



(86) Date de dépôt PCT/PCT Filing Date: 2007/11/20

(87) Date publication PCT/PCT Publication Date: 2008/05/29

(85) Entrée phase nationale/National Entry: 2009/05/20

(86) N° demande PCT/PCT Application No.: US 2007/024362

(87) N° publication PCT/PCT Publication No.: 2008/063667

(30) Priorité/Priority: 2006/11/20 (US60/860,195)

(51) Cl.Int./Int.Cl. *C07D 413/12* (2006.01),  
*A61K 31/519* (2006.01), *A61P 29/00* (2006.01),  
*C07D 491/04* (2006.01), *C07D 495/04* (2006.01),  
*C07D 495/14* (2006.01), *C07D 495/22* (2006.01)

(71) Demandeur/Applicant:  
ALANTOS PHARMACEUTICALS HOLDING, INC., US

(72) Inventeurs/Inventors:  
GEGE, CHRISTIAN, DE;  
CHEVRIER, CARINE, FR;  
SCHNEIDER, MATTHIAS, DE;  
BLUHM, HARALD, DE;  
HOCHGUERTEL, MATTHIAS, DE;  
...

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : INHIBITEURS DE METALLOPROTEASE HETEROTRICYCLIQUE

(54) Title: HETEROTRICYCLIC METALLOPROTEASE INHIBITORS

(57) **Abrégé/Abstract:**

The present invention relates generally to azatricyclic containing pharmaceutical agents, and in particular, to azatricyclic metalloprotease inhibiting compounds. More particularly, the present invention provides a new class of azatricyclic MMP-3, MMP-8 and/or MMP-13 inhibiting compounds, that exhibit an increased potency and selectivity in relation to currently known MMP-13, MMP-8 and MMP-3 inhibitors.



(72) **Inventeurs(suite)/Inventors(continued):** DENG, HONGBO, US; GALLAGHER, BRIAN M., JR., US;  
SUCHOLEIKI, IRVING, US; TAVERAS, ARTHUR, US

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
29 May 2008 (29.05.2008)

PCT

(10) International Publication Number  
**WO 2008/063667 A1**

## (51) International Patent Classification:

**C07D 413/12** (2006.01)      **C07D 495/22** (2006.01)  
**C07D 491/04** (2006.01)      **A61K 31/519** (2006.01)  
**C07D 495/04** (2006.01)      **A61P 29/00** (2006.01)  
**C07D 495/14** (2006.01)

Valley Parkway, Winchester, Massachusetts 01890 (US).  
**TAVERAS, Arthur** [US/US]; 6 Joslin Lane, Southbor-  
ough, Massachusetts 01772 (US).

## (21) International Application Number:

PCT/US2007/024362

## (22) International Filing Date:

20 November 2007 (20.11.2007)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

60/860,195      20 November 2006 (20.11.2006)      US

(71) Applicant (for all designated States except US): **ALAN-  
TOS PHARMACEUTICALS HOLDING, INC.**  
[US/US]; M/s 28-2-C, One Amgen Center Drive, Thou-  
sand Oaks, California 91320-1799 (US).

## (72) Inventors; and

(75) Inventors/Applicants (for US only): **GEGE, Christian**  
[DE/DE]; Mochentalerweg 26, D-89584 Ehingen (DE).  
**CHEVRIER, Carine** [FR/FR]; 3 Rue des tilleuls, F-88160  
Ramonchamp (FR). **SCHNEIDER, Matthias** [DE/DE];  
Adalbert-Stifter-Strasse 8, D-69221 Dossenheim (DE).  
**BLUHM, Harald** [DE/DE]; Bergstrasse 30c, D-69221  
Dossenheim (DE). **HOCHGÜRTEL, Matthias** [DE/DE];  
Lavendelweg 22, D-69198 Schriesheim (DE). **DENG,  
Hongbo** [CN/US]; 178 Woodland Road, Southborough,  
Massachusetts 01772 (US). **GALLAGHER, Brian M.**  
[US/US]; 28 Orchard Street, Merrimac, Massachusetts  
01860 (US). **SUCHOLEIKI, Irving** [US/US]; 225 Mystic

(74) Agent: **PERSON, Richard V.**; Amgen Inc., M/s 28-2-c,  
One Amgen Center Drive, Thousand Oaks, California  
91320-1799 (US).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,  
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,  
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,  
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,  
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,  
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,  
ZM, ZW.

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,  
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a  
patent (Rule 4.17(ii))

## Published:

— with international search report  
— before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(54) Title: HETEROTRICYCLIC METALLOPROTEASE INHIBITORS

(57) Abstract: The present invention relates generally to azatricyclic containing pharmaceutical agents, and in particular, to azatri-  
cyclic metalloprotease inhibiting compounds. More particularly, the present invention provides a new class of azatricyclic MMP-3,  
MMP-8 and/or MMP-13 inhibiting compounds, that exhibit an increased potency and selectivity in relation to currently known  
MMP-13, MMP-8 and MMP-3 inhibitors.

WO 2008/063667 A1

## **HETEROTRICYCLIC METALLOPROTEASE INHIBITORS**

This application claims the benefit of U.S. Provisional Application No. 60/860,195, filed November 20, 2006, which is hereby incorporated by reference.

5

### **FIELD OF THE INVENTION**

The present invention relates generally to amide containing azatricyclic metalloprotease inhibiting compounds, and more particularly to azatricyclic amide MMP-13, MMP-8, MMP-3 and MMP-2 inhibiting compounds.

10

### **BACKGROUND OF THE INVENTION**

Matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS = a disintegrin and metalloproteinase with thrombospondin motif) are a family of structurally related zinc-containing enzymes that have been reported to mediate the breakdown of connective tissue in normal physiological processes such as  
15 embryonic development, reproduction, and tissue remodelling. Over-expression of MMPs and aggrecanases or an imbalance between extracellular matrix synthesis and degradation has been suggested as factors in inflammatory, malignant and degenerative disease processes. MMPs and aggrecanases are, therefore, targets for therapeutic inhibitors in several inflammatory, malignant and  
20 degenerative diseases such as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation (which leads to restenosis and ischemic heart failure) and tumor metastasis.

The ADAMTSs are a group of proteases that are encoded in 19 ADAMTS  
25 genes in humans. The ADAMTSs are extracellular, multidomain enzymes whose functions include collagen processing, cleavage of the matrix proteoglycans, inhibition of angiogenesis and blood coagulation homeostasis (*Biochem. J.* **2005**, 386, 15-27; *Arthritis Res. Ther.* **2005**, 7, 160-169; *Curr. Med. Chem. Anti-Inflammatory Anti-Allergy Agents* **2005**, 4, 251-264).

30 The mammalian MMP family has been reported to include at least 20 enzymes (*Chem. Rev.* **1999**, 99, 2735-2776). Collagenase-3 (MMP-13) is among

three collagenases that have been identified. Based on identification of domain structures for individual members of the MMP family, it has been determined that the catalytic domain of the MMPs contains two zinc atoms; one of these zinc atoms performs a catalytic function and is coordinated with three histidines  
5 contained within the conserved amino acid sequence of the catalytic domain. MMP-13 is over-expressed in rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, breast carcinoma, squamous cell carcinomas of the head and neck, and vulvar squamous cell carcinoma. The principal substrates of MMP-13 are fibrillar collagens (types I, II, III) and gelatins, proteoglycans, cytokines and other  
10 components of ECM (extracellular matrix).

The activation of the MMPs involves the removal of a propeptide, which features an unpaired cysteine residue complexed with the catalytic zinc (II) ion. X-ray crystal structures of the complex between MMP-3 catalytic domain and TIMP-1 and MMP-14 catalytic domain and TIMP-2 also reveal ligation of the  
15 catalytic zinc (II) ion by the thiol of a cysteine residue. The difficulty in developing effective MMP inhibiting compounds comprises several factors, including choice of selective versus broad-spectrum MMP inhibitors and rendering such compounds bioavailable via an oral route of administration.

MMP-3 (stromelysin-1; transin-1) is another member of the MMP family  
20 (*FASEB J.* 1991, 5, 2145-2154). Human MMP-3 was initially isolated from cultured human synoviocytes. It is also expressed by chondrocytes and has been localized in OA cartilage and synovial tissues (*Am. J. Pathol.* 1989, 135, 1055-64).

MMP-3 is produced by basal keratinocytes in a variety of chronic ulcers.  
25 MMP-3 mRNA and Protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of proliferating epidermis. MMP-3 may thus prevent the epidermis from healing (*J. Clin. Invest.* 1994, 94, 79-88).

MMP-3 serum protein levels are significantly elevated in patients with  
30 early and long-term rheumatoid arthritis (*Arthritis Rheum.* 2000, 43, 852-8) and in osteoarthritis patients (*Clin. Orthop. Relat. Res.* 2004, 428, 272-85) as well as in

other inflammatory diseases like systemic lupus erythematosus and ankylosing spondylitis (*Rheumatology* **2006**, 45, 414-20).

MMP-3 acts on components of the ECM as aggrecan, fibronectin, gelatin, laminin, elastin, fibrillin and others and on collagens of type III, IV, V, VII, IX, X  
5 (*Clin. Orthop. Relat. Res.* **2004**, 428, 272-85). On collagens of type II and IX, MMP-3 exhibits telopeptidase activity (*Arthritis Res.* **2001**, 3, 107-13; *Clin. Orthop. Relat. Res.* **2004**, 427, S118-22). MMP-3 can activate other MMP family members such as MMP-1, MMP-7, MMP-8, MMP-9 and MMP-13 (*Ann. Rheum. Dis.* **2001**, 60 Suppl 3:iii62-7).

10 MMP-3 is involved in the regulation of cytokines and chemokines by releasing TGF $\beta$ 1 from the ECM, activating TNF $\alpha$ , inactivating IL-1 $\beta$  and releasing IGF (*Nat. Rev. Immunol.* **2004**, 4, 617-29). A potential role for MMP-3 in the regulation of macrophage infiltration is based on the ability of the enzyme to convert active MCP species into antagonistic peptides (*Blood* **2002**, 100, 1160-  
15 7).

MMP-8 (collagenase-2; neutrophil collagenase; EC 3.4.24.34) is another member of the MMP family (*Biochemistry* **1990**, 29, 10628-34). Human MMP-8 was initially located in human neutrophils (*Biochemistry* **1990**, 29, 10620-7). It is also expressed by macrophages, human mucosal keratinocytes, bronchial  
20 epithelial cells, gingival fibroblasts, resident synovial and articular chondrocytes mainly in the course of inflammatory conditions (*Cytokine & Growth Factor Rev.* **2006**, 17, 217-23).

The activity of MMP-8 is tightly regulated and mostly limited to the sites of inflammation. MMP-8 is expressed and stored as an inactive pro-enzyme in the  
25 granules of the neutrophils. Only after the activation of the neutrophils by proinflammatory mediators, MMP-8 is released and activated to exert its function.

MMP-8 plays a key role in the migration of immune cells to the sites of inflammation. MMP-8 degrades components of the extracellular matrix (ECM) such as collagen type I, II, III, VII, X, cartilage aggrecan, laminin-5, nidogen,  
30 fibronectin, proteoglycans and tenascin, thereby facilitating the cells migration through the ECM barrier. MMP-8 also influences the biological activity of its

substrates. Through proteolytic processing of the chemokines IL-8, GCP-2, ENA-78, MMP-8 increases the chemokines ability to activate the infiltrating immune cells. While MMP-8 inactivates the serine protease inhibitor alpha-1 antitrypsin through its cleavage (*Eur. J. Biochem.* **2003**, 270, 3739-49; *PloS One* **2007**, 3, 1-10; *Cytokine & Growth Factor Rev.* **2006**, 17, 217-23).

MMP-8 has been implicated in the pathogenesis of several chronic inflammatory diseases characterized by the excessive influx and activation of neutrophils, including cystic fibrosis (*Am. J. Respir. Critic. Care Med.* **1994**, 150, 818-22), rheumatoid arthritis (*Clin. Chim. Acta* **1996**, 129-43), chronic periodontal disease (*Annals Med.* **2006**, 38, 306-321) and chronic wounds (*J. Surg. Res.* **1999**, 81, 189-195).

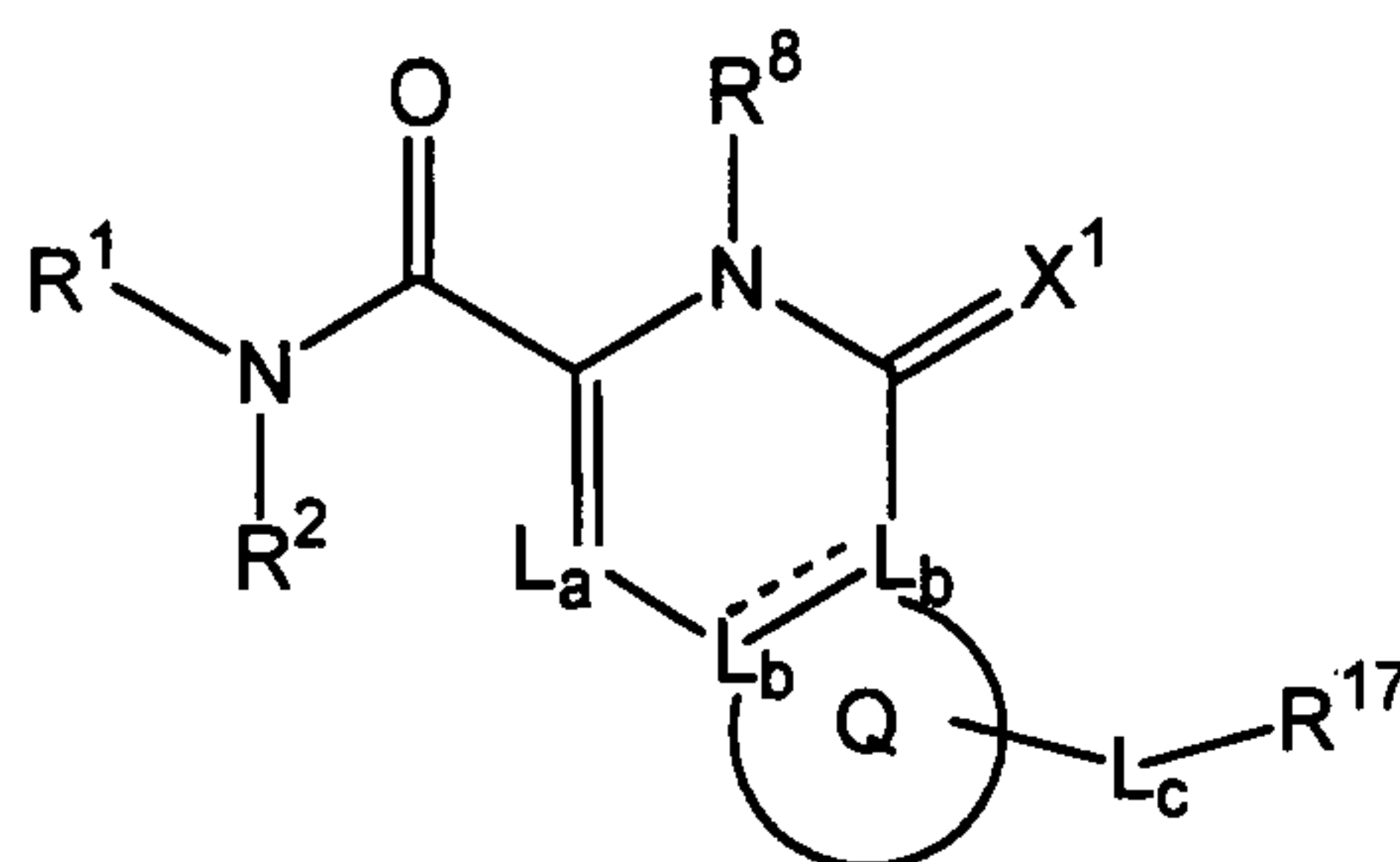
In osteoarthritis patients, MMP-8 protein expression is significantly elevated in inflamed human articular cartilage in the knee and ankle joints (*Lab Invest.* **1996**, 74, 232-40; *J. Biol. Chem.* **1996**, 271, 11023-6).

The levels of activated MMP-8 in BALF is an indicator of the disease severity and correlates with the airway obstruction in patients with asthma, COPD, pulmonary emphysema and bronchiectasis (*Lab Invest.* **2002**, 82, 1535-45; *Am. J. Respir. Crit. Care Med.* **1999**, 159, 1985-91; *Respir. Med.* **2005**, 99, 703-10; *J. Pathol.* **2001**, 194, 232-38).

## **SUMMARY OF THE INVENTION**

The present invention relates to a new class of azatricyclic amide containing pharmaceutical agents which inhibits metalloproteases. In particular, the present invention provides a new class of metalloprotease inhibiting compounds that exhibit potent MMP-13 inhibiting activity and/or activity towards MMP-8, MMP-3 and MMP-2.

The present invention provides several new classes of amide containing azatricyclic metalloprotease compounds, which are represented by the following general formula:



Formula (I)

wherein all variables in the preceding Formula (I) are as defined hereinbelow.

5           The azatricyclic metalloprotease inhibiting compounds of the present invention may be used in the treatment of metalloprotease mediated diseases, such as rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer (e.g. but not limited to melanoma, gastric carcinoma or non-small cell lung carcinoma), inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary

10   disease, ocular diseases (e.g. but not limited to ocular inflammation, retinopathy of prematurity, macular degeneration with the wet type preferred and corneal neovascularization), neurologic diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular

15   impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimers disease, arterial plaque formation, oncology, periodontal, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, chronic wound healing,

20   wound healing, hemorrhoid, skin beautifying, pain, inflammatory pain, bone pain and joint pain, acne, acute alcoholic hepatitis, acute inflammation, acute pancreatitis, acute respiratory distress syndrome, adult respiratory disease, airflow obstruction, airway hyperresponsiveness, alcoholic liver disease, allograft rejections, angiogenesis, angiogenic ocular disease, arthritis, asthma, atopic

25   dermatitis, bronchiectasis, bronchiolitis, bronchiolitis obliterans, burn therapy, cardiac and renal reperfusion injury, celiac disease, cerebral and cardiac ischemia, CNS tumors, CNS vasculitis, colds, contusions, cor pulmonae, cough, Crohn's

disease, chronic bronchitis, chronic inflammation, chronic pancreatitis, chronic sinusitis, crystal induced arthritis, cystic fibrosis, delayed type hypersensitivity reaction, duodenal ulcers, dyspnea, early transplantation rejection, emphysema, encephalitis, endotoxic shock, esophagitis, gastric ulcers, gingivitis,

5 glomerulonephritis, glossitis, gout, graft vs. host reaction, gram negative sepsis, granulocytic ehrlichiosis, hepatitis viruses, herpes, herpes viruses, HIV, hypercapnea, hyperinflation, hyperoxia-induced inflammation, hypoxia, hypersensitivity, hypoxemia, inflammatory bowel disease, interstitial pneumonitis, ischemia reperfusion injury, kaposi's sarcoma associated virus, liver fibrosis,

10 lupus, malaria, meningitis, multi-organ dysfunction, necrotizing enterocolitis, osteoporosis, chronic periodontitis, periodontitis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), pre-term labor, polymyositis, post surgical trauma, pruritis, psoriasis, psoriatic arthritis, pulmonary fibrosis, pulmonary hypertension, renal reperfusion injury, respiratory viruses, restinosis,

15 right ventricular hypertrophy, sarcoidosis, septic shock, small airway disease, sprains, strains, subarachnoid hemorrhage, surgical lung volume reduction, thrombosis, toxic shock syndrome, transplant reperfusion injury, traumatic brain injury, ulcerative colitis, vasculitis, ventilation-perfusion mismatching, and wheeze.

20 In particular, the azatricyclic metalloprotease inhibiting compounds of the present invention may be used in the treatment of MMP-13, MMP-8, MMP-3 and MMP-2 mediated osteoarthritis and may be used for other MMP-13, MMP-8, MMP-3 and MMP-2 mediated symptoms, inflammatory, malignant and degenerative diseases characterized by excessive extracellular matrix degradation

25 and/or remodelling, such as cancer, and chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, abdominal aortic aneurysm, inflammation, multiple sclerosis, and chronic obstructive pulmonary disease, and pain, such as inflammatory pain, bone pain and joint pain.

The present invention also provides azatricyclic metalloprotease inhibiting

30 compounds that are useful as active ingredients in pharmaceutical compositions for treatment or prevention of metalloprotease – especially MMP-13, MMP-8,

MMP-3 and MMP-2 – mediated diseases. The present invention also contemplates use of such compounds in pharmaceutical compositions for oral or parenteral administration, comprising one or more of the azatricyclic metalloprotease inhibiting compounds disclosed herein.

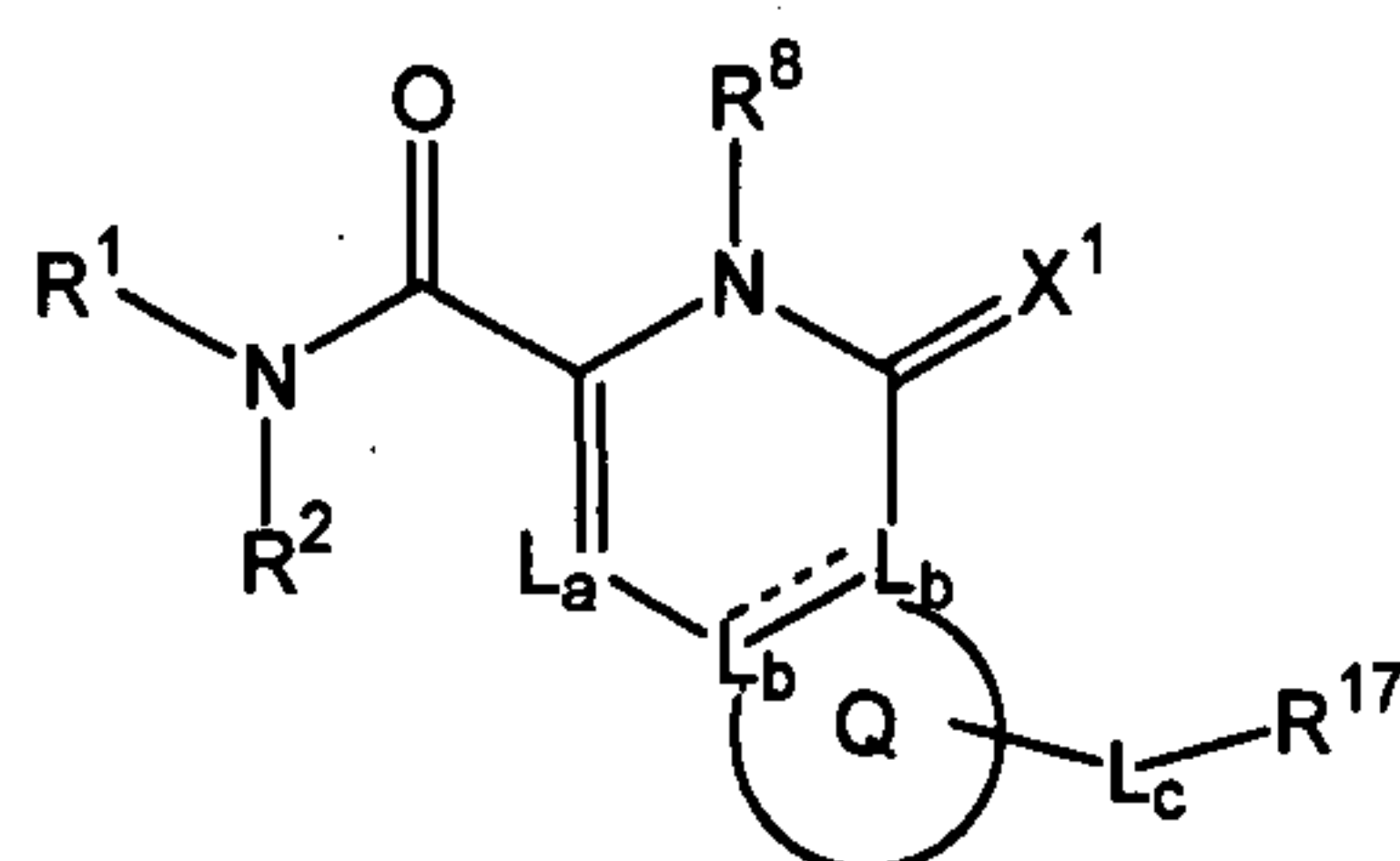
5           The present invention further provides methods of inhibiting metalloproteases, by administering formulations, including, but not limited to, oral, rectal, topical, intravenous, parenteral (including, but not limited to, intramuscular, intravenous), ocular (ophthalmic), transdermal, inhalative (including, but not limited to, pulmonary, aerosol inhalation), nasal, sublingual,  
10       subcutaneous or intraarticular formulations, comprising the azatricyclic metalloprotease inhibiting compounds by standard methods known in medical practice, for the treatment of diseases or symptoms arising from or associated with metalloprotease, especially MMP-13, MMP-8, MMP-3 and MMP-2, including prophylactic and therapeutic treatment. Although the most suitable route in any  
15       given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compounds from this invention are conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

          The azatricyclic metalloprotease inhibiting compounds of the present  
20       invention may be used in combination with a disease modifying antirheumatic drug, a nonsteroidal anti-inflammatory drug, a COX-2 selective inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, a biological response modifier or other anti-inflammatory agents or therapeutics useful for the treatment of chemokines mediated diseases.

25

### **DETAILED DESCRIPTION OF THE INVENTION**

One aspect of the invention relates to a compound of Formula (I):



Formula (I)

wherein

- $R^1$  in each occurrence is independently selected from hydrogen, alkyl,  
 5 alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl,  
 spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl,  
 heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused  
 heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl,  
 heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl,  
 10 heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl,  
 cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl,

wherein  $R^1$  is optionally substituted one or more times, or

wherein  $R^1$  is optionally substituted by one  $R^{16}$  group and optionally  
 substituted by one or more  $R^9$  groups;

- 15  $R^2$  is selected from hydrogen and alkyl, wherein alkyl is optionally  
 substituted one or more times or  $R^1$  and  $R^2$  when taken together with the nitrogen  
 to which they are attached complete a 3- to 8-membered ring containing carbon  
 atoms and optionally containing a heteroatom selected from O,  $S(O)_x$ , or  $NR^{50}$  and  
 which is optionally substituted one or more times;

- 20  $R^4$  in each occurrence is independently selected from  $R^{10}$ , hydrogen, alkyl,  
 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl,  $CF_3$ ,  $(C_0-C_6)$ -alkyl-  
 $COR^{10}$ ,  $(C_0-C_6)$ -alkyl- $OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NO_2$ ,  $(C_0-C_6)$ -  
 alkyl-CN,  $(C_0-C_6)$ -alkyl- $S(O)_yOR^{10}$ ,  $(C_0-C_6)$ -alkyl- $S(O)_yNR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl-  
 $NR^{10}CONR^{11}SO_2R^{30}$ ,  $(C_0-C_6)$ -alkyl- $S(O)_xR^{10}$ ,  $(C_0-C_6)$ -alkyl- $OC(O)R^{10}$ ,  $(C_0-C_6)$ -  
 25 alkyl- $OC(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(=NR^{10})NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl-  
 $NR^{10}C(=NR^{11})NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  
 $(C_0-C_6)$ -alkyl- $C(O)NR^{10}SO_2R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)-NR^{11}-CN$ ,  $O-(C_0-C_6)$ -alkyl-  
 $C(O)NR^{10}R^{11}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,

(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)R<sup>10</sup>,  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
 NR<sup>10</sup>-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-S(O)<sub>y</sub>R<sup>10</sup>, O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl and O-  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl,

5            wherein each R<sup>4</sup> group is optionally substituted one or more times, or  
              wherein each R<sup>4</sup> group is optionally substituted by one or more R<sup>14</sup> groups,  
 or

             wherein optionally two R<sup>4</sup> groups, when taken together with the nitrogen  
 or carbon to which they are attached complete a 3- to 8-membered saturated ring  
 10       or multicyclic ring or unsaturated ring containing carbon atoms and optionally  
              containing one or more heteroatom independently selected from O, S(O)<sub>x</sub>, N, or  
              NR<sup>50</sup> and which is optionally substituted one or more times, or

             optionally two R<sup>4</sup> groups together at one saturated carbon atom form =O,  
 =S, =NR<sup>10</sup> or =NOR<sup>10</sup>;

15            R<sup>5</sup> is independently selected from hydrogen, alkyl, C(O)NR<sup>10</sup>R<sup>11</sup>, aryl,  
              arylalkyl, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and C(O)OR<sup>10</sup> wherein alkyl, aryl and arylalkyl are  
              optionally substituted one or more times;

             R<sup>8</sup> is independently selected from hydrogen, alkyl, cycloalkyl,  
 heterocycloalkyl, aryl, heteroaryl, R<sup>10</sup> and NR<sup>10</sup>R<sup>11</sup> wherein alkyl, cycloalkyl,  
 20       heterocycloalkyl, aryl, and heteroaryl is optionally substituted one or more times;

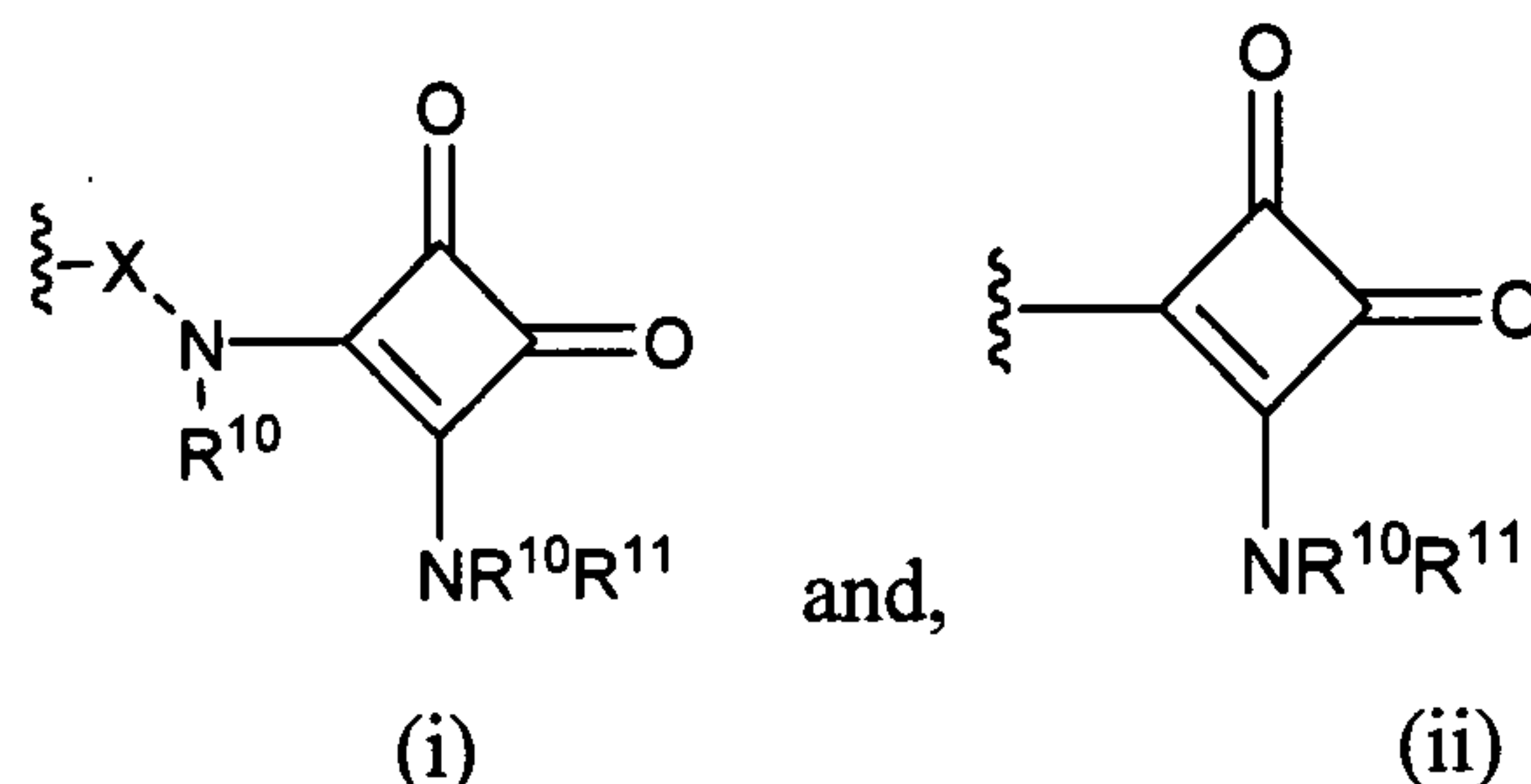
             R<sup>9</sup> in each occurrence is independently selected from R<sup>10</sup>, hydrogen, alkyl,  
 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF<sub>2</sub>, CF<sub>3</sub>, OR<sup>10</sup>, SR<sup>10</sup>,  
 COOR<sup>10</sup>, CH(CH<sub>3</sub>)CO<sub>2</sub>H, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-COR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-  
 alkyl-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NO<sub>2</sub>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-CN, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>y</sub>OR<sup>10</sup>,  
 25       (C<sub>0</sub>-C<sub>6</sub>)-alkyl-P(O)<sub>2</sub>OH, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
              NR<sup>10</sup>CONR<sup>11</sup>SO<sub>2</sub>R<sup>30</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>x</sub>R<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-OC(O)R<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-  
              alkyl-OC(O)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(=NR<sup>10</sup>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
              NR<sup>10</sup>C(=NR<sup>11</sup>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>C(=N-CN)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
              C(=N-CN)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>C(=N-NO<sub>2</sub>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(=N-  
 30       NO<sub>2</sub>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-  
              alkyl-C(O)NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>, C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl, C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-

alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-heteroaryl,  
 $S(O)_2NR^{10}$ -alkyl,  $S(O)_2-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2-(C_0-C_6)$ -alkyl-heteroaryl,  $(C_0-$   
 $C_6)$ -alkyl- $C(O)-NR^{11}-CN$ ,  $O-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl-  
 $C(O)OR^{10}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}-(C_0-C_6)-$   
5     $alkyl-NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)R^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)OR^{10}$ ,  $(C_0-$   
 $C_6)$ -alkyl- $NR^{10}-C(O)-NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-S(O)_yNR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl-  
 $NR^{10}-S(O)_yR^{11}$ ,  $O-(C_0-C_6)$ -alkyl-aryl and  $O-(C_0-C_6)$ -alkyl-heteroaryl,  
wherein each  $R^9$  group is optionally substituted, or  
wherein each  $R^9$  group is optionally substituted by one or more  $R^{14}$  groups;  
10     $R^{10}$  and  $R^{11}$  in each occurrence are independently selected from hydrogen,  
alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, bicycloalkyl,  
heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, fluoroalkyl,  
heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl,  
heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl,  
15    bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, heterocycloalkyl,  
fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl,  
heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or  
 $R^{10}$  and  $R^{11}$  when taken together with the nitrogen to which they are attached  
complete a 3- to 8-membered ring containing carbon atoms and optionally  
20    containing a heteroatom selected from O,  $S(O)_x$ , or  $NR^{50}$  and which is optionally  
substituted one or more times;

$R^{14}$  is independently selected from hydrogen, alkyl, arylalkyl,  
cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl,  
arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally  
25    substituted one or more times.

$R^{16}$  is selected from cycloalkyl, heterocycloalkyl, bicycloalkyl,  
heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused  
aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl  
fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl,  
30    heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl,  
heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl,

cycloalkyl fused heteroarylalkyl, heterocycloalkyl fused heteroarylalkyl, (i) and (ii):



5 wherein cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused  
 10 arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R<sup>17</sup> is selected from R<sup>1</sup>, R<sup>4</sup> and R<sup>21</sup>;

15 R<sup>21</sup> is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and

wherein R<sup>21</sup> is optionally substituted one or more times, or

wherein R<sup>21</sup> is optionally substituted by one or more R<sup>9</sup> groups;

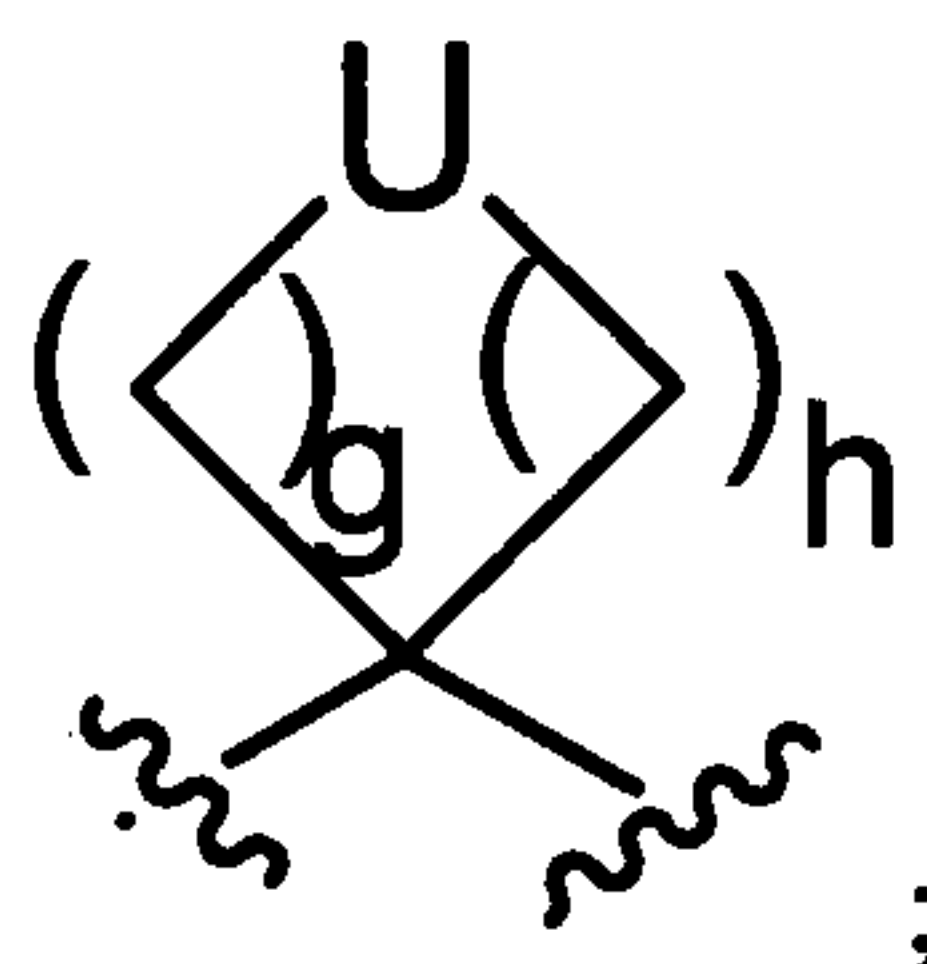
R<sup>30</sup> is selected from alkyl and (C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

20 R<sup>50</sup> in each occurrence is independently selected from hydrogen, alkyl, aryl, heteroaryl, C(O)R<sup>80</sup>, C(O)NR<sup>80</sup>R<sup>81</sup>, SO<sub>2</sub>R<sup>80</sup> and SO<sub>2</sub>NR<sup>80</sup>R<sup>81</sup>, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R<sup>80</sup> and R<sup>81</sup> in each occurrence are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl,  
 25 heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl,

heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or  $R^{80}$  and  $R^{81}$  when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O,  $S(O)_x$ , -NH, and -N(alkyl) and which is optionally substituted one or more times;

E is selected from a bond,  $CR^{10}R^{11}$ , O,  $NR^5$ , S,  $S=O$ ,  $S(=O)_2$ ,  $C(=O)$ ,  $N(R^{10})(C=O)$ ,  $(C=O)N(R^{10})$ ,  $N(R^{10})S(=O)_2$ ,  $S(=O)_2N(R^{10})$ ,  $C=N-OR^{11}$ ,  $-C(R^{10}R^{11})C(R^{10}R^{11})-$ ,  $-CH_2-W^1-$  and



$L_a$  is independently selected from  $CR^9$  and N;

$L_b$  is independently selected from C and N with the proviso, that both  $L_b$  are not N, and that the bond between  $L_b$  and  $L_b$  is optionally a double bond only if both  $L_b$  are C;

$L_c$  is selected from a single bond or an acyclic, straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 10 carbon atoms, optionally containing 1 to 3 groups independently selected from -S-, -O-,  $NR^{10}-$ , - $NR^{10}CO-$ , - $CONR^{10}-$ ,  $-S(O)_x-$ ,  $-SO_2NR^{10}-$ ,  $-NR^{10}SO_2-$ ,  $NR^{10}SO_2NR^{10}-$ , - $NR^{10}CONR^{10}-$ ,  $-OC(O)NR^{10}-$ ,  $-NR^{10}C(O)O-$ , which replace a corresponding number of non-adjacent carbon atoms, and wherein the hydrocarbon chain is optionally substituted one or more times;

Q is a 4- to 8-membered ring selected from cycloalkyl, heterocycloalkyl or a 5- or 6-membered ring selected from aryl and heteroaryl,

wherein Q is optionally substituted one or more times, or

wherein Q is optionally substituted one or more times with  $R^4$ , or

wherein Q is fused via two of its adjacent atoms, which are selected from N and C with a further cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl and heteroaryl system, which is optionally independently substituted one or more times;

U is selected from  $C(R^5R^{10})$ ,  $NR^5$ , O, S, S=O and  $S(=O)_2$ ;

$W^1$  is selected from O,  $NR^5$ , S, S=O,  $S(=O)_2$ ,  $N(R^{10})(C=O)$ ,  $N(R^{10})S(=O)_2$  and  $S(=O)_2N(R^{10})$ ;

X is selected from a bond and  $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$ ;

5  $X^1$  is independently selected from O, S,  $NR^{10}$ , N-CN,  $NCOR^{10}$ , N- $NO_2$ , or N- $SO_2R^{10}$ ;

g and h are independently selected from 0-2;

w is selected from 0-4;

x is selected from 0 to 2;

10 y is selected from 1 and 2;

the dotted line optionally represents a double bond; and

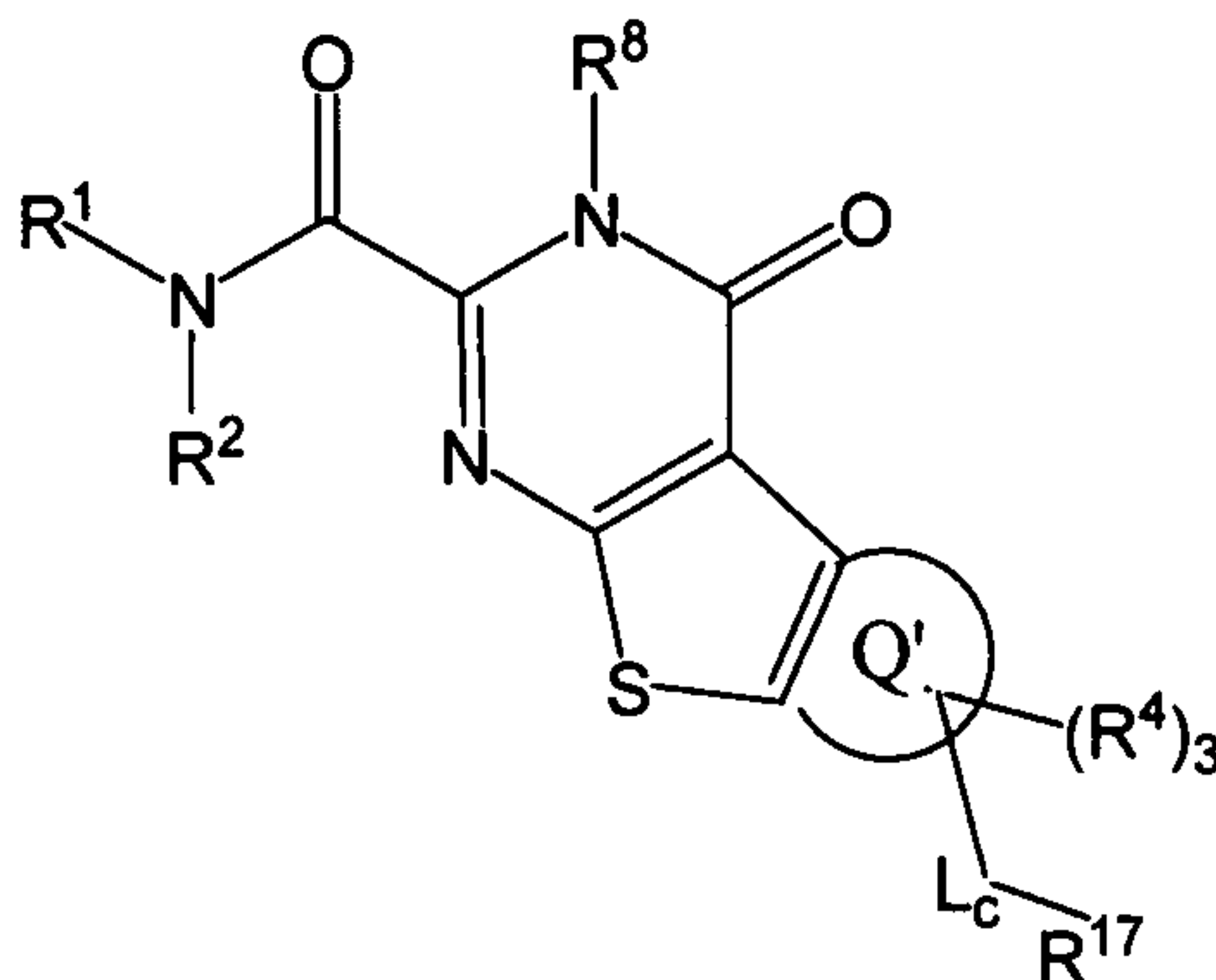
N-oxides, pharmaceutically acceptable salts, prodrugs, formulations, polymorphs, tautomers, racemic mixtures and stereoisomers thereof.

In one embodiment, in conjunction with any above or below embodiments,  
15 Q is phenyl or thiophene that is fused via two of its adjacent atoms with a further cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl and heteroaryl system, which is optionally independently substituted one or more times.

In another embodiment, in conjunction with any above or below embodiments,  $L_a$  is N.

20 In another embodiment, in conjunction with any above or below embodiments,  $L_a$  is N; and  $L_b$  is C.

In another embodiment, in conjunction with any above or below embodiments, the compound has the structure:



wherein Q' is a fused cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl or heteroaryl.

In another embodiment, in conjunction with any above or below embodiments, Q' is a fused cycloalkyl.

5 In another embodiment, in conjunction with any above or below embodiments, Q' is a fused heterocycloalkyl.

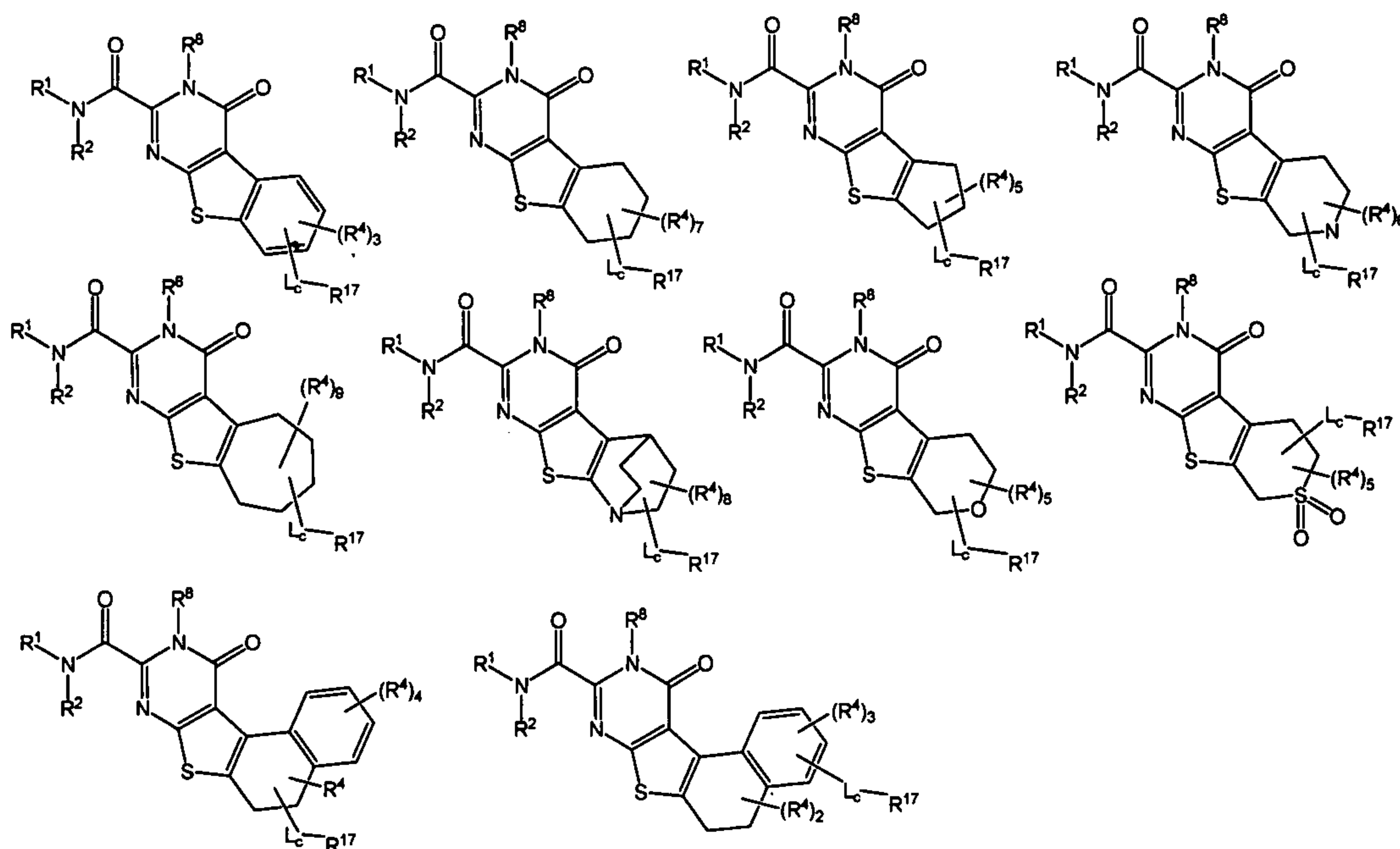
In another embodiment, in conjunction with any above or below embodiments, Q' is a fused heterobicycloalkyl.

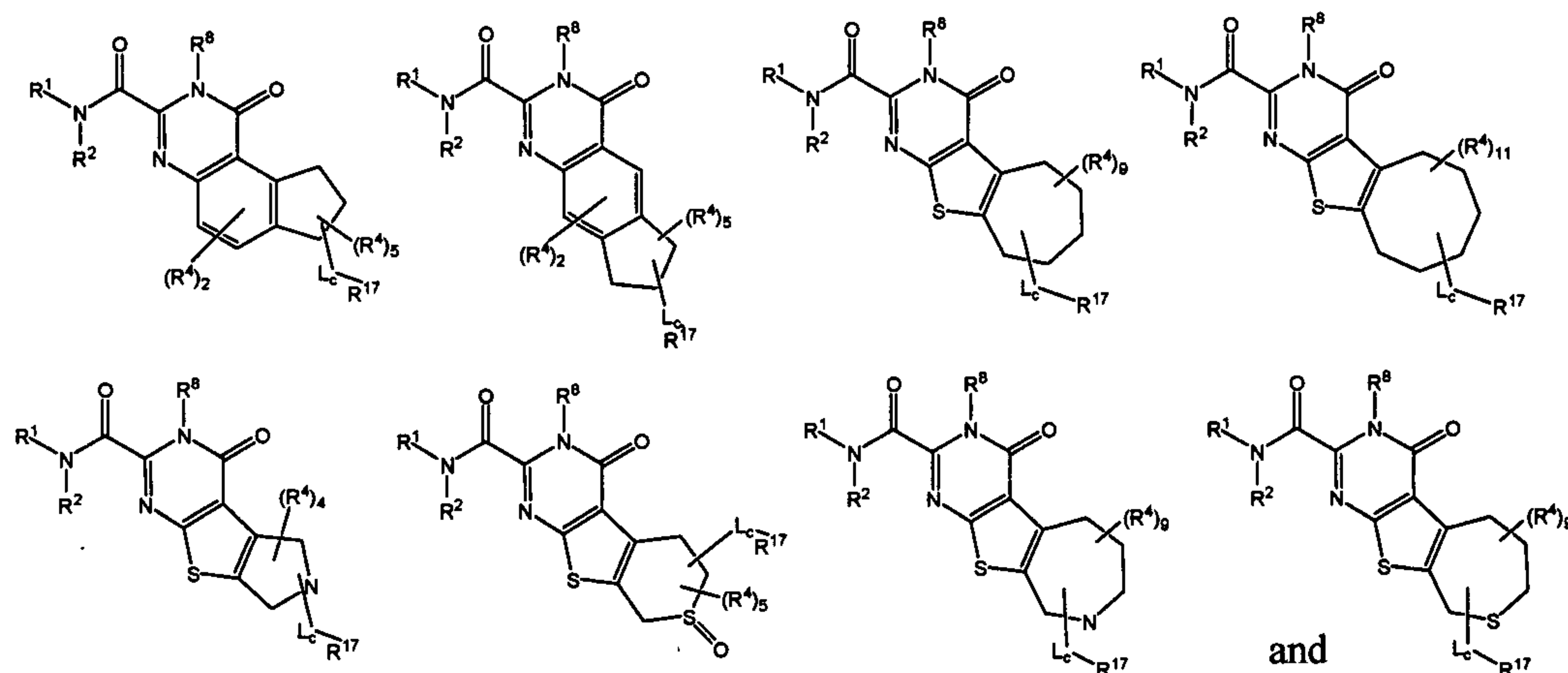
10 In another embodiment, in conjunction with any above or below embodiments, Q' is a fused cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl or heteroaryl.

In another embodiment, in conjunction with any above or below embodiments, Q' is a fused phenyl.

15 In another embodiment, in conjunction with any above or below embodiments, Q' is a fused heteroaryl.

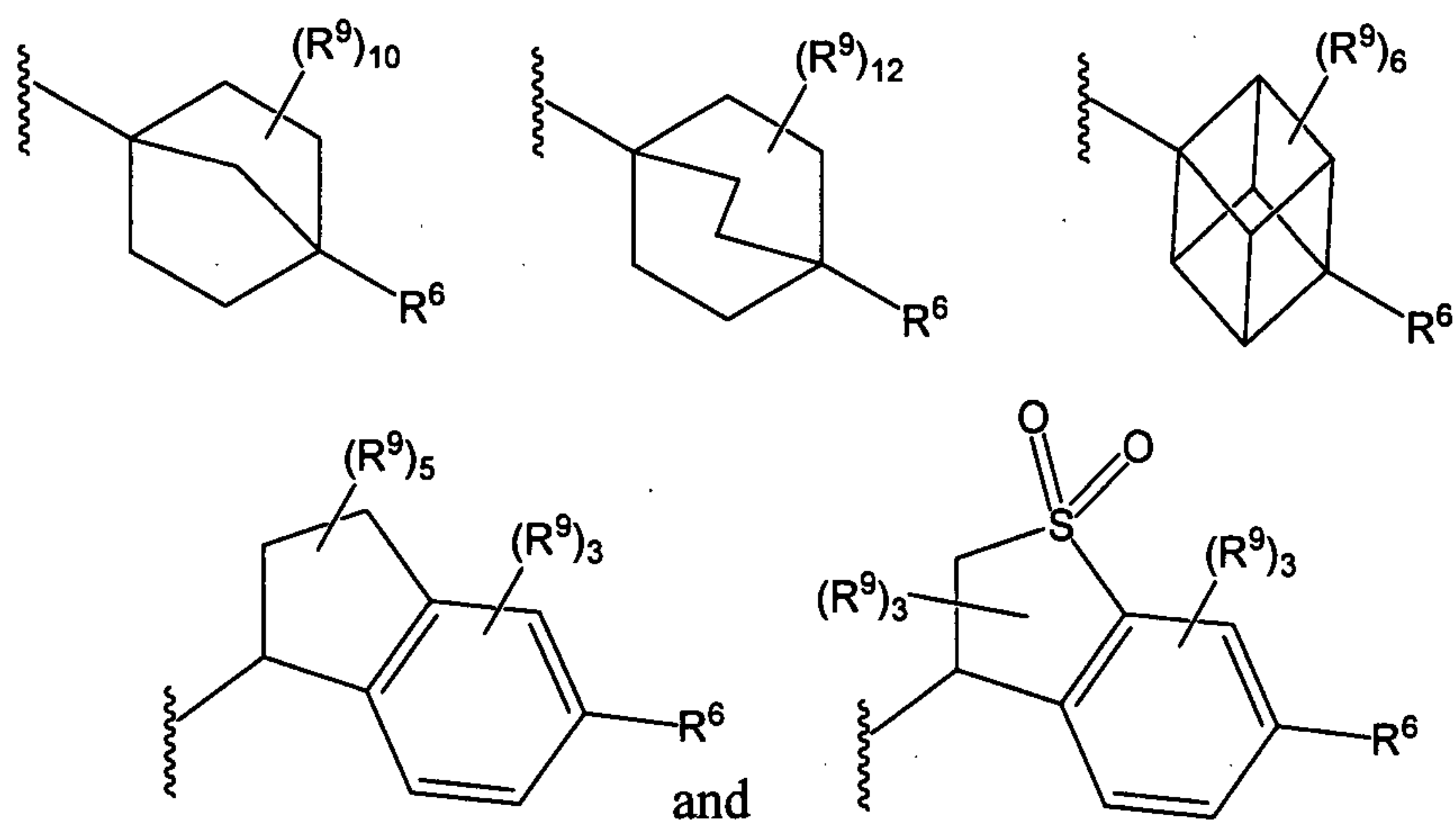
In another embodiment, in conjunction with any above or below embodiments, the compound is selected from:





In another embodiment, in conjunction with any above or below embodiments,  $R^8$  is H.

In another embodiment, in conjunction with any above or below  
5 embodiments,  $R^{17}$  is selected from



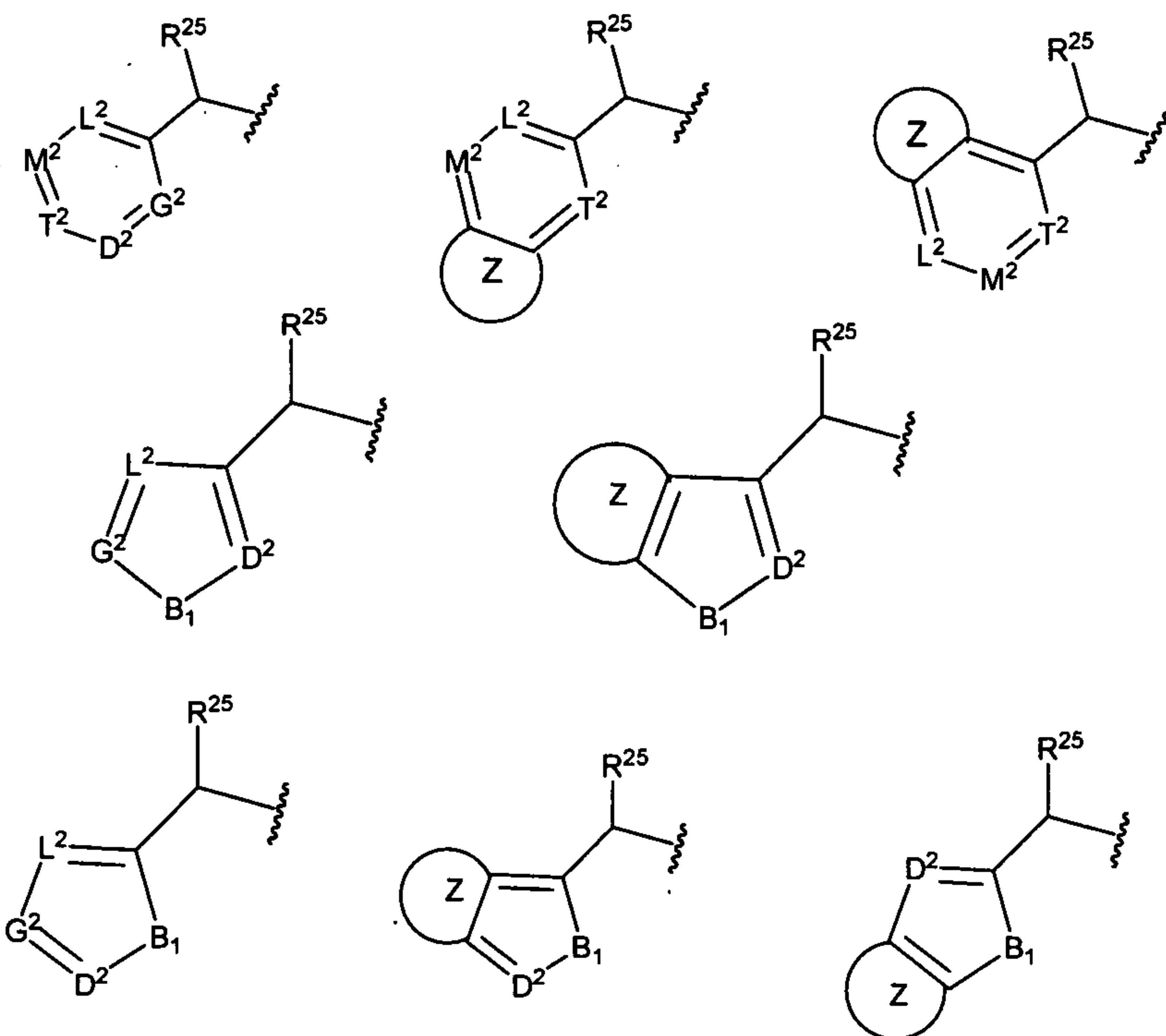
wherein:

$R^6$  is selected from  $R^9$ , cycloalkyl, heterocycloalkyl, aryl, heteroaryl,  
 $C(O)OR^{10}$ ,  $CH(CH_3)CO_2H$ ,  $(C_0-C_6)$ -alkyl-COR<sup>10</sup>,  $(C_0-C_6)$ -alkyl-OR<sup>10</sup>,  $(C_0-C_6)$ -  
 10 alkyl-NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-NO<sub>2</sub>,  $(C_0-C_6)$ -alkyl-CN,  $(C_0-C_6)$ -alkyl-S(O)<sub>y</sub>OR<sup>10</sup>,  
 $(C_0-C_6)$ -alkyl-P(O)<sub>2</sub>OH,  $(C_0-C_6)$ -alkyl-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-  
 NR<sup>10</sup>CONR<sup>11</sup>SO<sub>2</sub>R<sup>30</sup>,  $(C_0-C_6)$ -alkyl-S(O)<sub>x</sub>R<sup>10</sup>,  $(C_0-C_6)$ -alkyl-OC(O)R<sup>10</sup>,  $(C_0-C_6)$ -  
 alkyl-OC(O)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-C(=NR<sup>10</sup>)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-  
 NR<sup>10</sup>C(=NR<sup>11</sup>)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-NR<sup>10</sup>C(=N-CN)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-  
 15 C(=N-CN)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-NR<sup>10</sup>C(=N-NO<sub>2</sub>)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-C(=N-  
 NO<sub>2</sub>)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-C(O)OR<sup>10</sup>,  $(C_0-C_6)$ -alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -

alkyl-C(O)NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>, C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl, C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl, S(O)<sub>2</sub>NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl, S(O)<sub>2</sub>NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl, S(O)<sub>2</sub>NR<sup>10</sup>-alkyl, S(O)<sub>2</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl, S(O)<sub>2</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)-NR<sup>11</sup>-CN, O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>, S(O)<sub>x</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)OR<sup>10</sup>, S(O)<sub>x</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)R<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-S(O)<sub>y</sub>R<sup>11</sup>, O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl and O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl, wherein each R<sup>6</sup> group is optionally substituted by one or more R<sup>14</sup> groups;

R<sup>9</sup> is independently selected from hydrogen, alkyl, halo, CHF<sub>2</sub>, CF<sub>3</sub>, OR<sup>10</sup>, NR<sup>10</sup>R<sup>11</sup>, NO<sub>2</sub>, and CN, wherein alkyl is optionally substituted one or more times;

In another embodiment, in conjunction with any above or below embodiments, R<sup>1</sup> is selected from:



wherein:

R<sup>18</sup> is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, C(O)NR<sup>10</sup>R<sup>11</sup>, CO<sub>2</sub>R<sup>10</sup>, OR<sup>10</sup>, OCF<sub>3</sub>, OCHF<sub>2</sub>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>COR<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and NR<sup>10</sup>R<sup>11</sup>, wherein alkyl, haloalkyl, cycloalkyl,

heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

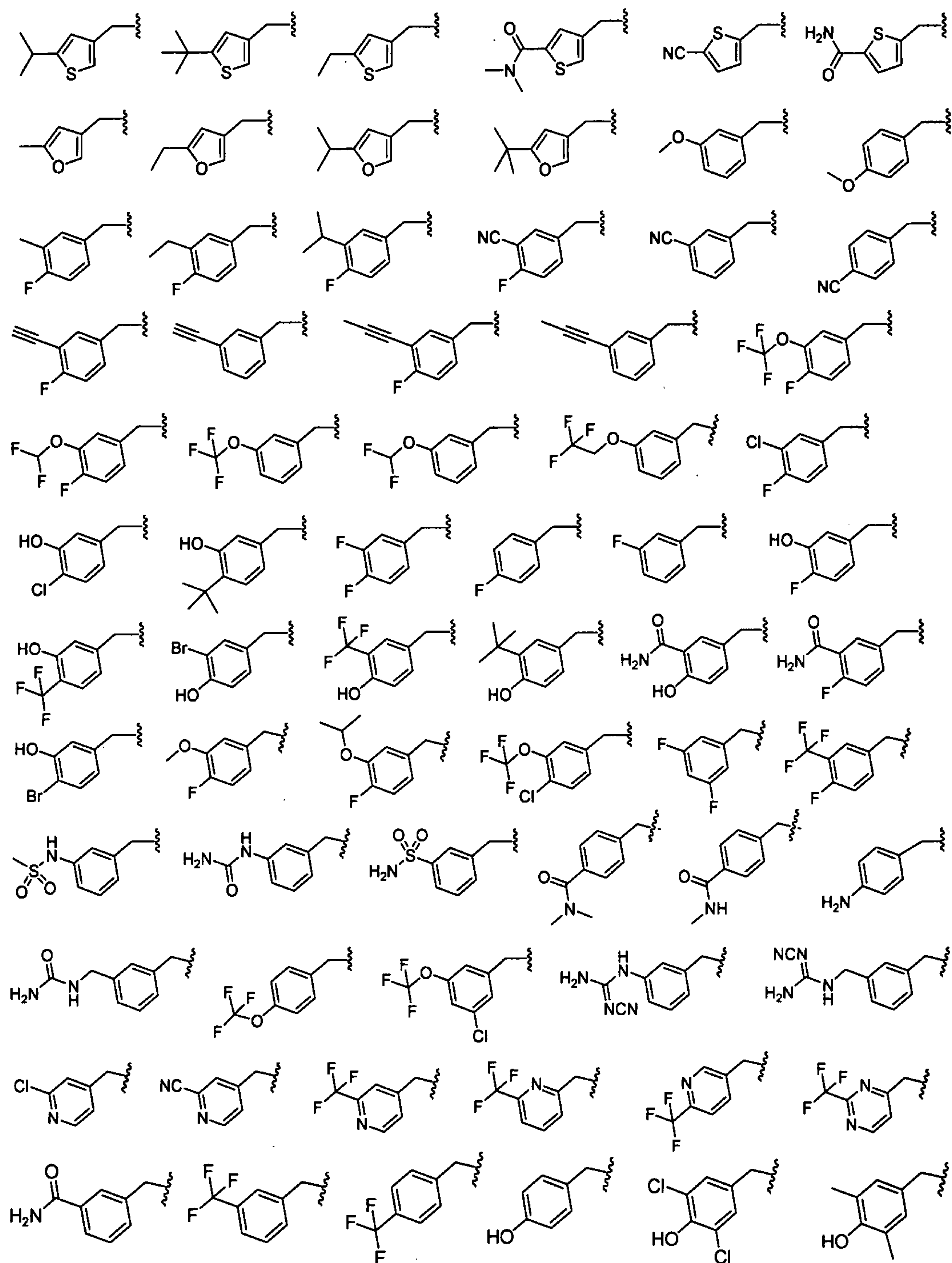
$R^{25}$  is selected from hydrogen, alkyl, cycloalkyl,  $C(O)NR^{10}R^{11}$  and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one  
5 or more times;

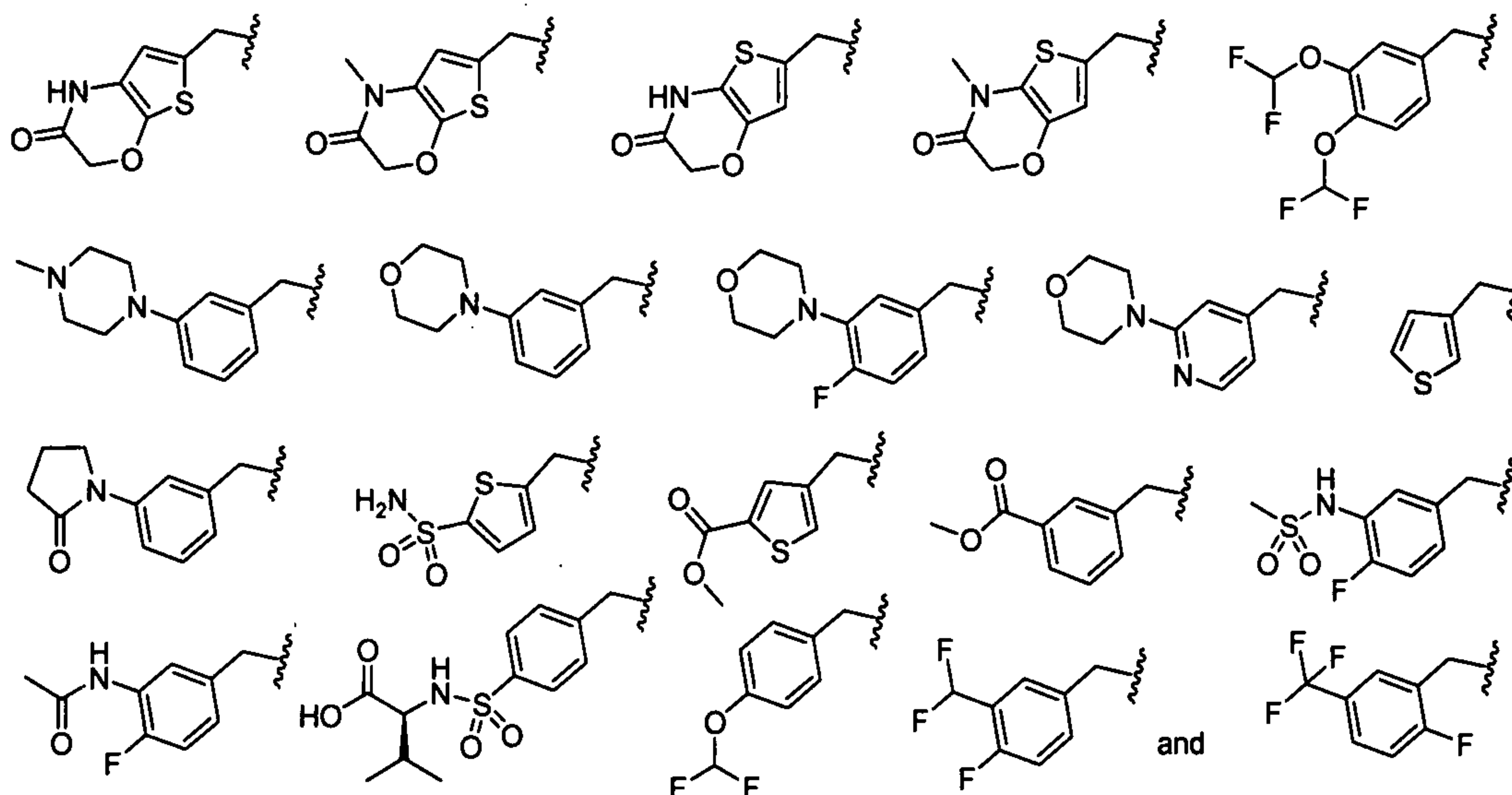
$B_1$  is selected from  $NR^{10}$ , O and S;

$D^2$ ,  $G^2$ ,  $L^2$ ,  $M^2$  and  $T^2$  are independently selected from  $CR^{18}$  and N; and

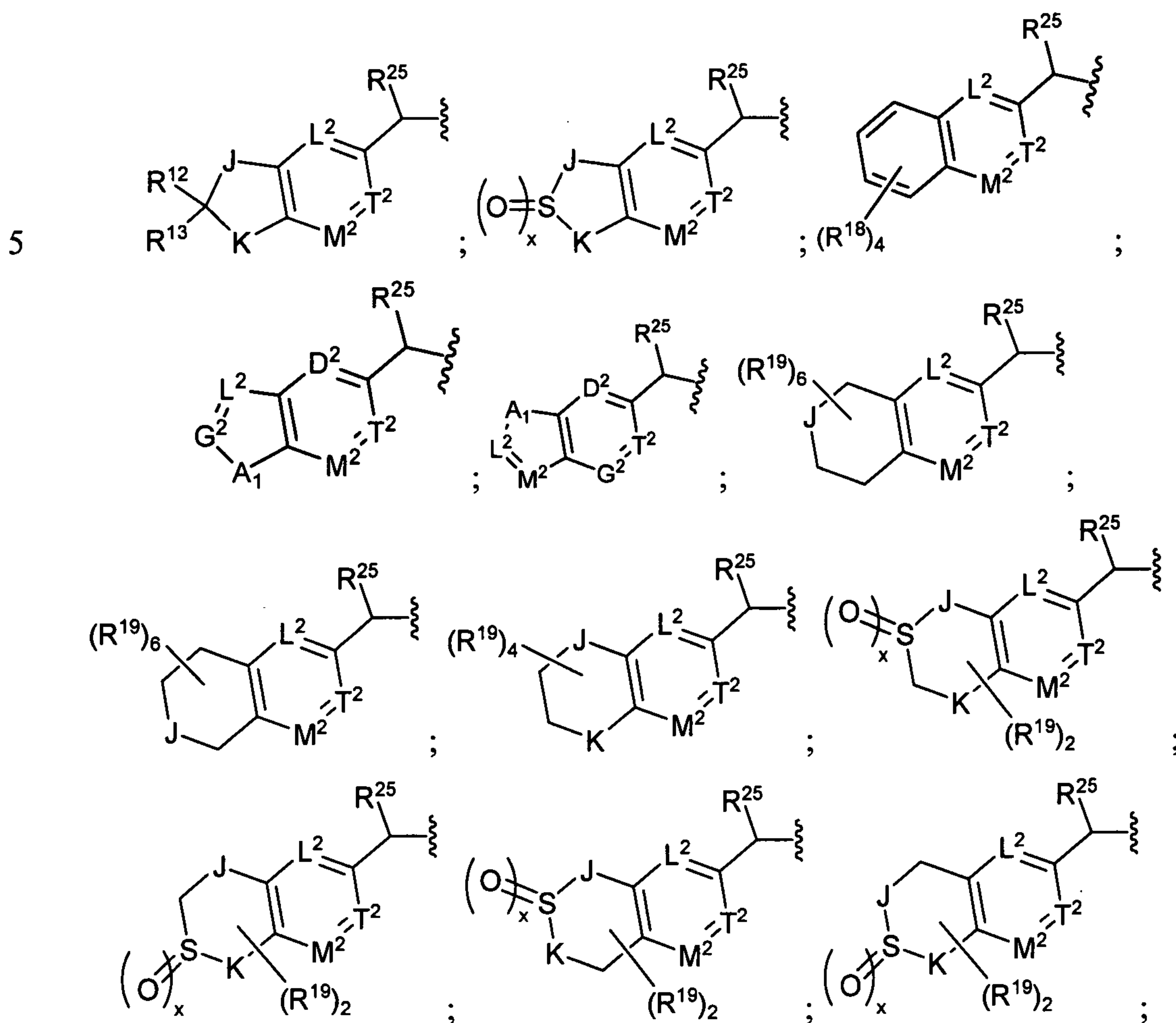
$Z$  is a 5- to 8-membered ring selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are  
10 optionally substituted one or more times.

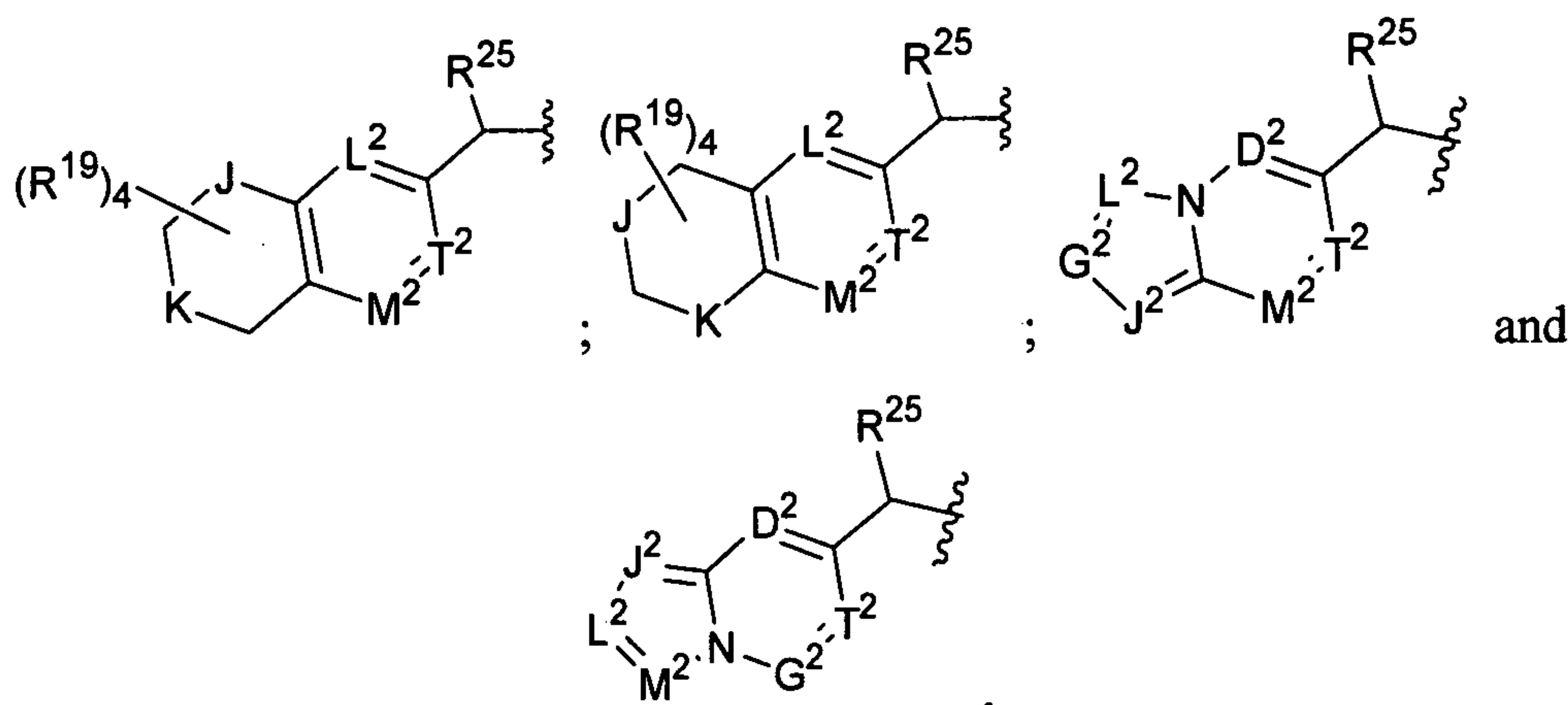
In another embodiment, in conjunction with any above or below embodiments,  $R^1$  is selected from:





In another embodiment, in conjunction with any above or below embodiments,  $R^1$  is selected from:





wherein:

- $R^{12}$  and  $R^{13}$  are independently selected from hydrogen, alkyl and halo,  
 5 wherein alkyl is optionally substituted one or more times, or optionally  $R^{12}$  and  $R^{13}$  together form  $=O$ ,  $=S$ ,  $=NR^{10}$  or  $=NOR^{10}$ ;  
 $R^{18}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  
 10  $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;  
 $R^{19}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  
 15  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two  $R^{19}$  groups together at one carbon atom form  $=O$ ,  $=S$ ,  $=NR^{10}$  or  $=NOR^{10}$ ;  
 20  $R^{25}$  is selected from hydrogen, alkyl, cycloalkyl,  $C(O)NR^{10}R^{11}$  and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

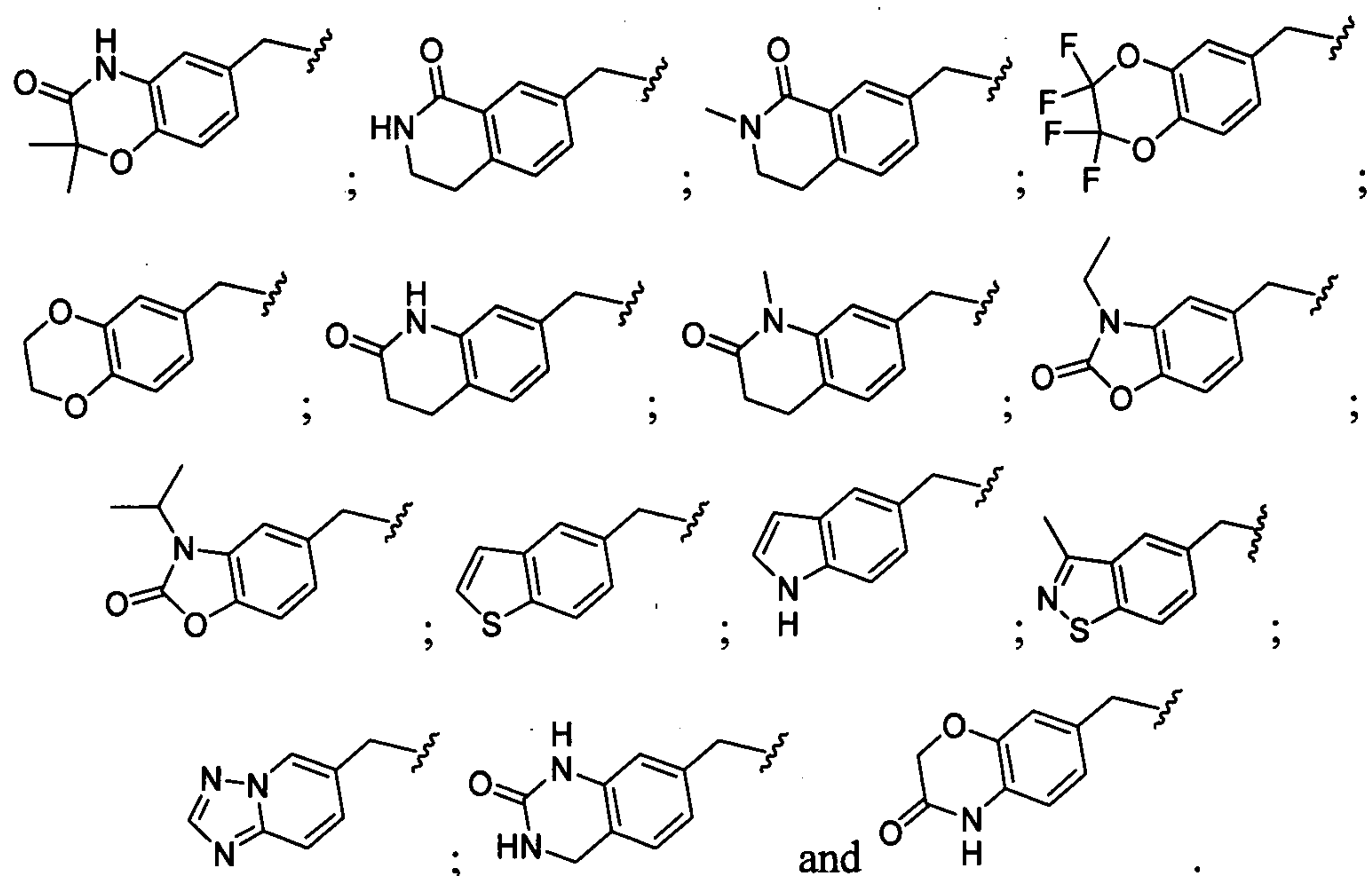
$J$  and  $K$  are independently selected from  $CR^{10}R^{18}$ ,  $NR^{10}$ , O and  $S(O)_x$ ;

$A_1$  is selected from  $NR^{10}$ , O and  $S(O)_x$ ; and

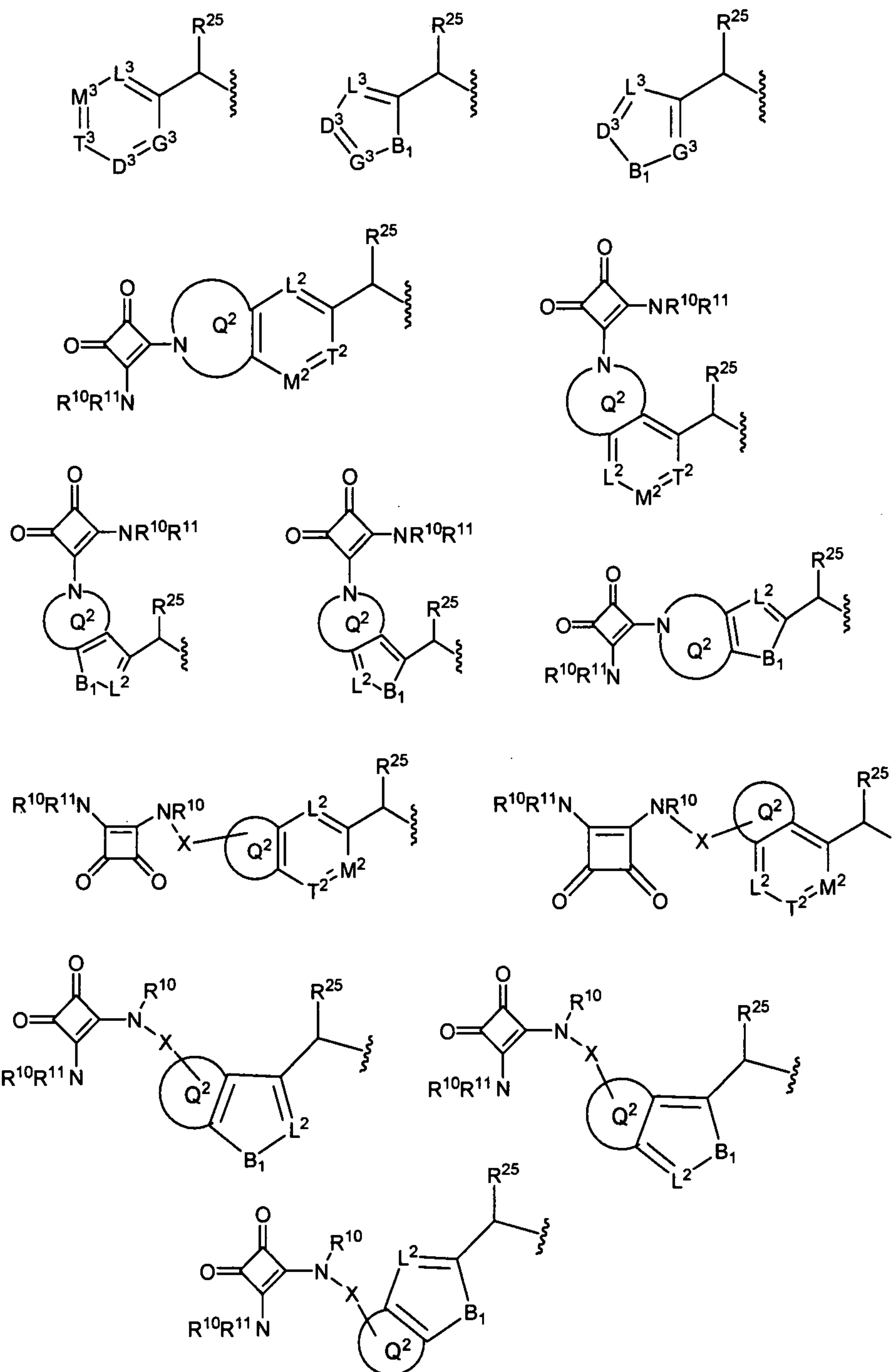
- 25  $D^2$ ,  $G^2$ ,  $J^2$ ,  $L^2$ ,  $M^2$  and  $T^2$  are independently selected from  $CR^{18}$  and N.

5





- 5 In another embodiment, in conjunction with any above or below embodiments, R<sup>1</sup> is selected from:



wherein:

$R^{18}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  
 5  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  
 $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl,

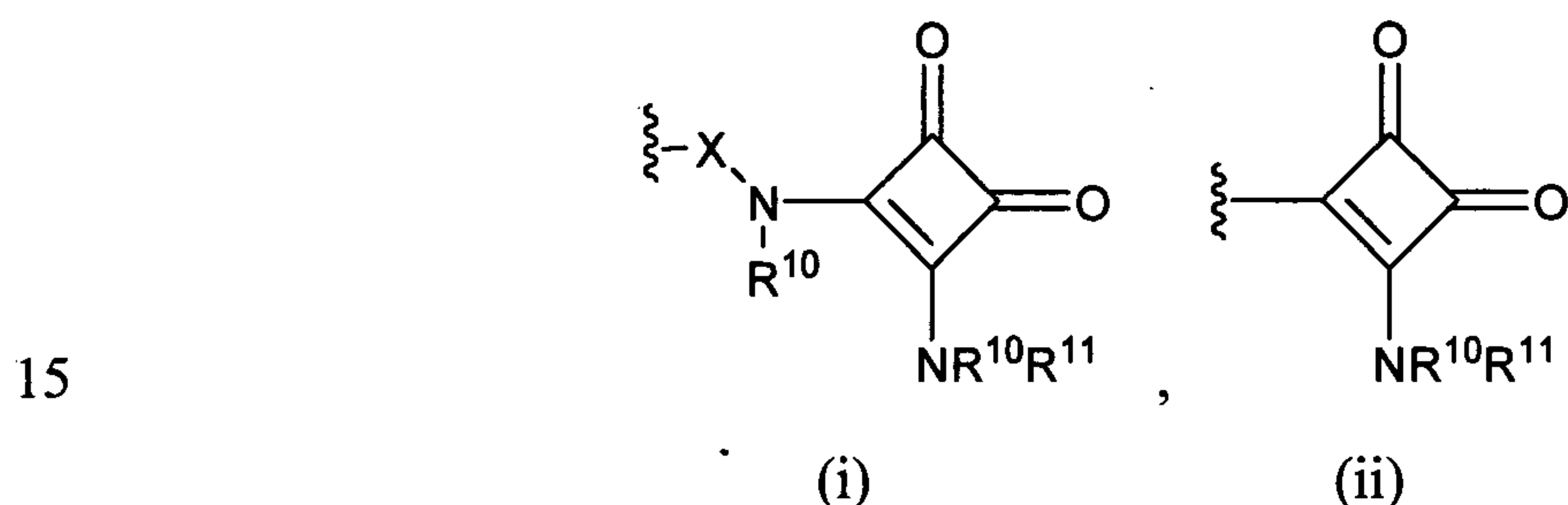
heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

$R^{19}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  
 5  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  
 $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two  $R^{19}$  groups together at one carbon atom form  $=O$ ,  $=S$ ,  $=NR^{10}$  or  $=NOR^{10}$ ;

10  $R^{25}$  is selected from hydrogen, alkyl, cycloalkyl,  $CONR^{10}R^{11}$  and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

$L^2$ ,  $M^2$ , and  $T^2$  are independently selected from  $CR^{18}$  and N;

$D^3$ ,  $G^3$ ,  $L^3$ ,  $M^3$ , and  $T^3$  are independently selected from N,  $CR^{18}$ , (i) and (ii)

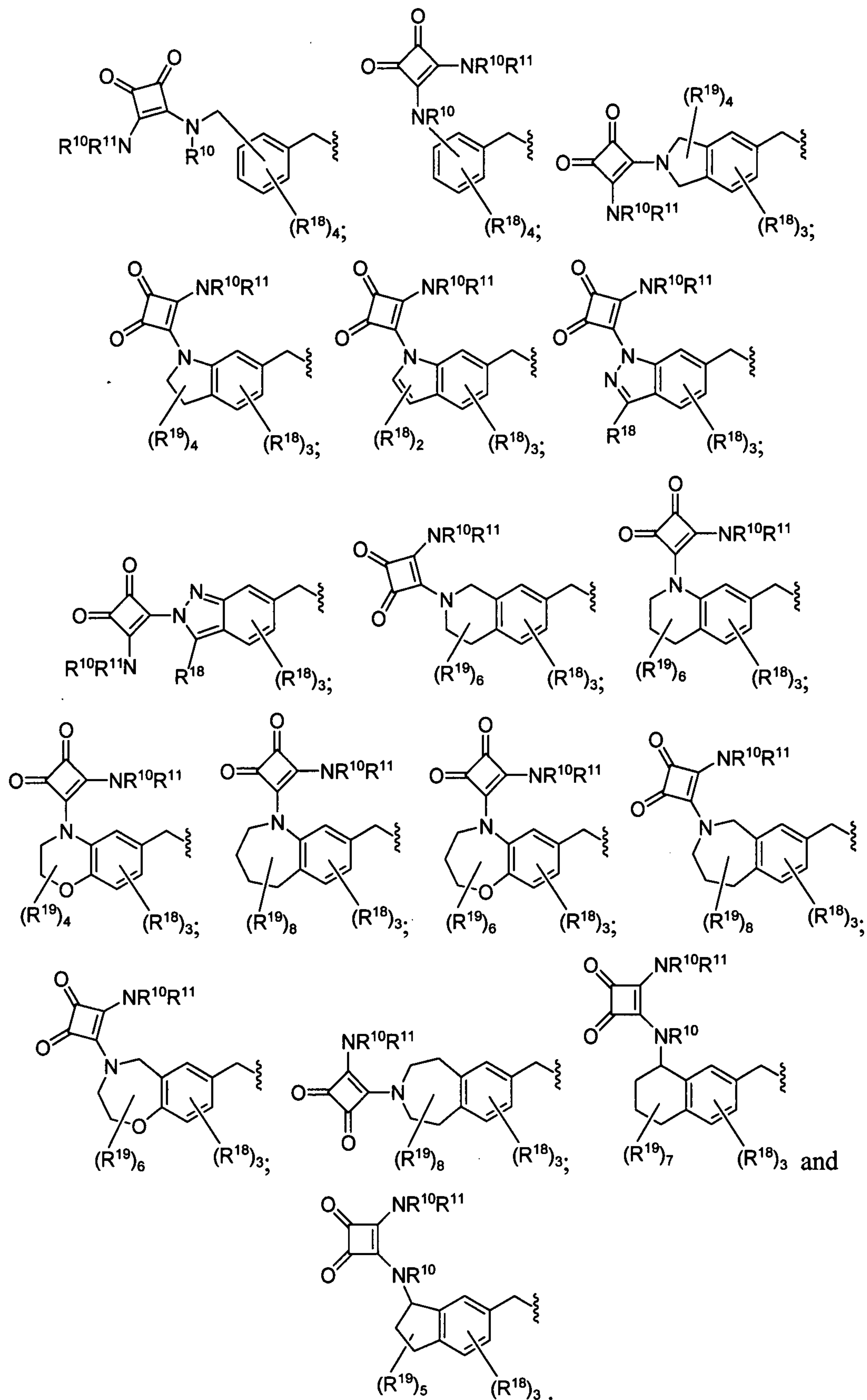


with the proviso that one of  $L^3$ ,  $M^3$ ,  $T^3$ ,  $D^3$ , and  $G^3$  is (i) or (ii);

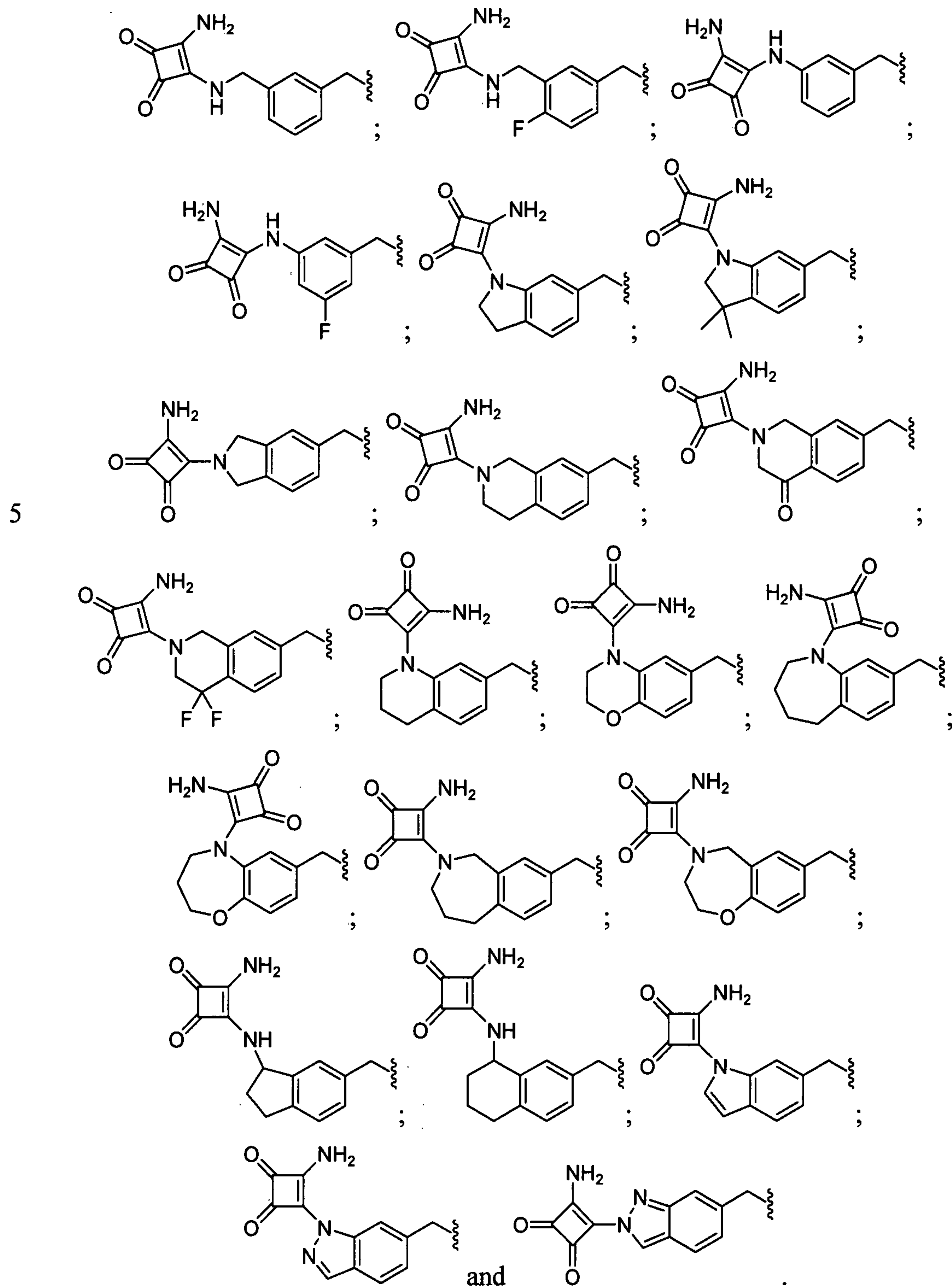
$B_1$  is selected from the group consisting of  $NR^{10}$ , O and  $S(O)_x$ ; and

20  $Q^2$  is a 5- to 8-membered ring selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, which is optionally substituted one or more times with  $R^{19}$ .

