (3H, s), 3.51 (2H, brs), 6.80-6.83 (1H, m), 7.01 (1H, s), 7.10 (1H, dd, *J* = 8.5, 2.9 Hz), 7.60 (1H, s), 7.63-7.64 (1H, m).

[0172]

The following compounds were produced in the same manner as in Reference Example 361 using appropriate starting materials.

20 Reference Example 362

6-(4-Bromo-5-chloro-2-methylphenoxy)pyridin-3-amine

¹H-NMR (CDCl₃) δ: 2.16 (3H, s), 3.53 (2H, brs), 6.76 (1H, d, *J* = 8.5 Hz), 7.05 (1H, s), 7.08-7.13 (1H, m), 7.46 (1H, s), 7.66 (1H, d, *J* = 2.9 Hz).

25 Reference Example 363

tert-Butyl 4-{4-[2-(4-aminophenoxy)ethyl]benzyl}piperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 2.38 (4H, t, *J* = 4.9 Hz), 3.02-3.06 (2H, m), 3.41-3.43 (6H, m), 3.48 (2H, brs), 4.07-4.11 (2H, m), 6.62 (2H, d, *J* = 8.8 Hz), 6.73 (2H, d, *J* = 8.8 Hz), 7.22 (2H, d, *J* = 8.3 Hz), 7.25 (2H, d, *J* = 8.8 Hz).

30

[0173]

Reference Example 364

To a THF (400 mL) solution of butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-chlorophenyl}prop-2-enoate (30.0 g) was slowly added H₂SO₄ (6.92 mL) at 0 °C. After stirring

for 10 minutes, *n*-pentyl nitrite (17.3 mL) was slowly added to the reaction mixture. Then the resultant mixture was stirred at 0 °C for 1 hour. The resulting precipitate was collected by filtration and dried under reduced pressure to afford a diazonium salt as a pale yellow powder. To acetic acid (400 mL) was slowly added the above diazonium salt at 100 °C, then the resultant mixture was stirred at 100 °C for 3 hours. After cooling, the solvent was evaporated and the residue was neutralized with 5 M aqueous NaOH, and the mixture was extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 2/1) to afford butyl (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]phenyl}prop-2-enoate (14.8 g) as a brown oil.

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.38-1.50 (2H, m), 1.64-1.74 (2H, m), 4.21 (2H, t, *J* = 6.8 Hz), 6.26 (1H, brs), 6.37 (1H, d, *J* = 16.1 Hz), 6.90 (1H, d, *J* = 8.8 Hz), 7.12 (1H, d, *J* = 8.8 Hz), 7.28 (1H, dd, *J* = 8.8, 2.9 Hz), 7.40 (1H, dd, *J* = 8.3, 2.0 Hz), 7.54-7.62 (2H, m), 7.75 (1H, d, *J* = 2.4 Hz).

[0174]

The following compounds were produced in the same manner as in Reference Example 364 using appropriate starting materials.

Reference Example 365

Butyl (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.41-1.46 (2H, m), 1.66-1.72 (2H, m), 2.19 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.59 (1H, s), 6.37 (1H, d, *J* = 16.2 Hz), 6.87 (1H, d, *J* = 8.9 Hz), 7.24-7.31 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.8 Hz), 7.67 (1H, d, *J* = 3.0 Hz).

Reference Example 366

Butyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-2-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.39-1.48 (2H, m), 1.65-1.72 (2H, m), 2.37 (3H, s), 4.21 (2H, t, *J* = 6.8 Hz), 6.29 (1H, d, *J* = 16.1 Hz), 6.81-6.87 (3H, m), 7.24-7.27 (1H, m), 7.52-7.54 (1H, m), 7.68 (1H, brs), 7.83 (1H, d, *J* = 3.4 Hz), 7.90 (1H, d, *J* = 16.1 Hz).

Reference Example 367

Ethyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3-methoxyphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 3.79 (3H, s), 4.27 (2H, q, *J* = 7.1 Hz), 6.36 (1H, d, *J* = 15.6 Hz), 6.45-6.75 (1H, m), 6.83 (1H, d, *J* = 8.8 Hz), 7.04-7.13 (3H, m), 7.22 (1H, dd, *J* =

8.8, 2.9 Hz), 7.61-7.73 (2H, m).

Reference Example 368

Ethyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]phenyl}prop-2-enoate

- 5 ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.2 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 6.35 (1H, brs), 6.35 (1H, d, *J* = 16.1 Hz), 6.87 (1H, d, *J* = 8.8 Hz), 7.06 (2H, dt, *J* = 9.2, 2.4 Hz), 7.27 (1H, dd, *J* = 8.8, 3.1 Hz), 7.51 (2H, dt, *J* = 9.2, 2.4 Hz), 7.65 (1H, d, *J* = 16.1 Hz), 7.85 (1H, dd, *J* = 3.2, 0.5 Hz).

Reference Example 369

- 10 Butyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.96 (3H, t, *J* = 7.3 Hz), 1.39-1.48 (2H, m), 1.65-1.72 (2H, m), 2.21 (3H, s), 4.21 (2H, t, *J* = 6.9 Hz), 6.35 (1H, d, *J* = 15.6 Hz), 6.77 (1H, d, *J* = 8.7 Hz), 6.92 (1H, d, *J* = 8.2 Hz), 7.24 (1H, dd, *J* = 8.9, 3.0 Hz), 7.32 (1H, dd, *J* = 8.5, 2.1 Hz), 7.40 (1H, d, *J* = 1.8 Hz), 7.44 (1H, s), 7.62 (1H, d, *J* = 16.0 Hz), 7.78 (1H, d, *J* = 2.7 Hz).

15

Reference Example 370

Butyl (*E*)-3-{3-fluoro-4-[(5-hydroxypyridin-2-yl)oxy]phenyl}prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 4.21 (2H, t, *J* = 6.7 Hz), 5.20 (1H, s), 6.37 (1H, d, *J* = 16.1 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.20 (1H, t, *J* = 8.1 Hz), 7.27-7.35 (3H, m), 7.61 (1H, d, *J* = 15.9 Hz), 7.75 (1H, d, *J* = 3.2 Hz).
- 20

Reference Example 371

6-(4-Bromo-2-chloro-6-methylphenoxy)pyridin-3-ol

- ¹H-NMR (CDCl₃) δ: 2.15 (3H, s), 6.24 (1H, brs), 6.84 (1H, d, *J* = 8.8 Hz), 7.22-7.29 (2H, m), 7.38-7.43 (1H, m), 7.63 (1H, d, *J* = 3.2 Hz).
- 25

Reference Example 372

Ethyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 2.09 (6H, s), 4.26 (2H, t, *J* = 7.1 Hz), 6.34 (1H, d, *J* = 15.9 Hz), 6.66 (1H, d, *J* = 8.8 Hz), 7.19-7.26 (3H, m), 7.57-7.61 (2H, m), 7.66 (1H, d, *J* = 2.2 Hz).
- 30

Reference Example 373

Ethyl 6-[(5-hydroxypyridin-2-yl)oxy]naphthalene-2-carboxylate

¹H-NMR (DMSO-*d*₆) δ: 1.37 (3H, t, *J* = 7.1 Hz), 4.38 (2H, q, *J* = 7.2 Hz), 7.03 (1H, dd, *J* = 8.7, 0.6 Hz), 7.33-7.37 (2H, m), 7.51 (1H, d, *J* = 2.4 Hz), 7.77 (1H, dd, *J* = 3.2, 0.5 Hz), 7.92-7.98 (2H, m), 8.16 (1H, d, *J* = 9.3 Hz), 8.61 (1H, d, *J* = 0.7 Hz), 9.82 (1H, brs).

5 Reference Example 374

6-(4-Bromo-2-chloro-5-methylphenoxy)pyridin-3-ol

¹H-NMR (DMSO-*d*₆) δ: 2.30 (3H, s), 6.96 (1H, d, *J* = 8.8 Hz), 7.23 (1H, s), 7.30 (1H, dd, *J* = 8.8, 2.9 Hz), 7.63 (1H, d, *J* = 2.9 Hz), 7.79 (1H, s), 9.66 (1H, s).

10 Reference Example 375

6-(4-Bromo-5-chloro-2-methylphenoxy)pyridin-3-ol

¹H-NMR (DMSO-*d*₆) δ: 2.09 (3H, s), 6.95 (1H, d, *J* = 8.8 Hz), 7.22 (1H, s), 7.30 (1H, dd, *J* = 8.8, 3.2 Hz), 7.66 (1H, d, *J* = 3.2 Hz), 7.71 (1H, s), 9.67 (1H, s).

15 Reference Example 376

Ethyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethoxyphenyl}prop-2-enoate

¹H-NMR (DMSO-*d*₆) δ: 1.27 (3H, t, *J* = 7.1 Hz), 3.72 (6H, s), 4.20 (2H, q, *J* = 7.1 Hz), 6.72 (1H, d, *J* = 16.1 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 7.14 (2H, s), 7.21 (1H, dd, *J* = 8.8, 2.9 Hz), 7.51 (1H, d, *J* = 2.7 Hz), 7.64 (1H, d, *J* = 16.1 Hz), 9.38 (1H, s).

20

[0175]

Reference Example 377

To a 1,4-dioxane (10 mL) solution of 2-(4-bromo-2-chloro-6-methylphenoxy)-5-nitropyridine (1.00 g) and butyl acrylate (0.480 mL) were added *N,N*-dicyclohexylmethylamine (0.655 mL), tri-*tert*-butylphosphine tetrafluoroborate (34 mg) and tris(dibenzylideneacetone)dipalladium (0) (40 mg) at room temperature. The resultant mixture was stirred at 70 °C under a nitrogen atmosphere for 4 hours. To the reaction mixture was added water, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 1/1) to afford butyl (*E*)-3-{3-chloro-5-methyl-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate as a yellow powder (1.05 g).

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s), 4.22 (2H, t, *J* = 6.8 Hz), 6.42 (1H, d, *J* = 16.1 Hz), 7.17 (1H, d, *J* = 9.0 Hz), 7.36-7.37 (1H, m), 7.50 (1H, d, *J* = 2.0 Hz), 7.59 (1H, d, *J* = 16.1 Hz), 8.54 (1H, dd, *J* = 9.0, 2.9 Hz), 8.98-8.99 (1H,

m).

[0176]

The following compounds were produced in the same manner as in Reference Example 377 using appropriate starting materials.

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Reference Example 378

Butyl (*E*)-3-{5-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-2-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.6 Hz), 1.39-1.48 (2H, m), 1.66-1.73 (2H, m), 2.37 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.38 (1H, brs), 6.32 (1H, d, *J* = 15.9 Hz), 6.90 (1H, d, *J* = 8.8 Hz), 6.97 (1H, s), 7.26-7.29 (1H, m), 7.62 (1H, s), 7.77 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 15.9 Hz).

Reference Example 379

Butyl (*E*)-3-{2-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s), 4.22 (2H, t, *J* = 6.8 Hz), 5.23-5.30 (1H, m), 6.38 (1H, d, *J* = 15.9 Hz), 6.87 (1H, d, *J* = 8.8 Hz), 7.01 (1H, s), 7.28 (1H, dd, *J* = 8.8, 2.9 Hz), 7.51 (1H, s), 7.82 (1H, d, *J* = 2.9 Hz), 8.02 (1H, d, *J* = 15.9 Hz).

[0177]

20 Reference Example 380

To a DMF (50 mL) solution of 6-(4-bromo-2-chloro-6-methylphenoxy)pyridin-3-ol (5.00 g) were added imidazole (1.41 g) and TBDMSCl (2.87 g) at room temperature. After stirring at room temperature for 5 hours, to the reaction mixture was added saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 2/1) to give 2-(4-bromo-2-chloro-6-methylphenoxy)-5-[[*tert*-butyl(dimethyl)silyl]oxy]pyridine as a colorless oil (6.16 g).

¹H-NMR (CDCl₃) δ: 0.18 (6H, s), 0.97 (9H, s), 2.15 (3H, s), 6.86 (1H, dd, *J* = 8.8, 0.7 Hz), 7.21 (1H, dd, *J* = 8.8, 2.9 Hz), 7.30-7.31 (1H, m), 7.43-7.44 (1H, m), 7.65-7.67 (1H, m).

[0178]

Reference Example 381

A THF (15 mL) solution of bis(pinacolato)diboron (3.03 g), copper(I) chloride (0.032 g), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.188 g) and sodium *tert*-butoxide

(0.063 g) was stirred at room temperature for 30 minutes under an argon atmosphere. To the mixture were added 2-(trimethylsilyl)ethyl but-2-ynoate (2.00 g) and MeOH (0.878 mL) in order. After stirring for 5 hours at room temperature, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 19/1 to 9/1) to afford 2-(trimethylsilyl)ethyl (*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate as a colorless oil (2.86 g).

¹H-NMR (CDCl₃) δ: 0.05(9H, s), 0.94-1.06(2H, m), 1.28(12H, s), 2.17(3H, d, *J* = 2.0 Hz), 4.15-4.26(2H, m), 6.42(1H, d, *J* = 1.6 Hz).

[0179]

Reference Example 382

A mixture of ethyl (*E*)-2-methyl-3-[[trifluoromethyl)sulfonyl]oxy}but-2-enoate (2.00 g), bis(pinacolato)diboron (2.02 g), dichlorobis(triphenylphosphine) palladium (II) (0.15 g), triphenylphosphine (0.11 g) and potassium *tert*-butoxide (1.44 g) in toluene (40 mL) was stirred at 50 °C for 2 hours under an argon atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 99/1 to 19/1) to afford ethyl (*Z*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate as a colorless oil (0.91 g).

¹H-NMR (CDCl₃) δ: 1.28(12H, s), 1.30(3H, t, *J* = 7.3 Hz), 1.87(3H, q, *J* = 1.6 Hz), 2.10(3H, q, *J* = 1.6 Hz), 4.22(2H, q, *J* = 7.3 Hz).

[0180]

Reference Example 383

To a solution of 6-(4-bromo-2-chloro-6-methylphenoxy)pyridin-3-ol (5.00 g) in CH₂Cl₂-THF (70 mL, 5:2) were added 3,4-dihydro-2*H*-pyran (4.35 mL) and PPTS (200 mg) at room temperature. After stirring at room temperature for 95 hours, the solvent was removed under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 4/1 to 1/1) to give 2-(4-bromo-2-chloro-6-methylphenoxy)-5-(tetrahydro-2*H*-pyran-2-yloxy)pyridine as a yellow oil (6.30 g).

¹H-NMR (CDCl₃) δ: 1.51-2.01 (6H, m), 2.16 (3H, s), 3.57-3.62 (1H, m), 3.86-3.94 (1H, m), 5.28 (1H, t, *J* = 3.2 Hz), 6.88-6.92 (1H, m), 7.30-7.31 (1H, m), 7.43-7.52 (2H, m), 7.87-7.89 (1H, m).

[0181]

The following compound was produced in the same manner as in Reference

Example 105 using appropriate starting materials.

Reference Example 384

3-Chloro-5-methyl-4-{[5-(tetrahydro-2*H*-pyran-2-yloxy)pyridin-2-yl]oxy}benzaldehyde

- 5 ¹H-NMR (CDCl₃) δ: 1.58-1.99 (6H, m), 2.26 (3H, s), 3.58-3.62 (1H, m), 3.86-3.92 (1H, m), 5.28-5.30 (1H, m), 6.96 (1H, d, *J* = 9.0 Hz), 7.49 (1H, dd, *J* = 9.0, 2.9 Hz), 7.70-7.71 (1H, m), 7.82 (1H, d, *J* = 1.7 Hz), 7.86 (1H, d, *J* = 2.9 Hz), 9.92 (1H, s).

[0182]

10 Reference Example 385

To a THF (100 mL) solution of triethyl phosphonoacetate (44.0 mL) was slowly added NaH (60% dispersion in mineral oil, 8.8 g) at 0 °C. After stirring for 1 hour, a THF (200 mL) solution of 3,5-dimethyl-4-[(5-nitropyridin-2-yl)oxy]benzaldehyde (54.5 g) was added to the reaction mixture. After stirring at room temperature for 2 hours, AcOEt and H₂O were

- 15 added to the reaction mixture. The resulting precipitate was collected to give ethyl (*E*)-3-{3,5-dimethyl-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate as a white powder (40.9 g).

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 2.12 (6H, s), 4.27 (2H, t, *J* = 7.1 Hz), 6.40 (1H, d, *J* = 16.1 Hz), 7.09 (1H, d, *J* = 9.0 Hz), 7.31 (2H, s), 7.64 (1H, d, *J* = 15.9 Hz), 8.51 (1H, dd, *J* = 9.0, 2.2 Hz), 9.01 (1H, d, *J* = 2.4 Hz).

20 [0183]

The following compounds were produced in the same manner as in Reference Example 385 using appropriate starting materials.

Reference Example 386

- 25 Ethyl (*E*)-3-{3,5-dimethoxy-4-[(5-nitropyridin-2-yl)oxy]phenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.36 (3H, t, *J* = 7.1 Hz), 3.81 (6H, s), 4.29 (2H, q, *J* = 7.1 Hz), 6.42 (1H, d, *J* = 16.2 Hz), 6.84 (2H, s), 7.13 (1H, d, *J* = 8.9 Hz), 7.66 (1H, d, *J* = 16.2 Hz), 8.48 (1H, dd, *J* = 9.1, 2.8 Hz), 8.99 (1H, d, *J* = 3.0 Hz).

30 Reference Example 387

Ethyl (*E*)-3-(3-chloro-5-methyl-4-{[5-(tetrahydro-2*H*-pyran-2-yloxy)pyridin-2-yl]oxy}phenyl)-2-methylprop-2-enoate

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 1.55-1.74 (3H, m), 1.82-1.89 (2H, m), 1.91-2.02 (1H, m), 2.13 (3H, d, *J* = 1.5 Hz), 2.20 (3H, s), 3.56-4.64 (1H, m), 3.85-3.96 (1H, m), 4.27 (2H,

q, $J = 7.1$ Hz), 5.29 (1H, t, $J = 3.3$ Hz), 6.91 (1H, dd, $J = 8.9, 0.5$ Hz), 7.20 (1H, d, $J = 2.0$ Hz), 7.35 (1H, d, $J = 2.1$ Hz), 7.46 (1H, dd, $J = 8.9, 3.1$ Hz), 7.55-7.60 (1H, m), 7.91 (1H, d, $J = 2.4$ Hz).

5 [0184]

Reference Example 388

To a solution of ethyl (*E*)-3-(3-chloro-5-methyl-4-{[5-(tetrahydro-2*H*-pyran-2-yloxy)pyridin-2-yl]oxy}phenyl)-2-methylprop-2-enoate (2.58 g) in EtOH (40 mL) was added *p*-toluenesulfonic acid (1.14 g) at room temperature, then the reaction mixture was stirred for 1
10 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 10/1 to 2/1) to afford ethyl (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-2-methylprop-2-
15 enoate as a colorless amorphous (1.98 g).

¹H-NMR (CDCl₃) δ : 1.35 (3H, t, $J = 7.1$ Hz), 2.13 (3H, d, $J = 1.5$ Hz), 2.20 (3H, s), 4.27 (2H, q, $J = 7.1$ Hz), 4.59 (1H, s), 6.90 (1H, d, $J = 8.8$ Hz), 7.18-7.22 (1H, m), 7.26-7.31 (1H, m), 7.35 (1H, d, $J = 2.0$ Hz), 7.56-7.59 (1H, m), 7.72 (1H, d, $J = 3.2$ Hz).

[0185]

20 Reference Example 389

To a DMF (40 mL) solution of butyl (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-2-methylphenyl}prop-2-enoate (3.54 g) was added NaH (60% in oil) (467 mg) at 0 °C. After stirring for 10 minutes, 1-(bromomethyl)-4-methylbenzene (2.10 g) was added, and the resultant mixture was stirred at room temperature for 3.5 hours. To the reaction mixture was added
25 saturated aqueous NH₄Cl, and extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 9/1 to 3/1) to afford (*E*)-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate as a yellow solid (4.72 g).

30 ¹H-NMR (CDCl₃) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.41-1.47 (2H, m), 1.65-1.73 (2H, m), 2.36 (3H, s), 2.41 (3H, s), 4.20 (2H, t, $J = 6.8$ Hz), 5.03 (2H, s), 6.30 (1H, d, $J = 15.6$ Hz), 6.87-6.93 (3H, m), 7.20 (2H, d, $J = 7.8$ Hz), 7.30 (2H, d, $J = 7.8$ Hz), 7.34 (1H, dd, $J = 9.0, 3.2$ Hz), 7.55-7.57 (1H, m), 7.90-7.94 (2H, m).

[0186]

The following compounds were produced in the same manner as in Reference Example 389 using appropriate starting materials.

Reference Example 390

- 5 Butyl (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.4 Hz), 1.37-1.51 (2H, m), 1.64-1.75 (2H, m), 2.20 (3H, s), 2.36 (3H, s), 4.21 (2H, t, *J* = 6.8 Hz), 4.99 (2H, s), 6.38 (1H, d, *J* = 16.2 Hz), 6.93 (1H, d, *J* = 8.9 Hz), 7.19 (2H, d, *J* = 8.2 Hz), 7.26-7.38 (4H, m), 7.47 (1H, d, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 16.2 Hz), 7.79 (1H, d, *J* = 3.0 Hz).

Reference Example 391

Butyl (*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

- 15 ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.4 Hz), 1.38-1.49 (2H, m), 1.64-1.75 (2H, m), 2.20 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.10 (2H, s), 6.38 (1H, d, *J* = 16.2 Hz), 6.95 (1H, d, *J* = 8.9 Hz), 7.02-7.21 (2H, m), 7.28-7.35 (2H, m), 7.39 (1H, dd, *J* = 8.9, 3.3 Hz), 7.43-7.50 (2H, m), 7.58 (1H, d, *J* = 15.8 Hz), 7.82 (1H, d, *J* = 3.0 Hz).

- 20 Reference Example 392

Butyl (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.41-1.47 (2H, m), 1.64-1.74 (2H, m), 2.20 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.14 (2H, s), 6.38 (1H, d, *J* = 15.8 Hz), 6.95 (1H, d, *J* = 8.9 Hz), 7.26-7.32 (3H, m), 7.38-7.42 (2H, m), 7.47-7.61 (3H, m), 7.82 (1H, d, *J* = 2.6 Hz).

Reference Example 393

Butyl (*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoate

- 30 ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.41-1.47 (2H, m), 1.66-1.71 (2H, m), 2.42 (3H, s), 4.21 (2H, t, *J* = 6.8 Hz), 5.18 (2H, s), 6.31 (1H, d, *J* = 15.6 Hz), 6.86-6.93 (3H, m), 7.26-7.33 (2H, m), 7.36-7.42 (2H, m), 7.52-7.58 (2H, m), 7.91-7.96 (2H, m).

Reference Example 394

Ethyl (*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J* = 7.1 Hz), 3.77 (3H, s), 4.25 (2H, q, *J* = 7.1 Hz), 5.11 (2H, s), 6.38 (1H, d, *J* = 16.1 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.07-7.14 (3H, m), 7.21-7.28 (2H, m), 7.33-7.37 (2H, m), 7.48-7.51 (1H, m), 7.65 (1H, d, *J* = 16.1 Hz), 7.86 (1H, d, *J* = 2.9 Hz).

5 Reference Example 395

Butyl (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.37-1.50 (2H, m), 1.64-1.75 (2H, m), 4.21 (2H, t, *J* = 6.8 Hz), 5.17 (2H, s), 6.38 (1H, d, *J* = 16.1 Hz), 6.98 (1H, d, *J* = 9.0 Hz), 7.17 (1H, d, *J* = 8.3 Hz), 7.25-7.32 (2H, m), 7.37-7.45 (3H, m), 7.48-7.55 (1H, m), 7.56-7.66 (2H, m), 7.88 (1H, d, *J* = 3.2 Hz).

Reference Example 396

Ethyl (*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.2 Hz), 4.26 (2H, q, *J* = 7.2 Hz), 5.18 (2H, s), 6.36 (1H, d, *J* = 15.9 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.10 (2H, d, *J* = 8.8 Hz), 7.28-7.31 (2H, m), 7.37-7.43 (2H, m), 7.52-7.54 (3H, m), 7.67 (1H, d, *J* = 15.9 Hz), 7.96 (1H, d, *J* = 2.9 Hz).

Reference Example 397

2-(4-Bromo-2-chloro-6-methylphenoxy)-5-[(2-chlorobenzyl)oxy]pyridine

¹H-NMR (CDCl₃) δ: 2.16 (3H, s), 5.14 (2H, s), 6.93 (1H, d, *J* = 9.0 Hz), 7.26-7.35 (3H, m), 7.36-7.42 (2H, m), 7.44 (1H, d, *J* = 2.4 Hz), 7.49-7.55 (1H, m), 7.81 (1H, d, *J* = 2.9 Hz).

Reference Example 398

Ethyl (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-

25 methylprop-2-enoate

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 2.13 (3H, d, *J* = 1.5 Hz), 2.21 (3H, s), 4.27 (2H, q, *J* = 7.1 Hz), 5.15 (2H, s), 6.94 (1H, dd, *J* = 9.0, 0.5 Hz), 7.17-7.22 (1H, m), 7.25-7.33 (2H, m), 7.35 (1H, d, *J* = 2.2 Hz), 7.37-7.44 (2H, m), 7.50-7.55 (1H, m), 7.55-7.60 (1H, m), 7.83 (1H, d, *J* = 2.9 Hz).

Reference Example 399

2-(Trimethylsilyl)ethyl (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]but-2-enoate

¹H-NMR (CDCl₃) δ: 0.07 (9H, s), 1.01-1.09 (2H, m), 2.21 (3H, s), 2.36 (3H, s), 2.55 (3H, d, *J* =

1.2 Hz), 4.21-4.29 (2H, m), 6.09-6.14 (1H, m), 6.82-7.45 (8H, m), 7.75-7.84 (1H, m).

Reference Example 400

2-(4-Bromo-2-chloro-6-methylphenoxy)-5-[(4-methylbenzyl)oxy]pyridine

- 5 ¹H-NMR (CDCl₃) δ: 2.16 (3H, s), 2.36 (3H, s), 4.99 (2H, s), 6.91 (1H, d, *J* = 8.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.26-7.34 (3H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.44 (1H, dd, *J* = 2.4, 0.5 Hz), 7.78 (1H, dd, *J* = 8.5, 2.9 Hz).

Reference Example 401

- 10 Ethyl (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylprop-2-enoate

¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 2.13 (3H, d, *J* = 1.5 Hz), 2.20 (3H, s), 2.36 (3H, s), 4.27 (2H, q, *J* = 7.1 Hz), 4.99 (2H, s), 6.91 (1H, dd, *J* = 9.0, 0.5 Hz), 7.16-7.22 (3H, m), 7.27-7.32 (2H, m), 7.33-7.37 (2H, m), 7.55-7.61 (1H, m), 7.80 (1H, d, *J* = 2.4 Hz).

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Reference Example 402

Butyl (*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoate

- 20 ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.42-1.46 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.09 (2H, s), 6.38 (1H, d, *J* = 15.9 Hz), 6.96 (1H, d, *J* = 9.0 Hz), 7.33 (1H, s), 7.38 (1H, dd, *J* = 8.9, 3.1 Hz), 7.47 (1H, d, *J* = 1.7 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.58 (1H, d, *J* = 15.9 Hz), 7.64 (2H, d, *J* = 8.3 Hz), 7.78 (1H, d, *J* = 2.9 Hz).

Reference Example 403

- 25 Ethyl (*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.2 Hz), 2.13 (6H, s), 4.26 (2H, q, *J* = 7.1 Hz), 5.13 (2H, s), 6.37 (1H, d, *J* = 15.9 Hz), 6.83 (1H, d, *J* = 9.0 Hz), 7.26-7.31 (4H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.38-7.40 (1H, m), 7.51-7.53 (1H, m), 7.63 (1H, d, *J* = 15.9 Hz), 7.84 (1H, d, *J* = 2.9 Hz).

- 30 Reference Example 404

Ethyl (*E*)-3-[3,5-dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.0 Hz), 2.12 (6H, s), 2.35 (3H, s), 4.26 (2H, q, *J* = 7.0 Hz), 4.98 (2H, s), 6.36 (1H, d, *J* = 16.1 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 7.6 Hz), 7.27-7.34 (5H, m), 7.63 (1H, d, *J* = 15.9 Hz), 7.82 (1H, d, *J* = 2.0 Hz).

Reference Example 405

Ethyl (*E*)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 2.12 (6H, s), 4.26 (2H, q, *J* = 7.1 Hz), 4.99 (2H, s),
5 6.36 (1H, d, *J* = 16.1 Hz), 6.83 (1H, d, *J* = 9.0 Hz), 7.05-7.09 (2H, m), 7.27 (2H, brs), 7.32 (1H,
dd, *J* = 9.0, 3.2 Hz), 7.36-7.40 (2H, m), 7.63 (1H, d, *J* = 16.1 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

Reference Example 406

Ethyl (*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.2 Hz), 2.12 (6H, s), 3.81 (3H, s), 4.26 (2H, q, *J* = 7.2 Hz),
10 4.95 (2H, s), 6.36 (1H, d, *J* = 15.9 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 6.91 (2H, dt, *J* = 9.3, 2.4 Hz),
7.27 (2H, brs), 7.31-7.34 (3H, m), 7.63 (1H, d, *J* = 15.9 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Reference Example 407

Ethyl (*E*)-3-[4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 2.12 (6H, s), 4.26 (2H, q, *J* = 7.1 Hz), 5.09 (2H, s),
15 6.37 (1H, d, *J* = 15.9 Hz), 6.85 (1H, d, *J* = 9.0 Hz), 7.27 (2H, s), 7.34 (1H, dd, *J* = 8.9, 3.1 Hz),
7.52 (2H, d, *J* = 8.3 Hz), 7.63 (1H, d, *J* = 15.9 Hz), 7.68 (2H, d, *J* = 8.3 Hz), 7.80 (1H, d, *J* = 2.9
Hz).

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Reference Example 408

Butyl (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.37-1.50 (2H, m), 1.64-1.74 (2H, m), 4.21 (2H, t,
J = 6.6 Hz), 5.02 (2H, s), 6.38 (1H, d, *J* = 15.9 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 7.03-7.12 (2H, m),
25 7.16 (1H, d, *J* = 8.5 Hz), 7.32-7.46 (4H, m), 7.56-7.66 (2H, m), 7.85 (1H, d, *J* = 3.2 Hz).

Reference Example 409

Butyl (*E*)-3-[5-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoate

- ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.6 Hz), 1.39-1.48 (2H, m), 1.66-1.73 (2H, m), 2.38 (3H, s),
30 4.21 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.32 (1H, d, *J* = 15.9 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 7.00
(1H, s), 7.27-7.32 (2H, m), 7.38-7.43 (2H, m), 7.51-7.54 (1H, m), 7.63 (1H, s), 7.84 (1H, d, *J* =
15.9 Hz), 7.89 (1H, d, *J* = 3.2 Hz).

Reference Example 410

Butyl (*E*)-3-[5-chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 2.36 (3H, s),
5 2.38 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.01 (2H, s), 6.32 (1H, d, *J* = 15.9 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 6.98 (1H, s), 7.19 (2H, d, *J* = 8.1 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 7.36 (1H, dd, *J* = 8.8, 2.9 Hz), 7.63 (1H, s), 7.84 (1H, d, *J* = 15.9 Hz), 7.87 (1H, d, *J* = 2.9 Hz).

Reference Example 411

10 Butyl (*E*)-3-[2-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.6 Hz), 1.40-1.49 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s),
4.22 (2H, t, *J* = 6.9 Hz), 5.17 (2H, s), 6.39 (1H, d, *J* = 15.9 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.04
(1H, s), 7.26-7.33 (2H, m), 7.38-7.42 (2H, m), 7.51-7.54 (2H, m), 7.92 (1H, d, *J* = 3.2 Hz), 8.02
15 (1H, d, *J* = 15.9 Hz).

Reference Example 412

Butyl (*E*)-3-[2-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

20 ¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.41-1.49 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s), 2.36 (3H, s), 4.21 (2H, t, *J* = 6.6 Hz), 5.02 (2H, s), 6.38 (1H, d, *J* = 15.9 Hz), 6.89 (1H, d, *J* = 9.0 Hz), 7.02 (1H, s), 7.19 (2H, d, *J* = 7.8 Hz), 7.30 (2H, d, *J* = 7.8 Hz), 7.35 (1H, dd, *J* = 9.0, 2.9 Hz), 7.51 (1H, s), 7.90 (1H, d, *J* = 2.9 Hz), 8.02 (1H, d, *J* = 15.9 Hz).

25 Reference Example 413

Ethyl (*E*)-3-[3,5-dimethyl-4-({5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.34 (3H, t, *J* = 7.1 Hz), 2.12 (6H, s), 2.56 (3H, s), 4.26 (2H, q, *J* = 7.1 Hz),
5.12 (2H, s), 6.36 (1H, d, *J* = 16.1 Hz), 6.83 (1H, d, *J* = 9.0 Hz), 7.09 (1H, d, *J* = 7.6 Hz), 7.28-
30 7.30 (3H, m), 7.37 (1H, dd, *J* = 8.9, 2.9 Hz), 7.60-7.64 (2H, m), 7.84 (1H, d, *J* = 2.9 Hz).

Reference Example 414

Ethyl (*E*)-3-[4-({5-[(2-cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethoxyphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 7.1 Hz), 3.83 (6H, s), 4.30 (2H, q, *J* = 7.1 Hz), 5.25 (2H, s),

6.41 (1H, d, $J = 15.9$ Hz), 6.85 (2H, s), 7.00 (1H, d, $J = 8.8$ Hz), 7.42 (1H, dd, $J = 8.8, 2.9$ Hz), 7.45-7.49 (1H, m), 7.63-7.69 (3H, m), 7.73 (1H, d, $J = 7.8$ Hz), 7.85 (1H, d, $J = 2.9$ Hz).

Reference Example 415

- 5 Ethyl (*E*)-3-[4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethoxyphenyl]prop-2-enoate
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, t, $J = 7.1$ Hz), 3.79 (6H, s), 4.28 (2H, q, $J = 7.1$ Hz), 5.09 (2H, s), 6.39 (1H, d, $J = 15.9$ Hz), 6.83 (2H, s), 6.97 (1H, d, $J = 9.0$ Hz), 7.33 (1H, dd, $J = 9.0, 2.9$ Hz), 7.52 (2H, d, $J = 8.3$ Hz), 7.62-7.69 (3H, m), 7.77 (1H, d, $J = 2.9$ Hz).

10 Reference Example 416

Ethyl (*E*)-3-(3,5-dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)prop-2-enoate
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.34 (3H, t, $J = 7.2$ Hz), 2.12 (6H, s), 4.26 (2H, q, $J = 7.1$ Hz), 5.06 (2H, s), 6.37 (1H, d, $J = 15.9$ Hz), 6.85 (1H, d, $J = 8.8$ Hz), 7.27 (2H, d, $J = 4.9$ Hz), 7.32-7.36 (3H, m), 7.63 (1H, d, $J = 16.1$ Hz), 7.80 (1H, d, $J = 2.9$ Hz), 8.63 (2H, d, $J = 5.6$ Hz).

15

Reference Example 417

- Butyl (*E*)-3-[3-chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate
 $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.37-1.50 (2H, m), 1.64-1.74 (2H, m), 4.21 (2H, t, $J = 7.3$ Hz), 5.12 (2H, s), 6.38 (1H, d, $J = 15.9$ Hz), 6.99 (1H, dd, $J = 9.0, 0.5$ Hz), 7.17 (1H, d, $J = 8.5$ Hz), 7.38 (1H, dd, $J = 9.0, 3.2$ Hz), 7.43 (1H, dd, $J = 8.5, 2.2$ Hz), 7.51-7.56 (2H, m), 7.58-7.65 (2H, m), 7.65-7.72 (2H, m), 7.83 (1H, dd, $J = 3.2, 0.5$ Hz).

20

Reference Example 418

- Ethyl (*E*)-3-(4-{{5-(1,3-benzothiazol-6-ylmethoxy)pyridin-2-yl}oxy}-3,5-dimethoxyphenyl)prop-2-enoate
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35 (3H, t, $J = 7.1$ Hz), 3.79 (6H, s), 4.28 (2H, q, $J = 7.1$ Hz), 5.19 (2H, s), 6.38 (1H, d, $J = 15.9$ Hz), 6.82 (2H, s), 6.96 (1H, d, $J = 9.0$ Hz), 7.36 (1H, dd, $J = 8.8, 2.7$ Hz), 7.55 (1H, d, $J = 8.3$ Hz), 7.64 (1H, d, $J = 16.1$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 8.03 (1H, s), 8.14 (1H, d, $J = 8.5$ Hz), 9.01 (1H, s).

25

30

Reference Example 419

- Butyl (*E*)-3-[5-chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoate
 $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.41-1.48 (2H, m), 1.67-1.71 (2H, m), 2.39 (3H, s),

4.21 (2H, t, $J = 6.6$ Hz), 5.11 (2H, s), 6.32 (1H, d, $J = 15.9$ Hz), 6.96-6.98 (1H, m), 7.00 (1H, s), 7.37 (1H, dd, $J = 9.0, 3.2$ Hz), 7.52-7.54 (2H, m), 7.63 (1H, s), 7.66-7.70 (2H, m), 7.82-7.86 (2H, m).

5 Reference Example 420

Butyl (*E*)-3-[2-chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.40-1.49 (2H, m), 1.66-1.73 (2H, m), 2.19 (3H, s), 4.22 (2H, t, $J = 6.8$ Hz), 5.13 (2H, s), 6.39 (1H, d, $J = 15.9$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 7.04 (1H, s), 7.37 (1H, dd, $J = 8.8, 3.2$ Hz), 7.52-7.55 (3H, m), 7.68-7.70 (2H, m), 7.88 (1H, d, $J = 3.2$ Hz), 8.02 (1H, d, $J = 15.9$ Hz).

Reference Example 421

15 Ethyl (*E*)-3-(3,5-dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-enoate

¹H-NMR (CDCl₃) δ : 1.34 (3H, t, $J = 7.1$ Hz), 2.12 (6H, s), 4.26 (2H, q, $J = 7.1$ Hz), 5.25 (2H, d, $J = 0.7$ Hz), 6.37 (1H, d, $J = 15.9$ Hz), 6.85 (1H, dd, $J = 8.8, 0.5$ Hz), 7.27 (2H, d, $J = 0.5$ Hz), 7.34 (1H, dd, $J = 8.8, 2.9$ Hz), 7.63 (1H, d, $J = 16.1$ Hz), 7.83 (1H, dd, $J = 2.0, 0.5$ Hz), 7.87 (1H, d, $J = 0.7$ Hz), 8.83 (1H, d, $J = 0.7$ Hz).

20

Reference Example 422

Ethyl (*E*)-3-(3,5-dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-enoate

25 ¹H-NMR (CDCl₃) δ : 1.33 (3H, d, $J = 7.1$ Hz), 2.12 (6H, s), 4.26 (2H, t, $J = 7.1$ Hz), 5.23 (2H, s), 6.36 (1H, d, $J = 15.9$ Hz), 6.82-6.85 (1H, m), 7.27 (2H, s), 7.37-7.40 (2H, m), 7.63 (1H, d, $J = 15.9$ Hz), 7.85-7.86 (1H, m), 8.83-8.85 (1H, m).

Reference Example 423

30 Butyl (*E*)-3-{3-chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}prop-2-enoate

¹H-NMR (CDCl₃) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.39-1.49 (2H, m), 1.66-1.73 (2H, m), 2.20 (3H, s), 4.21 (2H, t, $J = 6.6$ Hz), 5.01 (2H, s), 6.38 (1H, d, $J = 16.1$ Hz), 6.51 (1H, t, $J = 73.7$ Hz), 6.95 (1H, d, $J = 8.8$ Hz), 7.14 (2H, d, $J = 8.5$ Hz), 7.33 (1H, brs), 7.37 (1H, dd, $J = 8.8, 2.9$ Hz), 7.41 (2H, d, $J = 8.5$ Hz), 7.47 (1H, brs), 7.58 (1H, d, $J = 16.1$ Hz), 7.78 (1H, d, $J = 2.9$ Hz).

[0187]

Reference Example 424

To a solution of 2-(4-bromo-2-chloro-6-methylphenoxy)-5- $\{[tert\text{-butyl(dimethyl)silyl}]\text{oxy}\}$ pyridine (1.00 g) in 1,4-dioxane (23.3 mL) were added 2 M aqueous K_2CO_3 (2.33 mL) and $Pd(PPh_3)_4$ (81 mg) under a N_2 atmosphere, then the reaction mixture was stirred over night at 50 °C. Then the reaction mixture was added $Pd(PPh_3)_4$ (81 mg) and stirred at 80 °C for 6 hours. The reaction mixture was concentrated under reduced pressure, and diluted with AcOEt. The mixture was filtered off on celite, and the filtrate was concentrated under reduced pressure.

10 The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 10/1 to 4/1) to afford 2-(trimethylsilyl)ethyl (*E*)-3-{4-[(5- $\{[tert\text{-butyl(dimethyl)silyl}]\text{oxy}\}$ pyridin-2-yl)oxy]-3-chloro-5-methylphenyl}but-2-enoate as a colorless oil (0.630 g).

1H -NMR ($CDCl_3$) δ : 0.07 (9H, s), 0.18 (6H, s), 0.97 (9H, s), 1.00-1.10 (2H, m), 2.20 (3H, s), 2.54 (3H, d, J = 1.2 Hz), 4.22-4.29 (2H, m), 6.08-6.13 (1H, m), 6.87 (1H, dd, J = 8.8, 0.7 Hz),

15 7.22 (1H, d, J = 8.8, 2.9 Hz), 7.24-7.30 (1H, m), 7.38-7.44 (1H, m), 7.69 (1H, dd, J = 2.9, 0.5 Hz).

[0188]

The following compounds were produced in the same manner as in Reference Example 424 using appropriate starting materials.

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Reference Example 425

2-(Trimethylsilyl)ethyl (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]but-2-enoate

1H -NMR ($CDCl_3$) δ : 0.07 (9H, s), 1.01-1.09 (2H, m), 2.21 (3H, s), 2.55 (3H, d, J = 1.2 Hz), 4.21-4.29 (2H, m), 5.15 (2H, s), 6.09-6.12 (1H, m), 6.95 (1H, dd, J = 8.8, 0.5 Hz), 7.25-7.32 (3H, m), 7.36-7.43 (3H, m), 7.49-7.55 (1H, m), 7.83 (1H, d, J = 2.7 Hz).

Reference Example 426

Ethyl (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylbut-2-enoate

1H -NMR ($CDCl_3$) δ : 1.35 (3H, t, J = 7.1 Hz), 1.79-1.84 (3H, m), 2.18 (3H, s), 2.22-2.25 (3H, m), 2.36 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 5.00 (2H, s), 6.88 (1H, dd, J = 8.8, 0.5 Hz), 6.94 (1H, dd, J = 2.2, 0.7 Hz), 7.08 (1H, dd, J = 2.0, 0.5 Hz), 7.19 (2H, d, J = 7.6 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.35 (1H, dd, J = 8.8, 3.2 Hz), 7.82 (1H, dd, J = 3.0, 0.5 Hz).

Reference Example 427

Ethyl (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methylbut-2-enoate

- 5 ¹H-NMR (CDCl₃) δ: 1.35 (3H, t, *J* = 7.1 Hz), 1.79-1.84 (3H, m), 2.19 (3H, s), 2.20-2.25 (3H, m), 4.26 (2H, q, *J* = 7.1 Hz), 5.15 (2H, s), 6.91 (1H, dd, *J* = 8.8, 0.5 Hz), 6.94 (1H, dd, *J* = 2.2, 0.5 Hz), 7.08 (1H, dd, *J* = 2.2, 0.5 Hz), 7.25-7.35 (2H, m), 7.35-7.43 (2H, m), 7.50-7.55 (1H, m), 7.85 (1H, dd, *J* = 2.9, 0.5 Hz).

10 [0189]

Reference Example 428

To a solution of 2-(trimethylsilyl)ethyl (*E*)-3-{4-[(5-{[*tert*-butyl(dimethyl)silyl]-oxy}pyridin-2-yl)oxy]-3-chloro-5-methylphenyl}but-2-enoate (0.630 g) in EtOH (12 mL) was added PPTS (0.296 g) at room temperature, then the reaction mixture was stirred for 4 days.

- 15 The reaction mixture was warmed to 60 °C, and stirred over night. The reaction mixture was concentrated under reduced pressure. The residue was diluted with pH 7 phosphate buffer, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 8/1 to 2/1) to afford 2-
- 20 (trimethylsilyl)ethyl (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}but-2-enoate as a colorless oil (0.490 g).

¹H-NMR (CDCl₃) δ: 0.07 (9H, s), 1.01-1.09 (2H, m), 2.20 (3H, s), 2.54 (3H, d, *J* = 1.5 Hz), 4.21-4.29 (2H, m), 4.94 (1H, s), 6.09-6.12 (1H, m), 6.89 (1H, d, *J* = 8.8 Hz), 7.26-7.30 (2H, m), 7.39 (1H, d, *J* = 1.7 Hz), 7.70 (1H, dd, *J* = 3.0, 0.5 Hz).

25 [0190]

The following compounds were produced in the same manner as in Reference Example 20 using appropriate starting materials.

Reference Example 429

- 30 Butyl (*E*)-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

¹H-NMR (CDCl₃) δ: 0.97 (3H, t, *J* = 7.3 Hz), 1.41-1.47 (2H, m), 1.64-1.74 (2H, m), 2.19 (3H, s), 3.04 (2H, t, *J* = 6.6 Hz), 4.13 (2H, t, *J* = 6.4 Hz), 4.21 (2H, t, *J* = 6.6 Hz), 6.38 (1H, d, *J* = 15.8 Hz), 6.91 (1H, d, *J* = 8.9 Hz), 7.18-7.21 (2H, m), 7.28-7.31 (4H, m), 7.46 (1H, d, *J* = 2.0 Hz),

7.58 (1H, d, $J = 15.8$ Hz), 7.71 (1H, d, $J = 3.0$ Hz).

Reference Example 430

Butyl (*E*)-3-[3-chloro-5-methyl-4-({5-[2-(4-methylphenyl)ethoxy]pyridin-2-

5 yl}oxy)phenyl]prop-2-enoate

$^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J = 7.4$ Hz), 1.39-1.46 (2H, m), 1.64-1.74 (2H, m), 2.19 (3H, s), 2.33 (3H, s), 3.04 (2H, t, $J = 7.1$ Hz), 4.13 (2H, t, $J = 6.9$ Hz), 4.21 (2H, t, $J = 6.8$ Hz), 6.38 (1H, d, $J = 15.8$ Hz), 6.90 (1H, d, $J = 8.9$ Hz), 7.12-7.16 (4H, m), 7.28-7.32 (2H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.58 (1H, d, $J = 15.8$ Hz), 7.72 (1H, d, $J = 3.3$ Hz).

10

Reference Example 431

Butyl (*E*)-3-[3-chloro-4-({5-[2-(3,4-dichlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoate

15 $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (3H, t, $J = 7.3$ Hz), 1.37-1.52 (2H, m), 1.64-1.74 (2H, m), 2.19 (3H, s), 3.03 (2H, t, $J = 6.4$ Hz), 4.13 (2H, t, $J = 6.6$ Hz), 4.21 (2H, t, $J = 6.6$ Hz), 6.38 (1H, d, $J = 15.8$ Hz), 6.92 (1H, d, $J = 8.9$ Hz), 7.10 (1H, dd, $J = 8.2, 2.0$ Hz), 7.27-7.32 (2H, m), 7.36-7.38 (2H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.58 (1H, d, $J = 16.2$ Hz), 7.71 (1H, d, $J = 3.0$ Hz).

[0191]

20 Reference Example 432

To an EtOH (50 mL) solution of butyl (*E*)-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoate (4.67 g) was added 5 M NaOH (3.25 mL) at room temperature. After stirring for 14 hours, 5 M NaOH (1.08 mL) and water (25 mL) were added, and then the reaction mixture was refluxed for 2 hours. The solvent was removed under

25 reduced pressure. The residue was dissolved in water, and neutralized with 6 M HCl at 0 °C.

The resulting precipitate was collected by filtration and dried to afford (*E*)-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid as a colorless solid (4.06 g).

30 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.30 (3H, s), 2.36 (3H, s), 5.09 (2H, s), 6.37 (1H, d, $J = 15.9$ Hz), 6.88 (1H, dd, $J = 8.5, 2.7$ Hz), 6.94 (1H, d, $J = 2.7$ Hz), 7.04 (1H, d, $J = 9.0$ Hz), 7.20 (2H, d, $J = 7.8$ Hz), 7.34 (2H, d, $J = 7.8$ Hz), 7.58 (1H, dd, $J = 9.0, 3.2$ Hz), 7.72 (1H, d, $J = 8.5$ Hz), 7.77 (1H, d, $J = 15.9$ Hz), 7.95 (1H, d, $J = 3.2$ Hz), 12.39 (1H, brs).

[0192]

The following compounds were produced in the same manner as in Reference Example 432 using appropriate starting materials.

Reference Example 433

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

- 5 ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 3.02 (2H, t, *J* = 6.6 Hz), 4.20 (2H, t, *J* = 6.8 Hz), 6.57 (1H, d, *J* = 16.2 Hz), 7.06 (1H, d, *J* = 8.9 Hz), 7.34-7.37 (4H, m), 7.50-7.55 (2H, m), 7.64 (1H, d, *J* = 1.6 Hz), 7.73 (1H, d, *J* = 3.0 Hz), 7.75 (1H, d, *J* = 2.0 Hz), 12.43 (1H, brs).

Reference Example 434

- 10 (*E*)-3-[3-Chloro-5-methyl-4-({5-[2-(4-methylphenyl)ethoxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.26 (3H, s), 2.97 (2H, t, *J* = 6.9 Hz), 4.17 (2H, t, *J* = 6.9 Hz), 6.56 (1H, d, *J* = 16.2 Hz), 7.06 (1H, d, *J* = 8.9 Hz), 7.10 (2H, d, *J* = 7.9 Hz), 7.19 (2H, d, *J* = 7.9 Hz), 7.49-7.57 (2H, m), 7.64 (1H, d, *J* = 1.6 Hz), 7.73 (1H, d, *J* = 3.0 Hz), 7.75 (1H, d, *J* = 2.0 Hz), 12.45 (1H, brs).
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Reference Example 435

(*E*)-3-[3-Chloro-4-({5-[2-(3,4-dichlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

- 20 ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 3.04 (2H, t, *J* = 6.6 Hz), 4.22 (2H, t, *J* = 6.6 Hz), 6.57 (1H, d, *J* = 15.8 Hz), 7.07 (1H, d, *J* = 8.9 Hz), 7.33 (1H, dd, *J* = 8.4, 2.1 Hz), 7.51-7.58 (3H, m), 7.63-7.64 (2H, m), 7.74-7.75 (2H, m), 12.45 (1H, brs).

Reference Example 436

- 25 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 5.05 (2H, s), 6.57 (1H, d, *J* = 15.8 Hz), 7.09 (1H, d, *J* = 8.9 Hz), 7.20 (2H, d, *J* = 7.9 Hz), 7.33 (2H, d, *J* = 7.9 Hz), 7.52-7.61 (2H, m), 7.65 (1H, d, *J* = 1.3 Hz), 7.76 (1H, d, *J* = 2.0 Hz), 7.80 (1H, d, *J* = 3.0 Hz), 12.45 (1H, s).

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Reference Example 437

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

¹H-NMR (CDCl₃) δ: 2.21 (4H, s), 5.11 (2H, s), 6.37 (1H, d, *J* = 16.2 Hz), 6.97 (1H, d, *J* = 8.9

Hz), 7.04-7.22 (2H, m), 7.29-7.49 (5H, m), 7.64 (1H, d, $J = 15.8$ Hz), 7.82 (1H, d, $J = 3.0$ Hz).

Reference Example 438

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

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$^1\text{H-NMR}$ (CDCl_3) δ : 2.22 (3H, s), 5.15 (2H, s), 6.36 (1H, d, $J = 15.8$ Hz), 6.98 (1H, d, $J = 8.9$ Hz), 7.26-7.35 (3H, m), 7.37-7.44 (2H, m), 7.49-7.54 (2H, m), 7.64 (1H, d, $J = 15.8$ Hz), 7.83 (1H, d, $J = 2.6$ Hz).

10 Reference Example 439

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]prop-2-enoic acid

$^1\text{H-NMR}$ (CDCl_3) δ : 3.82 (3H, s), 5.16 (2H, s), 6.36 (1H, d, $J = 15.9$ Hz), 6.96 (1H, d, $J = 8.8$ Hz), 7.11-7.20 (3H, m), 7.26-7.32 (3H, m), 7.37-7.43 (2H, m), 7.51-7.55 (1H, m), 7.72 (1H, d, $J = 15.9$ Hz), 7.89 (1H, d, $J = 2.9$ Hz).

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Reference Example 440

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 5.19 (2H, s), 6.58 (1H, d, $J = 15.9$ Hz), 7.14 (1H, d, $J = 8.8$ Hz), 7.25 (1H, d, $J = 8.5$ Hz), 7.37-7.44 (2H, m), 7.48-7.74 (5H, m), 7.93 (1H, d, $J = 3.2$ Hz), 7.95 (1H, d, $J = 2.0$ Hz).

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Reference Example 441

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoic acid

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.37 (3H, s), 5.20 (2H, s), 6.38 (1H, d, $J = 15.6$ Hz), 6.90 (1H, dd, $J = 8.3, 2.4$ Hz), 6.96 (1H, d, $J = 2.4$ Hz), 7.07 (1H, d, $J = 8.8$ Hz), 7.38-7.46 (2H, m), 7.51-7.55 (1H, m), 7.61-7.65 (2H, m), 7.73 (1H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 15.6$ Hz), 8.01 (1H, d, $J = 2.9$ Hz), 12.40 (1H, brs).

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Reference Example 442

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

$^1\text{H-NMR}$ (CDCl_3) δ : 5.19 (2H, s), 6.37 (1H, d, $J = 15.9$ Hz), 6.95 (1H, d, $J = 8.8$ Hz), 7.12 (2H, dt, $J = 9.0, 2.3$ Hz), 7.29-7.32 (2H, m), 7.38-7.43 (2H, m), 7.52-7.55 (1H, m), 7.56 (2H, d, $J = 8.8$ Hz), 7.76 (1H, d, $J = 15.9$ Hz), 7.97 (1H, d, $J = 3.2$ Hz).

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Reference Example 443

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylprop-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.05 (3H, d, *J* = 1.5 Hz), 2.12 (3H, s), 2.30 (3H, s), 5.05 (2H, s), 7.09 (1H, dd, *J* = 9.0, 0.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.33 (2H, d, *J* = 8.1 Hz), 7.38 (1H, d, *J* = 2.0 Hz), 7.48 (1H, d, *J* = 2.0 Hz), 7.52-7.56 (1H, m), 7.58 (1H, dd, *J* = 8.8, 3.2 Hz), 7.81 (1H, dd, *J* = 3.2, 0.5 Hz), 12.61 (1H, brs).

Reference Example 444

- 10 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methylbut-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 1.73 (3H, d, *J* = 1.7 Hz), 2.11 (3H, s), 2.18-2.23 (3H, m), 5.17 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.12-7.15 (1H, m), 7.21 (1H, d, *J* = 2.0 Hz), 7.35-7.45 (2H, m), 7.48-7.55 (1H, m), 7.59-7.66 (2H, m), 7.88 (1H, d, *J* = 3.2 Hz), 12.51 (1H, brs).

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Reference Example 445

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylbut-2-enoic acid

- 20 ¹H-NMR (DMSO-*d*₆) δ: 1.71-1.75 (3H, m), 2.10 (3H, s), 2.17-2.22 (3H, m), 2.30 (3H, s), 5.05 (2H, s), 7.06 (1H, dd, *J* = 9.0, 0.5 Hz), 7.09-7.14 (1H, m), 7.17-7.23 (3H, m), 7.33 (2H, d, *J* = 8.1 Hz), 7.58 (1H, dd, *J* = 9.0, 3.2 Hz), 7.81 (1H, dd, *J* = 2.9, 0.5 Hz), 12.55 (1H, brs).

Reference Example 446

- 25 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methylprop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.05 (3H, d, *J* = 1.5 Hz), 2.13 (3H, s), 5.17 (2H, s), 7.12 (1H, dd, *J* = 9.0, 0.5 Hz), 7.36-7.46 (3H, m), 7.46-7.57 (3H, m), 7.58-7.67 (2H, m), 7.86 (1H, dd, *J* = 3.2, 0.5 Hz), 12.62 (1H, brs).

- 30 Reference Example 447

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 5.23 (2H, s), 6.58 (1H, d, *J* = 16.1 Hz), 7.13 (1H, d, *J* = 8.8 Hz), 7.55 (1H, d, *J* = 15.9 Hz), 7.62-7.69 (4H, m), 7.77-7.79 (3H, m), 7.84 (1H, d, *J* = 3.2 Hz),

12.49 (1H, s).

Reference Example 448

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoic acid

- 5 ¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 5.16 (2H, s), 6.47 (1H, d, *J* = 15.9 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 7.39-7.41 (2H, m), 7.45 (2H, brs), 7.49-7.53 (2H, m), 7.60-7.63 (2H, m), 7.85 (1H, d, *J* = 2.9 Hz).

Reference Example 449

- 10 (*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.30 (3H, s), 5.04 (2H, s), 6.47 (1H, d, *J* = 15.9 Hz), 6.98 (1H, d, *J* = 8.5 Hz), 7.19 (2H, d, *J* = 7.1 Hz), 7.32 (2H, d, *J* = 7.1 Hz), 7.43 (2H, brs), 7.50 (1H, d, *J* = 16.1 Hz), 7.55 (1H, d, *J* = 8.8 Hz), 7.80 (1H, brs).

- 15 Reference Example 450

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoic acid

¹H-NMR (CDCl₃) δ: 2.13 (6H, s), 4.99 (2H, s), 6.35 (1H, d, *J* = 16.1 Hz), 6.86 (1H, d, *J* = 9.0 Hz), 7.04-7.10 (2H, m), 7.29 (2H, brs), 7.33-7.40 (3H, m), 7.68 (1H, d, *J* = 16.1 Hz), 7.82 (1H, d, *J* = 3.2 Hz).

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Reference Example 451

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoic acid

¹H-NMR (CDCl₃) δ: 2.14 (6H, s), 3.82 (3H, s), 4.96 (2H, s), 6.35 (1H, d, *J* = 15.9 Hz), 6.85 (1H, d, *J* = 9.0 Hz), 6.91 (2H, dt, *J* = 9.2, 2.4 Hz), 7.29 (2H, brs), 7.31-7.36 (3H, m), 7.68 (1H, d, *J* = 15.9 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

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Reference Example 452

(*E*)-3-[4-({5-[(4-Cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoic acid

- 30 ¹H-NMR (CDCl₃) δ: 2.13 (6H, s), 5.10 (2H, s), 6.35 (1H, d, *J* = 16.1 Hz), 6.89 (1H, d, *J* = 8.8 Hz), 7.26-7.29 (3H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.53 (2H, d, *J* = 8.3 Hz), 7.67-7.69 (3H, m), 7.80 (1H, d, *J* = 2.9 Hz).

Reference Example 453

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.12 (2H, s), 6.57 (1H, d, *J* = 16.1 Hz), 7.12 (1H, d, *J* = 8.8 Hz), 7.18-7.28 (3H, m), 7.47-7.66 (4H, m), 7.69 (1H, dd, *J* = 8.5, 2.2 Hz), 7.90 (1H, d, *J* = 2.9 Hz), 7.95 (1H, d, *J* = 2.0 Hz), 12.49 (1H, brs).

5 Reference Example 454

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.30 (3H, s), 2.35 (3H, s), 5.08 (2H, s), 6.51 (1H, d, *J* = 15.9 Hz), 7.08 (1H, d, *J* = 8.8 Hz), 7.12 (1H, s), 7.20 (2H, d, *J* = 7.8 Hz), 7.33 (2H, d, *J* = 7.8 Hz), 7.59 (1H, dd, *J* = 9.0, 2.2 Hz), 7.71 (1H, d, *J* = 15.9 Hz), 7.87 (1H, d, *J* = 2.7 Hz), 7.90 (1H, s), 12.48 (1H, brs).

Reference Example 455

15 (*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.35 (3H, s), 5.19 (2H, s), 6.51 (1H, d, *J* = 15.9 Hz), 7.11 (1H, d, *J* = 9.0 Hz), 7.14 (1H, s), 7.37-7.43 (2H, m), 7.50-7.54 (1H, m), 7.59-7.66 (2H, m), 7.71 (1H, d, *J* = 15.9 Hz), 7.91-7.93 (2H, m), 12.49 (1H, s).

20 Reference Example 456

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

¹H-NMR (CDCl₃) δ: 2.13 (3H, s), 5.20 (2H, s), 6.58 (1H, d, *J* = 15.9 Hz), 7.11 (1H, d, *J* = 8.8 Hz), 7.16 (1H, s), 7.37-7.43 (2H, m), 7.50-7.54 (1H, m), 7.60-7.66 (2H, m), 7.82 (1H, d, *J* = 15.9 Hz), 7.92 (1H, s), 7.96-7.97 (1H, m), 12.55 (1H, brs).

Reference Example 457

(*E*)-3-{4-[(5-Hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 6.45 (1H, d, *J* = 15.9 Hz), 6.87 (1H, d, *J* = 8.8 Hz), 7.27 (1H, dd, *J* = 8.8, 2.9 Hz), 7.44 (2H, s), 7.52 (1H, d, *J* = 15.9 Hz), 7.55 (1H, d, *J* = 2.9 Hz), 9.49 (1H, s), 12.32 (1H, s).

