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(54) **BICYCLIC HETEROARYL INHIBITORS OF PDE4**

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(52) **U.S. Cl.** ..... **549/268**; 544/93; 549/269; 549/270; 549/271

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to compounds and methods which may be useful as inhibitors of phosphodiesterase 4 (PDE4) for the treatment or prevention of inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators.

**22 Claims, No Drawings**

## BICYCLIC HETEROARYL INHIBITORS OF PDE4

This application claims the benefit of U.S. Provisional Applications No. 60/819,509, filed Jul. 7, 2006, and No. 60/886,825, filed Jan. 26, 2007, the disclosures of which are hereby incorporated by reference as if written herein in their entireties.

Disclosed herein are potent and selective new bicyclic heteroaryl compounds, certain of which have been found to be useful as inhibitors of phosphodiesterase 4 (PDE4), compositions comprising the same, and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of PDE4 activity are also provided, as well as methods for the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators.

Chronic inflammation is a multi-factorial disease complication characterized by activation of multiple types of inflammatory cells, for example cells of lymphoid lineage (including T lymphocytes) and myeloid lineage (including granulocytes, macrophages, and monocytes). Proinflammatory mediators, including cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are produced by these activated cells. Accordingly, an agent that suppresses the activation of these cells, or their production of proinflammatory cytokines, would be useful in the therapeutic treatment of inflammatory diseases and other diseases involving elevated levels of cytokines.

Cyclic adenosine monophosphate (cAMP) is a second messenger that mediates the biologic responses of cells to a wide range of extracellular stimuli. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated to convert adenosine triphosphate (ATP) to cAMP. It is theorized that the agonist induced actions of cAMP within the cell are mediated predominately by the action of cAMP-dependent protein kinases. The intracellular actions of cAMP are terminated by either a transport of the nucleotide to the outside of the cell, or by enzymatic cleavage by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-adenosine monophosphate (5'-AMP). 5'-AMP is an inactive metabolite.

The superfamily of PDEs is subdivided into two major classes, class I and class II, which have no recognizable sequence similarity. Class I includes all known mammalian PDEs and is comprised of 11 identified families that are products of separate genes. Some PDEs are highly specific for hydrolysis of cAMP (PDE4, PDE7, PDE8), some are highly cGMP-specific (PDE5, PDE6, PDE9), and some have mixed specificity (PDE1, PDE2, PDE3, PDE10, PDE11). All of the characterized mammalian PDEs are dimeric, but the importance of the dimeric structure for function in each of the PDEs is unknown.

The PDE4 subfamily is comprised of 4 members: PDE4A, PDE4B, PDE4C, and PDE4D. These enzymes possess N-terminal regulatory domains that presumably mediate dimerization, which results in optimally regulated PDE activity. In addition, activity is regulated via cAMP-dependent protein kinase phosphorylation sites in this upstream regulatory domain. PDE4 enzymes are broadly expressed and distributed.

Elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation. The intracellular enzyme family of PDEs, therefore, regulates the level of cAMP in cells. PDE4 is a predominant PDE isotype in these cells, and is a major contributor to cAMP degradation. Accordingly, the inhibition of PDE func-

tion would prevent the conversion of cAMP to the inactive metabolite 5'-AMP and, consequently, maintain higher cAMP levels, and, accordingly, suppress cell activation.

PDE4 inhibitors have been shown to inhibit production of TNF $\alpha$  and partially inhibit IL-1 $\beta$  release by monocytes (see Semmler et al., *Int. J. Immunopharmacol.*, 15, pp. 409-413, (1993); Molnar-Kimber et al., *Mediators of Inflammation*, 1, pp. 411-417, (1992)). PDE4 inhibitors also have been shown to inhibit the production of superoxide radicals from human polymorphonuclear leukocytes (see Verghese et al., *J. Mol. Cell. Cardiol.*, 21 (Suppl. 2), S61 (1989); Nielson et al., *J. Allergy Immunol.*, 86, pp. 801-808, (1990)); to inhibit the release of vasoactive amines and prostanoids from human basophils (see Peachell et al., *J. Immunol.*, 148, pp. 2503-2510, (1992)); to inhibit respiratory bursts in eosinophils (see Dent et al., *J. Pharmacol.*, 103, pp. 1339-1346, (1991)); and to inhibit the activation of human T-lymphocytes (see Robicsek et al., *Biochem. Pharmacol.*, 42, pp. 869-877, (1991)).

Inflammatory cell activation and excessive or unregulated cytokine (e.g., TNF $\alpha$  and IL-1 $\beta$ ) production are implicated in allergic, autoimmune, and inflammatory diseases and disorders, such as rheumatoid arthritis, osteoarthritis, gouty arthritis, spondylitis, thyroid associated ophthalmopathy, Behcet's disease, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, toxic shock syndrome, asthma, chronic bronchitis, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, such as chronic obstructive pulmonary disease, silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain, and extremities, fibrosis, cystic fibrosis, keloid formation, scar formation, atherosclerosis, transplant rejection disorders, such as graft vs. host reaction and allograft rejection, chronic glomerulonephritis, lupus, inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, proliferative lymphocyte diseases, such as leukemia, ophthalmologic diseases such as dry eye and ocular pain resulting from inflammation or surgery, and inflammatory dermatoses, such as atopic dermatitis, psoriasis, and urticaria.

Other conditions characterized by elevated cytokine levels include brain injury due to moderate trauma, cardiomyopathies, such as congestive heart failure, cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), fever myalgias due to infection, cerebral malaria, osteoporosis and bone resorption diseases, keloid formation, scar tissue formation, and pyrexia.

Additionally, several properties of TNF $\alpha$ , such as stimulation of collagenases, stimulation of angiogenesis in vivo, stimulation of bone resorption, and an ability to increase the adherence of tumor cells to endothelium, are consistent with a role for TNF in the development and metastatic spread of cancer in the host. TNF $\alpha$  recently has been directly implicated in the promotion of growth and metastasis of tumor cells (see Orosz et al., *J. Exp. Med.*, 177, pp. 1391-1398, (1993)).

Investigators have shown considerable interest in the use of PDE4 inhibitors as anti-inflammatory agents. Early evidence indicates that PDE4 inhibition has beneficial effects on a variety of inflammatory cells such as monocytes, macrophages, T-cells of the Th-1 lineage, and granulocytes. The synthesis and/or release of many proinflammatory mediators, such as cytokines, lipid mediators, superoxide, and biogenic amines, such as histamine, have been attenuated in these cells by the action of PDE4 inhibitors. The PDE4 inhibitors also affect other cellular functions including T-cell proliferation,

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granulocyte transmigration in response to chemotoxic substances, and integrity of endothelial cell junctions within the vasculature.

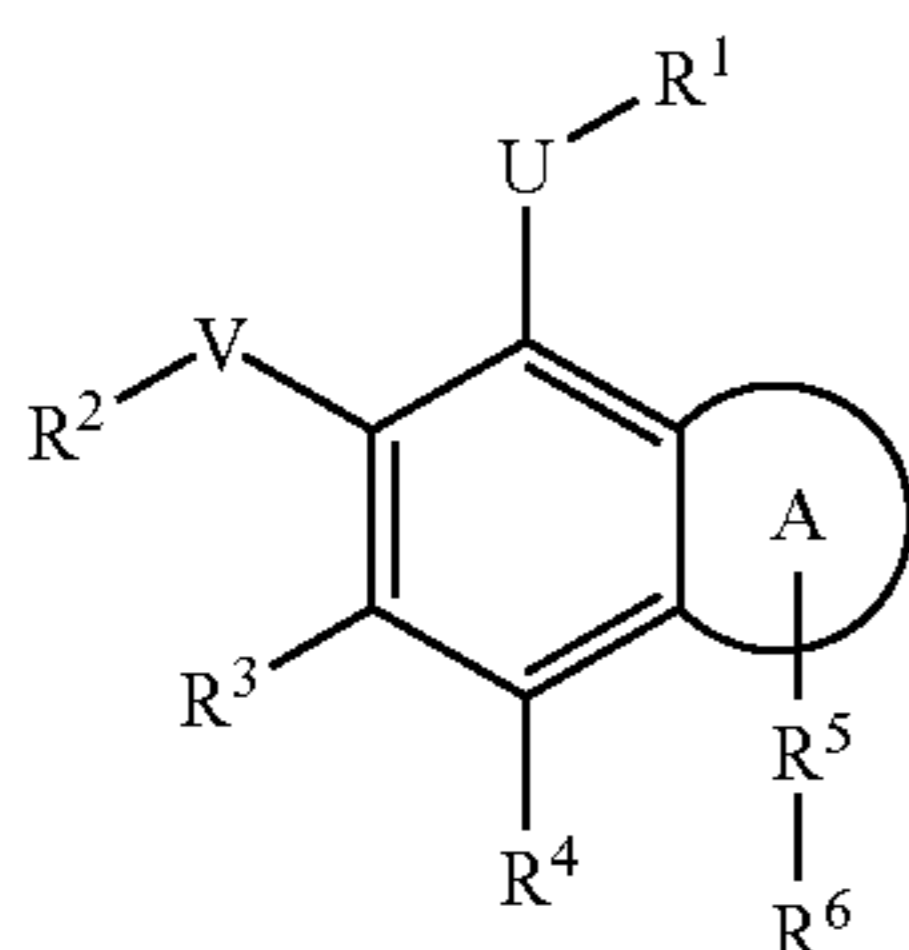
The design, synthesis, and screening of various PDE4 inhibitors have been reported. Methylxanthines, such as caffeine and theophylline, were the first PDE inhibitors discovered, but these compounds are nonselective with respect to which PDE is inhibited. The drug rolipram, an antidepressant agent, was one of the first reported specific PDE4 inhibitors, with a reported  $IC_{50}$  of about 200 nM with respect to inhibiting recombinant human PDE4.

Investigators have continued to search for PDE4 inhibitors that are more selective with respect to inhibiting PDE4, that have a lower  $IC_{50}$  than rolipram, and that avoid the undesirable central nervous system (CNS) side effects, such as retching, vomiting, and sedation, associated with the administration of rolipram. In addition, several companies are now undertaking clinical trials of other PDE4 inhibitors. However, problems relating to efficacy and adverse side effects, such as emesis and central nervous system disturbances, remain unsolved.

Accordingly, compounds that selectively inhibit PDE4, and that reduce or eliminate the adverse side effects associated with prior PDE4 inhibitors, would be useful in the treatment of allergic and inflammatory diseases, and other diseases associated with excessive or unregulated production of cytokines, such as TNF. In addition, selective PDE4 inhibitors would be useful in the treatment of diseases that are associated with elevated cAMP levels or PDE4 function in a particular target tissue.

Novel compounds and pharmaceutical compositions useful as anti-inflammatory agents via the inhibition of PDE4 have been found, together with methods of synthesizing and using the compounds including methods for inhibiting PDE4 in a patient by administering the compounds.

Disclosed herein is a class of compounds, certain of which have been found to be useful in treating PDE4-mediated disorders and conditions, defined by structural Formula I:



wherein:

$A$  is an optionally substituted saturated or unsaturated hydrocarbon chain or a heteroatom-comprising hydrocarbon chain having from 3 to 5 atoms, forming a five- to seven-membered ring;

$U$ ,  $V$ , and  $W$  are independently selected from the group consisting of  $O$ ,  $N(R^{7b})$  and  $SO_q$ ;

$R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

$s$  is 0-8;

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$G^1$  is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

$G^2$  is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

$G^3$  is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

$R^5$  is selected from the group consisting of  $-(CR^8R^9)_mW$  ( $CR^{10}R^{11})_n-$  and  $-(CR^{12}R^{13})_p-$ ;

$m$ ,  $n$ , and  $q$  are each independently 0, 1, 2, 3 or 4;

$p$  is 1 or 2;

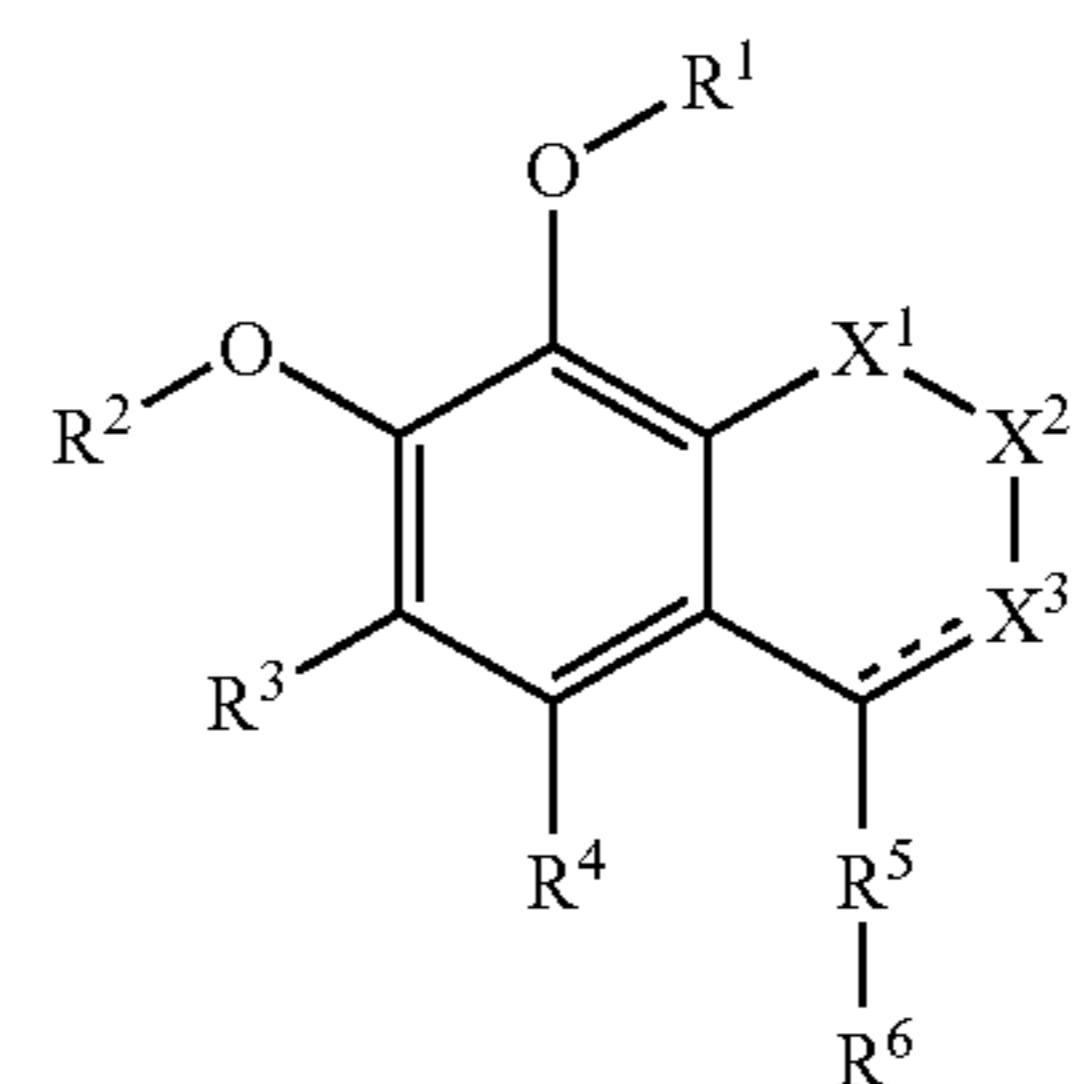
$W$  is selected from the group consisting of  $O$ ,  $N(R^7)$ ,  $C(O)N(R^7)$ , and  $SO_q$ ;

$R^6$  is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

$R^7$ ,  $R^{7b}$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ , and  $R^{13}$  are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl.

Certain compounds according to the present invention possess useful PDE4 inhibiting or modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which PDE4 plays an active role. Thus, in broad aspect, the certain embodiments of the present invention also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments of the present invention provide methods for inhibiting PDE4. Other embodiments of the present invention provide methods for treating a PDE4-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. Related embodiments disclose the use of certain compounds disclosed herein as therapeutic agents, for example, in treating inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators. The present invention also contemplates the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of PDE4.

In further embodiments, compounds of the present invention have structural formula II



wherein:

$X^1$  is  $O$ ;

$X^2$  is selected from the group consisting of  $C(O)$ ,  $(CR^{14}R^{15})$  and null;

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$X^3$  is selected from the group consisting of C(O), N(R<sup>16</sup>) and (CR<sup>17</sup>R<sup>18</sup>);

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 0-8;

G<sup>1</sup> is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G<sup>2</sup> is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G<sup>3</sup> is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R<sup>5</sup> is selected from the group consisting of  $-(CR^8R^9)_mW$  (CR<sup>10</sup>R<sup>11</sup>)<sub>n</sub>— and  $-(CR^{12}R^{13})_p$ —;

m, n, and q are each independently 0, 1, 2, 3 or 4;

p is 1 or 2;

W is selected from the group consisting of O, N(R<sup>7</sup>), C(O) N(R<sup>7</sup>), and SO<sub>q</sub>;

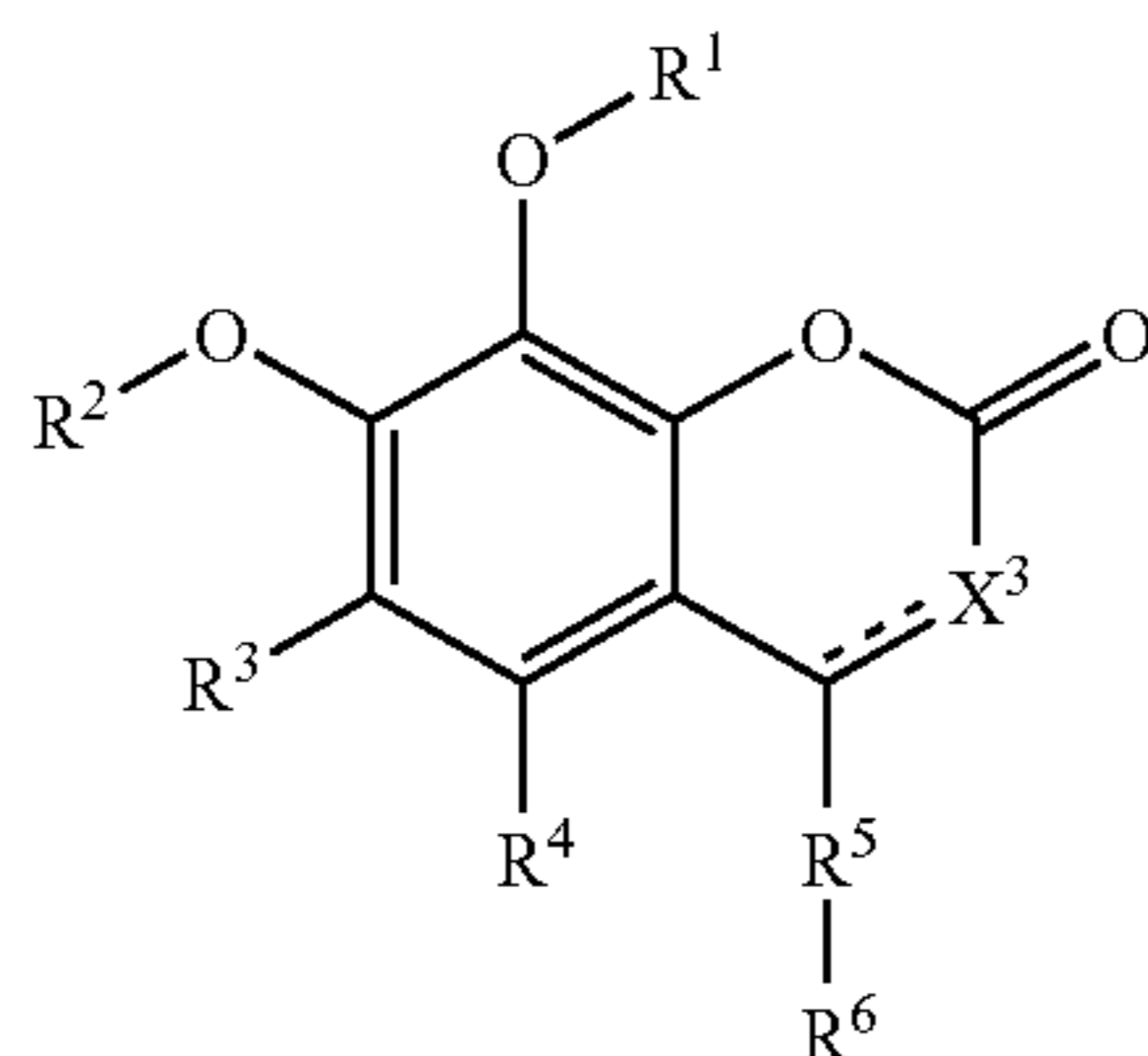
R<sup>6</sup> is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl;

R<sup>16</sup> is selected from the group consisting of hydrogen and a bond; and

R<sup>14</sup>, R<sup>15</sup>, R<sup>17</sup> and R<sup>18</sup> are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In certain embodiments, compounds of the present invention have structural Formula III



wherein:

$X^3$  is (CR<sup>17</sup>R<sup>18</sup>);

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

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cloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 0-8;

G<sup>1</sup> is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G<sup>2</sup> is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G<sup>3</sup> is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, halogen, alkoxy and lower alkyl;

R<sup>5</sup> is selected from the group consisting of  $-(CR^8R^9)_mW$  (CR<sup>10</sup>R<sup>11</sup>)<sub>n</sub>— and  $-(CR^{12}R^{13})_p$ —;

m, n, and q are each independently 0, 1, 2, 3 or 4;

p is 1 or 2;

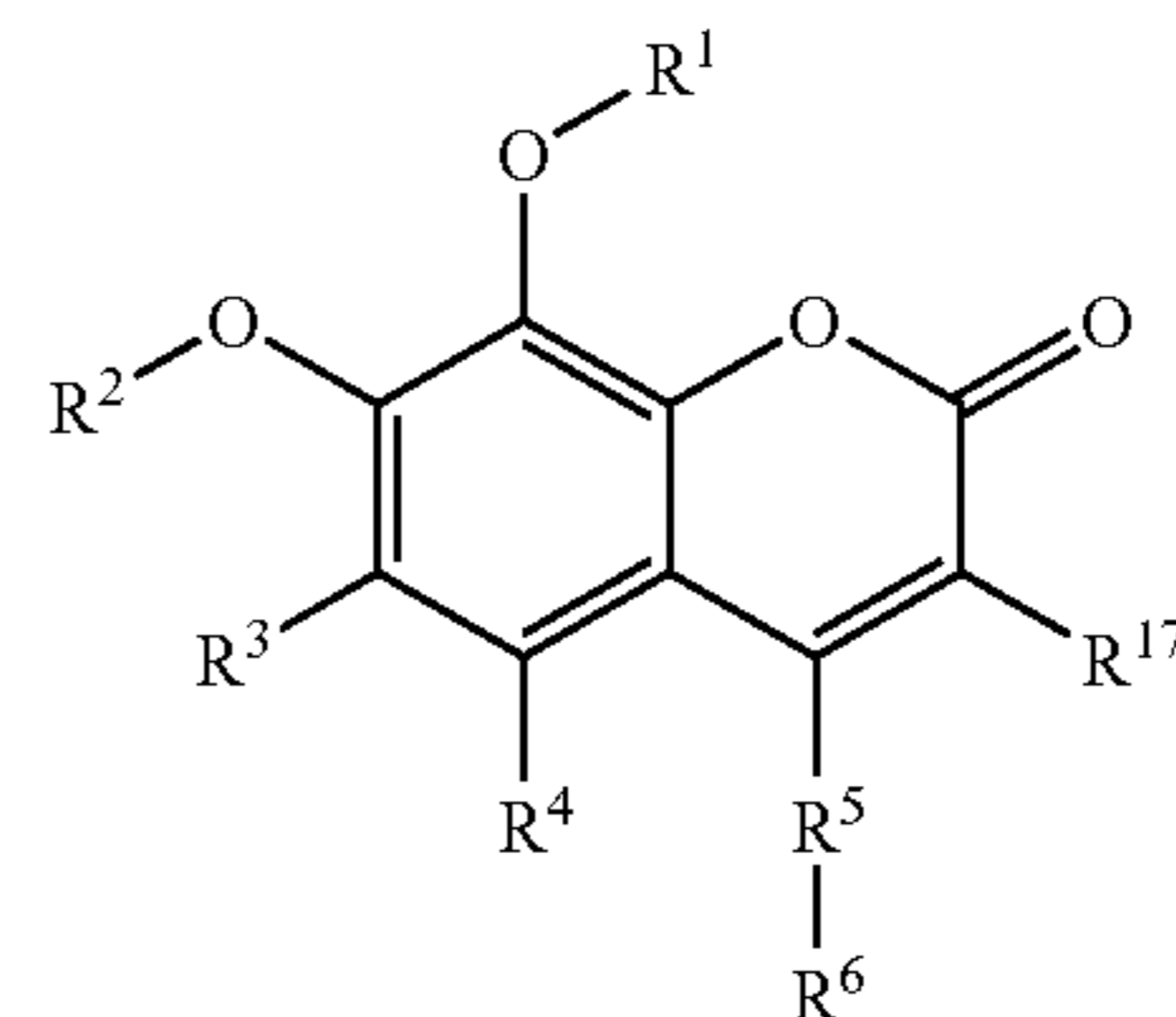
W is selected from the group consisting of O, N(R<sup>7</sup>), C(O) N(R<sup>7</sup>), and SO<sub>q</sub>;

R<sup>6</sup> is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl; and

R<sup>17</sup> and R<sup>18</sup> are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In certain embodiments, compounds of the present invention have structural Formula IV



(IV)

wherein:

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, hydrogen and hydroxyalkyl, any of which may be optionally substituted;

s is 0-8;

G<sup>1</sup> is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G<sup>2</sup> is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

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$G^3$  is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

$R^3$  and  $R^4$  are independently selected from the group consisting of alkoxy, lower alkyl, halogen and hydrogen;

$R^5$  is selected from the group consisting of  $-(CR^8R^9)_mW(CR^{10}R^{11})_n-$  and  $-(CR^{12}R^{13})_p-$ ;

$m$ ,  $n$ , and  $q$  are each independently 0, 1, 2, 3 or 4;

$p$  is 1 or 2;

$W$  is selected from the group consisting of O,  $N(R^7)$ ,  $C(O)$ ,  $N(R^7)$ , and  $SO_q$ ;

$R^6$  is selected from the group consisting of carboxyl, alkylcarboxy, amido, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, heteroalkyl, acyl, and hydroxamic acid, any of which may be optionally substituted;

$R^7$  is selected from the group consisting of hydrogen and optionally substituted lower alkyl;

$R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of hydrogen and optionally substituted lower alkyl; and

$R^{17}$  is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl, aminoalkoxy and a bond.

In yet further embodiments are provided compounds wherein  $R^{17}$  is hydrogen.

In yet further embodiments are provided compounds wherein  $R^6$  is selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, and pyrazine, any of which may be optionally substituted.

In yet further embodiments are provided compounds wherein  $R^6$  is selected from the group consisting of phenyl, pyridine, and pyrimidine, any of which may be optionally substituted.

In yet further embodiments are provided compounds wherein  $R^3$  and  $R^4$  are both hydrogen.

In yet further embodiments are provided compounds wherein:

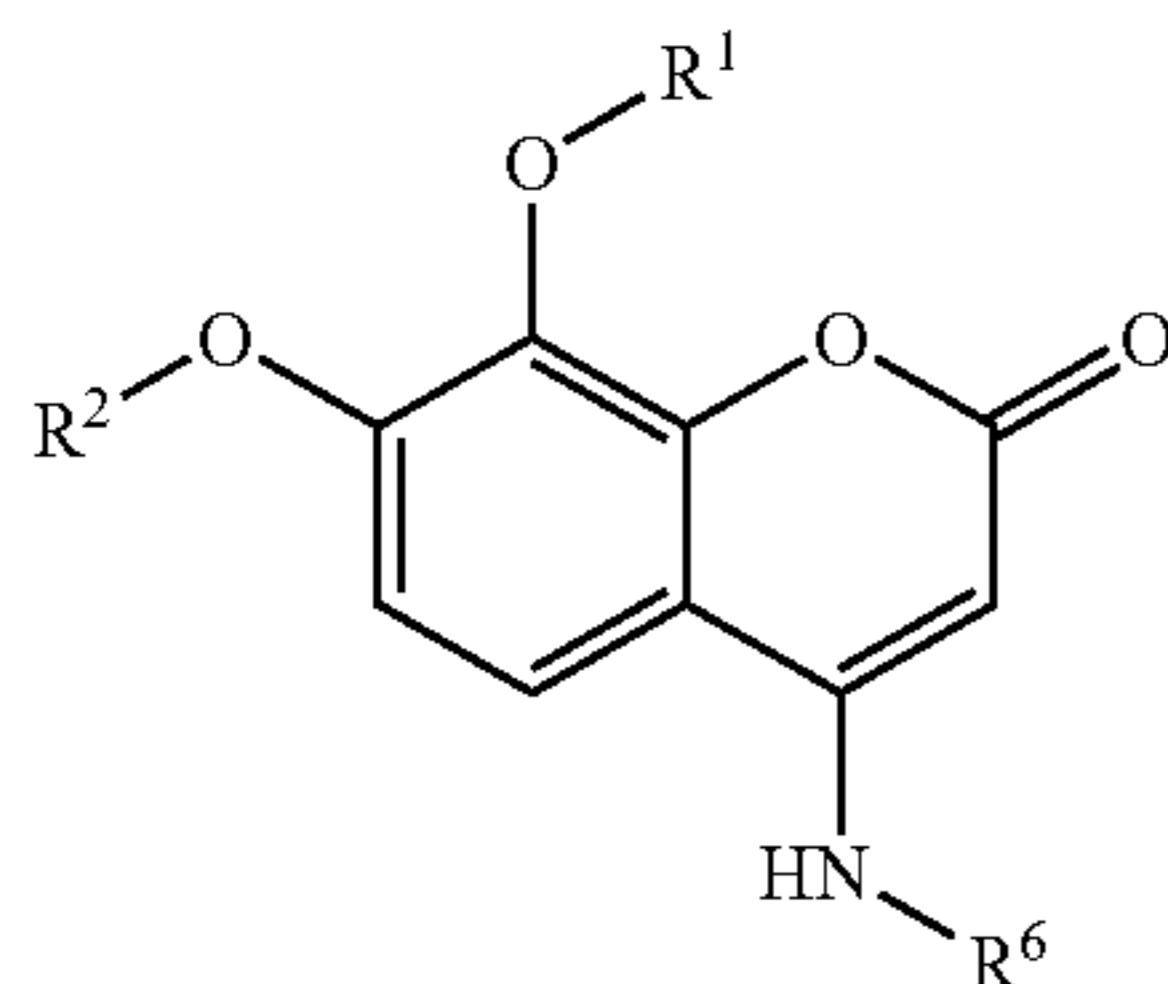
$R^5$  is  $-(CR^8R^9)_mW(CR^{10}R^{11})_n-$ ;

$m$  and  $n$  are both 0;

$W$  is  $N(R^7)$ ; and

$R^7$  is hydrogen.

In certain embodiments, compounds of the present invention have structural Formula V



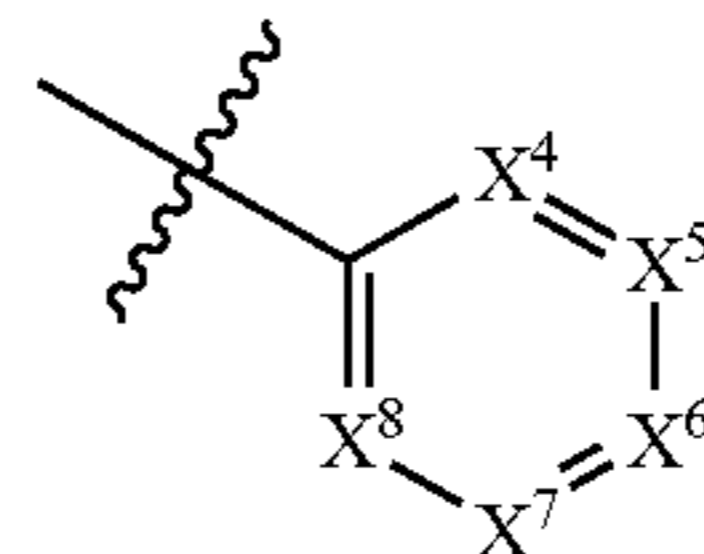
wherein:

$R^1$  and  $R^2$  are each independently selected from the group consisting of hydrogen, amidoalkyl, amino, alkyl, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, heteroaryl, heteroalkyl, hydroxyalkyl and acyl, any of which may be optionally substituted; and

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$R^6$  is selected from the group consisting of phenyl, pyridine and pyrimidine, any of which may be optionally substituted.

In yet further embodiments are provided compounds wherein  $R^6$  has the formula



$X^4$  is  $CR^{22}$  or N;

$X^5$  is  $CR^{23}$  or N;

$X^6$  is  $CR^{24}$  or N;

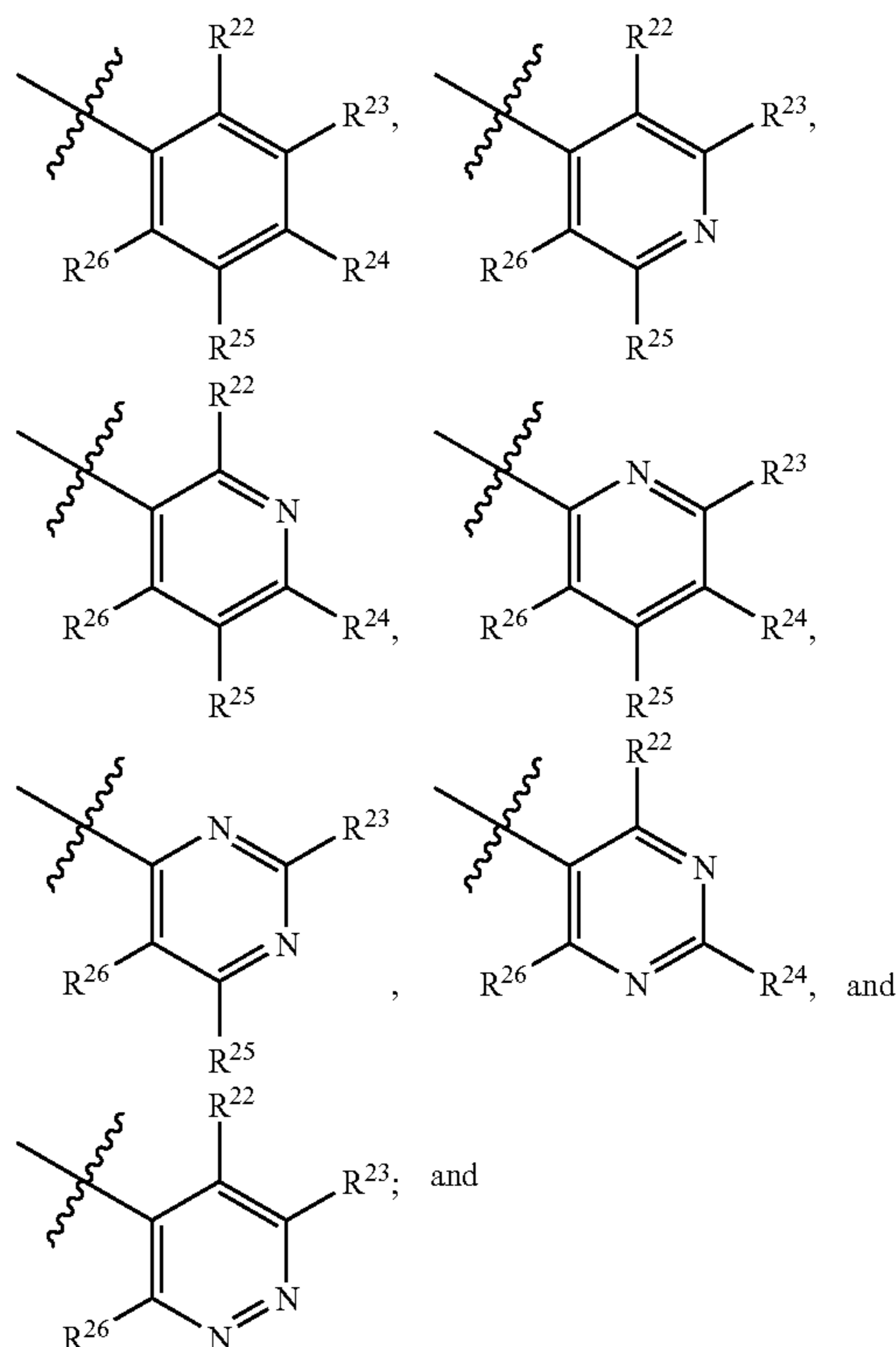
$X^7$  is  $CR^{25}$  or N;

$X^8$  is  $CR^{26}$  or N;

wherein no more than two of  $X^4$ - $X^8$  may be N; and

$R^{22}$ ,  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$  and  $R^{26}$  are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

In yet further embodiments are provided compounds wherein  $R^6$  has a formula selected from the group consisting of:



$R^{22}$ ,  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$  and  $R^{26}$  are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

In yet further embodiments are provided compounds wherein  $R^2$  is lower alkyl. In yet further embodiments,  $R^2$  is methyl.

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In yet further embodiments are provided compounds wherein:

$R^1$  is selected from the group consisting of  $-(CH_2)_s$ ,  $G^1G^2G^3$ , lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

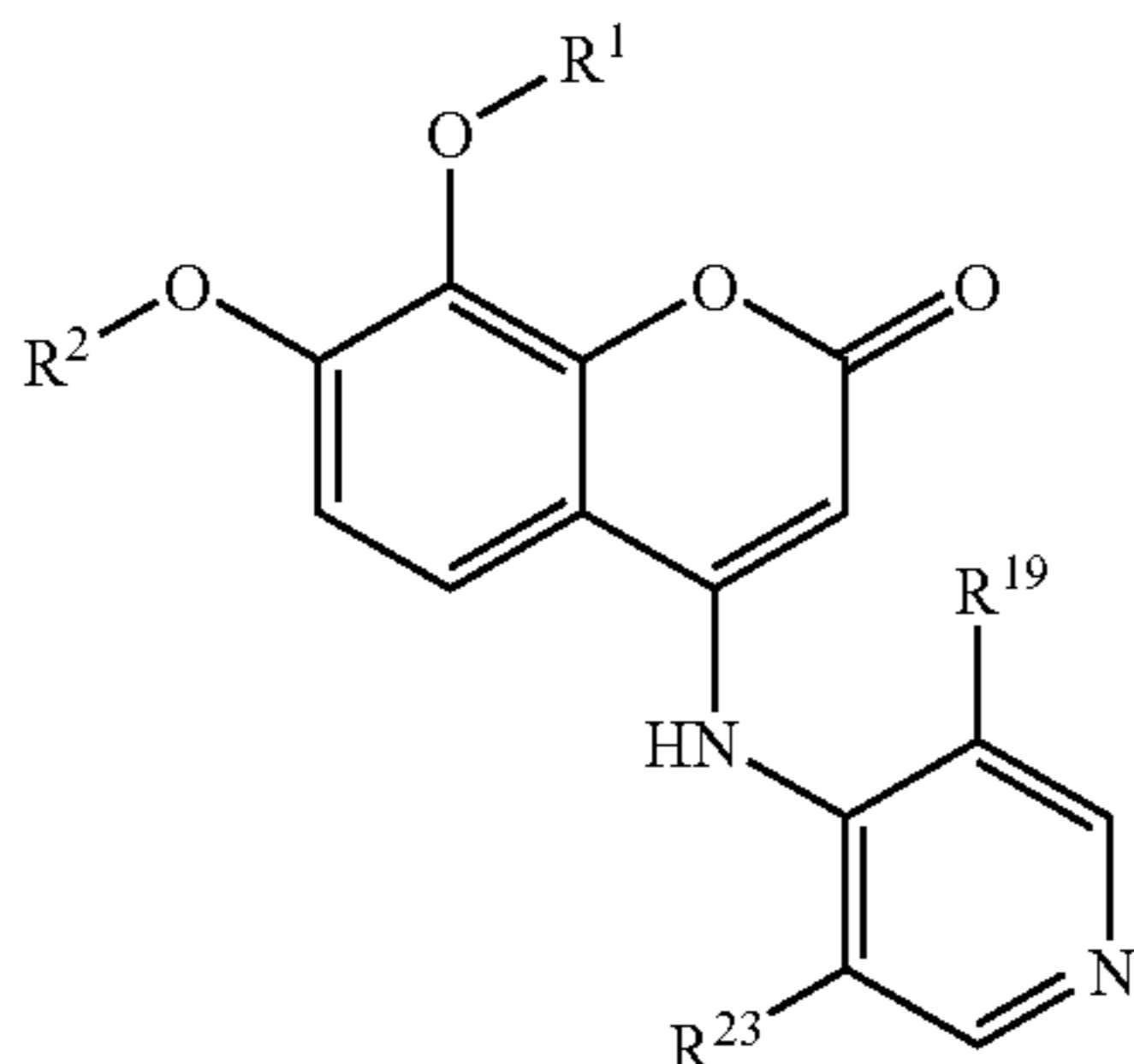
$s$  is 1-6;

$G^1$  is selected from the group consisting of amino, amido, and null;

$G^2$  is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

$G^3$  is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

In certain embodiments, compounds of the present invention have structural Formula VI



wherein:

$R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl and hydroxyalkyl, any of which may be optionally substituted;

$s$  is 1-8;

$G^1$  is selected from the group consisting of alkoxy, acyl, amino, amido, carbonyl, ether, an amino acid, and null;

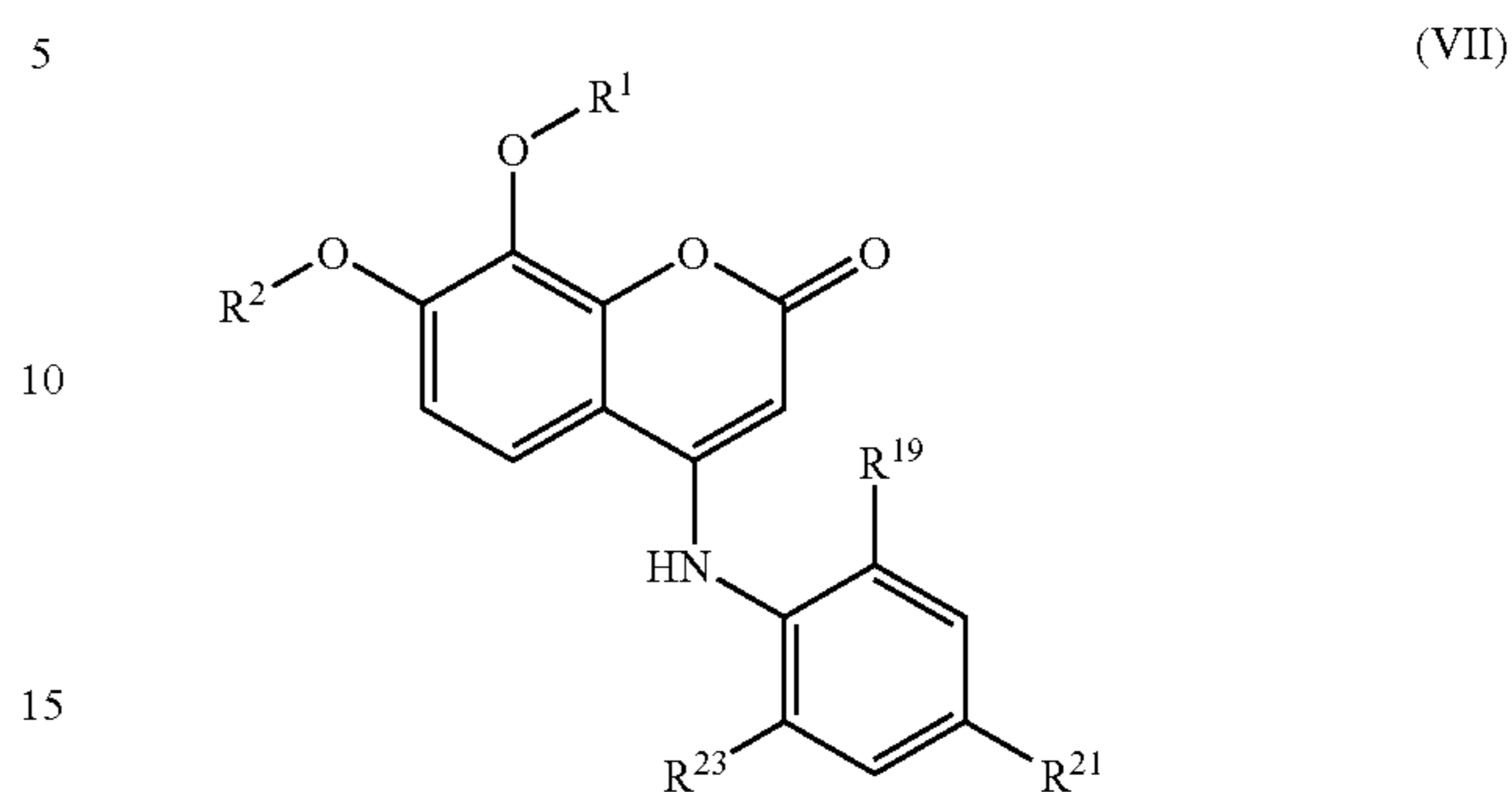
$G^2$  is selected from the group consisting of alkyl, alkoxy, acyl, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

$G^3$  is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

$R^{19}$  and  $R^{23}$  are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

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In certain embodiments, compounds of the present invention have structural Formula VII



wherein:

$R^1$  and  $R^2$  are independently selected from the group consisting of hydrogen,  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl and hydroxyalkyl, any of which may be optionally substituted;

$s$  is 1-8;

$G^1$  is selected from the group consisting of alkoxy, acyl, amino, amido, carbonyl, ether, an amino acid, and null;

$G^2$  is selected from the group consisting of alkyl, alkoxy, acyl, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

$G^3$  is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

$R^{19}$ ,  $R^{21}$ , and  $R^{23}$  are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

Compounds of the present invention may be selective amongst the PDE4 isoforms PDE4A, PDE4B, PDE4C, and PDE4D in various ways. For example, compounds described herein may be selective for PDE4B and PDE4D over the other two isoforms, be a pan-inhibitor of all the isoforms, or be selective for only one isoform. In certain embodiments, compounds of the present invention may be selective for PDE4B over other isoforms.

The present invention also relates to a method of inhibiting at least one PDE4 function comprising the step of contacting the PDE4 with a compound of Formula I, as described herein. The cell phenotype, cell proliferation, activity of PDE4, change in biochemical output produced by active PDE4, expression of PDE4, or binding of PDE4 with a natural binding partner may be monitored. Such methods may be modes of treatment of disease, biological assays, cellular assays, biochemical assays, or the like.

As used herein, the terms below have the meanings indicated.

When ranges of values are disclosed, and the notation "from  $n_1$  . . . to  $n_2$ " is used, where  $n_1$  and  $n_2$  are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and includ-

ing the end values. By way of example, the range “from 2 to 6 carbons” is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range “from 1 to 3  $\mu\text{M}$  (micromolar),” which is intended to include 1  $\mu\text{M}$ , 3  $\mu\text{M}$ , and everything in between to any number of significant figures (e.g., 1.255  $\mu\text{M}$ , 2.1  $\mu\text{M}$ , 2.9999  $\mu\text{M}$ , etc.).

The term “about,” as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

The term “acyl,” as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or any other moiety where the atom attached to the carbonyl is carbon. An “acetyl” group, which is a type of acyl, refers to a  $-\text{C}(\text{O})\text{CH}_3$  group. An “alkylcarbonyl” or “alkanoyl” group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

The term “alkenyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term “alkenylene” refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [ $(-\text{CH}=\text{CH}-)$ ,  $(-\text{C}::\text{C}-)$ ]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term “alkenyl” may include “alkenylene” groups.

The term “alkoxy,” as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term “alkyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term “alkylene,” as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ( $-\text{CH}_2-$ ). Unless otherwise specified, the term “alkyl” may include “alkylene” groups.

The term “alkylamino,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

The term “alkylidene,” as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

The term “alkylthio,” as used herein, alone or in combination, refers to an alkyl thioether

( $\text{R}-\text{S}-$ ) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

The term “alkynyl,” as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl comprises from 2 to 4 carbon atoms. The term “alkynylene” refers to a carbon-carbon triple bond attached at two positions such as ethynylene ( $-\text{C}::\text{C}-$ ,  $-\text{C}\equiv\text{C}-$ ). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term “alkynyl” may include “alkynylene” groups.

The terms “amido” and “carbamoyl,” as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term “C-amido” as used herein, alone or in combination, refers to a  $-\text{C}(=\text{O})-\text{N}(\text{R})_2$  group with R as defined herein. The term “N-amido” as used herein, alone or in combination, refers to a  $\text{RC}(=\text{O})\text{N}(\text{R}')-$  group, with R and R' as defined herein. The term “acylamino” as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an “acylamino” group is acetylamino ( $\text{CH}_3\text{C}(\text{O})\text{NH}-$ ).

The term “amino,” as used herein, alone or in combination, refers to  $-\text{N}(\text{R})(\text{R}')$  or  $-\text{N}^+(\text{R})(\text{R}')(\text{R}'')$ , wherein R, R' and R'' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted.

The term “amino acid,” as used herein, alone or in combination, means a substituent of the form  $-\text{NRCH}(\text{R}')\text{C}(\text{O})\text{OH}$ , wherein R is typically hydrogen, but may be cyclized with N (for example, as in the case of the amino acid proline), and R' is selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, amino, amido, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, aminoalkyl, amidoalkyl, hydroxyalkyl, thiol, thioalkyl, alkylthioalkyl, and alkylthio, any of which may be optionally substituted. The term “amino acid” includes all naturally occurring amino acids as well as synthetic analogues.

The term “aryl,” as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term “aryl” embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term “arylalkenyl” or “aralkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term “arylalkoxy” or “aralkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term “arylalkyl” or “aralkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term “arylalkynyl” or “aralkynyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term “arylalkanoyl” or “aralkanoyl” or “aroyl,” as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl(hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

The terms “benzo” and “benz,” as used herein, alone or in combination, refer to the divalent radical  $C_6H_4=$  derived from benzene. Examples include benzothiophene and benzimidazole.

The term “carbamate,” as used herein, alone or in combination, refers to an ester of carbamic acid ( $-NHCOO-$ ) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

The term “O-carbamyl” as used herein, alone or in combination, refers to a  $-OC(O)NRR'$ , group—with R and R' as defined herein.

The term “N-carbamyl” as used herein, alone or in combination, refers to a  $ROC(O)NR'$ — group, with R and R' as defined herein.

The term “carbonyl,” as used herein, when alone includes formyl [ $-C(O)H$ ] and in combination is a  $-C(O)-$  group.

The term “carboxyl” or “carboxyl,” as used herein, refers to  $-C(O)OH$ , O-carboxy, C-carboxy, or the corresponding “carboxylate” anion, such as is in a carboxylic acid salt. An “O-carboxy” group refers to a  $RC(O)O-$  group, where R is as defined herein. A “C-carboxy” group refers to a  $-C(O)OR$  groups where R is as defined herein.

The term “cyano,” as used herein, alone or in combination, refers to  $-CN$ .

The term “cycloalkyl,” or, alternatively, “carbocycle,” as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. “Bicyclic” and “tricyclic” as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

The term “ester,” as used herein, alone or in combination, refers to a carboxyl group bridging two moieties linked at carbon atoms.

The term “ether,” as used herein, alone or in combination, typically refers to an oxy group bridging two moieties linked at carbon atoms. “Ether” may also include polyethers, such as, for example,  $-RO(CH_2)_2O(CH_2)_2O(CH_2)_2OR'$ ,  $-RO(CH_2)_2O(CH_2)_2OR'$ ,  $-RO(CH_2)_2OR'$ , and  $-RO(CH_2)_2OH$ .

The term “halo,” or “halogen,” as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term “haloalkoxy,” as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term “haloalkyl,” as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. “Haloalkylene” refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene ( $-CFH-$ ), difluoromethylene ( $-CF_2-$ ), chloromethylene ( $-CHCl-$ ) and the like.

The term “heteroalkyl,” as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example,  $-CH_2-NH-OCH_3$ . The term heteroalkyl may include ethers.

The term “heteroaryl,” as used herein, alone or in combination, refers to 3 to 7 membered unsaturated heteromonocyclic rings, or fused polycyclic rings in which at least one of the fused rings is unsaturated, wherein at least one atom is selected from the group consisting of O, S, and N. In certain embodiments, said heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic radicals are fused with aryl radicals, wherein heteroaryl radicals are fused with other heteroaryl radicals, or wherein heteroaryl radicals are fused with cycloalkyl radicals. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizynyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalynyl, quinazolynyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothieryl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolynyl, tetrazolopyridazinyl, tetrahydroisoquinolynyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one heteroatom as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms ring



members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sugars, sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycloalkyl groups include aziridinyl, azetidiny, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinoliny, dihydrocinnoliny, dihydrobenzodioxiny, dihydro[1,3]oxazolo[4,5-b]pyridiny, benzothiazolyl, dihydroindolyl, dihydropyridiny, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindoliny, morpholiny, piperaziny, pyrrolidinyl, tetrahydropyridiny, piperidinyl, thiomorpholiny, and the like. The heterocycloalkyl groups may be optionally substituted unless specifically prohibited.

The term "hydraziny" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., —N—N—.

The term "hydroxamic acid" as used herein, refers to —C(O)ON(R)O(R'), wherein R and R' are as defined herein, or the corresponding "hydroxamate" anion, including any corresponding hydroxamic acid salt.

The term "hydroxy," as used herein, alone or in combination, refers to —OH.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to =N—.

The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N—O—.

The term "isocyanato" refers to a —NCO group.

The term "isothiocyanato" refers to a —NCS group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptyl" as used herein, alone or in combination, refers to an RS— group, where R is as defined herein.

The term "nitro," as used herein, alone or in combination, refers to —NO<sub>2</sub>.

The terms "oxy" or "oxa" as used herein, alone or in combination, refer to —O—.

The term "oxo," as used herein, alone or in combination, refers to =O.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The term "phosphoamide" as used herein, alone or in combination, refers to a phosphate group [(OH)<sub>2</sub>P(O)O—] in which one or more of the hydroxyl groups has been replaced by nitrogen, amino, or amido.

The term "phosphonate" as used herein, alone or in combination, refers to a group of the form ROP(OR')(OR)O— wherein R and R' are selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves

be optionally substituted. "Phosphonate" includes "phosphate [(OH)<sub>2</sub>P(O)O—] and related phosphoric acid anions which may form salts.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refers to the —SO<sub>3</sub>H group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to —S—.

The term "sulfinyl," as used herein, alone or in combination, refers to —S(O)—.

The term "sulfonyl," as used herein, alone or in combination, refers to —S(O)<sub>2</sub>—.

The term "N-sulfonamido" refers to a RS(=O)<sub>2</sub>NR'— group with R and R' as defined herein.

The term "S-sulfonamido" refers to a —S(=O)<sub>2</sub>NRR', group, with R and R' as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a —S— group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thiol," as used herein, alone or in combination, refers to an —SH group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl —C(S)H and in combination is a —C(S)— group.

The term "N-thiocarbamyl" refers to an ROC(S)NR'— group, with R and R' as defined herein.

The term "O-thiocarbamyl" refers to a —OC(S)NRR', group with R and R' as defined herein.

The term "thiocyanato" refers to a —CNS group.

The term "trihalomethanesulfonamido" refers to a X<sub>3</sub>CS(O)<sub>2</sub>NR— group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a X<sub>3</sub>CS(O)<sub>2</sub>— group where X is a halogen.

The term "trihalomethoxy" refers to a X<sub>3</sub>CO— group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethylsilyl, tert-butyl dimethylsilyl, triphenylsilyl and the like.

Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

When a group is defined to be "null," what is meant is that said group is absent. A "null" group occurring between two other groups may also be understood to be a collapsing of flanking groups. For example, if in —(CH<sub>2</sub>)<sub>s</sub>G<sup>1</sup>G<sup>2</sup>G<sup>3</sup>, the element G<sup>2</sup> were null, said group would become —(CH<sub>2</sub>)<sub>s</sub>G<sup>1</sup>G<sup>3</sup>.

The term "optionally substituted" means the antecedent group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower

alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N<sub>3</sub>, SH, SCH<sub>3</sub>, C(O)CH<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub>, CO<sub>2</sub>H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., —CH<sub>2</sub>CH<sub>3</sub>), fully substituted (e.g., —CF<sub>2</sub>CF<sub>3</sub>), monosubstituted (e.g., —CH<sub>2</sub>CH<sub>2</sub>F) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., —CH<sub>2</sub>CF<sub>3</sub>). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as “substituted,” the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, “optionally substituted with.”

The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, hydroxyl, halogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R" where n=(1, 2, 3, . . . n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as —C(O)N(R)— may be attached to the parent moiety at either the carbon or the nitrogen.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols “R” or “S,” depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers, including keto-enol tautomers; all tautomeric isomers are provided by this

invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The term “bond” refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

The term “disease” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disorder” and “condition” (as in medical condition), in that all reflect an abnormal condition of the body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms.

The term “combination therapy” means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

“PDE4 inhibitor” is used herein to refer to a compound that exhibits an IC<sub>50</sub> with respect to PDE4 activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the PDE4 assay described generally hereinbelow. “IC<sub>50</sub>” is that concentration of inhibitor which reduces the activity of an enzyme (e.g., PDE4) to half-maximal level. Certain representative compounds of the present invention have been discovered to exhibit inhibition against PDE4. In certain embodiments, compounds will exhibit an IC<sub>50</sub> with respect to PDE4 of no more than about 10 μM; in further embodiments, compounds will exhibit an IC<sub>50</sub> with respect to PDE4 of no more than about 5 μM; in yet further embodiments, compounds will exhibit an IC<sub>50</sub> with respect to PDE4 of not more than about 1 μM, as measured in the PDE4 assay described herein. In yet further embodiments, compounds will exhibit an IC<sub>50</sub> with respect to PDE4 of not more than about 200 nM.

The phrase “therapeutically effective” is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

As used herein, reference to “treatment” of a patient is intended to include prophylaxis. The term “patient” means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term “prodrug” refers to a compound that is made more active in vivo. Certain of the present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical

or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion.

Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxyl group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephedrine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds of the present invention, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; e.g., in Remington's *Pharmaceutical Sciences*. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-

in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or

hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Certain compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

Gels for topical or transdermal administration may comprise, generally, a mixture of volatile solvents, nonvolatile solvents, and water. In certain embodiments, the volatile solvent component of the buffered solvent system may include lower (C1-C6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. In further embodiments, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. In certain embodiments, propylene glycol is used. The nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent, while an excess may result in a lack of bioavailability due to poor release of drug from solvent mixture. The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art; in certain embodiments, water is used. A common ratio of ingredients is about 20% of the nonvolatile solvent, about 40% of the volatile solvent, and about 40% water. There are several optional ingredients which can be added to the topical composition. These include, but are not limited to, chelators and gelling agents. Appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives (such as hydroxypropylmethylcellulose) and synthetic polymers, and cosmetic agents.

Lotions include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by

methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and, in certain embodiments, including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having

regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds can be administered in various modes, e.g. orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating PDE4-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder

in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of PDE4-mediated disorders.

Compounds of the subject invention may be useful in treating PDE4-mediated disease, disorders and conditions. In certain embodiments, said compounds may find use in treating acute and chronic pain and inflammation. The compounds of the present invention may be useful to treat patients with neuropathy, neuropathic pain, or inflammatory pain such as reflex sympathetic dystrophy/causalgia (nerve injury), peripheral neuropathy (including diabetic neuropathy), intractable cancer pain, complex regional pain syndrome, and entrapment neuropathy (carpel tunnel syndrome). The compounds may also be useful in the treatment of pain associated with acute herpes zoster (shingles), postherpetic neuralgia (PHN), and associated pain syndromes such as ocular pain. The compounds may further be useful as analgesics in the treatment of pain such as surgical analgesia, or as an antipyretic for the treatment of fever. Pain indications include, but are not limited to, post-surgical pain for various surgical procedures including post-cardiac surgery, dental pain/dental extraction, pain resulting from cancer, muscular pain, mastalgia, pain resulting from dermal injuries, lower back pain, headaches of various etiologies, including migraine, and the like. The compounds may also be useful for the treatment of pain-related disorders such as tactile allodynia and hyperalgesia. The pain may be somatogenic (either nociceptive or neuropathic), acute and/or chronic. The PDE4 inhibitors of the subject invention may also be useful in conditions where NSAIDs, morphine or fentanyl opiates and/or other opioid analgesics would traditionally be administered.

Furthermore, compounds of the subject invention may be used in the treatment or prevention of opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behavior, for example, nicotine addiction, alcoholism, and eating disorders. Moreover, the compounds and methods of the present invention may be useful in the treatment or prevention of drug withdrawal symptoms, for example treatment or prevention of symptoms of withdrawal from opiate, alcohol, or tobacco addiction.

In addition, compounds of the subject invention may be used to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

The present invention encompasses therapeutic methods using novel selective PDE4 inhibitors to treat or prevent respiratory disease or conditions, including therapeutic methods of use in medicine for preventing and treating a respiratory disease or condition including: asthmatic conditions including allergen-induced asthma, exercise-induced asthma, pollution-induced asthma, cold-induced asthma, and viral-induced-asthma; asthma-related diseases such as airway hyperreactivity and small airway disease; chronic obstructive pulmonary diseases including chronic bronchitis with normal airflow, chronic bronchitis with airway obstruction (chronic obstructive bronchitis), emphysema, asthmatic bronchitis, and bullous disease; and other pulmonary diseases involving inflammation including bronchiolitis, bronchioectasis, cystic fibrosis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, pneumonia, pneumonitis, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, acute pulmonary edema, acute mountain sickness, acute pulmonary hypertension, persistent

pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthmaticus, hypoxia, dyspnea, hypercapnea, hyperinflation, hypoxemia, and cough. Further, compounds disclosed herein would find use in the treatment of allergic disorders such as delayed type hypersensitivity reaction, allergic contact dermatitis, allergic rhinitis, and chronic sinusitis.

Other disorders or conditions which may be treated by the compounds of the present invention include inflammation and related disorders. The compounds of the present invention may be useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compounds may be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, reactive arthritis (Reiter's syndrome), and pyogenic arthritis, and autoimmune diseases, including systemic lupus erythematosus, hemolytic syndromes, autoimmune hepatitis, autoimmune neuropathy, vitiglio (autoimmune thyroiditis), Hashimoto's thyroiditis, anemias, myositis including polymyositis, alopecia areata, Goodpasture's syndrome, hypophysitis, and pulmonary fibrosis.

The compounds may also be useful in treating osteoporosis and other related bone disorders.

These compounds may also be used to treat gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, Graves' disease (hyperthyroidism), necrotizing enterocolitis, and ulcerative colitis. The compounds may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis.

In addition, compounds of invention may also be useful in organ transplant patients either alone or in combination with conventional immunomodulators. Examples of conditions to be treated in said patients include graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), transplant reperfusion injury, and early transplantation rejection (e.g., acute allograft rejection).

Yet further, the compounds of the invention may be useful in the treatment of pruritis and vitiligo.

The compounds of the present invention may also be useful in treating tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Langerhans' cell histiocytosis, glomerulonephritis, reperfusion injury, pancreatitis, interstitial cystitis, Behcet's syndrome, polymyositis, gingivitis, periodontitis, hypersensitivity, swelling occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, cirrhosis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, ischemia reperfusion injury, multi-organ dysfunction, restenosis including restenosis following coronary bypass surgery, and the like.

The compounds of the subject invention may also be useful for the treatment of certain diseases and disorders of the nervous system. Central nervous system disorders in which PDE4 inhibition may be useful include cortical dementias including Alzheimer's disease and mild cognitive impairment (MCI), central nervous system damage resulting from stroke, ischemias including cerebral ischemia (both focal

ischemia, thrombotic stroke and global ischemia (for example, secondary to cardiac arrest), and trauma. Neurodegenerative disorders in which PDE4 inhibition may be useful include nerve degeneration or nerve necrosis in disorders such as hypoxia, hypoglycemia, epilepsy, and in cases of central nervous system (CNS) trauma (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia e.g. pre-senile dementia, and AIDS-related dementia, cachexia, Sydenham's chorea, Huntington's disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Korsakoff's syndrome, and imbecility relating to a cerebral vessel disorder. Further disorders in which PDE4 inhibition might prove useful include neuropathies of the central and peripheral nervous system (including, for example, IgA neuropathy, membranous neuropathy and idiopathic neuropathy), chronic inflammatory demyelinating polyneuropathy, transverse myelitis, Gullain-Barre disease, encephalitis, and cancers of the nervous system. Disorders of CNS function in which PDE4 inhibitors may find use include sleeping disorders, schizophrenia, depression, depression or other symptoms associated with Premenstrual Syndrome (PMS), and anxiety.

Furthermore, the compounds of the present invention may also be useful in inhibiting PDE4 activity for the amelioration of systemic disorders including systemic hypotension associated with septic and/or toxic hemorrhagic shock induced by a wide variety of agents; as a therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy.

Still other disorders or conditions which may be treated by the compounds of the subject invention include the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. Compounds of the invention may be used in the treatment and prevention of neoplasias including but not limited to brain cancer, bone cancer, leukemia, lymphoma, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. The neoplasia can be selected from gastrointestinal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell

and basal cell cancers. The present compounds and methods may also be used to treat the fibrosis which occurs with radiation therapy. The present compounds and methods may be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the present compounds and methods may be used to prevent polyps from forming in patients at risk of FAP.

The compounds of the subject invention may be used in the treatment of ophthalmic diseases, such as dry eye, glaucoma, corneal neovascularization, optic neuritis, Sjogren's syndrome, retinal ganglion degeneration, ocular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. Specifically, the compounds may be used to treat glaucomatous retinopathy and/or diabetic retinopathy. The compounds may also be used to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.

Moreover, compounds of the subject invention may be used in the treatment of menstrual cramps, dysmenorrhea, premature labor, endometriosis, tendonitis, bursitis, skin-related conditions such as psoriasis, eczema, burns, sunburn, dermatitis, pancreatitis, hepatitis, lichen planus, scleritis, scleroderma, dermatomyositis, and the like. Other conditions in which the compounds of the subject invention may be used include diabetes (type I or type II), atherosclerosis, congestive heart failure, myocarditis, atherosclerosis, cerebral ischemia, angiogenesis, pulmonary hypertension, and aortic aneurysm.

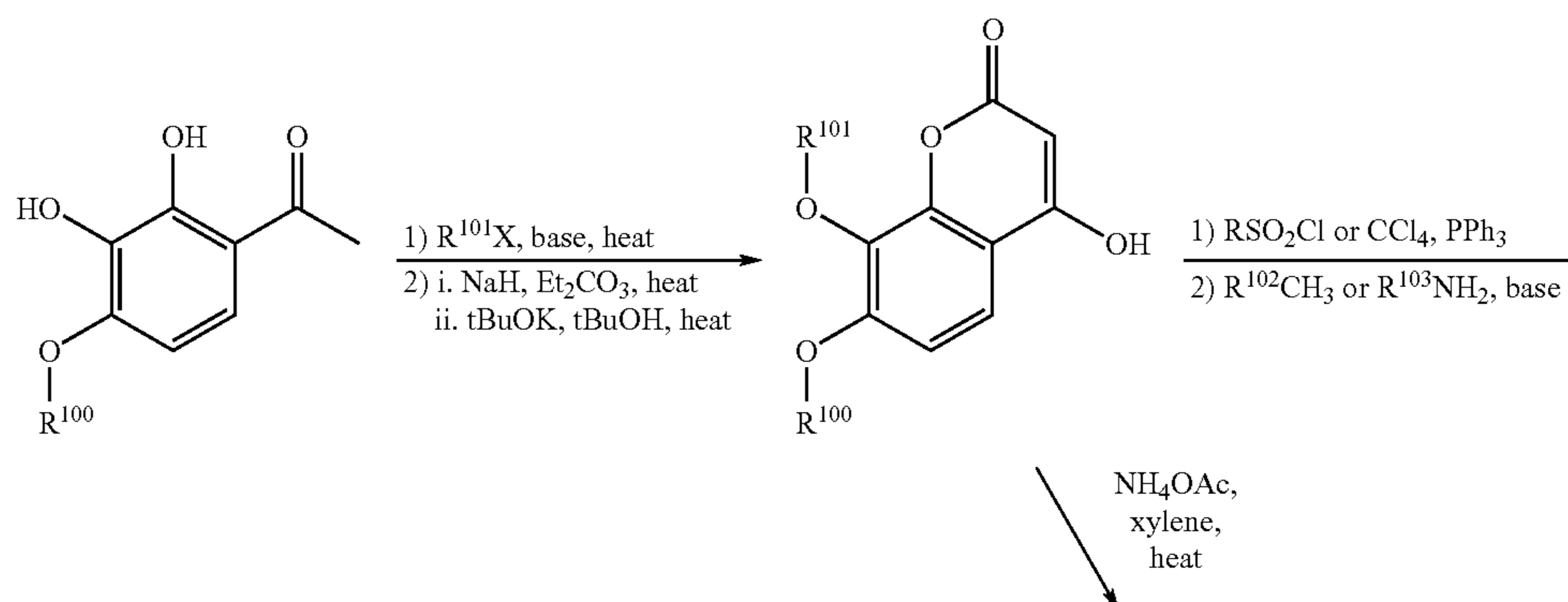
The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB<sub>4</sub> antagonists and LTA<sub>4</sub> hydrolase inhibitors. The compounds of the subject invention may also be used to prevent tissue damage when therapeutically combined with antibacterial or antiviral agents.

Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

#### General Synthetic Methods for Preparing Compounds

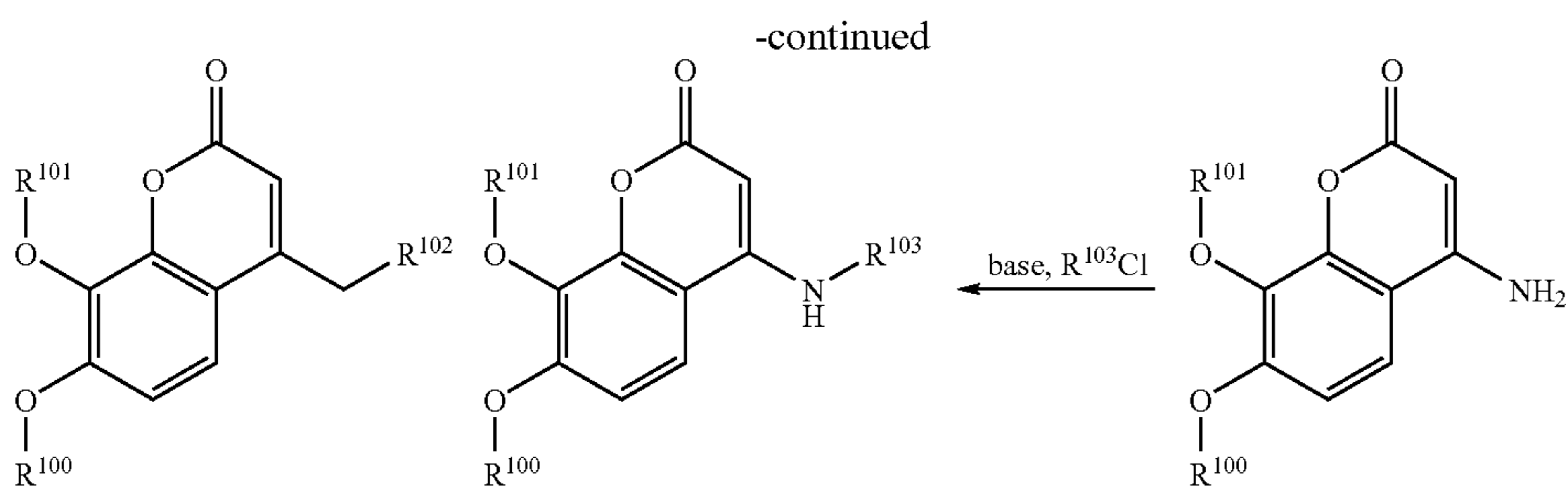
The following schemes can be used to practice the present invention.