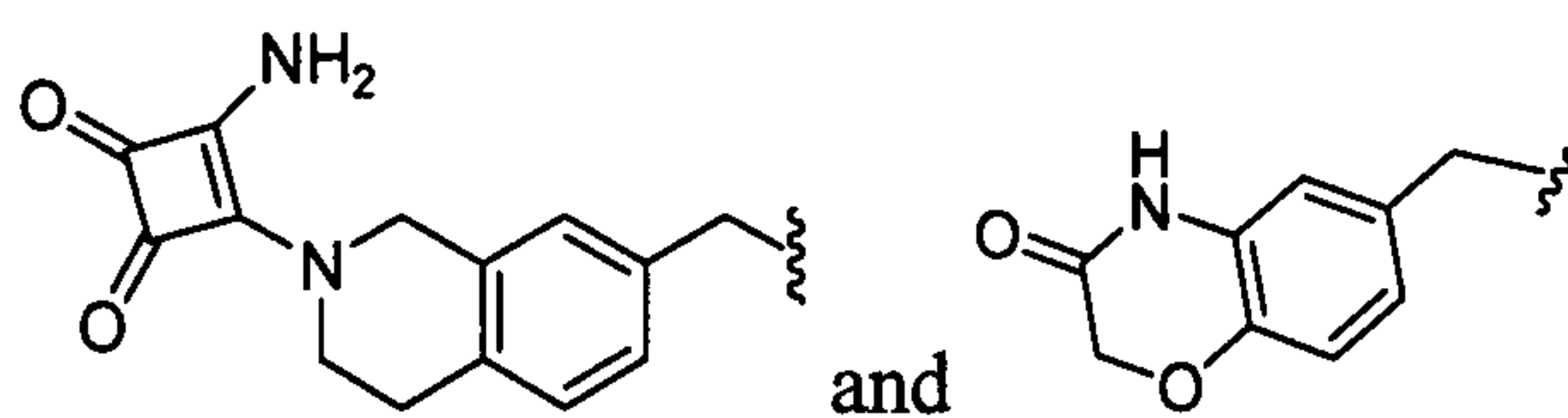
In another embodiment, in conjunction with any above or below embodiments,  $R^1$  is selected from:



In another embodiment, in conjunction with any above or below embodiments,  $R^1$  is selected from:

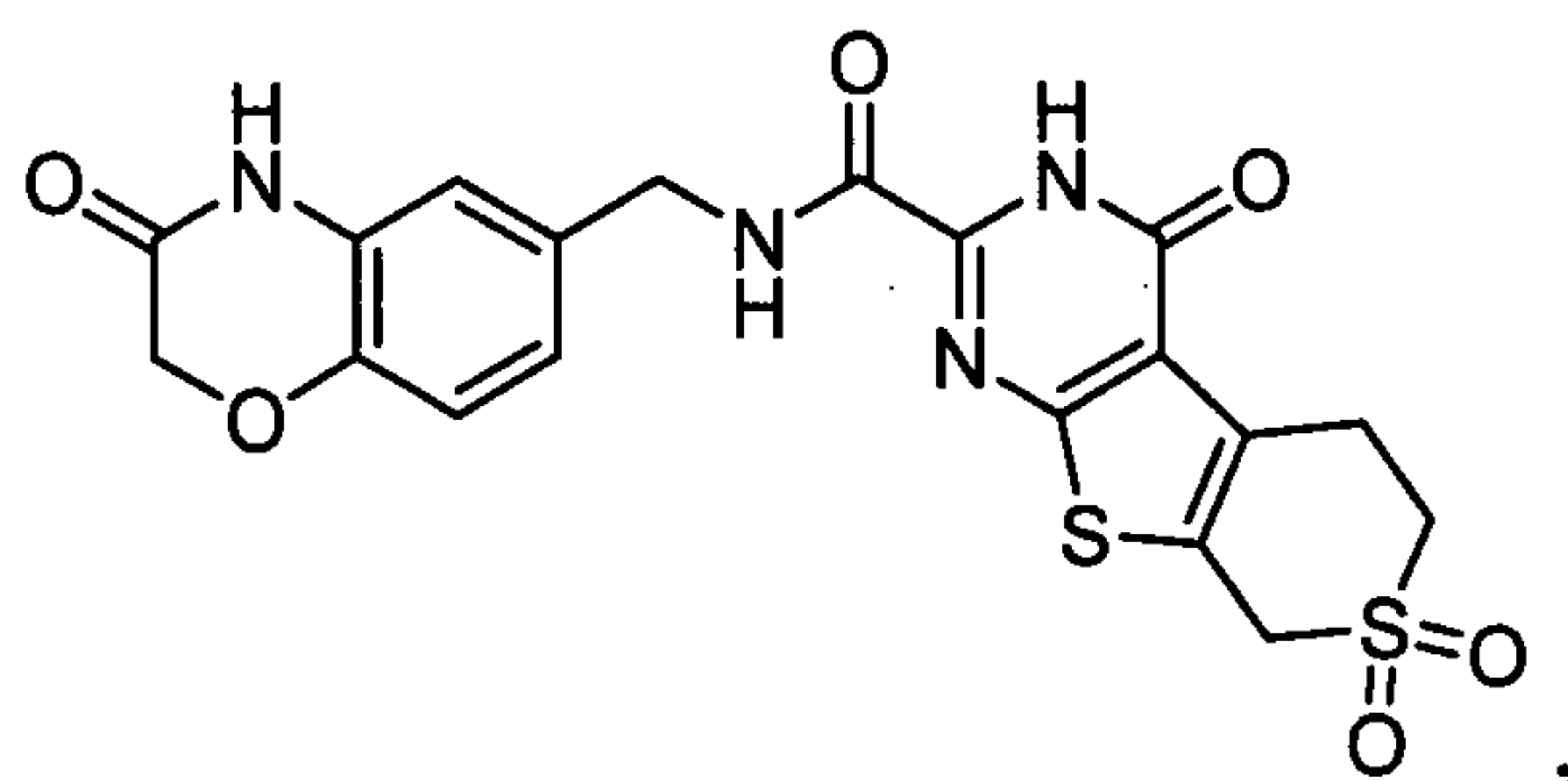
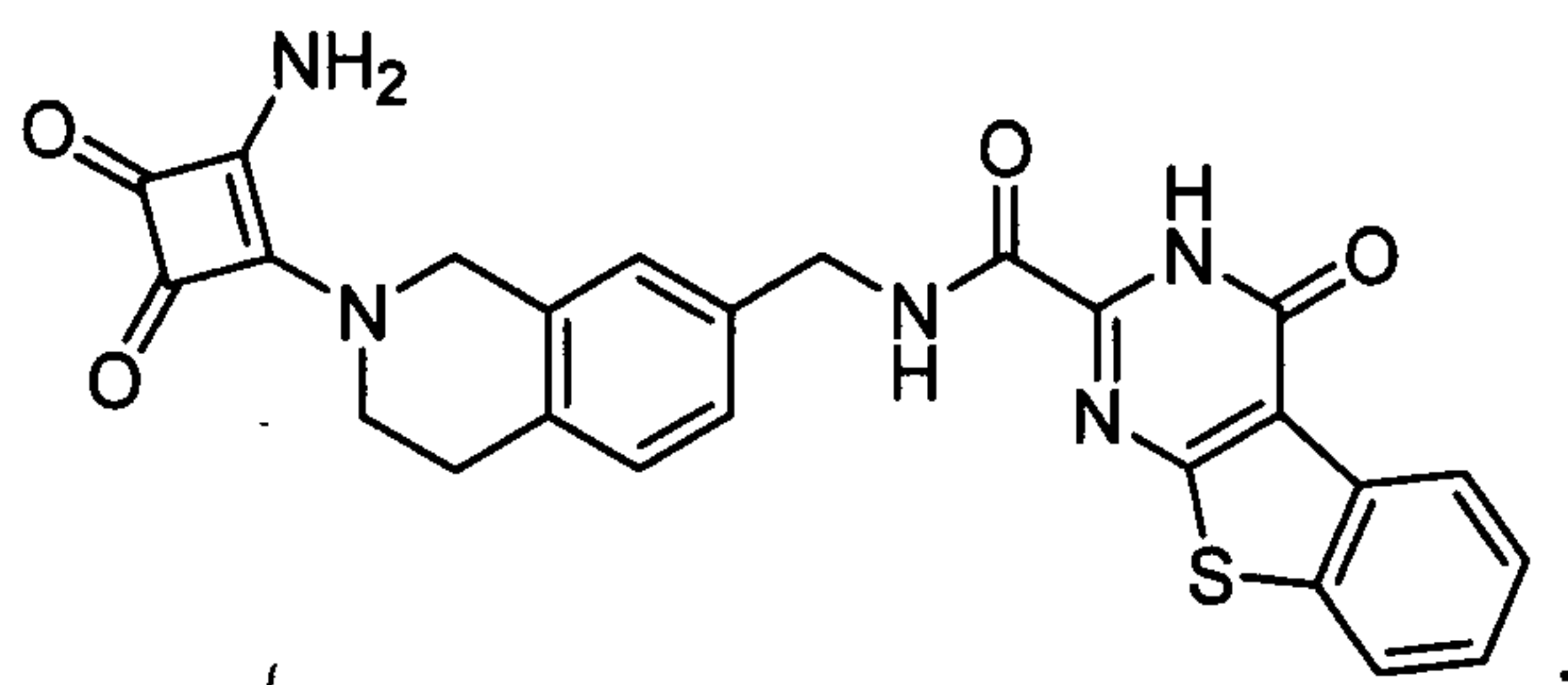
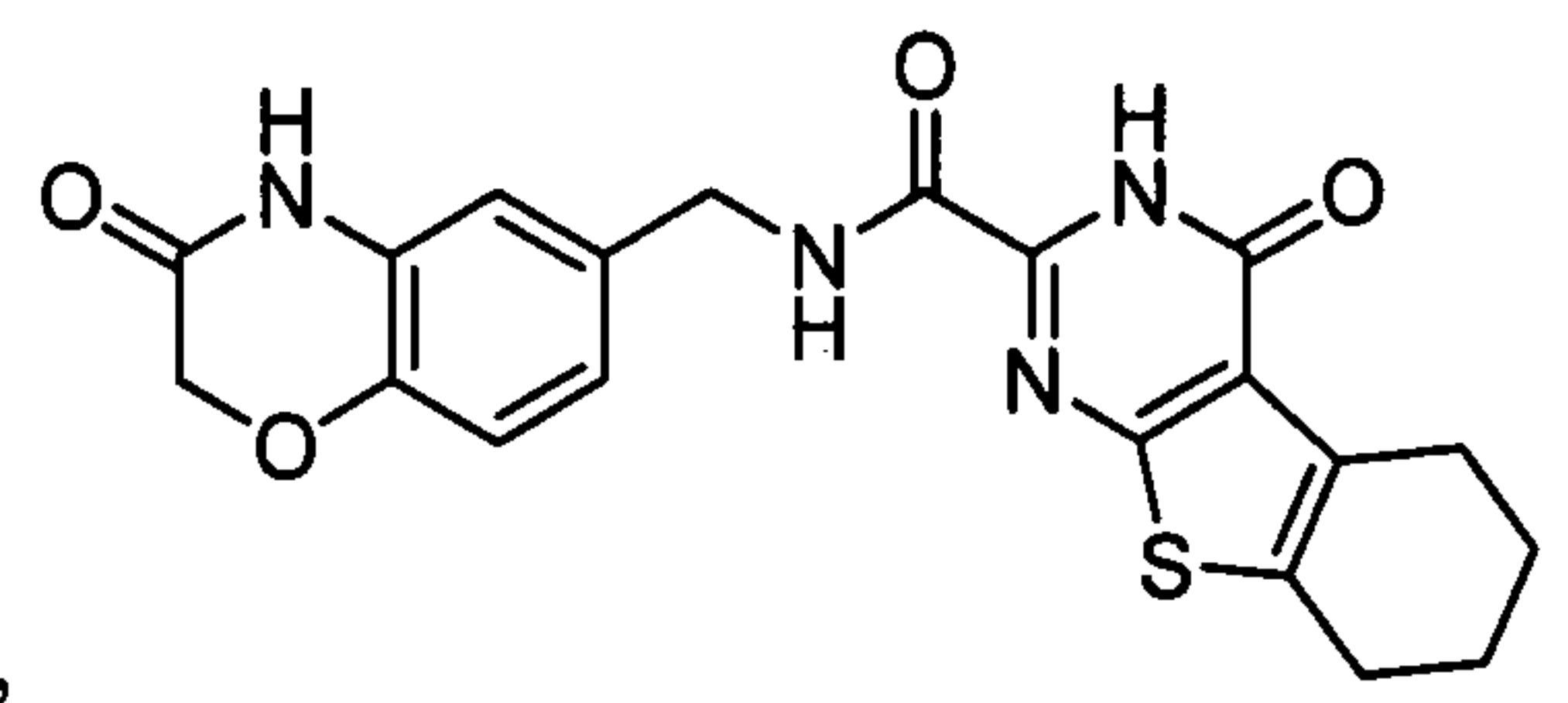
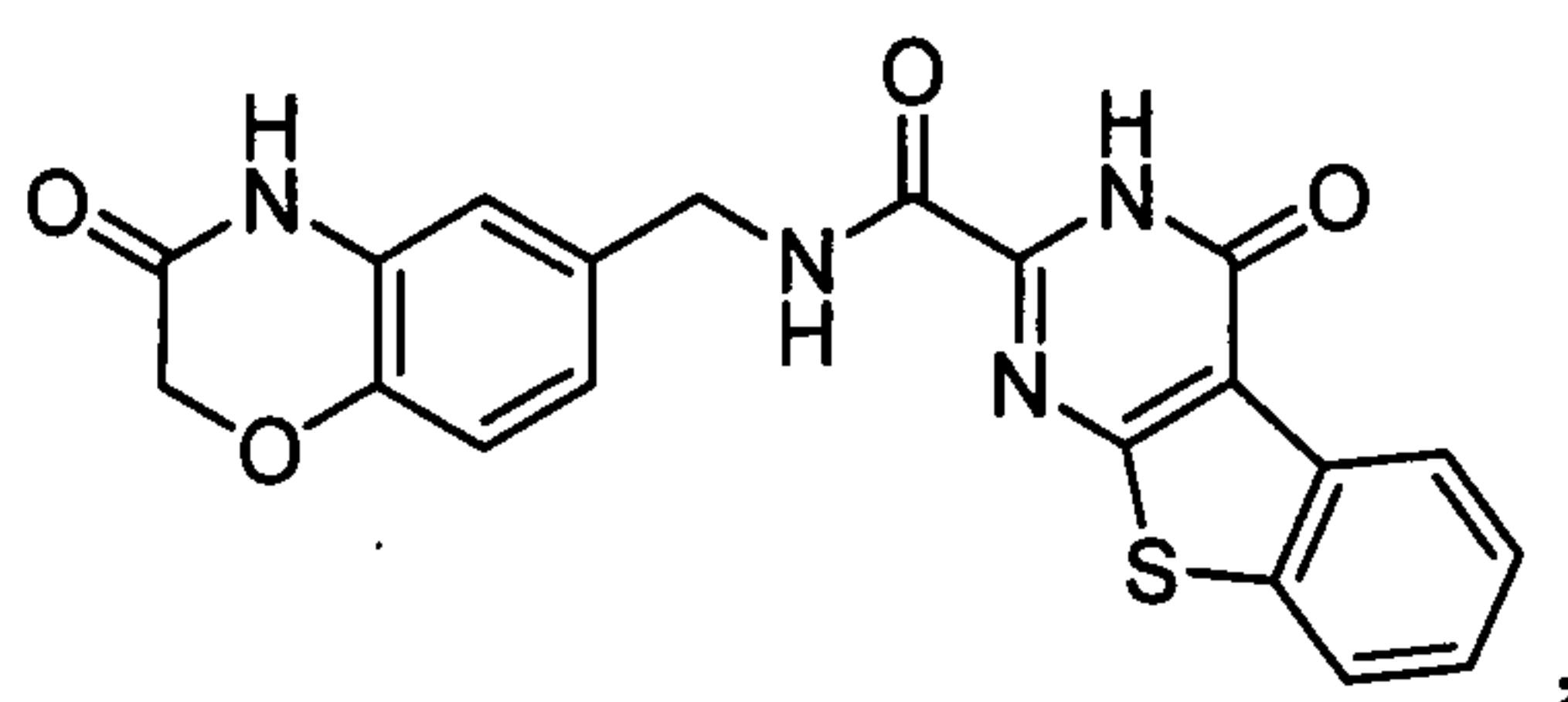
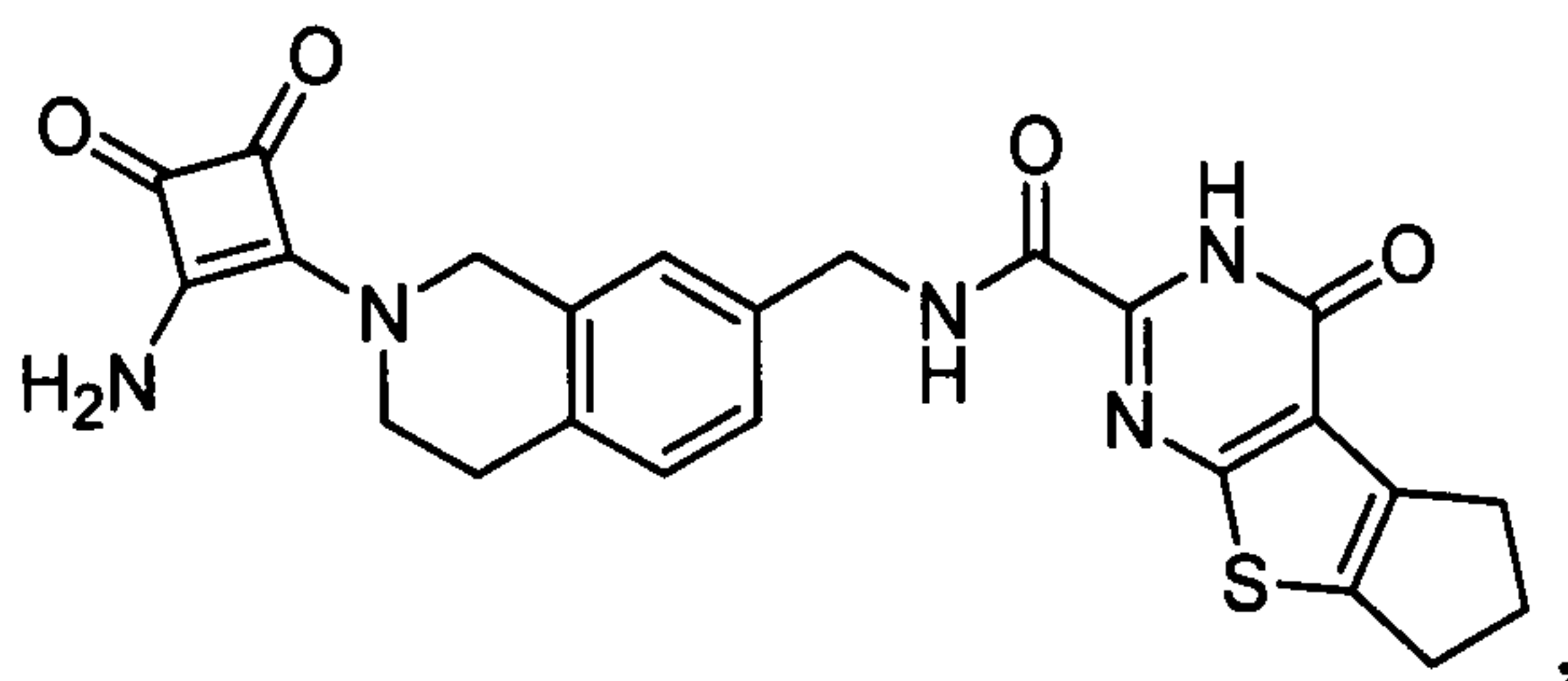
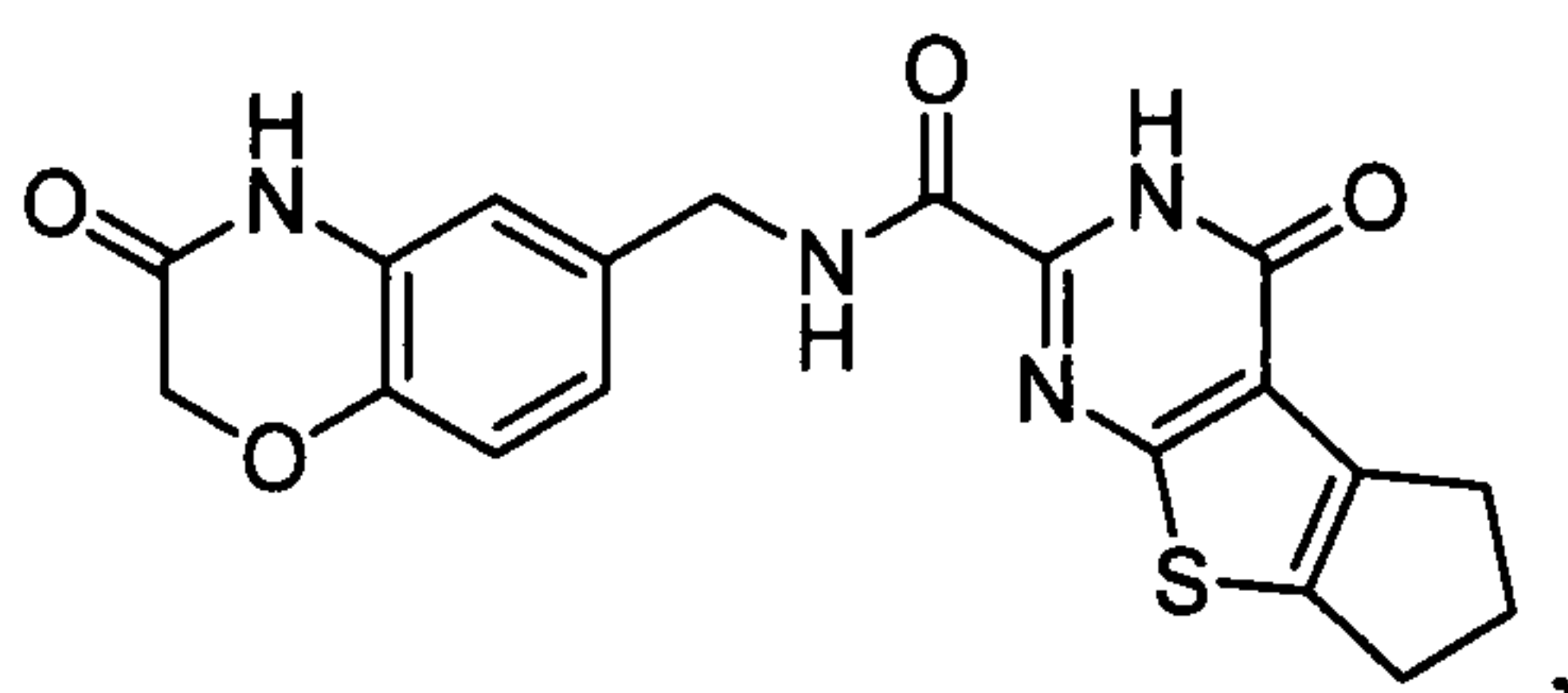


In another embodiment, in conjunction with any above or below embodiments,  $R^1$  is selected from:

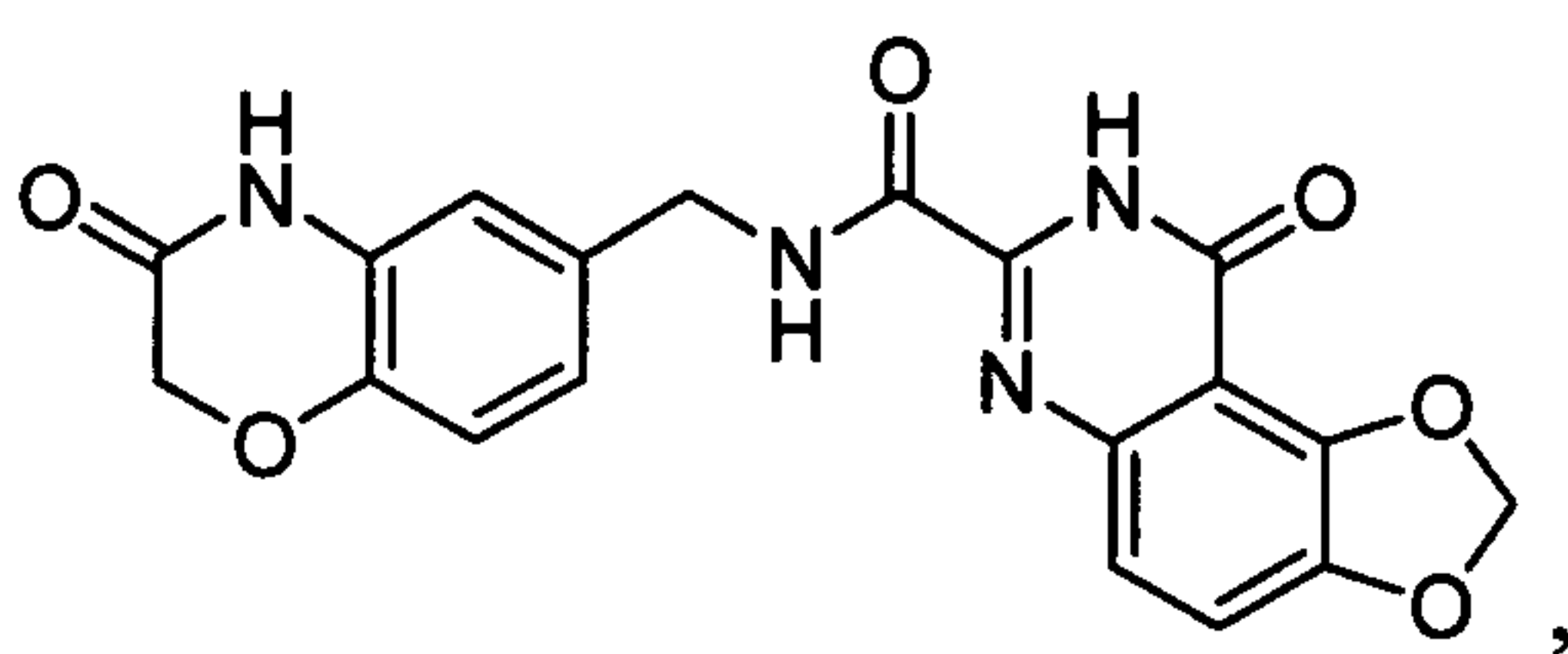
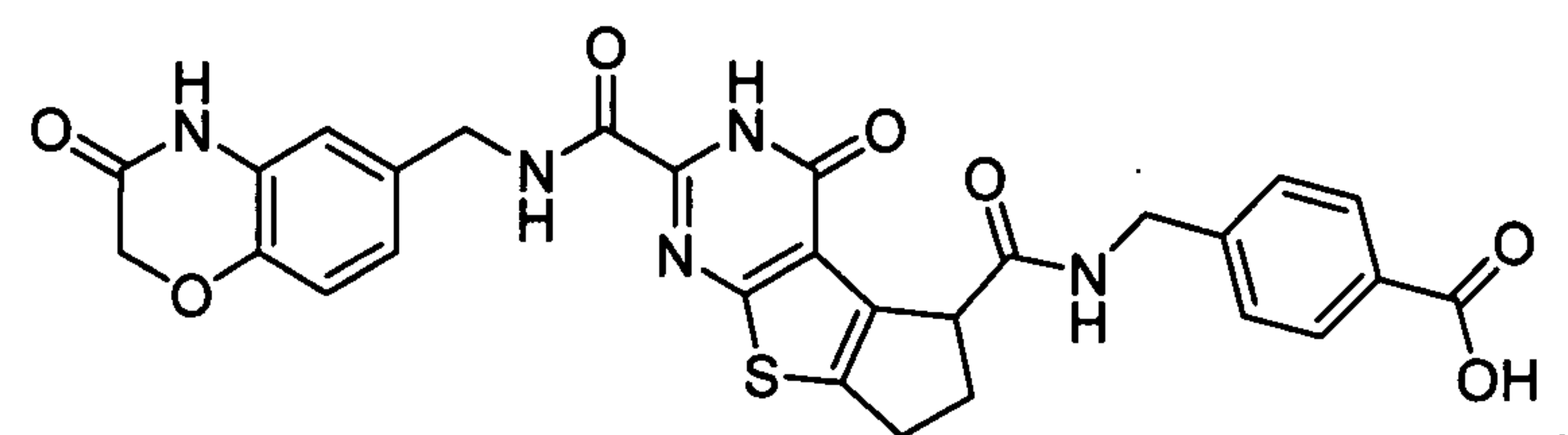
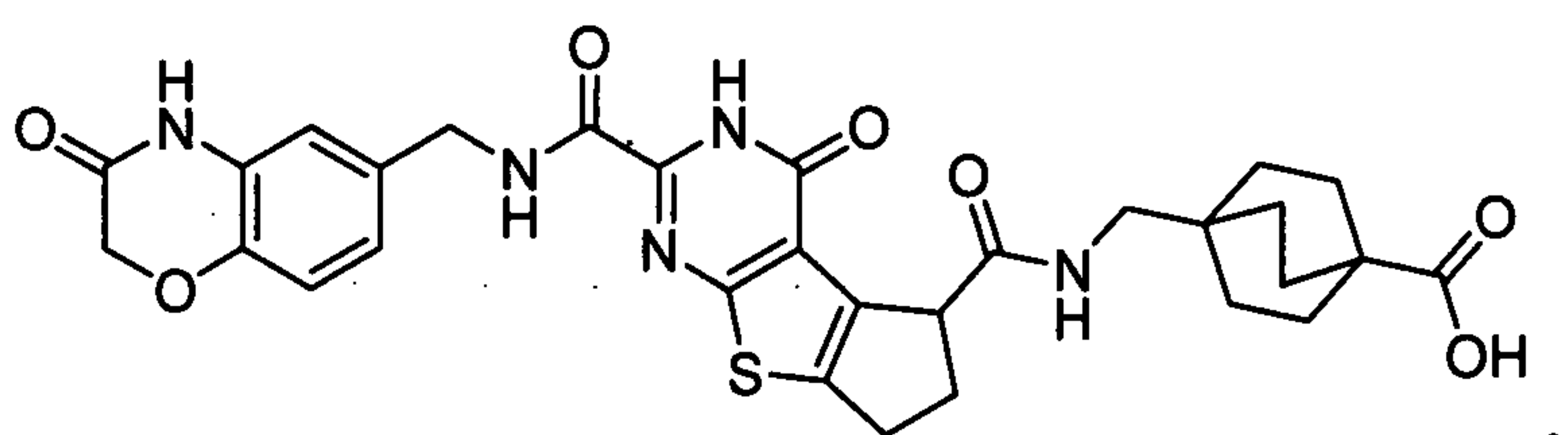
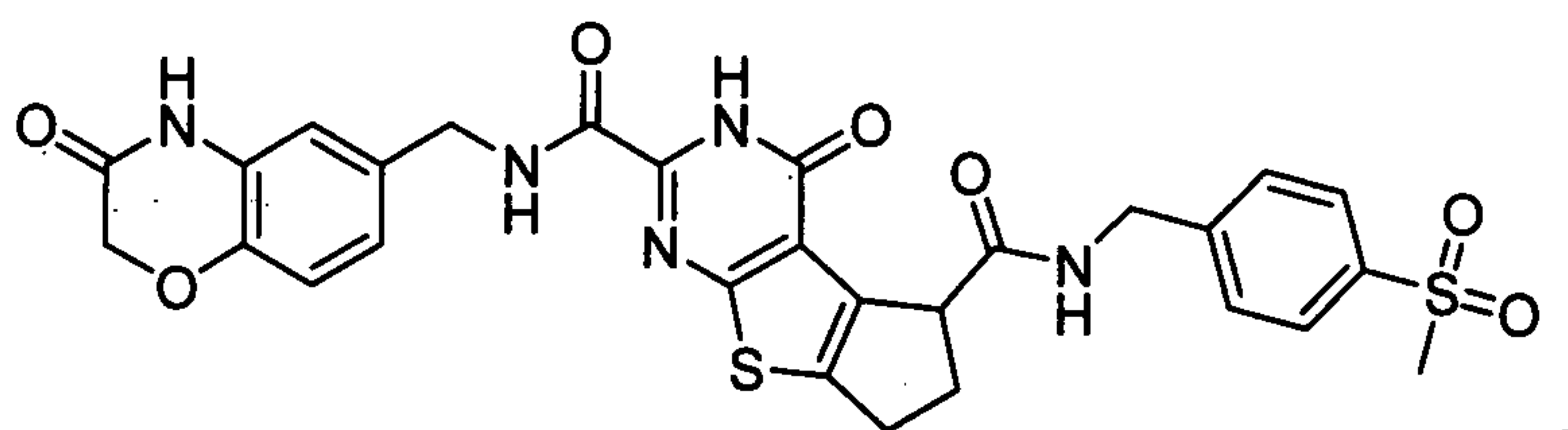
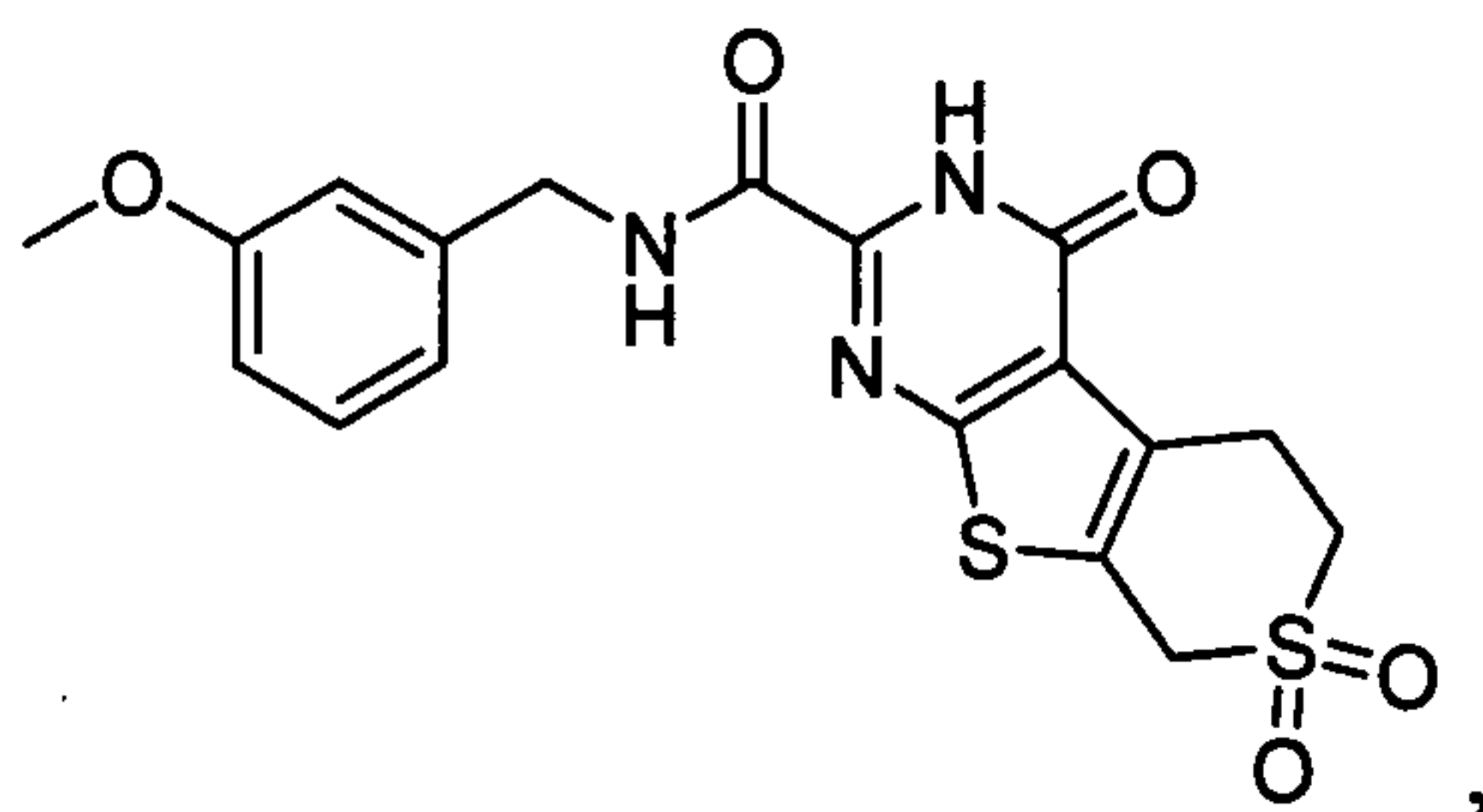
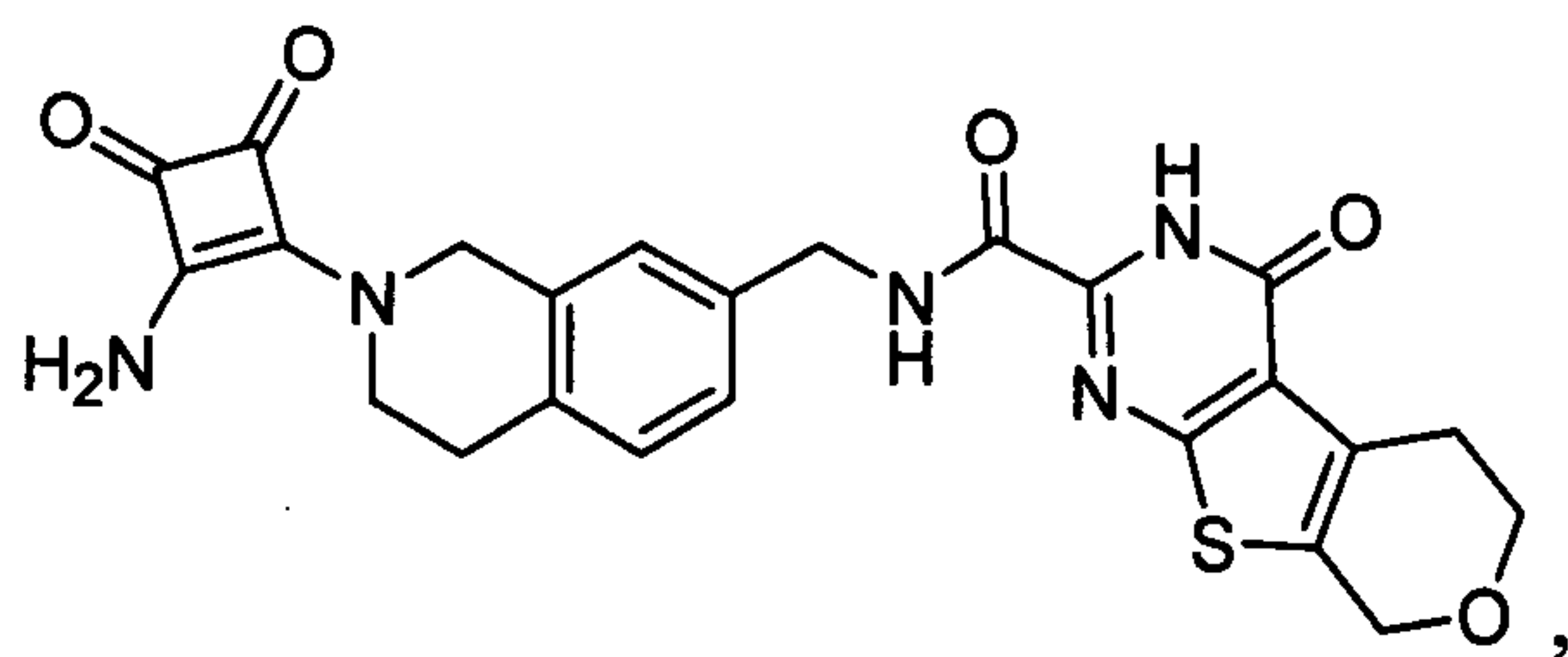
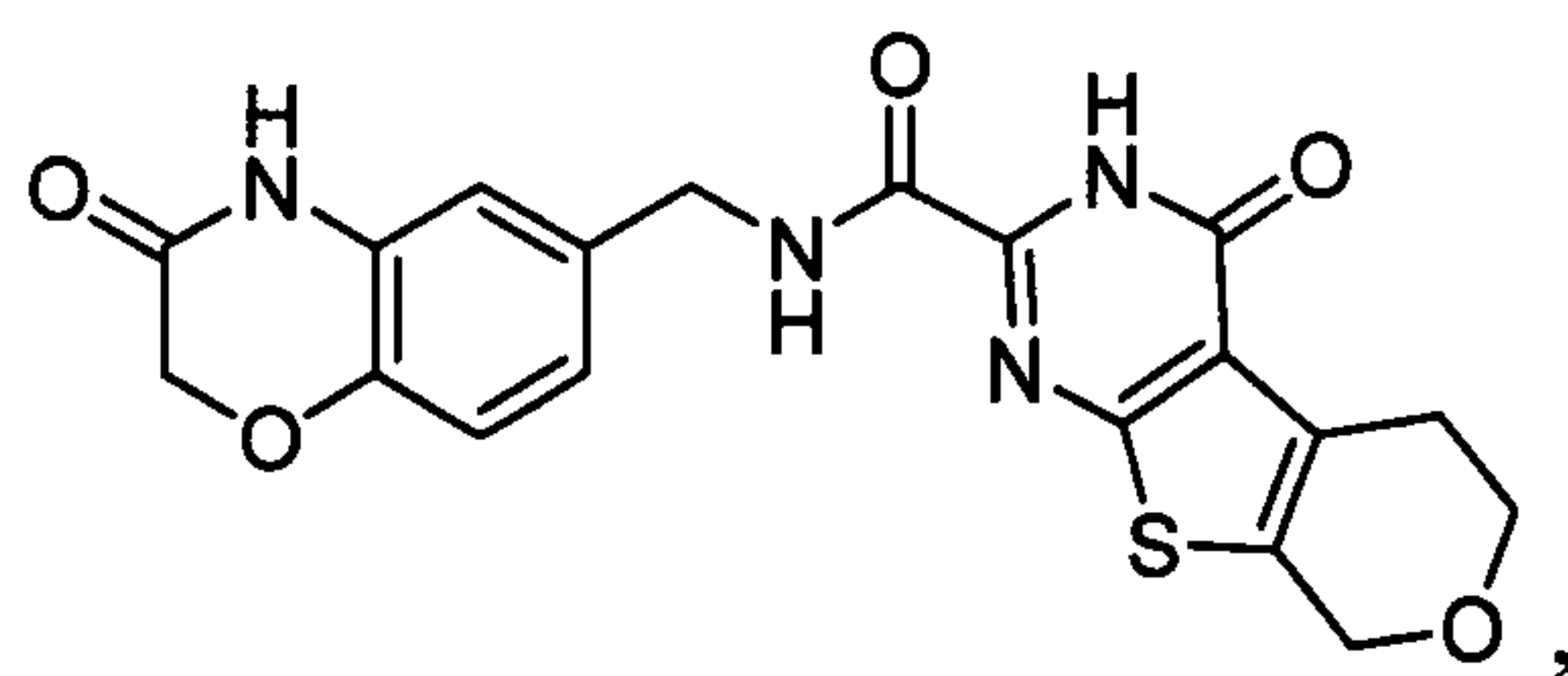


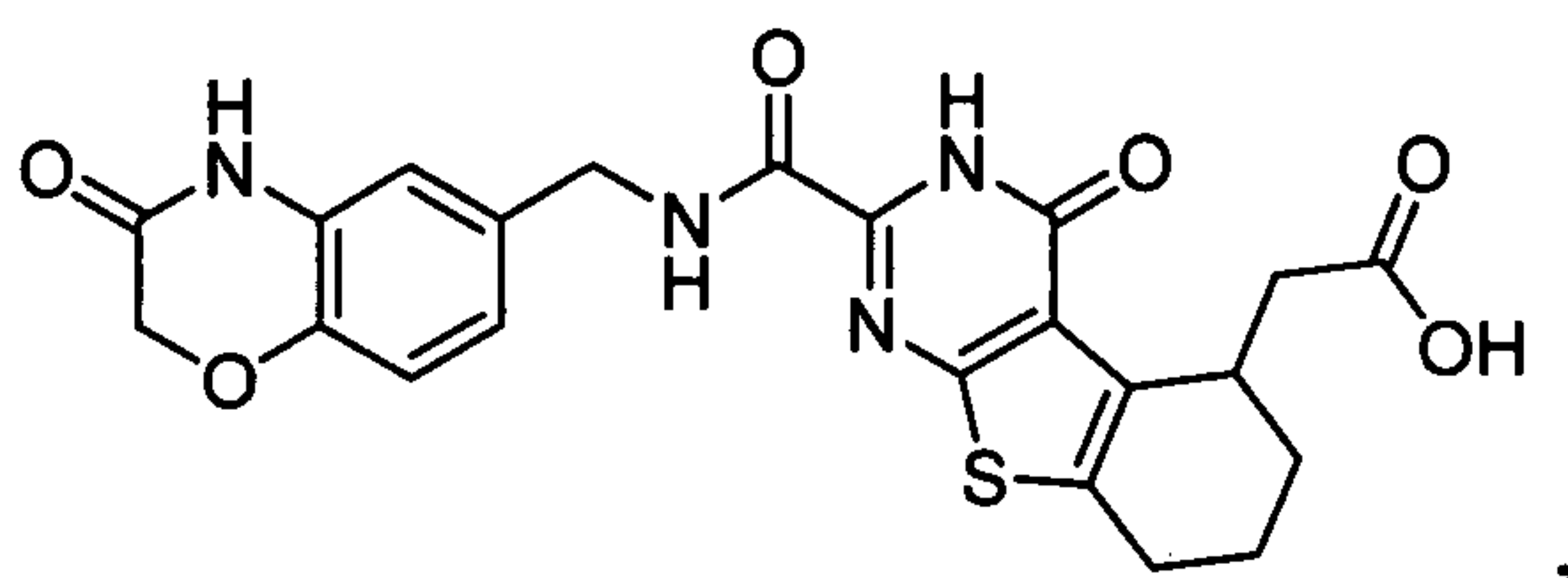
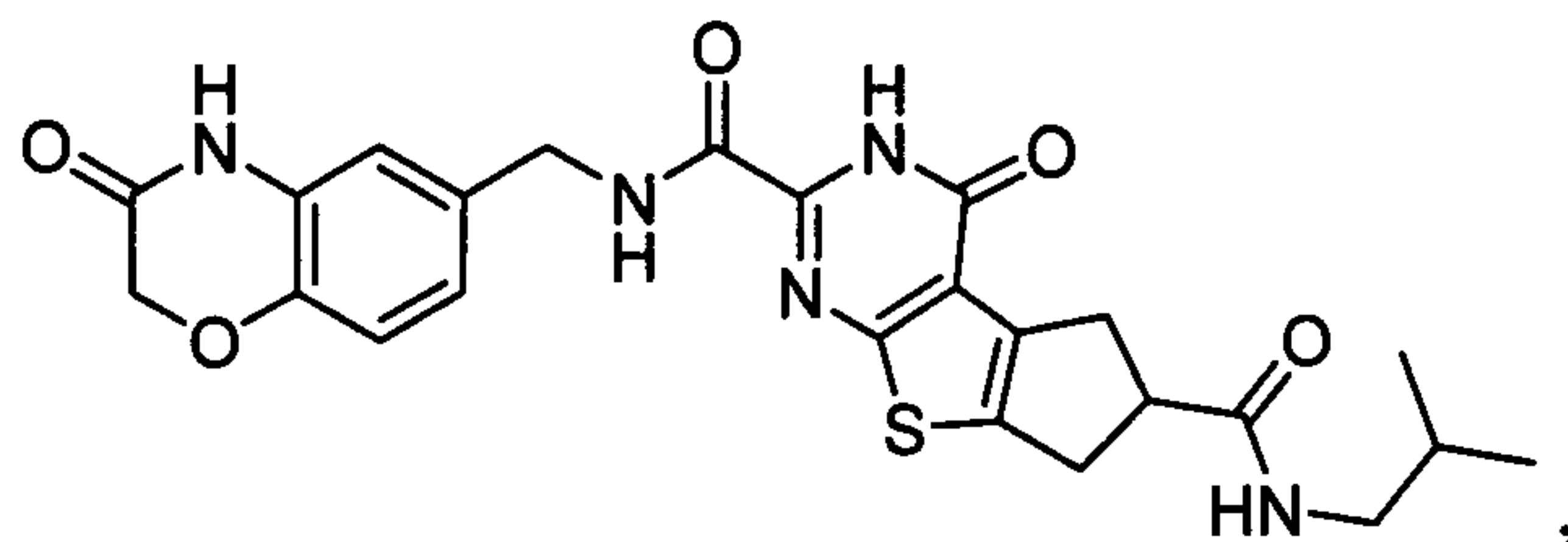
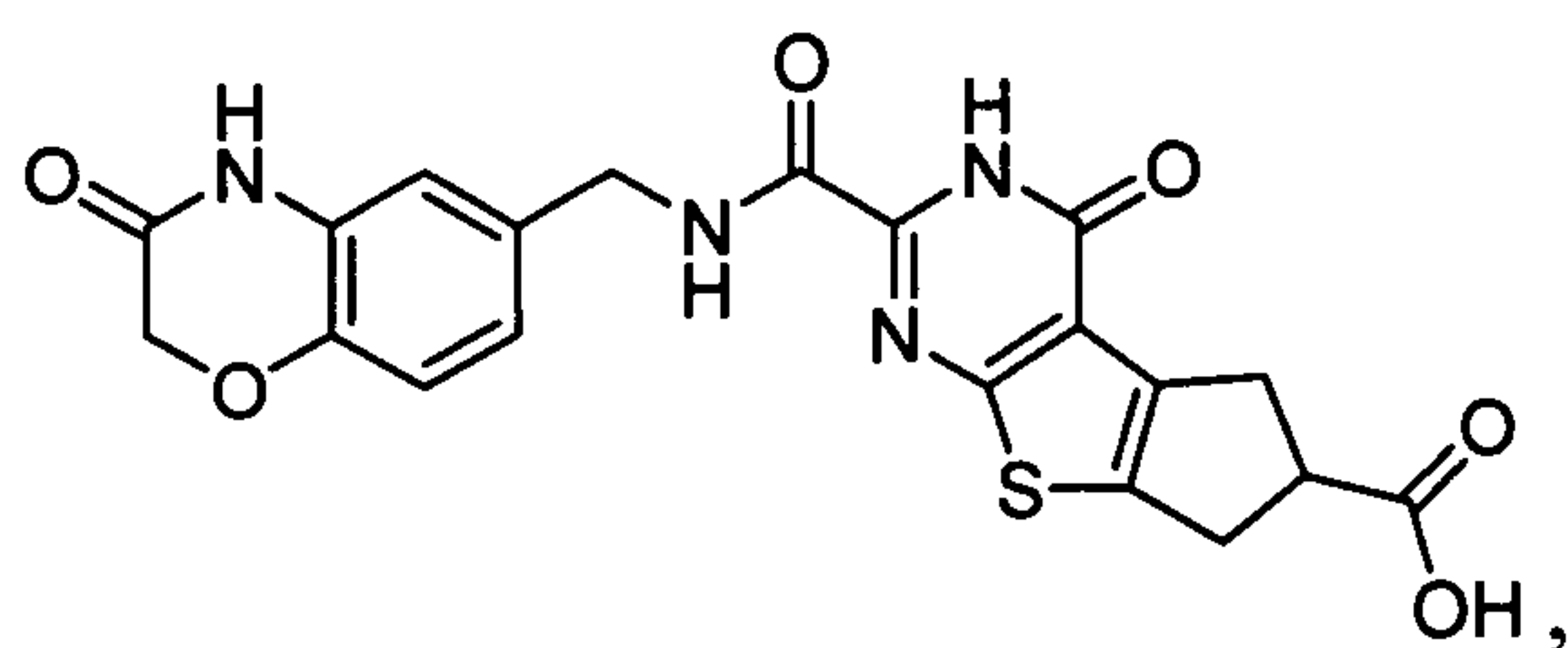
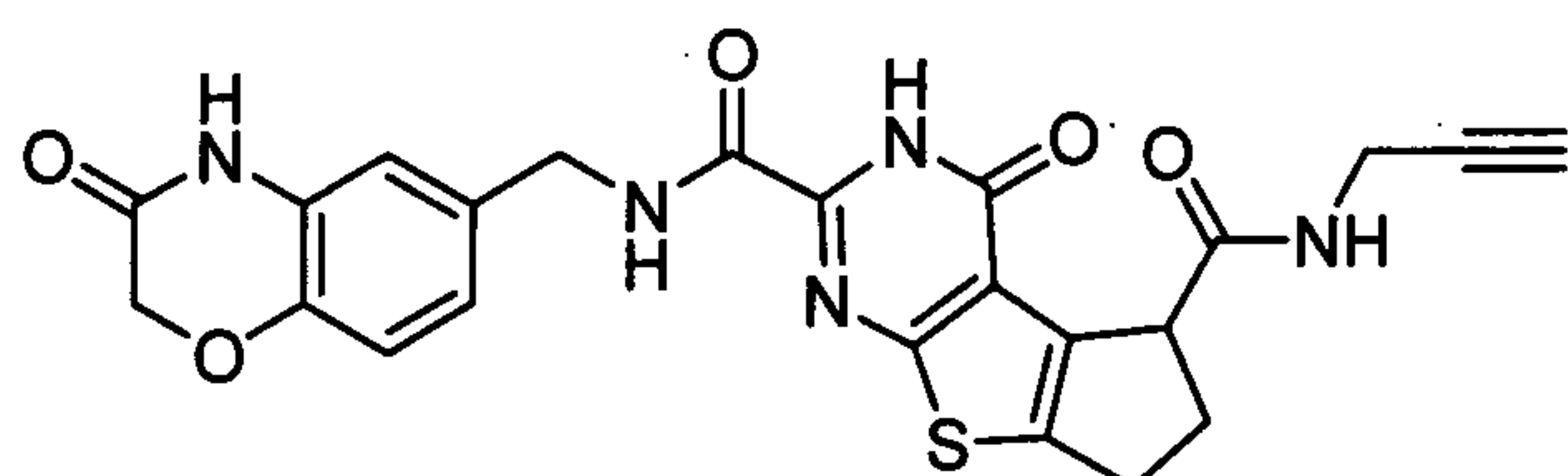
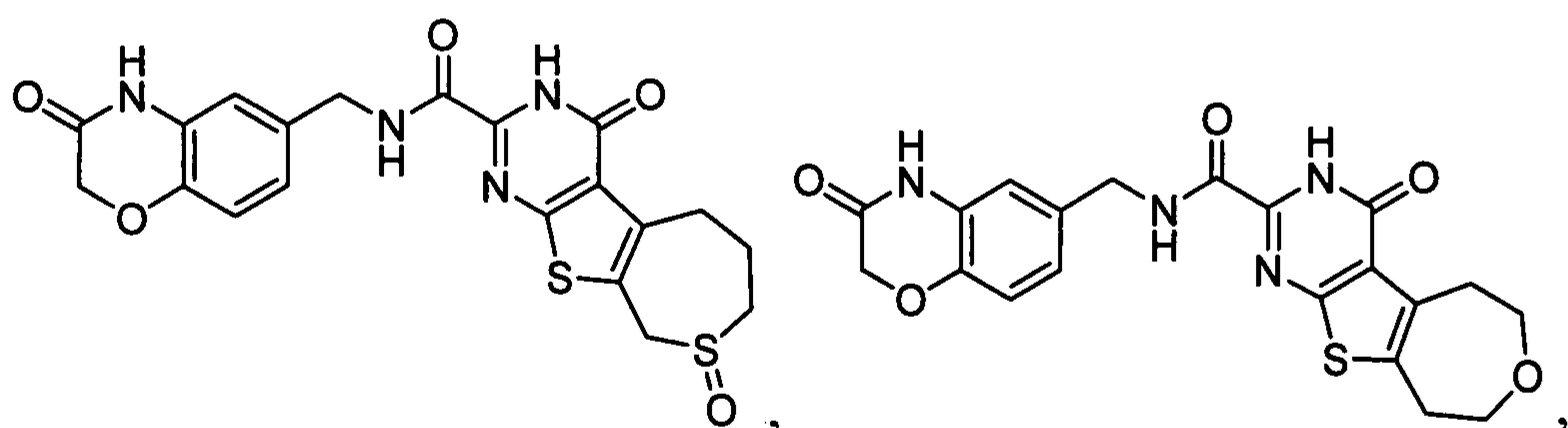
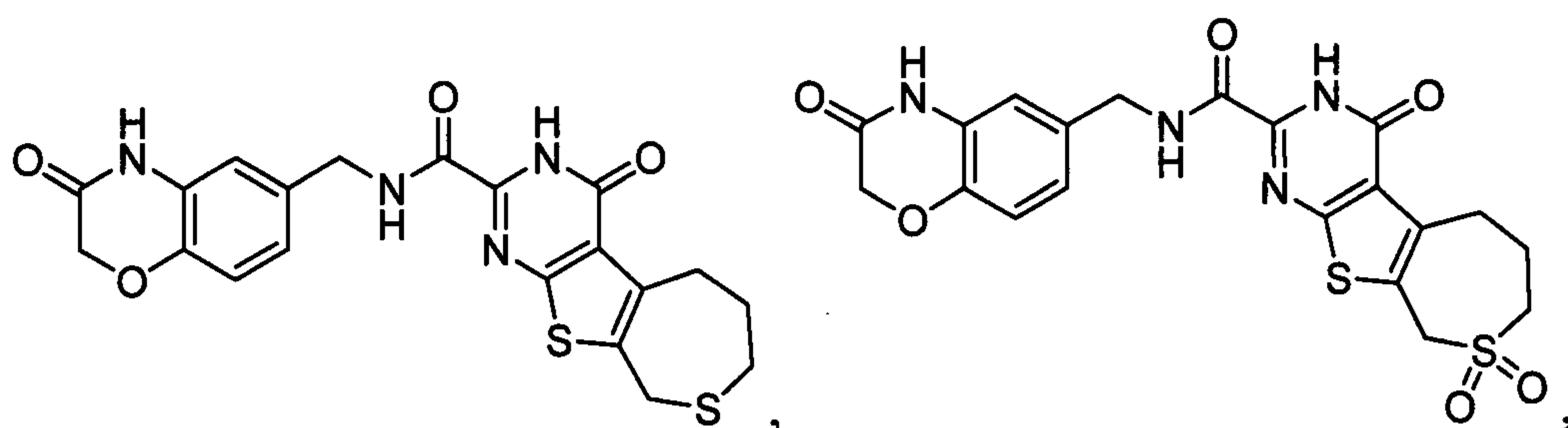
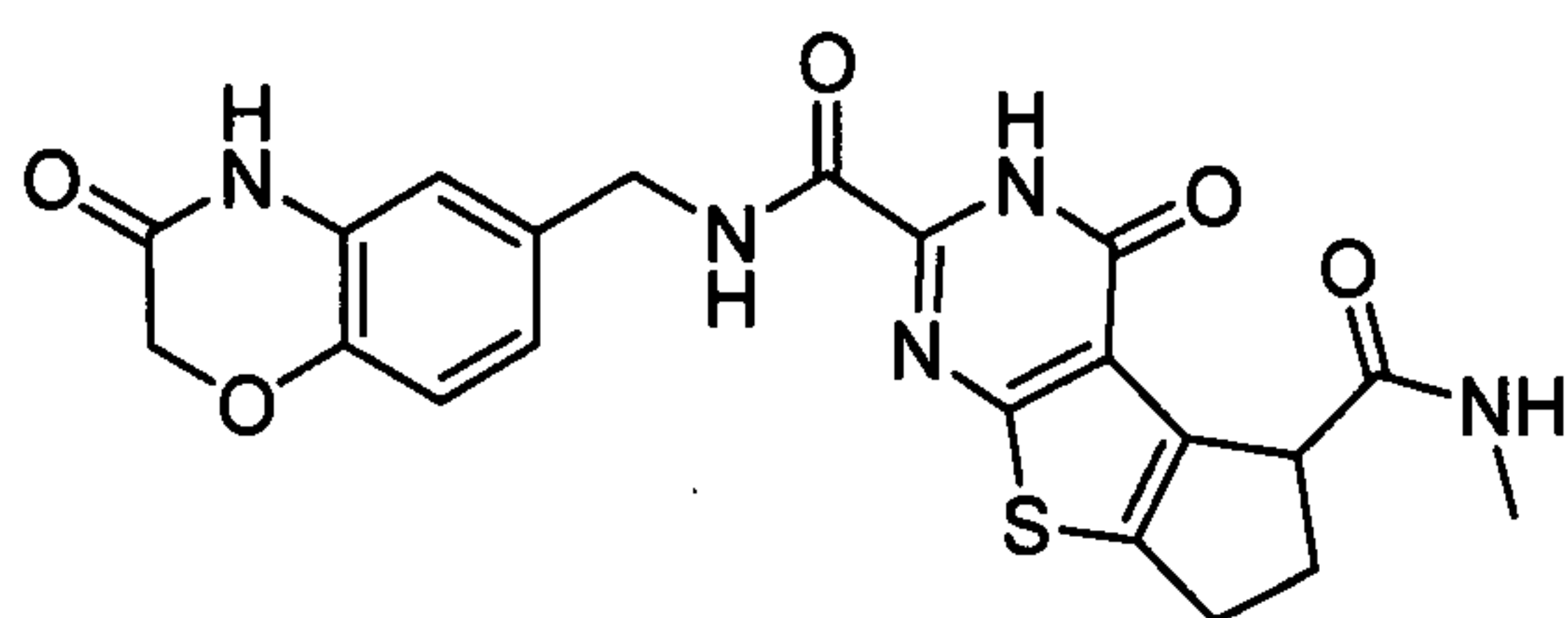
In another embodiment, in conjunction with any above or below embodiments, the compounds have the structure:

5

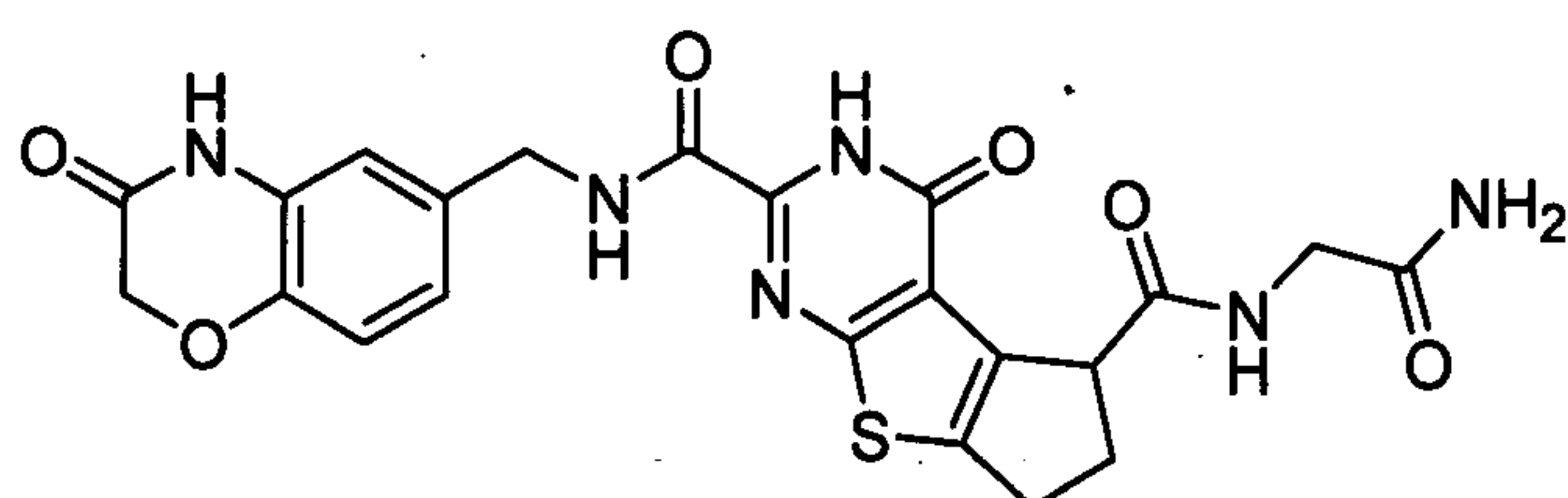
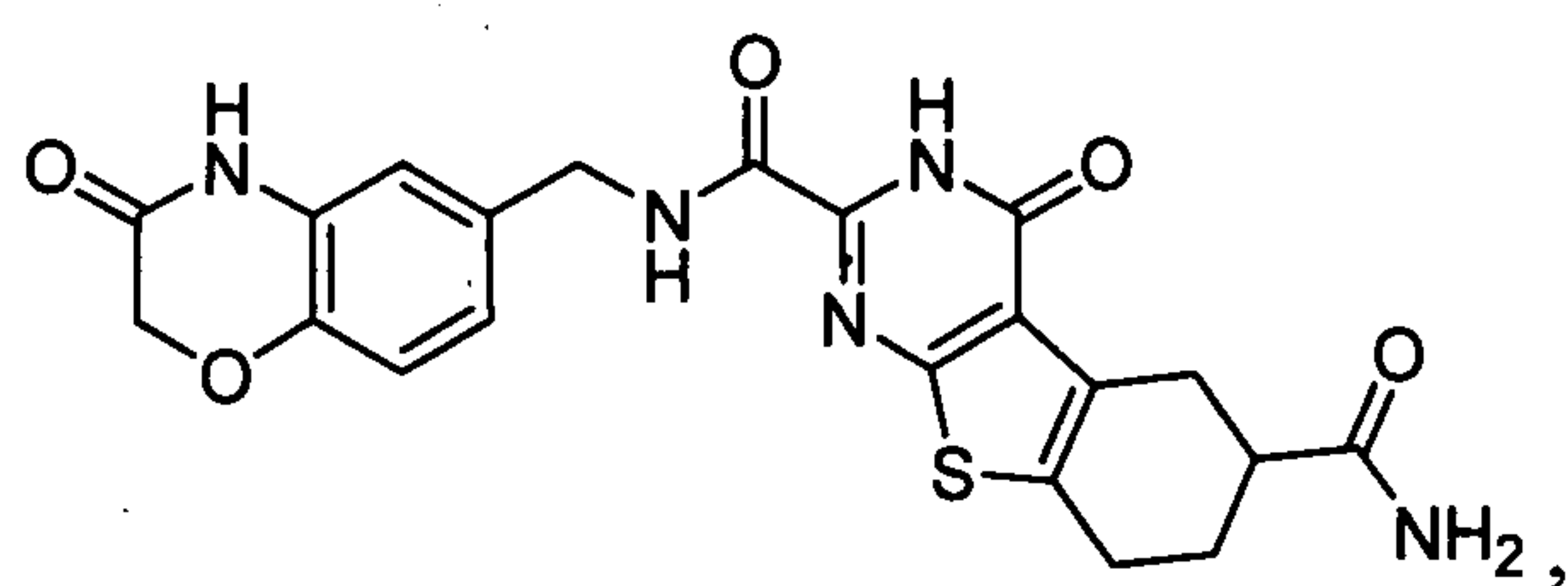
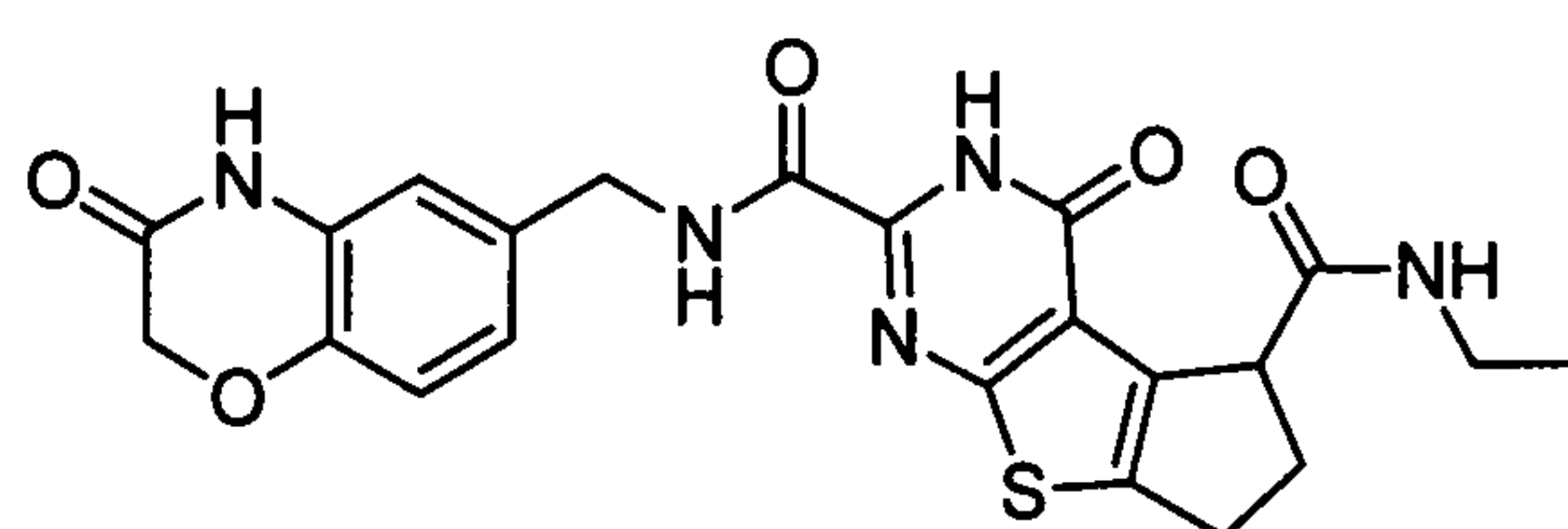
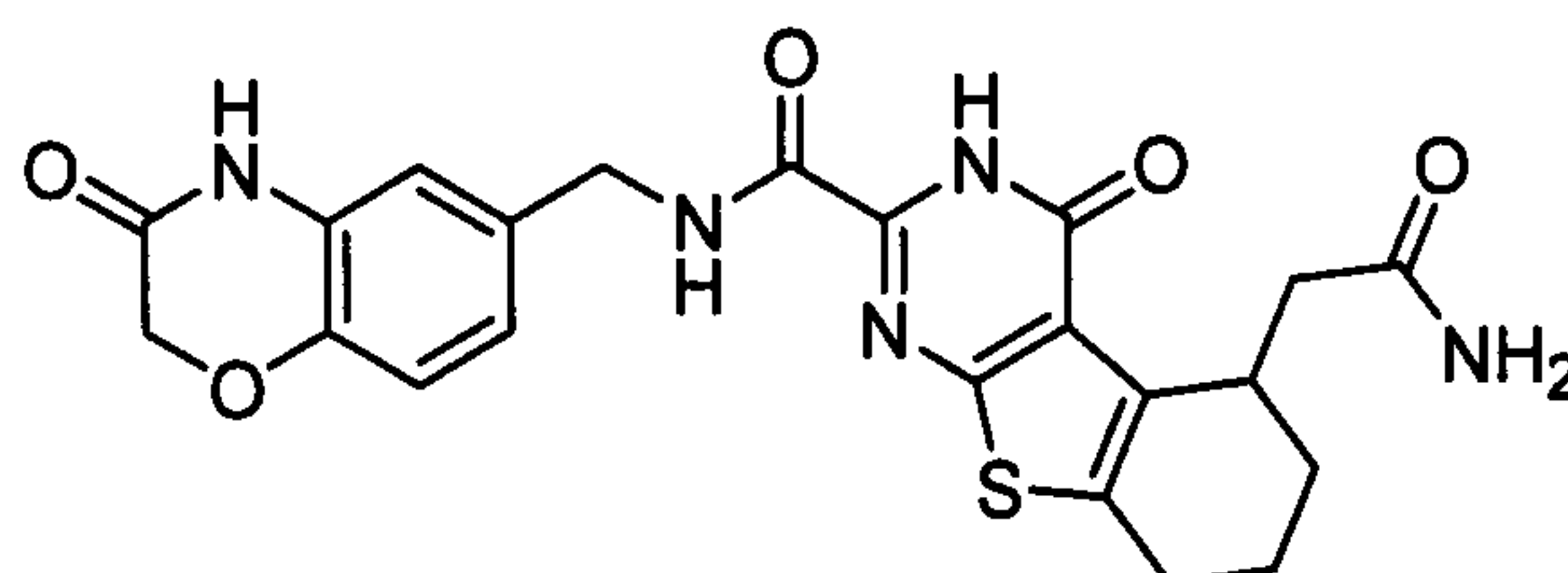
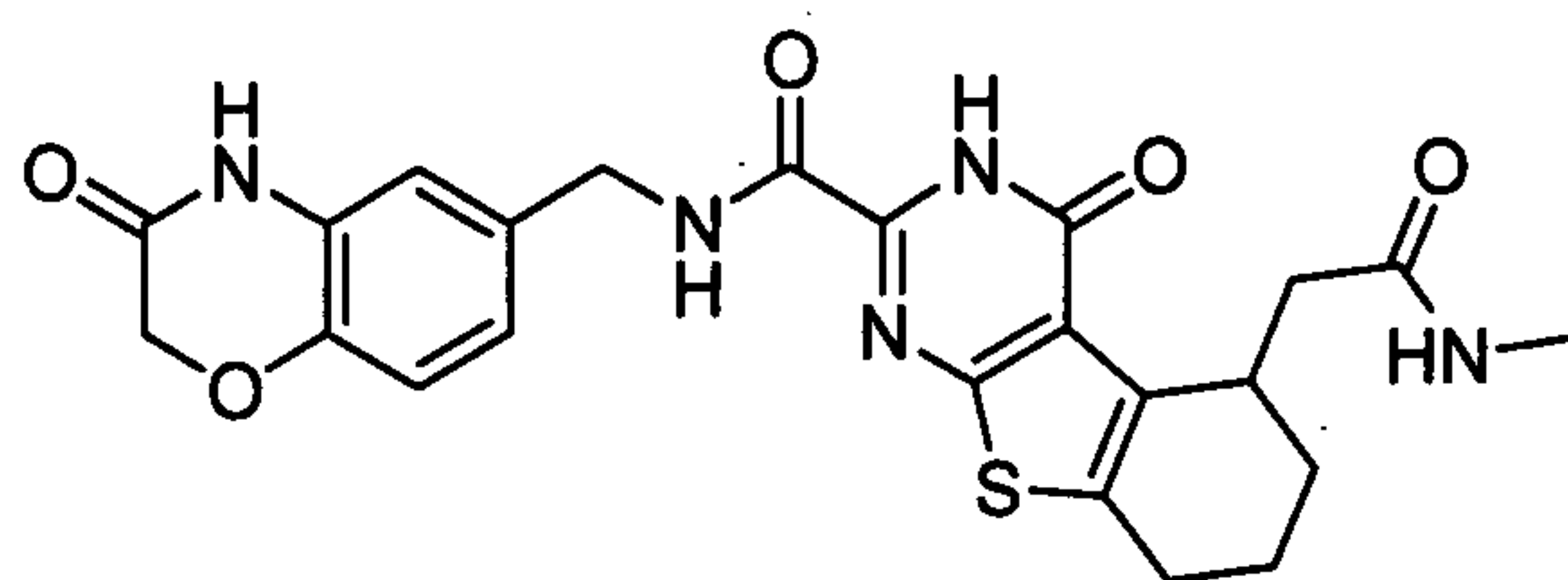




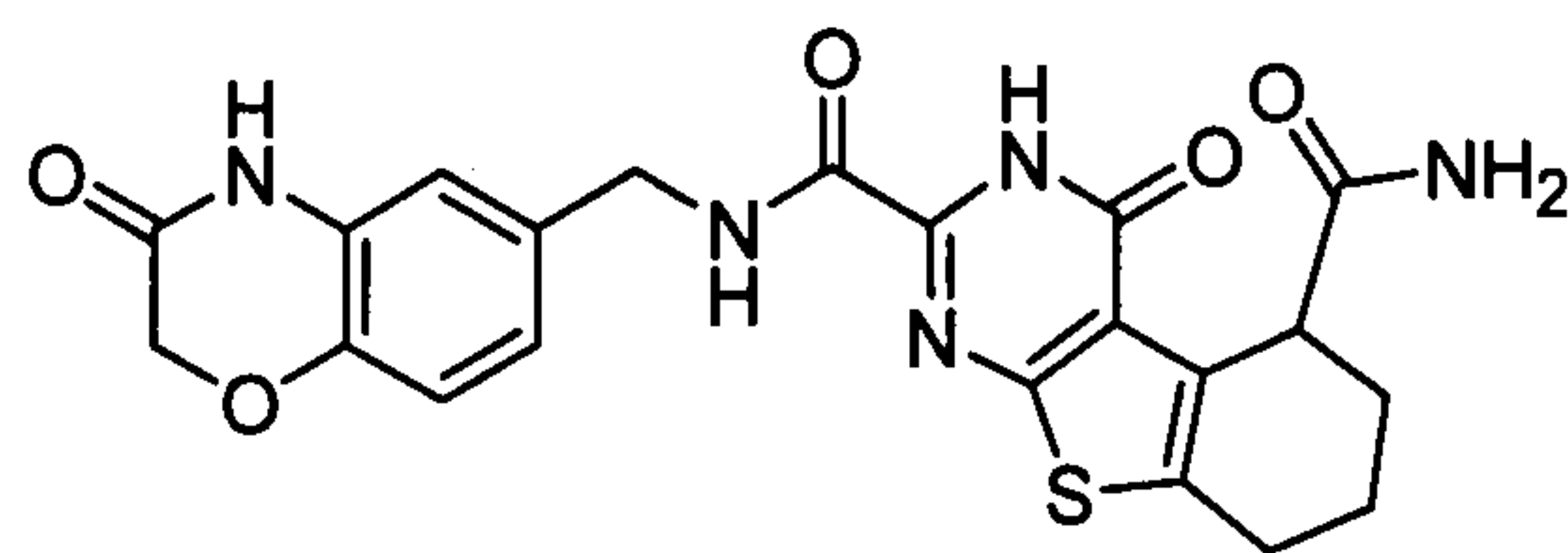
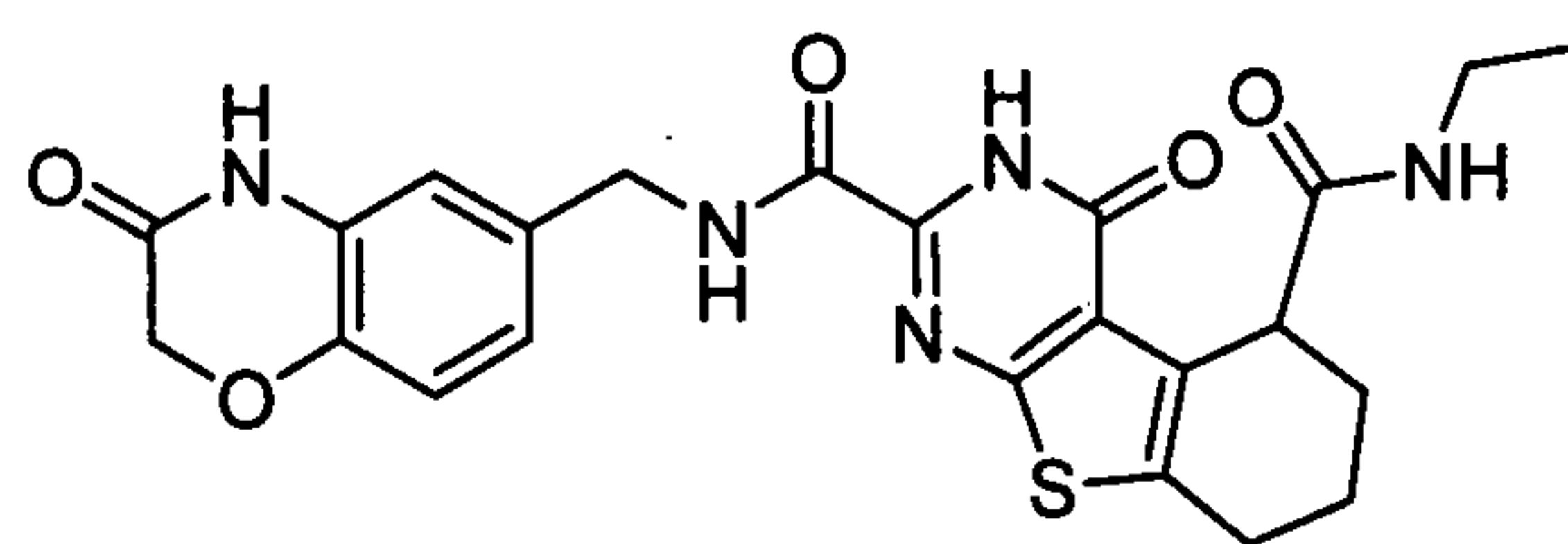
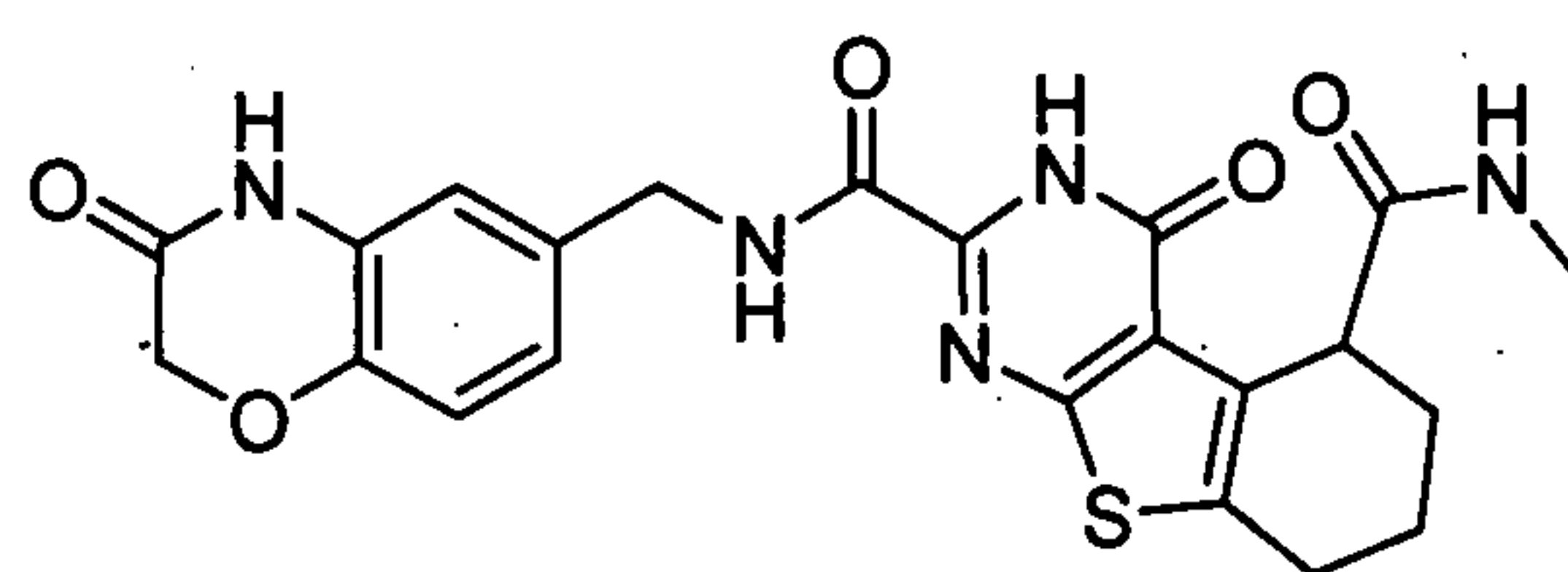