Reference Example 458

(*E*)-3-{4-[(5-Hydroxypyridin-2-yl)oxy]-2-methylphenyl}prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.36 (3H, s), 6.36 (1H, d, *J* = 15.9 Hz), 6.85 (1H, dd, *J* = 8.5, 2.0 Hz), 6.90 (1H, d, *J* = 2.0 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.30 (1H, dd, *J* = 8.7, 3.1 Hz), 7.71 (1H, d, *J* = 8.5 Hz), 7.75-7.78 (2H, m), 9.76 (1H, s), 12.37 (1H, s).

5 Reference Example 459

(*E*)-3-[4-({5-[(4-Cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethoxyphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 3.72 (6H, s), 5.21 (2H, s), 6.61 (1H, d, *J* = 15.9 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.11 (2H, s), 7.52 (1H, dd, *J* = 8.8, 2.9 Hz), 7.58 (1H, d, *J* = 15.9 Hz), 7.64 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz), 7.87 (2H, d, *J* = 8.1 Hz), 12.36 (1H, s).

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Reference Example 460

(*E*)-3-[4-({5-[(2-Cyanobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethoxyphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 3.73 (6H, s), 5.24 (2H, s), 6.61 (1H, d, *J* = 16.1 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 7.11 (2H, s), 7.54-7.61 (3H, m), 7.72-7.78 (2H, m), 7.81 (1H, d, *J* = 2.9 Hz), 7.91 (1H, d, *J* = 7.6 Hz), 12.35 (1H, s).

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Reference Example 461

(*E*)-3-(3,5-Dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 5.18 (2H, s), 6.46 (1H, d, *J* = 16.1 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 7.43-7.45 (4H, m), 7.52 (1H, d, *J* = 16.1 Hz), 7.60 (1H, dd, *J* = 9.0, 2.9 Hz), 7.83 (1H, d, *J* = 2.9 Hz), 8.58 (2H, d, *J* = 5.9 Hz), 12.33 (1H, s).

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Reference Example 462

(*E*)-3-[3,5-Dimethyl-4-({5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy)phenyl]prop-2-

25 enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.59 (3H, s), 5.25 (2H, s), 6.46 (1H, d, *J* = 15.9 Hz), 7.04 (1H, d, *J* = 9.0 Hz), 7.44-7.47 (3H, m), 7.52-7.55 (2H, m), 7.63 (1H, dd, *J* = 9.0, 2.9 Hz), 7.85 (1H, d, *J* = 2.9 Hz), 8.01 (1H, brs).

30 Reference Example 463

(*E*)-3-[3-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.25 (2H, s), 6.57 (1H, d, *J* = 15.9 Hz), 7.13 (1H, d, *J* = 9.0 Hz), 7.23 (1H, d, *J* = 8.5 Hz), 7.50-7.73 (4H, m), 7.84-7.95 (5H, m), 12.45 (1H, brs).

Reference Example 464

(*E*)-3-(4-{[5-(1,3-Benzothiazol-6-ylmethoxy)pyridin-2-yl]oxy}-3,5-dimethoxyphenyl)prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 3.72 (6H, s), 5.26 (2H, s), 6.61 (1H, d, *J* = 15.9 Hz), 6.93 (1H, d, *J* = 9.0 Hz), 7.11 (2H, s), 7.54 (1H, dd, *J* = 9.0, 2.9 Hz), 7.59 (1H, d, *J* = 15.9 Hz), 7.61-7.63 (1H, m), 7.81 (1H, d, *J* = 2.9 Hz), 8.10 (1H, d, *J* = 8.5 Hz), 8.26 (1H, s), 9.41 (1H, s), 12.36 (1H, s).

Reference Example 465

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.30 (3H, s), 5.09 (2H, s), 6.58 (1H, d, *J* = 15.9 Hz), 7.08 (1H, d, *J* = 8.8 Hz), 7.14 (1H, s), 7.20 (2H, d, *J* = 8.1 Hz), 7.33 (2H, d, *J* = 8.1 Hz), 7.59 (1H, dd, *J* = 8.8, 2.9 Hz), 7.82 (1H, d, *J* = 15.9 Hz), 7.91-7.92 (2H, m), 12.57 (1H, s).

Reference Example 466

(*E*)-3-[2-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 5.26 (2H, s), 6.59 (1H, d, *J* = 15.9 Hz), 7.11 (1H, d, *J* = 8.8 Hz), 7.15 (1H, s), 7.62-7.66 (3H, m), 7.82 (1H, d, *J* = 15.9 Hz), 7.88 (2H, d, *J* = 8.5 Hz), 7.92 (1H, s), 7.94 (1H, d, *J* = 2.9 Hz), 12.58 (1H, s).

Reference Example 467

(*E*)-3-[5-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.35 (3H, s), 5.25 (2H, s), 6.51 (1H, d, *J* = 15.9 Hz), 7.10-7.13 (2H, m), 7.61-7.66 (3H, m), 7.71 (1H, d, *J* = 15.9 Hz), 7.86-7.90 (4H, m), 12.49 (1H, s).

Reference Example 468

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 5.39 (2H, d, *J* = 0.5 Hz), 6.46 (1H, d, *J* = 16.1 Hz), 7.01 (1H, dd, *J* = 9.0, 0.5 Hz), 7.46 (2H, s), 7.52 (1H, d, *J* = 15.9 Hz), 7.60 (1H, dd, *J* = 9.0, 3.2 Hz), 7.83 (1H, dd, *J* = 3.2, 0.5 Hz), 8.00 (1H, d, *J* = 0.7 Hz), 9.13 (1H, d, *J* = 0.7 Hz), 12.35 (1H, brs).

Reference Example 469

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-enoic acid
¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 5.22 (2H, s), 6.46 (1H, d, *J* = 15.9 Hz), 7.01 (1H, d, *J* = 9.0 Hz), 7.45 (2H, s), 7.52 (1H, d, *J* = 15.9 Hz), 7.61 (1H, dd, *J* = 9.0, 3.2 Hz), 7.83 (1H, d, *J* = 2.0 Hz), 7.84 (1H, d, *J* = 3.2 Hz), 9.12 (1H, d, *J* = 2.0 Hz), 12.33 (1H, s).

5

Reference Example 470

(*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 5.10 (2H, s), 6.57 (1H, d, *J* = 15.9 Hz), 7.10 (1H, d, *J* = 8.8 Hz), 7.20 (2H, d, *J* = 8.3 Hz), 7.24 (1H, t, *J* = 74.1 Hz), 7.50-7.57 (3H, m), 7.60 (1H, dd, *J* = 8.8, 2.9 Hz), 7.65 (1H, brs), 7.75 (1H, brs), 7.81 (1H, d, *J* = 2.9 Hz), 12.45 (1H, s).

10

[0193]

Reference Example 471

15 To a DMF (40 mL) solution of butyl (*E*)-3-{3-fluoro-4-[(5-hydroxypyridin-2-yl)oxy]phenyl}prop-2-enoate (3.82 g) and 2-chlorobenzyl chloride (1.6 mL) was added sodium hydride (60% w/w in oil, 0.60 g) at 0 °C, and stirred at room temperature for 3 hours. The reaction mixture was quenched by addition of saturated NH₄Cl (90 mL), and extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaCl, dried over
20 anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 19/1 to 9/1) to afford (*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid butyl ester (3.53 g).

[0194]

25 To an EtOH (40 mL) solution of the ester was added 5 M NaOH (6.9 mL), and stirred for 2.5 hours at 50 °C, then EtOH was evaporated. The residue was dissolved in water, and acidified with 6 M HCl. The resulting precipitate was collected by filtration and dried to afford (*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid as a white powder (2.78 g).

¹H-NMR (DMSO-*d*₆) δ: 5.19 (2H, s), 6.57 (1H, d, *J* = 16.1 Hz), 7.15 (1H, d, *J* = 8.8 Hz), 7.30 (1H, t, *J* = 8.3 Hz), 7.37-7.44 (2H, m), 7.51-7.57 (3H, m), 7.60-7.63 (1H, m), 7.65 (1H, dd, *J* = 8.9, 3.1 Hz), 7.76 (1H, dd, *J* = 12.0, 2.0 Hz), 7.92 (1H, d, *J* = 2.9 Hz).

30

[0195]

The following compounds were produced in the same manner as in Reference Example 471 using appropriate starting materials.

Reference Example 472

(*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

- 5 ¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 5.20 (2H, s), 6.58 (1H, dd, *J* = 15.9, 0.7 Hz), 7.13 (1H, d, *J* = 9.0 Hz), 7.28 (1H, t, *J* = 7.9 Hz), 7.55 (2H, t, *J* = 7.9 Hz), 7.60-7.67 (3H, m), 7.77 (1H, d, *J* = 1.5 Hz), 7.85 (1H, d, *J* = 2.9 Hz), 12.50 (1H, s).

Reference Example 473

- 10 (*E*)-3-[3-Chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 5.21 (2H, s), 6.58 (1H, d, *J* = 15.9 Hz), 7.13 (1H, d, *J* = 9.0 Hz), 7.23-7.28 (1H, m), 7.39 (1H, t, *J* = 6.8 Hz), 7.43-7.49 (1H, m), 7.55 (1H, d, *J* = 16.1 Hz), 7.64-7.67 (2H, m), 7.77 (1H, d, *J* = 1.7 Hz), 7.85 (1H, d, *J* = 3.2 Hz), 12.48 (1H, s).

15

Reference Example 474

(*E*)-3-[3-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.31 (3H, s), 5.08 (2H, s), 6.46 (1H, d, *J* = 15.9 Hz), 6.96 (1H, d, *J* = 8.3 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 8.1 Hz), 7.33 (2H, d, *J* = 8.1 Hz),
20 7.50-7.59 (3H, m), 7.64 (1H, d, *J* = 2.0 Hz), 7.88 (1H, d, *J* = 3.2 Hz), 12.36 (1H, s).

Reference Example 475

(*E*)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]prop-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.13 (3H, s), 5.23 (2H, s), 6.47 (1H, d, *J* = 15.9 Hz), 6.99 (1H, d, *J* = 8.3
25 Hz), 7.05 (1H, d, *J* = 9.0 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.51-7.57 (2H, m), 7.60-7.68 (4H, m),
7.94 (1H, d, *J* = 3.2 Hz), 12.24 (1H, s).

Reference Example 476

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]prop-2-enoic acid

- 30 ¹H-NMR (DMSO-*d*₆) δ: 2.13 (3H, s), 5.19 (2H, s), 6.47 (1H, d, *J* = 16.1 Hz), 6.99 (1H, d, *J* = 8.3 Hz), 7.05 (1H, d, *J* = 8.8 Hz), 7.37-7.44 (2H, m), 7.52-7.58 (3H, m), 7.61-7.65 (3H, m), 7.93 (1H, d, *J* = 2.9 Hz), 12.38 (1H, s).

Reference Example 477

6-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)naphthalene-2-carboxylic acid

¹H-NMR (DMSO-*d*₆) δ: 5.22 (2H, s), 7.16 (1H, dd, *J* = 8.8, 0.5 Hz), 7.37-7.45 (3H, m), 7.51-7.56 (1H, m), 7.60 (1H, d, *J* = 2.2 Hz), 7.62-7.66 (1H, m), 7.68 (1H, dd, *J* = 8.8, 3.2 Hz), 7.93 (1H, d, *J* = 8.8 Hz), 7.97 (1H, dd, *J* = 8.5, 1.5 Hz), 8.03 (1H, dd, *J* = 3.2, 0.5 Hz), 8.15 (1H, d, *J* = 9.0 Hz), 8.61 (1H, d, *J* = 0.7 Hz), 13.03 (1H, brs).

Reference Example 478

(E)-3-[3-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoic acid

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 5.10 (2H, s), 6.09-6.33 (1H, m), 6.37 (1H, d, *J* = 16.1 Hz), 6.96-7.01 (1H, m), 7.34 (1H, s), 7.38-7.41 (1H, m), 7.48-7.54 (3H, m), 7.64 (1H, d, *J* = 16.1 Hz), 7.68-7.85 (3H, m).

Reference Example 479

6-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalene-2-carboxylic acid

¹H-NMR (DMSO-*d*₆) δ: 3.36 (1H, brs), 5.26 (2H, s), 7.15 (1H, dd, *J* = 8.8, 0.5 Hz), 7.24-7.30 (1H, m), 7.36 (1H, dd, *J* = 8.8, 2.4 Hz), 7.39-7.51 (2H, m), 7.58 (1H, d, *J* = 2.4 Hz), 7.68 (1H, dd, *J* = 8.8, 3.2 Hz), 7.89 (1H, d, *J* = 9.0 Hz), 7.98 (1H, dd, *J* = 8.5, 1.7 Hz), 8.02 (1H, dd, *J* = 3.2, 0.5 Hz), 8.12 (1H, d, *J* = 9.3 Hz), 8.58 (1H, d, *J* = 0.7 Hz).

Reference Example 480

(E)-3-[4-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.23 (2H, s), 6.57 (1H, d, *J* = 15.9 Hz), 7.14 (1H, d, *J* = 9.0 Hz), 7.23-7.32 (2H, m), 7.37-7.41 (1H, m), 7.42-7.49 (1H, m), 7.54 (1H, dd, *J* = 8.2, 1.8 Hz), 7.58 (1H, d, *J* = 16.1 Hz), 7.66 (1H, dd, *J* = 9.0, 3.2 Hz), 7.77 (1H, dd, *J* = 12.0, 2.0 Hz), 7.92 (1H, d, *J* = 2.7 Hz), 12.47 (1H, brs).

Reference Example 481

(E)-3-[4-({5-[(2,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.14 (2H, s), 6.57 (1H, d, *J* = 16.1 Hz), 7.11-7.16 (2H, m), 7.27-7.34 (2H, m), 7.54 (1H, dd, *J* = 8.3, 1.7 Hz), 7.59 (1H, d, *J* = 15.9 Hz), 7.62-7.67 (2H, m), 7.77 (1H, dd, *J* = 12.0, 2.0 Hz), 7.91 (1H, d, *J* = 2.9 Hz), 12.46 (1H, brs).

Reference Example 482

(*E*)-3-[4-({5-[(3,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.12 (2H, s), 6.57 (1H, d, *J* = 15.9 Hz), 7.13 (1H, dd, *J* = 9.0, 0.5 Hz), 7.27-7.34 (2H, m), 7.46 (1H, dt, *J* = 14.8, 5.4 Hz), 7.52-7.64 (4H, m), 7.77 (1H, dd, *J* = 12.0, 2.0 Hz), 7.89 (1H, dd, *J* = 3.2, 0.5 Hz), 12.45 (1H, brs).

5

Reference Example 483

(*E*)-3-[4-({5-[(4-Cyanobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-enoic acid

¹H-NMR (DMSO-*d*₆) δ: 5.25 (2H, s), 6.56 (1H, d, *J* = 16.1 Hz), 7.14 (1H, d, *J* = 8.8 Hz), 7.29 (1H, t, *J* = 8.3 Hz), 7.50-7.66 (5H, m), 7.77 (1H, dd, *J* = 12.0, 2.0 Hz), 7.87-7.90 (3H, m), 12.46 (1H, s).

10

[0196]

Reference Example 484

To a THF (50 mL) solution of butyl (*E*)-3-{4-[(5-aminopyridin-2-yl)oxy]-3-chloro-5-methylphenyl}prop-2-enoate (5.00 g) were added sulfuric acid (1.1 mL) and *n*-pentyl nitrite (2.44 g) at 0 °C. After stirring for 1 hour, the resulting precipitate was collected by filtration and dried under reduced pressure to afford a diazonium salt as a pale brown powder (6.45 g).

[0197]

20

To acetic acid (100 mL) was added an acetic acid (50 mL) solution of the diazonium salt (6.45 g) at 100-110 °C. After stirring for 1 hour, acetic acid was evaporated. K₂CO₃ (9.58 g) was added to an EtOH (50 mL) solution of the residue at room temperature. After stirring over night, EtOH was evaporated. To the residue were added water and AcOEt, and the mixture was acidified with 1 M HCl. The organic layer was washed with saturated NaHCO₃, saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 7/3 to 1/1) to afford (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}prop-2-enoic acid butyl ester (4.73 g).

25

[0198]

30

To a MeOH (10 mL) solution of the ester (4.73 g) was added 5 M NaOH (2 mL), and stirred for 1 hour at 50 °C, then MeOH was evaporated. The residue was dissolved in water, and acidified with 6 M HCl. The resulting precipitate was collected by filtration and dried to afford (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}prop-2-enoic acid as a pale yellow powder (3.77 g).

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 6.56 (1H, d, *J* = 16.2 Hz), 6.96 (1H, d, *J* = 8.9 Hz), 7.30 (1H, dd, *J* = 8.9, 3.0 Hz), 7.52 (1H, d, *J* = 10.2 Hz), 7.53 (1H, d, *J* = 15.8 Hz), 7.63 (1H, d, *J* = 1.6 Hz), 7.74 (1H, d, *J* = 2.0 Hz), 9.58 (1H, s), 12.45 (1H, brs).

[0199]

- 5 The following compounds were produced in the same manner as in Reference Example 15 using appropriate starting materials.

Reference Example 485

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]but-2-enoic acid

- 10 ¹H-NMR (DMSO-*d*₆) δ: 2.13 (3H, s), 2.45-2.54 (3H, m), 5.17 (2H, s), 6.14-6.18 (1H, m), 7.12 (1H, d, *J* = 8.8 Hz), 7.36-7.45 (2H, m), 7.48-7.54 (2H, m), 7.54-7.58 (2H, m), 7.60-7.70 (1H, m), 7.85 (1H, d, *J* = 2.9 Hz), 12.32 (1H, brs).

Reference Example 486

- 15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]but-2-enoic acid

- ¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.30 (3H, s), 2.48 (3H, d, *J* = 1.5 Hz), 5.05 (2H, s), 6.14-6.18 (1H, m), 7.09 (1H, dd, *J* = 9.0, 0.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.33 (2H, d, *J* = 8.1 Hz), 7.47-7.52 (1H, m), 7.54-7.57 (1H, m), 7.58 (1H, dd, *J* = 9.0, 3.2 Hz), 7.79 (1H, dd, *J* = 3.2, 0.5
20 Hz), 12.31 (1H, brs).

[0200]

Reference Example 487

- To a DMF (26 mL) solution of (*E*)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-enoic acid (1.300 g) and 1-{4-[2-(4-chlorophenoxy)ethyl]benzyl}-
25 piperazine hydrochloride (2.116 g) were added HOBt (0.070 g), WSC (1.310 g), and Et₃N (1.905 mL) at room temperature, then the resultant mixture was stirred at room temperature over night. The mixture was poured into water, and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated.
30 The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/0 and then AcOEt/MeOH = 4/1) to afford (*E*)-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-{4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}prop-2-en-1-one as a pale yellow amorphous powder (2.57 g).

¹H-NMR (CDCl₃) δ: 2.09 (6H, s), 2.47-2.48 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-

3.66 (2H, m), 3.73-3.76 (2H, m), 4.13 (2H, t, $J = 7.0$ Hz), 6.70 (1H, d, $J = 8.8$ Hz), 6.75 (1H, d, $J = 15.4$ Hz), 6.81 (2H, d, $J = 9.0$ Hz), 7.21-7.26 (10H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.72 (1H, d, $J = 2.7$ Hz).

[0201]

- 5 The following compounds were produced in the same manner as in Reference Example 487 using appropriate starting materials.

Reference Example 488

(*E*)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-[4-(4-

- 10 methylbenzyl)piperazin-1-yl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.17 (3H, s), 2.35 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.50 (2H, s), 3.63-3.73 (4H, m), 6.39 (1H, s), 6.77 (1H, d, $J = 15.5$ Hz), 6.86 (1H, d, $J = 8.9$ Hz), 7.14-7.20 (4H, m), 7.24-7.28 (2H, m), 7.41 (1H, d, $J = 2.0$ Hz), 7.54 (1H, d, $J = 15.2$ Hz), 7.67 (1H, d, $J = 3.0$ Hz).

- 15 Reference Example 489

(*E*)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- $^1\text{H-NMR}$ (CDCl_3) δ : 2.16 (3H, s), 2.48 (4H, t, $J = 4.6$ Hz), 3.07 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.13 (2H, t, $J = 6.9$ Hz), 6.78-6.81 (4H, m), 6.93-6.96 (2H, m), 7.22-7.28 (6H, m), 7.38 (1H, d, $J = 2.0$ Hz), 7.53 (1H, d, $J = 15.5$ Hz), 7.66 (1H, d, $J = 3.0$ Hz).

Reference Example 490

(*E*)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- 25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, $J = 6.9$ Hz), 2.18 (3H, s), 2.48 (4H, t, $J = 4.8$ Hz), 2.85 (1H, septet, $J = 6.9$ Hz), 3.08 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, $J = 6.9$ Hz), 6.10 (1H, s), 6.75-6.88 (4H, m), 7.13 (2H, d, $J = 8.9$ Hz), 7.26-7.28 (6H, m), 7.41 (1H, d, $J = 2.0$ Hz), 7.55 (1H, d, $J = 15.2$ Hz), 7.68 (1H, d, $J = 3.0$ Hz).

- 30 Reference Example 491

(*E*)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (3H, s), 2.28 (3H, s), 2.48 (4H, t, $J = 4.8$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65-3.75 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.97 (1H, s), 6.75-6.81 (3H, m), 6.87

(1H, d, $J = 8.9$ Hz), 7.07 (2H, d, $J = 8.6$ Hz), 7.24-7.29 (6H, m), 7.42 (1H, s), 7.55 (1H, d, $J = 15.2$ Hz), 7.68 (1H, d, $J = 3.0$ Hz).

Reference Example 492

- 5 (E)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.17 (3H, s), 2.48 (4H, t, $J = 4.8$ Hz), 3.07 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.64-3.76 (4H, m), 3.70 (3H, s), 4.12 (2H, t, $J = 6.9$ Hz), 6.76-6.84 (5H, m), 7.24-7.27 (8H, m), 7.40 (1H, d, $J = 2.0$ Hz), 7.54 (1H, d, $J = 15.2$ Hz), 7.67 (1H, d, $J = 3.0$ Hz).

10

Reference Example 493

(E)-3-{3-Chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 15 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.09 (3H, s), 2.35 (2H, s), 2.41 (2H, s), 3.01 (2H, t, $J = 6.8$ Hz), 3.49 (2H, s), 3.56 (2H, s), 3.72 (2H, s), 4.18 (2H, t, $J = 6.8$ Hz), 6.94-6.98 (3H, m), 7.24-7.32 (8H, m), 7.43 (1H, d, $J = 15.4$ Hz), 7.55 (1H, dd, $J = 2.9, 0.5$ Hz), 7.61 (1H, d, $J = 2.0$ Hz), 7.81 (1H, d, $J = 2.2$ Hz), 9.57 (1H, s).

Reference Example 494

- 20 *tert*-Butyl 4-{(E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoyl}piperazine-1-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 2.20 (3H, s), 3.49-3.70 (8H, m), 5.14 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.94-6.96 (1H, m), 7.25-7.32 (3H, m), 7.38-7.41 (2H, m), 7.47 (1H, d, $J = 2.2$ Hz), 7.51-7.53 (1H, m), 7.60 (1H, d, $J = 15.4$ Hz), 7.81-7.82 (1H, m).

25

Reference Example 495

tert-Butyl 4-{(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-prop-2-enoyl}piperazine-1-carboxylate

- 30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.20 (3H, s), 2.36 (3H, s), 3.49-3.72 (8H, m), 4.99 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.91-6.93 (1H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.28-7.30 (3H, m), 7.36 (1H, dd, $J = 8.9, 3.1$ Hz), 7.47 (1H, d, $J = 2.0$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.79-7.80 (1H, m).

Reference Example 496

(E)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-{4-[(5-hydroxypyridin-2-

yl)oxy]-2-methylphenyl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.31 (3H, s), 2.48-2.50 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.75-3.77 (2H, m), 4.12-4.14 (2H, m), 6.69 (1H, d, *J* = 15.4 Hz), 6.79-6.87 (5H, m), 6.94-6.96 (2H, m), 7.25-7.26 (5H, m), 7.48 (1H, d, *J* = 8.5 Hz), 7.85-7.89 (3H, m).

5

Reference Example 497

tert-Butyl (3*R*)-4-{(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoyl}-3-methylpiperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.25-1.27 (3H, m), 1.48 (9H, s), 2.19 (3H, s), 2.35 (3H, s), 2.90-4.88 (7H, m), 4.98 (2H, s), 6.77 (1H, d, *J* = 15.4 Hz), 6.92 (1H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.27-7.29 (3H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.59 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

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Reference Example 498

15 *tert*-Butyl (3*S*)-4-{(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoyl}-3-methylpiperazine-1-carboxylate

¹H-NMR (CDCl₃) δ: 1.25-1.27 (3H, m), 1.48 (9H, s), 2.19 (3H, s), 2.35 (3H, s), 2.89-4.87 (7H, m), 4.98 (2H, s), 6.77 (1H, d, *J* = 15.4 Hz), 6.91-6.93 (1H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.28-7.30 (3H, m), 7.36 (1H, dd, *J* = 8.8, 2.9 Hz), 7.46 (1H, d, *J* = 2.2 Hz), 7.59 (1H, d, *J* = 15.4 Hz), 20 7.78-7.79 (1H, m).

Reference Example 499

tert-Butyl (2*S*)-4-{(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoyl}-2-methylpiperazine-1-carboxylate

25 ¹H-NMR (CDCl₃) δ: 1.16 (3H, d, *J* = 6.6 Hz), 1.48 (9H, s), 2.20 (3H, s), 2.35 (3H, s), 2.78 (3H, m), 3.79-3.97 (2H, m), 4.35-4.62 (2H, m), 4.98 (2H, s), 6.72-6.83 (1H, m), 6.92 (1H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.28-7.30 (3H, m), 7.36 (1H, dd, *J* = 8.8, 2.9 Hz), 7.46 (1H, brs), 7.62 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

30 Reference Example 500

tert-Butyl 5-{(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoyl}-1,2,5-oxadiazepane-2-carboxylate

¹H-NMR (CDCl₃) δ: 1.49 (9H, s), 2.20 (3H, s), 2.36 (3H, s), 3.77-3.90 (6H, m), 4.06-4.10 (2H, m), 4.99 (2H, s), 6.72-6.80 (1H, m), 6.92 (1H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.28-7.30

(3H, m), 7.36 (1H, dd, $J = 8.8, 2.9$ Hz), 7.46-7.47 (1H, m), 7.61-7.66 (1H, m), 7.80 (1H, d, $J = 2.9$ Hz).

Reference Example 501

5 *tert*-Butyl 4-[(*E*)-3-[4-[(5-[(4-fluorobenzyl)oxy]pyridin-2-yl)oxy]-3,5-dimethylphenyl]prop-2-enoyl]piperazine-1-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.13 (6H, s), 3.49 (4H, brs), 3.65-3.69 (4H, m), 4.99 (2H, s), 6.78 (1H, d, $J = 15.4$ Hz), 6.82 (1H, dd, $J = 9.0, 0.5$ Hz), 7.04-7.10 (2H, m), 7.26 (2H, brs), 7.32 (1H, dd, $J = 9.0, 3.2$ Hz), 7.35-7.40 (2H, m), 7.64 (1H, d, $J = 15.4$ Hz), 7.81 (1H, dd, $J = 3.2, 0.5$ Hz).

Reference Example 502

tert-Butyl 4-[(*E*)-3-[4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl]prop-2-enoyl]piperazine-1-carboxylate

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.12 (6H, s), 3.49 (4H, brs), 3.65-3.70 (4H, m), 6.74-6.79 (2H, m), 7.23-7.25 (3H, m), 7.62 (1H, d, $J = 15.4$ Hz), 7.73 (1H, d, $J = 3.2$ Hz).

Reference Example 503

20 *tert*-Butyl 5-[(*E*)-3-[4-[(5-[(4-cyanobenzyl)oxy]pyridin-2-yl)oxy]-3,5-dimethylphenyl]prop-2-enoyl]-1,2,5-oxadiazepane-2-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ : 1.49 (9H, s), 2.12 (6H, s), 3.78-3.90 (6H, m), 4.06-4.11 (2H, m), 5.09 (2H, s), 6.75 (1H, t, $J = 14.9$ Hz), 6.85 (1H, d, $J = 9.0$ Hz), 7.25-7.27 (2H, m), 7.34 (1H, dd, $J = 9.0, 3.1$ Hz), 7.52 (2H, d, $J = 8.3$ Hz), 7.65-7.69 (3H, m), 7.79-7.80 (1H, m).

25 [0202]

Reference Example 504

To a solution of (*E*)-3-[4-(chloromethyl)-3-methylphenyl]prop-2-en-1-yl 4-methylphenyl ether (0.180 g) and (*E*)-3-[4-[(5-hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl]-1-(piperazin-1-yl)prop-2-en-1-one (0.222 g) in DMF (2 mL) was added KHCO_3 (0.063 g) at room temperature under an Ar atmosphere. The mixture was heated at 100 °C for 3 hours, and then cooled to room temperature, and evaporated under reduced pressure. To the residue was added saturated aqueous NaHCO_3 , and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 . The residue was purified by silica gel column chromatography (AcOEt) to afford (*2E*)-3-[4-[(5-hydroxypyridin-

2-yl)oxy]-3,5-dimethylphenyl}-1-(4-{2-methyl-4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one (0.286 g) as a colorless powder.

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.29 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.2 Hz), 3.47 (2H, s), 3.62 (2H, brs), 3.72 (2H, brs), 4.67 (2H, dd, *J* = 5.8, 1.4 Hz), 5.46 (1H, brs), 6.40 (1H, dt, *J* = 16.0, 5.8 Hz), 6.68 (1H, dt, *J* = 16.0, 1.4 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.86 (2H, dt, *J* = 9.3, 2.6 Hz), 7.09 (2H, d, *J* = 8.3 Hz), 7.20-7.25 (6H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.73 (1H, d, *J* = 3.2 Hz).

[0203]

The following compound was produced in the same manner as in Reference

10 Example 231 using appropriate starting materials.

Reference Example 505

(*E*)-3-{4-[(5-Hydroxypyridin-2-yl)oxy]-3,5-dimethylphenyl}-1-(piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.92 (4H, t, *J* = 5.1 Hz), 3.65-3.71 (4H, m), 6.72 (1H, d, *J* = 8.8 Hz), 6.77 (1H, d, *J* = 15.4 Hz), 7.21-7.24 (3H, m), 7.59 (1H, d, *J* = 15.4 Hz), 7.71 (1H, dd, *J* = 3.2, 0.5 Hz).

[0204]

The following compound was produced in the same manner as in Reference

Example 326 using appropriate starting materials.

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Reference Example 506

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.67 (1H, s), 2.20 (3H, s), 2.91 (4H, t, *J* = 5.1 Hz), 3.62-3.70 (4H, m), 5.14 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.93-6.95 (1H, m), 7.25-7.31 (3H, m), 7.36-7.42 (2H, m), 7.46 (1H, d, *J* = 2.2 Hz), 7.50-7.54 (1H, m), 7.58 (1H, d, *J* = 15.4 Hz), 7.81-7.82 (1H, m).

Reference Example 507

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.90-2.92 (4H, m), 3.63-3.73 (4H, m), 4.99 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.91 (1H, dd, *J* = 8.8, 0.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.28-7.30 (3H, m), 7.36 (1H, dd, *J* = 8.9, 2.9 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Reference Example 508

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2*S*)-2-methylpiperazin-1-yl]prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 1.35 (3H, d, *J* = 6.6 Hz), 1.59 (1H, brs), 2.19 (3H, s), 2.35 (3H, s), 2.70-4.98 (9H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.90-6.92 (1H, m), 7.18 (2H, d, *J* = 7.6 Hz), 7.28-7.30 (3H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.46 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79-7.80 (1H, m).

10 Reference Example 509

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2*R*)-2-methylpiperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.35 (3H, d, *J* = 6.4 Hz), 1.64 (1H, brs), 2.19 (3H, s), 2.35 (3H, s), 2.70-4.98 (9H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.90-6.93 (1H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.28-7.30 (3H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.46 (1H, d, *J* = 2.2 Hz), 7.58 (1H, d, *J* = 15.4 Hz), 7.79-7.80 (1H, m).
- 15

Reference Example 510

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-3-methylpiperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.13 (3H, d, *J* = 5.4 Hz), 1.64 (1H, brs), 2.19 (3H, s), 2.35-2.43 (3.5H, m), 2.77-2.87 (3H, m), 3.06-3.09 (1H, m), 3.17-3.24 (0.5H, m), 3.88-3.98 (1H, m), 4.57-4.61 (1H, m), 4.98 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.28-7.30 (3H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.46 (1H, brs), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).
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- 25

Reference Example 511

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(1,2,5-oxadiazepan-5-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 3.16-3.19 (2H, m), 3.76-3.97 (6H, m), 4.98 (2H, s), 6.74-6.82 (1H, m), 6.92 (1H, d, *J* = 9.0 Hz), 7.19 (2H, d, *J* = 8.1 Hz), 7.28-7.30 (3H, m), 7.36 (1H, dd, *J* = 9.0, 2.9 Hz), 7.45-7.47 (1H, m), 7.60-7.66 (1H, m), 7.79 (1H, d, *J* = 2.9 Hz).
- 30

Reference Example 512

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.91 (4H, t, *J* = 5.1 Hz), 3.65-3.71 (4H, m), 4.99 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.81 (1H, dd, *J* = 9.0, 0.6 Hz), 7.04-7.10 (2H, m), 7.24-7.27 (2H, m), 7.32 (1H, dd, *J* = 9.0, 3.1 Hz), 7.35-7.40 (2H, m), 7.62 (1H, d, *J* = 15.4 Hz), 7.81 (1H, dd, *J* = 3.1, 0.6 Hz).

Reference Example 513

4-{{(6-{2,6-Dimethyl-4-[(*E*)-3-(1,2,5-oxadiazepan-5-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 3.18 (2H, t, *J* = 5.4 Hz), 3.77-3.97 (6H, m), 5.09 (2H, s), 5.84 (1H, brs), 6.78 (1H, t, *J* = 15.4 Hz), 6.84 (1H, d, *J* = 9.0 Hz), 7.25-7.26 (2H, m), 7.33 (1H, dd, *J* = 9.0, 3.1 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.66-7.70 (3H, m), 7.80 (1H, d, *J* = 2.7 Hz).

[0205]

Example 1

To a solution of (*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-enoic acid (0.122 g) and 1-{4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazine dihydrochloride (0.119 g) in DMF (2 mL) were added Et₃N (0.08 mL), WSC (0.070 g), and HOBT (0.055 g) at room temperature under an Ar atmosphere. The mixture was stirred at room temperature for 14 hours, and evaporated under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt). The resulting powder was crystallized from EtOH (10 mL) to give (*2E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(*1E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one (0.195 g) as a colorless powder.

mp: 130-132 °C

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.29 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 4.68 (2H, dd, *J* = 5.9, 1.5 Hz), 4.95 (2H, s), 6.41 (1H, dt, *J* = 16.1, 5.9 Hz), 6.72 (1H, d, *J* = 16.1 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.79 (1H, dd, *J* = 8.8, 0.7 Hz), 6.86 (2H, dt, *J* = 9.3, 2.6 Hz), 6.91 (2H, dt, *J* = 9.3, 2.6 Hz), 7.09 (2H, dd, *J* = 8.8, 0.7 Hz), 7.25-7.34 (7H, m), 7.38 (2H, d, *J* = 8.3 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.7 Hz).

[0206]

The following compounds were produced in the same manner as in Example 1 using appropriate starting materials.

5 Example 2

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 136-138 °C

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.29 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.68 (2H, dd, *J* = 5.9, 1.5 Hz), 4.98 (2H, s), 6.41 (1H, dt, *J* = 16.0, 5.9 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.81 (1H, d, *J* = 9.0 Hz), 6.86 (2H, dt, *J* = 9.1, 2.5 Hz), 7.04-7.10 (4H, m), 7.25-7.26 (2H, m), 7.29 (2H, d, *J* = 8.3 Hz), 7.32 (1H, dd, *J* = 9.0, 3.2 Hz), 7.36-7.39 (4H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

15 Example 3

(2*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 152 °C

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.29 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 5.1 Hz), 3.53 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.68 (2H, dd, *J* = 5.7, 1.3 Hz), 4.98 (2H, s), 6.41 (1H, dt, *J* = 16.0, 5.7 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.79 (1H, d, *J* = 15.4 Hz), 6.86 (2H, dt, *J* = 9.2, 2.6 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.09 (2H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 8.1 Hz), 7.28-7.29 (5H, m), 7.33-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

25 Example 4

(2*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.21 (6H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 3.81 (3H, s), 4.70 (2H, dd, *J* = 5.7, 1.3 Hz), 4.94 (2H, s), 6.42 (1H, dt, *J* = 16.1, 5.7 Hz), 6.71-6.80 (3H, m), 6.89-6.92 (2H, m), 6.94-6.98 (3H, m), 7.25 (2H, s), 7.28-7.34 (7H, m), 7.38 (2H, d, *J* = 8.3 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 5

4-{{(6-{2,6-Dimethyl-4-[(1*E*)-3-oxo-3-(4-{4-[(1*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazin-

1-yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.71 (2H, dd, *J* = 5.7, 1.3 Hz), 5.09 (2H, s), 6.43 (1H, dt, *J* = 16.1, 5.7 Hz), 6.71-6.85 (3H, m), 6.94-6.98 (3H, m), 7.25-7.34 (7H, m), 7.38 (2H, d, *J* = 8.1 Hz), 7.51-7.53 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.67-7.70 (2H, m), 7.79-7.80 (1H, m).

Example 6

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.71 (2H, d, *J* = 5.7 Hz), 4.98 (2H, s), 6.42 (1H, dt, *J* = 16.1, 5.7 Hz), 6.71-6.82 (3H, m), 6.94-6.98 (3H, m), 7.04-7.10 (2H, m), 7.25-7.33 (7H, m), 7.36-7.39 (4H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

Example 7

4-{{[(6-{2-Chloro-4-[(1*E*)-3-(4-{4-[(1*E*)-3-(4-methoxyphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.51 (2H, s), 3.63-3.76 (7H, m), 4.64 (2H, dd, *J* = 5.8, 1.5 Hz), 5.08 (2H, s), 6.39 (1H, dt, *J* = 16.0, 5.8 Hz), 6.70 (1H, d, *J* = 16.0 Hz), 6.76-6.85 (3H, m), 6.87-6.90 (2H, m), 6.94 (1H, dd, *J* = 8.8, 0.5 Hz), 7.26-7.28 (3H, m), 7.34-7.37 (3H, m), 7.44 (1H, d, *J* = 2.2 Hz), 7.50-7.57 (3H, m), 7.65-7.68 (2H, m), 7.747-7.754 (1H, m).

Example 8

4-{{[(2*E*)-3-{4-[(4-{(2*E*)-3-[3-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-enoyl}piperazin-1-yl)methyl]phenyl}prop-2-en-1-yl]oxy}benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.54 (2H, s), 3.65-3.74 (4H, m), 4.76 (2H, dd, *J* = 5.8, 1.5 Hz), 5.09 (2H, s), 6.38 (1H, dt, *J* = 15.9, 5.8 Hz), 6.74 (1H, d, *J* = 15.9 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.95-7.02 (3H, m), 7.29-7.31 (3H, m), 7.35-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.51-7.62 (5H, m), 7.67-7.69 (2H, m), 7.76 (1H, d, *J* = 2.9 Hz).

Example 9

(2*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(1*E*)-3-(4-fluorophenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 112.7-113.3 °C

Example 10

4-({[6-(2-Chloro-6-methyl-4-{{(1E)-3-oxo-3-[4-(4-{{(1E)-3-[4-(propan-2-yl)phenoxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 2.81-2.92 (1H, m), 3.53 (2H, s), 3.64-3.75 (4H, m), 4.68 (2H, dd, *J* = 5.8, 1.5 Hz), 5.09 (2H, s), 6.42 (1H, dt, *J* = 16.0, 5.8 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.88-6.91 (2H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.13-7.17 (2H, m), 7.28-7.30 (3H, m), 7.35-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.67-7.70 (2H, m), 7.77 (1H, d, *J* = 2.9 Hz).

Example 11

4-({[6-(2-Chloro-4-{{(1E)-3-[4-(4-{{(1E)-3-[(6-chloropyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.54 (2H, s), 3.65-3.75 (4H, m), 4.74 (2H, dd, *J* = 5.9, 1.2 Hz), 5.09 (2H, s), 6.36 (1H, dt, *J* = 15.9, 5.9 Hz), 6.73 (1H, d, *J* = 15.9 Hz), 6.80 (1H, d, *J* = 15.5 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 7.238-7.243 (2H, m), 7.29-7.31 (3H, m), 7.36-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.51-7.53 (2H, m), 7.57 (1H, d, *J* = 15.5 Hz), 7.67-7.69 (2H, m), 7.76 (1H, d, *J* = 2.9 Hz), 8.12 (1H, t, *J* = 1.8 Hz).

Example 12

4-({[6-(2-Chloro-6-methyl-4-{{(1E)-3-[4-(4-{{(1E)-3-[(6-methylpyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.49 (7H, m), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.72 (2H, dd, *J* = 5.9, 1.2 Hz), 5.09 (2H, s), 6.39 (1H, dt, *J* = 15.9, 5.9 Hz), 6.73 (1H, d, *J* = 15.9 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 7.07 (1H, d, *J* = 8.5 Hz), 7.17 (1H, dd, *J* = 8.5, 2.9 Hz), 7.29 (3H, d, *J* = 7.6 Hz), 7.35-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.51-7.59 (3H, m), 7.68 (2H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 3.2 Hz), 8.25 (1H, d, *J* = 2.9 Hz).

Example 13

4-({[6-(4-{{(1E)-3-[4-(4-{{(1E)-3-[(5-Bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-2-chloro-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.53 (2H, s), 3.64-3.75 (4H, m), 4.97 (2H, dd, *J* = 6.1, 1.2 Hz), 5.10 (2H, s), 6.44 (1H, dt, *J* = 15.9, 6.1 Hz), 6.71-6.73 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 7.26-7.30 (3H, m), 7.36-7.39 (3H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.65-7.70 (3H, m), 7.77 (1H, d, *J* = 2.9 Hz), 8.21 (1H, d, *J* = 2.4 Hz).

Example 14

4-({[6-(2-Chloro-6-methyl-4-((1*E*)-3-[4-(4-((1*E*)-3-[(5-methylpyridin-2-yl)oxy]prop-1-en-1-yl)}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.25 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.97 (2H, dd, *J* = 6.1, 1.2 Hz), 5.09 (2H, s), 6.46 (1H, dt, *J* = 15.9, 6.1 Hz), 6.69-6.74 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 7.26-7.29 (3H, m), 7.35-7.42 (4H, m), 7.45 (1H, d, *J* = 2.2 Hz), 7.51-7.59 (3H, m), 7.68 (2H, dt, *J* = 8.2, 1.8 Hz), 7.77 (1H, d, *J* = 2.9 Hz), 7.96-7.97 (1H, m).

Example 15

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(4-chlorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 168.4-169.1 °C

¹H-NMR (DMSO-*d*₆) δ: 2.09 (3H, s), 2.30 (3H, s), 2.36-2.42 (4H, m), 3.52 (2H, s), 3.57 (2H, brs), 3.73 (2H, brs), 5.05 (2H, s), 5.08 (2H, s), 7.02-7.09 (3H, m), 7.18-7.46 (12H, m), 7.56-7.62 (2H, m), 7.79-7.83 (2H, m).

Example 16

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-chlorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 167.1-167.6 °C

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.39 (4H, brs), 3.52 (2H, s), 3.56 (2H, brs), 3.72 (2H, brs), 5.08 (2H, s), 5.16 (2H, s), 7.03 (2H, d, *J* = 8.9 Hz), 7.11 (1H, d, *J* = 8.9 Hz), 7.26-7.53 (11H, m), 7.60-7.66 (3H, m), 7.84-7.85 (2H, m).

Example 17

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.8 Hz), 3.54 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 5.03 (2H, s), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.91-6.95 (3H, m), 7.15 (2H, d, *J* = 8.8 Hz), 7.26-7.41 (9H, m), 7.45-7.47 (1H, m), 7.50-7.54 (1H, m), 7.57 (1H, d, *J* = 15.6 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

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Example 18

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz),
10 2.86 (1H, septet, *J* = 6.8 Hz), 3.54 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.98 (2H, s), 5.03 (2H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.90-6.93 (3H, m), 7.13-7.20 (4H, m), 7.28-7.30 (3H, m), 7.33-7.37 (3H, m), 7.40 (2H, d, *J* = 7.8 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.6 Hz), 7.79 (1H, d, *J* = 3.4 Hz).

15 Example 19

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 152.3-153.9 °C

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.35-2.43 (4H, m), 3.52 (2H, s), 3.56 (2H, brs), 3.73 (2H, brs),
20 5.06 (2H, s), 5.16 (2H, s), 6.99-7.04 (2H, m), 7.10-7.15 (3H, m), 7.27-7.45 (8H, m), 7.49-7.55 (1H, m), 7.59-7.65 (3H, m), 7.83-7.85 (2H, m).

Example 20

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 153.2-153.9 °C

¹H-NMR (DMSO-*d*₆) δ: 2.09 (3H, s), 2.30 (3H, s), 2.35-2.43 (4H, m), 3.52 (2H, s), 3.56 (2H, brs), 3.72 (2H, brs), 5.05 (2H, s), 5.06 (2H, s), 7.00-7.14 (5H, m), 7.19 (2H, d, *J* = 8.1 Hz), 7.27-7.35 (5H, m), 7.40-7.45 (3H, m), 7.58 (1H, dd, *J* = 8.6, 3.2 Hz), 7.62 (1H, d, *J* = 1.7 Hz), 7.79
30 (1H, d, *J* = 3.2 Hz), 7.82 (1H, d, *J* = 1.7 Hz).

Example 21

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.41 (3H, s), 2.49 (4H, brs), 3.54 (2H, s), 3.64 (2H, brs), 3.75 (2H, brs), 4.42 (1H, septet, *J* = 6.1 Hz), 5.00 (2H, s), 5.17 (2H, s), 6.71 (1H, d, *J* = 15.4 Hz), 6.81-6.86 (2H, m), 6.88-6.93 (5H, m), 7.26-7.43 (8H, m), 7.51-7.54 (2H, m), 7.90 (1H, d, *J* = 15.4 Hz), 7.95 (1H, d, *J* = 3.2 Hz).

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Example 22

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.51-2.53 (4H, m), 3.57 (2H, s), 3.65-3.67 (2H, m), 3.75-3.77 (2H, m), 3.81 (3H, s), 4.40-4.45 (1H, m), 5.00 (2H, s), 5.15 (2H, s), 6.76-6.93 (6H, m), 7.05-7.19 (3H, m), 7.26-7.40 (8H, m), 7.50-7.54 (1H, m), 7.64 (1H, d, *J* = 15.4 Hz), 7.87 (1H, d, *J* = 2.9 Hz).

Example 23

15 (*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.19 (3H, s), 2.49 (4H, t, *J* = 5.0 Hz), 3.55 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.42 (1H, septet, *J* = 6.1 Hz), 5.00 (2H, s), 5.11 (2H, s), 6.79-6.85 (3H, m), 6.88-6.92 (2H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.12 (1H, td, *J* = 7.8, 1.0 Hz), 7.29 (1H, d, *J* = 2.0 Hz), 7.33-7.41 (7H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 24

25 (*E*)-1-(4-{4-[(1,3-Benzodioxol-5-yloxy)methyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

mp: 149.0-151.2 °C

¹H-NMR (DMSO-*d*₆) δ: 2.09 (3H, s), 2.30 (3H, s), 2.35-3.42 (4H, m), 3.52 (2H, s), 3.56 (2H, brs), 3.72 (2H, brs), 5.00 (2H, s), 5.05 (2H, s), 5.95 (2H, s), 6.44 (1H, dd, *J* = 8.3, 2.7 Hz), 6.70 (1H, d, *J* = 2.7 Hz), 6.81 (1H, d, *J* = 8.3 Hz), 7.07 (1H, d, *J* = 9.0 Hz), 7.19 (2H, d, *J* = 8.1 Hz), 30 7.27-7.34 (5H, m), 7.38-7.45 (3H, m), 7.58 (1H, dd, *J* = 9.0, 3.2 Hz), 7.62 (1H, d, *J* = 1.7 Hz), 7.79 (1H, d, *J* = 3.2 Hz), 7.82 (1H, d, *J* = 1.7 Hz).

Example 25

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-

yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 7.1 Hz), 2.49 (4H, t, *J* = 4.8 Hz), 2.83-2.90 (1H, m), 3.54 (2H, s), 3.65-3.75 (4H, m), 5.03 (2H, s), 5.18 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.91-6.94 (3H, m), 7.09 (2H, d, *J* = 8.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 7.28-7.42 (8H, m), 7.51-7.54 (3H, m),
5 7.65 (1H, d, *J* = 15.4 Hz), 7.95 (1H, d, *J* = 3.2 Hz).

Example 26

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

10 ¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.49 (4H, t, *J* = 4.8 Hz), 3.55 (2H, s), 3.64 (2H, s), 3.75 (2H, s), 4.42 (1H, septet, *J* = 6.1 Hz), 5.00 (2H, s), 5.16 (2H, s), 6.78-6.93 (5H, m), 6.97 (1H, d, *J* = 8.8 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 7.26-7.41 (10H, m), 7.52 (1H, t, *J* = 4.6 Hz), 7.61 (1H, d, *J* = 15.1 Hz), 7.86 (1H, d, *J* = 2.9 Hz).

15 Example 27

(*E*)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.36 (3H, s), 2.40 (3H, s), 2.48 (4H, brs), 2.86 (1H, septet, *J* = 6.8 Hz), 3.54 (2H, s), 3.63-3.75 (4H, m), 5.02 (4H, s), 6.71 (1H, d, *J* = 15.1 Hz),
20 6.86-6.93 (5H, m), 7.13-7.17 (2H, m), 7.19 (2H, d, *J* = 7.8 Hz), 7.29-7.35 (5H, m), 7.40 (2H, d, *J* = 8.3 Hz), 7.51-7.53 (1H, m), 7.88-7.93 (2H, m).

Example 28

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[(4-fluorobenzyl)oxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

25 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.54 (2H, s), 3.64-3.74 (4H, m), 4.53 (2H, s), 4.54 (2H, s), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.02-7.06 (2H, m), 7.26-7.41 (11H, m), 7.46 (1H, brs), 7.51-7.53 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

30

Example 29

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[(4-fluorobenzyl)oxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.54 (2H, s), 3.64-3.74

(4H, m), 4.53 (2H, s), 4.54 (2H, s), 4.98 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.91 (1H, d, $J = 8.8$ Hz), 7.01-7.07 (2H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.28-7.37 (10H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.2$ Hz).

5 Example 30

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-({[4-(propan-2-yl)benzyl]oxy}methyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, $J = 7.1$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.90 (1H, septet, $J = 7.1$ Hz), 3.53 (2H, s), 3.64-3.74 (4H, m), 4.53 (2H, s), 4.54 (2H, s), 5.14 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.94 (1H, d, $J = 8.8$ Hz), 7.21 (2H, d, $J = 8.1$ Hz), 7.27-7.41 (11H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.50-7.53 (1H, m), 7.56 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

Example 31

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-({[4-(propan-2-yl)benzyl]oxy}methyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, $J = 6.8$ Hz), 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.90 (1H, septet, $J = 6.8$ Hz), 3.53 (2H, s), 3.63-3.74 (4H, m), 4.53 (2H, s), 4.54 (2H, s), 4.98 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.91 (1H, d, $J = 8.8$ Hz), 7.17-7.36 (14H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.2$ Hz).

Example 32

4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{2-fluoro-4-[(4-fluorophenoxy)methyl]benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.54-2.58 (4H, m), 3.64-3.68 (4H, m), 3.74-3.77 (2H, m), 5.01 (2H, s), 5.09 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.88-7.01 (5H, m), 7.12-7.18 (2H, m), 7.28 (1H, s), 7.35-7.40 (2H, m), 7.45 (1H, s), 7.51-7.58 (3H, m), 7.68 (2H, d, $J = 8.1$ Hz), 7.77 (1H, d, $J = 2.9$ Hz).

Example 33

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{2-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.35 (3H, s), 2.54-2.58 (4H, m), 3.65-3.68 (4H, m), 3.74-3.77 (2H, m), 4.98 (2H, s), 5.00 (2H, s), 6.78 (1H, d, $J = 15.1$ Hz), 6.88-6.92 (3H, m), 6.96-7.00 (2H, m), 7.12-7.20 (4H, m), 7.26-7.30 (3H, m), 7.34-7.40 (2H, m), 7.44 (1H, d, $J = 1.2$ Hz), 7.55 (1H,

d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 34

4-[[[(6-{2-Chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl]benzonitrile

¹H-NMR (CDCl₃) δ : 0.93 (3H, t, $J = 7.3$ Hz), 1.56-1.66 (2H, m), 2.19 (3H, s), 2.48-2.49 (4H, m), 2.52-2.54 (2H, m), 3.53 (2H, s), 3.64-3.66 (2H, m), 3.74-3.77 (2H, m), 5.09 (4H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.91 (2H, d, $J = 8.5$ Hz), 6.95 (1H, d, $J = 8.8$ Hz), 7.08-7.13 (4H, m), 7.29 (1H, s), 7.37 (1H, dd, $J = 9.0, 2.9$ Hz), 7.44-7.48 (2H, m), 7.52 (2H, d, $J = 8.1$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.68 (2H, d, $J = 8.3$ Hz), 7.77 (1H, d, $J = 2.9$ Hz).

Example 35

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 133.0-133.4 °C

Example 36

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.20 (3H, s), 2.48-2.49 (4H, m), 3.53 (2H, s), 3.64-3.67 (2H, m), 3.74-3.77 (2H, m), 5.07 (2H, s), 5.14 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.90-7.01 (5H, m), 7.12 (2H, d, $J = 9.3$ Hz), 7.26-7.31 (3H, m), 7.38-7.46 (4H, m), 7.50-7.53 (1H, m), 7.58 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

Example 37

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{3-fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 0.93 (3H, t, $J = 7.3$ Hz), 1.56-1.64 (2H, m), 2.19 (3H, s), 2.35 (3H, s), 2.48-2.49 (4H, m), 2.53 (2H, t, $J = 7.7$ Hz), 3.53 (2H, s), 3.64-3.66 (2H, m), 3.74-3.76 (2H, m), 4.98 (2H, s), 5.09 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.91 (3H, d, $J = 8.1$ Hz), 7.10 (2H, d, $J = 5.9$ Hz), 7.12 (2H, d, $J = 6.1$ Hz), 7.18 (2H, d, $J = 7.8$ Hz), 7.27-7.30 (3H, m), 7.35 (1H, dd, $J = 8.9, 3.1$ Hz), 7.43-7.48 (2H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 38

4-{{[6-{2-Chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl]oxy}methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48-2.50 (4H, m), 3.54 (2H, s), 3.64-3.67 (2H, m), 3.74-3.77 (2H, m), 5.08 (2H, s), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.90-7.01 (5H, m), 7.12 (2H, d, *J* = 9.3 Hz), 7.29 (1H, s), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.42-7.47 (2H, m), 7.52 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

Example 39

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(3-fluoro-4-{4-(propan-2-yloxy)phenoxy}methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 5.9 Hz), 2.20 (3H, s), 2.48-2.49 (4H, m), 3.53 (2H, s), 3.64-3.67 (2H, m), 3.74-3.77 (2H, m), 4.39-4.46 (1H, m), 5.06 (2H, s), 5.14 (2H, s), 6.78-6.85 (3H, m), 6.91 (2H, d, *J* = 9.0 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.11 (2H, d, *J* = 9.0 Hz), 7.27-7.31 (3H, m), 7.38-7.41 (2H, m), 7.43-7.48 (2H, m), 7.50-7.53 (1H, m), 7.58 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.7 Hz).

Example 40

4-({[6-(2-Chloro-4-({*E*)-3-[4-(3-fluoro-4-{4-(propan-2-yloxy)phenoxy}methyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.19 (3H, s), 2.48-2.49 (4H, m), 3.53 (2H, s), 3.64-3.66 (2H, m), 3.74-3.76 (2H, m), 4.39-4.45 (1H, m), 5.06 (2H, s), 5.09 (2H, s), 6.78-6.86 (3H, m), 6.91 (2H, d, *J* = 9.3 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 7.10 (1H, s), 7.12 (1H, s), 7.29 (1H, s), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.43-7.47 (2H, m), 7.52 (2H, d, *J* = 8.3 Hz), 7.57 (1H, d, *J* = 15.1 Hz), 7.68 (2H, d, *J* = 8.3 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

Example 41

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{4-(propan-2-yl)phenoxy}methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.37 (3H, s), 2.50 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.8 Hz), 3.55 (2H, s), 3.65-3.75 (4H, m), 5.03 (2H, s), 5.16 (2H, s), 6.73 (1H, d, *J* = 15.4 Hz), 6.91-6.96 (3H, m), 6.99 (1H, s), 7.15 (2H, d, *J* = 8.5 Hz), 7.26-7.35 (4H, m), 7.38-7.41 (4H, m), 7.51-7.53 (1H, m), 7.59 (1H, s), 7.83 (1H, d, *J* = 15.4 Hz), 7.88 (1H, d, *J* = 2.9 Hz).

Example 42

4-{[(6-{4-[(*E*)-3-(4-{4-[(4-Chlorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl]benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.48-2.49 (4H, m), 3.55 (2H, s), 3.64-3.67 (2H, m), 3.73-3.76 (2H, m), 5.03 (2H, s), 5.09 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.84 (1H, d, *J* = 8.8 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 7.23-7.25 (4H, m), 7.31-7.40 (5H, m), 7.52 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 43

10 4-({[6-(2,6-Dimethyl-4-({(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 1.31 (6H, d, *J* = 6.1 Hz), 2.11 (6H, s), 2.47-2.50 (4H, m), 3.54 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 4.41-4.43 (1H, m), 5.00 (2H, s), 5.09 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.82-6.84 (3H, m), 6.90 (2H, d, *J* = 9.0 Hz), 7.25-7.26 (2H, m), 7.31-7.35 (3H, m), 7.40 (2H, d, *J* = 8.1 Hz), 7.52 (2H, d, *J* = 8.3 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.3 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 44

20 (*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48-2.50 (4H, m), 2.86 (1H, septet, *J* = 6.8 Hz), 3.55 (2H, s), 3.64-3.75 (4H, m), 5.03 (2H, s), 5.17 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.89-6.93 (3H, m), 7.03 (1H, s), 7.13-7.17 (2H, m), 7.27-7.42 (8H, m), 7.46 (1H, s), 7.51-7.54 (1H, m), 7.91-7.95 (2H, m).

Example 45

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

30 ¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.12 (3H, s), 2.30 (3H, s), 2.37-2.43 (4H, m), 2.82 (1H, septet, *J* = 6.8 Hz), 3.52 (2H, s), 3.57-3.72 (4H, m), 5.04 (2H, s), 5.08 (2H, s), 6.90-6.93 (2H, m), 7.07 (1H, d, *J* = 9.0 Hz), 7.11 (1H, s), 7.12-7.16 (2H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.27 (1H, d, *J* = 15.4 Hz), 7.32-7.34 (4H, m), 7.40 (2H, d, *J* = 7.8 Hz), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.75 (1H, d, *J* = 15.4 Hz), 7.91 (1H, d, *J* = 3.2 Hz), 7.97 (1H, s).

Example 46

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.36 (3H, s), 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.8 Hz), 3.55 (2H, s), 3.65-3.75 (4H, m), 5.01 (2H, s), 5.03 (2H, s), 6.72 (1H, d, *J* = 15.4 Hz), 6.90-6.94 (3H, m), 6.97 (1H, s), 7.13-7.17 (2H, m), 7.19 (2H, d, *J* = 7.8 Hz), 7.29 (2H, d, *J* = 7.8 Hz), 7.33-7.37 (3H, m), 7.40 (2H, d, *J* = 8.3 Hz), 7.59 (1H, s), 7.81-7.87 (2H, m).

10

Example 47

4-({[6-(5-Chloro-2-methyl-4-({*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

- 15 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 3.49 (4H, brs), 2.86 (1H, septet, *J* = 6.8 Hz), 3.55 (2H, s), 3.64-3.75 (4H, m), 5.03 (2H, s), 5.12 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.90-6.93 (3H, m), 7.03 (1H, s), 7.13-7.17 (2H, m), 7.33-7.41 (5H, m), 7.46 (1H, s), 7.53 (2H, d, *J* = 8.3 Hz), 7.68-7.70 (2H, m), 7.87 (1H, d, *J* = 3.2 Hz), 7.93 (1H, d, *J* = 15.4 Hz).

20 Example 48

4-({[6-(2-Chloro-5-methyl-4-({*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

- 25 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.8 Hz), 3.55 (2H, s), 3.64-3.75 (4H, m), 5.03 (2H, s), 5.11 (2H, s), 6.73 (1H, d, *J* = 15.4 Hz), 6.90-6.93 (2H, m), 6.95-6.99 (2H, m), 7.13-7.17 (2H, m), 7.33-7.41 (5H, m), 7.51-7.53 (2H, m), 7.59 (1H, s), 7.67-7.70 (2H, m), 7.81-7.85 (2H, m).

Example 49

- 30 (*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.12 (6H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.86 (1H, septet, *J* = 6.8 Hz), 3.54 (2H, s), 3.65-3.75 (4H, m), 5.03 (2H, s), 5.23 (2H, s), 6.77-6.83 (2H, m), 6.90-6.94 (2H, m), 7.13-7.18 (2H, m), 7.25 (2H, s), 7.33-7.42 (6H, m), 7.61 (1H, d, *J* = 15.4 Hz),

7.86 (1H, d, $J = 2.9$ Hz), 8.83 (1H, d, $J = 2.2$ Hz).

