



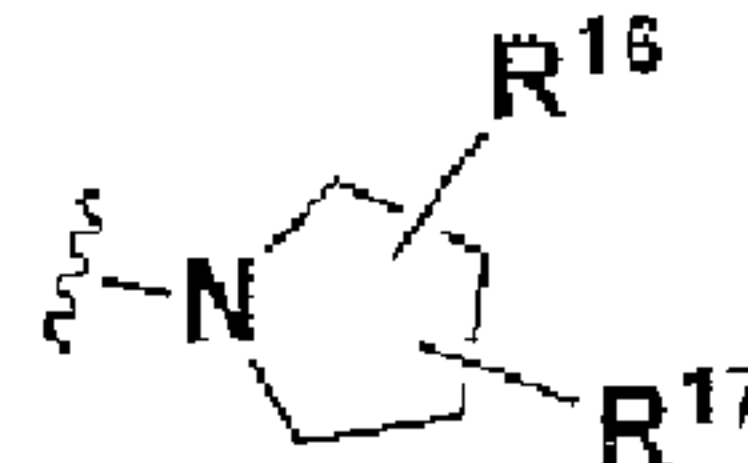
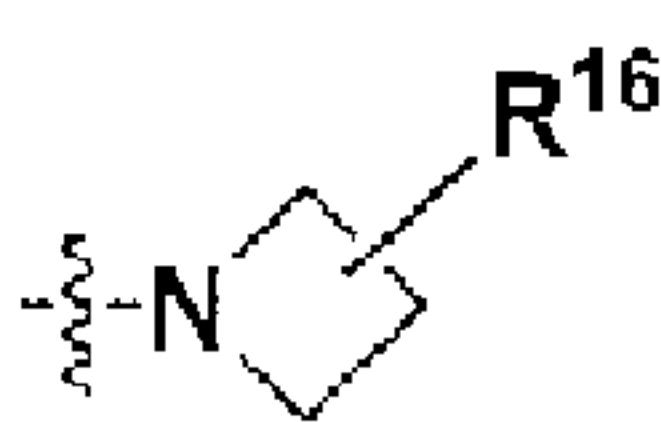
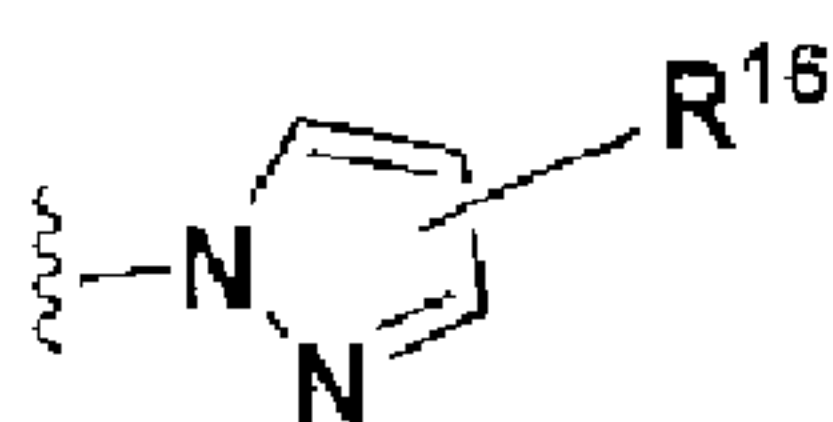
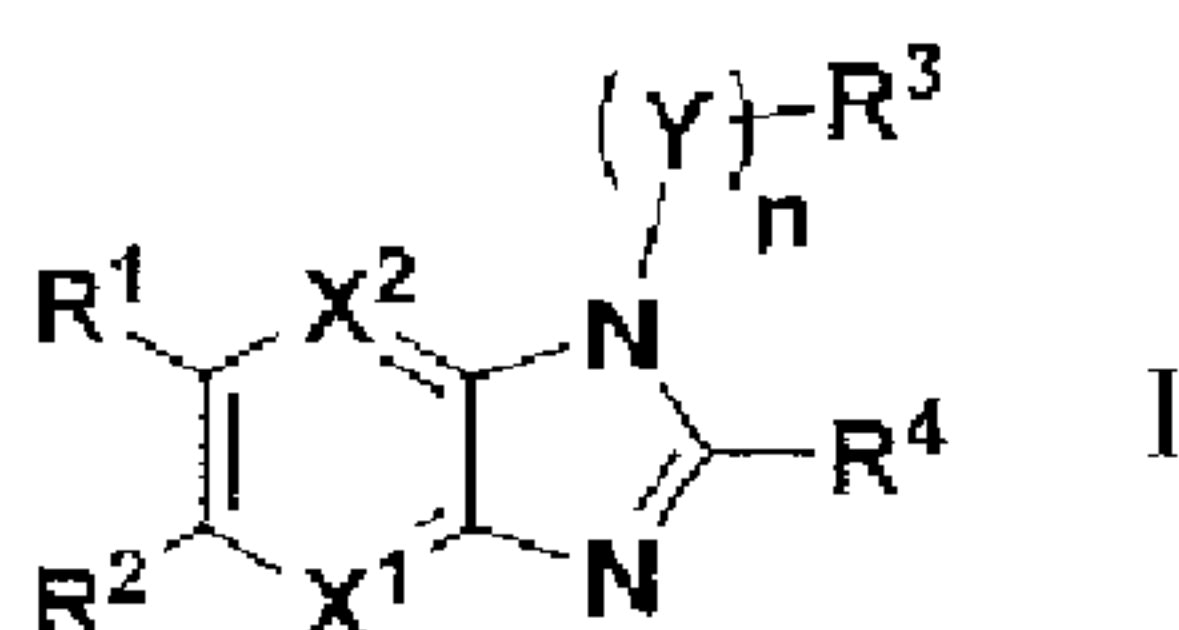
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(54) Titre : DERIVES 2-AMINO-BENZIMIDAZOLE ET LEUR UTILISATION COMME INHIBITEURS DE 5-LIPOXYGENASE  
ET/OU DE PROSTAGLANDINE E SYNTHASE  
(54) Title: 2-AMINO-BENZIMIDAZOLE DERIVATIVES AND THEIR USE AS 5-LIPOXYGENASE AND/OR  
PROSTAGLANDIN E SYNTHASE INHIBITORS



(57) **Abrégé/Abstract:**

The present invention relates to benzimidazole derivatives having the general formula I, wherein n is 0 or 1; X<sup>1</sup> and X<sup>2</sup> are independently, at each occurrence, CR<sup>5</sup> or N; Y is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to two C<sub>1</sub>-C<sub>3</sub> alkyl groups; R<sup>1</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NH<sub>2</sub>, -NHR<sup>6</sup>, -NR<sup>7</sup>R<sup>8</sup> and -NH-(R<sup>9</sup>)<sub>n</sub>-R<sup>10</sup>, n being 0 or 1; R<sup>2</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -NH<sub>2</sub>, -NHR<sup>6</sup>, -NR<sup>7</sup>R<sup>8</sup> and -NH-(R<sup>9</sup>)<sub>n</sub>-R<sup>10</sup>; R<sup>3</sup> is selected from the group consisting of hydrogen, hydroxyl, OR<sup>11</sup>, -NR<sup>7</sup>R<sup>8</sup>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, -C(O)NHR<sup>11</sup>, aryl, heteroaryl and heterocyclyl, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups; and R<sup>4</sup> is selected from the group consisting of -NH<sub>2</sub>, -N(R<sup>12</sup>)(V)<sub>p</sub>R<sup>13</sup>, -NH(V)<sub>p</sub>-OR<sup>14</sup>, -NHC(O)R<sup>15</sup>, and groups of formula Ia shown below, and their use in the treatment of diseases, in particular inflammatory diseases, cancer, stroke and/or Alzheimer's disease.



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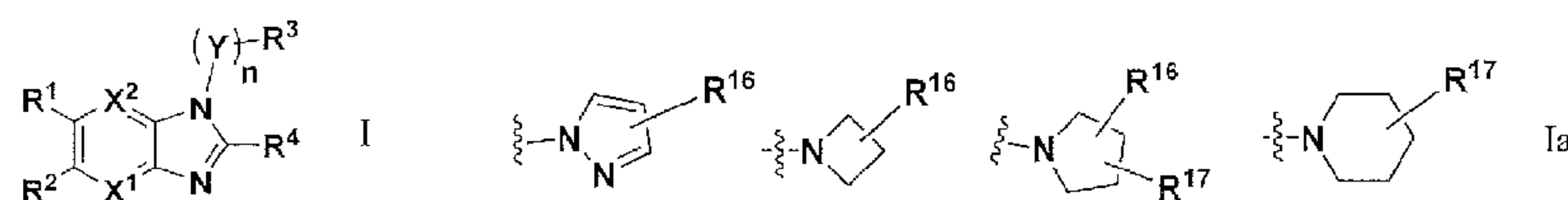
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(54) Title: 2-AMINO-BENZIMIDAZOLE DERIVATIVES AND THEIR USE AS 5-LIPOXYGENASE AND/OR PROSTAGLANDIN E SYNTHASE INHIBITORS



(57) Abstract: The present invention relates to benzimidazole derivatives having the general formula I, wherein n is 0 or 1; X<sup>1</sup> and X<sup>2</sup> are independently, at each occurrence, CR<sup>5</sup> or N; Y is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to two C<sub>1</sub>-C<sub>3</sub> alkyl groups; R<sup>1</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NH<sub>2</sub>, -NHR<sup>6</sup>, -NR<sup>7</sup>R<sup>8</sup> and -NH-(R<sup>9</sup>)<sub>n</sub>-R<sup>10</sup>, n being 0 or 1; R<sup>2</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -NH<sub>2</sub>, -NHR<sup>6</sup>, -NR<sup>7</sup>R<sup>8</sup> and -NH-(R<sup>9</sup>)<sub>n</sub>-R<sup>10</sup>; R<sup>3</sup> is selected from the group consisting of hydrogen, hydroxyl, OR<sup>11</sup>, -NR<sup>7</sup>R<sup>8</sup>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, -C(O)NHR<sup>11</sup>, aryl, heteroaryl and heterocyclyl, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups; and R<sup>4</sup> is selected from the group consisting of -NH<sub>2</sub>, -N(R<sup>12</sup>)(V)<sub>p</sub>-R<sup>13</sup>, -NH(V)<sub>p</sub>-OR<sup>14</sup>, -NHC(O)R<sup>15</sup>, and groups of formula Ia shown below, and their use in the treatment of diseases, in particular inflammatory diseases, cancer, stroke and/or Alzheimer's disease.

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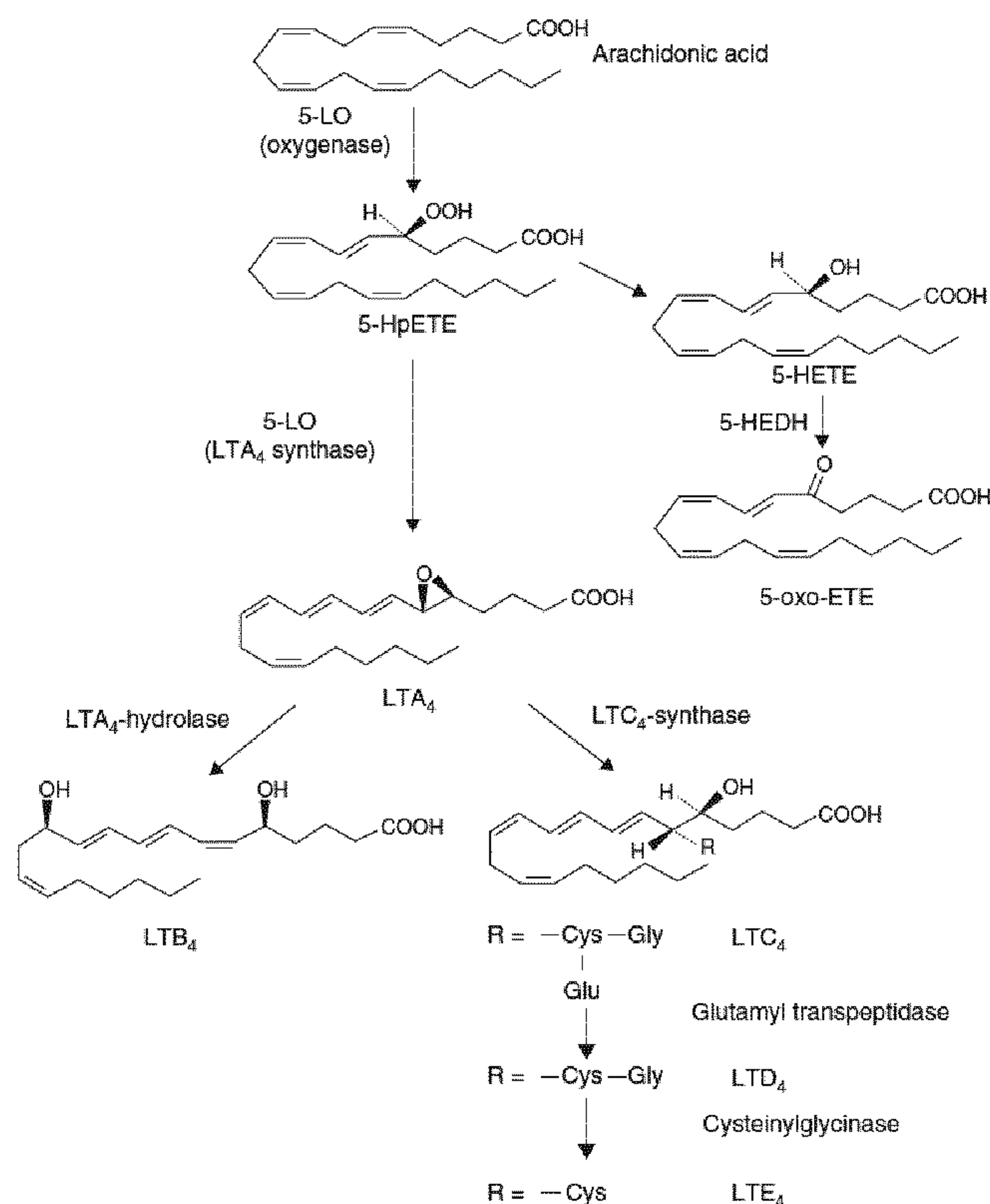
**2-AMINO-BENZIMIDAZOLE DERIVATIVES AND THEIR USE  
AS 5-LIPOXYGENASE AND/OR PROSTAGLANDIN E SYNTHASE INHIBITORS**

**Background of the invention**

The present invention relates to small molecule compounds and their use in the treatment of diseases, in particular inflammatory diseases, cancer, stroke and/or Alzheimer's disease.

The arachidonate 5-lipoxygenase (5-LOX, 5-LO, 5-lipoxygenase or Alox5) pathway has been shown to play an important role in the pathophysiology of many inflammatory diseases such as asthma, chronic obstructive pulmonary syndrome (COPD), allergic rhinitis, atherosclerosis, atopic dermatitis and pain by controlling the production of key inflammatory mediators. It has been also reported to be involved in cancer and Alzheimer's disease.

The 5-LOX enzyme is required in the production of LTB<sub>4</sub> (leukotriene B<sub>4</sub>), a primary chemo-attractant and activator for leukocytes. LTB<sub>4</sub> is primarily produced in neutrophils and macrophages where the enzyme LTA<sub>4</sub> hydrolase converts LTA<sub>4</sub> to LTB<sub>4</sub>. 5-LOX is also involved in the synthesis of LTC<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> (cysteinylleukotrienes; cys-LTs), which are strong bronchoconstrictors and proinflammatory mediators. Cys-LTs are also made from LTA<sub>4</sub>, a 5-LOX metabolite of arachidonic acid (AA). Another enzyme, LTC<sub>4</sub> synthase, present in several cells, including eosinophils, basophils, and mast cells, conjugates LTA<sub>4</sub> to glutathione to yield LTC<sub>4</sub>. LTC<sub>4</sub> is further metabolized into LTD<sub>4</sub> and LTE<sub>4</sub>. 5-LOX activity also results in the production of bioactive metabolites 5-hydroxyeicosatetraenoic acid (HETE) and 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxoETE). 5-oxoETE has been shown to induce tissue eosinophilia; thus, it may play a role in asthma and other diseases.



The clinical importance of the leukotriene pathway in inflammatory airway diseases has been demonstrated by the efficacy of various agents in the treatment of asthma and allergic rhinitis. Cys-LT receptor 1 antagonists (e.g., montelukast, zafirlukast, and pranlukast) have shown efficacy in asthma and allergic rhinitis, and the 5-LOX inhibitor zileuton has been shown to be efficacious in the treatment of asthma. 5-LOX inhibitors, which block both Cys-LTs and LTB<sub>4</sub> production, have the potential for enhanced efficacy in asthma and allergic rhinitis compared to leukotriene receptor antagonists. 5-LOX inhibitors will block the proinflammatory activity of LTB<sub>4</sub> and Cys-LTs as well as other leukotriene such as 5-HETE, and 5-oxo-EETE. Meta-analysis of several clinical trials suggest a better forced expiratory volume in 1 (FEV<sub>1</sub>) efficacy of zileuton versus the Cys-LT receptor antagonists in patients with severe asthma.

The only marketed 5-LOX inhibitor is zileuton, a redox hydroxyurea compound that chelates a critical active site iron moiety in the 5-LOX enzyme. Its efficacy and medical acceptance have been compromised by an inconvenient dosing regimen (i.e., four times daily), a suboptimal pharmacokinetic and pharmacodynamic profile, and a potential for hepatotoxicity. In addition, efforts to develop non-redox 5-LOX inhibitors have failed due to insufficient efficacy in human. Unmet medical needs therefore exist for more potent, better tolerated, non-

hepatotoxic 5-LOX inhibitors that could maximize the benefits of inhibiting the leukotriene pathway and provide superior efficacy than obtained with zileuton and Cys-LT receptor antagonists.

Prostaglandin E synthase (PGES) is an enzyme involved in eicosanoid and glutathione metabolism, catalyzing the reaction from prostaglandin H<sub>2</sub> to prostaglandin E. It requires glutathione as an essential cofactor for its activity. It has been implicated in osteoarthritis, rheumatoid arthritis, atherosclerosis, and inflammatory pain.

Furthermore, inflammation-induced microsomal prostaglandin E synthase-1 (mPGES) is the terminal enzyme that synthesizes prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) downstream of cyclooxygenase-2 (COX-2). mPGES-1 is up-regulated in response to various pro-inflammatory stimuli with a concomitant increased expression of COX-2. Increase in the coordinate expression of COX-2 and mPGES-1 is reversed by glucocorticoid. The inhibition of PGES provides a rationale for exploring mPGES-1 inhibition as a potential novel therapy for the above mentioned diseases. According to data of mPGES-1 knockout (KO) mice, these were less sensitive to inflammatory and neuropathic pain in rodent arthritis models, therefore, mPGES-1 has emerged as a potential target for the development of drugs for treatment of inflammation, pain, cancer, atherosclerosis, and stroke.

Herein are disclosed compounds with anti-inflammatory activity and anti-5-LOX activity and/or anti-PGES-activity.

It was an object of the present invention to identify compounds that interact and interfere with the 5-LOX-pathway and/or the PGES-pathway, in particular compounds having an inhibitory effect against arachidonate 5-lipoxygenase and/or prostaglandin E synthase.

It was also an object of the present invention to identify compounds with an anti-inflammatory activity.

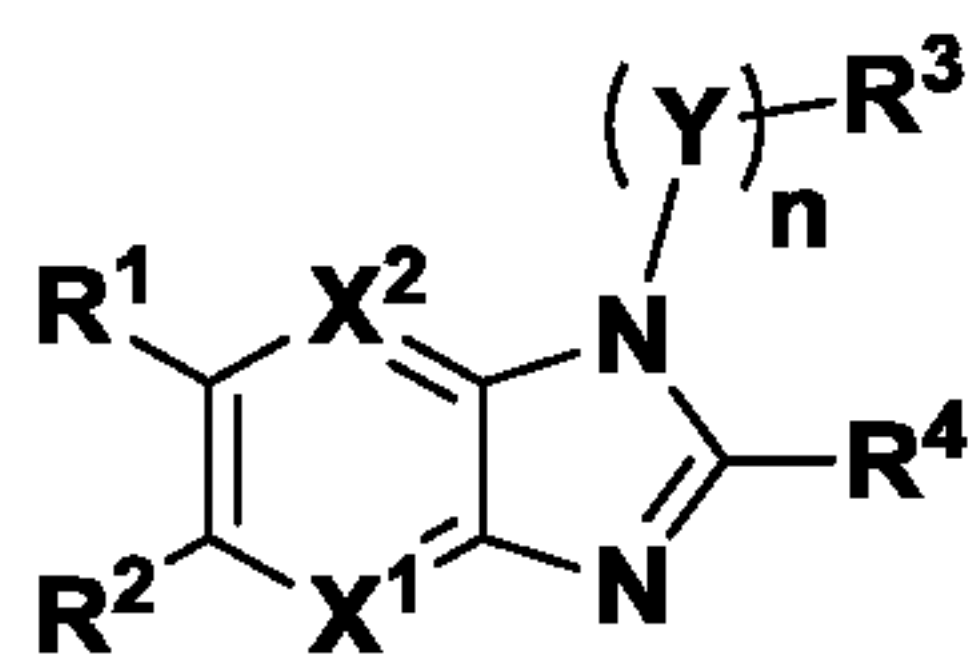
It was furthermore an object of the present invention to identify compounds effective against inflammatory disease, in particular asthma, atherosclerosis, pain, COPD, allergic rhinitis,

inflammation post infection, arthritis, dermatitis, pain, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, and against other diseases associated with a pathology of the 5-LOX-pathway and/or the PGES-pathway or diseases with an implication of the 5-LOX-pathway and/or the PGES-pathway, such as cancer and/or Alzheimer's disease and/or stroke.

1. Expert Opin. Ther. Patents **(2010) 20(3), 335-375**
2. Eur Respir J 2012; 40: 724.741
3. CurrOpin Allergy ClinImmunol. 2010 February ; 10(1): 60–66
4. Biochemical Pharmacology 70 (2005) 327–333
5. Int J ClinPract, April 2007, 61, 4, 663–676

### Description of the Invention

In one aspect, the present invention relates to a compound having the general formula I:



Formula I

wherein

$n$  is 0 or 1;

$X^1$  and  $X^2$  are independently, at each occurrence,  $CR^5$  or N;

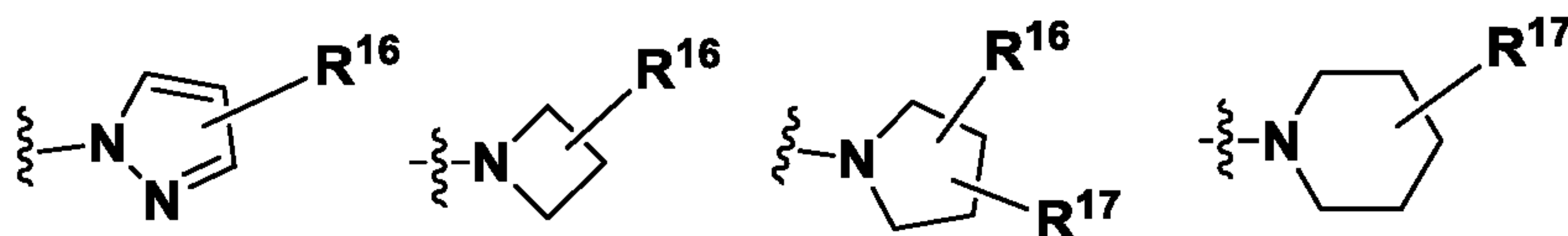
$Y$  is  $C_1$ - $C_6$  alkylene, wherein alkylene is optionally substituted with one to two  $C_1$ - $C_3$  alkyl groups;

$R^1$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkoxy,  $-NH_2$ ,  $-NHR^6$ ,  $-NR^7R^8$  and  $-NH-(R^9)_n-R^{10}$ ,  $n$  being 0 or 1;

$R^2$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $-NH_2$ ,  $-NHR^6$ ,  $-NR^7R^8$  and  $-NH-(R^9)_n-R^{10}$  group,  $n$  being 0 or 1;

$R^3$  is selected from the group consisting of hydrogen, hydroxyl,  $OR^{11}$ ,  $-NR^7R^8$ ,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_3$  haloalkyl,  $-C(O)NHR^{11}$ , aryl, heteroaryl and heterocyclyl group, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;

$R^4$  is selected from the group consisting of  $-NH_2$ ,  $-N(R^{12})(V)_pR^{13}$ ,  $-NH(V)_p-OR^{14}$ ,  $-NHC(O)R^{15}$ , and groups of formula Ia shown below,



Formula Ia

wherein,

p is 0 or 1,

V is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl or phenyl groups, or wherein a carbon atom of said alkylene forms part of a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy group;

R<sup>6</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>7</sup> and R<sup>8</sup> are independently, at each occurrence, C<sub>1</sub>-C<sub>6</sub> alkyl or heterocyclyl; or R<sup>7</sup> and R<sup>8</sup> are connected to each other to make a four, five or six membered heterocyclyl or heteroaryl group, wherein each of said heterocyclyl and heteroaryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

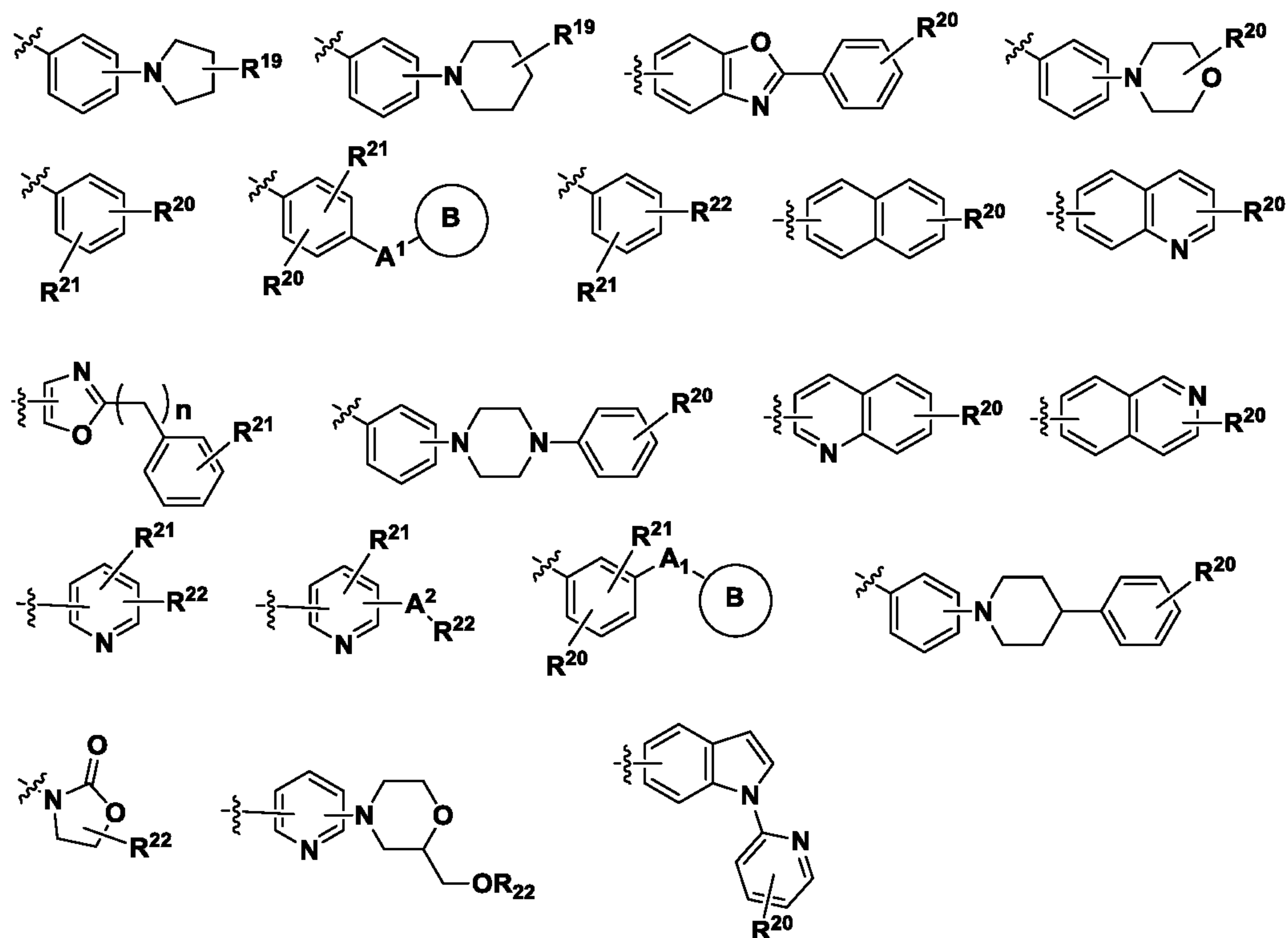
R<sup>9</sup> is C<sub>1</sub>-C<sub>4</sub> alkylene, wherein said alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>10</sup> is selected from the group consisting of hydroxyl, -OR<sup>11</sup>, -CN, -C(O)OR<sup>18</sup>, -C(O)NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, aryl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>11</sup> is independently, at each occurrence, selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>12</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-hydroxyl and C<sub>1</sub>-C<sub>4</sub> alkyl-alkoxy;

R<sup>13</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-hydroxyl, -OH, -C(O)NH<sub>2</sub>, -C(O)OR<sup>18</sup>, -CN, C<sub>1</sub>-C<sub>3</sub> haloalkyl and heterocyclyl, and groups of formula Ib shown below,



### Formula Ib

wherein,

n is 0 or 1;

A<sup>1</sup> is -O-, -CH<sub>2</sub>O-, -OCH<sub>2</sub><sup>-</sup>, -S-, -SO<sub>2</sub><sup>-</sup>, -SO<sub>2</sub>NH-, -C(O)-, -C(O)NH-, -C(O)N(R<sup>7</sup>)-, -CH(OH)-, -CH(OR<sup>7</sup>)-, -NH-, -N(CH<sub>3</sub>)- or -N(CH<sub>2</sub>COOR<sup>7</sup>)-;

A<sup>2</sup> is -O- or NH-;

B is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>14</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or C<sub>1</sub>-C<sub>3</sub> haloalkoxy groups;

R<sup>15</sup> is aryl, wherein aryl is optionally substituted with one to four halogen groups;

R<sup>16</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl and hydroxyl ;

R<sup>17</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)R<sup>11</sup>, -C(O)NHR<sup>11</sup>, -OR<sup>11</sup> and aryl , wherein each of said alkyl and aryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>18</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>19</sup> is selected from the group consisting of hydrogen, -OR<sup>22</sup> and -CH<sub>2</sub>OR<sup>22</sup>;

R<sup>20</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(O)R<sup>a</sup> and C<sub>1</sub>-C<sub>6</sub> haloalkoxy;

R<sup>21</sup> is selected from the group consisting of hydrogen, halogen and C<sub>1</sub>-C<sub>6</sub> alkyl group;

R<sup>22</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl, e.g. phenyl or benzyl, and heteroaryl, wherein each of said haloalkyl, aryl and heteroaryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>a</sup> is independently, at each occurrence, selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, -CH<sub>2</sub>OR<sup>c</sup>, -OCH<sub>2</sub>R<sup>c</sup>, -OR<sup>c</sup>, -CN, NO<sub>2</sub>, -NR<sup>b</sup>R<sup>c</sup>, -C(O)NR<sup>b</sup>R<sup>c</sup>, -C(NH)NH<sub>2</sub>, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>3</sub> haloalkyl, -CN, -C(O)NH<sub>2</sub>, -COOH, -CO<sub>2</sub>Et and heteroaryl;

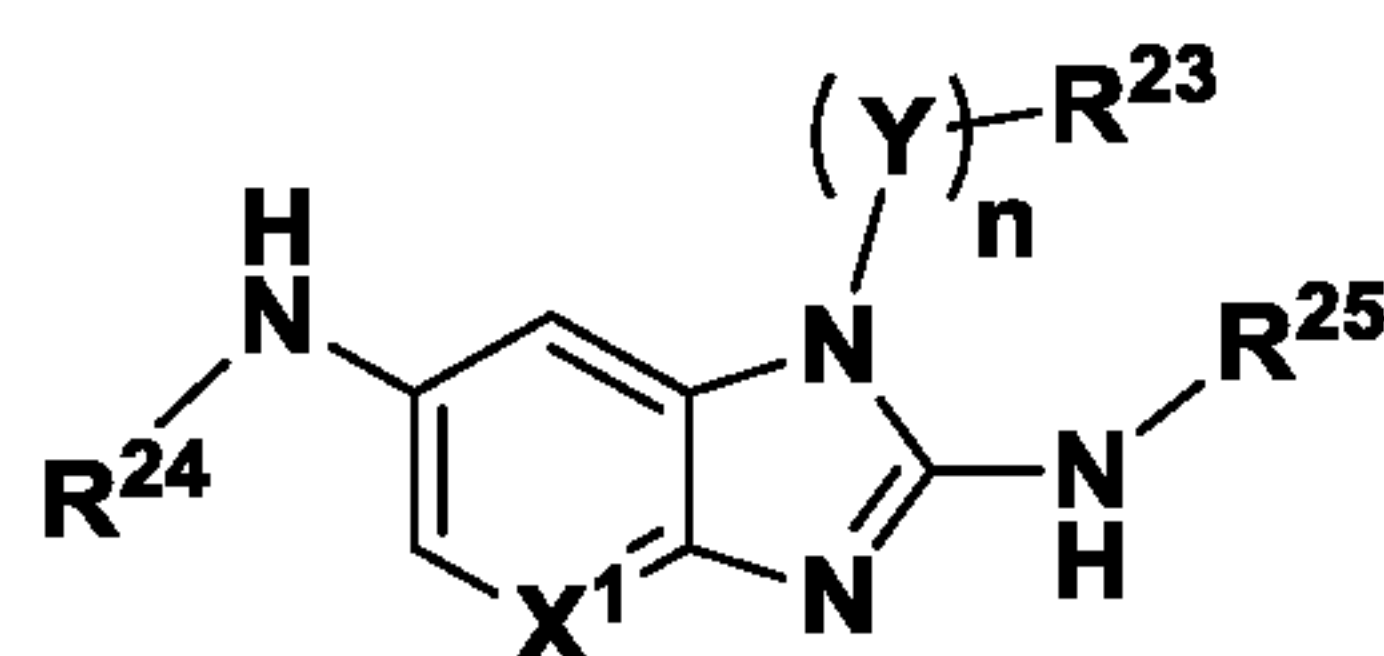
R<sup>b</sup> and R<sup>c</sup> are independently, at each occurrence, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-O-alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, C<sub>3</sub>-C<sub>10</sub> cycloalkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl, e.g. phenyl

or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, cycloalkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, -C(O)NH<sub>2</sub>, -COOH, -COOMe, -COOEt, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>; or

R<sup>b</sup> and R<sup>c</sup> are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;

and pharmaceutically acceptable salts thereof.

In a further aspect, the present invention relates to a compound having the general formula II:



Formula II

wherein

n is 0 or 1;

X<sup>1</sup> is CR<sup>5</sup> or N;

Y is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to two C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy group;

R<sup>23</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>24</sup> is selected from the group consisting of hydrogen, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

$R^{25}$  is selected from the group consisting of hydrogen,  $-(V)_pR^{26}$  and  $-(V)_pOR^{14}$ ;

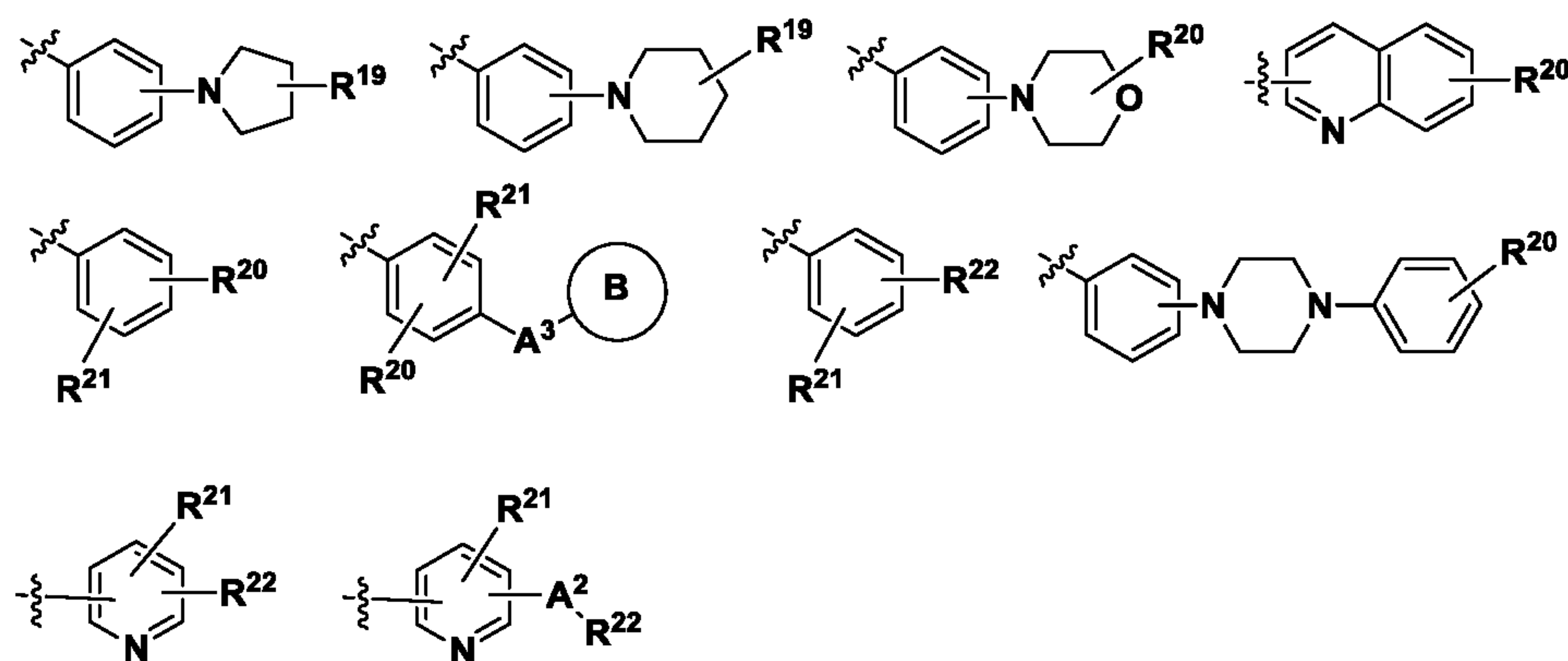
wherein,

p is 0 or 1,

V is  $C_1$ - $C_6$  alkylene, wherein alkylene is optionally substituted with one to three  $C_1$ - $C_3$  alkyl or phenyl groups, or wherein a carbon atom of said alkylene forms part of a  $C_3$ - $C_6$  cycloalkyl group;

$R^{14}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or  $C_1$ - $C_3$  haloalkoxy groups;

$R^{26}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl,  $-CN$  and  $C_1$ - $C_3$  haloalkyl, and groups of formula IIa shown below,



Formula IIa

wherein,

$A^2$  is  $-O-$  or  $NH-$ ;

$A^3$  is  $-O-$ ,  $-CH_2O-$ ,  $-OCH_2-$ , or  $-NH-$ ;

B is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;

$R^{19}$  is selected from the group consisting of hydrogen,  $-OR^{22}$  and  $-CH_2OR^{22}$  ;

$R^{20}$  is selected from the group consisting of hydrogen, halogen,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy and  $C_1-C_6$  haloalkoxy;

$R^{21}$  is selected from the group consisting of hydrogen, halogen and  $C_1-C_6$  alkyl;

$R^{22}$  is selected from the group consisting of aryl, e.g. phenyl or benzyl, and heteroaryl, wherein each of said aryl and heteroaryl is optionally and independently substituted with one to four  $R^a$  groups;

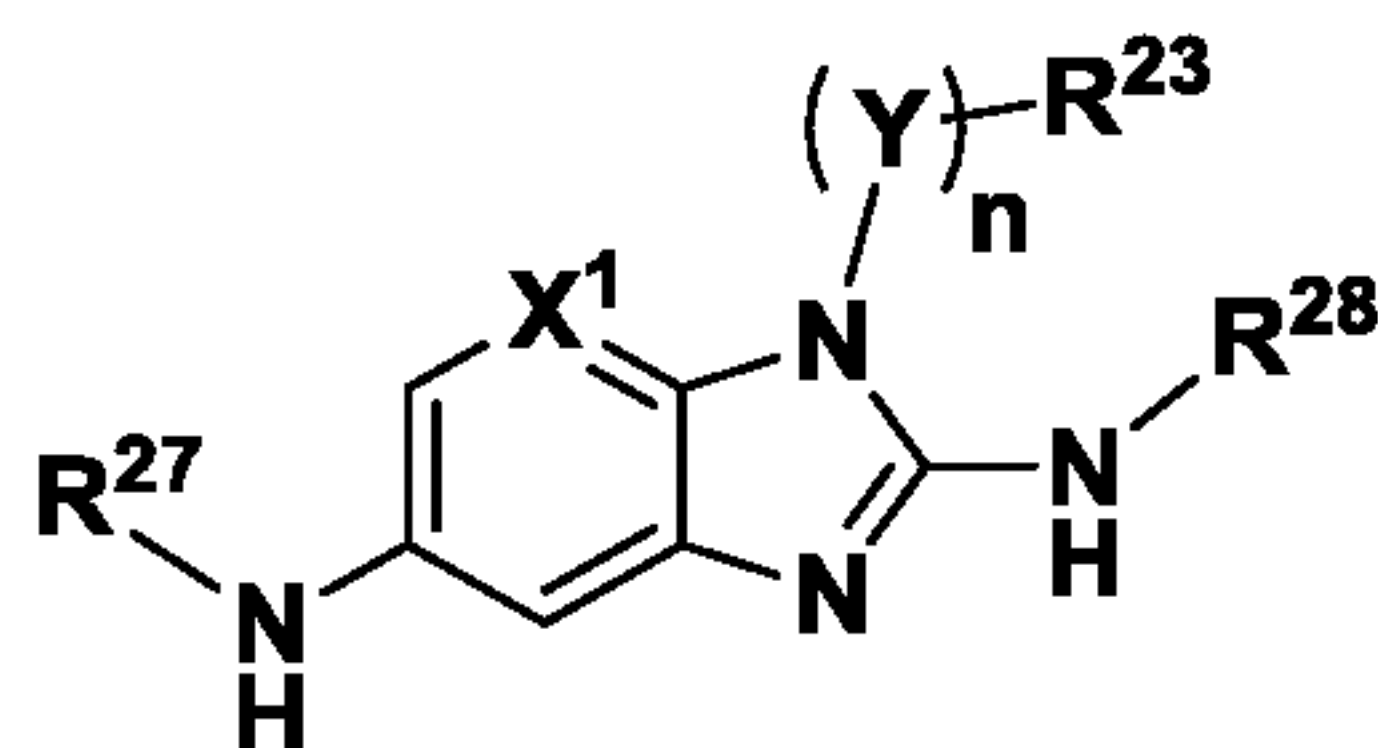
$R^a$  is independently, at each occurrence, selected from the group consisting of hydrogen, halogen,  $C_1-C_3$  alkyl,  $C_3-C_{10}$  cycloalkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  haloalkyl,  $C_1-C_6$  haloalkoxy, hydroxyl,  $C_1-C_3$  alkylhydroxyl,  $-CH_2OR^c$ ,  $-OCH_2R^c$ ,  $-OR^c$ ,  $-CN$ ,  $NO_2$ ,  $-NR^bR^c$ ,  $-C(O)NR^bR^c$ ,  $-C(NH)NH_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ , sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $C_1-C_3$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_1-C_3$  haloalkyl,  $-CN$ ,  $-C(O)NH_2$ ,  $-COOH$ ,  $-CO_2Et$  and heteroaryl;

$R^b$  and  $R^c$  are independently, at each occurrence, selected from the group consisting of hydrogen,  $C_1-C_{10}$  alkyl,  $C_3-C_{10}$  cycloalkyl,  $C_1-C_6$  alkyl-O-alkyl,  $C_2-C_{10}$  alkenyl,  $C_1-C_4$  alkoxy,  $C_1-C_3$  alkylhydroxyl,  $C_3-C_{10}$  cycloalkenyl,  $C_2-C_{10}$  alkynyl,  $C_1-C_6$  haloalkyl, aryl, e.g. phenyl or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $C_1-C_3$  alkyl,  $C_1-C_4$  alkoxy, halogen,  $C_1-C_6$  haloalkyl,  $C_1-C_6$  haloalkoxy, hydroxyl,  $-C(O)NH_2$ ,  $-COOH$ ,  $-COOMe$ ,  $-COOEt$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ; or

$R^b$  and  $R^c$  are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;

and pharmaceutically acceptable salts thereof.

In a further aspect, the present invention relates to a compound having the general formula III:



Formula III

wherein

n is 0 or 1;

X<sup>1</sup> is CR<sup>5</sup> or N;

Y is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to two C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy group;

R<sup>23</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>27</sup> is selected from the group consisting of hydrogen, -R<sup>6</sup>, and -R<sup>9</sup>-R<sup>10</sup>;

wherein,

R<sup>6</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein said alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>9</sup> is C<sub>1</sub>-C<sub>4</sub> alkylene, wherein said alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>10</sup> is selected from the group consisting of hydroxyl, -OR<sup>11</sup>, -C(O)OR<sup>18</sup>, -C(O)NH<sub>2</sub>, aryl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

$R^{11}$  is independently, at each occurrence selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;  
 $R^{18}$  is hydrogen or  $C_1$ - $C_6$  alkyl;

$R^{28}$  is selected from the group consisting of hydrogen,  $-(V)_pR^{29}$  and  $-(V)_pOR^{14}$  group;

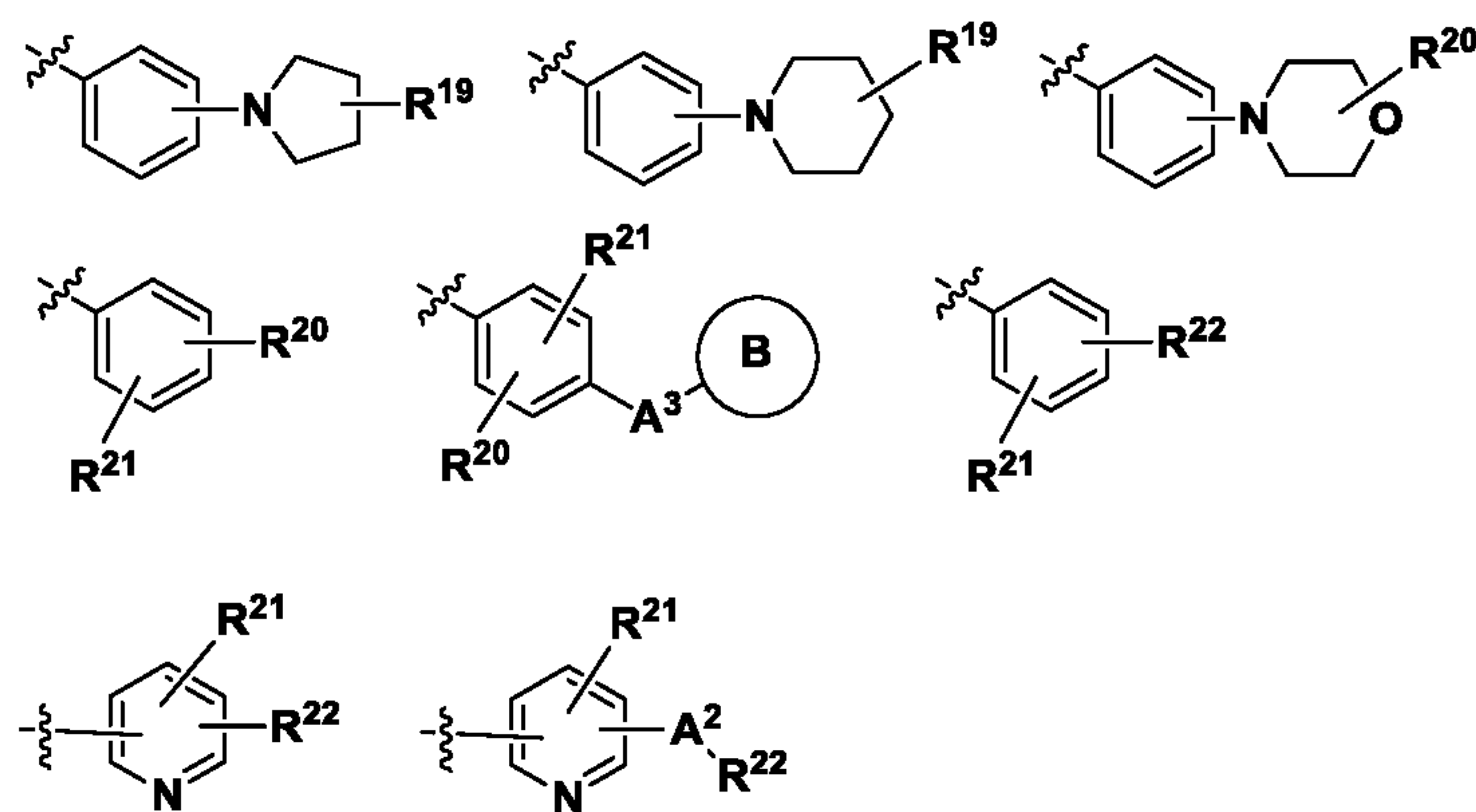
wherein,

$p$  is 0 or 1,

$V$  is  $C_1$ - $C_6$  alkylene, wherein alkylene is optionally substituted with one to three  $C_1$ - $C_6$  alkyl or phenyl groups;

$R^{14}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or  $C_1$ - $C_3$  haloalkoxy groups;

$R^{29}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl and  $C_1$ - $C_3$  haloalkyl, and groups of formula IIIa shown below,



Formula IIIa

wherein,

$A^2$  is  $-O-$  or  $NH-$ ;

$A^3$  is  $-O-$ ,  $-CH_2O-$ ,  $-OCH_2-$ , or  $-NH-$ ;

B is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>19</sup> is selected from the group consisting of hydrogen, -OR<sup>22</sup> and -CH<sub>2</sub>OR<sup>22</sup> ;

R<sup>20</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy and C<sub>1</sub>-C<sub>6</sub> haloalkoxy;

R<sup>21</sup> is selected from the group consisting of hydrogen, halogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>22</sup> is selected from the group consisting of aryl, e.g. phenyl or benzyl, and heteroaryl, wherein said aryl and heteroaryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

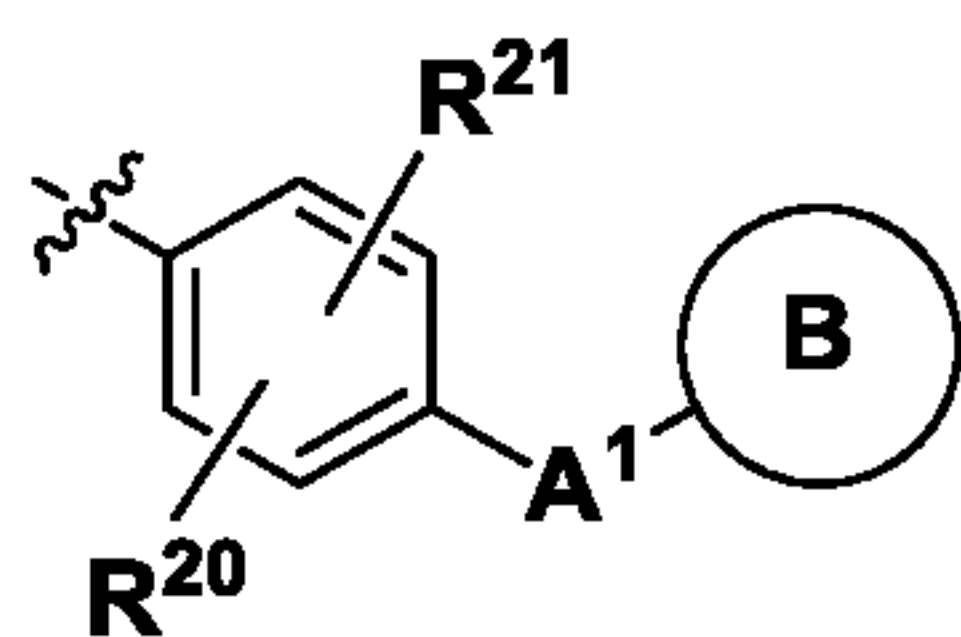
R<sup>a</sup> is independently, at each occurrence, selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, -CH<sub>2</sub>OR<sup>c</sup>, -OCH<sub>2</sub>R<sup>c</sup>, -OR<sup>c</sup>, -CN, NO<sub>2</sub>, -NR<sup>b</sup>R<sup>c</sup>, -C(O)NR<sup>b</sup>R<sup>c</sup>, -C(NH)NH<sub>2</sub>, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>3</sub> haloalkyl, -CN, -C(O)NH<sub>2</sub>, -COOH, -CO<sub>2</sub>Et and heteroaryl;

R<sup>b</sup> and R<sup>c</sup> are independently, at each occurrence, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-O-alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, C<sub>3</sub>-C<sub>10</sub> cycloalkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, aryl, e.g. phenyl or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, -C(O)NH<sub>2</sub>, -COOH, -COOMe, -COOEt, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>; or

$R^b$  and  $R^c$  are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;  
and pharmaceutically acceptable salts thereof.

In one embodiment, the compound according to the present invention has one of the formulae 1- 556, as shown in tables 1-6 and/or example 7 and/or table 7, or a pharmaceutically acceptable salt thereof, preferably having one of the formulae 1-12, 14-16, 19-21, 24, 28-34, 36-40, 44, 48, 51-54, 56-68, 70, 71, 73-77, 79-81, 84, 86-173, 175-192, 194-234, 236-241, 243, 244, 246-261, 263-278, 280-321, 323-354, 356-385, 387- 428, 430-440, 442-446, 449-463, 465-471, 473-487, 489-492, 495-496, 499, 501, 503, 505, 507, 509, 512-514, 525, 529-544, 546-556 as indicated in Tables 1 and 7, or formula 14 as indicated in Tables 2 and 7, or one of the formulae 53, 54, 86, 90, 91, 95, 99, 103, 226 as indicated in Tables 5 - 7; or one of the formulae 14, 17, 24, 29, 30, 32, 33, 38, 43-46, 48, 49, 51-60, 62, 65-70, 73, 74, 79-81, 84, 86-88, 90-107, 109-113, 116, 118-132, 134-138, 140, 145, 147-150, 152, 153, 155, 160-162, 164-166, 168, 169, 172, 175-177, 179, 180, 184-187, 190-197, 199, 200, 202-220, 223, 224, 226, 227, 229-231, 233-236, 238-255, 257-262, 264, 265, 267-302, 304-306, 313, 316, 322-333, 335, 340, 342, 346, 347, 349, 350, 352, 353, 357-359, 361, 365-369, 372-375, 377-380, 382-384, 387, 389-393, 395-403, 405-407, 410, 412-415, 419-428, 430-432, 434-437, 440, 442, 445-453, 455, 457-458, 460-461, 463-482, 486-487, 489-496, 499, 501-553, 556 as indicated in Tables 3 and 7, or one of the formulae, 11, 12, 14, 24, 30, 32, 48, 52-54, 62, 65, 77, 79-81, 86-88, 92, 94, 97, 98, 101-103, 106, 109-111, 113, 119, 120, 122, 123, 125, 130, 136-138, 145, 147, 149, 155, 165, 166, 176, 177, 184, 193, 195, 199, 204, 211, 226, 227, 229, 231, 233, 234, 238, 239, 243, 249, 251, 253, 256, 268-271, 275, 277, 279, 281, 284, 288, 289, 296, 306, 311, 324, 328, 336, 341, 345, 350, 351, 358, 360, 362, 367-369, 373, 374, 378, 381, 392, 412-415, 430, 431, 433, 447-450, 461, 464-466, 468-471, 473-477, 479, 481, 482, 486, 487, 489-496, 498, 499, 501-506, 508, 509, 512-514, 516-519, 525-538, 540-547, 550, 553-554 as indicated in Tables 4 and 7; or having the formula 211 as indicated in Figure 1 and Table 7; or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound having the formula I,  $R^4$  is  $-N(R^{12})(V)_pR^{13}$ ,  $R^{12}$  is H, V is  $C_1$ -alkylene, p is 1,  $R^{13}$  is



and B is heteroaryl which is optionally substituted with one to four  $R^a$  groups.

In one embodiment of the compound having formula I,  $R^1$  is  $-NH_2$  or  $-NHR^6$ ,  $R^6$  is heteroaryl or heterocyclyl wherein each of said heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups.

In a further aspect, the present invention relates to a compound, as defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with the 5LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said disease being selected from inflammatory diseases, e.g. asthma, atherosclerosis, pain, or COPD, cancer, stroke and Alzheimer's disease.

In one embodiment, said compound has an inhibitory activity on an enzyme involved in an inflammatory pathway or several inflammatory pathways, e.g. the arachidonate 5-lipoxygenase pathway and/or the prostaglandin E synthase pathway, preferably on arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5), at a concentration of said compound between 0.001-50  $\mu M$ , particularly preferably having an  $IC_{50}$  on arachidonate 5-lipoxygenase of less than 1  $\mu M$  and/or having an  $EC_{50}$  of less than 10  $\mu M$  on the production of leukotriene B4 (LTB4) in rat basophilic leucocyte cells (RBL) and/or rat whole blood (RWB), and/or having a 40-70 % inhibitory activity, preferably  $>70$  % inhibitory activity on the production of prostaglandin E2 in HeLaS3 cells, stimulated with  $TNF-\alpha$ , at a concentration of 10  $\mu M$  of said compound.

The present invention also relates to a composition comprising a compound or a pharmaceutically acceptable salt thereof, as defined above and a pharmaceutically acceptable carrier.

The present invention also relates to such composition for use in the treatment of a disease associated with the 5LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said

disease being selected from inflammatory diseases, e.g. asthma, atherosclerosis, pain, or COPD, cancer, stroke and Alzheimer's disease.

In one embodiment, said inflammatory disease is one or several of asthma, allergic rhinitis, dermatitis, chronic obstructive pulmonary disease (COPD), inflammation post infection, arthritis, atherosclerosis, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, or pain, e.g. inflammatory and/or neuropathic pain.

In one embodiment, said treatment comprises administering a suitable amount of a compound as defined in any of claims 1-6 , or of a composition as defined in claim 9 , to a patient in need thereof, suffering from an inflammatory disease, and/or of cancer, and/or of stroke, and/or of Alzheimer's disease.

The present invention also relates to a method of treatment of a disease associated with the 5-LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said disease being selected from inflammatory diseases, cancer and Alzheimer's disease, said method comprising the application of a suitable amount of a compound as defined above or of a composition as defined above, to a patient in need thereof, suffering from a disease associated with the 5-LOX-pathway and/or the prostaglandin E synthase (PGES) pathway.

In one embodiment, said inflammatory disease is selected from asthma, allergic rhinitis, dermatitis, chronic obstructive pulmonary disease (COPD), inflammation post infection, arthritis, atherosclerosis, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, and pain, e.g. inflammatory and/or neuropathic pain.

In one embodiment, said suitable amount is an amount in the range of 0.01mg/kg body weight to 1g/kg body weight of said patient.

The present invention also relates to a compound that competitively inhibits the specific binding of a compound as defined above to arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5) or to prostaglandin E synthase (PGES). Such competitively inhibiting

compound is herein also sometimes referred to as “competitive compound” or “competitively inhibiting compound”.

The present invention also relates to a method of treatment of an inflammatory disease, in particular asthma, atherosclerosis, pain, chronic obstructive pulmonary disease (COPD), inflammation post infection, allergic rhinitis, arthritis, pain, e.g. inflammatory or neuropathic pain, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn’s disease, celiac disease, acne, and/or dermatitis, or a method of treatment of cancer/and or of Alzheimer’s disease, said method comprising the application of a suitable amount of a competitively inhibiting compound as defined above, to a patient in need thereof.

In one embodiment, said patient is a patient suffering from an inflammatory disease and/or from cancer and/or from stroke and/or from Alzheimer’s disease.

In one aspect, the present invention also relates to the use of a compound according to the present invention or of a composition according to the present invention for the manufacture of a medicament for the treatment of a disease associated with the 5LOX-pathway or the prostaglandin E synthase (PGES) pathway said disease being selected from inflammatory diseases, e. g. asthma, atherosclerosis, pain or COPD, cancer, stroke and Alzheimer’s disease, wherein preferably, said inflammatory disease, in particular, is selected from asthma, atherosclerosis, pain, chronic obstructive pulmonary disease (COPD), inflammation post infection, allergic rhinitis, arthritis, pain, e. g. inflammatory or neuropathic pain, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn’s disease, celiac disease, acne, and / or dermatitis, wherein said treatment comprises the application of a suitable amount of a compound or a composition according to the present invention or composition according to the present invention, as defined above, to a patient in need thereof. The compound and the composition according to the present invention is either a compound according to the formula I, II or III, in particular, a compound according to any of claims 1 – 6, or it is a compound that is a competitive compound or competitively inhibiting compound, as defined further above.

The term “substituted” as used herein, for example as in “optionally substituted”, is meant to indicate that a hydrogen atom attached to a member atom within a group is (“optionally”) replaced by a group, such as halogen including fluorine, chlorine, bromine, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>haloalkyl, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, oxo, -OH, -OR<sup>23</sup>, -OC(O)R<sup>23</sup>, -CN, NO<sub>2</sub>, -N(R<sup>23</sup>)<sub>2</sub>, -N(R<sup>23</sup>)C(O)R<sup>23</sup>, -R<sup>23</sup>N(R<sup>23</sup>)C(O)R<sup>23</sup>, -C(O)R<sup>23</sup>, -R<sup>23</sup>C(O)R<sup>23</sup>, -C(O)OR<sup>23</sup>, -R<sup>23</sup>C(O)OR<sup>23</sup>, -C(O)N(R<sup>23</sup>)<sub>2</sub>, -R<sup>23</sup>C(O)N(R<sup>23</sup>)<sub>2</sub>, -S(O)R<sup>23</sup>, -S(O)<sub>2</sub>R<sup>23</sup>, -S(O)<sub>2</sub>N(R<sup>23</sup>)<sub>2</sub>, phenyl, benzyl, aryl, heteroaryl or heterocyclyl, any of which itself is “optionally substituted”; it should be noted that the term “substituted” as used herein may also refer to several such substitutions in the same moiety.

R<sup>23</sup> is, at each occurrence, independently selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, hydroxyl, oxo, -OR<sup>24</sup>, -C(O)OR<sup>24</sup>, -C(O)R<sup>24</sup>, -C(O)N(R<sup>24</sup>)<sub>2</sub>, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, -N(R<sup>24</sup>)<sub>2</sub>, -OR<sup>24</sup>HetA, -OR<sup>24</sup>N(R<sup>24</sup>)<sub>2</sub>, -C(O)N(R<sup>24</sup>)HetA, -C(O)HetA, -C(O)N(R<sup>24</sup>)R<sup>24</sup>S(O)<sub>2</sub>R<sup>24</sup>; -S(O)<sub>2</sub>N(R<sup>24</sup>)<sub>2</sub>, -S(O)<sub>2</sub>R<sup>24</sup>, -N(R<sup>24</sup>)C(O)R<sup>24</sup>SR<sup>24</sup>, -N(R<sup>24</sup>)R<sup>24</sup>S(O)<sub>2</sub>R<sup>24</sup>, or -N(R<sup>24</sup>)S(O)<sub>2</sub>R<sup>24</sup>, aryl, e.g. phenyl, benzyl, heteroaryl, and heterocyclyl, any of which is optionally substituted.

R<sup>24</sup> is, at each occurrence, independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl optionally substituted with at least one hydroxyl or halogen; C<sub>3</sub>-C<sub>7</sub>cycloalkyl, aryl, e.g. phenyl, benzyl, and heterocyclyl, any of which is optionally substituted.

In one embodiment, the present invention also relates to pharmaceutically acceptable salts of the compounds according to the present invention, and to such pharmaceutically acceptable salts for use in the treatment of an inflammatory disease and/or of cancer and/or of stroke and/or of Alzheimer's disease.

The term “alkyl” refers to a monovalent straight or branched chain, saturated aliphatic hydrocarbon radical having a number of carbon atoms in the specified range any of which is optionally substituted. Thus, for example, “C<sub>1</sub>-C<sub>6</sub> alkyl” refers to any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec-, and t-butyl, n- and isopropyl, ethyl and methyl, any of which is optionally substituted.

The term “alkoxy” means a group having the formula -O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an

alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C<sub>1</sub>-C<sub>20</sub>alkoxy), 1 to 12 carbon atoms (*i.e.*, C<sub>1</sub>-C<sub>12</sub>alkoxy), or 1 to 6 carbon atoms (*i.e.*, C<sub>1</sub>-C<sub>6</sub>alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH<sub>3</sub> or OMe), ethoxy (-OCH<sub>2</sub>CH<sub>3</sub> or -OEt), *t*-butoxy (-O-C(CH<sub>3</sub>)<sub>3</sub> or -OtBu) and the like. Such alkoxy group may itself be substituted once or several times.

The term “alkenyl” refers to a monovalent straight or branched chain aliphatic hydrocarbon radical containing one carbon-carbon double bond and having a number of carbon atoms in the specified range (and being optionally substituted). Thus, for example, “C<sub>2</sub>-C<sub>6</sub>alkenyl” refers to all of the hexenyl and pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl).

The term “alkynyl” refers to a monovalent straight or branched chain aliphatic hydrocarbon radical containing one carbon-carbon triple bond and having a number of carbon atoms in the specified range. Thus, for example, “C<sub>2</sub>-C<sub>6</sub>alkynyl” refers to all of the hexynyl and pentynyl isomers as well as 1-butyne, 2-butyne, 3-butyne, 1-propyne, 2-propyne, and ethynyl.

The term “alkylene” refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (-CH<sub>2</sub>-), 1,1-ethyl (-CH(CH<sub>3</sub>)-), 1,2-ethyl (-CH<sub>2</sub>CH<sub>2</sub>-), 1,1-propyl (-CH(CH<sub>2</sub>CH<sub>3</sub>)-), 1,2-propyl (-CH<sub>2</sub>CH(CH<sub>3</sub>)-), 1,3-propyl (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), 1,4-butyl (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), and the like.

The term “alkenylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethenyl (-CH=CH-).

The term “alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of parent alkyne. For example,

an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene ( $-\text{C}\equiv\text{C}-$ ), propargyl ( $-\text{CH}_2\text{C}\equiv\text{C}-$ ), and 4-pentynyl ( $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}-$ ).

The term “cycloalkyl”, alone or in combination with any other term, refers to a group, such as optionally substituted or non-substituted cyclic hydrocarbon, having from three to eight carbon atoms, unless otherwise defined. Thus, for example, “ $\text{C}_3\text{-C}_8$ cycloalkyl” refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term “haloalkyl” refers to an alkyl group, as defined herein that is substituted with at least one halogen. Examples of straight or branched chained “haloalkyl” groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, and *t*-butyl substituted independently with one or more halogens. The term “haloalkyl” should be interpreted to include such substituents such as  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-F}$ ,  $-\text{CH}_2\text{-CF}_3$ , and the like.

The term “heteroalkyl” refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of alkyl group which is attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (*e.g.*,  $-\text{OCH}_3$ , etc.), an amine (*e.g.*,  $-\text{NHCH}_3$ ,  $-\text{N}(\text{CH}_3)_2$ , etc.), or thioalkyl group (*e.g.*,  $-\text{SCH}_3$ , etc.). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (*e.g.*, O, N, or S) and the resulting heteroalkyl groups are, respectively, an alkyl ether (*e.g.*,  $-\text{CH}_2\text{CH}_2\text{-O-CH}_3$ , etc.), alkyl amine (*e.g.*,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{CH}_2\text{N}(\text{CH}_3)_2$ , etc.), or thioalkyl ether (*e.g.*,  $-\text{CH}_2\text{-S-CH}_3$ ).

The term “halogen” refers to fluorine, chlorine, bromine, or iodine.

The term “aryl” refers to (i) optionally substituted phenyl, (ii) optionally substituted 9- or 10 membered bicyclic, fused carbocyclic ring systems in which at least one ring is aromatic, and (iii) optionally substituted 11- to 14-membered tricyclic, fused carbocyclic ring systems in which at least one ring is aromatic. Suitable aryls include, for example, phenyl, biphenyl, naphthyl, tetrahydronaphthyl (tetralinyl), indenyl, anthracenyl, and fluorenyl.

The term “phenyl” as used herein is meant to indicate that optionally substituted or non-substituted phenyl group.

The term “benzyl” as used herein is meant to indicate that optionally substituted or non-substituted benzyl group.

The term “heteroaryl” (herein sometimes also abbreviated as “HetA”) refers to (i) optionally substituted 5- and 6-membered heteroaromatic rings and (ii) optionally substituted 9- and 10-membered bicyclic, fused ring systems in which at least one ring is aromatic, wherein the heteroaromatic ring or the bicyclic, fused ring system contains from 1 to 4 heteroatoms independently selected from N, O, and S, where each N is optionally in the form of an oxide and each S in a ring which is not aromatic is optionally S(O) or S(O)<sub>2</sub>. Suitable 5- and 6-membered heteroaromatic rings include, for example, pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Suitable 9- and 10-membered heterobicyclic, fused ring systems include, for example, benzofuranyl, indolyl, indazolyl, naphthyridinyl, isobenzofuranyl, benzopiperidinyl, benzisoxazolyl, benzoxazolyl, chromenyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, isoindolyl, benzodioxolyl, benzofuranyl, imidazo[1,2-a]pyridinyl, benzotriazolyl, dihydroindolyl, dihydroisoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, 2,3-dihydrobenzofuranyl, and 2,3-dihydrobenzo-1,4-dioxinyl.

The term “heterocyclyl” refers to (i) optionally substituted 4- to 8-membered, saturated and unsaturated but non-aromatic monocyclic rings containing at least one carbon atom and from 1 to 4 heteroatoms, (ii) optionally substituted bicyclic ring systems containing from 1 to 6 heteroatoms, and (iii) optionally substituted tricyclic ring systems, wherein each ring in (ii) or (iii) is independent of fused to, or bridged with the other ring or rings and each ring is saturated or unsaturated but nonaromatic, and wherein each heteroatom in (i), (ii), and (iii) is independently selected from N, O, and S, wherein each N is optionally in the form of an oxide and each S is optionally oxidized to S(O) or S(O)<sub>2</sub>. Suitable 4- to 8-membered saturated heterocyclyls include, for example, azetidiny, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrrolidinyl, imidazolidinyl,

piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, azepanyl, diazepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, dioxanyl, and azacyclooctyl. Suitable unsaturated heterocyclic rings include those corresponding to the saturated heterocyclic rings listed in the above sentence in which a single bond is replaced with a double bond. It is understood that the specific rings and ring systems suitable for use in the present invention are not limited to those listed in this and the preceding paragraphs. These rings and ring systems are merely representative.

In one embodiment, said compound has an inhibitory activity on an enzyme involved in an inflammatory pathway(s), preferably an arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox 5), at a concentration of said compound between 0.001-50  $\mu\text{M}$ , particularly preferably having an  $\text{IC}_{50}$  on arachidonate 5-lipoxygenase of less than 1  $\mu\text{M}$  and/or having an  $\text{EC}_{50}$  of less than 10  $\mu\text{M}$  on the production of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in rat basophilic leukocyte cells (RBL) or rat whole blood (RWB).

The term “5-LOX-Pathway” is meant to refer to the pathway starting from arachidonic acid to LTA<sub>4</sub>, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub> and 5-oxoETE (5-oxo-6,8,11,14-eicosatetraenoic acid). The 5-LOX-pathway involves one or several of the enzymes arachidonate-5-lipoxygenase (5-LOX), LTA<sub>4</sub>-hydrolase, LTC<sub>4</sub>-synthase, glutamyltranspeptidase, and 5-hydroxy-6,8,11,14-eicosatetraenoic acid dehydrogenase. In this 5-LOX-pathway one or several enzymes may malfunction and lead to a pathology which, in many instances, manifests itself in a disease or disease state. Such malfunctioning of an enzyme may be a deviation of activity as compared to the normal healthy state (which is not affected by such pathology). Such deviation may be an excess activity of the respective enzyme, or it may be an activity that is below the normal activity of such enzyme in a healthy individual. A “disease associated with the 5-LOX-pathway” may be a disease wherein one or several of the above mentioned enzymes show an excess activity. Preferably, it is the 5-lipoxygenase (5-LOX), which shows a deviant activity, preferably an excess activity in comparison to a healthy, non-pathological state. In one embodiment, the 5-lipoxygenase (5-LOX) is the only enzyme of the 5-LOX-pathway showing a decreased activity. In another embodiment, other enzyme(s) alone or in addition to the 5-lipoxygenase show decreased or increased activity as well. A person skilled in the art knows how to determine whether or not one or several enzymes of the 5-LOX-pathway show a deviant activity. For example this can be easily determined by measurement of one or several

leukotrienes which are reaction products of the respective reactions within the 5-LOX-pathway. Measurement of these leukotrienes, for example one or several of LTA<sub>4</sub>, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, 5-HpETE, 5-HETE and 5-oxo-ETE, may be performed in an appropriate body fluid of a patient, such as blood, nasal secretions, bronchial secretions, urine, semen, spinal fluid, lymph, interstitial fluid, mucosal fluid, fluid extracted from cells or a cell homogenate, vaginal fluid, tears, synovial fluid, sweat, pus, pleural fluid, peritoneal fluid, pericardial fluid, mucus, chyle, breast milk, cerebrospinal fluid, serum, and amniotic fluid. Measurement of such leukotrienes may be done by various means, such as chromatography alone or coupled with mass spectrometry, for example as published by Knapp et al. (N. Engl. J. Med. 1989; 320:1037-1043), Knapp, Prostaglandins 1990; 39:407-423; and Reilly et al. J. Clin. Pathol. 1988; 41:1163-1167; reverse phase-HPLC (Antonelli et al.) Intensive Care Med. 1989; 15(5):296-301, HPLC, as published by Otila et al. Acta Derm. Venereol. 1986; 66(5):381-385, ELISA-Technology, as for example commercially available in the form of a kit for leukotrienes from Oxford Biomedical Research or from Assay Designs Inc., or from Cayman (cat no. 520111), as for example published by Chu et al., American Journal of Pathology, 2011, Volume 178, No. 4, pp. 1762-1769, or by Tardif et al. Circ. Cardiovasc. Imaging, 2010, 298-307. Hence, methodology for determining the levels of leukotrienes and other reaction products/intermediates of the 5-LOX-pathway are available to someone skilled in the art, and hence, a person skilled in the art can easily determine whether or not a disease is associated with the 5-LOX-pathway by determining whether or not the activity of one or several of the enzymes from the 5-LOX-pathway show a deviant activity when compared to the normal/healthy state.

The term “PGES-pathway” is meant to refer to a pathway involving the production of prostaglandin E. The PGES-pathway involves one or several enzymes, including cyclooxygenase-2 (COX-2) and prostaglandin E synthase (PGES). In this PGES-pathway, one or several enzymes may malfunction and lead to a pathology which, in many instances, manifests itself in a disease or disease state. Such malfunctioning of an enzyme may be a deviation of activity as compared to the normal healthy state (which is not effected by such pathology). Such deviation may be an excess activity of the respective enzyme, or it may be an activity that is below the normal activity of such enzyme in a healthy individual. A “disease associated with the PGES-pathway” may be a disease wherein one or several of the above-mentioned enzyme show a deviant activity. Preferably it is the prostaglandin E

synthase (PGES) which shows a deviant activity, preferably an excess activity in comparison to a healthy-non-pathological state.

In a preferred embodiment, such a “disease associated with the 5-LOX-pathway” or “a disease associated with the PGES-pathway” is a disease selected from inflammatory diseases, cancer, stroke and Alzheimer’s disease. In a preferred embodiment, such disease is associated with an increased level of one or several reaction products or intermediates from the 5-LOX-pathway, such as the above mentioned leukotrienes or 5-HpETE, 5-HETE or 5-oxo-ETE, or one or several reaction products or intermediates from the PGES-pathway. In one embodiment, the inflammatory disease is a disease selected from inflammatory diseases of the respiratory system, such as asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), sinusitis, bronchitis, hay fever, inflammatory diseases of the skin, such as dermatitis, psoriasis, acne, inflammatory bowel diseases, such as Crohn’s disease, celiac disease, colitis ulcerosa, autoimmune diseases, such as lupus erythematosus arthritis, in particular rheumatoid arthritis, inflammatory diseases of the vascular system, such as atherosclerosis, vasculitis, Wegener granulomatosis, inflammation post infection and pain, e.g. inflammatory or neuropathic pain.

The 5-lipoxygenase pathway has been implicated in various diseases, and 5-lipoxygenase-products/intermediates have been measured for various diseases, as exemplified for atherosclerosis in Tardif et al. *Circ. Cardiovasc. Imaging*, 2010; 3: 298-307; for Alzheimer’s disease in Chu et al. *Am. J. Cathol.* 2011 April; 178(4); 1762-1769; for cancer in Lim et al. *J. Neurooncol.* 2010, May; 97(3); 339-346; for asthma in Berger et al. *Int. J. Clin. Pract.*, April 2007, 61, 4, 663-676; for COPD in Cazzola et al. *European Respiratory Journal* 2012; 40(3); 724-741, for allergic rhinitis in Knapp N. *Engl. J. Med.* 1990; 323; 1745-1748, for atopic dermatitis in Woodmansee et al. *Ann. Allergy Asthma Immunol.* 1999; 83:548-552, for Urticaria in Spector et al. *J. Allergy Clin. Immunol.* 1998; 101(4)572, for chronic nasal polyposis/sinusitis in Ravikumar, *J. Allergy Clin. Immunol.* 2005; 115(2) Supplemental S201; A 801, for arthritis, in Lewis et al., *N. Engl. J. Med.* 1990; 323:645-655, for pain in Noguchi et al. *Biol. Pharm. Bull.* 2011;34(8):1163-1169, for autoimmune diseases in *J. Rheumatol.* 1995 (March); 22(3):462-468, for Crohn’s disease in Lewis et al. *N. Engl. J. Med.* 1990; 323:645-655, for acne in Zouboulis, *Dermatoendocrinology* 2009 May/June; 1(3):188-192.

In one aspect, the present invention relates to compounds for use in the treatment of a disease associated with the 5-LOX-pathway and/or prostaglandin E synthase (PGES), e.g. an inflammatory disease or cancer or Alzheimer's disease, said compound having one of the formulae 1-415, as shown in Tables 1-6 and/or Example 7 and Table 7, preferably having one of the formulae 1-12, 14-16, 19-21, 24, 28-34, 36-40, 44, 48, 51-54, 56-68, 70, 71, 73-77, 79-81, 84, 86-173, 175-192, 194-234, 236-241, 243, 244, 246-261, 263-278, 280-321, 323-354, 356-385, 387-428, 430-440, 442-446, 449-463, 465-471, 473-487, 489-492, 495-496, 499, 501, 503, 505, 507, 509, 512-514, 525, 529-544, 546-556 as indicated in Tables 1 and 7 or formula 14 as indicated in Tables 2 and 7, or one of the formulae 53, 54, 86, 90, 91, 95, 99, 103, 226 as indicated in Tables 5 - 7; or one of the formulae 14, 17, 24, 29, 30, 32, 33, 38, 43-46, 48, 49, 51-60, 62, 65-70, 73, 74, 79-81, 84, 86-88, 90-107, 109-113, 116, 118-132, 134-138, 140, 145, 147-150, 152, 153, 155, 160-162, 164-166, 168, 169, 172, 175-177, 179, 180, 184-187, 190-197, 199, 200, 202-220, 223, 224, 226, 227, 229-231, 233-236, 238-255, 257-262, 264, 265, 267-302, 304-306, 313, 316, 322-333, 335, 340, 342, 346, 347, 349, 350, 352, 353, 357-359, 361, 365-369, 372-375, 377-380, 382-384, 387, 389-393, 395-403, 405-407, 410, 412-415, 419-428, 430-432, 434-437, 440, 442, 445-453, 455, 457-458, 460-461, 463-482, 486-487, 489-496, 499, 501-553, 556 as indicated in Tables 3 and 7, or one of the formulae 11, 12, 14, 24, 30, 32, 48, 52-54, 62, 65, 77, 79-81, 86-88, 92, 94, 97, 98, 101-103, 106, 109-111, 113, 119, 120, 122, 123, 125, 130, 136-138, 145, 147, 149, 155, 165, 166, 176, 177, 184, 193, 195, 199, 204, 211, 226, 227, 229, 231, 233, 234, 238, 239, 243, 249, 251, 253, 256, 268-271, 275, 277, 279, 281, 284, 288, 289, 296, 306, 311, 324, 328, 336, 341, 345, 350, 351, 358, 360, 362, 367-369, 373, 374, 378, 381, 392, 412-415, 430, 431, 433, 447-450, 461, 464-466, 468-471, 473-477, 479, 481, 482, 486, 487, 489-496, 498, 499, 501-506, 508, 509, 512-514, 516-519, 525-538, 540-547, 550, 553-554 as indicated in Tables 4 and 7; or the formula 211 as indicated in Figure 1 and Table 7; or a pharmaceutically acceptable salt thereof.

Preferably, the compounds as defined above have an inhibitory activity on an enzyme involved in an inflammatory pathway(s) e.g. the arachidonate 5-lipoxygenase pathway and/or the prostaglandin E synthase (PGES) pathway, preferably on arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5), at a concentration of said compound between 0.001-50  $\mu$ M, particularly preferably having an  $IC_{50}$  on arachidonate 5-lipoxygenase of less than 1  $\mu$ M and/or having an  $EC_{50}$  of less than 10  $\mu$ M on the production of leukotriene B4 (LTB4) in

rat basophilic leukocyte cells (RBL) or rat whole blood (RWB), and/or having a 40-70 % inhibitory activity, preferably > 70 % inhibitory activity on the production of prostaglandin E2 in HeLa S3 cells stimulated with TNF-alpha, at a concentration of 10 µM of said compound.

In one aspect the present invention relates to a composition comprising a compound according to the present invention and a pharmaceutically acceptable carrier, for use in the treatment of a disease associated with the 5-LOX-pathway and/or the PGES-pathway, said disease being selected from inflammatory disease, e.g. asthma or COPD, cancer, stroke and Alzheimer's disease.

In one embodiment, said inflammatory disease is asthma or allergic rhinitis or dermatitis or chronic obstructive pulmonary disease (COPD) or inflammation post infection or arthritis or atherosclerosis or pain. e.g. inflammatory and/or neuropathic pain.

In one embodiment, said treatment comprises administering a suitable amount of a compound or of a composition as defined above to a patient in need thereof, suffering from a disease associated with the 5-LOX-pathway and/or the PGES-pathway, said disease being selected from inflammatory disease, cancer, stroke and Alzheimer's disease.

In a further aspect the present invention relates to a method of treatment of a disease associated with the 5-LOX-pathway and/or the PGES-pathway, said disease being selected from an inflammatory disease, cancer, stroke and Alzheimer's disease, said method comprising the application of a suitable amount of a compound or composition as defined above to a patient in need thereof. In one embodiment said inflammatory disease is asthma or allergic rhinitis or dermatitis or chronic obstructive pulmonary disease (COPD) or inflammation post infection or arthritis or atherosclerosis or pain, e.g. inflammatory and/or neuropathic pain.

In one embodiment, said suitable amount is an amount in the range of 0.01 mg/kg body weight to 1 g/kg body weight of said patient.

The present invention also relates to the use of a compound or composition according to the present invention, as defined above, for the manufacture of a medicament for the treatment of a disease associated with the 5-LOX-pathway / or the PGES-pathway, said disease being selected from an inflammatory disease, cancer, stroke and Alzheimer's disease, said treatment comprising the application of a suitable amount of a compound or a composition as defined above to a patient in need thereof. The inflammatory disease and the suitable amount is as defined further above.

In a further aspect the present invention relates to compound that competitively inhibits the specific binding of a compound according to the present invention as defined above to arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5) and/or the prostaglandin E synthase (PGES).

In yet a further aspect the present invention relates to method of treatment of a disease associated with the 5-LOX-pathway and/or the PGES-pathway, said disease being selected from an inflammatory disease, in particular asthma, atherosclerosis, pain, COPD, inflammation post infection, allergic rhinitis and/or atopic dermatitis or cancer or stroke or Alzheimer's disease, said method comprising the application of a suitable amount of a compound as just defined, i.e. a compound that competitively inhibits the specific binding of a compound according to the present invention to arachidonate 5-lipoxygenase or to prostaglandin E synthase, to a patient in need thereof.

Such compound that competitively inhibits the specific binding of a compound according to the present invention to 5-LOX or to PGES, is herein also sometimes referred to as a "competitively inhibitory compound".

In one embodiment, such patient is a patient suffering from an inflammatory disease, preferably as defined further above.

The present invention also relates to the use of a competitively inhibitory compound for the manufacturer of a medicament for the treatment of a disease associated with the 5-LOX-pathway or the PGES-pathway, said disease being selected from an inflammatory disease, in particular, asthma, atherosclerosis, pain or COPD, inflammation post-infection, allergic

rhinitis and/or arthritis, or cancer or stroke or Alzheimer's disease, said treatment comprising the application of a suitable amount of a compound that competitively inhibits the specific binding as defined above, to a patient in need thereof.

The terms "IC<sub>50</sub>" and "EC<sub>50</sub>" refer to the half-maximal inhibitory concentration and the half-maximal effective concentration, respectively, of a compound with respect to a given activity, for example an inhibition of an enzyme through a compound, or the production of a substance stimulated by a compound. One example of an IC<sub>50</sub> is the half-maximum inhibitory concentration of a compound on the activity of arachidonate 5-lipoxygenase. One example for an EC<sub>50</sub>-value is the half maximum effective concentration of a compound on the production and/or secretion of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in a cell or whole blood, for example a rat basophilic leukocyte cell (RBL) or rat whole blood (RWB).

#### Pharmaceutical compositions

#### Pharmaceutically acceptable salts

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzenesulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enanthate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the nitrate derived from nitric acid, the oxalate derived from oxalic acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate

derived from sulphuric acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt, for use in the treatment of an inflammatory disease.

In another embodiment, the compounds of the invention are used in their respective free base form, for use in the treatment of an inflammatory disease, according to the present invention.

Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compounds of the invention may be provided in unsolvated or solvated forms together with a pharmaceutically acceptable solvent(s) such as water, ethanol, and the like. Solvated forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, solvated forms are considered equivalent to unsolvated forms for the purposes of this invention.

#### Administration and Formulation

The production of medicaments containing the compounds of the invention, its active metabolites or isomers and salts according to the invention and their application can be performed according to well-known pharmaceutical methods.

While the compounds of the invention, useable according to the invention for use in therapy, may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries. Such salts of the compounds of the invention may be anhydrous or solvated.

In a preferred embodiment, the invention provides medicaments comprising a compound useable according to the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

A medicament of the invention may be those suitable for oral, rectal, bronchial, nasal, topical, buccal, sub-lingual, transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intra-arterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The compounds useable according to the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of medicament and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such medicament and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The compounds useable according to the invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound(s) useable according to the invention or a pharmaceutically acceptable salt of a compound(s) useable according to the invention.

For preparing a medicament from a compound useable according to the invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify. Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate. Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion 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 formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

In one embodiment of the present invention, the medicament is applied topically or systemically or via a combination of the two routes.

For administration, the compounds of the present invention may, in one embodiment, be administered in a formulation containing 0,001% to 70% per weight of the compound, preferably between 0,01% to 70% per weight of the compound, even more preferred between 0,1% and 70% per weight of the compound. In one embodiment, a suitable amount of compound administered is in the range of 0.01 mg/kg body weight to 1 g/kg body weight.

Compositions suitable for administration also include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerol or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it

can be the appropriate number of any of these in packaged form. Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co. Easton, Pa.) and Remington: The science and practice of pharmacy", Lippincott Williams and Wilkins.

Appropriate formulations and ways of manufacturing them are, for example also disclosed in "Arzneiformenlehre, Paul Heinz List, EinLehrbuchfürPharmazeuten, WissenschaftlicheVerlagsgesellschaft Stuttgart, 4. Auflage, 1985", or "The theory and practice of industrial pharmacy" by Lachman et al., Varghese Publishing House, 1987", or "Modern Pharmaceutics", edited by James Swarbrick, 2. Edition".

## Figures and Tables

Reference is now made to the tables and figures, wherein

**Figure 1** illustrates the anti-inflammatory effect of compound 211 in OVA-induced airway inflammation model in Brown Norway Rats

**Table 1** summarizes 5-LOX IC<sub>50</sub> inhibitory activities (uM) as measured by fluorescence wherein the compound number refers to the compounds listed in Example 7;

**Table 2** summarizes 5-LOX IC<sub>50</sub> inhibitory activities (uM) as detected by ELISA wherein the compound number refers to the compounds listed in Example 7;

**Table 3** summarizes LTB<sub>4</sub> secretion assay (EC<sub>50</sub>, uM) in RBL (rat basophilic leukemia) cells wherein the compound number refers to the compounds listed in Example 7;

**Table 4** summarizes LTB<sub>4</sub> secretion assay (EC<sub>50</sub>, uM) in RWB (rat whole blood) wherein the compound number refers to the compounds listed in Example 7;

**Table 5** summarizes PGE<sub>2</sub> % inhibition at 10 uM as measured by HTRF (Homogeneous Time Resolved Fluorescence) wherein the compound number refers to the compounds listed in Example 7;

**Table 6** summarizes COX-2 (Cyclooxygenase 2) % inhibition at 10 uM as measured by EIA (Enzyme Immunoassay) wherein the compound number refers to the compounds listed in Example 7 and Table 7;

**Table 7** summarizes compounds 1 – 556 the synthesis of which is described in Example 7.

## Examples

The invention is now further described by reference to the following examples which are intended to illustrate, not to limit the scope of the invention.

### Example 1: Activity of compounds against 5-LOX enzyme

The activity of compounds against 5-LOX were determined by measuring LTB<sub>4</sub> (leukotriene B<sub>4</sub>) levels and/or by a fluorescence method. Both approaches are outlined in more detail below;

#### LTB<sub>4</sub> Measurement by ELISA:

Human 5-lipoxygenase (5-LOX) (Cayman, Cat#60402) produced in insect cells was pre-incubated with compounds for 5min at RT in incubation buffer (50mM Tris-Cl, pH 7.4, 2mM CaCl<sub>2</sub>, 0.1mM ATP, 2% DMSO). Compounds were tested in dose response from 0.5nM to 10uM. The enzymatic reaction was started by adding arachidonic acid to a final concentration of 3uM. After 5min of incubation at 25°C, the reaction was stopped by adding H<sub>2</sub>O<sub>2</sub> to a final concentration of 1mM. LTB<sub>4</sub> levels were quantified using a LTB<sub>4</sub> EIA kit (Cayman, Cat# 520111) as instructed.

#### Fluorescence Method:

Besides the above method for quantifying LTB<sub>4</sub> levels, a fluorescence assay measuring 5-hydroperoxyeicosatetraenoic acid (5- HPETE) was introduced for high-throughput screening in a 384 well microplate format (Pufahl et al., 2007) Development of a Fluorescence-based enzyme assay of human 5-lipoxygenase. ANALYTICAL BIOCHEMISTRY 364, 204–212). For nonspecific ester cleavage of the acetate groups in H<sub>2</sub>DCFDA (2',7'-dichlorodihydrofluorescein diacetate), the insect cell lysate expressing human 5-LOX (Cayman Cat# 60402) was incubated with H<sub>2</sub>DCFDA (50mM Tris-Cl, pH 7.5, 2mM CaCl<sub>2</sub>, 20uM H<sub>2</sub>DCFDA, 600mU 5-LOX per reaction) for 5 minutes. The compound, in a dose response manner (0.5nM to 10uM), and enzyme mixture was pre-incubated for 5 minutes, and the enzymatic reaction was initiated by addition of ATP and arachidonic acid to a final concentration of 100uM and 3uM, respectively. After 5 minutes of incubation, fluorescence

was measured using Spectramax M5 (Molecular Device, Ex/Em=485nm/530nm). All steps were carried out at room temperature.

Example 2: LTB<sub>4</sub> secretion assay in RBL(rat basophilic leukemia cells)

Rat basophilic leukemia (RBL) cells (ATCC, Cat# CRL-2256) were maintained in EMEM (ATCC, Cat# 30-2003) supplemented with 15% FBS. The day before RBL assay, cells were seeded at a concentration of  $2 \times 10^4$  cells per well in 96-well plates. The media was replaced with 100ul of EMEM supplemented with 0.5% FBS and compounds in dose response(5nM to 100uM) were added. After 15min of pre-incubation at 37°C, arachidonic acid and calcium ionophore (A23187) were added to give a final concentration of 2.5uM and 5uM, respectively. After a further 10min incubation at 37°C, culture supernatant was transferred and quantification of LTB<sub>4</sub> was done with a Leukotriene B<sub>4</sub> EIA kit (Cayman, Cat# 520111) as instructed.

Example 3: LTB<sub>4</sub> secretion assay in RWB(rat whole blood)

Rat blood was drawn from caudal vena cava from male Sprague Dawley rat (6-9 weeks old) in vacuette coated with sodium heparin (Greiner bio-one, Cat# 455051). The blood was pooled and diluted with RPMI (WelGENE, Cat# LM 011-05) to 1:1. The diluted blood was aliquoted into 96 well plate (200ul per well) and compounds were added in dose response to a desired concentration ranging from 2.5nM to 50uM.. After 15min of pre-incubation at 37°C, calcium ionophore (A23187) was added to the final concentration of 10uM. After 10min of further incubation at 37°C, the LTB<sub>4</sub> production was stopped by diluting the reaction mixture with ice cold PBS (1:4dilutions). Cells were removed by centrifugation at 1000Xg, 4°C for 10min, and the supernatant was transferred and then the quantification of LTB<sub>4</sub> was done with Leukotriene B<sub>4</sub> EIA kit (Cayman, Cat# 520111) as instructed.

Example 4: Inflammation efficacy in OVA-induced airway inflammation model in Brown Norway Rats

The objective of this study is to determine the efficacy of compounds in the lungs of ovalbumin (OVA) induced in Brown Norway rats. As with most models of induced allergic asthma, animals are systemically sensitized to specific antigens and then, after a period of time, challenged with the same allergen administered via the airway. Ovalbumin had been used as the standard allergen to sensitize and challenge animals in this study.

Thirty (30) male Brown Norway rats were randomized into 5 groups on the basis of body weight. For sensitization, 1% OVA in PBS solution was mixed with alum solution (with volume ratio of 1:9). All rats in groups 1 - 5 were sensitized by i.p injection (1 mL/rat) of 1% OVA-alum sensitization solution on day 1, 2 and 3. At day 21, rats in groups 1 - 5 were challenged with 1% OVA in PBS solution with aerosolizing dosing system for 20 min.

Test compounds were administered by p.o. from days 19-21 of the study as per schedule below:

Group 1: sensitized-vehicle,

Group 2: reference drug dexamethasone, 0.3 mg/kg, p.o., Day 19-21, BID,

Group 3: compound 211, 25 mg/kg, p.o., Day 19-21, BID,

Group 4: compound 211, 50 mg/kg, p.o., Day 19-21, BID,

Group 5: compound 211, 100 mg/kg, p.o., Day 19-21, BID,

On day 22, bronchoalveolar lavage and lung tissues were harvested. Total cell number and differential cell counts in BALF, leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in BALF and lung tissue, histopathology of lung by H&E staining will be evaluated.

The results are shown in figure 1. Treatment of rats using compound 211 significantly reduced the increase of inflammatory cells including total cell and eosinophils, reduced LTB<sub>4</sub> in BALF and Lung, and significantly reduced inflammation cell infiltration. These data indicate that compound 211 shows antiinflammatory activity in OVA-induced asthma.

#### Example 5: PGE<sub>2</sub> inhibition assay

Human epitheloid cervix carcinoma HeLa S3 cells ( $2 \times 10^6$  cells/ml) were seeded with modified F-12K buffer medium pH 7.4 in tissue culture plate and incubated for overnight at  $37^\circ\text{C}$  and 5%  $\text{CO}_2$ . Then medium was changed into new medium contained 10uM testing compounds or 0.1% DMSO and incubated overnight. After incubation, cells were stimulated with 30nM TNF-  $\alpha$  (Tumor necrosis factor-  $\alpha$ ) for 16h. For determination of  $\text{PGE}_2$ , the supernatant was measured by  $\text{PGE}_2$  HTRF (Homogeneous Time Resolved Fluorescence) assay kit. Inhibition of  $\text{PGE}_2$  by compounds is calculated as a percentage of activity in the presence of drug versus the activity in the stimulator TNF- $\alpha$ .

#### Example 6: COX-2 inhibition assay

Human recombinant cyclooxygenase-2 expressed in insect Sf21 cells was used. The testing compounds and reference compound (Rofecoxib) were dissolved in DMSO (Sigma, USA) and tested at 10uM. Test samples were pre-incubated with 0.11 U enzyme in 100 mM modified Tris-HCl buffer pH 7.7 for 15 minutes at  $37^\circ\text{C}$ . The reactions were initiated by addition of 0.3  $\mu\text{M}$  arachidonic acid for another 5-minute incubation period, then terminated by further addition of 1 N HCl. An aliquot was then combined with the EIA kit for spectrophotometric determination of the quantity of  $\text{PGE}_2$  formed. Inhibition % was determined by compared with relative amounts of  $\text{PGE}_2$  induced by arachidonic acid. The results show that the compounds according to the present, as exemplified by compounds (cpds.) 90 and 95, do not have an inhibitory effect on cyclooxygenase-2 (COX-2), thus lending support to the fact that their inhibitory action on the PGES-pathway occurs at the level of "PGES".

#### Example 7: Preparation of Compounds

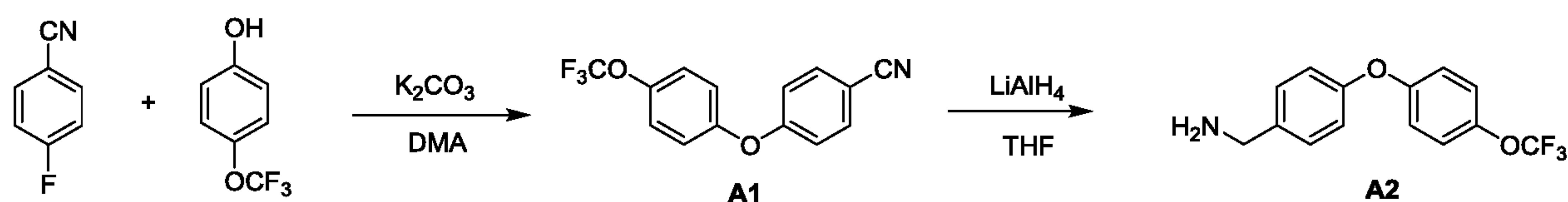
The synthesis of compounds described herein may be accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof.

Compounds described herein may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. In addition, solvents, temperatures and other reaction conditions presented herein may vary according to those of skill in the art. The starting material used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Aldrich Chemical Co. (Milwaukee, Wis.), or

Sigma Chemical Co. (St. Louis, Mo.). The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials described herein as well as those that are known to those of skill in the art. General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein. As a guide the synthetic method of Schemes may be utilized to prepare a compound described herein.

The compounds (scaffold I, II and III; see **Tables 1-7**) underwent derivatization according to the methods outlined below (**Schemes 1-37**), and the synthesized compounds as well as relevant NMR characterization data are shown in Table 7. Resulting derivatives were examined for inhibitory activity ( $IC_{50}$ ,  $EC_{50}$ , *in vivo*) using the assays described above (Examples 1, 2, 3, 4, 5 and 6), and the results are summarized in **Tables 1, 2, 3, 4, 5 and 6 and Figure 1**.

### Scheme 1. General synthesis 1 of an amine compound



#### General procedure for the synthesis of A1

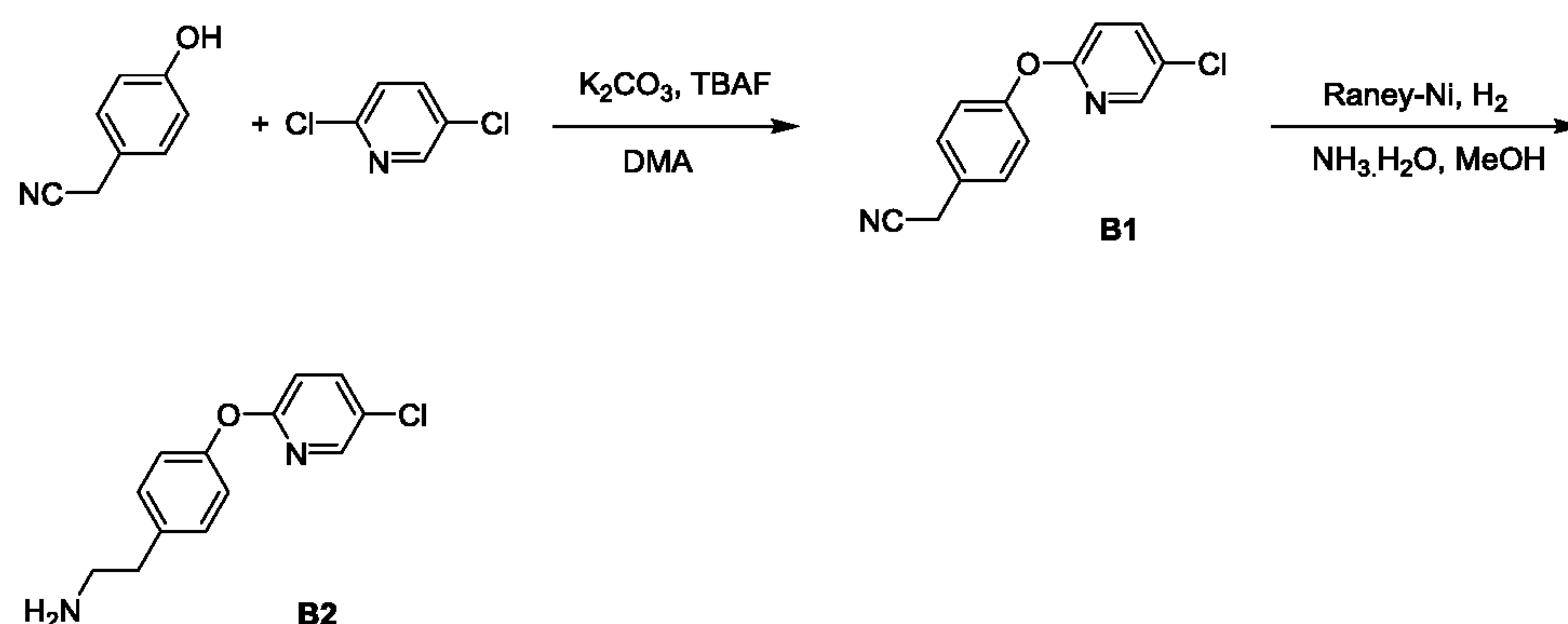
To a stirred solution of 4-fluorobenzonitrile (5.00 g, 41.3 mmol) and 4-trifluoromethoxyphenol (8.10 g, 45.5 mmol) in DMA (30 mL) was added  $K_2CO_3$  (6.30 g, 45.6 mmol). The resulting mixture was stirred at 120 °C for 16 hours. The mixture was cooled to 50 °C and 100 mL water was added dropwise under good stirring. The mixture was extracted with EtOAc (100 mL x 2), the combined organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous  $Na_2SO_4$  and concentrated under reduced pressure to afford **A1**.

#### General procedure for the synthesis of A2

To a stirred solution of **A1** (3.00 g, 10.7 mmol) in anhydrous THF (30 mL) at 0 °C was added  $LiAlH_4$  (1.63 g, 43.0 mmol) in portions, the reaction mixture was stirred at 0 °C for 3 hours, the resulting mixture was stirred at 50 °C for another 16 hours. The mixture was quenched

with water (1.6 mL) dropwise at 0 °C, then followed NaOH (10%, 3.2 mL) dropwise and water (1.6 mL) to the mixture. The mixture was filtered, the filter cake was washed with EtOAc (30 mL) and the filtrate was concentrated under reduced pressure to afford **A2**.

### Scheme 2. General synthesis 2 of an amine compound



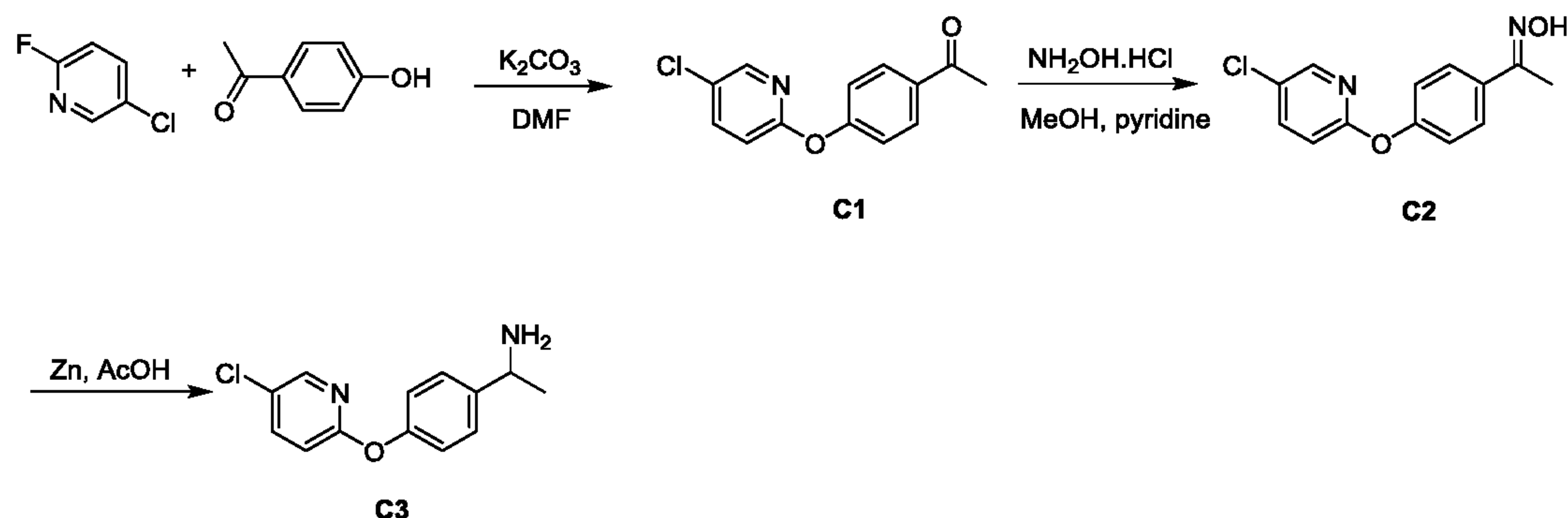
#### General procedure for the synthesis of B1

To a stirred solution of 2-(4-hydroxyphenyl)acetonitrile (10.0 g, 75.2 mmol) in DMA (120 mL) were added 2,5-dichloro pyridine (12.2 g, 82.7 mmol),  $K_2CO_3$  (15.6g, 113 mmol) and TBAF (589 mg, 2.26 mmol), then the mixture was stirred at 115 °C for 16 hours. The reaction mixture was poured into water (600 mL) with vigorous stirring for 1 hour. The precipitate was collected by filtration, dried in air for 2 hours and purified by Combi Flash (PE: EtOAc = 5 : 1 to 2 : 1) to afford **B1**.

#### General procedure for the synthesis of B2

To a stirred solution of **B1** (500 mg, 2.04 mmol) in MeOH (15 mL) were added Raney-Ni (400 mg) and  $NH_3.H_2O$  (0.5 mL, 28%). The reaction solution was stirred at 15 °C under  $H_2$  atmosphere (45 psi) for 6 hours. Then the solution was filtered through a pad of Celite. The filtrate was concentrated and diluted with DCM (30 mL), then dried over anhydrous  $Na_2SO_4$ , evaporated to afford **B2**.

### Scheme 3. General synthesis 3 of an amine compound



### General procedure for the synthesis of C1

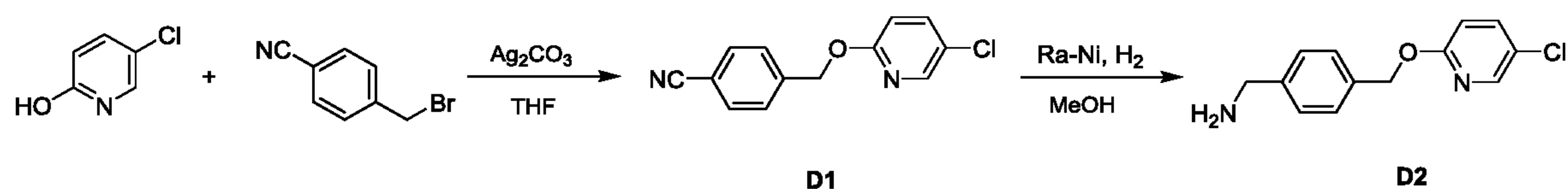
A mixture of 4'-hydroxyacetophenone (5.00 g, 36.7 mmol), 5-chloro-2-fluoropyridine (5.79 g, 44.0 mmol) and  $\text{K}_2\text{CO}_3$  (10.1 g, 73.4 mmol) in DMF (150 mL) was stirred at 100 °C for 6 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (200 mL), then filtered and the filtrate was washed with brine (150 mL  $\times$  3), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford a residue. The residue was washed with PE/ EtOAc = 20/1(40 mL) to afford **C1**.

### General procedure for the synthesis of C2

A mixture of **C1** (4.50 g, 18.2 mmol) and  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (1.26 g, 18.2 mmol) in MeOH/pyridine (25 mL/25 mL) was stirred at 8-10 °C for 16 hours. The resulting mixture was concentrated under reduced pressure, acidified with HCl (2 M, 120 mL), extracted with DCM (50 mL  $\times$  4), the combined organic layer was washed with water (200 mL  $\times$  3), brine (200 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford **C2**.

### General procedure for the synthesis of C3

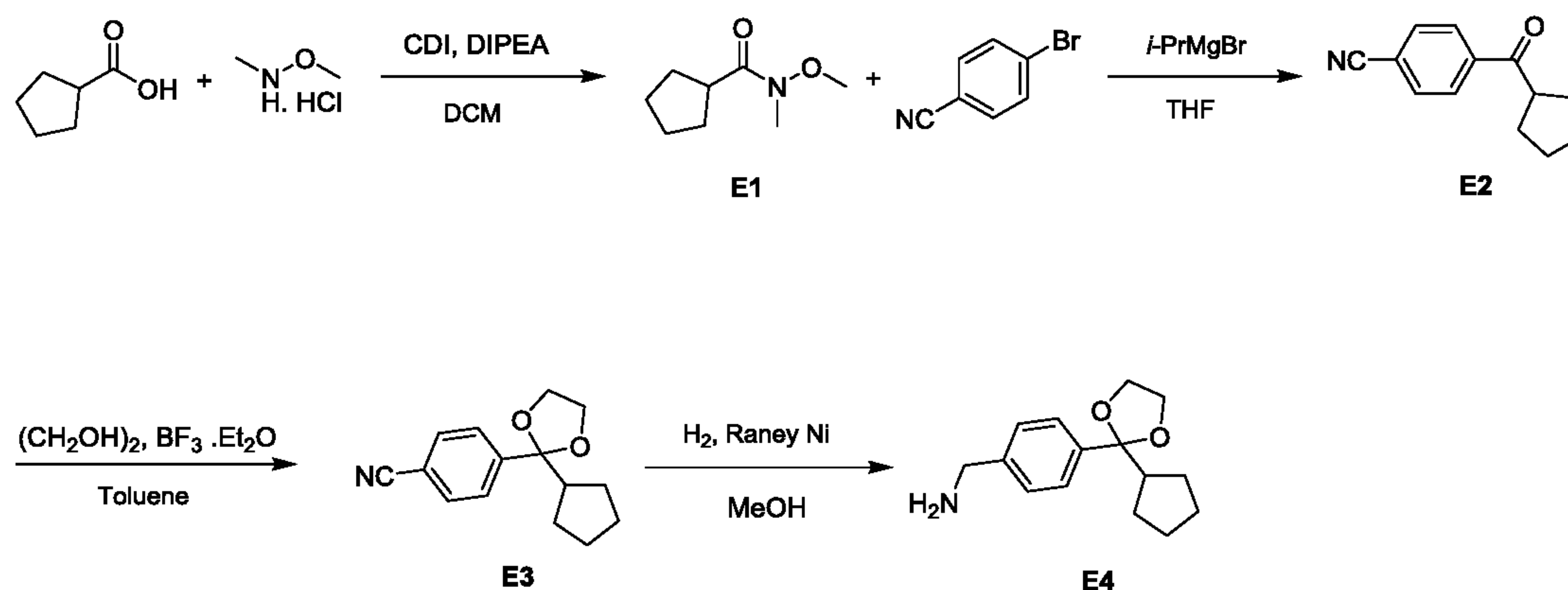
A mixture of **C2** (4.70 g, 17.9 mmol) and Zn powder (11.6 g, 179 mmol) in AcOH (120 mL) was stirred at 65-75 °C for 28 hours. After cooling to room temperature, the reaction mixture was filtered, washed with EtOAc (10 mL  $\times$  3) and the combined filtrate was concentrated under reduced pressure to afford a residue. The residue was diluted with saturated  $\text{NaHCO}_3$  (150 mL), extracted with EtOAc (100 mL  $\times$  3), the combined organic layer was washed with brine (200 mL  $\times$  2), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford **C3**.

**Scheme 4. General synthesis 4 of an amine compound****General procedure for the synthesis of D1**

To a stirred mixture of 5-chloro-2-hydroxypyridine (15.0 g, 76.5 mmol) in anhydrous THF (200 mL) were added 4-cyanobenzyl bromide (8.26 g, 63.8 mmol) and  $\text{Ag}_2\text{CO}_3$  (10.5 g, 38.3 mmol). The resulting mixture was refluxed for 16 hours. The mixture was cooled to room temperature and filtered. The filter cake was washed with THF (100 mL). The combined filtrate was concentrated under reduced pressure to afford a residue, which was purified by combi flash (PE/EtOAc=92/8 to 70/30) to afford **D1**.

**General procedure for the synthesis of D2**

To a stirred solution of **D1** (5.00 g, 2.04 mmol) in MeOH (100 mL) were added Raney-Ni (1.00 g) and  $\text{NH}_3 \cdot \text{H}_2\text{O}$  (0.5 mL, 28%) under  $\text{N}_2$  atmosphere. The suspension was degassed under vacuum and purged with  $\text{H}_2$  for three times. The solution was stirred at 12 °C under  $\text{H}_2$  (45 psi) atmosphere for 2 hours. The mixture was filtered through a pad of celite, and the pad was washed with MeOH (200 mL). The filtrate was concentrated under reduced pressure to afford **D2**.

**Scheme 5. General synthesis 5 of an amine compound****General procedure for the synthesis of E1**

To a stirred solution of cyclopentanecarboxylic acid (5.00 g, 44.2 mmol) in anhydrous DCM

(100 mL) was added CDI (8.10 g, 57.5 mmol) in portions at 28 °C. The reaction solution was stirred at 28 °C for 0.5 hour. Then DIEA (8.00 g, 61.9 mmol) and *N,O*-dimethyl hydroxylamine hydrochloride (5.13 g, 61.9 mmol) were added. The reaction solution was stirred at 28 °C for 16 hours. The reaction solution was diluted with saturated NaHCO<sub>3</sub> (50 mL) and separated. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by Combi Flash (PE: EtOAc= 5: 1 to 2: 1) to afford **E1**.

#### **General procedure for the synthesis of E2**

To a stirred solution of 4-bromobenzonitrile (1.40 g, 7.69 mmol) in anhydrous THF (15 mL) was added *i*-PrMgBr (19.2 mL, 19.2 mmol, 1 M in THF) dropwise at -30 °C under N<sub>2</sub> atmosphere. Then the mixture was stirred at -30 °C under N<sub>2</sub> atmosphere for 30 minutes. A solution of **E1** (1.00 g, 6.37 mmol) in anhydrous THF (5 mL) was added dropwise at -30 °C. The reaction solution was allowed to warm to 30 °C and stirred at 30 °C for 16 hours. The reaction solution was quenched by saturated NH<sub>4</sub>Cl solution (15 mL) at 0 °C. The organic phase was separated, concentrated under reduced pressure. The residue was purified by Combi Flash (PE: EtOAc= 10: 1) to afford **E2**.

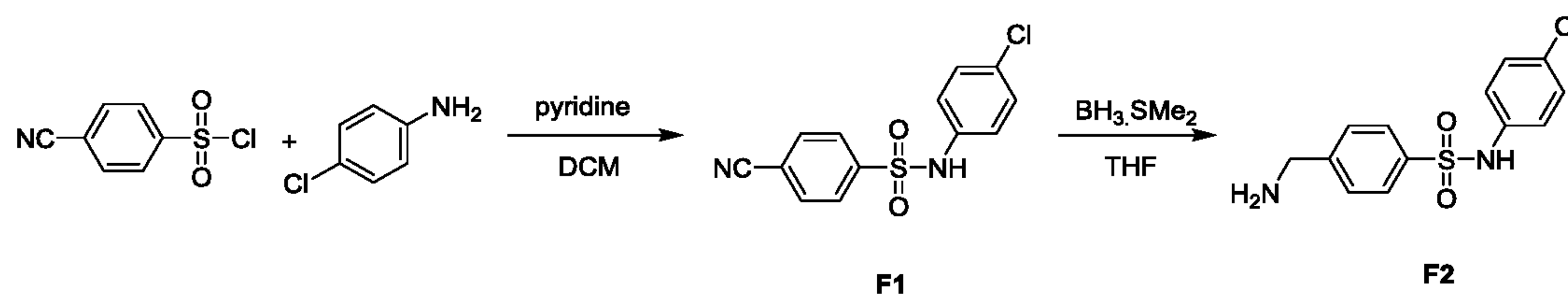
#### **General procedure for the synthesis of E3**

A mixture of **E2** (250 mg, 1.26 mmol), BF<sub>3</sub>·Et<sub>2</sub>O (0.5 mL), ethylene glycol (1 mL) in toluene (50 mL) was refluxed with azeotropic removal of water for 48 hours. The reaction solution was cooled to room temperature and diluted with saturated Na<sub>2</sub>CO<sub>3</sub> (30 mL). The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by prep-TLC (PE: EtOAc= 5: 1) to afford **E3**.

#### **General procedure for the synthesis of E4**

To a stirred solution of **E3** (100 mg, 0.410 mmol) in MeOH (5 mL) were added Raney-Ni (100 mg) and ammonia water (0.5 mL, 28%). The reaction solution was stirred at 25 °C under H<sub>2</sub> atmosphere (45 psi) for 2 hours. Then the solution was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford **E4**.

### **Scheme 6. General synthesis 6 of an amine compound**



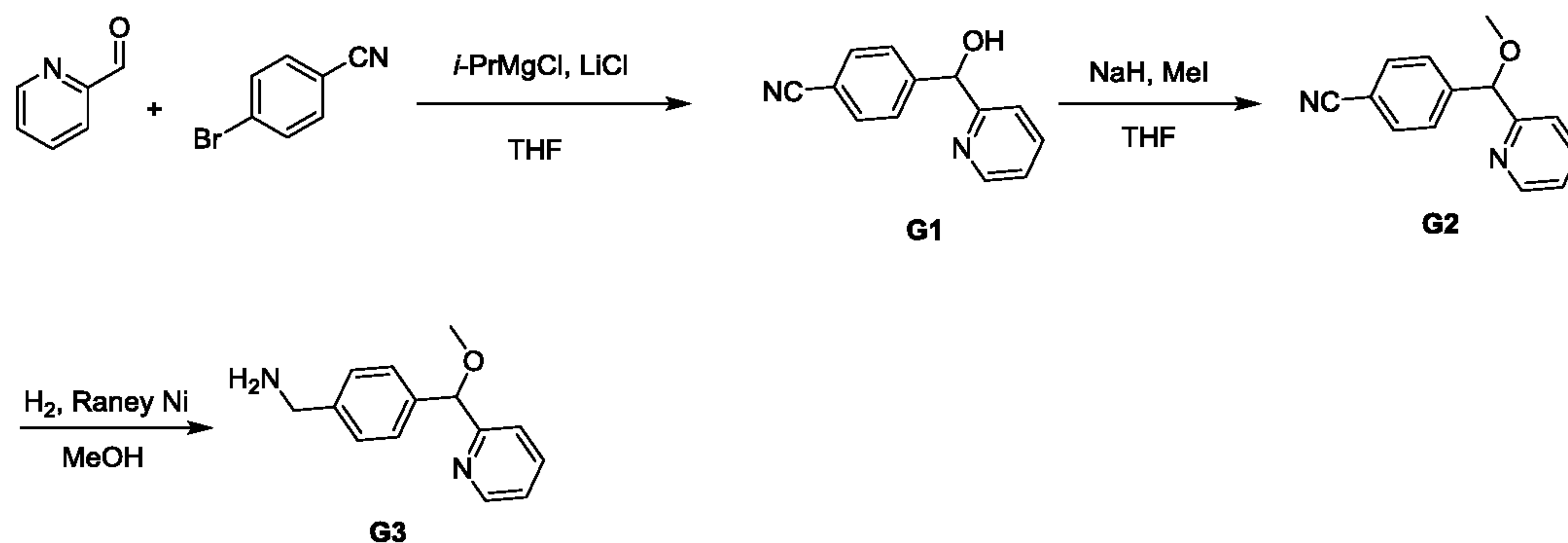
### General procedure for the synthesis of F1

To a stirred solution of 4-chloroaniline (634 mg, 4.96 mmol) and pyridine (1.17 g, 14.9 mmol) in DCM (10 mL) was added a solution of 4-cyanobenzenesulfonyl chloride (1.00 g, 4.96 mmol) in DCM (5 mL) under ice bath, then the mixture was stirred under N<sub>2</sub> atmosphere at 25 °C for 12 hours. The mixture was poured into water (30 mL), extracted with DCM (10 mL × 3). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue, which was purified by flash column chromatography (eluent: DCM) to afford **F1**.

### General procedure for the synthesis of F2

To a stirred solution of **F2** (500 mg, 1.71 mmol) in anhydrous THF (2.5 mL) was added BH<sub>3</sub>/Me<sub>2</sub>S (1.35 mL, 13.5 mmol, 10M) under ice bath, the mixture was stirred under N<sub>2</sub> atmosphere at 25 °C for 12 hours. MeOH (5 mL) was added dropwise carefully to quench the reaction, then the mixture was diluted with water (50 mL), adjusted pH 8 by saturated Na<sub>2</sub>CO<sub>3</sub>, extracted with EtOAc (30 mL × 3). The combined extract was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue, which was purified by Combi Flash (eluent: PE/EtOAc=1/1 to EtOAc) to afford **F2**.

### **Scheme 7. General synthesis 7 of an amine compound**



### General procedure for the synthesis of G1

To a stirred solution of 4-bromobenzonitrile (1.00 g, 5.50 mmol), LiCl (252 mg, 6.00 mmol) in anhydrous THF (10 mL) was added i-PrMgCl (3 mL, 6.0 mmol, 2 M in THF) dropwise at -15 °C under N<sub>2</sub> atmosphere. Then the mixture was stirred at -15 °C under N<sub>2</sub> atmosphere for 2 hours. Then picolinaldehyde (640 mg, 6.00 mmol) was added dropwise at -15 °C. The reaction solution was allowed to warm to 30 °C. TLC showed the reaction was complete. The reaction solution was quenched by saturated NH<sub>4</sub>Cl solution (10 mL) at 0 °C. The organic layer was separated and concentrated under reduced pressure. The residue was purified by Combi Flash (PE: EtOAc= 5: 1 to 2: 1) to afford **G1**.

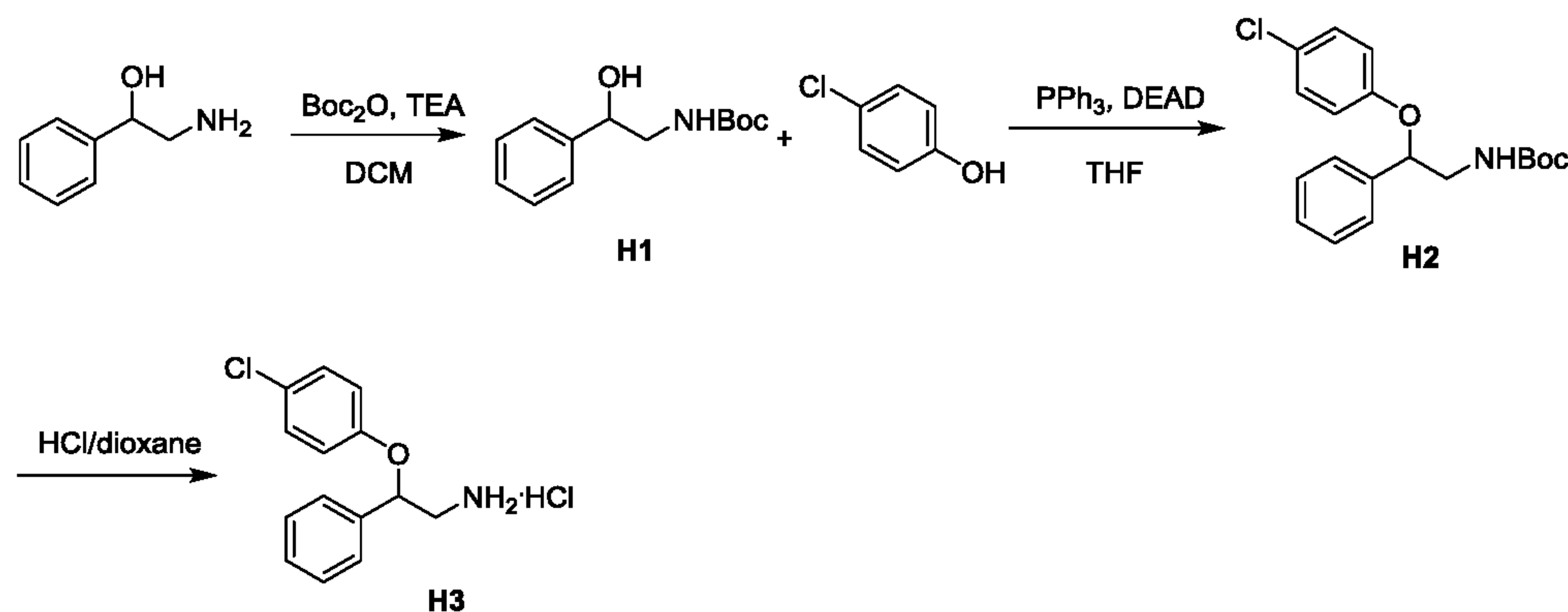
#### **General procedure for the synthesis of G2**

To a stirred solution of **G2** (400 mg, 1.90 mmol) in anhydrous THF (6 mL) was added NaH (298 mg, 2.10 mmol, 60% dispersion in mineral oil) at 0 °C, then the mixture was stirred at 0 °C for 15 minutes. Afterwards, MeI (298 mg, 2.10 mmol) was added to the mixture at 0 °C. The mixture was stirred under N<sub>2</sub> atmosphere at 25 °C for 1 hour. The reaction mixture was poured into water (10 mL), extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by Combi Flash (PE: EtOAc = 5: 1 to 1: 1) to afford **G2**.

#### **General procedure for the synthesis of G3**

To a stirred solution of **G2** (1.50 g, 6.70 mmol) in MeOH (40 mL) were added Raney-Ni (2.0 g) and concentrated ammonia water (4 mL, 28%). The reaction solution was stirred at 25 °C under H<sub>2</sub> atmosphere (45 psi) for 3 hours. Then the solution was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford 1.53 g of residue, which was purified by silica gel column chromatography (DCM: MeOH = 10: 1) to afford **G3**.

### **Scheme 8. General synthesis 8 of an amine compound**



### General procedure for the synthesis of H1

To a stirred solution of 2-amino-1-phenylethanol (5.00 g, 36.4 mmol) and TEA (5.51 g, 54.6 mmol) in DCM (100 mL) was added  $\text{Boc}_2\text{O}$  (9.54 g, 43.7 mmol), then the resulting mixture was stirred at 27-28 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove most of DCM. The residue was diluted with EtOAc (100 mL), then washed with 1% HCl solution (50 mL), brine (50 mL x2), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was washed with PE/EtOAc (50 mL/5 mL) to afford **H1**.

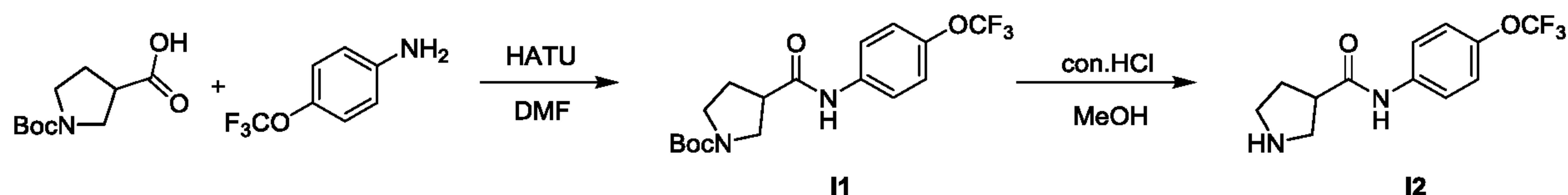
### General procedure for the synthesis of H2

To a stirred solution of **H1** (4.00 g, 16.9 mmol), 4-chlorophenol (4.33 g, 33.7 mmol) and  $\text{PPh}_3$  (6.63 g, 25.3 mmol) in anhydrous THF (150 mL) was added dropwise a solution of DEAD (4.40 g, 25.3 mmol) in THF (50 mL) at 0-5 °C. The resulting mixture was stirred at 26-30 °C for 16 hours. The reaction mixture was diluted with EtOAc (500 mL), then washed with brine (300 mL x3), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc = 20/1 to 5/1), diluted with MTBE (100 mL), then washed with 12 M NaOH solution (50 mL x3), brine (50 mL x3), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford **H2**.

### General procedure for the synthesis of H3

A mixture of **H2** (2.00 g, 5.75 mmol) in HCl/dioxane (30 mL, 4.0 M) was stirred at 27 °C for 20 minutes. The reaction mixture was concentrated under reduced pressure to afford **H3**.

### **Scheme 9. General synthesis 9 of an amine compound**



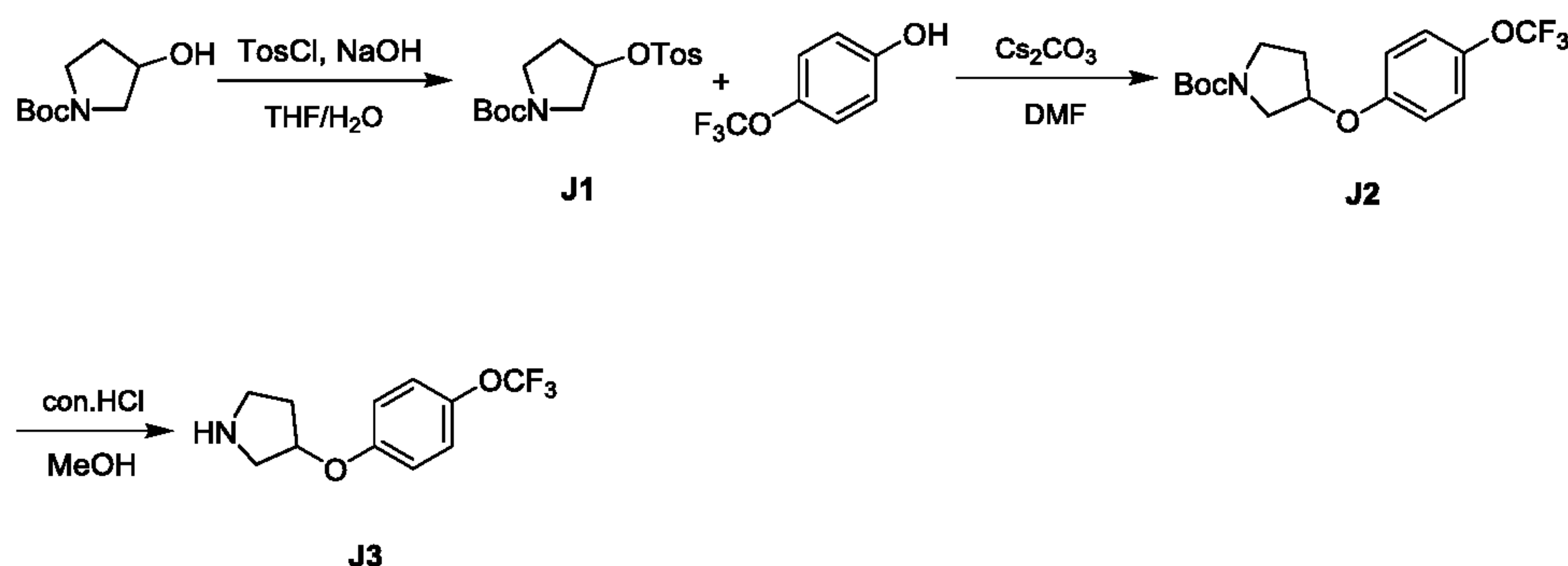
### General procedure for the synthesis of **I1**

To a stirred solution of 1-Boc-pyrrolidine-3-carboxylic acid (5.00 g, 23.3 mmol) and 4-(trifluoromethoxy)aniline (3.91 g, 22.1 mmol) in anhydrous DMF (50 mL) was added DIPEA (9.0 g, 69.8 mmol). Then HATU (13.2 g, 34.7 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at 25 °C for 4 hours. The mixture was quenched with water (100 mL), extracted with EtOAc (100 mL x 2). The combined organic phase was washed with saturated NaHCO<sub>3</sub> (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **I1**.

### General procedure for the synthesis of **I2**

To a stirred solution of **I1** (6.00 g, 16.0 mmol) in DCM (120 mL) was added TFA (40 mL) dropwise at 0 °C. After the addition, the mixture was stirred at 25 °C for 12 hours. The mixture was concentrated under reduced pressure and the residue was diluted with 100 mL water. Solid K<sub>2</sub>CO<sub>3</sub> was added to adjust pH 10 and extracted with EtOAc (200 mL x 2). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **I2**.

### **Scheme 10. General synthesis 10 of an amine compound**



### General procedure for the synthesis of **J1**

To a stirred solution of *tert*-butyl-3-hydroxypyrrolidine-1-carboxylate (10.0 g, 53.4 mmol) in THF (50 mL) was dropwise added aqueous NaOH (5.30 g/134 mmol in 5 mL water) under ice

bath (below 10 °C), then TosCl (13.2 g, 68.4 mmol) was added by portions below 10 °C. Then the mixture was warmed at 30 °C for 12 hours. THF was concentrated under reduced pressure to afford a residue, the residue was diluted with water (100 mL), extracted with EtOAc (50 mL x 3). The combined extract was washed with water (50 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a **J1**.

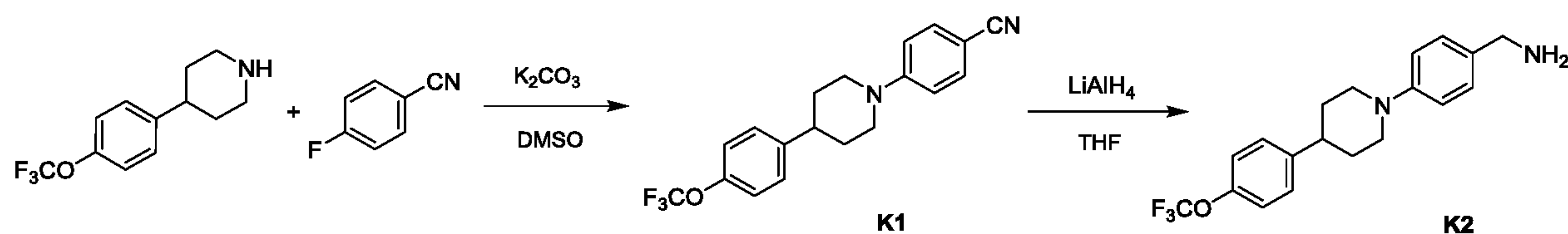
### **General procedure for the synthesis of J2**

A mixture of compound **2** (5.00 g, 14.6 mmol), 4-(trifluoromethoxy)phenol (2.73 g, 15.3 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (9.50 g, 29.2 mmol) in DMF (25 mL) was stirred at 80-90 °C for 2 hours. The mixture was diluted with water (150 mL), extracted with EtOAc (50 mL x 4). The combined extract was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford a crude, which was purified by flash column chromatography (eluent: EtOAc/PE=1/100 to 1/5) to afford **J2**

### **General procedure for the synthesis of J3**

To a stirred solution of **J2** (3.80 g, 10.9 mmol) in MeOH (20 mL) was added aq.HCl (5 mL, 12M) at 10 °C, the mixture was stirred at 10 °C for 2 hours. The mixture was concentrated under reduced pressure to afford a residue. The residue was diluted with water (50 mL), adjusted pH = 9 by aqueous NaOH (2M), extracted with EtOAc (30 mL x 3). The combined extract was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **J3**.

### **Scheme 11. General synthesis 11 of an amine compound**



### **General procedure for the synthesis of K1**

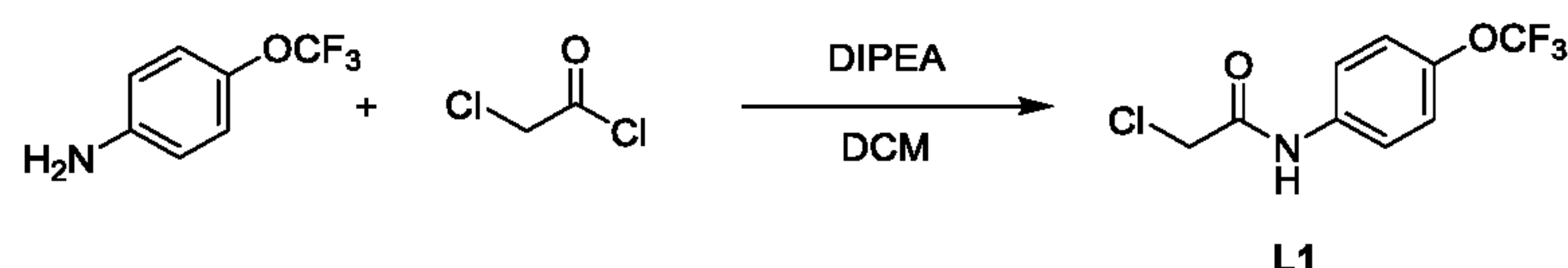
To a stirred solution of 4-(4-(trifluoromethoxy)phenyl)piperidine (86.0 g, 0.351 mol) in DMSO (1 L) was added K<sub>2</sub>CO<sub>3</sub> (121 g, 0.878 mol) and 4-fluorobenzonitrile (63.8 g, 0.527 mol) at 18 °C. The reaction mixture was heated to 120 °C for 16 hours under N<sub>2</sub>. After cooling to room temperature, the mixture was concentrated to about 400 mL over high vacuum. H<sub>2</sub>O (2 L) was poured into the mixture and the resulting precipitate was collected by filtration. The crude product was triturated with H<sub>2</sub>O (1.5 L), dried over high vacuum, then triturated with

EtOAc/PE (800 mL / 4 L), dried over high vacuum to afford **K1**.

### **General procedure for the synthesis of K2**

To a stirred solution of **K1** (60.0 g, 0.173 mol) in anhydrous THF (1.0 L) was added LiAlH<sub>4</sub> (32.9 g, 0.865 mol) at 0 °C. The reaction mixture was heated to reflux for 3 hours under N<sub>2</sub>. After cooling to room temperature, the mixture was quenched carefully with H<sub>2</sub>O (33 mL), 10% NaOH solution (33 mL), H<sub>2</sub>O (100 mL) in turn. The mixture was filtered, the filter cake was washed with THF (300 mL), and the filtrate was concentrated under high vacuum to afford **K2**.

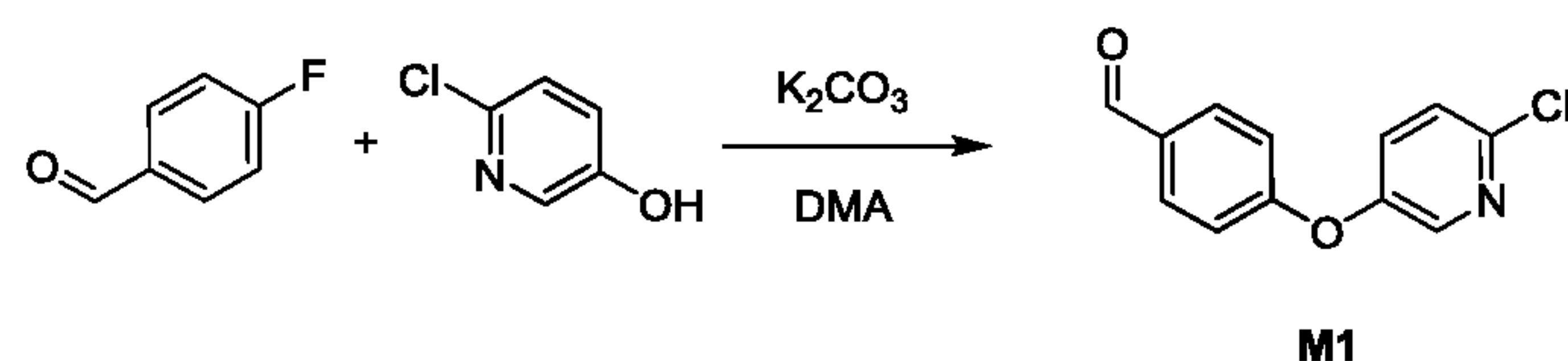
### **Scheme 12. General synthesis of an alkyl halide**



### **General procedure for the synthesis of L1**

To a stirred solution of 4-(trifluoromethoxy)aniline (2.00 g, 17.7 mmol), DIPEA (2.51 g, 19.3 mmol) in DCM (80 mL) was added a solution of chloroacetyl chloride (2.00 g, 17.7 mmol) in DCM (8 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour and poured into water (50 mL). The mixture was separated and the organic layer was washed with water (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by recrystallization from PE/EtOAc (1/1) to afford **L1**.

### **Scheme 13. General synthesis 1 of an aryl aldehyde**

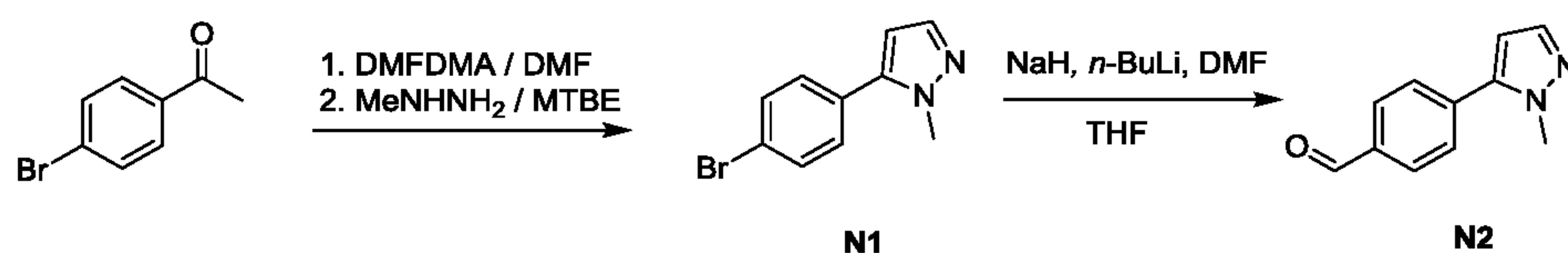


### **General procedure for the synthesis of M1**

To a stirred solution of 2-chloro-5-hydroxypyridine (3.00 g, 23.3 mmol) in anhydrous DMA (40 mL) were added 4-fluorobenzaldehyde (2.88 g, 23.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (6.40 g, 46.6 mmol). The resulting mixture was heated to 130 °C for 16 hours. Water (30 mL) was poured into the mixture, then extracted with EtOAc (40 mL×3). The combined organic phase was

washed with brine (40 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude product. The residue was purified by Combi-flash (PE: EtOAc= 20:1 to 15:1) to afford **M1**.

#### Scheme 14. General synthesis 2 of an aryl aldehyde

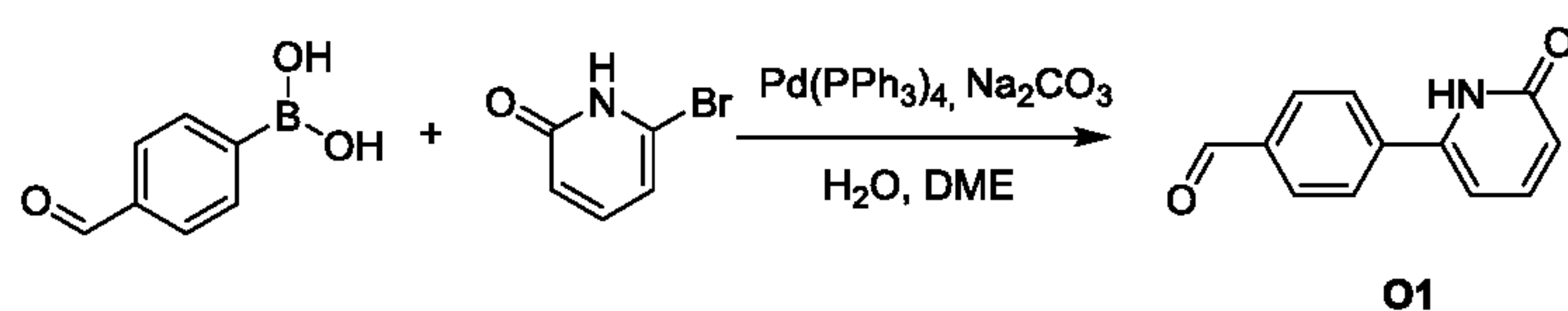


#### General procedure for the synthesis of N1

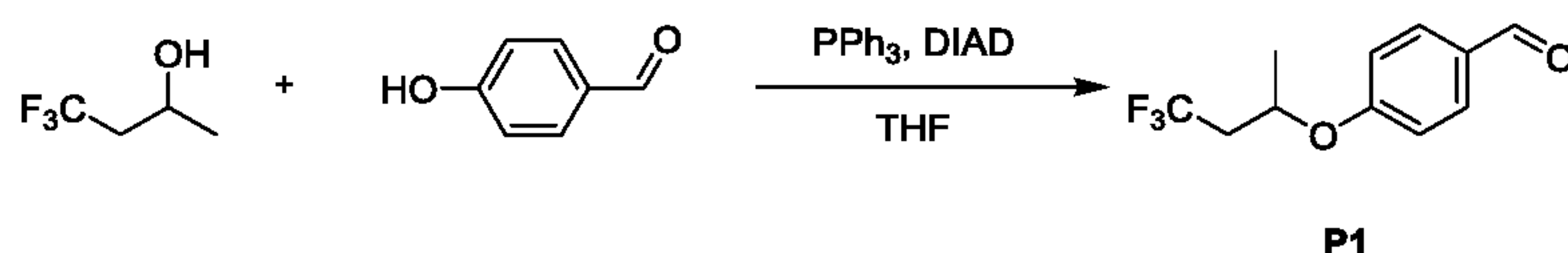
To a stirred solution of 1-(4-bromophenyl)ethan-1-one (30.0 g, 150 mmol) in DMF (18 mL) was added DMFDMA (43.5 mL, 300 mmol), the resulting mixture was stirred at 110 °C for 4 hours. After cooling to room temperature, MTBE (150 mL) was added to the mixture, then MeNHNH<sub>2</sub> (78.9 g, 600 mmol) was added into above mixture, the resulting mixture was stirred at 25 °C for 17 hours. The mixture was diluted with EtOAc (100 mL), filtered and the filter cake was washed with EtOAc (150 mL). The combined organic layer was washed with water (200 mL×3) and brine (200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue. The residue was purified by flash column chromatography (eluted: PE/EtOAc=8/1 to 4/1) to afford **N1**.

#### General procedure for the synthesis of N2

To a stirred solution of **N1** (1.20 g, 5.10 mmol) in anhydrous THF (10 mL) was added NaH (240 mg, 6.00 mmol, 60% dispersion in mineral oil), the resulting mixture was stirred at 0 °C for 1 hour, then *n*-BuLi (2.3 mL, 5.75 mmol, 2.5 M in hexane) was added into above mixture at -70 °C and stirred at -70 °C for 1 hour, freshly distilled DMF (1.85 g, 25.3 mmol) was added into above mixture and stirred at -70 °C for 1 hour, then the reaction mixture was allowed to warm to 0 °C. TLC showed the reaction was completed. The reaction was quenched with water (30 mL) at 0 °C, extracted with EtOAc (30 mL×3). The combined organic phase washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue. The residue was purified by flash column chromatography (eluted: PE/EtOAc=2/1) to afford **N2**.

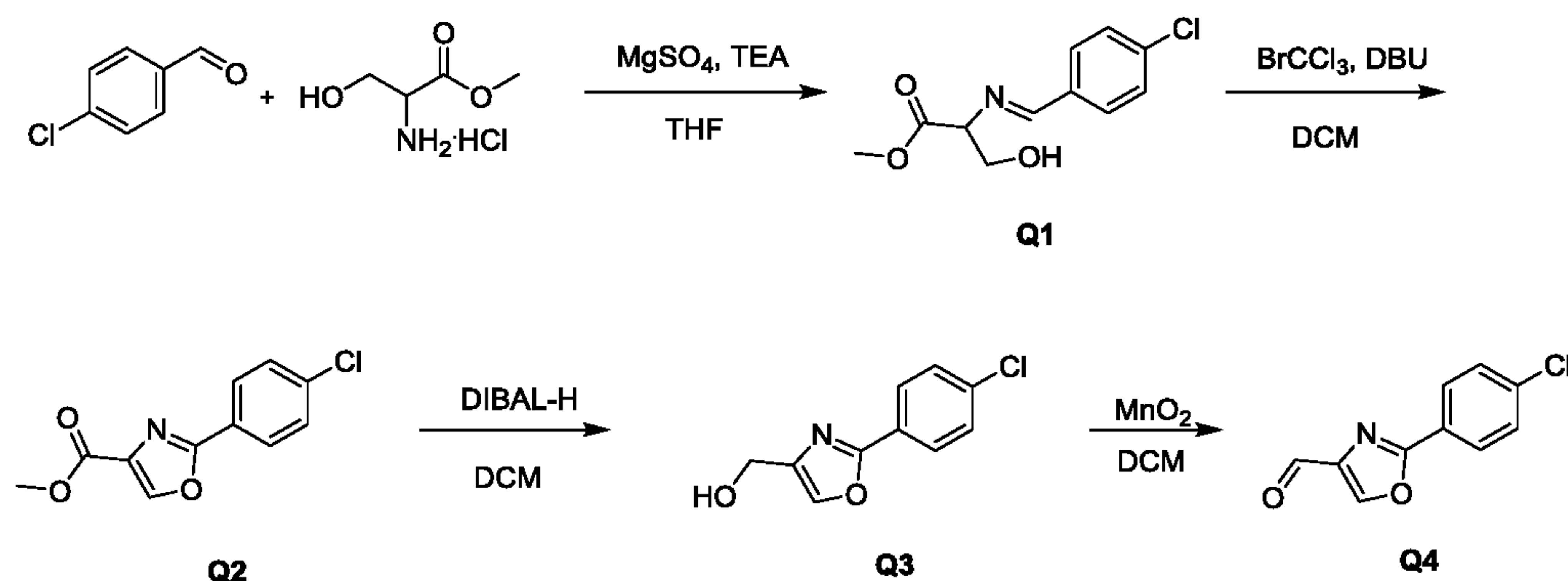
**Scheme 15. General synthesis 3 of an aryl aldehyde****General procedure for the synthesis of O1**

To a stirred solution of 2-bromo-6-hydroxypyridine (100 mg, 0.57 mmol) and 4-formylphenylboronic acid (72 mg, 0.48 mmol) in DME (2 mL) were added Pd(PPh<sub>3</sub>)<sub>4</sub> (55 mg, 0.05 mmol) and Na<sub>2</sub>CO<sub>3</sub> solution (0.63 mL, 2M). The mixture was stirred under N<sub>2</sub> atmosphere maintaining gentle reflux for 16 hours. The mixture was diluted with water (10 mL) extracted with EtOAc (20 mL×3). The combined extracts were washed with brine (20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a crude, which was purified by combi flash (eluent: EtOAc) to afford **O1**.

**Scheme 16. General synthesis 4 of an aryl aldehyde****General procedure for the synthesis of P1**

To a stirred solution of 4,4,4-trifluoro-2-butanol (450 mg, 3.51 mmol) in anhydrous THF (10 mL) were added 4-hydroxybenzaldehyde (390 mg, 3.19 mmol), PPh<sub>3</sub> (1.26 g, 4.28 mmol) and DIAD (967 mg, 4.78 mmol). Then the mixture was stirred at 27-30°C for 16 hours. Then the mixture was diluted with water (50 mL), extracted with EtOAc (30 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude residue which was purified by Combi Flash (PE/EtOAc=10/1) to afford **P1**.

**Scheme 17. General synthesis 5 of an aryl aldehyde**



### General procedure for the synthesis of Q1

To a stirred solution of DL-serine methyl ester hydrochloride (11.1 g, 71.4 mmol),  $\text{MgSO}_4$  (8.64 g, 71.4 mmol) in anhydrous THF (350 mL) were added 4-chloro-benzaldehyde (10.0 g, 71.4 mmol) and TEA (14.4 g, 143 mmol), then the mixture was stirred at 25-30 °C for 12 hours. The resulting mixture was filtered, washed with MTBE (100 mL x 2). The combined filtrate was concentrated under reduced pressure to afford a crude **Q1**.

### General procedure for the synthesis of Q2

To a stirred solution of **Q1** (13.8 g, crude) in anhydrous DCM (220 mL) were added  $\text{BrCCl}_3$  (16.4 mL, 166 mmol) and DBU (25 mL, 166 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours and then at 25-30 °C for 10 hours. The mixture was concentrated under reduced pressure to dryness. The residue was dissolved in EtOAc (250 mL), washed with water (140 mL x 2), brine (80 mL) in turn, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated to afford a residue. The residue was washed with EtOAc (20 mL) to afford **Q2**.

### General procedure for the synthesis of Q3

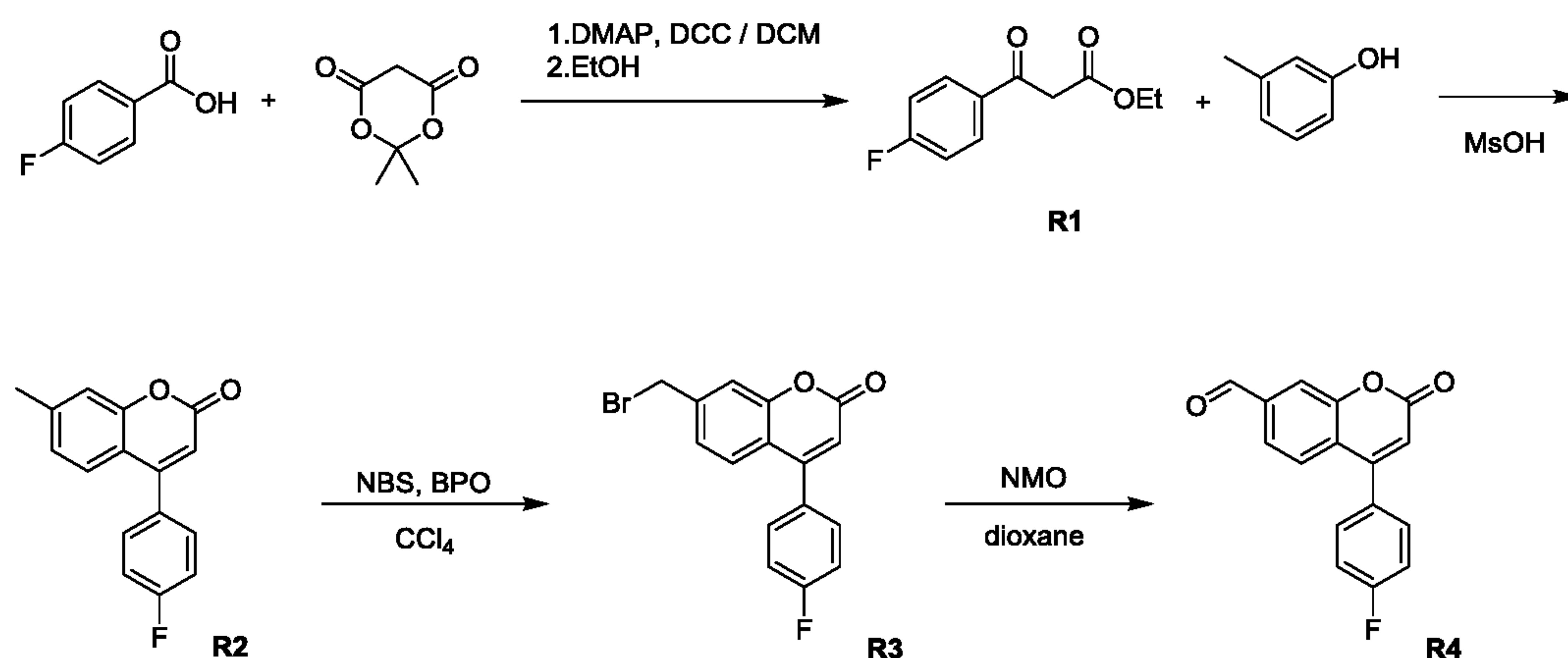
To a stirred solution of **Q2** (3.46 g, 14.6 mmol) in anhydrous DCM (65 mL) was added DIBAL-H (16.1 mL, 16.1 mmol, 1M in toluene) at -78 °C under  $\text{N}_2$  atmosphere. The resulting mixture was stirred at 0 °C for 4 hours. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  (25 mL) at 0 °C. Then the mixture was warmed to room temperature, adjusted pH 2 by HCl (1M). The mixture was extracted with DCM (50 mL x 3), the combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford a residue. The residue was washed with DCM (15 mL) to afford **Q3**.

### General procedure for the synthesis of Q4

A mixture of **Q3** (1.49 g, 7.13 mmol) and  $\text{MnO}_2$  (6.20 g, 71.3 mmol) in DCM (65 mL) was

stirred under N<sub>2</sub> atmosphere at 25-30 °C for 18 hours. The mixture was filtered and the filter cake was washed with DCM (10 mL x 2), the filtrate was concentrated under reduced pressure to dryness to afford **Q4**.

### Scheme 18. General synthesis 6 of an aryl aldehyde



### General procedure for the synthesis of **R1**

To a stirred solution of 4-fluorobenzoic acid (50.0 g, 357 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (61.7 g, 428 mmol) and DMAP (65.5 g, 536 mmol) in DCM (1.5 L) was added DCC (97.5 g, 464 mmol) dropwise at 0 °C and stirred at 0 °C for 30 minutes, then stirred at 25 °C for 17 hours. The mixture was filtered, the filtrate was washed with aqueous HCl (1 M, 800 mL×3), washed with brine (800 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue. The residue was dissolved in EtOH (600 mL) and stirred at 100 °C for 17 hours. The excessive EtOH was removed under reduced pressure to afford a residue, which was purified by flash column chromatography (eluted: PE/EtOAc = 20/1) to afford **R1**.

### General procedure for the synthesis of **R2**

A mixture of **R1** (7.50 g, 35.7 mmol) and m-cresol (3.86 g, 35.7 mmol) in MsOH (9.5 mL) was stirred at 40 °C for 17 hours. After cooling to room temperature, the reaction mixture was poured into cooling EtOH (-30 °C, 60 mL) and stirred at -30 °C for 1 hour. The precipitate was filtered. The solid was dissolved in EtOAc (50 mL) and then washed with saturated NaHCO<sub>3</sub> (50 mL × 2), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **R2**.

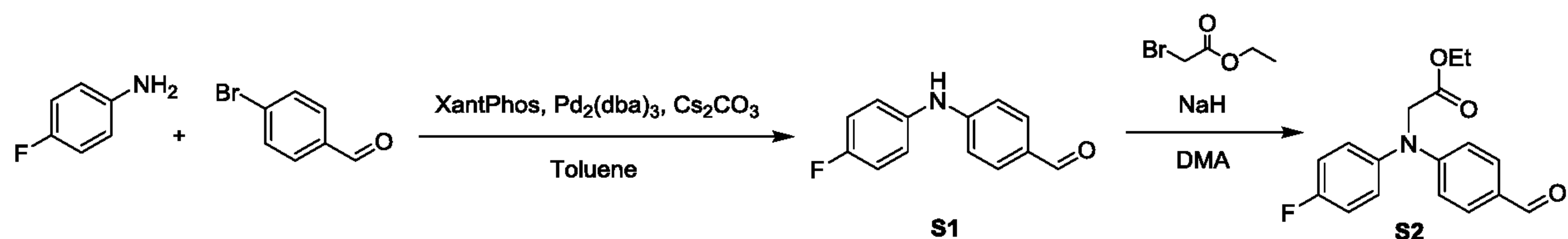
### General procedure for the synthesis of R3

To a stirred solution of **R2** (1.00 g, 3.94 mmol) in  $\text{CCl}_4$  (30 mL) were added NBS (842 mg, 4.73 mmol) and BPO (195 mg, 0.806 mmol), the resulting mixture was stirred at reflux for 48 hours. Then the mixture was filtered, the filtrate was concentrated under reduced pressure to afford a residue, which was purified by flash column chromatography (PE/EtOAc = 30/1) to afford **R3**.

### General procedure for the synthesis of R4

To a stirred solution of **R4** (1.00 g, 3.00 mmol) in dioxane (15 mL) was added NMO (882 mg, 7.53 mmol) and the resulting mixture was stirred at reflux for 6 hours. After cooling to room temperature, the mixture was diluted with water (50 mL), extracted with EtOAc (30 mL  $\times$  3). The combined organic layer was washed with brine (50 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford a residue, which was purified flash column chromatography (PE/EtOAc = 20/1) to afford **R4**.

### **Scheme 19. General synthesis 7 of an aryl aldehyde**



### General procedure for the synthesis of S1

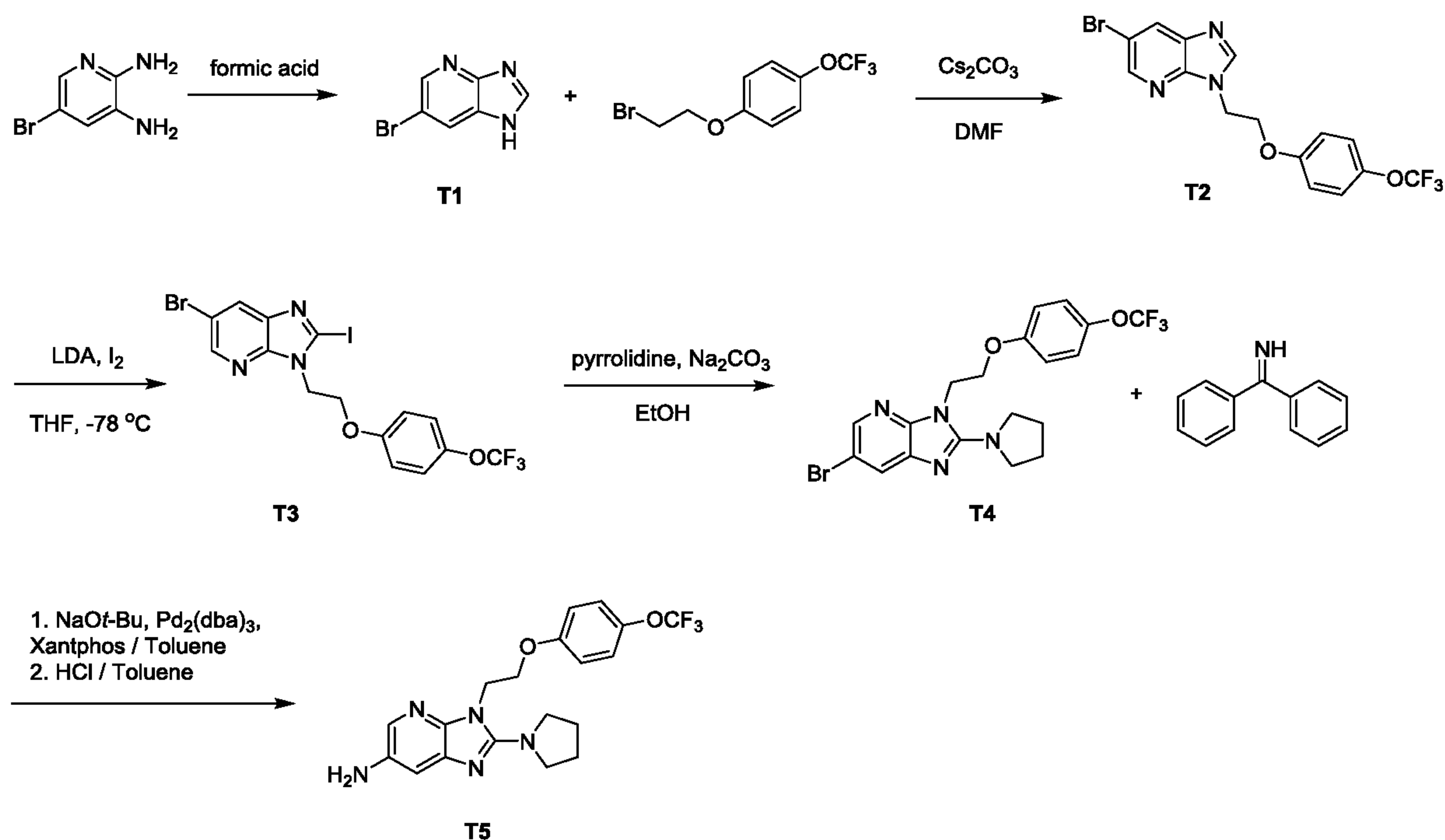
To a stirred solution of 4-fluoro aniline (360 mg, 3.24 mmol), 4-Bromobenzaldehyde (500 mg, 2.70 mmol), XantPhos (60 mg, 0.108 mmol) and  $\text{Pd}_2(\text{dba})_3$  (25 mg, 0.027 mmol) in anhydrous toluene (15 mL) was added  $\text{Cs}_2\text{CO}_3$  (1.32 g, 4.05 mmol) under  $\text{N}_2$  atmosphere. The reaction mixture was purged under  $\text{N}_2$  atmosphere for 3 times, then heated to reflux (oil bath  $120^\circ\text{C}$ ) under  $\text{N}_2$  atmosphere for 16 hours. 40 mL water was poured into the mixture, then extracted with EtOAc (20 mL  $\times$  2), the combined organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give crude product. The residue was purified by Combi-flash (PE: EtOAc= 20:1 to 9:1) to afford **S1**.

### General procedure for the synthesis of S2

To a stirred solution of **S1** (200 mg, 0.929 mmol) in anhydrous DMA (20 mL) was added  $\text{NaH}$

(74 mg, 1.86 mmol, 60% dispersion in mineral oil) at 0 °C for 0.5 hour, then ethyl bromoacetate (186 mg, 1.12 mmol) was added, after 1 hour, the resulting mixture was stirred at 60 °C for another 16 hours. The mixture was quenched with water (20 mL), then extracted with EtOAc (30 mL×2). The combined organic phase was washed with brine (20 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford S2.

### Scheme 20. General synthesis of an imidazopyridine derivative



### General procedure for the synthesis of T1

A mixture of 5-bromopyridine-2,3-diamine (5.00 g, 26.6 mmol) in formic acid (80 mL) was heated to 110 °C for 16 hours. The reaction solution was concentrated under reduced pressure. The residue was partitioned between 2 N NaOH (200 mL) and DCM (100 mL). The organic phase was separated and the aqueous layer was cooled to 0 °C for 1 hour. The precipitate was collected by filtration, dried over high vacuum to afford T1.

### General procedure for the synthesis of T2

To a stirred solution of T1 (200 mg, 1.01 mmol) in DMF (4 mL) were added 1-(2-bromoethoxy)-4-(trifluoromethoxy)benzene (432 mg, 1.52 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (823 mg, 2.53 mmol) and stirred at 50 °C for 16 hours. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was washed with water

(10 mL x 3), brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by Combi Flash (PE: EtOAc= 1:1) to afford **T2**.

#### **General procedure for the synthesis of T3**

To a stirred solution of diisopropylamine (0.125 mL, 0.894 mmol) in anhydrous THF (1.5 mL) was added *n*-BuLi (0.37 mL, 2.5 M in hexane) dropwise at -78 °C. The solution was stirred at -78 °C for 30 minutes. Then a solution of **T2** (200 mg, 0.447 mmol) in anhydrous THF (0.5 mL) was added dropwise at -78 °C and the solution was stirred at -78 °C for 0.5 hours. Then a solution of iodine (226 mg, 0.894 mmol) in anhydrous THF (0.5 mL) was added dropwise. The reaction solution was stirred at -78 °C for 1.5 hours and warmed to room temperature. The reaction mixture was quenched by saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1.5 mL) and diluted with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was recrystallized from PE/EtOAc (3 mL/ 3 mL) to afford **T3**.

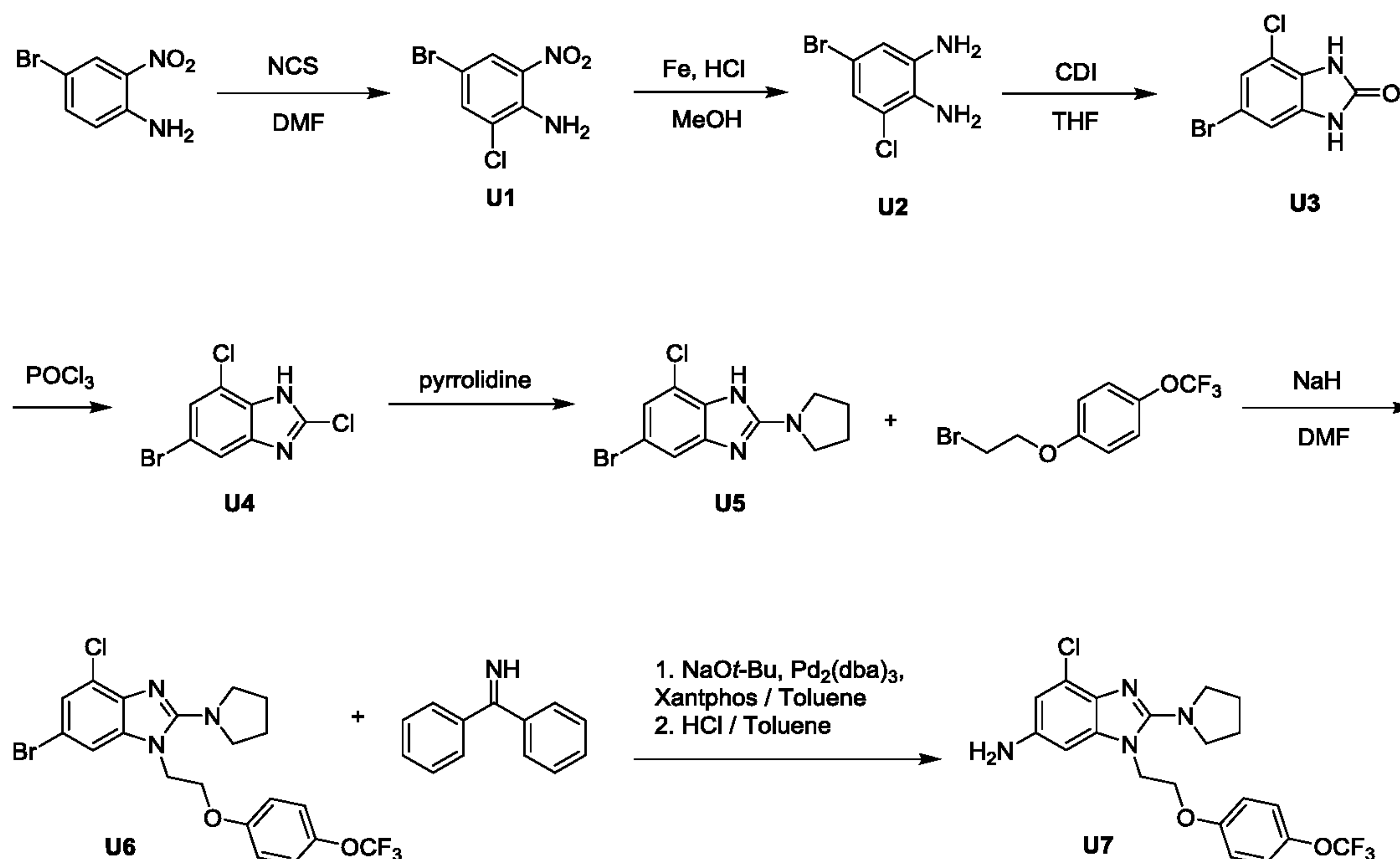
#### **General procedure for the synthesis of T4**

A mixture of **T3** (70 mg, 0.133 mmol), pyrrolidine (13 µg, 0.159 mmol) and Na<sub>2</sub>CO<sub>3</sub> (21 mg, 0.200 mmol) in EtOH (1 mL) was stirred at 80 °C for 16 hours. The reaction mixture was diluted with EtOAc (20 mL), washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by prep-TLC (PE: EtOAc= 1:1) to afford **T4**.

#### **General procedure for the synthesis of T5**

To a stirred solution of XantPhos (5 mg, 0.00847 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (8 mg, 0.00847 mmol) and NaOt-Bu (20 mg, 0.211 mmol) in anhydrous toluene (1 mL) were added **T4** (40 mg, 0.0847 mmol) and benzophenone imine (18 mg, 0.101 mmol). The reaction mixture was stirred at 120 °C under N<sub>2</sub> for 1.5 hours. HCl (1 mL, 4 N) was added to the reaction mixture and the mixture was stirred at 16 °C for 5 minutes. The aqueous layer was basified with NaOH (4 mL, 2 N) and extracted with EtOAc (10 mL x 2). The combined extract was washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, evaporated under reduced pressure. The resulting oil was purified by prep-TLC (DCM/MeOH, 15/1) to afford **T5**.

**Scheme 21. General synthesis of a *N*<sup>4</sup> substituted benzimidazole derivative**



### General procedure for the synthesis of U1

A mixture of 4-bromo-2-nitroaniline (10.0 g, 0.046 mol) and NCS (6.15 g, 0.046 mol) in DMF (100 mL) was stirred at 120°C for 16 hours. The mixture was poured into water (100 mL), the precipitate was filtered, washed with water (50 mL) and dried under reduced pressure to afford **U1**.

### General procedure for the synthesis of U2

To a stirred solution of **U1** in MeOH (100 mL) were added concentrated HCl (9 mL, 108 mmol, 12M) and iron powder (10.0 g, 179 mmol). The reaction mixture was stirred at 8-16°C for 16 hours. After reaction was completed, the mixture was filtered. The filtrate was neutralized to pH 8 with NaHCO<sub>3</sub> aqueous solution and filtered. The filtrate was extracted with EtOAc (100 mL×2). The combined extracts were washed with brine (200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **U2**.

### General procedure for the synthesis of U3

A mixture of **U2** (7.2 g, 32.5 mmol) and CDI (6.32 g, 39.0 mmol) in anhydrous THF (100 mL) was refluxed for 16 hours. After cooling to room temperature, the white precipitate was collected by filtration and dried under reduced pressure to afford **U3**.

### General procedure for the synthesis of U4

A mixture of **U3** (4.90 g, 19.8 mmol) in POCl<sub>3</sub> (30 mL) was refluxed for 16 hours. After the

mixture was cooled to room temperature, the mixture was poured into water (100 mL) under stirring. The white precipitate was collected by filtration, washed with water (50 mL) and dried under reduced pressure to afford **U4**.

#### **General procedure for the synthesis of U5**

A mixture of **U4** (2.10 g, 7.90 mmol) in pyrrolidine (20 mL) was refluxed for 16 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford crude residue which was purified by flash column chromatography (PE/EtOAc=5/1-2/1) to afford **U5**.

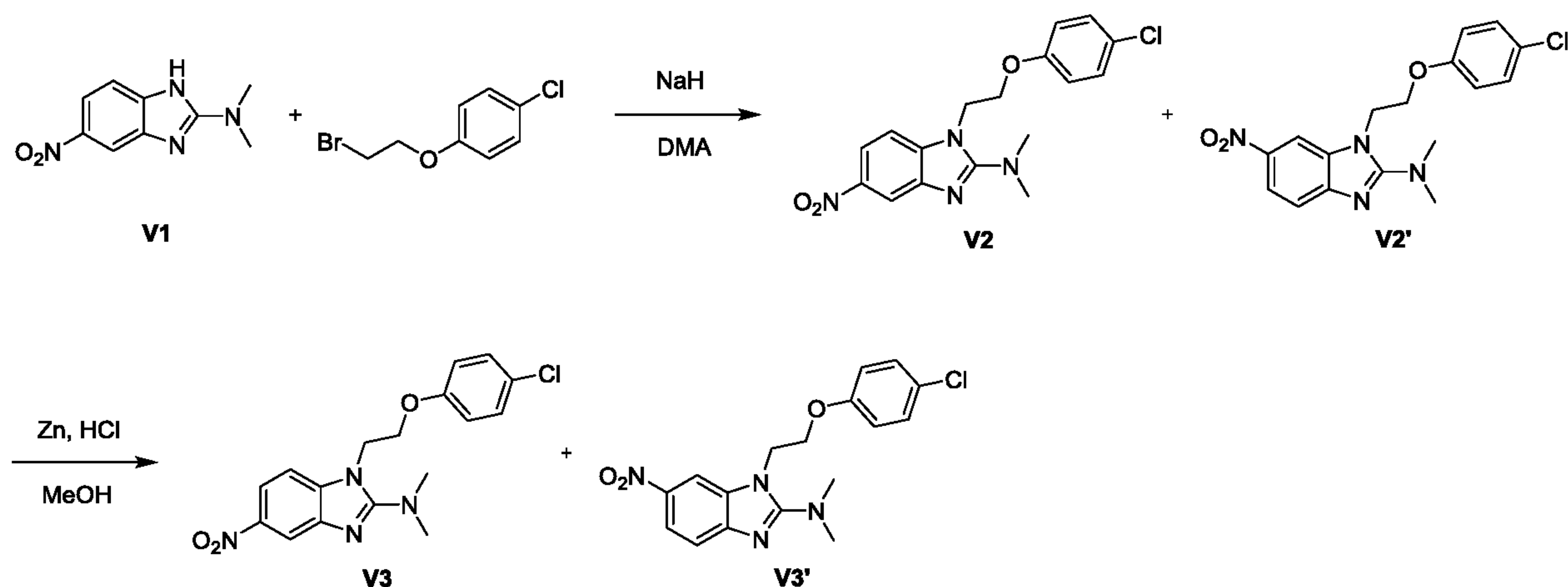
#### **General procedure for the synthesis of U6**

To a stirred solution of **U5** (850 mg, 2.83 mmol) in anhydrous DMF (10 mL) was added NaH (170 mg, 4.24 mmol, 60% in mineral oil) at 0°C. The mixture was stirred at 0°C for 30 minutes, added a solution of 1-(2-bromoethoxy)-4-(trifluoromethoxy)benzene (1.61 g, 5.66 mmol) in anhydrous DMF (5 mL) and stirred at 60°C for 16 hours. The mixture was quenched with water (50 mL), extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford crude residue which was purified by Combi Flash to afford **U6**.

#### **General procedure for the synthesis of U7**

To a stirred solution of **U6** (680 mg, 1.35 mmol), benzophenone imine (488 mg, 2.69 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (124 mg, 0.135 mmol) and XantPhos (156 mg, 0.270 mmol) in anhydrous toluene (10 mL) was added NaOt-Bu (324 mg, 3.38 mmol) under N<sub>2</sub> atmosphere. The reaction mixture was purged in N<sub>2</sub> atmosphere for three times. The mixture was heated to 80-100°C for 16 hours. The mixture was concentrated, dissolved in MeOH (2 mL), added HCl (3 M, 2 mL) and stirred at 20-25°C for 2 hours. Then the mixture was neutralized to pH 8 with NaHCO<sub>3</sub> aqueous solution and extracted with EtOAc (30 mL x 2), the combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude residue, which was purified by prep-HPLC (0.05% HCl) to afford **U7**.

### **Scheme 22. General synthesis 1 of a *N*<sup>1</sup> substituted benzimidazole derivative**



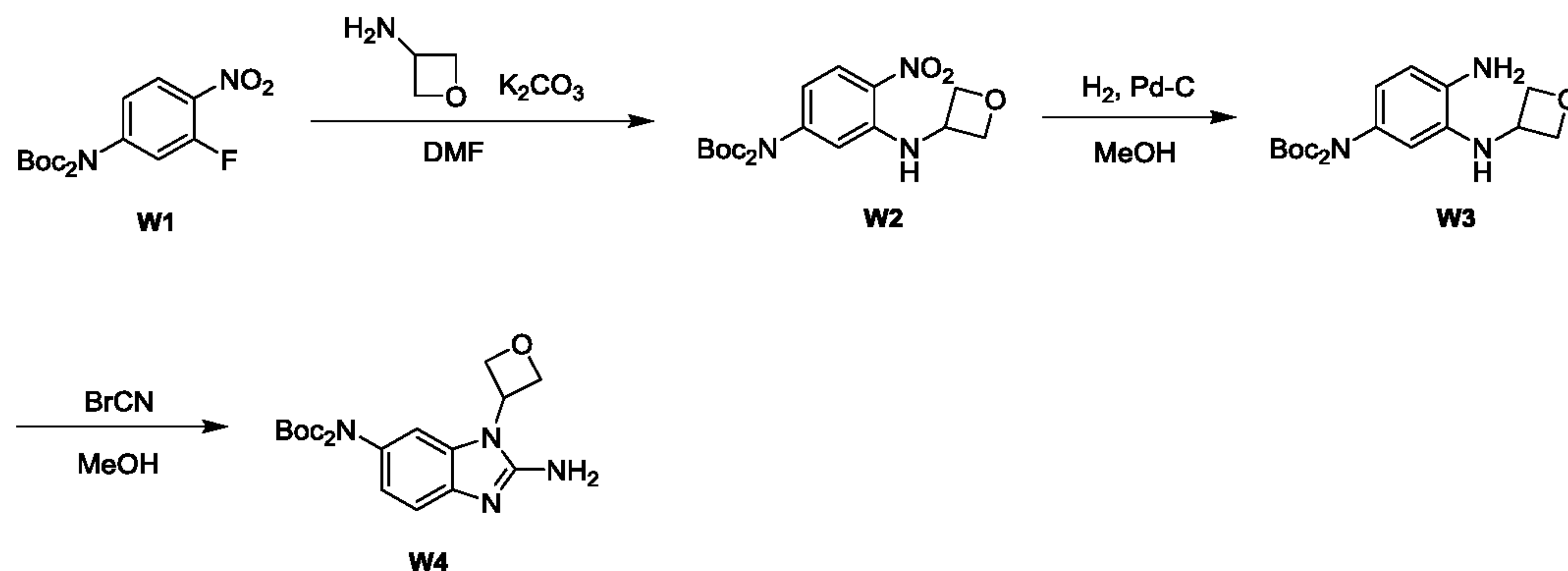
### General procedure for the synthesis of V2

To a stirred solution of compound **2** (538 mg, 2.61 mmol) in DMA (10 mL) was added NaH (125mg, 3.13 mmol, 60% dispersion in mineral oil) portionwise. The mixture was stirred at 0 °C under N<sub>2</sub> atmosphere for 5 minutes. Then a solution of 1-(2-bromoethoxy)-4-chlorobenzene (908 mg, 3.90 mmol) in DMA (8 mL) was added to the mixture and the solution was stirred at 60 °C under N<sub>2</sub> for 24 hours. The mixture was diluted with water (80 mL) and extracted with EtOAc (40 mL×3), the combined extracts were washed with water (20 mL x 2), brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the crude product, which was recrystallized from EtOAc (5 mL) to afford a mixture of **V2** and **V2'**.

### General procedure for the synthesis of V3

To a stirred solution of a mixture of **V2** and **V2'** (100 mg, 0.302 mmol) in MeOH were added Zn powder (98.2 mg, 1.51 mmol) and NH<sub>4</sub>Cl (326 mg, 6004 mmol) at 19 °C. The mixture was stirred at 45 °C for 16 hours. The reaction solution was diluted with EtOAc (10 mL) and filtered. The filtrate was concentrated under reduced pressure. The resulting oil was purified by prep-TLC (DCM/MeOH, 20/1) to afford **V3**.