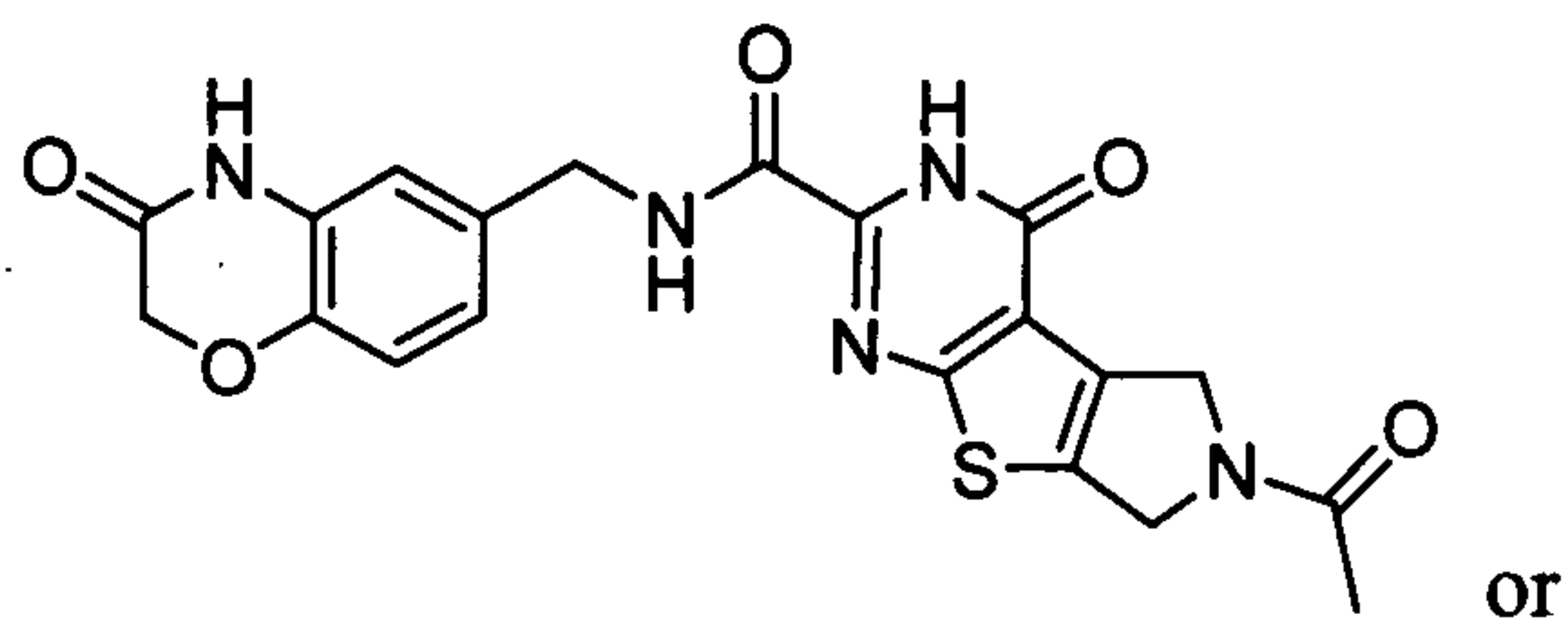
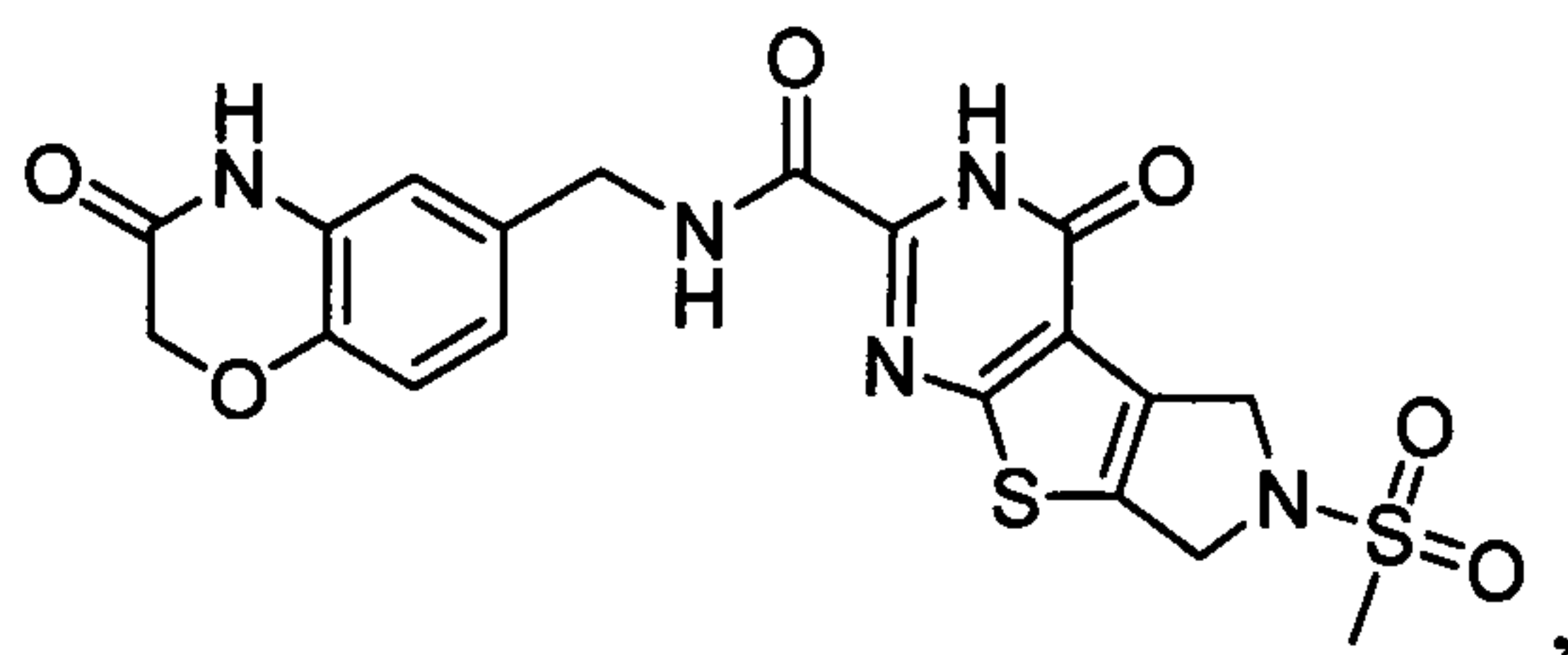
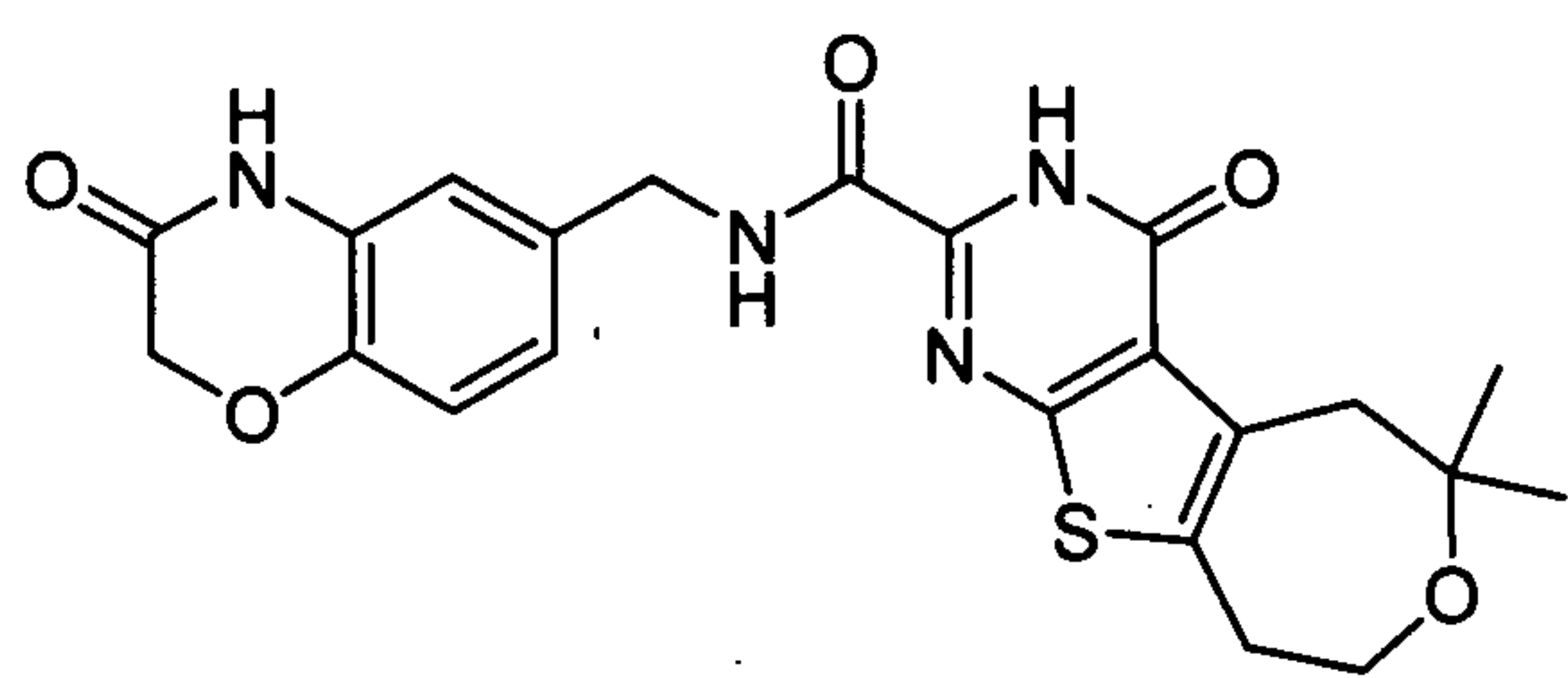
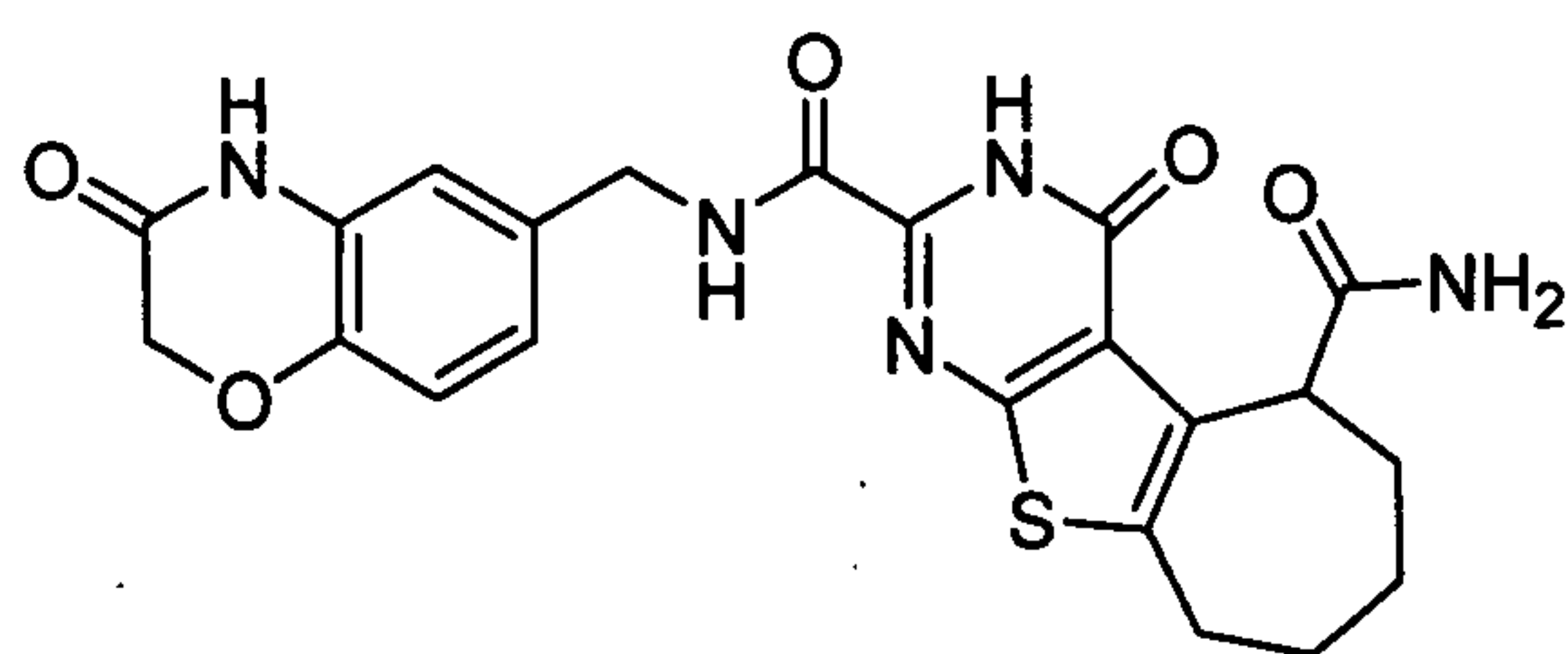
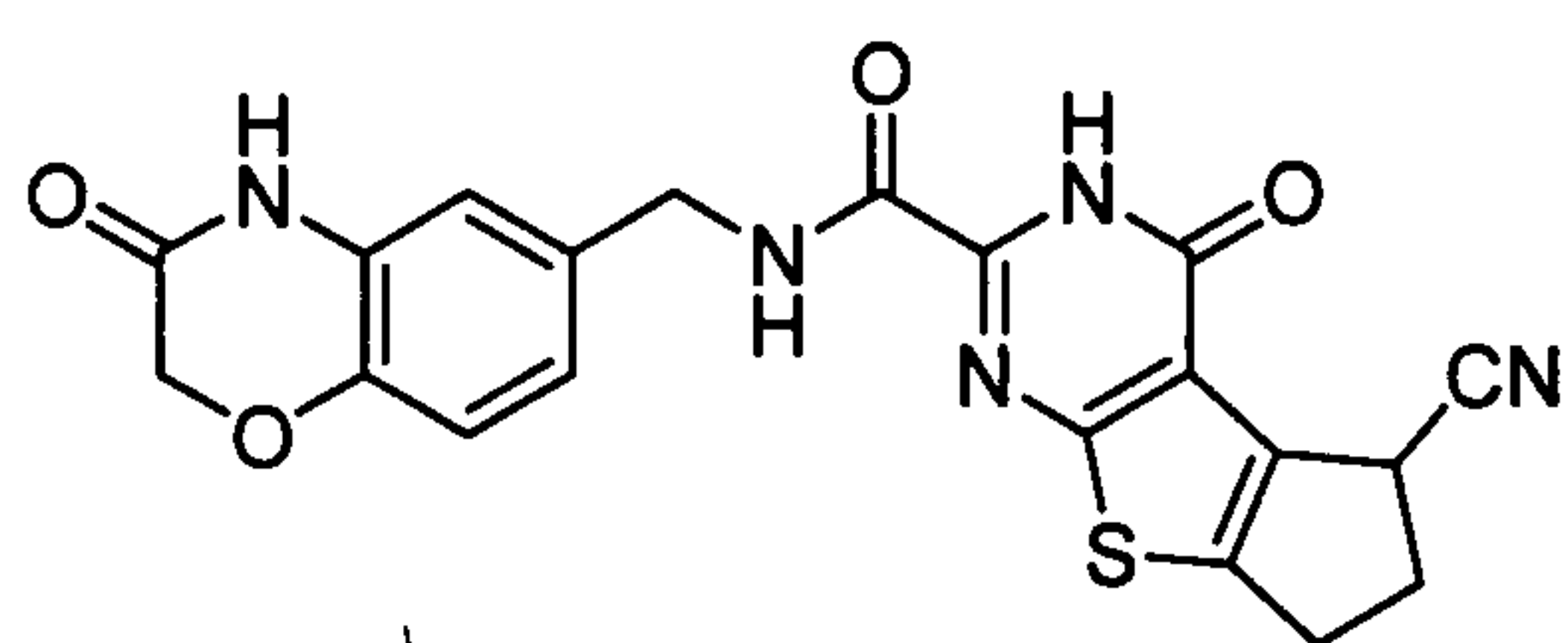
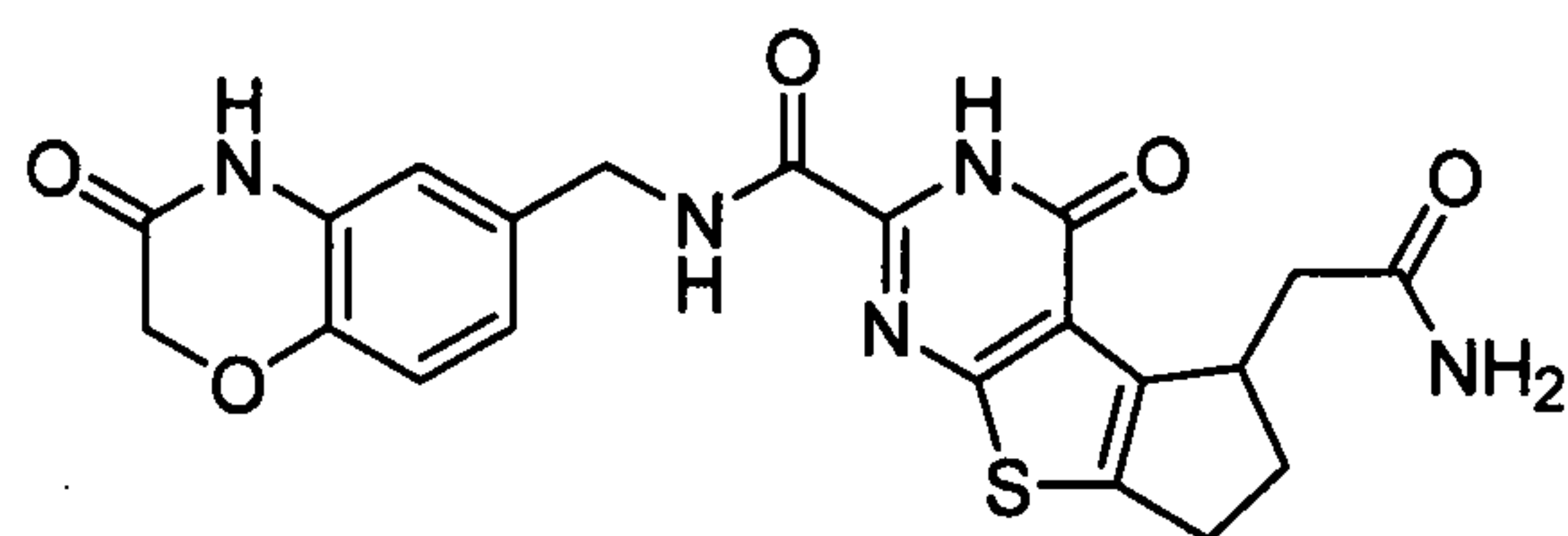
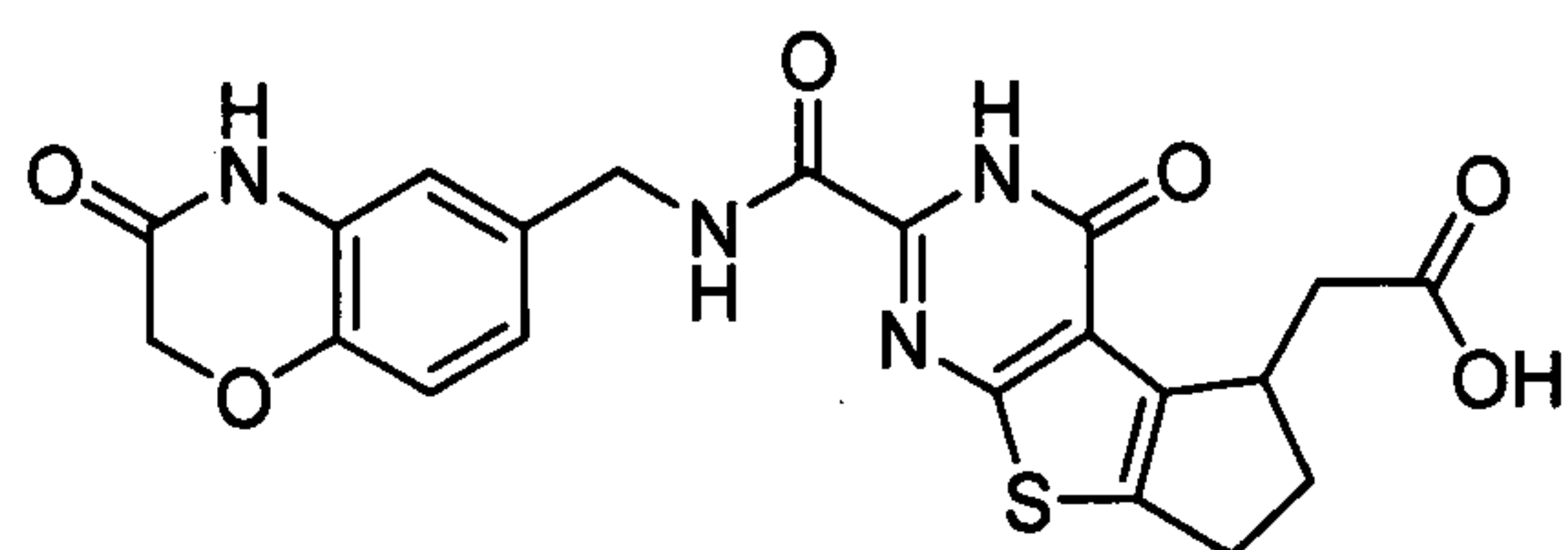


5

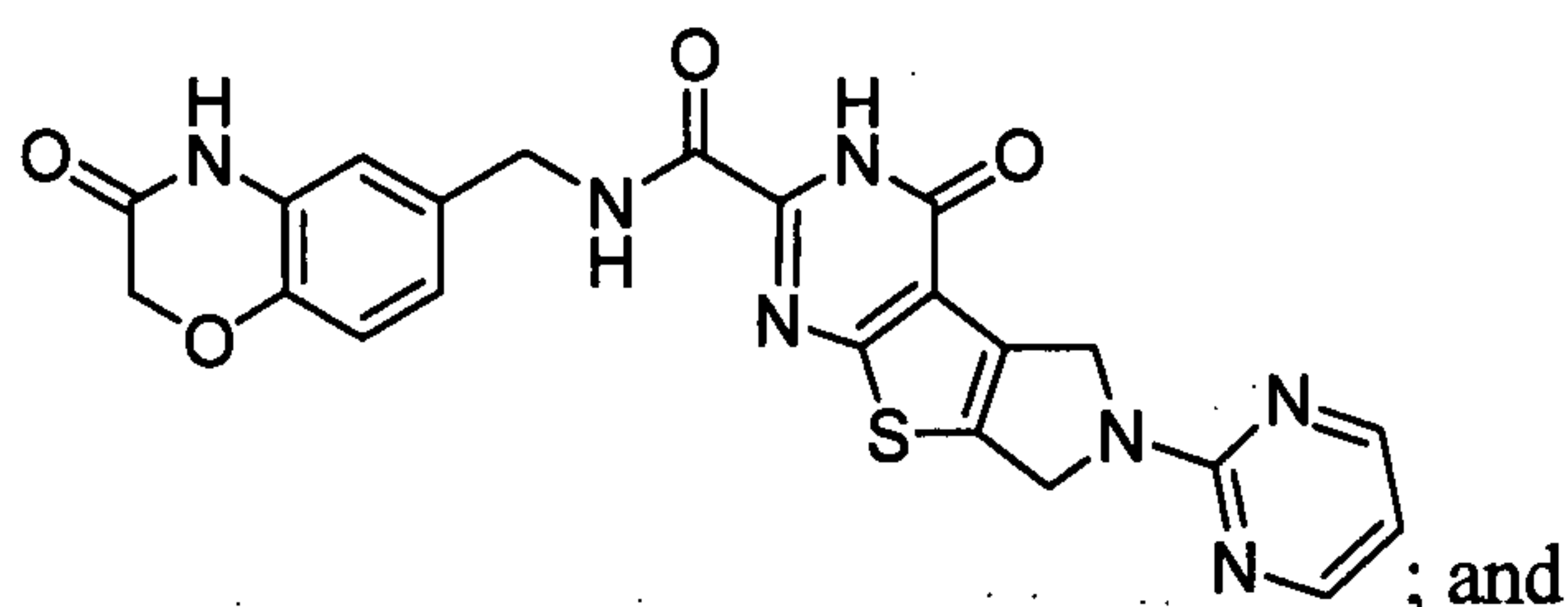


5





or



N-oxides, pharmaceutically acceptable salts, prodrugs, formulations, polymorphs, tautomers, racemic mixtures and stereoisomers thereof.

Another aspect of the invention relates to a pharmaceutical composition  
 5 comprising an effective amount of the compound according to any of the above or below embodiments.

Another aspect of the invention relates to a method of treating a metalloprotease mediated disease, comprising administering to a subject in need of such treatment an effective amount of a compound according to any of the  
 10 above or below embodiments.

In another embodiment, in conjunction with any above or below embodiments, the disease is selected from rheumatoid arthritis, osteoarthritis, inflammation, atherosclerosis and multiple sclerosis.

Another aspect of the invention relates to a pharmaceutical composition  
 15 comprising:

- A) an effective amount of a compound according to any of the above or below embodiments;
- B) a pharmaceutically acceptable carrier; and
- C) a drug, agent or therapeutic selected from: (a) a disease modifying  
 20 antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

Another aspect of the invention relates to a method of inhibiting a  
 25 metalloprotease enzyme, comprising administering a compound according to any of the above or below embodiments.

In another embodiment, in conjunction with any above or below embodiments, the metalloproteinase is selected from MMP-2, MMP-3, MMP-8, and MMP-13.

In another embodiment, in conjunction with any above or below  
5    embodiments, the disease is selected from the group consisting of: rheumatoid  
arthritis, osteoarthritis, abdominal aortic aneurysm, cancer (e.g. but not limited to  
melanoma, gastric carcinoma or non-small cell lung carcinoma), inflammation,  
atherosclerosis, chronic obstructive pulmonary disease, ocular diseases (e.g. but  
not limited to ocular inflammation, retinopathy of prematurity, macular  
10    degeneration with the wet type preferred and corneal neovascularization),  
neurologic diseases, psychiatric diseases, thrombosis, bacterial infection,  
Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the  
retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes,  
psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and  
15    fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimers disease,  
arterial plaque formation, oncology, periodontal, viral infection, stroke,  
atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical  
exposure or oxidative damage to tissues, wound healing, hemorrhoid, skin  
beautifying, pain, inflammatory pain, bone pain and joint pain, acne, acute  
20    alcoholic hepatitis, acute inflammation, acute pancreatitis, acute respiratory  
distress syndrome, adult respiratory disease, airflow obstruction, airway  
hyperresponsiveness, alcoholic liver disease, allograft rejections, angiogenesis,  
angiogenic ocular disease, arthritis, asthma, atopic dermatitis, bronchiectasis,  
bronchiolitis, bronchiolitis obliterans, burn therapy, cardiac and renal reperfusion  
25    injury, celiac disease, cerebral and cardiac ischemia, CNS tumors, CNS vasculitis,  
colds, contusions, cor pulmonae, cough, Crohn's disease, chronic bronchitis,  
chronic inflammation, chronic pancreatitis, chronic sinusitis, crystal induced  
arthritis, cystic fibrosis, delayed type hypersensitivity reaction, duodenal ulcers,  
dyspnea, early transplantation rejection, emphysema, encephalitis, endotoxic  
30    shock, esophagitis, gastric ulcers, gingivitis, glomerulonephritis, glossitis, gout,  
graft vs. host reaction, gram negative sepsis, granulocytic ehrlichiosis, hepatitis

viruses, herpes, herpes viruses, HIV, hypercapnea, hyperinflation, hyperoxia-induced inflammation, hypoxia, hypersensitivity, hypoxemia, inflammatory bowel disease, interstitial pneumonitis, ischemia reperfusion injury, kaposi's sarcoma associated virus, lupus, malaria, meningitis, multi-organ dysfunction, necrotizing  
5 enterocolitis, osteoporosis, chronic periodontitis, periodontitis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), pre-term labor, polymyositis, post surgical trauma, pruritis, psoriasis, psoriatic arthritis, pulmonary fibrosis, pulmonary hypertension, renal reperfusion injury, respiratory viruses, restinosis, right ventricular hypertrophy, sarcoidosis, septic shock, small airway  
10 disease, sprains, strains, subarachnoid hemorrhage, surgical lung volume reduction, thrombosis, toxic shock syndrome, transplant reperfusion injury, traumatic brain injury, ulcerative colitis, vasculitis, ventilation-perfusion mismatching, and wheeze.

Another aspect of the invention relates to the use of a compound according  
15 to any of the above or below embodiments for the manufacture of a medicament for treating an metalloprotease mediated disease.

In another embodiment, in conjunction with any of the above or below embodiments, the metalloprotease mediated disease is selected from the group consisting of MMP-2, MMP-3, MMP-8 and MMP-13 mediated diseases.

20 The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and  
25 is not meant in any way to limit the removal of individual elements or subgroups as needed.

The terms "alkyl" or "alk", as used herein alone or as part of another group, denote optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 10 carbons in the normal chain, most  
30 preferably lower alkyl groups. Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl,

heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkenyl, alkynyl, aryl (e.g., to form a benzyl group), cycloalkyl, cycloalkenyl, hydroxy or protected  
 5 hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH<sub>2</sub>--CO--), substituted carbamoyl ((R<sup>10</sup>)(R<sup>11</sup>)N--CO-- wherein R<sup>10</sup> or R<sup>11</sup> are as defined below, except that at least one of R<sup>10</sup> or R<sup>11</sup> is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

The terms "alkyl" or "alk", as used herein alone or as part of another  
 10 group, denote optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 10 carbons in the normal chain, most preferably lower alkyl groups. Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl,  
 15 dodecyl and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkenyl, alkynyl, aryl (e.g., to form a benzyl group), cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH<sub>2</sub>--CO--), substituted carbamoyl ((R<sup>10</sup>)(R<sup>11</sup>)N--CO-- wherein R<sup>10</sup> or  
 20 R<sup>11</sup> are as defined below, except that at least one of R<sup>10</sup> or R<sup>11</sup> is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

The terms "lower alk" or "lower alkyl" as used herein, denote such optionally substituted groups as described above for alkyl having 1 to 4 carbon atoms in the normal chain.

25 The term "alkoxy" denotes an alkyl group as described above bonded through an oxygen linkage (--O--).

The term "alkenyl", as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon double bond in the chain, and preferably  
 30 having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include ethenyl, propenyl, isobutenyl, butenyl, pentenyl, hexenyl, heptenyl,

octenyl, nonenyl, decenyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH<sub>2</sub>--CO--), substituted carbamoyl ((R<sup>10</sup>)(R<sup>11</sup>)N--CO-- wherein R<sup>10</sup> or R<sup>11</sup> are as defined below, except that at least one of R<sup>10</sup> or R<sup>11</sup> is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

The term "alkynyl", as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon triple bond in the chain, and preferably having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH<sub>2</sub>--CO--), substituted carbamoyl ((R<sup>10</sup>)(R<sup>11</sup>)N--CO-- wherein R<sup>10</sup> or R<sup>11</sup> are as defined below, except that at least one of R<sup>10</sup> or R<sup>11</sup> is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

The term "cycloalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated cyclic hydrocarbon ring systems, containing one ring with 3 to 9 carbons. Exemplary unsubstituted such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, and cyclododecyl. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The term "bicycloalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated cyclic bridged hydrocarbon ring systems, desirably containing 2 or 3 rings and 3 to 9 carbons per ring. Exemplary unsubstituted such groups include, but are not limited to, adamantyl, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane and cubane. Exemplary substituents

include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The term “spiroalkyl”, as used herein alone or as part of another group, denotes optionally substituted, saturated hydrocarbon ring systems, wherein two  
5 rings of 3 to 9 carbons per ring are bridged via one carbon atom. Exemplary unsubstituted such groups include, but are not limited to, spiro[3.5]nonane, spiro[4.5]decane or spiro[2.5]octane. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

10 The term “spiroheteroalkyl”, as used herein alone or as part of another group, denotes optionally substituted, saturated hydrocarbon ring systems, wherein two rings of 3 to 9 carbons per ring are bridged via one carbon atom and at least one carbon atom is replaced by a heteroatom independently selected from N, O and S. The nitrogen and sulfur heteroatoms may optionally be oxidized.  
15 Exemplary unsubstituted such groups include, but are not limited to, 1,3-diaza-spiro[4.5]decane-2,4-dione. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms “ar” or “aryl”, as used herein alone or as part of another group,  
20 denote optionally substituted, homocyclic aromatic groups, preferably containing 1 or 2 rings and 6 to 12 ring carbons. Exemplary unsubstituted such groups include, but are not limited to, phenyl, biphenyl, and naphthyl. Exemplary substituents include, but are not limited to, one or more nitro groups, alkyl groups as described above or groups described above as alkyl substituents.

25 The term “heterocycle” or “heterocyclic system” denotes a heterocyclyl, heterocyclenyl, or heteroaryl group as described herein, which contains carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S and including any bicyclic or tricyclic group in which any of the above-defined heterocyclic rings is fused to one or more heterocycle, aryl or cycloalkyl groups.  
30 The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or

carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 5 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazoliny, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H- 10 1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4- 15 oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidiny, oxindolyl, phenanthridiny, phenanthroliny, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiiny, phenoxazinyl, phthalazinyl, piperazinyl, piperidiny, pteridiny, piperidonyl, 4-piperidonyl, pteridiny, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, 20 pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, carboliny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 25 thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

Further examples of heterocycles include, but not are not limited to, “heterobicycloalkyl” groups such as 7-oxa-bicyclo[2.2.1]heptane, 7-aza- 30 bicyclo[2.2.1]heptane, and 1-aza-bicyclo[2.2.2]octane.

“Heterocyclenyl” denotes a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 atoms, desirably about 4 to about 8 atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more substituents as defined herein. The nitrogen or sulphur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

“Heterocyclenyl” as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960), the contents all of which are incorporated by reference herein. Exemplary monocyclic azaheterocyclenyl groups include, but are not limited to, 1,2,3,4-tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolyl, 2-pyrazolyl, and the like. Exemplary oxaheterocyclenyl groups include, but are not limited to, 3,4-dihydro-2*H*-pyran, dihydrofuranyl, and fluorodihydrofuranyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

“Heterocyclyl,” or “heterocycloalkyl,” denotes a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, desirably 4 to 8 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclyl

define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more substituents which may be the same or different, and are as defined herein. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Heterocyclyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary monocyclic heterocyclyl rings include, but are not limited to, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heteroaryl" denotes an aromatic monocyclic or multicyclic ring system of about 5 to about 10 atoms, in which one or more of the atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system include 5 to 6 ring atoms. The "heteroaryl" may also be substituted by one or more substituents which may be the same or different, and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. A nitrogen atom of a heteroaryl may be optionally oxidized to the corresponding N-oxide. Heteroaryl as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary heteroaryl and substituted heteroaryl groups include, but are not limited to, pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl,

furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalanyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindole, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 5 benzthiazolyl, dioxolyl, furanyl, imidazolyl, indolyl, indoliziny, isoxazolyl, isoquinolinyl, isothiazolyl, , oxadiazolyl, oxazinyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, tetrazinyl, tetrazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiatriazolyl, 10 thiazinyl, thiazolyl, thienyl, 5-thioxo-1,2,4-diazolyl, thiomorpholino, thiophenyl, thiopyranyl, triazolyl and triazolonyl.

The phrase "fused" means, that the group, mentioned before "fused" is connected via two adjacent atoms to the ring system mentioned after "fused" to form a bicyclic system. For example, "heterocycloalkyl fused aryl" includes, but is 15 not limited to, 2,3-dihydro-benzo[1,4]dioxine, 4*H*-benzo[1,4]oxazin-3-one, 3*H*-Benzooxazol-2-one and 3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one.

The term "amino" denotes the radical -NH<sub>2</sub> wherein one or both of the hydrogen atoms may be replaced by an optionally substituted hydrocarbon group. Exemplary amino groups include, but are not limited to, n-butylamino, tert- 20 butylamino, methylpropylamino and ethyldimethylamino.

The term "cycloalkylalkyl" denotes a cycloalkyl-alkyl group wherein a cycloalkyl as described above is bonded through an alkyl, as defined above. Cycloalkylalkyl groups may contain a lower alkyl moiety. Exemplary cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, 25 cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylpropyl, cyclopropylpropyl, cyclopentylpropyl, and cyclohexylpropyl.

The term "arylalkyl" denotes an aryl group as described above bonded through an alkyl, as defined above.

The term "heteroarylalkyl" denotes a heteroaryl group as described above 30 bonded through an alkyl, as defined above.

The term "heterocyclalkyl," or "heterocycloalkylalkyl," denotes a heterocycl group as described above bonded through an alkyl, as defined above.

The terms "halogen", "halo", or "hal", as used herein alone or as part of another group, denote chlorine, bromine, fluorine, and iodine.

5       The term "haloalkyl" denotes a halo group as described above bonded though an alkyl, as defined above. Fluoroalkyl is an exemplary group.

The term "aminoalkyl" denotes an amino group as defined above bonded through an alkyl, as defined above.

10       The phrase "bicyclic fused ring system wherein at least one ring is partially saturated" denotes an 8- to 13-membered fused bicyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-4 heteroatoms independently selected from N, O and S. Illustrative examples include, but are not limited to, indanyl, tetrahydronaphthyl, tetrahydroquinolyl and benzocycloheptyl.

15       The phrase "tricyclic fused ring system wherein at least one ring is partially saturated" denotes a 9- to 18-membered fused tricyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-7 heteroatoms independently selected from N, O and S. Illustrative examples include, but are not limited to, fluorene, 10,11-dihydro-5H-  
20       dibenzo[a,d]cycloheptene and 2,2a,7,7a-tetrahydro-1H-cyclobuta[a]indene.

25       The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Examples therefore may be, but are not limited to, sodium, potassium, choline, lysine, arginine or N-methyl-glucamine salts, and the like.

30       The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as,

but not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as, but not limited to, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, 5 salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting 10 the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Organic solvents include, but are not limited to, nonaqueous media like ethers, ethyl acetate, ethanol, isopropanol, or acetonitrile. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing 15 Company, Easton, PA, 1990, p. 1445, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" denotes those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and 20 animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" denotes media generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors 25 well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers 30 include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different

ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Non-limiting examples of a pharmaceutically acceptable carrier are hyaluronic acid and salts thereof, and microspheres (including, but not limited to poly(D,L)-lactide-co-glycolic acid copolymer (PLGA), poly(L-lactic acid) (PLA), poly(caprolactone (PCL) and bovine serum albumin (BSA)). Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, the contents of which are incorporated herein by reference.

Pharmaceutically acceptable carriers particularly suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

The compositions of the invention may also be formulated as suspensions including a compound of the present invention in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a

suspension. In yet another embodiment, pharmaceutical compositions of the invention may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of suitable excipients.

Carriers suitable for use in connection with suspensions include

5 suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene

10 oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid,

15 methyl and/or *n*-propyl *p*-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Cyclodextrins may be added as aqueous solubility enhancers. Preferred cyclodextrins include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and

20 maltotriosyl derivatives of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin. The amount of solubility enhancer employed will depend on the amount of the compound of the present invention in the composition.

The term "formulation" denotes a product comprising the active ingredient(s) and the inert ingredient(s) that make up the carrier, as well as any

25 product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of

30 the present invention and a pharmaceutical carrier.

The term "N-oxide" denotes compounds that can be obtained in a known manner by reacting a compound of the present invention including a nitrogen atom (such as in a pyridyl group) with hydrogen peroxide or a peracid, such as 3-chloroperoxy-benzoic acid, in an inert solvent, such as dichloromethane, at a  
5 temperature between about -10-80°C, desirably about 0°C.

The term "polymorph" denotes a form of a chemical compound in a particular crystalline arrangement. Certain polymorphs may exhibit enhanced thermodynamic stability and may be more suitable than other polymorphic forms for inclusion in pharmaceutical formulations.

10 The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding enantiomers and stereoisomers,  
15 that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

The term "racemic mixture" denotes a mixture that is about 50% of one enantiomer and about 50% of the corresponding enantiomer relative to all chiral  
20 centers in the molecule. Thus, the invention encompasses all enantiomerically-pure, enantiomerically-enriched, and racemic mixtures of compounds of Formulas (I) and (II).

Enantiomeric and stereoisomeric mixtures of compounds of the invention can be resolved into their component enantiomers or stereoisomers by well-known  
25 methods. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts. See, e.g., Jacques, J., et al., Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., Tetrahedron 33:2725 (1977); Eliel, E. L., Stereochemistry of  
30 Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S. H., Tables of Resolving Agents and Optical Resolutions p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame

Press, Notre Dame, Ind., 1972); Stereochemistry of Organic Compounds, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Manda (1994 John Wiley & Sons, Inc.), and Stereoselective Synthesis A Practical Approach, Mihaly Nogradi (1995 VCH Publishers, Inc., NY, N.Y.). Enantiomers and stereoisomers can also be obtained  
5 from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

“Substituted” is intended to indicate that one or more hydrogens on the atom indicated in the expression using “substituted” is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is  
10 not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

Unless moieties of a compound of the present invention are defined as being unsubstituted, the moieties of the compound may be substituted. In addition to any substituents provided above, the moieties of the compounds of the present  
15 invention may be optionally substituted with one or more groups independently selected from:

C<sub>1</sub>-C<sub>4</sub> alkyl;  
C<sub>2</sub>-C<sub>4</sub> alkenyl;  
C<sub>2</sub>-C<sub>4</sub> alkynyl;  
20 CF<sub>3</sub>;  
halo;  
OH;  
O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
OCH<sub>2</sub>F;  
25 OCHF<sub>2</sub>;  
OCF<sub>3</sub>;  
ONO<sub>2</sub>;  
OC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
OC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
30 OC(O)NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
OC(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

- OC(S)NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 OC(S)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 SH;  
 S-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 5 S(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 SC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 SC(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 NH<sub>2</sub>;  
 10 N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(H)C(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)C(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)C(O)-CF<sub>3</sub>;  
 15 N(CH<sub>3</sub>)C(O)-CF<sub>3</sub>;  
 N(H)C(S)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)C(S)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)C(O)NH<sub>2</sub>;  
 20 N(H)C(O)NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)C(O)NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(CH<sub>3</sub>)C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(H)S(O)<sub>2</sub>NH<sub>2</sub>;  
 25 N(H)S(O)<sub>2</sub>NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)S(O)<sub>2</sub>NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(CH<sub>3</sub>)S(O)<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(H)C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 30 N(CH<sub>3</sub>)C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(H)S(O)<sub>2</sub>O-(C<sub>1</sub>-C<sub>4</sub> alkyl);

- N(CH<sub>3</sub>)S(O)<sub>2</sub>O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)C(S)NH-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 N(CH<sub>3</sub>)C(S)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 N(CH<sub>3</sub>)C(S)O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 5 N(H)C(S)NH<sub>2</sub>;  
 NO<sub>2</sub>;  
 CO<sub>2</sub>H;  
 CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(O)N(H)OH;  
 10 C(O)N(CH<sub>3</sub>)OH;  
 C(O)N(CH<sub>3</sub>)OH;  
 C(O)N(CH<sub>3</sub>)O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(O)N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 15 C(S)N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(S)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 C(NH)N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(NH)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 C(NCH<sub>3</sub>)N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 20 C(NCH<sub>3</sub>)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;  
 C(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(NH)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(NCH<sub>3</sub>)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 C(NO<sub>2</sub>)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 25 C(NOCH<sub>3</sub>)-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 CN;  
 CHO;  
 CH<sub>2</sub>OH;  
 CH<sub>2</sub>O-(C<sub>1</sub>-C<sub>4</sub> alkyl);  
 30 CH<sub>2</sub>NH<sub>2</sub>;  
 CH<sub>2</sub>N(H)-(C<sub>1</sub>-C<sub>4</sub> alkyl);

CH<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

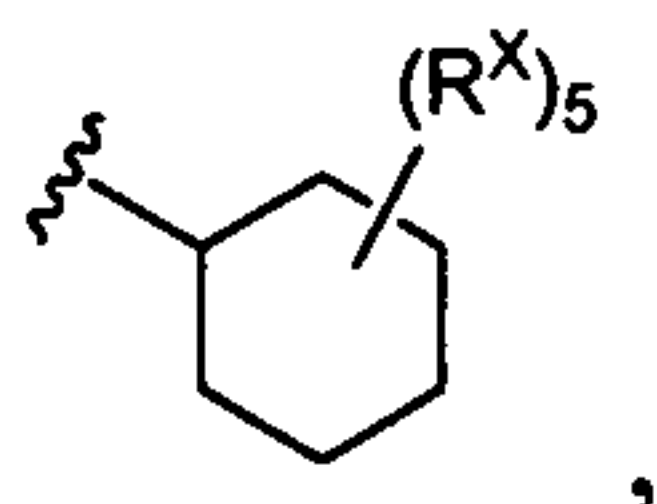
aryl;

heteroaryl;

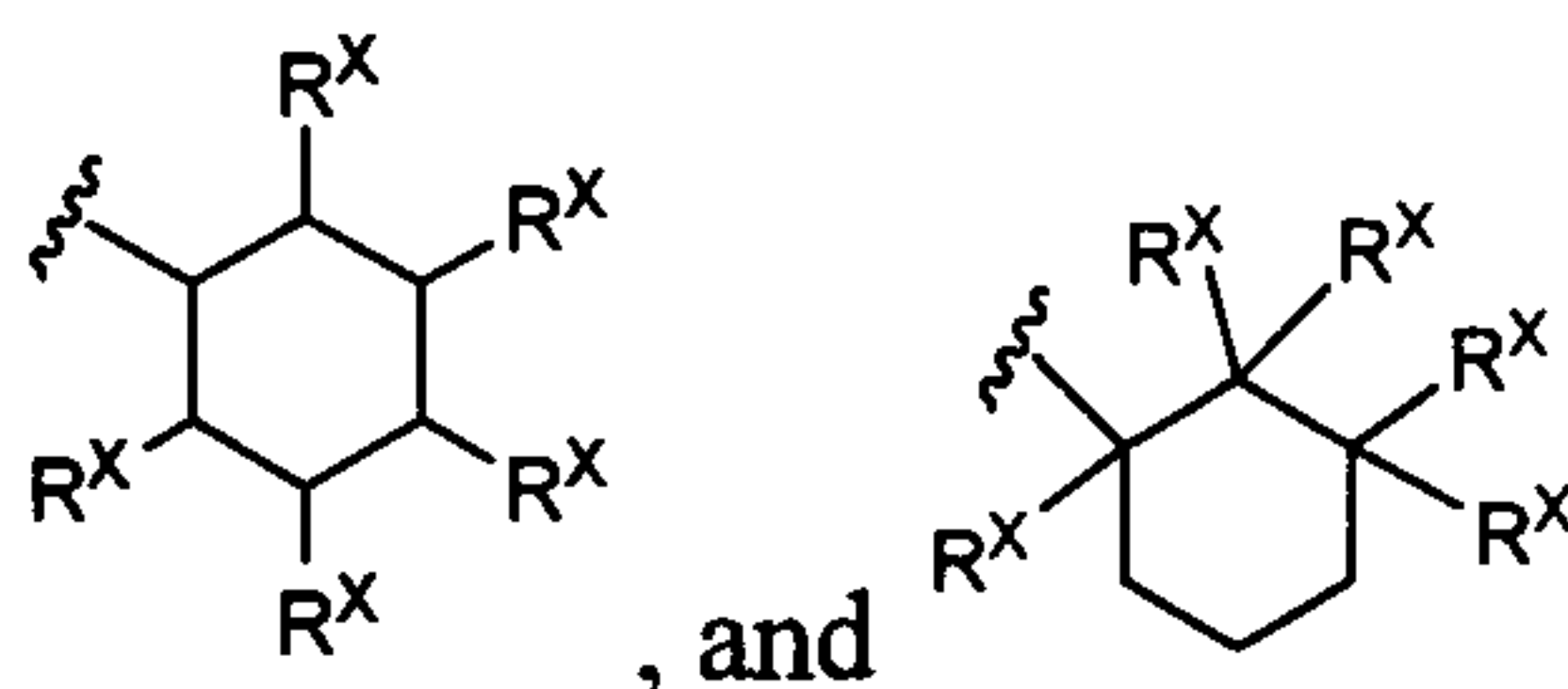
cycloalkyl; and

5 heterocyclyl.

In some cases, a ring substituent may be shown as being connected to the ring by a bond extending from the center of the ring. The number of such substituents present on a ring is indicated in subscript by a number. Moreover, the substituent may be present on any available ring atom, the available ring atom  
10 being any ring atom which bears a hydrogen which the ring substituent may replace. For illustrative purposes, if variable R<sup>X</sup> were defined as being:



this would indicate a cyclohexyl ring bearing five R<sup>X</sup> substituents. The R<sup>X</sup> substituents may be bonded to any available ring atom. For example, among the  
15 configurations encompassed by this are configurations such as:



These configurations are illustrative and are not meant to limit the scope of the invention in any way.

### **BIOLOGICAL ACTIVITY**

The inhibiting activity towards different metalloproteases of the heterocyclic metalloprotease inhibiting compounds of the present invention may be measured using any suitable assay known in the art. A standard *in vitro* assay for measuring the metalloprotease inhibiting activity is described in Examples 1700 to 1706. The heterocyclic metalloprotease inhibiting compounds show activity towards MMP-2, MMP-3, MMP-8, MMP-12, MMP-13, ADAMTS-4 and/or ADAMTS-5.

The heterocyclic metalloprotease inhibiting compounds of the invention have an MMP-13 inhibition activity (IC<sub>50</sub> MMP-13) ranging from below 0.2 nM to about 20  $\mu$ M, and typically, from about 0.2 nM to about 1  $\mu$ M. Heterocyclic metalloprotease inhibiting compounds of the invention desirably have an MMP inhibition activity ranging from about 0.2 nM to about 20 nM. Table 1 lists typical examples of heterocyclic metalloprotease inhibiting compounds of the invention that have an MMP-13 activity lower than 100 nM (Group A) and from 100 nM to 20  $\mu$ M (Group B).

**TABLE 1**

**Summary of MMP-13 Activity for Compounds**

| <b>Group</b> | <b>Ex. #</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A</b>     | 1, 2/25, 2/29, 2/33, 2/52, 2/67, 2/89, 2/90, 2/94, 2/95, 2/103, 2/104, 2/107, 2/108, 2/113, 2/114, 2/117, 2/118, 2/119, 2/120, 2/121, 2/122, 2/125, 2/126, 2/129, 2/131, 2/132, 2/145, 2/152, 2/153, 2/166, 2/167, 2/169, 2/170, 2/171, 2/173, 2/174, 2/175, 2/176, 2/188, 2/208, 2/209, 2/210, 2/211, 2/219, 2/224, 2/231, 2/240, 2/245, 2/246, 2/251, 2/255, 2/267, 2/290, 2/309, 2/313, 2/316, 2/332, 2/354, 2/359, 2/367, 3/382, 2/413, 2/417, 2/526, 2/528, 3, 4/14, 4/15, 15, 15/2, 15/4, 15/5, 19, 22, 22/1, 22/2, 26, 28, 41, 42/2, 43 |
| <b>B</b>     | 2/24, 2/34, 2/130, 2/143, 2/144, 2/146, 2/291, 2/292, 2/294, 2/302, 2/305, 2/307, 2/319, 2/323, 2/327, 2/328, 2/333, 2/344, 2/352, 2/355, 2/368, 2/383, 2/384, 2/428, 2/433, 2/530, 2/538, 39/7, 39/20                                                                                                                                                                                                                                                                                                                                         |

Some heterocyclic metalloprotease inhibiting compounds of the invention have an MMP-8 inhibition activity ( $IC_{50}$  MMP-8) ranging from below 5 nM to about 20  $\mu$ M, and typically, from about 10 nM to about 2  $\mu$ M. Heterocyclic metalloprotease inhibiting compounds of the invention desirably have an MMP inhibition activity ranging below 100 nM. Table 2 lists typical examples of heterocyclic metalloprotease inhibiting compounds of the invention that have an MMP-8 activity lower than 250 nM (Group A) and from 250 nM to 20  $\mu$ M (Group B).

**TABLE 2****Summary of MMP-8 Activity for Compounds**

| <b>Group</b> | <b>Ex. #</b>                                                                                                                                                                                                                                                                                                                                       |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A</b>     | 1, 2/25, 2/33, 2/52, 2/94, 2/95, 2/103, 2/104, 2/107, 2/113, 2/114, 2/117, 2/118, 2/121, 2/122, 2/125, 2/126, 2/131, 2/132, 2/152, 2/153, 2/166, 2/167, 2/169, 2/170, 2/171, 2/174, 2/175, 2/176, 2/188, 2/209, 2/211, 2/218, 2/223, 2/224, 2/230, 2/240, 2/251, 2/255, 2/267, 2/269, 2/313, 2/413, 4/14, 4/15, 15, 15/2, 19, 22/1, 26, 42/2, 43/1 |
| <b>B</b>     | 2/129, 2/130, 2/173, 2/290, 2/292, 2/316, 2/382, 2/383, 2/384, 2/387, 2/417, 2/428, 2/433, 2/528, 2/529, 2/538, 3, 15/3, 22, 22/2, 39/7, 39/20, 41, 42, 42/1                                                                                                                                                                                       |

Some heterocyclic metalloprotease inhibiting compounds of the invention have an MMP-3 inhibition activity ( $IC_{50}$  MMP-3) ranging from below 10 nM to about 20  $\mu$ M, and typically, from about 50 nM to about 2  $\mu$ M. Heterocyclic metalloprotease inhibiting compounds of the invention desirably have an MMP inhibition activity ranging below 100 nM. Table 3 lists typical examples of heterocyclic metalloprotease inhibiting compounds of the invention that have an MMP-3 activity lower than 250 nM (Group A) and from 250 nM to 20  $\mu$ M (Group B).

**TABLE 3****Summary of MMP-3 Activity for Compounds**

| Group | Ex. #                                                                                                                                                                |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A     | 2/103, 2/104, 28, 42/2, 43                                                                                                                                           |
| B     | 2/95, 2/107, 2/108, 2/132, 2/171, 2/188, 2/208, 2/209, 2/210, 2/211, 2/212, 2/231, 2/232, 2/236, 2/240, 2/245, 3, 4/15, 15, 15/2, 19, 22, 22/1, 22/2, 26, 39/7, 42/1 |

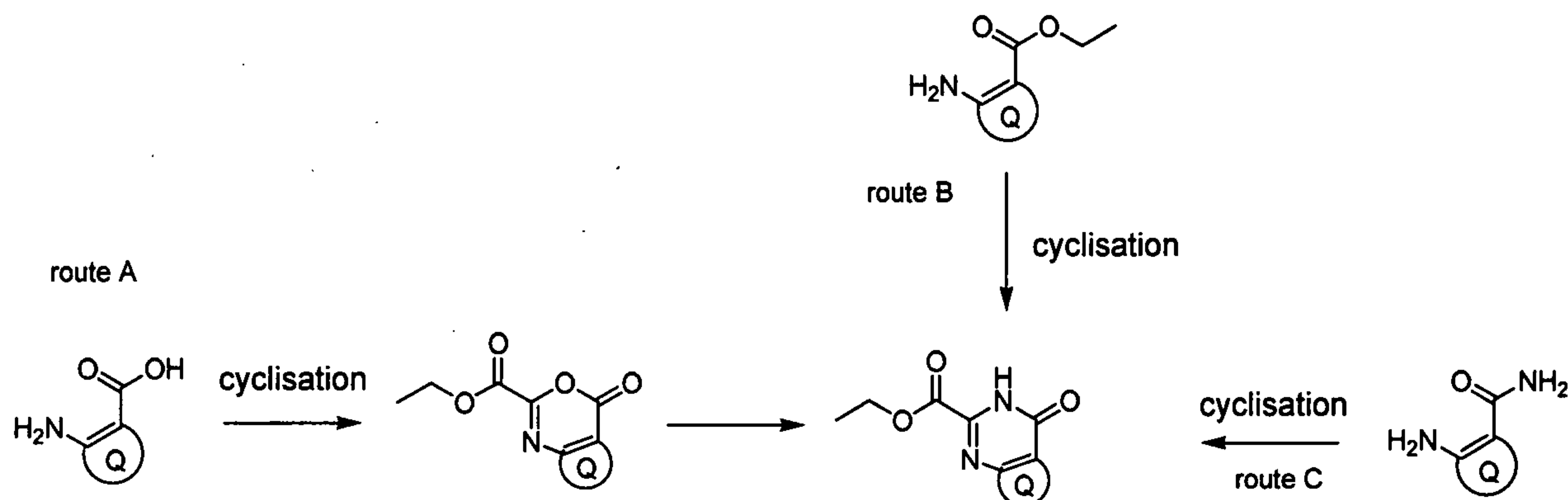
- 5           The synthesis of metalloprotease inhibiting compounds of the invention and their biological activity assay are described in the following examples which are not intended to be limiting in any way.

**Schemes**

- 10          Provided below are schemes according to which compounds of the present invention may be prepared.

In some embodiments the compounds of Formula (I) and (II) are synthesized by the general methods shown in Scheme 1 to Scheme 3.

15

**Scheme 1**

route A

An carbonic acid and amino substituted compound (e.g. 4-amino-nicotinic acid) is condensed (e.g. EtOH/reflux) with chloro-oxo-acetic acid ethyl ester as previously described e.g. in WO2005/105760 in pyridine to give an oxazine ethyl ester (Scheme 1). This intermediate is then converted into the corresponding pyrimidine derivative using a suitable reagent (e.g. NH<sub>4</sub>OAc, HOAc, EtOH/80°C). For example, when ring Q is a pyridine ring, the compound can be obtained according this route A.

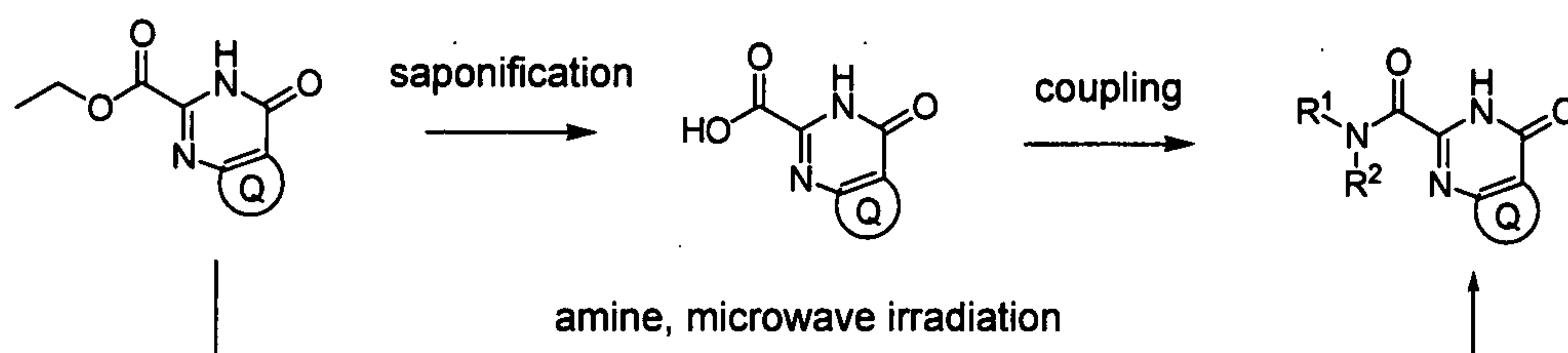
route B

An ester and amino substituted compound (e.g. 2-amino-benzoic acid ethyl ester) is condensed (e.g. 4N HCl, dioxane/50° C) with ethyl cyanoformate as previously described e.g. in WO2005/105760, to give a 1,3-pyrimidine-4-one ethyl ester (Scheme 1).

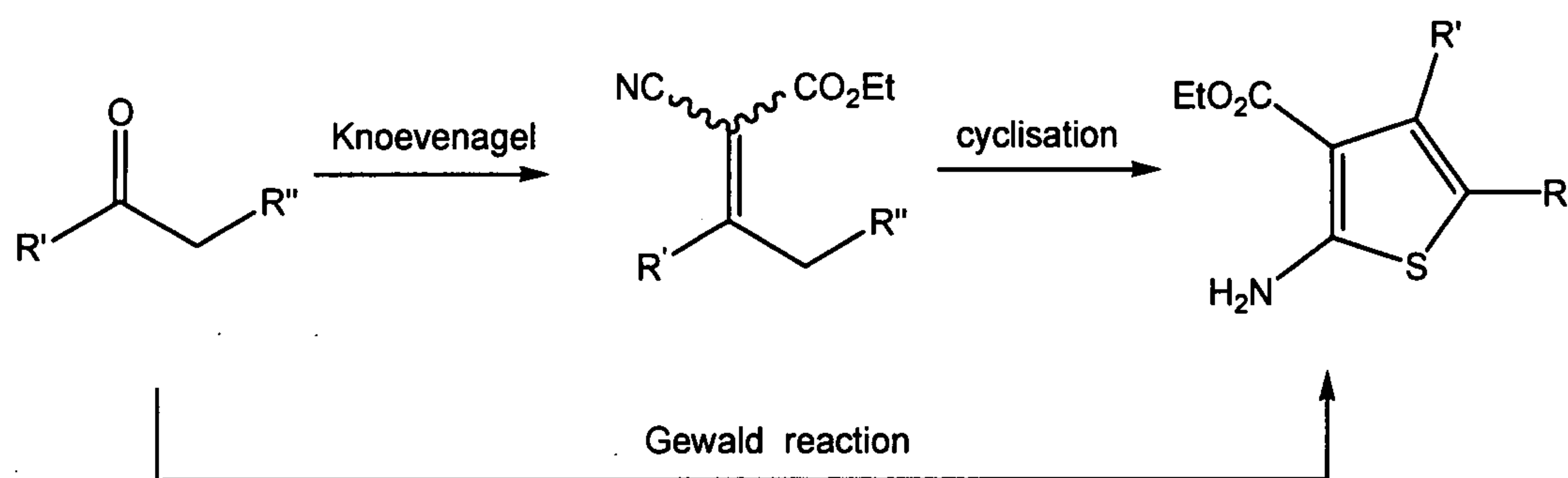
route C

An carboxamide and amino substituted compound (e.g. 2-amino-benzamide) is condensed with an suitable reagent ( e.g oxalic acid diethyl ester or acetic acid anhydride as describend in DD272079A1 or chloro-oxo-acetic acid ethyl ester as described in *J. Med. Chem.* **1979**, 22(5), 505-510) to give a 1,3-pyrimidine-4-one ethyl ester (Scheme 1).

20

Scheme 2

Saponification (e.g. aqueous LiOH) of the 1,3-pyrimidine-4-one derivative of Scheme 1 above gives the corresponding bicyclic carboxylic acid (Scheme 2). Activated acid coupling (e.g. EDCI/HOAt) with  $R^1R^2NH$  (e.g. 6-aminomethyl-4*H*-benzo[1,4]oxazin-3-one) in a suitable solvent gives the desired amide. The  
 5 saponification/coupling step can be combined by stirring the ester with the free amine at elevated temperature (e.g. 200°C, 15 min) under microwave irradiation.

**Scheme 3**

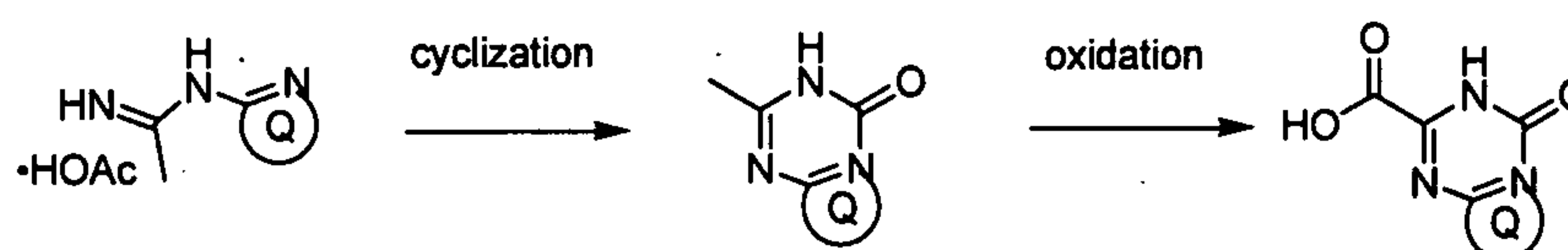
10

A substituted ketone (e.g. tetrahydrothiophen-3-one) is condensed (e.g. toluene/reflux with Dean-Stark apparatus) with ethyl cyanoacetate, acetic acid and ammonium acetate to afford the desired ethyl ester-cyano substituted double bond. (Scheme 3). This intermediate is then converted into the corresponding thiophene  
 15 derivative using suitable reagents (e.g. sulphur,  $Et_2NH$ ,  $EtOH/50^\circ C$ ) as previously described e.g. in *J. prakt. Chem.* **1973**, 315, 39-43 or *Monatsh. Chem.* **2001**, 132, 279-293.

The Knoevenagel/cyclisation step can be combined by stirring the ketone  
 20 with ethyl cyanoacetate, sulphur and a base (e.g.  $Et_3N$ ) in a suitable solvent (e.g.  $EtOH/50^\circ C$ ), following the Gewald type reaction as described e.g. in *J. prakt. Chem.* **1973**, 315, 39-43 or *Bioorg. Med. Chem.* **2002**, 10, 3113-3122.

In compounds, where the one L<sub>b</sub> in formula (I) is a nitrogen atom, the following procedure can be applied (Scheme 4).

**Scheme 4**



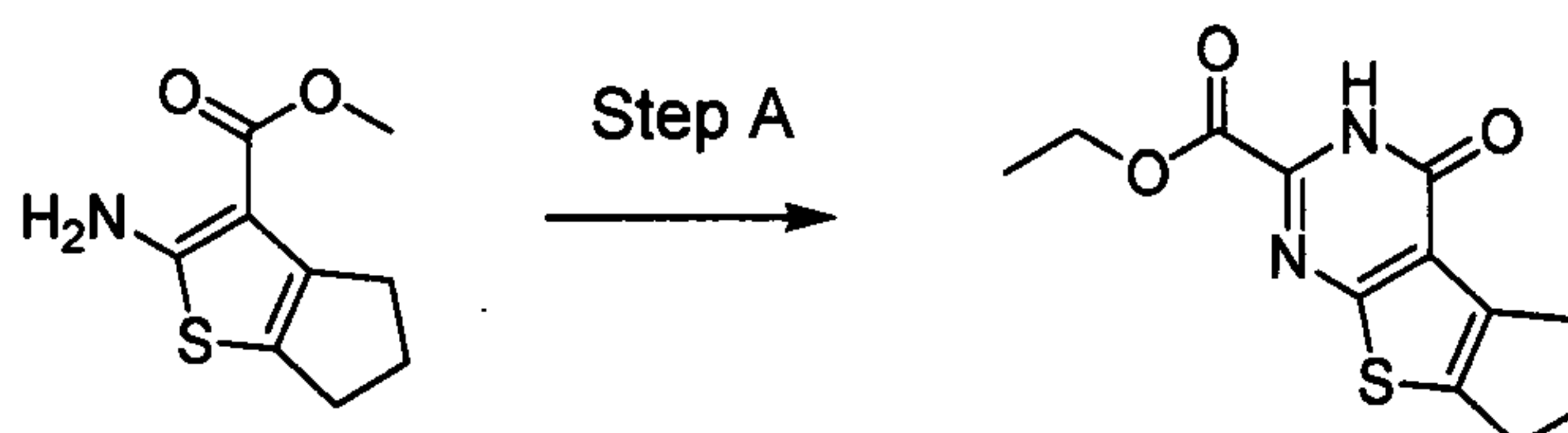
- 5 For example, N-(pyrazol-3-yl) acetamide acetate can be cyclized with carbonic acid diethyl ester to 2-methylpyrazolo[1,5a]-s-triazine-4-one (*J. Heterocycl. Chem.* **1985**, 22, 601-634) and further oxidized to the corresponding acid (e.g. by SeO<sub>2</sub> and then oxone).

10 In ring Q of the product in Scheme 1 to Scheme 4, further functional group manipulation can be applied (e.g. J. March, *Advanced Organic Chemistry*, Wiley&Sons), e.g. palladium catalyzed halogen-cyanide exchange or nucleophilic substitution.

## **EXAMPLES AND METHODS**

- 15 All reagents and solvents were obtained from commercial sources and used without further purification. Proton spectra (<sup>1</sup>H-NMR) were recorded on a 400 MHz and a 250 MHz NMR spectrometer in deuterated solvents. Purification by column chromatography was performed using silica gel, grade 60, 0.06-0.2 mm (chromatography) or silica gel, grade 60, 0.04-0.063 mm
- 20 (flash chromatography) and suitable organic solvents as indicated in specific examples. Preparative thin layer chromatography was carried out on silica gel plates with UV detection.

Preparative Examples are directed to intermediate compounds useful in preparing the compounds of the present invention.

**Preparative Example 4****Step A**

- 5            2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylic acid methyl ester (1 g) was dissolved in a 4M solution of HCl in 1,4-dioxane (20 mL) and cyanoacetic acid ethyl ester (0.6 mL) was added. The mixture was stirred at 40°C overnight, concentrated and purified by extraction with ethyl acetate from an aqueous solution to afford the title compound (1.3g, 99%).  $[MH]^+ = 265$ .

10

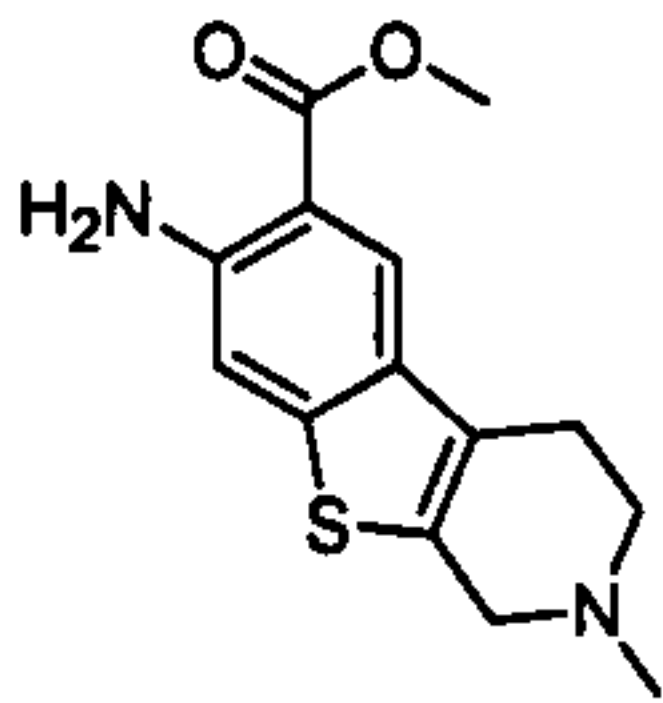
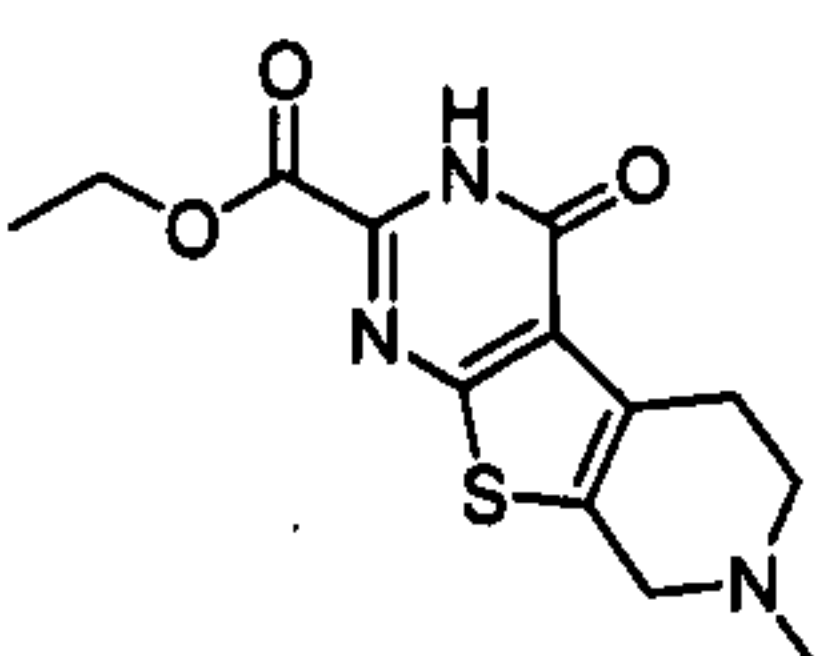
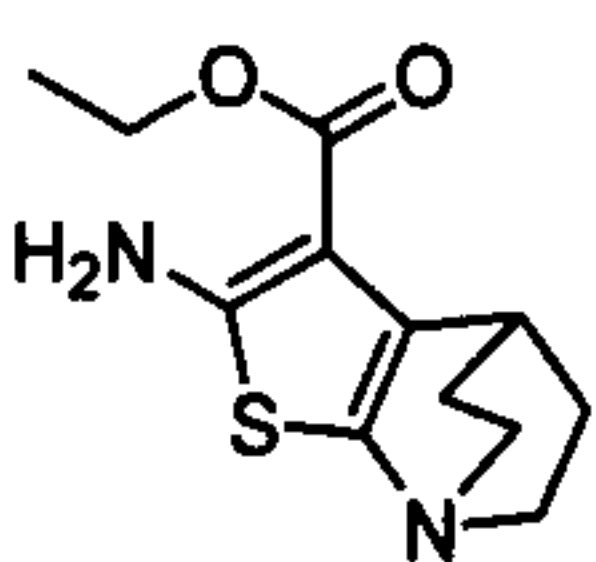
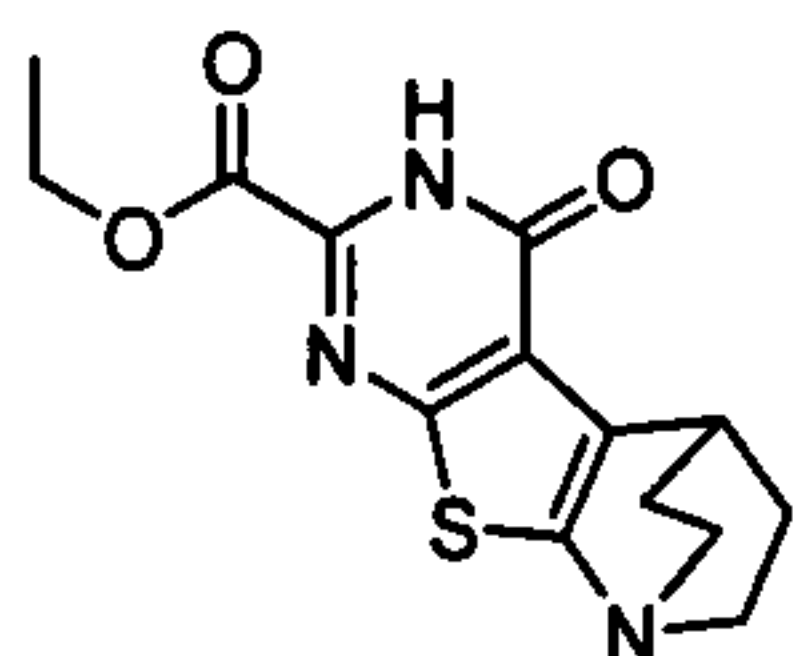
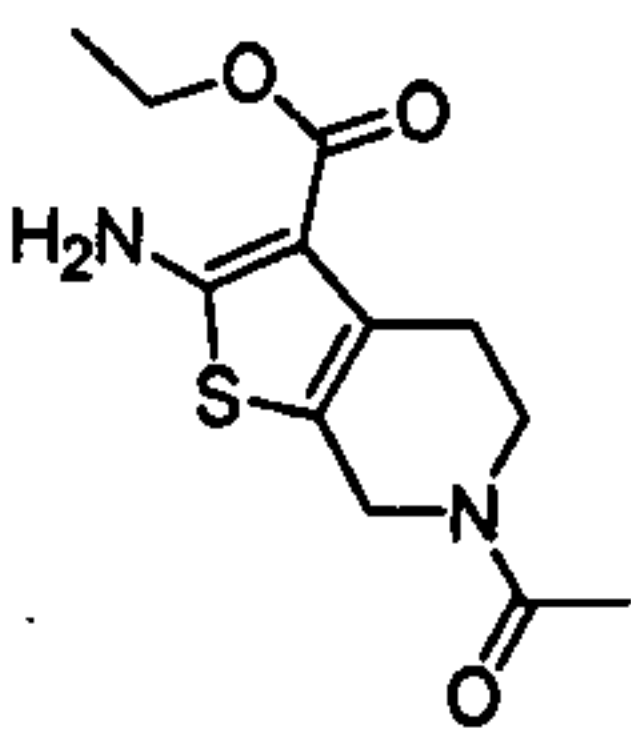
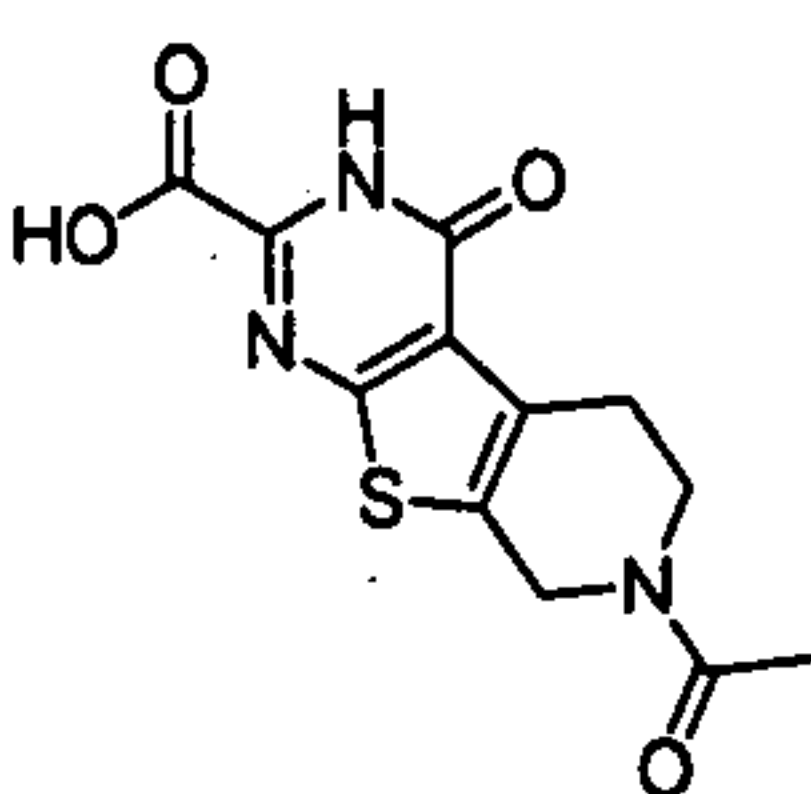
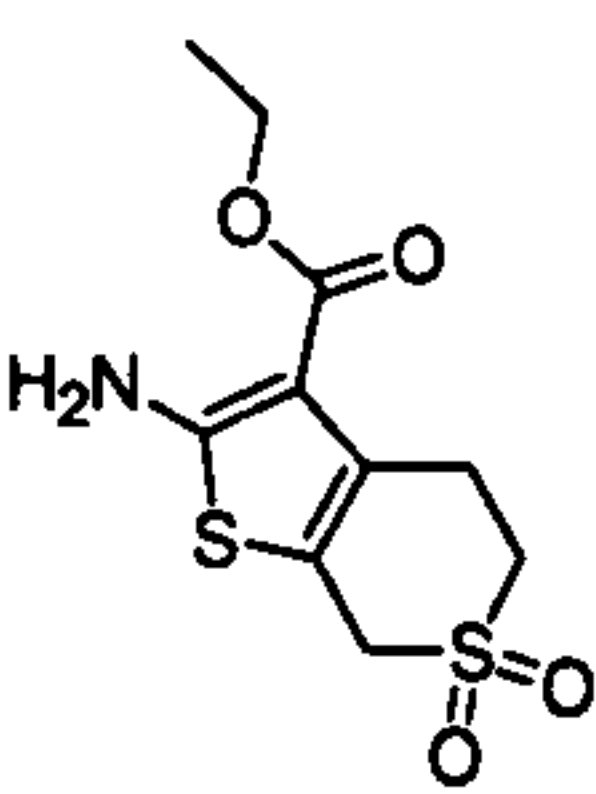
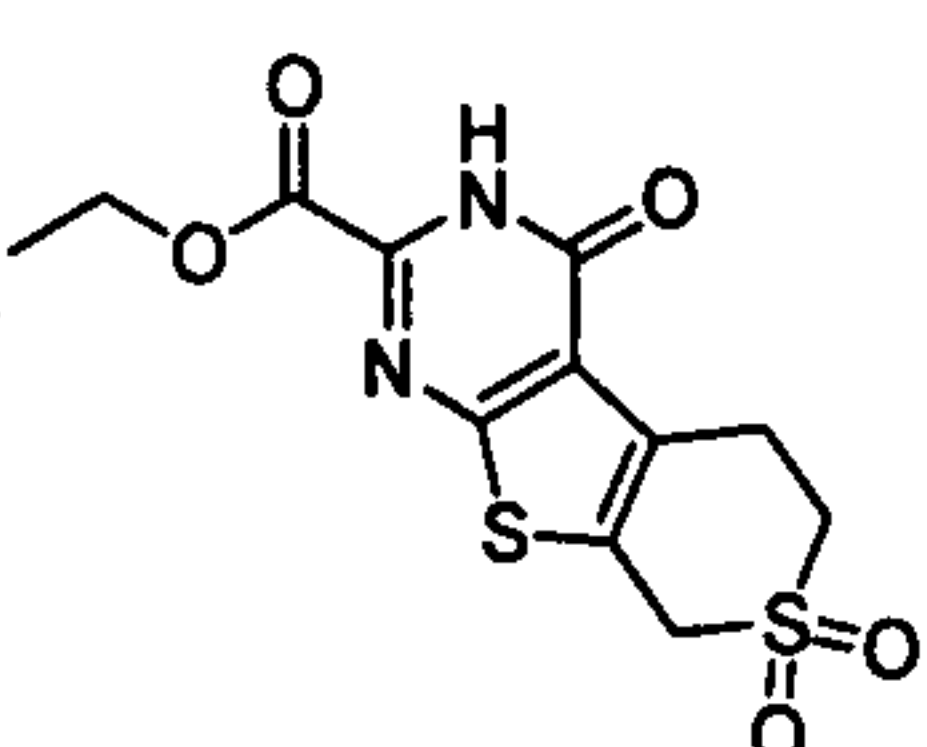
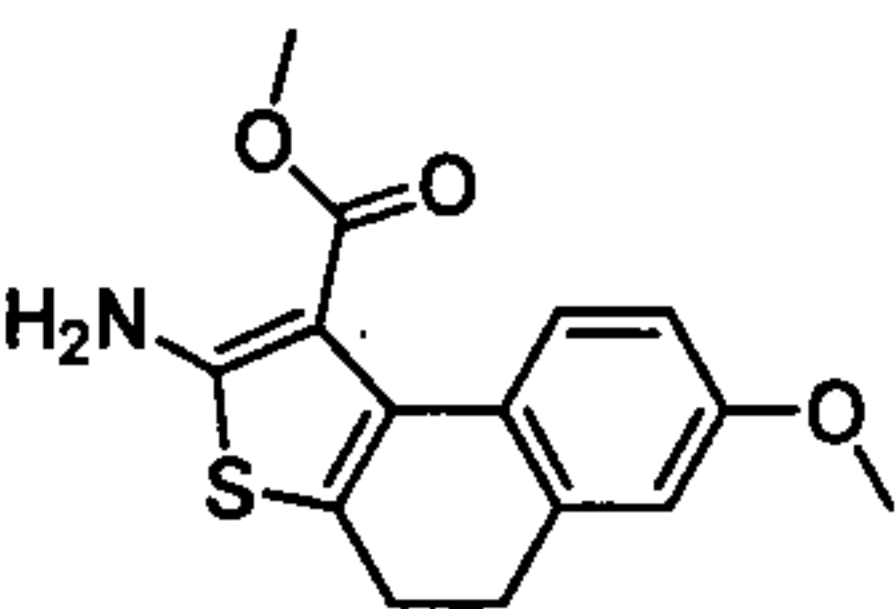
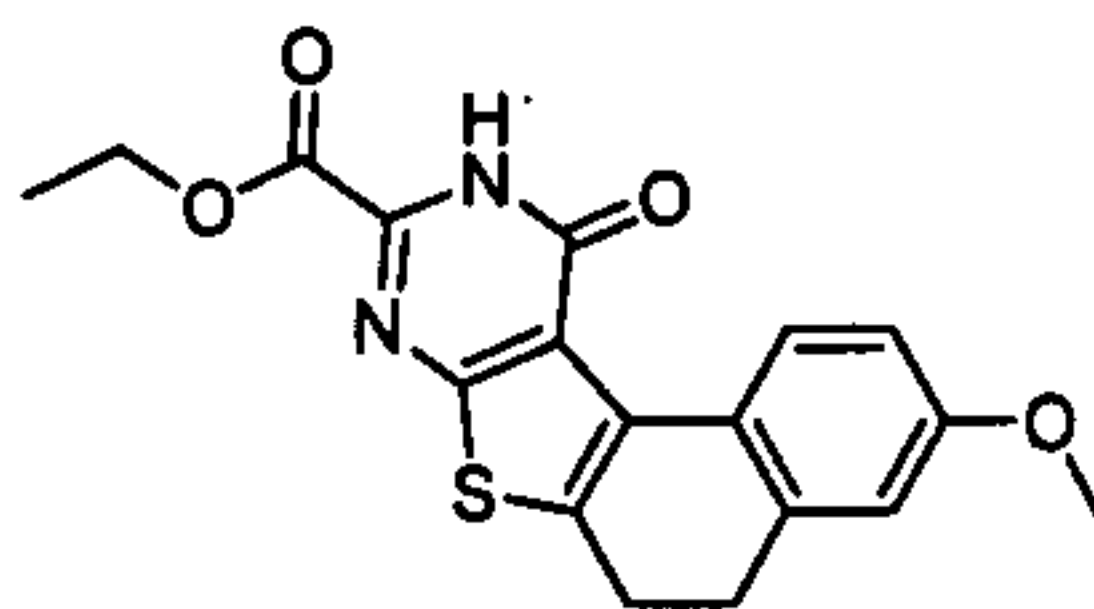
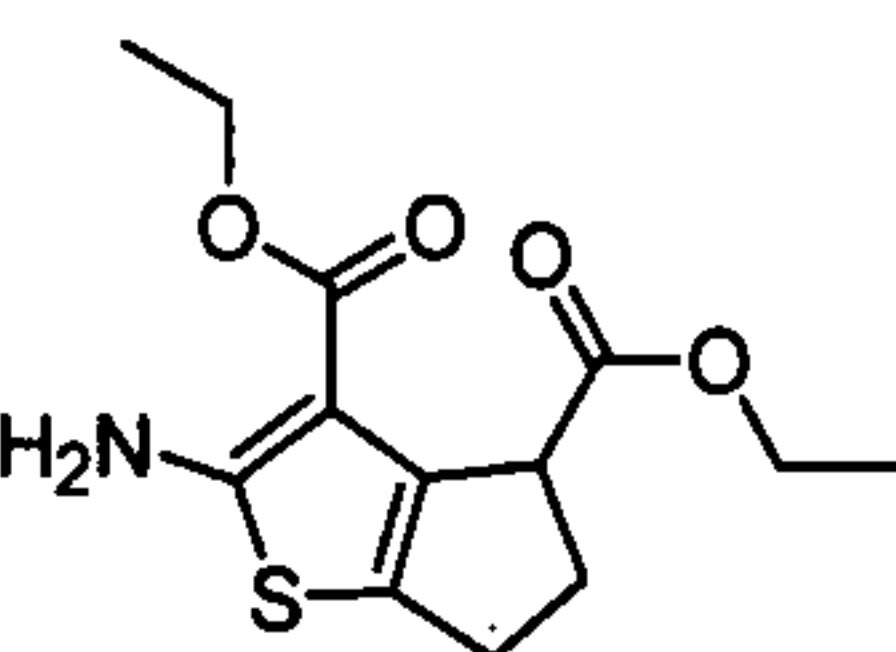
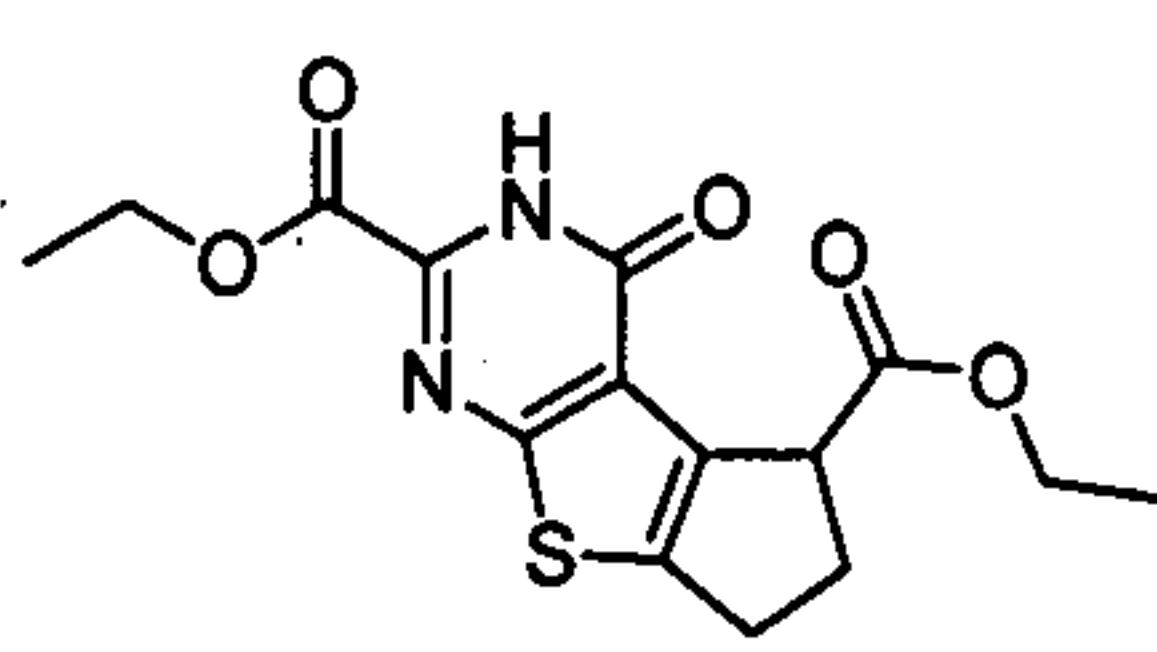
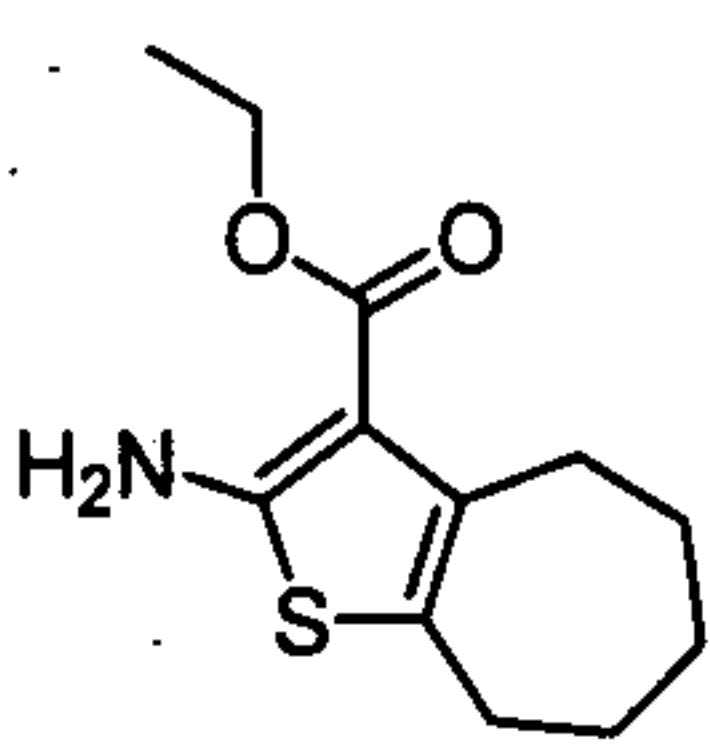
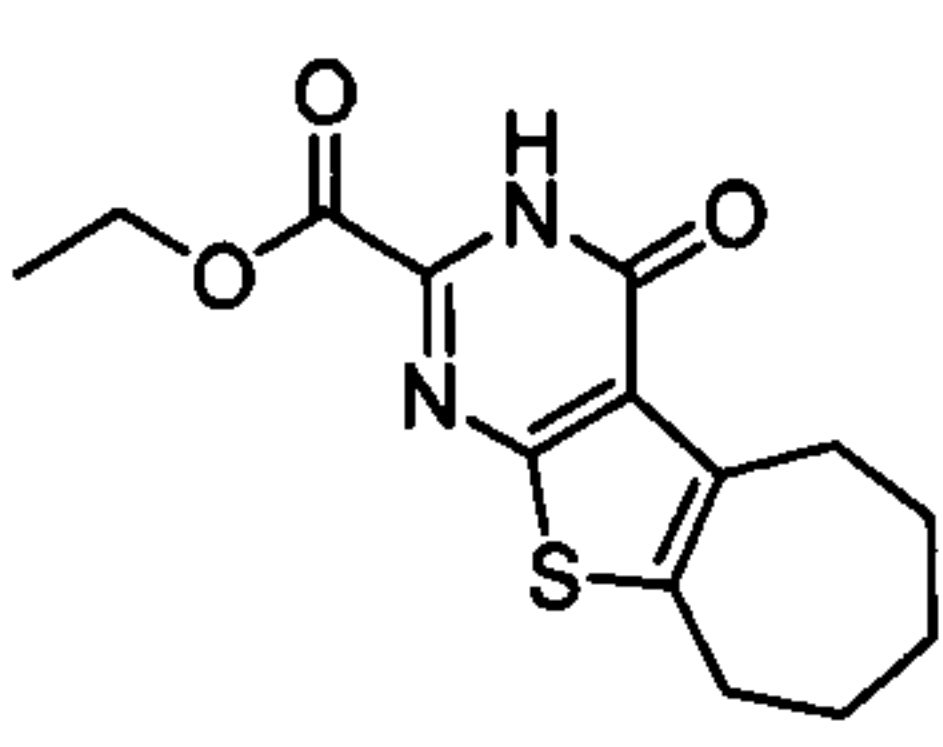
**Preparative Examples 5/7 to 5/106**