Example 50

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.8$ Hz), 2.11 (3H, d, $J = 1.5$ Hz), 2.18 (3H, s), 2.36 (3H, s), 2.46 (4H, brs), 2.86 (1H, septet, $J = 6.8$ Hz), 3.55 (2H, s), 3.61 (4H, brs), 4.99 (2H, s), 5.03 (2H, s), 6.41 (2H, s), 6.88-6.95 (3H, m), 7.09 (1H, d, $J = 1.7$ Hz), 7.11-7.21 (4H, m), 7.24-7.42 (7H, m), 7.80 (1H, d, $J = 2.9$ Hz).

10

Example 51

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.8$ Hz), 2.19 (3H, s), 2.22 (3H, d, $J = 1.0$ Hz), 2.36 (3H, s), 2.45 (4H, dt, $J = 17.6, 4.9$ Hz), 2.87 (1H, septet, $J = 6.8$ Hz), 3.50-3.58 (4H, m), 3.72 (2H, t, $J = 4.9$ Hz), 4.99 (2H, s), 5.03 (2H, s), 6.24 (1H, d, $J = 1.2$ Hz), 6.89-6.95 (3H, m), 7.11-7.21 (4H, m), 7.24-7.31 (3H, m), 7.31-7.43 (6H, m), 7.80 (1H, d, $J = 2.7$ Hz).

Example 52

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, $J = 6.4$ Hz), 2.20 (3H, s), 2.49 (4H, t, $J = 4.9$ Hz), 3.55 (2H, s), 3.59-3.79 (4H, m), 4.42 (1H, septet, $J = 6.4$ Hz), 5.00 (2H, s), 5.14 (2H, s), 6.77-6.86 (3H, m), 6.88-6.97 (3H, m), 7.24-7.42 (9H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.49-7.54 (1H, m), 7.57 (1H, d, $J = 15.1$ Hz), 7.81 (1H, d, $J = 3.4$ Hz).

25

Example 53

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-methoxyphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.49 (4H, t, $J = 4.9$ Hz), 3.55 (2H, s), 3.60-3.80 (7H, m), 5.01 (2H, s), 5.14 (2H, s), 6.77-6.87 (3H, m), 6.89-6.97 (3H, m), 7.24-7.42 (9H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.49-7.54 (1H, m), 7.57 (1H, d, $J = 15.1$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

30

Example 54

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-ethoxyphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.39 (3H, t, *J* = 6.8 Hz), 2.20 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 3.55 (2H, s), 3.60-3.82 (4H, m), 3.98 (2H, q, *J* = 6.8 Hz), 5.00 (2H, s), 5.14 (2H, s), 6.78-6.86 (3H, m), 6.88-6.98 (3H, m), 7.24-7.42 (9H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.48-7.54 (1H, m), 7.57 (1H, d, *J* = 15.1 Hz), 7.81 (1H, d, *J* = 3.4 Hz).

Example 55

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.49 (4H, t, *J* = 4.9 Hz), 3.55 (2H, s), 3.60-3.80 (4H, m), 4.42 (1H, septet, *J* = 6.1 Hz), 5.00 (2H, s), 5.16 (2H, s), 6.77-6.86 (3H, m), 6.88-6.92 (2H, m), 6.97 (1H, dd, *J* = 9.0, 0.5 Hz), 7.15 (1H, d, *J* = 8.5 Hz), 7.27-7.38 (4H, m), 7.37-7.43 (5H, m), 7.48-7.55 (1H, m), 7.56-7.64 (2H, m), 7.88 (1H, d, *J* = 2.9 Hz).

Example 56

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{4-(1*H*-pyrrol-1-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.50 (4H, t, *J* = 4.9 Hz), 3.56 (2H, s), 3.60-3.80 (4H, m), 5.08 (2H, s), 5.14 (2H, s), 6.32 (2H, t, *J* = 2.2 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 6.99-7.06 (4H, m), 7.25-7.33 (5H, m), 7.36-7.44 (6H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.49-7.54 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 57

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-{4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.11 (3H, d, *J* = 1.7 Hz), 2.19 (3H, s), 2.46 (4H, brs), 2.87 (1H, septet, *J* = 7.1 Hz), 3.55 (2H, s), 3.62 (4H, brs), 5.03 (2H, s), 5.14 (2H, s), 6.41 (1H, d, *J* = 1.5 Hz), 6.86-6.96 (3H, m), 7.10 (1H, d, *J* = 2.0 Hz), 7.11-7.18 (2H, m), 7.24-7.42 (9H, m), 7.49-7.56 (1H, m), 7.83 (1H, d, *J* = 2.9 Hz).

Example 58

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 1.80 (3H, d, *J* = 1.5 Hz), 1.96 (3H, d, *J* = 1.5 Hz), 2.17 (3H, s), 2.36 (3H, s), 2.40-2.56 (4H, m), 2.87 (1H, septet, *J* = 6.8 Hz), 3.52 (2H, t, *J* = 4.9 Hz), 3.55 (2H, s), 3.73 (2H, brs), 4.99 (2H, s), 5.03 (2H, s), 6.86-6.94 (3H, m), 6.98 (1H, d, *J* = 1.5 Hz), 7.09-7.21 (5H, m), 7.24-7.42 (7H, m), 7.81 (1H, d, *J* = 2.9 Hz).

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Example 59

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 1.80 (3H, d, *J* = 1.5 Hz), 1.96 (3H, d, *J* = 1.5 Hz), 10 2.18 (3H, s), 2.40-2.56 (4H, m), 2.87 (1H, septet, *J* = 6.8 Hz), 3.52 (2H, t, *J* = 4.9 Hz), 3.55 (2H, s), 3.73 (2H, brs), 5.03 (2H, s), 5.15 (2H, s), 6.88-6.94 (3H, m), 6.95-7.00 (1H, m), 7.11 (1H, d, *J* = 2.2 Hz), 7.13-7.18 (2H, m), 7.24-7.43 (8H, m), 7.50-7.55 (1H, m), 7.84 (1H, d, *J* = 2.9 Hz).

Example 60

15 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.20 (3H, s), 2.23 (3H, d, *J* = 0.7 Hz), 2.40-2.51 (4H, m), 2.87 (1H, septet, *J* = 7.1 Hz), 3.50-3.57 (4H, m), 3.72 (2H, brs), 5.03 (2H, s), 5.14 (2H, s), 6.24 (1H, d, *J* = 1.2 Hz), 6.90-6.97 (3H, m), 7.12-7.18 (2H, m), 7.24-7.42 (10H, m), 7.49-7.55 20 (1H, m), 7.83 (1H, d, *J* = 3.2 Hz).

Example 61

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

25 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.53 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.13 (2H, t, *J* = 7.0 Hz), 5.10 (2H, s), 6.74 (1H, dd, *J* = 8.9, 2.8 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, dd, *J* = 8.8, 0.5 Hz), 6.98 (1H, d, *J* = 2.9 Hz), 7.06-7.11 (1H, m), 7.17 (1H, td, *J* = 7.5, 1.1 Hz), 7.22-7.33 (7H, m), 7.39 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45-7.49 (2H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, t, *J* = 1.6 Hz).

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Example 62

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.53

(2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.13 (3H, t, $J = 7.0$ Hz), 4.98 (2H, s), 6.74 (1H, dd, $J = 8.9, 2.8$ Hz), 6.80 (1H, d, $J = 15.4$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 6.98 (1H, d, $J = 2.9$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.23 (2H, d, $J = 8.1$ Hz), 7.26-7.31 (6H, m), 7.36 (1H, dd, $J = 8.9, 3.1$ Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

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Example 63

(*E*)-1-(4-{4-[2-(4-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

mp: 124.5-124.8 °C

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Example 64

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.9$ Hz), 2.18 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.9$ Hz), 3.04-3.08 (4H, m), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13-4.15 (4H, m), 6.78-6.83 (3H, m), 6.90 (1H, d, $J = 8.9$ Hz), 7.13 (2H, d, $J = 8.9$ Hz), 7.19 (2H, d, $J = 8.6$ Hz), 7.25-7.29 (8H, m), 7.45 (1H, d, $J = 1.6$ Hz), 7.56 (1H, d, $J = 15.5$ Hz), 7.71 (1H, d, $J = 3.3$ Hz).

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Example 65

20 (*E*)-3-[3-Chloro-5-methyl-4-({5-[2-(4-methylphenyl)ethoxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.33 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.03 (2H, t, $J = 6.9$ Hz), 3.08 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.12 (2H, t, $J = 6.9$ Hz), 4.13 (2H, t, $J = 6.9$ Hz), 6.78-6.83 (3H, m), 6.88-6.99 (3H, m), 7.12-7.16 (4H, m), 7.22-7.30 (6H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.72 (1H, d, $J = 3.0$ Hz).

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Example 66

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(2-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.11 (2H, t, $J = 6.8$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.17 (2H, t, $J = 6.6$ Hz), 4.98 (2H, s), 6.77-6.88 (3H, m), 6.91 (1H, d, $J = 8.9$ Hz), 7.10-7.20 (4H, m), 7.26-7.31 (7H, m), 7.36 (1H, dd, $J = 8.9, 3.0$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.2$ Hz), 7.79 (1H, d, $J = 3.0$ Hz).

Example 67

(*E*)-1-(4-{4-[2-(4-Butylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 0.91 (3H, t, *J* = 7.4 Hz), 1.26-1.40 (2H, m), 1.50-1.61 (2H, m), 2.19 (3H, s),
5 2.36 (3H, s), 2.46-2.57 (6H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15
(2H, t, *J* = 6.9 Hz), 4.98 (2H, s), 6.77-6.83 (3H, m), 6.91 (1H, d, *J* = 8.9 Hz), 7.05-7.10 (2H, m),
7.19 (2H, d, *J* = 7.9 Hz), 7.23-7.31 (7H, m), 7.36 (1H, dd, *J* = 8.9, 3.0 Hz), 7.45 (1H, d, *J* = 2.0
Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.79 (1H, d, *J* = 3.0 Hz).

10 Example 68

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.46-2.50 (4H, m), 2.81-2.91 (1H,
m), 3.09 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.62-3.66 (2H, m), 3.72-3.76 (2H, m), 4.17 (2H, t, *J* =
15 7.1 Hz), 5.13 (2H, s), 6.68-6.75 (1H, m), 6.76-6.85 (3H, m), 6.94 (1H, d, *J* = 8.9 Hz), 7.16-7.28
(8H, m), 7.36-7.61 (5H, m), 7.81 (1H, d, *J* = 2.6 Hz).

Example 69

(*E*)-1-(4-{4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 6.9 Hz), 3.52 (2H, s),
3.64 (2H, brs), 3.74 (2H, brs), 4.09 (2H, t, *J* = 6.9 Hz), 5.14 (2H, s), 5.90 (2H, s), 6.31 (1H, dd, *J*
= 8.7, 2.3 Hz), 6.48 (1H, d, *J* = 2.3 Hz), 6.69 (1H, d, *J* = 8.7 Hz), 6.80 (1H, d, *J* = 15.6 Hz), 6.94
(1H, d, *J* = 9.2 Hz), 7.22-7.32 (7H, m), 7.38-7.41 (2H, m), 7.45 (1H, d, *J* = 1.8 Hz), 7.52 (1H,
25 m), 7.57 (1H, d, *J* = 15.6 Hz), 7.81 (1H, d, *J* = 2.7 Hz).

Example 70

(*E*)-1-(4-{4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 6.9 Hz),
30 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.09 (2H, t, *J* = 6.9 Hz), 4.98 (2H, s), 5.90 (2H, s),
6.31 (1H, dd, *J* = 8.7, 2.3 Hz), 6.48 (1H, d, *J* = 2.3 Hz), 6.68 (1H, d, *J* = 8.7 Hz), 6.79 (1H, d, *J* =
15.6 Hz), 6.91 (1H, d, *J* = 9.2 Hz), 7.19 (2H, d, *J* = 9.2 Hz), 7.22-7.30 (7H, m), 7.35 (1H, dd, *J* =
9.2, 3.2 Hz), 7.45 (1H, d, *J* = 2.3 Hz), 7.56 (1H, d, *J* = 15.6 Hz), 7.79 (1H, d, *J* = 3.2 Hz).

Example 71

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.19 (3H, s), 2.22 (3H, s), 2.49-2.52 (4H, m), 3.07 (2H, t, *J* = 6.9 Hz), 3.55 (2H, s), 3.64-3.67 (2H, m), 3.74-3.77 (2H, m), 4.13 (2H, t, *J* = 6.9 Hz), 5.13 (2H, s), 6.64 (1H, dd, *J* = 8.2, 2.3 Hz), 6.71 (1H, d, *J* = 1.8 Hz), 6.80 (1H, d, *J* = 15.1 Hz), 6.94 (1H, d, *J* = 8.7 Hz), 7.01 (1H, d, *J* = 8.2 Hz), 7.23-7.31 (7H, m), 7.37-7.58 (5H, m), 7.81 (1H, d, *J* = 3.2 Hz).

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Example 72

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.50-2.53 (4H, m), 3.09 (2H, t, *J* = 7.1 Hz), 3.55 (2H, s), 3.65-
15 3.67 (2H, m), 3.73-3.79 (5H, m), 4.16 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.45-6.52 (3H, m), 6.79 (1H, d, *J* = 15.1 Hz), 6.95 (1H, d, *J* = 8.7 Hz), 7.17 (1H, t, *J* = 8.2 Hz), 7.24-7.30 (7H, m), 7.37-7.46 (3H, m), 7.51-7.58 (2H, m), 7.82 (1H, d, *J* = 2.7 Hz).

Example 73

- 20 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(2-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.50 (4H, m), 3.15 (2H, t, *J* = 6.9 Hz), 3.53 (2H, s), 3.63-
3.66 (2H, m), 3.73-3.76 (2H, m), 4.22 (2H, t, *J* = 6.9 Hz), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.1 Hz),
6.85-6.91 (2H, m), 6.95 (1H, d, *J* = 9.2 Hz), 7.18 (1H, t, *J* = 7.1 Hz), 7.26-7.32 (7H, m), 7.33-
25 7.42 (3H, m), 7.45 (1H, s), 7.51-7.59 (2H, m), 7.81 (1H, d, *J* = 2.7 Hz).

Example 74

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 30 mp: 125.8-126.2 °C

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.06-3.10 (2H, m), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.11-4.15 (2H, m), 4.98 (2H, brs), 6.67 (2H, d, *J* = 8.8 Hz), 6.80 (1H, d, *J* = 15.6 Hz), 6.92 (1H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 8.3 Hz), 7.24 (2H, d, *J* = 7.8 Hz), 7.26-7.28 (3H, m), 7.29 (2H, d, *J* = 7.8 Hz), 7.34-7.37 (1H, m), 7.45 (1H, d, *J* = 2.0

Hz), 7.54 (2H, d, $J = 8.8$ Hz), 7.55-7.59 (1H, m), 7.78 (1H, d, $J = 2.9$ Hz).

Example 75

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.06-3.10 (2H, m), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.11-4.15 (2H, m), 5.14 (2H, brs), 6.67 (2H, d, $J = 8.8$ Hz), 6.80 (1H, d, $J = 15.1$ Hz), 6.95 (1H, d, $J = 8.8$ Hz), 7.22-7.32 (7H, m), 7.38-7.41 (2H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.51-7.59 (4H, m), 7.81 (1H, d, $J = 3.4$ Hz).

Example 76

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.20 (3H, s), 2.47-2.50 (4H, m), 3.08 (2H, t, $J = 6.8$ Hz), 3.53 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 4.14 (2H, t, $J = 6.8$ Hz), 5.14 (2H, s), 6.76-6.85 (3H, m), 6.95 (1H, d, $J = 8.8$ Hz), 7.21-7.29 (9H, m), 7.38-7.59 (5H, m), 7.81 (1H, d, $J = 2.9$ Hz).

Example 77

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, $J = 6.8$ Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.76 (2H, m), 4.15 (2H, t, $J = 6.8$ Hz), 5.13 (2H, s), 6.76-6.83 (2H, m), 6.88-6.95 (3H, m), 7.17 (1H, t, $J = 8.3$ Hz), 7.22-7.30 (7H, m), 7.37-7.41 (2H, m), 7.45 (1H, s), 7.50-7.53 (1H, m), 7.57 (1H, d, $J = 15.6$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

Example 78

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(quinolin-6-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.47-2.51 (4H, m), 3.17 (2H, t, $J = 7.1$ Hz), 3.53 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 4.30 (2H, t, $J = 7.1$ Hz), 5.13 (2H, s), 6.81 (1H, d, $J = 15.1$ Hz), 6.94 (1H, d, $J = 8.8$ Hz), 7.06 (1H, d, $J = 2.9$ Hz), 7.26-7.41 (11H, m), 7.45-7.61 (3H, m), 7.81 (1H, d, $J = 2.9$ Hz), 7.98-8.03 (2H, m), 8.74-8.78 (1H, m).

Example 79

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(2,3-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (3H, s), 2.19 (3H, s), 2.25 (3H, s), 2.47-2.48 (4H, m), 3.10 (2H, t, *J* = 7.2 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.76 (2H, m), 4.15 (2H, t, *J* = 7.2 Hz), 5.14 (2H, s), 6.68 (1H, d, *J* = 8.3 Hz), 6.76 (1H, d, *J* = 7.6 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.02 (1H, t, *J* = 7.9 Hz), 7.25-7.31 (7H, m), 7.38-7.41 (2H, m), 7.45-7.59 (3H, m), 7.81 (1H, d, *J* = 2.9 Hz).

Example 80

10 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.31 (3H, s), 2.47-2.48 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.75 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.13 (2H, s), 6.68-6.83 (4H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.15 (1H, t, *J* = 7.7 Hz), 7.22-7.30 (7H, m), 7.36-7.41 (2H, m), 15 7.44-7.60 (3H, m), 7.81 (1H, d, *J* = 2.9 Hz).

Example 81

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,5-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

20 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (6H, s), 2.48-2.49 (4H, m), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.76 (2H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.13 (2H, s), 6.53 (2H, s), 6.59 (1H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.26-7.31 (7H, m), 7.38-7.59 (5H, m), 7.81 (1H, d, *J* = 2.9 Hz).

25 Example 82

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.75 (2H, s), 4.15 (2H, t, *J* = 7.2 Hz), 5.16 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 6.97 (1H, d, *J* = 9.0 Hz), 7.13 (2H, d, *J* = 8.8 Hz), 7.19 (1H, t, *J* = 8.1 Hz), 7.24-7.35 (8H, m), 7.38-7.41 (2H, m), 7.50-7.53 (1H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.86 (1H, d, *J* = 3.2 Hz).

Example 83

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.55-2.56 (4H, m), 2.82-2.87 (1H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.59 (2H, s), 3.67-3.69 (2H, m), 3.76-3.79 (2H, m), 3.80 (3H, s), 4.14 (3H, t, *J* = 6.3 Hz), 5.15 (2H, s), 6.77 (1H, d, *J* = 15.4 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.06-7.15 (5H, m), 7.22-7.32 (6H, m), 7.34-7.42 (2H, m), 7.49-7.54 (1H, m), 7.63 (1H, d, *J* = 15.4 Hz), 7.87 (1H, d, *J* = 2.9 Hz).

Example 84

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.31 (3H, s), 2.52-2.54 (4H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.56 (2H, s), 3.66-3.68 (2H, m), 3.75-3.78 (2H, m), 3.80 (3H, s), 4.15 (2H, t, *J* = 7.0 Hz), 5.15 (2H, s), 6.68-6.80 (4H, m), 6.92 (1H, d, *J* = 8.8 Hz), 7.06-7.18 (4H, m), 7.25-7.32 (6H, m), 7.33-7.42 (2H, m), 7.50-7.53 (1H, m), 7.63 (1H, d, *J* = 15.4 Hz), 7.87 (1H, d, *J* = 2.9 Hz).

Example 85

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.46-2.49 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 3.80 (3H, s), 4.12 (2H, t, *J* = 7.0 Hz), 5.14 (2H, s), 6.77-6.84 (3H, m), 6.89-6.97 (3H, m), 7.07-7.15 (3H, m), 7.23-7.30 (6H, m), 7.33-7.41 (2H, m), 7.49-7.54 (1H, m), 7.64 (1H, d, *J* = 15.4 Hz), 7.86 (1H, d, *J* = 2.9 Hz).

Example 86

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.48-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.74-3.76 (2H, m), 3.81 (3H, s), 4.14 (2H, t, *J* = 7.1 Hz), 5.15 (2H, s), 6.76-6.82 (3H, m), 6.92 (1H, d, *J* = 8.8 Hz), 7.06-7.10 (4H, m), 7.13-7.16 (1H, m), 7.24-7.31 (6H, m), 7.34-7.41 (2H, m), 7.50-7.54 (1H, m), 7.64 (1H, d, *J* = 15.4 Hz), 7.87 (1H, d, *J* = 2.9 Hz).

Example 87

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-

fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63 (2H, brs), 3.75 (2H, brs), 4.13 (2H, t, *J* = 7.1 Hz), 5.17 (2H, s), 6.71 (1H, d, *J* = 15.1 Hz), 6.80-6.85 (2H, m), 6.89-6.99 (5H, m), 7.23-7.33 (6H, m), 7.36-7.42 (2H, m), 7.51-7.53 (2H, m),
5 7.90 (1H, d, *J* = 15.1 Hz), 7.94 (1H, d, *J* = 3.2 Hz).

Example 88

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 10 ¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.40 (3H, s), 2.48 (4H, brs), 3.07 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63 (2H, brs), 3.75 (2H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 5.17 (2H, s), 6.71 (1H, d, *J* = 15.1 Hz), 6.79 (2H, d, *J* = 8.8 Hz), 6.89-6.91 (3H, m), 7.06 (2H, d, *J* = 8.8 Hz), 7.22-7.42 (8H, m), 7.51-7.53 (2H, m), 7.90 (1H, d, *J* = 15.1 Hz), 7.94 (1H, d, *J* = 3.2 Hz).

15 Example 89

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.40 (3H, s), 2.48 (4H, brs), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63 (2H, brs), 3.75 (2H, brs), 4.15 (2H, t, *J* = 7.1
20 Hz), 5.17 (2H, s), 6.71 (1H, d, *J* = 15.1 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 6.89-6.91 (3H, m), 7.13 (2H, d, *J* = 8.5 Hz), 7.22-7.42 (8H, m), 7.51-7.53 (2H, m), 7.90 (1H, d, *J* = 15.1 Hz), 7.94 (1H, d, *J* = 2.9 Hz).

Example 90

- 25 (*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
mp: 127.3-128.5 °C

Example 91

- 30 (*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.13 (2H, t, *J* = 7.2 Hz), 5.11 (2H, s), 6.78-6.85 (3H, m), 6.93-6.99 (3H, m), 7.12 (1H, td, *J* = 7.9, 1.1 Hz), 7.23-7.29 (5H, m), 7.36-7.41 (3H, m), 7.46 (1H, d, *J* =

2.0 Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 2.9$ Hz).

Example 92

(*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.22 (6H, d, $J = 6.8$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.8$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, $J = 7.0$ Hz), 5.10 (2H, s), 6.78-6.85 (3H, m), 6.95 (1H, d, $J = 9.0$ Hz), 7.09-7.15 (3H, m), 7.24-7.29 (5H, m), 7.37-7.40 (3H, m), 7.46 (1H, d, $J = 1.7$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 3.2$ Hz).

Example 93

(*E*)-3-[3-Chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.19 (3H, s), 2.28 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.15 (2H, t, $J = 7.1$ Hz), 5.11 (2H, s), 6.78-6.82 (3H, m), 6.95 (1H, d, $J = 8.8$ Hz), 7.07 (2H, d, $J = 8.8$ Hz), 7.09-7.19 (2H, m), 7.22-7.29 (6H, m), 7.38 (1H, dd, $J = 8.9, 3.1$ Hz), 7.46 (1H, d, $J = 1.7$ Hz), 7.57 (1H, d, $J = 15.1$ Hz), 7.81 (1H, d, $J = 3.2$ Hz).

Example 94

(*E*)-3-[3-Chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.22 (6H, d, $J = 6.8$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.16 (2H, d, $J = 7.1$ Hz), 5.11 (2H, s), 6.78-6.85 (3H, m), 6.95 (1H, d, $J = 9.0$ Hz), 7.10-7.17 (4H, m), 7.22-7.29 (6H, m), 7.38 (1H, dd, $J = 8.9, 3.1$ Hz), 7.46 (1H, d, $J = 1.7$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 3.2$ Hz).

Example 95

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.22 (6H, d, $J = 7.1$ Hz), 2.48 (4H, t, $J = 4.9$ Hz), 2.80-2.90 (1H, m), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.15 (2H, t, $J = 7.1$ Hz), 5.18

(2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 6.92 (1H, d, $J = 9.0$ Hz), 7.08 (2H, d, $J = 8.8$ Hz), 7.13 (2H, d, $J = 8.8$ Hz), 7.23-7.31 (6H, m), 7.37-7.42 (2H, m), 7.51-7.54 (3H, m), 7.65 (1H, d, $J = 15.4$ Hz), 7.95 (1H, d, $J = 3.2$ Hz).

5 Example 96

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.47-2.48 (4H, m), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 3.80 (3H, s), 4.13 (2H, t, $J = 7.0$ Hz), 5.14 (2H, s), 6.76-6.83 (3H, m), 6.92 (1H, d, $J = 8.8$ Hz), 7.07-7.16 (3H, m), 7.20-7.31 (8H, m), 7.34-7.41 (2H, m), 7.50-7.53 (1H, m), 7.64 (1H, d, $J = 15.4$ Hz), 7.86 (1H, d, $J = 2.9$ Hz).

Example 97

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.19 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, $J = 6.8$ Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.13 (2H, t, $J = 6.8$ Hz), 5.14 (2H, s), 6.72-6.83 (2H, m), 6.93-6.99 (2H, m), 7.22-7.32 (8H, m), 7.37-7.47 (3H, m), 7.50-7.53 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

20

Example 98

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.19 (3H, s), 2.36 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.14 (2H, t, $J = 7.0$ Hz), 4.98 (2H, s), 6.77-6.85 (3H, m), 6.92 (1H, d, $J = 9.0$ Hz), 7.17-7.30 (11H, m), 7.36 (1H, dd, $J = 8.9, 3.1$ Hz), 7.45 (1H, s), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 99

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-nitrophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.19 (3H, s), 2.48 (4H, brs), 3.14 (2H, t, $J = 6.8$ Hz), 3.53 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.27 (2H, d, $J = 6.8$ Hz), 5.14 (2H, brs), 6.80 (1H, d, $J = 15.4$ Hz), 6.95 (2H, d, $J = 9.0$ Hz), 7.24-7.32 (9H, m), 7.38-7.41 (2H, m), 7.46 (1H, d, $J = 1.7$ Hz), 7.51-7.53 (1H,

m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz), 8.19 (2H, d, $J = 9.0$ Hz).

Example 100

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-nitrophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, brs), 3.14 (2H, t, $J = 6.8$ Hz), 3.53 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.27 (2H, d, $J = 6.8$ Hz), 4.98 (2H, brs), 6.80 (1H, d, $J = 15.4$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 6.94 (2H, d, $J = 9.3$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.25 (2H, d, $J = 7.8$ Hz), 7.28-7.30 (5H, m), 7.36 (1H, dd, $J = 8.8, 2.9$ Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz), 8.19 (2H, d, $J = 9.3$ Hz).

Example 101

(*E*)-1-(4-{4-[2-(4-Methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.60-3.85 (7H, m), 4.13 (2H, t, $J = 7.1$ Hz), 5.01 (2H, s), 6.76-6.86 (6H, m), 6.97 (1H, d, $J = 8.3$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.35 (8H, m), 7.40 (1H, s), 7.63 (1H, d, $J = 15.4$ Hz), 7.88 (1H, d, $J = 2.9$ Hz).

Example 102

(*E*)-3-[3-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.15 (2H, t, $J = 7.1$ Hz), 5.01 (2H, s), 6.76-6.82 (3H, m), 6.84 (1H, dd, $J = 8.9, 0.6$ Hz), 6.97 (1H, d, $J = 8.3$ Hz), 7.07 (2H, dd, $J = 8.7, 0.6$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.35 (8H, m), 7.40 (1H, d, $J = 2.0$ Hz), 7.63 (1H, d, $J = 15.4$ Hz), 7.88 (1H, dd, $J = 3.2, 0.5$ Hz).

Example 103

(*E*)-3-[3-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 7.1$ Hz), 2.21 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.15 (2H, t, $J = 7.1$ Hz), 5.01 (2H, s), 6.78 (1H, d, $J = 15.4$ Hz), 6.82-6.85 (3H, m), 6.97 (1H, d, J

= 8.3 Hz), 7.11-7.15 (2H, m), 7.19 (2H, d, $J = 7.6$ Hz), 7.23-7.35 (8H, m), 7.40 (1H, s), 7.63 (1H, d, $J = 15.4$ Hz), 7.88 (1H, d, $J = 2.9$ Hz).

Example 104

5 (E)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.8$ Hz), 2.21 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.15 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.82-6.85 (2H, m), 6.88 (1H, d, $J = 8.8$ Hz),
10 6.99 (1H, d, $J = 8.3$ Hz), 7.11-7.15 (2H, m), 7.23-7.27 (5H, m), 7.34-7.37 (2H, m), 7.41 (1H, d, $J = 2.0$ Hz), 7.45 (2H, d, $J = 7.8$ Hz), 7.63 (1H, d, $J = 15.4$ Hz), 7.89 (1H, d, $J = 3.2$ Hz).

Example 105

15 (E)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.21 (3H, s), 2.28 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.14 (2H, t, $J = 7.0$ Hz), 5.16 (2H, s), 6.77-6.81 (3H, m), 6.88 (1H, d, $J = 8.8$ Hz), 6.99 (1H, d, $J = 8.3$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.23-7.28 (5H, m), 7.34-7.37 (2H, m), 7.41 (1H, s), 7.45 (2H, d, $J = 7.8$ Hz), 7.63 (1H, d, $J = 15.4$ Hz), 7.89 (1H, d,
20 $J = 3.2$ Hz).

Example 106

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

25 $^1\text{H-NMR}$ (CDCl_3) δ : 2.22 (3H, s), 2.28 (3H, s), 2.48 (4H, t, $J = 5.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.14 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.76-6.81 (3H, m), 6.87 (1H, d, $J = 8.8$ Hz), 6.98 (1H, d, $J = 8.3$ Hz), 7.07 (2H, d, $J = 8.8$ Hz), 7.23-7.32 (6H, m), 7.34-7.42 (4H, m), 7.50-7.55 (1H, m), 7.63 (1H, d, $J = 15.6$ Hz), 7.91 (1H, d, $J = 3.4$ Hz).

30 Example 107

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.22 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.77-6.89 (4H, m), 6.92-6.99 (3H, m),

7.23-7.30 (6H, m), 7.32-7.42 (4H, m), 7.51-7.54 (1H, m), 7.63 (1H, d, $J = 15.1$ Hz), 7.90 (1H, d, $J = 2.9$ Hz).

Example 108

- 5 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.8$ Hz), 2.22 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.8$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.15 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.79 (1H, d, $J = 15.1$ Hz), 6.82-6.88 (3H, m), 6.98 (1H, d, $J = 8.3$ Hz),
10 7.11-7.15 (2H, m), 7.24-7.32 (5H, m), 7.34-7.41 (5H, m), 7.50-7.55 (1H, m), 7.63 (1H, d, $J = 15.1$ Hz), 7.91 (1H, d, $J = 3.4$ Hz).

Example 109

- 15 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.22 (3H, s), 2.32 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.09 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.16 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.70-6.81 (4H, m), 6.87 (1H, d, $J = 8.8$ Hz), 6.98 (1H, d, $J = 8.3$ Hz), 7.15 (1H, t, $J = 7.8$ Hz), 7.24-7.41 (10H, m), 7.51-7.54 (1H, m), 7.63 (1H, d, $J = 15.1$ Hz), 7.91 (1H, d, $J = 3.4$ Hz).

20

Example 110

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- $^1\text{H-NMR}$ (CDCl_3) δ : 2.28 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s),
25 3.64 (2H, s), 3.75 (2H, s), 4.15 (2H, t, $J = 7.2$ Hz), 5.16 (2H, s), 6.77-6.84 (3H, m), 6.97 (1H, d, $J = 9.0$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.15-7.45 (11H, m), 7.47-7.56 (1H, m), 7.60 (1H, d, $J = 2.9$ Hz), 7.86 (1H, d, $J = 15.4$ Hz).

Example 111

- 30 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.64 (2H, s), 3.75 (2H, s), 4.13 (2H, t, $J = 7.2$ Hz), 5.16 (2H, s), 6.77-6.84 (3H, m), 6.93-6.98 (3H, m), 7.19 (1H, t, $J = 8.1$ Hz), 7.23-7.35 (8H, m), 7.38-7.41 (2H, m), 7.50-7.53 (1H, m), 7.61 (1H, d, $J =$

15.4 Hz), 7.86 (1H, d, $J = 3.2$ Hz).

Example 112

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.32 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.09 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64 (2H, s), 3.75 (2H, s), 4.16 (2H, t, $J = 7.1$ Hz), 5.16 (2H, s), 6.69-6.77 (3H, m), 6.79 (1H, d, $J = 15.4$ Hz), 6.97 (1H, d, $J = 9.0$ Hz), 7.13-7.21 (2H, m), 7.24-7.35 (8H, m), 7.38-7.41 (2H, m), 7.50-7.53 (1H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.86 (1H, d, $J = 2.9$ Hz).

Example 113

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one
mp: 124.3-125.0 °C

$^1\text{H-NMR}$ (CDCl_3) δ : 3.26 (3H, s), 2.40 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.52-3.63 (4H, m), 4.13 (2H, t, $J = 7.1$ Hz), 5.02 (2H, s), 6.70 (1H, d, $J = 15.1$ Hz), 6.80-6.99 (7H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.35 (7H, m), 7.50-7.53 (1H, m), 7.88-7.93 (2H, m).

Example 114

(*E*)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.27 (3H, s), 2.36 (3H, s), 2.40 (3H, s), 2.47 (4H, t, $J = 4.6$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.14 (2H, t, $J = 7.1$ Hz), 5.02 (2H, s), 6.70 (1H, d, $J = 15.1$ Hz), 6.78-6.81 (2H, m), 6.86-6.91 (3H, m), 7.05-7.07 (2H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.28 (4H, m), 7.30 (2H, d, $J = 8.1$ Hz), 7.33 (1H, dd, $J = 8.8, 3.2$ Hz), 7.05-7.53 (1H, m), 7.90 (1H, d, $J = 15.1$ Hz), 7.92 (1H, d, $J = 3.2$ Hz).

Example 115

(*E*)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (6H, d, $J = 7.1$ Hz), 2.36 (3H, s), 2.40 (3H, s), 2.47 (4H, brs), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.02 (2H, s), 6.70 (1H, d, $J = 15.1$ Hz), 6.81-6.85 (2H, m), 6.86-6.91 (3H, m), 7.11-7.14

(2H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.35 (7H, m), 7.50-7.53 (1H, m), 7.88-7.93 (2H, m).

Example 116

(*E*)-1-(4-{4-[2-(4-Acetylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.55 (3H, s), 3.12 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.24 (2H, t, $J = 7.1$ Hz), 5.14 (2H, s), 6.80 (1H, d, $J = 15.1$ Hz), 6.91-6.95 (3H, m), 7.24-7.31 (7H, m), 7.38-7.41 (2H, m), 7.45-7.46 (1H, m), 7.50-7.53 (1H, m), 7.57 (1H, d, $J = 15.1$ Hz), 7.81 (1H, d, $J = 2.9$ Hz), 7.91 (2H, d, $J = 8.3$ Hz).

Example 117

(*E*)-1-(4-{4-[2-(4-Acetylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.55 (3H, s), 3.12 (2H, t, $J = 7.1$ Hz), 3.53 (2H, s), 3.64-3.74 (4H, m), 4.13 (2H, t, $J = 7.1$ Hz), 4.98 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.90-6.94 (3H, m), 7.19 (2H, d, $J = 7.8$ Hz), 7.24-7.30 (7H, m), 7.35 (1H, dd, $J = 8.8$, 3.2 Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.2$ Hz), 7.90-7.94 (2H, m).

Example 118

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.29 (3H, d, $J = 6.1$ Hz), 2.19 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.47 (4H, t, $J = 5.0$ Hz), 2.80 (1H, dd, $J = 13.7$, 6.6 Hz), 3.07 (1H, dd, $J = 13.7$, 5.9 Hz), 3.51 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.48-4.55 (1H, m), 4.98 (2H, s), 6.76-6.81 (3H, m), 6.91 (1H, d, $J = 9.0$ Hz), 7.06 (2H, dd, $J = 8.7$, 0.6 Hz), 7.18-7.30 (9H, m), 7.35 (1H, dd, $J = 9.0$, 3.1 Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.1$ Hz).

Example 119

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, d, $J = 7.1$ Hz), 2.19 (3H, s), 2.27 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.18-3.27 (1H, m), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 3.93 (1H, dd, $J = 9.3$, 7.8 Hz), 4.06 (1H, dd, $J = 9.3$, 5.9 Hz), 4.98 (2H, s), 6.76-6.82 (3H, m), 6.91 (1H, d, $J = 9.0$

Hz), 7.06 (2H, d, $J = 8.3$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.23-7.30 (7H, m), 7.35 (1H, dd, $J = 9.0$, 3.1 Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.1$ Hz).

Example 120

- 5 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one
- $^1\text{H-NMR}$ (CDCl_3) δ : 1.40 (3H, d, $J = 7.1$ Hz), 2.19 (3H, s), 2.27 (3H, s), 2.49 (4H, t, $J = 5.1$ Hz), 3.20-3.25 (1H, m), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 3.93 (1H, dd, $J = 9.3$, 7.7 Hz), 4.06 (1H, dd, $J = 9.3$, 5.9 Hz), 5.14 (2H, s), 6.78 (2H, d, $J = 8.5$ Hz), 6.80 (1H, d, $J = 15.4$ Hz),
- 10 6.94 (1H, d, $J = 9.0$ Hz), 7.06 (2H, d, $J = 8.1$ Hz), 7.22-7.32 (7H, m), 7.38-7.41 (2H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.51-7.53 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.82 (1H, d, $J = 3.2$ Hz).

Example 121

- (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one
- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, d, $J = 6.1$ Hz), 2.19 (3H, s), 2.27 (3H, s), 2.47 (4H, t, $J = 5.0$ Hz), 2.80 (1H, dd, $J = 13.7$, 6.3 Hz), 3.07 (1H, dd, $J = 13.7$, 5.9 Hz), 3.51 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.48-4.55 (1H, m), 5.14 (2H, s), 6.77-6.81 (3H, m), 6.94 (1H, dd, $J = 8.8$, 0.5 Hz), 7.06 (2H, dd, $J = 8.7$, 0.6 Hz), 7.20 (2H, d, $J = 8.1$ Hz), 7.24 (2H, d, $J = 8.1$ Hz), 7.27-7.31 (3H, m),
- 20 7.38-7.41 (2H, m), 7.45 (1H, d, $J = 2.2$ Hz), 7.51-7.53 (1H, m), 7.56 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.7$ Hz).

Example 122

- (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one
- 25 $^1\text{H-NMR}$ (CDCl_3) δ : 1.20-1.26 (6H, m), 1.91-1.93 (2H, m), 2.19-2.21 (3H, m), 2.63-2.67 (2H, m), 2.72-2.76 (2H, m), 2.80-2.89 (1H, m), 3.05-3.10 (2H, m), 3.62 (2H, s), 3.67-3.77 (4H, m), 4.12-4.17 (2H, m), 5.14 (2H, s), 6.74-6.86 (3H, m), 6.94 (1H, d, $J = 8.8$ Hz), 7.11-7.15 (2H, m), 7.22-7.32 (7H, m), 7.37-7.41 (2H, m), 7.44-7.48 (1H, m), 7.50-7.55 (1H, m), 7.58-7.64 (1H, m),
- 30 7.82 (1H, d, $J = 2.9$ Hz).

Example 123

- (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.20-1.23 (6H, m), 1.88-1.96 (2H, m), 2.19-2.20 (3H, m), 2.35 (3H, s), 2.63-2.67 (2H, m), 2.72-2.76 (2H, m), 2.80-2.89 (1H, m), 3.05-3.10 (2H, m), 3.62 (2H, s), 3.66-3.77 (4H, m), 4.09-4.17 (2H, m), 4.98 (2H, s), 6.74-6.86 (3H, m), 6.91 (1H, d, *J* = 8.8 Hz), 7.11-7.14 (2H, m), 7.16-7.30 (9H, m), 7.35 (1H, dd, *J* = 8.8, 3.2 Hz), 7.45 (1H, dd, *J* = 8.5, 2.2 Hz),
5 7.58-7.63 (1H, m), 7.79 (1H, d, *J* = 2.9 Hz).

Example 124

4-({[6-(2-Chloro-6-methyl-4-({(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-

10 yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.81-2.88 (1H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.75 (2H, m), 4.15 (2H, t, *J* = 7.0 Hz), 5.09 (2H, s), 6.78-6.84 (3H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.25-7.27 (4H, m), 7.27-7.30 (1H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.52 (2H, d, *J* = 8.1
15 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.3 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

Example 125

4-({[(6-{2-Chloro-6-methyl-4-[(*E*)-3-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

20 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (3H, s), 2.47-2.48 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.75 (2H, m), 4.14 (2H, t, *J* = 7.0 Hz), 5.08 (2H, s), 6.78-6.82 (3H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 7.25-7.29 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.51 (2H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.67 (2H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

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Example 126

[6-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.41-2.54 (4H, m), 2.84 (1H, septet, *J* = 6.8 Hz),
30 3.07 (2H, t, *J* = 7.1 Hz), 3.49-3.83 (4H, m), 3.52 (2H, s), 4.14 (2H, t, *J* = 7.1 Hz), 5.19 (2H, s), 6.81-6.84 (2H, m), 6.96 (1H, d, *J* = 9.0 Hz), 7.10-7.14 (2H, m), 7.22-7.33 (7H, m), 7.39-7.42 (2H, m), 7.47 (1H, dd, *J* = 8.3, 1.5 Hz), 7.49 (1H, d, *J* = 2.2 Hz), 7.52-7.55 (1H, m), 7.76 (1H, d, *J* = 8.5 Hz), 7.85-7.88 (2H, m), 7.96 (1H, d, *J* = 3.2 Hz).

Example 127

[6-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.41-2.53 (4H, m), 2.84 (1H, septet, *J* = 6.8 Hz),
5 3.07 (2H, t, *J* = 7.1 Hz), 3.48 (2H, brs), 3.52 (2H, s), 3.83 (2H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 5.16
(2H, s), 6.81-6.84 (2H, m), 6.95-7.00 (1H, m), 7.09-7.18 (4H, m), 7.23-7.27 (5H, m), 7.32 (1H,
dd, *J* = 8.9, 2.3 Hz), 7.40 (1H, dd, *J* = 8.9, 3.1 Hz), 7.47 (1H, dd, *J* = 8.4, 1.6 Hz), 7.49 (1H, d, *J*
= 2.2 Hz), 7.77 (1H, d, *J* = 8.5 Hz), 7.86-7.89 (2H, m), 7.95 (1H, dd, *J* = 3.2, 0.5 Hz).

10 Example 128

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.40 (3H, d, *J* = 6.8 Hz), 2.12 (6H, s), 2.27 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz),
3.18-3.29 (1H, m), 3.52 (2H, s), 3.66 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 3.92 (1H, dd, *J* =
15 9.3, 7.7 Hz), 4.06 (1H, dd, *J* = 9.3, 5.9 Hz), 4.95 (2H, s), 6.76-6.80 (4H, m), 6.91 (2H, dt, *J* = 9.1,
2.7 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 7.23-7.34 (9H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* =
3.2 Hz).

Example 129

20 (*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.40 (3H, d, *J* = 7.1 Hz), 2.12 (6H, s), 2.27 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz),
3.18-3.27 (1H, m), 3.52 (2H, s), 3.66 (2H, brs), 3.75 (2H, brs), 3.91-3.95 (1H, m), 4.06 (1H, dd,
J = 9.2, 6.2 Hz), 4.99 (2H, s), 6.77-6.82 (4H, m), 7.05-7.09 (4H, m), 7.24-7.33 (7H, m), 7.36-
25 7.39 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 130

(*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 ¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.08 (2H, t, *J* = 7.0 Hz),
3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.13 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.76-6.84 (4H,
m), 6.95 (2H, t, *J* = 8.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.24-7.33 (9H, m), 7.60 (1H, d, *J* = 15.4
Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 131

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, s), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.76 (5H, brs), 4.12 (2H, q, *J* = 6.8 Hz), 5.13 (2H, s), 6.76-6.83 (6H, m), 7.26-7.29 (8H, m), 7.36 (1H, dd, *J* = 9.0, 2.7 Hz), 7.39-7.41 (1H, m), 7.51-7.52 (1H, m), 7.60 (1H, d, *J* = 15.1 Hz), 7.84 (1H, d, *J* = 2.4 Hz).

Example 132

10 (*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.05-08 (2H, m), 3.52 (3H, s), 3.65 (2H, brs), 3.76 (4H, brs), 4.11-4.15 (2H, m), 4.98 (2H, s), 6.76-6.86 (5H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.24-7.33 (10H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

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Example 133

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.13 (2H, t, *J* = 7.0 Hz), 5.13 (2H, s), 6.78 (1H, d, *J* = 15.6 Hz), 6.80-6.84 (3H, m), 6.93-6.97 (2H, m), 7.23-7.31 (8H, m), 7.34-7.37 (1H, m), 7.38-7.40 (1H, m), 7.51-7.53 (1H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.84 (1H, d, *J* = 2.9 Hz).

Example 134

25 (*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.28 (3H, d, *J* = 6.1 Hz), 2.12 (6H, s), 2.27 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.80 (1H, dd, *J* = 13.8, 6.5 Hz), 3.07 (1H, dd, *J* = 13.8, 6.1 Hz), 3.50 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 4.48-4.55 (1H, m), 4.95 (2H, s), 6.76-6.80 (4H, m), 6.91 (2H, dt, *J* = 9.2, 2.3 Hz), 7.06 (2H, d, *J* = 8.8 Hz), 7.19-7.34 (9H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 135

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-

methoxyphenyl]propyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.29 (3H, d, *J* = 6.1 Hz), 2.12 (6H, s), 2.28 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.80 (1H, dd, *J* = 13.7, 6.6 Hz), 3.07 (1H, dd, *J* = 13.7, 6.1 Hz), 3.51 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.48-4.56 (1H, m), 4.98 (2H, s), 6.76-6.82 (4H, m), 7.04-7.10 (4H, m), 7.19-7.28 (6H, m), 7.32 (1H, dd, *J* = 9.0, 3.2 Hz), 7.36-7.39 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

Example 136

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.75 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.72 (1H, d, *J* = 15.1 Hz), 6.78-6.81 (2H, m), 6.95-6.96 (1H, m), 6.99 (1H, s), 7.05-7.08 (1H, m), 7.23-7.32 (7H, m), 7.37-7.41 (2H, m), 7.51-7.53 (1H, m), 7.58 (1H, s), 7.83 (1H, d, *J* = 15.1 Hz), 7.88-7.89 (1H, m).

Example 137

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 7.1 Hz), 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.72 (1H, d, *J* = 15.4 Hz), 6.82-6.84 (2H, m), 6.95 (1H, d, *J* = 8.8 Hz), 6.99 (1H, s), 7.11-7.14 (2H, m), 7.23-7.32 (6H, m), 7.37-7.41 (2H, m), 7.51-7.53 (1H, m), 7.58 (1H, s), 7.83 (1H, d, *J* = 15.4 Hz), 7.88 (1H, d, *J* = 3.2 Hz).

Example 138

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.49 (4H, brs), 3.07 (2H, t, *J* = 6.8 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.72 (1H, d, *J* = 15.4 Hz), 6.81-6.84 (2H, m), 6.93-6.99 (4H, m), 7.23-7.31 (6H, m), 7.38-7.40 (2H, m), 7.50-7.53 (1H, m), 7.58 (1H, s), 7.83 (1H, d, *J* = 15.4 Hz), 7.88 (1H, d, *J* = 2.7 Hz).

Example 139

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-

(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.35 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.72 (1H, d, *J* = 15.1 Hz), 6.81-6.85 (2H, m), 6.91-6.93 (1H, m), 6.97 (1H, s), 7.11-7.14 (2H, m), 7.19 (2H, d, *J* = 7.8 Hz), 7.23-7.30 (6H, m), 7.34-7.37 (1H, m), 7.58 (1H, s), 7.83 (1H, d, *J* = 15.1 Hz), 7.86 (1H, d, *J* = 2.7 Hz).

Example 140

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.35 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.10 (2H, s), 6.72 (1H, d, *J* = 15.1 Hz), 6.78-6.81 (2H, m), 6.91-6.94 (1H, m), 6.97 (1H, s), 7.05-7.08 (2H, m), 7.19 (2H, d, *J* = 7.8 Hz), 7.23-7.30 (6H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.58 (1H, s), 7.82 (1H, d, *J* = 15.1 Hz), 7.86 (1H, d, *J* = 2.7 Hz).

Example 141

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (DMSO-*d*₆) δ: 2.30 (3H, s), 2.32 (3H, s), 2.35-2.40 (4H, m), 3.00 (2H, t, *J* = 6.8 Hz), 3.48 (2H, s), 3.56-3.72 (4H, m), 4.16 (2H, t, *J* = 6.8 Hz), 5.07 (2H, s), 6.91-6.96 (2H, m), 7.05-7.12 (4H, m), 7.18-7.29 (7H, m), 7.33 (2H, d, *J* = 8.1 Hz), 7.56-7.64 (2H, m), 7.86-7.87 (1H, m), 8.01 (1H, s).

Example 142

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.19 (3H, s), 2.49 (4H, d, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.10-4.15 (2H, m), 4.38-4.44 (1H, m), 5.14 (2H, s), 6.70-6.82 (5H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.23-7.31 (7H, m), 7.38-7.41 (2H, m), 7.45 (1H, s), 7.51-7.53 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 143

(*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-

(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.12 (6H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.12 (2H, t, *J* = 7.1 Hz), 4.38-4.44 (1H, m), 4.98 (2H, s), 6.76-6.82 (6H, m), 7.19 (2H, d, *J* = 7.8 Hz), 7.24-7.33 (9H, m), 7.61 (1H, d, *J* = 15.1 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 144

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.19 (3H, s), 2.36 (3H, s), 2.49 (4H, d, *J* = 4.4 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.12 (2H, t, *J* = 7.0 Hz), 4.38-4.44 (1H, m), 4.98 (2H, s), 6.78-6.82 (5H, m), 6.92 (1H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.23-7.31 (7H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 145

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 5.9 Hz), 2.12 (6H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs), 4.12 (2H, t, *J* = 7.1 Hz), 4.38-4.44 (1H, m), 5.13 (2H, s), 6.77-6.83 (6H, m), 7.25-7.31 (8H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.39-7.41 (1H, m), 7.51-7.53 (1H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.84 (1H, d, *J* = 2.9 Hz).

Example 146

4-{{[(6-{4-[(*E*)-3-(4-{4-[2-(4-Chlorophenoxy)ethyl]benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.47-2.48 (4H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.14 (3H, t, *J* = 7.0 Hz), 5.09 (2H, s), 6.79-6.82 (4H, m), 7.20-7.28 (8H, m), 7.33 (1H, dd, *J* = 8.9, 3.1 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.60 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 147

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 4.9 Hz), 5.17 (2H, s), 6.76-6.84 (3H, m), 6.89-6.97 (3H, m), 7.03 (1H, s), 7.23-7.32 (6H, m), 7.37-7.42 (2H, m), 7.45 (1H, s), 7.51-7.53 (1H, m), 7.90-7.94 (2H, m).

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Example 148

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.21 (3H, s), 2.30 (3H, s), 2.35-2.42 (4H, m), 2.99 (2H, t, *J* = 6.8 Hz), 3.49 (2H, s), 3.57-3.71 (4H, m), 4.13 (2H, t, *J* = 6.8 Hz), 5.08 (2H, s), 6.79-6.83 (2H, m), 7.05-7.08 (3H, m), 7.11 (1H, s), 7.20 (2H, d, *J* = 7.8 Hz), 7.24-7.29 (5H, m), 7.33 (2H, d, *J* = 7.8 Hz), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.75 (1H, d, *J* = 15.4 Hz), 7.90 (1H, d, *J* = 3.2 Hz), 7.97 (1H, s).

15 Example 149

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.30 (3H, s), 2.35-2.41 (4H, m), 3.00 (2H, t, *J* = 6.8 Hz), 3.49 (2H, s), 3.57-3.71 (4H, m), 4.16 (2H, t, *J* = 6.8 Hz), 5.08 (2H, s), 6.91-6.96 (2H, m), 7.06-7.12 (4H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.24-7.29 (5H, m), 7.33 (2H, d, *J* = 7.8 Hz), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.75 (1H, d, *J* = 15.4 Hz), 7.90-7.91 (1H, m), 7.97 (1H, s).

Example 150

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.17 (2H, s), 6.76-6.81 (3H, m), 6.89-6.91 (1H, m), 7.03-7.07 (3H, m), 7.23-7.33 (6H, m), 7.37-7.42 (2H, m), 7.45 (1H, s), 7.51-7.53 (1H, m), 7.90-7.94 (2H, m).

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Example 151

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz),

2.85 (1H, septet, $J = 6.8$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.02 (2H, s), 6.78 (1H, d, $J = 15.4$ Hz), 6.83 (2H, d, $J = 8.3$ Hz), 6.87 (1H, d, $J = 8.8$ Hz), 7.01 (1H, s), 7.12 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.1$ Hz), 7.23-7.31 (6H, m), 7.34 (1H, dd, $J = 9.0, 3.2$ Hz), 7.44 (1H, s), 7.89-7.94 (2H, m).

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Example 152

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, $J = 6.8$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.8$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.17 (2H, s), 6.76-6.85 (3H, m), 6.89-6.91 (1H, m), 7.03 (1H, s), 7.11-7.15 (2H, m), 7.23-7.32 (6H, m), 7.37-7.42 (2H, m), 7.45 (1H, s), 7.51-7.54 (1H, m), 7.90-7.94 (2H, m).

Example 153

4-{{[(6-{4-[(*E*)-3-(4-{4-[2-(3,5-Dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.27 (6H, s), 2.47-2.48 (4H, m), 3.07 (2H, t, $J = 7.0$ Hz), 3.51 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.14 (2H, t, $J = 7.0$ Hz), 5.08 (2H, s), 6.53 (2H, s), 6.58 (1H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.83 (1H, d, $J = 8.9$ Hz), 7.25-7.27 (6H, m), 7.33 (1H, dd, $J = 8.9, 3.1$ Hz), 7.51 (2H, d, $J = 8.3$ Hz), 7.61 (1H, d, $J = 15.4$ Hz), 7.67 (2H, d, $J = 8.3$ Hz), 7.79 (1H, d, $J = 3.1$ Hz).

Example 154

4-{{[(6-{2,6-Dimethyl-4-[(*E*)-3-oxo-3-(4-{4-[2-(quinolin-6-yloxy)ethyl]benzyl}piperazin-1-yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.47-2.49 (4H, m), 3.17 (2H, t, $J = 7.0$ Hz), 3.53 (2H, s), 3.64-3.67 (2H, m), 3.73-3.75 (2H, m), 4.30 (2H, t, $J = 7.0$ Hz), 5.08 (2H, s), 6.79 (1H, d, $J = 15.1$ Hz), 6.83 (1H, d, $J = 9.0$ Hz), 7.06 (1H, d, $J = 2.4$ Hz), 7.25 (2H, s), 7.29-7.34 (6H, m), 7.37 (1H, dd, $J = 9.3, 2.9$ Hz), 7.51 (2H, d, $J = 8.1$ Hz), 7.61 (1H, d, $J = 15.1$ Hz), 7.67 (2H, d, $J = 8.1$ Hz), 7.79 (1H, d, $J = 2.9$ Hz), 7.98-8.00 (2H, m), 8.75 (1H, dd, $J = 4.2, 1.2$ Hz).

Example 155

2-({[6-(2,6-Dimethoxy-4-[(*E*)-3-oxo-3-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.8 Hz), 2.49 (4H, s), 2.83-2.90 (1H, m), 3.09 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.76 (2H, brs), 3.80 (4H, s), 4.17 (2H, t, *J* = 7.0 Hz), 5.22 (2H, s), 6.72 (1H, d, *J* = 8.1 Hz), 6.76-6.83 (5H, m), 6.97 (1H, d, *J* = 8.8 Hz), 7.19 (1H, t, *J* = 7.9 Hz), 7.26-7.27 (6H, m), 7.38 (1H, dd, *J* = 9.0, 2.9 Hz), 7.42-7.46 (1H, m), 7.60-7.64 (3H, m),
 5 7.70 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 2.7 Hz).

Example 156

2-{{{6-{{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethoxyphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

10 ¹H-NMR (CDCl₃) δ: 2.49 (4H, brs), 3.08 (2H, t, *J* = 7.0 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.76 (2H, brs), 3.80 (6H, s), 4.13 (2H, t, *J* = 7.0 Hz), 5.22 (2H, s), 6.76-6.84 (5H, m), 6.93-6.98 (3H, m), 7.26 (4H, brs), 7.38 (1H, dd, *J* = 9.0, 2.9 Hz), 7.43-7.46 (1H, m), 7.60-7.64 (3H, m), 7.70 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 2.7 Hz).

15 Example 157

4-{{{6-{{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethoxyphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.49 (4H, brs), 3.08 (2H, t, *J* = 7.0 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.76 (2H, brs), 3.79 (6H, s), 4.13 (2H, t, *J* = 7.1 Hz), 5.08 (2H, s), 6.77 (1H, d, *J* = 15.4 Hz), 6.79 (2H,
 20 s), 6.82 (2H, dd, *J* = 9.0, 4.4 Hz), 6.93-6.97 (3H, m), 7.23-7.29 (4H, m), 7.32 (1H, dd, *J* = 9.0, 2.9 Hz), 7.52 (2H, d, *J* = 8.3 Hz), 7.61 (1H, d, *J* = 15.1 Hz), 7.67 (2H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 158

25 4-({[6-(2,6-Dimethoxy-4-{(*E*)-3-oxo-3-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.23 (6H, d, *J* = 6.8 Hz), 2.49 (4H, s), 2.82-2.88 (1H, m), 3.09 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.76 (2H, brs), 3.79 (4H, s), 4.17 (2H, t, *J* = 7.1 Hz), 5.08 (2H, s), 6.72 (1H, d, *J* = 8.1 Hz), 6.76-6.83 (5H, m), 6.96 (1H, d, *J* = 9.0 Hz), 7.19 (1H, t, *J* = 7.8
 30 Hz), 7.26-7.27 (4H, m), 7.32 (1H, dd, *J* = 9.0, 2.9 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.67 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 159

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-[2-

(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.28 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.09 (2H, t, *J* = 7.4 Hz), 3.49 (2H, s), 3.65-3.74 (4H, m), 4.11 (2H, t, *J* = 7.4 Hz), 4.98 (2H, s), 6.76-6.82 (4H, m), 7.05-7.12 (6H, m), 7.18 (1H, d, *J* = 7.6 Hz), 7.25-7.26 (2H, m), 7.32 (1H, dd, *J* = 8.9, 3.1 Hz), 7.36-7.39 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.1 Hz).

Example 160

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 3.49 (2H, s), 3.65-3.74 (4H, m), 4.12 (2H, t, *J* = 7.3 Hz), 4.98 (2H, s), 6.78-6.81 (3H, m), 6.91 (1H, dd, *J* = 8.9, 0.6 Hz), 7.06-7.12 (4H, m), 7.17-7.20 (3H, m), 7.28-7.30 (3H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, dd, *J* = 3.1, 0.6 Hz).

Example 161

(*E*)-1-(4-{4-[2-(3,4-Dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-(3,5-dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.18 (3H, s), 2.22 (3H, s), 2.47-2.49 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.76 (2H, m), 4.14 (2H, t, *J* = 7.0 Hz), 5.05 (2H, s), 6.64 (1H, dd, *J* = 8.1, 2.4 Hz), 6.71 (1H, d, *J* = 2.0 Hz), 6.79 (1H, d, *J* = 15.4 Hz), 6.83 (1H, d, *J* = 9.0 Hz), 7.01 (1H, d, *J* = 8.3 Hz), 7.26-7.27 (6H, m), 7.32-7.35 (3H, m), 7.61 (1H, d, *J* = 15.1 Hz), 7.80 (1H, d, *J* = 2.9 Hz), 8.62 (2H, d, *J* = 5.6 Hz).

Example 162

4-{{[(6-{5-Chloro-2-methyl-4-[(*E*)-3-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.27 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.12 (2H, s), 6.77-6.81 (3H, m), 6.90-6.92 (1H, m), 7.03 (1H, s), 7.05-7.08 (2H, m), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, s), 7.53 (2H, d, *J* = 8.5 Hz), 7.68-7.70 (2H, m), 7.87 (1H, d, *J* = 3.2 Hz), 7.92 (1H, d, *J* = 15.4 Hz).

Example 163

4-{[(6-{2-Chloro-4-[(*E*)-3-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-5-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65-3.75 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s), 6.73 (1H, d, *J* = 15.4 Hz), 6.80-6.85 (2H, m), 6.92-6.99 (4H, m), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.58 (1H, s), 7.67-7.70 (2H, m), 7.81-7.85 (2H, m).

Example 164

4-{[(6-{5-Chloro-4-[(*E*)-3-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.12 (2H, s), 6.77-6.85 (3H, m), 6.90-6.99 (3H, m), 7.03 (1H, s), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, s), 7.52-7.54 (2H, m), 7.68-7.71 (2H, m), 7.87 (1H, d, *J* = 3.2 Hz), 7.92 (1H, d, *J* = 15.4 Hz).