**Scheme 23. General synthesis 2 of a *N*<sup>1</sup> substituted benzimidazole derivative**



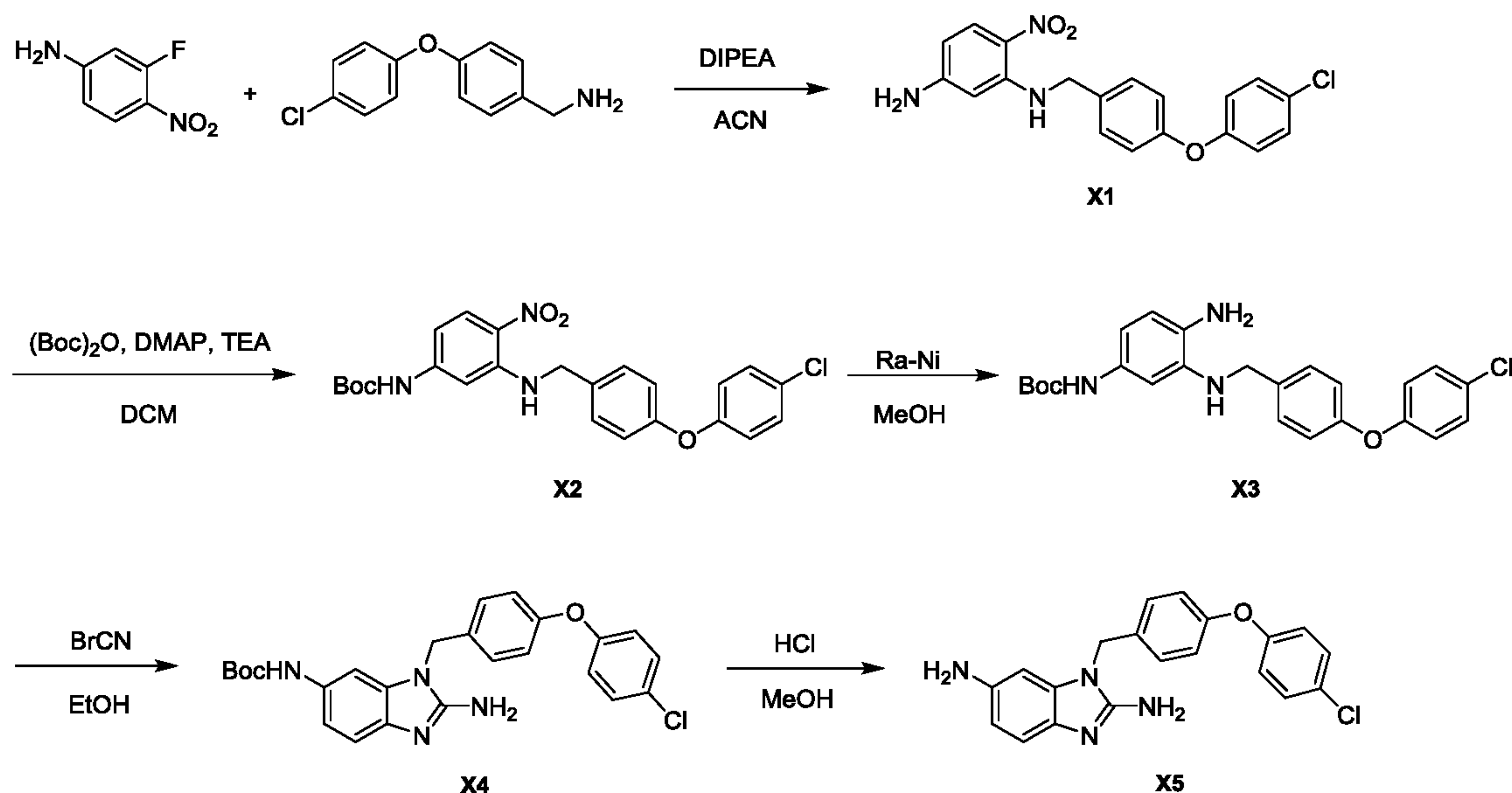
### General procedure for the synthesis of **W2**

A mixture of compound **W1** (300 mg, 0.843 mmol), oxetan-3-amine (74 mg, 1.0 mmol),  $K_2CO_3$  (175 mg, 1.26 mmol) in DMF (3 mL) was stirred at 10 °C for 16 hours. The reaction solution was diluted with water (15 mL) and extracted with EtOAc (20 mL x 2). The combined extract was washed with water (10 mL x 2), brine (10 mL), dried over anhydrous  $Na_2SO_4$  and concentrated under reduced pressure to afford **W2**.

### General procedure for the synthesis of **W4**

To a stirred solution of **W2** (500 mg, 1.22 mmol) in MeOH (20 mL) was added Pd/C (50 mg, 5%, 60% wet) in  $N_2$  atmosphere. The suspension was degassed under vacuum and purged with  $H_2$  several times. The mixture was stirred under  $H_2$  atmosphere (1 atm) for 1.5 hours. The reaction mixture was filtered through a pad of Celite. To the filtrate (**W3** in MeOH) was added BrCN (261 mg, 2.44 mmol). The reaction solution was stirred at 10 °C for 16 hours. The reaction solution was concentrated under reduced pressure. The residue was diluted with water (30 mL) and EtOAc (30 mL). Then solid  $Na_2CO_3$  was added with stirring until aqueous layer was basified to pH 9. The organic layer was separated and dried over anhydrous  $Na_2SO_4$  and concentrated under reduced pressure to afford **W4**.

### **Scheme 24. General synthesis 3 of a $N^1$ substituted benzimidazole derivative**



### General procedure for the synthesis of X1

A mixture of 3-fluoro-4-nitroaniline (1.00 g, 6.40 mmol), (4-(4-chlorophenoxy)phenyl) methanamine (1.79 g, 7.28 mmol), and DIPEA (1.65 g, 12.8 mmol) in ACN (15 mL) was refluxed 16 hours. The mixture was cooled to room temperature and diluted with water (40 mL). The mixture was extracted with EtOAc (40 mL x 2). The combined extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford 3.42 g of crude residue, which was purified by Combi Flash to afford **X1**.

### General procedure for the synthesis of X2

To a stirred solution of **X1** (1.50 g, 4.06 mmol), di-tert-butyl dicarbonate (1.15 g, 5.27 mmol) in DCM (20 mL) were added DMAP (248 mg, 2.03 mmol) and TEA (413 mg, 4.06 mmol). The mixture was stirred at 20 °C for 16 hours. The mixture was diluted with water (50 mL) and extracted with EtOAc (40 mL x 2). The combined extracts were washed with brine (100 mL x 2), dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford 3.00 g of crude residue, which was purified by Combi flash (PE/EtOAc = 25/1 to 20/1 to 15/1) to afford **X2**.

### General procedure for the synthesis of X3

To a stirred solution of **X2** (100 mg, 0.213 mmol) in MeOH (5 mL) was added Raney-Ni (20 mg) under Ar. The suspension was degassed under vacuum and purged with  $\text{H}_2$  for three times. The solution was stirred at 28 °C under  $\text{H}_2$  (50 psi) for 16 hours. The mixture was filtered through a pad of celite, and the pad was washed with MeOH (200 mL). The filtrate

was concentrated under reduced pressure to afford **X3**.

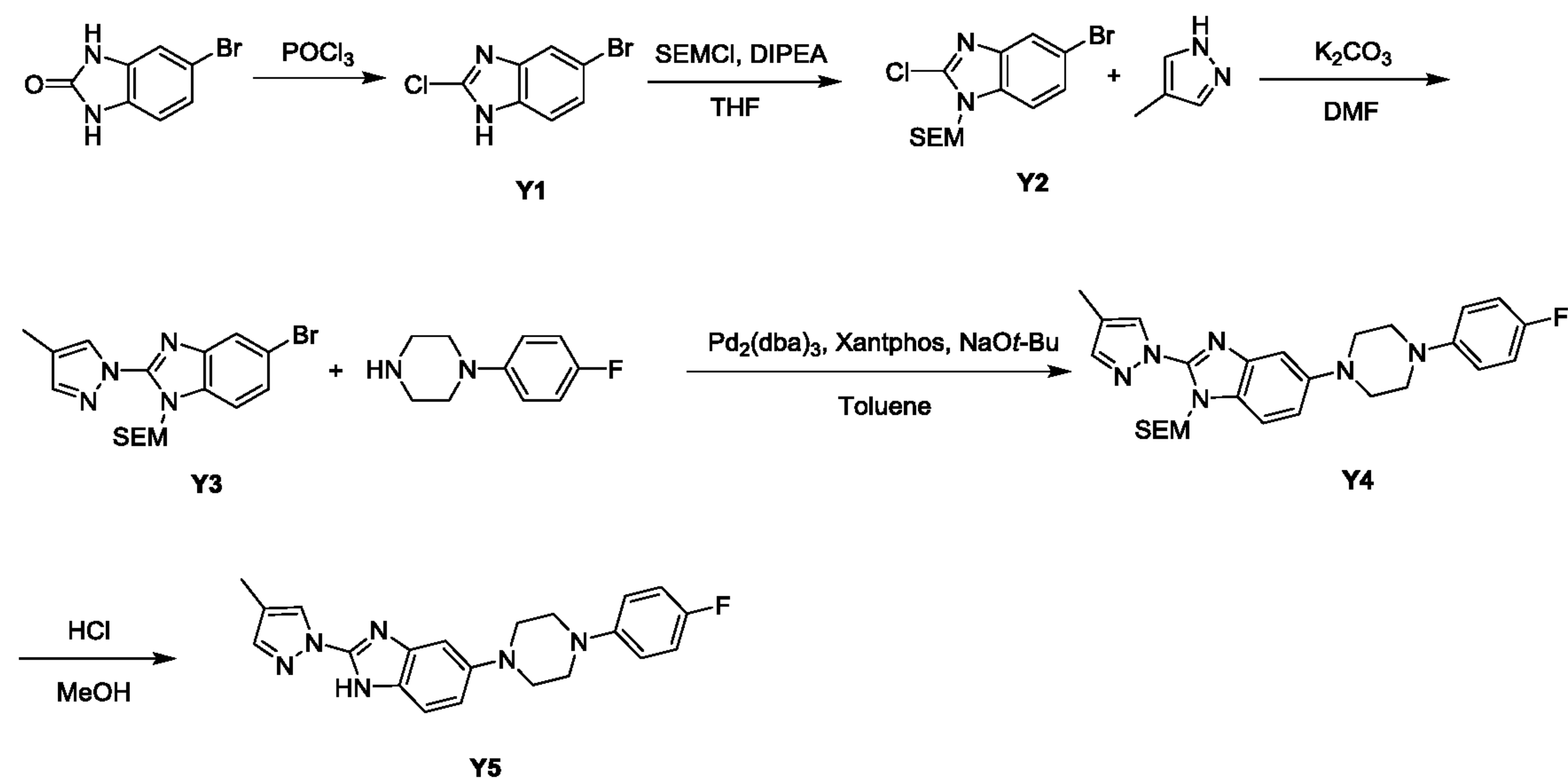
#### General procedure for the synthesis of **X4**

A mixture of **X3** (80 mg, 182  $\mu$ mol), cyanogen bromide (29 mg, 0.273 mmol) in EtOH (4 mL) was stirred at 25 °C for 16 hours. The mixture was basified to pH 9 with Na<sub>2</sub>CO<sub>3</sub> aqueous solution, diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined extracts were washed with brine (40 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **X4**.

#### General procedure for the synthesis of **X5**

To a stirred solution of **X4** (80 mg, 0.172 mmol) in MeOH (2 mL) was added HCl solution of MeOH (4M, 2 mL). The resulting solution was stirred at 25 °C for 2 hours. The mixture was diluted with water (20 mL), basified to pH 9 with Na<sub>2</sub>CO<sub>3</sub> aqueous solution and extracted with EtOAc (20 mL x 2). The combined extracts were washed with brine (40 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude residue, which was purified by prep-HPLC (0.01% NH<sub>3</sub>.H<sub>2</sub>O) to afford **X5**.

#### **Scheme 25. General synthesis 1 of a *N*<sup>2</sup> substituted benzimidazole derivative**



#### General procedure for the synthesis of **Y1**

A mixture of 5-bromo-1,3-dihydro-2H-benzo[d]imidazol-2-one (5.00 g, 23.5 mmol) and POCl<sub>3</sub> (80 mL) was refluxed for 16 hours. After cooled to room temperature, the mixture was poured into water (300 mL) and NaOH aqueous solution (5 M, 80 mL) was added. The

precipitate was filtered and washed with water. The filtrate was dried over high vacuum to afford **Y1**.

#### **General procedure for the synthesis of Y2**

To a stirred solution of **Y1** (500 mg, 2.16 mmol) and DIPEA (558 mg, 4.32 mmol) in THF (5 mL) was added SEMCl (540 mg, 3.24 mmol) at 0°C and the resulting mixture was stirred at 35°C for 16 hours. The mixture was diluted with water (50 mL), extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford a residue. The residue was purified by flash column chromatography to afford **Y2**.

#### **General procedure for the synthesis of Y3**

A mixture of **Y2** (480 mg, 1.33 mmol), 4-methyl-1*H*-pyrazole (109 mg, 1.33 mmol) and K<sub>2</sub>CO<sub>3</sub> (275 mg, 1.99 mmol) in DMF (5 mL) was stirred at 100°C for 16 hours. The mixture was diluted with water (50 mL), extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford a residue. The residue was purified by flash column chromatography to afford **Y3**.

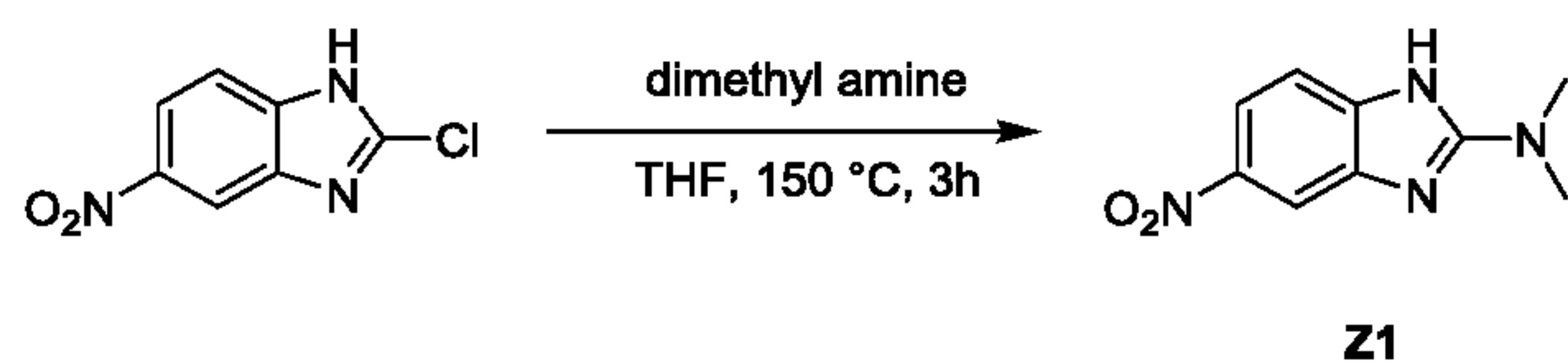
#### **General procedure for the synthesis of Y4**

A mixture of **Y3** (500 mg, 1.23 mmol), 1-(4-fluorophenyl)piperazine (243 mg, 1.35 mmol), NaOt-Bu (236 mg, 2.45 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (112 mg, 0.123 mmol) and Xantphos (71 mg, 0.12 mmol) in toluene (5 mL) was stirred at 120°C for 16 hours. The mixture was diluted with water (50 mL), extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford a residue. The residue was purified by flash column chromatography to afford **Y4**.

#### **General procedure for the synthesis of Y5**

A mixture of **Y4** (160 mg, 0.316 mmol) and conc.HCl (2 mL) in MeOH (6 mL) was stirred at 32°C for 16 hours. The mixture was diluted with water (50 mL), neutralized with NaOH aqueous solution and extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure to afford **Y5**.

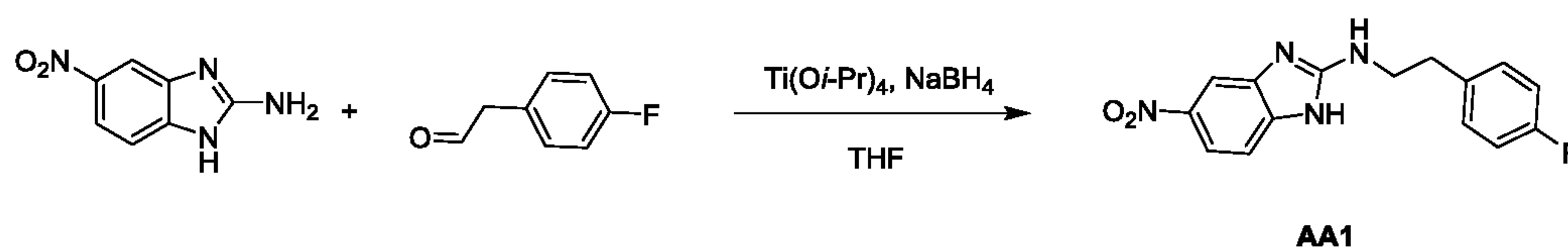
**Scheme 26. General synthesis 2 of a *N*<sup>2</sup> substituted benzimidazole derivative**



### General procedure for the synthesis of Z1

To a stirred solution of dimethyl amine in THF (18 mL, 2 N) was added 2-chloro-5-nitro-1*H*-benzo[*d*]imidazole (1.80 g, 9.1 mmol) at 20 °C. The reaction solution was stirred at 150 °C in a sealed tube for 3 hours. The reaction solution was poured into water (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford **Z1**.

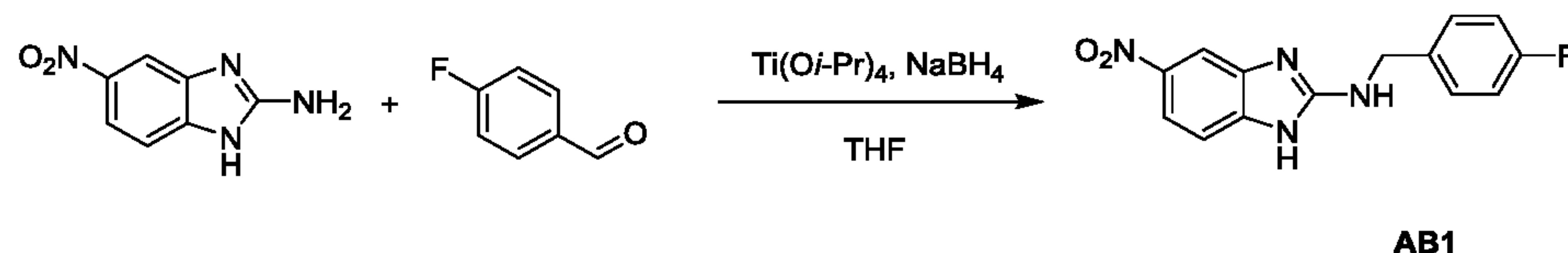
### **Scheme 27. General coupling reaction 1 of a benzimidazole *N*<sup>2</sup> amine**



### General procedure for the synthesis of AA1

A mixture of 5-nitro-1*H*-benzo[*d*]imidazol-2-amine (200 mg, 1.12 mmol), (4-fluoro-phenyl)-acetaldehyde (388 mg, 2.80 mmol) and Ti(*Oi*-Pr)<sub>4</sub> (637 mg, 2.24 mmol) in anhydrous THF (5 mL) was stirred at 60 °C for 30 minutes, then cooled to 20 °C and kept at this temperature for 30 minutes under stirring. Then NaBH<sub>4</sub> (213 mg, 5.60 mmol) was added into the mixture at 0 °C and stirred at 20 °C for 3 hours, then at 60 °C for 16 hours. The mixture was cooled and quenched with aqueous NH<sub>3</sub>.H<sub>2</sub>O (2M, 10 mL). The precipitate was filtered and washed with THF (20 mL). The filtrate was diluted with water (20 mL) and extracted with EtOAc (20 mLx2). The combined extracts were washed with brine (50 mLx2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude product, which was purified by prep-HPLC (0.01% NH<sub>3</sub>.H<sub>2</sub>O) to afford **AA1**.

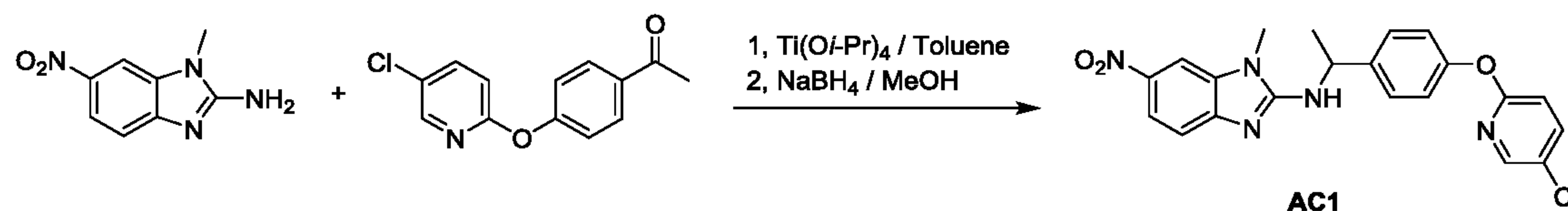
### **Scheme 28. General coupling reaction 2 of a benzimidazole *N*<sup>2</sup> amine**



### General procedure for the synthesis of AB1

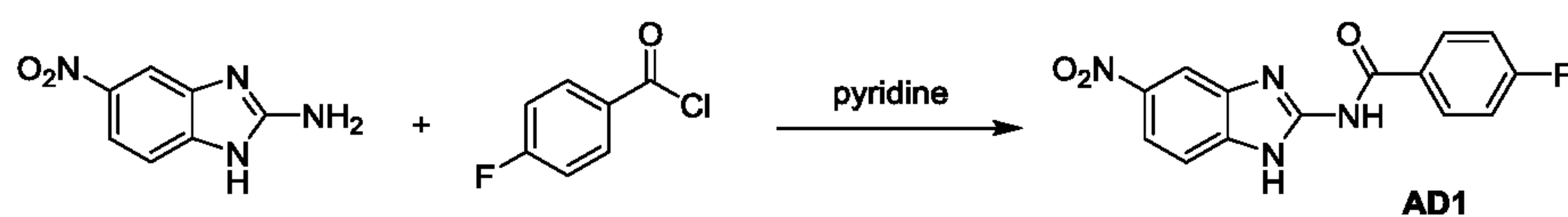
A mixture of 5-nitro-1*H*-benzo[*d*]imidazol-2-amine (1.00 g, 5.60 mmol), 4-fluorobenzaldehyde (2.78 g, 22.4 mmol) and Ti(*Oi*-Pr)<sub>4</sub> (3.18 g, 11.2 mmol) in THF (6 mL) was stirred at 60°C for 30 minutes, the mixture was cooled to 20 °C and kept at this temperature for 30 minutes. Then NaBH<sub>4</sub> (851 mg, 22.4 mmol) was added into the mixture at 0°C and stirred at 20°C for 3 hours and at 60 °C for 16 hours. The mixture was cooled to 20°C and quenched with aqueous NH<sub>3</sub>.H<sub>2</sub>O (2M, 15 mL). The precipitate was filtered, washed with THF (50 mL). The filtrate was diluted with water (50 mL) and extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (100 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude product, which was purified by prep-HPLC (0.01% NH<sub>3</sub>.H<sub>2</sub>O) to afford **AB1**.

### **Scheme 29. General coupling reaction 3 of a benzimidazole *N*<sup>2</sup> amine**

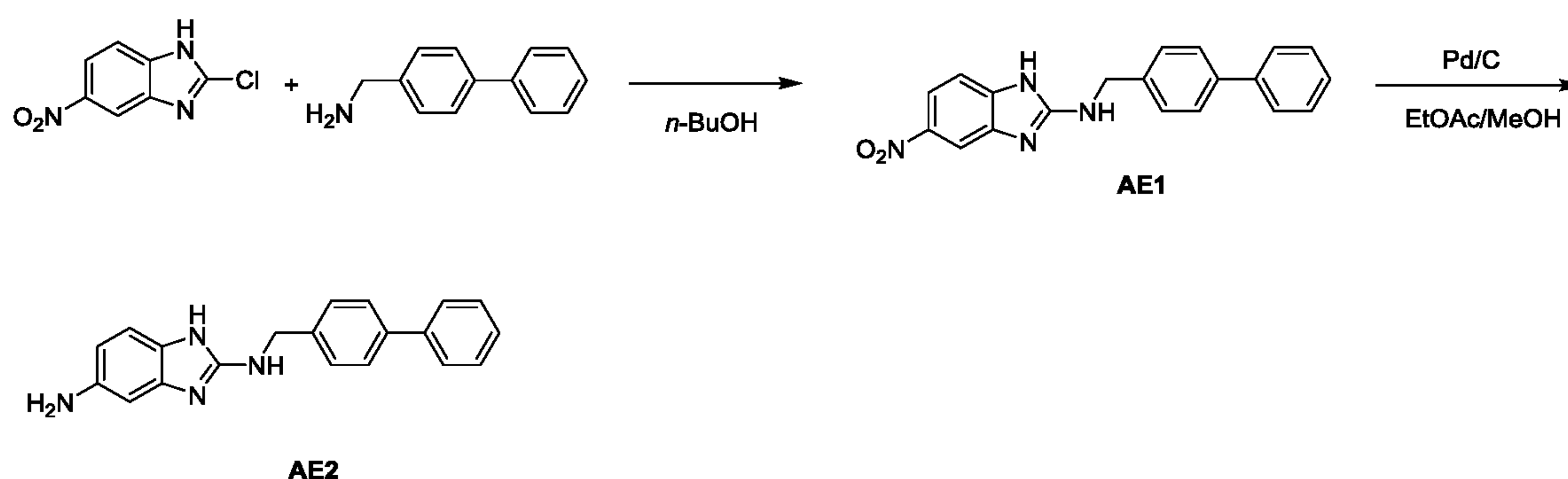


### General procedure for the synthesis of AC1

To a stirred solution of 1-methyl-6-nitro-1*H*-benzo[*d*]imidazol-2-amine (900 mg, 3.63 mmol) and acetophenone (700 mg, 3.64 mmol) in anhydrous toluene (150 mL) was added Ti(*Oi*-Pr)<sub>4</sub> (3.13 g, 10.9 mmol). The resulting mixture was stirred under reflux under N<sub>2</sub> atmosphere for 24 hours. After cooling to room temperature, NaBH<sub>4</sub> (290 mg, 7.26 mmol) was added to the mixture followed by MeOH (5 mL). The resulting mixture was stirred at 12 °C for 2 hours. The mixture was diluted with EtOAc (200 mL), washed with brine (200 mL) and water (200 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude product, which was purified by flash column chromatography (eluted with PE/EtOAc = 50/1 to 5/1) to afford **AC1**.

**Scheme 30. General coupling reaction 4 of a benzimidazole  $N^2$  amine****General procedure for the synthesis of AD1**

A mixture of 5-nitro-1H-benzo[d]imidazol-2-amine (3.00 g, 16.8 mmol) and 4-fluorobenzoyl chloride (8.10 g, 53.6 mmol) in pyridine (30 mL) was stirred at 20°C for 10 minutes. The mixture was diluted with water (150 mL) and filtered. The filter cake was washed with water (100 mL) and dried over high vacuum to afford a crude residue which was purified by flash column chromatography to afford **AD1**.

**Scheme 31. General coupling reaction 5 of a benzimidazole  $N^2$  amine****General procedure for the synthesis of AE1**

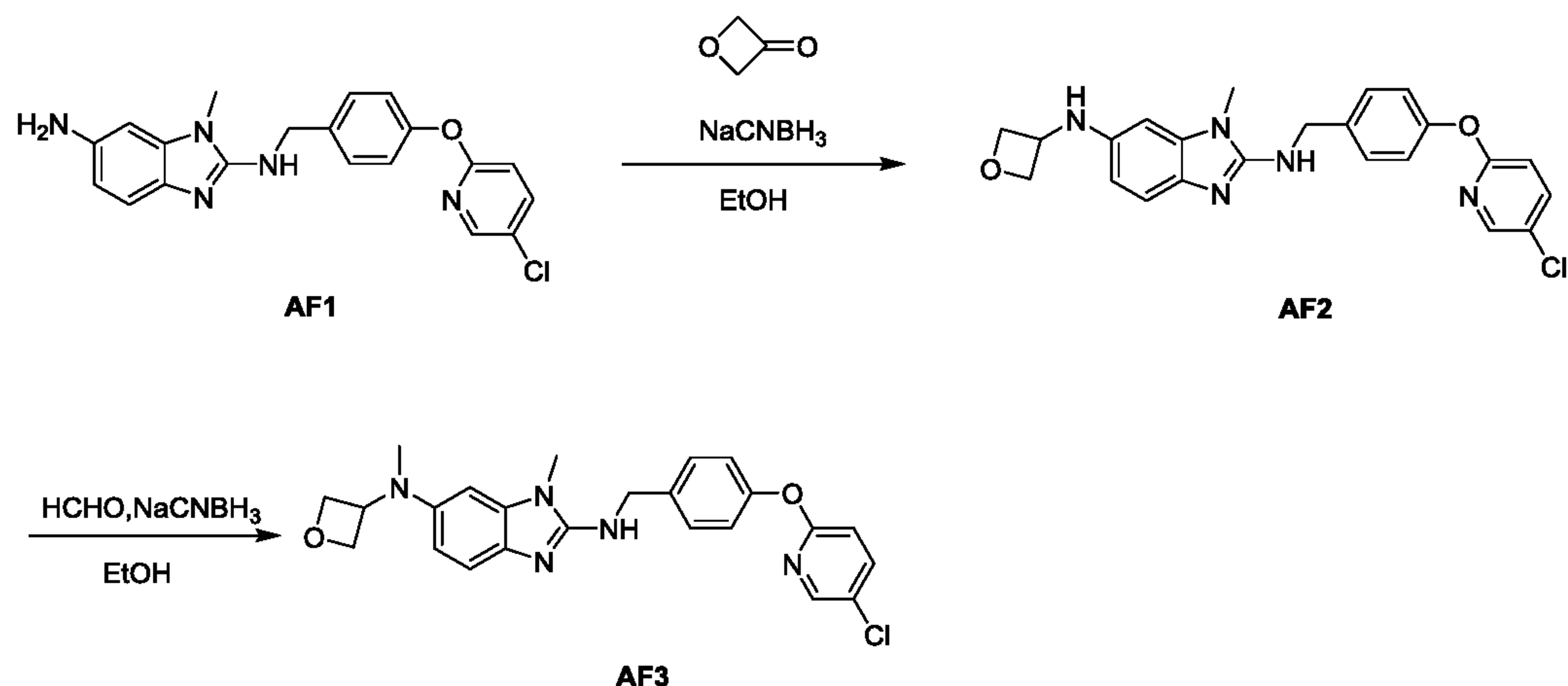
A mixture of 2-chloro-5-nitro-1H-benzo[d]imidazole (500 mg, 2.53 mmol), 4-phenylbenzylamine (696 mg, 3.80 mmol) in *n*-BuOH (8 mL) was refluxed for 36 hours. After reaction was complete, the mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL×2). The combined extracts were washed with brine (100 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude residue, which was purified by combi flash (PE/EtOAc=3/1 to 2/1 to 1/1) to afford **AE1**.

**General procedure for the synthesis of AE2**

To a stirred solution of **AE1** (150 mg, 0.436 mmol) in EtOAc/MeOH (8 mL/2 mL) was added Pd/C (30 mg, 10%) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> for three times. The solution was stirred at 22 °C under H<sub>2</sub> balloon for 16 hours. The

mixture was filtered through a pad of celite and washed with EtOAc (30 mL). The filtrate was concentrated under reduced pressure to afford crude residue which was purified by washing with EtOAc/MeOH (5 mL/1 mL) to afford **AE2**.

**Scheme 32. General coupling reaction 1 of a benzimidazole *N*<sup>6</sup> amine**

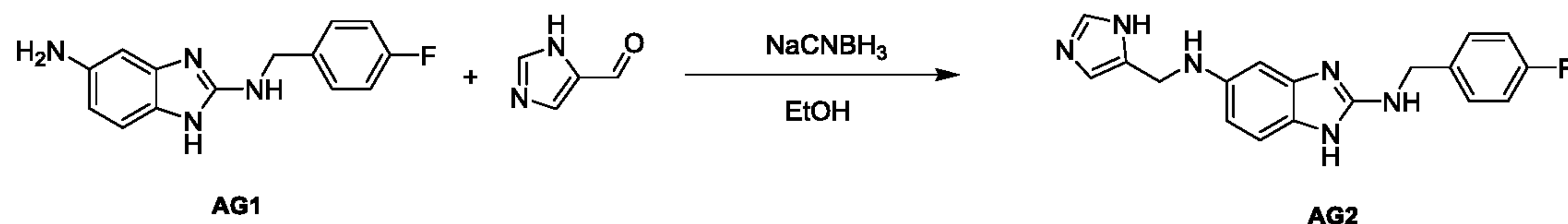


**General procedure for the synthesis of AF2**

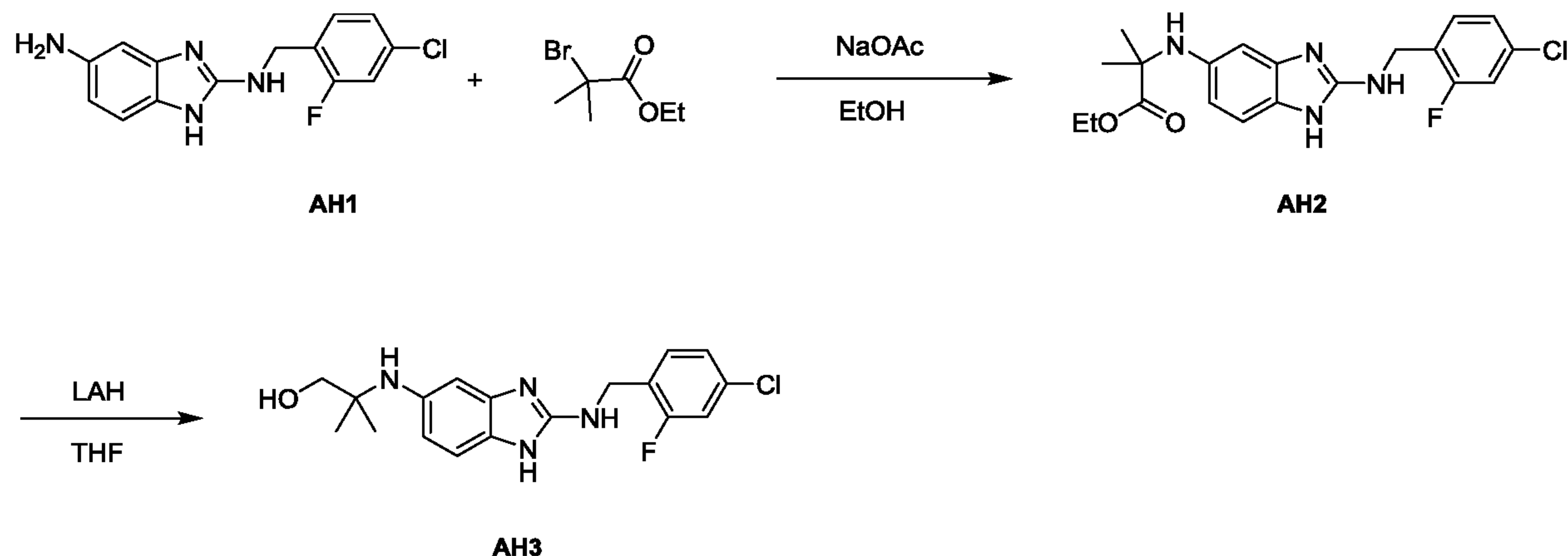
A mixture of **A1** (200 mg, 0.488 mmol), AcOH (0.3 mL) and 3-oxetanone (42 mg, 0.59 mmol) in absolute EtOH (3 mL) was stirred at 18-22 °C for 16 hours. Then to the reaction mixture was added NaBH<sub>3</sub>CN (92 mg, 1.5 mmol), the resulting mixture was stirred at 18-20 °C for 4 hours. The reaction mixture was diluted with EtOAc (50 mL), then washed with water (40 mL) and brine (40 mL x3), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.01% NH<sub>3</sub>.H<sub>2</sub>O as additive) to afford **AF2**.

**General procedure for the synthesis of AF3**

A mixture of **AF2** (100 mg, 0.229 mmol) and formaldehyde (86 mg, 1.15 mmol, 40% aqueous solution in water) in EtOH (5 mL) was added AcOH (adjusted to pH 4 of reaction mixture). The resulting mixture was stirred at 10 °C for 16 hours. NaBH<sub>3</sub>CN (72 mg, 1.15 mmol) was added to the mixture and the reaction mixture was stirred at 10 °C for 4 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2), the combined extracts were washed with brine (40 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a residue, which was purified by prep-HPLC (0.01% NH<sub>3</sub>.H<sub>2</sub>O) to afford **AF3**.

**Scheme 33. General coupling reaction 2 of a benzimidazole *N*<sup>6</sup> amine****General procedure for the synthesis of AG2**

To a stirred solution of **AG1** (150 mg, 0.583 mmol), 1*H*-imidazole-5-carbaldehyde (39 mg, 0.416 mmol) in EtOH (3 mL) was added AcOH (adjusted to pH 4 of reaction mixture). The resulting mixture was stirred at 20°C for 16 hours. Then NaBH<sub>3</sub>CN (73 mg, 1.17 mmol) was added and the mixture was stirred at 20°C for 16 hours. The mixture was neutralized with Na<sub>2</sub>CO<sub>3</sub>, diluted with water (20 mL) and extracted with EtOAc (20 mL×2). The combined extracts were washed with brine (40 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude residue, which was purified by prep-HPLC (0.01% NH<sub>3</sub>·H<sub>2</sub>O) to afford **AG2**.

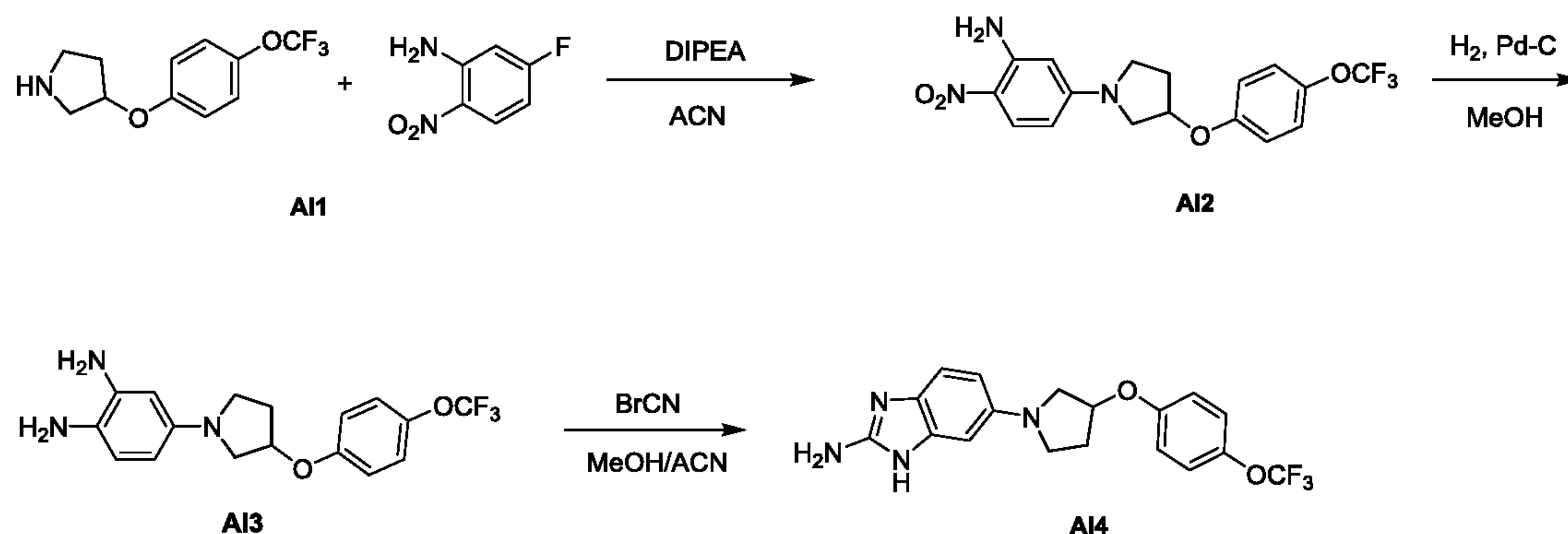
**Scheme 34. General coupling reaction 3 of a benzimidazole *N*<sup>6</sup> amine****General procedure for the synthesis of AH2**

To a stirred solution of **AH1** (200 mg, 0.69 mmol) and ethyl 2-bromoisobutyrate (537 mg, 2.75 mmol) in EtOH (10 mL) was added NaOAc (226 mg, 2.75 mmol). The mixture was refluxed under N<sub>2</sub> for 16 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL×2). The combined extracts were washed with brine (10 mL×2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure afford a crude **AH2**.

### General procedure for the synthesis of AH3

To a stirred solution of compound **AH2** (200 mg, crude) in anhydrous THF (5 mL) was added  $\text{LiAlH}_4$  (75 mg, 1.98 mmol) at 0°C. After stirred at 0°C for 2 hours, the mixture was allowed to stir at 25°C under  $\text{N}_2$  for 16 hours. The mixture was quenched with NaOH aqueous solution (5 M, 0.2 mL) and filtered. The filtrate was diluted with water (10 mL) and extracted with EtOAc (10 mL $\times$ 2), the combined extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford crude product, which was purified by prep-TLC (MeOH : DCM = 1 : 10) to afford **AH3**.

### **Scheme 35. General synthesis of a $N^6$ substituted benzimidazole derivative**



### General procedure for the synthesis of AI2

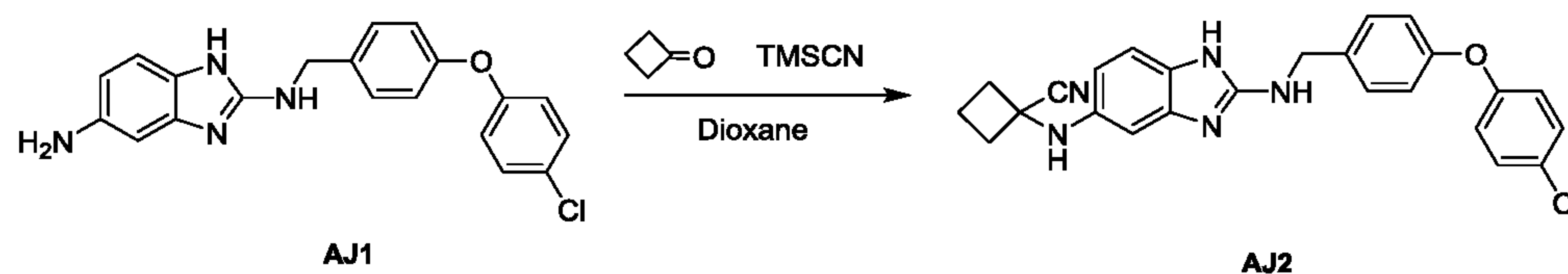
A mixture of **AI1** (1.00 g, 4.05 mmol), 5-fluoro-2-nitroaniline (631 mg, 4.05 mmol) and DIPEA (1.55 g, 12.2 mmol) in ACN (10 mL) was heated to reflux for 12 hours. The mixture was concentrated under reduced pressure to afford a residue, which was purified by silica gel column (eluent: EtOAc/PE= 1/10 to DCM to DCM/EtOAc= 1/1) to afford **AI2**.

### General procedure for the synthesis of AI3

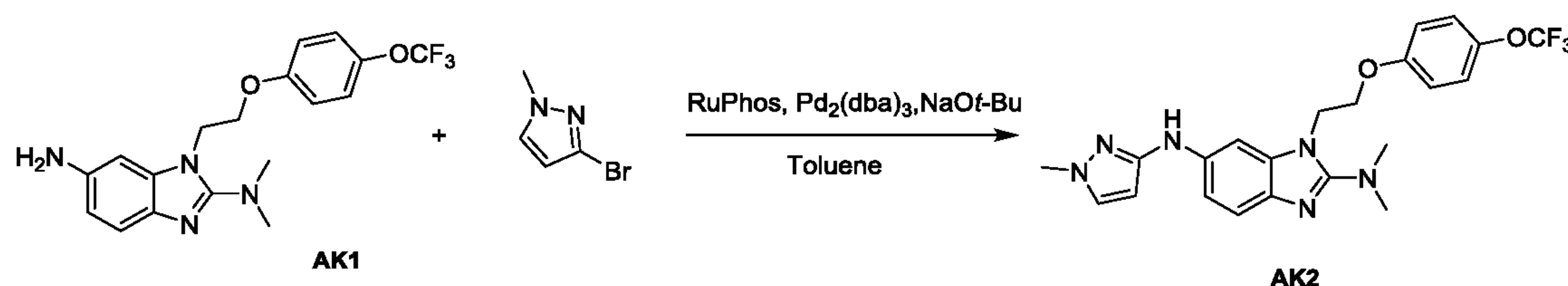
A mixture of compound **AI2** (1.30 g, 3.39 mmol) and Pd-C (200 mg, 10%) in MeOH (30 mL) was stirred at 10 °C under  $\text{H}_2$  (1 atm) for 2 hours. The mixture was filtered, the filtrate was concentrated under reduced pressure to afford a crude **AI3**.

### General procedure for the synthesis of AI4

To a stirred solution of compound **AI3** (100 mg, 0.283 mmol) in MeOH (5 mL) was added BrCN (31 mg, in 0.5 mL ACN) with ice bath, the mixture was stirred at 10 °C for 1 hour. The reaction solution was purified by prep-HPLC (0.01% HCl) to afford **AI4**.

**Scheme 36. General coupling reaction 4 of a benzimidazole  $N^6$  amine****General procedure for the synthesis of AJ2**

To a stirred solution of **AJ1** (100 mg, 0.274 mmol) in anhydrous dioxane (3 mL) were added cyclobutanone (23 mg, 0.329 mmol) and TMSCN (38 mg, 0.384 mmol), the resulting mixture was stirred at 50 °C under N<sub>2</sub> atmosphere for 16 hours. The mixture was diluted with water (15 mL) and extracted with EtOAc (15 mL x 2), the combined extracts were washed with brine (30 mL x 2), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford 90 mg of crude residue, which was purified by prep-HPLC (0.05% HCl) to afford **AJ2**.

**Scheme 37. General coupling reaction 5 of a benzimidazole  $N^6$  amine****General procedure for the synthesis of AK2**

To a stirred solution of **AK1** (100 mg, 0.244 mmol) in anhydrous toluene (5 mL) were added RuPhos (12 mg, 0.0244 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (23 mg, 0.0244 mmol), 3-bromo-1-methyl-1H-pyrazole (47 mg, 0.293 mmol) and NaOt-Bu (58 mg, 0.610 mmol). The mixture was stirred at 110 °C under N<sub>2</sub> for 16 hours. The reaction was diluted with brine (5 mL) and filtered. The filtrate was extracted with EtOAc (5 mL x 3). The combined extract was washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated under reduced pressure. The resulting oil was purified by prep-HPLC (0.01% NH<sub>3</sub>·H<sub>2</sub>O as additive) to afford **AK2**.

Using the above procedures, compounds 1-556 as shown in **Table 7** (further below) were synthesized.

Table 1. 5-LO activity by fluorescence method

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 1      | +++                             | 35     | ++                              | 69     | ++                              |
| 2      | +++                             | 36     | +++                             | 70     | +++                             |
| 3      | +++                             | 37     | +++                             | 71     | +++                             |
| 4      | +++                             | 38     | +++                             | 72     | +                               |
| 5      | +++                             | 39     | +++                             | 73     | +++                             |
| 6      | +++                             | 40     | +++                             | 74     | +++                             |
| 7      | +++                             | 41     | ++                              | 75     | +++                             |
| 8      | +++                             | 42     | ++                              | 76     | +++                             |
| 9      | +++                             | 43     | ++                              | 77     | +++                             |
| 10     | +++                             | 44     | +++                             | 78     | +                               |
| 11     | +++                             | 45     | +                               | 79     | +++                             |
| 12     | +++                             | 46     | +                               | 80     | +++                             |
| 13     | ++                              | 47     | +                               | 81     | +++                             |
| 14     | +++                             | 48     | +++                             | 82     | +                               |
| 15     | +++                             | 49     | +                               | 83     | ++                              |
| 16     | +++                             | 50     | ++                              | 84     | +++                             |
| 17     | ++                              | 51     | +++                             | 85     | ++                              |
| 18     | ++                              | 52     | +++                             | 86     | +++                             |
| 19     | +++                             | 53     | +++                             | 87     | +++                             |
| 20     | +++                             | 54     | +++                             | 88     | +++                             |
| 21     | +++                             | 55     | ++                              | 89     | +++                             |
| 22     | +                               | 56     | +++                             | 90     | +++                             |
| 23     | ++                              | 57     | +++                             | 91     | +++                             |
| 24     | +++                             | 58     | +++                             | 92     | +++                             |
| 25     | +                               | 59     | +++                             | 93     | +++                             |
| 26     | ++                              | 60     | +++                             | 94     | +++                             |
| 27     | ++                              | 61     | +++                             | 95     | +++                             |
| 28     | +++                             | 62     | +++                             | 96     | +++                             |
| 29     | +++                             | 63     | +++                             | 97     | +++                             |
| 30     | +++                             | 64     | +++                             | 98     | +++                             |
| 31     | +++                             | 65     | +++                             | 99     | +++                             |
| 32     | +++                             | 66     | +++                             | 100    | +++                             |
| 33     | +++                             | 67     | +++                             | 101    | +++                             |
| 34     | +++                             | 68     | +++                             | 102    | +++                             |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

Table 1 continued

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 103    | +++                             | 137    | +++                             | 171    | +++                             |
| 104    | +++                             | 138    | +++                             | 172    | +++                             |
| 105    | +++                             | 139    | +++                             | 173    | +++                             |
| 106    | +++                             | 140    | +++                             | 174    | ++                              |
| 107    | +++                             | 141    | +++                             | 175    | +++                             |
| 108    | +++                             | 142    | +++                             | 176    | +++                             |
| 109    | +++                             | 143    | +++                             | 177    | +++                             |
| 110    | +++                             | 144    | +++                             | 178    | +++                             |
| 111    | +++                             | 145    | +++                             | 179    | +++                             |
| 112    | +++                             | 146    | +++                             | 180    | +++                             |
| 113    | +++                             | 147    | +++                             | 181    | +++                             |
| 114    | +++                             | 148    | +++                             | 182    | +++                             |
| 115    | +++                             | 149    | +++                             | 183    | +++                             |
| 116    | +++                             | 150    | +++                             | 184    | +++                             |
| 117    | +++                             | 151    | +++                             | 185    | +++                             |
| 118    | +++                             | 152    | +++                             | 186    | +++                             |
| 119    | +++                             | 153    | +++                             | 187    | +++                             |
| 120    | +++                             | 154    | +++                             | 188    | +++                             |
| 121    | +++                             | 155    | +++                             | 189    | +++                             |
| 122    | +++                             | 156    | +++                             | 190    | +++                             |
| 123    | +++                             | 157    | +++                             | 191    | +++                             |
| 124    | +++                             | 158    | +++                             | 192    | +++                             |
| 125    | +++                             | 159    | +++                             | 193    | +                               |
| 126    | +++                             | 160    | +++                             | 194    | +++                             |
| 127    | +++                             | 161    | +++                             | 195    | +++                             |
| 128    | +++                             | 162    | +++                             | 196    | +++                             |
| 129    | +++                             | 163    | +++                             | 197    | +++                             |
| 130    | +++                             | 164    | +++                             | 198    | +++                             |
| 131    | +++                             | 165    | +++                             | 199    | +++                             |
| 132    | +++                             | 166    | +++                             | 200    | +++                             |
| 133    | +++                             | 167    | +++                             | 201    | +++                             |
| 134    | +++                             | 168    | +++                             | 202    | +++                             |
| 135    | +++                             | 169    | +++                             | 203    | +++                             |
| 136    | +++                             | 170    | +++                             | 204    | +++                             |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

Table 1 continued

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 205    | +++                             | 239    | +++                             | 273    | +++                             |
| 206    | +++                             | 240    | +++                             | 274    | +++                             |
| 207    | +++                             | 241    | +++                             | 275    | +++                             |
| 208    | +++                             | 242    | ++                              | 276    | +++                             |
| 209    | +++                             | 243    | +++                             | 277    | +++                             |
| 210    | +++                             | 244    | +++                             | 278    | +++                             |
| 211    | +++                             | 245    | +                               | 279    | ++                              |
| 212    | +++                             | 246    | +++                             | 280    | +++                             |
| 213    | +++                             | 247    | +++                             | 281    | +++                             |
| 214    | +++                             | 248    | +++                             | 282    | +++                             |
| 215    | +++                             | 249    | +++                             | 283    | +++                             |
| 216    | +++                             | 250    | +++                             | 284    | +++                             |
| 217    | +++                             | 251    | +++                             | 285    | +++                             |
| 218    | +++                             | 252    | +++                             | 286    | +++                             |
| 219    | +++                             | 253    | +++                             | 287    | +++                             |
| 220    | +++                             | 254    | +++                             | 288    | +++                             |
| 221    | +++                             | 255    | +++                             | 289    | +++                             |
| 222    | +++                             | 256    | +++                             | 290    | +++                             |
| 223    | +++                             | 257    | +++                             | 291    | +++                             |
| 224    | +++                             | 258    | +++                             | 292    | +++                             |
| 225    | +++                             | 259    | +++                             | 293    | +++                             |
| 226    | +++                             | 260    | +++                             | 294    | +++                             |
| 227    | +++                             | 261    | +++                             | 295    | +++                             |
| 228    | +++                             | 262    | +                               | 296    | +++                             |
| 229    | +++                             | 263    | +++                             | 297    | +++                             |
| 230    | +++                             | 264    | +++                             | 298    | +++                             |
| 231    | +++                             | 265    | +++                             | 299    | +++                             |
| 232    | +++                             | 266    | +++                             | 300    | +++                             |
| 233    | +++                             | 267    | +++                             | 301    | +++                             |
| 234    | +++                             | 268    | +++                             | 302    | +++                             |
| 235    | +                               | 269    | +++                             | 303    | +++                             |
| 236    | +++                             | 270    | +++                             | 304    | +++                             |
| 237    | +++                             | 271    | +++                             | 305    | +++                             |
| 238    | +++                             | 272    | +++                             | 306    | +++                             |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

Table 1 continued

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 307    | +++                             | 341    | +++                             | 375    | +++                             |
| 308    | +++                             | 342    | +++                             | 376    | +++                             |
| 309    | +++                             | 343    | +++                             | 377    | +++                             |
| 310    | +++                             | 344    | +++                             | 378    | +++                             |
| 311    | +++                             | 345    | +++                             | 379    | +++                             |
| 312    | +++                             | 346    | +++                             | 380    | +++                             |
| 313    | +++                             | 347    | +++                             | 381    | +++                             |
| 314    | +++                             | 348    | +++                             | 382    | +++                             |
| 315    | +++                             | 349    | +++                             | 383    | +++                             |
| 316    | +++                             | 350    | +++                             | 384    | +++                             |
| 317    | +++                             | 351    | +++                             | 385    | +++                             |
| 318    | +++                             | 352    | +++                             | 386    | ++                              |
| 319    | +++                             | 353    | +++                             | 387    | +++                             |
| 320    | +++                             | 354    | +++                             | 388    | +++                             |
| 321    | +++                             | 355    | ++                              | 389    | +++                             |
| 322    | +                               | 356    | +++                             | 390    | +++                             |
| 323    | +++                             | 357    | +++                             | 391    | +++                             |
| 324    | +++                             | 358    | +++                             | 392    | +++                             |
| 325    | +++                             | 359    | +++                             | 393    | +++                             |
| 326    | +++                             | 360    | +++                             | 394    | +++                             |
| 327    | +++                             | 361    | +++                             | 395    | +++                             |
| 328    | +++                             | 362    | +++                             | 396    | +++                             |
| 329    | +++                             | 363    | +++                             | 397    | +++                             |
| 330    | +++                             | 364    | +++                             | 398    | +++                             |
| 331    | +++                             | 365    | +++                             | 399    | +++                             |
| 332    | +++                             | 366    | +++                             | 400    | +++                             |
| 333    | +++                             | 367    | +++                             | 401    | +++                             |
| 334    | +++                             | 368    | +++                             | 402    | +++                             |
| 335    | +++                             | 369    | +++                             | 403    | +++                             |
| 336    | +++                             | 370    | +++                             | 404    | +++                             |
| 337    | +++                             | 371    | +++                             | 405    | +++                             |
| 338    | +++                             | 372    | +++                             | 406    | +++                             |
| 339    | +++                             | 373    | +++                             | 407    | +++                             |
| 340    | +++                             | 374    | +++                             | 408    | +++                             |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

Table 1 continued

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 409    | +++                             | 443    | +++                             | 477    | +++                             |
| 410    | +++                             | 444    | +++                             | 478    | +++                             |
| 411    | +++                             | 445    | +++                             | 479    | +++                             |
| 412    | +++                             | 446    | +++                             | 480    | +++                             |
| 413    | +++                             | 447    | ++                              | 481    | +++                             |
| 414    | +++                             | 448    | ++                              | 482    | +++                             |
| 415    | +++                             | 449    | +++                             | 483    | +++                             |
| 416    | +++                             | 450    | +++                             | 484    | +++                             |
| 417    | +++                             | 451    | +++                             | 485    | +++                             |
| 418    | +++                             | 452    | +++                             | 486    | +++                             |
| 419    | +++                             | 453    | +++                             | 487    | +++                             |
| 420    | +++                             | 454    | +++                             | 488    | ++                              |
| 421    | +++                             | 455    | +++                             | 489    | +++                             |
| 422    | +++                             | 456    | +++                             | 490    | +++                             |
| 423    | +++                             | 457    | +++                             | 491    | +++                             |
| 424    | +++                             | 458    | +++                             | 492    | +++                             |
| 425    | +++                             | 459    | +++                             | 493    | ++                              |
| 426    | +++                             | 460    | +++                             | 494    | ++                              |
| 427    | +++                             | 461    | +++                             | 495    | +++                             |
| 428    | +++                             | 462    | +++                             | 496    | +++                             |
| 429    | +                               | 463    | +++                             | 497    | ++                              |
| 430    | +++                             | 464    | ++                              | 498    | +                               |
| 431    | +++                             | 465    | +++                             | 499    | +++                             |
| 432    | +++                             | 466    | +++                             | 500    | ++                              |
| 433    | +++                             | 467    | +++                             | 501    | +++                             |
| 434    | +++                             | 468    | +++                             | 502    | ++                              |
| 435    | +++                             | 469    | +++                             | 503    | +++                             |
| 436    | +++                             | 470    | +++                             | 504    | ++                              |
| 437    | +++                             | 471    | +++                             | 505    | +++                             |
| 438    | +++                             | 472    | ++                              | 506    | +                               |
| 439    | +++                             | 473    | +++                             | 507    | +++                             |
| 440    | +++                             | 474    | +++                             | 508    | ++                              |
| 441    | +                               | 475    | +++                             | 509    | +++                             |
| 442    | +++                             | 476    | +++                             | 510    | +                               |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

Table 1 continued

| # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) | # cpds | 5-LO<br>(IC <sub>50</sub> , uM) |
|--------|---------------------------------|--------|---------------------------------|--------|---------------------------------|
| 511    | +                               | 527    | +                               | 543    | +++                             |
| 512    | +++                             | 528    | +                               | 544    | +++                             |
| 513    | +++                             | 529    | +++                             | 545    | ++                              |
| 514    | +++                             | 530    | +++                             | 546    | +++                             |
| 515    | +                               | 531    | +++                             | 547    | +++                             |
| 516    | +                               | 532    | +++                             | 548    | +++                             |
| 517    | ++                              | 533    | +++                             | 549    | +++                             |
| 518    | +                               | 534    | +++                             | 550    | +++                             |
| 519    | +                               | 535    | +++                             | 551    | +++                             |
| 520    | +                               | 536    | +++                             | 552    | +++                             |
| 521    | ++                              | 537    | +++                             | 553    | +++                             |
| 522    | +                               | 538    | +++                             | 554    | +++                             |
| 523    | +                               | 539    | +++                             | 555    | +++                             |
| 524    | +                               | 540    | +++                             | 556    | +++                             |
| 525    | +++                             | 541    | +++                             |        |                                 |
| 526    | ++                              | 542    | +++                             |        |                                 |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-10uM, + indicates >10 uM

**Table 2. 5-LO activity by ELISA method**

| # cpds | 5LO<br>(IC <sub>50</sub> , uM) |
|--------|--------------------------------|
| 14     | +++                            |
| 48     | ++                             |
| 49     | ++                             |

Activity range: +++ indicates < 1 uM, ++ indicates between 1-20 uM, + indicates > 20 uM

**Table 3. LTB4 secretion assay in RBL**

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 14     | +++                            | 57     | +++                            | 91     | +++                            |
| 17     | +++                            | 58     | +++                            | 92     | +++                            |
| 24     | +++                            | 59     | +++                            | 93     | +++                            |
| 26     | +                              | 60     | +++                            | 94     | +++                            |
| 27     | +                              | 61     | ++                             | 95     | +++                            |
| 28     | ++                             | 62     | +++                            | 96     | +++                            |
| 29     | +++                            | 63     | ++                             | 97     | +++                            |
| 30     | +++                            | 64     | +                              | 98     | +++                            |
| 31     | +                              | 65     | +++                            | 99     | +++                            |
| 32     | +++                            | 66     | +++                            | 100    | +++                            |
| 33     | +++                            | 67     | +++                            | 101    | +++                            |
| 34     | ++                             | 68     | +++                            | 102    | +++                            |
| 35     | +                              | 69     | +++                            | 103    | +++                            |
| 36     | ++                             | 70     | +++                            | 104    | +++                            |
| 37     | +                              | 71     | ++                             | 105    | +++                            |
| 38     | +++                            | 72     | +                              | 106    | +++                            |
| 39     | ++                             | 73     | +++                            | 107    | +++                            |
| 40     | ++                             | 74     | +++                            | 108    | +                              |
| 41     | ++                             | 75     | ++                             | 109    | +++                            |
| 42     | ++                             | 76     | +                              | 110    | +++                            |
| 43     | +++                            | 77     | ++                             | 111    | +++                            |
| 44     | +++                            | 78     | ++                             | 112    | +++                            |
| 45     | +++                            | 79     | +++                            | 113    | +++                            |
| 46     | +++                            | 80     | +++                            | 114    | ++                             |
| 47     | +                              | 81     | +++                            | 115    | +                              |
| 48     | +++                            | 82     | ++                             | 116    | +++                            |
| 49     | +++                            | 83     | +                              | 117    | ++                             |
| 50     | ++                             | 84     | +++                            | 118    | +++                            |
| 51     | +++                            | 85     | +                              | 119    | +++                            |
| 52     | +++                            | 86     | +++                            | 120    | +++                            |
| 53     | +++                            | 87     | +++                            | 121    | +++                            |
| 54     | +++                            | 88     | +++                            | 122    | +++                            |
| 55     | +++                            | 89     | +                              | 123    | +++                            |
| 56     | +++                            | 90     | +++                            | 124    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 3 continued

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 125    | +++                            | 159    | +                              | 193    | +++                            |
| 126    | +++                            | 160    | +++                            | 194    | +++                            |
| 127    | +++                            | 161    | +++                            | 195    | +++                            |
| 128    | +++                            | 162    | +++                            | 196    | +++                            |
| 129    | +++                            | 163    | +                              | 197    | +++                            |
| 130    | +++                            | 164    | +++                            | 198    | ++                             |
| 131    | +++                            | 165    | +++                            | 199    | +++                            |
| 132    | +++                            | 166    | +++                            | 200    | +++                            |
| 133    | ++                             | 167    | +                              | 201    | +                              |
| 134    | +++                            | 168    | +++                            | 202    | +++                            |
| 135    | +++                            | 169    | +++                            | 203    | +++                            |
| 136    | +++                            | 170    | ++                             | 204    | +++                            |
| 137    | +++                            | 171    | +                              | 205    | +++                            |
| 138    | +++                            | 172    | +++                            | 206    | +++                            |
| 139    | +                              | 173    | +                              | 207    | +++                            |
| 140    | +++                            | 174    | +                              | 208    | +++                            |
| 141    | +                              | 175    | +++                            | 209    | +++                            |
| 142    | ++                             | 176    | +++                            | 210    | +++                            |
| 143    | ++                             | 177    | +++                            | 211    | +++                            |
| 144    | ++                             | 178    | ++                             | 212    | +++                            |
| 145    | +++                            | 179    | +++                            | 213    | +++                            |
| 146    | ++                             | 180    | +++                            | 214    | +++                            |
| 147    | +++                            | 181    | +                              | 215    | +++                            |
| 148    | +++                            | 182    | ++                             | 216    | +++                            |
| 149    | +++                            | 183    | +                              | 217    | +++                            |
| 150    | +++                            | 184    | +++                            | 218    | +++                            |
| 151    | +                              | 185    | +++                            | 219    | +++                            |
| 152    | +++                            | 186    | +++                            | 220    | +++                            |
| 153    | +++                            | 187    | +++                            | 221    | +                              |
| 154    | +                              | 188    | +                              | 222    | ++                             |
| 155    | +++                            | 189    | +                              | 223    | +++                            |
| 156    | ++                             | 190    | +++                            | 224    | +++                            |
| 157    | +                              | 191    | +++                            | 225    | +                              |
| 158    | +                              | 192    | +++                            | 226    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 3 continued

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 227    | +++                            | 261    | +++                            | 295    | +++                            |
| 228    | +                              | 262    | +++                            | 296    | +++                            |
| 229    | +++                            | 263    | ++                             | 297    | +++                            |
| 230    | +++                            | 264    | +++                            | 298    | +++                            |
| 231    | +++                            | 265    | +++                            | 299    | +++                            |
| 232    | +                              | 266    | ++                             | 300    | +++                            |
| 233    | +++                            | 267    | +++                            | 301    | +++                            |
| 234    | +++                            | 268    | +++                            | 302    | +++                            |
| 235    | +++                            | 269    | +++                            | 303    | +                              |
| 236    | +++                            | 270    | +++                            | 304    | +++                            |
| 237    | +                              | 271    | +++                            | 305    | +++                            |
| 238    | +++                            | 272    | +++                            | 306    | +++                            |
| 239    | +++                            | 273    | +++                            | 307    | ++                             |
| 240    | +++                            | 274    | +++                            | 308    | +                              |
| 241    | +++                            | 275    | +++                            | 309    | +                              |
| 242    | +++                            | 276    | +++                            | 310    | +                              |
| 243    | +++                            | 277    | +++                            | 311    | +                              |
| 244    | +++                            | 278    | +++                            | 312    | +                              |
| 245    | +++                            | 279    | +++                            | 313    | +++                            |
| 246    | +++                            | 280    | +++                            | 314    | ++                             |
| 247    | +++                            | 281    | +++                            | 315    | ++                             |
| 248    | +++                            | 282    | +++                            | 316    | +++                            |
| 249    | +++                            | 283    | +++                            | 317    | +                              |
| 250    | +++                            | 284    | +++                            | 318    | +                              |
| 251    | +++                            | 285    | +++                            | 319    | +                              |
| 252    | +++                            | 286    | +++                            | 320    | +                              |
| 253    | +++                            | 287    | +++                            | 321    | ++                             |
| 254    | +++                            | 288    | +++                            | 322    | +++                            |
| 255    | +++                            | 289    | +++                            | 323    | +++                            |
| 256    | ++                             | 290    | +++                            | 324    | +++                            |
| 257    | +++                            | 291    | +++                            | 325    | +++                            |
| 258    | +++                            | 292    | +++                            | 326    | +++                            |
| 259    | +++                            | 293    | +++                            | 327    | +++                            |
| 260    | +++                            | 294    | +++                            | 328    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 3 continued

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 329    | +++                            | 363    | +                              | 397    | +++                            |
| 330    | +++                            | 364    | +                              | 398    | +++                            |
| 331    | +++                            | 365    | +++                            | 399    | +++                            |
| 332    | +++                            | 366    | +++                            | 400    | +++                            |
| 333    | +++                            | 367    | +++                            | 401    | +++                            |
| 334    | ++                             | 368    | +++                            | 402    | +++                            |
| 335    | +++                            | 369    | +++                            | 403    | +++                            |
| 336    | ++                             | 370    | ++                             | 404    | +                              |
| 337    | ++                             | 371    | ++                             | 405    | +++                            |
| 338    | +                              | 372    | +++                            | 406    | +++                            |
| 339    | ++                             | 373    | +++                            | 407    | +++                            |
| 340    | +++                            | 374    | +++                            | 408    | +                              |
| 341    | ++                             | 375    | +++                            | 409    | +                              |
| 342    | +++                            | 376    | +                              | 410    | +++                            |
| 343    | +                              | 377    | +++                            | 411    | +                              |
| 344    | +                              | 378    | +++                            | 412    | +++                            |
| 345    | +                              | 379    | +++                            | 413    | +++                            |
| 346    | +++                            | 380    | +++                            | 414    | +++                            |
| 347    | +++                            | 381    | +                              | 415    | +++                            |
| 348    | +                              | 382    | +++                            | 416    | ++                             |
| 349    | +++                            | 383    | +++                            | 417    | +                              |
| 350    | +++                            | 384    | +++                            | 418    | +                              |
| 351    | ++                             | 385    | ++                             | 419    | +++                            |
| 352    | +++                            | 386    | +                              | 420    | +++                            |
| 353    | +++                            | 387    | +++                            | 421    | +++                            |
| 354    | +                              | 388    | ++                             | 422    | +++                            |
| 355    | +                              | 389    | +++                            | 423    | +++                            |
| 356    | ++                             | 390    | +++                            | 424    | +++                            |
| 357    | +++                            | 391    | +++                            | 425    | +++                            |
| 358    | +++                            | 392    | +++                            | 426    | +++                            |
| 359    | +++                            | 393    | +++                            | 427    | +++                            |
| 360    | ++                             | 394    | ++                             | 428    | +++                            |
| 361    | +++                            | 395    | +++                            | 429    | ++                             |
| 362    | ++                             | 396    | +++                            | 430    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 3 continued

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 431    | +++                            | 465    | +++                            | 499    | +++                            |
| 432    | +++                            | 466    | +++                            | 500    | ++                             |
| 433    | ++                             | 467    | +++                            | 501    | +++                            |
| 434    | +++                            | 468    | +++                            | 502    | +++                            |
| 435    | +++                            | 469    | +++                            | 503    | +++                            |
| 436    | +++                            | 470    | +++                            | 504    | +++                            |
| 437    | +++                            | 471    | +++                            | 505    | +++                            |
| 438    | ++                             | 472    | +++                            | 506    | +++                            |
| 439    | ++                             | 473    | +++                            | 507    | +++                            |
| 440    | +++                            | 474    | +++                            | 508    | +++                            |
| 441    | +                              | 475    | +++                            | 509    | +++                            |
| 442    | +++                            | 476    | +++                            | 510    | +++                            |
| 443    | +                              | 477    | +++                            | 511    | +++                            |
| 444    | ++                             | 478    | +++                            | 512    | +++                            |
| 445    | +++                            | 479    | +++                            | 513    | +++                            |
| 446    | +++                            | 480    | +++                            | 514    | +++                            |
| 447    | +++                            | 481    | +++                            | 515    | +++                            |
| 448    | +++                            | 482    | +++                            | 516    | +++                            |
| 449    | +++                            | 483    | +                              | 517    | +++                            |
| 450    | +++                            | 484    | +                              | 518    | +++                            |
| 451    | +++                            | 485    | ++                             | 519    | +++                            |
| 452    | +++                            | 486    | +++                            | 520    | +++                            |
| 453    | +++                            | 487    | +++                            | 521    | +++                            |
| 454    | ++                             | 488    | +                              | 522    | +++                            |
| 455    | +++                            | 489    | +++                            | 523    | +++                            |
| 456    | +                              | 490    | +++                            | 524    | +++                            |
| 457    | +++                            | 491    | +++                            | 525    | +++                            |
| 458    | +++                            | 492    | +++                            | 526    | +++                            |
| 459    | ++                             | 493    | +++                            | 527    | +++                            |
| 460    | +++                            | 494    | +++                            | 528    | +++                            |
| 461    | +++                            | 495    | +++                            | 529    | +++                            |
| 462    | +                              | 496    | +++                            | 530    | +++                            |
| 463    | +++                            | 497    | +                              | 531    | +++                            |
| 464    | +++                            | 498    | +                              | 532    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 3 continued

| # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) | # cpds | RBL<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 533    | +++                            | 541    | +++                            | 549    | +++                            |
| 534    | +++                            | 542    | +++                            | 550    | +++                            |
| 535    | +++                            | 543    | +++                            | 551    | +++                            |
| 536    | +++                            | 544    | +++                            | 552    | +++                            |
| 537    | +++                            | 545    | +++                            | 553    | +++                            |
| 538    | +++                            | 546    | +++                            | 554    | ++                             |
| 539    | +++                            | 547    | +++                            | 555    | ++                             |
| 540    | +++                            | 548    | +++                            | 556    | +++                            |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

**Table 4. LTB4 secretion assay in Rat whole blood (RWB)**

| # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 1      | +                              | 57     | +                              | 108    | +                              |
| 3      | +                              | 58     | +                              | 109    | +++                            |
| 4      | +                              | 59     | +                              | 110    | +++                            |
| 5      | ++                             | 62     | +++                            | 111    | +++                            |
| 6      | +                              | 65     | +++                            | 112    | ++                             |
| 7      | +                              | 66     | +                              | 113    | +++                            |
| 8      | +                              | 67     | +                              | 114    | +                              |
| 9      | ++                             | 68     | +                              | 116    | ++                             |
| 10     | ++                             | 70     | +                              | 118    | +                              |
| 11     | +++                            | 73     | ++                             | 119    | +++                            |
| 12     | +++                            | 74     | ++                             | 120    | +++                            |
| 13     | +                              | 75     | +                              | 121    | +                              |
| 14     | +++                            | 77     | +++                            | 122    | +++                            |
| 15     | +                              | 79     | +++                            | 123    | +++                            |
| 16     | +                              | 80     | +++                            | 125    | +++                            |
| 17     | +                              | 81     | +++                            | 126    | +                              |
| 20     | +                              | 86     | +++                            | 127    | +                              |
| 21     | +                              | 87     | +++                            | 128    | +                              |
| 22     | +                              | 88     | +++                            | 129    | +                              |
| 23     | ++                             | 90     | ++                             | 130    | +++                            |
| 24     | +++                            | 91     | ++                             | 132    | +                              |
| 30     | +++                            | 92     | +++                            | 135    | ++                             |
| 32     | +++                            | 93     | +                              | 136    | +++                            |
| 38     | +                              | 94     | +++                            | 137    | +++                            |
| 43     | +                              | 97     | +++                            | 138    | +++                            |
| 44     | +                              | 98     | +++                            | 145    | +++                            |
| 48     | +++                            | 99     | +                              | 147    | +++                            |
| 49     | ++                             | 101    | +++                            | 148    | +                              |
| 51     | ++                             | 102    | +++                            | 149    | +++                            |
| 52     | +++                            | 103    | +++                            | 150    | +                              |
| 53     | +++                            | 104    | +                              | 152    | ++                             |
| 54     | +++                            | 105    | +                              | 154    | +                              |
| 55     | +                              | 106    | +++                            | 155    | +++                            |
| 56     | ++                             | 107    | +                              | 160    | +                              |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 4 continued

| # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 161    | ++                             | 253    | +++                            | 345    | +++                            |
| 164    | +                              | 256    | +++                            | 350    | +++                            |
| 165    | +++                            | 268    | +++                            | 351    | +++                            |
| 166    | +++                            | 269    | +++                            | 357    | ++                             |
| 172    | ++                             | 270    | +++                            | 358    | +++                            |
| 175    | +                              | 271    | +++                            | 360    | +++                            |
| 176    | +++                            | 273    | ++                             | 362    | +++                            |
| 177    | +++                            | 275    | +++                            | 364    | +                              |
| 184    | +++                            | 277    | +++                            | 367    | +++                            |
| 190    | +                              | 279    | +++                            | 368    | +++                            |
| 191    | +                              | 281    | +++                            | 369    | +++                            |
| 193    | +++                            | 284    | +++                            | 371    | ++                             |
| 195    | +++                            | 288    | +++                            | 373    | +++                            |
| 196    | ++                             | 289    | +++                            | 374    | +++                            |
| 197    | +                              | 291    | ++                             | 378    | +++                            |
| 199    | +++                            | 294    | +                              | 381    | +++                            |
| 202    | +                              | 296    | +++                            | 383    | +                              |
| 203    | +                              | 298    | +                              | 392    | +++                            |
| 204    | +++                            | 300    | ++                             | 394    | +                              |
| 211    | +++                            | 302    | ++                             | 409    | +                              |
| 219    | +                              | 303    | +                              | 412    | +++                            |
| 226    | +++                            | 305    | +                              | 413    | +++                            |
| 227    | +++                            | 306    | +++                            | 414    | +++                            |
| 229    | +++                            | 307    | +                              | 415    | +++                            |
| 231    | +++                            | 309    | +                              | 417    | +                              |
| 233    | +++                            | 311    | +++                            | 418    | +                              |
| 234    | +++                            | 315    | +                              | 430    | +++                            |
| 238    | +++                            | 324    | +++                            | 431    | +++                            |
| 239    | +++                            | 328    | +++                            | 433    | +++                            |
| 241    | +                              | 336    | +++                            | 447    | +++                            |
| 243    | +++                            | 337    | ++                             | 448    | +++                            |
| 245    | ++                             | 341    | +++                            | 449    | +++                            |
| 249    | +++                            | 343    | ++                             | 450    | +++                            |
| 251    | +++                            | 344    | ++                             | 459    | ++                             |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 4 continued

| # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) | # cpds | RWB<br>(EC <sub>50</sub> , uM) |
|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|
| 461    | +++                            | 496    | +++                            | 528    | +++                            |
| 464    | +++                            | 497    | +                              | 529    | +++                            |
| 465    | +++                            | 498    | +++                            | 530    | +++                            |
| 466    | +++                            | 499    | +++                            | 531    | +++                            |
| 468    | +++                            | 501    | +++                            | 532    | +++                            |
| 469    | +++                            | 502    | +++                            | 533    | +++                            |
| 470    | +++                            | 503    | +++                            | 534    | +++                            |
| 471    | +++                            | 504    | +++                            | 535    | +++                            |
| 473    | +++                            | 505    | +++                            | 536    | +++                            |
| 474    | +++                            | 506    | +++                            | 537    | +++                            |
| 475    | +++                            | 507    | ++                             | 538    | +++                            |
| 476    | +++                            | 508    | +++                            | 540    | +++                            |
| 477    | +++                            | 509    | +++                            | 541    | +++                            |
| 479    | +++                            | 512    | +++                            | 542    | +++                            |
| 481    | +++                            | 513    | +++                            | 543    | +++                            |
| 482    | +++                            | 514    | +++                            | 544    | +++                            |
| 486    | +++                            | 516    | +++                            | 545    | +++                            |
| 487    | +++                            | 517    | +++                            | 546    | +++                            |
| 489    | +++                            | 518    | +++                            | 547    | +++                            |
| 490    | +++                            | 519    | +++                            | 550    | +++                            |
| 491    | +++                            | 523    | ++                             | 552    | ++                             |
| 492    | +++                            | 524    | ++                             | 553    | +++                            |
| 493    | +++                            | 525    | +++                            | 554    | +++                            |
| 494    | +++                            | 526    | +++                            | 555    | ++                             |
| 495    | +++                            | 527    | +++                            |        |                                |

Activity range: +++ indicates <10uM, ++ indicates between 10-20uM, + indicates > 20 uM

Table 5. PGE<sub>2</sub> inhibition assay

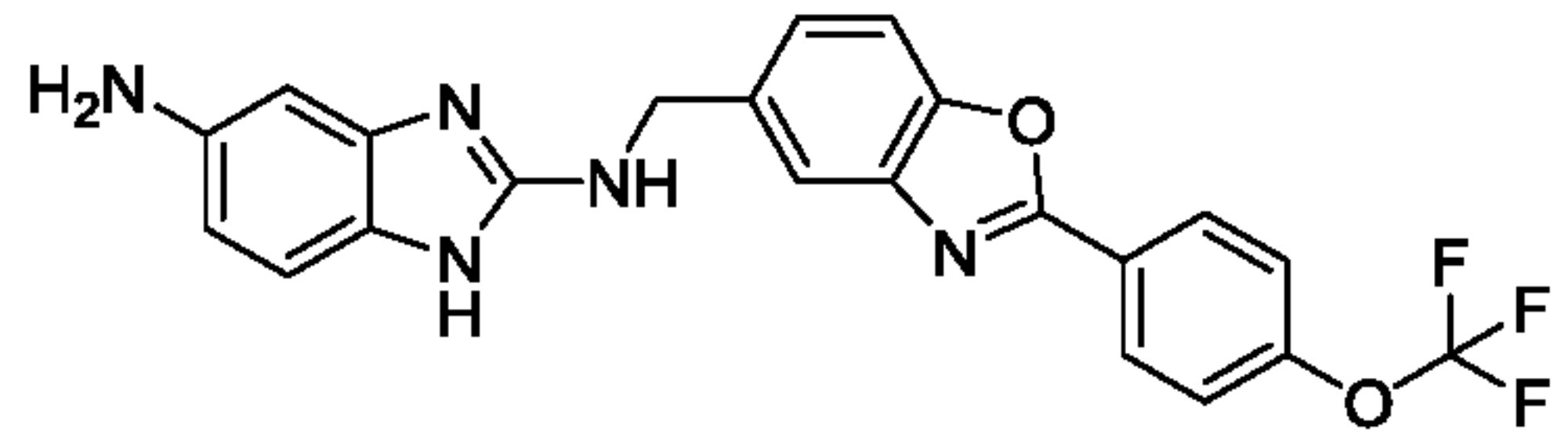
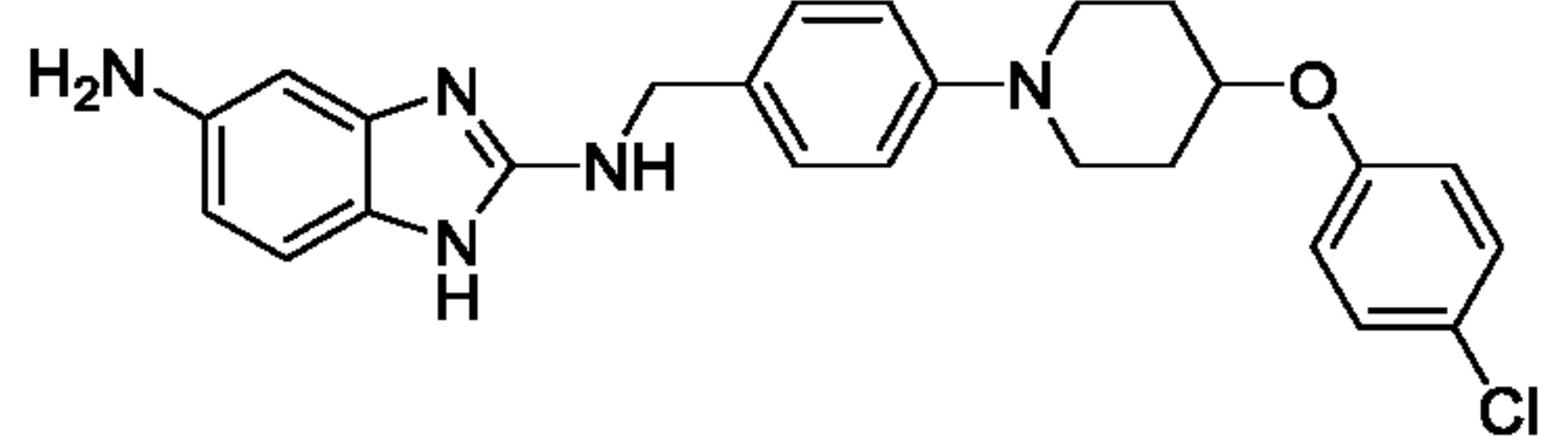
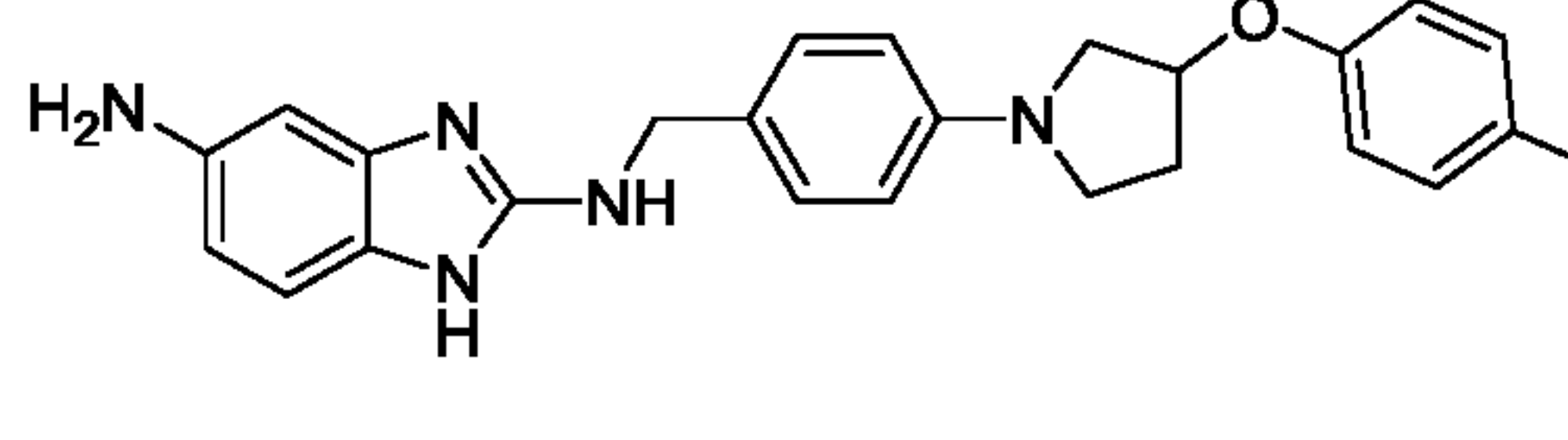
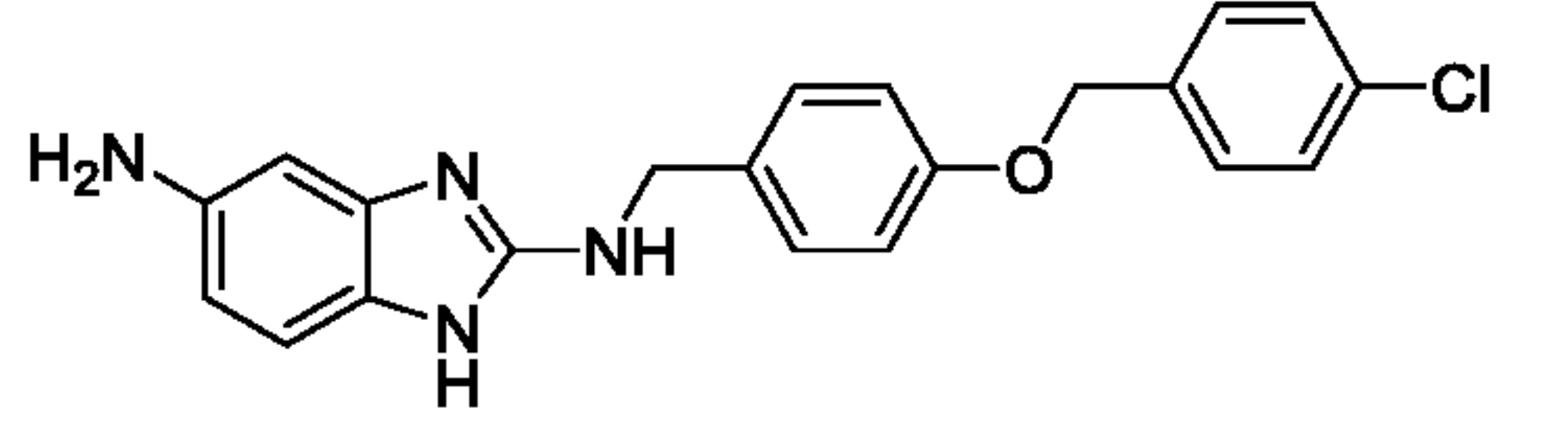
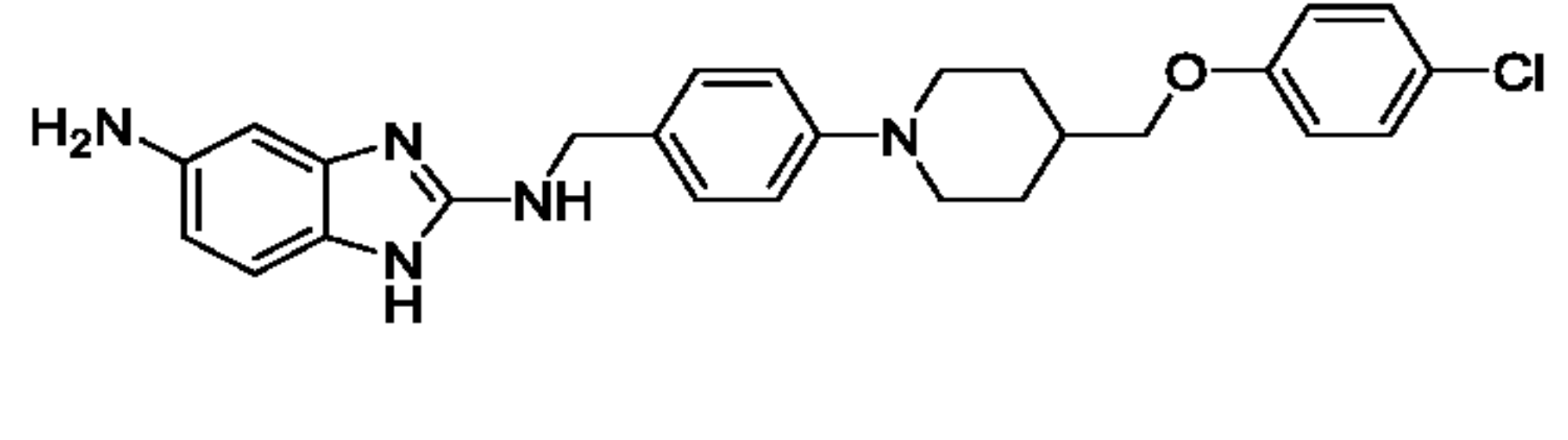
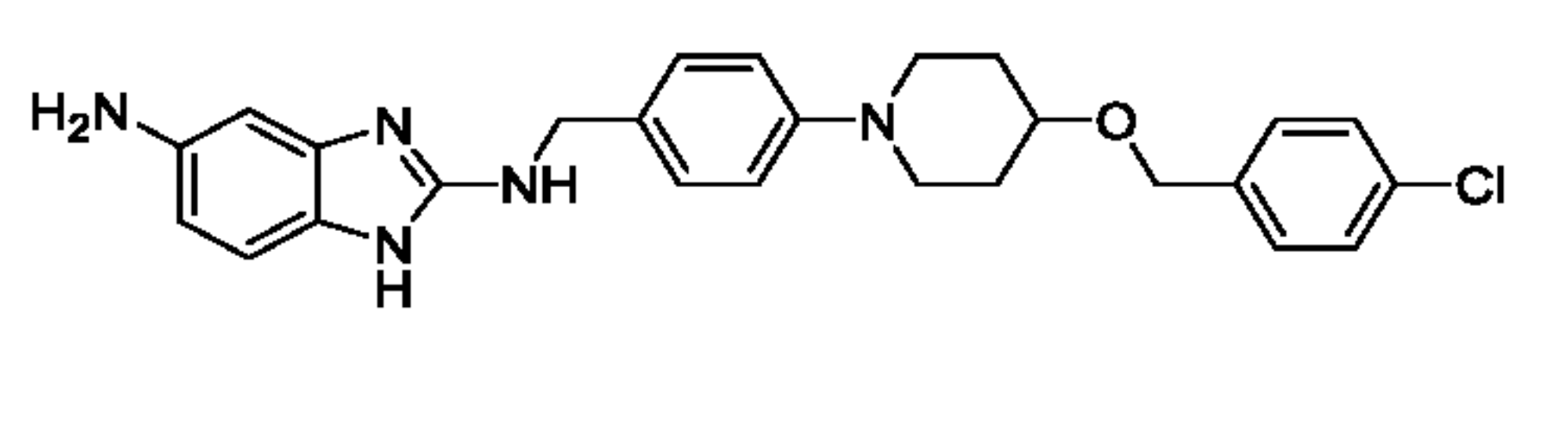
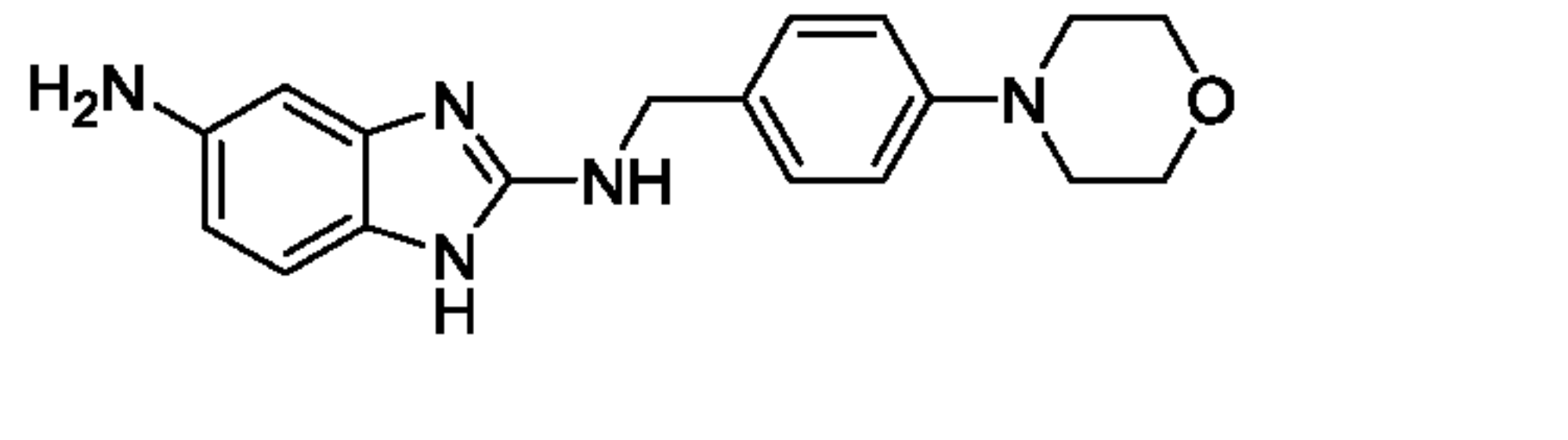
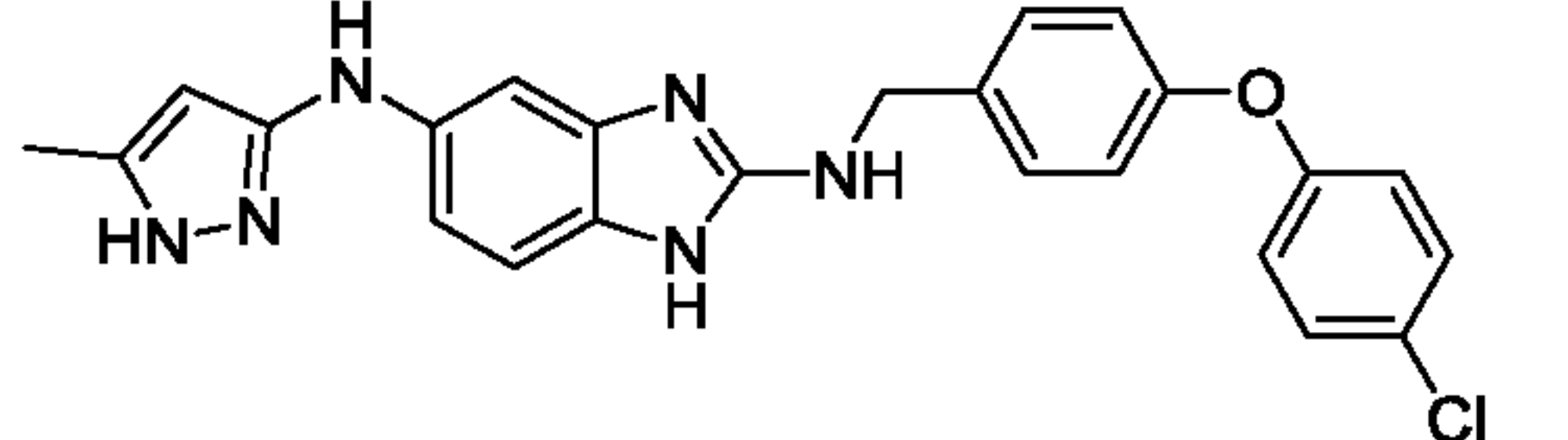
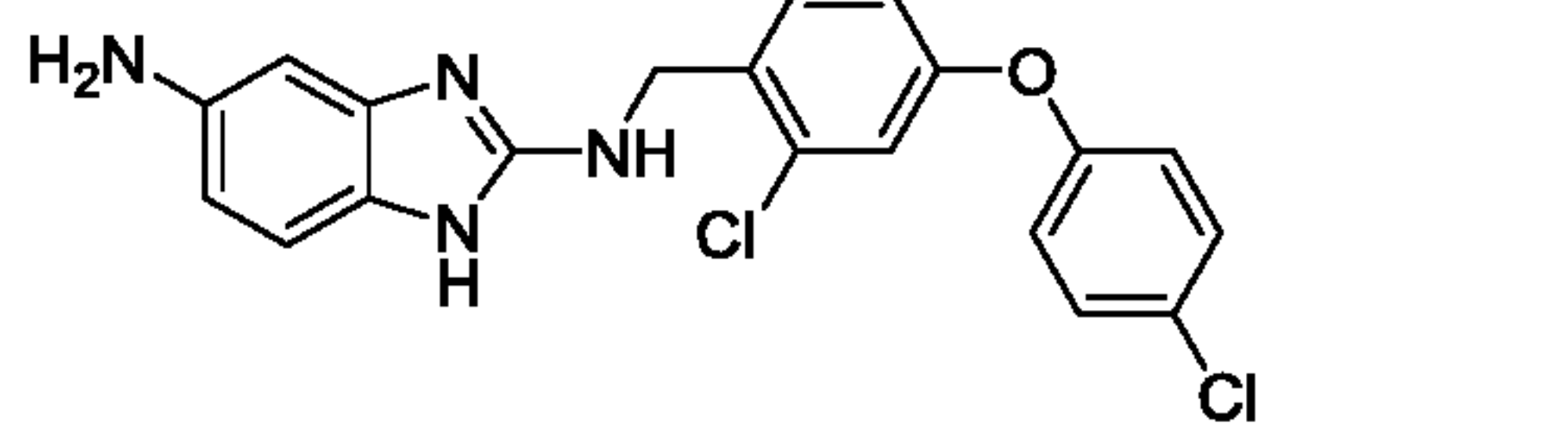
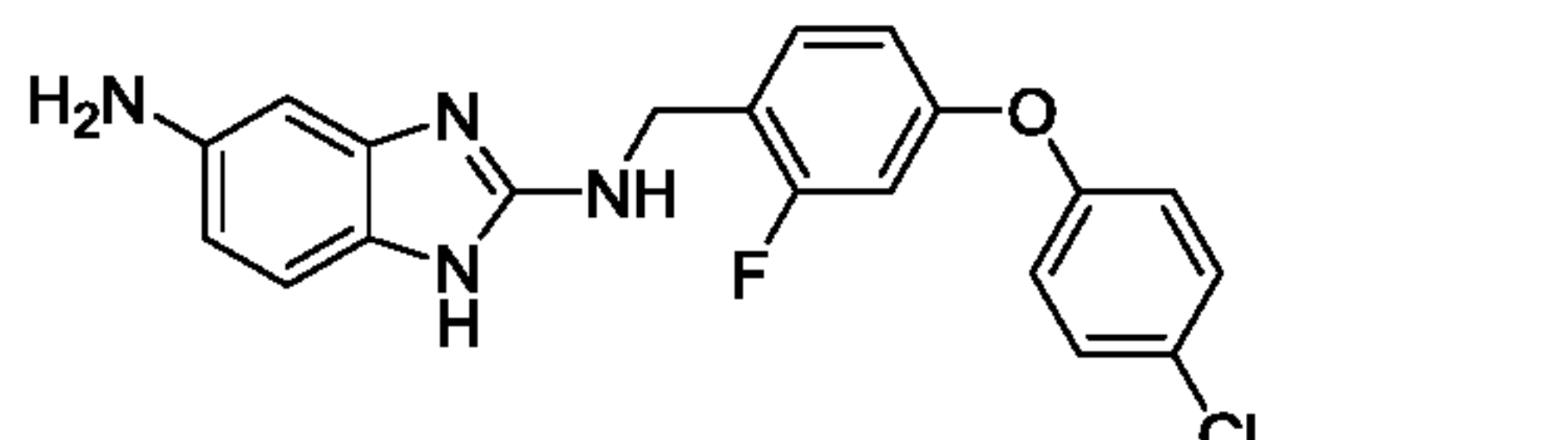
| # cpds | Inhibition<br>(%, 10 uM) | # cpds | Inhibition<br>(%, 10 uM) | # cpds | Inhibition<br>(%, 10 uM) |
|--------|--------------------------|--------|--------------------------|--------|--------------------------|
| 44     | ++                       | 90     | +++                      | 103    | +++                      |
| 53     | +++                      | 91     | +++                      | 195    | +                        |
| 54     | +++                      | 95     | +++                      | 211    | ++                       |
| 86     | +++                      | 99     | +++                      | 226    | +++                      |

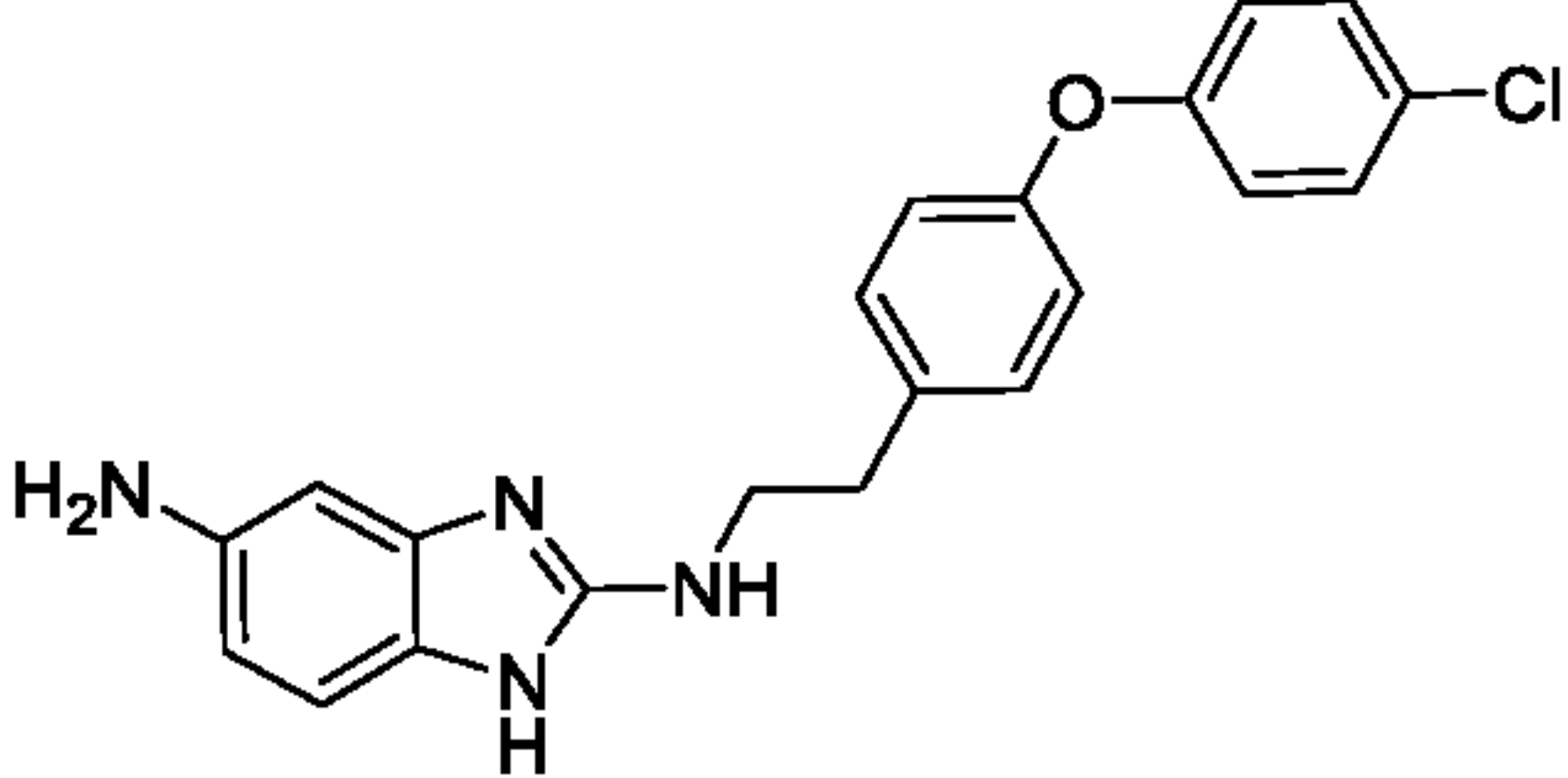
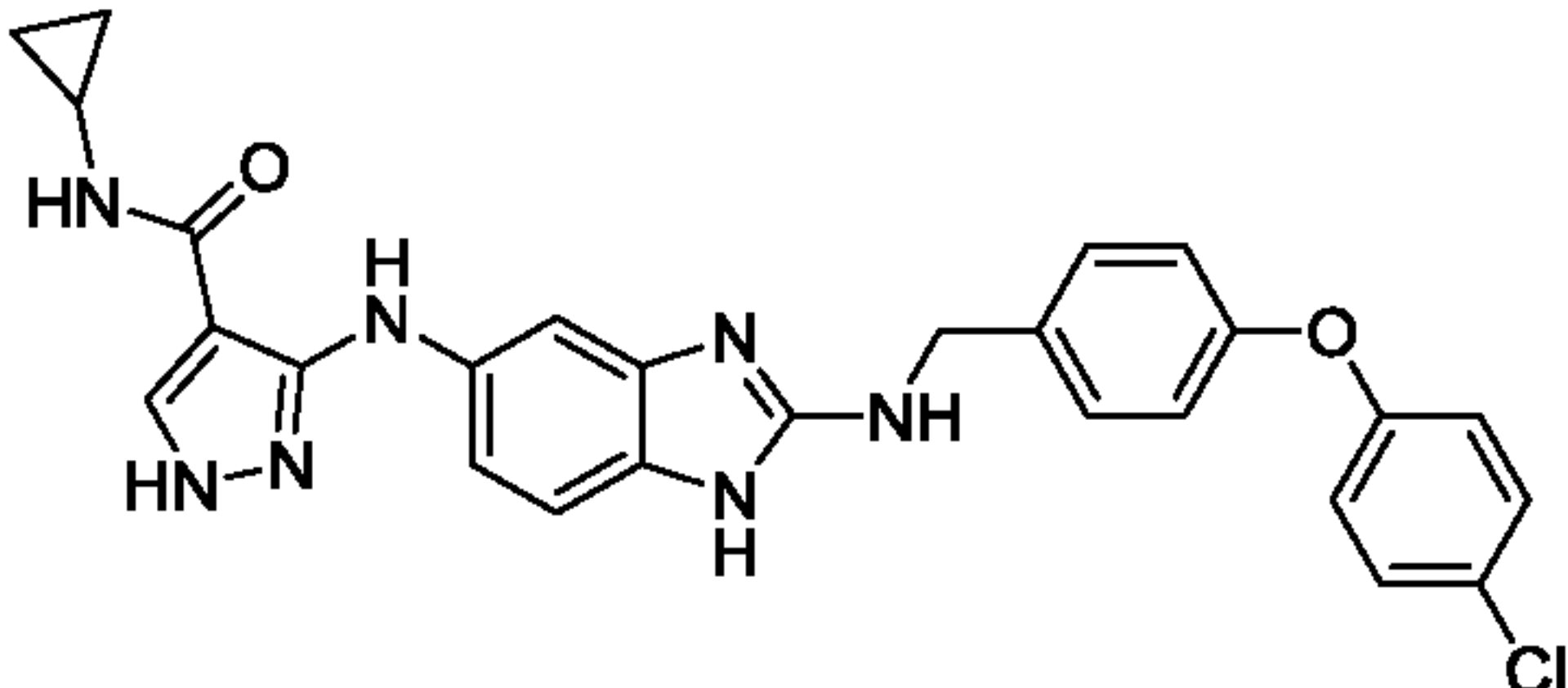
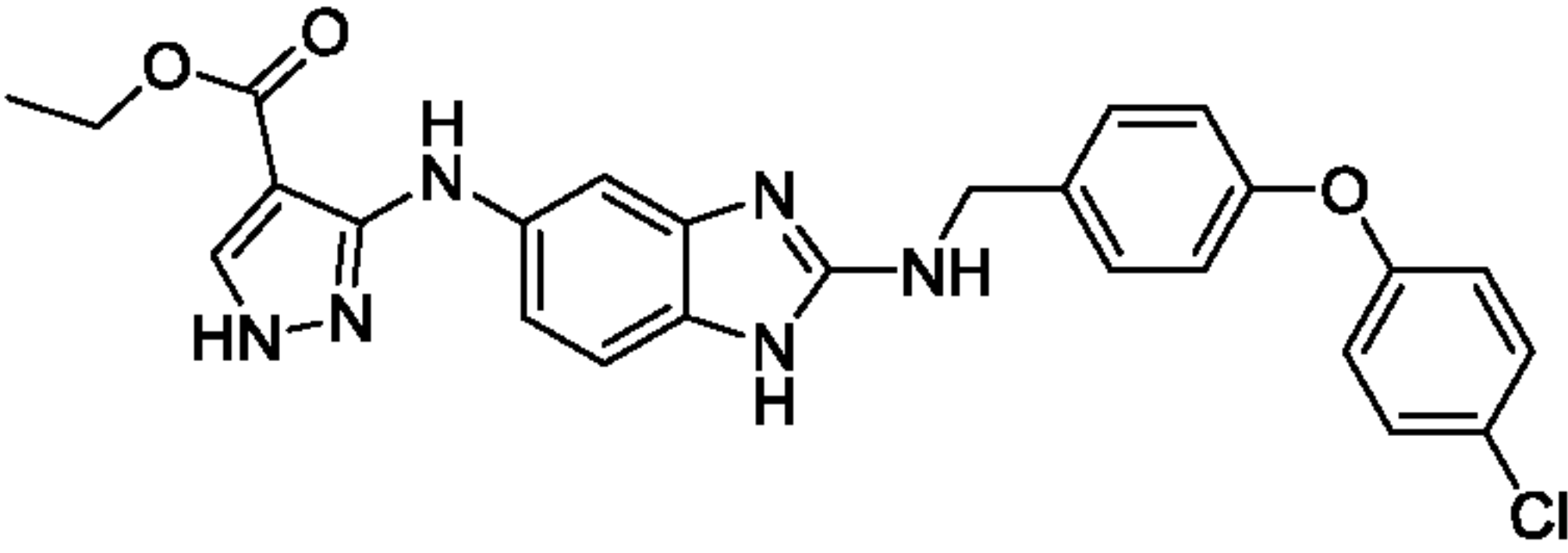
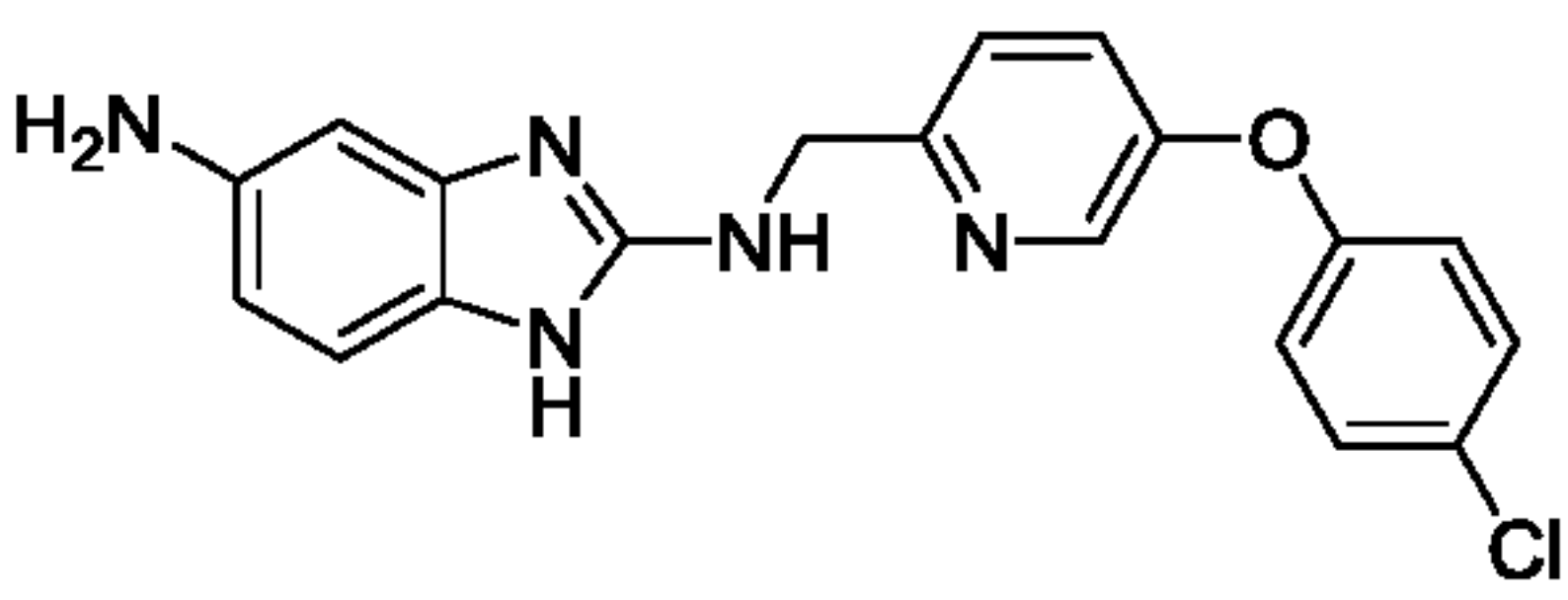
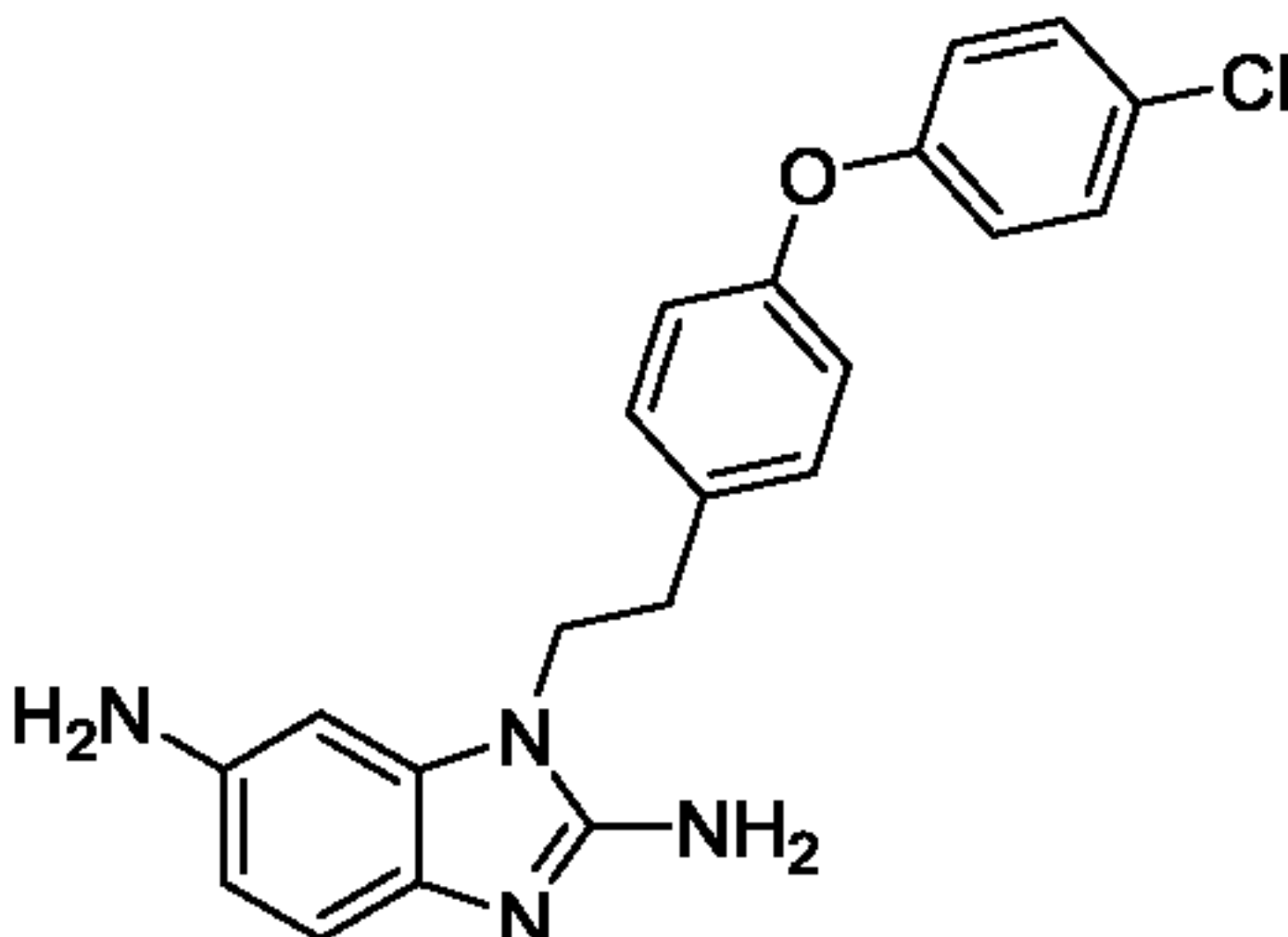
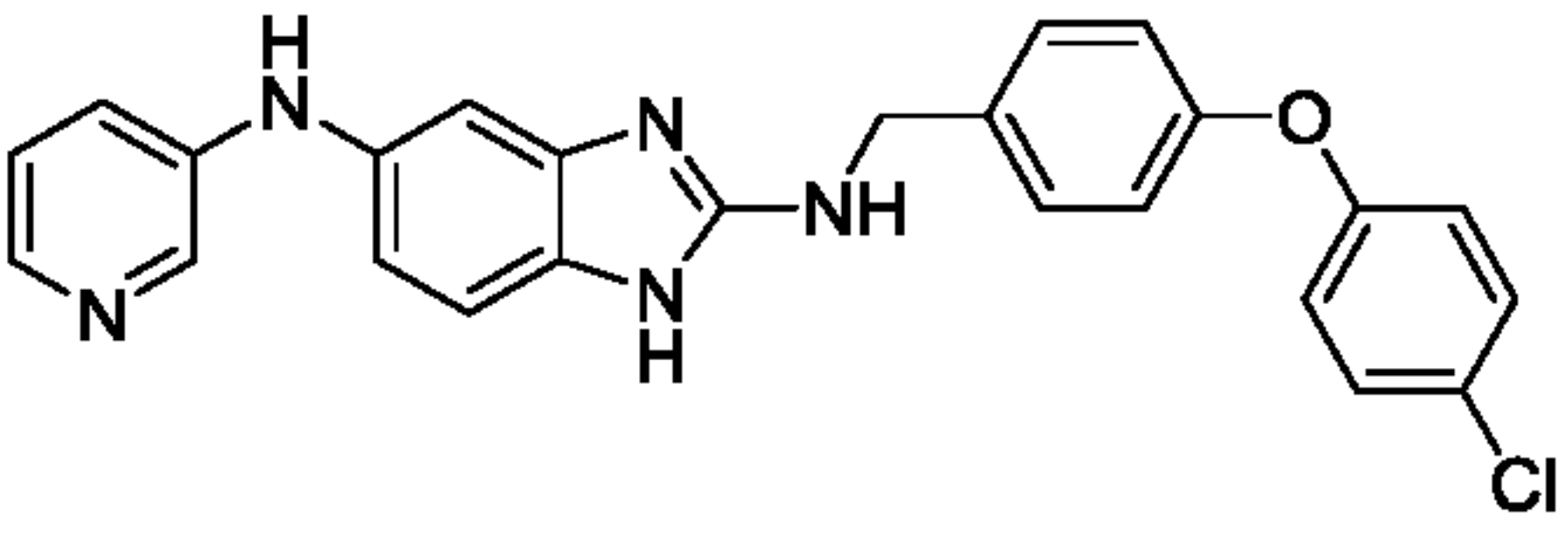
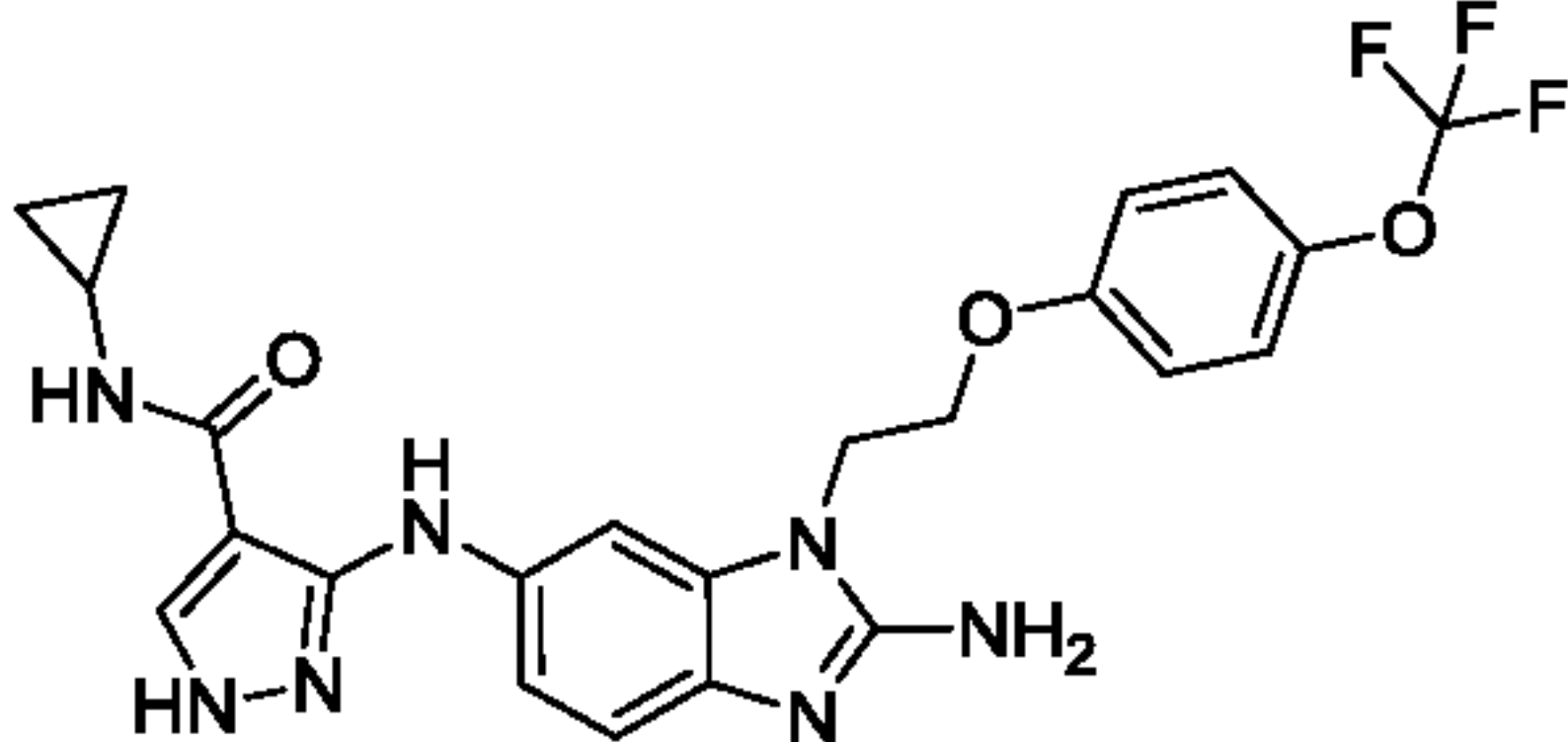
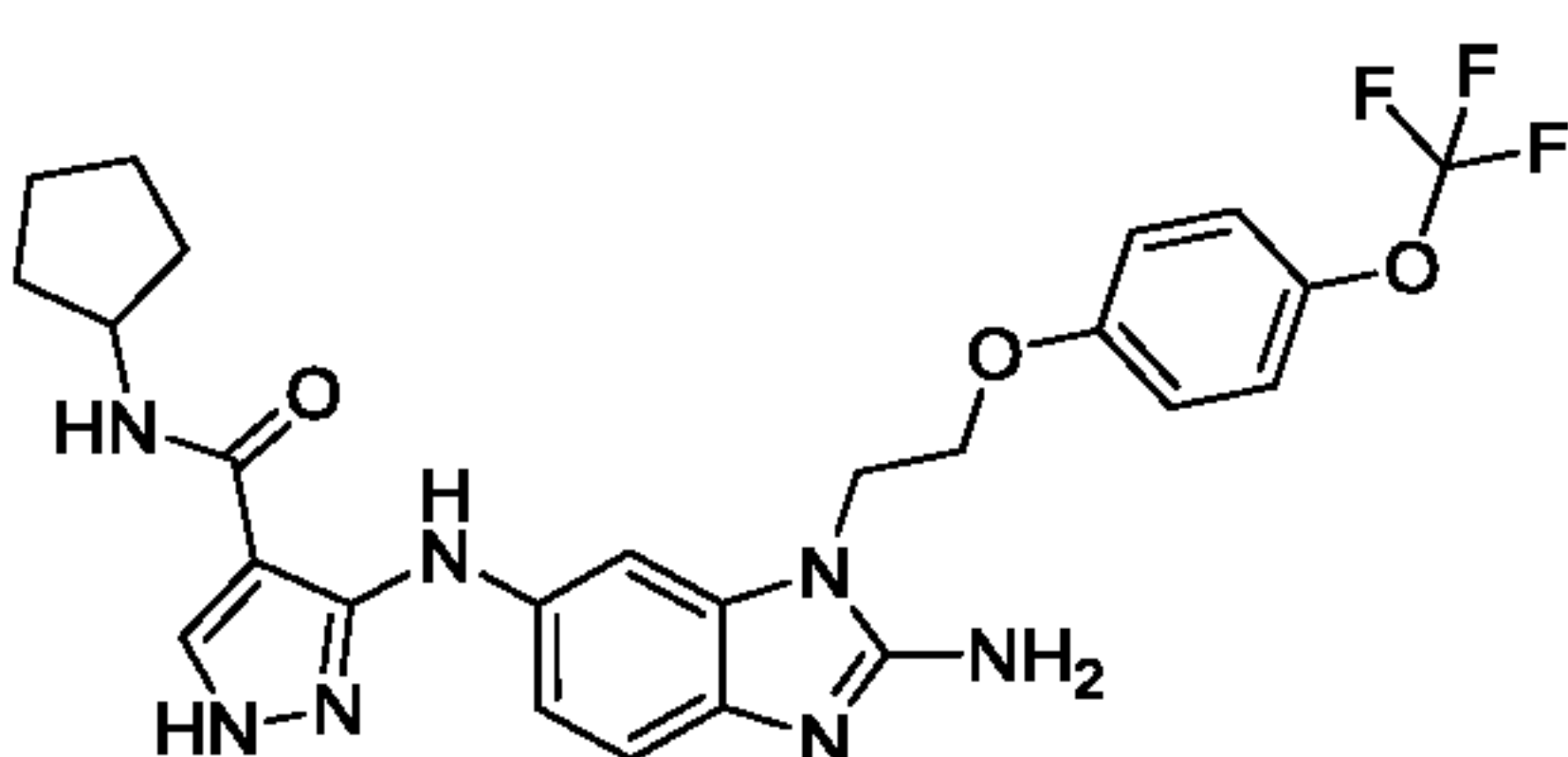
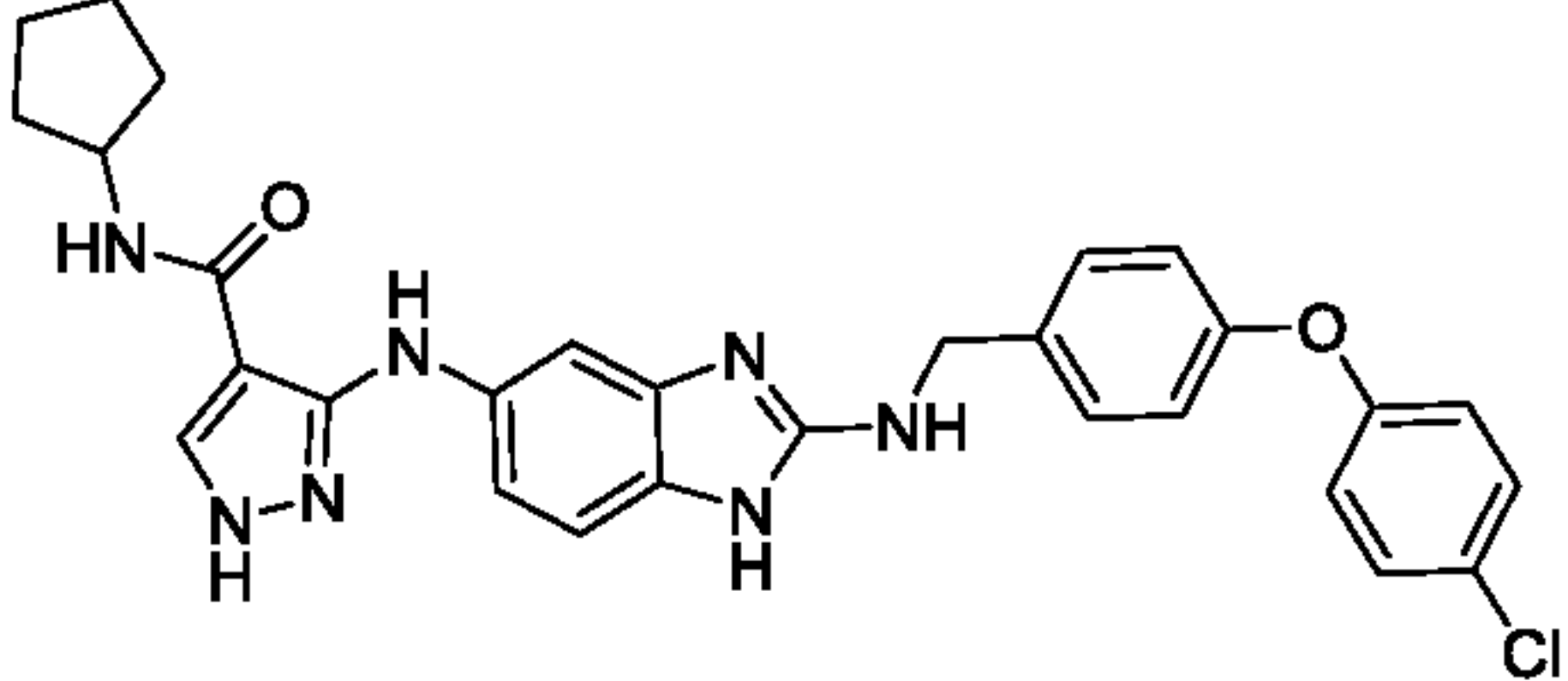
Activity range: +++ indicates > 70 %, ++ indicates between 40-70 %, + indicates < 40 %

Table 6. COX-2 inhibition assay

| # cpds | Inhibition<br>(%, 10 uM) | # cpds | Inhibition<br>(%, 10 uM) |
|--------|--------------------------|--------|--------------------------|
| 90     | NA                       | 95     | NA                       |

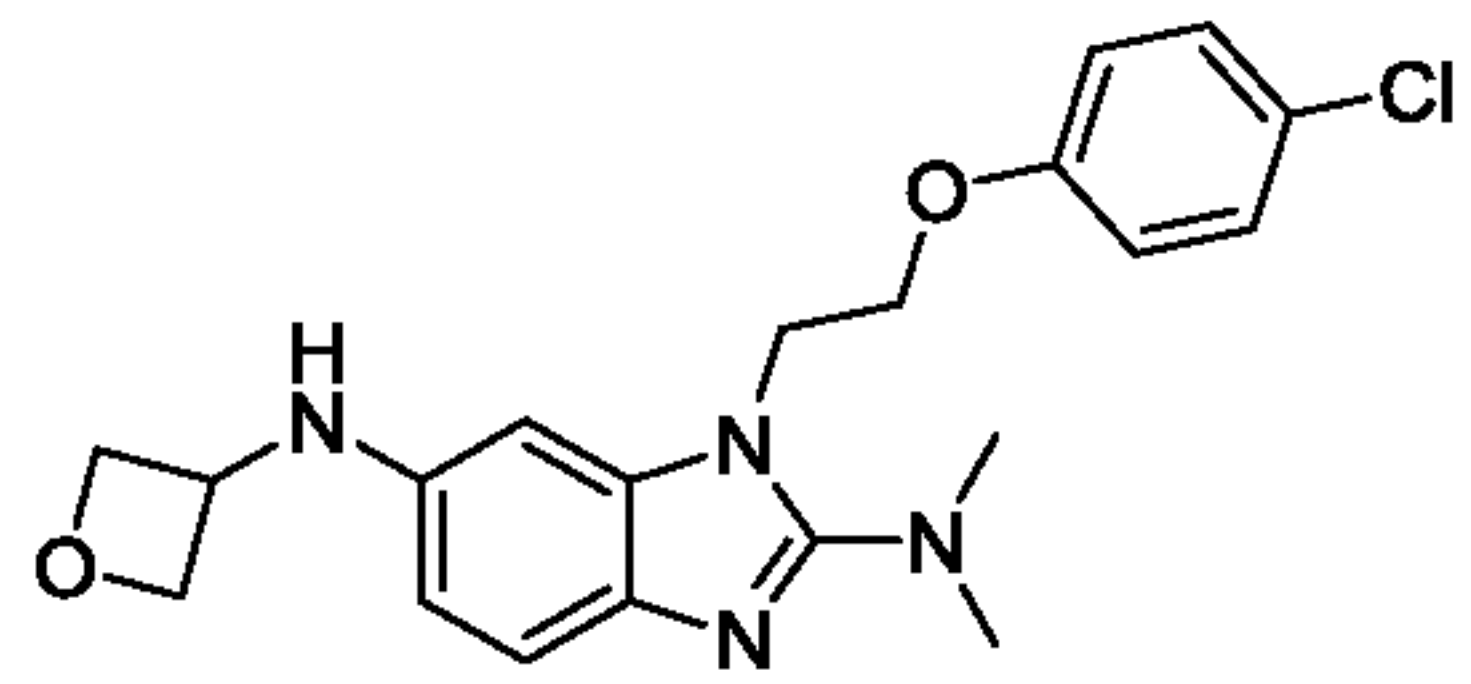
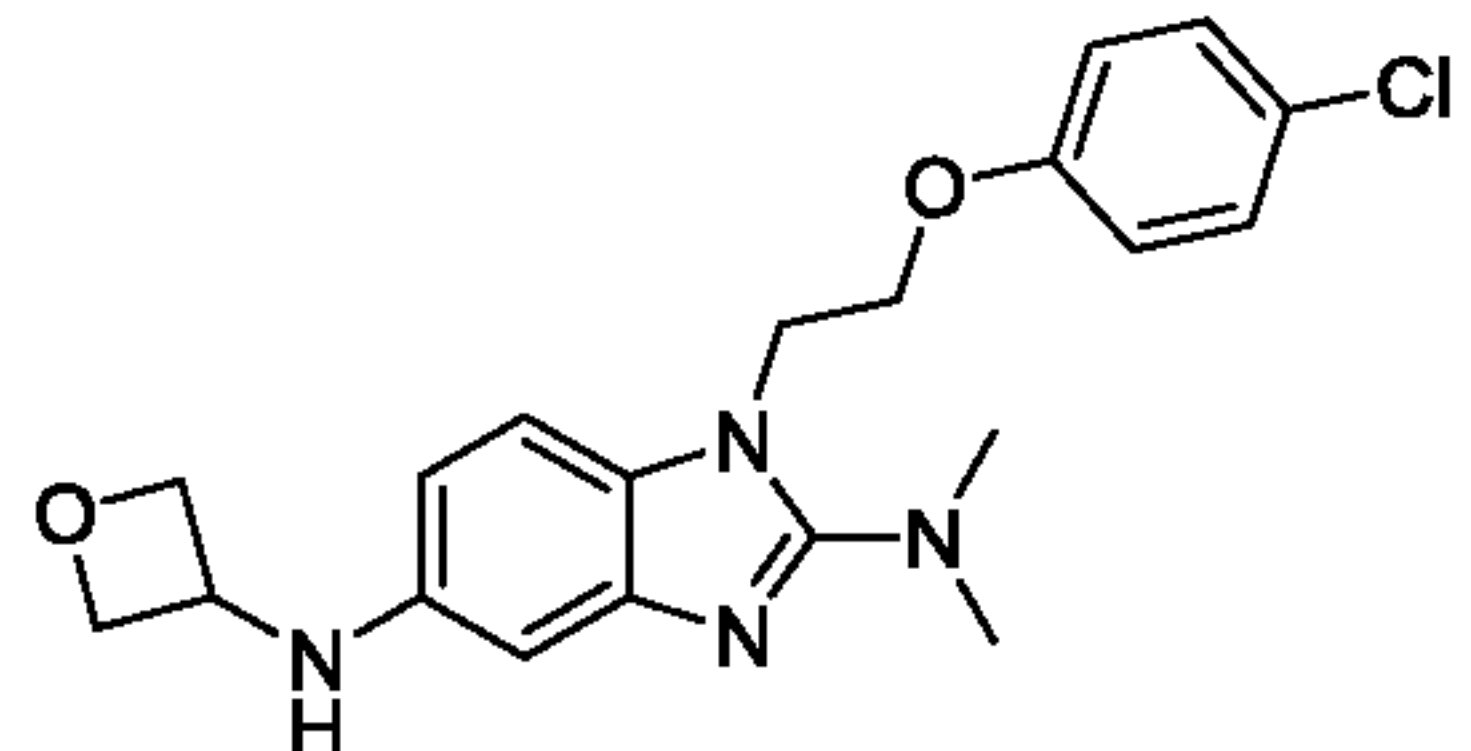
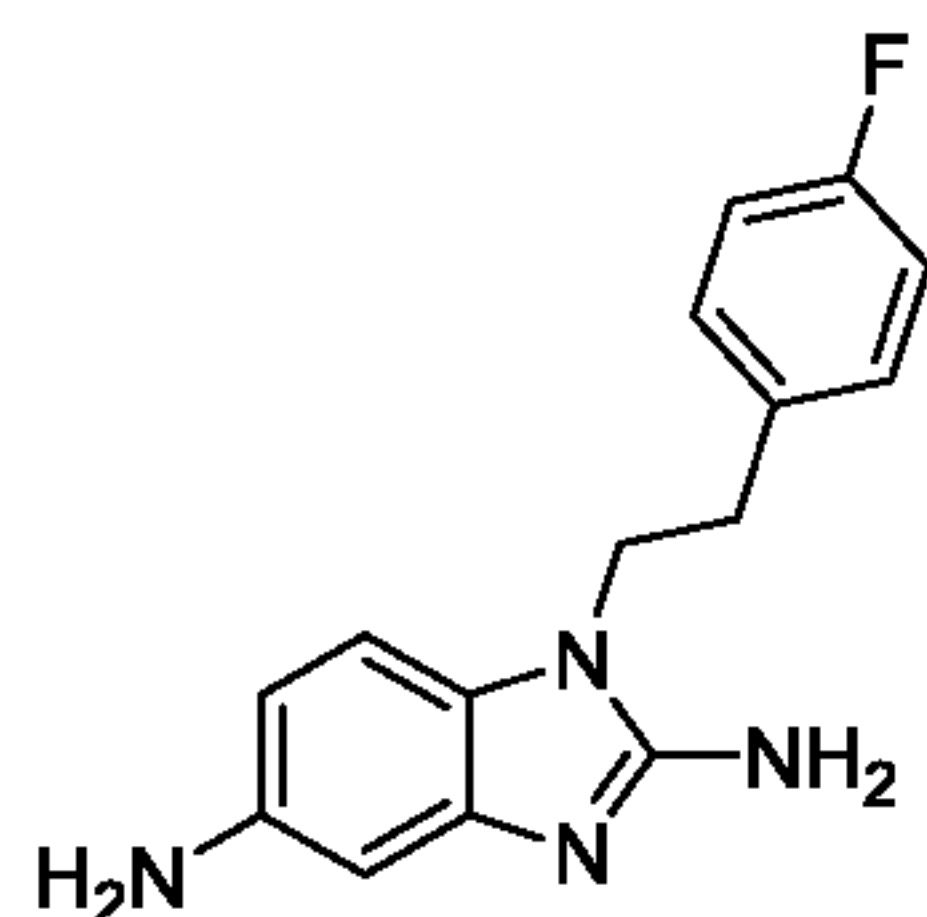
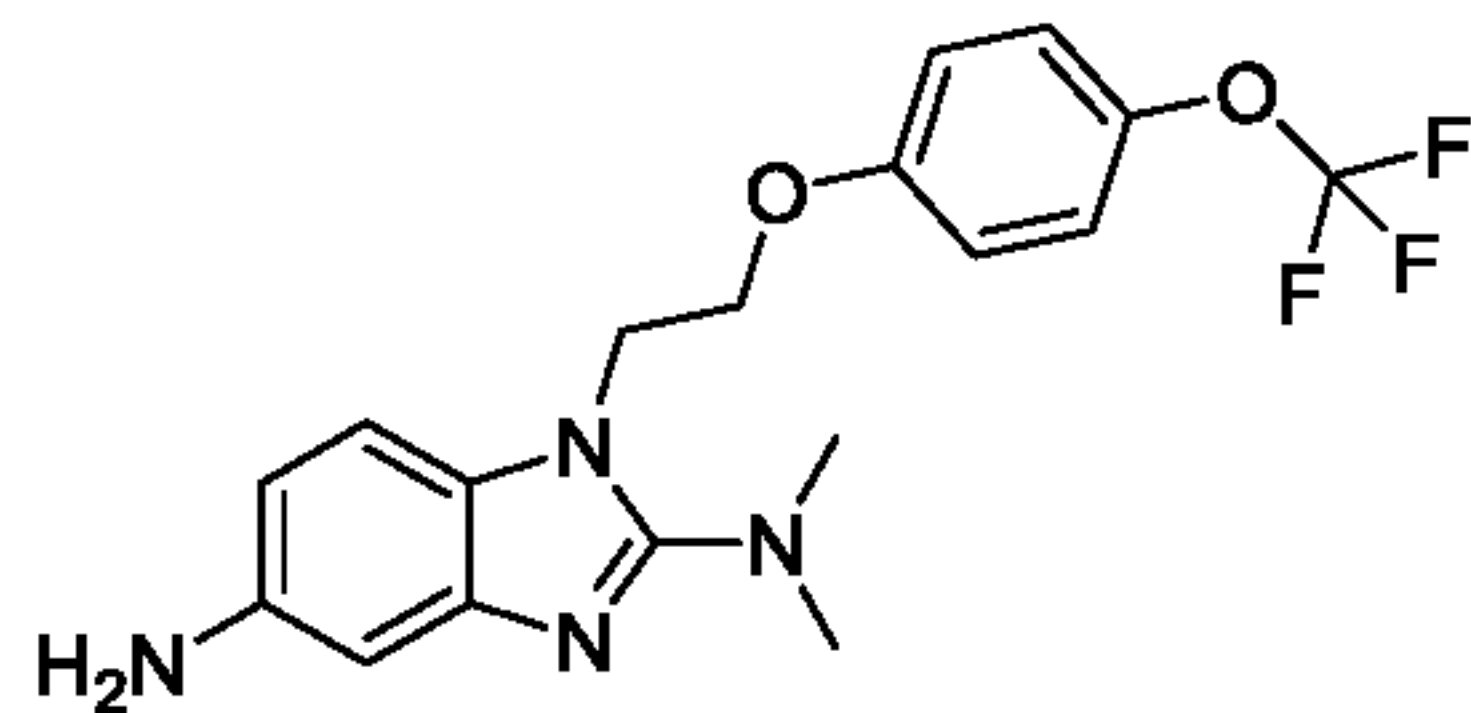
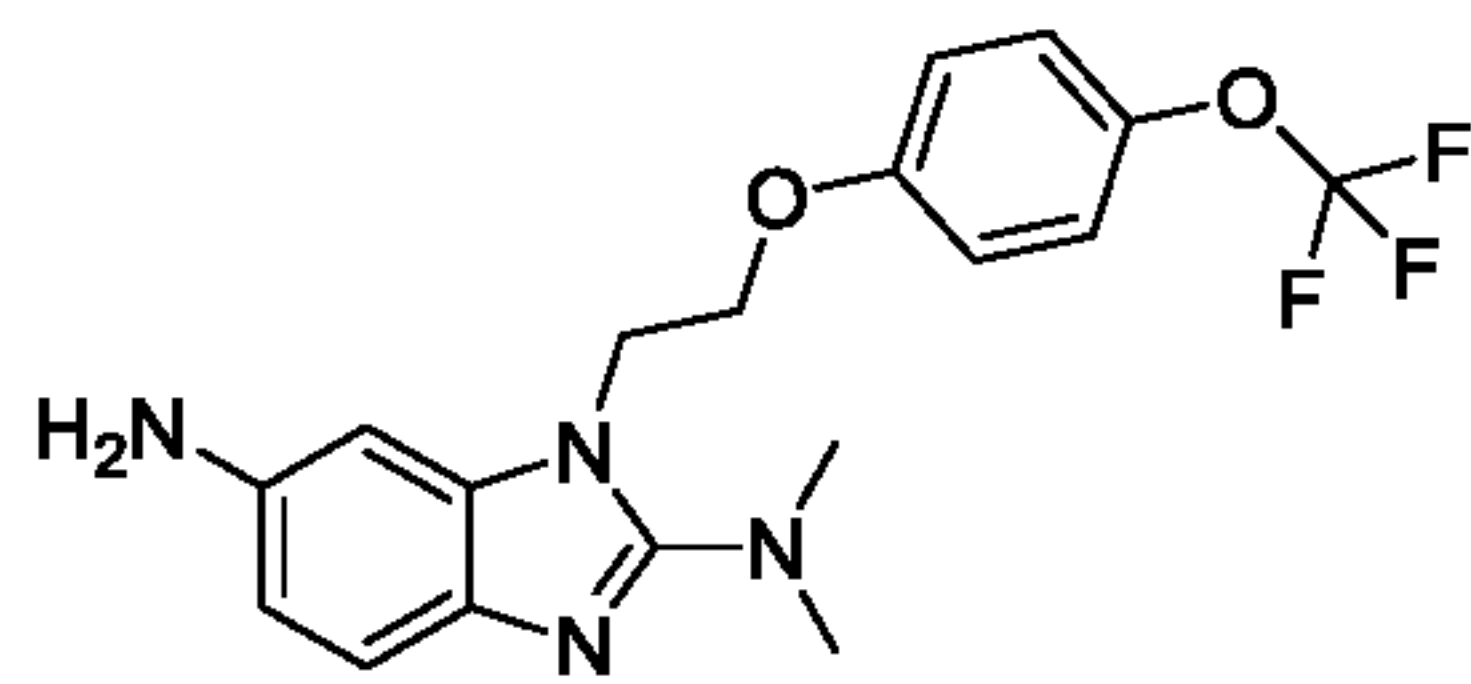
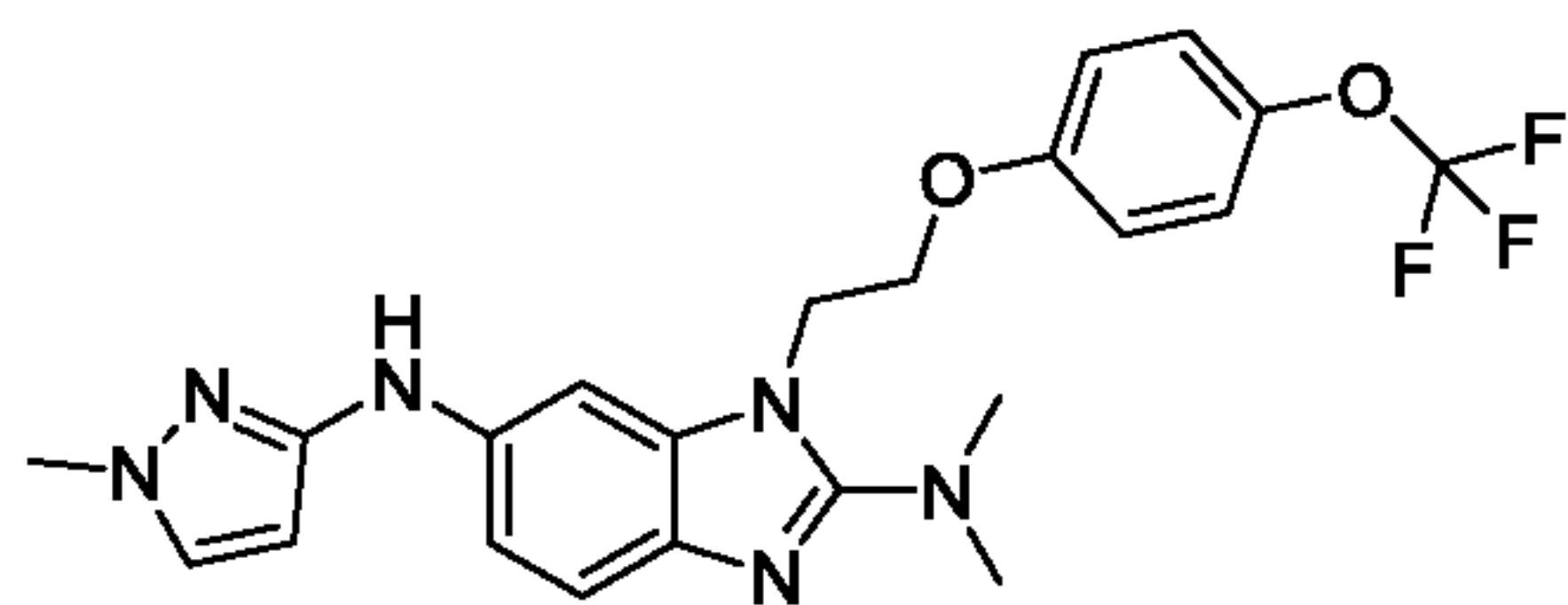
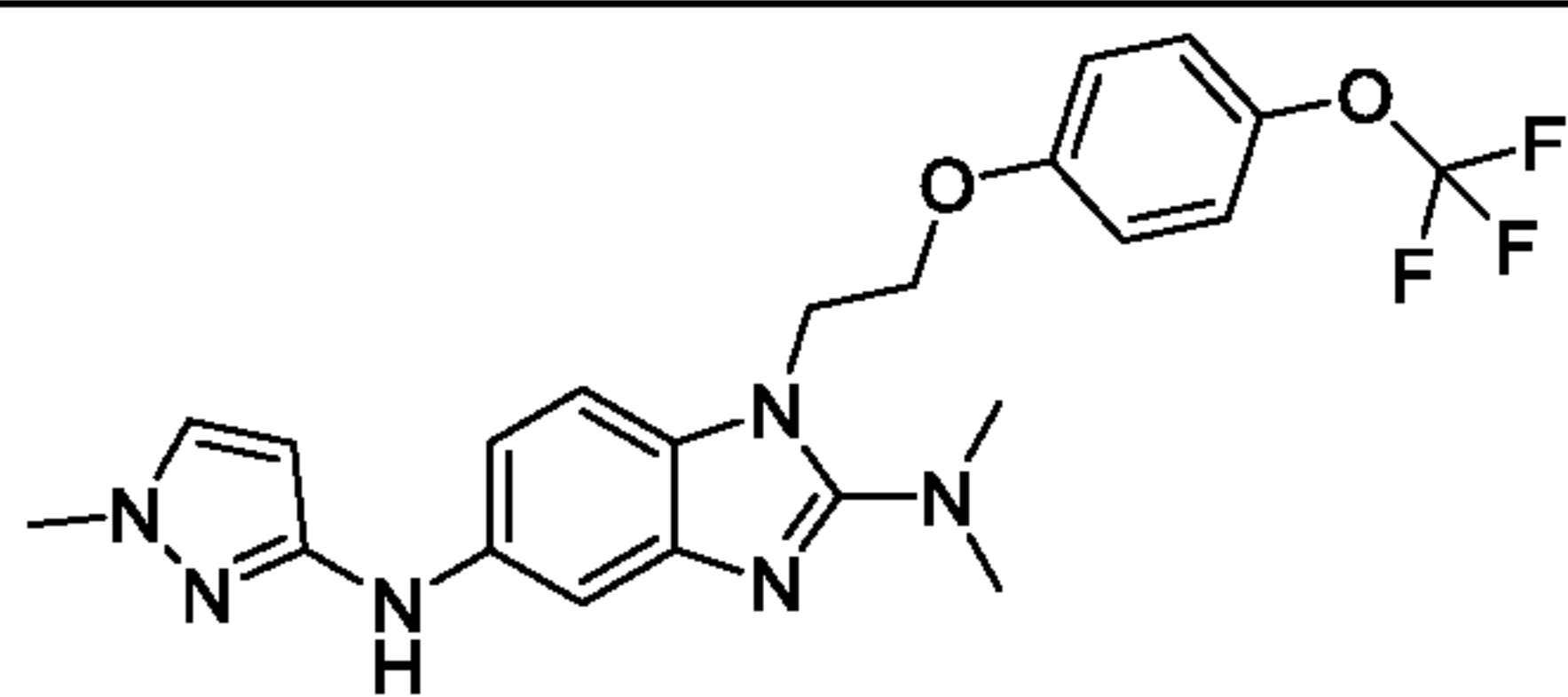
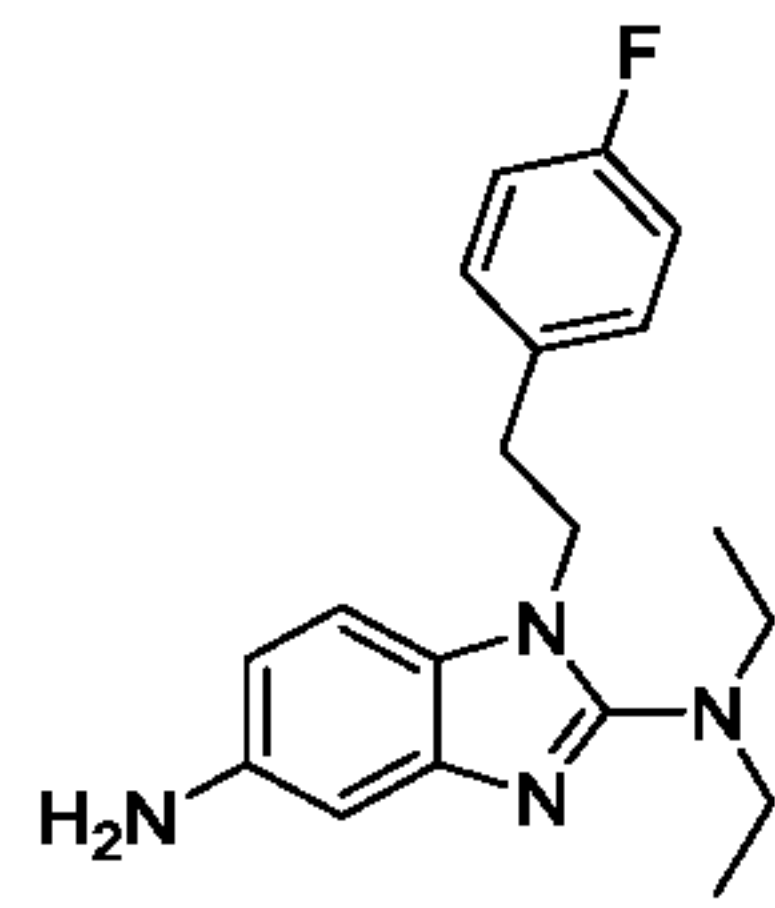
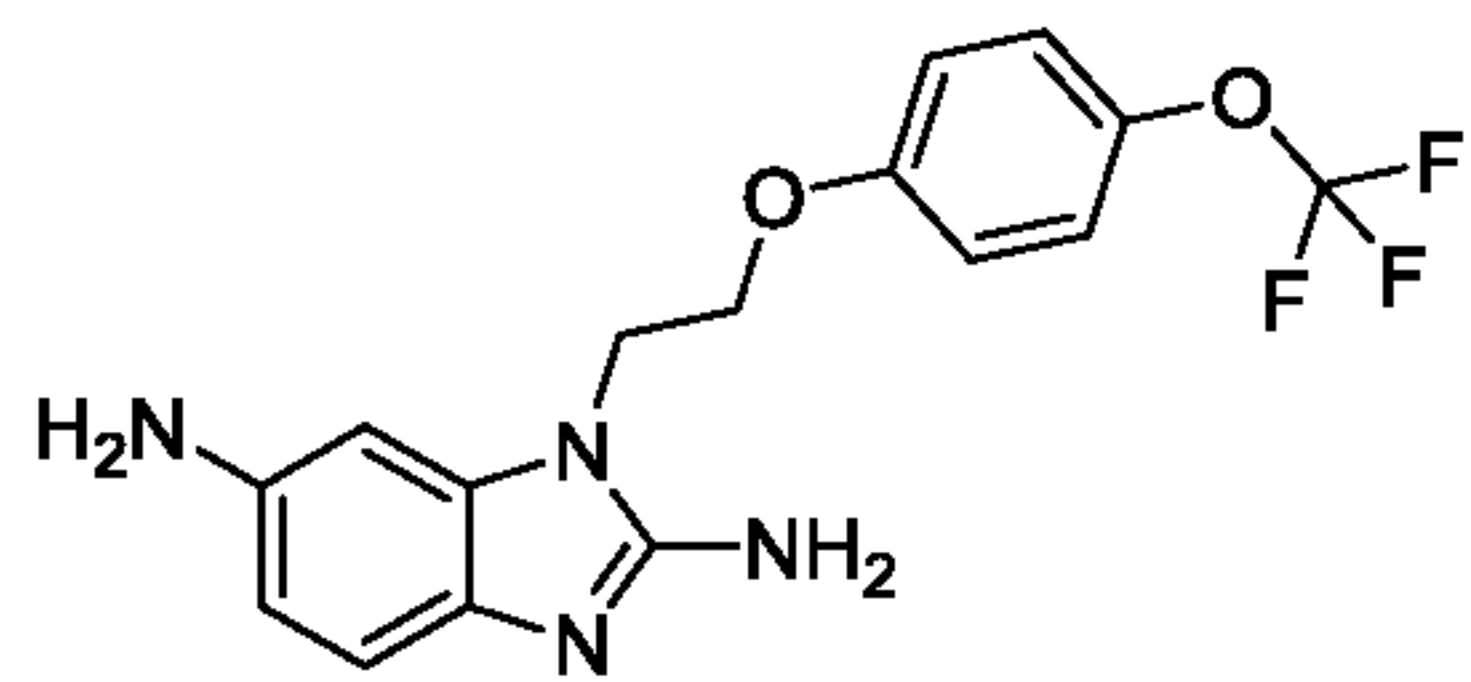
NA : not active (&lt; 1 %)

| No. | Structure                                                                           | NMR Characterization                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   |    | Pale violet solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 9.77 (brs, 1H), 8.34 – 8.36 (m, 2H), 7.85 (s, 1H), 7.52 – 7.64 (m, 4H), 6.89 (s, 1H), 6.57 (s, 1H), 6.30 – 6.34 (m, 2H), 4.75 (s, 2H), 4.03 (brs, 2H); LCMS (electrospray) <i>m/z</i> 440 [M+H] <sup>+</sup> .                                                                                                                                                    |
| 2   |    | Green solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 7.22 – 7.27 (m, 4H), 6.90 – 6.99 (m, 5H), 6.69 (d, <i>J</i> = 1.6 Hz, 1H), 6.48 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 4.43 (s, 2H), 3.43 – 3.50 (m, 3H), 3.03 – 3.09 (m, 2H), 2.06 – 2.10 (m, 2H), 1.81 – 1.87 (m, 2H); LCMS (electrospray) <i>m/z</i> 448 [M+H] <sup>+</sup> .                                                                                                |
| 3   |   | Pale brown solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 7.25 (d, <i>J</i> = 8.4 Hz, 2H), 7.22 (d, <i>J</i> = 8.4 Hz, 2H), 6.97-6.99 (m, 1H), 6.90-6.92 (m, 3H), 6.69 (m, 1H), 6.57 (d, <i>J</i> = 8.4 Hz, 2H), 6.50-6.52 (m, 1H), 4.58 (s, 2H, NH), 4.40 (s, 2H), 3.64-3.68 (m, 1H), 3.37-3.51 (m, 4H), 2.27-2.34 (m, 2H); LCMS (electrospray) <i>m/z</i> 434, 436 [M+H] <sup>+</sup> .                                       |
| 4   |  | <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 7.49 (dd, <i>J</i> = 8.4 2.4 Hz, 2H), 7.41 (dd, <i>J</i> = 8.4 2.4 Hz, 2H), 7.33 (t, <i>J</i> = 9.2 Hz, 2H), 7.08 (d, <i>J</i> = 8.0 Hz, 1H), 6.91 (t, <i>J</i> = 9.2 Hz, 2H), 6.60 (d, <i>J</i> = 34.0 Hz, 1H), 6.40 (dd, <i>J</i> = 34.0 8.0 Hz, 1H), 5.08 (d, <i>J</i> = 8.0 Hz, 2H), 4.56 (d, <i>J</i> = 8.8 Hz, 2H); LCMS (electrospray) <i>m/z</i> 378 [M+H] <sup>+</sup> .    |
| 5   |  | Gray solid; <sup>1</sup> H NMR (400 MHz, Methanol- <i>d</i> <sub>4</sub> ); δ 7.27 (d, <i>J</i> = 8.8 Hz, 2H), 7.22-7.25 (m, 2H), 6.94-7.00 (m, 3H), 6.89-6.91 (m, 2H), 6.70 (d, <i>J</i> = 2.0 Hz, 1H), 6.52 (dd, <i>J</i> = 8.2, 2.2 Hz, 1H), 4.44 (s, 2H), 3.85 (d, <i>J</i> = 6.0 Hz, 2H), 3.69-3.72 (m, 2H), 3.60-3.62 (m, 1H), 2.68-2.74 (m, 2H), 1.92-1.95 (m, 2H), 1.50-1.54 (m, 2H); LCMS (electrospray) <i>m/z</i> 462 [M+H] <sup>+</sup> . |
| 6   |  | Pale yellow solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 7.33 (s, 4H), 7.25 (d, <i>J</i> = 8.8 Hz, 2H), 6.95 - 7.01 (m, 3H), 6.70 (d, <i>J</i> = 2.4 Hz, 1H), 6.54 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 4.56 (s, 2H), 4.44 (s, 2H), 3.58 - 3.59 (m, 1H), 3.48 - 3.51 (m, 2H), 2.88 - 2.94 (m, 2H), 1.91 - 2.05 (m, 2H), 1.28 - 1.74 (m, 2H); LCMS (electrospray) <i>m/z</i> 461 [M+H] <sup>+</sup> .                             |
| 7   |  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ); δ 7.22 (d, <i>J</i> = 8.8 Hz, 2H), 6.87 (d, <i>J</i> = 8.8 Hz, 2H), 6.77 (d, <i>J</i> = 8.0 Hz, 1H), 6.65 (brs, 1H, NH), 6.39 (d, <i>J</i> = 1.6 Hz, 1H), 6.18 (dd, <i>J</i> = 8.0 1.6 Hz, 1H), 4.32 (d, <i>J</i> = 2.0 Hz, 2H), 3.67 – 3.70 (m, 4H), 3.01 – 3.05 (m, 4H); LCMS (electrospray) <i>m/z</i> 323 [M+H] <sup>+</sup> .                                                        |
| 8   |  | Dark green solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 9.81 (s, 1H, NH), 7.44-7.50 (m, 3H), 7.37 (d, <i>J</i> = 6.8 Hz, 2H), 7.05 (s, 1H, NH), 6.91-7.00 (m, 5H), 6.83 (d, <i>J</i> = 8.4 Hz, 1H), 6.15-6.25 (m, 1H), 4.63 (s, 2H), 2.21 (s, 3H); LCMS (electrospray) <i>m/z</i> 445 [M+H] <sup>+</sup> .                                                                                                                 |
| 9   |  | Dark yellow solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 7.60 (d, <i>J</i> = 8.4 Hz, 1H), 7.40-7.43 (m, 2H), 7.02-7.07 (m, 3H), 6.94-6.96 (m, 1H), 6.91 (d, <i>J</i> = 8.4 Hz, 1H), 6.58-6.59 (m, 1H), 6.35-6.38 (m, 1H), 4.70 (s, 2H); LCMS (electrospray) <i>m/z</i> 400 [M+H] <sup>+</sup> .                                                                                                                            |
| 10  |  | Dark yellow solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 7.53-7.59 (m, 1H), 7.39-7.43 (m, 2H), 7.17 (s, 1H, NH), 7.03-7.07 (m, 2H), 6.90 (d, <i>J</i> = 8.4 Hz, 1H), 6.72-6.81 (m, 2H), 6.58 (d, <i>J</i> = 2.4 Hz, 1H), 6.35 (dd, <i>J</i> = 8.2, 2.4 Hz, 1H), 4.65 (s, 2H); LCMS (electrospray) <i>m/z</i> 383 [M+H] <sup>+</sup> .                                                                                      |

|    |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 |    | Pale brown solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 7.25-7.29 (m, 4H), 7.00-7.08 (m, 2H), 6.80-6.90 (m, 4H), 6.68 (m, 1H), 6.58-6.60 (m, 2H), 3.60 (t, <i>J</i> = 6.0 Hz, 2H), 2.96 (t, <i>J</i> = 6.0 Hz, 2H); LCMS (electrospray) <i>m/z</i> 379, 381 [M+H] <sup>+</sup> .                                                                                                                                 |
| 12 |    | Yellow solid; <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ); δ 8.87 (s, 1H), 8.10 (s, 1H), 7.99 – 8.00 (m, 1H), 7.62 (s, 1H), 7.20 – 7.43 (m, 5H), 7.09 – 7.12 (m, 1H), 6.96 – 7.02 (m, 5H), 6.84 – 6.86 (m, 1H), 4.47 (d, <i>J</i> = 4.4 Hz, 2H), 2.71 – 2.76 (m, 1H), 0.66 – 0.70 (m, 2H), 0.47 – 0.51 (m, 2H); LCMS (electrospray) <i>m/z</i> 514 [M+H] <sup>+</sup> .                                                   |
| 13 |   | Pale yellow solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 8.07 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.44 – 7.48 (m, 2H), 7.33 – 7.37 (m, 2H), 7.08 – 7.10 (m, 2H), 6.93 – 7.01 (m, 4H), 6.60 – 6.78 (m, 2H), 4.65 (s, 2H), 4.26 (q, <i>J</i> = 7.2 Hz, 2H), 1.31 (t, <i>J</i> = 7.2 Hz, 3H); LCMS (electrospray) <i>m/z</i> 503 [M+H] <sup>+</sup> .                                                           |
| 14 |  | Pale yellow solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 8.27 - 8.28 (m, 1H), 7.45 - 7.48 (m, 1H), 7.40 - 7.42 (m, 2H), 7.35 - 7.39 (m, 1H), 7.03 - 7.04 (m, 1H), 7.01 - 7.02 (m, 1H), 6.98 - 7.00 (m, 1H), 6.70 (d, <i>J</i> = 2.0 Hz, 1H), 6.52 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 4.65 (s, 2H); LCMS (electrospray) <i>m/z</i> 365 [M+H] <sup>+</sup> .                                                        |
| 15 |  | Pale yellow solid; <sup>1</sup> H NMR (400 MHz, MeOH- <i>d</i> <sub>4</sub> ); δ 7.31 - 7.33 (m, 1H), 7.28 - 7.29 (m, 1H), 7.12 (d, <i>J</i> = 8.4 Hz, 2H), 7.05 - 7.09 (m, 1H), 6.99 - 7.01 (m, 1H), 6.88 - 6.90 (m, 1H), 6.85 - 6.86 (m, 1H), 6.83 - 6.84 (m, 1H), 6.55 - 6.57 (m, 1H), 6.50 - 6.51 (m, 1H), 4.15 (t, <i>J</i> = 7.2 Hz, 2H), 3.02 (t, <i>J</i> = 7.2 Hz, 2H); LCMS (electrospray) <i>m/z</i> 378 [M+H] <sup>+</sup> . |
| 16 |  | Brown solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 8.27 (s, 1H), 7.90 (s, 1H), 7.46 (d, <i>J</i> = 7.6 Hz, 2H), 7.36 (d, <i>J</i> = 8.0 Hz, 2H), 7.23 – 7.28 (m, 2H), 7.07 – 7.14 (m, 3H), 6.97 – 6.99 (m, 4H), 6.78 (d, <i>J</i> = 8.0 Hz, 1H), 6.57 (brs, 1H), 4.66 (s, 2H);                                                                                                                                |
| 17 |  | <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 9.21 (s, 1H, NH), 8.09 (s, 1H), 7.83 (s, 1H), 7.40 (s, 1H, NH), 7.15 – 7.24 (m, 4H), 7.05 – 7.09 (m, 2H), 6.41 (brs, 2H, NH <sub>2</sub> ), 4.52 (t, <i>J</i> = 2.8 Hz, 2H), 4.42 (t, <i>J</i> = 2.8 Hz, 2H), 2.82 – 2.86 (m, 1H), 0.71 – 0.74 (m, 2H), 0.51 – 0.55 (m, 2H); LCMS (electrospray) <i>m/z</i> 502 [M+H] <sup>+</sup> .                                    |
| 18 |  | <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 9.16 (s, 1H, NH), 8.11 (s, 1H), 7.74 (s, 1H), 7.22 (d, <i>J</i> = 8.8 Hz, 2H), 7.06 – 7.16 (m, 4H), 5.55 (brs, 2H, NH <sub>2</sub> ), 4.46 (t, <i>J</i> = 2.8 Hz, 2H), 4.39 (t, <i>J</i> = 2.8 Hz, 2H), 4.32 – 4.37 (m, 1H), 1.94 – 2.20 (m, 4H), 1.60 – 1.71 (m, 1H), 1.52 – 1.59 (m, 3H); LCMS (electrospray) <i>m/z</i> 530 [M+H] <sup>+</sup> .                     |
| 19 |  | Pale green solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 9.13 (s, 1H, NH), 8.10 (m, 1H); 7.84 (s, 1H, NH), 7.49 (d, <i>J</i> = 8.4 Hz, 2H), 7.37 (d, <i>J</i> = 8.4 Hz, 2H), 7.10-7.15 (m, 3H), 6.96-7.02 (m, 4H), 4.68 (s, 2H), 4.32-4.36 (m, 1H), 1.96-1.99 (m, 2H), 1.68-1.72 (m, 2H), 1.50-1.61 (m, 4H); LCMS (electrospray) <i>m/z</i> 542, 544 [M+H] <sup>+</sup> .                                      |

|    |  |                                                                                                                                                                                                                                                                                                                                                                                                              |
|----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 |  | Dark beige solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 7.65 (s, 1H, NH), 7.56 (d, <i>J</i> = 8.4 Hz, 2H), 7.37 (d, <i>J</i> = 8.4 Hz, 2H), 6.97-7.02 (m, 4H), 6.88 (d, <i>J</i> = 8.4 Hz, 1H), 6.55 (s, 1H), 6.39 (d, <i>J</i> = 7.6 Hz, 1H), 1.82 (s, 6H); LCMS (electrospray) <i>m/z</i> 393 [M+H] <sup>+</sup> .                                                              |
| 21 |  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ); δ 7.67 (d, <i>J</i> = 8.4 Hz, 2H), 7.62 (d, <i>J</i> = 8.4 Hz, 2H), 7.51 (d, <i>J</i> = 8.4 Hz, 2H), 7.24 (t, <i>J</i> = 8.4 Hz, 2H), 6.86 (d, <i>J</i> = 8.0 Hz, 1H), 6.29 (s, 1H), 6.27 (d, <i>J</i> = 8.0 Hz, 1H), 6.11 (s, 2H); LCMS (electrospray) <i>m/z</i> 348 [M+H] <sup>+</sup> .                                                      |
| 22 |  | <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 8.15 (s, 1H), 8.02 (s, 1H), 7.78 (s, 1H, NH), 7.21 (d, <i>J</i> = 8.8 Hz, 2H), 7.12 – 7.17 (m, 2H), 7.06 (d, <i>J</i> = 8.8 Hz, 2H), 5.85 (brs, 2H, NH <sub>2</sub> ), 4.74 – 4.48 (m, 2H), 4.38 – 4.30 (m, 2H), 4.28 – 4.35 (m, 2H), 1.32 – 1.37 (m, 3H); LCMS (electrospray) <i>m/z</i> 491 [M+H] <sup>+</sup> .                          |
| 23 |  | Pale green solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 10.00 (s, 1H, NH), 7.81 (s, 1H), 7.47-7.49 (m, 3H), 7.37 (d, <i>J</i> = 8.4 Hz, 2H), 7.14-7.18 (m, 1H), 7.11 (s, 1H, NH), 7.02-7.06 (m, 1H), 6.94-7.02 (m, 4H), 6.84 (d, <i>J</i> = 6.8 Hz, 1H), 6.76 (d, <i>J</i> = 6.8 Hz, 1H), 6.41 (s, 1H, NH), 4.66 (s, 2H); LCMS (electrospray) <i>m/z</i> 460 [M+H] <sup>+</sup> . |
| 24 |  | Pale green solid; <sup>1</sup> H NMR (400 MHz, Acetone- <i>d</i> <sub>6</sub> ); δ 7.45-7.50 (m, 3H), 7.37 (d, <i>J</i> = 7.2 Hz, 2H), 6.98-7.00 (m, 4H), 6.78 (s, 1H), 6.55 (d, <i>J</i> = 8.4 Hz, 1H), 6.30-6.35 (m, 2H), 4.63 (s, 2H); LCMS (electrospray) <i>m/z</i> 431 [M+H] <sup>+</sup> .                                                                                                            |
| 25 |  | white solid; mp > 220 °C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.74 (1H, brs), 8.30 (1H, s), 7.74 (1H, d, <i>J</i> = 3.6 Hz), 7.44 (0.6H, d, <i>J</i> = 8.8 Hz), 7.31 (0.4H, d, <i>J</i> = 8.4 Hz), 6.91-7.18 (6H, m), 3.20-3.30 (8H, m), 2.14 (3H, s); LCMS: 99.3%, MS (ESI); <i>m/z</i> 377.0[M+ H] <sup>+</sup> .                                                               |
| 26 |  | brown solid; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.02 (1H, brs), 8.07-8.44 (2H, m), 7.28 (2H, t, <i>J</i> = 8.8 Hz), 7.09 (1H, d, <i>J</i> = 8.4 Hz), 6.63 (1H, d, <i>J</i> = 1.6 Hz), 6.57 (1H, dd, <i>J</i> = 8.4, 2.0 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 271.0 [M+H] <sup>+</sup> .                                                                                         |
| 27 |  | yellow amorphous; mp >142.9 °C, decomposed; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 4.06-4.22 (2H, m), 5.62-5.80 (1H, m), 6.57 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.83 (0.3H, s), 6.98 (0.7H, s), 7.13 (1H, d, <i>J</i> = 8.4 Hz), 7.28 (2H, t, <i>J</i> = 8.8 Hz), 7.50-7.62 (1H, m), 8.12-8.24 (2H, m), 12.02 (3H, brs); LCMS: 100%, MS (ESI); <i>m/z</i> 351.0 [M+H] <sup>+</sup> .  |
| 28 |  | gray powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 4.42 (2H, d, <i>J</i> = 5.6 Hz), 4.43 (2H, brs), 6.19 (1H, d, <i>J</i> = 8.0 Hz), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.68-6.86 (2H, m), 7.08-7.20 (2H, m), 7.36-7.47 (2H, m), 10.38 (1H, brs); LCMS: 99.9%, MS (ESI); <i>m/z</i> 256.9 [M+H] <sup>+</sup> .                                                                         |
| 29 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 4.07 (2H, s), 4.42 (2H, d, <i>J</i> = 6.0 Hz), 5.08 (1H, brs), 6.29 (1H, d, <i>J</i> = 7.2 Hz), 6.46 (1H, d, <i>J</i> = 1.6 Hz), 6.78-6.93 (3H, m), 7.08-7.17 (2H, m), 7.35-7.45 (2H, m), 7.54 (1H, s), 10.42 (1H, brs), 11.82 (1H, brs); LCMS: 98.4%, MS (ESI); <i>m/z</i> 337.0 [M+H] <sup>+</sup> .                        |
| 30 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.95 (1H, brs), 7.50-7.43 (2H, m), 7.28 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.93 (1H, d, <i>J</i> = 8.0 Hz), 6.52 (1H, s), 6.35 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, s); LCMS: 99.0%, MS (ESI); <i>m/z</i> 291.1 [M+H] <sup>+</sup> .                                                                                       |