Scheme 1



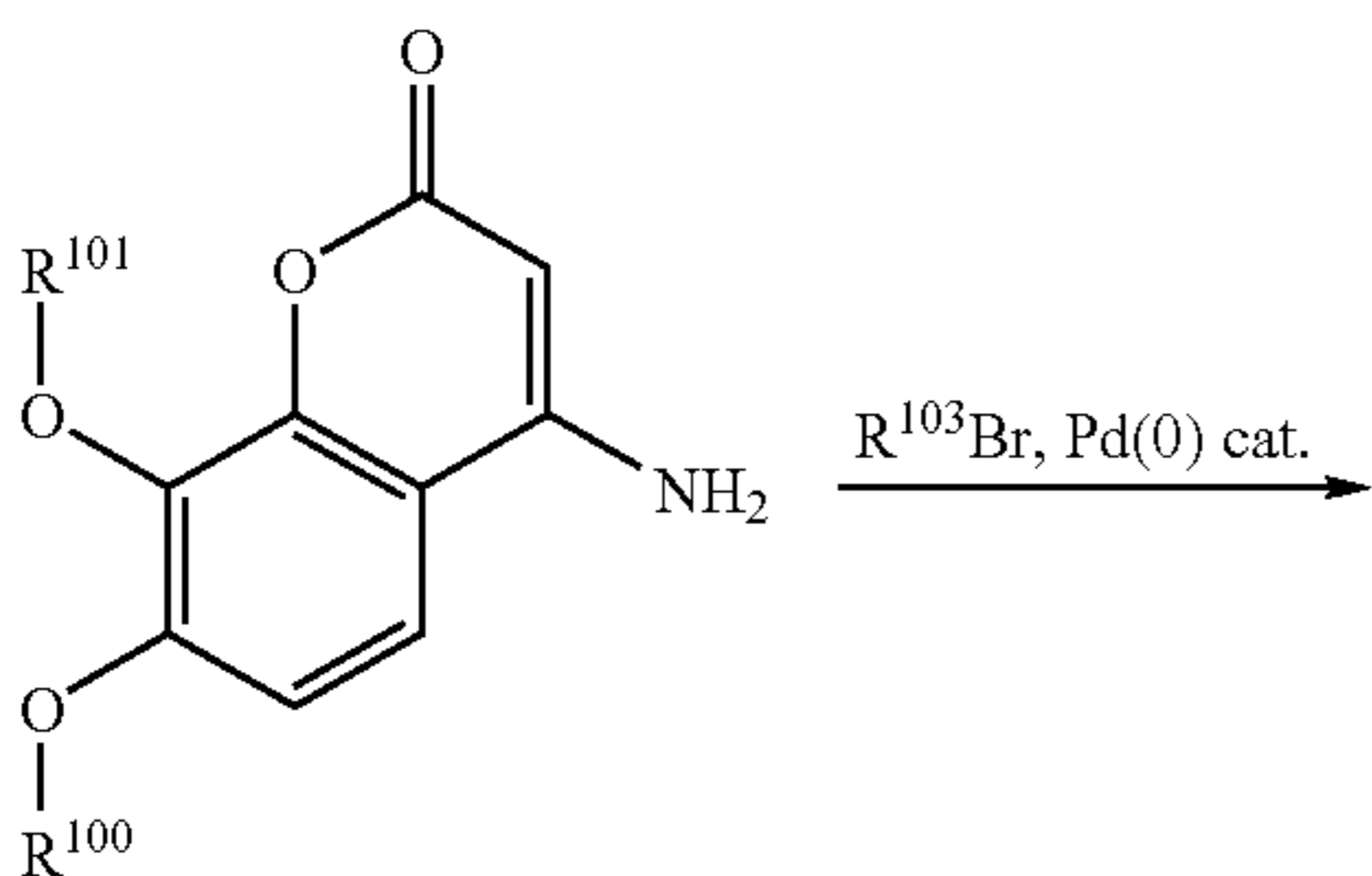
29

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Scheme 2

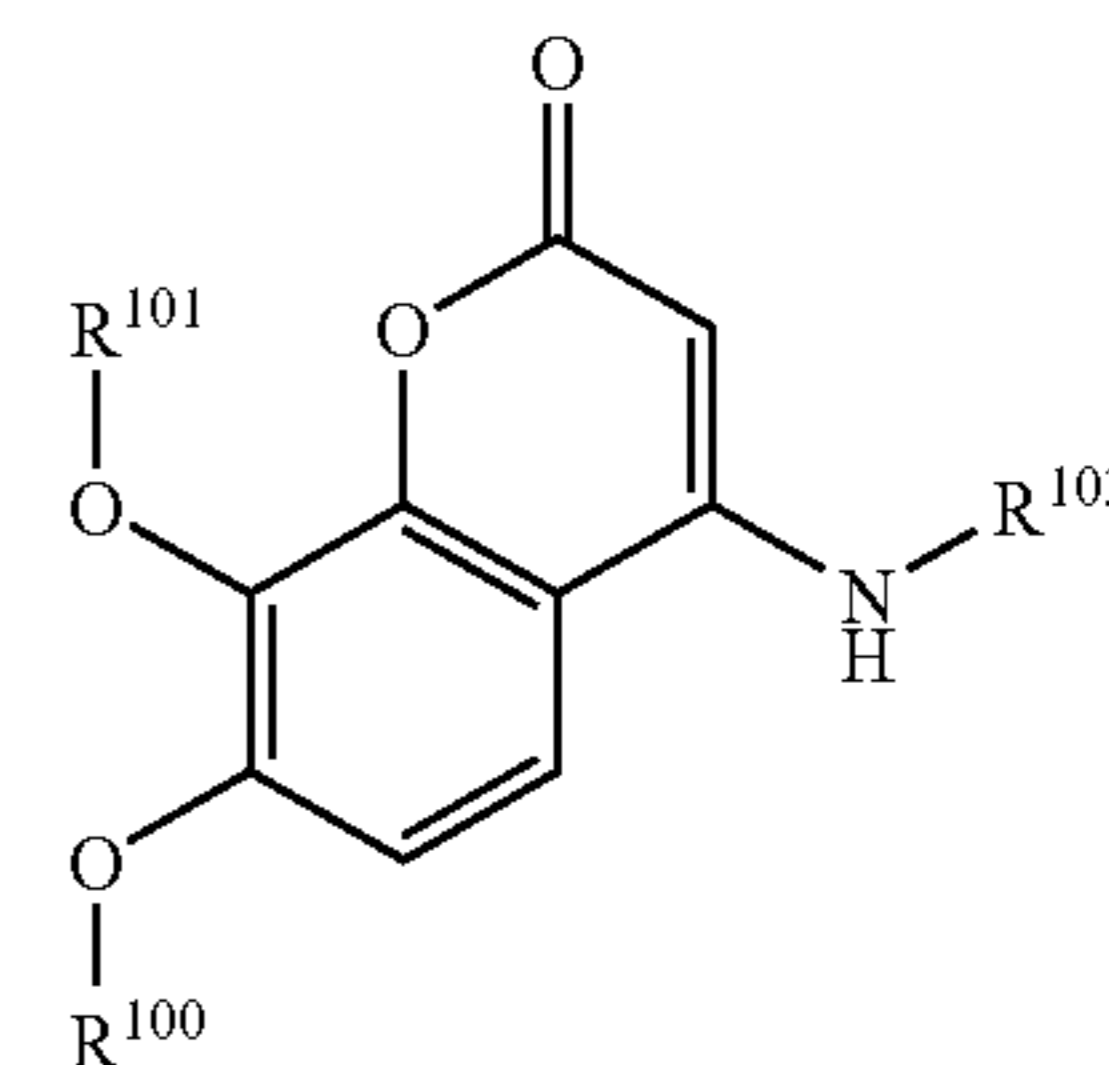
15



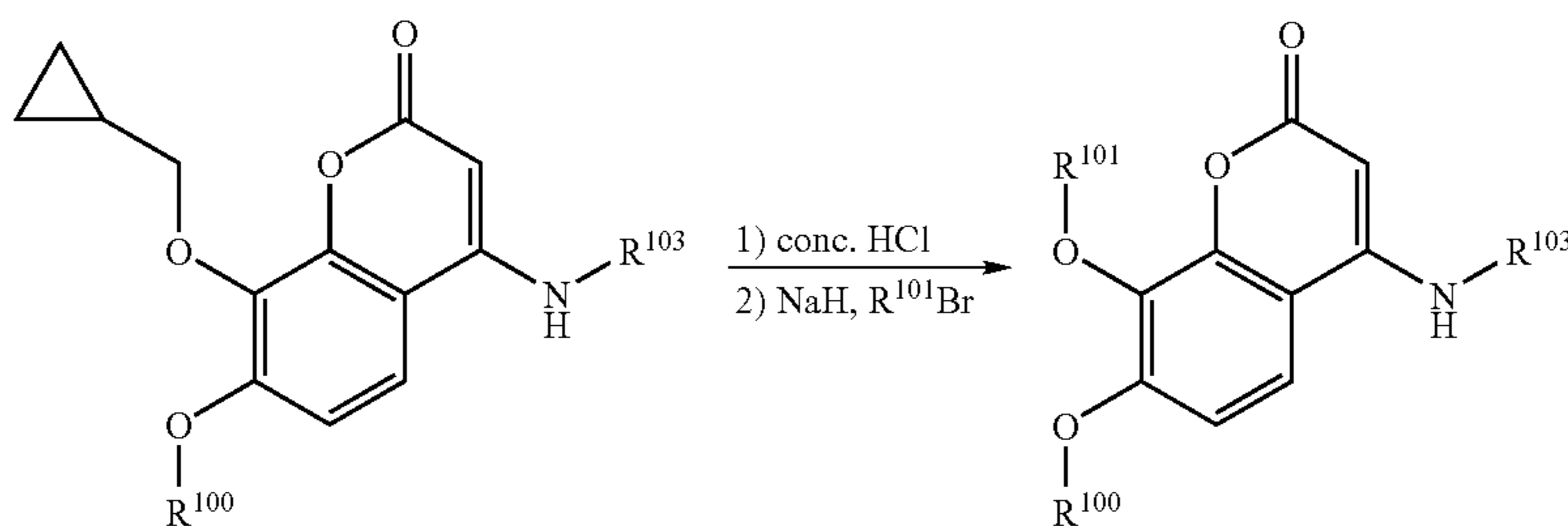
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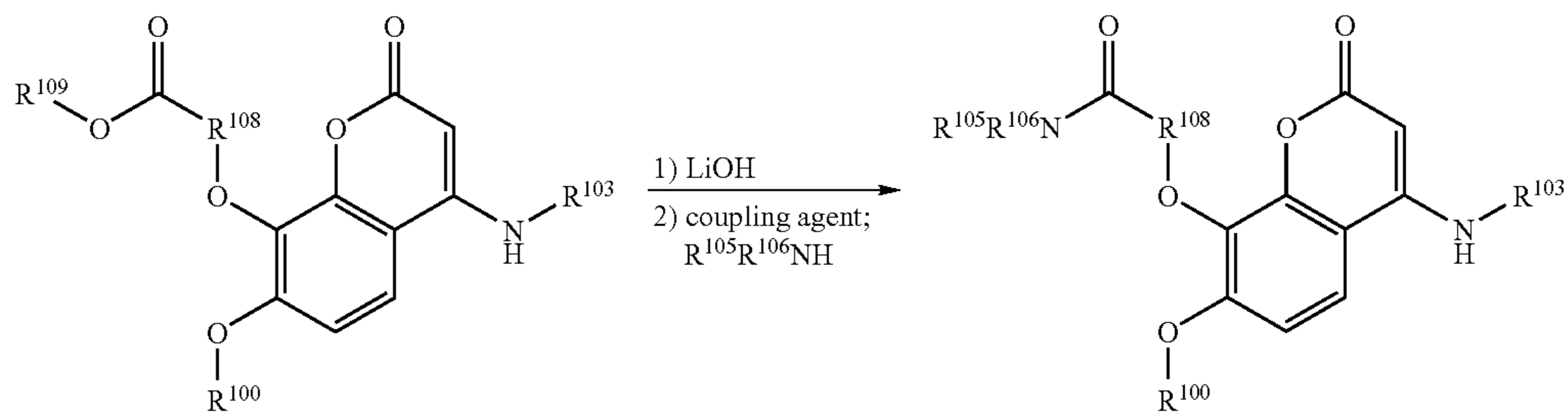
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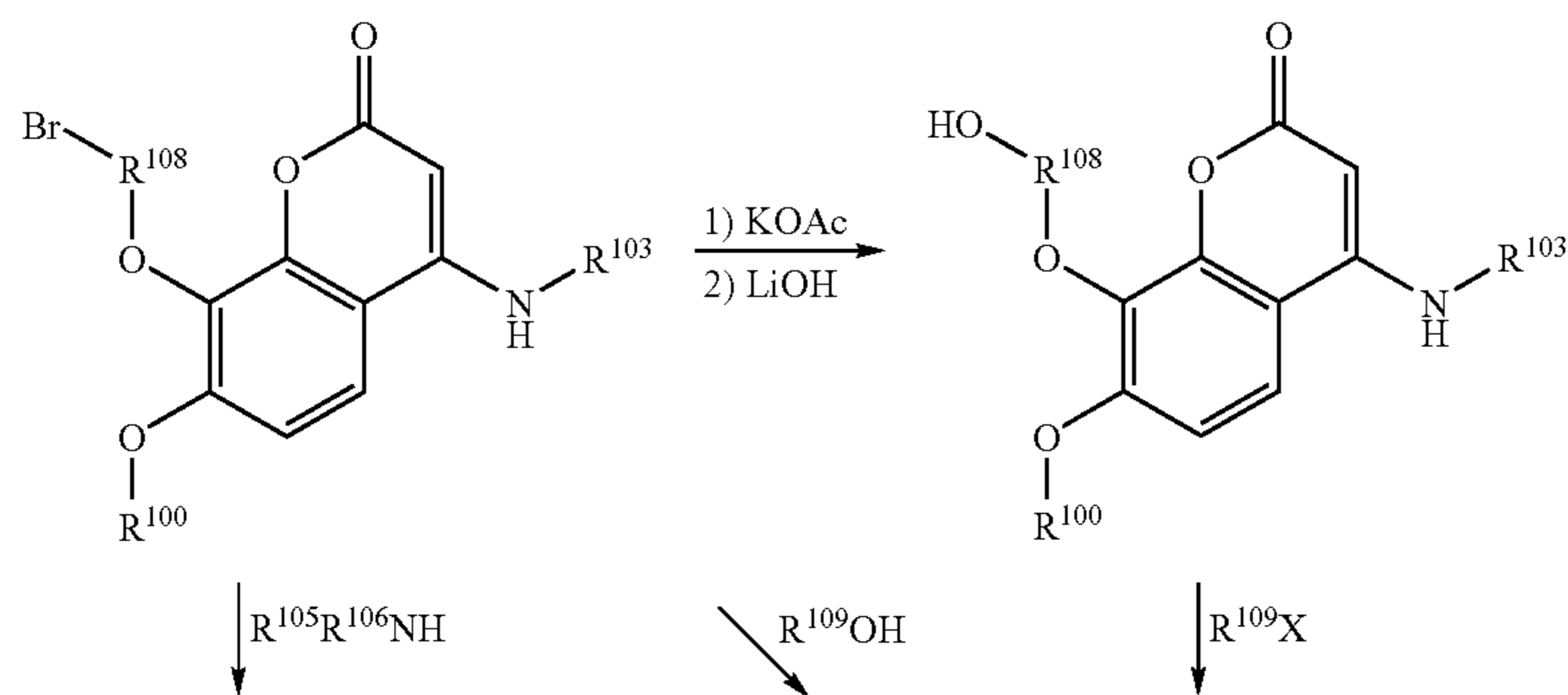
Scheme 3



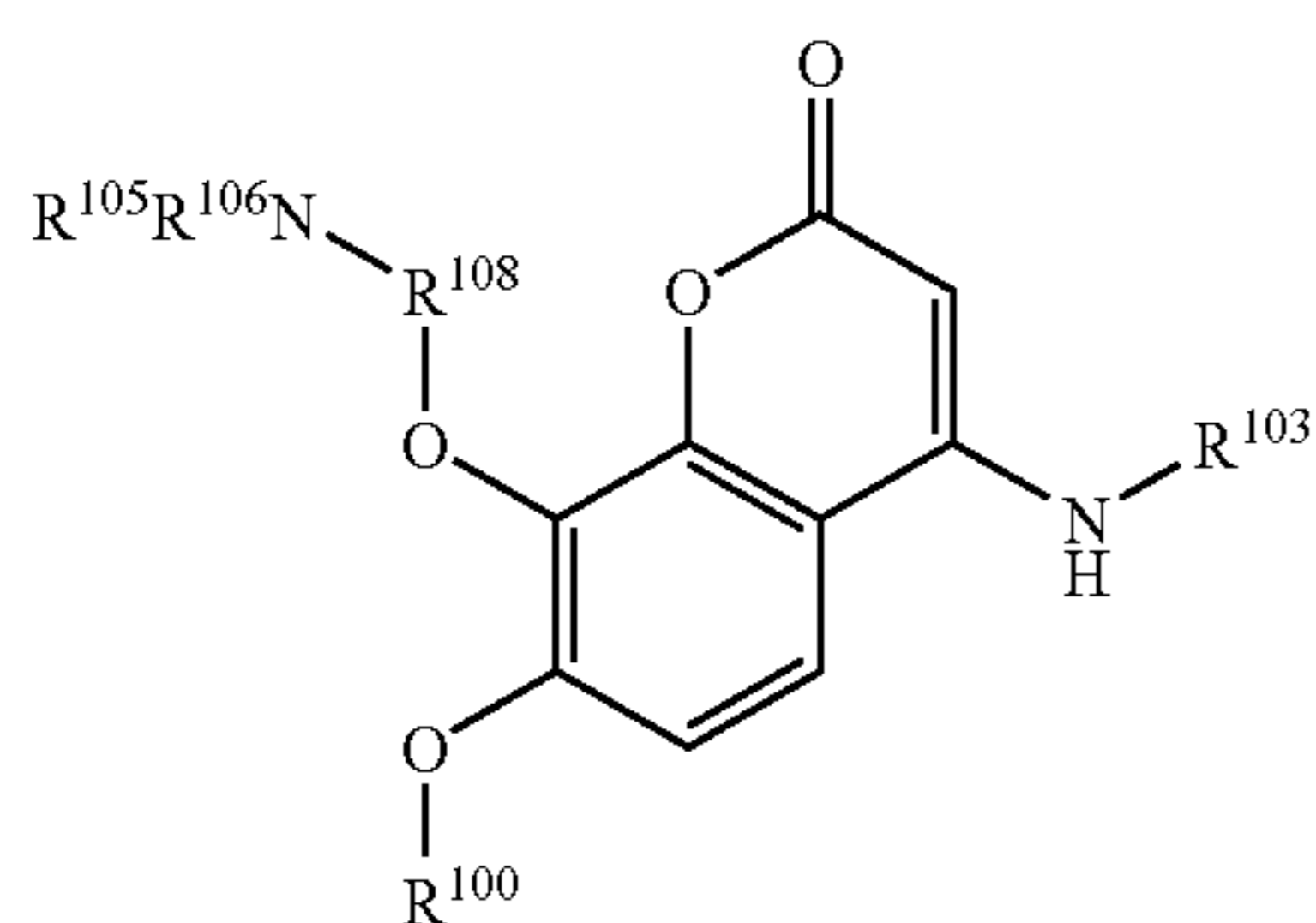
when R<sup>101</sup> contains an ester:



when R<sup>101</sup> contains a bromide:



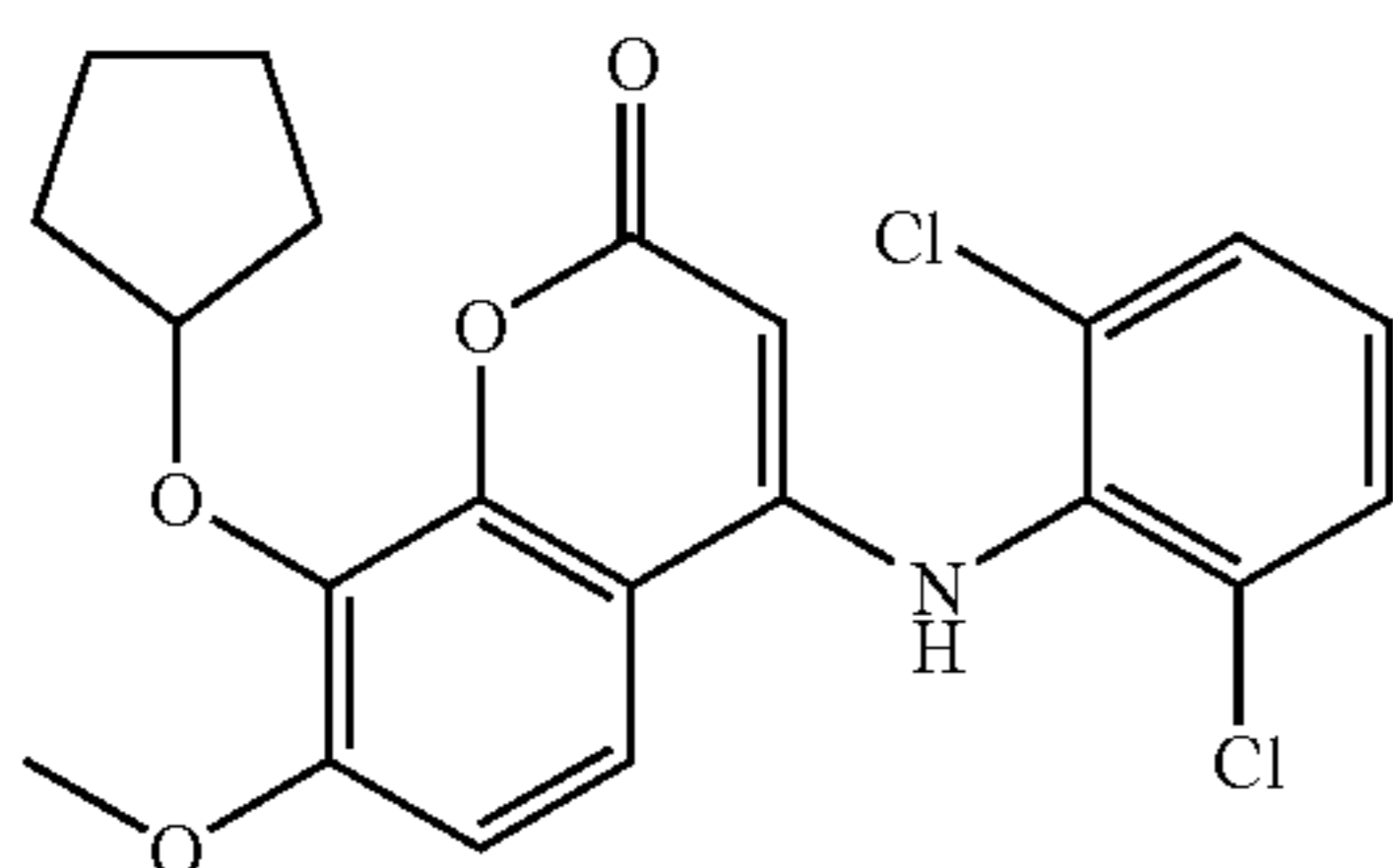




The invention is further illustrated by the following examples.

## EXAMPLE 1

## 8-(Cyclopentyloxy)-4-(2,6-dichlorophenylamino)-7-methoxy-2H-chromen-2-one



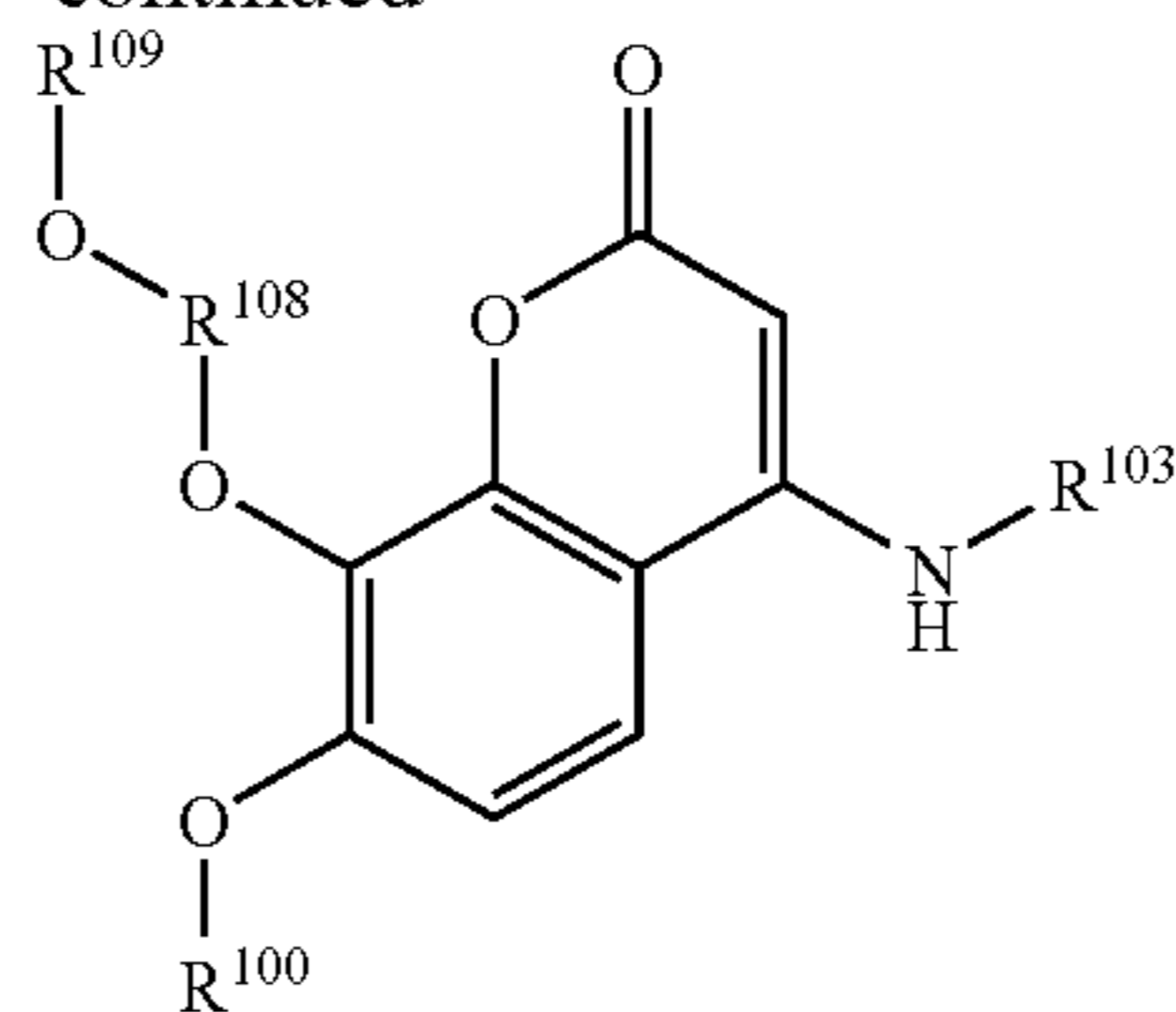
## Step 1

A mixture of 1-(2,3-dihydroxy-4-methoxyphenyl)ethanone (10 g, 55 mmol), bromocyclopentane (6.0 mL, 56 mmol), potassium carbonate (15.5 g, 112 mmol), and anhydrous DMF (100 mL) was heated at 110° C. under N<sub>2</sub> for 17 h and then allowed to cool to rt. The mixture was poured into 0.5N HCl (600 mL) and extracted with diethyl ether (250 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (1:0→17:3; hexanes:ethyl acetate) to give 1-[3-(cyclopentyloxy)-2-hydroxy-4-methoxyphenyl]ethanone: MS (ESI): 251.2.

## Step 2

1-[3-(Cyclopentyloxy)-2-hydroxy-4-methoxyphenyl]ethanone (4.25 g, 17 mmol) was added portionwise to a mixture of sodium hydride (1.4 g, 60%, 35 mmol) and diethyl carbonate (30 mL) at rt under N<sub>2</sub>. The reaction was refluxed for 1 h and then cooled to rt. 10% Hydrochloric acid (30 mL) was added, and the mixture was stirred for 1 h. The reaction was diluted with water (100 mL) and extracted with ethyl acetate (200 mL×2). The combined extracts were dried, filtered, concentrated, and redissolved in t-butanol (50 mL). Potassium t-butoxide (4.0 g, 36 mmol) was added, and the reaction was refluxed. After 42 h, additional potassium t-butoxide (2.0 g, 18 mmol) was added. After an additional 2 d, the reaction was allowed to cool to rt, concentrated, diluted with 1N HCl (100 mL), and extracted with ethyl acetate (200 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (3:2→0:1; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one: MS (ESI): 277.1.

-continued



## Step 3

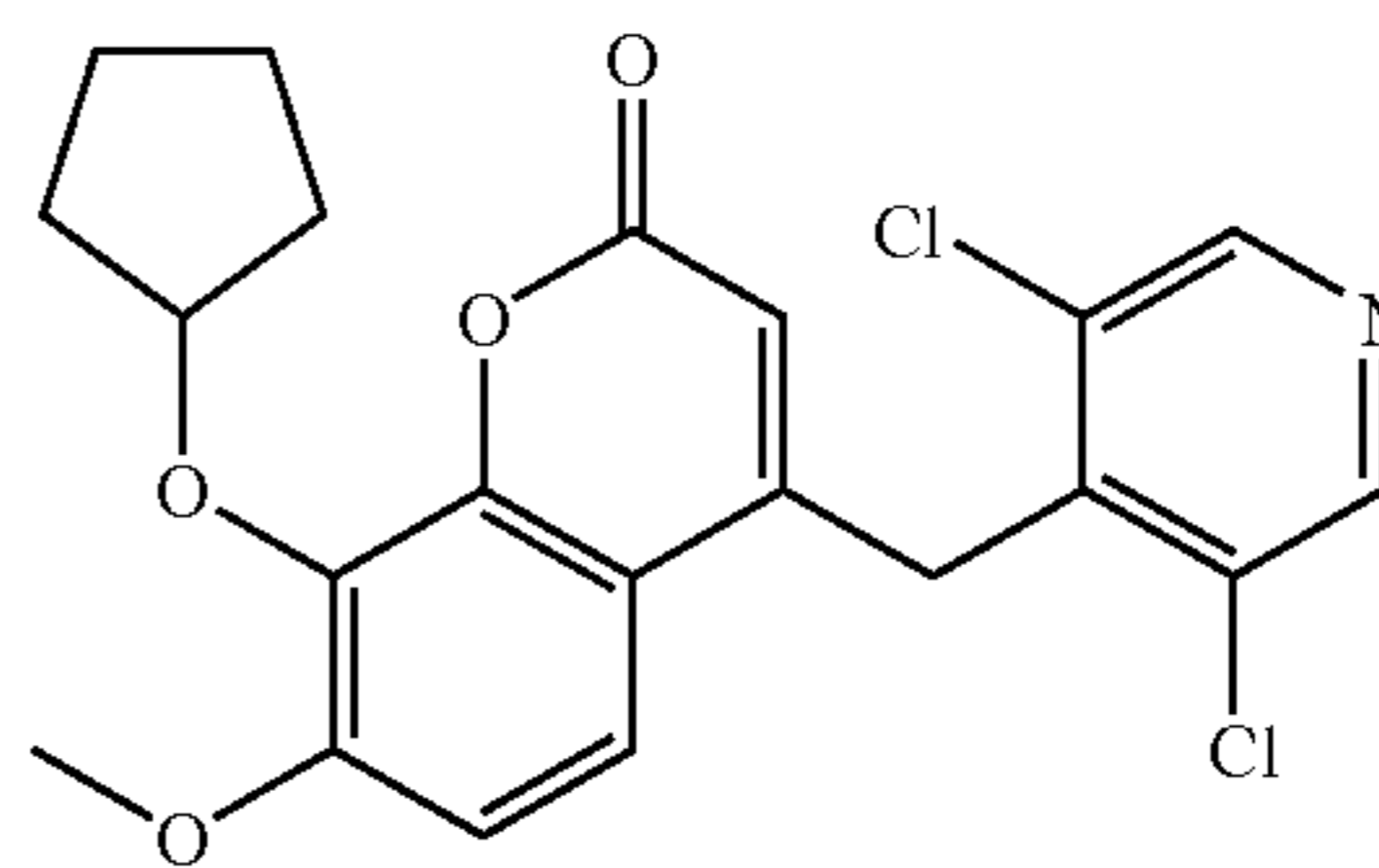
4-Methylbenzene-1-sulfonyl chloride (135 mg, 0.71 mmol) was added to a solution of 8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one (175 mg, 0.63 mmol), pyridine (0.15 mL, 1.85 mmol), and anhydrous dichloromethane (4 mL) at rt under N<sub>2</sub>. After 20 h, the reaction was concentrated and purified by silica gel chromatography (1:0→7:3; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-yl 4-methylbenzenesulfonate: MS (ESI): 431.3.

## Step 4

Sodium hydride (10 mg, 60%, 0.25 mmol) was added to a solution of 2,6-dichloroaniline (40 mg, 0.25 mmol) and anhydrous DMSO (2 mL) at rt under N<sub>2</sub>. After 40 min, this mixture was added to a solution of 8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-yl 4-methylbenzenesulfonate (70 mg, 0.16 mmol) and anhydrous DMSO (2 mL) at rt under N<sub>2</sub>. After 1.5 h at rt, the reaction was heated at 50° C. After an additional 1.5 h, a second aliquot of the sodium 2,6-dichloroanilide mixture was added. After an additional hour, the reaction was allowed to cool to rt, diluted with 1M KH<sub>2</sub>PO<sub>4</sub> (40 mL), and extracted with ethyl acetate (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (4:1→3:2; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-(2,6-dichlorophenylamino)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.39 (s, 1H), 7.95 (d, 1H), 7.69 (d, 2H), 7.50 (t, 1H), 7.18 (d, 1H), 4.83 (m, 1H), 4.36 (s, 1H), 3.90 (s, 3H), 1.80-1.00 (m, 8H); MS (ESI): 419.9.

## EXAMPLE 2

## 8-(Cyclopentyloxy)-4-[(3,5-dichloropyridin-4-yl)methyl]-7-methoxy-2H-chromen-2-one

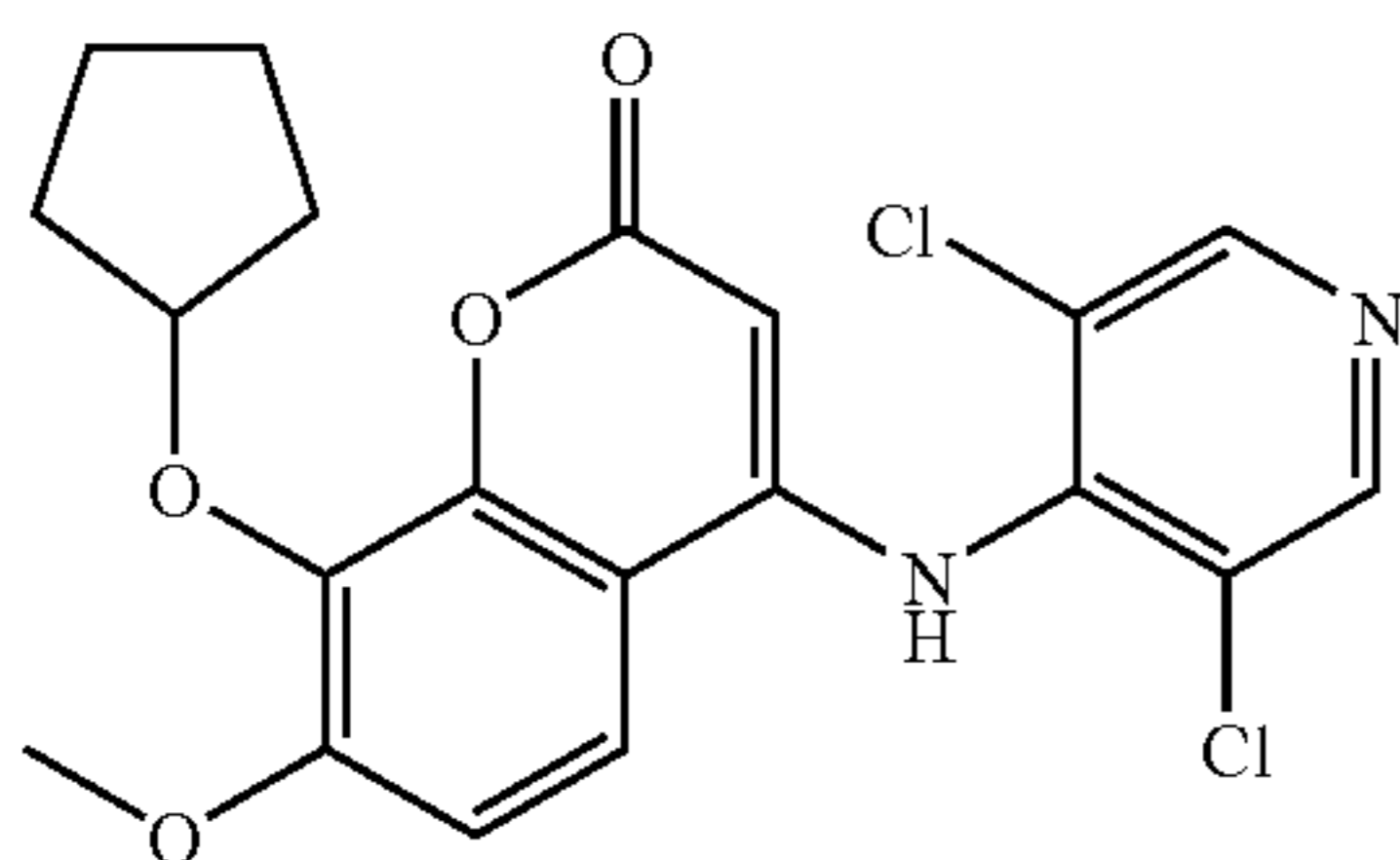


The title compound was prepared from 3,5-dichloro-4-methylpyridine and 8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-yl 4-methylbenzenesulfonate following the procedure outlined in Example 1, Step 4. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.73 (s, 2H), 7.77 (d, 1H), 7.19 (d, 1H), 5.32 (s, 1H), 4.83 (m, 1H), 4.45 (s, 2H), 3.92 (s, 3H), 1.80-1.00 (m, 8H); MS (ESI): 419.9.

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## EXAMPLE 3

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



## Step 1

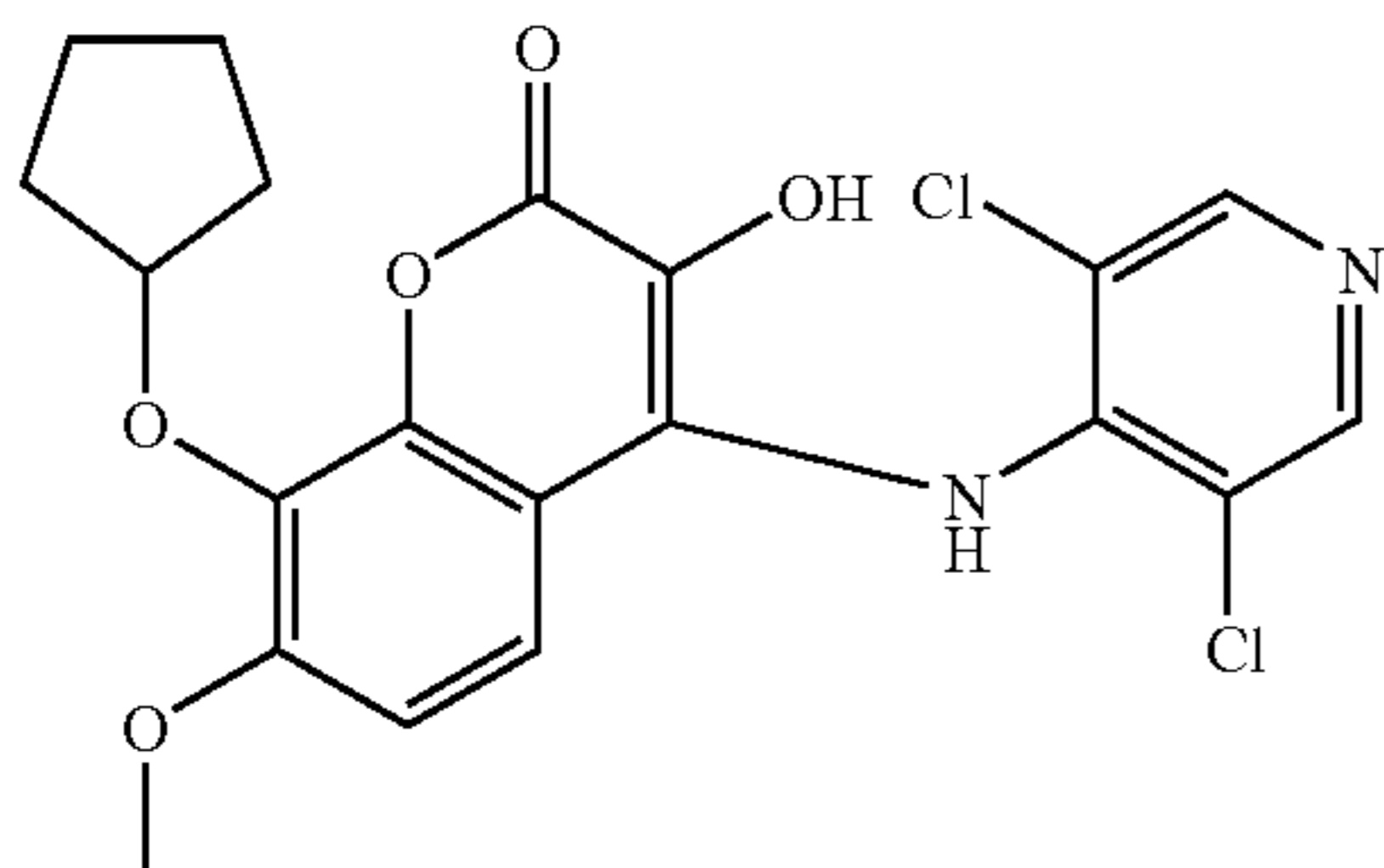
A mixture of 8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one (450 mg, 1.63 mmol, Example 1, Step 2), ammonium acetate (3.0 g, 39 mmol), and anhydrous m-xylene (8 mL) was refluxed under N<sub>2</sub>. After 3 h, the reaction was concentrated and purified by silica gel chromatography (3:2→0:1; hexanes:ethyl acetate) to give 4-amino-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one: MS (ESI): 275.9.

## Step 2

Sodium hydride (12 mg, 60%, 0.30 mmol) was added to a solution of 4-amino-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (40 mg, 0.15 mmol), 3,4,5-trichloropyridine (27 mg, 0.15 mmol), and anhydrous DMSO (3 mL) at rt under N<sub>2</sub>. After 4 h, the reaction was poured into 1M KH<sub>2</sub>PO<sub>4</sub> (40 mL) and extracted with ethyl acetate (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (13:7→9:11; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.20 (d, 1H), 4.83 (m, 1H), 4.63 (s, 1H), 3.91 (s, 3H), 1.80-1.00 (m, 8H); MS (ESI): 421.1.

## EXAMPLE 4

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-3-hydroxy-7-methoxy-2H-chromen-2-one



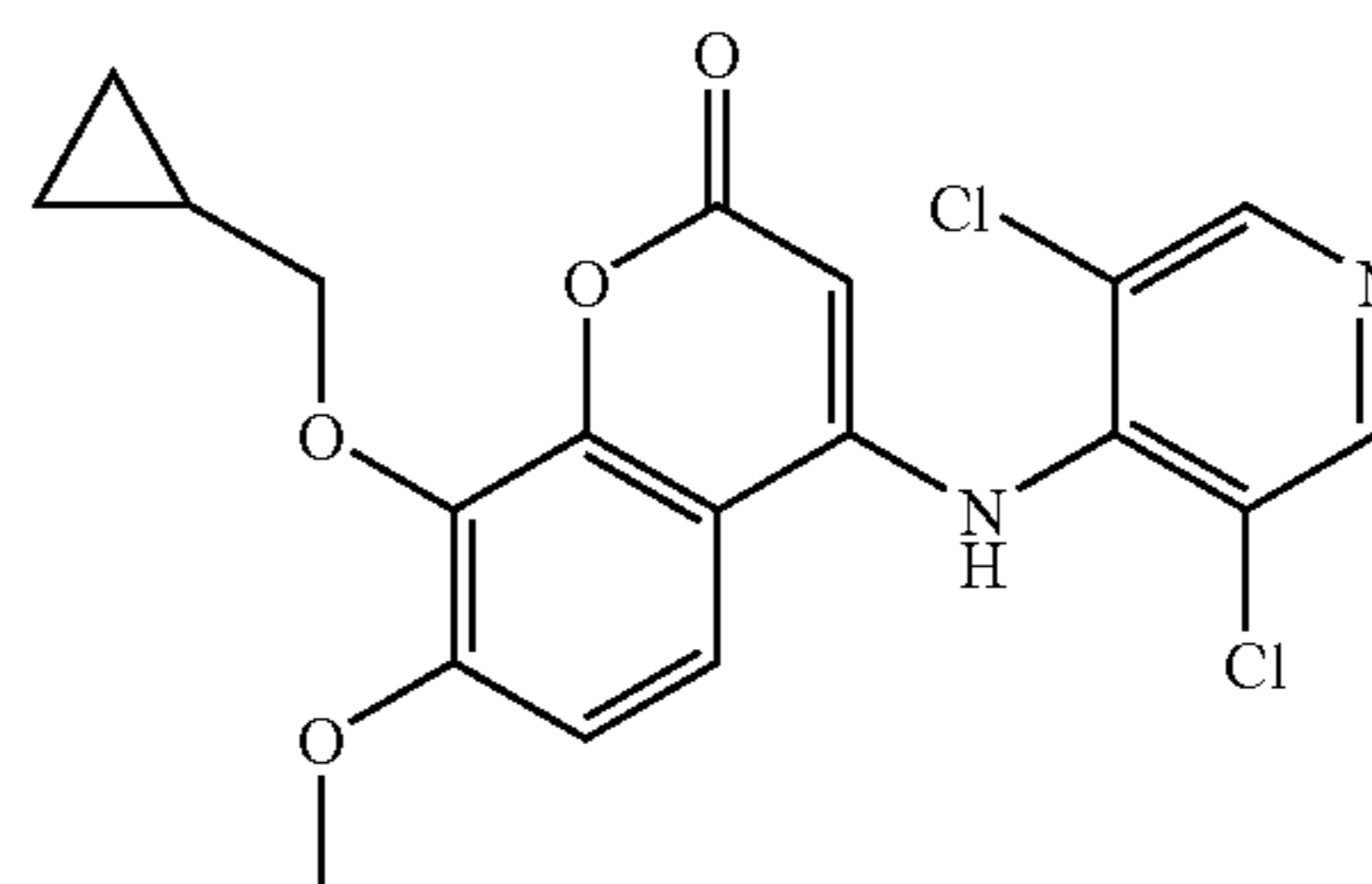
Trifluoroacetic anhydride (0.04 mL, 0.29 mmol) was added to a solution of 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (42 mg, 0.1 mmol, Example 3), urea•H<sub>2</sub>O<sub>2</sub> (28.5 mg, 0.3 mmol), and dichloromethane (2 mL) at rt under N<sub>2</sub>. After 1.5 h, sat'd Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (8 mL) was added, and the mixture was stirred vigorously for 15 min. The reaction was then diluted with

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0.5N HCl (40 mL), and extracted with dichloromethane (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (4:1→1:1; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-3-hydroxy-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.30 (s, 1H), 8.42 (s, 2H), 8.40 (s, 1H), 7.59 (d, 1H), 7.12 (d, 1H), 4.84 (m, 1H), 3.86 (s, 3H), 1.90-1.50 (m, 8H); MS (ESI): 436.9.

## EXAMPLE 5

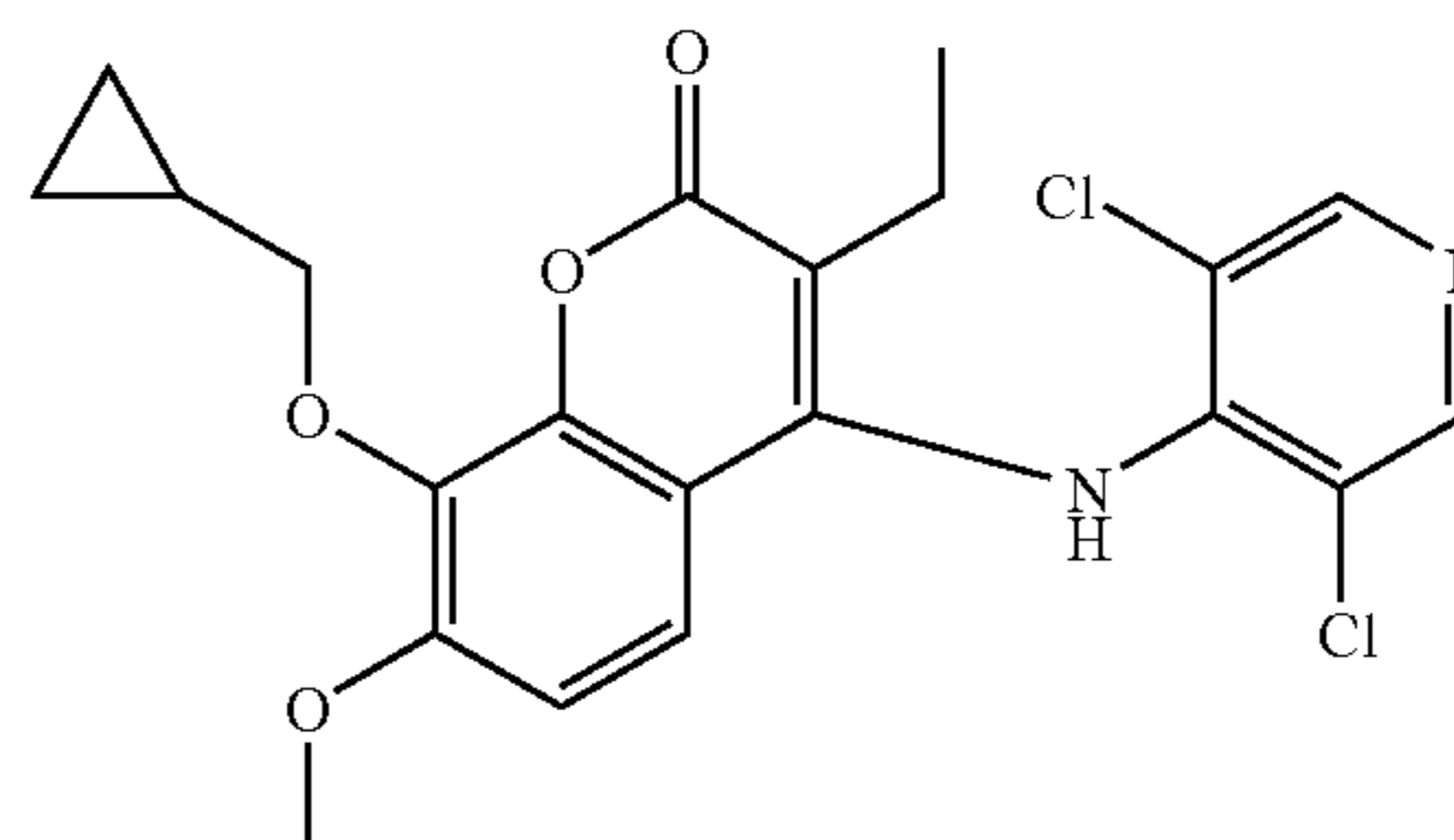
8-(Cyclopropylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 1-(2,3-dihydroxy-4-methoxyphenyl)ethanone and (bromomethyl)cyclopropane following the procedure outlined in Example 3. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 3.91 (s, 3H), 3.82 (d, 2H), 1.19 (m, 1H), 0.49 (m, 2H), 0.25 (m, 2H); MS (ESI): 406.8.

## EXAMPLE 6

8-(Cyclopropylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-3-ethyl-7-methoxy-2H-chromen-2-one



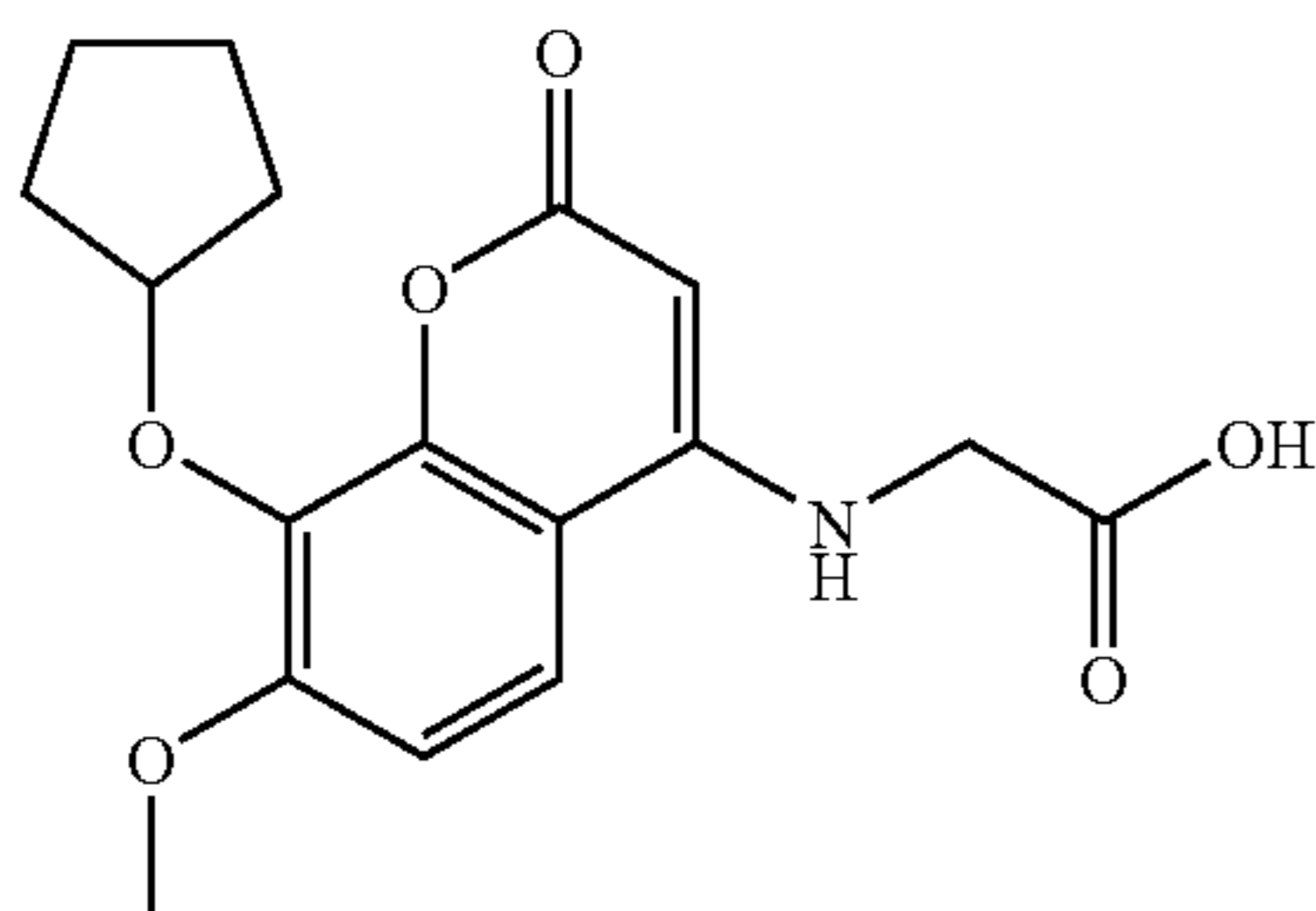
4-Amino-8-(cyclopropylmethoxy)-3-ethyl-7-methoxy-2H-chromen-2-one was isolated from the sequence of reactions that provided Example 5.

Sodium hydride (8 mg, 60%, 0.2 mmol) was added to a solution of 4-amino-8-(cyclopropylmethoxy)-3-ethyl-7-methoxy-2H-chromen-2-one (24 mg, 0.083 mmol) and DMSO (3 mL) at rt under N<sub>2</sub>. After 5 min, 3,4,5-trichloropyridine (19 mg, 0.1 mmol) was added, and the reaction was heated at 60° C. After 2 h, more 3,4,5-trichloropyridine (25 mg, 0.14 mmol) was added followed by more sodium hydride (15 mg, 60%, 0.38 mmol). After an additional 2 h at 60° C., the reaction was poured into 1M KH<sub>2</sub>PO<sub>4</sub> (40 mL) and extracted with ethyl acetate (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (7:3→1:4; hexanes:ethyl acetate) to give 8-(cyclopropylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-3-ethyl-7-methoxy-2H-chromen-2-one: MS (ESI): 434.8.

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## EXAMPLE 7

2-(8-(Cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetic acid



## Step 1

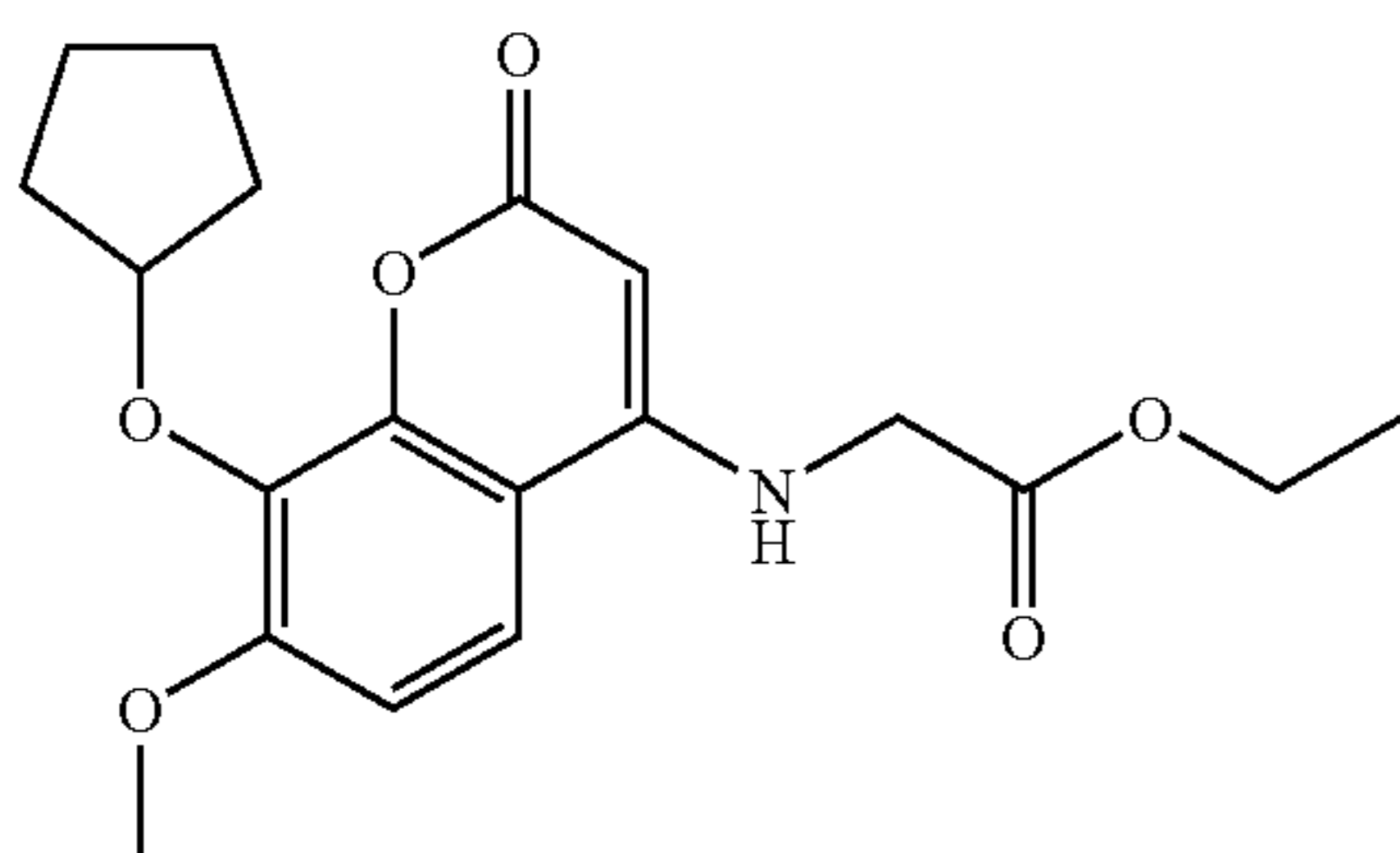
A mixture of 8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one (415 mg, 1.5 mmol, Example 1, Step 2), triphenylphosphine (787 mg, 3.0 mmol), CCl<sub>4</sub> (0.75 mL, 7.8 mmol), and chloroform (2 mL) was heated at 80° C. in a sealed vial for 4.5 h and then allowed to cool to rt. The reaction was concentrated and purified by silica gel chromatography (1:0→4:1; hexanes:ethyl acetate) to give 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one: MS (ESI): 294.8.

## Step 2

A mixture of 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (170 mg, 0.58 mmol), glycine (52 mg, 0.69 mmol), triethylamine (0.2 mL, 1.4 mmol), and ethanol (2 mL) was heated at 75° C. in a sealed vial. After 2 d, more glycine (136 mg, 1.8 mmol) and triethylamine (0.3 mL, 2.2 mmol) were added. The reaction was heated at 75° C. for an additional day, allowed to cool to rt, concentrated, diluted with ethyl acetate (40 mL), and then washed with 1N HCl (50 mL×3). The organic layer was dried, filtered, and concentrated to give 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetic acid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.87 (t, 1H), 7.68 (d, 1H), 7.08 (d, 1H), 4.88 (s, 1H), 4.81 (m, 1H), 4.00 (d, 2H), 3.87 (s, 3H), 1.90-1.44 (m, 8H); MS (ESI): 333.9.

## EXAMPLE 8

Ethyl 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetate

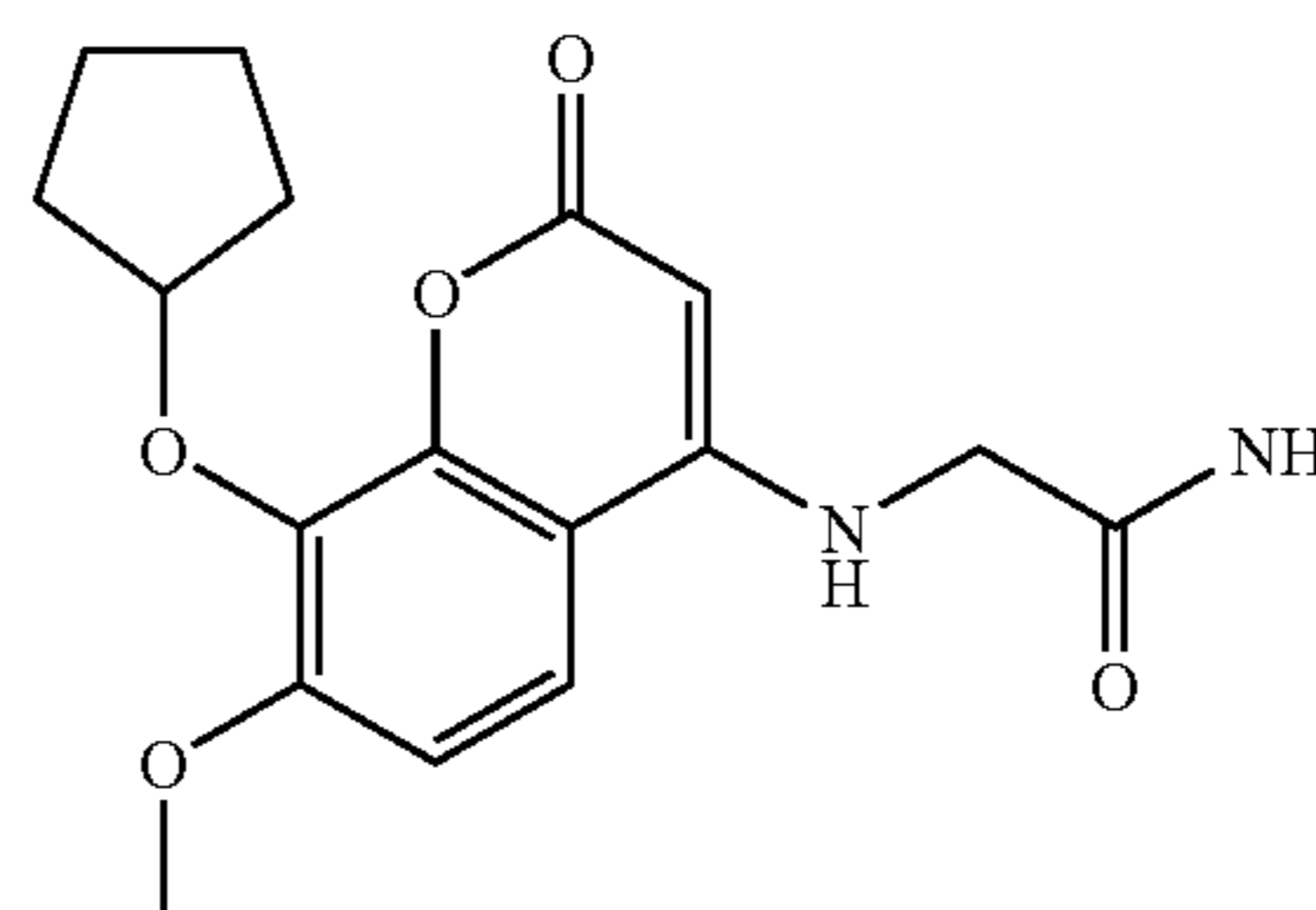


A mixture of 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (170 mg, 0.58 mmol, Example 7, Step 1), glycine ethyl ester•HCl (97 mg, 0.69 mmol), triethylamine (0.2 mL, 1.4 mmol), and ethanol (2 mL) was heated at 75° C. in a sealed vial for 30 h. The reaction was allowed to cool to rt, concentrated, and purified by silica gel chromatography

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## EXAMPLE 9

2-(8-(Cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetamide

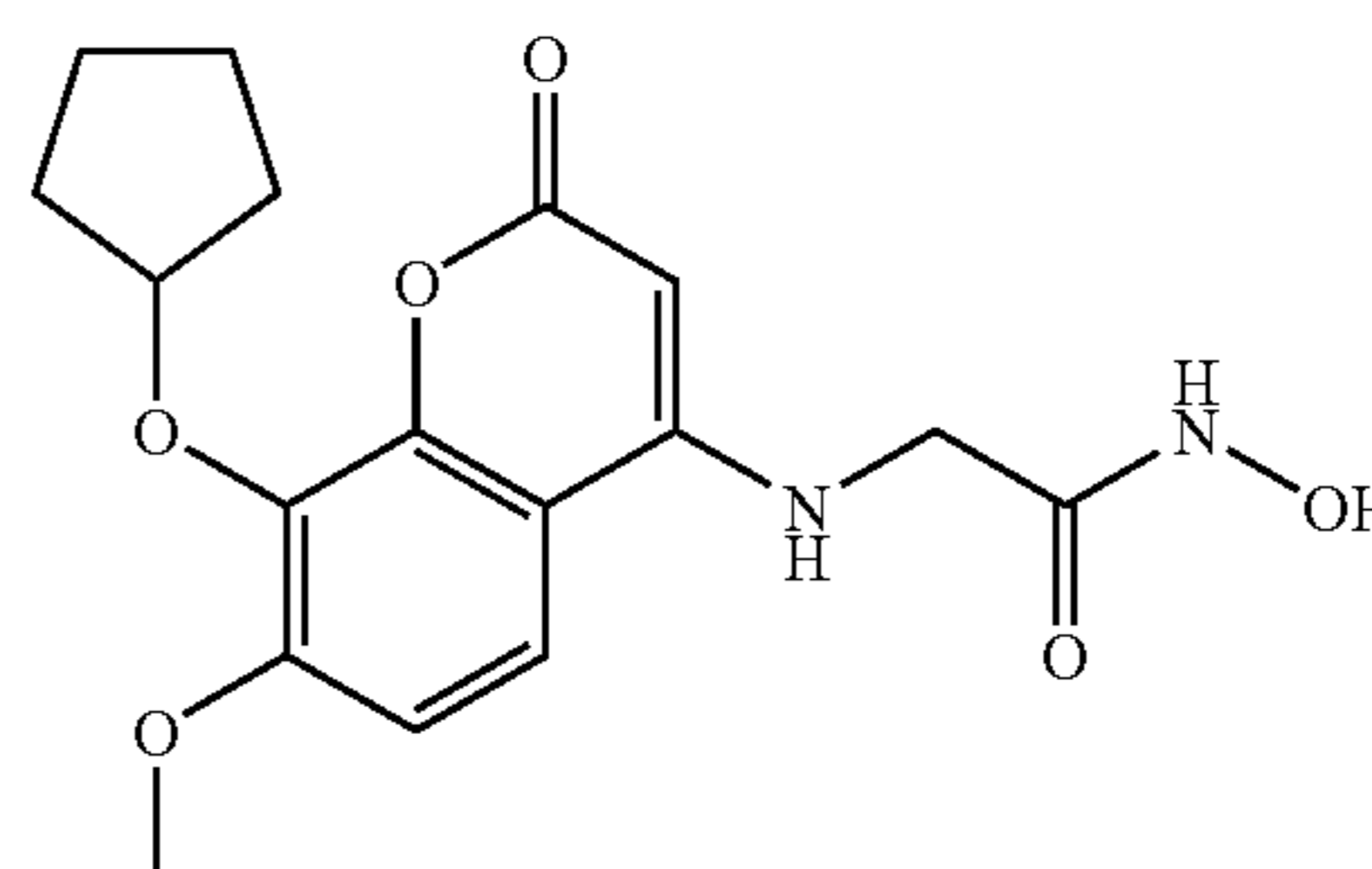


(3:2→1:4; hexanes:ethyl acetate) to give ethyl 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetate: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.93 (t, 1H), 7.68 (d, 1H), 7.08 (d, 1H), 4.92 (s, 1H), 4.80 (m, 1H), 4.13 (q, 2H), 4.10 (d, 2H), 3.86 (s, 3H), 1.90-1.45 (m, 8H), 1.20 (t, 3H); MS (ESI): 361.9.

A mixture of 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (170 mg, 0.58 mmol, Example 7, Step 1), glycine•HCl (77 mg, 0.70 mmol), triethylamine (0.2 mL, 1.4 mmol), and ethanol (2 mL) was heated at 75° C. in a sealed vial for 30 h. The reaction was allowed to cool to rt, concentrated, diluted with dichloromethane (10 mL), and let stand. After 10 min, the free-flowing solid was filtered and dried to give 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetamide: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.89 (t, 1H), 7.70 (d, 1H), 7.57 (s, 1H), 7.22 (s, 1H), 7.07 (d, 1H), 4.83 (s, 1H), 4.81 (m, 1H), 3.86 (s, 3H), 3.80 (d, 2H), 1.90-1.48 (m, 8H); MS (ESI): 333.0.

## EXAMPLE 10

2-(8-(Cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)-N-hydroxyacetamide

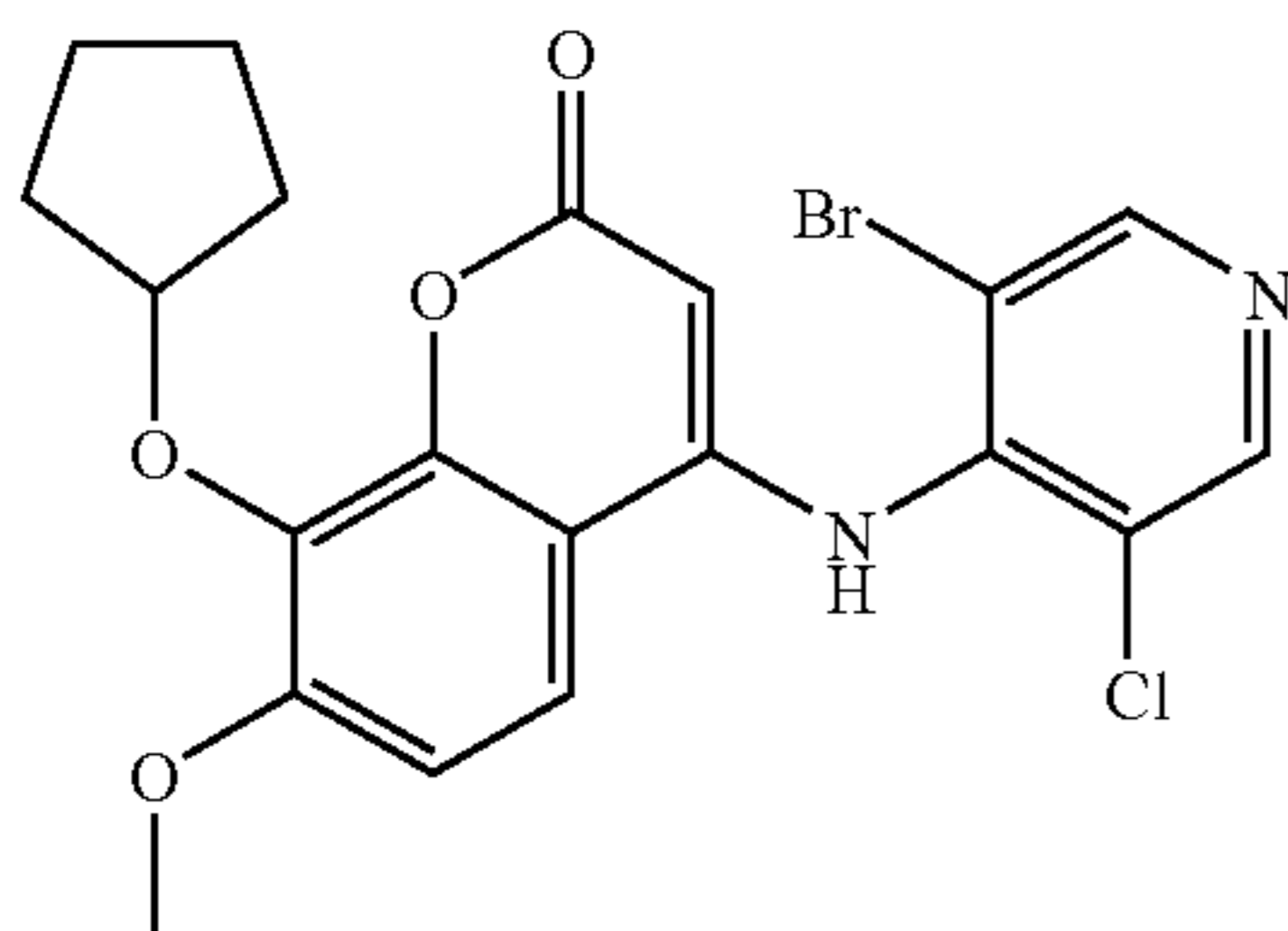


Hydroxylamine (0.5 mL, 50% water, 8.2 mmol) was added to a solution of ethyl 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)acetate (40 mg, 0.11 mmol, Example 8) and ethanol (0.5 mL) and stirred vigorously. After 6 h, the precipitate was filtered, washed with 65% ethanol (2 mL), and dried to give 2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)-N-hydroxyacetamide: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.77 (s, 1H), 8.97 (s, 1H), 7.93 (t, 1H), 7.71 (d, 1H), 7.07 (d, 1H), 4.90 (s, 1H), 4.80 (m, 1H), 3.86 (s, 3H), 3.77 (d, 2H), 1.90-1.46 (m, 8H); MS (ESI): 348.9.

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## EXAMPLE 11

4-(3-Bromo-5-chloropyridin-4-ylamino)-8-(cyclopentylloxy)-7-methoxy-2H-chromen-2-one



## Step 1

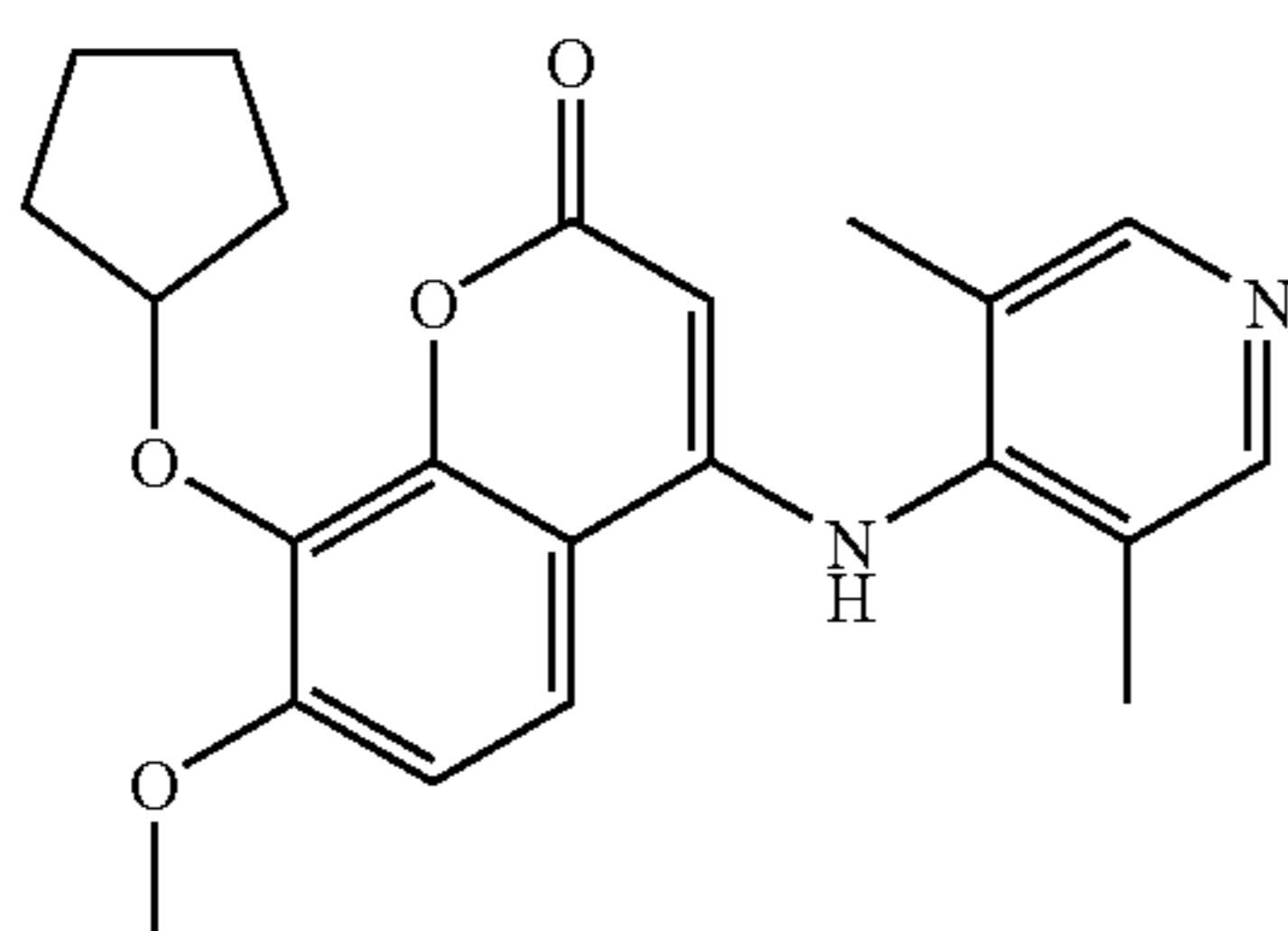
A solution of lithium diisopropylamide (7.0 mL, 2.0 M heptane/THF, 14.0 mmol) was added to a solution of 3,4-dichloropyridine (1.88 g, 12.7 mmol) and anhydrous THF (30 mL) at  $-78^{\circ}\text{C}$ . under  $\text{N}_2$ . After 1 h, bromine (0.71 mL, 14.0 mmol) was added. After an additional 30 min, the reaction was allowed to warm to rt and maintained for 30 min. The mixture was poured into water, extracted with EtOAc, dried, filtered, concentrated, and purified by silica gel chromatography (0 $\rightarrow$ 30% EtOAc/hexanes) to give 2-bromo-3,4-dichloropyridine after recrystallization from methanol. MS (ESI): 225.9.

## Step 2

Sodium hydride (7 mg, 60%, 0.18 mmol) was added to a solution of 4-amino-8-(cyclopentylloxy)-7-methoxy-2H-chromen-2-one (77 mg, 0.28 mmol, Example 3, Step 1) and anhydrous DMSO (3 mL) under  $\text{N}_2$ . After 10 min, 3-bromo-4,5-dichloropyridine (69 mg, 0.31 mmol) was added, and the reaction was stirred for 20 h, poured into brine, and extracted with EtOAc. The organic extract was dried, filtered, concentrated, and purified by reverse-phase HPLC (20 $\rightarrow$ 100% MeCN/ $\text{H}_2\text{O}$ ) to give 4-(3-bromo-5-chloropyridin-4-ylamino)-8-(cyclopentylloxy)-7-methoxy-2H-chromen-2-one:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.54 (s, 1H), 8.91 (s, 1H), 8.84 (s, 1H), 7.95 (d, 1H), 7.21 (d, 1H), 4.85 (m, 1H), 4.59 (s, 1H), 3.92 (s, 3H), 1.87-1.79 (m, 4H), 1.68-1.54 (m, 4H); MS (ESI): 464.7.

## EXAMPLE 12

8-(Cyclopentylloxy)-4-(3,5-dimethylpyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



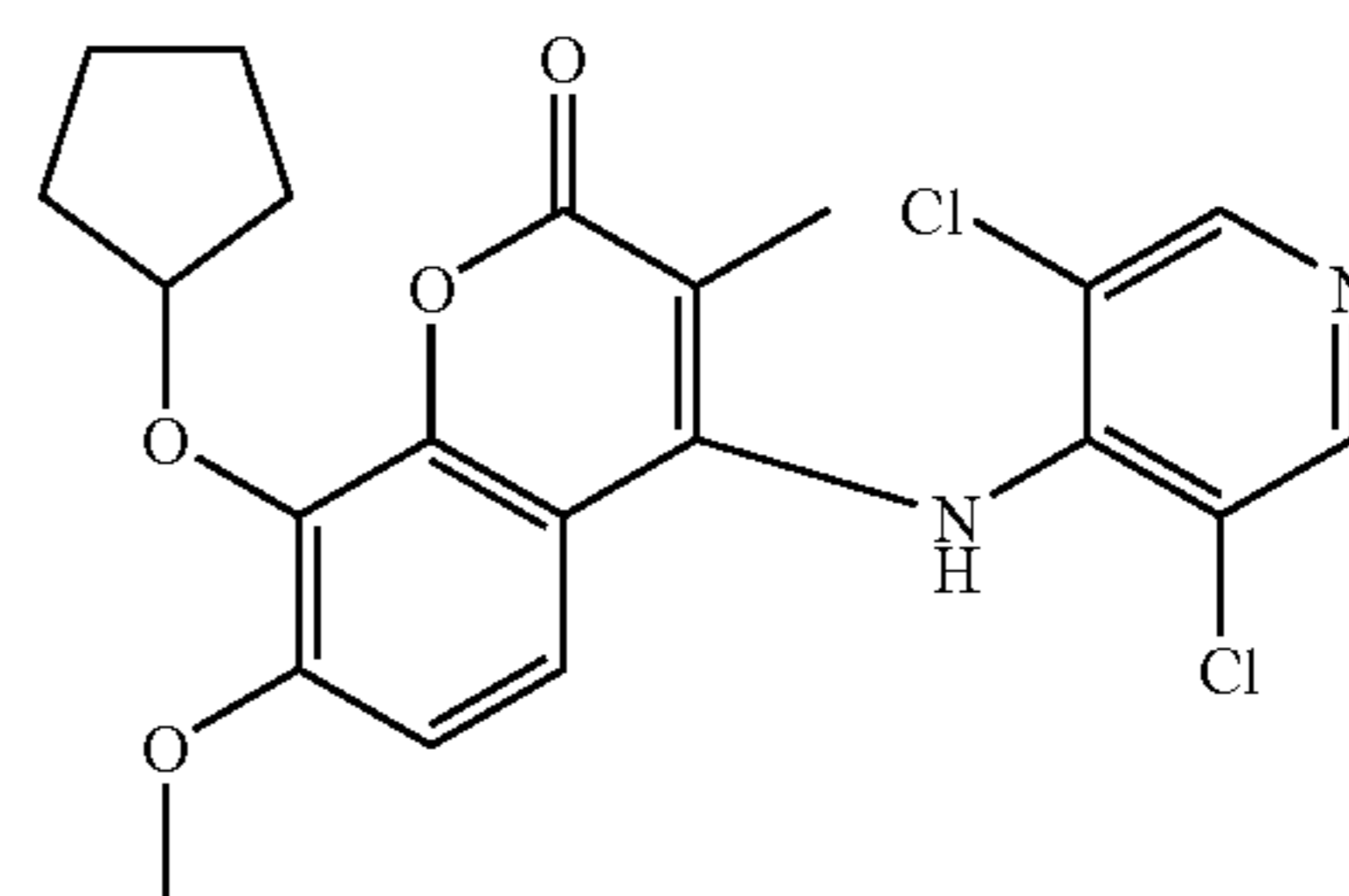
A mixture of 4-amino-8-(cyclopentylloxy)-7-methoxy-2H-chromen-2-one (0.176 g, 0.640 mmol, Example 3, Step 1),

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4-bromo-3,5-dimethylpyridine (0.108 g, 0.580 mmol),  $\text{Pd}_2(\text{dba})_3$  (55 mg, 0.06 mmol), 2,2-dicyclohexylphosphorane triisopropylbiphenyl (55 mg, 0.12 mmol), sodium tert-butoxide (67 mg, 0.69 mmol), and dry toluene (3 mL) was heated to  $110^{\circ}\text{C}$ . under  $\text{N}_2$  for 2 h. The mixture was allowed to cool to rt, filtered through Celite, washed with EtOAc, concentrated, and purified by reverse-phase HPLC (20 $\rightarrow$ 100% acetonitrile: water) to give 8-(cyclopentylloxy)-4-(3,5-dimethylpyridin-4-ylamino)-7-methoxy-2H-chromen-2-one:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.10 (s, 1H), 8.43 (s, 2H), 7.93 (d, 1H), 7.17 (d, 1H), 4.83 (m, 1H), 4.29 (s, 1H), 3.90 (s, 3H), 2.15 (s, 6H) 1.86-1.53 (m, 8H); MS (ESI): 380.9.

## EXAMPLE 13

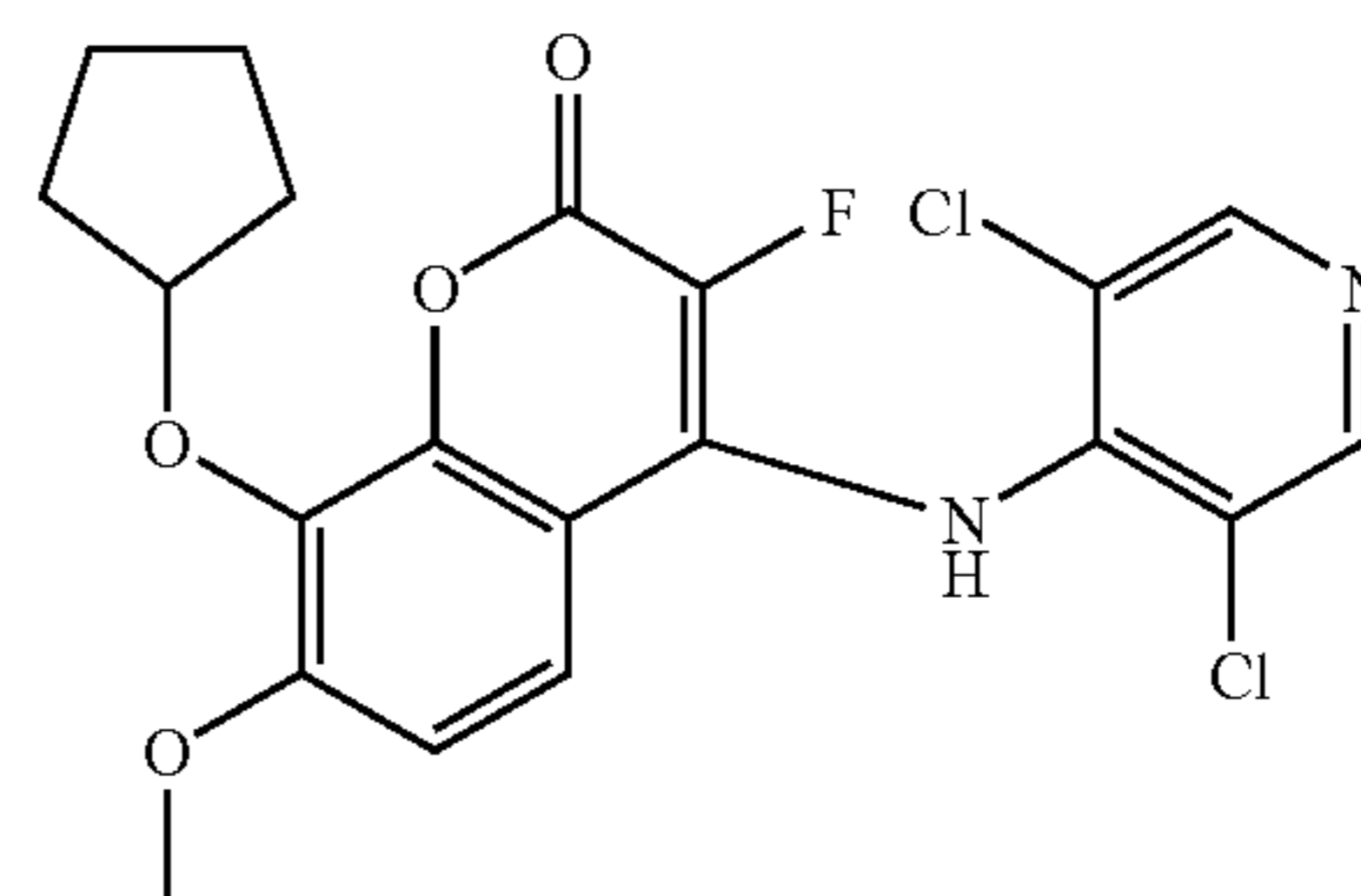
8-(Cyclopentylloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-3-methyl-2H-chromen-2-one



The title compound was prepared from 1-(2,3-dihydroxy-4-methoxyphenyl)propan-1-one following the procedure outlined in Example 3.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.83 (s, 1H), 8.53 (s, 2H), 7.53 (d, 1H), 7.08 (d, 1H), 4.84 (m, 1H), 3.87 (s, 3H), 1.90-1.45 (m, 8H), 1.53 (s, 3H); MS (ESI): 434.8.

## EXAMPLE 14

8-(Cyclopentylloxy)-4-(3,5-dichloropyridin-4-ylamino)-3-fluoro-7-methoxy-2H-chromen-2-one



## Step 1

A mixture of 4-amino-8-(cyclopentylloxy)-7-methoxy-2H-chromen-2-one (100 mg, 0.36 mmol, Example 3, Step 1), Selectfluor (160 mg, 0.45 mmol), and acetonitrile (1.5 mL) were stirred vigorously for 18 h, concentrated, and then purified by silica gel chromatography (7:3 $\rightarrow$ 1:4; hexanes:ethyl acetate) to give 4-amino-8-(cyclopentylloxy)-3-fluoro-7-methoxy-2H-chromen-2-one: MS (ESI): 294.0.