Example 165

4-({[6-(2-Chloro-5-methyl-4-{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 7.1 Hz), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.75 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s), 6.73 (1H, d, *J* = 15.4 Hz), 6.81-6.85 (2H, m), 6.96 (1H, dd, *J* = 8.8, 0.5 Hz), 6.99 (1H, s), 7.11-7.14 (2H, m), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 8.8, 3.2 Hz), 7.51-7.53 (2H, m), 7.58 (1H, s), 7.67-7.70 (2H, m), 7.81-7.85 (2H, m).

Example 166

4-({[6-(5-Chloro-2-methyl-4-{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.18 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.75 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.12 (2H, s), 6.77-6.85 (3H, m), 6.90-6.92 (1H, m), 7.03 (1H, s), 7.11-7.14 (2H, m), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, s), 7.52-7.54 (2H, m), 7.68-7.71 (2H, m), 7.86-7.87 (1H, m), 7.92 (1H, d, *J* = 15.4 Hz).

Example 167

4-[[[(6-{2-Chloro-5-methyl-4-[(*E*)-3-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl]benzonitrile

¹H-NMR (CDCl₃) δ: 2.27 (3H, s), 2.37 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.75 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s), 6.73 (1H, d, *J* = 15.1 Hz),
5 6.78-6.81 (2H, m), 6.96 (1H, d, *J* = 8.8 Hz), 6.99 (1H, s), 7.05-7.08 (2H, m), 7.23-7.28 (4H, m), 7.36 (1H, dd, *J* = 8.8, 3.2 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.58 (1H, s), 7.67-7.69 (2H, m), 7.81-7.85 (2H, m).

Example 168

10 (*E*)-1-(4-{4-[2-(2-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3,5-dimethyl-4-({5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.47-2.48 (4H, m), 2.55 (3H, s), 3.14 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.21 (2H, t, *J* = 7.0 Hz), 5.12 (2H, s), 6.78-6.81 (2H, m), 6.85-6.89 (2H, m), 7.08 (1H, d, *J* = 7.8 Hz), 7.16-7.18 (1H, m), 7.24-7.30 (7H, m),
15 7.33-7.37 (2H, m), 7.58-7.63 (2H, m), 7.84 (1H, d, *J* = 2.9 Hz).

Example 169

(*E*)-1-(4-{4-[2-(3-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-(3,5-dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)prop-2-en-1-one

20 ¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.67 (2H, m), 3.73-3.75 (2H, m), 4.15 (2H, t, *J* = 7.0 Hz), 5.05 (2H, s), 6.79-6.83 (3H, m), 6.89-6.91 (2H, m), 7.16-7.18 (1H, m), 7.25-7.27 (6H, m), 7.32-7.35 (3H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz), 8.62 (2H, d, *J* = 5.9 Hz).

25 Example 170

(*E*)-3-(4-{{5-(1,3-Benzothiazol-6-ylmethoxy)pyridin-2-yl}oxy}-3,5-dimethoxyphenyl)-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.30 (6H, d, *J* = 6.1 Hz), 2.49 (4H, s), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.65 (2H, brs), 3.75 (2H, brs), 3.79 (6H, s), 4.12 (2H, t, *J* = 7.0 Hz), 4.41 (1H, septet, *J* = 6.1
30 Hz), 5.18 (2H, s), 6.75-6.79 (3H, m), 6.81 (4H, s), 6.95 (1H, d, *J* = 8.8 Hz), 7.26 (4H, brs), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.54 (1H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz), 8.02 (1H, s), 8.14 (1H, d, *J* = 8.5 Hz), 9.01 (1H, s).

Example 171

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 3.49 (2H, s), 3.66-3.73 (4H, m), 4.10 (2H, t, *J* = 7.3 Hz), 4.99 (2H, s), 6.76-6.85 (4H, m), 6.93-7.00 (2H, m), 7.05-7.13 (4H, m), 7.18 (1H, d, *J* = 7.6 Hz), 7.25-7.26 (2H, m), 7.32 (1H, dd, *J* = 8.9, 3.1 Hz), 7.36-7.39 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.1 Hz).

Example 172

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 3.49 (2H, s), 3.64-3.74 (4H, m), 4.10 (2H, t, *J* = 7.3 Hz), 4.99 (2H, s), 6.78-6.84 (3H, m), 6.90-7.00 (3H, m), 7.10-7.13 (2H, m), 7.17-7.20 (3H, m), 7.28-7.30 (3H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 3.1 Hz).

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Example 173

(*E*)-3-(4-{[5-(1,3-Benzothiazol-6-ylmethoxy)pyridin-2-yl]oxy}-3,5-dimethoxyphenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.49 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.75 (2H, brs), 3.79 (6H, s), 4.13 (2H, t, *J* = 7.1 Hz), 5.18 (2H, s), 6.75-6.79 (3H, m), 6.81-6.84 (2H, m), 6.93-6.98 (3H, m), 7.24 (2H, d, *J* = 8.1 Hz), 7.27 (2H, d, *J* = 8.1 Hz), 7.35 (1H, dd, *J* = 9.0, 2.9 Hz), 7.54 (1H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz), 8.02 (1H, s), 8.14 (1H, d, *J* = 8.5 Hz), 9.01 (1H, s).

Example 174

(*E*)-1-(4-{4-[2-(4-*tert*-Butylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[4-({5-[(3,4-difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.29 (9H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.74 (4H, m), 4.16 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.82-6.86 (2H, m), 6.96 (1H, dd, *J* = 9.0, 0.5 Hz), 7.10-7.37 (13H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.81 (1H, dd, *J* = 3.1, 0.6 Hz).

30

Example 175

4-({[6-(2,6-Dimethyl-4-({(*E*)-3-[4-(4-{2-[(6-methylpyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-

yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.43 (3H, s), 2.47-2.48 (4H, m), 3.08 (2H, t, *J* = 7.2 Hz), 3.51 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.49 (2H, t, *J* = 7.2 Hz), 5.09 (2H, s), 6.51 (1H, d, *J* = 8.3 Hz), 6.69-6.70 (1H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.83 (1H, d, *J* = 8.9 Hz), 7.25-7.26 (6H, m), 7.33 (1H, dd, *J* = 8.9, 2.9 Hz), 7.43-7.45 (1H, m), 7.52 (2H, d, *J* = 8.1 Hz), 7.60 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 176

(*E*)-3-[4-({5-[(3,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[(4-methylphenoxy)acetyl]benzyl}piperazin-1-yl)prop-2-en-1-one
mp: 152.9-154.3 °C

Example 177

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-methylphenoxy)acetyl]benzyl}piperazin-1-yl)prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.28 (3H, s), 2.50 (4H, t, *J* = 5.0 Hz), 3.60 (2H, s), 3.67-3.76 (4H, m), 5.14 (2H, s), 5.22 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.83-6.87 (2H, m), 6.95 (1H, dd, *J* = 9.0, 0.5 Hz), 7.08 (2H, dd, *J* = 8.7, 0.6 Hz), 7.25-7.32 (3H, m), 7.38-7.41 (2H, m), 7.46-7.53 (4H, m), 7.58 (1H, d, *J* = 15.4 Hz), 7.81 (1H, dd, *J* = 2.9, 0.5 Hz), 7.97-8.00 (2H, m).

Example 178

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 3.49 (2H, s), 3.66 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 4.10 (2H, t, *J* = 7.3 Hz), 4.95 (2H, s), 6.76-6.85 (4H, m), 6.89-7.00 (4H, m), 7.10-7.13 (2H, m), 7.18 (1H, d, *J* = 7.8 Hz), 7.25-7.26 (2H, m), 7.30-7.34 (3H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 179

4-{{{6-[2-Fluoro-4-[(*E*)-3-(4-{4-[(4-methylphenoxy)acetyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy}methyl}benzonitrile
mp: 137.1-137.9 °C

Example 180

4-([6-(2-Fluoro-4-{(E)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.48 (4H, t, *J* = 5.0 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.74 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.82-6.85 (2H, m), 6.97 (1H, dd, *J* = 8.9, 0.6 Hz), 7.11-7.15 (2H, m), 7.19 (1H, t, *J* = 8.1 Hz), 7.23-7.38 (7H, m), 7.51-7.54 (2H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.67-7.70 (2H, m), 7.81 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 181

10 (E)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.27 (3H, s), 2.46-2.49 (4H, m), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.22 (2H, s), 6.76-6.83 (4H, m), 7.05-7.08 (2H, m), 7.23-7.28 (6H, m), 7.36-7.41 (2H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.86 (1H, d, *J* = 3.2 Hz), 8.83 (1H, d, *J* = 2.2 Hz).

Example 182

(E)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

20 ¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.22 (2H, s), 6.76-6.84 (4H, m), 6.92-6.97 (2H, m), 7.23-7.28 (6H, m), 7.36-7.40 (2H, m), 7.60 (1H, d, *J* = 15.4 Hz), 7.86 (1H, d, *J* = 2.9 Hz), 8.83-8.84 (1H, m).

25 Example 183

(E)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.12 (6H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.65-3.74 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.22 (2H, s), 6.77-6.85 (4H, m), 7.11-7.15 (2H, m), 7.23-7.28 (6H, m), 7.36-7.41 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.86 (1H, dd, *J* = 3.2, 2.7 Hz), 8.83 (1H, d, *J* = 2.0 Hz).

Example 184

(E)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-

[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.28 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.09 (2H, t, *J* = 7.4 Hz), 3.49 (2H, s), 3.66 (2H, brs), 3.75 (2H, brs), 3.81 (3H, s), 4.11 (2H, t, *J* = 7.4 Hz), 4.95 (2H, s), 6.76-6.82 (4H, m), 6.91 (2H, dt, *J* = 9.1, 2.4 Hz), 7.06-7.13 (4H, m), 7.18 (1H, d, *J* = 7.6 Hz), 7.25-7.26 (2H, m), 7.30-7.34 (3H, m), 7.61 (1H, d, *J* = 15.1 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 185

4-{[(6-{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.09 (2H, t, *J* = 7.3 Hz), 3.65 (2H, brs), 3.75 (2H, brs), 4.10 (2H, t, *J* = 7.3 Hz), 5.09 (2H, s), 6.76-6.85 (4H, m), 6.93-6.98 (2H, m), 7.10-7.13 (2H, m), 7.18 (1H, d, *J* = 7.6 Hz), 7.25-7.26 (4H, m), 7.33 (1H, dd, *J* = 8.9, 3.1 Hz), 7.52 (2H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.5 Hz), 7.79 (1H, d, *J* = 3.1 Hz).

Example 186

(*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.47-2.49 (4H, m), 3.06-3.09 (2H, m), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.11-4.16 (2H, m), 5.00 (2H, s), 6.51 (1H, t, *J* = 73.8 Hz), 6.80 (1H, d, *J* = 15.3 Hz), 6.80 (2H, d, *J* = 8.3 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 7.14 (2H, d, *J* = 8.3 Hz), 7.26 (4H, brs), 7.28 (1H, brs), 7.36 (1H, dd, *J* = 8.8, 2.9 Hz), 7.40 (2H, d, *J* = 8.3 Hz), 7.45 (1H, brs), 7.56 (1H, d, *J* = 15.3 Hz), 7.78 (1H, d, *J* = 2.9 Hz).

Example 187

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.29 (3H, d, *J* = 6.1 Hz), 2.12 (6H, s), 2.46 (4H, t, *J* = 4.9 Hz), 2.81 (1H, dd, *J* = 13.7, 6.3 Hz), 3.05 (1H, dd, *J* = 13.7, 6.1 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.81 (3H, s), 4.43-4.51 (1H, m), 4.95 (2H, s), 6.76-6.82 (4H, m), 6.90-6.96 (4H, m), 7.19 (2H, d, *J* = 8.1 Hz), 7.24-7.26 (4H, m), 7.30-7.34 (3H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 3.2 Hz).

Example 188

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.29 (3H, d, *J* = 6.1 Hz), 2.12 (6H, s), 2.47 (4H, t, *J* = 5.0 Hz), 2.81 (1H, dd, *J* = 13.7, 6.3 Hz), 3.05 (1H, dd, *J* = 13.7, 6.1 Hz), 3.51 (2H, s), 3.65 (2H, brs), 3.74 (2H, brs),
 5 4.43-4.51 (1H, m), 4.98 (2H, s), 6.76-6.82 (4H, m), 6.91-6.95 (2H, m), 7.05-7.09 (2H, m), 7.19 (2H, d, *J* = 8.1 Hz), 7.24-7.26 (4H, m), 7.32 (1H, dd, *J* = 8.9, 3.1 Hz), 7.36-7.40 (2H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.1 Hz).

Example 189

10 (*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.28 (3H, s), 2.36 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.04 (2H, t, *J* = 7.2 Hz), 3.47 (2H, s), 3.63 (2H, brs), 3.71 (2H, brs), 4.14 (2H, t, *J* = 7.2 Hz), 4.99 (2H, s),
 15 6.79 (1H, d, *J* = 15.6 Hz), 6.79-6.82 (2H, m), 7.05-7.09 (5H, m), 7.19 (1H, d, *J* = 7.3 Hz), 7.25-7.26 (4H, m), 7.32 (1H, dd, *J* = 8.9, 3.1 Hz), 7.36-7.39 (2H, m), 7.61 (1H, d, *J* = 15.6 Hz), 7.81 (1H, d, *J* = 3.1 Hz).

Example 190

20 (*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.28 (3H, s), 2.37 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.04 (2H, t, *J* = 7.3 Hz), 3.47 (2H, s), 3.63 (2H, brs), 3.71 (2H, brs), 3.81 (3H, s), 4.14 (2H, t, *J* = 7.3 Hz),
 25 4.95 (2H, s), 6.77-6.82 (3H, m), 6.91 (2H, dt, *J* = 9.3, 2.4 Hz), 7.06-7.09 (3H, m), 7.19 (1H, d, *J* = 7.6 Hz), 7.25-7.26 (4H, m), 7.30-7.34 (3H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.7 Hz).

Example 191

4-({[6-(2-Chloro-4-({(*E*)-3-[4-(4-{2-[4-(2-hydroxyethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

30 ¹H-NMR (CDCl₃) δ: 1.74-1.76 (1H, m), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.80 (2H, t, *J* = 6.5 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.75 (2H, m), 3.81 (2H, t, *J* = 6.5 Hz), 4.15 (2H, t, *J* = 7.1 Hz), 5.09 (2H, s), 6.80-6.84 (3H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.13 (2H, d, *J* = 8.3 Hz), 7.25-7.27 (5H, m), 7.36-7.38 (1H, m), 7.45-7.58 (4H, m), 7.68 (2H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 2.7 Hz).

Example 192

4-[[[6-(2-Chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

- 5 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.09 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.58 (2H, t, *J* = 7.1 Hz), 5.09 (2H, s), 6.79 (1H, d, *J* = 5.1 Hz), 6.82 (1H, d, *J* = 1.5 Hz), 6.96 (1H, dd, *J* = 9.0, 0.5 Hz), 7.24-7.29 (5H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.51-7.59 (3H, m), 7.68 (2H, dt, *J* = 8.2, 1.7 Hz), 7.74-7.77 (2H, m), 8.42-8.43 (1H, m).

10

Example 193

4-[[[6-(4-[(*E*)-3-(4-{4-[2-(4-Chlorophenoxy)ethyl]-3-fluorobenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

- 15 ¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.47-2.48 (4H, m), 3.11 (2H, t, *J* = 7.0 Hz), 3.51 (2H, s), 3.65-3.67 (2H, m), 3.73-3.76 (2H, m), 4.15 (2H, t, *J* = 7.0 Hz), 5.09 (2H, s), 6.79-6.82 (4H, m), 7.04-7.07 (2H, m), 7.21-7.25 (5H, m), 7.33 (1H, dd, *J* = 8.9, 3.1 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.1 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 194

- 20 4-[[[6-(4-{(*E*)-3-[4-(2-Fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-2,6-dimethylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile

- ¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.51-2.53 (4H, m), 3.10 (2H, t, *J* = 6.7 Hz), 3.61 (2H, s), 3.65-3.67 (2H, m), 3.73-3.76 (2H, m), 4.21 (2H, t, *J* = 6.7 Hz), 5.09 (2H, s), 6.78-6.83 (2H, m), 6.96-7.03 (4H, m), 7.27-7.32 (4H, m), 7.52-7.53 (4H, m), 7.60 (1H, d, *J* = 15.1 Hz), 7.67 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

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Example 195

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 30 ¹H-NMR (CDCl₃) δ: 2.10 (3H, d, *J* = 1.5 Hz), 2.18 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.45 (4H, brs), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.54-3.75 (4H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.41 (1H, d, *J* = 1.5 Hz), 6.77-6.93 (2H, m), 6.90 (1H, dd, *J* = 9.0, 0.5 Hz), 7.02-7.11 (3H, m), 7.18 (2H, d, *J* = 7.6 Hz), 7.22-7.31 (7H, m), 7.35 (1H, dd, *J* = 9.0, 2.9 Hz), 7.80 (1H, dd, *J* = 2.9, 0.5 Hz).

Example 196

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.22 (3H, d, *J* = 1.2 Hz), 2.36 (3H, s), 2.44 (4H, dt, *J* = 17.3, 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.53 (2H, t, *J* = 4.9 Hz), 3.72 (2H, t, *J* = 4.9 Hz), 4.15 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.23 (1H, d, *J* = 1.0 Hz), 6.80-6.88 (2H, m), 6.91 (1H, dd, *J* = 8.8, 0.5 Hz), 7.09-7.15 (2H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.22-7.31 (7H, m), 7.32-7.39 (2H, m), 7.80 (1H, d, *J* = 2.4 Hz).

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Example 197

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 1.2 Hz), 2.28 (3H, s), 2.36 (3H, s), 2.44 (4H, dt, *J* = 17.1, 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.53 (2H, t, *J* = 4.9 Hz), 3.72 (2H, t, *J* = 4.9 Hz), 4.14 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.23 (1H, d, *J* = 1.2 Hz), 6.76-6.82 (2H, m), 6.91 (1H, dd, *J* = 8.8, 0.5 Hz), 7.04-7.09 (2H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.21-7.31 (7H, m), 7.33-7.39 (2H, m), 7.80 (1H, dd, *J* = 2.9, 0.5 Hz).

20 Example 198

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 1.2 Hz), 2.36 (3H, s), 2.44 (4H, dt, *J* = 16.7, 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.53 (2H, t, *J* = 4.9 Hz), 3.72 (2H, t, *J* = 4.9 Hz), 4.13 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.23 (1H, d, *J* = 1.0 Hz), 6.79-6.87 (2H, m), 6.89-7.01 (3H, m), 7.16-7.31 (9H, m), 7.32-7.39 (2H, m), 7.80 (1H, dd, *J* = 2.9, 0.5 Hz).

Example 199

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 30 ¹H-NMR (CDCl₃) δ: 2.32 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.599-3.80 (4H, m), 4.16 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.67-6.84 (4H, m), 6.97 (1H, dd, *J* = 8.8, 0.5 Hz), 7.12-7.18 (2H, m), 7.24-7.32 (6H, m), 7.36-7.42 (3H, m), 7.48-7.55 (1H, m), 7.58-7.63 (2H, m), 7.87 (1H, d, *J* = 2.7 Hz).

Example 200

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.59-3.80 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.78-6.86 (3H, m), 6.91-7.00 (3H, m), 7.15 (1H, d, *J* = 8.3 Hz), 7.22-7.34 (6H, m), 7.36-7.43 (3H, m), 7.48-7.55 (1H, m), 7.56-7.63 (2H, m), 7.87 (1H, d, *J* = 2.9 Hz).

10 Example 201

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 7.1 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.77-6.88 (3H, m), 6.97 (1H, d, *J* = 8.5 Hz), 7.10-7.18 (3H, m), 7.23-7.33 (6H, m), 7.37-7.44 (3H, m), 7.49-7.56 (1H, m), 7.66-7.64 (2H, m), 7.87 (1H, d, *J* = 2.9 Hz).

Example 202

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 20 ¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.16 (2H, s), 6.77-6.84 (3H, m), 6.97 (1H, d, *J* = 9.0 Hz), 7.04-7.10 (2H, m), 7.15 (1H, d, *J* = 8.5 Hz), 7.23-7.33 (6H, m), 7.37-7.43 (3H, m), 7.48-7.55 (1H, m), 7.56-7.64 (2H, m), 7.88 (1H, d, *J* = 3.2 Hz).

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Example 203

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 30 ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J* = 7.1 Hz), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.00 (2H, q, *J* = 7.1 Hz), 4.14 (2H, q, *J* = 7.7 Hz), 5.14 (2H, s), 6.43-6.52 (3H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.10-7.60 (13H, m), 7.81 (1H, d, *J* = 2.9 Hz).

Example 204

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylprop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.09-2.13 (3H, m), 2.18 (3H, s), 2.36 (3H, s), 2.45 (4H, brs), 3.07 (2H, t, *J* = 6.8 Hz), 3.52 (2H, s), 3.62 (4H, brs), 4.13 (2H, q, *J* = 7.1 Hz), 4.99 (2H, s), 6.41 (1H, brs),
5 6.79-6.86 (2H, m), 6.88-6.99 (3H, m), 7.09 (1H, s), 7.19 (2H, d, *J* = 7.8 Hz), 7.24-7.32 (7H, m),
7.32-7.38 (1H, m), 7.80 (1H, d, *J* = 2.9 Hz).

Example 205

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.10 (3H, d, *J* = 1.7 Hz), 2.18 (3H, s), 2.45 (4H, brs), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.61 (4H, brs), 4.15 (2H, t, *J* = 7.3 Hz), 5.14 (2H, s), 6.39-6.43 (1H, m), 6.80-6.86 (2H, m), 6.93 (1H, dd, *J* = 9.0, 0.5 Hz), 7.06-7.15 (3H, m), 7.24-7.32 (7H, m), 7.37-7.42 (2H, m), 7.49-7.55 (1H, m), 7.83 (1H, dd,
15 *J* = 3.2, 0.5 Hz).

Example 206

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylprop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.11 (3H, d, *J* = 1.7 Hz), 2.18 (3H, s), 2.45 (4H, brs), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.62 (4H, brs), 4.13 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.39-6.43 (1H, m), 6.79-6.86 (2H, m), 6.91-7.00 (3H, m), 7.08-7.11 (1H, m), 7.24-7.32 (7H, m), 7.36-7.42 (2H, m), 7.49-7.55 (1H, m), 7.83 (1H, d, *J* = 3.2 Hz).

25 Example 207

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.10 (3H, d, *J* = 1.5 Hz), 2.18 (3H, s), 2.28 (3H, s), 2.45 (4H, brs), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.62 (4H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.39-6.43 (1H, m), 6.77-6.83 (2H, m), 6.93 (1H, d, *J* = 9.0 Hz), 7.03-7.12 (3H, m), 7.24-7.32 (7H, m),
30 7.36-7.42 (2H, m), 7.49-7.56 (1H, m), 7.83 (1H, d, *J* = 3.2 Hz).

Example 208

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-

(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.10 (3H, d, *J* = 1.5 Hz), 2.18 (3H, s), 2.28 (3H, s), 2.45 (4H, brs), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.62 (4H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.39-6.43 (1H, m), 6.77-6.83 (2H, m), 6.93 (1H, d, *J* = 9.0 Hz), 7.03-7.12 (3H, m), 7.24-7.32 (7H, m),
5 7.36-7.42 (2H, m), 7.49-7.56 (1H, m), 7.83 (1H, d, *J* = 3.2 Hz).

Example 209

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

- 10 ¹H-NMR (CDCl₃) δ: 1.80 (3H, d, *J* = 1.5 Hz), 1.95 (3H, d, *J* = 1.5 Hz), 2.17 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.40-2.55 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.54 (4H, m), 3.73 (2H, brs), 4.14 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.76-6.82 (2H, m), 6.88 (1H, dd, *J* = 8.8, 0.5 Hz), 6.96-6.99 (1H, m), 7.00-7.08 (2H, m), 7.10 (1H, d, *J* = 1.7 Hz), 7.15-7.32 (8H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.81 (1H, d, *J* = 2.7 Hz).

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Example 210

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one

- 20 ¹H-NMR (CDCl₃) δ: 1.80 (3H, d, *J* = 1.5 Hz), 1.95 (3H, d, *J* = 1.5 Hz), 2.17 (3H, s), 2.36 (3H, s), 2.40-2.56 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.55 (4H, m), 3.73 (2H, brs), 4.13 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.79-6.86 (2H, m), 6.88 (1H, dd, *J* = 8.8, 0.5 Hz), 6.91-7.00 (3H, m), 7.10 (1H, d, *J* = 1.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.24-7.32 (6H, m), 7.35 (1H, dd, *J* = 8.8, 3.2 Hz), 7.81 (1H, dd, *J* = 2.9, 0.5 Hz).

25 Example 211

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one

- 30 ¹H-NMR (CDCl₃) δ: 1.80 (3H, d, *J* = 1.5 Hz), 1.96 (3H, d, *J* = 1.5 Hz), 2.18 (3H, s), 2.40-2.55 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.55 (4H, m), 3.73 (2H, brs), 4.13 (2H, t, *J* = 7.1 Hz), 5.15 (2H, s), 6.79-6.86 (2H, m), 6.89-7.00 (4H, m), 7.11 (1H, d, *J* = 2.0 Hz), 7.24-7.32 (6H, m), 7.36-7.43 (2H, m), 7.49-7.55 (1H, m), 7.84 (1H, d, *J* = 3.2 Hz).

Example 212

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-

(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 1.80 (3H, d, *J* = 1.5 Hz), 1.96 (3H, d, *J* = 1.5 Hz),
2.17 (3H, s), 2.38-2.56 (4H, m), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.55
(4H, m), 3.74 (2H, brs), 4.15 (2H, t, *J* = 7.1 Hz), 5.15 (2H, s), 6.80-6.87 (2H, m), 6.91 (1H, d, *J* =
5 8.8 Hz), 6.98 (1H, d, *J* = 1.5 Hz), 7.09-7.16 (3H, m), 7.24-7.32 (6H, m), 7.35-7.43 (2H, m), 7.49-
7.55 (1H, m), 7.84 (1H, d, *J* = 2.9 Hz).

Example 213

10 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-(4-
{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.80 (3H, d, *J* = 1.5 Hz), 1.95 (3H, d, *J* = 1.5 Hz), 2.18 (3H, s), 2.28 (3H, s),
2.38-2.55 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.55 (4H, m), 3.73 (2H, brs), 4.14 (2H, t, *J* =
7.1 Hz), 5.25 (2H, s), 6.78-6.82 (2H, m), 6.91 (1H, d, *J* = 8.8 Hz), 6.96-6.99 (1H, m), 7.03-7.09
(2H, m), 7.10 (1H, d, *J* = 2.0 Hz), 7.24-7.32 (6H, m), 7.35-7.43 (2H, m), 7.49-7.55 (1H, m), 7.84
15 (1H, d, *J* = 2.9 Hz).

Example 214

(E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-
methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

20 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 1.0 Hz), 2.28 (3H, s), 2.44 (4H, dt, *J* = 17.3,
4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.56 (4H, m), 3.66-3.76 (2H, m), 4.14 (2H, t, *J* = 7.1 Hz),
5.14 (2H, s), 6.24 (1H, d, *J* = 1.0 Hz), 6.76-6.82 (2H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.06 (2H, d, *J*
= 8.3 Hz), 7.23-7.32 (7H, m), 7.34-7.42 (3H, m), 7.49-7.55 (1H, m), 7.82 (1H, d, *J* = 2.7 Hz).

25 Example 215

(E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-
chlorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 0.7 Hz), 2.44 (4H, dt, *J* = 16.8, 5.1 Hz), 3.08
(2H, t, *J* = 7.1 Hz), 3.49-3.56 (4H, m), 3.66-3.77 (2H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s),
30 6.24 (1H, s), 6.79-6.85 (2H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.20-7.32 (9H, m), 7.34-7.42 (3H, m),
7.50-7.55 (1H, m), 7.82 (1H, d, *J* = 3.2 Hz).

Example 216

(E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-

fluorophenoxy)ethyl]benzyl}piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 1.0 Hz), 2.44 (4H, dt, *J* = 16.6, 4.5 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.57 (4H, m), 3.68-3.76 (2H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.24 (1H, d, *J* = 1.2 Hz), 6.80-6.87 (2H, m), 6.91-7.00 (3H, m), 7.20-7.32 (7H, m), 7.34-7.42 (3H, m), 7.49-7.54 (1H, m), 7.82 (1H, d, *J* = 3.2 Hz).

Example 217

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.22 (3H, d, *J* = 1.0 Hz), 2.44 (4H, dt, *J* = 16.4, 4.6 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.49-3.57 (4H, m), 3.68-3.74 (2H, m), 3.76 (3H, s), 4.12 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.24 (1H, s), 6.79-6.87 (4H, m), 6.94 (1H, d, *J* = 8.8 Hz), 7.34-7.43 (7H, m), 7.34-7.42 (3H, m), 7.49-7.55 (1H, m), 7.82 (1H, d, *J* = 3.2 Hz).

15 Example 218

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.22 (3H, d, *J* = 1.0 Hz), 2.40-2.50 (4H, m), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.49-3.56 (4H, m), 3.68-3.75 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.23 (1H, d, *J* = 1.2 Hz), 6.80-6.86 (2H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.10-7.16 (2H, m), 7.20-7.32 (7H, m), 7.34-7.42 (3H, m), 7.49-7.54 (1H, m), 7.82 (1H, d, *J* = 2.9 Hz).

Example 219

²⁵ (*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.77-6.86 (3H, m), 6.90-7.00 (3H, m), 7.02-7.10 (2H, m), 7.15 (1H, d, *J* = 8.5 Hz), 7.22-7.32 (4H, m), 7.32-7.42 (4H, m), 7.56-7.63 (2H, m), 7.84 (1H, d, *J* = 3.2 Hz).

Example 220

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.8 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.77-6.87 (3H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.03-7.17 (5H, m), 7.22-7.29 (4H, m), 7.34-7.42 (4H, m), 7.56-7.63 (2H, m), 7.84 (1H, d, *J* = 2.9 Hz).

5

Example 221

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.28 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s),
 10 3.60-3.80 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.76-6.84 (3H, m), 6.95 (1H, dd, *J* = 9.0, 0.5 Hz), 7.03-7.11 (4H, m), 7.15 (1H, d, *J* = 8.3 Hz), 7.22-7.30 (4H, m), 7.33-7.42 (4H, m), 7.56-7.62 (2H, m), 7.84 (1H, d, *J* = 2.7 Hz).

Example 222

15 4-{{(6-{2-Chloro-4-[(*E*)-3-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 1.39 (3H, t, *J* = 7.1 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz),
 3.52 (2H, s), 3.60-3.80 (4H, m), 4.00 (2H, q, *J* = 7.1 Hz), 4.15 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s),
 6.44-6.51 (3H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.97 (1H, dd, *J* = 8.8, 0.5 Hz), 7.11-7.18 (2H, m),
 20 7.22-7.30 (4H, m), 7.34-7.42 (2H, m), 7.49-7.55 (2H, m), 7.56-7.62 (2H, m), 7.67-7.71 (2H, m), 7.82 (1H, dd, *J* = 2.9, 0.5 Hz).

Example 223

25 4-{{(6-{2-Chloro-4-[(*E*)-3-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.48 (4H, t, *J* = 4.9 Hz), 3.09 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80
 (4H, m), 3.78 (3H, s), 4.16 (2H, t, *J* = 7.1 Hz), 5.11 (2H, s), 6.45-6.53 (3H, m), 6.80 (1H, d, *J* =
 15.4 Hz), 6.97 (1H, dd, *J* = 9.0, 0.5 Hz), 7.13-7.20 (2H, m), 7.22-7.30 (4H, m), 7.34-7.42 (2H,
 m), 7.50-7.55 (2H, m), 7.56-7.62 (2H, m), 7.64-7.72 (2H, m), 7.82 (1H, dd, *J* = 2.9, 0.5 Hz).

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Example 224

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.40 (3H, t, *J* = 7.1 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz),

3.52 (2H, s), 3.60-3.80 (4H, m), 4.00 (2H, q, $J = 7.1$ Hz), 4.15 (2H, t, $J = 7.1$ Hz), 5.01 (2H, s), 6.44-6.51 (3H, m), 6.80 (1H, d, $J = 15.4$ Hz), 6.95 (1H, d, $J = 8.8$ Hz), 7.02-7.11 (2H, m), 7.11-7.18 (2H, m), 7.22-7.30 (4H, m), 7.33-7.42 (4H, m), 7.56-7.63 (2H, m), 7.84 (1H, d, $J = 2.9$ Hz).

5 Example 225

(*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.40 (3H, t, $J = 7.1$ Hz), 2.11 (6H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.00 (2H, q, $J = 7.1$ Hz), 4.15 (2H, t, $J = 7.1$ Hz),
10 5.25 (2H, d, $J = 0.7$ Hz), 6.44-6.51 (3H, m), 6.78 (1H, d, $J = 15.4$ Hz), 6.83 (1H, d, $J = 9.0$ Hz), 7.15 (1H, t, $J = 8.1$ Hz), 7.23-7.29 (6H, m), 7.33 (1H, dd, $J = 9.0, 3.2$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.83 (1H, d, $J = 2.9$ Hz), 7.87 (1H, d, $J = 0.7$ Hz), 8.83 (1H, d, $J = 0.5$ Hz).

Example 226

15 (*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.21 (6H, d, $J = 6.8$ Hz), 2.11 (6H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.8$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 2.60-3.80 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.25 (2H, s), 6.78 (1H, d, $J = 15.4$ Hz), 6.81-6.86 (3H, m), 7.10-7.16 (2H, m), 7.23-7.30
20 (6H, m), 7.33 (1H, dd, $J = 9.0, 3.2$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.83 (1H, d, $J = 3.2$ Hz), 7.87 (1H, s), 8.83 (1H, s).

Example 227

25 (*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.11 (6H, s), 2.28 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.25 (2H, d, $J = 0.7$ Hz), 6.75-6.85 (4H, m), 7.04-7.10 (2H, m), 7.24-7.30 (6H, m), 7.33 (1H, dd, $J = 9.0, 3.2$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.83 (1H, d, $J = 2.7$ Hz), 7.87 (1H, d, $J = 0.7$ Hz), 8.83 (1H, d, $J = 0.5$ Hz).

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Example 228

(*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 2.12 (6H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s),

3.60-3.80 (4H, m), 4.13 (2H, t, $J = 7.1$ Hz), 5.25 (2H, d, $J = 0.7$ Hz), 6.78 (1H, d, $J = 15.4$ Hz), 6.81-6.86 (3H, m), 6.92-6.99 (2H, m), 7.22-7.30 (6H, m), 7.33 (1H, dd, $J = 9.0, 3.2$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.80-7.85 (1H, m), 7.87 (1H, d, $J = 0.7$ Hz), 8.83 (1H, d, $J = 0.7$ Hz).

5 Example 229

(*E*)-3-(3,5-Dimethyl-4-{{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl}-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ : 1.29 (6H, d, $J = 5.9$ Hz), 2.11 (6H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.12 (2H, t, $J = 7.1$ Hz), 4.41 (1H, septet, $J = 5.9$ Hz),
10 5.25 (2H, d, $J = 0.7$ Hz), 6.78 (1H, d, $J = 15.4$ Hz), 6.81-6.85 (5H, m), 7.24-7.30 (6H, m), 7.33 (1H, dd, $J = 9.0, 3.2$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.83 (1H, d, $J = 3.2$ Hz), 7.87 (1H, d, $J = 0.7$ Hz), 8.83 (1H, d, $J = 0.5$ Hz).

Example 230

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 132.9-133.6 °C

¹H-NMR (CDCl₃) δ : 2.07-2.11 (2H, m), 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.80 (2H, t, $J = 7.3$ Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.92 (2H, t, $J = 6.4$ Hz), 4.98 (2H, s), 6.77-
20 6.85 (3H, m), 6.90-6.99 (3H, m), 7.16-7.20 (4H, m), 7.23-7.30 (5H, m), 7.34-7.37 (1H, m), 7.45 (1H, d, $J = 2.2$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.79-7.80 (1H, m).

Example 231

25 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{3-[4-(propan-2-yl)phenoxy]propyl}benzyl)piperazin-1-yl]prop-2-en-1-one

mp: 108.6-109.2 °C

¹H-NMR (CDCl₃) δ : 1.22 (6H, d, $J = 6.8$ Hz), 2.07-2.11 (2H, m), 2.18 (3H, s), 2.35 (3H, s), 2.47 (4H, t, $J = 4.9$ Hz), 2.80 (2H, t, $J = 7.6$ Hz), 2.85 (1H, septet, $J = 6.8$ Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.95 (2H, t, $J = 6.4$ Hz), 4.98 (2H, s), 6.77-6.85 (3H, m), 6.91 (1H, d, $J = 9.0$ Hz), 7.11-
30 7.15 (2H, m), 7.17-7.20 (4H, m), 7.23-7.30 (5H, m), 7.35 (1H, dd, $J = 9.0, 2.9$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 232

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[3-(4-

fluorophenoxy)propyl]benzyl}piperazin-1-yl]prop-2-en-1-one

mp: 110.6-112.3 °C

¹H-NMR (CDCl₃) δ: 2.07-2.11 (2H, m), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.80 (2H, t, *J* = 7.3 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.92 (2H, t, *J* = 6.4 Hz), 5.14 (2H, s), 6.78-6.85 (3H, m),
5 6.93-6.99 (3H, m), 7.17 (2H, d, *J* = 8.3 Hz), 7.23-7.32 (5H, m), 7.37-7.41 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.50-7.53 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81-7.82 (1H, m).

Example 233

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{3-[4-
10 (propan-2-yl)phenoxy]propyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.07-2.11 (2H, m), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.80 (2H, t, *J* = 7.6 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.95 (2H, t, *J* = 6.4 Hz), 5.14 (2H, s), 6.78-6.85 (3H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.13 (2H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.23-7.31 (5H, m), 7.37-7.40 (2H, m), 7.45 (1H, d, *J* = 2.0
15 Hz), 7.50-7.53 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 234

4-{{[(6-{2-Chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(3-phenoxypropyl)benzyl]piperazin-1-yl}prop-
1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile
20 ¹H-NMR (CDCl₃) δ: 2.11 (2H, tt, *J* = 6.9, 6.9 Hz), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 2.81 (2H, t, *J* = 6.9 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.97 (2H, t, *J* = 6.9 Hz), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.89-6.96 (4H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.23-7.30 (5H, m), 7.37 (1H, ddd, *J* = 8.9, 3.1, 1.0 Hz), 7.45 (1H, s), 7.51-7.58 (3H, m), 7.68 (2H, d, *J* = 7.8 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

25

Example 235

4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-
1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile
30 ¹H-NMR (CDCl₃) δ: 2.06-2.13 (2H, m), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.80 (2H, t, *J* = 7.6 Hz), 3.52 (2H, s), 3.65-3.75 (4H, m), 3.93 (2H, t, *J* = 6.2 Hz), 5.10 (2H, s), 6.78-6.85 (3H, m), 6.93-7.00 (3H, m), 7.18 (2H, d, *J* = 8.2 Hz), 7.25 (2H, d, *J* = 8.2 Hz), 7.29 (1H, d, *J* = 2.0 Hz), 7.37 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.52 (2H, dd, *J* = 7.9, 0.6 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.69 (2H, dt, *J* = 8.2, 1.7 Hz), 7.77 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 236

4-({[6-(2-Chloro-4-{(E)-3-[4-(4-{3-[(6-chloropyridin-3-yl)oxy]propyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.09-2.16 (2H, m), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.81 (2H, t, *J* = 7.6 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 3.99 (2H, t, *J* = 6.2 Hz), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 7.15-7.18 (3H, m), 7.21-7.26 (3H, m), 7.29 (1H, d, *J* = 1.5 Hz), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.52 (2H, d, *J* = 8.3 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.67-7.69 (2H, m), 7.76 (1H, d, *J* = 3.2 Hz), 8.03 (1H, d, *J* = 2.9 Hz).

10 Example 237

4-({[6-(2-Chloro-6-methyl-4-{(E)-3-[4-(4-{3-[(6-methylpyridin-3-yl)oxy]propyl}benzyl)-piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.07-2.14 (2H, m), 2.19 (3H, s), 2.47-2.49 (7H, m), 2.81 (2H, t, *J* = 7.6 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.98 (2H, t, *J* = 6.2 Hz), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.95 (1H, dd, *J* = 8.9, 0.6 Hz), 7.05 (1H, d, *J* = 8.3 Hz), 7.09 (1H, dd, *J* = 8.5, 2.9 Hz), 7.17 (2H, d, *J* = 8.1 Hz), 7.24 (2H, d, *J* = 8.3 Hz), 7.29 (1H, t, *J* = 1.1 Hz), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.51-7.59 (3H, m), 7.68 (2H, dt, *J* = 8.2, 1.8 Hz), 7.76 (1H, dd, *J* = 3.2, 0.5 Hz), 8.18 (1H, dd, *J* = 2.9, 0.7 Hz).

20 Example 238

4-({[6-(2-Chloro-6-methyl-4-{(E)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.05-2.12 (2H, m), 2.19 (3H, s), 2.28 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 2.80 (2H, t, *J* = 7.6 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.94 (2H, t, *J* = 6.2 Hz), 5.09 (2H, s), 6.78-6.82 (3H, m), 6.95 (1H, d, *J* = 9.0 Hz), 7.07 (2H, d, *J* = 8.4 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.24 (2H, d, *J* = 8.1 Hz), 7.29 (1H, d, *J* = 1.7 Hz), 7.37 (1H, dd, *J* = 8.9, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.51-7.58 (3H, m), 7.68 (2H, dt, *J* = 8.4, 1.7 Hz), 7.77 (1H, d, *J* = 3.2 Hz).

Example 239

30 4-({[6-(2-Chloro-6-methyl-4-{(E)-3-oxo-3-[4-(4-{3-[4-(propan-2-yl)phenoxy]propyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.22 (3H, s), 1.23 (3H, s), 2.06-2.13 (2H, m), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.78-2.91 (3H, m), 3.51 (2H, s), 3.64-3.74 (4H, m), 3.95 (2H, t, *J* = 6.3 Hz), 5.09 (2H, s), 6.78-6.85 (3H, m), 6.95 (1H, dd, *J* = 9.0, 0.5 Hz), 7.13 (2H, dt, *J* = 9.4, 2.4 Hz), 7.18 (2H, d, *J*

= 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz), 7.29 (1H, d, J = 2.0 Hz), 7.37 (1H, dd, J = 9.0, 3.1 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.51-7.59 (3H, m), 7.68 (2H, dt, J = 8.3, 1.7 Hz), 7.77 (1H, dd, J = 3.1, 0.5 Hz).

5 Example 240

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-({4-[2-(4-methylphenoxy)ethyl]phenyl}amino)piperidin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.36-1.49 (2H, m), 2.10-2.21 (5H, m), 2.28 (3H, s), 2.36 (3H, s), 2.93-3.07 (3H, m), 3.22-3.60 (3H, m), 4.00-4.11 (3H, m), 4.50-4.64 (1H, m), 4.98 (2H, s), 6.56-6.62 (2H, m), 6.76-6.82 (2H, m), 6.83 (1H, d, J = 15.4 Hz), 6.92 (1H, dd, J = 9.0, 0.5 Hz), 7.20-7.12 (4H, m), 7.18 (2H, d, J = 7.8 Hz), 7.24-7.31 (3H, m), 7.35 (1H, dd, J = 9.0, 3.2 Hz), 7.46 (1H, d, J = 2.2 Hz), 7.57 (1H, d, J = 15.1 Hz), 7.79 (1H, dd, J = 2.9, 0.5 Hz).

Example 241

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-({4-[2-(4-fluorophenoxy)ethyl]phenyl}amino)piperidin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.34-1.48 (2H, m), 2.10-2.20 (5H, m), 2.35 (3H, s), 2.92-3.07 (3H, m), 3.20-3.39 (1H, m), 3.42-3.60 (2H, m), 4.00-4.11 (3H, m), 4.48-4.64 (1H, m), 4.98 (2H, s), 6.56-6.62 (2H, m), 6.78-6.88 (3H, m), 6.90-6.99 (3H, m), 7.06-7.12 (2H, m), 7.18 (2H, d, J = 7.8 Hz), 7.26-7.31 (3H, m), 7.35 (1H, dd, J = 9.0, 3.2 Hz), 7.46 (1H, d, J = 2.2 Hz), 7.57 (1H, d, J = 15.4 Hz), 7.79 (1H, dd, J = 2.4, 0.5 Hz).

Example 242

25 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.20 (6H, d, J = 6.8 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.49 (4H, t, J = 4.9 Hz), 2.80 (1H, septet, J = 6.8 Hz), 2.90 (2H, t, J = 7.1 Hz), 3.38 (2H, t, J = 7.1 Hz), 3.52 (2H, s), 3.60-3.82 (5H, m), 4.98 (2H, s), 6.54-6.60 (2H, m), 6.79 (1H, d, J = 15.4 Hz), 6.91 (1H, dd, J = 8.8, 0.5 Hz), 7.01-7.08 (2H, m), 7.16-7.22 (4H, m), 7.25-7.30 (5H, m), 7.35 (1H, dd, J = 9.0, 3.2 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 15.4 Hz), 7.79 (1H, dd, J = 3.2, 0.5 Hz).

Example 243

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.20 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.80 (1H, septet, *J* = 7.1 Hz), 2.91 (2H, t, *J* = 7.1 Hz), 3.38 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.52-3.80 (5H, m), 5.14 (2H, s), 6.54-6.60 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, dd, *J* = 8.8, 0.5 Hz), 7.01-7.08 (2H, m), 7.16-7.22 (2H, m), 7.22-7.32 (5H, m), 7.36-7.42 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.48-7.54 (1H, m), 7.56 (1H, d, *J* = 15.4 Hz), 7.81 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 244

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(2-{methyl[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.76-2.90 (6H, m), 3.49-3.56 (4H, m), 3.60-3.80 (4H, m), 4.98 (2H, s), 6.66-6.72 (2H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.91 (1H, dd, *J* = 9.0, 0.5 Hz), 7.08-7.14 (2H, m), 7.15-7.21 (4H, m), 7.24-7.32 (5H, m), 7.35 (1H, dd, *J* = 8.8, 3.2 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.78 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 245

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorophenyl)(methyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.78-2.90 (5H, m), 3.48-3.55 (4H, m), 3.60-3.80 (4H, m), 5.14 (2H, s), 6.60-6.67 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.90-6.98 (3H, m), 7.15 (2H, d, *J* = 8.1 Hz), 7.22-7.31 (5H, m), 7.36-7.42 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.49-7.55 (1H, m), 7.56 (1H, d, *J* = 15.1 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

Example 246

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.90 (2H, t, *J* = 7.1 Hz), 3.36 (2H, t, *J* = 7.1 Hz), 3.50-3.80 (7H, m), 5.14 (2H, s), 6.51-6.56 (2H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.85-6.91 (2H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.24-7.31 (5H, m), 7.35-7.41 (2H, m), 7.45 (1H, d, *J* = 1.7 Hz), 7.49-7.54 (1H, m), 7.56 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

Example 247

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-

fluorophenyl)(methyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.78-2.90 (5H, m), 3.47-3.55 (4H, m), 3.60-3.80 (4H, m), 4.98 (2H, s), 6.60-6.66 (2H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.88-6.98 (3H, m), 7.12-7.21 (4H, m), 7.20-7.32 (5H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 248

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.49 (4H, t, *J* = 4.9 Hz), 2.90 (2H, t, *J* = 6.8 Hz), 3.36 (2H, t, *J* = 6.8 Hz), 3.50-3.80 (7H, m), 4.98 (2H, s), 6.50-6.58 (2H, m), 6.79 (1H, d, *J* = 15.4 Hz), 6.84-6.94 (3H, m), 7.18 (4H, d, *J* = 7.8 Hz), 7.24-7.31 (5H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.56 (1H, d, *J* = 15.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

15 Example 249

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.49 (4H, t, *J* = 4.9 Hz), 2.90 (2H, t, *J* = 6.8 Hz), 3.36 (2H, t, *J* = 7.1 Hz), 3.49-3.80 (7H, m), 5.01 (2H, s), 6.50-6.58 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.84-6.92 (2H, m), 6.95 (1H, dd, *J* = 8.8, 0.5 Hz), 7.04-7.11 (2H, m), 7.15 (1H, d, *J* = 8.3 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.24-7.30 (2H, m), 7.33-7.42 (4H, m), 7.56-7.63 (2H, m), 7.84 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 250

4-({[6-(2-Chloro-4-({*E*)-3-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

- ¹H-NMR (CDCl₃) δ: 2.49 (4H, t, *J* = 4.9 Hz), 2.90 (2H, t, *J* = 6.8 Hz), 3.36 (2H, t, *J* = 7.1 Hz), 3.49-3.80 (7H, m), 5.11 (2H, s), 6.50-6.57 (2H, m), 6.80 (1H, d, *J* = 15.4 Hz), 6.85-6.92 (2H, m), 6.97 (1H, dd, *J* = 8.8, 0.5 Hz), 7.12-7.21 (3H, m), 7.24-7.30 (2H, m), 7.33-7.43 (2H, m), 7.49-7.55 (2H, m), 7.57-7.62 (2H, m), 7.66-7.71 (2H, m), 7.82 (1H, d, *J* = 2.9 Hz).

30

Example 251

4-({[6-(2-Chloro-4-({*E*)-3-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.49 (4H, t, *J* = 4.9 Hz), 2.90 (2H, t, *J* = 6.8 Hz), 3.36 (2H, t, *J* = 7.1 Hz),

3.43 (1H, brs), 3.52 (2H, s), 3.60-3.80 (7H, m), 5.11 (2H, s), 6.55-6.61 (2H, m), 6.75-6.84 (3H, m), 6.97 (1H, d, $J = 8.8$ Hz), 7.15 (1H, d, $J = 8.3$ Hz), 7.18 (2H, d, $J = 8.1$ Hz), 7.24-7.30 (2H, m), 7.35-7.42 (2H, m), 7.52 (2H, d, $J = 15.6$ Hz), 7.55-7.63 (2H, m), 7.66-7.71 (2H, m), 7.82 (1H, d, $J = 3.2$ Hz).

5

Example 252

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.49 (4H, t, $J = 4.9$ Hz), 2.90 (2H, t, $J = 6.8$ Hz), 3.36 (2H, t, $J = 7.1$ Hz),
10 3.40-3.60 (3H, m), 3.60-3.80 (7H, m), 5.01 (2H, s), 6.56-6.62 (2H, m), 6.75-6.84 (3H, m), 6.95 (1H, d, $J = 9.0$ Hz), 7.04-7.11 (2H, m), 7.15 (1H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.1$ Hz), 7.24-7.30 (2H, m), 7.33-7.42 (4H, m), 7.56-7.63 (2H, m), 7.84 (1H, d, $J = 3.2$ Hz).

Example 253

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.49 (4H, t, $J = 4.9$ Hz), 2.90 (2H, t, $J = 6.8$ Hz),
3.36 (2H, t, $J = 7.1$ Hz), 3.40-3.50 (3H, m), 3.60-3.80 (7H, m), 4.98 (2H, s), 6.56-6.61 (2H, m),
6.76-6.82 (3H, m), 6.91 (1H, d, $J = 8.8$ Hz), 7.18 (4H, d, $J = 8.1$ Hz), 7.24-7.31 (5H, m), 7.35 (1H,
20 dd, $J = 9.0, 3.2$ Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 254

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)phenyl]amino}piperidin-1-yl)prop-2-en-1-one

25 ¹H-NMR (CDCl₃) δ: 1.20 (6H, d, $J = 6.8$ Hz), 1.32-1.48 (2H, m), 2.10-2.22 (5H, m), 2.35 (3H, s), 2.75-2.85 (3H, m), 2.90-3.10 (1H, m), 3.22-3.38 (3H, m), 3.41-3.60 (3H, m), 4.00-4.11 (1H, m), 4.49-4.67 (1H, m), 4.98 (2H, s), 6.53-6.62 (4H, m), 6.84 (1H, d, $J = 15.4$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 7.01-7.08 (4H, m), 7.18 (2H, d, $J = 7.8$ Hz), 7.26-7.31 (3H, m), 7.35 (1H, dd, $J = 9.0, 3.2$ Hz), 7.46 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 3.2$ Hz).

30

Example 255

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.52 (4H, t, $J = 5.0$ Hz), 3.60-3.80 (6H, m), 3.85 (3H, s), 5.14

(2H, s), 6.80 (1H, d, $J = 15.6$ Hz), 6.91-6.98 (3H, m), 7.05 (1H, d, $J = 8.7$ Hz), 7.13-7.21 (2H, m), 7.22-7.32 (2H, m), 7.36-7.42 (2H, m), 7.46 (1H, d, $J = 1.8$ Hz), 7.48-7.69 (4H, m), 7.76 (1H, d, $J = 8.2$ Hz), 7.81 (1H, d, $J = 3.2$ Hz), 8.02 (1H, s), 8.07 (1H, d, $J = 8.7$ Hz).

5 Example 256

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-({2-[4-(propan-2-yl)phenoxy]quinolin-6-yl}methyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.29 (6H, d, $J = 6.9$ Hz), 2.53 (4H, t, $J = 5.0$ Hz), 2.96 (1H, septet, $J = 6.9$ Hz), 3.60-3.82 (6H, m), 5.14 (2H, s), 6.80 (1H, d, $J = 15.6$ Hz), 6.94 (1H, d, $J = 8.7$ Hz), 7.05 (1H, d, $J = 8.7$ Hz), 7.12-7.19 (2H, m), 7.24-7.32 (5H, m), 7.36-7.42 (2H, m), 7.46 (1H, d, $J = 1.8$ Hz), 7.49-7.54 (1H, m), 7.57 (1H, d, $J = 15.6$ Hz), 7.63 (1H, dd, $J = 8.7, 1.8$ Hz), 7.67 (1H, s), 7.76-7.84 (2H, m), 8.08 (1H, d, $J = 8.7$ Hz).

Example 257

15 4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 2.52 (4H, t, $J = 4.9$ Hz), 3.60-3.80 (6H, m), 3.84 (3H, s), 5.11 (2H, s), 6.80 (1H, d, $J = 15.6$ Hz), 6.92-6.99 (3H, m), 7.04 (1H, d, $J = 8.8$ Hz), 7.12-7.20 (3H, m), 7.34-7.42 (2H, m), 7.49-7.55 (2H, m), 7.57-7.64 (3H, m), 7.65-7.71 (3H, m), 7.76 (1H, d, $J = 8.8$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 8.07 (1H, d, $J = 8.8$ Hz).

Example 258

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

25 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.46 (4H, t, $J = 4.9$ Hz), 3.47 (2H, s), 3.63-3.73 (4H, m), 5.14 (2H, s), 5.22 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.88-6.92 (2H, m), 6.95 (1H, d, $J = 8.8$ Hz), 7.15-7.21 (2H, m), 7.23-7.32 (5H, m), 7.38-7.41 (2H, m), 7.45 (1H, d, $J = 2.2$ Hz), 7.51-7.53 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz), 8.04-8.09 (2H, m).

30 Example 259

(*E*)-3-[4-({5-[(3,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(4-methylphenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 117.5-118.4 °C

Example 260

(*E*)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-methylphenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.21 (3H, s), 2.43-2.46 (7H, m), 3.47 (2H, s), 3.63-3.73 (4H, m), 5.16 (2H, s), 5.25 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.87-6.92 (3H, m), 6.98 (1H, d, *J* = 8.3 Hz), 7.21-7.27 (3H, m), 7.30 (2H, d, *J* = 8.1 Hz), 7.34-7.37 (2H, m), 7.41 (1H, d, *J* = 2.0 Hz), 7.45 (2H, d, *J* = 8.1 Hz), 7.63 (1H, d, *J* = 15.4 Hz), 7.89-7.93 (3H, m).

Example 261

4-{{[(6-{2-Fluoro-4-[(*E*)-3-(4-{4-[2-(4-methylphenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile
mp: 140.3-141.4 °C

Example 262

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[2-(4-methylphenyl)-ethoxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one
mp: 142.2-142.9 °C

Example 263

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(3,4-dichlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.03 (2H, t, *J* = 6.4 Hz), 3.50 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 6.4 Hz), 6.79 (1H, d, *J* = 15.5 Hz), 6.91 (1H, d, *J* = 8.9 Hz), 7.10 (1H, dd, *J* = 8.2, 2.0 Hz), 7.28-7.32 (6H, m), 7.37-7.38 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.2 Hz), 7.71 (1H, d, *J* = 3.0 Hz).

Example 264

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.40-1.43 (1H, m), 2.20 (3H, s), 2.47-2.50 (4H, m), 2.88 (2H, t, *J* = 6.6 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 3.85-3.90 (2H, m), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 7.19-7.32 (7H, m), 7.38-7.59 (5H, m), 7.81 (1H, d, *J* = 2.9 Hz).

35 Example 265

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.51 (4H, m), 3.52 (2H, s), 3.64-3.67 (2H, m), 3.74-3.77 (2H, m), 5.13 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.92-6.99 (5H, m), 7.25-7.31 (7H, m), 7.38-7.40 (2H, m), 7.46 (1H, d, *J* = 1.5 Hz), 7.50-7.53 (1H, m), 7.58 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 266

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.48-2.49 (4H, m), 3.52 (2H, s), 3.64-3.67 (2H, m), 3.74-3.76 (2H, m), 4.98 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.91-6.97 (5H, m), 7.17-7.20 (2H, m), 7.26-7.30 (7H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 1.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 267

(*E*)-1-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.52-2.53 (4H, m), 3.59 (2H, s), 3.66-3.68 (2H, m), 3.76-3.78 (2H, m), 5.14 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.25-7.47 (11H, m), 7.50-7.62 (6H, m), 7.81 (1H, d, *J* = 2.9 Hz).

Example 268

(*E*)-1-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.52-2.53 (4H, m), 3.59 (2H, s), 3.65-3.68 (2H, m), 3.76-3.78 (2H, m), 4.98 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.26-7.46 (10H, m), 7.55-7.62 (5H, m), 7.79 (1H, d, *J* = 2.9 Hz).

Example 269

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[4-(propan-2-yl)phenoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.48-2.49 (4H, m), 2.87-2.94 (1H, m), 3.51 (2H, s), 3.64-3.66 (2H, m), 3.74-3.76 (2H, m), 4.98 (2H, s), 6.81 (1H, d, *J* =

15.4 Hz), 6.90-6.98 (5H, m), 7.17-7.21 (4H, m), 7.25-7.30 (5H, m), 7.35 (1H, dd, $J = 8.9, 3.1$ Hz), 7.46 (1H, d, $J = 1.0$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

Example 270

5 4-{[(6-{2-Chloro-6-methyl-4-[(*E*)-3-oxo-3-(4-{4-[4-(propan-2-yl)phenoxy]benzyl}piperazin-1-yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

¹H-NMR (CDCl₃) δ: 1.25 (6H, d, $J = 6.8$ Hz), 2.19 (3H, s), 2.53-2.57 (4H, m), 2.88-2.93 (1H, m), 3.57 (2H, s), 3.66-3.69 (2H, m), 3.76-3.78 (2H, m), 5.09 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.92-6.97 (5H, m), 7.19 (2H, d, $J = 8.3$ Hz), 7.24-7.30 (3H, m), 7.37 (1H, dd, $J = 8.9, 3.1$ Hz),
10 7.45 (1H, d, $J = 1.5$ Hz), 7.52 (2H, d, $J = 8.1$ Hz), 7.56 (1H, d, $J = 15.4$ Hz), 7.68 (2H, d, $J = 8.1$ Hz), 7.77 (1H, d, $J = 2.9$ Hz).

Example 271

15 (*E*)-3-[4-({5-[(2,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenyl]ethoxy}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.8$ Hz), 2.48 (4H, t, $J = 5.0$ Hz), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.63-3.75 (4H, m), 4.15 (2H, t, $J = 7.0$ Hz), 5.06 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.82-6.88 (3H, m), 6.88-6.93 (1H, m), 6.96 (1H, dd, $J = 8.8, 0.5$ Hz), 7.11-7.15 (2H, m), 7.19 (1H, t, $J = 8.1$ Hz), 7.23-7.30 (5H, m), 7.33 (1H, dd, $J = 11.4, 2.1$ Hz), 7.37 (1H, dd, $J = 8.9, 3.1$ Hz), 7.41-7.47 (1H, m), 7.60 (1H, d, $J = 15.4$ Hz), 7.84 (1H, dd, $J = 3.2, 0.5$ Hz).

Example 272

25 (*E*)-3-[4-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenyl]ethoxy}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 7.1$ Hz), 2.48 (4H, t, $J = 5.0$ Hz), 2.85 (1H, septet, $J = 7.1$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, $J = 7.0$ Hz), 5.13 (2H, s), 6.79 (1H, d, $J = 15.6$ Hz), 6.82-6.85 (2H, m), 6.97 (1H, d, $J = 9.0$ Hz), 7.08-7.30 (11H, m), 7.33 (1H, dd, $J = 11.2, 2.0$ Hz), 7.38 (1H, dd, $J = 8.9, 3.1$ Hz), 7.60 (1H, d, $J = 15.4$ Hz), 7.85
30 (1H, d, $J = 3.2$ Hz).

Example 273

4-({[6-(2-Chloro-4-({(*E*)-3-[4-(4-chlorobenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.46-2.47 (4H, m), 3.50 (2H, s), 3.63-3.66 (2H, m), 3.73-3.75 (2H, m), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.96 (1H, d, *J* = 9.0 Hz), 7.26-7.32 (5H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 1.2 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.3 Hz), 7.76 (1H, d, *J* = 2.9 Hz).