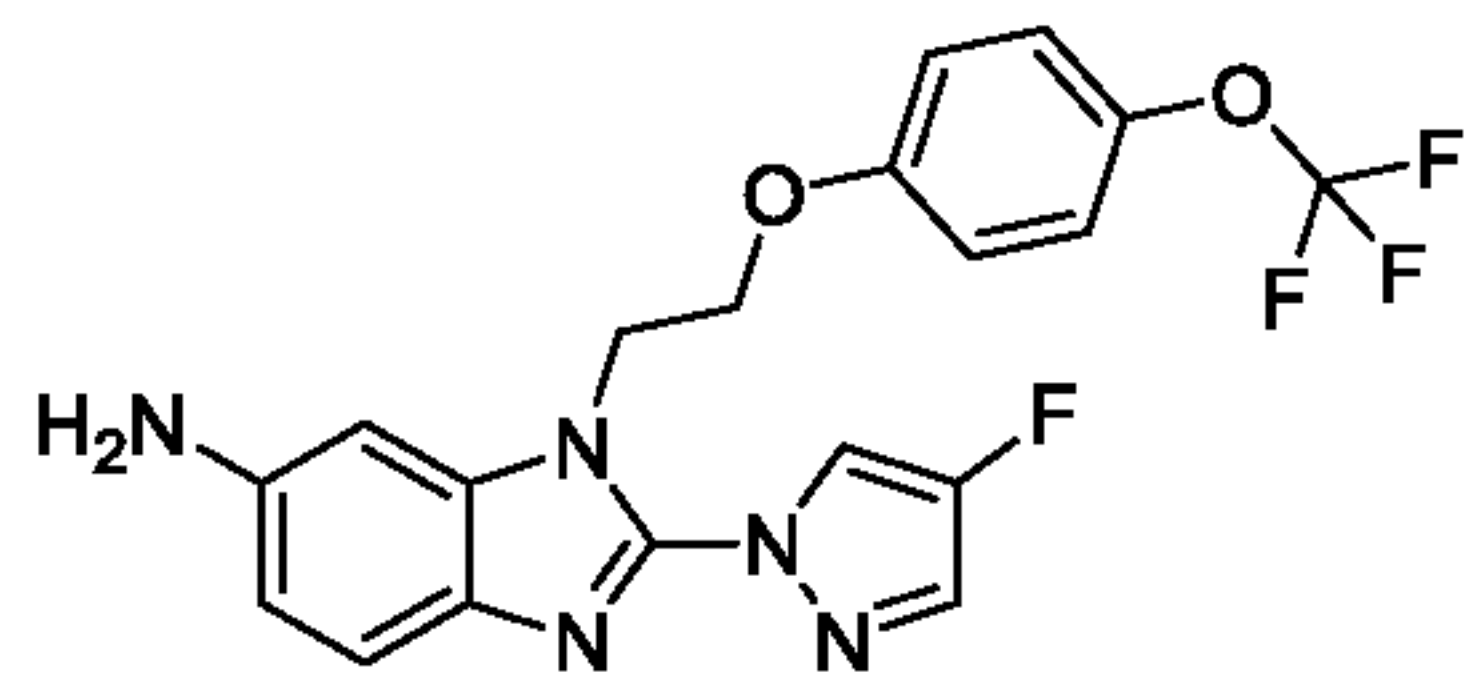
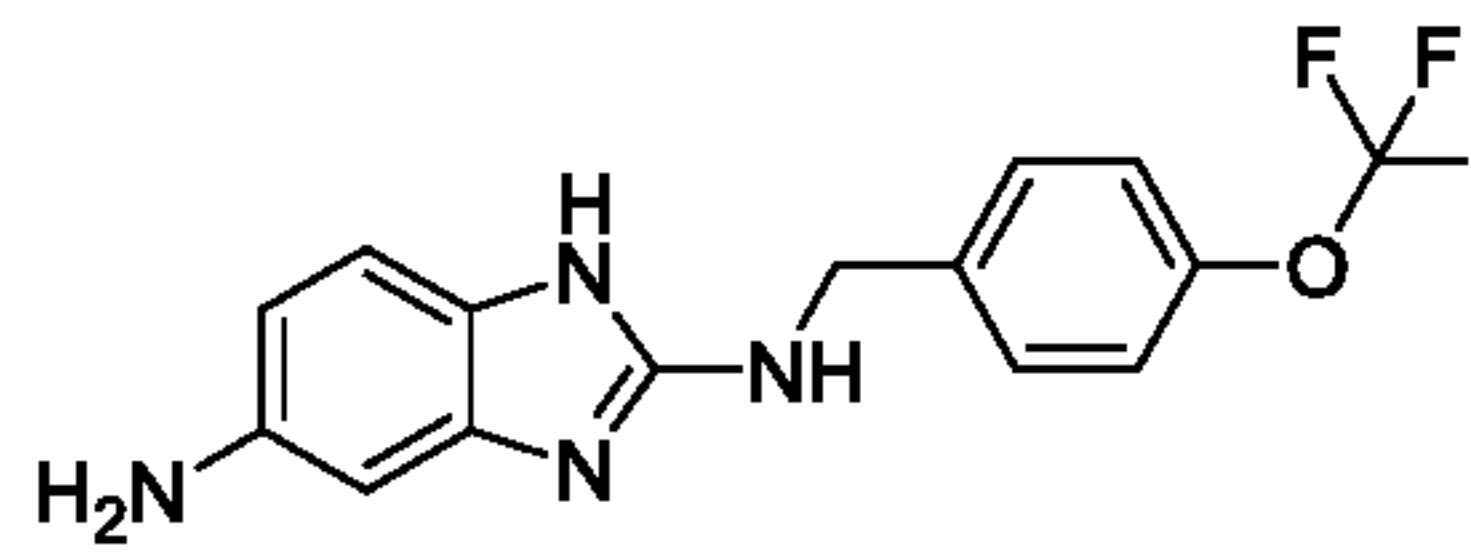
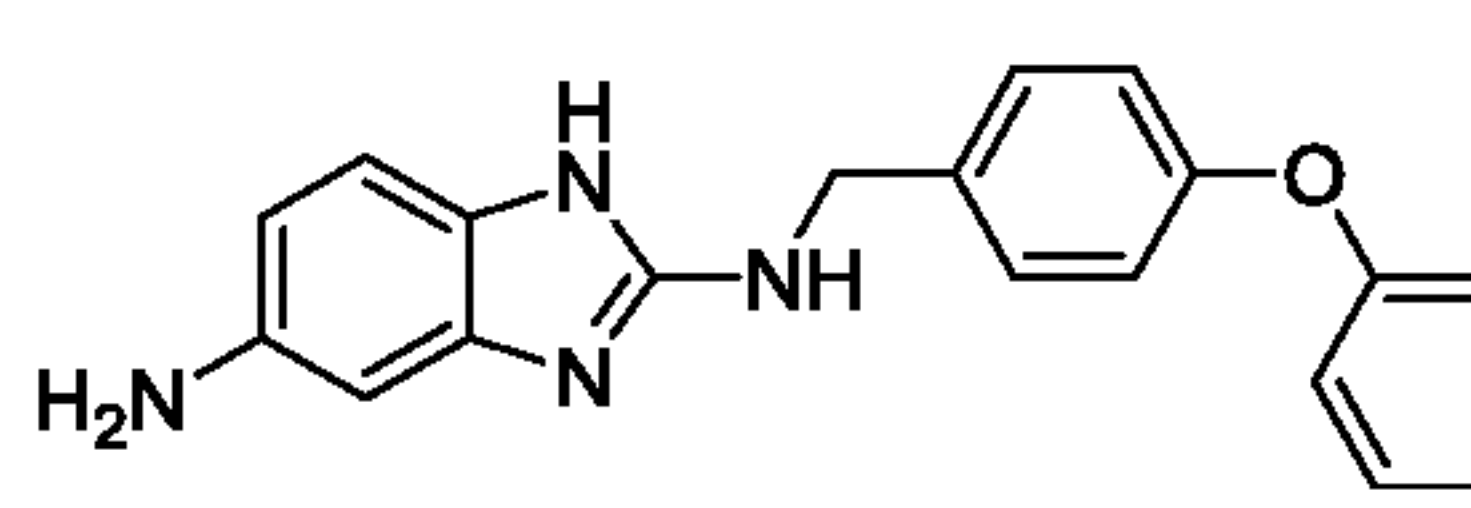
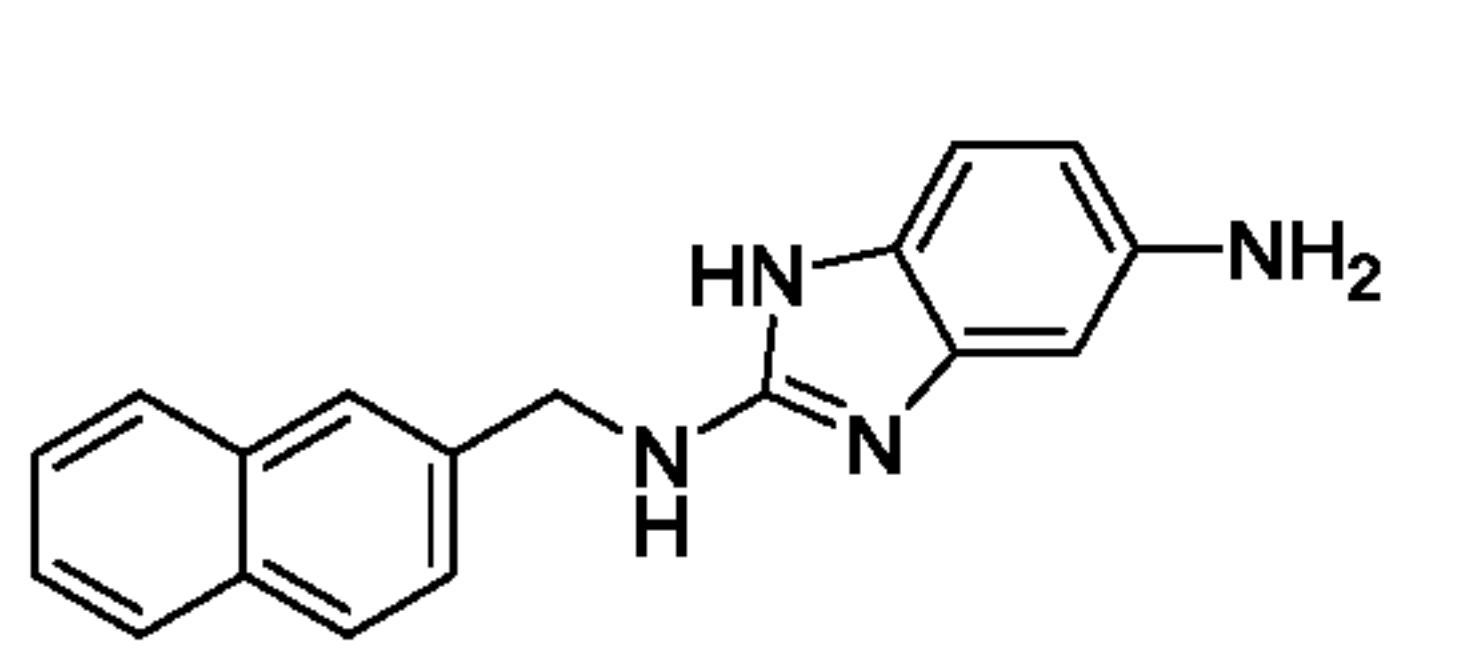
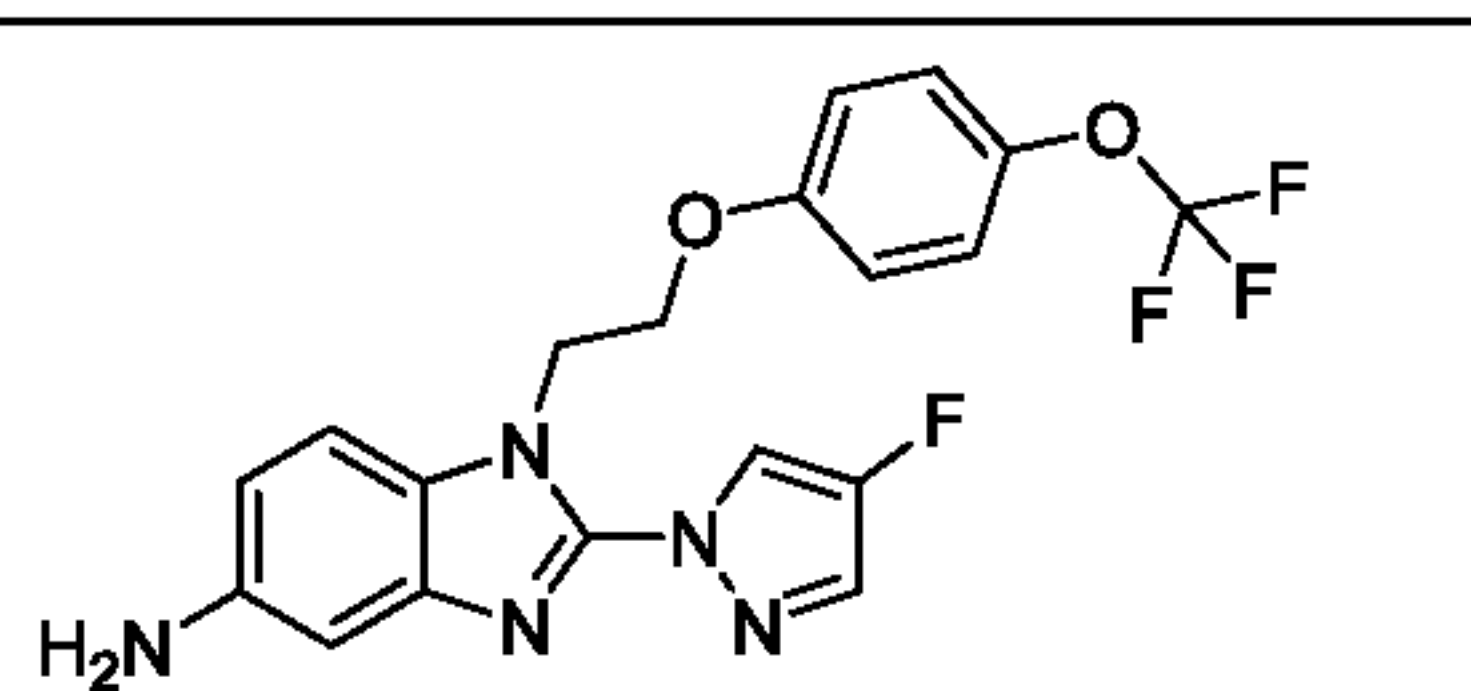
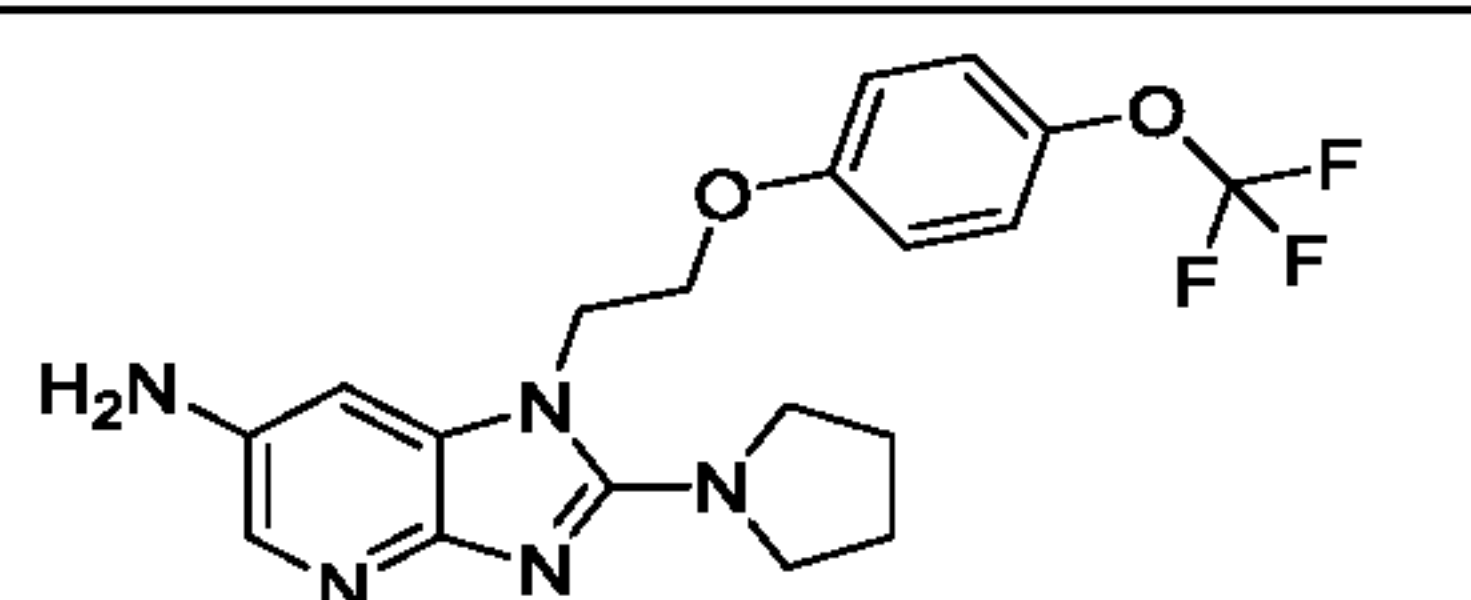
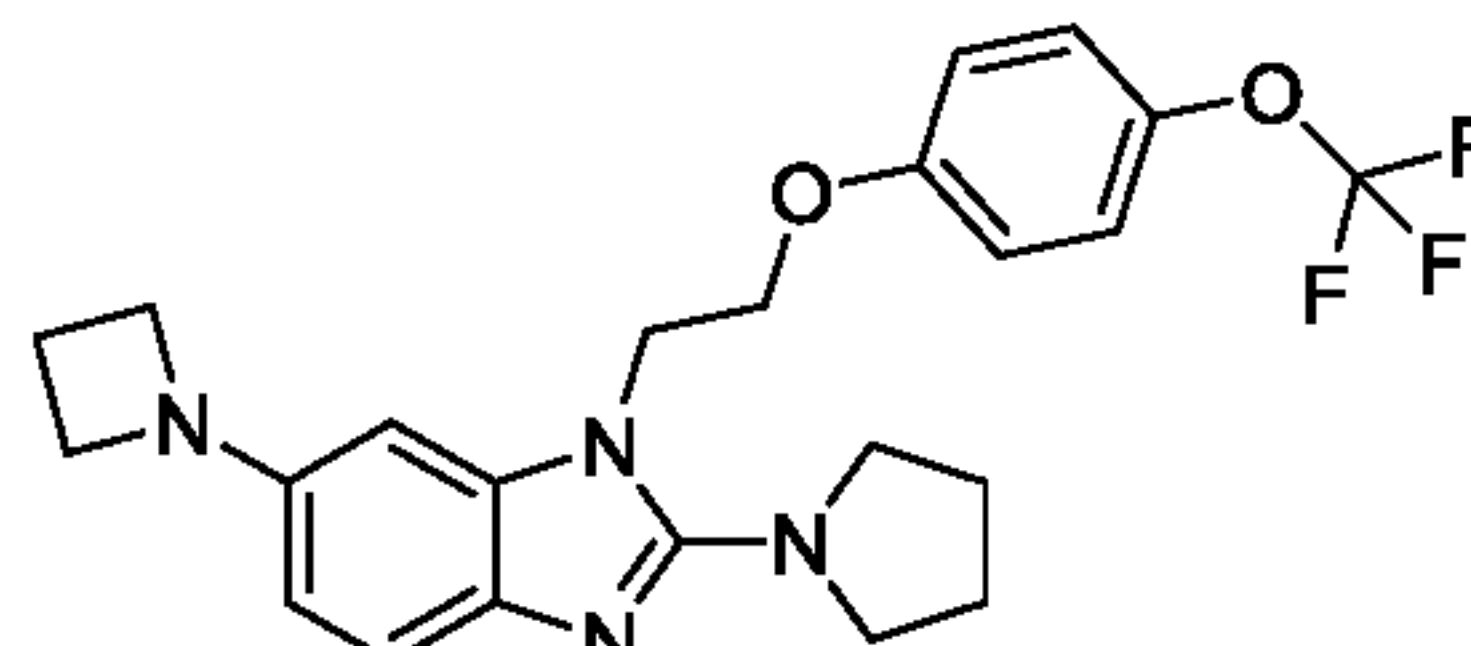
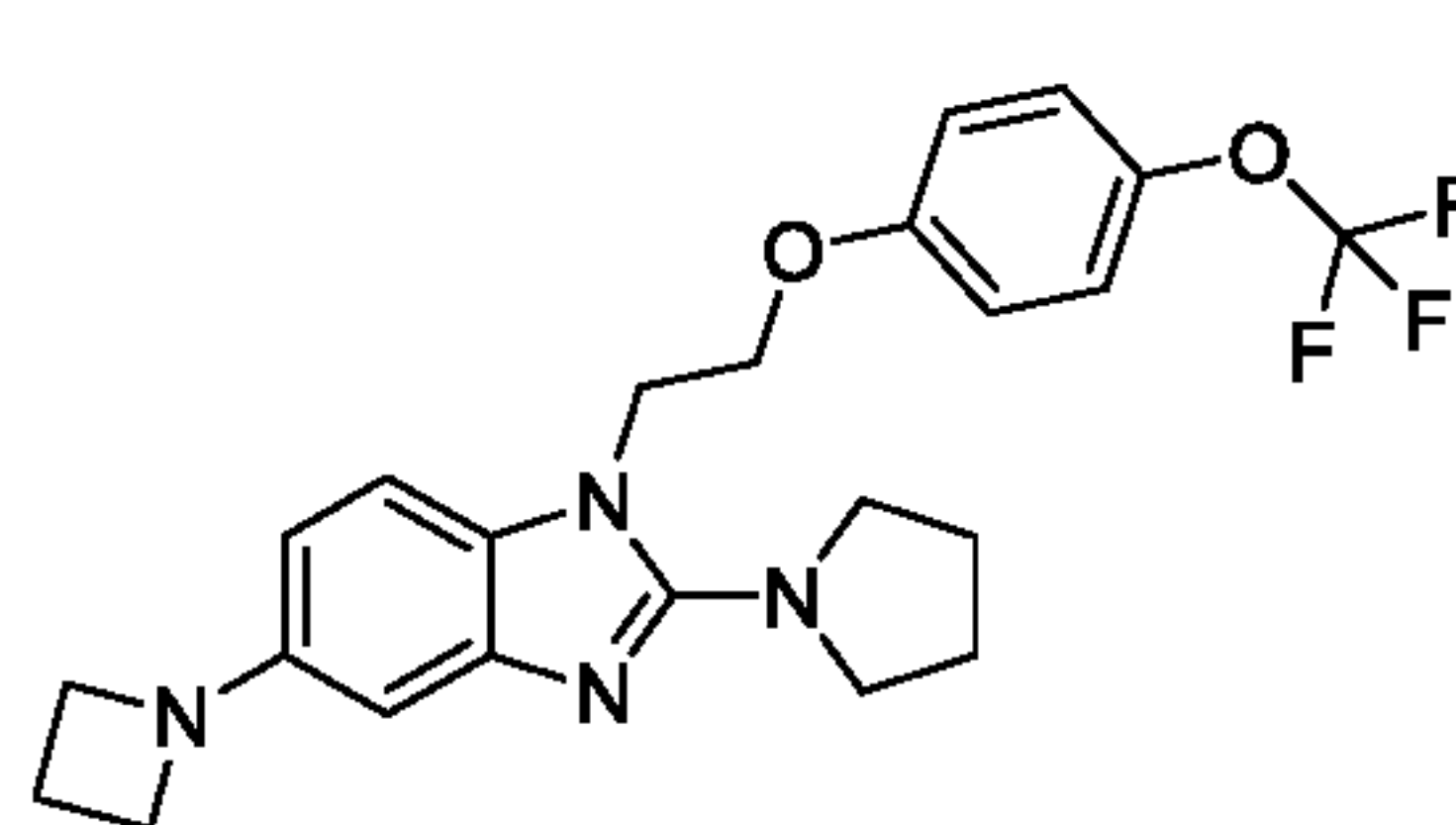
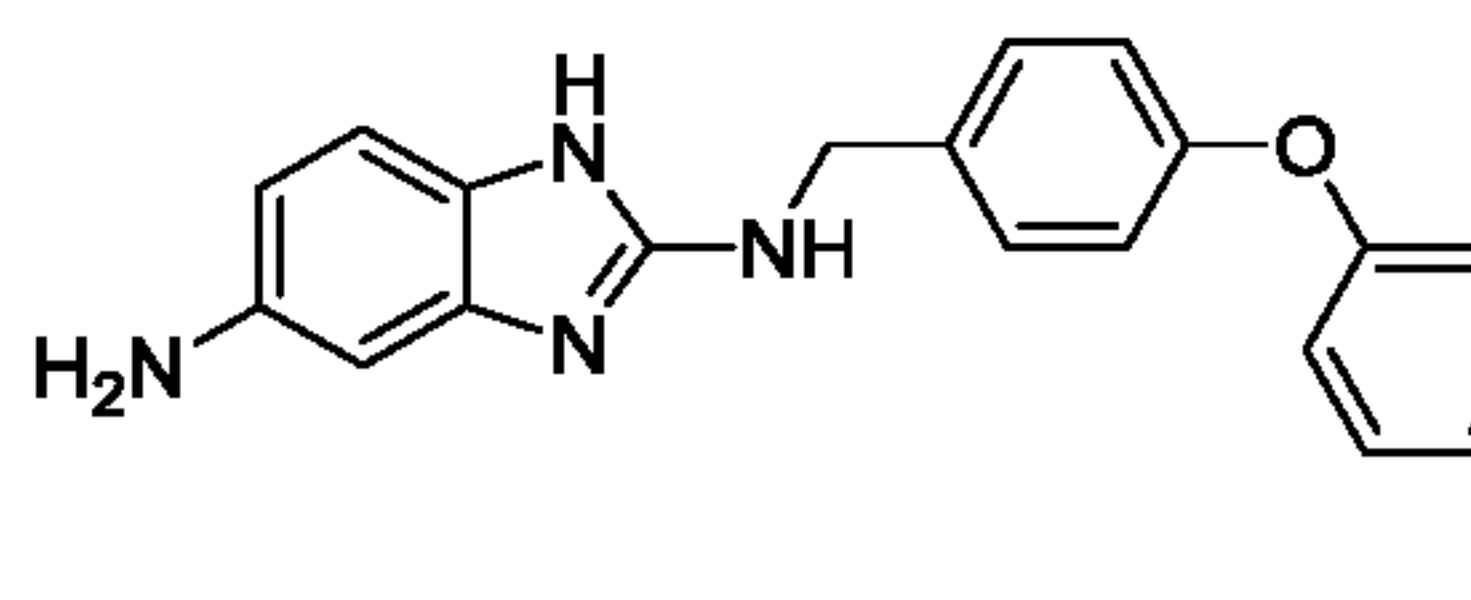
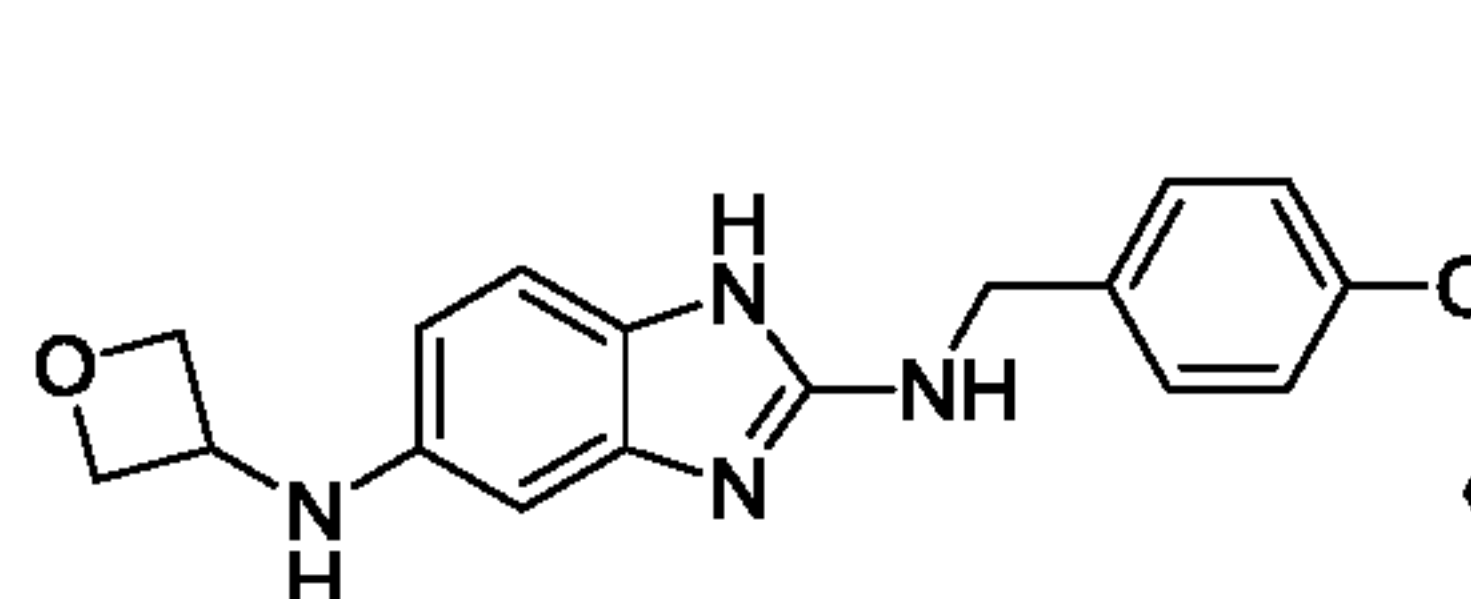
|    |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 31 |  | pale powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.14 (1H, brs), 7.49-7.40 (2H, m), 7.29-7.25 (1H, m), 7.18-7.01 (2H, m), 6.90-6.75 (1H, m), 5.40 (1H, brs), 4.56 (2H, d, <i>J</i> = 4.8 Hz), 3.26 (2H, s, overlapped with water peak, confirmed after adding D <sub>2</sub> O), 1.19 (6H, s); LCMS: 96.5%, MS (ESI); <i>m/z</i> 363.2 [M+H] <sup>+</sup> .                                                                                             |
| 32 |  | white powder; hygroscopic; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.45 (1H, brs), 7.35 (2H, dd, <i>J</i> = 8.0, 6.0 Hz), 7.13 (2H, t, <i>J</i> = 8.8 Hz), 7.01 (1H, d, <i>J</i> = 8.0 Hz), 6.57 (1H, s), 6.43 (1H, d, <i>J</i> = 7.6 Hz), 3.49 (2H, t, <i>J</i> = 7.2 Hz, overlapped with H <sub>2</sub> O peak), 2.85 (2H, t, <i>J</i> = 7.2 Hz); LCMS: 96.1%, MS (ESI); <i>m/z</i> 271.2 [M+H] <sup>+</sup> .                                            |
| 33 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.32-7.25 (2H, m), 7.22-7.18 (2H, m), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.39 (1H, brs), 6.27 (1H, d, <i>J</i> = 2.0 Hz), 6.14 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.71 (1H, d, <i>J</i> = 6.8 Hz), 4.81 (2H, t, <i>J</i> = 6.0 Hz), 4.50-4.40 (1H, m), 4.38 (2H, t, <i>J</i> = 6.0 Hz), 3.50-3.45 (2H, m), 2.85 (2H, t, <i>J</i> = 7.2 Hz); LCMS: 99.5%, MS (ESI); <i>m/z</i> 327.2 [M+H] <sup>+</sup> . |
| 34 |  | brown amorphous; mp = 193.3-205°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.17-7.07 (2H, m), 7.06-6.98 (2H, m), 6.92 (1H, d, <i>J</i> = 8.4 Hz), 6.51 (1H, s), 6.33 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 4.62-4.50 (1H, m), 3.86-3.70 (2H, m), 3.46-3.40 (2H, m), 2.08-1.95 (2H, m), 1.74-1.59 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 327.2[M+ H] <sup>+</sup> .                                                                                           |
| 35 |  | brown gum; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.43 (1H, d, <i>J</i> = 8.8 Hz), 7.19-7.09 (2H, m), 7.09-6.96 (3H, m), 6.89 (1H, dd, <i>J</i> = 8.8, 1.6 Hz), 4.72-4.57 (1H, m), 3.75-3.65 (2H, m), 3.67 (3H, s), 3.49-3.40 (2H, m), 2.18-2.05 (2H, m), 1.90-1.77 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 341.2[M+ H] <sup>+</sup> .                                                                                                                   |
| 36 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.99 (1H, brs), 7.06-7.16 (2H, m), 6.98-7.05 (2H, m), 6.94 (1H, brs), 6.29 (1H, s), 6.20 (1H, d, <i>J</i> = 8.0 Hz), 5.78 (1H, brs), 4.82 (2H, t, <i>J</i> = 6.0 Hz), 4.54 (1H, brs), 4.43-4.50 (1H, m), 4.33-4.43 (2H, m), 3.79 (2H, d, m), 3.37-3.43 (2H, m), 1.98 (2H, m), 1.63 (2H, m); LCMS: 98.4%, MS (ESI); <i>m/z</i> 383.2[M+ H] <sup>+</sup> .                                      |
| 37 |  | light green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.25 (1H, brs), 7.19-7.08 (2H, m), 7.08-6.92 (4H, m), 6.51-6.36 (2H, m), 5.44 (1H, brs), 4.60-4.52 (1H, m), 3.87-3.75 (2H, m), 3.43-3.41 (2H, m, overlapped with H <sub>2</sub> O peak), 2.10-2.00 (2H, m), 1.78-1.60 (2H, m), 1.35 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 412.1 [M+H] <sup>+</sup> .                                                                                        |
| 38 |  | brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.80 (1H, d, <i>J</i> = 8.4 Hz), 7.56 (1H, s), 7.41-7.25 (3H, m), 6.89 (2H, d, <i>J</i> = 8.8 Hz), 4.72 (2H, t, <i>J</i> = 4.8 Hz), 4.37 (2H, t, <i>J</i> = 4.8 Hz), 3.34 (6H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 330.9 [M+ H] <sup>+</sup> .                                                                                                                                                               |
| 39 |  | brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.34-7.24 (2H, m), 7.07 (1H, d, <i>J</i> = 8.0 Hz), 6.98-6.89 (2H, m), 6.66 (1H, d, <i>J</i> = 2.0 Hz), 6.41 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.80 (2H, brs), 4.30 (4H, s), 2.81 (6H, s); LCMS: 99.8%, MS (ESI); <i>m/z</i> 330.9 [M+ H] <sup>+</sup> .                                                                                                                                                       |

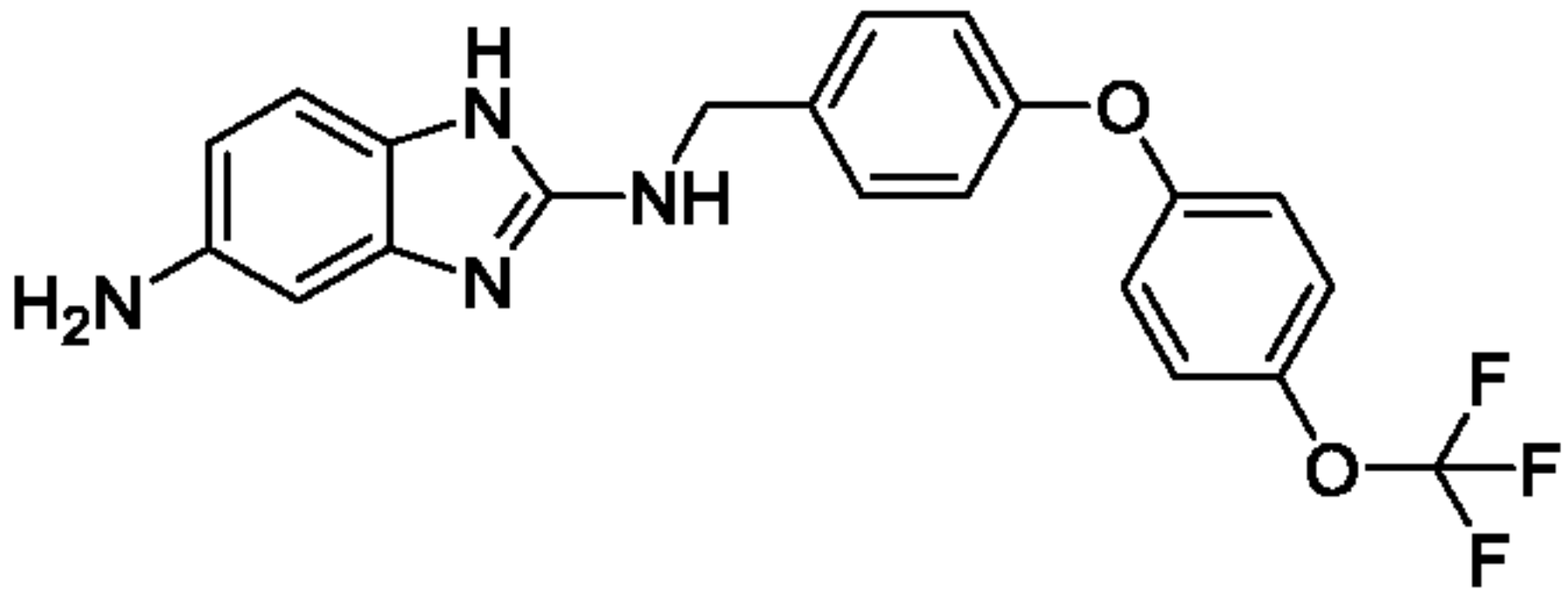
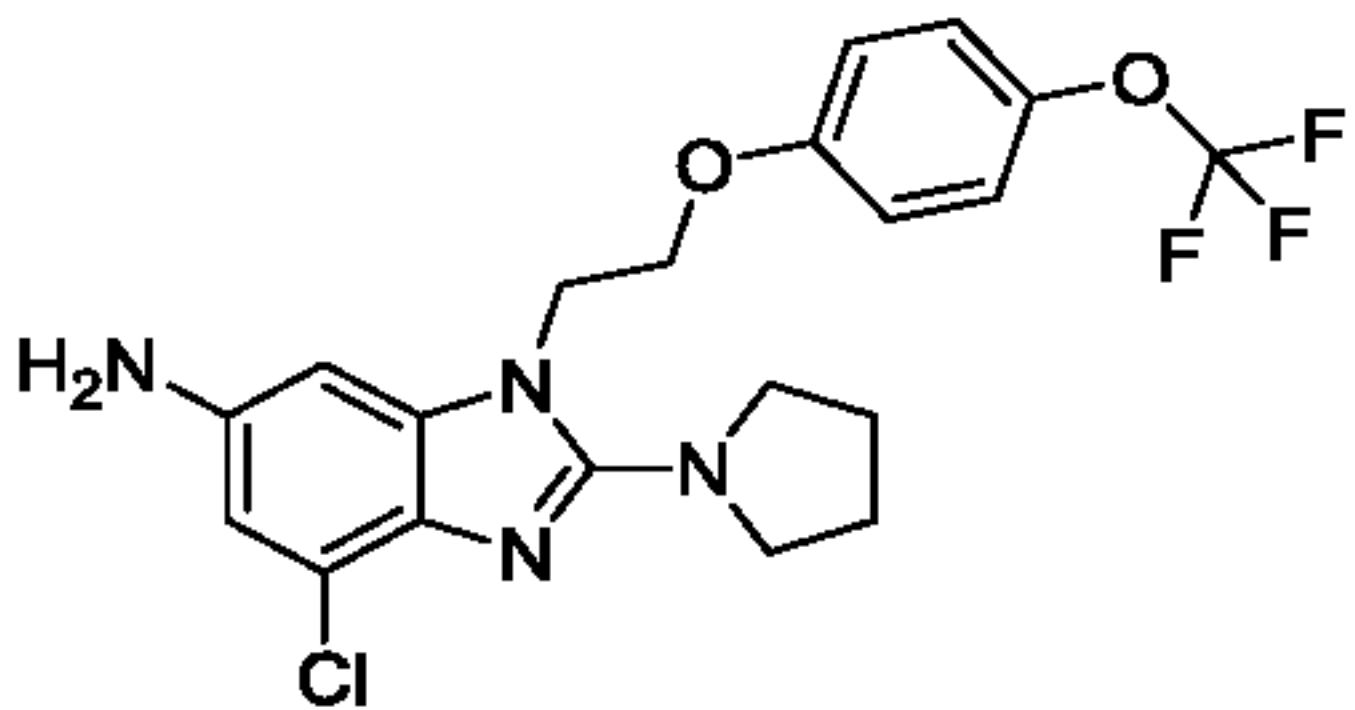
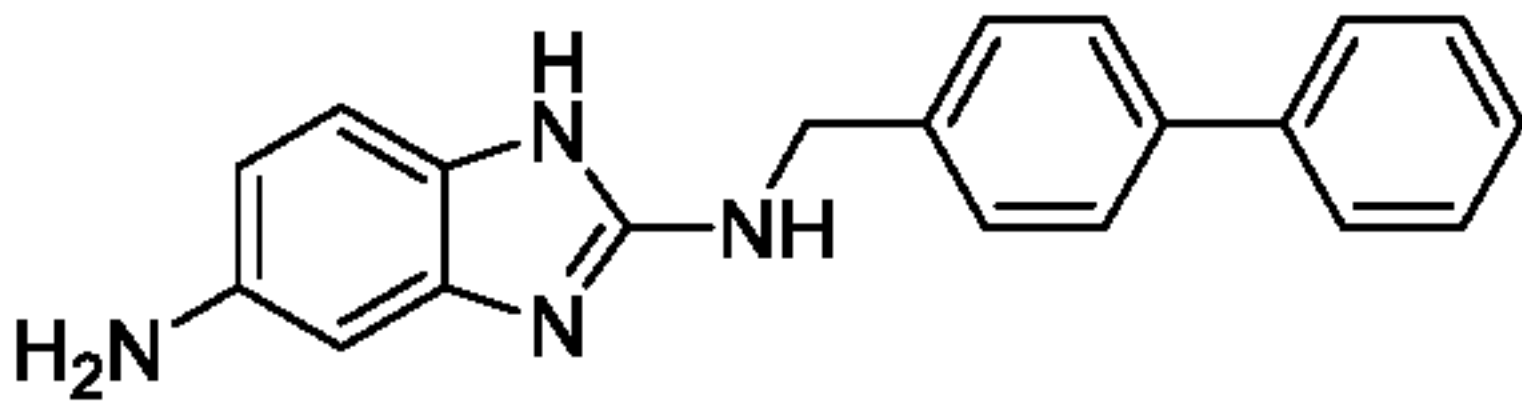
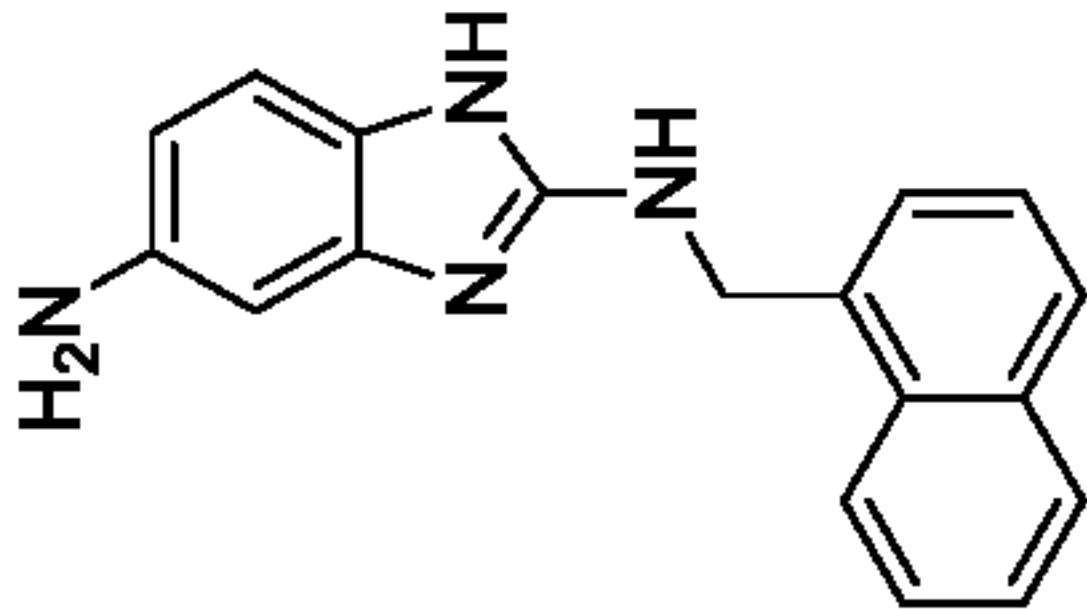
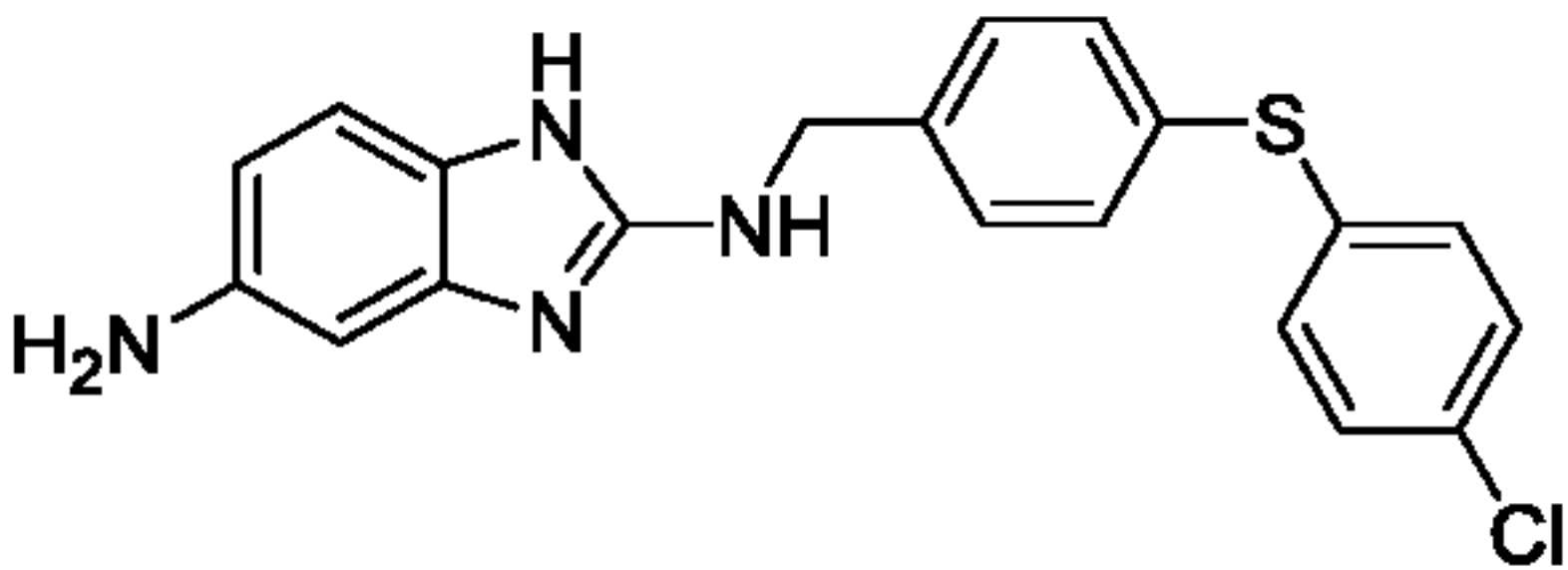
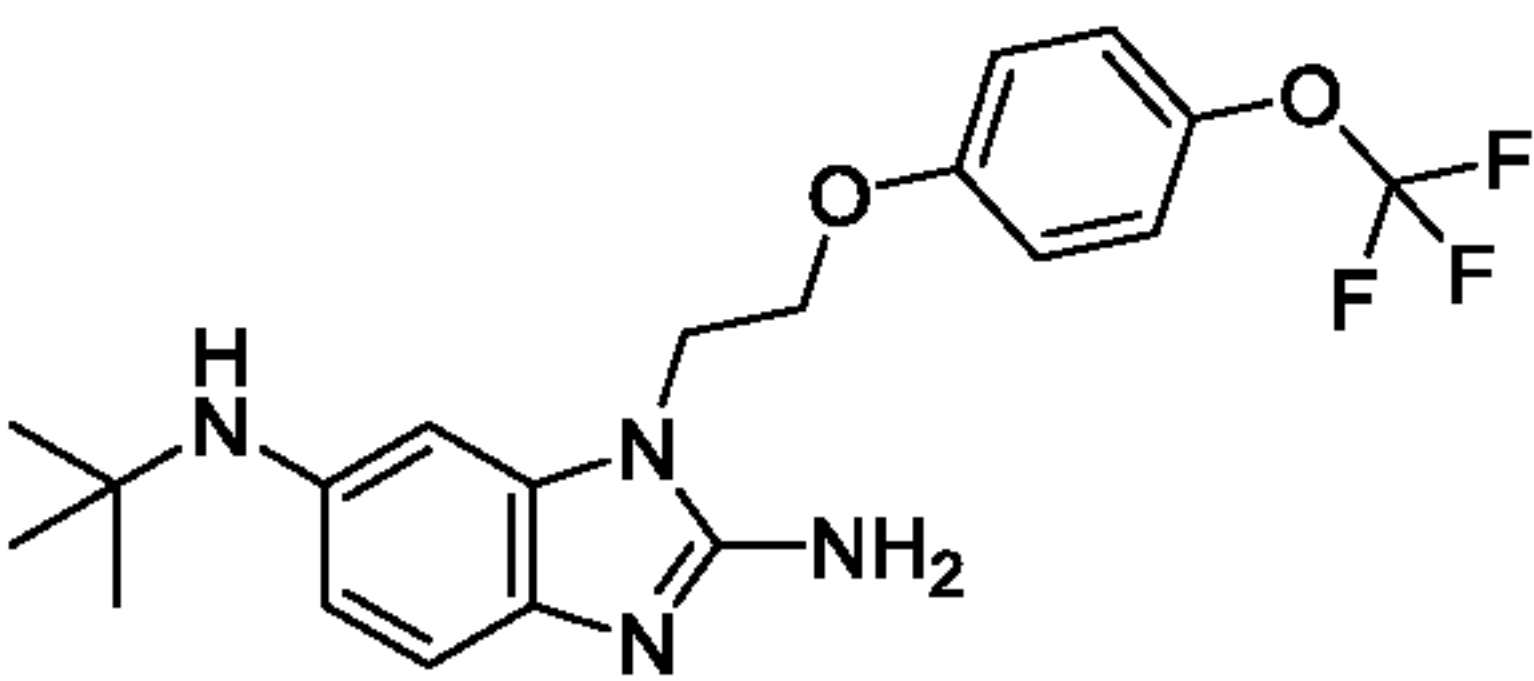
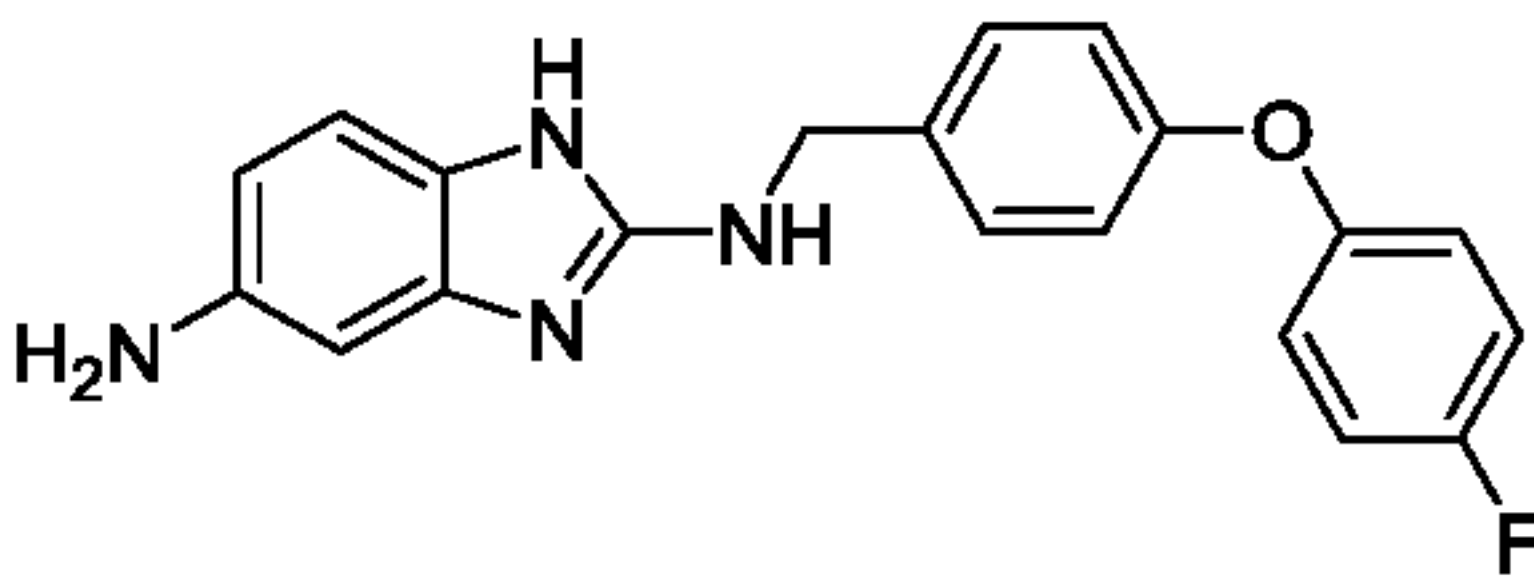
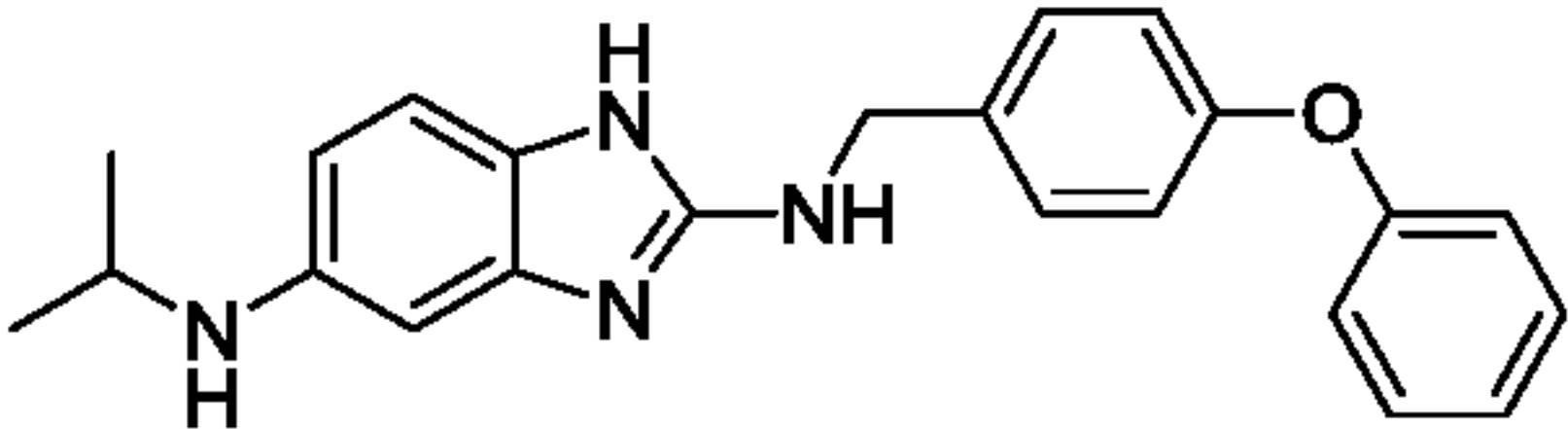
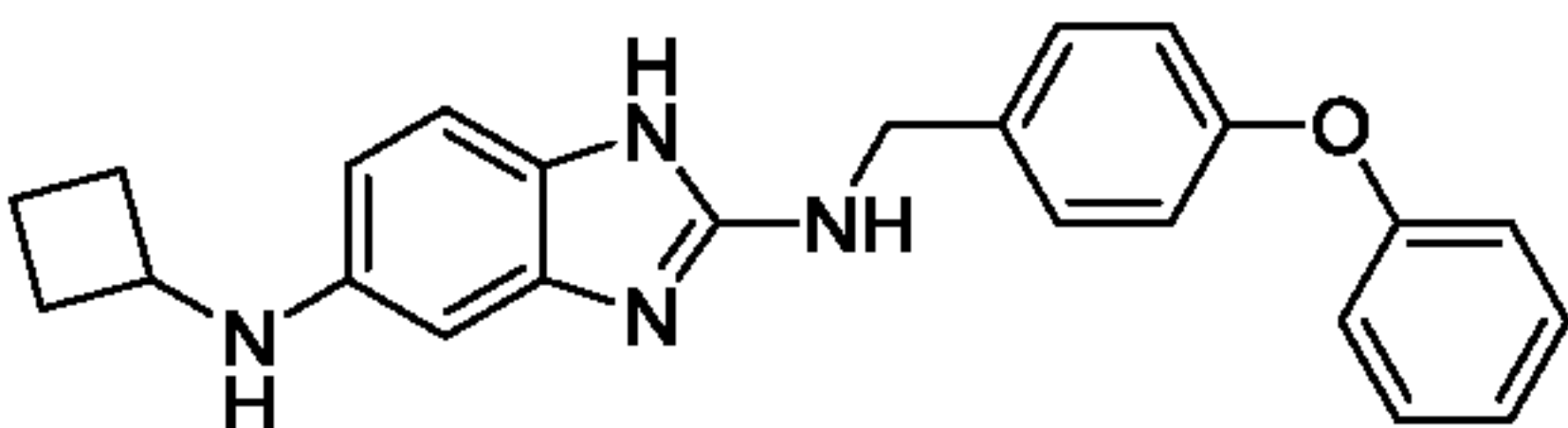
|    |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 40 |    | green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.39-7.25 (2H, m), 7.13 (1H, d, <i>J</i> = 8.4 Hz), 6.99-6.85 (2H, m), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.37 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.08 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.62-4.47 (1H, m), 4.45-4.36 (2H, m), 4.35-4.25 (4H, m), 2.81 (6H, s); LCMS: 99.8%, MS (ESI); <i>m/z</i> 386.9 [M+ H] <sup>+</sup> .                            |
| 41 |    | brown amorphous; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.24-7.18 (2H, m), 7.14 (1H, d, <i>J</i> = 8.8 Hz), 6.80-6.72 (2H, m), 6.66 (1H, d, <i>J</i> = 2.4 Hz), 6.49 (1H, dd, <i>J</i> = 8.4 Hz, 2.0 Hz), 5.02 (2H, t, <i>J</i> = 6.4 Hz), 4.68-4.57 (1H, m), 4.53 (2H, d, <i>J</i> = 6.0 Hz), 4.42-4.32 (2H, m), 4.30-4.21 (2H, m), 4.06 (1H, brs), 2.98 (6H, s); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 387.0 [M+ H] <sup>+</sup> .               |
| 42 |   | white solid; mp = 178.2-179.6°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.95 (2H, brs), 7.44 (1H, d, <i>J</i> = 8.8 Hz), 7.39 (1H, s), 7.35-7.45 (2H, m), 7.10-7.25 (3H, m), 4.37 (2H, t, <i>J</i> = 7.2 Hz), 2.99 (2H, t, <i>J</i> = 7.2 Hz); LCMS: 99.2%, MS (ESI); <i>m/z</i> 271.0 [M+H] <sup>+</sup> .                                                                                                                           |
| 43 |  | white powder; mp = 60.8-61.6°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.26 (2H, d, <i>J</i> = 8.4 Hz), 7.14 (1H, d, <i>J</i> = 8.4 Hz), 6.97 (2H, d, <i>J</i> = 9.2 Hz), 6.59 (1H, d, <i>J</i> = 1.6 Hz), 6.41 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.61 (2H, brs), 4.32 (4H, s), 2.85 (6H, s); LCMS: 99.6%, MS (ESI); <i>m/z</i> 380.9 [M+ H] <sup>+</sup> .                                                                                    |
| 44 |  | white powder; mp > 133°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.27 (2H, d, <i>J</i> = 8.4 Hz), 7.14-6.94 (3H, m), 6.66 (1H, s), 6.41 (1H, d, <i>J</i> = 8.0 Hz), 4.77 (2H, brs), 4.25-4.35 (4H, m), 2.80 (6H, s); LCMS: 97.9 %, MS (ESI); <i>m/z</i> 381.0 [M+ H] <sup>+</sup> .                                                                                                                                                            |
| 45 |  | white powder: <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.23 (1H, s), 7.62 (1H, d, <i>J</i> = 2.0 Hz), 7.47 (1H, d, <i>J</i> = 2.0 Hz), 7.26 (2H, d, <i>J</i> = 8.8 Hz), 7.19 (1H, d, <i>J</i> = 8.4 Hz), 7.00-7.08 (2H, m), 6.97 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.76 (1H, d, <i>J</i> = 2.0 Hz), 4.37 (4H, dd, <i>J</i> = 8.0 Hz, 4.0 Hz), 3.68 (3H, s), 2.84 (6H, s); LCMS: 98.7%, MS (ESI); <i>m/z</i> 460.8 [M+ H] <sup>+</sup> . |
| 46 |  | white powder: <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.11 (1H, s), 7.56 (1H, d, <i>J</i> = 2.0 Hz), 7.45 (1H, d, <i>J</i> = 2.0 Hz), 7.22-7.33 (3H, m), 6.91-7.03 (3H, m), 5.70 (1H, d, <i>J</i> = 2.0 Hz), 4.36 (4H, s), 3.72 (3H, s), 2.88 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 461.0 [M+ H] <sup>+</sup> .                                                                                                                    |
| 47 |  | yellow gum; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.10 (1H, s), 6.95-7.07 (5H, m), 6.63 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.18 (2H, t, <i>J</i> = 7.6 Hz), 3.25-3.40 (4H, m), 3.06 (2H, t, <i>J</i> = 7.6 Hz), 1.14 (6H, t, <i>J</i> = 7.2 Hz); LCMS: 95.7%, MS (ESI); <i>m/z</i> 327.2[M+ H] <sup>+</sup> .                                                                                                                                   |
| 48 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26(2H, d, <i>J</i> = 8.8 Hz), 6.99 (2H, d, <i>J</i> = 8.8 Hz), 6.81 (1H, d, <i>J</i> = 8.4 Hz), 6.48 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.98 (2H, brs), 4.55 (2H, brs), 4.22 - 4.24 (2H, m), 4.18 (2H, t, <i>J</i> = 5.2 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 353.1 [M+H] <sup>+</sup> .                                                      |

|    |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 49 |  | white powder: <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26 (1H, d, <i>J</i> = 8.8 Hz), 6.96 (2H, d, <i>J</i> = 9.2 Hz), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.17 (2H, brs), 4.39 (2H, brs), 4.22-4.29 (2H, m), 4.11-4.22 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 352.9 [M+H] <sup>+</sup> .                                                                 |
| 50 |  | yellow gum: <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.06 (2H, dd, <i>J</i> = 8.4, 4.2 Hz), 7.00 (2H, t, <i>J</i> = 7.2 Hz), 6.95-6.85 (2H, m), 6.49 (1H, dd, <i>J</i> = 8.4, 6.4 Hz), 4.19 (2H, t, <i>J</i> = 7.2 Hz), 3.52 (4H, t, <i>J</i> = 6.8 Hz), 3.00 (2H, t, <i>J</i> = 7.2 Hz), 1.95-2.05 (4H, m); LCMS: 97.4%, MS (ESI); <i>m/z</i> 324.9[M+ H] <sup>+</sup> .                                                                     |
| 51 |  | yellow powder: <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.31 (1H, d, <i>J</i> = 8.0 Hz), 7.13 (2H, d, <i>J</i> = 8.8 Hz), 6.83 (2H, dd, <i>J</i> = 6.8, 2.0 Hz), 6.60 (1H, d, <i>J</i> = 1.6 Hz), 6.57 (1H, d, <i>J</i> = 8.0 Hz), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 4.25 (2H, t, <i>J</i> = 6.8 Hz), 3.59 (4H, t, <i>J</i> = 6.8 Hz), 1.99 (4H, m); LCMS: 98.3%, MS (ESI); <i>m/z</i> 407.1[M+ H] <sup>+</sup> .                              |
| 52 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.28 (2H, d, <i>J</i> = 9.2 Hz), 7.08 (2H, d, <i>J</i> = 9.6 Hz), 6.89 (1H, d, <i>J</i> = 8.0 Hz), 6.58 (1H, t, <i>J</i> = 5.6 Hz), 6.35 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.19 (2H, t, <i>J</i> = 5.6 Hz), 3.52-3.68 (2H, m), 3.36 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 336.9 [M+H] <sup>+</sup> .                    |
| 53 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.28 (2H, d, <i>J</i> = 8.8 Hz), 7.09 (2H, d, <i>J</i> = 9.2 Hz), 6.79 (1H, d, <i>J</i> = 8.4 Hz), 6.68 (1H, t, <i>J</i> = 5.6 Hz), 6.48 (1H, d, <i>J</i> = 1.6 Hz), 6.24 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.41 (2H, brs), 4.19 (2H, t, <i>J</i> = 5.6 Hz), 3.65-3.70 (2H, m), 3.38 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 367.1 [M+H] <sup>+</sup> .                    |
| 54 |  | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.72 (1H, brs), 7.30 (2H, d, <i>J</i> = 8.4 Hz), 7.06 (2H, d, <i>J</i> = 8.8 Hz), 6.82 (1H, d, <i>J</i> = 8.0 Hz), 6.45 (1H, s), 6.21 (1H, d, <i>J</i> = 8.0 Hz), 5.16 (1H, s), 4.50 (2H, brs), 3.65-3.85 (1H, m), 3.45-3.65 (3H, m), 2.23-2.40 (1H, m), 2.08-2.23 (1H, m); LCMS: 97.3%, MS (ESI); <i>m/z</i> 378.9 [M+H] <sup>+</sup> .                               |
| 55 |  | yellow powder: <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.12 (2H, d, <i>J</i> = 8.4 Hz), 7.00 (1H, d, <i>J</i> = 8.0 Hz), 6.88 (1H, d, <i>J</i> = 2.0 Hz), 6.82 (2H, dd, <i>J</i> = 6.8, 2.4 Hz), 6.50 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.41 (2H, t, <i>J</i> = 6.0 Hz), 4.24 (2H, t, <i>J</i> = 6.4 Hz), 3.63 (4H, t, <i>J</i> = 6.8 Hz), 2.00 (4H, m); LCMS: 98.5%, MS (ESI); <i>m/z</i> 407.2[M+ H] <sup>+</sup> .                        |
| 56 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.56 (1H, d, <i>J</i> = 2.8 Hz) 7.36-7.43 (1H, m), 7.30-7.36 (1H, m), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.55 (1H, t, <i>J</i> = 5.6 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.28 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.54 (2H, brs), 4.31 (2H, t, <i>J</i> = 6.0 Hz), 3.44-3.68 (2H, m), 3.36 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 400.9 [M+H] <sup>+</sup> .                |
| 57 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.56 (1H, d, <i>J</i> = 2.0 Hz), 7.39 (1H, d, <i>J</i> = 9.2 Hz), 7.29-7.36 (1H, m), 6.79 (1H, d, <i>J</i> = 8.4 Hz), 6.67 (1H, t, <i>J</i> = 5.6 Hz), 6.49 (1H, d, <i>J</i> = 2.0 Hz), 6.24 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.41 (2H, brs), 4.30 (2H, t, <i>J</i> = 6.0 Hz), 3.67-3.72 (2H, m), 3.38 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 401.0 [M+H] <sup>+</sup> . |
| 58 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.47 (1H, d, <i>J</i> = 8.4 Hz), 7.41 (1H, d, <i>J</i> = 3.2 Hz), 7.08 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.57 (1H, t, <i>J</i> = 5.2 Hz), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.54 (2H, brs), 4.24 (2H, t, <i>J</i> = 5.6 Hz), 3.60-                                                                    |

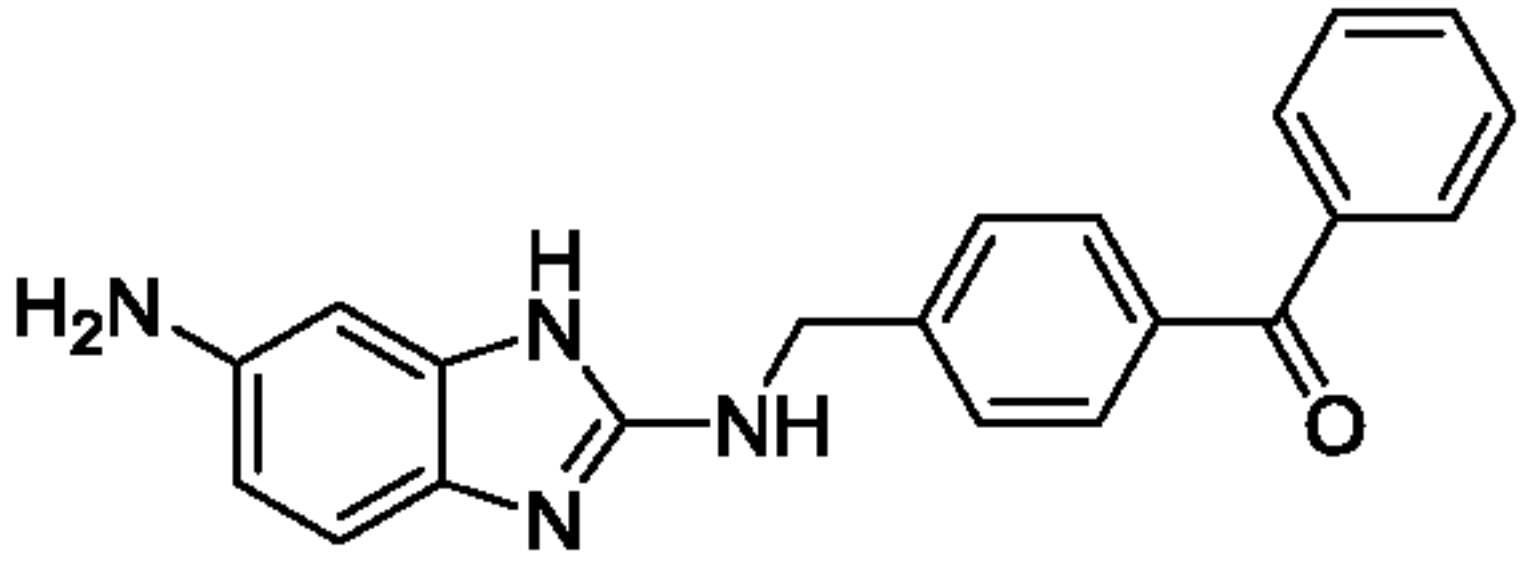
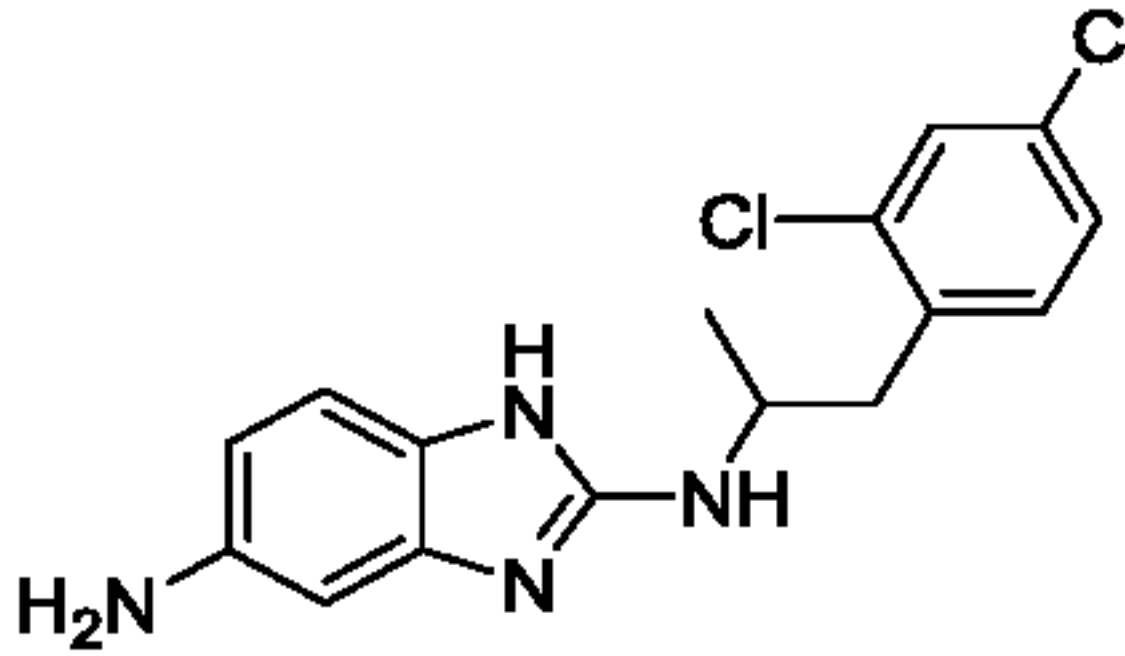
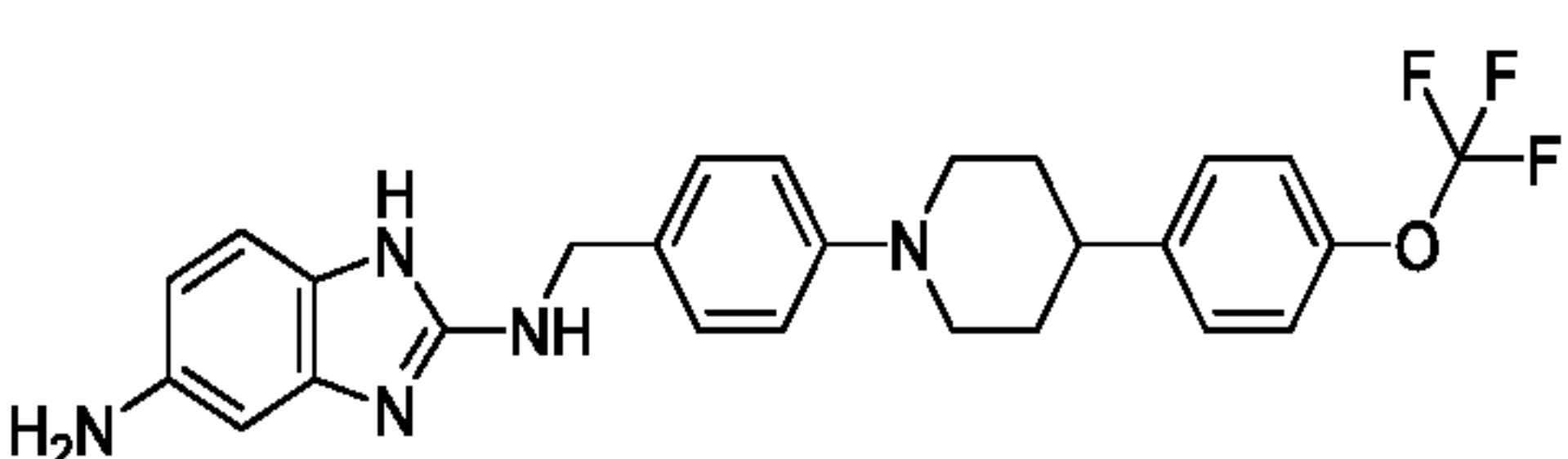
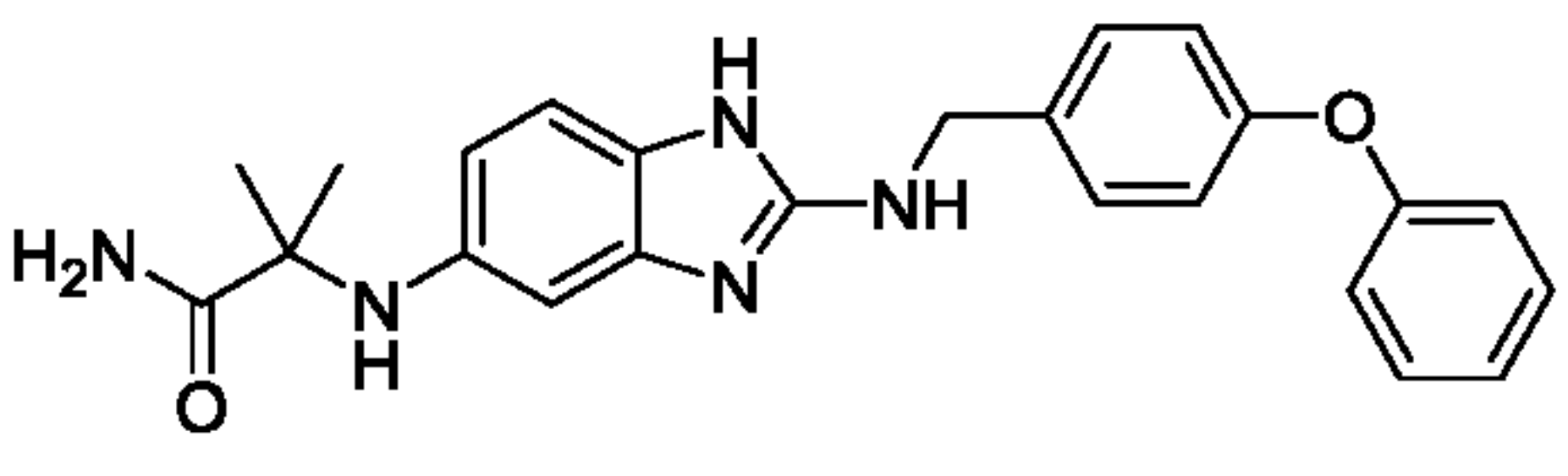
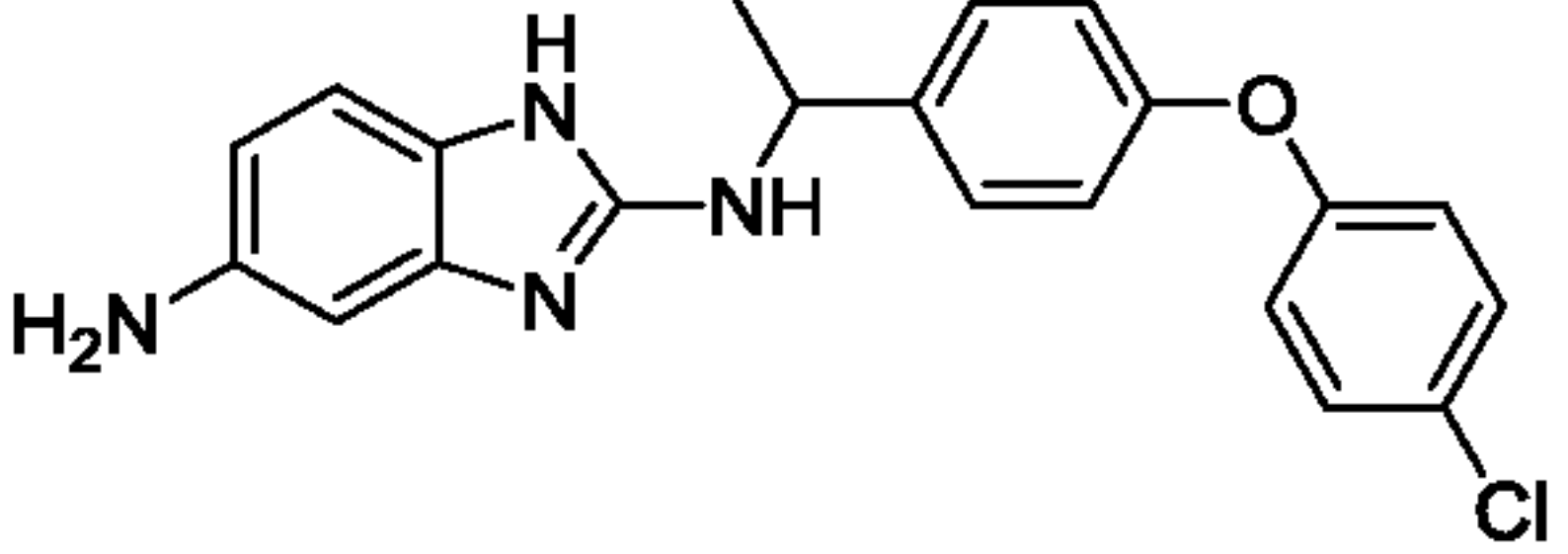
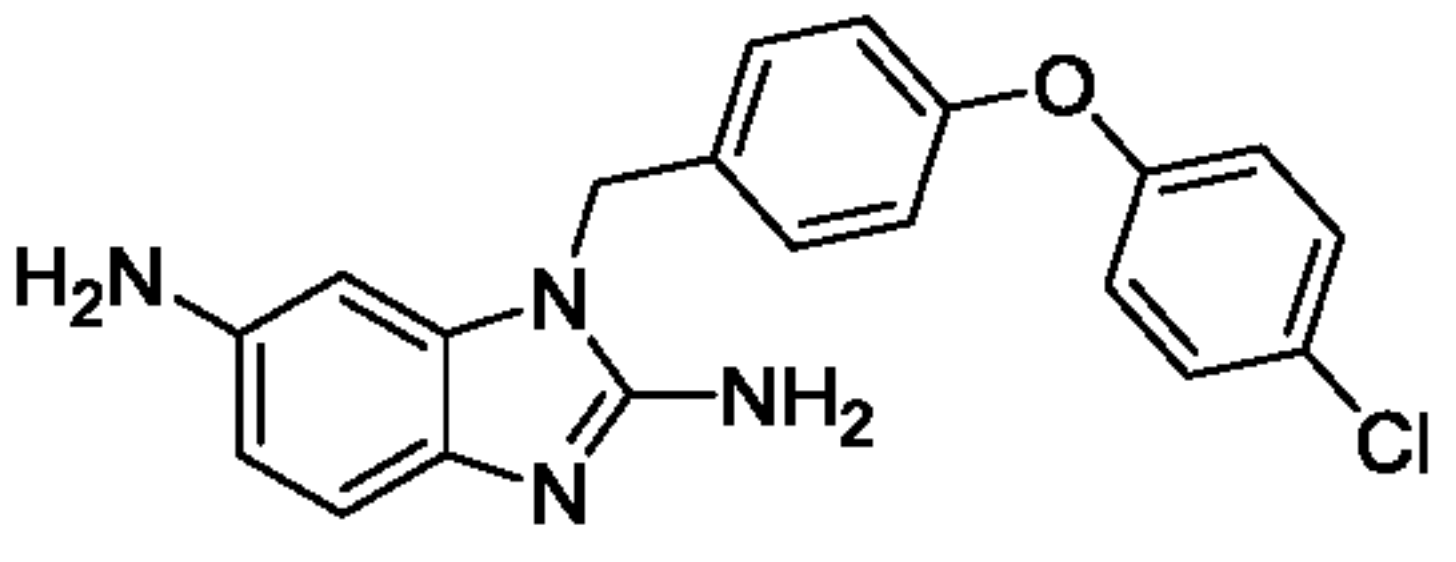
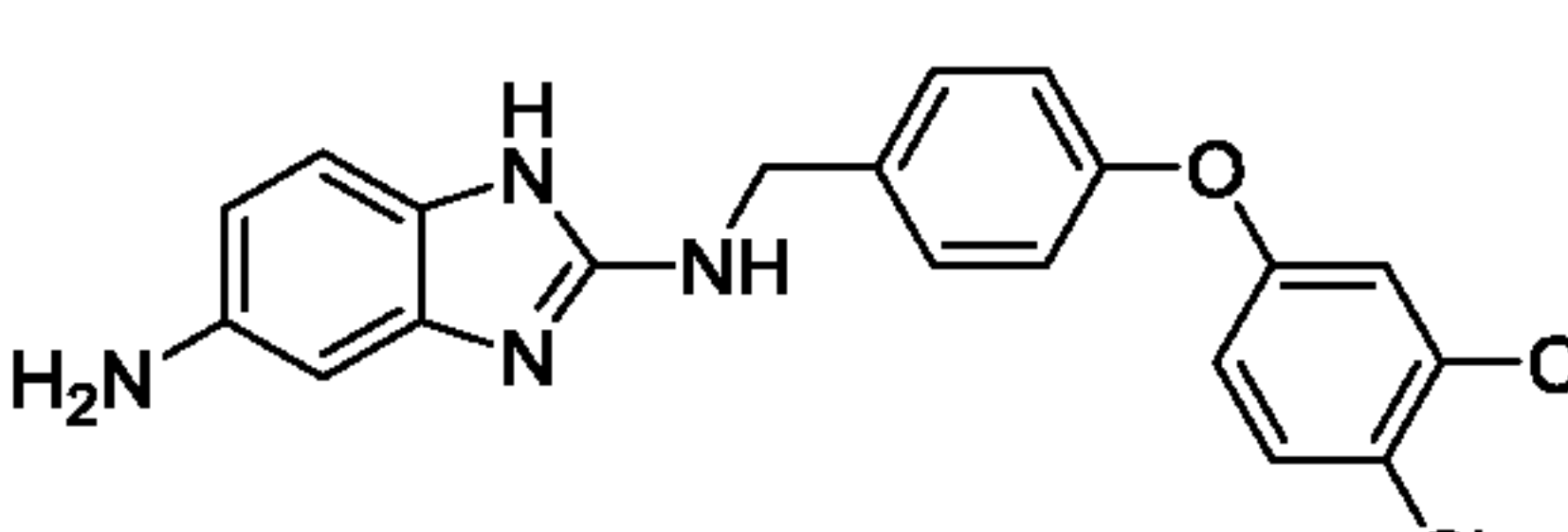
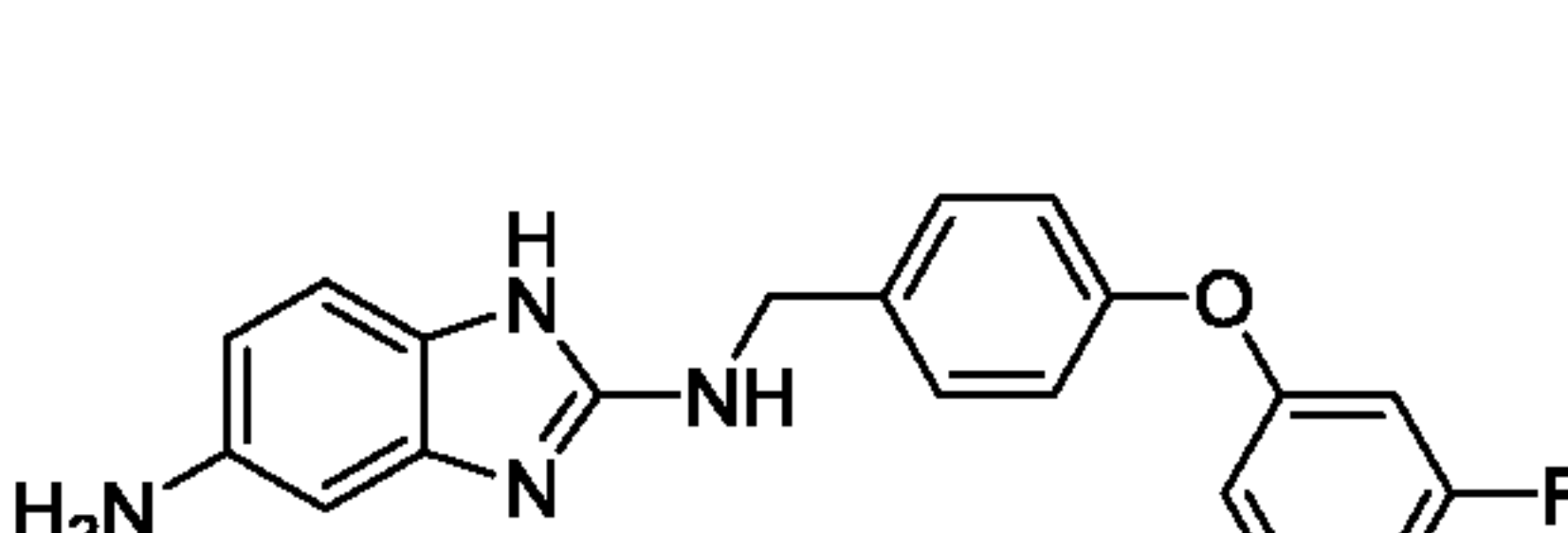
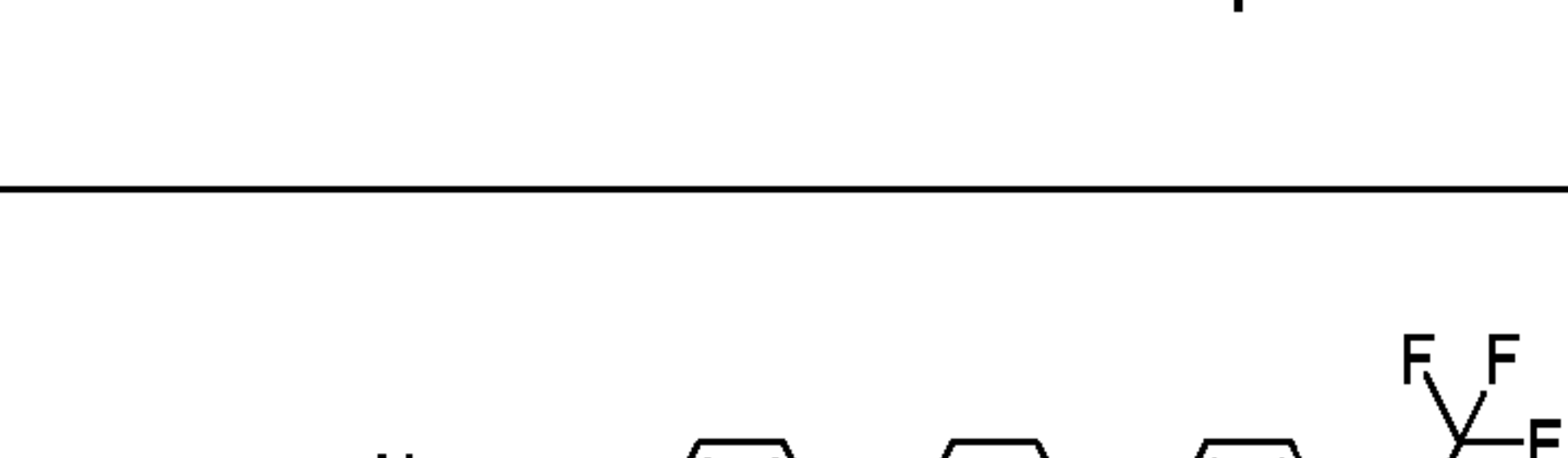
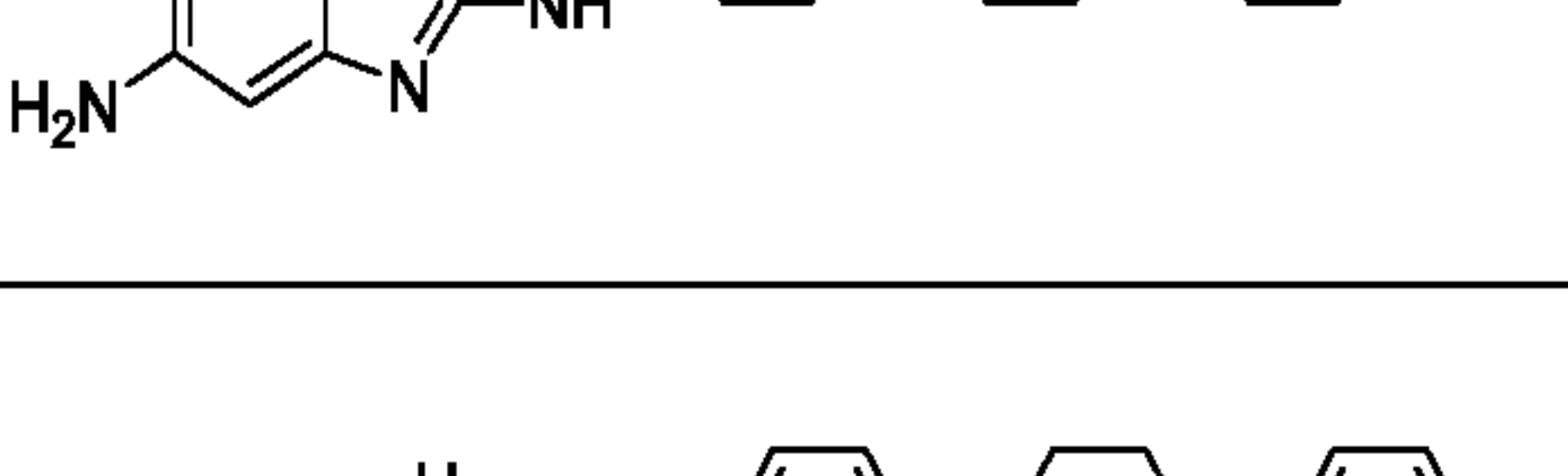
|    |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |  | 3.66 (2H, m), 3.36 (3H, s); LCMS: 99.6%, MS (ESI); m/z 400.9 [M+H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                                                                      |
| 59 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36 - 7.47 (2H, m) 7.05 (1H, dd, <i>J</i> = 9.2, 2.8 Hz), 6.77 (1H, d, <i>J</i> = 8.0 Hz), 6.66 (1H, t, <i>J</i> = 5.2 Hz), 6.48 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.43 (2H, brs), 4.21 (2H, t, <i>J</i> = 6.0 Hz), 3.62-3.69 (2H, m), 3.37 (3H, s); LCMS: 95.5%, MS (ESI); m/z 400.9 [M+H] <sup>+</sup> .                                               |
| 60 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.51 (1H, d, <i>J</i> = 9.2 Hz), 7.37 (1H, d, <i>J</i> = 2.8 Hz), 7.01 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.57 (1H, t, <i>J</i> = 5.2 Hz), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.57 (2H, brs), 4.21 (2H, t, <i>J</i> = 6.0 Hz), 3.58-3.66 (2H, m), 3.36 (3H, s); LCMS: 99.7%, MS (ESI); m/z 350.9 [M+H] <sup>+</sup> . |
| 61 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.48 (1H, d, <i>J</i> = 8.8 Hz), 7.39 (1H, d, <i>J</i> = 2.8 Hz), 7.01 (1H, dd, <i>J</i> = 8.8, 3.2 Hz), 6.79 (1H, d, <i>J</i> = 8.0 Hz), 6.69 (1H, t, <i>J</i> = 5.2 Hz), 6.50 (1H, d, <i>J</i> = 2.0 Hz), 6.24 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.46 (2H, brs), 4.21 (2H, t, <i>J</i> = 6.0 Hz), 3.63-3.68 (2H, m), 3.38 (3H, s); LCMS: 100%, MS (ESI); m/z 350.9 [M+H] <sup>+</sup> .  |
| 62 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.36 (1H, brs), 7.28 (1H, d, <i>J</i> = 8.8 Hz), 7.07 (1H, d, <i>J</i> = 9.2 Hz), 6.78-6.83 (1H, m), 6.40-6.44 (2H, m), 6.18-6.22 (1H, m), 4.42 (2H, brs), 4.14 (2H, t, <i>J</i> = 5.6 Hz), 3.59-3.61 (2H, m); LCMS: 100%, MS (ESI); m/z 353.1 [M+H] <sup>+</sup> .                                                                                                                       |
| 63 |  | dark powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.17 (2H, brs), 8.23 (2H, brs), 7.30 (2H, d, <i>J</i> = 8.8 Hz), 7.17 (2H, d, <i>J</i> = 8.4 Hz), 7.06 (2H, d, <i>J</i> = 9.2 Hz), 6.45-6.55 (2H, m), 5.10-5.20 (1H, m), 3.55-3.75 (1H, m), 3.25-3.48 (3H, m), 2.28-2.49 (1H, m), 2.11-2.25 (1H, m); LCMS: 93.4%, MS (ESI); m/z 379.1 [M+H] <sup>+</sup> .                                                                                 |
| 64 |  | white gum; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.50 (1H, brs), 7.74 (1H, d, <i>J</i> = 8.8 Hz), 7.32 (2H, d, <i>J</i> = 8.8 Hz), 6.91 (2H, d, <i>J</i> = 8.4 Hz), 6.52 (1H, s), 6.30-6.34 (1H, m), 3.70-3.80 (1H, m), 3.50-3.70 (2H, m), 3.39-3.50 (2H, overlap with water peak), 2.20-2.33 (2H, m); LCMS: 99.7%, MS (ESI); m/z 406.1 [M+H] <sup>+</sup> .                                                                                  |
| 65 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.28 (2H, d, <i>J</i> = 8.8 Hz), 6.95-7.02 (2H, m), 6.92 (1H, d, <i>J</i> = 8.4 Hz), 6.49 (1H, d, <i>J</i> = 2.0 Hz), 6.29 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.51 (1H, brs), 4.67 (2H, brs), 4.27 (2H, t, <i>J</i> = 5.2 Hz), 4.18 (2H, t, <i>J</i> = 5.2 Hz), 1.42 (9H, s); LCMS: 99.8%, MS (ESI); m/z 409.2 [M+H] <sup>+</sup> .                                                                  |
| 66 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.27 (2H, d, <i>J</i> = 8.8 Hz), 6.95 (2H, d, <i>J</i> = 8.8 Hz), 6.88 (1H, d, <i>J</i> = 8.0 Hz), 6.50 (1H, d, <i>J</i> = 2.0 Hz), 6.24 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.58 (1H, brs), 4.40 (2H, brs), 4.28 (2H, t, <i>J</i> = 5.2 Hz), 4.16 (2H, t, <i>J</i> = 5.2 Hz), 1.43 (9H, s); LCMS: 99.5%, MS (ESI); m/z 409.3 [M+H] <sup>+</sup> .                                                |
| 67 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 10.57 (1H, brs), 7.73 (2H, d, <i>J</i> = 9.2 Hz), 7.34 (2H, d, <i>J</i> = 8.8 Hz), 6.93 (1H, d, <i>J</i> = 8.0 Hz), 6.22-6.33 (2H, m), 5.67-5.79 (1H, m), 4.74 (2H, s), 4.63 (2H, brs), 1.42 (9H, s); LCMS: 99.3%, MS (ESI); m/z 422.2 [M+H] <sup>+</sup> .                                                                                                                                     |

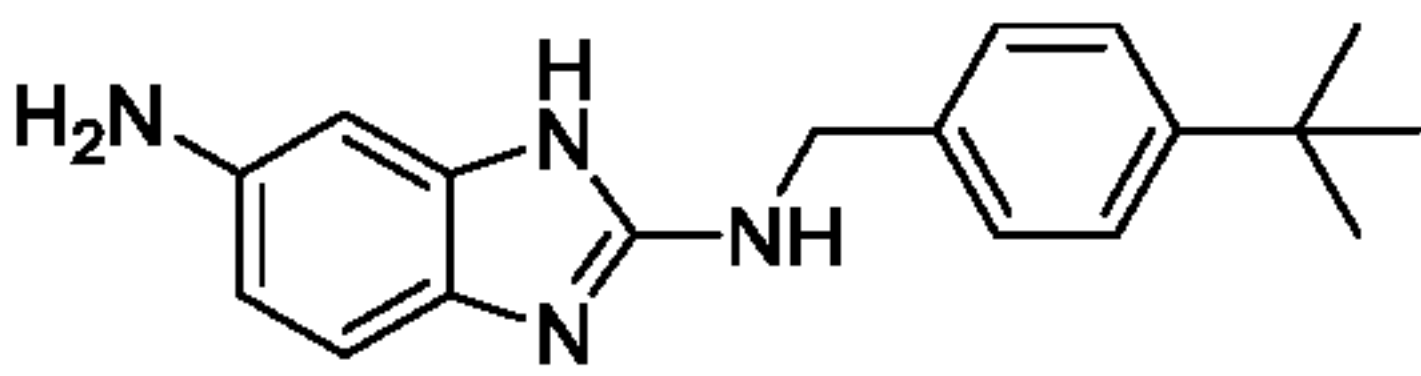
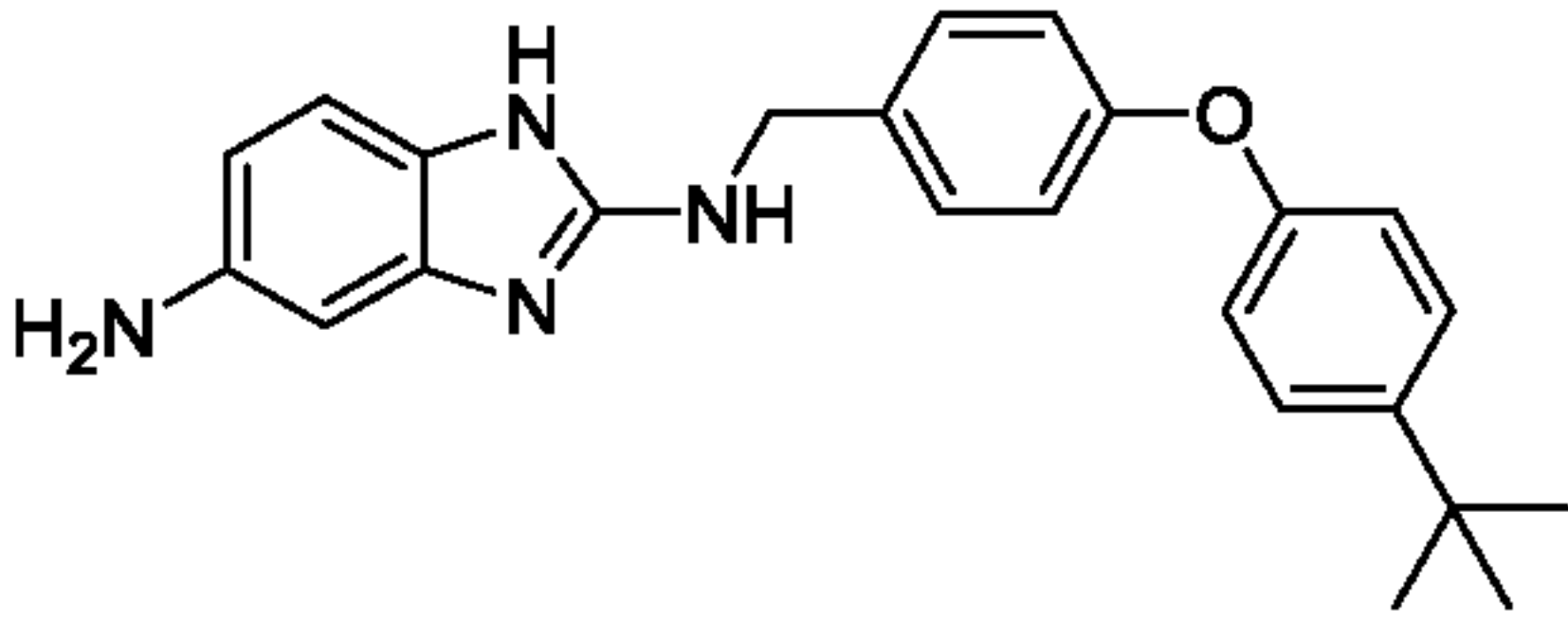
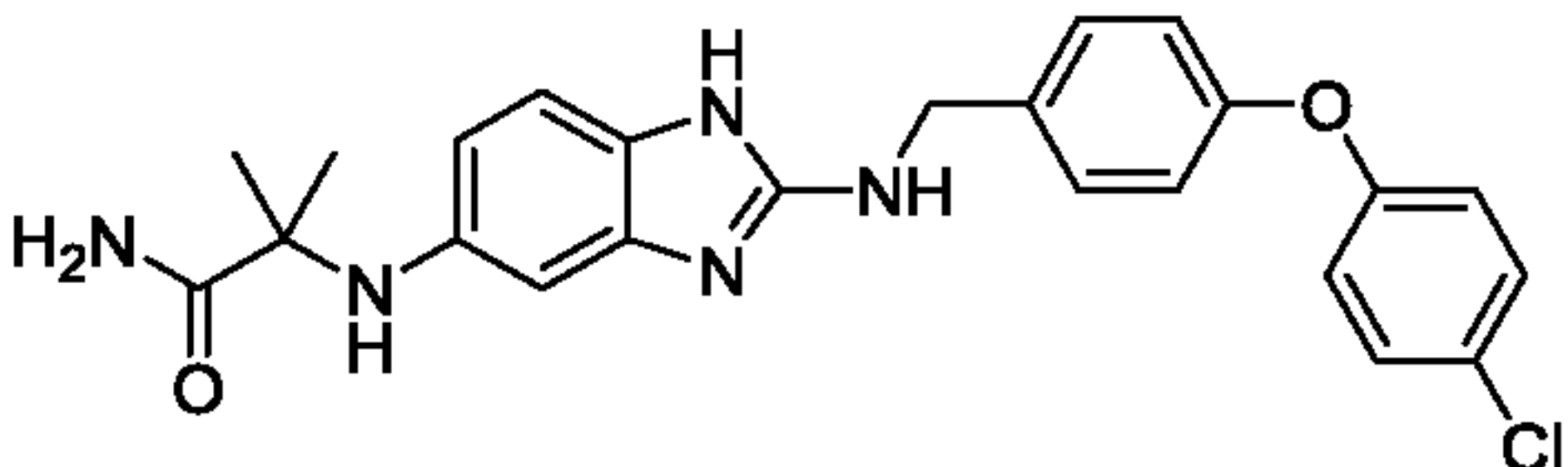
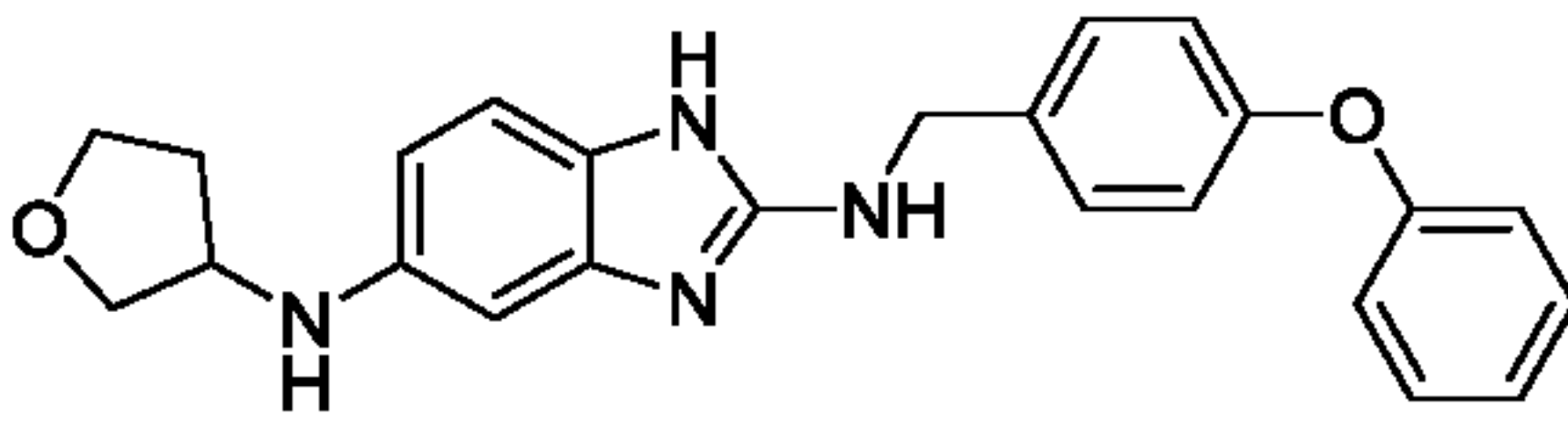
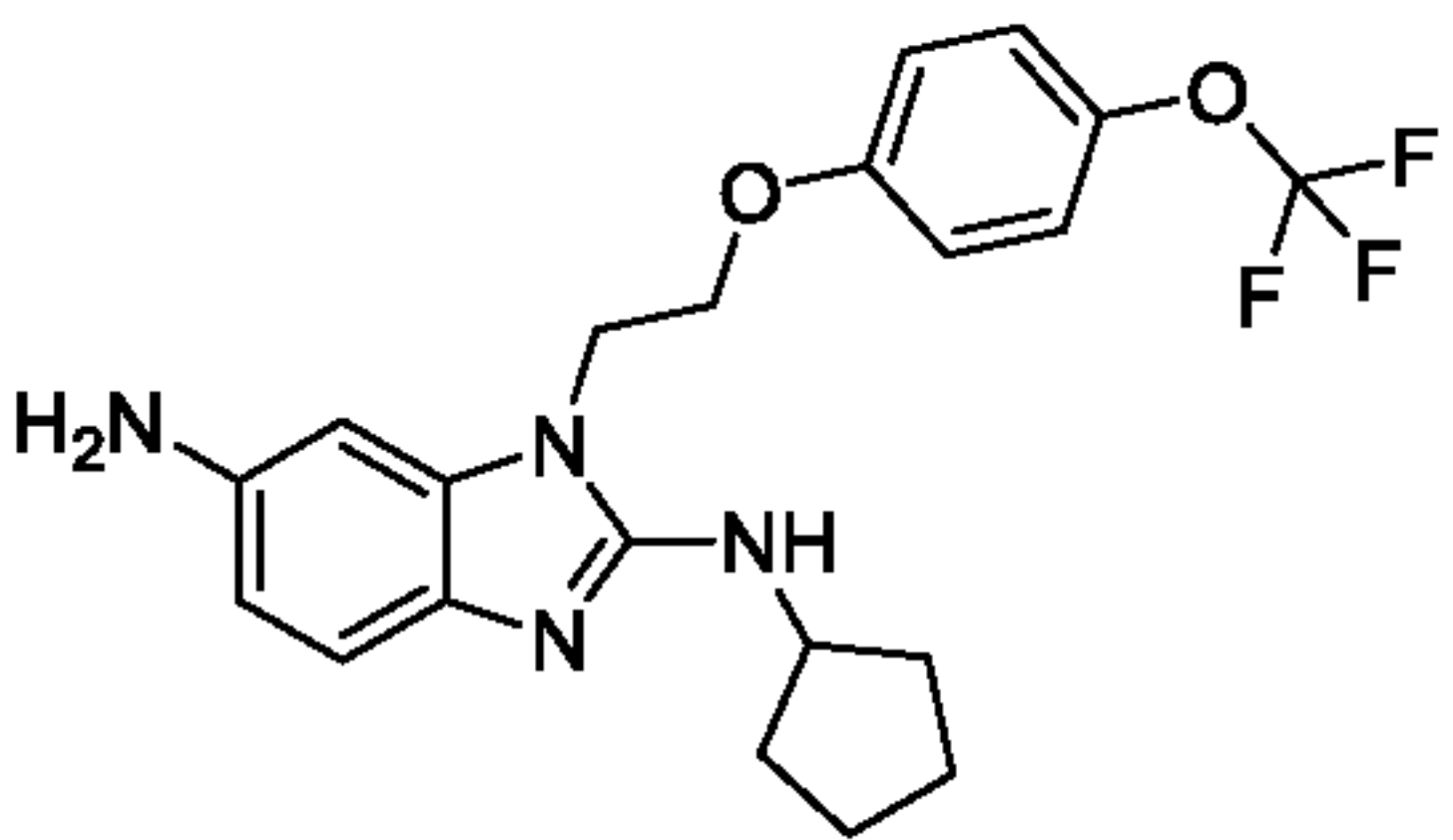
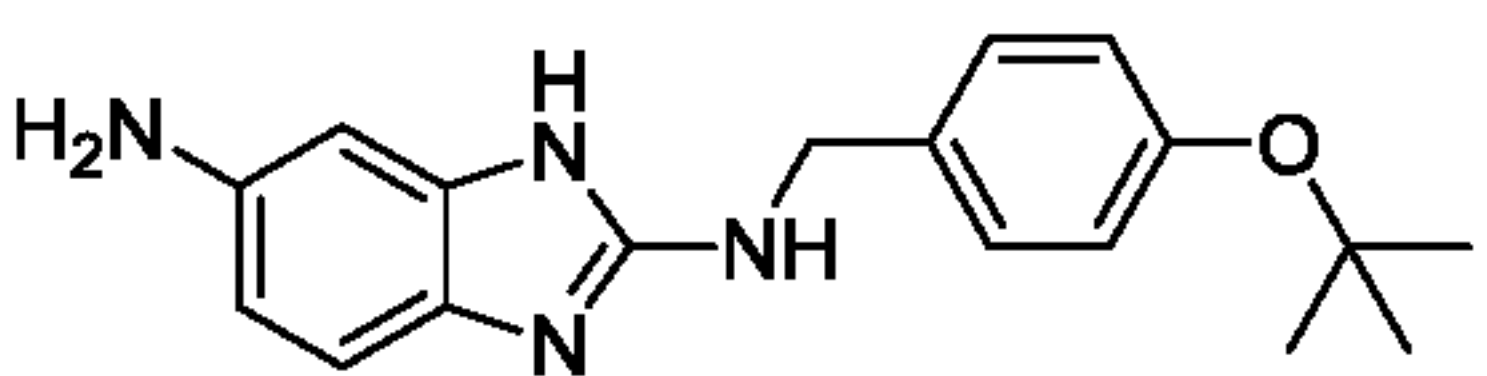
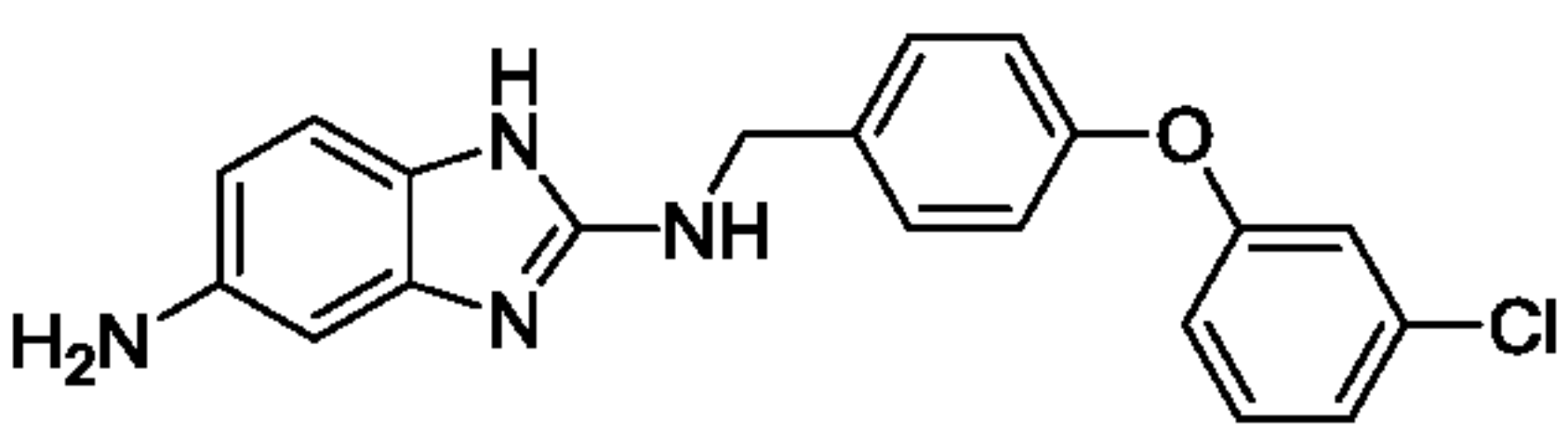
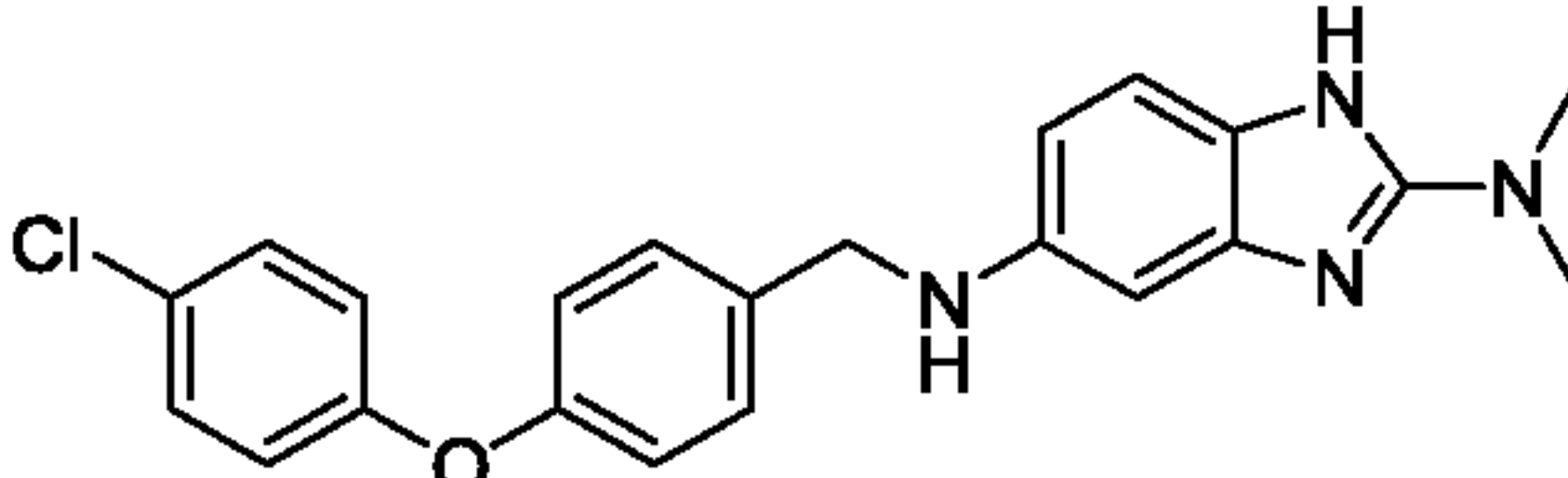
|    |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 68 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.28(2H, d, <i>J</i> = 8.8 Hz), 7.02-7.06 (2H, m), 6.98 (1H, d, <i>J</i> = 8.4 Hz), 6.60 (1H, d, <i>J</i> = 2.0 Hz), 6.37 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.80 (2H, brs), 4.26 (2H, t, <i>J</i> = 4.8 Hz), 4.19 (2H, t, <i>J</i> = 5.2 Hz), 4.08 (4H, t, <i>J</i> = 7.2 Hz), 2.28-2.34 (2H, m); LCMS: 95.7%, MS (ESI); <i>m/z</i> 393.3[M+ H] <sup>+</sup> .                               |
| 69 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 10.50 (1H, brs), 7.71 (2H, d, <i>J</i> = 8.8 Hz), 7.34 (2H, d, <i>J</i> = 8.8 Hz), 6.70 (1H, d, <i>J</i> = 8.0 Hz), 6.51 (1H, s), 6.19 (1H, d, <i>J</i> = 8.0 Hz), 5.84 (1H, s), 4.74 (2H, s), 4.42 (2H, brs), 1.43 (9H, s); LCMS: 92.7%, MS (ESI); <i>m/z</i> 422.0 [M+ H] <sup>+</sup> .                                                                                                        |
| 70 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26 (2H, d, <i>J</i> = 8.4 Hz), 7.02 (1H, d, <i>J</i> = 8.4 Hz), 6.95-7.05 (2H, m), 6.52 (1H, d, <i>J</i> = 2.0 Hz), 6.32 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.53 (2H, brs), 4.25 (2H, t, <i>J</i> = 4.2 Hz), 4.20 (2H, t, <i>J</i> = 4.8 Hz), 4.10 (4H, t, <i>J</i> = 7.6 Hz), 2.28-2.33 (2H, m); LCMS: 95.9%, MS (ESI); <i>m/z</i> 393.2[M+ H] <sup>+</sup> .                              |
| 71 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.75 (1H, brs), 7.59 (2H, d, <i>J</i> = 2.4 Hz), 7.33-7.42 (2H, m), 6.77-6.83 (1H, m), 6.44 (1H, s), 6.17-6.24 (1H, m), 5.25-5.30 (1H, m), 4.45 (2H, brs), 3.70-3.82 (1H, m), 3.50-3.62 (3H, m), 2.28-2.38 (1H, m), 2.16-2.22 (1H, m); LCMS: 95.9%, MS (ESI); <i>m/z</i> 413.3 [M+H] <sup>+</sup> .                                                                                         |
| 72 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 7.38 (1H, d, <i>J</i> = 2.4 Hz), 7.25 (2H, d, <i>J</i> = 8.8 Hz), 6.91-6.99 (2H, m), 6.80 (1H, d, <i>J</i> = 2.0 Hz), 4.67 (2H, brs), 4.48 (2H, t, <i>J</i> = 5.6 Hz), 4.32 (2H, t, <i>J</i> = 5.6 Hz), 3.51-3.63 (4H, m), 1.85-1.94 (4H, m); LCMS: 97.6%, MS (ESI); <i>m/z</i> 408.3 [M+ H] <sup>+</sup> .                                                                                       |
| 73 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.20 (1H, brs), 7.59 (1H, s), 7.30-7.40 (2H, m), 6.68-6.89 (1H, m), 6.10-6.48 (3H, m), 4.43 (2H, brs), 3.43-3.52 (2H, m), 2.99 (2H, t, <i>J</i> = 7.2 Hz); LCMS: 99.5%, MS (ESI); <i>m/z</i> 321.1[M+ H] <sup>+</sup> .                                                                                                                                                                      |
| 74 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.13-10.34 (1H, m), 7.49-7.61 (2H, m), 7.38 (1H, d, <i>J</i> = 8.4 Hz), 6.83-7.10 (1H, m), 6.80 (1H, dd, <i>J</i> = 8.4, 2.8 Hz), 6.31-6.43 (1H, m), 6.10-6.24 (1H, m), 5.08-5.25 (1H, m), 4.25-4.55 (2H, m), 1.40 (3H, d, <i>J</i> = 6.8 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 321.2[M+ H] <sup>+</sup> .                                                                                   |
| 75 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.27 (1H, brs.), 7.28 (2H, d, <i>J</i> = 8.4 Hz), 7.05 (2H, d, <i>J</i> = 9.2 Hz), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.45 (1H, s), 6.27 (1H, d, <i>J</i> = 7.6 Hz), 5.77 (2H, brs.), 5.06 (1H, brs), 4.13 (2H, t, <i>J</i> = 5.6 Hz), 3.38 (2H, t, <i>J</i> = 5.6 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 353.3 [M+H] <sup>+</sup> .                                                           |
| 76 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.58 (1H, brs), 7.76 (2H, d, <i>J</i> = 8.8 Hz), 7.34 (2H, d, <i>J</i> = 8.4 Hz), 7.09 (1H, d, <i>J</i> = 8.4 Hz), 6.61 (1H, s), 6.54 (1H, d, <i>J</i> = 8.4 Hz), 3.78-3.95 (5H, m), 3.68 (3H, s), 2.27-2.40 (1H, m), 2.11-2.25 (1H, m); LCMS: 93.9%, MS (ESI); <i>m/z</i> 420.0[M+ H] <sup>+</sup> .                                                                                      |
| 77 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.5 (2H, brs), 9.23 (1H, brs), 7.29-7.49 (2H, m), 7.31 (2H, d, <i>J</i> = 8.8 Hz), 7.18-7.21 (3H, m), 7.08 (2H, d, <i>J</i> = 9.6 Hz), 6.50-6.52 (2H, m), 5.20-5.21 (1H, m), 4.60 (2H, d, <i>J</i> = 6.0 Hz), 3.67-3.72 (1H, m), 3.30-3.42 (3H, overlap with H <sub>2</sub> O peak), 2.33-2.38 (1H, m), 1.90-2.23 (1H, m); LCMS: 98.1%, MS (ESI); <i>m/z</i> 487.3[M+ H] <sup>+</sup> . |

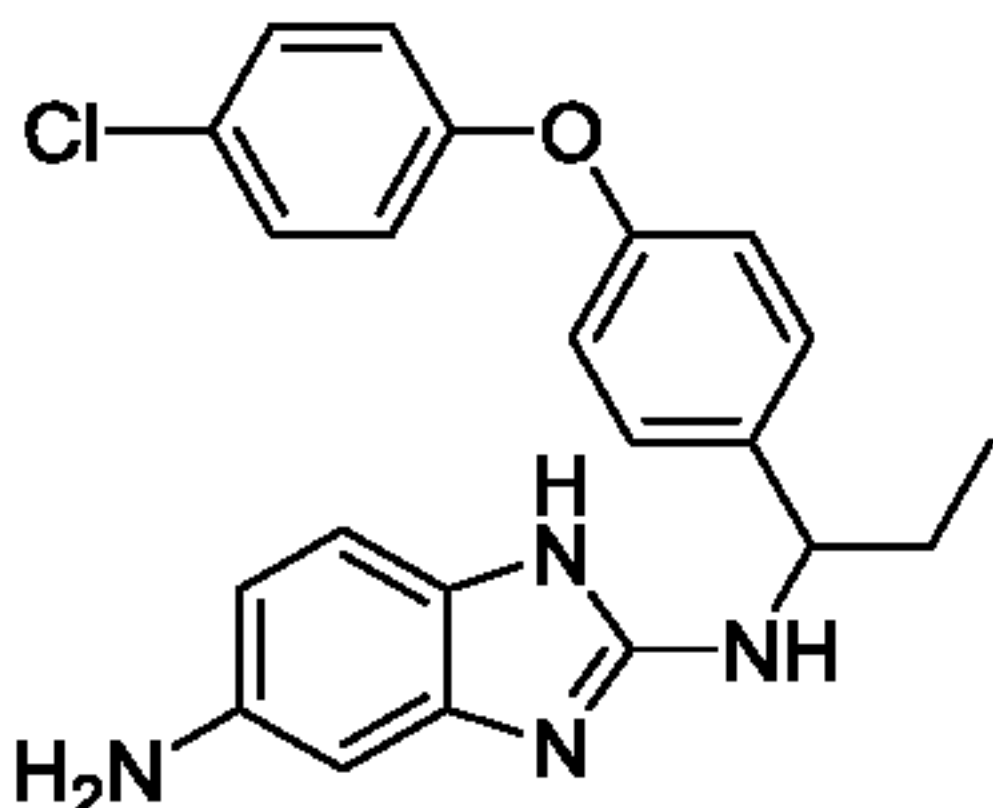
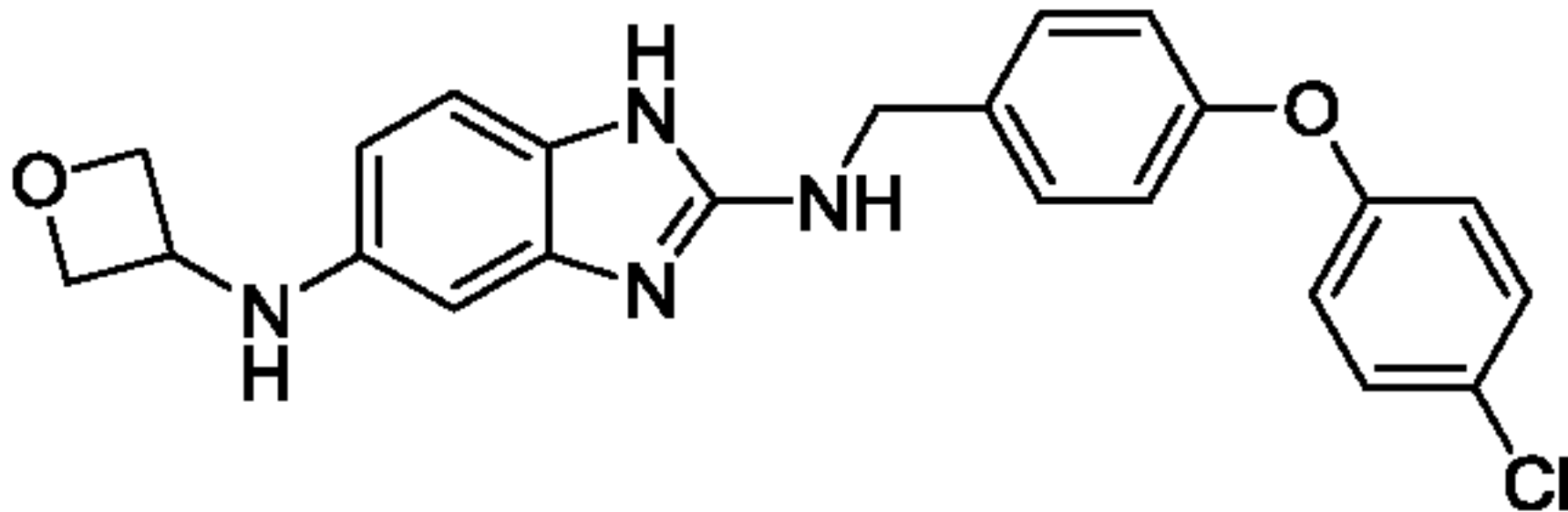
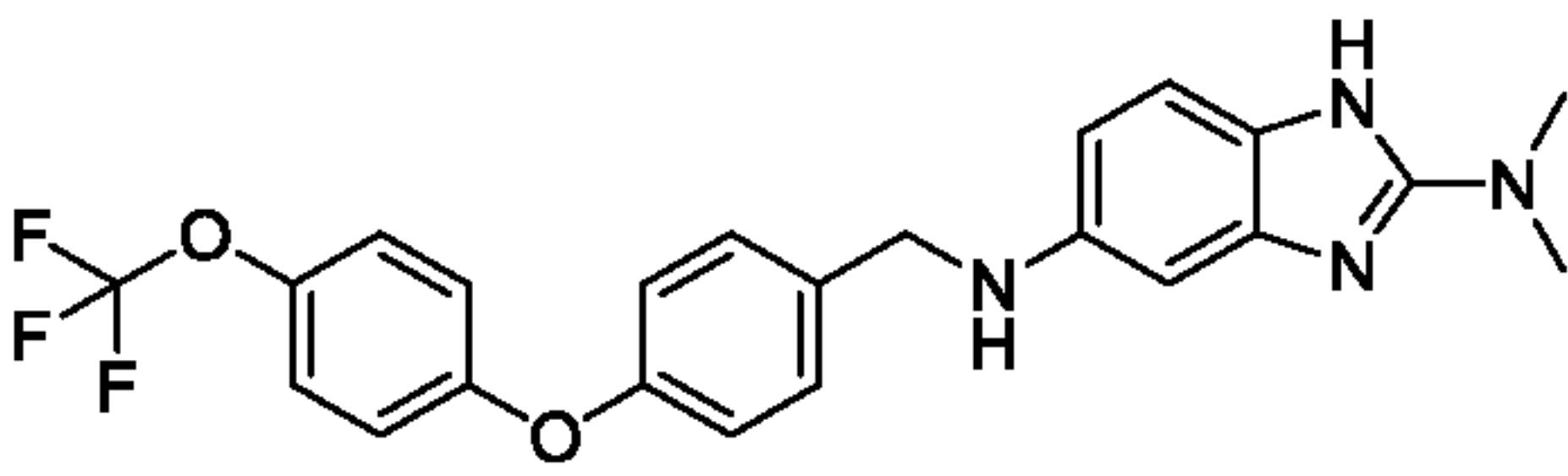
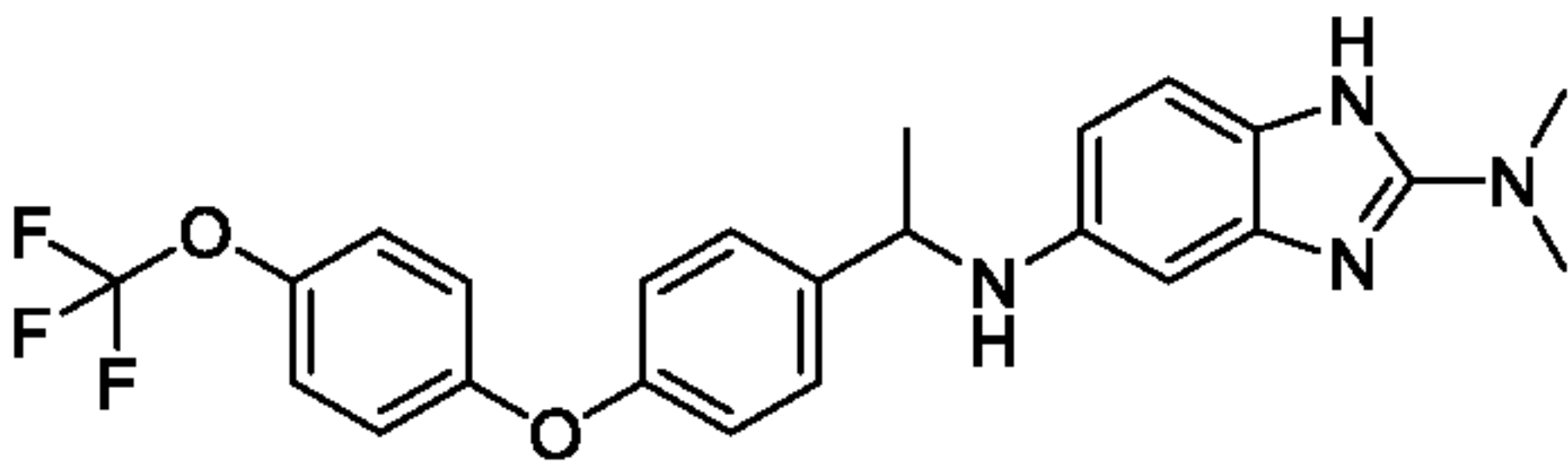
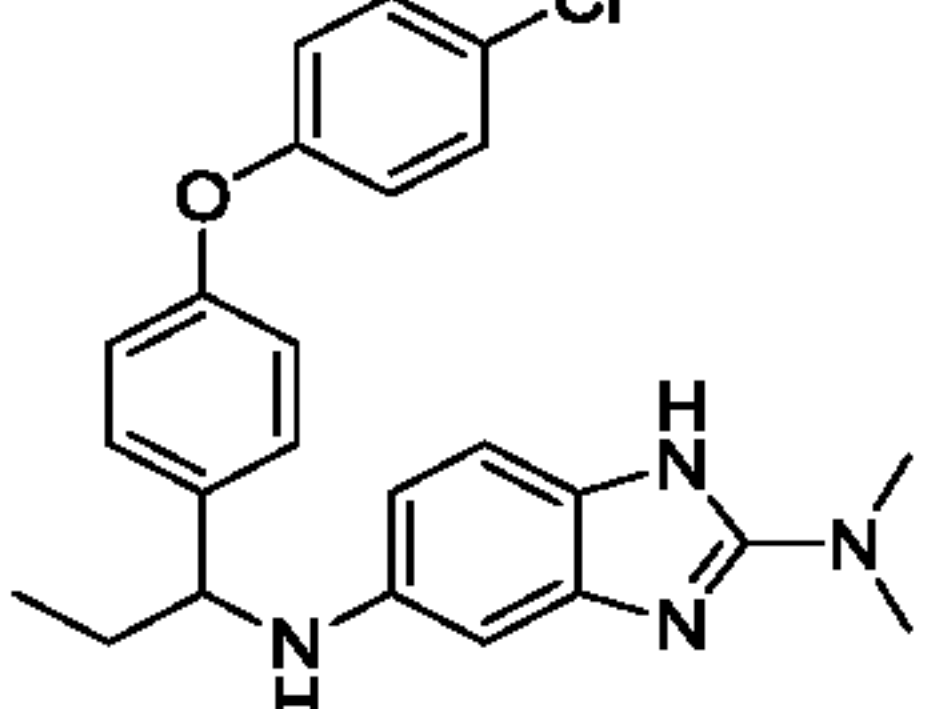
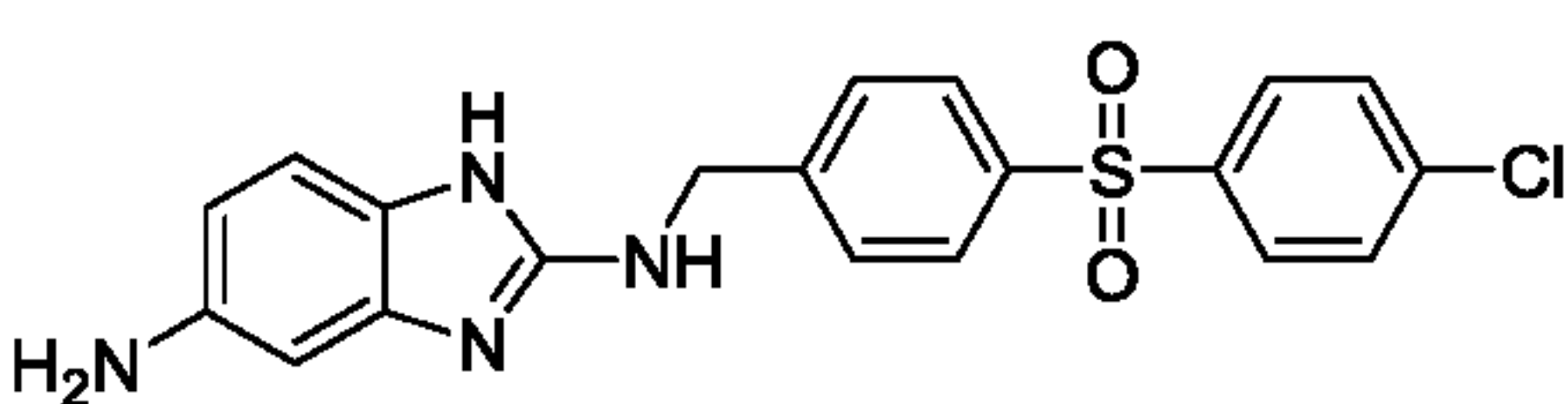
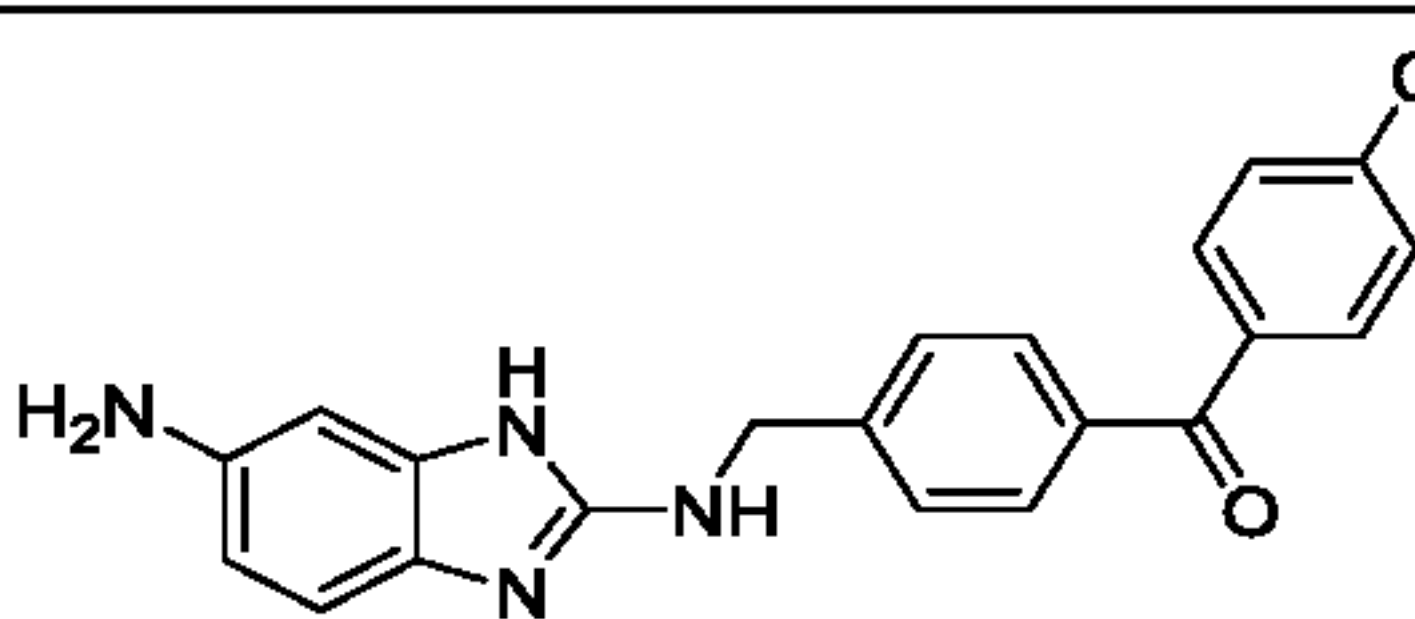
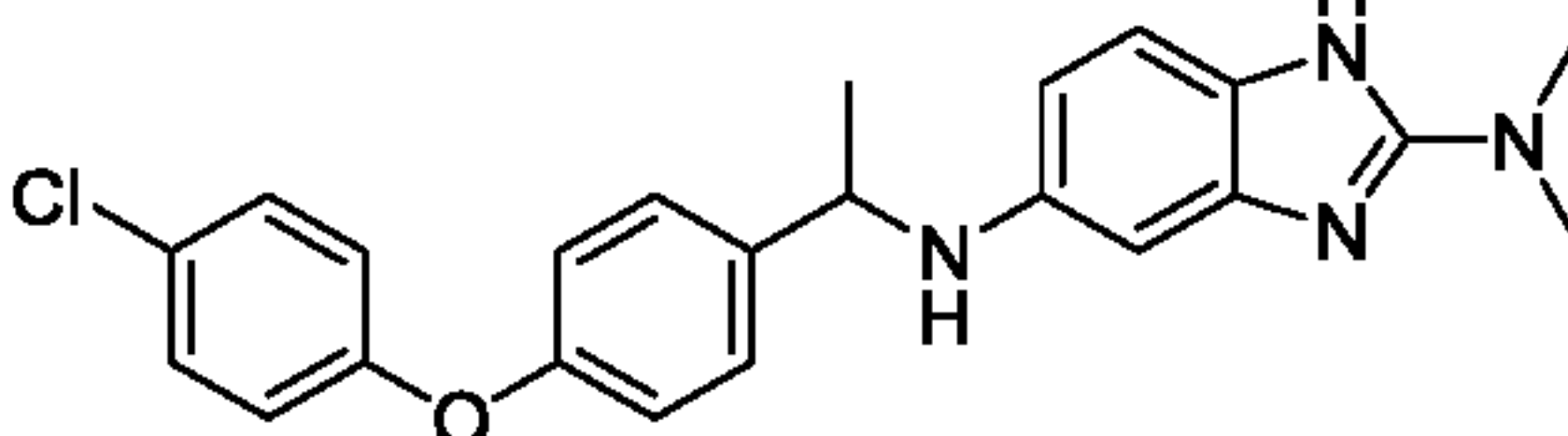
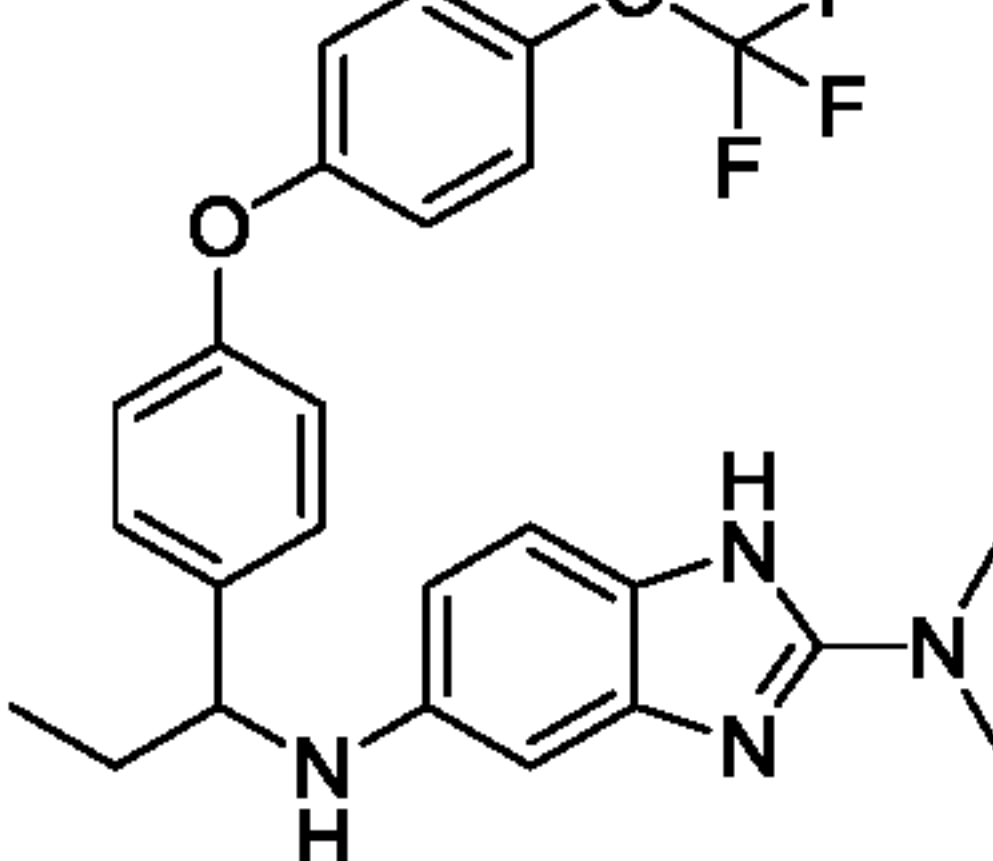
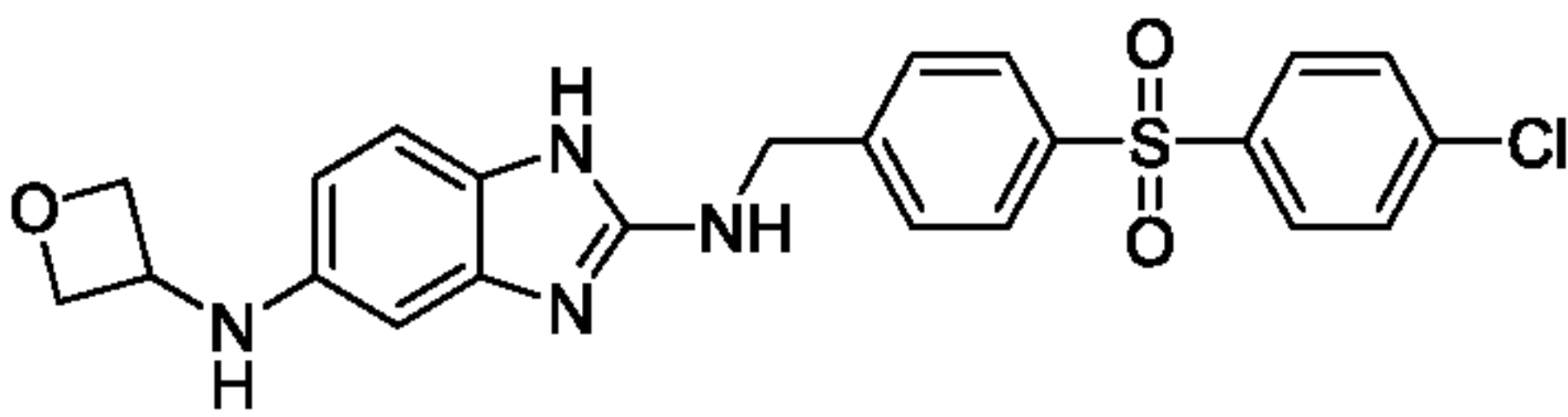
|    |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 78 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.56 (1H, d, <i>J</i> = 4.4 Hz), 7.98 (1H, d, <i>J</i> = 4.0 Hz), 7.30 (1H, d, <i>J</i> = 8.4 Hz), 7.24 (2H, d, <i>J</i> = 8.4 Hz), 6.85-6.95 (2H, m), 6.79 (1H, d, <i>J</i> = 2.0 Hz), 6.55-6.60 (1H, m), 5.17 (2H, brs), 4.68 (2H, t, <i>J</i> = 5.2 Hz), 4.30 (2H, t, <i>J</i> = 5.2 Hz); LCMS: 95.6%, MS (ESI); <i>m/z</i> 422.2 [M+H] <sup>+</sup> .                              |
| 79 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.29 (2H, d, <i>J</i> = 8.0 Hz), 6.88 (1H, brs), 6.77 (1H, d, <i>J</i> = 8.4 Hz), 6.40 (1H, d, <i>J</i> = 1.6 Hz), 6.17 (1H, dd, <i>J</i> = 8.4, 2.4, Hz), 4.45 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 95.7 %, MS (ESI); <i>m/z</i> 323.1[M+ H] <sup>+</sup> .                                                                                             |
| 80 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.72 (1H, t, <i>J</i> = 6.0 Hz), 7.49 (2H, d, <i>J</i> = 8.4 Hz), 7.35-7.45 (4H, m), 7.10-7.20 (2H, m), 6.95-7.09 (4H, m), 4.65 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 331.2[M+ H] <sup>+</sup> .                                                                                                                                                                |
| 81 |   | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35 (1H, brs), 8.09-8.18 (1H, m), 7.90-7.99 (1H, m), 7.82 (1H, d, <i>J</i> = 8.0 Hz), 7.49-7.59 (3H, m), 7.46 (1H, t, <i>J</i> = 8.0 Hz), 6.66-6.91 (2H, m), 6.41 (1H, s), 6.10-6.20 (1H, m), 4.91 (2H, d, <i>J</i> = 4.4 Hz), 4.43 (2H, brs); LCMS: 96.0 %, MS (ESI); <i>m/z</i> 289.1[M+ H] <sup>+</sup> .                                                                         |
| 82 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.60 (1H, d, <i>J</i> = 4.8 Hz), 7.99 (1H, d, <i>J</i> = 4.4 Hz), 7.38 (1H, d, <i>J</i> = 8.4 Hz), 7.15-7.28 (2H, m), 6.80-6.93 (2H, m), 6.70-6.80 (1H, m), 6.63-6.75 (1H, m), 4.91 (2H, brs), 4.78 (2H, t, <i>J</i> = 5.2 Hz), 4.29 (2H, t, <i>J</i> = 5.2 Hz); LCMS: 99.1%, MS (ESI); <i>m/z</i> 422.2 [M+H] <sup>+</sup> .                                                          |
| 83 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.54 (1H, d, <i>J</i> = 2.4 Hz), 7.27 (2H, d, <i>J</i> = 8.4 Hz), 6.96-7.04 (3H, m), 4.78 (2H, brs), 4.38 (2H, t, <i>J</i> = 5.2 Hz), 4.26-4.34 (2H, m), 3.46-3.58 (4H, m), 1.85-1.95 (4H, m); LCMS: 97.7%, MS (ESI); <i>m/z</i> 408.0[M+ H] <sup>+</sup> .                                                                                                                        |
| 84 |  | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.65 (1H, d, <i>J</i> = 8.4 Hz), 7.14 (2H, d, <i>J</i> = 8.8 Hz), 6.75-6.90 (2H, m), 6.39 (1H, d, <i>J</i> = 8.4 Hz), 6.21 (1H, s), 4.55-4.65 (2H, m), 4.29 (1H, t, <i>J</i> = 4.2 Hz), 3.95-4.05 (4H, m), 3.85-3.95 (4H, m), 2.35-2.45 (2H, m), 2.05-2.20 (4H, m); LCMS: 92%, MS (ESI); <i>m/z</i> 447.1[M+ H] <sup>+</sup> .                                                                   |
| 85 |  | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.12 (1H, d, <i>J</i> = 8.4 Hz), 7.08 (1H, d, <i>J</i> = 8.4 Hz), 6.81 (1H, d, <i>J</i> = 2.4 Hz), 6.75 (2H, d, <i>J</i> = 9.2 Hz), 6.31 (1H, dd, <i>J</i> = 8.8, 2.0 Hz), 4.55-4.65 (2H, m), 4.25-4.35 (2H, m), 3.90-4.00 (4H, m), 3.80-3.90 (4H, m), 2.35-2.45 (2H, m), 2.05-2.15 (4H, m); H NMR and NOE confirmed the structure; LCMS: 96.3%, MS (ESI); <i>m/z</i> 447.3[M+ H] <sup>+</sup> . |
| 86 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40-7.45 (4H, m), 6.95-7.05 (4H, m), 6.90-6.98 (1H, brs), 6.81 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, s), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.44 (2H, d, <i>J</i> = 4.8 Hz); LCMS: 99.5 %, MS (ESI); <i>m/z</i> 365.1[M+ H] <sup>+</sup> .                                                                                                                                  |
| 87 |  | pale yellow powder; hygroscopic; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.60 (2H, brs), 9.24-9.38 (1H, m), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.39 (2H, t, <i>J</i> = 7.6 Hz), 7.02 (2H, t, <i>J</i> = 8.4 Hz), 6.97-7.08 (4H, m), 6.74 (1H, s), 6.66 (1H, d, <i>J</i> = 8.4 Hz), 4.60 (2H, d, <i>J</i> = 6.4 Hz), 3.83-4.00 (2H, m), 3.71-3.82 (2H, m), 3.42-3.53 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 387.0[M+ H] <sup>+</sup> .      |

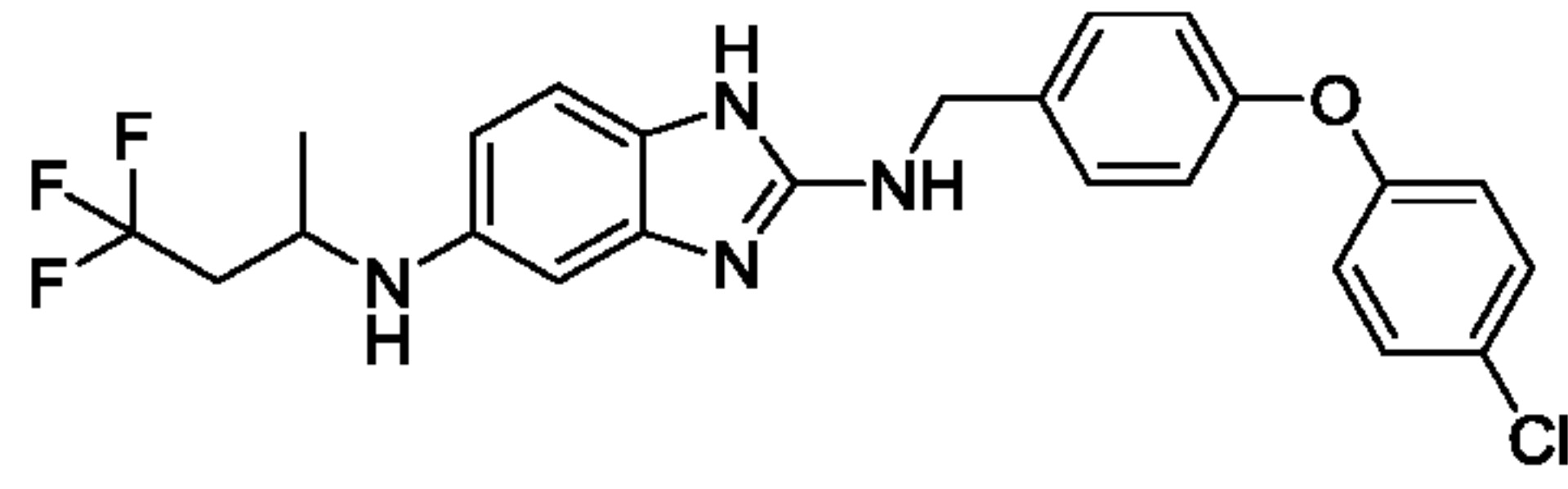
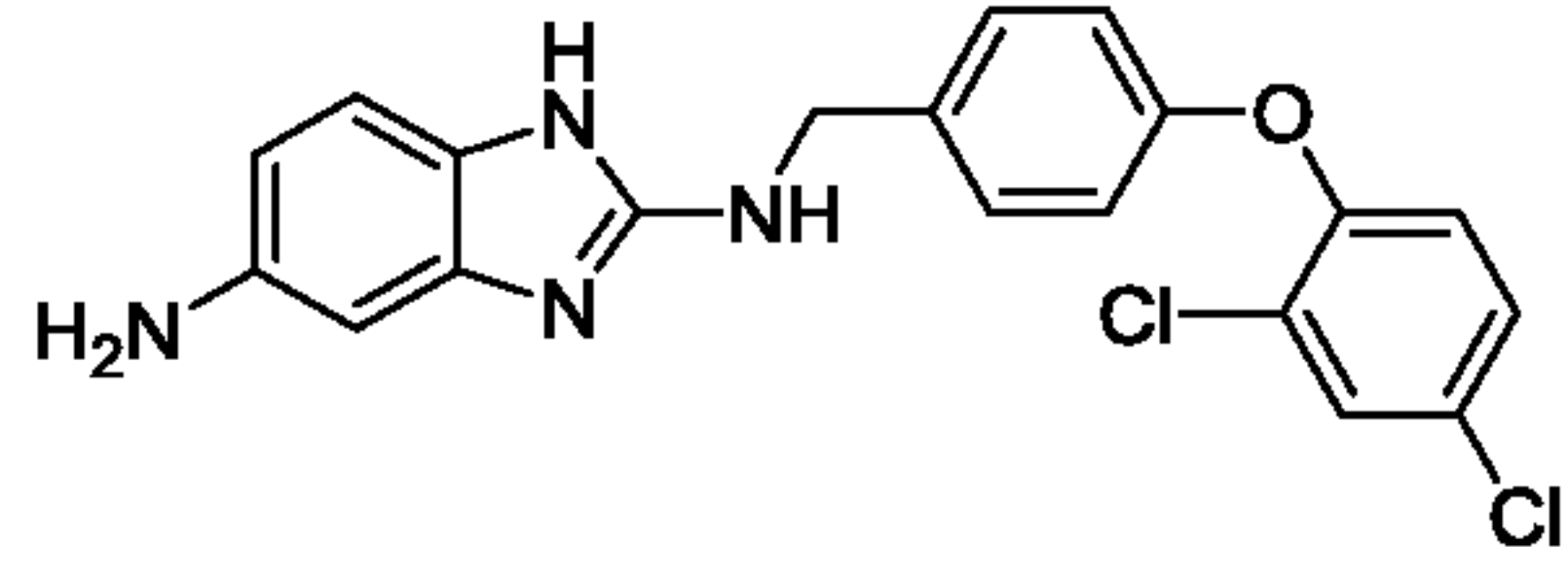
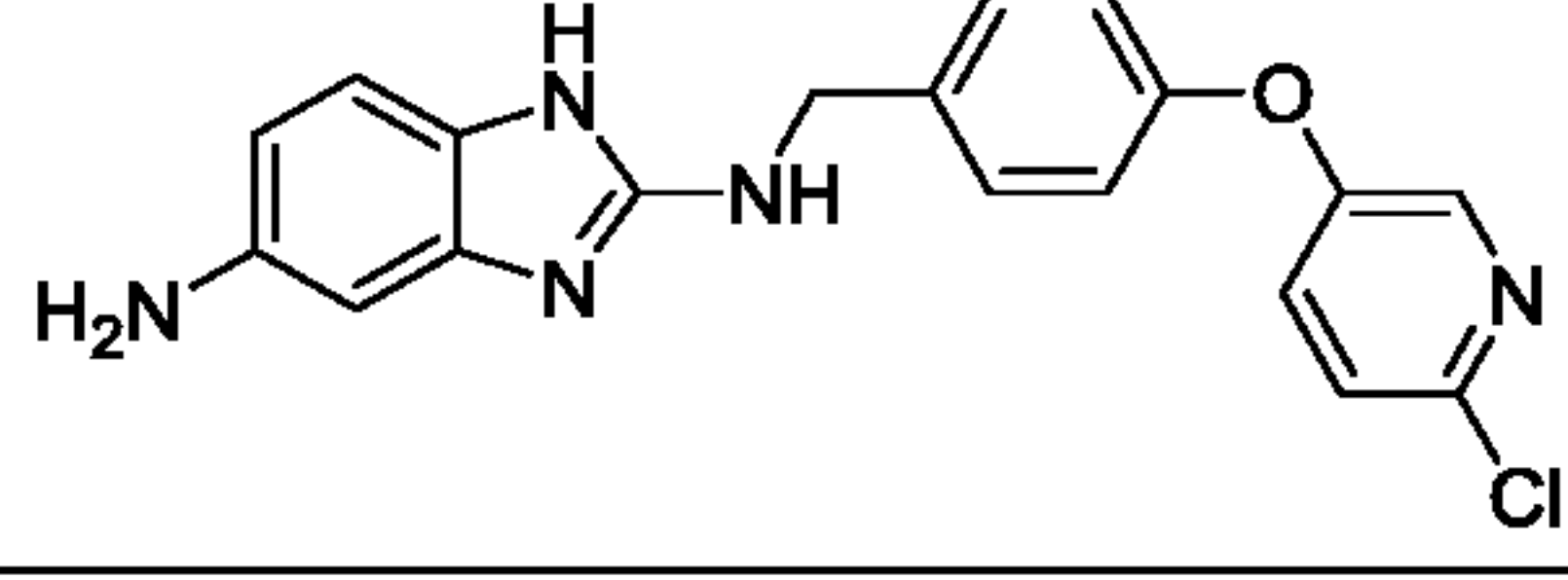
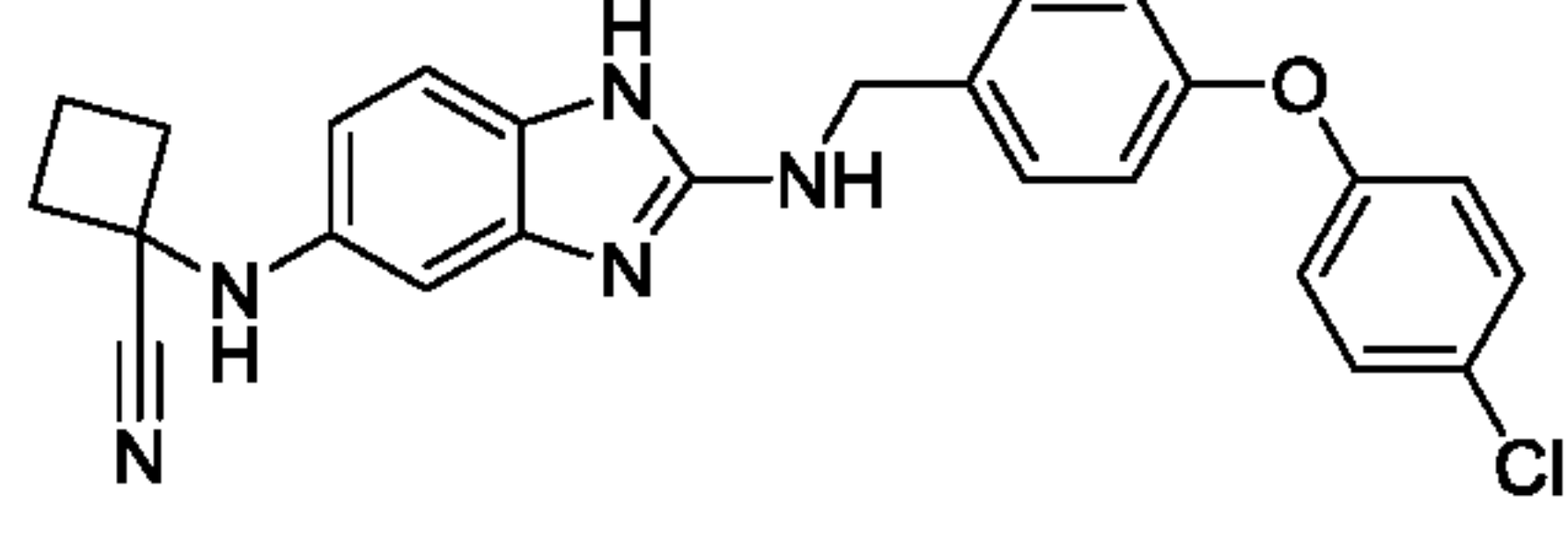
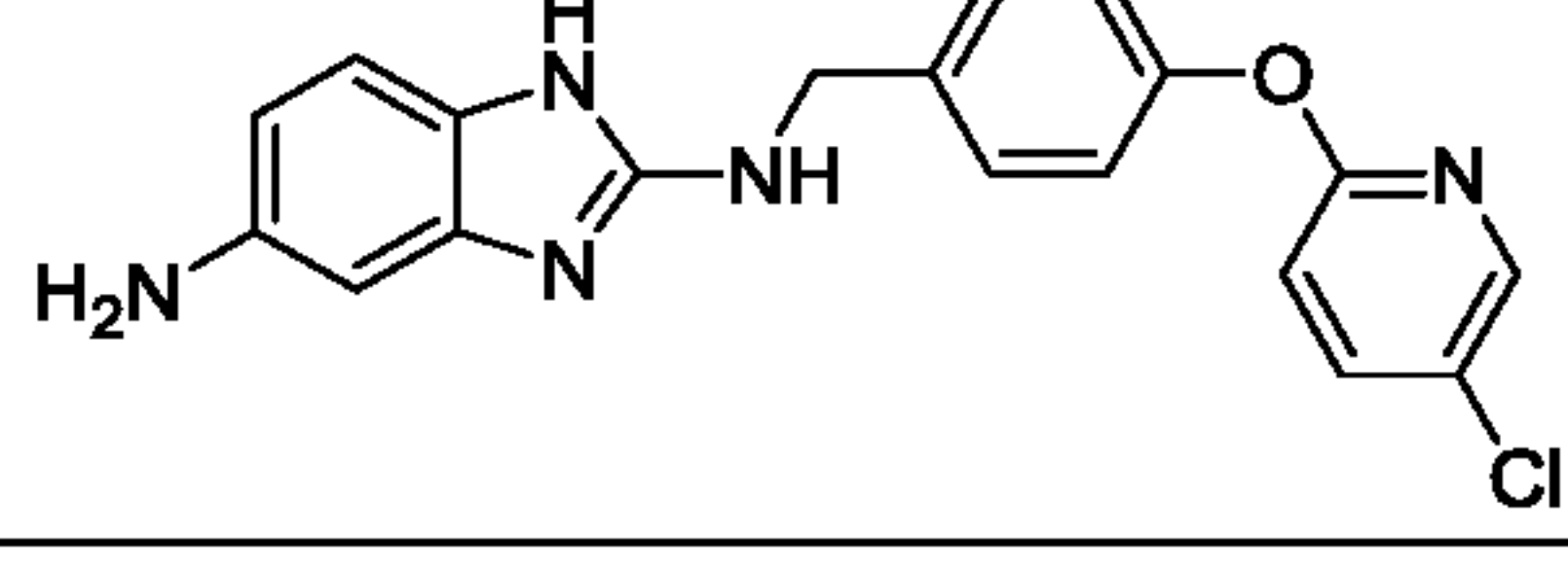
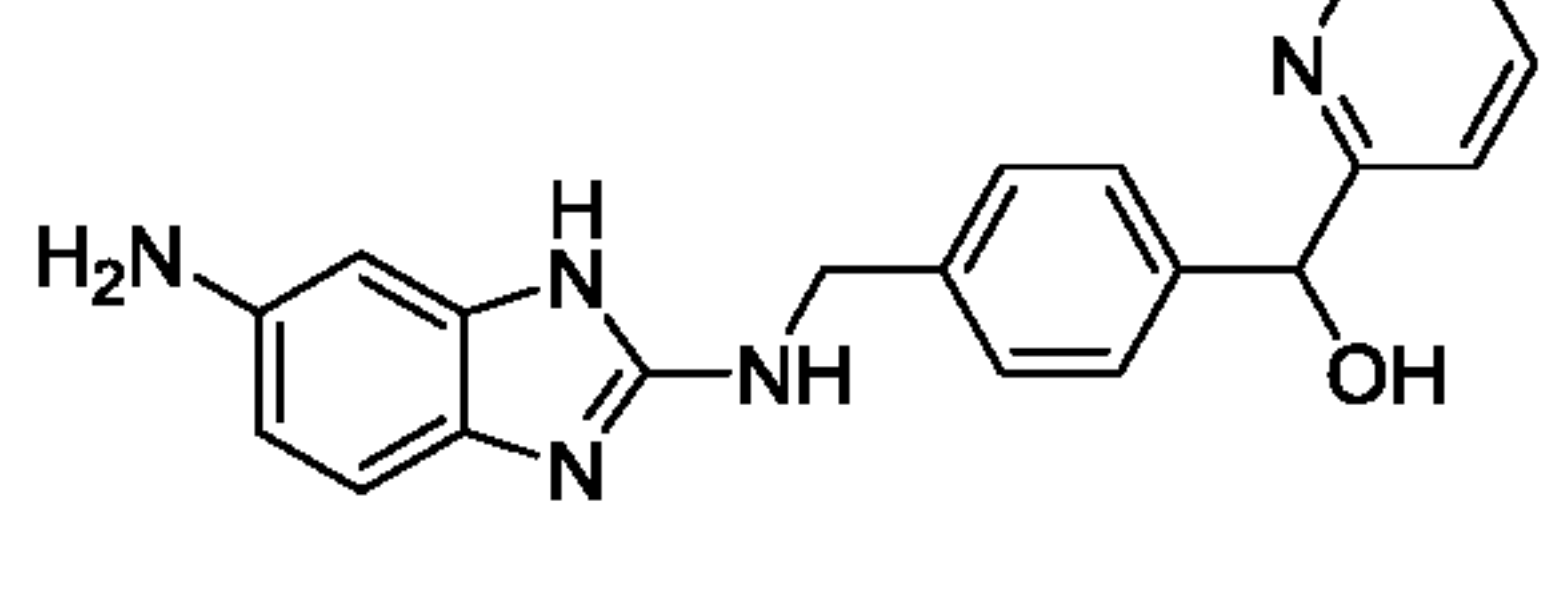
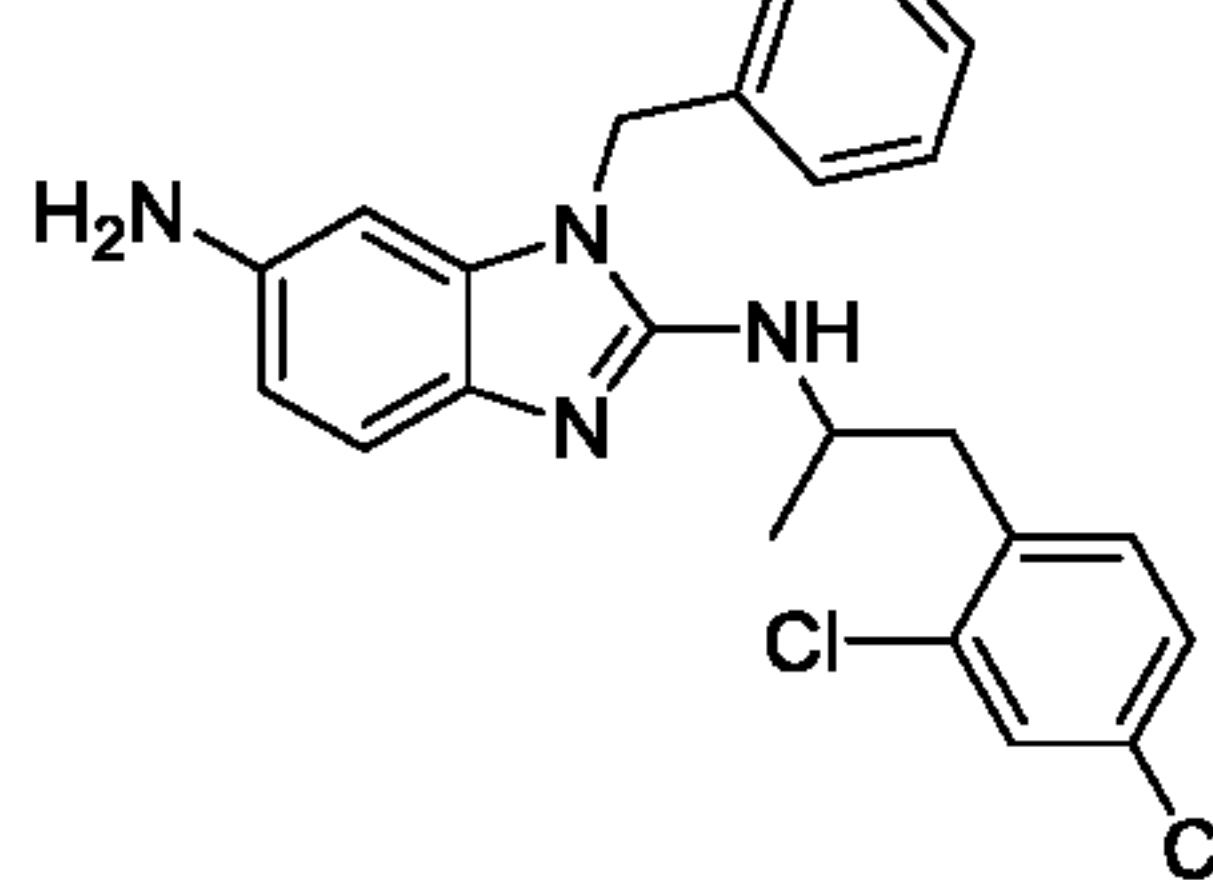
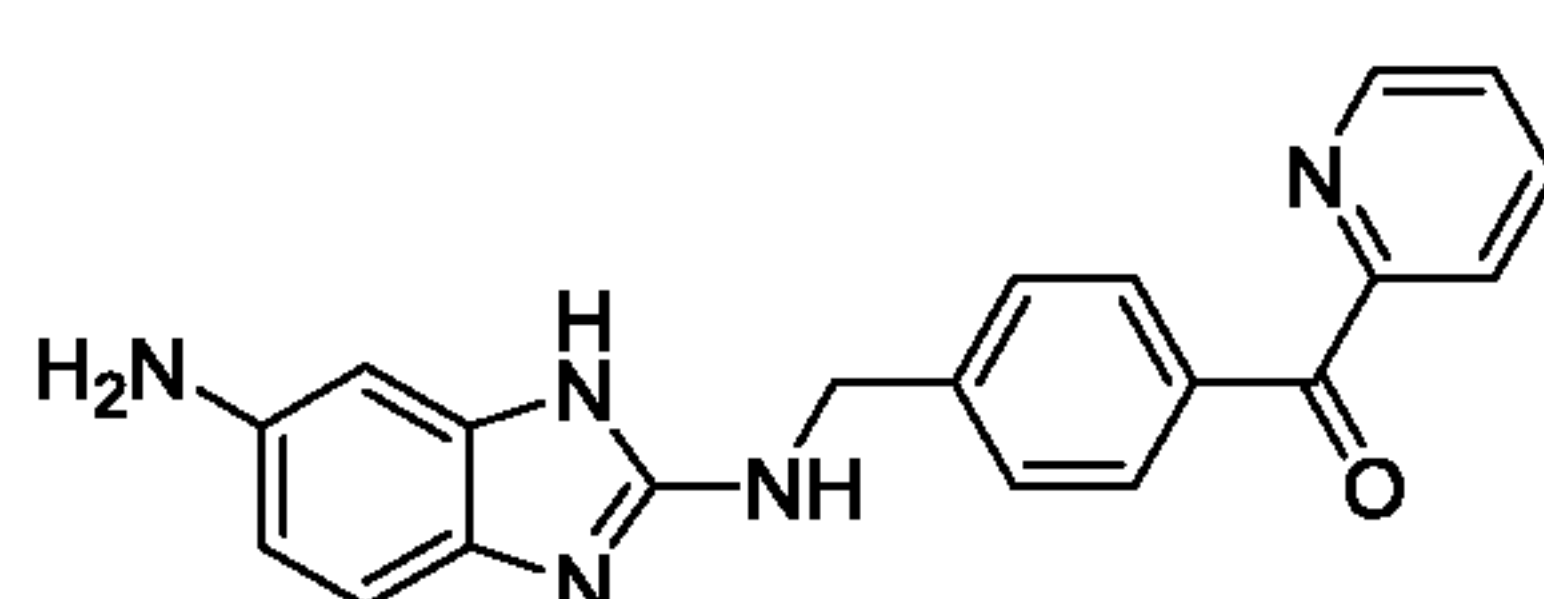
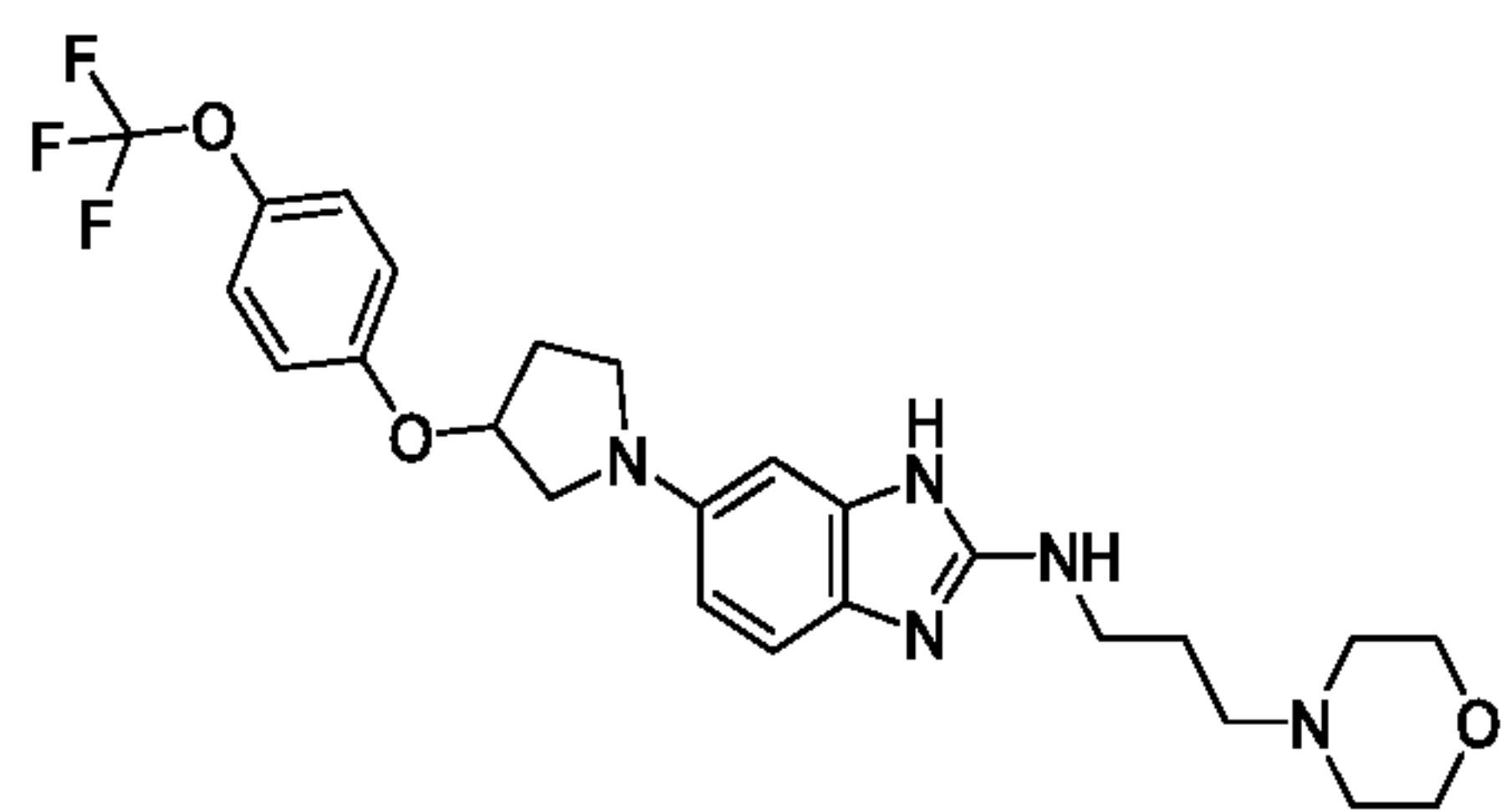
|    |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 88 |    | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.42 (2H, d, <i>J</i> = 8.8 Hz), 7.37 (2H, d, <i>J</i> = 8.0 Hz), 7.00-7.10 (4H, m), 6.90-7.00 (1H, brs), 6.82 (1H, d, <i>J</i> = 8.0 Hz), 6.44 (1H, d, <i>J</i> = 2.0 Hz), 6.20-6.25 (1H, m), 4.45 (2H, d, <i>J</i> = 5.2 Hz); LCMS: 99.5 %, MS (ESI); <i>m/z</i> 415.0[M+ H] <sup>+</sup> .                                                                                      |
| 89 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26 (2H, d, <i>J</i> = 8.8 Hz), 7.11 (1H, s), 6.90-7.00 (2H, m), 6.88 (1H, s), 4.61 (2H, t, <i>J</i> = 4.8 Hz), 4.35 (2H, t, <i>J</i> = 4.8 Hz), 3.74-3.76 (4H, m), 1.96-1.99 (4H, m); LCMS: 100 %, MS (ESI); <i>m/z</i> 441.2[M+ H] <sup>+</sup> .                                                                                                                                   |
| 90 |    | grey powder; mp > 200°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.58-7.65 (4H, m), 7.41-7.48 (4H, m), 7.34 (1H, t, <i>J</i> = 7.6 Hz), 6.75-6.85 (2H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.18 (1H, d, <i>J</i> = 6.8 Hz), 4.30-4.65 (4H, m); LCMS: 99.1%, MS (ESI); <i>m/z</i> 315.1[M+H] <sup>+</sup>                                                                                                                                    |
| 91 |  | white powder; mp > 107.8°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, d, <i>J</i> = 7.6 Hz), 7.94 (1H, d, <i>J</i> = 2.4 Hz), 7.83 (1H, d, <i>J</i> = 8.0 Hz), 7.50-7.61 (3H, m), 7.44-7.48 (1H, m), 6.80 (1H, d, <i>J</i> = 8.0 Hz), 6.79 (1H, brs), 6.43 (1H, d, <i>J</i> = 2.0 Hz), 6.20 (1H, d, <i>J</i> = 6.8 Hz), 4.92 (2H, d, <i>J</i> = 5.6 Hz), 4.41 (2H, brs); LCMS: 99.3%, MS (ESI); <i>m/z</i> 289.1[M+H] <sup>+</sup> . |
| 92 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.56 (1H, brs), 7.36-7.42 (6H, m), 7.24-7.26 (2H, m), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.29 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.50 (2H, s); LCMS: 95.5 %, MS (ESI); <i>m/z</i> 381.1[M+ H] <sup>+</sup> .                                                                                                                                       |
| 93 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26 (2H, d, <i>J</i> = 8.8 Hz), 6.92-7.01 (2H, m), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.69 (1H, d, <i>J</i> = 2.0 Hz), 6.49 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.12 (2H, brs), 4.29 (2H, t, <i>J</i> = 5.2 Hz), 4.17-4.25 (2H, m), 4.04 (1H, brs), 1.17 (9H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 409.1[M+ H] <sup>+</sup> .                                                         |
| 94 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37 (2H, d, <i>J</i> = 8.8 Hz), 7.16 - 7.24 (2H, m), 6.96 - 7.05 (2H, m), 6.94 (2H, d, <i>J</i> = 8.4 Hz), 6.70-6.79 (2H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.41 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 99.2%, MS (ESI); <i>m/z</i> 349.2[M+H] <sup>+</sup> .                                                                              |
| 95 |  | mp > 137.5 °C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.40 (1H, m), 7.35-7.45 (4H, m), 7.12 (1H, t, <i>J</i> = 7.6 Hz), 6.95-7.05 (4H, m), 6.70-6.90 (2H, m), 6.39 (1H, s), 6.20-6.30 (1H, m), 4.40-4.70 (3H, m), 3.45-3.50 (1H, m), 1.10 (6H, d, <i>J</i> = 6.4 Hz); LCMS: 99.4%, MS (ESI); <i>m/z</i> 373.2[M+ H] <sup>+</sup> .                                                                                                   |
| 96 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.45 (1H, m), 7.35-7.45 (4H, m), 7.12 (1H, t, <i>J</i> = 7.2 Hz), 6.95-7.05 (4H, m), 6.60-6.90 (2H, m), 6.32 (1H, d, <i>J</i> = 2.0 Hz), 6.15-6.25 (1H, m), 5.16 (1H, brs), 4.42 (2H, d, <i>J</i> = 6.0 Hz), 3.65-3.80 (1H, m), 2.25-2.35 (2H, m), 1.65-1.85 (4H, m); LCMS: 98.8%, MS (ESI); <i>m/z</i> 385.3[M+ H] <sup>+</sup> .                                              |