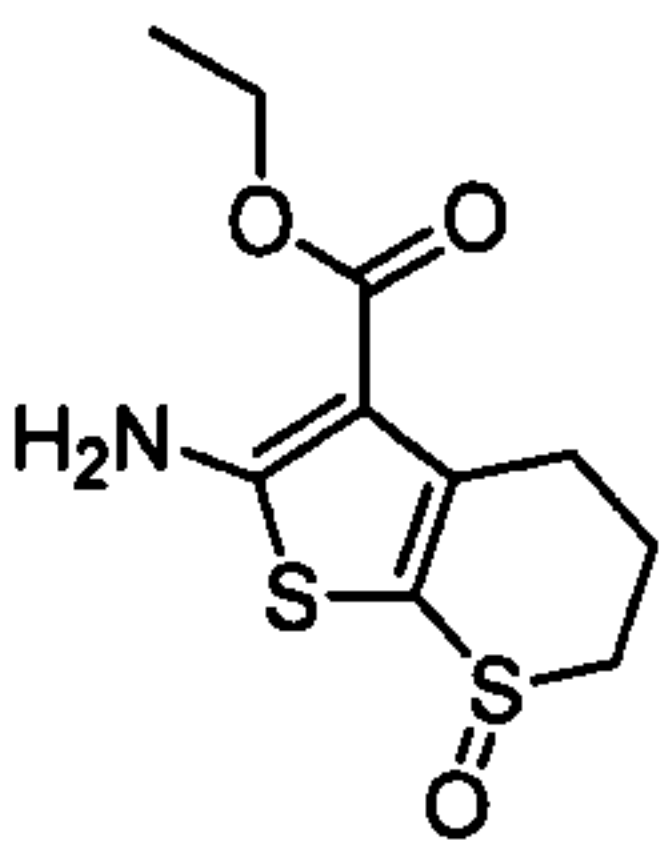
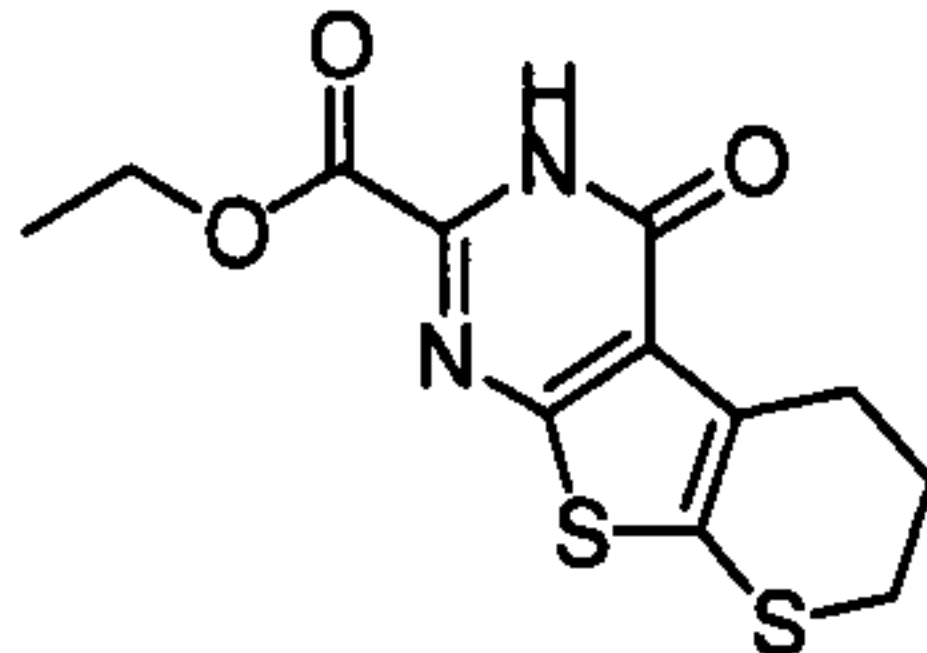
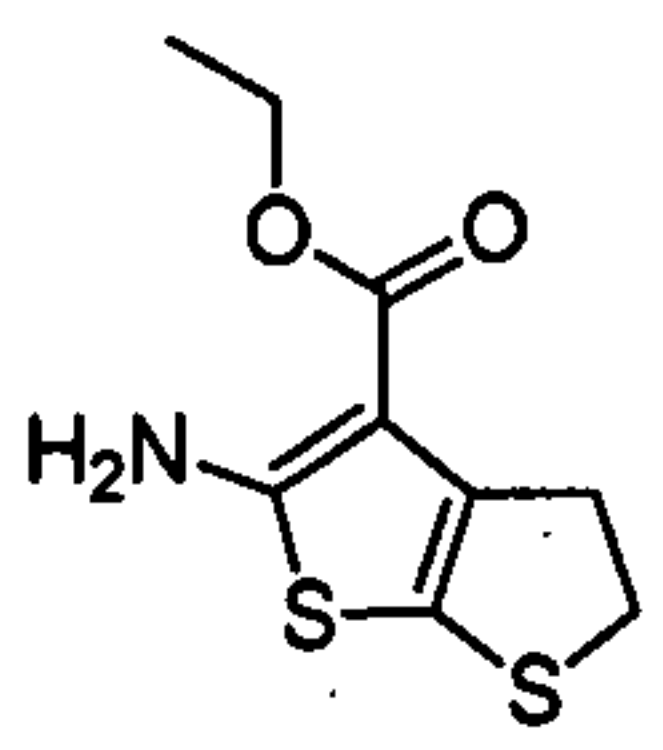
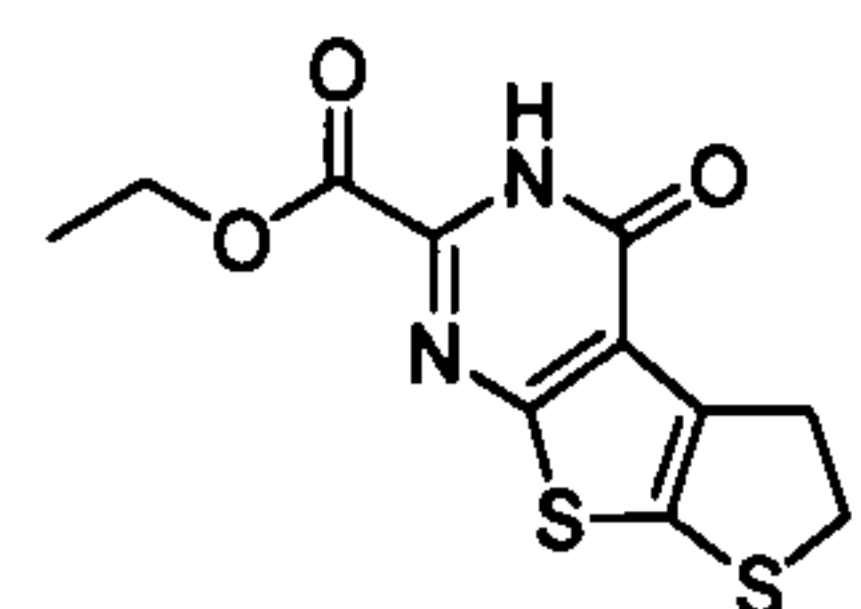
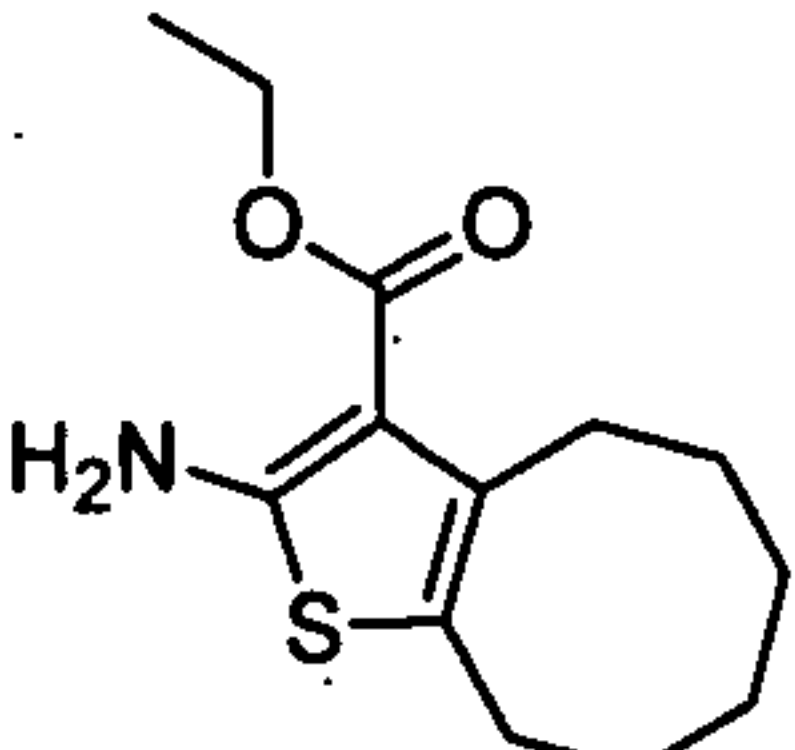
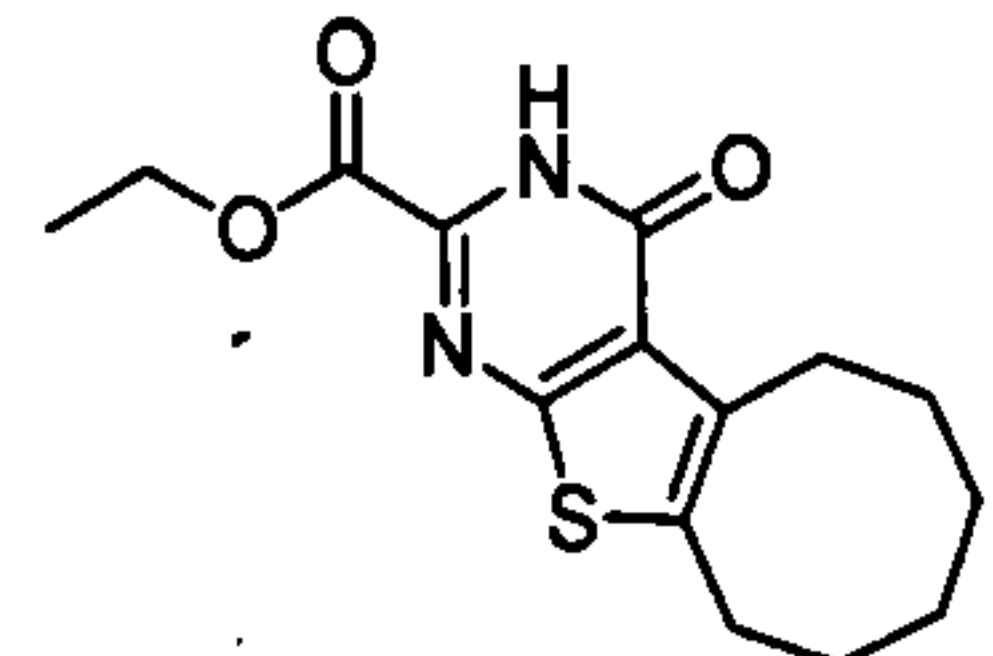
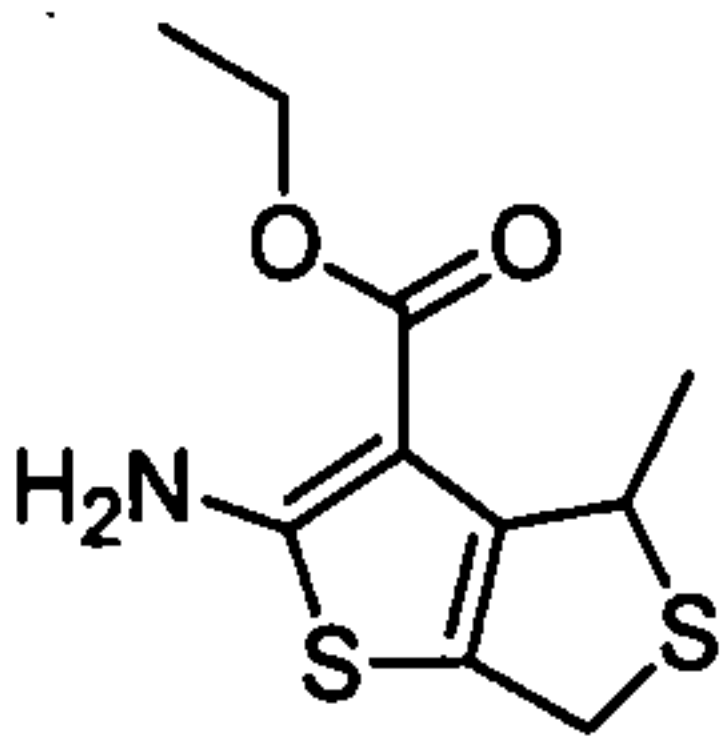
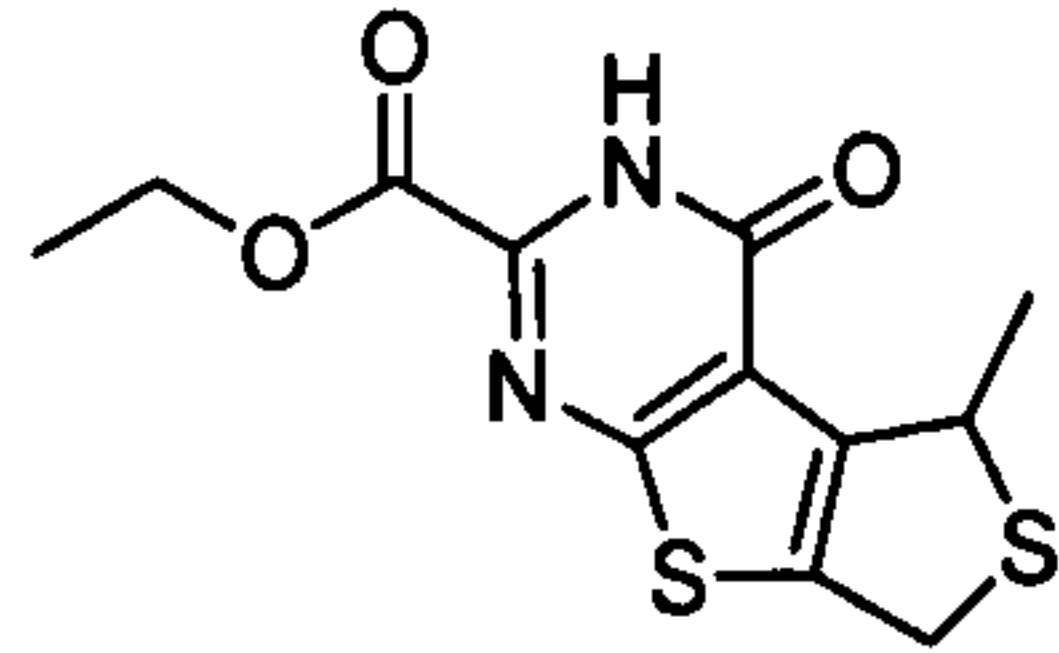
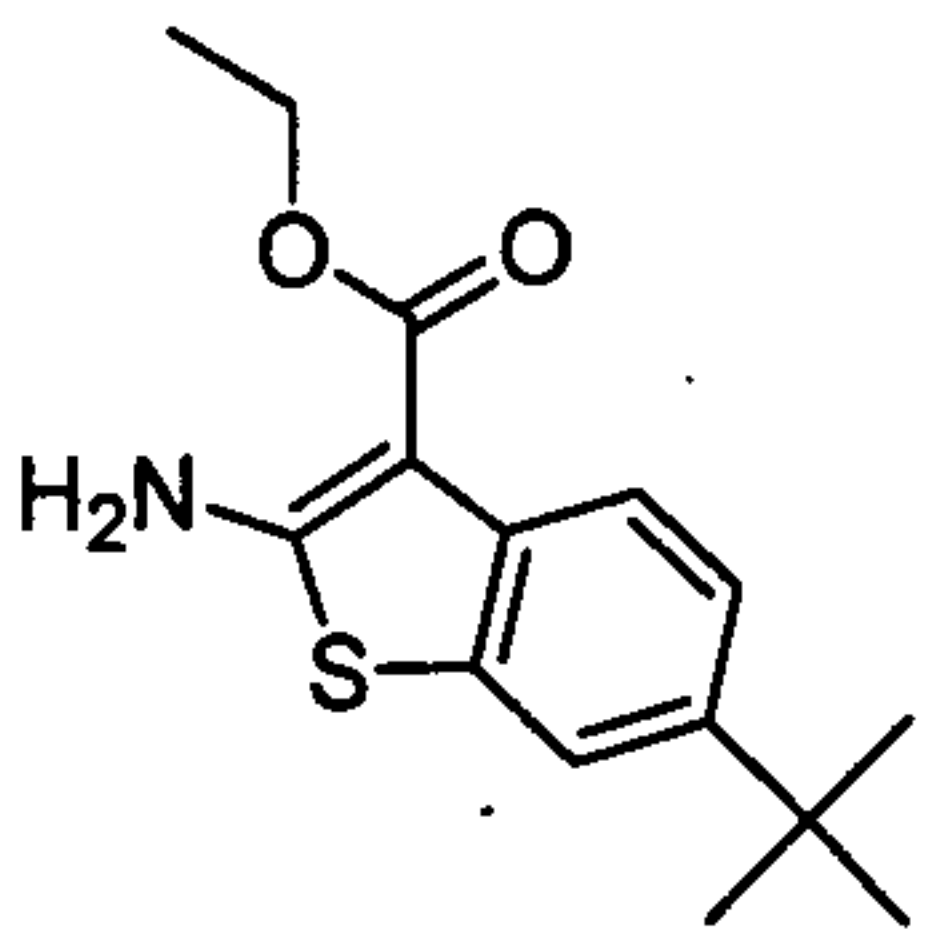
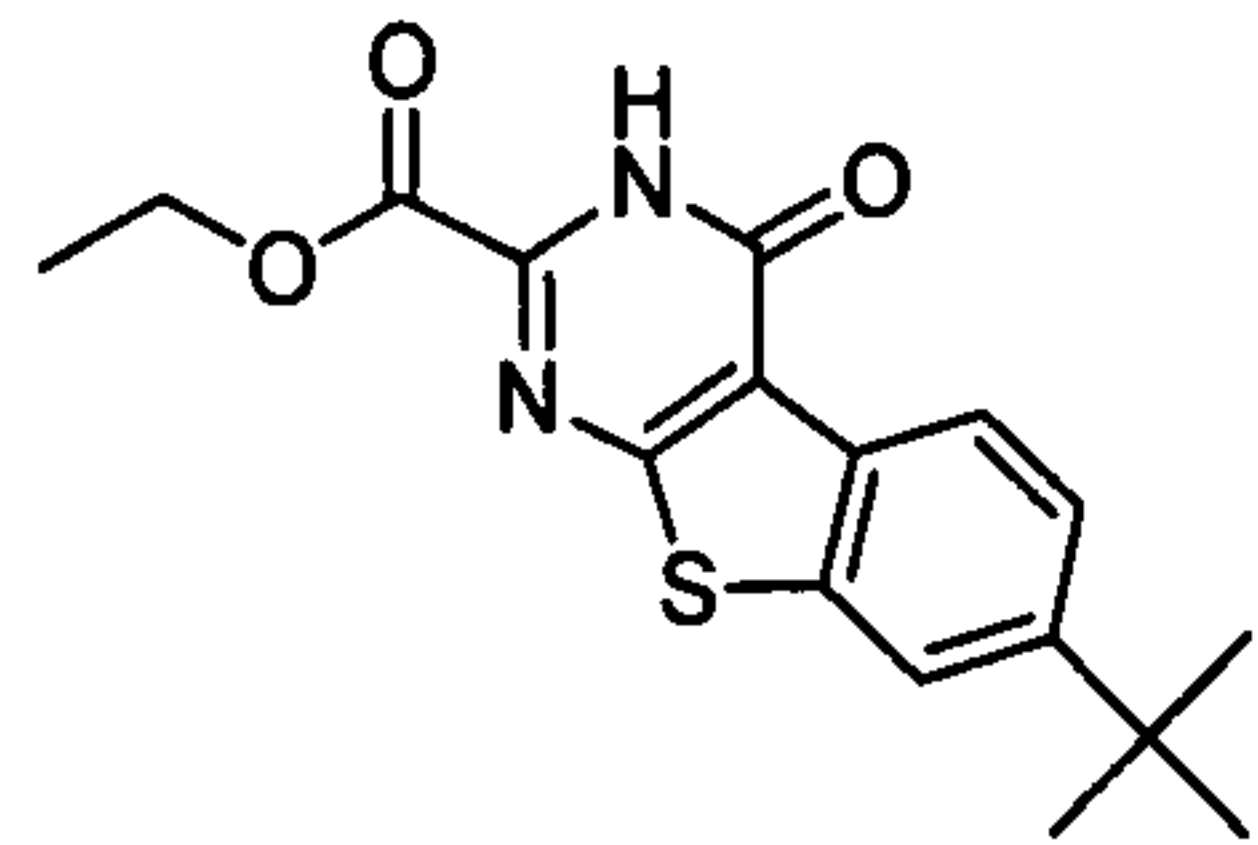
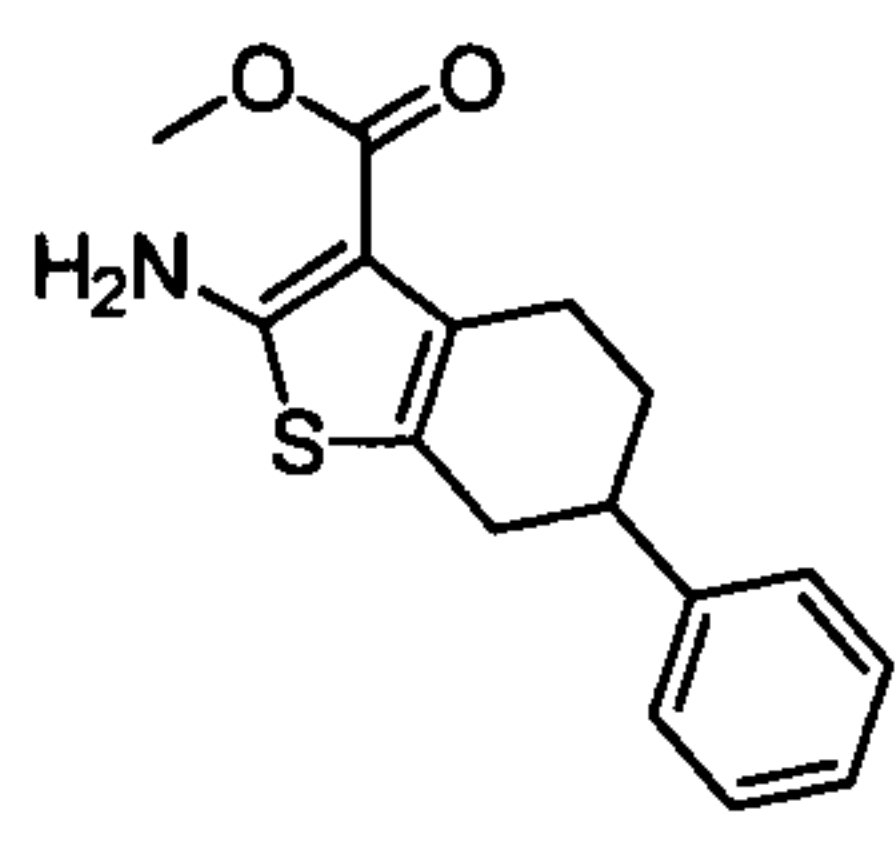
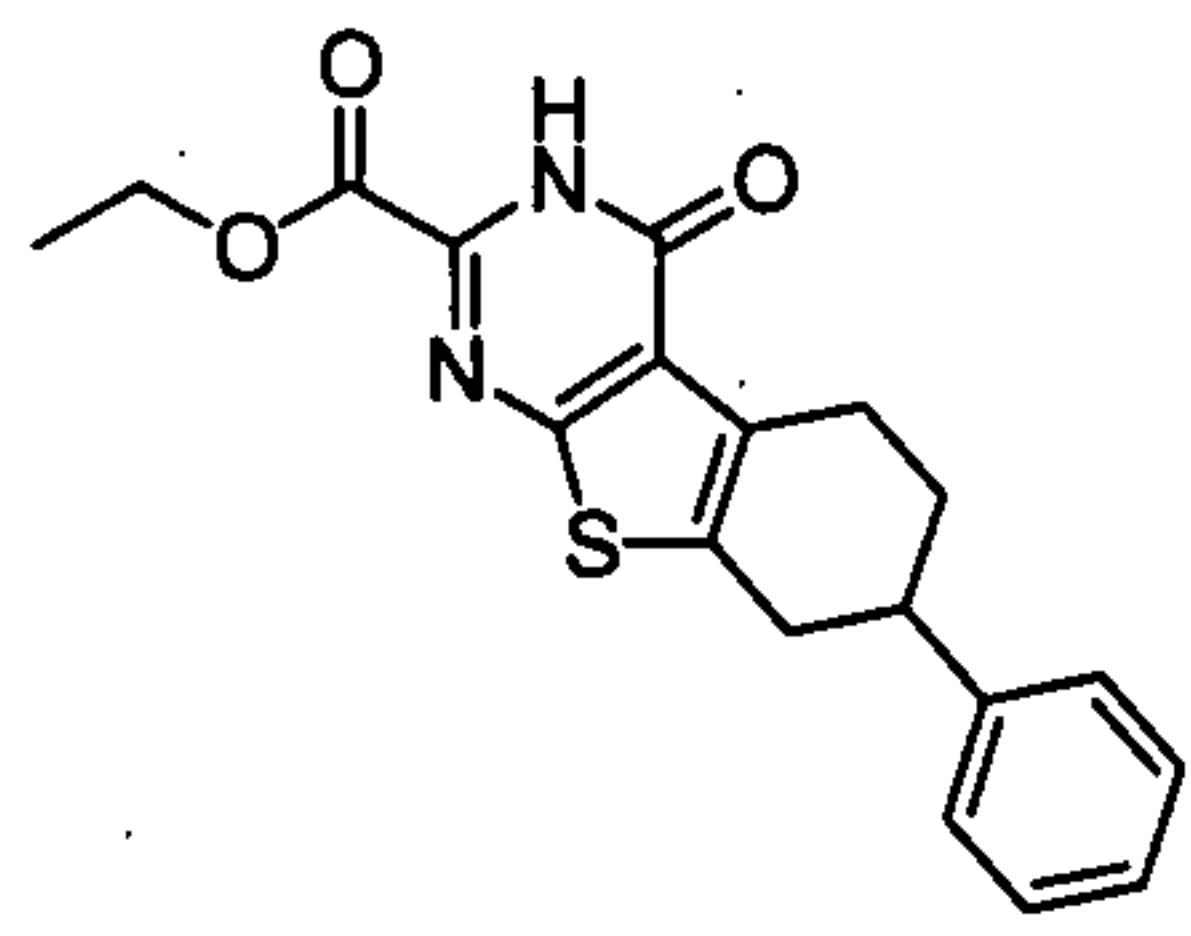
Following similar procedures as described in the Preparative Examples 4 except using the amines indicated in Table I.2 below, the following compounds were prepared.

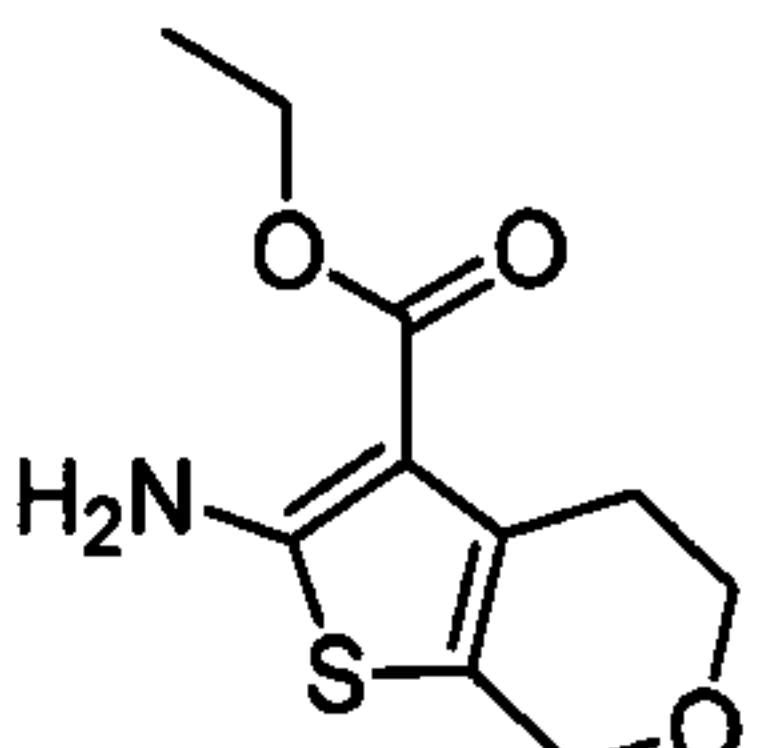
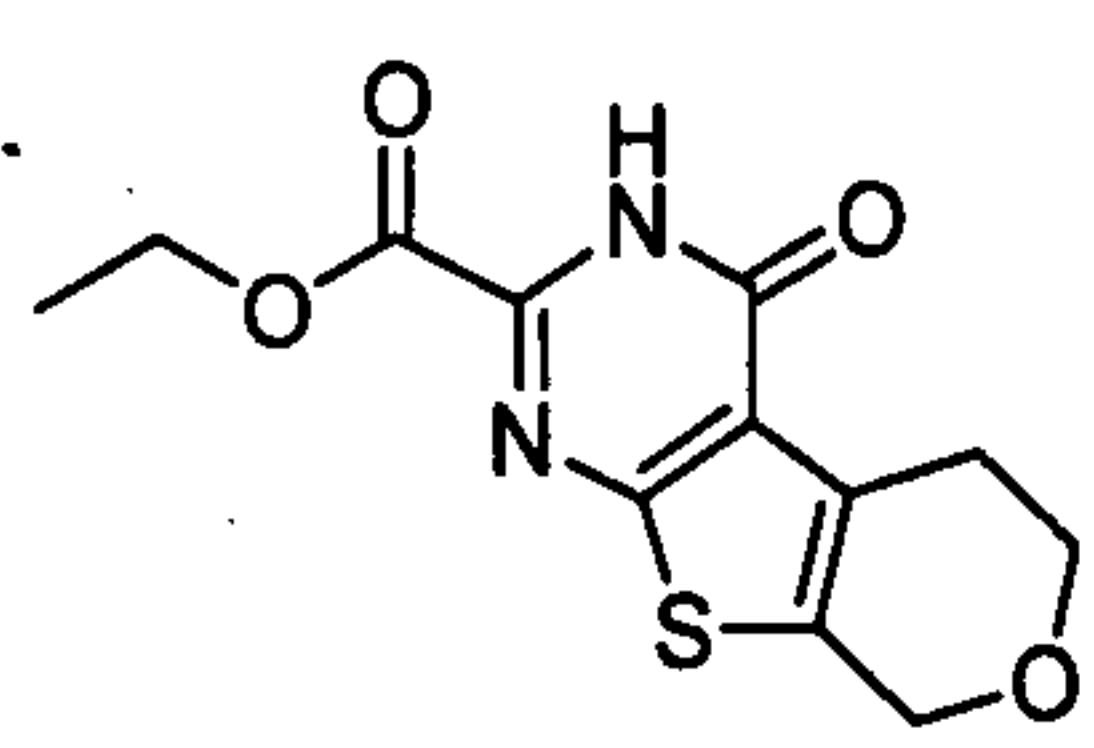
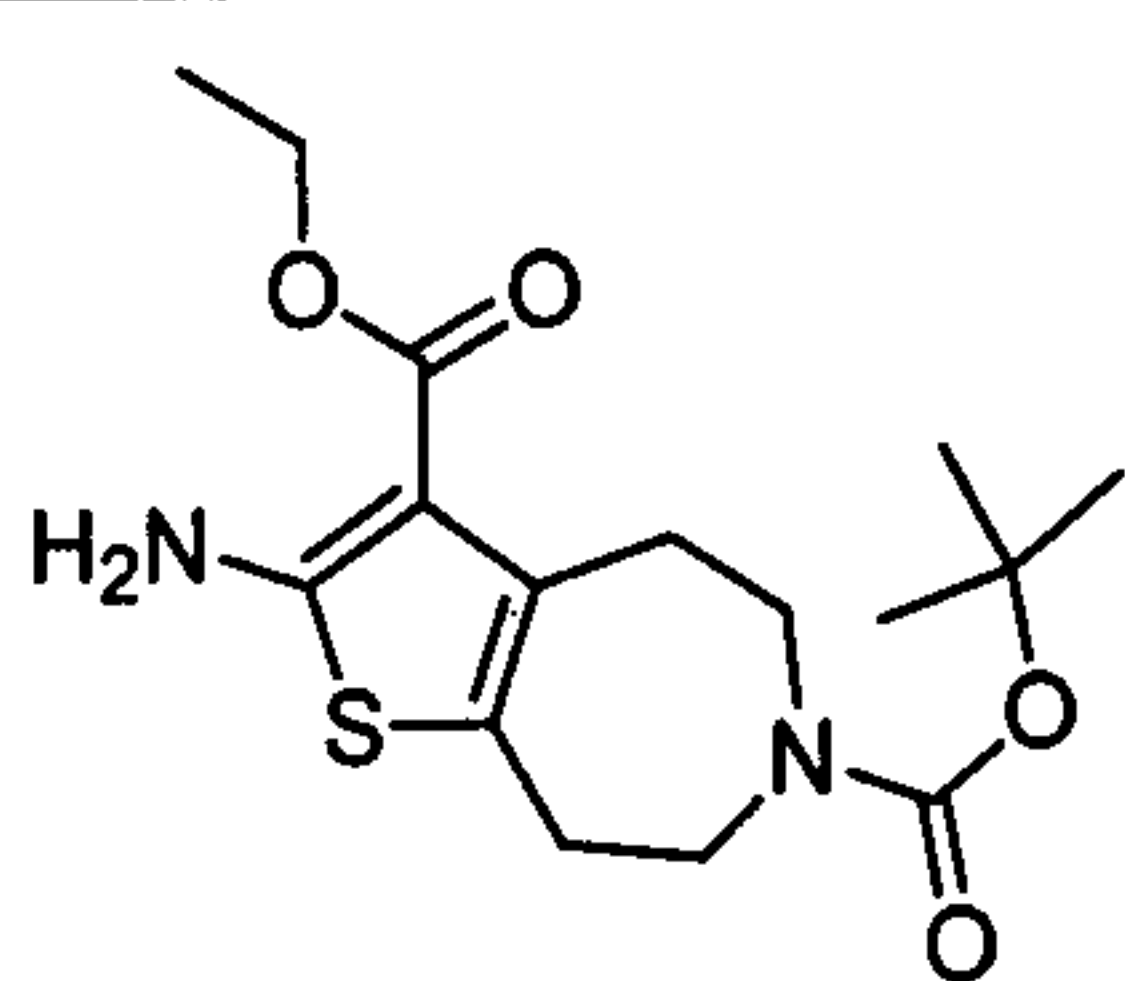
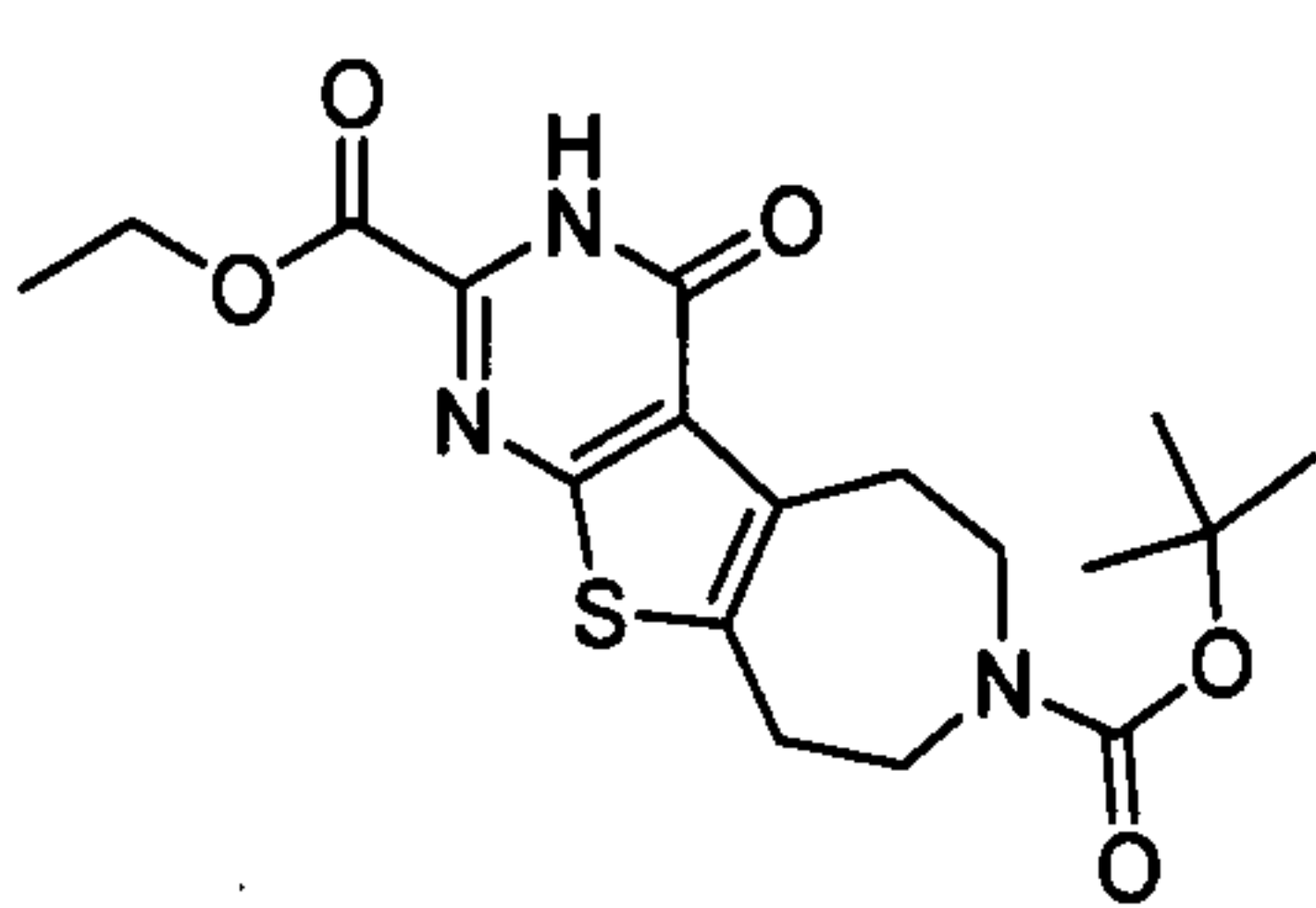
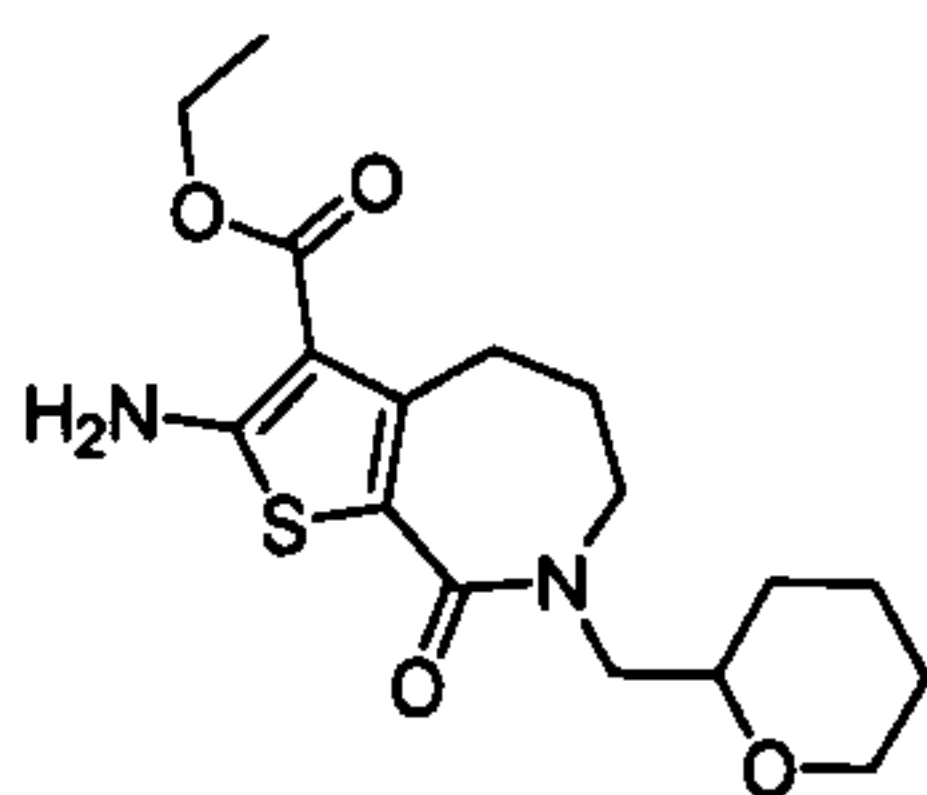
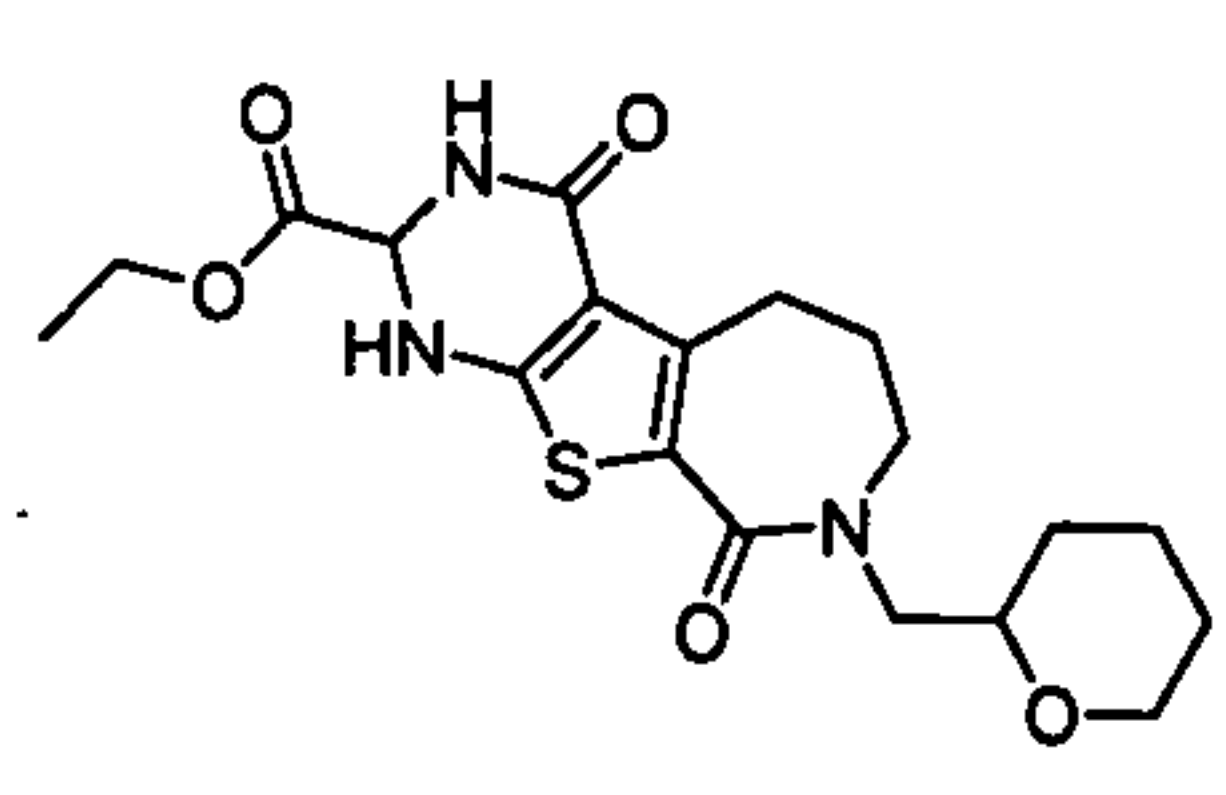
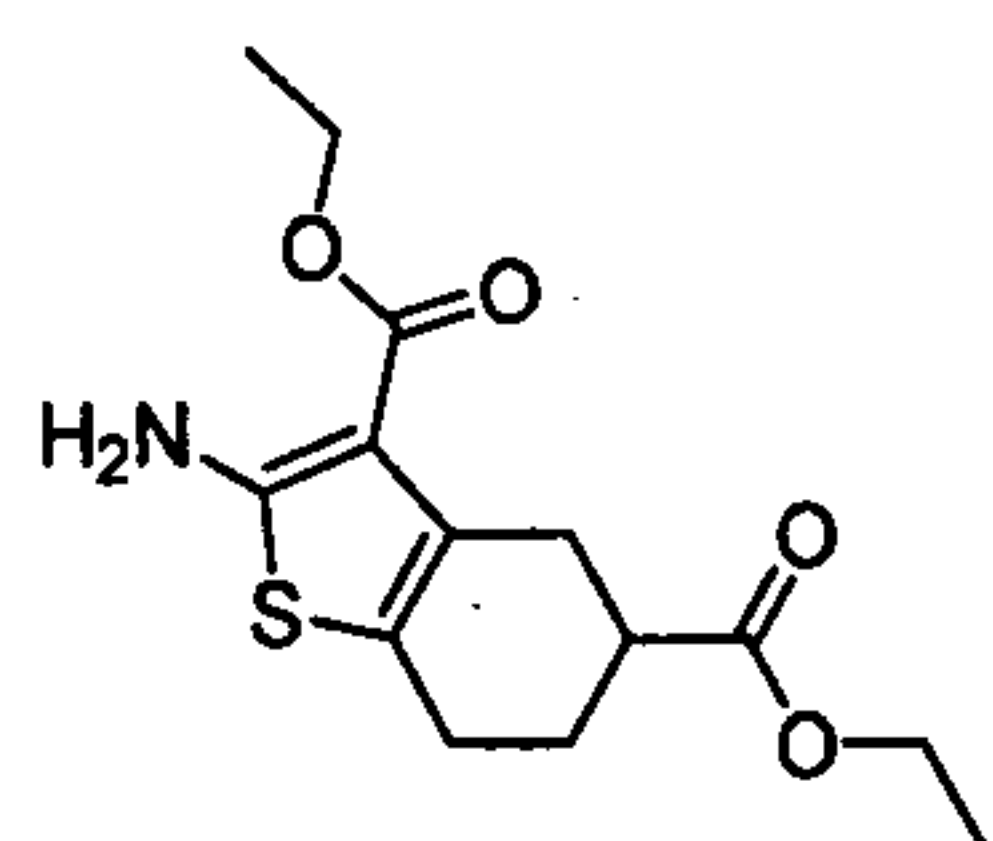
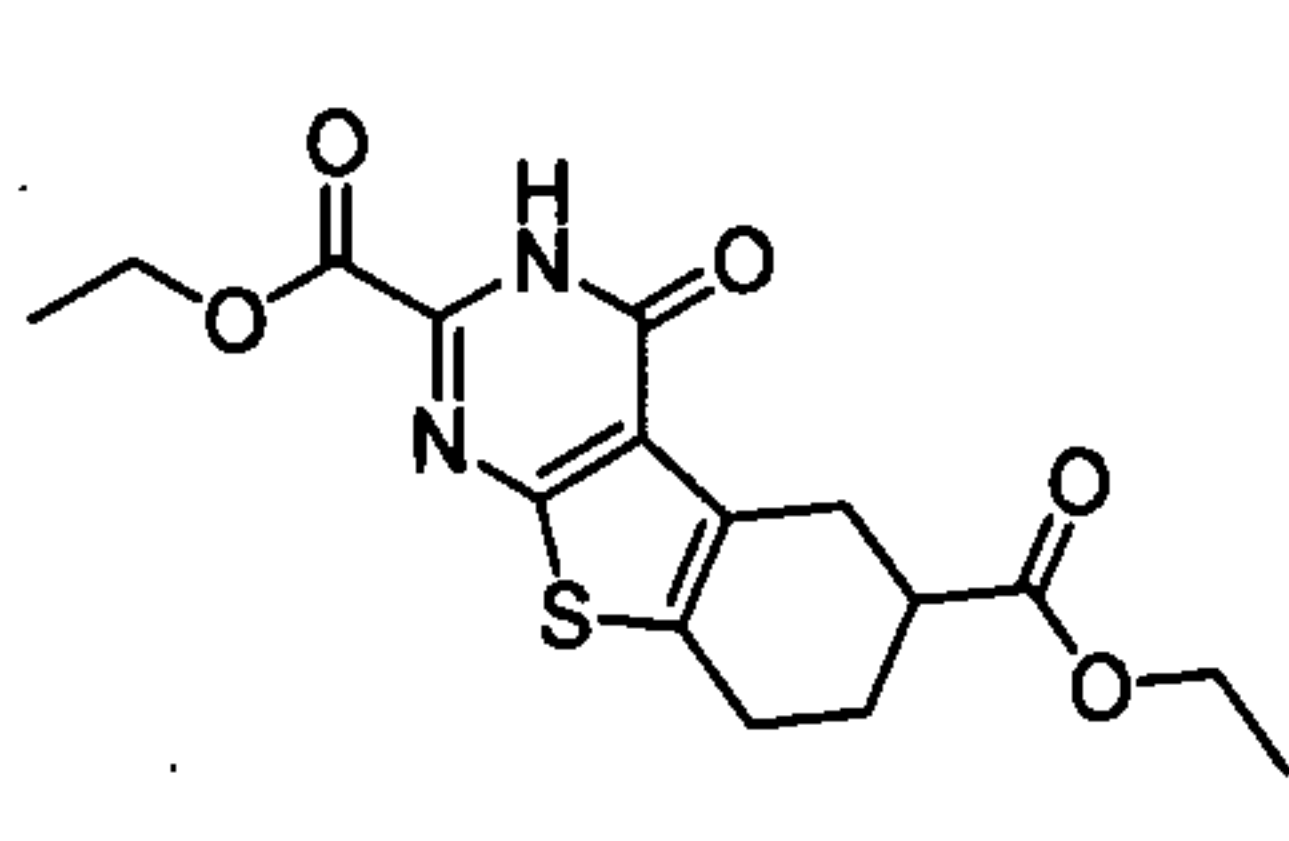
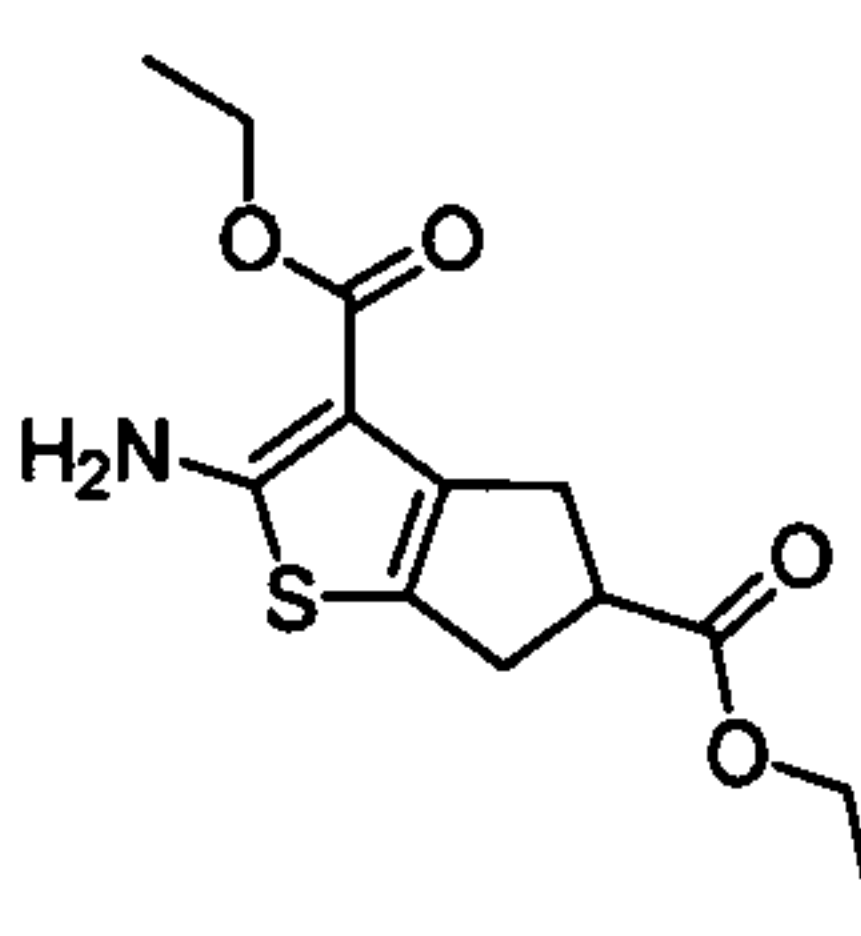
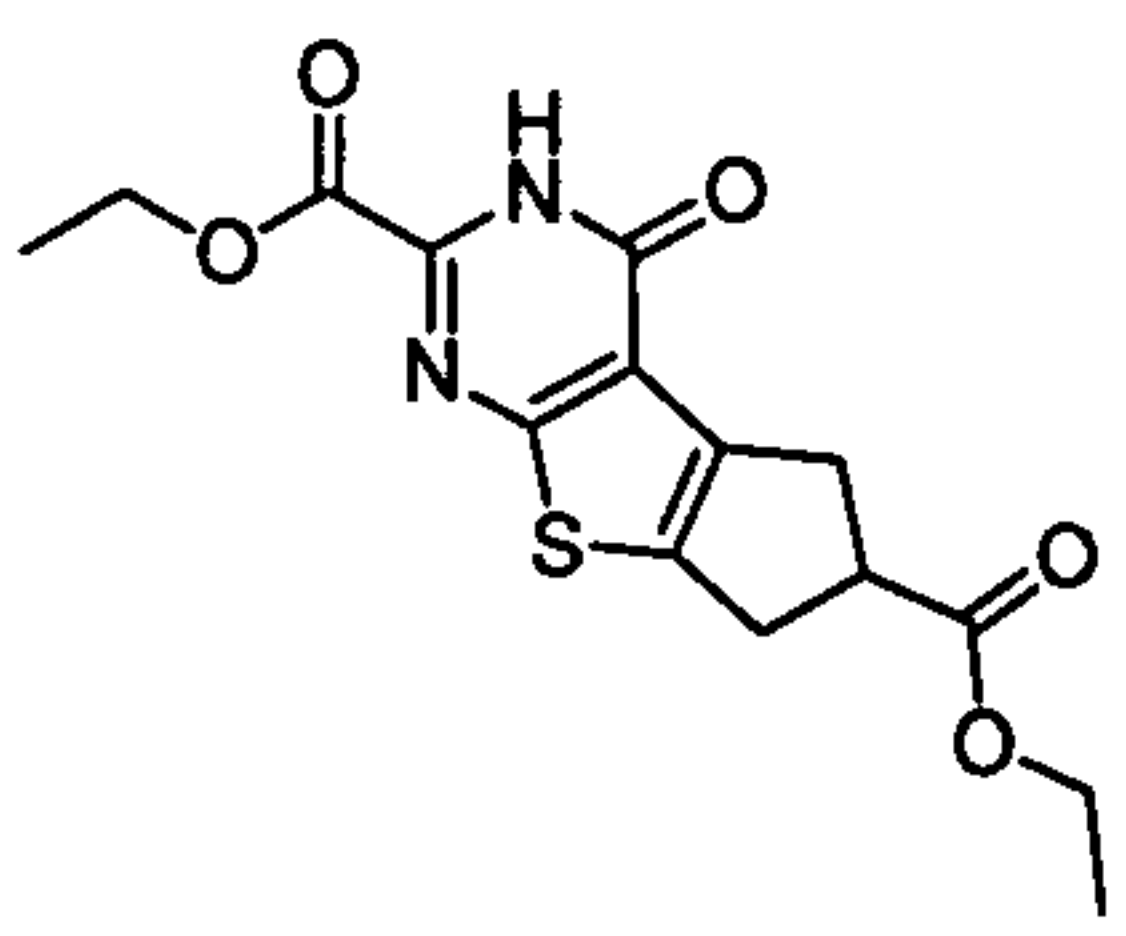
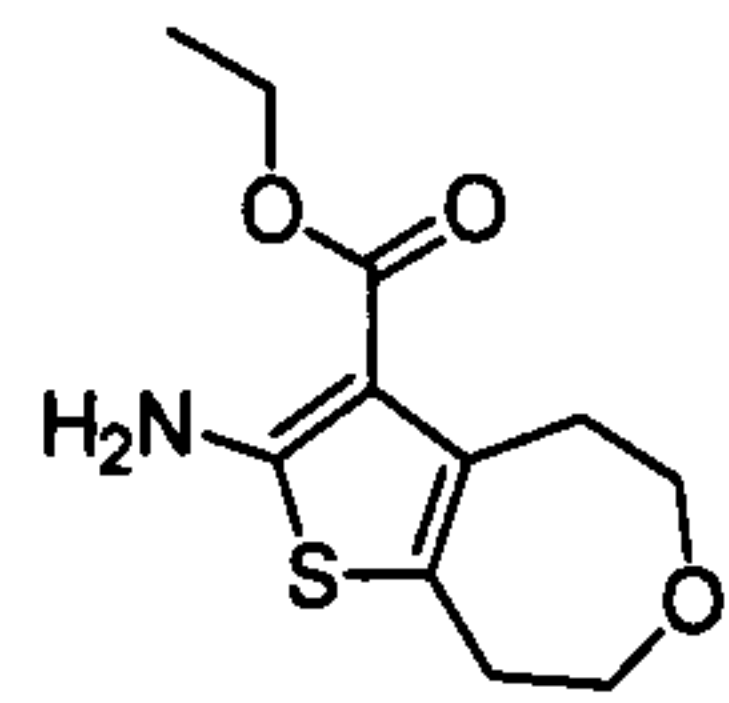
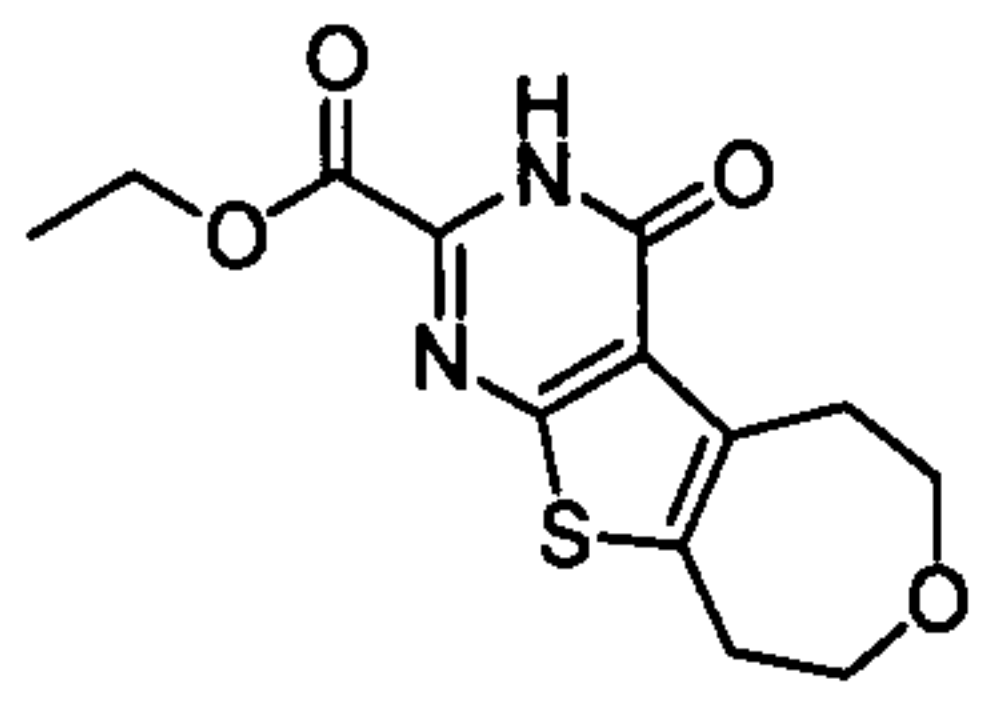
15

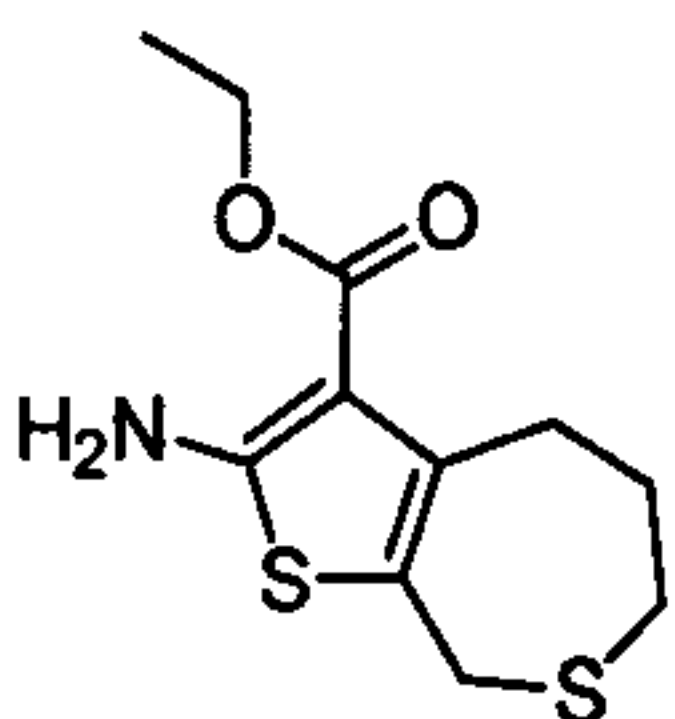
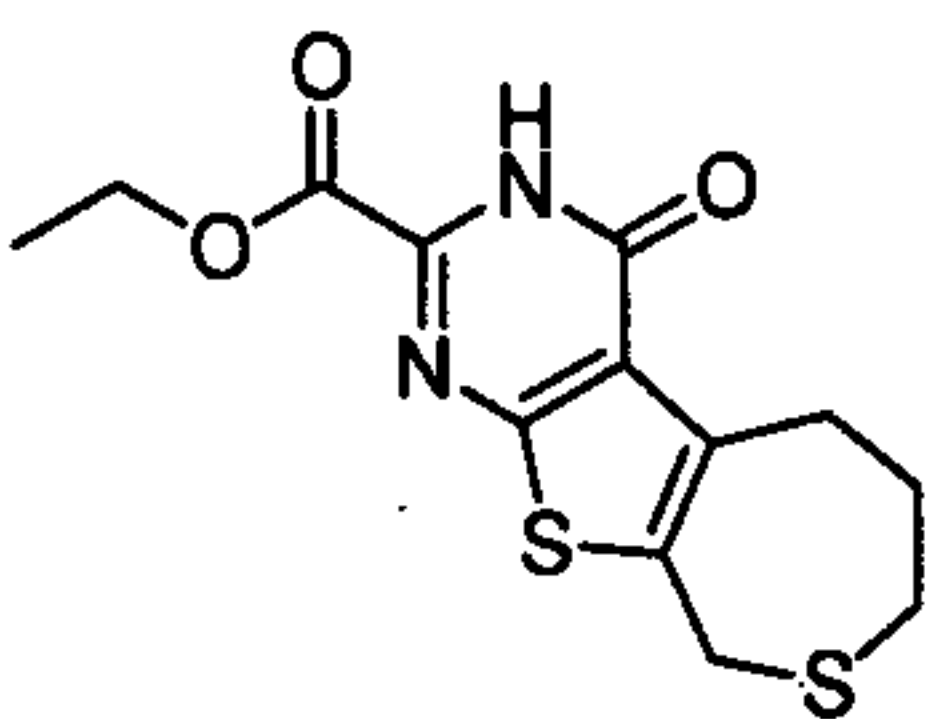
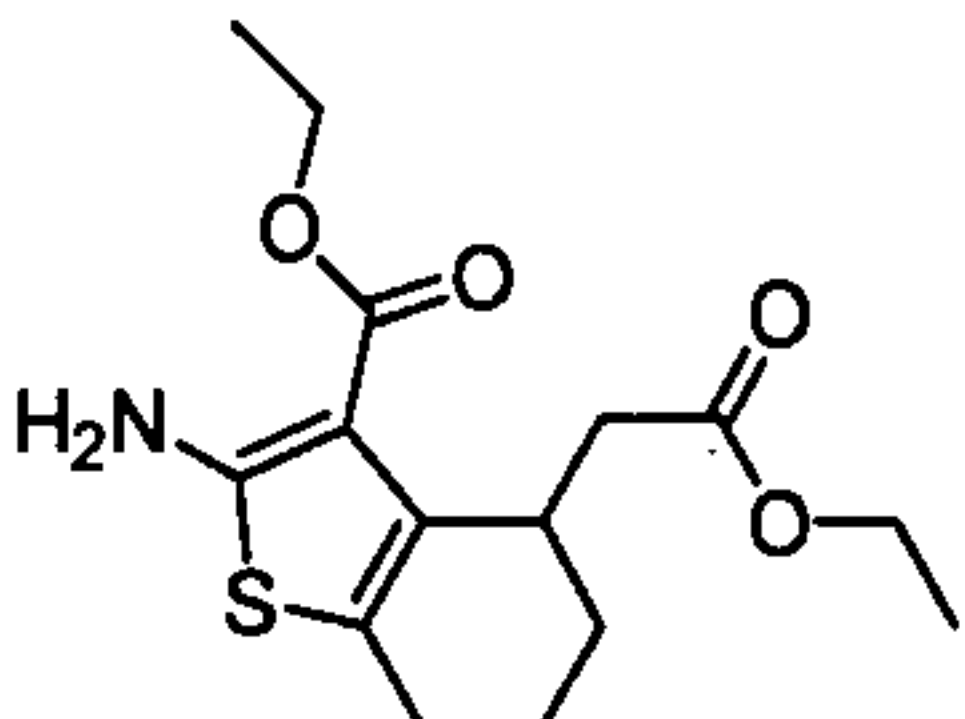
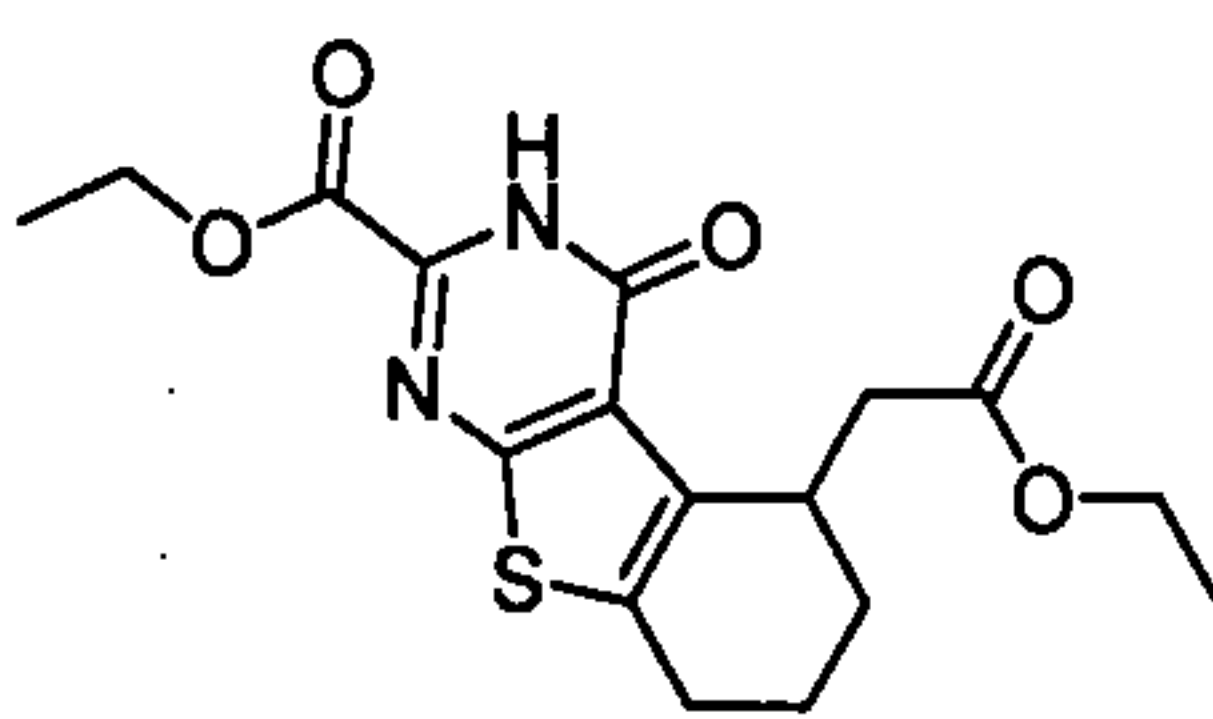
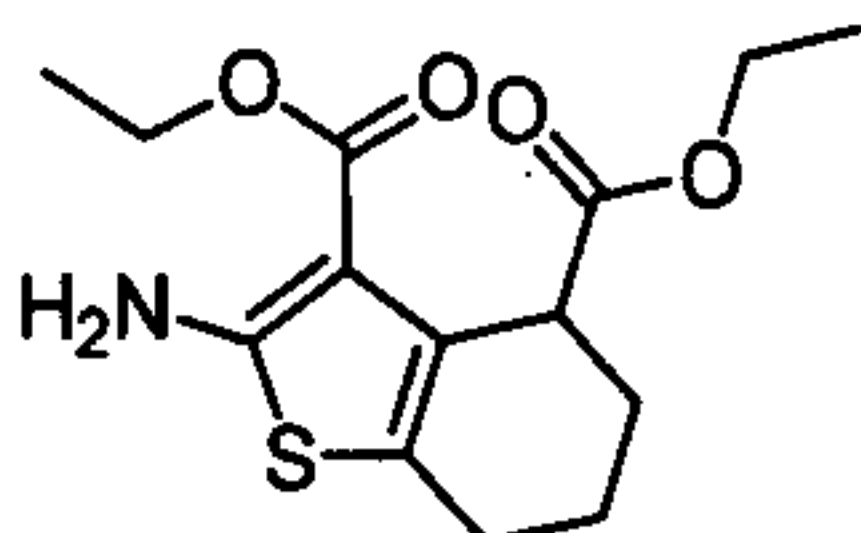
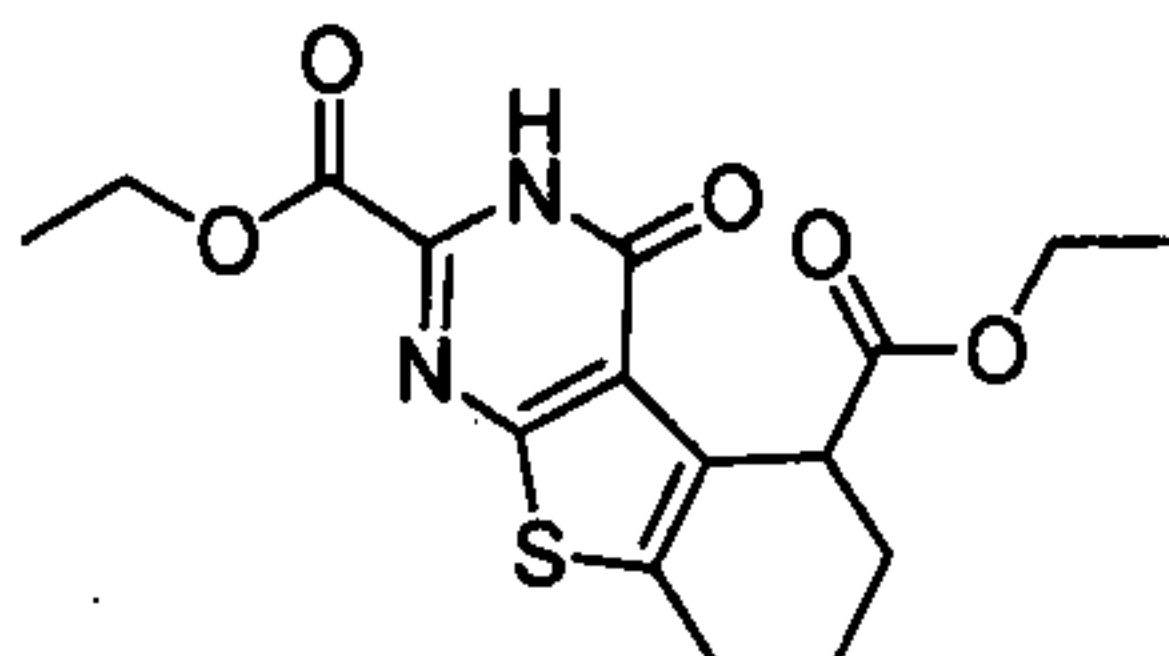
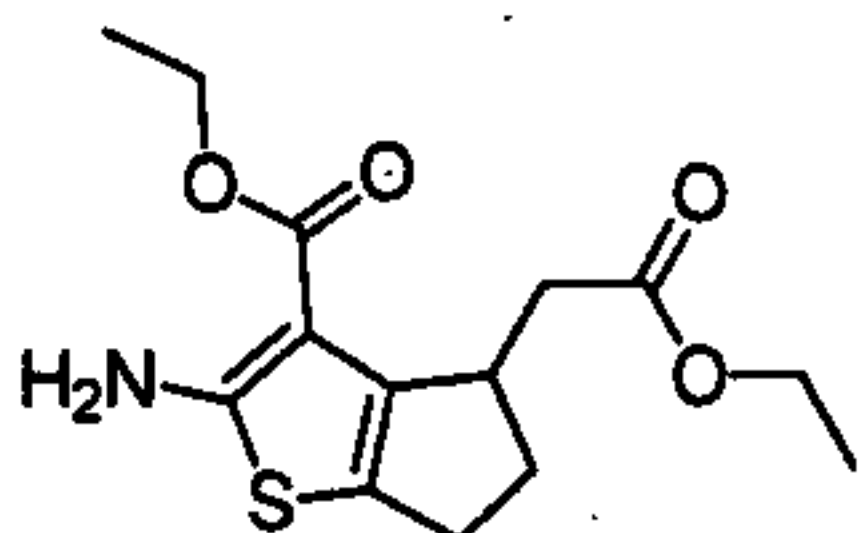
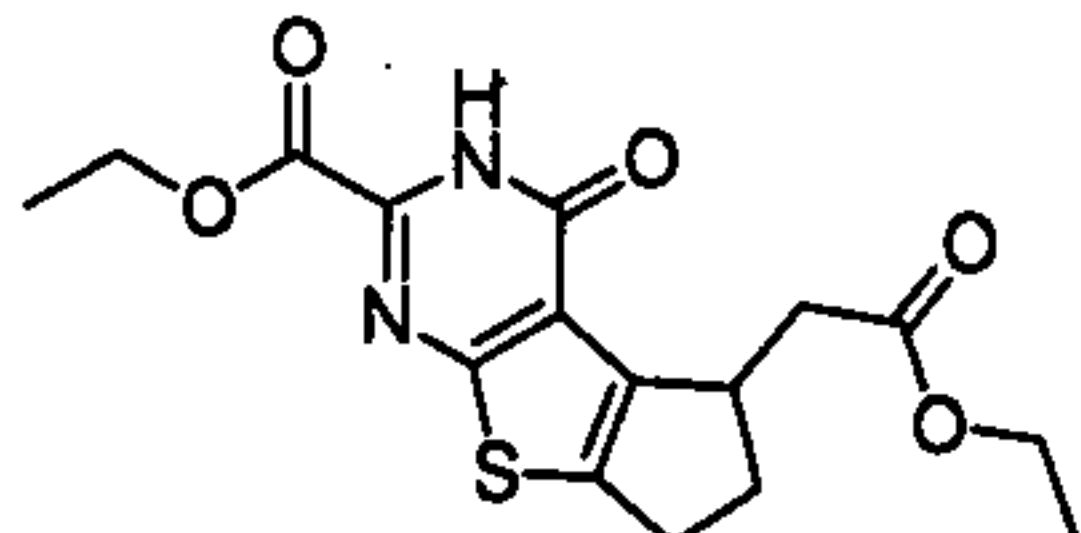
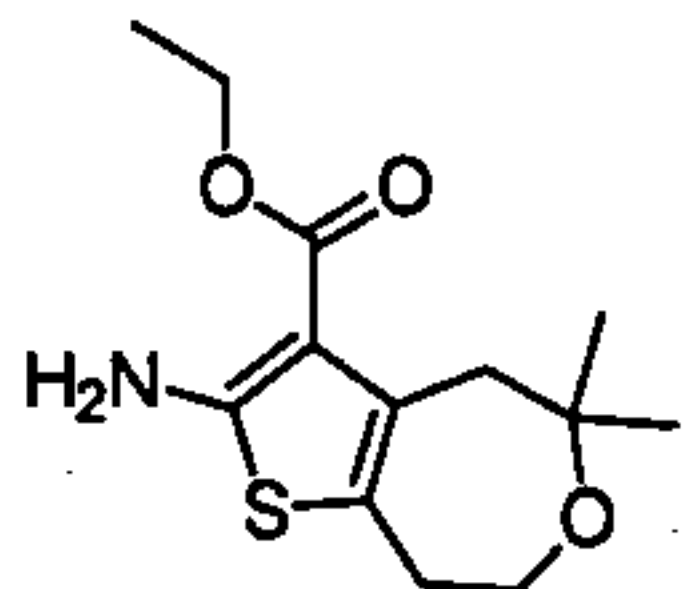
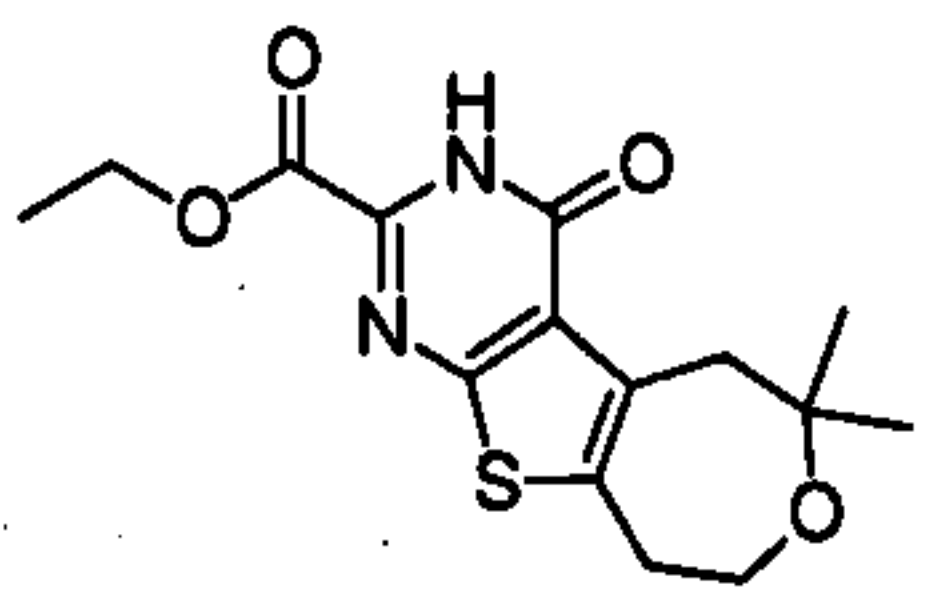
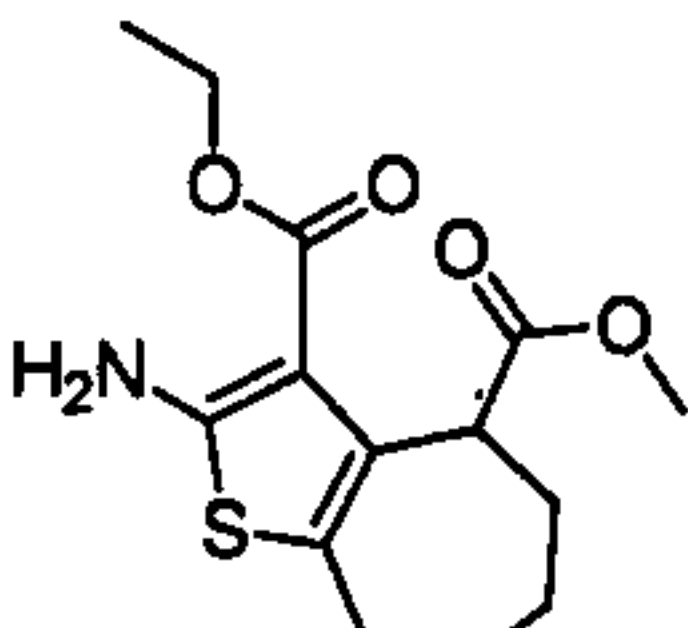
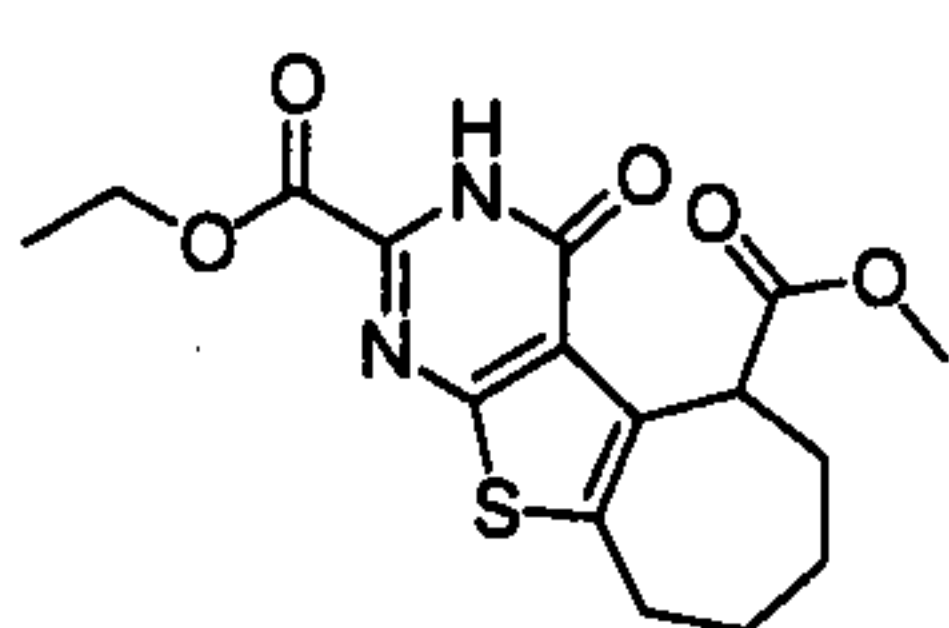
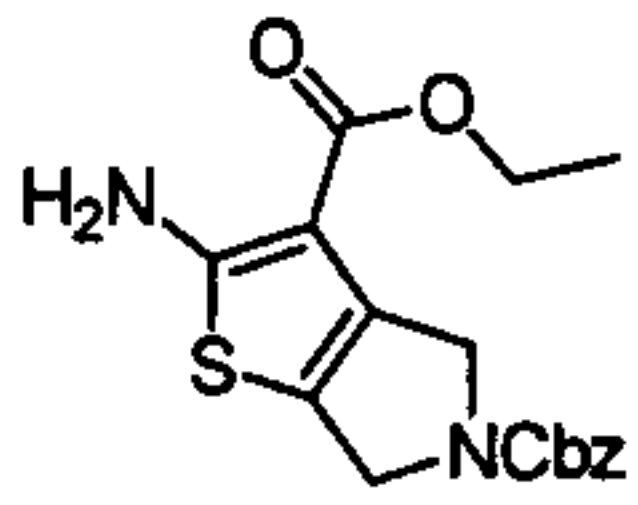
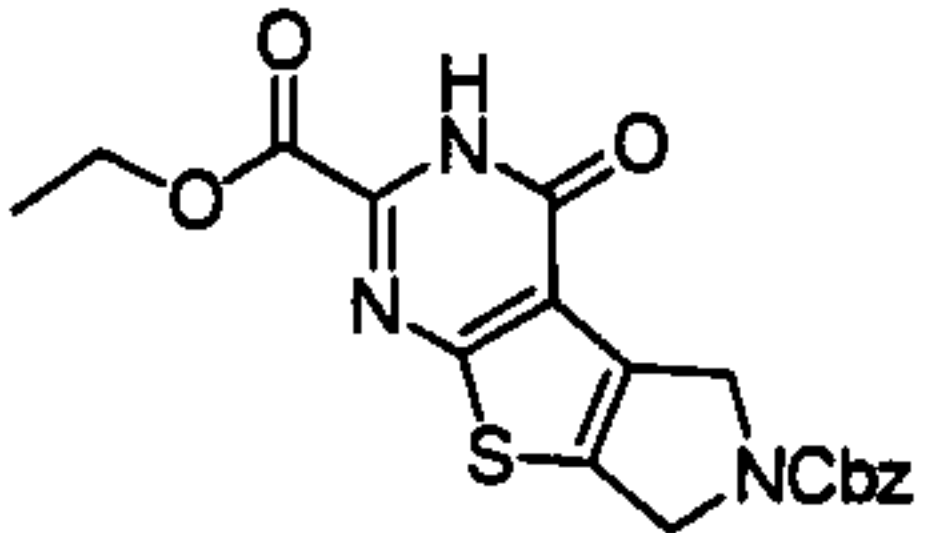
**Table I.2**

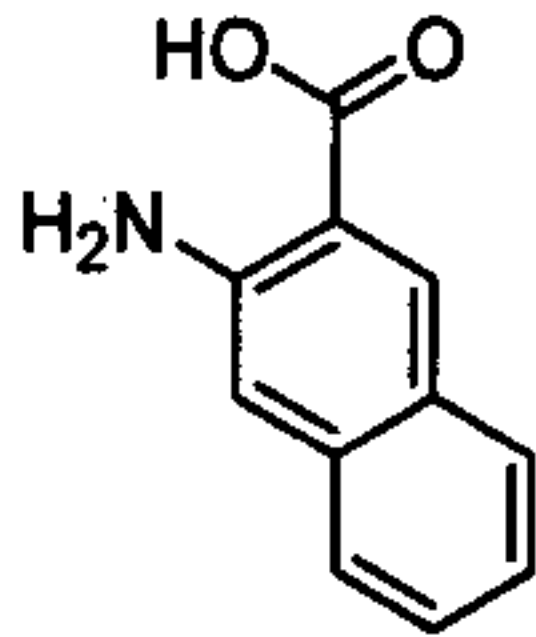
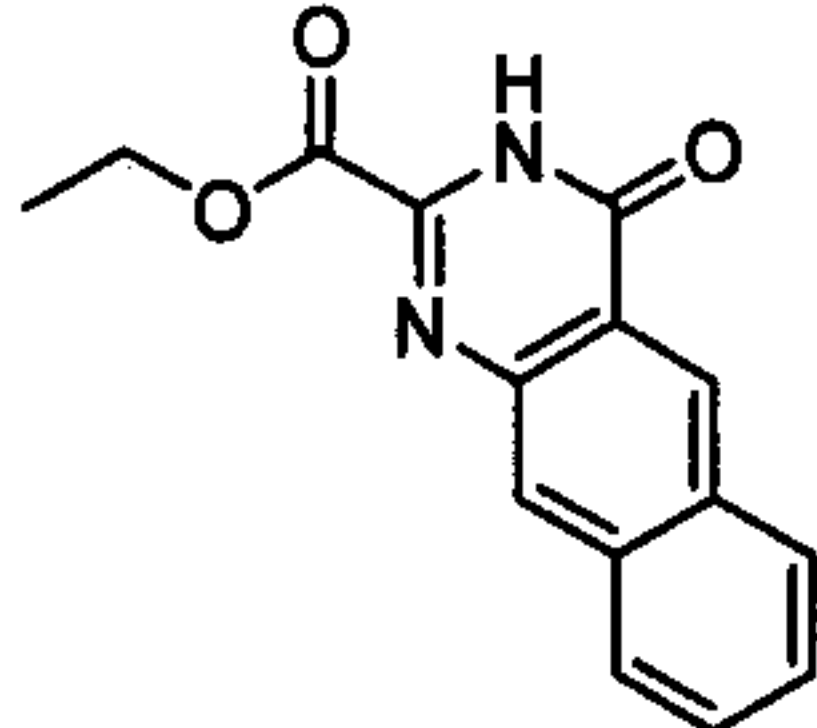
| Ex. # | amine | product | yield                 |
|-------|-------|---------|-----------------------|
| 5/7   |       |         | 59%<br>$[MH]^+ = 275$ |

| Ex. # | amine                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 5/10  |    |    | n.d.<br>[MH] <sup>+</sup> = 294 |
| 5/35  |    |   | 74%<br>[MH] <sup>+</sup> = 306  |
| 5/36  |  |  | 36%<br>[MH] <sup>+</sup> = 322  |
| 5/41  |  |  | 88%<br>[MH] <sup>+</sup> = 329  |
| 5/43  |  |  | 46%<br>[MH] <sup>+</sup> = 357  |
| 5/45  |  |  | 89%<br>[MH] <sup>+</sup> = 337  |
| 5/47  |  |  | 100%<br>[MH] <sup>+</sup> = 293 |

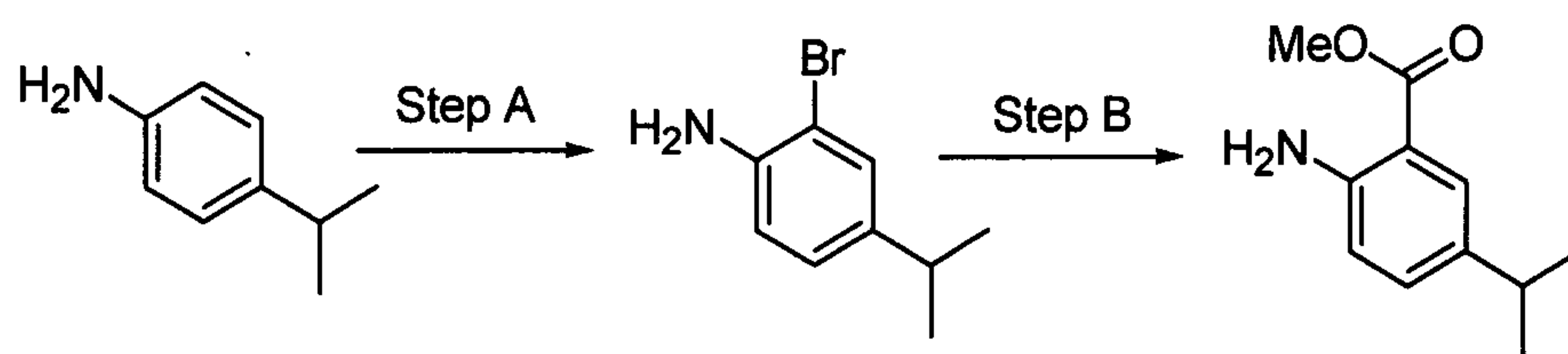
| Ex. # | amine                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 5/48  |    |    | 27%<br>[MH] <sup>+</sup> = 297  |
| 5/49  |   |   | 100%<br>[MH] <sup>+</sup> = 283 |
| 5/51  |  |  | 95%<br>[MH] <sup>+</sup> = 307  |
| 5/53  |  |  | 100%<br>[MH] <sup>+</sup> = 297 |
| 5/59  |  |  | 84%<br>[MH] <sup>+</sup> = 331  |
| 5/60  |  |  | 96%<br>[MH] <sup>+</sup> = 355  |

| Ex. # | amine                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 5/63  |    |    | 7%<br>[MH] <sup>+</sup> = 281   |
| 5/64  |   |   | 28%<br>[MH] <sup>+</sup> = 394  |
| 5/69  |  |  | n.d.<br>[MH] <sup>+</sup> = 406 |
| 5/71  |  |  | 97%<br>[MH] <sup>+</sup> = 351  |
| 5/72  |  |  | 96%<br>[MH] <sup>+</sup> = 337  |
| 5/73  |  |  | 35%<br>[MH] <sup>+</sup> = 295  |

| Ex. # | amine                                                                                                      | product                                                                               | yield                                                                                               |
|-------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| 5/74  |                           |    | 30%<br>(cryst from,<br>CH <sub>2</sub> Cl <sub>2</sub> -<br>cyclohexane)<br>[MH] <sup>+</sup> = 311 |
| 5/76  |                          |   | 38%<br>[MH] <sup>+</sup> = 365                                                                      |
| 5/87  |                         |  | 100%<br>[MH] <sup>+</sup> = 351                                                                     |
| 5/88  |                         |  | 69%<br>[MH] <sup>+</sup> = 351                                                                      |
| 5/89  |                         |  | n.d.<br>[MH] <sup>+</sup> = 323                                                                     |
| 5/91  |                         |  | 100%<br>[MH] <sup>+</sup> = 351                                                                     |
| 5/95  | <br>Synthesis US6387912 |  | 35%<br>[MH] <sup>+</sup> = 400                                                                      |

| Ex. # | amine                                                                             | product                                                                             | yield                            |
|-------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------|
| 5/106 |  |  | n.d.<br>[MH] <sup>+</sup> = n.d. |

### Preparative Example 9



#### Step A

5           A solution of the commercially available 4-Isopropyl-phenylamine (1.35 g) and *N*-Bromosuccinimide (2.0 g) in benzene (20 mL) was stirred at room temperature. After 12h, the precipitated solid was filtered off, and the filtrate was concentrated and purified by chromatography (silica, hexane/EtOAc) to afford the title compound (1.8 g, 89%). [MH]<sup>+</sup> = 214.

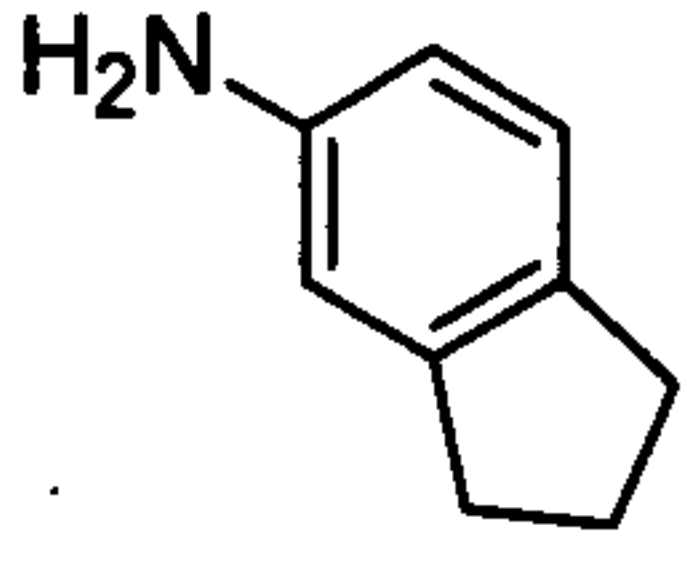
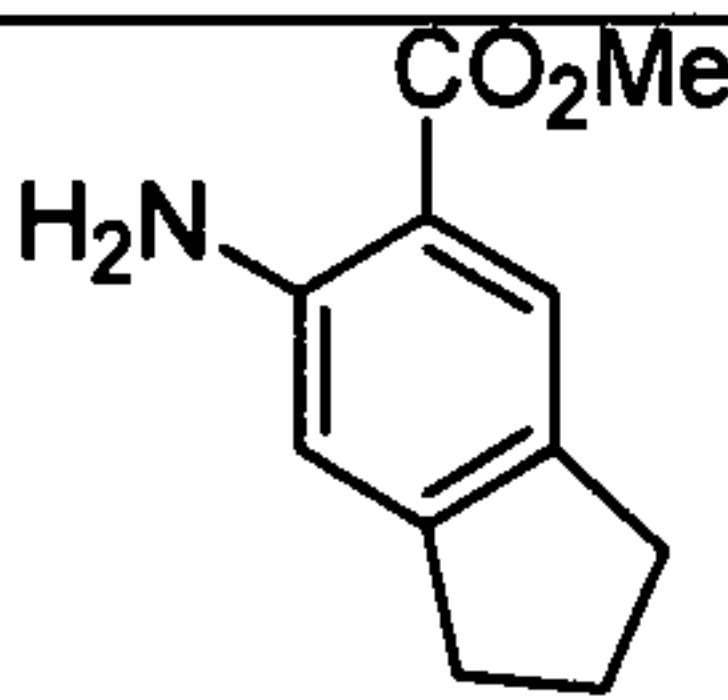
#### 10   Step B

          A solution of the intermediate from Step A above (800 mg), xantphos (36 mg), Pd<sub>2</sub>(dba)<sub>3</sub> (20 mg), triethylamine (1.4 mL) in methanol (10 mL) was heated in autoclave under carbon monoxide at 50 *psi* at 100°C for 6h. The solution was concentrated and purified by chromatography (silica, hexane/EtOAc) to  
15   afford the title compound (360 mg, 49%). [MH]<sup>+</sup> = 194.

### Preparative Example 10/4

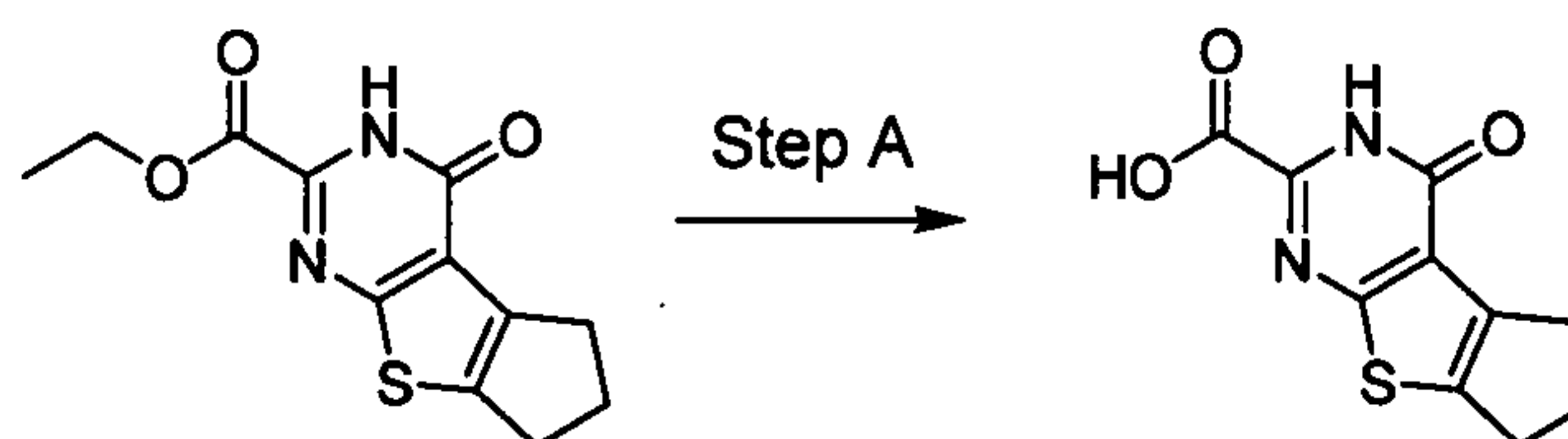
Following similar procedures as described in the Preparative Example 9 except using the aniline derivative indicated in Table I.4 below, the following compounds were prepared.