5

Example 274

4-({[6-(2-Chloro-6-methyl-4-({(*E*)-3-[4-(4-methylbenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.34 (3H, s), 2.47-2.48 (4H, m), 3.50 (2H, s), 3.64-3.68 (2H, m), 3.71-3.73 (2H, m), 5.09 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 7.14 (2H, d, *J* = 7.8 Hz), 7.21 (2H, d, *J* = 7.8 Hz), 7.29 (1H, s), 7.37 (1H, dd, *J* = 9.0, 2.9 Hz), 7.47-7.55 (4H, m), 7.67 (2H, d, *J* = 8.1 Hz), 7.76 (1H, d, *J* = 2.7 Hz).

10

Example 275

15 (2*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(1*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.39 (3H, s), 3.52 (2H, s), 3.64 (2H, brs), 3.73 (2H, brs), 4.10 (2H, dd, *J* = 6.1, 1.5 Hz), 4.98 (2H, s), 6.28 (1H, dt, *J* = 16.1, 6.1 Hz), 6.61 (1H, d, *J* = 16.1 Hz), 6.79 (1H, d, *J* = 15.4 Hz), 6.91 (1H, dd, *J* = 8.9, 0.6 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.27-7.30 (5H, m), 7.34-7.37 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, dd, *J* = 3.2, 0.6 Hz).

20

Example 276

25 4-({[6-(2,6-Dimethyl-4-({(*E*)-3-[4-(4-methylbenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.35 (3H, s), 2.47-2.48 (4H, m), 3.50 (2H, s), 3.63-3.66 (2H, m), 3.72-3.75 (2H, m), 5.09 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.83 (1H, d, *J* = 8.8 Hz), 7.14 (2H, d, *J* = 7.8 Hz), 7.21 (2H, d, *J* = 8.1 Hz), 7.25-7.26 (2H, m), 7.33 (1H, dd, *J* = 8.9, 3.1 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.60 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

30

Example 277

4-({[6-({4-[(*E*)-3-{4-[4-(4-Chlorophenoxy)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48-2.49 (4H, m), 3.52 (2H, s), 3.65-3.68 (2H, m), 3.74-3.76 (2H, m), 5.09 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.84 (1H, d, *J* = 8.8 Hz), 6.94-6.96 (4H, m), 7.25-7.35 (7H, m), 7.52 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

5

Example 278

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.39 (3H, s), 3.52 (2H, s), 3.65 (2H, 10 brs), 3.73 (2H, brs), 4.10 (2H, dd, *J* = 6.0, 1.3 Hz), 4.98 (2H, s), 6.28 (1H, dt, *J* = 15.9, 6.0 Hz), 6.61 (1H, d, *J* = 15.9 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 7.04-7.09 (2H, m), 7.24-7.39 (9H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 279

15 4-({[6-(4-{(*E*)-3-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 2.11 (6H, s), 2.52-2.53 (4H, m), 3.58 (2H, s), 3.66-3.69 (2H, m), 3.75-3.78 (2H, m), 5.08 (2H, s), 6.79-6.83 (2H, m), 7.25 (2H, s), 7.31-7.36 (2H, m), 7.39-7.46 (4H, m), 7.52 (2H, d, *J* = 8.3 Hz), 7.58-7.61 (5H, m), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

20

Example 280

4-({[6-(4-{(*E*)-3-{4-[4-(2-Hydroxyethyl)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.40-1.41 (1H, m), 2.11 (6H, s), 2.47-2.49 (4H, m), 2.87 (2H, t, *J* = 6.5 Hz), 25 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 3.87-3.88 (2H, m), 5.09 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.84 (1H, d, *J* = 8.9 Hz), 7.20 (2H, d, *J* = 8.1 Hz), 7.26-7.28 (4H, m), 7.33 (1H, dd, *J* = 8.9, 2.9 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.68 (2H, d, *J* = 8.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

30 Example 281

(*E*)-3-(3,5-Dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.42-1.45 (1H, m), 2.12 (6H, s), 2.47-2.49 (4H, m), 2.88 (2H, t, *J* = 6.5 Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 3.87-3.88 (2H, m), 5.06 (2H, s), 6.78 (1H, d,

$J = 15.4$ Hz), 6.84 (1H, d, $J = 8.8$ Hz), 7.20 (2H, d, $J = 8.1$ Hz), 7.26-7.28 (4H, m), 7.33-7.34 (3H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 2.9$ Hz), 8.62 (2H, d, $J = 5.9$ Hz).

Example 282

- 5 (2*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, $J = 5.0$ Hz), 3.39 (3H, s), 3.52 (2H, s), 3.66 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 4.10 (2H, dd, $J = 6.2, 1.5$ Hz), 4.95 (2H, s), 6.28 (1H, dt, $J = 15.9, 6.2$ Hz), 6.61 (1H, d, $J = 15.9$ Hz), 6.76-6.80 (2H, m), 6.91 (2H, dt, $J = 9.1, 2.4$ Hz), 7.24-10 7.37 (9H, m), 7.61 (1H, d, $J = 15.1$ Hz), 7.82 (1H, d, $J = 2.7$ Hz).

Example 283

- (*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one
- 15 ¹H-NMR (CDCl₃) δ: 2.15-2.18 (1H, m), 2.46-2.48 (4H, m), 2.85 (2H, t, $J = 6.7$ Hz), 3.50 (2H, s), 3.63-3.65 (2H, m), 3.72-3.75 (2H, m), 3.79 (3H, s), 3.84 (2H, t, $J = 6.7$ Hz), 5.14 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.90-6.91 (1H, m), 7.08-7.14 (3H, m), 7.19 (2H, d, $J = 8.1$ Hz), 7.26-7.29 (4H, m), 7.34-7.40 (2H, m), 7.50-7.52 (1H, m), 7.63 (1H, d, $J = 15.4$ Hz), 7.86-7.86 (1H, m).

20 Example 284

- (*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.51 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 5.01 (2H, s), 6.51 (1H, t, $J = 73.8$ Hz), 6.80 (1H, d, $J = 15.4$ Hz), 6.93 (1H, 25 d, $J = 8.8$ Hz), 7.13-7.15 (4H, m), 7.21 (2H, d, $J = 7.8$ Hz), 7.29 (1H, brs), 7.36 (1H, dd, $J = 8.8, 2.9$ Hz), 7.41 (2H, d, $J = 8.5$ Hz), 7.45 (1H, brs), 7.56 (1H, d, $J = 15.4$ Hz), 7.78 (1H, d, $J = 2.9$ Hz).

Example 285

- 30 (*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-{4-[4-(propan-2-yloxy)benzyl]piperazin-1-yl}prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 1.34 (6H, d, $J = 6.1$ Hz), 2.19 (3H, s), 2.47 (4H, brs), 3.47 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.54 (1H, septet, $J = 6.1$ Hz), 5.00 (2H, s), 6.51 (1H, t, $J = 73.8$ Hz), 6.80 (1H, d, $J = 15.4$ Hz), 6.85 (2H, d, $J = 8.3$ Hz), 6.93 (1H, d, $J = 8.8$ Hz), 7.14 (2H, d, $J = 8.3$ Hz).

Hz), 7.21 (2H, d, $J = 8.3$ Hz), 7.29 (1H, brs), 7.36 (1H, dd, $J = 8.8, 2.7$ Hz), 7.40 (2H, d, $J = 8.3$ Hz), 7.45 (1H, brs), 7.56 (1H, d, $J = 15.4$ Hz), 7.78 (1H, d, $J = 2.7$ Hz).

Example 286

5 4-{[(6-{2-Chloro-4-[(*E*)-3-{4-[4-(3-hydroxypropyl)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (1H, brs), 1.87-1.94 (2H, m), 2.19 (3H, s), 2.48 (4H, t, $J = 5.0$ Hz), 2.71 (2H, t, $J = 7.8$ Hz), 3.51 (2H, s), 3.64-3.74 (6H, m), 5.09 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.95 (1H, dd, $J = 9.0, 0.5$ Hz), 7.17 (2H, d, $J = 8.1$ Hz), 7.23-7.29 (3H, m), 7.37 (1H, dd, $J = 8.9,$
10 3.1 Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.51-7.58 (3H, m), 7.67-7.70 (2H, m), 7.76-7.77 (1H, m).

Example 287

4-{[(6-{2-Chloro-4-[(*E*)-3-(4-{4-[(*E*)-3-hydroxyprop-1-en-1-yl]benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.52 (1H, brs), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.53 (2H, s), 3.64-3.74 (4H, m), 4.33 (2H, d, $J = 5.7$ Hz), 5.09 (2H, s), 6.37 (1H, dt, $J = 16.0, 5.7$ Hz), 6.62 (1H, d, $J = 16.0$ Hz), 6.80 (1H, d, $J = 15.6$ Hz), 6.96 (1H, d, $J = 8.8$ Hz), 7.26-7.29 (3H, m), 7.35-7.39 (3H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.51-7.59 (3H, m), 7.68 (2H, d, $J = 8.1$ Hz), 7.77 (1H, d, $J = 2.9$ Hz).

20

Example 288

4-{[(6-{2-Chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(1-hydroxy-2-methylpropan-2-yl)oxy]benzyl]-piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ : 1.30 (6H, s), 2.19 (3H, s), 2.47-2.49 (5H, m), 3.49 (2H, s), 3.60 (2H, s),
25 3.65-3.67 (2H, m), 3.74-3.77 (2H, m), 5.09 (2H, s), 6.81 (1H, d, $J = 15.4$ Hz), 6.94-7.05 (3H, m), 7.12 (1H, d, $J = 11.0$ Hz), 7.28-7.29 (1H, m), 7.36-7.38 (1H, m), 7.44-7.47 (1H, m), 7.53-7.57 (3H, m), 7.68 (2H, d, $J = 8.1$ Hz), 7.76 (1H, d, $J = 2.9$ Hz).

[0207]

30 Example 289

To a solution of (*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]-oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoic acid (139 mg) and 4-{2-[4-(piperazin-1-yl)methyl]-phenyl}ethoxy}benzonitrile trifluoroacetate (131 mg) in DMF (6 mL) was added DEPC (0.073 mL) and Et_3N (0.165 mL) at 0 °C. After stirring at 0 °C for 1 hour, to the reaction mixture was

added H₂O, and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to give 4-{2-[4-({4-[(*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoyl]piperazin-1-yl)methyl]phenyl]ethoxy}benzonitrile as a pale yellow amorphous (195 mg).

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, brs), 3.11 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.21 (2H, t, *J* = 7.1 Hz), 5.09 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.92-6.95 (3H, m), 7.25-7.29 (5H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.51-7.59 (5H, m), 7.64 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 3.2 Hz).

10 [0208]

The following compounds were produced in the same manner as in Example 289 using appropriate starting materials.

Example 290

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(2,3-dihydro-1*H*-inden-5-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.02-2.08 (2H, m), 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 2.81-2.88 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.69 (1H, dd, *J* = 8.1, 2.4 Hz), 6.79-6.81 (2H, m), 6.92 (1H, d, *J* = 9.0 Hz), 7.10 (1H, d, *J* = 8.1 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.23-7.28 (7H, m, *J* = 8.6 Hz), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

20

Example 291

25 (*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.26 (3H, s), 2.47 (4H, brs), 3.07 (2H, t, *J* = 7.1 Hz), 3.50 (2H, s), 3.63-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.06 (2H, s), 6.79-6.82 (3H, m), 6.94 (1H, d, *J* = 8.8 Hz), 7.05 (2H, d, *J* = 8.5 Hz), 7.24-7.27 (5H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.50 (2H, d, *J* = 8.3 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.62 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 3.2 Hz).

30

Example 292

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.0 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.12 (2H, t, *J* = 7.0 Hz), 5.07 (2H, s), 6.79-6.83 (3H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.20-7.26 (7H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

5

Example 293

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.12 (2H, t, *J* = 7.1 Hz), 5.07 (2H, s), 6.64-6.67 (2H, m), 6.81 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.22-7.28 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.50-7.52 (4H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

15 **Example 294**

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 7.1 Hz), 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.81-2.88 (1H, m), 3.07 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.06 (2H, s), 6.80-6.83 (3H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.12 (2H, d, *J* = 8.8 Hz), 7.25-7.27 (5H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.50 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 295

25 (*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.74-1.76 (4H, m), 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 2.67-2.71 (4H, m), 3.06 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.06 (2H, s), 6.61 (1H, s), 6.66 (1H, dd, *J* = 8.3, 2.4 Hz), 6.81 (1H, d, *J* = 15.4 Hz), 6.93-6.95 (2H, m), 7.25-7.27 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.50 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 3.2 Hz).

Example 296

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-

(4-{4-[2-(naphthalen-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.46 (4H, brs), 3.15 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.61-3.74 (4H, m), 4.27 (2H, t, *J* = 7.1 Hz), 5.04 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.93 (1H, d, *J* = 8.8 Hz), 7.12-7.15 (2H, m), 7.28-7.35 (7H, m), 7.38-7.42 (1H, m), 7.45-7.49 (3H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.62 (2H, d, *J* = 8.1 Hz), 7.67-7.74 (3H, m), 7.77 (1H, d, *J* = 3.2 Hz).

Example 297

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methylphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.28 (3H, s), 2.45 (4H, brs), 3.47 (2H, s), 3.62-3.73 (4H, m), 4.27-4.30 (4H, brs), 5.06 (2H, s), 6.81-6.84 (3H, m), 6.91-6.94 (3H, m), 7.08 (2H, d, *J* = 8.5 Hz), 7.23 (2H, d, *J* = 9.0 Hz), 7.29 (1H, s), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.47-7.50 (3H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

15 Example 298

(*E*)-1-[4-(4-{2-[(6-Bromopyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.10 (2H, t, *J* = 6.8 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.19 (2H, t, *J* = 6.8 Hz), 5.08 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 7.07 (1H, dd, *J* = 8.5, 3.2 Hz), 7.23-7.30 (5H, m), 7.33 (1H, d, *J* = 8.5 Hz), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.64 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 2.9 Hz), 8.03 (1H, d, *J* = 3.2 Hz).

Example 299

²⁵ (*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.1 Hz), 2.18 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 3.96 (2H, q, *J* = 7.1 Hz), 4.11 (2H, t, *J* = 7.1 Hz), 5.07 (2H, s), 6.79-6.83 (5H, m), 6.94 (1H, d, *J* = 8.8 Hz), 7.23-7.28 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.51 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 300

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-

[4-(4-{2-[4-(methylsulfonyl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47 (4H, brs), 3.01 (3H, s), 3.12 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.25 (2H, t, *J* = 7.1 Hz), 5.09 (2H, s), 6.83 (1H, d, *J* = 15.4 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 6.99-7.01 (2H, m), 7.24-7.30 (5H, m), 7.38 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.52 (2H, d, *J* = 7.8 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.64 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 2.7 Hz), 7.83-7.85 (2H, m).

Example 301

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-

10 (4-{4-[2-(4-fluoro-3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.22 (3H, d, *J* = 1.7 Hz), 2.47 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.10 (2H, t, *J* = 7.0 Hz), 5.07 (2H, s), 6.62-6.66 (1H, m), 6.68-6.71 (1H, m), 6.81 (1H, d, *J* = 15.4 Hz), 6.87 (1H, t, *J* = 9.0 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.23-7.28 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 3.2 Hz).

Example 302

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-

20 (4-{4-[2-(4-chlorophenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.46 (4H, t, *J* = 4.9 Hz), 3.48 (2H, s), 3.63-3.73 (4H, m), 4.27-4.31 (4H, m), 5.08 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.87-6.95 (5H, m), 7.21-7.25 (4H, m), 7.29 (1H, s), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 3.2 Hz).

25 Example 303

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-

(4-{4-[2-(4-methylphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.32 (3H, s), 2.45 (4H, t, *J* = 4.9 Hz), 3.05 (2H, t, *J* = 7.1 Hz), 3.46 (2H, s), 3.62-3.73 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.07 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.12 (2H, d, *J* = 7.8 Hz), 7.16-7.24 (4H, m), 7.28 (1H, s), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 304

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.45 (4H, t, *J* = 4.9 Hz), 3.03 (2H, t, *J* = 7.1 Hz), 3.46 (2H, s), 3.62-3.73 (4H, m), 3.78 (3H, s), 4.12 (2H, t, *J* = 7.1 Hz), 5.07 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.82-6.87 (4H, m), 6.94 (1H, d, *J* = 8.8 Hz), 7.18-7.25 (4H, m), 7.28 (1H, s), 7.36 (1H, dd, *J* = 8.8, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 305

10 (*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-{2-[(5-chloropyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 4.49 (2H, t, *J* = 7.1 Hz), 5.08 (2H, s), 6.67 (1H, dd, *J* = 8.8, 0.5 Hz), 6.81 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.22-7.29 (5H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.48-7.53 (3H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.64 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 2.7 Hz), 8.07 (1H, dd, *J* = 2.7, 0.5 Hz).

Example 306

20 (*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-cyclopropylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 0.57-0.61 (2H, m), 0.85-0.90 (2H, m), 1.80-1.86 (1H, m), 2.19 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.07 (2H, s), 6.78-6.82 (3H, m), 6.94 (1H, dd, *J* = 8.8, 0.5 Hz), 6.97-7.00 (2H, m), 7.23-7.28 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 2.7 Hz).

Example 307

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(pyridin-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 ¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.63-3.74 (4H, m), 4.52 (2H, t, *J* = 7.1 Hz), 5.08 (2H, s), 6.70-6.73 (1H, m), 6.79-6.85 (2H, m), 6.94 (1H, dd, *J* = 9.0, 0.5 Hz), 7.26-7.29 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.50-7.59 (4H, m), 7.63 (2H, d, *J* = 8.3 Hz), 7.78 (1H, d, *J* = 2.7 Hz), 8.12-8.14 (1H, m).

Example 308

(*E*)-1-(4-{4-[2-(4-Bromophenoxy)ethyl]benzyl}piperazin-1-yl)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.0 Hz), 3.51 (2H, s),
5 3.63-3.74 (4H, m), 4.12 (2H, t, *J* = 7.0 Hz), 5.07 (2H, s), 6.73-6.80 (3H, m), 6.94 (1H, d, *J* = 8.8 Hz), 7.22-7.28 (5H, m), 7.32-7.37 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.51 (2H, d, *J* = 8.1 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.63 (2H, d, *J* = 8.1 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 309

10 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(5-methylpyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.22 (3H, s), 2.34 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.50 (2H, s), 3.63-3.74 (4H, m), 4.47 (2H, t, *J* = 7.1 Hz), 4.97 (2H, s), 6.63 (1H, d, *J* = 8.3 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.90 (1H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 8.1 Hz), 7.25-7.29
15 (7H, m), 7.33-7.38 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz), 7.94 (1H, d, *J* = 2.4 Hz).

Example 310

20 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(6-chloropyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, brs), 3.10 (2H, t, *J* = 6.7 Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.20 (2H, t, *J* = 6.7 Hz), 4.98 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.14-7.29 (11H, m), 7.35 (1H, dd, *J* = 8.2, 2.3 Hz), 7.45 (1H, s), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.2 Hz), 8.03 (1H, d, *J* = 2.0 Hz).

25

Example 311

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(6-methylpyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.47-2.49 (7H, m), 3.09 (2H, t, *J* = 7.0 Hz), 3.52
30 (2H, s), 3.64-3.74 (4H, m), 4.19 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 4.6 Hz), 7.04 (1H, d, *J* = 8.3 Hz), 7.09 (1H, dd, *J* = 8.4, 2.8 Hz), 7.18 (2H, d, *J* = 7.6 Hz), 7.23-7.29 (7H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.7 Hz), 8.18 (1H, d, *J* = 2.9 Hz).

Example 312

(*E*)-1-[4-(4-{2-[(5-Bromopyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.34 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.06 (2H, t, *J* = 7.1 Hz),
5 3.51 (2H, s), 3.63-3.74 (4H, m), 4.48 (2H, t, *J* = 7.1 Hz), 4.97 (2H, s), 6.63 (1H, dd, *J* = 8.8, 0.5 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, dd, *J* = 8.8, 0.5 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.22-7.29 (7H, m), 7.34 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.61 (1H, dd, *J* = 8.8, 2.7 Hz), 7.79 (1H, d, *J* = 2.7 Hz), 8.16 (1H, dd, *J* = 2.6, 0.6 Hz).

10 Example 313

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(6-methoxypyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.35 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.0 Hz),
15 3.52 (2H, s), 3.64-3.74 (4H, m), 3.87 (3H, s), 4.16 (2H, t, *J* = 7.0 Hz), 4.97 (2H, s), 6.66 (1H, d, *J* = 8.8 Hz), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 9.0 Hz), 7.17-7.20 (3H, m), 7.23-7.29 (7H, m), 7.35 (1H, dd, *J* = 8.9, 3.2 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (2H, t, *J* = 3.2 Hz).

Example 314

20 (*E*)-1-[4-(4-{2-[(6-Chloro-1,3-benzoxazol-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.34 (3H, s), 2.38-2.40 (4H, m), 3.04 (2H, t, *J* = 7.1 Hz), 3.47 (2H, s), 3.63-3.73 (4H, m), 4.01 (2H, t, *J* = 7.1 Hz), 4.97 (2H, s), 6.57 (1H, d, *J* = 8.3 Hz), 6.82 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 8.8 Hz), 7.01 (1H, dd, *J* = 8.3, 2.0 Hz), 7.12 (2H, d, *J* = 8.1
25 Hz), 7.16-7.22 (5H, m), 7.27-7.29 (3H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.44 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.78 (1H, d, *J* = 2.9 Hz).

Example 315

30 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 7.0 Hz), 2.18 (3H, s), 2.35 (3H, s), 2.46 (4H, t, *J* = 5.0 Hz), 3.48 (2H, s), 3.66-3.73 (4H, m), 3.97 (2H, q, *J* = 7.0 Hz), 4.26-4.29 (4H, m), 4.97 (2H, s), 6.78-6.92 (8H, m), 7.18 (2H, d, *J* = 8.1 Hz), 7.22-7.29 (5H, m), 7.35 (1H, dd, *J* = 8.8, 3.2 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.56 (1H, d, *J* = 15.1 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 316

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, brs), 3.50 (2H, brs), 3.68-3.74 (7H, m), 4.27-4.32 (4H, m), 4.99 (2H, s), 6.77-6.84 (3H, m), 6.92-6.97 (5H, m), 7.19 (2H, d, *J* = 8.1 Hz), 7.24-7.30 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 1.7 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 3.2 Hz).

10 Example 317

(*E*)-1-(4-{4-[2-(1,3-Benzothiazol-2-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.34 (3H, s), 2.43 (4H, brs), 3.02 (2H, t, *J* = 7.3 Hz), 3.49 (2H, s), 3.64-3.72 (4H, m), 4.14 (2H, t, *J* = 7.3 Hz), 4.97 (2H, s), 6.81 (1H, d, *J* = 15.4 Hz), 6.89-6.93
15 (2H, m), 7.12-7.18 (5H, m), 7.21-7.29 (6H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.40 (1H, dd, *J* = 7.8, 1.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.78 (1H, d, *J* = 2.9 Hz).

Example 318

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(2-methyl-1,3-benzothiazol-5-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.80 (3H, s), 3.13 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.25 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.91 (1H, d, *J* = 9.3 Hz), 6.98 (1H, dd, *J* = 8.8, 2.4 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.28-7.29 (7H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.43-7.46 (2H, m), 7.57 (1H, d, *J* = 15.4 Hz),
25 7.64 (1H, d, *J* = 8.8 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 319

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-3-[methyl(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)amino]pyrrolidin-1-yl]prop-2-en-1-one

- 30 ¹H-NMR (CDCl₃) δ: 1.21 (6H, d, *J* = 6.9 Hz), 1.86-2.03 (1H, m), 2.17-2.19 (7H, m), 2.34 (3H, s), 2.81-2.88 (1H, m), 3.02-3.08 (2.5H, m), 3.15-3.17 (0.5H, m), 3.40-3.64 (4H, m), 3.82-3.91 (1.5H, m), 3.99-4.02 (0.5H, m), 4.14 (2H, t, *J* = 7.1 Hz), 4.96 (2H, s), 6.64 (1H, dd, *J* = 15.4, 8.8 Hz), 6.81-6.84 (2H, m), 6.91 (1H, dd, *J* = 8.8, 2.4 Hz), 7.12 (2H, dd, *J* = 8.5, 2.2 Hz), 7.17 (2H, d, *J* = 7.8 Hz), 7.22-7.30 (7H, m), 7.33-7.36 (1H, m), 7.47 (1H, d, *J* = 1.7 Hz), 7.61 (1H, dd, *J* =

15.4, 4.9 Hz), 7.78-7.80 (1H, m).

Example 320

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

5 cyclopropylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 0.58-0.61 (2H, m), 0.86-0.89 (2H, m), 1.81-1.86 (1H, m), 2.18 (3H, s), 2.35 (3H, s), 2.47 (4H, t, *J* = 5.0 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.51 (2H, s), 3.64-3.74 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.82 (3H, m), 6.91 (1H, d, *J* = 9.0 Hz), 6.98-7.00 (2H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.23-7.29 (7H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2

10 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

[0209]

Example 321

To a CH₂Cl₂ (5 mL) solution of (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methyl-

15 benzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid (200 mg) was added *N,N*-dimethyl-4-{2-[4-(piperazin-1-ylmethyl)phenyl]ethoxy}aniline (191 mg), DCC (151 mg), and DMAP (5.96 mg) at room temperature, then the resultant mixture was stirred over night. The mixture was evaporated. The residue was added AcOEt, then filtered off, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/0 and

20 then AcOEt/MeOH = 4/1) to afford (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]-pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one as a pale brown amorphous powder (184 mg).

¹H-NMR (DMSO-*d*₆) δ: 2.09 (3H, s), 2.30 (3H, s), 2.34-2.36 (2H, m), 2.40-2.42 (2H, m), 2.78 (6H, s), 2.97 (2H, t, *J* = 7.0 Hz), 3.32 (2H, s), 3.49 (2H, s), 3.55-3.57 (2H, m), 3.70-3.73 (2H, m),

25 4.08 (2H, t, *J* = 7.0 Hz), 5.05 (2H, s), 6.67-6.69 (2H, m), 6.79-6.81 (2H, m), 7.07 (1H, d, *J* = 9.3 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.24-7.34 (7H, m), 7.43 (1H, d, *J* = 15.4 Hz), 7.57-7.59 (1H, m), 7.62-7.62 (1H, m), 7.79-7.82 (2H, m).

[0210]

Example 322

To a DMF (5 mL) solution of (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (479

30 mg) and 4-methylbenzyl bromide (155 mg) was added sodium hydride (60% w/w in oil, 42 mg) at 0 °C, and stirred for 1 hour. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl (10 mL), and extracted with AcOEt. The organic layer was washed with water,

saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (AcOEt/MeOH = 1/0 to 9/1) to afford (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (480 mg).

- 5 ¹H-NMR (CDCl₃) δ: 2.18 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.76-6.84 (3H, m), 6.91 (1H, d, *J* = 8.8 Hz), 7.06 (2H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 8.3 Hz), 7.23-7.29 (7H, m), 7.35 (1H, ddd, *J* = 9.0, 3.2, 0.7 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.56 (1H, d, *J* = 15.1 Hz), 7.79 (1H, d, *J* = 3.2 Hz).

10 [0211]

The following compounds were produced in the same manner as in Example 322 using appropriate starting materials.

Example 323

- 15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.60-3.80 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.75-6.87 (3H, m), 6.88-6.99 (3H, m), 7.17-7.31 (9H, m), 7.35 (1H, dd, *J* = 8.9, 3.3 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.56
20 (1H, d, *J* = 15.5 Hz), 7.79 (1H, d, *J* = 3.0 Hz).

Example 324

- (*E*)-3-[3-Chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
25 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.60-3.80 (4H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.00 (2H, s), 6.77-6.87 (3H, m), 6.90-7.01 (3H, m), 7.21-7.38 (10H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.2 Hz), 7.77 (1H, d, *J* = 3.0 Hz).

Example 325

- 30 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one
¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 2.85 (1H, septet, *J* = 6.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65-3.73 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.79-6.84 (3H, m), 6.91 (1H, d, *J* = 8.9 Hz), 7.11-7.30 (11H, m), 7.35

(1H, dd, $J = 8.9, 3.3$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.2$ Hz), 7.79 (1H, d, $J = 3.0$ Hz).

Example 326

5 (E)-3-[3-Chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (6H, d, $J = 6.9$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.85 (1H, septet, $J = 6.9$ Hz), 3.08 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, $J = 7.1$ Hz), 5.00 (2H, s), 6.77-6.86 (3H, m), 6.93 (1H, d, $J = 8.9$ Hz), 7.13 (2H, d, $J = 8.6$ Hz), 7.28-
10 7.34 (10H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.77 (1H, d, $J = 3.0$ Hz).

Example 327

(E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

15 $^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, $J = 6.9$ Hz), 5.09 (2H, s), 6.79-6.83 (3H, m), 6.92-6.99 (3H, m), 7.24-7.27 (5H, m), 7.37 (1H, dd, $J = 8.9, 3.0$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.53-7.57 (3H, m), 7.65 (2H, d, $J = 7.9$ Hz), 7.78 (1H, d, $J = 3.0$ Hz).

20 Example 328

(E)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 6.9$ Hz), 3.53 (2H, s), 3.59-3.83 (4H, m), 4.13 (2H, t, $J = 7.1$ Hz), 4.99 (2H, s), 6.65-6.87 (3H, m), 6.90-6.99 (3H, m),
25 7.02-7.11 (2H, m), 7.20-7.30 (5H, m), 7.31-7.41 (3H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.78 (1H, d, $J = 3.0$ Hz).

Example 329

(E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (6H, d, $J = 6.9$ Hz), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.91 (1H, septet, $J = 6.9$ Hz), 3.08 (2H, t, $J = 6.9$ Hz), 3.52 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, $J = 6.9$ Hz), 4.99 (2H, s), 6.76-6.85 (3H, m), 6.93-6.96 (3H, m), 7.28-7.34 (10H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.80 (1H, d, $J = 3.0$ Hz).

Example 330

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64-3.74 (4H, m), 4.15 (2H, t, *J* = 7.1 Hz), 4.99 (2H, s), 6.78-6.81 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.04-7.10 (4H, m), 7.27-7.28 (5H, m), 7.35-7.39 (3H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.78 (1H, d, *J* = 3.0 Hz).

10 Example 331

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.58-3.82 (4H, m), 4.15 (2H, t, *J* = 6.9 Hz), 4.99 (2H, s), 6.72-6.87 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.01-7.18 (4H, m), 7.22-7.29 (5H, m), 7.32-7.41 (3H, m), 7.45 (1H, d, *J* = 1.6 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.78 (1H, d, *J* = 3.0 Hz).
- 15

Example 332

- 20 (*E*)-3-(3-Chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 6.9 Hz), 5.05 (2H, s), 6.81-6.83 (3H, m), 6.93-6.97 (3H, m), 7.23-7.31 (5H, m), 7.35-7.38 (2H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.75 (1H, d, *J* = 7.9 Hz), 7.80 (1H, d, *J* = 3.0 Hz), 8.60 (1H, dd, *J* = 4.8, 1.5 Hz), 8.66 (1H, d, *J* = 2.0 Hz).
- 25

Example 333

- 30 (*E*)-3-(3-Chloro-5-methyl-4-{[5-(pyridin-2-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, *J* = 6.9 Hz), 5.17 (2H, s), 6.79 (1H, d, *J* = 9.2 Hz), 6.80-6.85 (2H, m), 6.92-6.99 (3H, m), 7.25-7.27 (6H, m), 7.41 (1H, dd, *J* = 8.9, 3.0 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.50 (1H, d, *J* = 7.9 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.73 (1H, td, *J* = 7.7, 1.8 Hz), 7.82 (1H,

d, $J = 3.0$ Hz), 8.59 (1H, d, $J = 4.6$ Hz).

Example 334

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.07 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.55-3.83 (7H, m), 4.13 (2H, t, $J = 7.1$ Hz), 4.98 (2H, s), 6.77-6.87 (5H, m), 6.92 (1H, d, $J = 8.9$ Hz), 7.19 (2H, d, $J = 7.9$ Hz), 7.23-7.31 (7H, m), 7.36 (1H, dd, $J = 8.9, 3.3$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.79 (1H, d, $J = 3.3$ Hz).

Example 335

(*E*)-3-[3-Chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.1$ Hz), 3.53 (2H, s), 3.65-3.74 (4H, m), 4.13 (2H, t, $J = 6.9$ Hz), 5.03 (2H, s), 6.78-6.85 (3H, m), 6.94-6.98 (3H, m), 7.24-7.28 (5H, m), 7.35-7.39 (2H, m), 7.46 (1H, d, $J = 2.0$ Hz), 7.57 (1H, d, $J = 15.5$ Hz), 7.73 (1H, dd, $J = 8.2, 2.6$ Hz), 7.78 (1H, d, $J = 3.0$ Hz), 8.43 (1H, d, $J = 2.3$ Hz).

Example 336

(*E*)-3-(3-Chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, $J = 6.9$ Hz), 2.05 (2H, s), 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 2.79-2.91 (1H, m), 3.08 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.12 (3H, t, $J = 10.7$ Hz), 5.05 (2H, s), 6.73-6.89 (3H, m), 6.90-6.99 (1H, m), 7.08-7.18 (2H, m), 7.27-7.42 (0H, m), 7.43-7.48 (1H, m), 7.52-7.62 (1H, m), 7.75 (1H, dt, $J = 7.8, 1.9$ Hz), 7.80 (2H, d, $J = 3.0$ Hz), 8.60 (2H, dd, $J = 4.9, 1.6$ Hz), 8.66 (2H, d, $J = 1.3$ Hz).

Example 337

(*E*)-3-[3-Chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.20-1.25 (6H, m), 2.19 (3H, s), 2.47-2.51 (4H, m), 2.82-2.88 (1H, m), 3.08 (2H, t, $J = 6.9$ Hz), 3.53 (2H, s), 3.65-3.71 (4H, m), 4.07-4.18 (2H, m), 5.03 (2H, s), 6.81-6.86 (3H, m), 6.95 (1H, d, $J = 9.2$ Hz), 7.13 (2H, d, $J = 8.2$ Hz), 7.24-7.28 (3H, m), 7.34-7.39 (3H, m), 7.47 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.5$ Hz), 7.73-7.78 (2H, m), 8.42 (1H, d, $J = 2.0$

Hz).

Example 338

(*E*)-3-(3-Chloro-5-methyl-4-{{5-(pyridin-2-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[4-

5 (propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.80-2.90 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 5.17 (2H, s), 6.77-6.95 (4H, m), 7.11-7.15 (2H, m), 7.22-7.27 (6H, m), 7.40-7.44 (2H, m), 7.51-7.57 (2H, m), 7.72-7.75 (1H, m), 7.82 (1H, d, *J* = 3.0 Hz), 8.58-8.60 (1H, m).

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Example 339

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.13 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.75-6.87 (3H, m), 6.90-7.01 (3H, m), 7.22-7.26 (3H, m), 7.28-7.32 (3H, m), 7.35-7.43 (2H, m), 7.45 (1H, d, *J* = 2.0 Hz), 7.48-7.61 (3H, m), 7.79-7.84 (1H, m).

15

Example 340

20 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.36 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 6.9 Hz), 3.53 (2H, s), 3.63-3.66 (2H, m), 3.72-3.76 (2H, m), 4.13 (2H, t, *J* = 6.9 Hz), 5.01 (2H, s), 6.77-6.89 (3H, m), 6.89-7.00 (3H, m), 7.14-7.25 (4H, m), 7.25-7.27 (3H, m), 7.27-7.31 (1H, m), 7.34-7.41 (2H, m), 7.46 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.82 (1H, d, *J* = 2.6 Hz).

25

Example 341

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.63-3.67 (2H, m), 3.72-3.76 (2H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.10 (2H, s), 6.77-6.99 (6H, m), 7.02-7.23 (3H, m), 7.23-7.27 (2H, m), 7.29-7.49 (6H, m), 7.57 (1H, d, *J* = 15.2 Hz), 7.82 (1H, d, *J* = 3.0 Hz).

Example 342

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.72-3.76 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.10 (2H, s), 6.80 (3H, dd, *J* = 11.9, 3.3 Hz), 6.94 (1H, d, *J* = 8.9 Hz), 7.03-7.20 (4H, m), 7.21-7.41 (7H, m), 7.43-7.51 (2H, m), 7.57 (1H, d, *J* = 15.5 Hz), 7.82 (1H, d, *J* = 3.0 Hz).

Example 343

- 10 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.72-3.76 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.79-6.81 (3H, m), 6.94 (1H, d, *J* = 8.9 Hz), 7.07 (2H, d, *J* = 8.2 Hz), 7.23-7.32 (7H, m), 7.39-7.44 (3H, m), 7.53-7.57 (2H, m), 7.81 (1H, d, *J* = 3.0 Hz).

Example 344

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 20 ¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 2.47-2.49 (4H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.72-3.76 (2H, m), 4.14 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.76-6.85 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.07 (2H, d, *J* = 8.2 Hz), 7.20-7.29 (8H, m), 7.33-7.41 (2H, m), 7.46 (1H, d, *J* = 2.3 Hz), 7.57 (1H, d, *J* = 15.5 Hz), 7.82 (1H, d, *J* = 3.0 Hz).

25 Example 345

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.56 (3H, s), 2.80-2.90 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.62-3.66 (2H, m), 3.72-3.76 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.13 (2H, s), 6.77-6.86 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.08-7.15 (3H, m), 7.22-7.27 (4H, m), 7.27-7.34 (2H, m), 7.40 (1H, dd, *J* = 8.9, 3.0 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.54-7.64 (2H, m), 7.81 (1H, d, *J* = 3.0 Hz).

Example 346

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.80-2.90 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.72-3.76 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.10 (2H, s), 6.74-6.87 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.05-7.19 (4H, m), 7.22-7.27 (3H, m), 7.29-7.41 (4H, m), 7.42-7.51 (2H, m), 7.57 (1H, d, *J* = 15.2 Hz), 7.81 (1H, d, *J* = 3.0 Hz).

Example 347

10 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.20 (3H, s), 2.36 (3H, s), 2.45-2.53 (4H, m), 2.80-2.90 (1H, m), 3.08 (2H, t, *J* = 6.9 Hz), 3.52 (2H, s), 3.63-3.67 (2H, m), 3.72-3.76 (2H, m), 4.15 (2H, t, *J* = 6.9 Hz), 5.01 (2H, s), 6.75-6.86 (3H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.13 (2H, d, *J* = 8.2 Hz), 7.19-7.30 (8H, m), 7.33-7.42 (2H, m), 7.46 (1H, s), 7.57 (1H, d, *J* = 15.5 Hz), 7.82 (1H, d, *J* = 3.0 Hz).

Example 348

20 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.46-2.50 (4H, m), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.78 (5H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.76-6.85 (5H, m), 6.94 (1H, d, *J* = 8.9 Hz), 7.23-7.32 (7H, m), 7.37-7.60 (5H, m), 7.81 (1H, d, *J* = 2.6 Hz).

25 Example 349

(*E*)-3-[3-Chloro-4-({5-[(2-methoxybenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48-2.49 (4H, m), 2.82-2.89 (1H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 3.84 (3H, s), 4.15 (2H, t, *J* = 7.0 Hz), 5.08 (2H, s), 6.78-6.85 (3H, m), 6.89-6.92 (2H, m), 6.97 (1H, t, *J* = 7.4 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.21-7.33 (6H, m), 7.37-7.42 (2H, m), 7.45 (1H, s), 7.57 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 350

(*E*)-3-[3-Chloro-4-({5-[(2-chloro-4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48-2.49 (4H, m), 2.81-2.89 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.75 (2H, m), 4.15-4.18 (2H, m), 5.09 (2H, s), 6.77-6.85 (3H, m), 6.95 (1H, d, *J* = 8.8 Hz), 7.02 (1H, td, *J* = 8.3, 2.4 Hz), 7.11-7.18 (3H, m), 7.23-7.30 (5H, m), 7.38 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45-7.51 (2H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 351

2-({[6-(2-Chloro-6-methyl-4-({(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.81-2.88 (1H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.15 (2H, t, *J* = 7.0 Hz), 5.22 (2H, s), 6.77-6.86 (3H, m), 6.96 (1H, d, *J* = 8.8 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.20-7.29 (5H, m), 7.41-7.47 (3H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.64 (2H, d, *J* = 4.2 Hz), 7.71 (1H, d, *J* = 7.6 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 352

(*E*)-3-[3-Chloro-4-({5-[(3-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48-2.49 (4H, m), 2.81-2.89 (1H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.66 (2H, m), 3.73-3.76 (2H, m), 4.14-4.18 (2H, m), 5.03 (2H, s), 6.78-6.85 (3H, m), 6.94 (1H, d, *J* = 8.8 Hz), 6.98-7.05 (1H, m), 7.10-7.18 (4H, m), 7.23-7.30 (5H, m), 7.31-7.39 (2H, m), 7.45 (1H, s), 7.57 (1H, d, *J* = 15.4 Hz), 7.78 (1H, d, *J* = 2.9 Hz).

Example 353

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(3-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.36 (3H, s), 2.47-2.49 (4H, m), 2.80-2.89 (1H, m), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.76 (2H, m), 4.15 (2H, t, *J* = 7.0 Hz), 4.99 (2H, s), 6.77-6.85 (3H, m), 6.92 (1H, d, *J* = 9.0 Hz), 7.11-7.16 (3H, m), 7.18-7.29 (8H, m), 7.37 (1H, dd, *J* = 9.0, 2.9 Hz), 7.45 (1H, s), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 354

(*E*)-3-[3-Chloro-4-({5-[(3-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.81-2.89 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.63-3.65 (2H, m), 3.73-3.75 (2H, m), 4.15 (2H, t, *J* = 7.1 Hz), 5.00 (2H, s), 6.78-6.86 (3H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.24-7.32 (8H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.41 (1H, s), 7.45-7.46 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

10

Example 355

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- 15 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.9 Hz), 2.20 (3H, s), 2.41-2.54 (4H, m), 2.79-2.91 (1H, m), 3.08 (2H, t, *J* = 6.9 Hz), 3.52 (2H, s), 3.63-3.67 (2H, m), 3.72-3.76 (2H, m), 4.16 (2H, t, *J* = 6.9 Hz), 5.14 (2H, s), 6.77-6.85 (3H, m), 6.94 (1H, d, *J* = 8.9 Hz), 7.13 (2H, d, *J* = 8.6 Hz), 7.25-7.31 (7H, m), 7.36-7.62 (5H, m), 7.82 (1H, d, *J* = 2.6 Hz).

Example 356

- 20 (*2E*)-1-(4-{4-[(1*E*)-3-(4-Fluorophenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one

mp: 136-137 °C

- ¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.74 (2H, brs), 3.81 (3H, s), 4.67 (2H, dd, *J* = 5.9, 1.3 Hz), 4.95 (2H, s), 6.39 (1H, dt, *J* = 15.9, 5.9 Hz),
25 6.72 (1H, d, *J* = 15.9 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.79 (1H, d, *J* = 8.8 Hz), 6.88-6.93 (4H, m), 6.95-7.00 (2H, m), 7.25-7.26 (2H, m), 7.28-7.34 (5H, m), 7.38 (2H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 357

- 30 (*2E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.29 (3H, s), 2.37 (3H, s), 2.47 (4H, t, *J* = 4.9 Hz), 3.47 (2H, s), 3.62-3.75 (4H, m), 3.81 (3H, s), 4.67 (2H, dd, *J* = 5.7, 1.3 Hz), 4.95 (2H, s), 6.40 (1H, dt, *J* = 16.1, 5.7 Hz), 6.68 (1H, d, *J* = 16.1 Hz), 6.77-6.80 (2H, m), 6.86 (2H, dt, *J* = 9.2, 2.4 Hz), 6.91

(2H, dt, $J = 9.2, 2.4$ Hz), 7.09 (2H, d, $J = 8.8$ Hz), 7.21-7.22 (3H, m), 7.25-7.26 (2H, m), 7.30-7.34 (3H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.82 (1H, d, $J = 2.9$ Hz).

Example 358

5 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.24 (6H, d, $J = 6.9$ Hz), 2.18 (3H, s), 2.34 (3H, s), 2.46 (4H, t, $J = 4.9$ Hz), 2.91 (1H, septet, $J = 6.9$ Hz), 3.49 (2H, s), 3.60-3.82 (4H, m), 4.97 (2H, s), 6.80 (1H, d, $J = 15.5$ Hz), 6.91 (1H, d, $J = 8.9$ Hz), 7.09-7.39 (10H, m), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.5$ Hz), 7.79 (1H, d, $J = 3.0$ Hz).

Example 359

(E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one

15 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.35 (3H, s), 2.47 (4H, t, $J = 4.9$ Hz), 3.50 (2H, s), 3.64-3.73 (4H, m), 4.98 (2H, s), 6.79 (1H, d, $J = 15.5$ Hz), 6.91 (1H, dd, $J = 4.5, 2.2$ Hz), 7.13-7.23 (6H, m), 7.27-7.29 (3H, m), 7.35 (1H, dd, $J = 8.9, 3.3$ Hz), 7.45 (1H, d, $J = 2.0$ Hz), 7.56 (1H, d, $J = 15.5$ Hz), 7.79 (1H, d, $J = 2.6$ Hz).

20 [0212]

Example 360

To a solution of (E)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (400 mg) was added 3-fluoro-4-methylbenzyl bromide (144 mg) and K₂CO₃ (134 mg) at room temperature, then the reaction mixture was stirred for 4 hours. The reaction mixture was diluted with H₂O and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to afford (E)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one as a colorless amorphous (430 mg).

30 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (3H, d, $J = 1.7$ Hz), 2.48 (4H, t, $J = 4.9$ Hz), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.14 (2H, t, $J = 7.0$ Hz), 4.98 (2H, s), 6.78-6.84 (3H, m), 6.93 (1H, dd, $J = 8.8, 0.5$ Hz), 7.16-7.29 (10H, m), 7.35 (1H, dd, $J = 8.9, 3.1$ Hz), 7.45 (1H, d, $J = 2.2$ Hz), 7.57 (1H, d, $J = 15.4$ Hz), 7.77 (1H, d, $J = 3.2$ Hz).

[0213]

The following compounds were produced in the same manner as in Example 360 using appropriate starting materials.

5 Example 361

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.23 (3H, s), 2.29 (3H, d, *J* = 1.7 Hz), 2.31 (3H, s), 2.51 (4H, t, *J* = 4.9 Hz), 3.11 (2H, t, *J* = 7.1 Hz), 3.55 (2H, s), 3.67 (2H, s), 3.77 (2H, s), 4.18 (2H, t, *J* = 7.1 Hz), 5.04
10 (2H, s), 6.81-6.85 (3H, m), 6.97 (1H, dd, *J* = 9.0, 0.5 Hz), 7.03-7.12 (3H, m), 7.17-7.23 (2H, m), 7.26-7.32 (5H, m), 7.40 (1H, dd, *J* = 8.9, 3.1 Hz), 7.49 (1H, d, *J* = 2.2 Hz), 7.60 (1H, d, *J* = 15.4 Hz), 7.83 (1H, d, *J* = 2.9 Hz).

Example 362

15 (*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.20 (3H, s), 2.27 (3H, d, *J* = 2.0 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.81 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.78-6.85 (3H, m), 6.94 (1H, d, *J* = 8.8 Hz),
20 7.00-7.07 (1H, m), 7.11-7.20 (4H, m), 7.24-7.29 (5H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 1.7 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz).

Example 363

25 (*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.27 (3H, d, *J* = 2.0 Hz), 2.49 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65 (2H, s), 3.75 (2H, s), 4.13 (2H, t, *J* = 7.1 Hz), 5.01 (2H, s), 6.78-6.85 (3H, m), 6.91-6.99 (3H, m), 7.00-7.07 (1H, m), 7.15-7.18 (2H, m), 7.24-7.30 (5H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 3.2
30 Hz).

Example 364

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.27 (3H, d, *J* = 2.0 Hz), 2.48 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.14 (2H, t, *J* = 7.0 Hz), 5.01 (2H, s), 6.78-6.84 (3H, m), 6.95 (1H, dd, *J* = 8.9, 0.6 Hz), 7.00-7.05 (1H, m), 7.15-7.29 (9H, m), 7.37 (1H, dd, *J* = 8.9, 3.1 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.80 (1H, dd, *J* = 3.1, 0.6 Hz).

Example 365

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.53 (2H, s), 3.65 (2H, s), 3.74 (2H, s), 4.14 (2H, d, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.85 (4H, m), 6.91-6.98 (5H, m), 7.23-7.29 (5H, m), 7.36 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

15 Example 366

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (3H, d, *J* = 1.7 Hz), 2.48 (4H, t, *J* = 4.8 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.53 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.13 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.78-6.85 (3H, m), 6.92-7.00 (3H, m), 7.05-7.07 (2H, m), 7.18 (1H, t, *J* = 7.7 Hz), 7.23-7.29 (5H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 367

²⁵ (*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.27 (3H, d, *J* = 1.7 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.60-3.80 (7H, m), 4.13 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.86 (5H, m), 6.93 (1H, dd, *J* = 8.8, 0.5 Hz), 7.05-7.07 (2H, m), 7.16-7.20 (1H, m), 7.24-7.29 (5H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, dd, *J* = 3.2, 0.5 Hz).

Example 368

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-

{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.14 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.78-6.85 (4H, m), 6.91-6.95 (2H, m), 6.98 (1H, s), 7.20-7.29 (7H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 369

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.58-3.80 (7H, m), 4.13 (2H, t, *J* = 6.6 Hz), 4.98 (2H, s), 6.78-6.85 (6H, m), 6.90-7.00 (1H, m), 6.98 (1H, s), 7.23-7.29 (6H, m), 7.36 (1H, dd, *J* = 8.8, 3.2 Hz), 7.45 (1H, d, *J* = 1.7 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 370

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.18 (3H, d, *J* = 4.9 Hz), 2.27-2.28 (6H, m), 2.48 (4H, t, *J* = 4.9 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.75 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.82 (3H, m), 6.93 (1H, d, *J* = 8.8 Hz), 7.05-7.08 (4H, m), 7.18 (1H, t, *J* = 7.7 Hz), 7.24-7.29 (5H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 371

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.27 (3H, d, *J* = 1.7 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.0 Hz), 4.98 (2H, s), 6.78-6.85 (3H, m), 6.93 (1H, dd, *J* = 9.0, 0.5 Hz), 7.05-7.07 (2H, m), 7.11-7.15 (2H, m), 7.18 (1H, t, *J* = 7.9 Hz), 7.24-7.29 (5H, m), 7.35 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.7 Hz).

Example 372

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-

{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.35 (3H, d, *J* = 0.5 Hz), 2.48 (4H, t, *J* = 5.0 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.85 (4H, m), 6.91-6.98 (3H, m), 7.07 (2H, dd, *J* = 8.7, 0.6 Hz), 7.23-7.29 (5H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77-7.78 (1H, m).

Example 373

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-

(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.35 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 2.85 (1H, septet, *J* = 7.1 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 4.98 (2H, s), 6.78-6.85 (4H, m), 6.91-6.98 (1H, m), 6.98 (1H, s), 7.13 (2H, d, *J* = 8.3 Hz), 7.24-7.29 (6H, m), 7.36 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.77 (1H, d, *J* = 2.9 Hz).

Example 374

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.20 (3H, s), 2.47-2.49 (4H, m), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.76 (5H, brs), 4.13 (2H, t, *J* = 7.1 Hz), 5.46 (2H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.82 (2H, d, *J* = 9.6 Hz), 6.84 (2H, d, *J* = 9.6 Hz), 6.96 (1H, d, *J* = 9.0 Hz), 7.26 (4H, s), 7.28 (1H, s), 7.41 (1H, dd, *J* = 9.0, 2.9 Hz), 7.45 (1H, s), 7.51 (1H, t, *J* = 7.8 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.68-7.72 (1H, m), 7.82 (1H, d, *J* = 2.9 Hz), 7.86 (1H, d, *J* = 7.6 Hz), 8.16 (1H, d, *J* = 8.1 Hz).

Example 375

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 6.8 Hz), 2.19 (3H, s), 2.48 (4H, s), 2.85 (1H, qq, *J* = 6.8, 6.8 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, s), 3.74 (2H, s), 4.15 (2H, t, *J* = 7.1 Hz), 5.46 (2H, s), 6.78-6.84 (3H, m), 6.96 (1H, d, *J* = 9.0 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.26 (4H, s), 7.29 (1H, s), 7.41 (1H, dd, *J* = 9.0, 2.9 Hz), 7.45 (1H, s), 7.51 (1H, t, *J* = 7.7 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.69-7.72 (1H, m), 7.82 (1H, d, *J* = 2.9 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 8.16 (1H, d, *J* = 8.1 Hz).

Example 376

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.48 (4H, t, *J* = 4.6 Hz), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.15 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.80 (2H, d, *J* = 8.5 Hz), 6.80 (1H, d, *J* = 15.1 Hz), 6.96 (1H, d, *J* = 9.0 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 7.26 (4H, s), 7.29 (1H, s), 7.38 (1H, dd, *J* = 9.0, 2.9 Hz), 7.45 (1H, s), 7.57 (1H, d, *J* = 15.1 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 7.78 (1H, d, *J* = 2.9 Hz), 8.25 (2H, d, *J* = 8.5 Hz).

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Example 377

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

- 15 ¹H-NMR (CDCl₃) δ: 1.22 (6H, d, *J* = 7.1 Hz), 2.19 (3H, s), 2.47-2.49 (4H, m), 2.82-2.88 (1H, m), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, brs), 3.64 (2H, brs), 3.74 (2H, brs), 4.15 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.78-6.84 (3H, m), 6.96 (1H, d, *J* = 8.8 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 7.26 (4H, s), 7.29 (1H, s), 7.38 (1H, dd, *J* = 8.8, 2.9 Hz), 7.45 (1H, s), 7.54-7.60 (3H, m), 7.78 (1H, d, *J* = 2.9 Hz), 8.25 (2H, d, *J* = 8.8 Hz).

20 Example 378

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- 25 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.28 (3H, s), 2.48 (4H, s), 3.08 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.15 (2H, t, *J* = 7.1 Hz), 5.46 (2H, s), 6.80 (2H, d, *J* = 8.5 Hz), 6.80 (1H, d, *J* = 14.9 Hz), 6.96 (1H, d, *J* = 8.8 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 7.26 (4H, s), 7.28 (1H, s), 7.41 (1H, dd, *J* = 8.8, 2.9 Hz), 7.45 (1H, s), 7.49-7.53 (1H, m), 7.56 (1H, d, *J* = 15.4 Hz), 7.70 (1H, t, *J* = 7.3 Hz), 7.82 (1H, d, *J* = 2.9 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 8.16 (1H, d, *J* = 8.1 Hz).

30 Example 379

(*E*)-3-[4-({5-[(3-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

- ¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 2.46-2.49 (4H, m), 3.07 (2H, t, *J* = 7.0 Hz), 3.52 (2H, s), 3.62-3.65 (2H, m), 3.73-3.76 (2H, m), 4.13 (2H, t, *J* = 7.0 Hz), 5.06 (2H, s), 6.71 (1H, d, *J* = 15.1 Hz),

6.81-6.84 (2H, m), 6.88-6.97 (5H, m), 7.02 (1H, td, $J = 8.4, 2.0$ Hz), 7.13-7.17 (2H, m), 7.23-7.28 (2H, m), 7.34-7.36 (2H, m), 7.52-7.53 (1H, m), 7.89-7.91 (2H, m).

Example 380

5 (E)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[4-({5-[(2-methoxybenzyl)-oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.40 (3H, s), 2.46-2.49 (4H, m), 3.07 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.62-3.65 (2H, m), 3.73-3.76 (2H, m), 3.85 (3H, s), 4.13 (2H, t, $J = 7.0$ Hz), 5.12 (2H, s), 6.70 (1H, d, $J = 15.1$ Hz), 6.81-6.99 (9H, m), 7.23-7.33 (5H, m), 7.36 (1H, dd, $J = 8.8, 2.9$ Hz), 7.42 (1H, d, $J = 7.1$ Hz), 7.51-7.52 (1H, m), 7.90 (1H, d, $J = 15.1$ Hz), 7.95 (1H, d, $J = 3.2$ Hz).

Example 381

(E)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[2-methyl-4-({5-[(3-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one

15 ¹H-NMR (CDCl₃) δ: 2.36 (3H, s), 2.40 (3H, s), 2.46-2.48 (4H, m), 3.07 (2H, t, $J = 7.0$ Hz), 3.51 (2H, s), 3.62-3.64 (2H, m), 3.73-3.76 (2H, m), 4.12 (2H, t, $J = 7.0$ Hz), 5.02 (2H, s), 6.71 (1H, d, $J = 15.1$ Hz), 6.80-6.84 (2H, m), 6.86-6.97 (5H, m), 7.14 (1H, d, $J = 7.3$ Hz), 7.19-7.28 (7H, m), 7.34 (1H, dd, $J = 8.9, 3.1$ Hz), 7.51-7.52 (1H, m), 7.90-7.92 (2H, m).

20 Example 382

(E)-3-[4-({5-[(2-Chloro-4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.47-2.48 (4H, m), 3.08 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.14 (2H, t, $J = 7.0$ Hz), 5.07 (2H, s), 6.79-6.81 (4H, m), 7.01
25 (1H, td, $J = 8.3, 2.4$ Hz), 7.15 (1H, dd, $J = 8.3, 2.4$ Hz), 7.22-7.26 (8H, m), 7.34 (1H, dd, $J = 8.9, 3.1$ Hz), 7.49 (1H, dd, $J = 8.5, 6.1$ Hz), 7.61 (1H, d, $J = 15.4$ Hz), 7.83 (1H, d, $J = 2.9$ Hz).

Example 383

30 (E)-3-[4-({5-[(3-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.47-2.48 (4H, m), 3.07 (2H, t, $J = 7.0$ Hz), 3.52 (2H, s), 3.64-3.66 (2H, m), 3.73-3.75 (2H, m), 4.13 (2H, t, $J = 7.0$ Hz), 4.99 (2H, s), 6.78-6.81 (4H, m), 7.20-7.34 (12H, m), 7.40 (1H, s), 7.61 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 2.9$ Hz).

[0214]

Example 384

To a DMF (5 mL) solution of (*E*)-3-(3,5-dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one (400 mg) was added NaH (35.9 mg, 60% in mineral oil) at 0 °C, then the resultant mixture was stirred for 1 hour. To the mixture was added 4-chlorobenzyl chloride (0.093 mL) at 0 °C, then the resultant mixture was stirred at room temperature for 3 hours. The mixture was poured into saturated aqueous NH₄Cl, and extracted with AcOEt. The organic layer was washed with H₂O and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/0 and then AcOEt/MeOH = 4/1) to afford (*E*)-1-[4-(4-{2-[(4-chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one as a pale yellow amorphous powder (91 mg).

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48-2.50 (4H, m), 2.92 (2H, t, *J* = 7.0 Hz), 3.53 (2H, s), 3.67-3.69 (4H, m), 3.73-3.76 (2H, m), 4.49 (2H, s), 5.06 (2H, s), 6.78 (1H, d, *J* = 15.4 Hz), 6.84 (1H, d, *J* = 8.8 Hz), 7.18-7.35 (13H, m), 7.61 (1H, d, *J* = 15.4 Hz), 7.80 (1H, d, *J* = 2.9 Hz), 8.62 (2H, d, *J* = 5.6 Hz).

[0215]

The following compounds were produced in the same manner as in Example 384 using appropriate starting materials.

Example 385

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-methylbenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.34 (3H, s), 2.47-2.48 (4H, m), 2.92 (2H, t, *J* = 7.2 Hz), 3.51 (2H, s), 3.63-3.70 (4H, m), 3.73-3.75 (2H, m), 4.49 (2H, s), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.4 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.12-7.15 (2H, m), 7.18-7.31 (9H, m), 7.38-7.41 (2H, m), 7.45 (1H, s), 7.49-7.54 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

Example 386

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.34 (3H, s), 2.47-2.48 (4H, m), 2.92 (2H, t, *J* = 7.2 Hz), 3.51 (2H, s), 3.63-3.70 (4H, m), 3.73-3.75 (2H, m), 4.49 (2H, s), 5.14 (2H, s), 6.80 (1H, d, *J* = 15.4

Hz), 6.94 (1H, d, $J = 9.0$ Hz), 7.12-7.15 (2H, m), 7.18-7.31 (9H, m), 7.38-7.41 (2H, m), 7.45 (1H, s), 7.49-7.54 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

Example 387

- 5 (E)-1-[4-(4-{2-[(4-Chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one
- $^1\text{H-NMR}$ (CDCl_3) δ : 2.19 (3H, s), 2.47-2.49 (4H, m), 2.92 (2H, t, $J = 7.1$ Hz), 3.52 (2H, s), 3.61-3.71 (2H, m), 3.73-3.75 (2H, m), 4.49 (2H, s), 5.14 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.94 (1H, d, $J = 9.0$ Hz), 7.18-7.31 (11H, m), 7.38-7.41 (2H, m), 7.45 (1H, d, $J = 1.2$ Hz), 7.50-7.54 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).
- 10

Example 388

- (E)-3-(3,5-Dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[(4-fluorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one
- 15 $^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (6H, s), 2.48-2.50 (4H, m), 2.92 (2H, t, $J = 7.0$ Hz), 3.53 (2H, s), 3.67-3.69 (4H, m), 3.73-3.76 (2H, m), 4.48 (2H, s), 5.05 (2H, s), 6.78 (1H, d, $J = 15.4$ Hz), 6.83 (1H, d, $J = 9.0$ Hz), 6.99-7.02 (2H, m), 7.18-7.20 (2H, m), 7.25-7.27 (6H, m), 7.33-7.34 (3H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 2.9$ Hz), 8.62 (2H, d, $J = 5.9$ Hz).