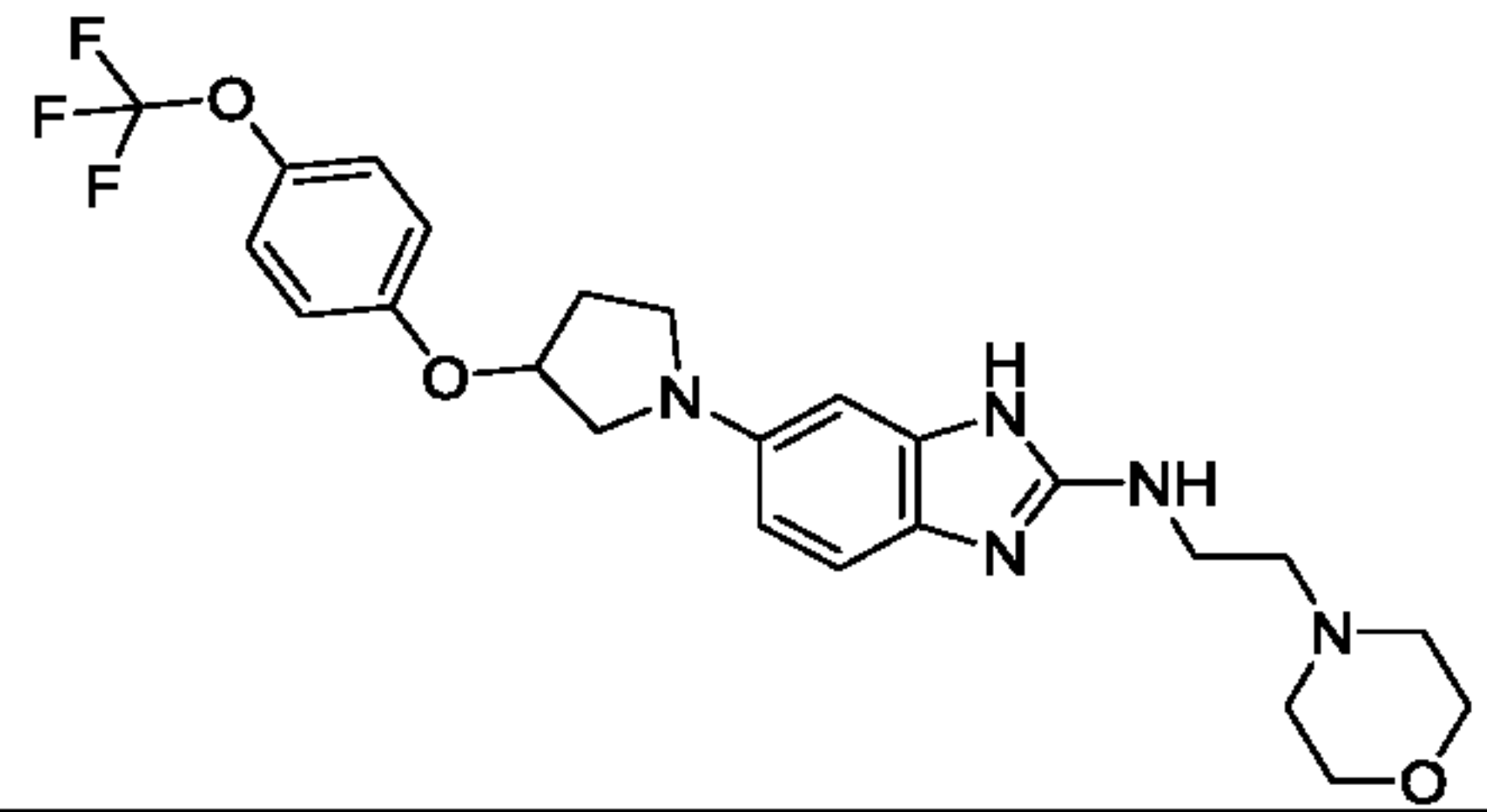
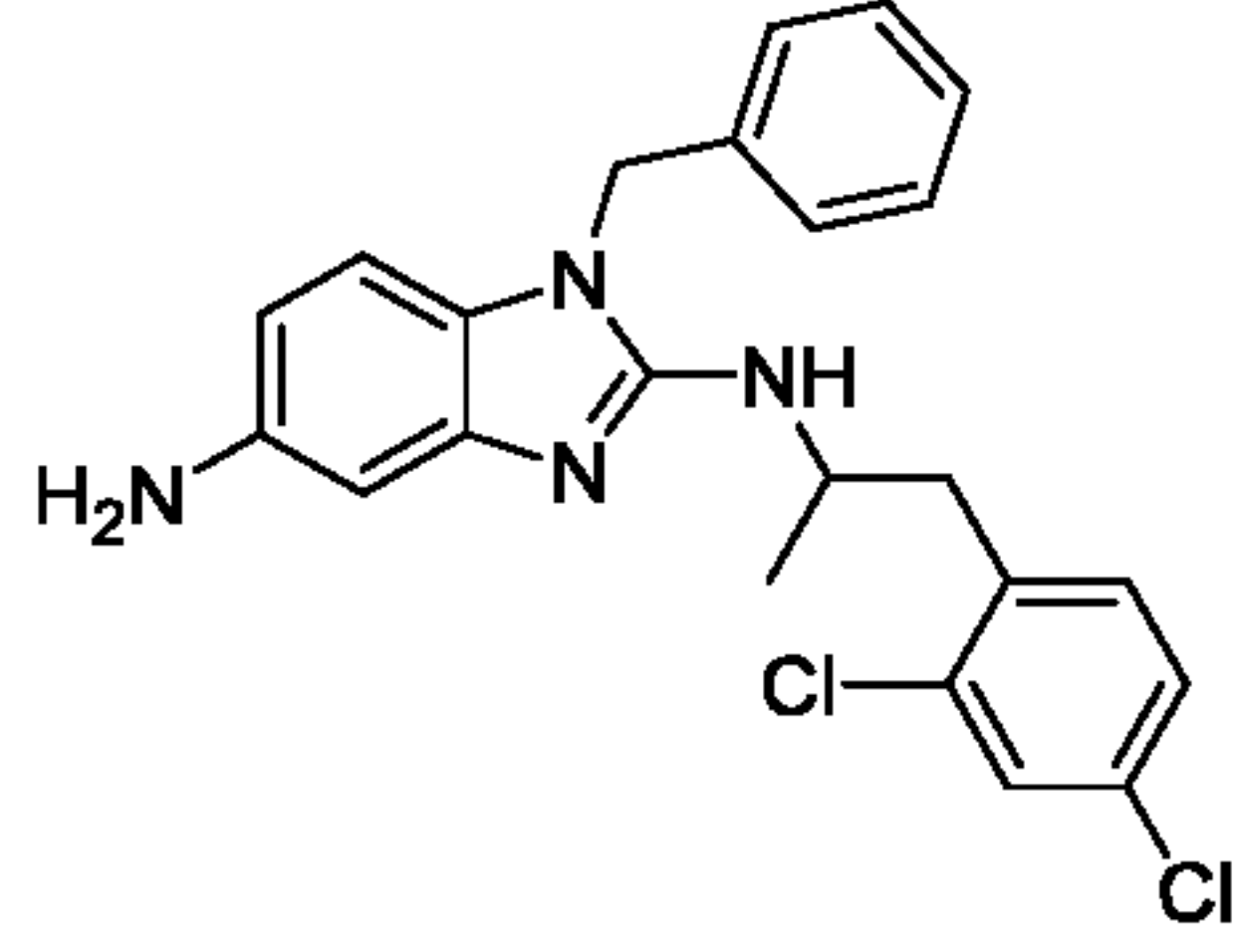
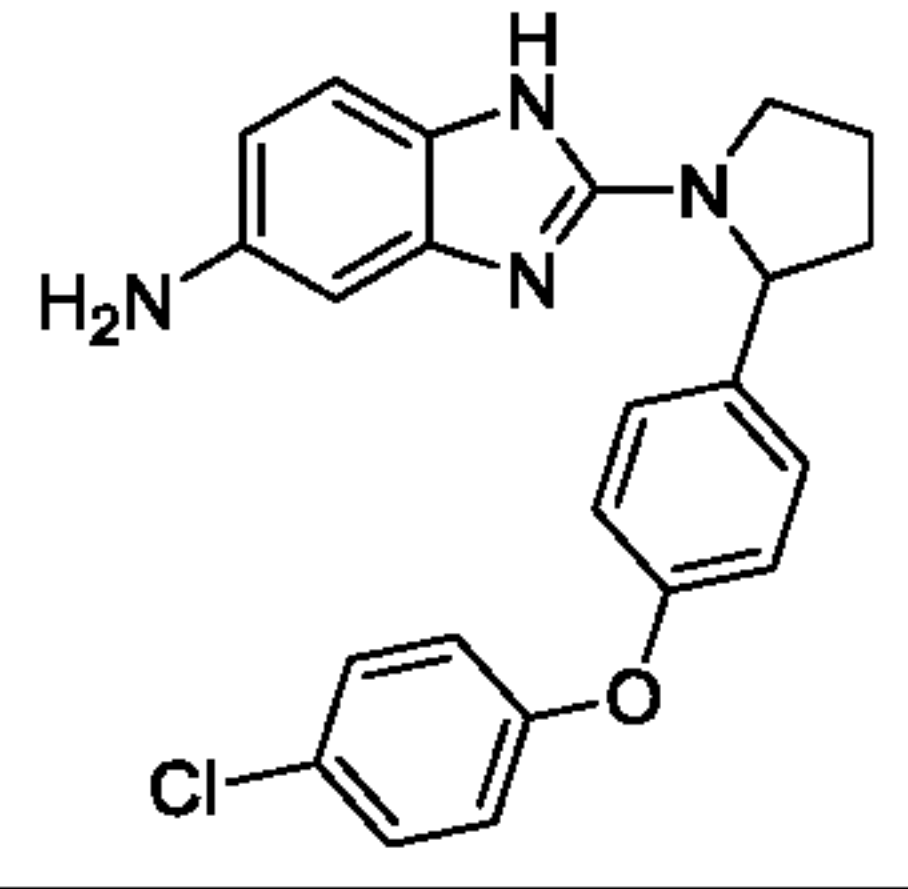
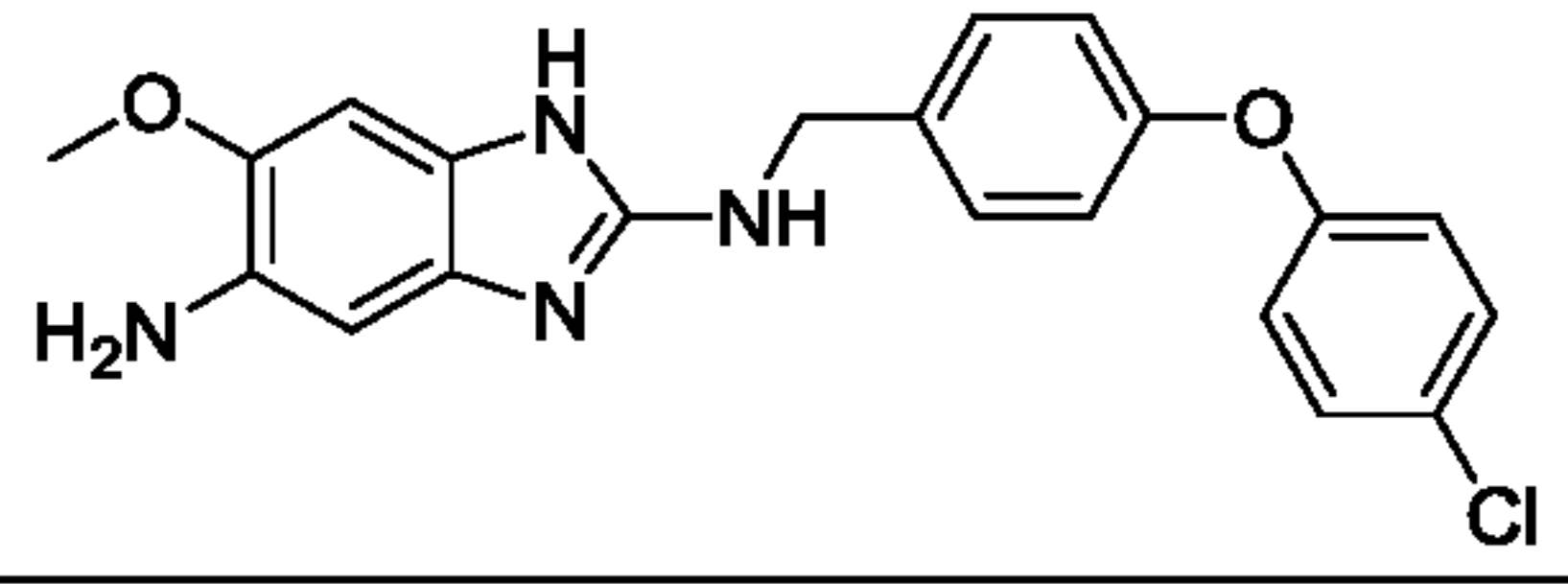
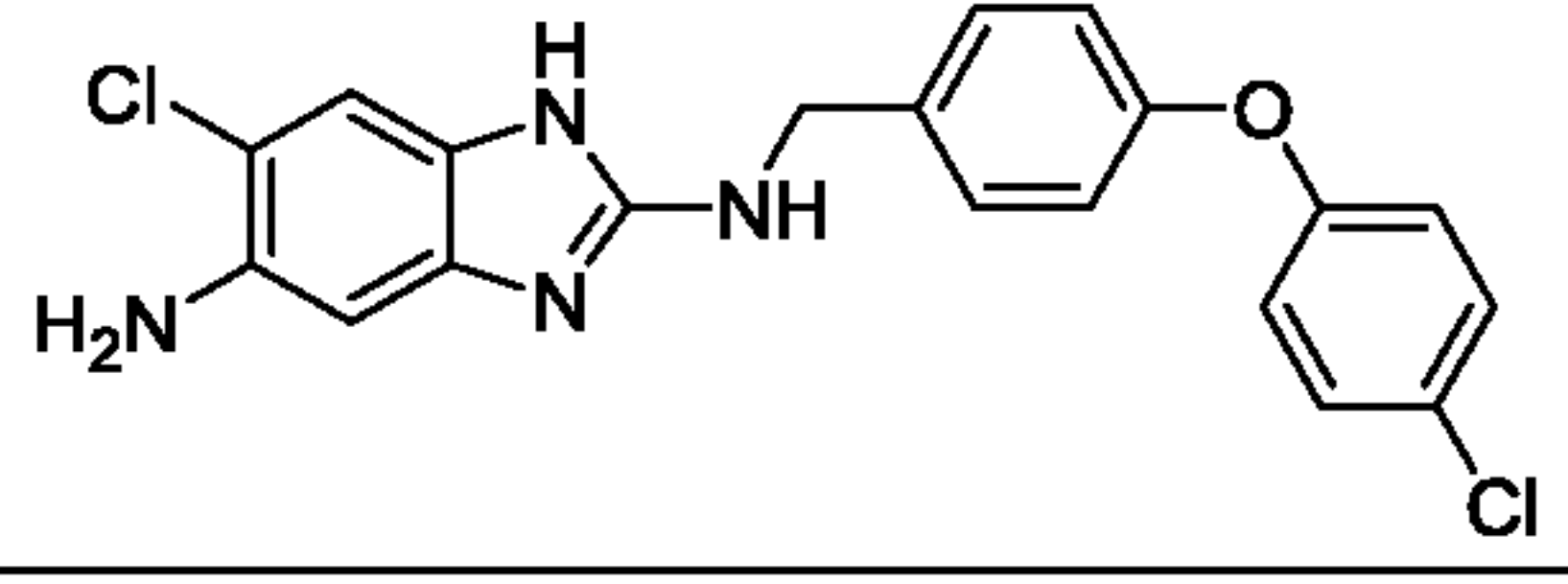
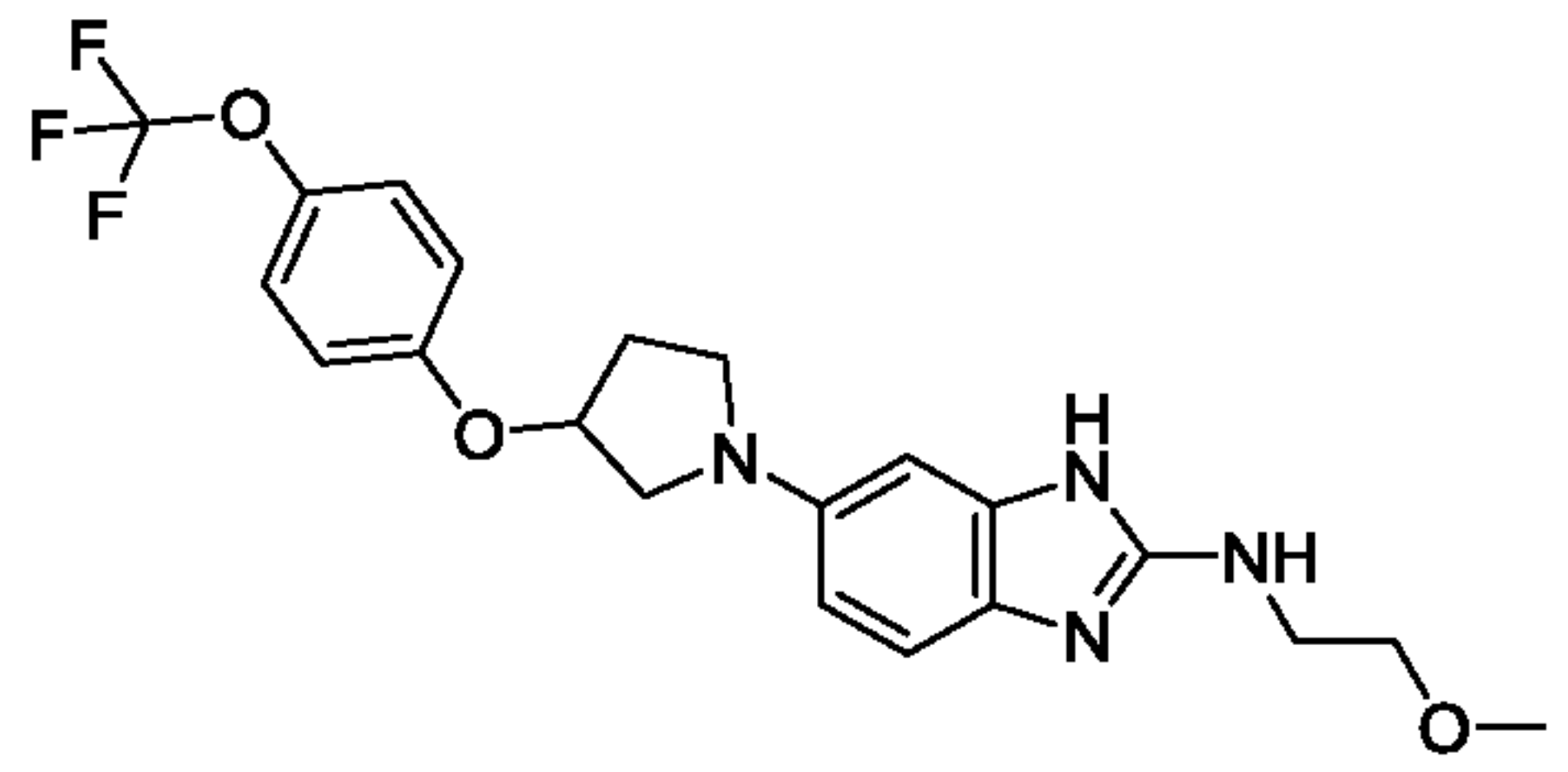
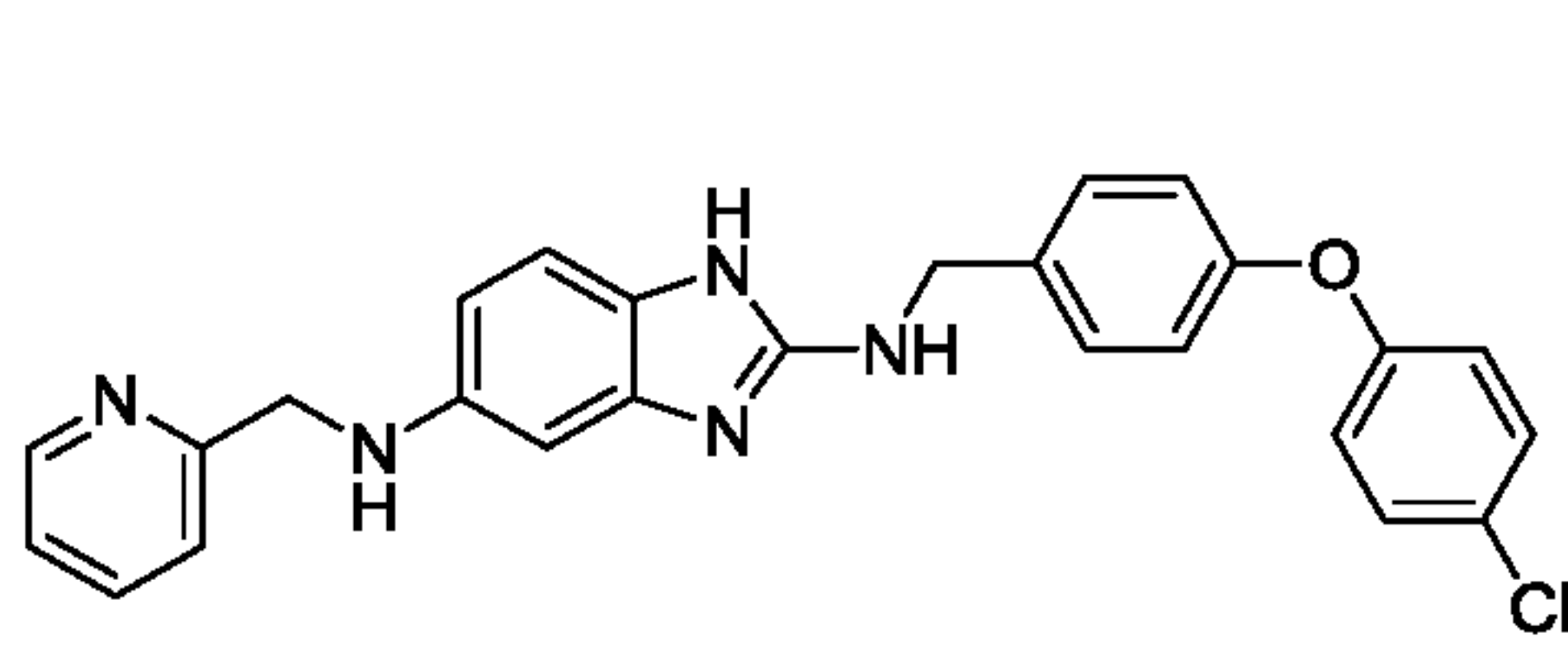
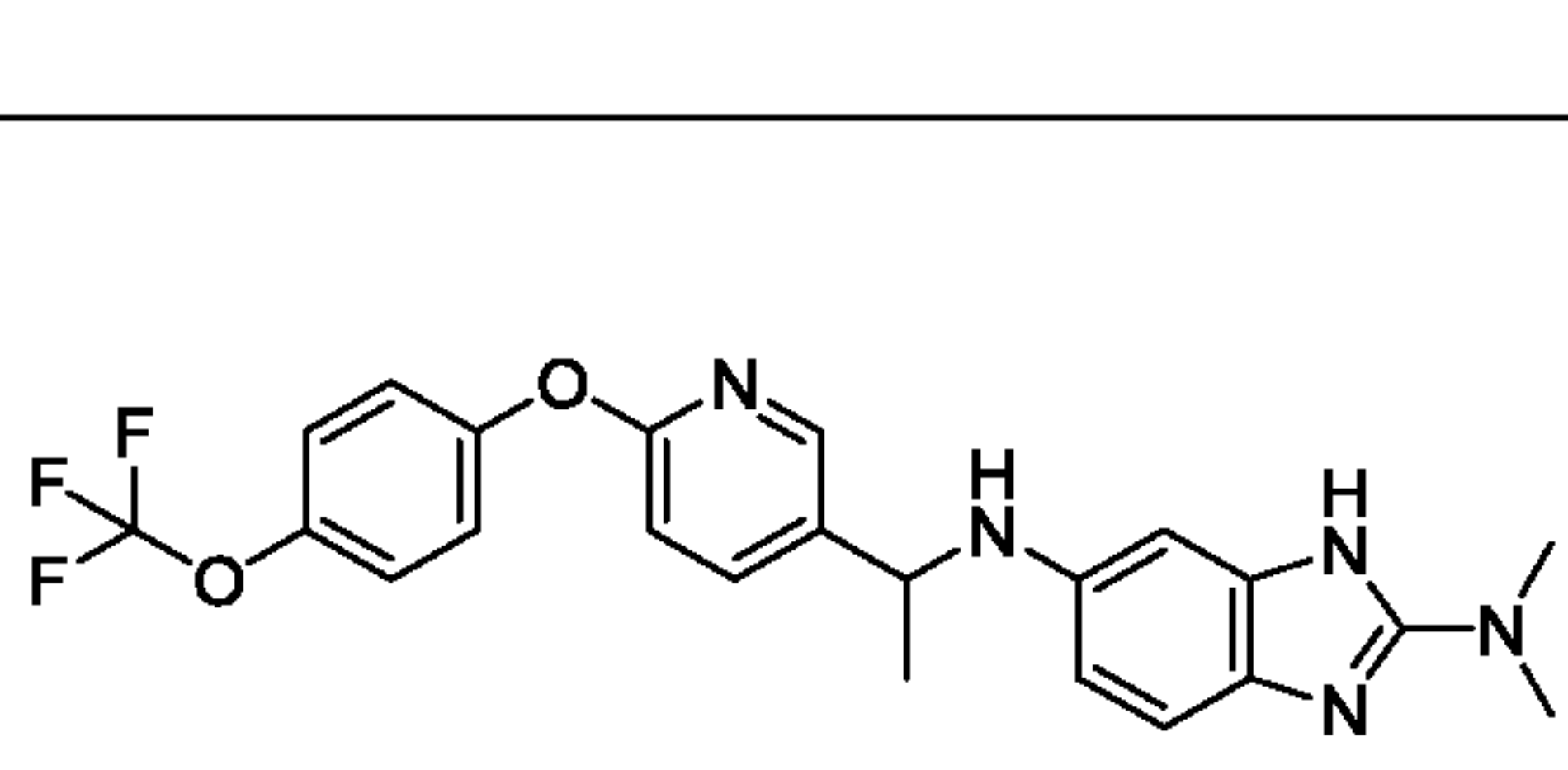
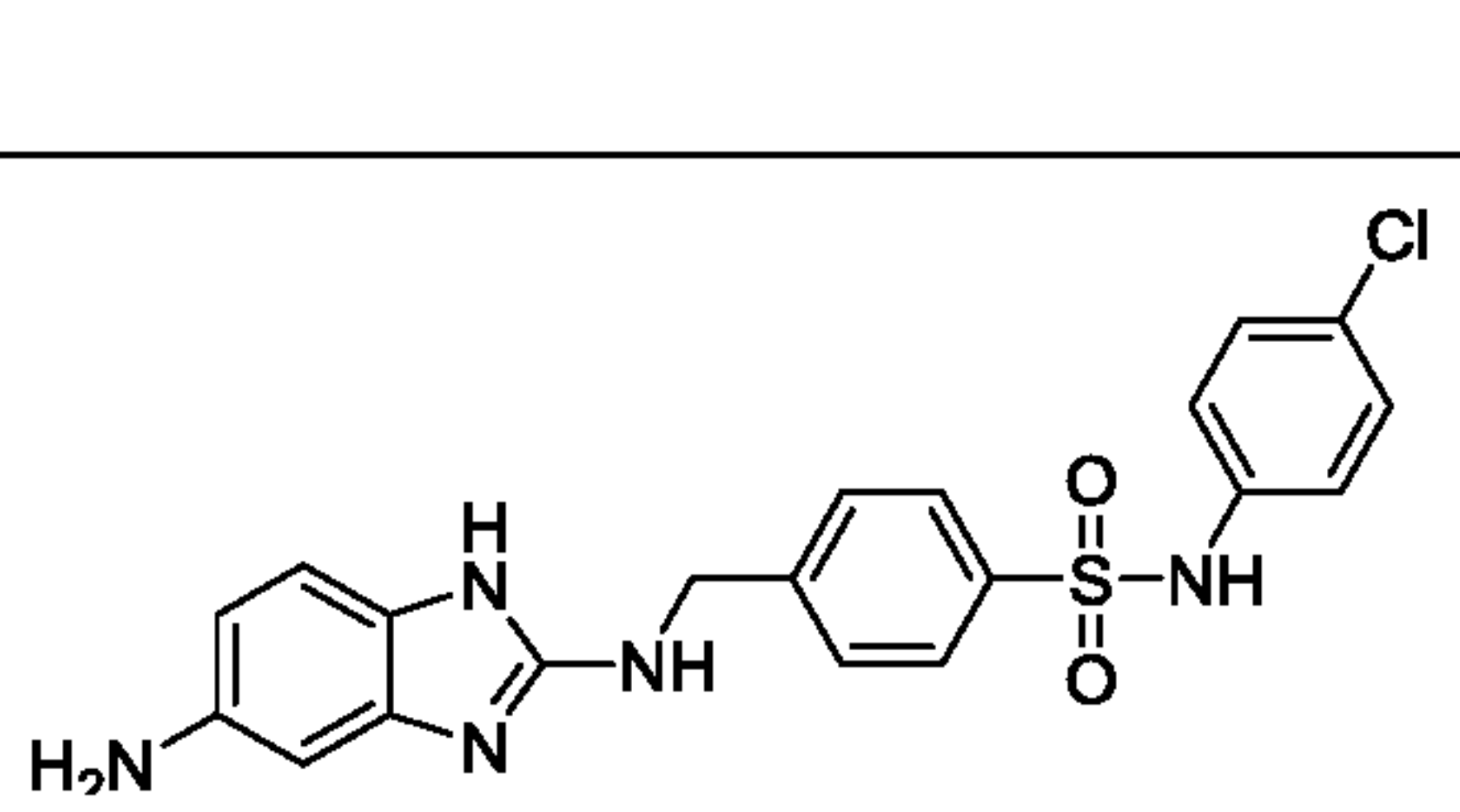
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 97  |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.40 (1H, m), 7.30-7.40 (4H, m), 7.12 (1H, t, <i>J</i> = 7.6 Hz), 6.95-7.00 (4H, m), 6.60-6.90 (2H, m), 6.39 (1H, s), 6.15-6.30 (1H, m), 4.70-4.85 (1H, m), 4.40-4.50 (2H, m), 3.60-3.65 (1H, m), 1.75-1.95 (2H, m), 1.60-1.70 (2H, m), 1.45-1.55 (2H, m), 1.35-1.45 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 399.2[M+ H] <sup>+</sup> .                            |
| 98  |  | white solid; mp = 116.8-118.7°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.45 (1H, brs), 7.30-7.45 (4H, m), 7.12 (1H, t, <i>J</i> = 7.2 Hz), 6.75-7.05 (6H, m), 6.60 (1H, s), 6.40-6.50 (1H, m), 4.45 (2H, d, <i>J</i> = 6.0 Hz), 2.79 (6H, s); LCMS: 99.2%, MS (ESI); <i>m/z</i> 359.2[M+ H] <sup>+</sup> .                                                                                                                     |
| 99  |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.70 (1H, brs), 7.29 (2H, d, <i>J</i> = 8.8 Hz), 7.00-7.08 (2H, m), 6.95-7.00 (1H, m), 6.42-6.48 (1H, m), 6.19-6.24 (1H, m), 5.12-5.19 (1H, m), 3.61-3.68 (1H, m), 3.30-3.40 (5H, m), 3.24-3.26 (2H, m), 2.32-2.35 (1H, m), 2.10-2.19 (1H, m), 1.90-1.95 (4H, m); LCMS: 95.2%, MS (ESI); <i>m/z</i> 433.2[M+ H] <sup>+</sup> .                                            |
| 100 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.27 (2H, d, <i>J</i> = 4.2 Hz), 6.95-7.10 (3H, m), 6.66 (1H, d, <i>J</i> = 2.0 Hz), 6.35-6.45 (1H, m), 4.78 (2H, brs), 4.33 (4H, s), 3.83 (2H, t, <i>J</i> = 14.0 Hz), 3.64 (2H, <i>J</i> = 7.6 Hz), 2.40-2.55 (2H, M); LCMS: 95.3%, MS (ESI); <i>m/z</i> 443.2 [M+H] <sup>+</sup> .                                                                                      |
| 101 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.30-7.40 (3H, m), 7.17 (1H, d, <i>J</i> = 7.6 Hz), 7.00-7.10 (2H, m), 6.92-7.01 (2H, m), 6.89 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.81 (1H, d, <i>J</i> = 8.0 Hz), 6.43 (1H, d, <i>J</i> = 1.6 Hz), 6.23 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.46 (2H, s); LCMS: 99.5 %, MS (ESI); <i>m/z</i> 365.1[M + H] <sup>+</sup> .                                                       |
| 102 |  | white powder; mp = 58.4-66.6°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.46 (3H, m), 7.22 (1H, dd, <i>J</i> = 6.4, 3.2 Hz), 6.96-7.03 (3H, m), 6.70-6.80 (2H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, d, <i>J</i> = 7.6 Hz), 4.30-4.55 (4H, m); LCMS: 95.7%, MS (ESI); <i>m/z</i> 383.1[M+H] <sup>+</sup> .                                                                                                          |
| 103 |  | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.30-7.40 (3H, m), 7.10-7.20 (2H, m), 7.04 (1H, s), 6.98 (2H, dd, <i>J</i> = 8.8, 1.2 Hz), 6.71-6.82 (3H, m), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.20 (1H, d, <i>J</i> = 8.0 Hz), 4.44 (2H, d, <i>J</i> = 6.4 Hz); LCMS: 97.3 %, MS (ESI); <i>m/z</i> 331.2[M+ H] <sup>+</sup> .                                                                                         |
| 104 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.44 (1H, brs), 7.30 (2H, d, <i>J</i> = 8.8 Hz), 7.06 (2H, d, <i>J</i> = 8.8 Hz), 6.90-6.99 (1H, m), 6.37-6.45 (1H, m), 6.07-6.28 (2H, m), 5.14-5.16 (1H, m), 3.62-3.67 (1H, m), 3.30-3.42 (3H, overlapped with H <sub>2</sub> O peak), 2.1 (3H, d, <i>J</i> = 4.0 Hz), 2.31-2.35 (1H, m), 2.14-2.17 (1H, m); LCMS: 96.2%, MS (ESI); <i>m/z</i> 393.1[M+ H] <sup>+</sup> . |
| 105 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.30 (2H, d, <i>J</i> = 8.8 Hz), 7.06 (2H, d, <i>J</i> = 9.2 Hz), 6.98 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, s), 6.25 (1H, d, <i>J</i> = 8.4 Hz), 5.14-5.17 (1H, m), 3.62-3.68 (1H, m), 3.30-3.42 (3H, overlap with H <sub>2</sub> O peak), 2.99 (6H, s), 2.32-2.38 (1H, m), 2.14-2.17 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 407.1[M+ H] <sup>+</sup> .                 |

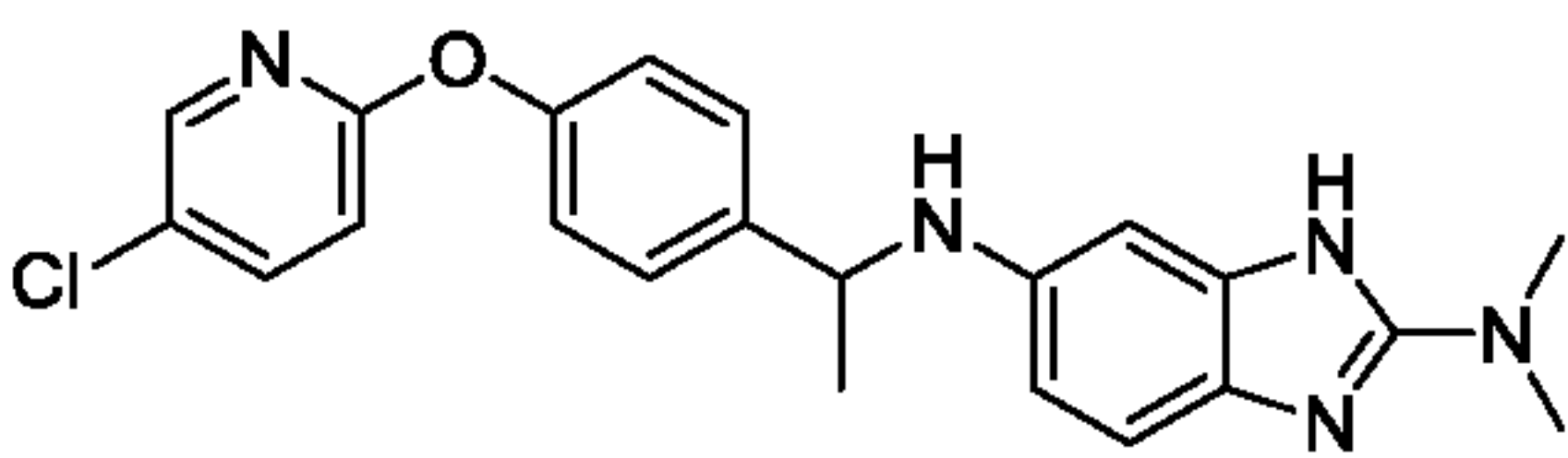
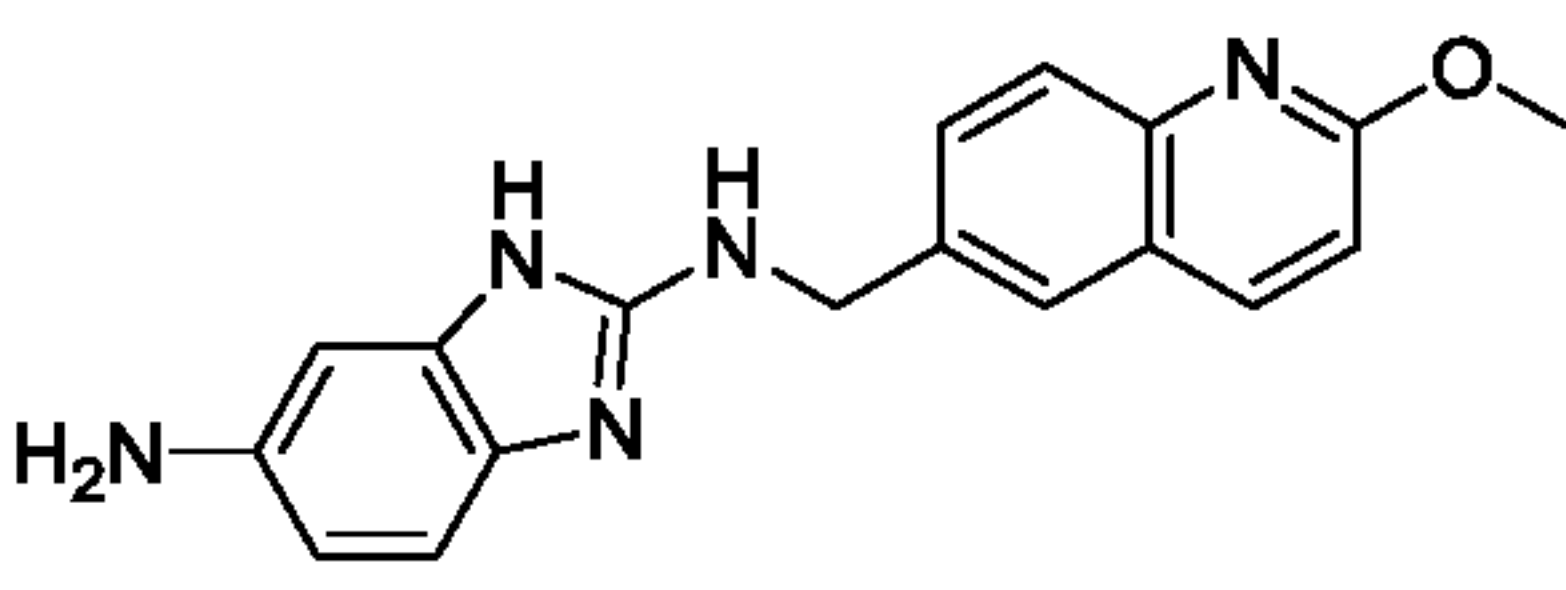
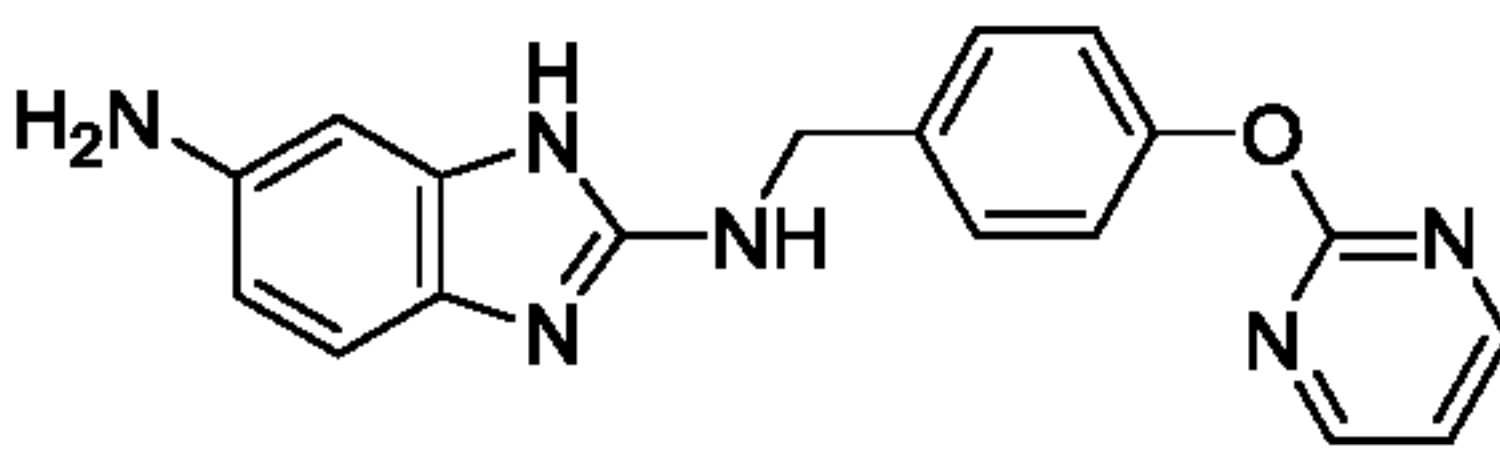
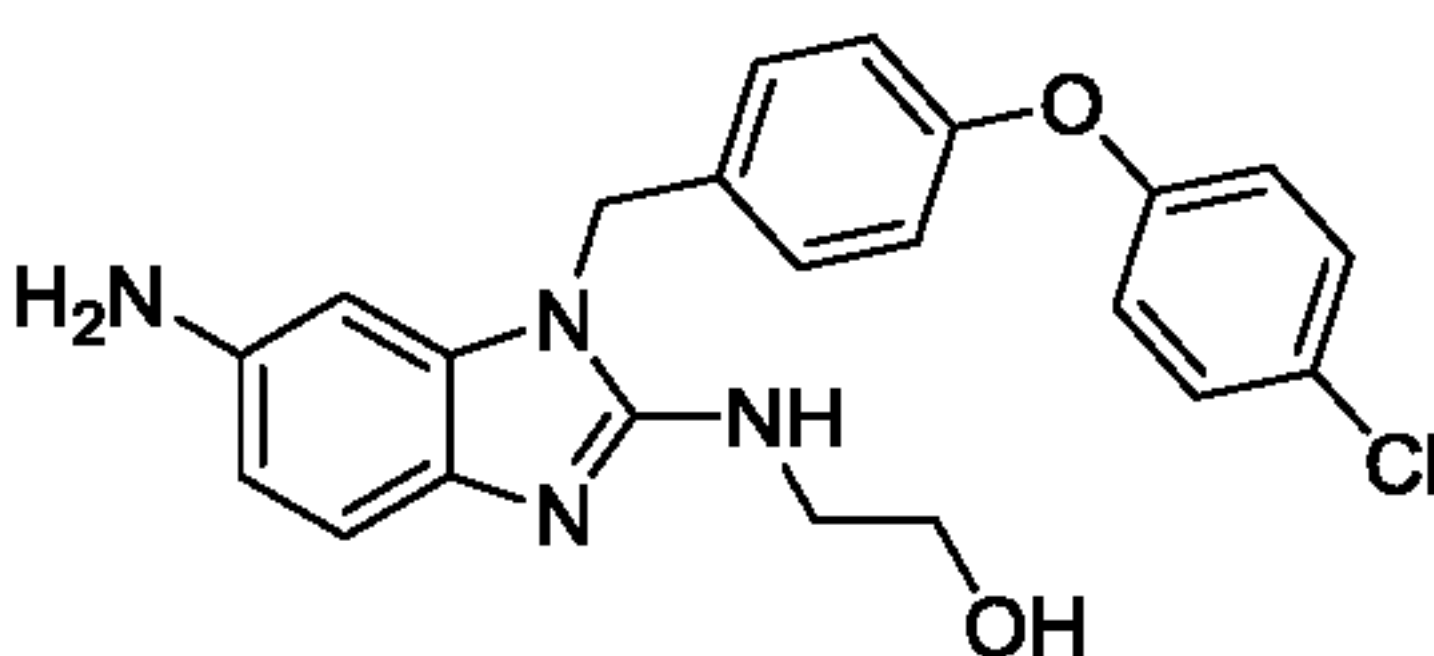
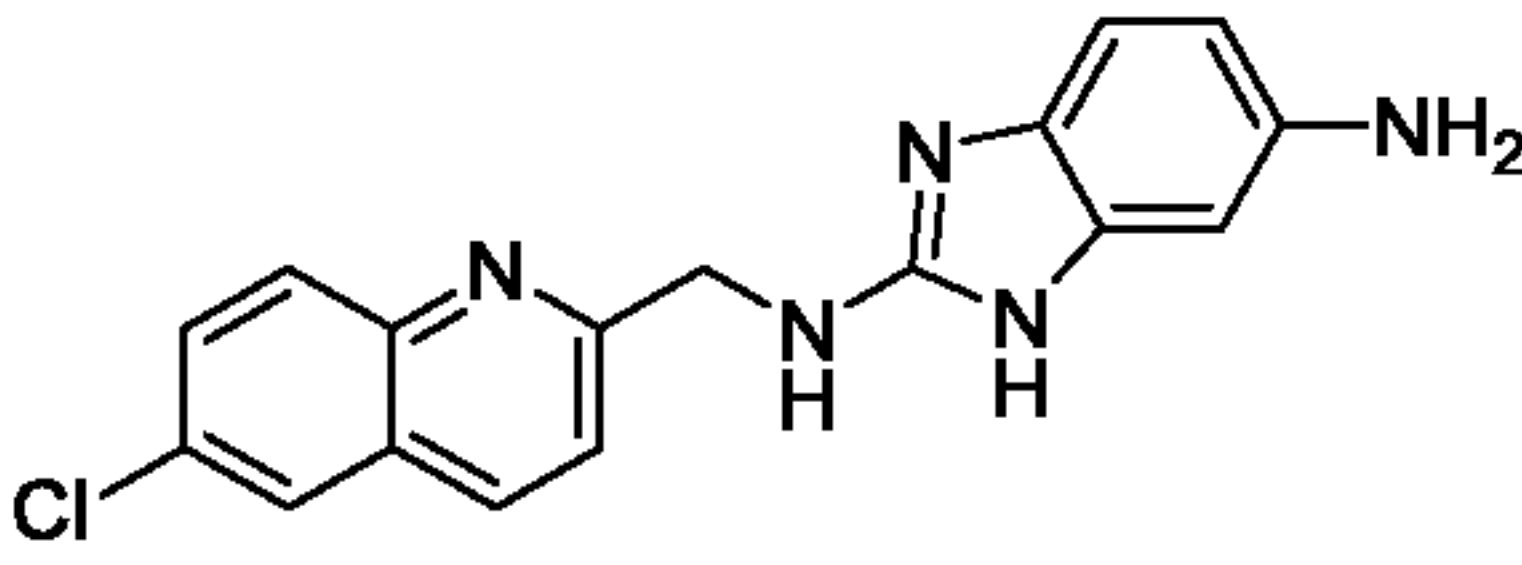
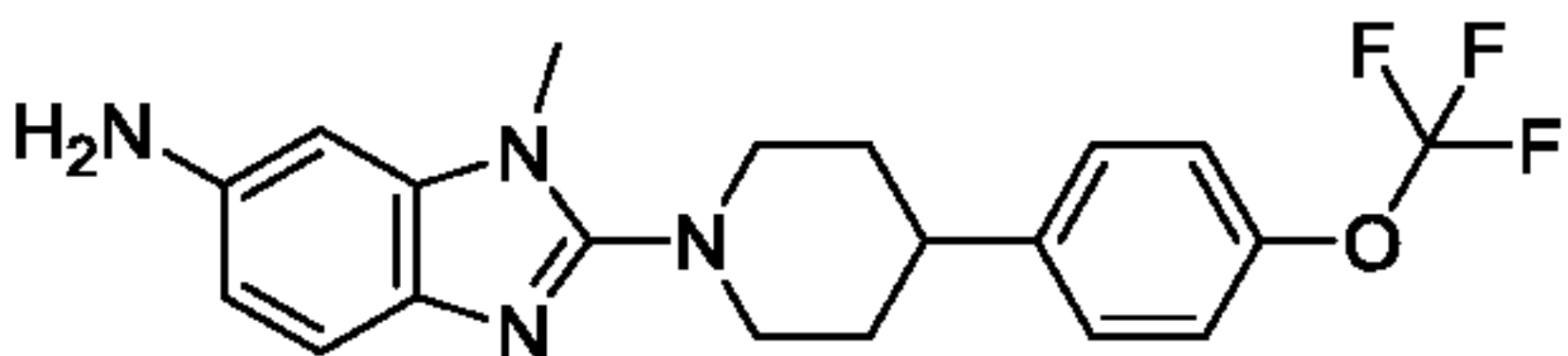
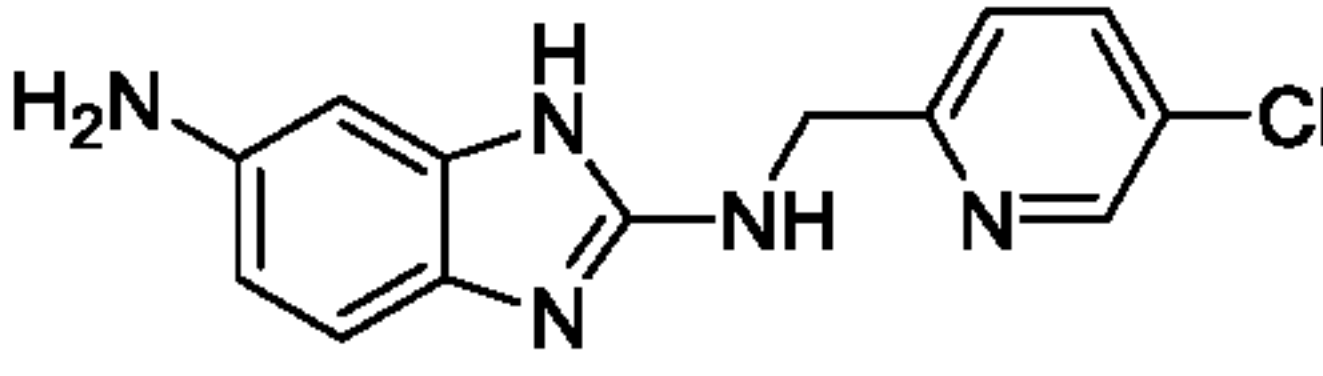
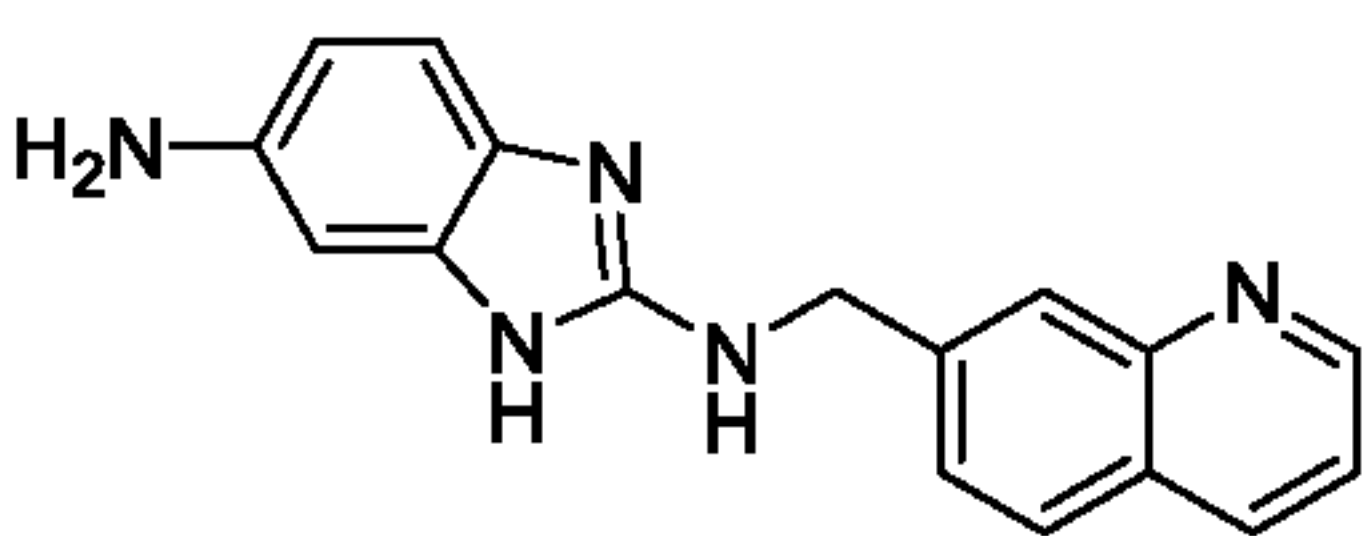
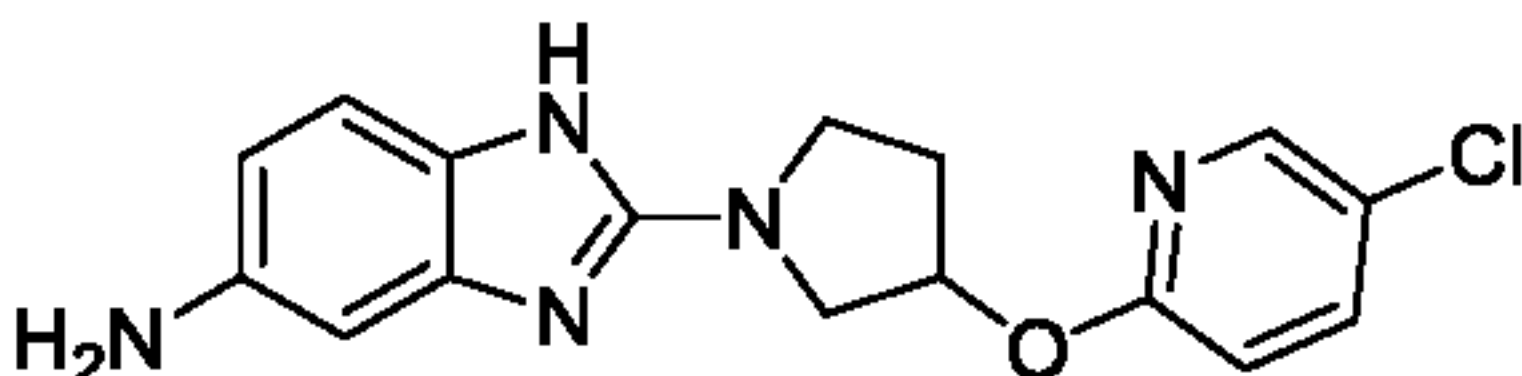
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 106 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35-10.49 (1H, brs), 7.64-7.73 (5H, m), 7.51-7.58 (4H, m), 6.78-7.01 (2H, m), 6.42 (1H, s), 6.18-6.22 (1H, m), 4.54-4.58 (2H, m), 4.42-4.45 (2H, m); LCMS: 99.1%, MS (ESI); m/z 343.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                                              |
| 107 |    | white powder; mp > 200.9°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.51 (1H, d, <i>J</i> = 8.8 Hz), 7.54-7.66 (2H, m), 7.33-7.51 (3H, m), 7.12-7.22 (1H, m), 4.15-4.29 (1H, m), 3.00-3.15 (2H, m), 1.29 (3H, d, <i>J</i> = 6.8 Hz); LCMS: 100 %, MS (ESI); m/z 334.9[M+ H] <sup>+</sup> .                                                                                                                                                                                                      |
| 108 |    | yellow solid; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.41 (2H, d, <i>J</i> = 8.8 Hz), 7.29 (2H, d, <i>J</i> = 8.0 Hz), 7.23 (2H, d, <i>J</i> = 8.0 Hz), 6.94 (2H, d, <i>J</i> = 8.4 Hz), 6.80 (1H, d, <i>J</i> = 8.0 Hz), 6.64 (1H, brs), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, d, <i>J</i> = 7.2 Hz), 4.34 (2H, d, <i>J</i> = 6.0 Hz), 4.04 (2H, d, <i>J</i> = 12.4 Hz), 2.68-2.75 (3H, m), 1.80-1.91 (2H, m), 1.65-1.80 (2H, m); LCMS: 98.0 %, MS (ESI); m/z 482.1[M+ H] <sup>+</sup> . |
| 109 |  | white powder; mp > 173°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.40 (1H, brs), 7.30-7.40 (4H, m), 7.18 (1H, s), 7.11 (1H, t, <i>J</i> = 7.2 Hz), 6.90-7.00 (5H, m), 6.70-6.85 (2H, m), 6.39 (1H, d, <i>J</i> = 2.0 Hz), 6.24 (1H, d, <i>J</i> = 7.6 Hz), 5.00 (1H, brs), 4.42 (2H, d, <i>J</i> = 6.0 Hz), 1.31 (6H, s); LCMS: 100%, MS (ESI); m/z 416.1[M+ H] <sup>+</sup> .                                                                                                                |
| 110 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.03 - 10.31 (1H, m), 7.30-7.55 (4H, m), 6.91-7.07 (4H, m), 6.60-6.88 (2H, m), 6.39 (1H, brs), 6.05-6.15 (1H, m), 4.80-4.90 (1H, m), 4.40 (2H, brs), 1.44 (3H, d, <i>J</i> = 6.8 Hz); LCMS: 100%, MS (ESI); m/z 379.0[M+H] <sup>+</sup> .                                                                                                                                                                                          |
| 111 |  | white solid; mp = 156.4-158.5°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40 (1H, d, <i>J</i> = 8.8 Hz), 7.21 (1H, d, <i>J</i> = 8.4 Hz), 6.95 - 7.04 (4H, m), 6.83 (1H, d, <i>J</i> = 8.4 Hz), 6.31 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.08 (2H, brs), 5.10 (2H, s), 4.47 (2H, brs); LCMS: 99.8%, MS (ESI); m/z 365.1 [M+H] <sup>+</sup> .                                                                                                                    |
| 112 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.60 (1H, d, <i>J</i> = 8.8 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.40 (1H, brs), 7.23 (1H, d, <i>J</i> = 3.2 Hz), 7.07 (2H, d, <i>J</i> = 8.8 Hz), 6.96 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.48 (2H, s); LCMS: 97.6%, MS (ESI); m/z 399.1[M+ H] <sup>+</sup> .                                                               |
| 113 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.65 (1H, brs), 7.32-7.50 (3H, m), 7.08-7.20 (1H, m), 7.02 (2H, d, <i>J</i> = 8.4 Hz), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.74-6.84 (1H, m), 6.48 (1H, d, <i>J</i> = 2.0 Hz), 6.29 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.48 (2H, s); LCMS: 98.7%, MS (ESI); m/z 367.1[M+ H] <sup>+</sup> .                                                                                                                                                |
| 114 |  | white powder; mp > 220°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30 (1H, brs), 7.15-7.35 (4H, m), 7.06 (2H, d, <i>J</i> = 9.6 Hz), 6.95 (1H, d, <i>J</i> = 8.8 Hz), 6.78 (1H, d, <i>J</i> = 7.2 Hz), 6.50-6.70 (1H, m), 6.41 (1H, s), 6.15-6.25 (1H, m), 4.25-4.55 (4H, m), 3.25-3.40 (4H, m), 3.15-3.25 (4H, m); LCMS: 98.8%, MS (ESI); m/z 483.2[M+ H] <sup>+</sup> .                                                                                                                     |
| 115 |  | white powder; mp > 220°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30 (1H, brs), 7.30-7.55 (4H, m), 7.22 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (2H, d, <i>J</i> = 8.4 Hz), 6.79 (1H, d, <i>J</i> = 8.0 Hz), 6.50-6.75 (1H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.15-6.25 (1H, m), 4.25-4.50 (2H, brs), 4.33 (2H, <i>J</i> = 6.0 Hz) 3.60-3.80 (2H, m) 2.60-2.75 (3H, m) 1.80-1.95 (2H, m) 1.65-1.80                                                                                               |

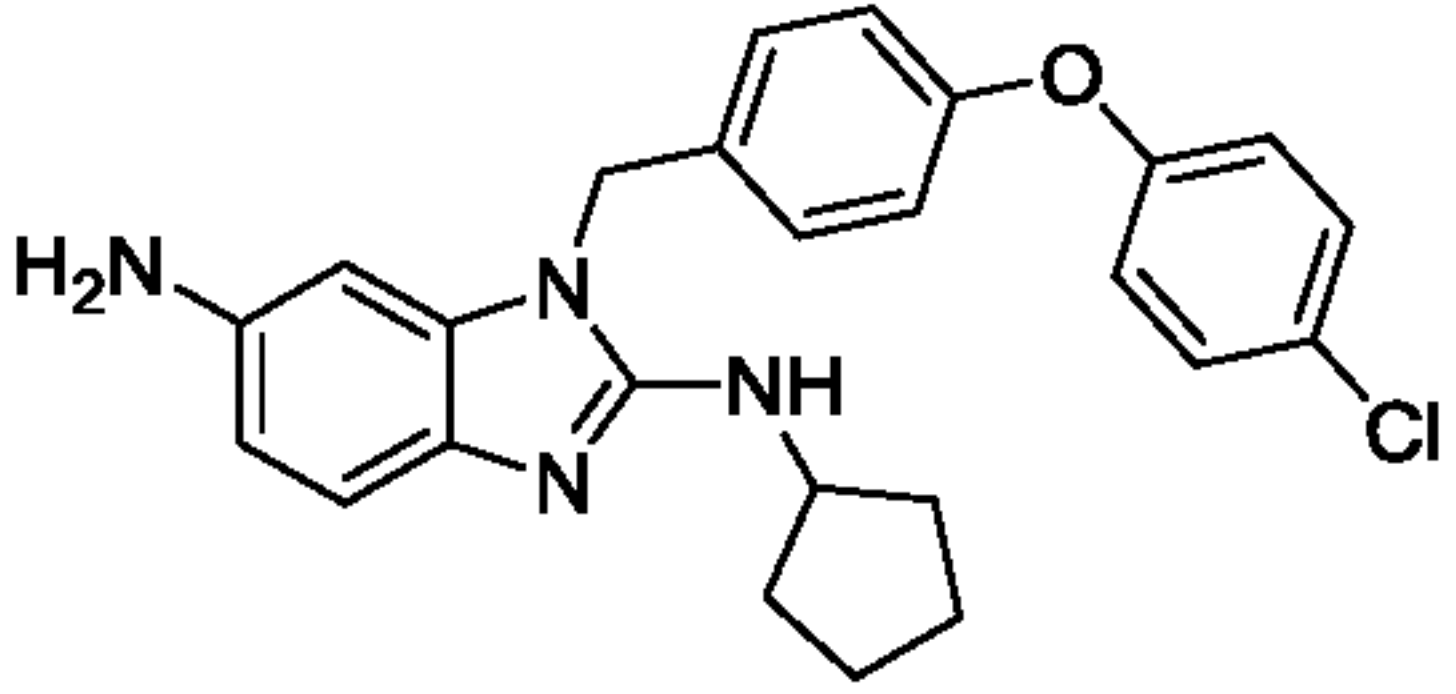
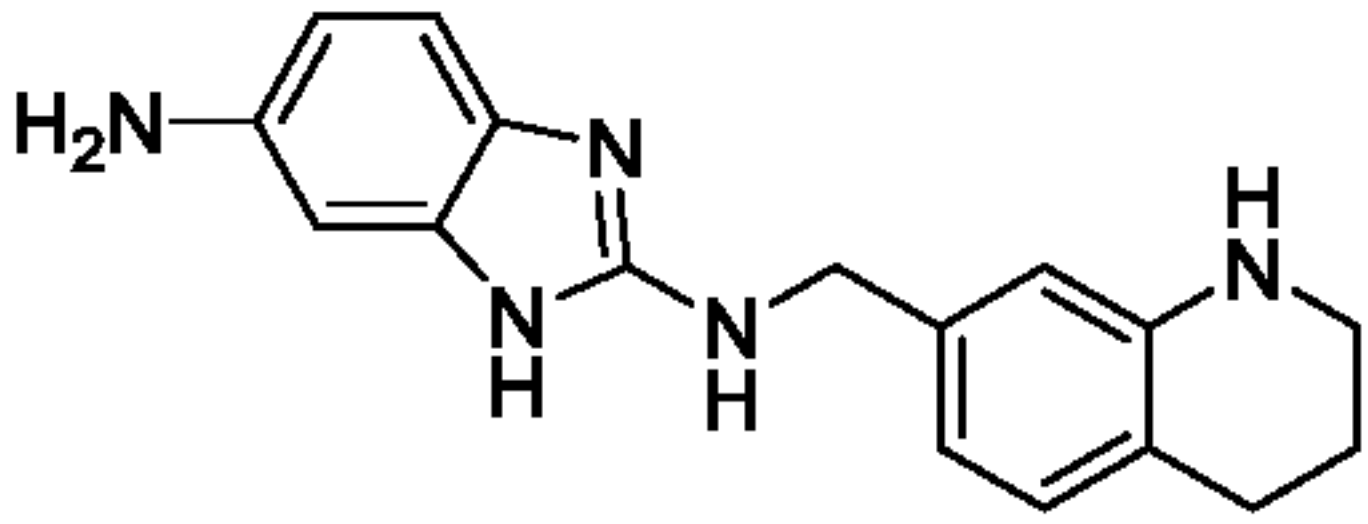
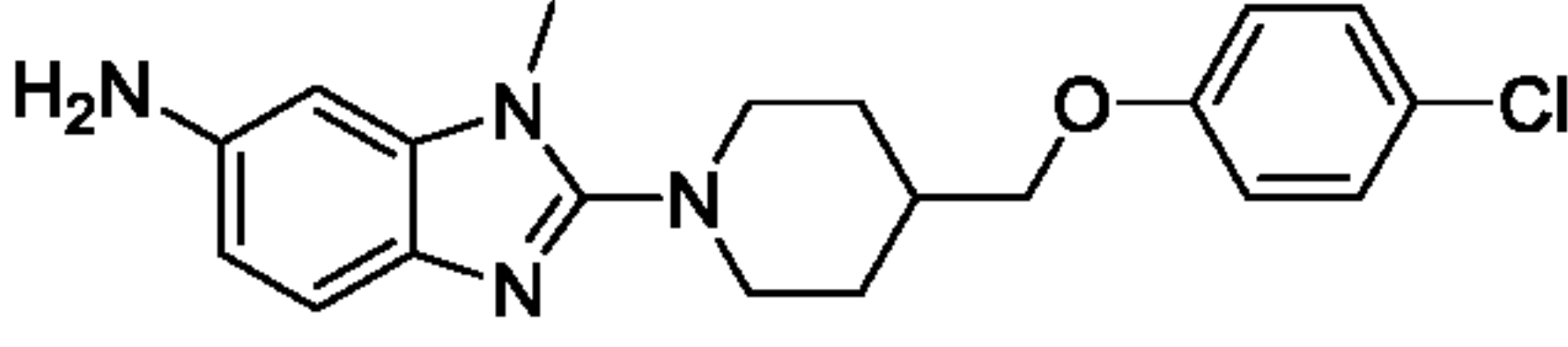
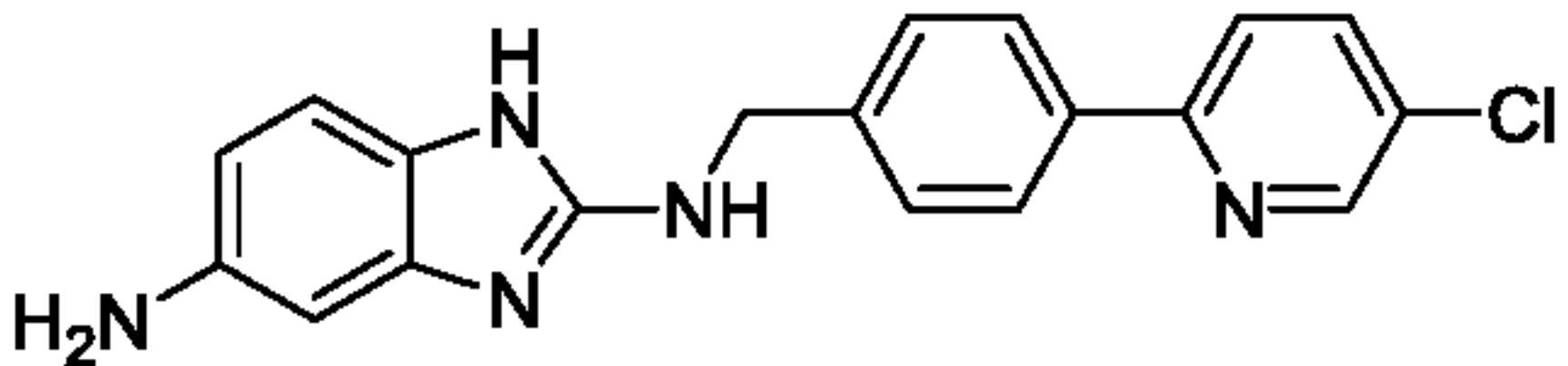
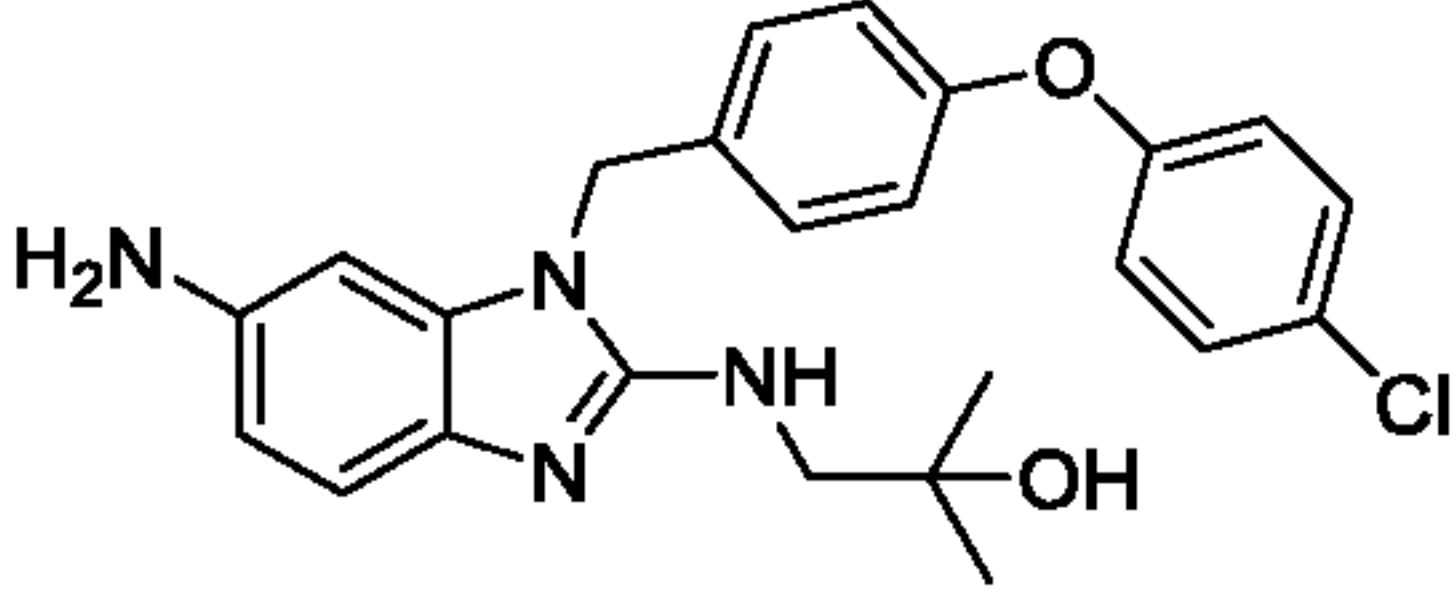
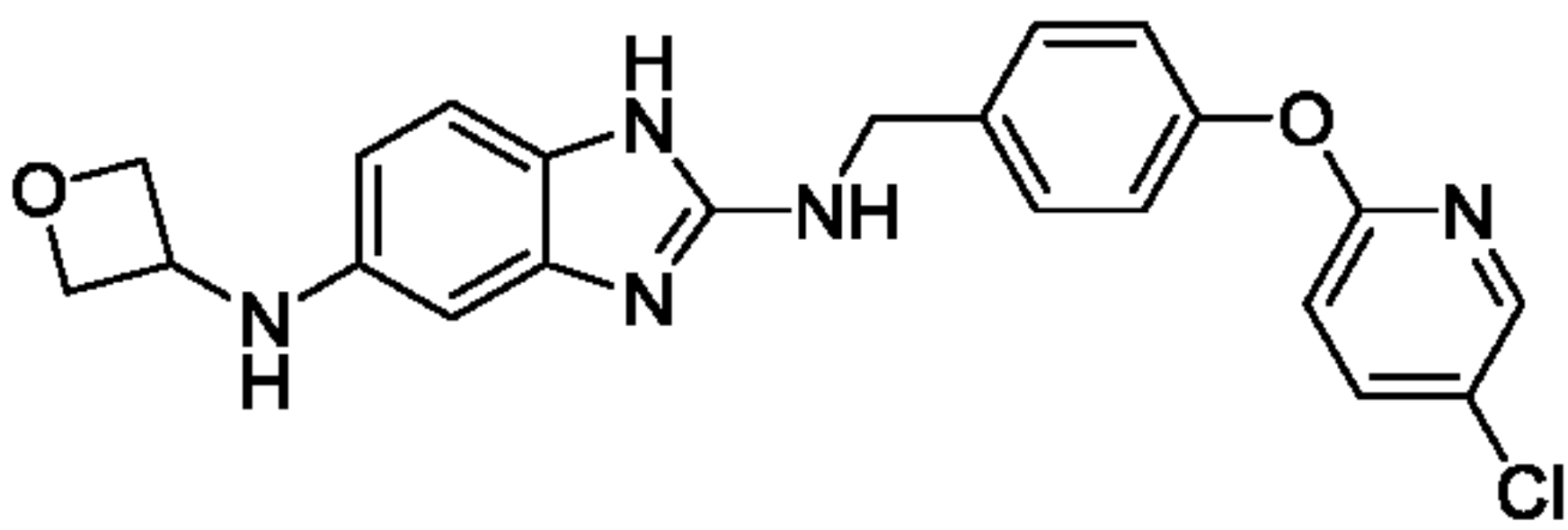
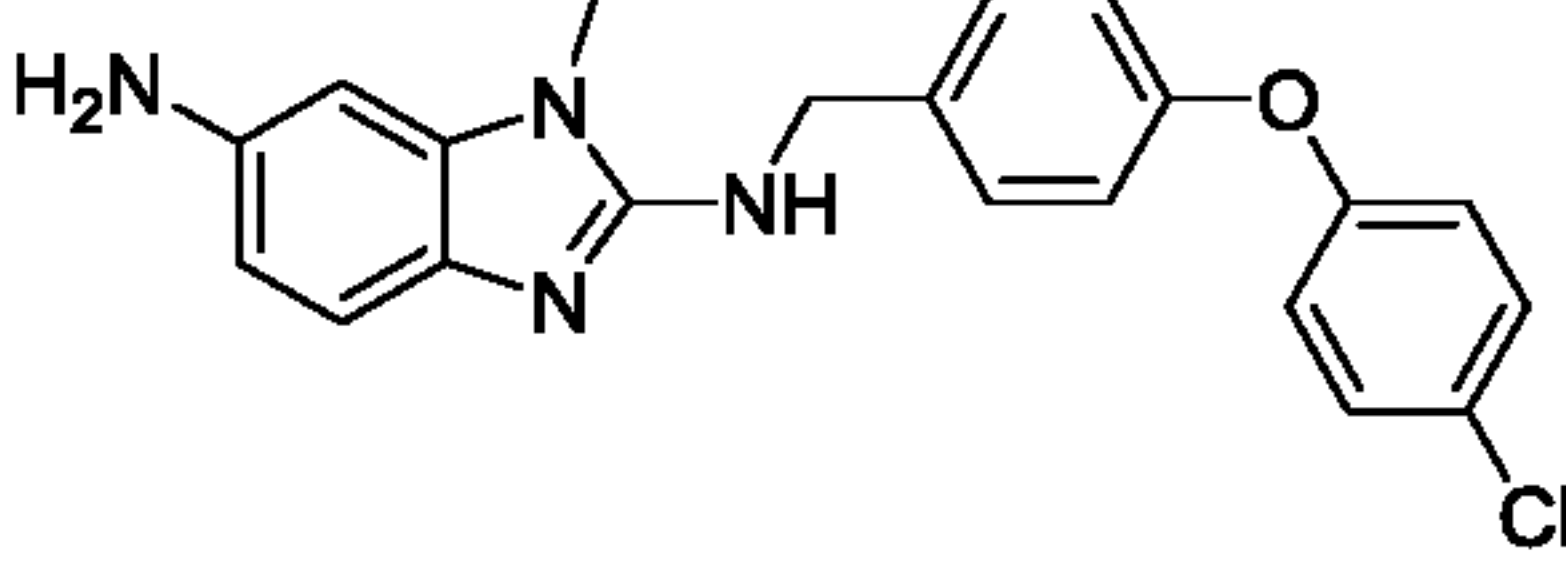
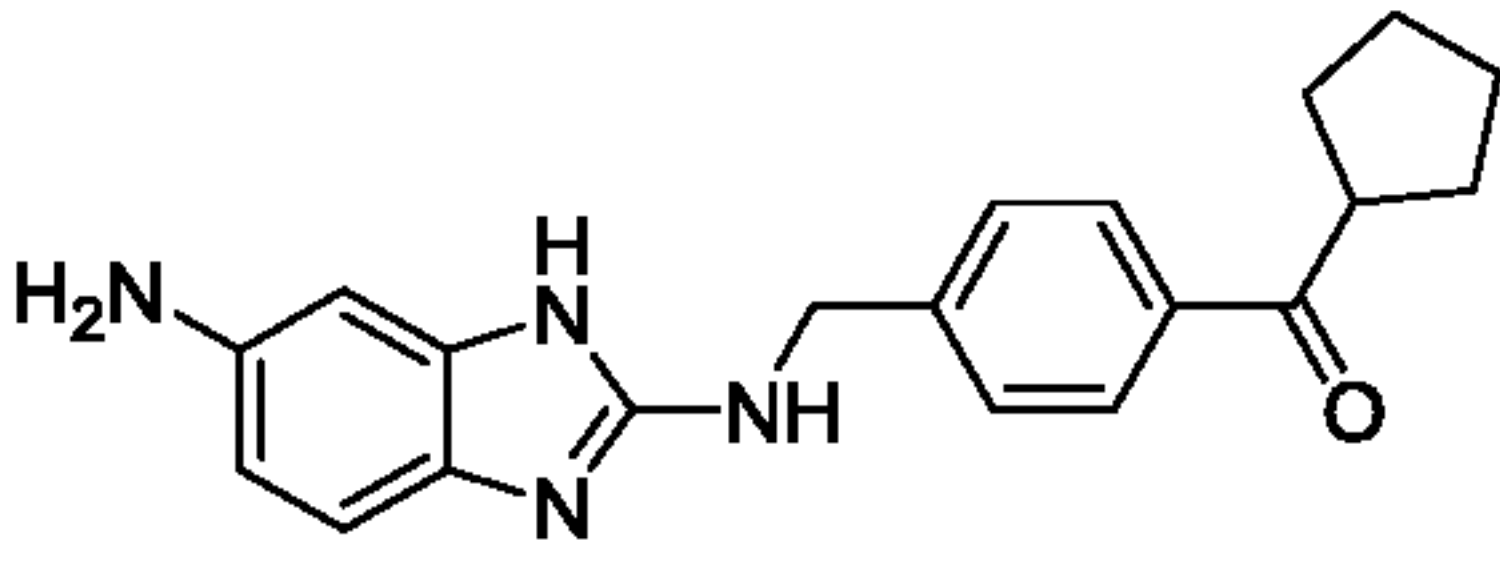
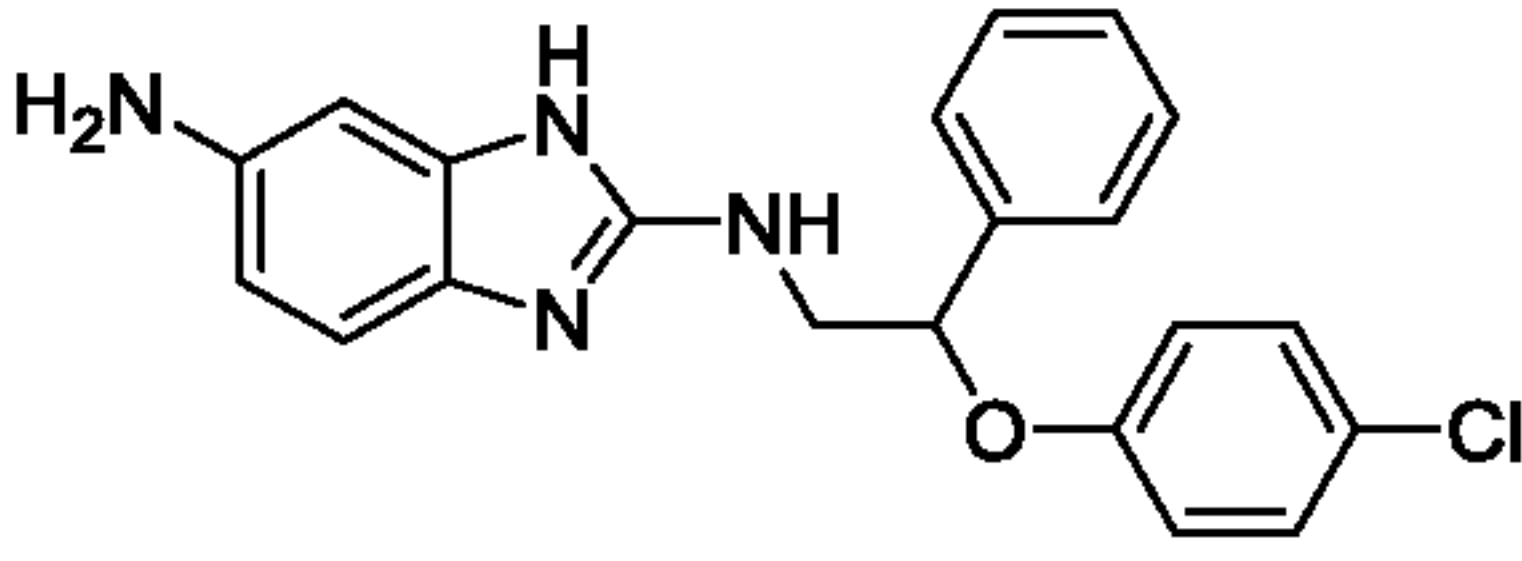
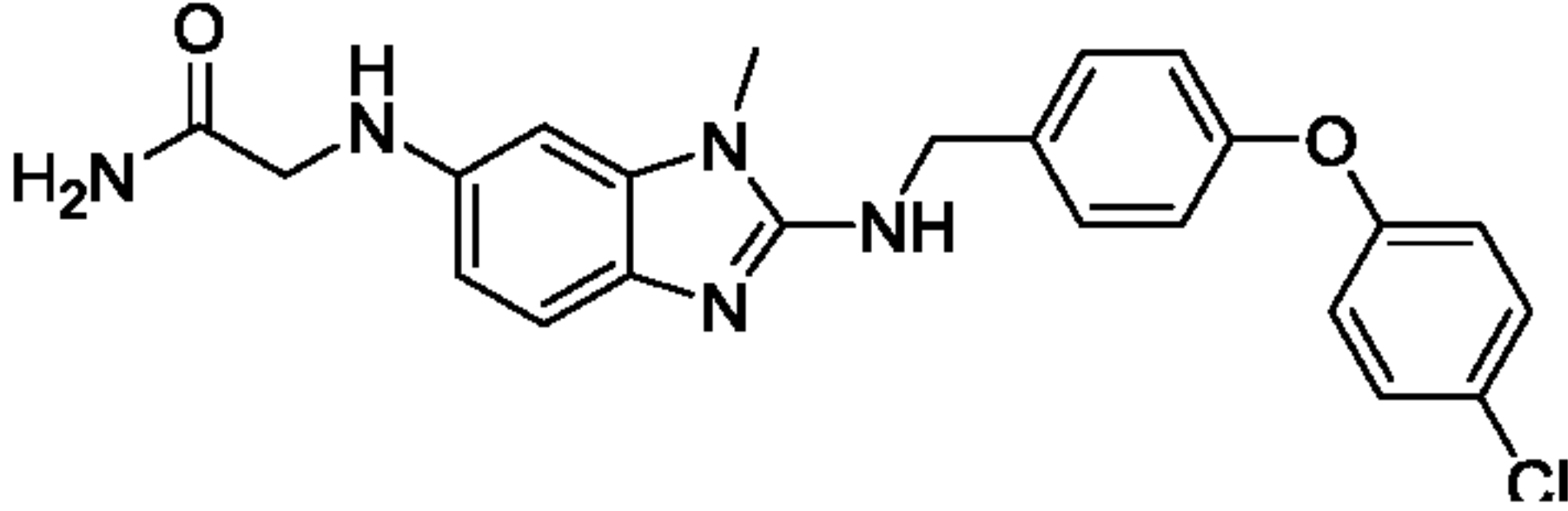
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |                                                                                     | (2H, m); LCMS: 98.7%, MS (ESI); m/z 432.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                                                                                     |
| 116 |    | pale yellow powder; mp > 130.8°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.34 (2H, d, <i>J</i> = 8.4 Hz), 7.28 (2H, d, <i>J</i> = 8.4 Hz), 7.02 (1H, brs), 6.75-6.85 (1H, m), 6.44 (1H, s), 6.22 (1H, d, <i>J</i> = 8.0 Hz), 4.43 (2H, s), 1.25 (9H, s); LCMS: 99.6%, MS (ESI); m/z 295.0[M+H] <sup>+</sup> .                                                                                                                               |
| 117 |    | off-white powder; mp > 207.2°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.78 (1H, t, <i>J</i> = 6.0 Hz), 7.42-7.49 (4H, m), 7.36-7.42 (2H, m), 7.19 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 7.00 (2H, d, <i>J</i> = 8.8 Hz), 6.88-6.96 (2H, m), 4.66 (2H, d, <i>J</i> = 6.0 Hz), 1.27 (9H, s); LCMS: 98.5%, MS (ESI); m/z 387.1[M+ H] <sup>+</sup> .                                                                                               |
| 118 |   | pale green powder; mp > 113.2°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.56 (0.4H, brs), 10.40 (0.4H, brs), 7.35-7.50 (4H, m), 7.19-7.25 (1H, m), 6.90-7.05 (5H, m), 6.75-6.95 (2H, m), 6.39 (1H, s), 6.15-6.35 (1H, m), 4.97 (0.5H, brs), 5.07 (0.5H, brs), 4.38-4.49 (2H, m), 1.31 (6H, d, <i>J</i> = 3.6 Hz); LCMS: 99.5%, MS (ESI); m/z 450.0[M+ H] <sup>+</sup> .                                                                    |
| 119 |  | white powder; mp > 54.3°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35-10.65 (1H, m), 7.30-7.60 (5H, m), 7.10-7.20 (1H, m), 6.90-7.10 (4H, m), 6.75-6.90 (1H, m), 6.40 (1H, s), 6.15-6.30 (1H, m), 5.00-5.25 (1H, m), 4.40-4.60 (2H, m), 3.85-4.05 (2H, m), 3.75-3.85 (1H, m), 3.60-3.75 (1H, m), 3.45-3.60 (1H, m), 2.05-2.25 (1H, m), 1.65-1.80 (1H, m); LCMS: 97.3%, MS (ESI); m/z 401.1[M+ H] <sup>+</sup> .                           |
| 120 |  | white powder; mp = 200.7-201.3°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.27 (2H, d, <i>J</i> = 8.8 Hz), 6.92-7.05 (2H, m), 6.87 (1H, d, <i>J</i> = 8.0 Hz), 6.48 (1H, s), 6.26 (2H, dd, <i>J</i> = 8.4, 2.4 Hz), 6.01 (1H, d, <i>J</i> = 6.8 Hz), 4.53 (2H, brs), 4.20-4.30 (2H, m), 4.13-4.20 (2H, m), 4.05-4.13 (1H, m), 1.85-2.05 (2H, m), 1.60-1.75 (2H, m), 1.45-1.60 (4H, m); LCMS: 98.6%, MS (ESI); m/z 421.1 [M+H] <sup>+</sup> . |
| 121 |  | white powder; mp > 59.7°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.26 (2H, d, <i>J</i> = 8.4 Hz), 6.90 (2H, d, <i>J</i> = 8.4 Hz), 6.79 (1, d, <i>J</i> = 8.4 Hz), 6.69 (1H, brs), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.39 (2H, d, <i>J</i> = 6.0 Hz), 1.26 (9H, s); LCMS: 99.5%, MS (ESI); m/z 311.1[M+H] <sup>+</sup> .                                                                             |
| 122 |  | off-white powder; mp > 160.8°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 9.73 (1H, t, <i>J</i> = 6.4 Hz), 7.52 (2H, d, <i>J</i> = 8.4 Hz), 7.35-7.46 (3H, m), 7.19 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 7.14 (1H, d, <i>J</i> = 8.4 Hz), 7.10 (2H, d, <i>J</i> = 8.8 Hz), 7.02 (1H, t, <i>J</i> = 2.4 Hz), 6.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 4.67 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 100%, MS (ESI); m/z 365.0[M+ H] <sup>+</sup> .                   |
| 123 |  | yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.35-7.47 (4H, m), 6.95-7.05 (4H, m), 6.91 (1H, d, <i>J</i> = 8.0 Hz), 6.40 (1H, s), 6.34 (1H, d, <i>J</i> = 8.4 Hz), 5.79 (1H, brs), 4.22 (2H, s), 2.98 (6H, s); LCMS: 98.7%, MS (ESI); m/z 393.1 [M + H] <sup>+</sup> .                                                                                                                                                  |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 124 |    | gray powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.14 (1H, brs), 7.30-7.40 (4H, m), 6.90-7.00 (4H, m), 6.55-6.87 (2H, m), 6.37 (1H, s), 6.14 (1H, d, <i>J</i> = 8.4 Hz), 4.20-4.70 (3H, m), 1.60-1.80 (2H, m), 0.87 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 393.0[M+ H] <sup>+</sup> .                                                                                                                    |
| 125 |    | pale yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.40 (1H, brs), 7.36 - 7.45 (4H, m), 6.95 - 7.06 (4H, m), 6.75-6.80 (2H, m), 6.26 (1H, s), 6.13 (1H, d, <i>J</i> = 7.6 Hz), 5.69 (1H, brs), 4.81 (2H, t, <i>J</i> = 6.0 Hz), 4.31 - 4.50 (5H, m); LCMS: 99.1%, MS (ESI); <i>m/z</i> 421.1 [M+H] <sup>+</sup> .                                                                                                         |
| 126 |    | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 13.14 (2H, brs), 7.78 (2H, d, <i>J</i> = 8.8 Hz), 7.39 (2H, d, <i>J</i> = 8.4 Hz), 7.30 (1H, d, <i>J</i> = 8.8 Hz), 6.90-7.10 (6H, m), 4.42 (2H, s), 3.21 (6H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 443.1[M+ H] <sup>+</sup> .                                                                                                                                                    |
| 127 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 13.20 (2H, brs), 7.50 (2H, d, <i>J</i> = 8.8 Hz), 7.38 (2H, d, <i>J</i> = 8.4 Hz), 7.29 (1H, d, <i>J</i> = 8.8 Hz), 7.16 (1H, brs), 6.80-7.10 (5H, m), 4.71 (1H, d, <i>J</i> = 5.6 Hz), 3.20 (6H, s), 1.66 (3H, d, <i>J</i> = 6.0 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 457.1[M + H] <sup>+</sup> .                                                                               |
| 128 |  | pale green powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.66 (2H, brs), 7.36-7.47 (4H, m), 7.13 (1H, d, <i>J</i> = 7.6 Hz), 6.90-7.00 (4H, m), 6.60-6.85 (2H, m), 4.25-4.35 (1H, m), 3.15 (6H, s), 1.70-2.00 (2H, m), 0.87 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 99.39%, MS (ESI); <i>m/z</i> 421.1 [M+H] <sup>+</sup> .                                                                                                            |
| 129 |  | gray powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35-10.50 (1H, m), 7.80-7.98 (4H, m), 7.66 (2H, d, <i>J</i> = 8.8 Hz), 7.57 (2H, d, <i>J</i> = 8.4 Hz), 6.75-7.00 (1H, m), 6.70-6.80 (1H, m), 6.39 (1H, s), 6.10-6.25 (1H, m), 4.45-4.55 (2H, m), 4.25-4.45 (2H, m); LCMS: 98.0%, MS (ESI); <i>m/z</i> 413.0 [M+H] <sup>+</sup> .                                                                                                       |
| 130 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 9.92 (1H, t, <i>J</i> = 6.0 Hz), 7.69-7.83 (4H, m), 7.58-7.69 (4H, m), 7.39-7.51 (2H, m), 7.18 (1H, d, <i>J</i> = 8.8 Hz), 4.83 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 377.0 [M+H] <sup>+</sup> .                                                                                                                                                                           |
| 131 |  | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.91 (2H, brs), 7.41-7.47 (4H, m), 7.22 (1H, d, <i>J</i> = 8.4 Hz), 6.86-6.99 (6H, m), 4.50-4.70 (1H, m), 3.17 (6H, s), 1.58 (3H, d, <i>J</i> = 5.2 Hz); LCMS: 99.7 %, MS (ESI); <i>m/z</i> 407.0[M+ H] <sup>+</sup> .                                                                                                                                                             |
| 132 |  | pale green powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.76 (2H, brs), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.38 (2H, d, <i>J</i> = 8.8 Hz), 7.16 (1H, d, <i>J</i> = 7.2 Hz), 7.02-7.08 (2H, m), 7.00 (2H, d, <i>J</i> = 8.8 Hz), 6.60-6.85 (2H, m), 4.30-4.40 (1H, m), 3.16 (6H, s), 1.75-2.10 (2H, m), 0.87 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 471.1[M+ H] <sup>+</sup> .                            |
| 133 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.52 (1H, brs), 7.85-7.99 (4H, m), 7.61-7.70 (2H, m), 7.56 (2H, d, <i>J</i> = 8.4 Hz), 6.96 (1H, brs), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.23 (1H, s), 6.12 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.70 (1H, brs), 4.80 (2H, t, <i>J</i> = 6.0 Hz), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 4.38-4.45 (1H, m), 4.30-4.38 (2H, m); LCMS: 95.3%, MS (ESI); <i>m/z</i> 469.0 [M+H] <sup>+</sup> . |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| 134 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.24 - 10.59 (1H, m), 7.34-7.44 (4H, m), 6.94-7.09 (4H, m), 6.85-6.88 (2H, m), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.20-6.25 (1H, m), 4.83 (1H, brs), 4.44 (2H, d, <i>J</i> = 6.4 Hz), 3.63-3.67 (1H, m), 2.51-2.53 (1H, m), 2.26-2.30 (1H, m), 1.21 (3H, d, <i>J</i> = 6.0 Hz); LCMS: 98.0%, MS (ESI); <i>m/z</i> 375.1[M+H] <sup>+</sup> .                                                                                                          |
| 135 |    | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.76 (1H, d, <i>J</i> = 2.8 Hz), 7.30-7.45 (4H, m), 7.05 (1H, d, <i>J</i> = 8.8 Hz), 6.97 (2H, d, <i>J</i> = 8.4 Hz), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.46 (2H, s); LCMS: 98.2 %, MS (ESI); <i>m/z</i> 398.9[M + H] <sup>+</sup> .                                                                                                                                       |
| 136 |   | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.4 Hz), 7.41-7.52 (4H, m), 7.07 (2H, d, <i>J</i> = 8.8 Hz), 6.75-6.85 (2H, m), 6.42 (1H, d, <i>J</i> = 1.6 Hz), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.45 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 97.8 %, MS (ESI); <i>m/z</i> 366.0[M + H] <sup>+</sup> .                                                                                                                                                                   |
| 137 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.47-10.63 (1H, m), 7.40 (4H, d, <i>J</i> = 8.8 Hz), 6.86-7.04 (6H, m), 6.40-6.45 (1H, m), 6.18-6.32 (1H, m), 5.91-6.08 (1H, m), 4.42-4.48 (2H, m), 2.59-2.72 (2H, m), 2.27-2.40 (2H, m), 1.98-2.15 (2H, m); LCMS: 92.6%, MS (ESI); <i>m/z</i> 444.2[M+H] <sup>+</sup> .                                                                                                                                                                       |
| 138 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 9.78 (1H, t, <i>J</i> = 6.0 Hz), 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.96 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.51 (2H, d, <i>J</i> = 8.4 Hz), 7.37-7.45 (2H, m), 7.08-7.20 (4H, m), 4.69 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 99.6%, MS (ESI); <i>m/z</i> 365.9[M+ H] <sup>+</sup> .                                                                                                                                                                                   |
| 139 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 8.41 (1H, d, <i>J</i> = 4.8 Hz), 7.71-7.78 (1H, m), 7.53 (1H, d, <i>J</i> = 8.0 Hz), 7.29-7.35 (2H, m), 7.23-7.28 (2H, m), 7.16-7.22 (1H, m), 6.70-6.82 (2H, m), 6.40 (1H, s), 6.18 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.04 (1H, brs), 5.66 (1H, s), 4.38 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 98.3%, MS (ESI); <i>m/z</i> 346.0 [M+H] <sup>+</sup> .                                                                                                               |
| 140 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.52 (1H, d, <i>J</i> = 2.0 Hz), 7.33 (1H, d, <i>J</i> = 8.0 Hz), 7.20-7.30 (4H, m), 7.03 (2H, d, <i>J</i> = 6.8 Hz), 6.86 (1H, d, <i>J</i> = 8.8 Hz), 6.31 (1H, d, <i>J</i> = 8.4 Hz), 6.15-6.27 (2H, m), 5.00-5.20 (2H, m), 4.46 (2H, brs), 4.10-4.25 (1H, m), 2.87-3.08 (2H, m), 1.22 (3H, d, <i>J</i> = 6.4 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 425.1[M+ H] <sup>+</sup> .                                                                   |
| 141 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 8.70 (1H, d, <i>J</i> = 4.0 Hz), 8.01-8.10 (1H, m), 7.96 (1H, d, <i>J</i> = 8.0 Hz), 7.91 (2H, d, <i>J</i> = 8.4 Hz), 7.61-7.68 (1H, m), 7.50 (2H, d, <i>J</i> = 8.4 Hz), 7.04 (brs), 6.77-6.84 (1H, m), 6.43 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.55 (2H, s); LCMS: 89.4%, MS (ESI); <i>m/z</i> 344.1 [M+H] <sup>+</sup> .                                                                                               |
| 142 |  | white amorphous; hygroscopic; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 12.52 (2H, brs), 10.73 (1H, brs), 8.87 (1H, t, <i>J</i> = 6.0 Hz), 7.29 (2H, d, <i>J</i> = 8.4 Hz), 7.11-7.22 (1H, m), 7.05 (2H, d, <i>J</i> = 9.2 Hz), 6.41-6.59 (2H, m), 5.10-5.22 (1H, m), 3.89-4.00 (2H, m), 3.71-3.81 (2H, m), 3.61-3.70 (3H, m), 3.50-3.60 (4H, m), 3.11-3.24 (4H, m), 2.92-3.10 (2H, m), 2.50-2.60 (2H, m), 2.11-2.21 (1H, m), 1.95-2.08 (1H, m); LCMS: 99.5 %, MS (ESI); <i>m/z</i> 506.3[M+ H] <sup>+</sup> . |

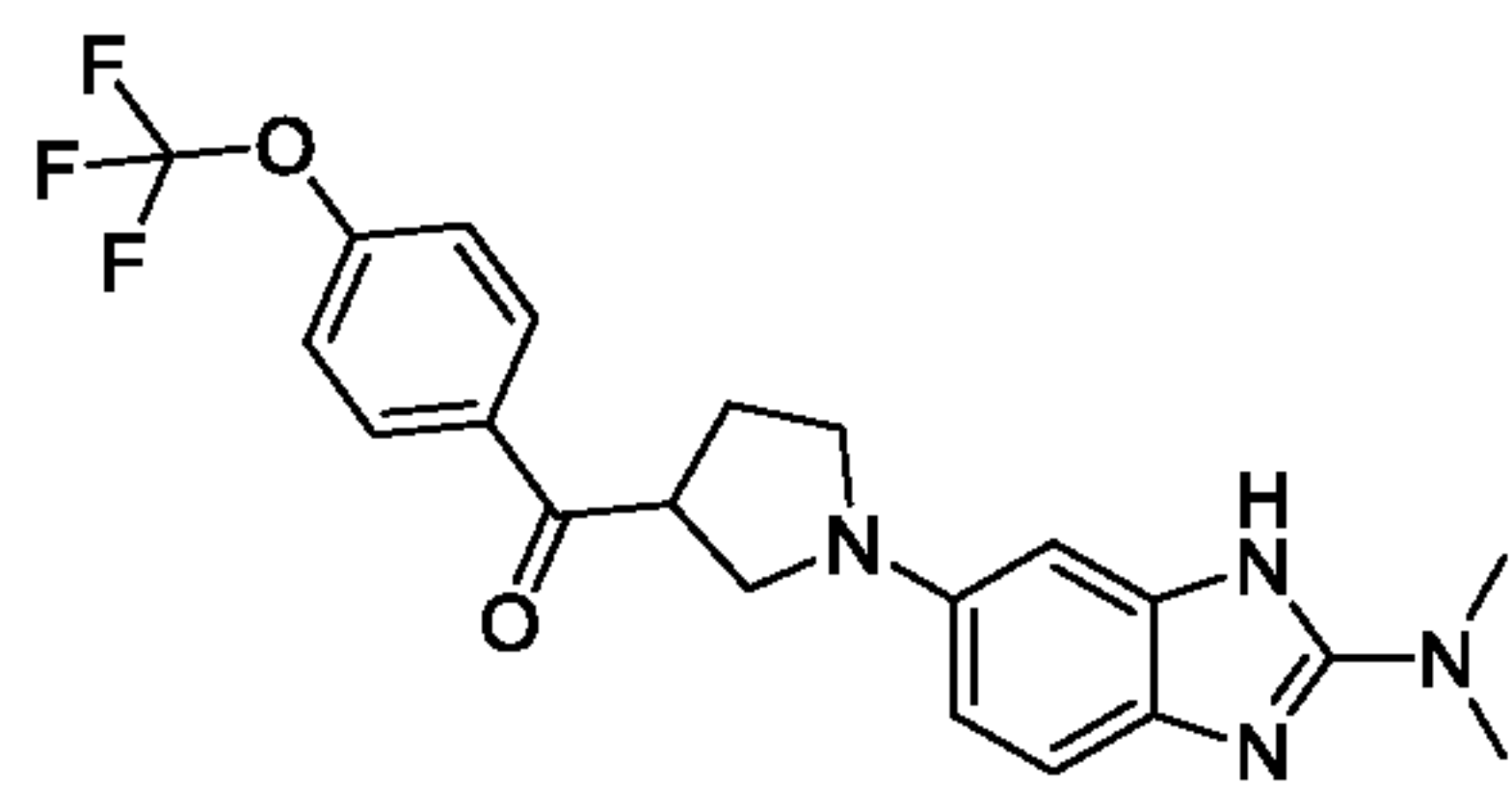
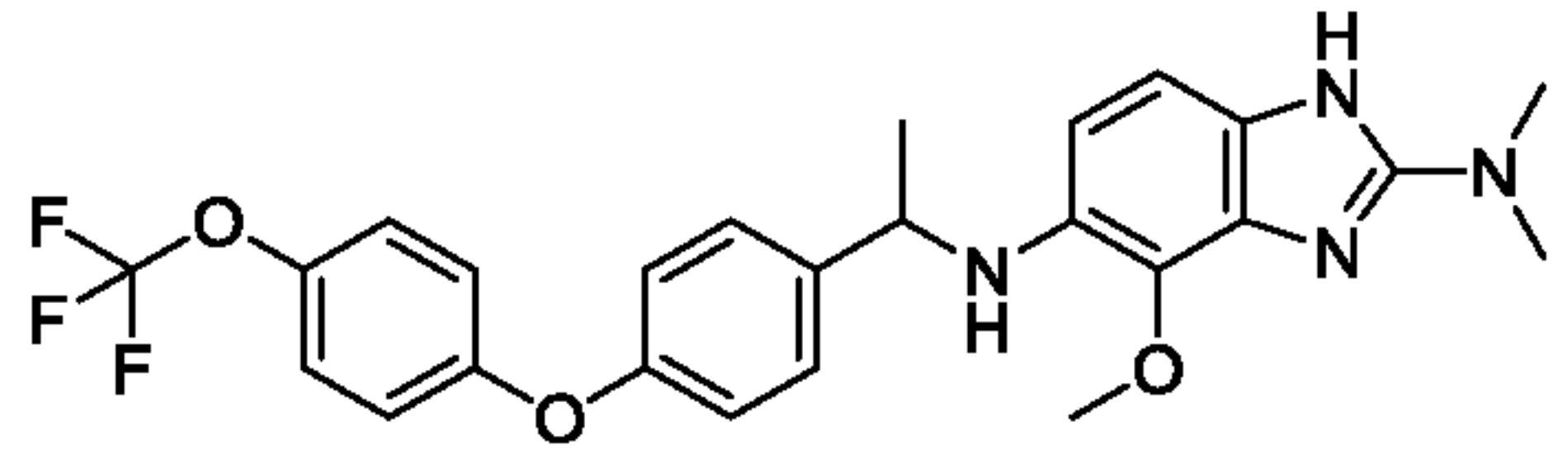
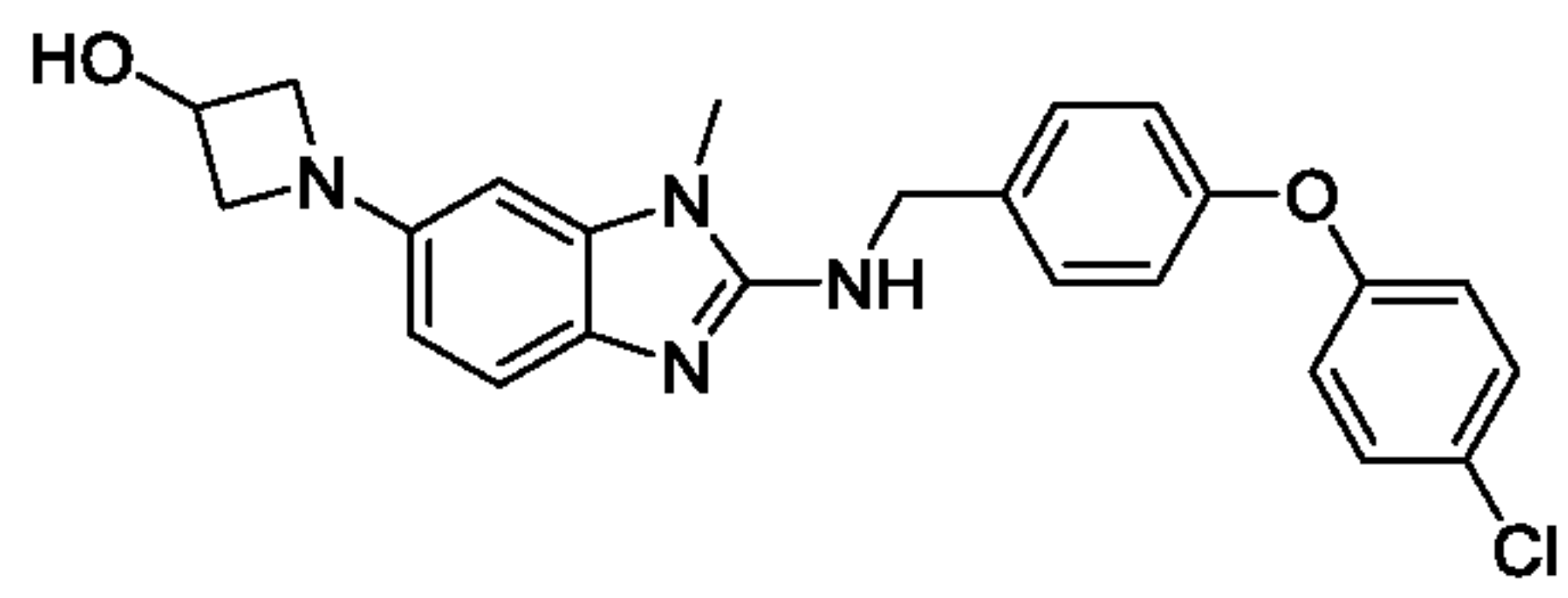
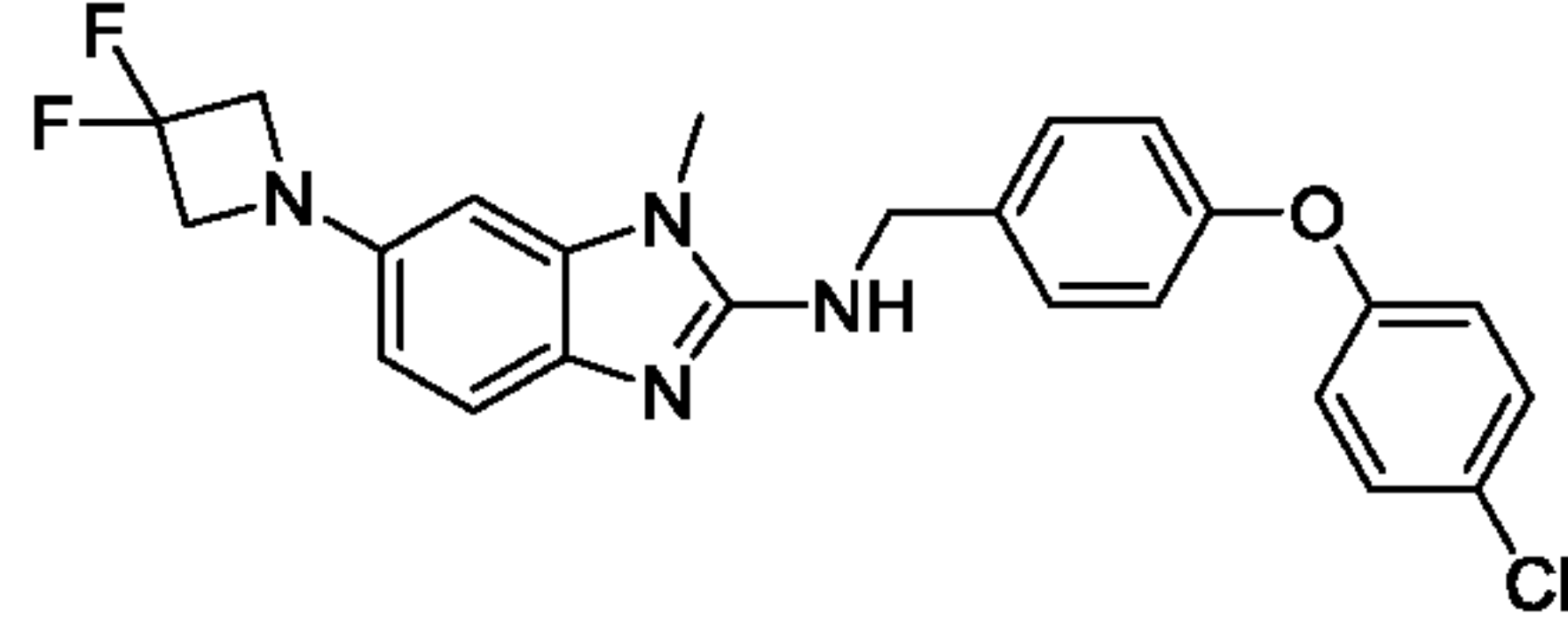
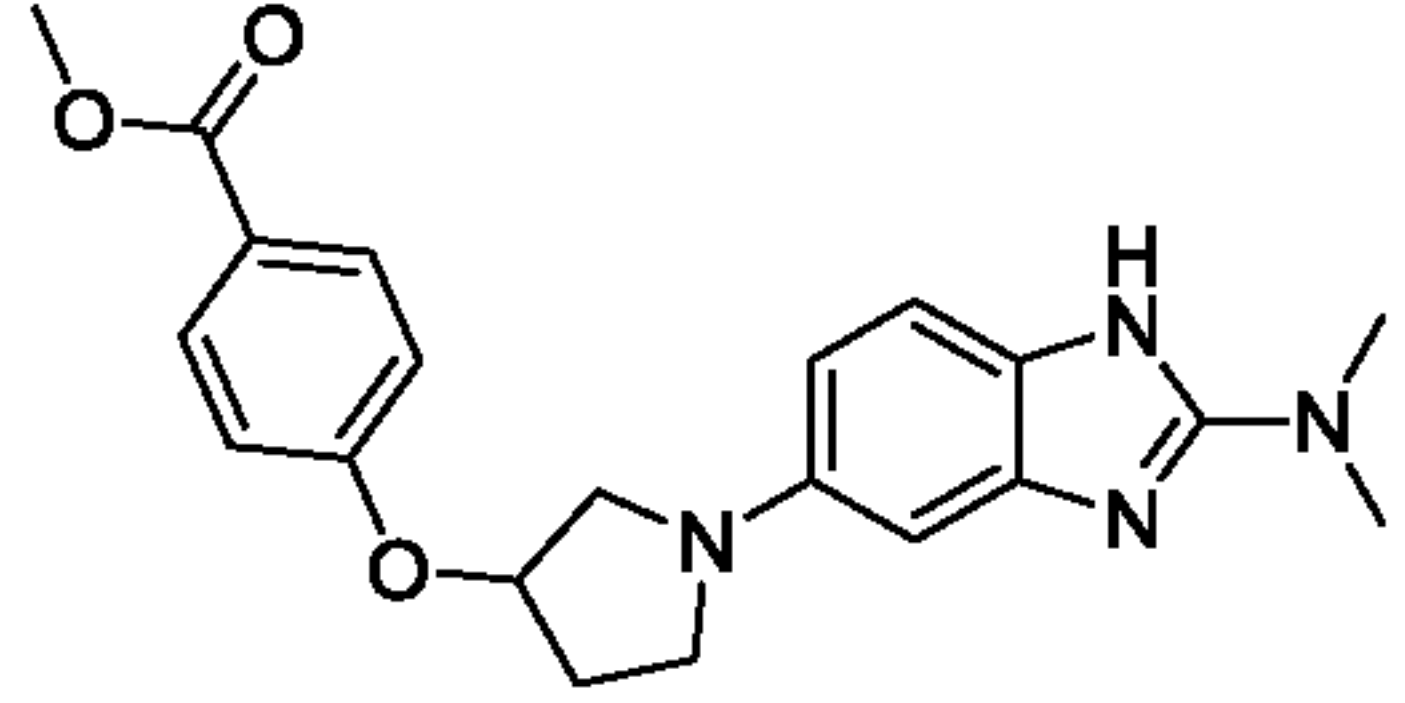
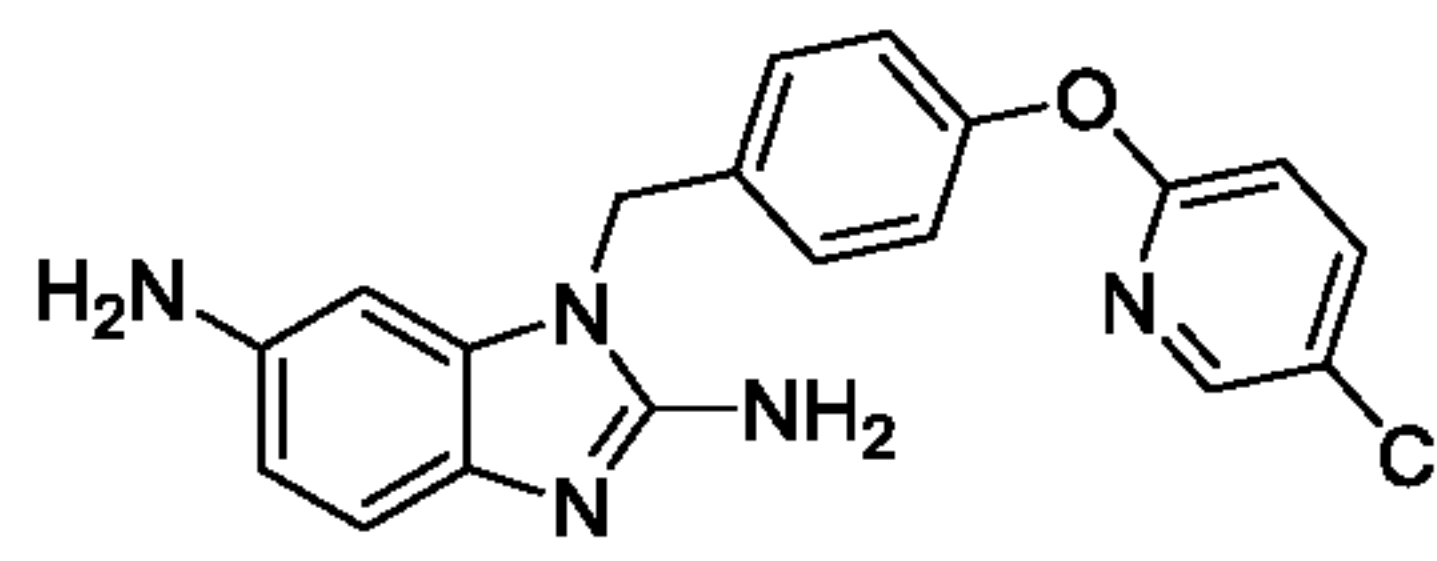
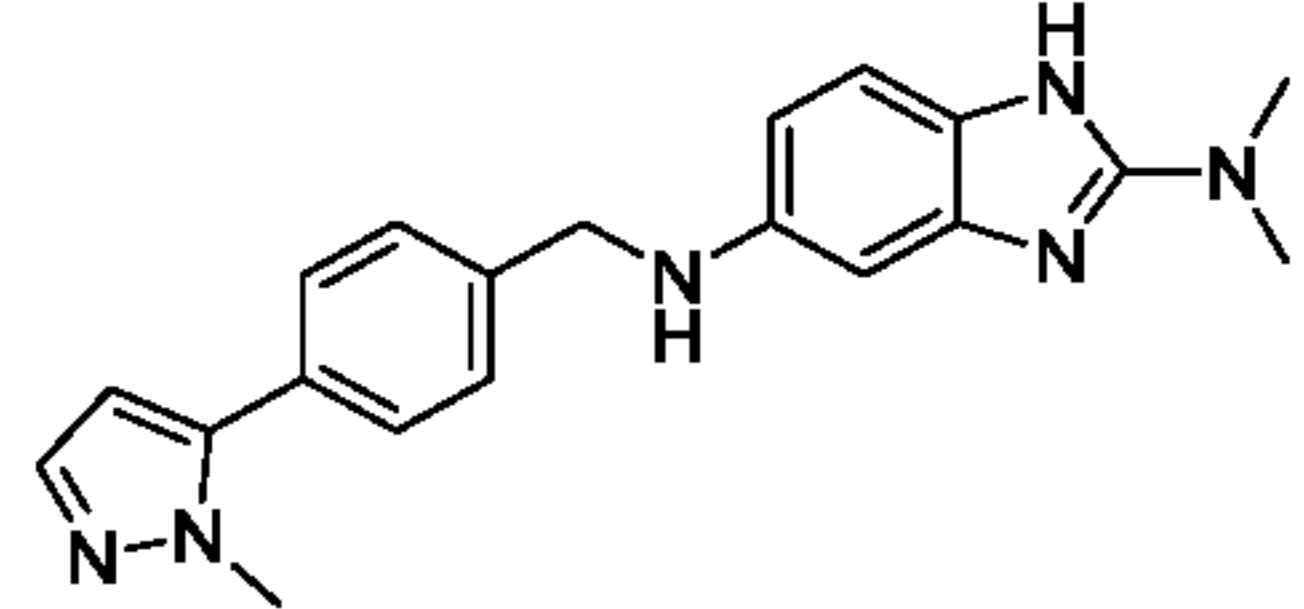
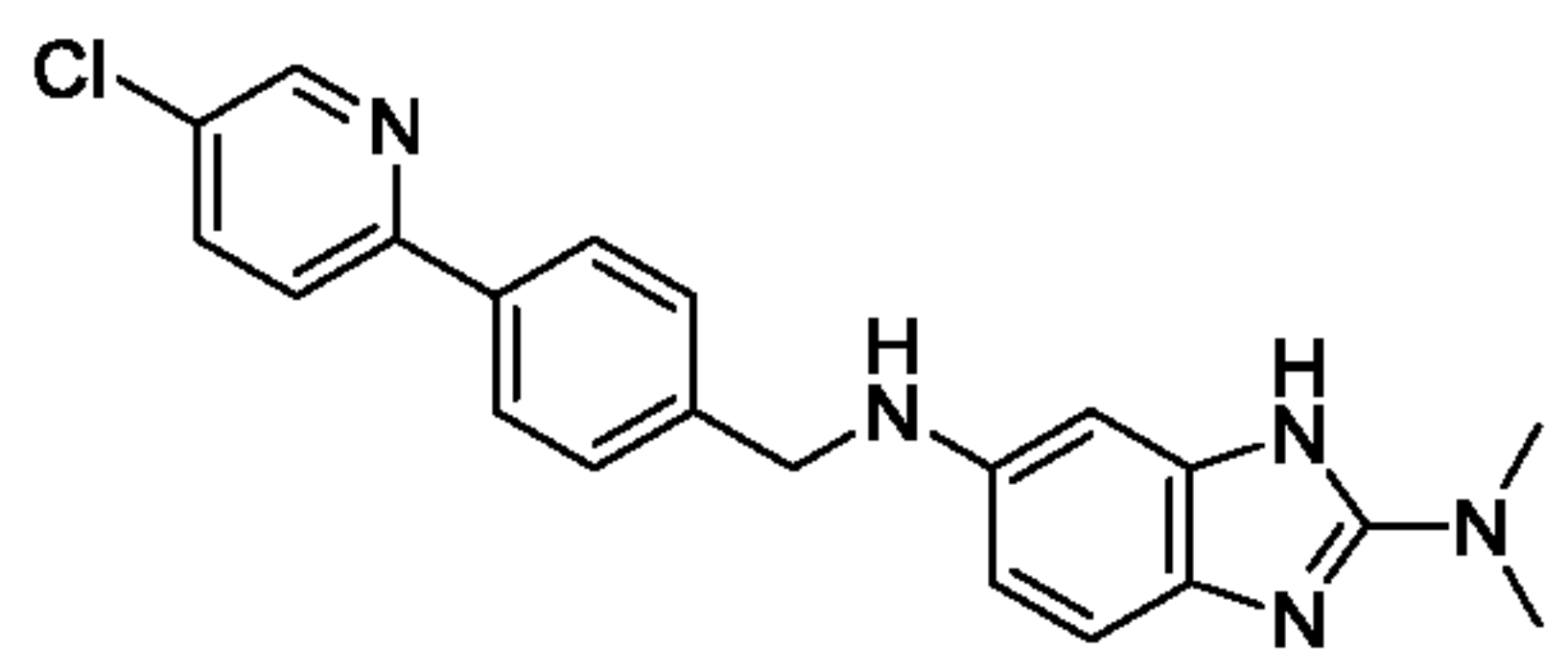
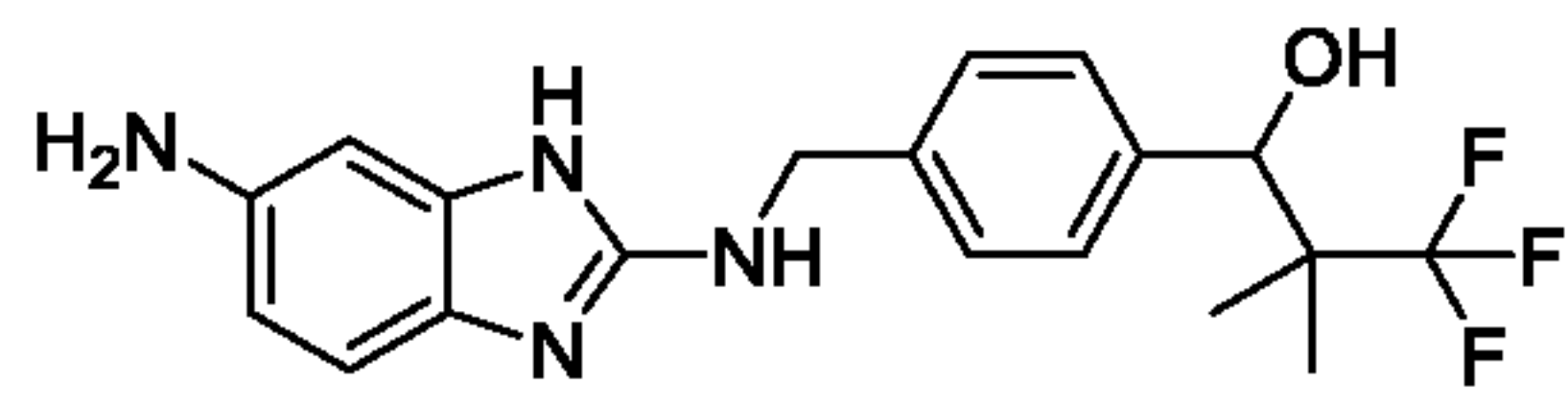
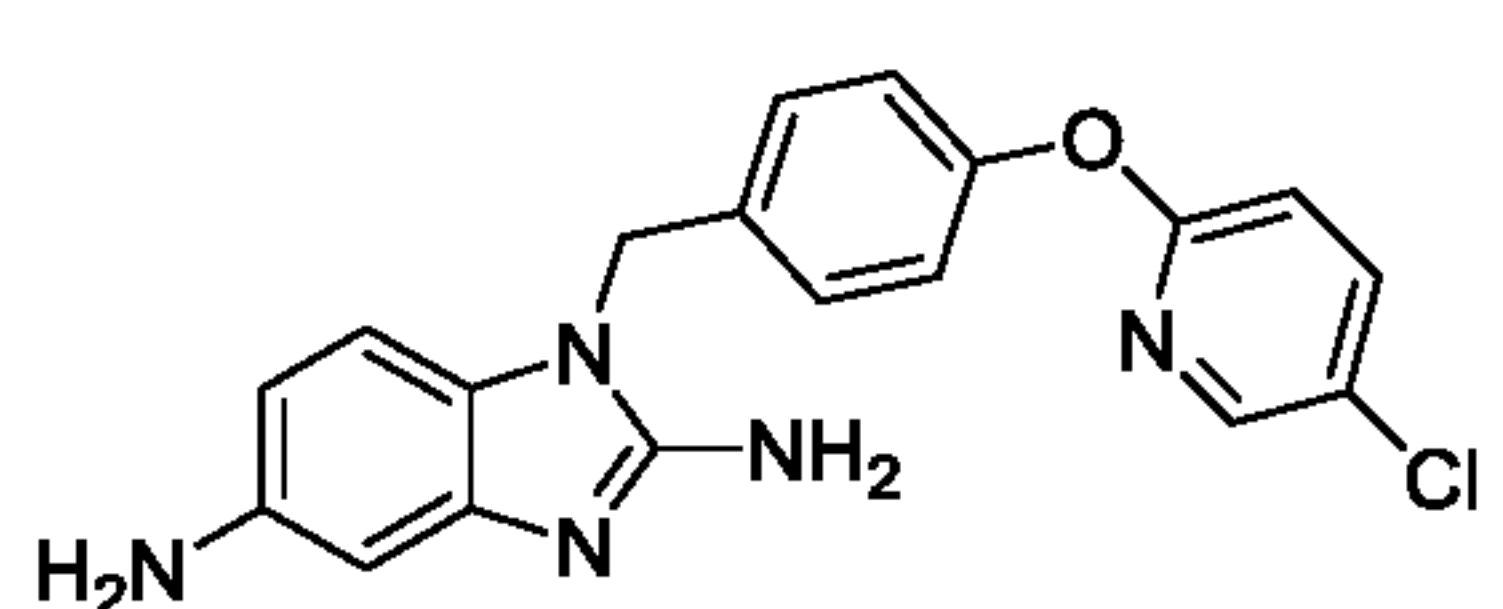
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 143 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.43 (1H, m), 7.29 (2H, d, <i>J</i> = 8.8 Hz), 7.04 (2H, d, <i>J</i> = 9.2 Hz), 6.86-6.99 (1H, m), 6.34-6.45 (1H, m), 5.95-6.25 (2H, m), 5.10-5.20 (1H, m), 3.60-3.69 (1H, m), 3.47-3.58 (4H, m), 3.30-3.37 (2H, m), 3.20-3.29 (2H, m), 2.53-2.61 (2H, m), 2.43-2.49 (2H, m), 2.28-2.40 (5H, m), 2.05-2.17 (1H, m); LCMS: 100 %, MS (ESI); <i>m/z</i> 492.1[M+ H] <sup>+</sup> .                |
| 144 |    | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.53 (1H, d, <i>J</i> = 2.0 Hz), 7.33 (1H, d, <i>J</i> = 8.0 Hz), 7.15-7.28 (4H, m), 7.04 (2H, d, <i>J</i> = 7.6 Hz), 6.64 (1H, d, <i>J</i> = 8.0 Hz), 6.37-6.50 (2H, m), 6.05-6.15 (2H, m), 5.00-5.20 (2H, m), 4.40 (2H, brs), 4.15-4.29 (1H, m), 2.88-3.04 (2H, m), 1.23 (3H, d, <i>J</i> = 6.8 Hz); LCMS: 98.1 %, MS (ESI); <i>m/z</i> 425.1[M+ H] <sup>+</sup> .                          |
| 145 |   | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.62 (1H, brs), 7.35-7.45 (2H, m), 7.25 (1H, d, <i>J</i> = 8.8 Hz), 6.90-7.10 (4H, m), 6.78 (1H, d, <i>J</i> = 8.4 Hz), 6.40 (1H, s), 6.19 (1H, d, <i>J</i> = 6.4 Hz), 5.07 (1H, d, <i>J</i> = 8.0 Hz), 4.45 (2H, brs), 3.65-3.75 (1H, m), 3.40-3.55 (1H, m), 2.30-2.40 (1H, m), 1.75-2.00 (3H, m); LCMS: 97.0%, MS (ESI); <i>m/z</i> 405.1[M+ H] <sup>+</sup> .                                      |
| 146 |  | gray powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.20-10.40 (1H, m), 7.30-7.45 (4H, m), 6.90-7.10 (4H, m), 6.60-6.75 (2H, m), 6.45-6.55 (1H, m), 4.41 (2H, d, <i>J</i> = 6.0 Hz), 4.00-4.30 (2H, m), 3.70 (3H, s); LCMS: 99.5%, MS (ESI); <i>m/z</i> 394.9[M+ H] <sup>+</sup> .                                                                                                                                                                         |
| 147 |  | off-white solid; mp = 191.4 C - 193.5 C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35-10.60 (1H, m), 7.35-7.45 (4H, m), 6.90-7.05 (6H, m), 6.63 (1H, s), 4.52-4.70 (2H, m), 4.40-4.45 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 399.0 [M+ H] <sup>+</sup> .                                                                                                                                                                                                 |
| 148 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.15-10.35 (1H, m), 7.28 (2H, d, <i>J</i> = 8.8 Hz), 7.04 (2H, d, <i>J</i> = 9.2 Hz), 6.86-6.98 (1H, m), 6.32-6.44 (1H, m), 6.12-6.26 (1H, m), 5.08-5.18 (1H, m), 3.60-3.70 (3H, m), 3.51-3.59 (2H, m), 3.36-3.41 (2H, m), 3.30-3.35 (1H, m), 3.21-3.29 (4H, m), 2.27-2.36 (1H, m), 2.05-2.18 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 437.2[M+ H] <sup>+</sup> .                                    |
| 149 |  | pink amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.29-10.47 (1H, m), 8.51 (1H, d, <i>J</i> = 4.0 Hz), 7.70 (1H, t, <i>J</i> = 8.0 Hz), 7.29-7.47 (5H, m), 7.22 (1H, t, <i>J</i> = 6.0 Hz), 6.92-7.06 (4H, m), 6.65-6.90 (2H, m), 6.34 (1H, s), 6.15 - 6.31 (1H, m), 5.60-5.86 (1H, m), 4.41 (2H, t, <i>J</i> = 6.8 Hz), 4.30 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 99.5%, MS (ESI); <i>m/z</i> 456.1 [M+H] <sup>+</sup> .                                |
| 150 |  | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.60-10.85 (1H, m), 8.15 (1H, d, <i>J</i> = 2.0 Hz), 7.87 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.38 (2H, d, <i>J</i> = 8.4 Hz), 7.22 (2H, d, <i>J</i> = 9.2 Hz), 7.01 (1H, d, <i>J</i> = 8.8 Hz), 6.75-6.94 (1H, m), 6.18-6.40 (2H, m), 5.46-5.69 (1H, m), 4.41-4.55 (1H, m), 2.90-2.95 (6H, m), 1.42 (3H, d, <i>J</i> = 6.4 Hz); LCMS: 97.6 %, MS (ESI); <i>m/z</i> 458.1[M+ H] <sup>+</sup> . |
| 151 |  | grey powder; mp > 200°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.56 (1H, s), 6.83 (2H, d, <i>J</i> = 8.4 Hz), 6.61 (2H, d, <i>J</i> = 8.4 Hz), 6.39 (2H, d, <i>J</i> = 8.8 Hz), 6.21 (2H, d, <i>J</i> = 8.8 Hz), 5.97 (1H, brs), 5.90 (1H, d, <i>J</i> = 8.0 Hz), 5.53 (1H, d, <i>J</i> = 2.0 Hz), 5.32 (1H, d, <i>J</i> = 8.0 Hz), 3.62 (4H, d, <i>J</i> = 6.0 Hz); LCMS: 97.1 %, MS (ESI); <i>m/z</i> 428.1[M+ H] <sup>+</sup> .                         |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| 152 |    | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.60-10.85 (1H, m), 8.19 (1H, s), 7.93 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.42 (2H, d, <i>J</i> = 8.8 Hz), 7.00-7.10 (3H, m), 6.75-6.90 (1H, m), 6.19-6.36 (2H, m), 5.46-5.67 (1H, m), 4.36-4.50 (1H, m), 2.90-2.95 (6H, m), 1.42 (3H, d, <i>J</i> = 5.2 Hz); LCMS: 99.2 %, MS (ESI); <i>m/z</i> 408.1[M+ H] <sup>+</sup> .                                                                |
| 153 |    | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 8.12-8.23 (1H, m), 7.79 (1H, s), 7.71-7.77 (1H, m), 7.64-7.71 (1H, m), 6.98 (1H, d, <i>J</i> = 8.8 Hz), 6.89 (1H, brs), 6.79 (1H, d, <i>J</i> = 8.0 Hz), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, dd, <i>J</i> = 8.0 Hz, 2.0 Hz), 4.59 (2H, d, <i>J</i> = 5.6 Hz), 3.96 (3H, s); LCMS: 93%, MS (ESI); <i>m/z</i> 319.9[M+ H] <sup>+</sup> .                                                            |
| 154 |    | grey amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.33-10.54 (1H, m), 8.60 (1H, d, <i>J</i> = 4.8 Hz), 7.40 (2H, d, <i>J</i> = 8.4 Hz), 7.22 (1H, t, <i>J</i> = 4.8 Hz), 7.10 (2H, d, <i>J</i> = 8.4 Hz), 6.70-6.94 (2H, m), 6.36-6.45 (1H, m), 6.11-6.22 (1H, m), 4.27-4.50 (4H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 333.1[M+ H] <sup>+</sup> .                                                                                                  |
| 155 |  | white solid; mp = 203.8-204.6°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.44 (1H, m), 7.19 (1H, d, <i>J</i> = 8.4 Hz), 6.90 -7.04 (4H, m), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.53 (1H, t, <i>J</i> = 5.2 Hz), 6.30 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.10 (2H, s), 5.02 (1H, brs), 4.51 (2H, brs), 3.50-3.60 (2H, m), 3.34-3.38 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 409.0[M+H] <sup>+</sup> .                 |
| 156 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.30 (1H, d, <i>J</i> = 8.8 Hz), 8.08 (1H, d, <i>J</i> = 2.0 Hz), 7.99 (1H, d, <i>J</i> = 9.2 Hz), 7.75 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.60 (1H, d, <i>J</i> = 8.4 Hz), 6.97 (1H, brs), 6.79 (1H, d, <i>J</i> = 8.0 Hz), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, d, <i>J</i> = 6.4 Hz), 4.72 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 93.1%, MS (ESI); <i>m/z</i> 323.9 [M+ H] <sup>+</sup> . |
| 157 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (2H, d, <i>J</i> = 8.0 Hz), 7.08 (1H, d, <i>J</i> = 8.4 Hz), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.41 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.77 (2H, brs), 3.50-3.60 (2H, m), 3.48 (3H, s), 2.88-3.01 (2H, m), 2.73-2.85 (1H, m), 1.80-1.95 (4H, m); LCMS: 100 %, MS (ESI); <i>m/z</i> 390.9[M+ H] <sup>+</sup> .                                                |
| 158 |  | off-white powder; mp = 101.8-104.0°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.49 (1H, brs), 8.56 (1H, d, <i>J</i> = 2.0 Hz), 7.87 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.40 (1H, d, <i>J</i> = 8.0 Hz), 6.85 (1H, brs), 6.79 (1H, d, <i>J</i> = 8.4 Hz), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.19 (1H, d, <i>J</i> = 7.2 Hz), 4.54 (2H, d, <i>J</i> = 6.0 Hz), 4.42 (2H, brs); LCMS: 99.2%, MS (ESI); <i>m/z</i> 273.9[M+ H] <sup>+</sup> .                  |
| 159 |  | green solid; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.84-8.86 (1H, m), 8.33 (1H, d, <i>J</i> = 8.4 Hz), 7.91-8.00 (2H, m), 7.61-7.64 (1H, m), 7.49 (1H, dd, <i>J</i> = 8.0, 4.0 Hz), 7.13 (1H, brs), 6.81 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.68 (2H, d, <i>J</i> = 6.0 Hz); LCMS: 93.2 %, MS (ESI); <i>m/z</i> 290.3[M + H] <sup>+</sup> .                                            |
| 160 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.64-10.85 (1H, m), 8.25 (1H, d, <i>J</i> = 2.4 Hz), 7.81 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.76-6.86 (1H, m), 6.44 (1H, d, <i>J</i> = 1.6 Hz), 6.14-6.28 (1H, m), 5.50-5.56 (1H, m), 4.30-4.57 (2H, m), 3.70-3.81 (1H, m), 3.49-3.67 (3H, m), 2.26-2.37 (1H, m), 2.10-2.24 (1H, m); LCMS: 96.8%, MS (ESI); <i>m/z</i> 329.9[M+H] <sup>+</sup> .           |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 161 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40 (2H, d, <i>J</i> = 8.8 Hz), 7.16 (2H, d, <i>J</i> = 8.8 Hz), 6.93-7.05 (4H, m), 6.89 (1H, d, <i>J</i> = 8.0 Hz), 6.22-6.30 (2H, m), 6.19 (1H, d, <i>J</i> = 6.8 Hz), 5.12 (2H, s), 4.47 (2H, brs), 4.06-4.19 (1H, m), 1.91-1.94 (2H, m), 1.48-1.56 (2H, m), 1.56-1.66 (4H, m); LCMS: 98.4%, MS (ESI); <i>m/z</i> 433.0[M+H] <sup>+</sup> .                                                  |
| 162 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 6.71-6.81 (2H, m), 6.69 (1H, brs), 6.35-6.45 (3H, m), 6.20 (1H, d, <i>J</i> = 8.4 Hz), 5.58 (1H, brs), 4.25 (2H, d, <i>J</i> = 6.0 Hz), 3.09-3.18 (2H, m), 2.55-2.65 (2H, m), 1.65-1.80 (2H, m); LCMS: 96.9 %, MS (ESI); <i>m/z</i> 293.9[M + H] <sup>+</sup> .                                                                                                                                     |
| 163 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.32 (2H, d, <i>J</i> = 8.8 Hz), 7.01 (1H, d, <i>J</i> = 8.4 Hz), 7.00 (2H, d, <i>J</i> = 8.8 Hz), 6.50 (1H, s), 6.40 (1H, d, <i>J</i> = 8.4 Hz), 4.73 (2H, brs), 3.90 (2H, d, <i>J</i> = 6.0 Hz), 3.40-3.50 (5H, m), 2.80-2.87 (2H, m), 1.94-2.00 (1H, m), 1.80-1.88 (2H, m), 1.46-1.55 (2H, m); LCMS: 95%, MS (ESI); <i>m/z</i> 370.9[M+H] <sup>+</sup> .                                      |
| 164 |  | grey amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.40 (1H, m), 8.68 (1H, d, <i>J</i> = 1.2 Hz), 8.02 (2H, d, <i>J</i> = 8.4 Hz), 7.98 (2H, d, <i>J</i> = 1.6 Hz), 7.47 (2H, d, <i>J</i> = 8.0 Hz), 6.70-6.91 (2H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.10-6.22 (1H, m), 4.49 (2H, d, <i>J</i> = 6.0 Hz), 4.30-4.45 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 349.9 [M+ H] <sup>+</sup> .                                                  |
| 165 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.45 (2H, m), 7.20 (2H, d, <i>J</i> = 8.4 Hz), 6.94-7.04 (4H, m), 6.87 (1H, d, <i>J</i> = 8.3 Hz), 6.51 (1H, brs), 6.33 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.15 (2H, s), 3.27-3.30 (2H, m), 1.08 (6H, s); LCMS: 97.8%, MS (ESI); <i>m/z</i> 437.0[M+H] <sup>+</sup> .                                                                                    |
| 166 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.30-10.50 (1H, m), 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.92 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.38 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.09 (3H, m), 6.75-6.95 (2H, m), 6.24 (1H, d, <i>J</i> = 4.8 Hz), 6.08-6.20 (1H, m), 5.60-5.78 (1H, m), 4.81 (2H, t, <i>J</i> = 6.4 Hz), 4.35-4.50 (5H, m); LCMS: 98.13%, MS (ESI); <i>m/z</i> 422.0 [M+H] <sup>+</sup> .                                 |
| 167 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.44 (4H, m), 6.93-7.05 (4H, m), 6.86 (2H, d, <i>J</i> = 8.4 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.57 (2H, brs), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.40 (3H, s); LCMS: 97.8%, MS (ESI); <i>m/z</i> 378.9[M+H] <sup>+</sup> .                                                                                                                     |
| 168 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.93 (1H, d, <i>J</i> = 8.4 Hz), 7.48 (1H, d, <i>J</i> = 8.4 Hz), 7.14 (1H, brs), 6.81 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.53 (2H, s), 3.73-3.84 (1H, m), 1.79-1.93 (2H, m), 1.65-1.77 (2H, m), 1.59 (4H, m); LCMS: 94%, MS (ESI); <i>m/z</i> 335.1[M+ H] <sup>+</sup> .                                                   |
| 169 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.44 (2H, d, <i>J</i> = 7.2 Hz), 7.38 (2H, t, <i>J</i> = 7.6 Hz), 7.25-7.34 (1H, m), 7.23 (2H, d, <i>J</i> = 8.8 Hz), 6.93 (2H, d, <i>J</i> = 8.8 Hz), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.52 (1H, brs), 6.45 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.54 (1H, t, <i>J</i> = 6.0 Hz), 3.59-3.70 (2H, m); LCMS: 97.4%, MS (ESI); <i>m/z</i> 378.9[M+H] <sup>+</sup> . |
| 170 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.38-7.45 (4H, m), 7.28 (1H, brs), 7.09 (1H, brs), 6.96-7.02 (4H, m), 6.88-6.96 (2H, m), 6.33 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.37 (1H, t, <i>J</i> = 6.0 Hz), 4.50 (2H, d, <i>J</i> = 5.6 Hz), 3.57 (2H, d, <i>J</i> = 5.6 Hz), 3.42 (3H, s); LCMS: 95.5%, MS (ESI); <i>m/z</i> 435.9[M+H] <sup>+</sup> .                                                    |

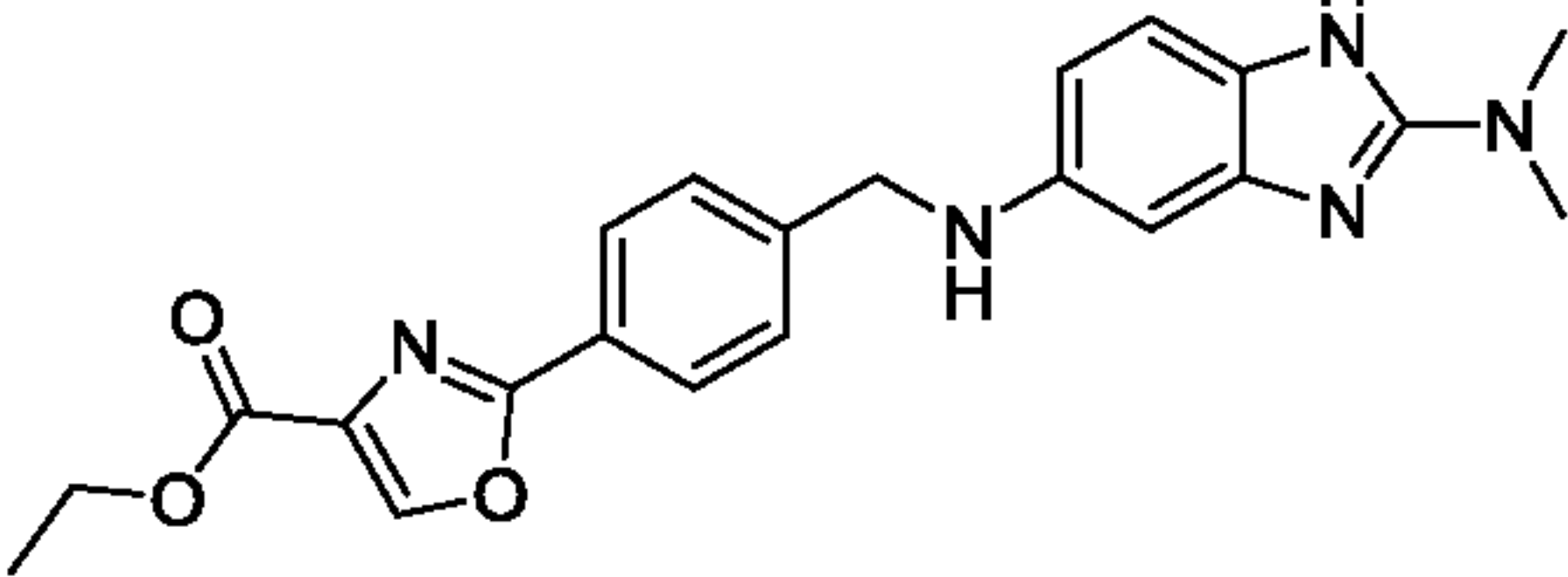
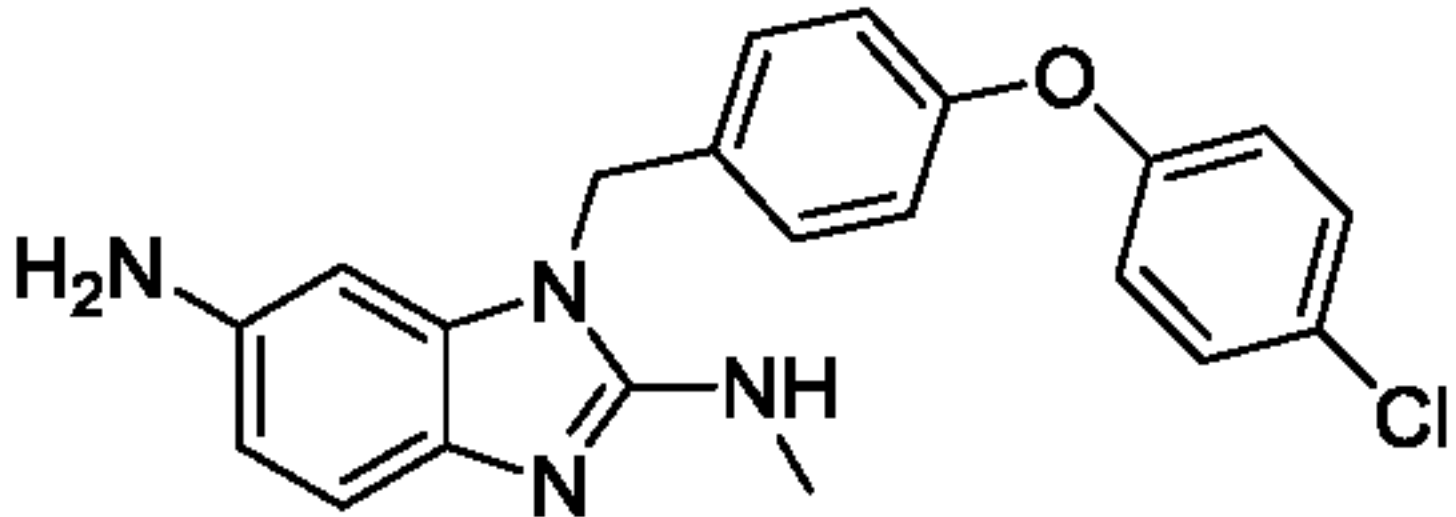
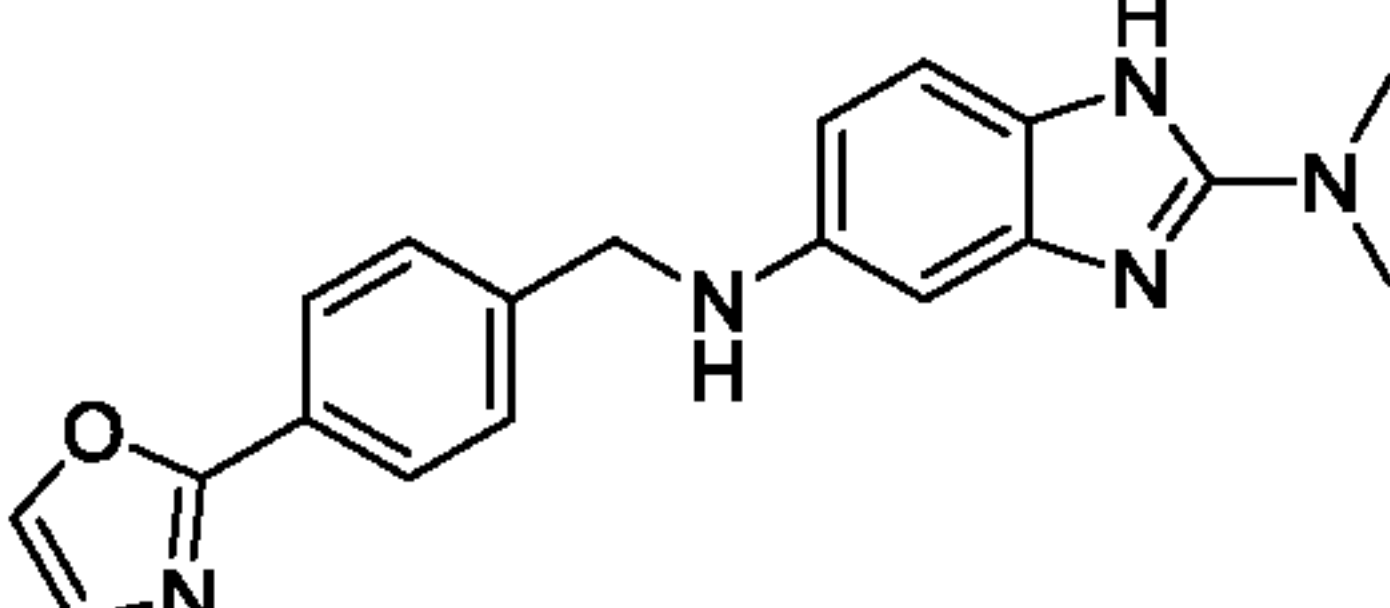
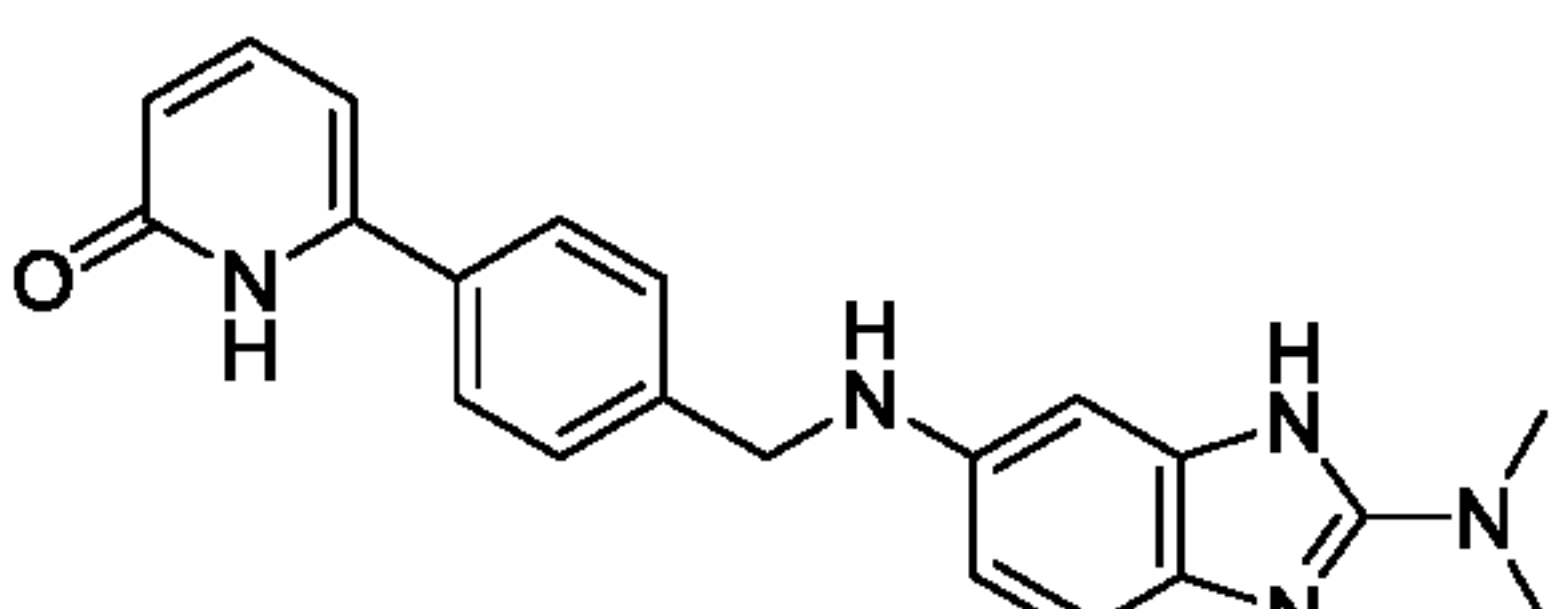
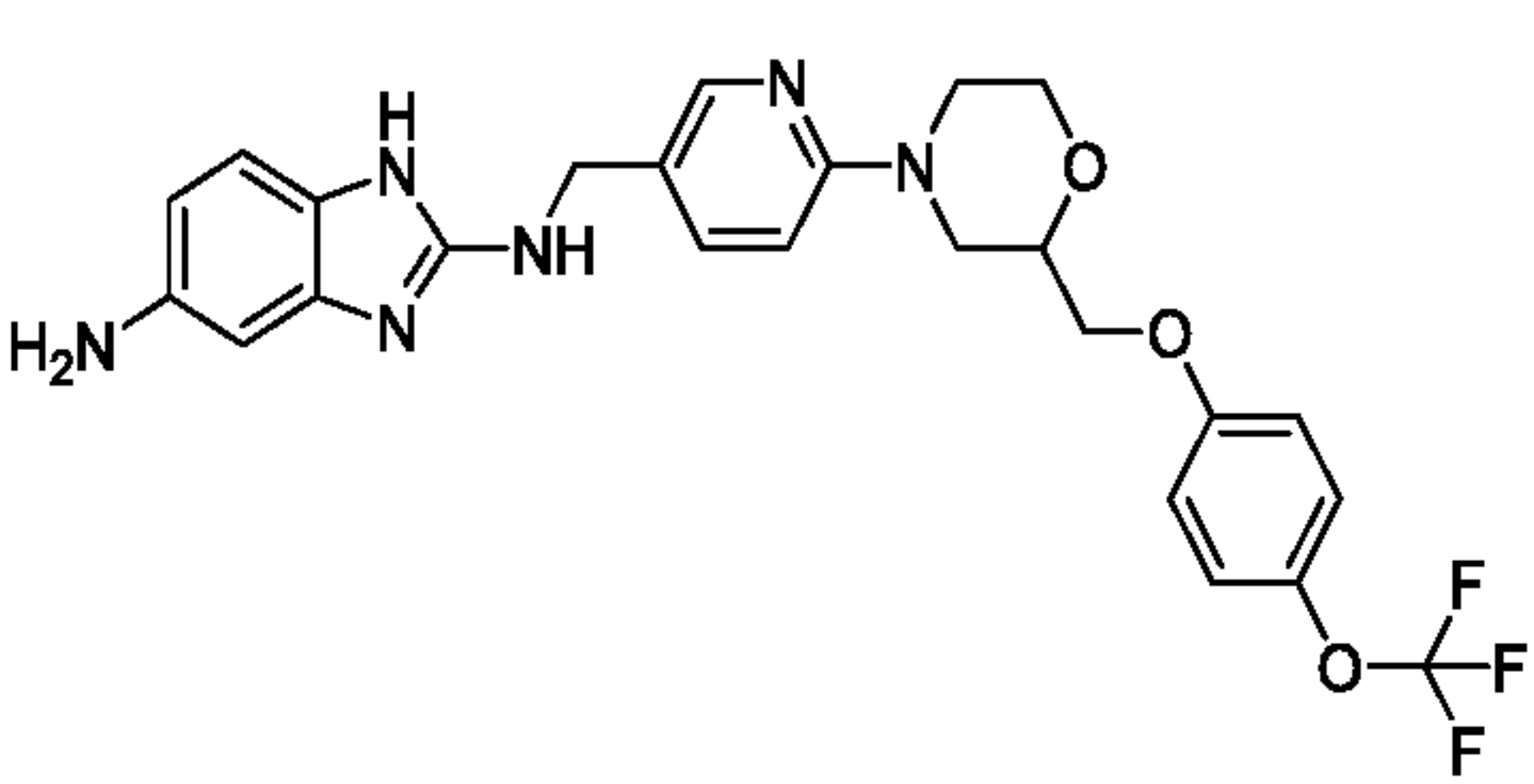
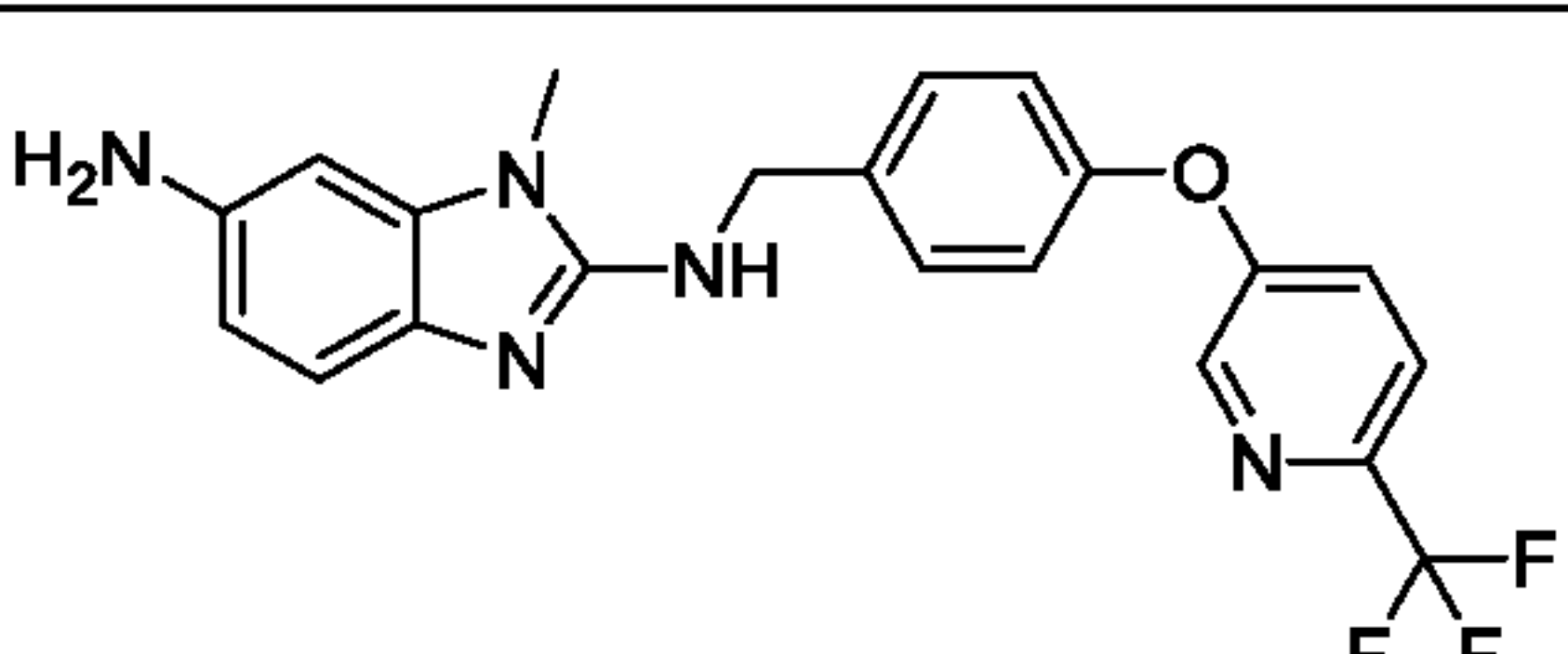
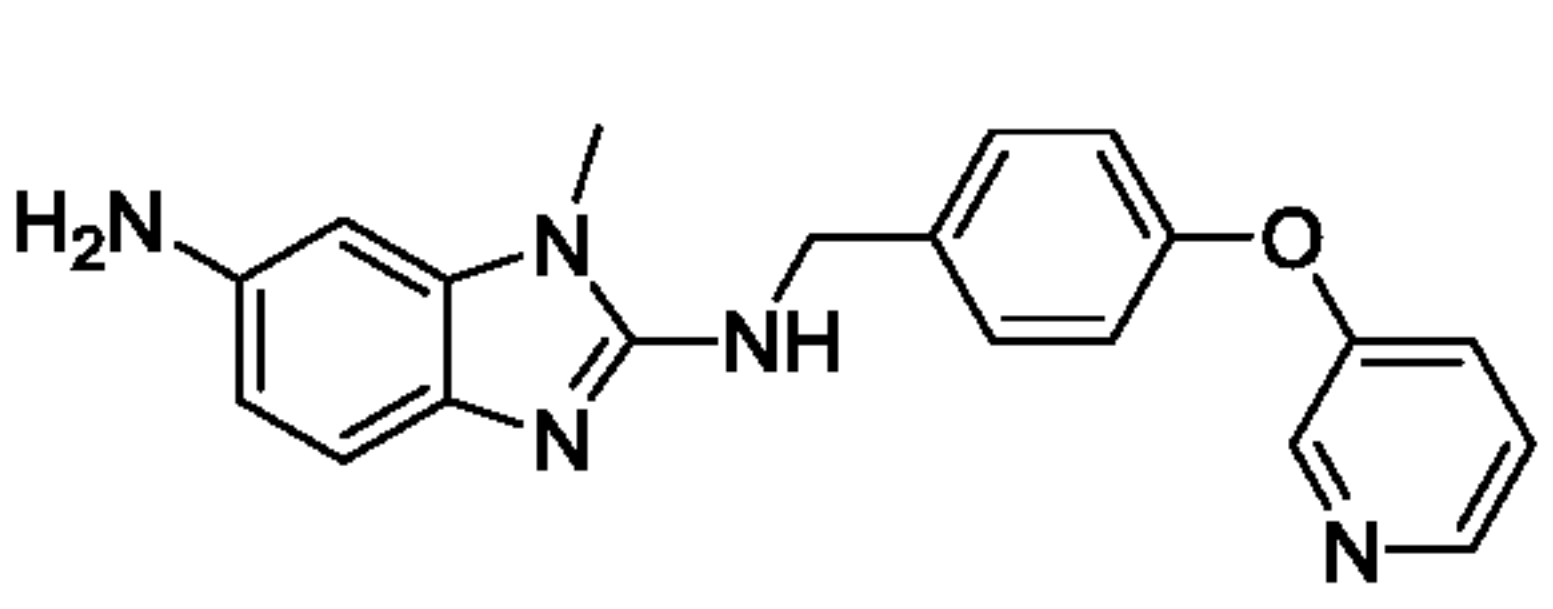
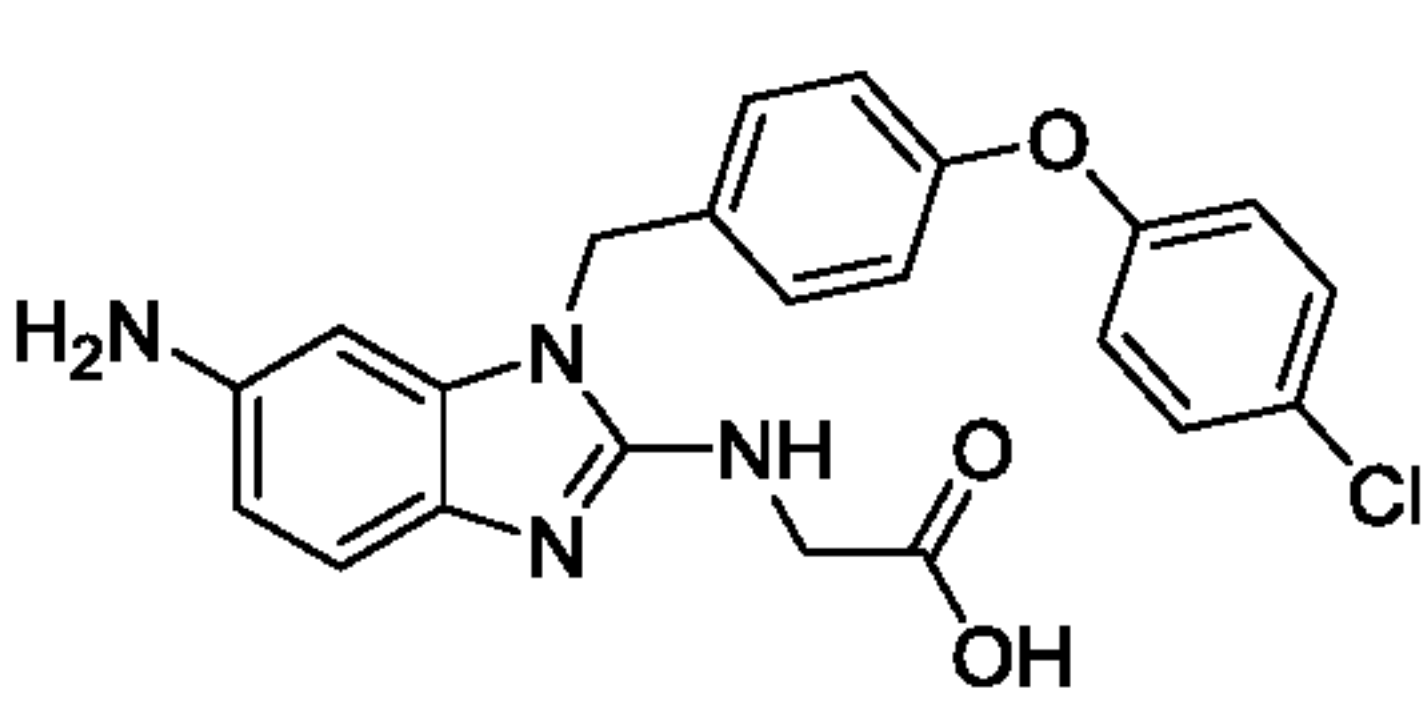
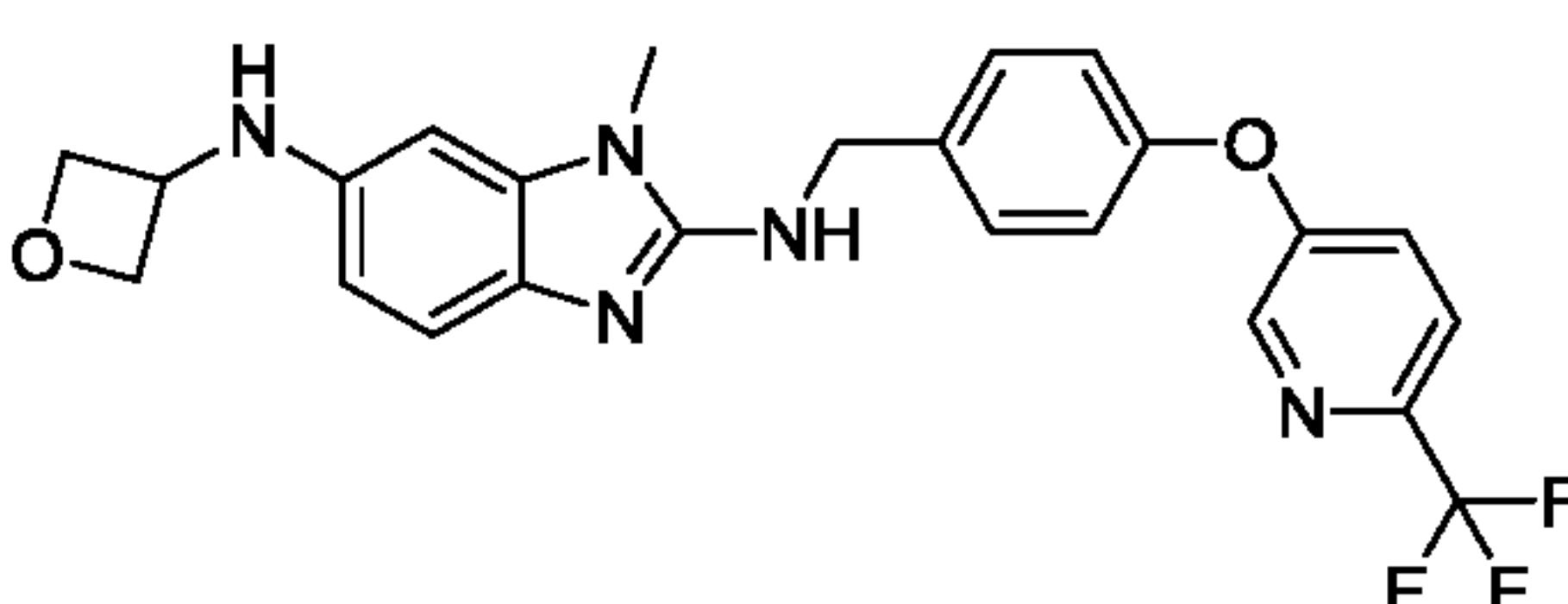
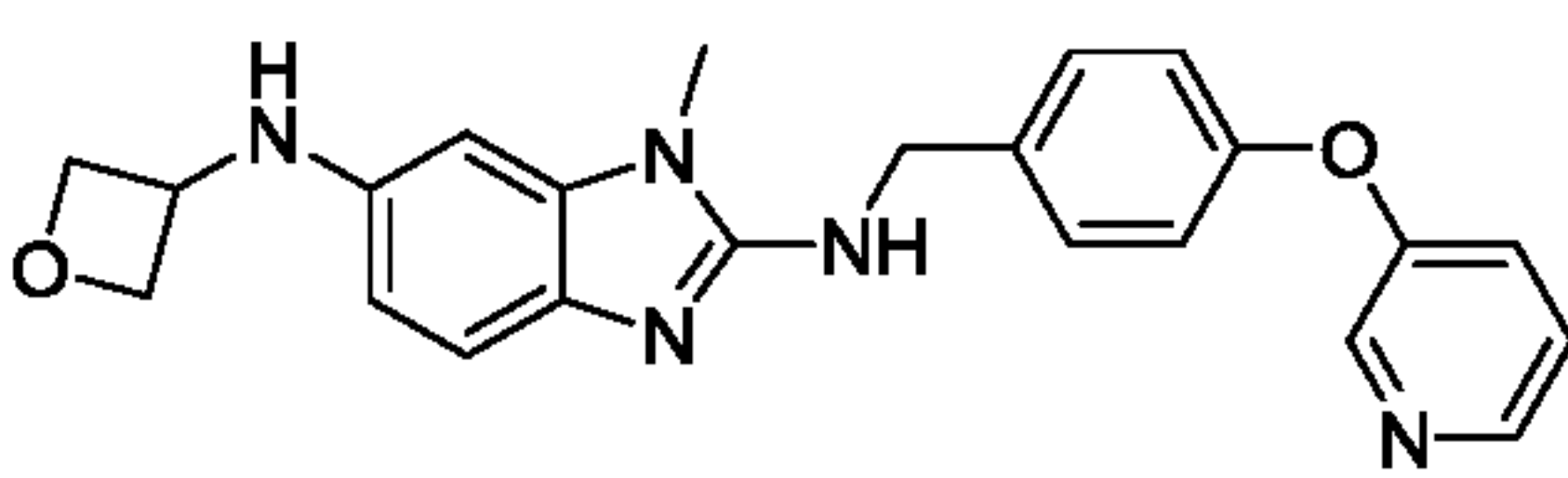
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 171 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.46 (4H, m), 6.95-7.04 (6H, m), 6.58 (1H, d, <i>J</i> = 2.0 Hz), 6.41 (1H, dd, <i>J</i> = 8.4, 2.1 Hz), 5.74 (1H, t, <i>J</i> = 7.2 Hz), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 4.21 (2H, d, <i>J</i> = 7.2 Hz), 3.47 (3H, s); LCMS: 96.6%, MS (ESI); <i>m/z</i> 418.0[M+H] <sup>+</sup> .                                                                                                                                                                   |
| 172 |  | grey powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.27 (2H, d, <i>J</i> = 8.4 Hz), 6.87 (2H, d, <i>J</i> = 8.4 Hz), 6.77 (1H, d, <i>J</i> = 8.4 Hz), 6.66 (1H, brs), 6.40 (1H, d, <i>J</i> = 1.6 Hz), 6.17 (1H, d, <i>J</i> = 8.4 Hz), 4.62-4.78 (1H, m), 4.34 (2H, d, <i>J</i> = 6.4 Hz), 2.56-2.74 (2H, m), 1.28 (3H, d, <i>J</i> = 6.0 Hz); LCMS: 99.4 %, MS (ESI); <i>m/z</i> 364.9[M+ H] <sup>+</sup> .                                                                                         |
| 173 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.32-10.50 (1H, m), 8.16 (2H, d, <i>J</i> = 8.4 Hz), 7.56 (1H, s), 7.47 (2H, d, <i>J</i> = 8.0 Hz), 7.17 (1H, s), 6.88-6.98 (0.5H, m), 6.70-6.84 (1.5H, m), 6.40 (1H, s), 6.10-6.23 (1H, m), 4.25-4.60 (4H, m), 3.97 (3H, s); LCMS: 90%, MS (ESI); <i>m/z</i> 347.1[M+ H] <sup>+</sup> .                                                                                                                                                              |
| 174 |  | off-white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.11-7.39 (6H, m), 6.93 (1H, d, <i>J</i> = 7.6 Hz), 6.42 (1H, d, <i>J</i> = 1.6 Hz), 6.34 (1H, d, <i>J</i> = 8.4 Hz), 4.66-4.83 (3H, m), 3.72 (1H, t, <i>J</i> = 8.8 Hz), 3.36-3.43 (4H, m), 2.91 (2H, d, <i>J</i> = 6.4 Hz); LCMS: 97.0%, MS (ESI); <i>m/z</i> 352.0[M+H] <sup>+</sup> .                                                                                                                                                     |
| 175 |  | off-white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.03 (1H, s), 7.96 (2H, d, <i>J</i> = 8.4 Hz), 7.59 (2H, d, <i>J</i> = 8.4 Hz), 6.81 (1H, d, <i>J</i> = 8.0 Hz), 6.43 (1H, d, <i>J</i> = 1.6 Hz), 6.20 (1H, d, <i>J</i> = 7.6 Hz), 4.39 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 340.1 [M+H] <sup>+</sup> .                                                                                                                                                               |
| 176 |  | grey powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.50-9.62 (1H, m), 7.34-7.42 (3H, m), 7.31 (1H, s), 7.07 (1H, d, <i>J</i> = 7.6 Hz), 6.97 (2H, d, <i>J</i> = 8.4 Hz), 4.56 (2H, d, <i>J</i> = 5.6 Hz), 4.18 (2H, t, <i>J</i> = 6.0 Hz), 2.67-2.85 (2H, m); LCMS: 100 %, MS (ESI); <i>m/z</i> 351.1[M+ H] <sup>+</sup> .                                                                                                                                                                            |
| 177 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.35-10.60 (1H, m), 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.92 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.39 (2H, d, <i>J</i> = 8.0 Hz), 7.14-7.25 (1H, m), 7.05-7.12 (3H, m), 6.77 -6.97 (3H, m), 6.38 (1H, s), 6.15-6.33 (1H, m), 4.90-5.10 (1H, m), 4.40-4.70 (2H, m), 1.31 (6H, s); LCMS: 96.3%, MS (ESI); <i>m/z</i> 451.0 [M+ H] <sup>+</sup> .                                                                                                            |
| 178 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (2H, d, <i>J</i> = 8.8 Hz), 7.54 (2H, d, <i>J</i> = 8.0 Hz), 6.83 (1H, d, <i>J</i> = 8.4 Hz), 6.44 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (2H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.28-4.35 (1H, m), 3.70-3.79 (1H, m), 3.57-3.68 (1H, m), 3.45-3.51 (2H, m), 2.25-2.35 (1H, m), 2.08-2.20 (1H, m); LCMS: 99.5 %, MS (ESI); <i>m/z</i> 390.9[M+ H] <sup>+</sup> .                                                                                             |
| 179 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.60-10.89 (1H, m), 7.90 (2H, d, <i>J</i> = 8.0 Hz), 7.51 (2H, d, <i>J</i> = 8.0 Hz), 6.74-7.00 (1H, m), 6.14-6.45 (2H, m), 5.63-5.96 (1H, m), 4.31 (2H, d, <i>J</i> = 4.8 Hz), 3.83 (3H, s), 2.94 (3H, s), 2.93 (3H, s); LCMS: 99.3%, MS (ESI); <i>m/z</i> 324.9[M+ H] <sup>+</sup> .                                                                                                                                                               |
| 180 |  | off-white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.29 (1H, brs), 7.42 (2H, d, <i>J</i> = 7.2 Hz), 7.36 (2H, t, <i>J</i> = 7.6 Hz), 7.28 (1H, t, <i>J</i> = 7.2 Hz), 7.18-7.24 (2H, m), 6.83-6.95 (3H, m), 6.58 (1H, brs), 6.27 (1H, d, <i>J</i> = 1.6 Hz), 6.13 (1H, d, <i>J</i> = 8.0 Hz), 5.71 (1H, brs), 5.52 (1H, t, <i>J</i> = 6.4 Hz), 4.81 (2H, t, <i>J</i> = 6.0 Hz), 4.31-4.49 (3H, m), 3.63 (2H, t, <i>J</i> = 6.0 Hz); LCMS: 99.1%, MS (ESI); <i>m/z</i> 435.0[M+H] <sup>+</sup> . |

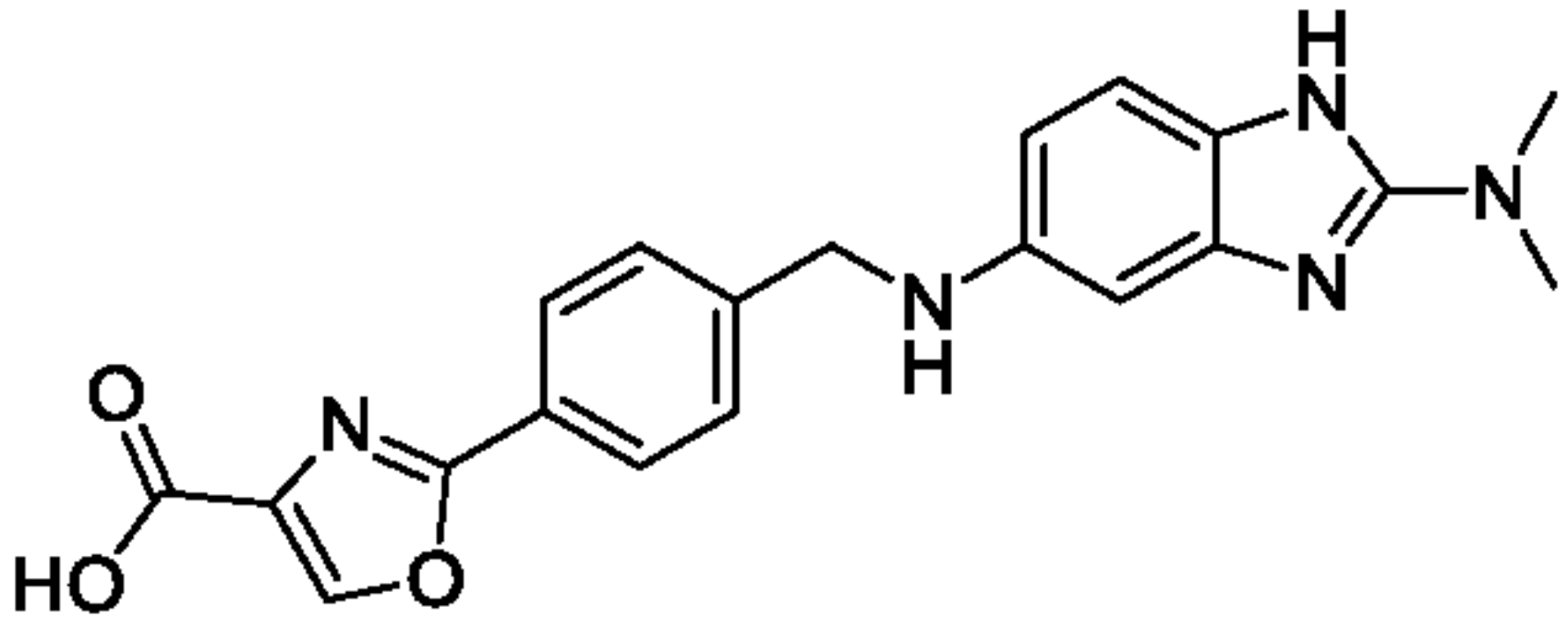
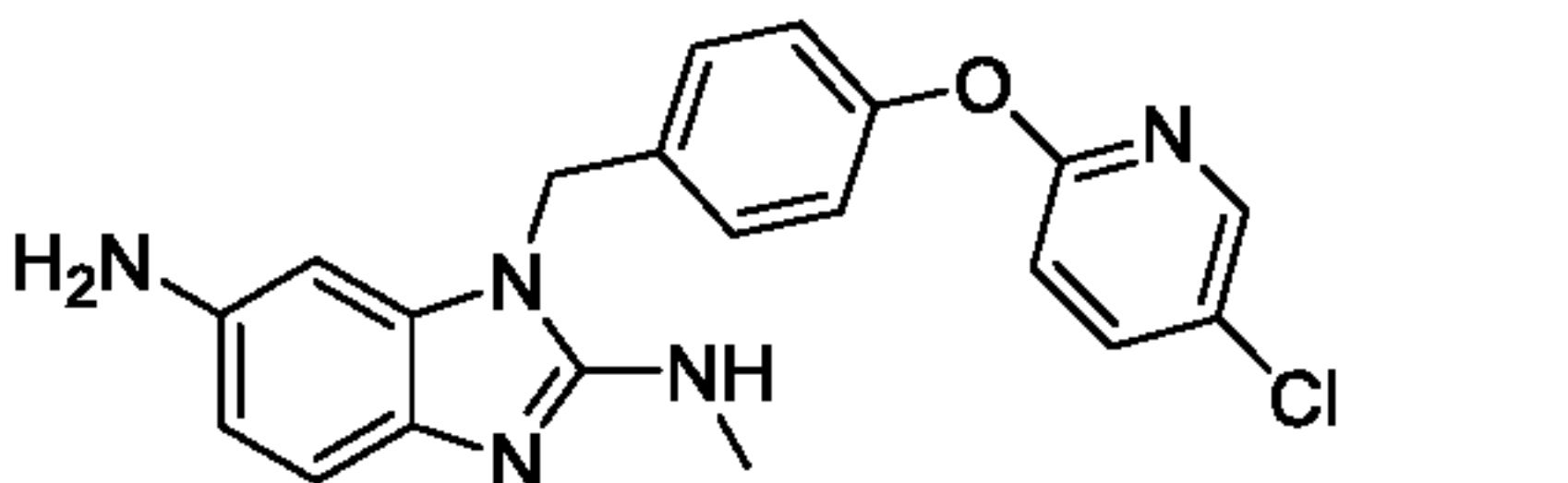
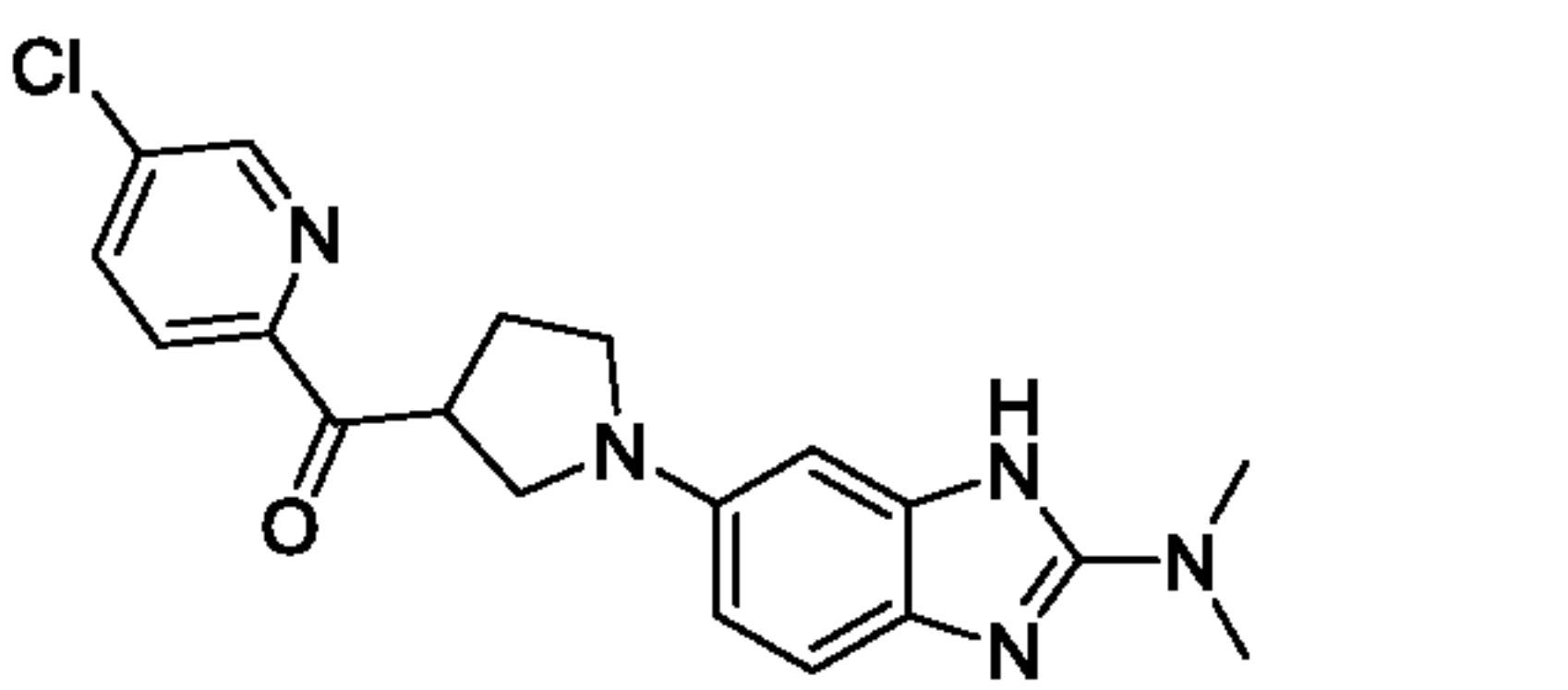
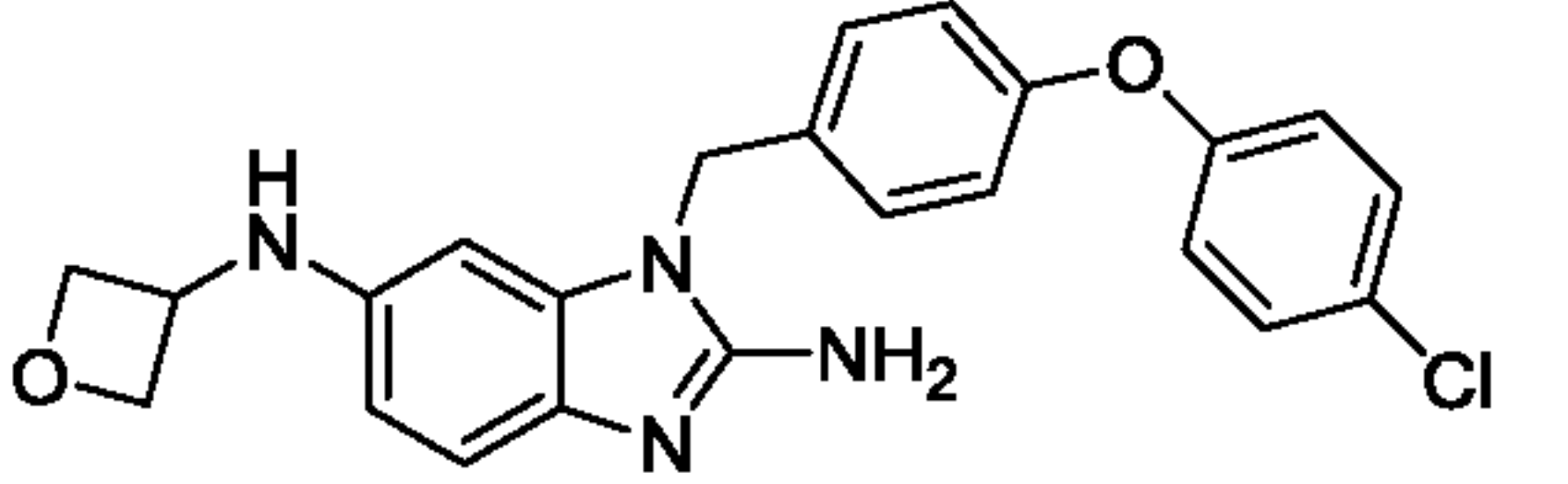
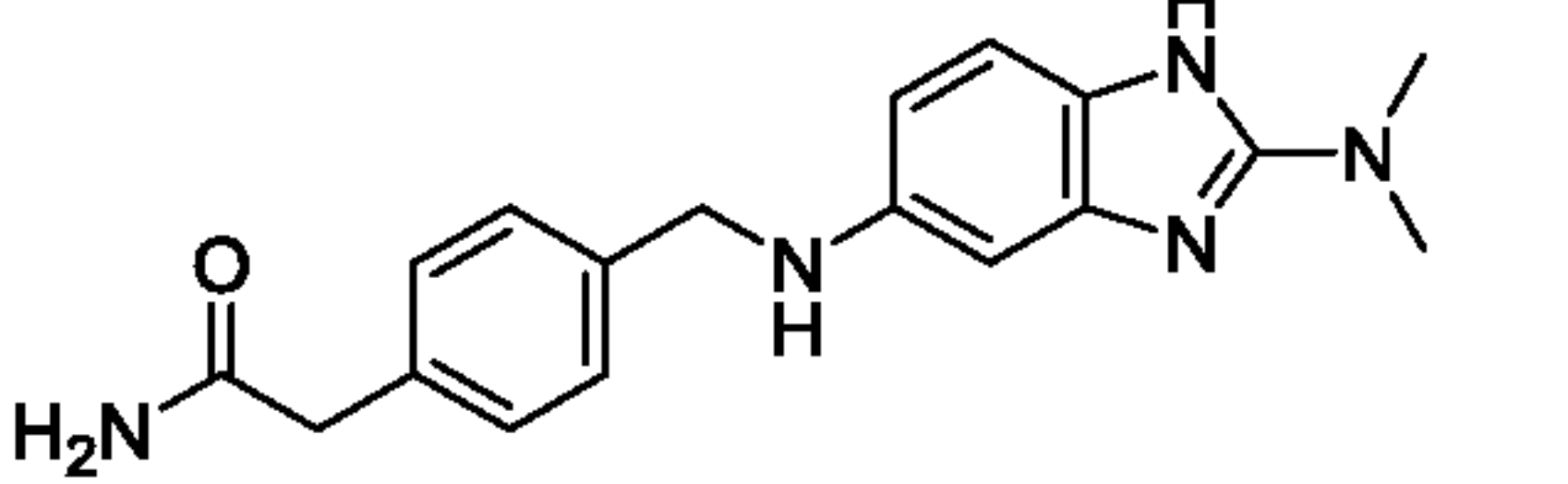
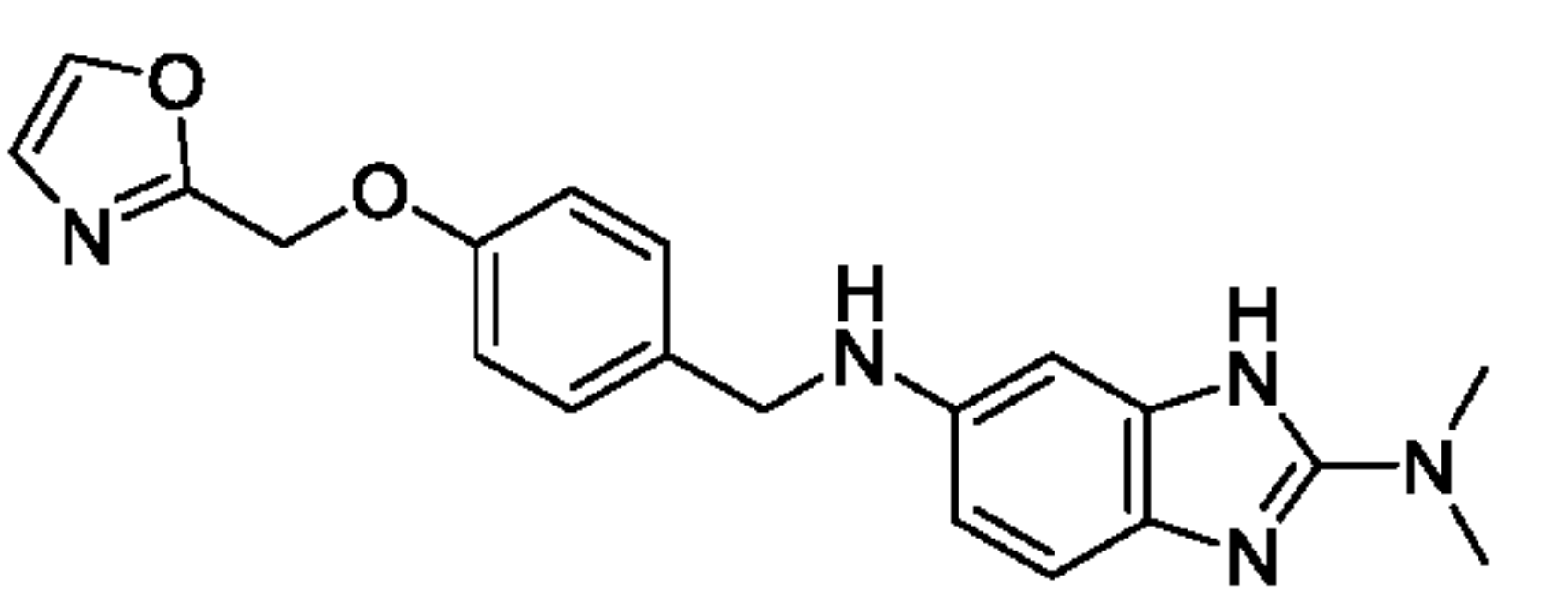
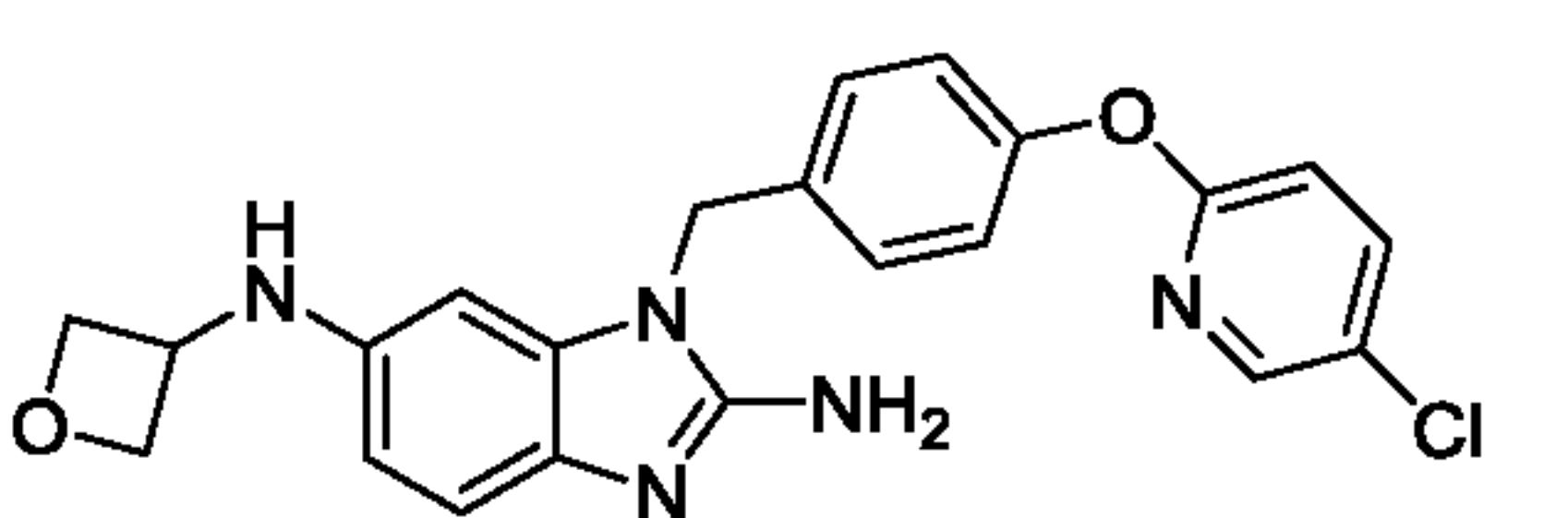
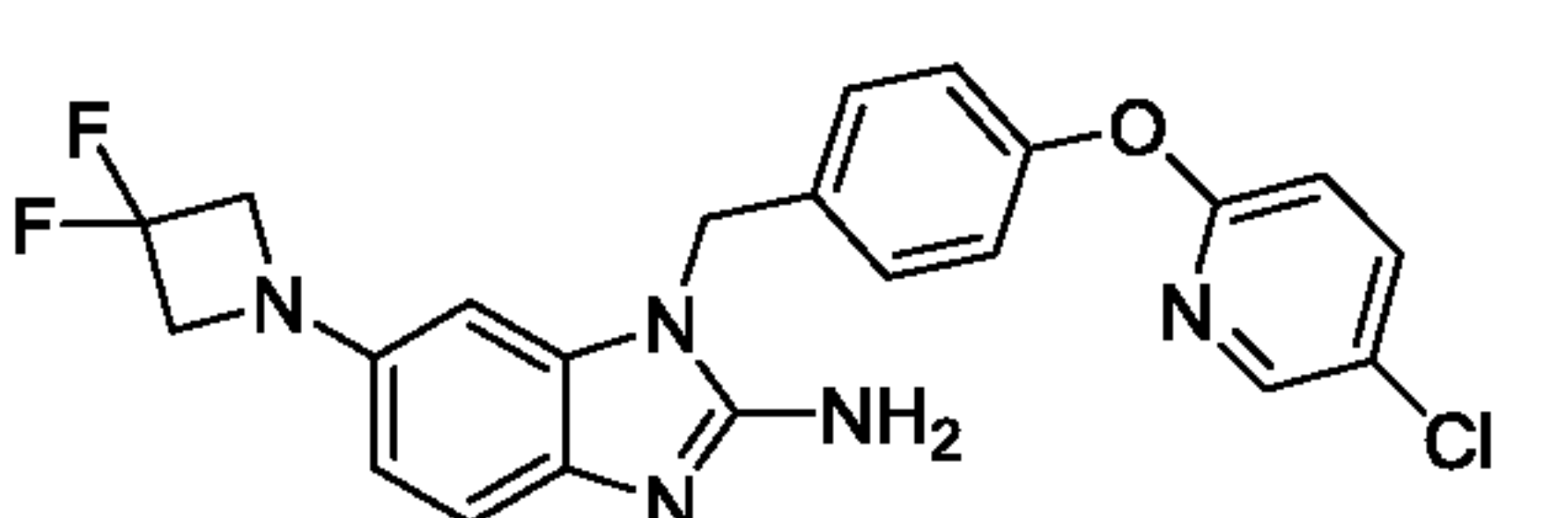
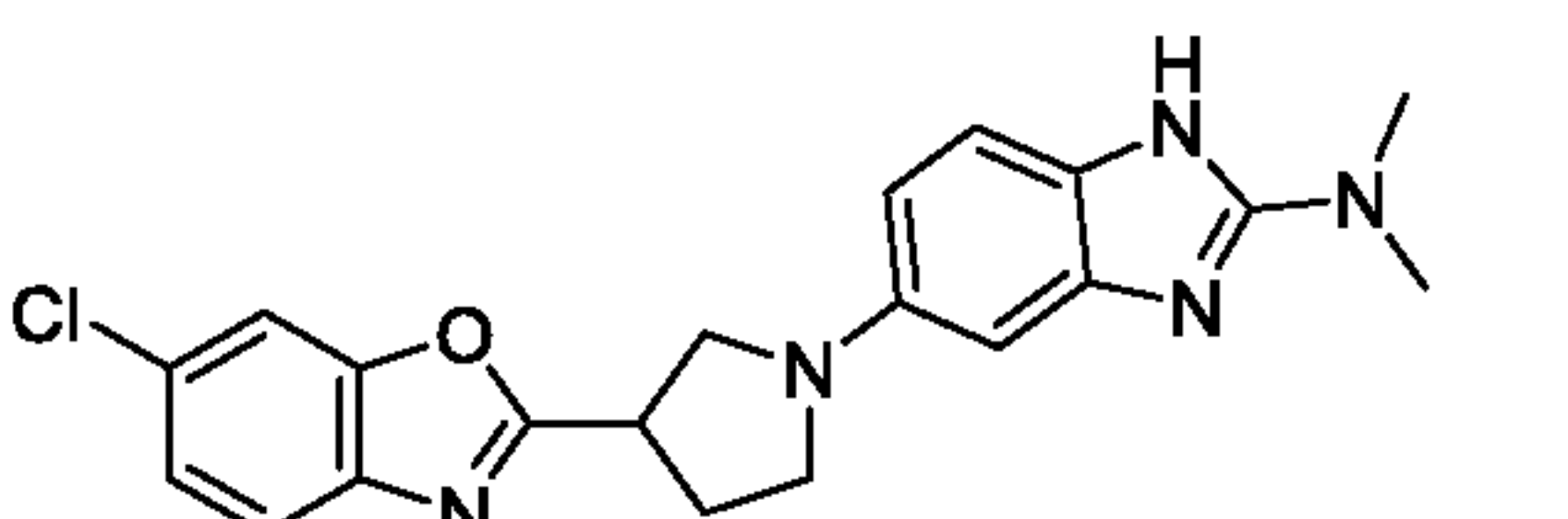
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 181 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.44 (1H, d, <i>J</i> = 4.0 Hz), 7.77 (1H, t, <i>J</i> = 7.2 Hz), 7.50 (1H, d, <i>J</i> = 8.0 Hz), 7.25-7.36 (4H, m), 7.16-7.25 (1H, m), 6.78 (1H, d, <i>J</i> = 8.4 Hz), 6.72 (1H, brs), 6.41 (1H, s), 6.19 (1H, d, <i>J</i> = 8.0 Hz), 5.32 (1H, s), 4.40 (2H, d, <i>J</i> = 4.4 Hz), 3.29 (3H, s); LCMS: 96.7%, MS (ESI); <i>m/z</i> 359.9[M+ H] <sup>+</sup> .                                     |
| 182 |  | pale green powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.12 (1H, brs), 7.40-7.55 (4H, m), 7.15 (1H, d, <i>J</i> = 8.4 Hz), 7.07 (2H, d, <i>J</i> = 8.4 Hz), 6.99-7.02 (2H, m), 6.65 (1H, s), 6.59 (1H, d, <i>J</i> = 8.8 Hz), 4.62 (2H, d, <i>J</i> = 5.6 Hz), 3.72-3.80 (2H, m), 3.60 (3H, s), 3.14-3.23 (2H, m), 1.95-2.06 (2H, m); LCMS: 96.6 %, MS (ESI); <i>m/z</i> 419.0[M + H] <sup>+</sup> .                                                            |
| 183 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.27 (2H, d, <i>J</i> = 8.8 Hz), 7.00-7.12 (3H, m), 6.79 (1H, s), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 4.49-4.61 (1H, m), 3.48-3.55 (1H, m), 3.19-3.24 (1H, m), 3.05 (6H, s), 2.73-2.89 (2H, m), 1.98-2.10 (1H, m), 1.80-1.90 (1H, m), 1.62-1.76 (1H, m), 1.45-1.58 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 421.0[M+H] <sup>+</sup> .                                                                       |
| 184 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.44 (4H, m), 6.86-7.04 (6H, m), 6.17-6.28 (2H, m), 5.82 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.46-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.43 (3H, s); LCMS: 98.4%, MS (ESI); <i>m/z</i> 434.9 [M+H] <sup>+</sup> .                                                                                                                                                     |
| 185 |  | pale yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.65-10.86 (1H, m), 7.26 (2H, d, <i>J</i> = 8.0 Hz), 7.05-7.18 (2H, m), 6.95-7.04 (2H, m), 6.81-6.95 (3H, m), 6.20-6.45 (2H, m), 5.45-5.66 (1H, m), 4.49 (2H, s), 4.04-4.21 (4H, m), 2.97 (3H, s), 2.94 (3H, s), 1.17 (3H, t, <i>J</i> = 7.2 Hz); Based on H NMR, it is a mixture of tautomers; LCMS: 99.3 %, MS (ESI); <i>m/z</i> 462.1[M + H] <sup>+</sup> .                              |
| 186 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.91 (1H, s), 7.38-7.40 (2H, m), 7.30-7.33 (2H, m), 6.89 (1H, d, <i>J</i> = 8.4 Hz), 6.48 (1H, d, <i>J</i> = 2.0 Hz), 6.30 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.34 (2H, s), 4.13 (2H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 354.1 [M+H] <sup>+</sup> .                                                                                                                                                      |
| 187 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.39-7.43 (2H, m), 7.21 (2H, d, <i>J</i> = 8.4 Hz), 6.96-7.03 (5H, m), 6.36-6.40 (3H, m), 5.26 (2H, s), 3.53 (2H, s), 1.32 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 437.0[M+H] <sup>+</sup> .                                                                                                                                                                                                            |
| 188 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.16-10.45 (1H, m), 8.44 (1H, d, <i>J</i> = 4.4 Hz), 7.77 (1H, t, <i>J</i> = 7.6 Hz), 7.51 (1H, d, <i>J</i> = 7.6 Hz), 7.26-7.35 (4H, m), 7.17-7.25 (1H, m), 6.55-6.88 (2H, m), 6.39 (1H, d, <i>J</i> = 1.6 Hz), 6.17 (1H, brs), 5.42 (1H, s), 4.20-4.63 (4H, m), 3.40-3.49 (2H, q, <i>J</i> = 6.8 Hz), 1.17 (3H, t, <i>J</i> = 7.0 Hz); LCMS: 95.4%, MS (ESI); <i>m/z</i> 373.8[M+ H] <sup>+</sup> . |
| 189 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.29-10.48 (1H, m), 8.40-8.49 (1H, m), 7.72-7.82 (1H, m), 7.50 (1H, d, <i>J</i> = 7.6 Hz), 7.26-7.35 (4H, m), 7.19-7.26 (1H, m), 6.79-6.90 (2H, m), 6.24 (1H, d, <i>J</i> = 4.8 Hz), 6.06-6.17 (1H, m), 5.59-5.79 (1H, m), 5.32 (1H, s), 4.81 (2H, t, <i>J</i> = 6.0 Hz), 4.30-4.50 (5H, m), 3.29 (3H, s); LCMS: 95.7%, MS (ESI); <i>m/z</i> 416.0[M+ H] <sup>+</sup> .                                  |