## Step 2

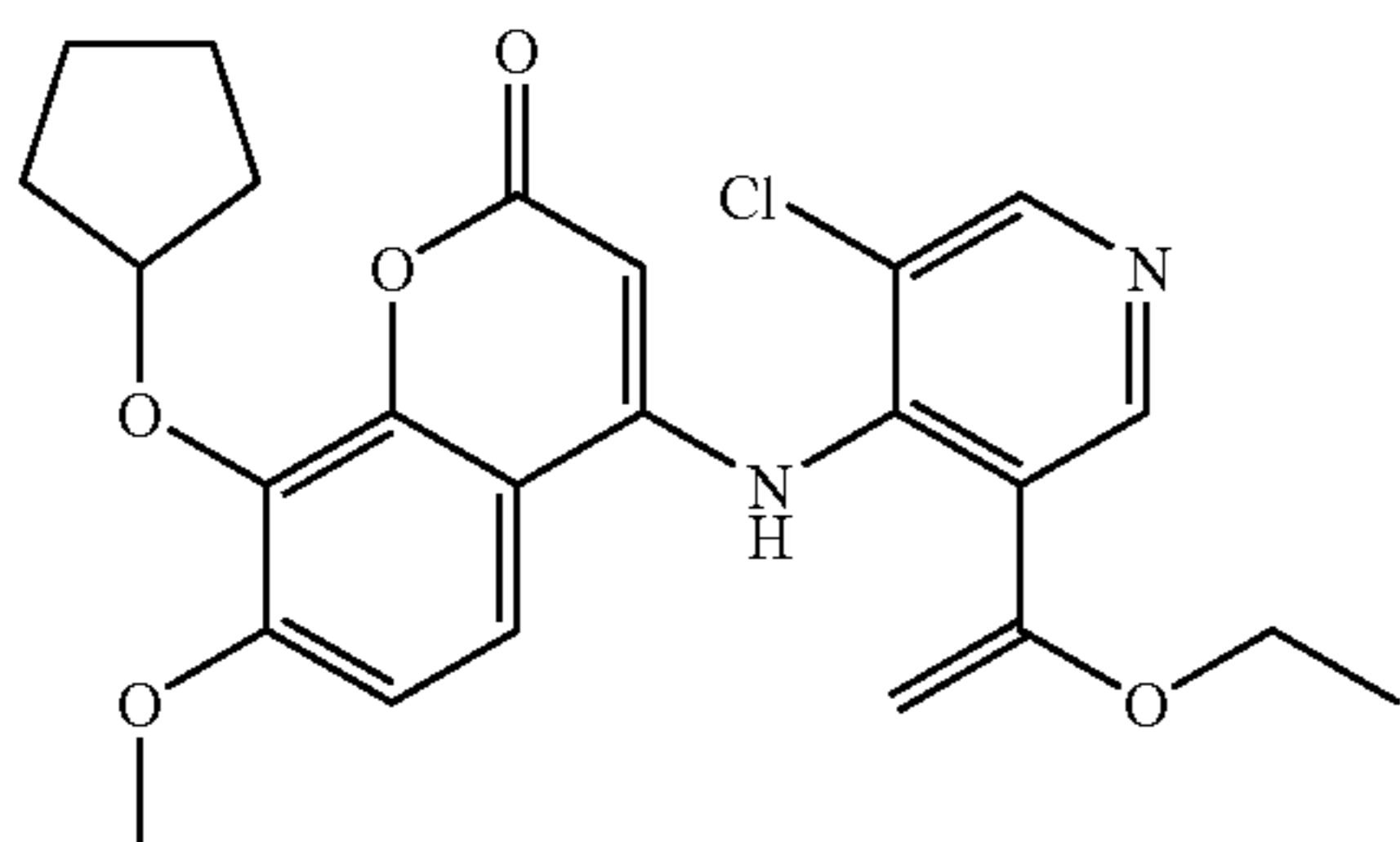
Sodium hydride (40 mg, 60%, 1.0 mmol) was added to a solution of 4-amino-8-(cyclopentylloxy)-3-fluoro-7-meth-

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oxy-2H-chromen-2-one (95 mg, 0.32 mmol), 3,4,5-trichloropyridine (118 mg, 0.65 mmol), and DMSO (3 mL) at rt under N<sub>2</sub>. After 1.5 h, the reaction was heated at 50° C. for 2 h and then 70° C. for 2 h. The reaction was allowed to cool to rt, poured into 1M KH<sub>2</sub>PO<sub>4</sub> (30 mL) and extracted with ethyl acetate (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (7:3→0:1; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-3-fluoro-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.36 (s, 1H), 8.70 (s, 2H), 7.90 (d, 1H), 7.25 (d, 1H), 4.84 (m, 1H), 3.90 (s, 3H), 1.90-1.45 (m, 8H); MS (ESI): 438.8.

## EXAMPLE 15

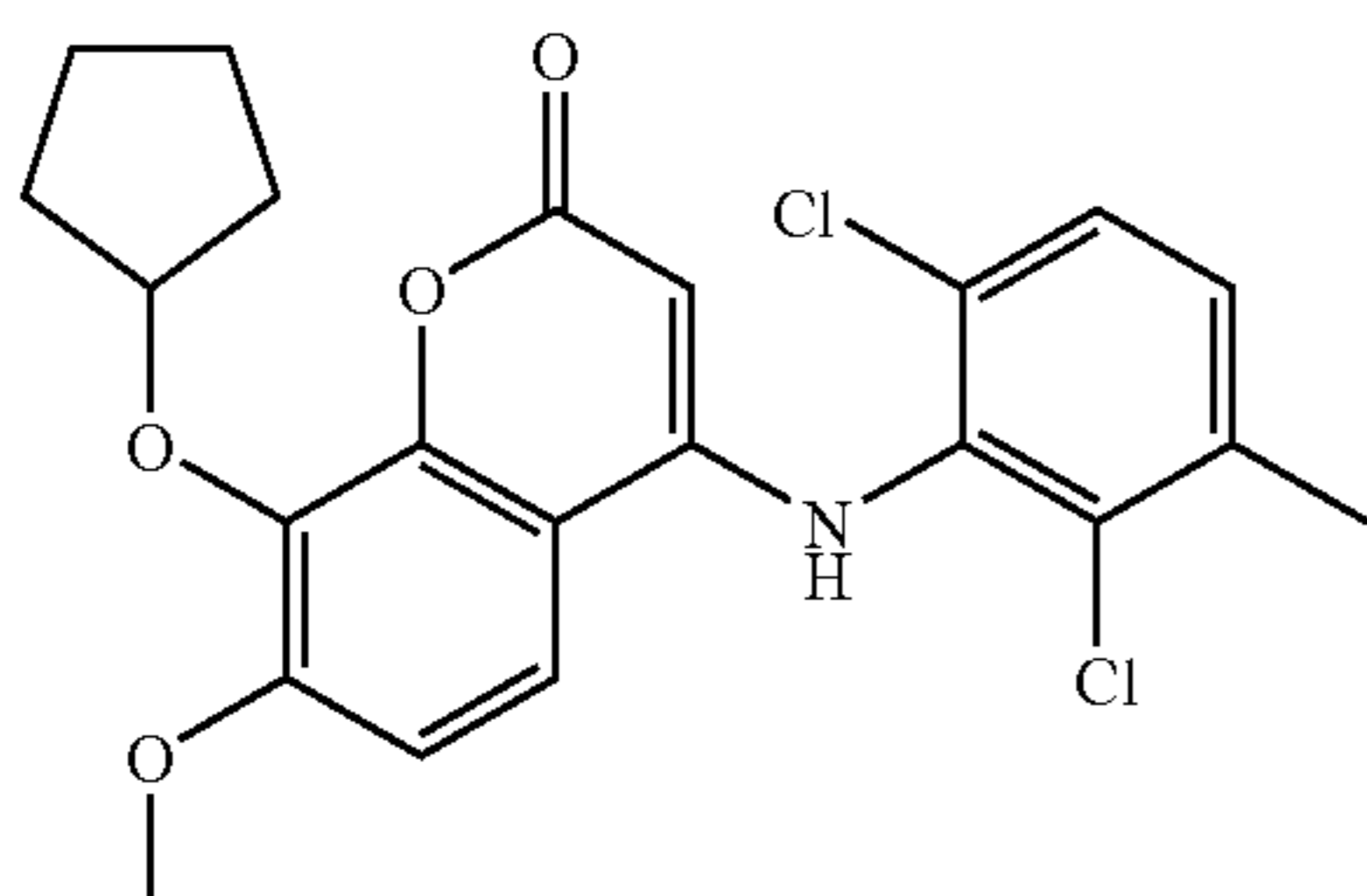
4-(3-Chloro-5-(1-ethoxyvinyl)pyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one



A mixture of 4-(3-bromo-5-chloropyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (0.206 g, 0.441 mmol, Example 11), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (31 mg, 0.044 mmol), tributyl(1-ethoxyvinyl)tin (0.20 mL, 0.57 mmol), and toluene (5 mL) was heated at 80° C. under N<sub>2</sub> for 4 h. After allowing to cool to rt, the mixture was filtered through Celite and washed with EtOAc. The filtrate was washed with aqueous KF, dried, filtered, concentrated, and purified by silica gel chromatography (0→50% EtOAc/hexanes) to give 4-(3-chloro-5-(1-ethoxyvinyl)pyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.19 (s, 1H), 8.80 (s, 1H), 8.65 (s, 1H), 7.94 (d, 1H), 7.16 (d, 1H), 4.83 (m, 1H), 4.53 (m, 2H), 4.41 (d, 1H), 3.90 (s, 3H), 3.61 (m, 2H), 1.85-1.52 (m, 8H), 0.89 (t, 3H); MS (ESI): 457.1.

## EXAMPLE 16

8-(Cyclopentyloxy)-4-(2,6-dichloro-3-methylphenylamino)-7-methoxy-2H-chromen-2-one



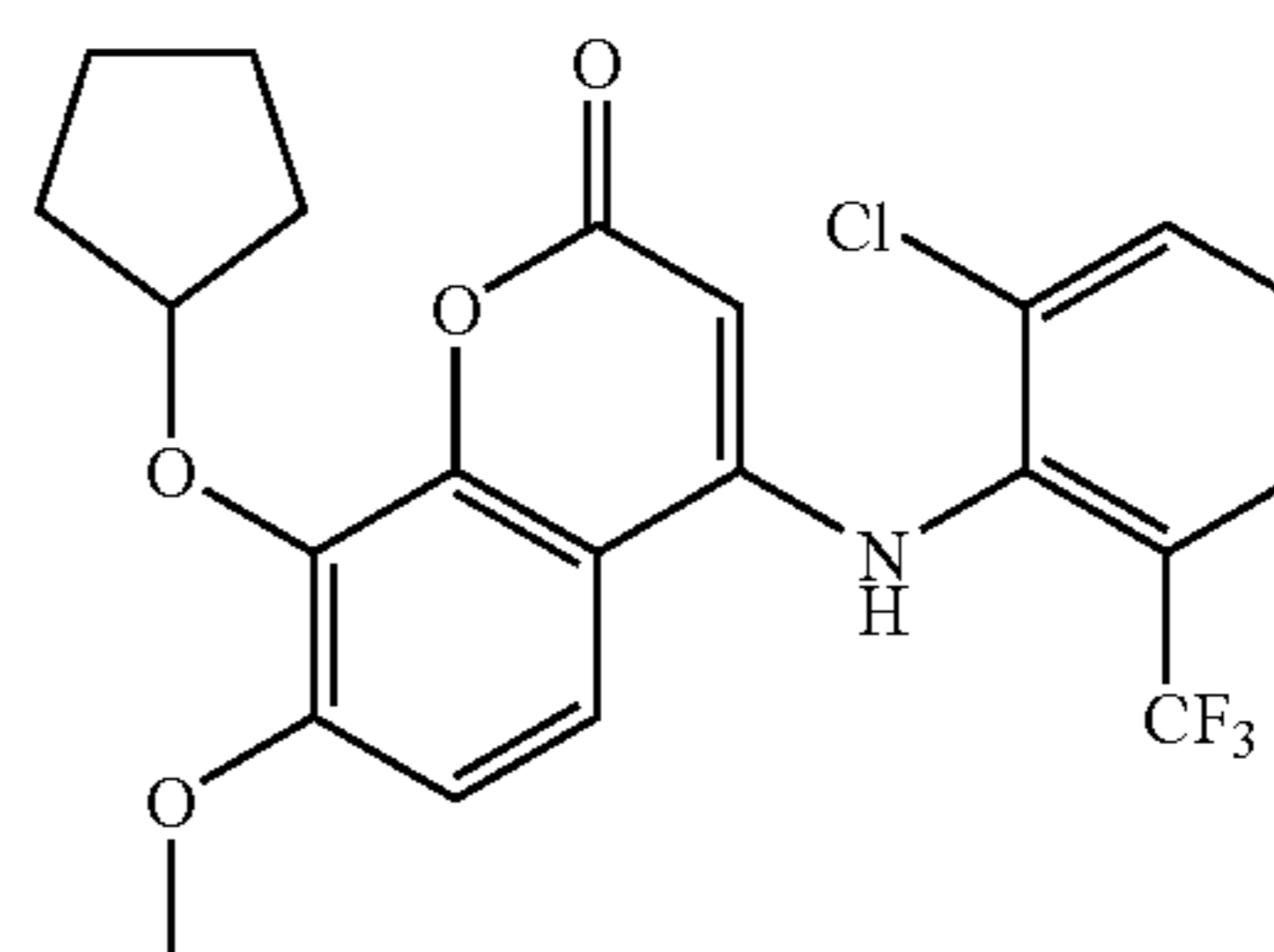
Potassium t-butoxide (35 mg, 0.3 mmol) was added to a solution of 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-

## 40

chromen-2-one (29 mg, 0.1 mmol, Example 7, Step 1), 2,6-dichloro-3-methylaniline (26 mg, 0.15 mmol), and DMSO (1 mL). After 14 h, the reaction was poured into 1MKH<sub>2</sub>PO<sub>4</sub> (20 mL), and extracted with ethyl acetate (20 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (4:1→0:1; hexanes:ethyl acetate) to give 8-(cyclopentyloxy)-4-(2,6-dichloro-3-methylphenylamino)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.38 (s, 1H), 7.95 (d, 1H), 7.58 (d, 1H), 7.48 (d, 1H), 7.18 (d, 1H), 4.82 (m, 1H), 4.33 (s, 1H), 3.90 (s, 3H), 2.40 (s, 3H), 1.90-1.45 (m, 8H); MS (ESI): 433.9.

## EXAMPLE 17

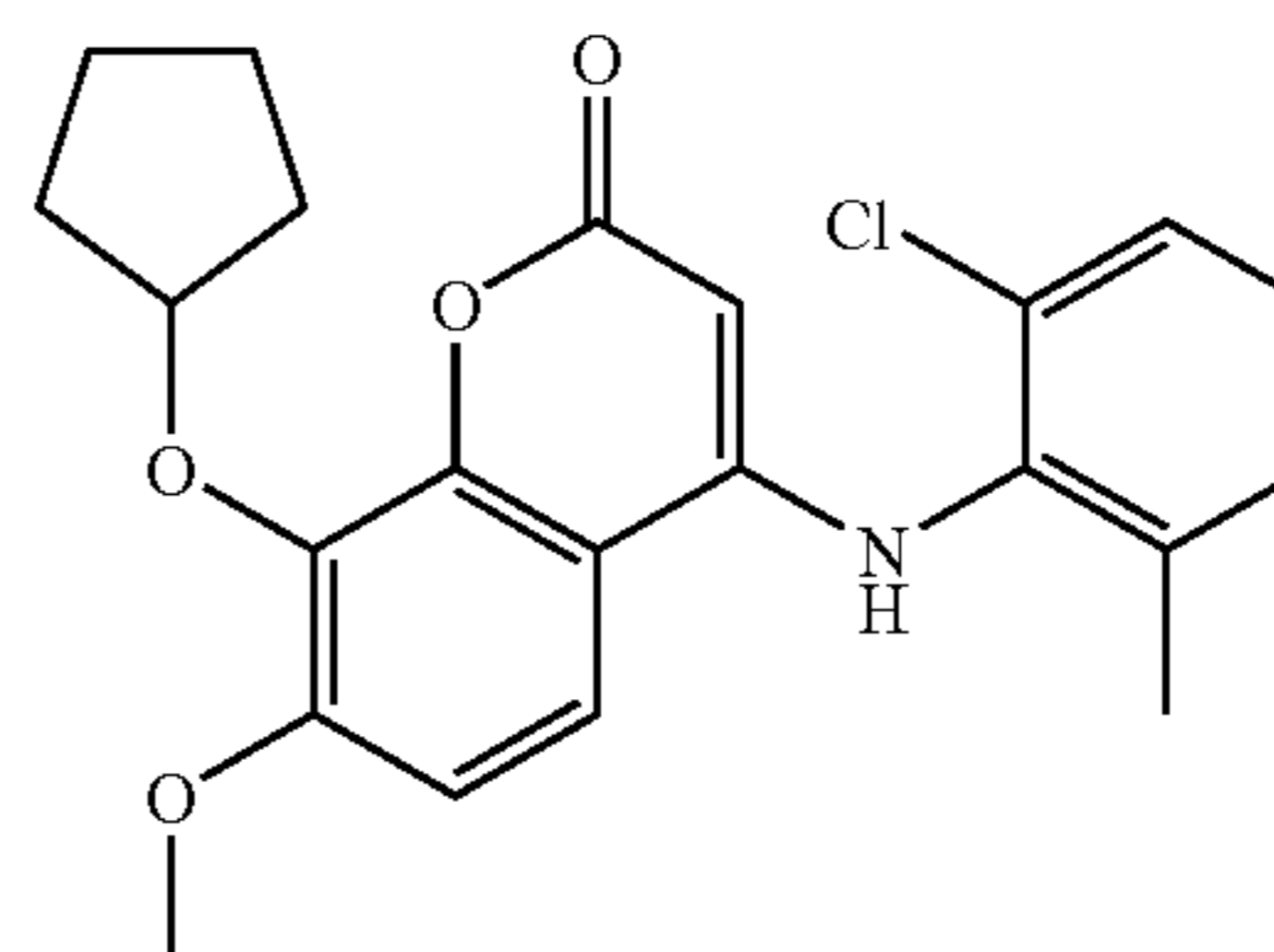
4-(2-Chloro-6-(trifluoromethyl)phenylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 2-chloro-6-(trifluoromethyl)aniline and 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one following the procedure outlined in Example 16. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.34 (s, 1H), 8.05 (d, 1H), 7.93 (d, 1H), 7.91 (d, 1H), 7.71 (t, 1H), 7.18 (d, 1H), 4.82 (m, 1H), 4.29 (s, 1H), 3.90 (s, 3H), 1.90-1.45 (m, 8H); MS (ESI): 453.9.

## EXAMPLE 18

4-(2-Chloro-6-methylphenylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one

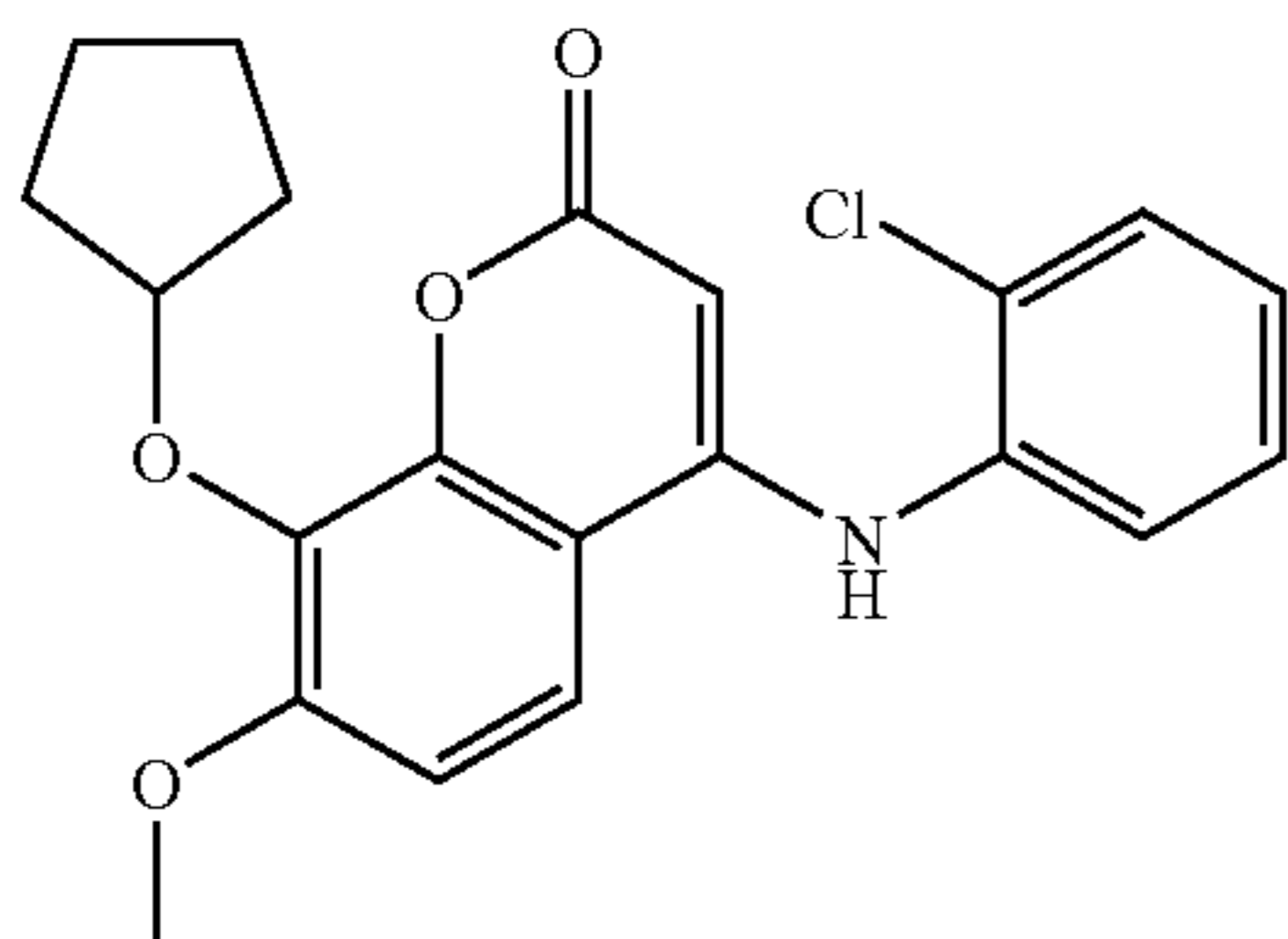


The title compound was prepared from 2-chloro-6-methylaniline and 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one following the procedure outlined in Example 16. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.18 (s, 1H), 7.94 (d, 1H), 7.50 (dd, 1H), 7.42-7.34 (m, 2H), 7.16 (d, 1H), 4.82 (m, 1H), 4.28 (s, 1H), 3.90 (s, 3H), 2.21 (s, 3H), 1.90-1.45 (m, 8H); MS (ESI): 399.9.

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## EXAMPLE 19

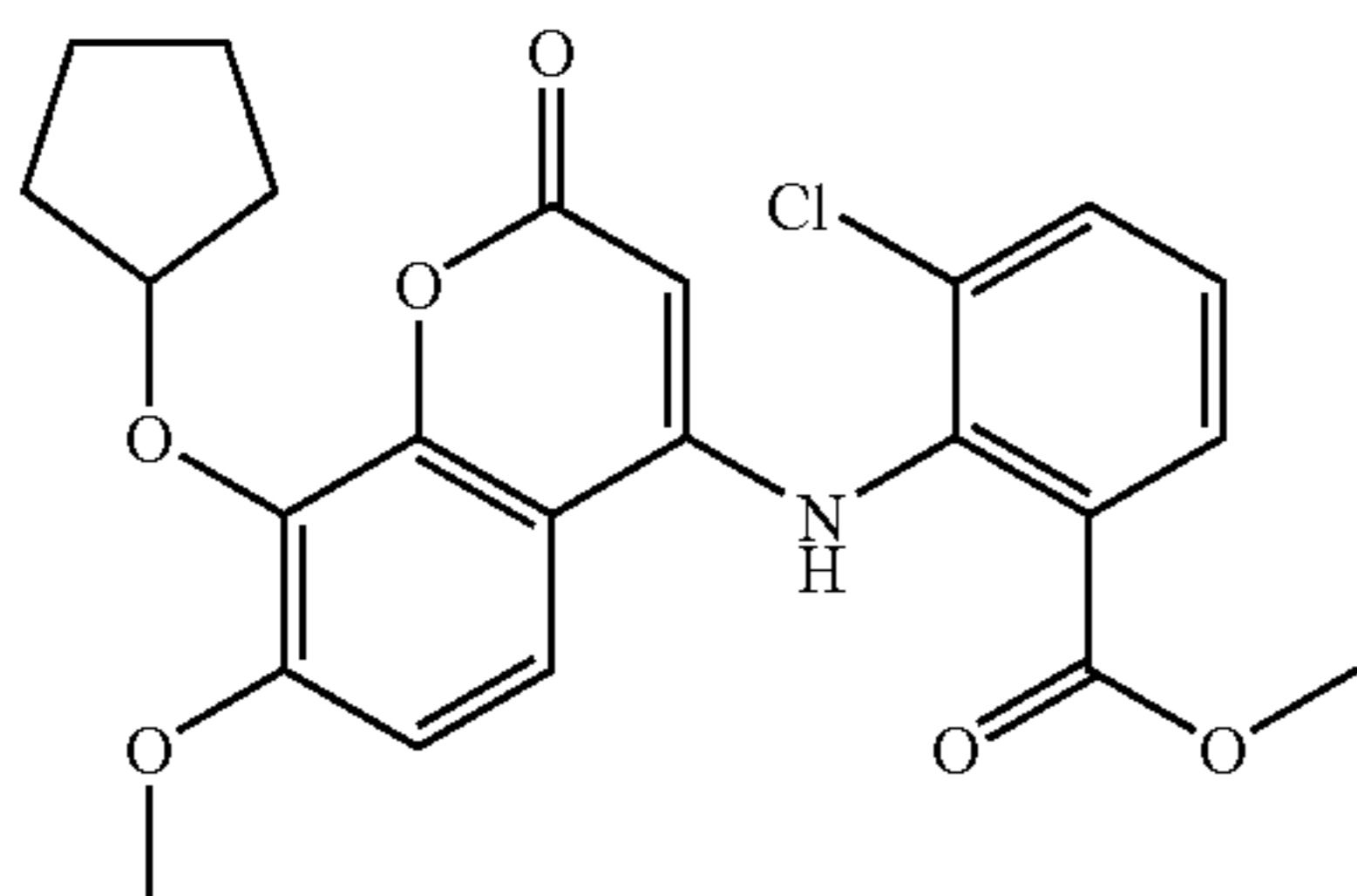
4-(2-Chlorophenylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 2-chloroaniline and 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one following the procedure outlined in Example 16. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.28 (s, 1H), 7.93 (d, 1H), 7.66 (d, 1H), 7.51-7.40 (m, 3H), 7.15 (d, 1H), 4.83 (m, 1H), 4.50 (s, 1H), 3.90 (s, 3H), 1.90-1.45 (m, 8H); MS (ESI): 385.9.

## EXAMPLE 20

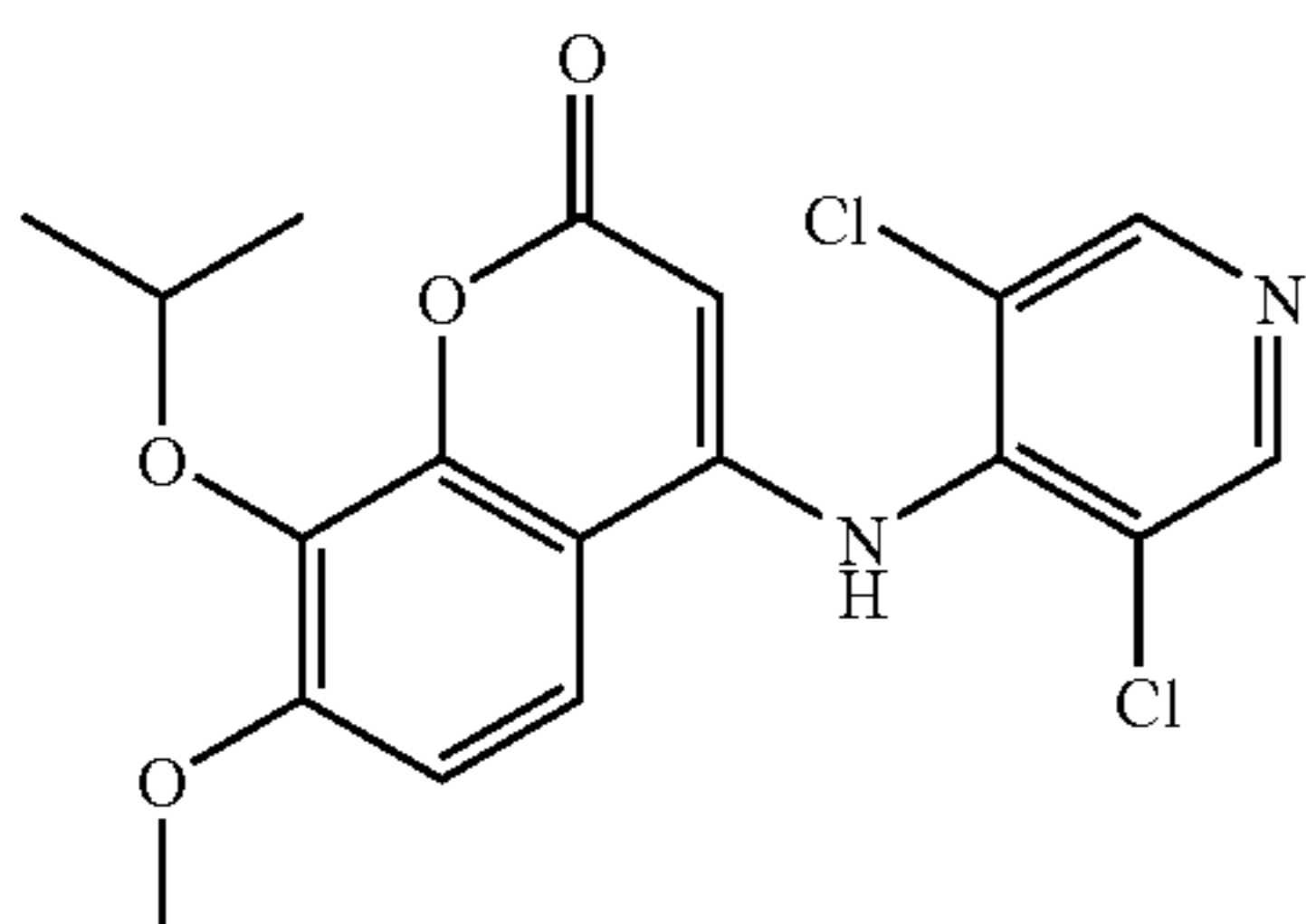
Methyl 3-chloro-2-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)benzoate



The title compound was prepared from methyl 2-amino-3-chlorobenzoate and 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one following the procedure outlined in Example 16 (30 min rxn time). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.29 (s, 1H), 7.92 (m, 3H), 7.59 (t, 1H), 7.19 (d, 1H), 4.85 (m, 1H), 4.40 (s, 1H), 3.92 (s, 3H), 3.70 (s, 3H), 1.90-1.50 (m, 8H); MS (ESI): 443.9.

## EXAMPLE 21

4-(3,5-Dichloropyridin-4-ylamino)-8-isopropoxy-7-methoxy-2H-chromen-2-one



The title compound was prepared from 2-bromopropane and 1-(2,3-dihydroxy-4-methoxyphenyl)ethanone following

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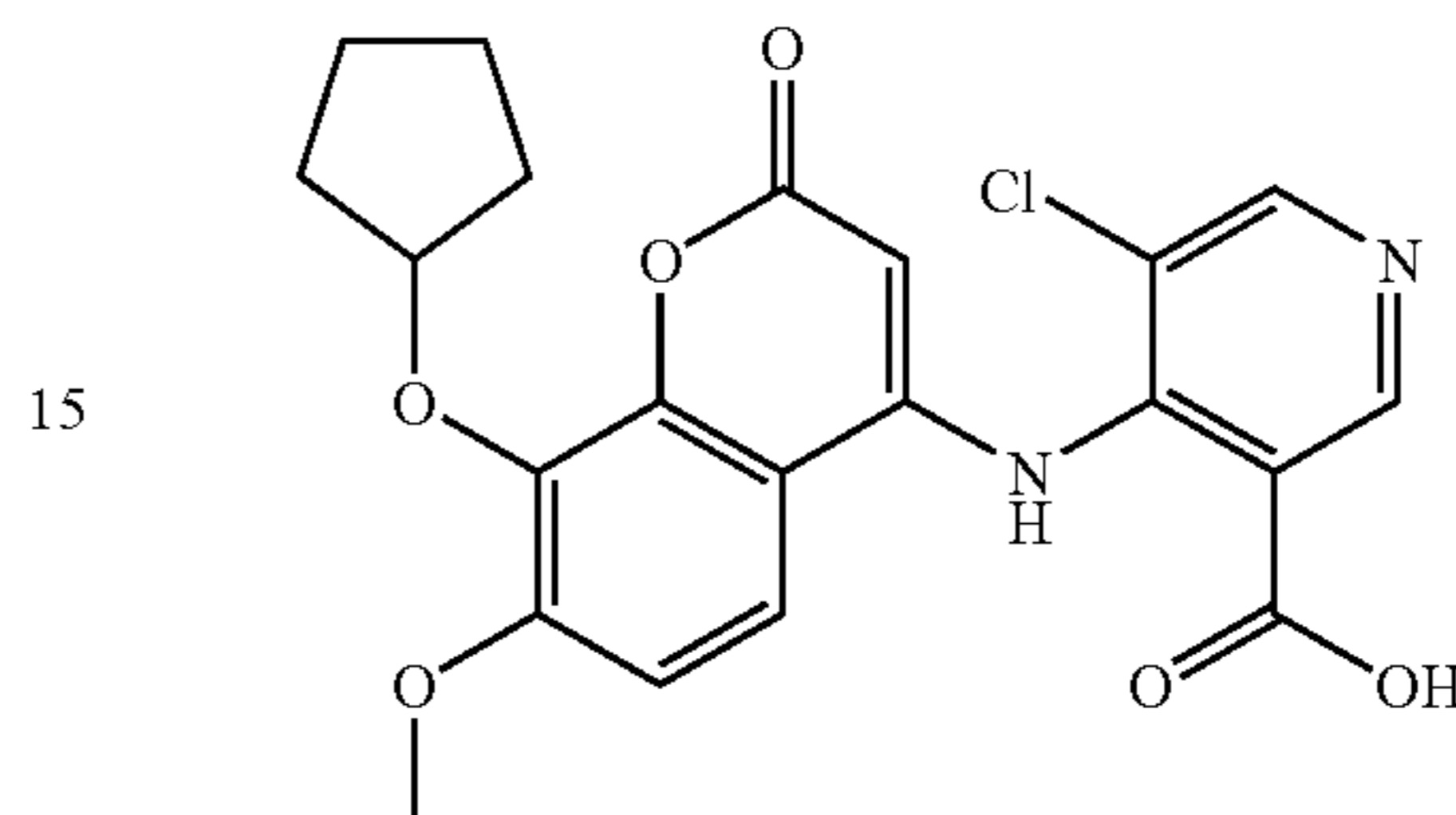
the procedure outlined in Example 3. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.45 (s, 1H), 8.76 (s, 2H), 7.88 (d, 1H), 7.15 (d, 1H), 4.58 (s, 1H), 4.35 (m, 1H), 3.86 (s, 3H), 1.19 (d, 6H); MS (ESI): 394.8.

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## EXAMPLE 22

5-Chloro-4-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)nicotinic acid

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## Step 1

Carbon monoxide was bubbled through a mixture of 4-(3-bromo-5-chloropyridin-4-ylamino)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (0.240 g, 0.514 mmol, Example 11), Pd(OAc)<sub>2</sub> (11 mg, 0.051 mmol), DPPP (21 mg, 0.051 mmol), triethylamine (0.22 mL, 1.5 mmol), methanol (1 mL), and anhydrous DMF (4 mL). The reaction was heated at 80° C. for 2 d under an atmosphere of CO and then allowed to cool to rt. The mixture was filtered through Celite, washed with EtOAc, and concentrated to give methyl 5-chloro-4-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)nicotinate.

## Step 2

Lithium hydroxide (1 mL, 1M, 1 mmol) was added to a solution of methyl 5-chloro-4-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)nicotinate, MeOH (0.8 mL), and THF (1.2 mL). The mixture was stirred for 3 h, quenched with 1N HCl (3 mL), and extracted with EtOAc. The organic extract was dried, filtered, concentrated and purified by reverse-phase HPLC (25→100% MeCN/H<sub>2</sub>O) to give 5-chloro-4-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)nicotinic acid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 8.97 (s, 1H), 8.92 (s, 1H), 7.85 (d, 1H), 7.19 (d, 1H), 4.83 (m, 1H), 4.74 (s, 1H), 3.90 (s, 3H) 1.85-1.54 (m, 8H); MS (ESI): 430.9.

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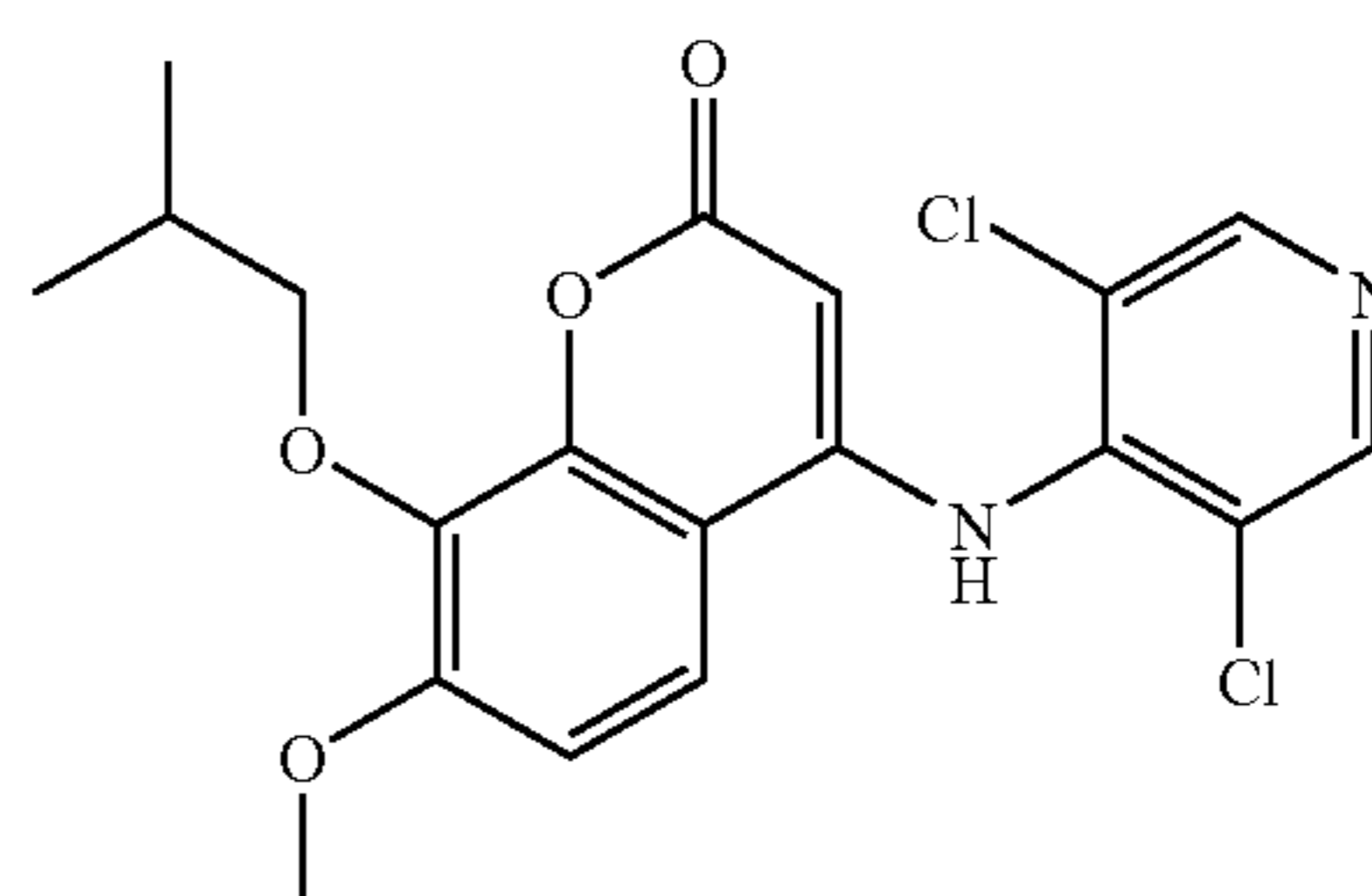
## EXAMPLE 23

4-(3,5-Dichloropyridin-4-ylamino)-8-isobutoxy-7-methoxy-2H-chromen-2-one

50

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60



65

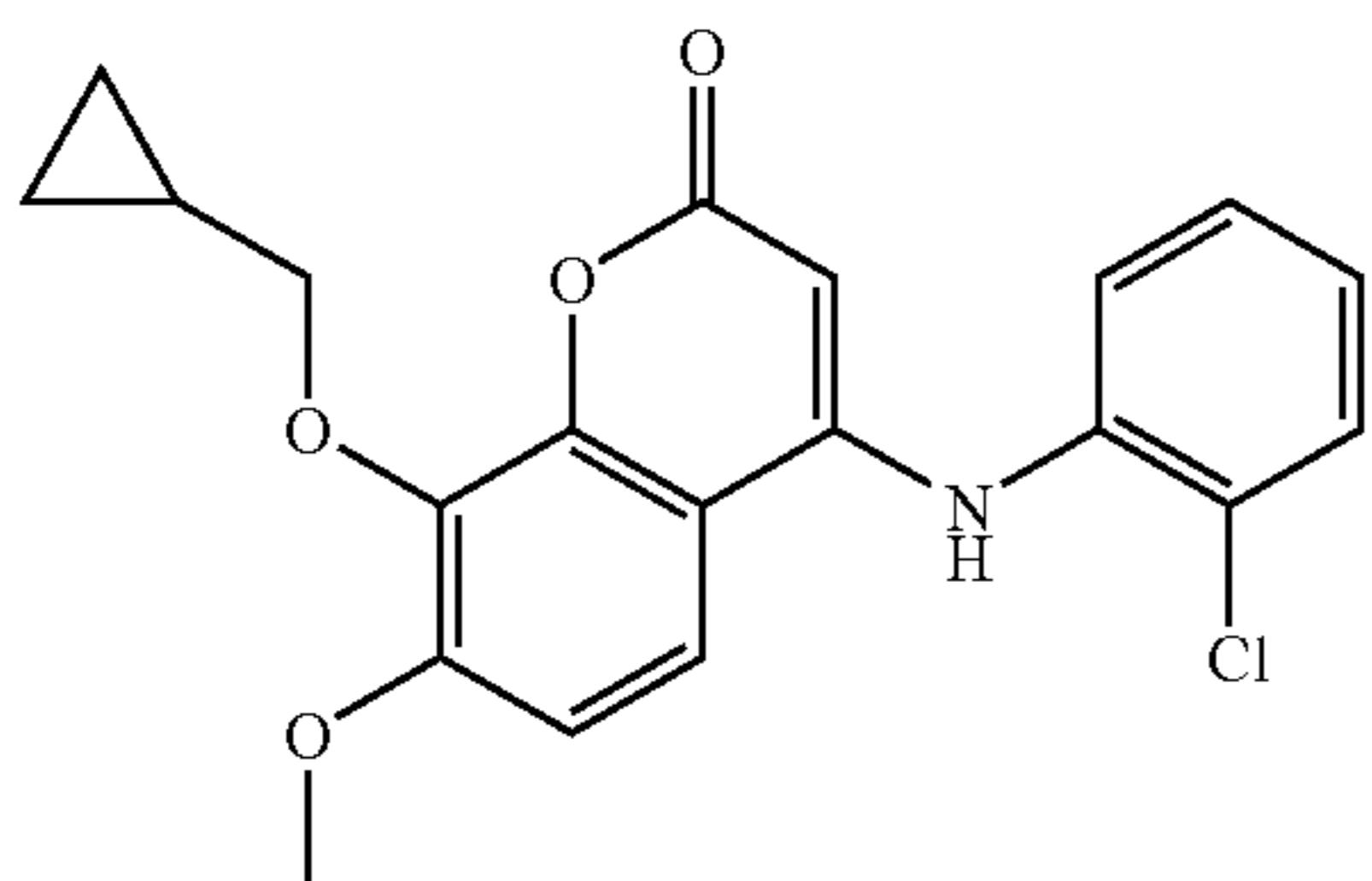
The title compound was prepared from 1-bromo-2-methylpropane and 1-(2,3-dihydroxy-4-methoxyphenyl)ethanone following the procedure outlined in Example 3. <sup>1</sup>H NMR

## 43

(400 MHz, DMSO- $d_6$ ):  $\delta$  9.52 (s, 1H), 8.80 (s, 2H), 7.93 (d, 1H), 7.19 (d, 1H), 4.62 (s, 1H), 3.91 (s, 3H), 3.76 (d, 2H), 1.97 (m, 1H), 0.99 (d, 6H); MS (ESI): 408.9.

## EXAMPLE 24

4-(2-Chlorophenylamino)-8-(cyclopropylmethoxy)-7-methoxy-2H-chromen-2-one



## Step 1

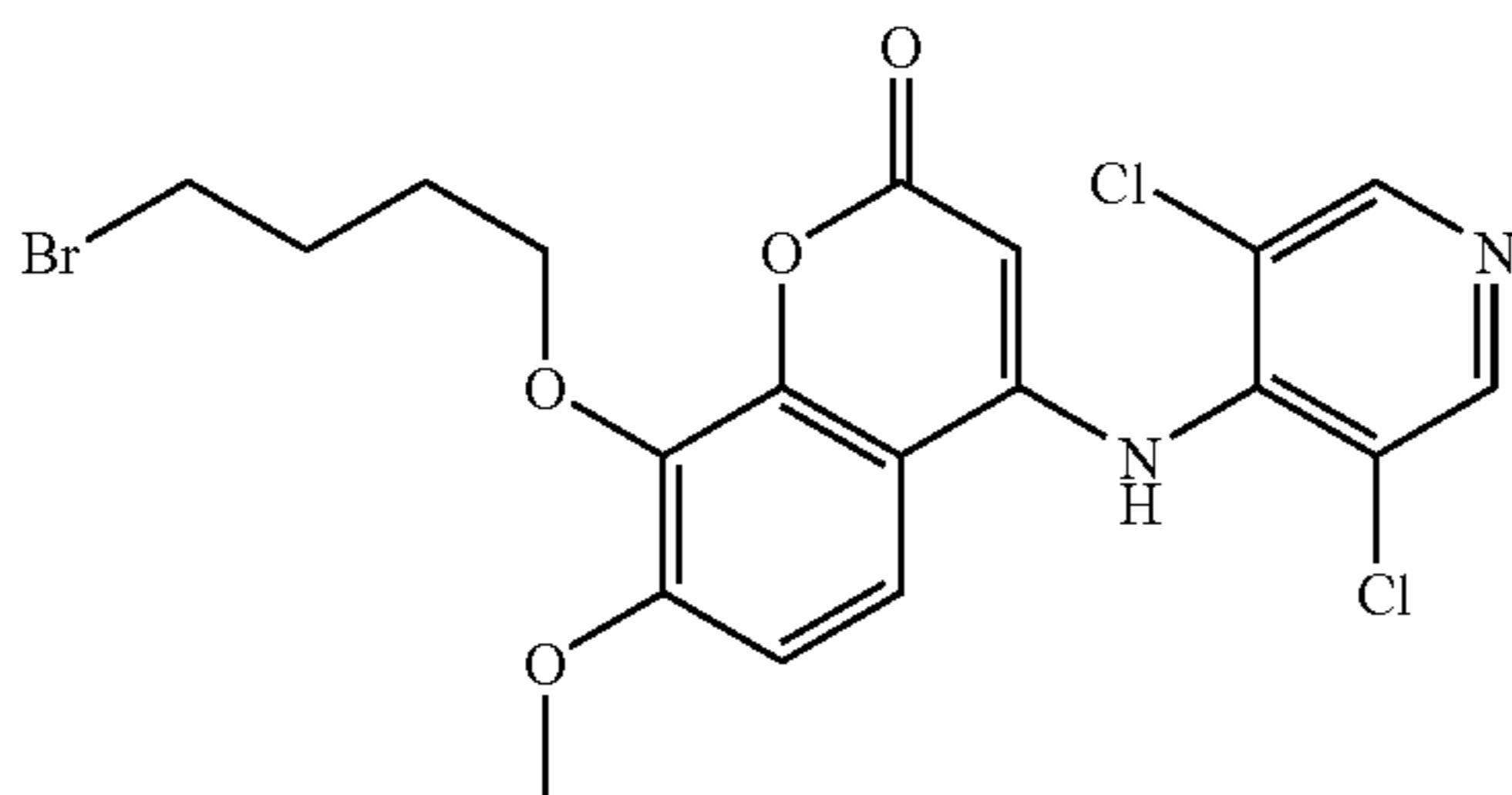
8-(Cyclopropylmethoxy)-7-methoxy-2-oxo-2H-chromen-4-yl 4-methylbenzenesulfonate was prepared from 8-(cyclopropylmethoxy)-4-hydroxy-7-methoxy-2H-chromen-2-one (intermediate of Example 5) following the procedure outlined in Example 1, Step 3. MS (ESI): 416.8.

## Step 2

The title compound was prepared from 2-chloroaniline and 8-(cyclopropylmethoxy)-7-methoxy-2-oxo-2H-chromen-4-yl 4-methylbenzenesulfonate following the procedure outlined in Example 16.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.28 (s, 1H), 7.94 (d, 1H), 7.66 (d, 1H), 7.51-7.40 (m, 3H), 7.15 (d, 1H), 4.51 (s, 1H), 3.90 (s, 3H), 3.81 (d, 2H), 1.18 (m, 1H), 0.48 (m, 2H), 0.25 (m, 2H); MS (ESI): 372.0.

## EXAMPLE 25

8-(4-Bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



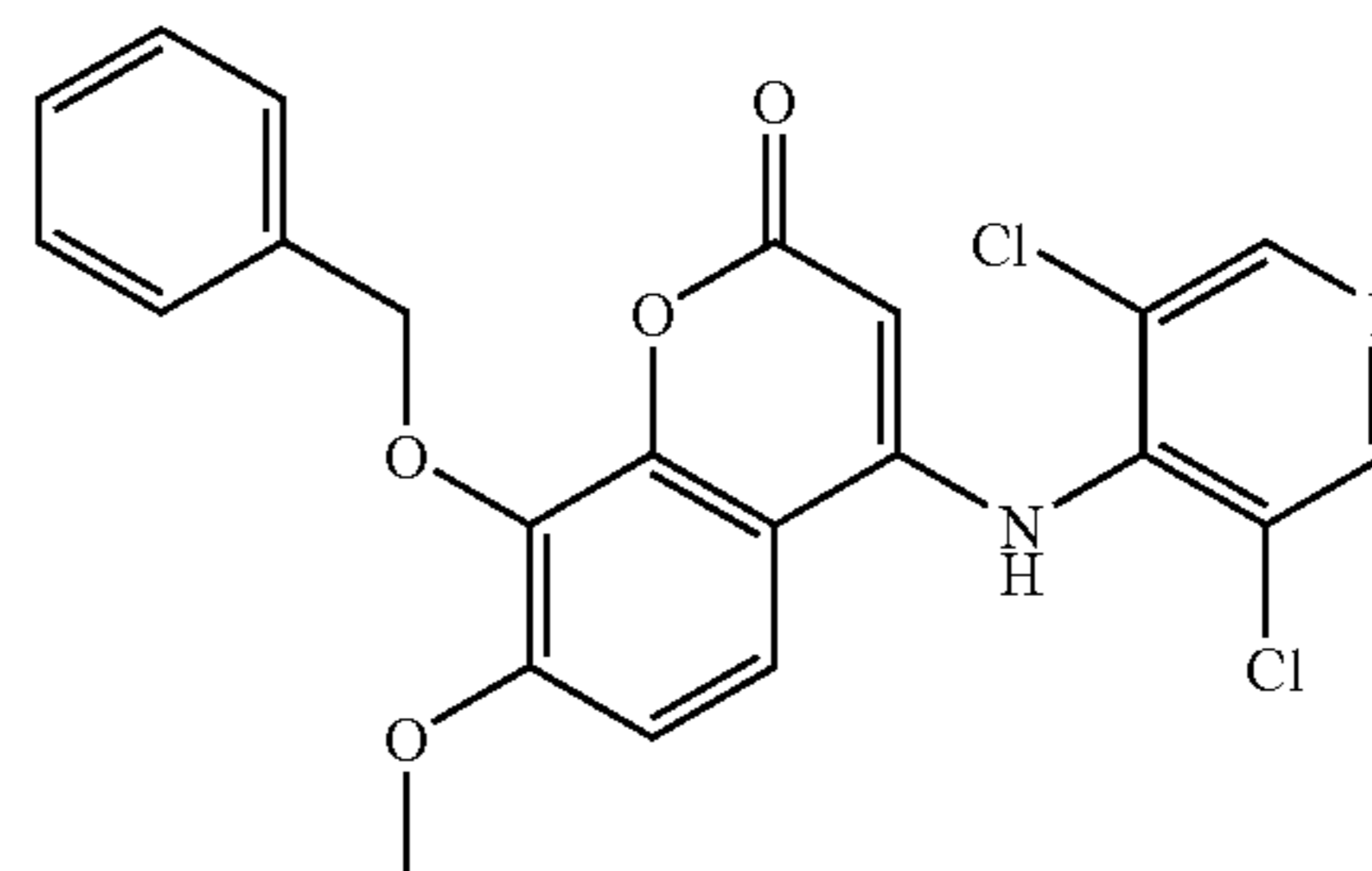
Sodium hydride (31 mg, 0.78 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (111 mg, 0.31 mmol, Example 29) and DMSO (2 mL) at rt under  $\text{N}_2$ . After 5 min, 1,4-dibromobutane (0.05 mL, 0.42 mmol) was added. After 3 h, the reaction was poured into 1M  $\text{KH}_2\text{PO}_4$  (30 mL) and

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extracted with ethyl acetate (40 mL $\times$ 2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (3:2 $\rightarrow$ 1:4; hexanes:ethyl acetate) to give 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.95 (d, 1H), 7.21 (d, 1H), 4.64 (s, 1H), 4.01 (t, 2H), 3.92 (s, 3H), 3.63 (t, 2H), 2.05 (m, 2H), 1.80 (m, 2H); MS (ESI): 486.8.

## EXAMPLE 26

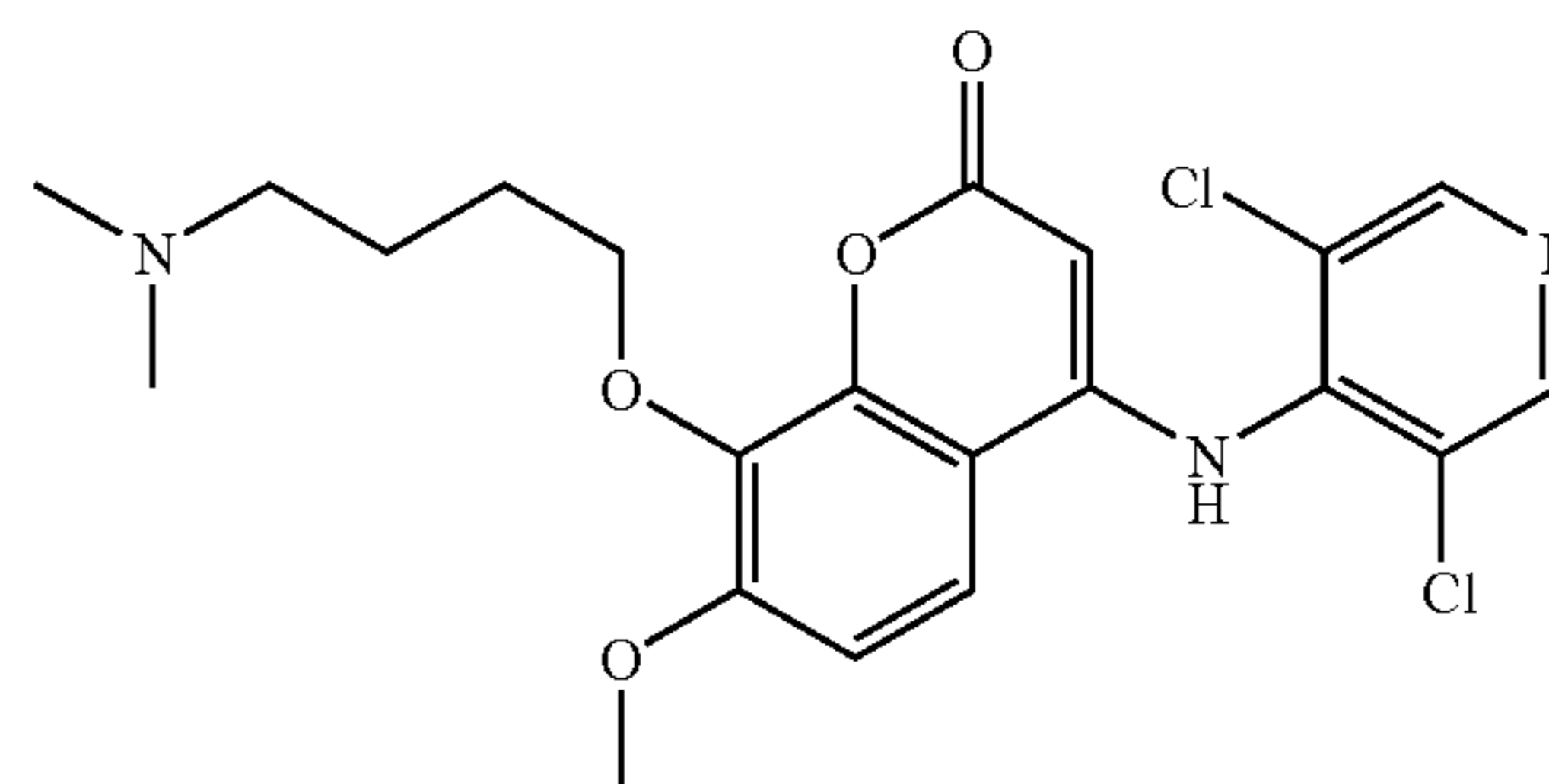
8-(Benzylloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from benzyl bromide and 1-(2,3-dihydroxy-4-methoxyphenyl)ethanone following the procedure outlined in Example 3.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.52 (s, 1H), 8.81 (s, 2H), 7.96 (d, 1H), 7.50 (d, 2H), 7.40-7.29 (m, 3H), 7.22 (d, 1H), 5.05 (s, 2H), 4.65 (s, 1H), 3.94 (s, 3H); MS (ESI): 442.8

## EXAMPLE 27

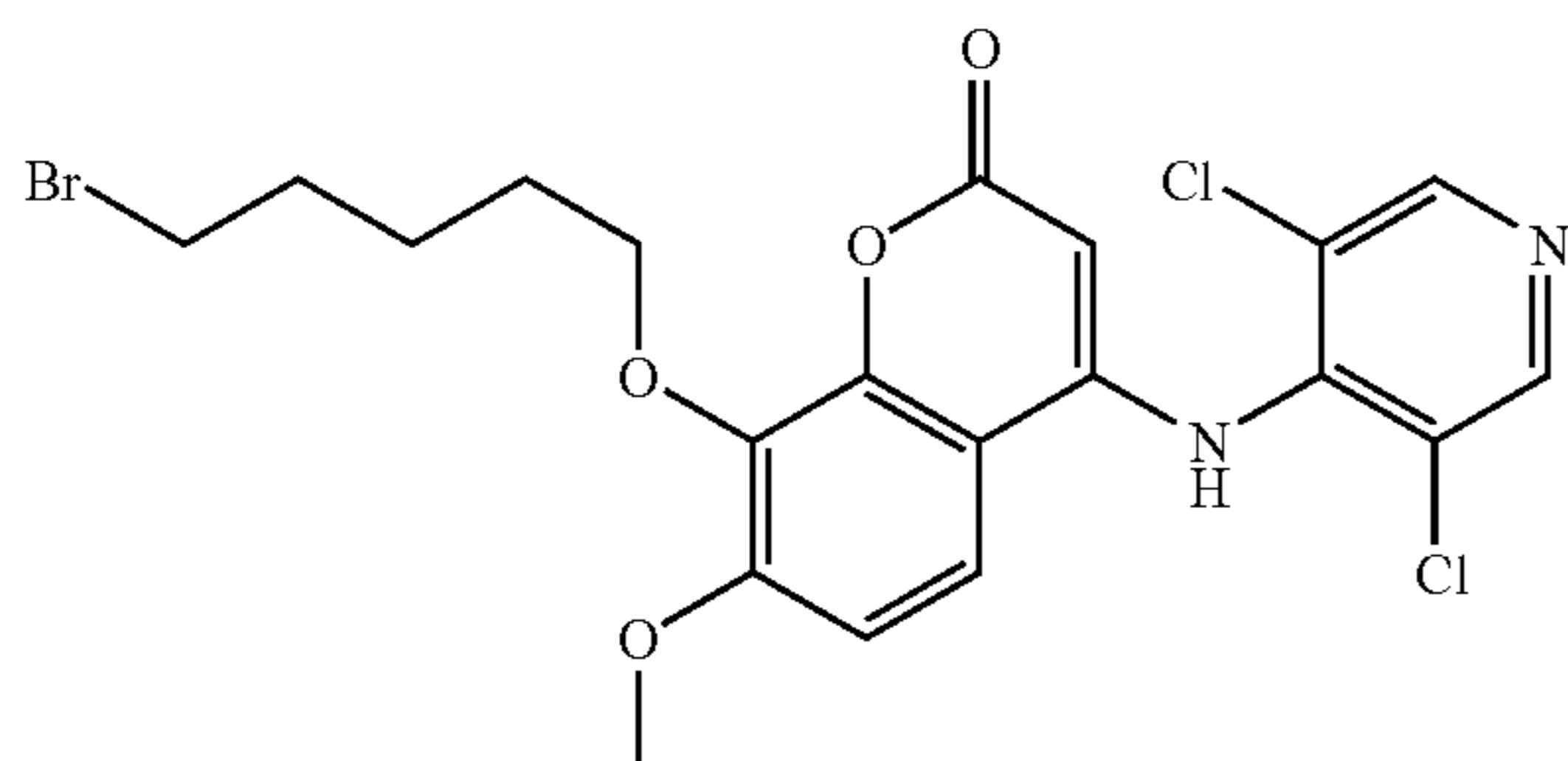
4-(3,5-Dichloropyridin-4-ylamino)-8-(4-(dimethylamino)butoxy)-7-methoxy-2H-chromen-2-one



A solution of dimethylamine (3 mL, 2M THF, 6 mmol) was added to a solution of 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (293 mg, 0.6 mmol, Example 25) and DMSO (6 mL). After 1 h, the reaction was concentrated and purified by reverse-phase HPLC (1:4 $\rightarrow$ 3:2; acetonitrile:water) to give 4-(3,5-dichloropyridin-4-ylamino)-8-(4-(dimethylamino)butoxy)-7-methoxy-2H-chromen-2-one:  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.53 (br s, 1H), 8.58 (s, 2H), 7.87 (d, 1H), 7.07 (d, 1H), 4.22 (br s, 1H), 3.99 (t, 2H), 3.90 (s, 3H), 2.76 (br, 2H), 2.47 (s, 6H), 1.85-1.65 (m, 4H); MS (ESI): 451.9.

**45**  
EXAMPLE 28

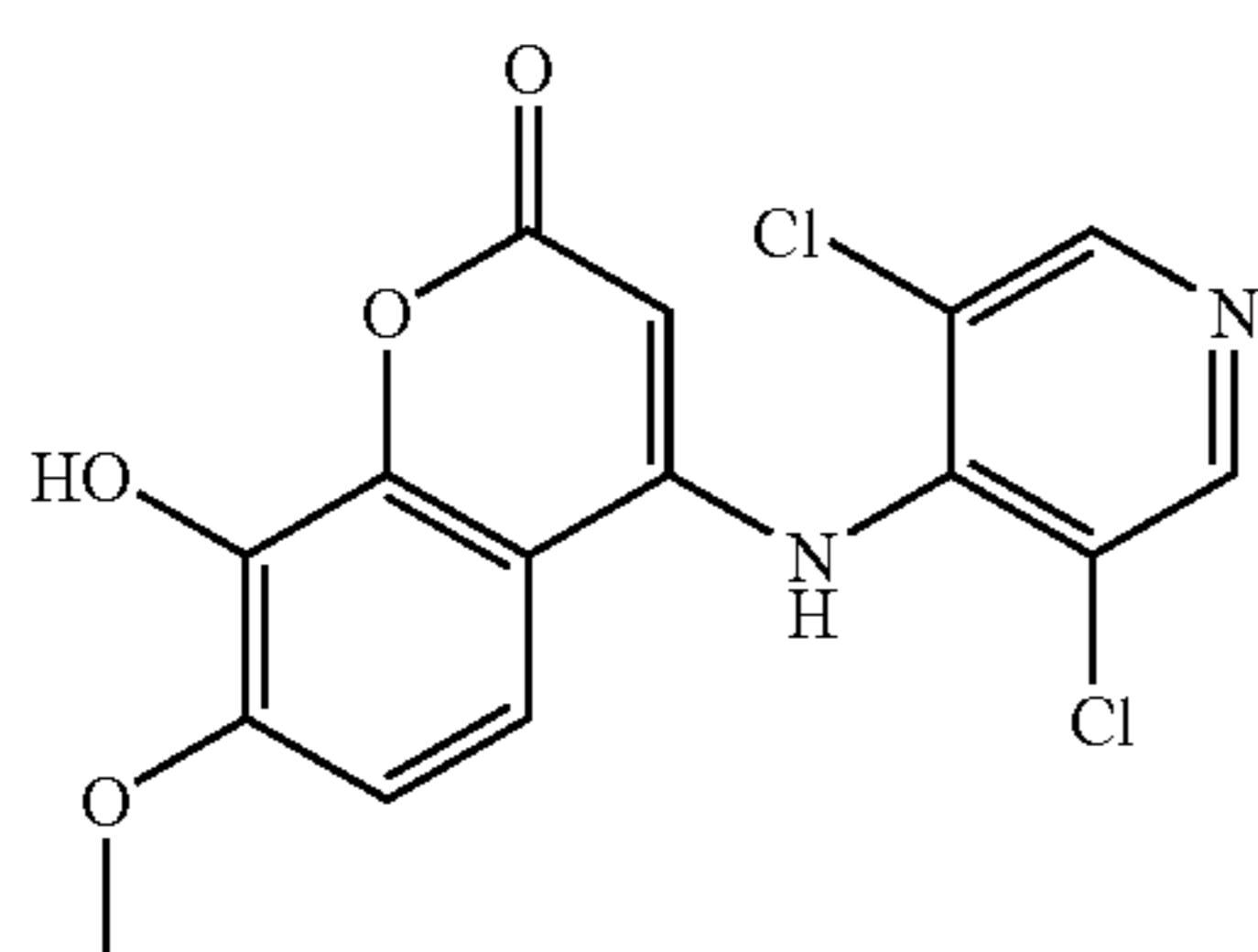
8-(5-Bromopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 1,5-dibromopentane and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 8.83 (s, 2H), 7.96 (d, 1H), 7.22 (d, 1H), 4.66 (s, 1H), 4.01 (t, 2H), 3.94 (s, 3H), 3.57 (t, 2H), 1.88 (m, 2H), 1.72 (m, 2H), 1.62 (m, 2H); MS (ESI): 500.7.

EXAMPLE 29

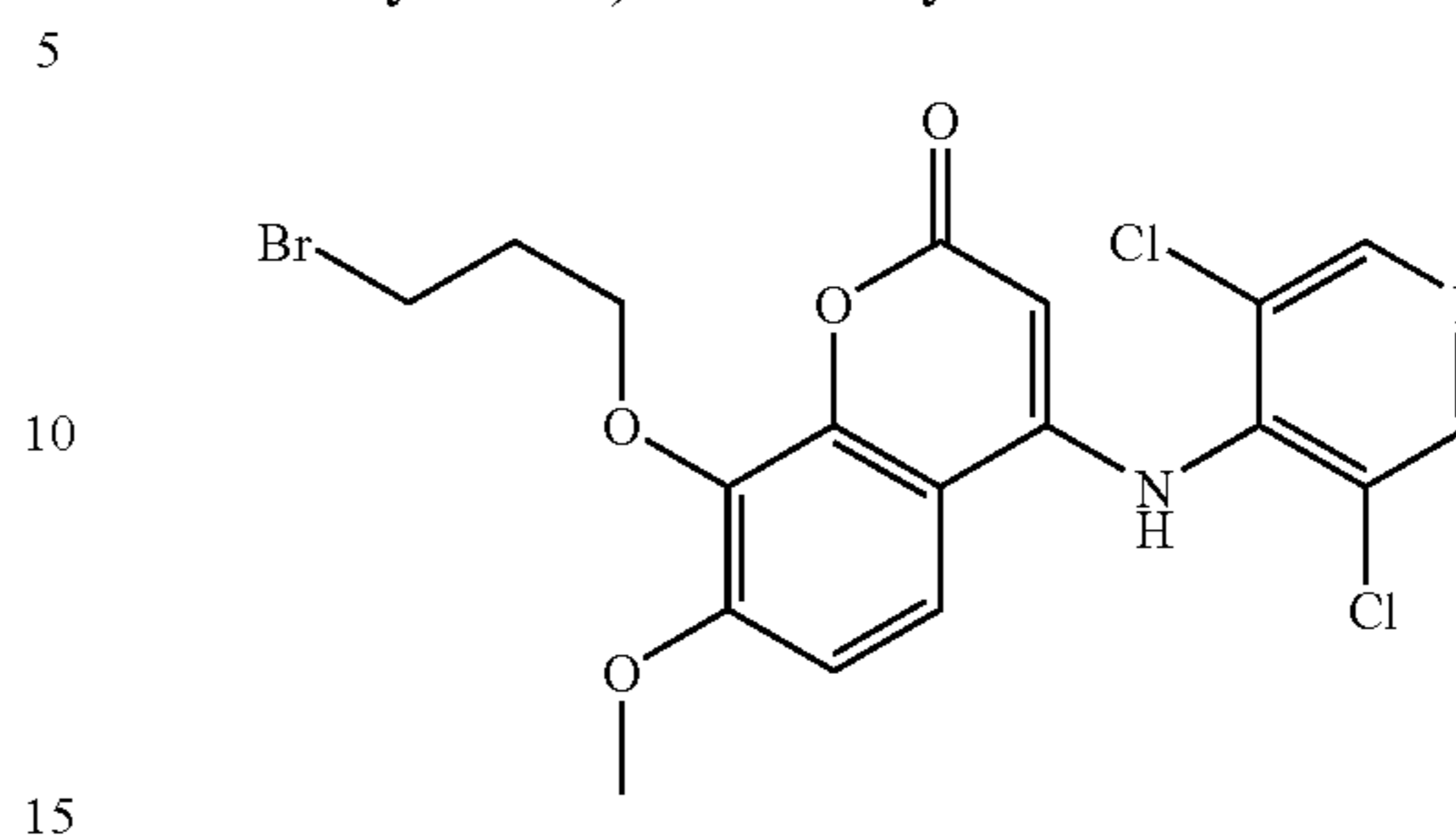
4-(3,5-Dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one



8-(Cyclopropylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (5.4 g, 13.3 mmol, Example 5) was added in one portion to conc. HCl (90 mL). After 1 h of vigorous stirring, the mixture was diluted with water (50 mL, 0° C.) and cooled to 0° C. The white precipitate was filtered, washed with water (100 mL, 0° C.), and then resuspended in water (100 mL, 0° C.). After 30 min of vigorous stirring, the white solid was filtered, washed with water (100 mL, 0° C.), and dried to give 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (br, 2H), 8.79 (s, 2H), 7.66 (d, 1H), 7.12 (d, 1H), 4.60 (s, 1H), 3.90 (s, 3H); MS (ESI): 352.9.

**46**  
EXAMPLE 30

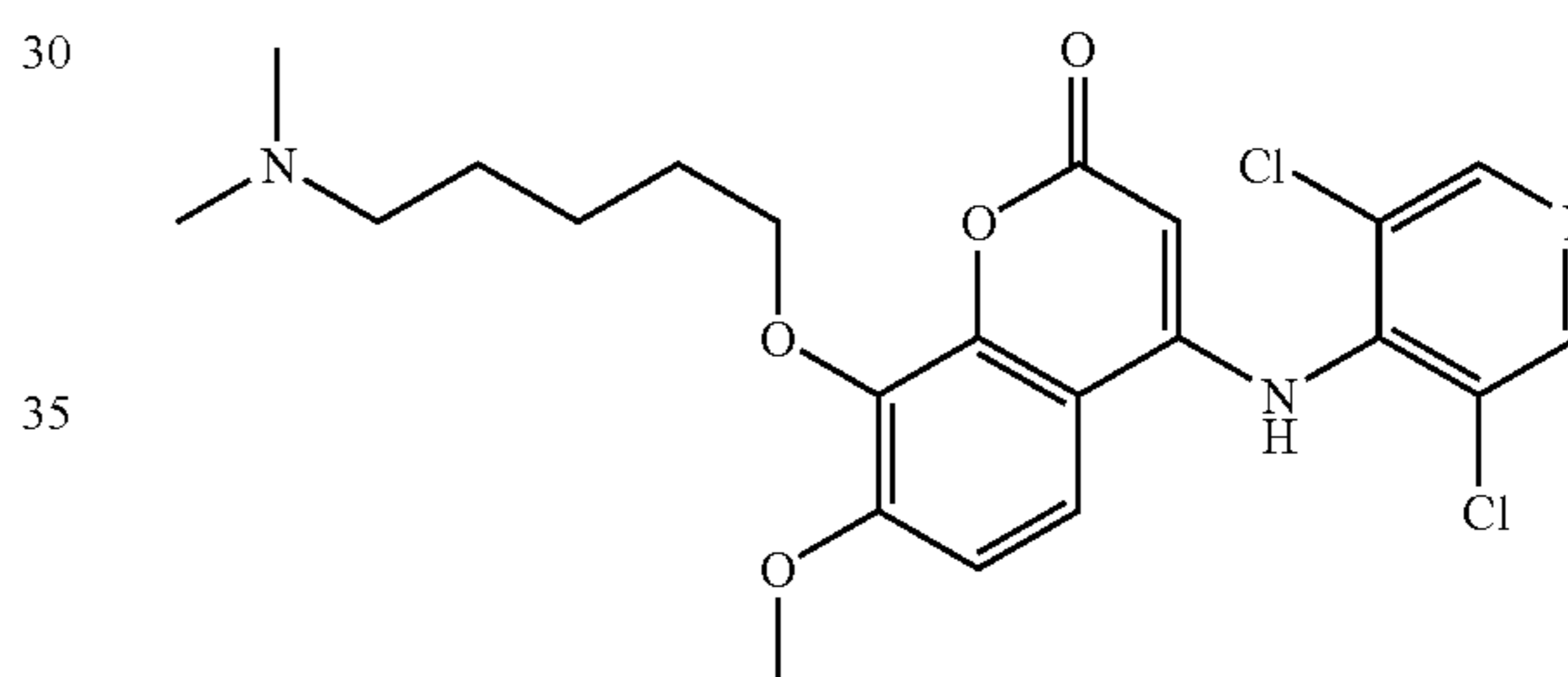
8-(3-Bromopropoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 1,3-dibromopropane and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 8.81 (s, 2H), 7.96 (d, 1H), 7.22 (d, 1H), 4.65 (s, 1H), 4.11 (t, 2H), 3.93 (s, 3H), 3.77 (t, 2H), 2.18 (m, 2H); MS (ESI): 472.7.

EXAMPLE 31

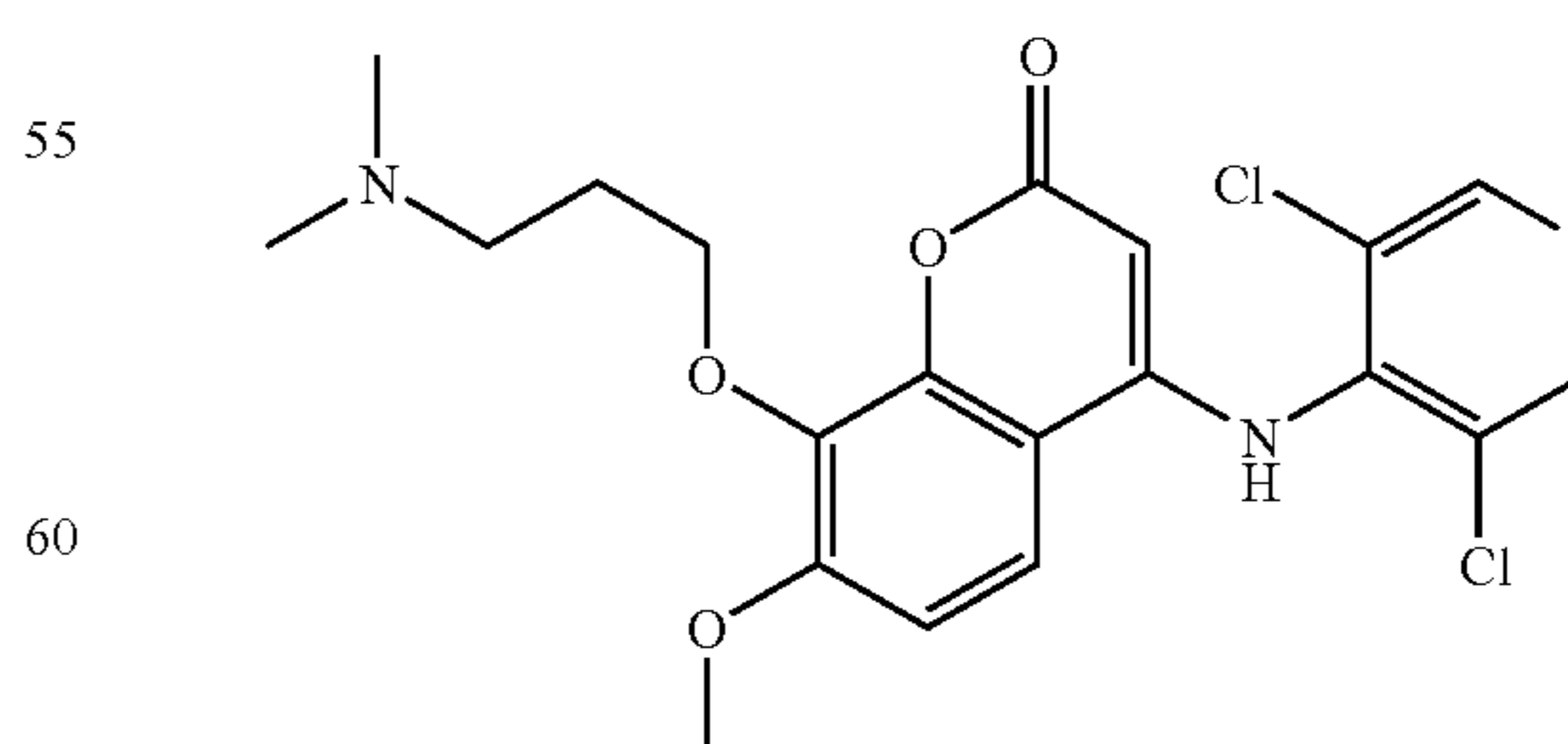
4-(3,5-Dichloropyridin-4-ylamino)-8-(5-(dimethylamino)pentyl)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 8-(5-bromopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.45 (br s, 1H), 8.57 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.23 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.63 (br, 2H), 2.42 (s, 6H), 1.75-1.40 (m, 6H); MS (ESI): 465.9.

EXAMPLE 32

4-(3,5-Dichloropyridin-4-ylamino)-8-(3-(dimethylamino)propyl)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 8-(3-bromopropoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 30) following the procedure out-

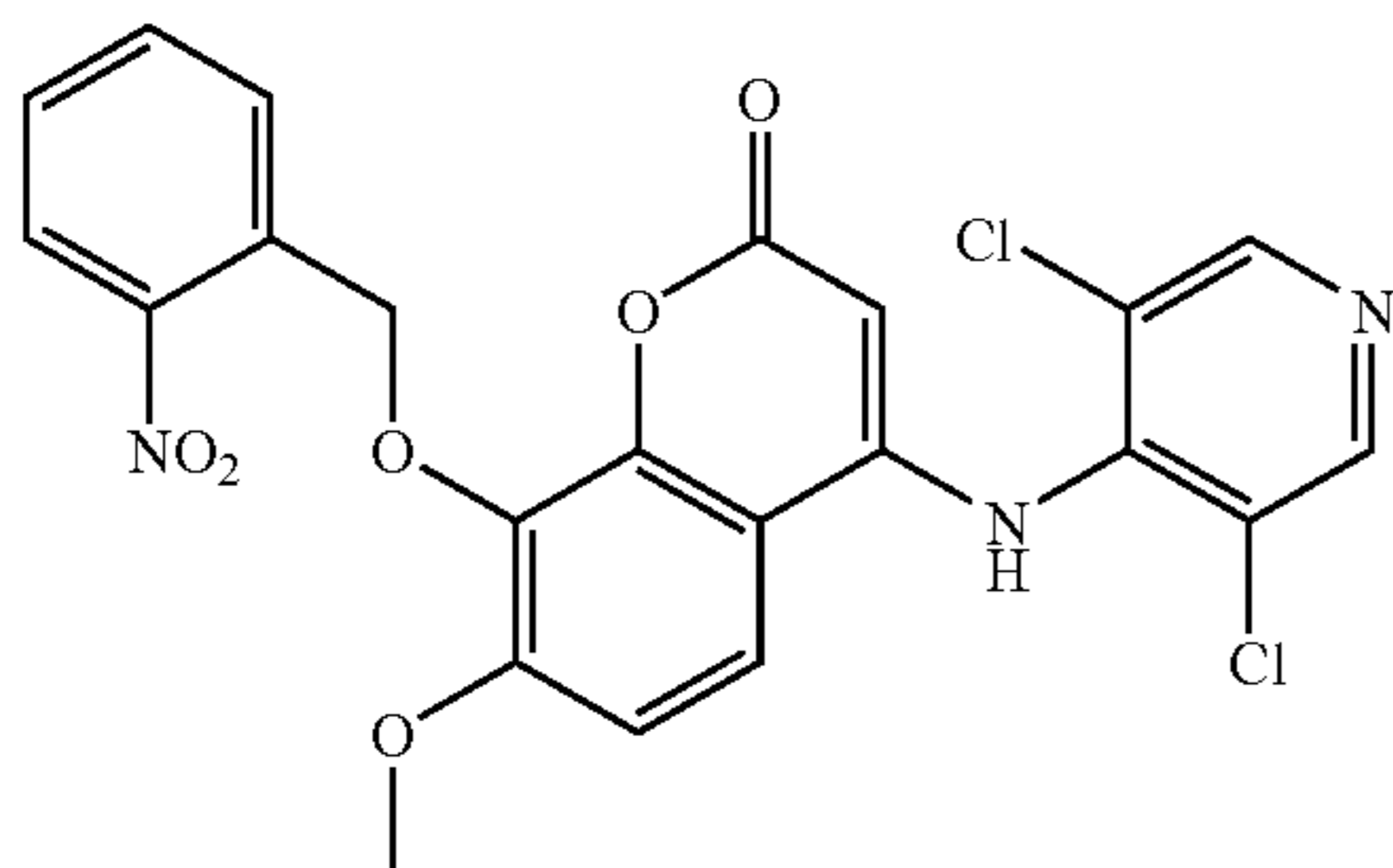


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lined in Example 27.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.39 (br s, 1H), 8.61 (s, 2H), 7.88 (d, 1H), 7.09 (d, 1H), 4.30 (br s, 1H), 4.03 (t, 2H), 3.89 (s, 3H), 2.82 (br, 2H), 2.41 (s, 6H), 1.88 (m, 2H); MS (ESI): 437.9.