20 Example 389

- (E)-3-(3,5-Dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[(4-methylbenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one
- $^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (6H, s), 2.33 (3H, s), 2.47-2.48 (4H, m), 2.91 (2H, t, $J = 7.1$ Hz), 3.51 (2H, s), 3.66-3.68 (4H, m), 3.73-3.75 (2H, m), 4.49 (2H, s), 5.04 (2H, s), 6.79 (1H, d, $J = 15.4$ Hz), 6.83 (1H, d, $J = 9.0$ Hz), 7.13 (2H, d, $J = 7.8$ Hz), 7.18-7.26 (8H, m), 7.32-7.35 (3H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.80 (1H, d, $J = 2.9$ Hz), 8.62 (2H, d, $J = 5.6$ Hz).
- 25

Example 390

- (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(cyclopropylmethoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one
- 30 $^1\text{H-NMR}$ (CDCl_3) δ : 0.18-0.22 (2H, m), 0.51-0.56 (2H, m), 1.04-1.10 (1H, m), 2.19 (3H, s), 2.46-2.49 (4H, m), 2.91 (2H, t, $J = 7.3$ Hz), 3.30 (2H, d, $J = 6.8$ Hz), 3.51 (2H, s), 3.65-3.67 (4H, m), 3.73-3.75 (2H, m), 5.14 (2H, s), 6.80 (1H, d, $J = 15.4$ Hz), 6.94 (1H, d, $J = 8.8$ Hz), 7.18-7.32 (7H, m), 7.37-7.42 (2H, m), 7.46 (1H, s), 7.51-7.53 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81

(1H, d, $J = 2.9$ Hz).

[0216]

Example 391

- 5 To a DMF (7 mL) solution of (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(piperazin-1-yl)prop-2-en-1-one (0.70 g) and 4-vinylbenzyl chloride (240 μ L) was added K_2CO_3 (291 mg) at room temperature. After stirring at room temperature for 36 hours, to the reaction mixture was added water, and extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaCl, dried over anhydrous
- 10 Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 0/1 and then AcOEt/MeOH = 19/1) to give (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one as a colorless powder (0.73 g).
- 1H -NMR ($CDCl_3$) δ : 2.19 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.53 (2H, s), 3.64-3.74 (4H, m), 5.14
- 15 (2H, s), 5.24 (1H, d, $J = 11.0$ Hz), 5.74 (1H, d, $J = 17.6$ Hz), 6.71 (1H, dd, $J = 17.6, 11.0$ Hz), 6.80 (1H, d, $J = 15.4$ Hz), 6.94 (1H, d, $J = 9.3$ Hz), 7.26-7.31 (5H, m), 7.37-7.41 (4H, m), 7.45 (1H, brs), 7.51-7.53 (1H, m), 7.57 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 2.9$ Hz).

[0217]

Example 392

- 20 To a CH_2Cl_2 (5 mL) solution of (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-3-methylpiperazin-1-yl]prop-2-en-1-one (0.50 g) and 4-[2-(4-fluorophenoxy)ethyl]benzaldehyde (298 mg) was added $NaBH(OAc)_3$ (323 mg) at room temperature. The resultant mixture was stirred at room temperature for 3 days. To the reaction mixture was added saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 . The
- 25 organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 0/1) to give (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}-3-methylpiperazin-1-yl]prop-2-en-1-one as a yellow powder (451 mg).
- 30 1H -NMR ($CDCl_3$) δ : 1.19 (3H, d, $J = 6.1$ Hz), 2.13-2.19 (4H, m), 2.35 (3H, s), 2.51-2.54 (1H, m), 2.73-2.76 (1H, m), 2.94-3.41 (5H, m), 3.75-3.79 (1H, m), 3.94-4.26 (4H, m), 4.98 (2H, s), 6.75-6.86 (3H, m), 6.90-7.00 (3H, m), 7.18 (2H, d, $J = 8.1$ Hz), 7.22-7.30 (7H, m), 7.35 (1H, dd, $J = 8.9, 2.9$ Hz), 7.43-7.47 (1H, m), 7.56 (1H, d, $J = 15.4$ Hz), 7.79 (1H, d, $J = 2.9$ Hz).

[0218]

The following compounds were produced in the same manner as in Example 392 using appropriate starting materials.

Example 393

- 5 (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2S)-2-methyl-4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 1.37 (3H, brs), 2.03-2.09 (1H, m), 2.18-2.20 (4H, m), 2.27 (3H, s), 2.35 (3H, s), 2.69-4.98 (13H, m), 6.76-6.82 (3H, m), 6.98-6.92 (1H, m), 7.04-7.08 (2H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.23-7.30 (7H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.44 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.78-7.79 (1H, m).
- 10

Example 394

- (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2S)-4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}-2-methylpiperazin-1-yl]prop-2-en-1-one
- 15 ¹H-NMR (CDCl₃) δ: 1.37 (3H, brs), 2.04-2.10 (1H, m), 2.18-2.21 (4H, m), 2.35 (3H, s), 2.69-4.98 (13H, m), 6.76-6.85 (3H, m), 6.90-6.99 (3H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.22-7.31 (7H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 3.2 Hz).

20 Example 395

- (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2R)-4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}-2-methylpiperazin-1-yl]prop-2-en-1-one
- ¹H-NMR (CDCl₃) δ: 1.37 (3H, brs), 2.03-2.10 (1H, m), 2.18-2.20 (4H, m), 2.35 (3H, s), 2.69-4.98 (13H, m), 6.76-6.85 (3H, m), 6.90-6.99 (3H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.22-7.29 (7H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.45 (1H, d, *J* = 2.2 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).
- 25

Example 396

- (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(2R)-2-methyl-4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one
- 30 ¹H-NMR (CDCl₃) δ: 1.37 (3H, brs), 2.03-2.09 (1H, m), 2.18-2.20 (4H, m), 2.28 (3H, s), 2.35 (3H, s), 2.69-4.98 (13H, m), 6.76-6.82 (3H, m), 6.91 (1H, d, *J* = 8.8 Hz), 7.06 (2H, d, *J* = 8.3 Hz), 7.18 (2H, d, *J* = 7.8 Hz), 7.23-7.31 (7H, m), 7.35 (1H, dd, *J* = 8.8, 2.9 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 2.9 Hz).

Example 397

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-3-methyl-4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one

- 5 ¹H-NMR (CDCl₃) δ: 1.18 (3H, d, *J* = 5.9 Hz), 2.11-2.19 (4H, m), 2.27 (3H, s), 2.35 (3H, s), 2.51-2.53 (1H, m), 2.73-2.76 (1H, m), 2.94-3.41 (5H, m), 3.74-3.78 (1H, m), 3.93-4.27 (4H, m), 4.98 (2H, s), 6.75-6.82 (3H, m), 6.91 (1H, d, *J* = 9.0 Hz), 7.04-7.08 (2H, m), 7.18 (2H, d, *J* = 7.8 Hz), 7.22-7.30 (7H, m), 7.35 (1H, dd, *J* = 9.0, 3.2 Hz), 7.43-7.46 (1H, m), 7.56 (1H, d, *J* = 15.4 Hz), 7.79 (1H, d, *J* = 3.2 Hz).

10

Example 398

(2*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(1*E*)-3-(4-fluorophenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 142-144 °C

- 15 ¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.36 (3H, s), 2.48 (4H, t, *J* = 5.0 Hz), 3.53 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 4.66 (2H, dd, *J* = 5.9, 1.5 Hz), 4.98 (2H, s), 6.39 (1H, dt, *J* = 16.0, 5.9 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.79 (1H, d, *J* = 15.4 Hz), 6.87-6.93 (3H, m), 6.95-7.01 (2H, m), 7.19 (2H, d, *J* = 7.6 Hz), 7.28-7.30 (5H, m), 7.34-7.39 (3H, m), 7.45 (1H, d, *J* = 2.2 Hz), 7.57 (1H, d, *J* = 15.4 Hz), 7.79 (1H, dd, *J* = 2.9, 0.5 Hz).

20

Example 399

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-(4-fluorophenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

mp: 101-104 °C

- 25 ¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.74 (2H, brs), 4.67 (2H, dd, *J* = 5.8, 1.3 Hz), 4.99 (2H, s), 6.39 (1H, dt, *J* = 16.0, 5.8 Hz), 6.72 (1H, d, *J* = 16.0 Hz), 6.76-6.82 (2H, m), 6.87-6.92 (2H, m), 6.95-7.00 (2H, m), 7.04-7.10 (2H, m), 7.25-7.33 (5H, m), 7.36-7.39 (4H, m), 7.61 (1H, d, *J* = 15.6 Hz), 7.81 (1H, d, *J* = 3.2 Hz).

30 Example 400

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[2-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,2,5-oxadiazepan-5-yl]prop-2-en-1-one

¹H-NMR (DMSO-*d*₆ at 70 °C) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.10 (3H, s), 2.30 (3H, s), 2.78-2.85 (1H, m), 2.90-3.00 (4H, m), 3.63-3.70 (4H, m), 3.83-3.85 (4H, m), 4.13-4.16 (2H, m), 5.05 (2H,

s), 6.81-6.84 (2H, m), 7.02 (1H, d, $J = 9.0$ Hz), 7.10-7.12 (2H, m), 7.17-7.32 (9H, m), 7.44 (1H, d, $J = 15.1$ Hz), 7.54-7.57 (2H, m), 7.75 (1H, brs), 7.78 (1H, d, $J = 2.9$ Hz).

Example 401

5 4-{[(6-{4-[(*E*)-3-(2-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (3H, s), 2.12 (3H, s), 2.96-3.08 (4H, m), 3.70-3.86 (8H, m), 4.09-4.14 (2H, m), 5.08 (2H, s), 6.71-6.85 (4H, m), 6.94 (2H, t, $J = 8.4$ Hz), 7.21-7.35 (7H, m), 7.52 (2H, d, $J = 8.1$ Hz), 7.63-7.69 (3H, m), 7.79 (1H, d, $J = 2.2$ Hz).

10

Example 402

4-{[(6-{4-[(*E*)-3-(2-{4-[2-(4-Methoxyphenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile

15 $^1\text{H-NMR}$ (CDCl_3) δ : 2.11 (3H, s), 2.12 (3H, s), 2.96-3.08 (4H, m), 3.70-3.86 (11H, m), 4.09-4.15 (2H, m), 5.08 (2H, s), 6.75 (1H, t, $J = 15.8$ Hz), 6.82-6.85 (5H, m), 7.21-7.24 (4H, m), 7.28-7.35 (3H, m), 7.52 (2H, d, $J = 8.3$ Hz), 7.64-7.69 (3H, m), 7.80 (1H, d, $J = 2.9$ Hz).

Example 403

20 (2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(2*E*)-4-(4-methylphenoxy)but-2-en-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

$^1\text{H-NMR}$ (CDCl_3) δ : 2.12 (6H, s), 2.14 (3H, d, $J = 1.5$ Hz), 2.29 (3H, s), 2.48 (4H, t, $J = 4.9$ Hz), 3.53 (2H, s), 3.65 (2H, brs), 3.73 (2H, brs), 4.72 (2H, d, $J = 6.3$ Hz), 4.99 (2H, s), 6.05-6.08 (1H, m), 6.78 (1H, d, $J = 15.4$ Hz), 6.81 (1H, d, $J = 9.0$ Hz), 6.85 (2H, dt, $J = 9.3, 2.5$ Hz), 7.05-7.10 (4H, m), 7.25-7.33 (5H, m), 7.36-7.41 (4H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 3.2$ Hz).

25

Example 404

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-2-methyl-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one

30 $^1\text{H-NMR}$ (CDCl_3) δ : 1.98 (3H, d, $J = 1.2$ Hz), 2.12 (6H, s), 2.29 (3H, s), 2.49 (4H, t, $J = 4.9$ Hz), 3.53 (2H, s), 3.66 (2H, brs), 3.75 (2H, brs), 4.54 (2H, s), 4.98 (2H, s), 6.61 (1H, brs), 6.79 (1H, d, $J = 15.4$ Hz), 6.81 (1H, dd, $J = 9.0, 0.5$ Hz), 6.87 (2H, dt, $J = 9.1, 2.4$ Hz), 7.04-7.10 (4H, m), 7.25-7.33 (7H, m), 7.36-7.40 (2H, m), 7.61 (1H, d, $J = 15.4$ Hz), 7.81 (1H, dd, $J = 3.2, 0.5$ Hz).

Example 405

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 1.38 (3H, t, *J* = 7.1 Hz), 2.19 (3H, s), 2.48 (4H, brs), 3.07 (2H, t, *J* = 7.1 Hz), 3.52 (2H, s), 3.64 (2H, brs), 3.74 (2H, brs), 3.97 (2H, q, *J* = 7.1 Hz), 4.12 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.78-6.82 (5H, m), 6.94 (1H, d, *J* = 9.0 Hz), 7.23-7.31 (7H, m), 7.38-7.41 (2H, m), 7.45 (1H, brs), 7.51-7.53 (1H, m), 7.57 (1H, d, *J* = 15.4 Hz), 7.82 (1H, d, *J* = 2.9 Hz).

Example 406

10 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one

¹H-NMR (CDCl₃) δ: 2.19 (3H, s), 2.46 (4H, t, *J* = 4.6 Hz), 3.04 (2H, t, *J* = 7.1 Hz), 3.47 (2H, s), 3.63 (2H, brs), 3.73 (2H, brs), 3.80 (3H, s), 4.13 (2H, t, *J* = 7.1 Hz), 5.14 (2H, s), 6.79 (1H, d, *J* = 15.4 Hz), 6.86 (4H, d, *J* = 8.4 Hz), 6.94 (1H, d, *J* = 8.8 Hz), 7.20 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 7.26-7.31 (3H, m), 7.38-7.41 (2H, m), 7.45 (1H, brs), 7.51-7.53 (1H, m), 7.56 (1H, d, *J* = 15.4 Hz), 7.81 (1H, d, *J* = 2.9 Hz).

[0219]

Example 407

20 To a solution of (*E*)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(piperazin-1-yl)prop-2-en-1-one (0.328 g) and (*E*)-3-[4-(chloromethyl)-2-methylphenyl]prop-2-en-1-yl 4-methylphenyl ether (0.204 g) in DMF (2 mL) was added DIPEA (0.13 mL) at room temperature under an Ar atmosphere. The mixture was stirred at room temperature for 20.5 hours, and then heated at 50 °C for 1 hour, and then cooled to room temperature, and evaporated under reduced pressure. To the residue was added saturated aqueous NaHCO₃, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to afford

25 [(*E*)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-[(*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one (0.370 g) as a colorless oil.

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.29 (3H, s), 2.34 (3H, s), 2.48 (4H, t, *J* = 4.9 Hz), 3.49 (2H, s), 3.66-3.75 (4H, m), 4.69 (2H, dd, *J* = 5.8, 1.3 Hz), 4.98 (2H, s), 6.29 (1H, dt, *J* = 15.9, 5.8 Hz), 6.78 (1H, d, *J* = 15.4 Hz), 6.81 (1H, d, *J* = 9.0 Hz), 6.87 (2H, dt, *J* = 9.3, 2.6 Hz), 6.92 (1H, d, *J*

= 15.9 Hz), 7.05-7.13 (6H, m), 7.25 (2H, brs), 7.32 (1H, dd, $J = 9.0, 3.1$ Hz), 7.36-7.39 (2H, m), 7.44 (1H, d, $J = 7.8$ Hz), 7.61 (1H, d, $J = 15.4$ Hz), 7.81 (1H, d, $J = 3.1$ Hz).

[0220]

Example 408

5 To a solution of (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (3.410 g) in EtOH (50 mL) was added 6 M HCl (0.86 mL) at 50 °C. The mixture was stirred at room temperature for 16 hours. The resulting precipitate was collected, and crystallized from EtOH (300 mL) and water (100 mL) to give (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride (3.060 g) as a colorless powder.

¹H-NMR (DMSO-*d*₆) δ : 2.10 (3H, s), 2.30 (3H, s), 3.06-3.58 (6H, m), 3.07 (2H, t, $J = 6.7$ Hz), 4.22 (2H, t, $J = 6.7$ Hz), 4.33 (2H, brs), 4.53-4.57 (2H, m), 5.06 (2H, s), 6.96 (2H, dt, $J = 9.9, 2.9$ Hz), 7.09 (1H, d, $J = 9.0$ Hz), 7.20 (2H, d, $J = 7.8$ Hz), 7.27-7.34 (5H, m), 7.42-7.52 (5H, m), 7.59 (1H, dd, $J = 9.0, 3.1$ Hz), 7.63 (1H, d, $J = 2.0$ Hz), 7.79 (1H, d, $J = 3.1$ Hz), 7.84 (1H, d, $J = 2.0$ Hz), 10.82 (1H, s).

[0221]

The following compounds were produced in the same manner as in Example 408 using appropriate starting materials.

Example 409

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
25 mp: 186.6-189.0 °C

Example 410

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
30 mp: 215.1-215.5 °C

Example 411

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 134.7-136.4 °C

Example 412

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-methylbenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
5 mp: 200.7-201.4 °C

Example 413

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
10 mp: 183.8-184.2 °C

Example 414

(*E*)-1-[4-(4-{2-[(4-Chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride
15 mp: 189.4-190.5 °C

Example 415

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
20 mp: 175.1-176.7 °C

Example 416

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
25 mp: 192.8-193.8 °C

Example 417

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
30 mp: 175.1-176.7 °C

Example 418

(*E*)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-

yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 180.2-182.7 °C (dec.)

Example 419

- 5 (E)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 196.6-198.0 °C

Example 420

- 10 (E)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 185.2-186.4 °C

Example 421

- 15 (E)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 207.4-207.9 °C

Example 422

- 20 (E)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 199.8-201.6 °C

Example 423

- 25 (E)-3-[3-Chloro-4-({5-[(3-fluoro-5-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 186.7-187.8 °C

Example 424

- 30 (E)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 224.7-225.8 °C

Example 425

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 207.9-208.3 °C

5 Example 426

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 225.4-225.9 °C

10 Example 427

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 224.7-224.8 °C

15 Example 428

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 219.8-220.2 °C

20 Example 429

(*E*)-3-[3-Chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 224.4-228.8 °C

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.80-3.80 (8H, m), 4.19 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs),
25 4.45-4.63 (2H, m), 5.11 (2H, s), 6.90-6.98 (2H, m), 7.05-7.15 (3H, m), 7.29 (1H, d, *J* = 15.5 Hz),
7.39-7.57 (9H, m), 7.58-7.65 (2H, m), 7.80 (1H, d, *J* = 3.3 Hz), 7.84 (1H, d, *J* = 1.6 Hz), 11.08
(1H, brs).

Example 430

30 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 227.1-227.2 °C

Example 431

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 201.9-202.6 °C

5 Example 432

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 232.1-232.7 °C

10 Example 433

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 180.1-181.1 °C

15 Example 434

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 225.9-226.5 °C

20 Example 435

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 214.3-216.2 °C

25 Example 436

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 231.5-231.8 °C

30 Example 437

(*E*)-3-[3-Chloro-5-methyl-4-({5-[2-(4-methylphenyl)ethoxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 228.9-229.5 °C

Example 438

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.9 Hz), 2.11 (3H, s), 2.82 (1H, septet, *J* = 6.9 Hz),
5 2.90-3.50 (7H, m), 3.55 (1H, brs), 4.18 (2H, t, *J* = 6.6 Hz), 4.33 (2H, brs), 4.45-4.62 (2H, m),
5.09 (2H, s), 6.80-6.88 (2H, m), 7.06-7.16 (3H, m), 7.18-7.32 (3H, m), 7.40-7.55 (7H, m), 7.56-
7.65 (2H, m), 7.80 (1H, d, *J* = 3.0 Hz), 7.84 (1H, d, *J* = 1.6 Hz), 10.83 (1H, brs).

Example 439

10 (*E*)-3-[3-Chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 230.5-230.6 °C

Example 440

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 225.1-226.6 °C

Example 441

20 (*E*)-3-(3-Chloro-5-methyl-4-{{5-(pyridin-2-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 240.5-241.0 °C

Example 442

25 (*E*)-3-(3-Chloro-5-methyl-4-{{5-(pyridin-3-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 227.7-229.3 °C

Example 443

30 (*E*)-3-[3-Chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 214.8-215.3 °C

Example 444

(*E*)-3-(3-Chloro-5-methyl-4-{[5-(pyridin-2-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 180.9-182.0 °C

5 Example 445

(*E*)-3-(3-Chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 166.4-167.7 °C

10 Example 446

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
¹H-NMR (DMSO- *d*₆) δ: 1.15 (6H, d, *J* = 6.9 Hz), 2.11 (3H, s), 2.76-2.87 (1H, m), 3.00-3.11 (4H, m), 3.35-3.38 (7H, m), 4.18 (2H, t, *J* = 6.8 Hz), 4.32 (2H, brs), 4.52-4.57 (2H, br m), 5.16 (2H, s), 6.84 (2H, d, *J* = 8.6 Hz), 7.07-7.18 (3H, m), 7.21-7.70 (11H, m), 7.71-7.89 (3H, m), 10.73 (1H, s).

Example 447

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 224.0-224.5 °C

Example 448

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 210.3-210.6 °C

Example 449

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 211.9-214.0 °C

Example 450

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 2.32 (3H, s), 2.89-3.40 (8H, m), 4.17 (2H, t, *J* = 6.8 Hz), 4.30-4.34 (2H, m), 4.51-4.56 (2H, m), 5.10 (2H, s), 6.77-6.85 (2H, m), 7.01-7.14 (4H, m), 7.19-7.33 (4H, m), 7.39-7.56 (6H, m), 7.62-7.66 (2H, m), 7.81-7.87 (2H, m), 11.25 (1H, s).

5

Example 451

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 3.03-3.59 (8H, m), 4.17 (2H, t, *J* = 6.8 Hz),
10 4.31-4.34 (2H, m), 4.51-4.56 (2H, m), 5.15 (2H, s), 6.80-6.84 (2H, m), 7.07-7.12 (3H, m), 7.21-7.33 (3H, m), 7.44-7.63 (9H, m), 7.83-7.85 (2H, m), 11.06-11.10 (1H, m).

Example 452

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.22 (3H, s), 2.94-3.60 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz),
15 4.31-4.35 (2H, m), 4.52-4.57 (2H, m), 5.17 (2H, s), 6.79-6.84 (2H, m), 7.10 (3H, dd, *J* = 14.0, 8.7 Hz), 7.30 (1H, d, *J* = 15.2 Hz), 7.37-7.54 (8H, m), 7.59-7.69 (3H, m), 7.82-7.87 (2H, m), 10.93-10.97 (1H, m).

20

Example 453

(*E*)-3-[3-Chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 218.0-218.2 °C

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Example 454

(*E*)-3-[3-Chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 188.0-189.5 °C

30

Example 455

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 168.4-169.8 °C

Example 456

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(2-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

5 mp: 200.7-201.9 °C

Example 457

(*E*)-1-(4-{4-[2-(4-Butylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

10 mp: 176.0-177.8 °C

Example 458

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

15 ¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.05 (2H, t, *J* = 6.4 Hz), 3.14-3.62 (6H, m), 3.68 (3H, s), 4.15 (2H, t, *J* = 6.4 Hz), 4.31-4.34 (2H, m), 4.52-4.57 (2H, m), 5.17 (2H, s), 6.85 (4H, s), 7.12 (1H, d, *J* = 8.9 Hz), 7.27-7.54 (9H, m), 7.60-7.68 (3H, m), 7.83-7.86 (2H, m), 10.84 (1H, s).

Example 459

20 (*E*)-1-(4-{4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride

mp: 182.0-182.5 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.01-3.63 (8H, m), 4.13 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.51-4.57 (2H, m), 5.17 (2H, s), 5.94 (2H, s), 6.36 (1H, dd, *J* = 8.6, 2.6 Hz), 6.63 (1H, d, *J* = 2.6 Hz), 6.79 (1H, d, *J* = 8.6 Hz), 7.12 (1H, d, *J* = 8.9 Hz), 7.28-7.67 (12H, m), 7.84-7.85 (2H, m), 11.36 (1H, brs).

Example 460

30 (*E*)-1-(4-{4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 229.5-231.3 °C (dec.)

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.01-3.58 (8H, m), 4.13 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.51-4.57 (2H, m), 5.05 (2H, s), 5.94 (2H, s), 6.36 (1H, dd, *J* = 8.6, 2.6 Hz), 6.62 (1H, d, *J* = 2.6 Hz), 6.79 (1H, d, *J* = 8.6 Hz), 7.09 (1H, d, *J* = 8.9 Hz), 7.18-7.63 (12H, m), 7.78-

7.84 (2H, m), 11.01 (1H, brs).

Example 461

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 210.3-210.9 °C

Example 462

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.12 (6H, s), 2.16 (3H, s), 3.04-3.05 (3H, m), 3.13-3.67 (5H, m), 4.15 (2H, t, *J* = 6.6 Hz), 4.33 (2H, s), 4.54 (2H, d, *J* = 11.9 Hz), 5.17 (2H, s), 6.64 (1H, d, *J* = 8.2 Hz), 6.73 (1H, s), 7.01 (1H, d, *J* = 8.2 Hz), 7.13 (1H, d, *J* = 8.7 Hz), 7.31 (1H, d, *J* = 15.6 Hz), 7.38-7.53 (8H, m), 7.61-7.67 (3H, m), 7.83-7.87 (2H, m), 11.26 (1H, s).

Example 463

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.99-3.19 (4H, m), 3.46-3.57 (4H, m), 3.72 (3H, s), 4.20 (2H, t, *J* = 6.6 Hz), 4.32-4.35 (2H, m), 4.53-4.56 (2H, m), 5.17 (2H, s), 6.45-6.54 (3H, m), 7.12-7.19 (2H, m), 7.31 (1H, d, *J* = 15.1 Hz), 7.38-7.54 (8H, m), 7.60-7.68 (3H, m), 7.83-7.87 (2H, m), 10.94 (1H, s).

Example 464

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(2-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.97-3.19 (4H, m), 3.35-3.61 (4H, m), 4.26-4.37 (4H, m), 4.53-4.56 (2H, m), 5.17 (2H, s), 6.94 (1H, t, *J* = 7.6 Hz), 7.11-7.17 (2H, m), 7.26-7.33 (2H, m), 7.38-7.53 (9H, m), 7.61-7.67 (3H, m), 7.84-7.86 (2H, m), 11.00 (1H, s).

Example 465

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 214.2-214.7 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.05-4.53 (14H, m), 5.17 (2H, s), 6.79 (2H, d, *J* = 8.8 Hz), 7.13 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 15.6 Hz), 7.40-7.43 (4H, m), 7.48-7.53 (4H, m), 7.58 (2H, d, *J* = 8.3 Hz), 7.61-7.67 (3H, m), 7.84-7.85 (2H, m), 10.92 (1H, brs).

5 Example 466

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.00-3.16 (4H, m), 3.33-3.60 (4H, m), 4.21 (2H, t, *J* = 6.6 Hz), 4.32 (2H, s), 4.53 (2H, s), 5.17 (2H, s), 6.96 (2H, d, *J* = 8.8 Hz), 7.13 (1H, d, *J* = 8.8 Hz),
10 7.28-7.34 (3H, m), 7.37-7.55 (8H, m), 7.60-7.68 (3H, m), 7.83-7.86 (2H, m), 10.99 (1H, s).

Example 467

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(quinolin-6-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.96-3.22 (4H, m), 3.32-3.76 (4H, m), 4.32-4.35 (2H, m),
15 4.42 (2H, t, *J* = 6.6 Hz), 4.53-4.56 (2H, m), 5.17 (2H, s), 7.13 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 15.1 Hz), 7.38-7.43 (2H, m), 7.48-7.53 (4H, m), 7.57-7.71 (7H, m), 7.83-7.89 (3H, m), 8.19 (1H, d, *J* = 9.3 Hz), 8.77 (1H, d, *J* = 8.3 Hz), 9.01 (1H, d, *J* = 4.4 Hz), 11.39 (1H, s).

20 Example 468

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.07-3.08 (2H, m), 3.17-3.68 (6H, m), 4.25 (2H, t, *J* = 6.6 Hz), 4.32-4.34 (2H, m), 4.53-4.55 (2H, m), 5.17 (2H, s), 6.91 (1H, d, *J* = 6.3 Hz), 6.96-7.03 (2H,
25 m), 7.13 (1H, d, *J* = 8.8 Hz), 7.28-7.32 (2H, m), 7.38-7.54 (8H, m), 7.61-7.67 (3H, m), 7.82-7.86 (2H, m), 10.47 (1H, s).

Example 469

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.26 (3H, s), 2.99-3.11 (4H, m), 3.18-3.65 (4H, m), 4.19 (2H, t, *J* = 6.6 Hz), 4.31-4.34 (2H, m), 4.53-4.56 (2H, m), 5.17 (2H, s), 6.70-6.77 (3H, m), 7.11-7.16 (2H, m), 7.31 (1H, d, *J* = 15.4 Hz), 7.38-7.44 (4H, m), 7.47-7.58 (4H, m), 7.60-7.67 (3H, m), 7.84-7.87 (2H, m), 11.32 (1H, s).

Example 470

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,5-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

- 5 ¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.21 (6H, s), 3.00-3.07 (4H, m), 3.25-3.63 (4H, m), 4.16 (2H, t, *J* = 6.6 Hz), 4.30-4.33 (2H, m), 4.53-4.56 (2H, m), 5.17 (2H, s), 6.53-6.56 (3H, m), 7.12 (1H, d, *J* = 8.8 Hz), 7.31 (1H, d, *J* = 15.4 Hz), 7.38-7.44 (4H, m), 7.47-7.57 (4H, m), 7.60-7.67 (3H, m), 7.84-7.86 (2H, m), 11.38 (1H, s).

10 Example 471

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(2,3-dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

- ¹H-NMR (DMSO-*d*₆) δ: 2.00 (3H, s), 2.12 (3H, s), 2.18 (3H, s), 2.97-3.67 (8H, m), 4.16 (2H, t, *J* = 6.3 Hz), 4.31-4.34 (2H, m), 4.53-4.56 (2H, m), 5.17 (2H, s), 6.73 (1H, d, *J* = 7.3 Hz), 6.78 (1H, d, *J* = 8.1 Hz), 7.00 (1H, t, *J* = 7.8 Hz), 7.13 (1H, d, *J* = 9.0 Hz), 7.31 (1H, d, *J* = 15.4 Hz), 7.38-7.48 (5H, m), 7.51-7.58 (3H, m), 7.60-7.68 (3H, m), 7.84-7.87 (2H, m), 11.30 (1H, s).

Example 472

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-

- 20 methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 201.2-202.5 °C

Example 473

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

- 25 fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 197.0-199.5 °C

Example 474

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-

- 30 yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 185.6-186.3 °C

Example 475

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 193.5-195.8 °C

Example 476

- 5 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.36 (3H, s), 3.04-3.57 (8H, m), 4.19 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.48-4.57 (2H, m), 5.20 (2H, s), 6.91-6.97 (4H, m), 7.05-7.12 (4H, m), 7.38-7.44 (4H, m), 7.51-7.55 (3H, m), 7.61-7.65 (2H, m), 7.74 (1H, d, *J* = 15.1 Hz), 7.81 (1H, d, *J* = 9.0 Hz), 7.99 (1H, d, *J* = 3.2 Hz), 10.98 (1H, brs).

Example 477

- 15 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.21 (3H, s), 2.35 (3H, s), 3.03-3.54 (8H, m), 4.16 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.48-4.56 (2H, m), 5.20 (2H, s), 6.81 (2H, m), 6.93-6.96 (2H, m), 7.05-7.12 (4H, m), 7.38-7.44 (4H, m), 7.49-7.54 (3H, m), 7.61-7.65 (2H, m), 7.74 (1H, d, *J* = 15.1 Hz), 7.81 (1H, d, *J* = 9.0 Hz), 7.99 (1H, d, *J* = 3.2 Hz), 10.79 (1H, brs).

20 Example 478

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 209.6-212.0 °C

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.9 Hz), 2.35 (3H, s), 2.81 (1H, septet, *J* = 6.9 Hz), 3.03-3.56 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.32-4.53 (4H, m), 5.20 (2H, s), 6.81-6.87 (2H, m), 6.93-6.96 (2H, m), 7.04-7.14 (4H, m), 7.37-7.44 (4H, m), 7.50-7.55 (3H, m), 7.61-7.66 (2H, m), 7.74 (1H, d, *J* = 15.5 Hz), 7.79-7.83 (1H, m), 7.99 (1H, d, *J* = 3.0 Hz), 10.91 (1H, brs).

Example 479

- 30 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 194.9-197.8 °C

Example 480

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.26 (3H, s), 3.06 (2H, t, *J* = 6.5 Hz), 3.14-3.67 (6H, m), 3.75 (3H, s), 4.19 (2H, t, *J* = 6.5 Hz), 4.31-4.34 (2H, m), 4.52-4.55 (2H, m), 5.17 (2H, s), 6.70-6.76 (3H, m),
5 6.99 (1H, d, *J* = 8.8 Hz), 7.09-7.17 (2H, m), 7.25 (1H, d, *J* = 15.4 Hz), 7.31 (1H, d, *J* = 8.1 Hz), 7.39-7.44 (4H, m), 7.49-7.62 (7H, m), 7.86 (1H, d, *J* = 2.9 Hz), 11.07 (1H, s).

Example 481

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-[4-(4-{2-[4-(propan-
10 2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 196.7-198.7 °C

Example 482

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-
15 methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 203.4-205.7 °C

Example 483

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3-
20 ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 209.8-211.0 °C

Example 484

(*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-
25 (4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 181.4-182.0 °C

Example 485

(*E*)-3-[3-Chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-
30 {4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 228.9-229.4 °C

Example 486

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-

yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 7.1 Hz), 2.78-2.85 (1H, m), 2.99-3.60 (6H, m), 3.06 (2H, t, *J* = 6.6 Hz), 4.17 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.53 (2H, brs), 5.21 (2H, s), 6.84 (2H, d, *J* = 8.8 Hz), 7.07-7.14 (5H, m), 7.21 (1H, d, *J* = 15.4 Hz), 7.40-7.43 (4H, m), 7.52-7.56 (4H, m), 7.62-7.67 (2H, m), 7.75 (2H, d, *J* = 8.5 Hz), 8.00 (1H, d, *J* = 3.2 Hz), 11.28 (1H, brs).

Example 487

(*E*)-3-[3-Chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 2.95-3.60 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.33 (2H, s), 4.53 (2H, s), 5.21 (2H, s), 6.82 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.5 Hz), 7.13 (1H, d, *J* = 8.8 Hz), 7.23-7.32 (2H, m), 7.38-7.51 (7H, m), 7.64-7.68 (2H, m), 7.84-7.86 (2H, m), 10.71 (1H, s).

15 Example 488

(*E*)-3-[3-Chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 180.1-181.7 °C

20 Example 489

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-nitrophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 200.9-202.3 °C

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.11-4.53 (14H, m), 5.05 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.16 (2H, d, *J* = 8.6 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.33 (2H, d, *J* = 7.8 Hz), 7.44 (2H, d, *J* = 7.8 Hz), 7.49 (1H, d, *J* = 15.4 Hz), 7.54 (2H, d, *J* = 7.3 Hz), 7.58-7.61 (1H, m), 7.63 (1H, brs), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, brs), 8.20 (2H, d, *J* = 8.3 Hz), 11.09 (1H, brs).

30 Example 490

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-nitrophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 194.8-195.2 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.11-4.53 (14H, m), 5.17 (2H, s), 7.12 (1H, d, *J* = 9.0 Hz),

7.16 (2H, d, $J = 9.0$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.39-7.47 (5H, m), 7.51-7.55 (3H, m), 7.61-7.67 (3H, m), 7.84-7.85 (2H, m), 8.20 (2H, d, $J = 9.0$ Hz), 10.98 (1H, brs).

Example 491

- 5 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(cyclopropylmethoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 200.2-202.1 °C

Example 492

- 10 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(3,4-dichlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 199.2-200.2 °C

Example 493

- 15 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 218.8-219.2 °C

Example 494

- 20 (E)-3-[3-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ : 1.15 (6H, d, $J = 7.1$ Hz), 2.13 (3H, s), 2.30 (3H, s), 2.81 (1H, septet, $J = 6.8$ Hz), 2.90-3.70 (8H, m), 4.18 (2H, t, $J = 6.6$ Hz), 4.32 (2H, s), 4.52 (2H, s), 5.08 (2H, s), 6.82-6.86 (2H, m), 6.98 (1H, d, $J = 8.3$ Hz), 7.01 (1H, d, $J = 9.0$ Hz), 7.11-7.15 (2H, m), 7.17-
25 7.21 (3H, m), 7.33 (2H, d, $J = 8.1$ Hz), 7.43 (2H, d, $J = 8.1$ Hz), 7.49-7.59 (5H, m), 7.68 (1H, d, $J = 1.7$ Hz), 7.87 (1H, d, $J = 3.2$ Hz), 10.67 (1H, brs).

Example 495

- 30 (E)-3-[3-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 227.6-228.7 °C

Example 496

(E)-1-(4-{4-[2-(4-Methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-methyl-4-({5-[(4-

methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 216.2-216.9 °C

Example 497

- 5 (E)-3-[3-Chloro-4-({5-[(2-methoxybenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 171.1-172.6 °C

Example 498

- 10 (E)-3-[3-Chloro-4-({5-[(2-chloro-4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 194.6-197.5 °C

Example 499

- 15 (E)-3-[3-Chloro-4-({5-[(3-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 186.5-186.8 °C

Example 500

- 20 (E)-3-[3-Chloro-5-methyl-4-({5-[(3-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 179.1-179.9 °C

Example 501

- 25 (E)-3-[3-Chloro-4-({5-[(3-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.11 (3H, s), 2.79-2.84 (1H, m), 2.99-3.64 (8H, m), 4.18 (2H, t, *J* = 6.6 Hz), 4.31-4.34 (2H, m), 4.52-4.55 (2H, m), 5.13 (2H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.10-7.15 (3H, m), 7.30 (1H, d, *J* = 15.4 Hz), 7.40-7.48 (6H, m), 7.50-7.56 (3H, m),

- 30 7.61-7.65 (2H, m), 7.81 (1H, d, *J* = 2.7 Hz), 7.85 (1H, s), 11.13 (1H, s).

Example 502

2-({[6-(2-Chloro-6-methyl-4-{{(E)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

mp: 180.7-181.2 °C

Example 503

(*E*)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.14 (3H, s), 2.22 (3H, s), 2.90-3.60 (8H, m), 4.17 (2H, t, *J* = 6.7 Hz), 4.33 (2H, s), 4.54 (2H, s), 5.23 (2H, s), 6.80-6.83 (2H, m), 6.99-7.08 (4H, m), 7.20 (1H, d, *J* = 15.1 Hz), 7.41-7.56 (7H, m), 7.60 (1H, dd, *J* = 7.6, 1.5 Hz), 7.64 (1H, dd, *J* = 9.0, 3.2 Hz), 7.67 (2H, dd, *J* = 8.1, 1.5 Hz), 7.93 (1H, d, *J* = 3.2 Hz), 10.56 (1H, brs).

Example 504

(*E*)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 171.3-172.3 °C

Example 505

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.14 (3H, s), 2.22 (3H, s), 2.90-3.70 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.32 (2H, s), 4.53 (2H, s), 5.19 (2H, s), 6.80-6.83 (2H, m), 7.00 (1H, d, *J* = 8.3 Hz), 7.06 (3H, t, *J* = 8.8 Hz), 7.21 (1H, d, *J* = 15.1 Hz), 7.38-7.43 (4H, m), 7.49-7.56 (5H, m), 7.60-7.65 (2H, m), 7.69 (1H, d, *J* = 2.0 Hz), 7.92 (1H, d, *J* = 3.4 Hz), 10.91 (1H, brs).

Example 506

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 192.9-194.6 °C

Example 507

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 178.2-178.9 °C

Example 508

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 174.5-174.9 °C

5 Example 509

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 203.1-203.8 °C

10 Example 510

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 205.4-206.0 °C

15 Example 511

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 196.6-197.3 °C

20 Example 512

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-(4-{4-[2-(3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 184.2-186.2 °C

25 Example 513

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 2.80-3.80 (8H, m), 4.17 (2H, t, *J* = 6.8 Hz), 4.32 (2H, brs), 4.51-4.56 (2H, m), 5.09 (2H, s), 6.82 (2H, d, *J* = 8.6 Hz), 7.09 (3H, t, *J* = 8.9 Hz), 7.19-7.26 (2H, m), 7.30 (1H, d, *J* = 15.5 Hz), 7.41-7.55 (8H, m), 7.60-7.63 (2H, m), 7.81 (1H, d, *J* = 3.0 Hz), 7.85 (1H, d, *J* = 1.6 Hz), 11.15 (1H, brs).

Example 514

(*E*)-3-[3-Chloro-4-({5-[(3-fluoro-2-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-

{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 176.8-177.7 °C

Example 515

5 (E)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 212.6-212.9 °C (dec.)

¹H-NMR (DMSO-*d*₆) δ: 2.21 (3H, s), 2.31 (3H, s), 2.35 (3H, s), 3.03-3.45 (8H, m), 4.16 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.52 (2H, brs), 5.09 (2H, s), 6.80-6.83 (2H, m), 6.91-6.93 (2H, m),
10 7.01-7.12 (4H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.34 (2H, d, *J* = 7.8 Hz), 7.41-7.43 (2H, m), 7.49-7.51 (2H, m), 7.57-7.60 (1H, m), 7.74 (1H, d, *J* = 15.1 Hz), 7.79 (1H, d, *J* = 9.5 Hz), 7.93-7.94 (1H, m), 10.76 (1H, brs).

Example 516

15 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-iodophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.05-3.15 (5H, m), 3.39-3.57 (3H, m), 4.20 (2H, t, *J* = 6.6 Hz), 4.32-4.35 (2H, m), 4.52-4.56 (2H, m), 5.24 (2H, s), 6.77-6.81 (2H, m), 7.12 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.41-7.53 (5H, m), 7.56-7.59 (2H, m), 7.62-7.69 (4H, m), 7.78
20 (2H, d, *J* = 8.3 Hz), 7.83 (1H, d, *J* = 3.2 Hz), 7.85 (1H, d, *J* = 1.5 Hz), 10.97 (1H, brs).

Example 517

(E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

25 ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.22 (3H, s), 3.04-3.15 (5H, m), 3.35-3.56 (3H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.33 (2H, brs), 4.52-4.56 (2H, m), 5.24 (2H, s), 6.82 (2H, d, *J* = 8.8 Hz), 7.07 (2H, d, *J* = 8.8 Hz), 7.12 (1H, d, *J* = 9.0 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.42-7.53 (5H, m), 7.62-7.69 (4H, m), 7.78 (2H, d, *J* = 8.3 Hz), 7.83 (1H, d, *J* = 3.2 Hz), 7.85 (1H, d, *J* = 1.7 Hz), 10.89 (1H, brs).

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Example 518

(E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.01-3.19 (3H, m), 3.34-3.62 (5H, m), 4.22 (2H, t, *J* = 6.6

Hz), 4.31-4.33 (2H, m), 4.52-4.56 (2H, m), 5.24 (2H, s), 6.95-6.98 (2H, m), 7.12 (1H, d, $J = 9.0$ Hz), 7.29-7.33 (3H, m), 7.41-7.56 (5H, m), 7.62-7.69 (4H, m), 7.78 (2H, d, $J = 8.1$ Hz), 7.83 (1H, d, $J = 2.9$ Hz), 7.85 (1H, s), 11.30 (1H, brs).

5 Example 519

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, $J = 6.8$ Hz), 2.10 (3H, s), 2.78-2.85 (1H, m), 3.04-3.08 (5H, m), 3.35-3.55 (3H, m), 4.18 (2H, t, $J = 6.7$ Hz), 4.34 (2H, brs), 4.52-4.56 (2H, m), 5.24 (2H, s),
10 6.84 (2H, d, $J = 8.5$ Hz), 7.11-7.14 (3H, m), 7.30 (1H, d, $J = 15.1$ Hz), 7.42-7.52 (5H, m), 7.62-7.67 (4H, m), 7.78 (2H, d, $J = 8.1$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.85 (1H, s), 10.80 (1H, s).

Example 520

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-
15 (4-{4-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 1.68-1.70 (4H, m), 2.10 (3H, s), 2.61-2.66 (4H, m), 3.03-3.15 (5H, m), 3.35-3.54 (3H, m), 4.15 (2H, t, $J = 6.6$ Hz), 4.33 (2H, brs), 4.51-4.54 (2H, m), 5.24 (2H, s), 6.60-6.66 (2H, m), 6.93 (1H, d, $J = 8.3$ Hz), 7.12 (1H, d, $J = 8.8$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.41-
20 7.51 (5H, m), 7.62-7.68 (4H, m), 7.77 (2H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.85 (1H, s), 10.73 (1H, brs).

Example 521

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-
25 (4-{4-[2-(naphthalen-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 3.11-3.18 (5H, m), 3.42-3.53 (3H, m), 4.33-4.36 (4H, m), 4.53-4.56 (2H, m), 5.24 (2H, s), 7.11-7.16 (2H, m), 7.29-7.35 (3H, m), 7.45-7.53 (6H, m), 7.62-7.69 (4H, m), 7.77-7.85 (7H, m), 10.64 (1H, brs).

30 Example 522

(*E*)-1-[4-(4-{2-[(6-Bromopyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.07-3.11 (5H, m), 3.36-3.54 (3H, m), 4.30-4.33 (4H, m), 4.52-4.54 (2H, m), 5.24 (2H, s), 7.12 (1H, d, $J = 8.8$ Hz), 7.30 (1H, d, $J = 15.6$ Hz), 7.39-7.55

(7H, m), 7.62-7.69 (4H, m), 7.77 (2H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 3.2$ Hz), 7.85 (1H, s), 8.11 (1H, d, $J = 2.9$ Hz), 10.70 (1H, brs).

Example 523

5 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.28 (3H, t, $J = 7.1$ Hz), 2.11 (3H, s), 3.01-3.15 (5H, m), 3.35-3.56 (3H, m), 3.93 (2H, q, $J = 7.1$ Hz), 4.14 (2H, t, $J = 6.6$ Hz), 4.33 (2H, brs), 4.52-4.56 (2H, m), 5.24 (2H, s), 6.81-6.86 (4H, m), 7.12 (1H, d, $J = 9.0$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.41-7.53 (5H, m), 7.63-7.69 (4H, m), 7.77 (2H, d, $J = 8.1$ Hz), 7.83 (1H, d, $J = 3.2$ Hz), 7.85 (1H, d, $J = 1.7$ Hz), 10.93 (1H, brs).

Example 524

15 (E)-1-(4-{4-[2-(4-Acetylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[4-methylbenzyl]oxy}pyridin-2-yl)oxy]phenyl]prop-2-en-1-one hydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.10 (3H, s), 2.30 (3H, s), 2.50 (3H, s), 3.00-3.61 (8H, m), 4.30-4.34 (4H, m), 4.52-4.55 (2H, m), 5.05 (2H, s), 7.04 (2H, d, $J = 9.0$ Hz), 7.09 (1H, d, $J = 9.0$ Hz), 7.19 (2H, d, $J = 8.1$ Hz), 7.28-7.34 (3H, m), 7.43-7.63 (7H, m), 7.79 (1H, d, $J = 2.9$ Hz), 7.84-7.85 (1H, m), 7.91 (2H, d, $J = 8.8$ Hz), 11.25 (1H, brs).

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Example 525

4-{2-[4-({4-[(E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoyl]piperazin-1-yl)methyl]phenyl]ethoxy}benzonitrile hydrochloride

25 $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.11 (3H, s), 3.00-3.18 (5H, m), 3.42-3.60 (3H, m), 4.31-4.34 (4H, m), 4.52-4.56 (2H, m), 5.24 (2H, s), 7.11-7.14 (3H, m), 7.31 (1H, d, $J = 15.4$ Hz), 7.43-7.55 (5H, m), 7.62-7.69 (4H, m), 7.75-7.79 (4H, m), 7.83 (1H, d, $J = 3.2$ Hz), 7.85 (1H, s), 11.19 (1H, brs).

Example 526

30 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-fluoro-3-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

$^1\text{H-NMR}$ (DMSO- d_6) δ : 2.11 (3H, s), 2.19 (3H, d, $J = 1.7$ Hz), 3.02-3.08 (5H, m), 3.39-3.56 (3H, m), 4.17 (2H, t, $J = 6.6$ Hz), 4.34 (2H, brs), 4.52-4.55 (2H, m), 5.24 (2H, s), 6.72-6.76 (1H, m), 6.83-6.86 (1H, m), 7.02 (1H, t, $J = 9.2$ Hz), 7.12 (1H, d, $J = 8.8$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.42-7.52 (5H, m), 7.64-7.68 (4H, m), 7.77 (2H, d, $J = 8.1$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.84

(1H, s), 10.83 (1H, brs).

Example 527

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 193.6-194.8 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 3.04-4.55 (14H, m), 5.29 (2H, s), 6.82 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 7.12 (1H, d, *J* = 9.0 Hz), 7.29 (1H, d, *J* = 15.4 Hz), 7.42 (2H, d, *J* = 7.3 Hz), 7.47-7.51 (3H, m), 7.63-7.66 (2H, m), 7.73 (2H, d, *J* = 8.5 Hz), 7.83-7.84 (2H, m), 8.27 (2H, d, *J* = 8.5 Hz), 11.08 (1H, s).

Example 528

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 221.7-222.9 °C

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 7.1 Hz), 2.10 (3H, s), 2.81 (1H, septet, *J* = 6.8 Hz), 3.05-4.53 (14H, m), 5.29 (2H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.12 (2H, d, *J* = 9.3 Hz), 7.13 (1H, d, *J* = 8.5 Hz), 7.29 (1H, d, *J* = 15.4 Hz), 7.44-7.49 (5H, m), 7.63-7.66 (2H, m), 7.73 (2H, d, *J* = 8.5 Hz), 7.83-7.84 (2H, m), 8.27 (2H, d, *J* = 8.5 Hz), 10.61 (1H, brs).

Example 529

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 175.7-176.6 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.22 (3H, s), 3.04-4.53 (14H, m), 5.47 (2H, s), 6.81 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 7.11 (1H, d, *J* = 8.8 Hz), 7.29 (1H, d, *J* = 15.4 Hz), 7.42-7.51 (5H, m), 7.62-7.66 (3H, m), 7.80-7.84 (4H, m), 8.13 (1H, d, *J* = 8.1 Hz), 10.57 (1H, brs).

Example 530

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 182.3-184.5 °C

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.11 (3H, s), 2.81 (1H, qq, *J* = 6.8, 6.8 Hz), 3.05-4.53 (14H, m), 5.47 (2H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.11 (1H, d, *J* = 8.5 Hz), 7.13 (2H, d,

$J = 8.3$ Hz), 7.29 (1H, d, $J = 15.4$ Hz), 7.42-7.51 (5H, m), 7.63-7.66 (3H, m), 7.80-7.84 (4H, m), 8.13 (1H, d, $J = 8.1$ Hz), 10.45 (1H, brs).

Example 531

- 5 (E)-3-[3-Chloro-5-methyl-4-({5-[(2-nitrobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 156.6-159.1 °C

- $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.11 (3H, s), 3.03-4.55 (17H, m), 5.47 (2H, s), 6.84 (2H, d, $J = 9.3$ Hz), 6.87 (2H, d, $J = 9.5$ Hz), 7.11 (1H, d, $J = 9.0$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.42 (2H, d, $J = 7.8$ Hz), 7.49 (1H, d, $J = 15.6$ Hz), 7.53 (2H, d, $J = 7.6$ Hz), 7.62-7.66 (3H, m), 7.78-7.84 (4H, m), 8.13 (1H, d, $J = 8.3$ Hz), 11.09 (1H, s).

Example 532

- 15 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-{2-[(5-chloropyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
- $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.11 (3H, s), 3.03-3.15 (5H, m), 3.34-3.57 (3H, m), 4.32 (2H, brs), 4.46-4.55 (4H, m), 5.24 (2H, s), 6.85 (1H, d, $J = 9.0$ Hz), 7.12 (1H, d, $J = 8.8$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.41 (2H, d, $J = 7.6$ Hz), 7.47-7.53 (3H, m), 7.62-7.69 (4H, m), 7.76-7.85 (5H, m), 8.21 (1H, d, $J = 2.7$ Hz), 10.97 (1H, brs).

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Example 533

- (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
- 25 $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.32 (3H, d, $J = 7.1$ Hz), 2.11 (3H, s), 2.21 (3H, s), 3.06-3.59 (7H, m), 4.02 (1H, dd, $J = 9.5, 6.8$ Hz), 4.07 (1H, dd, $J = 9.5, 6.8$ Hz), 4.32 (2H, brs), 4.52-4.55 (2H, m), 5.17 (2H, s), 6.79 (2H, dt, $J = 9.2, 2.4$ Hz), 7.06 (2H, d, $J = 8.1$ Hz), 7.12 (1H, d, $J = 9.0$ Hz), 7.30 (1H, d, $J = 15.4$ Hz), 7.39-7.66 (11H, m), 7.84-7.85 (2H, m), 11.02 (1H, brs).

Example 534

- 30 (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
- $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.20 (3H, d, $J = 6.1$ Hz), 2.10 (3H, s), 2.21 (3H, s), 2.30 (3H, s), 2.85-3.59 (6H, m), 2.87 (1H, dd, $J = 13.7, 5.6$ Hz), 2.98 (1H, dd, $J = 13.7, 6.6$ Hz), 4.31 (2H, brs), 4.51-4.54 (2H, m), 4.61-4.68 (1H, m), 5.05 (2H, s), 6.80 (2H, dt, $J = 9.0, 2.4$ Hz), 7.05 (2H, d, J

= 8.1 Hz), 7.08 (1H, d, J = 8.9 Hz), 7.20 (2H, d, J = 7.8 Hz), 7.27-7.52 (8H, m), 7.59 (1H, dd, J = 8.9, 3.1 Hz), 7.62 (1H, d, J = 1.7 Hz), 7.79 (1H, d, J = 3.1 Hz), 7.83 (1H, d, J = 1.7 Hz), 11.14 (1H, brs).

5 Example 535

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[1-(4-methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ : 1.32 (3H, d, J = 7.1 Hz), 2.10 (3H, s), 2.21 (3H, s), 2.30 (3H, s), 3.06-3.56 (7H, m), 4.02 (1H, dd, J = 9.6, 6.8 Hz), 4.07 (1H, dd, J = 9.6, 7.0 Hz), 4.33 (2H, brs), 4.52-10 4.55 (2H, m), 5.05 (2H, s), 6.79 (2H, dt, J = 9.3, 2.5 Hz), 7.05-7.10 (3H, m), 7.20 (2H, d, J = 7.8 Hz), 7.29 (1H, d, J = 15.6 Hz), 7.33 (2H, d, J = 8.1 Hz), 7.43-7.53 (5H, m), 7.59 (1H, dd, J = 8.9, 3.2 Hz), 7.62 (1H, d, J = 1.7 Hz), 7.78 (1H, d, J = 3.2 Hz), 7.84 (1H, d, J = 1.7 Hz), 10.82 (1H, brs).

15 Example 536

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(pyridin-2-yloxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ : 2.11 (3H, s), 3.00-3.39 (7H, m), 3.63 (1H, brs), 4.32 (2H, brs), 4.48-4.55 (4H, m), 5.24 (2H, s), 6.81 (1H, d, J = 8.3 Hz), 6.97-6.99 (1H, m), 7.12 (1H, d, J = 9.0 Hz), 7.301 20 (1H, d, J = 15.4 Hz), 7.39-7.56 (5H, m), 7.62-7.73 (5H, m), 7.77 (2H, d, J = 8.3 Hz), 7.82-7.85 (2H, m), 8.16 (1H, dd, J = 5.0, 1.3 Hz), 11.41 (1H, brs).

Example 537

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-25 (4-{4-[2-(4-cyclopropylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ : 0.53-0.57 (2H, m), 0.84-0.88 (2H, m), 1.80-1.87 (1H, m), 2.11 (3H, s), 3.00-3.07 (5H, m), 3.38-3.63 (3H, m), 4.17 (2H, t, J = 6.6 Hz), 4.33 (2H, brs), 4.51-4.53 (2H, m), 5.24 (2H, s), 6.80-6.83 (2H, m), 6.97-6.99 (2H, m), 7.12 (1H, d, J = 9.3 Hz), 7.30 (1H, d, J = 15.4 Hz), 7.43-7.51 (5H, m), 7.62-7.68 (4H, m), 7.77 (2H, d, J = 8.1 Hz), 7.83 (1H, d, J = 2.730 Hz), 7.84 (1H, d, J = 2.0 Hz), 10.87 (1H, brs).

Example 538

4-({[6-(2-Chloro-6-methyl-4-({(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride

mp: 219.4-221.0 °C

Example 539

4-{{(6-{2-Chloro-6-methyl-4-[(*E*)-3-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.22 (3H, s), 2.98-3.13 (5H, m), 3.35-3.41 (2H, m), 3.52-3.54 (1H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.32-4.34 (2H, m), 4.53-4.55 (2H, m), 5.23 (2H, s), 6.81 (2H, d, *J* = 8.3 Hz), 7.09 (3H, dd, *J* = 18.9, 8.7 Hz), 7.29 (1H, d, *J* = 15.1 Hz), 7.42-7.51 (5H, m), 7.62-7.66 (4H, m), 7.81-7.84 (2H, m), 7.88 (2H, d, *J* = 8.3 Hz), 10.64 (1H, s).

Example 540

(*E*)-1-(4-{4-[2-(4-Bromophenoxy)ethyl]benzyl}piperazin-1-yl)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.01-3.08 (4H, m), 3.32-3.47 (3H, m), 3.58 (1H, brs), 4.21 (2H, t, *J* = 6.6 Hz), 4.33 (2H, brs), 4.51-4.53 (2H, m), 5.24 (2H, s), 6.89-6.93 (2H, m), 7.12 (1H, d, *J* = 9.0 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.42-7.53 (7H, m), 7.62-7.69 (4H, m), 7.77 (2H, d, *J* = 8.1 Hz), 7.83 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 10.97 (1H, brs).

Example 541

[6-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone hydrochloride

mp: 198.1-199.8 °C

Example 542

[6-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 7.1 Hz), 2.81 (1H, septet, *J* = 7.1 Hz), 3.05 (2H, t, *J* = 6.7 Hz), 3.14-3.16 (2H, m), 3.24-3.70 (4H, m), 3.71-4.88 (2H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.29-4.35 (2H, m), 5.26 (2H, s), 6.81-6.85 (2H, m), 7.10-7.15 (3H, m), 7.24-7.30 (1H, m), 7.36-7.55 (8H, m), 7.60 (1H, d, *J* = 2.4 Hz), 7.68 (1H, dd, *J* = 9.0, 3.2 Hz), 7.94 (1H, d, *J* = 8.5 Hz), 8.00 (1H, dd, *J* = 3.2, 0.5 Hz), 8.04 (2H, d, *J* = 9.0 Hz), 10.83 (1H, brs).

Example 543

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[1-(4-

methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.32 (3H, d, *J* = 7.1 Hz), 2.03 (6H, s), 2.21 (3H, s), 3.04-3.60 (7H, m),
3.75 (3H, s), 4.02 (1H, dd, *J* = 9.5, 6.8 Hz), 4.07 (1H, dd, *J* = 9.5, 6.8 Hz), 4.32 (2H, brs), 4.53
(2H, brs), 5.01 (2H, s), 6.79 (2H, dt, *J* = 9.2, 2.4 Hz), 6.94 (2H, dt, *J* = 9.2, 2.4 Hz), 6.99 (1H, d,
5 *J* = 9.1 Hz), 7.06 (2H, d, *J* = 8.3 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.37 (2H, dt, *J* = 9.1, 2.9 Hz),
7.42-7.50 (5H, m), 7.54-7.57 (3H, m), 7.78 (1H, d, *J* = 2.9 Hz), 11.19 (1H, brs).

Example 544

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[1-(4-
10 methylphenoxy)propan-2-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.32 (3H, d, *J* = 7.1 Hz), 2.03 (6H, s), 2.21 (3H, s), 3.03-3.60 (7H, m),
4.02 (1H, dd, *J* = 9.4, 6.7 Hz), 4.07 (1H, dd, *J* = 9.4, 6.7 Hz), 4.32 (2H, brs), 4.53 (2H, brs), 5.08
(2H, s), 6.79 (2H, dt, *J* = 9.3, 2.5 Hz), 7.00 (1H, d, *J* = 9.0 Hz), 7.06 (2H, d, *J* = 8.1 Hz), 7.17-
7.25 (3H, m), 7.42-7.60 (10H, m), 7.80 (1H, d, *J* = 2.7 Hz), 11.15 (1H, brs).

15

Example 545

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(5-
methylpyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.20 (3H, s), 2.30 (3H, s), 3.01-3.08 (4H, m), 3.33-3.58
20 (4H, m), 4.32 (2H, brs), 4.44 (2H, t, *J* = 6.8 Hz), 4.51-4.53 (2H, m), 5.06 (2H, s), 6.69 (1H, d, *J* =
8.3 Hz), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.27-7.34 (3H, m), 7.40 (2H, d, *J* =
7.6 Hz), 7.47-7.53 (4H, m), 7.58-7.63 (2H, m), 7.79 (1H, d, *J* = 3.2 Hz), 7.84 (1H, s), 7.96 (1H,
s), 10.80 (1H, brs).

25 Example 546

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-
fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 196.3-196.9 °C

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 3.05-4.53 (14H, m), 5.16 (2H, s), 6.95 (2H, dd, *J* = 7.3, 4.4
30 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 7.10 (2H, t, *J* = 8.3 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.39-7.43 (4H,
m), 7.46-7.53 (6H, m), 7.61-7.63 (2H, m), 7.84 (1H, brs), 11.24 (1H, brs).