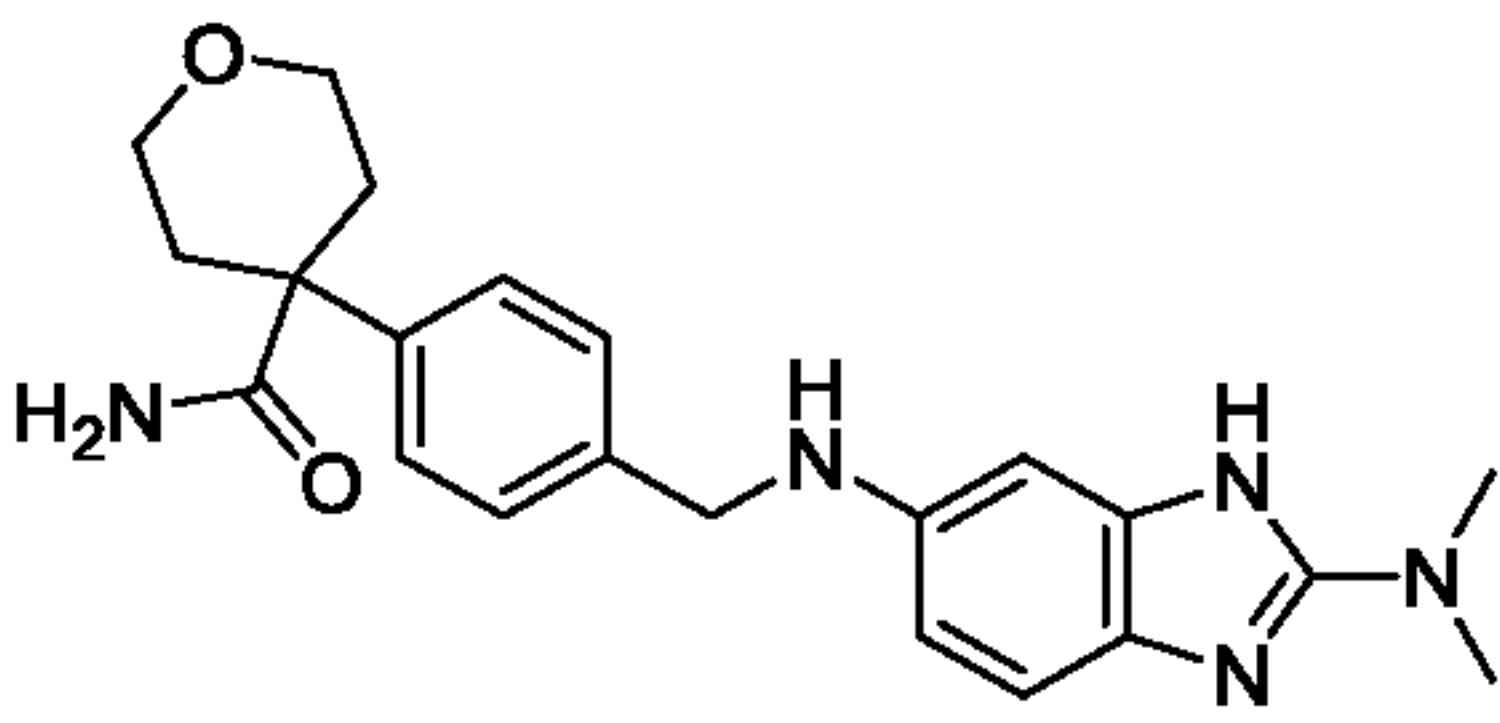
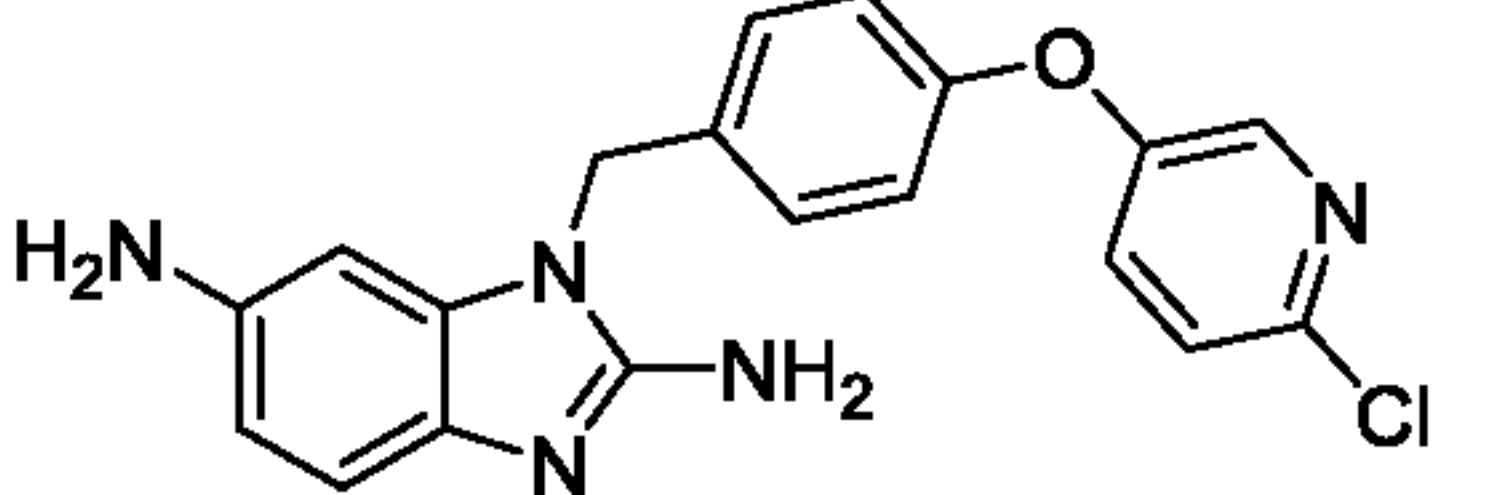
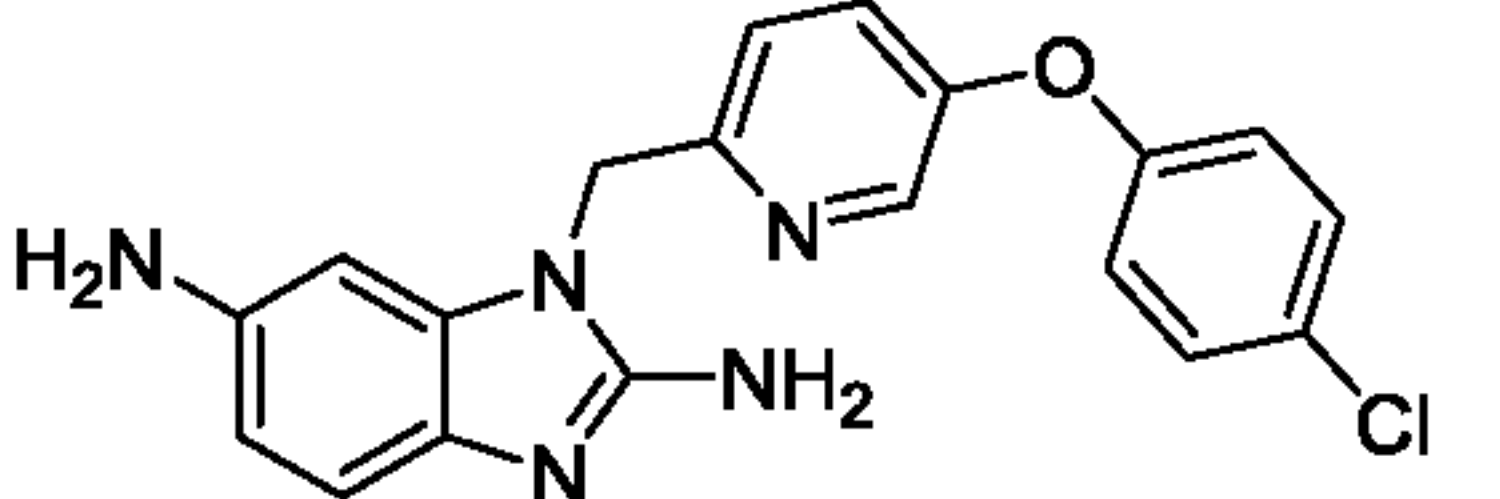
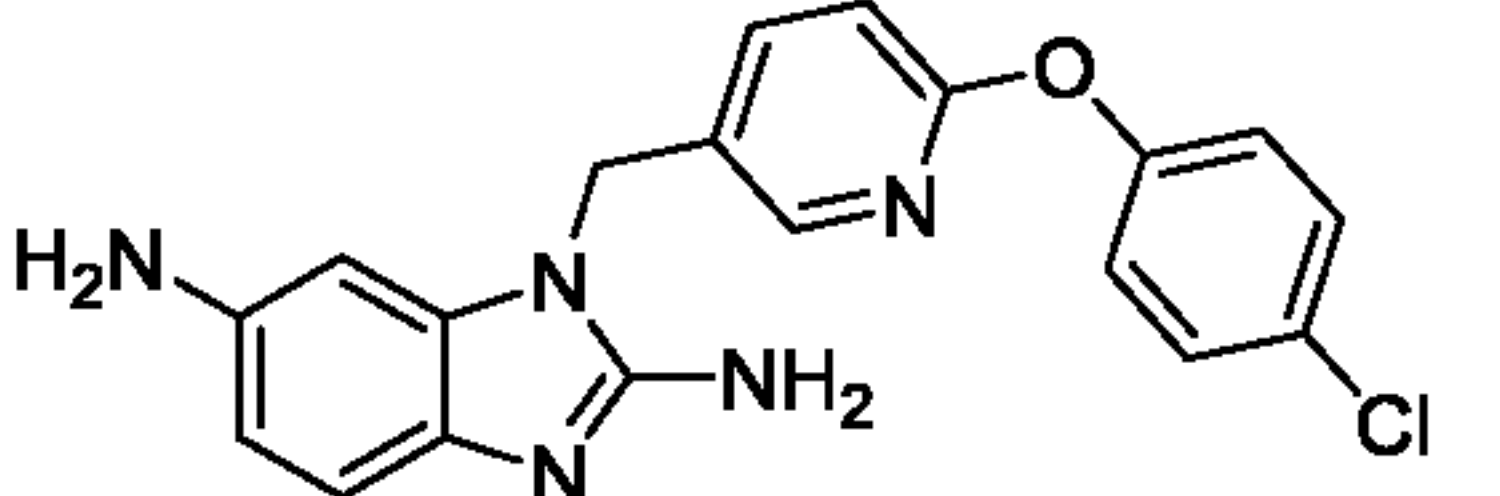
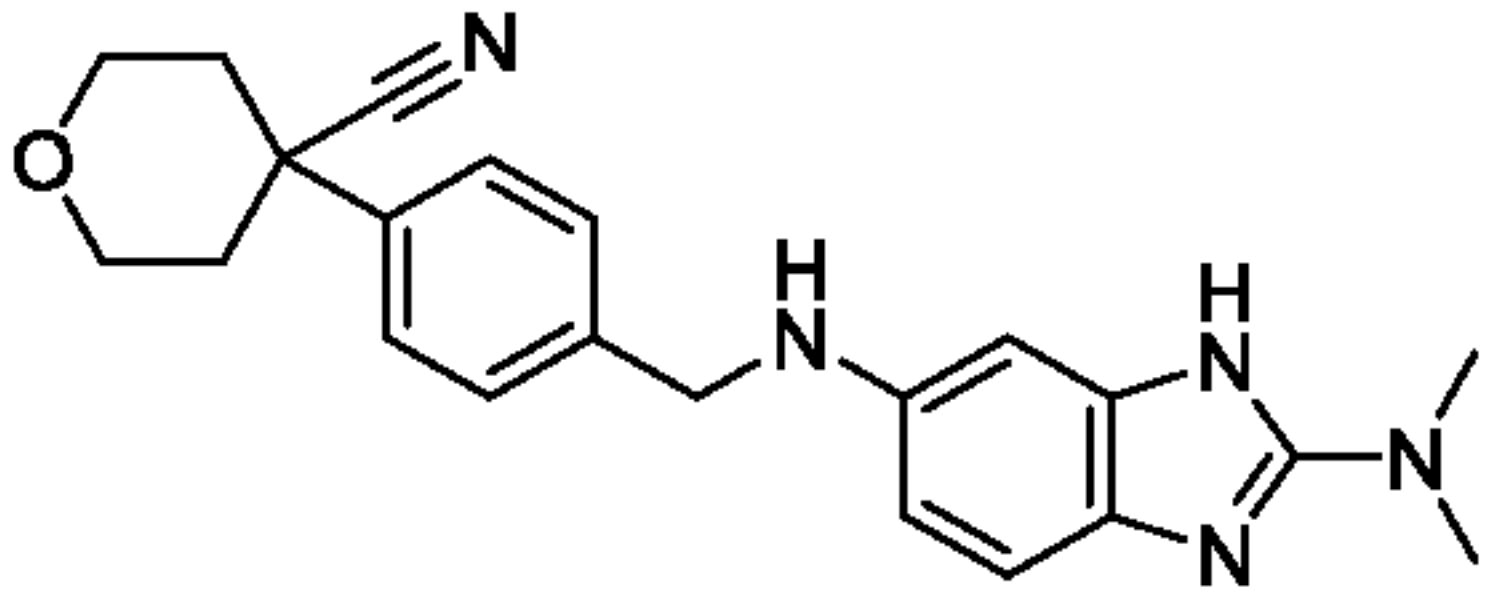
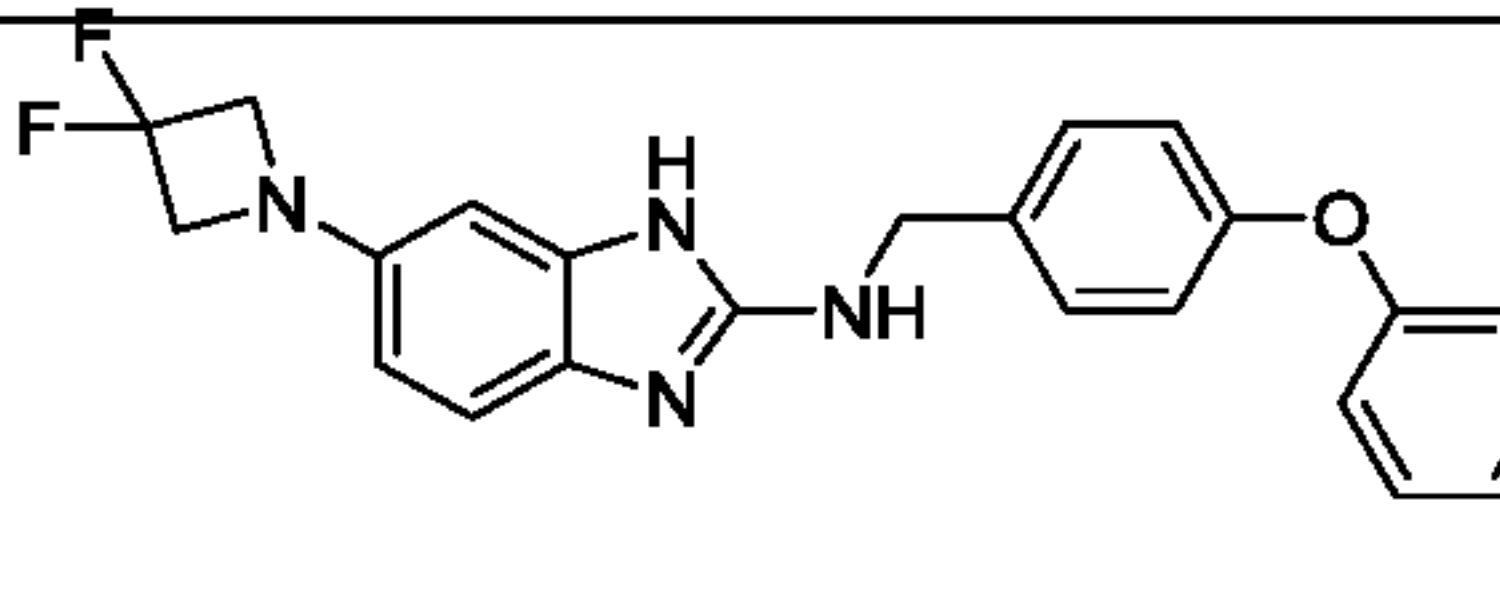
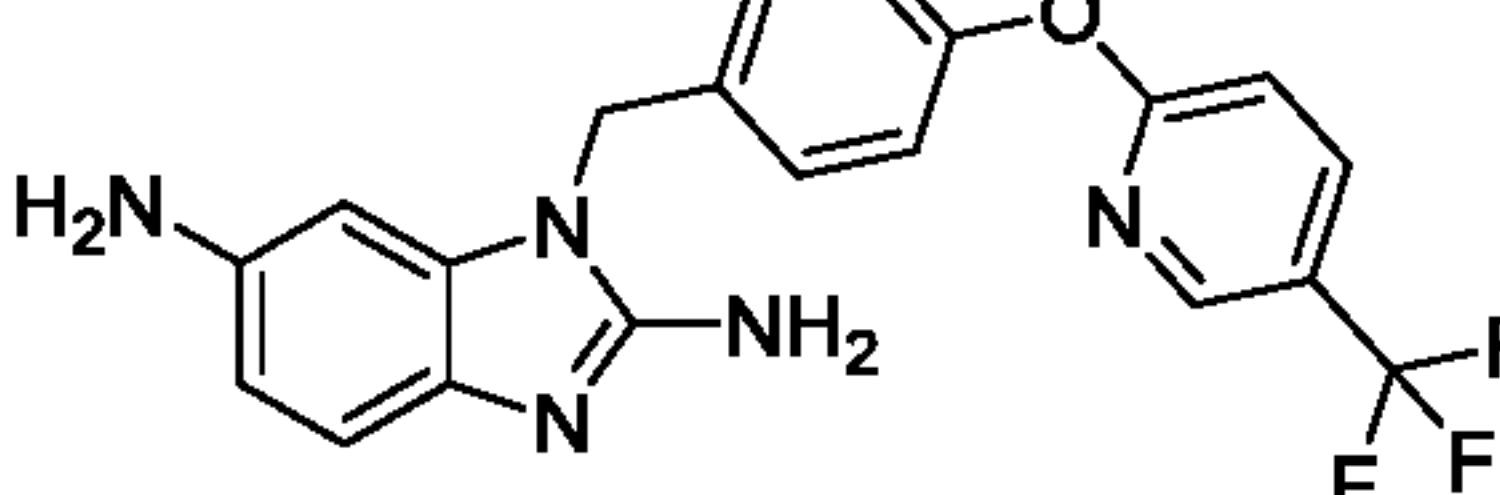
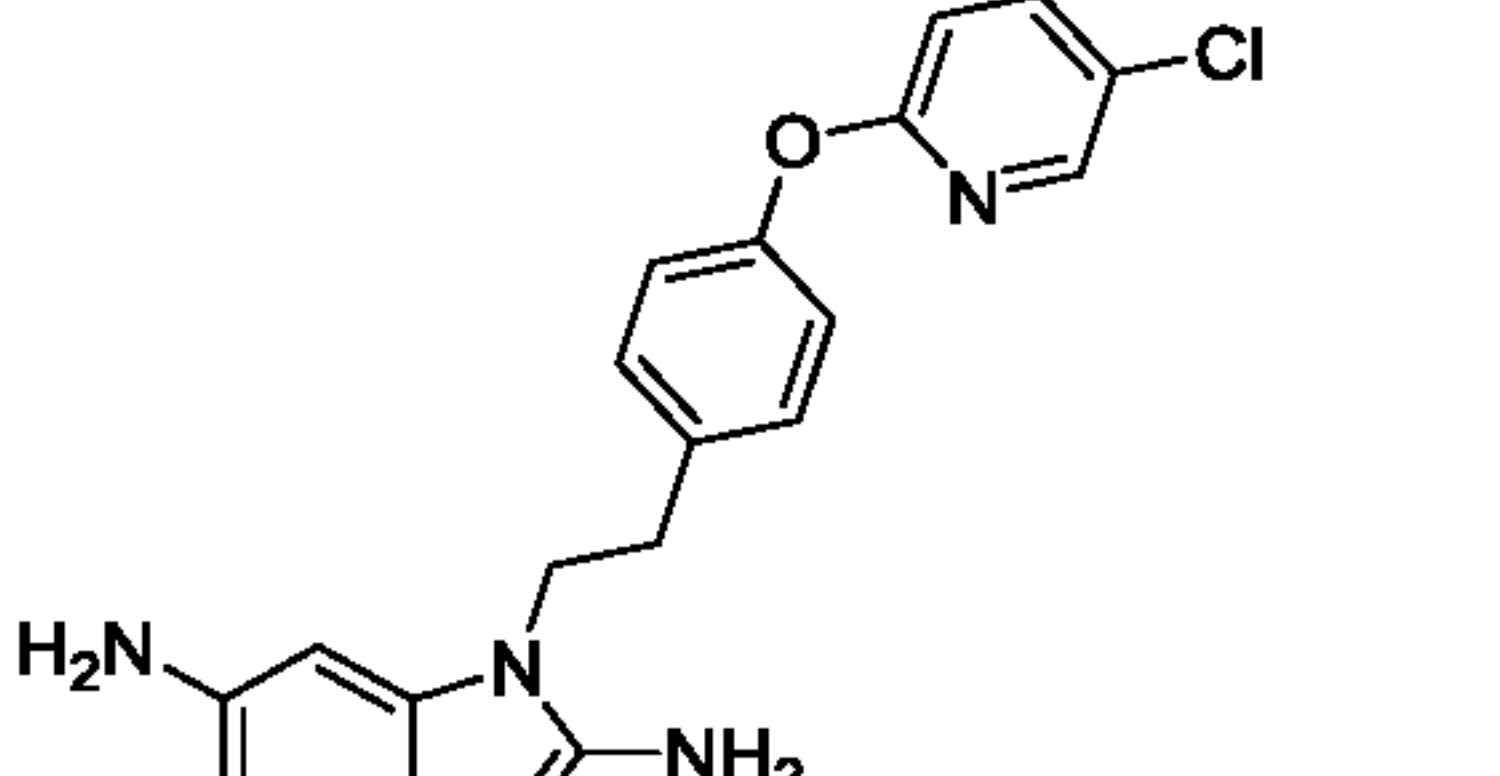
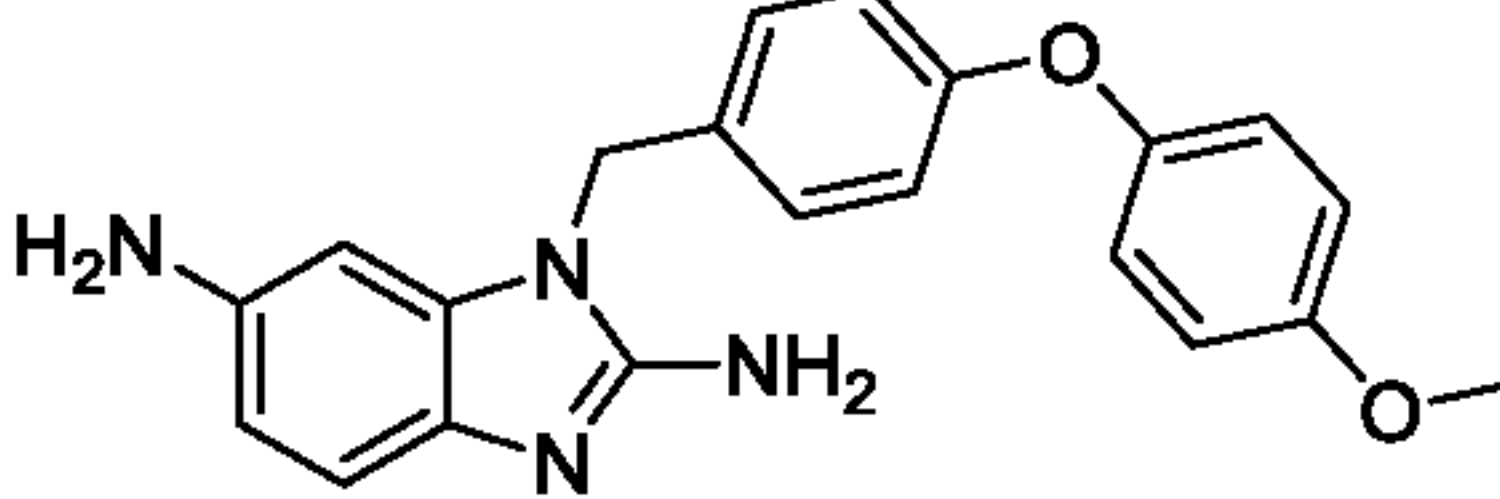
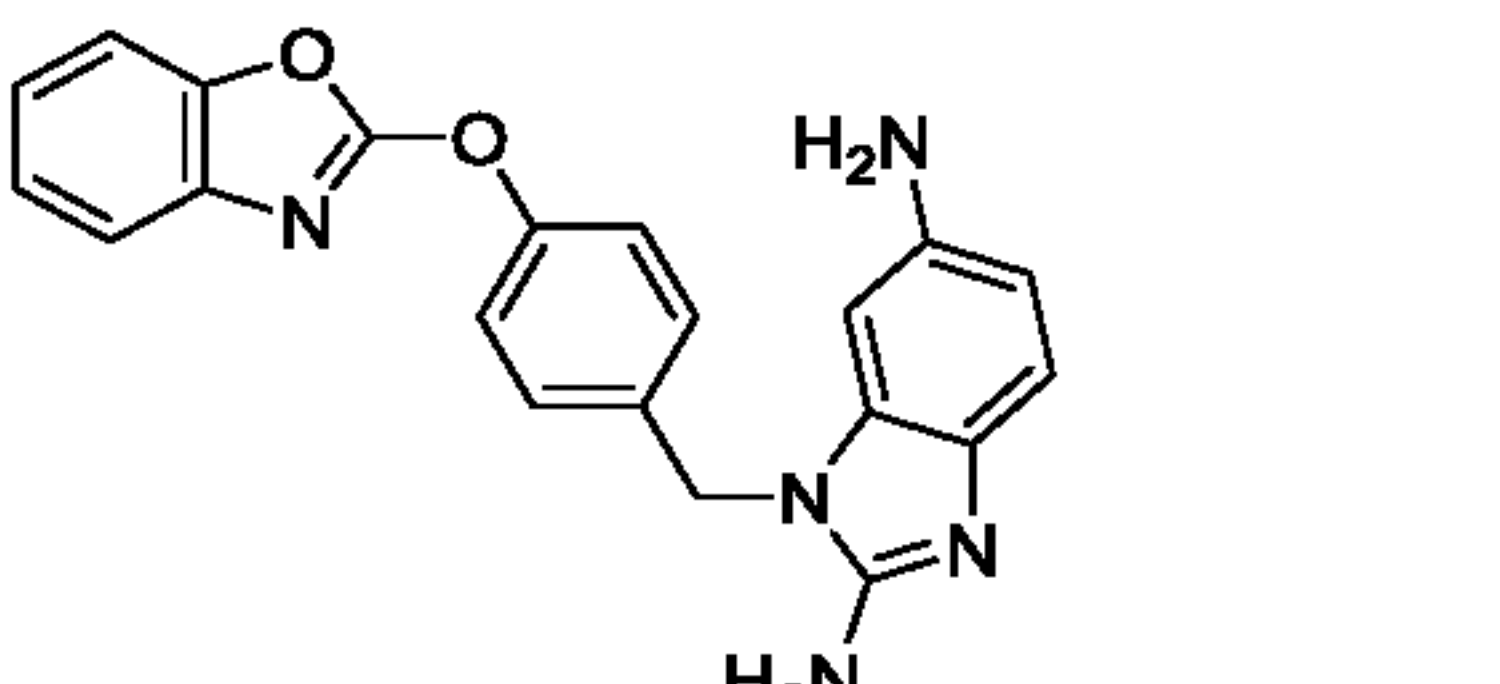
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 190 |    | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.67-10.95 (1H, m), 8.18 (2H, d, <i>J</i> = 8.8 Hz), 7.53 (2H, d, <i>J</i> = 8.4 Hz), 6.88-7.07 (1H, m), 6.12-6.54 (2H, m), 4.23-4.40 (1H, m), 3.53 (1H, t, <i>J</i> = 8.8 Hz), 3.37-3.43 (1H, m, overlap with H <sub>2</sub> O signal), 3.20-3.30 (2H, m, overlap with H <sub>2</sub> O signal), 2.97 (6H, s), 2.25-2.34 (1H, m), 2.10-2.21 (1H, m); LCMS: 97.4%, MS (ESI, TOF); <i>m/z</i> 419.1985[M+H] <sup>+</sup> . |
| 191 |    | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.74-10.84 (1H, m), 7.32-7.42 (4H, m), 7.03 (2H, d, <i>J</i> = 9.2 Hz), 6.95 (2H, d, <i>J</i> = 8.4 Hz), 6.51-6.64 (1H, m), 6.05-6.18 (1H, m), 4.58-4.75 (1H, m), 4.43-4.50 (1H, m), 3.76-4.02 (1H, m), 2.96-2.98 (6H, m), 1.42-1.47 (3H, m); LCMS: 96.6%, MS (ESI); <i>m/z</i> 486.9 [M+ H] <sup>+</sup> .                                                                                                                  |
| 192 |   | pale brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.35-7.51 (4H, m), 6.91-7.06 (6H, m), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.09 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.50 (1H, d, <i>J</i> = 6.8 Hz), 4.46-4.57 (3H, m), 3.90-4.05 (2H, m), 3.44 (3H, s), 3.30-3.45 (2H, m); LCMS: 96.0%, MS (ESI); <i>m/z</i> 435.0[M + H] <sup>+</sup> .                                                                                                                                          |
| 193 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.45 (4H, m), 7.01-7.09 (2H, m), 6.93-7.01 (4H, m), 6.43 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 4.17 (4H, t, <i>J</i> = 12.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 455.0[M + H] <sup>+</sup> .                                                                                                                                              |
| 194 |  | brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.92 (2H, d, <i>J</i> = 8.8 Hz), 7.08 (2H, d, <i>J</i> = 9.2 Hz), 6.95-7.05 (1H, m), 6.21-6.47 (2H, m), 5.20-5.30 (1H, m), 3.82 (3H, s), 3.60-3.70 (1H, m), 3.30-3.36 (3H, m), 2.97 (3H, s), 3.92 (3H, s), 2.37-2.40 (2H, m); LCMS: 95.3%, MS (ESI); <i>m/z</i> 380.8 [M+H] <sup>+</sup> .                                                                                                                                        |
| 195 |  | off-white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, d, <i>J</i> = 2.8 Hz), 7.92 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.19 (2H, d, <i>J</i> = 8.4 Hz), 7.03-7.12 (3H, m), 6.82 (1H, d, <i>J</i> = 8.4 Hz), 6.32 (1H, d, <i>J</i> = 1.6 Hz), 6.25 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.14 (2H, brs), 5.11 (2H, s), 4.49 (2H, brs); LCMS: 97.1%, MS (ESI); <i>m/z</i> 365.9[M+H] <sup>+</sup> .                                                                                 |
| 196 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40-7.60 (5H, m), 7.06 (1H, d, <i>J</i> = 8.4 Hz), 6.45-6.60 (2H, m), 6.32-6.37 (1H, m), 4.34 (2H, s), 3.83 (3H, s), 3.10 (6H, s); LCMS: 98.1%, MS (ESI); <i>m/z</i> 346.8[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                 |
| 197 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.74 (1H, brs), 8.68 (1H, s), 7.90-8.05 (4H, m), 7.49 (2H, d, <i>J</i> = 8.0 Hz), 6.87 (1H, d, <i>J</i> = 6.8 Hz), 6.37 (1H, s), 6.15-6.45 (1H, m), 5.78 (1H, brs), 4.29 (2H, d, <i>J</i> = 5.6 Hz), 2.93 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 377.9[M+ H] <sup>+</sup> .                                                                                                                                            |
| 198 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.37 (1H, brs), 7.20-7.38 (4H, m), 6.52-6.95 (2H, m), 6.41 (1H, d, <i>J</i> = 2.0 Hz), 6.18 (1H, d, <i>J</i> = 6.4 Hz), 5.63 (1H, d, <i>J</i> = 4.0 Hz), 4.67 (1H, d, <i>J</i> = 4.0 Hz), 4.17-4.56 (4H, m), 1.06 (3H, s), 0.86 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 379.1[M+ H] <sup>+</sup> .                                                                                                                          |
| 199 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.14 (1H, d, <i>J</i> = 2.4 Hz), 7.92 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.21 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.02 (3H, m), 6.74 (1H, d, <i>J</i> = 8.4 Hz), 6.41 (1H, d, <i>J</i> = 1.2 Hz), 6.29 (2H, brs), 6.14 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.11 (2H, s), 4.39 (2H, brs); LCMS: 92.3%, MS (ESI); <i>m/z</i> 365.8[M+H] <sup>+</sup> .                                                                                    |

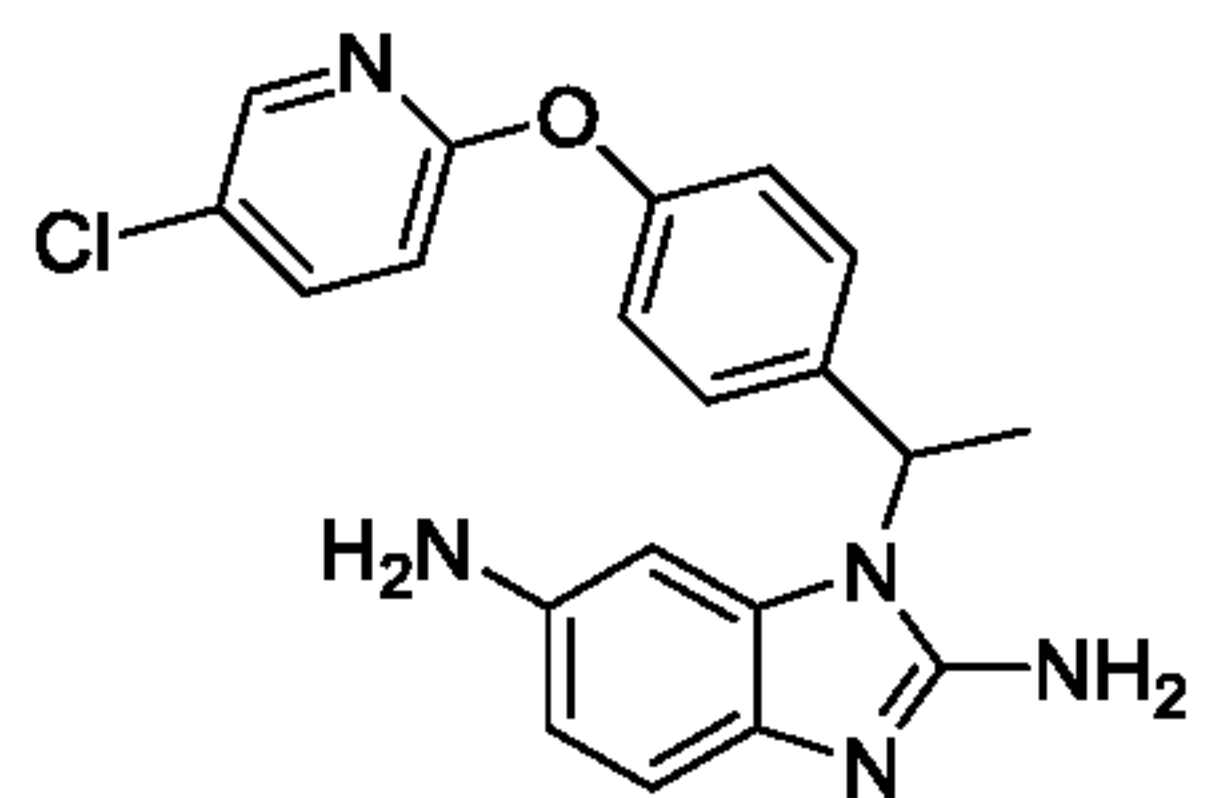
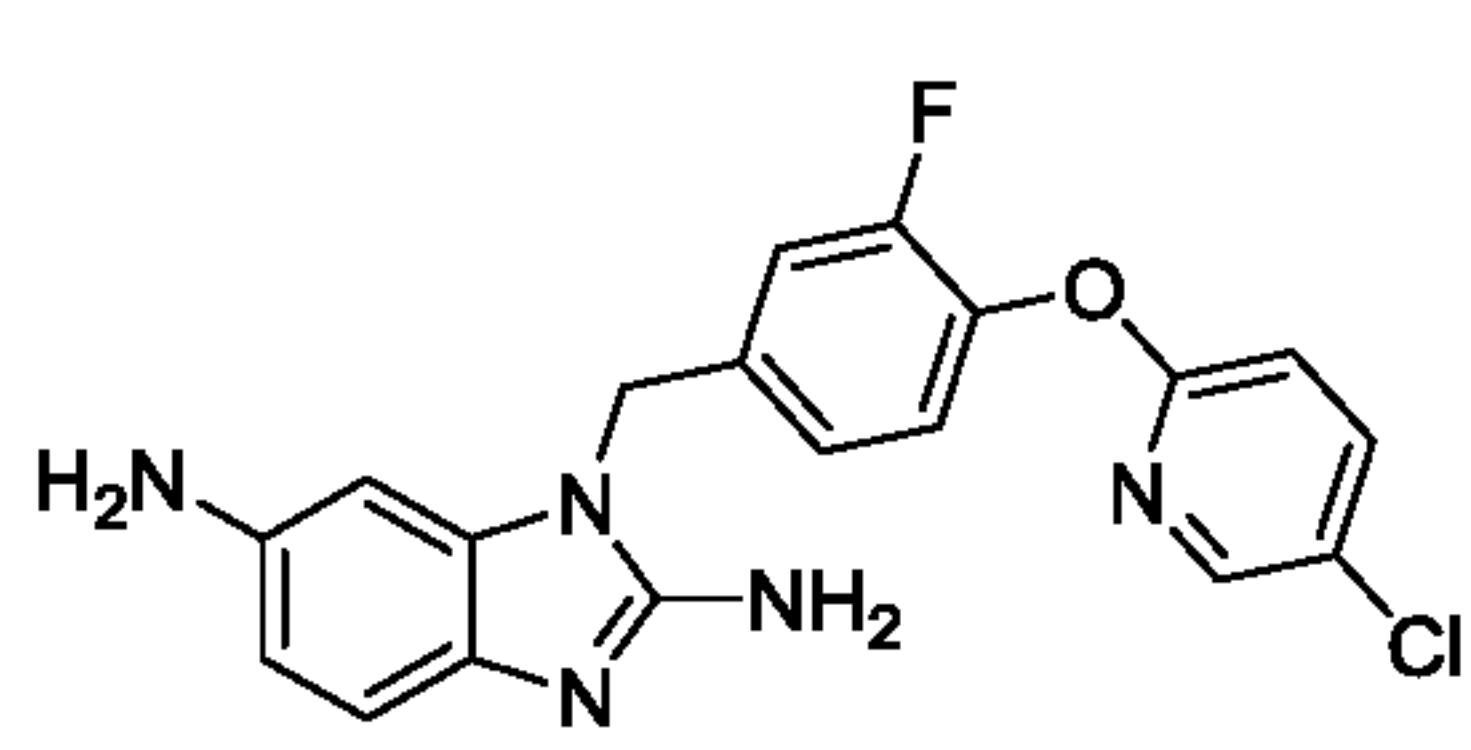
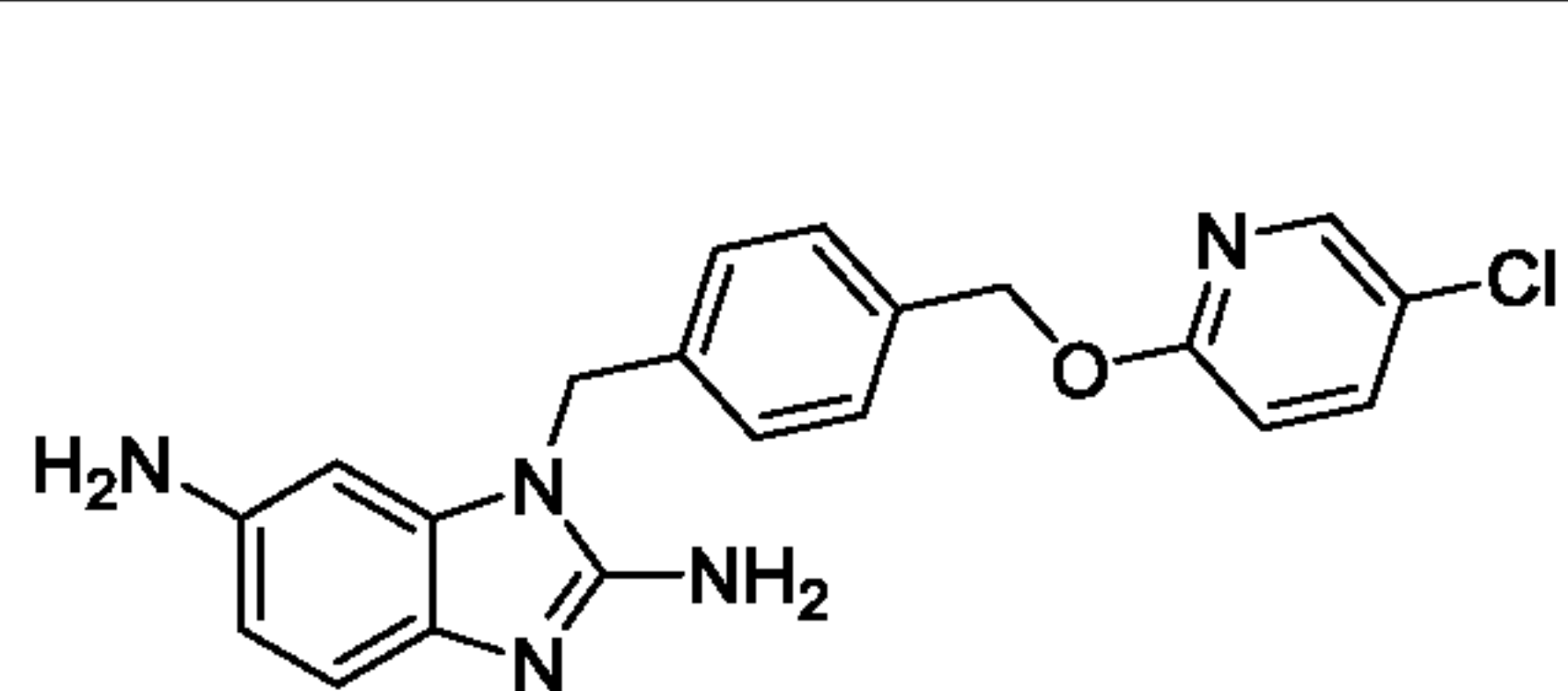
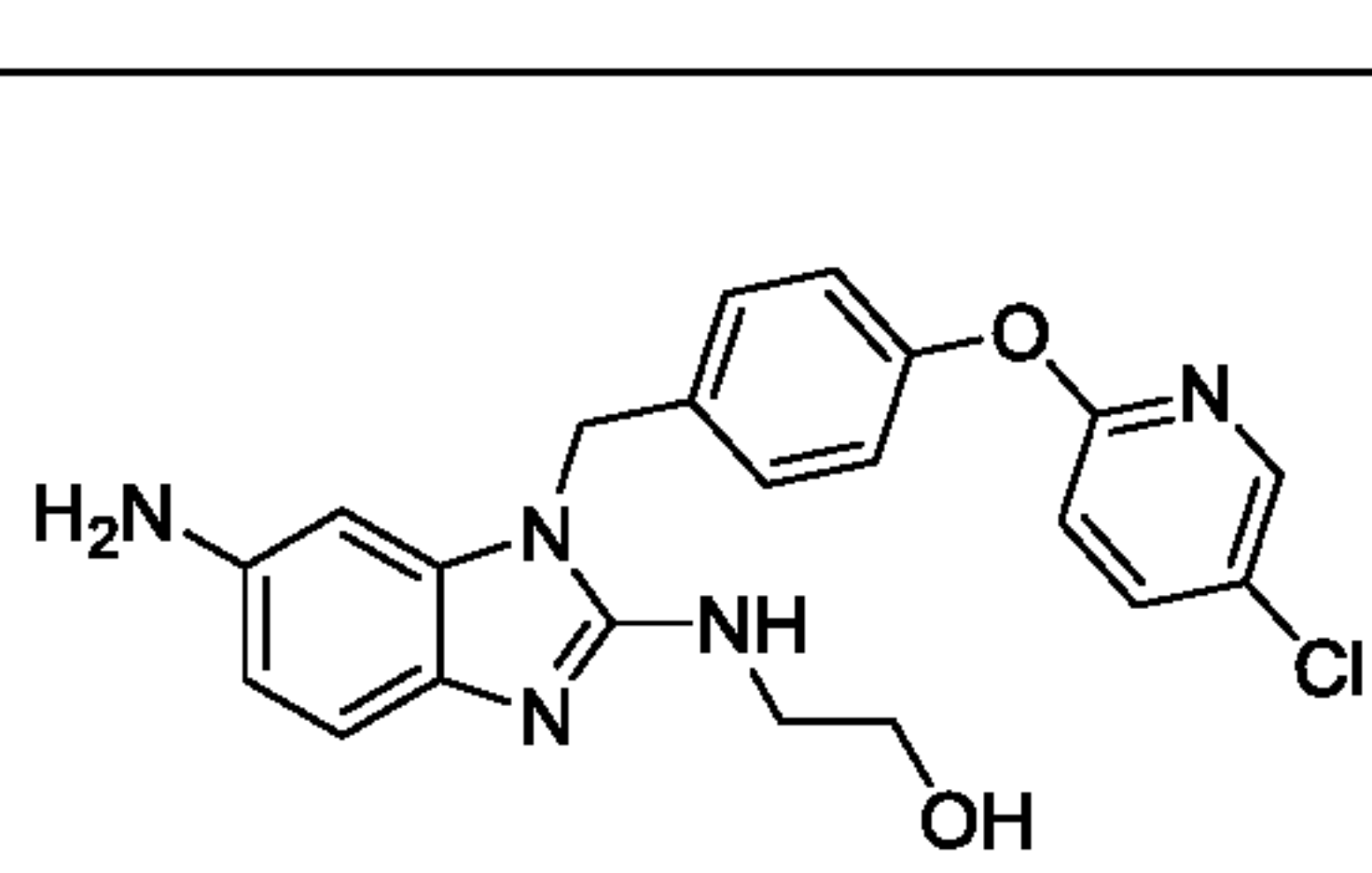
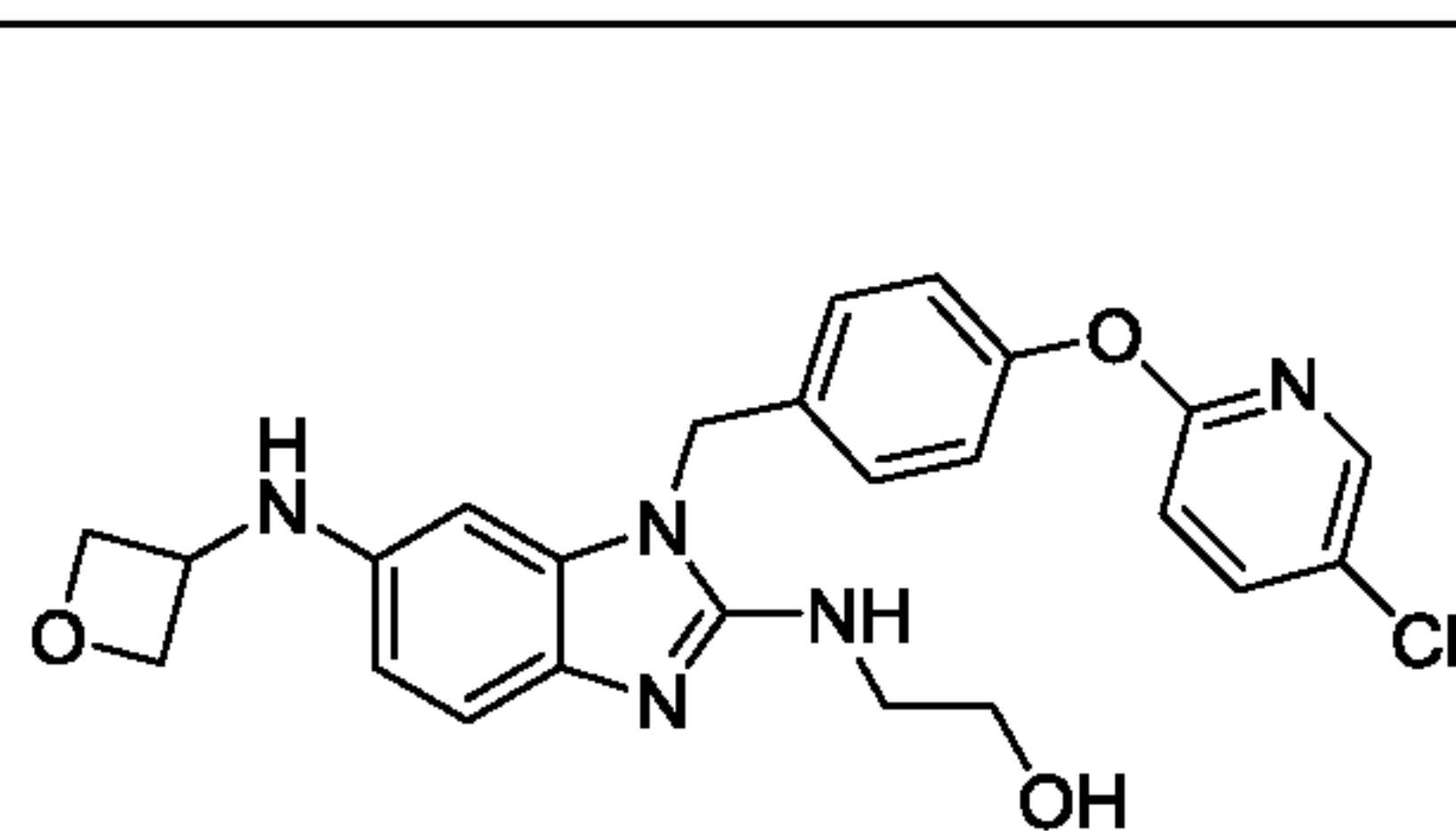
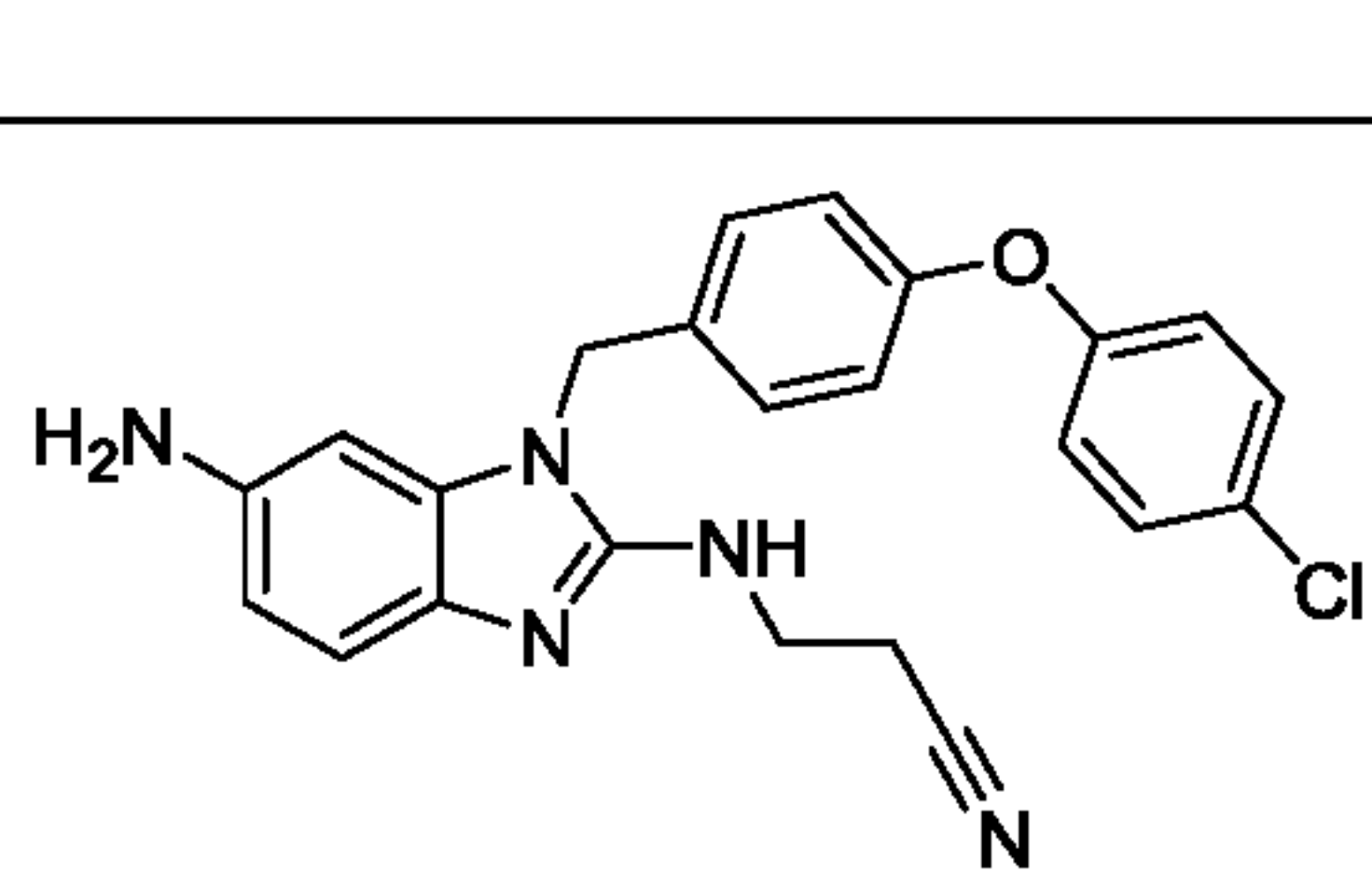
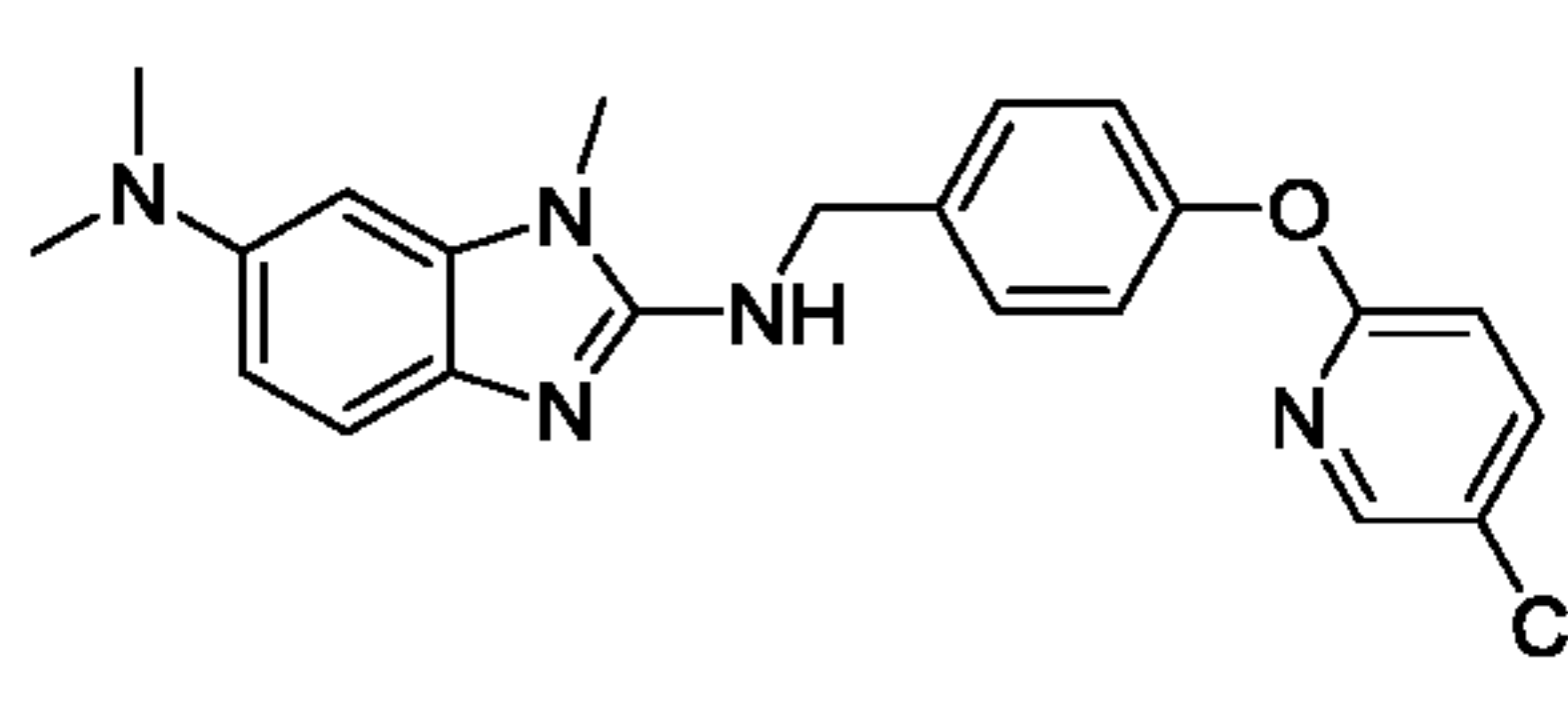
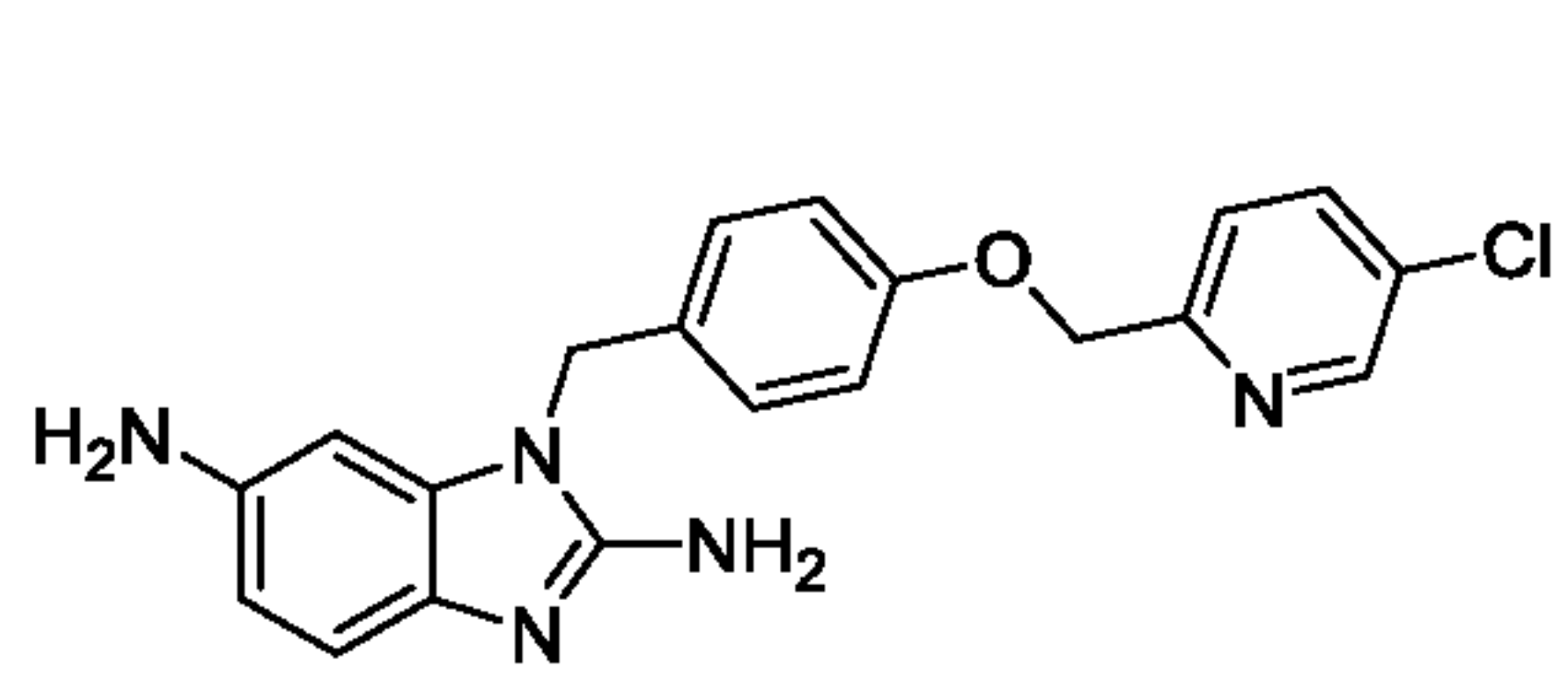
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 200 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.25-10.60 (1H, m), 7.35-7.60 (5H, m), 6.65-7.00 (2H, m), 6.41 (1H, s), 6.35 (1H, d, <i>J</i> = 1.6 Hz), 6.10-6.25 (1H, m), 4.25-4.60 (4H, m), 3.82 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 318.9[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                               |
| 201 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.40-10.60 (1H, m), 7.40-7.50 (5H, m), 6.80-7.10 (2H, m), 6.35 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, s), 6.10-6.20 (1H, m), 5.60-5.80 (1H, m), 4.81 (1H, t, <i>J</i> = 6.0 Hz), 4.30-4.60 (5H, m), 3.83 (3H, s); LCMS: 99.8%, MS (ESI); <i>m/z</i> 374.9[M+ H] <sup>+</sup> .                                                                                                                                                                                                                           |
| 202 |  | red amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.76-10.90 (1H, m), 8.38 (2H, d, <i>J</i> = 6.0 Hz), 6.90-7.03 (3H, m), 6.37-6.47 (1H, m), 6.17-6.30 (1H, m), 5.24-5.26 (1H, m), 3.64-3.71 (1H, m), 3.30-3.32 (3H, m), 2.99 (3H, s), 2.97 (3H, s), 2.37-2.45 (1H, m), 2.16-2.25 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 324.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                   |
| 203 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.05-7.10 (3H, m), 6.88 (1H, d, <i>J</i> = 8.0 Hz), 6.60 (1H, t, <i>J</i> = 6.0 Hz), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.26 (1H, s), 4.40-4.60 (4H, m), 3.75 (2H, s), 1.19 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 438.0[M+ H] <sup>+</sup> .                                                                                                    |
| 204 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.43 (2H, m), 7.24 (2H, d, <i>J</i> = 8.8 Hz), 6.92-7.03 (5H, m), 6.62 (1H, t, <i>J</i> = 5.2 Hz), 6.14-6.21 (2H, m), 5.82 (1H, d, <i>J</i> = 6.8 Hz), 5.14 (2H, s), 5.00 (1H, brs), 4.77 (2H, t, <i>J</i> = 6.4 Hz), 4.38-4.48 (1H, m), 4.29-4.37 (2H, m), 3.52-3.59 (2H, m), 3.30-3.45 (2H, m); LCMS: 99.4%, MS (ESI); <i>m/z</i> 465.0 [M+H] <sup>+</sup> .                                                                                                                                   |
| 205 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , t = 80 °C, 400 MHz); δ 10.15 (1H, brs), 7.60-7.67 (2H, m), 7.46-7.52 (2H, m), 6.83 (1H, d, <i>J</i> = 8.4 Hz), 6.40-6.60 (2H, m), 6.24 (1H, d, <i>J</i> = 7.6 Hz), 4.56 (2H, s), 4.17 (2H, brs), 1.49-1.56 (6H, m); LCMS: 98.9%, MS (ESI); <i>m/z</i> 377.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                              |
| 206 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.42 (2H, d, <i>J</i> = 8.8 Hz), 7.17 (2H, d, <i>J</i> = 8.4 Hz), 6.95-7.10 (5H, m), 6.38 (2H, d, <i>J</i> = 8.8 Hz), 6.32 (1H, s), 5.17-5.28 (2H, m), 4.99 (1H, brs), 4.25-4.35 (1H, m), 3.50-3.70 (2H, m), 3.10-3.22 (2H, m), 1.92-1.95 (1H, m), 1.70-1.80 (1H, m); LCMS: 97.8%, MS (ESI); <i>m/z</i> 434.9[M+H] <sup>+</sup> .                                                                                                                                                                        |
| 207 |  | off-white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.38-7.43 (2H, m), 7.25 (2H, d, <i>J</i> = 8.4 Hz), 7.05 (1H, t, <i>J</i> = 6.4 Hz), 6.96-7.02 (4H, m), 6.89 (1H, d, <i>J</i> = 8.4 Hz), 6.32 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.14 (2H, s), 4.54 (2H, brs), 4.10 (2H, q, <i>J</i> = 7.2 Hz), 4.05 (2H, d, <i>J</i> = 6.0 Hz), 1.19 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 98.5%, MS (ESI); <i>m/z</i> 451.0[M+H] <sup>+</sup> .                                                                             |
| 208 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.41 (2H, d, <i>J</i> = 8.4 Hz), 7.08 (3H, d, <i>J</i> = 8.8 Hz), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 6.64 (1H, t, <i>J</i> = 6.0 Hz), 6.35 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.80 (1H, d, <i>J</i> = 7.6 Hz), 5.22 (1H, s), 4.83 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.59 (3H, m), 4.32-4.44 (2H, m), 3.80 (2H, s), 1.18 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 494.0[M+ H] <sup>+</sup> . |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| 209 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.46 (4H, m), 6.95-7.04 (4H, m), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.55 (1H, t, <i>J</i> = 6.0 Hz), 6.45 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.23 (1H, brs), 4.45-4.50 (4H, m), 3.74 (2H, s), 1.18 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 437.0[M+ H] <sup>+</sup> .                                                    |
| 210 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.04-7.13 (3H, m), 6.82-6.97 (2H, m), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.42-4.65 (4H, m), 3.42 (3H, s); LCMS: 99.7%, MS (TOF, ESI); <i>m/z</i> 380.1267[M+H] <sup>+</sup> .                                           |
| 211 |  | off-white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.33-7.51 (3H, m), 7.05-7.18 (3H, m), 6.99 (1H, d, <i>J</i> = 8.8 Hz), 6.21-6.37 (2H, m), 5.99 (1H, d, <i>J</i> = 2.0 Hz), 4.86 (2H, t, <i>J</i> = 6.4 Hz), 4.48-4.61 (3H, m), 4.41 (2H, t, <i>J</i> = 6.0 Hz), 3.49 (3H, s); LCMS: 99.2%, MS (ESI); <i>m/z</i> 436.0[M+H] <sup>+</sup> . |
| 212 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.54-10.91 (1H, m), 7.43 (1H, s), 7.23 (2H, d, <i>J</i> = 8.4 Hz), 6.95-7.19 (5H, m), 6.75-6.91 (3H, m), 6.37 (1H, s), 6.28 (1H, d, <i>J</i> = 7.6 Hz), 5.52 (1H, brs), 4.05-4.21 (4H, m), 2.93 (6H, s); LCMS: 99.0 %, MS (ESI); <i>m/z</i> 432.9[M + H] <sup>+</sup> .                                                                                       |
| 213 |  | pale-yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.04 (1H, s), 7.25 (2H, d, <i>J</i> = 8.4 Hz), 7.06-7.18 (5H, m), 6.88-6.97 (3H, m), 6.42 (1H, d, <i>J</i> = 1.6 Hz), 6.38 (1H, d, <i>J</i> = 8.4 Hz), 5.78 (1H, brs), 5.01 (2H, s), 4.15 (2H, s), 3.01 (6H, s); LCMS: 97.6 %, MS (ESI); <i>m/z</i> 457.0[M+ H] <sup>+</sup> .                                                                      |
| 214 |  | white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.64-10.86 (1H, m), 10.19 (1H, brs), 7.63 (2H, d, <i>J</i> = 9.2 Hz), 7.41 (1H, d, <i>J</i> = 10.4 Hz), 7.33 (2H, d, <i>J</i> = 8.8 Hz), 6.80-6.96 (1H, m), 6.45-6.55 (1H, m), 6.24-6.40 (1H, m), 5.15-5.43 (1H, m), 4.02 (2H, t, <i>J</i> = 5.2 Hz), 2.96 (3H, s), 2.93 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 382.9[M+ H] <sup>+</sup> .            |
| 215 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.31-10.49 (1H, m), 7.29-7.46 (4H, m), 6.88-7.06 (4H, m), 6.65-6.88 (2H, m), 6.41 (1H, d, <i>J</i> = 6.4 Hz), 6.15-6.29 (1H, m), 4.50-4.81 (3H, m), 4.34-4.50 (2H, m), 3.55-3.71 (1H, m), 3.04-3.18 (1H, m), 2.70-2.91 (1H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 439.0[M + H] <sup>+</sup> .                                                                        |
| 216 |  | white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 11.86 (1H, brs), 10.60-10.82 (1H, m), 7.19-7.25 (2H, m), 7.02-7.18 (4H, m), 6.74-7.00 (5H, m), 6.35-6.38 (1H, m), 6.18-6.31 (1H, m), 5.39-5.65 (1H, m), 4.80 (2H, s), 4.10 (2H, s), 2.94 (3H, s), 2.92 (3H, s); LCMS: 99.1 %, MS (ESI); <i>m/z</i> 456.0[M+ H] <sup>+</sup> .                                                                             |
| 217 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.41 (2H, d, <i>J</i> = 8.8 Hz), 7.33 (1H, brs), 7.25 (1H, d, <i>J</i> = 8.0 Hz), 6.94-7.06 (5H, m), 6.89 (1H, d, <i>J</i> = 8.0 Hz), 6.77 (1H, t, <i>J</i> = 6.0 Hz), 6.32 (1H, s), 6.27 (1H, d, <i>J</i> = 8.4 Hz), 5.13 (2H, s), 4.53 (2H, brs), 3.84 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 99.4%, MS (ESI); <i>m/z</i> 422.0 [M+ H] <sup>+</sup> .                |

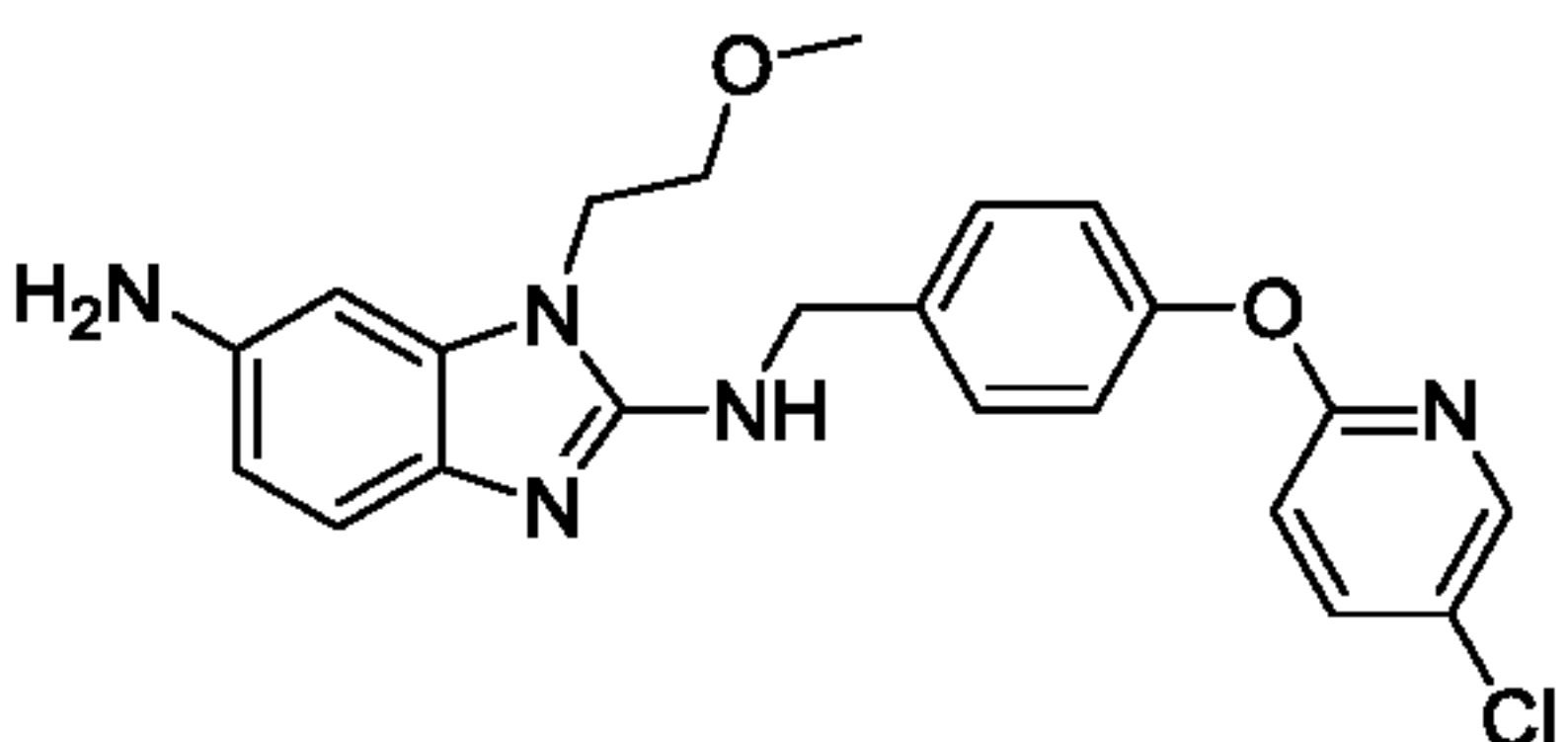
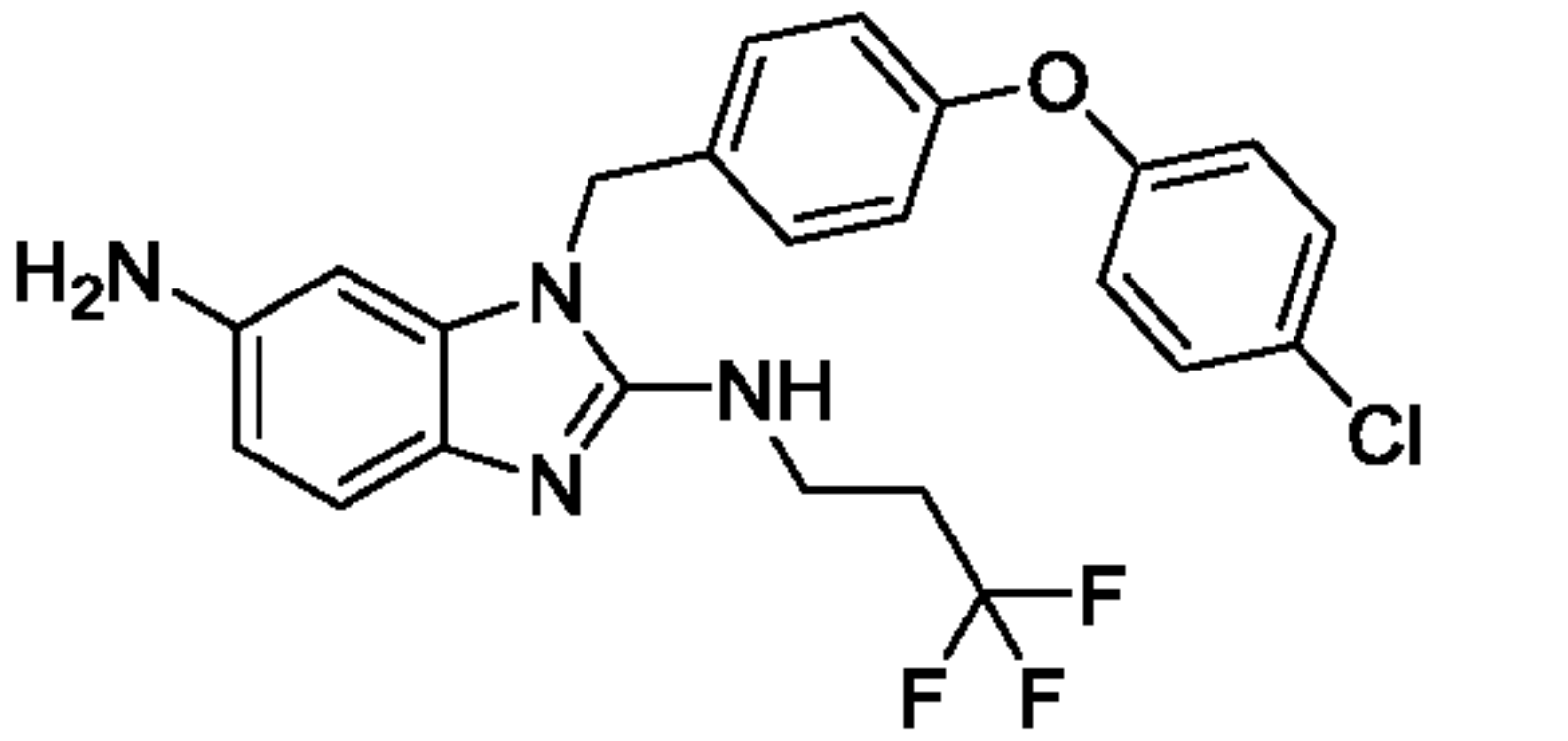
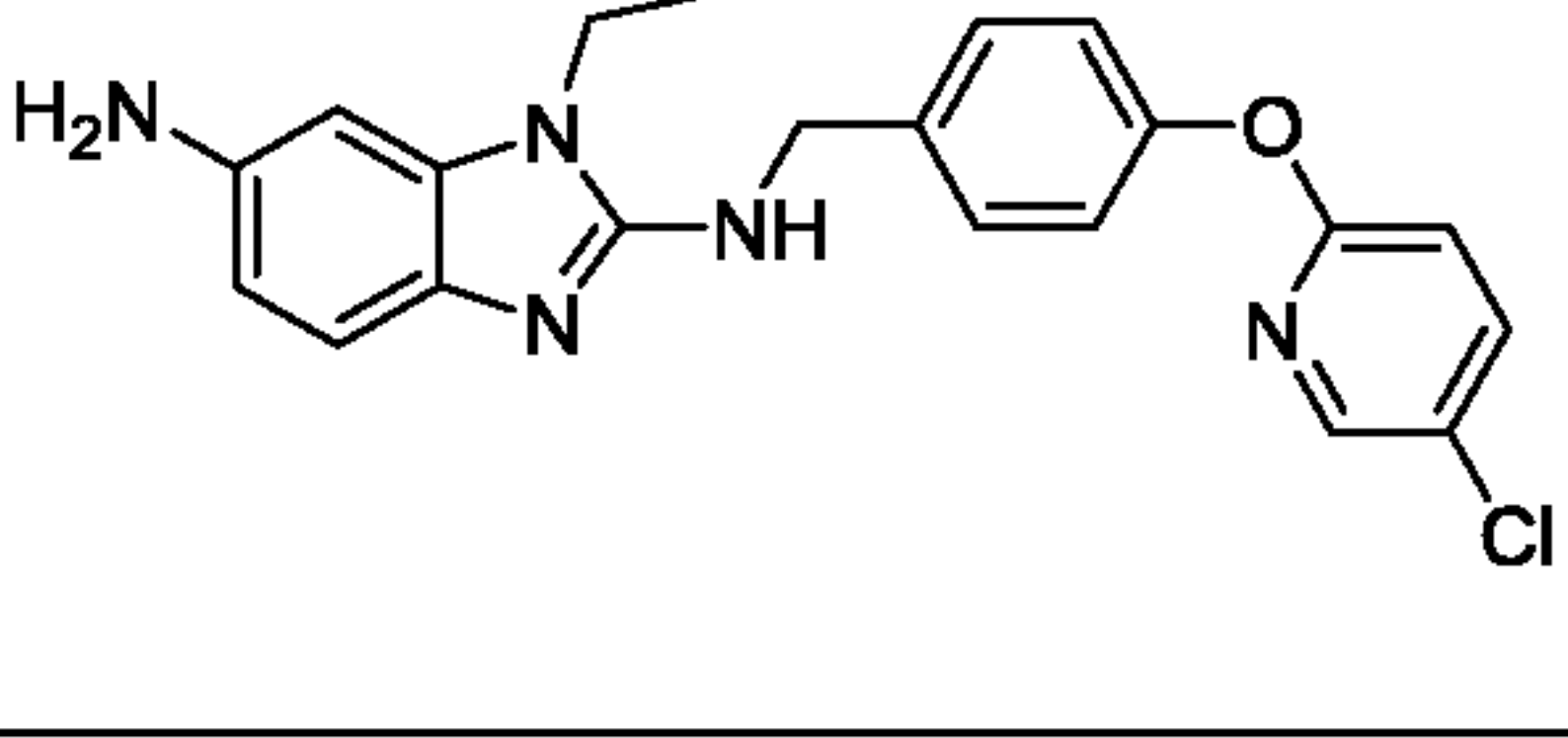
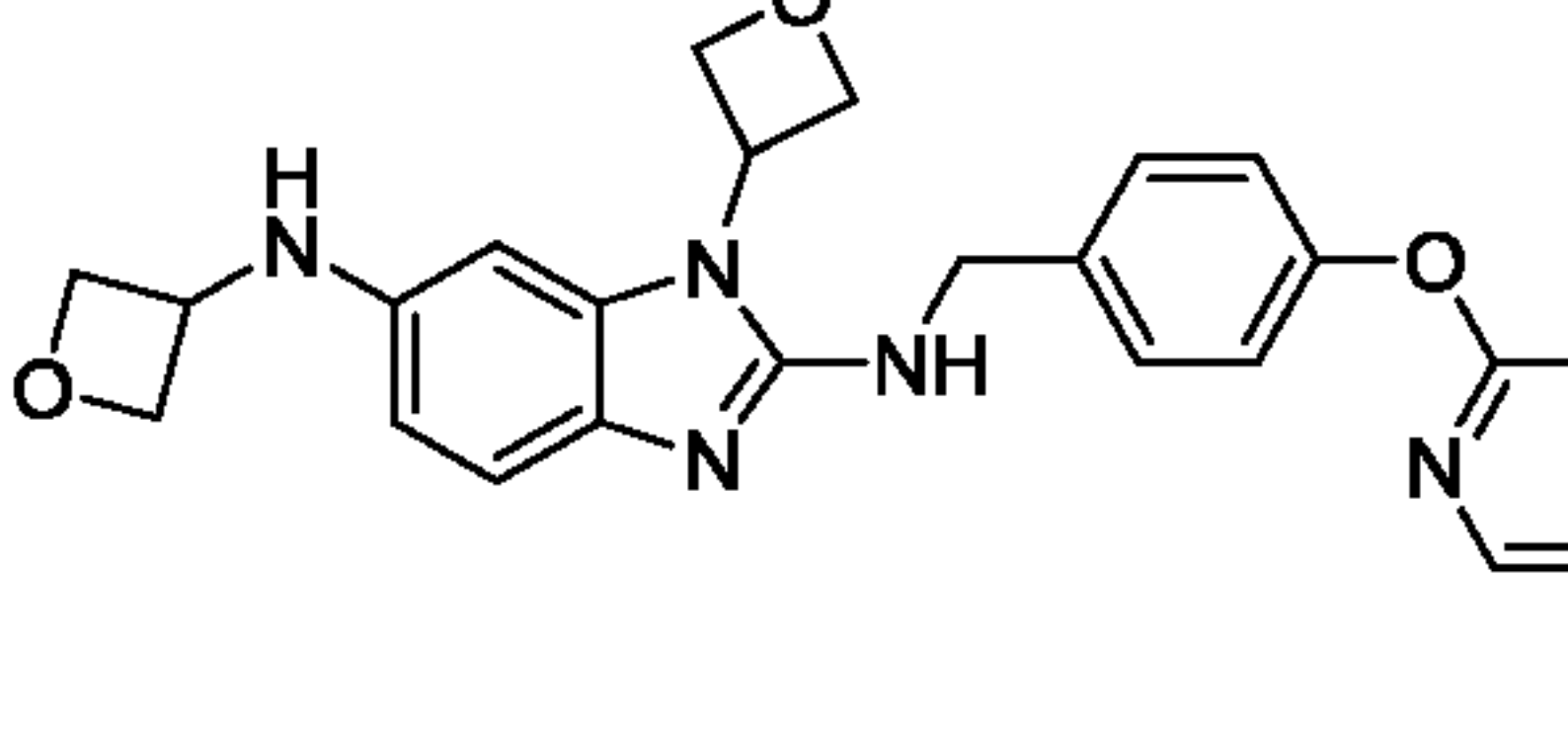
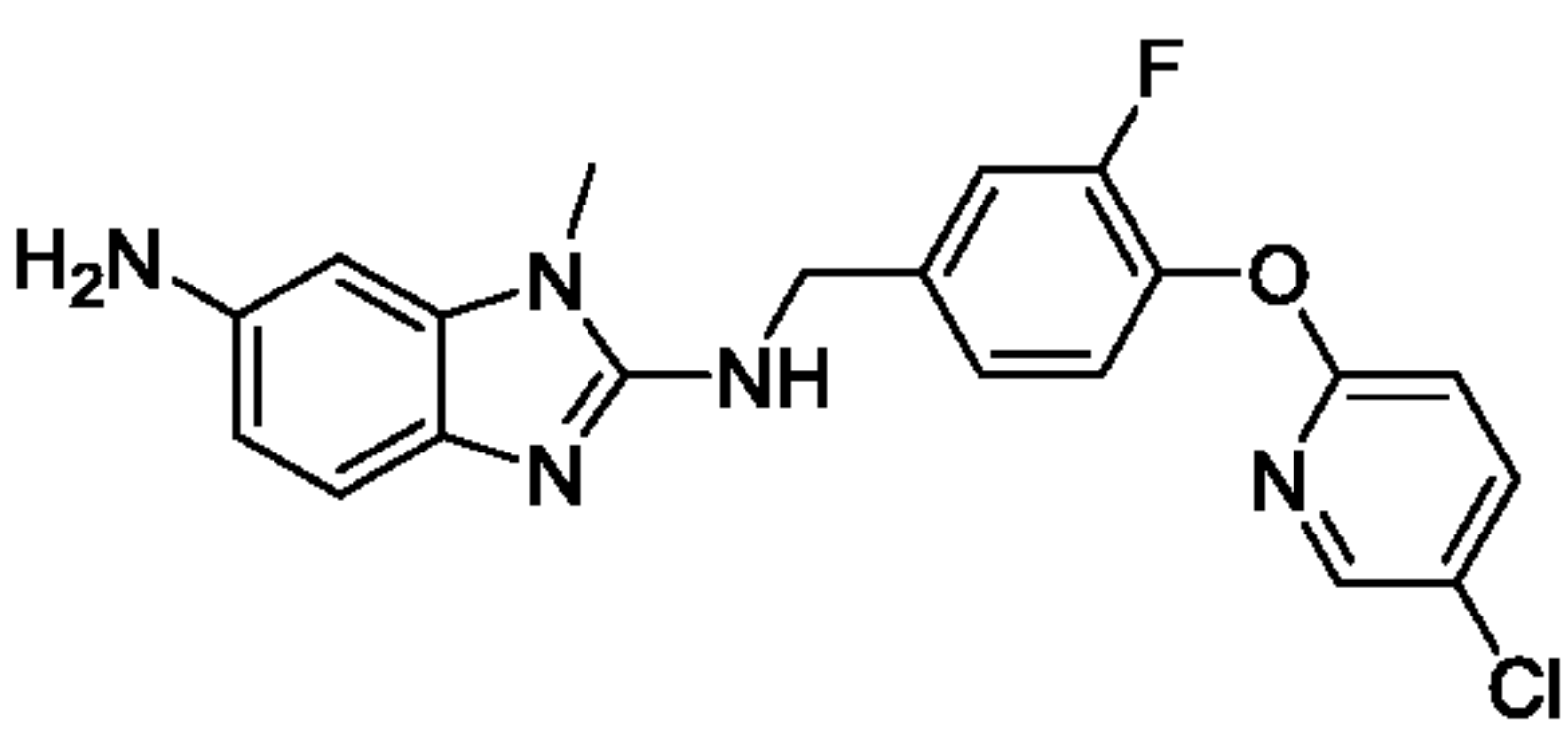
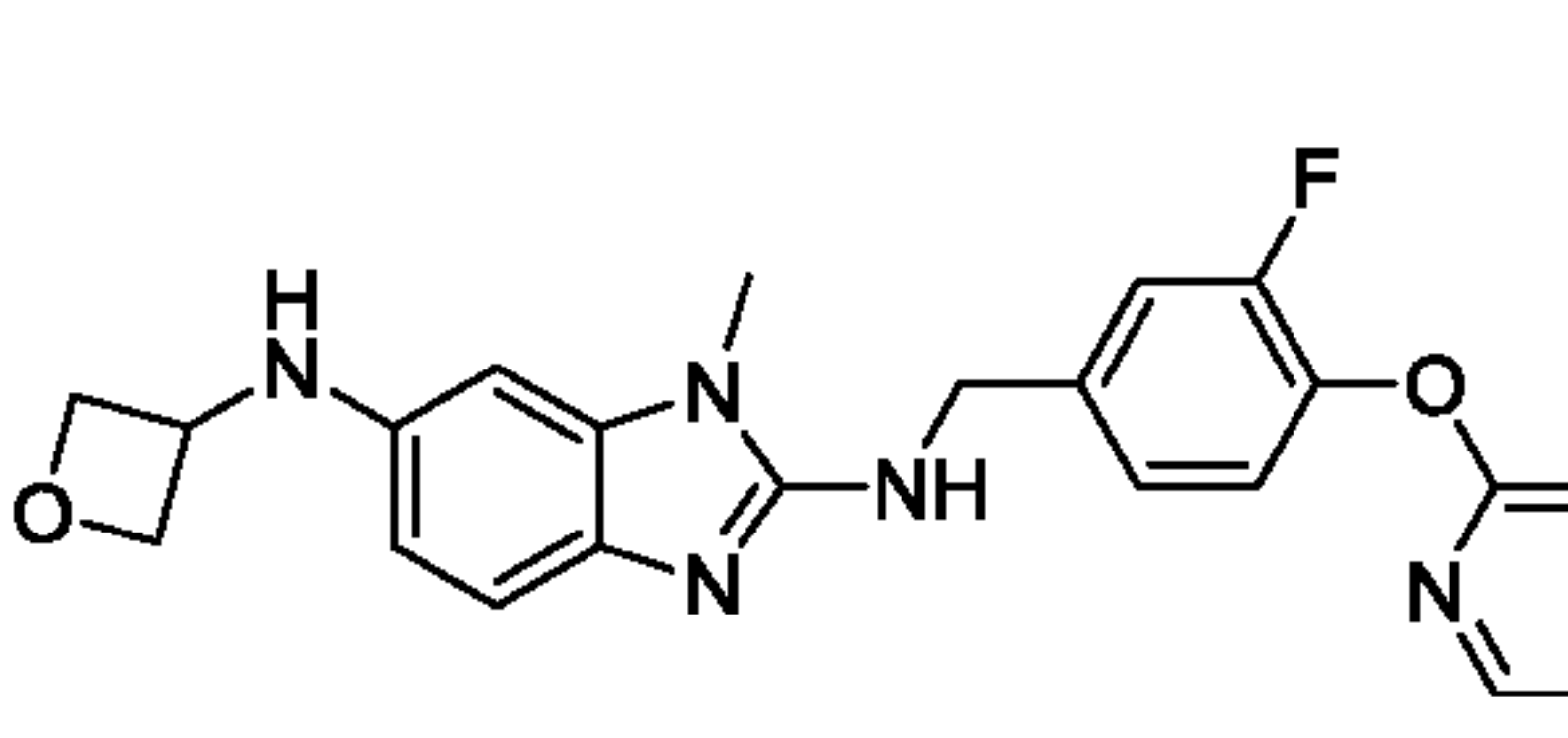
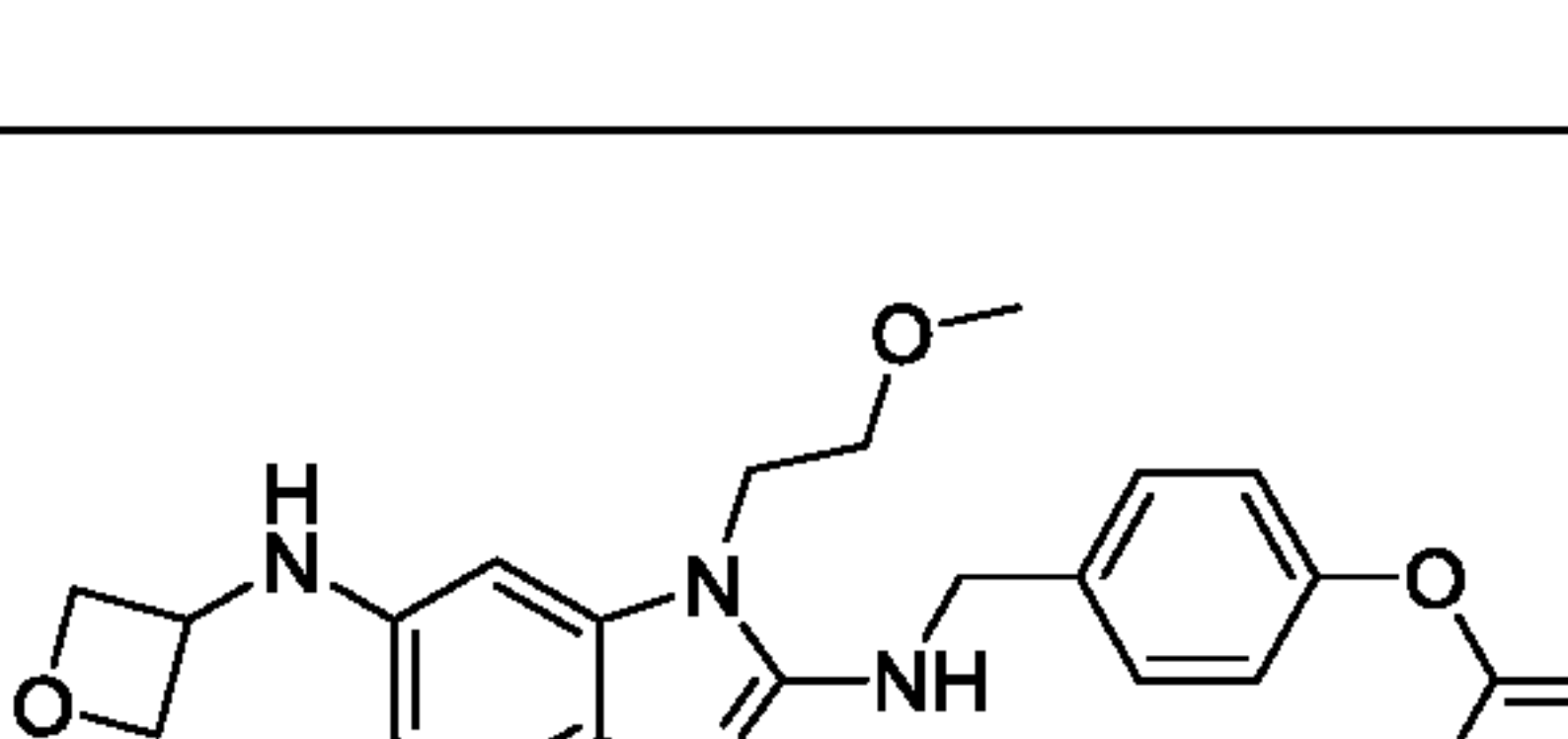
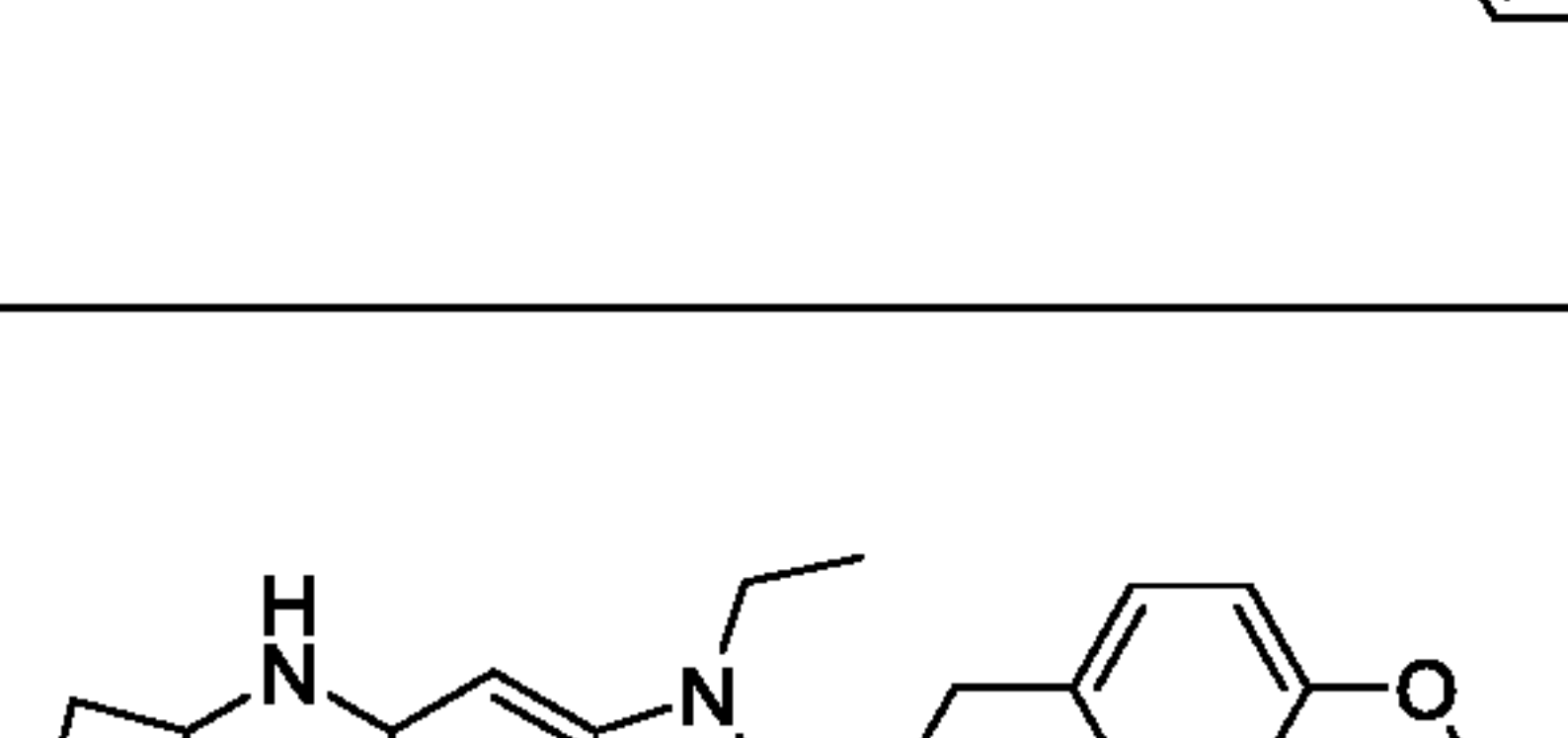
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 218 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.92 (1H, s), 7.98 (2H, d, <i>J</i> = 8.4 Hz), 7.55 (2H, d, <i>J</i> = 8.4 Hz), 7.09 (1H, d, <i>J</i> = 8.4 Hz), 6.49-6.59 (2H, m), 6.46 (1H, d, <i>J</i> = 2.0 Hz), 4.38 (2H, d, <i>J</i> = 5.2 Hz), 4.31 (2H, q, <i>J</i> = 7.2 Hz), 3.12 (6H, s), 1.30 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 98.7%, MS (ESI); <i>m/z</i> 406.0[M+ H] <sup>+</sup> .                                                                                                                                               |
| 219 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.44 (1H, m), 7.17 (1H, d, <i>J</i> = 8.4 Hz), 6.95-7.03 (4H, m), 6.90 (1H, d, <i>J</i> = 8.4 Hz), 6.42 (1H, q, <i>J</i> = 4.4 Hz), 6.31 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.07 (2H, s), 4.50 (2H, brs), 2.85 (3H, d, <i>J</i> = 4.4 Hz); LCMS: 97.7%, MS (ESI); <i>m/z</i> 378.9 [M+ H] <sup>+</sup> .                                                                                                                                                    |
| 220 |    | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, s), 7.92 (2H, d, <i>J</i> = 8.4 Hz), 7.52 (2H, d, <i>J</i> = 8.4 Hz), 7.35 (1H, s), 6.91 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, <i>J</i> = 2.0 Hz), 6.34 (1H, <i>J</i> = 8.0, 2.0 Hz), 5.92 (1H, brs), 4.31 (2H, s), 2.97 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 333.9[M+ H] <sup>+</sup> .                                                                                                                                                                                      |
| 221 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 11.56 (1H, brs), 10.68-10.79 (1H, m), 7.70 (2H, d, <i>J</i> = 6.8 Hz), 7.45-7.53 (3H, m), 6.82-6.89 (1H, m), 6.50-6.60 (1H, m), 6.26-6.35 (3H, m), 5.71-5.83 (1H, m), 4.25-4.35 (2H, m), 2.94 (3H, s), 2.93 (3H, s); LCMS: 98.9%, MS (ESI); <i>m/z</i> 359.9[M+ H] <sup>+</sup> .                                                                                                                                                                                                                  |
| 222 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.21 (1H, d, <i>J</i> = 2.4 Hz), 7.65 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.30 (2H, d, <i>J</i> = 8.4 Hz), 7.08 (2H, dd, <i>J</i> = 6.8, 2.4 Hz), 7.00 (1H, d, <i>J</i> = 8.4 Hz), 6.89 (1H, d, <i>J</i> = 8.8 Hz), 6.56 (1H, s), 6.43 (1H, d, <i>J</i> = 7.2 Hz), 4.42 (2H, d, <i>J</i> = 5.2 Hz), 4.20-4.30 (1H, m), 4.10-4.18 (2H, m), 3.95-4.05 (2H, m), 3.80-3.90 (1H, m), 3.55-3.65 (1H, m), 2.80-2.90 (1H, m), 2.65-2.75 (1H, m); LCMS: 98.1%, MS (ESI); <i>m/z</i> 515.0[M+ H] <sup>+</sup> . |
| 223 |  | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.54 (1H, d, <i>J</i> = 2.8 Hz), 7.88 (1H, d, <i>J</i> = 8.8 Hz), 7.45-7.52 (3H, m), 7.17 (2H, d, <i>J</i> = 8.8 Hz), 6.84-6.93 (2H, m), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.50-4.58 (4H, m); 3.41 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 414.0 [M+ H] <sup>+</sup> .                                                                                                                                                                             |
| 224 |  | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.32-8.37 (2H, m), 7.35-7.46 (4H, m), 7.03 (2H, <i>J</i> = 8.8 Hz), 6.83-6.88 (2H, m), 6.36 (1H, d, <i>J</i> = 2.8 Hz), 6.24-6.28 (1H, m), 4.53 (2H, brs), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.40 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 345.9 [M+ H] <sup>+</sup> .                                                                                                                                                                                                                     |
| 225 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.68 (1H, brs), 7.35-7.48 (5H, m), 6.96-7.17 (6H, m), 5.49 (2H, brs), 4.29 (2H, d, <i>J</i> = 6.4 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 423.0[M+H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                               |
| 226 |  | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.53 (1H, d, <i>J</i> = 2.8 Hz), 7.87 (1H, d, <i>J</i> = 8.8 Hz), 7.45-7.54 (3H, m), 7.16 (2H, d, <i>J</i> = 8.8 Hz), 6.91-6.99 (2H, m), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.80-4.88 (2H, m), 4.48-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.8 Hz), 3.44 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 469.9 [M+ H] <sup>+</sup> .                                                                                        |
| 227 |  | pale-yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.32-8.36 (2H, m), 7.35-7.46 (4H, m), 7.03 (2H, d, <i>J</i> = 8.8 Hz), 6.89-6.96 (2H, m), 6.18-6.26 (2H, m), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, d, <i>J</i> = 6.4 Hz), 4.48-4.55 (3H, m), 4.39 (2H, t, <i>J</i> = 5.6 Hz), 3.43 (3H, s); LCMS:                                                                                                                                                                                                                                     |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|     |                                                                                     | 100%, MS (ESI); m/z 402.2 [M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                                                                                       |
| 228 |    | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.71 (1H, s), 7.94 (2H, d, <i>J</i> = 8.4 Hz), 7.54 (2H, d, <i>J</i> = 8.0 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.27-6.43 (2H, m), 4.32 (2H, s), 2.97 (6H, s); LCMS: 97.9%, MS (ESI); m/z 377.9[M+ H] <sup>+</sup> .                                                                                                                                              |
| 229 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.17 (2H, d, <i>J</i> = 8.4 Hz), 7.04-7.12 (3H, m), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.44 (1H, brs), 6.33 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 5.10 (2H, s), 4.51 (2H, brs), 2.86 (3H, d, <i>J</i> = 4.4 Hz); LCMS: 100.0%, MS (ESI); m/z 379.9[M+H] <sup>+</sup> . |
| 230 |   | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> +D <sub>2</sub> O, 400 MHz); δ 8.72 (1H, s), 7.94-8.11 (2H, m), 7.03 (1H, d, <i>J</i> = 8.0 Hz), 6.47 (1H, s), 6.32 (1H, d, <i>J</i> = 7.6 Hz), 4.40-4.54 (1H, m), 3.44-3.56 (1H, m), 3.29-3.40 (1H, m), 3.14-3.29 (2H, m), 2.97 (6H, s), 2.04-2.21 (1H, m), 2.22-2.35 (1H, m); LCMS: 100%, MS (ESI); m/z 369.9[M+ H] <sup>+</sup> .                                              |
| 231 |  | white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.43 (1H, m), 7.25 (1H, d, <i>J</i> = 8.8 Hz), 6.94-7.04 (2H, m), 6.89 (1H, d, <i>J</i> = 8.4 Hz), 6.14-6.23 (4H, m), 5.78 (1H, d, <i>J</i> = 6.8 Hz), 5.13 (2H, s), 4.78 (2H, t, <i>J</i> = 6.4 Hz), 4.38-4.80 (1H, m), 4.29-4.37 (2H, t, <i>J</i> = 6.0 Hz); LCMS: 98.8%, MS (ESI); m/z 421.0 [M+H] <sup>+</sup> .                                      |
| 232 |  | white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.60-10.80 (1H, m), 7.40-7.50 (1H, m), 7.27 (2H, d, <i>J</i> = 8.0 Hz), 7.17 (2H, d, <i>J</i> = 7.2 Hz), 6.80-6.95 (2H, m), 6.15-6.45 (2H, m), 5.45-5.75 (1H, m), 4.17 (2H, s), 3.30 (2H, s), 2.93 (3H, s), 2.91 (3H, s); LCMS: 95.2%, MS (ESI); m/z 324.0[M+ H] <sup>+</sup> .                                                                               |
| 233 |  | pale-yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.60-10.80 (1H, m), 8.14 (1H, s), 7.28 (2H, d, <i>J</i> = 8.4 Hz), 7.24 (1H, s), 6.95 (2H, d, <i>J</i> = 6.8 Hz), 6.77-6.91 (1H, m), 6.17-6.40 (2H, m), 5.44-5.65 (1H, m), 5.17 (2H, s), 4.13 (2H, s), 2.94 (3H, s), 2.91 (3H, s); LCMS: 98.8 %, MS (ESI); m/z 364.1[M+ H] <sup>+</sup> .                                                               |
| 234 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.26 (2H, d, <i>J</i> = 8.8 Hz), 7.05-7.13 (3H, m), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.13-6.25 (4H, m), 5.79 (1H, d, <i>J</i> = 7.2 Hz), 5.16 (2H, s), 4.79 (2H, t, <i>J</i> = 6.4 Hz), 4.40-4.50 (1H, m), 4.35 (2H, t, <i>J</i> = 6.0 Hz); LCMS: 97.8%, MS (ESI); m/z 421.9[M+H] <sup>+</sup> .  |
| 235 |  | off-white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.24 (2H, d, <i>J</i> = 8.4 Hz), 7.07-7.13 (3H, m), 7.03 (1H, d, <i>J</i> = 8.4 Hz), 6.45 (1H, d, <i>J</i> = 7.6 Hz), 6.33 (2H, brs), 6.23 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.22 (2H, s), 4.15 (4H, t, <i>J</i> = 12.0 Hz); LCMS: 100.0%, MS (ESI); m/z 442.1[M+H] <sup>+</sup> . |
| 236 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.86 (1H, brs), 7.84 (1H, d, <i>J</i> = 2.0 Hz), 7.76 (1H, d, <i>J</i> = 8.8 Hz), 7.43 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.99 (1H, d, <i>J</i> = 8.4 Hz), 6.46 (1H, s), 6.27 (1H, d, <i>J</i> = 6.4 Hz), 3.85-4.00 (1H, m), 3.63-3.72 (2H, m), 3.35-3.43 (2H, m), 2.98 (3H, s), 2.33-2.45 (2H, m); LCMS: 99.0%, MS (ESI); m/z 382.0 [M+H] <sup>+</sup> .           |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 237 |    | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.72 (1H, brs), 7.25-7.40 (4H, m), 7.15 (1H, d, <i>J</i> = 6.8 Hz), 6.95 (1H, s), 6.87 (1H, d, <i>J</i> = 7.6 Hz), 6.37 (1H, s), 6.29 (1H, s), 5.63 (1H, brs), 4.19 (2H, d, <i>J</i> = 6.0 Hz), 3.68-3.79 (2H, m), 3.44-3.53 (2H, m), 2.94 (6H, s), 2.36-2.45 (2H, m), 1.71-1.83 (2H, m); LCMS: 97.1 %, MS (ESI); <i>m/z</i> 394.1[M+ H] <sup>+</sup> .                                                   |
| 238 |    | white powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, s), 7.45-7.54 (2H, m), 7.23 (2H, d, <i>J</i> = 8.4 Hz), 7.08 (2H, d, <i>J</i> = 8.8 Hz), 6.31 (1H, s), 6.26 (1H, dd, <i>J</i> = 2.0, 8.0 Hz), 6.10 (2H, s), 5.11 (2H, s), 4.48 (2H, s); LCMS: 99.8 %, MS (ESI); <i>m/z</i> 365.9[M+ H] <sup>+</sup> .                                                                                                                                  |
| 239 |   | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.37 (1H, d, <i>J</i> = 2.8 Hz), δ 7.43-7.47 (3H, m), 7.00-7.07 (2H, m), 7.01 (1H, d, <i>J</i> = 8.8 Hz), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.25-6.28 (2H, m), 6.09 (2H, brs), 5.18 (2H, s), 4.49 (2H, brs); LCMS: 100%, MS (ESI); <i>m/z</i> 366.0 [M+H] <sup>+</sup> .                                                                                                                                 |
| 240 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.08 (1H, s), 7.64 (1H, d, <i>J</i> = 8.4 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.14 (2H, d, <i>J</i> = 8.8 Hz), 7.04 (1H, d, <i>J</i> = 8.8 Hz), 6.82 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, s), 6.26 (1H, d, <i>J</i> = 8.4 Hz), 6.17 (2H, brs), 5.10 (2H, s), 4.49 (2H, brs); LCMS: 100%, MS (ESI); <i>m/z</i> 366.0 [M+H] <sup>+</sup> .                                                                  |
| 241 |  | pale-yellow powder (amorphous) <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.41-7.52 (4H, m), 6.88 (2H, d, <i>J</i> = 8.4 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.31 (1H, d, <i>J</i> = 8.4 Hz), 5.75 (1H, brs), 4.25 (2H, d, <i>J</i> = 4.4 Hz), 3.94-4.06 (2H, m), 3.60-3.71 (2H, m), 2.95 (6H, s), 1.96-2.13 (4H, m); LCMS: 97.5%, MS (ESI); <i>m/z</i> 376.1[M+ H] <sup>+</sup> .                                                                                 |
| 242 |  | pale white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.35-7.49 (4H, m), 7.13 (1H, d, <i>J</i> = 6.4 Hz), 6.95-7.09 (4H, m), 6.46 (1H, s), 6.32 (1H, d, <i>J</i> = 8.4 Hz), 4.53 (2H, d, <i>J</i> = 5.6 Hz), 4.22 (4H, t, <i>J</i> = 12.0 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 440.9[M + H] <sup>+</sup> .                                                                                                                                                  |
| 243 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 8.54 (1H, s), 8.21 (1H, dd, <i>J</i> = 8.8, 2.0 Hz), 7.19-7.28 (3H, m), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.84 (1H, d, <i>J</i> = 8.4 Hz), 6.34 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.15 (2H, brs), 5.14 (2H, s), 4.50 (2H, brs); LCMS: 97.7%, MS (ESI); <i>m/z</i> 400.0[M+ H] <sup>+</sup> .                                                                                         |
| 244 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.10 (2H, brs), 8.19 (1H, d, <i>J</i> = 2.4 Hz), 7.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.65 (1H, s), 7.48 (1H, d, <i>J</i> = 8.4 Hz), 7.39 (2H, d, <i>J</i> = 8.4 Hz), 7.29 (1H, d, <i>J</i> = 8.0 Hz), 7.06 (2H, d, <i>J</i> = 8.4 Hz), 7.00 (1H, d, <i>J</i> = 8.8 Hz), 4.42 (2H, t, <i>J</i> = 7.4 Hz), 3.01 (2H, t, <i>J</i> = 7.4 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 379.9[M+ H] <sup>+</sup> . |
| 245 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36 (2H, d, <i>J</i> = 8.8 Hz), 7.23 (2H, d, <i>J</i> = 8.8 Hz), 6.98-7.11 (4H, m), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.32 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.12 (2H, brs), 5.11 (2H, s), 4.49 (2H, brs); LCMS: 100 %, MS (ESI); <i>m/z</i> 415.0[M+ H] <sup>+</sup>                                                                                                      |
| 246 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.57-7.65 (1H, m), 7.42-7.54 (3H, m), 7.22-7.33 (4H, m), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.33 (1H, d, <i>J</i> = 1.6 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 6.18 (2H, brs), 5.18 (2H, s), 4.50 (2H, brs); LCMS: 99.7%, MS (ESI); <i>m/z</i> 372.0[M+ H] <sup>+</sup> .                                                                                                                             |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| 247 |    | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), δ 7.95 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.27 (2H, d, <i>J</i> = 8.8 Hz), 7.08-7.14 (3H, m), 6.82 (1H, d, <i>J</i> = 8.0 Hz), 6.19-6.24 (2H, m), 6.02 (2H, brs), 5.64 (1H, q, <i>J</i> = 7.2 Hz), 4.39 (2H, brs), 1.83 (3H, d, <i>J</i> = 7.2 Hz); LCMS: 99.8%, MS (ESI); <i>m/z</i> 380.0 [M+H] <sup>+</sup> .                                                                                                                                                                     |
| 248 |    | purple powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, d, <i>J</i> = 2.4 Hz), δ 7.97 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.31 (1H, t, <i>J</i> = 8.4 Hz), 7.20 (1H, d, <i>J</i> = 8.8 Hz), 7.14 (1H, d, <i>J</i> = 11.2 Hz), 7.01 (1H, d, <i>J</i> = 8.0 Hz), 6.87 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (2H, brs), 6.38 (1H, s), 6.30 (1H, d, <i>J</i> = 7.2 Hz), 5.18 (2H, s); LCMS: 95.5%, MS (ESI); <i>m/z</i> 383.9 [M+H] <sup>+</sup> .                                                                                                                            |
| 249 |   | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.4 Hz), 7.80 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.38 (2H, d, <i>J</i> = 8.0 Hz), 7.14 (2H, d, <i>J</i> = 8.0 Hz), 6.91 (1H, d, <i>J</i> = 8.8 Hz), 6.79-6.85 (1H, m), 6.24 (2H, dd, <i>J</i> = 4.4, 2.0 Hz), 6.08 (2H, brs), 5.27 (2H, s), 5.11 (2H, s), 4.45 (2H, brs); LCMS: 100%, MS (ESI); <i>m/z</i> 379.9 [M+H] <sup>+</sup> .                                                                                                                                                   |
| 250 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.19 (2H, d, <i>J</i> = 8.8 Hz), 7.04-7.13 (3H, m), 6.89 (1H, d, <i>J</i> = 8.0 Hz), 6.58 (1H, t, <i>J</i> = 5.6 Hz), 6.32 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.13 (2H, s), 5.05 (1H, brs), 4.52 (2H, brs), 3.53-3.64 (2H, m), 3.36-3.43 (2H, m); LCMS: 100 %, MS (ESI); <i>m/z</i> 410.0[M+ H] <sup>+</sup> .                                                                                                |
| 251 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.23 (2H, d, <i>J</i> = 8.4 Hz), 7.03-7.15 (3H, m), 6.96 (1H, d, <i>J</i> = 8.4 Hz), 6.64 (1H, t, <i>J</i> = 5.6 Hz), 6.21 (1H, s), 6.17 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 5.16 (2H, s), 4.99 (1H, t, <i>J</i> = 5.2 Hz), 4.78 (2H, t, <i>J</i> = 6.0 Hz), 4.38-4.50 (1H, m), 4.33 (2H, d, <i>J</i> = 6.0 Hz), 3.54-3.63 (2H, m), 3.36-3.44 (2H, m); LCMS: 99.4 %, MS (ESI); <i>m/z</i> 466.0[M+ H] <sup>+</sup> . |
| 252 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.36-7.43 (2H, m), 7.22 (1H, d, <i>J</i> = 8.8 Hz), 6.95-7.02 (5H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.33 (1H, d, <i>J</i> = 2.0 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.11 (2H, s), 4.55 (2H, brs), 3.54 (2H, q, <i>J</i> = 6.0 Hz), 2.88 (2H, t, <i>J</i> = 6.8 Hz); LCMS: 100%, MS (ESI); <i>m/z</i> 418.0[M+H] <sup>+</sup> .                                                                                                                                                                        |
| 253 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 6.93-7.16 (5H, m), 6.60 (1H, d, <i>J</i> = 1.6 Hz), 6.46-6.49 (1H, m), 4.54 (2H, d, <i>J</i> = 5.6 Hz), 3.49 (3H, s), 2.83 (6H, s); LCMS: 99.9%, MS (ESI); <i>m/z</i> 407.9 [M+H] <sup>+</sup> .                                                                                                                                                                                                          |
| 254 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ); δ 8.61 (1H, d, <i>J</i> = 2.4 Hz), 7.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.52 (1H, d, <i>J</i> = 8.4 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.97 (2H, d, <i>J</i> = 8.4 Hz), 6.82 (1H, d, <i>J</i> = 8.0 Hz), 6.29 (1H, d, <i>J</i> = 1.6 Hz), 6.24 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.08 (2H, brs), 5.14 (2H, s), 5.03 (2H, s), 4.45 (2H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 379.9[M+ H] <sup>+</sup> .                                                                                                                   |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 255 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.14 (1H, d, <i>J</i> = 2.4 Hz), 7.97 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.26-7.37 (2H, m), 7.10-7.22 (2H, m), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.35 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 6.18 (2H, brs), 5.15 (2H, s), 4.53 (2H, brs); LCMS: 100%, MS (ESI); <i>m/z</i> 399.9[M+ H] <sup>+</sup> .                                                                                                                                                                                      |
| 256 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.0 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.02-7.10 (3H, m), 6.90 (1H, d, <i>J</i> = 8.4 Hz), 6.70 (1H, d, <i>J</i> = 8.0 Hz), 6.23 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 5.00-5.12 (1H, m), 4.83 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.55 (1H, m), 4.35-4.40 (2H, m), 3.46 (3H, s), 1.50 (3H, d, <i>J</i> = 6.8 Hz); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 450.1 [M+H] <sup>+</sup> .           |
| 257 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.41 (2H, d, <i>J</i> = 8.4 Hz), 6.90-7.00 (3H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.79 (1H, t, <i>J</i> = 6.0 Hz), 6.31 (1H, d, <i>J</i> = 1.6 Hz), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.82 (1H, d, <i>J</i> = 7.2 Hz), 5.03 (1H, brs), 4.83 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.98 (2H, t, <i>J</i> = 5.2 Hz), 3.59-3.70 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 466.1[M+ H] <sup>+</sup> . |
| 258 |  | off-white solid; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.11 (1H, d, <i>J</i> = 2.4 Hz), 7.66 (1H, dd, <i>J</i> = 8.8, <i>J</i> = 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.31 (1H, d, <i>J</i> = 8.4 Hz), 7.11 (2H, d, <i>J</i> = 8.4 Hz), 6.91 (1H, d, <i>J</i> = 8.8 Hz), 6.66 (1H, d, <i>J</i> = 2.0 Hz), 6.54 (1H, dd, <i>J</i> = 8.4 Hz, <i>J</i> = 2.0 Hz), 4.67 (2H, d, <i>J</i> = 4.8 Hz), 4.29-4.38 (1H, m), 4.24 (1H, brs), 3.55 (2H, brs), 1.56 (6H, d, <i>J</i> = 6.8 Hz); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 408.1 [M+H] <sup>+</sup> .                                    |
| 259 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.05-7.10 (3H, m), 6.87 (1H, d, <i>J</i> = 8.0 Hz), 6.75 (1H, t, <i>J</i> = 5.2 Hz), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 5.06 (1H, t, <i>J</i> = 4.8 Hz), 4.57 (2H, brs), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.95 (2H, t, <i>J</i> = 5.2 Hz), 3.64 (2H, q, <i>J</i> = 5.2 Hz); LCMS: 99.3%, MS (ESI); <i>m/z</i> 410.0[M+ H] <sup>+</sup> .                                      |
| 260 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 7.05-7.10 (3H, m), 6.83 (1H, d, <i>J</i> = 8.4 Hz), 6.65 (1H, d, <i>J</i> = 8.0 Hz), 6.35 (1H, d, <i>J</i> = 1.6 Hz), 6.25 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.00-5.09 (1H, m), 4.55 (2H, brs), 3.44 (3H, s), 1.51 (3H, d, <i>J</i> = 7.2 Hz); LCMS: 98.2%, MS (ESI); <i>m/z</i> 394.0 [M+H] <sup>+</sup> .                                                                                                    |
| 261 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.04-7.14 (3H, m), 7.01 (1H, d, <i>J</i> = 1.2 Hz), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 6.76 (1H, t, <i>J</i> = 5.6 Hz), 6.35 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 5.53-5.65 (1H, m), 5.04-5.17 (2H, m), 4.90-5.03 (2H, m), 4.71 (2H, brs), 4.45 (2H, d, <i>J</i> = 5.6 Hz); LCMS: 98.3%, MS (ESI); <i>m/z</i> 422.1[M+ H] <sup>+</sup> .                                                                             |
| 262 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.39 (2H, d, <i>J</i> = 8.8 Hz), 7.27 (2H, d, <i>J</i> = 8.8 Hz), 7.07 (1H, t, <i>J</i> = 5.6 Hz), 6.94-7.02 (5H, m), 6.17-6.24 (2H, m), 5.87 (1H, d, <i>J</i> = 6.8 Hz), 5.14 (2H, s), 4.78 (2H, t, <i>J</i> = 6.4 Hz), 4.39-4.48 (1H, m), 4.34 (2H, t, <i>J</i> = 6.0 Hz), 3.55 (2H, q, <i>J</i> = 6.0 Hz), 2.88 (2H, t, <i>J</i> = 6.4 Hz); LCMS: 98.6%, MS (ESI); <i>m/z</i> 474.2 [M+H] <sup>+</sup> .                                                                                                                 |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 263 |    | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.8 Hz), 7.05-7.11 (3H, m), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.78 (1H, t, <i>J</i> = 5.6 Hz), 6.41 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.49-4.51 (4H, m), 4.06 (2H, t, <i>J</i> = 5.6 Hz), 3.57 (2H, t, <i>J</i> = 4.8 Hz), 3.24 (3H, s); LCMS: 98.5%, MS (ESI); <i>m/z</i> 424.1 [M+ H] <sup>+</sup> .                                                                                        |
| 264 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.44 (2H, m), 7.18 (2H, d, <i>J</i> = 8.8 Hz), 6.95-7.03 (4H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.75 (1H, t, <i>J</i> = 5.6 Hz), 6.31 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.08 (2H, s), 4.5 (2H, brs), 3.53 (2H, q, <i>J</i> = 6.4 Hz), 2.59-2.70 (2H, m); LCMS: 100%, MS (ESI); <i>m/z</i> 461.0[M+H] <sup>+</sup> .                                                                                                                                                                   |
| 265 |   | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.41 (2H, d, <i>J</i> = 8.8 Hz), 7.05-7.10 (3H, m), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.39 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.43-4.60 (4H, m), 3.93 (2H, q, <i>J</i> = 7.2 Hz), 1.20 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 99.2 %, MS (ESI); <i>m/z</i> 394.1 [M+H] <sup>+</sup> .                                                                                                   |
| 266 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.16 (4H, m), 6.84-6.97 (2H, m), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.05 (1H, d, <i>J</i> = 6.0 Hz), 5.51-5.68 (1H, m), 5.04-5.12 (2H, m), 4.96-5.04 (2H, m), 4.82 (2H, t, <i>J</i> = 6.0 Hz), 4.39-4.54 (5H, m); LCMS: 98.8%, MS (ESI); <i>m/z</i> 478.1[M+ H] <sup>+</sup> .                                                                                                                           |
| 267 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.97 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.36 (1H, d, <i>J</i> = 11.2 Hz), 7.24-7.30 (2H, m), 7.20 (1H, d, <i>J</i> = 8.8 Hz), 6.97 (1H, t, <i>J</i> = 6.0 Hz), 6.87 (1H, d, <i>J</i> = 8.4 Hz), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.56 (2H, brs), 4.52 (2H, d, <i>J</i> = 5.6 Hz), 3.42 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 398.0[M+ H] <sup>+</sup> .                                                                                         |
| 268 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.98 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.36 (1H, d, <i>J</i> = 11.2 Hz), 7.23-7.31 (2H, m), 7.20 (1H, d, <i>J</i> = 8.8 Hz), 7.04 (1H, t, <i>J</i> = 6.0 Hz), 6.95 (1H, d, <i>J</i> = 8.0 Hz), 6.27 (1H, d, <i>J</i> = 2.0 Hz), 6.23 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.87 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.60 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 454.1[M+ H] <sup>+</sup> .                    |
| 269 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.41 (2H, d, <i>J</i> = 8.0 Hz), 7.05-7.10 (3H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.84 (1H, t, <i>J</i> = 5.6 Hz), 6.31 (1H, s), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 4.10 (2H, t, <i>J</i> = 5.2 Hz), 3.58 (2H, t, <i>J</i> = 5.2 Hz), 3.25 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 480.2[M+ H] <sup>+</sup> .     |
| 270 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.40 (2H, d, <i>J</i> = 8.8 Hz), 7.05-7.10 (3H, m), 6.99 (1H, t, <i>J</i> = 6.0 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.28 (1H, d, <i>J</i> = 2.0 Hz), 6.19 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.97 (2H, q, <i>J</i> = 6.8 Hz), 1.20 (2H, d, <i>J</i> = 7.2 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 450.0 [M+H] <sup>+</sup> . |

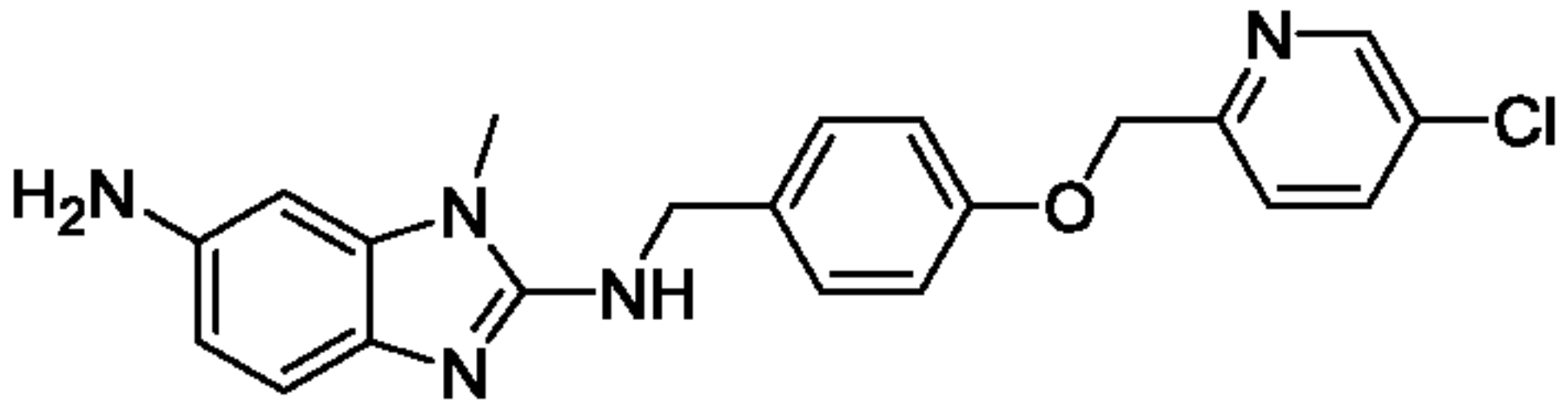
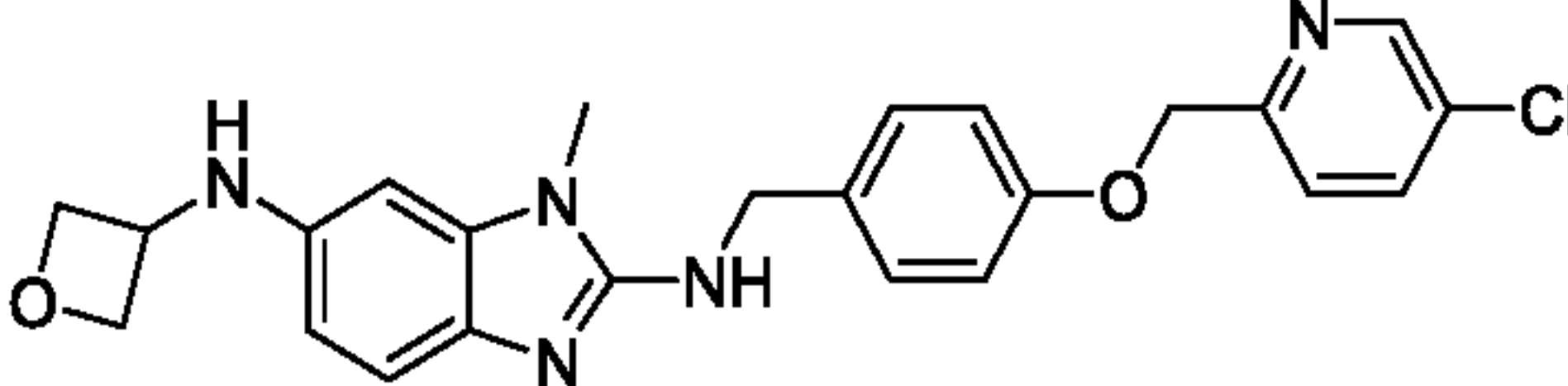
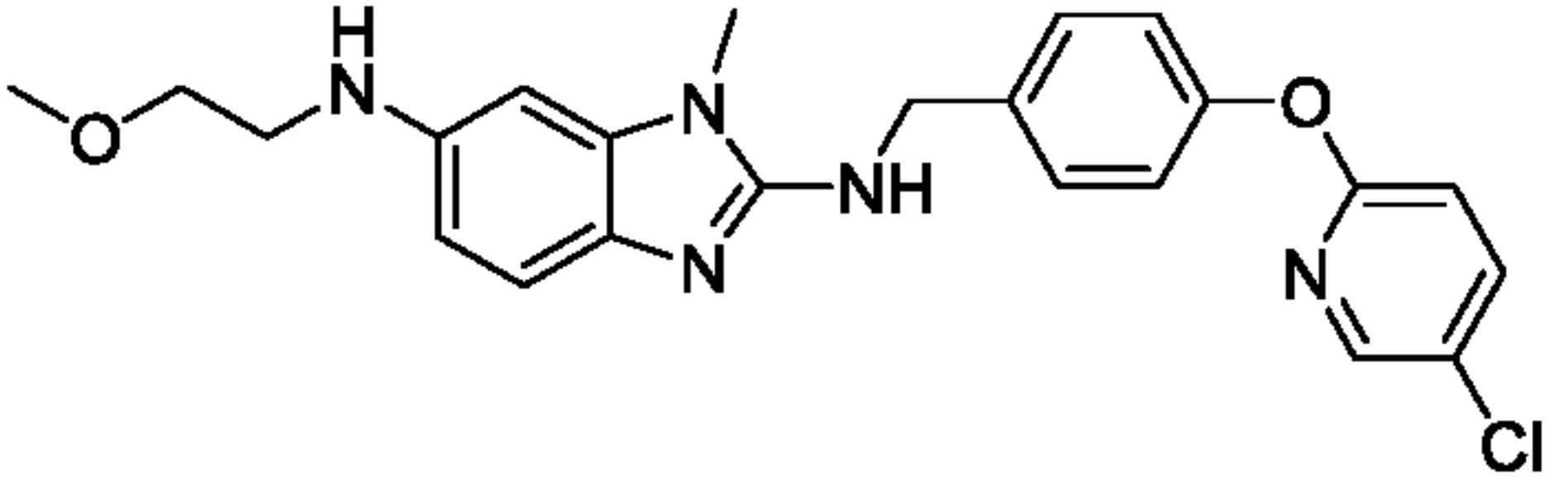
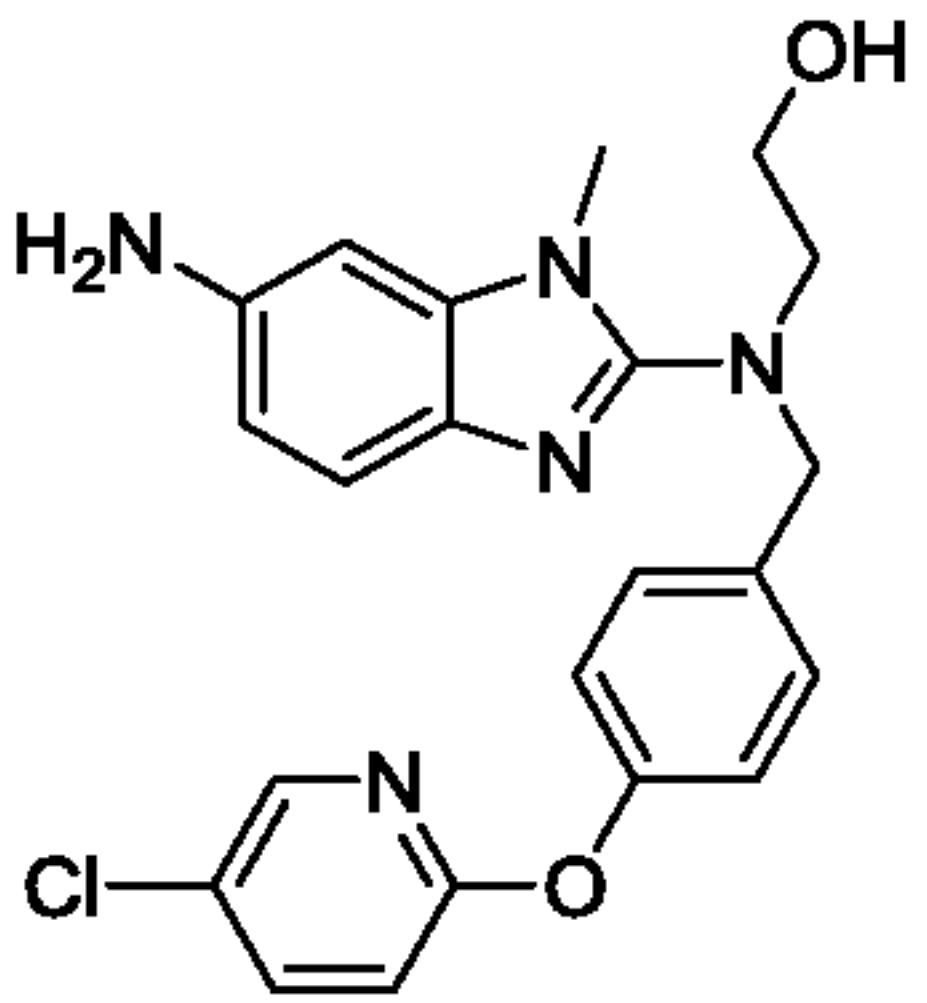
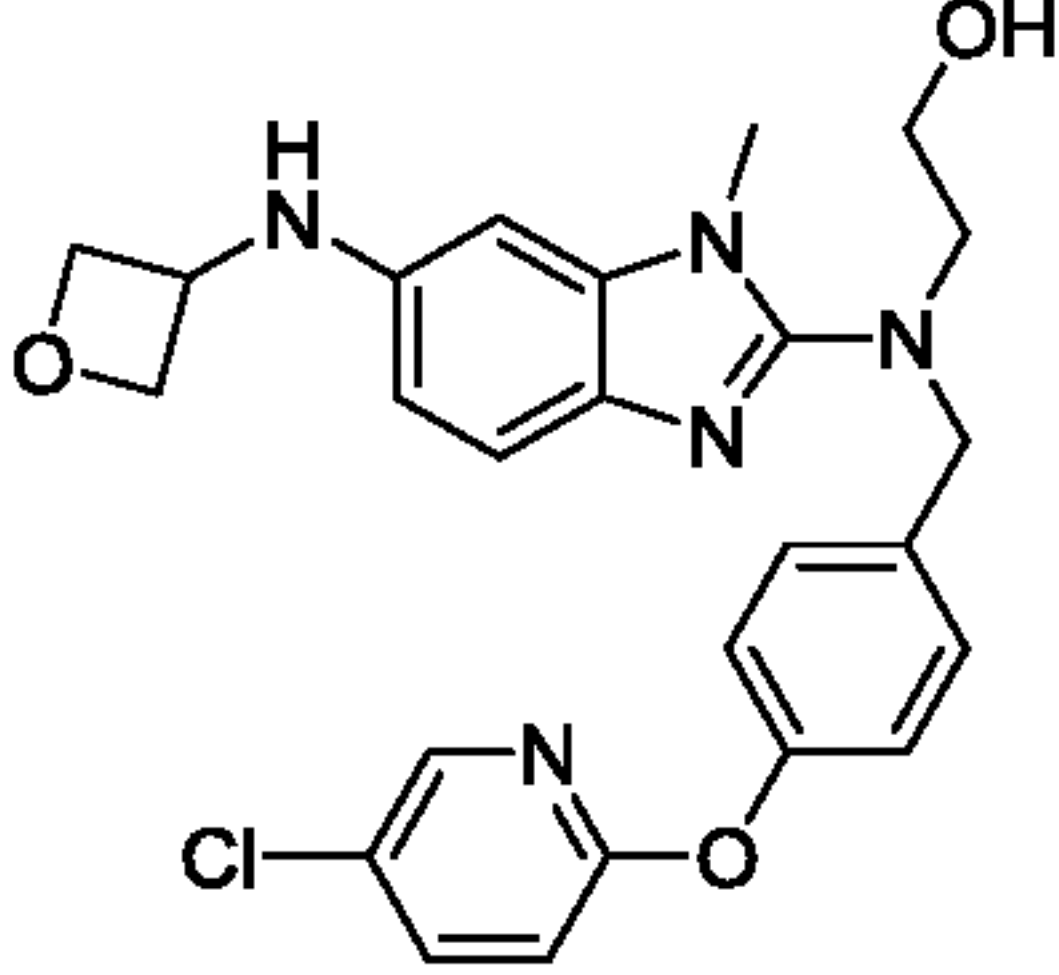
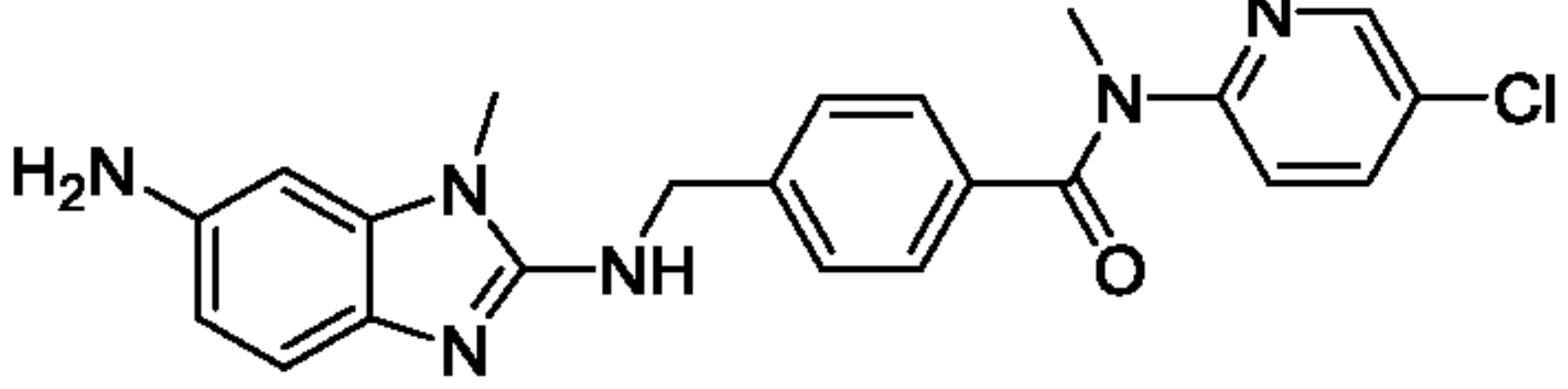
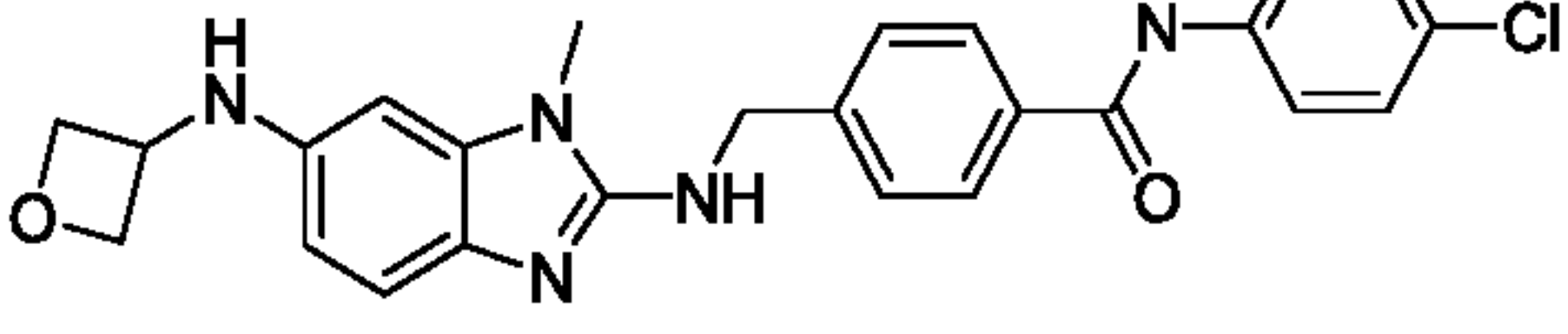
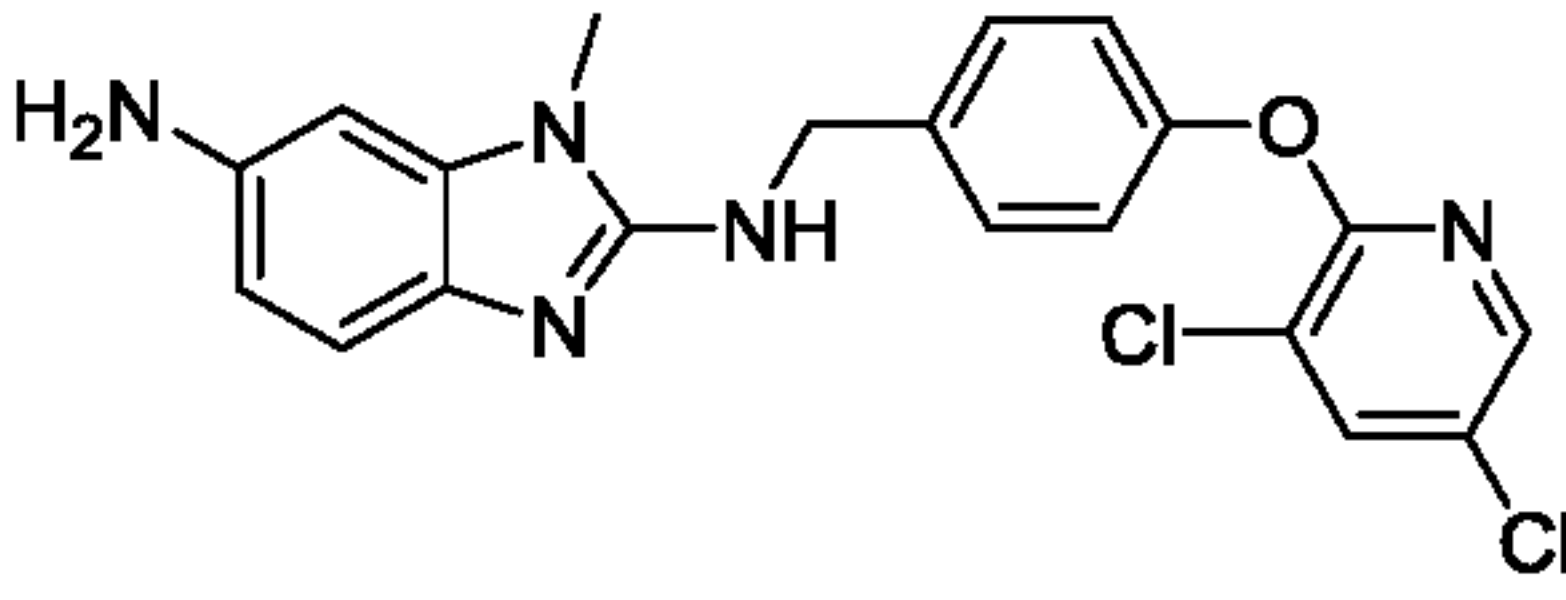
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 271 |  | brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.40 (2H, d, <i>J</i> = 8.4 Hz), 7.05-7.10 (3H, m), 6.94 (1H, d, <i>J</i> = 8.4 Hz), 6.84 (1H, t, <i>J</i> = 5.6 Hz), 6.47 (1H, d, <i>J</i> = 1.6 Hz), 6.16 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.80 (1H, d, <i>J</i> = 7.2 Hz), 4.83 (2H, t, <i>J</i> = 6.8 Hz), 4.56-4.65 (1H, m), 4.45-4.55 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 1.47 (2H, d, <i>J</i> = 6.8 Hz); LCMS: 98.8 %, MS (ESI); <i>m/z</i> 464.1 [M+H] <sup>+</sup> .                           |
| 272 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.4 Hz), 7.97 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.48 (1H, t, <i>J</i> = 8.8 Hz), 7.13 (1H, d, <i>J</i> = 9.2 Hz), 7.10 (1H, dd, <i>J</i> = 11.2, 2.4 Hz), 6.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 6.83-6.92 (2H, m), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 4.56 (2H, brs), 4.53 (2H, d, <i>J</i> = 6.0 Hz), 3.42 (3H, s); LCMS: 99.6%, MS (ESI); <i>m/z</i> 398.0[M+ H] <sup>+</sup> .                                                                                  |
| 273 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.4 Hz), 7.96 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.48 (1H, t, <i>J</i> = 8.4 Hz), 7.05-7.18 (2H, m), 6.89-7.02 (3H, m), 6.16-6.33 (2H, m), 5.87 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.62 (3H, m), 4.34-4.45 (2H, m), 3.46 (3H, s); LCMS: 98.6%, MS (ESI); <i>m/z</i> 454.1[M+ H] <sup>+</sup> .                                                                                                                                                                             |
| 274 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.12 (3H, m), 6.81 (1H, d, <i>J</i> = 8.4 Hz), 6.61 (1H, d, <i>J</i> = 2.4 Hz), 6.33 (1H, d, <i>J</i> = 1.6 Hz), 6.23 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.75-4.86 (1H, m), 4.52 (1H, brs), 3.44 (3H, s), 1.84-1.95 (1H, m), 1.70-1.83 (1H, m), 0.93 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 97.2 %, MS (ESI); <i>m/z</i> 408.0[M+ H] <sup>+</sup> .                                                                             |
| 275 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.02-7.12 (3H, m), 7.07 (1H, d, <i>J</i> = 8.4 Hz), 6.89 (1H, t, <i>J</i> = 8.4 Hz), 6.22 (1H, d, <i>J</i> = 2.0 Hz), 6.18 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.82 (1H, d, <i>J</i> = 7.2 Hz), 4.76-4.88 (3H, m), 4.45-4.51 (1H, m), 4.35-4.44 (2H, m), 3.48 (3H, s), 1.85-1.96 (1H, m), 1.73-1.84 (1H, m), 0.94 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 95.9 %, MS (ESI); <i>m/z</i> 464.2[M+ H] <sup>+</sup> .                      |
| 276 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.55 (1H, s), 8.22 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.23 (1H, d, <i>J</i> = 8.8 Hz), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.93 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.34 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.42 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 414.1[M+ H] <sup>+</sup> .                                                                                                            |
| 277 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.8 Hz), 7.05-7.13 (4H, m), 7.02 (1H, d, <i>J</i> = 8.4 Hz), 6.59 (1H, d, <i>J</i> = 2.0 Hz), 6.40 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.69-4.75 (2H, m), 4.54 (2H, d, <i>J</i> = 6.0 Hz), 4.43-4.49 (2H, m), 4.34-4.41 (1H, m), 3.49 (3H, s), 2.70 (3H, s); LCMS: 98.7%, MS (ESI); <i>m/z</i> 450.0 [M+H] <sup>+</sup> .                                                                                                                 |
| 278 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.0 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.13 (1H, t, <i>J</i> = 6.0 Hz), 7.05-7.10 (3H, m), 7.03 (1H, d, <i>J</i> = 8.4 Hz), 6.61 (1H, d, <i>J</i> = 2.0 Hz), 6.44 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.68 (2H, t, <i>J</i> = 6.4 Hz), 4.55 (2H, d, <i>J</i> = 6.0 Hz), 4.44-4.52 (1H, m), 4.36 (2H, t, <i>J</i> = 6.4 Hz), 3.49 (3H, s), 3.12 (2H, q, <i>J</i> = 6.8 Hz) 0.83 (3H, t, <i>J</i> = 7.2 Hz); LCMS: 99.8%, MS (ESI); <i>m/z</i> 464.1 [M+H] <sup>+</sup> . |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| 279 |  | white powder; mp = 155.5-159.8°C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.37-7.43 (2H, m), 7.23 (2H, d, <i>J</i> = 8.4 Hz), 6.95-7.03 (5H, m), 6.80-6.84 (1H, m), 6.16-6.23 (2H, m), 5.86 (1H, d, <i>J</i> = 6.8 Hz), 5.11 (2H, s), 4.78 (2H, t, <i>J</i> = 6.4 Hz), 4.41-4.48 (1H, m), 4.33 (2H, d, <i>J</i> = 6.0 Hz), 3.54 (2H, q, <i>J</i> = 6.8 Hz), 2.60-2.71 (2H, m); LCMS: 98.9%, MS (ESI); <i>m/z</i> 417.0 [M+H] <sup>+</sup> .                                                                                                                   |
| 280 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.8 Hz), 7.41-7.52 (4H, m), 7.07 (2H, d, <i>J</i> = 8.8 Hz), 6.75-6.85 (2H, m), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.51 (1H, d, <i>J</i> = 5.6 Hz), 3.41 (3H, s); LCMS: 98.7 %, MS (ESI); <i>m/z</i> 380.0[M + H] <sup>+</sup> .                                                                                                                                                                                          |
| 281 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.4 Hz), 7.41-7.56 (4H, m), 7.07 (2H, d, <i>J</i> = 8.4 Hz), 6.90-6.95 (2H, m), 6.25 (1H, s), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.57 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 98.1%, MS (ESI); <i>m/z</i> 436.1[M+ H] <sup>+</sup> .                                                                                                                                       |
| 282 |  | brown powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.14 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.31 (1H, s), 7.25 (1H, d, <i>J</i> = 8.4 Hz), 7.07 (1H, d, <i>J</i> = 8.8 Hz), 7.00 (1H, d, <i>J</i> = 8.0 Hz), 6.83-6.90 (2H, m), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.54 (2H, brs), 4.48 (2H, d, <i>J</i> = 5.6 Hz), 3.41 (3H, s), 2.04 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 394.0 [M+H] <sup>+</sup> .                                                                           |
| 283 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.14 (1H, d, <i>J</i> = 2.8 Hz), 7.92 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.30 (1H, s), 7.25 (1H, d, <i>J</i> = 8.0 Hz), 7.07 (1H, d, <i>J</i> = 8.8 Hz), 7.00 (1H, d, <i>J</i> = 8.0 Hz), 6.89-6.96 (2H, m), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.46-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s), 2.03 (3H, s); LCMS: 99.8 %, MS (ESI); <i>m/z</i> 450.1 [M+H] <sup>+</sup> . |
| 284 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.54 (1H, s), 8.21 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.45 (2H, d, <i>J</i> = 8.0 Hz), 7.22 (1H, d, <i>J</i> = 8.4 Hz), 7.13 (2H, d, <i>J</i> = 8.4 Hz), 6.98 (1H, t, <i>J</i> = 5.6 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.25 (1H, s), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.79-4.88 (2H, m), 4.45-4.57 (3H, m), 4.35-4.44 (2H, m), 3.45 (3H, s); LCMS: 99.6%, MS (ESI); <i>m/z</i> 470.0[M+ H] <sup>+</sup> .                                                      |
| 285 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.4 Hz), 7.97 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (1H, d, <i>J</i> = 8.8 Hz), 7.33 (1H, d, <i>J</i> = 2.4 Hz), 7.14 (1H, d, <i>J</i> = 8.8 Hz), 7.10 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 6.97 (1H, t, <i>J</i> = 6.0 Hz), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.38 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.51-4.61 (4H, m), 3.45 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 414.0[M+ H] <sup>+</sup> .                                         |
| 286 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.0 Hz), 7.13 (1H, t, <i>J</i> = 5.6 Hz), 7.06-7.10 (3H, m), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.39 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.50 (2H, d, <i>J</i> = 5.6 Hz), 3.95 (2H, t, <i>J</i> = 6.8 Hz), 2.47-2.49 (2H, m), 2.20 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 437.0 [M+H] <sup>+</sup> .                                                |
| 287 |  | white amorphous; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.20 (1H, s) 7.83 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 7.35 (2H, d, <i>J</i> = 8.8 Hz), 7.26-7.29 (1H, m), 7.07 (2H, d, <i>J</i> = 8.4 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.54 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.45 (1H, d, <i>J</i> = 1.6 Hz), 4.65 (2H, d, <i>J</i> = 5.6 Hz), 4.21 (1H, t, <i>J</i> = 5.2 Hz), 3.58 (2H, brs), 3.41 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 380.0[M+H] <sup>+</sup> .                                                                                                   |

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| 288 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.58 (2H, brs), 4.51 (2H, d, <i>J</i> = 5.6 Hz), 3.41 (3H, s); LCMS: 99.7 %, MS (ESI); <i>m/z</i> 381.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                     |
| 289 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 8.32 (1H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.89-7.01 (2H, m), 6.25 (1H, s), 6.21 (1H, dd, <i>J</i> = 2.4, 8.4 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 437.1[M + H] <sup>+</sup> .                                                                                                                                                                                                                    |
| 290 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.35 (1H, d, <i>J</i> = 8.4 Hz), 7.06 (1H, d, <i>J</i> = 8.8 Hz), 6.96 (1H, s), 6.91 (1H, d, <i>J</i> = 8.0 Hz), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.73 (1H, t, <i>J</i> = 5.6 Hz), 6.37 (1H, s), 6.26 (1H, dd, <i>J</i> = 8.0, 1.2 Hz), 4.64 (2H, brs), 4.46 (2H, d, <i>J</i> = 5.2 Hz), 3.42 (3H, s), 2.34 (3H, s); LCMS: 98.8%, MS (ESI); <i>m/z</i> 394.1[M+ H] <sup>+</sup> .                                                                                                                                 |
| 291 |  | off-white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.92 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.34 (1H, d, <i>J</i> = 8.4 Hz), 7.05 (1H, d, <i>J</i> = 8.8 Hz), 6.85-7.00 (3H, m), 6.81 (1H, t, <i>J</i> = 5.6 Hz), 6.26 (1H, d, <i>J</i> = 1.2 Hz), 6.22 (1H, d, <i>J</i> = 8.4 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.0 Hz), 4.44-4.56 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s), 2.34 (3H, s); LCMS: 99.6%, MS (ESI); <i>m/z</i> 450.0[M+ H] <sup>+</sup> .                                                                                                            |
| 292 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.37 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.12 (4H, m), 6.82-6.93 (2H, m), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, s), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 98.5 %, MS (ESI); <i>m/z</i> 429.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                                       |
| 293 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.37 (2H, d, <i>J</i> = 8.4 Hz), 6.98-7.10 (4H, m), 6.89-6.98 (2H, m), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.57 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 97.4%, MS (ESI); <i>m/z</i> 485.2[M+ H] <sup>+</sup> .                                                                                                                                                                                                                 |
| 294 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.8 Hz), 7.96 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.45 (1H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 2.4 Hz), 7.13 (1H, d, <i>J</i> = 8.8 Hz), 7.09 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.01 (1H, t, <i>J</i> = 5.6 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.27 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.86 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.57 (2H, d, <i>J</i> = 5.6 Hz), 4.45-4.55 (1H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.49 (3H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 470.1[M+ H] <sup>+</sup> . |
| 295 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.41 (1H, d, <i>J</i> = 1.2 Hz), 8.32 (1H, s), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.16 (2H, d, <i>J</i> = 8.4 Hz), 6.90 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.54 (2H, brs), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 98.7 %, MS (ESI); <i>m/z</i> 381.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                    |
| 296 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.41 (1H, s), 8.32 (1H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.16 (2H, d, <i>J</i> = 8.4 Hz), 6.89-7.02 (2H, m), 6.24 (1H, s), 6.21 (1H, d, <i>J</i> = 8.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.58 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 97.5 %, MS (ESI); <i>m/z</i> 437.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                          |