## EXAMPLE 33

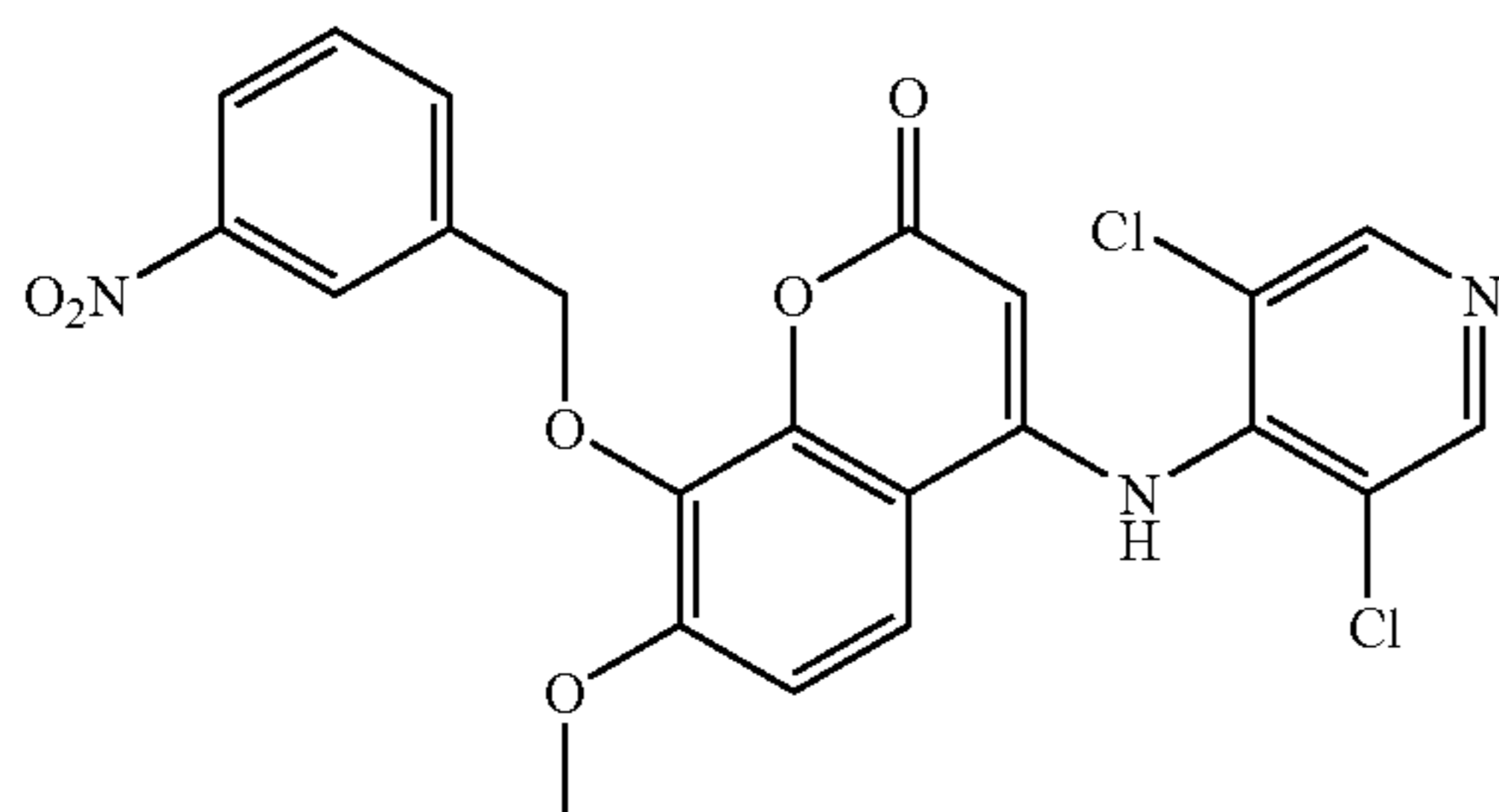
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(2-nitrobenzyloxy)-2H-chromen-2-one



The title compound was prepared from 1-(bromomethyl)-2-nitrobenzene and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.55 (s, 1H), 8.81 (s, 2H), 8.12 (dd, 1H), 8.05 (d, 1H), 7.99 (d, 1H), 7.82 (td, 1H), 7.62 (td, 1H), 7.22 (d, 1H), 5.43 (s, 2H), 4.65 (s, 1H), (s, 3H); MS (ESI): 487.8.

## EXAMPLE 34

4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(3-nitrobenzyloxy)-2H-chromen-2-one

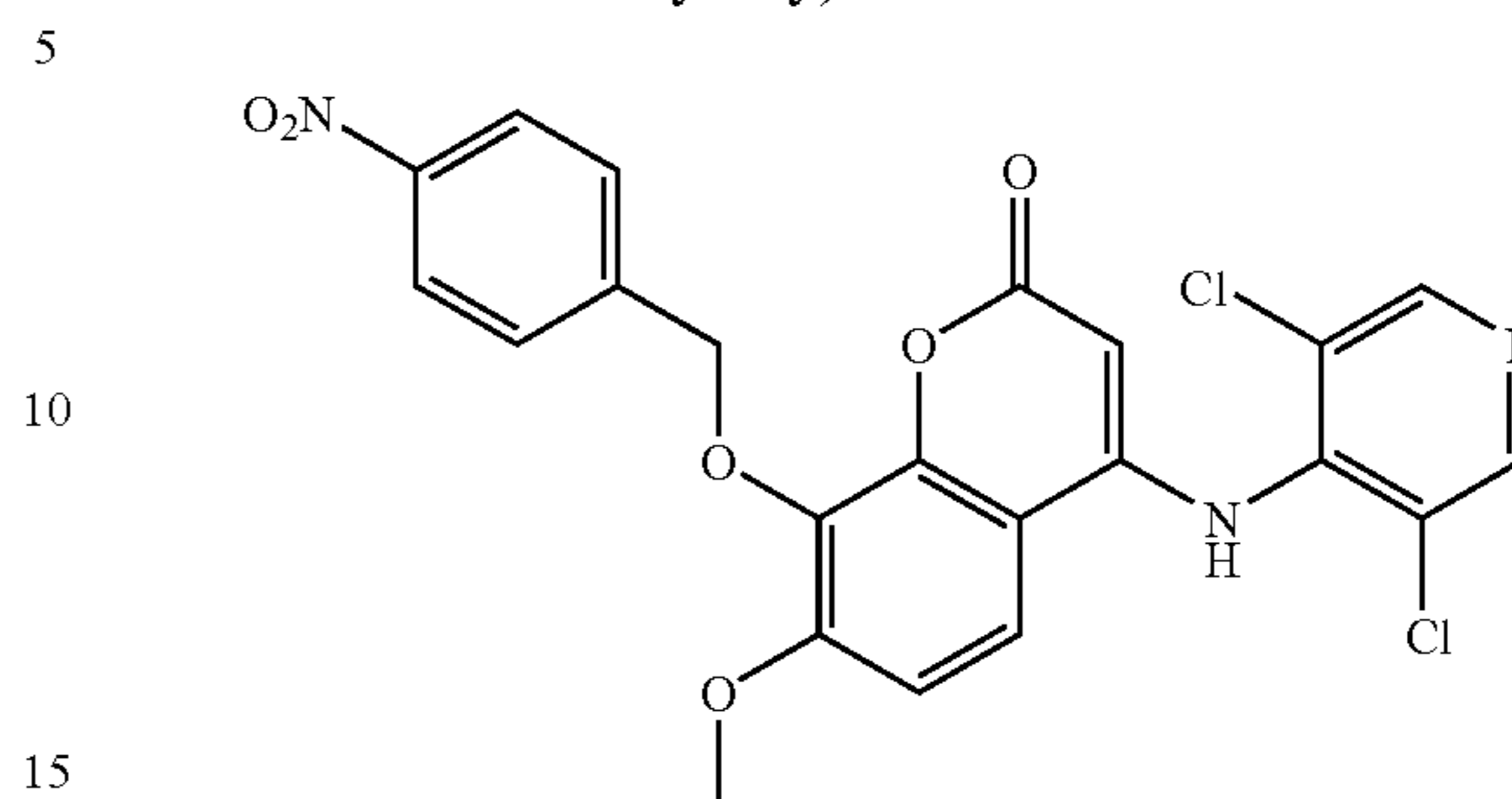


The title compound was prepared from 1-(bromomethyl)-3-nitrobenzene and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.55 (s, 1H), 8.81 (s, 2H), 8.40 (s, 1H), 8.19 (ddd, 1H), 7.99 (d, 1H), 7.95 (d, 1H), 7.68 (t, 1H), 7.24 (d, 1H), 5.20 (s, 2H), 4.65 (s, 1H), 3.94 (s, 3H); MS (ESI): 487.8.

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## EXAMPLE 35

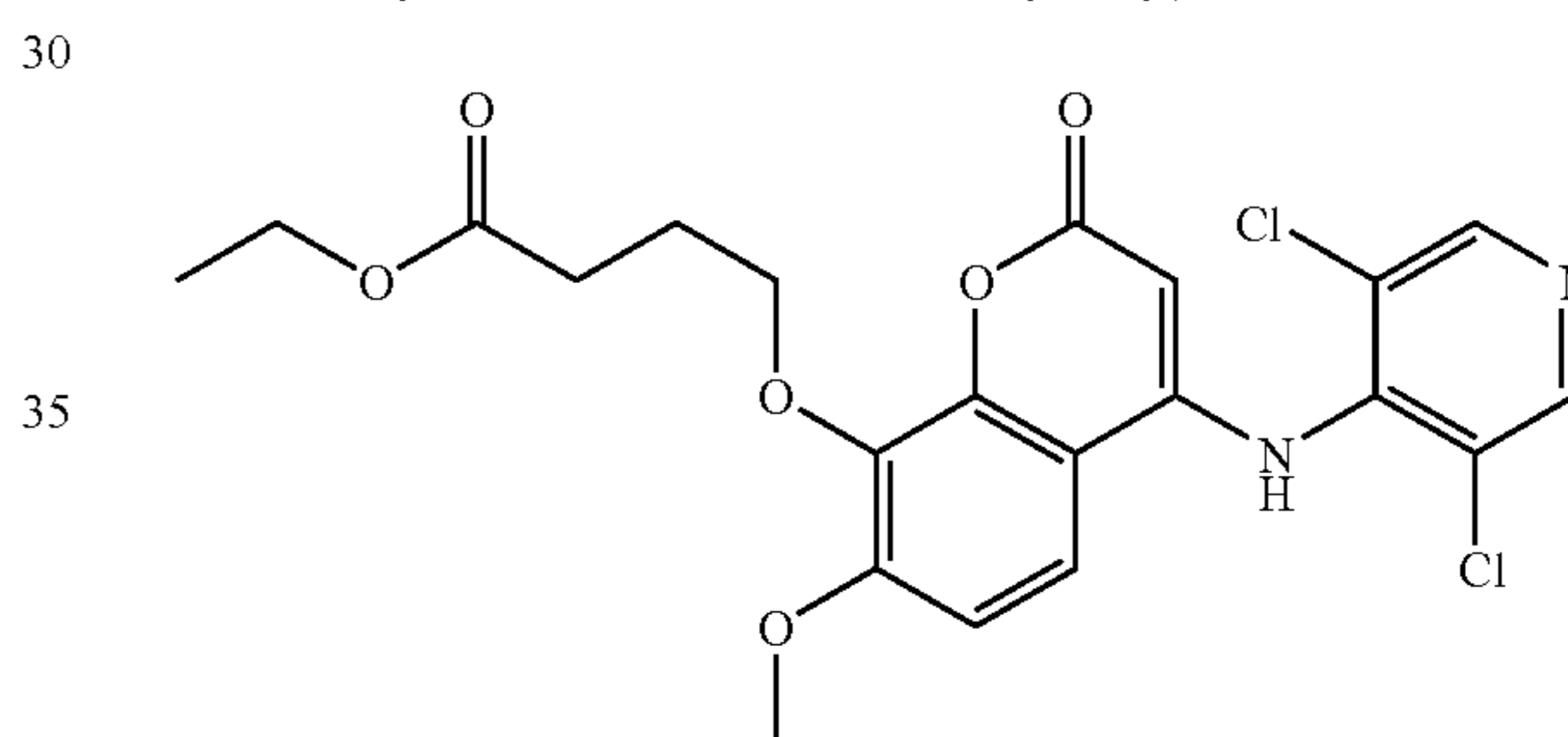
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(4-nitrobenzyloxy)-2H-chromen-2-one



The title compound was prepared from 1-(bromomethyl)-4-nitrobenzene and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.55 (s, 1H), 8.81 (s, 2H), 8.25 (d, 2H), 7.99 (d, 1H), 7.80 (d, 2H), 7.25 (d, 1H), 5.20 (s, 2H), 4.66 (s, 1H), 3.93 (s, 3H); MS (ESI): 487.8.

## EXAMPLE 36

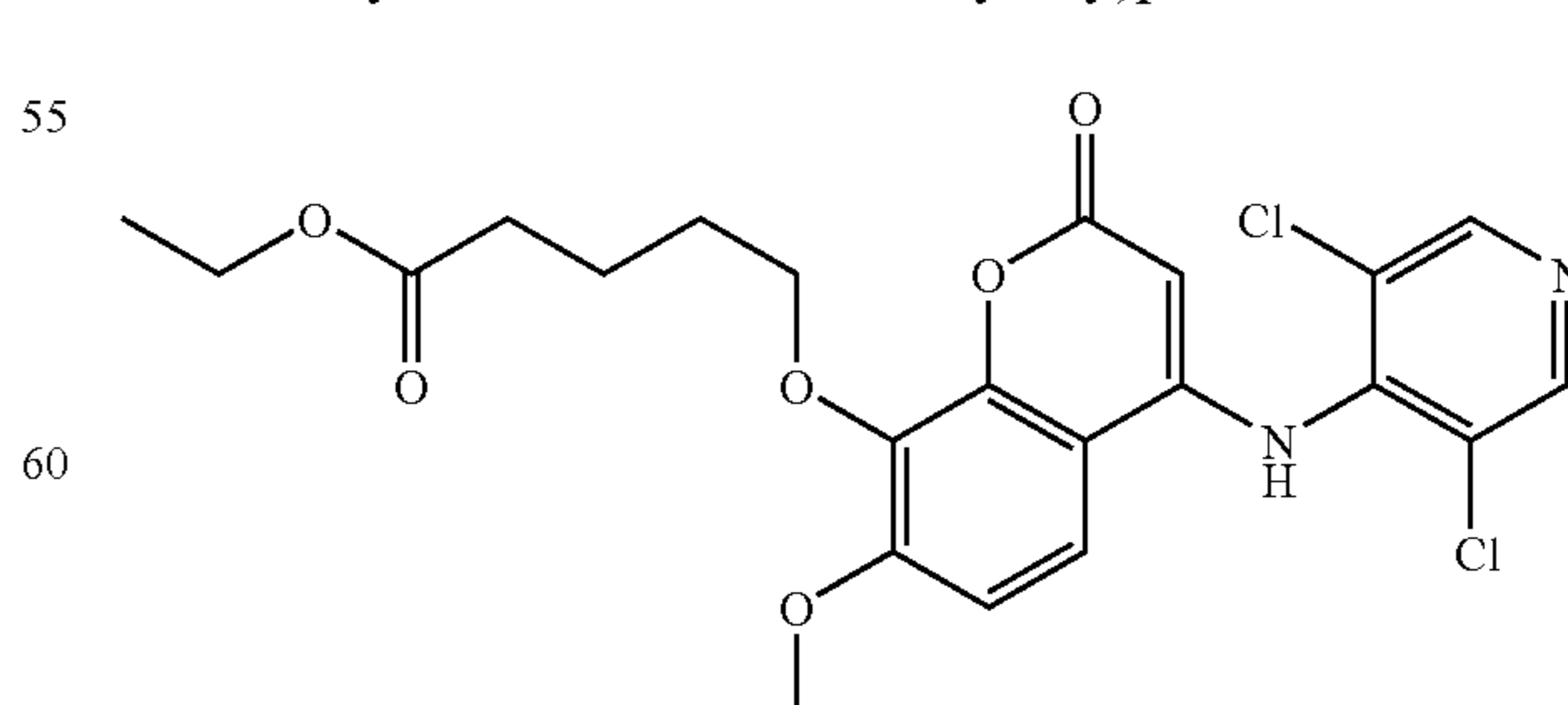
Ethyl 4-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butanoate



The title compound was prepared from ethyl 4-bromobutanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.95 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.10-3.95 (m, 4H), 3.91 (s, 3H), 2.54 (t, 2H), 1.90 (m, 2H), 1.16 (t, 3H); MS (ESI): 466.9.

## EXAMPLE 37

Ethyl 5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentanoate



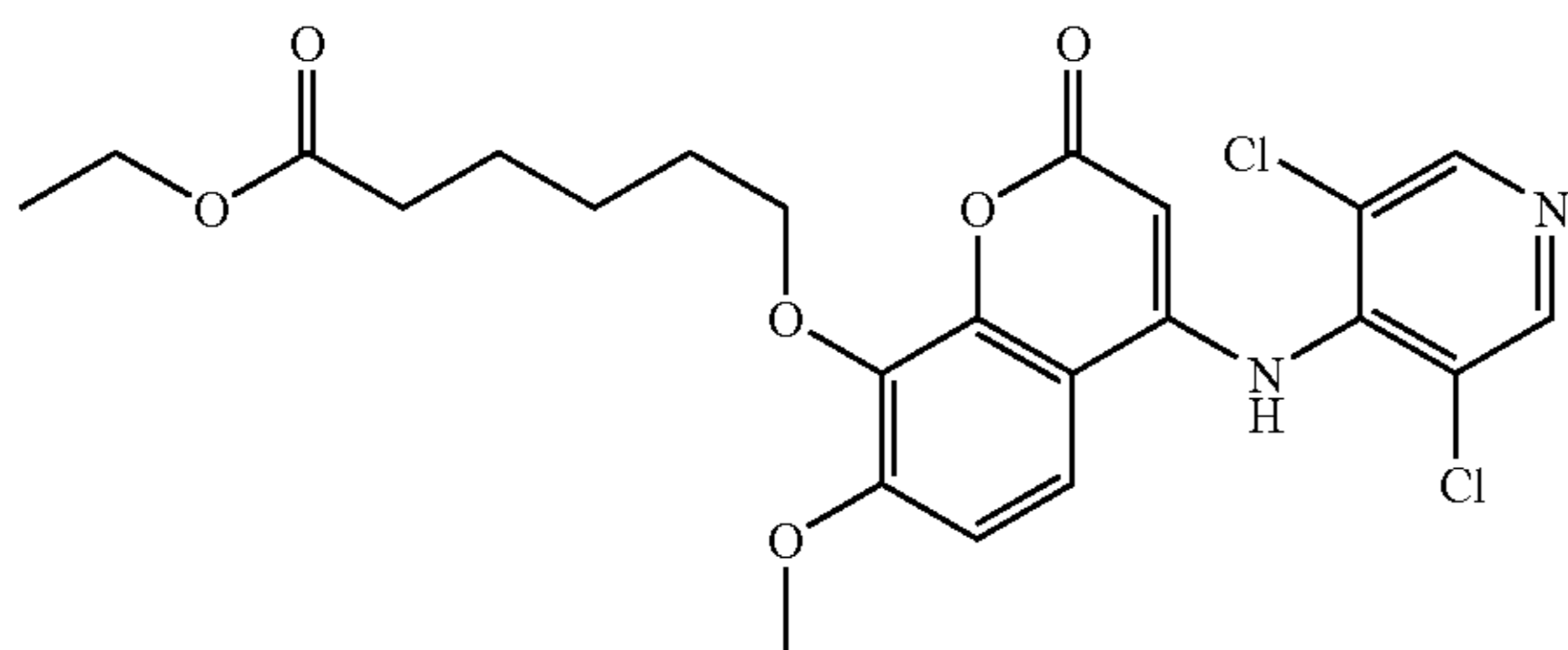
The title compound was prepared from ethyl 5-bromopentanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-

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7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.03 (q, 2H), 3.98 (t, 2H), 3.91 (s, 3H), 2.36 (t, 2H), 1.80-1.60 (m, 4H), 1.15 (t, 3H); MS (ESI): 480.9.

## EXAMPLE 38

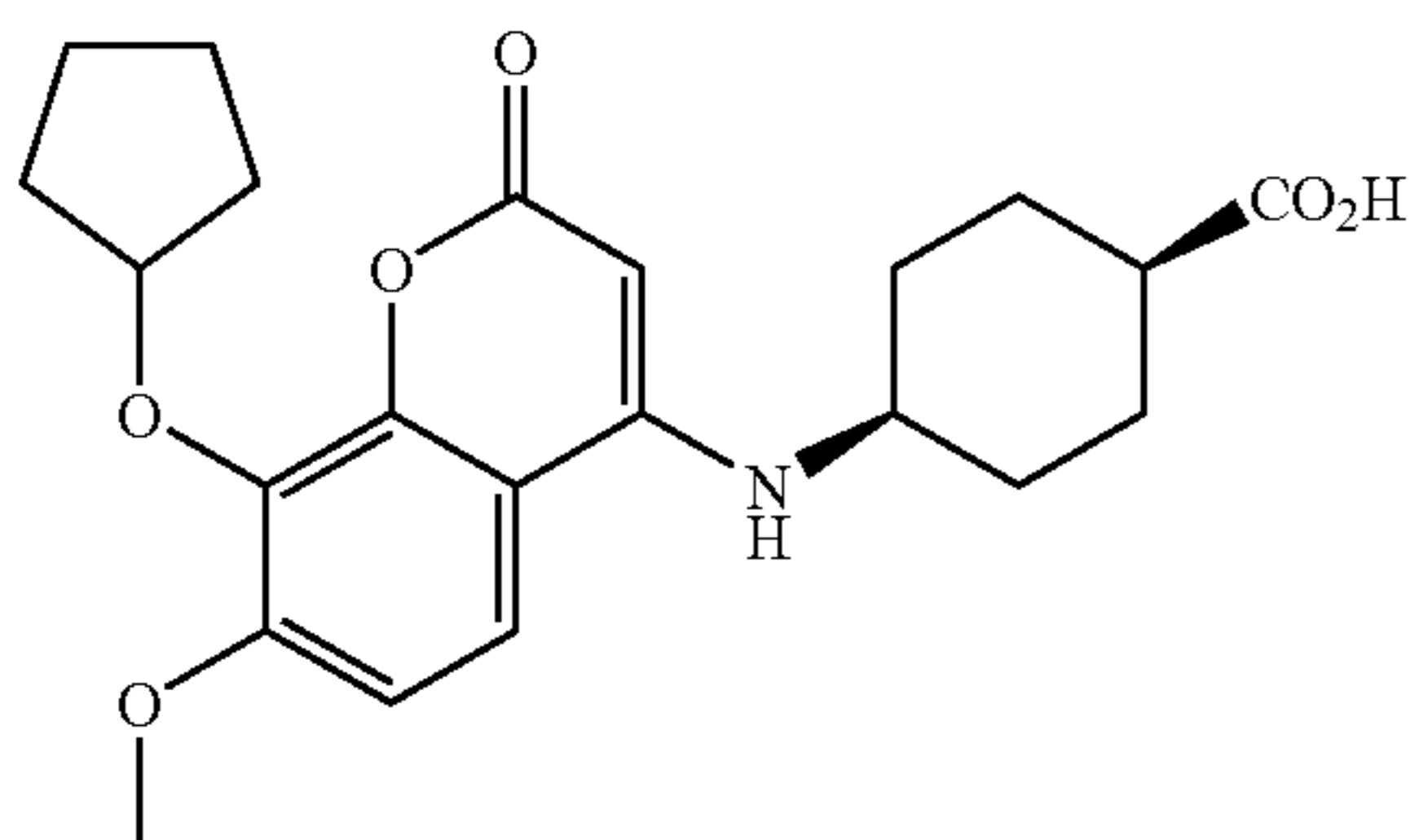
Ethyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoate



The title compound was prepared from ethyl 6-bromohexanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 4.02 (q, 2H), 3.97 (t, 2H), 3.91 (s, 3H), 2.39 (t, 2H), 1.67 (m, 2H), 1.57 (m, 2H), 1.46 (m, 2H), 1.15 (t, 3H); MS (ESI): 494.9.

## EXAMPLE 39

cis-4-(8-(Cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)cyclohexanecarboxylic acid

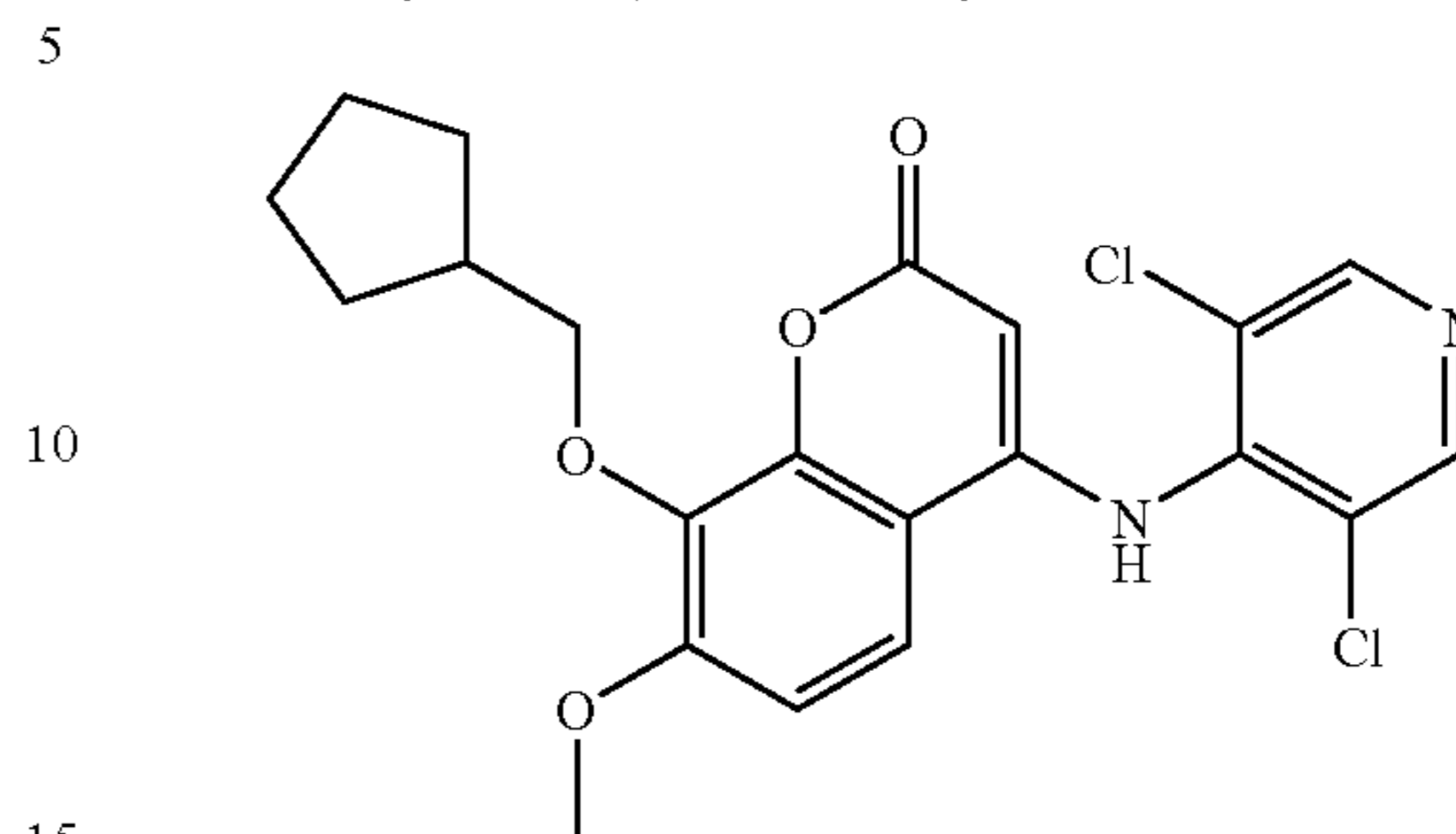


Sodium hydride (50 mg, 60%, 1.25 mmol) was added to a solution of cis-4-amino-1-cyclohexanecarboxylic acid (83 mg, 0.580 mmol) and anhydrous  $\text{DMSO}$  (2 mL) at rt under  $\text{N}_2$ . After 10 min, 4-chloro-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (114 mg, 0.387 mmol, Example 7, Step 1) was added, and the mixture was stirred for 3 d, poured into 1M  $\text{KH}_2\text{PO}_4$  and extracted with ethyl acetate. The extract was dried, filtered, concentrated, and purified by reverse-phase HPLC (30 $\rightarrow$ 100% MeCN/ $\text{H}_2\text{O}$ ) to give cis-4-(8-(cyclopentyloxy)-7-methoxy-2-oxo-2H-chromen-4-ylamino)cyclohexanecarboxylic acid:  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  7.85 (d, 1H), 7.10 (d, 1H), 7.01 (d, 1H), 5.10 (s, 1H), 4.81 (m, 1H), 3.87 (s, 3H), 3.50 (m, 1H), 2.56 (m, 1H), 2.04 (m, 2H), 1.79-1.58 (m, 14H); MS (ESI): 402.0.

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## EXAMPLE 40

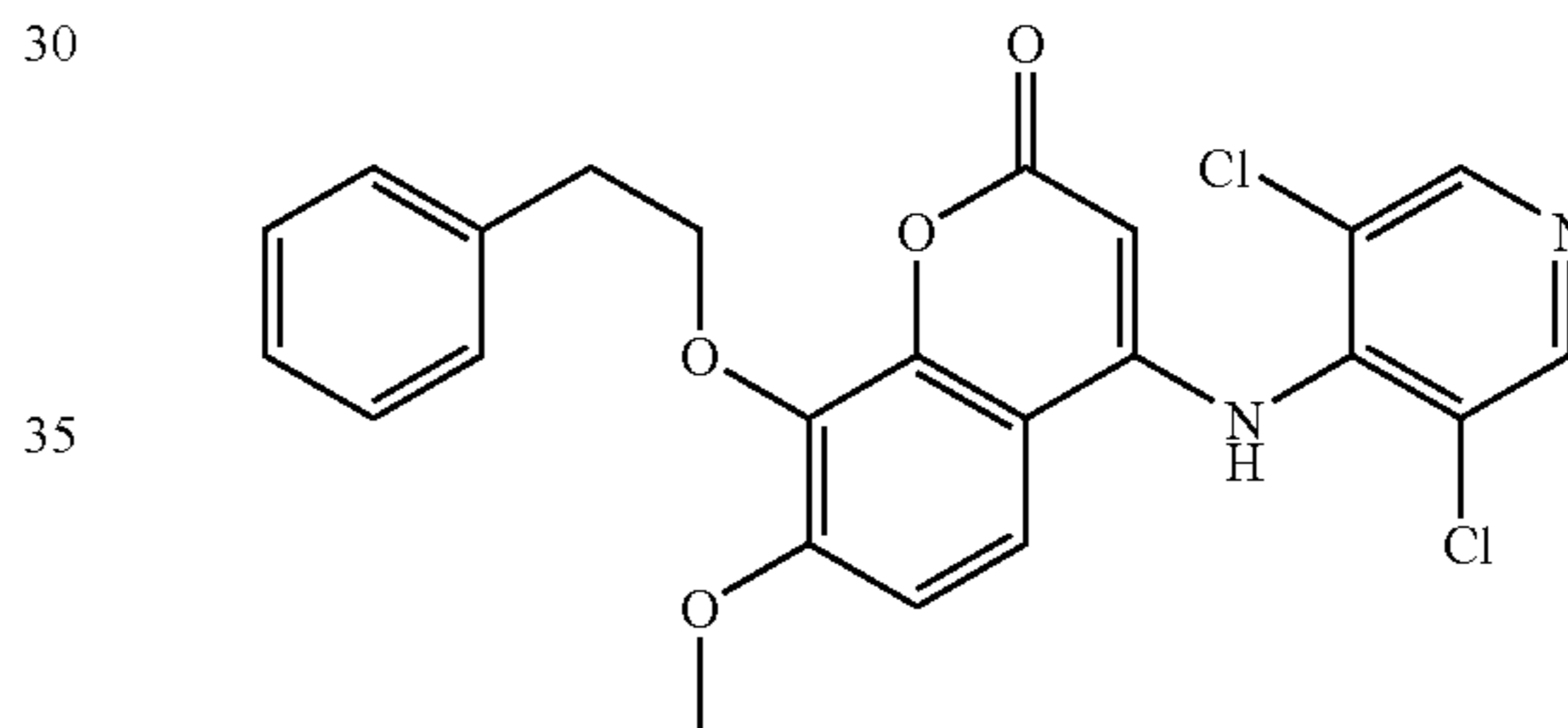
8-(Cyclopentylmethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from cyclopentylmethyl 4-methylbenzenesulfonate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 3.91 (s, 3H), 3.84 (d, 2H), 2.28 (m, 1H), 1.80-1.35 (m, 8H); MS (ESI): 434.9.

## EXAMPLE 41

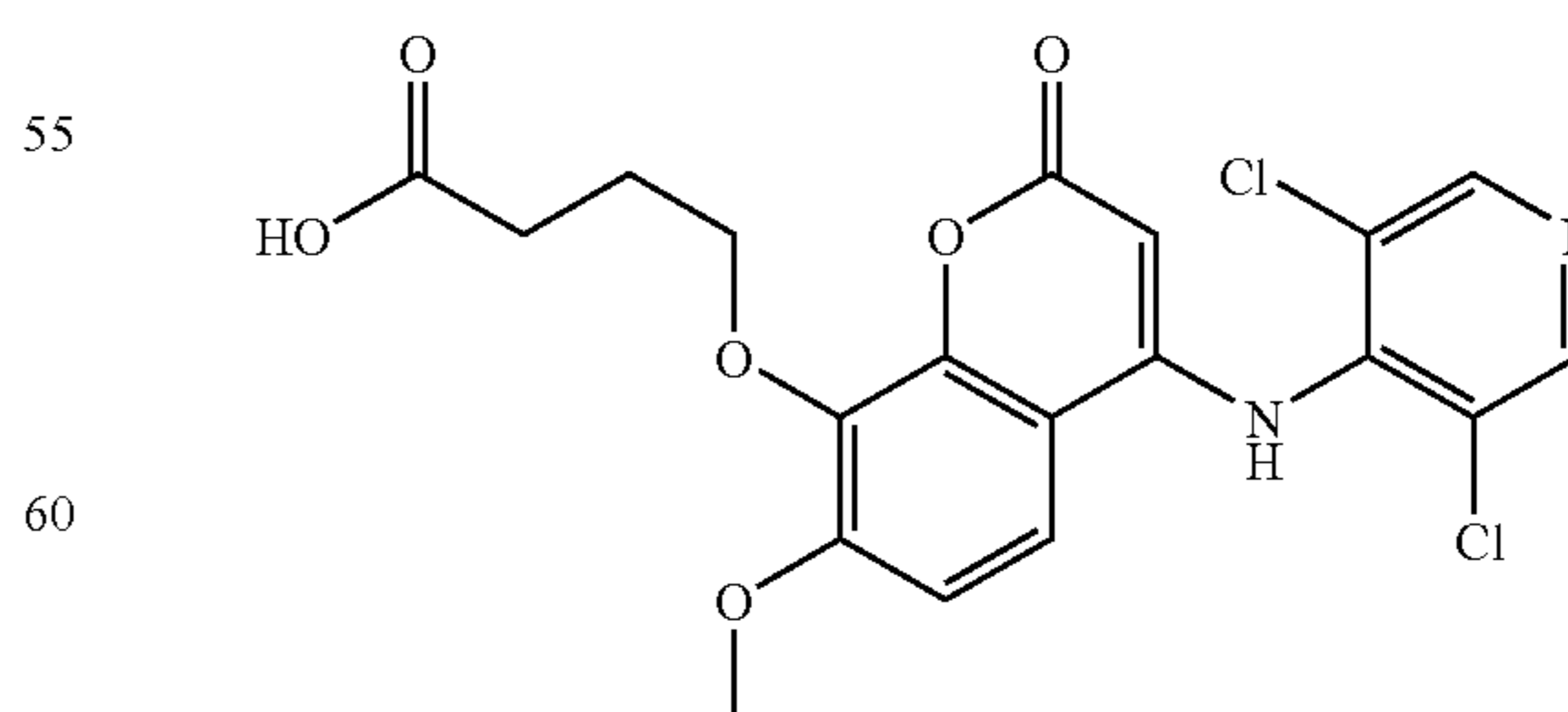
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-phenethoxy-2H-chromen-2-one



The title compound was prepared from (2-bromoethyl) benzene and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.35-7.23 (m, 4H), 7.19 (d, 2H), 4.64 (s, 1H), 4.22 (t, 2H), 3.89 (s, 3H), 3.03 (t, 2H); MS (ESI): 456.9.

## EXAMPLE 42

4-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butanoic acid



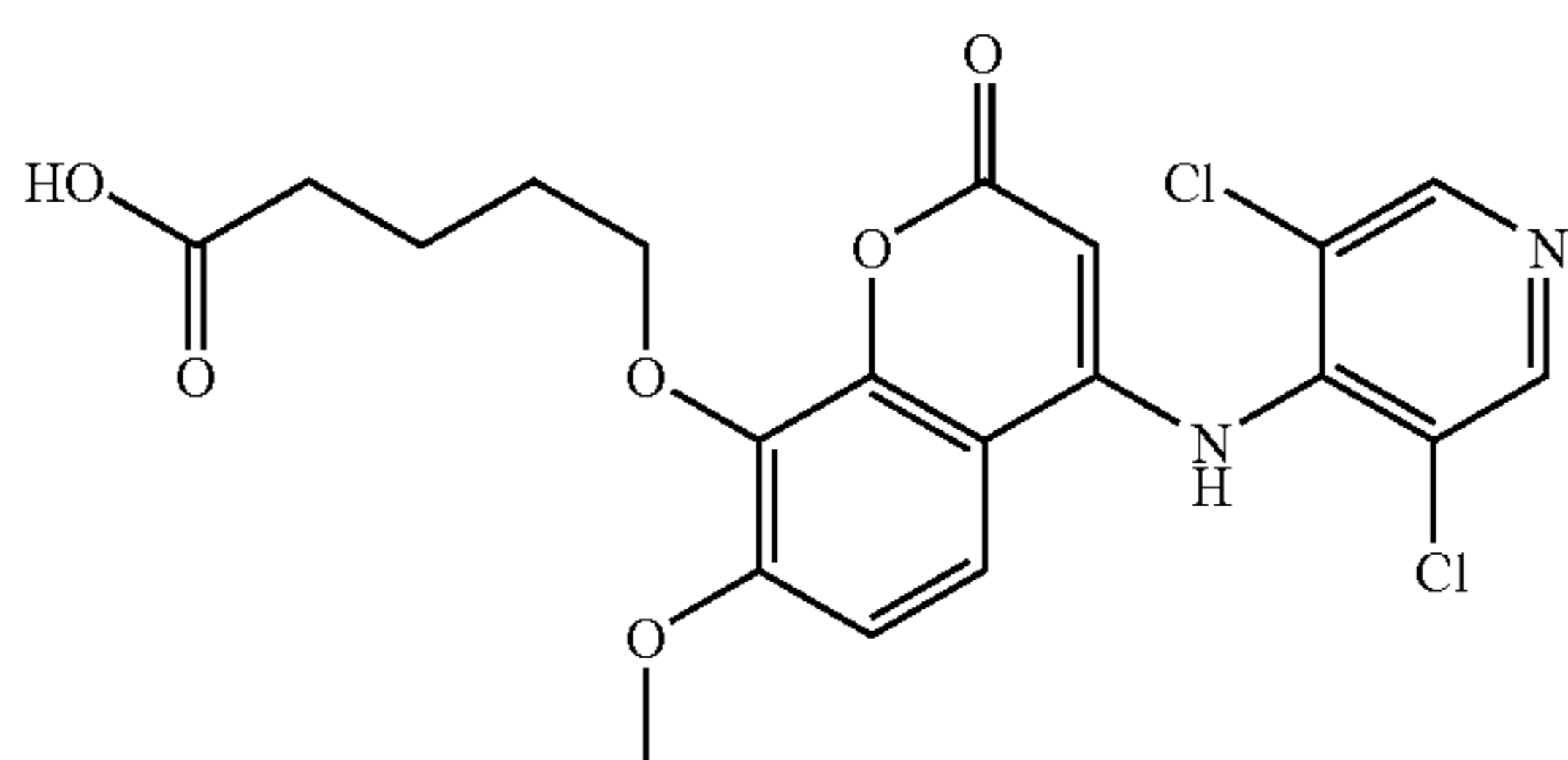
Lithium hydroxide (0.5 mL, 1M, 0.5 mmol) was added to a solution of ethyl 4-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butanoate (12 mg,

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0.026 mmol, Example 36), MeOH (0.5 mL), and THF (1.5 mL). The mixture was stirred 4 h, quenched with 1N HCl (20 mL), and extracted with EtOAc (30 mL×2). The organic extract was dried, filtered, and concentrated to give 4-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butanoic acid: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.00 (t, 2H), 3.91 (s, 3H), 2.46 (t, 2H), 1.88 (m, 2H); MS (ESI): 438.9.

## EXAMPLE 43

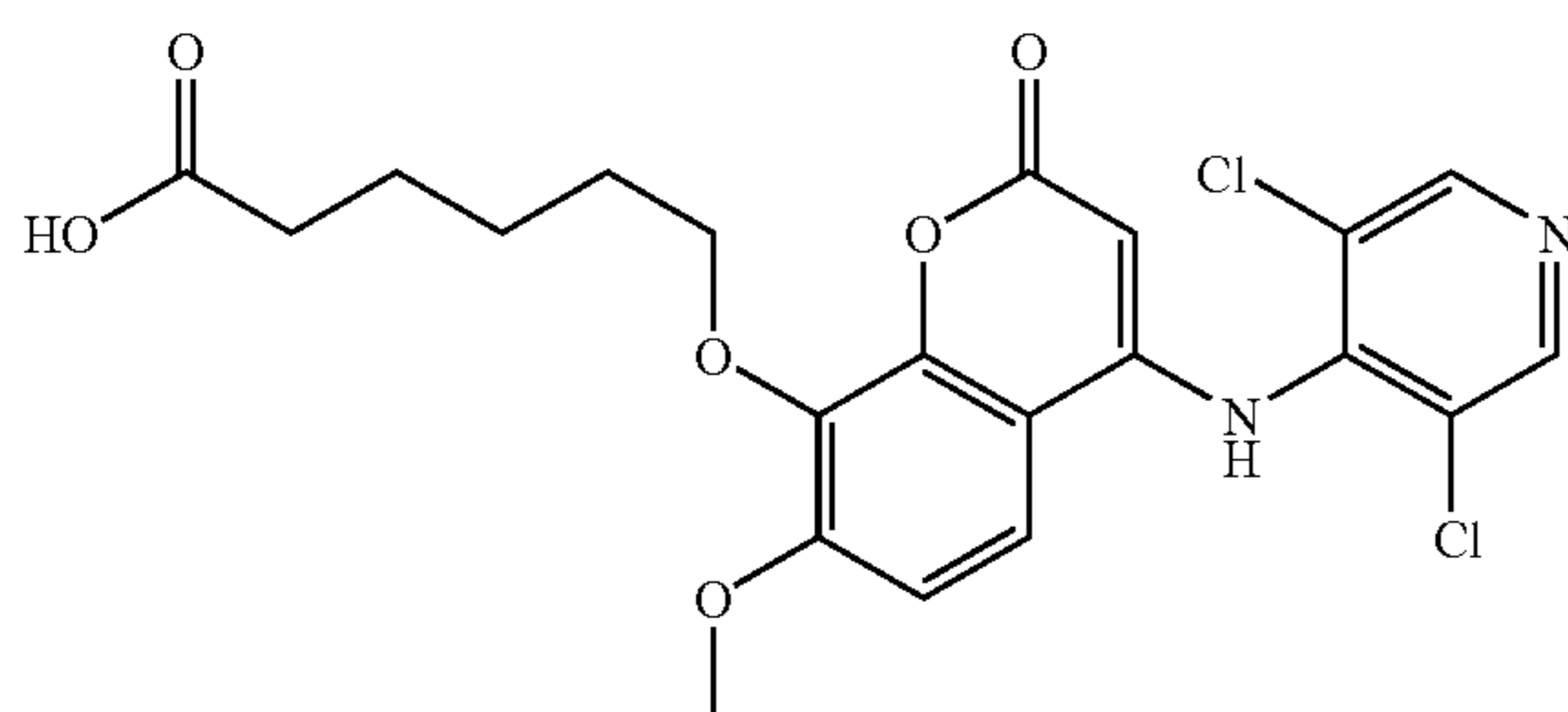
5-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentanoic acid



The title compound was prepared from ethyl 5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentanoate (Example 37) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 2.28 (t, 2H), 1.69 (m, 4H); MS (ESI): 452.9.

## EXAMPLE 44

6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid

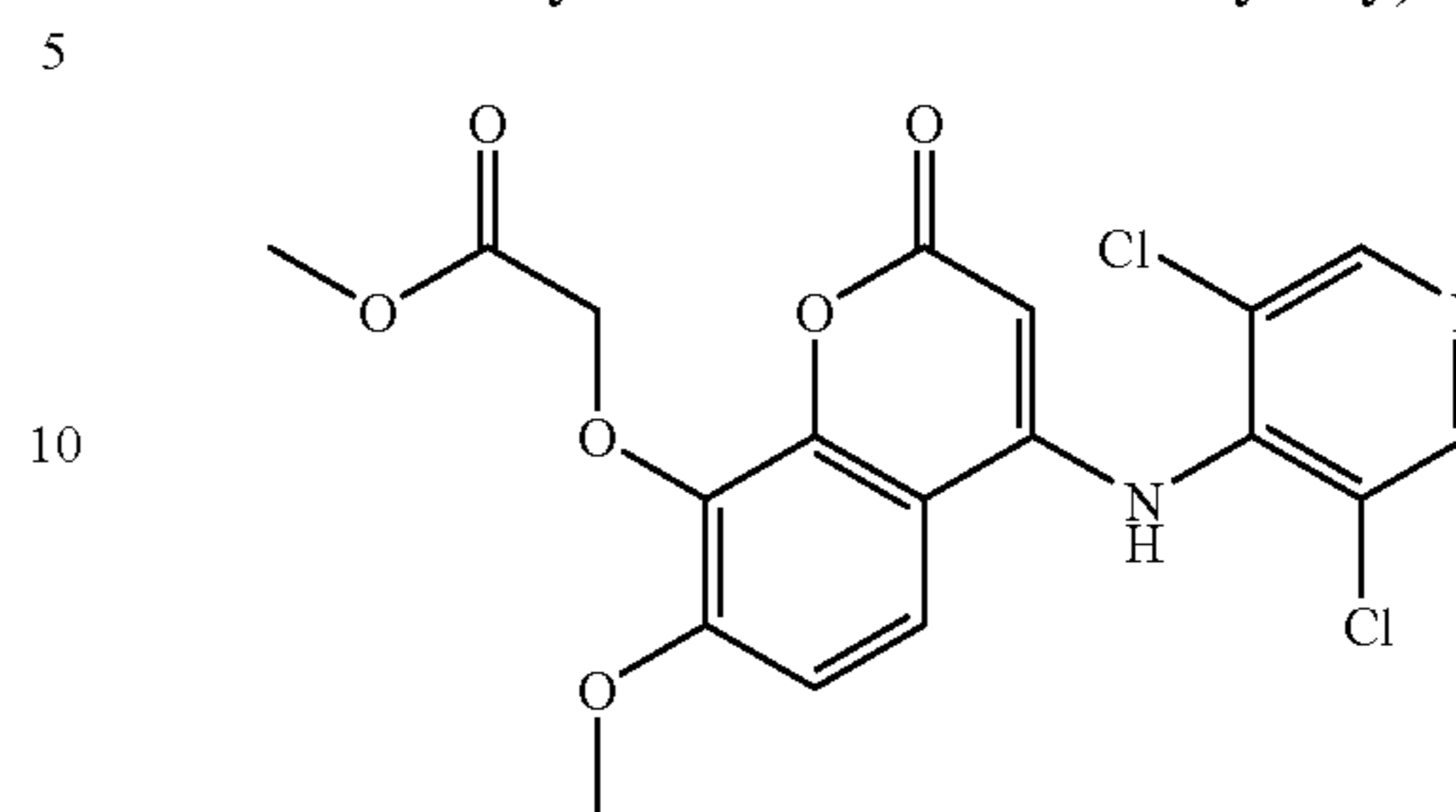


The title compound was prepared from ethyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoate (Example 38) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 11.92 (br, 1H), 9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 2.21 (t, 2H), 1.67 (m, 2H), 1.54 (m, 2H), 1.46 (m, 2H); MS (ESI): 466.9.

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## EXAMPLE 45

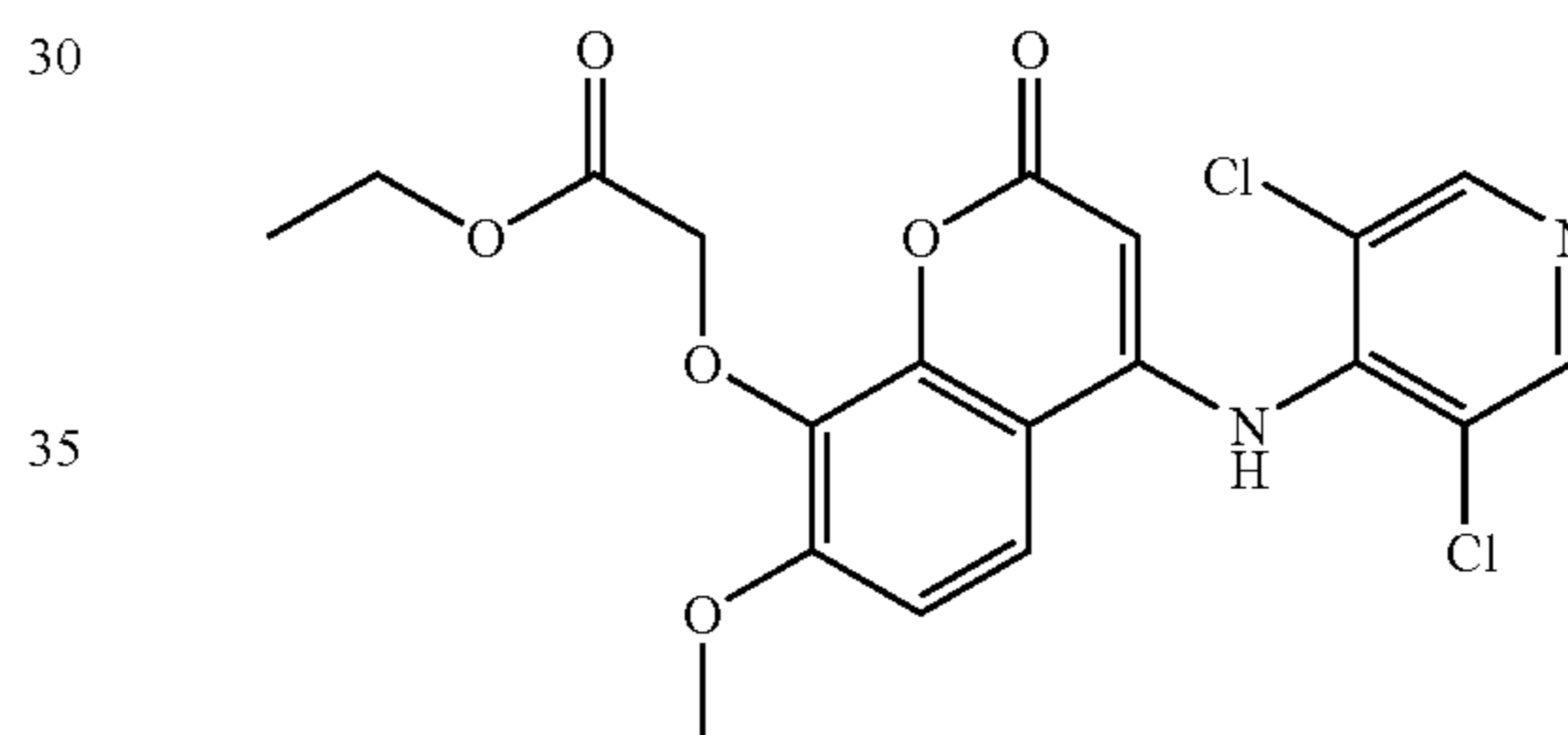
Methyl 2-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetate



The title compound was prepared from methyl 2-bromoacetate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.54 (s, 1H), 8.83 (s, 2H), 7.97 (d, 1H), 7.23 (d, 1H), 4.73 (s, 2H), 4.66 (s, 1H), 3.92 (s, 3H), 3.69 (s, 3H); MS (ESI): 424.8.

## EXAMPLE 46

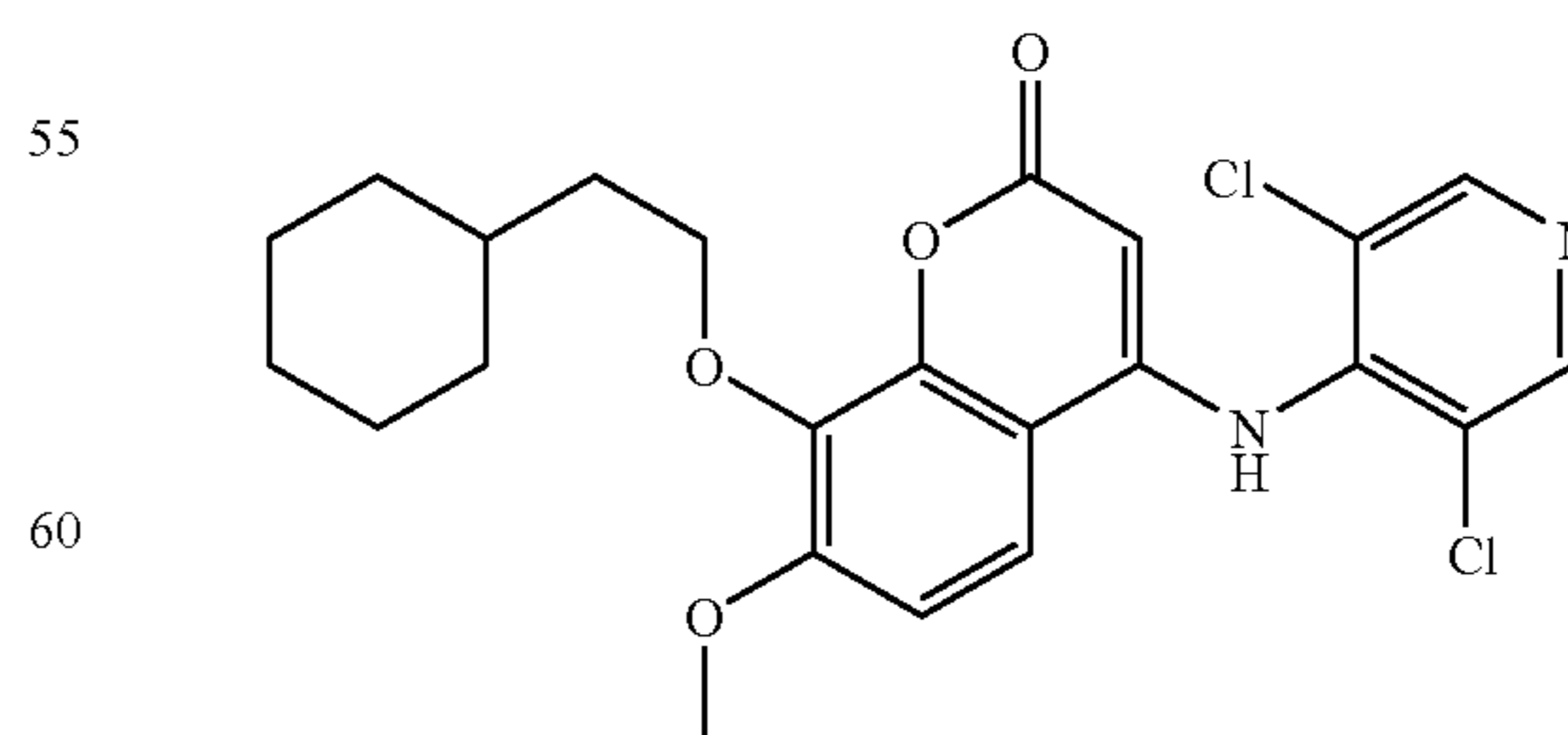
Ethyl 2-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetate



The title compound was prepared from ethyl 2-bromoacetate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.61 (s, 2H), 7.43 (d, 1H), 6.98 (d, 1H), 6.60 (s, 1H), 5.12 (s, 1H), 4.84 (s, 2H), 4.28 (q, 2H), 3.99 (s, 3H), 1.31 (t, 3H); MS (ESI): 438.9.

## EXAMPLE 47

8-(2-Cyclohexylethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



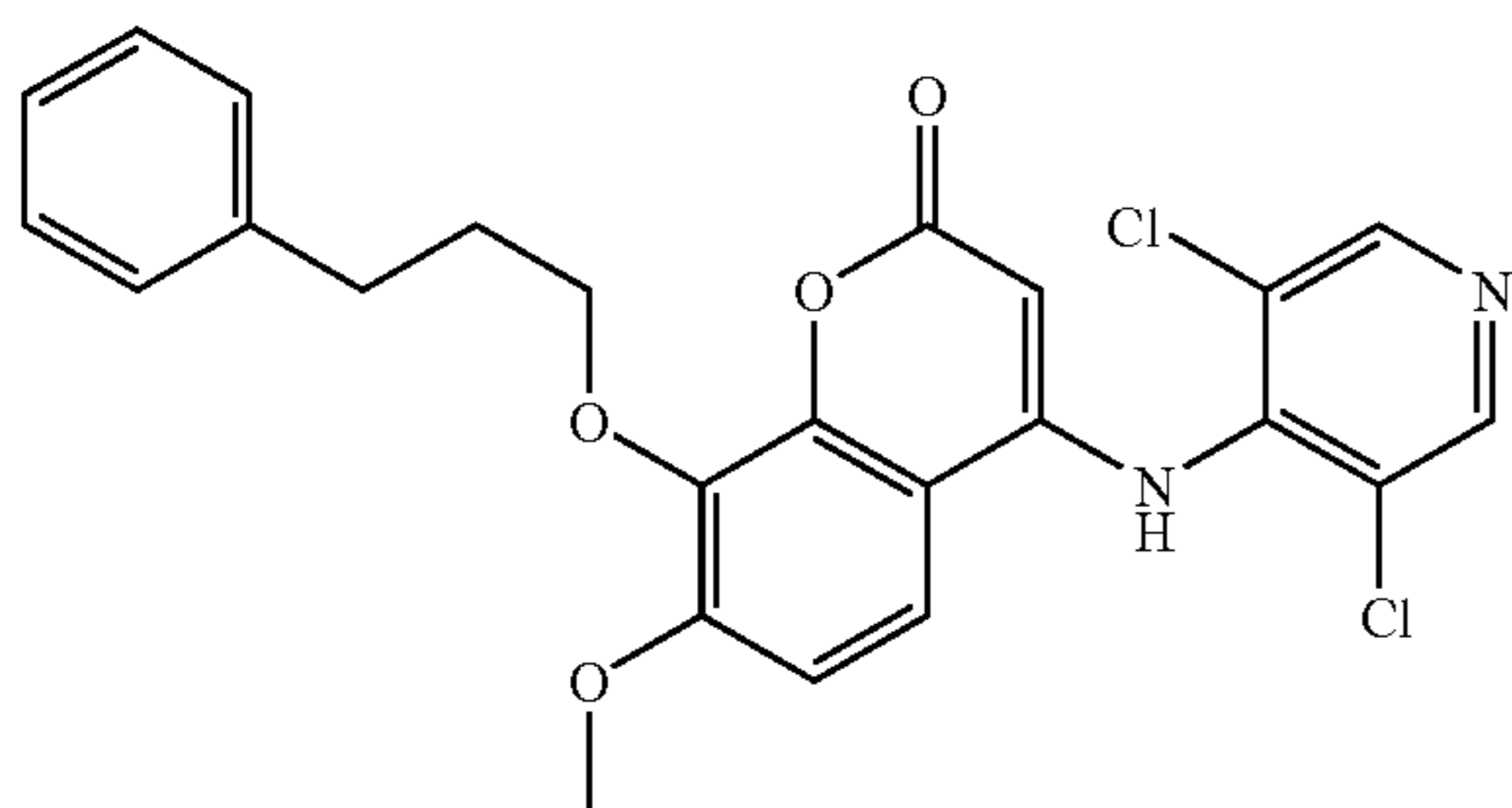
The title compound was prepared from (2-bromoethyl) cyclohexane and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) follow-

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ing the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.82 (s, 2H), 7.95 (d, 1H), 7.21 (d, 1H), 4.64 (s, 1H), 4.02 (t, 2H), 3.92 (s, 3H), 1.80-1.50 (m, 8H), 1.70 (m, 3H), 0.90 (m, 2H); MS (ESI): 463.0.

## EXAMPLE 48

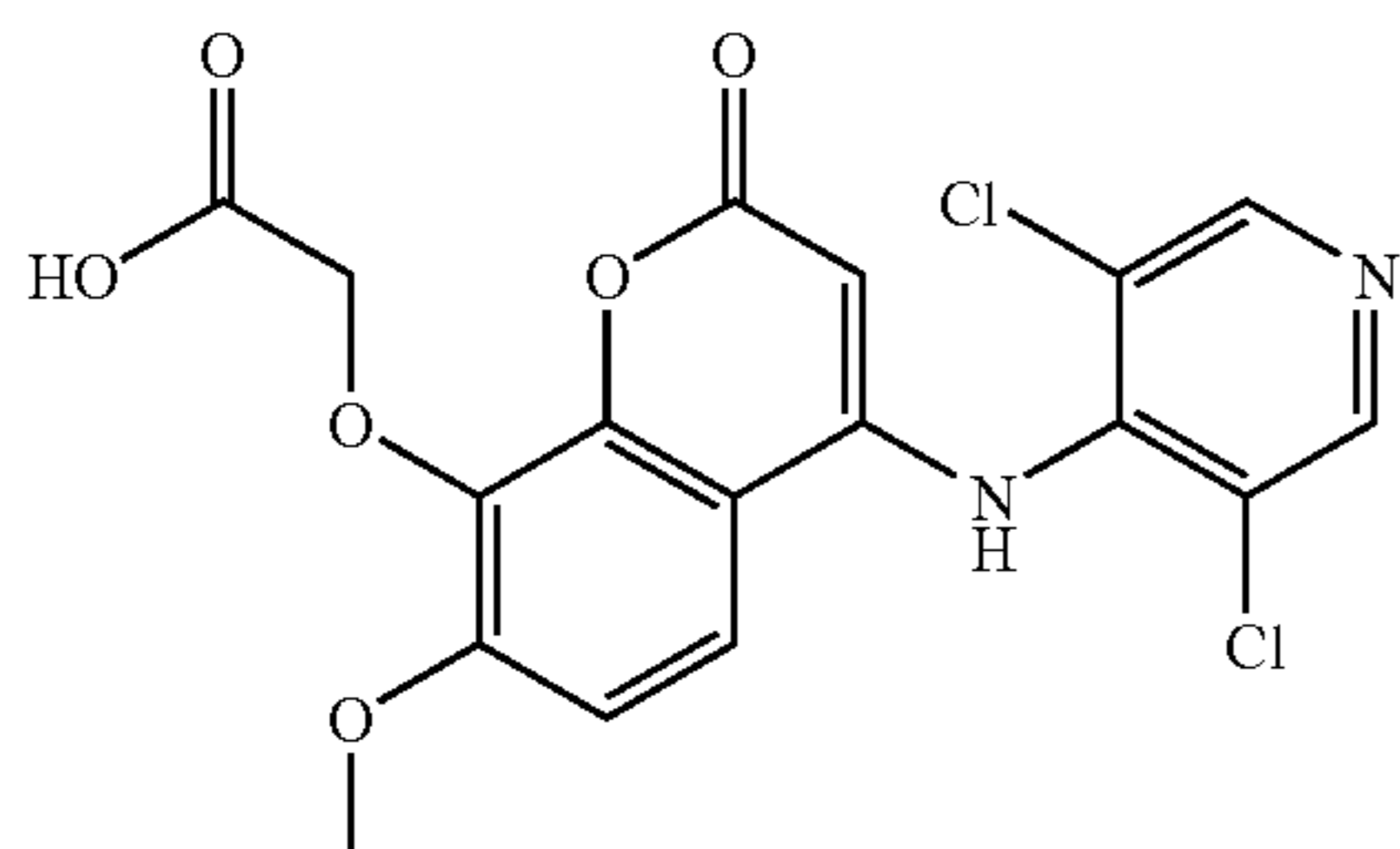
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(3-phenylpropoxy)-2H-chromen-2-one



The title compound was prepared from (3-bromopropyl) benzene and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.61 (s, 2H), 7.39 (d, 1H), 7.35-7.15 (m, 5H), 6.97 (d, 1H), 6.54 (s, 1H), 5.14 (s, 1H), 4.19 (t, 2H), 3.98 (s, 3H), 2.91 (t, 2H), 2.15 (m, 2H); MS (ESI): 470.9.

## EXAMPLE 49

2-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetic acid

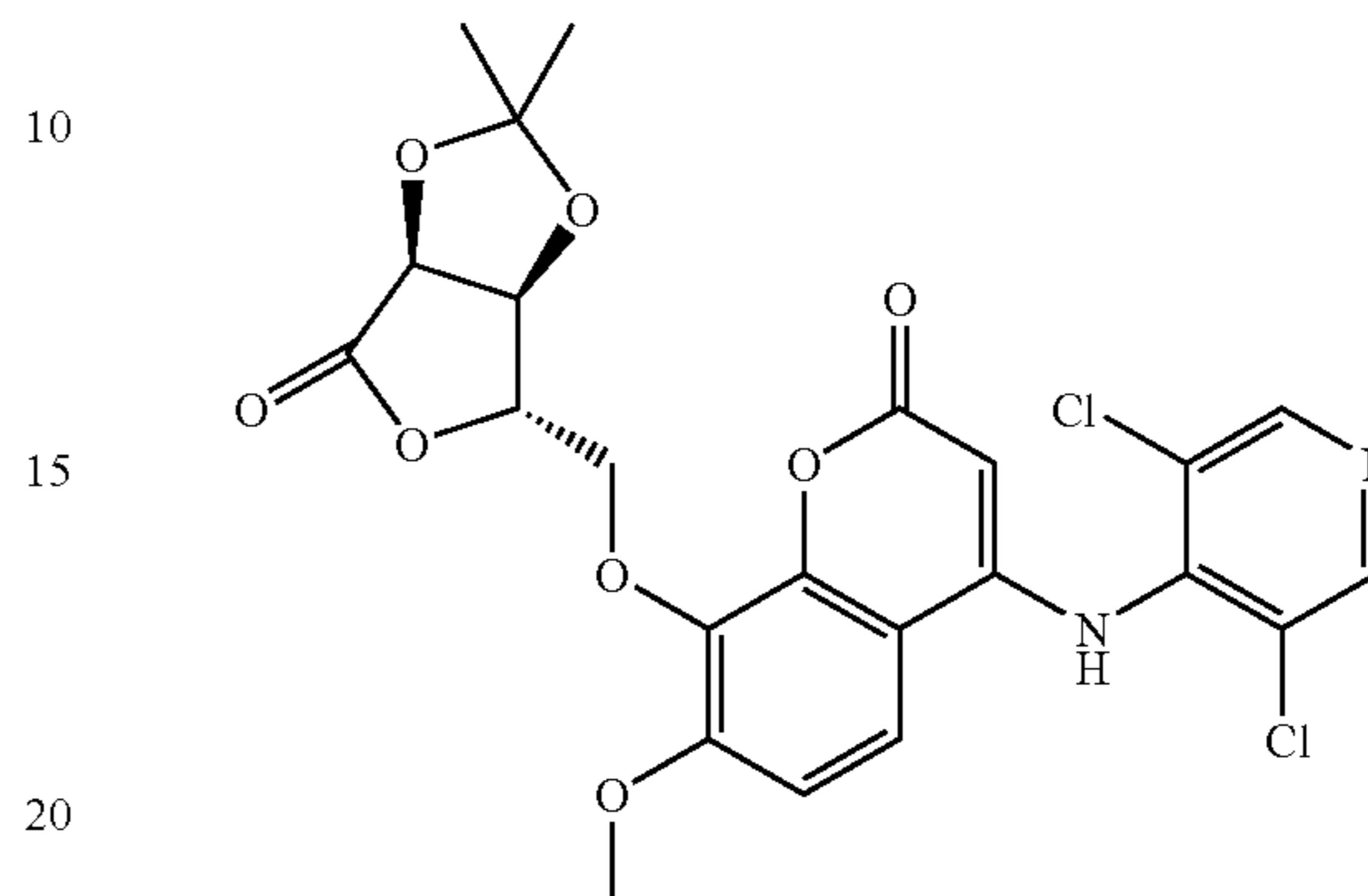


The title compound was prepared from 2-bromoacetic acid and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.90 (br, 1H), 9.56 (br s, 1H), 8.83 (s, 2H), 7.97 (d, 1H), 7.23 (d, 1H), 4.66 (s, 1H), 4.65 (s, 2H), 3.94 (s, 3H); MS (ESI): 410.8.

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## EXAMPLE 50

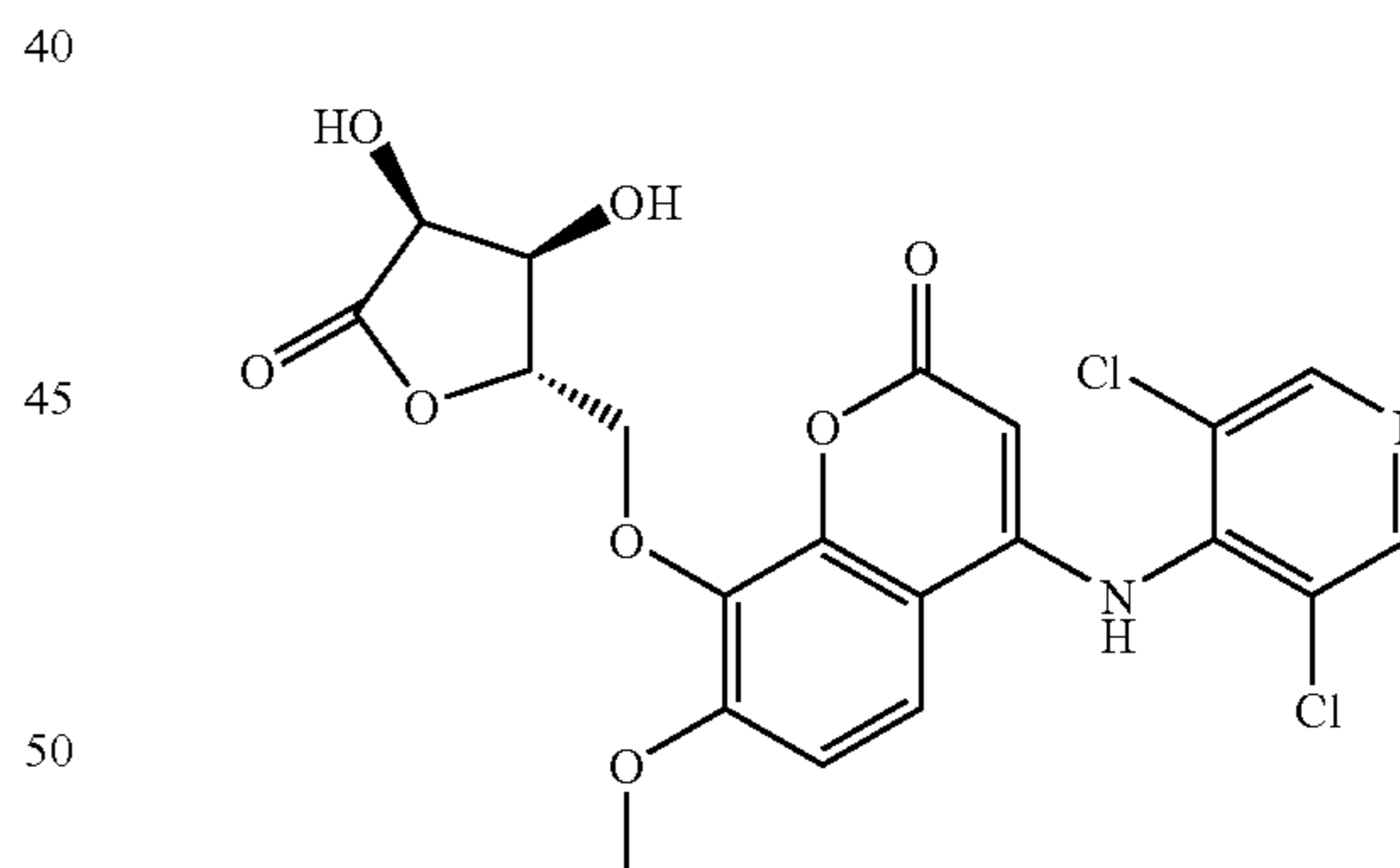
4-(3,5-Dichloropyridin-4-ylamino)-8-(((3aS,4S,6aS)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from (3aS,6R,6aR)-6-(bromomethyl)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-(3aH)-one and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.57 (s, 1H), 8.83 (s, 2H), 7.98 (d, 1H), 7.23 (s, 1H), 5.16 (m, 2H), 4.87 (m, 1H), 4.67 (s, 1H), 4.36 (m, 2H), 3.93 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H); MS (ESI): 522.8.

## EXAMPLE 51

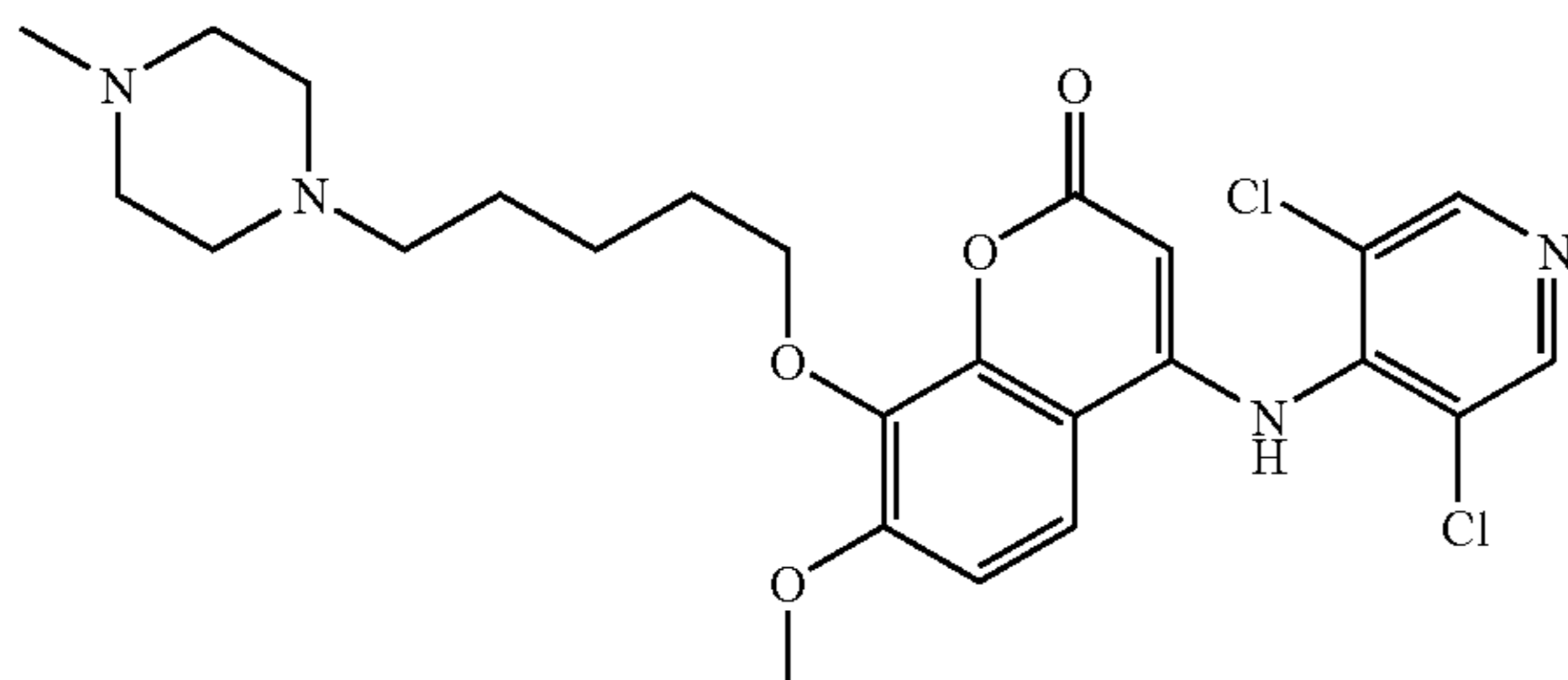
4-(3,5-Dichloropyridin-4-ylamino)-8-(((2S,3R,4S)-3,4-dihydroxy-5-oxotetrahydrofuran-2-yl)methoxy)-7-methoxy-2H-chromen-2-one



Trifluoroacetic acid (0.1 mL) was added to a mixture of 4-(3,5-dichloropyridin-4-ylamino)-8-(((3aS,4S,6aS)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)-7-methoxy-2H-chromen-2-one (60 mg, 0.12 mmol, Example 50), water (0.1 mL), and THF (3 mL). The mixture was stirred at rt for 2 d. Then, more trifluoroacetic acid (3 mL) was added over time until the reaction was complete by LCMS. The mixture was concentrated to give 4-(3,5-dichloropyridin-4-ylamino)-8-(((2S,3R,4S)-3,4-dihydroxy-5-oxotetrahydrofuran-2-yl)methoxy)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.55 (s, 1H), 8.81 (s, 2H), 7.97 (d, 1H), 7.21 (d, 1H), 5.74 (s, 1H), 4.63 (s, 1H), 4.61 (d, 1H), 4.49 (m, 1H), 4.42 (d, 1H), 4.23 (d, 1H), 3.91 (s, 3H); MS (ESI): 482.8.

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EXAMPLE 52

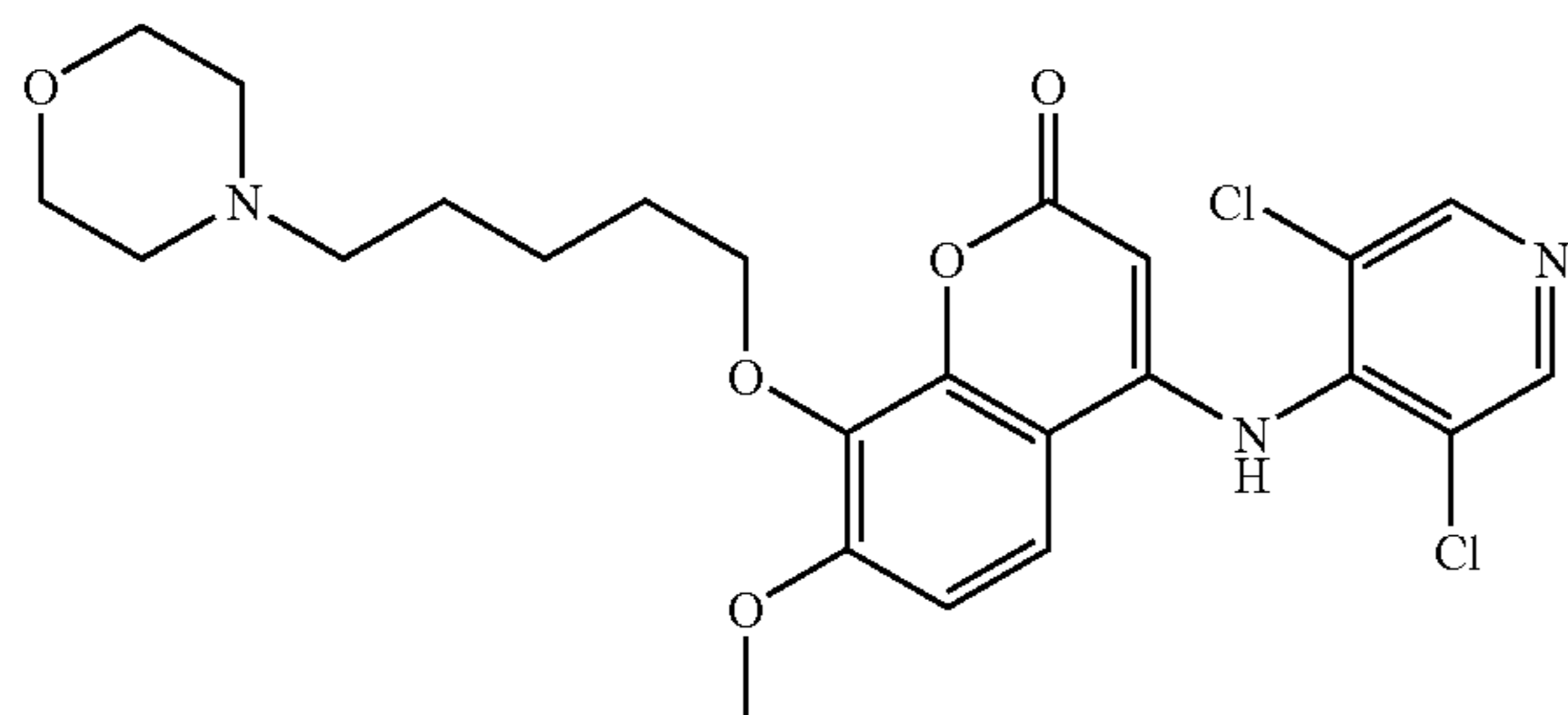
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(4-methylpiperazin-1-yl)pentyl)oxy)-2H-chromen-2-one



1-Methylpiperazine (0.2 mL, 1.8 mmol) was added to a solution of 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (50 mg, 0.1 mmol, Example 28) and DMSO (1.5 mL). After 10 h, the reaction was poured into 10% K<sub>2</sub>CO<sub>3</sub> (30 mL) and extracted with ethyl acetate (30 mL×3). The combined organic extracts were dried, filtered, concentrated, and purified by reverse-phase HPLC (acetonitrile:water) to give 4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-8-(5-(4-methylpiperazin-1-yl)pentyl)oxy)-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.45 (br s, 1H), 8.71 (s, 2H), 7.90 (d, 1H), 7.13 (d, 1H), 4.46 (br s, 1H), 3.97 (t, 2H), 3.90 (s, 3H), 2.60-2.20 (br, 10H), 2.21 (s, 3H), 1.68 (m, 2H), 1.47 (m, 4H); MS (ESI): 520.9.