Example 547

(*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 212.1-212.5 °C

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.30 (3H, s), 3.03-4.53 (17H, m), 5.04 (2H, s), 6.82-6.88 (4H, m), 6.99 (1H, d, *J* = 8.8 Hz), 7.17-7.20 (3H, m), 7.32 (2H, d, *J* = 7.8 Hz), 7.42 (2H, d, *J* = 7.6 Hz), 7.47 (2H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 7.6 Hz), 7.52 (1H, d, *J* = 7.6 Hz), 7.55-7.58 (1H, m), 7.79 (1H, d, *J* = 2.4 Hz), 10.90 (1H, s).

Example 548

(*E*)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 221.1-221.5 °C

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.30 (3H, s), 3.05-4.53 (14H, m), 5.04 (2H, s), 6.94 (2H, dd, *J* = 9.0, 4.4 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 7.10 (2H, t, *J* = 8.8 Hz), 7.17-7.20 (3H, m), 7.32 (2H, d, *J* = 7.8 Hz), 7.43 (2H, d, *J* = 7.6 Hz), 7.47 (2H, d, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 7.6 Hz), 7.51-7.58 (3H, m), 7.79 (1H, d, *J* = 2.9 Hz), 10.95 (1H, s).

Example 549

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 172.6-173.8 °C

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 3.03-4.53 (17H, m), 5.16 (2H, s), 6.84 (2H, d, *J* = 9.8 Hz), 6.87 (2H, d, *J* = 9.8 Hz), 7.02 (1H, d, *J* = 9.0 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.39-7.43 (4H, m), 7.46-7.55 (6H, m), 7.61-7.62 (2H, m), 7.84 (1H, d, *J* = 2.2 Hz), 11.23 (1H, s).

Example 550

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(6-chloropyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.03-3.15 (5H, m), 3.30-3.48 (2H, m), 3.58 (1H, brs), 4.30-4.34 (4H, m), 4.52-4.55 (2H, m), 5.05 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.27-7.34 (3H, m), 7.41-7.54 (7H, m), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, s), 7.79 (1H, d, *J* = 3.2 Hz), 7.84 (1H, d, *J* = 1.5 Hz), 8.11 (1H, d, *J* = 3.2 Hz), 11.01 (1H, brs).

Example 551

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-

fluorophenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 218.2-219.3 °C

Example 552

- 5 (E)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 179.6-180.7 °C

Example 553

- 10 (E)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 211.1-212.3 °C

Example 554

- 15 (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 187.3-189.2 °C

- ¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 5.9 Hz), 2.10 (3H, s), 2.30 (3H, s), 3.04-4.52 (14H, m), 5.05 (2H, s), 6.83 (4H, brs), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.27-7.34 (3H, m), 7.42 (2H, d, *J* = 7.8 Hz), 7.47-7.51 (3H, m), 7.59 (1H, dd, *J* = 9.0, 2.9 Hz), 7.63 (1H, brs), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, brs), 10.83 (1H, brs).

Example 555

- 25 (E)-3-[3,5-Dimethyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 168.5-169.2 °C

- ¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 5.9 Hz), 2.03 (6H, s), 2.30 (3H, s), 3.04-4.52 (15H, m), 5.04 (2H, s), 6.83 (4H, brs), 6.99 (1H, d, *J* = 8.8 Hz), 7.16-7.20 (3H, m), 7.32 (2H, d, *J* = 7.6 Hz), 7.42 (2H, d, *J* = 7.6 Hz), 7.46-7.57 (6H, m), 7.78 (1H, brs), 11.00 (1H, brs).

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Example 556

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 184.2-187.5 °C

¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 6.1 Hz), 2.04 (6H, s), 3.03-4.52 (15H, m), 5.16 (2H, s), 6.83 (4H, brs), 7.02 (1H, d, *J* = 8.8 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.39-7.43 (4H, m), 7.46-7.51 (4H, m), 7.54 (2H, d, *J* = 8.5 Hz), 7.60-7.63 (2H, m), 7.84 (1H, d, *J* = 2.9 Hz), 11.23 (1H, brs).

5 Example 557

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 163.2-163.9 °C

10 ¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 5.9 Hz), 2.11 (3H, s), 3.03-4.52 (15H, m), 5.17 (2H, s), 6.83 (4H, brs), 7.12 (1H, d, *J* = 8.8 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.39-7.43 (4H, m), 7.47-7.53 (4H, m), 7.60-7.67 (3H, m), 7.84 (2H, brs), 11.02 (1H, brs).

Example 558

15 4-{{{6-{{4-[(*E*)-3-(4-{4-[2-(4-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 219.7-220.7 °C

Example 559

20 4-{{{6-{{2-Chloro-4-[(*E*)-3-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 217.3-219.0 °C

Example 560

25 4-{{{6-{{2-Chloro-4-[(*E*)-3-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 186.1-187.6 °C

Example 561

30 (*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 213.2-214.6 °C

Example 562

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(6-

methylpyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 2.59 (3H, s), 3.04-3.56 (8H, m), 4.32-4.43 (4H, m), 4.51-4.54 (2H, m), 5.06 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.6 Hz), 7.28-7.34 (3H, m), 7.43-7.49 (3H, m), 7.55-7.68 (5H, m), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 1.5 Hz), 7.95 (1H, brs), 8.45 (1H, s), 11.33 (1H, brs).

Example 563

(*E*)-1-[4-(4-{2-[(5-Bromopyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.00-3.09 (4H, m), 3.38-3.47 (3H, m), 3.58 (1H, brs), 4.32 (2H, brs), 4.45-4.52 (4H, m), 5.06 (2H, s), 6.80 (1H, dd, *J* = 8.8, 0.5 Hz), 7.09 (1H, d, *J* = 8.8 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.28-7.34 (3H, m), 7.40 (2H, d, *J* = 8.1 Hz), 7.47-7.53 (3H, m), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, s), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 7.89 (1H, dd, *J* = 8.8, 2.4 Hz), 8.28 (1H, dd, *J* = 2.6, 0.6 Hz), 11.00 (1H, brs).

Example 564

(*E*)-3-[4-(5-[(3-Fluorobenzyl)oxy]pyridin-2-yl)oxy)-2-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 209.6-210.0 °C

Example 565

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[2-methyl-4-({5-[(3-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 194.2-195.2 °C

Example 566

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[4-({5-[(2-methoxybenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]prop-2-en-1-one hydrochloride

mp: 182.8-182.9 °C

Example 567

4-{[(6-{4-[(*E*)-3-(4-{4-[2-(3,5-Dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy]pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.21 (6H, s), 3.04-3.06 (4H, m), 3.19-3.21 (1H, m), 3.33-

3.36 (2H, m), 3.61-3.63 (1H, m), 4.16 (2H, t, $J = 6.6$ Hz), 4.31-4.33 (2H, m), 4.51-4.54 (2H, m), 5.22 (2H, s), 6.54-6.55 (3H, m), 7.01 (1H, d, $J = 9.0$ Hz), 7.19 (1H, d, $J = 15.4$ Hz), 7.41-7.43 (2H, m), 7.47-7.49 (3H, m), 7.54-7.56 (2H, m), 7.60 (1H, dd, $J = 9.0, 3.2$ Hz), 7.64 (2H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.87 (2H, d, $J = 8.3$ Hz), 11.37 (1H, brs).

5

Example 568

4-{{[6-(2,6-Dimethyl-4-[(*E*)-3-oxo-3-(4-{4-[2-(quinolin-6-yloxy)ethyl]benzyl}piperazin-1-yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ : 2.03 (6H, s), 3.02-3.04 (2H, m), 3.18-3.20 (3H, m), 3.32-3.35 (2H, m),
10 3.63-3.65 (1H, m), 4.31-4.34 (2H, m), 4.41 (2H, t, $J = 6.6$ Hz), 4.51-4.54 (2H, m), 5.22 (2H, s),
7.01 (1H, d, $J = 9.0$ Hz), 7.19 (1H, d, $J = 15.4$ Hz), 7.47-7.49 (5H, m), 7.56-7.65 (7H, m), 7.77
(1H, s), 7.82 (1H, d, $J = 2.9$ Hz), 7.87 (2H, d, $J = 8.3$ Hz), 8.12 (1H, d, $J = 8.3$ Hz), 8.64 (1H, s),
8.94 (1H, s), 11.30 (1H, s).

15 Example 569

4-({[6-(2,6-Dimethoxy-4-[(*E*)-3-oxo-3-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride
mp: 136.8-140.2 °C

¹H-NMR (DMSO-*d*₆) δ : 1.17 (6H, d, $J = 6.8$ Hz), 2.80-2.87 (1H, m), 3.05-4.57 (20H, m), 5.22
20 (2H, s), 6.73-6.75 (1H, m), 6.77 (1H, s), 6.80 (1H, d, $J = 7.8$ Hz), 6.93 (1H, d, $J = 9.0$ Hz), 7.13
(2H, s), 7.18 (1H, t, $J = 7.8$ Hz), 7.25 (1H, d, $J = 15.4$ Hz), 7.43 (2H, d, $J = 7.8$ Hz), 7.51-7.57
(4H, m), 7.64 (2H, d, $J = 8.1$ Hz), 7.77 (1H, d, $J = 2.9$ Hz), 7.87 (2H, d, $J = 8.3$ Hz), 11.23 (1H,
s).

25 Example 570

2-({[6-(2,6-Dimethoxy-4-[(*E*)-3-oxo-3-[4-(4-{2-[3-(propan-2-yl)phenoxy]ethyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride
mp: 154.9-157.7 °C

¹H-NMR (DMSO-*d*₆) δ : 1.17 (6H, d, $J = 7.1$ Hz), 2.80-2.87 (1H, m), 3.05-4.57 (20H, m), 5.24
30 (2H, s), 6.74 (1H, d, $J = 8.1$ Hz), 6.77 (1H, s), 6.80 (1H, d, $J = 7.8$ Hz), 6.95 (1H, d, $J = 9.0$ Hz),
7.14 (2H, s), 7.18 (1H, t, $J = 7.8$ Hz), 7.26 (1H, d, $J = 15.4$ Hz), 7.43 (2H, d, $J = 7.8$ Hz), 7.54-
7.60 (5H, m), 7.72-7.78 (2H, m), 7.81 (1H, d, $J = 2.9$ Hz), 7.92 (1H, d, $J = 7.8$ Hz), 11.30 (1H,
s).

Example 571

2-{[(6-{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethoxyphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

mp: 136.8-137.1 °C

- 5 ¹H-NMR (DMSO-*d*₆) δ: 3.05-4.57 (20H, m), 5.24 (2H, s), 6.93-6.96 (3H, m), 7.10 (2H, t, *J* = 8.8 Hz), 7.14 (2H, s), 7.26 (1H, d, *J* = 15.4 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.54-7.61 (5H, m), 7.72-7.78 (2H, m), 7.81 (1H, d, *J* = 2.9 Hz), 7.92 (1H, d, *J* = 7.6 Hz), 11.29 (1H, s).

Example 572

- 10 4-{[(6-{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethoxyphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

mp: 142.0-143.6 °C

- ¹H-NMR (DMSO-*d*₆) δ: 3.05-4.57 (20H, m), 5.22 (2H, s), 6.92-6.96 (3H, m), 7.08-7.13 (4H, m), 7.25 (1H, d, *J* = 15.4 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.51-7.57 (4H, m), 7.64 (2H, d, *J* = 8.1 Hz),
15 7.77 (1H, d, *J* = 2.9 Hz), 7.87 (2H, d, *J* = 8.1 Hz), 11.31 (1H, s).

Example 573

(*E*)-3-[4-({5-[(2-Chloro-4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

- 20 mp: 178.3-180.6 °C

Example 574

(*E*)-1-(4-{4-[2-(3,4-Dimethylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-(3,5-dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one hydrochloride

- 25 mp: 186.7-189.5 °C

Example 575

(*E*)-3-[4-({5-[(3-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

- 30 mp: 186.9-189.4 °C

Example 576

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.22 (3H, s), 2.30 (3H, s), 2.35 (3H, s), 3.00-3.58 (6H, m), 3.05 (2H, t, *J* = 6.8 Hz), 4.15 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.52-4.55 (2H, m), 5.06 (2H, s), 6.82 (2H, dt, *J* = 9.2, 2.6 Hz), 7.06-7.10 (3H, m), 7.20 (2H, d, *J* = 7.6 Hz), 7.28-7.39 (6H, m), 7.49 (1H, d, *J* = 15.4 Hz), 7.59 (1H, dd, *J* = 8.9, 3.2 Hz), 7.63 (1H, d, *J* = 2.0 Hz), 7.79 (1H, dd, *J* = 3.2, 0.5 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 10.99 (1H, brs).

Example 577

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.22 (3H, s), 2.35 (3H, s), 3.00-3.57 (6H, m), 3.05 (2H, t, *J* = 6.8 Hz), 4.15 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.53 (2H, brs), 5.08 (2H, s), 6.82 (2H, dt, *J* = 9.3, 2.6 Hz), 7.00 (1H, dd, *J* = 9.0, 0.5 Hz), 7.06-7.08 (2H, m), 7.17-7.25 (3H, m), 7.33-7.39 (3H, m), 7.46-7.52 (5H, m), 7.58 (1H, dd, *J* = 9.0, 3.2 Hz), 7.80 (1H, dd, *J* = 3.2, 0.5 Hz), 10.96 (1H, brs).

Example 578

(*E*)-3-(3,5-Dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[(4-methylbenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 2.28 (3H, s), 2.88 (2H, t, *J* = 6.6 Hz), 3.01-3.03 (2H, m), 3.30-3.32 (3H, m), 3.63-3.65 (3H, m), 4.29-4.32 (2H, m), 4.44 (2H, s), 4.50-4.52 (2H, m), 5.44 (2H, s), 7.06 (1H, d, *J* = 9.0 Hz), 7.14-7.20 (5H, m), 7.33 (2H, d, *J* = 7.8 Hz), 7.46-7.50 (3H, m), 7.54 (2H, d, *J* = 8.1 Hz), 7.66 (1H, dd, *J* = 9.0, 3.2 Hz), 7.87 (1H, d, *J* = 2.9 Hz), 7.98 (2H, d, *J* = 6.1 Hz), 8.88 (2H, d, *J* = 6.1 Hz), 11.67 (1H, s).

Example 579

(*E*)-1-(4-{4-[2-(3-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-(3,5-dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 3.06-3.08 (4H, m), 3.31-3.33 (3H, m), 3.64-3.66 (1H, m), 4.25 (2H, t, *J* = 6.6 Hz), 4.30-4.33 (2H, m), 4.51-4.53 (2H, m), 5.44 (2H, s), 6.92 (1H, dd, *J* = 8.3, 1.7 Hz), 6.98-7.08 (3H, m), 7.20 (1H, d, *J* = 15.4 Hz), 7.29 (1H, t, *J* = 8.1 Hz), 7.43-7.48 (5H, m), 7.57 (2H, d, *J* = 8.1 Hz), 7.65 (1H, dd, *J* = 8.9, 3.1 Hz), 7.87 (1H, d, *J* = 2.9 Hz), 7.96 (2H, d, *J* = 6.1 Hz), 8.87 (2H, d, *J* = 6.3 Hz), 11.63 (1H, s).

Example 580

(*E*)-3-(3,5-Dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[(4-fluorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 2.90 (2H, t, *J* = 6.6 Hz), 2.94-3.01 (2H, m), 3.16-3.19 (1H, m), 3.31-3.34 (2H, m), 3.61-3.68 (3H, m), 4.30-4.32 (2H, m), 4.47 (2H, s), 4.50-4.53 (2H, m),
5 5.40 (2H, s), 7.05 (1H, d, *J* = 9.0 Hz), 7.15-7.20 (3H, m), 7.30-7.35 (4H, m), 7.48-7.51 (5H, m),
7.64 (1H, dd, *J* = 9.0, 2.9 Hz), 7.86-7.89 (3H, m), 8.82-8.85 (2H, m), 11.23 (1H, s).

Example 581

(*E*)-1-[4-(4-{2-[(4-Chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-dimethyl-4-{{5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 2.90 (2H, t, *J* = 6.5 Hz), 3.01-3.03 (2H, m), 3.17-3.19 (1H, m), 3.31-3.34 (2H, m), 3.61-3.69 (3H, m), 4.30-4.32 (2H, m), 4.47-4.55 (4H, m), 5.40 (2H, s),
10 7.05 (1H, d, *J* = 8.8 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.28-7.52 (11H, m), 7.64 (1H, dd, *J* = 9.0, 2.9 Hz), 7.86-7.89 (3H, m), 8.83 (2H, d, *J* = 5.9 Hz), 11.20 (1H, s).

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Example 582

(*E*)-1-(4-{4-[2-(2-Chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3,5-dimethyl-4-{{5-[(6-methylpyridin-2-yl)methoxy]pyridin-2-yl}oxy}phenyl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 2.63 (3H, s), 3.01-3.04 (2H, m), 3.11 (2H, t, *J* = 6.5 Hz),
20 3.19-3.21 (1H, m), 3.33-3.35 (2H, m), 3.60-3.62 (1H, m), 4.28-4.31 (4H, m), 4.51-4.53 (2H, m),
5.30 (2H, s), 6.94 (1H, t, *J* = 7.1 Hz), 7.04 (1H, d, *J* = 9.0 Hz), 7.17-7.20 (2H, m), 7.26-7.30 (1H, m),
7.40 (1H, dd, *J* = 7.9, 1.3 Hz), 7.46-7.48 (5H, m), 7.55-7.57 (3H, m), 7.65 (2H, dd, *J* = 8.9, 3.1 Hz), 7.85 (1H, d, *J* = 2.9 Hz), 8.10 (1H, s), 11.39 (1H, s).

25 Example 583

(*E*)-3-[3-Chloro-5-methyl-4-{{5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[(6-methoxypyridin-3-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.00-3.17 (5H, m), 3.34-3.47 (2H, m), 3.57 (1H, brs), 3.78 (3H, s), 4.23 (2H, t, *J* = 6.6 Hz), 4.33 (2H, brs), 4.51-4.53 (2H, m), 5.06 (2H, s),
30 6.75 (1H, d, *J* = 8.8 Hz), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.27-7.32 (3H, m),
7.38 (1H, dd, *J* = 9.0, 3.2 Hz), 7.42-7.53 (5H, m), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, s),
7.79 (1H, d, *J* = 3.2 Hz), 7.84-7.85 (2H, m), 10.92 (1H, brs).

Example 584

(*E*)-3-(4-{[5-(1,3-Benzothiazol-6-ylmethoxy)pyridin-2-yl]oxy}-3,5-dimethoxyphenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 133.1-134.4 °C

¹H-NMR (DMSO-*d*₆) δ: 3.05-4.57 (20H, m), 5.26 (2H, s), 6.92-6.96 (3H, m), 7.10 (2H, t, *J* = 8.8 Hz), 7.12 (2H, s), 7.25 (1H, d, *J* = 15.4 Hz), 7.43 (2H, d, *J* = 7.6 Hz), 7.53-7.57 (4H, m), 7.61 (1H, d, *J* = 8.3 Hz), 7.80 (1H, d, *J* = 2.9 Hz), 8.10 (1H, d, *J* = 8.3 Hz), 8.26 (1H, s), 9.41 (1H, s), 11.12 (1H, s).

Example 585

10 (*E*)-3-(4-{[5-(1,3-Benzothiazol-6-ylmethoxy)pyridin-2-yl]oxy}-3,5-dimethoxyphenyl)-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 133.4-135.1 °C

¹H-NMR (DMSO-*d*₆) δ: 1.21 (6H, d, *J* = 5.9 Hz), 3.03-4.57 (21H, m), 5.26 (2H, s), 6.82 (2H, d, *J* = 9.8 Hz), 6.84 (2H, d, *J* = 9.8 Hz), 6.92 (1H, d, *J* = 9.0 Hz), 7.13 (2H, s), 7.25 (1H, d, *J* = 15.4 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.53-7.57 (4H, m), 7.62 (1H, d, *J* = 7.3 Hz), 7.80 (1H, d, *J* = 2.9 Hz), 8.10 (1H, d, *J* = 8.3 Hz), 8.26 (1H, s), 9.41 (1H, s), 11.23 (1H, s).

Example 586

20 (*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.36 (3H, s), 3.04-3.57 (6H, m), 3.06 (2H, t, *J* = 6.8 Hz), 4.17 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.53 (2H, brs), 5.08 (2H, s), 6.92-6.97 (2H, m), 7.00 (1H, d, *J* = 8.9 Hz), 7.07-7.14 (2H, m), 7.17-7.25 (3H, m), 7.36-7.38 (3H, m), 7.46-7.52 (5H, m), 7.58 (1H, dd, *J* = 8.9, 3.1 Hz), 7.80 (1H, d, *J* = 3.1 Hz), 10.91 (1H, brs).

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Example 587

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

30 ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 2.36 (3H, s), 3.06 (2H, t, *J* = 6.8 Hz), 3.06-3.55 (6H, m), 4.17 (2H, t, *J* = 6.8 Hz), 4.29 (2H, brs), 4.52-4.56 (2H, m), 5.05 (2H, s), 6.92-6.97 (2H, m), 7.08-7.14 (3H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.28-7.37 (6H, m), 7.49 (1H, d, *J* = 15.4 Hz), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, d, *J* = 1.7 Hz), 7.79 (1H, d, *J* = 3.1 Hz), 7.84 (1H, d, *J* = 1.7 Hz), 10.81 (1H, brs).

Example 588

(*E*)-1-[4-(4-{2-[(6-Chloro-1,3-benzoxazol-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.03-3.37 (6H, m), 3.41-3.56 (2H, m), 4.09
5 (2H, t, *J* = 6.8 Hz), 4.30 (2H, brs), 4.50-4.53 (2H, m), 5.05 (2H, s), 7.09 (1H, d, *J* = 9.3 Hz),
7.17-7.22 (4H, m), 7.29-7.33 (5H, m), 7.45-7.51 (4H, m), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.63
(1H, d, *J* = 2.0 Hz), 7.79 (1H, d, *J* = 2.7 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 10.87 (1H, brs).

Example 589

10 (*E*)-1-(4-{4-[2-(4-*tert*-Butylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[4-({5-[(3,4-difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 1.24 (9H, d, *J* = 3.9 Hz), 2.90-3.45 (7H, m), 3.52 (1H, s), 4.18 (2H, t, *J*
= 6.6 Hz), 4.33 (2H, brs), 4.53 (2H, brs), 5.12 (2H, s), 6.82-6.86 (2H, m), 7.13 (1H, d, *J* = 9.3
Hz), 7.26-7.33 (5H, m), 7.43-7.57 (8H, m), 7.63 (1H, dd, *J* = 8.9, 3.1 Hz), 7.83 (1H, dd, *J* = 12.0,
15 2.0 Hz), 7.87 (1H, d, *J* = 2.4 Hz), 10.58 (1H, brs).

Example 590

4-({[6-(2,6-Dimethyl-4-({*E*)-3-[4-(4-{2-[(6-methylpyridin-2-yl)oxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride
20 ¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.37 (3H, s), 3.05-3.07 (4H, m), 3.15-3.18 (1H, m), 3.34-
3.36 (2H, m), 3.58-3.60 (1H, m), 4.31-4.34 (2H, m), 4.45 (2H, t, *J* = 6.7 Hz), 4.51-4.54 (2H, m),
5.22 (2H, s), 6.57 (1H, d, *J* = 8.1 Hz), 6.82 (1H, d, *J* = 7.1 Hz), 7.01 (1H, d, *J* = 9.0 Hz), 7.19
(1H, d, *J* = 15.4 Hz), 7.41 (2H, d, *J* = 7.6 Hz), 7.51-7.61 (9H, m), 7.82 (1H, d, *J* = 2.9 Hz), 7.87
(2H, d, *J* = 8.1 Hz), 11.14 (1H, s).

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Example 591

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-methylphenoxy)acetyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.23 (3H, s), 2.90-3.70 (7H, m), 4.47-4.54 (3H, m), 5.17
30 (2H, s), 5.53 (2H, s), 6.84-6.88 (2H, m), 7.07-7.13 (3H, m), 7.31 (1H, d, *J* = 15.4 Hz), 7.37-7.44
(2H, m), 7.48-7.54 (2H, m), 7.60-7.67 (3H, m), 7.77 (2H, d, *J* = 5.9 Hz), 7.84-7.86 (2H, m), 8.11
(2H, d, *J* = 8.1 Hz), 11.07 (1H, brs).

Example 592

(*E*)-1-(4-{4-[2-(4-Fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.36 (3H, s), 3.06 (2H, t, *J* = 6.8 Hz), 3.06-3.51 (6H, m), 3.75 (3H, s), 4.17 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.53 (2H, brs), 5.01 (2H, s), 6.92-7.00 (5H, m), 7.07-7.14 (2H, m), 7.19 (1H, d, *J* = 15.4 Hz), 7.35-7.38 (5H, m), 7.46-7.50 (3H, m), 7.56 (1H, dd, *J* = 9.0, 3.2 Hz), 7.78 (1H, d, *J* = 3.2 Hz), 10.82 (1H, brs).

Example 593

4-({[6-(2-Fluoro-4-{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.81 (1H, septet, *J* = 7.1 Hz), 2.90-3.65 (8H, m), 4.18 (2H, t, *J* = 6.7 Hz), 4.33 (2H, brs), 4.53 (2H, brs), 5.26 (2H, s), 6.82-6.86 (2H, m), 7.11-7.15 (3H, m), 7.27-7.32 (2H, m), 7.42-7.58 (6H, m), 7.62-7.66 (3H, m), 7.83 (1H, dd, *J* = 12.2, 2.0 Hz), 7.87-7.89 (3H, m), 10.71 (1H, brs).

Example 594

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 190.4-191.8 °C

Example 595

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 199.2-200.9 °C

Example 596

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 207.0-207.2 °C

Example 597

(*E*)-3-(3,5-Dimethyl-4-{[5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 216.7-216.9 °C

Example 598

(*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yloxy)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

5 mp: 177.7-178.6 °C

Example 599

(*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

10 ¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 3.04-3.58 (8H, m), 4.19 (2H, t, *J* = 6.8 Hz), 4.32 (2H, brs), 4.52 (2H, brs), 5.22 (2H, s), 6.91-6.97 (2H, m), 7.00 (1H, d, *J* = 9.0 Hz), 7.07-7.14 (2H, m), 7.19 (1H, d, *J* = 15.4 Hz), 7.41-7.56 (7H, m), 7.62 (1H, dd, *J* = 9.0, 3.2 Hz), 7.81 (1H, d, *J* = 2.0 Hz), 7.83 (1H, d, *J* = 3.2 Hz), 8.13 (1H, d, *J* = 2.0 Hz), 10.97 (1H, brs).

15 Example 600

(*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.03 (6H, s), 2.81 (1H, septet, *J* = 6.8 Hz), 3.04-3.60 (8H, m), 4.17 (2H, t, *J* = 6.8 Hz), 4.32 (2H, brs), 4.52 (2H, brs), 5.22 (2H, s), 6.82-6.87 (2H, m), 7.00 (1H, d, *J* = 9.0 Hz), 7.11-7.15 (2H, m), 7.19 (1H, d, *J* = 15.4 Hz), 7.41-7.55 (7H, m), 7.62 (1H, dd, *J* = 8.8, 3.2 Hz), 7.81 (1H, d, *J* = 2.0 Hz), 7.84 (1H, d, *J* = 3.2 Hz), 9.13 (1H, d, *J* = 2.0 Hz), 11.16 (1H, brs).

Example 601

25 (*E*)-3-(3,5-Dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DSMO-*d*₆) δ: 2.03 (6H, s), 2.21 (3H, s), 3.03-3.61 (8H, m), 4.16 (2H, t, *J* = 6.8 Hz), 4.32 (2H, brs), 4.52 (2H, brs), 5.22 (2H, s), 6.79-6.84 (2H, m), 7.00 (1H, d, *J* = 8.8 Hz), 7.06 (2H, d, *J* = 8.3 Hz), 7.14 (1H, d, *J* = 15.6 Hz), 7.40-7.56 (7H, m), 7.62 (1H, dd, *J* = 8.8, 2.9 Hz), 7.81 (1H, d, *J* = 2.0 Hz), 7.84 (1H, d, *J* = 2.9 Hz), 9.13 (1H, d, *J* = 2.0 Hz), 11.25 (1H, brs).

Example 602

(*E*)-1-(4-{4-[2-(1,3-Benzothiazol-2-yloxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.30 (3H, s), 2.95-3.03 (4H, m), 3.17-3.58 (4H, m), 4.20 (2H, t, *J* = 7.1 Hz), 4.29 (2H, brs), 4.52 (2H, brs), 5.05 (2H, s), 7.09 (1H, d, *J* = 9.0 Hz), 7.15-7.21 (3H, m), 7.28-7.34 (7H, m), 7.44-7.46 (2H, m), 7.50 (1H, d, *J* = 15.4 Hz), 7.58-7.64 (3H, m), 7.79 (1H, d, *J* = 3.2 Hz), 7.85 (1H, d, *J* = 2.0 Hz), 10.97 (1H, brs).

5

Example 603

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(2-methyl-1,3-benzothiazol-5-yl)oxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 2.76 (3H, s), 3.11-3.13 (5H, m), 3.36-3.57 (3H, m), 4.29-4.33 (4H, m), 4.52-4.55 (2H, m), 5.05 (2H, s), 7.02 (1H, dd, *J* = 8.7, 2.6 Hz), 7.09 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.28-7.34 (3H, m), 7.45-7.55 (6H, m), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, s), 7.79 (1H, d, *J* = 3.2 Hz), 7.84 (1H, d, *J* = 1.7 Hz), 7.87 (1H, d, *J* = 8.8 Hz), 10.98 (1H, brs).

15 Example 604

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3*S*)-3-[methyl(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)amino]pyrrolidin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 7.1 Hz), 2.11 (3H, s), 2.30 (3H, s), 2.33-2.47 (2H, m), 2.61 (3H, s), 2.78-2.85 (1H, m), 3.07 (2H, t, *J* = 6.7 Hz), 3.35-3.44 (1H, m), 3.72-3.99 (4H, m), 4.16-4.20 (3H, m), 4.42-4.49 (1H, m), 5.05 (2H, s), 6.84-6.85 (2H, m), 7.05-7.12 (4H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.33 (2H, d, *J* = 7.3 Hz), 7.48-7.65 (7H, m), 7.79 (1H, d, *J* = 3.2 Hz), 7.81-7.83 (1H, m), 10.75 (0.5H, brs), 10.96 (0.5H, brs).

25 Example 605

4-{{[(6-{4-[(*E*)-3-(4-{4-[2-(4-Fluorophenoxy)ethyl]-3-methylbenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.36 (3H, s), 3.00-3.56 (6H, m), 3.06 (2H, t, *J* = 6.8 Hz), 4.17 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.53 (2H, brs), 5.22 (2H, s), 6.92-6.97 (2H, m), 7.02 (1H, d, *J* = 9.3 Hz), 7.07-7.14 (2H, m), 7.19 (1H, d, *J* = 15.4 Hz), 7.36-7.38 (3H, m), 7.46-7.50 (3H, m), 7.60 (1H, dd, *J* = 9.3, 3.2 Hz), 7.64 (2H, d, *J* = 8.3 Hz), 7.82 (1H, dd, *J* = 3.2, 0.5 Hz), 7.88 (2H, dt, *J* = 8.3, 1.8 Hz), 10.90 (1H, brs).

30

Example 606

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.22 (3H, s), 2.35 (3H, s), 3.01-3.57 (6H, m), 3.05 (2H, t, *J* = 6.8 Hz), 3.75 (3H, s), 4.15 (2H, t, *J* = 6.8 Hz), 4.28 (2H, brs), 4.53 (2H, brs), 5.01 (2H, s),
5 6.82 (2H, dt, *J* = 9.3, 2.5 Hz), 6.94 (2H, dt, *J* = 9.3, 2.5 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 7.07 (2H, d, *J* = 8.1 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.35-7.38 (5H, m), 7.46-7.50 (3H, m), 7.56 (1H, dd, *J* = 9.0, 3.2 Hz), 7.78 (1H, d, *J* = 3.2 Hz), 10.92 (1H, brs).

Example 607

10 (*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 206.1-206.4 °C

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.22 (3H, s), 3.04-4.55 (14H, m), 5.10 (2H, s), 6.80-7.41 (1H, m), 6.82 (2H, d, *J* = 8.2 Hz), 7.07 (2H, d, *J* = 8.2 Hz), 7.10 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.43-7.52 (7H, m), 7.61 (1H, dd, *J* = 9.0, 2.9 Hz), 7.63 (1H, brs), 7.80 (1H, d, *J* = 2.9 Hz), 7.84 (1H, brs), 11.04 (1H, brs).
15

Example 608

20 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.9 Hz), 2.12 (3H, s), 2.81 (1H, septet, *J* = 6.9 Hz), 2.90-3.18 (4H, m), 3.20-3.47 (3H, m), 3.60-3.80 (1H, m), 4.18 (2H, t, *J* = 6.9 Hz), 4.34 (2H, brs), 4.56 (2H, d, *J* = 13.7 Hz), 5.18 (2H, s), 6.82-6.88 (2H, m), 7.09-7.16 (3H, m), 7.33 (1H, d, *J* = 15.6 Hz), 7.36-7.45 (4H, m), 7.47-7.55 (2H, m), 7.57-7.68 (5H, m), 7.86 (2H, d, *J* = 2.7 Hz),
25 11.89 (1H, brs).

Example 609

30 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-cyclopropylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 0.53-0.57 (2H, m), 0.84-0.88 (2H, m), 1.80-1.87 (1H, m), 2.10 (3H, s), 2.30 (3H, s), 3.00-3.16 (5H, m), 3.31-3.75 (3H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.32 (2H, brs), 4.52-4.54 (2H, m), 5.05 (2H, s), 6.80-6.83 (2H, m), 6.96-6.99 (2H, m), 7.09 (1H, dd, *J* = 8.8, 0.5 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.29-7.32 (3H, m), 7.41-7.43 (2H, m), 7.47-7.52 (3H, m), 7.59 (1H, dd, *J* = 9.0, 2.9 Hz), 7.63 (1H, d, *J* = 2.0 Hz), 7.78 (1H, d, *J* = 3.4 Hz), 7.84 (1H, d, *J* = 2.0 Hz),

10.81 (1H, brs).

Example 610

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO- *d*₆) δ: 2.04 (6H, s), 2.22 (3H, s), 2.42 (3H, s), 3.01 (2H, t, *J* = 6.8 Hz), 3.19-3.63 (6H, m), 4.16 (2H, t, *J* = 6.8 Hz), 4.34 (2H, brs), 4.54 (2H, brs), 5.08 (2H, s), 6.82 (2H, dt, *J* = 9.3, 2.6 Hz), 7.00 (1H, d, *J* = 9.3 Hz), 7.07 (2H, d, *J* = 8.1 Hz), 7.18-7.26 (5H, m), 7.47-7.53 (5H, m), 7.55 (1H, d, *J* = 7.8 Hz), 7.58 (1H, dd, *J* = 9.3, 3.2 Hz), 7.80 (1H, d, *J* = 3.2 Hz), 10.52 (1H, brs).

Example 611

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO- *d*₆) δ: 2.04 (6H, s), 2.22 (3H, s), 2.42 (3H, s), 3.01 (2H, t, *J* = 6.8 Hz), 3.18-3.62 (6H, m), 3.75 (3H, s), 4.16 (2H, t, *J* = 6.8 Hz), 4.34 (2H, brs), 4.54 (2H, brs), 5.01 (2H, s), 6.82 (2H, dt, *J* = 9.3, 2.5 Hz), 6.94 (2H, dt, *J* = 9.3, 2.5 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 7.07 (2H, d, *J* = 8.1 Hz), 7.18-7.26 (3H, m), 7.37 (2H, dt, *J* = 9.0, 2.3 Hz), 7.47-7.58 (5H, m), 7.78 (1H, d, *J* = 2.9 Hz), 10.59 (1H, brs).

Example 612

4-({[6-(2-Chloro-4-{(*E*)-3-[4-(4-{2-[4-(2-hydroxyethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy)methyl}benzonitrile hydrochloride
mp: 198.5-198.8 °C

Example 613

4-({[6-(2-Chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride

mp: 193.7-194.2 °C

Example 614

4-({[6-(4-[(*E*)-3-(4-{4-[2-(4-Chlorophenoxy)ethyl]-3-fluorobenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile hydrochloride

mp: 240.5-243.5 °C

Example 615

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 161.0-163.1 °C

¹H-NMR (DMSO-*d*₆) δ: 1.28 (3H, t, *J* = 6.8 Hz), 2.11 (3H, s), 3.03-4.56 (16H, m), 5.17 (2H, s), 6.82 (2H, d, *J* = 9.5 Hz), 6.85 (2H, d, *J* = 9.5 Hz), 7.12 (1H, d, *J* = 9.0 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.39-7.43 (4H, m), 7.47-7.51 (4H, m), 7.60-7.67 (3H, m), 7.84-7.85 (2H, m), 10.87 (1H, brs).

Example 616

4-({[6-(4-({(*E*)-3-[4-(2-Fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-2,6-dimethylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 3.05-3.20 (4H, m), 3.40-3.43 (3H, m), 3.61-3.63 (1H, m), 4.33-4.37 (4H, m), 4.53-4.56 (2H, m), 5.22 (2H, s), 7.01 (1H, d, *J* = 8.8 Hz), 7.14-7.20 (3H, m), 7.31-7.35 (2H, m), 7.46-7.49 (3H, m), 7.60-7.64 (5H, m), 7.70-7.73 (1H, m), 7.82 (1H, d, *J* = 2.9 Hz), 7.88 (2H, d, *J* = 8.1 Hz), 11.34 (1H, s).

Example 617

4-({[6-(2-Chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(3-phenoxypropyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

¹H-NMR (CDCl₃) δ: 2.11 (2H, tt, *J* = 6.9, 6.9 Hz), 2.19 (3H, s), 2.72 (2H, brs), 2.85 (2H, t, *J* = 6.9 Hz), 3.46 (2H, brs), 3.67 (1H, brs), 3.97 (2H, t, *J* = 6.9 Hz), 4.15-4.23 (4H, m), 4.78 (1H, brs), 5.09 (2H, s), 6.70 (1H, d, *J* = 15.3 Hz), 6.89 (2H, d, *J* = 8.1 Hz), 6.93-6.98 (2H, m), 7.26-7.32 (5H, m), 7.38 (1H, dd, *J* = 8.9, 3.1 Hz), 7.45 (1H, s), 7.52 (4H, d, *J* = 7.8 Hz), 7.60 (1H, d, *J* = 15.3 Hz), 7.68 (2H, d, *J* = 7.8 Hz), 7.75 (1H, d, *J* = 2.9 Hz), 13.52 (1H, brs).

Example 618

4-({[6-(2-Chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

mp: 166.2-166.7 °C

Example 619

4-({[6-(2-Chloro-4-{(E)-3-[4-(4-{3-[(6-chloropyridin-3-yl)oxy]propyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride
mp: 168.5-170.0 °C

5 Example 620

4-({[6-(2-Chloro-6-methyl-4-{(E)-3-[4-(4-{3-[(6-methylpyridin-3-yl)oxy]propyl}benzyl)-piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.04-2.10 (5H, m), 2.59 (3H, s), 2.79 (2H, t, *J* = 7.6 Hz), 3.38 (6H, brs),
10 4.16 (2H, t, *J* = 6.2 Hz), 4.31 (2H, brs), 4.53 (2H, brs), 5.23 (2H, s), 7.12 (1H, d, *J* = 9.0 Hz),
7.30 (1H, d, *J* = 15.4 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 7.47-7.53 (3H, m), 7.62-7.69 (5H, m), 7.82
(1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 7.88 (2H, dt, *J* = 8.3, 1.8 Hz), 7.93 (1H, d, *J* = 8.5
Hz), 8.43 (1H, d, *J* = 2.9 Hz), 11.24 (1H, brs).

15 Example 621

4-({[6-(2-Chloro-6-methyl-4-{(E)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride
mp: 193.0-194.8 °C

20 Example 622

4-({[6-(2-Chloro-6-methyl-4-{(E)-3-oxo-3-[4-(4-{3-[4-(propan-2-yl)phenoxy]propyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride
mp: 197.8-198.7 °C

25 Example 623

(E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{4-(propan-2-yloxy)phenoxy}methyl)benzyl]piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 204.9-206.2 °C

30 Example 624

(E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-methoxyphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 2.80-3.80 (6H, m), 3.69 (3H, s), 4.25-4.45 (2H, m), 4.46-
4.62 (2H, m), 5.08 (2H, s), 5.17 (2H, s), 6.83-6.90 (2H, m), 6.92-6.99 (2H, m), 7.12 (1H, d, *J* =

9.0 Hz), 7.27-7.57 (7H, m), 7.59-7.69 (5H, m), 7.82-7.89 (2H, m), 11.28 (1H, brs).

Example 625

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[(4-ethoxyphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 194.7-197.0 °C

Example 626

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 203.8-204.4 °C

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.9 Hz), 2.10 (3H, s), 2.30 (3H, s), 2.82 (1H, septet, *J* = 6.9 Hz), 3.11-3.57 (6H, m), 4.36-4.57 (4H, m), 5.05 (2H, s), 5.11 (2H, s), 6.91-6.96 (2H, m), 7.07-7.34 (8H, m), 7.46-7.63 (7H, m), 7.78 (1H, d, *J* = 3.0 Hz), 7.84 (1H, d, *J* = 1.6 Hz), 10.98 (1H, brs).

Example 627

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 209.6-212.0 °C

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.11 (3H, s), 2.82 (1H, septet, *J* = 6.8 Hz), 3.02-3.59 (6H, m), 4.35-4.38 (2H, m), 4.53-4.57 (2H, m), 5.11 (2H, s), 5.17 (2H, s), 6.93 (2H, d, *J* = 7.8 Hz), 7.11-7.17 (3H, m), 7.29-7.67 (12H, m), 7.84-7.85 (2H, m), 11.06 (1H, brs).

Example 628

(*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.22 (6H, d, *J* = 5.9 Hz), 2.90-3.60 (6H, m), 4.37 (2H, s), 4.44-4.50 (1H, m), 4.54 (2H, s), 5.07 (2H, s), 5.19 (2H, s), 6.83-6.87 (2H, m), 6.91-6.95 (2H, m), 7.15 (1H, d, *J* = 8.8 Hz), 7.28-7.34 (2H, m), 7.38-7.44 (2H, m), 7.52-7.63 (8H, m), 7.66 (1H, dd, *J* = 8.9, 3.1 Hz), 7.85 (1H, dd, *J* = 12.1, 1.8 Hz), 7.91 (1H, d, *J* = 2.9 Hz), 10.76 (1H, s).

Example 629

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-

yl oxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 207.7-208.0 °C

Example 630

- 5 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(1H-pyrrol-1-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 199.9-201.6 °C

Example 631

- 10 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-[4-(4-{[4-(propan-2-yl oxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 196.2-196.4 °C

Example 632

- 15 (E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{[4-(propan-2-yl oxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 182.5-183.2 °C

- ¹H-NMR (DMSO-*d*₆) δ: 1.22 (6H, d, *J* = 6.2 Hz), 2.36 (3H, s), 3.04-3.59 (6H, m), 4.35-4.51 (5H, m), 5.07 (2H, s), 5.20 (2H, s), 6.82-6.96 (6H, m), 7.04-7.14 (2H, m), 7.37-7.66 (9H, m), 7.72-
20 7.83 (2H, m), 7.99 (1H, d, *J* = 3.0 Hz), 11.11 (1H, brs).

Example 633

(E)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

- 25 ¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.79-2.86 (1H, m), 3.03-3.56 (6H, m), 4.36 (2H, brs), 4.53 (2H, brs), 5.11 (2H, s), 5.21 (2H, s), 6.93 (2H, dt, *J* = 9.4, 2.5 Hz), 7.07-7.12 (3H, m), 7.16 (2H, dt, *J* = 9.4, 2.5 Hz), 7.21 (1H, d, *J* = 15.4 Hz), 7.38-7.45 (2H, m), 7.51-7.67 (8H, m), 7.75 (2H, d, *J* = 8.5 Hz), 8.00 (1H, d, *J* = 3.2 Hz), 10.91 (1H, brs).

- 30 Example 634

(E)-3-[2-Methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 189.6-190.9 °C (dec.)

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.31 (3H, s), 2.35 (3H, s), 2.82 (1H, septet, *J* =

6.8 Hz), 3.09-3.52 (6H, m), 4.36 (2H, brs), 4.53 (2H, brs), 5.09 (2H, s), 5.11 (2H, s), 6.92-6.94 (4H, m), 7.03 (1H, d, $J = 8.8$ Hz), 7.10 (1H, d, $J = 15.1$ Hz), 7.15 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.3$ Hz), 7.34 (2H, d, $J = 8.3$ Hz), 7.53-7.60 (5H, m), 7.74 (1H, d, $J = 15.1$ Hz), 7.79-7.81 (1H, m), 7.94 (1H, d, $J = 3.2$ Hz), 10.73 (1H, brs).

5

Example 635

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrochloride
mp: 181.4-182.3 °C

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Example 636

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[(4-fluorobenzyl)oxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 2.97-3.62 (6H, m), 4.34-4.36 (2H, m), 4.52-
15 5.57 (6H, m), 5.05 (2H, s), 7.09 (1H, d, $J = 9.0$ Hz), 7.17-7.22 (4H, m), 7.28-7.34 (3H, m), 7.38-
7.51 (5H, m), 7.57-7.63 (4H, m), 7.78 (1H, d, $J = 2.9$ Hz), 7.84 (1H, d, $J = 1.7$ Hz), 11.08 (1H, brs).

Example 637

20 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[(4-fluorobenzyl)oxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.97-3.65 (6H, m), 4.34-4.36 (2H, m), 4.52-4.57 (6H, m),
5.17 (2H, s), 7.12 (1H, d, $J = 8.8$ Hz), 7.16-7.22 (2H, m), 7.31 (1H, d, $J = 15.4$ Hz), 7.37-7.54
(8H, m), 7.58-7.67 (5H, m), 7.84-7.86 (2H, m), 11.28 (1H, brs).

25

Example 638

4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{2-fluoro-4-[(4-fluorophenoxy)methyl]benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.09-3.22 (3H, m), 3.41-3.46 (2H, m), 3.60-3.62 (1H, m),
30 4.40-4.42 (2H, m), 4.54-4.56 (2H, m), 5.15 (2H, s), 5.23 (2H, s), 7.03-7.06 (2H, m), 7.10-7.17
(3H, m), 7.31 (1H, d, $J = 15.4$ Hz), 7.38-7.43 (2H, m), 7.49 (1H, d, $J = 15.4$ Hz), 7.62-7.67 (4H, m),
7.76-7.90 (5H, m), 11.29 (1H, s).

Example 639

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{2-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.12-3.14 (2H, m), 3.43-3.46 (2H, m), 3.54-3.56 (2H, m), 4.41-4.43 (2H, m), 4.55-4.57 (2H, m), 5.05 (2H, s), 5.15 (2H, s), 7.02-7.21 (7H, m), 7.28-7.32 (2H, m), 7.34 (1H, s), 7.39-7.44 (2H, m), 7.49 (1H, d, *J* = 15.4 Hz), 7.59 (1H, dd, *J* = 8.9, 3.1 Hz), 7.63 (1H, s), 7.71 (1H, s), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, s), 10.78 (1H, s).

Example 640

4-({[6-(2-Chloro-4-({(*E*)-3-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile hydrochloride

mp: 141.8-141.9 °C

Example 641

4-({[6-(2-Chloro-4-({(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile hydrochloride

mp: 218.0-220.5 °C

Example 642

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 176.7-176.9 °C

Example 643

4-({[6-(2-Chloro-4-({(*E*)-3-(4-{3-fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy)pyridin-3-yl]oxy}methyl}benzonitrile hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 0.87 (3H, t, *J* = 7.2 Hz), 1.53-1.56 (2H, m), 2.10 (3H, s), 3.09-3.12 (3H, m), 3.35-3.57 (5H, m), 4.39-4.41 (2H, m), 4.53-4.55 (2H, m), 5.13 (2H, s), 5.23 (2H, s), 6.94 (2H, d, *J* = 8.5 Hz), 7.12 (3H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.39-7.54 (3H, m), 7.62-7.67 (5H, m), 7.82 (1H, d, *J* = 2.9 Hz), 7.84 (1H, s), 7.88 (2H, d, *J* = 8.1 Hz), 10.71 (1H, s).

Example 644

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.12 (3H, s), 3.00-3.18 (3H, m), 3.35-3.60 (3H, m), 4.38-4.40 (2H, m), 4.53-4.57 (2H, m), 5.15 (2H, s), 5.17 (2H, s), 7.04-7.08 (2H, m), 7.10-7.17 (3H, m), 7.30 (1H, d, *J* = 15.4 Hz), 7.38-7.53 (6H, m), 7.60-7.67 (4H, m), 7.83-7.86 (2H, m), 11.01 (1H, s).

5 Example 645

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{3-fluoro-4-[(4-propylphenoxy)methyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 0.87 (3H, t, *J* = 7.3 Hz), 1.50-1.60 (2H, m), 2.10 (3H, s), 2.30 (3H, s), 3.03-3.09 (2H, m), 3.20-3.23 (1H, m), 3.37-3.47 (3H, m), 3.62-3.65 (2H, m), 4.37-4.40 (2H, m), 4.53-4.56 (2H, m), 5.06 (2H, s), 5.13 (2H, s), 6.94 (2H, d, *J* = 8.3 Hz), 7.07-7.15 (3H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.28-7.35 (3H, m), 7.45-7.52 (2H, m), 7.58-7.63 (4H, m), 7.79 (1H, d, *J* = 2.9 Hz), 7.84 (1H, s), 11.52 (1H, s).

Example 646

15 4-{{[(6-{4-[(*E*)-3-(4-{4-[(4-Chlorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 213.9-214.8 °C

Example 647

20 4-({[6-(2,6-Dimethyl-4-{{(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride
mp: 216.2-219.2 °C

Example 648

25 (*E*)-3-(3,5-Dimethyl-4-{{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.04 (6H, s), 2.82 (1H, septet, *J* = 6.8 Hz), 3.04-3.60 (6H, m), 4.36 (2H, brs), 4.53 (2H, brs), 5.11 (2H, s), 5.22 (2H, s), 6.91-6.95 (2H, m), 7.00 (1H, d, *J* = 8.8 Hz), 7.14-7.22 (3H, m), 7.46-7.55 (5H, m), 7.60-7.64 (3H, m), 7.81 (1H, d, *J* = 2.0 Hz), 7.84 (1H, d, *J* = 2.9 Hz), 9.13 (1H, d, *J* = 2.0 Hz), 11.23 (1H, brs).

Example 649

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 207.4-207.6 °C

Example 650

4-{{[(6-{2,6-Dimethyl-4-[(1*E*)-3-oxo-3-(4-{4-[(1*E*)-3-phenoxyprop-1-en-1-yl]benzyl}piperazin-
5 1-yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

¹H-NMR (CDCl₃) δ: 2.12 (6H, s), 2.72 (2H, brs), 3.45-3.66 (3H, m), 4.15 (4H, brs), 4.72-4.78 (3H, m), 5.09 (2H, s), 6.48 (1H, dt, *J* = 16.1, 5.5 Hz), 6.68 (1H, d, *J* = 15.1 Hz), 6.75 (1H, d, *J* = 16.1 Hz), 6.86 (1H, d, *J* = 9.0 Hz), 6.95-7.00 (3H, m), 7.25-7.36 (5H, m), 7.47-7.70 (9H, m), 7.78 (1H, d, *J* = 2.7 Hz), 13.58 (1H, brs).

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Example 651

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-
[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO- *d*₆) δ: 2.03 (6H, s), 2.23 (3H, s), 2.33 (3H, s), 3.07-3.52 (6H, m), 4.30 (2H, brs), 4.53 (2H, brs), 4.73 (2H, dd, *J* = 5.7, 1.1 Hz), 5.08 (2H, s), 6.43 (1H, dt, *J* = 15.9, 5.7 Hz), 6.89 (2H, dt, *J* = 9.3, 2.5 Hz), 6.98 (1H, d, *J* = 15.9 Hz), 7.00 (1H, d, *J* = 9.0 Hz), 7.10 (2H, dd, *J* = 8.7, 0.6 Hz), 7.17-7.25 (3H, m), 7.37 (2H, brs), 7.46-7.52 (5H, m), 7.58 (1H, dd, *J* = 9.0, 3.2 Hz), 7.63 (1H, d, *J* = 8.3 Hz), 7.80 (1H, dd, *J* = 3.2, 0.5 Hz), 10.59 (1H, brs).

20 Example 652

4-{{[(6-{2-Chloro-4-[(1*E*)-3-(4-{4-[(1*E*)-3-(4-methoxyphenoxy)prop-1-en-1-yl]benzyl}piperazin-
1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile
hydrochloride

mp: 188.2-189.1 °C

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Example 653

4-{{[(2*E*)-3-{4-[(4-[(2*E*)-3-[3-Chloro-4-({5-[(4-cyanobenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]prop-2-enoyl}piperazin-1-yl)methyl]phenyl}prop-2-en-1-yl]oxy}benzonitrile
hydrochloride

30 mp: 210.4-212.2 °C

Example 654

(2*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-
[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO- *d*₆) δ: 2.04 (6H, s), 2.23 (3H, s), 2.43 (3H, s), 3.15-3.57 (6H, m), 3.75 (3H, s), 4.36 (2H, brs), 4.55 (2H, brs), 4.70 (2H, d, *J* = 5.4 Hz), 5.01 (2H, s), 6.57 (1H, dt, *J* = 15.6, 5.4 Hz), 6.73 (1H, d, *J* = 15.6 Hz), 6.88 (2H, dt, *J* = 9.2, 2.4 Hz), 6.94 (2H, dt, *J* = 9.2, 2.4 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 7.09 (2H, d, *J* = 8.1 Hz), 7.20 (1H, d, *J* = 15.6 Hz), 7.35-7.38 (2H, m), 7.48-
 5 7.51 (5H, m), 7.56 (2H, dd, *J* = 9.0, 3.1 Hz), 7.78 (1H, d, *J* = 3.1 Hz), 10.34 (1H, brs).

Example 655

4-({[6-(2-Chloro-4-{{(1*E*)-3-[4-(4-{{(1*E*)-3-[(6-chloropyridin-3-yl)oxy]prop-1-en-1-yl}benzyl)-
 piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile
 10 hydrochloride
 mp: 204.7-206.2 °C

Example 656

4-({[6-(2-Chloro-6-methyl-4-{{(1*E*)-3-[4-(4-{{(1*E*)-3-[(6-methylpyridin-3-yl)oxy]prop-1-en-1-
 15 yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile
 hydrochloride
 mp: 162.7-163.3 °C

Example 657

4-({[6-(4-{{(1*E*)-3-[4-(4-{{(1*E*)-3-[(5-Bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl)piperazin-1-
 20 yl]-3-oxoprop-1-en-1-yl}-2-chloro-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile
 hydrochloride
 mp: 145.0-145.8 °C

25 Example 658

4-({[6-(2-Chloro-6-methyl-4-{{(1*E*)-3-[4-(4-{{(1*E*)-3-[(5-methylpyridin-2-yl)oxy]prop-1-en-1-
 yl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile
 hydrochloride
 mp: 169.5-170.0 °C

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Example 659

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(2*E*)-4-(4-
 methylphenoxy)but-2-en-2-yl]benzyl)piperazin-1-yl)prop-2-en-1-one hydrochloride
¹H-NMR (DMSO- *d*₆) δ: 2.04 (6H, s), 2.12 (3H, s), 2.23 (3H, s), 3.04-3.60 (6H, m), 4.35 (2H,

brs), 4.53 (2H, brs), 4.75 (2H, d, $J = 6.3$ Hz), 5.08 (2H, s), 6.10 (1H, t, $J = 6.3$ Hz), 6.88 (2H, dt, $J = 9.2, 2.4$ Hz), 7.00 (1H, d, $J = 9.0$ Hz), 7.09 (2H, d, $J = 8.3$ Hz), 7.17-7.25 (3H, m), 7.46-7.52 (5H, m), 7.55-7.60 (5H, m), 7.80 (1H, d, $J = 3.2$ Hz), 11.21 (1H, s).

5 Example 660

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-2-methyl-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO- d_6) δ : 1.93 (3H, s), 2.03 (6H, s), 2.23 (3H, s), 3.06-3.57 (6H, m), 4.35 (2H, brs), 4.53 (2H, brs), 4.58 (2H, s), 5.08 (2H, s), 6.64 (1H, brs), 6.90 (2H, dt, $J = 9.2, 2.4$ Hz), 7.00 (1H, d, $J = 8.8$ Hz), 7.09 (2H, d, $J = 8.3$ Hz), 7.17-7.24 (3H, m), 7.40 (2H, d, $J = 8.1$ Hz), 7.46-7.52 (5H, m), 7.56-7.60 (3H, m), 7.80 (1H, d, $J = 2.9$ Hz), 10.95 (1H, brs).

Example 661

15 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl}prop-2-en-1-one dihydrochloride

¹H-NMR (DMSO- d_6) δ : 1.19 (6H, d, $J = 6.8$ Hz), 2.10 (3H, s), 2.30 (3H, s), 2.70-4.00 (13H, m), 4.20-4.40 (2H, m), 4.45-4.62 (2H, m), 5.56 (2H, s), 7.08 (1H, dd, $J = 8.8, 0.5$ Hz), 7.19 (2H, d, $J = 7.8$ Hz), 7.25-7.35 (7H, m), 7.37 (2H, d, $J = 8.1$ Hz), 7.48 (1H, d, $J = 15.4$ Hz), 7.54-7.62 (3H, m), 7.63 (1H, d, $J = 2.0$ Hz), 7.78 (1H, dd, $J = 3.1, 0.5$ Hz), 7.84 (1H, d, $J = 2.0$ Hz), 11.59 (1H, brs).

Example 662

25 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(2-{[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl}prop-2-en-1-one dihydrochloride

¹H-NMR (DMSO- d_6) δ : 1.19 (6H, d, $J = 6.8$ Hz), 2.11 (3H, s), 2.70-4.00 (13H, m), 4.24-4.40 (2H, m), 4.45-4.61 (2H, m), 5.17 (2H, s), 7.11 (1H, d, $J = 9.5$ Hz), 7.25-7.69 (16H, m), 7.82-7.88 (2H, m), 11.57 (1H, brs).

30 Example 663

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(2-{methyl[4-(propan-2-yl)phenyl]amino}ethyl)benzyl]piperazin-1-yl}prop-2-en-1-one hydrochloride

mp: 184.2-186.2 °C

Example 664

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorophenyl)(methyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride

5 mp: 204.6-208.5 °C

Example 665

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride

10 mp: 206.3-207.8 °C

Example 666

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-fluorophenyl)(methyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride

15 mp: 200.3-202.4 °C

Example 667

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride

20 mp: 193.7-194.9 °C

Example 668

4-({[6-(2-Chloro-4-({(*E*)-3-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile dihydrochloride

25 mp: 211.2-211.9 °C

Example 669

4-({[6-(2-Chloro-4-({(*E*)-3-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile dihydrochloride

30 mp: 219.5-222.3 °C

Example 670

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride

mp: 219.5-221.3 °C

Example 671

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrochloride
5 mp: 217.5-218.4 °C

Example 672

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-({4-[2-(4-methylphenoxy)ethyl]phenyl}amino)piperidin-1-yl]prop-2-en-1-one hydrochloride
10 mp: 191.3-192.5 °C

Example 673

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{[4-(2-
15 {4-(propan-2-yl)phenyl]amino}ethyl)phenyl]amino}piperidin-1-yl)prop-2-en-1-one
dihydrochloride
¹H-NMR (DMSO-*d*₆) δ: 1.19 (6H, d, *J* = 6.8 Hz), 1.45-1.71 (2H, m), 1.90-2.06 (2H, m), 2.10
(3H, s), 2.30 (3H, s), 2.72 (1H, t, *J* = 12.0 Hz), 2.91 (1H, septet, *J* = 6.8 Hz), 2.98-3.07 (2H, m),
3.13 (1H, t, *J* = 12.2 Hz), 3.30-4.00 (7H, m), 4.32-4.58 (2H, m), 5.06 (2H, s), 7.08 (1H, dd, *J* =
20 9.0, 0.5 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.28-7.47 (12H, m), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.63
(1H, d, *J* = 2.0 Hz), 7.79 (1H, dd, *J* = 3.2, 0.5 Hz), 7.83 (1H, d, *J* = 2.0 Hz).

Example 674

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-({4-[2-(4-
25 fluorophenoxy)ethyl]phenyl}amino)piperidin-1-yl]prop-2-en-1-one hydrochloride
mp: 171.7-174.5 °C

Example 675

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-
30 methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 228.0-228.9 °C

Example 676

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-({2-[4-

(propan-2-yl)phenoxy]quinolin-6-yl)methyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 1.25 (6H, d, *J* = 6.8 Hz), 2.11 (3H, s), 2.96 (1H, septet, *J* = 6.8 Hz), 3.00-3.80 (6H, m), 4.42-4.64 (4H, m), 5.17 (2H, s), 7.12 (1H, d, *J* = 8.8 Hz), 7.15-7.20 (2H, m), 7.25-7.55 (8H, m), 7.59-7.69 (3H, m), 7.72 (1H, d, *J* = 8.8 Hz), 7.82-7.90 (3H, m), 8.12 (1H, brs), 8.43 (1H, d, *J* = 8.8 Hz), 11.22 (1H, brs).

Example 677

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methylphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.23 (3H, s), 2.99-3.13 (3H, m), 3.40-3.54 (3H, m), 4.28-4.33 (6H, m), 4.53-4.56 (2H, m), 5.24 (2H, s), 6.87 (2H, d, *J* = 8.5 Hz), 7.07-7.14 (5H, m), 7.31 (1H, d, *J* = 15.4 Hz), 7.49-7.52 (3H, m), 7.64-7.67 (4H, m), 7.78 (2H, d, *J* = 8.1 Hz), 7.83 (1H, d, *J* = 3.2 Hz), 7.85 (1H, s), 10.99 (1H, brs).