**Table I.4**

| Ex. # | aniline                                                                            | product                                                                              | yield                          |
|-------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------|
| 10/4  |  |  | 10%<br>[MH] <sup>+</sup> = 259 |

5

**Preparative Example 11**



**Step A**

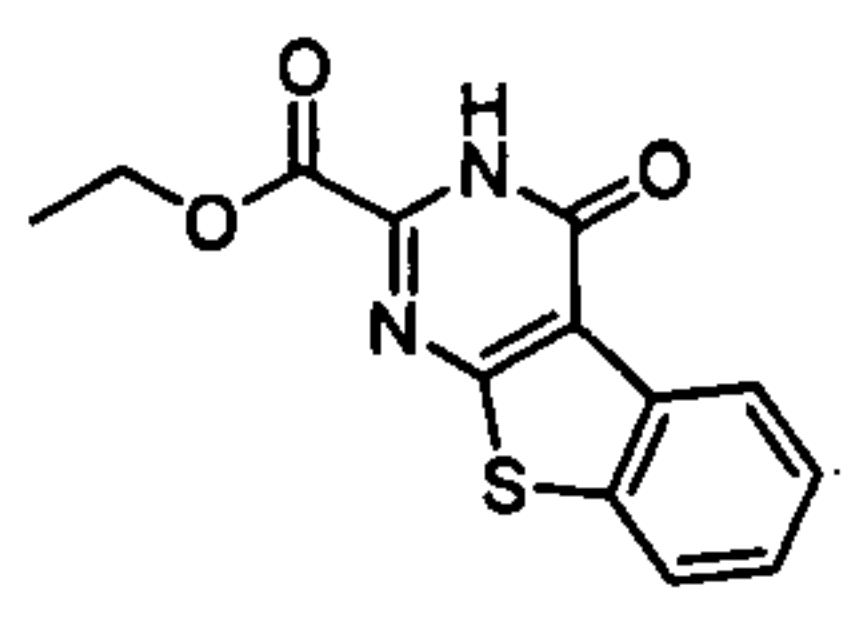
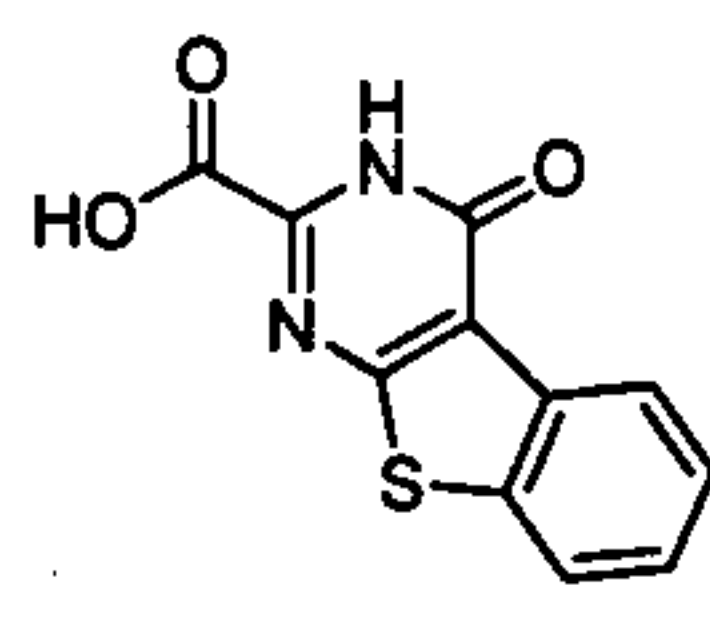
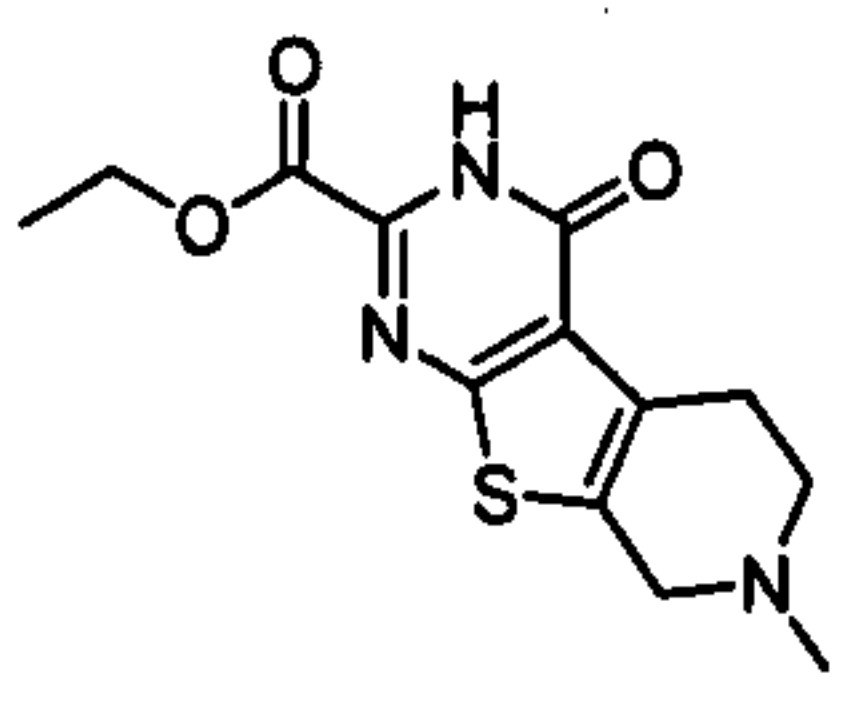
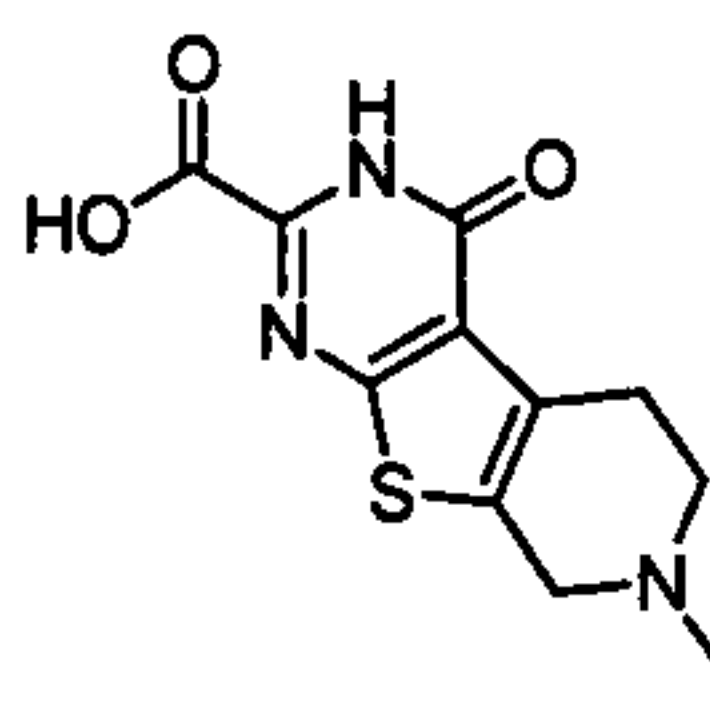
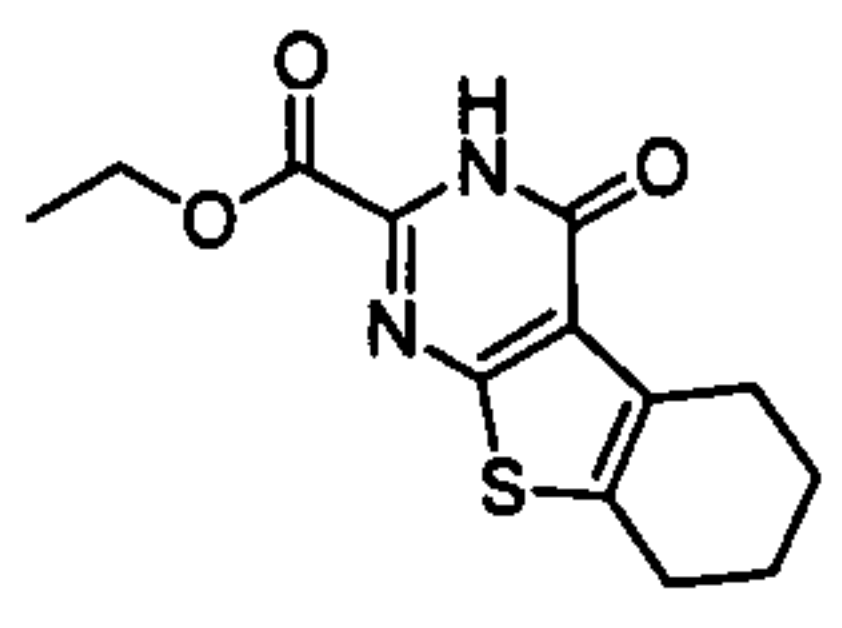
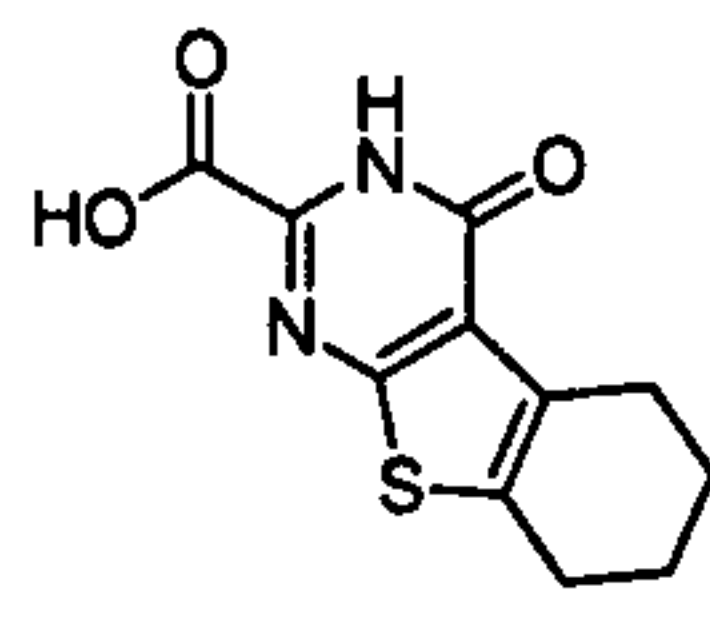
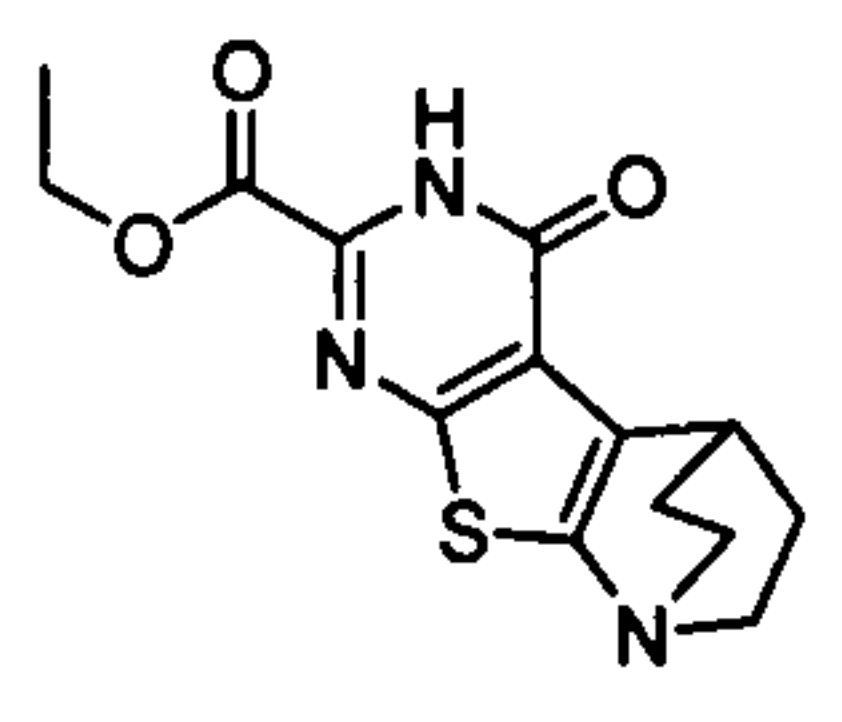
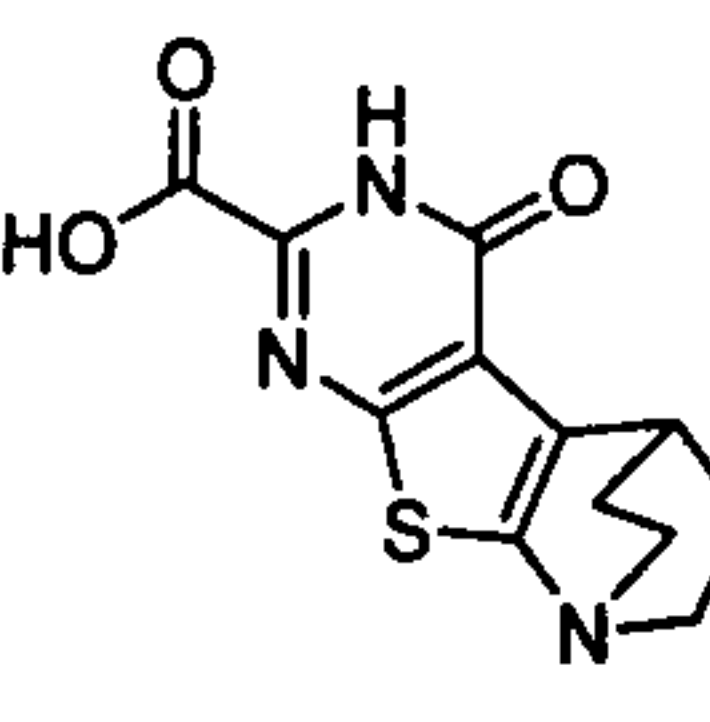
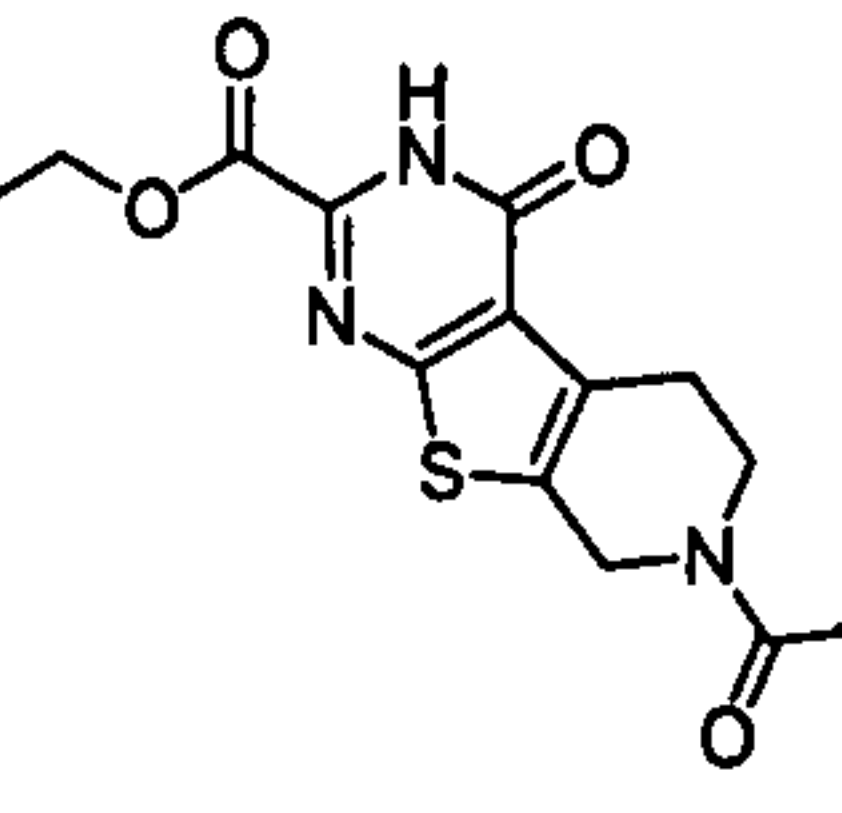
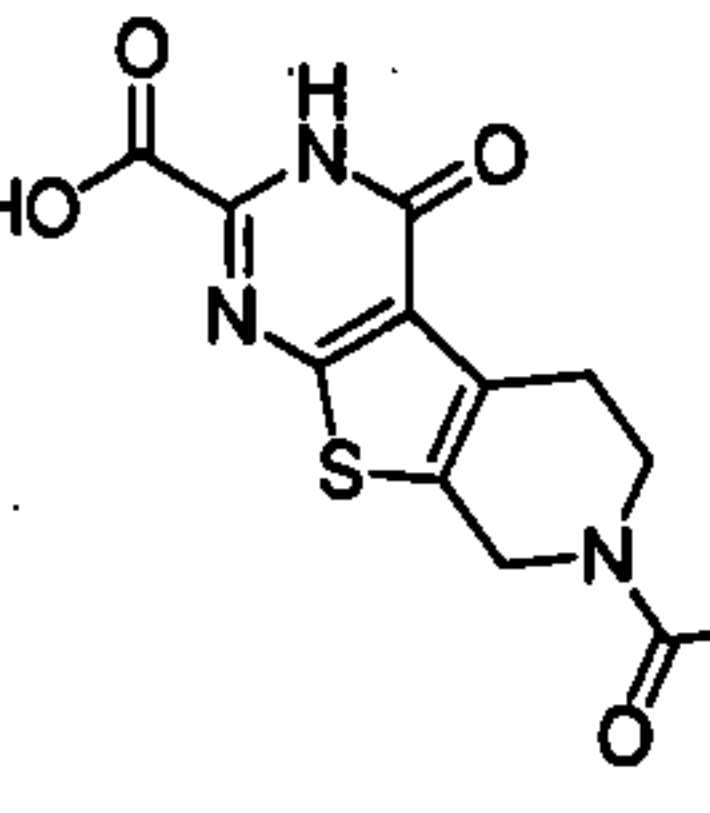
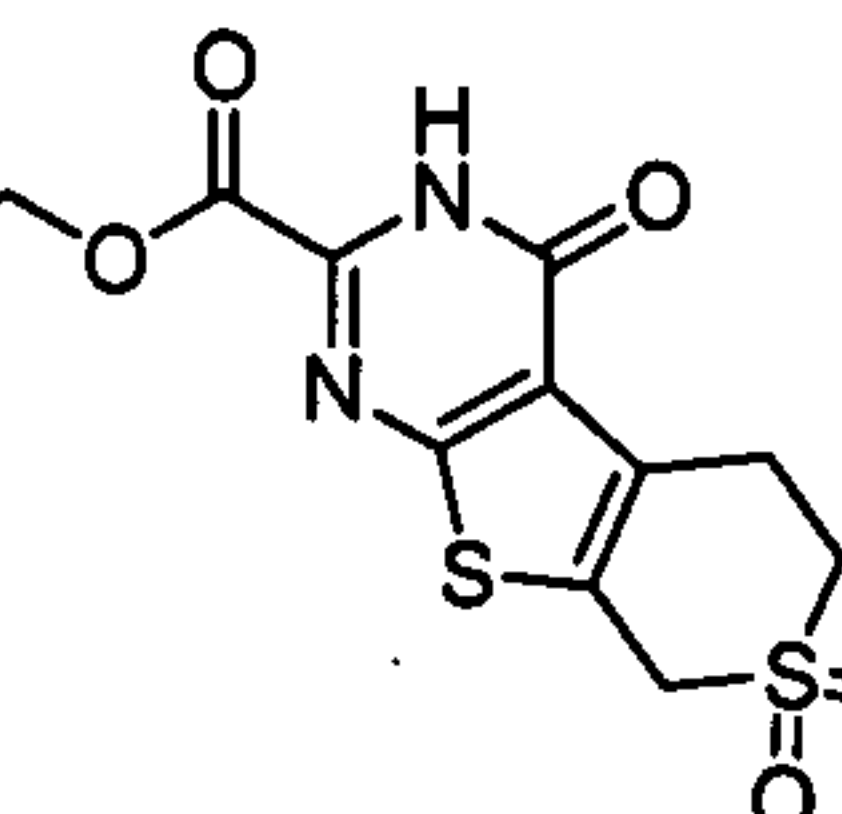
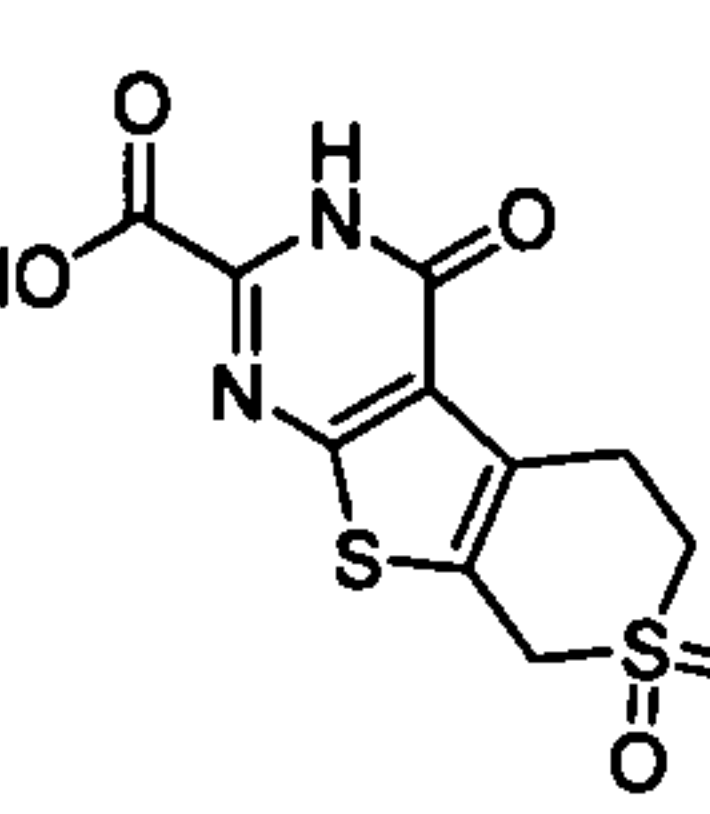
To a solution of the Preparative Example 4 above (503 mg) in THF (20 mL) was added 1M aqueous LiOH (5 mL). The resulting mixture was stirred at room temperature for 1 h, concentrated and neutralized with 1M aqueous HCl. The residue was filtered off and used without further purification (420 mg, 87%). [MH]<sup>+</sup> = 237.

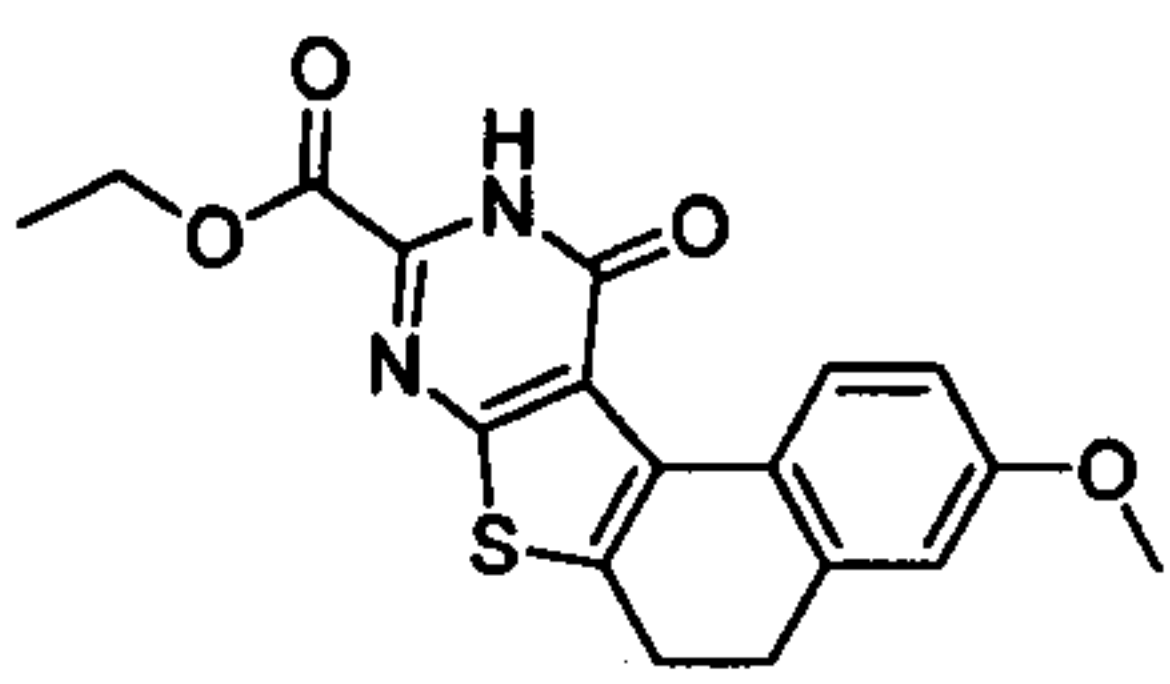
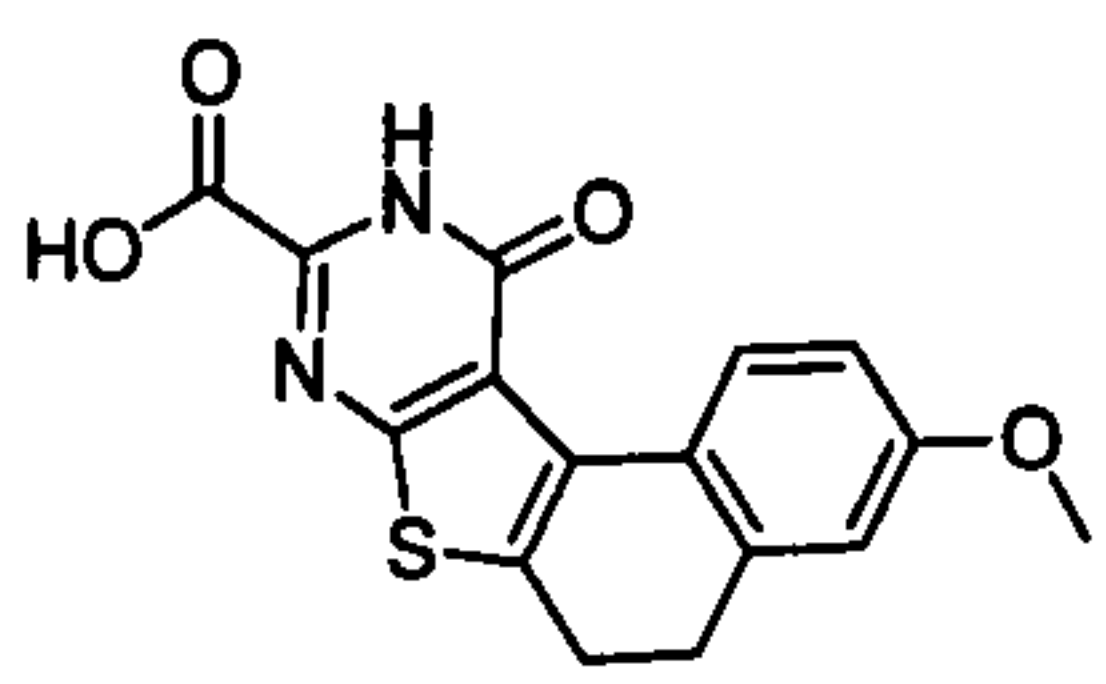
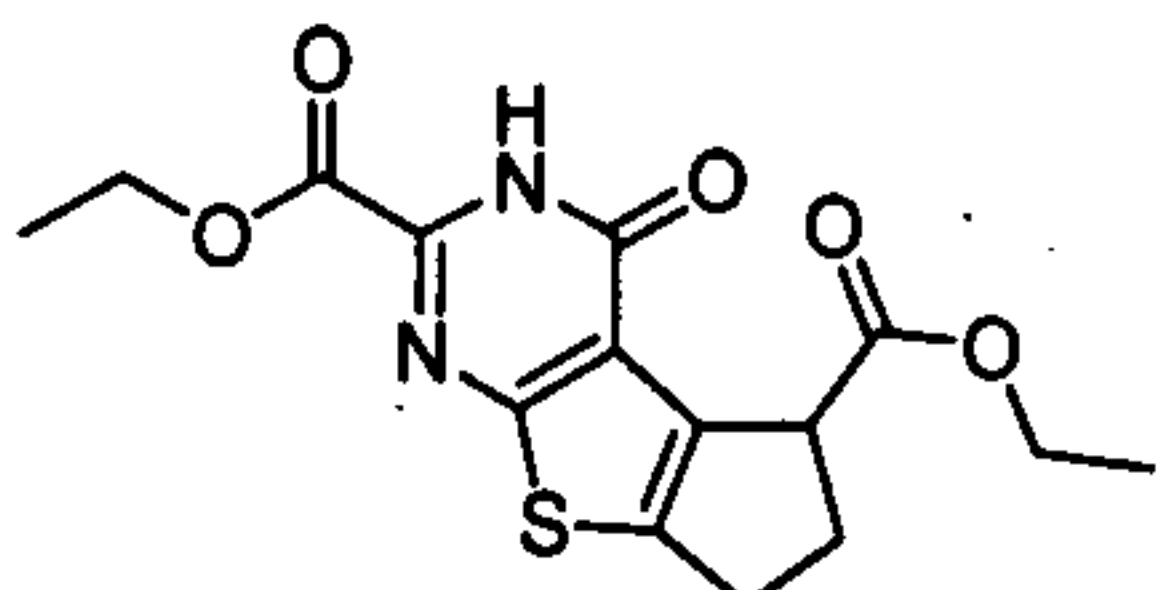
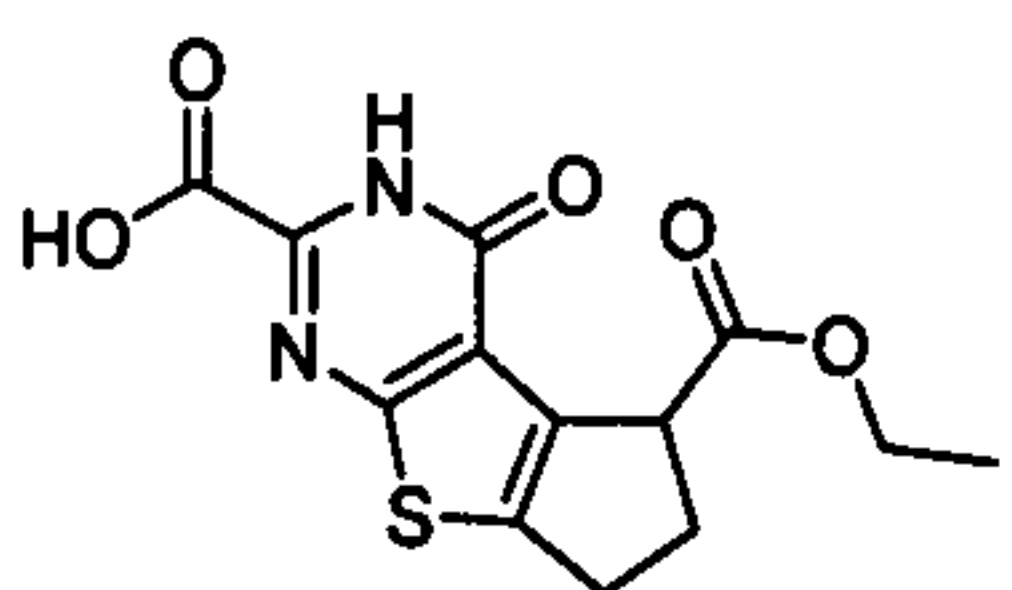
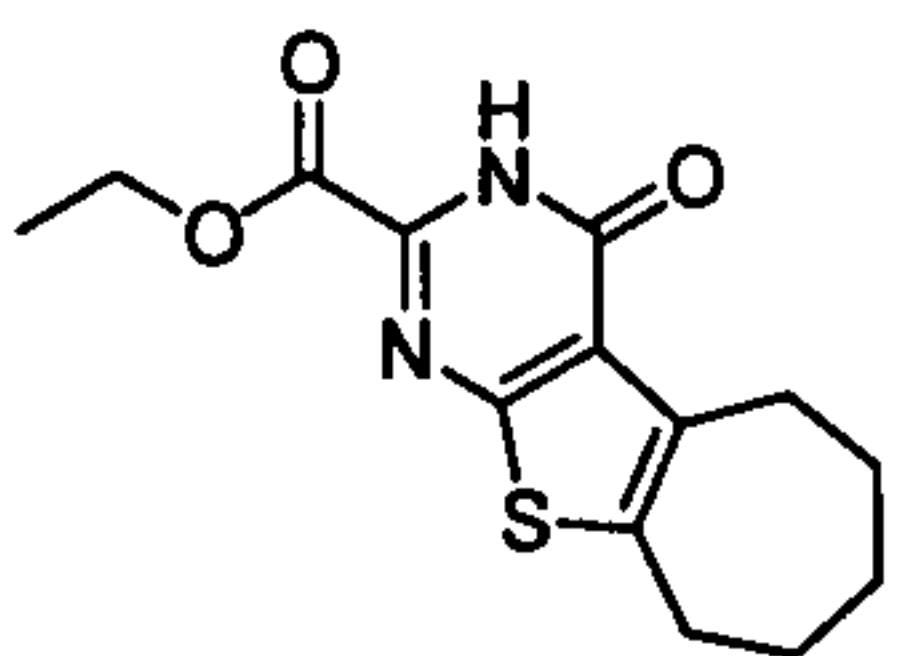
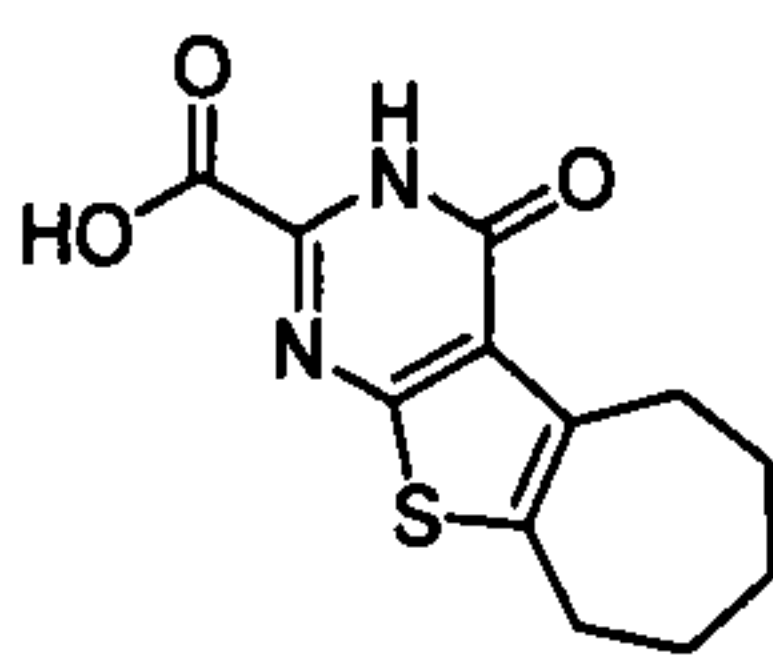
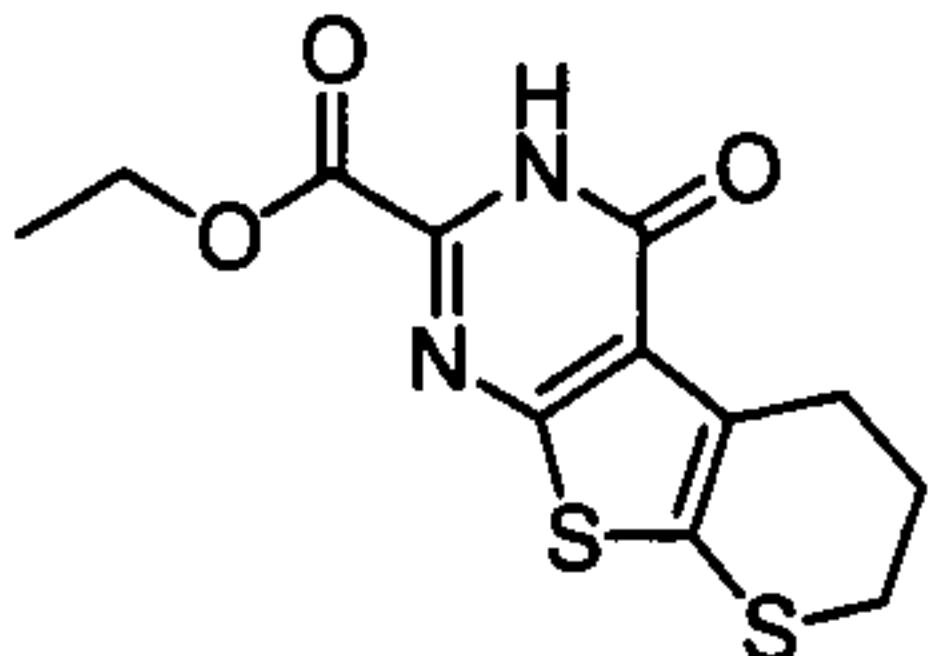
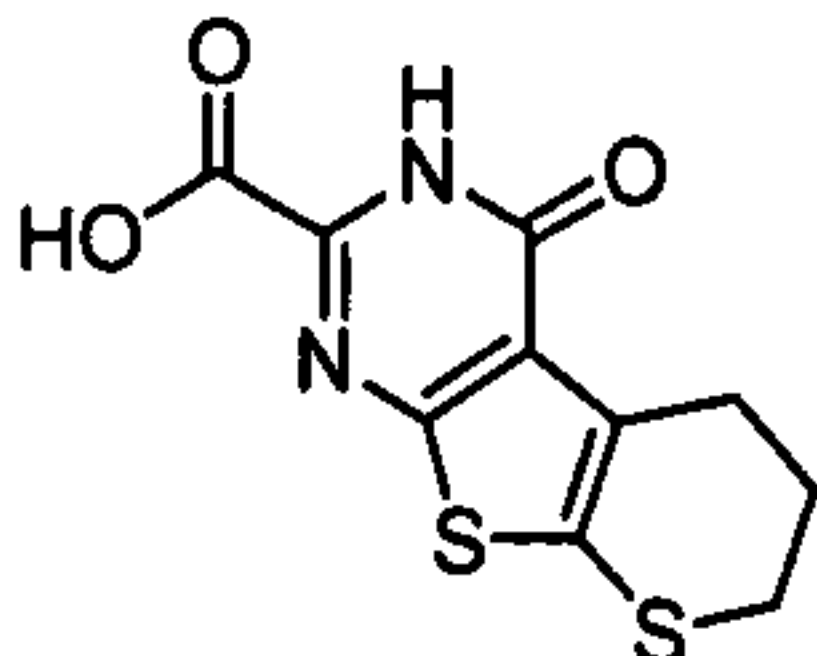
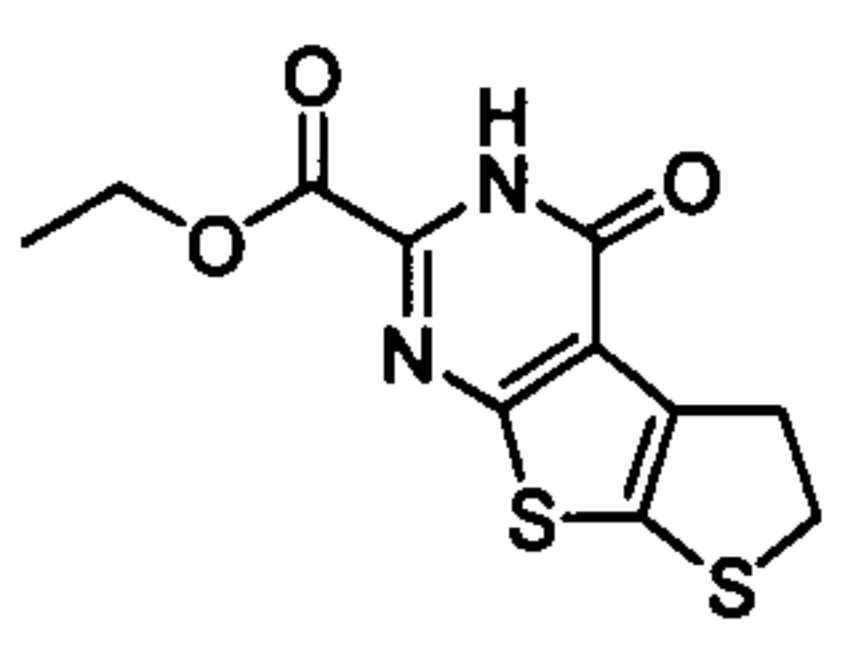
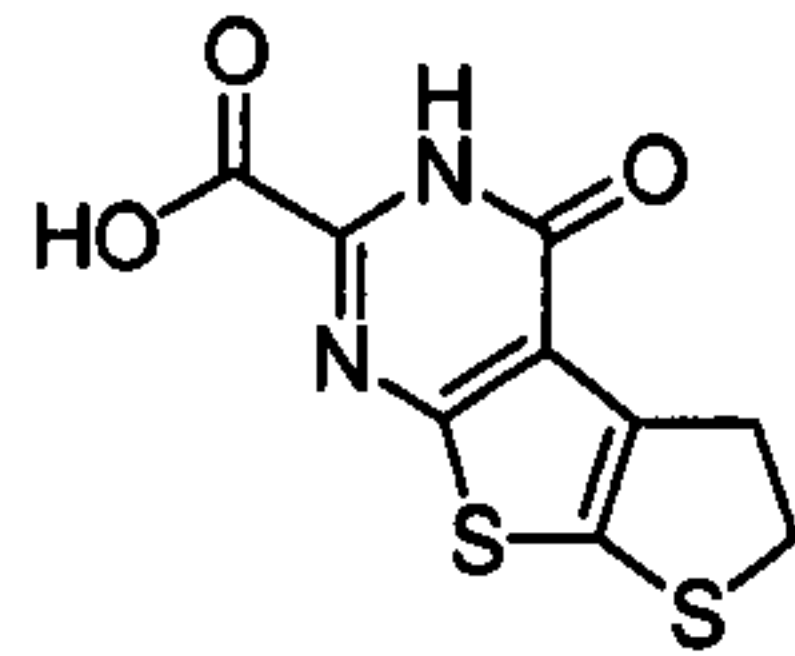
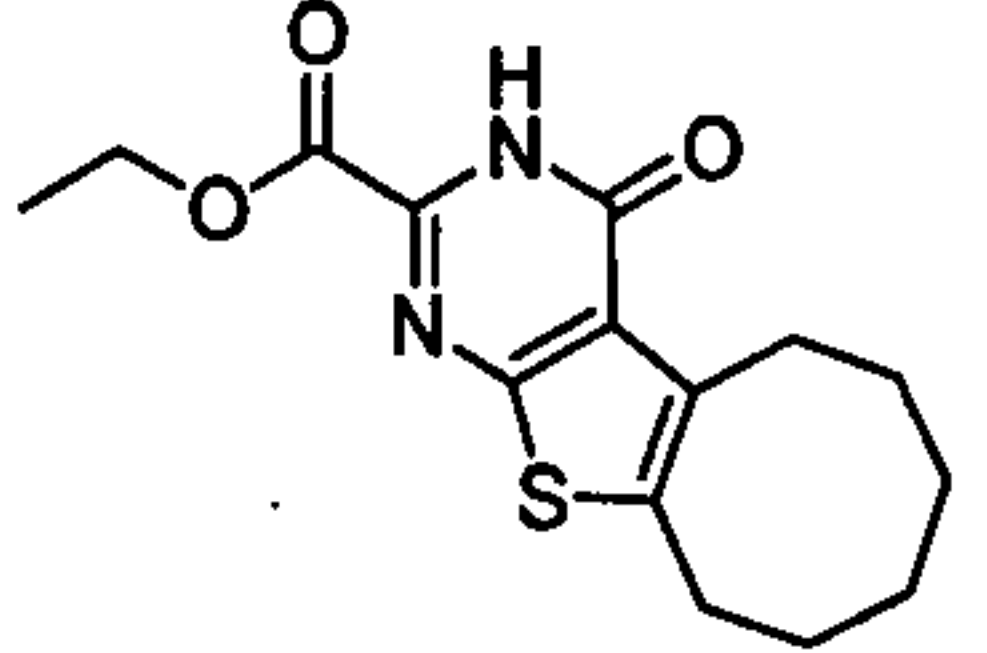
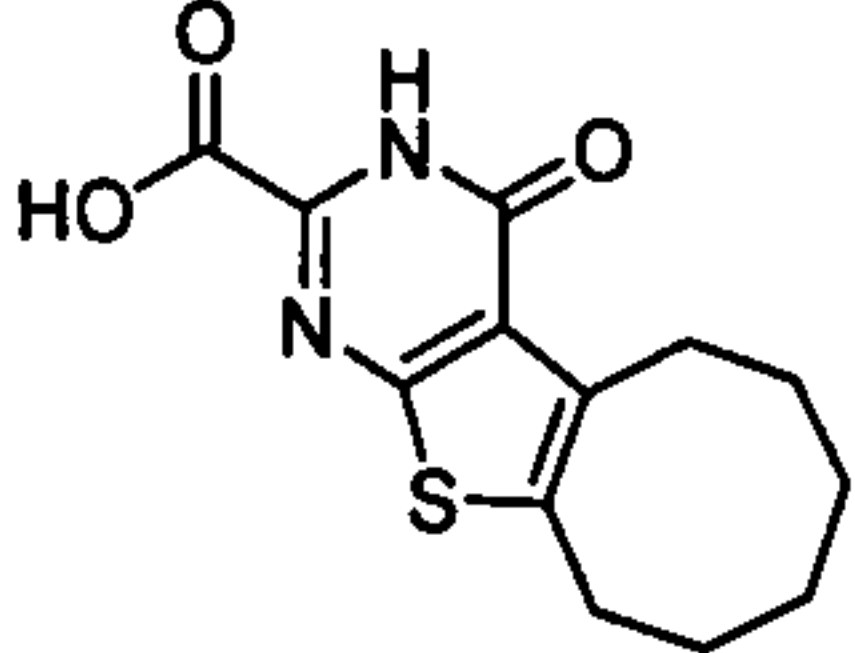
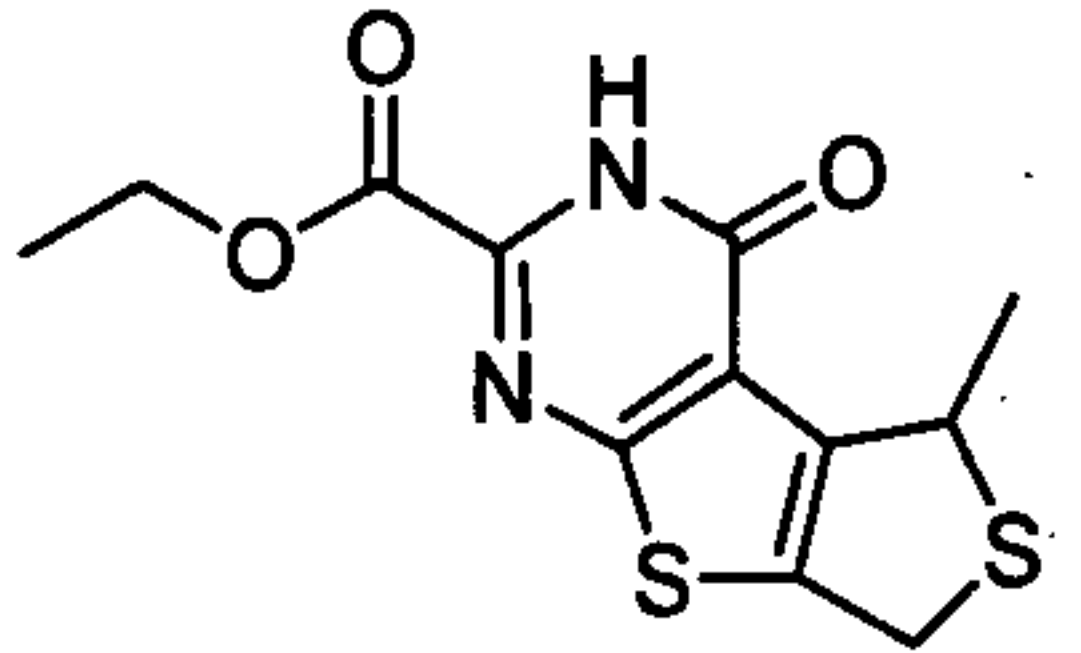
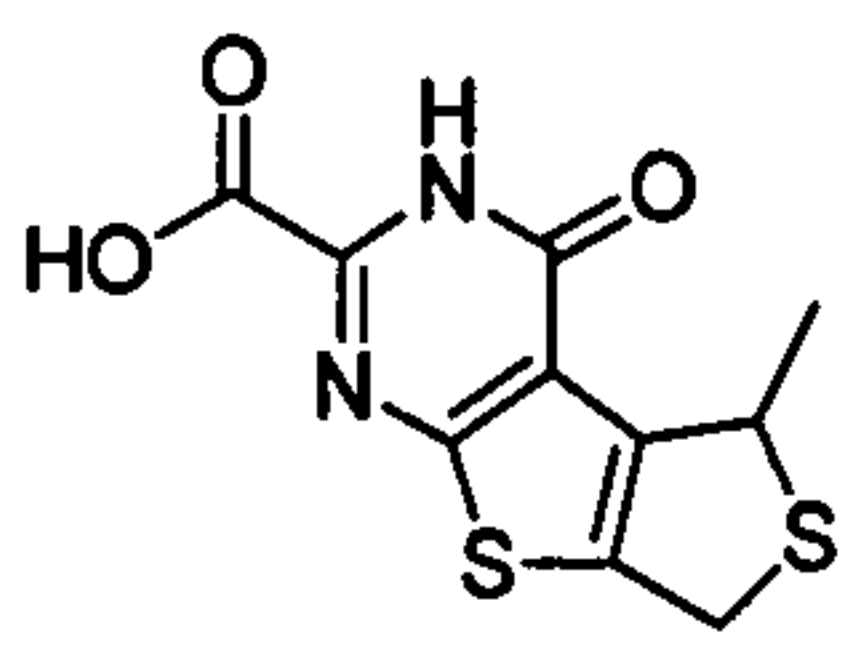
15

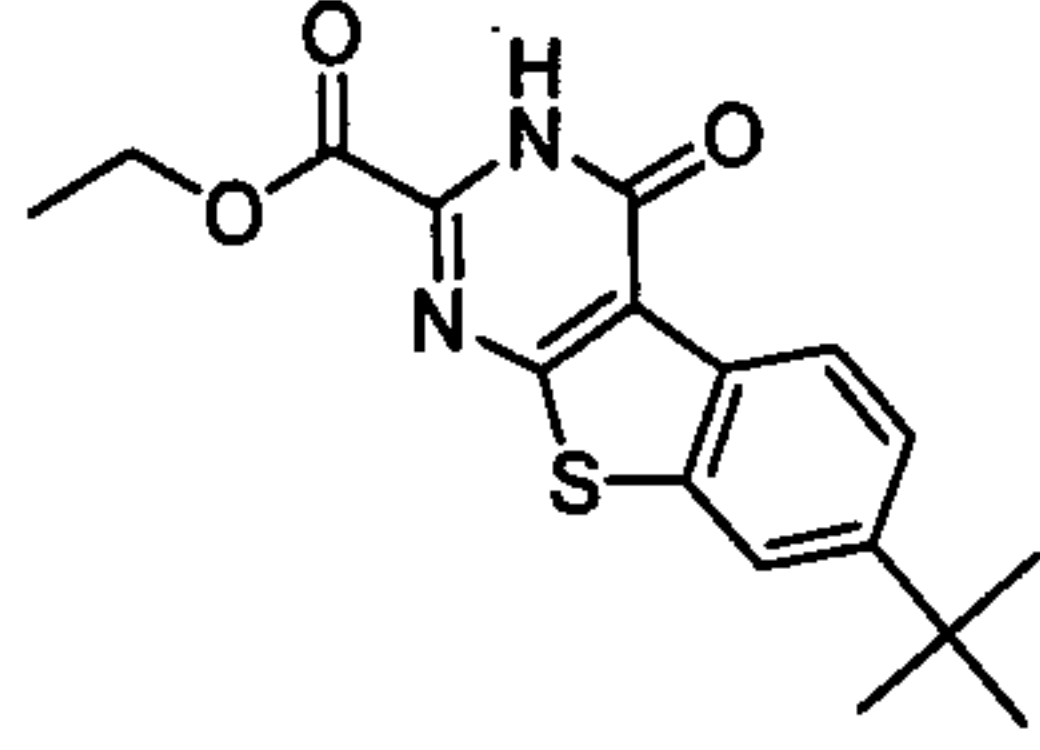
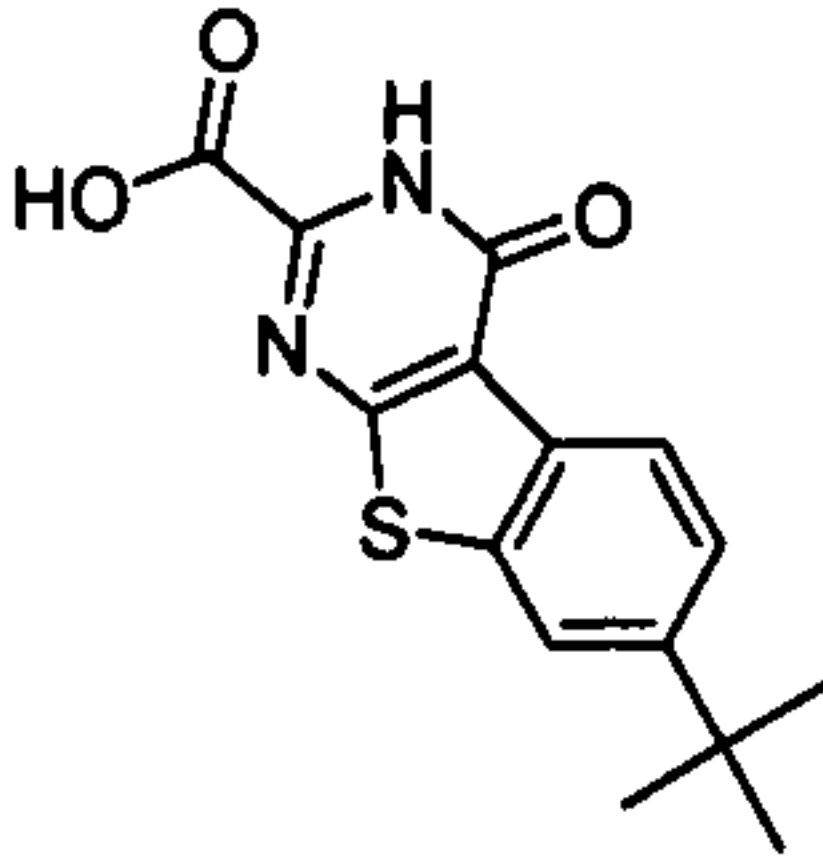
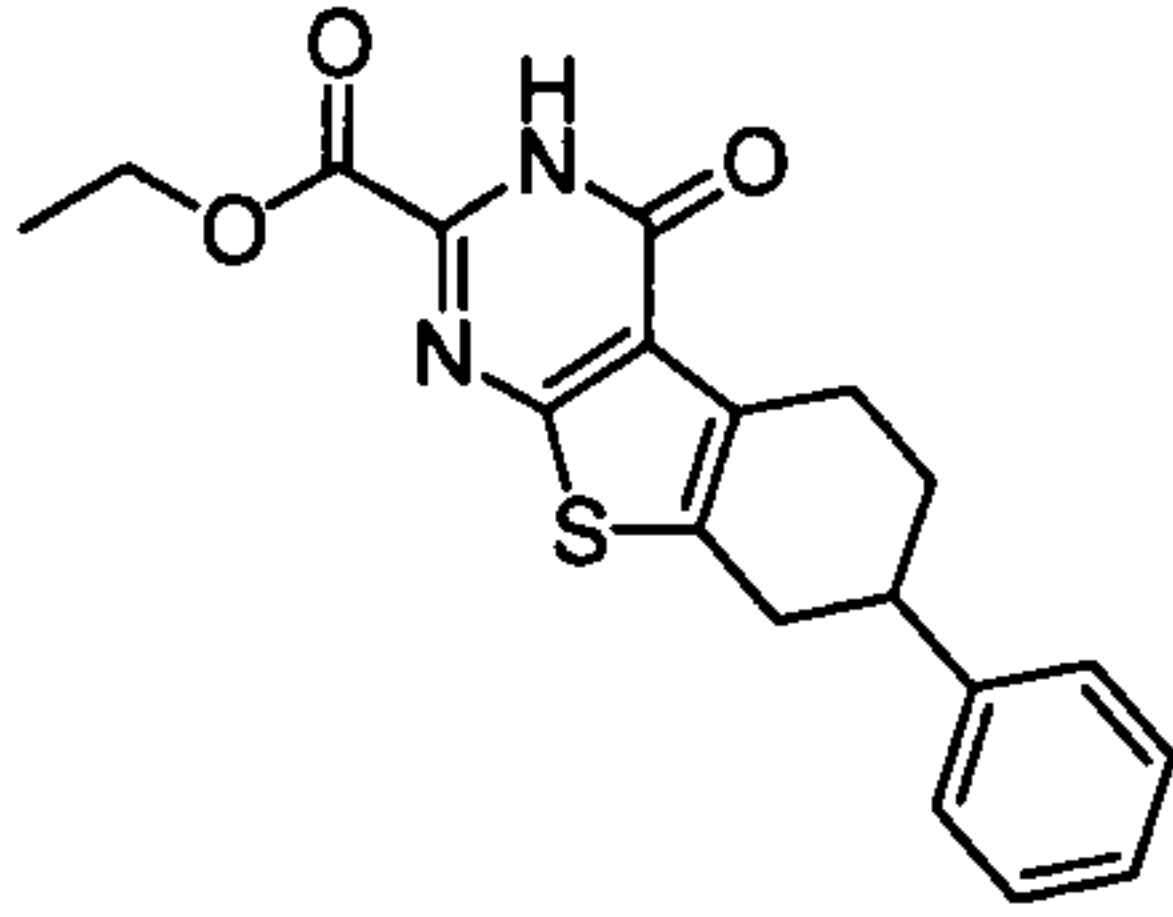
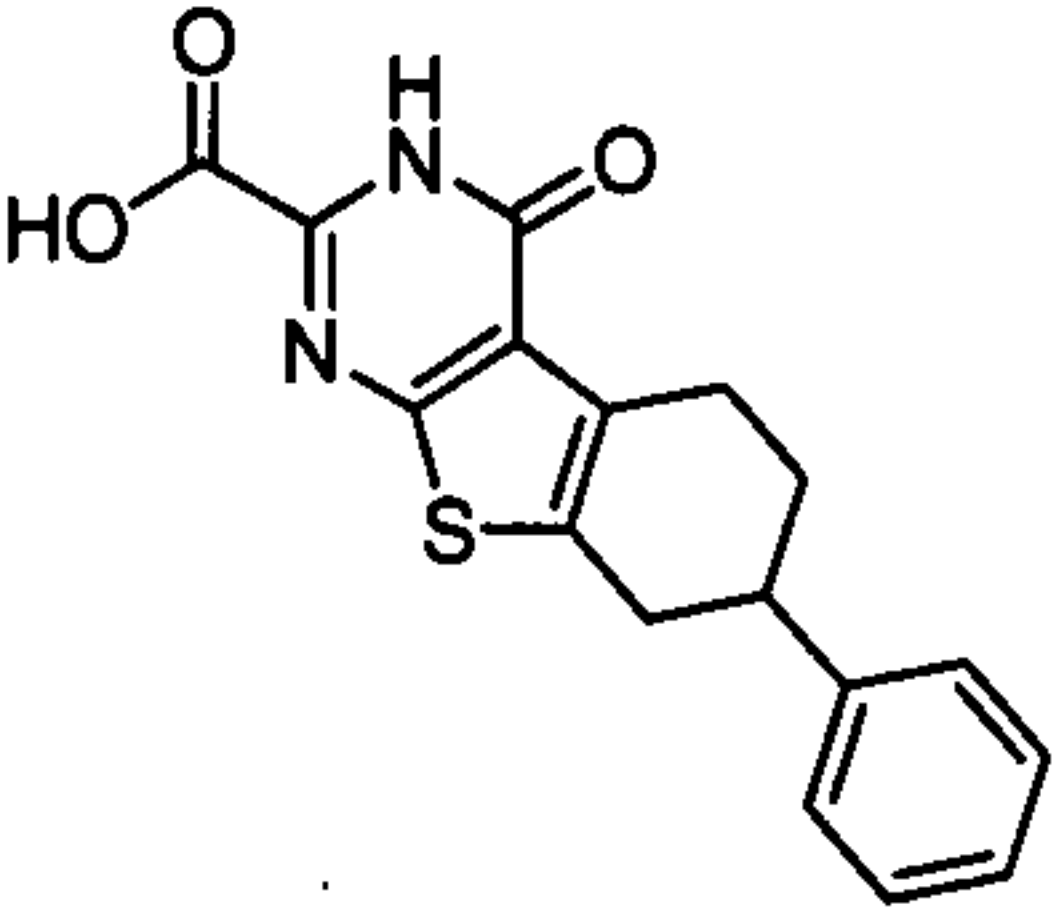
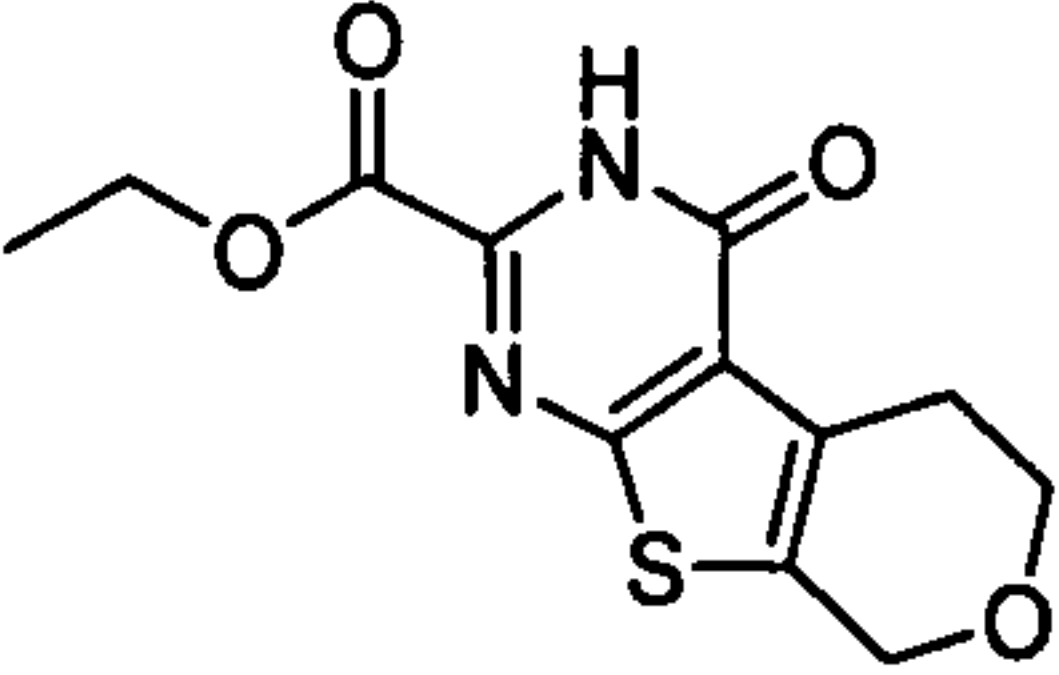
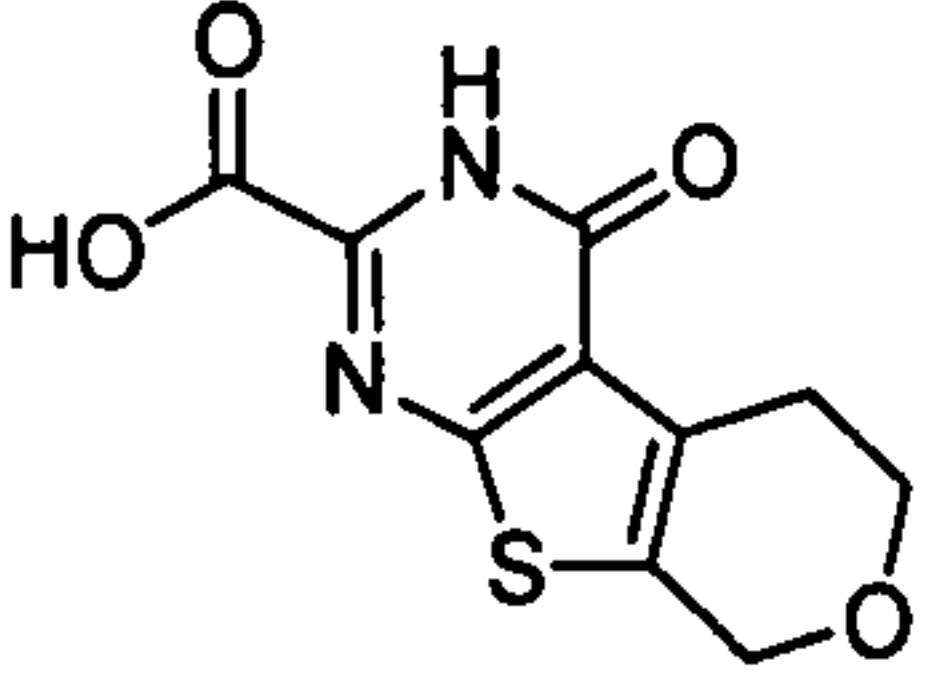
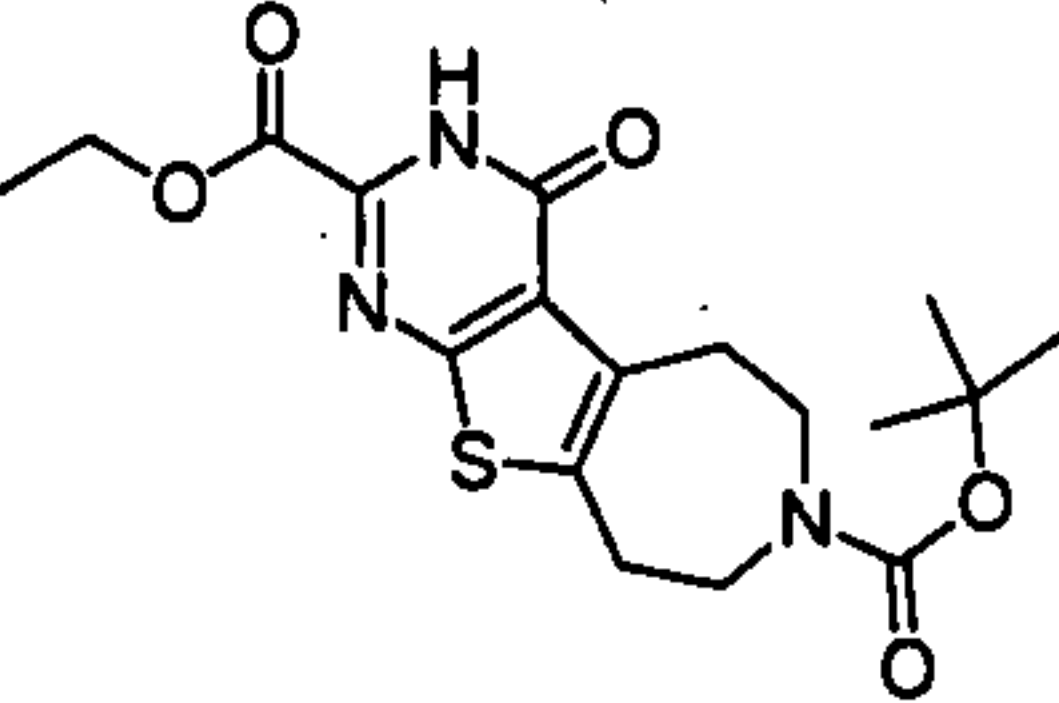
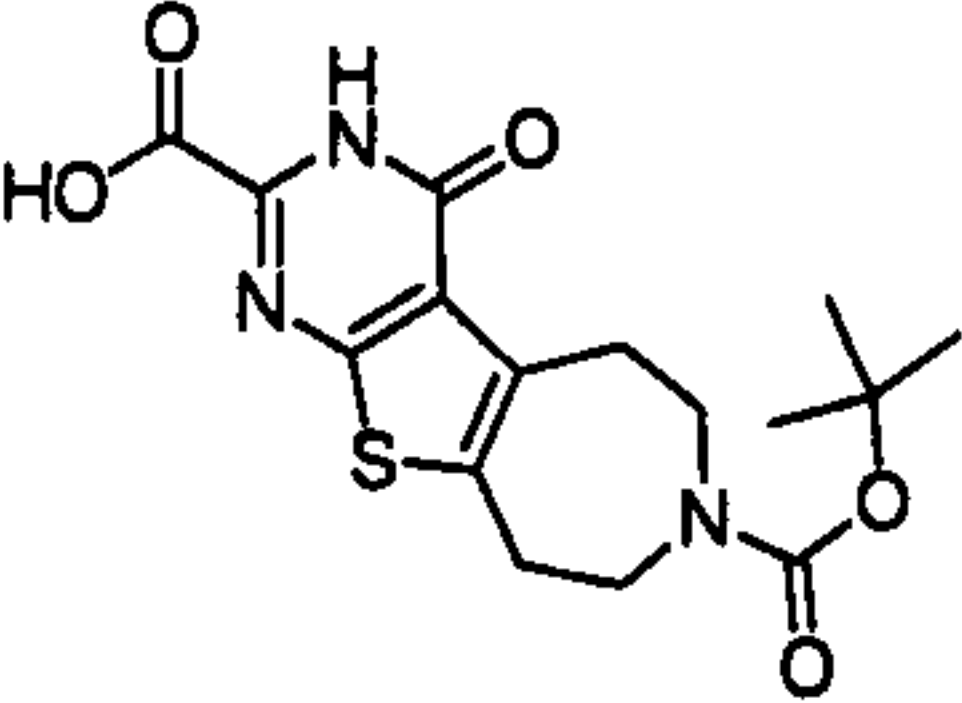
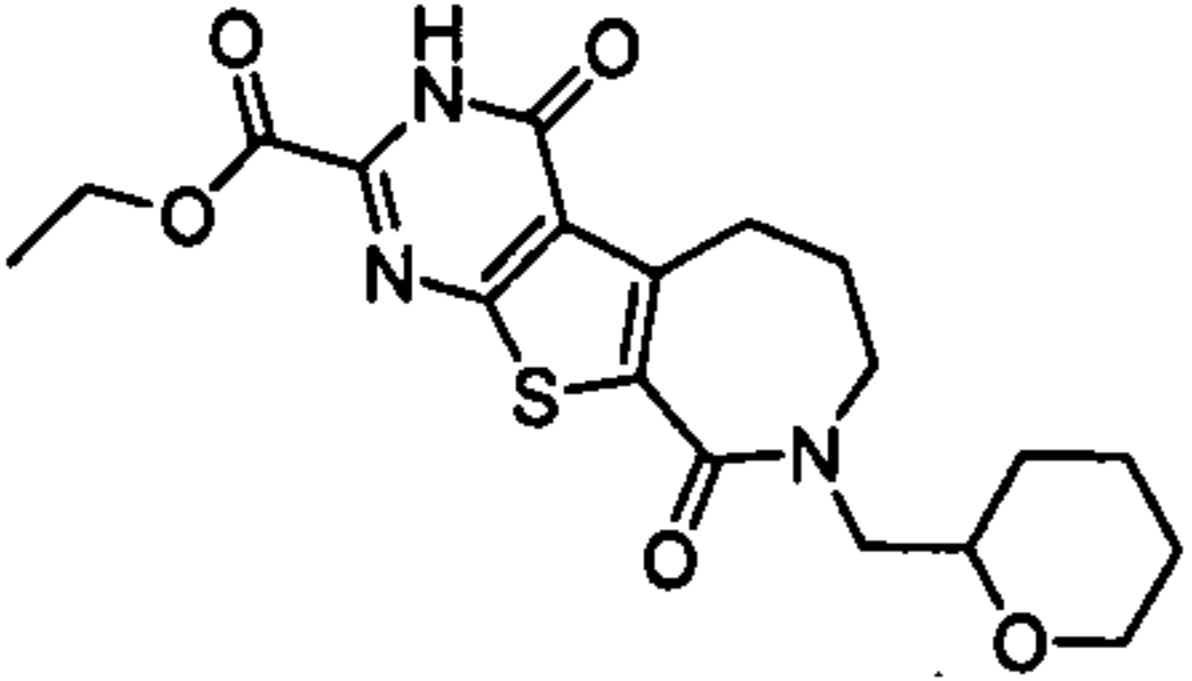
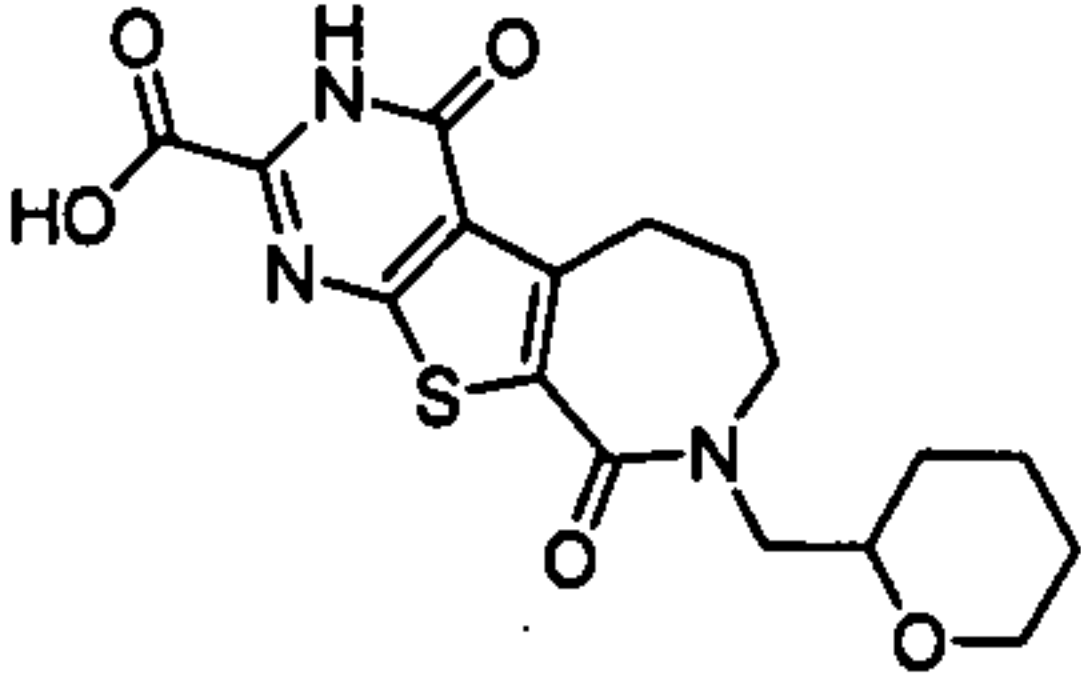
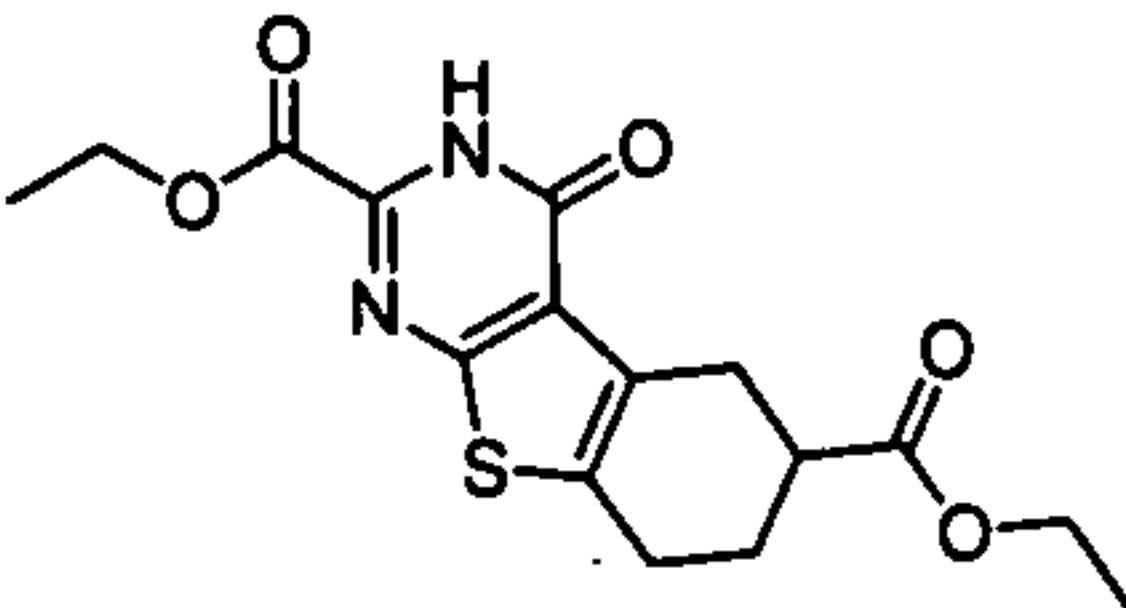
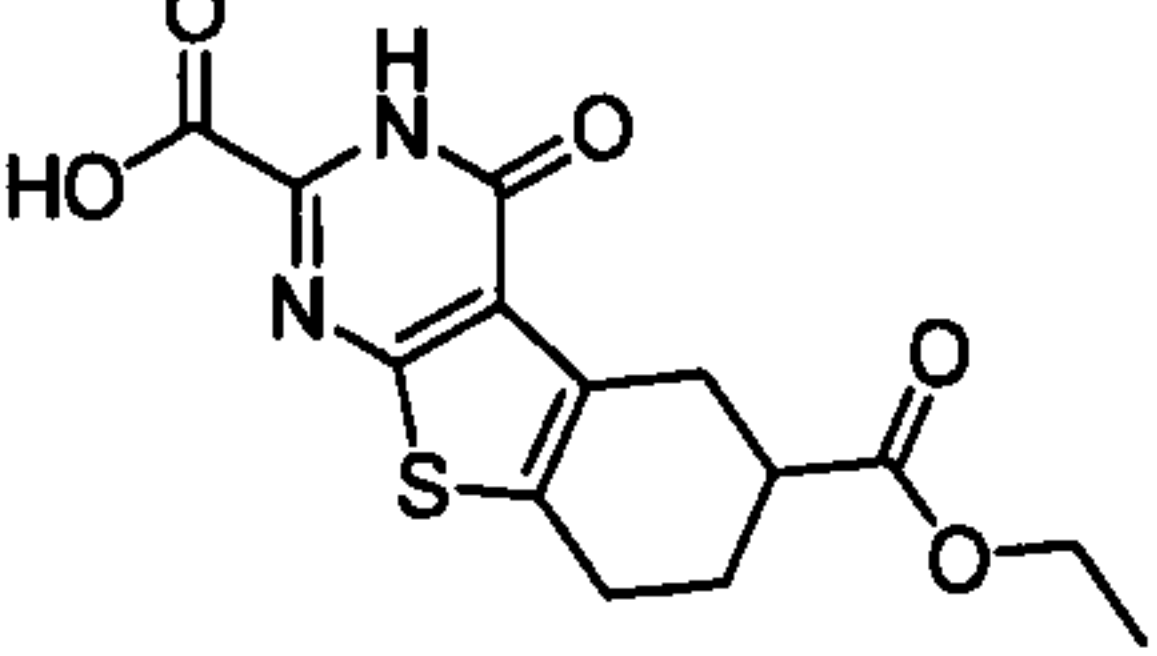
**Preparative Examples 12/9-12/104**

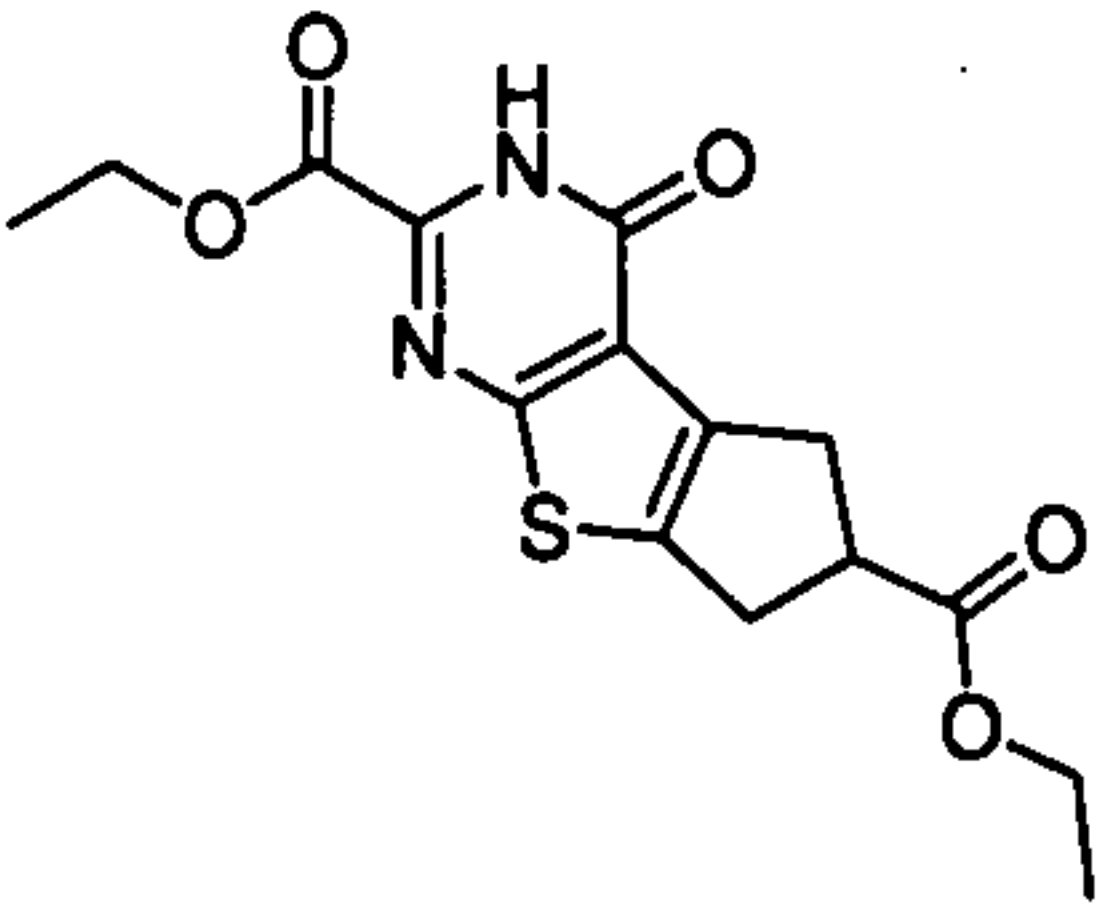
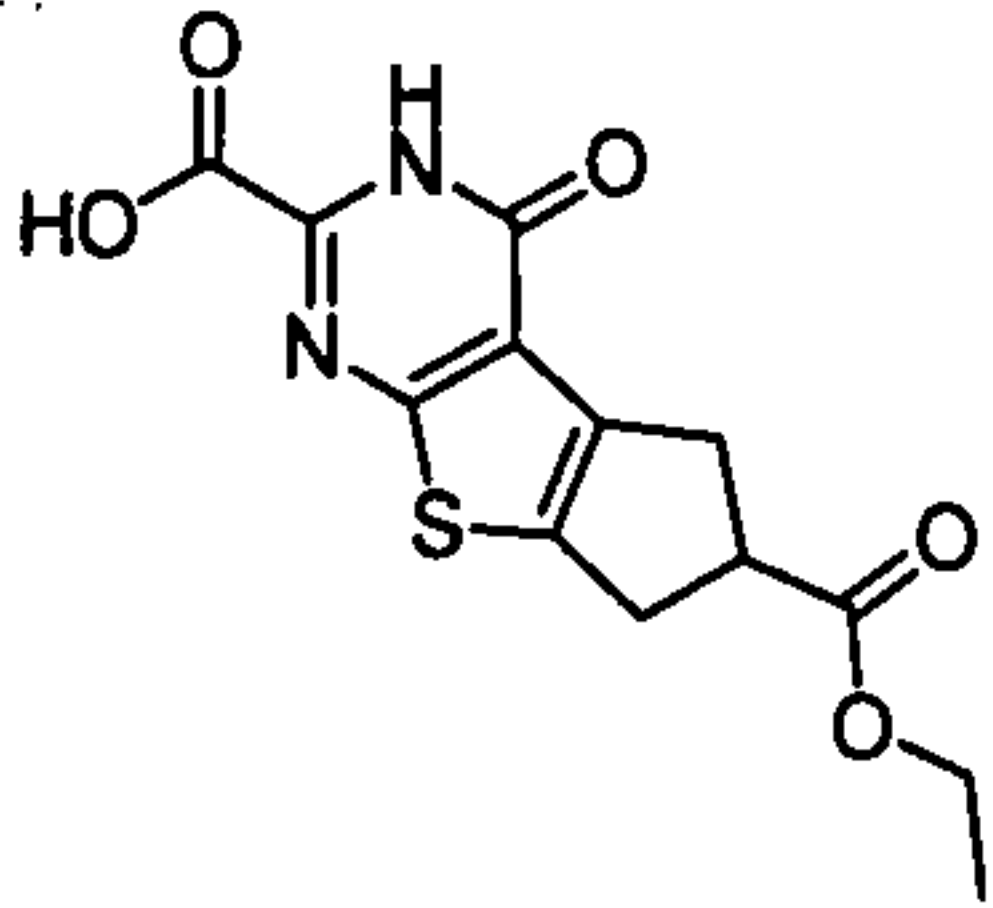
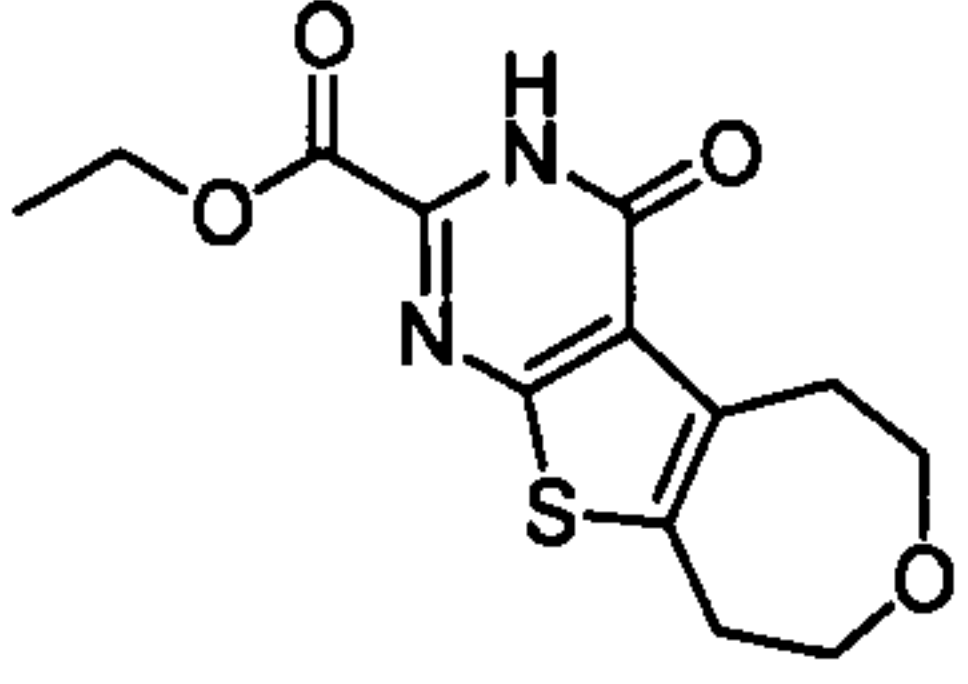
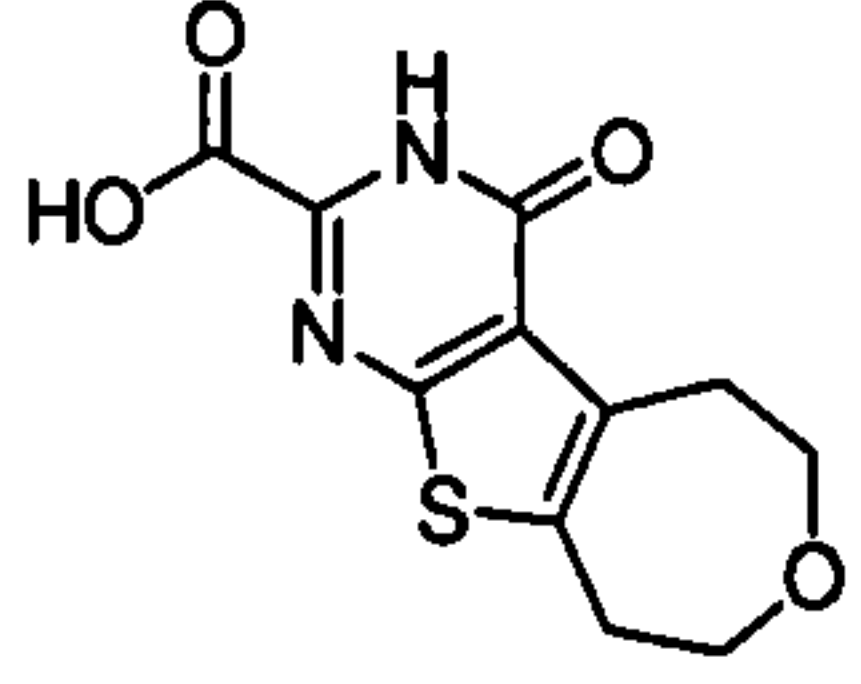
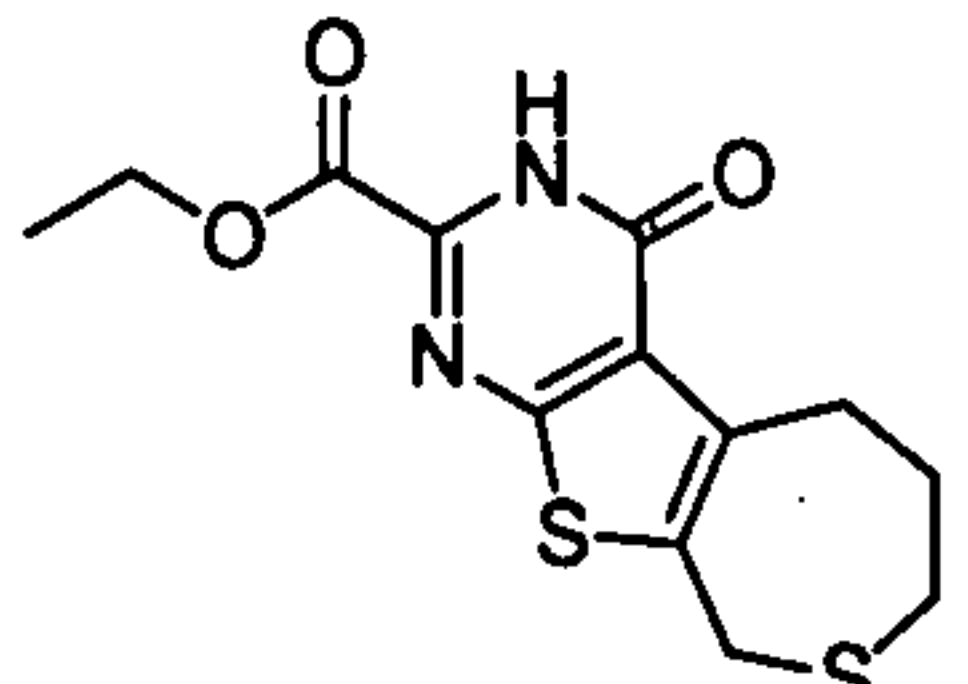
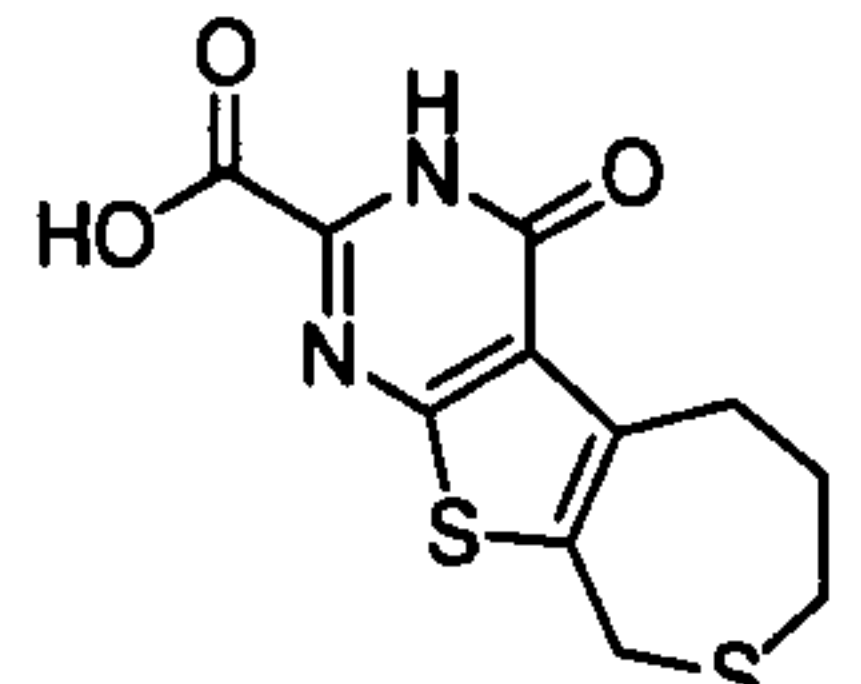
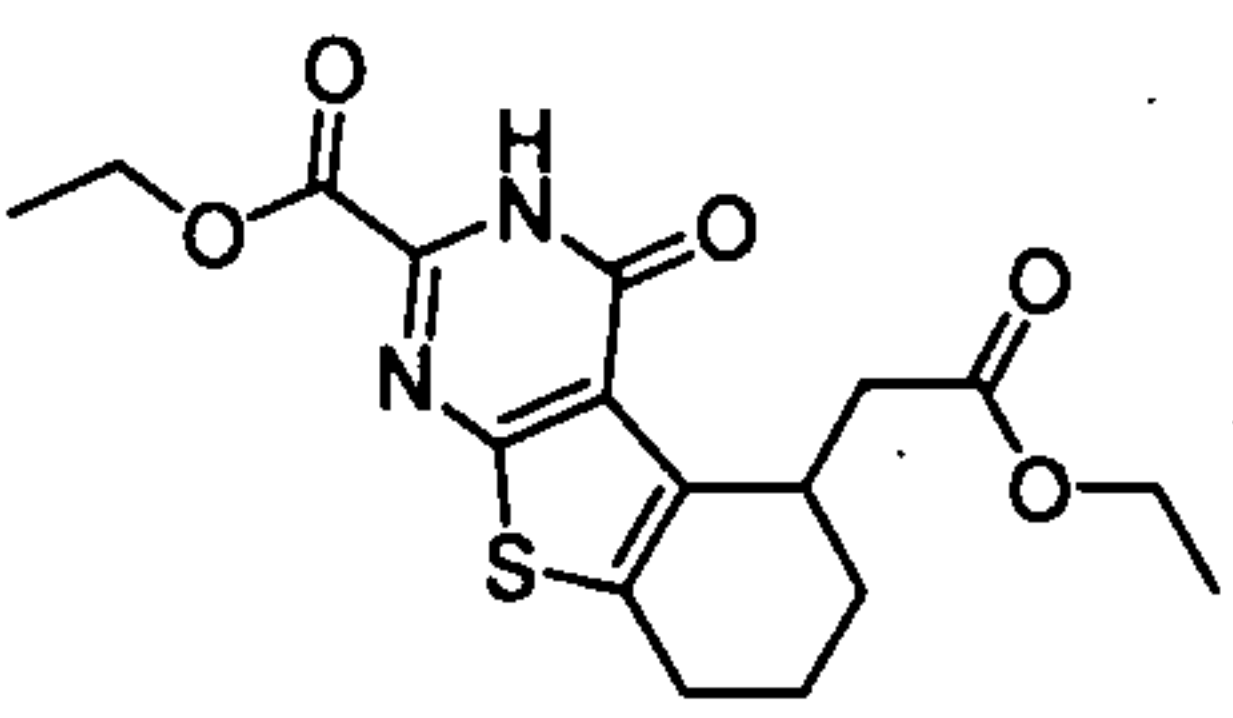
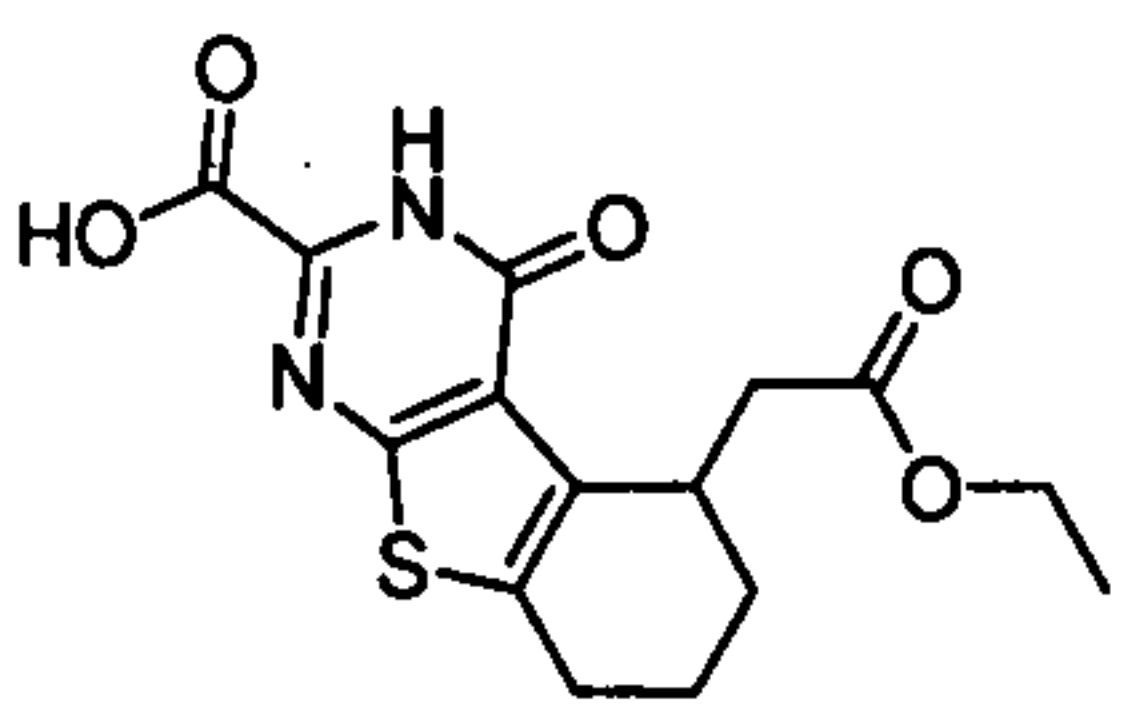
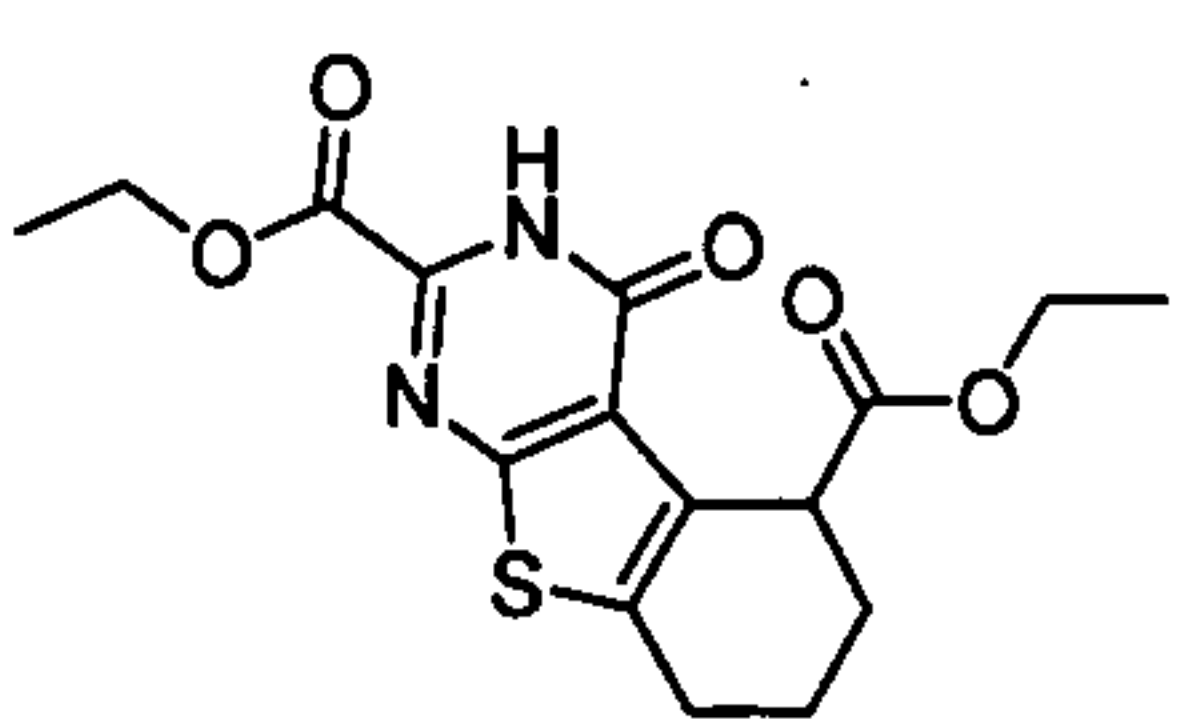
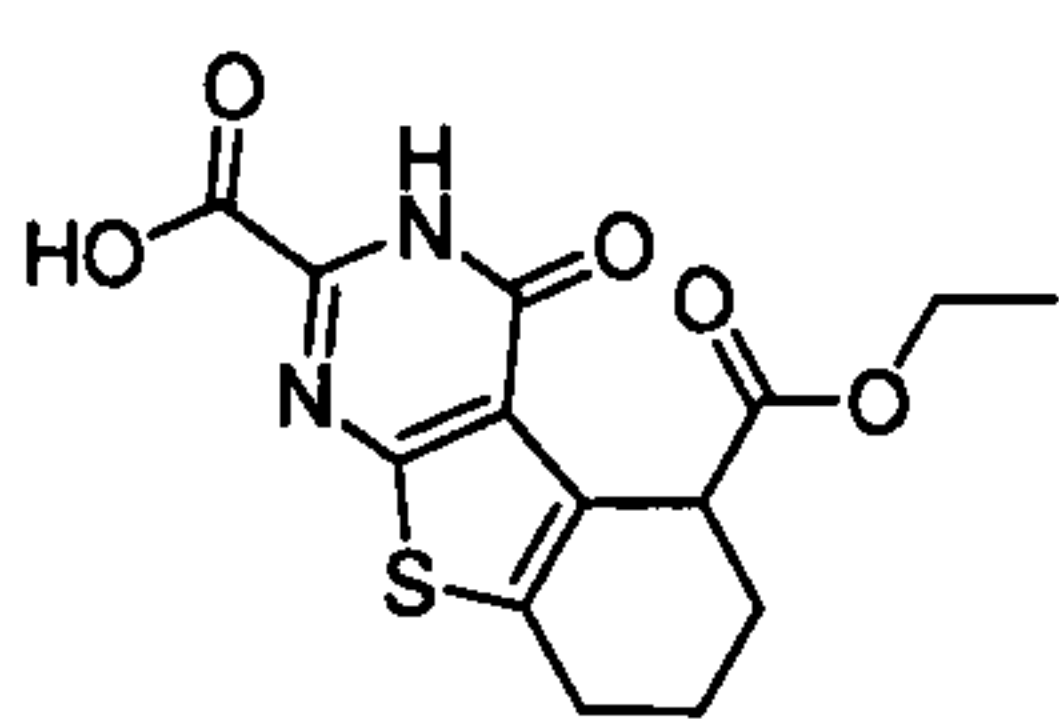
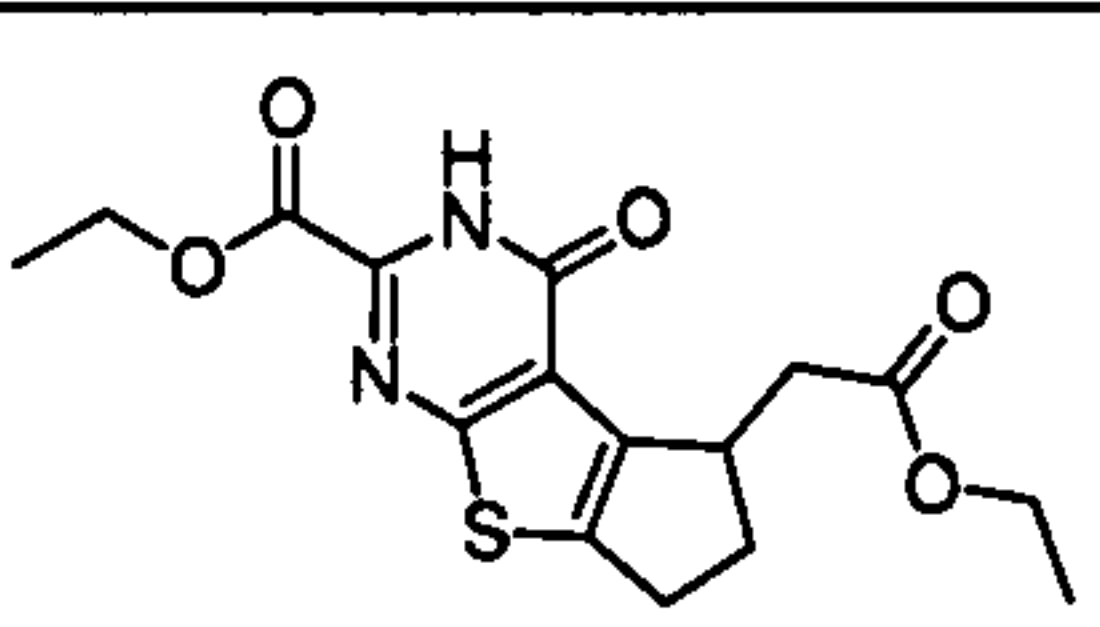
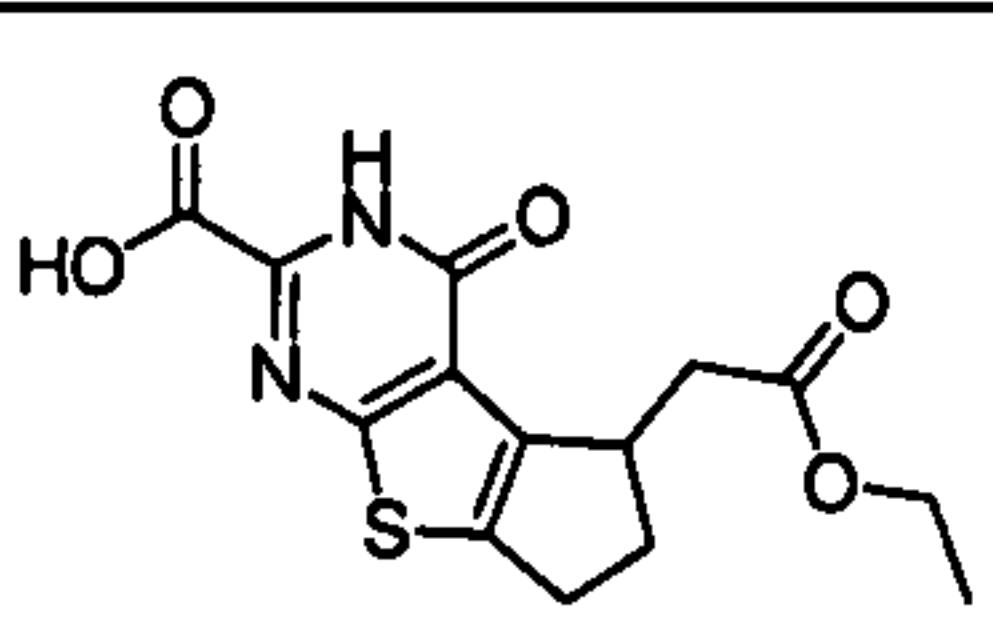
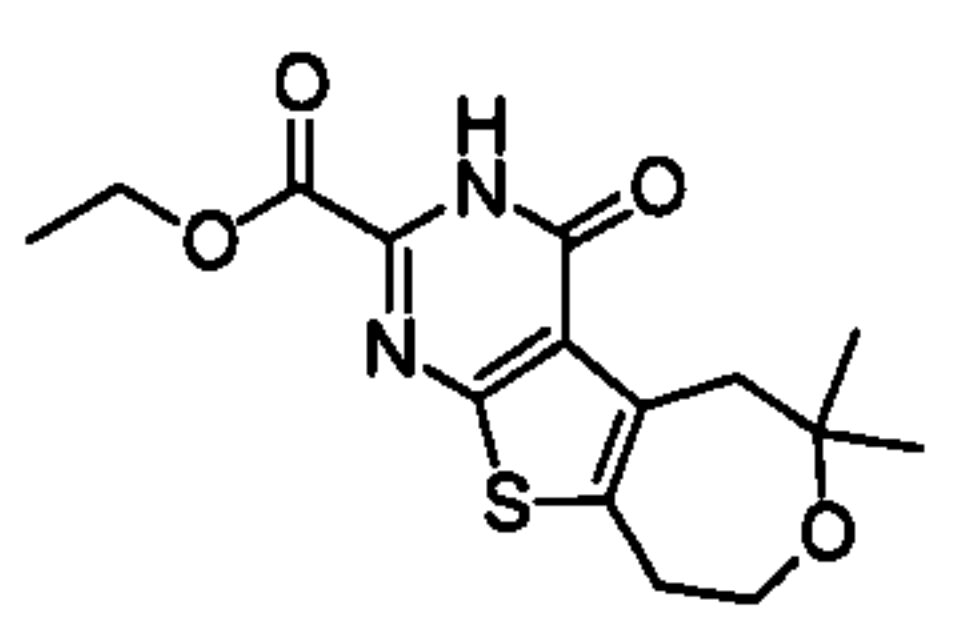
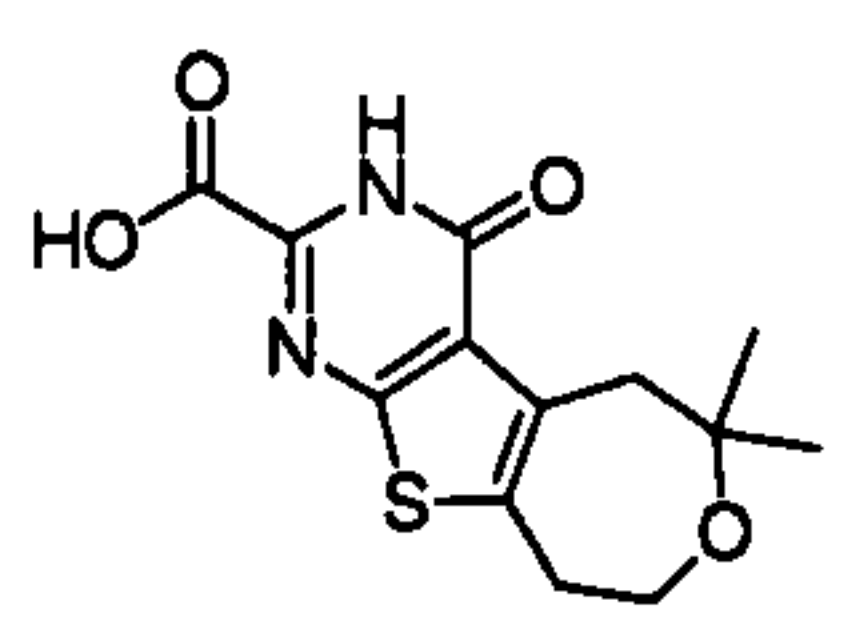
Following a similar procedure as described in the Preparative Example 11 except using the ester indicated in Table I.5 below, the following compounds were prepared.