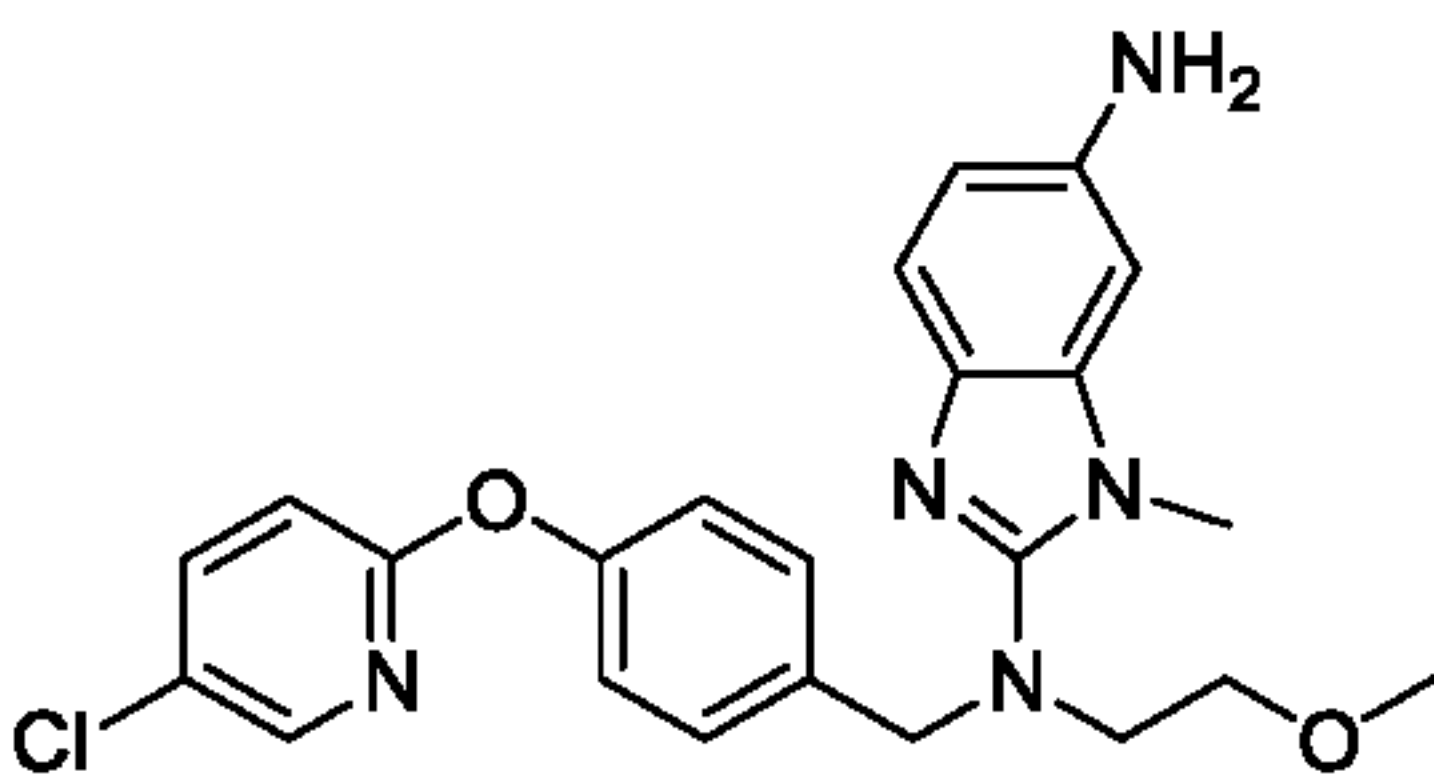
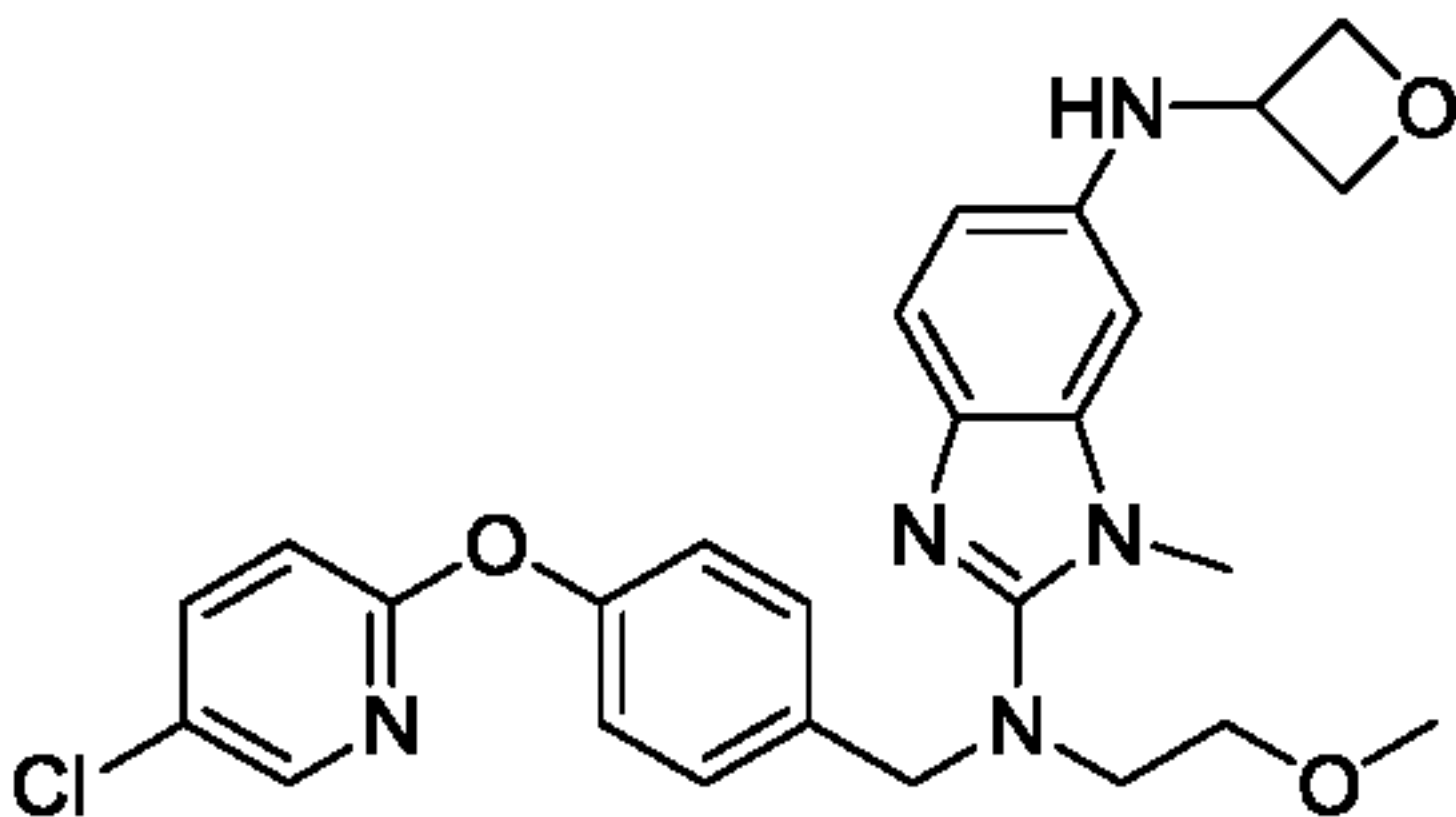
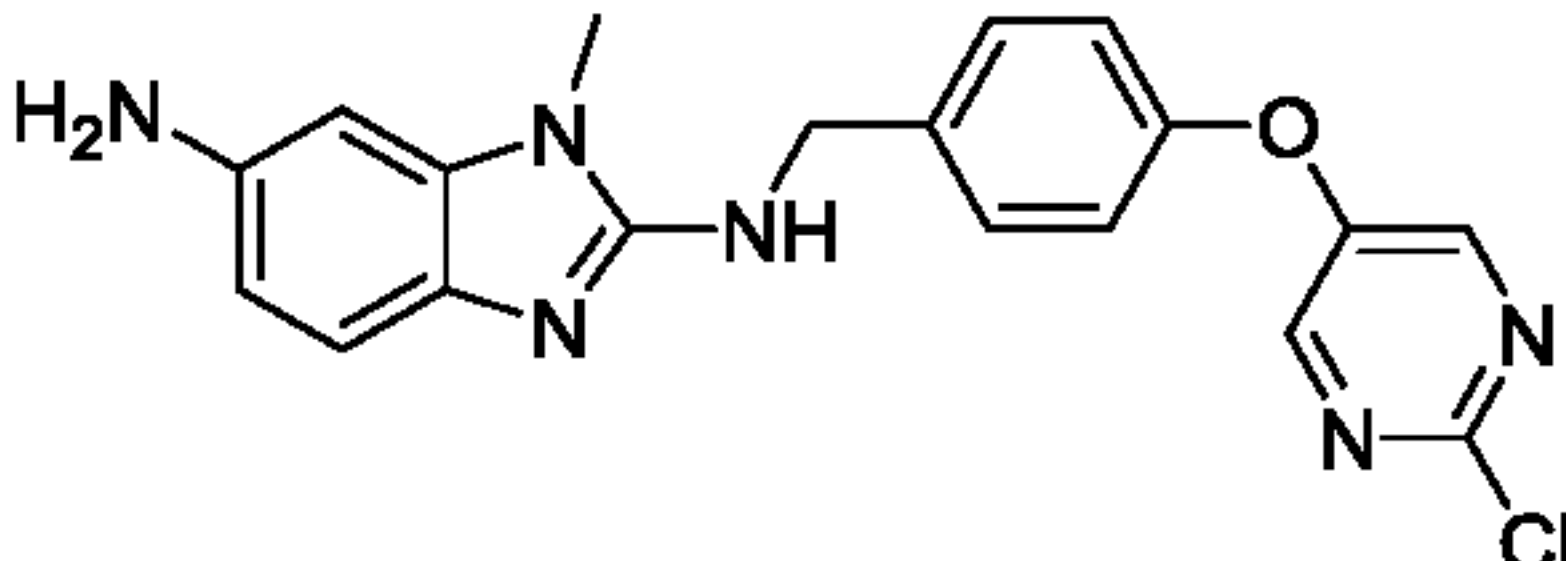
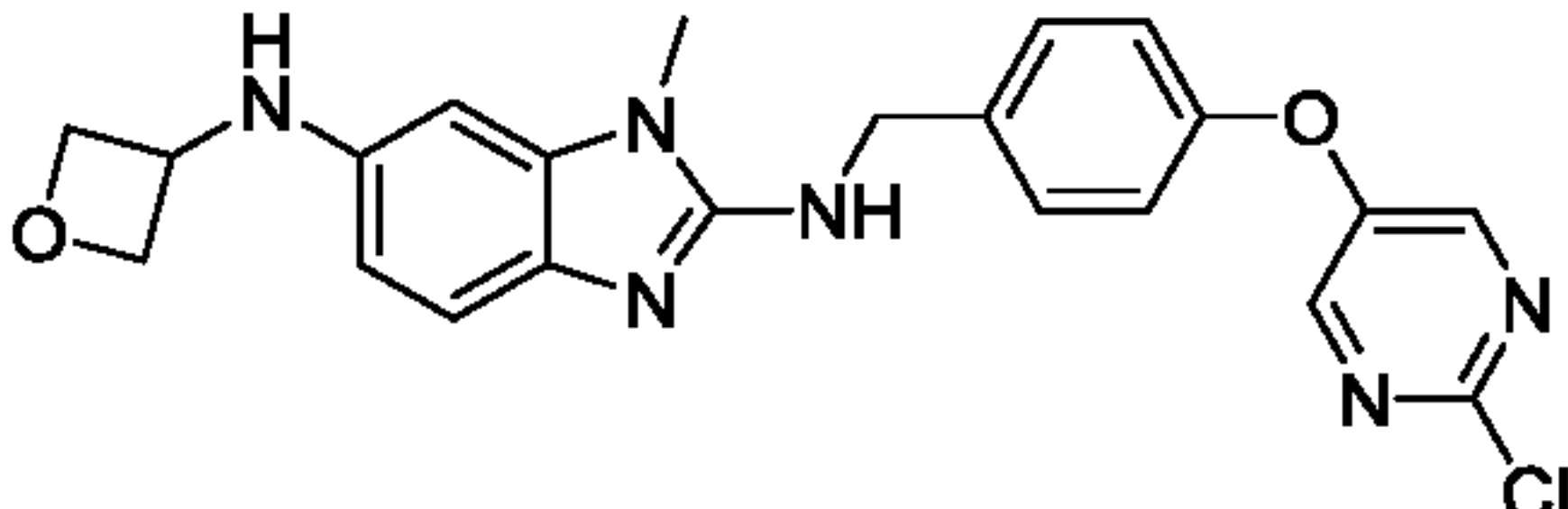
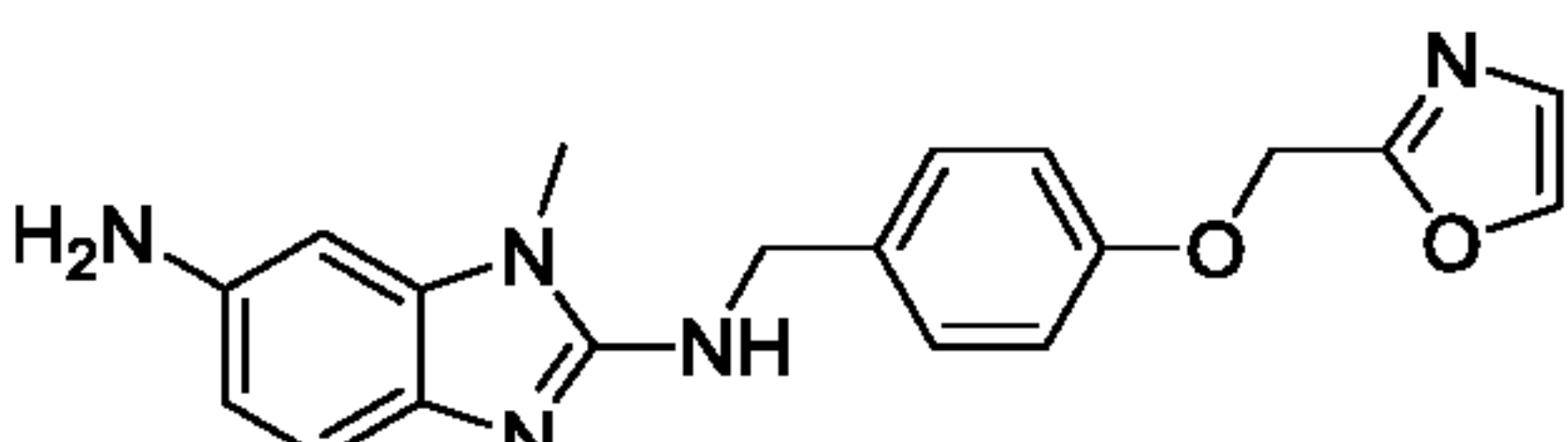
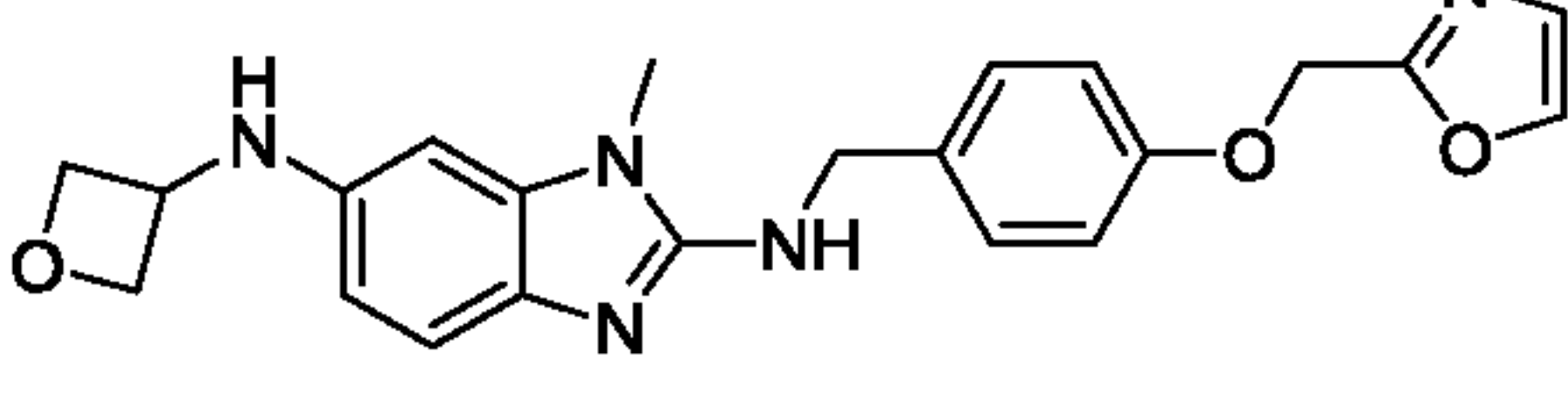
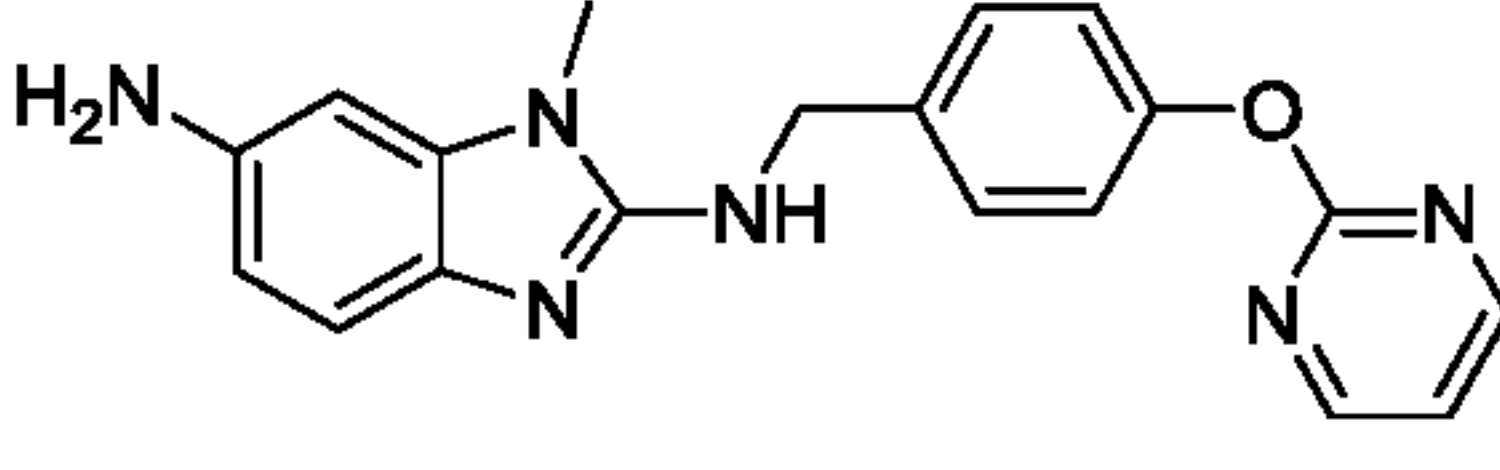
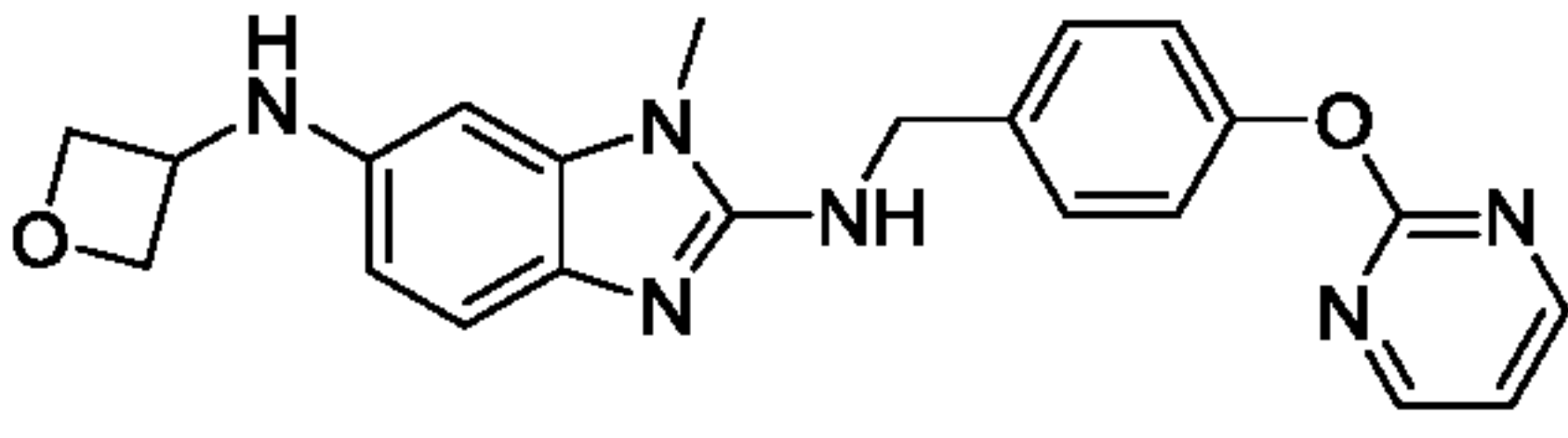
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 297 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.35 (1H, s), 7.43-7.46 (4H, m), 7.01-7.07 (3H, m), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, s), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.59 (2H, d, <i>J</i> = 6.0 Hz), 4.56 (2H, brs), 3.44 (3H, s); LCMS: 99.5%, MS (ESI); <i>m/z</i> 380.0 [M+H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                 |
| 298 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.34 (1H, s), 7.41-7.45 (4H, m), 7.03-7.07 (3H, m), 6.92 (1H, d, <i>J</i> = 8.8 Hz), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.4 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.59 (2H, d, <i>J</i> = 5.6 Hz), 4.48-4.51 (1H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 436.0[M+H] <sup>+</sup> .                                                                                                                                                                                                                                   |
| 299 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.39 (1H, d, <i>J</i> = 2.4 Hz), 8.18 (1H, d, <i>J</i> = 2.8 Hz), 7.98 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.58 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (1H, d, <i>J</i> = 8.8 Hz), 7.20 (1H, d, <i>J</i> = 8.8 Hz), 7.04 (1H, t, <i>J</i> = 6.0 Hz), 6.85 (1H, d, <i>J</i> = 8.0 Hz), 6.38 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.60 (2H, d, <i>J</i> = 6.0 Hz), 4.55 (2H, brs), 3.45 (3H, s); LCMS: 99.3 %, MS (ESI); <i>m/z</i> 381.0 [M+H] <sup>+</sup> .                                                                                                         |
| 300 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.39 (1H, d, <i>J</i> = 2.4 Hz), 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.98 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.58 (1H, dd, <i>J</i> = 8.4, 2.8 Hz), 7.45 (1H, d, <i>J</i> = 8.4 Hz), 7.19 (1H, d, <i>J</i> = 8.8 Hz), 7.09 (1H, t, <i>J</i> = 5.6 Hz), 6.92 (1H, d, <i>J</i> = 8.0 Hz), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (1H, t, <i>J</i> = 6.0 Hz), 4.61 (1H, d, <i>J</i> = 6.0 Hz), 4.45-4.57 (1H, m), 4.39 (1H, t, <i>J</i> = 6.0 Hz), 3.48 (3H, s); LCMS: 99.0 %, MS (ESI); <i>m/z</i> 437.0 [M + H] <sup>+</sup> . |
| 301 |  | pale yellow solid; mp = 121.4-124.6 °C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.12 (1H, d, <i>J</i> = 3.2 Hz), 7.74-7.85 (1H, m), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.02-7.12 (3H, m), 6.82-6.92 (2H, m), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.54 (2H, brs), 4.50 (2H, d, <i>J</i> = 5.6 Hz), 3.41 (3H, s); LCMS: 98.8 %, MS (ESI); <i>m/z</i> 364.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                            |
| 302 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.11 (1H, d, <i>J</i> = 3.2 Hz), 7.76-7.85 (1H, m), 7.41 (2H, d, <i>J</i> = 8.4 Hz), 7.01-7.12 (3H, m), 6.90-6.97 (2H, m), 6.24 (1H, s), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 98.4 %, MS (ESI); <i>m/z</i> 420.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                              |
| 303 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.92 (1H, brs), 8.42 (1H, d, <i>J</i> = 2.4 Hz), 8.22 (1H, d, <i>J</i> = 8.8 Hz), 7.92-7.98 (3H, m), 7.48 (2H, d, <i>J</i> = 8.4 Hz), 7.04 (1H, t, <i>J</i> = 6.0 Hz), 6.91(1H, d, <i>J</i> = 8.0 Hz), 6.25 (1H, s), 6.20 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.58 (2H, d, <i>J</i> = 6.0 Hz), 4.45-4.55 (1H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 463.2[M+H] <sup>+</sup> .                                                                                                                |
| 304 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.21 (1H, d, <i>J</i> = 2.4 Hz), 7.80 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.33-7.42 (4H, m), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.81-6.89 (2H, m), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.29 (2H, s), 4.54 (2H, brs), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.40 (3H, s); LCMS: 98.1%, MS (ESI); <i>m/z</i> 394.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                  |
| 305 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.21 (1H, d, <i>J</i> = 2.4 Hz), 7.80 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.31-7.42 (4H, m), 6.97-6.85 (3H, m), 6.24 (1H, d, <i>J</i> = 2.0 Hz), 6.20 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 5.29 (2H, s), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.44-4.58 (3H, m), 4.33-4.43 (2H, m), 3.43 (3H, s); LCMS: 99.1%, MS (ESI); <i>m/z</i> 450.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                            |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 306 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.21-7.23 (1H, m), 7.05-7.09 (3H, m), 6.96-7.02 (2H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.33 (1H, d, <i>J</i> = 1.6 Hz), 6.29 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.14 (1H, brs), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.40 (3H, s) 1.33 (6H, s); LCMS: 99.1%, MS (ESI); <i>m/z</i> 465.1 [M+H] <sup>+</sup> .                                                                                        |
| 307 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.4 Hz), 7.90 (1H, dd, <i>J</i> = 8.0, 2.4 Hz), 7.40-7.46 (2H, m), 7.09-7.16 (2H, m), 7.02 (1H, d, <i>J</i> = 8.0 Hz), 6.89-6.96 (2H, m), 6.24 (1H, d, <i>J</i> = 2.4 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.82-4.86 (2H, m), 4.43-4.55 (3H, m), 4.38 (2H, t, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 99.0%, MS (ESI); <i>m/z</i> 436.1 [M+H] <sup>+</sup> .                                                                               |
| 308 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.25-8.30 (2H, m), 7.99 (1H, dd, <i>J</i> = 8.4, 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.0, 2.4 Hz), 7.18 (1H, d, <i>J</i> = 8.8 Hz), 7.11 (1H, d, <i>J</i> = 8.0 Hz), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.87 (1H, d, <i>J</i> = 8.0 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.55 (2H, brs), 4.50 (2H, t, <i>J</i> = 5.6 Hz), 3.39 (3H, s); LCMS: 99.0%, MS (ESI); <i>m/z</i> 381.0[M+ H] <sup>+</sup> .                                                                      |
| 309 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.25-8.35 (2H, m), 7.99 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.18 (1H, d, <i>J</i> = 8.8 Hz), 7.12 (1H, d, <i>J</i> = 8.4 Hz), 6.98 (1H, t, <i>J</i> = 5.6 Hz), 6.95 (1H, d, <i>J</i> = 8.0 Hz), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.86 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.60 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.39 (3H, s); LCMS: 98.4%, MS (ESI); <i>m/z</i> 437.0[M+ H] <sup>+</sup> . |
| 310 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 10.94 (1H, brs), 8.43 (1H, d, <i>J</i> = 2.4 Hz), 8.23 (1H, d, <i>J</i> = 8.8 Hz), 7.94-7.98 (3H, m), 7.49 (2H, d, <i>J</i> = 8.4 Hz), 6.99 (1H, t, <i>J</i> = 6.0 Hz), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.25 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.58 (2H, d, <i>J</i> = 6.0 Hz), 4.55 (2H, brs), 3.43 (3H, s); LCMS: 98.6%, MS (ESI); <i>m/z</i> 407.0 [M+H] <sup>+</sup> .                                                                                                  |
| 311 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.62 (1H, d, <i>J</i> = 8.8 Hz), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 8.8 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.82-6.92 (2H, m), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.46-4.55 (4H, m), 3.41 (3H, s), 2.54 (3H, s); LCMS: 97.7 %, MS (ESI); <i>m/z</i> 361.1[M+ H] <sup>+</sup> .                                                                                                                                                             |
| 312 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.61 (1H, d, <i>J</i> = 9.2 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 8.8 Hz), 7.12 (2H, d, <i>J</i> = 8.8 Hz), 6.94 (2H, d, <i>J</i> = 8.0 Hz), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 5.6 Hz), 3.44 (3H, s), 2.53 (3H, s); LCMS: 96.4 %, MS (ESI); <i>m/z</i> 417.1[M+ H] <sup>+</sup> .                                            |
| 313 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.0 Hz), 7.94 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.06-7.10 (3H, m), 6.88-6.73 (2H, m), 6.39 (1H, d, <i>J</i> = 2.0 Hz), 6.31 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.90 (1H, brs), 4.66 (1H, t, <i>J</i> = 5.6 Hz), 4.51 (2H, d, <i>J</i> = 5.6 Hz), 3.57 (2H, q, <i>J</i> = 6.0 Hz), 3.45 (3H, s), 3.00-3.10 (2H, m); LCMS: 99.0%, MS (ESI); <i>m/z</i> 424.0 [M+H] <sup>+</sup> .                                                                    |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 314 |    | white solid; m.p = 96.6-100.9 °C; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.62 (1H, d, <i>J</i> = 2.4 Hz), 7.95 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.53 (1H, d, <i>J</i> = 8.4 Hz), 7.31 (2H, d, <i>J</i> = 8.8 Hz), 6.96 (2H, d, <i>J</i> = 8.4 Hz), 6.85 (1H, d, <i>J</i> = 8.0 Hz), 6.75 (1H, t, <i>J</i> = 6.0 Hz), 6.35 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.16 (2H, s), 4.55 (2H, brs), 4.42 (2H, d, <i>J</i> = 5.6 Hz), 3.38 (3H, s); LCMS: 97.0%, MS (ESI); <i>m/z</i> 394.1[M+ H] <sup>+</sup> .              |
| 315 |    | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.62 (1H, d, <i>J</i> = 2.4 Hz), 7.95 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.53 (1H, d, <i>J</i> = 8.4 Hz), 7.31 (2H, d, <i>J</i> = 8.8 Hz), 6.88-7.01 (3H, m), 6.81 (1H, t, <i>J</i> = 6.0 Hz), 6.23 (1H, d, <i>J</i> = 2.0 Hz), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 5.15 (2H, s), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.56 (1H, m), 4.34-4.45 (4H, m), 3.41 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 450.1[M+ H] <sup>+</sup> .                        |
| 316 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.43 (2H, d, <i>J</i> = 8.4 Hz), 7.00-7.13 (3H, m), 6.83-6.98 (2H, m), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.32 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.94 (1H, t, <i>J</i> = 6.0 Hz), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.50 (2H, t, <i>J</i> = 5.6 Hz), 3.45 (3H, s), 3.28 (3H, s), 3.18 (2H, q, <i>J</i> = 5.8 Hz); LCMS: 98.0%, MS (ESI); <i>m/z</i> 438.1[M+ H] <sup>+</sup> .                                          |
| 317 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.40 (2H, d, <i>J</i> = 8.8 Hz), 6.99-7.15 (4H, m), 6.45 (1H, d, <i>J</i> = 1.6 Hz), 6.40 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 4.90 (1H, t, <i>J</i> = 5.6 Hz), 4.77 (2H, brs), 4.44 (2H, s), 3.59 (2H, q, <i>J</i> = 5.6 Hz), 3.52 (3H, s), 3.24 (1H, t, <i>J</i> = 6.0 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 424.0 [M+H] <sup>+</sup> .                                                                             |
| 318 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.40 (2H, d, <i>J</i> = 8.8 Hz), 7.12 (1H, d, <i>J</i> = 8.4 Hz), 7.04-7.10 (3H, m), 6.38 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.30 (1H, d, <i>J</i> = 2.0 Hz), 6.08 (1H, d, <i>J</i> = 6.8 Hz), 4.87 (1H, t, <i>J</i> = 6.4 Hz), 4.50-4.62 (1H, m), 4.45 (2H, brs), 4.40 (1H, t, <i>J</i> = 6.0 Hz), 3.53-3.62 (5H, m), 3.24 (2H, t, <i>J</i> = 6.0 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 480.1 [M+H] <sup>+</sup> . |
| 319 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.41 (1H, d, <i>J</i> = 2.4 Hz), 7.80 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.19-7.33 (5H, m), 6.89 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, s), 6.33 (1H, d, <i>J</i> = 7.6 Hz), 4.53 (2H, d, <i>J</i> = 5.2 Hz), 3.44 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 421.1 [M+H] <sup>+</sup> .                                                                                                                                                                                                            |
| 320 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.41 (1H, d, <i>J</i> = 2.4 Hz), 7.99 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.18-7.30 (5H, m), 6.89-6.94 (2H, m), 6.24 (1H, s), 6.20 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.48-4.53 (3H, m), 4.38 (2H, t, <i>J</i> = 6.4 Hz), 3.42 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 477.1[M+H] <sup>+</sup> .                                                                                                                                      |
| 321 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.33 (1H, d, <i>J</i> = 2.0 Hz), 8.13 (1H, d, <i>J</i> = 2.4 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.11 (2H, d, <i>J</i> = 8.8 Hz), 6.91 (1H, t, <i>J</i> = 6.0 Hz), 6.85 (1H, d, <i>J</i> = 8.0 Hz), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz); LCMS: 100 %, MS (ESI); <i>m/z</i> 414.0[M+ H] <sup>+</sup> .                                                                                                                                                       |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| 322 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.32 (1H, d, <i>J</i> = 2.0 Hz), 8.12 (1H, d, <i>J</i> = 2.4 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.11 (2H, d, <i>J</i> = 8.4 Hz), 6.89-7.00 (2H, m), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 99.7%, MS (ESI); <i>m/z</i> 470.0[M+ H] <sup>+</sup> .                                                                                                                                                                                  |
| 323 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, dd, <i>J</i> = 10.0, 2.4 Hz), 8.02 (1H, d, <i>J</i> = 2.0 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.14 (2H, d, <i>J</i> = 8.8 Hz), 6.93 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.57 (2H, brs), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 398.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                 |
| 324 |  | white power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, dd, <i>J</i> = 10.0, 2.0 Hz), 8.01 (1H, d, <i>J</i> = 2.0 Hz), 7.43 (2H, d, <i>J</i> = 8.4 Hz), 7.13 (2H, d, <i>J</i> = 8.8 Hz), 6.89-7.00 (2H, m), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.8 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 98.6%, MS (ESI); <i>m/z</i> 454.1[M+ H] <sup>+</sup> .                                                                                                                                                                           |
| 325 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.43 (2H, d, <i>J</i> = 8.4 Hz), 7.02-7.11 (4H, m), 6.94 (1H, d, <i>J</i> = 8.4 Hz), 6.62 (1H, d, <i>J</i> = 2.0 Hz), 6.49 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.75 (1H, t, <i>J</i> = 5.2 Hz), 4.54 (2H, d, <i>J</i> = 5.6 Hz), 3.46 (3H, s), 3.27 (2H, d, <i>J</i> = 5.6 Hz), 1.10 (6H, s); LCMS: 98.9%, MS (ESI); <i>m/z</i> 452.0 [M+H] <sup>+</sup> .                                                                                                                                                                            |
| 326 |  | off-white solid; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.05-7.10 (3H, m), 7.02 (1H, t, <i>J</i> = 4.8 Hz), 6.92 (1H, d, <i>J</i> = 8.4 Hz), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.31 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.52 (2H, d, <i>J</i> = 5.2 Hz), 3.41 (3H, s), 1.40 (6H, s); LCMS: 93.1 %, MS (ESI); <i>m/z</i> 466.1 [M+H] <sup>+</sup> .                                                                                                                                                                                                             |
| 327 |  | yellow powder; <sup>1</sup> H NMR (Methanol- <i>d</i> <sub>4</sub> , 400 MHz); δ 8.16 (1H, d, <i>J</i> = 2.8 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.55-7.62 (2H, m), 7.45 (1H, d, <i>J</i> = 8.4 Hz), 7.39 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 7.04 (1H, d, <i>J</i> = 8.8 Hz), 6.90 (1H, d, <i>J</i> = 2.0 Hz), 6.75 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 4.73 (2H, s), 3.84 (3H, s), 3.76 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 410.0 [M+H] <sup>+</sup> .                                                                                                                                                                                                                          |
| 328 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.19 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.27 (1H, d, <i>J</i> = 8.4 Hz), 7.06 (1H, d, <i>J</i> = 8.4 Hz), 6.91 (1H, d, <i>J</i> = 8.0 Hz), 6.81 (1H, d, <i>J</i> = 2.0 Hz), 6.76 (1H, t, <i>J</i> = 6.0 Hz), 6.64 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (1H, t, <i>J</i> = 6.4 Hz), 4.49-4.57(1H, m), 4.47 (2H, d, <i>J</i> = 6.0 Hz), 4.39 (1H, t, <i>J</i> = 6.0 Hz), 3.80 (3H, s), 3.47 (3H, s); LCMS: 98.9 %, MS (ESI); <i>m/z</i> 466.0 [M+H] <sup>+</sup> . |
| 329 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.51 (1H, dd, <i>J</i> = 4.8, 0.8 Hz), 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.70 (1H, dt, <i>J</i> = 8.0, 2.0 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.32 (1H, d, <i>J</i> = 7.6 Hz), 7.18-7.25 (1H, m), 7.03-7.14 (3H, m), 6.87-6.97 (2H, m), 6.40 (1H, d, <i>J</i> = 2.0 Hz), 6.32 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 5.15 (1H, t, <i>J</i> = 6.0 Hz), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.45 (3H, s), 3.35-3.40 (2H, m), 3.00 (2H, t, <i>J</i> = 7.2 Hz); LCMS: 96.1%, MS (ESI); <i>m/z</i> 485.1[M+ H] <sup>+</sup> .                                                    |

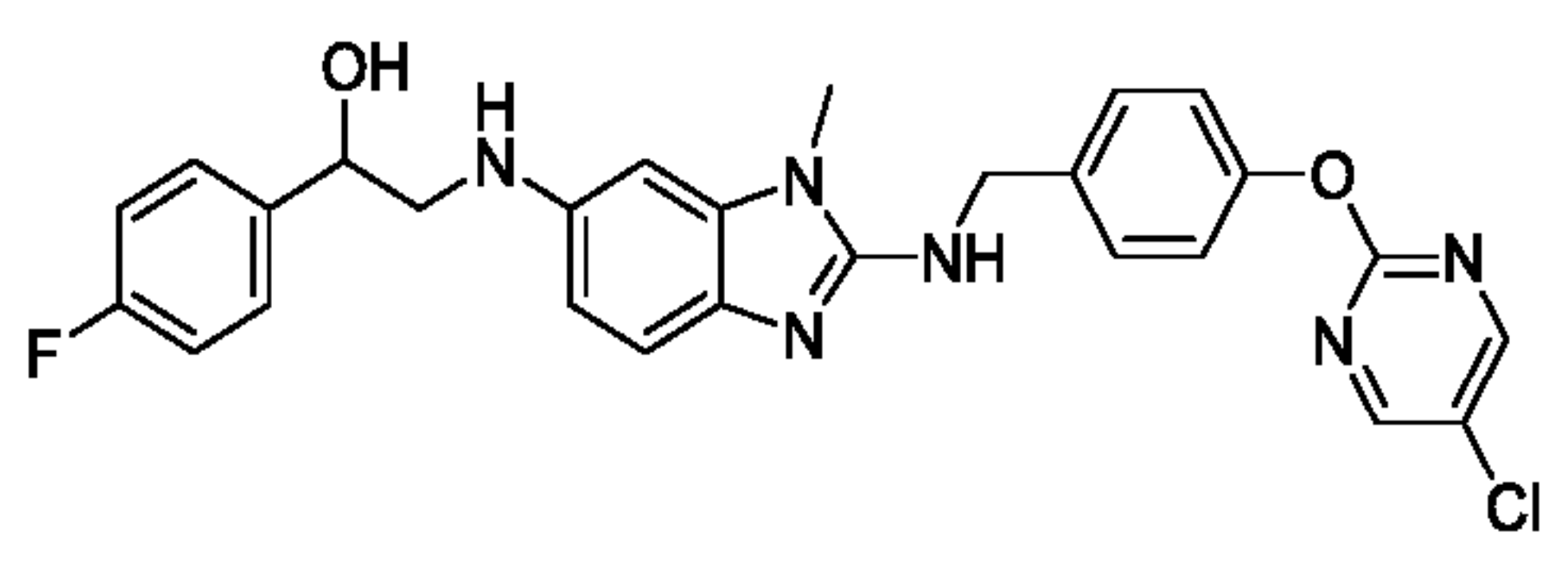
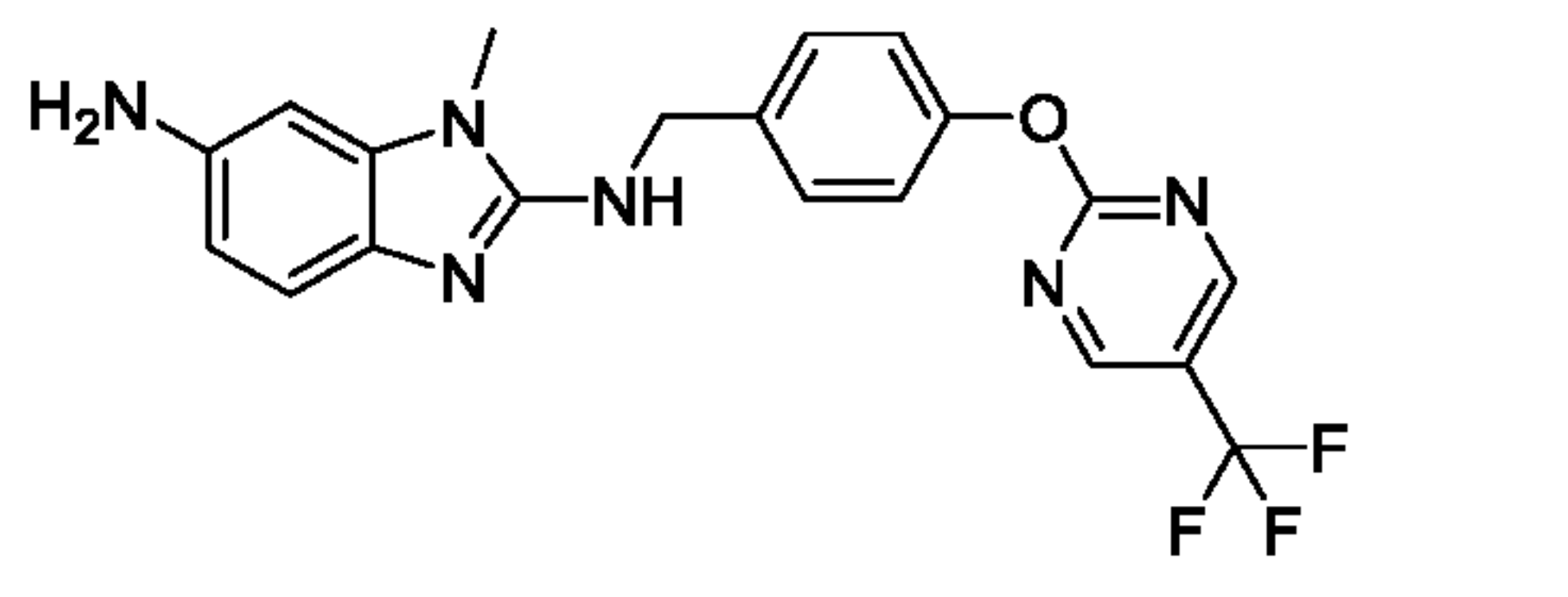
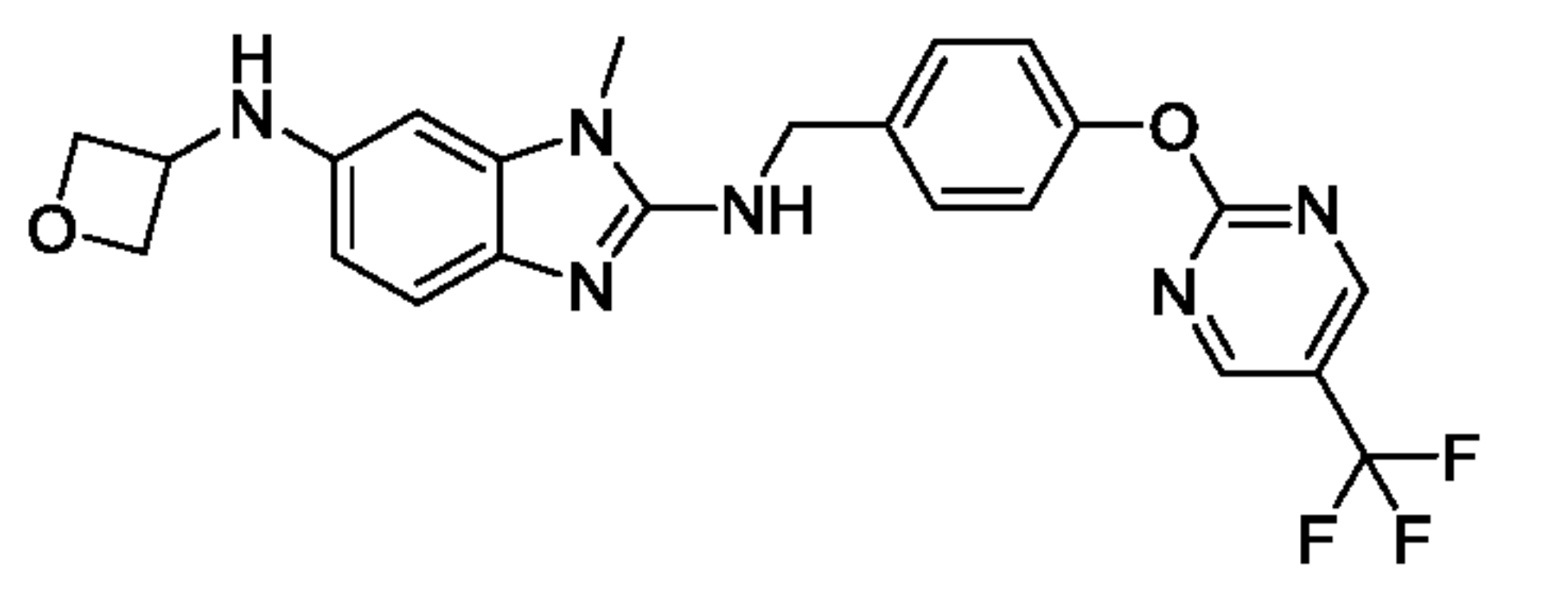
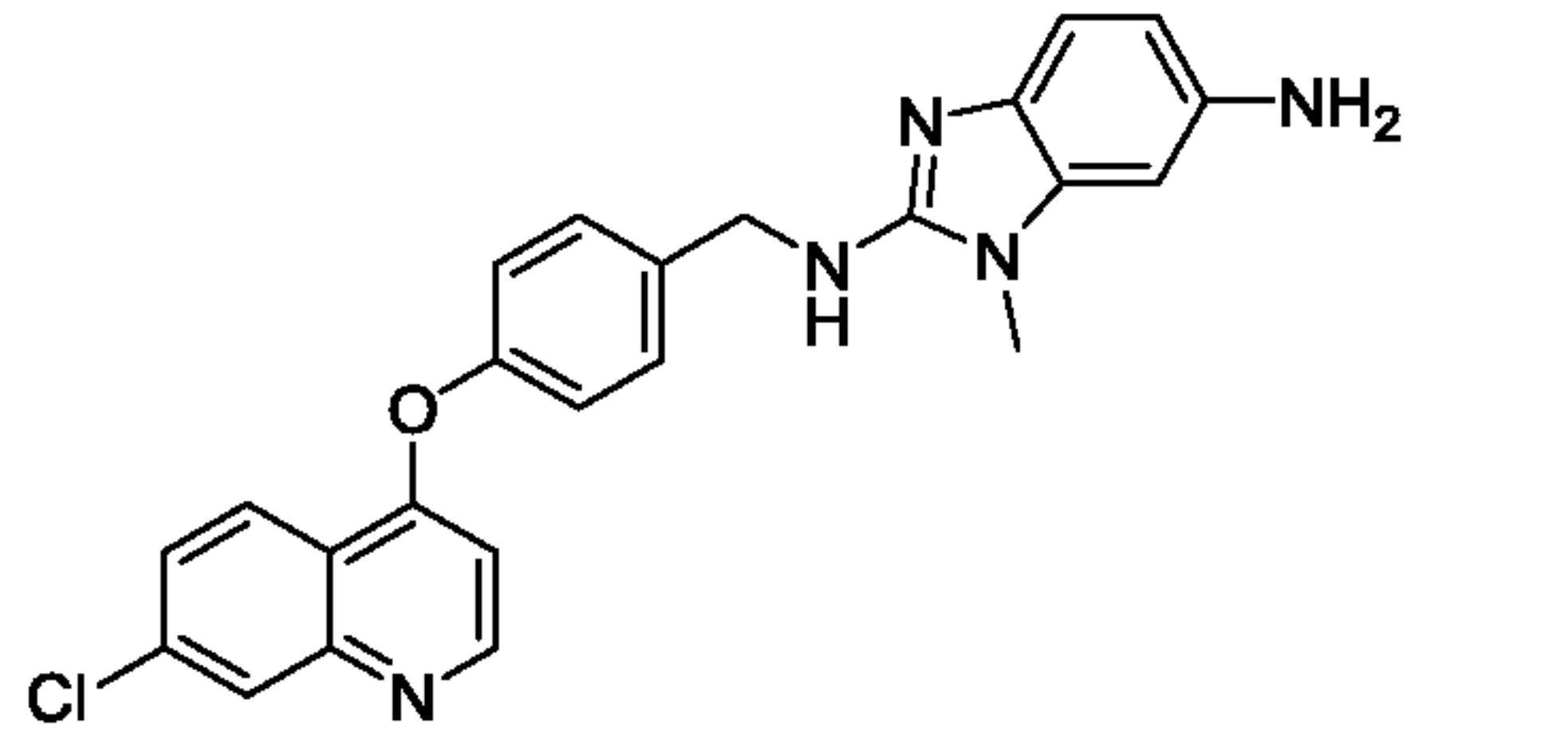
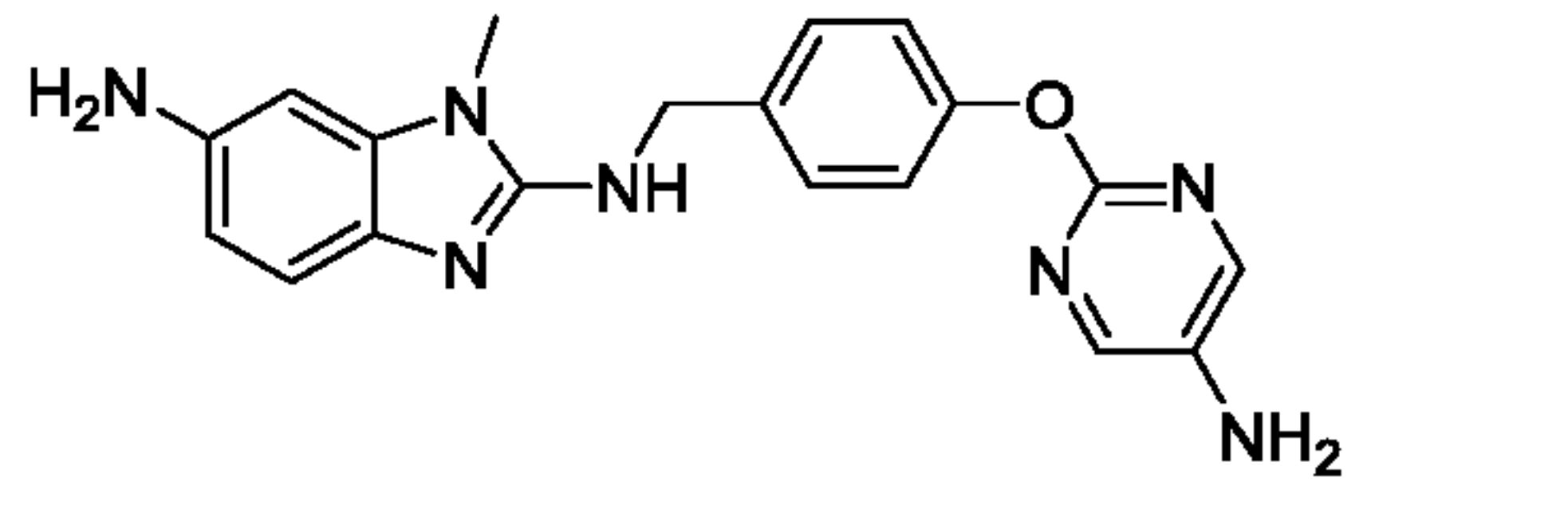
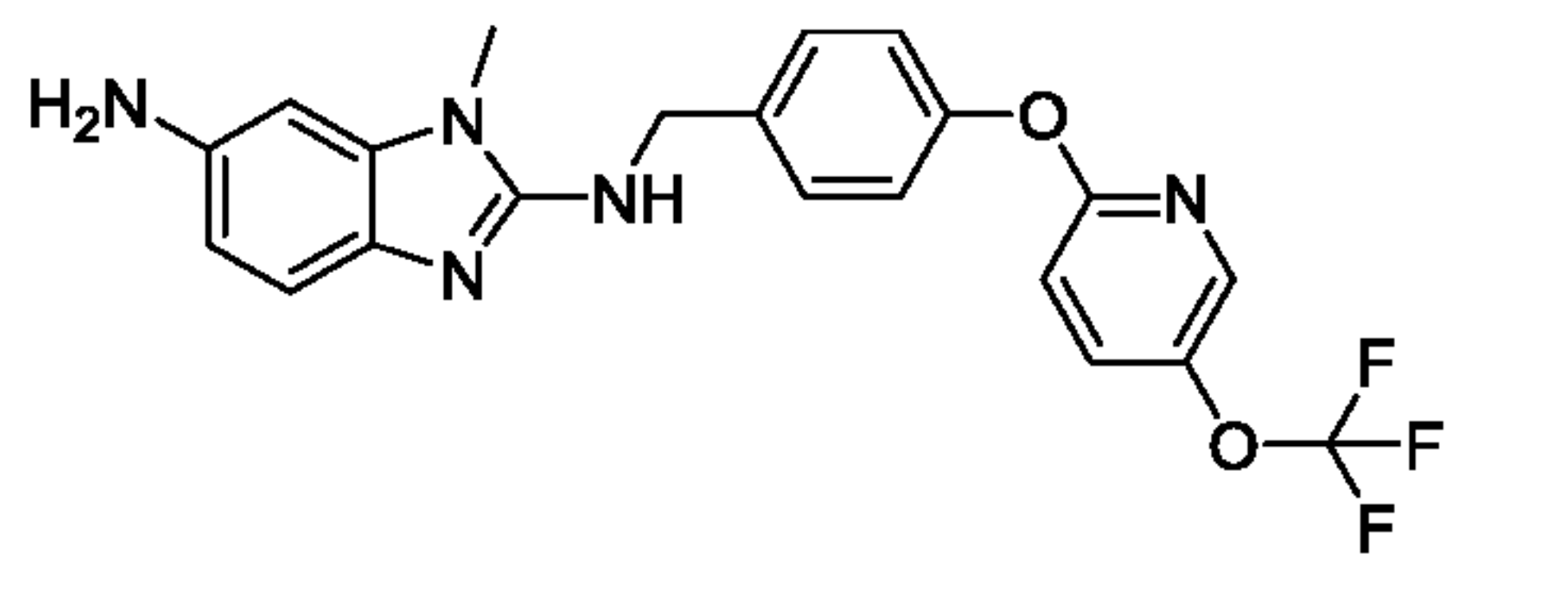
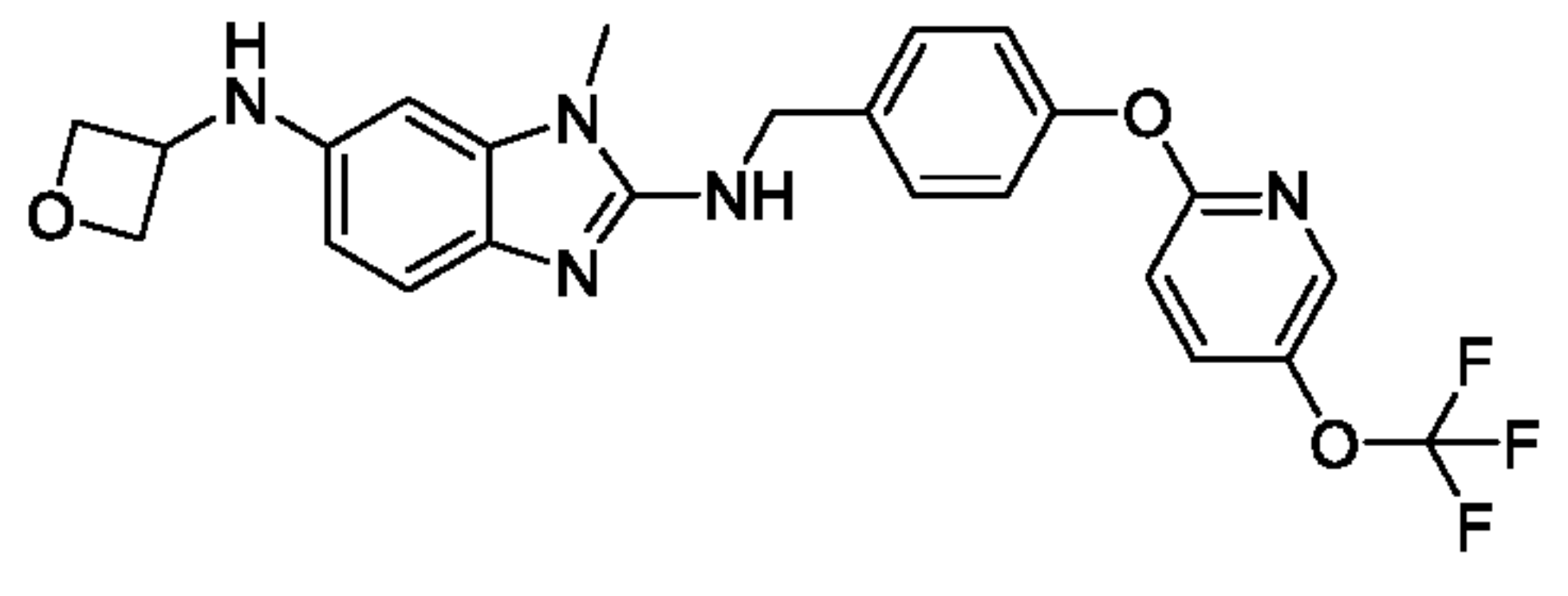
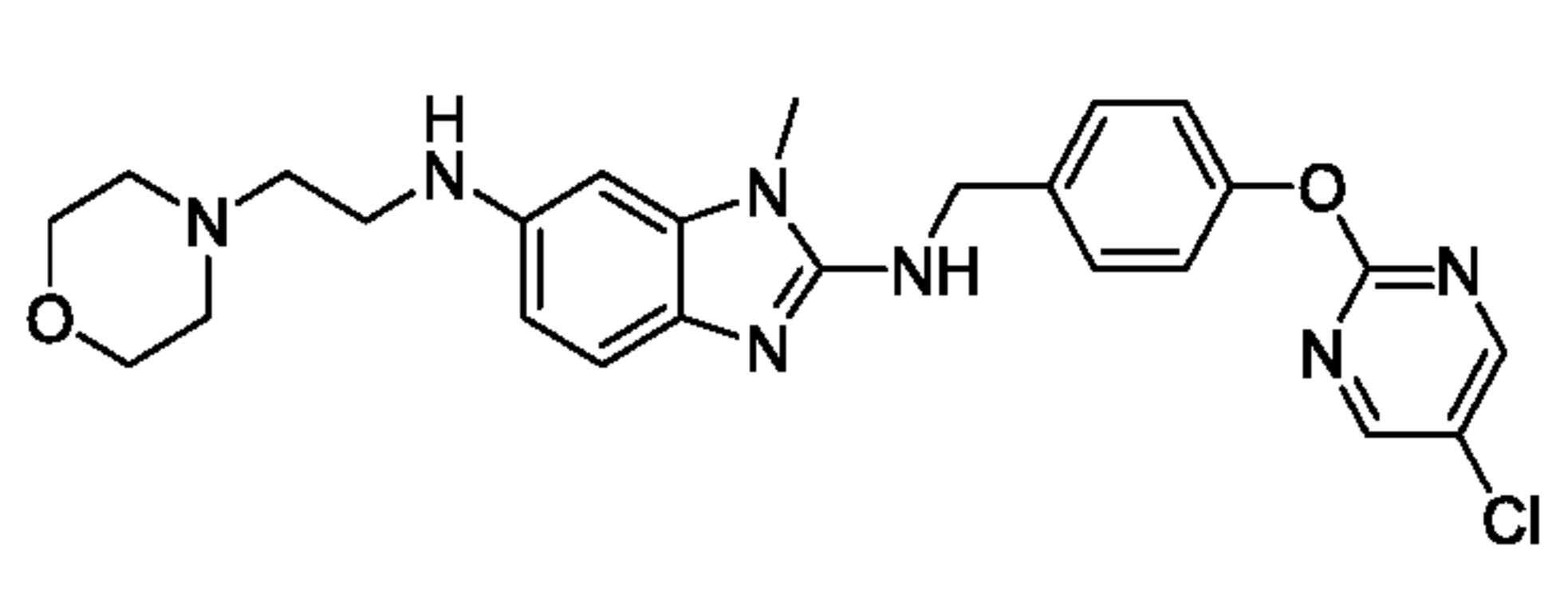
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 330 |  | white powder (amorphous); (note: HNMR showed 10% of methyl isomer); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.84 (1H, d, <i>J</i> = 3.2 Hz), 7.48 (1H, dd, <i>J</i> = 8.8, 3.2 Hz), 7.39 (2H, d, <i>J</i> = 8.8 Hz), 6.93-7.05 (3H, m), 6.80-6.90 (2H, m), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.54 (2H, brs), 4.48 (2H, d, <i>J</i> = 6.0 Hz), 3.78 (3H, s), 3.40 (3H, s); LCMS: 98.8 %, MS (ESI); <i>m/z</i> 376.1[M+ H] <sup>+</sup> .                                                                                                               |
| 331 |  | white powder (amorphous); (Note: HNMR showed 10% of methyl isomer); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.84 (1H, d, <i>J</i> = 2.8 Hz), 7.48 (1H, dd, <i>J</i> = 8.8, 3.2 Hz), 7.38 (2H, d, <i>J</i> = 8.8 Hz), 6.89-7.02 (5H, m), 6.24 (1H, d, <i>J</i> = 2.0 Hz), 6.20 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.78 (3H, s), 3.44 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 432.1[M+ H] <sup>+</sup> .                                                              |
| 332 |  | white powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.40 (2H, d, <i>J</i> = 8.4 Hz), 7.21 (1H, t, <i>J</i> = 6.0 Hz), 7.06-7.10 (3H, m), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.27 (1H, d, <i>J</i> = 1.6 Hz), 6.19 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.80-4.86 (2H, m), 4.47-4.55 (3H, m), 4.36-4.42 (2H, m), 3.99 (2H, t, <i>J</i> = 6.8 Hz), 2.51-2.54 (2H, m, overlapped with DMSO peak), 2.20 (6H, s); LCMS: 96.1%, MS (ESI); <i>m/z</i> 493.1 [M+H] <sup>+</sup> . |
| 333 |  | white powder (amorphous); <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.12 (1H, d, <i>J</i> = 2.8 Hz), 7.66 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.48 (2H, d, <i>J</i> = 8.4 Hz), 7.34 (1H, d, <i>J</i> = 8.4 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, d, <i>J</i> = 8.8 Hz), 6.53 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.40 (1H, d, <i>J</i> = 1.6 Hz), 4.70 (2H, d, <i>J</i> = 5.6 Hz), 4.14 (1H, t, <i>J</i> = 5.4 Hz), 3.45 (3H, s), 3.21 (2H, t, <i>J</i> = 5.6 Hz), 2.68 (2H, t, <i>J</i> = 5.8 Hz), 2.30-2.65 (8H, m), 2.31 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 506.2[M+ H] <sup>+</sup> .  |
| 334 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.0 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.07 (1H, d, <i>J</i> = 8.8 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.84 (2H, s), 6.36 (1H, s), 6.29 (1H, d, <i>J</i> = 8.0 Hz), 6.22 (1H, brs), 4.59 (2H, brs), 4.43 (2H, d, <i>J</i> = 4.0 Hz), 3.36 (3H, s), 2.38 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 408.1[M+ H] <sup>+</sup> .                                                                                                                                                                    |
| 335 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.20 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.07 (1H, d, <i>J</i> = 8.8 Hz), 7.01 (1H, d, <i>J</i> = 9.2 Hz), 6.84 (2H, s), 6.18-6.32 (3H, m), 5.86 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.48-4.58 (1H, m), 4.45 (2H, d, <i>J</i> = 4.4 Hz), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.39 (3H, s), 2.37 (6H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 464.1[M+ H] <sup>+</sup> .                                                                                                         |
| 336 |  | pale yellow powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.71 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.13 (2H, d, <i>J</i> = 8.8 Hz), 6.91 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.36 (1H, d, <i>J</i> = 1.2 Hz), 6.26 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.55 (2H, brs), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 365.0[M+H] <sup>+</sup> .                                                                                                                                                                 |
| 337 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.71 (2H, s), 7.43 (2H, d, <i>J</i> = 8.0 Hz), 7.13 (2H, d, <i>J</i> = 8.4 Hz), 6.97 (1H, brs), 6.93 (1H, d, <i>J</i> = 8.0 Hz), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.82-4.86 (2H, m), 4.47-4.55 (3H, m), 4.36-4.42 (2H, m), 3.45 (3H, s); LCMS: 99.5%, MS (ESI); <i>m/z</i> 421.1[M+H] <sup>+</sup> .                                                                                                                                                 |

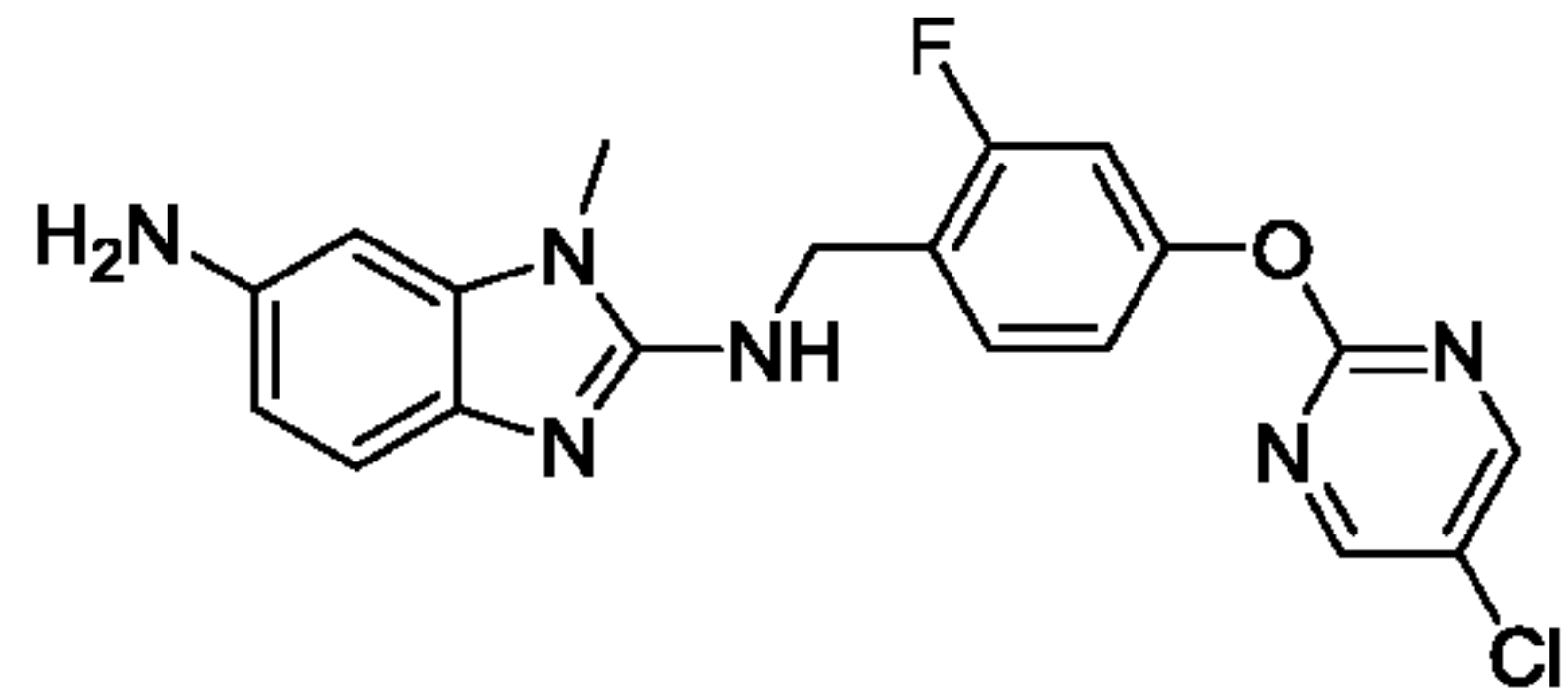
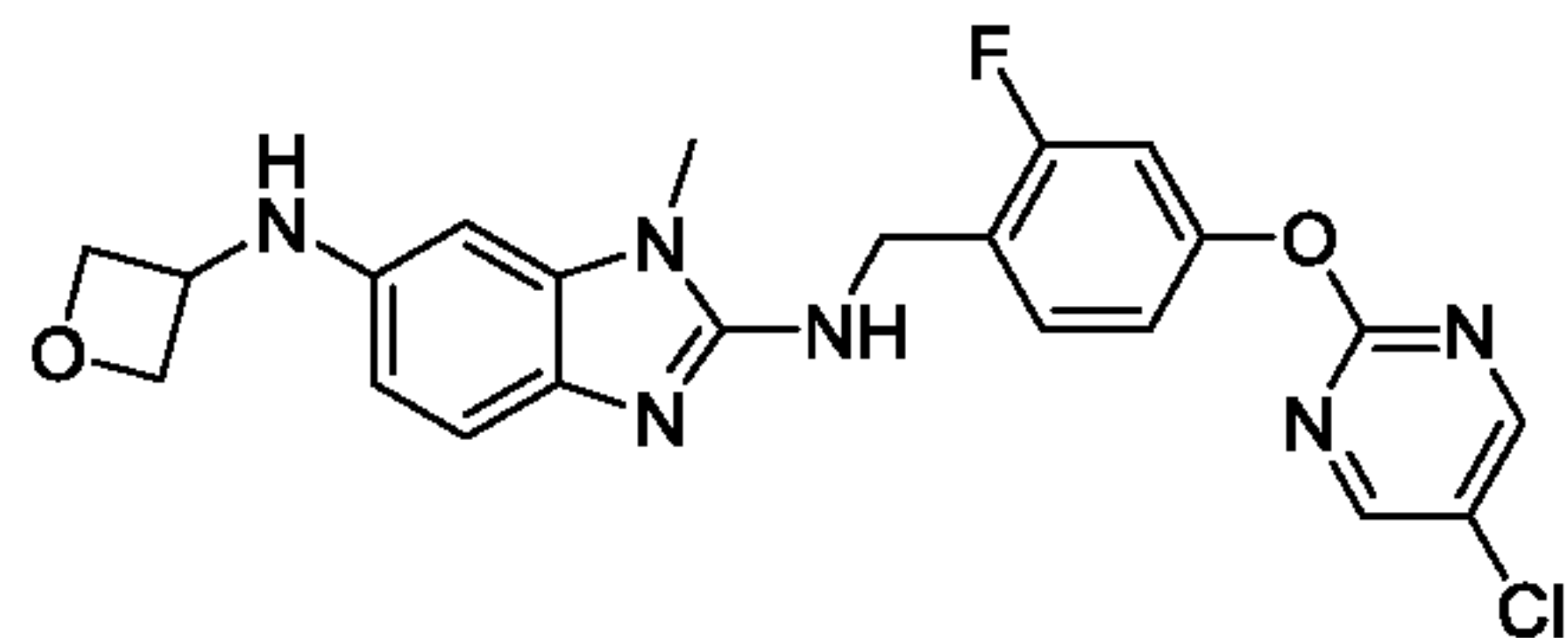
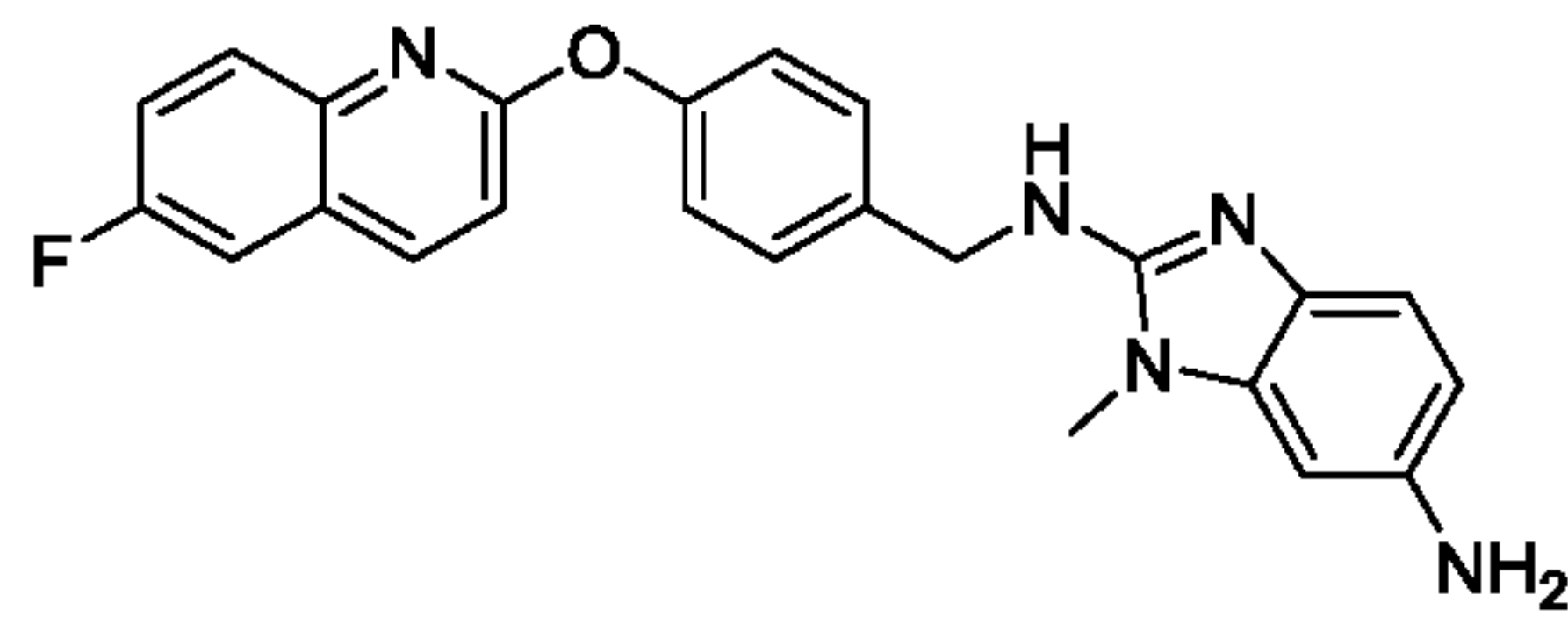
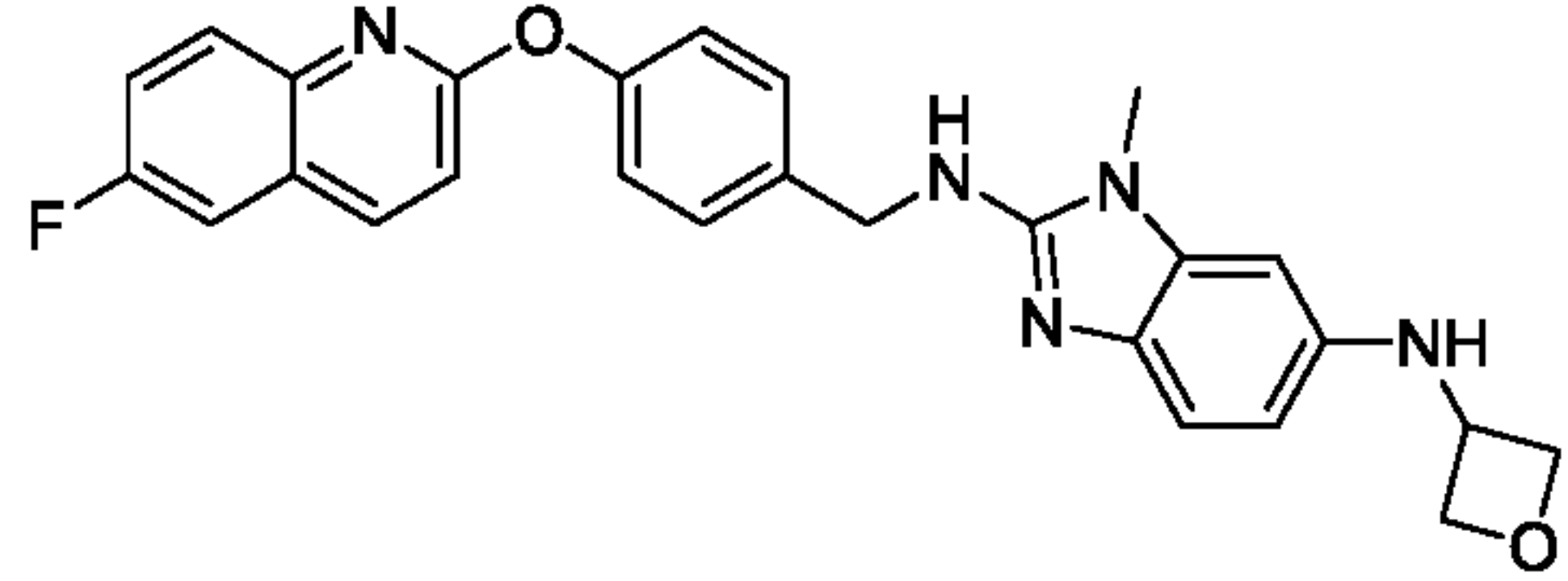
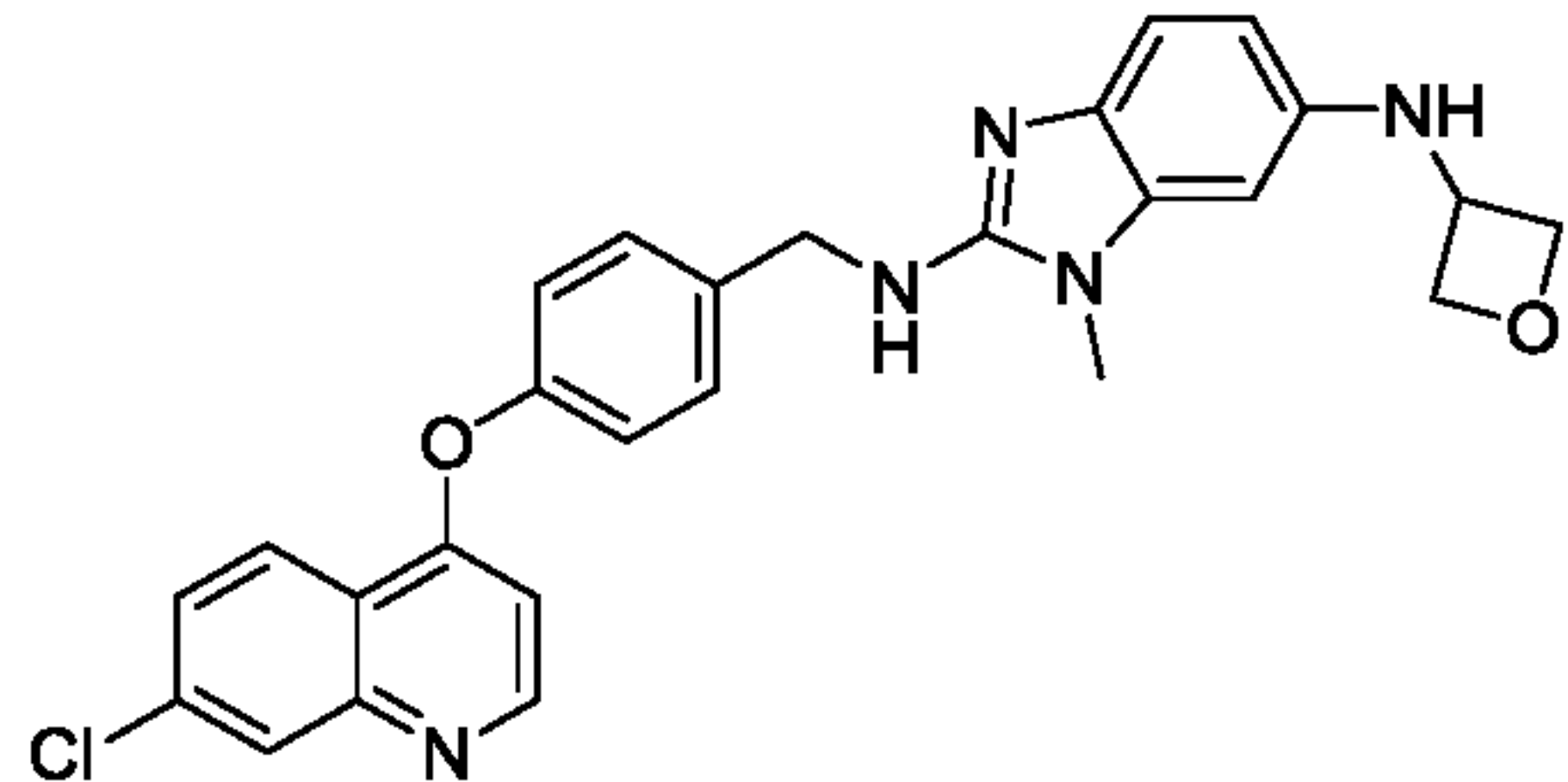
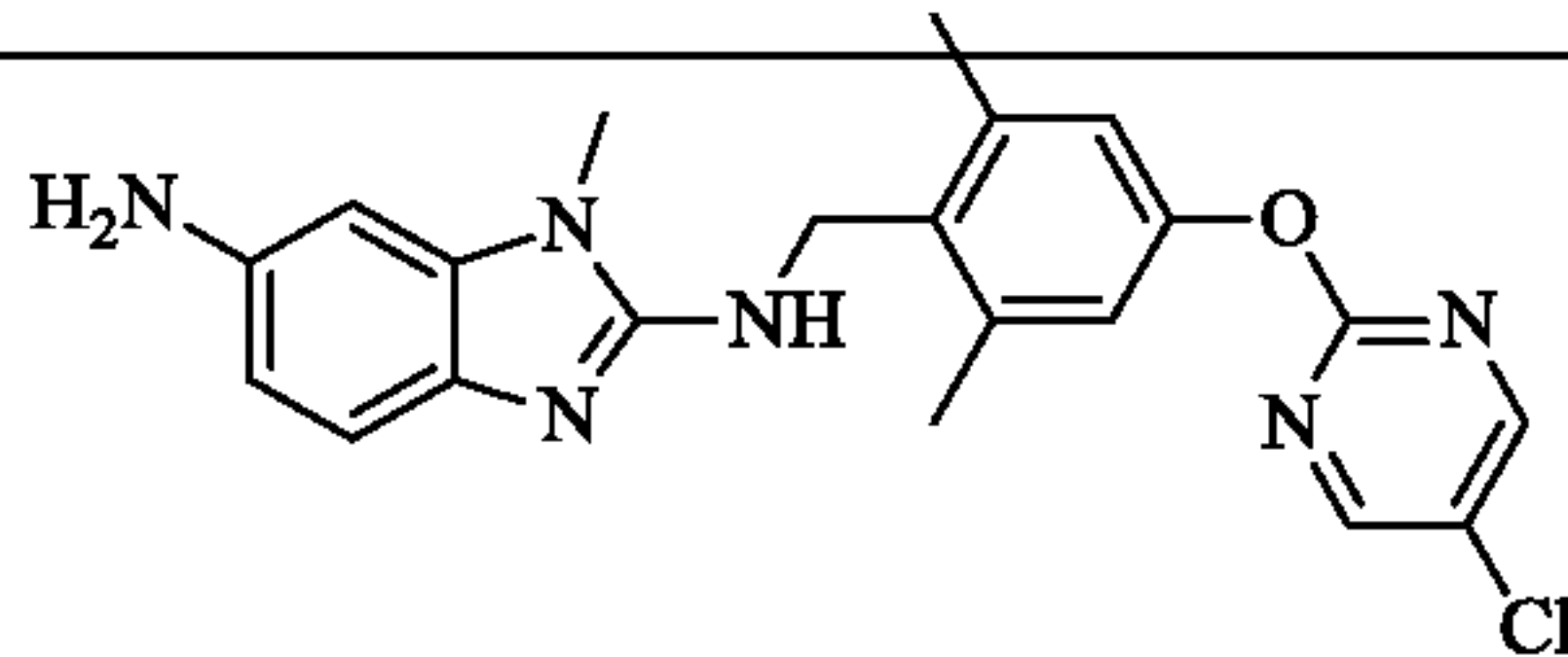
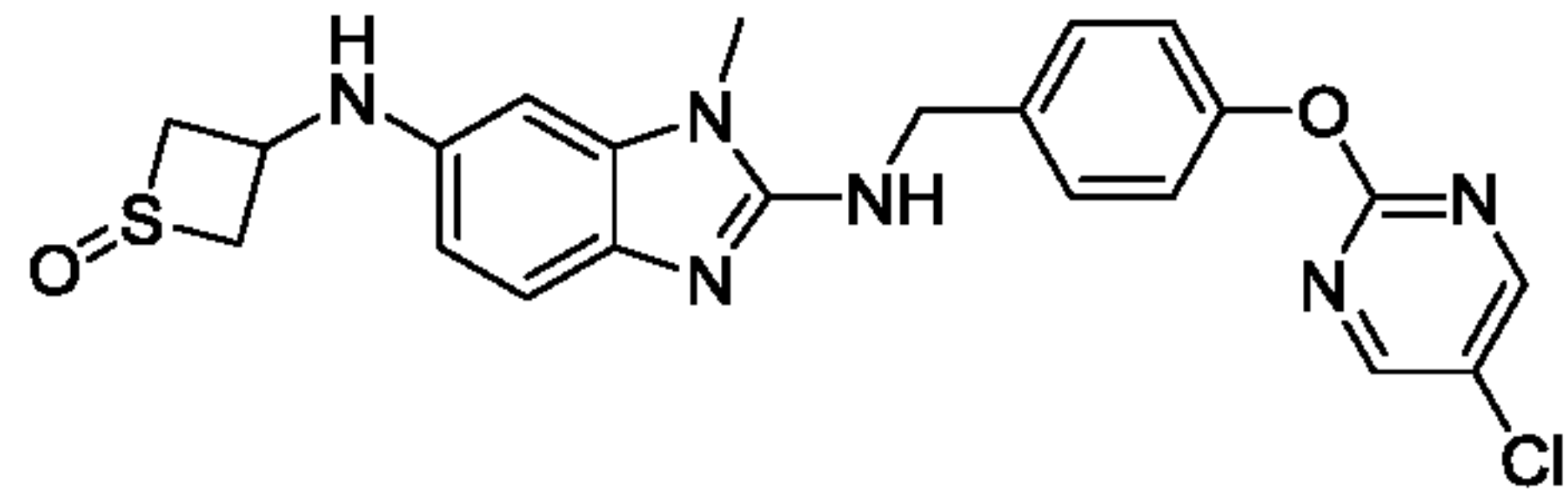
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 338 |    | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.8 Hz), 7.94 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.38 (1H, d, <i>J</i> = 8.8 Hz), 7.01-7.12 (4H, m), 6.45 (1H, d, <i>J</i> = 1.6 Hz), 6.40 (1H, dd, <i>J</i> = 8.8, 2.0 Hz), 4.78 (2H, brs), 4.43 (2H, s), 3.53-3.47 (5H, m), 3.29-3.34 (2H, m), 3.21 (3H, s); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 438.1 [M+H] <sup>+</sup> .                                                                                                                                                                    |
| 339 |   | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.18 (1H, d, <i>J</i> = 2.4 Hz), 7.94 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.37 (2H, d, <i>J</i> = 8.8 Hz), 7.13 (1H, d, <i>J</i> = 8.4 Hz), 7.00-7.10 (3H, m), 6.38 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 6.30 (1H, d, <i>J</i> = 2.0 Hz), 6.09 (1H, d, <i>J</i> = 6.4 Hz), 4.86 (2H, t, <i>J</i> = 6.4 Hz), 4.51-4.58 (1H, m), 4.44 (2H, s), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.55 (3H, s), 3.49 (2H, t, <i>J</i> = 5.6 Hz), 3.28-3.33 (2H, m), 3.21 (3H, s); LCMS: 99.6 %, MS (ESI); <i>m/z</i> 494.1 [M+H] <sup>+</sup> . |
| 340 |  | pale yellow powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.58 (2H, s), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.81-6.92 (2H, m), 6.36 (1H, d, <i>J</i> = 2.0 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.51 (2H, d, <i>J</i> = 5.6 Hz), 3.40 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 381.0[M+H] <sup>+</sup> .                                                                                                                                                                                                     |
| 341 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.57 (2H, s), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.92-6.95 (2H, m), 6.14-6.28 (2H, m), 5.85 (1H, d, <i>J</i> = 6.4 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.35-4.45 (3H, m), 4.39 (2H, t, <i>J</i> = 5.6 Hz), 3.44 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 436.9[M+H] <sup>+</sup> .                                                                                                                                                                                              |
| 342 |  | grey powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, s), 7.32 (2H, d, <i>J</i> = 8.4 Hz), 7.26 (1H, s), 6.97 (2H, d, <i>J</i> = 8.4 Hz), 6.85 (1H, d, <i>J</i> = 8.4 Hz), 6.77 (1H, brs), 6.35 (1H, s), 6.26 (1H, dd, <i>J</i> = 8.0, 2.4 Hz), 5.19 (2H, s), 4.55 (2H, brs), 4.42 (2H, d, <i>J</i> = 6.0 Hz), 3.38 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 350.2[M+ H] <sup>+</sup> .                                                                                                                                                                   |
| 343 |  | white powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.15 (1H, s), 7.31 (2H, d, <i>J</i> = 8.4 Hz), 7.25 (1H, s), 6.90-7.02 (3H, m), 6.82 (1H, t, <i>J</i> = 6.0 Hz), 6.15-6.25 (2H, m), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 5.19 (2H, s), 4.77-4.89 (2H, m), 4.34-4.55 (5H, m), 3.41 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 406.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                            |
| 344 |  | pale-yellow power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.61 (2H, d, <i>J</i> = 4.8 Hz), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.25 (1H, t, <i>J</i> = 4.8 Hz), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, d, <i>J</i> = 8.4 Hz), 6.43 (1H, s), 6.33 (1H, d, <i>J</i> = 8.0 Hz), 4.54 (2H, d, <i>J</i> = 5.6 Hz), 3.46 (3H, s); LCMS: 98.4%, MS (ESI); <i>m/z</i> 347.0 [M+H] <sup>+</sup> .                                                                                                                                                                                       |
| 345 |  | pale-yellow power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.61 (2H, d, <i>J</i> = 4.4 Hz), 7.43 (2H, d, <i>J</i> = 8.4 Hz), 7.24 (2H, t, <i>J</i> = 4.8 Hz), 7.11 (2H, d, <i>J</i> = 8.4 Hz), 6.93-6.98 (2H, m), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.49-4.53 (3H, m), 4.39 (2H, t, <i>J</i> = 5.6 Hz), 3.45 (3H, s); LCMS: 99.5%, MS (ESI); <i>m/z</i> 403.0[M+H] <sup>+</sup> .                                                                                                                 |

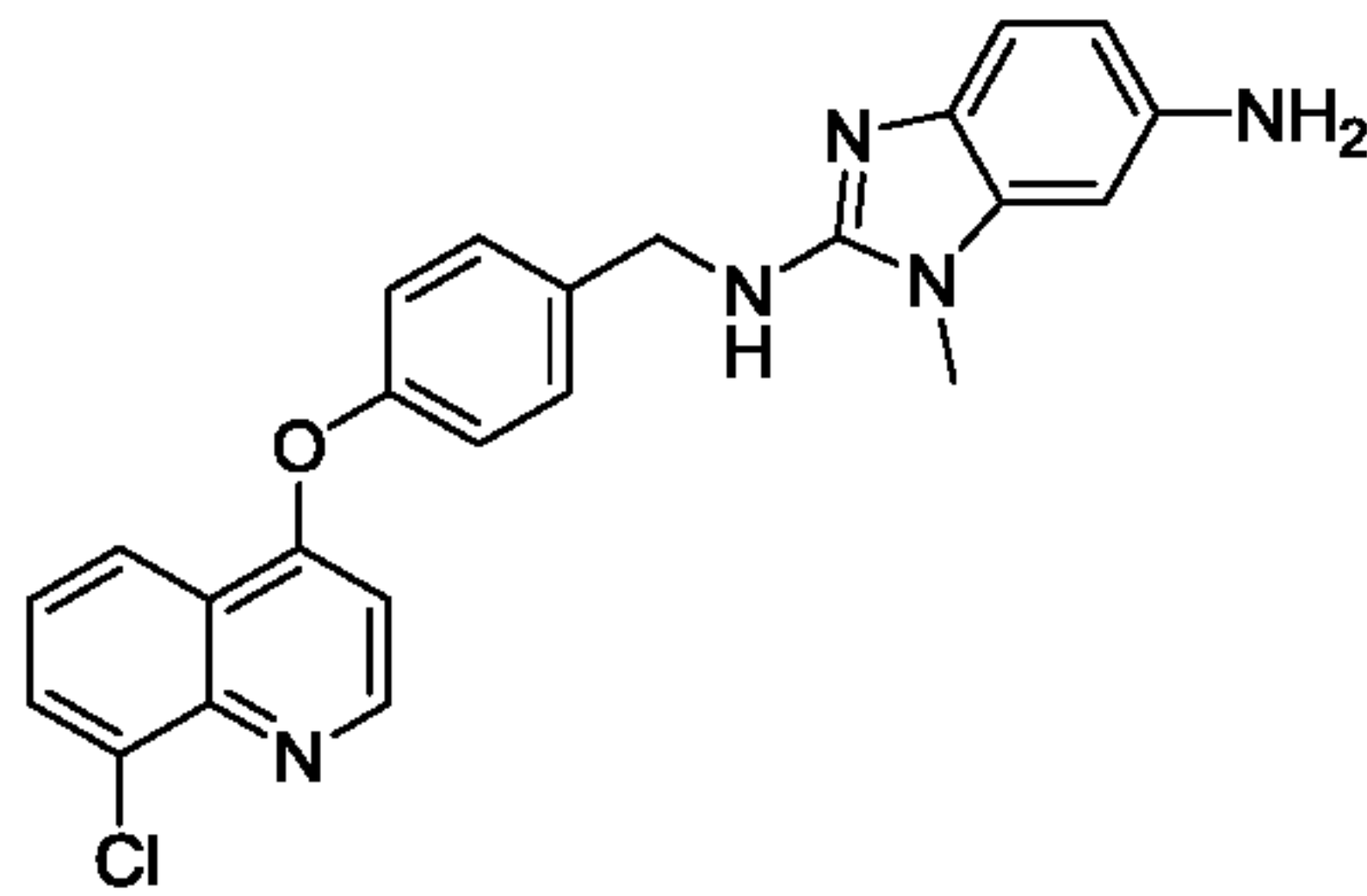
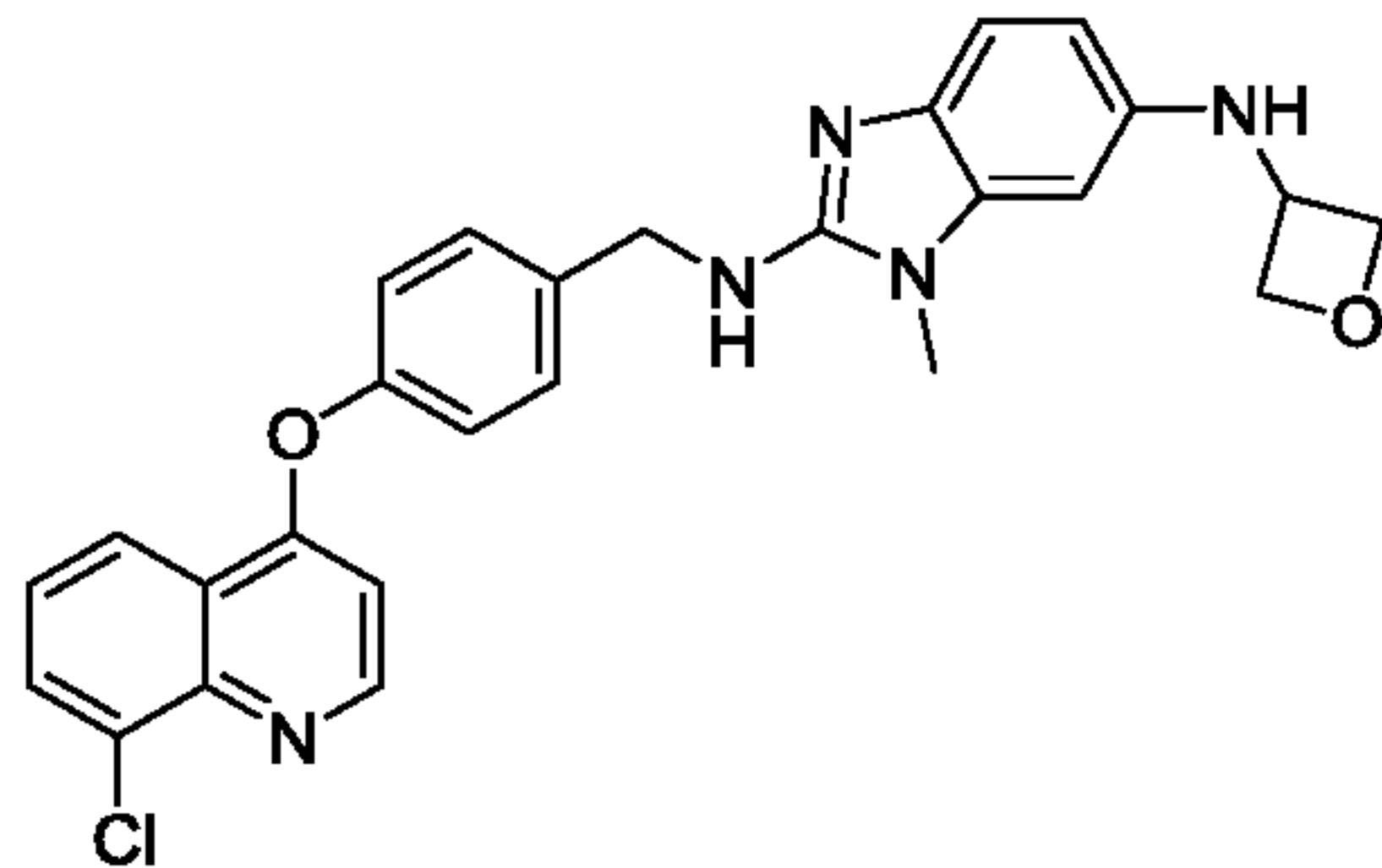
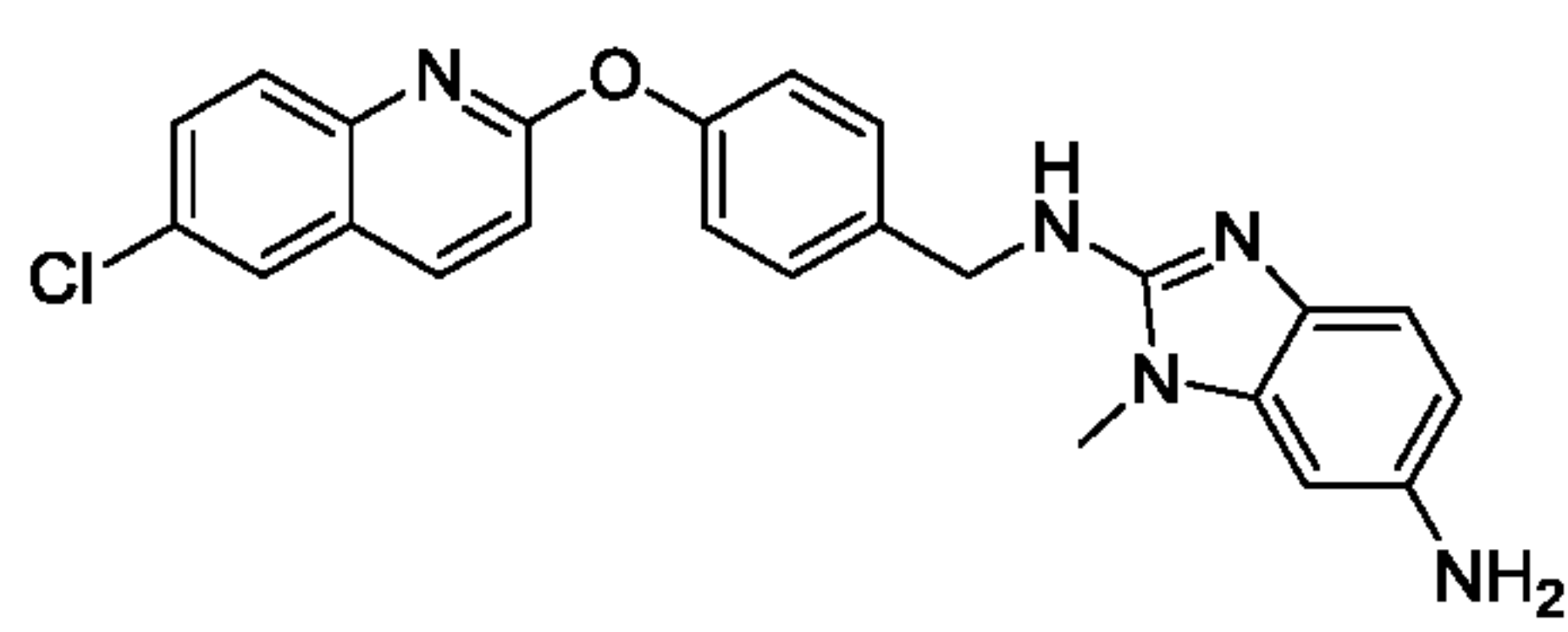
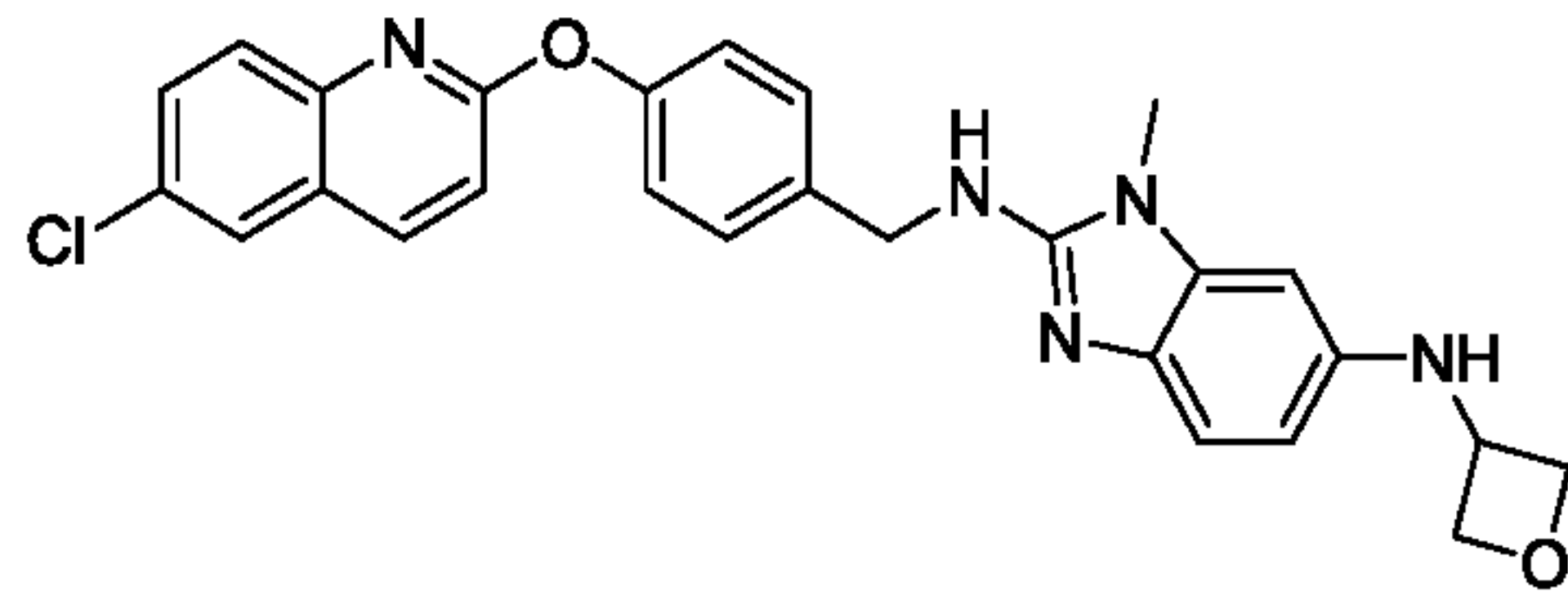
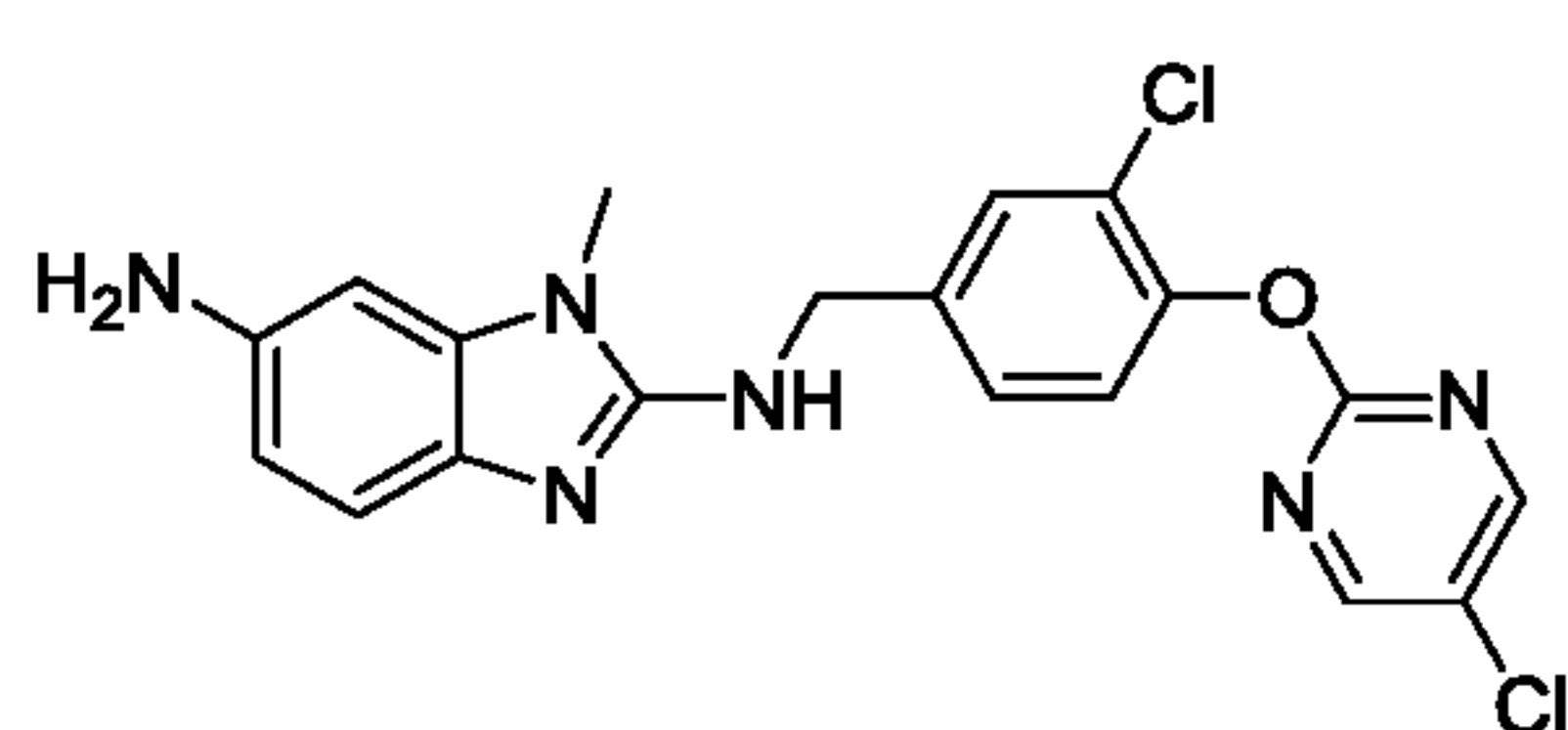
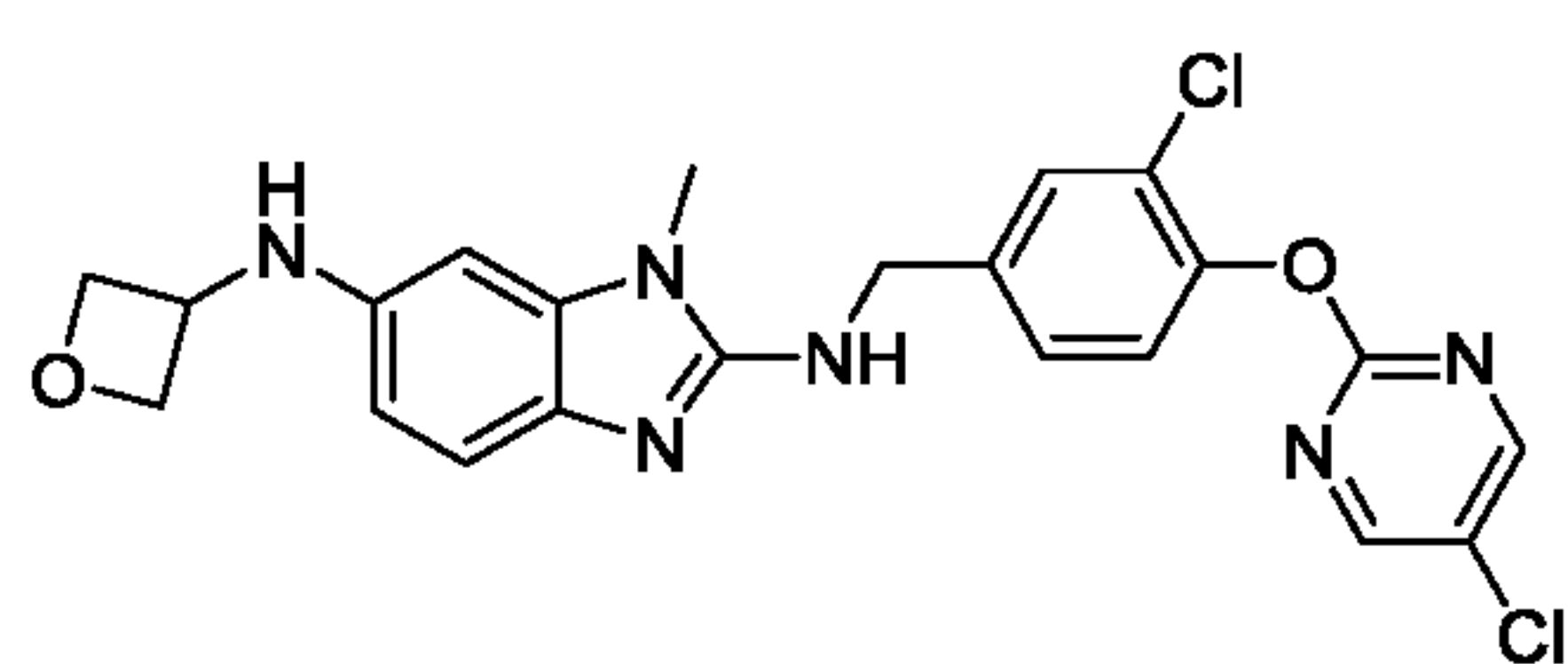
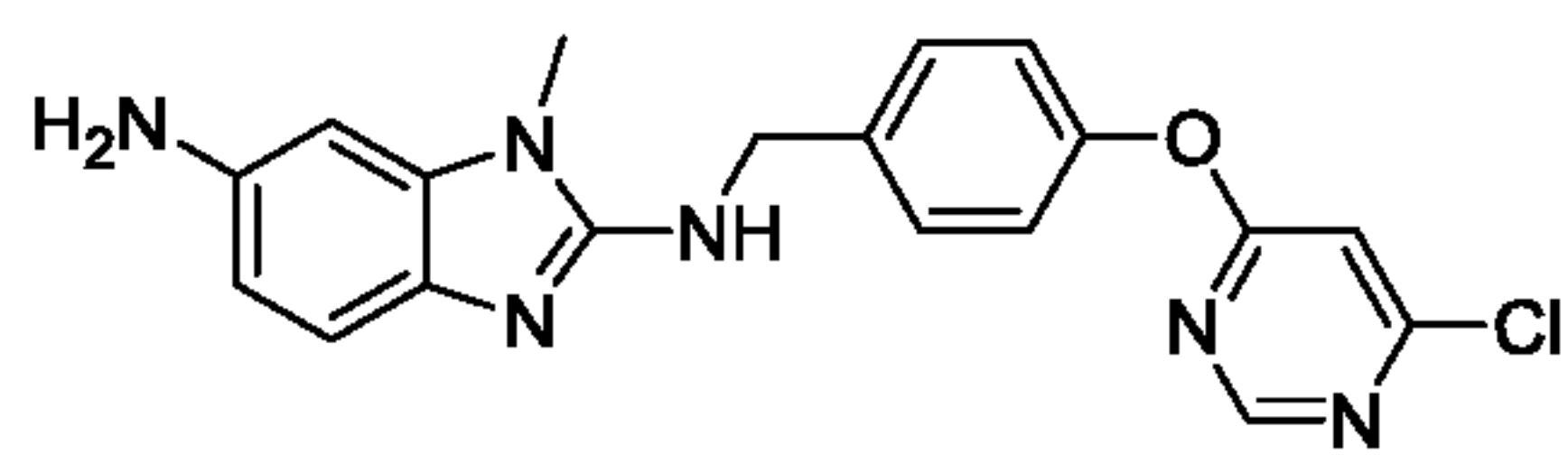
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 346 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.12 (1H, dd, <i>J</i> = 4.8, 1.2 Hz), 7.77-7.89 (1H, m), 7.43 (2H, d, <i>J</i> = 8.0 Hz), 7.04-7.12 (3H, m), 7.00 (1H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, t, <i>J</i> = 5.2 Hz), 6.88 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.36-4.83 (4H, m), 3.42 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 346.0 [M+H] <sup>+</sup> .                                                                |
| 347 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.11 (1H, dd, <i>J</i> = 4.8, 1.6 Hz), 7.78-7.88 (1H, m), 7.41 (2H, d, <i>J</i> = 8.4 Hz), 7.03-7.13 (3H, m), 7.00 (1H, d, <i>J</i> = 8.8 Hz), 6.90-7.02 (2H, m), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.62 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 402.0 [M+H] <sup>+</sup> .            |
| 348 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.45 (2H, s), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.13 (2H, d, <i>J</i> = 8.4 Hz), 6.96 (1H, d, <i>J</i> = 8.4 Hz), 6.47 (1H, s), 6.38 (1H, d, <i>J</i> = 8.4 Hz), 4.56 (2H, d, <i>J</i> = 5.2 Hz), 3.48 (3H, s), 2.20 (3H, s); LCMS: 97.8%, MS (ESI); <i>m/z</i> 361.0 [M+H] <sup>+</sup> .                                                                                                                                                             |
| 349 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.44 (2H, s), 7.41 (2H, d, <i>J</i> = 8.0 Hz), 7.08 (2H, d, <i>J</i> = 8.4 Hz), 6.92-6.96 (2H, m), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.52 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s), 2.19 (3H, s); LCMS: 98.5%, MS (ESI); <i>m/z</i> 417.1[M+H] <sup>+</sup> .                                                                                       |
| 350 |  | off white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.62 (1H, d, <i>J</i> = 2.0 Hz), 8.30 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.47 (2H, d, <i>J</i> = 8.0 Hz), 7.23 (1H, d, <i>J</i> = 8.8 Hz), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.85-6.94 (2H, m), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.45-4.61 (4H, m), 3.42 (3H, s); LCMS: 99.8 %, MS (ESI); <i>m/z</i> 371.1[M+ H] <sup>+</sup> .                                                                                  |
| 351 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.62 (1H, d, <i>J</i> = 2.0 Hz), 8.30 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.46 (2H, d, <i>J</i> = 8.8 Hz), 7.23 (1H, d, <i>J</i> = 8.8 Hz), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.90-7.01 (2H, m), 6.26 (1H, s), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.48-4.59 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s); LCMS: 98.3%, MS (ESI); <i>m/z</i> 427.1[M+ H] <sup>+</sup> . |
| 352 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.95 (1H, d, <i>J</i> = 2.4 Hz), 7.65 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.41 (2H, d, <i>J</i> = 8.4 Hz), 7.03 (2H, d, <i>J</i> = 8.4 Hz), 6.95-6.83 (3H, m), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.54 (2H, s), 4.50 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s), 2.23 (3H, s); LCMS: 98.3 %, MS (ESI); <i>m/z</i> 360.0[M+ H] <sup>+</sup> .                                                                             |
| 353 |  | a white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.95 (1H, s), 7.65 (1H, dd, <i>J</i> = 8.4, 2.4 Hz), 7.40 (2H, d, <i>J</i> = 8.4 Hz), 7.02 (2H, d, <i>J</i> = 8.4 Hz), 6.86-6.98 (3H, m), 6.16-6.31 (2H, m), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.57 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.44 (3H, s), 2.23 (3H, s); LCMS: 98.0%, MS (ESI); <i>m/z</i> 416.2[M+ H] <sup>+</sup> .                                                                             |
| 354 |  | pale yellow powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.77 (2H, s), 8.46 (1H, d, <i>J</i> = 2.8 Hz), 7.66 (1H, dd, <i>J</i> = 8.4, 2.8 Hz), 7.48 (1H, d, <i>J</i> = 8.8 Hz), 7.05 (1H, t, <i>J</i> = 6.0 Hz), 6.84 (1H, d, <i>J</i> = 8.0 Hz), 6.38 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.61 (2H, d, <i>J</i> = 6.0 Hz), 4.55 (2H, s), 3.45 (3H, s); LCMS: 99.5%, MS (ESI); <i>m/z</i> 382.0[M+H] <sup>+</sup> .                                               |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 355 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.76 (2H, s), 8.46 (1H, d, <i>J</i> = 2.4 Hz), 7.66 (1H, dd, <i>J</i> = 8.4, 2.8 Hz), 7.47 (1H, d, <i>J</i> = 8.8 Hz), 7.10 (1H, t, <i>J</i> = 6.0 Hz), 6.92 (1H, d, <i>J</i> = 8.0 Hz), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.62 (2H, d, <i>J</i> = 6.0 Hz), 4.547-4.55 (1H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.48 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 438.1[M+H] <sup>+</sup> . |
| 356 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40-7.53 (3H, m), 7.25-7.40 (3H, m), 7.05-7.20 (2H, m), 6.82-6.96 (2H, m), 6.37 (1H, d, <i>J</i> = 1.2 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.40-4.65 (4H, m), 3.71 (3H, s), 3.42 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 399.1[M+H] <sup>+</sup> .                                                                                                                                                                                                                                           |
| 357 |  | white amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.40-7.52 (3H, m), 7.27-7.39 (3H, m), 7.06-7.19 (2H, m), 6.91-7.02 (2H, m), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.6 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.62 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.70 (3H, s), 3.45 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 455.2[M+H] <sup>+</sup> .                                                                                                                                        |
| 358 |  | pale-yellow powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.22 (1H, brs), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.96-7.05 (2H, m), 6.92 (1H, d, <i>J</i> = 8.4 Hz), 6.33 (1H, d, <i>J</i> = 1.6 Hz), 6.30 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.15 (1H, brs), 4.52 (2H, d, <i>J</i> = 6.4 Hz), 3.40 (3H, s), 1.32 (6H, s); LCMS: 99.1 %, MS (ESI); <i>m/z</i> 466.1[M + H] <sup>+</sup> .                                                                                                                  |
| 359 |  | yellow powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.44 (2H, d, <i>J</i> = 8.8 Hz), 7.14 (2H, d, <i>J</i> = 8.0 Hz), 7.05 (1H, s), 6.87-7.00 (2H, m), 6.79 (1H, s), 6.57 (1H, s), 6.42 (1H, d, <i>J</i> = 8.4 Hz), 5.46 (1H, brs), 4.51 (2H, d, <i>J</i> = 5.6 Hz), 4.24 (2H, d, <i>J</i> = 4.8 Hz), 3.64 (3H, s), 3.44 (3H, s); LCMS: 99.53%, MS (ESI); <i>m/z</i> 475.1[M+H] <sup>+</sup> .                                                                                                                                      |
| 360 |  | white powder (amorphous); <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.11 (2H, s), 7.35 (1H, d, <i>J</i> = 8.4 Hz), 6.89 (2H, d, <i>J</i> = 8.8 Hz), 6.75-6.88 (2H, m), 6.62 (2H, brs), 6.35 (1H, d, <i>J</i> = 1.2 Hz), 6.25 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 4.53 (2H, brs), 4.44 (2H, d, <i>J</i> = 5.6 Hz), 3.38 (3H, s); LCMS: 97.1%, MS (ESI); <i>m/z</i> 362.1[M+ H] <sup>+</sup> .                                                                                                                                                                         |
| 361 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.78 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.16 (2H, d, <i>J</i> = 8.4 Hz), 7.02 (1H, brs), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, s), 6.27 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 4.77 (2H, brs), 4.51 (2H, d, <i>J</i> = 5.6 Hz), 3.42 (3H, s); LCMS: 98.8%, MS (ESI); <i>m/z</i> 425.0 [M+H] <sup>+</sup> .                                                                                                                                                                                    |
| 362 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.77 (2H, s), 7.43 (2H, d, <i>J</i> = 8.0 Hz), 7.14 (2H, t, <i>J</i> = 8.4 Hz), 6.90-6.98 (2H, m), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.4 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.52 (3H, m), 4.39 (2H, t, <i>J</i> = 5.6 Hz), 3.45 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 482.9[M+3] <sup>+</sup> .                                                                                                                                                     |
| 363 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.95 (1H, d, <i>J</i> = 4.8 Hz), 7.76 (1H, d, <i>J</i> = 5.2 Hz), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 7.22 (2H, d, <i>J</i> = 8.8 Hz), 6.90 (1H, d, <i>J</i> = 8.0 Hz), 6.41 (1H, s), 6.31 (1H, d, <i>J</i> = 8.4 Hz), 4.55 (2H, d, <i>J</i> = 5.6 Hz), 3.45 (3H, s); LCMS: 97.7%, MS (ESI); <i>m/z</i> 415.1 [M+H] <sup>+</sup> .                                                                                                                                                                      |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 364 |  | pale-yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.96 (1H, d, <i>J</i> = 4.4 Hz), 7.75 (1H, d, <i>J</i> = 4.8 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.20 (2H, d, <i>J</i> = 8.4 Hz), 6.93-6.99 (2H, m), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.8 Hz), 5.83 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.47-4.55 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 471.1[M+H] <sup>+</sup> .                                                            |
| 365 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.79 (2H, d, <i>J</i> = 5.2 Hz), 8.72 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.39 (1H, t, <i>J</i> = 4.8 Hz), 7.12-7.17 (2H, m), 6.95 (1H, t, <i>J</i> = 6.0 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.50 (1H, d, <i>J</i> = 2.0 Hz), 6.39 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.63 (1H, t, <i>J</i> = 6.0 Hz), 4.52 (2H, d, <i>J</i> = 5.6 Hz), 4.45 (2H, d, <i>J</i> = 5.6 Hz), 3.43 (3H, s); LCMS: 96.7%, MS (ESI); <i>m/z</i> 473.1[M+H] <sup>+</sup> .           |
| 366 |  | pale-yellow power; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.72 (2H, s), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.14 (2H, d, <i>J</i> = 8.4 Hz), 6.96 (1H, t, <i>J</i> = 6.0 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.42 (1H, s), 6.27 (1H, dd, <i>J</i> = 8.8, 1.6 Hz), 5.76 (1H, d, <i>J</i> = 9.6 Hz), 4.70-4.78 (1H, m), 4.51 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s), 3.30-3.35 (2H, m, after exchange with D <sub>2</sub> O), 3.25 (2H, t, <i>J</i> = 8.4 Hz); LCMS: 98.5%, MS (ESI); <i>m/z</i> 453.0 [M+H] <sup>+</sup> . |
| 367 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.12 (2H, s), 7.47 (2H, d, <i>J</i> = 8.0 Hz), 7.19 (2H, d, <i>J</i> = 8.0 Hz), 6.93 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.41 (3H, s); LCMS: 99.3%, MS (ESI); <i>m/z</i> 372.1 [M+H] <sup>+</sup> .                                                                                                                           |
| 368 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.12 (2H, s), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.19 (2H, d, <i>J</i> = 8.4 Hz), 6.98 (1H, t, <i>J</i> = 6.0 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.25 (1H, d, <i>J</i> = 2.0 Hz), 6.21 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.47-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), (2H, m) 3.45 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 428.0[M+H] <sup>+</sup> .                             |
| 369 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.12 (2H, s), 7.35 (1H, d, <i>J</i> = 8.4 Hz), 6.80-7.00 (4H, m), 6.63 (1H, s), 6.75-6.88 (2H, m), 6.63 (2H, s), 6.24 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.8, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.8 Hz), 4.50-4.60 (1H, m), 4.46 (2H, d, <i>J</i> = 6.0 Hz), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 418.1[M+ H] <sup>+</sup> .                                             |
| 370 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.74 (1H, s), 8.67 (1H, d, <i>J</i> = 5.6 Hz), 7.48 (2H, d, <i>J</i> = 8.8 Hz), 7.09-7.21 (3H, m), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.87 (1H, d, <i>J</i> = 8.4 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.49-4.61 (4H, m), 3.43 (3H, s); LCMS: 99.0 %, MS (ESI); <i>m/z</i> 347.1[M+ H] <sup>+</sup> .                                                                                                                           |
| 371 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.74 (1H, s), 8.67 (1H, d, <i>J</i> = 2.0 Hz), 7.47 (2H, d, <i>J</i> = 8.8 Hz), 7.09-7.26 (3H, m), 6.98 (1H, t, <i>J</i> = 5.6 Hz), 6.95 (1H, d, <i>J</i> = 8.0 Hz), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.44-4.69 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 403.2[M+ H] <sup>+</sup> .                          |

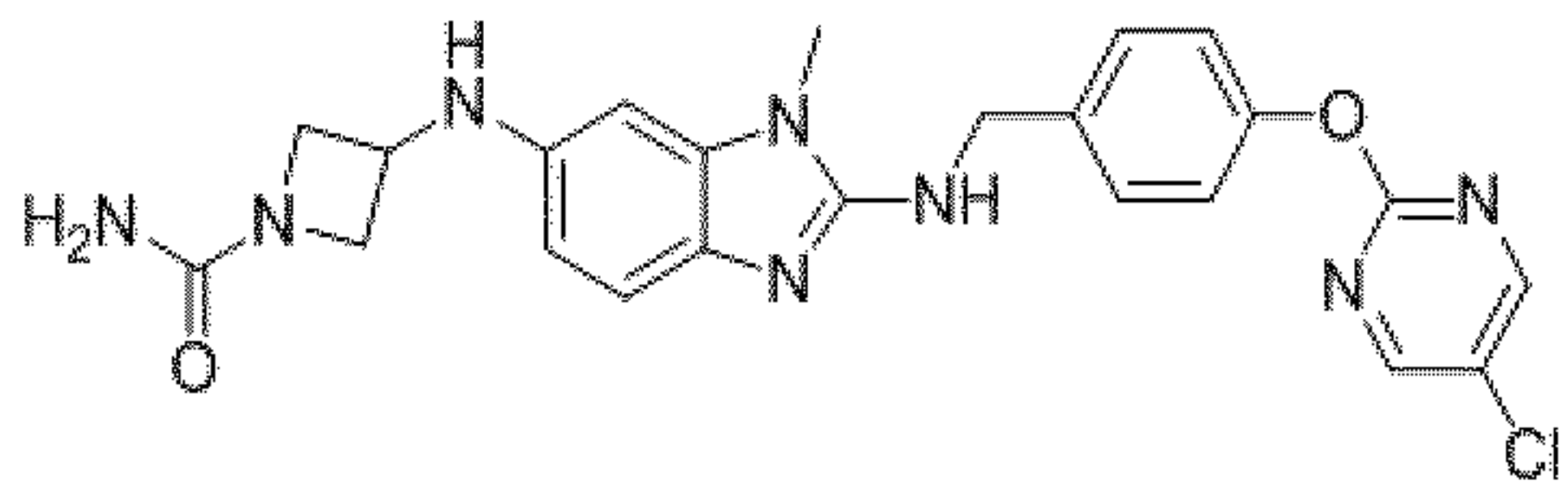
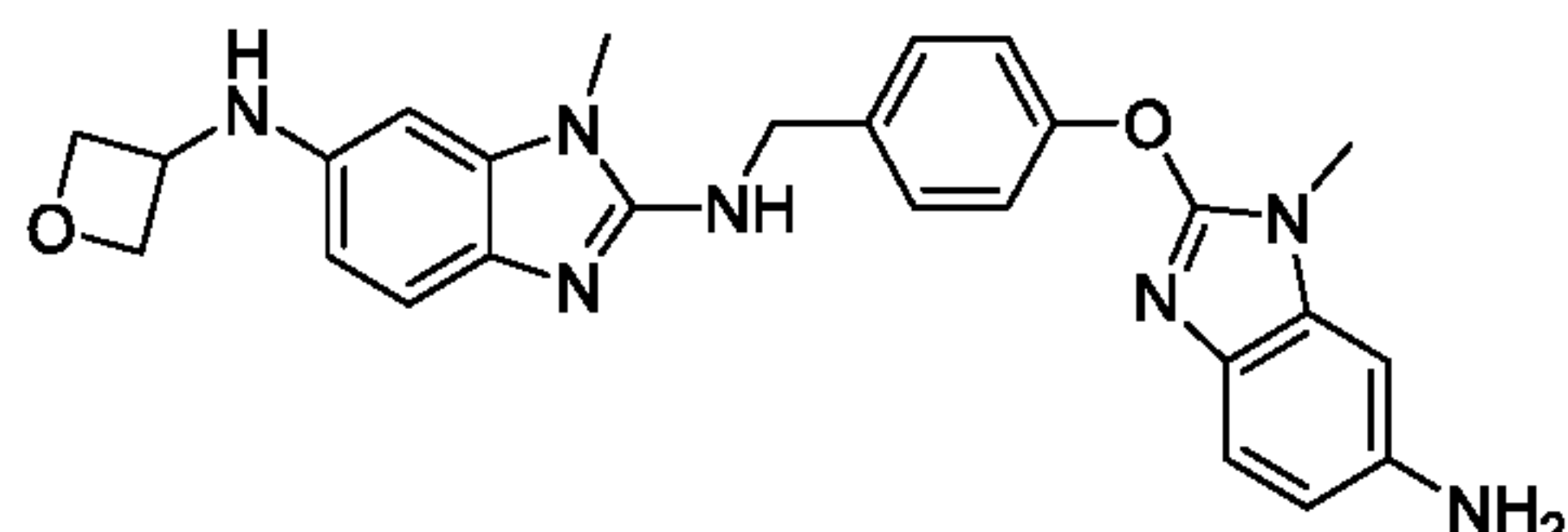
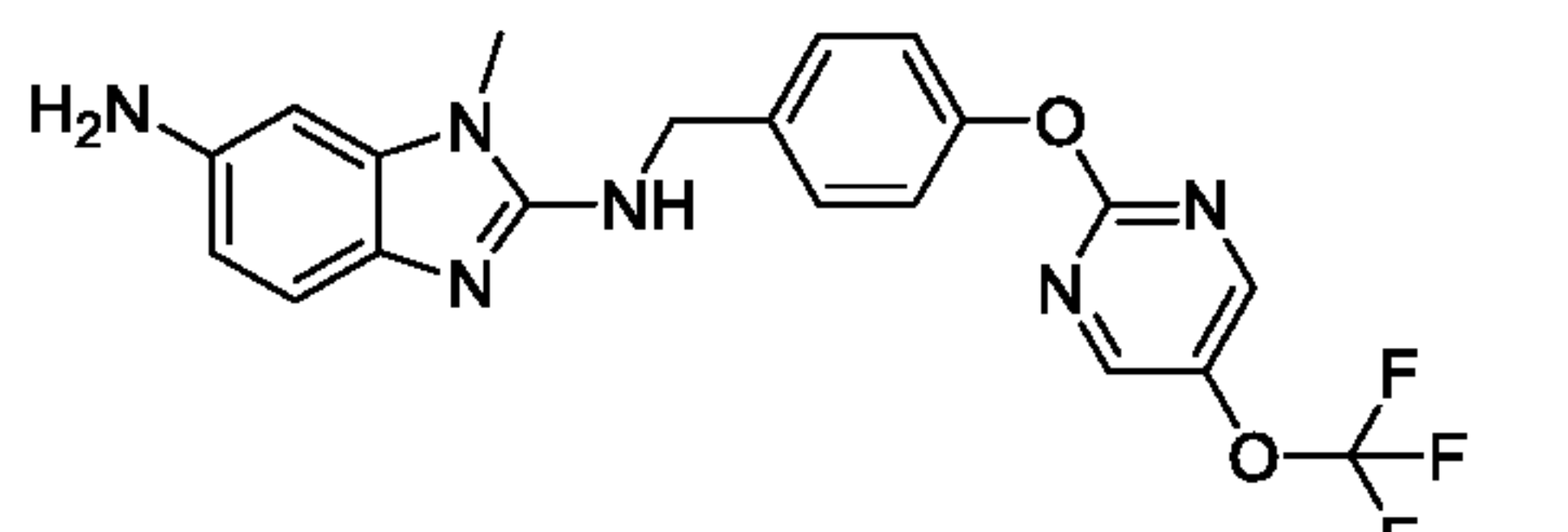
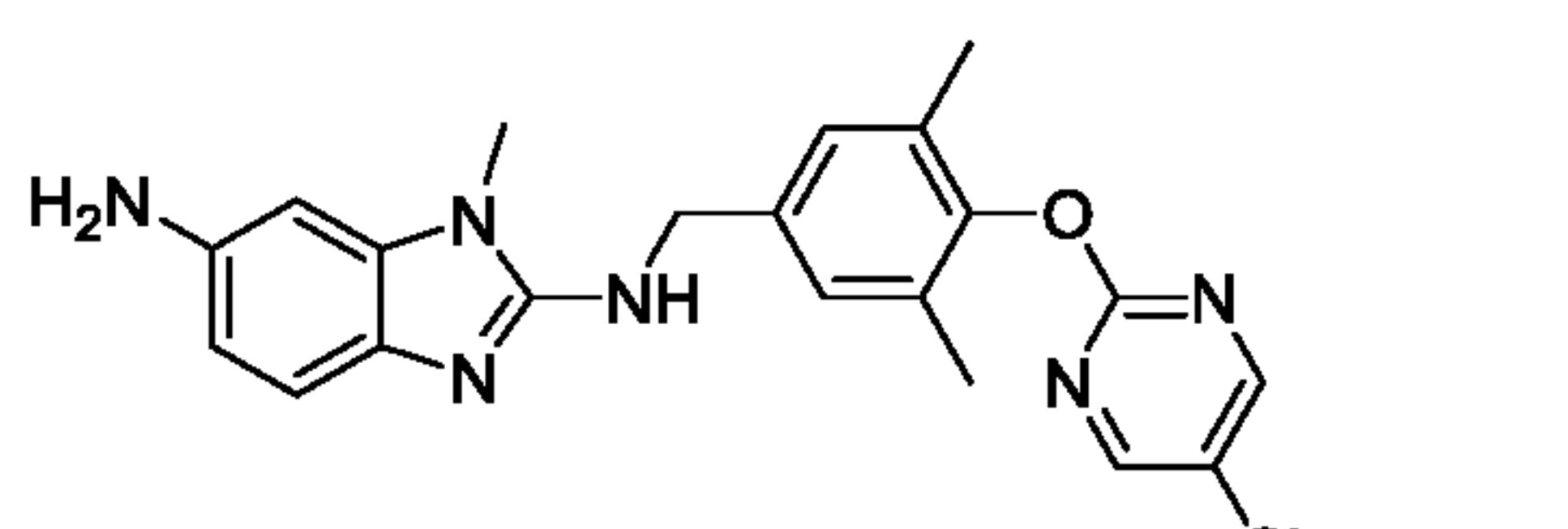
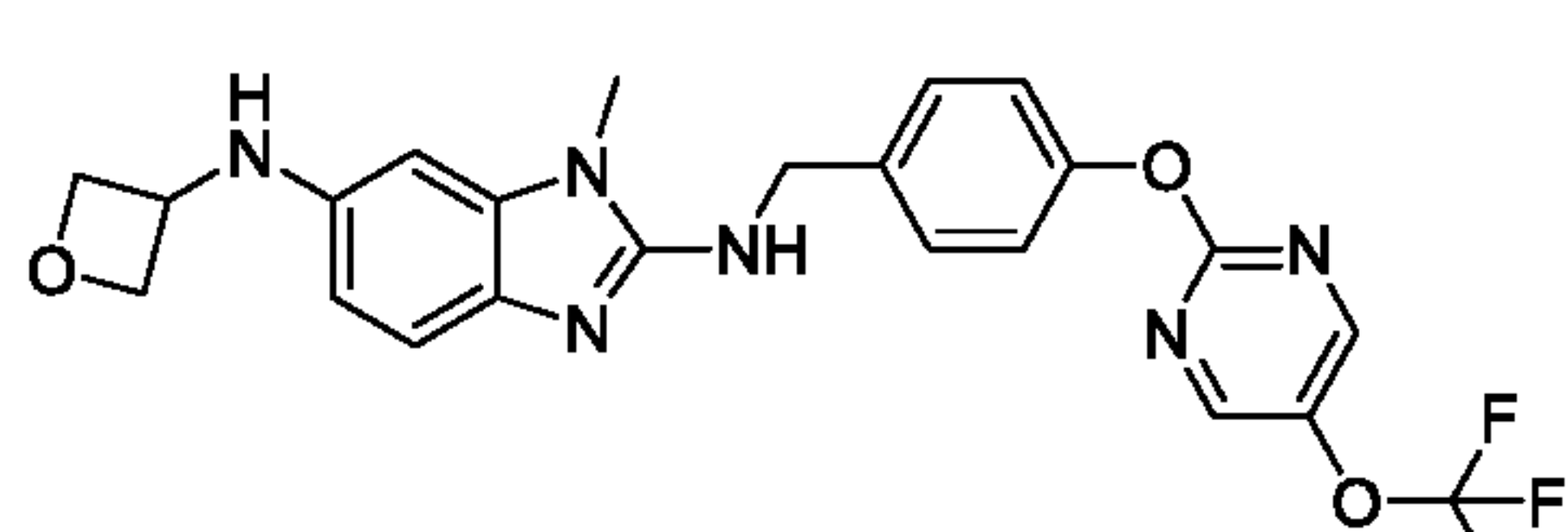
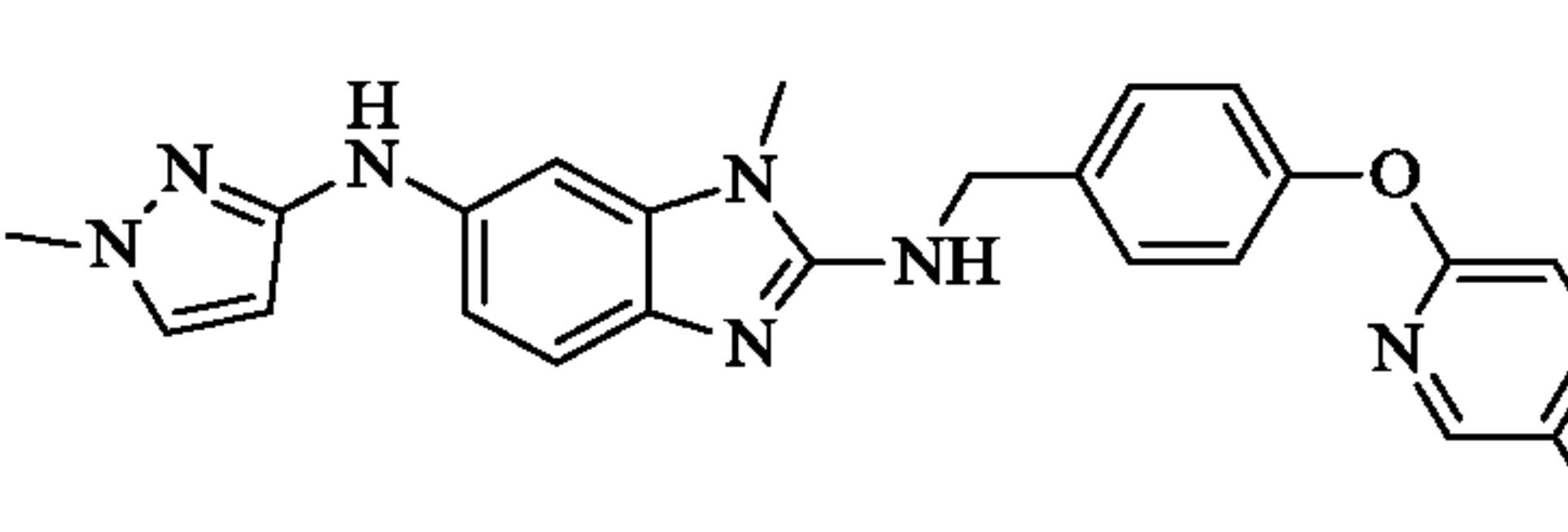
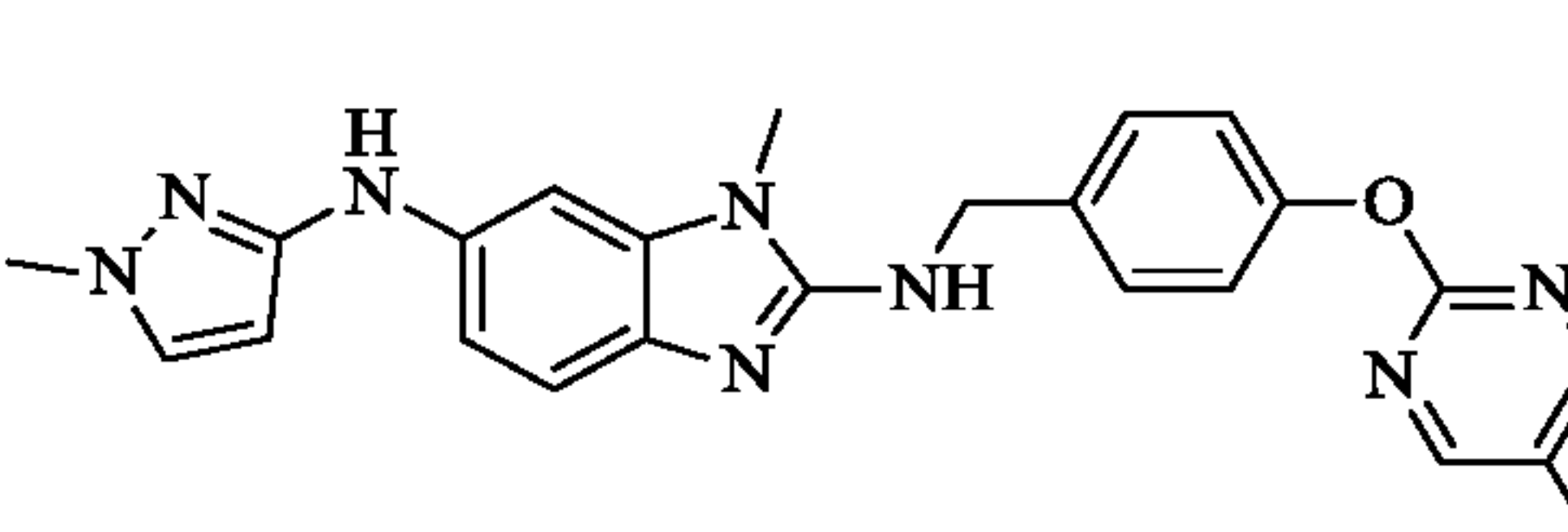
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 372 |    | yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.40-7.48 (4H, m), 7.10-7.20 (4H, m), 6.87-6.95 (2H, m), 6.41 (1H, s), 6.34 (1H, d, <i>J</i> = 8.4 Hz), 5.51 (1H, brs), 4.92-4.97 (1H, m), 4.74-4.80 (1H, m), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.44 (3H, s), 3.17-3.25 (1H, m), 3.02-3.17 (1H, m); LCMS: 99.77%, MS (ESI); <i>m/z</i> 519.1[M+H] <sup>+</sup> .                                                                                                                                                      |
| 373 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.09 (2H, s), 7.47 (2H, d, <i>J</i> = 7.6 Hz), 7.20 (2H, d, <i>J</i> = 7.6 Hz), 6.90-6.99 (1H, m), 6.86 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, s), 6.26 (1H, d, <i>J</i> = 8.4 Hz), 4.45-4.65 (4H, m), 3.41 (3H, s); LCMS: 99.7 %, MS (ESI); <i>m/z</i> 415.1[M+ H] <sup>+</sup> .                                                                                                                                                                                                      |
| 374 |   | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.09 (2H, s), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.20 (2H, d, <i>J</i> = 8.4 Hz), 6.99 (1H, t, <i>J</i> = 6.0 Hz), 6.93 (1H, d, <i>J</i> = 8.4 Hz), 6.17-6.28 (2H, m), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.60 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s); LCMS: 98.2 %, MS (ESI); <i>m/z</i> 471.1[M + H] <sup>+</sup> .                                                                                                          |
| 375 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.71(1H, d, <i>J</i> = 5.6 Hz), 8.33 (1H, d, <i>J</i> = 8.8 Hz), 8.09 (1H, d, <i>J</i> = 2.0 Hz), 7.68 (1H, dd, <i>J</i> = 9.2, 2.4 Hz), 7.55 (2H, d, <i>J</i> = 8.4 Hz), 7.26 (2H, d, <i>J</i> = 8.4 Hz), 6.95 (1H, t, <i>J</i> = 6.0 Hz), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.60 (1H, d, <i>J</i> = 5.6 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.45-4.69 (4H, m), 3.43 (3H, s); LCMS: 99.3%, MS (ESI); <i>m/z</i> 430.0[M+H] <sup>+</sup> . |
| 376 |  | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.95 (2H, s), 7.38 (2H, d, <i>J</i> = 8.0 Hz), 7.00 (2H, d, <i>J</i> = 8.4 Hz), 6.82-6.90 (2H, m), 6.36 (1H, d, <i>J</i> = 1.6 Hz), 6.26 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.21 (2H, s), 4.55 (2H, brs), 4.48 (2H, d, <i>J</i> = 5.6 Hz), 3.40 (3H, s); LCMS: 94.7%, MS (ESI); <i>m/z</i> 362.0[M+H] <sup>+</sup> .                                                                                                                                                                     |
| 377 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.24 (1H, d, <i>J</i> = 2.8 Hz), 7.95 (1H, dd, <i>J</i> = 8.8, 2.0 Hz), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.16 (1H, d, <i>J</i> = 9.2 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.83-6.95 (2H, m), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.56 (2H, brs), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.42 (3H, s); LCMS: 99.9%, MS (ESI); <i>m/z</i> 430.1[M+H] <sup>+</sup> .                                                                                       |
| 378 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.23 (1H, d, <i>J</i> = 2.8 Hz), 7.95 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.16 (1H, d, <i>J</i> = 8.8 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.90-7.01 (2H, m), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (2H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.0 Hz), 4.46-4.58 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s); LCMS: 97.9%, MS (ESI); <i>m/z</i> 486.1[M+H] <sup>+</sup> .                  |
| 379 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.45 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (2H, d, <i>J</i> = 8.4 Hz), 6.85-6.98 (2H, m), 6.42 (1H, d, <i>J</i> = 2.0 Hz), 6.31 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.82 (1H, t, <i>J</i> = 5.6 Hz), 4.52 (2H, d, <i>J</i> = 5.6 Hz), 3.59 (4H, t, <i>J</i> = 4.6 Hz), 3.45 (3H, s), 3.12 (2H, q, <i>J</i> = 6.0 Hz), 2.51-2.54 (2H, m), 2.35-2.46 (4H, m); LCMS: 99.5%, MS (ESI); <i>m/z</i> 494.1[M+H] <sup>+</sup> .                                                     |

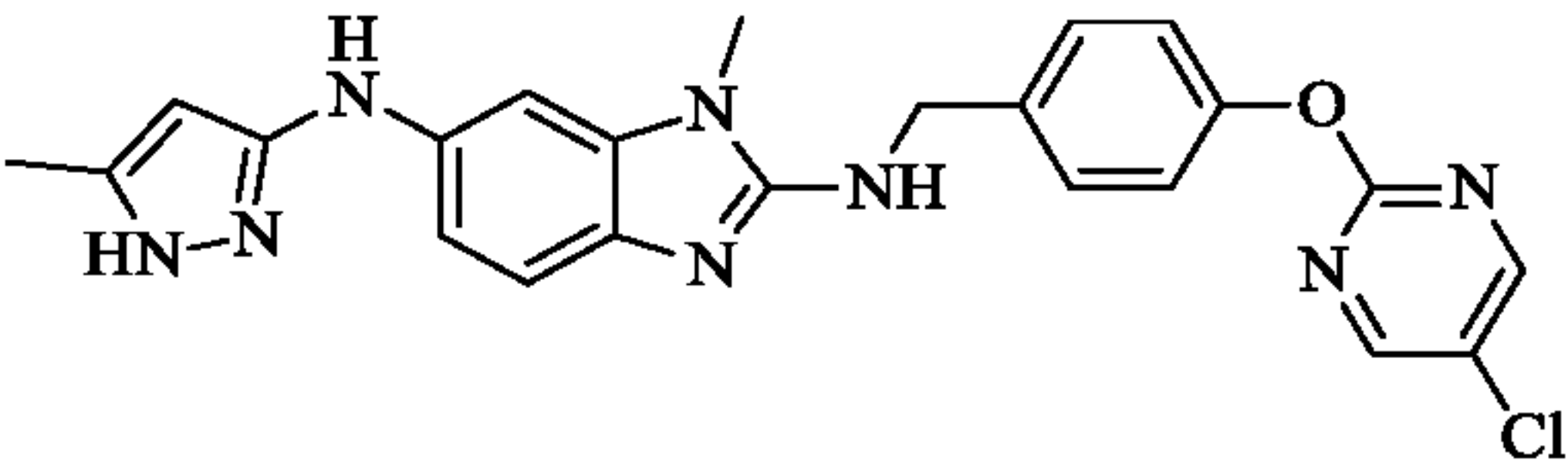
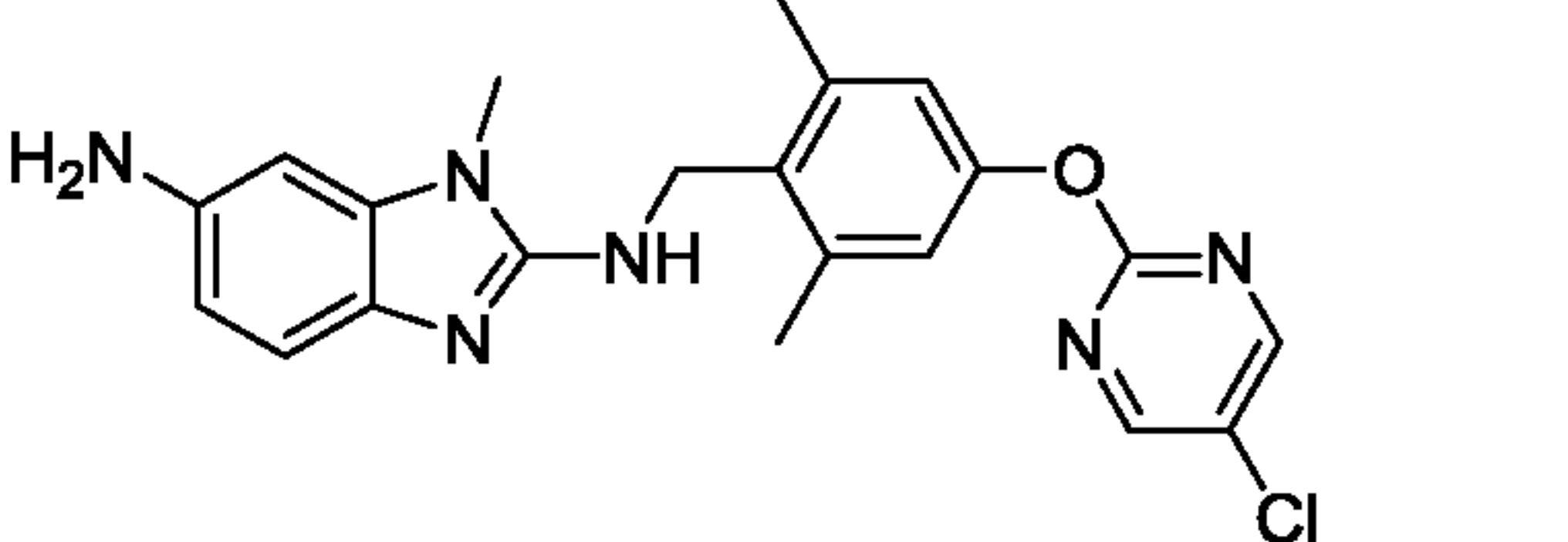
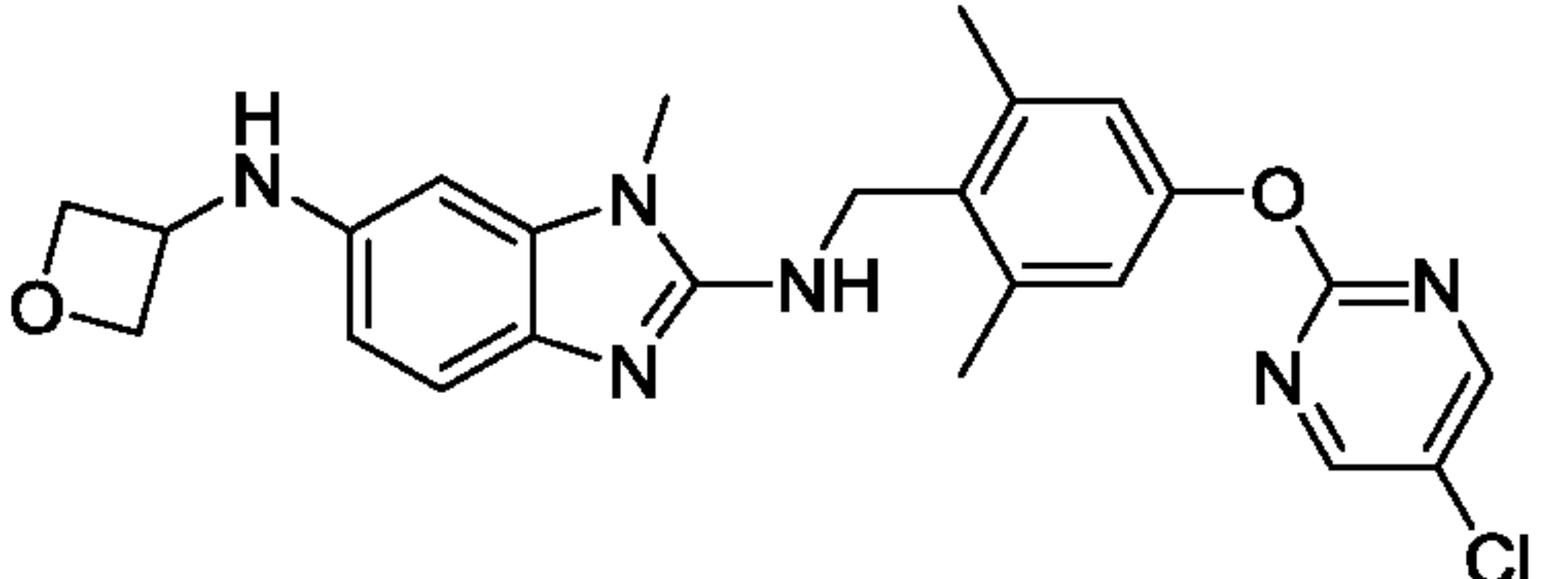
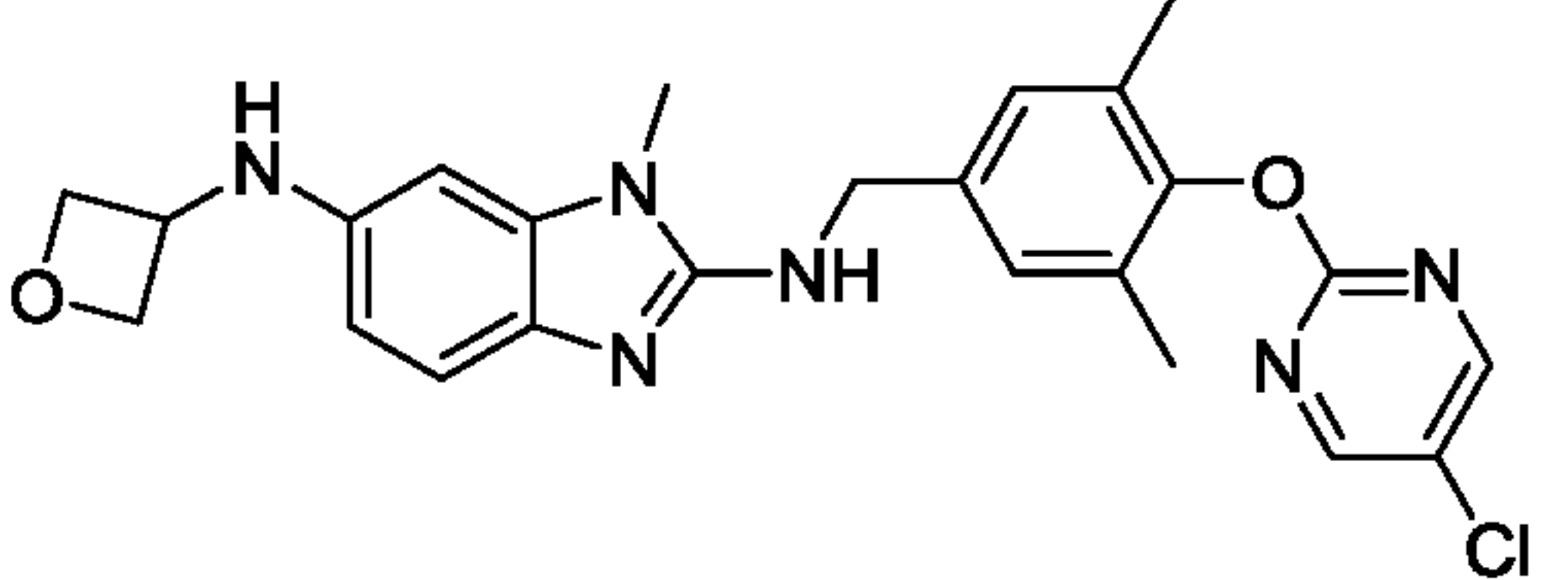
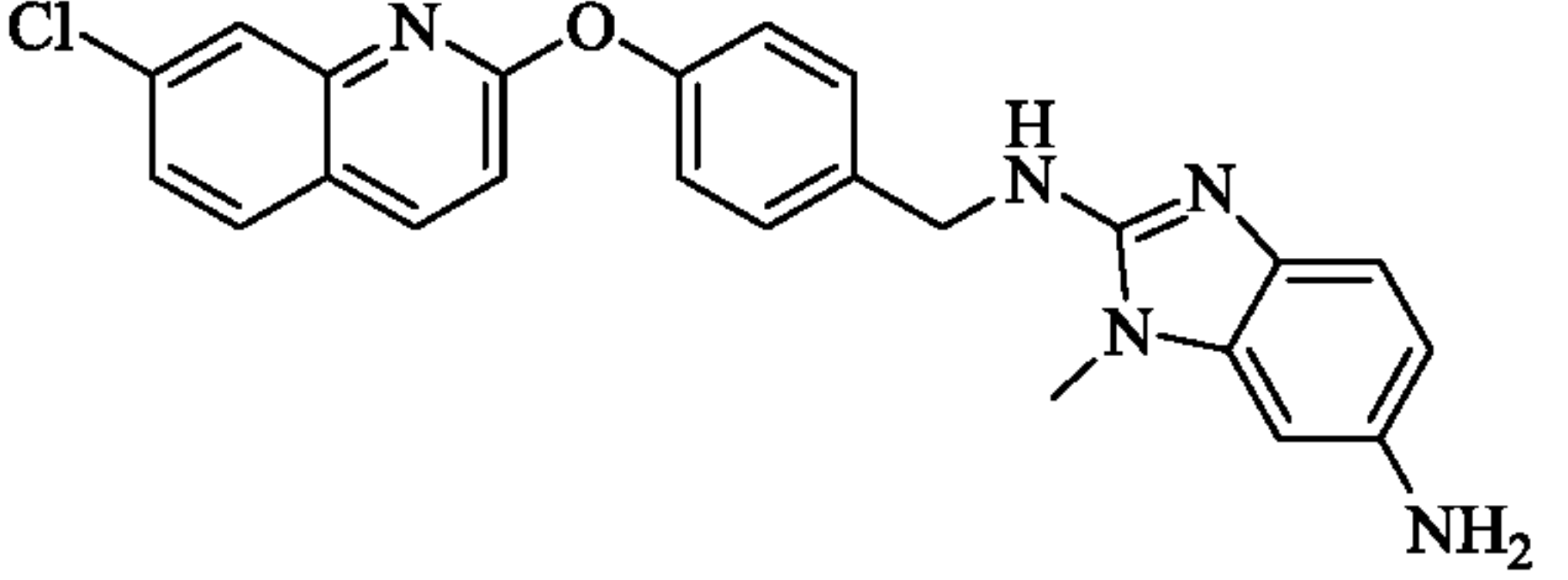
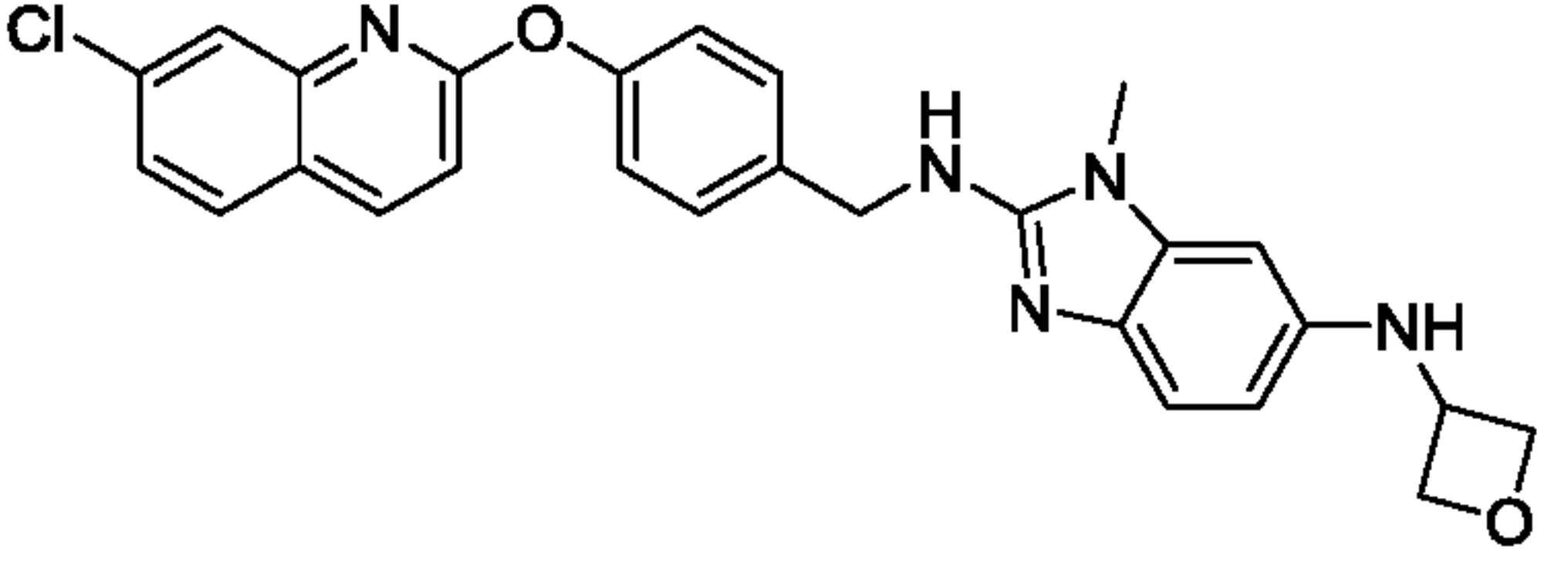
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 380 |    | grey powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.76 (2H, s), 7.50 (1H, t, <i>J</i> = 8.8 Hz), 7.21 (1H, dd, <i>J</i> = 10.8, 2.0 Hz), 7.03 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.84-6.93 (2H, m), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.48-4.62 (4H, m), 3.42 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 399.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                        |
| 381 |    | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.76 (2H, s), 7.50 (1H, t, <i>J</i> = 8.8 Hz), 7.21 (1H, dd, <i>J</i> = 11.2, 2.4 Hz), 7.03 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.92-7.00 (2H, m), 6.18-6.31 (2H, m), 5.86 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.61 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 455.1[M + H] <sup>+</sup> .                                                                                                                                                                                                                                                 |
| 382 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.38 (1H, d, <i>J</i> = 8.8 Hz), 7.76 (1H, dd, <i>J</i> = 9.2, 2.8 Hz), 7.68 (1H, dd, <i>J</i> = 9.2, 5.2 Hz), 7.53 (1H, td, <i>J</i> = 8.8, 3.2 Hz), 7.43-7.48 (2H, m), 7.31 (1H, d, <i>J</i> = 9.2 Hz), 7.15-7.21 (2H, m), 6.94 (1H, t, <i>J</i> = 5.8 Hz), 6.88 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.46-4.65 (4H, m), 3.43 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 414.1[M+H] <sup>+</sup> .                                                                                                                                                      |
| 383 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.38 (1H, d, <i>J</i> = 8.8 Hz), 7.76 (1H, dd, <i>J</i> = 9.2, 2.8 Hz), 7.68 (1H, dd, <i>J</i> = 8.8, 5.2 Hz), 7.52 (1H, td, <i>J</i> = 8.8, 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.30 (1H, d, <i>J</i> = 8.8 Hz), 7.18 (2H, d, <i>J</i> = 8.4 Hz), 6.92-7.02 (2H, m), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.0 Hz), 4.56 (2H, d, <i>J</i> = 5.6 Hz), 4.47-4.55 (1H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 470.1[M+H] <sup>+</sup> .                                         |
| 384 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.70 (1H, d, <i>J</i> = 5.2 Hz), 8.32 (1H, d, <i>J</i> = 8.8 Hz), 8.08 (1H, d, <i>J</i> = 2.0 Hz), 7.68 (1H, dd, <i>J</i> = 9.2, 2.4 Hz), 7.54 (2H, d, <i>J</i> = 8.0 Hz), 7.26 (2H, d, <i>J</i> = 8.4 Hz), 7.02 (1H, t, <i>J</i> = 6.0 Hz), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 6.59 (1H, d, <i>J</i> = 5.2 Hz), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.58 (2H, d, <i>J</i> = 6.0 Hz), 4.45-4.55 (1H, m), 4.40 (2H, d, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 97.1%, MS (ESI); <i>m/z</i> 481.2[M+H] <sup>+</sup> . |
| 385 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz): δ 8.75 (2H, s), 6.86-6.97 (3H, m), 6.36 (1H, s), 6.29 (1H, d, <i>J</i> = 8.0 Hz), 6.22 (1H, t, <i>J</i> = 4.8 Hz ), 4.56 (2H, brs), 4.44 (2H, d, <i>J</i> = 4.8 Hz), 3.36 (3H, s), 2.39 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 409.2[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                                                                                                            |
| 386 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (2H, t, <i>J</i> = 8.4 Hz), 7.01 (1H, brs), 6.96 (1H, d, <i>J</i> = 8.4 Hz), 6.30 (1H, s), 6.23 (1H, d, <i>J</i> = 8.4 Hz), 5.73 (1H, d, <i>J</i> = 4.8 Hz), 4.61-4.63 (1H, m), 4.53 (2H, d, <i>J</i> = 5.6 Hz), 3.44-3.52 (7H, m); LCMS: 98.9%, MS (ESI); <i>m/z</i> 469.2[M+H] <sup>+</sup> .                                                                                                                                                                                                                                                                   |

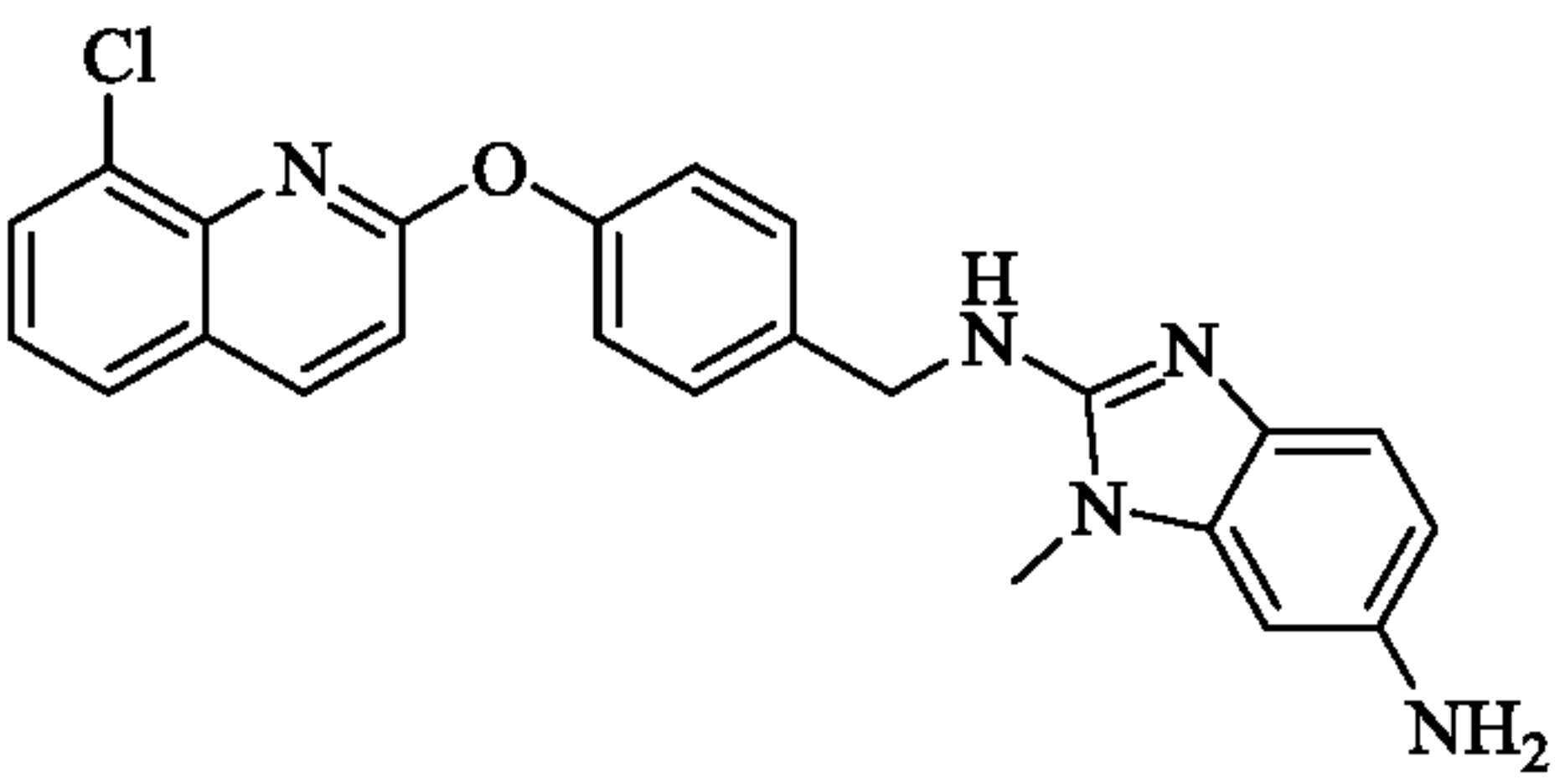
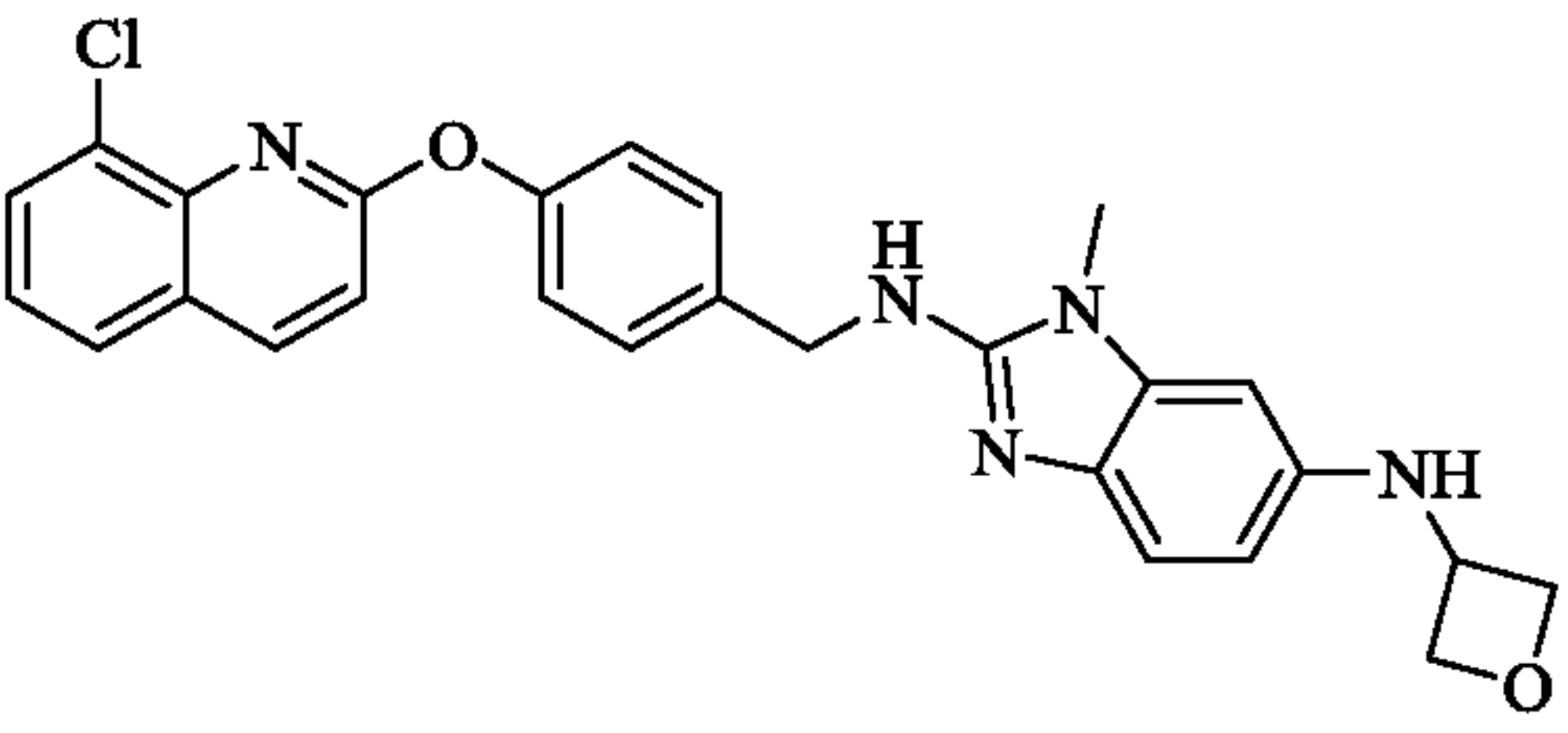
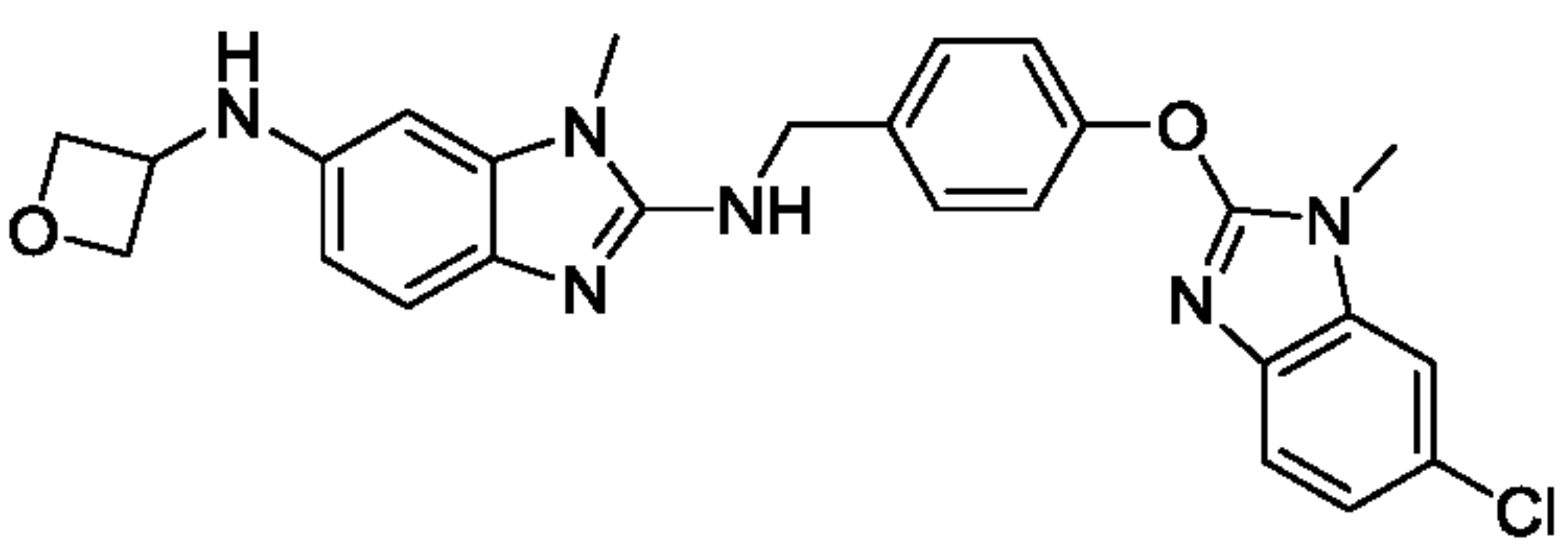
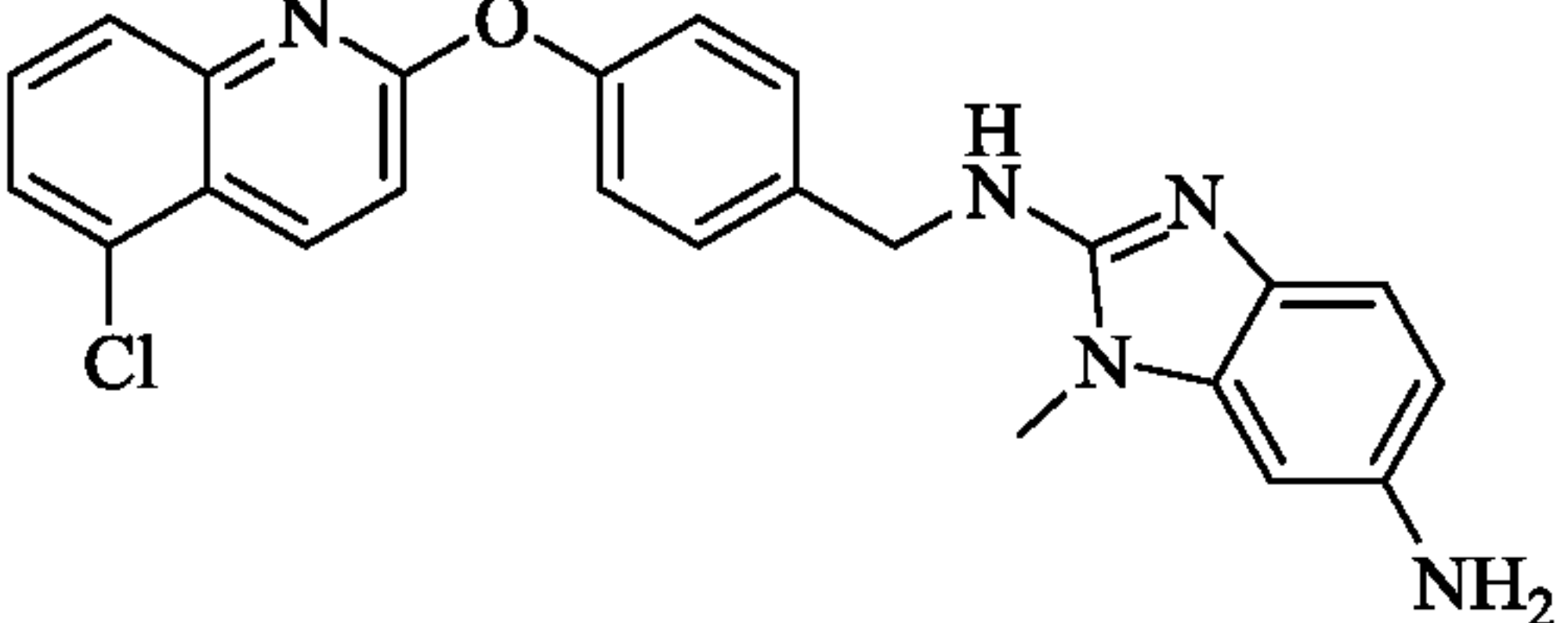
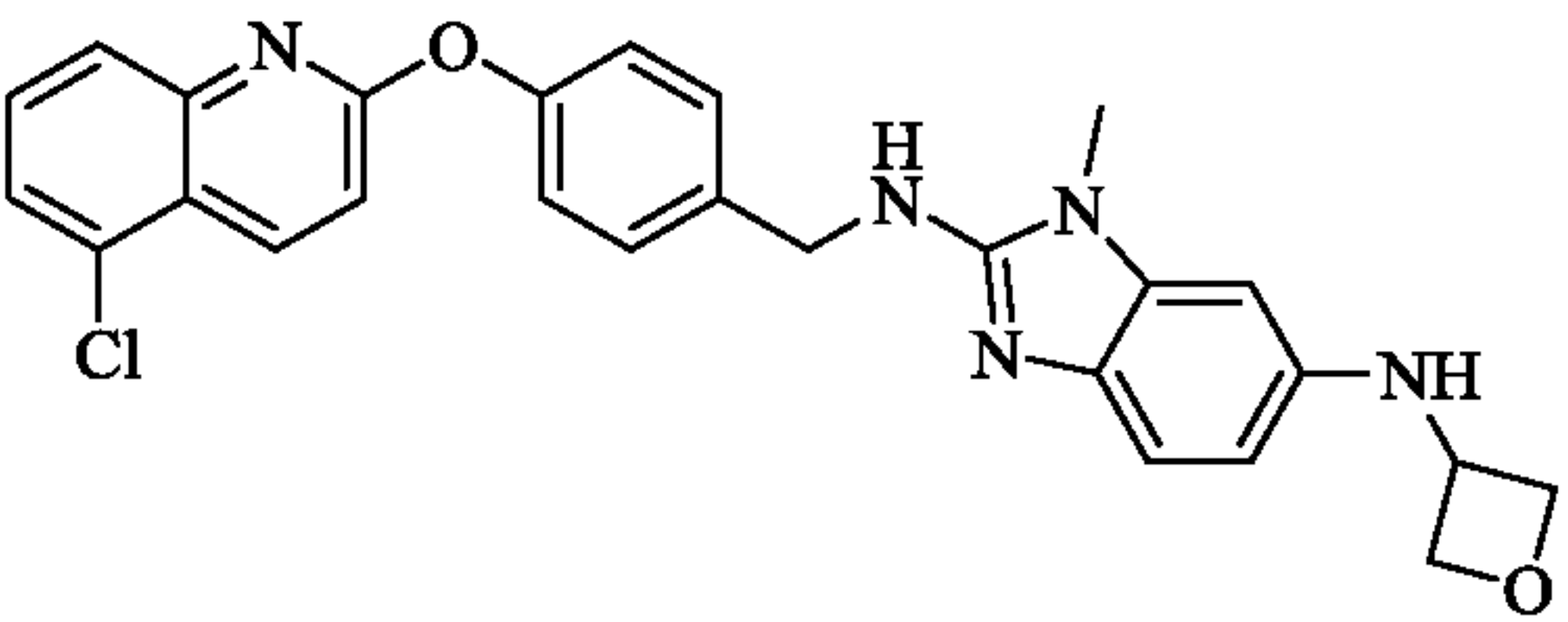
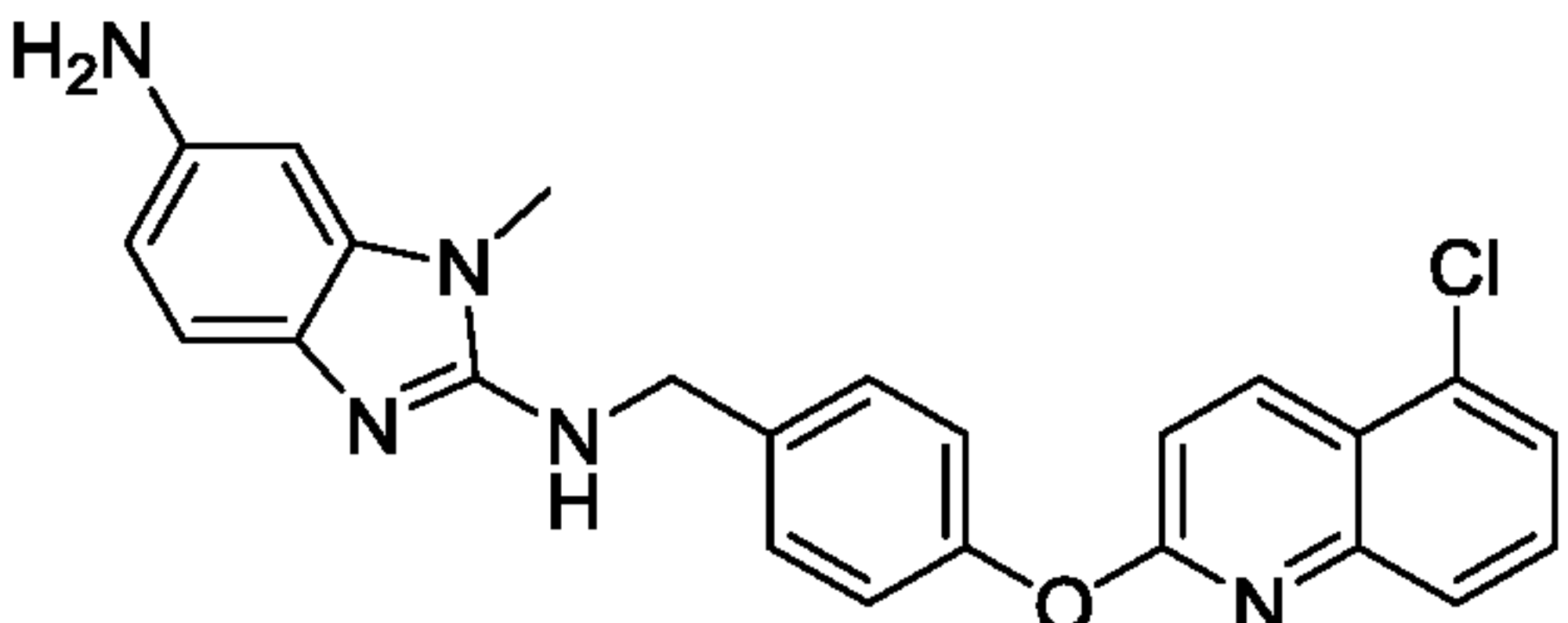
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 387 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.78 (1H, d, <i>J</i> = 5.2 Hz), 8.30 (1H, d, <i>J</i> = 8.4 Hz), 8.02 (1H, d, <i>J</i> = 6.4 Hz), 7.63 (1H, t, <i>J</i> = 8.0 Hz), 7.55 (2H, d, <i>J</i> = 8.8 Hz), 7.27 (2H, d, <i>J</i> = 8.0 Hz), 6.94 (1H, t, <i>J</i> = 6.0 Hz), 6.87 (1H, d, <i>J</i> = 8.0 Hz), 6.69 (1H, d, <i>J</i> = 4.8 Hz), 6.37 (1H, s), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.48-4.65 (4H, m), 3.43 (3H, s); LCMS: 98.7 %, MS (ESI); <i>m/z</i> 430.1[M+ H] <sup>+</sup> .                                                                                                                                                      |
| 388 |   | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.78 (1H, d, <i>J</i> = 5.2 Hz), 8.30-8.35 (1H, m), 8.02 (1H, dd, <i>J</i> = 7.6, 1.6 Hz), 7.62 (1H, t, <i>J</i> = 8.4 Hz), 7.55 (2H, d, <i>J</i> = 8.4 Hz), 7.26 (2H, d, <i>J</i> = 8.4 Hz), 7.01 (1H, t, <i>J</i> = 6.0 Hz), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 6.68 (1H, d, <i>J</i> = 5.2 Hz), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.58 (2H, d, <i>J</i> = 6.0 Hz), 4.45-4.56 (1H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 97.1%, MS (ESI); <i>m/z</i> 486.1[M + H] <sup>+</sup> . |
| 389 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.38 (1H, d, <i>J</i> = 9.2 Hz), 8.07 (1H, d, <i>J</i> = 1.6 Hz), 7.60-7.67 (2H, m), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 8.8 Hz), 7.19 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.50-4.60 (4H, m), 3.43 (3H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 430.1[M+H] <sup>+</sup> .                                                                                                                                                                              |
| 390 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.38 (1H, d, <i>J</i> = 9.2 Hz), 8.07 (1H, s), 7.60-7.66 (2H, m), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.31 (1H, d, <i>J</i> = 9.2 Hz), 7.19 (2H, d, <i>J</i> = 8.4 Hz), 6.93-7.00 (2H, m), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.60 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 486.1[M+H] <sup>+</sup> .                                                                                                                                           |
| 391 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.77 (2H, s), 7.59 (1H, d, <i>J</i> = 1.6 Hz), 7.43 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 7.35 (1H, d, <i>J</i> = 8.4 Hz), 6.99 (1H, t, <i>J</i> = 6.0 Hz), 6.86 (1H, d, <i>J</i> = 8.4 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.56 (2H, brs), 4.52 (2H, d, <i>J</i> = 6.0 Hz), 3.42 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 415.0 [M+H] <sup>+</sup> .                                                                                                                                                                                                              |
| 392 |  | pale yellow amorphous; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.77 (2H, s), 7.58 (1H, d, <i>J</i> = 2.0 Hz), 7.43 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 7.35 (1H, d, <i>J</i> = 2.4 Hz), 7.05 (1H, t, <i>J</i> = 6.0 Hz), 6.94 (1H, d, <i>J</i> = 8.4 Hz), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.86 (1H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.56 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 471.0[M+H] <sup>+</sup> .                                                                                                                                          |
| 393 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.61 (1H, s), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.37 (1H, s), 7.16 (2H, d, <i>J</i> = 8.8 Hz), 6.91 (1H, t, <i>J</i> = 5.6 Hz), 6.85 (1H, d, <i>J</i> = 8.0 Hz), 6.35 (1H, d, <i>J</i> = 2.0 Hz), 6.25 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.46-4.57 (4H, m), 3.40 (3H, s); LCMS: 100 %, MS (ESI); <i>m/z</i> 381.0[M+ H] <sup>+</sup> .                                                                                                                                                                                                                                                                       |