EXAMPLE 53

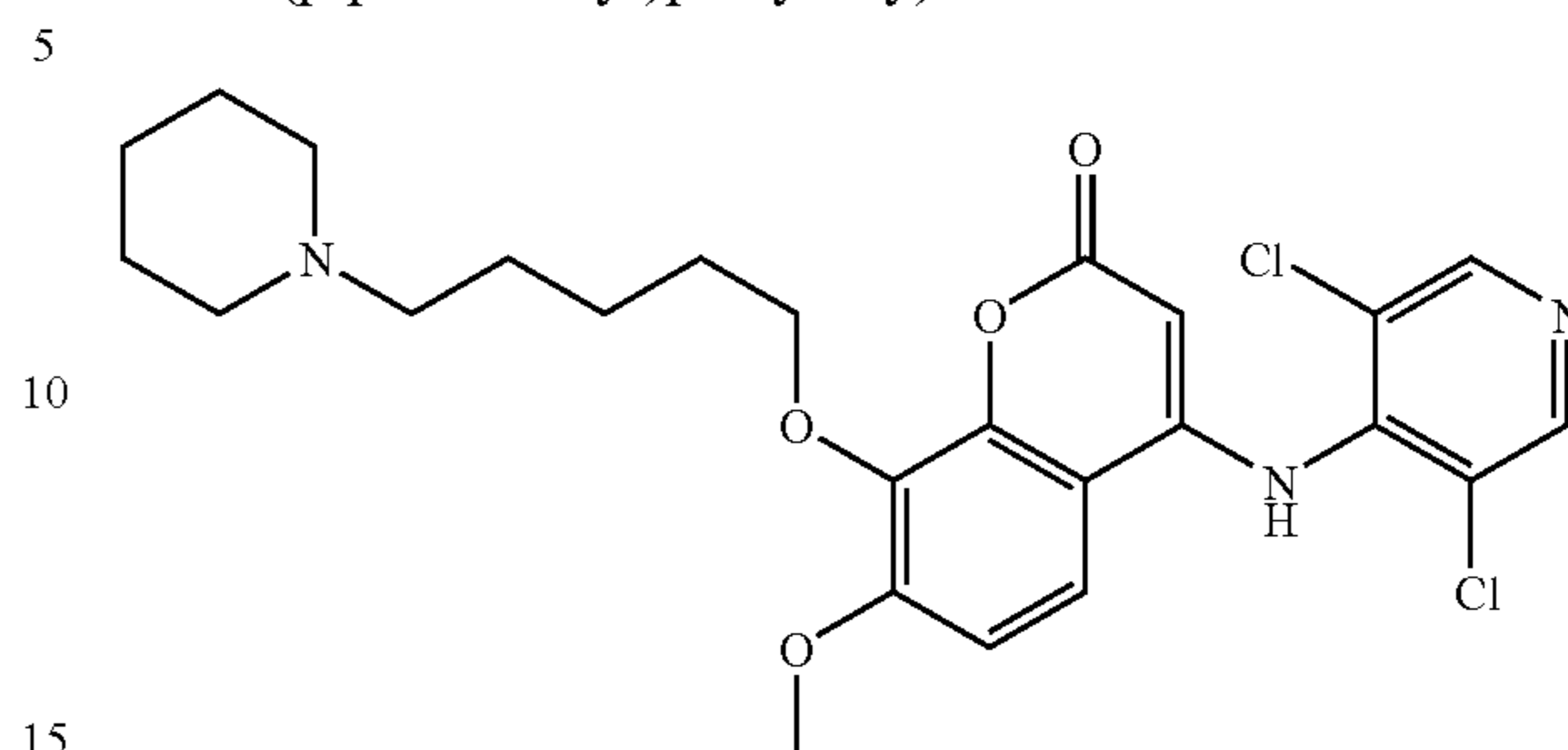
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-morpholinopentyl)oxy)-2H-chromen-2-one



The title compound was prepared from morpholine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (br s, 1H), 8.80 (s, 2H), 7.94 (d, 1H), 7.19 (d, 1H), 4.62 (s, 1H), 3.98 (t, 2H), 3.91 (s, 3H), 3.55 (br, 4H), 2.51-2.15 (br, 6H), 1.69 (m, 2H), 1.47 (m, 4H); MS (ESI): 507.9.

**56**  
EXAMPLE 54

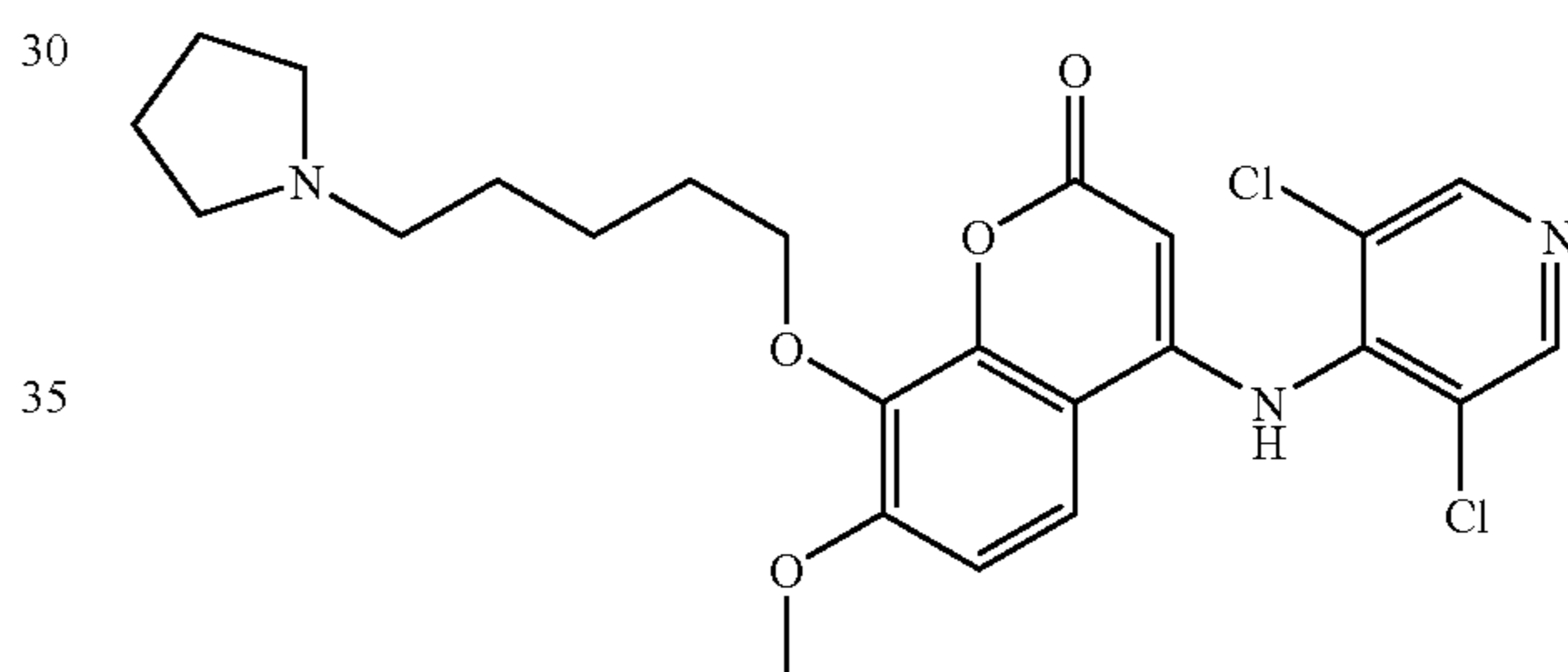
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(piperidin-1-yl)pentyl)oxy)-2H-chromen-2-one



The title compound was prepared from piperidine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.31 (br s, 1H), 8.55 (s, 2H), 7.85 (d, 1H), 7.04 (d, 1H), 4.20 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.90-2.30 (br, 6H), 1.75-1.35 (m, 12H); MS (ESI): 505.9.

EXAMPLE 55

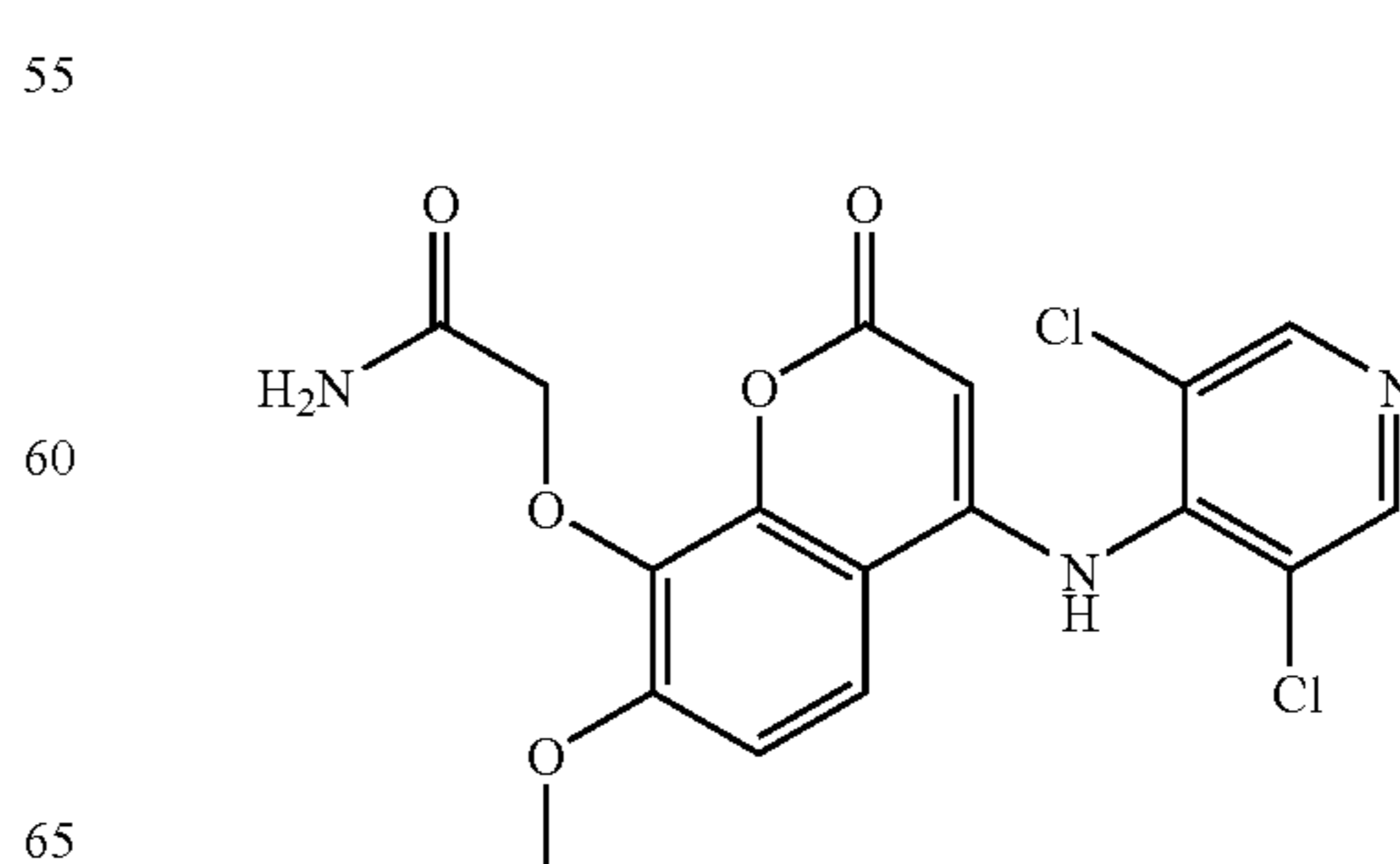
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(pyrrolidin-1-yl)pentyl)oxy)-2H-chromen-2-one



The title compound was prepared from pyrrolidine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.58 (br s, 1H), 8.50 (s, 2H), 7.83 (d, 1H), 7.02 (d, 1H), 4.12 (br s, 1H), 3.97 (t, 2H), 3.87 (s, 3H), 2.87 (br, 6H), 1.80 (m, 4H), 1.70 (m, 4H), 1.53 (m, 2H); MS (ESI): 491.9.

EXAMPLE 56

2-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetamide

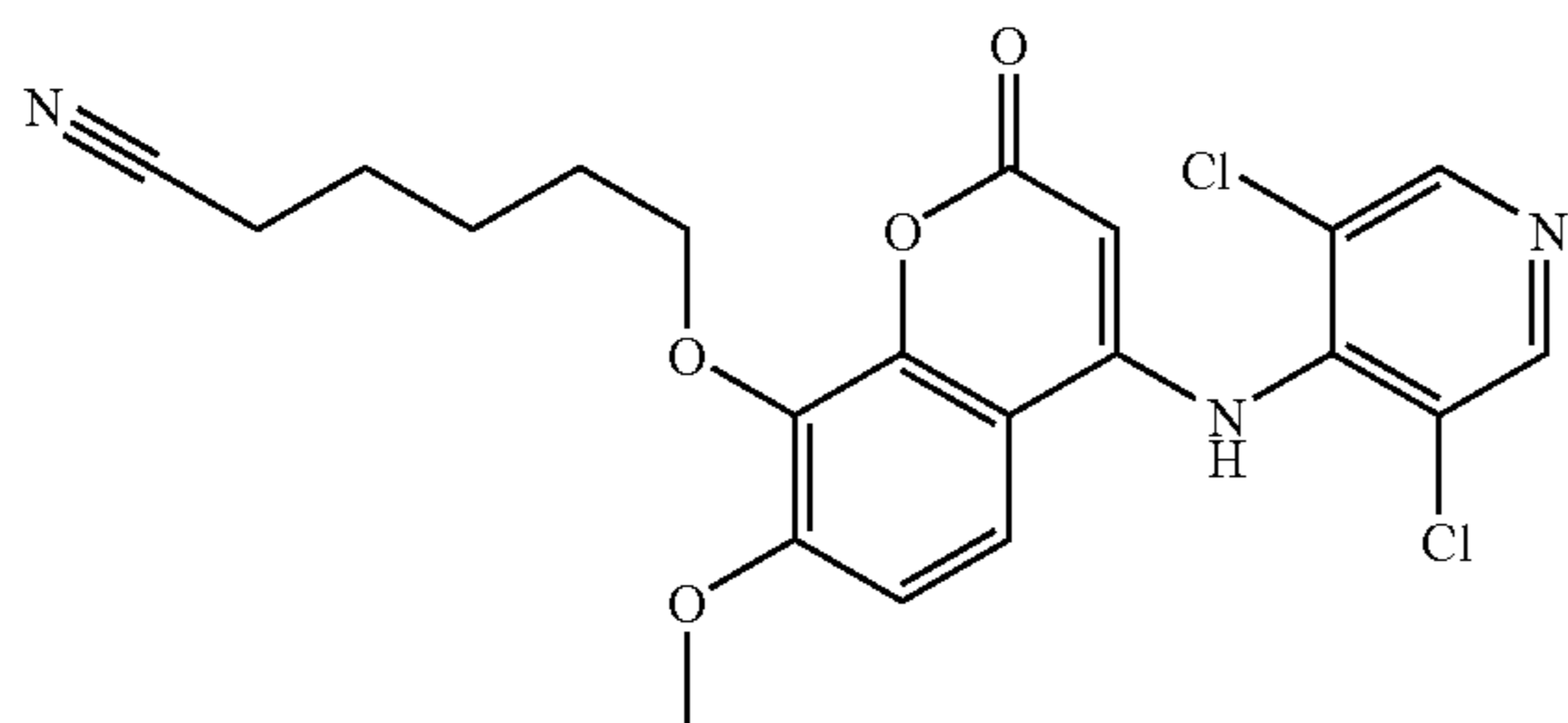


## 57

EDC.HCl (85.8 mg, 0.37 mmol), HOBt (49.4 mg, 0.37 mmol), and DMAP (cat.) were sequentially added to a solution of 2-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetic acid (100 mg, 0.24 mmol, Example 49) and pyridine (10 mL). After 5 min, a saturated solution of ammonia in THF (10 mL) was added, and the reaction was heated at 40° C. overnight. The reaction was allowed to cool to rt, concentrated to remove THF, and then 2N HCl was added to pH=3. The precipitate was filtered, washed with water, and dried. The crude product was refluxed in ethyl acetate (20 mg/mL) for 10 min, sonicated to break up large particles, refluxed for another 10 min, and then let stand overnight. Filtration and drying gave 2-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetamide: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.58 (br s, 1H), 8.79 (s, 2H), 7.97 (d, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 7.23 (d, 1H), 4.62 (s, 1H), 4.40 (s, 2H), 3.94 (s, 3H); MS (ESI): 409.8.

## EXAMPLE 57

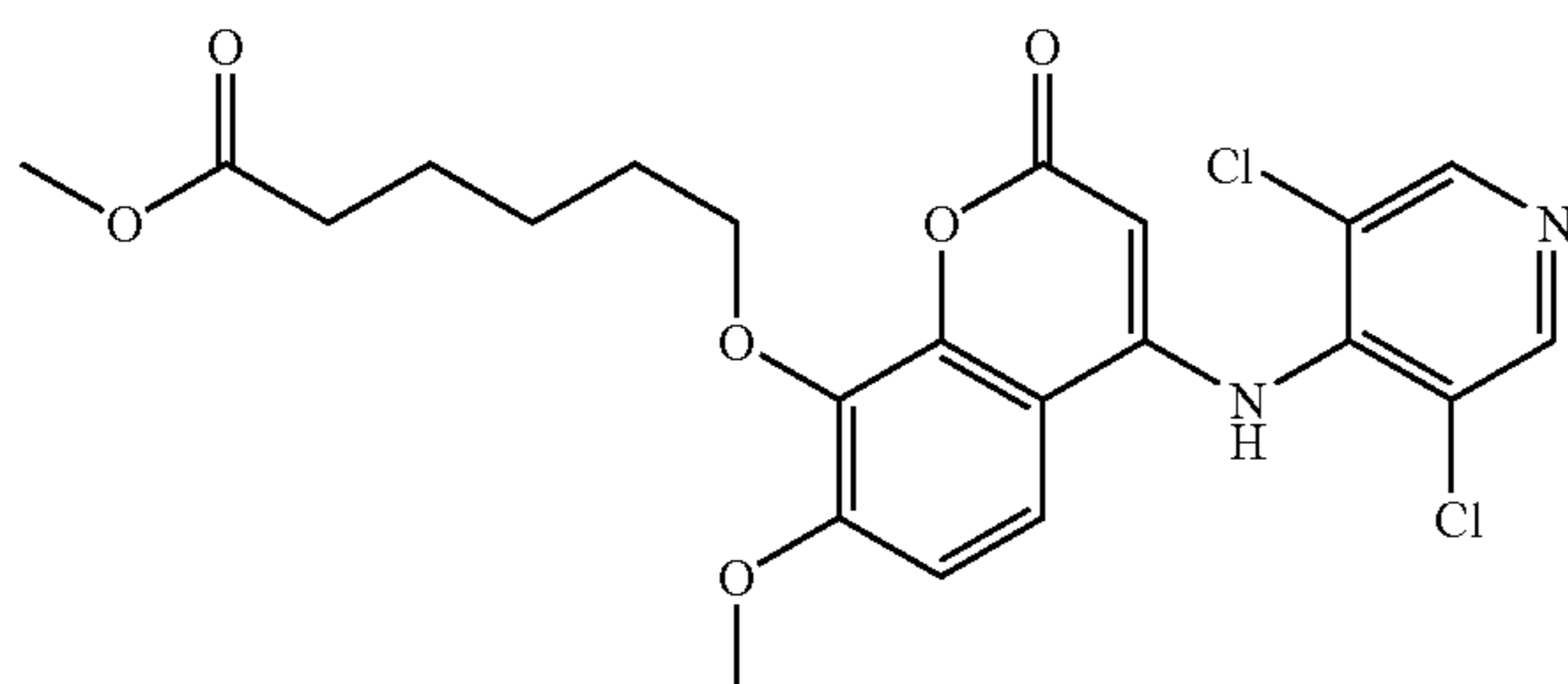
6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanenitrile



The title compound was prepared from potassium cyanide and 8-(5-bromopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 3.98 (t, 2H), 3.92 (s, 3H), 2.51 (t, 2H), 1.75-1.55 (m, 6H); MS (ESI): 447.9.

## EXAMPLE 58

Methyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoate



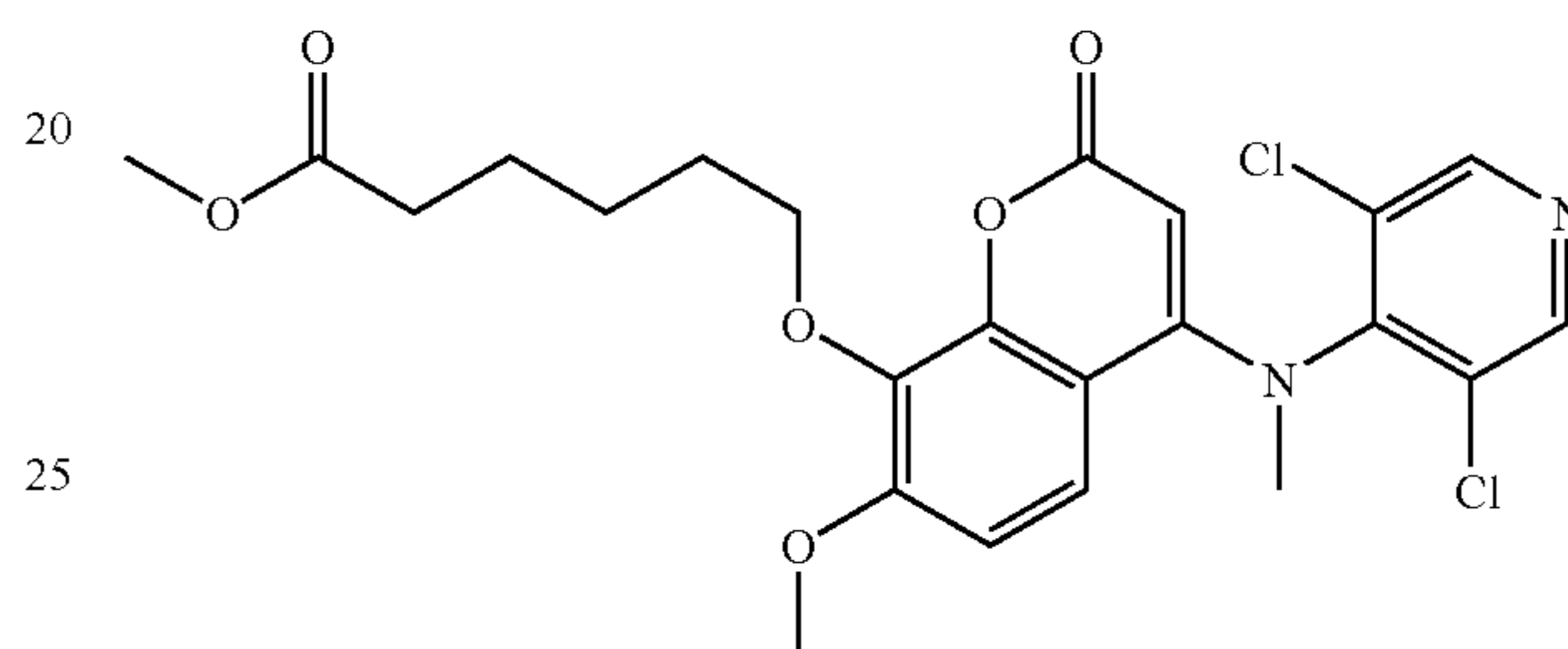
A solution of TMSCHN<sub>2</sub> (0.75 mL, 2M Et<sub>2</sub>O, 1.5 mmol) was added to a solution of 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid (115 mg, 0.25 mmol, Example 44), methanol (1 mL), and toluene (8 mL). After 10 min, the reaction was concentrated

## 58

and purified by silica gel chromatography (4:1→1:4; hexanes:ethyl acetate) to give methyl 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoate: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 3.56 (s, 3H), 2.31 (t, 2H), 1.67 (m, 2H), 1.57 (m, 2H), 1.46 (m, 2H); MS (ESI): 480.9.

## EXAMPLE 59

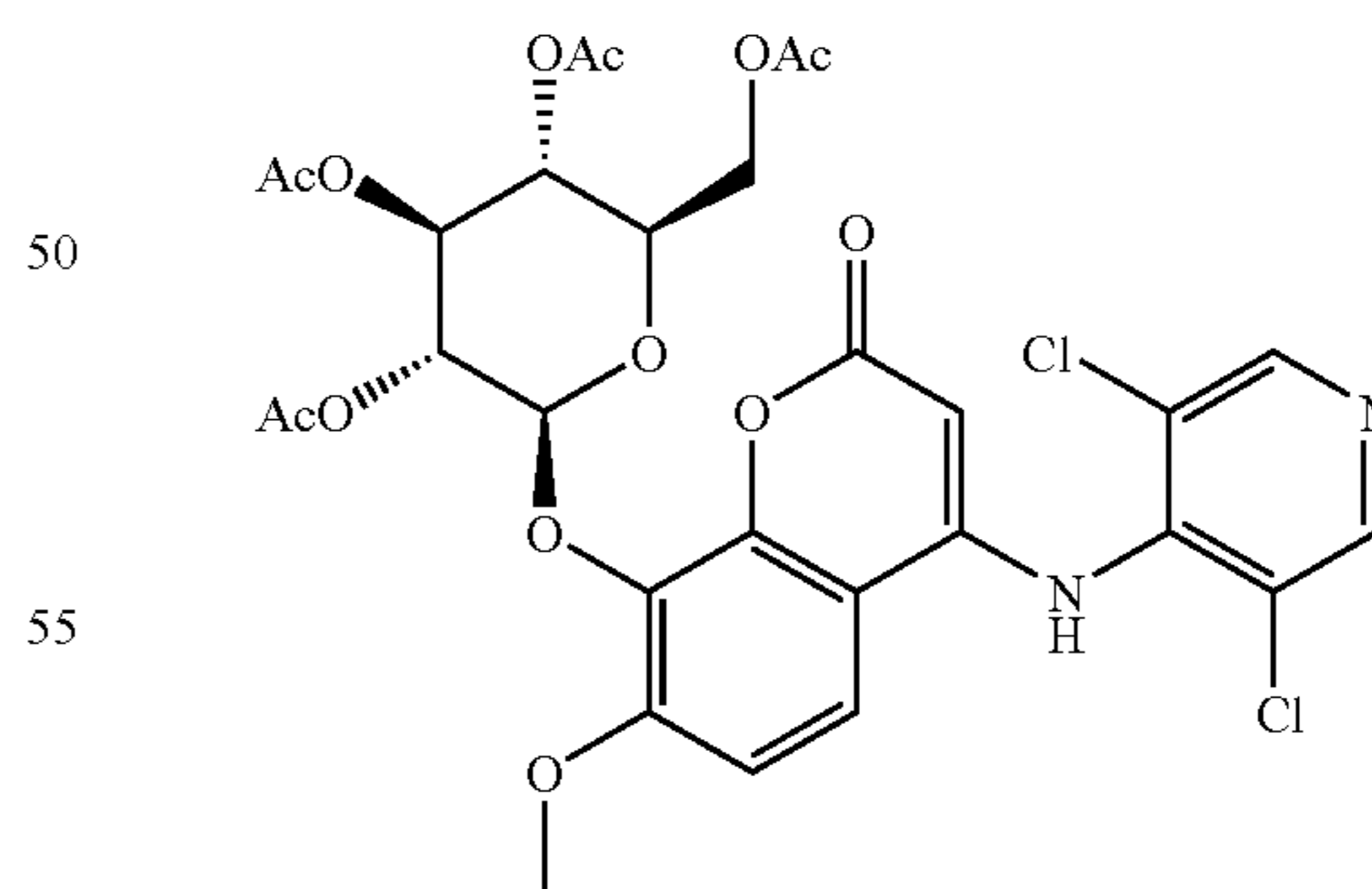
Methyl 6-(4-((3,5-dichloropyridin-4-yl)(methyl)amino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoate



The title compound was isolated during the purification of Example 58. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.50 (s, 2H), 7.95 (d, 1H), 7.23 (d, 1H), 4.92 (s, 1H), 4.00 (t, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.57 (s, 3H), 2.31 (t, 2H), 1.68 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H); MS (ESI): 494.9.

## EXAMPLE 60

(2R,3R,4S,5R,6S)-2-(Acetoxymethyl)-6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



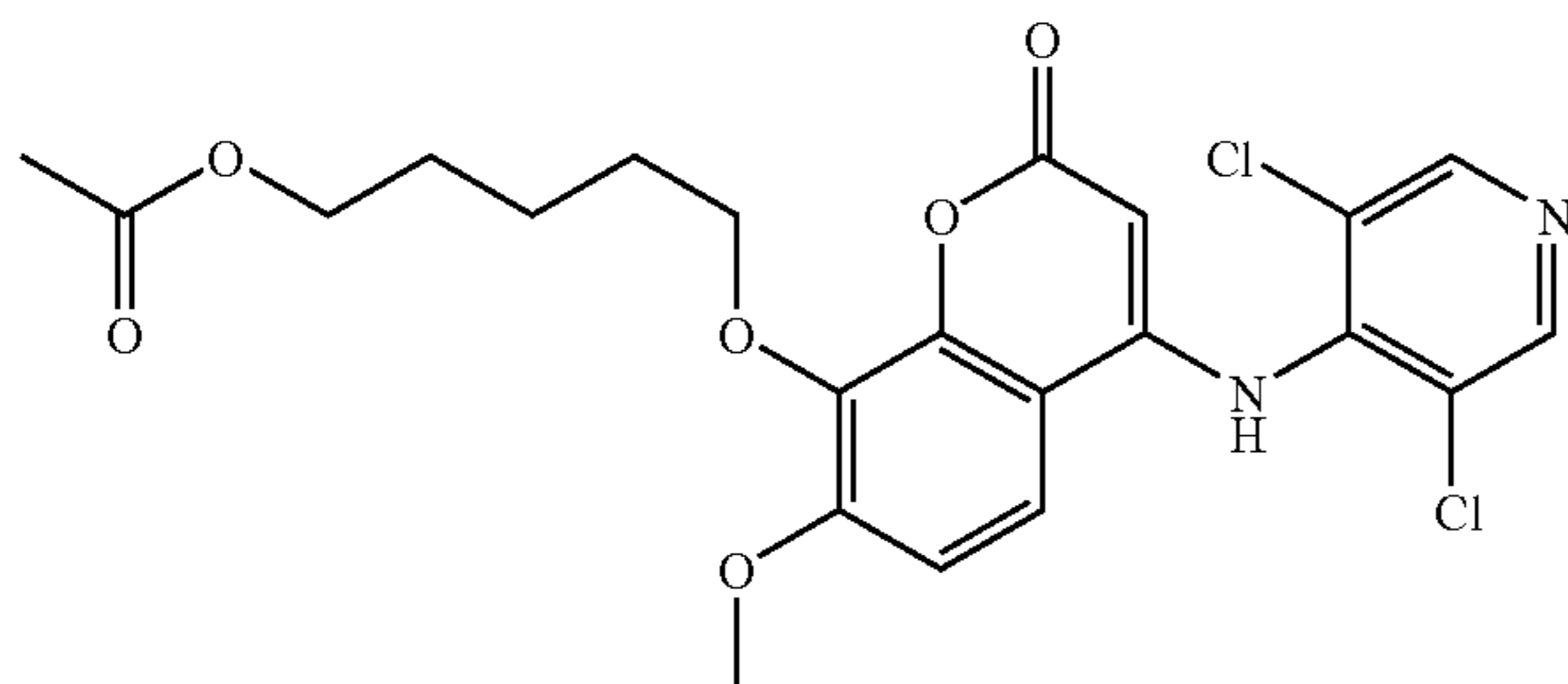
Boron trifluoride•OEt<sub>2</sub> (54 μL, 0.43 mmol) was added to a suspension of (3R,4S,5S,6R)-2-(acetoxymethyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (0.168 g, 0.341 mmol), 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (60 mg, 0.17 mmol, Example 29), and anhydrous acetonitrile (2 mL)

## 59

at  $-40^{\circ}\text{C}$ . under  $\text{N}_2$ . After 2 h at  $-40^{\circ}\text{C}$ ., the reaction was allowed to warm to rt and stirred overnight. The mixture was concentrated and purified by reverse-phase HPLC to give (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy) tetrahydro-2H-pyran-3,4,5-triyl triacetate:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.55 (s, 1H), 8.83 (s, 2H), 8.03 (d, 1H), 7.25 (d, 1H), 5.34 (m, 2H), 5.08 (m, 1H), 4.98 (m, 1H), 4.67 (s, 1H), 4.12 (m, 1H), 3.99 (m, 2H), 3.91 (s, 3H), 2.06 (s, 3H), 1.98 (m, 6H), 1.94 (s, 3H); MS (ESI): 682.8.

## EXAMPLE 61

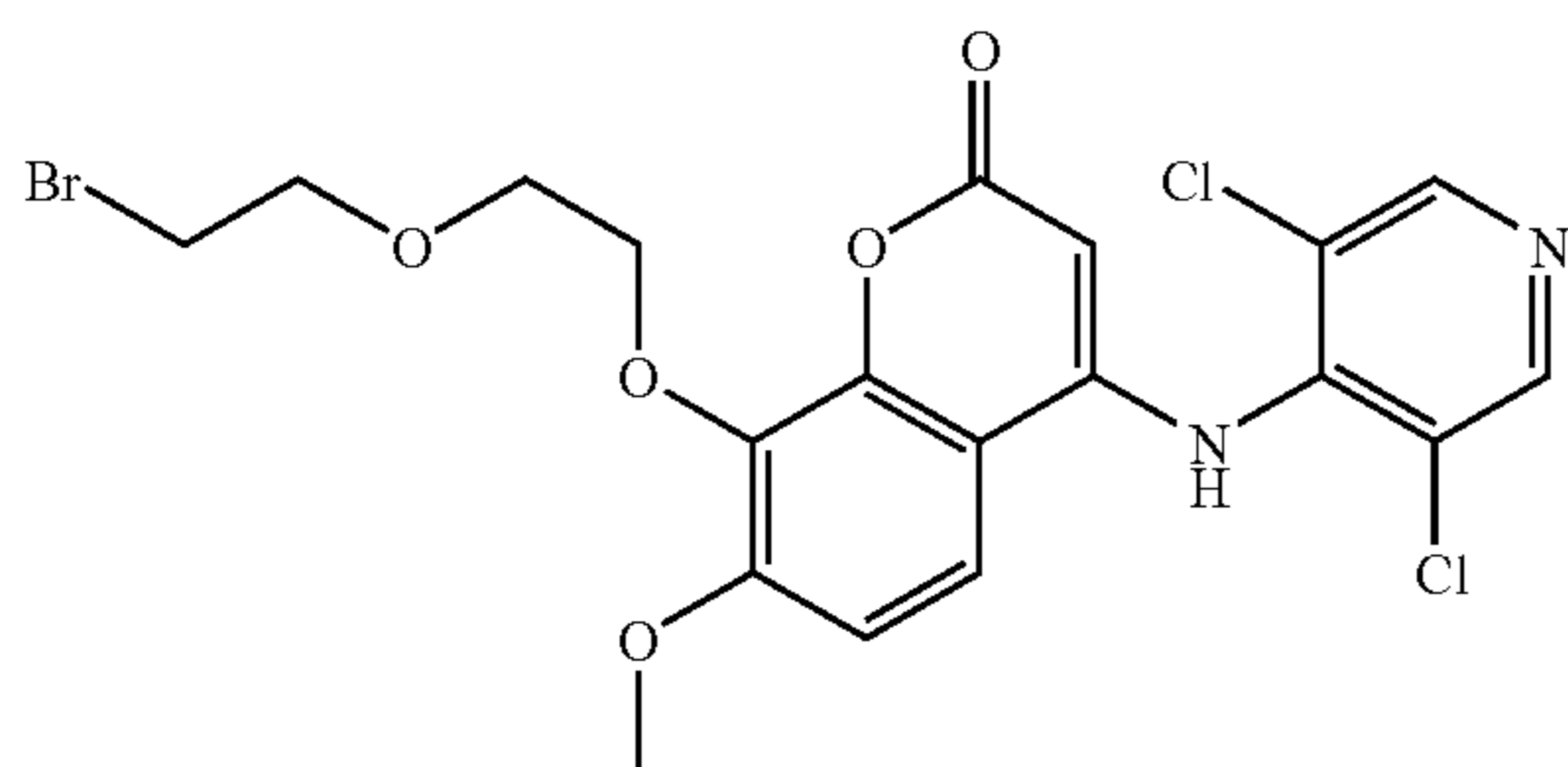
5-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl acetate



The title compound can be prepared from potassium acetate and 8-(5-bromopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.53 (s, 1H), 8.83 (s, 2H), 7.95 (d, 1H), 7.22 (s, 1H), 4.65 (s, 1H), 4.00 (m, 4H), 3.93 (s, 3H), 2.00 (s, 3H), 1.73-1.52 (m, 6H); MS (ESI): 480.9.

## EXAMPLE 62

8-(2-(2-Bromoethoxy)ethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



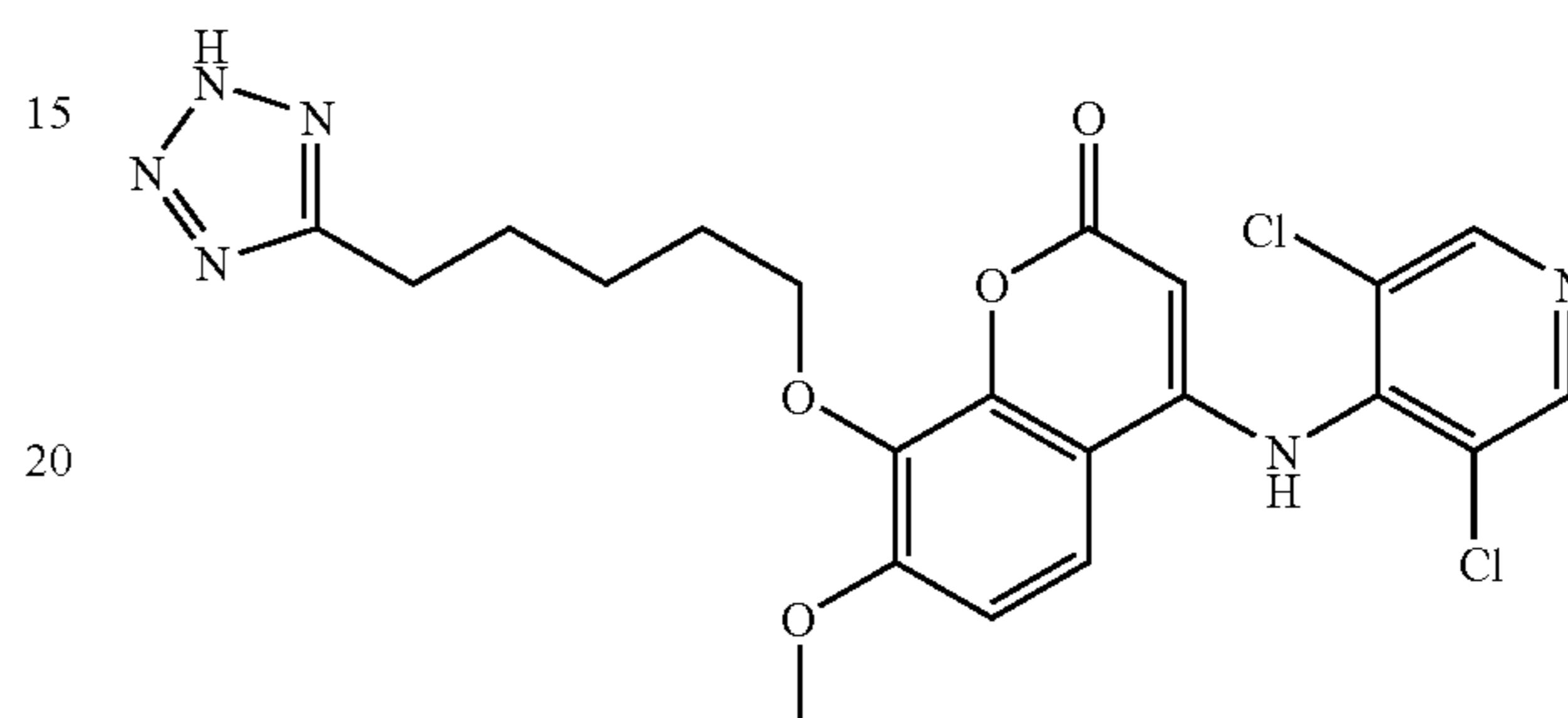
The title compound was prepared from 2-bromoethyl ether and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H),

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4.64 (s, 1H), 4.13 (m, 2H), 3.93 (s, 3H), 3.80-3.74 (m, 4H), 3.55 (t, 2H); MS (ESI): 502.7.

## EXAMPLE 63

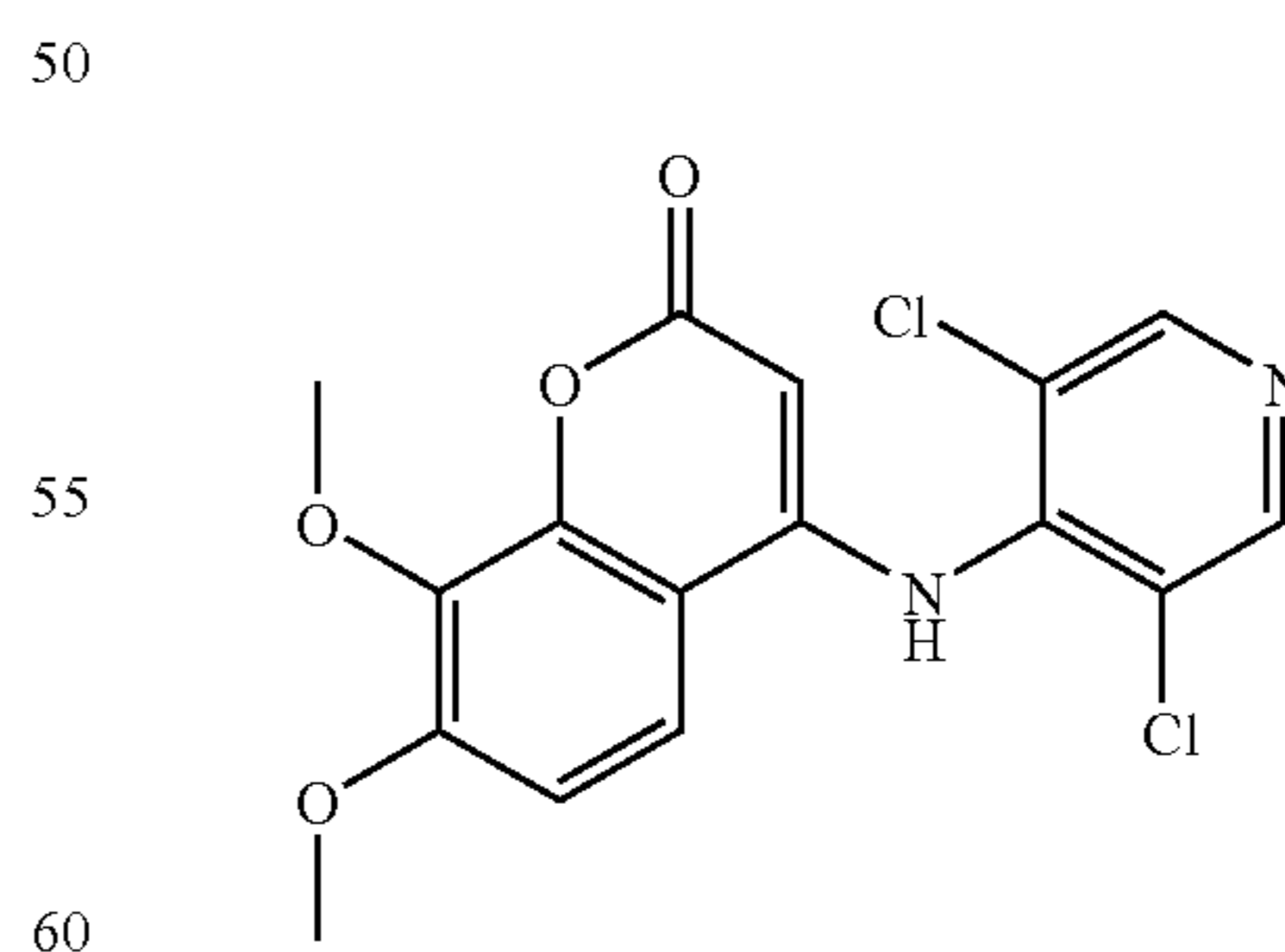
8-(5-(2H-Tetrazol-5-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



A mixture of 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanenitrile (170 mg, 0.38 mmol, Example 57), dibutyltin oxide (100 mg, 0.4 mmol),  $\text{TMSN}_3$  (0.5 mL, 3.8 mmol), and anhydrous toluene (5 mL) was heated at  $110^{\circ}\text{C}$ . under  $\text{N}_2$  for 15.5 h, allowed to cool to rt, and then quenched with methanol (1 mL). The reaction was concentrated and purified by silica gel chromatography (1:0 $\rightarrow$ 4:1; dichloromethane:methanol) to give 8-(5-(2H-tetrazol-5-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.51 (br s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 3.98 (t, 2H), 3.90 (s, 3H), 2.89 (t, 2H), 1.80-1.65 (m, 4H), 1.51 (m, 2H); MS (ESI): 490.9.

## EXAMPLE 64

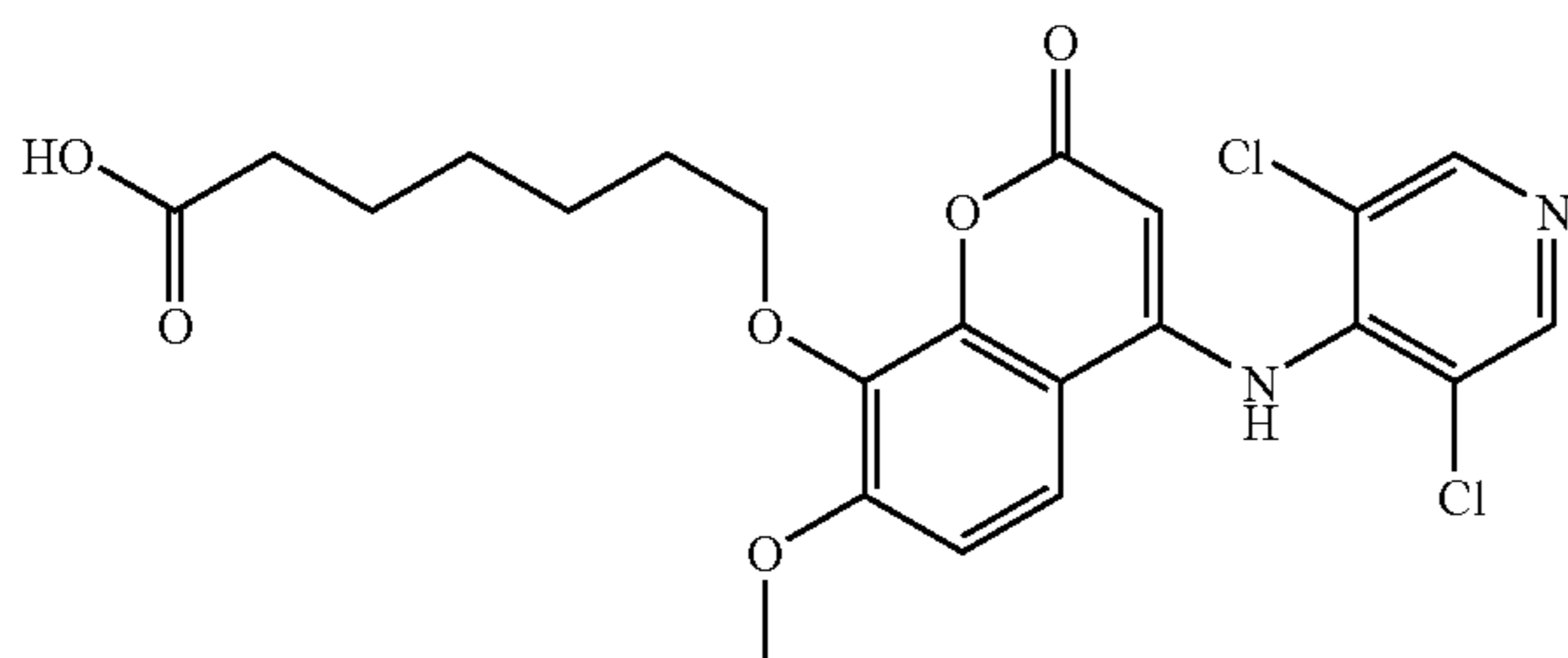
4-(3,5-Dichloropyridin-4-ylamino)-7,8-dimethoxy-2H-chromen-2-one



The title compound was isolated during the purification of Example 58.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  9.53 (s, 1H), 8.81 (s, 2H), 7.95 (d, 1H), 7.21 (d, 1H), 4.64 (s, 1H), 3.93 (s, 3H), 3.80 (s, 3H); MS (ESI): 366.8.

**61**  
EXAMPLE 65

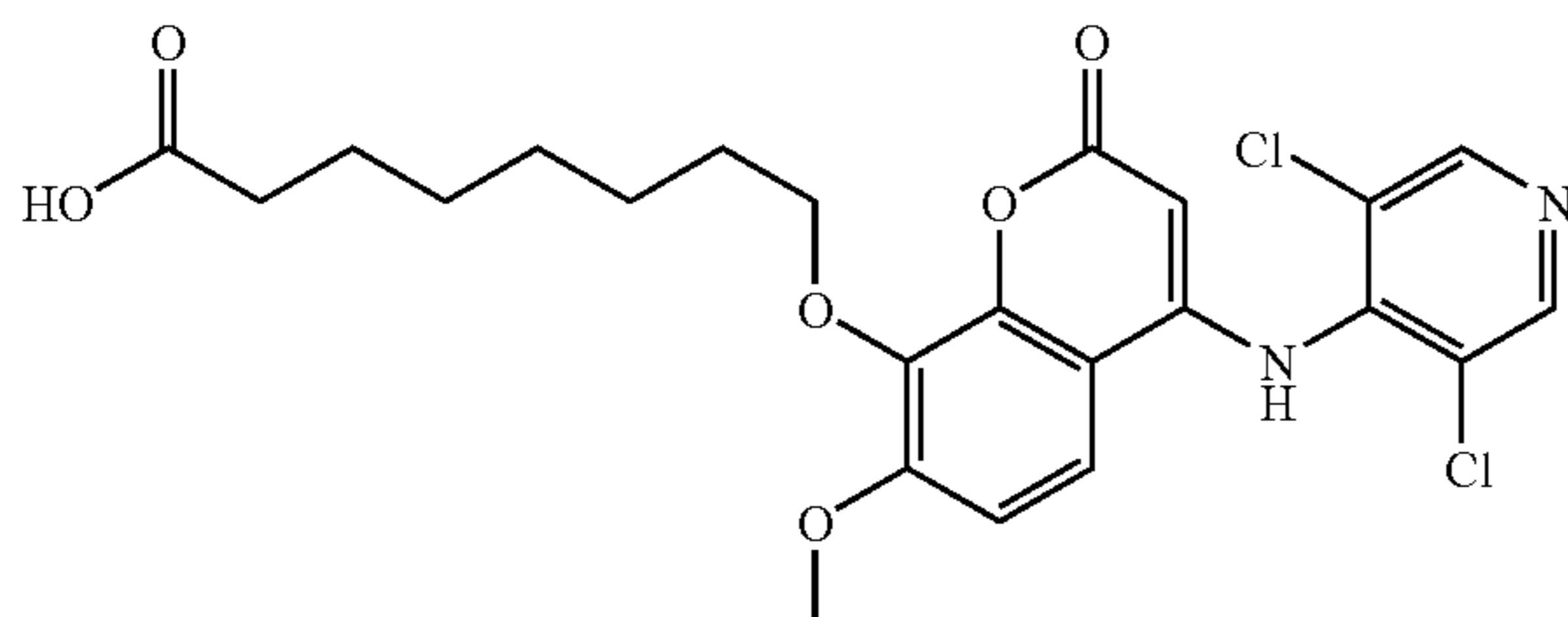
7-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)heptanoic acid



The title compound was prepared from ethyl 7-bromoheptanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 2.19 (t, 2H), 1.66 (m, 2H), 1.54-1.40 (m, 4H), 1.31 (m, 2H); MS (ESI): 480.9.

EXAMPLE 66

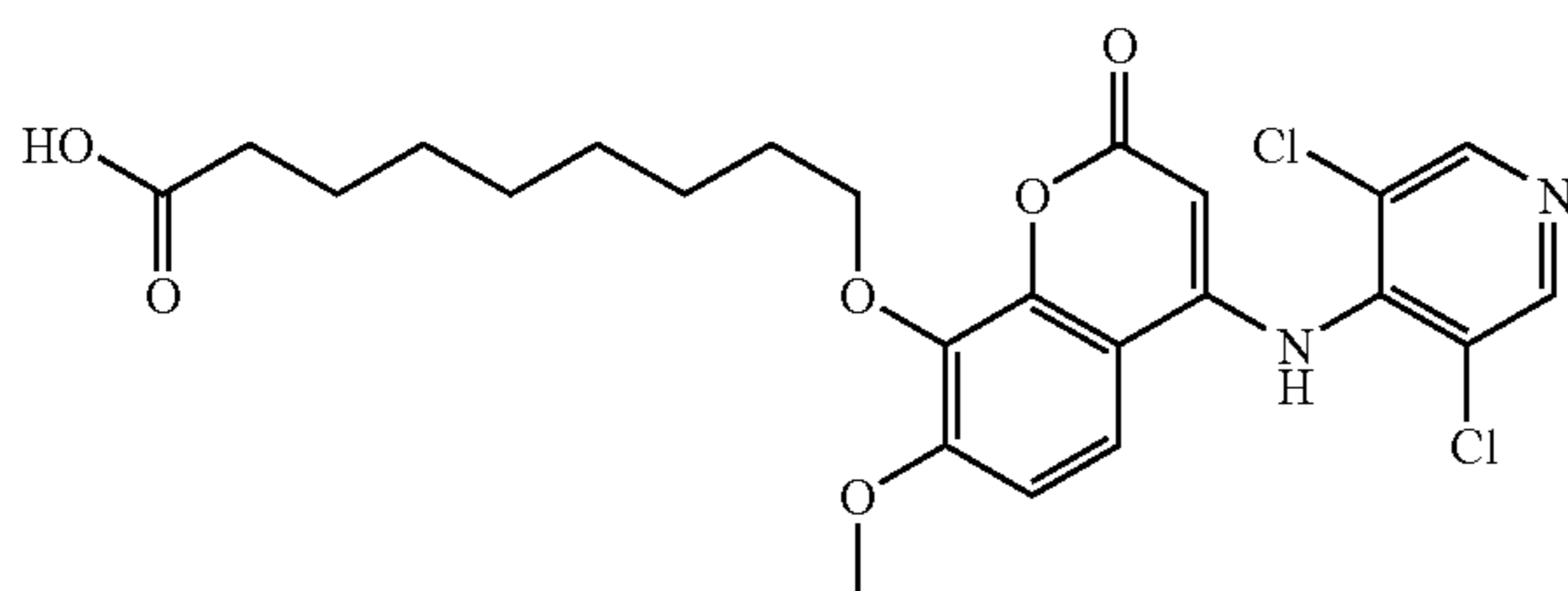
8-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)octanoic acid



The title compound was prepared from ethyl 8-bromo-octanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 2.18 (t, 2H), 1.66 (m, 2H), 1.54-1.40 (m, 4H), 1.36-1.24 (m, 4H); MS (ESI): 494.9.

EXAMPLE 67

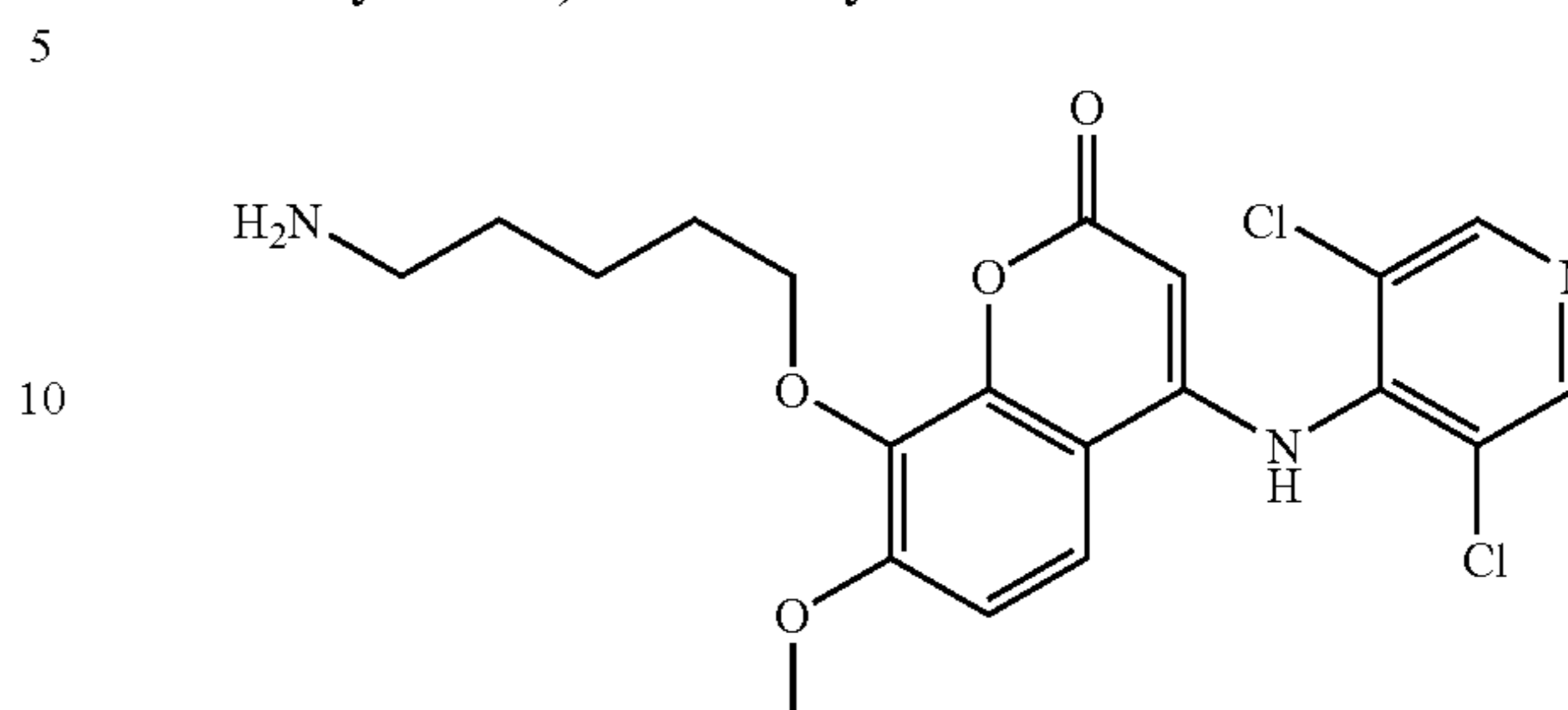
9-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)nonanoic acid



The title compound was prepared from ethyl 9-bromononanoate and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 2.17 (t, 2H), 1.66 (m, 2H), 1.52-1.38 (m, 4H), 1.34-1.22 (m, 6H); MS (ESI): 508.9.

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EXAMPLE 68

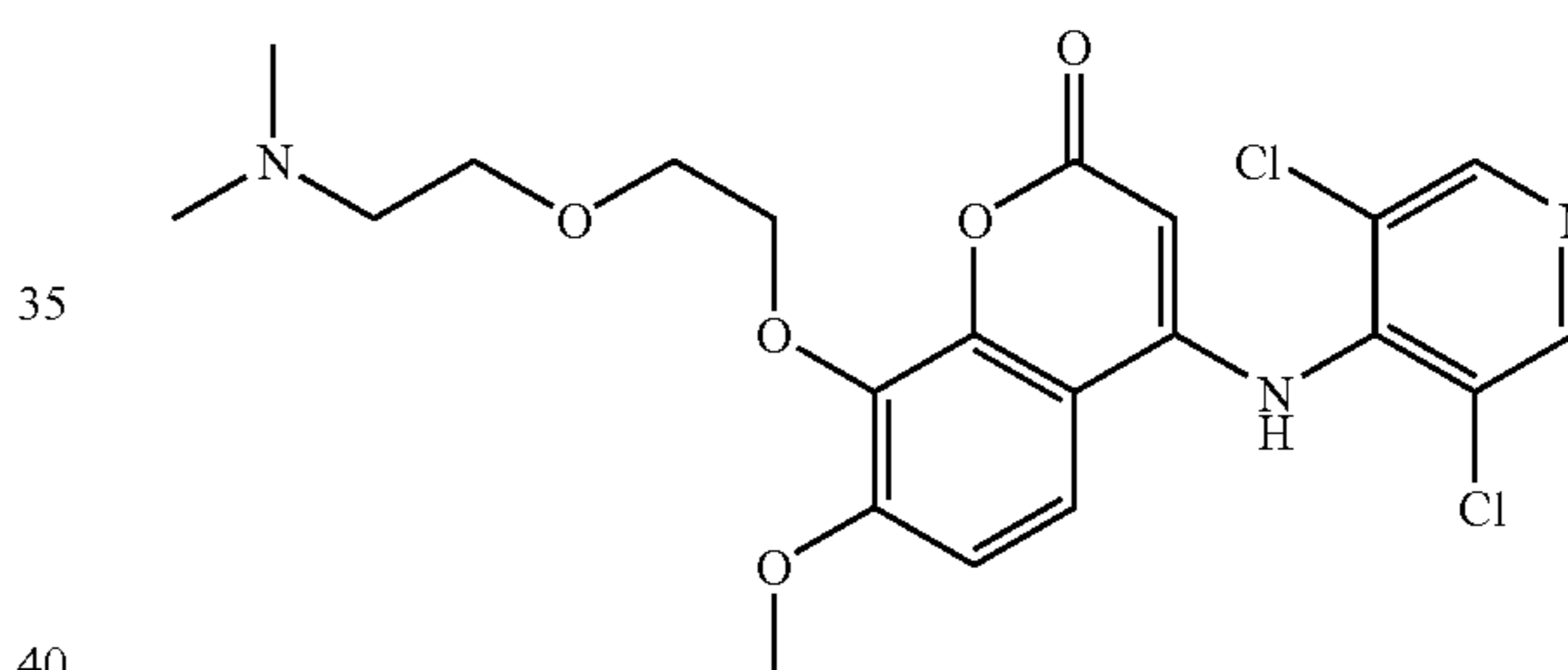
8-(5-Aminopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 28% NH<sub>4</sub>OH solution and 8-(5-bromopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>; HCl salt): δ 9.64 (s, 1H), 8.81 (s, 2H), 8.00 (d, 1H), 7.83 (br, 3H), 7.21 (d, 1H), 4.63 (s, 1H), 3.98 (t, 2H), 3.92 (s, 3H), 2.79 (m, 2H), 1.75-1.50 (m, 6H); MS (ESI): 437.9.

EXAMPLE 69

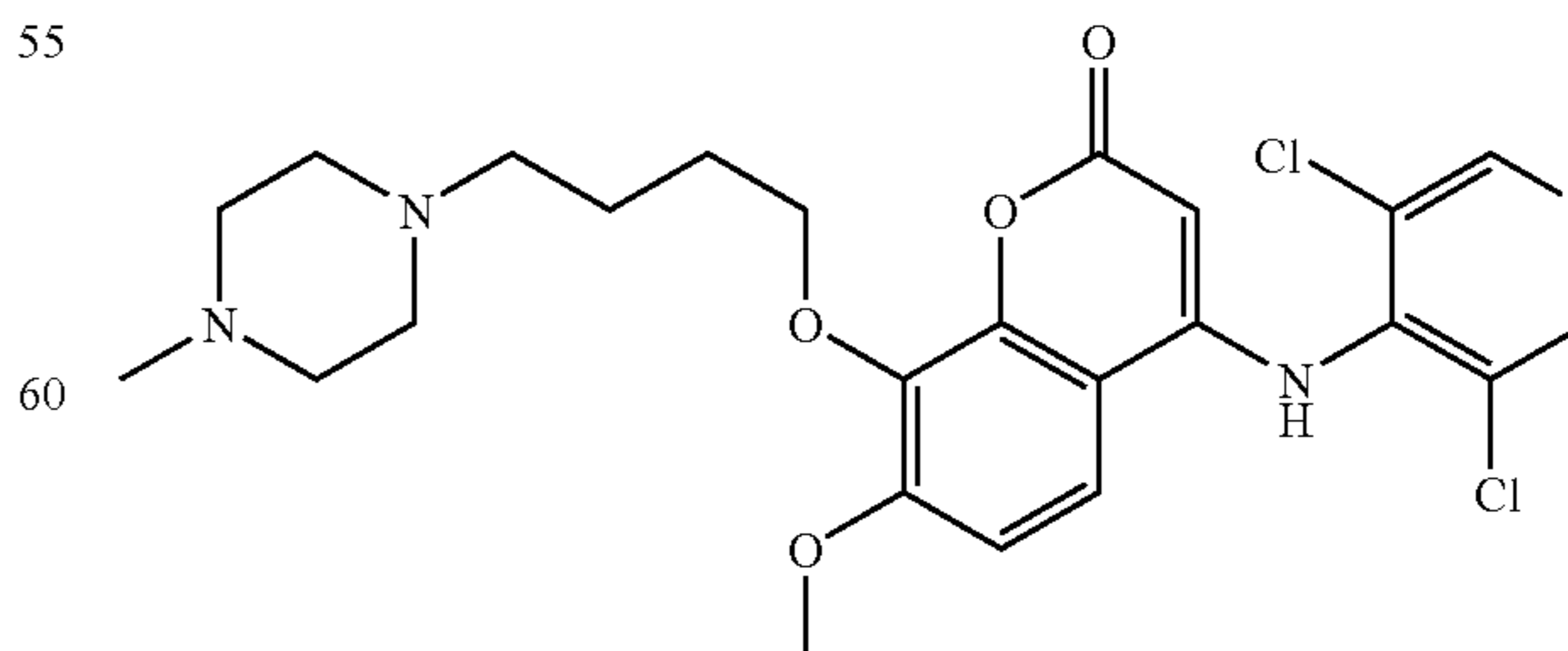
4-(3,5-Dichloropyridin-4-ylamino)-8-(2-(2-(dimethylamino)ethoxy)ethoxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 8-(2-(2-bromoethoxy)ethoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 62) following the procedure outlined in Example 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.73 (br s, 1H), 8.58 (s, 2H), 7.87 (d, 1H), 7.07 (d, 1H), 4.25 (br s, 1H), 4.10 (m, 2H), 3.88 (s, 3H), 3.72-3.62 (m, 4H), 2.78 (br, 2H), 2.44 (s, 6H); MS (ESI): 467.9.

EXAMPLE 70

4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(4-(4-methylpiperazin-1-yl)butoxy)-2H-chromen-2-one



The title compound was prepared from 1-methylpiperazine and 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-

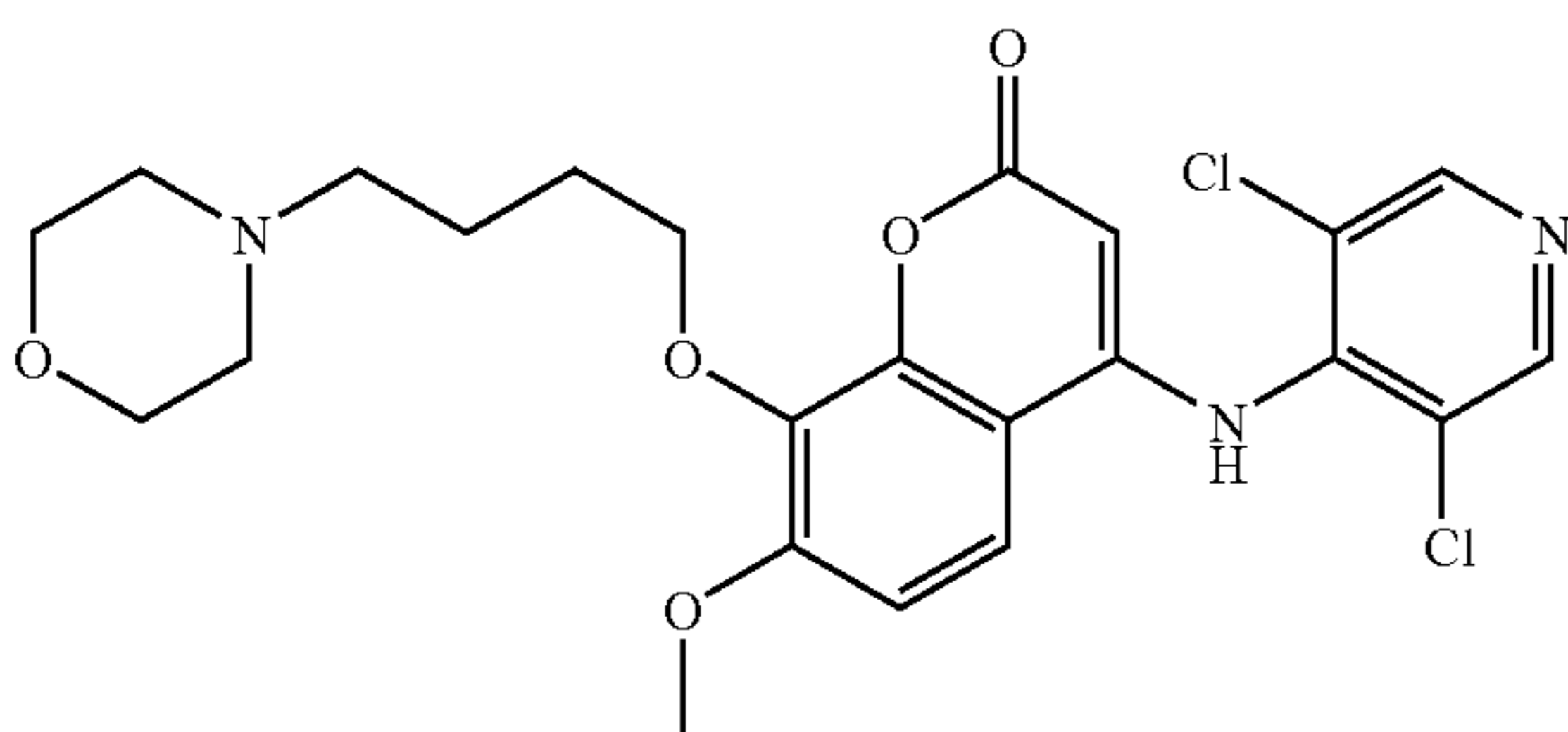


## 63

7-methoxy-2H-chromen-2-one (Example 25) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>; bis HCl salt): δ 11.74 (br, 2H), 9.66 (s, 1H), 8.82 (s, 2H), 8.02 (d, 1H), 7.22 (d, 1H), 4.63 (s, 1H), 4.01 (t, 2H), 3.94 (s, 3H), 3.84-3.18 (br m, 10H), 2.81 (s, 3H), 1.97 (m, 2H), 1.75 (m, 2H); MS (ESI): 507.0.

## EXAMPLE 71

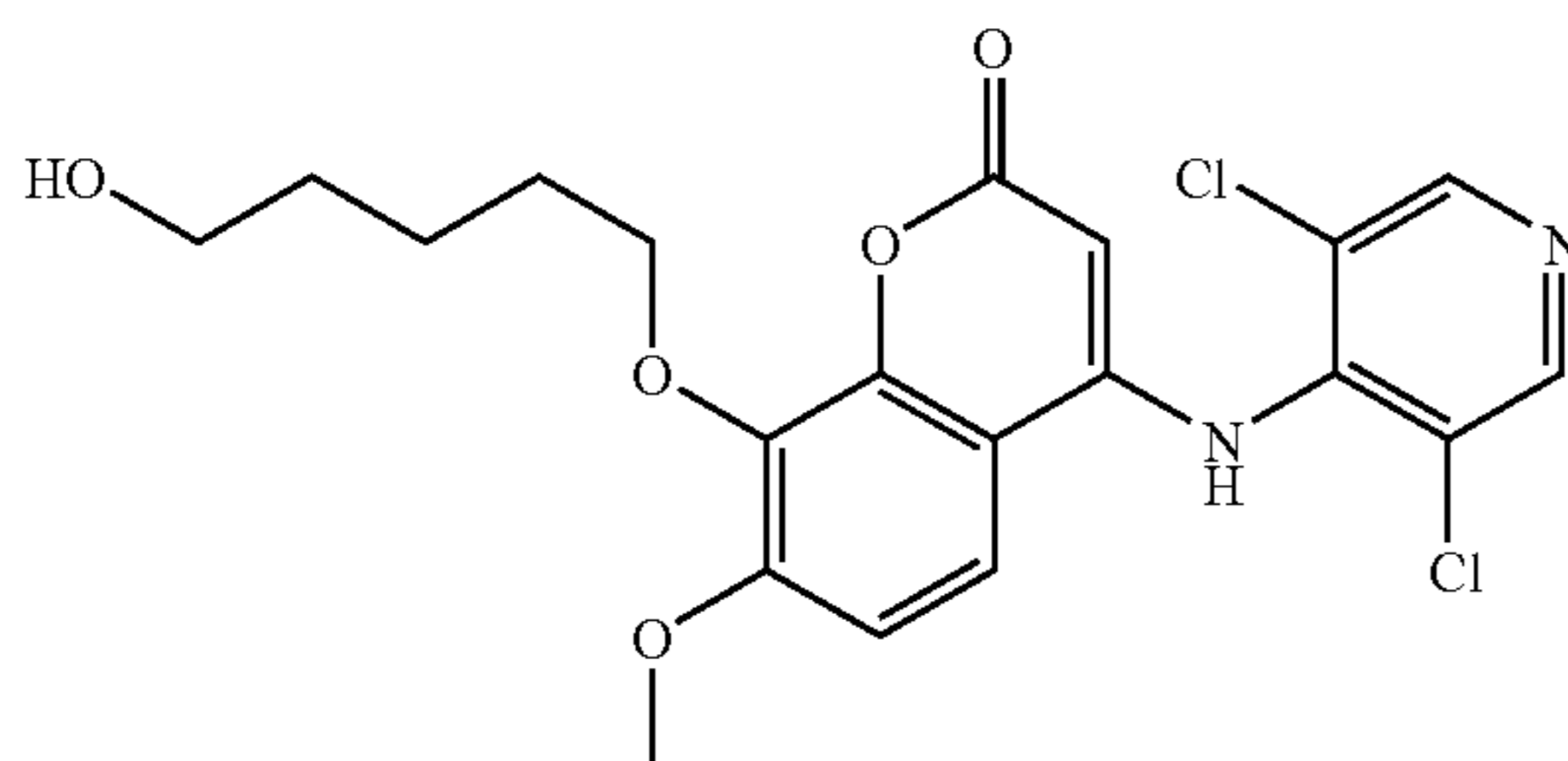
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(4-morpholinobutoxy)-2H-chromen-2-one



The title compound was prepared from morpholine and 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 25) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>; HCl salt): δ 10.67 (br, 1H), 9.65 (br s, 1H), 8.82 (s, 2H), 8.01 (d, 1H), 7.22 (d, 1H), 4.64 (s, 1H), 4.01 (t, 2H), 3.93 (s, 3H), 3.92 (m, 2H), 3.76 (t, 2H), 3.42 (d, 2H), 3.20 (m, 2H), 3.05 (m, 2H), 1.97 (m, 2H), 1.74 (m, 2H); MS (ESI): 494.0.

## EXAMPLE 72

4-(3,5-Dichloropyridin-4-ylamino)-8-(5-hydroxypentyl)-7-methoxy-2H-chromen-2-one

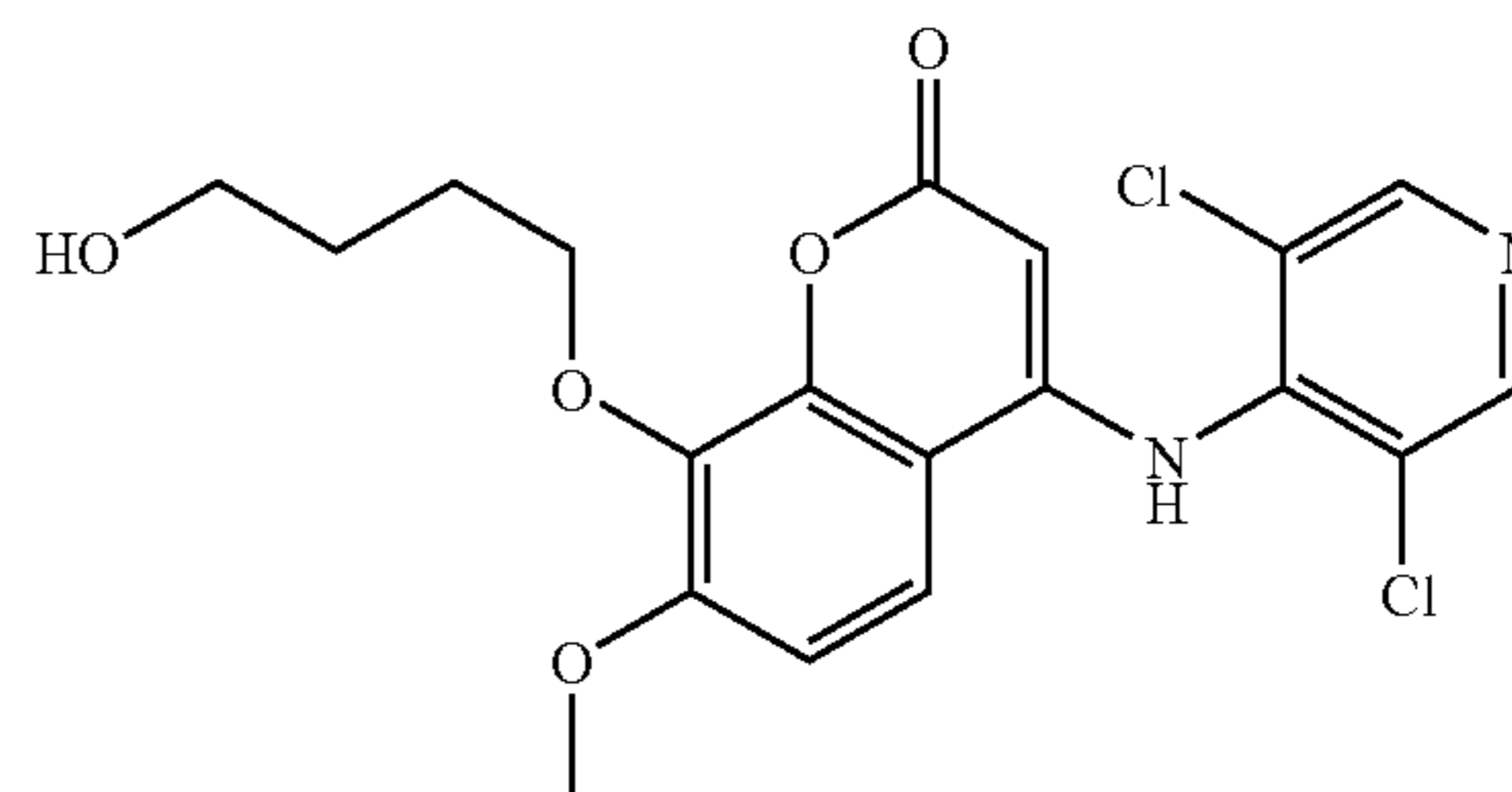


## 64

The title compound can be prepared from 5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl acetate (Example 61) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 7.93 (d, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 4.34 (t, 1H), 3.97 (t, 2H), 3.91 (s, 3H), 3.39 (m, 2H), 1.68 (m, 2H), 1.46 (m, 4H); MS (ESI): 438.9.

## EXAMPLE 73

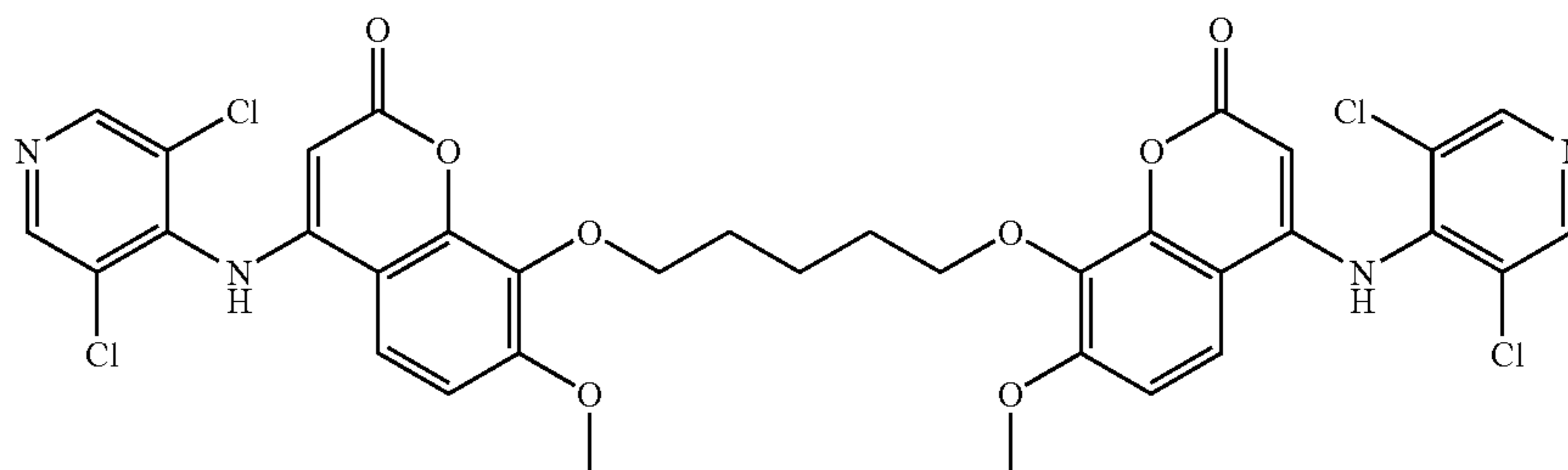
4-(3,5-Dichloropyridin-4-ylamino)-8-(4-hydroxybutyl)-7-methoxy-2H-chromen-2-one



The title compound can be prepared from 4-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butyl acetate (Example 86) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 8.83 (s, 2H), 7.95 (d, 1H), 7.21 (d, 1H), 4.65 (s, 1H), 4.00 (t, 2H), 3.93 (s, 3H), 3.45 (t, 2H), 1.73 (m, 2H), 1.60 (m, 2H); MS (ESI): 424.9.