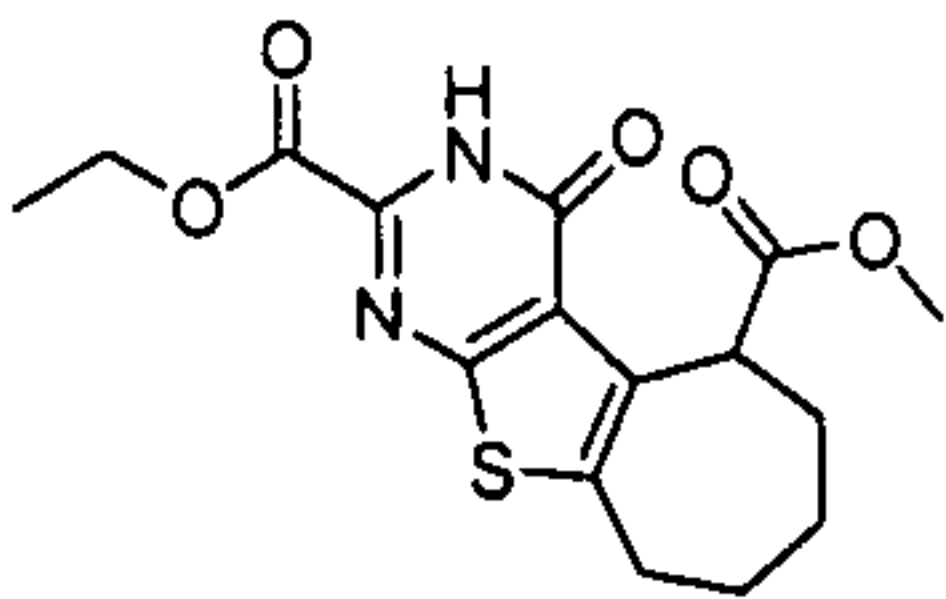
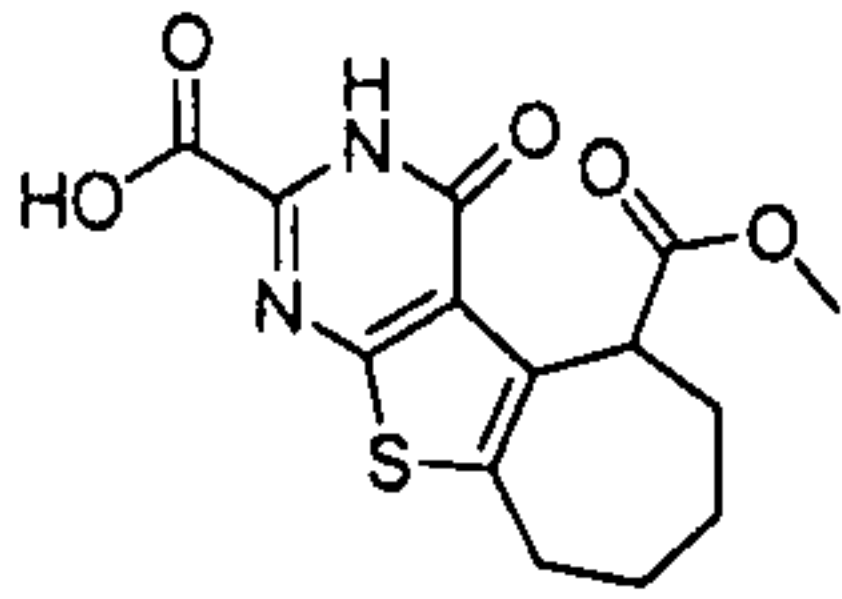
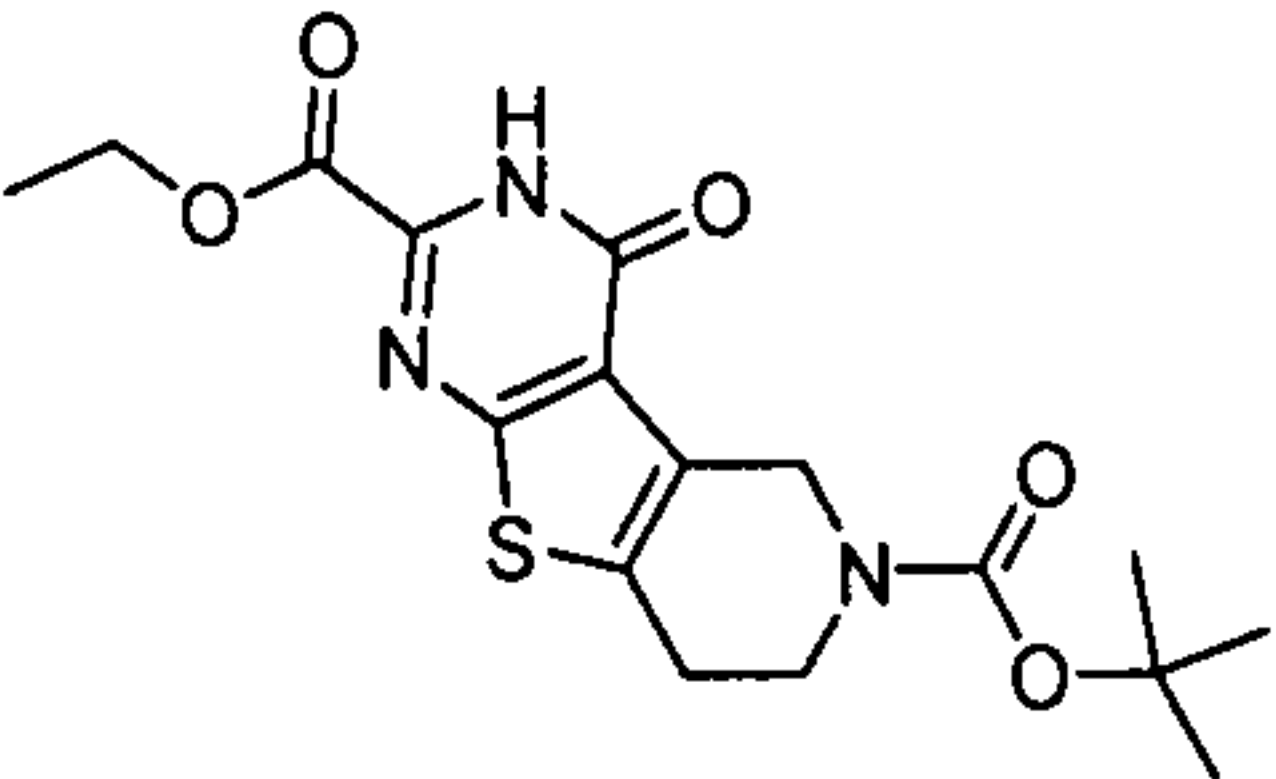
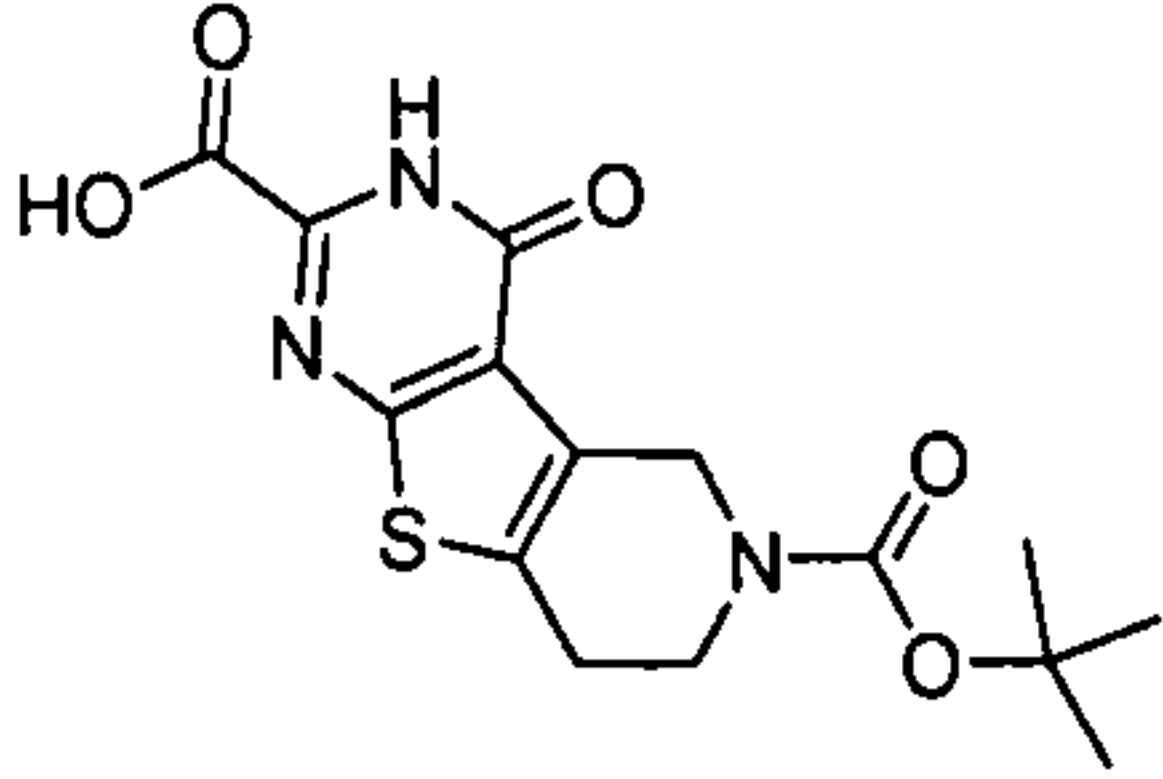
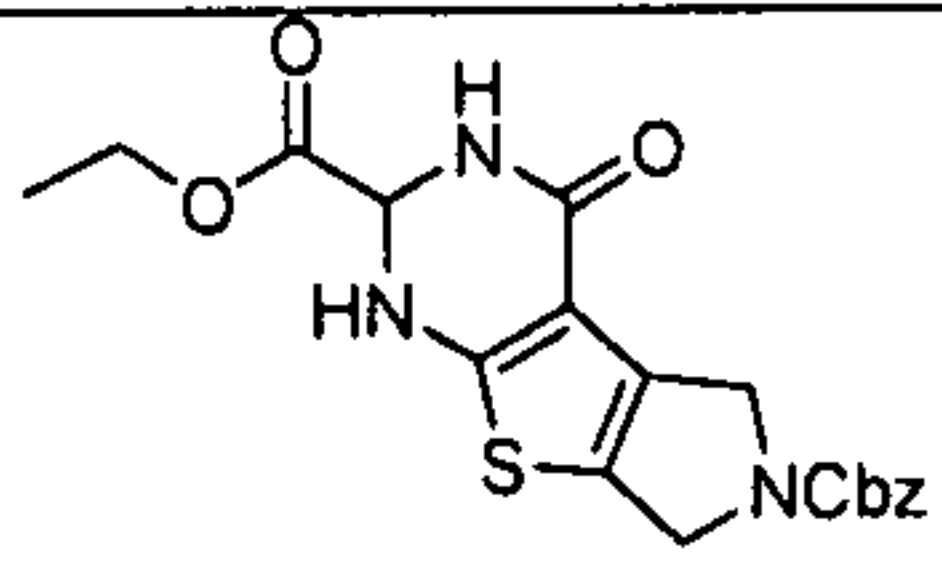
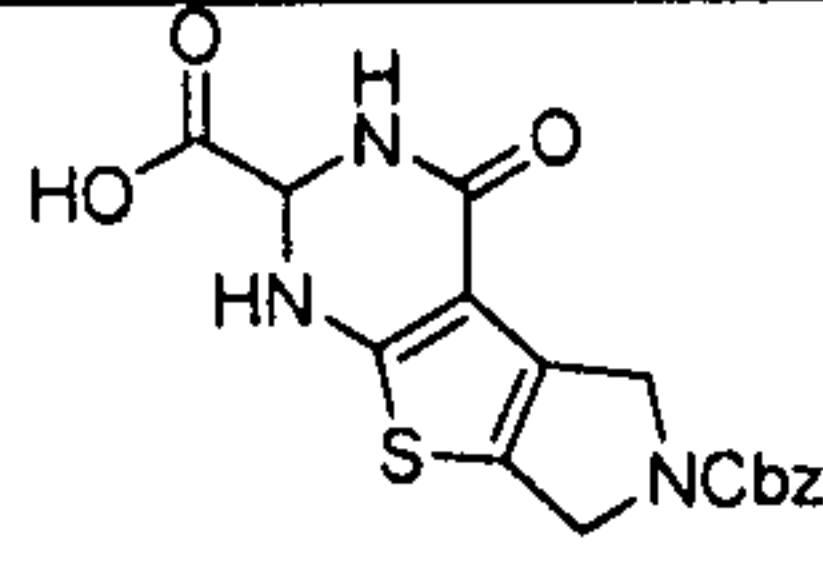
**Table I.5**

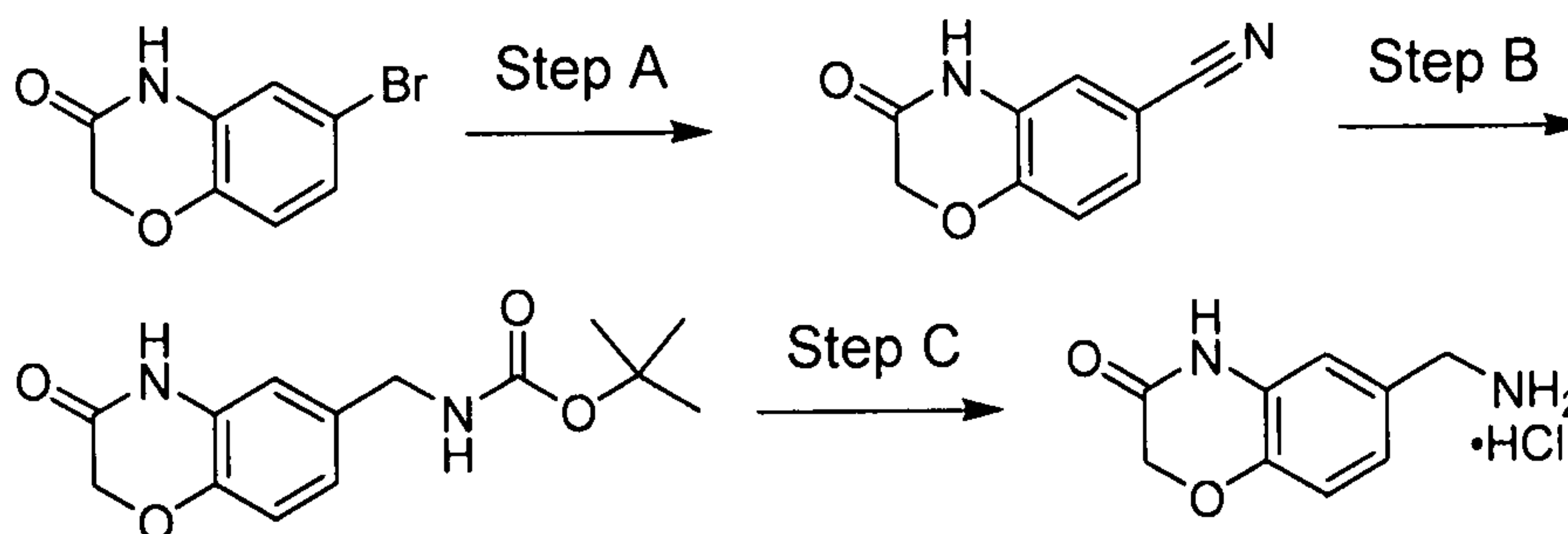
| Ex. # | ester                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 12/9  |    |    | >99%<br>[MH] <sup>+</sup> = 247 |
| 12/12 |   |   | n.d.<br>[MH] <sup>+</sup> = 266 |
| 12/13 |  |  | 83%<br>[MH] <sup>+</sup> = 251  |
| 12/43 |  |  | n.d.<br>[MH] <sup>+</sup> = 278 |
| 12/44 |  |  | 92%<br>[MH] <sup>+</sup> = 294  |
| 12/49 |  |  | 31%<br>[MH] <sup>+</sup> = 301  |

| Ex. # | ester                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 12/51 |    |    | 78%<br>[MH] <sup>+</sup> = 329  |
| 12/54 |   |   | 56%<br>[MH] <sup>+</sup> = 309  |
| 12/56 |  |  | 68%<br>[MH] <sup>+</sup> = 265  |
| 12/57 |  |  | 100%<br>[MH] <sup>+</sup> = 269 |
| 12/58 |  |  | 69%<br>[MH] <sup>+</sup> = 255  |
| 12/60 |  |  | 84%<br>[MH] <sup>+</sup> = 279  |
| 12/62 |  |  | 65%<br>[MH] <sup>+</sup> = 269  |

| Ex. # | ester                                                                               | product                                                                               | yield                           |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------|
| 12/68 |    |    | 89%<br>[MH] <sup>+</sup> = 303  |
| 12/69 |   |   | 100%<br>[MH] <sup>+</sup> = 327 |
| 12/73 |  |  | 100%<br>[MH] <sup>+</sup> = 253 |
| 12/77 |  |  | 45%<br>[MH] <sup>+</sup> = 366  |
| 12/84 |  |  | n.d.<br>[MH] <sup>+</sup> = 378 |
| 12/85 |  |  | 63%<br>[MH] <sup>+</sup> = 323  |

| Ex. # | ester                                                                               | product                                                                               | yield                                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------|
| 12/86 |    |    | 18%<br>[MH] <sup>+</sup> = 309            |
| 12/87 |   |   | 74%<br>[MH] <sup>+</sup> = 267            |
| 12/89 |  |  | 93%<br>[MH] <sup>+</sup> = 283            |
| 12/91 |  |  | 63%<br>[MH] <sup>+</sup> = 337            |
| 12/92 |  |  | 91%<br>[MH] <sup>+</sup> = 323            |
| 12/93 |  |  | 70%<br>[MH] <sup>+</sup> = 323            |
| 12/94 |  |  | 21% ( 2 steps)<br>[MH] <sup>+</sup> = 295 |

| Ex. #  | ester                                                                               | product                                                                               | yield                          |
|--------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------|
| 12/96  |    |    | 47%<br>[MH] <sup>+</sup> = 323 |
| 12/97  |   |   | 68%<br>[MH] <sup>+</sup> = 352 |
| 12/104 |  |  | 92%<br>[MH] <sup>+</sup> = 372 |

**Preparative Example 13****Step A**

A degassed suspension of commercially available 6-Bromo-4H-benzo[1,4]oxazin-3-one (8.39 g), Zn(CN)<sub>2</sub> (3.46 g) and Pd(PPh<sub>3</sub>)<sub>4</sub> (2.13 g) in DMF (70 mL) was stirred in a oil bath (80°C) overnight. The mixture was cooled to room temperature and then poured into water (500 mL). The precipitate was collected by suction, air dried, washed with pentane, dissolved in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), filtered through an silica pad and concentrated to yield a yellow solid (5.68 g, 89%). [MH]<sup>+</sup> = 175.

**Step B**

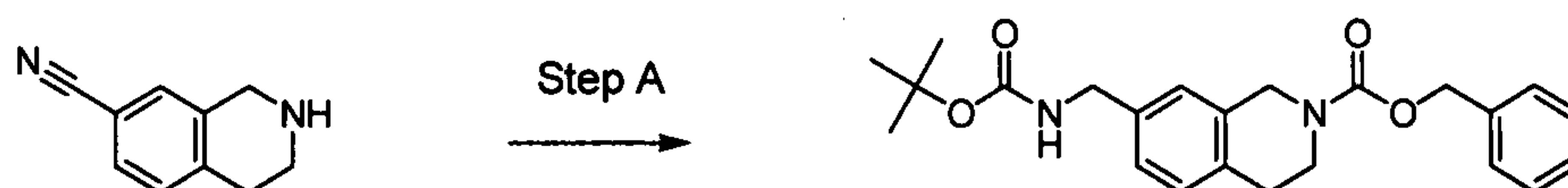
To an ice cooled solution of the title compound from Step A above (5.6 g), di-*tert*-butyl dicarbonate (14.06 g) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (1.53 g) in MeOH,  $\text{NaBH}_4$  (8.51 g) was added in portions. The mixture was vigorously stirred for 1h at 0°C and 1h at room temperature. After the addition of diethylenetriamine (3.5 mL) the mixture was concentrated, diluted with EtOAc, washed subsequently with 1N HCl, saturated aqueous  $\text{NaHCO}_3$  and saturated aqueous NaCl, dried ( $\text{MgSO}_4$ ), concentrated to afford the title compound as an off-white solid (7.91 g, 88%).  $[\text{M}+\text{Na}]^+ = 397$ .

### Step C

The title compound from Step B above (7.91 g) was dissolved in a 4M solution of HCl in 1,4-dioxane (120 mL), stirred for 14 h, concentrated, suspended in  $\text{Et}_2\text{O}$ , filtered and dried to afford the title compound as an off-white solid (5.81 g, 96%).  $[\text{M}-\text{NH}_3\text{Cl}]^+ = 162$ .

15

### Preparative Example 14



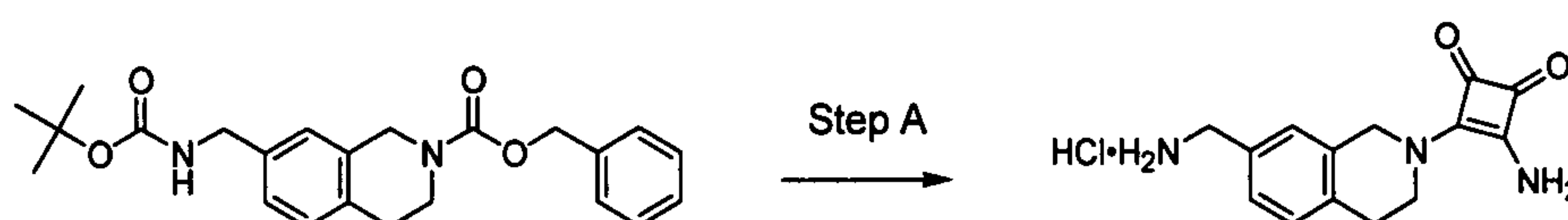
### Step A

A solution of commercially available 7-cyano-1,2,3,4-tetrahydroisoquinoline (2.75 g),  $\text{K}_2\text{CO}_3$  (3.60 g) and benzylchloroformate (2.7 mL) in THF/ $\text{H}_2\text{O}$  was stirred overnight and then concentrated. The residue was diluted with EtOAc, washed with 10% aqueous citric acid, saturated aqueous  $\text{NaHCO}_3$  and brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was dissolved in MeOH (100 mL) and di-*tert*-butyl dicarbonate (7.60 g) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (400 mg) was added. The solution was cooled to 0°C and  $\text{NaBH}_4$  (2.60 g) was added in portions. The mixture was allowed to reach room temperature and then vigorously stirred overnight. After the addition of diethylenetriamine (2 mL) the

mixture was concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid, saturated aqueous NaHCO<sub>3</sub> and saturated aqueous NaCl, dried (MgSO<sub>4</sub>), concentrated and purified by chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford the title compound as a colorless oil (1.81 g, 26%). [MH]<sup>+</sup> = 397.

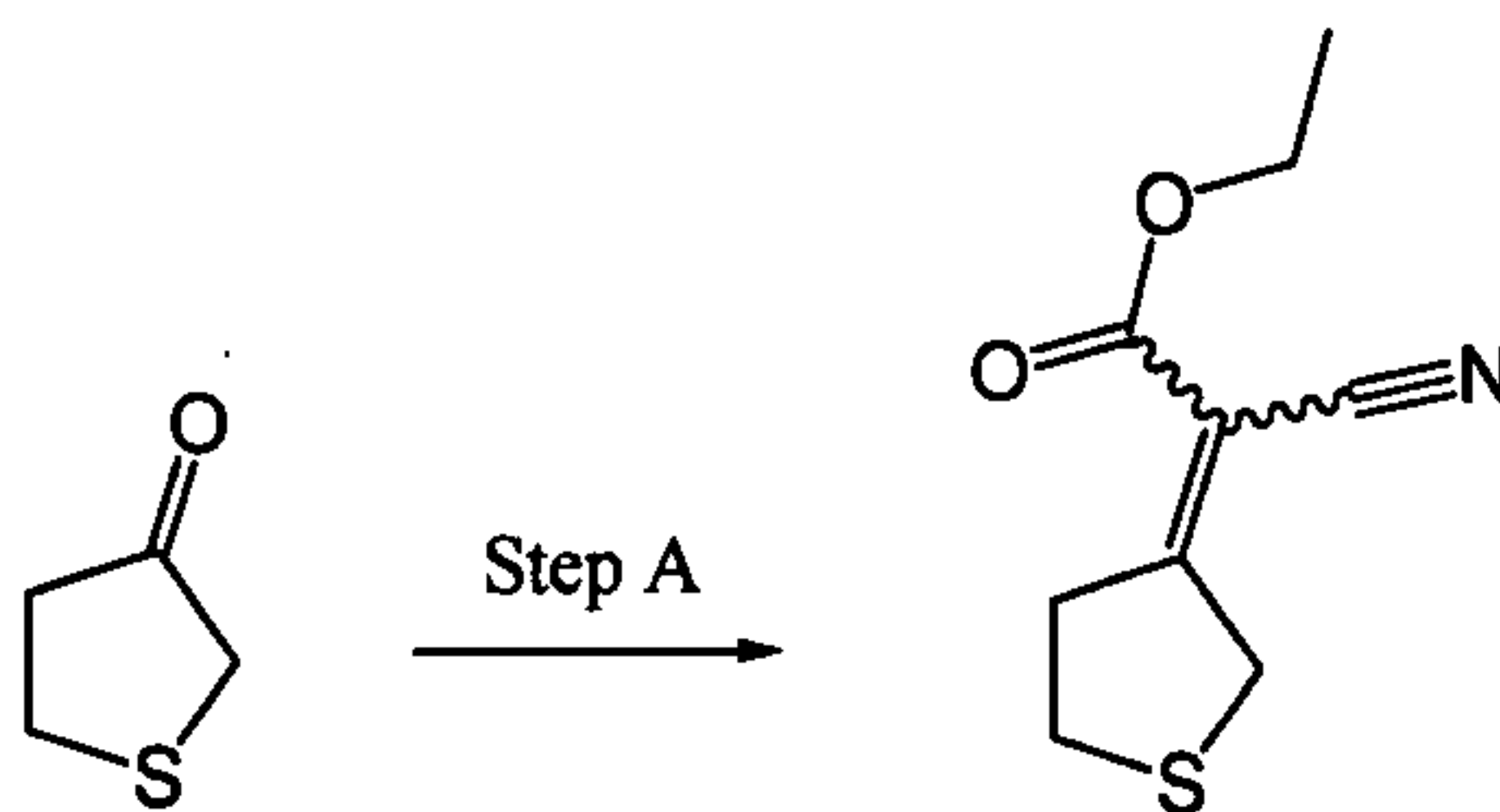
5

### **Preparative Example 15**



#### **Step A**

A mixture of the title compound from the Preparative Example 14 (1.81 g) and Pd/C (10wt%, 200 mg) in EtOH (50 mL) was hydrogenated at atmospheric pressure overnight, filtered and concentrated to a volume of ~20 mL. 3,4-Diethoxy-3-cyclobutene-1,2-dione (0.68 mL) and NEt<sub>3</sub> (0.5 mL) were added and the mixture was heated to reflux for 4 h. Concentration and purification by chromatography (silica, cyclohexane/EtOAc) afforded a slowly crystallizing colorless oil. This oil was dissolved in EtOH (20 mL) and a 28% solution of NH<sub>3</sub> in H<sub>2</sub>O (100 mL) was added. The mixture was stirred for 3 h, concentrated, slurried in H<sub>2</sub>O, filtered and dried under reduced pressure. The remaining residue was dissolved in a 4M solution of HCl in 1,4-dioxane (20 mL), stirred for 14 h, concentrated, suspended in Et<sub>2</sub>O, filtered and dried to afford the title compound as an off-white solid (1.08 g, 92%). [M-Cl]<sup>+</sup> = 258.

**Preparative Example 16****Step A**

5 Tetrahydrothiophen-3-one (1 g), ethyl cyanoacetate (1.44 g), acetic acid (70  $\mu$ L) and ammonium acetate (30 mg) in toluene were heated to reflux in presence of a Dean-Stark overnight. After concentration of the mixture, a purification by chromatography (silica cyclohexane/EtOAc 9/1) afforded a yellow oil (1.04 g, 54%).  $[MH]^+ = 198$ .

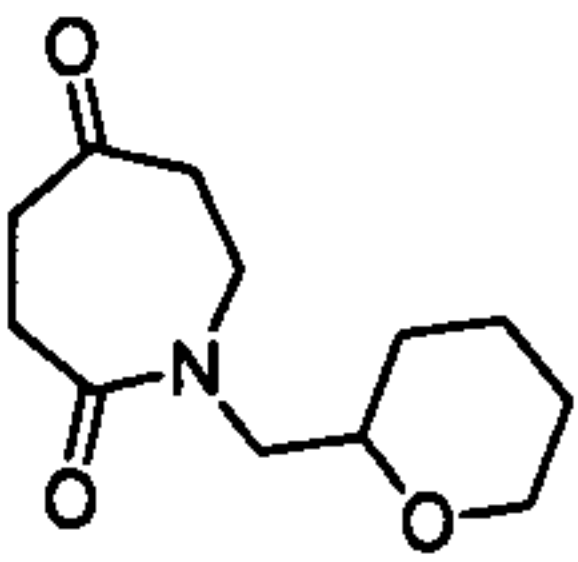
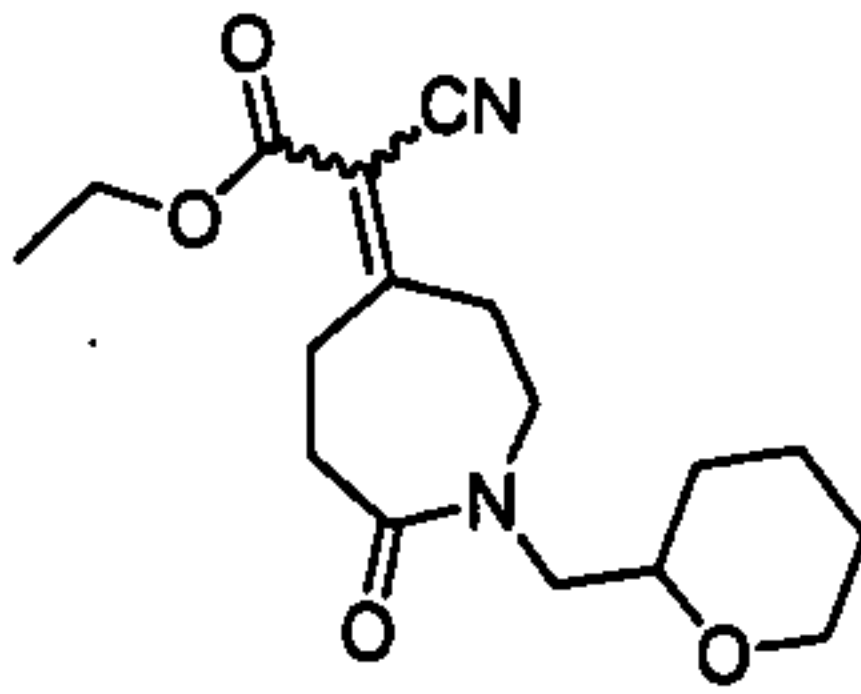
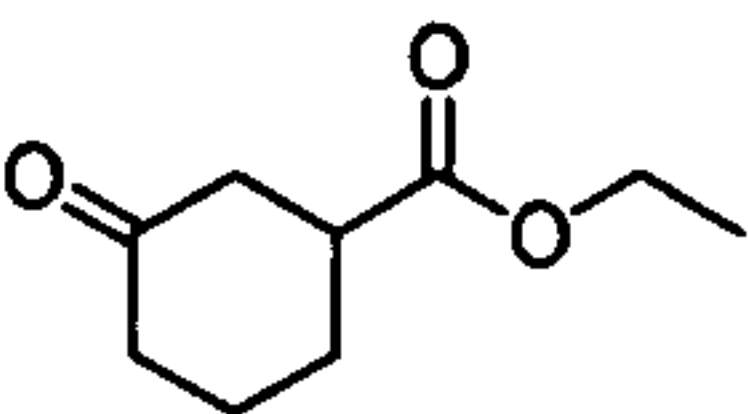
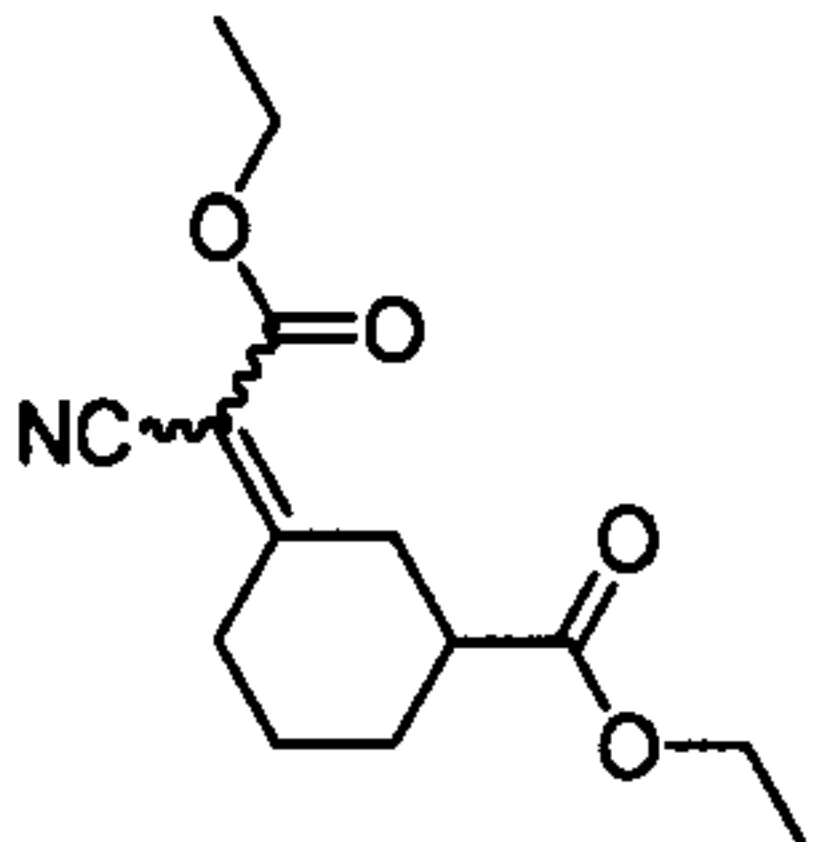
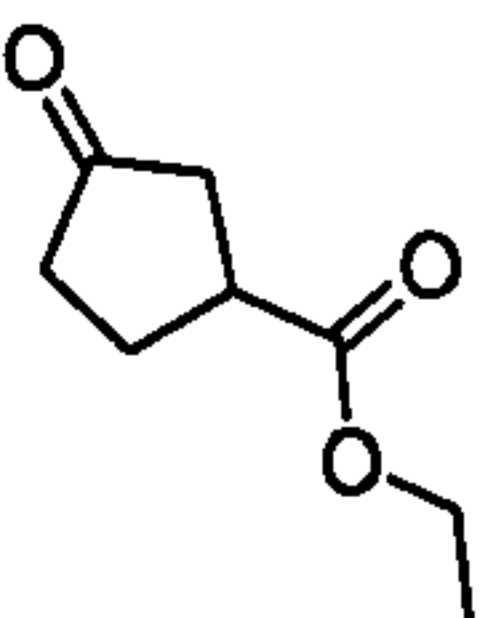
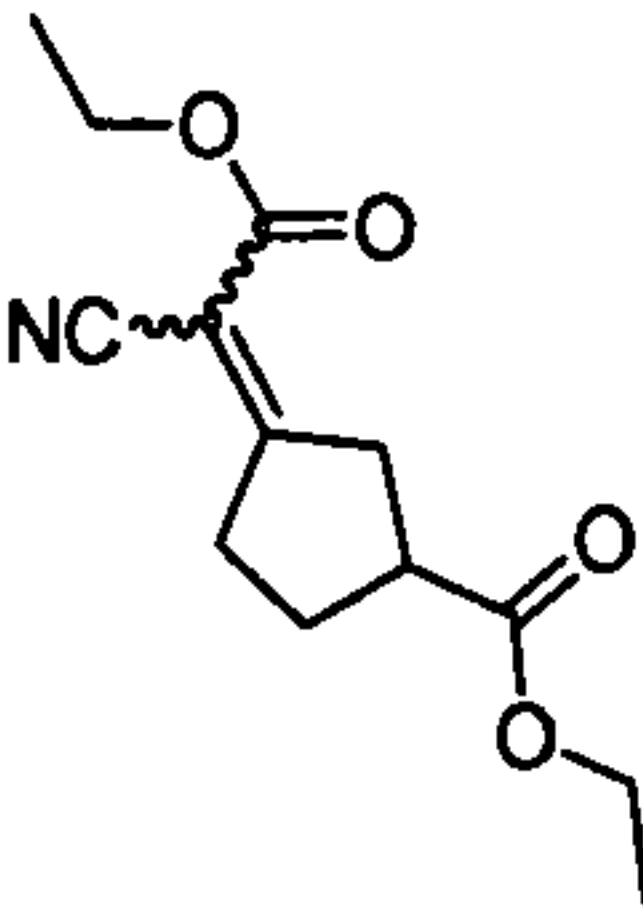
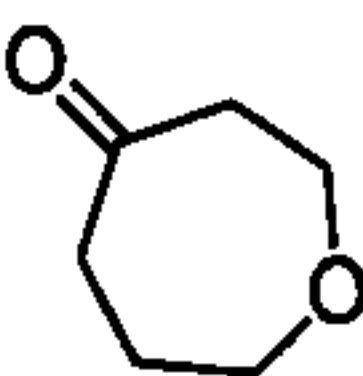
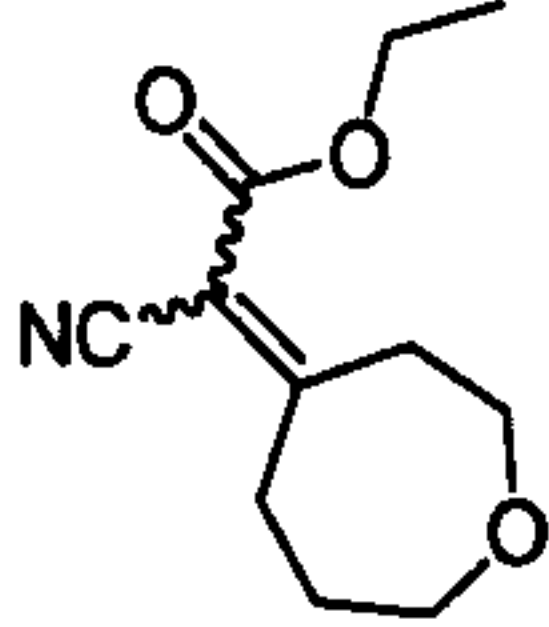
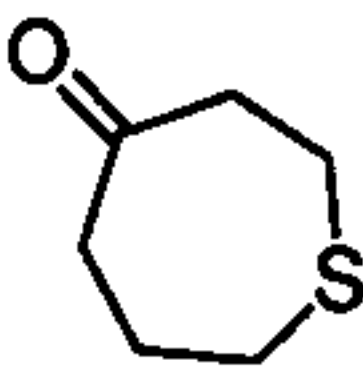
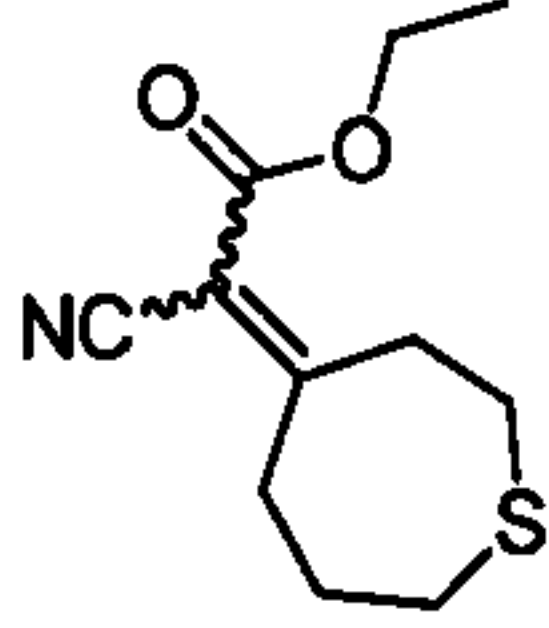
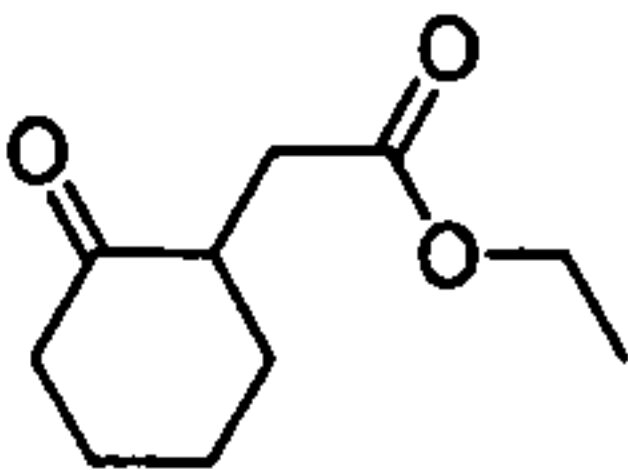
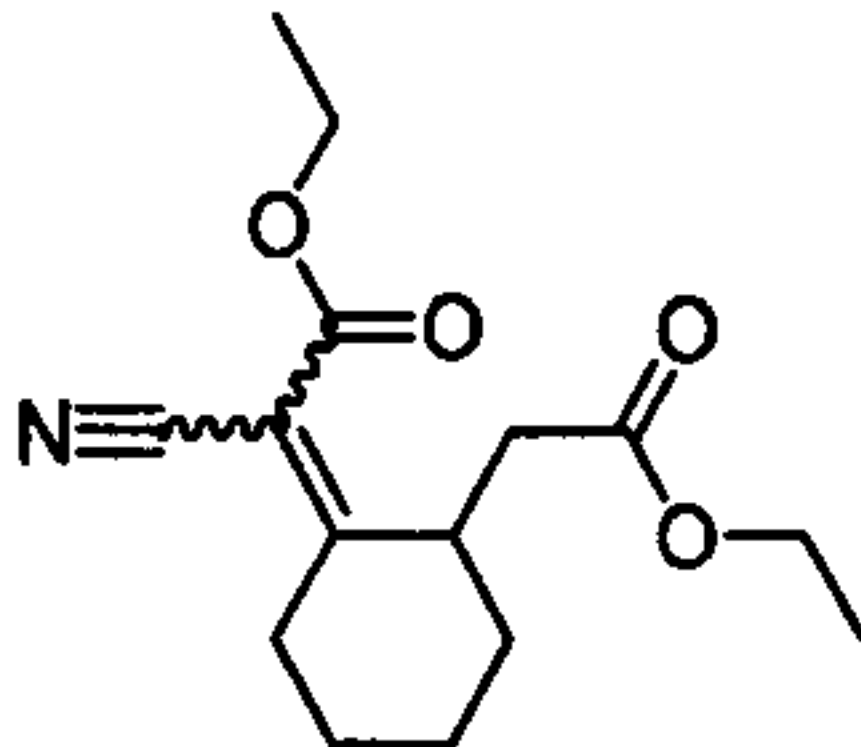
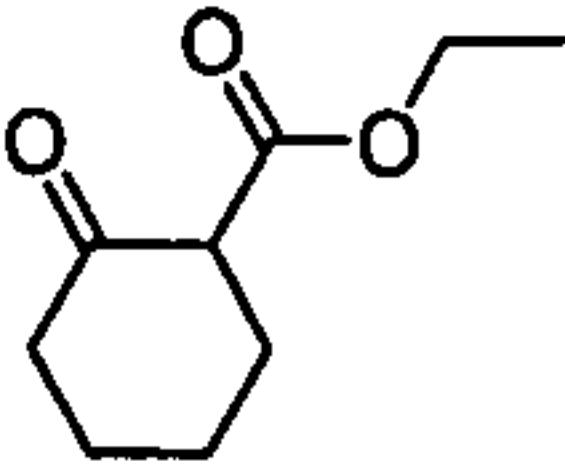
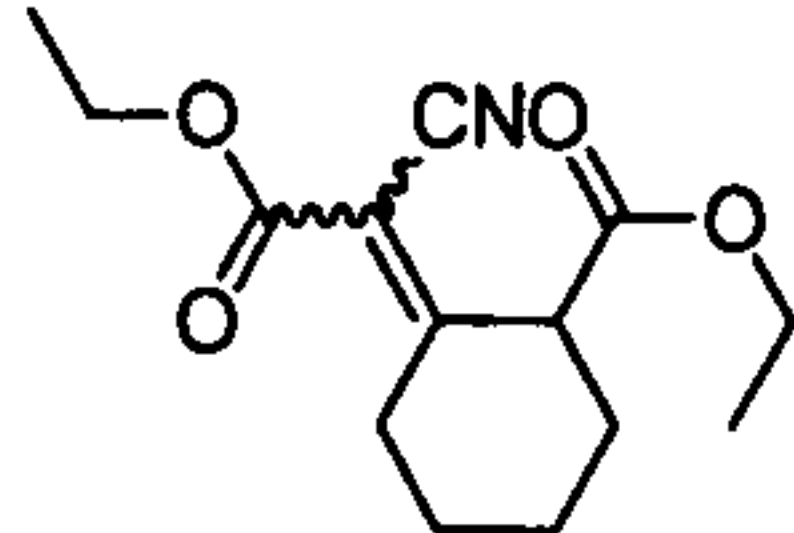
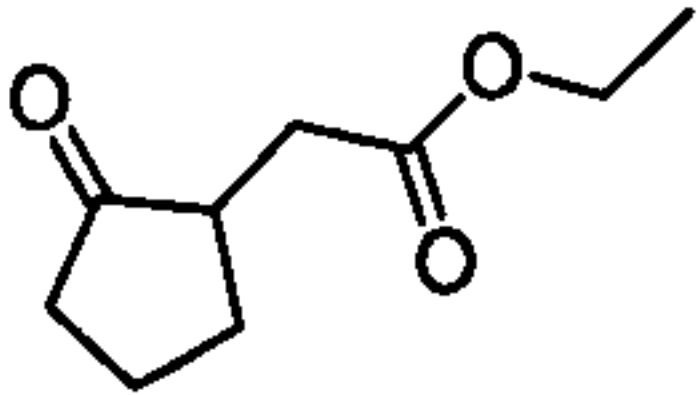
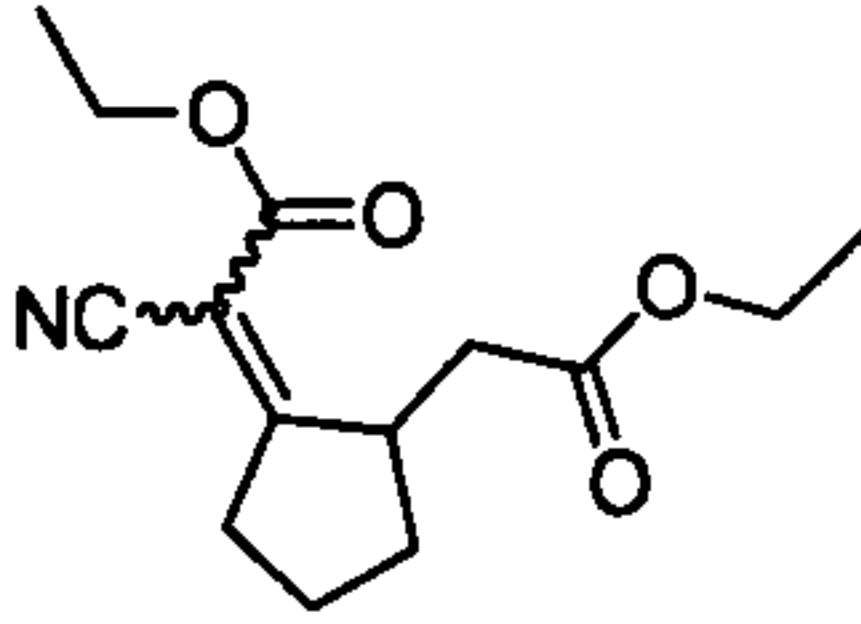
10

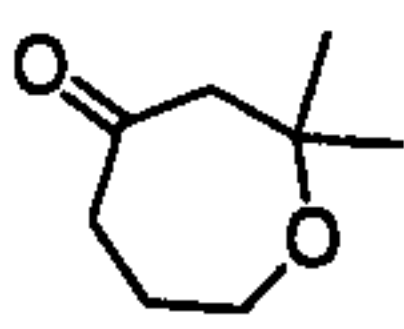
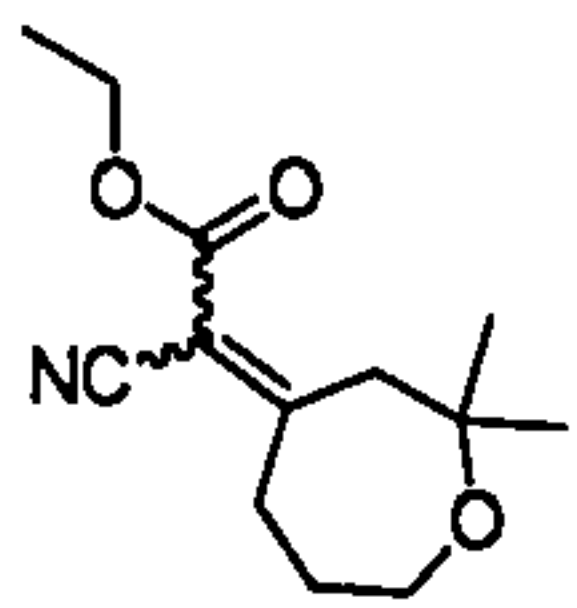
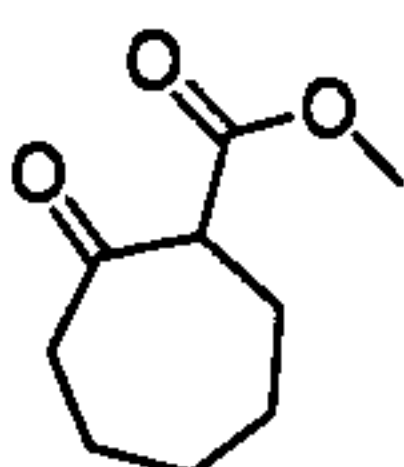
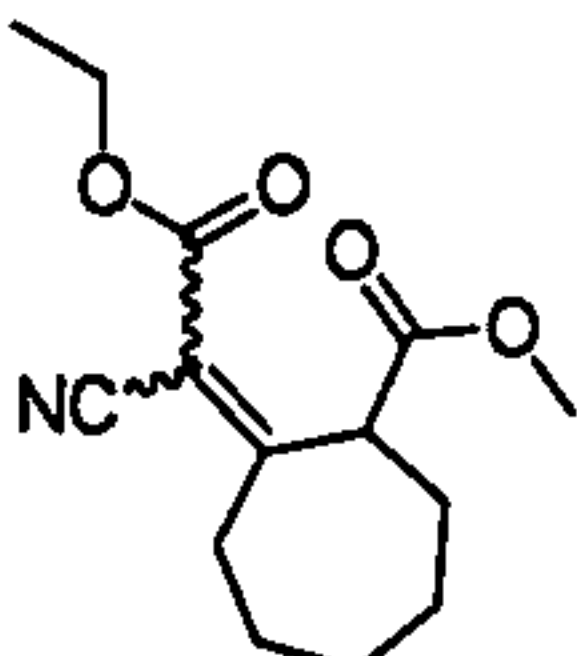
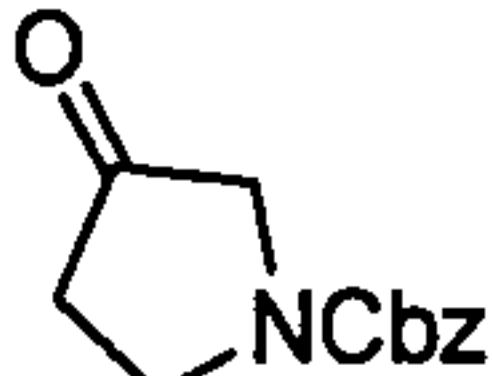
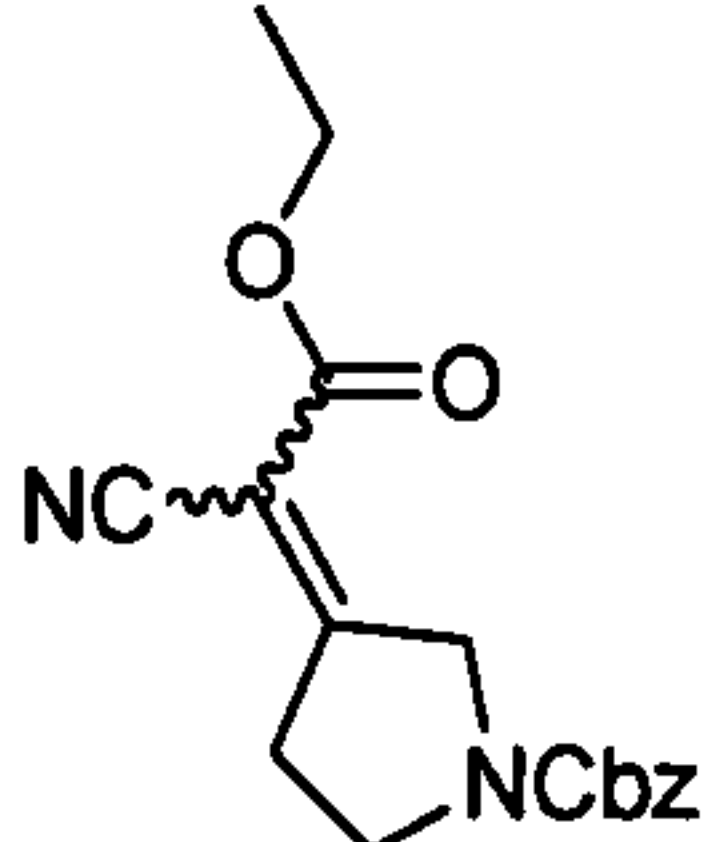
**Preparative Examples 17/1 to 17/20**

Following similar procedures as described in the Preparative Examples 16 except using the ketones indicated in Table I.6 below, the following compounds were prepared.

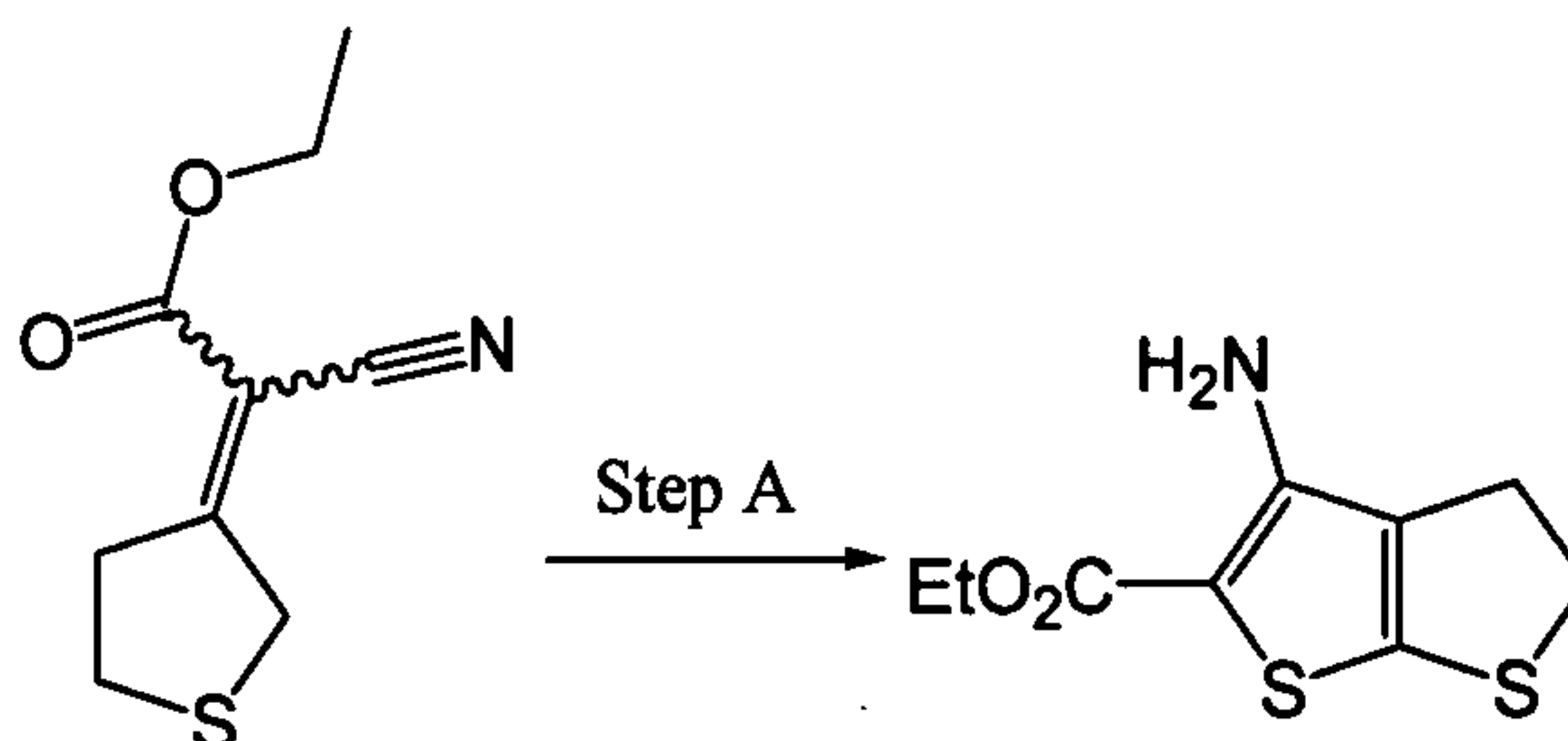
**Table I.6**

| Ex. # | Ketone | product | yield                 |
|-------|--------|---------|-----------------------|
| 17/1  |        |         | 27%<br>$[MH]^+ = 212$ |
| 17/2  |        |         | n.d<br>$[MH]^+ = 309$ |

| Ex. # | Ketone                                                                              | product                                                                               | yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------|
| 17/5  |    |    | n.d.<br>[MH] <sup>+</sup> = n.d. |
| 17/7  |    |    | 93%<br>[MH] <sup>+</sup> = 266   |
| 17/8  |  |  | 83%<br>[MH] <sup>+</sup> = 252   |
| 17/9  |  |  | 37%<br>[MH] <sup>+</sup> = 210   |
| 17/10 |  |  | n.d.<br>[MH] <sup>+</sup> = 226  |
| 17/12 |  |  | n.d.<br>[MH] <sup>+</sup> = 280  |
| 17/13 |  |  | 40 %<br>[MH] <sup>+</sup> = 266  |
| 17/14 |  |  | n.d.<br>[MH] <sup>+</sup> = 266  |

| Ex. # | Ketone                                                                              | product                                                                              | yield                            |
|-------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------|
| 17/15 |    |   | n.d.<br>[MH] <sup>+</sup> = 238  |
| 17/17 |    |   | 41 %<br>[MH] <sup>+</sup> = 266  |
| 17/20 |  |  | n.d.<br>[MH] <sup>+</sup> = n.d. |

### Preparative Example 18



#### Step A

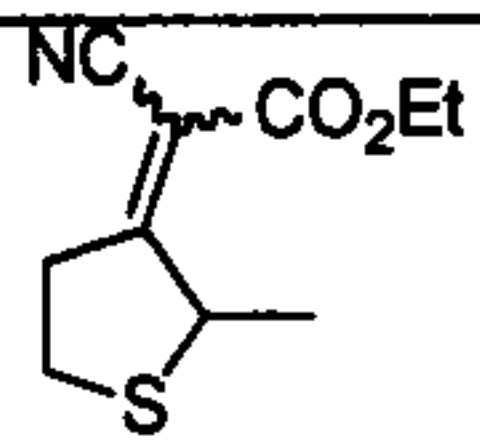
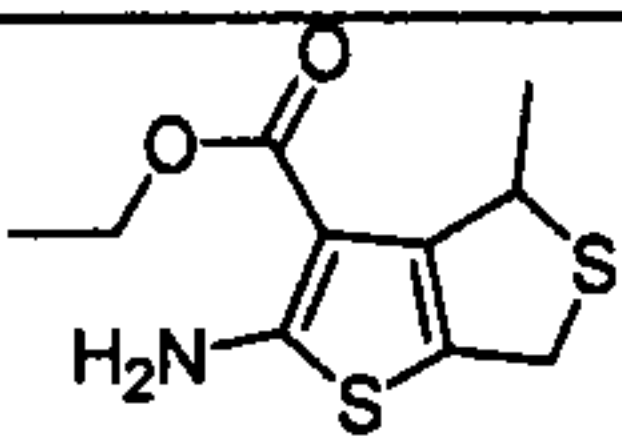
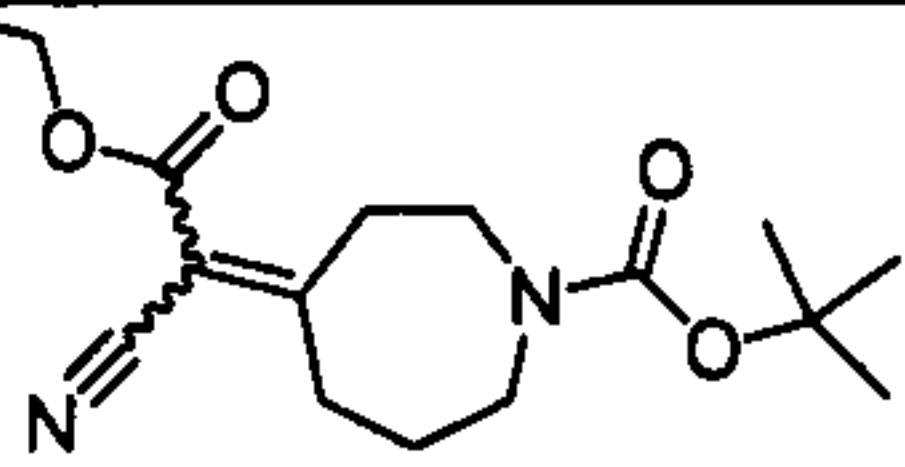
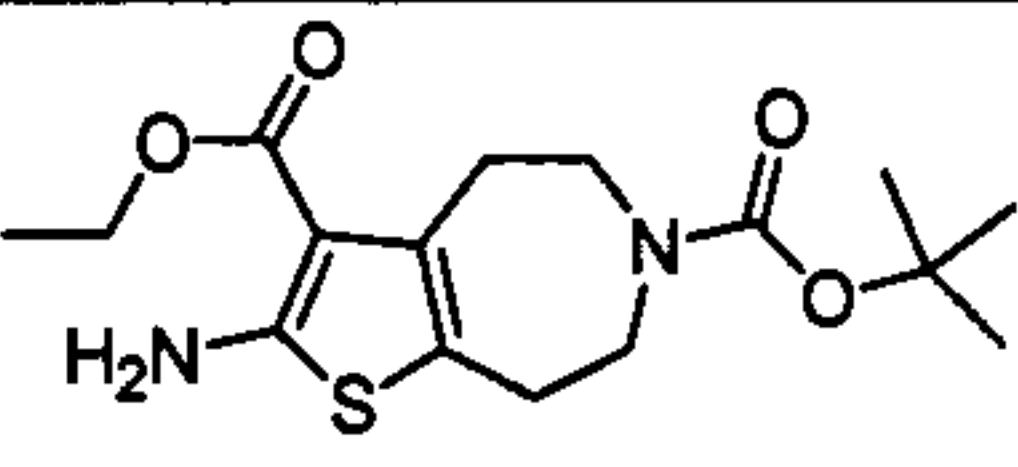
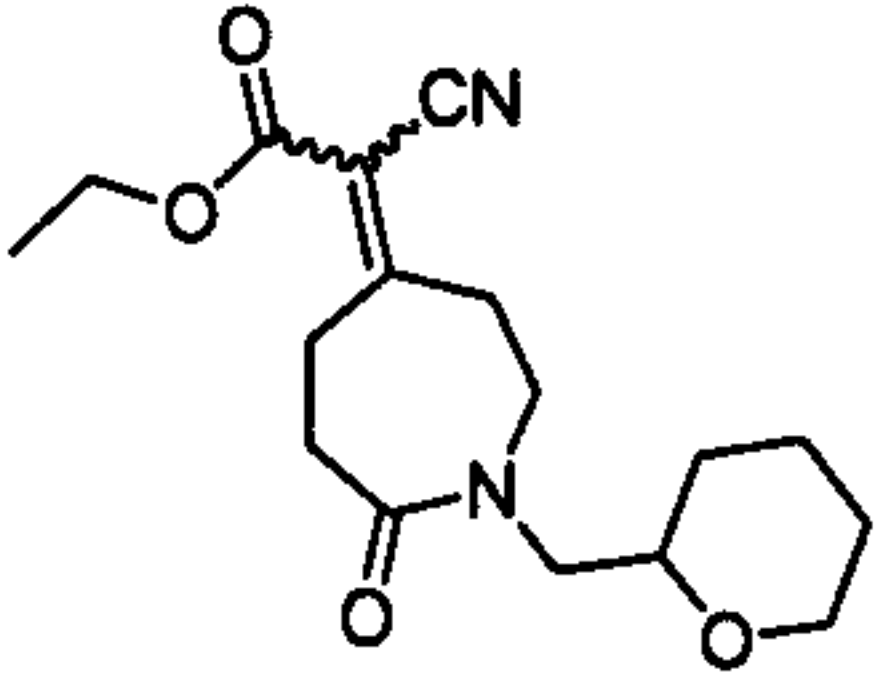
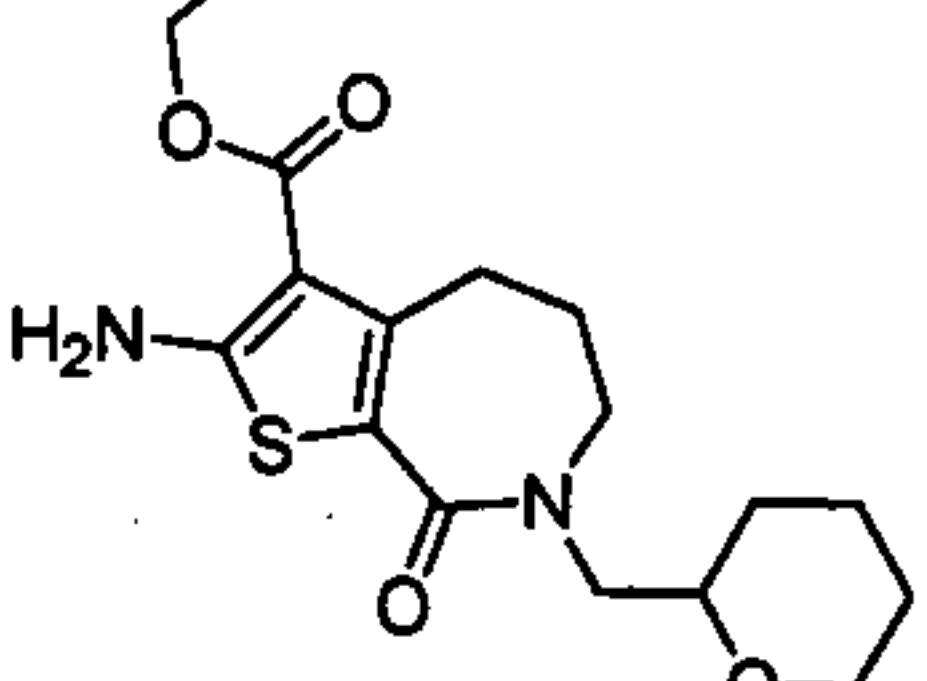
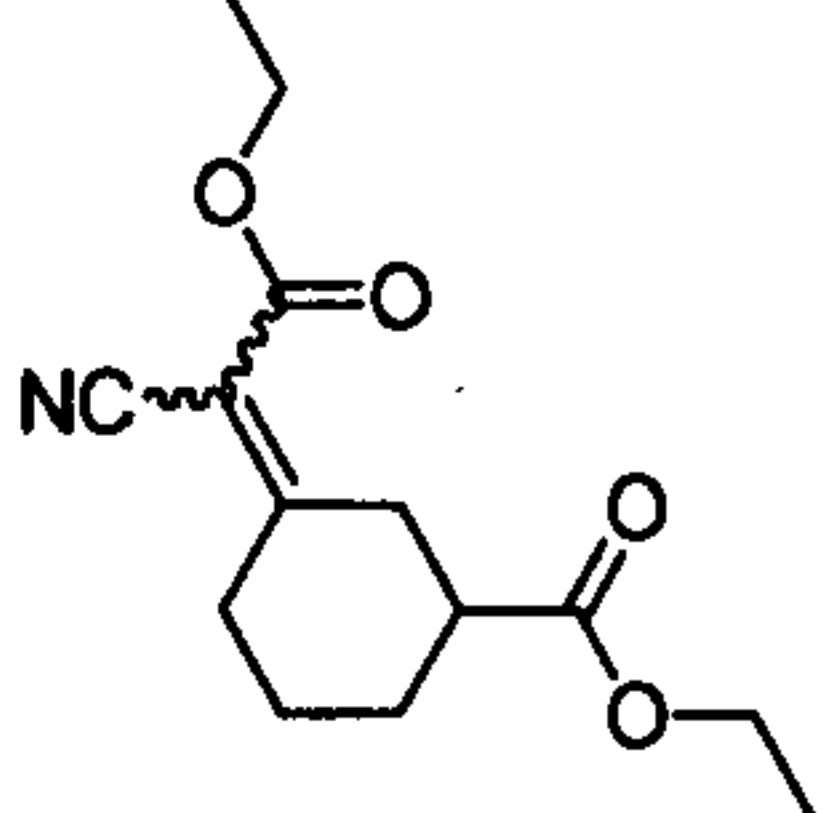
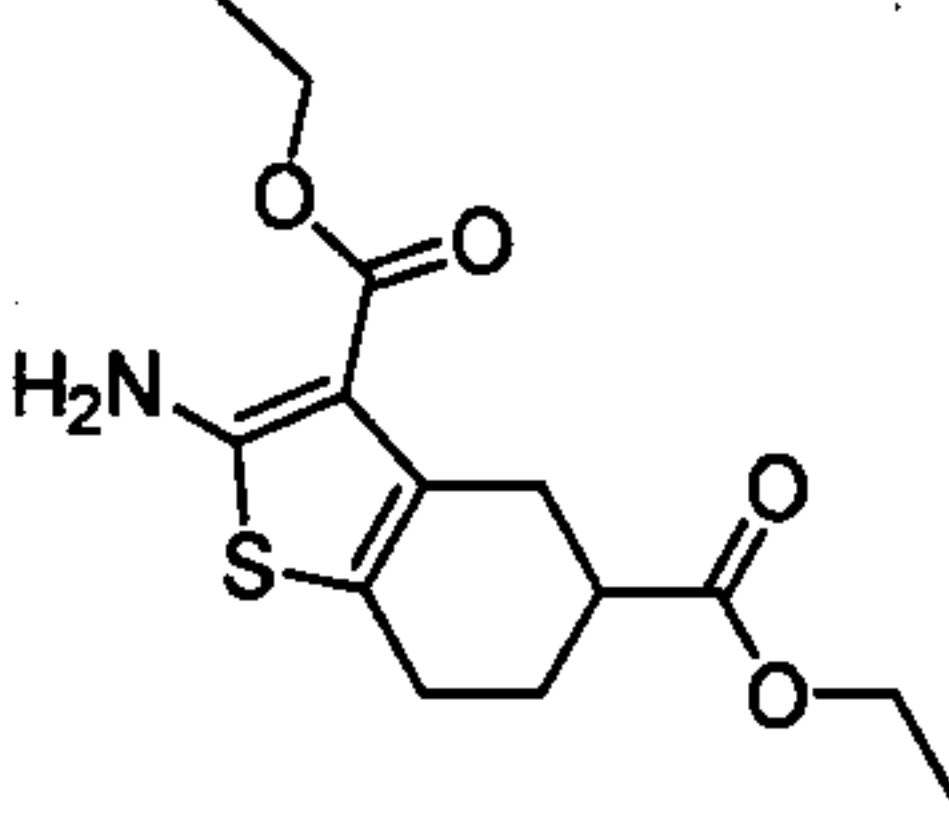
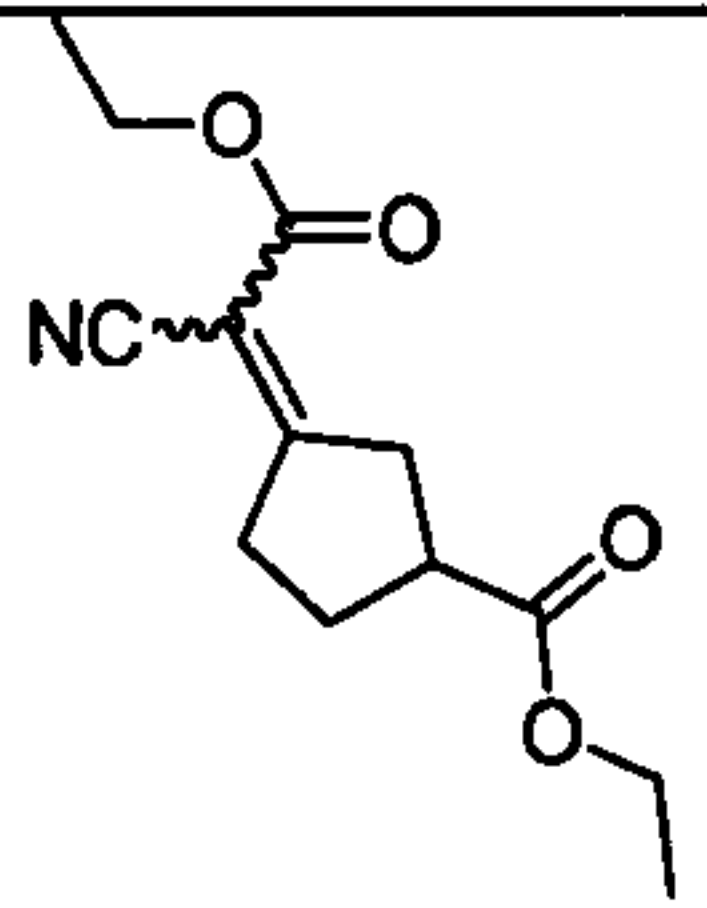
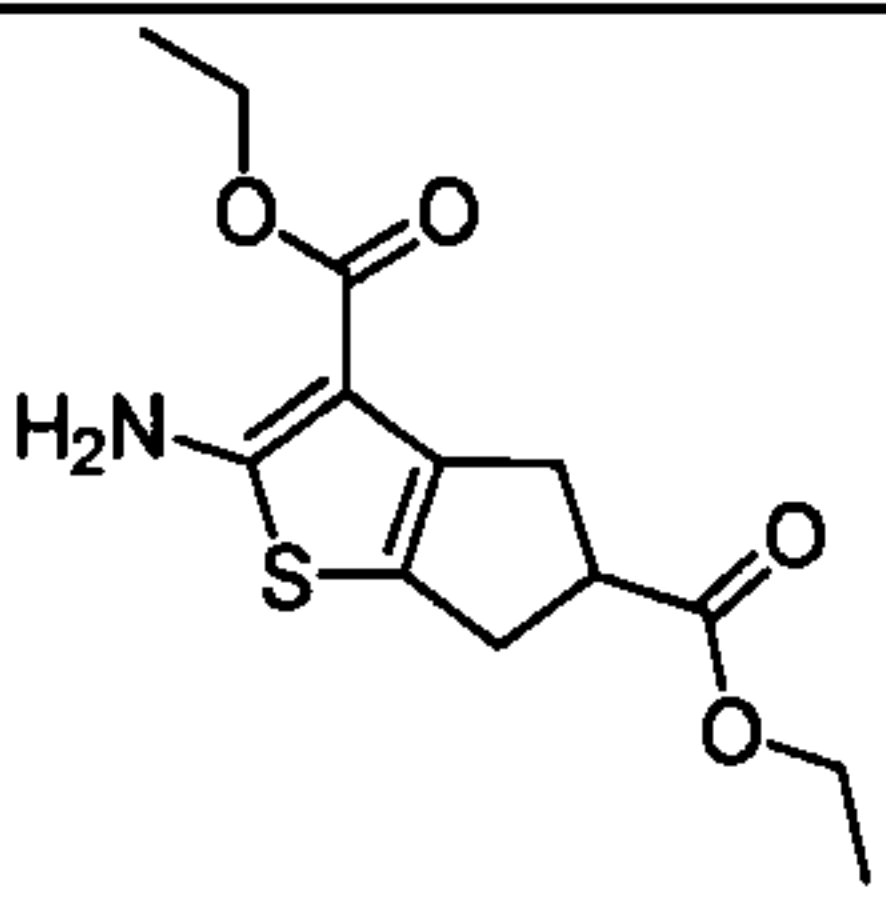
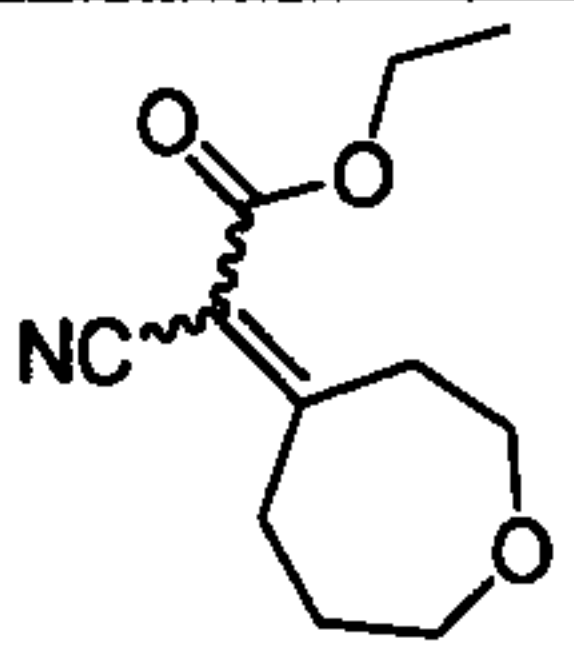
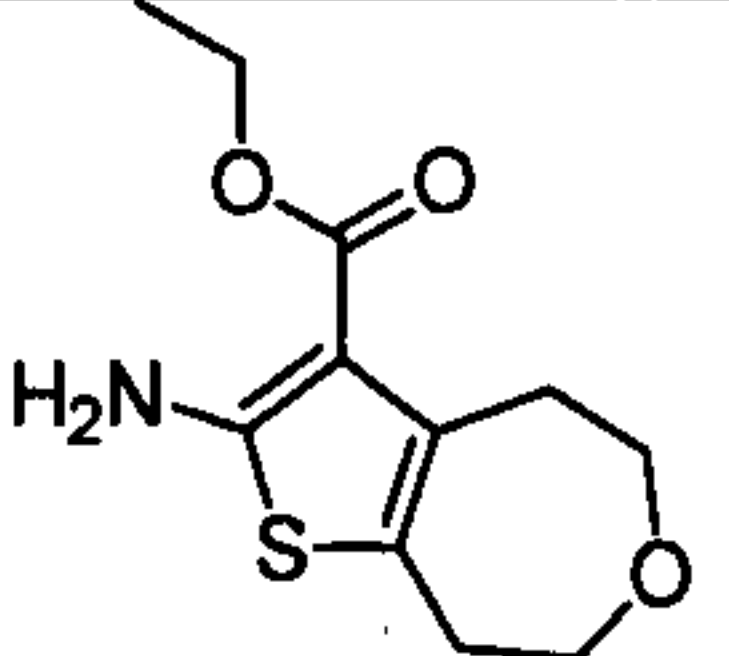
- 5 A mixture of the title compound from the Preparative Example 16 (0.5 g) and sulfur (86 mg) in MeOH (5 mL) were heated at 50 °C. Diethylamine (135  $\mu$ L) was added slowly and the mixture was stirred at 50 °C for 2h. After concentration of the mixture, a purification by chromatography (silica cyclohexane/EtOAc 9/1) afforded a orange solid (345 mg , 59%). [MH]<sup>+</sup> = 230.