15 Example 678

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
mp: 190.3-191.9 °C

20 Example 679

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-chlorophenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.02-3.14 (3H, m), 3.34-3.55 (3H, m), 4.30-4.34 (6H, m), 4.52-4.56 (2H, m), 5.24 (2H, s), 7.00-7.04 (2H, m), 7.07-7.12 (3H, m), 7.28-7.37 (3H, m), 7.47-7.51 (3H, m), 7.62-7.68 (4H, m), 7.77 (2H, d, *J* = 8.3 Hz), 7.82 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J* = 1.5 Hz), 10.80 (1H, brs).

Example 680

4-{[(6-{2-Chloro-4-[(*E*)-3-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 232.0-234.1 °C

Example 681

(*E*)-3-[4-({5-[(2,3-Dichlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-(4-{4-[2-(4-

methylphenyl)-2-oxoethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 178.9-181.1 °C

Example 682

- 5 (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[4-(propan-2-yl)phenoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

mp: 227.6-228.9 °C

Example 683

- 10 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}prop-2-en-1-one hydrochloride

mp: 227.1-228.0 °C

Example 684

- 15 (E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}prop-2-en-1-one hydrochloride

mp: 221.4-221.6 °C

Example 685

- 20 (E)-1-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride

mp: 228.3-230.2 °C

Example 686

- 25 (E)-1-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 225.0-227.1 °C

Example 687

- 30 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methylphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.27 (3H, s), 3.00-3.14 (5H, m), 3.39-3.55 (3H, m), 4.19 (2H, t, *J* = 6.8 Hz), 4.27 (2H, brs), 4.52-4.55 (2H, m), 5.24 (2H, s), 7.02 (2H, d, *J* = 8.5 Hz), 7.12 (3H, d, *J* = 8.8 Hz), 7.21 (2H, d, *J* = 7.8 Hz), 7.29 (1H, d, *J* = 15.6 Hz), 7.47-7.51 (3H, m), 7.62-

7.68 (4H, m), 7.77 (2H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.84 (1H, d, $J = 1.7$ Hz), 10.80 (1H, brs).

Example 688

- 5 (E)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride
- $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.11 (3H, s), 2.97-3.12 (5H, m), 3.33-3.54 (3H, m), 3.72 (3H, s), 4.17 (2H, t, $J = 6.8$ Hz), 4.28 (2H, brs), 4.52-4.55 (2H, m), 5.24 (2H, s), 6.86-6.89 (2H, m), 7.02 (2H, d, $J = 8.5$ Hz), 7.12 (1H, d, $J = 8.8$ Hz), 7.23-7.27 (2H, m), 7.29 (1H, d, $J = 15.4$ Hz), 7.45-7.51
- 10 (3H, m), 7.62-7.68 (4H, m), 7.77 (2H, d, $J = 8.3$ Hz), 7.82 (1H, d, $J = 2.9$ Hz), 7.84 (1H, d, $J = 2.0$ Hz), 10.71 (1H, brs).

Example 689

- 4-[(6-{2-Chloro-6-methyl-4-[(E)-3-oxo-3-(4-{4-[4-(propan-2-yl)phenoxy]benzyl}piperazin-1-
- 15 yl)prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
- $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.21 (6H, d, $J = 6.8$ Hz), 2.11 (3H, s), 2.87-2.94 (1H, m), 3.01-3.17 (2H, m), 3.36-3.39 (2H, m), 3.55-3.58 (2H, m), 4.31-4.34 (2H, m), 4.53-4.56 (2H, m), 5.23 (2H, s), 6.99 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.3$ Hz), 7.12 (1H, d, $J = 9.0$ Hz), 7.28-7.33 (3H, m), 7.49 (1H, d, $J = 15.4$ Hz), 7.56 (2H, d, $J = 8.3$ Hz), 7.62-7.66 (4H, m), 7.81-7.89 (4H, m), 10.90
- 20 (1H, s).

Example 690

- (E)-3-[4-({5-[(2,3-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenyl]ethoxy}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
- 25 mp: 196.5-197.4 °C

Example 691

- (E)-3-[4-({5-[(2,4-Difluorobenzyl)oxy]pyridin-2-yl}oxy)-3-fluorophenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenyl]ethoxy}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
- 30 mp: 195.2-198.7 °C
- $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.16 (6H, d, $J = 6.8$ Hz), 2.82 (1H, septet, $J = 6.8$ Hz), 2.90-3.65 (8H, m), 4.18 (2H, t, $J = 6.7$ Hz), 4.32 (2H, brs), 4.52 (2H, brs), 5.14 (2H, s), 6.84 (2H, d, $J = 8.8$ Hz), 7.12-7.17 (4H, m), 7.27-7.34 (3H, m), 7.43 (2H, d, $J = 7.8$ Hz), 7.50-7.56 (4H, m), 7.60-7.66 (2H, m), 7.83 (1H, dd, $J = 12.1, 1.8$ Hz), 7.89 (1H, d, $J = 3.2$ Hz), 10.76 (1H, brs).

Example 692

4-{{[(6-{4-[(*E*)-3-{4-[4-(4-Chlorophenoxy)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

5 mp: 231.9-233.7 °C

Example 693

4-({[6-(4-{(*E*)-3-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride

10 mp: 231.3-231.5 °C

Example 694

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

15 mp: 200.2-200.3 °C

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.96-4.55 (17H, m), 5.17 (2H, s), 6.87 (2H, d, *J* = 8.5 Hz), 7.02 (2H, d, *J* = 8.1 Hz), 7.12 (1H, d, *J* = 8.8 Hz), 7.24 (2H, d, *J* = 8.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.39-7.42 (2H, m), 7.46-7.53 (4H, m), 7.60-7.67 (3H, m), 7.84-7.84 (2H, m), 10.83 (1H, brs).

20

Example 695

(*E*)-1-[4-(4-Methylbenzyl)piperazin-1-yl]-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 224.8-225.5 °C (dec.)

25

Example 696

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-en-1-one hydrochloride

mp: 222.2-224.2 °C (dec.)

30

Example 697

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(3,4-dichlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride

mp: 218.3-218.5 °C

Example 698

4-({[6-(2-Chloro-6-methyl-4-({(E)-3-[4-(4-methylbenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

5 mp: 152.0-152.1 °C

Example 699

4-({[6-(2-Chloro-4-({(E)-3-[4-(4-chlorobenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

10 mp: 223.7-223.8 °C

Example 700

(2E)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[(1E)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride

15 ¹H-NMR (DMSO-*d*₆) δ: 2.10 (3H, s), 2.30 (3H, s), 3.06-3.57 (6H, m), 3.29 (3H, s), 4.06 (2H, dd, *J* = 5.5, 1.3 Hz), 4.34 (2H, brs), 4.52-4.55 (2H, m), 5.05 (2H, s), 6.45 (1H, dt, *J* = 16.1, 5.5 Hz), 6.64 (1H, d, *J* = 16.1 Hz), 7.09 (1H, d, *J* = 9.3 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.28-7.34 (3H, m), 7.49 (1H, d, *J* = 15.4 Hz), 7.52-7.57 (4H, m), 7.59 (1H, dd, *J* = 9.3, 3.2 Hz), 7.63 (1H, d, *J* = 2.0 Hz), 7.79 (1H, d, *J* = 3.2 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 10.93 (1H, brs).

20

Example 701

4-({[6-(2,6-Dimethyl-4-({(E)-3-[4-(4-methylbenzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrochloride

mp: 224.7-226.0 °C

25

Example 702

(E)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 216.1-216.5 °C

30 ¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.34 (3H, s), 3.05-4.56 (10H, m), 5.11 (2H, s), 7.10 (1H, d, *J* = 8.8 Hz), 7.21 (2H, d, *J* = 7.8 Hz), 7.26 (1H, t, *J* = 74.0 Hz), 7.26-7.33 (3H, m), 7.48-7.53 (5H, m), 7.60-7.64 (2H, m), 7.81 (1H, brs), 7.85 (1H, brs), 11.62 (1H, brs).

Example 703

4-{{[(6-{2-Chloro-4-[(*E*)-3-{4-[4-(3-hydroxypropyl)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 191.6-193.1 °C

5 Example 704

4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{4-[(*E*)-3-hydroxyprop-1-en-1-yl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 3.04-3.61 (6H, m), 4.15 (2H, dd, *J* = 4.6, 1.5 Hz), 4.32 (2H, brs), 4.54 (2H, brs), 5.23 (2H, s), 6.48 (1H, dt, *J* = 16.0, 4.8 Hz), 6.60 (1H, dt, *J* = 16.0, 1.5 Hz), 7.12 (1H, dd, *J* = 9.0, 0.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.47-7.56 (5H, m), 7.62-7.66 (4H, m), 7.82 (1H, dd, *J* = 3.2, 0.5 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 7.88 (2H, dt, *J* = 8.3, 1.7 Hz), 11.12 (1H, brs).

Example 705

15 4-{{[(6-{2-Chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(1-hydroxy-2-methylpropan-2-yl)oxy]benzyl}-piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride
mp: 170.2-170.5 °C

20 Example 706

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 205.5-206.5 °C

25 Example 707

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrobromide
mp: 147.6-149.7 °C

30 Example 708

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 156.5-158.2 °C

Example 709

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrobromide
mp: 197.8-198.4 °C

5

Example 710

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 196.4-197.6 °C

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Example 711

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 155.5-157.0 °C

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Example 712

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 142.2-144.1 °C

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Example 713

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide
mp: 144.3-145.8 °C

25

Example 714

(*E*)-1-(4-{4-[2-(4-Acetylphenoxy)ethyl]benzyl}piperazin-1-yl)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.51 (3H, s), 3.05-3.44 (8H, m), 4.31-4.57 (6H, m), 5.17 (2H, s), 7.03 (2H, d, *J* = 8.8 Hz), 7.12 (1H, d, *J* = 9.0 Hz), 7.29-7.53 (9H, m), 7.60-7.67 (3H, m), 7.83-7.85 (2H, m), 7.92 (2H, d, *J* = 8.8 Hz), 9.87 (1H, brs).

30

Example 715

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-

methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO- *d*₆) δ: 1.21 (3H, d, *J* = 6.1 Hz), 2.12 (3H, s), 2.21 (3H, s), 2.89 (1H, dd, *J* = 13.9, 5.4 Hz), 2.98 (1H, dd, *J* = 13.9, 6.6 Hz), 3.05-3.46 (6H, m), 4.35 (2H, brs), 4.54-4.56 (2H, m), 4.61-4.69 (1H, m), 5.17 (2H, s), 6.79 (2H, dt, *J* = 9.2, 2.4 Hz), 7.05 (2H, d, *J* = 8.1 Hz), 7.12 (1H, d, *J* = 9.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 7.37-7.53 (8H, m), 7.60-7.67 (3H, m), 7.84 (1H, d, *J* = 3.2 Hz), 7.85 (1H, d, *J* = 2.0 Hz), 9.85 (1H, brs).

Example 716

(*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO- *d*₆) δ: 1.21 (3H, d, *J* = 6.1 Hz), 2.03 (6H, s), 2.21 (3H, s), 2.89 (1H, dd, *J* = 13.8, 5.7 Hz), 2.99 (1H, dd, *J* = 13.8, 6.6 Hz), 3.05-3.39 (6H, m), 3.76 (3H, s), 4.35 (2H, brs), 4.55 (2H, brs), 4.62-4.67 (1H, m), 5.01 (2H, s), 6.79 (2H, dt, *J* = 9.3, 2.6 Hz), 6.94 (2H, dt, *J* = 9.3, 2.6 Hz), 6.99 (1H, d, *J* = 9.0 Hz), 7.05 (2H, d, *J* = 8.3 Hz), 7.19 (1H, d, *J* = 15.4 Hz), 7.35-7.50 (9H, m), 7.56 (1H, dd, *J* = 9.0, 3.2 Hz), 7.78 (1H, d, *J* = 3.2 Hz), 9.87 (1H, brs).

Example 717

(*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO- *d*₆) δ: 1.21 (3H, d, *J* = 6.1 Hz), 2.04 (6H, s), 2.21 (3H, s), 2.89 (1H, dd, *J* = 13.8, 5.7 Hz), 2.99 (1H, dd, *J* = 13.8, 6.7 Hz), 3.06-3.47 (6H, m), 4.35 (2H, brs), 4.53-4.56 (2H, m), 4.61-4.69 (1H, m), 5.08 (2H, s), 6.79 (2H, dt, *J* = 9.0, 2.4 Hz), 7.00 (1H, d, *J* = 9.3 Hz), 7.05 (2H, d, *J* = 8.1 Hz), 7.17-7.25 (3H, m), 7.39 (2H, d, *J* = 8.3 Hz), 7.44-7.52 (7H, m), 7.58 (1H, dd, *J* = 9.3, 3.2 Hz), 7.80 (1H, d, *J* = 3.2 Hz), 9.90 (1H, brs).

Example 718

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.34 (3H, s), 3.05-3.41 (8H, m), 4.20 (2H, t, *J* = 6.4 Hz), 4.37 (2H, brs), 4.55-4.58 (2H, m), 5.19 (2H, s), 6.92-6.95 (2H, m), 7.08-7.14 (4H, m), 7.24 (1H, d, *J* = 15.1 Hz), 7.38-7.53 (7H, m), 7.61-7.70 (3H, m), 7.91-7.92 (1H, m), 8.02 (1H, s), 9.92 (1H, brs).

Example 719

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-

(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.30 (3H, s), 2.33 (3H, s), 2.81 (1H, septet, *J* = 6.8 Hz), 3.05-3.63 (8H, m), 4.18 (2H, t, *J* = 6.6 Hz), 4.37 (2H, brs), 4.55-4.58 (2H, m), 5.08 (2H, s), 6.82-6.85 (2H, m), 7.07-7.14 (4H, m), 7.19-7.25 (3H, m), 7.33 (2H, d, *J* = 8.1 Hz), 7.43-7.48 (4H, m), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.68 (1H, d, *J* = 15.1 Hz), 7.86 (1H, d, *J* = 3.2 Hz), 8.01 (1H, s), 9.93 (1H, brs).

Example 720

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.21 (3H, s), 2.30 (3H, s), 2.33 (3H, s), 3.04-3.60 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.36 (2H, brs), 4.55-4.58 (2H, m), 5.08 (2H, s), 6.79-6.83 (2H, m), 7.06-7.12 (4H, m), 7.19-7.25 (3H, m), 7.33 (2H, d, *J* = 7.8 Hz), 7.43-7.48 (4H, m), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.67 (1H, d, *J* = 15.4 Hz), 7.86 (1H, d, *J* = 3.2 Hz), 8.01 (1H, s), 9.93 (1H, brs).

Example 721

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.15 (3H, s), 2.21 (3H, s), 3.04-3.42 (8H, m), 4.17 (2H, t, *J* = 6.6 Hz), 4.35 (2H, brs), 4.55 (2H, brs), 5.20 (2H, s), 6.80-6.82 (2H, m), 7.08 (2H, d, *J* = 8.1 Hz), 7.11 (1H, d, *J* = 9.3 Hz), 7.16 (1H, s), 7.29 (1H, d, *J* = 15.1 Hz), 7.36-7.44 (6H, m), 7.51-7.53 (1H, m), 7.61-7.67 (2H, m), 7.80 (1H, d, *J* = 15.1 Hz), 7.95-7.96 (2H, m), 9.83 (1H, brs).

Example 722

(*E*)-3-[2-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 7.1 Hz), 2.14 (3H, s), 2.30 (3H, s), 2.81 (1H, septet, *J* = 7.1 Hz), 3.05-3.56 (8H, m), 4.18 (2H, t, *J* = 6.6 Hz), 4.36-4.55 (4H, m), 5.09 (2H, s), 6.82-6.85 (2H, m), 7.08 (1H, d, *J* = 8.8 Hz), 7.11-7.14 (3H, m), 7.20 (2H, d, *J* = 7.8 Hz), 7.29 (1H, d, *J* = 15.1 Hz), 7.33 (2H, d, *J* = 7.8 Hz), 7.45 (4H, brs), 7.60 (1H, dd, *J* = 8.8, 2.9 Hz), 7.80 (1H, d, *J* = 15.1 Hz), 7.90-7.91 (1H, m), 7.96 (1H, s), 9.86 (1H, brs).

Example 723

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-

(propan-2-yl)phenoxy]ethyl]benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.15 (6H, d, *J* = 6.8 Hz), 2.15 (3H, s), 2.81 (1H, septet, *J* = 6.8 Hz),
3.05-3.38 (8H, m), 4.18 (2H, t, *J* = 6.4 Hz), 4.36-4.55 (4H, m), 5.20 (2H, s), 6.82-6.84 (2H, m),
7.10-7.16 (4H, m), 7.29 (1H, d, *J* = 15.4 Hz), 7.38-7.54 (7H, m), 7.61-7.67 (2H, m), 7.80 (1H, d,
5 *J* = 15.4 Hz), 7.95-7.96 (2H, m), 9.84 (1H, brs).

Example 724

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

10 ¹H-NMR (DMSO-*d*₆) δ: 2.15 (3H, s), 3.05-3.48 (8H, m), 4.20 (2H, t, *J* = 6.6 Hz), 4.36-4.55 (4H, m), 5.20 (2H, s), 6.92-6.96 (2H, m), 7.07-7.16 (4H, m), 7.29 (1H, d, *J* = 15.1 Hz), 7.37-7.54 (7H, m), 7.61-7.68 (2H, m), 7.80 (1H, d, *J* = 15.1 Hz), 7.95-7.96 (2H, m), 9.87 (1H, brs).

Example 725

15 (*E*)-1-(4-{4-[2-(4-Fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)-oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.22 (3H, d, *J* = 5.9 Hz), 2.03 (6H, s), 2.90 (1H, dd, *J* = 13.9, 5.4 Hz),
2.99 (1H, dd, *J* = 13.9, 6.6 Hz), 3.05-3.38 (6H, m), 3.76 (3H, s), 4.35 (2H, brs), 4.56 (2H, brs),
4.62-4.71 (1H, m), 5.01 (2H, s), 6.90-6.96 (4H, m), 6.99 (1H, d, *J* = 9.3 Hz), 7.05-7.12 (2H, m),
20 7.19 (1H, d, *J* = 15.4 Hz), 7.35-7.50 (9H, m), 7.57 (1H, dd, *J* = 9.3, 3.2 Hz), 7.78 (1H, d, *J* = 3.2 Hz), 9.88 (1H, brs).

Example 726

25 (*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.22 (3H, d, *J* = 6.1 Hz), 2.03 (6H, s), 2.90 (1H, dd, *J* = 13.9, 5.6 Hz),
2.99 (1H, dd, *J* = 13.9, 6.7 Hz), 3.04-3.39 (6H, m), 4.35 (2H, brs), 4.55 (2H, brs), 4.62-4.70 (1H, m),
5.08 (2H, s), 6.89-6.94 (2H, m), 7.01 (1H, d, *J* = 9.0 Hz), 7.05-7.11 (2H, m), 7.17-7.26 (3H, m),
7.39-7.52 (9H, m), 7.59 (1H, dd, *J* = 9.0, 3.2 Hz), 7.80 (1H, d, *J* = 3.2 Hz), 9.85 (1H, brs).

30

Example 727

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide
mp: 197.0-199.1 °C

Example 728

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrobromide

5 mp: 166.7-168.8 °C

Example 729

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

10 mp: 211.3-211.9 °C

Example 730

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{3-[4-(propan-2-yl)phenoxy]propyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

15 ¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 1.99-2.05 (2H, m), 2.11 (3H, s), 2.76-3.48 (9H, m), 3.94 (2H, t, *J* = 6.4 Hz), 4.36 (2H, brs), 4.54-4.57 (2H, m), 5.17 (2H, s), 6.82-6.85 (2H, m), 7.11-7.14 (3H, m), 7.29-7.53 (9H, m), 7.59-7.67 (3H, m), 7.83-7.86 (2H, m), 9.88-9.96 (1H, m).

Example 731

20 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrobromide
mp: 200.5-202.1 °C

Example 732

25 (*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]but-2-en-1-one hydrobromide
mp: 167.3-168.9 °C

Example 733

30 (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-{4-[4-({[4-(propan-2-yl)benzyl]oxy}methyl)benzyl]piperazin-1-yl}prop-2-en-1-one hydrobromide
¹H-NMR (DMSO-*d*₆) δ: 1.19 (6H, d, *J* = 6.8 Hz), 2.10 (3H, s), 2.30 (3H, s), 2.85-3.48 (7H, m), 4.38 (2H, brs), 4.52-4.56 (6H, m), 5.05 (2H, s), 7.08 (1H, d, *J* = 9.0 Hz), 7.18-7.24 (4H, m), 7.27-7.33 (5H, m), 7.46-7.51 (5H, m), 7.58-7.62 (2H, m), 7.78 (1H, d, *J* = 2.9 Hz), 7.84 (1H, d, *J*

= 1.7 Hz), 9.89 (1H, brs).

Example 734

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-({[4-(propan-2-yl)benzyl]oxy}methyl)benzyl]piperazin-1-yl}prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.19 (6H, d, *J* = 6.8 Hz), 2.11 (3H, s), 2.85-3.54 (7H, m), 4.39 (2H, brs), 4.52-4.56 (6H, m), 5.17 (2H, s), 7.12 (1H, d, *J* = 9.0 Hz), 7.22-7.32 (5H, m), 7.37-7.32 (8H, m), 7.60-7.66 (3H, m), 7.83-7.85 (2H, m), 9.93 (1H, brs).

10 Example 735

(*E*)-3-[5-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-2-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.34 (3H, s), 2.83 (1H, septet, *J* = 6.8 Hz), 3.06-3.60 (6H, m), 4.40 (2H, brs), 4.55-4.58 (2H, m), 5.12 (2H, s), 5.19 (2H, s), 6.91-6.95 (2H, m), 7.11-7.17 (4H, m), 7.24 (1H, d, *J* = 15.1 Hz), 7.37-7.44 (2H, m), 7.50-7.70 (8H, m), 7.91-7.92 (1H, m), 8.02 (1H, s), 9.92 (1H, brs).

Example 736

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[(4-fluorophenyl)amino]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one dihydrobromide

mp: 194.9-196.6 °C

Example 737

(*E*)-3-[5-Chloro-2-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.30 (3H, s), 2.33 (3H, s), 2.83 (1H, septet, *J* = 6.8 Hz), 3.07-3.40 (6H, m), 4.40-4.58 (4H, m), 5.08 (2H, s), 5.12 (2H, s), 6.91-6.95 (2H, m), 7.07-7.25 (7H, m), 7.33 (2H, d, *J* = 8.1 Hz), 7.53-7.61 (5H, m), 7.68 (1H, d, *J* = 15.1 Hz), 7.86-7.87 (1H, m), 8.01 (1H, s), 9.91 (1H, brs).

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Example 738

(*E*)-3-[2-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, *J* = 6.8 Hz), 2.15 (3H, s), 2.83 (1H, septet, *J* = 6.8 Hz),

3.09-3.58 (6H, m), 4.41-4.57 (4H, m), 5.12 (2H, s), 5.20 (2H, s), 6.93 (2H, d, $J = 8.6$ Hz), 7.10-7.17 (4H, m), 7.31 (1H, d, $J = 15.4$ Hz), 7.38-7.44 (2H, m), 7.50-7.68 (7H, m), 7.81 (1H, d, $J = 15.4$ Hz), 7.95 (1H, d, $J = 3.2$ Hz), 7.98 (1H, s), 9.97 (1H, brs).

5 Example 739

4-({[6-(2-Chloro-5-methyl-4-({(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)-piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 1.16 (6H, d, $J = 6.8$ Hz), 2.34 (3H, s), 2.83 (1H, septet, $J = 6.8$ Hz), 3.06-3.63 (6H, m), 4.41-4.58 (4H, m), 5.12 (2H, s), 5.26 (2H, s), 6.91-6.95 (2H, m), 7.10-7.18
10 (4H, m), 7.24 (1H, d, $J = 15.1$ Hz), 7.56 (4H, s), 7.61-7.70 (4H, m), 7.87-7.90 (3H, m), 8.02 (1H, s), 10.00 (1H, brs).

Example 740

(2*E*)-3-[4-({5-[(4-Fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 3.05-3.52 (6H, m), 3.30 (3H, s), 4.06 (2H, dd, $J = 5.5, 1.3$ Hz), 4.37 (2H, brs), 4.55 (2H, brs), 5.08 (2H, s), 6.46 (1H, dt, $J = 16.4, 5.5$ Hz), 6.65 (1H, d, $J = 16.4$ Hz), 7.01 (1H, d, $J = 8.8$ Hz), 7.18-7.25 (3H, m), 7.46-7.52 (7H, m), 7.57-7.60 (3H, m),
20 7.80 (1H, d, $J = 3.2$ Hz), 9.87 (1H, brs).

Example 741

4-({[6-{4-[(*E*)-3-{4-[4-(2-Hydroxyethyl)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 2.77 (2H, t, $J = 7.0$ Hz), 3.05-3.07 (3H, m), 3.39-3.41 (3H, m), 3.63 (2H, t, $J = 7.0$ Hz), 4.34-4.37 (2H, m), 4.55-4.57 (2H, m), 5.22 (2H, s), 7.02 (1H, d, $J = 8.8$ Hz), 7.20 (1H, d, $J = 15.4$ Hz), 7.34 (2H, d, $J = 7.8$ Hz), 7.43-7.50 (5H, m), 7.60-7.64 (3H, m), 7.82-7.88 (3H, m), 9.90 (1H, s).

Example 742

30 (*E*)-3-(3,5-Dimethyl-4-({5-(pyridin-4-ylmethoxy)pyridin-2-yl}oxy)phenyl)-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one hydrobromide

¹H-NMR (DMSO-*d*₆) δ: 2.04 (6H, s), 2.77 (2H, t, $J = 6.8$ Hz), 3.08-3.10 (3H, m), 3.38-3.41 (3H, m), 3.63 (2H, t, $J = 6.8$ Hz), 4.36-4.38 (2H, m), 4.54-4.56 (2H, m), 5.45 (2H, s), 7.06 (1H, d, $J = 9.0$ Hz), 7.21 (1H, d, $J = 15.4$ Hz), 7.34 (2H, d, $J = 8.1$ Hz), 7.46-7.49 (5H, m), 7.66 (1H, dd, $J =$

8.9, 2.9 Hz), 7.87 (1H, d, $J = 2.9$ Hz), 7.98 (2H, d, $J = 6.3$ Hz), 8.89 (2H, d, $J = 6.3$ Hz), 10.03 (1H, s).

Example 743

- 5 (2*E*)-3-[4-({5-[(4-Methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1*E*)-3-methoxyprop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrobromide
¹H-NMR (DMSO-*d*₆) δ: 2.03 (6H, s), 3.06-3.42 (6H, m), 3.30 (3H, s), 3.75 (3H, s), 4.06 (2H, dd, $J = 5.6, 1.2$ Hz), 4.37 (2H, brs), 4.56 (2H, brs), 5.01 (2H, s), 6.46 (1H, dt, $J = 15.9, 5.6$ Hz), 6.65 (1H, d, $J = 15.9$ Hz), 6.94 (2H, dt, $J = 9.4, 2.6$ Hz), 6.99 (1H, d, $J = 9.0$ Hz), 7.20 (1H, d, $J = 15.4$ Hz), 7.37 (2H, dt, $J = 9.4, 2.6$ Hz), 7.47-7.50 (5H, m), 7.55-7.59 (3H, m), 7.78 (1H, d, $J = 3.2$ Hz), 9.91 (1H, brs).
- 10

Example 744

- (*E*)-3-[4-({5-[(2-Chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-{4-[4-(2-hydroxyethyl)benzyl]piperazin-1-yl}prop-2-en-1-one hydrobromide
mp: 206.8-207.6 °C
- 15

Example 745

- (*E*)-3-{3-Chloro-4-[(5-{[4-(difluoromethoxy)benzyl]oxy}pyridin-2-yl)oxy]-5-methylphenyl}-1-{4-[4-(propan-2-yloxy)benzyl]piperazin-1-yl}prop-2-en-1-one hydrobromide
mp: 176.7-178.2 °C
¹H-NMR (DMSO-*d*₆) δ: 1.28 (6H, d, $J = 6.1$ Hz), 2.11 (3H, s), 3.03-4.57 (10H, m), 4.66 (1H, septet, $J = 6.1$ Hz), 5.10 (2H, s), 7.01 (2H, d, $J = 8.5$ Hz), 7.11 (1H, d, $J = 8.8$ Hz), 7.20 (2H, d, $J = 8.3$ Hz), 7.24 (1H, t, $J = 74.0$ Hz), 7.30 (1H, d, $J = 15.1$ Hz), 7.41-7.52 (5H, m), 7.60-7.63 (2H, m), 7.80 (1H, d, $J = 2.9$ Hz), 7.84 (1H, brs), 9.75 (1H, brs).
- 20
- 25

Example 746

- (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one ethanedioate
mp: 211.3-211.7 °C
- 30

Example 747

- (*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylprop-2-en-1-one ethanedioate

mp: 196.8-197.0 °C

Example 748

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-
5 (4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one ethanedioate
mp: 198.6-198.8 °C

Example 749

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-
10 fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylprop-2-en-1-one ethanedioate
mp: 201.4-201.6 °C

Example 750

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-(4-
15 {4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one ethanedioate
mp: 199.2-199.6 °C

Example 751

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-
20 fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one ethanedioate
mp: 236.1-236.6 °C

Example 752

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-
25 fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one ethanedioate
mp: 234.4-235.2 °C

Example 753

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-
30 (4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one ethanedioate
mp: 233.5-233.9 °C

Example 754

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-

fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one ethanedioate

mp: 174.1-175.0 °C

Example 755

5 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]but-2-en-1-one ethanedioate

mp: 167.3-169.4 °C

Example 756

10 (E)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one (2Z)-but-2-enedioate

¹H-NMR (DMSO-*d*₆) δ: 2.11 (3H, s), 2.93-4.05 (10H, m), 5.17 (2H, s), 5.31 (1H, d, *J* = 11.0 Hz), 5.88 (1H, d, *J* = 17.6 Hz), 6.11 (2H, s), 6.76 (1H, dd, *J* = 17.6, 11.0 Hz), 7.11 (1H, d, *J* = 9.0 Hz), 7.29 (1H, d, *J* = 15.4 Hz), 7.37-7.55 (8H, m), 7.60-7.66 (3H, m), 7.83-7.85 (2H, m).

15

[0222]

Example 757

To a solution of (E)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]prop-2-enoic acid (212 mg) in DMF (7.0 mL) were added 1-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazine (190 mg), HOBt (89 mg) and WSC (112 mg) at room temperature, then the reaction mixture was stirred over night. The reaction mixture was basified with saturated aqueous NaHCO₃, extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/4 to 0/1 and then MeOH/AcOEt = 1/9) to afford (E)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}-piperazin-1-yl)prop-2-en-1-one (387 mg) as a colorless amorphous. To a solution of that amorphous (387 mg) in AcOEt (7.0 mL) was added 6 M aqueous HCl (0.088 mL) at room temperature, and then the reaction mixture was stirred for 30 minutes. The reaction mixture was filtered off, and the crude crystal was recrystallized from EtOH-H₂O to afford (E)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride as a colorless powder (333 mg).

30

mp: 201.5-202.0 °C

[0223]

The following compounds were produced in the same manner as in Example 757 using appropriate starting materials.

5 Example 758

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one ethanedioate
mp: 193.3-193.5 °C

10 Example 759

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylprop-2-en-1-one hydrobromide
mp: 212.4-213.0 °C

15 Example 760

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]but-2-en-1-one hydrobromide
mp: 188.2-188.5 °C

20 Example 761

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]but-2-en-1-one hydrobromide
mp: 194.5-195.2 °C

25 Example 762

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 217.7-218.4 °C

30 Example 763

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methoxybenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 192.9-193.4 °C

Example 764

(*E*)-3-[3-Chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-{4-[4-(trifluoromethoxy)benzyl]piperazin-1-yl}prop-2-en-1-one hydrochloride
mp: 202.4-203.2 °C

5

Example 765

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride
mp: 220.0-220.9 °C

10

Example 766

(*E*)-3-[3-Chloro-5-methyl-4-({5-[2-(4-methylphenyl)ethoxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 219.7-220.0 °C

15

Example 767

(*E*)-3-[3-Chloro-4-({5-[2-(3,4-dichlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 208.3-209.7 °C

20

Example 768

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride
mp: 194.2-195.0 °C

25

Example 769

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrobromide
mp: 205.8-205.9 °C

30

Example 770

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methylprop-2-en-1-one hydrobromide
mp: 209.3-209.6 °C

Example 771

(*E*)-3-[3-Chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-[4-(4-methylbenzyl)piperazin-1-yl]but-2-en-1-one hydrobromide

5 mp: 228.2-228.5 °C

Example 772

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methylbut-2-en-1-one hydrobromide

10 mp: 227.5-228.3 °C

Example 773

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methylbut-2-en-1-one hydrobromide

15 mp: 242.4-243.1 °C

Example 774

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-2-methyl-1-[4-(4-methylbenzyl)piperazin-1-yl]but-2-en-1-one hydrobromide

20 mp: 240.4-240.9 °C

Example 775

(*E*)-1-[4-(4-Chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]but-2-en-1-one hydrobromide

25 mp: 205.8-206.5 °C

Example 776

(*E*)-3-[3-Chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]but-2-en-1-one hydrobromide

30 mp: 156.4-158.6 °C

[0224]

Example 777

To a solution of (*E*)-3-{3-chloro-4-[(5-hydroxypyridin-2-yl)oxy]-5-methyl-

phenyl}-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (479 mg) and *p*-chlorobenzyl chloride (129 mg) in DMF (5.0 mL) was added NaH (41.6 mg, 60% in mineral oil) at 0 °C. Then the reaction mixture was stirred over night at room temperature. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl, and extracted with
5 AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/0 to 9/1) to afford (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)-ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one (507 mg) as a colorless amorphous. To a solution
10 of that amorphous (507 mg) in EtOH (10 mL) was added 6 M aqueous HCl (0.129 mL) at room temperature, then the reaction mixture was stirred for 3 hours. The reaction mixture was filtered off, and the precipitate was dried at 50 °C under reduced pressure to afford (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride (486 mg) as a
15 colorless crystal.

mp: 220.1-220.3 °C

[0225]

The following compounds were produced in the same manner as in Example 777 using appropriate starting materials.

20 Example 778

(*E*)-3-{3-Chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 227.1-228.2 °C

25 Example 779

(*E*)-3-[3-Chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 223.9-224.5 °C

30 Example 780

(*E*)-3-[3-Chloro-4-({5-[(3,4-dichlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

mp: 218.7-220.1 °C

Example 781

(*E*)-3-[3-Chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride

5 mp: 223.1-224.0 °C

[0226]

Pharmacological Test

Antiproliferative effect on cancer cell (in vitro)

10 The growth inhibition on a bicalutamide resistant human prostate cancer cell line established from LNCaP.FGC (LNCaP-Bic) (Hobisch A, et al. Prostate. 2006;66(4):413-20.) was determined by a WST-8 assay according to the method of Singh AK, et al. (Cancer Lett. 1996 Oct 1; 107(1): 109-15.). In this method, LNCaP-Bic cells were seeded in RPMI 1640 medium containing 10% fetal bovine serum in a 96-well microplate and incubated at 37 °C for 24 hours
15 in the presence of 5% carbon dioxide. Then, the test compound was added and the cells were incubated for another 5 days. After incubation, a 15-μL volume of WST-8 (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfenyl)-2*H*- tetrazolium, monosodium salt) was added. After the incubation for the time, the color reaction was stopped by adding 15 μL of 1% SDS (sodium dodecyl sulfate) solution and the optical density was determined at the measurement
20 wavelength of 450 nm and the reference wavelength of 630 nm, and the difference was calculated. The cell growth activity in each well was defined as the value determined by subtracting the OD in the control well not containing cells (the difference in absorbance between 450 nm and 630 nm) from that in the test well.

[0227]

25 The 50% inhibitory concentration (IC₅₀ (nM)) of the test compound was determined by comparing the cell growth activity in the well containing the test compound with that of the control not containing the test compound.

[0228]

The growth inhibition on a human prostate (carcinoma) cell line (LNCaP.FGC)
30 (van Bokhoven A, et al. Prostate. 2003; 57(3):205-25.) was also determined by the above method.

[0229]

The growth inhibition on a human prostate (adenocarcinoma) cell line (VcaP) (Korenchuk S, et al. In Vivo. 2001; 15(2):163-8.) was also determined by the above method.

[0230]

The growth inhibition on a human prostate (carcinoma) cell line (DU 145) (van Bokhoven A, et al. Prostate. 2003; 57(3):205-25.) was also determined by the above method.

[0231]

5 The growth inhibition on a human prostate (adenocarcinoma) cell line (PC-3) (van Bokhoven A, et al. Prostate. 2003; 57(3):205-25.) was also determined by the above method.

[0232]

The results are shown in Table 2.

10 [0233]

Growth inhibition of a human breast cancer cell line (MDA-MB-468) was determined by the sulforhodamine B method based on the method of Skehan P. et al. (J Natl Cancer Inst. 1990 Jul 4; 82(13): 1107 – 12). In the study, MDA-MB-468 cells were seeded on DMEM medium containing 10% fetal bovine serum in a 96-well microplate. After 24-h incubation at 37 °C in the presence of 5% carbon dioxide, the test compound was added and the cells were incubated for another 5 days. After incubation, a trichloroacetic acid solution was added to yield the final concentration of 10% and the cells were left to stand at 4 °C for 1 hour to fix. Then, the cells were washed with water to remove the medium and trichloroacetic acid and dried in the air. The dried cells were stored at 4 °C until they were stained with sulforhodamine B. To each well, 1% acetic acid solution containing 0.4 % sulforhodamine B was added and left to stand for 20 to 30 minutes at room temperature. After discarding the supernatant, each well was washed with 1% acetic acid solution, and 10 mM Tris (tris-hydroxyaminomethane) solution was added while stirring to elute the dye taken into the cells. Then, the optical density was determined at the measurement wavelength of 492 nm and the reference wavelength of 690 nm, and the difference was calculated. The cell growth activity in each well was defined as the value determined by subtracting the OD in the control well not containing cells (the difference in absorbance between 492 nm and 690 nm) from that in the test well.

[0234]

30 The 50% inhibitory concentration (IC₅₀ (nM)) of the test compound was determined by comparing the cell growth activity in the well containing the test compound with that of the control not containing the test compound.

[0235]

The results are shown in Table 3.

[0236]

The growth inhibition on a human hepatic cancer cell line (HuH-7) was also determined by the above method.

[0237]

5 The results are shown in Table 4.

[0238]

Antitumor effect on prostate cancer cells, LNCaP-Bic (in vivo)

Human prostate cancer cells (LNCaP-Bic) were transplanted in nude mice (6 males/group) and the inhibitory effect of the invention on their growth was examined. In the
10 study, the tumor cell suspension with matrigel was inoculated at 0.12 mL/body (2.4×10^6 cells/body) into the subcutaneous space of the right axillary region to prepare tumor bearing mice. When the tumor diameter became 5 mm or more, the animals were allocated to groups based on the tumor volume. The test compound was administered orally as a suspension in 5% gum arabic, once daily, for 14 consecutive days. The control group received 5% gum arabic.
15 Tumor volumes were measured on the following day of the last administration. Tumors were removed and the wet weight of the tumor was measured using an electronic balance. The ratio of the tumor weight in the treated group to that in the control group (T/C%) was calculated as the index for the effect.

[0239]

20
$$T/C\% = (\text{Mean tumor weight in the treatment group} / \text{Mean tumor weight in the control group}) \times 100.$$

[0240]

The results are shown in Table 5.

[0241]

25 The heparinized blood was collected from the postcava under diethylether anesthesia. The plasma levels of PSA were measured using ELISA. The ratio of the plasma levels of PSA in the treated group to that in the control group (T/C%) was calculated as the index for the effect.

[0242]

30
$$T/C\% = (\text{Mean plasma levels of PSA in the treatment group} / \text{Mean plasma levels of PSA in the control group}) \times 100.$$

[0243]

The results are shown in Table 6.

Table 2

Test compound	IC ₅₀ (nM)				
	LNCaP-Bic	LNCaP.FGC	VcaP	DU 145	PC-3
Compound of Example 1	<10	<10	<10	<10	<10
Compound of Example 392	<10	<10	<10	<10	<10
Compound of Example 408	<10	<10	<10	<10	<10
Compound of Example 427	<10	<10	<10	<10	<10
Compound of Example 429	<10	<10	<10	<10	<10
Compound of Example 430	<10	<10	<10	<10	<10
Compound of Example 432	<10	<10	<10	<10	<10
Compound of Example 435	<10	<10	<10	<10	<10
Compound of Example 438	<10	<10	<10	<10	<10
Compound of Example 440	<10	<10	<10	<10	<10
Compound of Example 447	<10	<10	<10	<10	<10
Compound of Example 448	<10	<10	<10	<10	<10
Compound of Example 451	<10	<10	<10	<10	<10
Compound of Example 452	<10	<10	<10	<10	<10
Compound of Example 454	<10	<10	<10	<10	<10
Compound of Example 466	<10	<10	<10	<10	<10
Compound of Example 507	<10	<10	<10	<10	<10
Compound of Example 558	<10	<10	<10	<10	<10
Compound of Example 593	<10	<10	<10	<10	<10
Compound of Example 594	<10	<10	<10	<10	<10
Compound of Example 595	<10	<10	<10	<10	<10
Compound of Example 600	<10	<10	<10	<10	<10
Compound of Example 601	<10	<10	<10	<10	<10
Compound of Example 608	<10	<10	<10	<10	<10
Compound of Example 611	<10	<10	<10	<10	<10
Compound of Example 613	<10	<10	<10	<10	<10
Compound of Example 621	<10	<10	<10	<10	<10
Compound of Example 657	<10	<10	<10	<10	<10
Compound of Example 669	<10	<10	<10	<10	<10
Compound of Example 777	<10	<10	<10	<10	<10

Table 3

Test compound	IC ₅₀ (nM)
Compound of Example 123	<10
Compound of Example 289	<10
Compound of Example 321	<10
Compound of Example 359	<10
Compound of Example 408	<10
Compound of Example 411	<10
Compound of Example 430	<10
Compound of Example 432	<10
Compound of Example 435	<10
Compound of Example 438	<10
Compound of Example 448	<10
Compound of Example 454	<10
Compound of Example 485	<10
Compound of Example 487	<10
Compound of Example 534	<10
Compound of Example 608	<10
Compound of Example 614	<10
Compound of Example 616	<10
Compound of Example 618	<10
Compound of Example 640	<10
Compound of Example 641	<10
Compound of Example 648	<10
Compound of Example 706	<10
Compound of Example 708	<10
Compound of Example 725	<10
Compound of Example 746	<10
Compound of Example 765	<10
Compound of Example 777	<10
Compound of Example 779	<10
Compound of Example 781	<10

Table 4

Test compound	IC50(nM)
Compound of Example 315	<10
Compound of Example 358	<10
Compound of Example 384	<10
Compound of Example 391	<10
Compound of Example 402	<10
Compound of Example 407	<10
Compound of Example 408	<10
Compound of Example 428	<10
Compound of Example 430	<10
Compound of Example 432	<10
Compound of Example 435	<10
Compound of Example 438	<10
Compound of Example 443	<10
Compound of Example 445	<10
Compound of Example 448	<10
Compound of Example 449	<10
Compound of Example 454	<10
Compound of Example 482	<10
Compound of Example 542	<10
Compound of Example 558	<10
Compound of Example 596	<10
Compound of Example 600	<10
Compound of Example 608	<10
Compound of Example 647	<10
Compound of Example 675	<10
Compound of Example 688	<10
Compound of Example 692	<10
Compound of Example 751	<10
Compound of Example 757	<10
Compound of Example 777	<10

Table 5

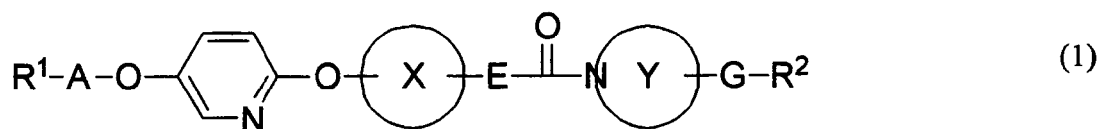
Test compound	T/C(%) (10 mg/kg/day)
Compound of Example 408	<50
Compound of Example 429	<50
Compound of Example 430	<50
Compound of Example 432	<50
Compound of Example 435	<50
Compound of Example 438	<50
Compound of Example 440	<50
Compound of Example 777	<50

Table 6

Test compound	T/C(%) (10 mg/kg/day)
Compound of Example 408	<50
Compound of Example 429	<50
Compound of Example 430	<50
Compound of Example 432	<50
Compound of Example 435	<50
Compound of Example 438	<50
Compound of Example 440	<50
Compound of Example 777	<50

CLAIMS

1. A compound represented by the following general formula (1) or a salt thereof;
[Formula 1]



wherein

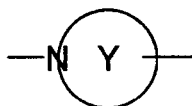
R^1 and R^2 are each independently aryl or unsaturated heterocyclic ring, each of which is optionally substituted with one or more substituents,

A is lower alkylene,

Ring X is optionally substituted arylene,

E is bond or lower alkenylene,

the partial structural formula:



is optionally substituted heterocycloalkylene containing one or more nitrogen atoms, one of which is attached to the adjacent carbonyl group,

G is $-NH-G_2-$, $-N(\text{lower alkyl})-G_2-$, $-NH-CH_2-G_2-$, $-N(\text{lower alkyl})-CH_2-G_2-$ or $-CH_2-G_2-$,

wherein G_2 of said G binds to R^2 ,

G_2-R^2 is bond- R^2 , phenylene- G_3-R^2 , phenylene- G_4-O-R^2 , phenylene- G_5-NH-R^2 , phenylene- $G_6-N(\text{lower alkyl})-R^2$ or quinolinediyl- $O-R^2$, wherein the phenylene of said phenylene- G_3-R^2 , phenylene- G_4-O-R^2 , phenylene- G_5-NH-R^2 and phenylene- $G_6-N(\text{lower alkyl})-R^2$ is optionally substituted with one or more substituents selected from the group consisting of halogen and lower alkyl,

G_3-R^2 is bond- R^2 , $-O$ -lower alkylene- R^2 , lower alkylene- O -lower alkylene- R^2 or $-O$ -lower alkylene- $CO-R^2$,

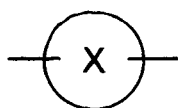
G_4-O- is bond- $O-$, lower alkylene- $O-$, lower alkenylene- $O-$, $-O$ -lower alkylene- $O-$ or $-CO$ -lower alkylene- $O-$, and

G_5 and G_6 are each lower alkylene.

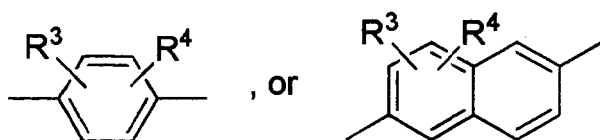
2. The compound according to Claim 1 or a salt thereof;
wherein

R^1 is phenyl, pyridyl, benzothiazolyl or thiazolyl, each of which is optionally substituted with one or more substituents,

the partial structural formula:



is the following formula:



wherein R^3 and R^4 are the same or different, and are each independently hydrogen, halogen, lower alkyl or lower alkoxy,

the partial structural formula:



is piperazinediyl, piperidinediyl, pyrrolidinediyl, diazepanediyl or oxadiazepanediyl, each of which is optionally substituted with one or more substituents, and

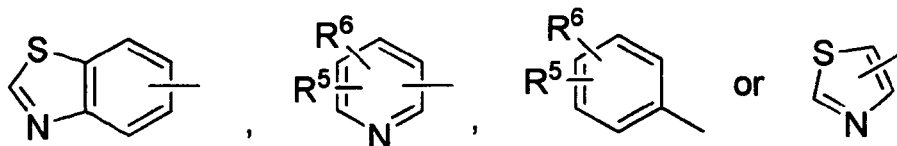
R^2 is:

(i) aryl which may be substituted with one or more substituents selected from the group consisting of halogen, cyano, nitro, methylenedioxy, trimethylene, tetramethylene, pyrrolyl, lower alkyl carbonyl, lower alkyl sulfonyl, lower alkyl which may be substituted with one or more halogen, lower alkoxy which may be substituted with one or more halogen, cyclo lower alkyl, lower alkoxy lower alkyl, lower alkenyl, hydroxy lower alkenyl, lower alkoxy lower alkenyl, hydroxy lower alkyl, amino which may be substituted with one or more lower alkyl, and hydroxy lower alkoxy,

(ii) unsaturated heterocyclic ring which may be substituted with one or more substituents selected from the group consisting of halogen, lower alkyl which may be substituted with one or more halogen, and lower alkoxy.

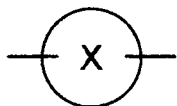
3. The compound according to Claim 2 or a salt thereof;
wherein

R^1 is the following formula:

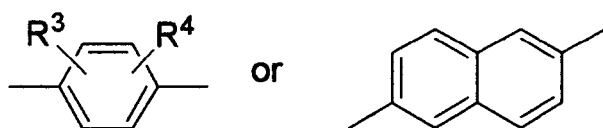


wherein R^5 and R^6 are the same or different, and are each independently hydrogen, halogen, cyano, nitro, lower alkoxy which may be substituted with one or more halogen, or lower alkyl which may be substituted with one or more halogen,

the partial structural formula:

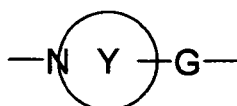


is the following formula:

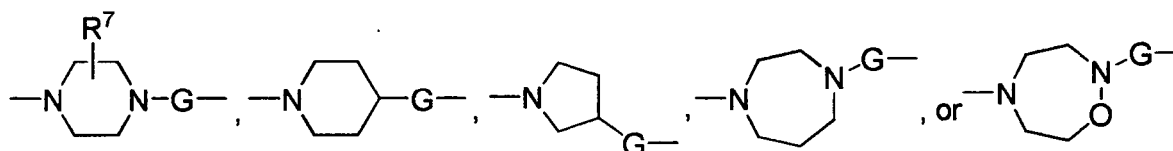


and,

the partial structural formula:



is the following formula:



wherein R^7 is hydrogen or lower alkyl.

4. The compound according to Claim 3 or a salt thereof;

wherein

R^2 is:

(i) phenyl which may be substituted with one or more substituents selected from the group consisting of halogen, cyano, nitro, methylenedioxy, trimethylene, tetramethylene, pyrrolyl, lower alkyl carbonyl, lower alkyl sulfonyl, lower alkyl which may be substituted with one or more halogen, lower alkoxy which may be substituted with one or more halogen, cyclo lower alkyl, lower alkoxy lower alkyl, lower alkenyl, hydroxy lower alkenyl, lower alkoxy lower alkenyl, hydroxy lower alkyl, amino which may be substituted with one or more lower alkyl, and hydroxy lower alkoxy,

(ii) naphthyl,

(iii) pyridyl which may be substituted with one or more substituents selected from

the group consisting of halogen, lower alkyl which may be substituted with one or more halogen, and lower alkoxy,

- (iv) benzoxazolyl which may be substituted with one or more halogen,
- (v) benzothiazolyl which may be substituted with one or more lower alkyl, or
- (vi) quinolyl.

5. The compound according to Claim 4 or a salt thereof;

wherein

G is -NH-G₂-, -N(lower alkyl)-CH₂-G₂- or -CH₂-G₂-,

wherein G₂ of said G binds to R²,

G₂-R² is phenylene-G₃-R², phenylene-G₄-O-R², phenylene-G₅-NH-R², phenylene-G₆-N(lower alkyl)-R² or quinolinediyl-O-R², wherein the phenylene of said phenylene-G₃-R², phenylene-G₄-O-R², phenylene-G₅-NH-R² and phenylene-G₆-N(lower alkyl)-R² is optionally substituted with one or more substituents selected from the group consisting of halogen and lower alkyl.

6. The compound according to Claim 4 or a salt thereof, wherein G of the general formula (1) is methylene.

7. The compound according to Claim 1 or a salt thereof, which is selected from the group consisting of:

(2E)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1E)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one,

4-{2-[4-({4-[(E)-3-[3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}prop-2-en-1-yl]piperazin-1-yl}methyl)phenyl]ethoxy}benzonitrile,

(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,

(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-[3-chloro-5-methyl-4-[(5-{[4-(propan-2-yl)benzyl]oxy}pyridin-2-yl)oxy]phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,

(E)-1-[4-(4-{2-[(4-chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-

dimethyl-4-([5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-[(3*S*)-4-{4-[2-(4-fluorophenoxy)ethyl]-benzyl}-3-methylpiperazin-1-yl]prop-2-en-1-one,
4-{[(6-{4-[(*E*)-3-(2-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-
5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
(2*E*)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-
{3-methyl-4-[(1*E*)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-
1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-
methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-
one,
(*E*)-3-(3-chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-
1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[3-chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

[6-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone,

4-{{6-{{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl}oxy)methyl}benzonitrile,

4-{{6-(2-fluoro-4-{{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl}oxy)methyl}benzonitrile,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-

[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-5-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
(*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
4-{{(6-{2-chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
4-{{(6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]-3-fluorobenzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
4-{{(6-{4-[(*E*)-3-[4-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy}methyl)benzonitrile,
4-{{(6-{2-chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
4-{{(6-{2-chloro-6-methyl-4-[(*E*)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy)methyl}benzonitrile,
4-{{(6-{2-chloro-4-[(*E*)-3-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy}methyl)benzonitrile,
4-{{(6-{2-chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy)methyl}benzonitrile
4-{{(6-{2,6-dimethyl-4-[(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl)oxy}methyl}benzonitrile,
(*E*)-3-(3,5-dimethyl-4-{{5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl}oxy}phenyl)-1-

[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
 4-({[6-(4-((1*E*)-3-[4-(4-((1*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl)benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}-2-chloro-6-methylphenoxy)pyridin-3-yl]oxy}methyl)benzonitrile,
 4-({[6-(2-chloro-4-((*E*)-3-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl)piperazin-1-yl]-3-oxoprop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl)benzonitrile,
 (*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl]-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,
 4-({[6-(4-[(*E*)-3-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl]-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl]oxy}methyl)benzonitrile,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one,
 (*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-1-[4-(4-chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one, and
 (*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one.

8. The compound according to Claim 1, which is selected from the group consisting

of:

(2E)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{4-[(1E)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)-1,4-diazepan-1-yl]prop-2-en-1-one,
 4-{2-[4-({4-[(E)-3-{3-chloro-5-methyl-4-[(5-{4-(trifluoromethyl)benzyl}oxy}pyridin-2-yl)oxy]phenyl}prop-2-enoyl)piperazin-1-yl}methyl)phenyl]ethoxy}benzonitrile,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-ethoxyphenoxy)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]-pyridin-2-yl}oxy)phenyl]-1-[4-(4-{2-[4-(dimethylamino)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-3-{3-chloro-5-methyl-4-[(5-{4-(propan-2-yl)benzyl}oxy}pyridin-2-yl)oxy]phenyl}-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-1-[4-(4-{2-[(4-chlorobenzyl)oxy]ethyl}benzyl)piperazin-1-yl]-3-(3,5-dimethyl-4-{[5-(pyridin-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)prop-2-en-1-one,
 (E)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-ethenylbenzyl)piperazin-1-yl]prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-[(3S)-4-{4-[2-(4-fluorophenoxy)ethyl]-benzyl}-3-methylpiperazin-1-yl]prop-2-en-1-one,
 4-{[(6-{4-[(E)-3-(2-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}-1,2,5-oxadiazepan-5-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile,
 (2E)-3-[4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{3-methyl-4-[(1E)-3-(4-methylphenoxy)prop-1-en-1-yl]benzyl}piperazin-1-yl)prop-2-en-1-one,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
 (E)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,
 (E)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(3-fluoro-4-methylbenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(6-chloropyridin-3-yl)methoxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-(3-chloro-5-methyl-4-{[5-(pyridin-3-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(2-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methoxyphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(3-chloro-2-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-3-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)propyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

[6-({5-[(2,3-difluorobenzyl)oxy]pyridin-2-yl}oxy)naphthalen-2-yl][4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]methanone hydrochloride,

4-{{[(6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]benzyl}piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[6-(2-fluoro-4-{{(*E*)-3-oxo-3-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-1-en-1-yl}phenoxy)pyridin-3-yl]oxy}methyl}benzonitrile hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(3-ethoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-5-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{{5-[(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-{2-[4-(propan-2-yl)phenoxy]ethyl}benzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride,

(*E*)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]-1-(4-{2-methyl-4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

4-{{[(6-{2-chloro-6-methyl-4-[(*E*)-3-oxo-3-{4-[4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)benzyl]piperazin-1-yl}prop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[(6-{4-[(*E*)-3-(4-{4-[2-(4-chlorophenoxy)ethyl]-3-fluorobenzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[(6-(4-{(*E*)-3-[4-(2-fluoro-4-{2-[4-(trifluoromethyl)phenoxy]ethyl}benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy)pyridin-3-yl)oxy}methyl}benzonitrile hydrochloride,

4-{{[(6-{2-chloro-4-[(*E*)-3-(4-{4-[3-(4-fluorophenoxy)propyl]benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[(6-{2-chloro-6-methyl-4-[(*E*)-3-(4-{4-[3-(4-methylphenoxy)propyl]benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[(6-(2-chloro-4-{(*E*)-3-[4-(3-fluoro-4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy)pyridin-3-yl)oxy}methyl}benzonitrile hydrochloride,

4-{{[(6-{2-chloro-4-[(*E*)-3-(4-{3-fluoro-4-[(4-fluorophenoxy)methyl]benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-6-methylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

4-{{[(6-(2,6-dimethyl-4-{(*E*)-3-oxo-3-[4-(4-{[4-(propan-2-yloxy)phenoxy]methyl}benzyl]piperazin-1-yl)prop-1-en-1-yl]phenoxy)pyridin-3-yl)oxy}methyl}benzonitrile hydrochloride,

(*E*)-3-(3,5-dimethyl-4-{[5-(1,3-thiazol-4-ylmethoxy)pyridin-2-yl]oxy}phenyl)-1-[4-(4-{[4-(propan-2-yl)phenoxy]methyl}benzyl]piperazin-1-yl]prop-2-en-1-one hydrochloride,

4-{{[(6-(4-{(1*E*)-3-[4-(4-{(1*E*)-3-[(5-bromopyridin-2-yl)oxy]prop-1-en-1-yl}benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-chloro-6-methylphenoxy)pyridin-3-yl)oxy}methyl}benzonitrile hydrochloride,

4-{{[(6-(2-chloro-4-{(*E*)-3-[4-(4-{2-[(4-methoxyphenyl)amino]ethyl}benzyl]piperazin-1-yl)-3-oxoprop-1-en-1-yl]phenoxy)pyridin-3-yl)oxy}methyl}benzonitrile dihydrochloride,

(*E*)-3-[3-chloro-4-({5-[(2-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{[2-(4-methoxyphenoxy)quinolin-6-yl]methyl}piperazin-1-yl)prop-2-en-1-one

hydrochloride,

(*E*)-3-{3-chloro-5-methyl-4-[(5-{[4-(trifluoromethyl)benzyl]oxy}pyridin-2-yl)oxy]phenyl}-1-(4-{4-[2-(4-methoxyphenyl)ethoxy]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

4-{[(6-{4-[(*E*)-3-{4-[4-(4-chlorophenoxy)benzyl]piperazin-1-yl}-3-oxoprop-1-en-1-yl]-2,6-dimethylphenoxy}pyridin-3-yl)oxy]methyl}benzonitrile hydrochloride,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-2-methyl-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one hydrobromide,

(*E*)-1-(4-{4-[2-(4-fluorophenoxy)propyl]benzyl}piperazin-1-yl)-3-[4-({5-[(4-methoxybenzyl)oxy]pyridin-2-yl}oxy)-3,5-dimethylphenyl]prop-2-en-1-one hydrobromide,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)but-2-en-1-one ethanedioate,

(*E*)-3-[3-chloro-5-methyl-4-({5-[(4-methylbenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(4-fluorophenoxy)ethyl]benzyl}piperazin-1-yl)-2-methylbut-2-en-1-one ethanedioate,

(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)phenyl]-1-(4-{4-[2-(3-methoxyphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-1-[4-(4-chlorobenzyl)piperazin-1-yl]-3-[3-chloro-4-({5-[2-(4-chlorophenyl)ethoxy]pyridin-2-yl}oxy)-5-methylphenyl]prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-(4-{4-[2-(4-methylphenoxy)ethyl]benzyl}piperazin-1-yl)prop-2-en-1-one hydrochloride,

(*E*)-3-[3-chloro-4-({5-[(4-fluorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride, and

(*E*)-3-[3-chloro-4-({5-[(4-chlorobenzyl)oxy]pyridin-2-yl}oxy)-5-methylphenyl]-1-[4-(4-methylbenzyl)piperazin-1-yl]prop-2-en-1-one hydrochloride.

9. A pharmaceutical composition comprising a compound represented by the general formula (1) or a salt thereof according to Claim 1, and a pharmacologically acceptable carrier.

10. A pharmaceutical composition according to Claim 9 for preventing and/or treating cancer.

11. A compound represented by the general formula (1) or a salt thereof according to Claim 1 for use in the pharmaceutical composition.

12. Use of a compound represented by the general formula (1) or a salt thereof

according to Claim 1 as a pharmaceutical composition.

13. Use of a compound represented by the general formula (1) or a salt thereof according to Claim 1 for the production of a pharmaceutical composition.

14. A method of preventing and/or treating cancer, comprising administering to a patient a compound represented by the general formula (1) or a salt thereof according to Claim 1.