## EXAMPLE 74

8,8'-(Pentane-1,5-diylbis(oxy))bis(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one)

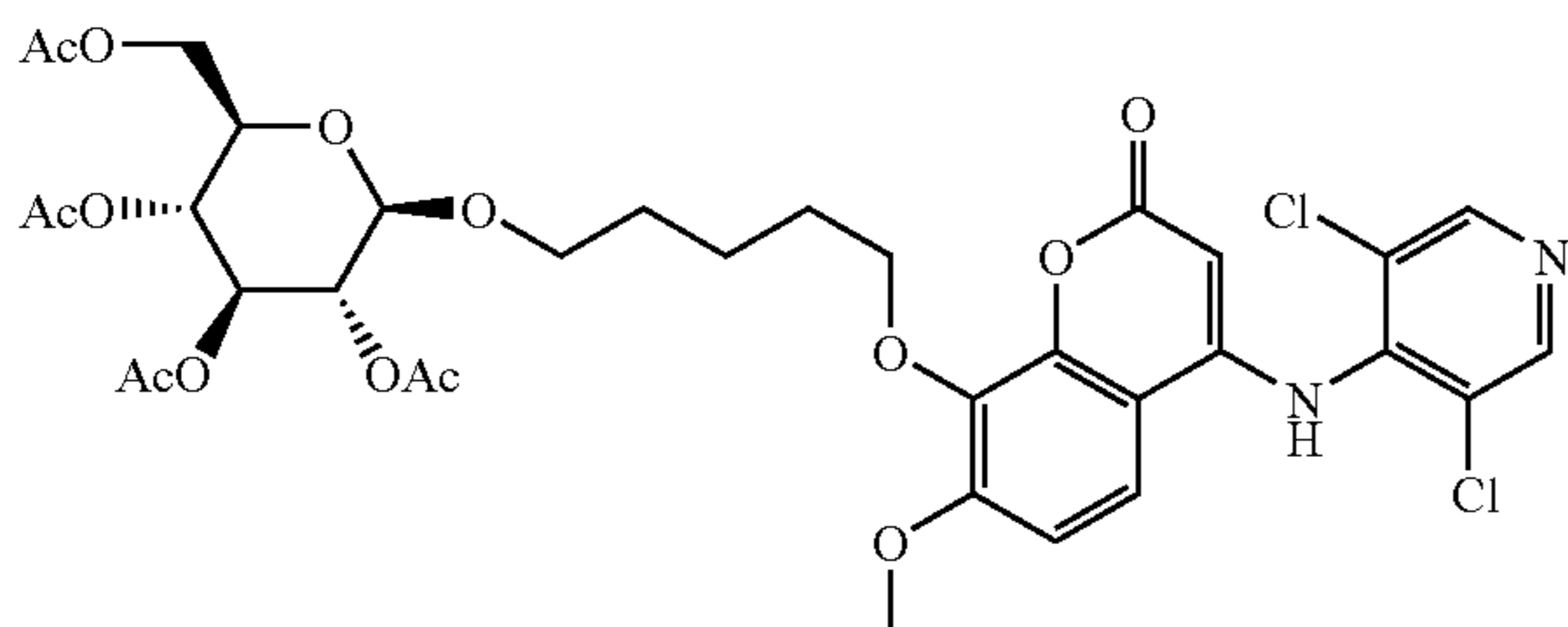


## 65

The title compound was isolated during the purification of Example 28. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.50 (s, 2H), 8.81 (s, 4H), 7.94 (d, 2H), 7.19 (d, 2H), 4.63 (s, 2H), 4.01 (t, 4H), 3.91 (s, 6H), 1.76 (m, 4H), 1.67 (m, 2H); MS (ESI): 773.0.

## EXAMPLE 75

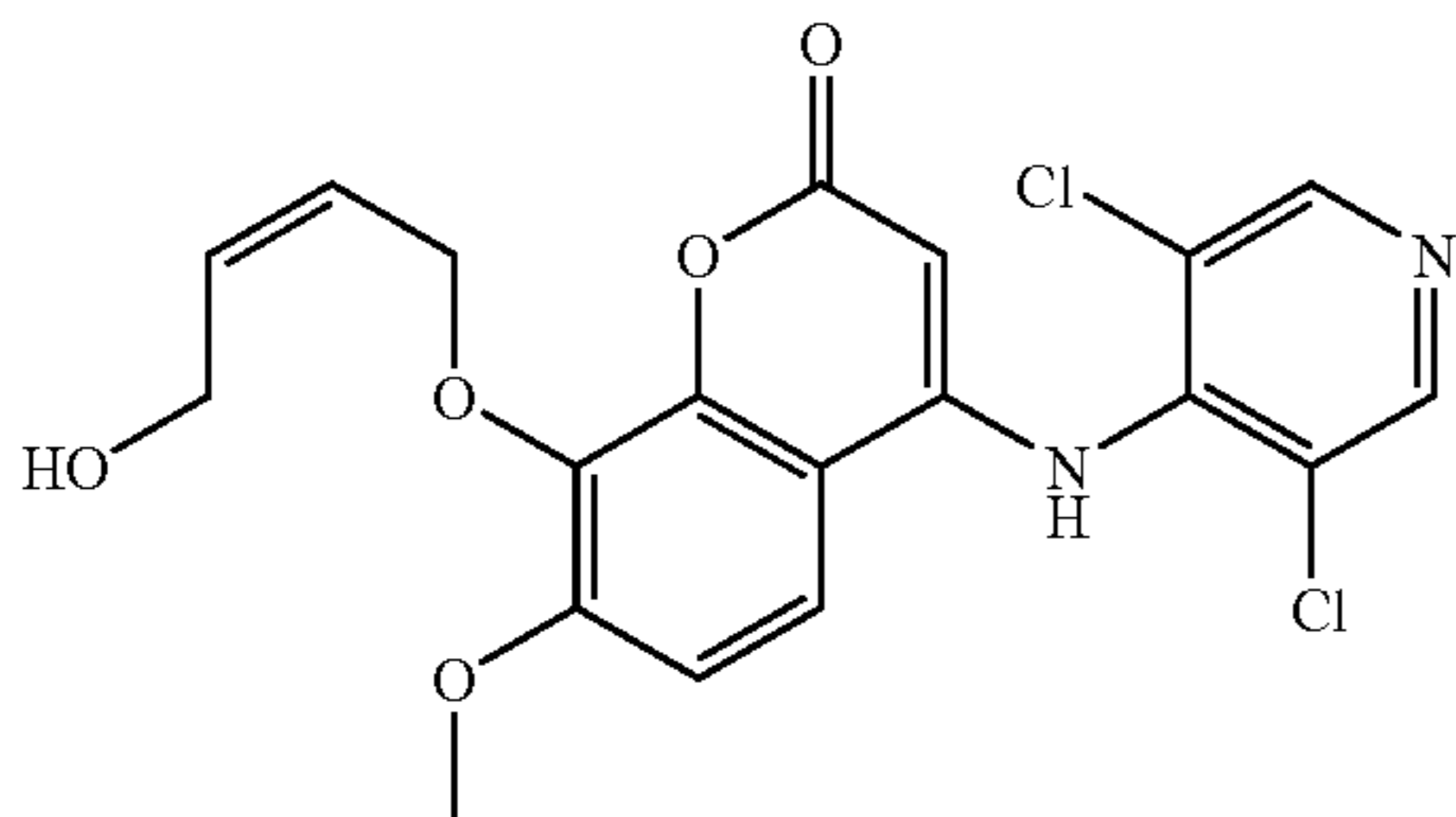
(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



The title compound was prepared from 4-(3,5-dichloropyridin-4-ylamino)-8-(5-hydroxypentyl)oxy)-7-methoxy-2H-chromen-2-one (Example 72) following the procedure outlined in Example 60 (except: solvent was CH<sub>2</sub>Cl<sub>2</sub>, time was 5 h) <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 8.83 (s, 2H), 7.95 (d, 1H), 7.21 (d, 1H), 5.58 (m, 1H), 5.28 (m, 1H), 4.89 (m, 1H), 4.77 (m, 1H), 4.65 (s, 1H), 4.16 (m, 1H), 3.99 (m, 4H), 3.93 (s, 3H), 3.75 (m, 1H), 3.50 (m, 1H), 2.03 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.93 (s, 3H), 1.73-1.47 (m, 6H); MS (ESI): 769.2.

## EXAMPLE 76

(Z)-4-(3,5-Dichloropyridin-4-ylamino)-8-(4-hydroxybut-2-enyloxy)-7-methoxy-2H-chromen-2-one



## Step 1

(Z)-8-(4-(tert-Butyldimethylsilyloxy)but-2-enyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one was prepared from (Z)-(4-bromobut-2-enyloxy)(tert-butyl)dimethylsilane and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedure outlined in Example 25. MS (ESI): 537.0.

## Step 2

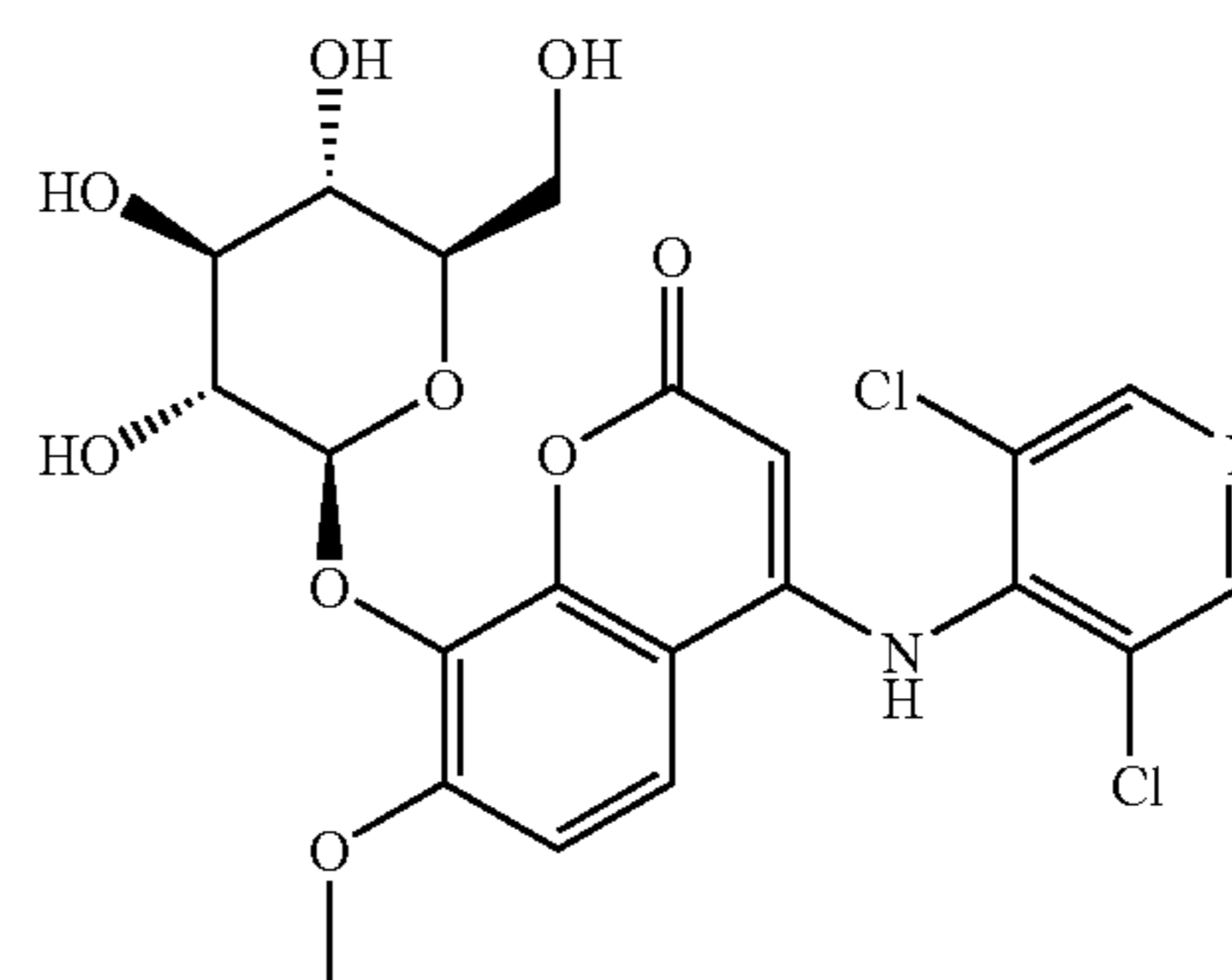
A solution of (Z)-8-(4-(tert-butyl)dimethylsilyloxy)but-2-enyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one and TBAF (2 mL, 2M THF) was main-

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tained at rt for 18 h, poured into water, and then extracted with EtOAc. The extract was dried, filtered, concentrated, and purified by reverse-phase HPLC (25→100% MeCN/H<sub>2</sub>O) to give (Z)-4-(3,5-dichloropyridin-4-ylamino)-8-(4-hydroxybut-2-enyloxy)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD-d<sub>6</sub>): δ 8.71 (s, 2H), 7.85 (d, 1H), 7.18 (d, 1H), 7.83 (m, 2H), 4.77 (m, 3H), 4.15 (d, 2H), 4.01 (s, 3H); MS (ESI): 422.8.

## EXAMPLE 77

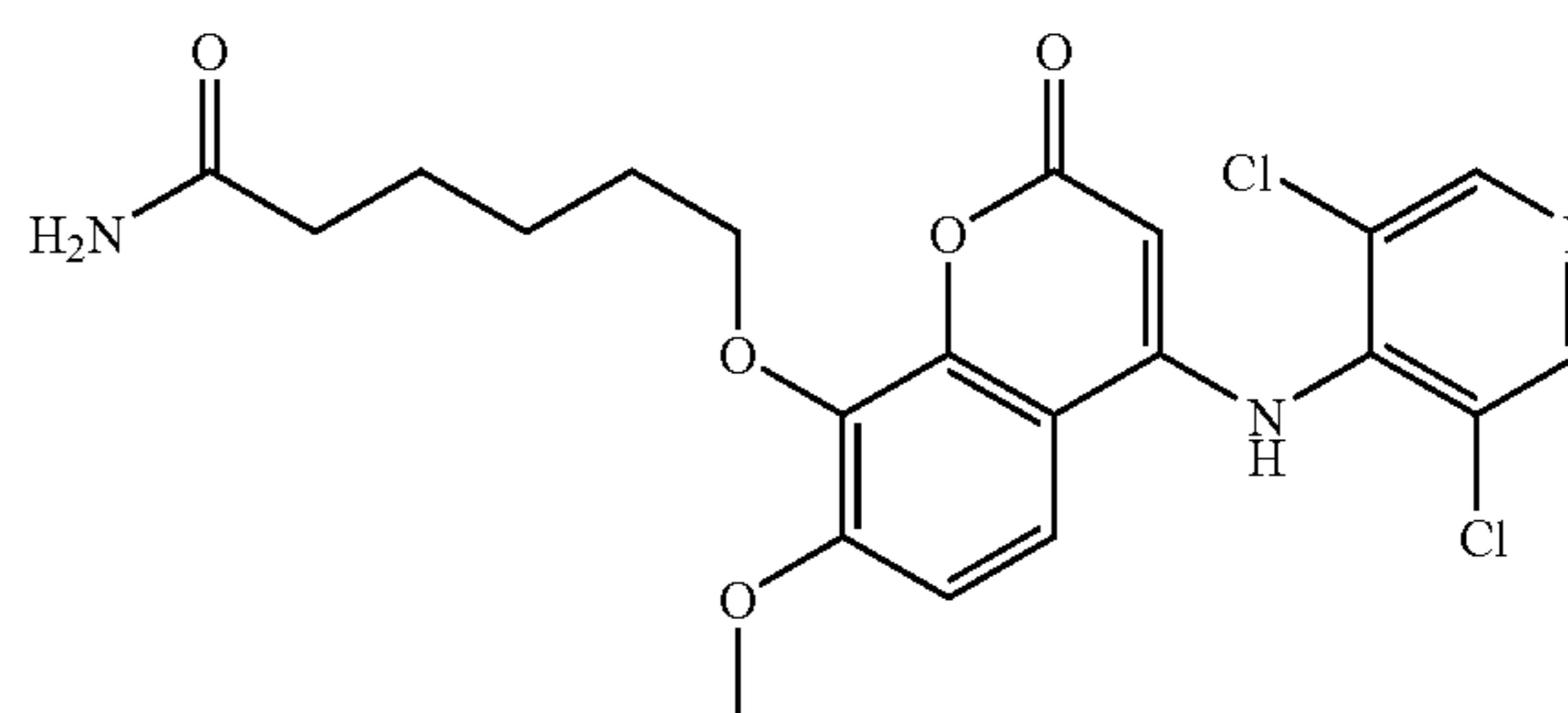
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-2H-chromen-2-one



Water (1.5 mL) and then triethylamine (1.5 mL) were added to a solution of (2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (0.137 g, 0.200 mmol Example 60) and MeOH (1.5 mL). The mixture was stirred at rt overnight, concentrated, and then purified by reverse-phase HPLC (25→100% MeCN/H<sub>2</sub>O) to give 4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-8-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.72 (s, 2H), 7.88 (d, 1H), 7.20 (d, 1H), 5.17 (d, 1H), 4.77 (s, 1H), 4.01 (s, 3H), 3.76 (dd, 1H), 3.63 (dd, 1H), 3.54 (dd, 1H), 3.43 (m, 2H), 3.25 (m, 1H); MS (ESI): 514.9.

## EXAMPLE 78

6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamide



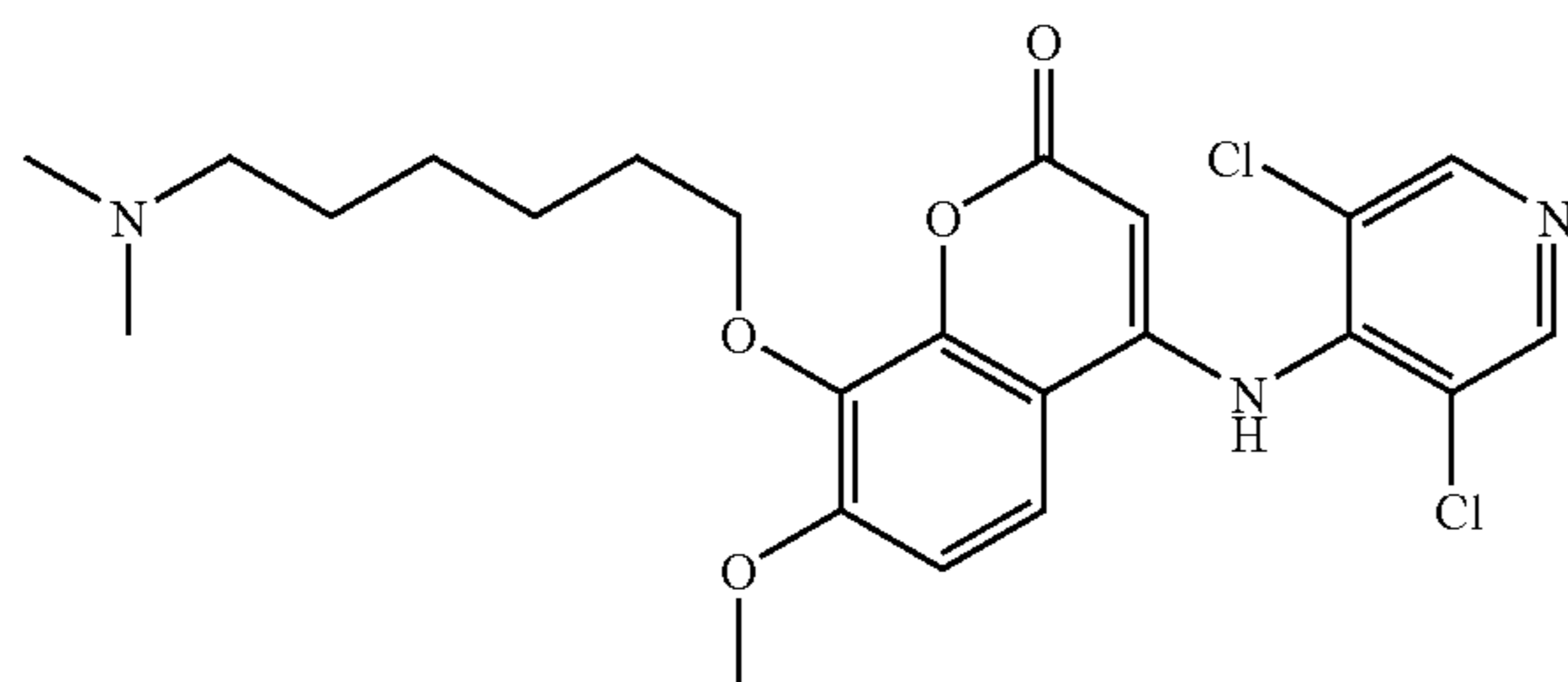
HATU (100 mg, 0.26 mmol) was added to a solution of 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid (100 mg, 0.21 mmol,

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Example 44) and DMSO (2 mL). After 1 h, 28% NH<sub>4</sub>OH solution (0.4 mL, 2.9 mmol) was added. After an additional hour, the reaction was concentrated and purified by reverse-phase HPLC (1:4→7:3; acetonitrile:water) to give 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamide: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.21 (br, 1H), 7.20 (d, 1H), 6.67 (br, 1H), 4.63 (s, 1H), 3.97 (t, 2H), 3.92 (s, 3H), 2.05 (t, 2H), 1.67 (m, 2H), 1.52 (m, 2H), 1.44 (m, 2H); MS (ESI): 465.8.

## EXAMPLE 79

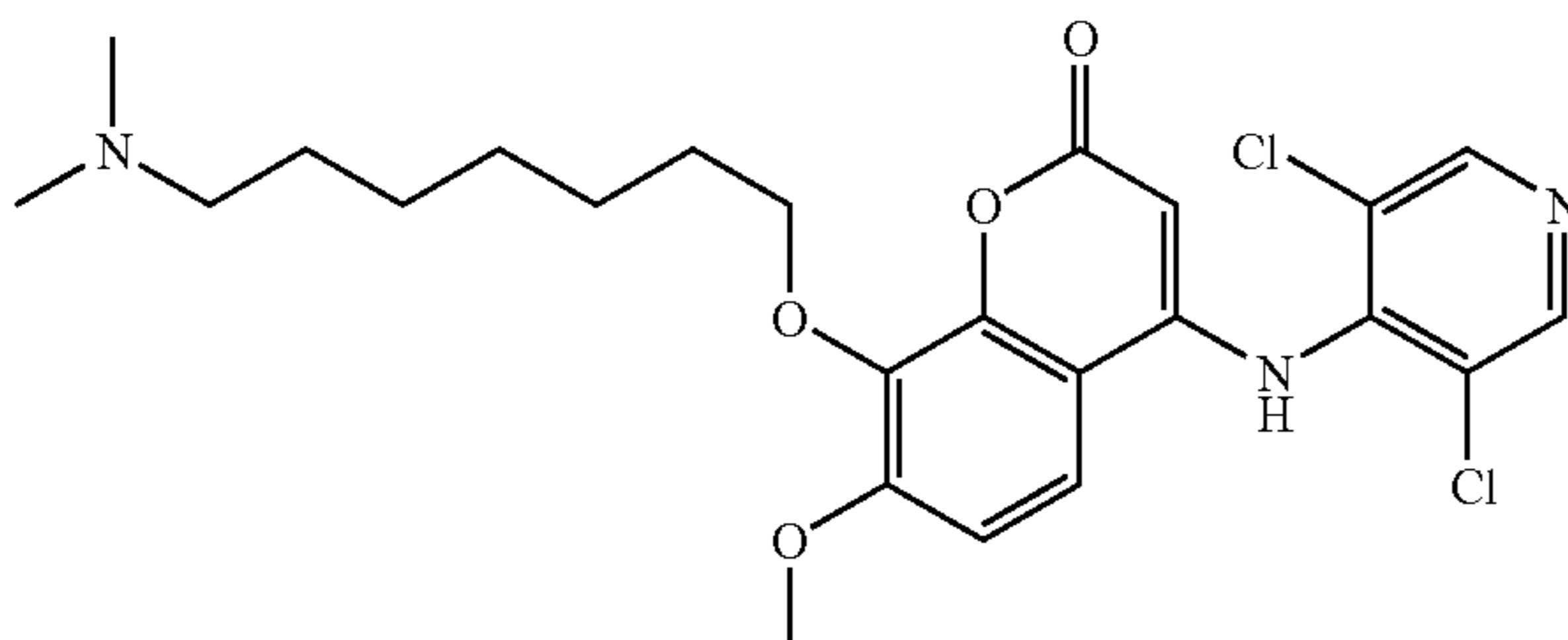
4-(3,5-Dichloropyridin-4-ylamino)-8-(6-(dimethylamino)hexyloxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from dimethylamine, 1,6-dibromohexane, and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.38 (br s, 1H), 8.57 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.24 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.55 (br, 2H), 2.37 (s, 6H), 1.67 (m, 2H), 1.49 (m, 4H), 1.34 (m, 2H); MS (ESI): 479.9.

## EXAMPLE 80

4-(3,5-Dichloropyridin-4-ylamino)-8-(7-(dimethylamino)heptyloxy)-7-methoxy-2H-chromen-2-one

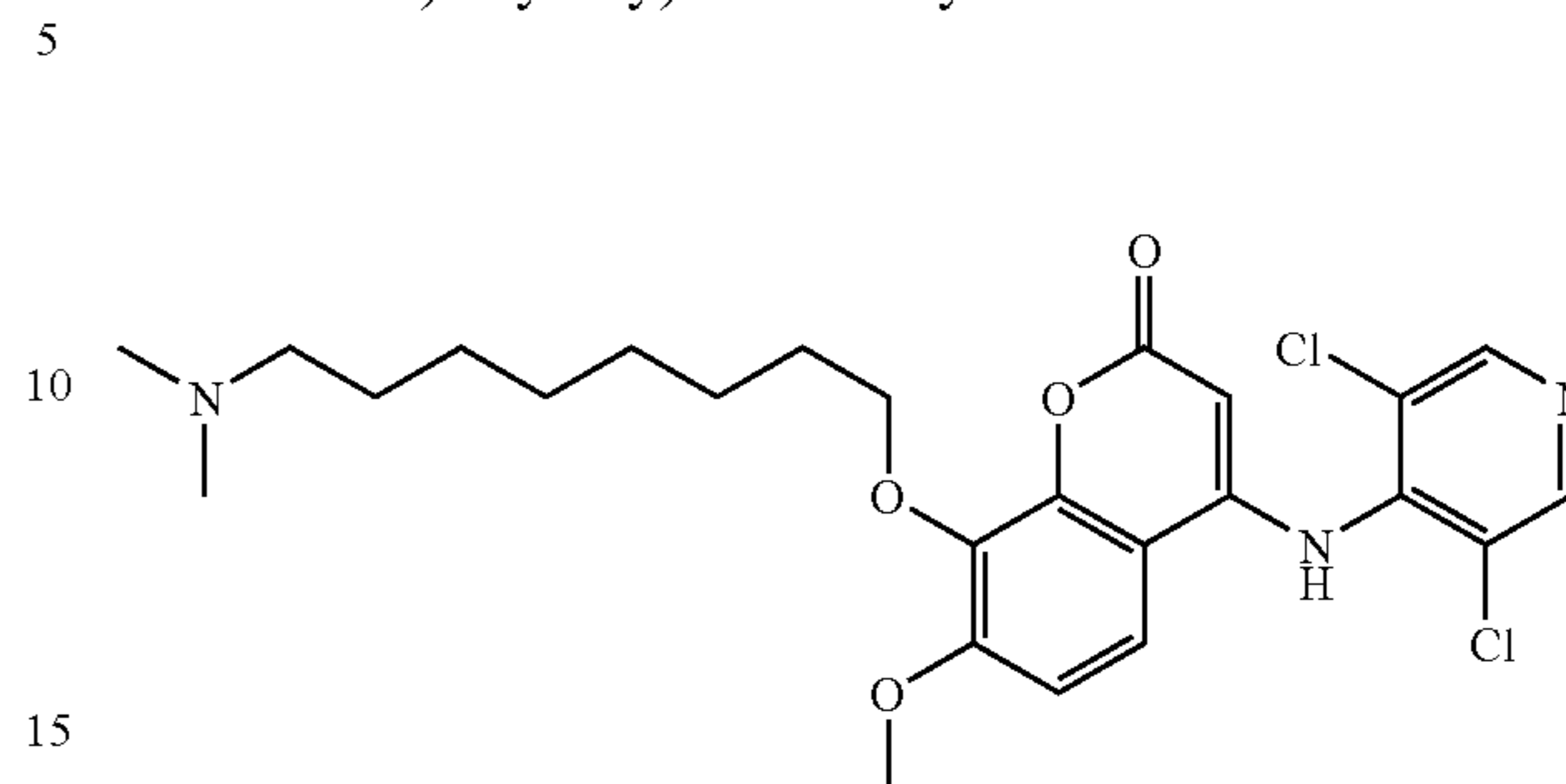


The title compound was prepared from dimethylamine, 1,7-dibromoheptane, and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.38 (br s, 1H), 8.58 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.26 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.51 (br, 2H), 2.35 (s, 6H), 1.67 (m, 2H), 1.46 (m, 4H), 1.30 (m, 4H); MS (ESI): 493.9.

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## EXAMPLE 81

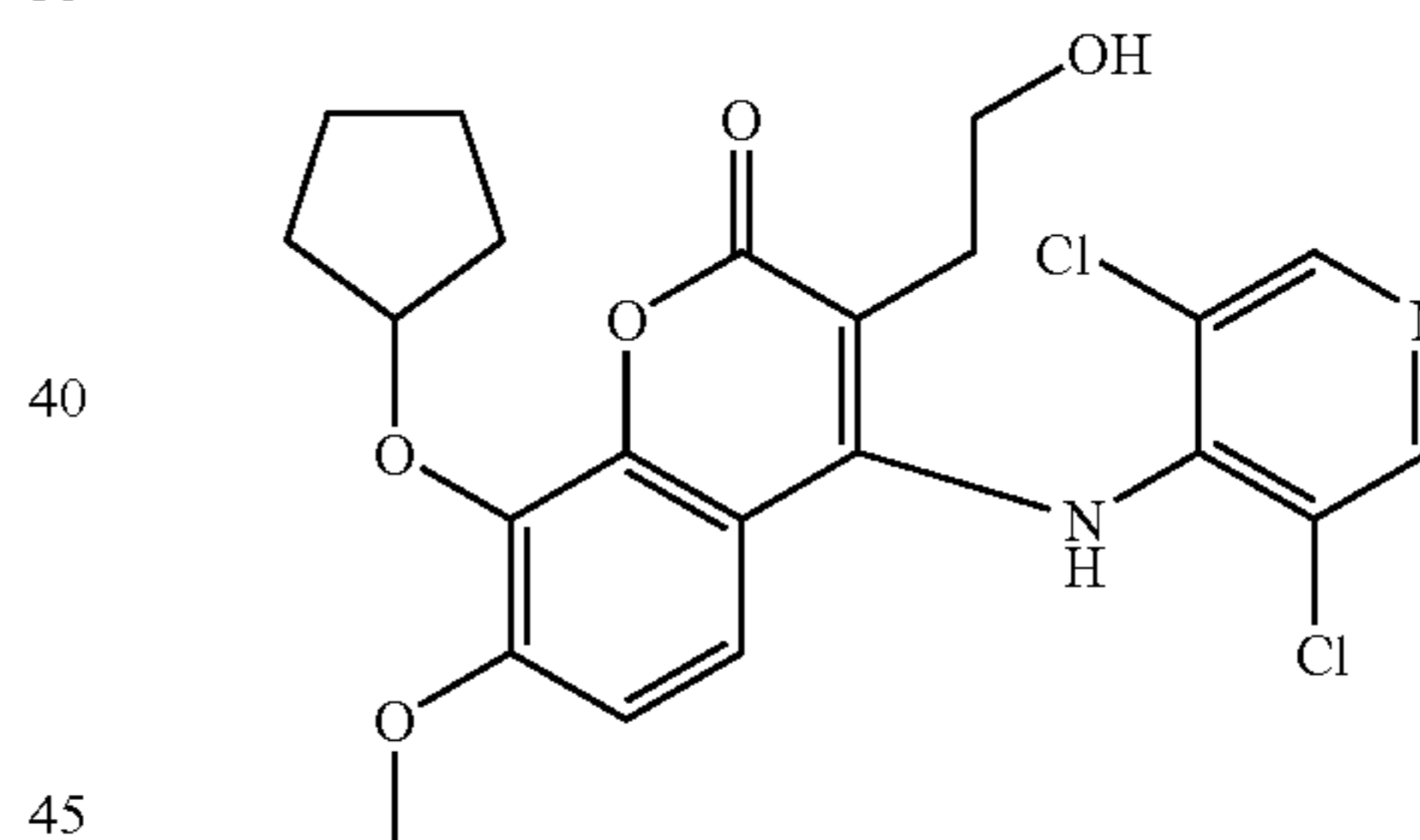
4-(3,5-Dichloropyridin-4-ylamino)-8-(8-(dimethylamino)octyloxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from dimethylamine, 1,8-dibromooctane, and 4-(3,5-dichloropyridin-4-ylamino)-8-hydroxy-7-methoxy-2H-chromen-2-one (Example 29) following the procedures outlined in Examples 25 & 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.38 (br s, 1H), 8.59 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.26 (br s, 1H), 3.95 (t, 2H), 3.87 (s, 3H), 2.50 (br, 2H), 2.34 (s, 6H), 1.67 (m, 2H), 1.45 (m, 4H), 1.28 (m, 6H); MS (ESI): 508.0.

## EXAMPLE 82

8-(Cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-3-(2-hydroxyethyl)-7-methoxy-2H-chromen-2-one



## Step 1

1-(3-(cyclopentyloxy)-2-hydroxy-4-methoxyphenyl) ethanone and 1-(2,3-bis(cyclopentyloxy)-4-methoxyphenyl) ethanone can be isolated as a 3:1 mixture from Example 1, Step 1 before purification.

## Step 2

Sodium hydride (17.3 g, 60%, 432 mmol) was added portionwise to the above mixture (33 g) and dimethylcarbonate (120 mL) at rt. The reaction was heated at 80° C. for 20 min, allowed to cool to rt, quenched with ethanol (10 mL), and then poured into water (100 mL). The pH was adjusted to 3 with 6N HCl, and the mixture was extracted with ethyl acetate (120 mL×3). The combined extracts were washed with brine (50 mL×3), dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give methyl 3-(3-(cyclopentyloxy)-2-hydroxy-4-methoxyphenyl)-3-oxopropanoate and methyl 3-(2,3-bis(cyclopentyloxy)-4-methoxyphenyl)-3-oxopropanoate.

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## Step 3

Sodium ethoxide (2.0 g, 29 mmol) was added to a solution of methyl 3-(2,3-bis(cyclopentyloxy)-4-methoxyphenyl)-3-oxopropanoate (11 g, 29 mmol) and ethanol (150 mL) at rt. After refluxing for 1 h, ((2-bromoethoxy)methyl)benzene (12.5 g, 57.8 mmol) was added and refluxing was continued overnight. The reaction was allowed to cool to rt, concentrated, diluted with ethyl acetate (300 mL), and then washed with brine (50 mL $\times$ 2). The organic layer was dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give ethyl 4-(benzyloxy)-2-(2,3-bis(cyclopentyloxy)-4-methoxybenzoyl)butanoate: MS (ESI): 525.

## Step 4

Trifluoroacetic acid (35 mL) was added dropwise to a solution of ethyl 4-(benzyloxy)-2-(2,3-bis(cyclopentyloxy)-4-methoxybenzoyl)butanoate (14 g, 25 mmol) and dichloromethane (280 mL) at rt. The reaction was maintained overnight, diluted with dichloromethane (200 mL), and washed with sat'd NaHCO<sub>3</sub> (200 mL $\times$ 2) and then brine (200 mL). The organic layer was dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give 3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one: MS (ESI): 411.

## Step 5

Ammonium acetate (27.7 g, 360 mmol) was added to a solution of 3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-4-hydroxy-7-methoxy-2H-chromen-2-one (5 g, 12 mmol), acetic acid (25 mL), and toluene (100 mL). The reaction was refluxed with the water being removed using a Dean-Stark apparatus. After 2 h, the toluene was removed by distillation. After an additional 5 h at reflux, the reaction was allowed to cool to rt, poured into cold water (100 mL), and then extracted with ethyl acetate (100 mL $\times$ 3). The combined extracts were washed with sat'd NaHCO<sub>3</sub> (100 mL $\times$ 4) and then brine (50 mL $\times$ 3), filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give 4-amino-3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one: MS (ESI): 410.

## Step 6

Sodium hydride (230 mg, 60%, 5.8 mmol) was added portionwise to a solution of 4-amino-3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-7-methoxy-2H-chromen-2-one (800 mg, 1.86 mmol) and DMSO (20 mL). After 10 min at rt, 3,4,5-trichloropyridine (1.0 g, 5.47 mmol) was added. The reaction was then heated at 50° C. overnight, allowed to cool to rt, quenched with drops of water, poured into 0.5M KH<sub>2</sub>PO<sub>4</sub> (15 mL), and then extracted with ethyl acetate (50 mL $\times$ 2). The combined extracts were washed with brine (50 mL), dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give 3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one.

## Step 7

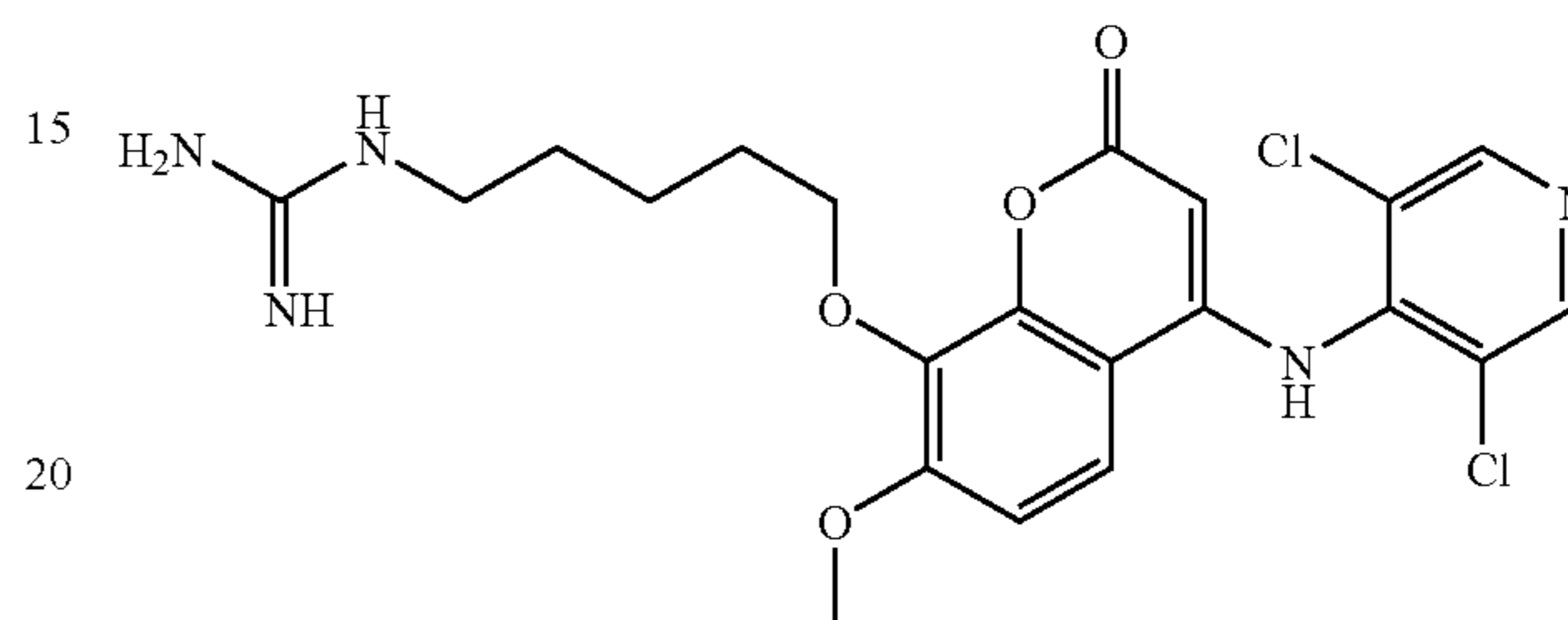
N,N-Dimethylaniline (174 mg, 1.44 mmol) and aluminum trichloride (143 mg, 1.08 mmol) were sequentially added to a solution of 3-(2-(benzyloxy)ethyl)-8-(cyclopentyloxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (100 mg, 0.18 mmol) and dichloromethane (10 mL). The reaction was refluxed for 8 h, allowed to cool to rt, quenched with cold water (1 mL), and then poured into ice water (20 mL). The mixture was extracted with dichloromethane (15 mL $\times$ 3), and the combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate:petroleum ether) to give 8-(cyclopentyloxy)-4-(3,5-

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dichloropyridin-4-ylamino)-3-(2-hydroxyethyl)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.26 (s, 1H), 8.47 (s, 2H), 6.94 (d, 1H), 6.85 (d, 1H), 5.58 (m, 1H), 4.83 (m, 1H), 3.81 (s, 3H), 3.60 (m, 2H), 2.68 (m, 2H), 1.90-1.50 (m, 8H); MS (ESI): 464.9.

## EXAMPLE 83

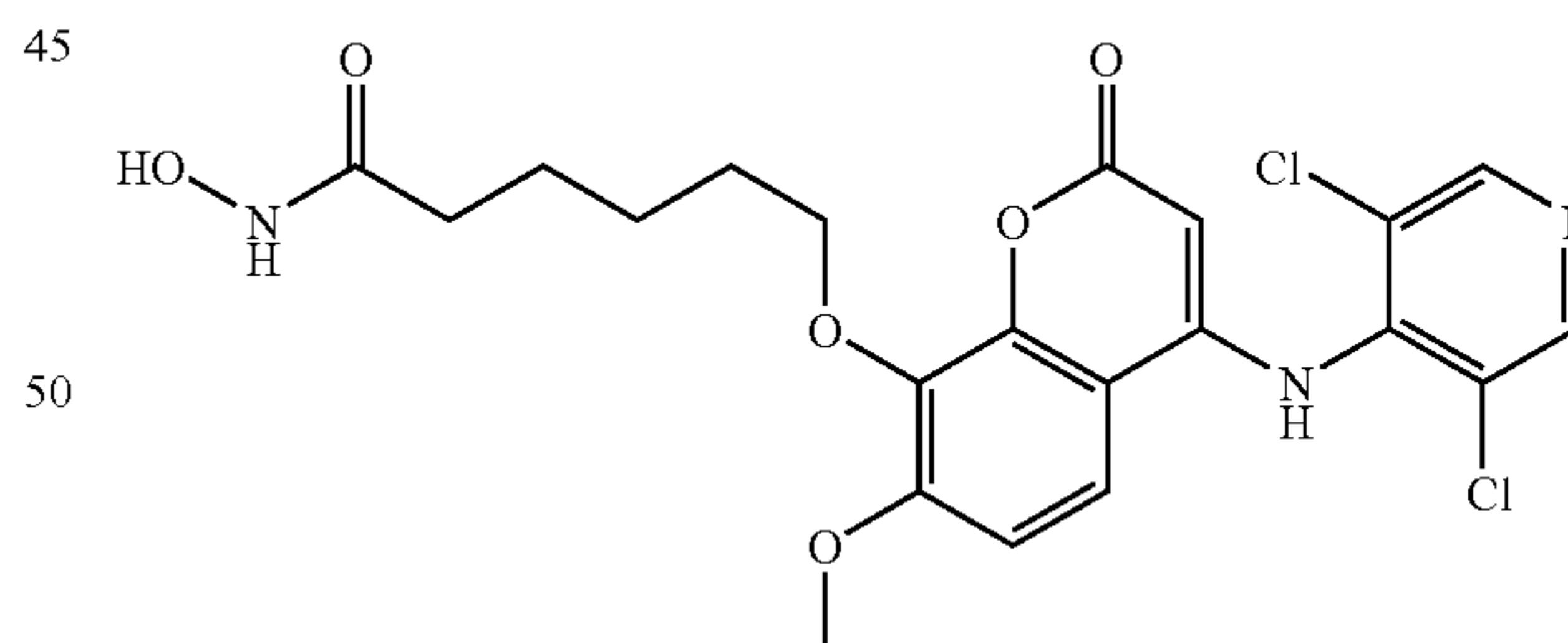
1-(5-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl)guanidine



N,N'-Di-Boc-1H-pyrazole-1-carboxamide (40 mg, 0.13 mmol) was added to a mixture of 8-(5-aminopentyl)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (40 mg, 0.09 mmol, Example 68) and dichloromethane (3 mL). After stirring for 30 min, trifluoroacetic acid (0.3 mL) was added. After an additional 19 h, the reaction was concentrated and purified by reverse-phase HPLC (1:9 $\rightarrow$ 3:2; acetonitrile:water) to give 1-(5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl)guanidine: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>; HCl salt):  $\delta$  9.60 (s, 1H), 8.82 (s, 2H), 7.98 (d, 1H), 7.57 (t, 1H), 7.50-6.70 (br, 4H), 7.21 (d, 1H), 4.63 (s, 1H), 3.98 (t, 2H), 3.92 (s, 3H), 3.11 (m, 2H), 1.70 (m, 2H), 1.52 (m, 4H); MS (ESI): 479.9.

## EXAMPLE 84

6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)-N-hydroxyhexanamide



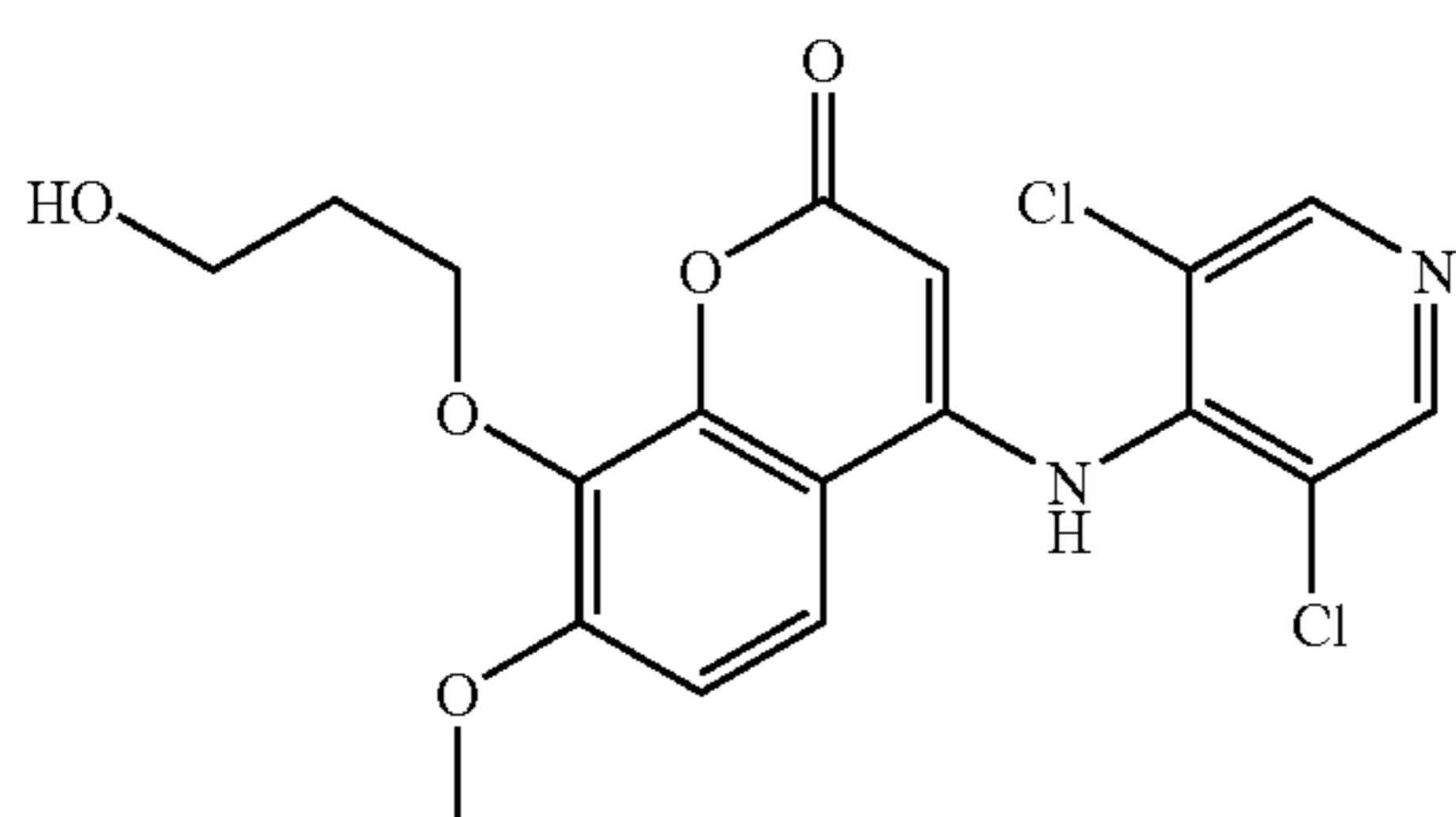
HATU (25 mg, 0.066 mmol) was added to a solution of 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid (25 mg, 0.053 mmol, Example 44), triethylamine (0.05 mL, 0.36 mmol), and DMSO (0.5 mL). After 5 min, NH<sub>2</sub>OH $\cdot$ HCl (10 mg, 0.14 mmol) was added. After an additional 17 h, the mixture was diluted with DMSO (1 mL), filtered through cotton, and the filtrate purified by reverse-phase HPLC (1:9 $\rightarrow$ 3:2; acetonitrile:water) to give 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)-N-hydroxyhexanamide: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  10.32 (s, 1H), 9.51 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H),

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3.96 (t, 2H), 3.92 (s, 3H), 1.96 (t, 2H), 1.67 (m, 2H), 1.54 (m, 2H), 1.43 (m, 2H); MS (ESI): 481.9.

## EXAMPLE 85

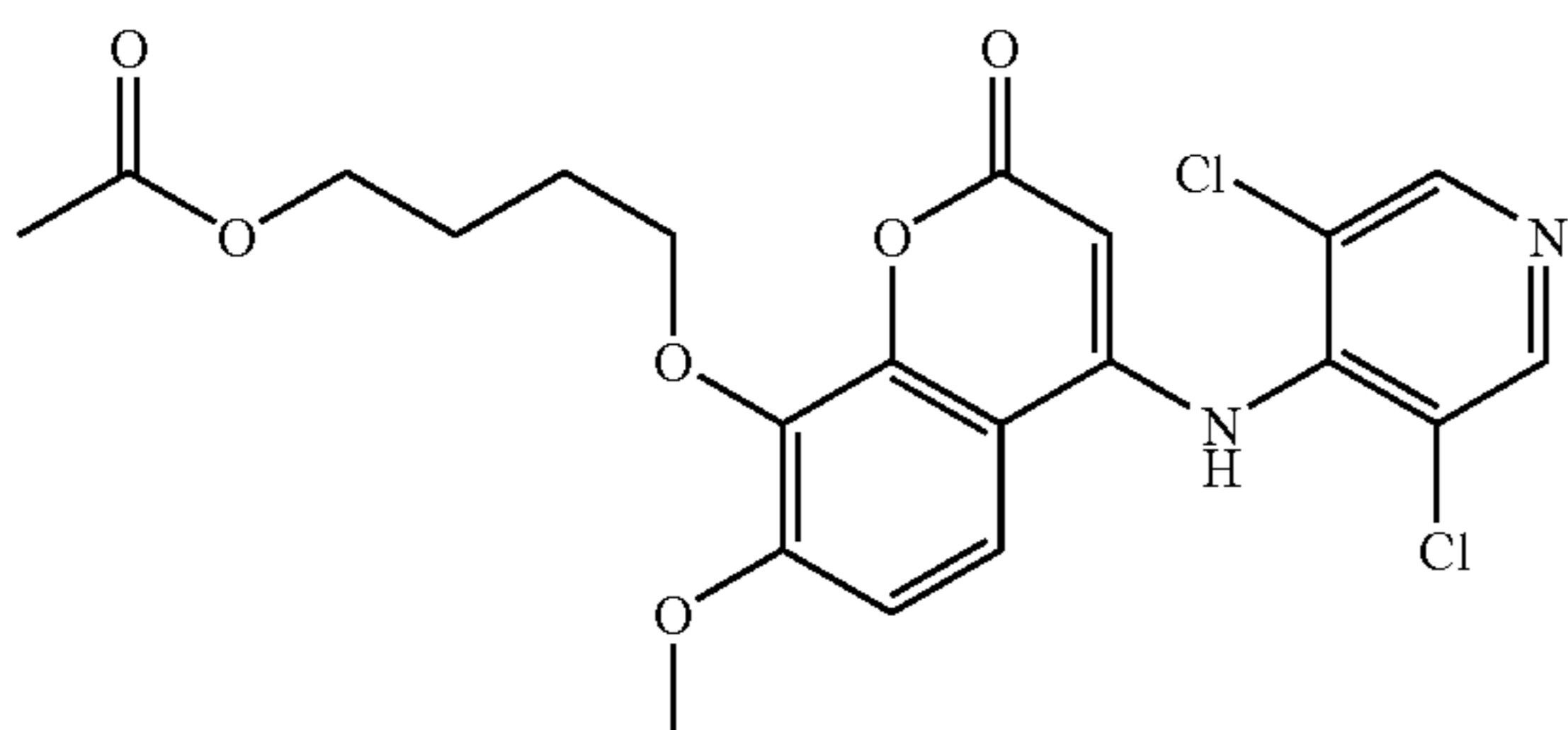
4-(3,5-Dichloropyridin-4-ylamino)-8-(3-hydroxypropoxy)-7-methoxy-2H-chromen-2-one



The title compound can be prepared from potassium acetate and 8-(3-bromopropoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 30) following the procedures outlined in Examples 52 & 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.44 (t, 1H), 4.07 (t, 2H), 3.92 (s, 3H), 3.57 (q, 2H), 1.82 (m, 2H); MS (ESI): 410.8.

## EXAMPLE 86

4-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butyl acetate

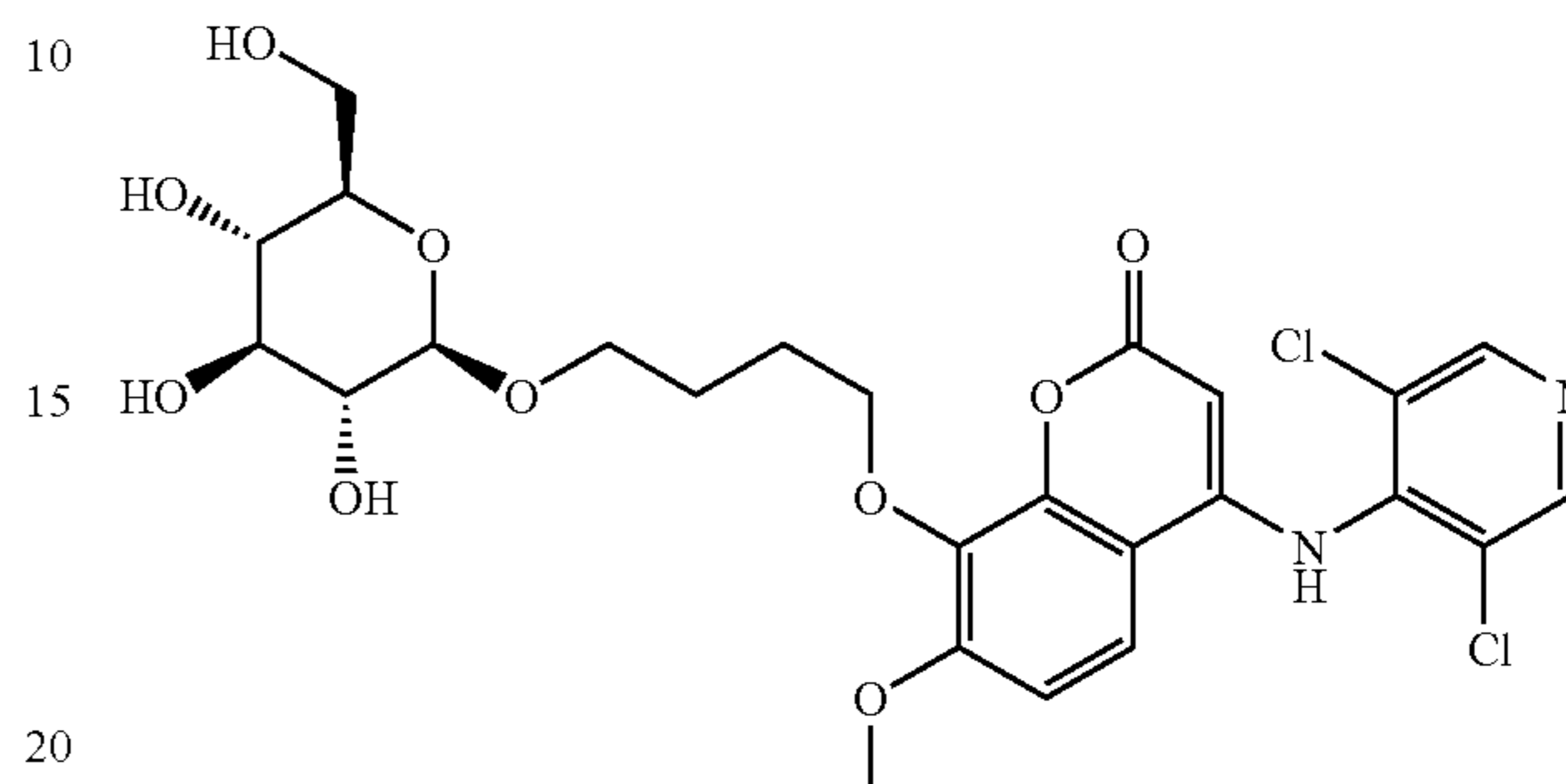


The title compound can be prepared from potassium acetate and 8-(4-bromobutoxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 25) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.70 (s, 2H), 7.84 (d, 1H), 7.16 (d, 1H), 4.77 (s, 1H), 4.16 (t, 2H), 4.11 (t, 2H), 3.98 (s, 3H), 2.02 (s, 3H), 1.91 (m, 2H), 1.84 (m, 2H); MS (ESI): 466.9.

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## EXAMPLE 87

4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(4-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy)butoxy)-2H-chromen-2-one



## Step 1

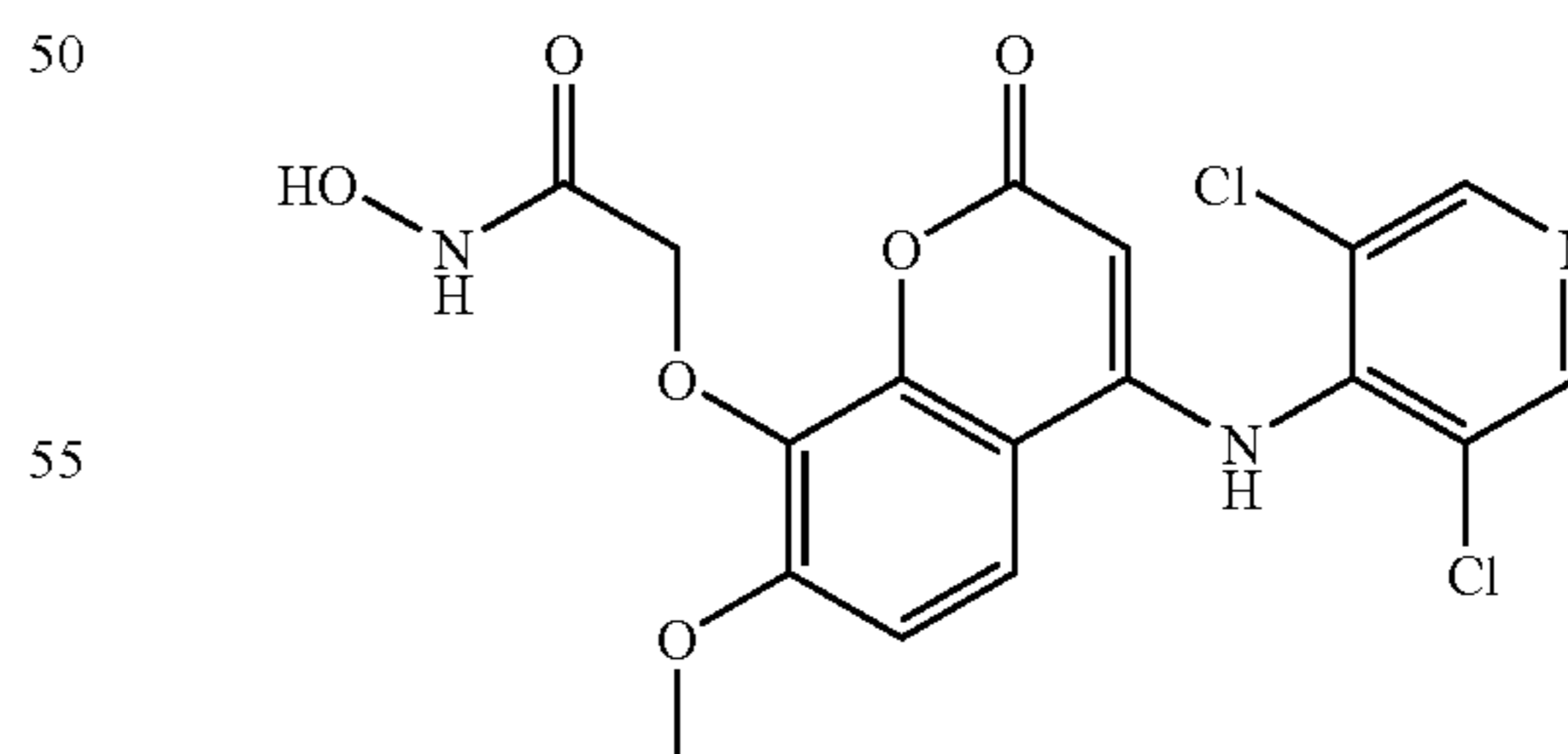
(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate was prepared from 4-(3,5-dichloropyridin-4-ylamino)-8-(4-hydroxybutoxy)-7-methoxy-2H-chromen-2-one (Example 73) following the procedure outlined in Example 60 (except solvent was CH<sub>2</sub>Cl<sub>2</sub>). MS (ESI): 755.1.

## Step 2

The title compound was prepared from (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)butoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate following the procedure outline in Example 116. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 8.71 (s, 2H), 7.84 (d, 1H), 7.17 (d, 1H), 4.76 (s, 1H), 4.28 (m, 1H), 4.13 (m, 2H), 3.99 (s, 3H), 3.85 (m, 1H), 3.65 (m, 2H), 3.34 (m, 2H), 3.27 (m, 2H), 3.17 (m, 1H), 1.89 (m, 4H). MS (ESI): 587.0.

## EXAMPLE 88

2-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)-N-hydroxyacetamide

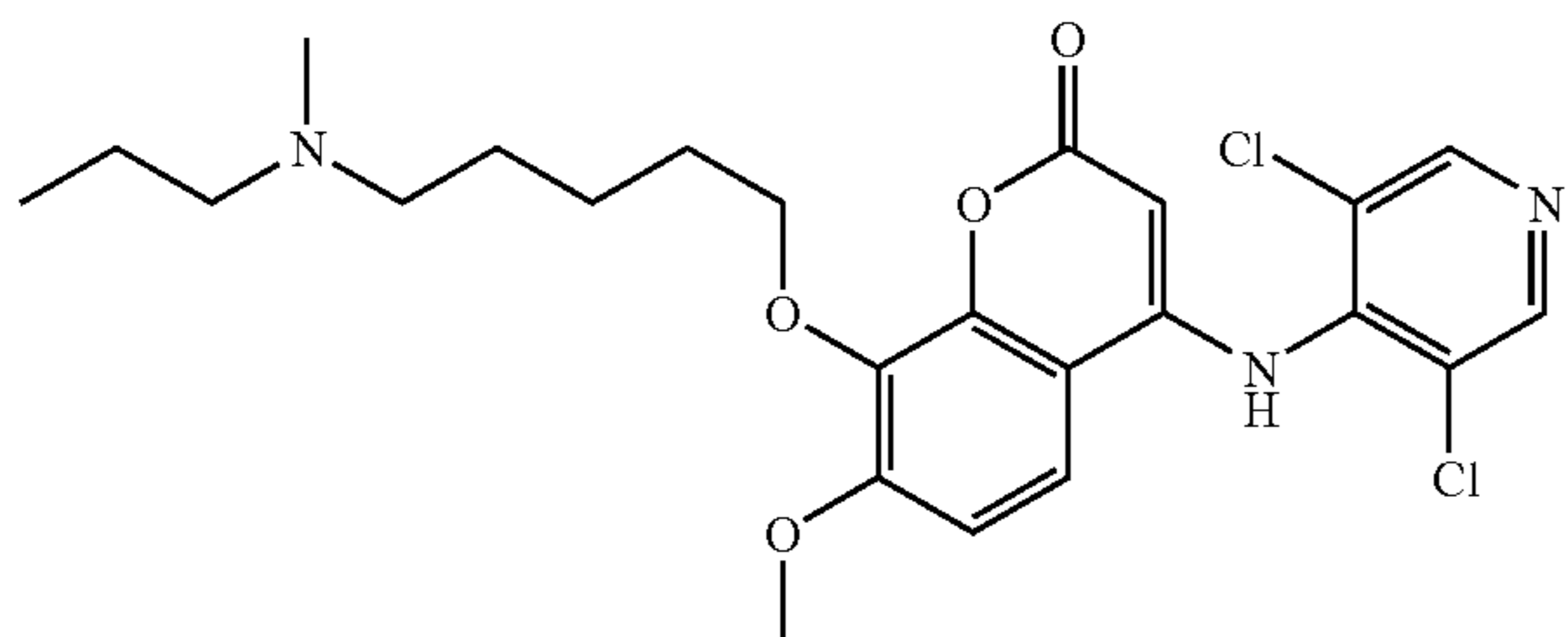


The title compound was prepared from 2-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)acetic acid (Example 49) following the procedure outlined in Example 84 (except TMSO-NH<sub>2</sub> in place of NH<sub>2</sub>OH·HCl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.64 (s, 1H), 9.54 (s, 1H), 8.82 (s, 2H), 7.97 (d, 1H), 7.23 (d, 1H), 4.65 (s, 1H), 4.43 (s, 2H), 3.93 (s, 3H); MS (ESI): 425.8.

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## EXAMPLE 89

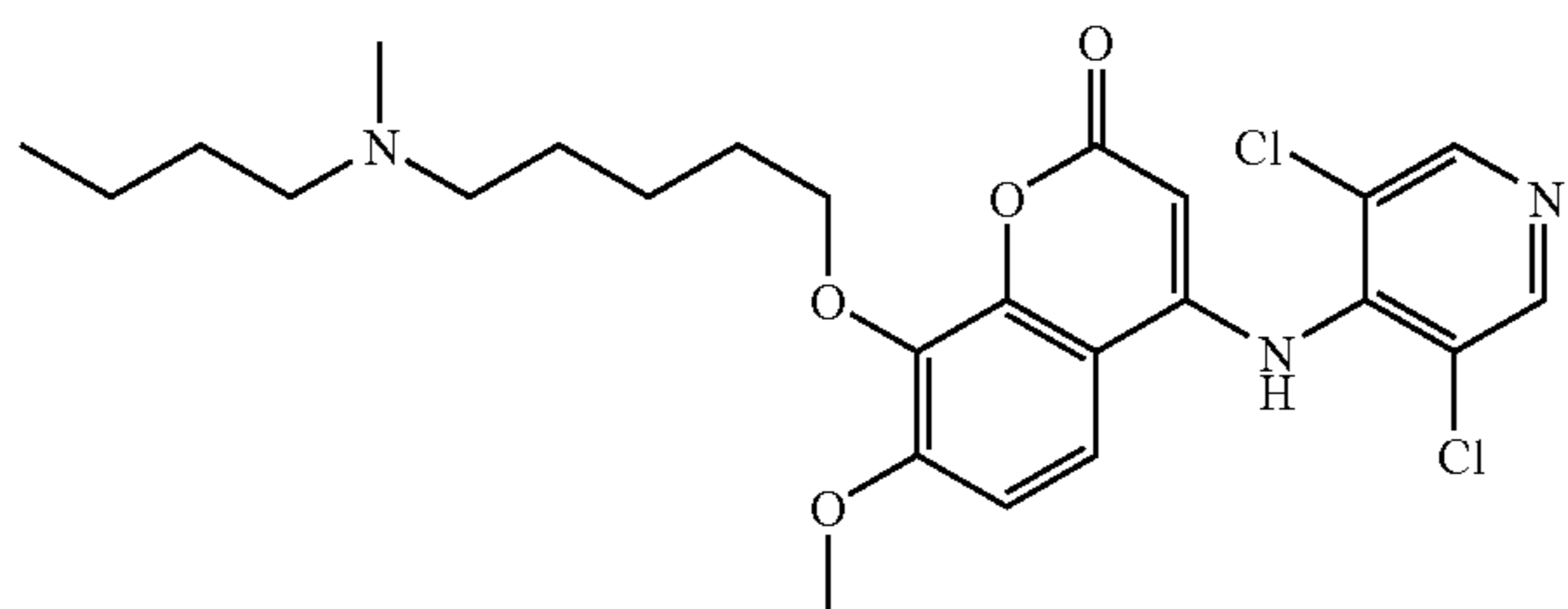
4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(methyl(propyl)amino)pentyl)oxy)-2H-chromen-2-one



The title compound was prepared from N-methylpropan-1-amine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.42 (br s, 1H), 8.58 (s, 2H), 7.86 (d, 1H), 7.06 (d, 1H), 4.24 (br s, 1H), 3.97 (t, 2H), 3.87 (s, 3H), 2.75-2.40 (br, 4H), 2.38 (br s, 3H), 1.70 (m, 2H), 1.60 (m, 2H), 1.49 (m, 4H), 0.83 (t, 3H); MS (ESI): 494.0.

## EXAMPLE 90

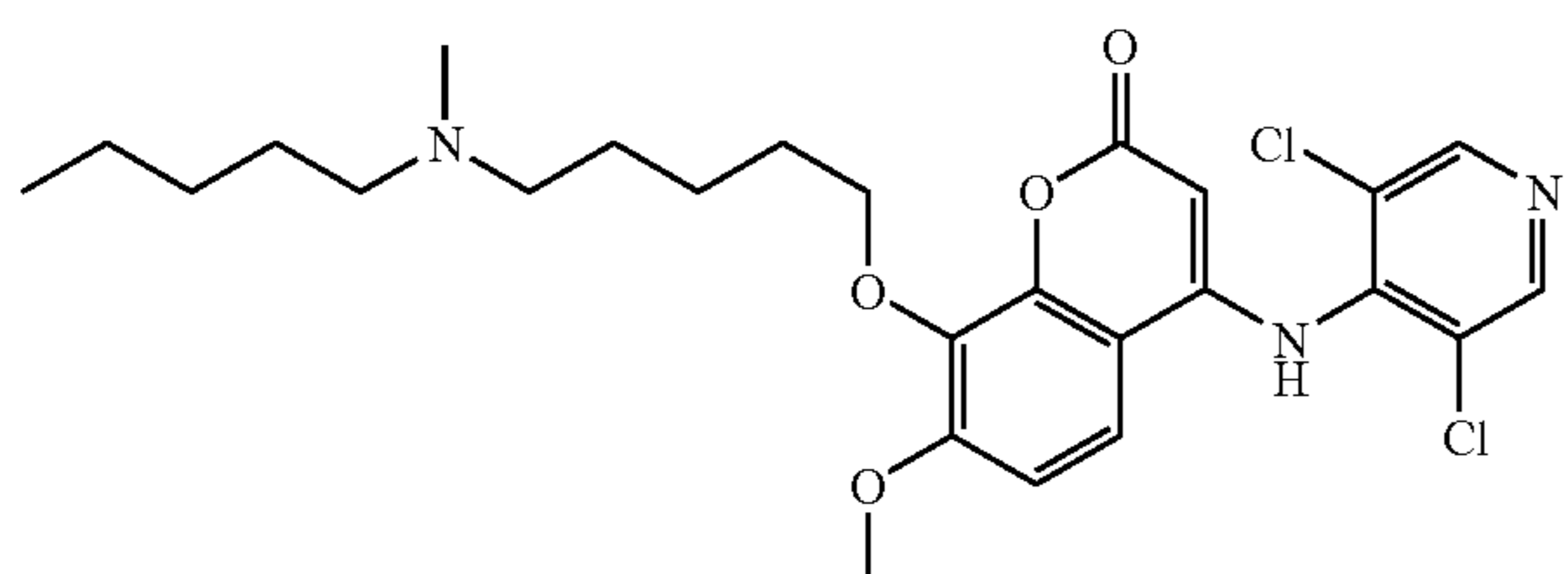
8-(5-(Butyl(methyl)amino)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from N-methylbutan-1-amine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.40 (br s, 1H), 8.57 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.24 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.62 (br, 4H), 2.39 (br s, 3H), 1.70 (m, 2H), 1.60 (m, 2H), 1.47 (m, 4H), 1.26 (m, 2H), 0.85 (t, 3H); MS (ESI): 508.1.

## EXAMPLE 91

4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(methyl(pentyl)amino)pentyl)oxy)-2H-chromen-2-one



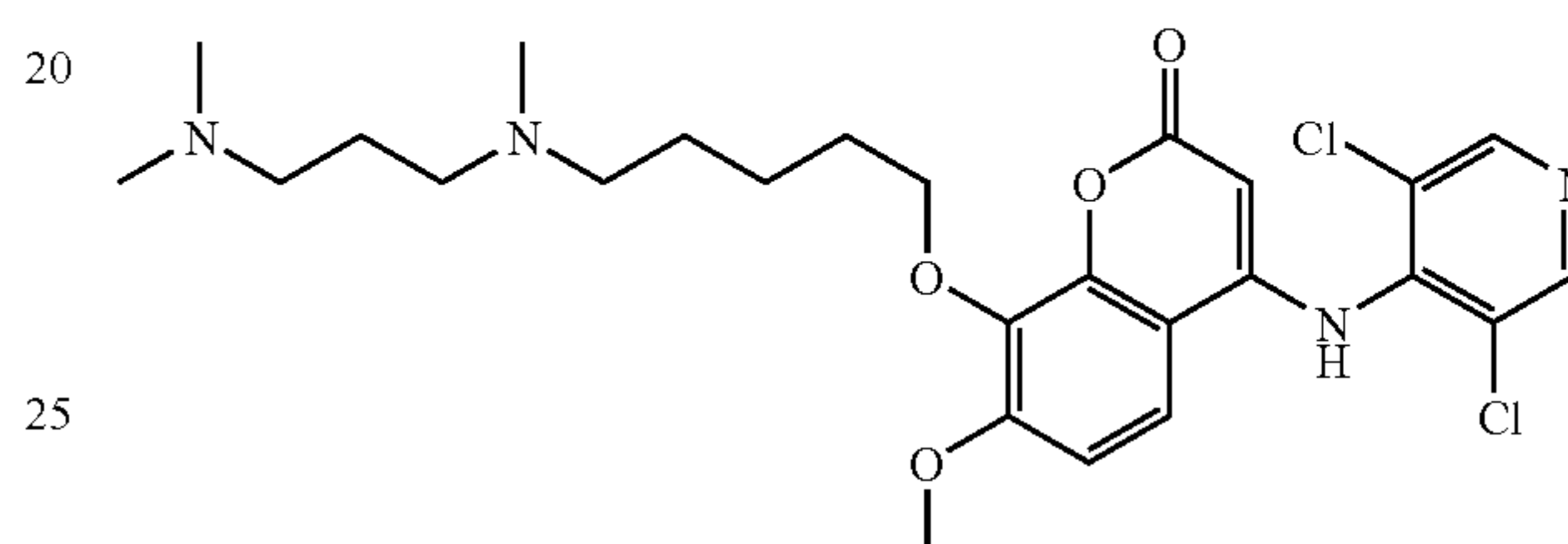
The title compound was prepared from N-methylpentan-1-amine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-

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4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.41 (br s, 1H), 8.57 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.23 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.61 (br, 4H), 2.39 (br s, 3H), 1.70 (m, 2H), 1.60 (m, 2H), 1.47 (m, 4H), 1.23 (m, 4H), 0.83 (t, 3H); MS (ESI): 522.1.

## EXAMPLE 92

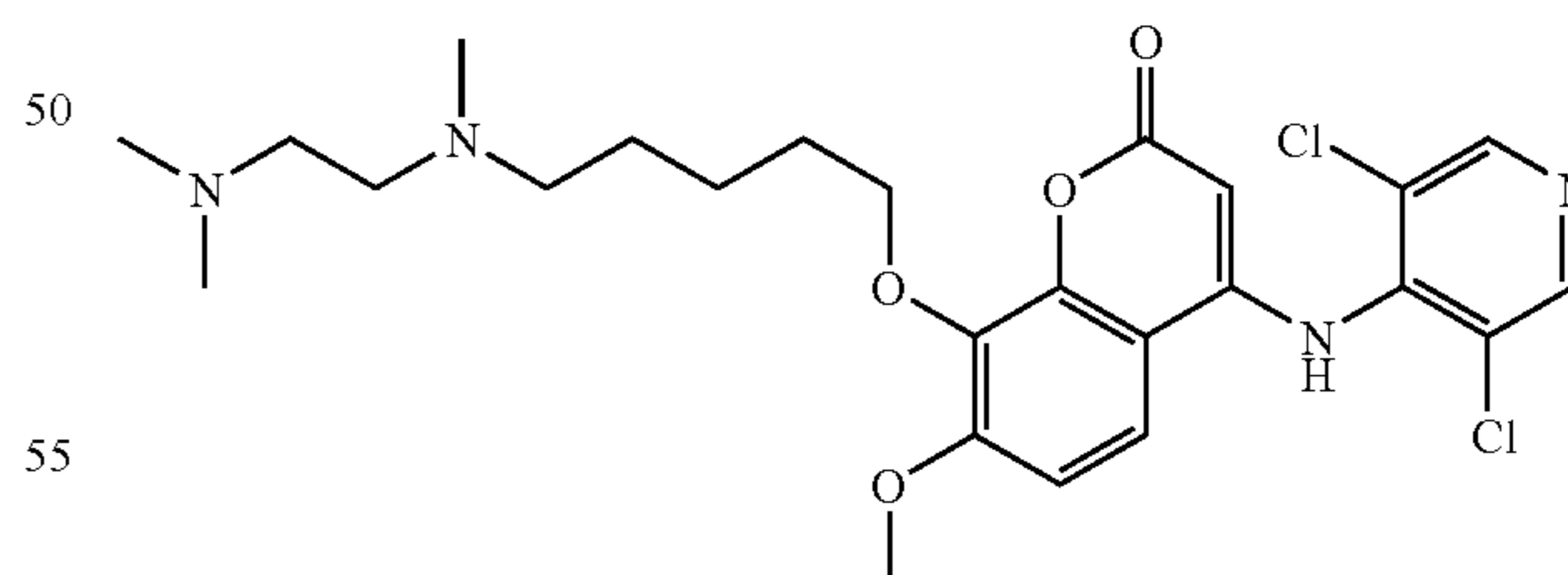
4-(3,5-Dichloropyridin-4-ylamino)-8-(5-((3-(dimethylamino)propyl)(methyl)amino)pentyl)oxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from N1,N1,N3-trimethylpropane-1,3-diamine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.53 (s, 2H), 7.84 (d, 1H), 7.03 (d, 1H), 4.17 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.54 (t, 4H), 2.45 (t, 2H), 2.31 (s, 3H), 2.27 (s, 6H), 1.69 (m, 2H), 1.64 (m, 2H), 1.56 (m, 2H), 1.47 (m, 2H); MS (ESI): 537.1.

## EXAMPLE 93

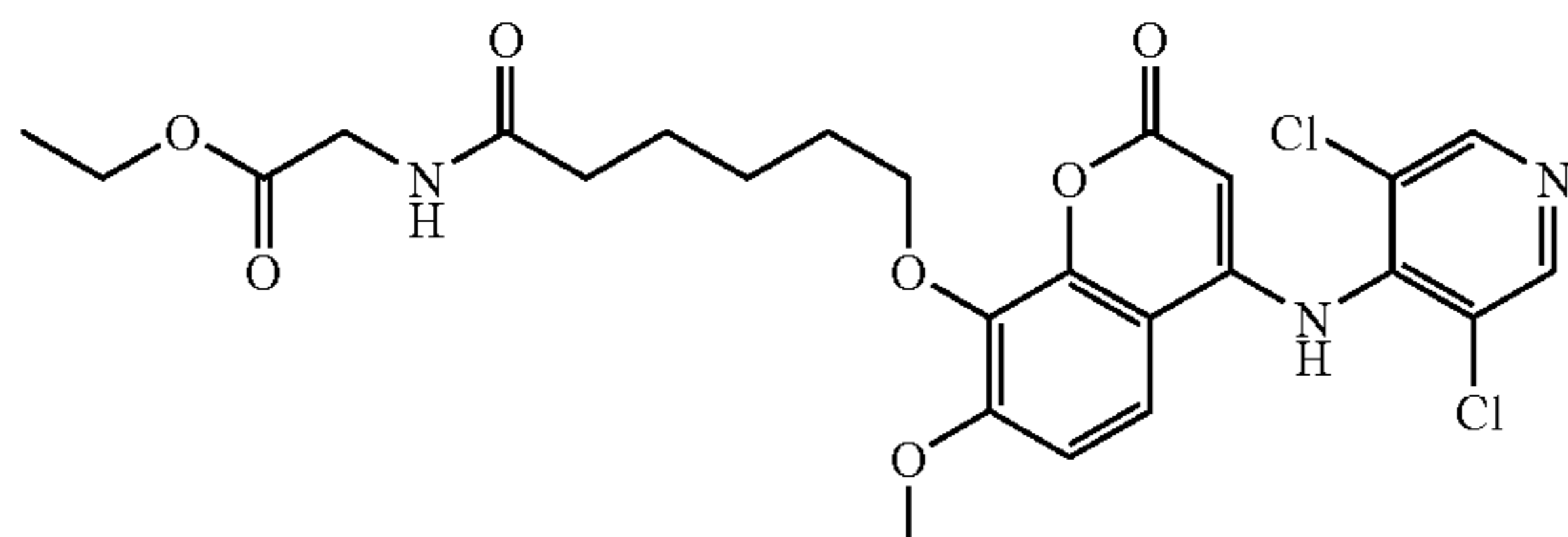
4-(3,5-Dichloropyridin-4-ylamino)-8-(5-((2-(dimethylamino)ethyl)(methyl)amino)pentyl)oxy)-7-methoxy-2H-chromen-2-one



The title compound was prepared from N1,N1,N2-trimethylethane-1,2-diamine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 52. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.57 (s, 2H), 7.85 (d, 1H), 7.05 (d, 1H), 4.23 (br s, 1H), 3.96 (t, 2H), 3.87 (s, 3H), 2.65 (m, 4H), 2.55 (m, 2H), 2.34 (s, 6H), 2.31 (s, 3H), 1.69 (m, 2H), 1.51 (m, 4H); MS (ESI): 523.0.