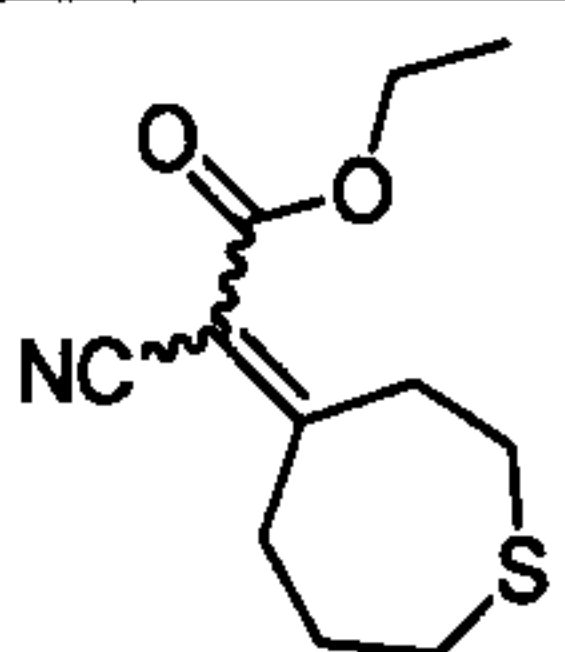
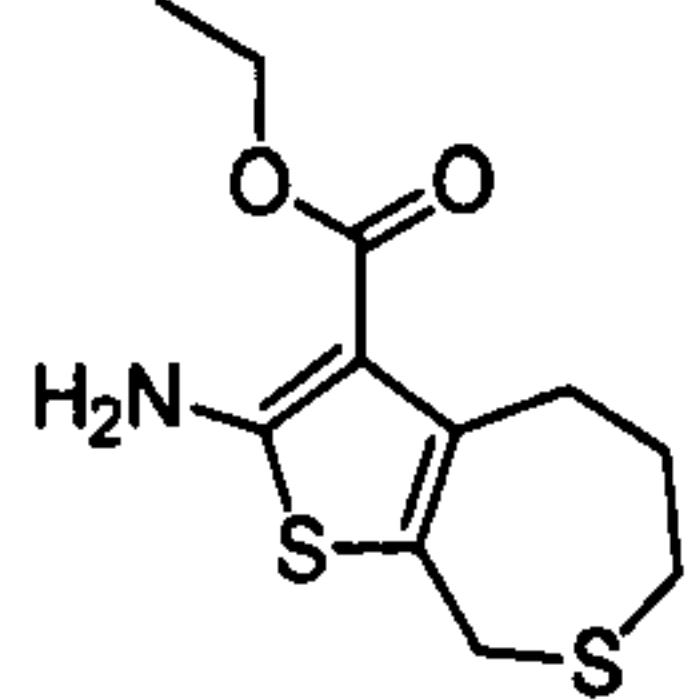
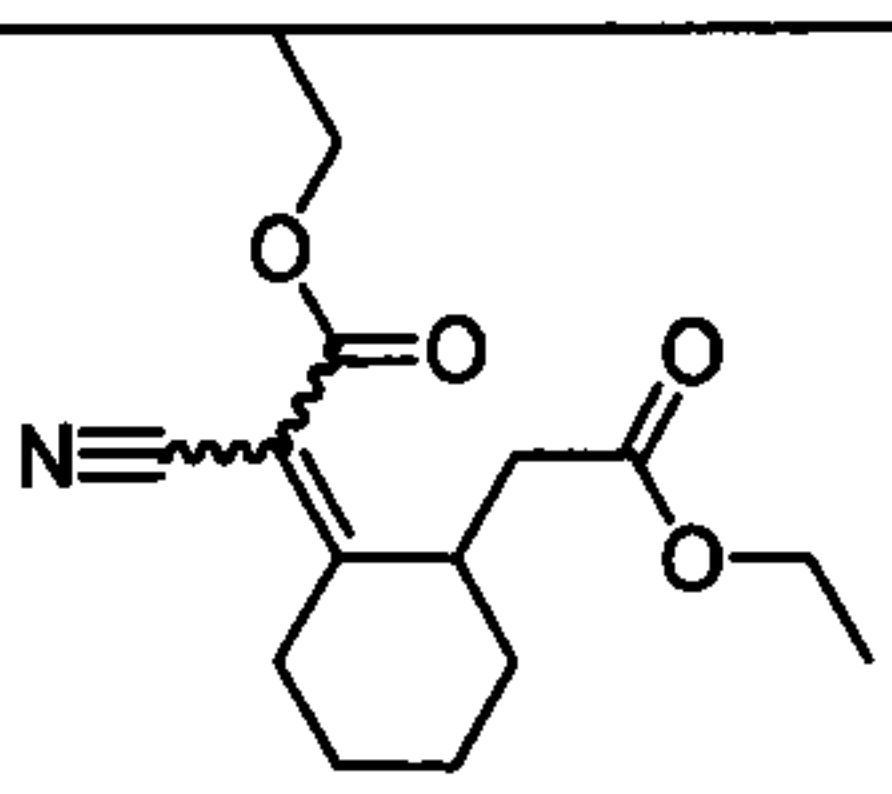
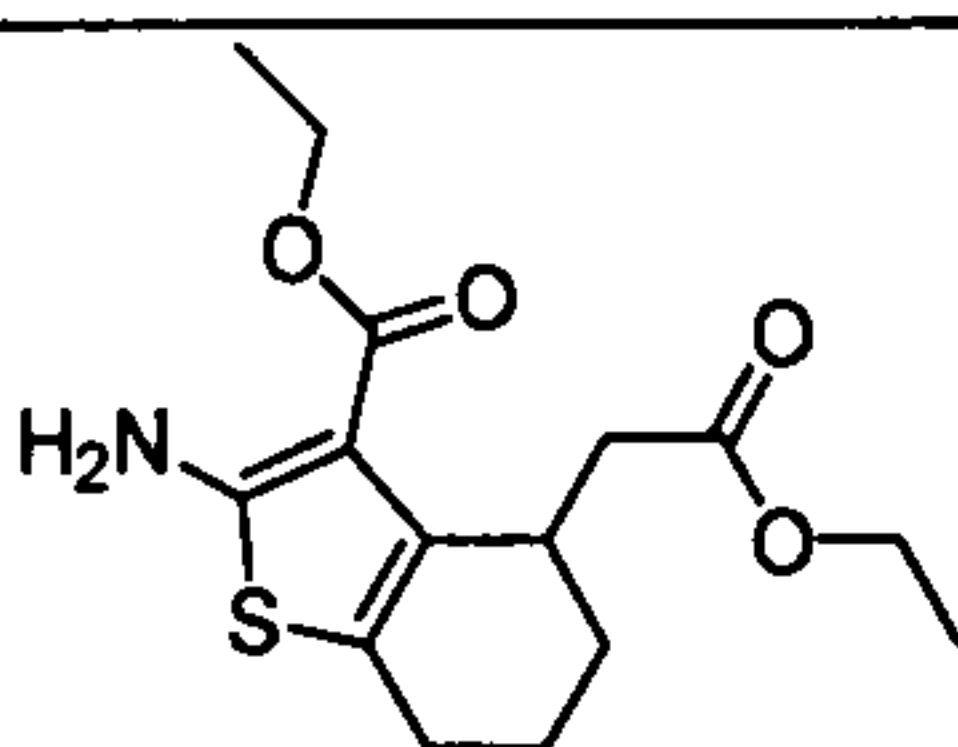
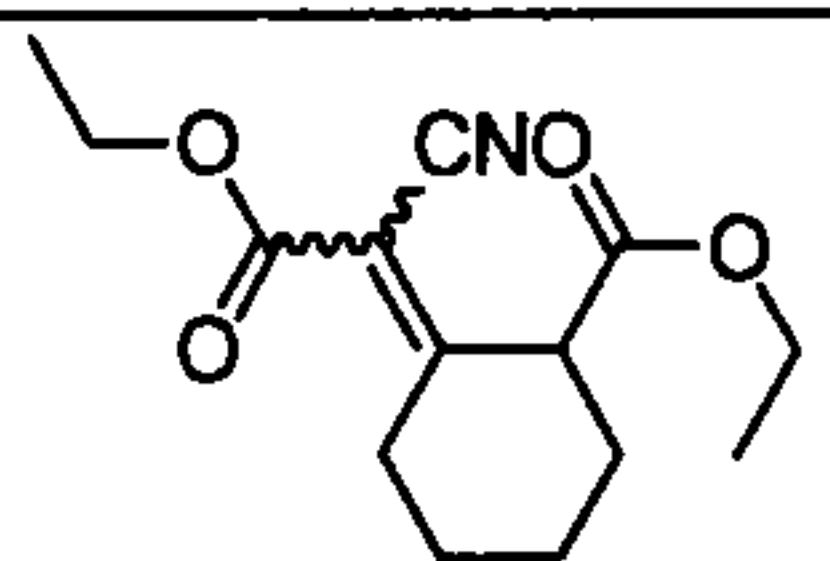
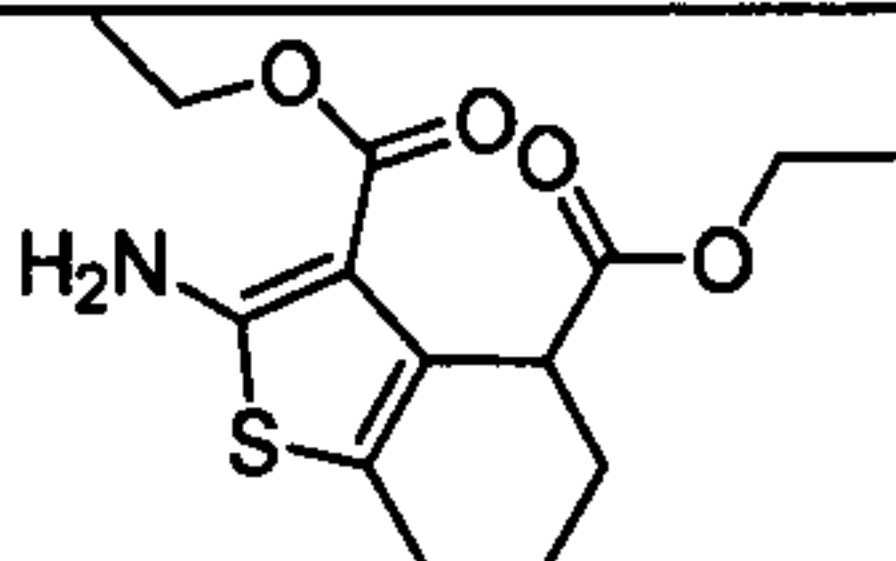
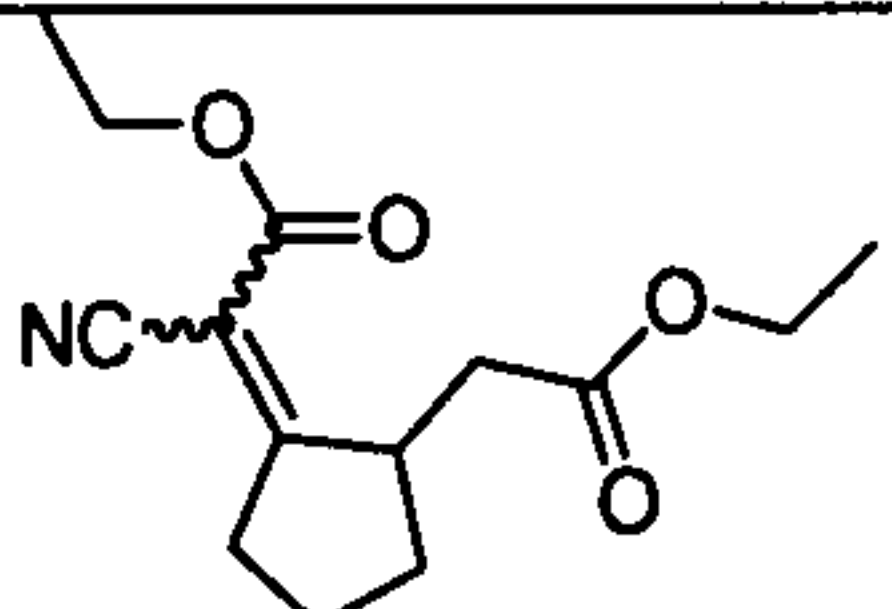
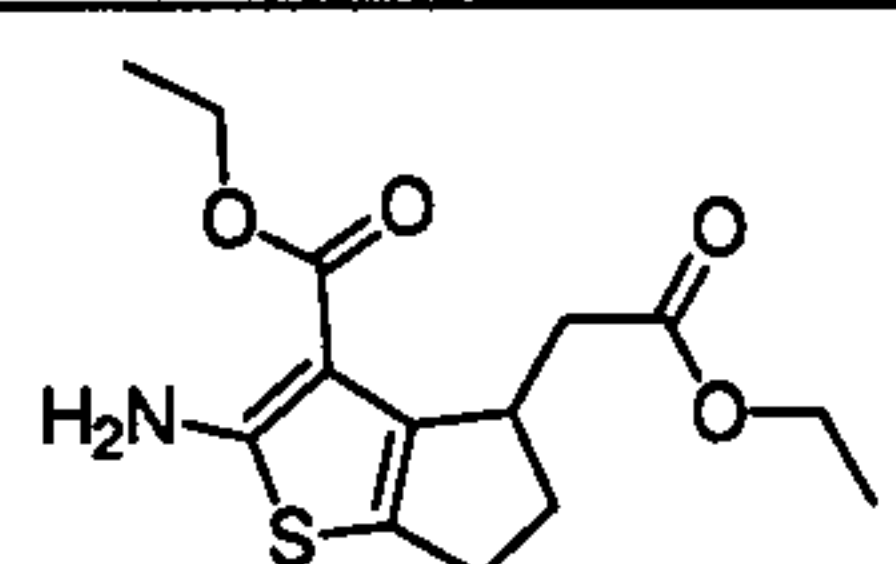
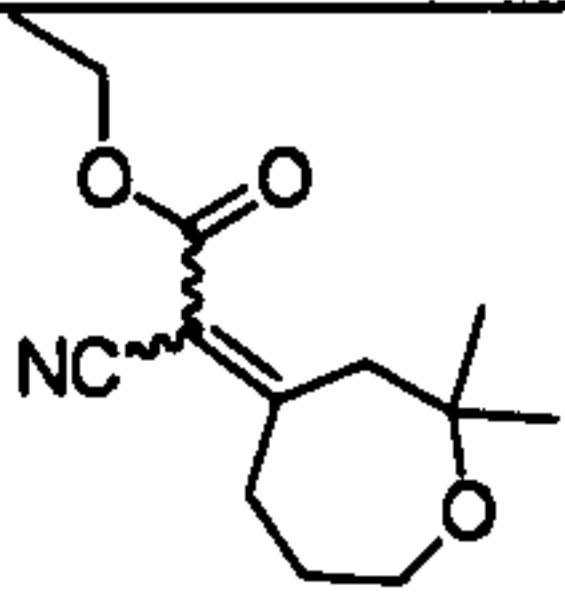
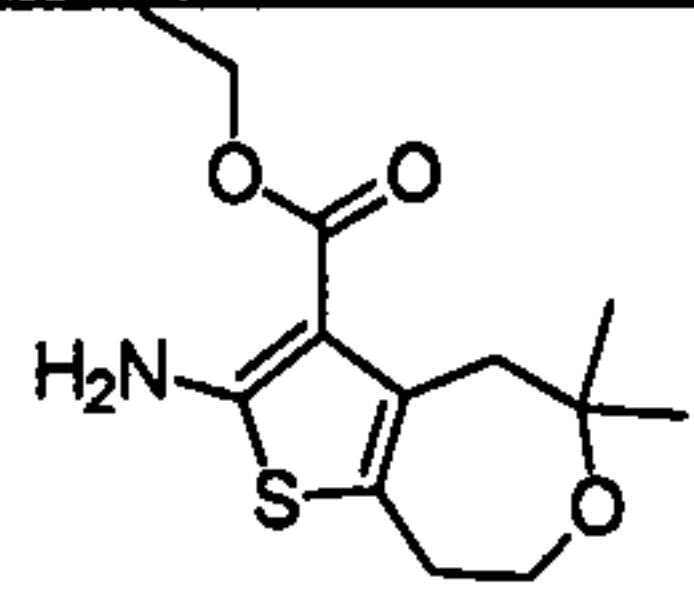
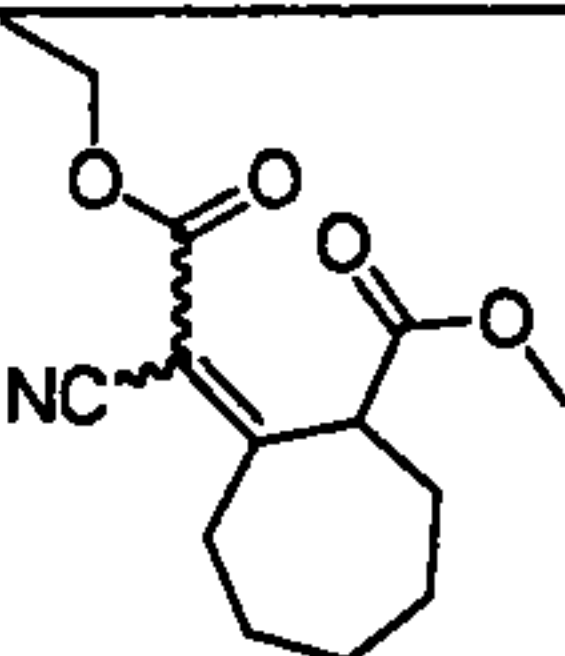
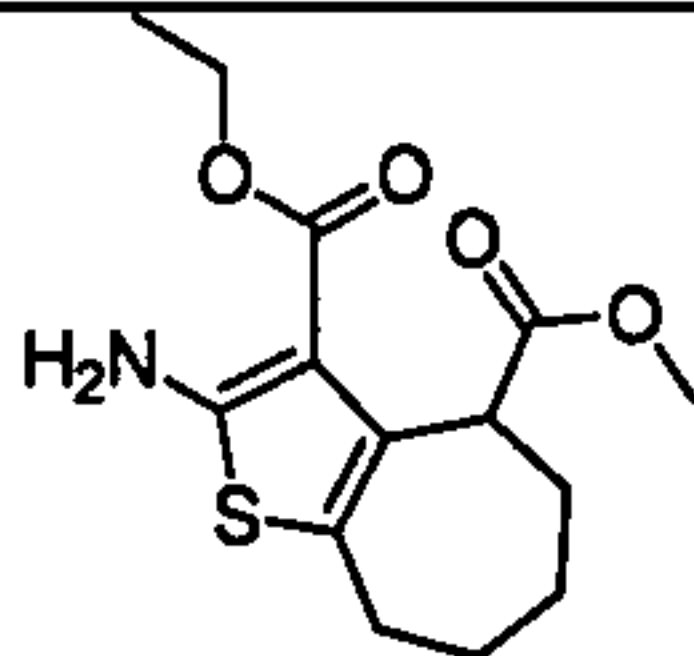
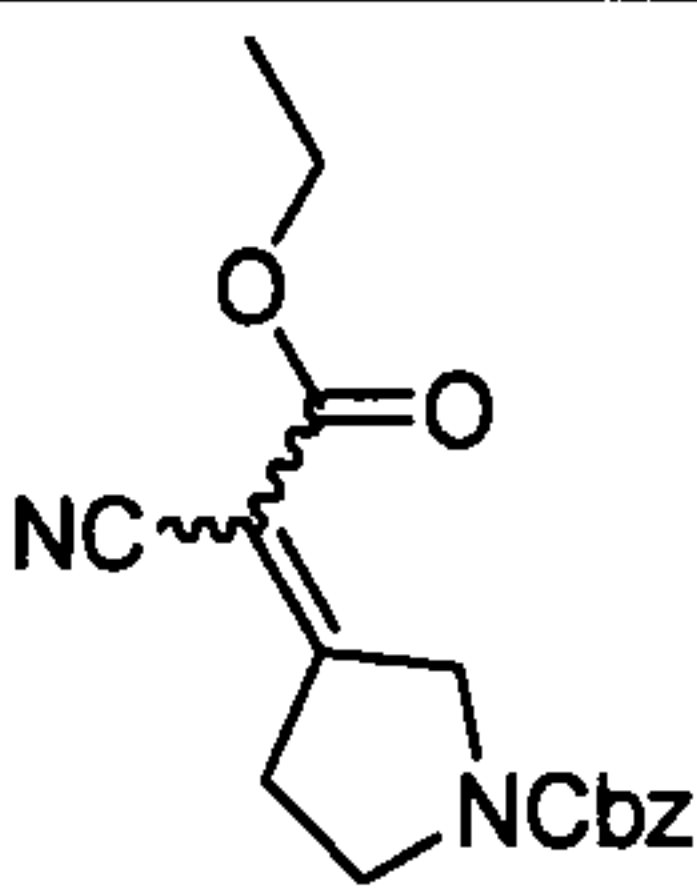
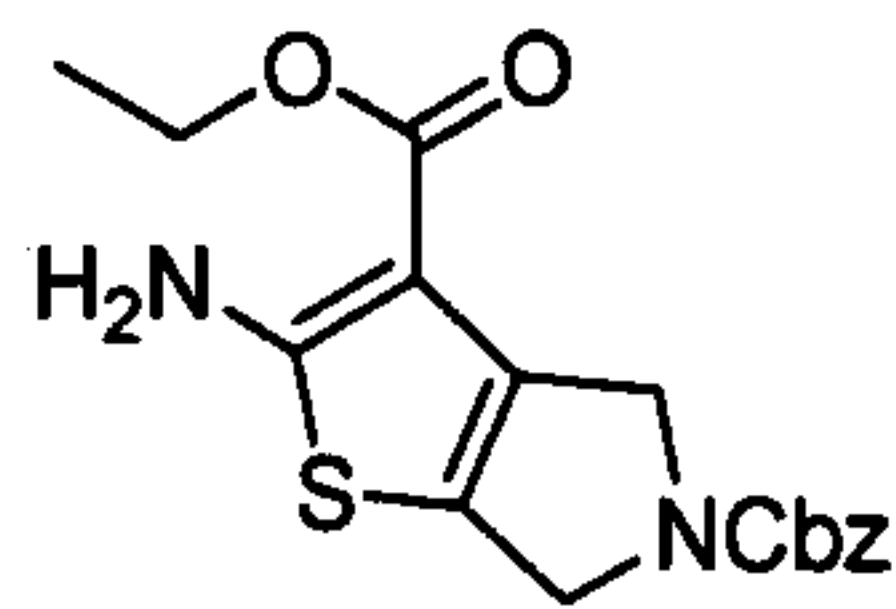
**Preparative Examples 18/1 to 18/21**

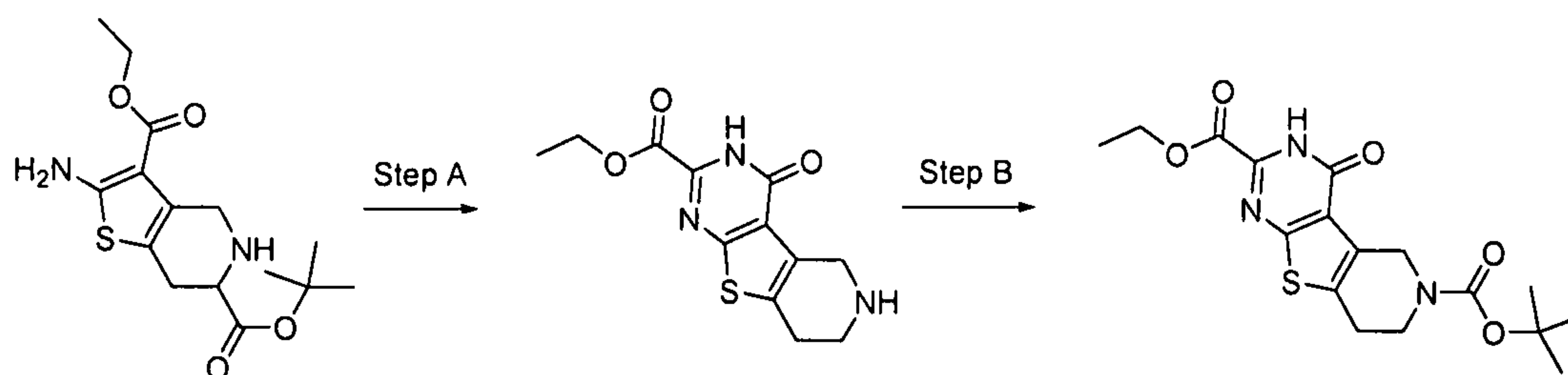
Following similar procedures as described in the Preparative Examples 18 except using the adduct indicated in Table I.7 below, the following compounds were prepared.

5

**Table I.7**

| Ex. # | adduct                                                                              | product                                                                               | yield                                    |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 18/1  |   |   | 43%<br>[MH] <sup>+</sup> = 244           |
| 18/2  |  |  | 62% (2 steps)<br>[MH] <sup>+</sup> = 341 |
| 18/5  |  |  | 98% (2 steps)<br>[MH] <sup>+</sup> = 353 |
| 18/7  |  |  | 82%<br>[MH] <sup>+</sup> = 298           |
| 18/8  |  |  | 65%<br>[MH] <sup>+</sup> = 284           |
| 18/9  |  |  | 80%<br>[MH] <sup>+</sup> = 242           |

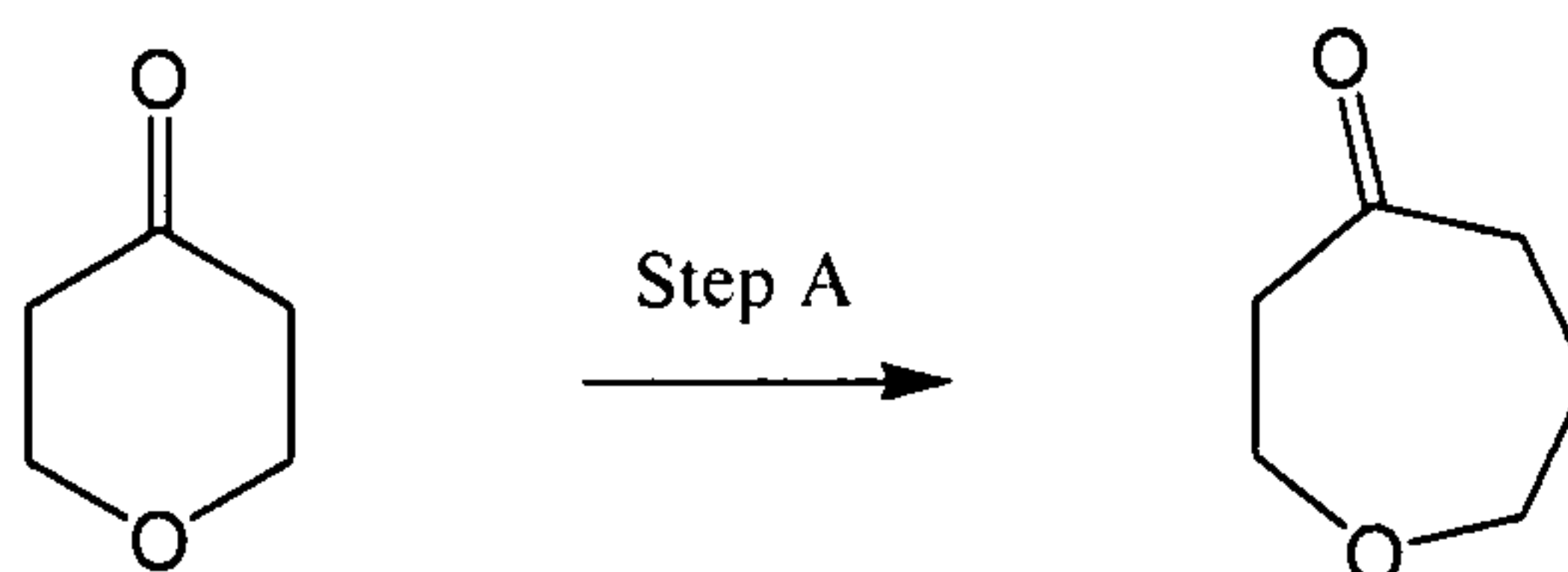
| Ex. # | adduct                                                                              | product                                                                               | yield                                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------|
| 18/10 |    |    | 92% (2 steps)<br>[MH] <sup>+</sup> = 258  |
| 18/12 |    |    | 47% (2 steps)<br>[MH] <sup>+</sup> = 312  |
| 18/13 |  |  | 79%<br>[MH] <sup>+</sup> = 298            |
| 18/14 |  |  | 38% (2 steps)<br>[MH] <sup>+</sup> = 298  |
| 18/15 |  |  | 62% (2 steps)<br>[MH] <sup>+</sup> = 270  |
| 18/17 |  |  | 61%<br>[MH] <sup>+</sup> = 298            |
| 18/21 |  |  | 30% (2 steps).<br>[MH] <sup>+</sup> = 347 |

**Preparative Example 19****Step A**

5 Ethyl-2-amino-6-terbutoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-3-carboxylate (0.5 g) was dissolved in a 4M solution of HCl in 1,4-dioxane (20 mL) and nitriloacetic acid ethyl ester (0.25 mL) was added. The mixture was stirred at 50°C for 3 h and concentrated. The decarboxylation of the ester was observed. This product was used in the following step without further purification.  $[MH]^+ = 280$ .

10 **Step B**

The title compound of Step A above was dissolved in DMF and triethylamine (0.32 mL) was added. Di-*tert*-butyl dicarbonate (0.5 g) was added and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation. The residue was dissolved in dichloromethane and washed with  
15 water, dried and evaporated to give the title compound (580 mg) as a yellow solid.  $[MH]^+ = 380$ .

**Preparative Example 20**

Step A

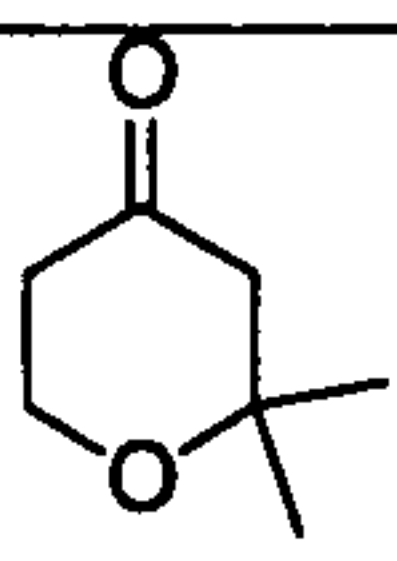
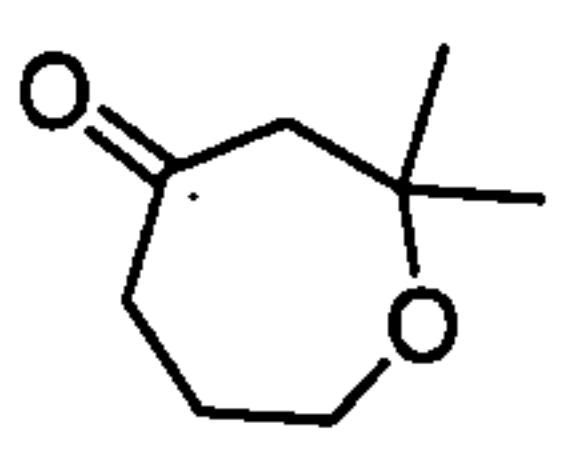
Tetrahydro-2*H*-pyran-4-one (1 g) was placed in methanol in presence of barium oxide (0.1 g). Nitrosomethylurethane (1.3 g) was added slowly to the reaction mixture. During the addition, barium oxide (0.2 g) was added by small portion. The reaction was stirred 3 hours at room temperature and then filtrated. The methanol was evaporated, diethyl ether was then added to the residue, a precipitate was formed. The mixture was filtrated and diethyl ether evaporated to afford the title compound (790 mg, 70%) as a yellow oil.  $[MH]^+ = 115$ .

10

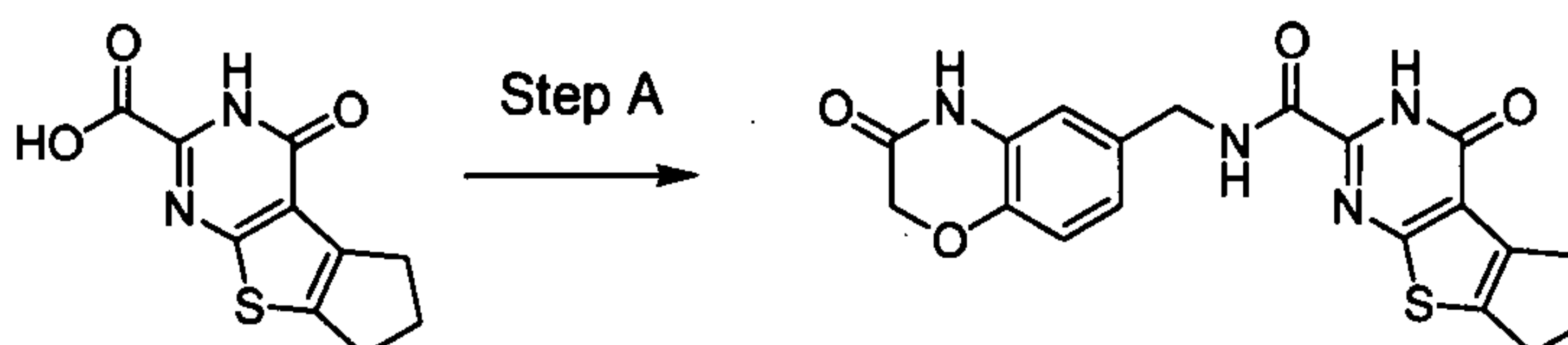
Preparative Example 20/1

Following similar procedures as described in the Preparative Examples 20, except using the educt indicated in Table I.13 below, the following compounds were prepared.

Table I.13

| Ex. # | Educt                                                                               | product                                                                               | yield                  |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------|
| 20/1  |  |  | 76 %<br>$[MH]^+ = 143$ |

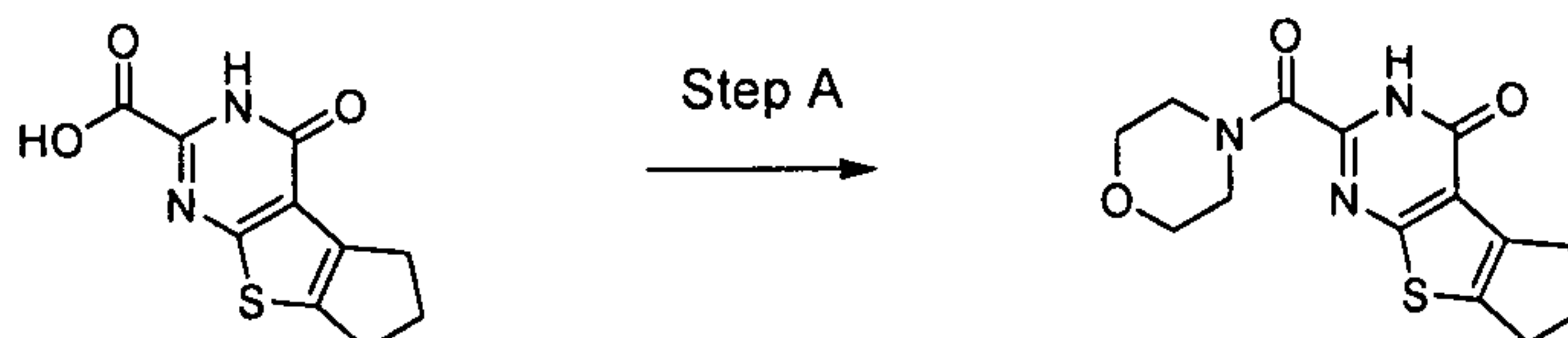
15

Example 1Step A

To a solution of the title compound from Preparative Example 11 above (30 mg), EDCI (50 mg) and HOAt (22 mg) in DMF (10 mL) were added *N*-methylmorpholine (50  $\mu$ L) and the title compound from the Preparative Example 13 (50 mg). The mixture was stirred overnight and then concentrated.

- 5 The remaining residue was suspended in 10% aqueous citric acid and the residue was filtered to afford the title compound as an off white solid (38 mg, 74%).  
[MH]<sup>+</sup> = 397.

### Example 1a



### Step A

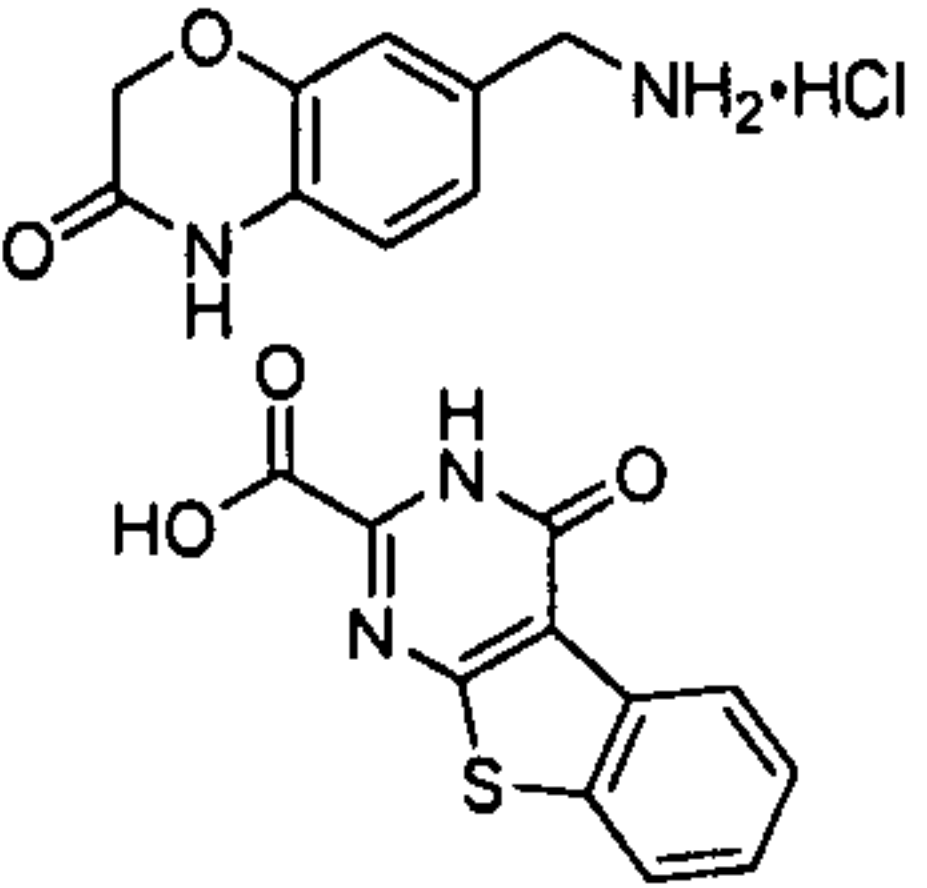
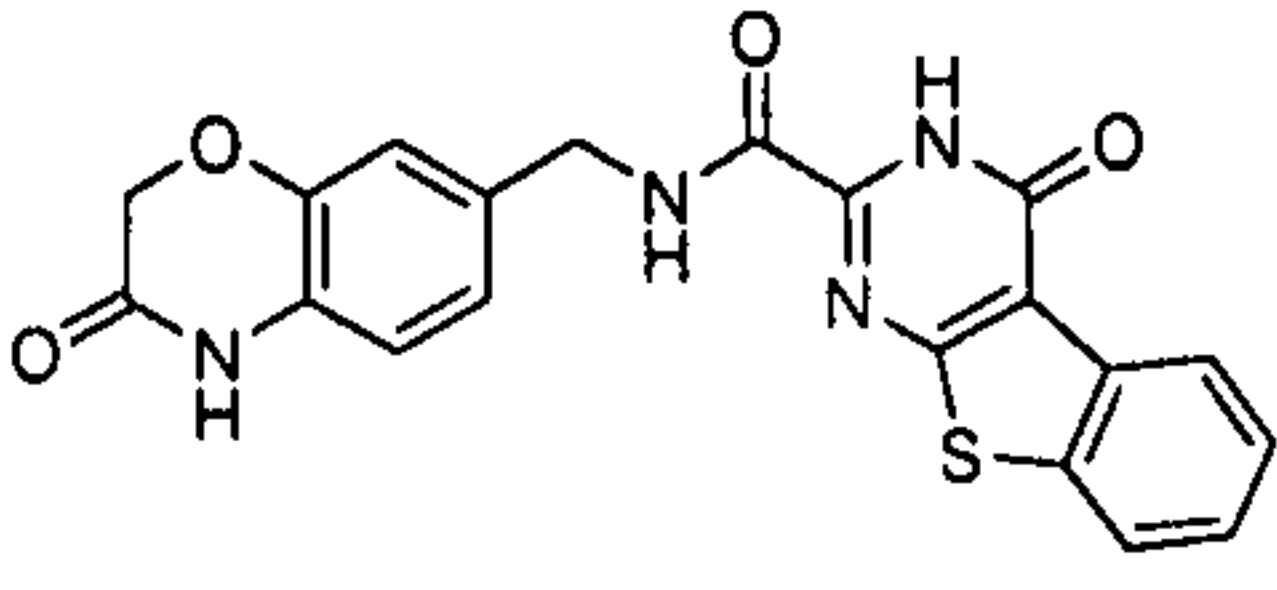
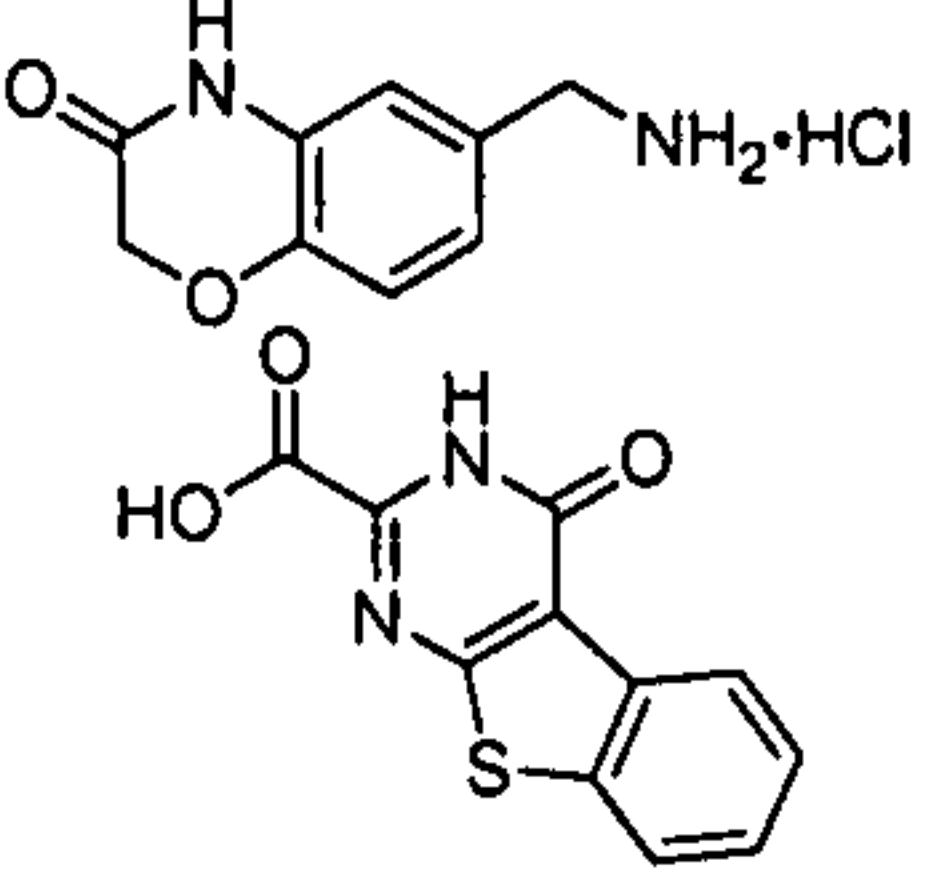
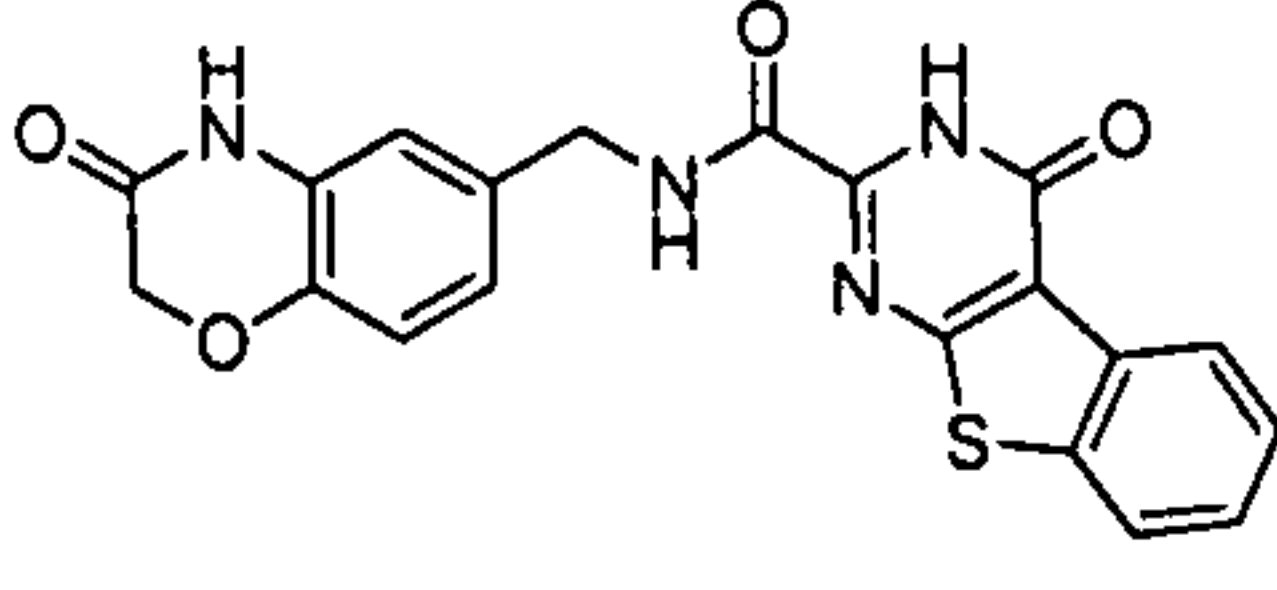
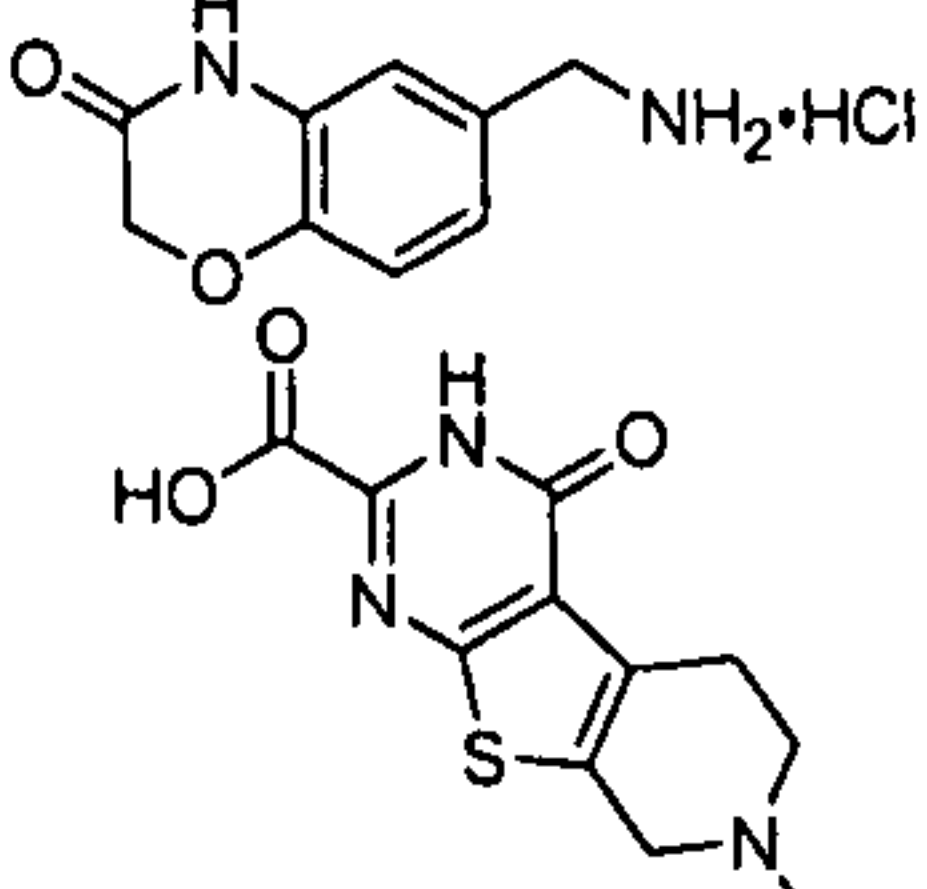
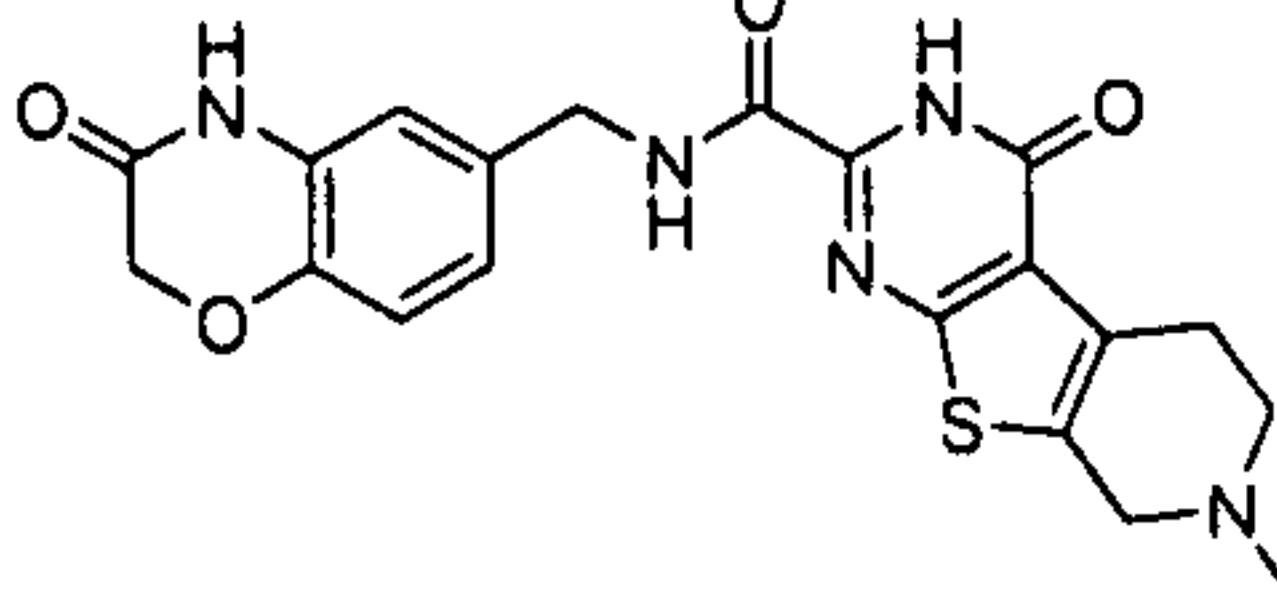
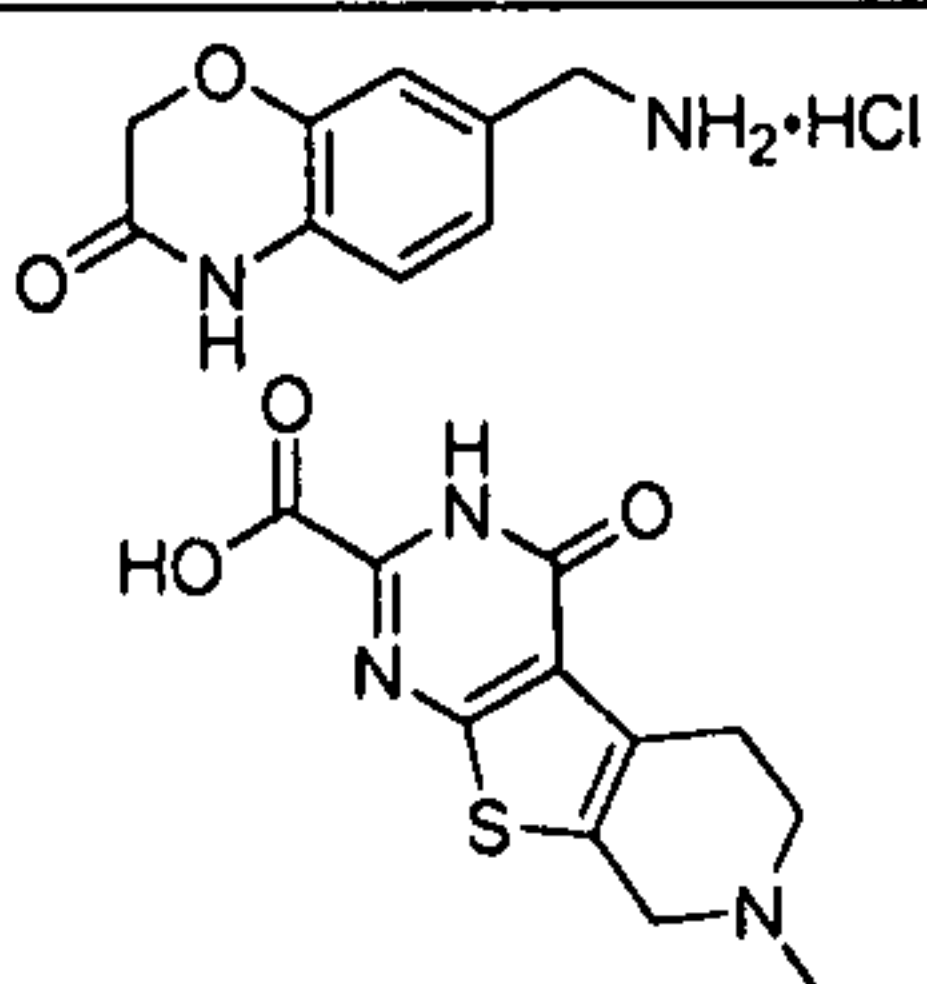
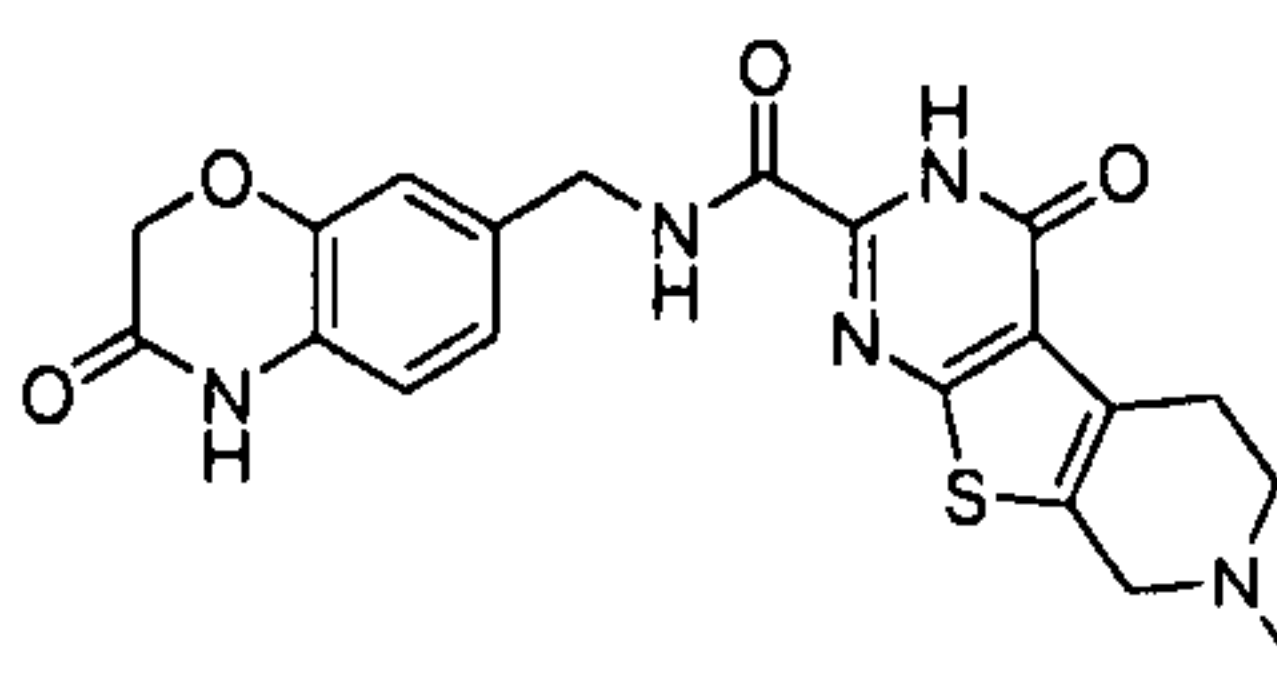
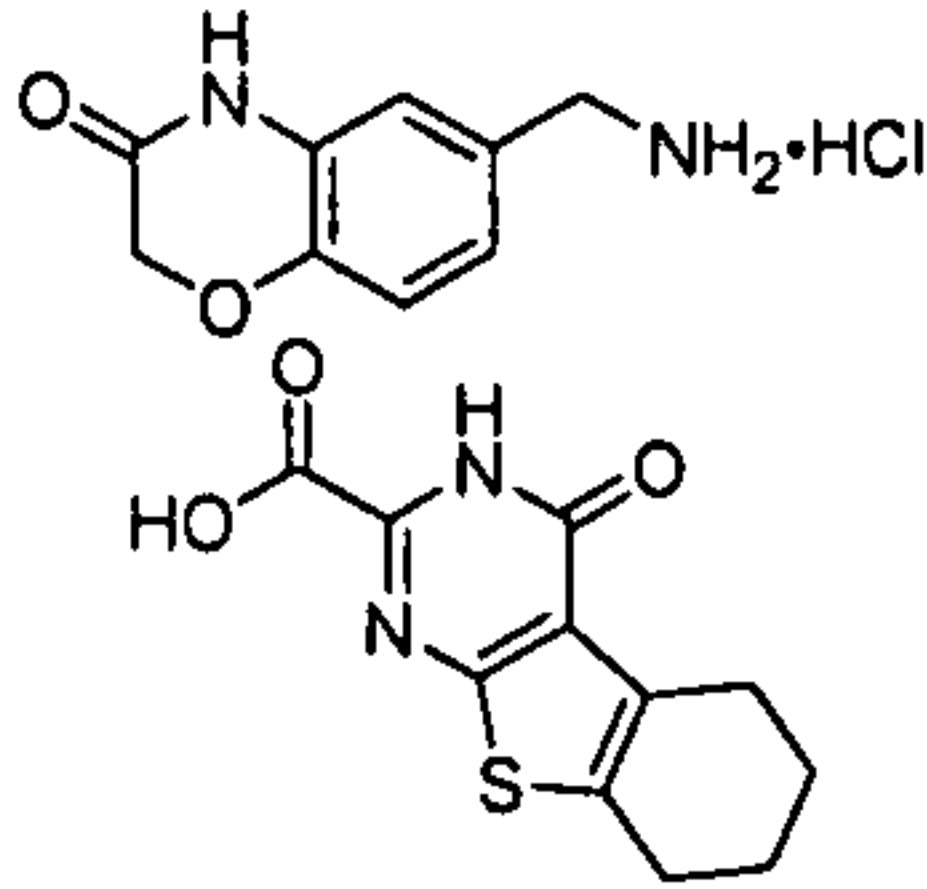
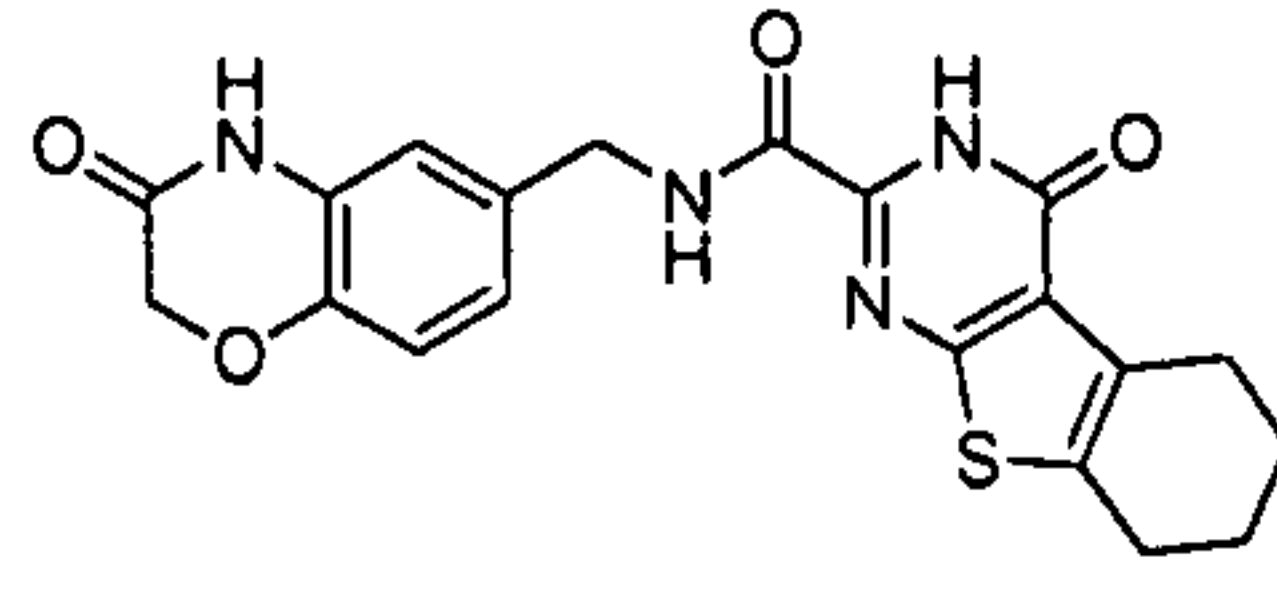
- To a solution of the title compound from Preparative Example 12/16 above (9.5 mg), HATU (23.3 mg) and HOAt (8.2 mg) in DMA (200  $\mu$ L) was added a 0.1 M solution of morpholine in DMA/pyridine(1:1, 440  $\mu$ L). The resulting mixture  
15 was agitated (~600 rpm) at room temperature for 4 h, concentrated and purified by HPLC (RP-C18, ACN/H<sub>2</sub>O) to afford the title compound. [MH]<sup>+</sup> = 305.

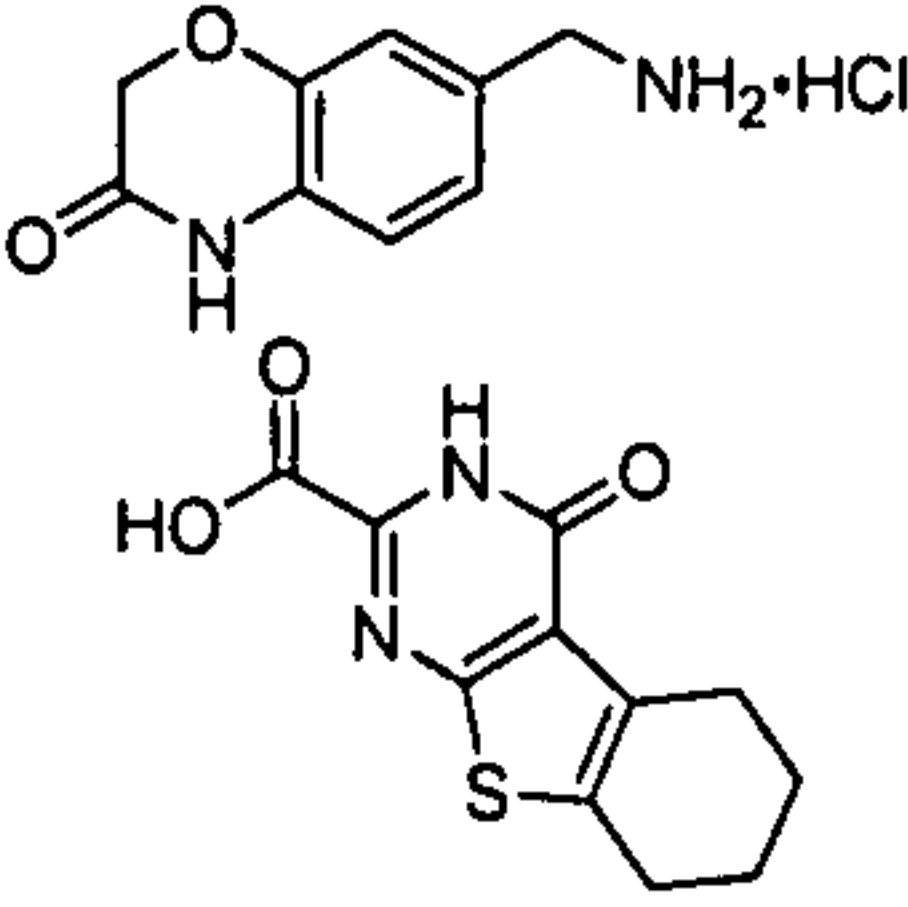
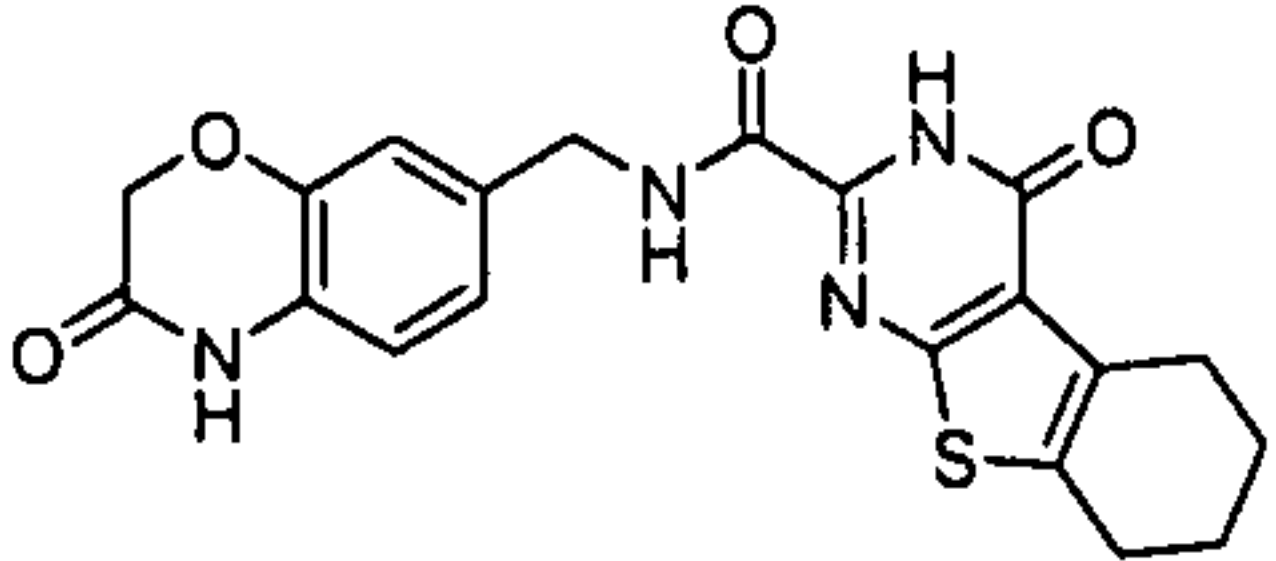
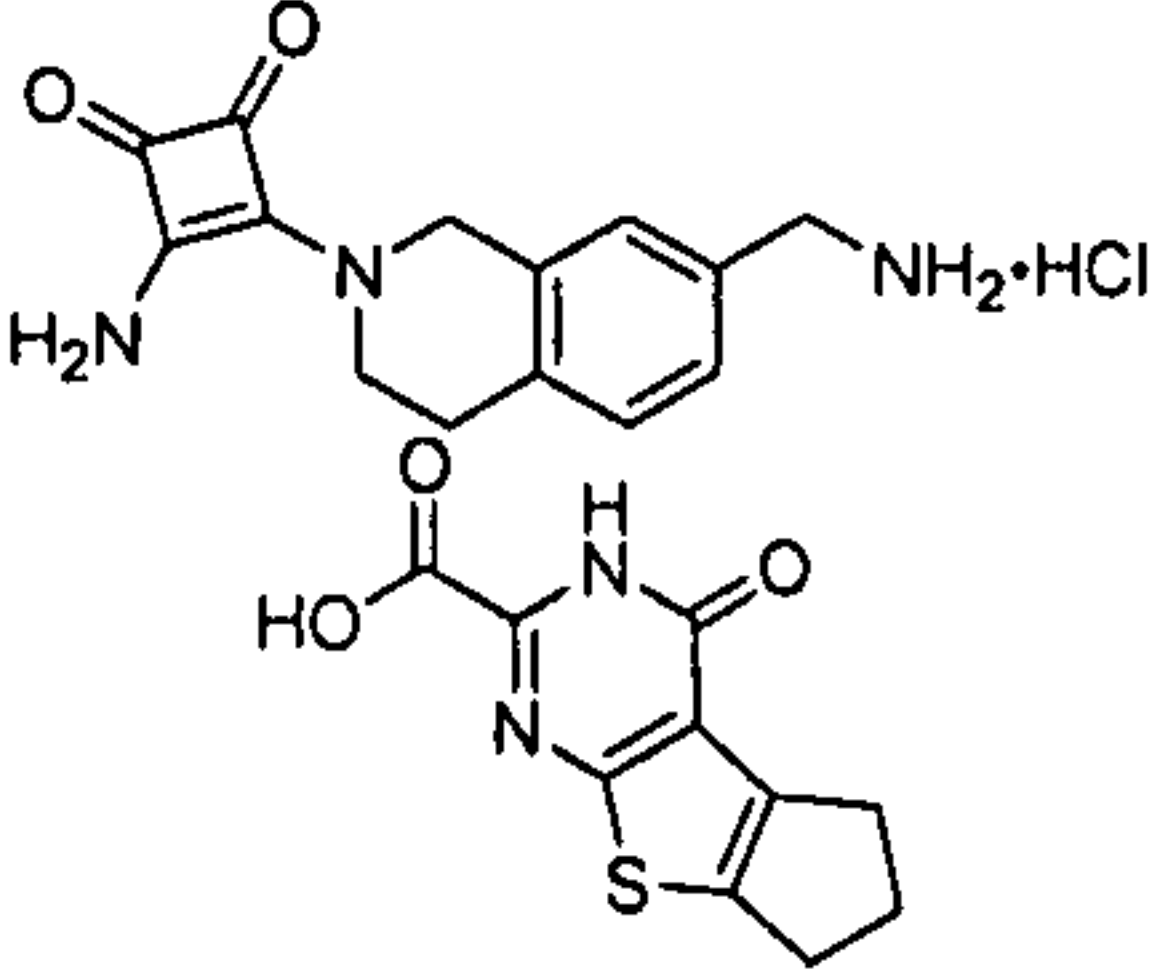
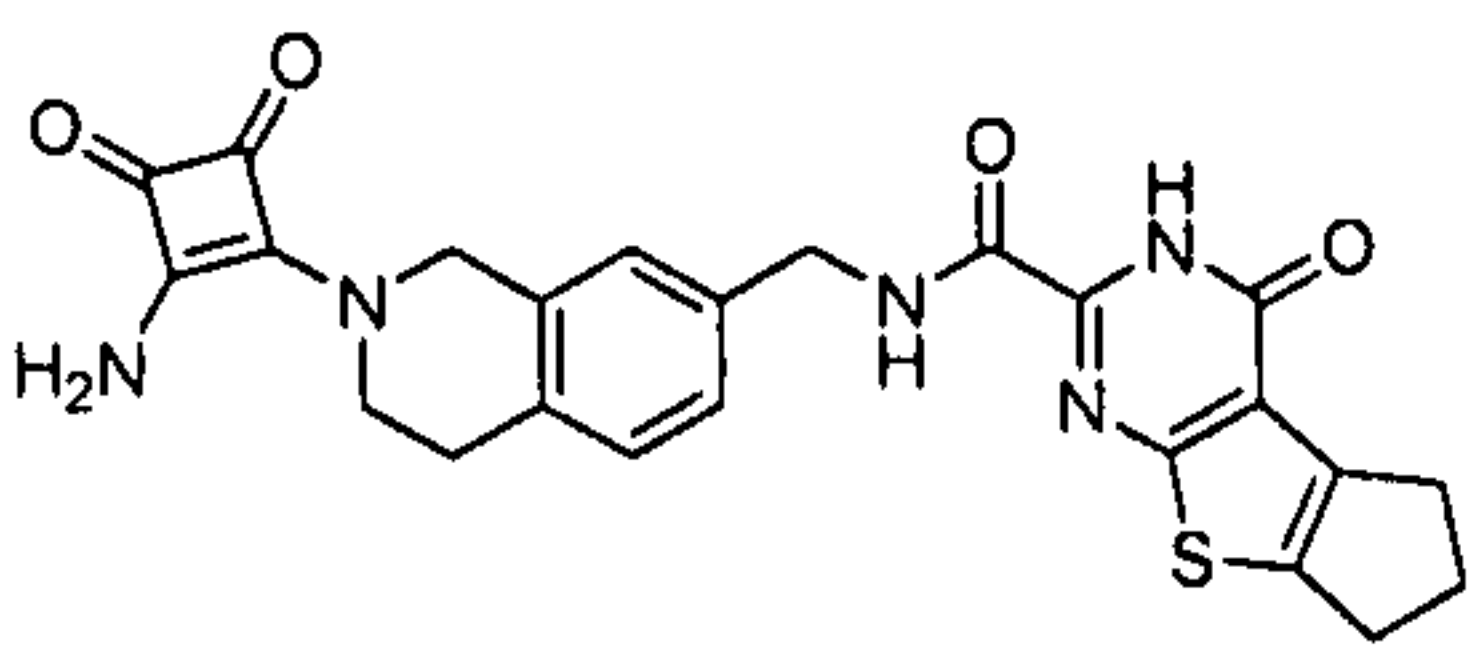
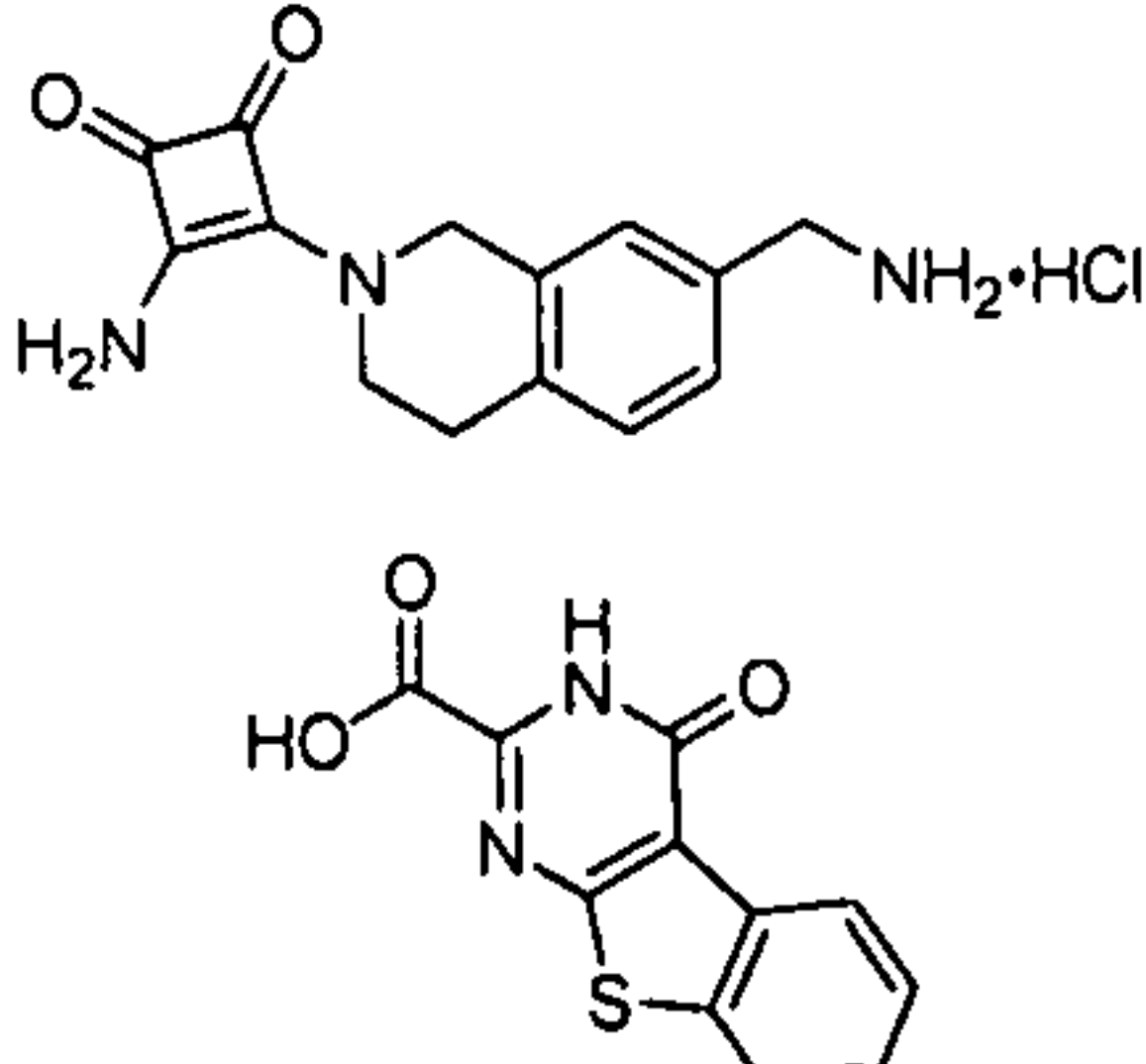
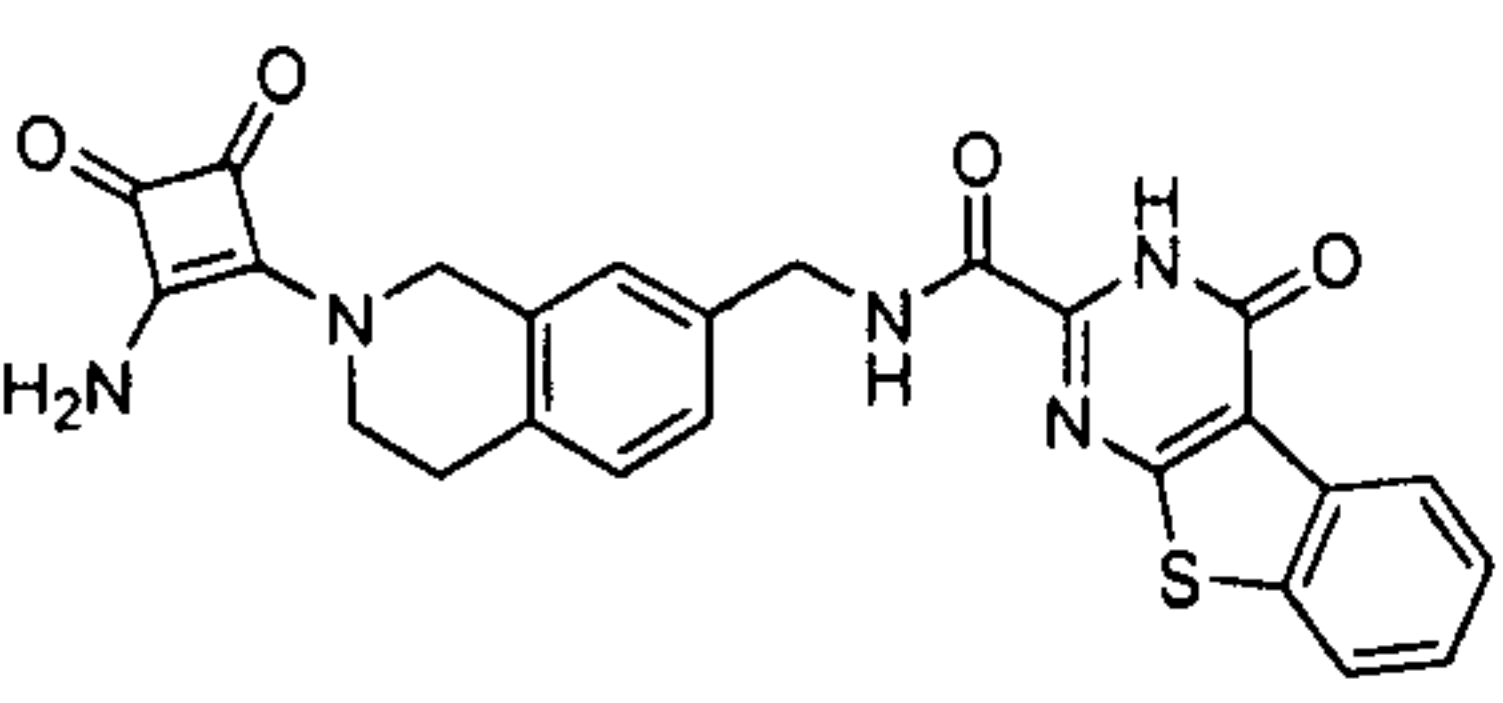
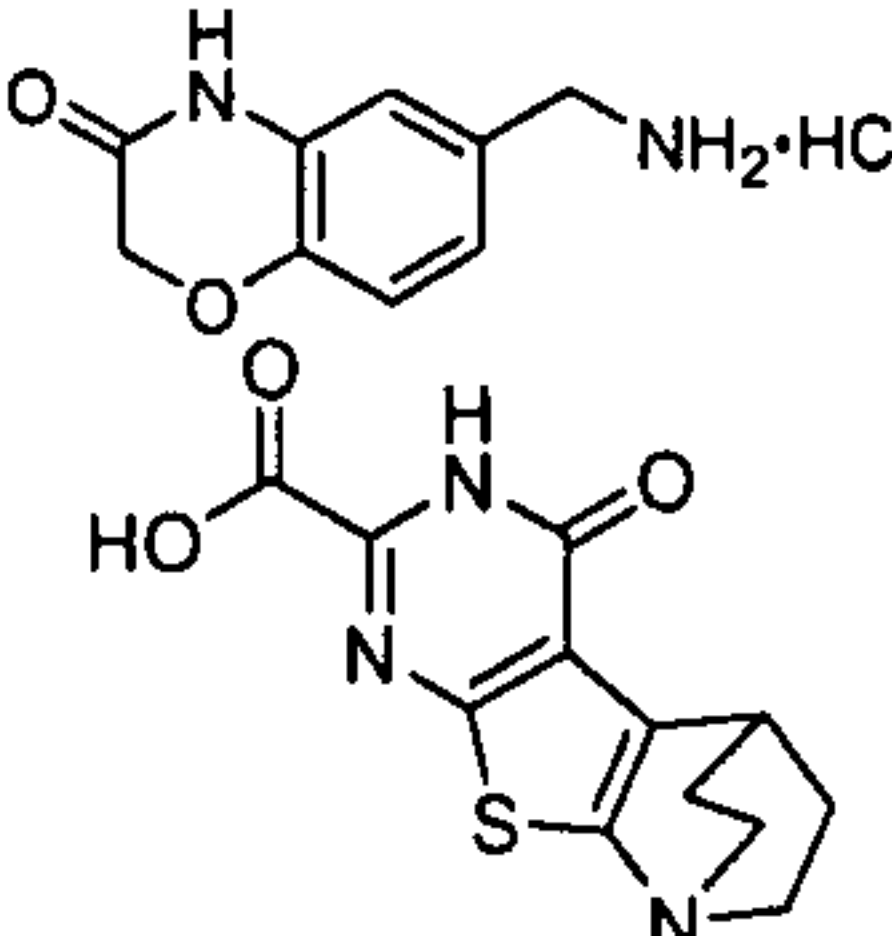
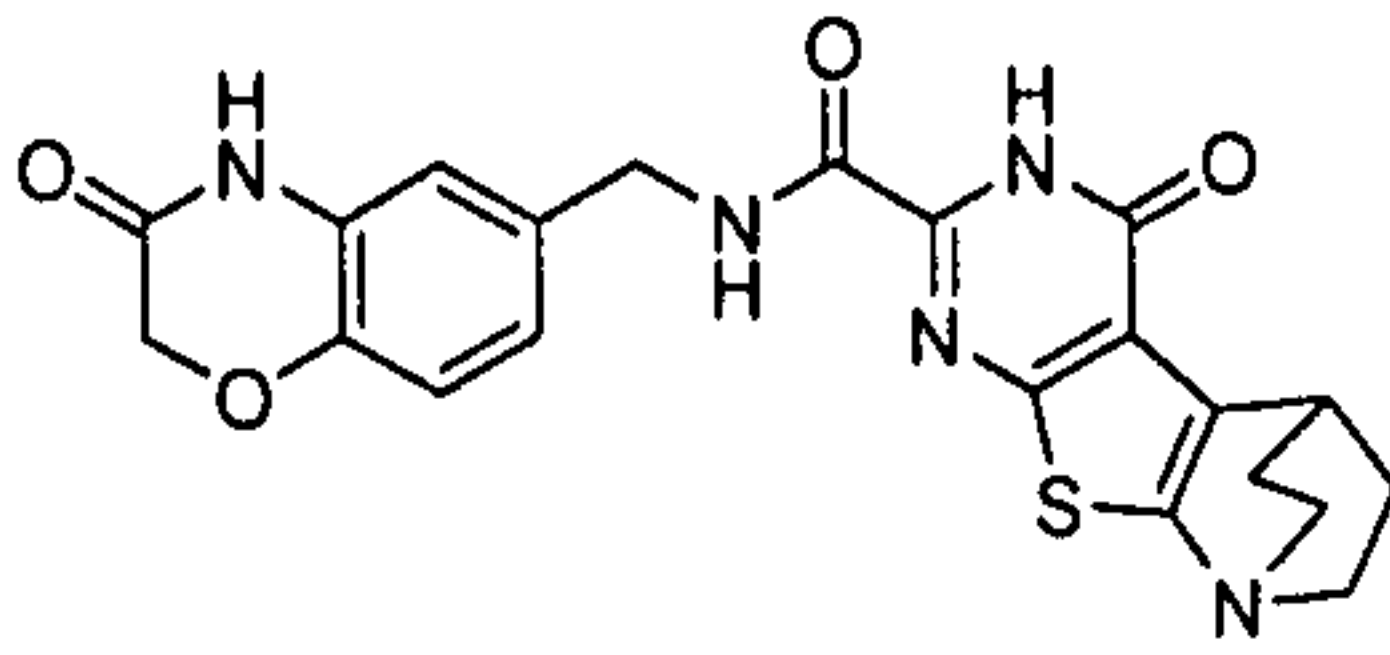
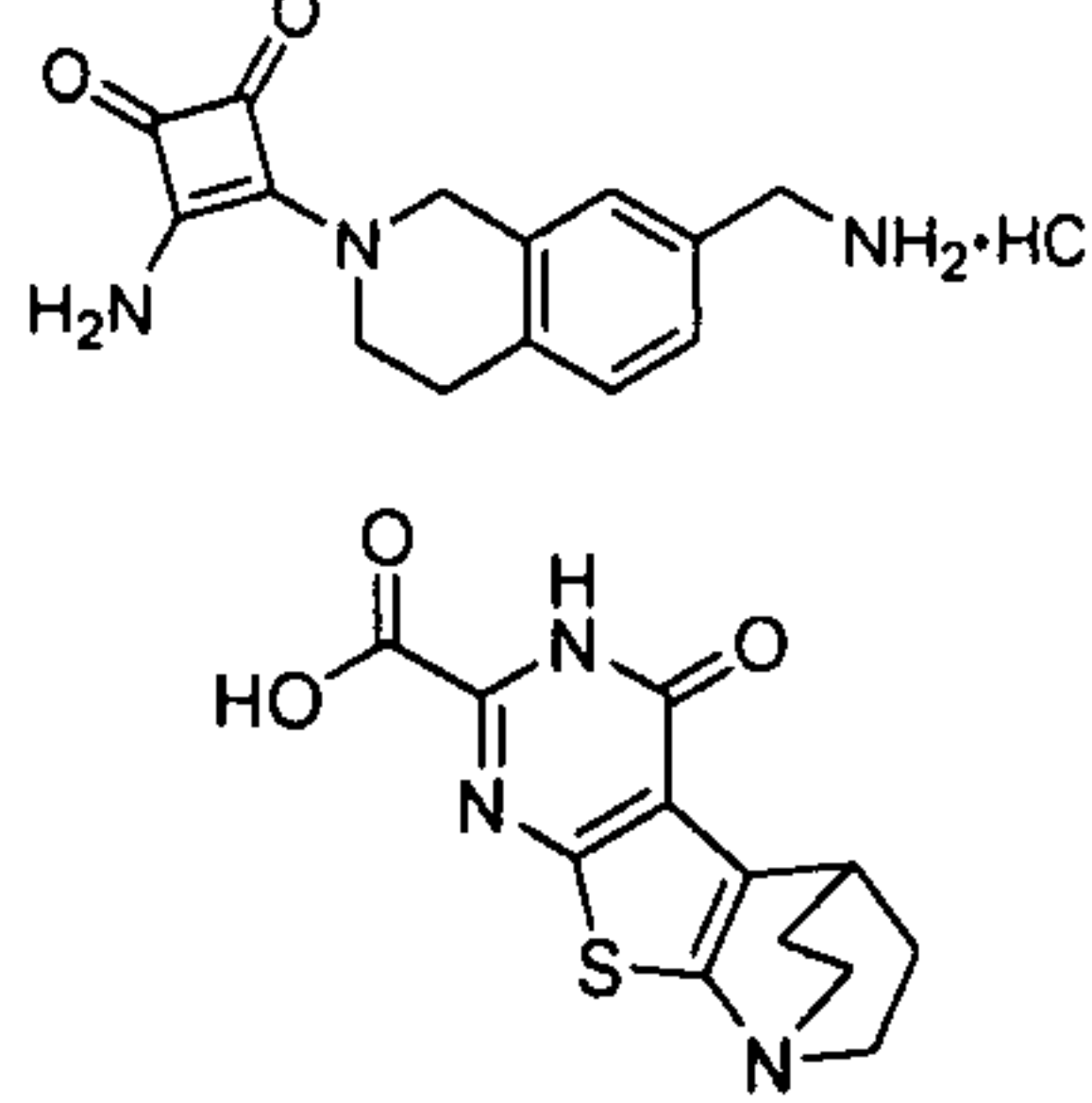
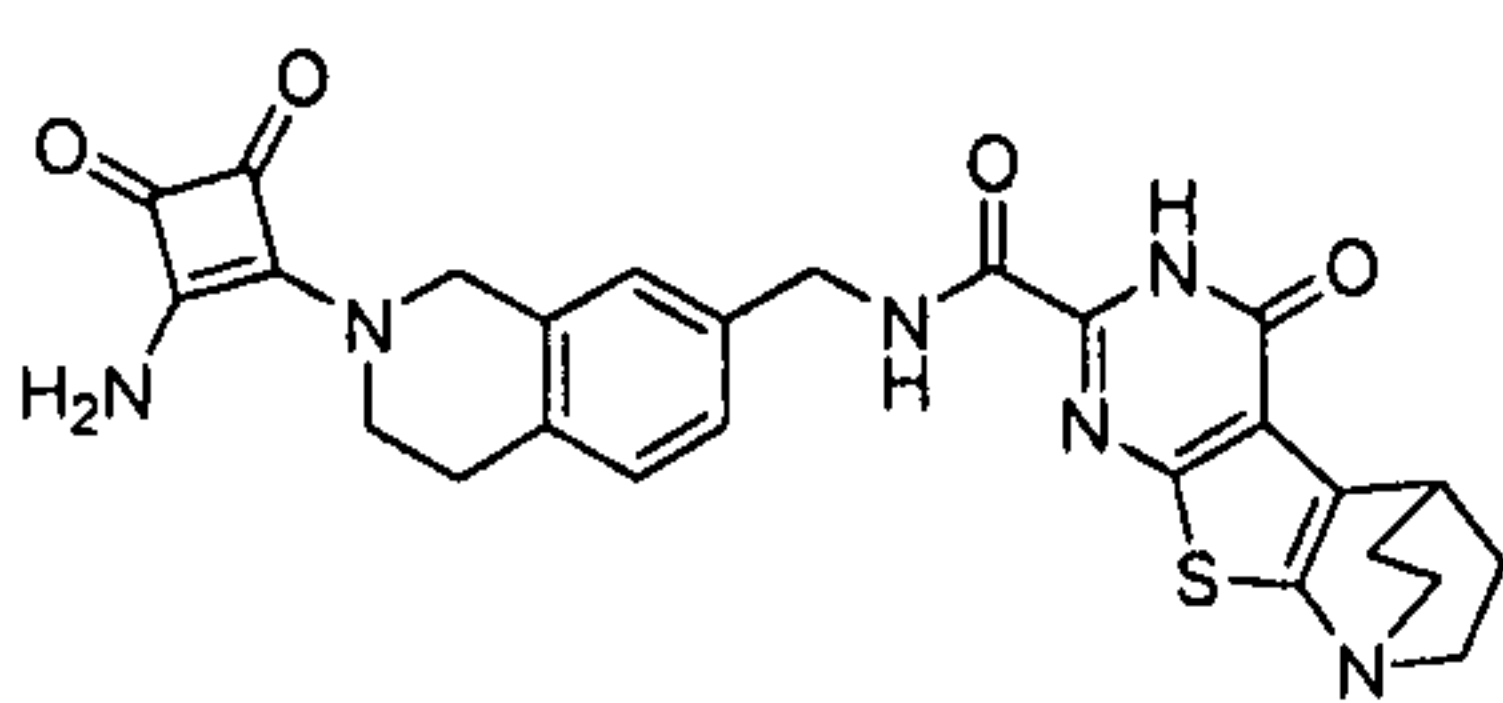
**Examples 2/24-2/547**