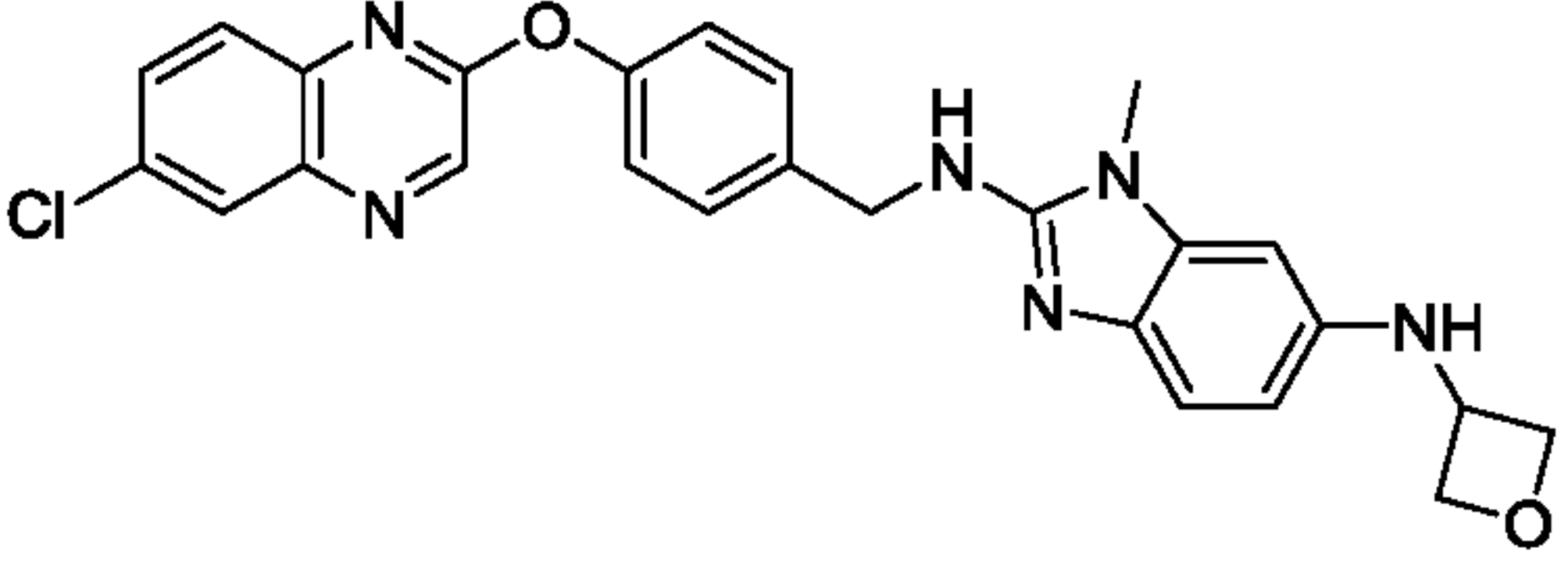
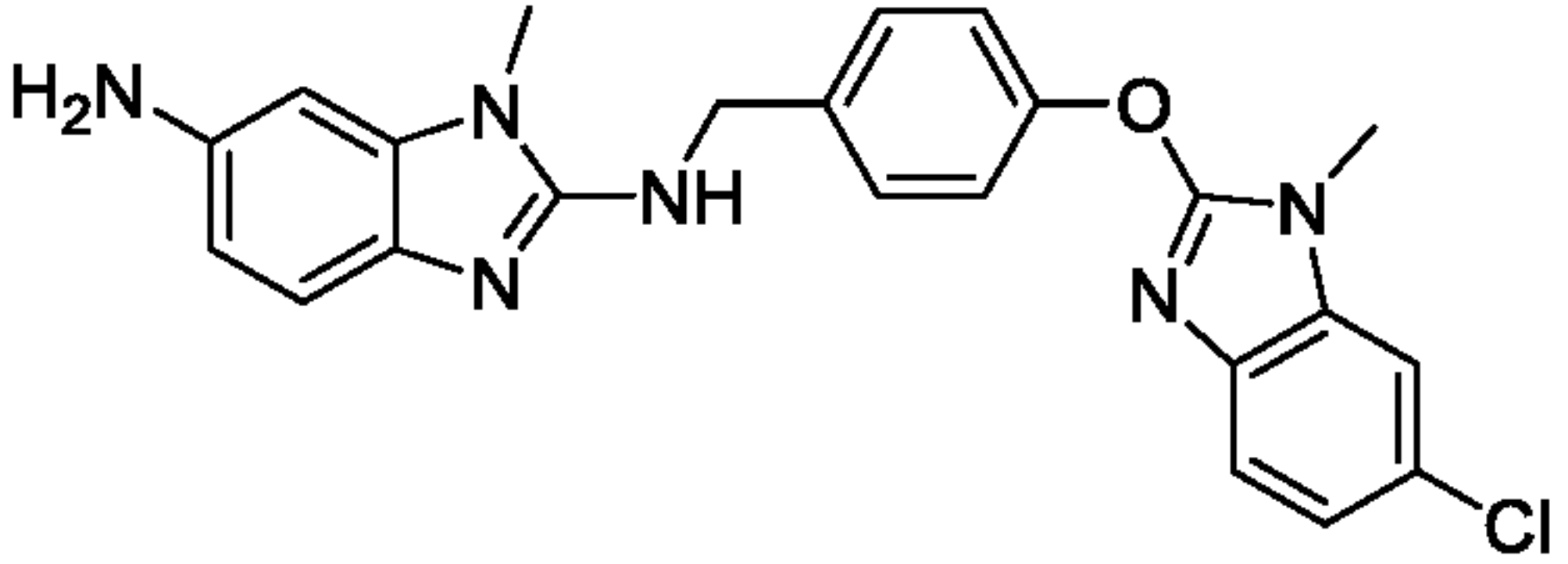
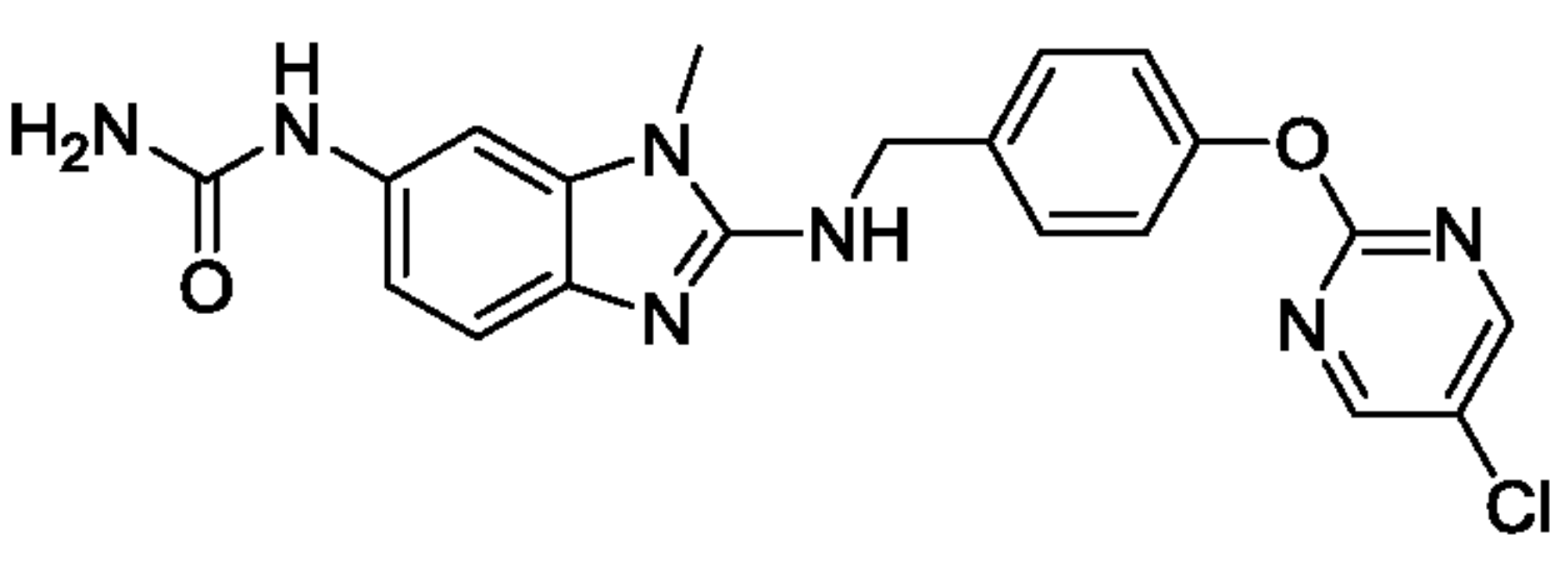
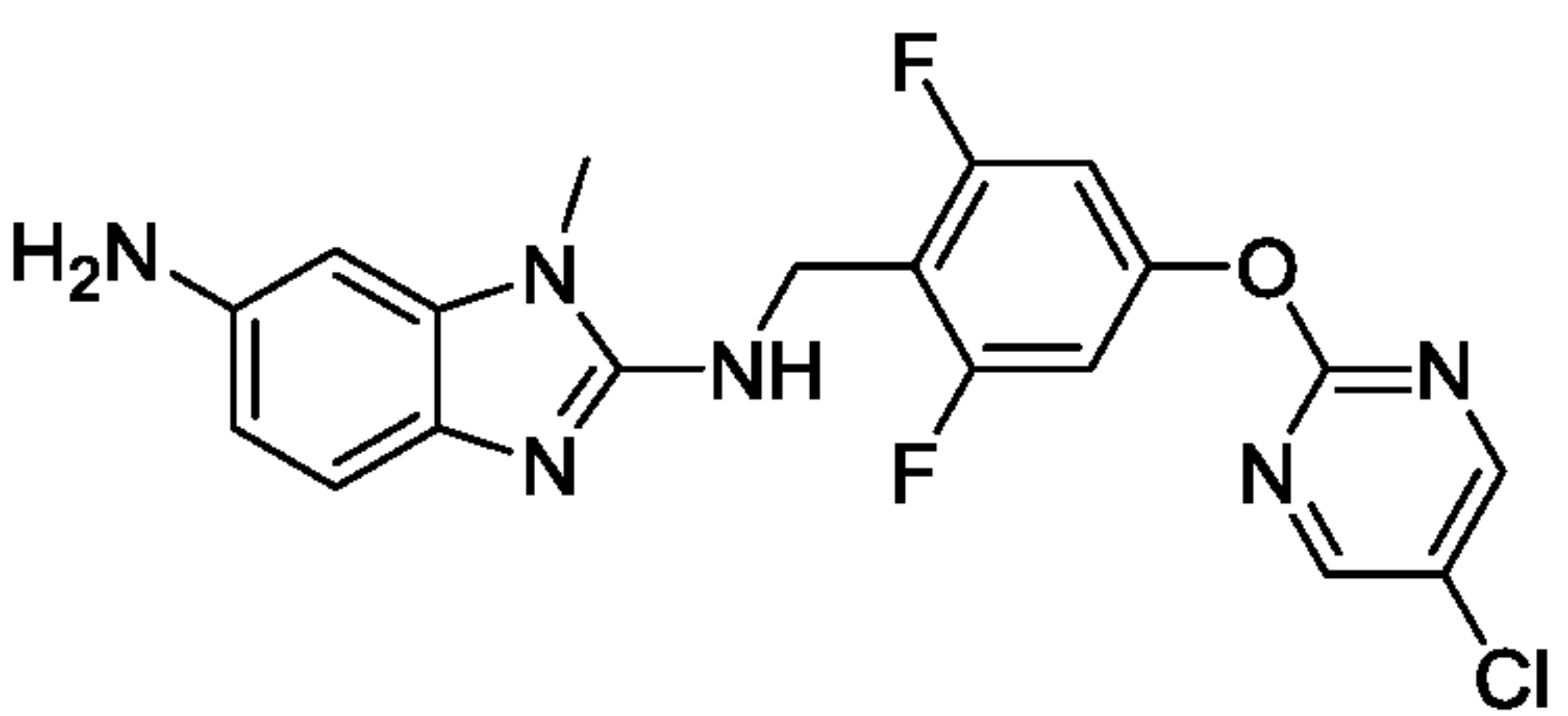
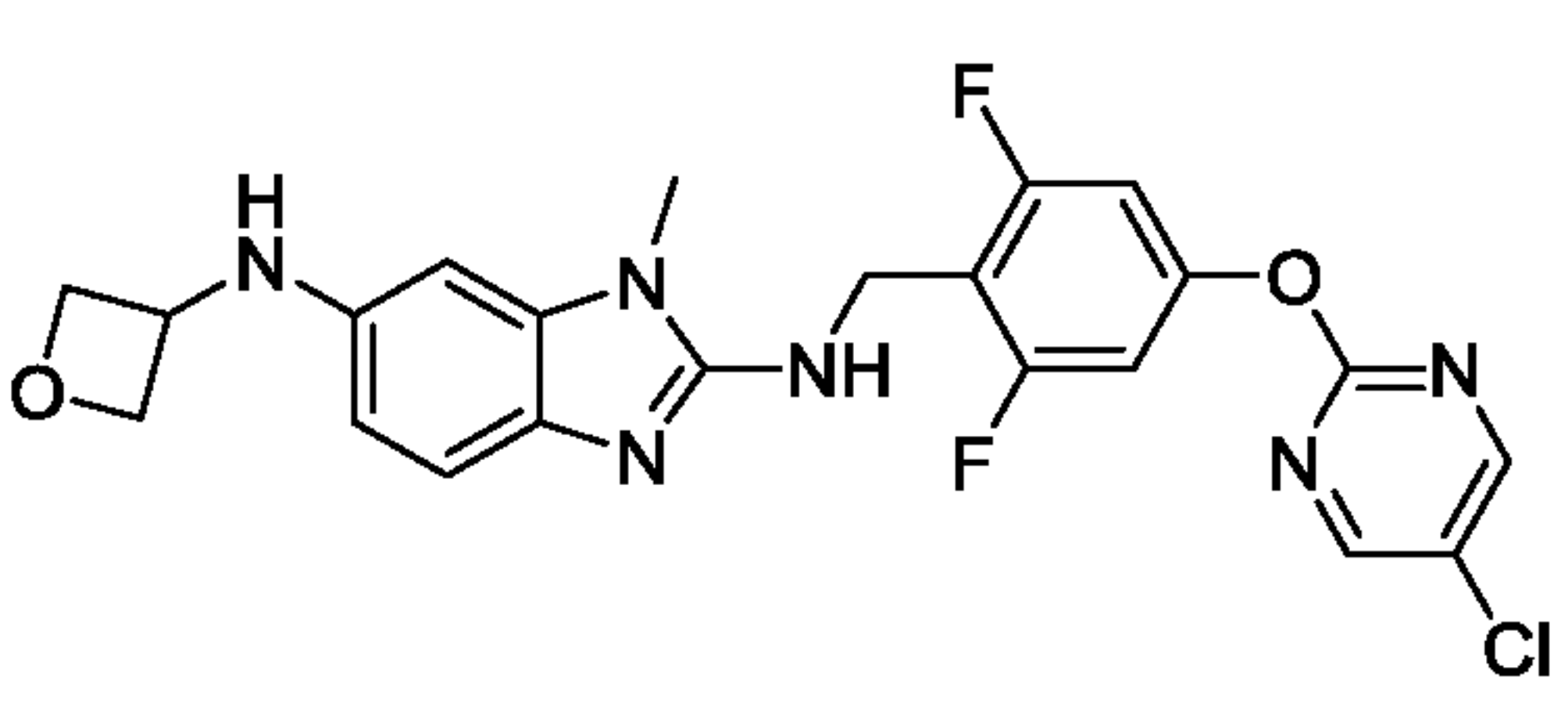
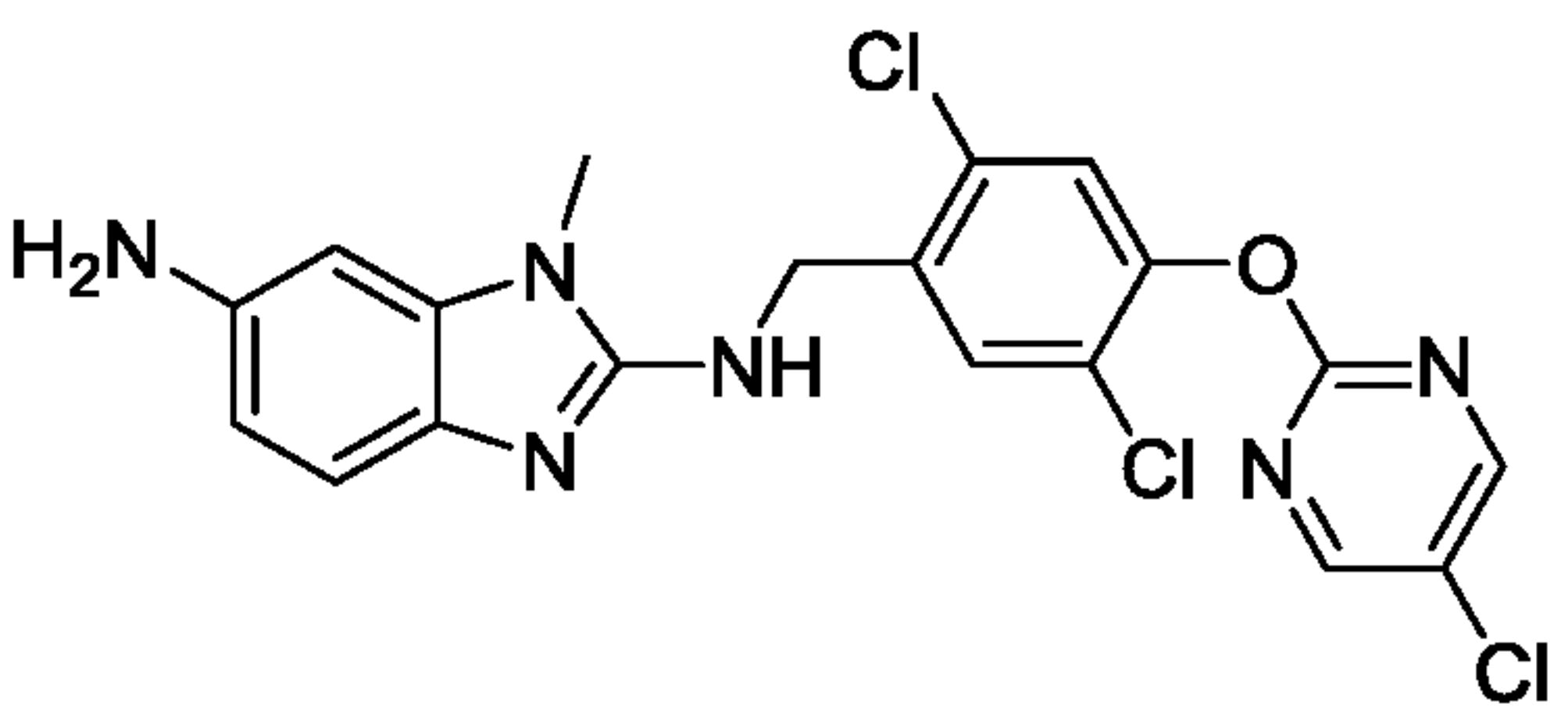
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 394 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.63 (1H, s), 7.47 (2H, d, <i>J</i> = 8.8 Hz), 7.38 (1H, s), 7.18 (2H, d, <i>J</i> = 8.4 Hz), 6.98 (1H, t, <i>J</i> = 6.0 Hz), 6.94 (1H, d, <i>J</i> = 8.0 Hz), 6.26 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.45-4.61 (3H, m), 4.40 (2H, t, <i>J</i> = 5.6 Hz), 3.45 (3H, s); LCMS: 99.3%, MS (ESI); <i>m/z</i> 437.0[M+ H] <sup>+</sup> .                                                                                                      |
| 395 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.44 (1H, d, <i>J</i> = 1.6 Hz), 7.26 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 7.02-7.05 (2H, m), 6.87 (1H, d, <i>J</i> = 8.0 Hz), 6.38 (1H, d, <i>J</i> = 1.6 Hz), 6.28 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 4.51 (2H, d, <i>J</i> = 6.0 Hz), 3.43 (3H, s), 2.89-2.97 (1H, m), 1.11 (6H, d, <i>J</i> = 6.8 Hz); LCMS: 99.2%, MS (ESI); <i>m/z</i> 423.1 [M+H] <sup>+</sup> .                                                                                                                                                        |
| 396 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.72 (2H, s), 7.43 (1H, d, <i>J</i> = 1.6 Hz), 7.25 (1H, dd, <i>J</i> = 8.0, 1.6 Hz), 7.02 (1H, d, <i>J</i> = 8.4 Hz), 6.92-6.95 (2H, m), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.21 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (2H, d, <i>J</i> = 6.8 Hz), 4.84 (2H, t, <i>J</i> = 6.0 Hz), 4.49-4.54 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s), 2.89-2.96 (1H, m), 1.10 (6H, d, <i>J</i> = 6.8 Hz); LCMS: 99.3%, MS (ESI); <i>m/z</i> 479.2[M+H] <sup>+</sup> .                                                                    |
| 397 |  | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.28 (1H, s), 7.48 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (2H, d, <i>J</i> = 8.4 Hz), 7.15 (1H, d, <i>J</i> = 8.4 Hz), 6.56 (1H, d, <i>J</i> = 8.0 Hz), 6.48 (1H, s), 4.71 (2H, d, <i>J</i> = 3.6 Hz), 4.24 (1H, brs), 3.45 (3H, s), 2.41-2.52 (1H, m), 1.12-1.30 (4H, m); LCMS: 99.8%, MS (ESI); <i>m/z</i> 421.1[M+H] <sup>+</sup> .                                                                                                                                                                                                                         |
| 398 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.51 (1H, s), 7.42 (2H, d, <i>J</i> = 8.4 Hz), 7.12 (2H, d, <i>J</i> = 8.4 Hz), 6.91-7.00 (2H, m), 6.25 (1H, d, <i>J</i> = 1.6 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 5.85 (1H, d, <i>J</i> = 7.2 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.59 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.45 (3H, s), 2.38-2.46 (1H, m), 1.01-2.01 (2H, m), 0.80-1.05 (2H, m); LCMS: 99.7%, MS (ESI); <i>m/z</i> 477.1[M+H] <sup>+</sup> .                                                                                                            |
| 399 |  | off-white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.45 (1H, d, <i>J</i> = 8.0 Hz), 8.14 (1H, d, <i>J</i> = 8.4 Hz), 8.07 (1H, s), 8.03 (1H, t, <i>J</i> = 7.6 Hz), 7.86 (1H, t, <i>J</i> = 7.8 Hz), 7.48 (2H, d, <i>J</i> = 8.0 Hz), 7.22 (2H, d, <i>J</i> = 8.4 Hz), 7.01 (1H, brs), 6.88 (1H, d, <i>J</i> = 8.4 Hz), 6.38 (1H, d, <i>J</i> = 1.2 Hz), 6.28 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.55 (2H, d, <i>J</i> = 5.6 Hz), 3.43 (3H, s); LCMS: 99.8%, MS (ESI); <i>m/z</i> 430.1[M+H] <sup>+</sup> .                                                                                    |
| 400 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.45 (1H, d, <i>J</i> = 8.4 Hz), 8.14 (1H, d, <i>J</i> = 8.4 Hz), 8.07 (1H, s), 7.99-8.06 (1H, m), 7.86 (1H, t, <i>J</i> = 7.4 Hz), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 7.21 (2H, d, <i>J</i> = 8.4 Hz), 6.99 (1H, t, <i>J</i> = 6.2 Hz), 6.95 (1H, d, <i>J</i> = 8.4 Hz), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 6.8 Hz), 4.85 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.60 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 486.1[M+H] <sup>+</sup> . |
| 401 |  | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.11 (1H, d, <i>J</i> = 2.4 Hz), 7.65 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 8.4 Hz), 7.11 (2H, d, <i>J</i> = 8.4 Hz), 6.91 (1H, d, <i>J</i> = 8.4 Hz), 6.42 (1H, dd, <i>J</i> = 8.4, 1.6 Hz), 6.28 (1H, d, <i>J</i> = 2.0 Hz), 4.67 (2H, d, <i>J</i> = 4.0 Hz), 4.35-4.47 (1H, m), 4.25 (1H, brs), 3.97 (2H, t, <i>J</i> = 7.2 Hz), 3.54 (2H, t, <i>J</i> = 7.0 Hz), 3.43 (3H, s); LCMS: 98.6%, MS (ESI); <i>m/z</i>                                                                                |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |  | 435.1[M+H] +.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 402 |  | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 7.52 (2H, d, <i>J</i> = 8.4 Hz), 7.45 (1H, d, <i>J</i> = 2.0 Hz), 7.33-7.40 (3H, m), 7.29 (1H, s), 7.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.55 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.47 (1H, d, <i>J</i> = 2.0 Hz), 4.61-4.82 (3H, m), 3.46 (3H, s); LCMS: 98.4%, MS (ESI); <i>m/z</i> 420.1[M+H] +.                                                                                                                                                                                                                 |
| 403 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.66 (1H, d, <i>J</i> = 8.4 Hz), 7.62 (1H, d, <i>J</i> = 2.0 Hz), 7.51 (2H, d, <i>J</i> = 8.8 Hz), 7.44 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, dd, <i>J</i> = 8.8, 2.4 Hz), 7.00 (1H, t, <i>J</i> = 6.0 Hz), 6.94 (1H, d, <i>J</i> = 8.4 Hz), 6.26 (1H, d, <i>J</i> = 2.0 Hz), 6.22 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.84 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.47-4.60 (3H, m), 4.40 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 99.2%, MS (ESI); <i>m/z</i> 476.2[M+H] +. |
| 404 |  | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.4 Hz), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.43 (2H, d, <i>J</i> = 8.8 Hz), 7.03-7.11 (3H, m), 6.91-7.00 (2H, m), 6.29 (1H, d, <i>J</i> = 2.0 Hz), 6.24 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 5.75-5.84 (2H, m), 5.73 (1H, d, <i>J</i> = 4.8 Hz), 4.52 (2H, d, <i>J</i> = 5.6 Hz), 4.10-4.30 (3H, m), 3.56 (2H, d, <i>J</i> = 4.0 Hz), 3.45 (3H, s); LCMS: 99.7%, MS (ESI); <i>m/z</i> 478.2[M+H] +.                                                                            |
| 405 |  | yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.52 (1H, s), 8.26 (1H, d, <i>J</i> = 2.4 Hz), 7.91 (1H, dd, <i>J</i> = 9.2, 2.4 Hz), 7.75 (1H, d, <i>J</i> = 9.2 Hz), 7.47 (2H, d, <i>J</i> = 8.4 Hz), 7.22 (2H, d, <i>J</i> = 8.4 Hz), 6.92 (1H, t, <i>J</i> = 6.0 Hz), 6.88 (1H, d, <i>J</i> = 8.0 Hz), 6.37 (1H, d, <i>J</i> = 2.0 Hz), 6.27 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 4.48-4.64 (4H, m), 3.43 (3H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 431.1[M+ H] +.                                                                                    |
| 406 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 9.51 (1H, s), 8.26 (1H, d, <i>J</i> = 2.4 Hz), 7.91 (1H, dd, <i>J</i> = 9.2, 2.4 Hz), 7.74 (1H, d, <i>J</i> = 9.2 Hz), 7.46 (2H, d, <i>J</i> = 8.4 Hz), 7.21 (2H, d, <i>J</i> = 8.4 Hz), 6.93-7.04 (2H, m), 6.26 (1H, s), 6.22 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 5.83 (1H, d, <i>J</i> = 7.2 Hz), 4.84 (2H, t, <i>J</i> = 6.4 Hz), 4.46-4.60 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.46 (3H, s); LCMS: 97.3%, MS (ESI); <i>m/z</i> 487.2[M + H] +.                                             |
| 407 |  | off-white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.50 (2H, s), 7.51 (2H, d, <i>J</i> = 8.4 Hz), 7.32 (1H, d, <i>J</i> = 8.4 Hz), 7.18 (2H, d, <i>J</i> = 8.4 Hz), 6.43(1H, dd, <i>J</i> = 8.4, 1.6 Hz), 6.28 (1H, s), 4.71 (2H, d, <i>J</i> = 3.2 Hz), 4.34-4.46 (1H, m), 4.21 (1H, brs), 3.97 (2H, t, <i>J</i> = 7.2 Hz), 3.54 (2H, t, <i>J</i> = 7.2 Hz), 3.44 (3H, s); LCMS: 98.5%, MS (ESI); <i>m/z</i> 436.1[M+H] +.                                                                                                                                       |

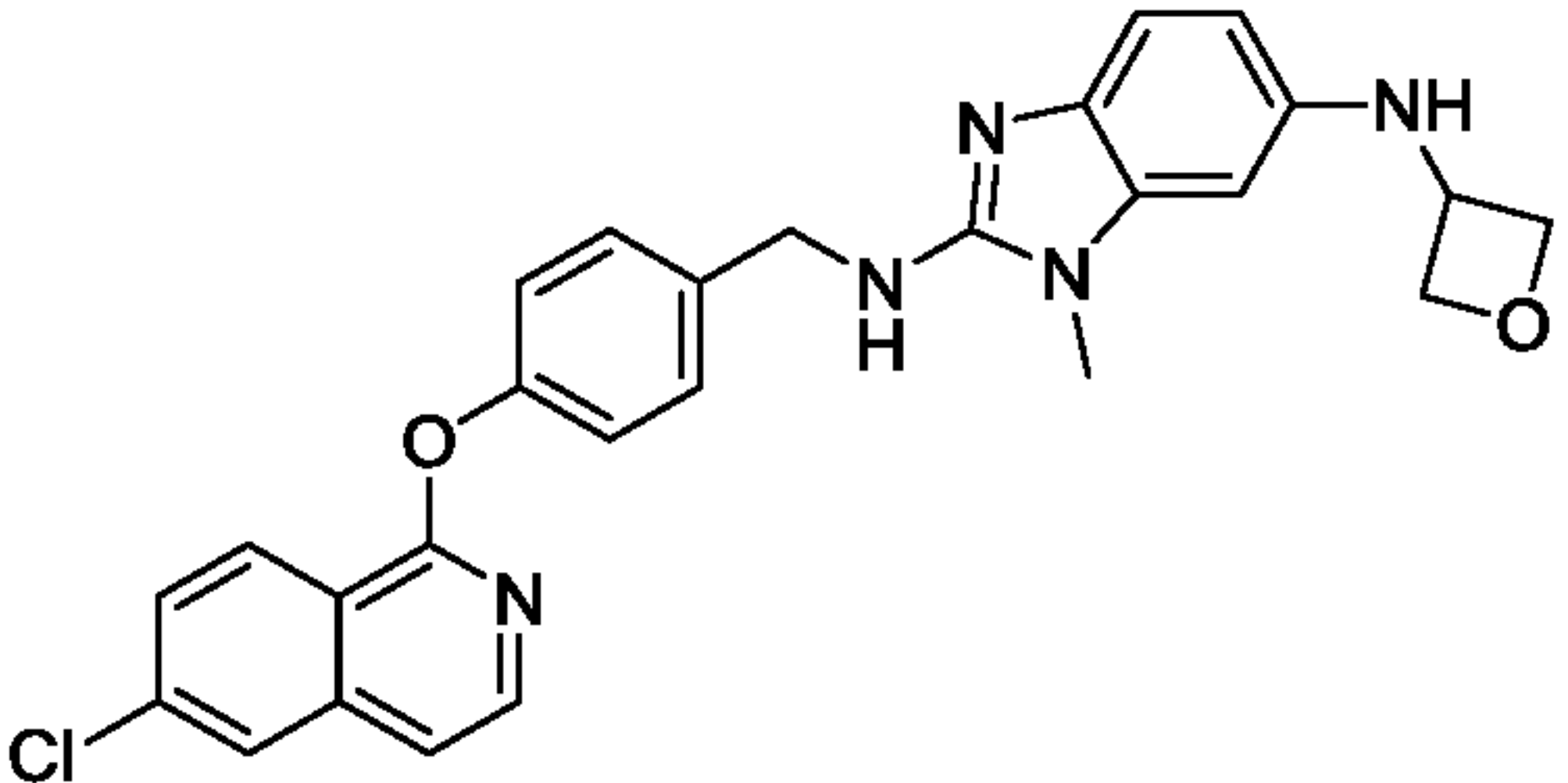
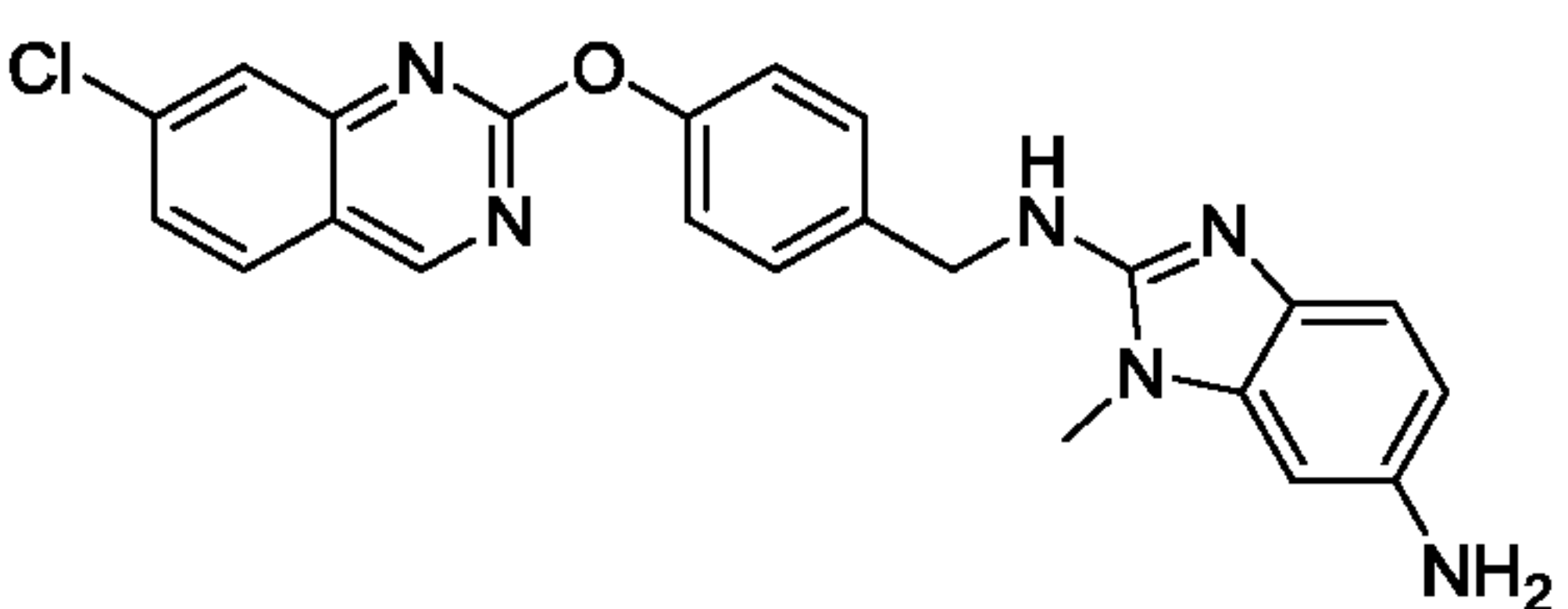
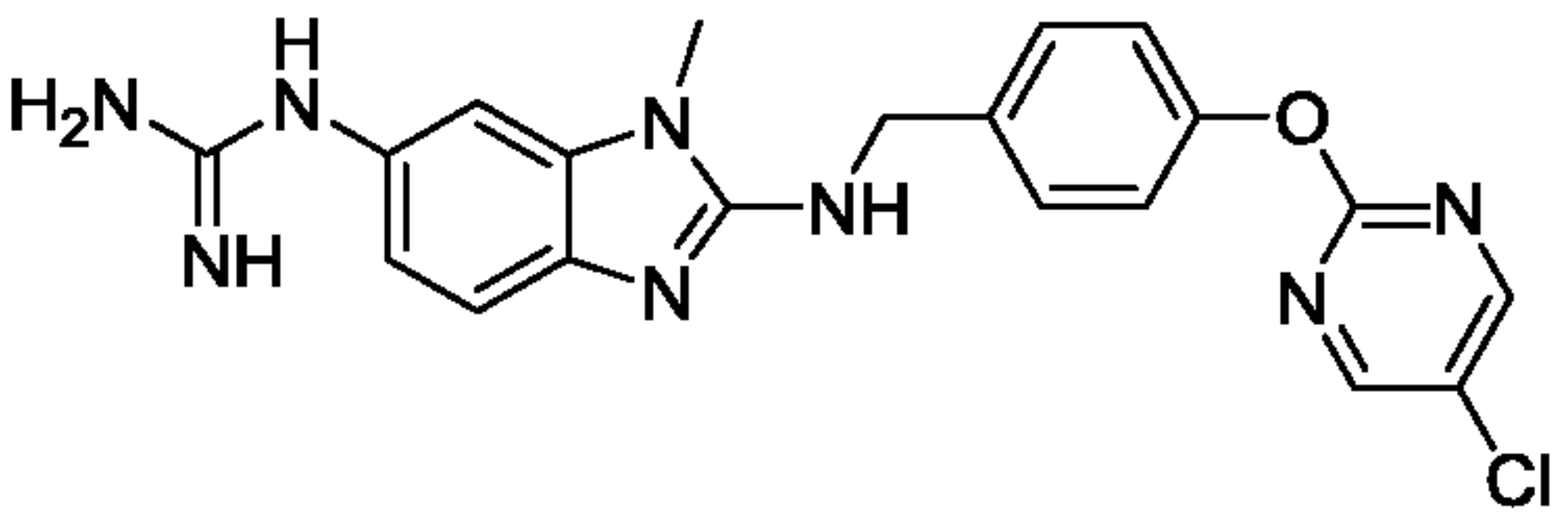
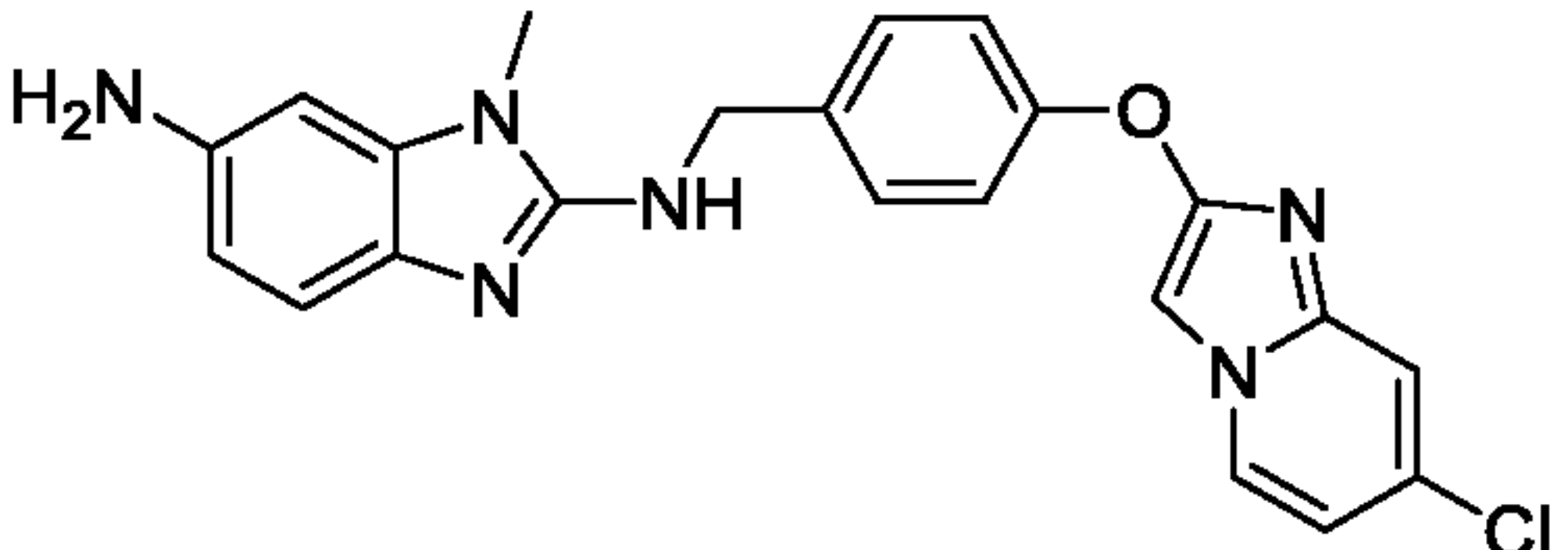
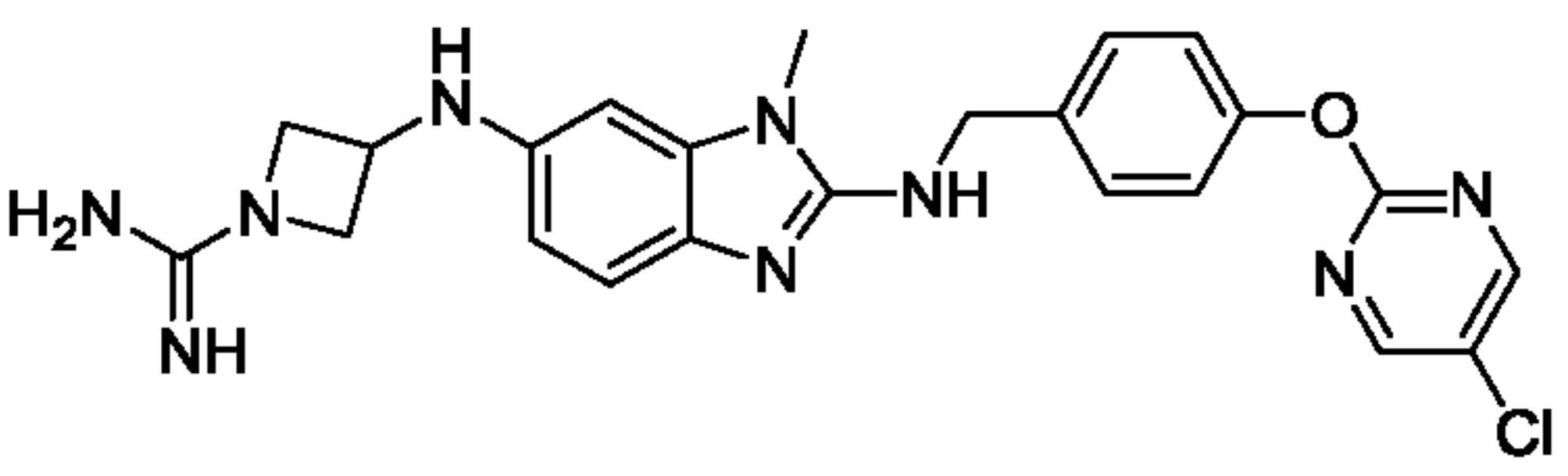
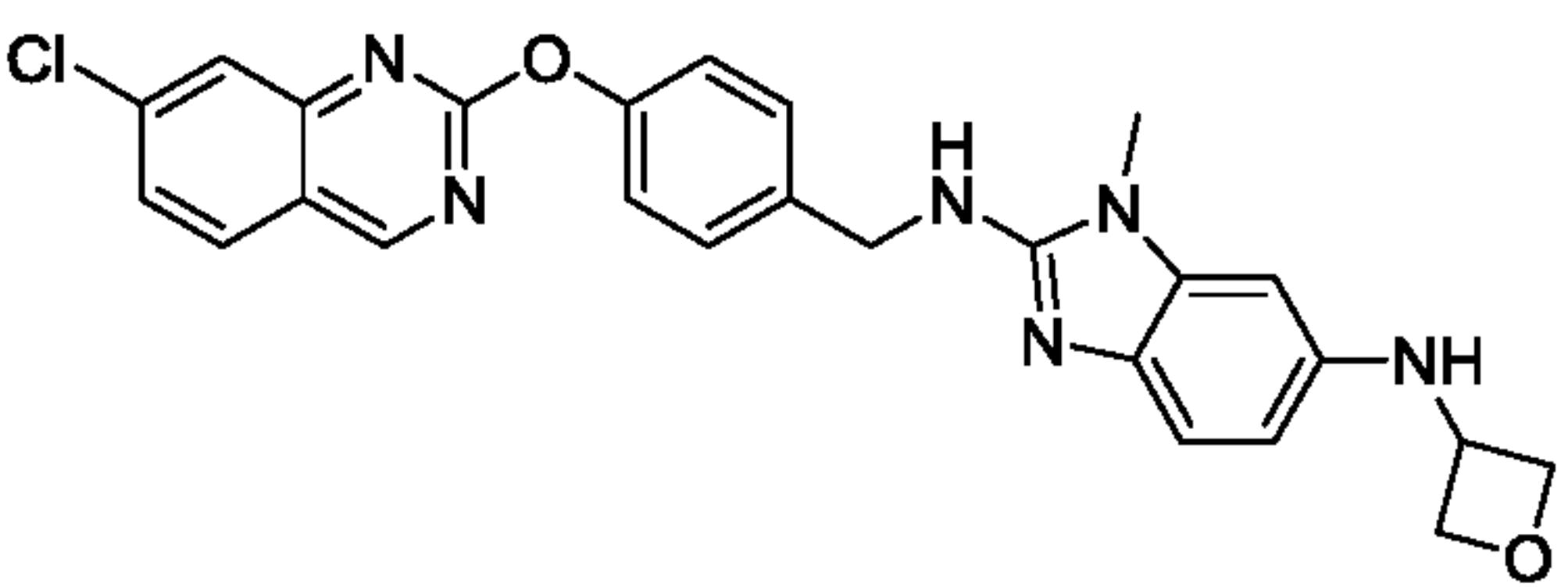
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 408 |    | white powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.50 (2H, s), 7.51 (1H, d, <i>J</i> = 8.4 Hz), 7.35 (1H, d, <i>J</i> = 8.4 Hz), 7.18 (2H, d, <i>J</i> = 8.8 Hz), 6.41 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.28 (1H, d, <i>J</i> = 2.0 Hz), 4.72 (2H, d, <i>J</i> = 5.6 Hz), 4.29-4.43 (5H, m), 4.26 (1H, t, <i>J</i> = 5.0 Hz), 3.93 (1H, brs), 3.76-3.86 (2H, m), 3.45 (3H, s); LCMS: 97.7%, MS (ESI); <i>m/z</i> 479.2[M+H] <sup>+</sup> .                                    |
| 409 |    | white powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 7.43 (2H, d, <i>J</i> = 8.4 Hz), 7.27 (2H, d, <i>J</i> = 8.8 Hz), 7.03 (1H, d, <i>J</i> = 8.4 Hz), 6.90-6.98 (2H, m), 6.52 (1H, s), 6.42 (1H, d, <i>J</i> = 8.4 Hz), 6.25 (1H, s), 6.21 (1H, d, <i>J</i> = 8.4 Hz), 5.82 (1H, d, <i>J</i> = 6.8 Hz), 4.77-4.91 (4H, m), 4.47-4.57 (3H, m), 4.39 (2H, t, <i>J</i> = 6.0 Hz), 3.54 (3H, s), 3.44 (3H, s); LCMS: 98.5%, MS (ESI); <i>m/z</i> 470.3[M+H] <sup>+</sup> . |
| 410 |  | yellow powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.50 (2H, s), 7.53 (2H, d, <i>J</i> = 8.4 Hz), 7.31 (1H, d, <i>J</i> = 8.4 Hz), 7.20 (2H, d, <i>J</i> = 8.4 Hz), 6.55 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 6.47 (1H, d, <i>J</i> = 1.6 Hz), 4.72 (2H, d, <i>J</i> = 4.8 Hz), 4.18 (1H, brs), 3.43 (3H, s); LCMS: 96.9%, MS (ESI); <i>m/z</i> 431.1[M+H] <sup>+</sup> .                                                                                                          |
| 411 |  | pale yellow powder; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.73 (2H, s), 7.15 (2H, s), 6.81-6.90 (2H, m), 6.37 (1H, d, <i>J</i> = 1.6 Hz), 6.27 (1H, dd, <i>J</i> = 8.0, 2.0 Hz), 4.55 (2H, brs), 4.45 (2H, d, <i>J</i> = 6.0 Hz), 3.42 (3H, s), 2.02 (6H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 409.1[M+ H] <sup>+</sup> .                                                                                                                                               |
| 412 |  | yellow powder; <sup>1</sup> H NMR (CDCl <sub>3</sub> , 400 MHz); δ 8.50 (2H, s), 7.52 (2H, d, <i>J</i> = 8.8 Hz), 7.34 (1H, d, <i>J</i> = 8.4 Hz), 7.19 (2H, d, <i>J</i> = 8.4 Hz), 6.40 (1H, dd, <i>J</i> = 8.4, 2.0 Hz), 6.24 (1H, d, <i>J</i> = 2.0 Hz), 5.03 (2H, t, <i>J</i> = 6.4 Hz), 4.73 (2H, d, <i>J</i> = 4.4 Hz), 4.63-4.70 (1H, m), 4.56 (2H, t, <i>J</i> = 6.0 Hz), 4.36 (1H, brs), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 487.3[M+H] <sup>+</sup> .                      |
| 413 |  | <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.17 (1H, d, <i>J</i> = 2.8 Hz), 8.02 (1H, s), 7.93 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 7.45-7.42 (3H, m), 7.23 (1H, d, <i>J</i> = 2.4 Hz), 7.09-7.06 (3H, m), 7.05-6.98 (m, 2H), 6.85 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 5.73 (1H, d, <i>J</i> = 2.4 Hz), 4.53 (2H, d, <i>J</i> = 6.0 Hz), 3.71 (3H, s), 3.46 (3H, s); LCMS: 100%, MS (ESI); <i>m/z</i> 460.3[M+H] <sup>+</sup> .                                                   |
| 414 |  | pale yellow solid; <sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , 400 MHz); δ 8.74 (2H, s), 8.03 (1H, s), 7.48-7.45 (m, 3H), 7.23 (1H, d, <i>J</i> = 1.6 Hz), 7.17 (2H, d, <i>J</i> = 8.4 Hz), 7.04-6.99 (2H, m), 6.86 (1H, dd, <i>J</i> = 8.8, 2.8 Hz), 5.74 (1H, d, <i>J</i> = 1.6 Hz), 4.56 (2H, d, <i>J</i> = 5.6 Hz), 3.73 (3H, s), 3.48 (3H, s); LCMS: 99.4%, MS (ESI); <i>m/z</i> 461.2[M+H] <sup>+</sup> .                                                                           |

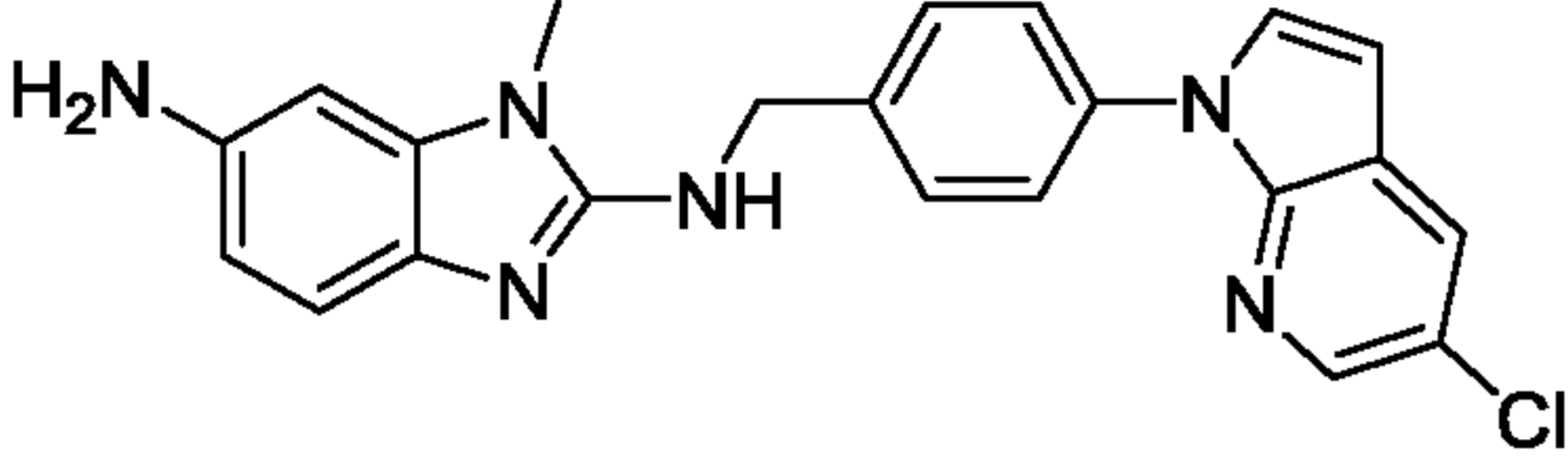
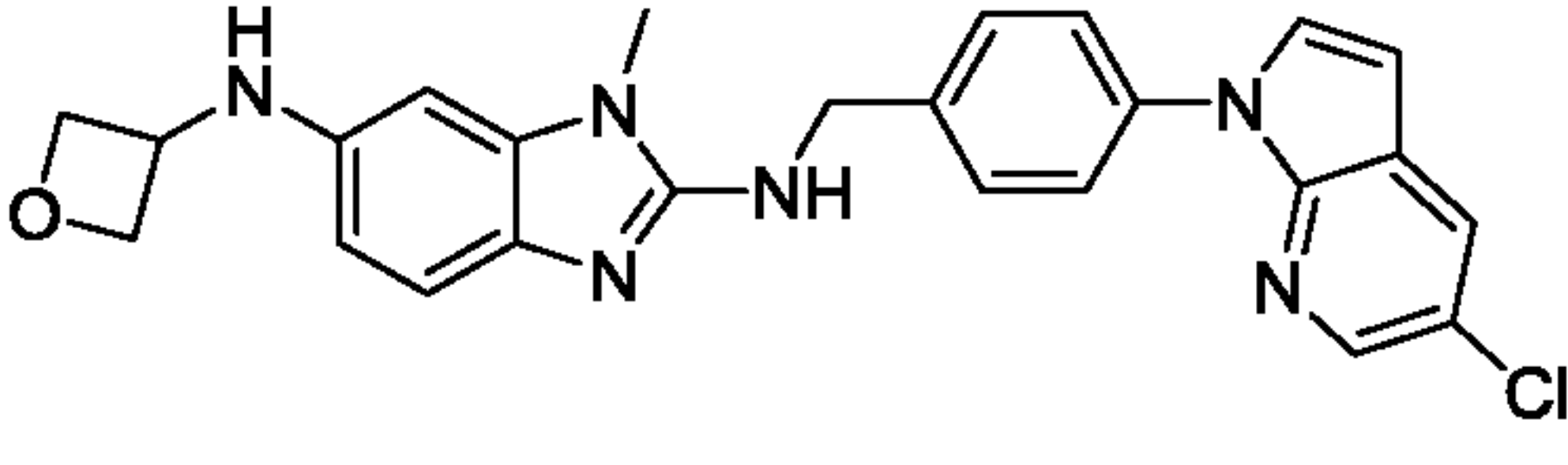
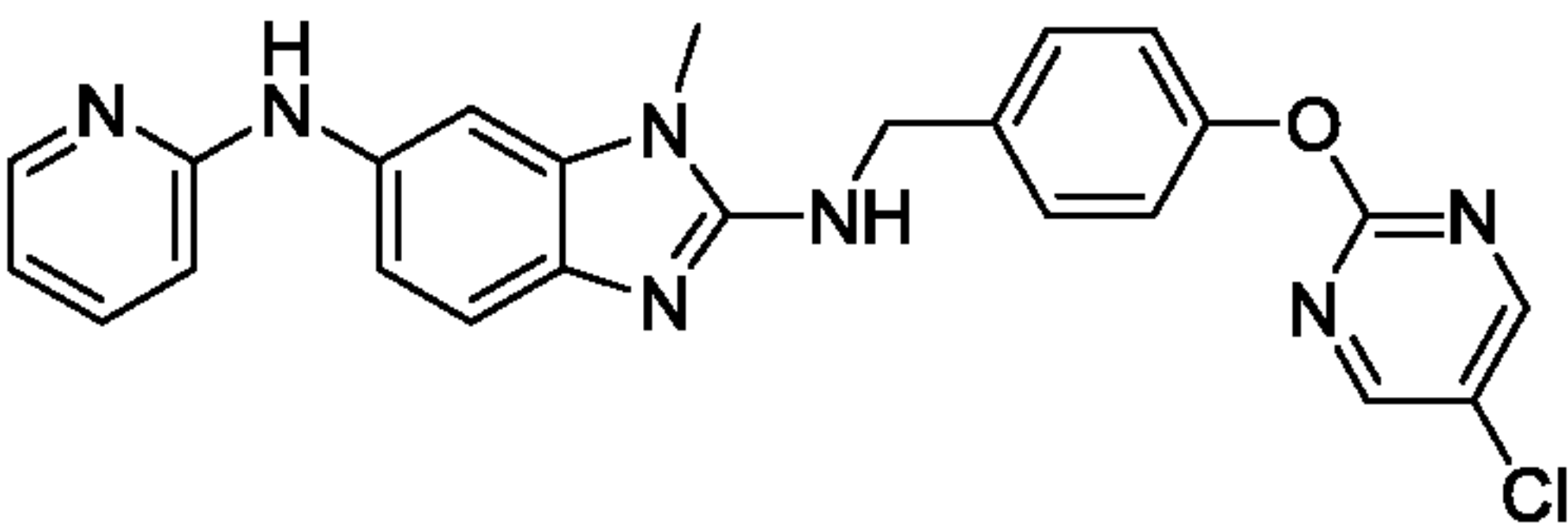
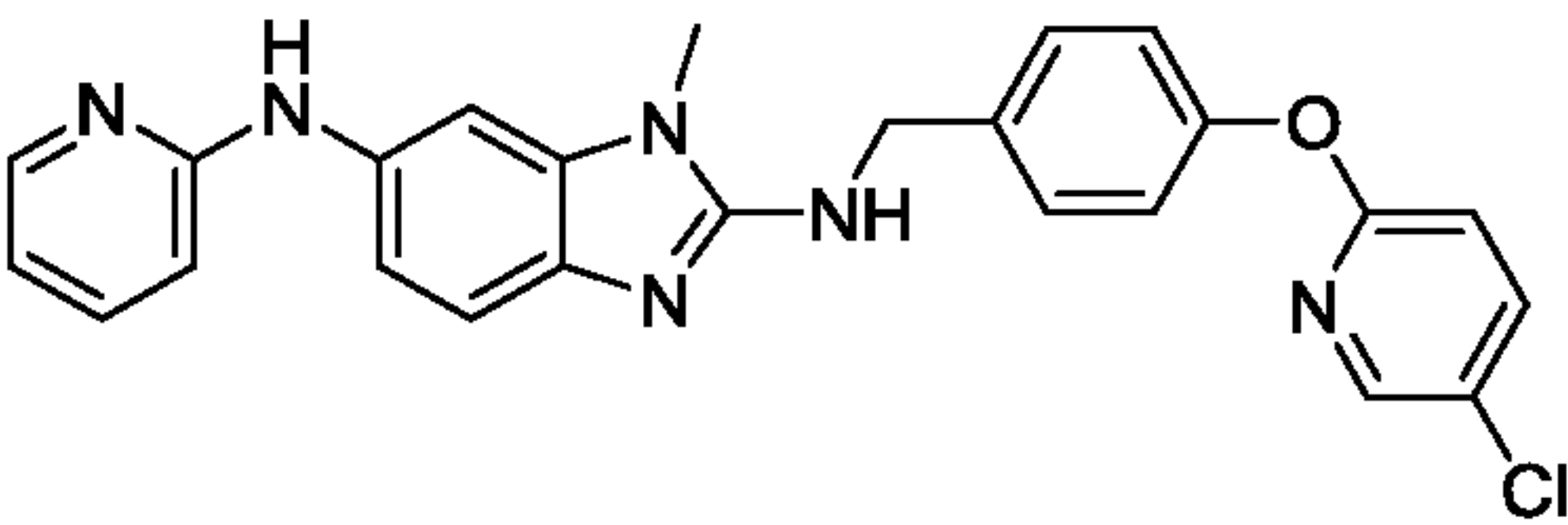
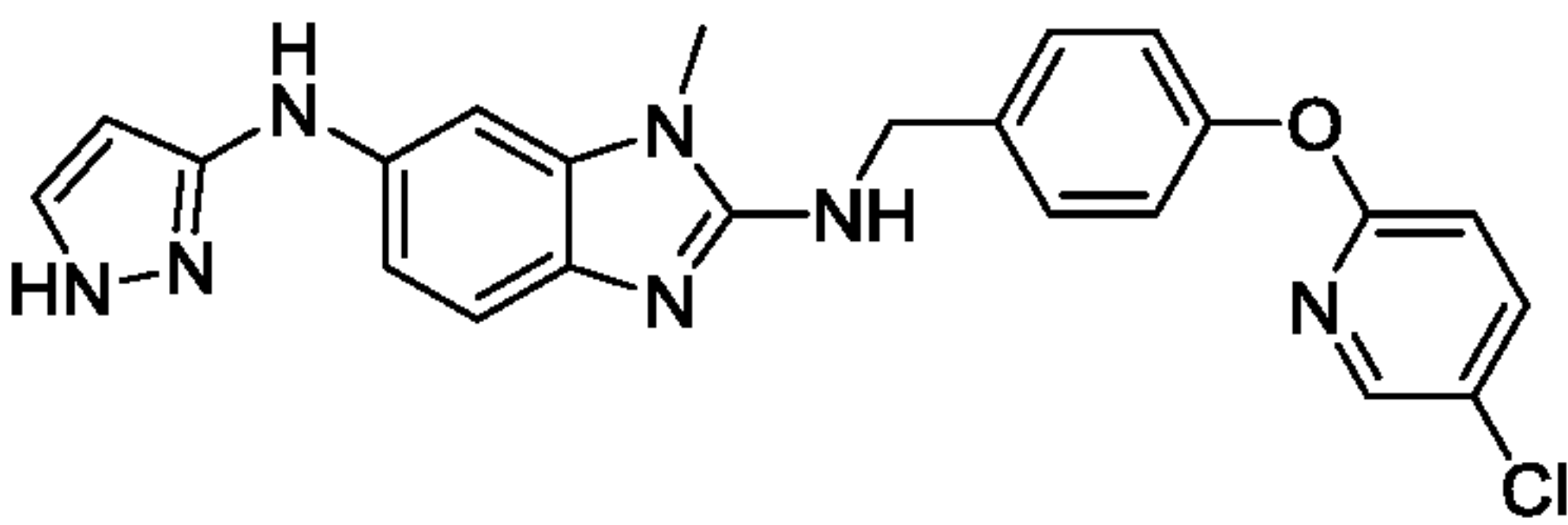
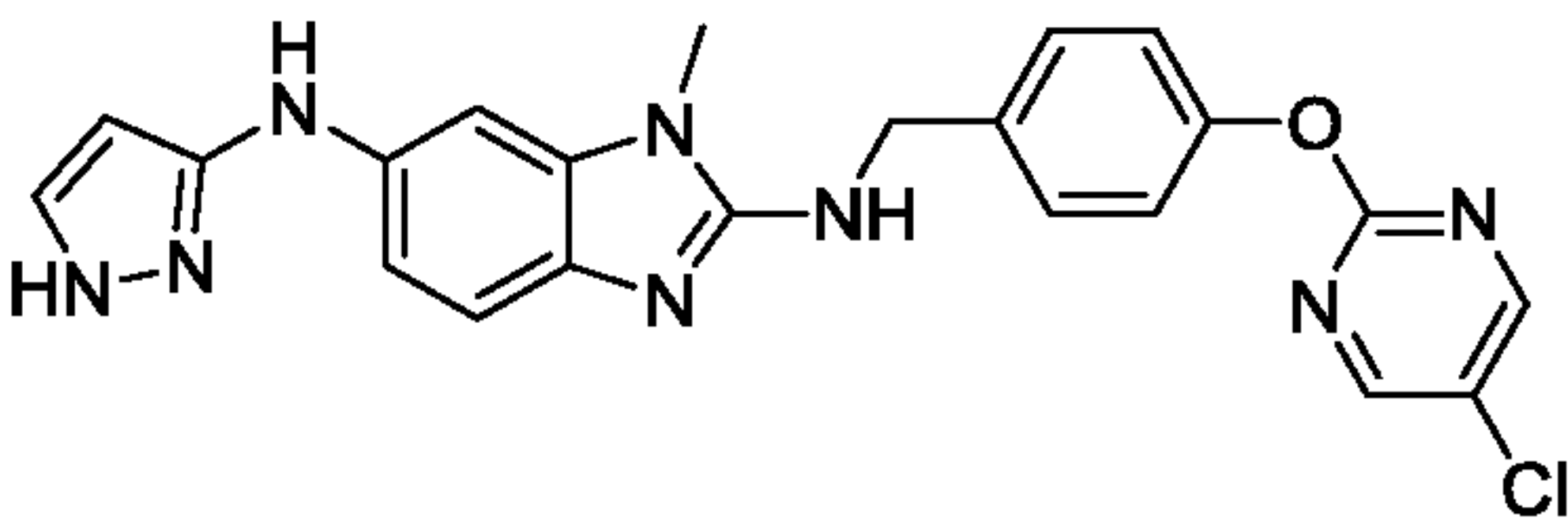
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 415 |    | yellow powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz); δ 11.48 (1H, s), 8.73 (2H, s), 7.92-7.91 (1H, m), 7.46 (2H, d, J = 8.4 Hz), 7.33 (1H, s), 7.16 (2H, d, J = 8.4 Hz), 7.02-6.07 (2H, m), 6.78-6.75 (1H, m), 5.55 (1H, s), 4.54 (2H, d, J = 5.2 Hz), 3.46 (s, 3H), 2.16 (s, 3H); LCMS: 95.5%, MS (ESI); m/z 461.2[M+H] <sup>+</sup> .                                                                                                                                                                                      |
| 416 |    | pale yellow powder (amorphous); <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.75 (2H, s), 6.86-6.97 (3H, m), 6.36 (1H, s), 6.29 (1H, d, J = 8.0 Hz), 6.22 (1H, t, J = 4.8 Hz), 4.56 (2H, brs), 4.44 (2H, d, J = 4.8 Hz), 3.36 (3H, s), 2.39 (6H, s); LCMS: 100%, MS (ESI): m/z 409.2[M+ H] <sup>+</sup> .                                                                                                                                                                                                                        |
| 417 |  | off-white powder (amorphous); <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.74 (2H, s), 7.00 (1H, d, J = 8.8 Hz), 6.90 (2H, s), 6.29 (1H, t, J = 4.8 Hz), 6.19-6.25 (2H, m), 5.85 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.47-4.56 (1H, m), 4.44 (1H, d, J = 4.8 Hz), 4.39 (1H, t, J = 6.0 Hz), 3.37 (3H, s, D <sub>2</sub> O added), 2.38 (6H, s); LCMS: 100%, MS (ESI): m/z 465.2[M + H] <sup>+</sup> .                                                                                                                |
| 418 |  | a white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 8.14 (2H, s), 6.94 (1H, d, J = 8.4 Hz), 6.90 (1H, t, J = 5.6 Hz), 6.25 (1H, d, J = 2.0 Hz), 6.22 (1H, dd, J = 8.4, 2.0 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.85 (2H, t, J = 6.0 Hz), 4.49-4.54 (1H, m), 4.46 (1H, d, J = 6.0 Hz), 4.40 (2H, t, J = 6.0 Hz), 3.45 (3H, s), 2.01 (6H, s); LCMS: 96.9%, MS (ESI): m/z 465.2[M+H] <sup>+</sup> .                                                                                                                |
| 419 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.43 (1H, d, J = 9.2 Hz), 7.98 (1H, d, J = 8.4 Hz), 7.68 (1H, d, J = 2.4 Hz), 7.51 (1H, dd, J = 8.4, 2.0 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 6.93 (1H, t, J = 6.0 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.38 (1H, d, J = 2.0 Hz), 6.27 (1H, dd, J = 8.4, 2.0 Hz), 4.50-4.55 (4H, m), 3.43 (3H, s); LCMS: 100%, MS (ESI): m/z 430.1[M+H] <sup>+</sup> .                                                                         |
| 420 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.43 (1H, d, J = 8.8 Hz), 7.98 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 2.0 Hz), 7.51 (1H, dd, J = 8.4, 2.0 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.19 (2H, d, J = 8.4 Hz), 6.93-7.02 (2H, m), 6.26 (1H, d, J = 2.0 Hz), 6.22 (1H, dd, J = 8.4, 2.0 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.56 (2H, d, J = 6.0 Hz), 4.46-4.54 (1H, m), 4.40 (2H, t, J = 5.8 Hz), 3.46 (3H, s); LCMS: 99.8%, MS (ESI): m/z 486.2[M+H] <sup>+</sup> . |

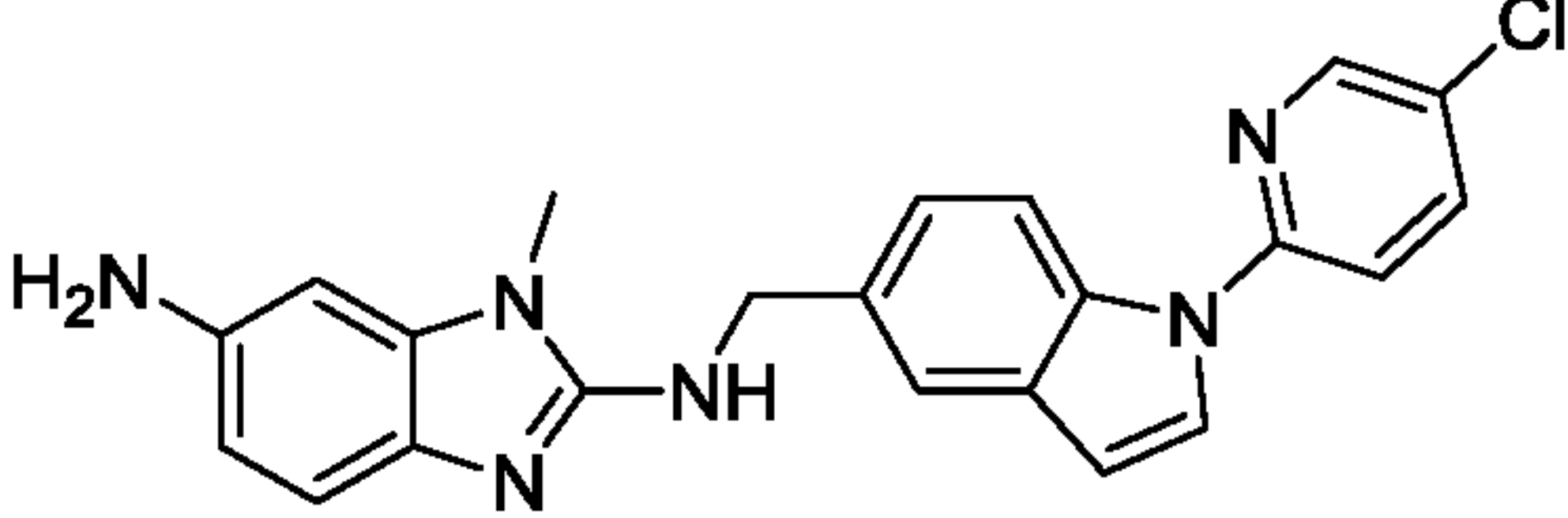
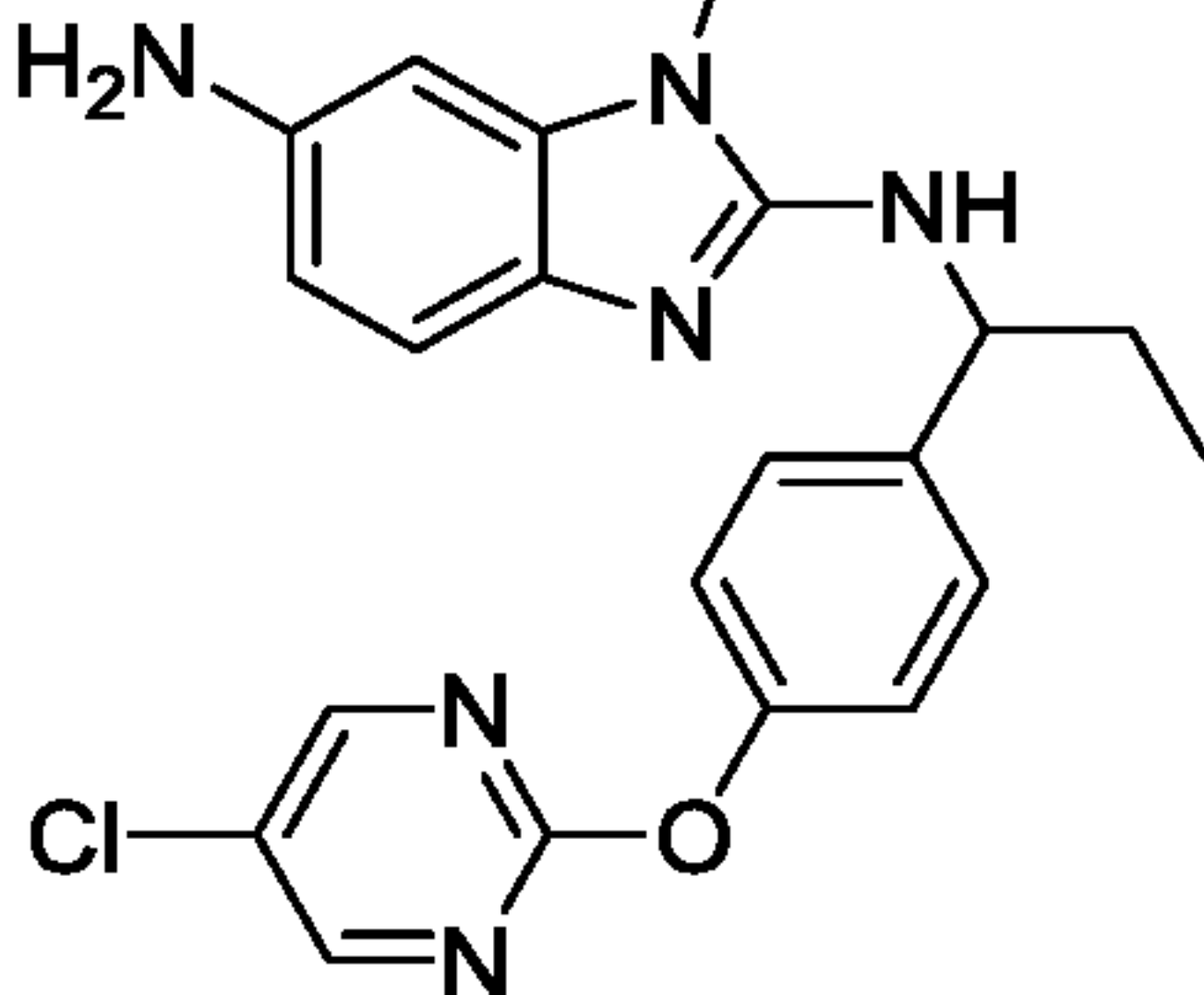
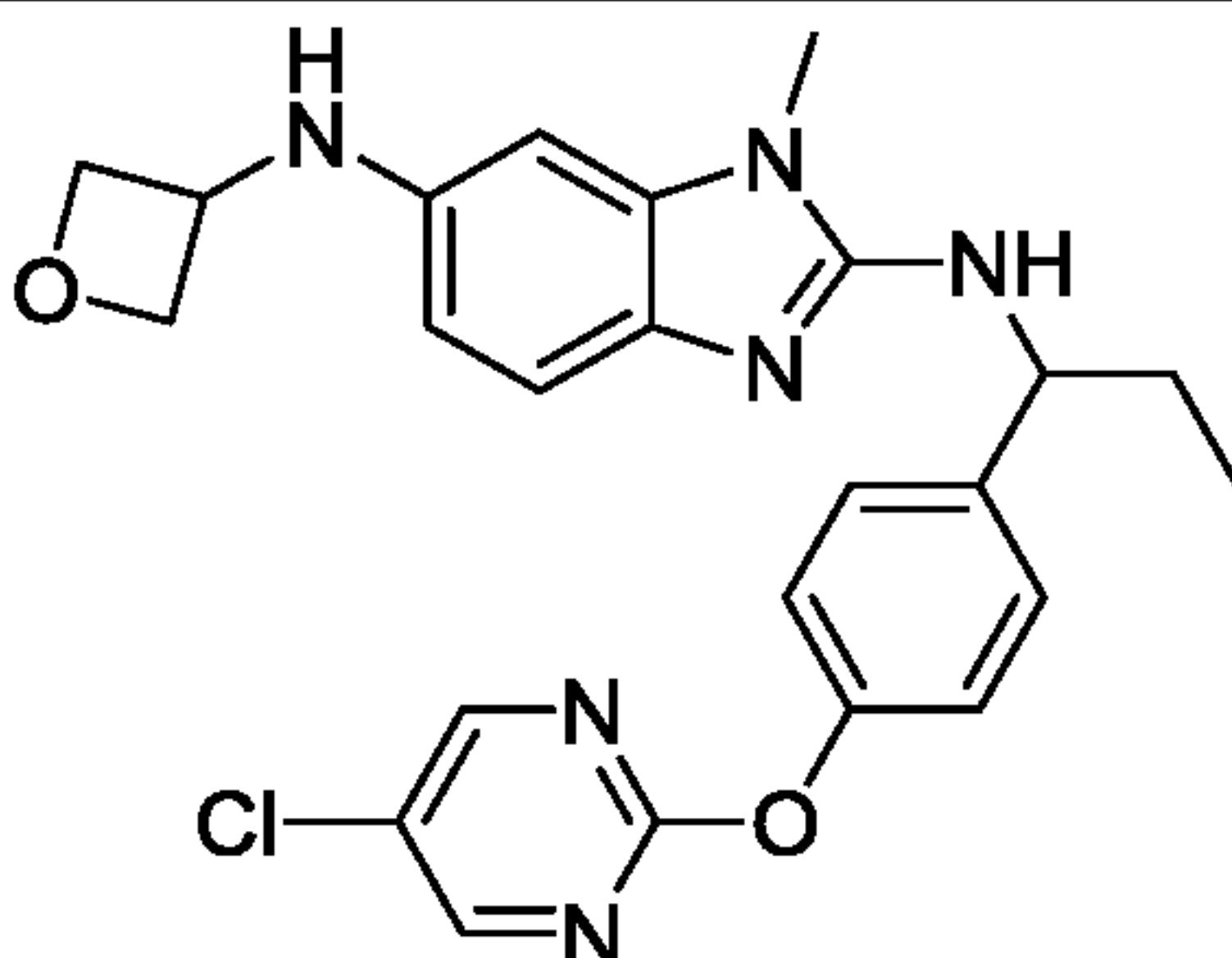
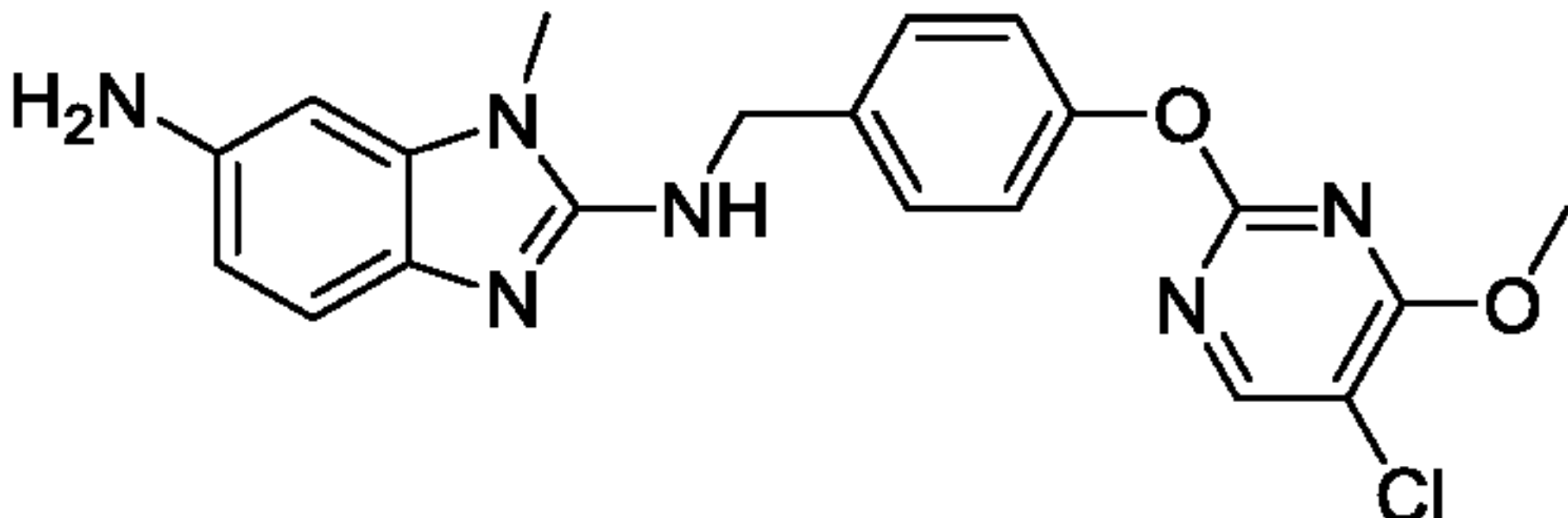
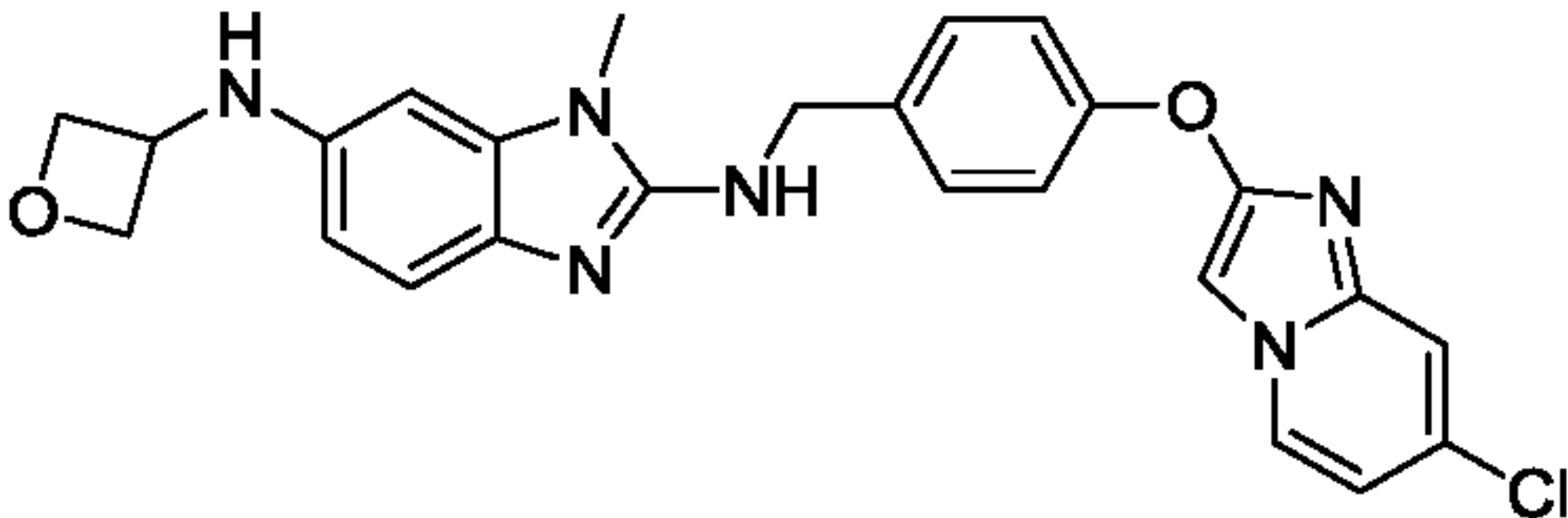
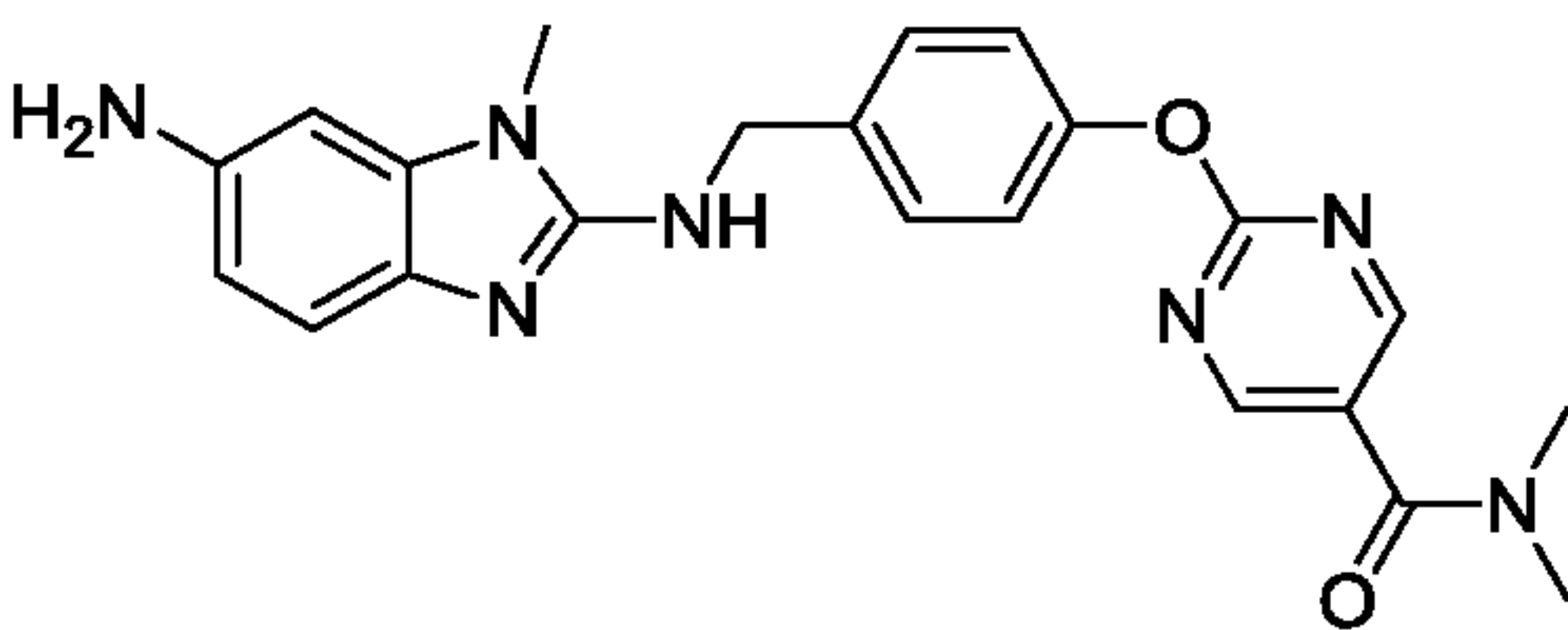
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 421 |    | white amorphous; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.47 (1H, d, J = 9.2 Hz), 7.94 (1H, dd, J = 8.0, 1.2 Hz), 7.85 (1H, dd, J = 8.0, 1.2 Hz), 7.43-7.50 (3H, m), 7.29-7.33 (3H, m), 6.93 (1H, brs), 6.88 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 2.0 Hz), 6.27 (1H, dd, J = 8.0, 2.0 Hz), 4.50-4.65 (4H, m), 3.43 (3H, s); LCMS: 100%, MS (ESI): m/z 430.1[M+H] <sup>+</sup> .                                                                                                                                                               |
| 422 |    | white amorphous; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.47 (1H, d, J = 9.2 Hz), 7.94 (1H, dd, J = 8.0, 1.2 Hz), 7.85 (1H, dd, J = 7.6, 1.2 Hz), 7.42-7.51 (3H, m), 7.27-7.34 (3H, m), 6.91-7.00 (2H, m), 6.26 (1H, d, J = 2.0 Hz), 6.22 (1H, dd, J = 8.0, 2.0 Hz), 5.83 (1H, d, J = 7.6 Hz), 4.84 (2H, t, J = 6.0 Hz), 4.57 (2H, d, J = 5.6 Hz), 4.47-4.55 (1H, m), 4.40 (2H, t, J = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI): m/z 486.2[M+H] <sup>+</sup> .                                                                              |
| 423 |  | white solid; mp 138.9-140.8 °C; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 7.61 (1H, d, J = 2.0 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.29-7.40 (3H, m), 7.12 (1H, dd, J = 8.8, 2.0 Hz), 6.90-7.02 (2H, m), 6.25 (1H, d, J = 2.0 Hz), 6.21 (1H, dd, J = 8.4, 2.4 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.46-4.59 (3H, m), 4.40 (2H, t, J = 6.0 Hz), 3.71 (3H, s), 3.45 (3H, s); LCMS: 98.5%, MS (ESI): m/z 489.2[M+H] <sup>+</sup> .                                                                                                   |
| 424 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.58 (1H, d, J = 8.8 Hz), 7.58-7.67 (3H, m), 7.48 (2H, d, J = 8.4 Hz), 7.40 (1H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.4 Hz), 6.93 (1H, t, J = 6.0 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.38 (1H, d, J = 1.6 Hz), 6.28 (1H, dd, J = 8.0, 2.0 Hz), 4.49-4.60 (4H, m), 3.43 (3H, s); LCMS: 95.9%, MS (ESI): m/z 430.1[M+H] <sup>+</sup> .                                                                                                                                                        |
| 425 |  | white solid; mp: 102.3-107.3 °C; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.43 (1H, d, J = 8.8 Hz), 7.98 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 2.0 Hz), 7.51 (1H, dd, J = 8.4, 2.0 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.19 (2H, d, J = 8.4 Hz), 6.93-7.02 (2H, m), 6.26 (1H, d, J = 2.0 Hz), 6.22 (1H, dd, J = 8.4, 2.0 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.56 (2H, d, J = 6.0 Hz), 4.46-4.54 (1H, m), 4.40 (2H, t, J = 6.0 Hz), 3.46 (3H, s); LCMS: 99.8%, MS (ESI): m/z 486.2[M+H] <sup>+</sup> . |
| 426 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.90 (1H, s), 8.15 (1H, s), 7.74-7.77 (2H, m), 7.49 (2H, d, J = 8.8 Hz), 7.27 (2H, dd, J = 6.8, 2.0 Hz), 6.95 (3H, t, J = 5.6 Hz), 6.87 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 1.6 Hz), 6.27 (1H, dd, J = 8.4, 2.0 Hz), 4.45-4.70 (4H, m), 3.43 (3H, s); LCMS: 100%, MS (ESI): m/z 431.1[M+H] <sup>+</sup> .                                                                                                                                                                               |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 427 |    | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.90 (1H, s), 8.15 (1H, s), 7.74 (2H, s), 7.49 (2H, d, J = 8.4 Hz), 7.27 (2H, dd, J = 8.8 Hz), 6.99 (1H, t, J = 6.4 Hz), 6.95 (1H, d, J = 8.4 Hz), 6.26 (1H, d, J = 2.0 Hz), 6.22 (1H, dd, J = 8.4, 2.0 Hz), 5.83 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.45-4.70 (3H, m), 4.40 (2H, t, J = 6.0 Hz), 3.46 (3H, s); LCMS: 100%, MS (ESI): m/z 487.2[M+ H] <sup>+</sup> . |
| 428 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 7.61 (1H, d, J = 2.0 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.30-7.40 (3H, m), 7.12 (1H, dd, J = 8.0, 2.0 Hz), 6.93 (1H, t, J = 6.0 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 1.6 Hz), 6.27 (1H, dd, J = 8.4, 2.4 Hz), 4.56 (1H, brs), 4.53 (2H, d, J = 5.6 Hz), 3.71 (3H, s), 3.42 (3H, s); LCMS: 100%, MS (ESI): m/z 433.2[M+H] <sup>+</sup> .                                         |
| 429 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 13.10 (1H, brs), 9.39 (1H, t, J = 5.2 Hz), 8.88 (1H, s), 8.74 (2H, s), 7.78 (1H, d, J = 2.0 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.21-7.31 (3H, m), 7.08 (1H, d, J = 8.4 Hz), 5.94 (2H, brs), 4.70 (2H, d, J = 6.0 Hz), 3.63 (3H, s); LCMS: 100%, MS (ESI): m/z 424.2[M + H] <sup>+</sup> .                                                                                                  |
| 430 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.80 (2H, s), 7.12-7.21 (2H, m), 6.91 (1H, d, J = 8.0 Hz), 6.64 (1H, t, J = 5.2 Hz), 6.36 (1H, d, J = 2.0 Hz), 6.29 (1H, dd, J = 8.4, 2.0 Hz), 4.57 (2H, brs), 4.51 (2H, d, J = 4.8 Hz); LCMS: 97.4%, MS (ESI): m/z 417.1 [M+H] <sup>+</sup> .                                                                                                                                   |
| 431 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.80 (2H, s), 7.17 (2H, d, J = 8.4 Hz), 6.99 (1H, d, J = 8.8 Hz), 6.70 (1H, t, J = 5.6 Hz), 6.20-6.25 (2H, m), 5.86 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.48-4.55 (3H, m), 4.40 (2H, t, J = 6.0 Hz), 3.39 (3H, s); LCMS: 100%, MS (ESI): m/z 473.1[M+H] <sup>+</sup> .                                                                                                      |
| 432 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.80 (2H, s), 7.70 (1H, s), 7.59 (1H, s), 7.02 (1H, t, J = 6.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.39 (1H, d, J = 2.0 Hz), 6.28 (1H, dd, J = 8.0, 2.0 Hz), 4.50-4.66 (4H, m), 3.46 (3H, s); LCMS: 97.1%, MS (ESI): m/z 449.0[M+ H] <sup>+</sup> .                                                                                                                                         |

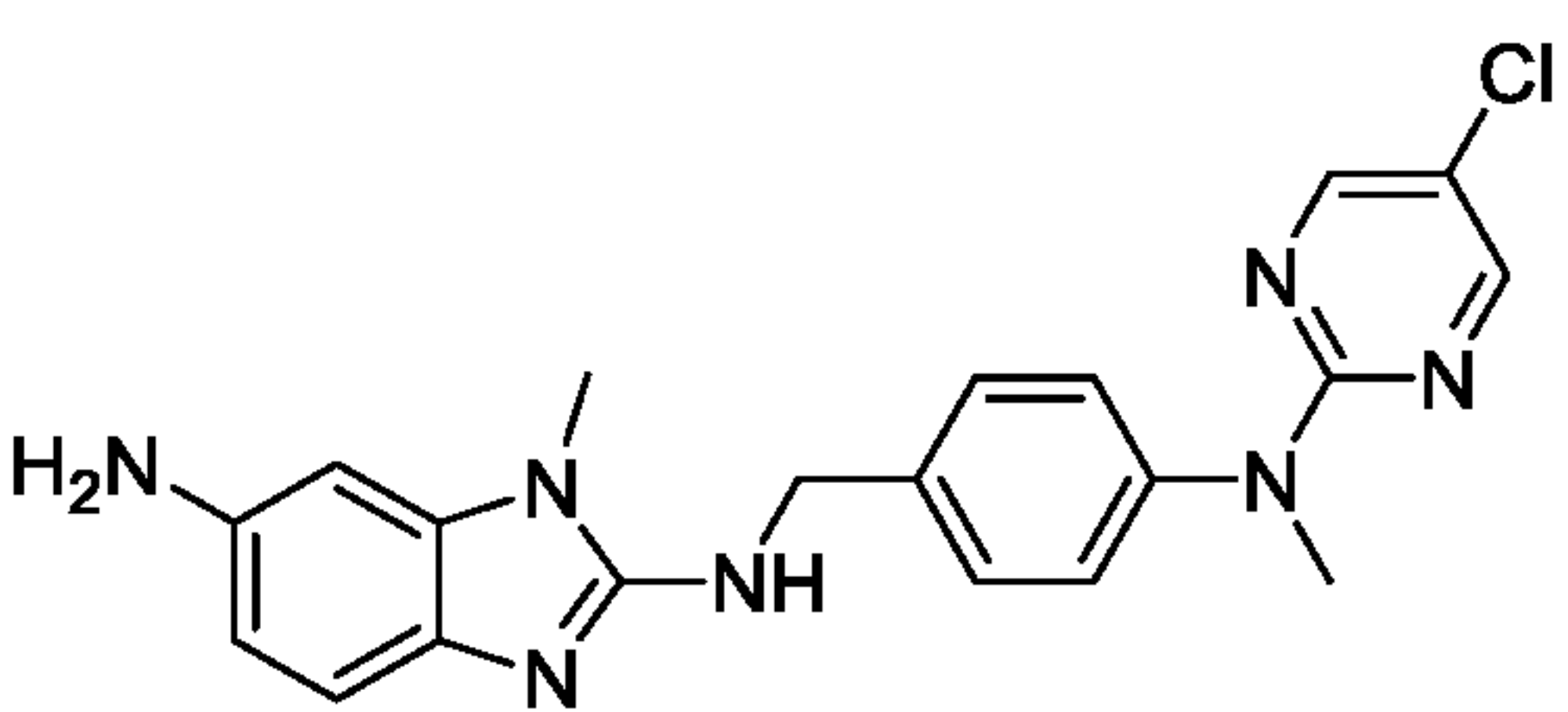
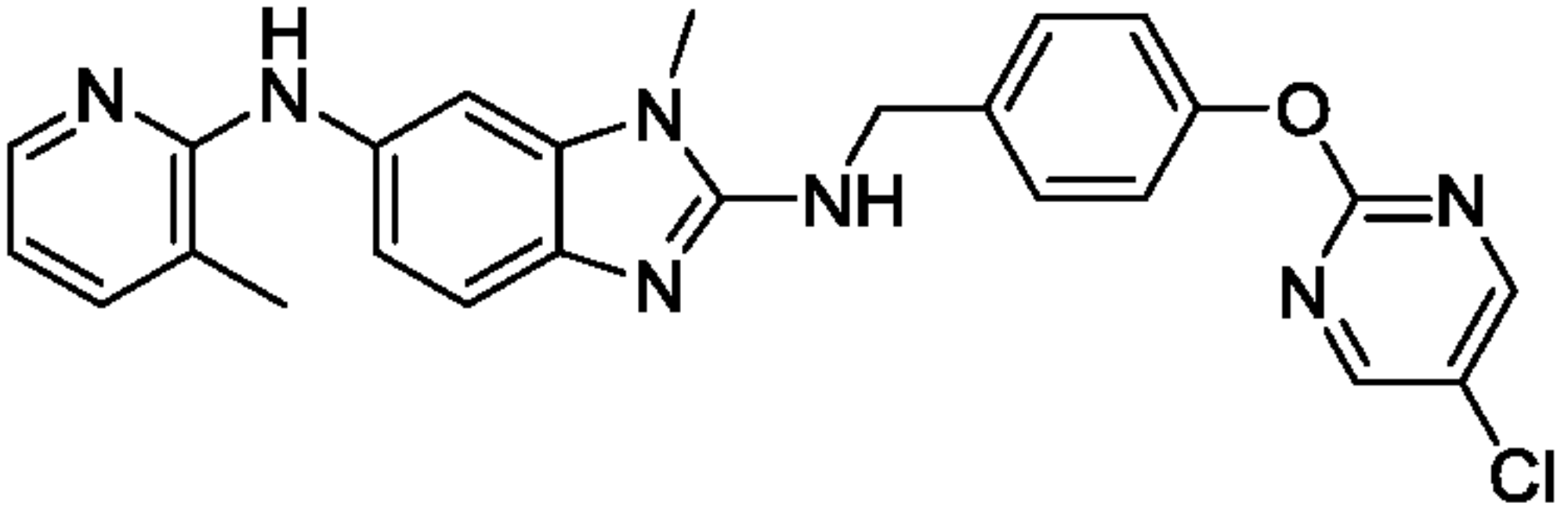
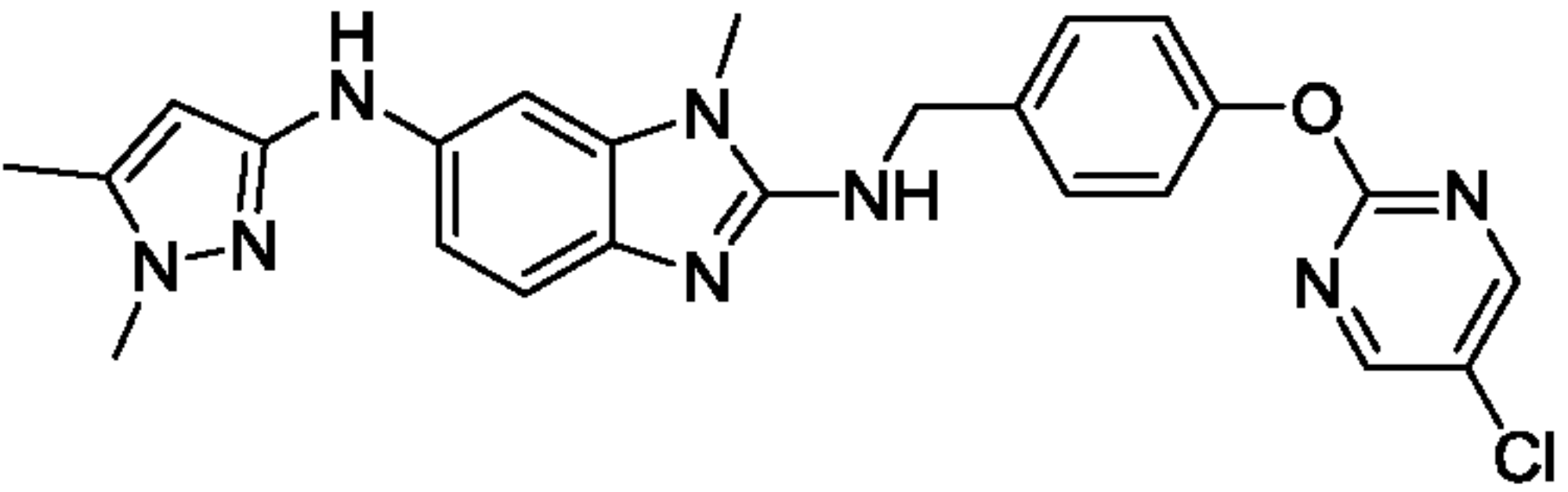
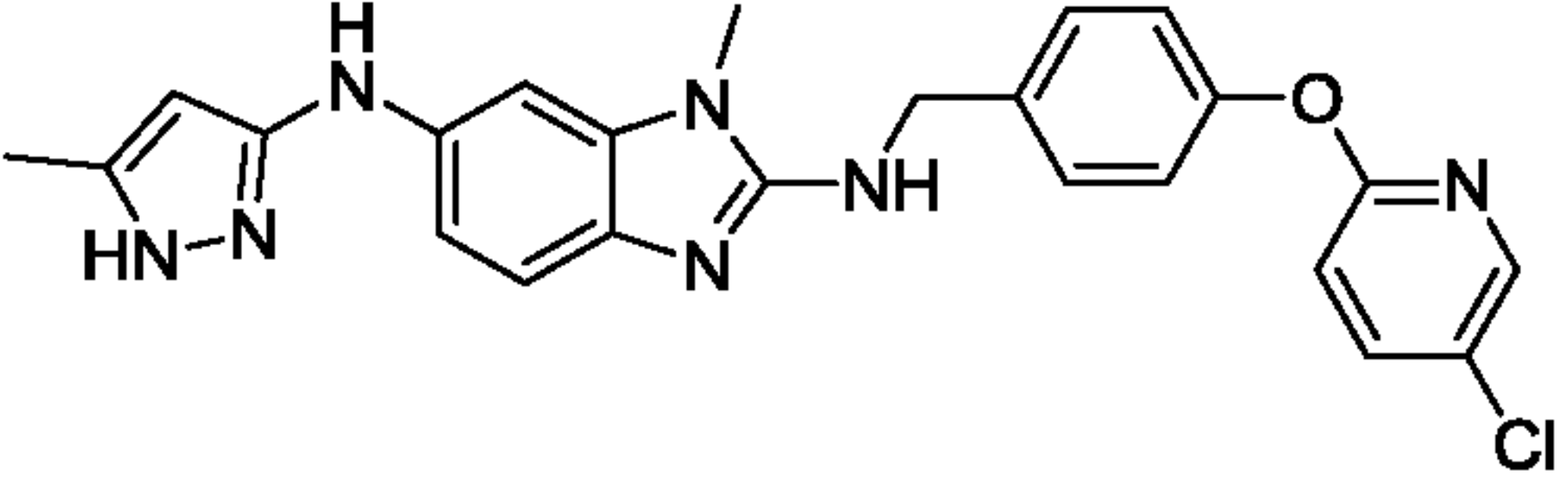
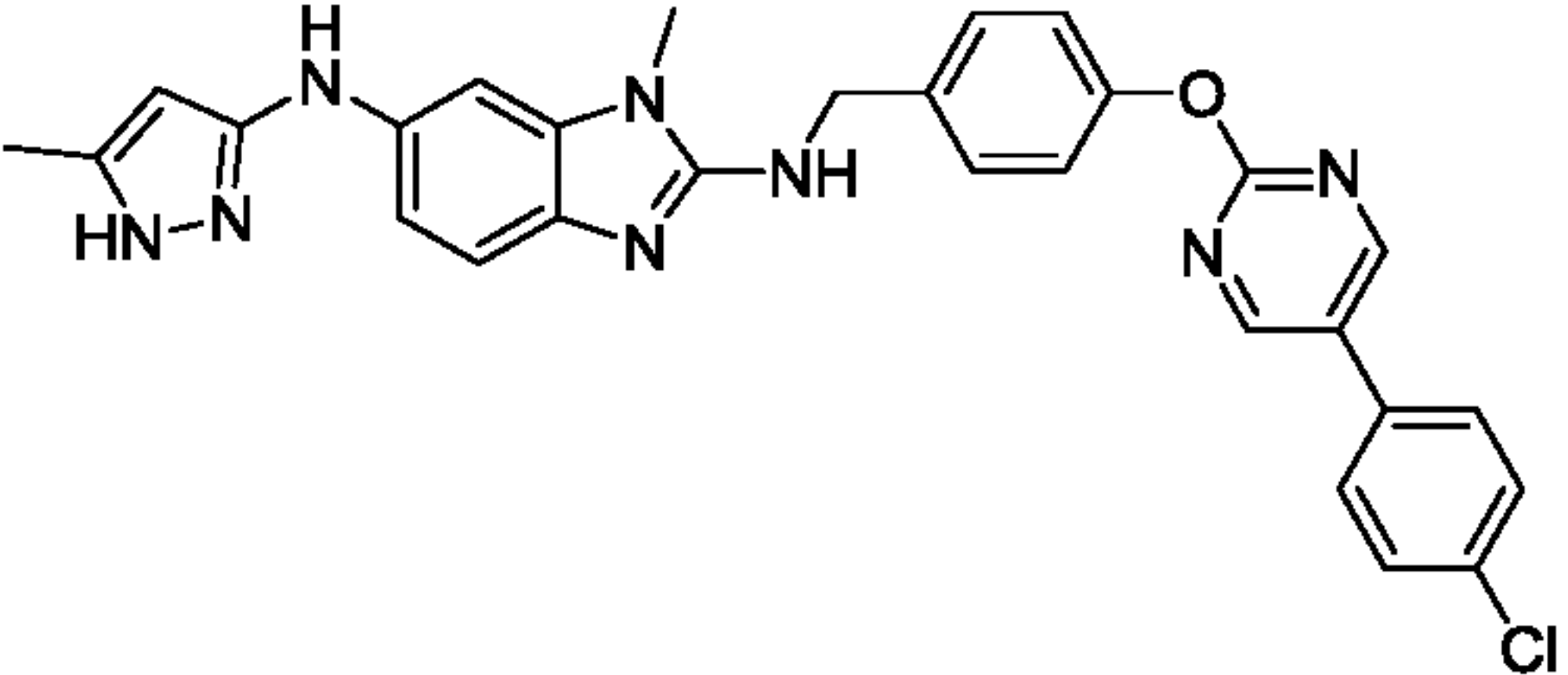
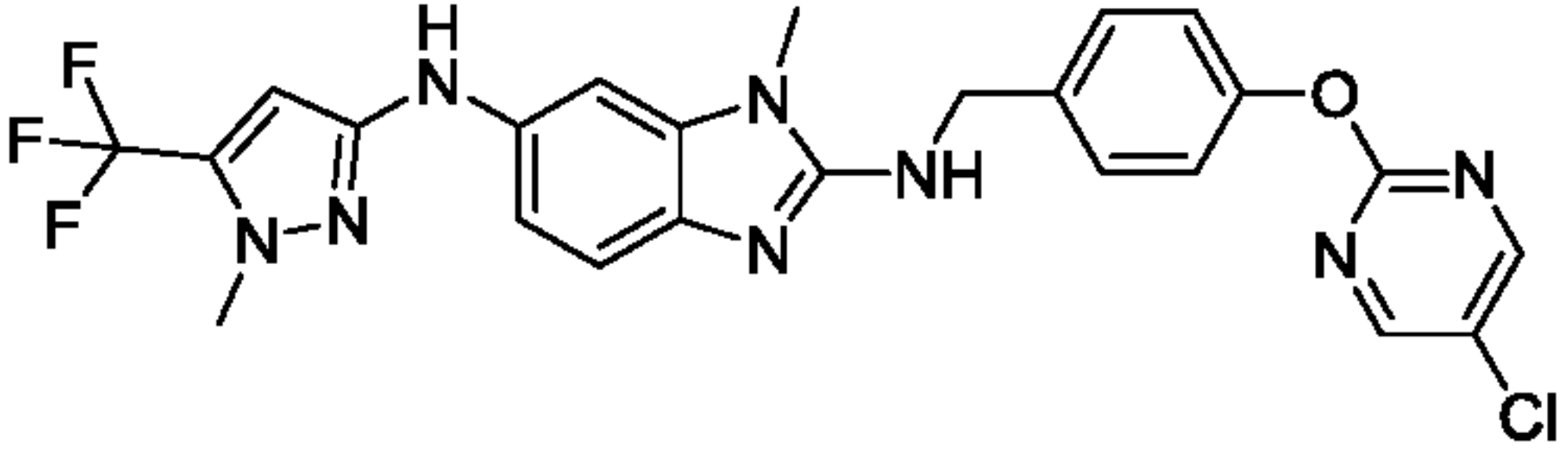
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 433 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.80 (2H, s), 7.70 (1H, s), 7.58 (1H, s), 7.08 (1H, t, J = 6.0 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.28 (1H, d, J = 2.0 Hz), 6.23 (1H, dd, J = 8.0, 2.0 Hz), 5.88 (1H, d, J = 6.8 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.57 (2H, d, J = 6.0 Hz), 4.46-4.54 (1H, m), 4.40 (2H, t, J = 6.0 Hz), 3.50 (3H, s); LCMS: 100%, MS (ESI): m/z 507.0[M + H] <sup>+</sup> .                       |
| 434 |  | off-white powder; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 9.67 (1H, s), 7.71-7.80 (2H, m), 7.49-7.58 (3H, m), 7.29-7.33 (2H, m), 6.57 (1H, dd, J = 8.4, 2.0 Hz), 6.49 (1H, d, J = 2.0 Hz), 4.76 (2H, s), 4.63 (1H, brs), 3.48 (3H, s); LCMS: 97.5%, MS (ESI): m/z 431.2[M+H]                                                                                                                                                         |
| 435 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.68 (1H, s), 7.88 (1H, t, J = 8.0 Hz), 7.65-7.72 (2H, m), 7.47 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 6.98 (1H, brs), 6.95 (1H, d, J = 8.4 Hz), 6.25 (1H, s), 6.20 (1H, dd, J = 8.4, 2.0 Hz), 5.84 (1H, d, J = 6.8 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.46-4.58 (3H, m), 4.39 (2H, t, J = 6.0 Hz), 3.44 (3H, s); LCMS: 99.1%, MS (ESI): m/z 487.2[M+H] <sup>+</sup> .  |
| 436 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.58 (1H, s), 8.08-8.17 (2H, m), 7.59 (1H, t, J = 8.0 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.8 Hz), 6.90 (1H, t, J = 6.0 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 1.6 Hz), 6.26 (1H, dd, J = 8.0, 2.0 Hz), 4.47-4.61 (4H, m), 3.43 (3H, s); LCMS: 99.1%, MS (ESI): m/z 431.1[M+ H] <sup>+</sup> .                                                         |
| 437 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.57 (1H, s), 8.06-8.19 (2H, m), 7.59 (1H, t, J = 8.0 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.02-7.23 (1H, brs), 6.97 (1H, d, J = 8.0 Hz), 6.28 (1H, s), 6.24 (1H, d, J = 8.4 Hz), 5.89 (1H, d, J = 6.8 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.46-4.62 (3H, m), 4.40 (2H, t, J = 6.0 Hz), 3.47 (3H, s); LCMS: 97.8%, MS (ESI): m/z 487.2[M + H] <sup>+</sup> . |
| 438 |  | pale green powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.38 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 2.0 Hz), 7.96 (1H, d, J = 6.0 Hz), 7.74 (1H, d, J = 9.2, 2.0 Hz), 7.40-7.55 (3H, m), 7.21 (2H, d, J = 8.4 Hz), 6.94 (1H, brs), 6.89 (1H, d, J = 8.0 Hz), 6.38 (1H, d, J = 2.0 Hz), 6.28 (1H, d, J = 8.4, 2.0 Hz), 4.42-4.69 (4H, m), 3.45 (3H, s); LCMS: 100%, MS (ESI): m/z 430.1[M+ H] <sup>+</sup> .                      |

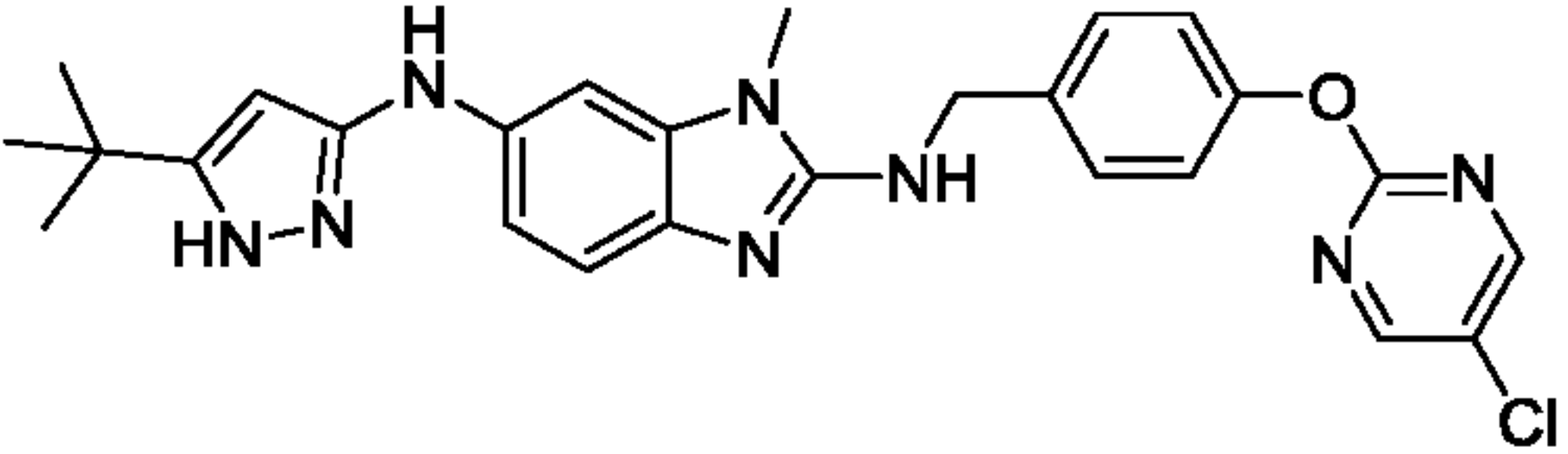
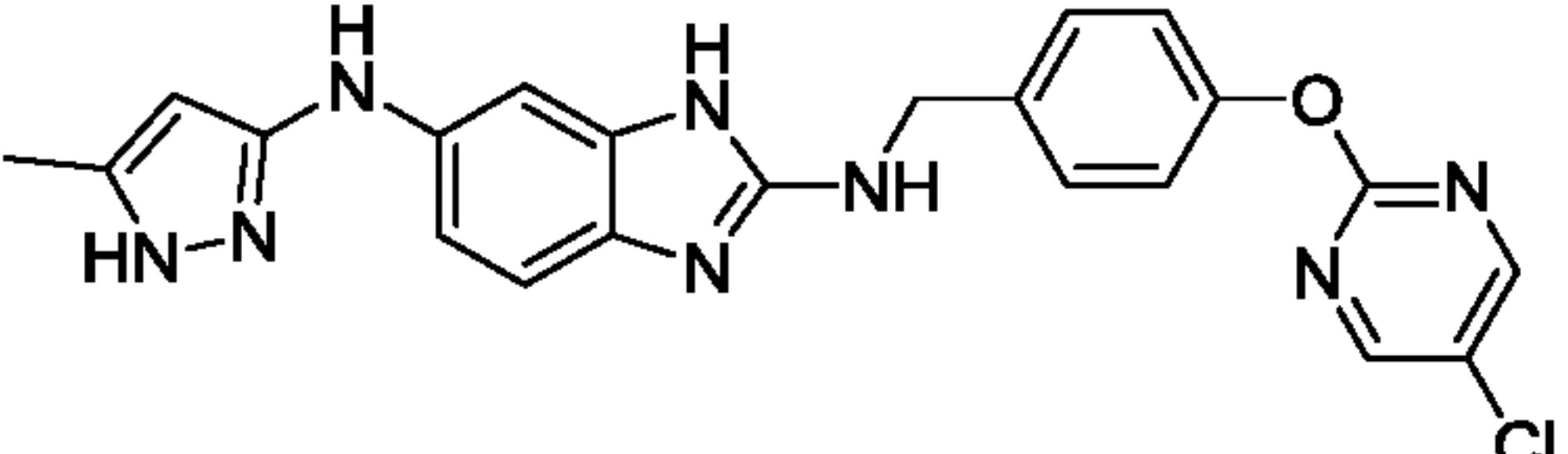
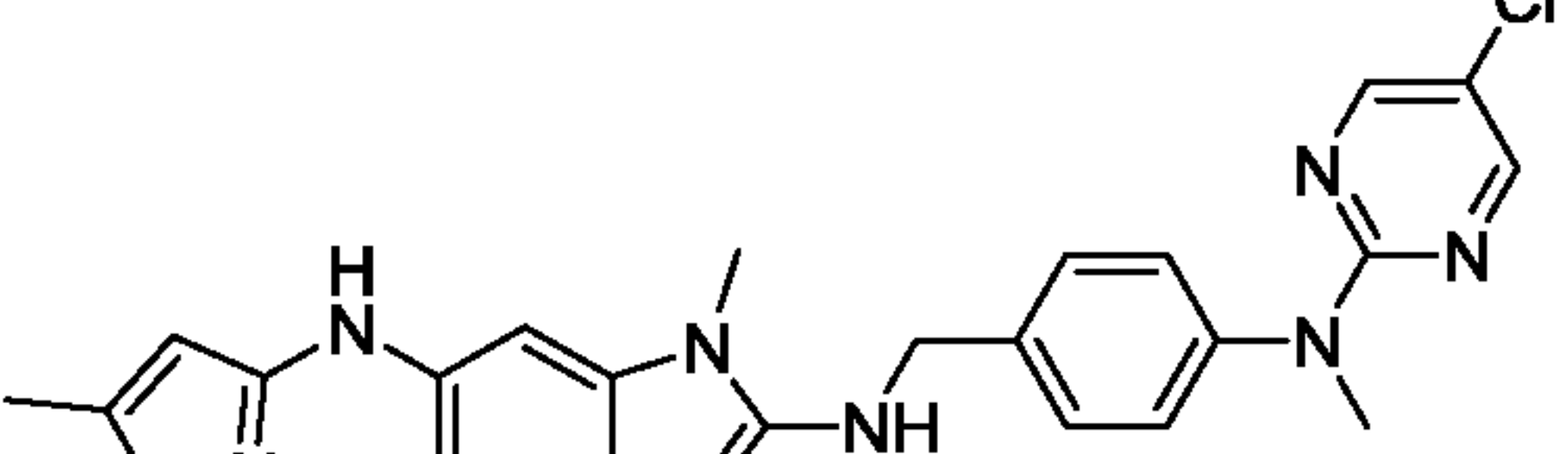
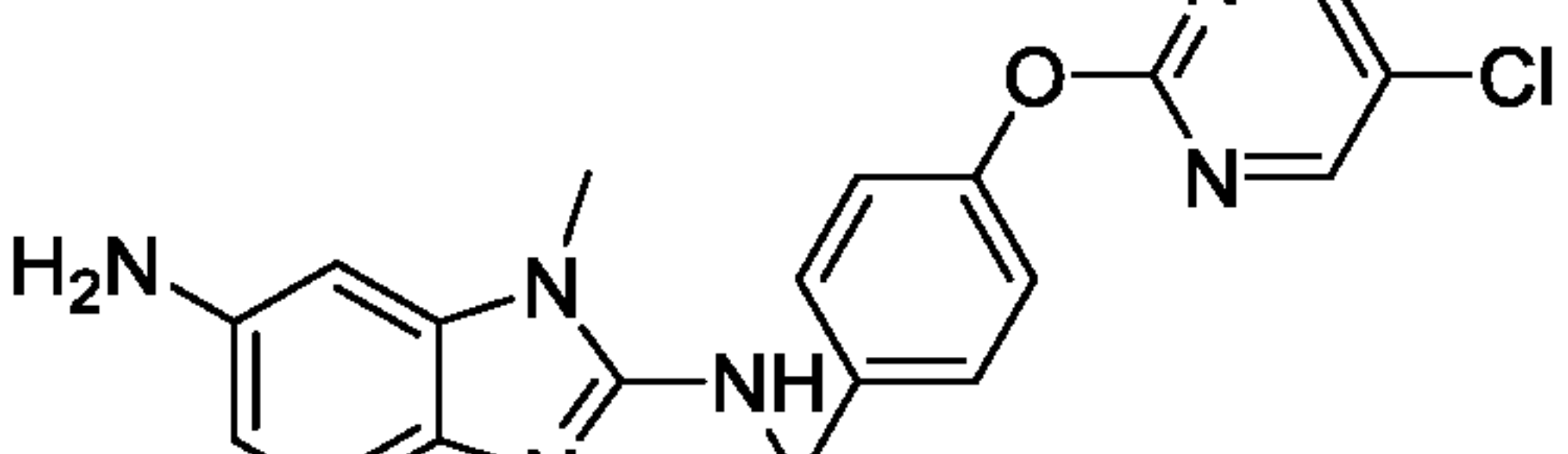
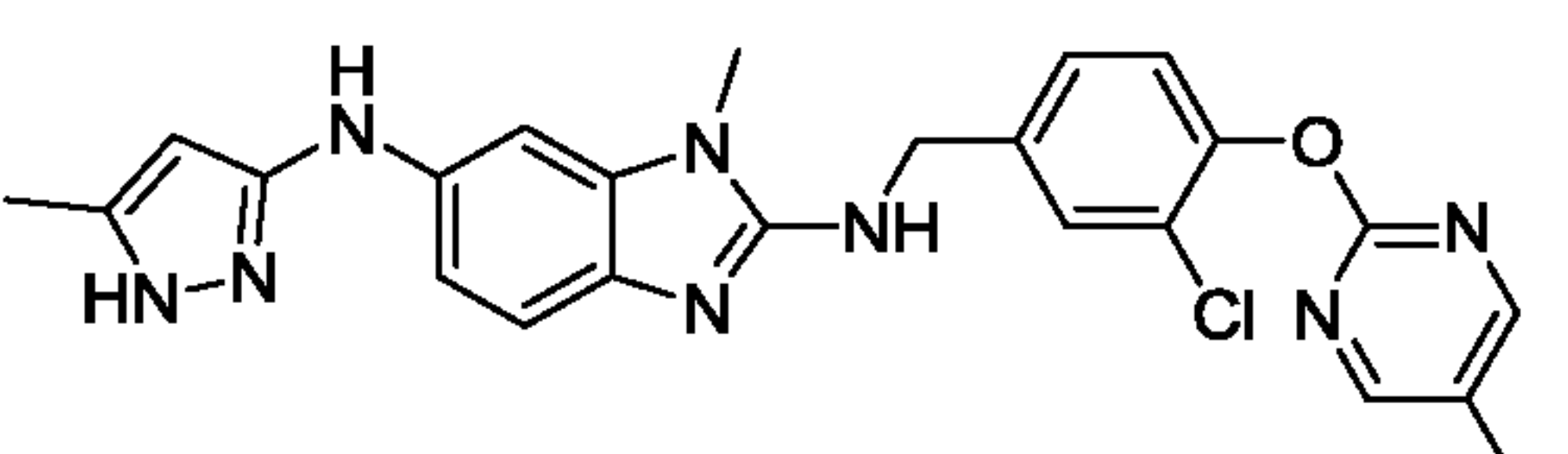
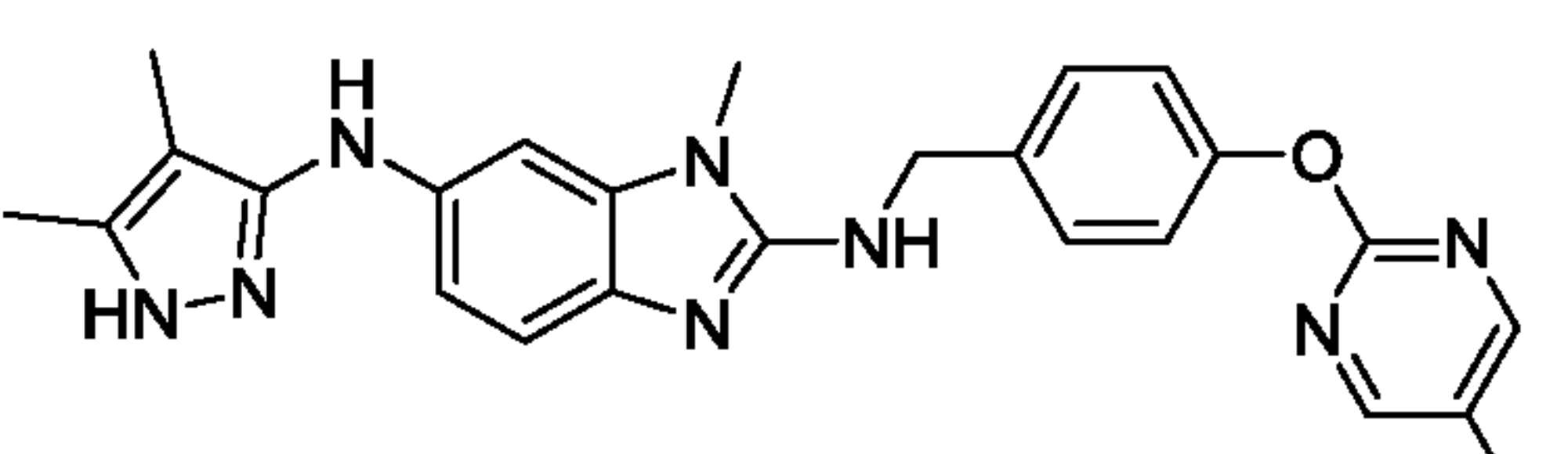
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 439 |    | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.36 (1H, d, J = 8.8 Hz), 8.12 (1H, d, J = 2.0 Hz), 7.93 (1H, d, J = 5.6 Hz), 7.71 (1H, dd, J = 8.8, 2.0 Hz), 7.47 (1H, d, J = 6.0 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.18 (2H, d, J = 8.4 Hz), 6.96 (1H, brs), 6.94 (1H, d, J = 8.0 Hz), 6.24 (1H, d, J = 1.6 Hz), 6.20 (1H, dd, J = 8.0, 2.0 Hz), 5.82 (1H, d, J = 7.6 Hz), 4.83 (2H, t, J = 6.4 Hz), 4.43-4.56 (3H, m), 4.38 (2H, t, J = 6.0 Hz), 3.44 (3H, s); LCMS: 99.1%, MS (ESI): m/z 486.2[M+H] <sup>+</sup> . |
| 440 |    | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.55 (1H, s), 8.16 (1H, d, J = 8.4 Hz), 7.83 (1H, s), 7.63 (1H, dd, J = 8.8, 2.0 Hz), 7.47 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.4 Hz), 6.98 (1H, brs), 6.89 (1H, d, J = 8.0 Hz), 6.38 (1H, d, J = 1.6 Hz), 6.28 (1H, dd, J = 8.0, 1.6 Hz), 4.67 (2H, brs), 4.55 (2H, d, J = 5.6 Hz), 3.43 (3H, s); LCMS: 98.1%, MS (ESI): m/z 431.2[M+H] <sup>+</sup> .                                                                                                          |
| 441 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 13.90 (1H, brs), 10.08 (1H, s), 9.80 (1H, brs), 8.74 (2H, s), 7.40-7.65 (8H, m), 7.24 (2H, d, J = 8.8 Hz), 7.09-7.18 (1H, m), 4.79 (2H, d, J = 6.0 Hz), 3.73 (3H, s); LCMS: 100%, MS (ESI): m/z 423.2[M+H] <sup>+</sup> .                                                                                                                                                                                                                                               |
| 442 |  | off-white powder; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 8.48 (1H, d, J = 7.6 Hz), 7.95 (1H, s), 7.49 (2H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.8 Hz), 7.02 (1H, brs), 6.89 (1H, d, J = 8.0 Hz), 6.84 (1H, dd, J = 7.6, 2.4 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.39 (1H, d, J = 1.6 Hz), 6.29 (1H, dd, J = 8.0, 1.6 Hz), 4.54 (2H, d, J = 5.6 Hz), 3.43 (3H, s); LCMS: 98.7%, MS (ESI): m/z 419.1[M+H] <sup>+</sup> .                                                                                                                |
| 443 |  | white powder (hygroscopic); <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 13.11 (1H, s), 9.40 (1H, t, J = 6.0 Hz), 8.74 (2H, s), 7.54 (2H, d, J = 8.4 Hz), 7.33-7.48 (4H, m), 7.12-7.28 (4H, m), 6.61 (1H, s), 6.54 (1H, d, J = 8.4 Hz), 4.70 (2H, d, J = 6.0 Hz), 4.40-4.50 (2H, m), 4.28-4.39 (1H, m), 3.77-3.86 (2H, m), 3.63 (3H, s); LCMS: 99.4%, MS (ESI): m/z 478.3[M+H] <sup>+</sup> .                                                                                                                                      |
| 444 |  | yellow powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.55 (1H, s), 8.16 (1H, d, J = 8.8 Hz), 7.82 (1H, d, J = 1.6 Hz), 7.63 (1H, dd, J = 8.4, 2.0 Hz), 7.46 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.04 (1H, brs), 6.96 (1H, d, J = 8.0 Hz), 6.26 (1H, d, J = 1.6 Hz), 6.20-6.25 (1H, dd, J = 8.0, 2.0 Hz), 5.86 (1H, d, J = 6.8 Hz), 4.85 (2H, t, J = 6.0 Hz), 4.56 (2H, d, J = 6.0 Hz), 4.47-4.54 (1H, m), 4.40 (2H, d, J = 6.0 Hz), 3.46 (3H, s); LCMS: 96.9%, MS (ESI): m/z 487.2[M+H] <sup>+</sup> .           |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 445 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.29 (1H, d, J = 2.4 Hz), 8.21 (1H, d, J = 2.4 Hz), 7.99 (1H, d, J = 3.6 Hz), 7.76 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.8 Hz), 6.94 (1H, t, J = 6.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.71 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 1.6 Hz), 6.26 (1H, d, J = 8.4, 2.0 Hz), 4.40-4.60 (4H, m), 3.43 (3H, s); LCMS: 99.3%, MS (ESI): m/z 403.1[M+ H] <sup>+</sup> .                                                                                                          |
| 446 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.28 (1H, d, J = 2.4 Hz), 8.21 (1H, d, J = 2.4 Hz), 7.99 (1H, d, J = 4.0 Hz), 7.76 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.00 (1H, t, J = 6.0 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.70 (1H, d, J = 3.6 Hz), 6.26 (1H, d, J = 2.0 Hz), 6.21 (1H, dd, J = 8.4, 2.0 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.8 Hz), 4.57 (2H, d, J = 6.0 Hz), 4.55-4.60 (1H, m), 4.39 (2H, d, J = 6.0 Hz), 3.46 (3H, s); LCMS: 98.3%, MS (ESI): m/z 459.3[M+ H] <sup>+</sup> . |
| 447 |  | pale yellow solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (2H, s), 8.68 (1H, brs), 8.07 (1H, dd, J = 4.8, 1.2 Hz), 7.54 (1H, d, J = 2.0 Hz), 7.40-7.49 (3H, m), 7.11-7.20 (3H, m), 7.07 (1H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 8.4, 2.0 Hz), 6.72 (1H, d, J = 8.4 Hz), 6.61 (1H, dd, J = 6.8, 6.0 Hz), 4.56 (2H, d, J = 6.0 Hz), 3.50 (3H, s); LCMS: 100 %, MS (ESI): m/z 458.2[M+ H] <sup>+</sup> .                                                                                                                     |
| 448 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.69 (1H, s), 8.17 (1H, d, J = 2.8 Hz), 8.08 (1H, dd, J = 4.8, 2.0 Hz), 7.94 (1H, dd, J = 8.8, 2.8 Hz), 7.55 (1H, d, J = 2.0 Hz), 7.42-7.49 (3H, m), 7.15 (1H, t, J = 6.0 Hz), 7.06-7.11 (4H, m), 7.01 (1H, dd, J = 8.1, 2.0 Hz), 6.73 (1H, d, J = 8.4 Hz), 6.62 (1H, dd, J = 6.4, 5.2 Hz), 4.57 (2H, d, J = 6.0 Hz), 3.51 (3H, s); LCMS: 99.3%, MS (ESI): m/z 457.2[M+H] <sup>+</sup> .                                                                                 |
| 449 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.80 (1H, brs), 8.17 (1H, d, J = 2.8 Hz), 8.02 (1H, brs), 7.93 (1H, dd, J = 8.8, 2.8 Hz), 7.50 (1H, d, J = 2.4 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.33 (1H, s), 7.06-7.10 (3H, m), 6.97-7.03 (2H, m), 6.78 (1H, dd, J = 8.4, 2.0 Hz), 5.78 (1H, d, J = 2.4 Hz), 4.54 (2H, d, J = 5.6 Hz), 3.46 (3H, s); LCMS: 97.2%, MS (ESI): m/z 446.1[M + H] <sup>+</sup> .                                                                                                              |
| 450 |  | pale yellow solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.81 (1H, brs), 8.72 (2H, s), 8.02 (1H, s), 7.48 (1H, s), 7.45 (2H, d, J = 8.4 Hz), 7.33 (1H, s), 7.14 (2H, d, J = 8.4 Hz), 7.01 (1H, t, J = 6.0 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 8.8 Hz), 5.77 (1H, d, J = 2.0 Hz), 4.53 (2H, d, J = 6.0 Hz), 3.45 (3H, s); LCMS: 100%, MS (ESI): m/z 447.2[M + H] <sup>+</sup> .                                                                                                                                  |

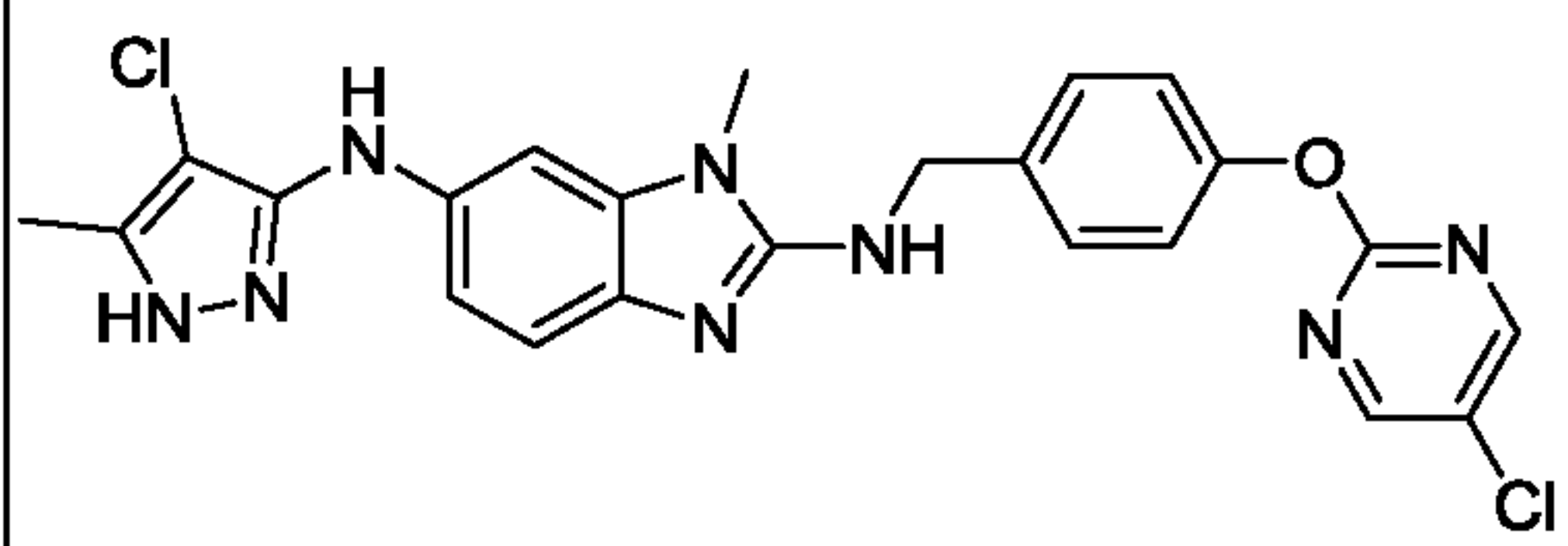
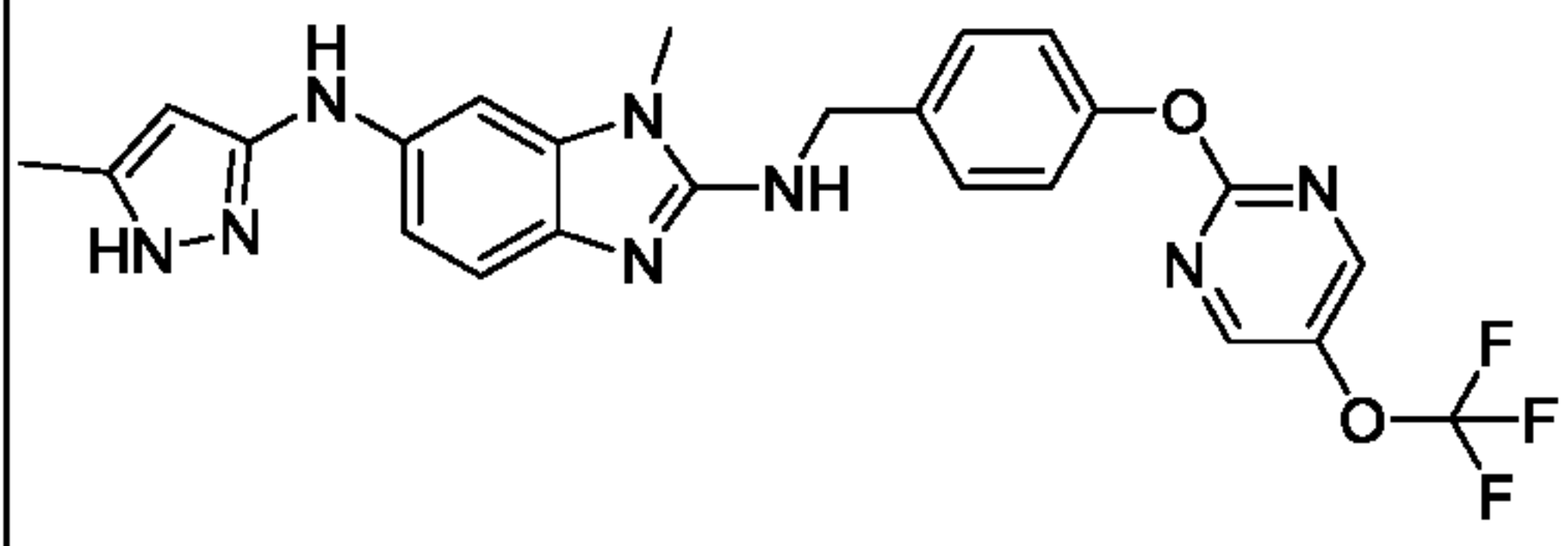
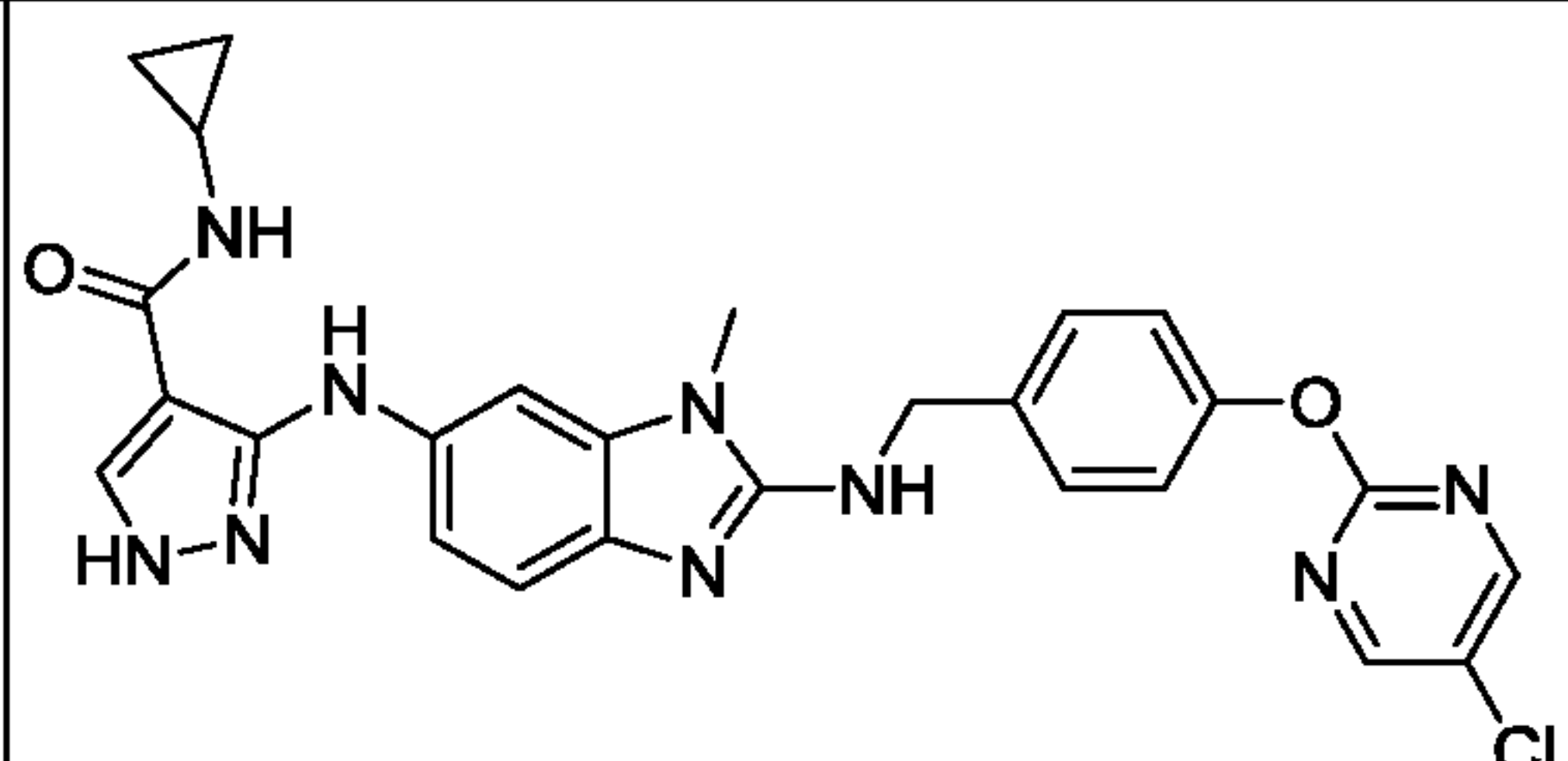
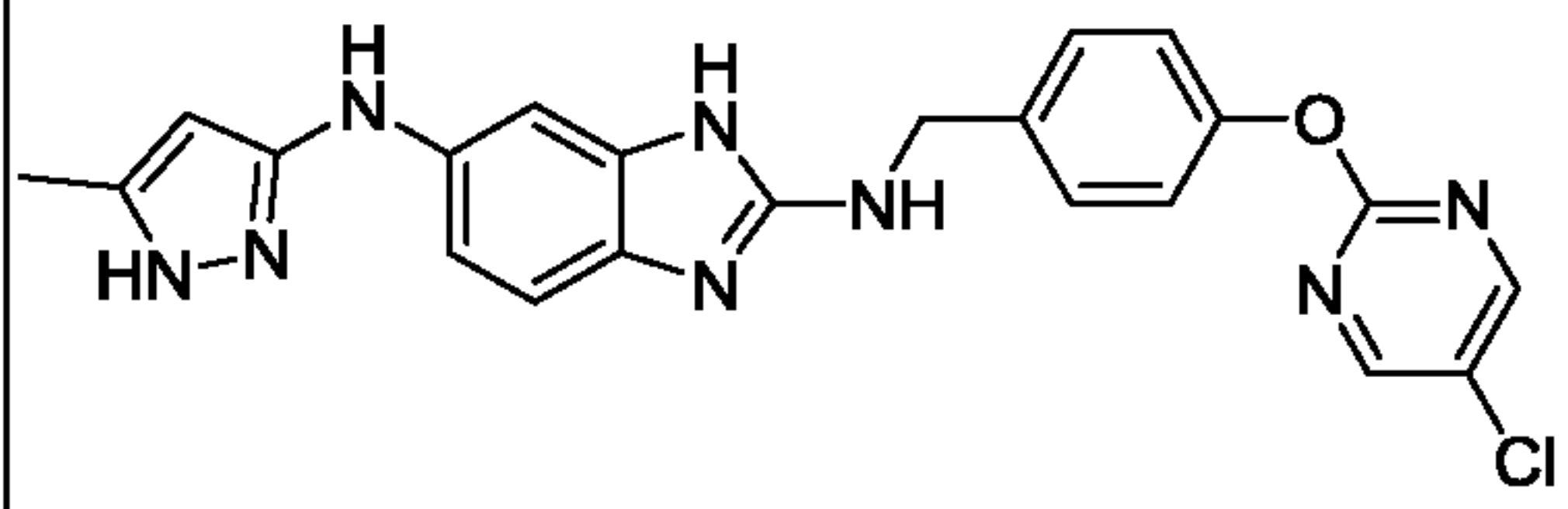
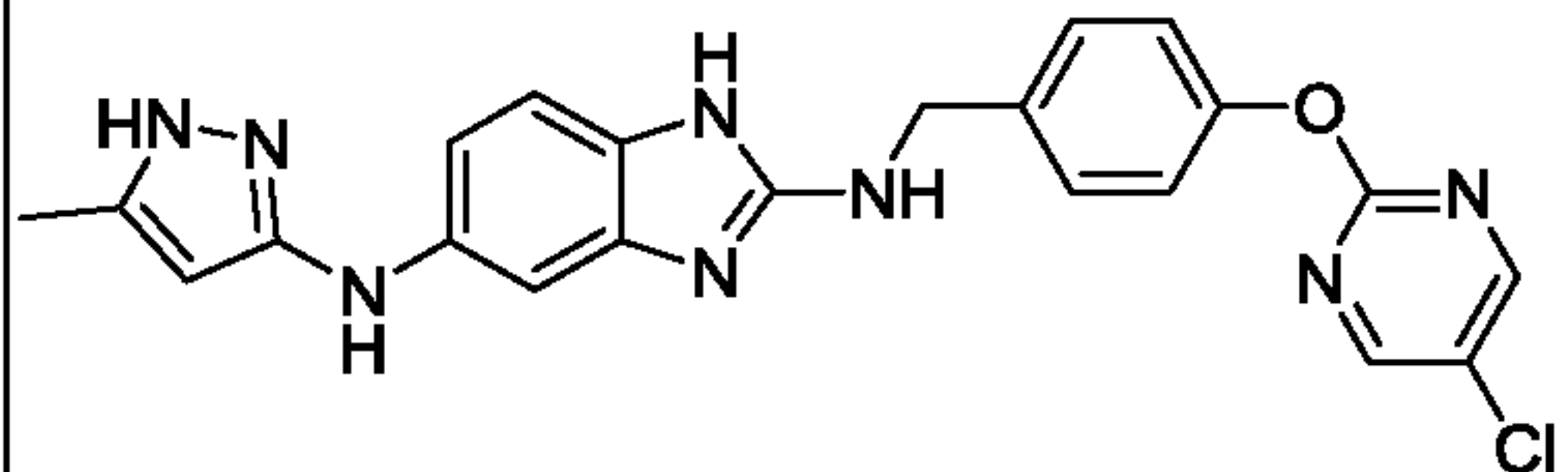
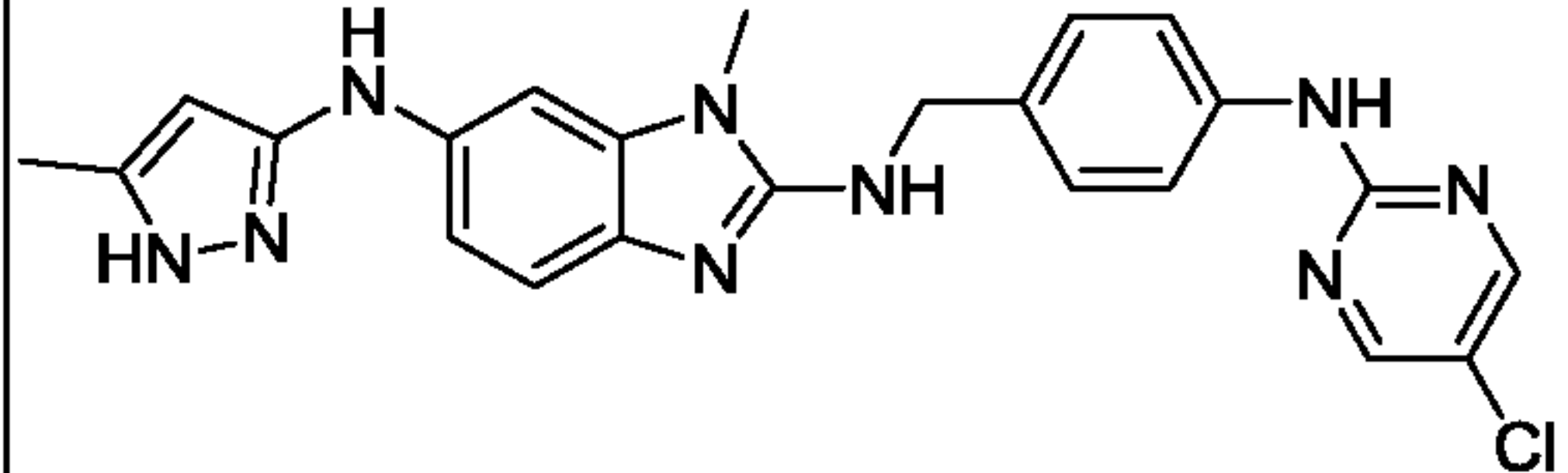
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 451 |    | off-white solid; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 8.61 (1H, d, J = 2.8 Hz), 8.34 (1H, d, J = 8.8 Hz), 8.09 (1H, dd, J = 8.8, 2.4 Hz), 8.02 (1H, d, J = 3.2 Hz), 7.83 (1H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.4 Hz), 6.85-6.95 (2H, m), 6.76 (1H, d, J = 3.6 Hz), 6.38 (1H, d, J = 1.6 Hz), 6.28 (1H, dd, J = 8.4, 2.0 Hz), 4.41-4.72 (4H, m), 3.43 (3H, s); LCMS: 99.6%, MS (ESI): m/z 403.2[M + H] <sup>+</sup> .                             |
| 452 |   | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.71 (2H, s), 7.46 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 6.80 (1H, d, J = 8.0 Hz), 6.60 (1H, d, J = 8.4 Hz), 6.32 (1H, d, J = 1.6 Hz), 6.22 (1H, dd, J = 8.4, 2.0 Hz), 4.79 (1H, q, J = 8.0 Hz), 4.50 (2H, brs), 3.43 (3H, s), 1.65-1.96 (2H, m), 0.93 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 409.2[M + H] <sup>+</sup> .                                              |
| 453 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 7.49 (2H, d, J = 8.8 Hz), 7.15 (2H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.4 Hz), 6.74 (1H, brs), 6.24 (1H, d, J = 1.6 Hz), 6.20 (1H, dd, J = 8.4, 2.0 Hz), 5.85 (1H, d, J = 6.8 Hz), 4.75-4.91 (3H, m), 4.45-4.61 (1H, m), 4.39 (2H, td, J = 6.0, 2.4 Hz), 3.49 (3H, s), 1.69-2.01 (2H, m), 0.95 (3H, t, J = 7.2 Hz); LCMS: 98.7%, MS (ESI): m/z 465.3[M + H] <sup>+</sup> . |
| 454 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.39 (1H, s), 7.44 (2H, d, J = 8.4 Hz), 7.16 (2H, d, J = 8.8 Hz), 6.87-6.94 (1H, m), 6.85 (1H, d, J = 8.0 Hz), 6.36 (1H, d, J = 2.0 Hz), 6.26 (1H, dd, J = 8.4, 2.0 Hz), 4.55 (2H, brs), 4.51 (2H, d, J = 5.6 Hz), 3.97 (3H, s), 3.41 (3H, s); LCMS: 100%, MS (ESI): m/z 411.1[M + H] <sup>+</sup> .                                                                                          |
| 455 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.48 (1H, d, J = 7.6 Hz), 7.95 (1H, s), 7.48 (2H, d, J = 8.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 6.91-6.98 (2H, m), 6.83 (1H, dd, J = 7.6, 2.4 Hz), 6.73 (1H, d, J = 2.4 Hz), 6.20-6.30 (2H, m), 5.83 (1H, d, J = 6.8 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.40 (2H, t, J = 6.0 Hz), 4.49-4.60 (3H, m), 3.45 (3H, s); LCMS: 97.2%, MS (ESI): m/z 475.0[M+H] <sup>+</sup> .                           |
| 456 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (2H, s), 7.45 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 6.90 (1H, t, J = 6.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.36 (1H, d, J = 2.0 Hz), 6.26 (1H, dd, J = 8.4, 2.0 Hz), 4.50-4.53 (4H, m), 3.41 (3H, s), 2.98 (6H, s); LCMS: 100%, MS (ESI): m/z 418.3[M + H] <sup>+</sup> .                                                                                                          |

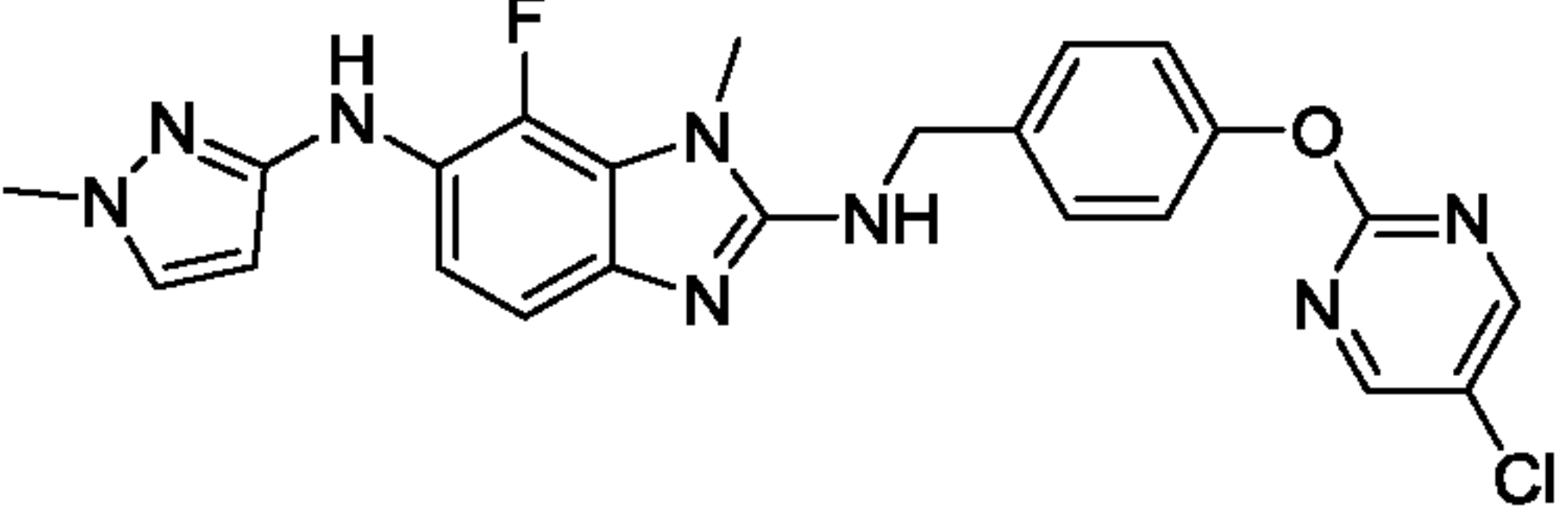
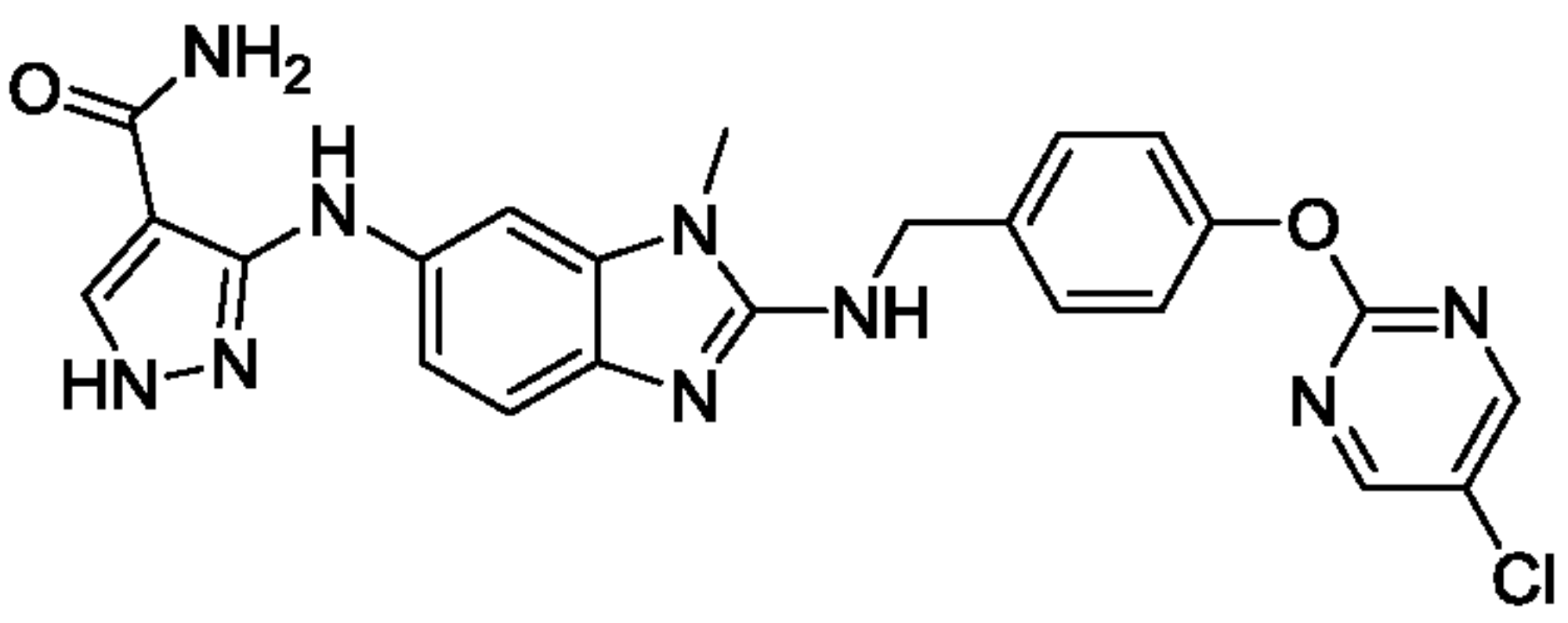
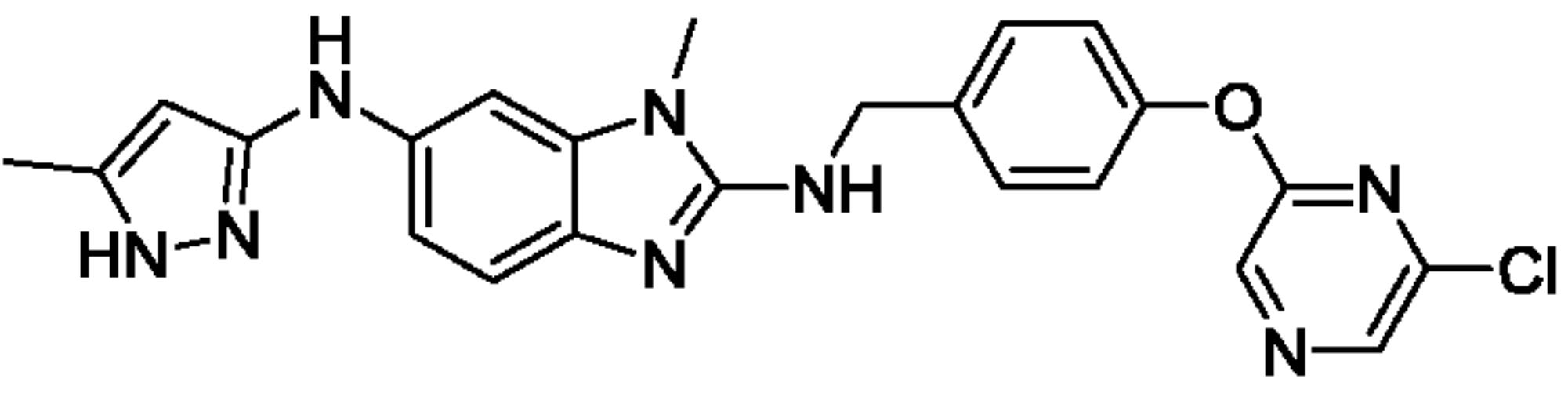
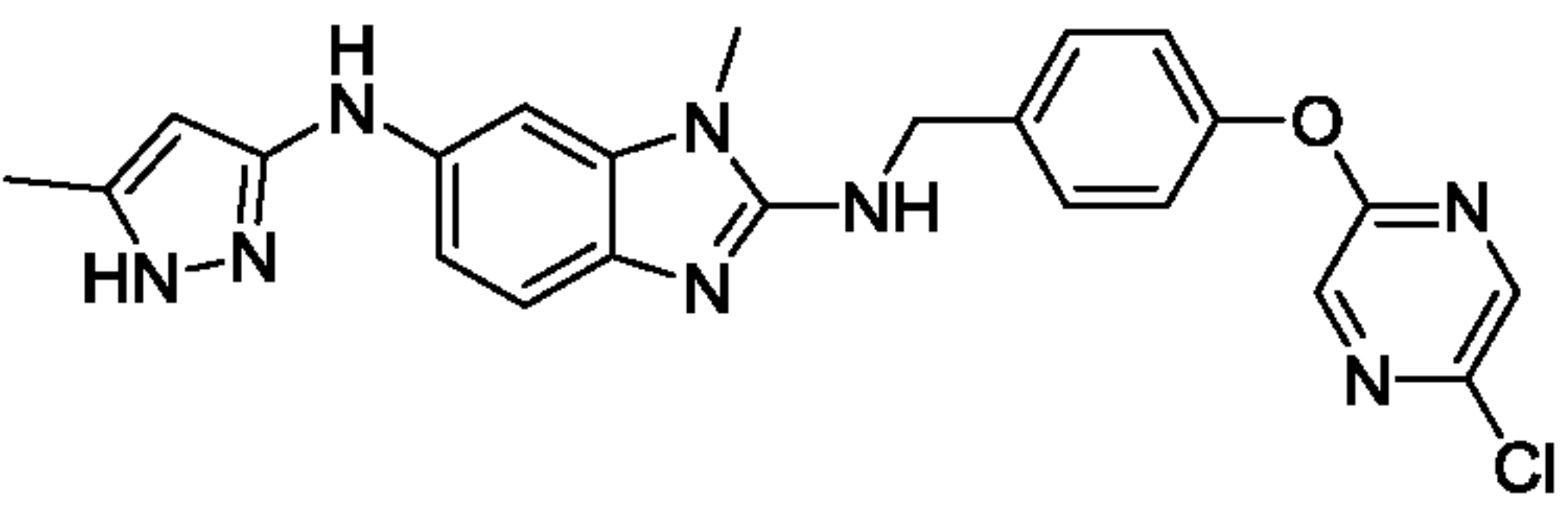
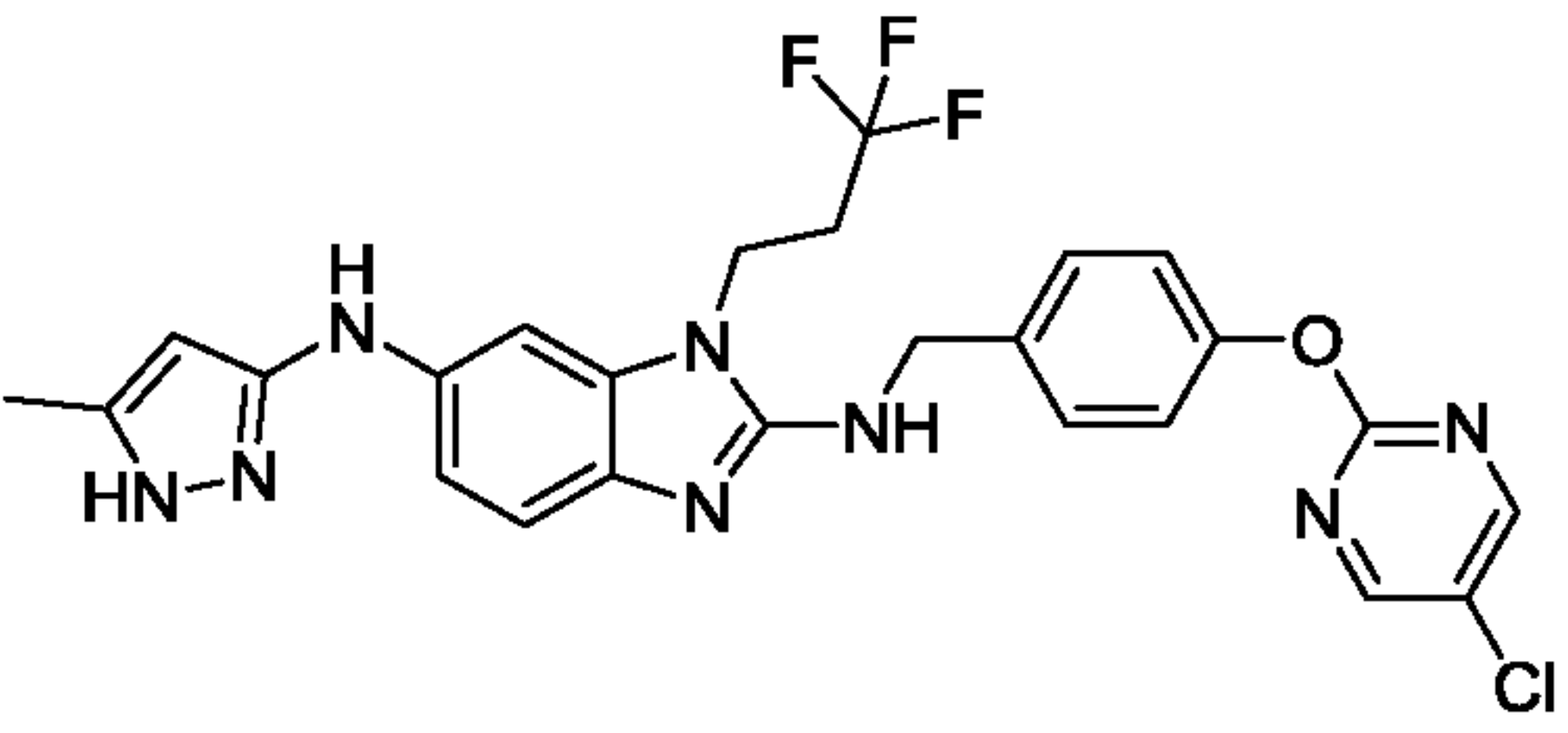
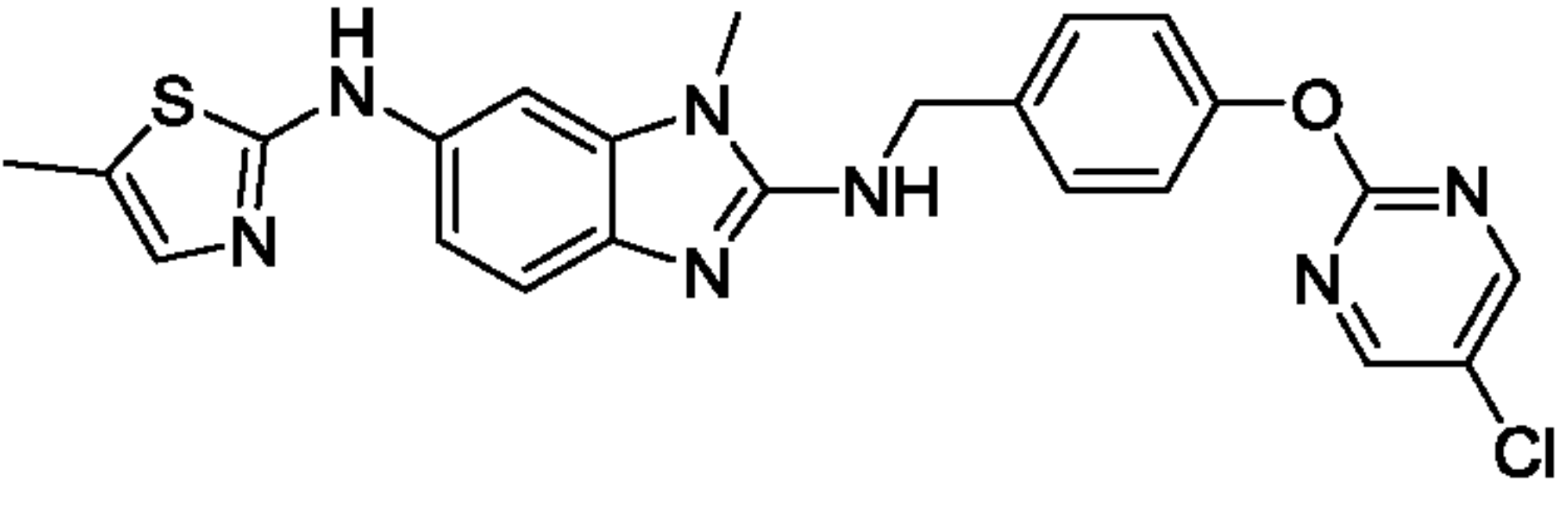
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 457 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.61 (1H, d, J = 2.4 Hz), 8.33 (1H, dd, J = 8.8 Hz), 8.08 (1H, dd, J = 8.8, 2.4 Hz), 8.01 (1H, d, J = 3.2 Hz), 7.82 (1H, d, J = 8.8 Hz), 7.64 (1H, s), 7.33 (1H, d, J = 8.4 Hz), 6.83-6.97 (2H, m), 6.75 (1H, d, J = 3.2 Hz), 6.25 (1H, s), 6.21 (1H, d, J = 8.4 Hz), 5.82 (1H, d, J = 7.6 Hz), 4.85 (2H, t, J = 6.4 Hz), 4.62 (2H, d, J = 6.0 Hz), 4.46-4.57 (1H, m), 4.40 (2H, t, J = 6.0 Hz), 3.45 (3H, s); LCMS: 97.8%, MS (ESI): m/z 459.1[M+H] <sup>+</sup> . |
| 458 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.80 (1H, s), 8.51 (2H, s), 7.61 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.77 (1H, t, J = 5.8 Hz), 6.36 (1H, d, J = 1.6 Hz), 6.26 (1H, dd, J = 8.4, 2.0 Hz), 4.56 (2H, brs), 4.44 (2H, d, J = 6.0 Hz), 3.40 (3H, s); LCMS: 98.5%, MS (ESI): m/z 380.1[M + H] <sup>+</sup> .                                                                                                                                                        |
| 459 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.39 (1H, s), 7.43 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 6.90-6.97 (2H, m), 6.25 (1H, d, J = 2.0 Hz), 6.21 (1H, dd, J = 8.4, 2.0 Hz), 5.82 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.45-4.56 (3H, m), 4.39 (2H, t, J = 6.0 Hz), 3.97 (3H, s), 3.44 (3H, s); LCMS: 99.5%, MS (ESI): m/z 467.1[M + H] <sup>+</sup> .                                                                                                                                      |
| 460 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.95 (2H, s), 7.74-7.77 (2H, m), 7.54-7.59 (2H, m), 7.46 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 6.90 (1H, t, J = 5.8 Hz), 6.87 (1H, d, J = 8.0 Hz), 6.37 (1H, d, J = 2.0 Hz), 6.27 (1H, dd, J = 8.4, 2.0 Hz), 4.47-4.58 (4H, m), 3.42 (3H, s); LCMS: 100%, MS (ESI): m/z 457.1[M+H] <sup>+</sup> .                                                                                                                                                          |
| 461 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.80 (1H, brs), 8.51 (2H, s), 7.61 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz), 6.93 (1H, d, J = 8.4 Hz), 6.81 (1H, t, J = 5.8 Hz), 6.24 (1H, d, J = 1.6 Hz), 6.20 (1H, dd, J = 8.4, 1.6 Hz), 5.82 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.48-4.56 (1H, m), 4.45 (2H, d, J = 6.0 Hz), 4.36-4.42 (2H, t, J = 5.8 Hz), 3.43 (3H, s); LCMS: 99.7%, MS (ESI): m/z 436.1[M + H] <sup>+</sup> .                                                                   |
| 462 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.96 (1H, s), 8.65 (1H, brs), 7.47 (2H, d, J = 8.4 Hz), 7.18 (2H, d, J = 8.8 Hz), 6.92 (1H, brs), 6.88 (1H, d, J = 8.4 Hz), 6.37 (1H, d, J = 2.0 Hz), 6.27 (1H, dd, J = 8.0, 2.0 Hz), 4.50-4.70 (4H, m), 3.43 (3H, s), 2.80(3H, d, J = 4.8 Hz); LCMS: 99.3%, MS (ESI): m/z 404.2 [M + H] <sup>+</sup> .                                                                                                                                                           |

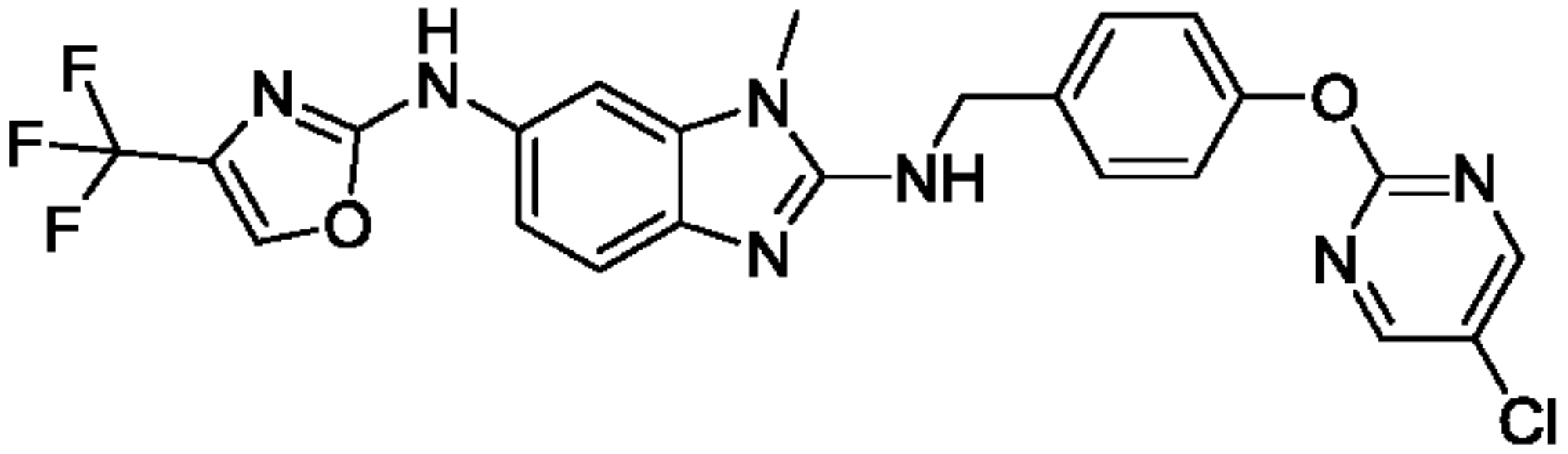
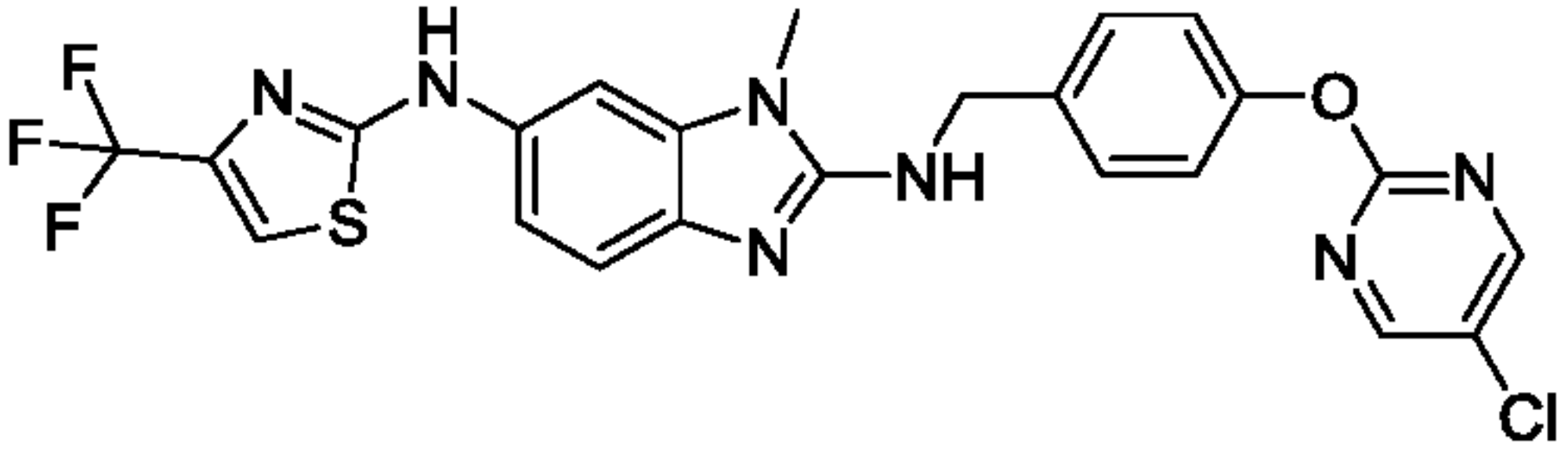
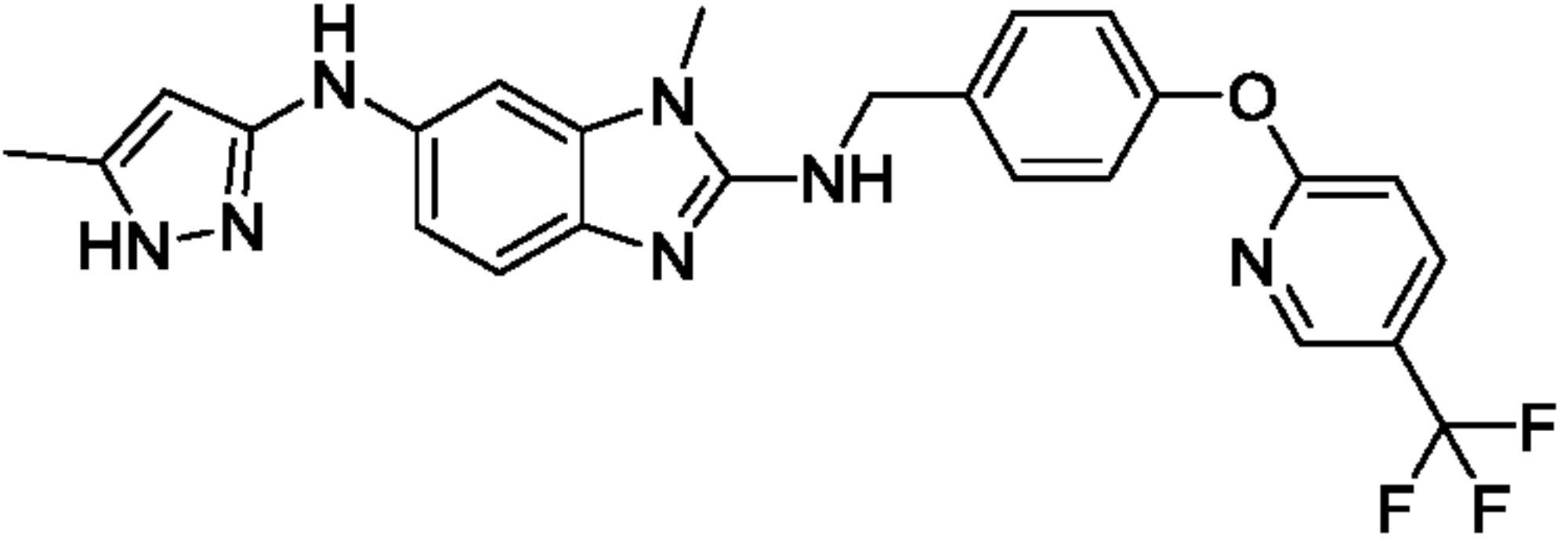
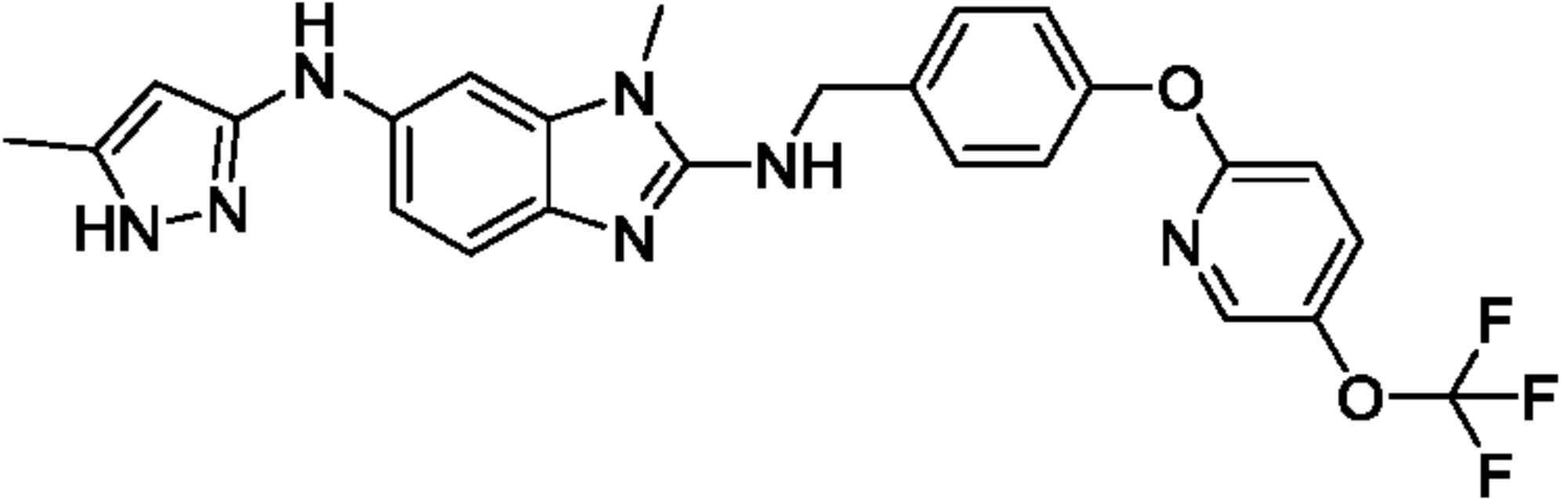
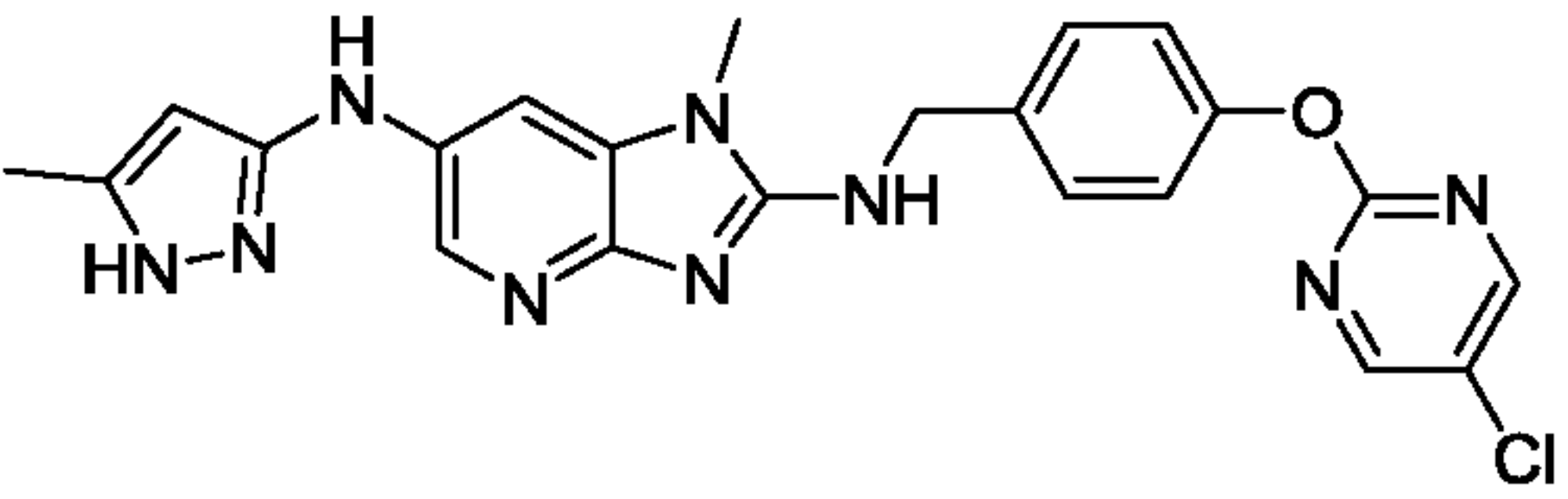
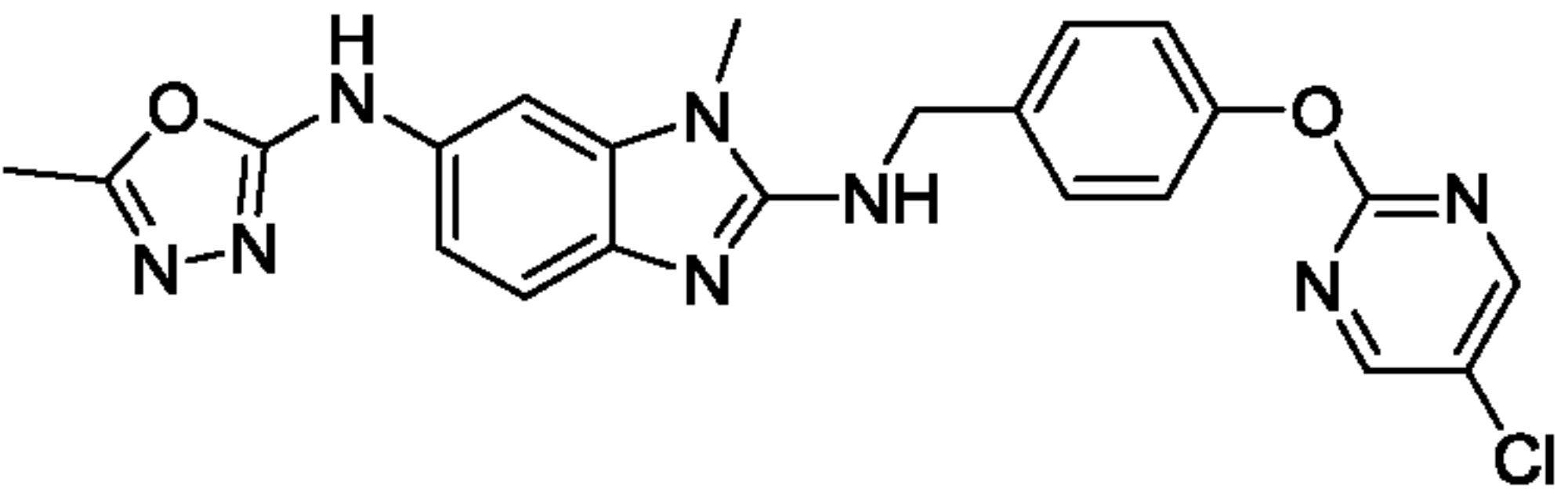
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 463 |    | brown powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.40 (2H, s), 7.40 (2H, d, J = 8.4 Hz), 7.26 (2H, d, J = 8.4 Hz), 6.90 (1H, t, J = 5.8 Hz), 6.86 (1H, d, J = 8.4 Hz), 6.36 (1H, d, J = 1.6 Hz), 6.26 (1H, dd, J = 8.4, 1.6 Hz), 4.59 (2H, brs), 4.50 (2H, d, J = 5.6 Hz), 3.41 (6H, s); LCMS: 100%, MS (ESI): m/z 394.2[M+H] <sup>+</sup> .                                                                                |
| 464 |    | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (2H, s), 7.90 (1H, d, J = 3.6 Hz), 7.59 (1H, s), 7.49 (1H, d, J = 1.6 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.34 (1H, d, J = 6.8 Hz), 7.10-7.19 (4H, m), 7.05 (1H, d, J = 8.8 Hz), 6.57-6.62 (1H, m), 4.57 (2H, d, J = 5.6 Hz), 3.49 (3H, s), 2.22 (3H, s); LCMS: 96.4 %, MS (ESI): m/z 472.2[M+ H] <sup>+</sup> .                                                          |
| 465 |  | pale yellow solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.74 (2H, s), 7.91 (1H, brs), 7.47 (2H, d, J = 8.4 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.04 (1H, t, J = 6.0 Hz), 6.99 (1H, d, J = 8.4 Hz), 6.84 (1H, dd, J = 8.4, 2.0 Hz), 5.58 (1H, s), 4.55 (2H, d, J = 5.6 Hz), 3.60 (3H, s), 3.48 (3H, s), 2.19 (3H, s); LCMS: 98.3 %, MS (ESI): m/z 475.3[M+ H] <sup>+</sup> .                              |
| 466 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1H, brs), 8.17 (1H, d, J = 2.0 Hz), 7.90-7.95 (2H, m), 7.44 (2H, d, J = 8.8 Hz), 7.32-7.35 (1H, m), 7.04-7.15 (3H, m), 6.92-7.04 (2H, m), 6.77 (1H, d, J = 8.0 Hz), 5.55 (1H, s), 4.54 (2H, d, J = 6.0 Hz), 3.46 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 460.3[M + H] <sup>+</sup> .                                                                   |
| 467 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1H, s), 8.95 (2H, s), 7.92 (1H, s), 7.75 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.34 (1H, s), 7.17 (2H, d, J = 8.0 Hz), 7.01 (1H, t, J = 5.6 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 7.2 Hz), 5.55 (1H, s), 4.55 (2H, d, J = 5.6 Hz), 3.47 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 537.1[M+H] <sup>+</sup> . |
| 468 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.74 (2H, s), 8.38 (1H, brs), 7.47 (2H, d, J = 8.8 Hz), 7.24 (1H, d, J = 2.0 Hz), 7.17 (2H, d, J = 8.4 Hz), 7.12 (1H, brs), 7.05 (2H, d, J = 8.4 Hz), 6.89 (1H, dd, J = 8.4, 2.0 Hz), 6.27 (1H, s), 4.57 (2H, d, J = 5.6 Hz), 3.85 (3H, s), 3.51 (3H, s); LCMS: 100%, MS (ESI): m/z 529.4[M + H] <sup>+</sup> .                                                      |