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EXAMPLE 94

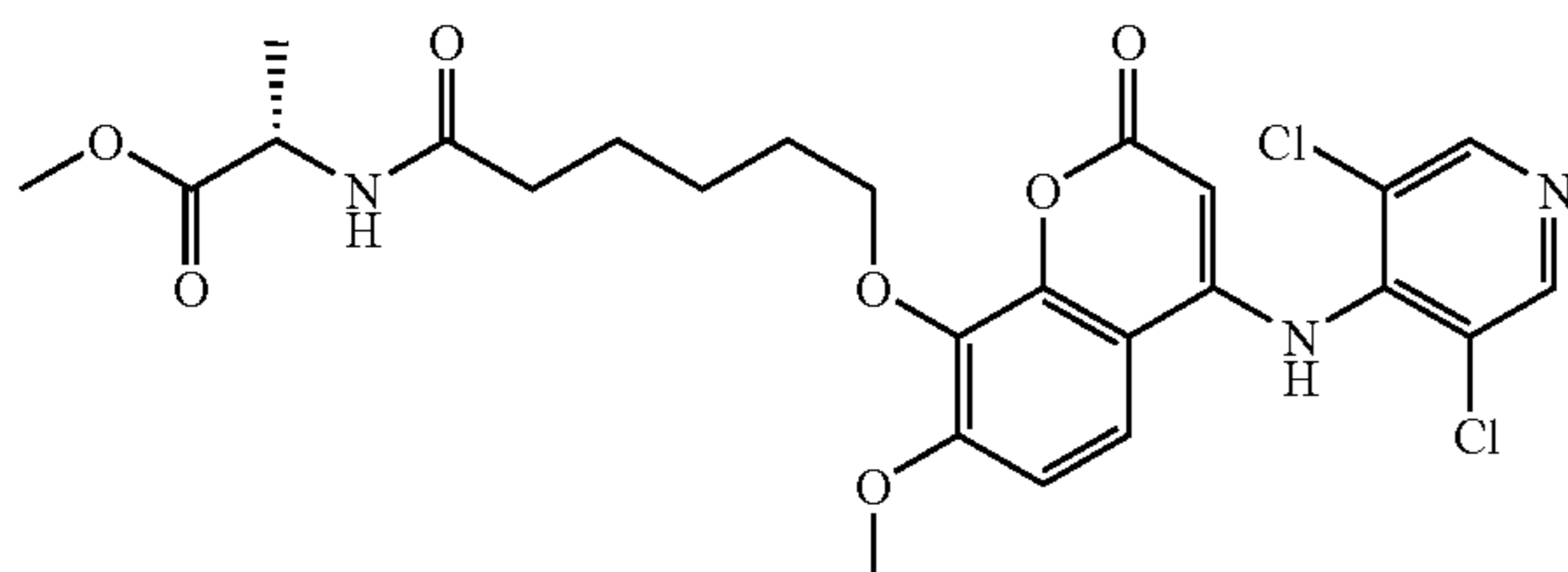
Ethyl 2-(6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)acetate



HATU (180 mg, 0.47 mmol) was added to a solution of 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid (187 mg, 0.4 mmol, Example 44), 4-methylmorpholine (0.2 mL, 1.8 mmol), and DMF (2 mL). After 5 min, this solution was added to Gly-OEt•HCl (65 mg, 0.47 mmol). After 75 min, the reaction was poured into 1M KH<sub>2</sub>PO<sub>4</sub> (30 mL) and extracted with ethyl acetate (40 mL×2). The combined extracts were dried, filtered, concentrated, and purified by silica gel chromatography (1:4→0:1; hexanes:ethyl acetate) to give ethyl 2-(6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)acetate: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 8.21 (t, 1H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 4.05 (q, 2H), 3.97 (t, 2H), 3.92 (s, 3H), 3.77 (d, 2H), 2.14 (t, 2H), 1.68 (m, 2H), 1.55 (m, 2H), 1.44 (m, 2H), 1.16 (t, 3H); MS (ESI): 552.0.

EXAMPLE 95

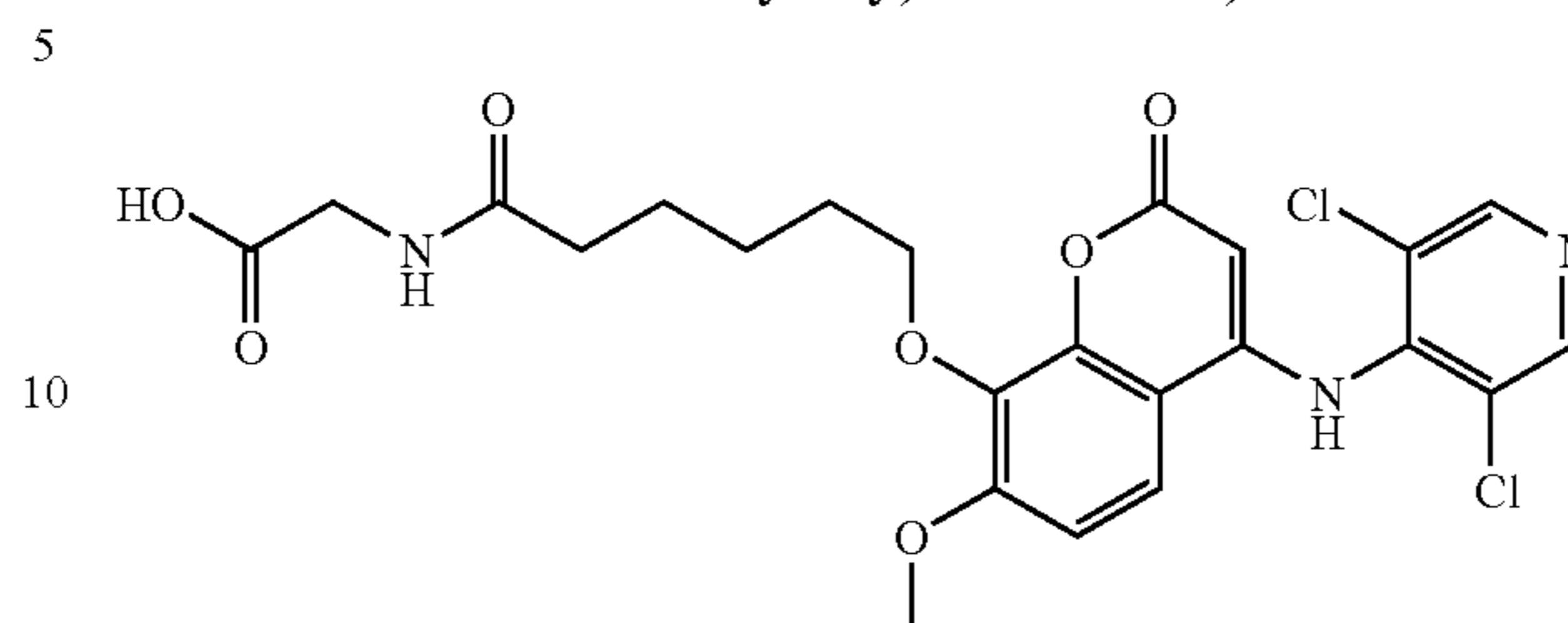
(S)-Methyl 2-(6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)propanoate



The title compound was prepared from Ala-OMe•HCl and 6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanoic acid (Example 44) following the procedure outlined in Example 94. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 8.20 (d, 1H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 4.22 (m, 1H), 3.96 (t, 2H), 3.92 (s, 3H), 3.58 (s, 3H), 2.11 (t, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 1.43 (m, 2H), 1.23 (d, 3H); MS (ESI): 552.0.

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EXAMPLE 96

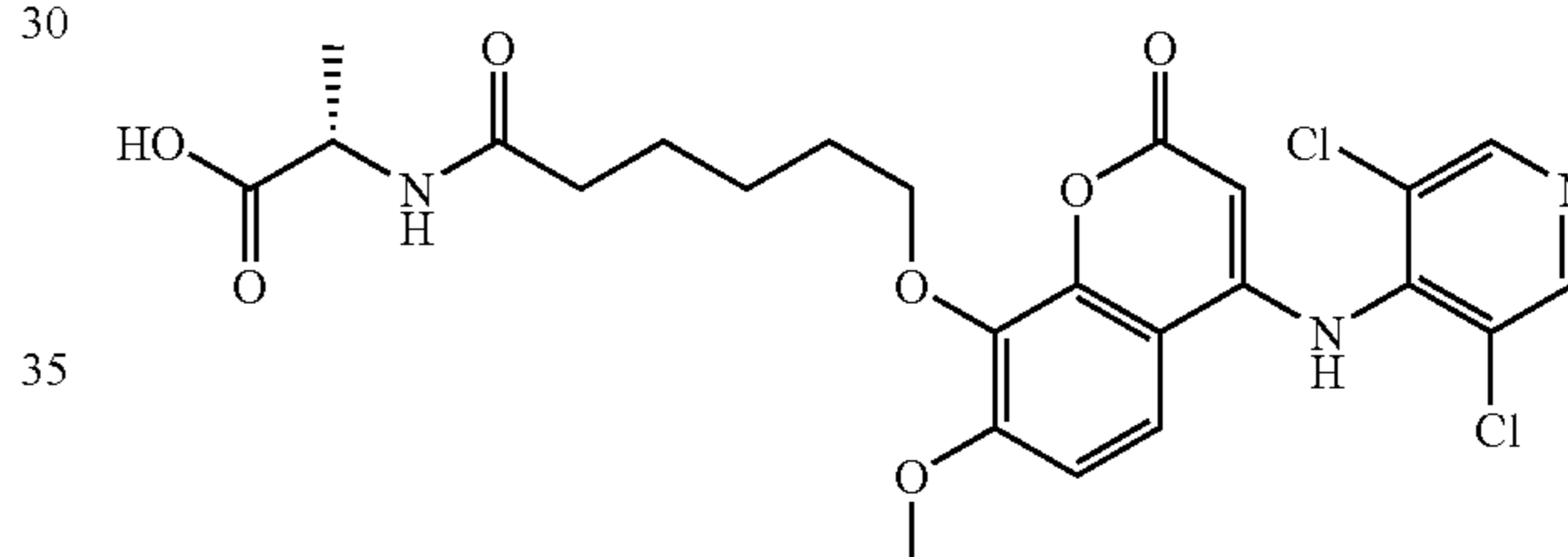
2-(6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)acetic acid



The title compound was prepared from ethyl 2-(6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)acetate (Example 94) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.51 (s, 1H), 8.81 (s, 2H), 8.10 (t, 1H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 3.96 (t, 2H), 3.92 (s, 3H), 3.70 (d, 2H), 2.13 (t, 2H), 1.69 (m, 2H), 1.55 (m, 2H), 1.44 (m, 2H); MS (ESI): 554.0.

EXAMPLE 97

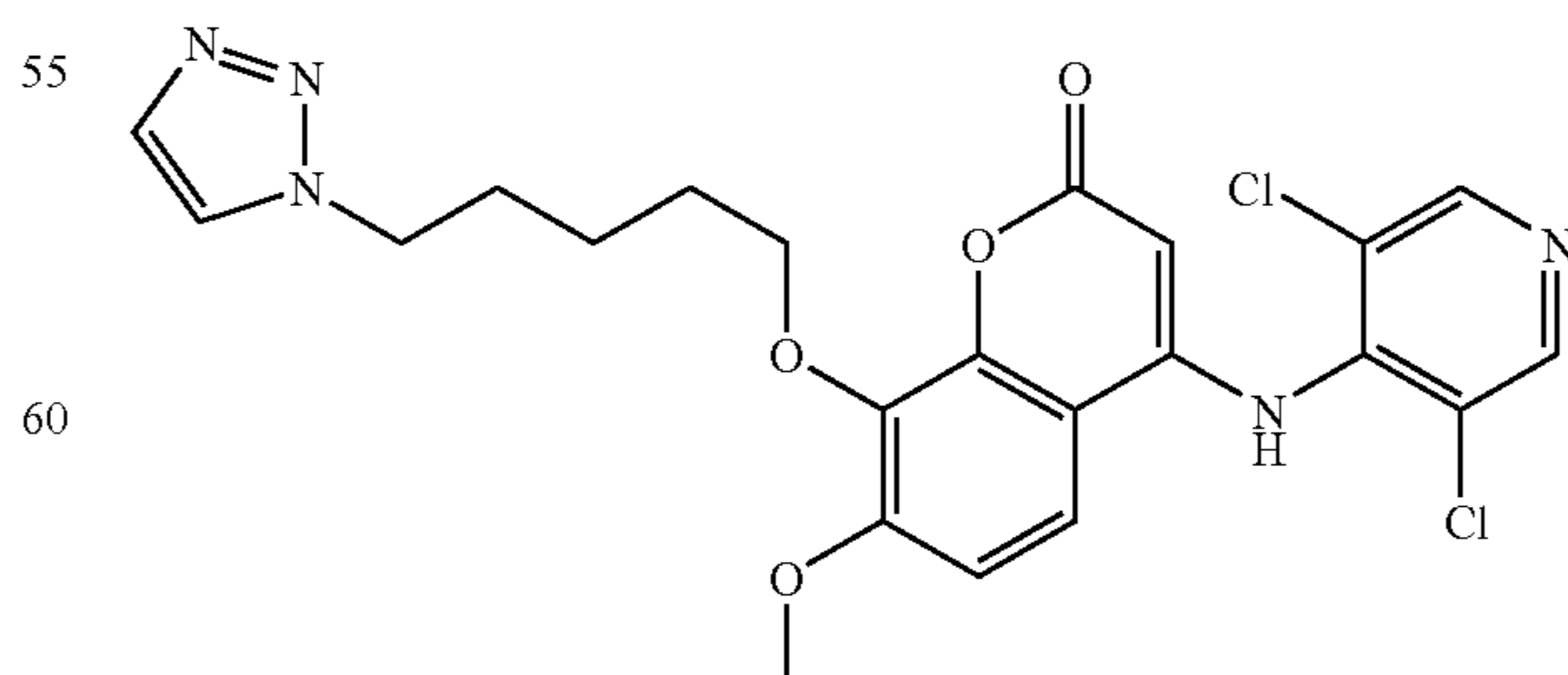
(S)-2-(6-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)propanoic acid



The title compound was prepared from (S)-methyl 2-(6-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)hexanamido)propanoate (Example 95) following the procedure outlined in Example 42. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.39 (br s, 1H), 9.51 (s, 1H), 8.81 (s, 2H), 8.06 (d, 1H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.16 (m, 1H), 3.96 (t, 2H), 3.92 (s, 3H), 2.11 (t, 2H), 1.67 (m, 2H), 1.54 (m, 2H), 1.43 (m, 2H), 1.22 (d, 3H); MS (ESI): 538.0.

EXAMPLE 98

8-(5-(1H-1,2,3-Triazol-1-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



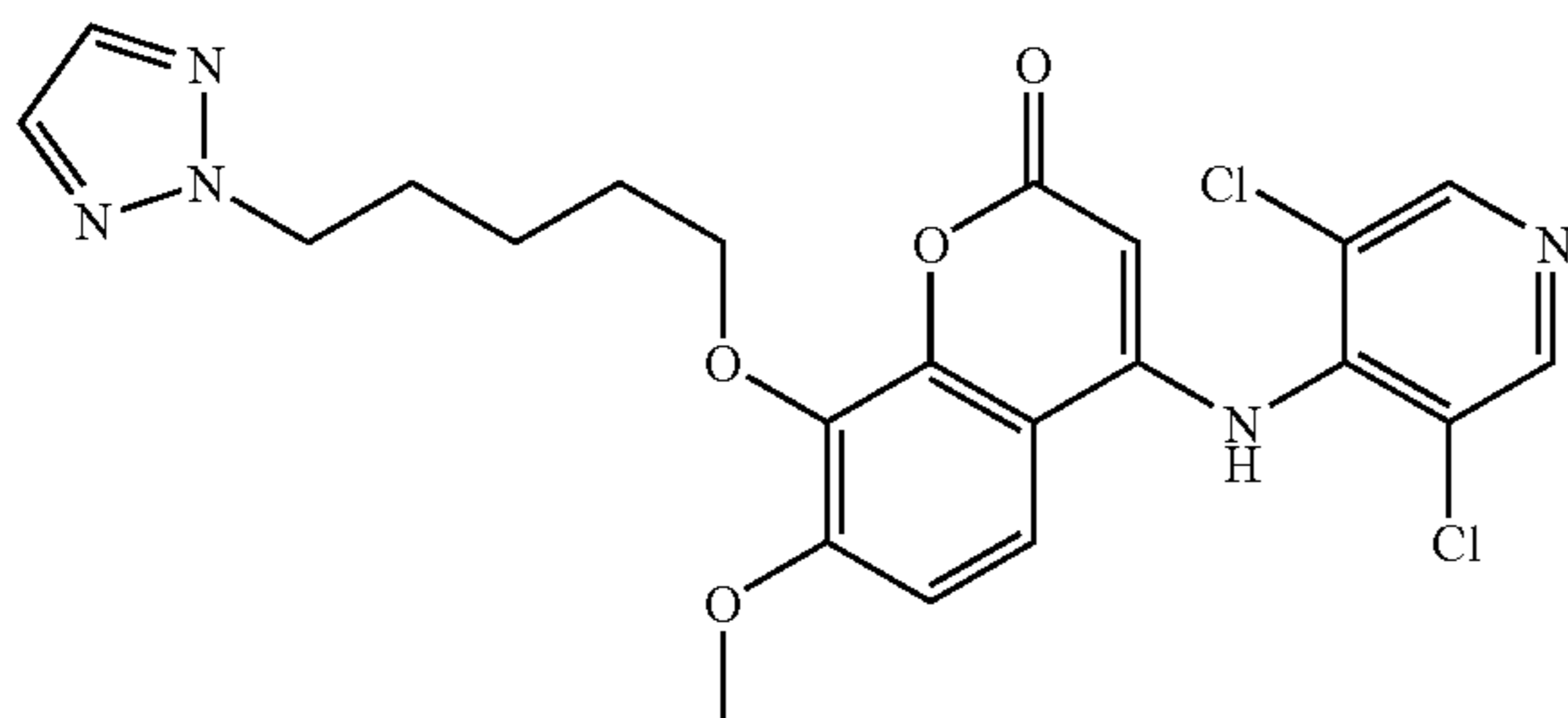
Potassium carbonate (350 mg, 2.54 mmol) was added to a solution of 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-

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ylamino)-7-methoxy-2H-chromen-2-one (1.0 g, 2.0 mmol, Example 28), 1H-1,2,3-triazole (210 mg, 3.04 mmol), and DMF (15 mL) at rt. After 3.5 h at 80° C., the mixture was allowed to cool to rt, quenched with water (10 mL), and then extracted with ethyl acetate (20 mL×3). The combined extracts were washed with brine, dried, filtered, concentrated, and then purified by silica gel chromatography (dichloromethane:methanol) to give 8-(5-(1H-1,2,3-triazol-1-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 8.13 (s, 1H), 7.94 (d, 1H), 7.69 (s, 1H), 7.19 (d, 1H), 4.63 (s, 1H), 4.40 (t, 2H), 3.97 (t, 2H), 3.90 (s, 3H), 1.88 (m, 2H), 1.75 (m, 2H), 1.45 (m, 2H); MS (ESI): 490.0.

## EXAMPLE 99

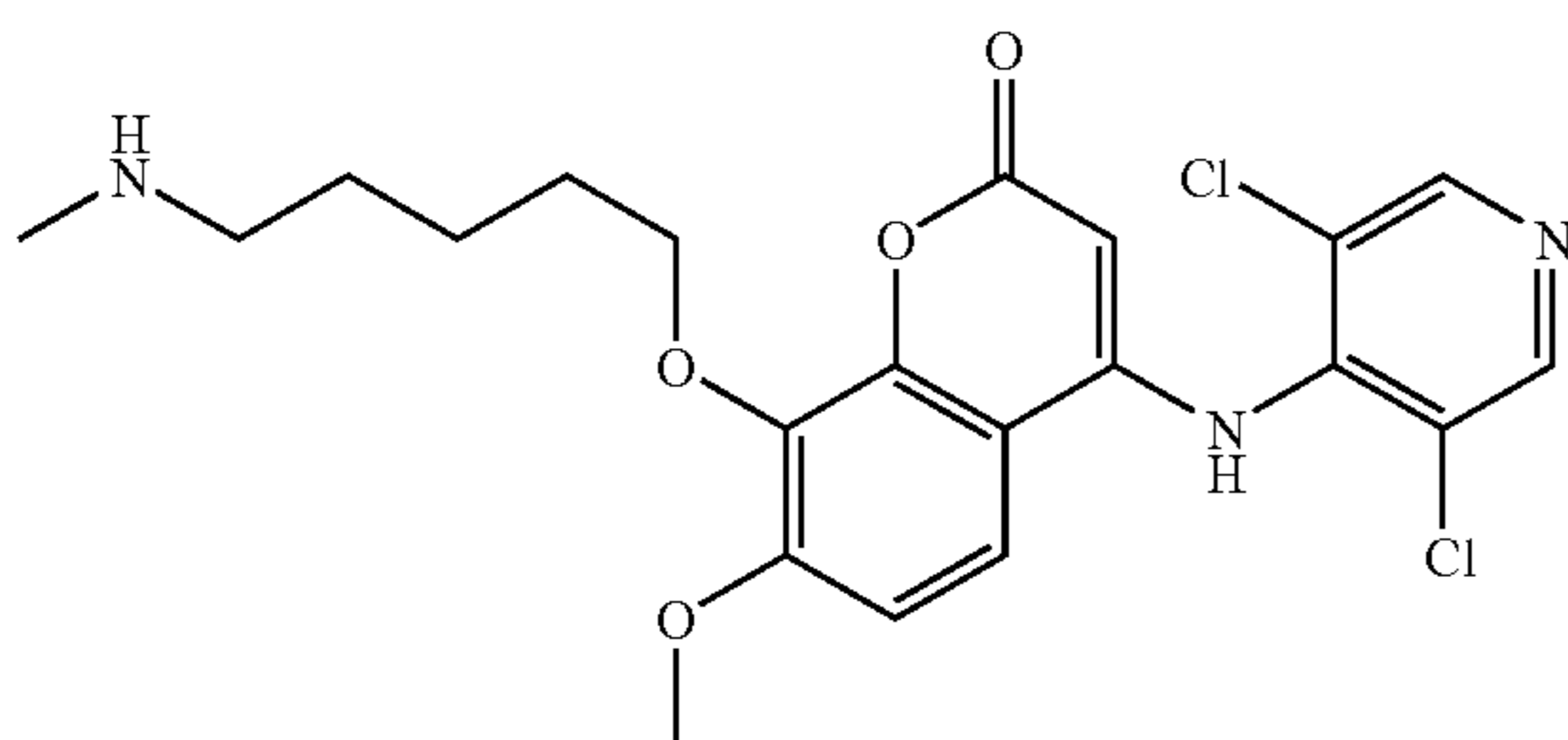
8-(5-(2H-1,2,3-Triazol-2-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was isolated during the purification of Example 98. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.74 (s, 2H), 7.19 (d, 1H), 4.63 (s, 1H), 4.42 (t, 2H), 3.96 (t, 2H), 3.90 (s, 3H), 1.92 (m, 2H), 1.69 (m, 2H), 1.42 (m, 2H); MS (ESI): 490.0.

## EXAMPLE 100

4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-8-(5-(methylamino)pentyl)oxy)-2H-chromen-2-one

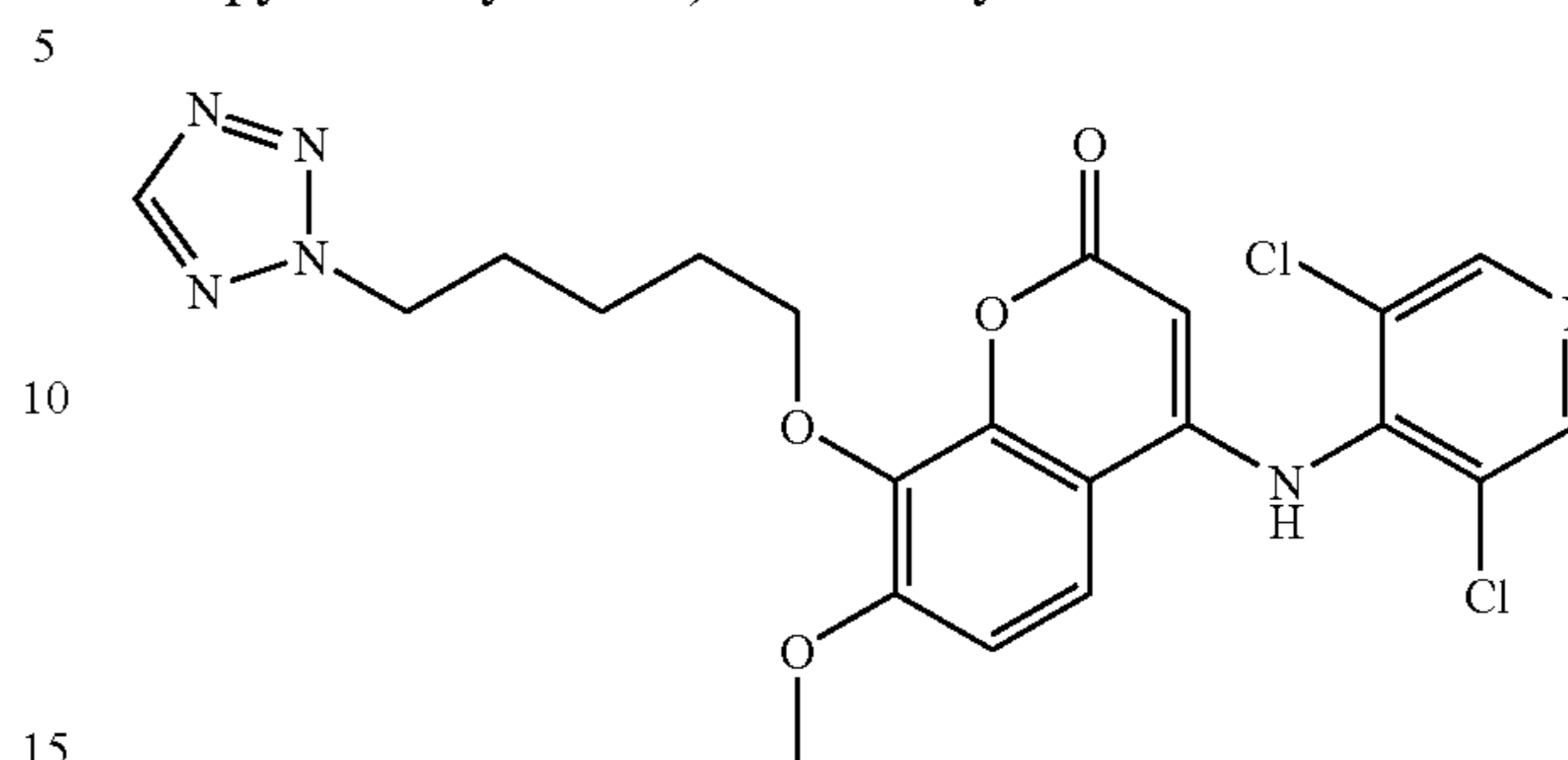


The title compound was prepared from methylamine and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 27. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.44 (br s, 2H), 8.33 (s, 2H), 7.78 (d, 1H), 6.92 (d, 1H), 3.94 (t, 2H), 3.85 (s, 1H), 3.84 (s, 3H), 2.93 (t, 2H), 2.53 (s, 3H), 1.82-1.56 (m, 6H); MS (ESI): 452.0.

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## EXAMPLE 101

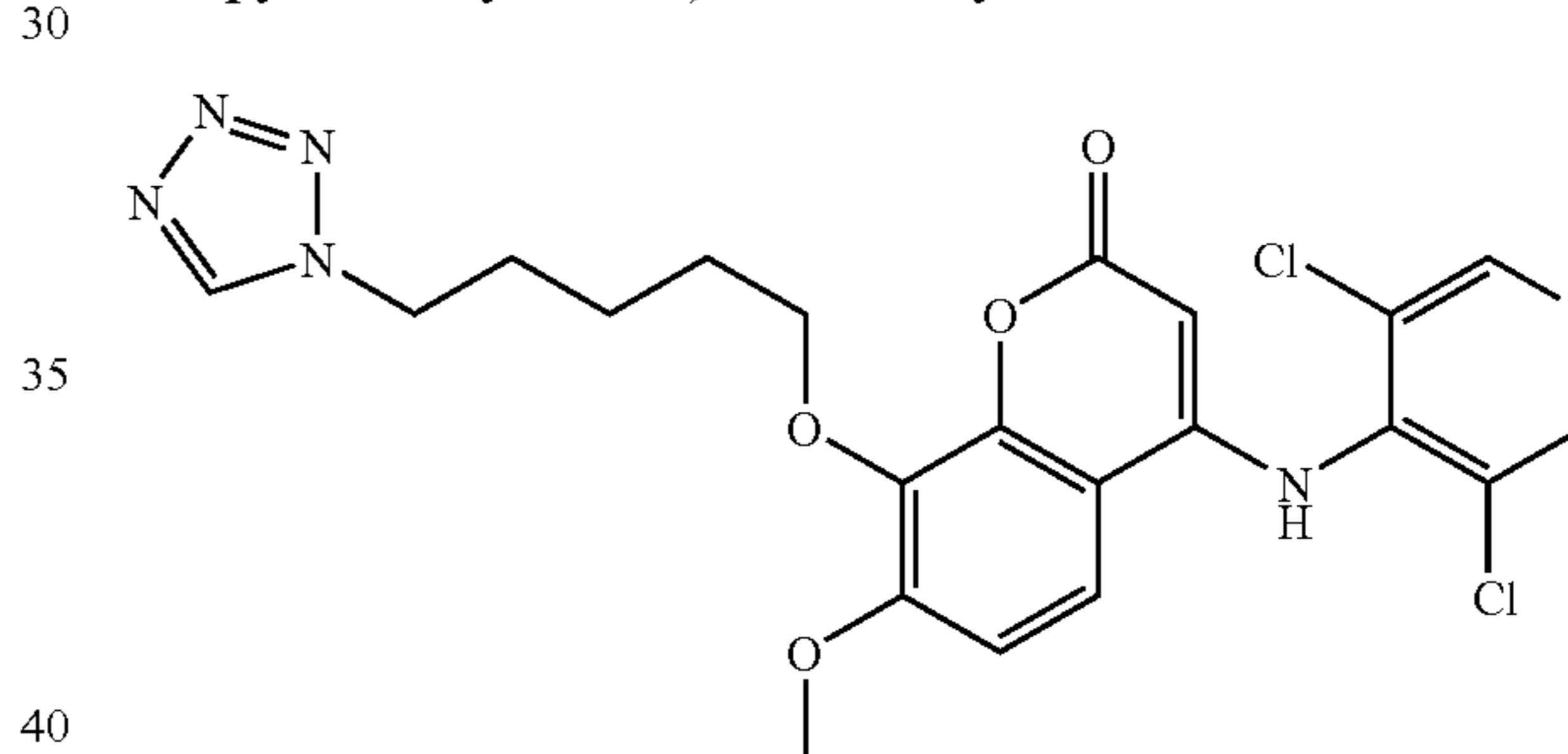
8-(5-(2H-Tetrazol-2-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from tetrazole and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 98. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.94 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.19 (d, 1H), 4.72 (t, 2H), 4.63 (s, 1H), 3.96 (t, 2H), 3.90 (s, 3H), 1.98 (m, 2H), 1.70 (m, 2H), 1.46 (m, 2H); MS (ESI): 490.9.

## EXAMPLE 102

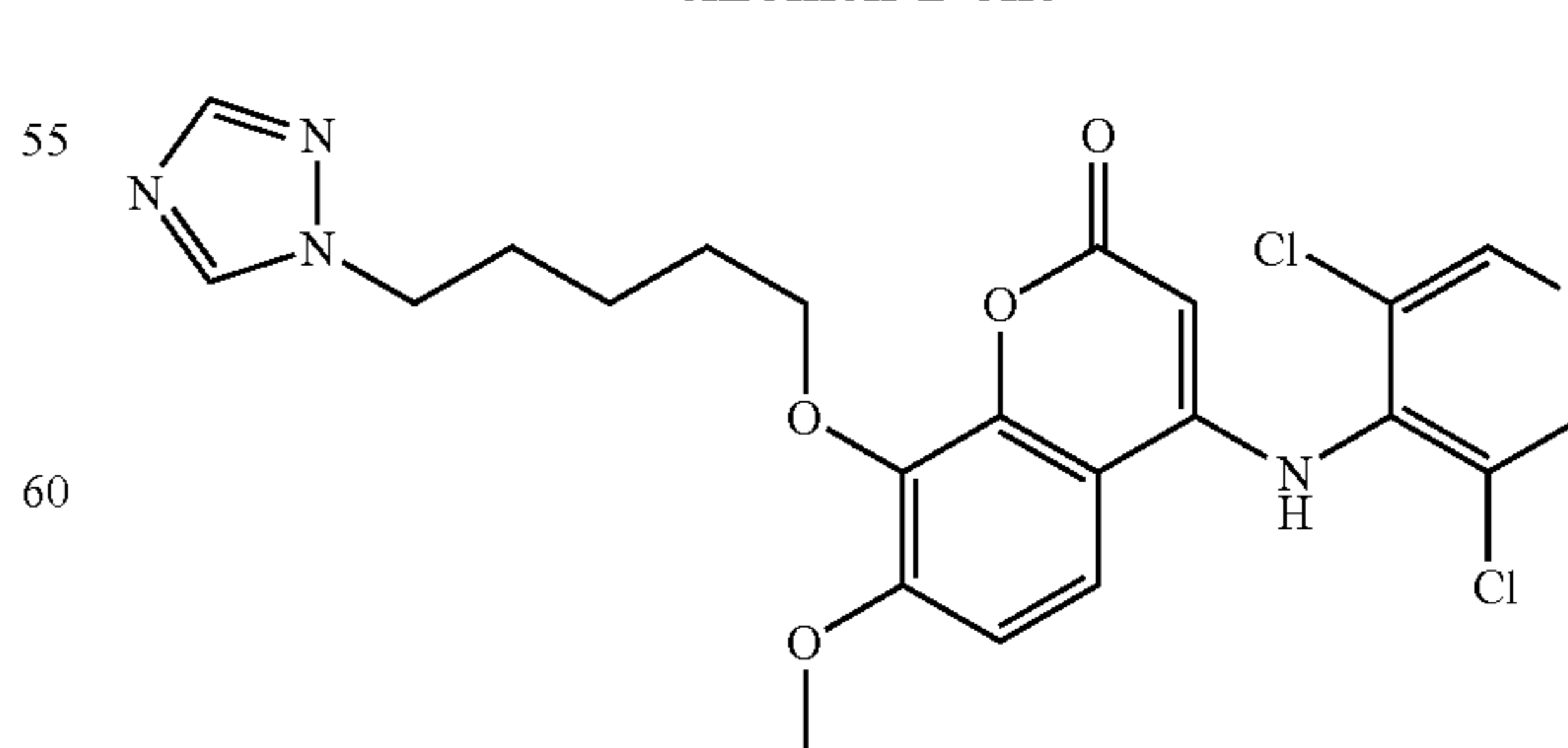
8-(5-(1H-Tetrazol-1-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was isolated during the purification of Example 101. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.53 (s, 1H), 9.41 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 4.48 (t, 2H), 3.97 (t, 2H), 3.90 (s, 3H), 1.92 (m, 2H), 1.71 (m, 2H), 1.47 (m, 2H); MS (ESI): 490.9.

## EXAMPLE 103

8-(5-(1H-1,2,4-Triazol-1-yl)pentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2H-chromen-2-one



The title compound was prepared from 1,2,4-triazole and 8-(5-bromopentyl)oxy)-4-(3,5-dichloropyridin-4-ylamino)-

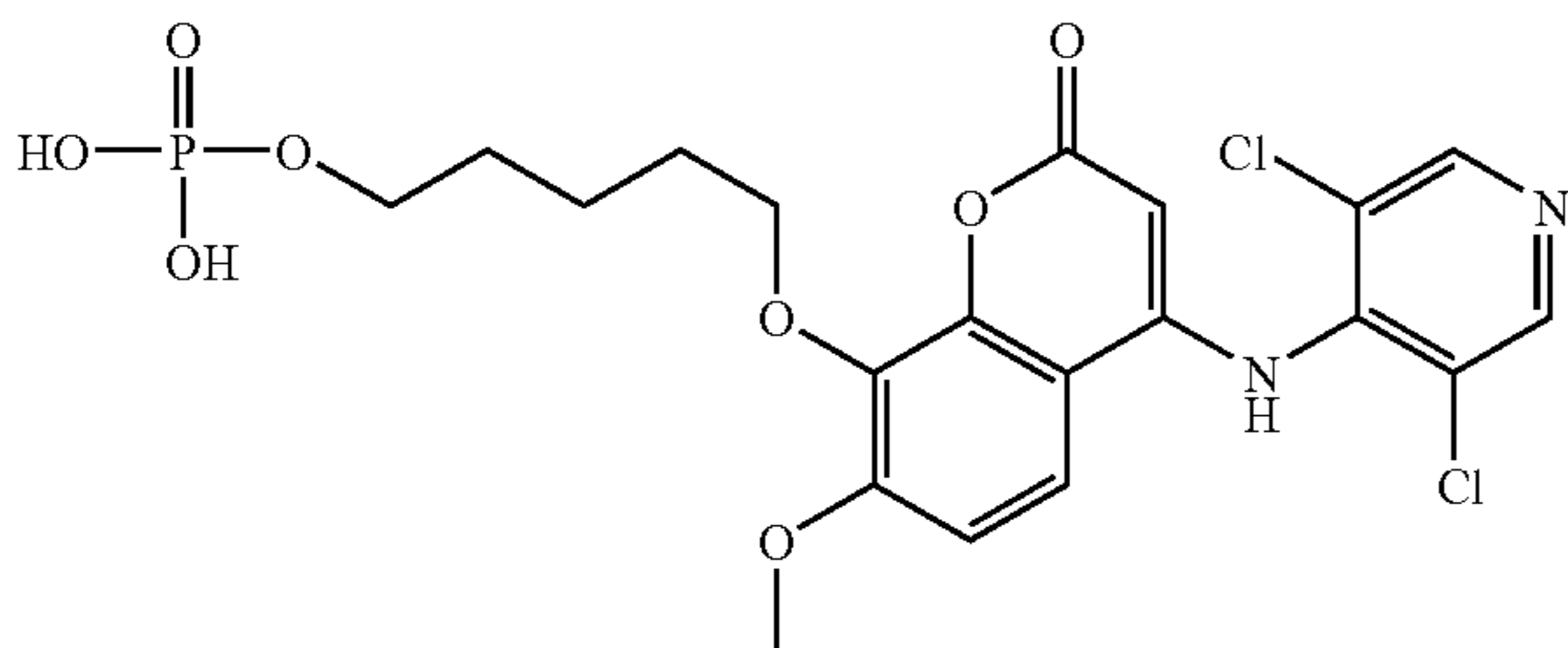


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7-methoxy-2H-chromen-2-one (Example 28) following the procedure outlined in Example 98. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 8.50 (s, 1H), 7.94 (d, 1H), 7.93 (s, 1H), 7.19 (d, 1H), 4.64 (s, 1H), 4.19 (t, 2H), 3.96 (t, 2H), 3.90 (s, 3H), 1.84 (m, 2H), 1.69 (m, 2H), 1.43 (m, 2H); MS (ESI): 489.9.

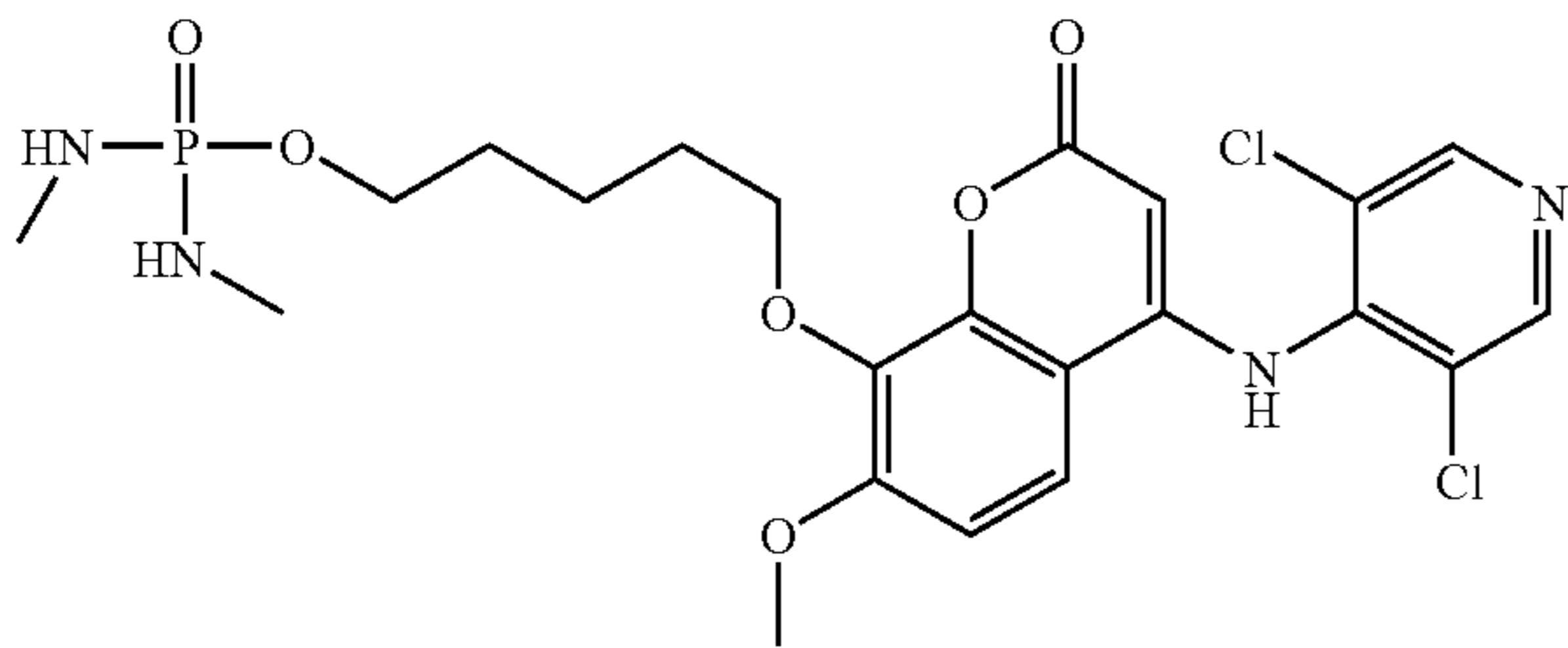
## EXAMPLE 104

5-(4-(3,5-Dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl dihydrogen phosphate



Phosphoryl trichloride (69.4 mg, 0.46 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-(5-hydroxypentyl)-7-methoxy-2H-chromen-2-one (100 mg, 0.22 mmol, Example 72) and trimethyl phosphate (2 mL). After 1 h at rt, water (0.5 mL) was added, and the reaction was stirred for an additional 2 h. The solution was directly purified by reverse-phase HPLC to give 5-(4-(3,5-dichloropyridin-4-ylamino)-7-methoxy-2-oxo-2H-chromen-8-yloxy)pentyl dihydrogen phosphate: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.88 (br, 2H), 9.52 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.64 (s, 1H), 3.98 (t, 2H), 3.92 (s, 3H), 3.82 (m, 2H), 1.70 (m, 2H), 1.62 (m, 2H), 1.51 (m, 2H); MS (ESI): 518.9.

## EXAMPLE 105



Phosphoryl trichloride (70 mg, 0.46 mmol) was added to a solution of 4-(3,5-dichloropyridin-4-ylamino)-8-(5-hydroxypentyl)-7-methoxy-2H-chromen-2-one (100 mg, 0.23 mmol, Example 72) and trimethyl phosphate (3 mL). After 1 h at 0° C., a saturated solution of methylamine in methanol (2 mL) was added. The reaction was stirred for an additional hour, concentrated, and purified by silica gel chromatography (dichloromethane:methanol) to give the title compound: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.52 (s, 1H), 8.81 (s, 2H), 7.94 (d, 1H), 7.20 (d, 1H), 4.63 (s, 1H), 4.07 (m, 2H), 3.98 (t, 2H), 3.92 (s, 3H), 3.75 (m, 2H), 2.33 (dd, 6H), 1.70 (m, 2H), 1.61 (m, 2H), 1.51 (m, 2H); MS (ESI): 545.0.

The following compounds can generally be made using the methods described above. It is expected that these com-

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pounds when made will have activity similar to those that have been made in the examples above.

The following compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, 28, 31-36. All SMILES strings, and many of the IUPAC names, used herein were generated using either Accelrys's Pipeline Pilot 6.0 or CambridgeSoft's ChemDraw 10.0.

15 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCC(NCC(O)=O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCC(N[C@@H](C)C(O)=O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
20 (OCCCC(NCC(O)=O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N[C@@H](C)C(O)=O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(NCC(O)=O)=O)=C(OC)C=C3  
25 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N[C@@H](C)C(O)=O)=O)=C(OC)  
C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N)=O)=C(OC)C=C3  
30 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(OCCN(C)C)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
35 (OCCCC(OCC[N+](C)(C)C)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(NCCN(C)C)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(NCC[N+](C)(C)C)=O)=C(OC)C=C3  
40 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N(C)CCN(C)C)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCC(N(C)CC[N+](C)(C)C)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
45 (OCCCCN)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCNC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCNCC)=C(OC)C=C3  
50 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCNCCC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
55 (OCCCCN(CC)CC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CCC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CCCC)=C(OC)C=C3  
60 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CCOC)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CCN(C)C)=C(OC)C=C3  
65 O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C  
(OCCCCN(C)CCN(C)C)=C(OC)C=C3

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O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4CCNCC4)=C(OC)C=C3O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4C=CC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=CC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4C=NC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=NC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=CC=N4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=CN=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4C=NN=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=NN=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCN4N=NC=N4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOC4=CN=CC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOC4=CN=CC=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOC4=CC=CN=C4)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCN(C)C)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCN(C)C)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCC(O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OCCCCN4CCN(C)CC4)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OCCCCN4CCOCC4)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCC(O)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OCC(N)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCC(N)=O)=C(OC)C=C3  
O=C1C=C(NC2=C(C)C=NC=C2C)C3=C(O1)C(OC-CCCC(O)=O)=C(OC)C=C3  
O=C(O1)C=C(NC2=C(C1)C=NC=C2C1)C3=C1C(OCCCO[C@@H]4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O)=C(OC)C=C3  
O=C(O1)C=C(NC2=C(C1)C=NC=C2C1)C3=C1C(OCCCCO[C@@H]4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOCCO)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOCCOCCO)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOCCOCCO)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOCCOCCOCCO)=C(OC)C=C3  
O=C1C=C(NC2=C(C1)C=NC=C2C1)C3=C(O1)C(OCCCCOCCOCCOCCOCCO)=C(OC)C=C3  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(C)cncc3C  
CNCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cncc3C  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCN)Nc3c(C)cncc3C

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Cc1encc(C)c1NC2=CC(=O)O)c3c(OCC(=O)N)c(OCF)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N)Nc3c(C)cncc3C  
5 COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(C)cncc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cncc3F  
Cc1encc(F)c1NC2=CC(=O)O)c3c(OCC(=O)N)c(OCF)ccc23  
10 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cncc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(F)cncc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cncc3F  
15 NC(=O)COc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(F)cncc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cncc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(C)cccc3C  
20 CNCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cccc3C  
Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCC(=O)N)c(OCF)ccc23  
25 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N)Nc3c(C)cccc3C  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(C)cccc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cccc3F  
30 Cc1cccc(F)c1NC2=CC(=O)O)c3c(OCC(=O)N)c(OCF)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cccc3C1  
35 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cc(F)cc3C  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cc(F)cc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cc(O)cc3C  
40 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(C)cc(O)cc3F  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN)Nc3c(F)cccc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cccc3F  
45 NC(=O)COc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(F)cccc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cccc3C1  
50 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cc(F)cc3F  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N)Nc3c(F)cc(O)cc3F  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN3CCCC(F)(F)C3)Nc4c(C)cccc4C  
55 Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCCCCn4cn4)c(OC(F)F)ccc23  
Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCCCCO)c4cncc4)c(OCF)ccc23  
60 CCCCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C  
Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCCCCn4cn4)c(OC(F)(F)F)ccc23  
Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCCCCCN4CCC(F)CC4)c(OC(F)F)ccc23  
65 Cc1cccc(C)c1NC2=CC(=O)O)c3c(OCCCCCN4CCC(F)(F)C4)c(OCF)ccc23

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Cc1cccc(C)c1NC2=CC(=O)Oc3c(OCCCCCn4cnnn4)c(OC(F)(F)F)ccc23  
CN(CCC[N+](C)(C)C)C(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C  
Cc1cccc(C)c1NC2=CC(=O)Oc3c(OCC(=O)N[C@@H](CCC(=O)O)C(=O)O)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N3CCNCC3)Nc4c(C)cccc4C  
CN1CCN(CC1)C(=O)CCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C)cccc4C  
CN(C)CCNC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C  
Cc1cccc(C)c1NC2=CC(=O)Oc3c(OCCCC(=O)N4CCNCC4)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](CCSC)C(=O)O)Nc3c(C)cccc3C  
Cc1cccc(C)c1NC2=CC(=O)Oc3c(OCCCC(=O)N)c(OCF)ccc23  
CN(C)CCOC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](Cc3c[nH]c4cccc34)C(=O)O)Nc5c(C)cccc5C  
CCCN(C)CCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3F  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCCn4cnnn4)c(OCF)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCCN)c(OC(F)(F)F)ccc23  
CCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3F  
CNCCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3F  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCCCOe4cncnc4)c(OCF)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCCCOCCO)c(OC(F)F)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCC(=O)OCC[N+](C)(C)C)c(OC(F)F)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCC(=O)N4CCC[C@@H]4C(=O)O)c(OCF)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)Nc3c(C)cccc3F  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N)Nc3c(C)cccc3F  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCC(=O)NCC[N+](C)(C)C)c(OCF)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](Cc4c[nH]c5cccc45)C(=O)O)c(OC(F)(F)F)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCC(=O)N4CCC[C@@H]4C(=O)O)c(OCF)ccc23  
Cc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)(F)F)ccc23  
CCN(CC)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCCn4cnnn4)c(OC(F)(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCCOe3cncnc3)Nc4c(C)cccc4C1  
CNCCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
COCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCCN4CCCC(F)C4)c(OC(F)(F)F)ccc23  
CCNCCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)ccc(F)ccc3C  
CCN(CC)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)ccc(F)ccc3C

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COc1ccc2C(=CC(=O)O)c2c1OCCCCOe3cncnc3)Nc4c(C)cccc4C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCCCN)c(OC(F)F)ccc23  
CCCCCN(C)CCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCCCn4cnnc4)c(OCF)ccc23  
CN(C)CCNC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](CCSC)C(=O)O)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCC(=O)N[C@@H](CCCN)C(=O)O)c(OC(F)(F)F)ccc23  
CN(CC[N+](C)(C)C)C(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
CN1CCN(CC1)C(=O)CCCOe2c(OC(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C)cccc4C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)NCC(=O)O)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](Cc4cccc4)C(=O)O)c(OC(F)(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](CCC(=O)O)C(=O)O)Nc3c(C)cccc3C1  
CN(C)CCOC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3C1  
Cc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)c(OC(F)(F)F)ccc23  
CCN(CC)CCCCOe1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3Br  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCCOCCO)c(OC(F)F)ccc23  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCCn4cccc4)c(OCF)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCOCCO)Nc3c(C)cccc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCn3cncnc3)Nc4c(C)cccc4Br  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCCCn4cnnc4)c(OC(F)(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N(C)CCC[N+](C)(C)C)Nc3c(C)cccc3Br  
CC(C)[C@@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cccc3Br)C(=O)O  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCC(=O)N[C@@H](CC(=O)N)C(=O)O)c(OCF)ccc23  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)OCC[N+](C)(C)C)c(OC(F)F)ccc23  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](CC(=O)N)C(=O)O)c(OCF)ccc23  
Cc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](Cc4ccc(O)cc4)C(=O)O)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)OCC[N+](C)(C)C)Nc3c(C)cccc3Br  
Cc1cc(F)cc(C)c1NC2=CC(=O)Oc3c(OCCCCN)c(OC(F)F)ccc23  
CCCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)ccc(F)ccc3C  
COc1ccc2C(=CC(=O)O)c2c1OCCCCN3CCC(F)CC3)Nc4c(C)ccc(F)ccc4C  
Cc1cc(F)cc(C)c1NC2=CC(=O)Oc3c(OCCCCN4CCCC(F)C4)c(OC(F)(F)F)ccc23  
CCNCCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)ccc(F)ccc3C  
CCN(CC)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)ccc(F)ccc3C

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COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)(F)C3)Nc4c(C)cc(F)cc4C  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCCCOCCO)c(OCF)ccc23  
 COCCOCCOCCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C  
 CN1CCN(CC 1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C)cc(F)cc4C  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](CCSC)C(=O)O)Nc3c(C)cc(F)cc3C  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23  
 CN(CCC[N+](C)(C)C)C(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N[C@@H](CCCN)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](Cc3cnc[nH]3)C(=O)O)Nc4c(C)cc(F)cc4C  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N[C@@H](CCC(=O)O)C(=O)O)c(OCF)ccc23  
 CN(C)CCNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C  
 CN1CCN(CC 1)C(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C)cc(F)cc4C  
 C[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)Nc3c(C)cc(F)cc3C  
 C[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C)C(=O)O  
 CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C)C(=O)O  
 CCCC(C)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCCN4CCCC(F)F)C4)c(OC(F)F)ccc23  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCCn4ccn4)c(OCF)ccc23  
 COCCOCCOCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 CNCCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCCN4CCCC(F)F)C4)c(OC(F)F)ccc23  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCCO4ccncc4)c(OC(F)F)ccc23  
 CCN(CC)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 CCCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCCCN4CCCC(F)F)C4)c(OC(F)F)ccc23  
 C[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](CC(C)C)C(=O)O)Nc3c(C)cc(F)cc3F  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCC(=O)N[C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)F)ccc23  
 CN(CCC[N+](C)(C)C)C(=O)CCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](CC(=O)N)C(=O)O)Nc3c(C)cc(F)cc3F  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CC[N+](C)(C)C)Nc3c(C)cc(F)cc3F  
 Ce1cc(F)cc(F)c1NC2=CC(=O)O)c3c(OCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)c(OCF)ccc23

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CSCC[C@H](NC(=O)CCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3F)C(=O)O  
 CCCC(C)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C1  
 CCCCCN(C)CCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C1  
 COCCOCCOCCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C1  
 CCN(C)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C1  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCCC(F)C3)Nc4c(C)cc(F)cc4C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCCn4ccn4)c(OCF)ccc23  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCCOCCO)c(OC(F)F)ccc23  
 CCCNCCCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCCCN4CCCC4)c(OCF)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)(F)CC3)Nc4c(C)cc(F)cc4C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCC(=O)N4CCNCC4)c(OCF)ccc23  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](CC(=O)O)C(=O)O)Nc3c(C)cc(F)cc3C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)NCC[N+](C)(C)C)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CC[N+](C)(C)C)Nc3c(C)cc(F)cc3C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N[C@@H](Cc4c[nH]c5ccccc45)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CCN(C)C)Nc3c(C)cc(F)cc3C1  
 Ce1cc(F)cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N4CCC[C@H]4C(=O)O)c(OC(F)F)ccc23  
 CCCNCCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br  
 Ce1cc(F)cc(Br)c1NC2=CC(=O)O)c3c(OCCCCN(C(=N)N)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCn3ccn3)Nc4c(C)cc(F)cc4Br  
 Ce1cc(F)cc(Br)c1NC2=CC(=O)O)c3c(OCCCCO4cccc4)c(OCF)ccc23  
 CCNCCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br  
 CCN(CC)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br  
 CNCCCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br  
 Ce1cc(F)cc(Br)c1NC2=CC(=O)O)c3c(OCC(=O)N[C@@H](Cc4c[nH]c5ccccc45)C(=O)O)c(OC(F)F)ccc23  
 CC[C@H](C)[C@H](NC(=O)CCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br)C(=O)O  
 C[C@H](NC(=O)CCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br)C(=O)O  
 CC(C)C[C@H](NC(=O)CCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](Cc3c[nH]c4ccccc34)C(=O)O)Nc5c(C)cc(F)cc5Br  
 CN(C)CCNC(=O)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br

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CN(C)CCCN(C)C(=O)CCCCCOc1c(OC(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cc(F)cc3Br  
 Ce1cc(F)cc(Br)c1NC2=CC(=O)Oe3c(OCCCCC(=O)  
 N4CCNCC4)c(OCF)ccc23  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N  
 [C@@H](Cc3ccc(O)cc3)C(=O)O)Nc4c(C)cc(F)cc4Br  
 CCCCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3C  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c  
 (OCCCCN4CCOCC4)c(OCF)ccc23  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCCn4cncn4)c  
 (OC(F)F)ccc23  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCCN4CCC  
 (F)CC4)c(OC(F)F)ccc23  
 COCCOCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C  
 CNCCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c  
 (C)cc(O)cc3C  
 COCCN(C)CCCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C)cc(O)cc3C  
 CN(CC[N+](C)(C)C)C(=O)COe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C  
 CN(C)CCOC(=O)CCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C  
 COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (Cc3cccc3)C(=O)O)Nc4c(C)cc(O)cc4C  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CCCN)C(=O)O)c(OC(F)F)ccc23  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CCC(=O)O)C(=O)O)c(OCF)ccc23  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)  
 NCC(=O)O)c(OCF)ccc23  
 C[C@H](NC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C)C(=O)O  
 Ce1cc(O)cc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N  
 [C@@H](Cc3cnc[nH]3)C(=O)O)Nc4c(C)cc(O)cc4C  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCCCCn4cncn4)c  
 (OC(F)F)ccc23  
 COCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3F  
 CCCCCN(C)CCCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C)cc(O)cc3F  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCCCCCn4ccn4)c  
 (OC(F)F)ccc23  
 CCCCCN(C)CCCCCOe1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3F  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC  
 (F)CC4)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N3CCC[C@H]  
 3C(=O)O)Nc4c(C)cc(O)cc4F  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OCF)ccc23  
 C[C@@H](O)[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C)cc(O)cc3F)C(=O)O  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N[C@@H]  
 (CCNC(=N)N)C(=O)O)Nc3c(C)cc(O)cc3F  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OC(F)F)ccc23  
 CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)F)  
 ccc2C(=CC(=O)Oc12)Nc3c(C)cc(O)cc3F  
 Ce1cc(O)cc(F)c1NC2=CC(=O)Oe3c(OCCCCC(=O)  
 N4CCC[C@H]4C(=O)O)c(OC(F)F)ccc23  
 CCCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(C)cc(O)cc3C1

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Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCCN4CCCC  
 (F)C4)c(OCF)ccc23  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCn3cccn3)Nc4c(C)cc  
 (O)cc4C1  
 5 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCCNC(=N)  
 N)c(OCF)ccc23  
 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCCN4CCC  
 (F)C4)c(OC(F)F)ccc23  
 COCCOCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C1  
 10 CNCCCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(C)  
 cc(O)cc3C1  
 CCCCCN(C)CCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3C1  
 15 COc1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC(F)C3)  
 Nc4c(C)cc(O)cc4C1  
 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c  
 (OCCCCCOe4ccnc4)c(OC(F)F)ccc23  
 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCC(=O)  
 N4CCNCC4)c(OC(F)F)ccc23  
 20 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCC(=O)NCC  
 (=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](Cc3c  
 [nH]c4cccc34)C(=O)O)Nc5c(C)cc(O)cc5C1  
 25 CN(C)CCNC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3C1  
 CC(C)[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C)cc(O)cc3C1)C(=O)O  
 CC(C)[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C)cc(O)cc3C1)C(=O)O  
 30 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](Cc4cccc4)C(=O)O)c(OCF)ccc23  
 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CCCN)C(=O)O)c(OC(F)F)ccc23  
 35 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N(C)CCN  
 (C)C)Nc3c(C)cc(O)cc3C1  
 CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)  
 ccc2C(=CC(=O)Oc12)Nc3c(C)cc(O)cc3C1  
 Ce1cc(O)cc(C1)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](Cc4ccc(O)cc4)C(=O)O)c(OCF)ccc23  
 40 COc1ccc2C(=CC(=O)Oe2c1OCCCCN(C)C)Nc3c(C)cc  
 (O)cc3Br  
 COCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3Br  
 45 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oe3c(OCCCCN)c(OC  
 (F)F)ccc23  
 CCCCCN(C)CCCCCOe1c(OC)ccc2C(=CC(=O)Oc12)  
 Nc3c(C)cc(O)cc3Br  
 50 COCCOCCCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c  
 (C)cc(O)cc3Br  
 CCCCCN(C)CCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3Br  
 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oe3c  
 (OCCCCCN4CCCC4)c(OCF)ccc23  
 55 COc1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCC(F)F)  
 C3)Nc4c(C)cc(O)cc4Br  
 CN(C)CCNC(=O)COe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3Br  
 60 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oe3c(OCC(=O)NCC  
 [N+](C)(C)C)c(OC(F)F)ccc23  
 CSCC[C@H](NC(=O)COe1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C)cc(O)cc3Br)C(=O)O  
 65 CN(CC[N+](C)(C)C)C(=O)CCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C)cc(O)cc3Br  
 CN(CCC[N+](C)(C)C)C(=O)CCCOe1c(OCF)ccc2C  
 (=CC(=O)Oc12)Nc3c(C)cc(O)cc3Br

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COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
 (CO)C(=O)O)Nc3c(C)cc(O)cc3Br  
 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N  
 [C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)NCC(=O)  
 O)Nc3c(C)cc(O)cc3Br  
 CC(C)[C@H](NC(=O)CCCCO)c1c(OCF)ccc2C(=CC  
 (=O)O)c12)Nc3c(C)cc(O)cc3Br)C(=O)O  
 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)  
 N4CCC[C@H]4C(=O)O)c(OC(F)F)ccc23  
 CN(CCC[N+](C)(C)C)C(=O)CCCCO)c1c(OCF)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cc(O)cc3Br  
 C[C@H](NC(=O)CCCCO)c1c(OC(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(C)cc(O)cc3Br)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N  
 [C@@H](CC(=O)O)C(=O)O)Nc3c(C)cc(O)cc3Br  
 Ce1cc(O)cc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OC(F)F)ccc23  
 CCN(CC)CCCCO)c1c(OC)ccc2C(=CC(=O)O)c12)Nc3c  
 (C)cc(cc3C)C(=O)O  
 CCN(CC)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cc(cc3C)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCn4cncn4)c(OC  
 (F)F)ccc23)C(=O)O  
 CN(C)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cc(cc3C)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCCC3)  
 Nc4c(C)cc(cc4C)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCn4 cnc4)c  
 (OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCO)c4cncnc4)c  
 (OCF)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)F)  
 CC3)Nc4c(C)cc(cc4C)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCCN4CCC(F)  
 (F)CC4)c(OC(F)F)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)OCCN(C)C)  
 Nc3c(C)cc(cc3C)C(=O)O  
 CN(C)CCCN(C)C(=O)CO)c1c(OC(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(C)cc(cc3C)C(=O)O  
 C[C@H](NC(=O)CO)c1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cc(cc3C)C(=O)O)C(=O)O  
 CN(C)CCOC(=O)CCCO)c1c(OCF)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cc(cc3C)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)  
 N4CCC[C@H]4C(=O)O)c(OC(F)F)ccc23)C(=O)O  
 CSCC[C@H](NC(=O)CCCCO)c1c(OCF)ccc2C(=CC  
 (=O)O)c12)Nc3c(C)cc(cc3C)C(=O)O)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N3CCC  
 [C@H]3C(=O)O)Nc4c(C)cc(cc4C)C(=O)O  
 COCCN(C)CCCCO)c1c(OC)ccc2C(=CC(=O)O)c12)Nc3c  
 (C)cc(cc3F)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCCN4CCOCC4)c  
 (OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCCn4cncn4)c  
 (OCF)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCO)c3ccnc3)Nc4c  
 (C)cc(cc4F)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCCCO)c4ccnc4)c  
 (OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCCCO)c4cncnc4)c  
 (OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCCCN4 cenn4)c  
 (OCF)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N3CCC[C@H]  
 3C(=O)O)Nc4c(C)cc(cc4F)C(=O)O

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Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCC(=O)N[C@@H]  
 (CO)C(=O)O)c(OCF)ccc23)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](CO)C(=O)O)c(OCF)ccc23)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](CCC(=O)O)C(=O)O)c(OC(F)F)ccc23)C  
 (=O)O  
 CN(CC [N+](C)(C)C)C(=O)CCCCO)c1c(OCF)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cc(cc3F)C(=O)O  
 Ce1cc(cc(F)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)F)ccc23)C  
 (=O)O  
 CN(CC[N+](C)(C)C)C(=O)CCCCO)c1c(OC(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cc(cc3F)C(=O)O  
 CN1CCN(CC 1)C(=O)CCCCO)c2c(OC(F)F)ccc3C  
 (=CC(=O)O)c23)Nc4c(C)cc(cc4F)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCN4CCCC4)c  
 (OCF)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCN3CCCC(F)F)C3)  
 Nc4c(C)cc(cc4C1)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCOCCO)c(OC  
 (F)F)ccc23)C(=O)O  
 CCCNCCCCO)c1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cc(cc3C1)C(=O)O  
 CCCN(C)CCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cc(cc3C1)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)F)C3)  
 Nc4c(C)cc(cc4C1)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCCCN4CCC  
 (F)CC4)c(OC(F)F)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3cenn3)Nc4c  
 (C)cc(cc4C1)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c  
 (OCCCCCO)c4cccn4)c(OC(F)F)ccc23)C(=O)O  
 CN(CCC[N+](C)(C)C)C(=O)CO)c1c(OC(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cc(cc3C1)C(=O)O  
 C[C@H](NC(=O)CO)c1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cc(cc3C1)C(=O)O)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
 (Cc3cnc[nH]3)C(=O)O)Nc4c(C)cc(cc4C1)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](CCC(=O)N)C(=O)O)c(OC(F)F)ccc23)C  
 (=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
 (Cc3cccc3)C(=O)O)Nc4c(C)cc(cc4C1)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](Cc4c[nH]c5cccc45)C(=O)O)c(OC(F)F)  
 ccc23)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)N  
 [C@@H](CO)C(=O)O)c(OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(C)c1NC2=CC(=O)O)c3c(OCCCC(=O)  
 NCC(=O)O)c(OC(F)F)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCN3CCC(F)F)C3)  
 Nc4c(C)cc(cc4Br)C(=O)O  
 CCCN(C)CCCCO)c1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cc(cc3Br)C(=O)O  
 Ce1cc(cc(Br)c1NC2=CC(=O)O)c3c(OCCCCN4CCC(F)  
 CC4)c(OC(F)F)ccc23)C(=O)O  
 Ce1cc(cc(Br)c1NC2=CC(=O)O)c3c(OCCCCCN4CCC  
 (F)F)C4)c(OCF)ccc23)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCOCCO)Nc3c(C)  
 cc(cc3Br)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](C)C  
 (=O)O)Nc3c(C)cc(cc3Br)C(=O)O  
 Ce1cc(cc(Br)c1NC2=CC(=O)O)c3c(OCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OC(F)F)ccc23)C  
 (=O)O

CN(C)CCNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(C)cc(cc3Br)C(=O)O  
CN1CCN(CC1)C(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)Oc23)Nc4c(C)cc(cc4Br)C(=O)O  
CC(C)C[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(C)cc(cc3Br)C(=O)O)C(=O)O  
COc1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N[C@@H](CC(=O)N)C(=O)O)Nc3c(C)cc(cc3Br)C(=O)O  
Cc1cc(cc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)c(OC(F)F)ccc23)C(=O)O  
CN(C)CCN(C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(C)cc(cc3Br)C(=O)O  
CC(C)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(C)cc(cc3Br)C(=O)O)C(=O)O  
Cc1cc(cc(Br)c1NC2=CC(=O)Oc3c(OCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)c(OCF)ccc23)C(=O)O  
FC(F)Oc1ccc2C(=CC(=O)Oc2c1OCCCCN3CCOCC3)Nc4c(F)cccc4F  
Fc1cccc(F)c1NC2=CC(=O)Oc3c(OCCCN4CCC(F)F)CC4)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)Oc2c1OCCCCn3cccc3)Nc4c(F)cccc4F  
FCOc1ccc2C(=CC(=O)Oc2c1OCCCCOc3ccnc3)Nc4c(F)cccc4F  
CCN(C)CCCCOc1c(OC)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F  
CCNCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F  
FCOc1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCC(F)C3)Nc4c(F)cccc4F  
CN(CC[N+](C)(C)C)C(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F  
COc1ccc2C(=CC(=O)Oc2c1OCC(=O)N[C@@H](Cc3ccc(O)cc3)C(=O)O)Nc4c(F)cccc4F  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)COc3c(OCF)ccc4C(=CC(=O)Oc34)Nc5c(F)cccc5F  
C[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F)C(=O)O  
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)Oc23)Nc4c(F)cccc4F  
COc1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)Nc3c(F)cccc3F  
NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)Oc23)Nc4c(F)cccc4F  
NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cc(cc3F)C(=O)O  
CN(C)CCNC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3F  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCCOc3c(OCF)ccc4C(=CC(=O)Oc34)Nc5c(F)cccc5F  
CCN(C)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1  
Fc1cccc(C1)c1NC2=CC(=O)Oc3c(OCCCN4CCCC4)c(OC(F)F)ccc23  
FCOc1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCCC3)Nc4c(F)cccc4C1  
FC(F)Oc1ccc2C(=CC(=O)Oc2c1OCCCCCN3cnc3)Nc4c(F)cccc4C1  
COc1ccc2C(=CC(=O)Oc2c1OCCCCOCCO)Nc3c(F)cccc3C1  
COCCOCCOCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1

FC(F)Oc1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCCC(F)C3)Nc4c(F)cccc4C1  
COc1ccc2C(=CC(=O)Oc2c1OCCCCCN3cnc3)Nc4c(F)cccc4C1  
CN(CCC[N+](C)(C)C)C(=O)COc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1  
Fc1cccc(C1)c1NC2=CC(=O)Oc3c(OCC(=O)N4CCNCC4)c(OC(F)F)ccc23  
C(=O)CNC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1  
COc1ccc2C(=CC(=O)Oc2c1OCC(=O)N[C@@H](C(C)C)C(=O)O)Nc3c(F)cccc3C1  
CN(C)CCNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1  
COc1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N[C@@H](Cc3c[nH]c4cccc34)C(=O)O)Nc5c(F)cccc5C1  
C[C@H](O)[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1)C(=O)O  
CSCC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1)C(=O)O  
OC(=O)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1)C(=O)O  
NC(=O)[C@H](NC(=O)CCCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3C1)C(=O)O  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCCOc2c(OCF)ccc3C(=CC(=O)Oc23)Nc4c(F)cccc4C1  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCCOc3c(OC(F)F)ccc4C(=CC(=O)Oc34)Nc5c(F)cccc5C1  
COc1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)Nc3c(F)cccc3C1  
FC(F)Oc1ccc2C(=CC(=O)Oc2c1OCCCCN3CCCC3)Nc4c(F)cccc4Br  
FCOc1ccc2C(=CC(=O)Oc2c1OCCCCn3cccn3)Nc4c(F)cccc4Br  
Fc1cccc(Br)c1NC2=CC(=O)Oc3c(OCCCN4ccn4)c(OC(F)F)ccc23  
NCCCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br  
COc1ccc2C(=CC(=O)Oc2c1OCCCCOCCOCCO)Nc3c(F)cccc3Br  
CCCN(C)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br  
COc1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCOCC3)Nc4c(F)cccc4Br  
OCCOCCOCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br  
Fc1cccc(Br)c1NC2=CC(=O)Oc3c(OCC(=O)N4CCNCC4)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)Oc2c1OCC(=O)N[C@@H](Cc3c[nH]c4cccc34)C(=O)O)Nc5c(F)cccc5Br  
OC(=O)[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br)C(=O)O  
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOc2c(OC(F)F)ccc3C(=CC(=O)Oc23)Nc4c(F)cccc4Br  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCOc3c(OC(F)F)ccc4C(=CC(=O)Oc34)Nc5c(F)cccc5Br  
COc1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N[C@@H](CO)C(=O)O)Nc3c(F)cccc3Br  
OC(=O)CC[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br)C(=O)O  
OC(=O)[C@@H]1CCCN1C(=O)CCCOc2c(OCF)ccc3C(=CC(=O)Oc23)Nc4c(F)cccc4Br  
NC(=N)NCCC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br)C(=O)O  
NC(=O)[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)Oc12)Nc3c(F)cccc3Br)C(=O)O

CNCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)  
 cc(F)cc3F  
 Fe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCn4 cccc4)c(OC(F)  
 (F)F)ccc23)c(F)c1  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCn3ccnc3)Nc4c(F)cc  
 (F)cc4F  
 CCCNCCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c  
 (F)cc(F)cc3F  
 CCN(CC)CCCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c  
 (F)cc(F)cc3F  
 FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCCOe3cccn3)  
 Nc4c(F)cc(F)cc4F  
 Fe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCOe4ccnc4)c(OC  
 (F)F)ccc23)c(F)c1  
 CCN(C)CCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCNC(=N)N)  
 Nc3c(F)cc(F)cc3F  
 FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCCn3ncn3)  
 Nc4c(F)cc(F)cc4F  
 CN(CC[N+](C)(C)C(=O)COe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)cc(F)cc3F  
 CN(C)CCCN(C)C(=O)COe1c(OCF)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](C(C)  
 C)C(=O)O)Nc3c(F)cc(F)cc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)OCCN(C)C)  
 Nc3c(F)cc(F)cc3F  
 CN(C)CCCN(C)C(=O)CCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)cc(F)cc3F  
 CN1CCN(CC1)C(=O)CCCCOe2c(OC(F)(F)F)ccc3C  
 (=CC(=O)Oe23)Nc4c(F)cc(F)cc4F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N3CCC  
 [C@H]3C(=O)O)Nc4c(F)cc(F)cc4F  
 OC[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3F)C(=O)O  
 C[C@H](NC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3F)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)Nc3c(F)cc(F)cc3F  
 OC(=O)CC[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)  
 ccc2C(=CC(=O)Oe12)Nc3c(F)cc(F)cc3F)C(=O)O  
 NCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)  
 cc(F)cc3C1  
 CCN(CC)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)  
 Nc3c(F)cc(F)cc3C1  
 NCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)cc  
 (F)cc3C1  
 COCCOCCOCCOCCCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3C1  
 FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC  
 (F)C3)Nc4c(F)cc(F)cc4C1  
 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCC(F)C3)  
 Nc4c(F)cc(F)cc4C1  
 OC[C@H](NC(=O)COe1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3C1)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)NCCN(C)C)  
 Nc3c(F)cc(F)cc3C1  
 CSCC[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3C1)C(=O)O  
 CSCC[C@H](NC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3C1)C(=O)O  
 CC[C@H](C)[C@H](NC(=O)CCCCOe1c(OCF)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)cc(F)cc3C1)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (Cc3cccc3)C(=O)O)Nc4c(F)cc(F)cc4C1

NCCCC[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)cc(F)cc3C1)C(=O)O  
 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCn3nenn3)Nc4c(F)  
 cc(F)cc4Br  
 Fe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCOe4ccnc4)c(OC  
 (F)(F)F)ccc23)c(Br)c1  
 COCCOCCOCCOCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3Br  
 Fe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCn4 cccc4)c(OC  
 (F)(F)F)ccc23)c(Br)c1  
 COCCOCCOCCOCCOCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3Br  
 CCCNCCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)  
 Nc3c(F)cc(F)cc3Br  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCn3ncn3)Nc4c  
 (F)cc(F)cc4Br  
 Fe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCOe4ccnc4)c  
 (OC(F)(F)F)ccc23)c(Br)c1  
 OCCOCCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c  
 (F)cc(F)cc3Br  
 C[C@H](NC(=O)COe1c(OCF)ccc2C(=CC(=O)Oe12)  
 Nc3c(F)cc(F)cc3Br)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](CC  
 (C)C)C(=O)O)Nc3c(F)cc(F)cc3Br  
 OC(=O)CC[C@H](NC(=O)COe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)cc(F)cc3Br)C(=O)O  
 CN(C)CCNC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(F)cc3Br  
 OC(=O)CNC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3Br  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CCC(=O)O)C(=O)O)Nc3c(F)cc(F)cc3Br  
 CN(CC [N+](C)(C)C(=O)CCCOe1c(OC(F)(F)F)  
 ccc2C(=CC(=O)Oe12)Nc3c(F)cc(F)cc3Br  
 C[N+](C)(C)CCOC(=O)CCCCOe1c(OCF)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(F)cc3Br  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)NCC[N+]  
 (C)(C)Nc3c(F)cc(F)cc3Br  
 C[C@@H](O)[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)  
 ccc2C(=CC(=O)Oe12)Nc3c(F)cc(F)cc3Br)C(=O)O  
 CCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)  
 Nc3c(F)cc(O)cc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCN3CCCC(F)(F)C3)  
 Nc4c(F)cc(O)cc4F  
 Oe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCOe4ccnc4)c  
 (OCF)ccc23)c(F)c1  
 COCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)cc(O)cc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC3)  
 Nc4c(F)cc(O)cc4F  
 Oe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCCN4CCCC4)c  
 (OC(F)F)ccc23)c(F)c1  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCC(F)(F)  
 C3)Nc4c(F)cc(O)cc4F  
 Oe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)(F)  
 C4)c(OCF)ccc23)c(F)c1  
 Oe1cc(F)c(NC2=CC(=O)Oe3c(OCCCCCn4 cnc4)c(OC  
 (F)(F)F)ccc23)c(F)c1  
 CN(C)CCCN(C)C(=O)COe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(O)cc3F  
 CN(CCC[N+](C)(C)C(=O)COe1c(OCF)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(O)cc3F  
 OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)COe2c(OC(F)F)  
 ccc3C(=CC(=O)Oe23)Nc4c(F)cc(O)cc4F  
 CN(C)CCN(C)C(=O)CCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)cc(O)cc3F



COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CC[N+]  
(C)(C)Nc3c(F)cc(O)cc3F  
C[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)  
O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)(F)F)  
ccc2C(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)OCCN(C)  
C)Nc3c(F)cc(O)cc3F  
OC(=O)CNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3F  
CC(C)[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
CN(C)CCCN(C)C(=O)CCCOc1c(OC(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F  
CCNCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
Nc3c(F)cc(O)cc3C1  
CCCNCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(F)cc  
(O)cc3C1  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCOc4cccnc4)c(OC  
(F)F)ccc23)c(C1)c1  
OCCOCCOCCOCCCOc1c(OCF)ccc2C(=CC(=O)  
O)c12)Nc3c(F)cc(O)cc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCn3cncn3)Nc4c(F)  
cc(O)cc4C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCCC3)  
Nc4c(F)cc(O)cc4C1  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCCN4CCC(F)(F)  
C4)c(OC(F)F)ccc23)c(C1)c1  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N(C)CCCN(C)  
C)Nc3c(F)cc(O)cc3C1  
C[C@H](NC(=O)COc1c(OCF)ccc2C(=CC(=O)O)c12)  
Nc3c(F)cc(O)cc3C1)C(=O)O  
OC(=O)[C@@H]1CCCN1C(=O)COc2c(OC(F)(F)F)  
ccc3C(=CC(=O)O)c23)Nc4c(F)cc(O)cc4C1  
NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c  
(F)cc(O)cc3C1  
CN(C)CCOC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3C1  
CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)(F)F)  
ccc2C(=CC(=O)O)c12)Nc3c(F)cc(O)cc3C1)C(=O)O  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)  
CCCCOc3c(OCF)ccc4C(=CC(=O)O)c34)Nc5c(F)cc  
(O)cc5C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N[C@@H]  
(CCCN(C(=O)N)C(=O)O)Nc3c(F)cc(O)cc3C1  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCC(=O)  
N4CCNCC4)c(OC(F)F)ccc23)c(C1)c1  
NC(=O)CC[C@H](NC(=O)CCCOc1c(OCF)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3C1)C(=O)O  
CCCCN(C)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(F)cc(O)cc3Br  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCN4CCCC4)c  
(OC(F)F)ccc23)c(Br)c1  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCN4CCC(F)C4)c  
(OCF)ccc23)c(Br)c1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCn3cnnc3)Nc4c(F)cc  
(O)cc4Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCN(C)C)Nc3c(F)cc  
(O)cc3Br  
CN(C)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
Nc3c(F)cc(O)cc3Br  
CCN(CC)CCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)  
Nc3c(F)cc(O)cc3Br  
Oc1cc(F)c(NC2=CC(=O)O)c3c(OCCCCN4CCCC4)c  
(OC(F)F)ccc23)c(Br)c1  
CNCCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(F)  
cc(O)cc3Br

CCN(C)CCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c  
(F)cc(O)cc3Br  
COCCOCCOCCOCCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3Br  
5 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N3CCN(C)CC3)  
Nc4c(F)cc(O)cc4Br  
OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)COc2c(OCF)  
ccc3C(=CC(=O)O)c23)Nc4c(F)cc(O)cc4Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N)Nc3c(F)cc  
10 (O)cc3Br  
CN(C)CCOC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3Br  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OCF)  
ccc3C(=CC(=O)O)c23)Nc4c(F)cc(O)cc4Br  
15 NCCCC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3Br)C(=O)O  
CN1CCN(CC 1)C(=O)CCCOc2c(OC(F)(F)F)ccc3C  
(=CC(=O)O)c23)Nc4c(F)cc(O)cc4Br  
C[C@@H](O)[C@H](NC(=O)CCCOc1c(OC(F)F)  
ccc2C(=CC(=O)O)c12)Nc3c(F)cc(O)cc3Br)C(=O)O  
20 CC(C)[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3Br)C(=O)O  
COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N3CCC  
[C@H]3C(=O)O)Nc4c(F)cc(O)cc4Br  
25 OC(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3Br)C(=O)O  
COCCN(C)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)O)c3c(OCCCCN4CCCC  
(F)(F)C4)c(OCF)ccc23)c(F)c1  
30 OC(=O)c1cc(F)c(NC2=CC(=O)O)c3c(OCCCCn4cnnc4)c  
(OC(F)F)ccc23)c(F)c1  
COCCOCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(F)  
cc(O)cc3F)C(=O)O  
35 OC(=O)c1cc(F)c(NC2=CC(=O)O)c3c(OCCCCn4  
ccnc4)c(OCF)ccc23)c(F)c1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCOc3cccn3)Nc4c  
(F)cc(O)cc4F)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)O)c3c  
(OCCCCOc4ccnc4)c(OC(F)F)ccc23)c(F)c1  
40 CNCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
Nc3c(F)cc(O)cc3F)C(=O)O  
CCNCCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(F)  
cc(O)cc3F)C(=O)O  
45 OC(=O)c1cc(F)c(NC2=CC(=O)O)c3c  
(OCCCCCN4CCCC(F)C4)c(OCF)ccc23)c(F)c1  
OC(=O)CC[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O)C(=O)O  
50 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N)Nc3c(F)cc  
(O)cc3F)C(=O)O  
CN(C)CCOC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
C[N+](C)(C)CCOC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
55 C[N+](C)(C)CCN(C(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O  
COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N(C)CCN  
(C)C)Nc3c(F)cc(O)cc3F)C(=O)O  
60 OC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O)C(=O)O  
OC(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O)C(=O)O  
CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC)ccc2C  
(=CC(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O)C(=O)O  
65 OC[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(F)cc(O)cc3F)C(=O)O)C(=O)O

C[C@@H](O)[C@H](NC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3F)C(=O)O)C(=O)O  
NC(=O)C[C@H](NC(=O)CCCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3F)C(=O)O)C(=O)O  
CCCCN(C)CCCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCN4CCC(F)F)CC4)c(OC(F)F)ccc23)c(C1)c1  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCOe4ccccn4)c(OCF)ccc23)c(C1)c1  
CN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCCn4cccn4)c(OC(F)F)F)ccc23)c(C1)c1  
CCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O  
CN(C)CCOC(=O)COe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCC(=O)N4CCNCC4)c(OCF)ccc23)c(C1)c1  
C[C@H](NC(=O)COe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](Cc3ccc(O)cc3)C(=O)O)Nc4c(F)cc(cc4C1)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H](CC(C)C)C(=O)O)Nc3c(F)cc(cc3C1)C(=O)O  
CC[C@H](C)[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O  
CC[C@H](C)[C@H](NC(=O)CCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOe2c(OC(F)F)ccc3C(=CC(=O)Oe23)Nc4c(F)cc(cc4C1)C(=O)O  
CN(C)CCN(C)C(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N(C)CC[N+](C)(C)C)Nc3c(F)cc(cc3C1)C(=O)O  
C[C@@H](O)[C@H](NC(=O)CCCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N[C@@H](CO)C(=O)O)Nc3c(F)cc(cc3C1)C(=O)O  
OC[C@H](NC(=O)CCCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3C1)C(=O)O)C(=O)O  
CCN(CC)CCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCN4CCOCC4)c(OCF)ccc23)c(Br)c1  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCn4cccn4)c(OC(F)F)ccc23)c(Br)c1  
CCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O  
CCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC(F)F)C3)Nc4c(F)cc(cc4Br)C(=O)O  
OC(=O)c1cc(F)c(NC2=CC(=O)Oe3c(OCCCCCOe4ccccc4)c(OCF)ccc23)c(Br)c1  
OCCOCCOCCCCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N(C)CCN(C)C)Nc3c(F)cc(cc3Br)C(=O)O  
CC(C)[C@H](NC(=O)COe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O

CN(C)CCN(C)C(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H](CO)C(=O)O)Nc3c(F)cc(cc3Br)C(=O)O  
5 NCCCC[C@H](NC(=O)CCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O  
CC(C)[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)Nc3c(F)cc(cc3Br)C(=O)O  
10 CC(C)[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)cc(cc3Br)C(=O)O)C(=O)O  
COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N[C@@H](CCC(=O)N)C(=O)O)Nc3c(F)cc(cc3Br)C(=O)O  
15 COe1ccc2C(=CC(=O)Oe2c1OCCCCN)Nc3c(C1)cccc3C1  
CCCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1  
20 OCCOCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1  
NC(=N)NCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1  
FC1CCN(CCCCCOe2c(OC(F)F)F)ccc3C(=CC(=O)Oe23)Nc4c(C1)cccc4C1)CC1  
25 COe1ccc2C(=CC(=O)Oe2c1OCCCCCOCCOCCO)Nc3c(C1)cccc3C1  
FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCCN3cccn3)Nc4c(C1)cccc4C1  
30 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCCN3ccnc3)Nc4c(C1)cccc4C1  
COe1ccc2C(=CC(=O)Oe2c1OCCCCCN3cnnn3)Nc4c(C1)cccc4C1  
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)COe2c(OC(F)F)F)ccc3C(=CC(=O)Oe23)Nc4c(C1)cccc4C1  
35 OC[C@H](NC(=O)COe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
C[C@H](NC(=O)CCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
40 OC(=O)C[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
OC(=O)CC[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
45 CN(C)CCCN(C)C(=O)CCCOe1c(OC(F)F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1  
CC[C@H](C)[C@H](NC(=O)CCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
NCCCC[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
50 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)NCCN(C)C)Nc3c(C1)cccc3C1  
CN(CC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1  
NCCCC[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3C1)C(=O)O  
55 COe1ccc2C(=CC(=O)Oe2c1OCCCCN3cnnc3)Nc4c(C1)cccc4Br  
FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCN3cnnc3)Nc4c(C1)cccc4Br  
60 COe1ccc2C(=CC(=O)Oe2c1OCCCCCOe3cccn3)Nc4c(C1)cccc4Br  
FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCCOe3ccccc3)Nc4c(C1)cccc4Br  
CCN(CC)CCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C1)cccc3Br  
65 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCC(F)C3)Nc4c(C1)cccc4Br

COc1ccc2C(=CC(=O)O)c2c1OCCCCCn3nenn3)Nc4c  
(C1)cccc4Br  
FC(F)(F)Oc1ccc2C(=CC(=O)  
O)c2c1OCCCCCOc3cenncc3)Nc4c(C1)cccc4Br  
C[N+](C)(C)CCNC(=O)COc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cccc3Br  
CN(C)CCN(C)C(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cccc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N3CCC  
[C@H]3C(=O)O)Nc4c(C1)cccc4Br  
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOc2c(OCF)  
ccc3C(=CC(=O)O)c23)Nc4c(C1)cccc4Br  
CN(C)CCNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cccc3Br  
CN(C)CCCN(C)C(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cccc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
(CCCNC(=N)N)C(=O)O)Nc3c(C1)cccc3Br  
CSCC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cccc3Br)C(=O)O  
NC(=O)C[C@H](NC(=O)CCCOc1c(OCF)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cccc3Br)C(=O)O  
Fc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCCN4CCCC4)c(OC  
(F)(F)F)ccc23)c(C1)c1  
FC(F)Oc1ccc2C(=CC(=O)O)c2c1OCCCCn3cccn3)Nc4c  
(C1)cc(F)cc4C1  
COCCOCCOCCOCCCOc1c(OC)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3C1  
OC[C@H]1O[C@@H](OCCCCO)c2c(OC(F)F)ccc3C  
(=CC(=O)O)c23)Nc4c(C1)cc(F)cc4C1)[C@@H](O)  
[c@@H]1O  
COc1ccc2C(=CC(=O)O)c2c1OCCCCOCCOCCOCCO)  
Nc3c(C1)cc(F)cc3C1  
CCCN(C)CCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)  
Nc3c(C1)cc(F)cc3C1  
CCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)(F)  
CC3)Nc4c(C1)cc(F)cc4C1  
C[N+](C)(C)CCNC(=O)COc1c(OCF)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H]  
(Cc3cccc3)C(=O)O)Nc4c(C1)cc(F)cc4C1  
NCCCC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(F)cc3C1)C(=O)O  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
(CCCCN)C(=O)O)Nc3c(C1)cc(F)cc3C1  
OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c(OC(F)  
(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C1)cc(F)cc4C1  
OC(=O)CC[C@H](NC(=O)CCCOc1c(OCF)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cc(F)cc3C1)C(=O)O  
CN(C)CCN(C)C(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(F)cc3C1  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CC  
[N+](C)(C)C)Nc3c(C1)cc(F)cc3C1  
OC(=O)CNC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(F)cc3C1  
NC(=O)C[C@H](NC(=O)CCCCO)c1c(OCF)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cc(F)cc3C1)C(=O)O  
FCOc1ccc2C(=CC(=O)O)c2c1OCCCCn3ccnc3)Nc4c  
(C1)cc(F)cc4Br  
OCCOCCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c  
(C1)cc(F)cc3Br  
FC(F)Oc1ccc2C(=CC(=O)O)c2c1OCCCCn3cccn3)  
Nc4c(C1)cc(F)cc4Br  
OCCOCCOCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3Br

NCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c  
(C1)cc(F)cc3Br  
CNCCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c  
(C1)cc(F)cc3Br  
5 FC1CCN(CCCCCO)c2c(OC(F)(F)F)ccc3C(=CC(=O)  
O)c23)Nc4c(C1)cc(F)cc4Br)CC1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCCC(F)(F)  
C3)Nc4c(C1)cc(F)cc4Br  
CN(C)CCOC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3Br  
10 CN(C)CCN(C)C(=O)COc1c(OCF)ccc2C(=CC(=O)  
O)c12)Nc3c(C1)cc(F)cc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N(C)CC[N+](C)  
(C)C)Nc3c(C1)cc(F)cc3Br  
15 CN(C)CCOC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(F)cc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
(CC(=O)N)C(=O)O)Nc3c(C1)cc(F)cc3Br  
NC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cc(F)cc3Br)C(=O)O  
20 NC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cc(F)cc3Br)C(=O)O  
CN1CCN(CC1)C(=O)CCCOc2c(OC(F)F)ccc3C  
(=CC(=O)O)c23)Nc4c(C1)cc(F)cc4Br  
25 COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
[C@@H](CC(C)C)C(=O)O)Nc3c(C1)cc(F)cc3Br  
OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOc2c  
(OCF)ccc3C(=CC(=O)O)c23)Nc4c(C1)cc(F)cc4Br  
CNCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c(C1)cc  
(O)cc3C1  
30 Oc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCCN4CCC(F)C4)c  
(OC(F)F)ccc23)c(C1)c1  
COc1ccc2C(=CC(=O)O)c2c1OCCCCn3cccn3)Nc4c(C1)  
cc(O)cc4C1  
35 COCCOCCOCCOCCCOc1c(OC(F)(F)F)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(O)cc3C1  
Oc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCCN4CCC(F)(F)  
CC4)c(OC(F)(F)F)ccc23)c(C1)c1  
Oc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCCn4 ccnn4)c(OC  
(F)F)ccc23)c(C1)c1  
40 CNCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
Nc3c(C1)cc(O)cc3C1  
Oc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCCCN4CCCC4)c  
(OC(F)F)ccc23)c(C1)c1  
45 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H]  
(CCCCN)C(=O)O)Nc3c(C1)cc(O)cc3C1  
NC(=O)CC[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C  
(=CC(=O)O)c12)Nc3c(C1)cc(O)cc3C1)C(=O)O  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OC(F)(F)  
F)ccc3C(=CC(=O)O)c23)Nc4c(C1)cc(O)cc4C1  
50 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
(CCCNC(=N)N)C(=O)O)Nc3c(C1)cc(O)cc3C1  
CN(C)CCN(C)C(=O)CCCOc1c(OCF)ccc2C(=CC  
(=O)O)c12)Nc3c(C1)cc(O)cc3C1  
55 Oc1cc(C1)c(NC2=CC(=O)O)c3c(OCCCC(=O)  
N4CCNCC4)c(OC(F)F)ccc23)c(C1)c1  
OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCCO)c2c  
(OC(F)(F)F)ccc3C(=CC(=O)O)c23)Nc4c(C1)cc(O)  
cc4C1  
60 NC(=N)NCCC[C@H](NC(=O)CCCCO)c1c(OCF)  
ccc2C(=CC(=O)O)c12)Nc3c(C1)cc(O)cc3C1)C(=O)O  
CN(C)CCCCO)c1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c  
(C1)cc(O)cc3Br  
CCN(C)CCCCO)c1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
Nc3c(C1)cc(O)cc3Br  
65 COc1ccc2C(=CC(=O)O)c2c1OCCCCn3ccnn3)Nc4c(C1)  
cc(O)cc4Br

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COCCOCCOCCOCCOCCOCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)cc(O)cc3Br  
 CCN(CC)CCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)cc(O)cc3Br  
 CCN(CC)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12) 5  
 Nc3c(C1)cc(O)cc3Br  
 CCCC(C)CCCCOe1c(OC)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)cc(O)cc3Br  
 Oc1cc(C1)c(NC2=CC(=O)Oc3c(OCCCCN4 cenn4)c(OC  
 (F)(F)F)ccc23)c(Br)c1  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCCC(F)(F)  
 C3)Nc4c(C1)cc(O)cc4Br  
 Oc1cc(C1)c(NC2=CC(=O)Oc3c(OCCCCN4 cenn4)c  
 (OC(F)(F)F)ccc23)c(Br)c1  
 C[N+](C)(C)CCNC(=O)COe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)cc(O)cc3Br  
 OC(=O)[C@H](Cc1cccc1)NC(=O)COe2c(OCF)ccc3C  
 (=CC(=O)Oc23)Nc4c(C1)cc(O)cc4Br  
 CN(C)CCOC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)cc(O)cc3Br  
 COe1ccc2C(=CC(=O)Oc2c1OCCCC(=O)N3CCC  
 [C@H]3C(=O)O)Nc4c(C1)cc(O)cc4Br  
 CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OCF)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)cc(O)cc3Br  
 OC[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)cc(O)cc3Br)C(=O)O  
 CN1CCN(CC 1)C(=O)CCCCOe2c(OC(F)(F)F)ccc3C  
 (=CC(=O)Oc23)Nc4c(C1)cc(O)cc4Br  
 NC(=O)C[C@H](NC(=O)CCCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)cc(O)cc3Br)C(=O)O  
 CCN(C)CCCCOe1c(OC)ccc2C(=CC(=O)Oc12)Nc3c  
 (C1)cc(cc3C1)C(=O)O  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c  
 (OCCCCN4CCCC(F)(F)C4)c(OC(F)F)ccc23)c(C1)c1  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c  
 (OCCCCN4CCOCC4)c(OCF)ccc23)c(C1)c1  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCOe3ccccn3)Nc4c  
 (C1)cc(cc4C1)C(=O)O  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c  
 (OCCCCOe4ccccn4)c(OC(F)(F)F)ccc23)c(C1)c1  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c  
 (OCCCCN4nenn4)c(OC(F)F)ccc23)c(C1)c1  
 COCCOCCCCCOe1c(OC)ccc2C(=CC(=O)Oc12)Nc3c  
 (C1)cc(cc3C1)C(=O)O  
 NCCCC[C@H](NC(=O)COe1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)cc(cc3C1)C(=O)O)C(=O)O  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c(OCCCC(=O)  
 N4CCNCC4)c(OCF)ccc23)c(C1)c1  
 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOe2c(OC(F)F)  
 ccc3C(=CC(=O)Oc23)Nc4c(C1)cc(cc4C1)C(=O)O  
 CN1CCN(CC 1)C(=O)CCCCOe2c(OC(F)(F)F)ccc3C  
 (=CC(=O)Oc23)Nc4c(C1)cc(cc4C1)C(=O)O  
 CC(C)C[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)cc(cc3C1)C(=O)O)C(=O)O  
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)  
 CCCCCOe3c(OC(F)(F)F)ccc4C(=CC(=O)Oc34)Nc5c  
 (C1)cc(cc5C1)C(=O)O  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCN3CCC(F)(F)CC3)  
 Nc4c(C1)cc(cc4Br)C(=O)O  
 OCCOCCOCCOCCCOe1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)cc(cc3Br)C(=O)O  
 COCCOCCOCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)cc(cc3Br)C(=O)O  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCOCCOCCOCCO)  
 Nc3c(C1)cc(cc3Br)C(=O)O  
 OC(=O)e1cc(C1)c(NC2=CC(=O)Oc3c  
 (OCCCCN4CCC(F)C4)c(OC(F)(F)F)ccc23)c(Br)c1

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COCCOCCOCCOCCOCCOCCOe1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)cc(cc3Br)C(=O)O  
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)COe3c  
 (OCF)ccc4C(=CC(=O)Oc34)Nc5c(C1)cc(cc5Br)C  
 (=O)O  
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)COe3c(OC  
 (F)(F)F)ccc4C(=CC(=O)Oc34)Nc5c(C1)cc(cc5Br)C  
 (=O)O  
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)COe2c(OC(F)F)  
 ccc3C(=CC(=O)Oc23)Nc4c(C1)cc(cc4Br)C(=O)O  
 COe1ccc2C(=CC(=O)Oc2c1OCCCC(=O)NCCN(C)C)  
 Nc3c(C1)cc(cc3Br)C(=O)O  
 C[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)cc(cc3Br)C(=O)O)C(=O)O  
 C[N+](C)(C)CCNC(=O)CCCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)cc(cc3Br)C(=O)O  
 C[C@@H](O)[C@H](NC(=O)CCCCOe1c(OC(F)F)  
 ccc2C(=CC(=O)Oc12)Nc3c(C1)cc(cc3Br)C(=O)O)C  
 (=O)O  
 NCCCC[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)cc(cc3Br)C(=O)O)C  
 (=O)O  
 FCOe1ccc2C(=CC(=O)Oc2c1OCCCCN3ccnc3)Nc4c(Br)  
 cccc4Br  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCOe3ccnc3)Nc4c  
 (Br)cccc4Br  
 FC(F)Oe1ccc2C(=CC(=O)Oc2c1OCCCCOe3ccnc3)  
 Nc4c(Br)cccc4Br  
 CCNCCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(Br)cccc3Br  
 FC(F)(F)Oe1ccc2C(=CC(=O)Oc2c1OCCCCN3CCC(F)  
 (F)CC3)Nc4c(Br)cccc4Br  
 FCOe1ccc2C(=CC(=O)Oc2c1OCCCCN3ennn3)Nc4c  
 (Br)cccc4Br  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCCC3)  
 Nc4c(Br)cccc4Br  
 C[N+](C)(C)CCOC(=O)COe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(Br)cccc3Br  
 COe1ccc2C(=CC(=O)Oc2c1OCC(=O)N[C@@H]  
 ([C@@H](C)O)C(=O)O)Nc3c(Br)cccc3Br  
 C[C@@H](O)[C@H](NC(=O)COe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(Br)cccc3Br)C(=O)O  
 NC(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)Nc3c  
 (Br)cccc3Br  
 NC(=O)CC[C@H](NC(=O)CCCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(Br)cccc3Br)C(=O)O  
 OC(=O)[C@@H]1CCCN1C(=O)CCCCOe2c(OC(F)  
 F)ccc3C(=CC(=O)Oc23)Nc4c(Br)cccc4Br  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCC(=O)N  
 [C@@H](CCCCN)C(=O)O)Nc3c(Br)cccc3Br  
 Fe1cc(Br)c(NC2=CC(=O)Oc3c(OCCCCN4 cccc4)c(OC(F)  
 (F)F)ccc23)c(Br)c1  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCN3ccnc3)Nc4c(Br)  
 cc(F)cc4Br  
 FC(F)Oe1ccc2C(=CC(=O)Oc2c1OCCCCN3ennn3)Nc4c  
 (Br)cc(F)cc4Br  
 CCN(CC)CCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)cc(F)cc3Br  
 FCOe1ccc2C(=CC(=O)Oc2c1OCCCCCN3CCC(F)C3)  
 Nc4c(Br)cc(F)cc4Br  
 COe1ccc2C(=CC(=O)Oc2c1OCCCCOCCO)Nc3c(Br)  
 cc(F)cc3Br  
 CCN(C)CCCCCOe1c(OC)ccc2C(=CC(=O)Oc12)Nc3c  
 (Br)cc(F)cc3Br  
 CCCC(C)CCCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(Br)cc(F)cc3Br

Fc1cc(Br)c(NC2=CC(=O)Oe3c(OCCCCCN4ccn4)c(OC(F)(F)F)ccc23)c(Br)c1  
COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](CCC(=O)N)C(=O)O)Nc3c(Br)cc(F)cc3Br  
C[N+](C)(C)CCNC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(F)cc3Br  
OC(=O)[C@@H]1CCCN1C(=O)CCCOe2c(OC(F)F)ccc3C(=CC(=O)Oe23)Nc4c(Br)cc(F)cc4Br  
NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(F)cc3Br)C(=O)O  
COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)NCC(=O)O)Nc3c(Br)cc(F)cc3Br  
OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)CCCOc3c(OC(F)F)ccc4C(=CC(=O)Oe34)Nc5c(Br)cc(F)cc5Br  
CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(F)cc3Br  
COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N[C@@H](CC(=O)O)C(=O)O)Nc3c(Br)cc(F)cc3Br  
CCNCCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
OCCOCCOCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
COCCOCCOCCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
COCCOCCOCCOCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
COCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
Oc1cc(Br)c(NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)(F)C4)c(OCF)ccc23)c(Br)c1  
COc1ccc2C(=CC(=O)Oe2c1OCCCCN3cccc3)Nc4c(Br)cc(O)cc4Br  
CCN(C)CCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
Oc1cc(Br)c(NC2=CC(=O)Oe3c(OCC(=O)N4CCNCC4)c(OC(F)F)ccc23)c(Br)c1  
OC(=O)[C@H](Cc1cccc1)NC(=O)COe2c(OC(F)(F)F)ccc3C(=CC(=O)Oe23)Nc4c(Br)cc(O)cc4Br  
COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](Cc3c[nH]c4cccc34)C(=O)O)Nc5c(Br)cc(O)cc5Br  
C[N+](C)(C)CCOC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
CN(CCC[N+](C)(C)C)C(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)c3Br  
COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N3CCN(C)CC3)Nc4c(Br)cc(O)cc4Br  
OC(=O)CNC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br  
COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)NCC[N+](C)(C)C)Nc3c(Br)cc(O)cc3Br  
NC(=O)C[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(O)cc3Br)C(=O)O  
OC(=O)c1cc(Br)c(NC2=CC(=O)Oe3c(OCCCCN4nccn4)c(OC(F)F)ccc23)c(Br)c1  
OCCOCCOCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O  
CNCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O  
OC(=O)c1cc(Br)c(NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)C4)c(OC(F)F)ccc23)c(Br)c1  
COCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O  
OC(=O)c1cc(Br)c(NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)C4)c(OC(F)F)ccc23)c(Br)c1

COc1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCC(F)C3)Nc4c(Br)cc(cc4Br)C(=O)O  
COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H](CCC(=O)O)C(=O)O)Nc3c(Br)cc(cc3Br)C(=O)O  
NC(=O)CC[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O)C(=O)O  
CC(C)C[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O)C(=O)O  
COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N3CCN(C)CC3)Nc4c(Br)cc(cc4Br)C(=O)Nc(=O)C[C@H](NC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O)C(=O)O  
NC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O  
CN(CC[N+](C)(C)C)C(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(Br)cc(cc3Br)C(=O)O  
COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N3CCN(C)CC3)Nc4c(Br)cc(cc4Br)C(=O)O  
CCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCCN4CCCC(F)C4)c(OC(F)F)ccc23  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCCO[C@@H]4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O)c(OC(F)F)ccc23  
COc1ccc2C(=CC(=O)Oe2c1OCCCCOCCOCCOCCO)Nc3c(C)encc3C  
CCN(C)CCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
CCCCN(C)CCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
COCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
COCCOCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCCCN4CCCC(F)C4)c(OC(F)(F)F)ccc23  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)C4)c(OC(F)F)ccc23  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCCCN4ccn4)c(OCF)ccc23  
COCCOCCCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
CN(C)CCOC(=O)COe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N(C)CC[N+](C)(C)C)Nc3c(C)encc3C  
CC(C)C[C@H](NC(=O)COe1c(OC(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C)C(=O)O  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H](CCC(=O)O)C(=O)O)c(OC(F)(F)F)ccc23  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)N)c(OC(F)F)ccc23  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)NCC[N+](C)(C)C)c(OC(F)(F)F)ccc23  
COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)NCC(=O)O)Nc3c(C)encc3C  
C[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C)C(=O)O  
CN(C)CCN(C)C(=O)CCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C  
CC(C)[C@H](NC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(C)encc3C)C(=O)O  
Cc1encc(C)c1NC2=CC(=O)Oe3c(OCCCC(=O)N[C@@H](CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23

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COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N[C@@H]  
 (Cc3cnc[nH]3)C(=O)O)Nc4c(C)cncc4C  
 Ce1ence(C)c1NC2=CC(=O)Oe3c(OCCCCC(=O)OCC  
 [N+](C)(C)C)c(OC(F)F)ccc23  
 CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(C)cncc3C  
 C[C@@H](O)[C@H](NC(=O)CCCCOe1c(OCF)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cncc3C)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
 [C@@H](CCC(=O)O)C(=O)O)Nc3c(C)cncc3C  
 CCN(C)CCCCOe1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)  
 cncc3F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCN4CCC(F)F)  
 CC4)c(OCF)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCn4 cccc4)c(OC  
 (F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCn4 cenc4)c(OC  
 (F)F)ccc23  
 CCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cncc3F  
 CCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cncc3F  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)CC3)  
 Nc4c(C)cncc4F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)F)  
 C4)c(OC(F)F)ccc23  
 COCCOCCOCCCCOe1c(OC)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cncc3F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCCN4CCCC  
 (F)C4)c(OCF)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)  
 (F)C4)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCCN4ncn4)c  
 (OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCOCe3cccn3)  
 Nc4c(C)cncc4F  
 CN(C)CCOC(=O)COe1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cncc3F  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)NCC(=O)O)  
 Nc3c(C)cncc3F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H]  
 (Cc4ccccc4)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H]  
 (Cc4ccc(O)cc4)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H]  
 (CCCNC(=N)N)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCC(=O)N)c(OC  
 (F)F)ccc23  
 CN(C)CCOC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cncc3F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCC(=O)OCC[N+]  
 (C)(C)C)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCC(=O)  
 N4CCNCC4)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](Cc4ccccc4)C(=O)O)c(OC(F)F)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
 (Cc3ccc(O)cc3)C(=O)O)Nc4c(C)cncc4F  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)OCCN(C)  
 C)Nc3c(C)cncc3F  
 CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(C)cncc3F  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](Cc4ccc(O)cc4)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](CC(=O)O)C(=O)O)c(OCF)ccc23

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CN(CCC[N+](C)(C)C)C(=O)CCCCOe1c(OC(F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(C)cncc3F  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
 [C@@H](CC(C)C)C(=O)O)Nc3c(C)cncc3F  
 5 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](Cc4ccccc4)C(=O)O)c(OCF)ccc23  
 Ce1ence(F)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)F)ccc23  
 CCN(C)CCCCOe1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(C)  
 10 cncc3C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCN4CCOCC4)  
 c(OCF)ccc23  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCOe4ccccc4)c  
 (OC(F)F)ccc23  
 15 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCO[C@@H]  
 4O[C@H](CO)[C@H](O)[C@H](O)[C@H]4O)c(OC(F)  
 F)ccc23  
 CN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cncc3C1  
 20 CCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C)cncc3C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCCN4CCCC  
 (F)F)C4)c(OCF)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3cccc3)Nc4c(C)  
 25 cncc4C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCN4ncn4)c  
 (OCF)ccc23  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCOCCO)c  
 (OC(F)F)ccc23  
 30 CCCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cncc3C1  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)C3)  
 Nc4c(C)cncc4C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC  
 (F)C4)c(OCF)ccc23  
 35 COCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cncc3C1  
 COc1ccc2C(=CC(=O)O)c2c1OCC(=O)OCC[N+](C)(C)  
 C)Nc3c(C)cncc3C1  
 40 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCC(=O)NCC[N+]  
 (C)(C)C)c(OC(F)F)ccc23  
 C[C@H](NC(=O)COe1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C)cncc3C1)C(=O)O  
 CC[C@H](C)[C@H](NC(=O)COe1c(OCF)ccc2C(=CC  
 45 (=O)O)c12)Nc3c(C)cncc3C1)C(=O)O  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H]  
 (Cc4ccccc4)C(=O)O)c(OCF)ccc23  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCC(=O)N[C@@H]  
 (Cc4ccc(O)cc4)C(=O)O)c(OCF)ccc23  
 50 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](Cc4ccccc4)C(=O)O)c(OCF)ccc23  
 COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H]  
 (CCCNC(=N)N)C(=O)O)Nc3c(C)cncc3C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 55 [C@@H](Cc4cnc[nH]4)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OC(F)F)ccc23  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCC(=O)NCC  
 [N+](C)(C)C)c(OC(F)F)ccc23  
 60 CC[C@H](C)[C@H](NC(=O)CCCCOe1c(OC(F)F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(C)cncc3C1)C(=O)O  
 COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N[C@@H]  
 (Cc3ccccc3)C(=O)O)Nc4c(C)cncc4C1  
 Ce1ence(C1)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 65 [C@@H](CCCNC(=N)N)C(=O)O)c(OCF)ccc23  
 CN(CC [N+](C)(C)C)C(=O)CCCCOe1c(OCF)ccc2C  
 (=CC(=O)O)c12)Nc3c(C)cncc3C1

CN(CC[N+](C)(C)C(=O)CCCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(C)encc3C1  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N  
 [C@@H](Cc3cnc[nH]3)C(=O)O)Nc4c(C)encc4C1  
 Ce1encc(C1)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](CCC(=O)O)C(=O)O)c(OC(F)(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCn4 ccc4)c  
 (OC(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCn4 ccc4)c  
 (OC(F)(F)F)ccc23  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCOe3ccnc3)Nc4c  
 (C)encc4Br  
 COCCOCCOCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)  
 Nc3c(C)encc3Br  
 CCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oe12)  
 Nc3c(C)encc3Br  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCn4 cccc4)c  
 (OC(F)(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCCO[C@@H]  
 4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O)c  
 (OCF)ccc23  
 COCCOCCOCCCCOe1c(OC)ccc2C(=CC(=O)Oe12)  
 Nc3c(C)encc3Br  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)  
 (F)CC4)c(OC(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCCN4CCC(F)  
 C4)c(OC(F)(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCCOCCO)c  
 (OCF)ccc23  
 COe1ccc2C(=CC(=O)  
 Oe2c1OCCCCCOCCOCCOCCO)Nc3c(C)encc3Br  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCC(=O)N)c(OC(F)  
 (F)F)ccc23  
 COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N3CCN(C)CC3)  
 Nc4c(C)encc4Br  
 C[C@H](NC(=O)COe1c(OCF)ccc2C(=CC(=O)Oe12)  
 Nc3c(C)encc3Br)C(=O)O  
 CSCC[C@H](NC(=O)COe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(C)encc3Br)C(=O)O  
 CN1CCN(CC1)C(=O)CCCOe2c(OC(F)F)ccc3C(=CC  
 (=O)Oe23)Nc4c(C)encc4Br  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CC(C)C)C(=O)O)Nc3c(C)encc3Br  
 CSCC[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC(=O)  
 Oe12)Nc3c(C)encc3Br)C(=O)O  
 CSCC[C@H](NC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(C)encc3Br)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)OCCN(C)  
 C)Nc3c(C)encc3Br  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCC(=O)OCC  
 [N+](C)(C)C)c(OC(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](Cc4cccc4)C(=O)O)c(OC(F)(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCC(=O)N  
 [C@@H](CC(=O)N)C(=O)O)c(OCF)ccc23  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N)Nc3c  
 (C)encc3Br  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N)c  
 (OC(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](CCCN)C(=O)O)c(OC(F)(F)F)ccc23  
 Ce1encc(Br)c1NC2=CC(=O)Oe3c(OCCCCC(=O)N  
 [C@@H](CCC(=O)N)C(=O)O)c(OCF)ccc23  
 NCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)Nc3c(F)  
 encc3F  
 CNCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)  
 encc3F

COe1ccc2C(=CC(=O)Oe2c1OCCCCn3ccnc3)Nc4c(F)  
 encc4F  
 FC(F)Oe1ccc2C(=CC(=O)Oe2c1OCCCCn3ccnm3)Nc4c  
 (F)encc4F  
 5 CNCCCCCOe1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(F)  
 encc3F  
 FC1CCN(CCCCCOe2c(OC(F)(F)F)ccc3C(=CC(=O)  
 Oe23)Nc4c(F)encc4F)CC1  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC(F)C3)  
 10 Nc4c(F)encc4F  
 OCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)encc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCCCCCN(C)C)Nc3c(F)  
 encc3F  
 15 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCCN3CCCC3)  
 Nc4c(F)encc4F  
 OCCOCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 COCCOCCOCCOCCCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 20 C[N+](C)(C)CCOC(=O)COe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 COe1ccc2C(=CC(=O)Oe2c1OCC(=O)N(C)CCN(C)  
 C)Nc3c(F)encc3F  
 25 CN1CCN(CC1)C(=O)COe2c(OCF)ccc3C(=CC(=O)  
 Oe23)Nc4c(F)encc4F  
 NC(=O)CC[C@H](NC(=O)COe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)encc3F)C(=O)O  
 C[N+](C)(C)CCOC(=O)CCCOe1c(OCF)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 30 OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOe2c(OC(F)(F)  
 F)ccc3C(=CC(=O)Oe23)Nc4c(F)encc4F  
 OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOe2c(OC(F)  
 F)ccc3C(=CC(=O)Oe23)Nc4c(F)encc4F  
 35 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CCSC)C(=O)O)Nc3c(F)encc3F  
 CN(C)CCN(C)C(=O)CCCOe1c(OCF)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 40 C[C@H](NC(=O)CCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)encc3F)C(=O)O  
 COe1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CC(C)C)C(=O)O)Nc3c(F)encc3F  
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOe2c(OC  
 (F)(F)F)ccc3C(=CC(=O)Oe23)Nc4c(F)encc4F  
 45 CN(C)CCNC(=O)CCCOe1c(OC(F)F)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F  
 C[N+](C)(C)CCNC(=O)CCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oe12)Nc3c(F)encc3F  
 50 COe1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N(C)CCN  
 (C)C)Nc3c(F)encc3F  
 OC[C@H](NC(=O)CCCOe1c(OCF)ccc2C(=CC  
 (=O)Oe12)Nc3c(F)encc3F)C(=O)O  
 COCCN(C)CCCOe1c(OCF)ccc2C(=CC(=O)Oe12)  
 55 Nc3c(F)encc3C1  
 FCOe1ccc2C(=CC(=O)Oe2c1OCCCCN3CCC(F)CC3)  
 Nc4c(F)encc4C1  
 Fe1encc(C1)c1NC2=CC(=O)Oe3c(OCCCCN4CCC(F)(F)  
 CC4)c(OC(F)(F)F)ccc23  
 60 COe1ccc2C(=CC(=O)Oe2c1OCCCCn3ncnn3)Nc4c(F)  
 encc4C1  
 OCCOCCOCCOCCCCOe1c(OC(F)F)ccc2C(=CC(=O)  
 Oe12)Nc3c(F)encc3C1  
 CNCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oe12)  
 65 Nc3c(F)encc3C1  
 CCN(CC)CCCOe1c(OC)ccc2C(=CC(=O)Oe12)Nc3c  
 (F)encc3C1

CCCCCN(C)CCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(F)encc3C1  
 FC(F)Oe1ccc2C(=CC(=O)O)c2c1OCCCCN3cnnc3)  
 Nc4c(F)encc4C1  
 NCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(F)encc3C1  
 CNCCCCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c(F)  
 encc3C1  
 FCOe1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCCC(F)  
 C3)Nc4c(F)encc4C1  
 COCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3C1  
 CN1CCN(CC 1)C(=O)COc2c(OC(F)F)ccc3C(=CC(=O)  
 O)c23)Nc4c(F)encc4C1  
 OC(=O)[C @H]1CCCN1C(=O)COc2c(OCF)ccc3C  
 (=CC(=O)O)c23)Nc4c(F)encc4C1  
 COe1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](CC  
 (=O)O)C(=O)O)Nc3c(F)encc3C1  
 NC(=O)C[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3C1)C(=O)O  
 CN(C)CCNC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3C1  
 COe1ccc2C(=CC(=O)O)c2c1OCCCC(=O)NCC[N+](C)  
 (C)Nc3c(F)encc3C1  
 NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OC(F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(F)encc3C1)C(=O)O  
 NC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3C1)C(=O)O  
 CN(C)CCNC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3C1  
 CN(C)CCN(C)C(=O)CCCOc1c(OCF)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3C1  
 CN(CC [N+](C)(C)C)C(=O)CCCOc1c(OCF)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3C1  
 COe1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N3CCC  
 [C@H]3C(=O)O)Nc4c(F)encc4C1  
 OC(=O)[C@@H]1CCCN1C(=O)CCCOc2c(OC(F)F)  
 ccc3C(=CC(=O)O)c23)Nc4c(F)encc4C1  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
 [C@@H](CC(C)C)C(=O)O)Nc3c(F)encc3C1  
 CC[C@H](C)[C@H](NC(=O)CCCOc1c(OC(F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(F)encc3C1)C(=O)O  
 OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOc2c  
 (OCF)ccc3C(=CC(=O)O)c23)Nc4c(F)encc4C1  
 OC(=O)[C@H](Cc1c[nH]c2cccc12)NC(=O)  
 CCCCOC3c(OC(F)(F)F)ccc4C(=CC(=O)O)c34)Nc5c  
 (F)encc5C1  
 CCN(CC)CCCOc1c(OC)ccc2C(=CC(=O)O)c12)Nc3c  
 (F)encc3Br  
 FC(F)Oe1ccc2C(=CC(=O)O)c2c1OCCCCOC3cccn3)  
 Nc4c(F)encc4Br  
 Fe1encc(Br)c1NC2=CC(=O)O)c3c(OCCCCOC4cccn4)c  
 (OC(F)(F)F)ccc23  
 COCCOCCCCOc1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c  
 (F)encc3Br  
 CN(C)CCCCOo1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(F)encc3Br  
 CCN(C)CCCCOo1c(OCF)ccc2C(=CC(=O)O)c12)Nc3c  
 (F)encc3Br  
 Fe1encc(Br)c1NC2=CC(=O)O)c3c(OCCCCN4nenn4)c  
 (OC(F)(F)F)ccc23  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCCO[C@@H]3O  
 [C@H](CO)[C@@H](O)[C@H](O)[C@H]3O)Nc4c(F)  
 encc4Br  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCCN)Nc3c(F)  
 encc3Br

CCN(CC)CCCCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br  
 CCCCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3Br  
 5 COCCOCCOCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br  
 CN(C)CCN(C)C(=O)COc1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br  
 CN(C)CCN(C)C(=O)COc1c(OCF)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br  
 10 COe1ccc2C(=CC(=O)O)c2c1OCC(=O)N[C@@H](C)C  
 (=O)O)Nc3c(F)encc3Br  
 OC[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br)C(=O)O  
 15 CN(C)CCNC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(F)encc3Br  
 COe1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CC[N+]  
 (C)(C)Nc3c(F)encc3Br  
 CC(C)C[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3Br)C(O)O  
 20 OC(=O)C[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3Br)C(=O)O  
 NC(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3Br)C(=O)O  
 25 C[N+](C)(C)CCOC(=O)CCCOc1c(OCF)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3Br  
 CN(C)CCN(C)C(=O)CCCOc1c(OC(F)(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3Br  
 COe1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CCC  
 [N+](C)(C)Nc3c(F)encc3Br  
 30 CSCC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC  
 (=O)O)c12)Nc3c(F)encc3Br)C(=O)O  
 CN(CC[N+](C)(C)C)C(=O)CCCOc1c(OC(F)F)ccc2C  
 (=CC(=O)O)c12)Nc3c(F)encc3Br  
 35 CN(CC [N+](C)(C)C)C(=O)CCCOc1c(OC(F)(F)F)  
 ccc2C(=CC(=O)O)c12)Nc3c(F)encc3Br  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
 [C@@H](C(C)C)C(=O)O)Nc3c(F)encc3Br  
 40 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCCOC2c  
 (OCF)ccc3C(=CC(=O)O)c23)Nc4c(F)encc4Br  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N  
 [C@@H](CC(=O)O)C(=O)O)Nc3c(F)encc3Br  
 CCN(C)CCCCOo1c(OC(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C1)encc3C1  
 45 CCCCCN(C)CCCCOo1c(OC(F)(F)F)ccc2C(=CC(=O)  
 O)c12)Nc3c(C1)encc3C1  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCN3CCCC(F)C3)  
 Nc4c(C1)encc4C1  
 50 FC(F)Oe1ccc2C(=CC(=O)O)c2c1OCCCCN3CCC(F)C3)  
 Nc4c(C1)encc4C1  
 FCOe1ccc2C(=CC(=O)O)c2c1OCCCCOC3cccn3)Nc4c  
 (C1)encc4C1  
 OCCOCCCCOo1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c  
 (C1)encc3C1  
 55 CN(C)CCCCOo1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)  
 Nc3c(C1)encc3C1  
 CCN(CC)CCCCOo1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C1)encc3C1  
 60 NC(=N)NCCCCOo1c(OCF)ccc2C(=CC(=O)O)c12)  
 Nc3c(C1)encc3C1  
 FC(F)(F)Oe1ccc2C(=CC(=O)O)  
 O)c2c1OCCCCCN3CCOCC3)Nc4c(C1)encc4C1  
 FC(F)Oe1ccc2C(=CC(=O)O)c2c1OCCCCCN3CCC(F)  
 65 C3)Nc4c(C1)encc4C1  
 COe1ccc2C(=CC(=O)O)c2c1OCCCCN3cccn3)Nc4c  
 (C1)encc4C1



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CNCCCCCOc1c(OC)ccc2C(=CC(=O)Oe12)Nc3c(C1)  
 cnc3C1  
 CCCN(C)CCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3C1  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)  
 Ne4c(C1)encc4C1  
 OCCOCCOCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3C1  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N(C)CCCN(C)  
 C)Nc3c(C1)encc3C1  
 CN(C)CCCN(C)C(=O)COc1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3C1  
 FCOc1ccc2C(=CC(=O)Oe2c1OCC(=O)N3CCNCC3)  
 Ne4c(C1)encc4C1  
 C[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3C1)C(=O)O  
 CN(C)CCOC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3C1  
 OC(=O)[C@H](Cc1ccc(O)cc1)NC(=O)CCCOe2c(OC(F)  
 F)ccc3C(=CC(=O)Oe23)Ne4c(C1)encc4C1  
 COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CCSC)C(=O)O)Nc3c(C1)encc3C1  
 NC(=O)CC[C@H](NC(=O)CCCOc1c(OCF)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3C1)C(=O)O  
 NC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)encc3C1  
 COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (C(C)C)C(=O)O)Nc3c(C1)encc3C1  
 NC(=N)NCCC[C@H](NC(=O)CCCOc1c(OCF)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3C1)C(=O)O  
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCOe2c(OC  
 (F)F)ccc3C(=CC(=O)Oe23)Ne4c(C1)encc4C1  
 C[N+](C)(C)CCOC(=O)CCCCOe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3C1  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)NCC[N+]  
 (C)(C)C)Nc3c(C1)encc3C1  
 CC(C)[C@H](NC(=O)CCCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3C1)C(=O)O  
 OC(=O)[C@H](Cc1cnc[nH]1)NC(=O)CCCCOe2c(OC  
 (F)F)ccc3C(=CC(=O)Oe23)Ne4c(C1)encc4C1  
 CCCN(C)CCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)encc3Br  
 CCCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)encc3Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCN3CCOCC3)Ne4c  
 (C1)encc4Br  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCn3cenn3)Ne4c  
 (C1)encc4Br  
 CCCCN(C)CCCCOe1c(OCF)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)encc3Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCN3CCCC3)  
 Ne4c(C1)encc4Br  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCN3CCC(F)  
 CC3)Ne4c(C1)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCN3CCC(F)(F)C3)  
 Ne4c(C1)encc4Br  
 OCCOCCOCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br  
 FCOc1ccc2C(=CC(=O)Oe2c1OCCCCCn3ccen3)Ne4c  
 (C1)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3ccenn3)Ne4c  
 (C1)encc4Br  
 COCCOCCCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br  
 COCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br  
 COCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3CCCC(F)  
 (F)C3)Ne4c(Br)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)Ne4c  
 (Br)encc4Br  
 FCOc1ccc2C(=CC(=O)Oe2c1OCCCCCn3ccen3)Ne4c  
 (Br)encc4Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)  
 Ne4c(Br)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cenn3)Ne4c  
 (Br)encc4Br  
 OCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 COCCOCCOCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3CCCC(F)  
 (F)C3)Ne4c(Br)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)Ne4c  
 (Br)encc4Br  
 FCOc1ccc2C(=CC(=O)Oe2c1OCCCCCn3ccen3)Ne4c  
 (Br)encc4Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)  
 Ne4c(Br)encc4Br  
 CN(C)CCOC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)NCCN(C)C)  
 Nc3c(Br)encc3Br  
 OC(=O)[C@@H]1CCCN1C(=O)COe2c(OCF)ccc3C  
 (=CC(=O)Oe23)Ne4c(Br)encc4Br  
 OC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(Br)encc3Br)C(=O)O

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NC(=O)COc1c(OCF)ccc2C(=CC(=O)Oe12)Nc3c(C1)  
 cnc3Br  
 C[N+](C)(C)CCOC(=O)COc1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3Br  
 OC(=O)CNC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br  
 CC[C@H](C)[C@H](NC(=O)COc1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3Br)C(=O)O  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)N[C@@H]  
 (CCCNC(=N)N)C(=O)O)Nc3c(C1)encc3Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)  
 N3CCNCC3)Ne4c(C1)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCC(=O)N[C@@H]  
 (CCSC)C(=O)O)Nc3c(C1)encc3Br  
 CSCC[C@H](NC(=O)CCCOc1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(C1)encc3Br)C(=O)O  
 NC(=O)CC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3Br)C(=O)O  
 NC(=O)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(C1)encc3Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)NCCN(C)  
 C)Nc3c(C1)encc3Br  
 CN(C)CCN(C)C(=O)CCCCOe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3Br  
 C[C@H](NC(=O)CCCOe1c(OC(F)(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3Br)C(=O)O  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCC(=O)N)Nc3c  
 (C1)encc3Br  
 C[N+](C)(C)CCOC(=O)CCCCOe1c(OC(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3Br  
 CN(C)CCCN(C)C(=O)CCCCOe1c(OC(F)(F)F)ccc2C  
 (=CC(=O)Oc12)Nc3c(C1)encc3Br  
 CSCC[C@H](NC(=O)CCCCOe1c(OCF)ccc2C(=CC  
 (=O)Oc12)Nc3c(C1)encc3Br)C(=O)O  
 NC(=N)NCCCCOe1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 CCCCN(C)CCCCOe1c(OC(F)F)ccc2C(=CC(=O)Oc12)  
 Nc3c(Br)encc3Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCn3cenn3)Ne4c(Br)  
 encc4Br  
 FCOc1ccc2C(=CC(=O)Oe2c1OCCCCn3cenn3)Ne4c(Br)  
 encc4Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCn3ccen3)  
 Ne4c(Br)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cenn3)Ne4c  
 (Br)encc4Br  
 OCCOCCOCCOCCCCCOc1c(OC(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 COCCOCCOCCOCCCCCOc1c(OCF)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 FC(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3CCCC(F)  
 (F)C3)Ne4c(Br)encc4Br  
 COc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)Ne4c  
 (Br)encc4Br  
 FCOc1ccc2C(=CC(=O)Oe2c1OCCCCCn3ccen3)Ne4c  
 (Br)encc4Br  
 FC(F)(F)Oc1ccc2C(=CC(=O)Oe2c1OCCCCCn3cccc3)  
 Ne4c(Br)encc4Br  
 CN(C)CCOC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)  
 Oc12)Nc3c(Br)encc3Br  
 COc1ccc2C(=CC(=O)Oe2c1OCC(=O)NCCN(C)C)  
 Nc3c(Br)encc3Br  
 OC(=O)[C@@H]1CCCN1C(=O)COe2c(OCF)ccc3C  
 (=CC(=O)Oe23)Ne4c(Br)encc4Br  
 OC(=O)CC[C@H](NC(=O)COc1c(OC(F)F)ccc2C(=CC  
 (=O)Oc12)Nc3c(Br)encc3Br)C(=O)O

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OC(=O)CC[C@H](NC(=O)COc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br)C(=O)O  
CN(C)CCN(C)C(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N(C)CCC[N+](C)(C)C)Nc3c(Br)cncc3Br  
C[C@H](NC(=O)CCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br)C(=O)O  
COc1ccc2C(=CC(=O)O)c2c1OCCCC(=O)N[C@@H](C(C)C)C(=O)O)Nc3c(Br)cncc3Br  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OC(F)ccc3C(=CC(=O)O)c23)Nc4c(Br)cncc4Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)OCC[N+](C)(C)C)Nc3c(Br)cncc3Br  
CN(CC[N+](C)(C)C)C(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br  
OC(=O)[C@H](Cc1cccc1)NC(=O)CCCOc2c(OC(F)(F)F)ccc3C(=CC(=O)O)c23)Nc4c(Br)cncc4Br  
CSCC[C@H](NC(=O)CCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br)C(=O)O  
C[C@H](NC(=O)CCCCOc1c(OC(F)(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br)C(=O)O  
OC(=O)[C@@H]1CCCN1C(=O)CCCCOc2c(OC(F)F)ccc3C(=CC(=O)O)c23)Nc4c(Br)cncc4Br  
COc1ccc2C(=CC(=O)O)c2c1OCCCCC(=O)N[C@@H](Cc3cnc[nH]3)C(=O)O)Nc4c(Br)cncc4Br  
OC(=O)CC[C@H](NC(=O)CCCCOc1c(OC(F)F)ccc2C(=CC(=O)O)c12)Nc3c(Br)cncc3Br)C(=O)O

The activity of the compounds in Examples 1-105 as PDE4 inhibitors is illustrated in the following assay. The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in this assay as well.

#### Novel PDE/AK Biological Activity Assay Protocol

Phosphodiesterases regulate the activity of the second messenger cyclic adenosine monophosphate (cAMP) by hydrolyzing cAMP to adenosine monophosphate (AMP). We developed a novel coupled PDE/AK bioluminescent high-throughput assay to measure the activity of phosphodiesterases. In the PDE/AK assay, the AMP produced from the hydrolysis of cAMP by phosphodiesterase is converted to adenosine diphosphate (ADP) by the phosphotransferase activity of adenylate kinase (also known as ADK or myokinase). Adenylate kinase will catalyze the conversion of 1 mole of AMP and 1 mole of ATP into 2 moles of ADP. Thus the conversion of AMP to ADP will result in the subsequent loss of ATP. The decrease in ATP concentration can be monitored as light output using luciferase in a reaction that requires ATP to produce light. The PDE/AK assay uses luciferase, which catalyzes the production of light from ATP present in the reaction mix. The amount of emitted light is inversely proportional to the level of AMP present in the reaction. Test compounds are incubated with the phosphodiesterases and phosphodiesterase inhibitors will decrease the rate of cAMP hydrolysis and decrease the subsequent production of AMP. Thus phosphodiesterase inhibitors will decrease the conversion of ATP to ADP and result in the greatest emission of light.

Compounds may be screened for functional potency in in vitro biochemical assays for their ability to inhibit the activity of phosphodiesterase (PDE) enzymes. A novel coupled PDE/AK assay was utilized to measure the inhibitory activity of compounds on PDE isoforms. The catalytic domain of PDE4B was fused to an amino-terminus hex-histidine affinity tag and purified. PDE4B enzyme was incubated with compounds for 10 minutes. Cyclic AMP substrate, ATP and adenylate kinase were then added to the PDE enzyme mix and incubated for 45 minutes at room temperature. A commercial

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ATP detection assay, Perkin Elmer's easyLite ATP detection reagent, was then added to measure the relative amount of ATP present in the reaction. After 10 minute incubation, the luminescent signal was quantitated with either the Perkin Elmer Viewlux or Molecular Devices Acquest or Analyst. Roflumilast and Rolipram are the positive controls used in the assay.

The PDE/AK assay can be performed with any cAMP dependent phosphodiesterase, and can be performed in 96-, 384-, or 1536-well plates. Unlike other phosphodiesterase activity assays, the PDE/AK assay does not require radioactive substrates, modified substrates, beads, or antibodies, which each have disadvantages. Specifically, the use of radioactive substrates in a phosphodiesterase activity assay requires special protocols for handling and waste disposal, and reduced throughput. Modified substrates add the additional complexity of potentially altering the binding to the phosphodiesterase catalytic site. Fluorescently modified substrates may cause fluorescence artifacts that may interfere in the interpretation of assay results. The use of beads that selectively bind to either the cAMP or AMP may cause an additional complexity in reagent handling. The use of antibodies that selectively bind to either cAMP or AMP can be extremely costly with a relatively small signal to noise ratio. Therefore, the novel PDE/AK assay represents a simple, cost-effective alternative to known methods.

Additionally, the PDE/AK assay's mechanism offers advantages which make it useful for comparison to other phosphodiesterase activity assays. In conventional assays in which cAMP concentration is inversely proportional to the output of bioluminescence (such as Cambrex Biosciences's PDELIGHT), phosphodiesterase catalyzes the hydrolysis of cAMP to AMP that is subsequently converted to ATP, consumed by a luciferase enzyme, and results in an increased bioluminescent output. A phosphodiesterase inhibitor prevents the hydrolysis of cAMP to AMP and consequently results in a decreased bioluminescent output. However, compounds which exhibit luciferase inhibition activity would score as a false positive for PDE inhibition in the conventional assay. In contrast, the novel PDE/AK assay would not score luciferase inhibitors as false positive for PDE inhibition because inhibition of PDE activity would result in increased bioluminescence. However, compounds that are capable of inhibiting both PDE and luciferase would be false negatives. Compounds that inhibit adenylate kinase would score as false positives in the novel PDE/AK assay. Use of both types of assay, and comparison of the data from both, would yield a richer and more reliable data set.

Accordingly, contemplated herein is a method for the detection and quantitation of PDE inhibition which uses adenylate kinase coupled to an ATP-depleting assay.

In certain embodiments, said method comprises the steps of:

1. A first incubation, of PDE, or an isolated isoform thereof, with a compound to be tested;
2. Addition of ATP, cAMP, and AK substrates;
3. A second incubation of said PDE;
4. Coupling to a means for readout of ATP-depletion; and
5. Readout.

In further embodiments, said first incubation is for between about 5 and about 15 minutes; in yet further embodiments, said first incubation is for about 10 minutes.

In further embodiments, said second incubation is for longer than about 30 minutes; in yet further embodiments, said sufficient length of time is between about 30 minutes and about one hour; in even further embodiments, sufficient length of time is about 45 minutes.

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In further embodiments, said readout means is a luciferase assay. In yet further embodiments, said luciferase assay is a Perkin Elmer easyLite assay.

In further embodiments, said readout is done on a machine for detecting a luminescent signal. In yet further embodiments, said machine is selected from the group consisting of a Perkin Elmer Viewlux, a Molecular Devices Acquest, and a Molecular Devices Analyst.

Results are shown below in Table 1.

TABLE 1

Example No.	Biological Activity	
	IC <sub>50</sub> + indicates $\leq 1 \mu\text{M}$ - indicates $> 1 \mu\text{M}$	
1	+	
2	+	
3	+	
4	-	
5	+	
6	+	
7	-	
8	-	
9	-	
10	+	
11	+	
12	+	
13	+	
14	+	
15	+	
16	-	
17	+	
18	+	
19	+	
20	-	
21	+	
22	-	
23	+	
24	+	
25	+	
26	+	
27	+	
28	+	
29	+	
30	+	
31	+	
32	+	
33	+	
34	+	
35	+	
36	+	
37	+	
38	+	
39	-	
40	+	
41	+	
42	+	
43	+	
44	+	
45	+	
46	+	
47	+	
48	+	
49	-	
50	+	
51	+	
52	+	
53	+	
54	+	
55	+	
56	+	
57	+	
58	+	
59	-	
60	+	
61	+	
62	+	

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TABLE 1-continued

Example No.	Biological Activity	
	IC <sub>50</sub> + indicates $\leq 1 \mu\text{M}$ - indicates $> 1 \mu\text{M}$	
63	+	
64	+	
65	+	
66	+	
67	+	
68	+	
69	+	
70	+	
71	+	
72	+	
73	+	
74	+	
75	+	
76	+	
77	-	
78	+	
79	+	
80	+	
81	+	
82	-	
83	+	
84	+	
85	+	
86	+	
87	+	
88	+	
89	+	
90	+	
91	+	
92	+	
93	+	
94	+	
95	+	
96	+	
97	+	
98	+	
99	+	
100	+	
101	+	
102	+	
103	+	
104	+	
105	+	

## In Vivo Assay

## Lacrimal Gland Inflammation-Induced Dry Eye in Rabbits

A more detailed description of the assay used herein may be found in Naglehout, T J et al. 2005, "Preservation of Tear Film Integrity and Inhibition of Corneal Injury by Dexamethasone in a Rabbit Model of Lacrimal Gland Inflammation-Induced Dry Eye," *J. Ocular Pharm. Ther.*, 21:2. 139-148, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

## Initiation of Dry Eye and Treatment

Rabbits (n=4/group) were randomized into treatment groups and dosed topically BID with maxidex vehicle or test drug beginning one day prior to initiation of dry eye. Each rabbit received bilateral lacrimal gland injections of saline or ConA (300  $\mu\text{g}/30 \mu\text{l}$ ) and topical ocular dosing was continued BID throughout the study.

## 65 Corneal Staining

Desiccation was initiated 1-2 hours following lacrimal gland injection by placing conscious rabbits in the environ-

mental chamber (10-15% humidity/72° F.). Following 72 consecutive hours of exposure to this dry environment, the animals were anesthetized and sutures were placed in each upper and lower eyelid and lifted to form a corneal/conjunctival cup. Methylene blue dye (1 mL, 1% in dH<sub>2</sub>O) was added to the cup for three minutes and the excess removed by washing with 200 mL BSS®. The contralateral eye was then stained using the same procedure. Rabbits were euthanized immediately following the staining procedure and the eyes were excised. The corneas were isolated with a trephine and the 9.5-mm punch of the cornea was placed in 2 mL acetone/saturated sodium sulfate (7:3, vol./vol.). Absorbance of the extracted dye was determined at 660 nm.

#### Tear Breakup Time (TBUT)

TBUT was quantified in a separate group of treated animals. TBUT was determined by instilling 5 µL sodium fluorescein into the cul de sac and manually blinking the lids to distribute the fluorescein within the tear film. Under slit lamp observation, the eye was held open and the time whereby one or more black spots or streaks appeared in the precorneal tear film was recorded. The rabbits were euthanized 3 days following ConA injection.

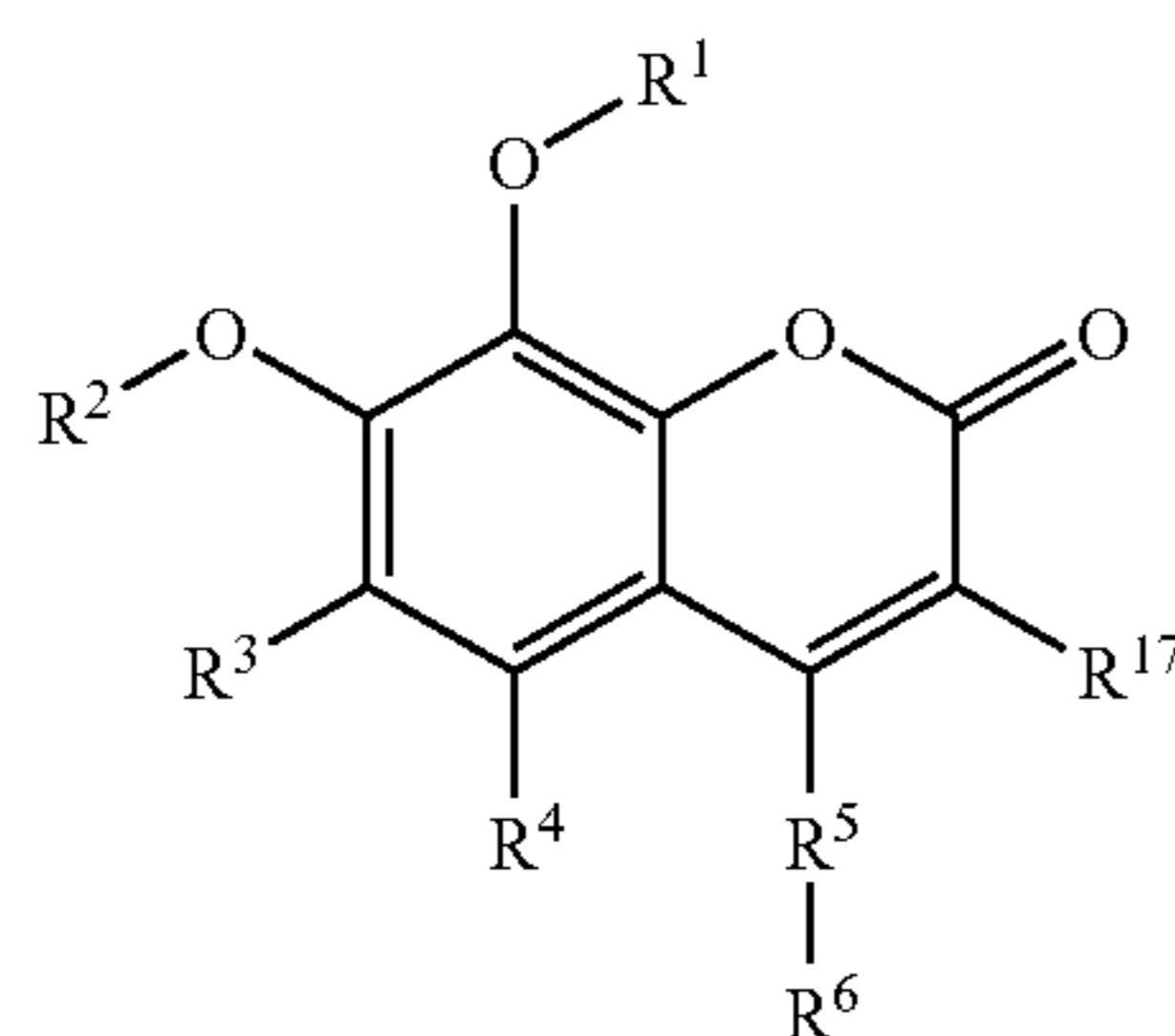
TABLE 2

Example	In Vivo Activity						
	Activity at Percent Concentration Tested						
No.	1 × 10 <sup>-6</sup>	1 × 10 <sup>-5</sup>	1 × 10 <sup>-4</sup>	1 × 10 <sup>-3</sup>	1 × 10 <sup>-2</sup>	1 × 10 <sup>-1</sup>	1
3	NT	NT	NT	NT	Inactive	Inactive	Inactive
5	NT	NT	NT	NT	Inactive	Inactive	Inactive
27	Active	Active	Active	Active	Inactive	Inactive	NT
31	Inactive	Inactive	Active	Inactive	Active	Inactive	NT
43	Inactive	NT	Inactive	NT	Inactive	NT	NT
44	Inactive	NT	Inactive	NT	Inactive	NT	NT
52	Inactive	NT	Inactive	NT	Inactive	NT	NT
53	Inactive	NT	Inactive	NT	Inactive	NT	NT
54	Inactive	NT	Inactive	NT	Inactive	NT	NT
55	Active	NT	Active	NT	Inactive	NT	NT
56	Inactive	NT	Inactive	NT	Inactive	NT	NT
63	Inactive	NT	Inactive	NT	Inactive	NT	NT
65	Inactive	NT	Inactive	NT	Inactive	NT	NT
66	Inactive	NT	Inactive	NT	Inactive	NT	NT
67	Inactive	NT	Inactive	NT	Inactive	NT	NT
68	Active	NT	Active	NT	Inactive	NT	NT
70	Inactive	NT	Inactive	NT	Inactive	NT	NT
71	Inactive	NT	Inactive	NT	Inactive	NT	NT
83	Inactive	NT	Inactive	NT	Inactive	NT	NT

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A compound of structural Formula IV



(IV)

or a salt thereof, wherein:

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of —(CH<sub>2</sub>)<sub>s</sub>G<sup>1</sup>G<sup>2</sup>G<sup>3</sup>, acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl, and hydroxyalkyl, any of which may be optionally substituted;

s is 0-8;

G<sup>1</sup> is selected from the group consisting of alkoxy, amino, amido, carbonyl, hydroxy, ether, an amino acid, and null;

G<sup>2</sup> is selected from the group consisting of alkyl, alkoxy, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

G<sup>3</sup> is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted;

when s is 0, G<sup>1</sup>, G<sup>2</sup>, and G<sup>3</sup> may not all together be null;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of alkoxy, lower alkyl, halogen and hydrogen;

R<sup>5</sup> is selected from the group consisting of (CH<sub>2</sub>)<sub>p</sub>, C(O)NH, N(R<sup>7</sup>) and S(O)<sub>q</sub>;

p is 1,2,3 or 4;

q is 0, 1 or 2;

R<sup>6</sup> is selected from the group consisting of aryl heteroaryl, either of which may be optionally substituted;

R<sup>7</sup> selected from the group consisting of hydrogen and optionally substituted lower alkyl; R<sup>17</sup> is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, hydroxyalkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl and aminoalkoxy.

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2. The compound as recited in claim 1, wherein  $R^{17}$  is selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, alkoxy, haloalkoxy, amino, aminoalkyl and aminoalkoxy.

3. The compound as recited in claim 2, wherein  $R^{17}$  is hydrogen.

4. The compound as recited in claim 3, wherein  $R^6$  is selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, and pyrazine, any of which may be optionally substituted.

5. The compound as recited in claim 4, wherein  $R^3$  and  $R^4$  are both hydrogen.

6. The compound as recited in claim 5, wherein:  
 $R^5$   $N(R^7)$ ; and  
 $R^7$  hydrogen.

7. The compound as recited in claim 6, wherein  $R^2$  is lower alkyl.

8. The compound as recited in claim 7, wherein:

$R^1$  is selected from the group consisting of  $-(CH_2)_s$ ,  $G^1G^2G^3$ , lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

$s$  is 1-6;

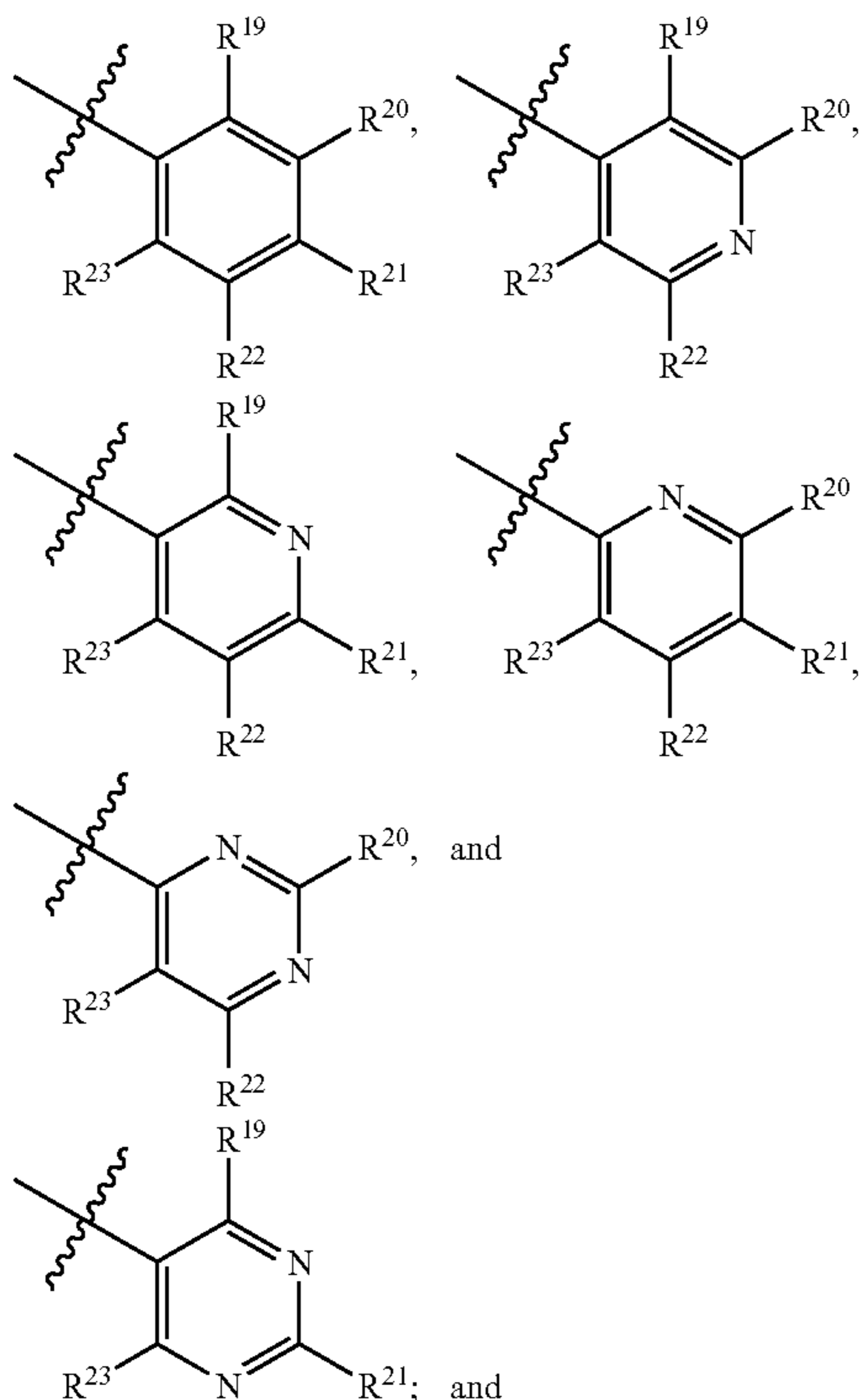
$G^1$  is selected from the group consisting of amino, amido, and null;

$G^2$  is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

$G^3$  is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

9. The compound as recited in claim 8, wherein  $R^2$  is methyl.

10. The compound as recited in claim 9, wherein  $R^6$  has a formula selected from the group consisting of:

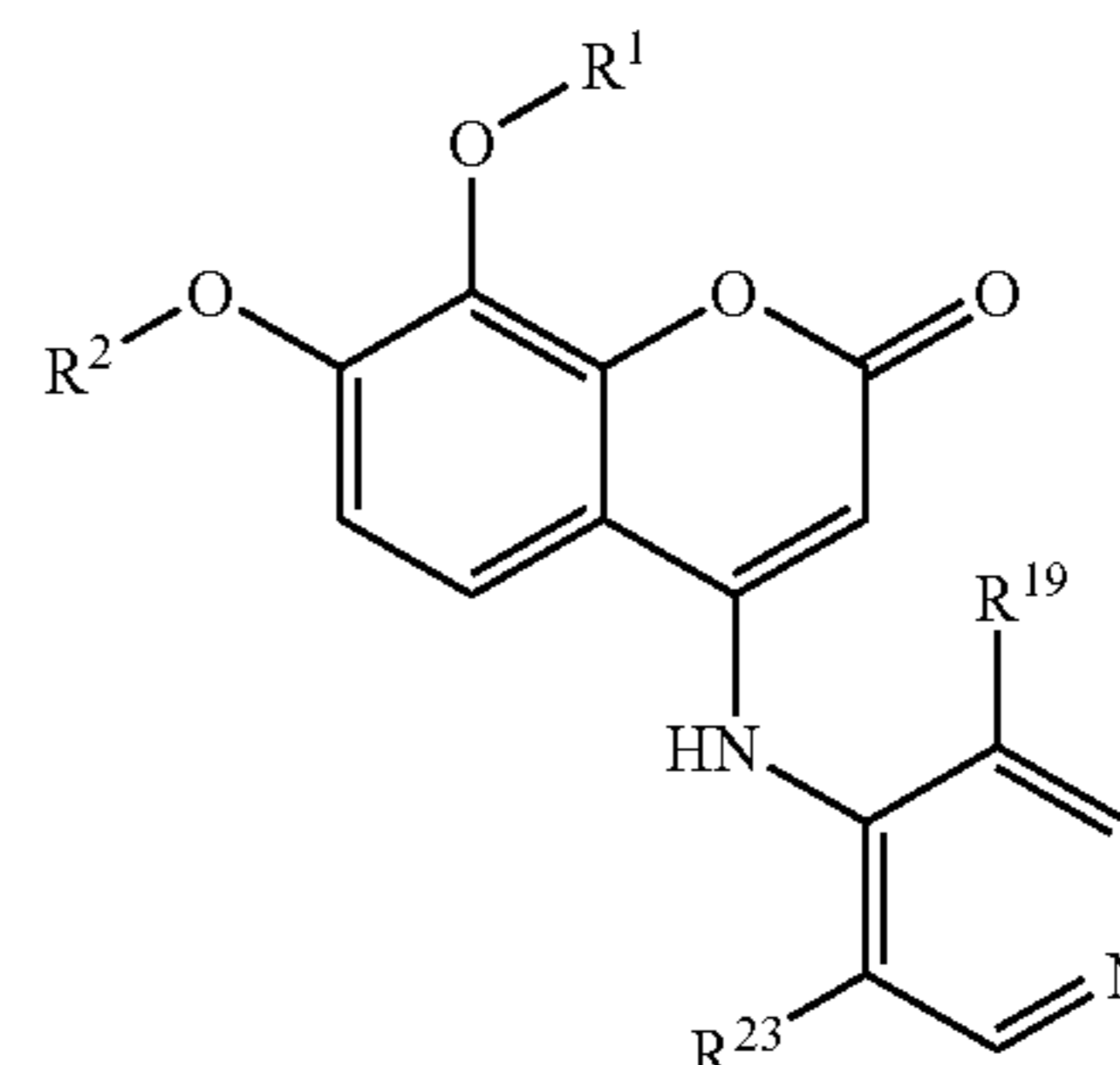


$R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$ , and  $R^{23}$  are independently selected from the group consisting of hydrogen, halogen,

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hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

11. A compound of structural Formula VI



(VI)

or a salt thereof, wherein:

$R^1$  and  $R^2$  are independently selected from the group consisting of  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl and hydroxyalkyl, any of which may be optionally substituted;

$s$  is 1-8;

$G^1$  is selected from the group consisting of alkoxy, acyl, amino, amido, carbonyl, ether, an amino acid, and null;

$G^2$  is selected from the group consisting of alkyl, alkoxy, acyl, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted;

$G^3$  is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydroxamic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

$R^{19}$  and  $R^{23}$  are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

12. The compound as recited in claim 11, wherein  $R^{19}$  and  $R^{23}$  are independently selected from the group consisting of hydrogen, halogen, and lower alkyl.

13. The compound as recited in claim 12, wherein  $R^2$  is lower alkyl.

14. The compound as recited in claim 13, wherein:

$R^1$  is selected from the group consisting of  $-(CH_2)_sG^1G^2G^3$ , lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

$s$  is 1-6;

$G^1$  is selected from the group consisting of amino, amido, and null;

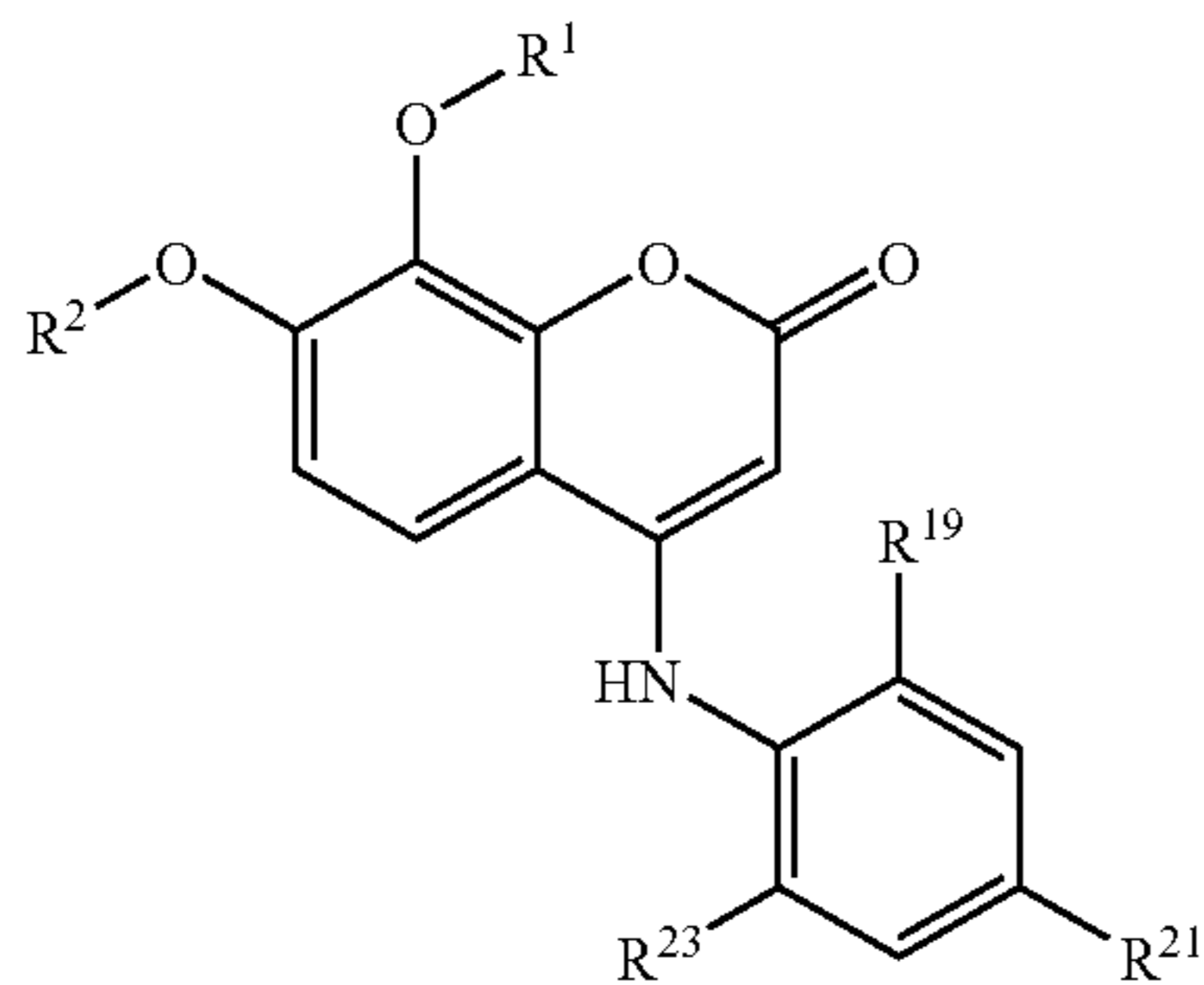
$G^2$  is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

$G^3$  is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

15. The compound as recited in claim 14, wherein  $R^2$  is methyl.

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16. A compound of structural Formula VII



or a salt thereof, wherein:

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of  $-(CH_2)_sG^1G^2G^3$ , acyl, acylalkyl, carboxyalkyl, cyanoalkyl, alkoxy, alkoxyalkyl, amidoalkyl, amino, alkyl, alkylalkoxy, aminoalkyl, alkenyl, alkynyl, carboxyl, carboxyalkyl, ether, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aralkyl, aryl, guanidine, heteroaryl, heteroaralkyl and hydroxyalkyl, any of which may be optionally substituted;

s is 1-8; G<sup>1</sup> is selected from the group consisting of alkoxy, acyl, amino, amido, carbonyl, ether, an amino acid, and null; G<sup>2</sup> is selected from the group consisting of alkyl, alkoxy, acyl, amino, aryl, halo, haloalkyl, heterocycloalkyl, heteroaryl, carboxylalkylamino, guanidine, an amino acid, and null, any of which may be optionally substituted; G<sup>3</sup> is selected from the group consisting of alkyl, alkoxy, amino, hydroxy, ether, carboxyl, hydrox-

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amic acid, an amino acid, phosphonate, phosphoamide, and null, any of which may be optionally substituted; and

(VII) R<sup>19</sup>, R<sup>21</sup>, and R<sup>23</sup> are independently selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, amino, and carboxyl.

17. The compound as recited in claim 16, wherein R<sup>19</sup>, R<sup>21</sup>, and R<sup>23</sup> are independently selected from the group consisting of hydrogen, halogen, and lower alkyl.

18. The compound as recited in claim 17, wherein R<sup>2</sup> is lower alkyl.

19. The compound as recited in claim 18, wherein:

R<sup>1</sup> is selected from the group consisting of  $-(CH_2)_sG^1G^2G^3$ , lower alkyl, cycloalkyl, cycloalkylalkyl, and heterocycloalkyl, any of which may be optionally substituted;

s is 1-6;

G<sup>1</sup> is selected from the group consisting of amino, amido, and null;

G<sup>2</sup> is selected from the group consisting of alkoxy, aryl, halo, heterocycloalkyl, and null, any of which may be optionally substituted; and

G<sup>3</sup> is selected from the group consisting of alkyl, carboxyl, and null, any of which may be optionally substituted.

20. The compound as recited in claim 19, wherein R<sup>2</sup> is methyl.

21. A compound selected from the group consisting of Examples 1 to 105.

22. A pharmaceutical composition comprising a compound as recited in claim 1 together with a pharmaceutically acceptable carrier.

\* \* \* \* \*