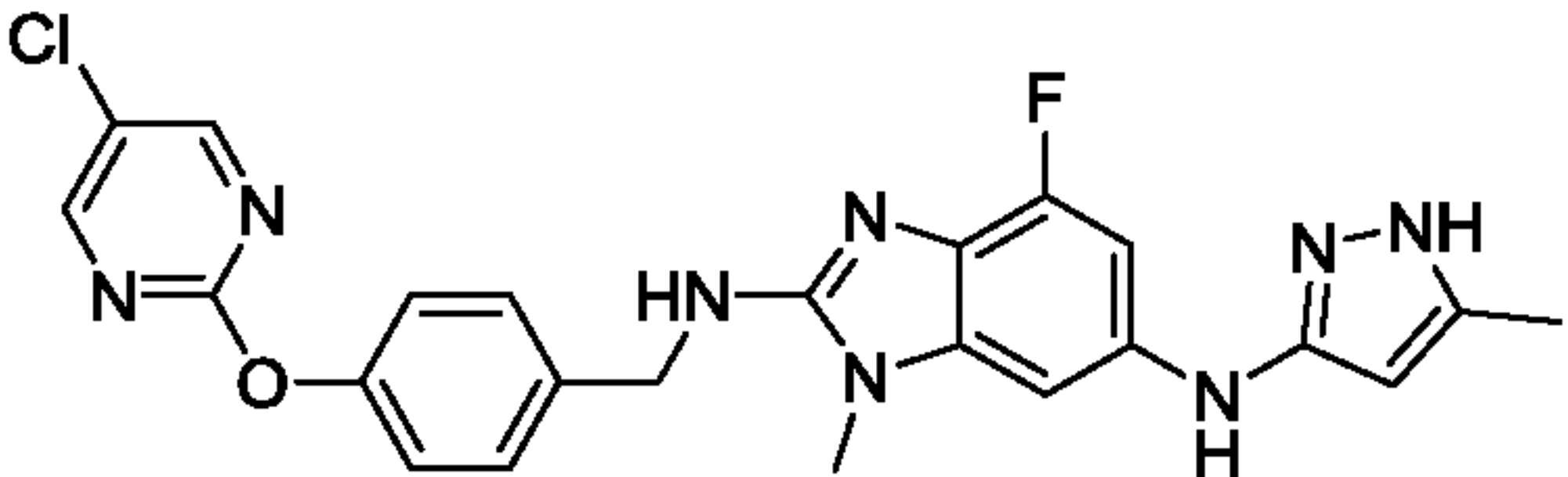
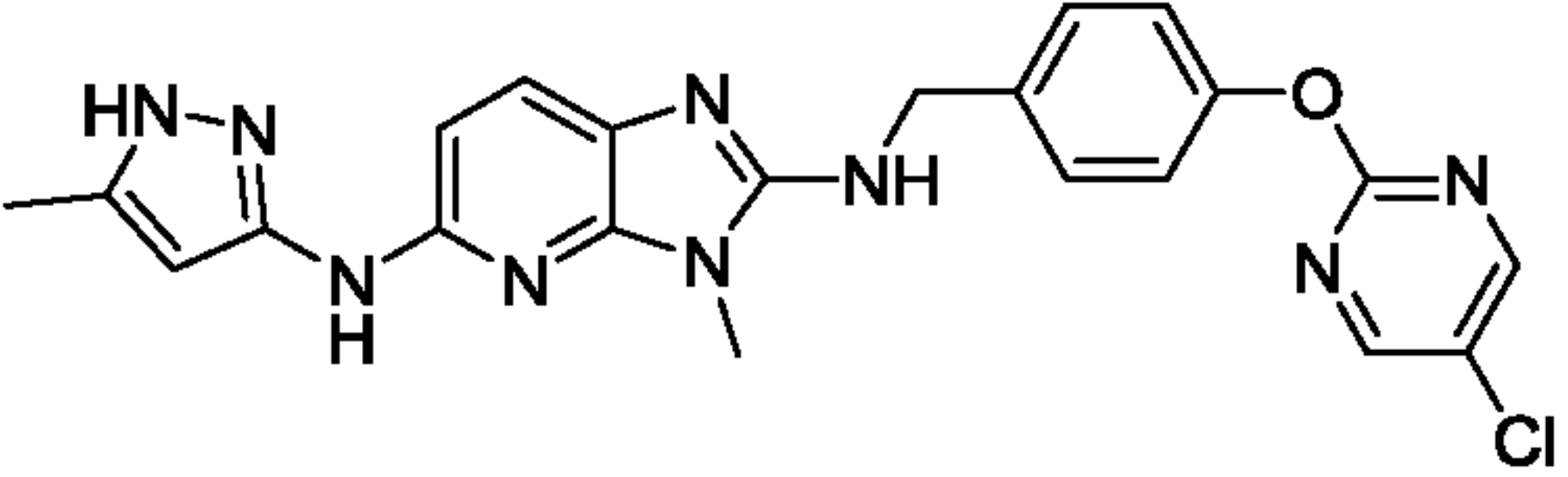
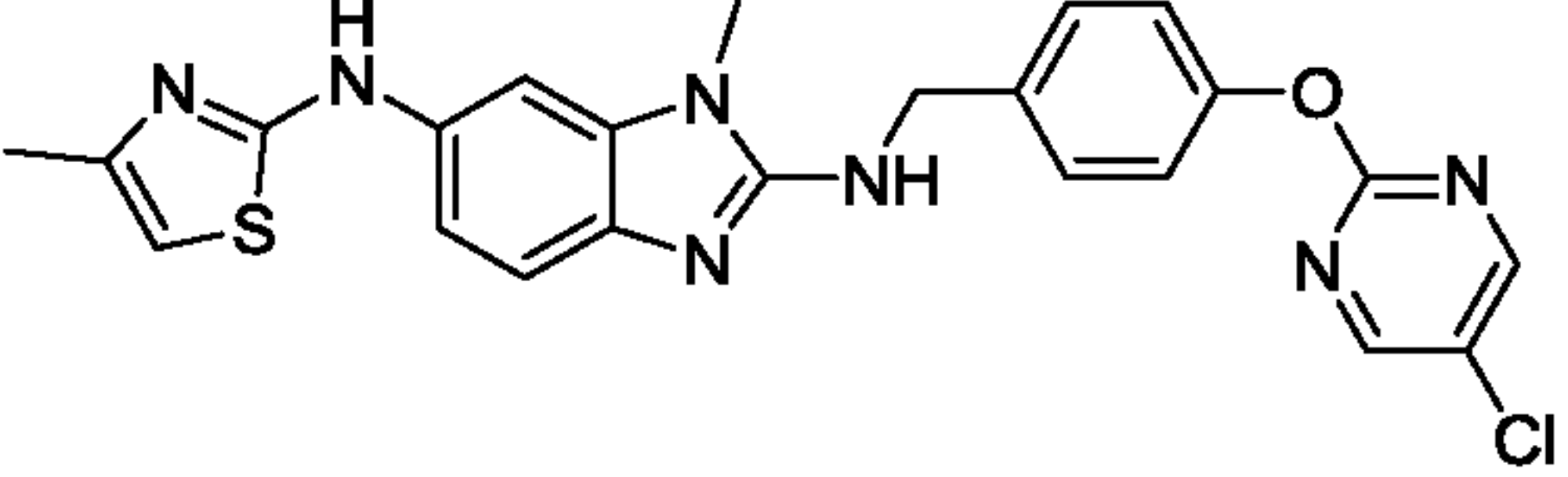
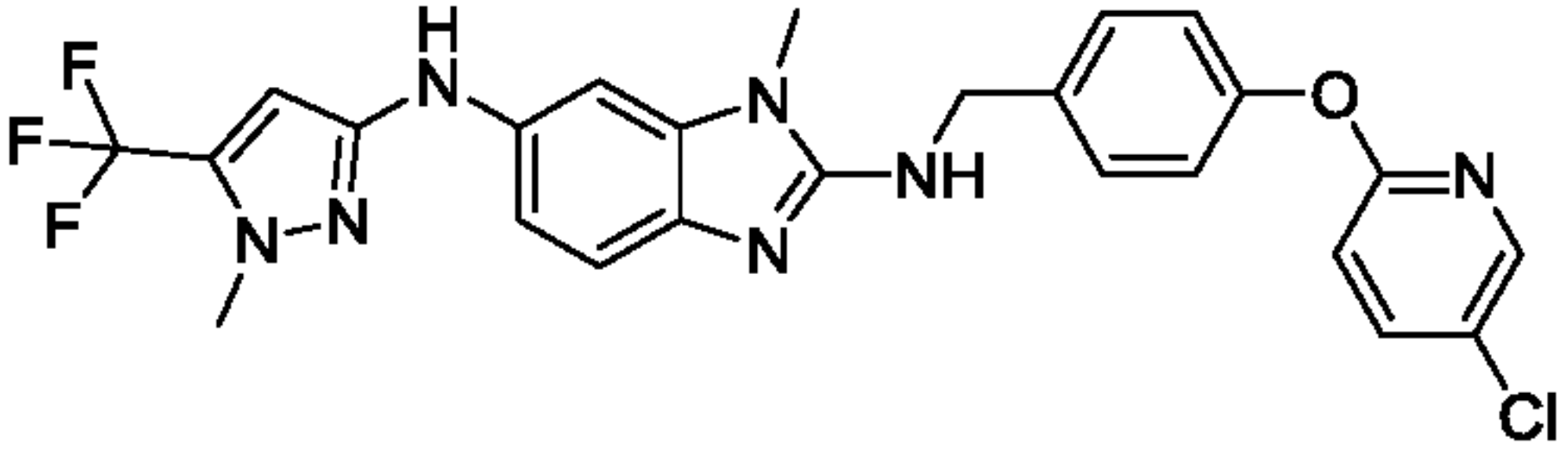
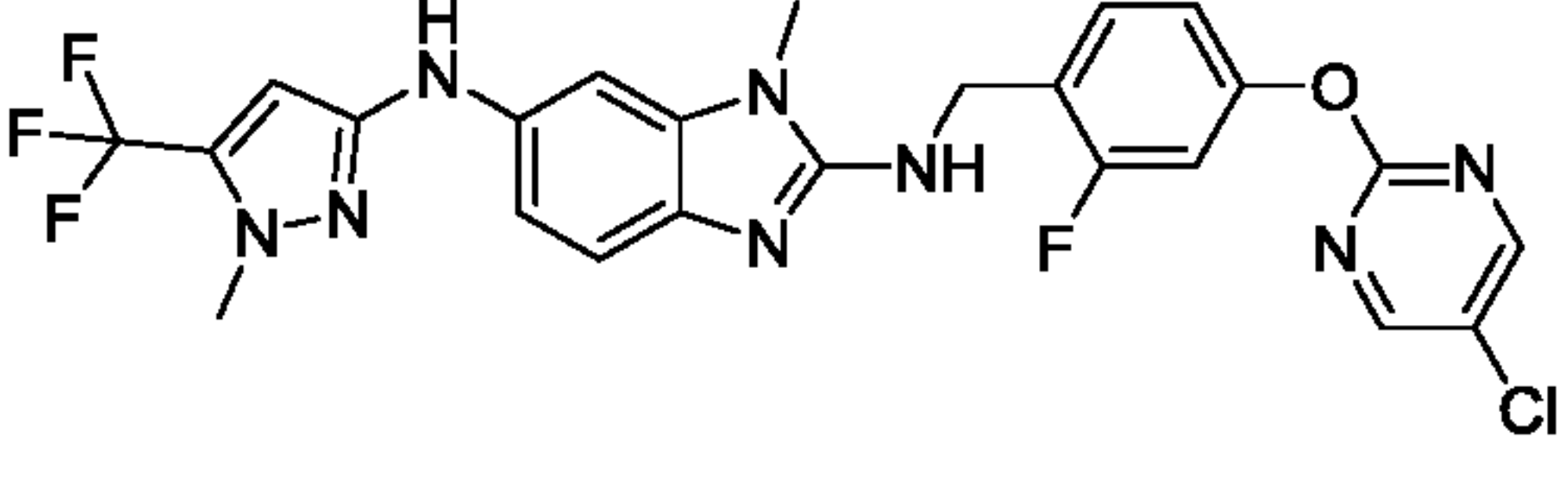
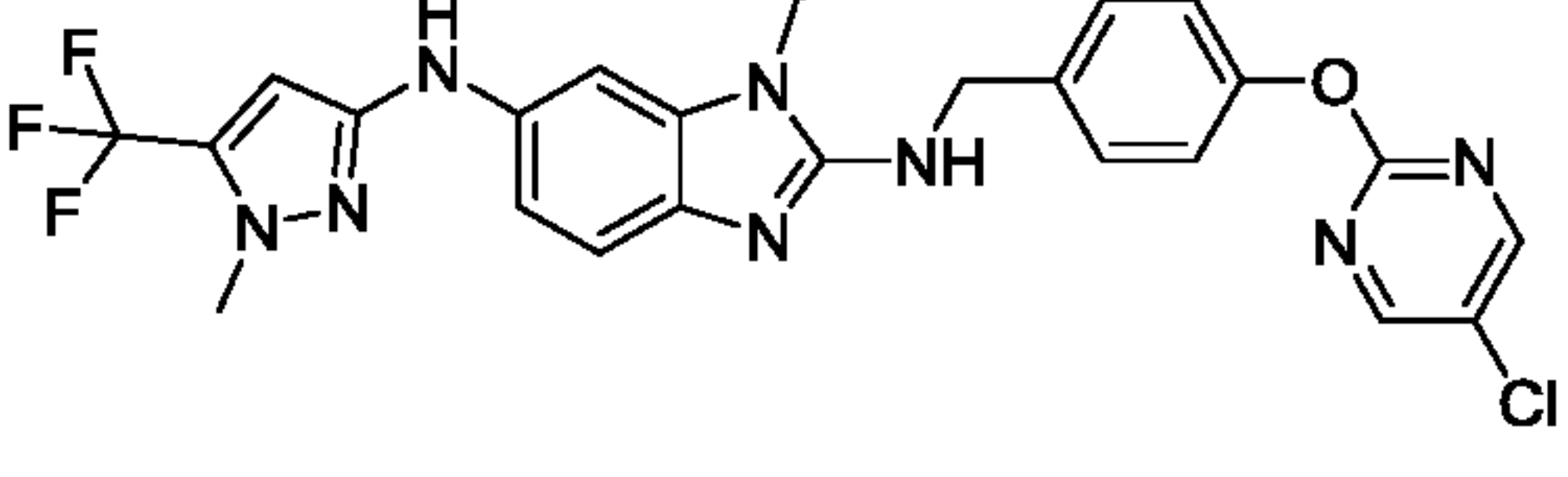
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 469 |    | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.57 (1H, brs), 8.74 (2H, s), 7.94 (1H, brs), 7.35-7.51 (3H, m), 7.17 (2H, d, J = 8.4 Hz), 7.01 (1H, brs), 6.99 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 8.8 Hz), 5.53 (1H, s), 4.56 (2H, d, J = 5.6 Hz), 3.46 (3H, s), 1.26 (9H, s); LCMS: 97.9 %, MS (ESI): m/z 503.2[M + H] <sup>+</sup> .                      |
| 470 |    | yellow solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.52 (1H, brs), 8.72 (2H, s), 8.06 (1H, brs), 7.93 (1H, brs), 7.40-7.53 (3H, m), 7.18 (2H, d, J = 8.4 Hz), 7.01 (1H, d, J = 8.4 Hz), 6.84 (1H, d, J = 8.0), 5.53 (1H, s), 4.51 (2H, d, J = 3.6 Hz), 2.15 (3H, s); LCMS: 95.9%, MS (ESI): m/z 447.2[M + H] <sup>+</sup> .                                            |
| 471 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1H, brs), 8.40 (2H, s), 7.91 (1H, brs), 7.41 (2H, d, J = 8.4 Hz), 7.33 (1H, s), 7.26 (2H, d, J = 8.0 Hz), 6.93-7.05 (2H, m), 6.77 (1H, d, J = 7.2 Hz), 5.55 (1H, s), 4.53 (2H, d, J = 5.2 Hz), 3.46 (3H, s), 3.42 (3H, s), 2.16 (3H, s); LCMS: 97.7%, MS (ESI): m/z 474.2[M + H] <sup>+</sup> .              |
| 472 |  | off-white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (2H, s), 7.21-7.39 (3H, m), 7.08 (2H, d, J = 8.4 Hz), 6.84 (1H, d, J = 8.0 Hz), 6.37 (1H, brs), 6.26 (1H, d, J = 7.6 Hz), 4.55 (2H, brs), 3.43 (3H, s), 1.20-1.38 (4H, m); LCMS: 99.8%, MS (ESI): m/z 407.1[M + H] <sup>+</sup> .                                                                            |
| 473 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.49 (1H, brs), 8.77 (2H, s), 7.95 (1H, brs), 7.60 (1H, d, J = 1.6 Hz), 7.46 (1H, dd, J = 8.4, 2.0 Hz), 7.32-7.42 (2H, m), 7.10 (1H, brs), 6.99 (1H, d, J = 8.4 Hz), 6.75-6.80 (1H, m), 5.55 (1H, s), 4.55 (2H, d, J = 4.8 Hz), 3.47 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 495.2 [M + H] <sup>+</sup> . |
| 474 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.42 (1H, brs), 8.72 (2H, s), 7.44 (2H, d, J = 8.8 Hz), 7.21-7.34 (2H, m), 7.14 (2H, d, J = 8.8 Hz), 7.02 (1H, brs), 6.95 (1H, d, J = 8.4 Hz), 6.76-6.88 (1H, m), 4.53 (2H, d, J = 5.6 Hz), 3.43 (3H, s), 2.08 (3H, s), 1.82 (3H, s); LCMS: 100 %, MS (ESI): m/z 475.2[M + H] <sup>+</sup> .                    |

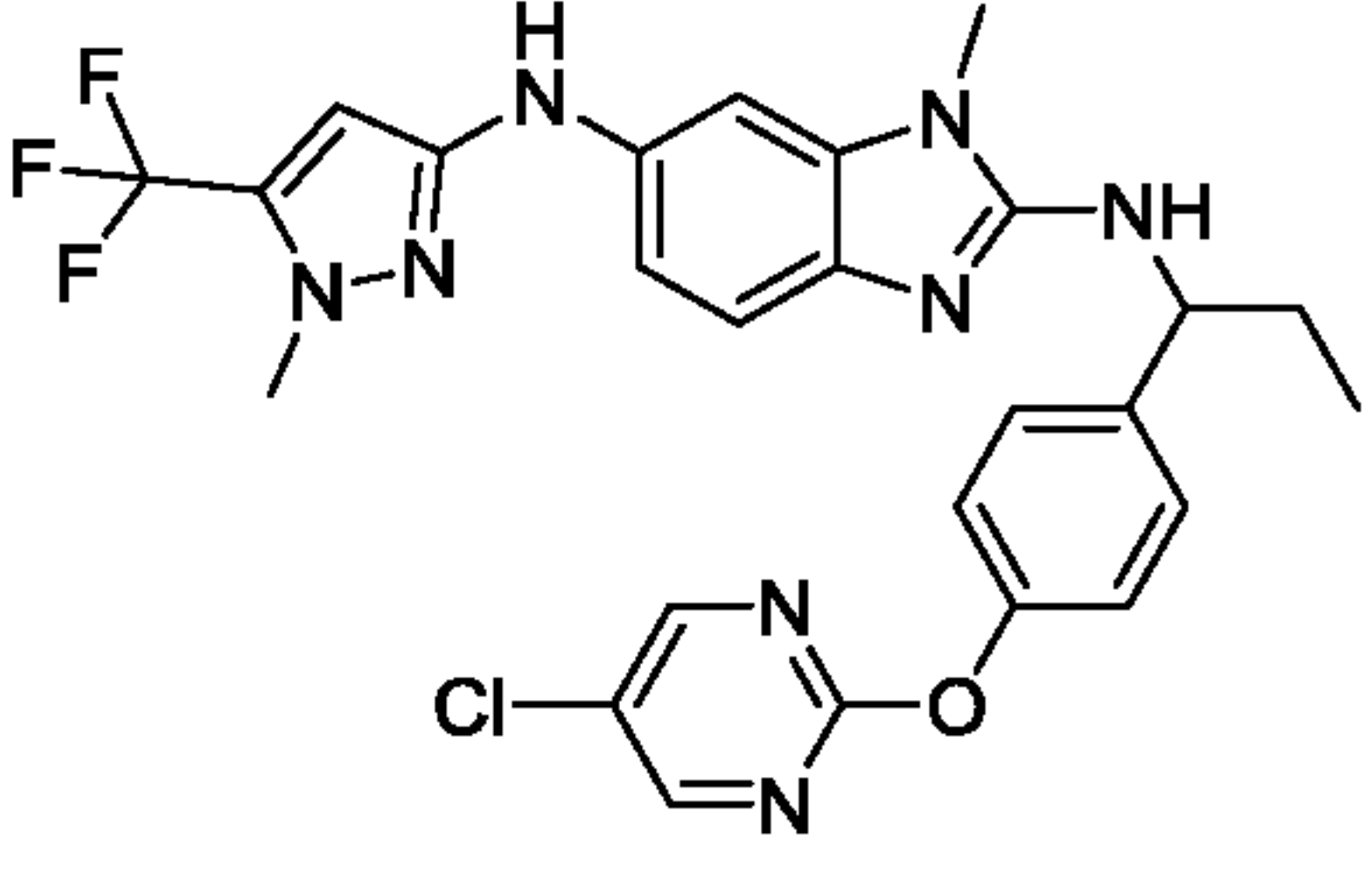
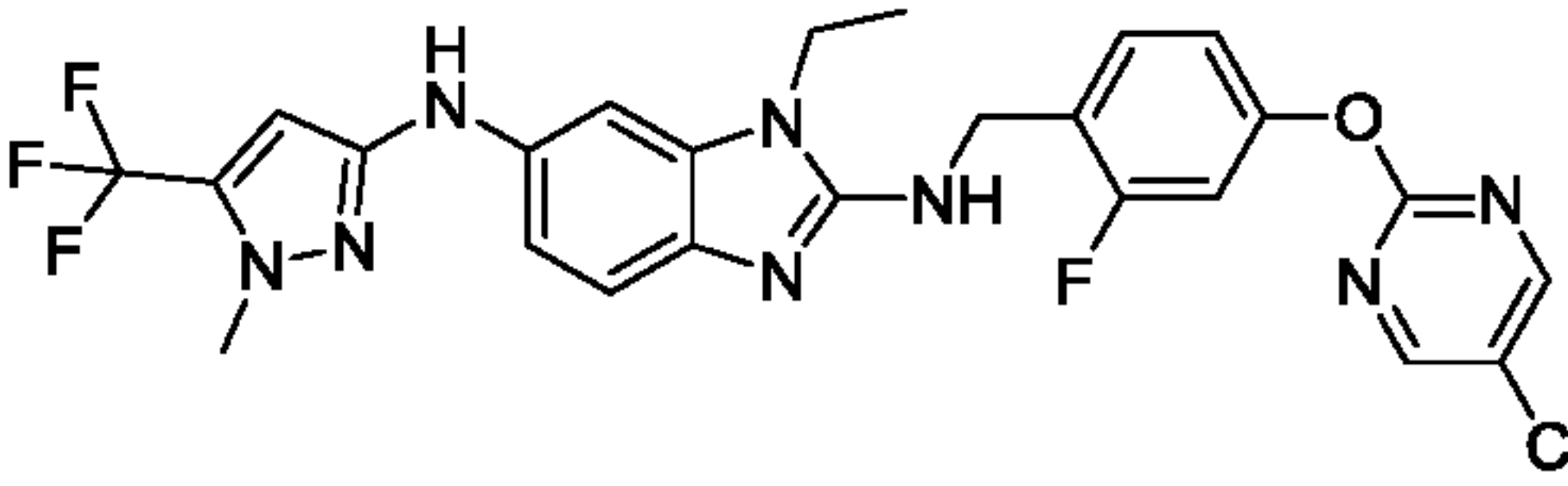
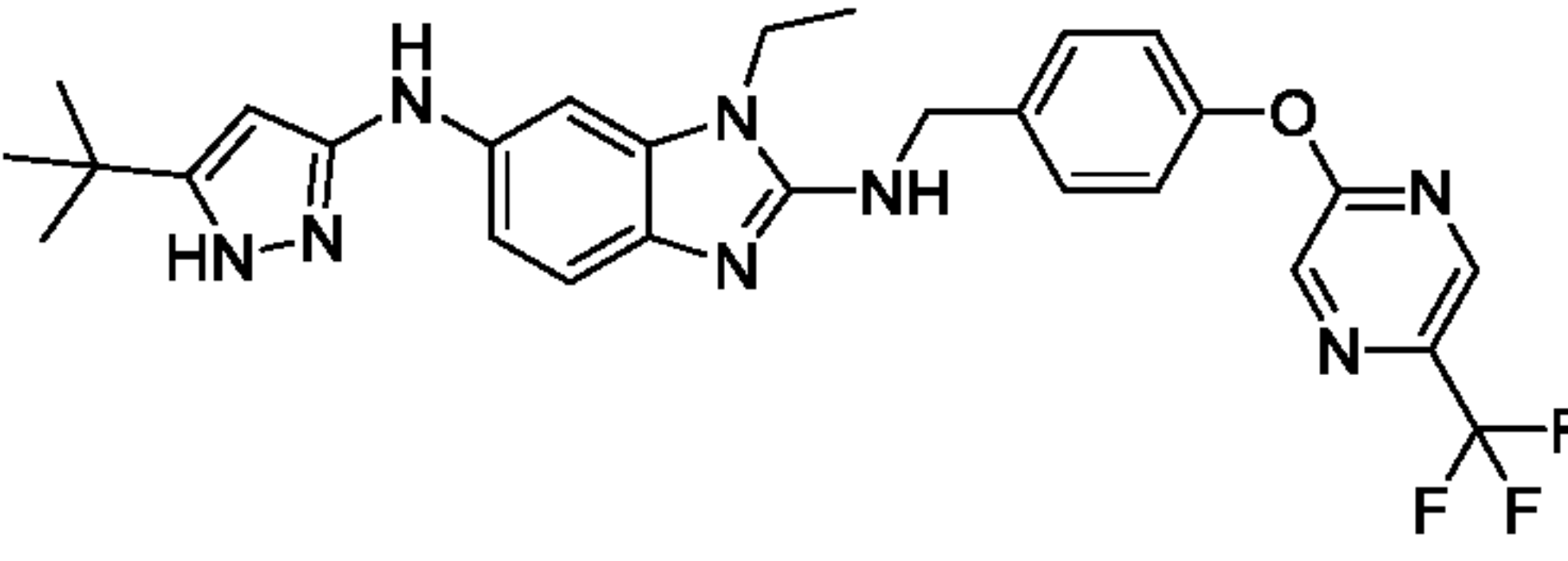
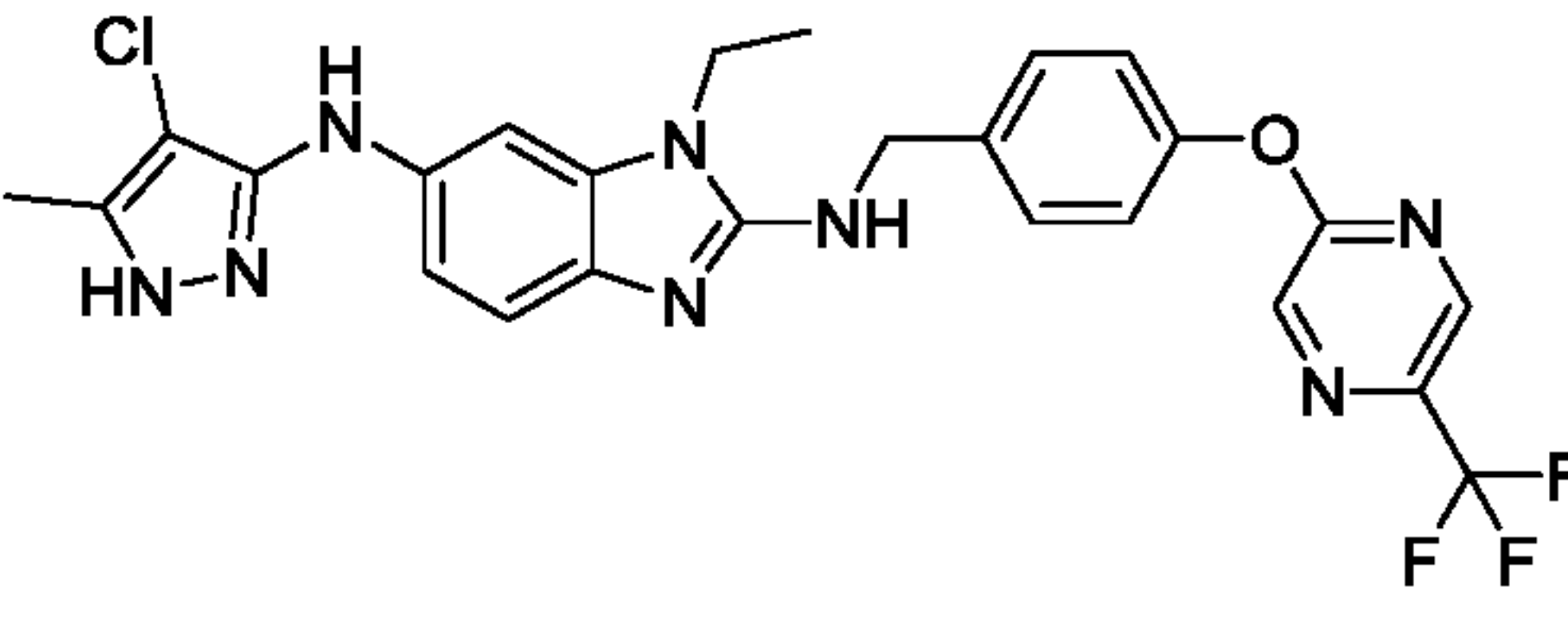
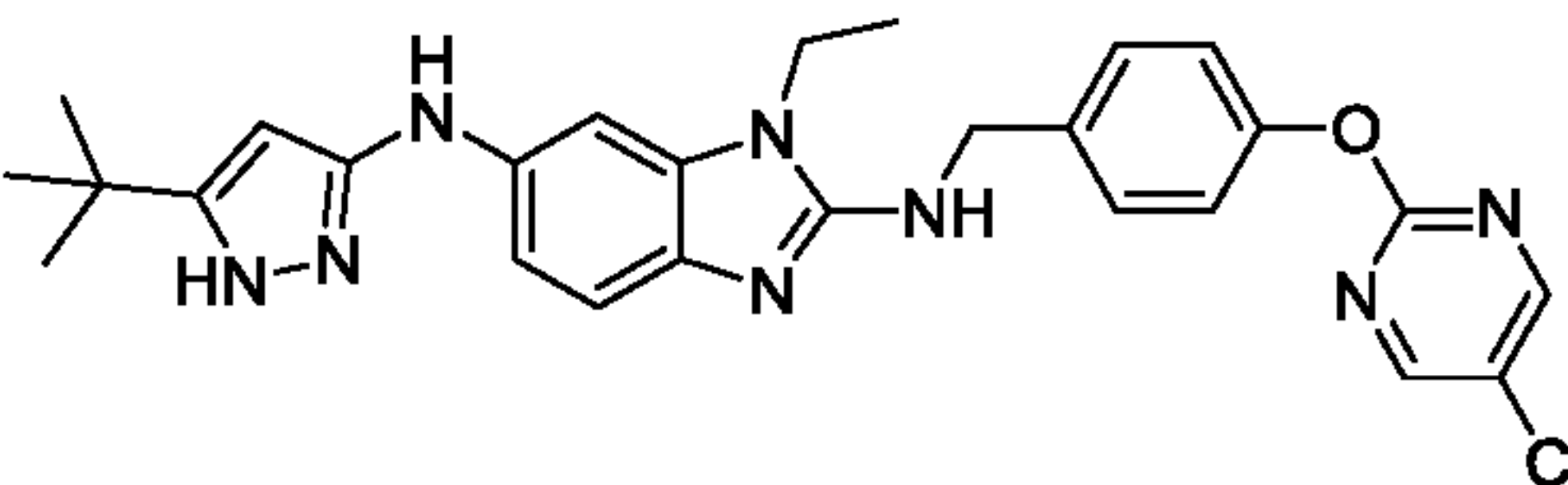
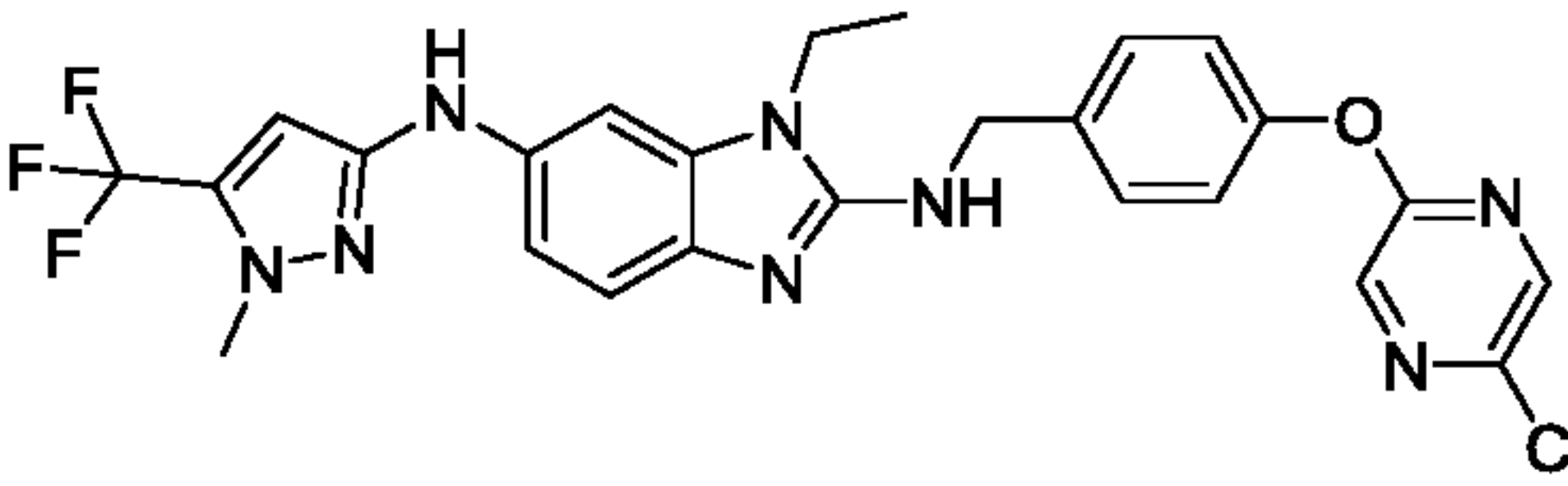
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 475 |  | brown powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 12.78 (1H, brs), 8.73 (2H, s), 8.27 (1H, brs), 7.45 (2H, d, J = 8.4 Hz), 7.11-7.23 (3H, m), 7.07 (1H, d, J = 8.0 Hz), 6.85 (1H, brs), 6.66 (1H, d, J = 8.0 Hz), 6.08 (1H, s), 4.56 (2H, d, J = 6.0 Hz), 3.50 (3H, s); LCMS: 100%, MS (ESI): m/z 515.1[M+H] <sup>+</sup> .                                                                                            |
| 476 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.49 (1H, brs), 8.72 (2H, s), 7.91 (1H, brs), 7.43 (2H, d, J = 8.8 Hz), 7.37 (1H, s), 7.14 (2H, d, J = 8.4 Hz), 7.04 (1H, brs), 6.96 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 8.0 Hz), 5.53 (1H, s), 4.54 (2H, d, J = 6.0 Hz), 3.96 (2H, q, J = 7.2 Hz), 2.14 (3H, s), 1.22 (3H, t, J = 6.8 Hz); LCMS: 100 %, MS (ESI): m/z 475.2[M + H] <sup>+</sup> . |
| 477 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.46 (1H, brs), 8.72 (2H, s), 7.89 (1H, s), 7.48 (2H, d, J = 8.4 Hz), 7.29 (1H, s), 7.13 (2H, d, J = 8.4 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.70-6.74 (2H, m), 5.54 (1H, s), 4.80-4.87 (1H, m), 3.48 (3H, s), 2.15 (3H, s), 1.76-1.94 (2H, m), 0.94 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 489.2[M + H] <sup>+</sup> .                             |
| 478 |  | red powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.49 (1H, brs), 8.72 (2H, s), 7.91 (1H, brs), 7.40 (1H, brs), 7.21-7.38 (3H, m), 7.08 (2H, d, J = 8.8 Hz), 6.95 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 8.0 Hz), 5.55 (1H, s), 3.48 (3H, s), 2.16 (3H, s), 1.20-1.39 (4H, m); LCMS: 89.0%, MS (ESI): m/z 487.2[M + H] <sup>+</sup> .                                                                           |
| 479 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 11.48 (1H, brs), 9.09 (2H, s), 7.91 (1H, brs), 7.48 (2H, d, J = 8.8 Hz), 7.34 (1H, s), 7.21 (2H, d, J = 8.4 Hz), 7.03 (1H, t, J = 6.0 Hz), 6.97 (1H, d, J = 8.0 Hz), 6.77 (1H, d, J = 8.0 Hz), 5.55 (1H, s), 4.56 (2H, d, J = 6.0 Hz), 3.46 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 495.2[M + H] <sup>+</sup> .                                         |
| 480 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.74 (2H, s), 7.79 (1H, brs), 7.59 (1H, brs), 7.42-7.50 (3H, m), 7.21 (3H, d, J = 8.4 Hz), 6.94 (1H, d, J = 9.2 Hz), 5.76 (1H, d, J = 2.0 Hz), 4.59 (2H, d, J = 6.0 Hz), 3.70 (3H, s); LCMS: 99.0%, MS (ESI): m/z 465.1[M + H] <sup>+</sup> .                                                                                                                    |

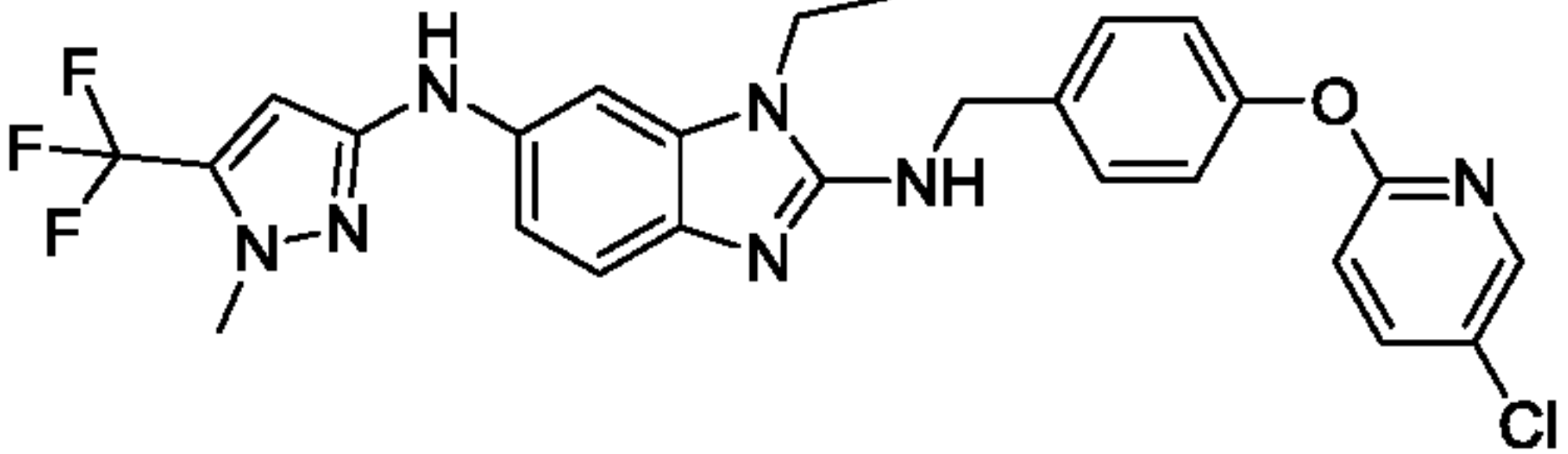
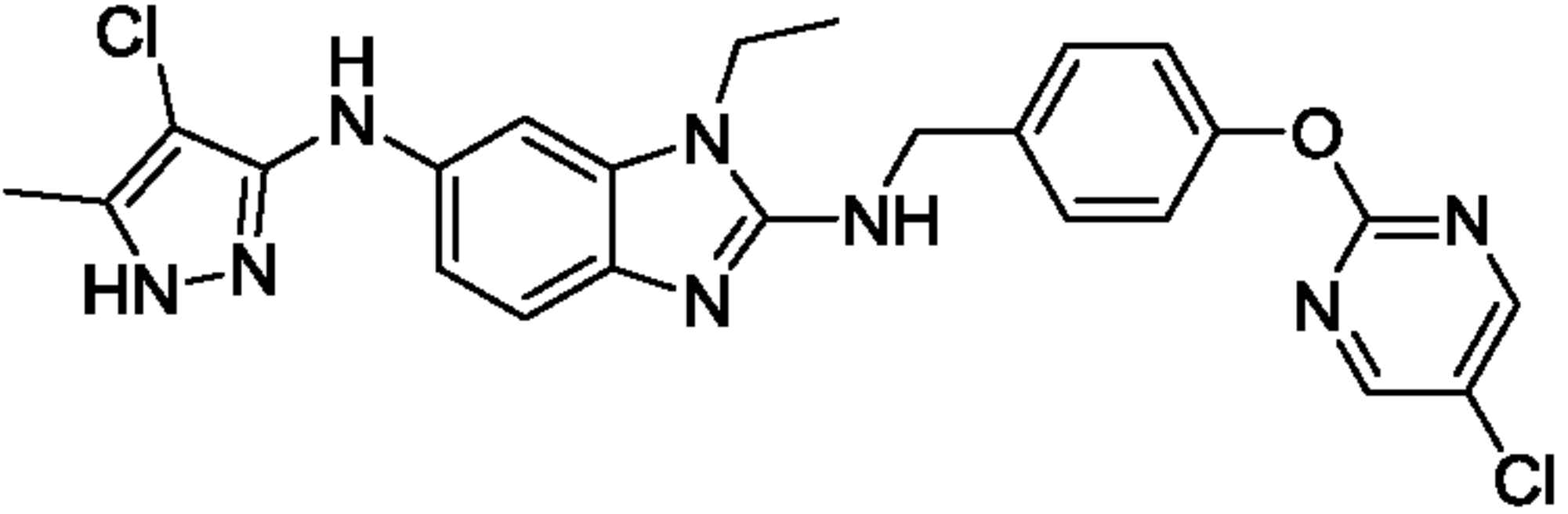
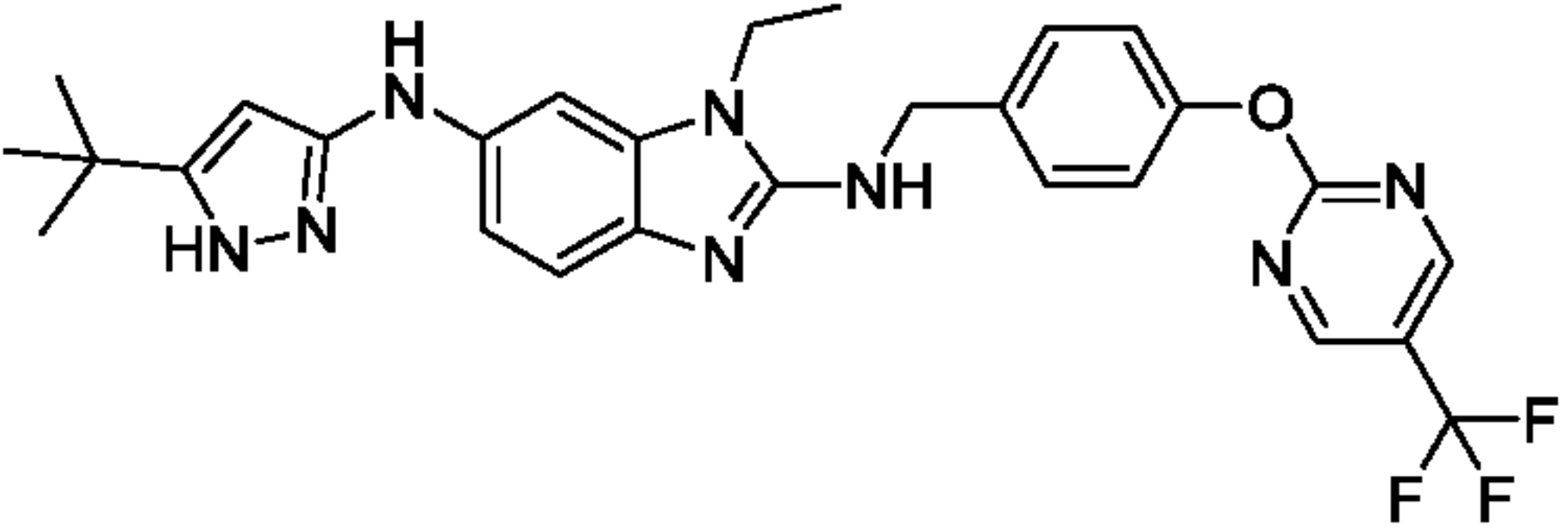
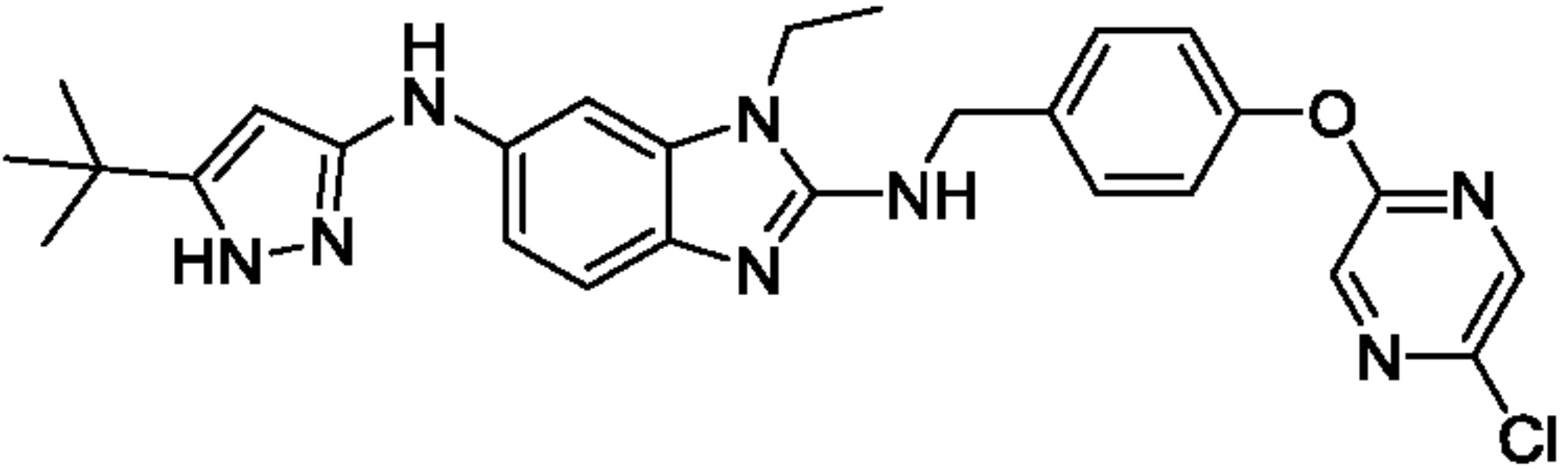
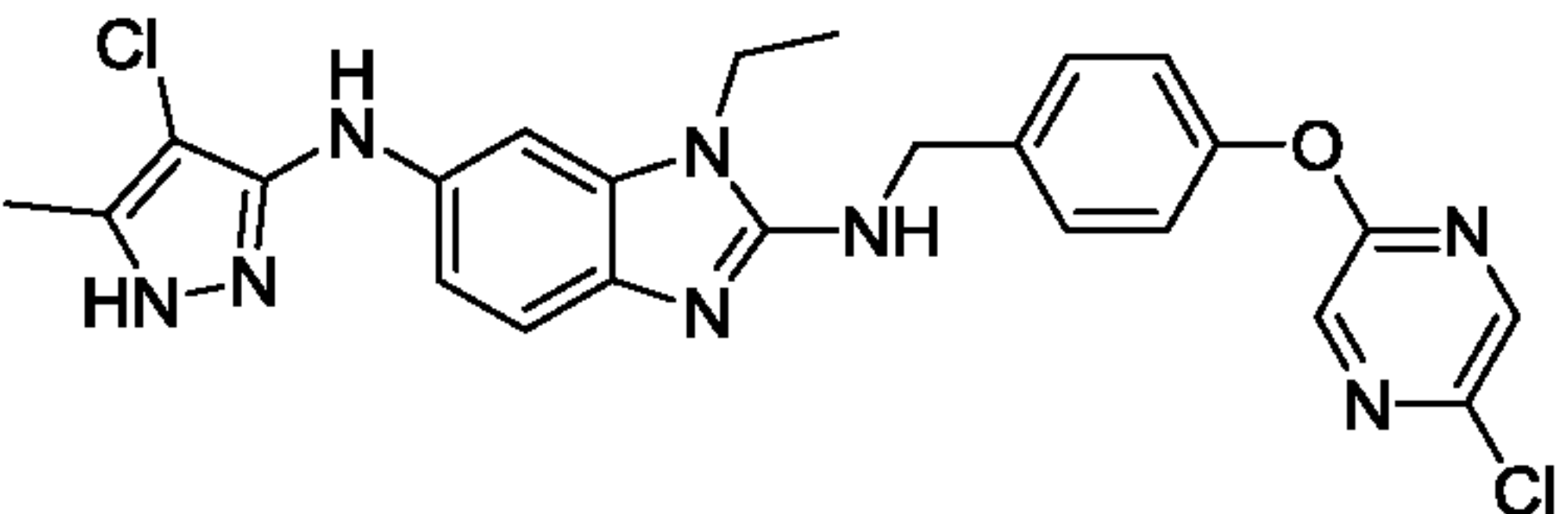
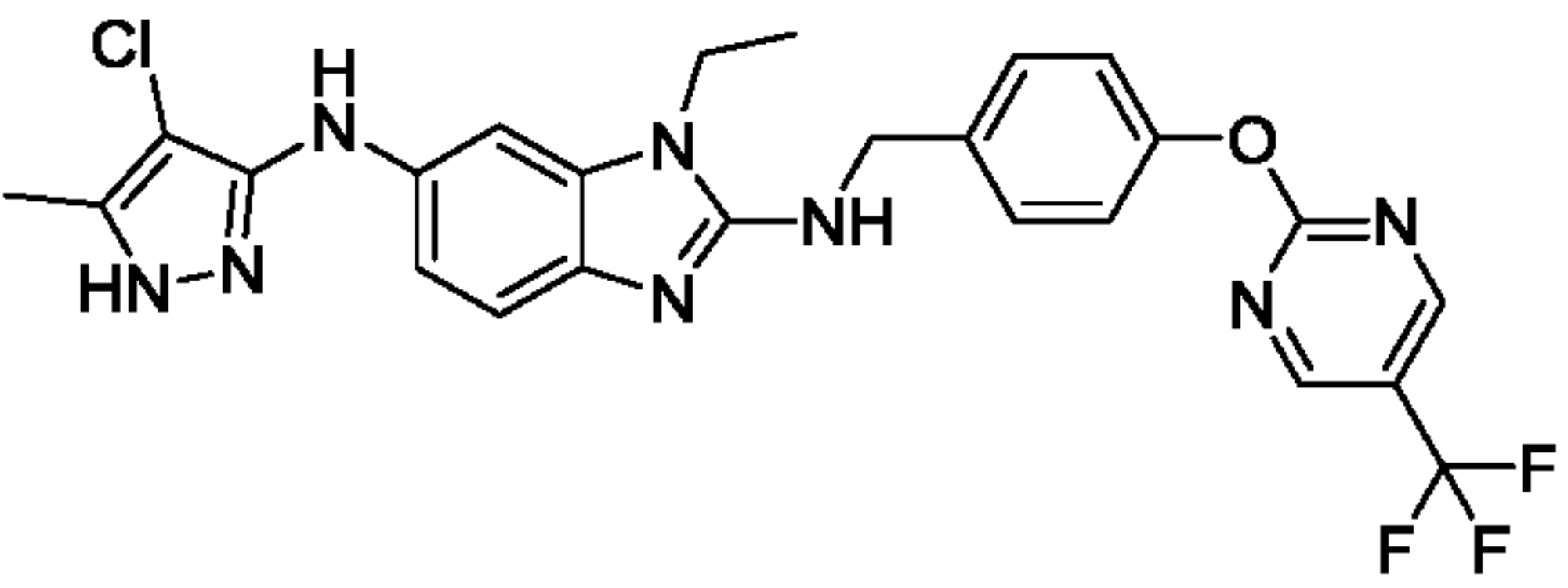
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 481 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.02 (1H, brs), 8.76 (2H, s), 7.52 (1H, brs), 7.47 (2H, d, J = 8.8 Hz), 7.30 (1H, s), 7.17 (2H, d, J = 8.0 Hz), 7.07 (1H, brs), 7.00 (1H, d, J = 8.8 Hz), 6.94 (1H, d, J = 8.0 Hz), 4.56 (2H, d, J = 6.0 Hz), 3.46 (3H, s), 2.18 (3H, s); LCMS: 95.4%, MS (ESI): m/z 475.2[M + H] <sup>+</sup> . From LCMS, the product contains 4.6% impurity of de-Cl of compound 1. |
| 482 |    | off-white powder; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 8.50 (2H, s), 7.52 (2H, d, J = 8.4 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.20 (2H, d, J = 8.4 Hz), 7.07 (1H, s), 6.83 (1H, dd, J = 8.4, 1.6 Hz), 6.05 (1H, brs), 5.75 (1H, s), 4.73 (2H, s), 4.33 (1H, brs), 3.41 (3H, s), 2.28 (3H, s); LCMS: 98.0%, MS (ESI): m/z 511.1[M+H] <sup>+</sup> .                                                                                |
| 483 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.25 (1H, brs), 8.95 (1H, s), 8.72 (2H, s), 8.11 (1H, s), 8.02 (1H, s), 7.55 (1H, s), 7.45 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.10 (1H, brs), 7.04 (1H, d, J = 8.8 Hz), 6.94 (1H, d, J = 8.4 Hz), 4.55 (2H, d, J = 5.6 Hz), 3.49 (3H, s), 2.64-2.81 (1H, m), 0.60-0.76 (2H, m), 0.41-0.53 (2H, m); LCMS: 100%, MS (ESI): m/z 530.4[M+ H] <sup>+</sup> .    |
| 484 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.43 (1H, brs), 10.60 (0.6H, brs), 10.48 (0.4H, brs), 8.74 (2H, s), 7.83 (0.6H, brs), 7.70 (0.4H, brs), 7.31-7.48 (2.6H, m), 7.10-7.26 (2.4H, m), 6.83-7.01 (2H, m), 6.62-6.80 (1H, m), 5.53 (1H, s), 4.41-4.55 (2H, m), 2.16 (3H, s); LCMS: 99.6%, MS (ESI): m/z 447.1[M + H] <sup>+</sup> .                                                                      |
| 485 |  | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.44 (1H, brs), 10.33-10.78 (1H, m), 8.74 (2H, s), 7.65-7.90 (1H, m), 7.44 (2H, d, J = 8.4 Hz), 7.21-7.40 (1H, m), 7.16 (2H, d, J = 8.8 Hz), 6.81-7.00 (2H, m), 6.73 (1H, d, J = 7.2 Hz), 5.53 (1H, s), 4.48 (2H, d, J = 5.6 Hz), 2.16 (3H, s); LCMS: 99.3%, MS (ESI): m/z 447.2[M + H] <sup>+</sup> .                                                             |
| 486 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 11.48 (1H, brs), 9.80 (1H, brs), 8.51 (2H, s), 7.91 (1H, brs), 7.62 (2H, d, J = 8.8 Hz), 7.25-7.39 (3H, m), 6.98 (1H, d, J = 8.4 Hz), 6.90 (1H, brs), 6.76 (1H, d, J = 7.2 Hz), 5.55 (1H, s), 4.47 (2H, d, J = 5.6 Hz), 3.44 (3H, s), 2.16 (3H, s); LCMS: 95.9%, MS (ESI): m/z 460.2[M + H] <sup>+</sup> .                                                                   |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                |
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| 487 |    | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.73 (2H, s), 7.56 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.37-7.43 (2H, m), 7.23 (1H, t, J = 6.0 Hz), 7.17 (2H, d, J = 8.4 Hz), 6.86 (1H, d, J = 8.8 Hz), 5.71 (1H, d, J = 2.4 Hz), 4.55 (2H, d, J = 6.0 Hz), 3.69 (3H, s), 3.68 (3H, s); LCMS: 98.6%, MS (ESI): m/z 479.2[M + H] <sup>+</sup> .                                 |
| 488 |    | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.27 (1H, brs), 8.91 (1H, s), 8.72 (2H, s), 8.14 (1H, brs), 7.53 (2H, brs), 7.45 (2H, d, J = 8.8 Hz), 7.10-7.21 (3H, m), 6.82-7.09 (3H, m), 4.55 (2H, d, J = 5.6 Hz), 3.49 (3H, s); LCMS: 100%, MS (ESI): m/z 489.9[M + H] <sup>+</sup> .                                                                           |
| 489 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.49 (1H, brs), 8.54 (1H, s), 8.49 (1H, s), 7.95 (1H, brs), 7.47 (2H, d, J = 8.4 Hz), 7.35 (1H, s), 7.20 (2H, d, J = 8.4 Hz), 6.99 (1H, d, J = 8.8 Hz), 6.70-6.80 (1H, m), 5.56 (1H, s), 4.56 (2H, d, J = 6.0 Hz), 3.47 (3H, s), 2.16 (3H, s); LCMS: 99%, MS (ESI): m/z 461.2[M + H] <sup>+</sup> .                      |
| 490 |  | light yellow powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 11.48 (1H, brs), 8.41 (1H, s), 8.32 (1H, s), 7.92 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.34 (1H, s), 7.17 (2H, d, J = 8.4 Hz), 7.03 (1H, brs), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 7.6 Hz), 5.55 (1H, s), 4.54 (2H, d, J = 5.6 Hz), 3.46 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 461.2[M + H] <sup>+</sup> . |
| 491 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.51 (1H, brs), 8.74 (2H, s), 7.97 (1H, brs), 7.47 (2H, d, J = 8.4 Hz), 7.31 (1H, s), 7.09-7.22 (3H, m), 7.01 (1H, d, J = 8.4 Hz), 6.86 (1H, d, J = 7.6 Hz), 5.57 (1H, s), 4.56 (2H, d, J = 5.2 Hz), 4.24 (2H, t, J = 7.2 Hz), 2.61-2.80 (2H, m), 2.17 (3H, s); LCMS: 98.6%, MS (ESI): m/z 543.3[M + H] <sup>+</sup> .   |
| 492 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.75 (1H, brs), 8.73 (2H, s), 7.62 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.8 Hz), 7.11 (1H, d, J = 8.0 Hz), 6.99 (1H, d, J = 8.0 Hz), 6.86 (1H, s), 4.58 (1H, d, J = 5.6 Hz), 3.52 (3H, s), 2.27 (3H, s). LCMS: 96.4%, MS (ESI): m/z 478.0[M + H] <sup>+</sup> .                                             |

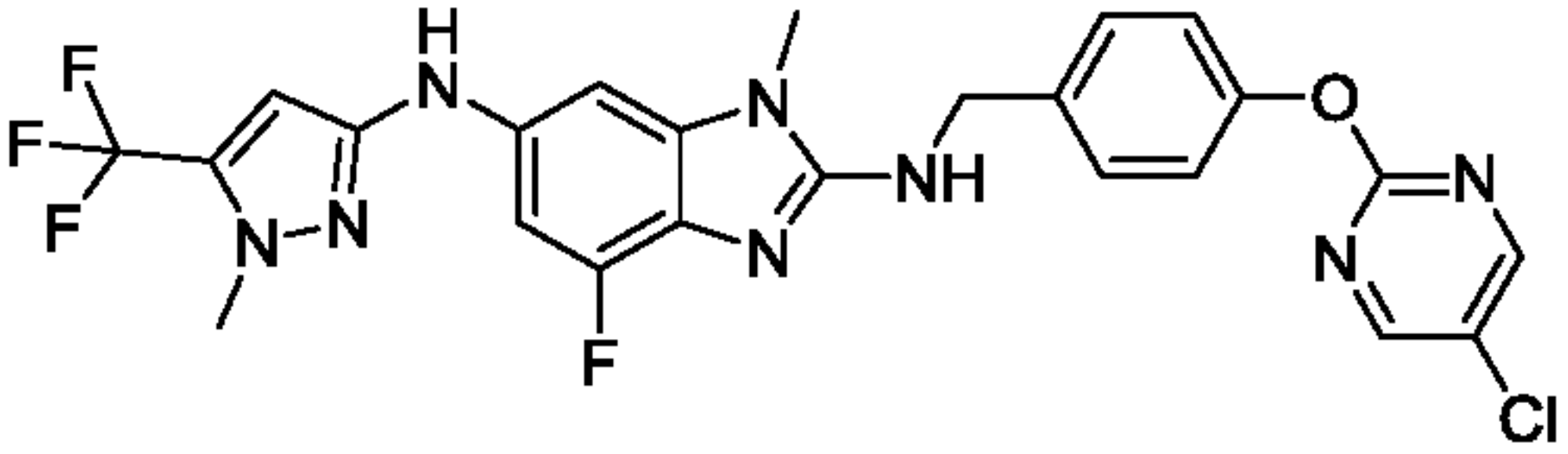
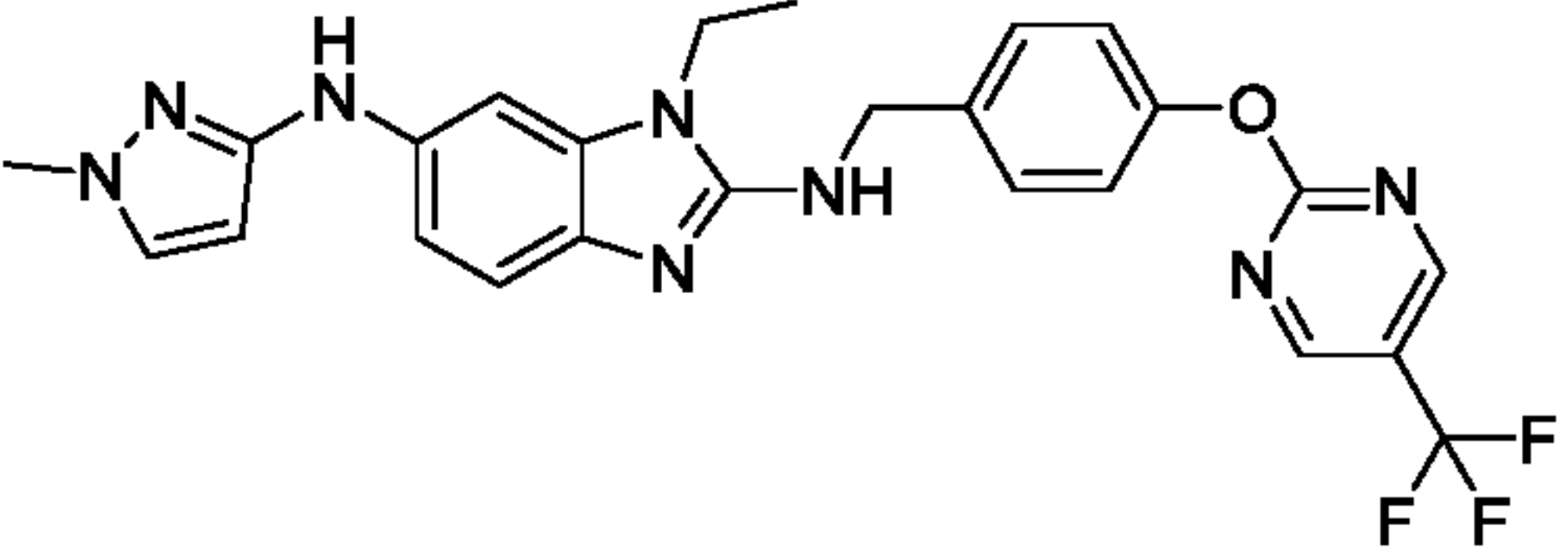
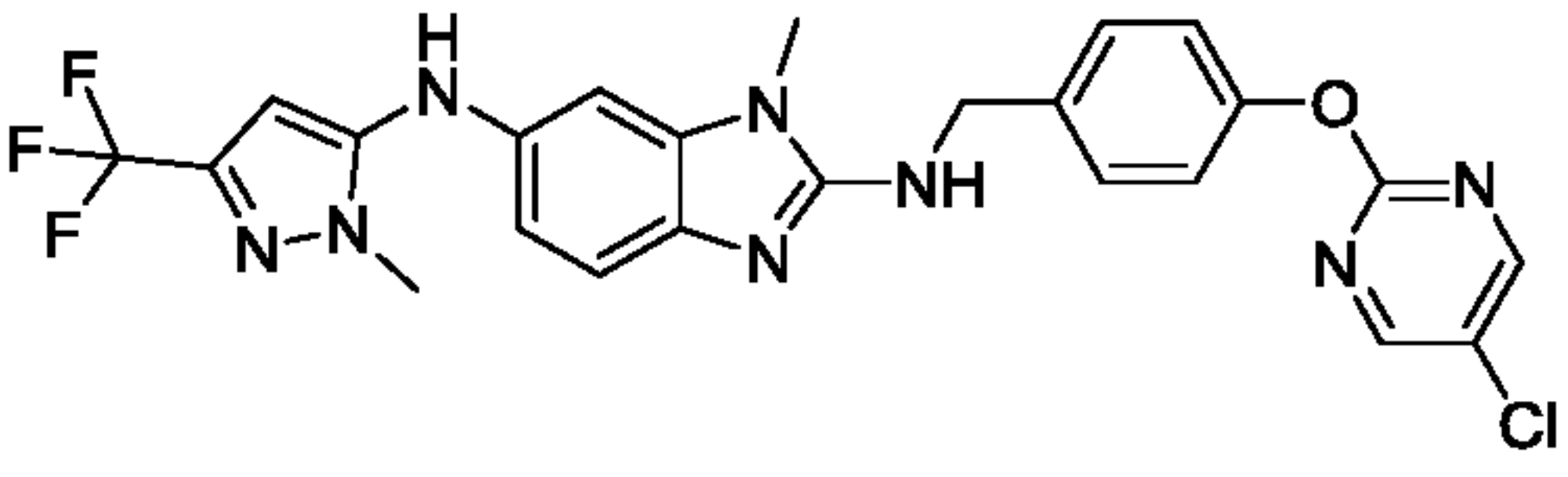
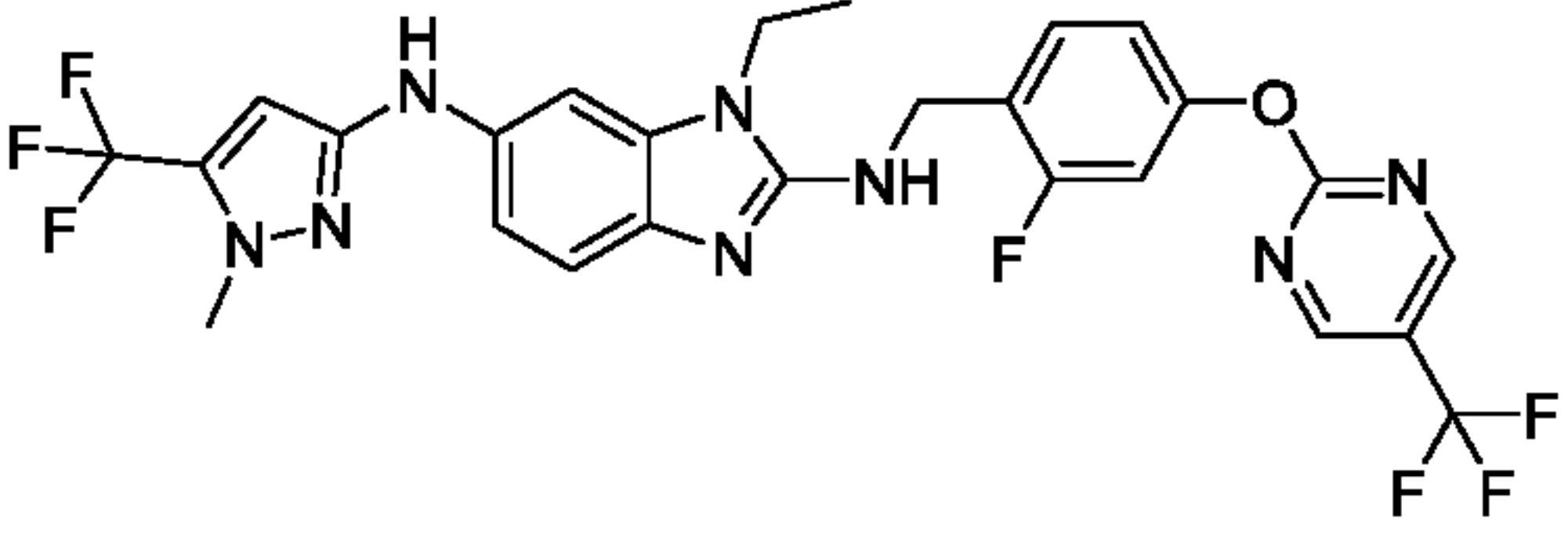
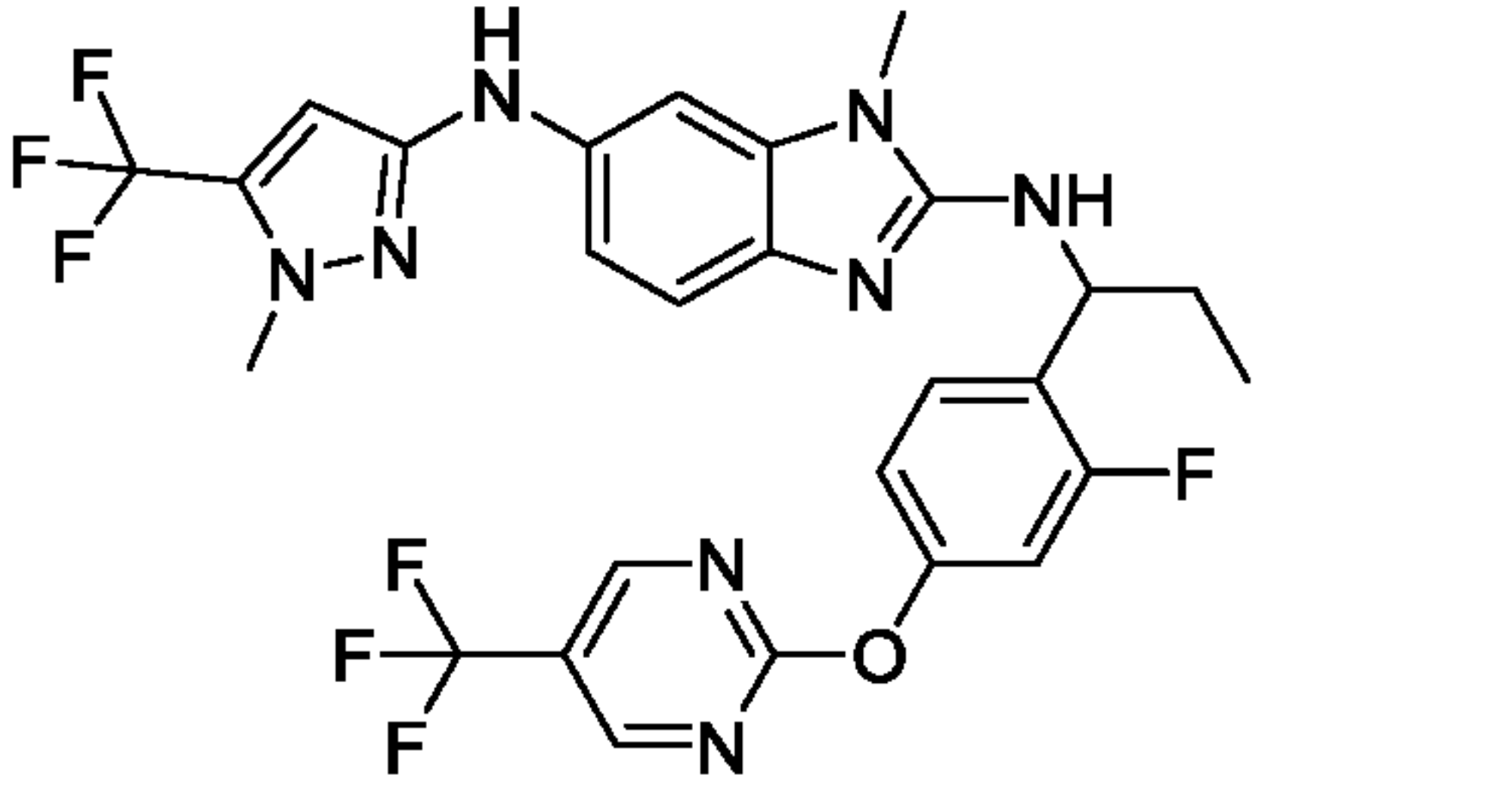
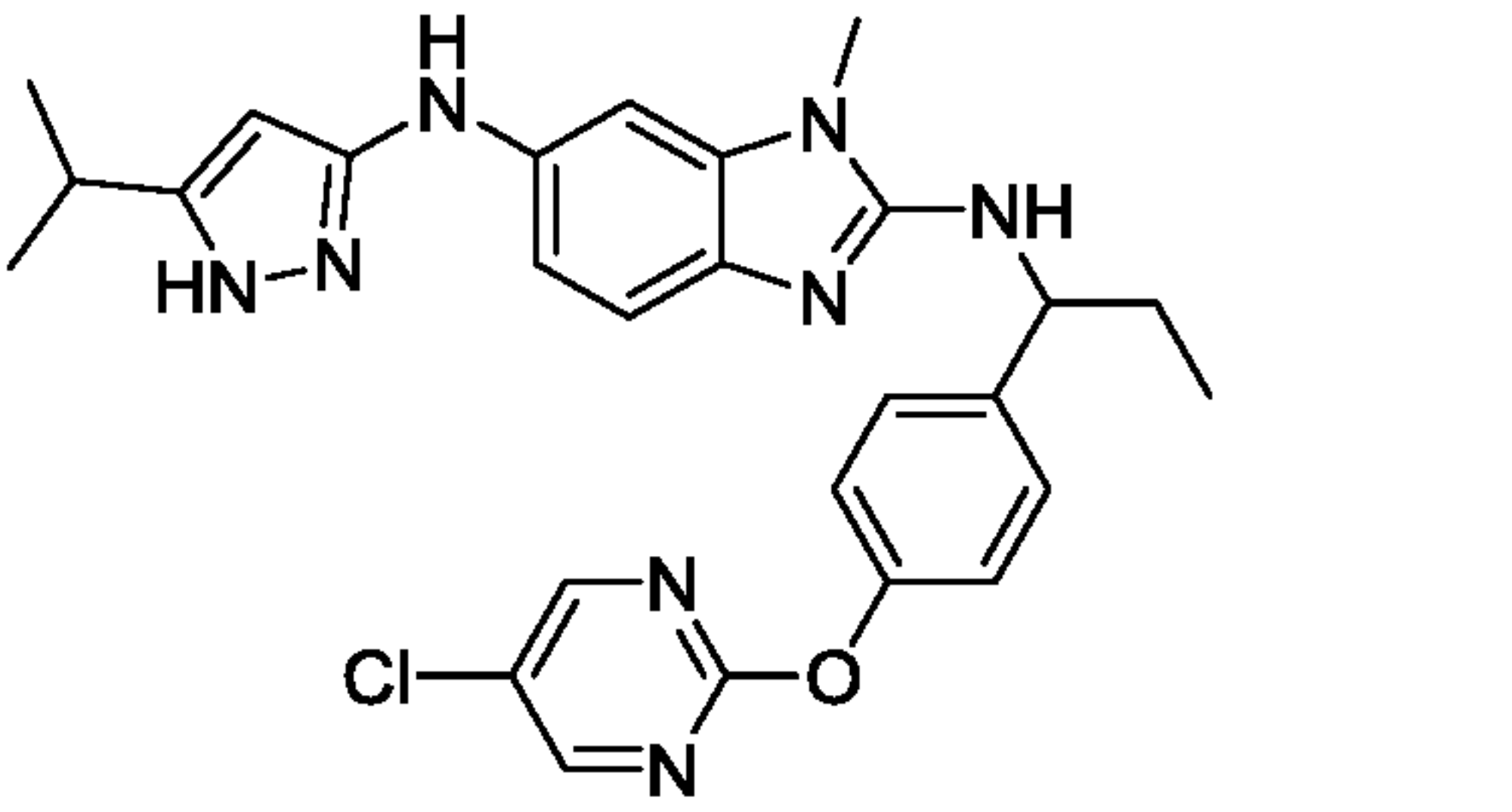
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 493 |    | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 10.24 (1H, brs), 8.73 (2H, s), 8.28-8.35 (1H, m), 7.46 (2H, d, J = 8.8 Hz), 7.38 (1H, d, J = 1.6 Hz), 7.27 (1H, t, J = 6.0 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.13 (1H, s), 7.08-7.12 (1H, dd, J = 8.4, 2.0 Hz), 4.57 (2H, d, J = 6.0 Hz), 3.51 (3H, s); LCMS: 100%, MS (ESI): m/z 516.1[M + H] <sup>+</sup> .                                                                      |
| 494 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 10.29 (1H, brs), 8.73 (2H, s), 7.45-7.60 (3H, m), 7.30-7.45 (2H, m), 7.10-7.25 (3H, m), 7.04 (1H, d, J = 8.8 Hz), 4.58 (1H, d, J = 6.0 Hz), 3.52 (3H, s); LCMS: 100%, MS (ESI): m/z 532.0[M + H] <sup>+</sup> .                                                                                                                                                                     |
| 495 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.49 (1H, brs), 8.55 (1H, s), 8.20 (1H, dd, J = 8.8, 2.4 Hz), 7.93 (1H, brs), 7.47 (2H, d, J = 8.0 Hz), 7.33 (1H, s), 7.23 (1H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.05 (1H, t, J = 5.6 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 8.0 Hz), 5.56 (1H, s), 4.50 (2H, d, J = 6.0 Hz), 3.47 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 494.2 [M + H] <sup>+</sup> . |
| 496 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1H, brs), 8.23 (1H, d, J = 2.4 Hz), 7.86-8.01 (2H, m), 7.45 (2H, d, J = 8.4 Hz), 7.34 (1H, s), 7.16 (1H, d, J = 9.2 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.01 (1H, t, J = 5.6 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 7.2 Hz), 5.55 (1H, s), 4.54 (2H, d, J = 5.6 Hz), 3.46 (3H, s), 2.16 (3H, s); LCMS: 100%, MS (ESI): m/z 510.1[M + H] <sup>+</sup> .               |
| 497 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.60 (1H, brs), 8.75 (2H, s), 8.22 (1H, brs), 7.95 (1H, s), 7.75 (1H, s), 7.61 (1H brs), 7.48 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.0 Hz), 5.57 (1H, s), 4.61 (2H, d, J = 4.4 Hz), 3.52 (3H, s), 2.19 (3H, s); LCMS: 96.4%, MS (ESI): m/z 462.0[M + H] <sup>+</sup> .                                                                                                           |
| 498 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 10.04 (1H, s), 8.73 (2H, s), 7.50 (1H, d, J = 2.0 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.25 (1H, t, J = 6.0 Hz), 7.17 (2H, d, J = 8.4 Hz), 7.11 (1H, d, J = 8.4 Hz), 6.99 (1H, dd, J = 8.4, 2.0 Hz), 4.57 (2H, d, J = 6.0 Hz), 3.52 (3H, s), 2.38 (3H, s); LCMS: 99.2%, MS (ESI): m/z 463.0[M + H] <sup>+</sup> .                                                                     |

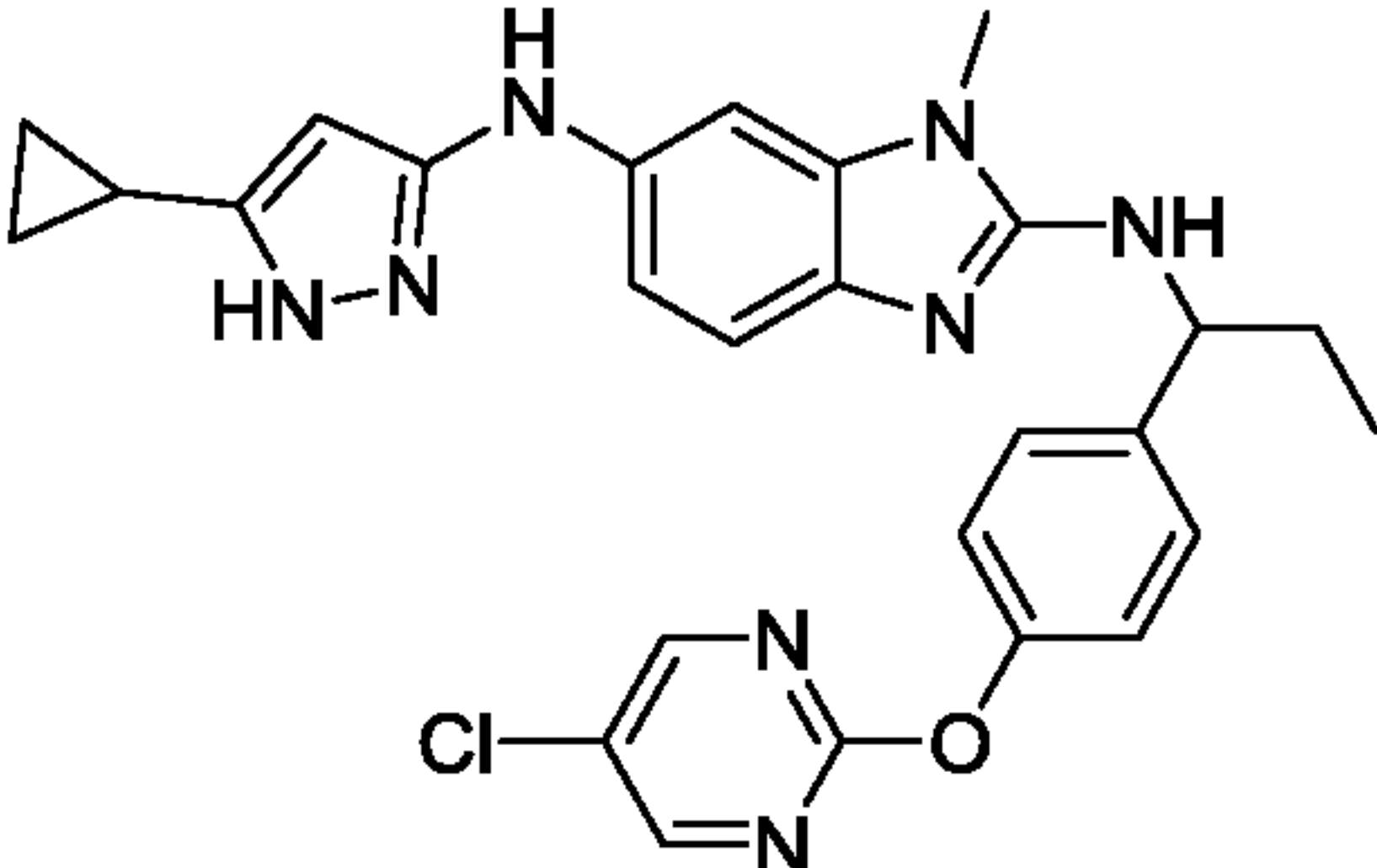
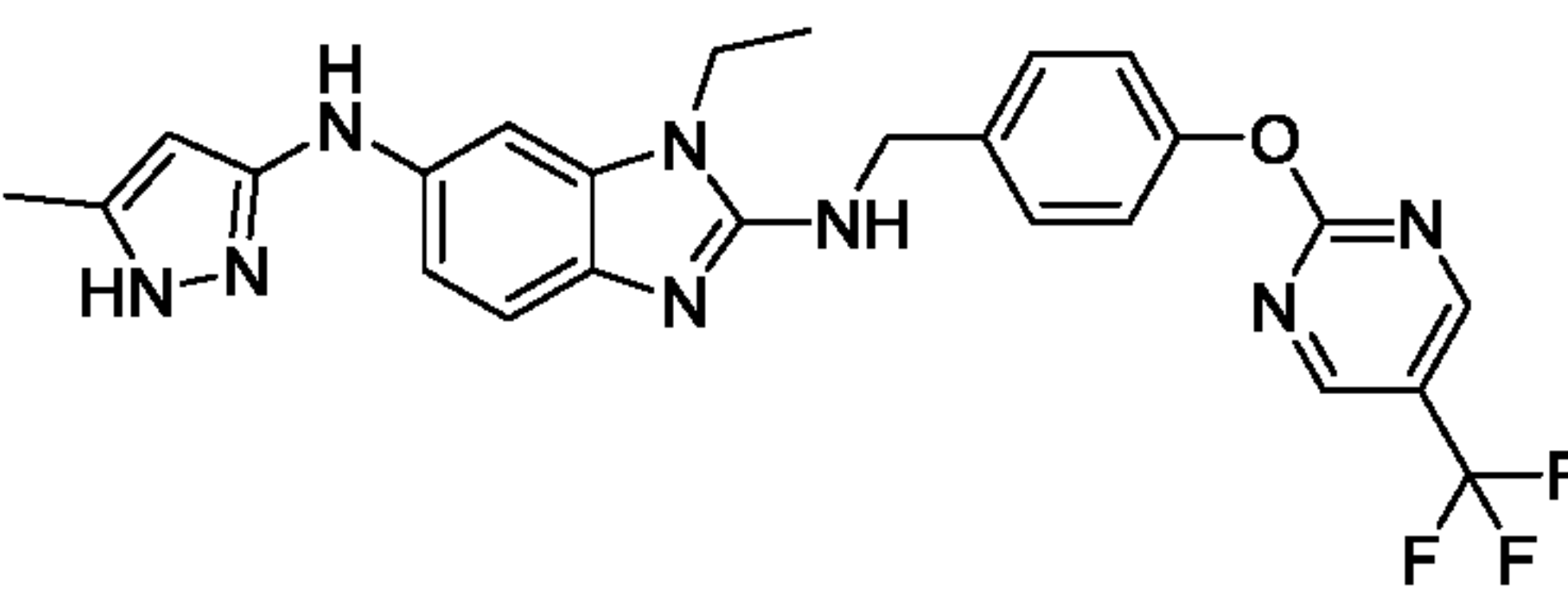
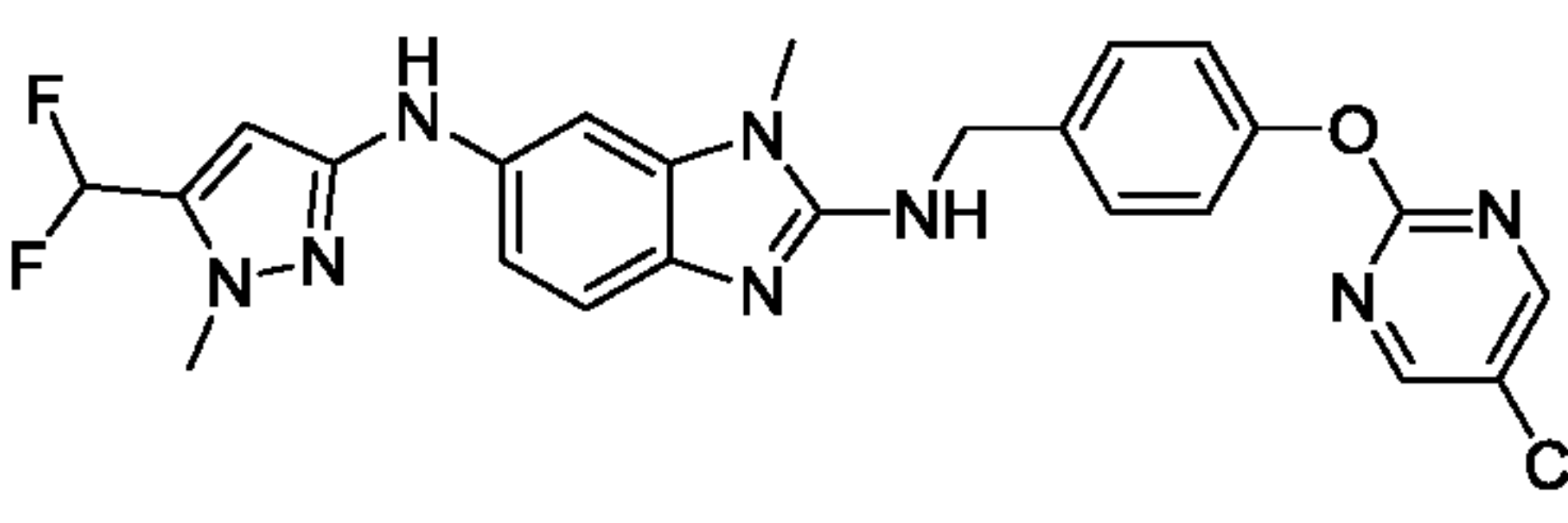
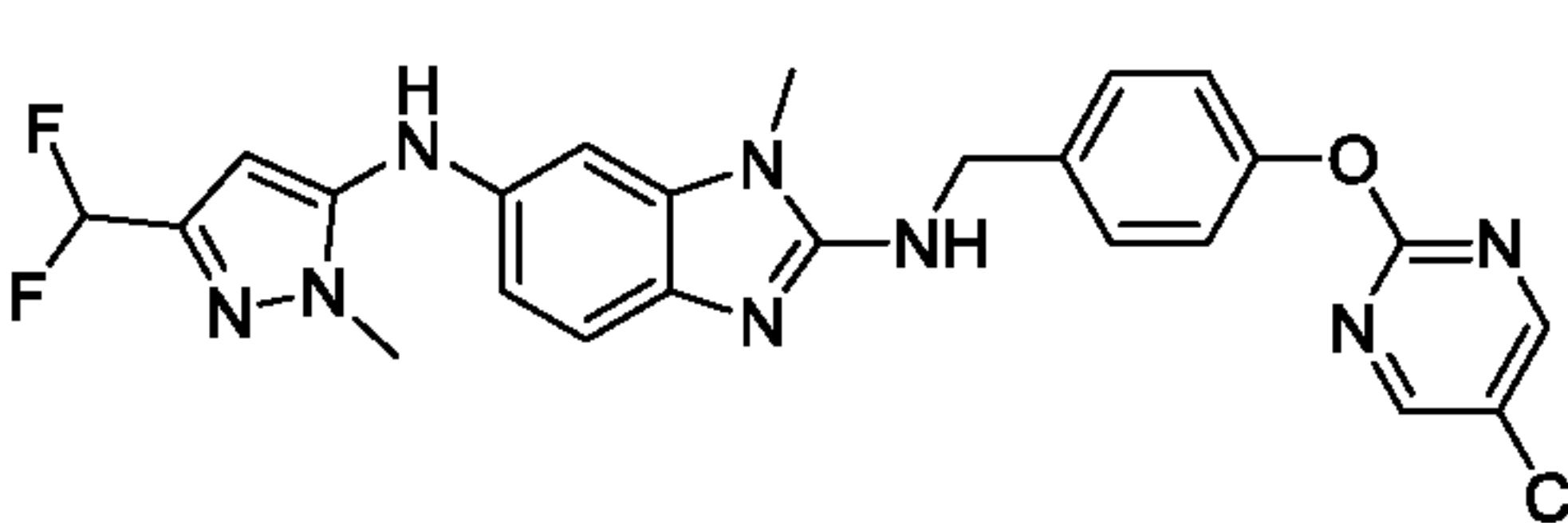
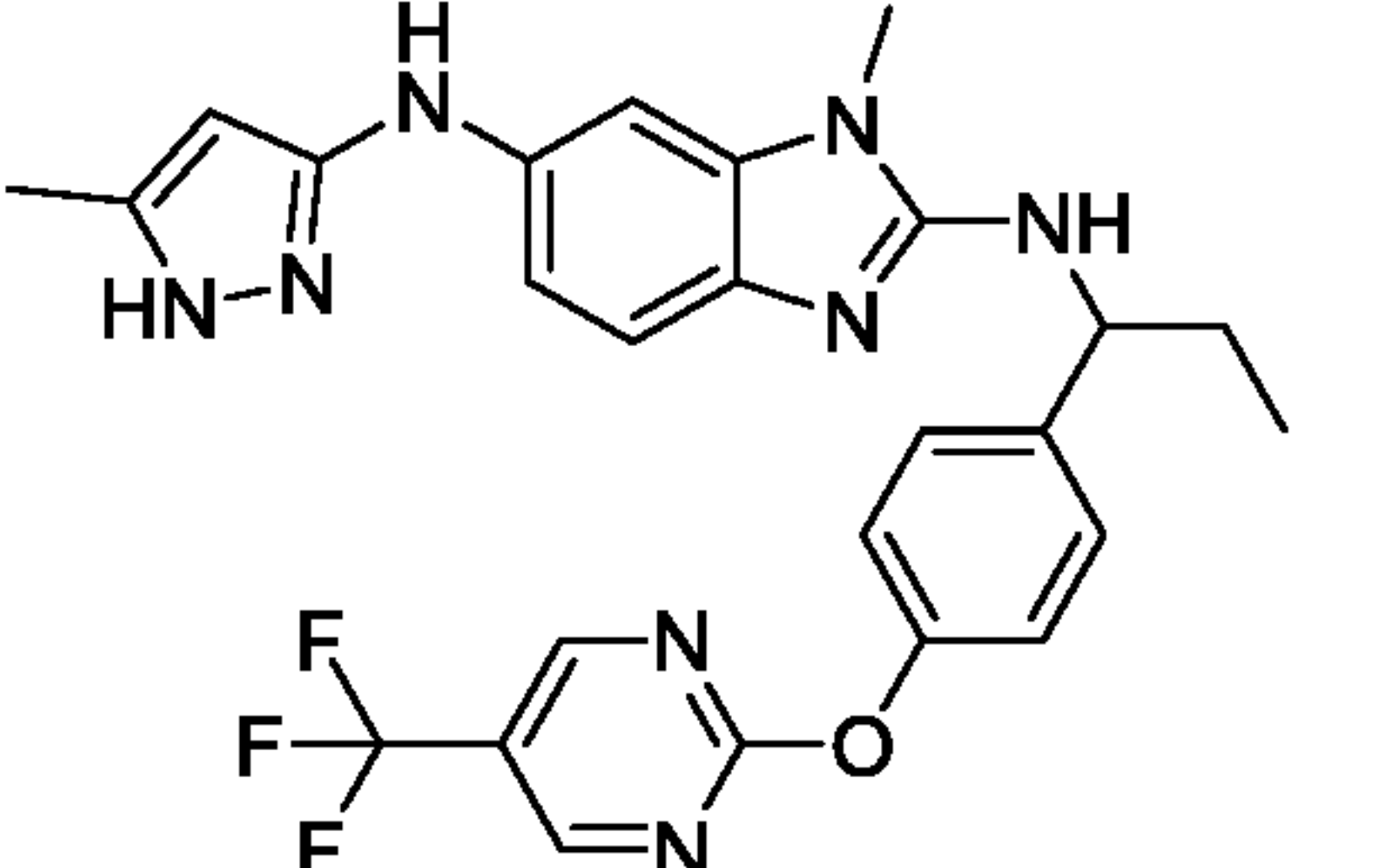
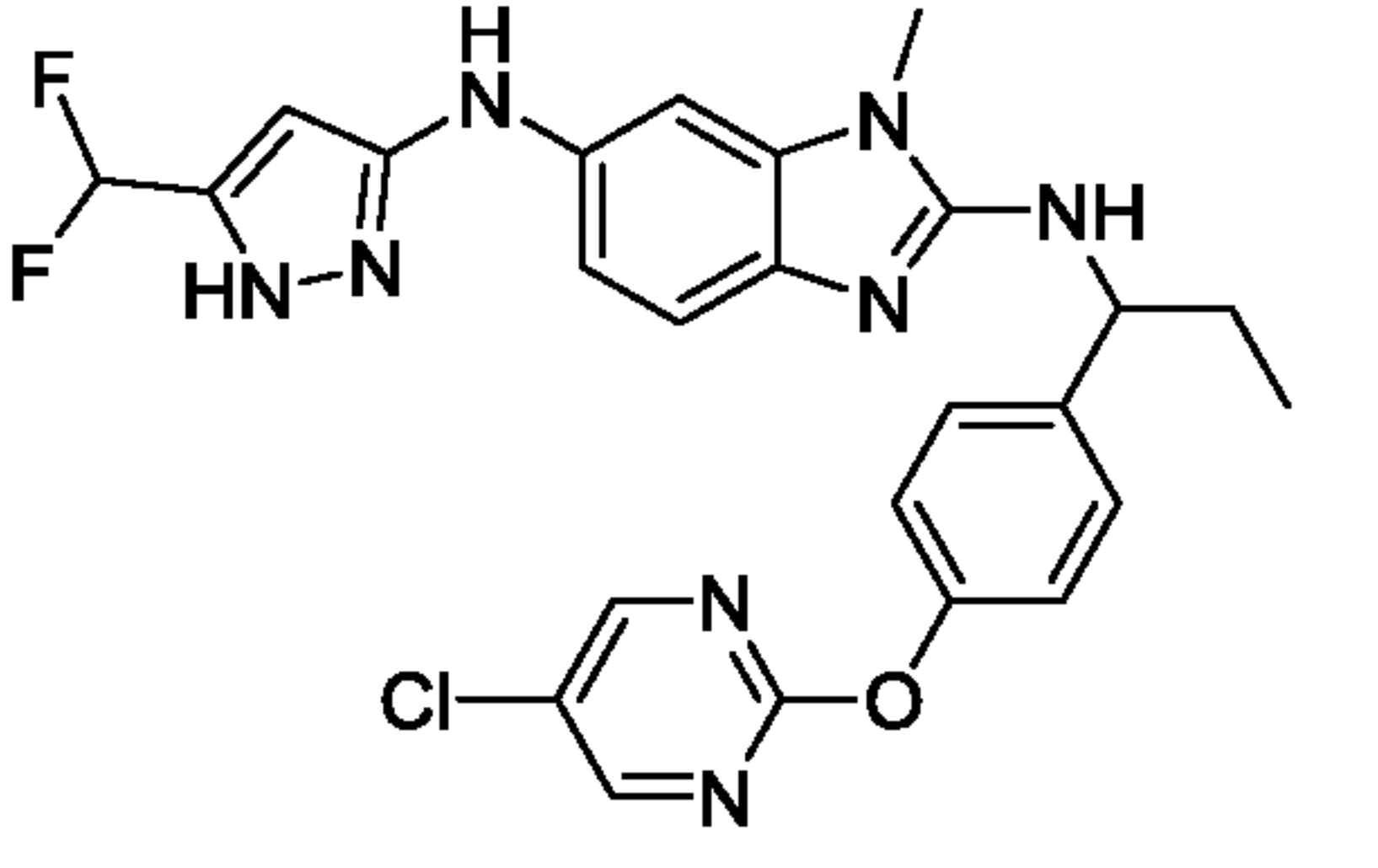
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 499 |    | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.56 (1H, brs), 8.73 (2H, s), 8.15 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.10-7.20 (3H, m), 7.05 (1H, s), 6.79 (1H, d, J = 13.6 Hz), 5.56 (1H, s), 4.56 (2H, d, J = 5.6 Hz), 3.46 (3H, s), 2.17 (3H, s); LCMS: 99.0%, MS (ESI): m/z 479.0[M + H] <sup>+</sup> .                                                         |
| 500 |    | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.75 (1H, s), 8.68 (2H, s), 8.63 (1H, s), 7.81 (1H, t, J = 6.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.41 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.8 Hz), 7.01 (1H, d, J = 8.0 Hz), 5.57 (1H, s), 4.61 (2H, d, J = 6.0 Hz), 3.54 (3H, s), 2.17 (3H, s); LCMS: 93.0%, MS (ESI): m/z 462.1[M + H] <sup>+</sup> .                     |
| 501 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.83 (1H, brs), 8.73 (2H, s), 7.35-7.70 (4H, m), 7.00-7.25 (5H, m), 6.32 (1H, s), 4.58 (2H, d, J = 6.0 Hz), 3.52 (3H, s), 2.20 (3H, s); LCMS: 98.7%, MS (ESI): m/z 478.1[M + H] <sup>+</sup> .                                                                                                                              |
| 502 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.37 (1H, s), 8.18 (1H, d, J = 2.4 Hz), 7.94 (1H, dd, J = 8.8, 2.8 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.23 (1H, d, J = 2.0 Hz), 7.01-7.16 (5H, m), 6.88 (1H, dd, J = 8.0, 2.0 Hz), 6.26 (1H, s), 4.55 (2H, d, J = 6.0 Hz), 3.84 (3H, s), 3.50 (3H, s); LCMS: 100%, MS (ESI): m/z 528.2[M + H] <sup>+</sup> .                    |
| 503 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.76 (2H, s), 8.39 (1H, brs), 7.52 (1H, t, J = 8.4 Hz), 7.20-7.25 (2H, m), 7.11 (1H, brs), 7.05 (2H, d, J = 8.0 Hz), 6.88 (1H, dd, J = 8.4, 2.0 Hz), 6.26 (1H, s), 4.58 (2H, d, J = 5.6 Hz), 3.83 (3H, s), 3.51 (3H, s); LCMS: 97.3%, MS (ESI): m/z 547.1[M + H] <sup>+</sup> .                                             |
| 504 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.74 (2H, s), 8.38 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.24-7.35 (2H, m), 7.18 (2H, d, J = 8.4 Hz), 7.06 (1H, d, J = 8.0 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.26 (1H, s), 4.58 (2H, d, J = 5.6 Hz), 4.03 (2H, q, J = 6.8 Hz), 3.84 (3H, s), 1.26 (3H, t, J = 6.8 Hz); LCMS: 98.4 %, MS (ESI): m/z 543.0[M + H] <sup>+</sup> . |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 505 |    | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (2H, s), 8.34 (1H, brs), 7.50 (2H, d, J = 8.4 Hz), 7.20 (1H, d, J = 1.6 Hz), 7.15 (2H, d, J = 8.8 Hz), 7.00 (1H, d, J = 8.4 Hz), 6.86 (1H, dd, J = 2.4, 0.4 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.24 (1H, s), 4.82-4.88 (1H, m), 3.83 (3H, s), 3.52 (3H, s), 1.76-1.94 (2H, m), 0.95 (3H, t, J = 7.2 Hz); LCMS: 99.8%, MS (ESI): m/z 557.1[M + H] <sup>+</sup> .                              |
| 506 |    | off-white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.78 (2H, s), 8.56 (1H, brs), 7.51 (1H, t, J = 8.4 Hz), 7.35 (1H, brs), 7.27 (1H, d, J = 9.2 Hz), 7.09-7.20 (2H, m), 6.95-7.06 (1H, m), 6.28 (1H, s), 4.63 (2H, d, J = 5.2 Hz), 4.00-4.10 (2H, m), 3.85 (3H, s), 1.28 (3H, t, J = 6.8 Hz); LCMS: 99.8%, MS (ESI): m/z 561.0[M + H] <sup>+</sup> .                                                                                           |
| 507 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.59 (1H, brs), 8.73 (1H, s), 8.70 (1H, s), 7.95 (1H, brs), 7.40-7.57 (3H, m), 7.22 (2H, d, J = 8.4 Hz), 7.07 (1H, t, J = 6.0 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.74 (1H, d, J = 8.4 Hz), 5.51 (1H, s), 4.57 (2H, d, J = 6.0 Hz), 3.97 (2H, q, J = 6.8 Hz), 1.21-1.28 (12H, m); LCMS: 98.9%, MS (ESI): m/z 551.0[M + H] <sup>+</sup> .                                                       |
| 508 |  | off-white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.09 (1H, brs), 8.74 (1H, s), 8.70 (1H, s), 7.60 (1H, brs), 7.49 (2H, d, J = 8.4 Hz), 7.43 (1H, s), 7.24 (2H, d, J = 8.4 Hz), 6.91-7.10 (2H, m), 4.59 (2H, d, J = 6.0 Hz), 4.00 (2H, q, J = 6.8 Hz), 2.18 (3H, s), 1.25 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 543.0[M + H] <sup>+</sup> .                                                                                         |
| 509 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.59 (1H, brs), 8.72 (2H, s), 7.94 (1H, brs), 7.50 (1H, s), 7.43 (2H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.04 (1H, brs), 6.96 (1H, d, J = 8.0 Hz), 6.72 (1H, d, J = 8.4 Hz), 5.49 (1H, s), 4.54 (2H, d, J = 5.6 Hz), 3.95-4.00 (2H, m), 1.20-1.25 (12H, m); LCMS: 98.7 %, MS (ESI): m/z 517.1[M + H] <sup>+</sup> .                                                                   |
| 510 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ): δ 8.41 (1H, d, J = 1.2 Hz), 8.35 (1H, s), 8.32 (1H, d, J = 1.6 Hz), 7.45 (2H, d, J = 8.8 Hz), 7.22 (1H, d, J = 1.6 Hz), 7.17 (2H, d, J = 8.4 Hz), 7.13 (1H, t, J = 5.6 Hz), 7.03 (1H, d, J = 8.4 Hz), 6.90 (1H, dd, J = 8.4, 2.0 Hz), 6.24 (1H, s), 4.56 (2H, d, J = 5.6 Hz), 4.01 (2H, q, J = 6.8 Hz), 3.82 (3H, s), 1.24 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 543.1[M + H] <sup>+</sup> . |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 511 |    | white powder; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 8.35 (1H, s), 8.17 (1H, d, J = 2.8 Hz), 7.94 (1H, dd, J = 8.8, 2.8 Hz), 7.42 (2H, d, J = 8.4 Hz), 7.22 (1H, d, J = 1.6 Hz), 7.06-7.16 (4H, m), 7.04 (1H, d, J = 8.8 Hz), 6.90 (1H, dd, J = 8.0, 2.0 Hz), 6.24 (1H, s), 4.55 (2H, d, J = 6.0 Hz), 4.01 (2H, q, J = 6.8 Hz), 3.83 (3H, s), 1.24 (3H, t, J = 7.2 Hz); LCMS: 99.0%, MS (ESI): m/z 542.0[M + H] <sup>+</sup> . |
| 512 |    | off-white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.05 (1H, brs), 8.74 (2H, s), 7.51 (1H, brs), 7.44 (2H, d, J = 8.4 Hz), 7.39 (1H, s), 7.16 (2H, d, J = 8.4 Hz), 7.10 (1H, s), 6.93-7.05 (2H, m), 4.60 (2H, d, J = 6.4 Hz), 3.97 (2H, q, J = 6.8 Hz), 2.17 (3H, s), 1.24 (3H, t, J = 7.2 Hz); LCMS: 97.6 %, MS (ESI): m/z 508.9[M + H] <sup>+</sup> .                                                               |
| 513 |  | off-white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.60 (1H, brs), 9.09 (2H, s), 7.96 (1H, brs), 7.51 (1H, s), 7.47 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.08 (1H, t, J = 6.0 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.74 (1H, d, J = 8.4 Hz), 5.51 (1H, s), 4.57 (2H, d, J = 6.0 Hz), 3.98 (2H, q, J = 6.8 Hz), 1.20-1.28 (12H, m); LCMS: 94.2%, MS (ESI): m/z 551.1[M + H] <sup>+</sup> .                         |
| 514 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400MHz): δ 11.59 (1H, brs), 8.41 (1H, s), 8.32 (1H, s), 7.95 (1H, brs), 7.50 (1H, s), 7.45 (2H, d, J = 8.4 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.06 (1H, brs), 6.98 (1H, d, J = 8.0 Hz), 6.74 (1H, d, J = 8.4 Hz), 5.51 (1H, s), 4.55 (2H, d, J = 5.6 Hz), 3.97 (2H, q, J = 6.8 Hz), 1.21-1.26 (12H, m); LCMS: 99.4%, MS (ESI): m/z 517.0[M + H] <sup>+</sup> .                          |
| 515 |  | off-white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.07 (1H, brs), 8.43 (1H, s), 8.34 (1H, s), 7.55 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.40 (1H, s), 7.11-7.27 (3H, m), 6.95-7.04 (2H, m), 4.57 (2H, d, J = 5.6 Hz), 3.90-4.00 (2H, m), 2.18 (3H, s), 1.25 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 508.9[M + H] <sup>+</sup> .                                                                                |
| 516 |  | yellow solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.06 (1H, brs), 9.10 (2H, s), 7.44-7.59 (3H, m), 7.39 (1H, s), 7.22 (2H, d, J = 8.4 Hz), 7.12 (1H, brs), 6.97-7.06 (2H, m), 4.58 (2H, d, J = 6.0 Hz), 3.98 (2H, q, J = 6.8 Hz), 2.18 (3H, s), 1.25 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 543.0[M + H] <sup>+</sup> .                                                                                          |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| 517 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.41 (1H, d, J = 1.2 Hz), 8.36 (1H, brs), 8.32 (1H, d, J = 1.2 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.20 (1H, s), 7.15 (2H, d, J = 8.8 Hz), 6.99 (1H, d, J = 8.4 Hz), 6.80-6.85 (2H, m), 6.24 (1H, s), 4.80-4.90 (1H, m), 3.83 (3H, s), 3.52 (3H, s), 1.74-1.97 (2H, m), 0.94 (3H, t, J = 8.8 Hz); LCMS: 100%, MS (ESI): m/z 557.0[M + H] <sup>+</sup> . |
| 518 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 12.02 (1H, brs), 8.17 (1H, d, J = 2.4 Hz), 7.94 (1H, dd, J = 8.8, 2.8 Hz), 7.49 (1H, s), 7.44 (2H, d, J = 8.8 Hz), 7.35 (1H, s), 7.01-7.11 (4H, m), 6.94-7.01 (2H, m), 4.54 (2H, d, J = 6.0 Hz), 3.45 (3H, s), 2.17 (3H, s); LCMS: 99.1%, MS (ESI): m/z 493.9[M + H] <sup>+</sup> .                                                                |
| 519 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.10 (2H, s), 8.39 (1H, brs), 7.50 (2H, d, J = 8.4 Hz), 7.25 (1H, d, J = 2.0 Hz), 7.22 (2H, d, J = 8.8 Hz), 7.14 (1H, brs), 7.05 (1H, d, J = 8.0 Hz), 6.89 (1H, dd, J = 8.4, 2.0 Hz), 6.27 (1H, s), 4.58 (2H, d, J = 6.0 Hz), 3.84 (3H, s), 3.51 (3H, s); LCMS: 100 %, MS (ESI): m/z 563.0[M + H] <sup>+</sup> .                                   |
| 520 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.09 (2H, s), 8.35 (1H, brs), 7.52 (2H, d, J = 8.4 Hz), 7.15-7.24 (3H, m), 6.99 (1H, d, J = 8.8 Hz), 6.78-6.89 (2H, m), 6.24 (1H, s), 4.79-4.95 (1H, m), 3.83 (3H, s), 3.53 (3H, s), 1.72-2.00 (2H, m), 0.96 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 591.0[M + H] <sup>+</sup> .                                                            |
| 521 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.10 (2H, s), 8.36 (1H, brs), 7.48 (2H, d, J = 8.8 Hz), 7.21-7.27 (3H, m), 7.17 (1H, brs), 7.05 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.4, 2.0 Hz), 6.25 (1H, s), 4.59 (2H, d, J = 5.6 Hz), 4.03 (2H, q, J = 7.2 Hz), 3.84 (3H, s), 1.26 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 577.0[M + H] <sup>+</sup> .                          |
| 522 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.72 (1H, s), 8.69 (1H, s), 8.36 (1H, brs), 7.53 (2H, d, J = 8.4 Hz), 7.19-7.24 (3H, m), 7.00 (1H, d, J = 8.0 Hz), 6.77-6.90 (2H, m), 6.24 (1H, s), 4.82-4.91 (1H, m), 3.83 (3H, s), 3.53 (3H, s), 1.73-1.99 (2H, m), 0.95 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 590.9[M + H] <sup>+</sup> .                                              |
| 523 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (1H, s), 8.70 (1H, s), 8.35 (1H, brs), 7.48 (2H, d, J = 8.4 Hz), 7.20-7.30 (3H, m), 7.15 (1H, t, J = 6.0 Hz), 7.03 (1H, d, J = 8.4 Hz), 6.89 (1H, dd, J = 8.4, 2.4 Hz), 6.24 (1H, s), 4.57 (1H, d, J = 6.0 Hz), 4.02 (2H, q, J = 6.8 Hz), 3.83 (3H, s), 1.24 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 577.1[M + H] <sup>+</sup> .        |

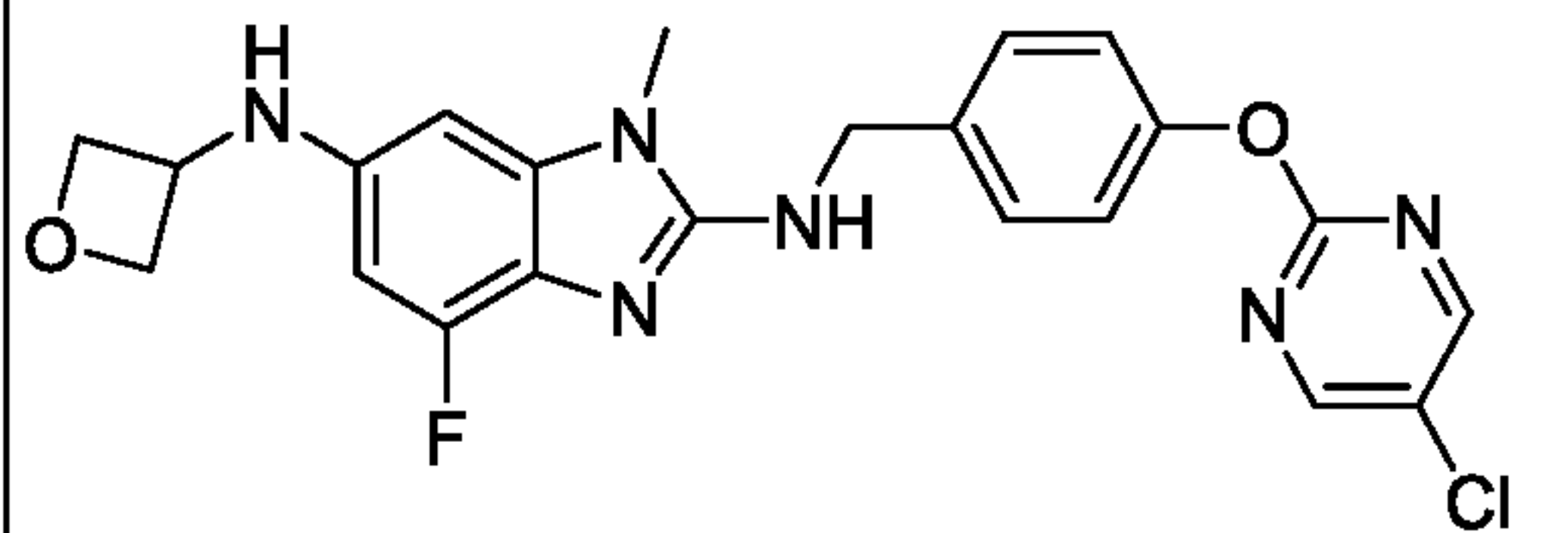
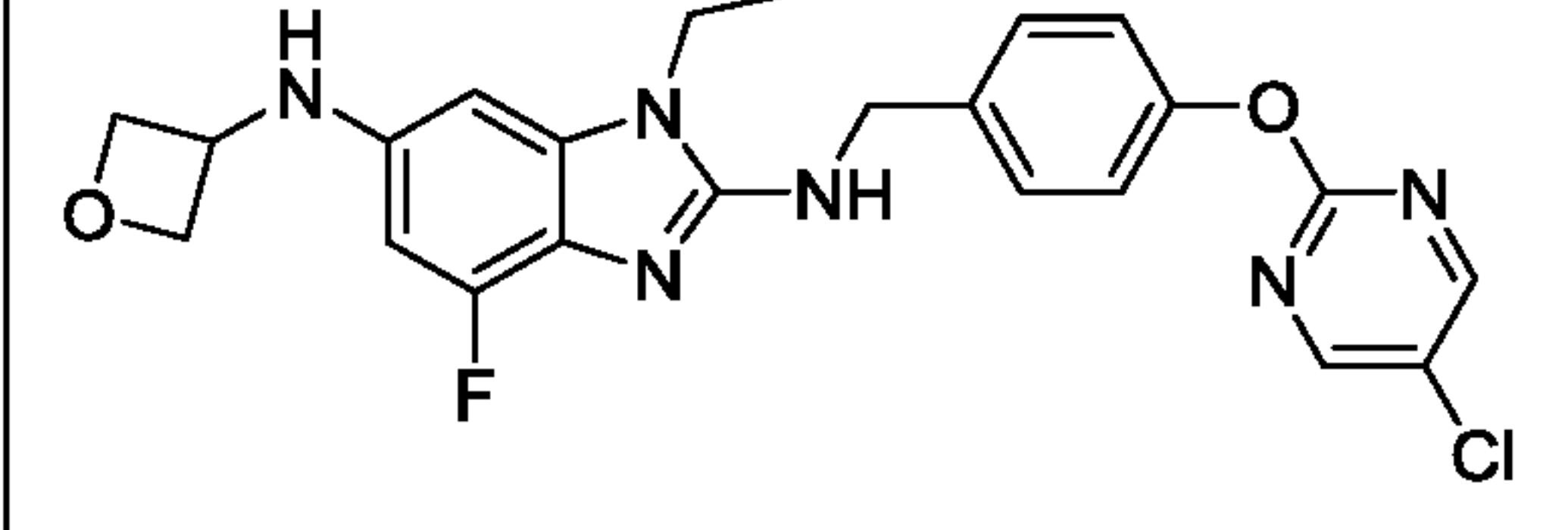
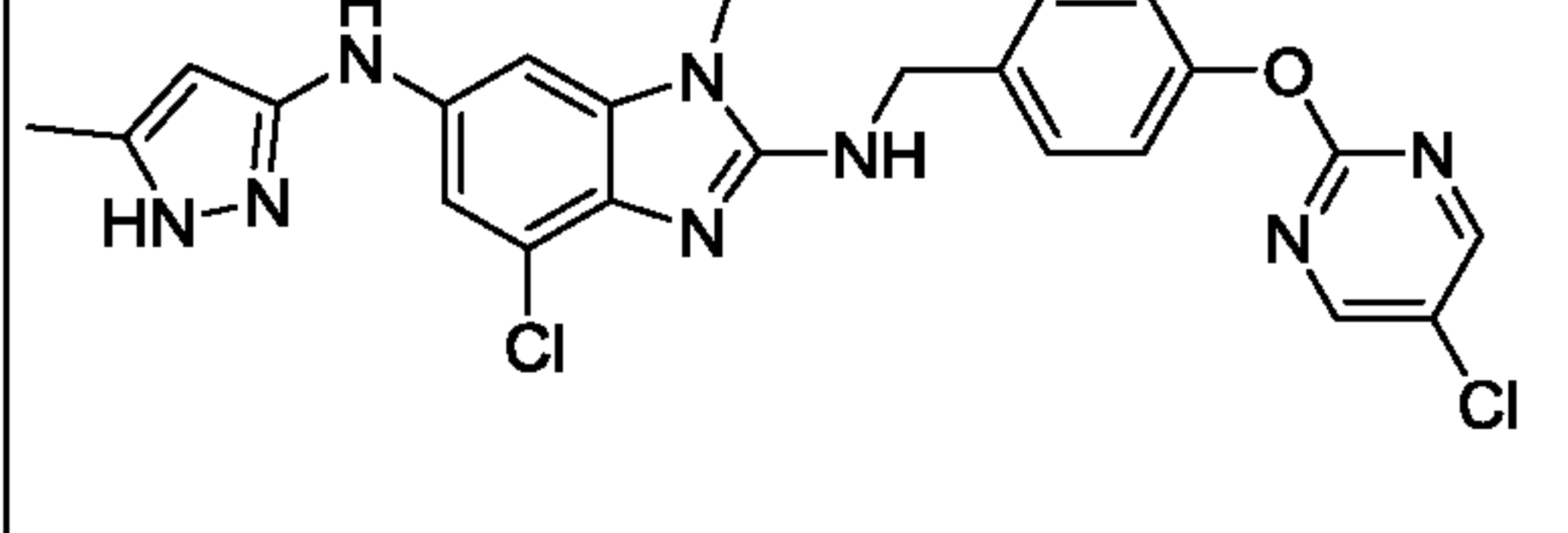
|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 524 |    | a white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 8.60 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.25 (1H, t, J = 6.0 Hz), 7.17 (2H, d, J = 8.4 Hz), 6.99 (1H, s), 6.87 (1H, d, J = 13.2 Hz), 6.29 (1H, s), 4.57 (2H, d, J = 6.0 Hz), 3.85 (3H, s), 3.50 (3H, s); LCMS: 100%, MS (ESI): m/z 546.9[M + H] <sup>+</sup> .                                                                                                               |
| 525 |    | off-white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.10 (2H, s), 8.01 (1H, brs), 7.42-7.51 (3H, m), 7.20-7.31 (3H, m), 7.11 (1H, brs), 7.00 (1H, d, J = 8.4 Hz), 6.88 (1H, d, J = 8.4 Hz), 5.73 (1H, d, J = 2.0 Hz), 4.57 (2H, d, J = 5.6 Hz), 4.00 (2H, q, J = 6.8 Hz), 3.72 (3H, s), 1.25 (3H, t, J = 7.2 Hz); LCMS: 99.2%, MS (ESI): m/z 509.0[M + H] <sup>+</sup> .                                                                        |
| 526 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.74 (2H, s), 8.02 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.23 (1H, brs), 7.17 (2H, d, J = 8.4 Hz), 7.10 (1H, d, J = 8.0 Hz), 6.83 (1H, d, J = 1.6 Hz), 6.69 (1H, dd, J = 8.4, 2.0 Hz), 6.14 (1H, s), 4.57 (2H, d, J = 6.0 Hz), 3.74 (3H, s), 3.50 (3H, s); LCMS: 98.4%, MS (ESI): m/z 529.1[M + H] <sup>+</sup> .                                                                              |
| 527 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.13 (2H, s), 8.38 (1H, brs), 7.52 (1H, t, J = 8.8 Hz), 7.29 (1H, dd, J = 10.8, 2.4 Hz), 7.25 (1H, d, J = 2.0 Hz), 7.16 (1H, brs), 7.11 (1H, dd, J = 8.4, 1.6 Hz), 7.06 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.0, 2.0 Hz), 6.26 (1H, s), 4.61 (2H, d, J = 6.0 Hz), 4.04 (2H, q, J = 2.8 Hz), 3.84 (3H, s), 1.26 (3H, t, J = 6.8 Hz); LCMS: 100 %, MS (ESI): m/z 595.1[M + H] <sup>+</sup> . |
| 528 |  | white solid; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.12 (2H, s), 8.38 (1H, brs), 7.60 (1H, t, J = 8.8 Hz), 7.19-7.28 (2H, m), 7.06-7.13 (1H, m), 7.01 (1H, d, J = 8.4 Hz), 6.80-6.94 (2H, m), 6.25 (1H, s) 5.10-5.20 (1H, m), 3.83 (3H, s) 3.55 (3H, s), 1.74-1.98 (2H, m), 0.99 (3H, t, J = 7.2 Hz); LCMS: 99.2%, MS (ESI): m/z 609.0[M + H] <sup>+</sup> .                                                                                       |
| 529 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.53 (1H, brs), 8.71 (2H, s), 7.90 (1H, brs), 7.48 (2H, d, J = 8.4 Hz), 7.31 (1H, s), 7.13 (2H, d, J = 8.4 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.60-6.81 (2H, m), 5.51 (1H, s), 4.83 (1H, q, J = 8.0 Hz), 3.47 (3H, s), 2.75-2.91 (1H, m), 1.70-2.01 (2H, m), 1.18 (6H, d, J = 7.2 Hz), 0.94 (3H, t, J = 7.2 Hz); LCMS: 98.0%, MS (ESI): m/z 517.1[M + H] <sup>+</sup> .                          |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 530 |    | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.51 (1H, brs), 8.69 (2H, s), 7.85 (1H, brs), 7.45 (2H, d, J = 8.8 Hz), 7.23 (1H, s), 7.11 (2H, d, J = 8.4 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.61-6.82 (2H, m), 5.41 (1H, s), 4.70-4.85 (1H, m), 3.66 (3H, s), 1.65-1.96 (3H, m), 0.76-0.99 (5H, m), 0.55-0.64 (2H, m); LCMS: 96.3%, MS (ESI): m/z 537.0[M + Na] <sup>+</sup> .           |
| 531 |    | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.50 (1H, brs), 9.09 (2H, s), 7.95 (1H, brs), 7.47 (2H, d, J = 8.4 Hz), 7.38 (1H, s), 7.21 (2H, d, J = 8.4 Hz), 7.14 (1H, brs), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 8.0 Hz), 5.54 (1H, s), 4.57 (2H, d, J = 5.6 Hz), 3.95-4.00 (2H, m), 2.16 (3H, s), 1.24 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 509.0[M + H] <sup>+</sup> . |
| 532 |  | light-yellow powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 8.23 (1H, brs), 7.46 (2H, d, J = 8.0 Hz), 7.07- 7.35 (1H, m), 7.22 (1H, s), 7.16 (2H, d, J = 8.4 Hz), 7.08 (1H, brs), 7.02 (1H, d, J = 8.4 Hz), 6.84-6.89 (1H, m), 6.06 (1H, s), 4.54 (2H, d, J = 5.6 Hz), 3.78 (3H, s), 3.48 (3H, s); LCMS: 99.3%, MS (ESI): m/z 510.9[M + H] <sup>+</sup> .                            |
| 533 |  | light-yellow powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 7.88 (1H, s), 7.45 (2H, d, J = 8.4 Hz), 7.12- 7.40 (3H, m), 7.07 (1H, d, J = 8.0 Hz), 6.80 (1H, t, J = 55.2 Hz), 6.78 (1H, s), 6.62-6.68 (1H, m), 5.98 (1H, s), 4.56 (1H, d, J = 5.6 Hz), 3.69 (3H, s), 3.49 (3H, s); LCMS: 97.7%, MS (ESI): m/z 511.0[M + H] <sup>+</sup> .                                             |
| 534 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.45 (1H, brs), 9.07 (2H, s), 7.89 (1H, brs), 7.50 (2H, d, J = 8.4 Hz), 7.29 (1H, s), 7.18 (2H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.4 Hz), 6.60-6.81 (2H, m), 5.53 (1H, s), 4.80-4.90 (1H, m), 3.48 (3H, s), 2.14 (3H, s), 1.65-1.96 (2H, m), 0.94 (3H, t, J = 6.8 Hz); LCMS: 96.7%, MS (ESI): 523.0 m/z [M + H] <sup>+</sup> .         |
| 535 |  | pale yellow powder; <sup>1</sup> H-NMR (CDCl <sub>3</sub> , 400 MHz): δ 8.43 (2H, s), 7.41 (2H, d, J = 8.4 Hz), 7.01-7.20 (3H, m), 6.41-6.85 (3H, m), 6.16 (1H, brs), 6.01(1H, s), 4.90-5.06 (1H, m), 4.44 (1H, brs), 3.30 (3H, s), 1.76-2.11 (2H, m), 0.93 (3H, t, J = 7.2 Hz); LCMS: 96.1%, MS (ESI): 525.0 m/z [M + H] <sup>+</sup> .                                                                          |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 536 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.51 (1H, brs), 8.76 (2H, s), 7.94 (1H, brs), 7.45-7.55 (1H, m), 7.40 (1H, s), 7.21 (1H, d, J = 10.8 Hz), 6.90-7.12 (3H, m), 6.71-6.82 (1H, m), 5.54 (1H, s), 4.58 (2H, d, J = 5.2 Hz), 3.95-4.00 (2H, m), 2.16 (3H, s), 1.24 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): 492.9 m/z [M+ H] <sup>+</sup> .                                                                              |
| 537 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1H, brs), 8.76 (2H, s), 7.93 (1H, brs), 7.57 (1H, t, J = 8.8 Hz), 7.32 (1H, s), 7.17 (1H, d, J = 10.8 Hz), 7.05 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.50-6.85 (2H, m), 5.55 (1H, s), 5.08-5.20 (1H, m), 3.51 (3H, s), 2.16 (3H, s), 1.60-1.95 (2H, m), 0.98 (3H, t, J = 7.2 Hz); LCMS: 98.6%, MS (ESI): m/z 507.0 [M+H] <sup>+</sup> .                                     |
| 538 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 8.11 (1H, brs), 7.46 (2H, d, J = 8.0 Hz), 7.21 (1H, s), 7.16 (2H, d, J = 8.4 Hz), 7.07 (1H, brs), 7.02 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 7.2 Hz), 5.96 (1H, d, J = 2.8 Hz), 5.43 (2H, d, J = 48.4 Hz), 4.55 (2H, d, J = 5.2 Hz), 3.73 (3H, s), 3.48 (3H, s); LCMS: 89.5%, MS (ESI): m/z 493.1[M + H] <sup>+</sup> .                                                        |
| 539 |  | white powder ; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.73 (2H, s), 7.76 (1H, brs), 7.46 (2H, d, J = 8.4 Hz), 7.15-7.17 (3H, m), 7.05 (1H, d, J = 8.0 Hz), 6.74 (1H, s), 6.62 (1H, dd, J = 8.4, 1.6 Hz), 5.96 (1H, s), 5.19 (2H, d, J = 48.8 Hz), 4.56 (2H, d, J = 6.0 Hz), 3.65 (3H, s), 3.48 (3H, s); LCMS: 95.3%, MS (ESI): m/z 493.1[M + H] <sup>+</sup> .                                                                                    |
| 540 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.12 (2H, s), 7.95 (1H, brs), 7.51 (1H, t, J = 8.4 Hz), 7.37 (1H, s), 7.28 (1H, dd, J = 10.8, 2.0 Hz), 7.03-7.14 (2H, m), 6.98 (1H, d, J = 8.4 Hz), 6.77 (1H, dd, J = 8.4, 1.6 Hz), 5.54 (1H, s), 4.59 (2H, d, J = 5.2 Hz), 3.94-4.03 (2H, m), 2.16 (3H, q, 6.8 Hz), 1.24 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 527.0[M+H] <sup>+</sup> .                                           |
| 541 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 11.48 (1 H, brs), 9.12 (2 H, s), 7.95 (1 H, brs), 7.58 - 7.62 (1 H, m), 7.32 (1 H, s), 7.24 (1 H, d, J=10.8 Hz), 7.10 (1 H, d, J=8.0 Hz), 6.95 (1 H, d, J=8.0 Hz), 6.80 - 6.90 (1 H, brs), 6.76 (1 H, d, J=7.6 Hz), 5.55 (1 H, s), 5.12 - 5.13 (1 H, m), 3.52 (3 H, s), 2.33 (3 H, s), 1.80 - 1.92 (2 H, m), 0.97 (3 H, t, J=7.2 Hz); LCMS: 95.9%, MS (ESI): m/z 541.0[M + H] <sup>+</sup> . |

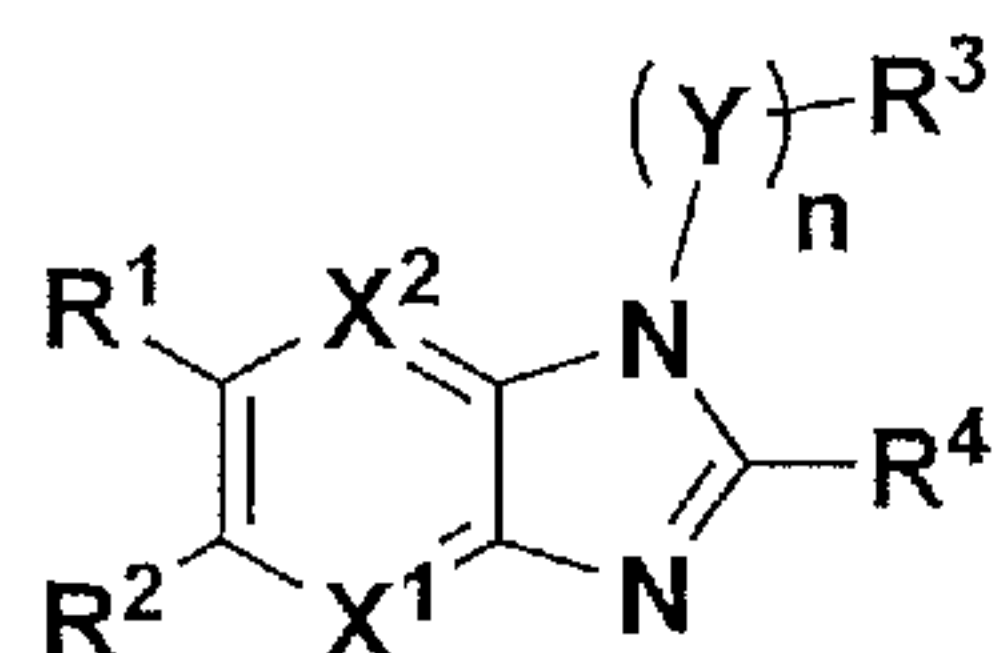
|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 542 |  | white solid; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.11 (2H, s), 7.47 (1H, t, J = 8.4 Hz), 7.26 (1H, d, J = 10.8 Hz), 7.07 (1H, d, J = 8.4 Hz), 6.95-7.05 (1H, m), 6.93 (1H, d, J = 8.4 Hz), 6.28 (1H, s), 6.19 (1H, d, J = 8.4 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.83 (2H, t, J = 6.4 Hz), 4.45-4.65 (3H, m), 4.38 (2H, t, J = 6.0 Hz), 3.90-4.10 (2H, m), 1.20 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 503.0[M + H] <sup>+</sup>                                  |
| 543 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.12 (2H, s), 7.58 (1H, t, J = 8.4 Hz), 7.23 (1H, d, J = 11.2 Hz), 7.09 (1H, d, J = 6.8 Hz), 6.90 (1H, d, J = 8.0 Hz), 6.76 (1H, brs), 6.15-6.25 (2H, m), 5.85 (1H, d, J = 5.2 Hz), 5.05-5.15 (1H, m), 4.70-4.90 (2H, m), 4.45-4.55 (1H, m), 4.30-4.40 (2H, m), 3.50 (3H, s), 1.60-2.00 (2H, m), 0.97 (3H, t, J = 7.2 Hz); LCMS: 98.15%, MS (ESI): m/z 517.0 [M+H] <sup>+</sup> .                                   |
| 544 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.54 (1H, s), 8.21 (1H, dd, J = 8.8, 2.0 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.22 (1H, d, J = 8.8 Hz), 7.14 (2H, d, J = 8.4 Hz), 6.95-7.00 (1H, m), 6.94 (1H, d, J = 8.0 Hz), 6.25 (1H, s), 6.22 (1H, d, J = 8.4 Hz), 5.85 (1H, d, J = 6.8 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.45-4.58 (3H, m), 4.39 (2H, t, J = 6.0 Hz), 3.45 (3H, s); LCMS: 100%, MS (ESI): m/z 470.0[M + H] <sup>+</sup> .                               |
| 545 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.83 (2H, s), 8.37 (1H, brs), 7.45 (2H, d, J = 8.4 Hz), 7.16-7.26 (3H, m), 7.05 (1H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.4 Hz), 6.25 (1H, s), 4.57 (2H, d, J = 4.8 Hz), 4.02-1-4.04 (2H, m), 3.83 (3H, s), 1.25 (3H, t, J = 6.8 Hz); LCMS: 100%, MS (ESI): m/z 593.0[M + H] <sup>+</sup> .                                                                                                                           |
| 546 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.57 (1H, s), 8.24 (1H, dd, J = 8.8, 2.4 Hz), 7.50 (1H, t, J = 8.4 Hz), 7.28 (1H, d, J = 8.4 Hz), 7.18 (1H, dd, J = 10.8, 2.4 Hz), 7.01 (2H, dd, J = 8.4, 2.0 Hz), 6.95 (1H, d, J = 8.4 Hz), 6.26 (1H, d, J = 1.2 Hz), 6.23 (1H, d, J = 8.0, 1.2 Hz), 5.87 (1H, d, J = 6.8 Hz), 4.84 (2H, t, J = 6.4 Hz), 4.46-4.61 (3H, m), 4.34-4.44 (2H, m), 3.46 (3H, s); LCMS: 100%, MS (ESI): m/z 487.9[M + H] <sup>+</sup> . |
| 547 |  | pale yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.05 (2H, s), 7.47 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.8 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.65 (1H, d, J = 8.4 Hz), 6.19 (1H, d, J = 1.6 Hz), 6.15 (1H, dd, J = 8.4, 2.0 Hz), 5.78 (1H, d, J = 7.2 Hz), 4.74-4.88 (3H, m), 4.35-4.50 (1H, m), 4.29-4.38 (2H, m), 3.44 (3H, s), 1.71-1.95 (2H, m), 0.91 (3H, t, J = 7.2 Hz); LCMS: 100%, MS (ESI): m/z 499.0[M + H] <sup>+</sup> .                           |

|     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 548 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.09 (2H, s), 7.45 (2H, d, J = 8.4 Hz), 7.20 (2H, d, J = 8.4 Hz), 7.04 (1H, brs), 6.93 (1H, d, J = 8.4 Hz), 6.29 (1H, d, J = 1.6 Hz), 6.19 (1H, dd, J = 8.0, 1.6 Hz), 5.84 (1H, d, J = 7.2 Hz), 4.84 (2H, t, J = 6.0 Hz), 4.47-4.57 (3H, m), 4.36-4.42 (2H, m), 3.98 (2H, q, J = 6.8 Hz), 1.20 (3H, t, J = 7.2 Hz); LCMS: 99.5%, MS (ESI): m/z 485.0[M + H] <sup>+</sup> .                                                                                |
| 549 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.53 (1H, s), 8.18 (1H, dd, J = 8.8, 2.4 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.8 Hz), 7.10 (2H, d, J = 8.8 Hz), 6.87 (1H, d, J = 8.0 Hz), 6.66 (1H, d, J = 8.4 Hz), 6.20 (1H, s), 6.16 (1H, dd, J = 8.4, 2.0 Hz), 5.80 (1H, d, J = 6.8 Hz), 4.72-4.85 (3H, m), 4.40-4.50 (1H, m), 4.33-4.41 (2H, m), 3.45 (3H, s), 1.69-1.96 (2H, m), 0.92 (3H, t, J = 7.6 Hz); LCMS: 100%, MS (ESI): m/z 498.1[M + H] <sup>+</sup> .                         |
| 550 |  | white powder; <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.58 (1H, s.), 8.23 (1H, d, J = 8.8 Hz), 7.56 (1H, t, J = 8.4 Hz), 7.26 (1H, d, J = 8.8 Hz), 7.13 (1H, d, J = 10.8 Hz), 7.01 (1H, d, J = 8.0 Hz), 6.90 (1H, d, J = 8.0 Hz), 6.73 (1H, d, J = 8.0 Hz), 6.13-6.25 (2H, m), 5.83 (1H, d, J = 6.8 Hz), 5.06-5.15 (1H, m), 4.83 (2H, t, J = 6.4 Hz), 4.44-4.55 (1H, m), 4.33-4.41 (2H, m), 3.50 (3H, s), 1.68- 1.96 (2H, m), 0.97 (3H, t, J = 7.2 Hz); LCMS: 99.3%, MS (ESI): m/z 516.0 [M + H] <sup>+</sup> . |
| 551 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 9.08 (2H, s), 7.45 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.4 Hz), 7.11 (1H, t, J = 6.0 Hz), 6.00-6.15 (3H, m), 4.83 (2H, t, J = 6.4 Hz), 4.46-4.57 (3H, m), 4.36 (2H, t, J = 6.0 Hz), 3.44 (3H, s); LCMS: 100%, MS (ESI): m/z 489.0[M + H] <sup>+</sup> .                                                                                                                                                                                                 |
| 552 |  | white powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.51 (1H, s), 8.18 (1H, dd, J = 8.4, 2.0 Hz), 7.42 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.8 Hz), 7.02-7.16 (3H, m), 5.95-6.12 (3H, m), 4.81 (2H, t, J = 6.4 Hz), 4.42-4.56 (3H, m), 4.34 (2H, t, J = 6.4 Hz), 3.42 (3H, s); LCMS: 100.0%, MS (ESI): m/z 488.0[M + H] <sup>+</sup> .                                                                                                                                                                      |
| 553 |  | yellow powder; <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , 400 MHz): δ 8.14 (1H, d, J = 2.4 Hz), 7.91 (1H, dd, J = 8.4, 2.4 Hz), 7.40 (2H, d, J = 8.0 Hz), 6.97-7.12 (3H, m), 5.95-6.27 (3H, m), 4.82 (2H, t, J = 6.4 Hz), 4.41-4.60 (3H, m), 4.35 (2H, t, J = 5.6 Hz), 3.44 (3H, s); LCMS: 86.5%, MS (ESI): m/z 476.0[M + Na] <sup>+</sup> .                                                                                                                                                                                   |

|     |                                                                                     |                                                                                                                                                                                                                                                                                                                                        |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 554 |    | pale yellow powder; $^1\text{H}$ -NMR (DMSO- $d_6$ , 400 MHz): $\delta$ 8.70 (2H, s), 7.41 (2H, d, $J$ = 8.0 Hz), 7.12 (2H, d, $J$ = 8.0 Hz), 7.07 (1H, t, $J$ = 6.0 Hz), 5.95-6.10 (3H, m), 4.81 (2H, t, $J$ = 6.0 Hz), 4.45-4.55 (3H, m), 4.34 (2H, t, $J$ = 6.0 Hz), 3.42 (3H, s); LCMS: 99.3%, MS (ESI): $m/z$ 455.0[M + H] $^+$ . |
| 555 |    | white powder; $^1\text{H}$ -NMR (DMSO- $d_6$ , 400 MHz): $\delta$ 8.73 (2H, s), 7.42 (2H, d, $J$ = 8.0 Hz), 7.16 (3H, d, $J$ = 8.0 Hz), 5.98-6.17 (3H, m), 4.84 (2H, t, $J$ = 6.4 Hz), 4.47-4.60 (3H, m), 4.34-4.42 (2H, m), 3.98 (2H, q, $J$ = 6.8 Hz), 1.19 (3H, t, $J$ = 6.8 Hz); LCMS: 100%, MS (ESI): $m/z$ 469.0[M + H] $^+$ .   |
| 556 |  | pink powder; $^1\text{H}$ NMR (DMSO- $d_6$ , 400 MHz): $\delta$ 11.57 (1H, brs), 8.74 (2H, s), 8.14 (1H, s), 7.47 (2H, d, $J$ = 8.0 Hz), 7.15-7.25 (4H, m), 7.03 (1H, s), 5.55 (1H, s), 4.59 (2H, d, $J$ = 5.6 Hz), 3.47 (3H, s), 2.17 (3H, s); LCMS: 100%, MS (ESI): $m/z$ = 517.0 [M + Na] $^+$ .                                    |

# Claims

1. A compound having the general formula I:



Formula I

wherein

$n$  is 0 or 1;

$X^1$  and  $X^2$  are independently, at each occurrence,  $CR^5$  or N;

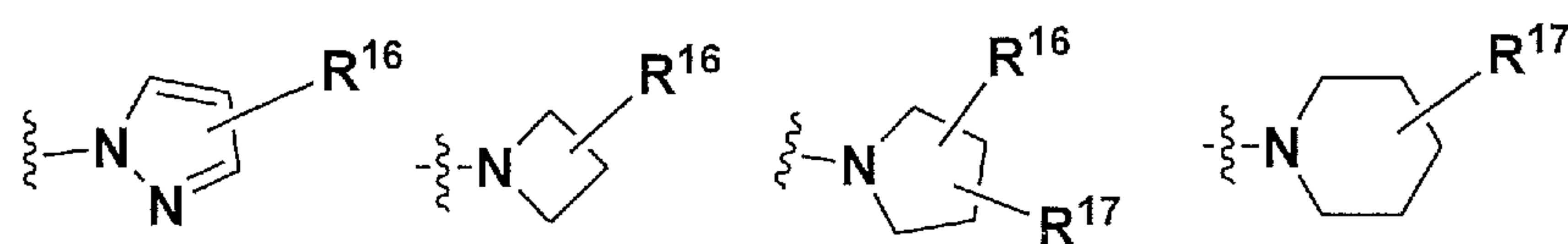
$Y$  is  $C_1$ - $C_6$  alkylene, wherein alkylene is optionally substituted with one to two  $C_1$ - $C_3$  alkyl groups;

$R^1$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkoxy,  $-NH_2$ ,  $-NHR^6$ ,  $-NR^7R^8$  and  $-NH-(R^9)_n-R^{10}$ ,  $n$  being 0 or 1;

$R^2$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $-NH_2$ ,  $-NHR^6$ ,  $-NR^7R^8$  and  $-NH-(R^9)_n-R^{10}$  group,  $n$  being 0 or 1;

$R^3$  is selected from the group consisting of hydrogen, hydroxyl,  $OR^{11}$ ,  $-NR^7R^8$ ,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_3$  haloalkyl,  $-C(O)NHR^{11}$ , aryl, heteroaryl and heterocyclyl group, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;

$R^4$  is selected from the group consisting of  $-NH_2$ ,  $-N(R^{12})(V)_pR^{13}$ ,  $-NH(V)_p-OR^{14}$ ,  $-NHC(O)R^{15}$ , and groups of formula Ia shown below,



Formula Ia

wherein,

p is 0 or 1,

V is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl or phenyl groups, or wherein a carbon atom of said alkylene forms part of a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy group;

R<sup>6</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>7</sup> and R<sup>8</sup> are independently, at each occurrence, C<sub>1</sub>-C<sub>6</sub> alkyl or heterocyclyl; or

R<sup>7</sup> and R<sup>8</sup> are connected to each other to make a four, five or six membered heterocyclyl or heteroaryl group, wherein each of said heterocyclyl and heteroaryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

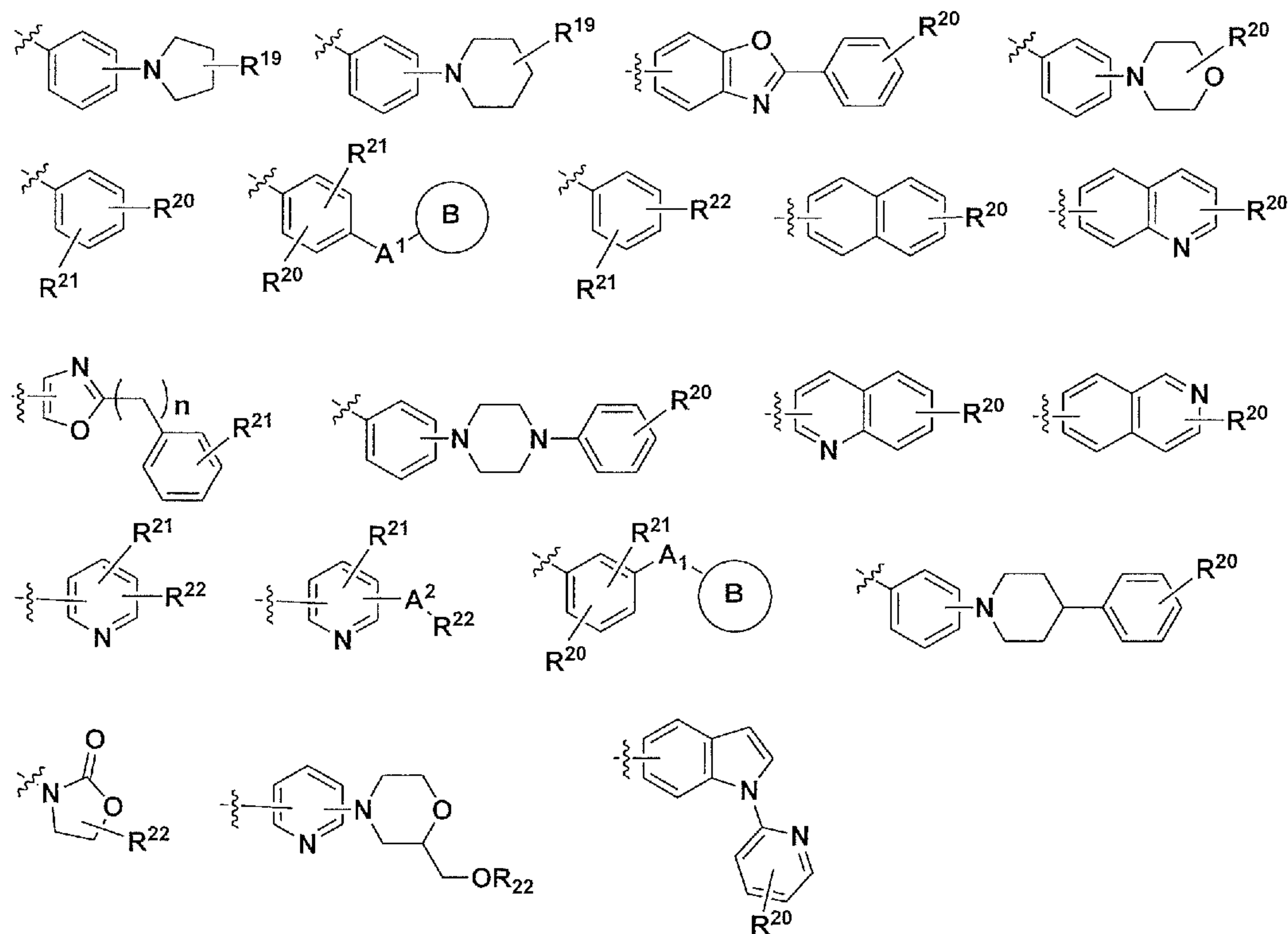
R<sup>9</sup> is C<sub>1</sub>-C<sub>4</sub> alkylene, wherein said alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>10</sup> is selected from the group consisting of hydroxyl, -OR<sup>11</sup>, -CN, -C(O)OR<sup>18</sup>, -C(O)NH<sub>2</sub>, -C(NH)NH<sub>2</sub>, aryl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>11</sup> is independently, at each occurrence, selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>12</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl-hydroxyl and C<sub>1</sub>-C<sub>4</sub> alkyl-alkoxy;

$R^{13}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_4$  alkyl-hydroxyl,  $-OH$ ,  $-C(O)NH_2$ ,  $-C(O)OR^{18}$ ,  $-CN$ ,  $C_1$ - $C_3$  haloalkyl and heterocyclyl, and groups of formula Ib shown below,



Formula Ib

wherein,

$n$  is 0 or 1;

$A^1$  is  $-O-$ ,  $-CH_2O-$ ,  $-OCH_2-$ ,  $-S-$ ,  $-SO_2-$ ,  $-SO_2NH-$ ,  $-C(O)-$ ,  $-C(O)NH-$ ,  $-C(O)N(R^7)-$ ,  $-CH(OH)-$ ,  $-CH(OR^7)-$ ,  $-NH-$ ,  $-N(CH_3)-$  or  $-N(CH_2COOR^7)-$ ;

$A^2$  is  $-O-$  or  $NH-$ ;

$B$  is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;

$R^{14}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or  $C_1$ - $C_3$  haloalkoxy groups;

$R^{15}$  is aryl, wherein aryl is optionally substituted with one to four halogen groups;

$R^{16}$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl and hydroxyl ;

$R^{17}$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $-C(O)R^{11}$ ,  $-C(O)NHR^{11}$ ,  $-OR^{11}$  and aryl , wherein each of said alkyl and aryl is optionally and independently substituted with one to four  $R^a$  groups;

$R^{18}$  is hydrogen or  $C_1$ - $C_6$  alkyl;

$R^{19}$  is selected from the group consisting of hydrogen,  $-OR^{22}$  and  $-CH_2OR^{22}$ ;

$R^{20}$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $-C(O)R^a$  and  $C_1$ - $C_6$  haloalkoxy;

$R^{21}$  is selected from the group consisting of hydrogen, halogen and  $C_1$ - $C_6$  alkyl group;

$R^{22}$  is selected from the group consisting of  $C_1$ - $C_6$  haloalkyl, aryl, e.g. phenyl or benzyl, and heteroaryl, wherein each of said haloalkyl, aryl and heteroaryl is optionally and independently substituted with one to four  $R^a$  groups;

$R^a$  is independently, at each occurrence, selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_3$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy, hydroxyl,  $C_1$ - $C_3$  alkylhydroxyl,  $-CH_2OR^c$ ,  $-OCH_2R^c$ ,  $-OR^c$ ,  $-CN$ ,  $NO_2$ ,  $-NR^bR^c$ ,  $-C(O)NR^bR^c$ ,  $-C(NH)NH_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ , sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_1$ - $C_3$  haloalkyl,  $-CN$ ,  $-C(O)NH_2$ ,  $-COOH$ ,  $-CO_2Et$  and heteroaryl;

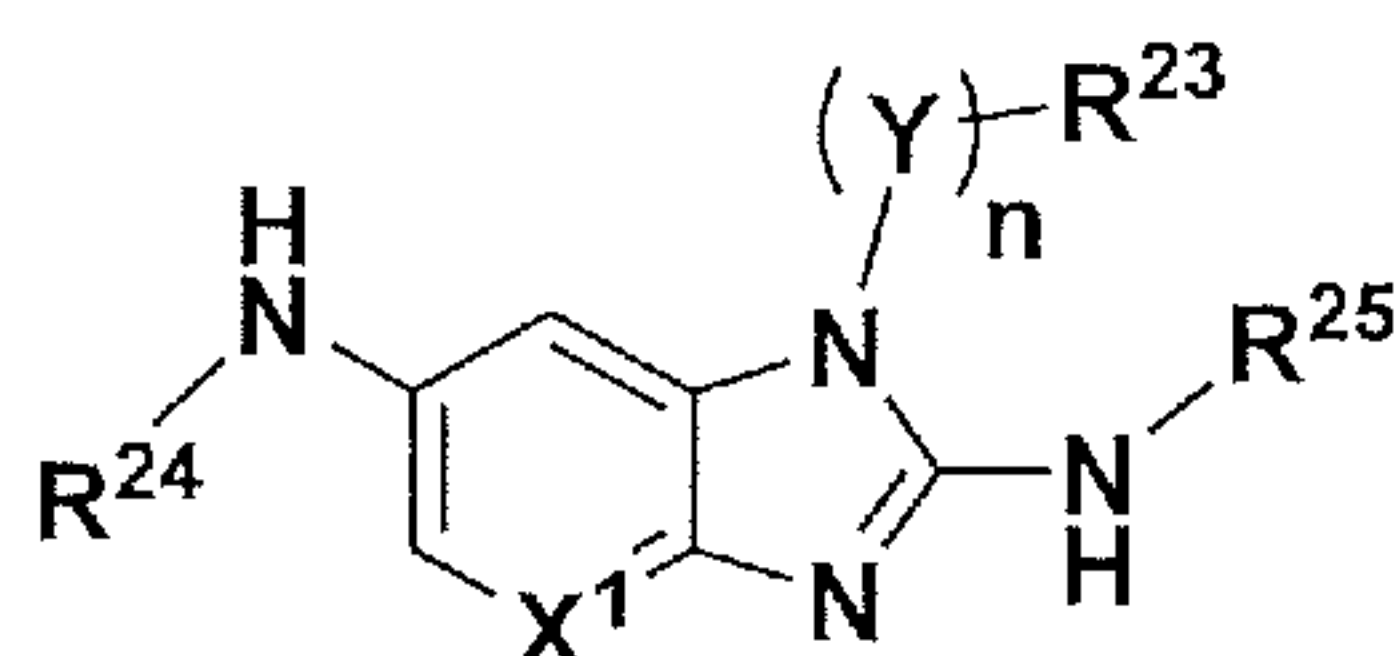
$R^b$  and  $R^c$  are independently, at each occurrence, selected from the group consisting of hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_6$  alkyl-O-alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_3$  alkylhydroxyl,  $C_3$ - $C_{10}$  cycloalkenyl,  $C_2$ - $C_{10}$  alkynyl,  $C_1$ - $C_6$  haloalkyl, aryl, e.g. phenyl

or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, cycloalkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, -C(O)NH<sub>2</sub>, -COOH, -COOMe, -COOEt, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>; or

R<sup>b</sup> and R<sup>c</sup> are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;

and pharmaceutically acceptable salts thereof.

2. The compound according to claim 1 having the general formula II:



Formula II

wherein

n is 0 or 1;

X<sup>1</sup> is CR<sup>5</sup> or N;

Y is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to two C<sub>1</sub>-C<sub>3</sub> alkyl groups;

R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl and C<sub>1</sub>-C<sub>6</sub> alkoxy group;

R<sup>23</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>24</sup> is selected from the group consisting of hydrogen, C<sub>3</sub>-C<sub>10</sub>cycloalkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

$R^{25}$  is selected from the group consisting of hydrogen,  $-(V)_pR^{26}$  and  $-(V)_pOR^{14}$ ;

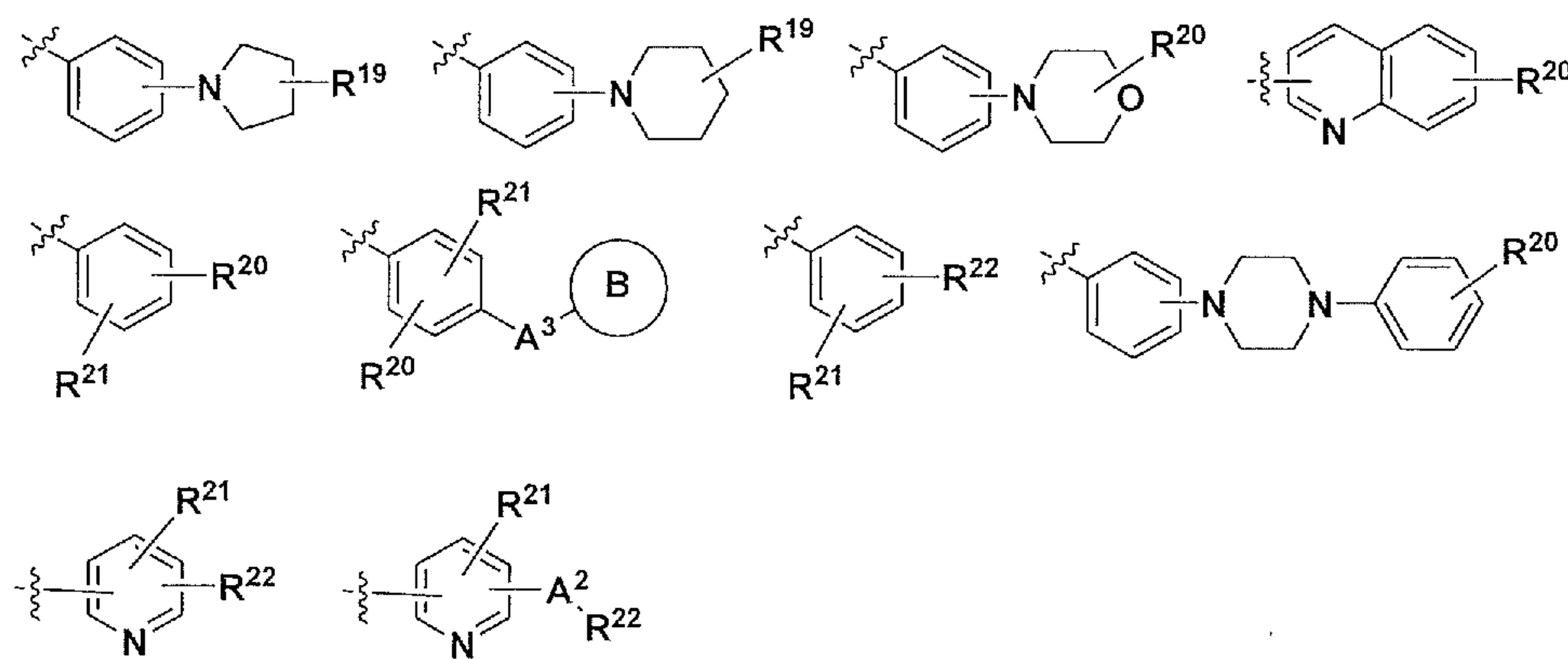
wherein,

$p$  is 0 or 1,

$V$  is  $C_1$ - $C_6$  alkylene, wherein alkylene is optionally substituted with one to three  $C_1$ - $C_3$  alkyl or phenyl groups, or wherein a carbon atom of said alkylene forms part of a  $C_3$ - $C_6$  cycloalkyl group;

$R^{14}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or  $C_1$ - $C_3$  haloalkoxy groups;

$R^{26}$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl,  $-CN$  and  $C_1$ - $C_3$  haloalkyl, and groups of formula IIa shown below,



Formula IIa

wherein,

$A^2$  is  $-O-$  or  $NH-$ ;

$A^3$  is  $-O-$ ,  $-CH_2O-$ ,  $-OCH_2-$ , or  $-NH-$ ;

$B$  is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups;

$R^{19}$  is selected from the group consisting of hydrogen,  $-OR^{22}$  and  $-CH_2OR^{22}$ ;

$R^{20}$  is selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy and  $C_1$ - $C_6$  haloalkoxy;

$R^{21}$  is selected from the group consisting of hydrogen, halogen and  $C_1$ - $C_6$  alkyl;

$R^{22}$  is selected from the group consisting of aryl, e.g. phenyl or benzyl, and heteroaryl, wherein each of said aryl and heteroaryl is optionally and independently substituted with one to four  $R^a$  groups;

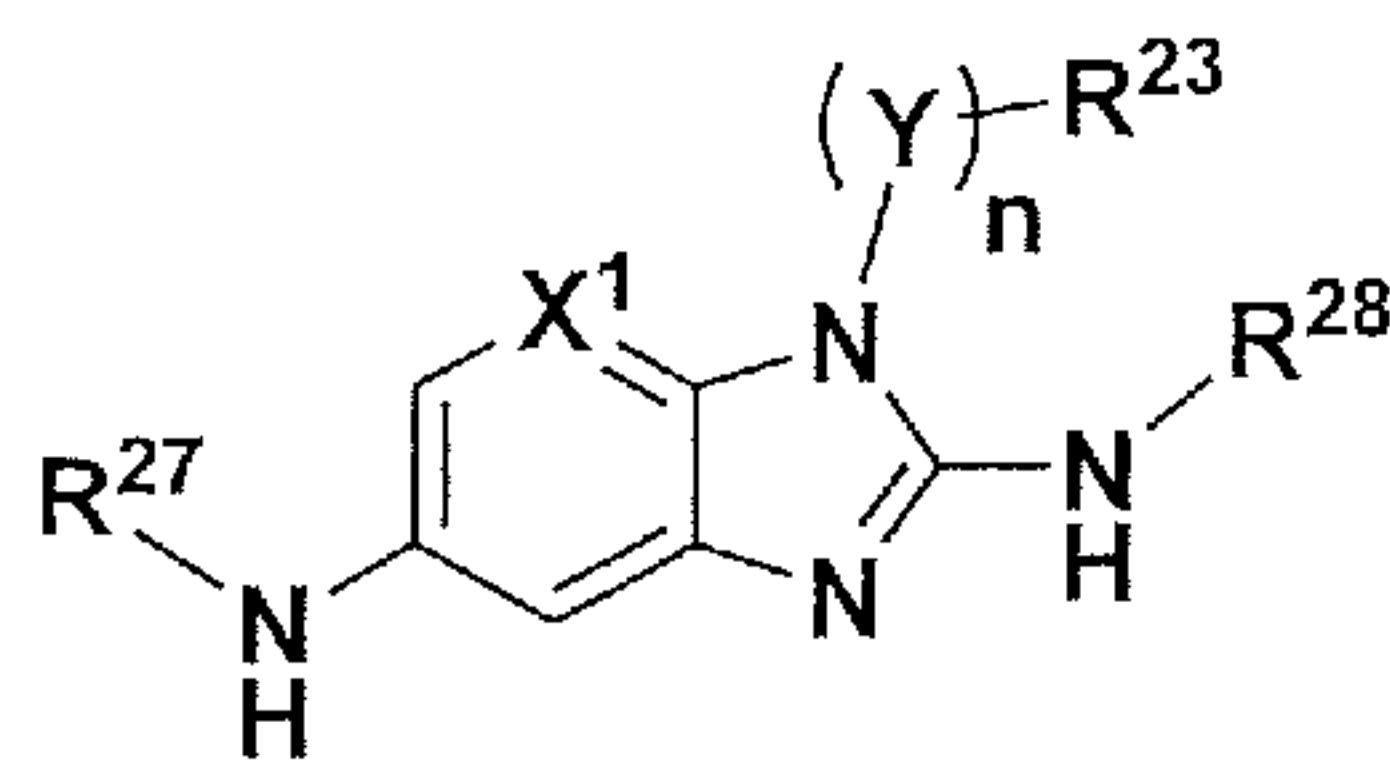
$R^a$  is independently, at each occurrence, selected from the group consisting of hydrogen, halogen,  $C_1$ - $C_3$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy, hydroxyl,  $C_1$ - $C_3$  alkylhydroxyl,  $-CH_2OR^c$ ,  $-OCH_2R^c$ ,  $-OR^c$ ,  $-CN$ ,  $NO_2$ ,  $-NR^bR^c$ ,  $-C(O)NR^bR^c$ ,  $-C(NH)NH_2$ ,  $-C(O)R^c$ ,  $-C(O)OR^c$ , sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_1$ - $C_3$  haloalkyl,  $-CN$ ,  $-C(O)NH_2$ ,  $-COOH$ ,  $-CO_2Et$  and heteroaryl;

$R^b$  and  $R^c$  are independently, at each occurrence, selected from the group consisting of hydrogen,  $C_1$ - $C_{10}$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_1$ - $C_6$  alkyl-O-alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_3$  alkylhydroxyl,  $C_3$ - $C_{10}$  cycloalkenyl,  $C_2$ - $C_{10}$  alkynyl,  $C_1$ - $C_6$  haloalkyl, aryl, e.g. phenyl or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $C_1$ - $C_3$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy, hydroxyl,  $-C(O)NH_2$ ,  $-COOH$ ,  $-COOMe$ ,  $-COOEt$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ; or

$R^b$  and  $R^c$  are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;

and pharmaceutically acceptable salts thereof.

3. The compound according to claim 1 having the general formula III:



Formula III

wherein

n is 0 or 1;

X¹ is CR⁵ or N;

Y is C₁-C₆ alkylene, wherein alkylene is optionally substituted with one to two C₁-C₃ alkyl groups;

R⁵ is selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl and C₁-C₆ alkoxy group;

R²³ is selected from the group consisting of hydrogen, C₁-C₆ alkyl, aryl, heteroaryl and heterocyclyl group, wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four Rᵃ groups;

R²⁷ is selected from the group consisting of hydrogen, -R⁶, and -R⁹-R¹⁰;

wherein,

R⁶ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₁-C₆ haloalkyl, aryl, heteroaryl and heterocyclyl group, wherein said alkyl, cycloalkyl, haloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four Rᵃ groups;

R⁹ is C₁-C₄ alkylene, wherein said alkylene is optionally substituted with one to three C₁-C₃ alkyl groups;

R<sup>10</sup> is selected from the group consisting of hydroxyl, -OR<sup>11</sup>, -C(O)OR<sup>18</sup>, -C(O)NH<sub>2</sub>, aryl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>11</sup> is independently, at each occurrence selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>18</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl;

$R^{28}$  is selected from the group consisting of hydrogen,  $-(V)_pR^{29}$  and  $-(V)_p-OR^{14}$  group;

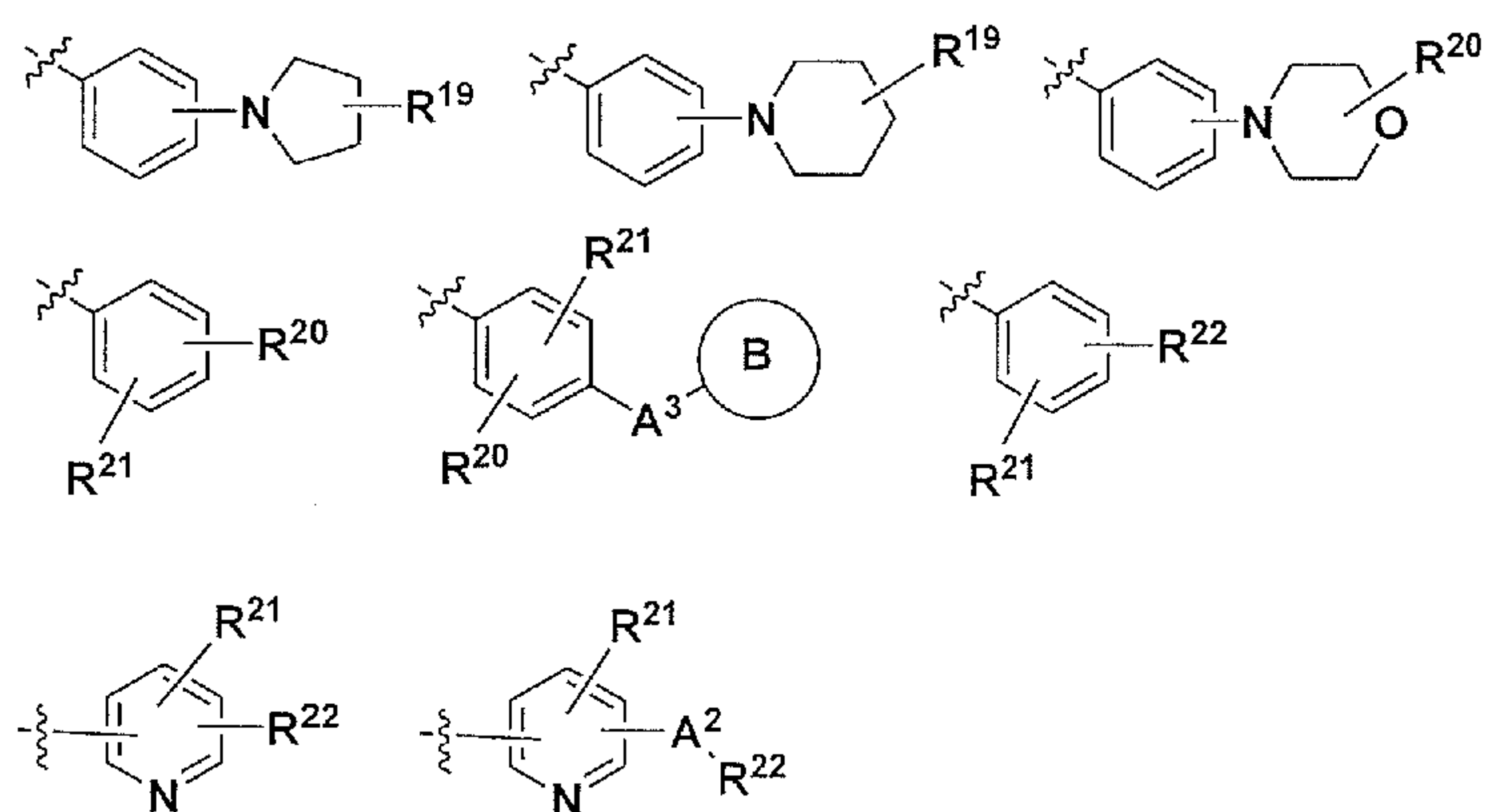
wherein,

$p$  is 0 or 1,

V is C<sub>1</sub>-C<sub>6</sub> alkylene, wherein alkylene is optionally substituted with one to three C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl groups;

R<sup>14</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl, wherein each of said alkyl and aryl is optionally and independently substituted with one to four halogen or C<sub>1</sub>-C<sub>3</sub> haloalkoxy groups;

R<sup>29</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and C<sub>1</sub>-C<sub>3</sub> haloalkyl, and groups of formula IIIa shown below,



### Formula IIIa

wherein,

A<sup>2</sup> is -O- or NH-;

A<sup>3</sup> is -O-, -CH<sub>2</sub>O-, -OCH<sub>2</sub>-, or -NH-;

B is selected from the group consisting of aryl, e.g. phenyl or benzyl, heteroaryl and heterocyclyl group wherein each of said aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>19</sup> is selected from the group consisting of hydrogen, -OR<sup>22</sup> and -CH<sub>2</sub>OR<sup>22</sup>;

R<sup>20</sup> is selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy and C<sub>1</sub>-C<sub>6</sub> haloalkoxy;

R<sup>21</sup> is selected from the group consisting of hydrogen, halogen and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>22</sup> is selected from the group consisting of aryl, e.g. phenyl or benzyl, and heteroaryl, wherein said aryl and heteroaryl is optionally and independently substituted with one to four R<sup>a</sup> groups;

R<sup>a</sup> is independently, at each occurrence, selected from the group consisting of hydrogen, halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, -CH<sub>2</sub>OR<sup>c</sup>, -OCH<sub>2</sub>R<sup>c</sup>, -OR<sup>c</sup>, -CN, NO<sub>2</sub>, -NR<sup>b</sup>R<sup>c</sup>, -C(O)NR<sup>b</sup>R<sup>c</sup>, -C(NH)NH<sub>2</sub>, -C(O)R<sup>c</sup>, -C(O)OR<sup>c</sup>, sulfonyl, sulfoxide, heterocyclyl, heteroaryl and aryl, e.g. phenyl, benzyl, wherein each of said alkyl, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, C<sub>1</sub>-C<sub>3</sub> haloalkyl, -CN, -C(O)NH<sub>2</sub>, -COOH, -CO<sub>2</sub>Et and heteroaryl;

R<sup>b</sup> and R<sup>c</sup> are independently, at each occurrence, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-O-alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> alkylhydroxyl, C<sub>3</sub>-C<sub>10</sub> cycloalkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, alkyl-O-alkyl, alkenyl, alkoxy, cycloalkenyl, alkynyl, haloalkyl, aryl, e.g. phenyl or benzyl, heteroaryl, and heterocyclyl wherein each of said alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is optionally and independently substituted with one to four C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen,

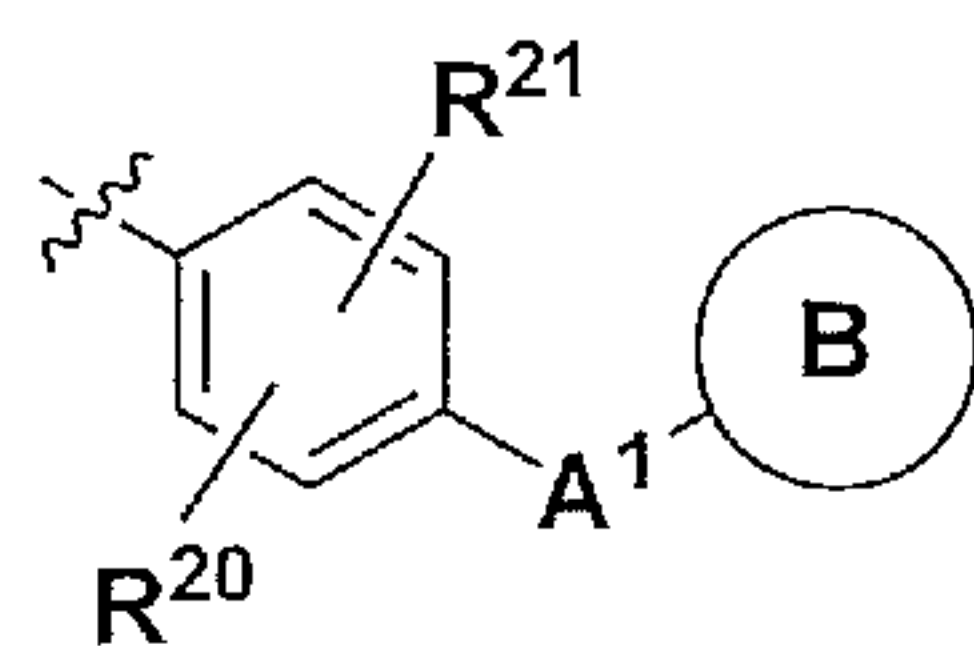
C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, hydroxyl, -C(O)NH<sub>2</sub>,  
-COOH, -COOMe, -COOEt, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>; or

R<sup>b</sup> and R<sup>c</sup> are connected to each other to make a four, five or six membered saturated or unsaturated cyclic or heterocyclic ring;

and pharmaceutically acceptable salts thereof.

4. The compound according to any of claims 1-3, having one of the formulae 1- 556, as shown in tables 1-6 and/or example 7 and/or table 7, or a pharmaceutically acceptable salt thereof, preferably having one of the formulae 1-12, 14-16, 19-21, 24, 28-34, 36-40, 44, 48, 51-54, 56-68, 70, 71, 73-77, 79-81, 84, 86-173, 175-192, 194-234, 236-241, 243, 244, 246-261, 263-278, 280-321, 323-354, 356-385, 387- 428, 430-440, 442-446, 449-463, 465-471, 473-487, 489-492, 495-496, 499, 501, 503, 505, 507, 509, 512-514, 525, 529-544, 546-556 as indicated in Tables 1 and 7, or formula 14 as indicated in Tables 2 and 7, or one of the formulae 53, 54, 86, 90, 91, 95, 99, 103, 226 as indicated in Tables 5 - 7; or one of the formulae 14, 17, 24, 29, 30, 32, 33, 38, 43-46, 48, 49, 51-60, 62, 65-70, 73, 74, 79-81, 84, 86-88, 90-107, 109-113, 116, 118-132, 134-138, 140, 145, 147-150, 152, 153, 155, 160-162, 164-166, 168, 169, 172, 175-177, 179, 180, 184-187, 190-197, 199, 200, 202-220, 223, 224, 226, 227, 229-231, 233-236, 238-255, 257-262, 264, 265, 267-302, 304-306, 313, 316, 322-333, 335, 340, 342, 346, 347, 349, 350, 352, 353, 357-359, 361, 365-369, 372-375, 377-380, 382-384, 387, 389-393, 395-403, 405-407, 410, 412-415, 419-428, 430-432, 434-437, 440, 442, 445-453, 455, 457-458, 460-461, 463-482, 486-487, 489-496, 499, 501-553, 556 as indicated in Tables 3 and 7, or one of the formulae, 11, 12, 14, 24, 30, 32, 48, 52-54, 62, 65, 77, 79-81, 86-88, 92, 94, 97, 98, 101-103, 106, 109-111, 113, 119, 120, 122, 123, 125, 130, 136-138, 145, 147, 149, 155, 165, 166, 176, 177, 184, 193, 195, 199, 204, 211, 226, 227, 229, 231, 233, 234, 238, 239, 243, 249, 251, 253, 256, 268-271, 275, 277, 279, 281, 284, 288, 289, 296, 306, 311, 324, 328, 336, 341, 345, 350, 351, 358, 360, 362, 367-369, 373, 374, 378, 381, 392, 412-415, 430, 431, 433, 447-450, 461, 464-466, 468-471, 473-477, 479, 481, 482, 486, 487, 489-496, 498, 499, 501-506, 508, 509, 512-514, 516-519, 525-538, 540-547, 550, 553-554 as indicated in Tables 4 and 7; or having the formula 211 as indicated in Figure 1 and Table 7; or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, wherein R<sup>4</sup> is -N(R<sup>12</sup>)(V)<sub>p</sub>R<sup>13</sup>, R<sup>12</sup> is H, V is C<sub>1</sub>-alkylene, p is 1, R<sup>13</sup> is



and B is heteroaryl which is optionally substituted with one to four  $R^a$  groups.

6. The compound according to any of claims 1 or 5 wherein  $R^1$  is  $-NH_2$  or  $-NHR^6$ ,  $R^6$  is heteroaryl or heterocyclyl wherein each of said heteroaryl and heterocyclyl is optionally and independently substituted with one to four  $R^a$  groups.

7. The compound according to any of claims 1- 6 or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with the 5LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said disease being selected from inflammatory diseases, e.g. asthma, atherosclerosis, pain, or COPD, cancer, stroke and Alzheimer's disease.

8. The compound according to any of claims 1- 7, wherein said compound has an inhibitory activity on an enzyme involved in an inflammatory pathway or several inflammatory pathways, e.g. the arachidonate 5-lipoxygenase pathway and/or the prostaglandin E synthase pathway, preferably on arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5), at a concentration of said compound between 0.001-50  $\mu M$ , particularly preferably having an  $IC_{50}$  on arachidonate 5-lipoxygenase of less than 1  $\mu M$  and/or having an  $EC_{50}$  of less than 10  $\mu M$  on the production of leukotriene B4 (LTB4) in rat basophilic leucocyte cells (RBL) and/or rat whole blood (RWB), and/or having a 40-70 % inhibitory activity, preferably  $>70$  % inhibitory activity on the production of prostaglandin E2 in HeLaS3 cells, stimulated with  $TNF-\alpha$ , at a concentration of 10  $\mu M$  of said compound.

9. A composition comprising a compound or a pharmaceutically acceptable salt thereof, as defined in any of claims 1- 6, and a pharmaceutically acceptable carrier.

10. The composition according to claim 9, for use in the treatment of a disease associated with the 5LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said disease

being selected from inflammatory diseases, e.g. asthma, atherosclerosis, pain, or COPD, cancer, stroke and Alzheimer's disease.

11. The compound or composition for use according to any of claims 7-8, 10 wherein said inflammatory disease is one or several of asthma, allergic rhinitis, dermatitis, chronic obstructive pulmonary disease (COPD), inflammation post infection, arthritis, atherosclerosis, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, or pain, e.g. inflammatory and/or neuropathic pain.

12. The compound or composition for use according to any of claims 7-8, 10-11 wherein said treatment comprises administering a suitable amount of a compound as defined in any of claims 1-6 , or of a composition as defined in claim 9 , to a patient in need thereof, suffering from an inflammatory disease, and/or of cancer, and/or of stroke, and/or of Alzheimer's disease.

13. A method of treatment of a disease associated with the 5-LOX-pathway and/or the prostaglandin E synthase (PGES) pathway, said disease being selected from inflammatory diseases, cancer and Alzheimer's disease, said method comprising the application of a suitable amount of a compound as defined in any of claims 1-6 or of a composition as defined in claim 9 , to a patient in need thereof, suffering from a disease associated with the 5-LOX-pathway and/or the prostaglandin E synthase (PGES) pathway.

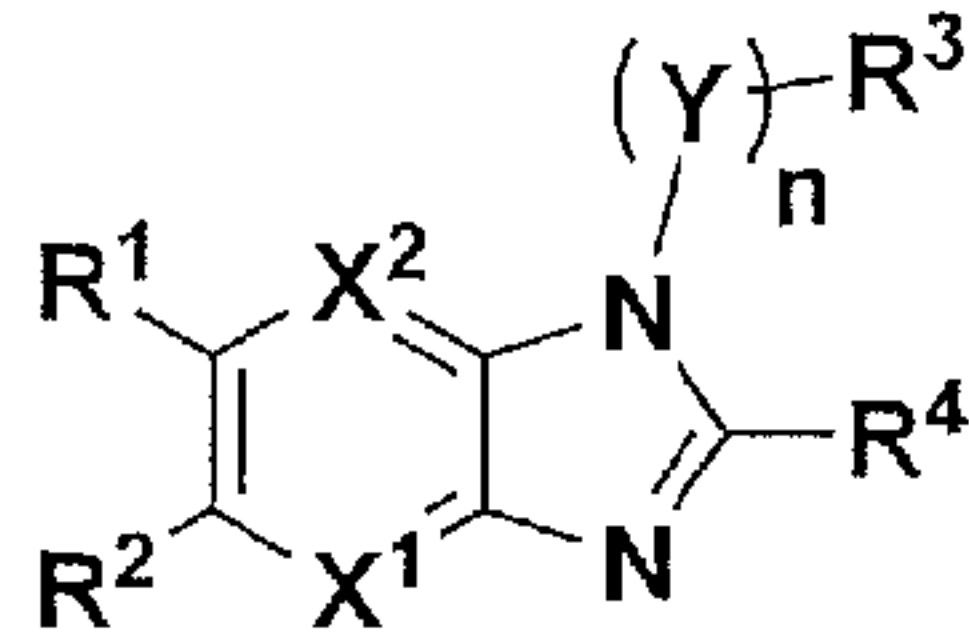
14. The method of treatment according to claim 13 , wherein said inflammatory disease is selected from asthma, allergic rhinitis, dermatitis, chronic obstructive pulmonary disease (COPD), inflammation post infection, arthritis, atherosclerosis, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, and pain, e.g. inflammatory and/or neuropathic pain.

15. The compound or composition for use according to claim 12 or the method of treatment according to any of claims 13-14, wherein said suitable amount is an amount in the range of 0.01mg/kg body weight to 1g/kg body weight of said patient.

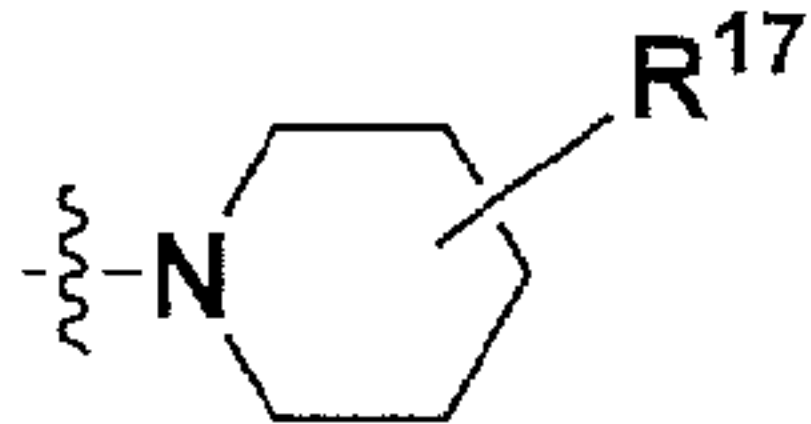
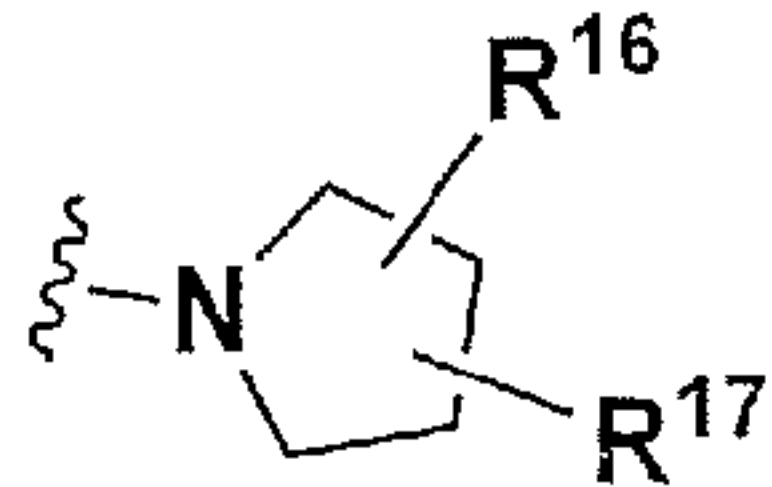
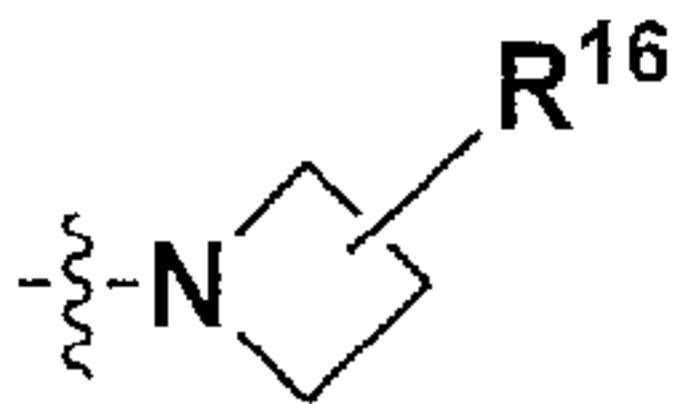
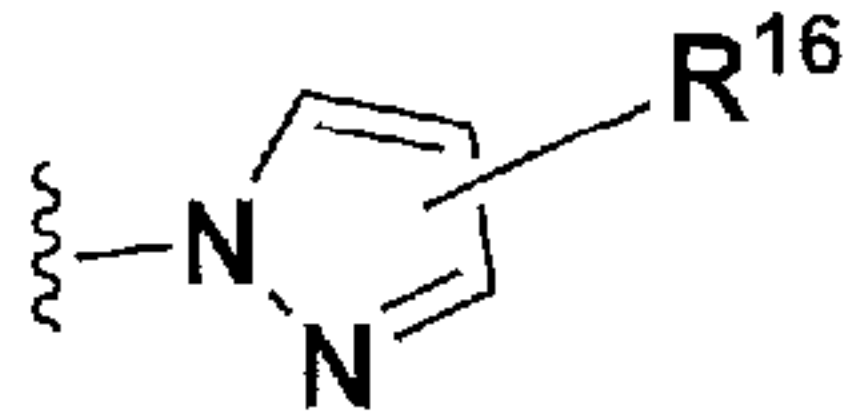
16. A compound that competitively inhibits the specific binding of a compound as defined in any of claims 1-6 to arachidonate 5-lipoxygenase (5-lipoxygenase, 5-LO, 5-LOX, Alox5) or to prostaglandin E synthase (PGES).

17. A method of treatment of an inflammatory disease, in particular asthma, atherosclerosis, pain, chronic obstructive pulmonary disease (COPD), inflammation post infection, allergic rhinitis, arthritis, pain, e.g. inflammatory or neuropathic pain, allergies, such as hay fever, autoimmune diseases, such as lupus erythematosus, inflammatory bowel diseases, such as Crohn's disease, celiac disease, acne, and/or dermatitis, or a method of treatment of cancer/and or of Alzheimer's disease, said method comprising the application of a suitable amount of a compound according to claim 16, to a patient in need thereof.

18. The method of treatment according to claim 17 wherein said patient is a patient suffering from an inflammatory disease and/or from cancer and/or from stroke and/or from Alzheimer's disease.



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