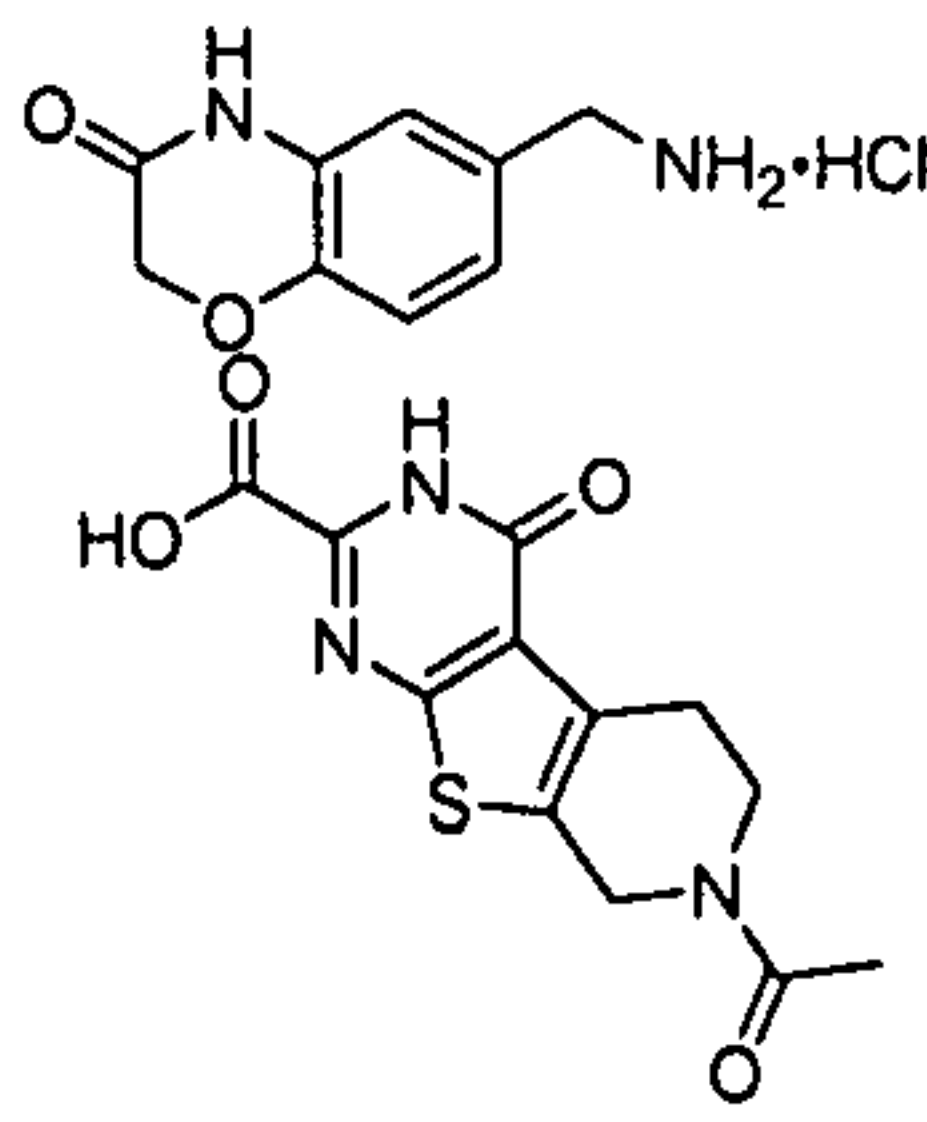
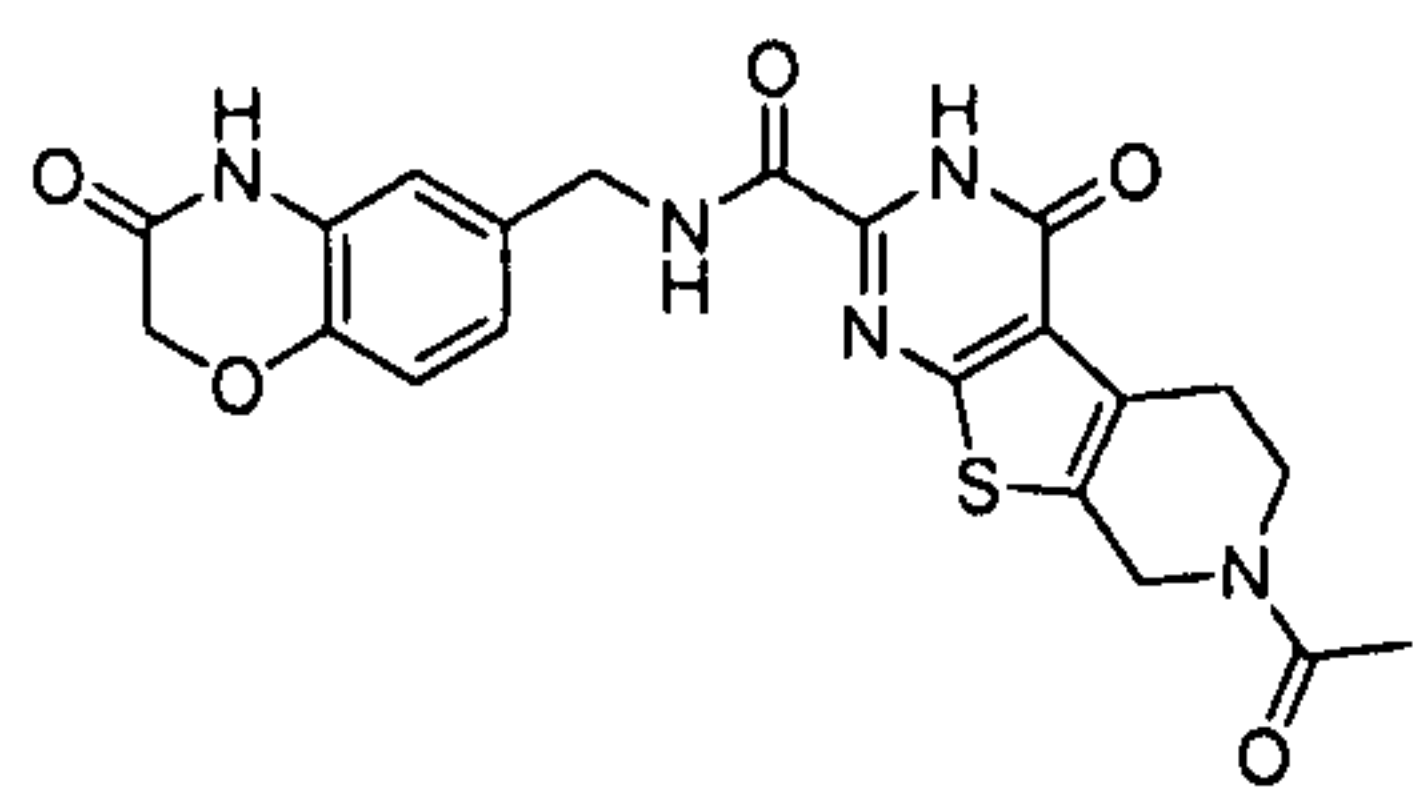
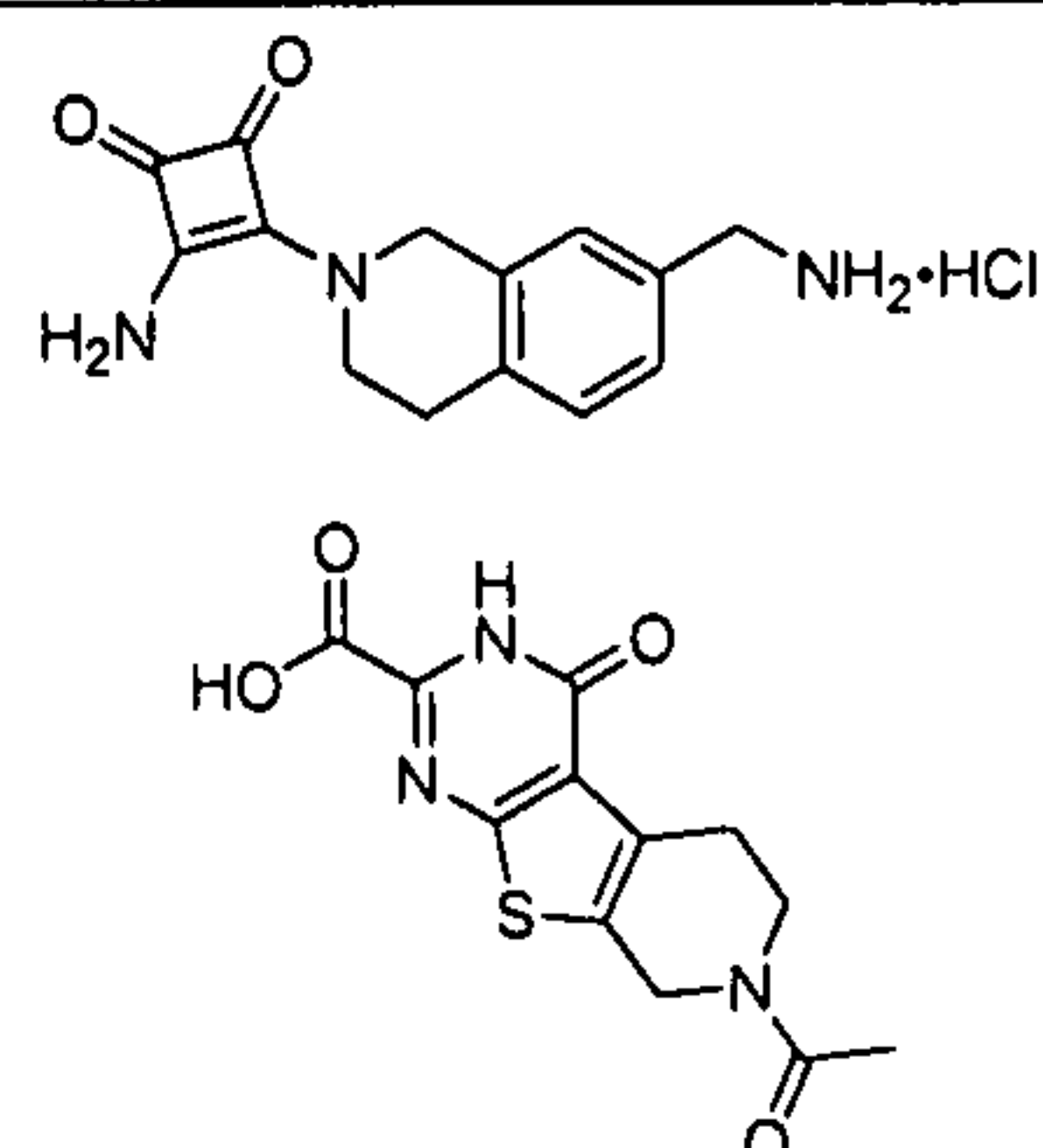
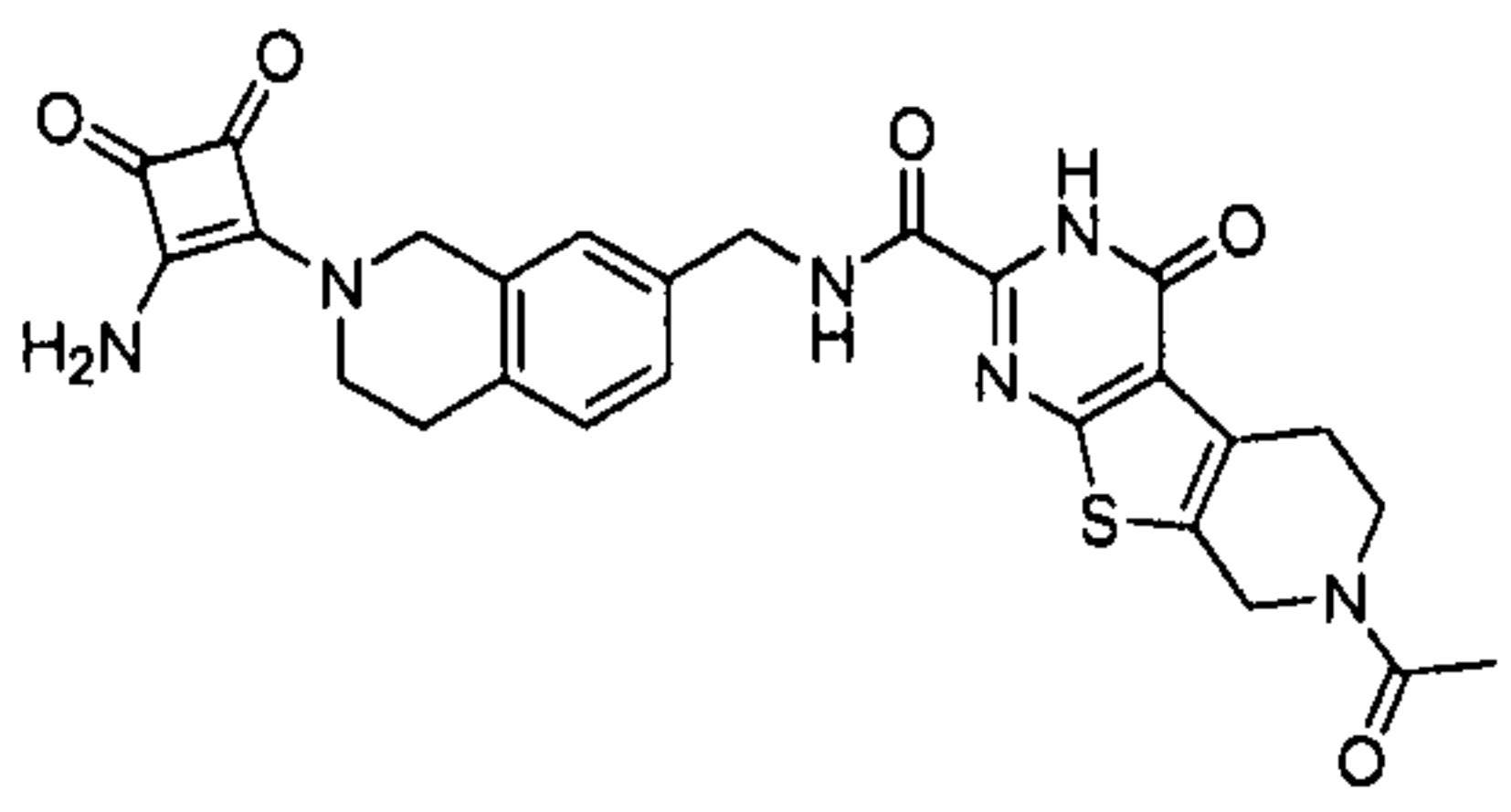
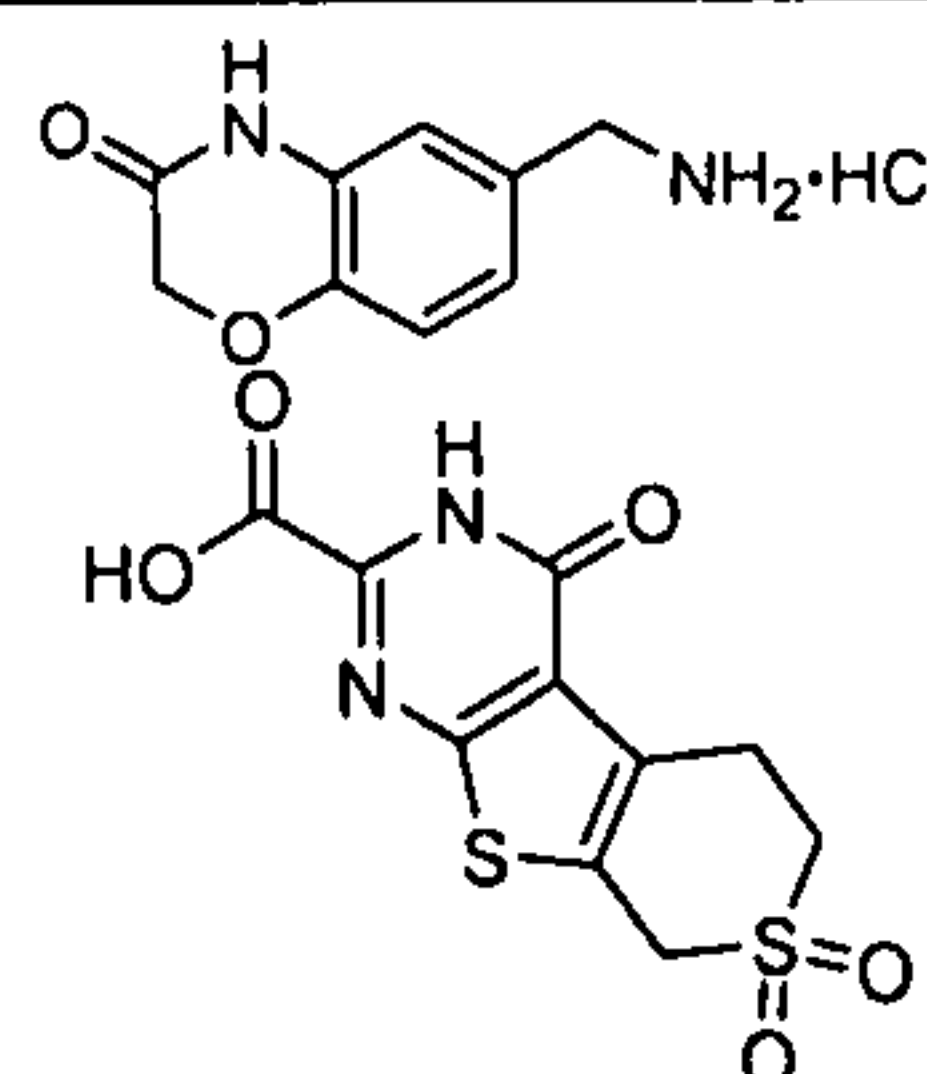
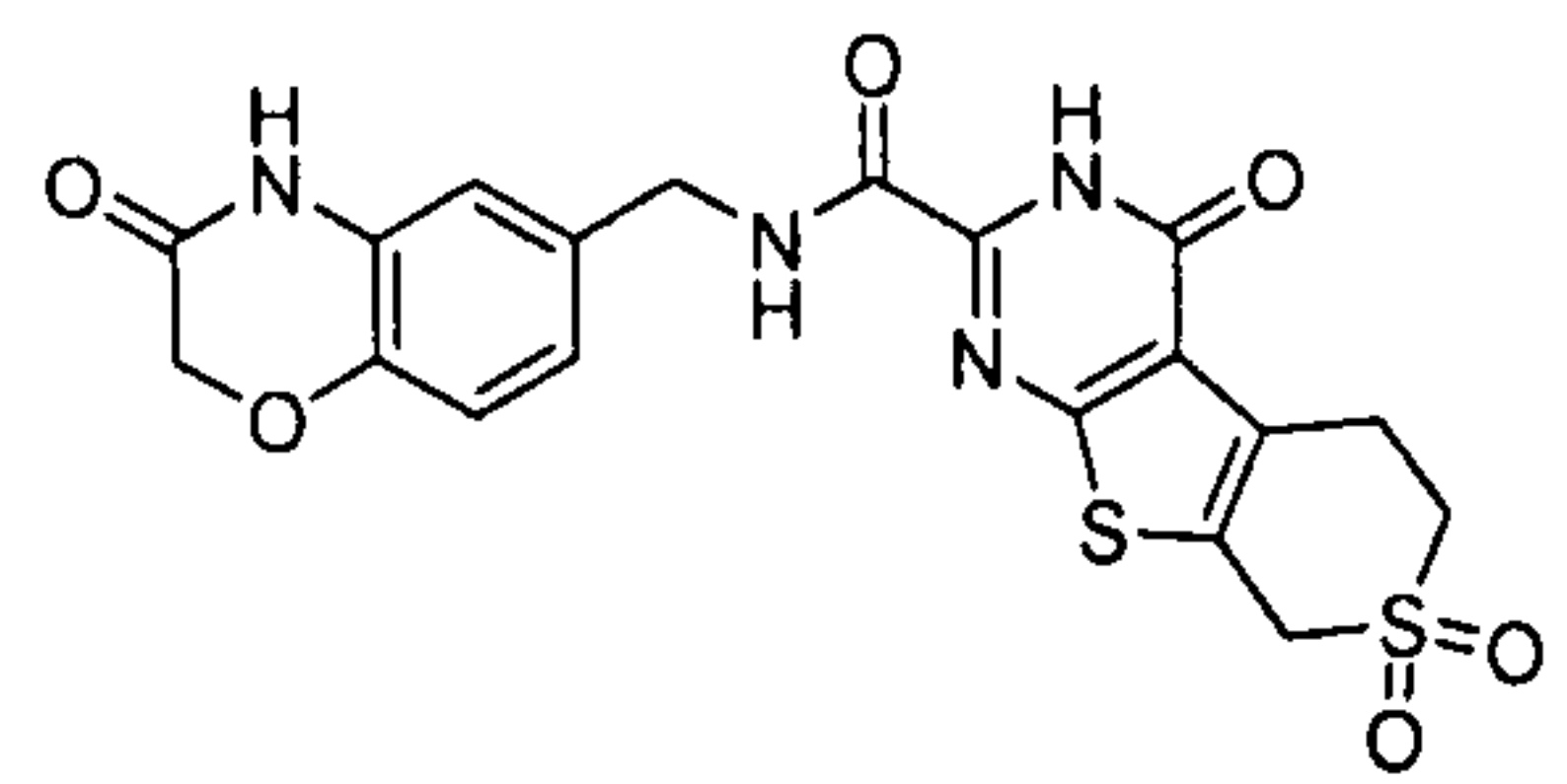
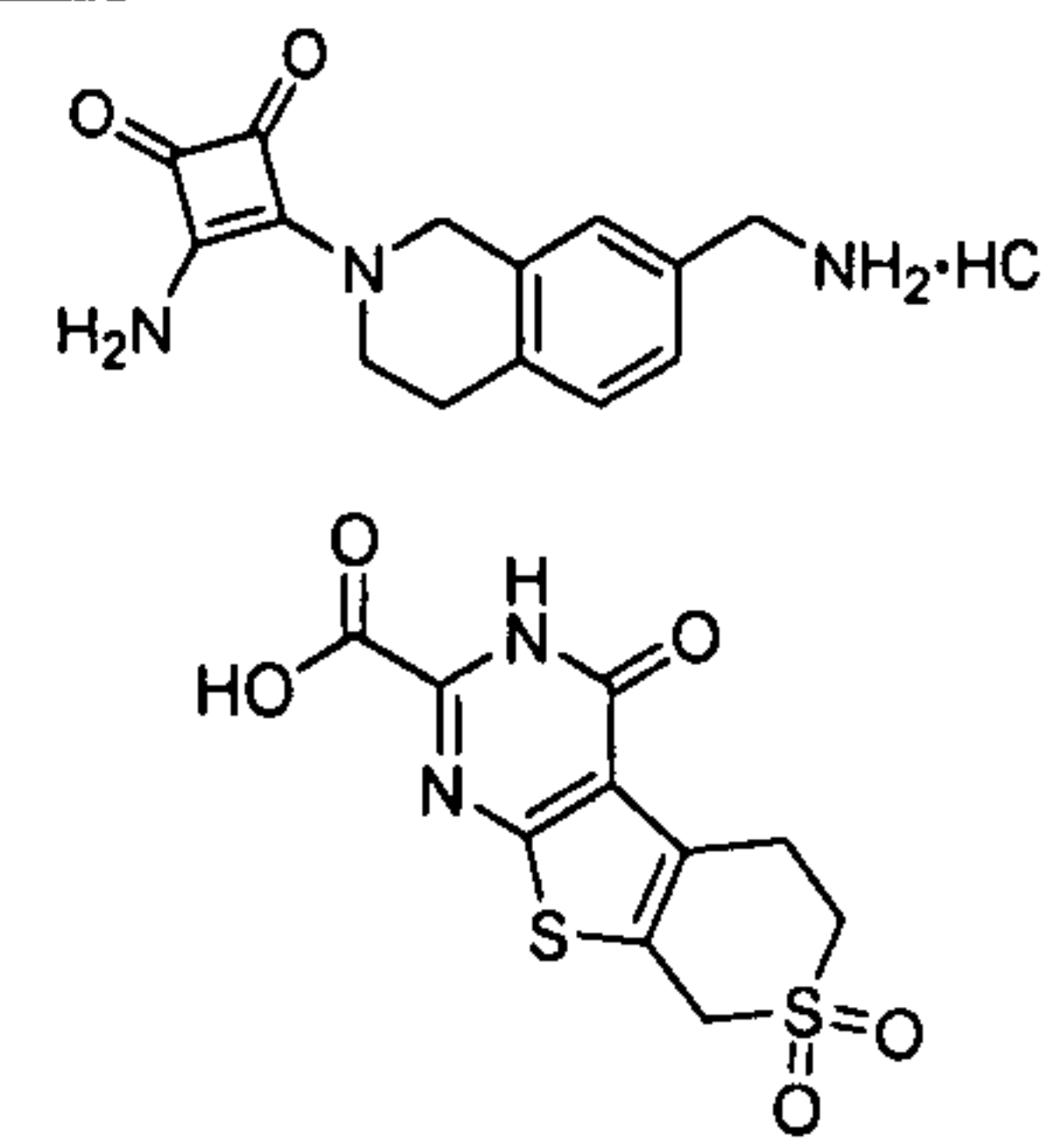
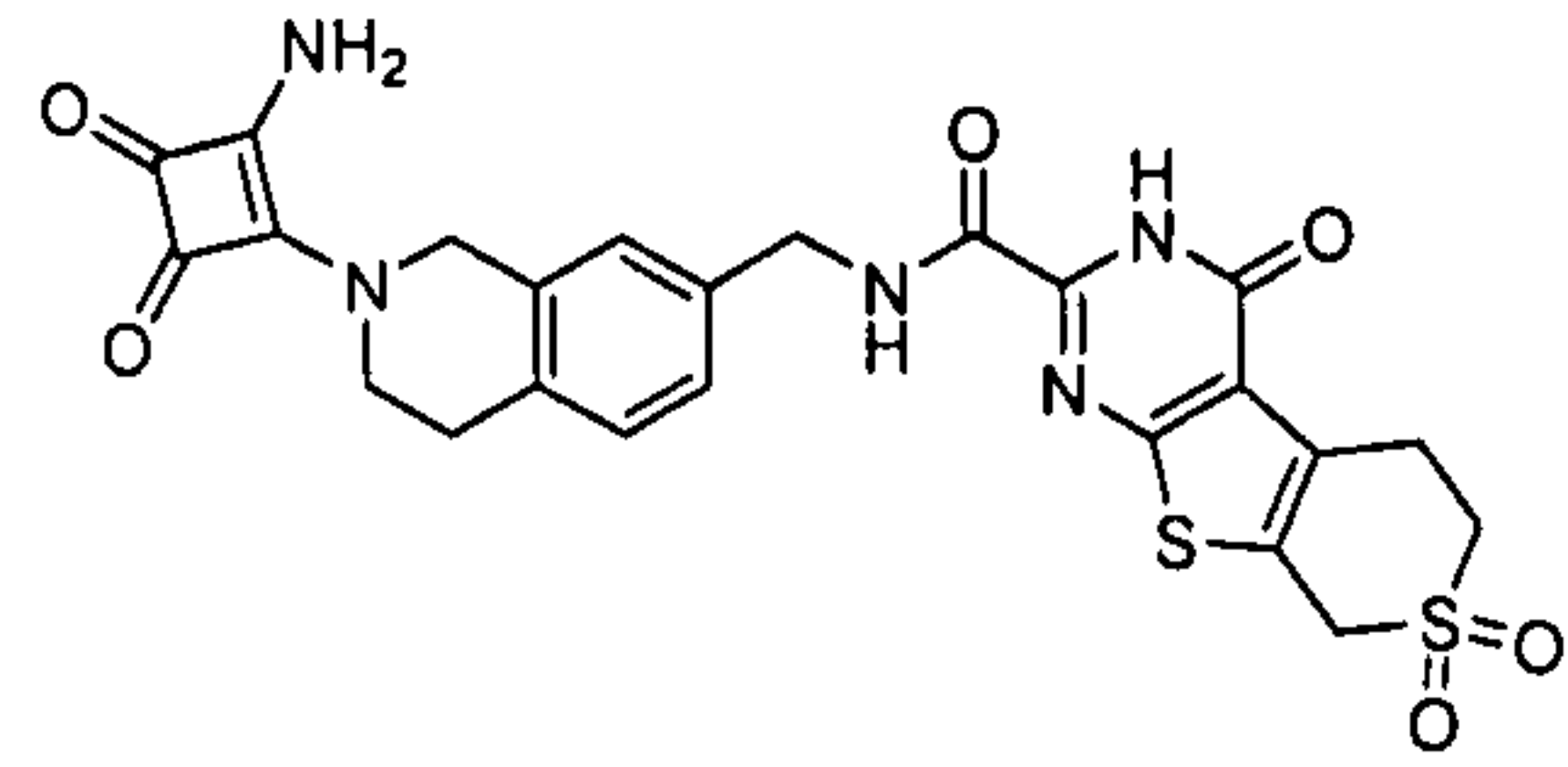
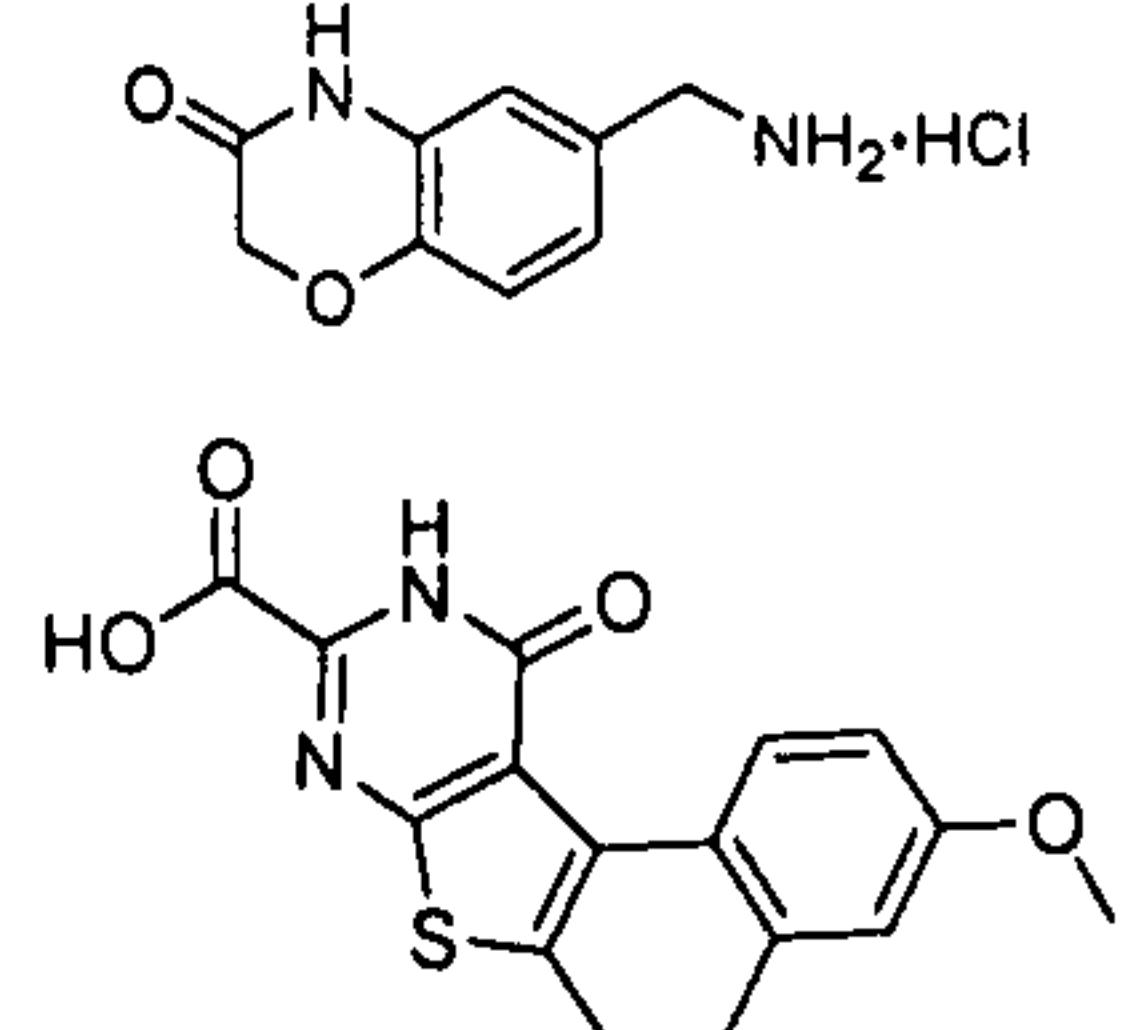
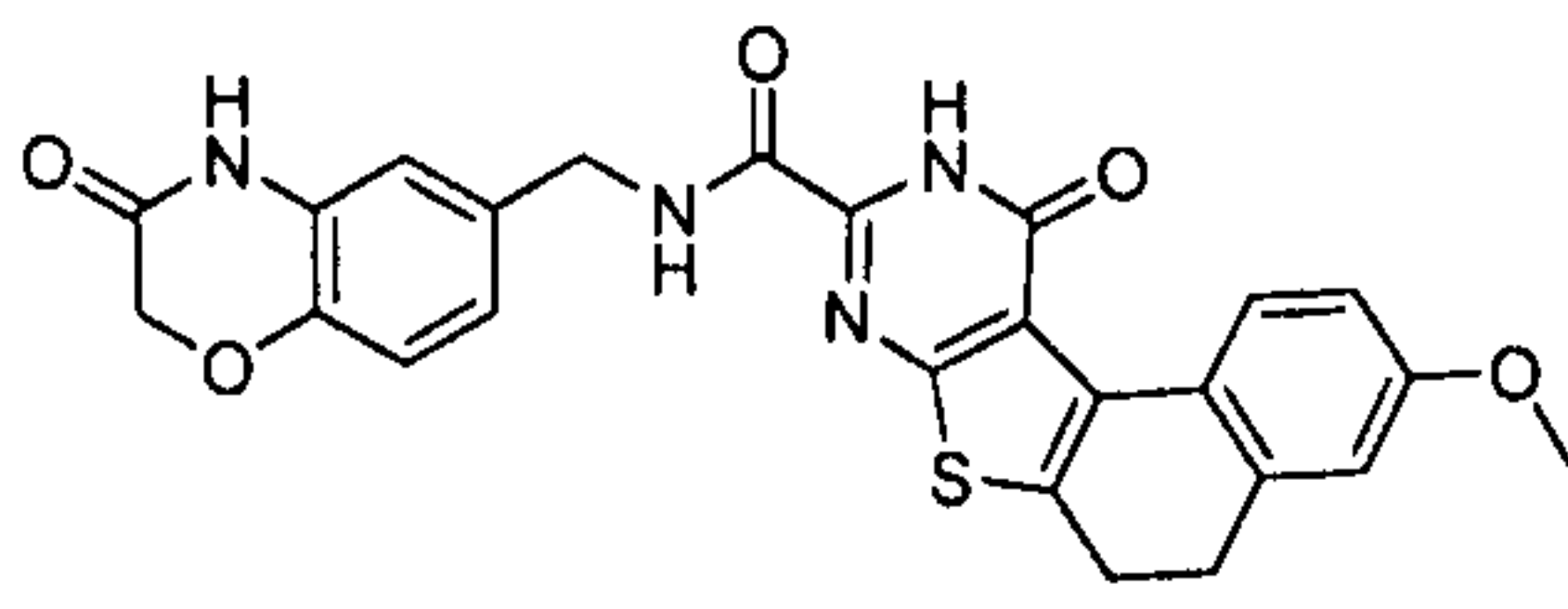
Following similar procedures as described in the Examples 1 (method A) or 1a (method B), except using the amines and acids indicated in Table II.1 below, the following compounds were prepared.

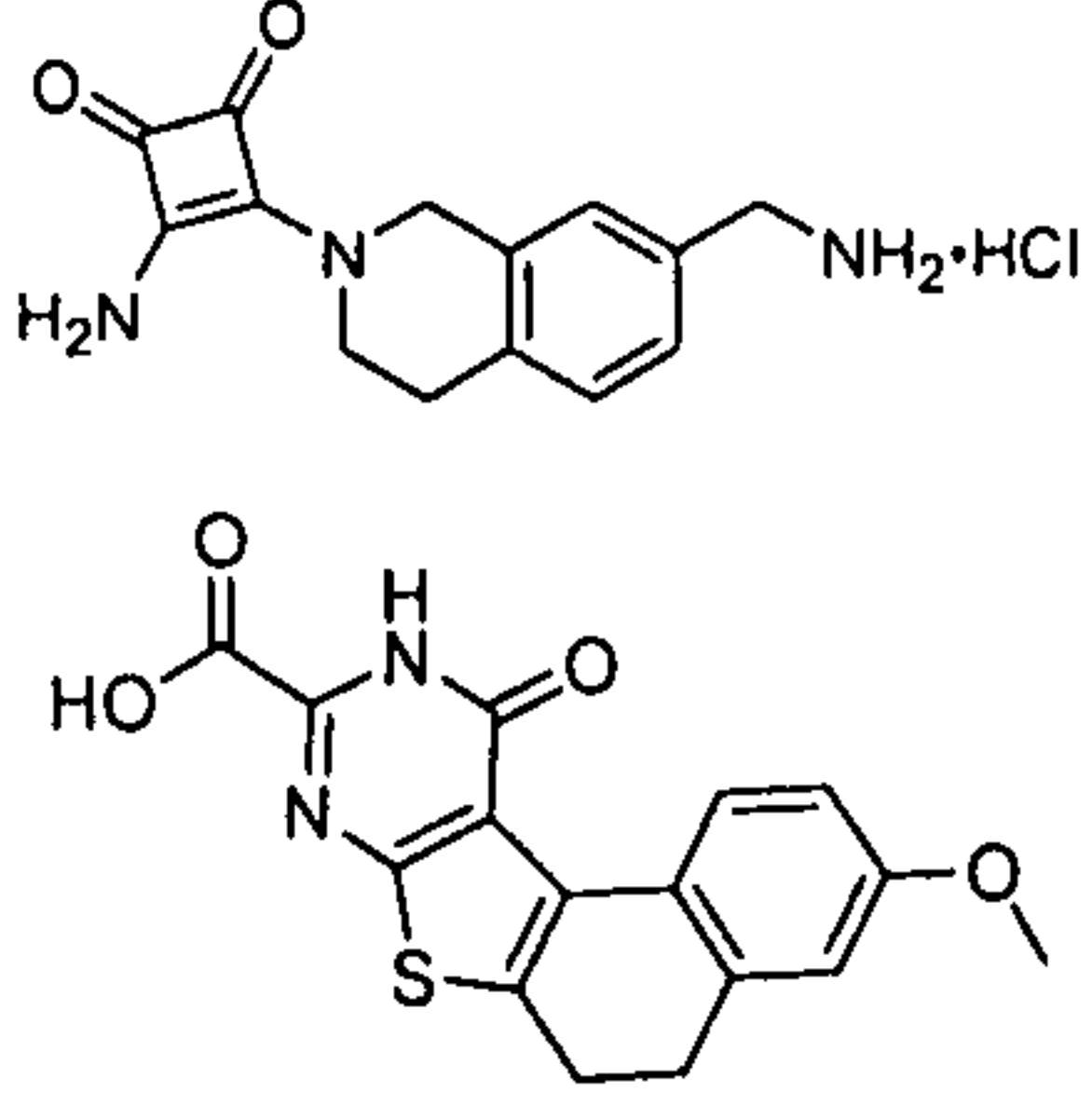
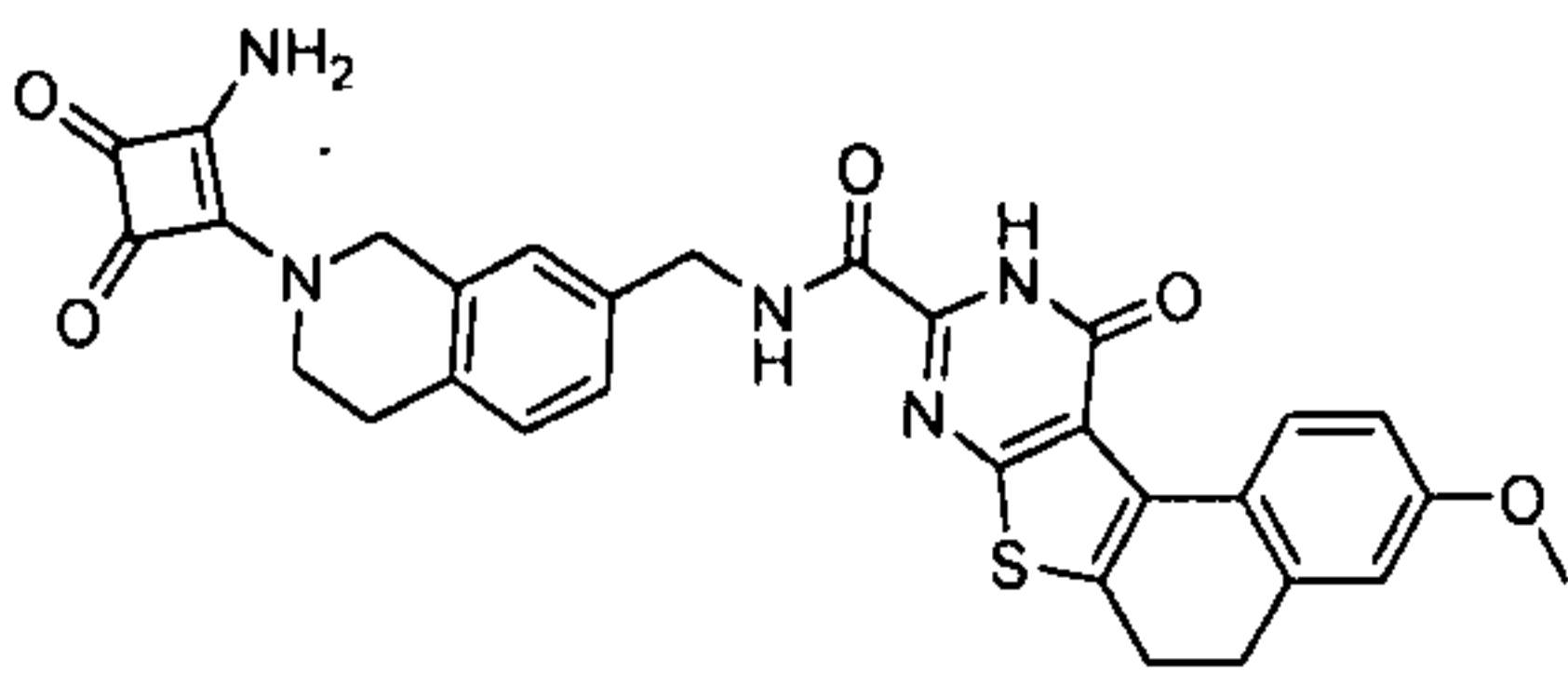
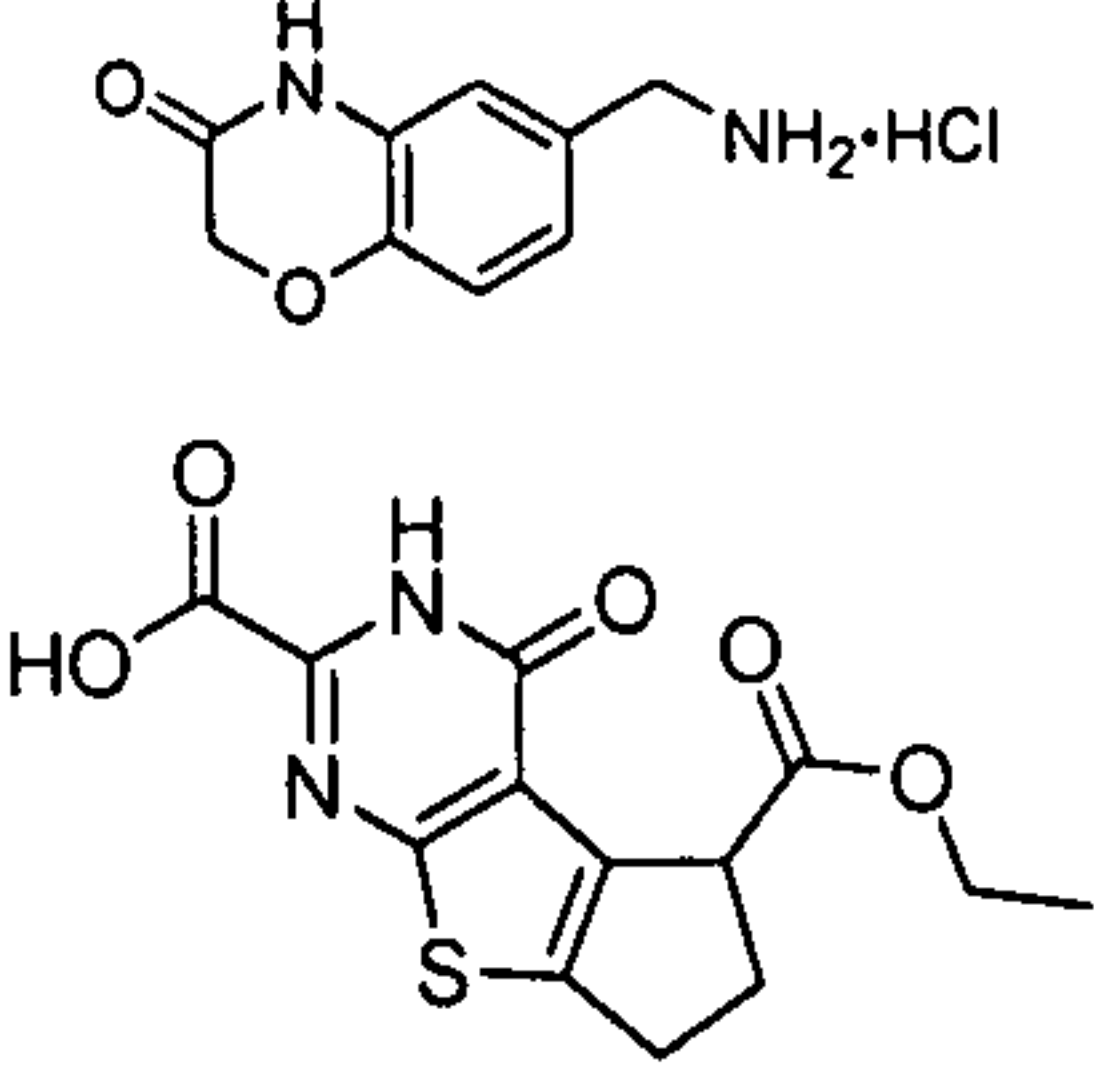
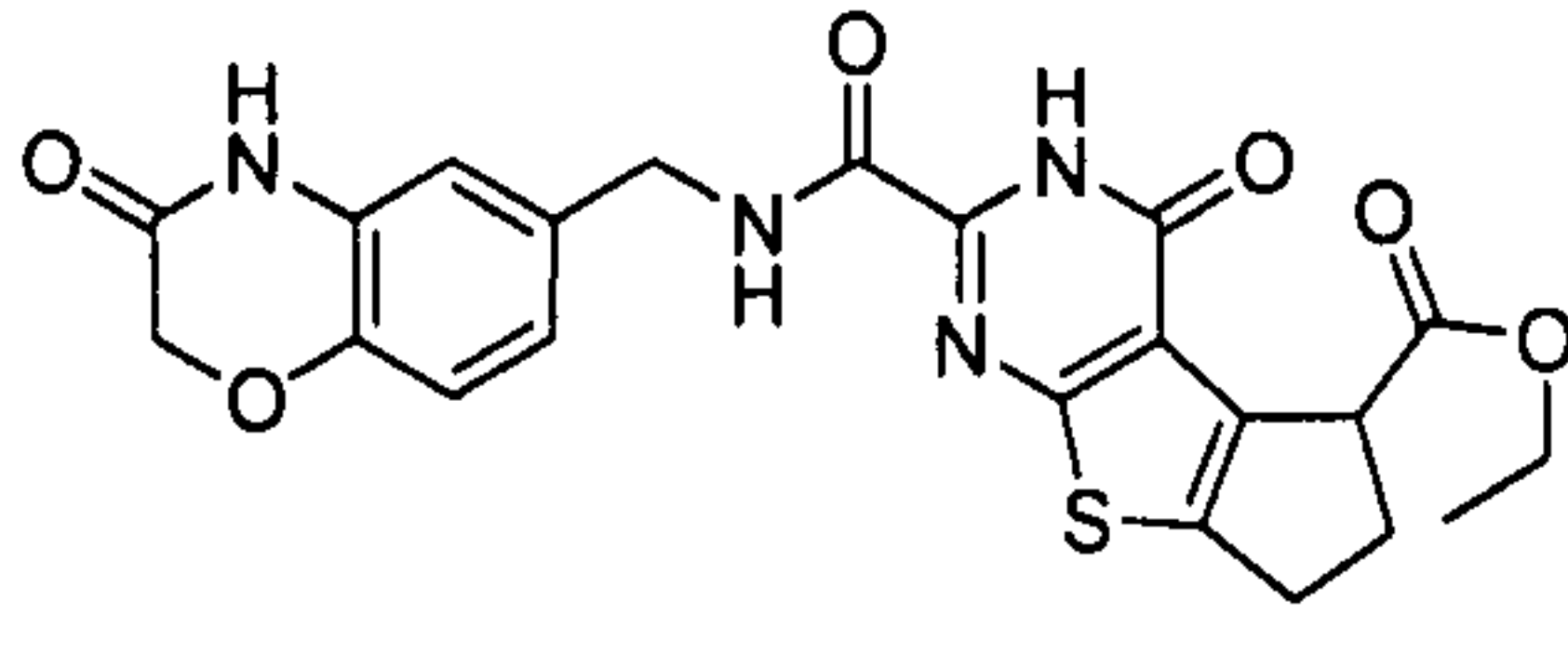
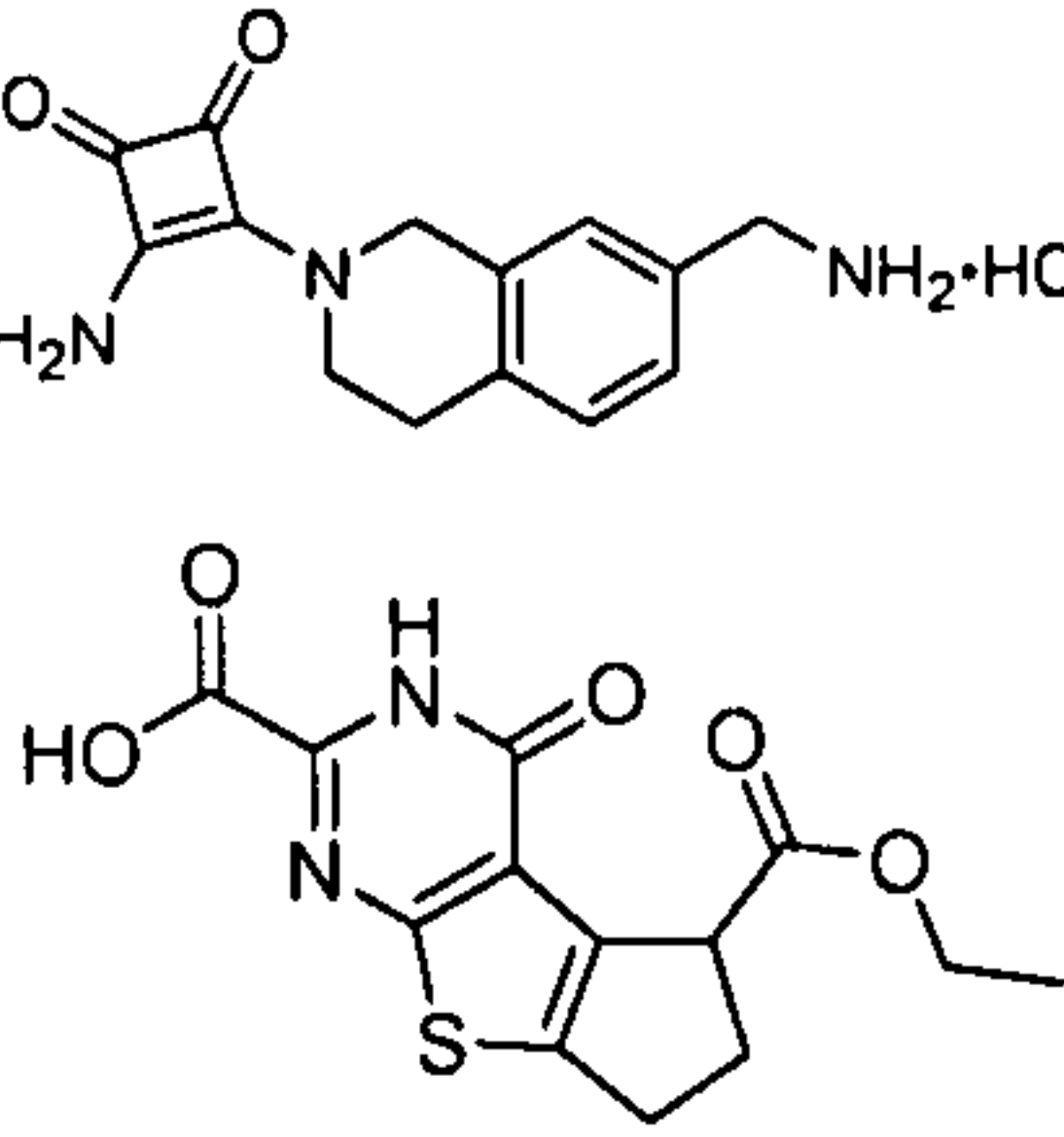
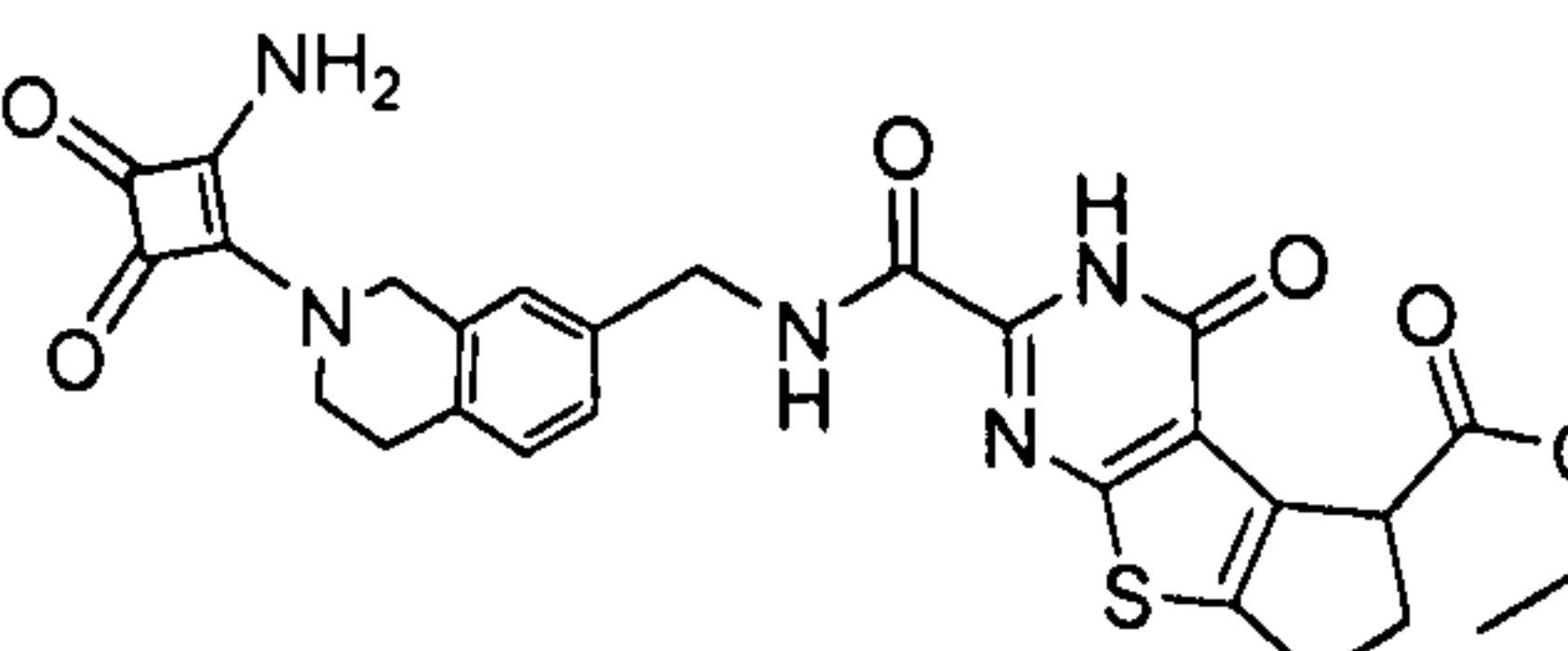
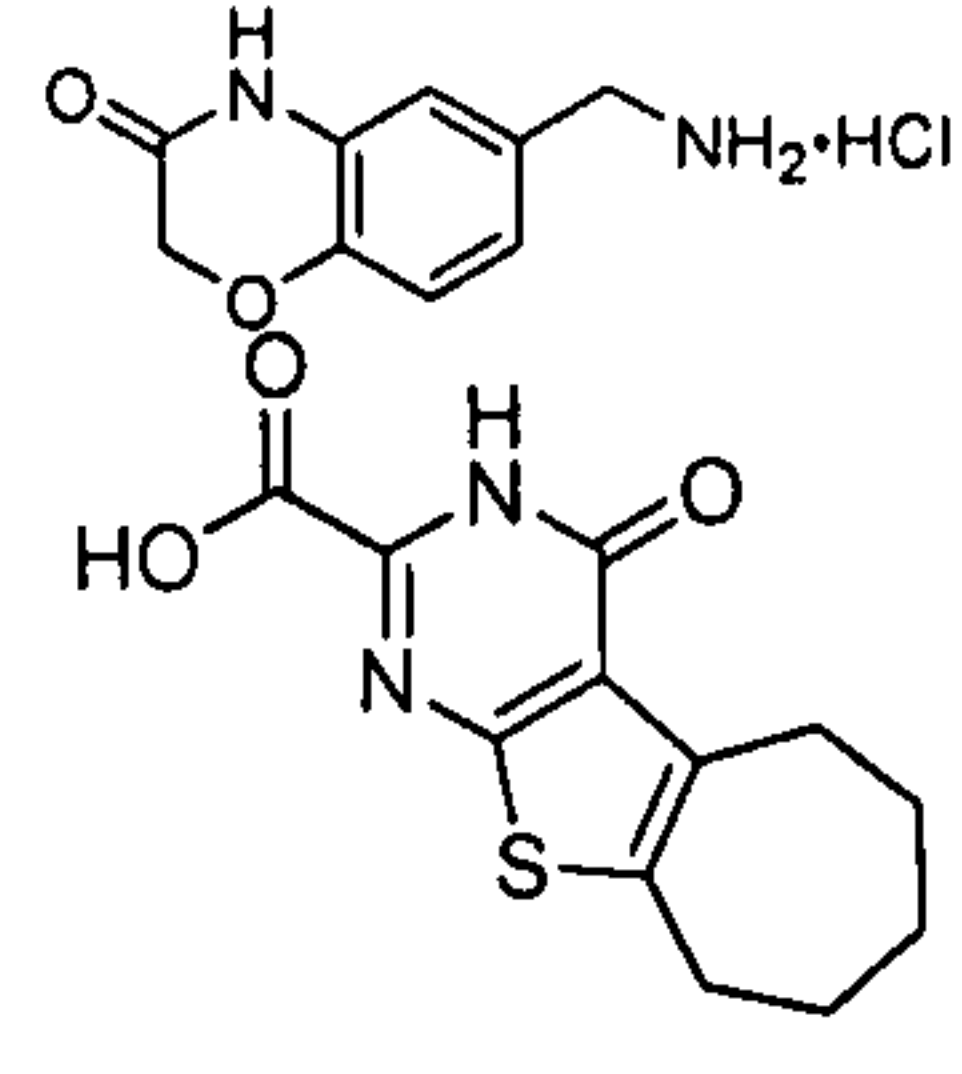
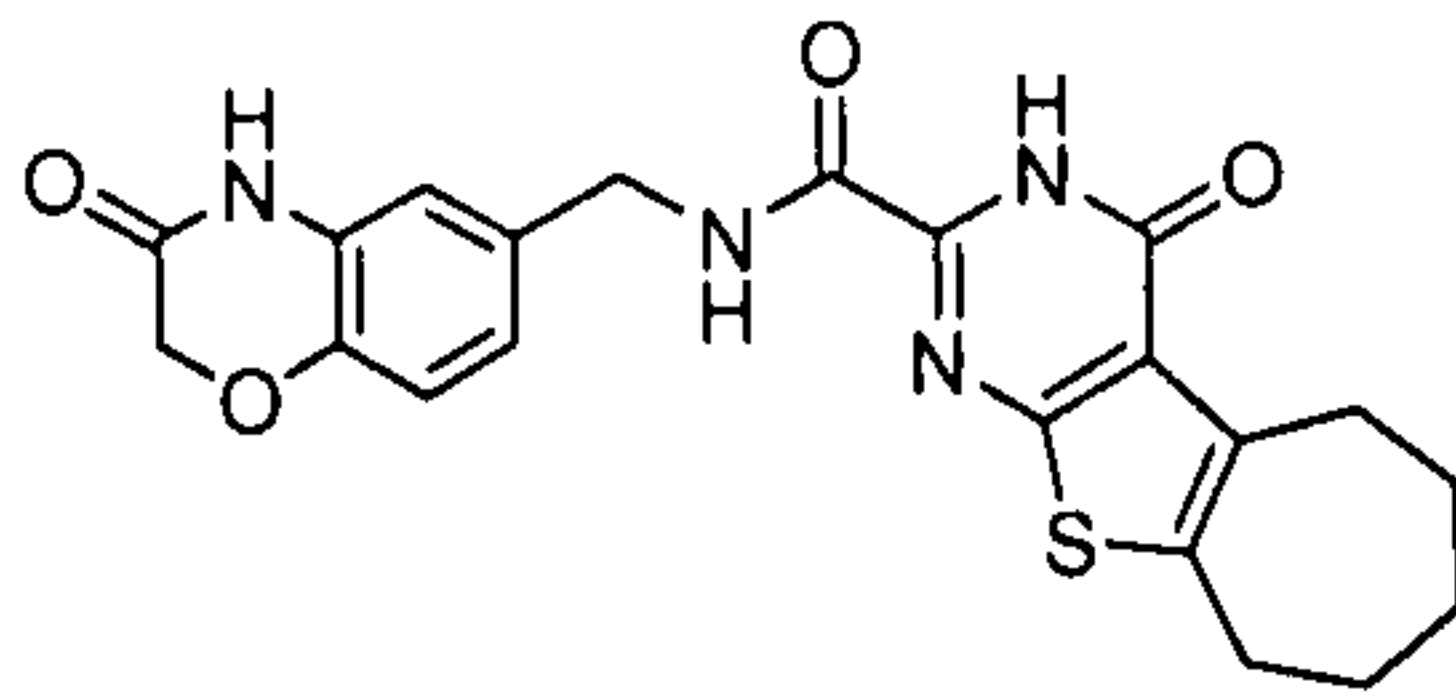
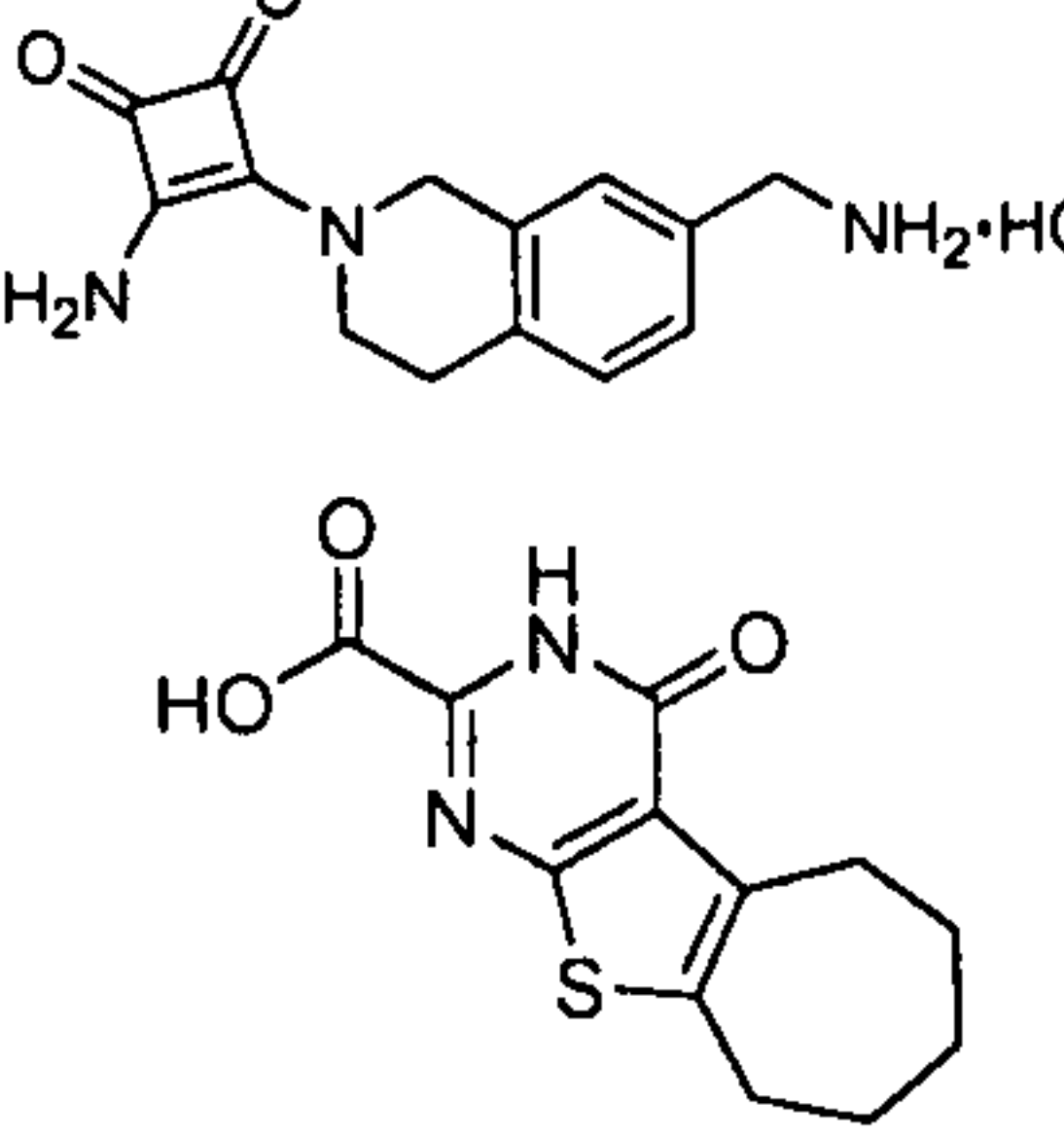
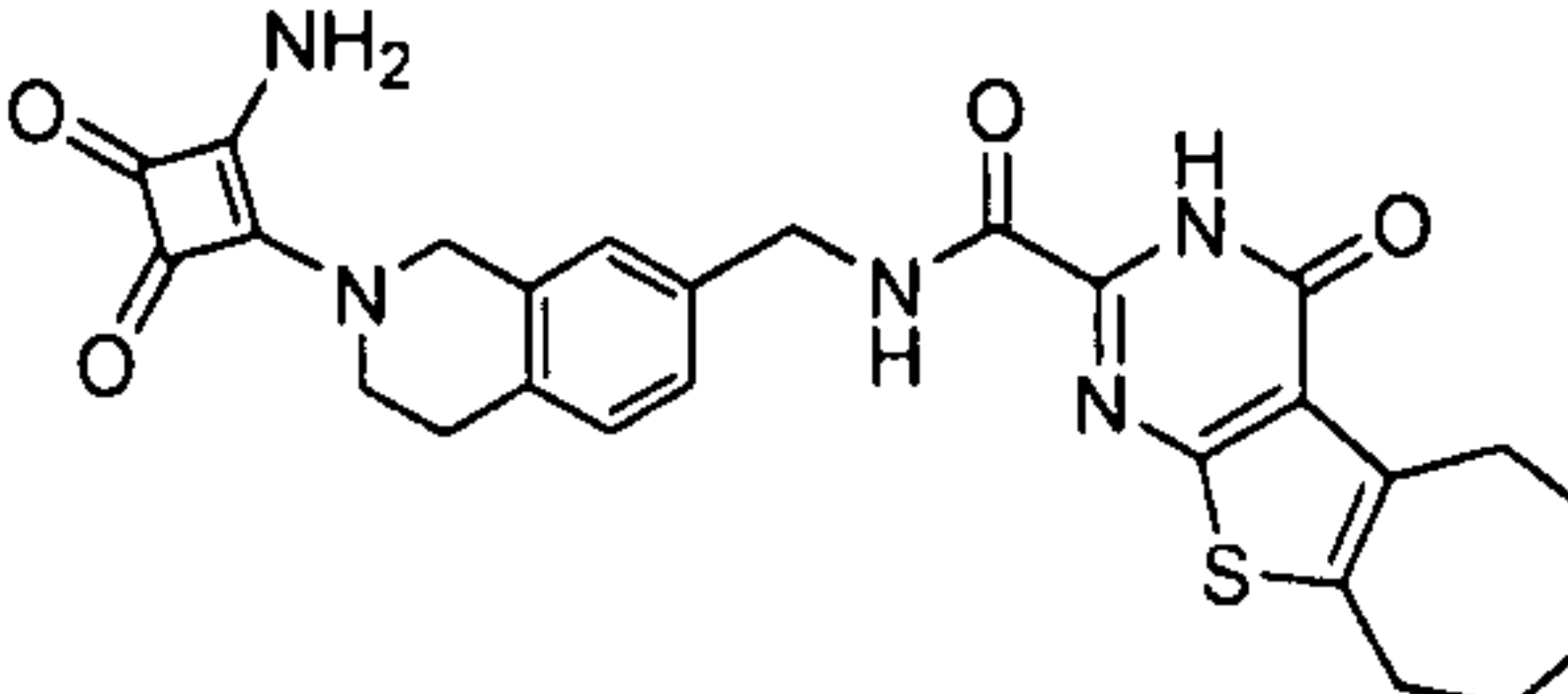
5

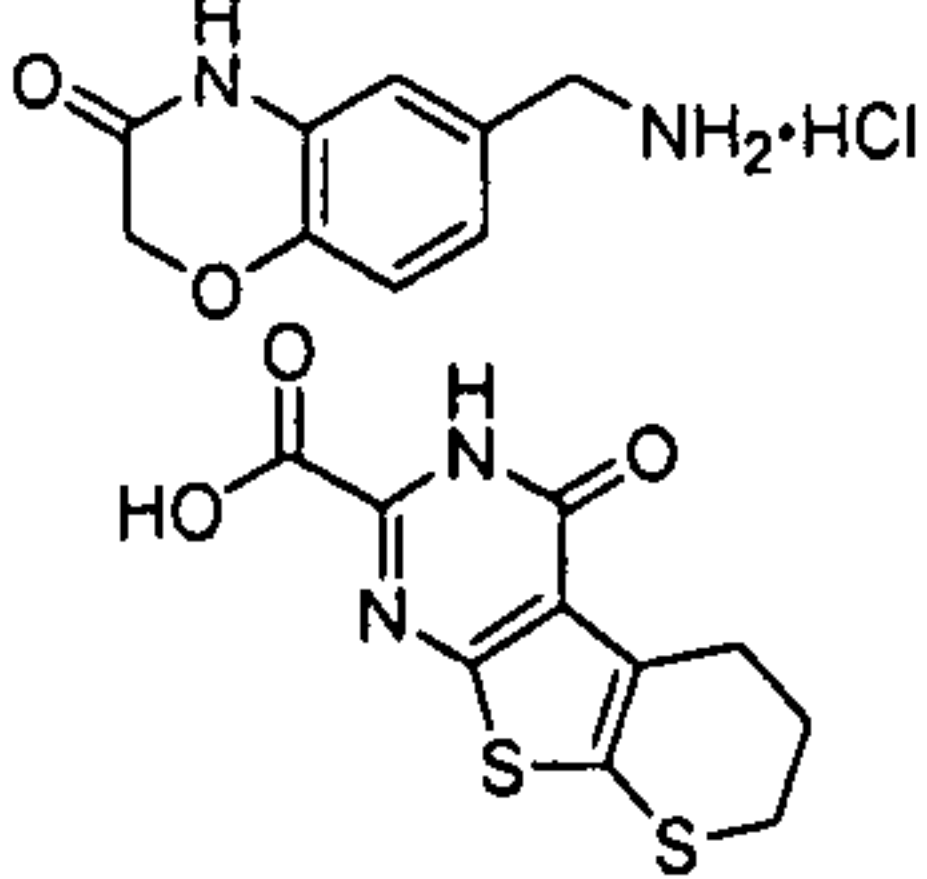
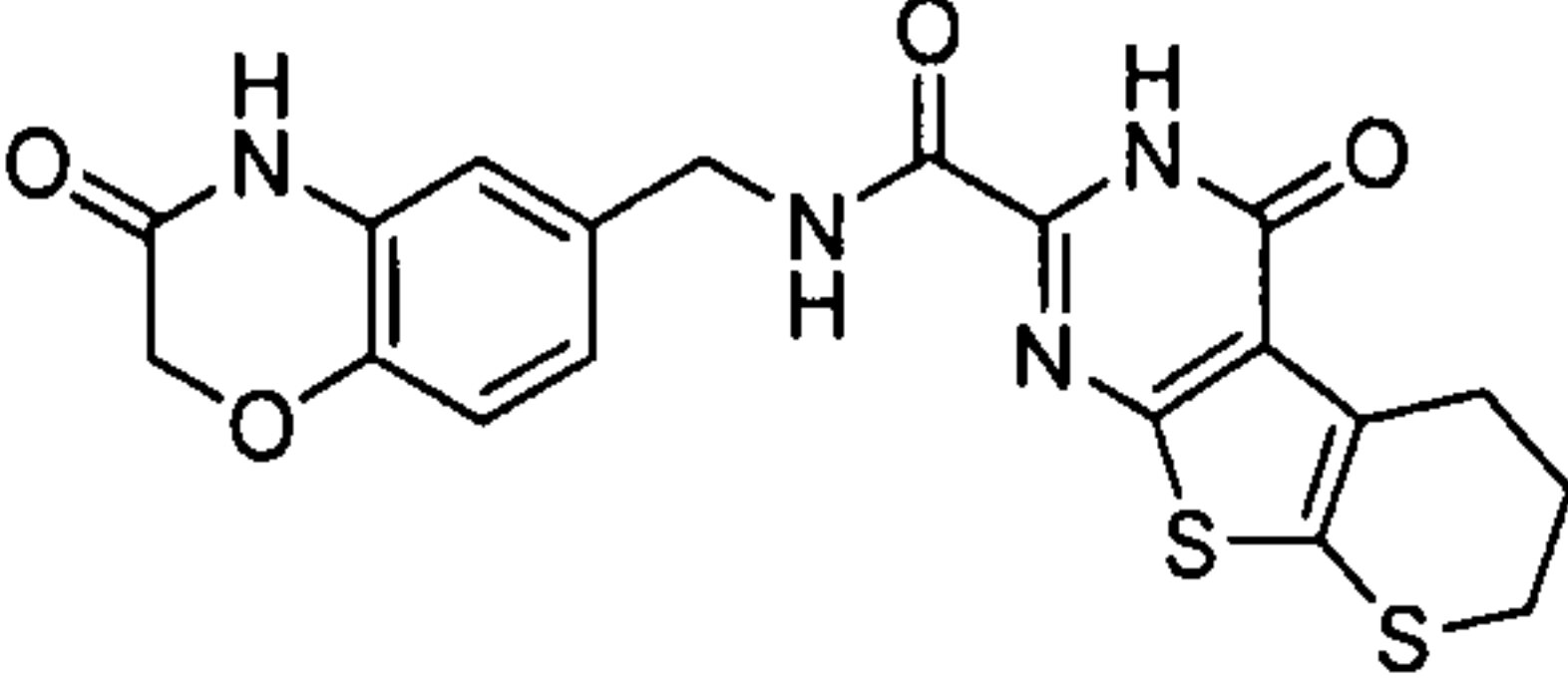
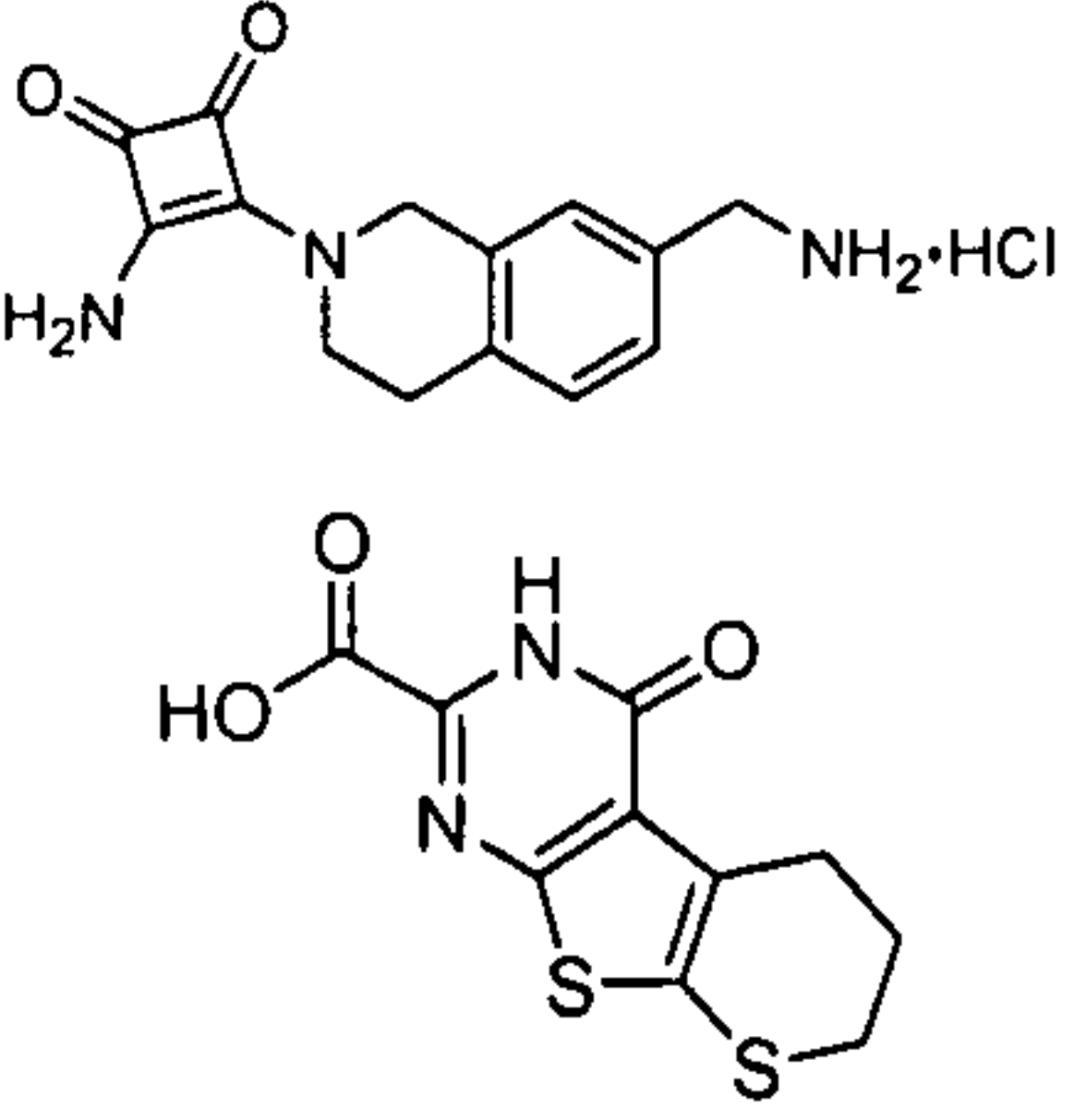
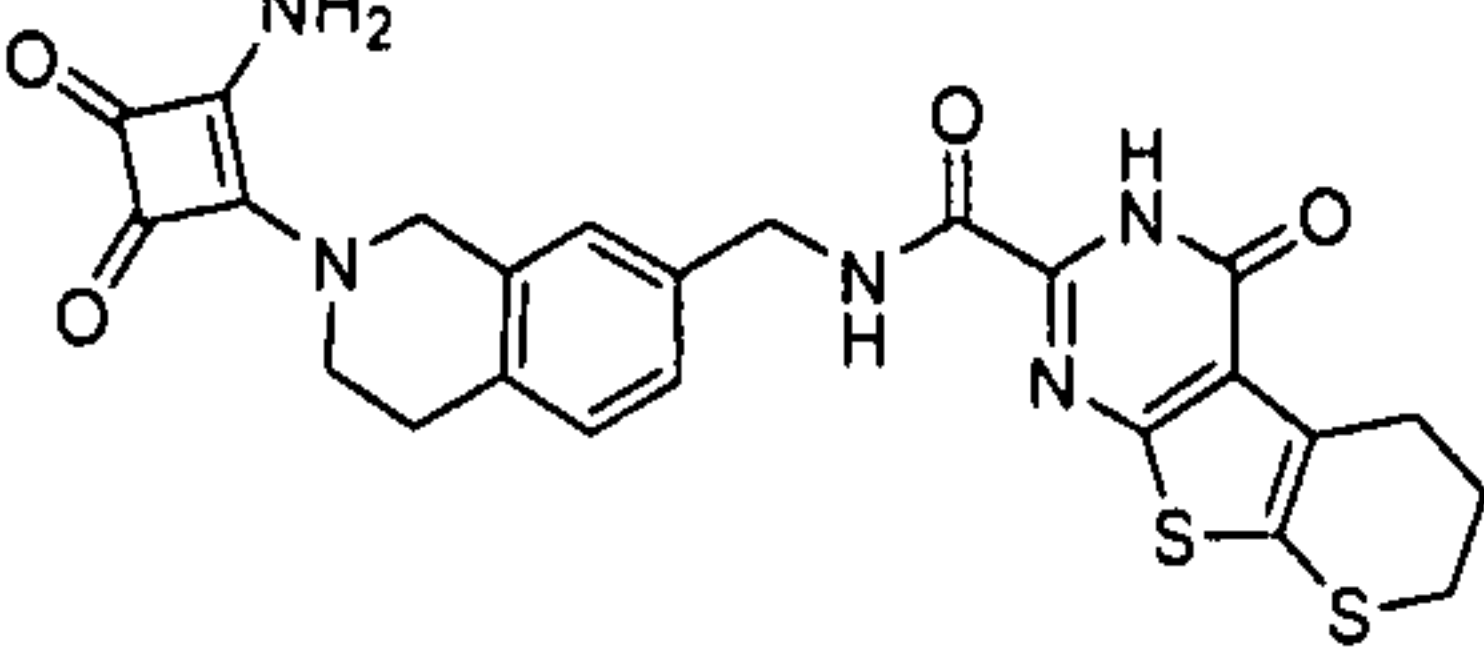
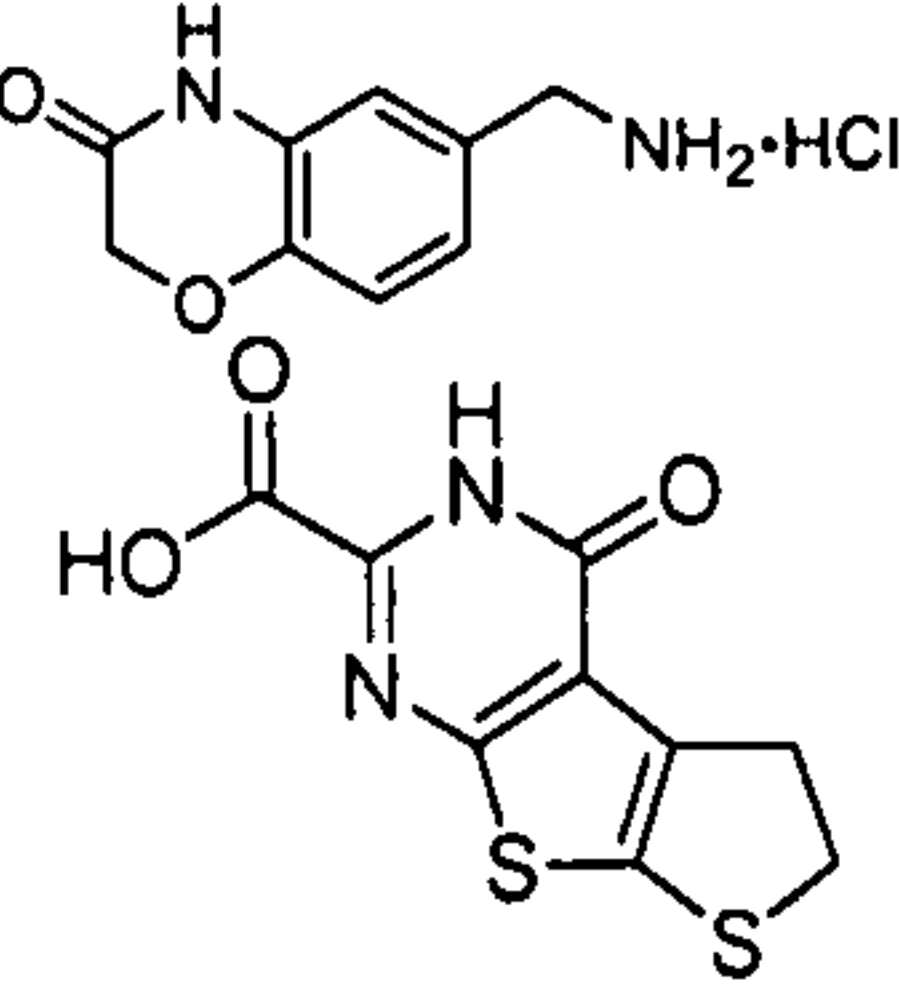
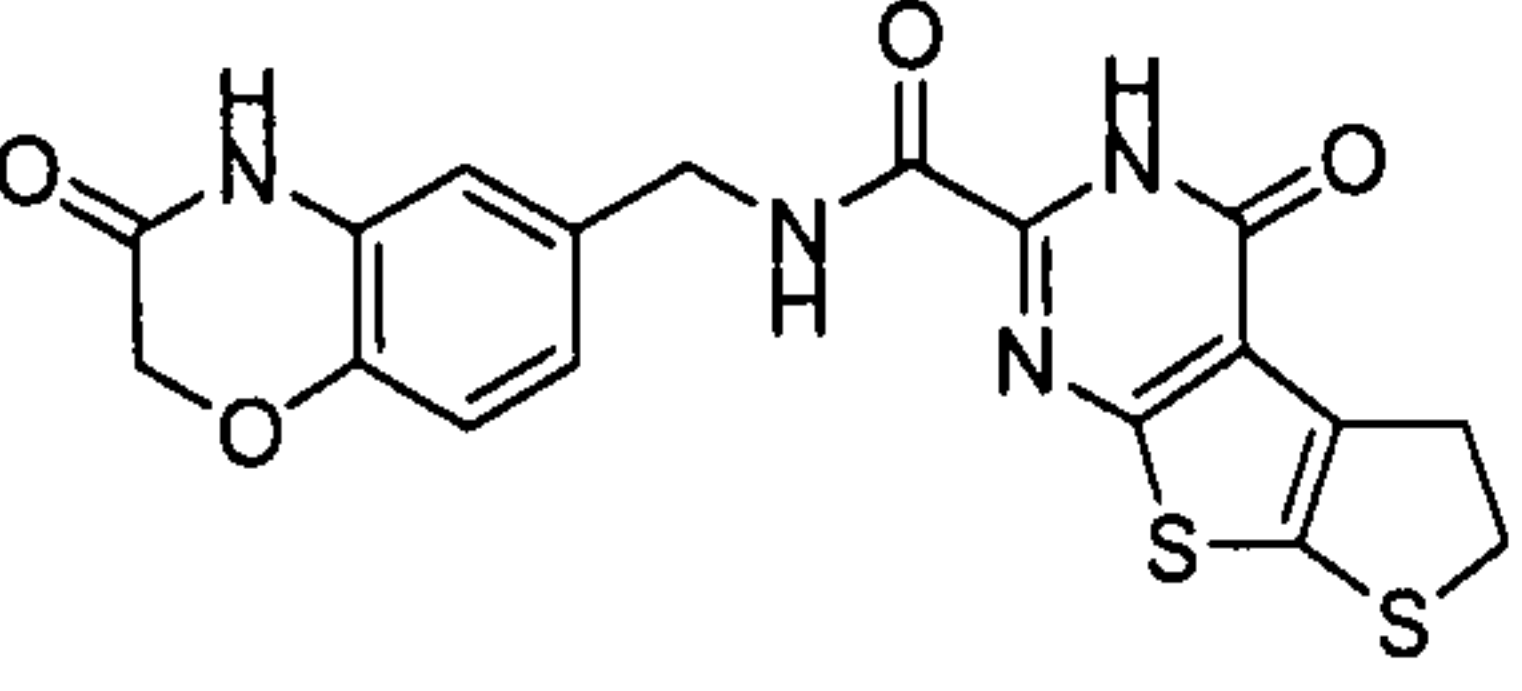
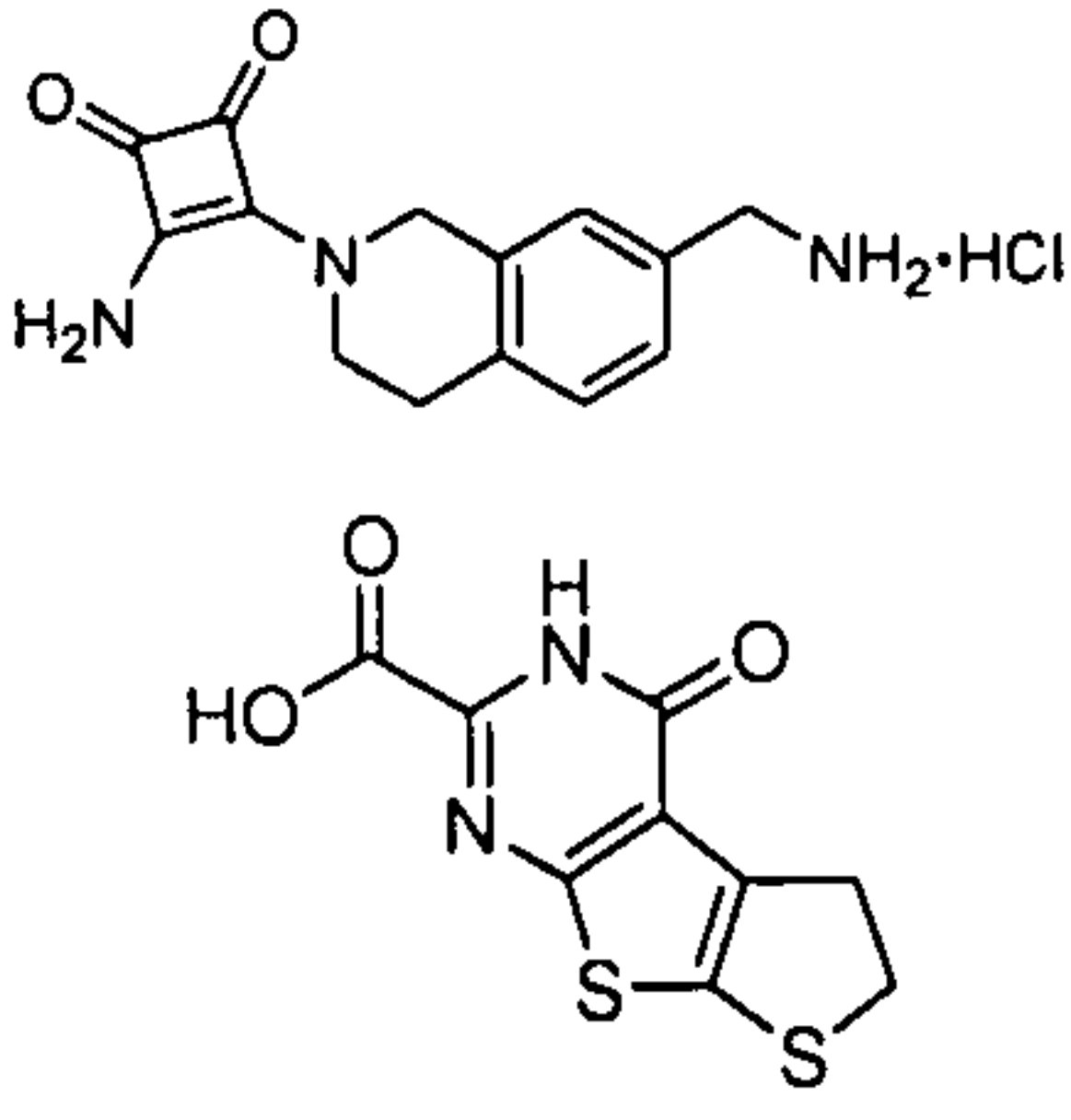
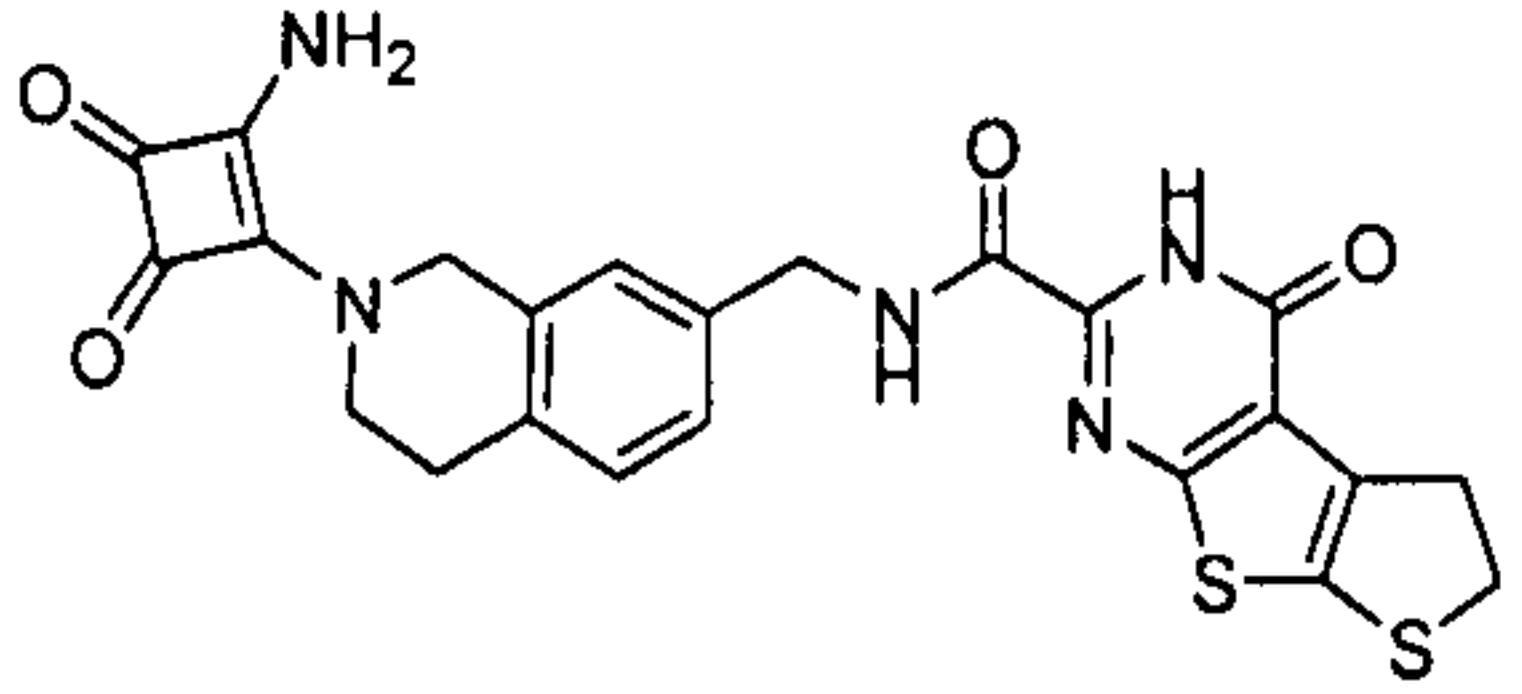
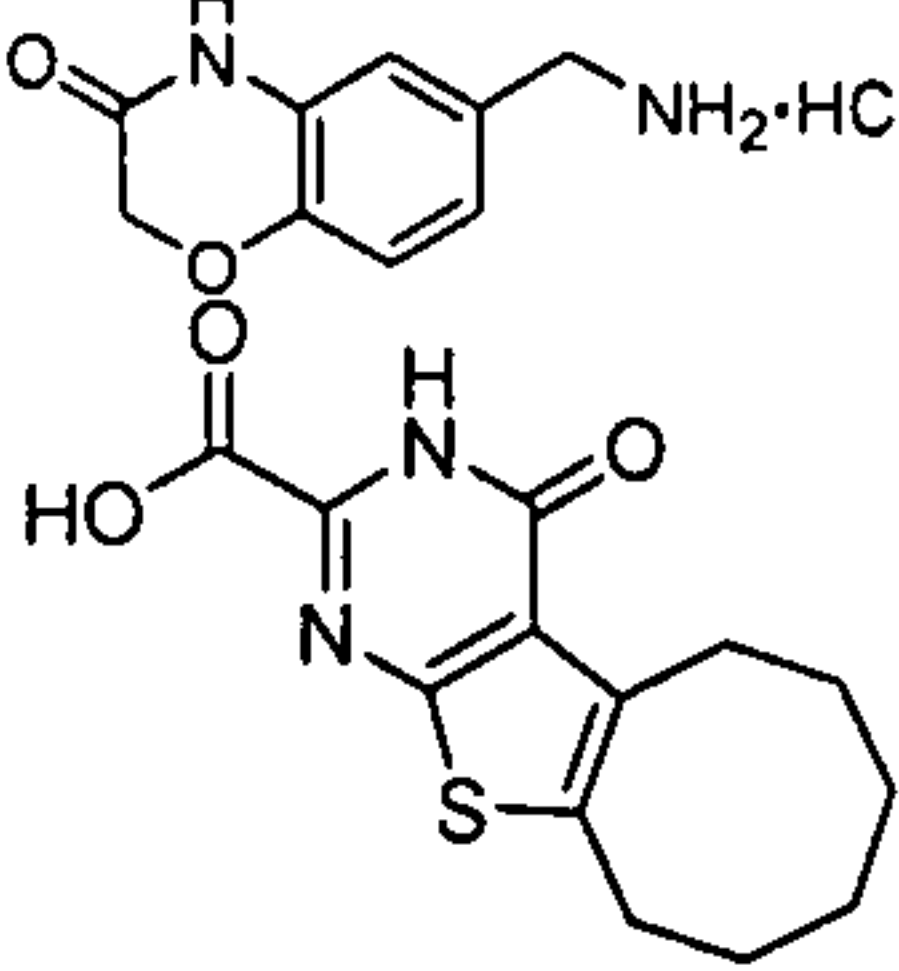
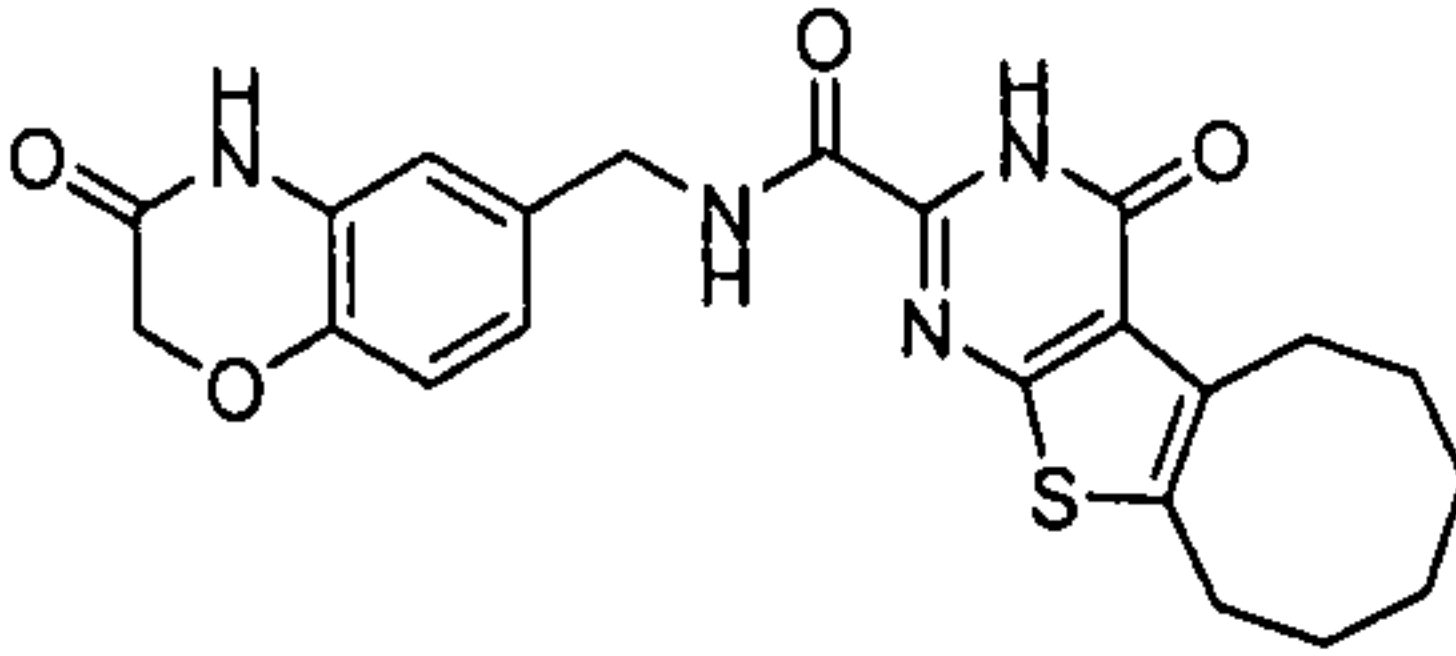
**Table II.1**

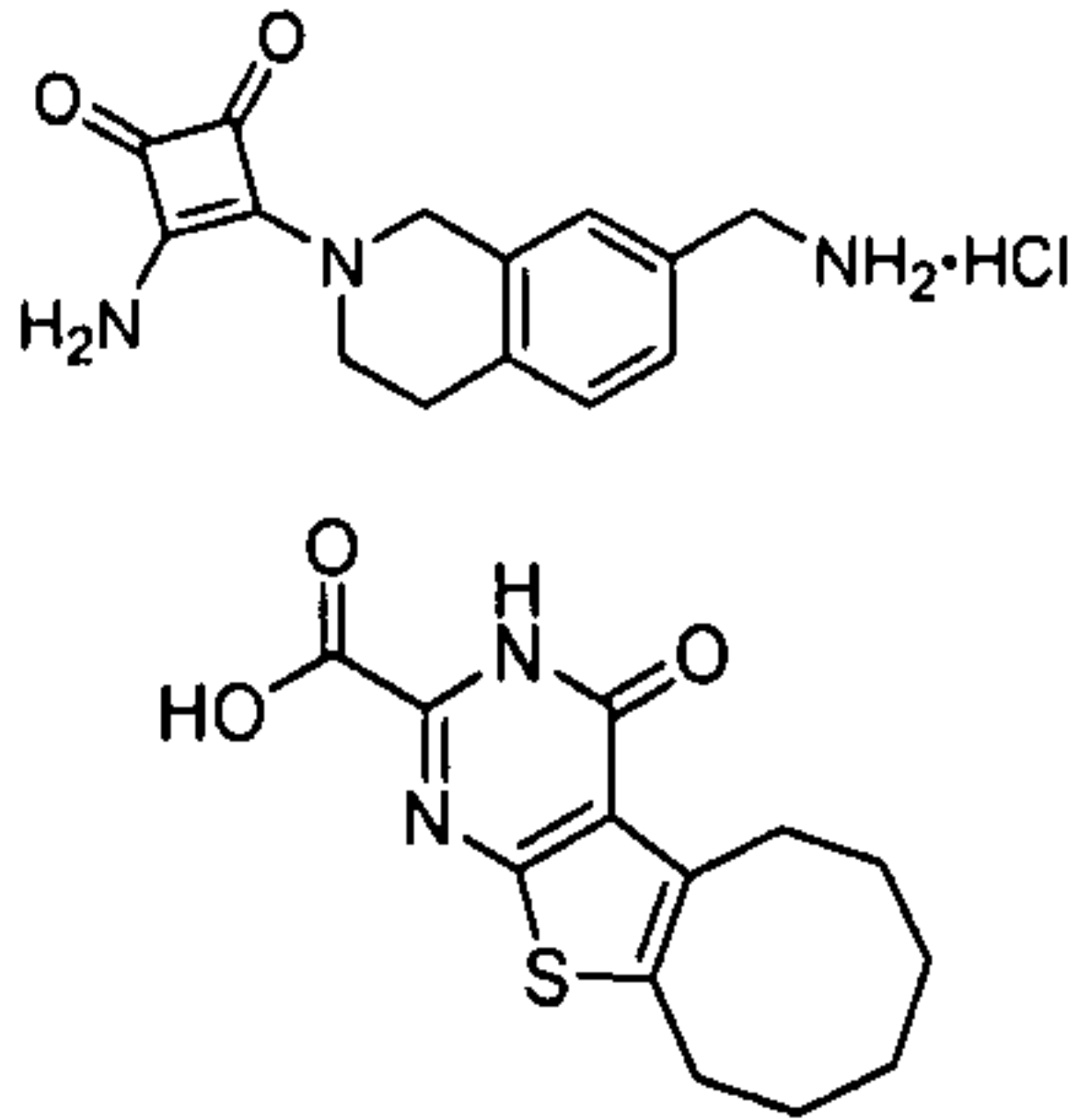
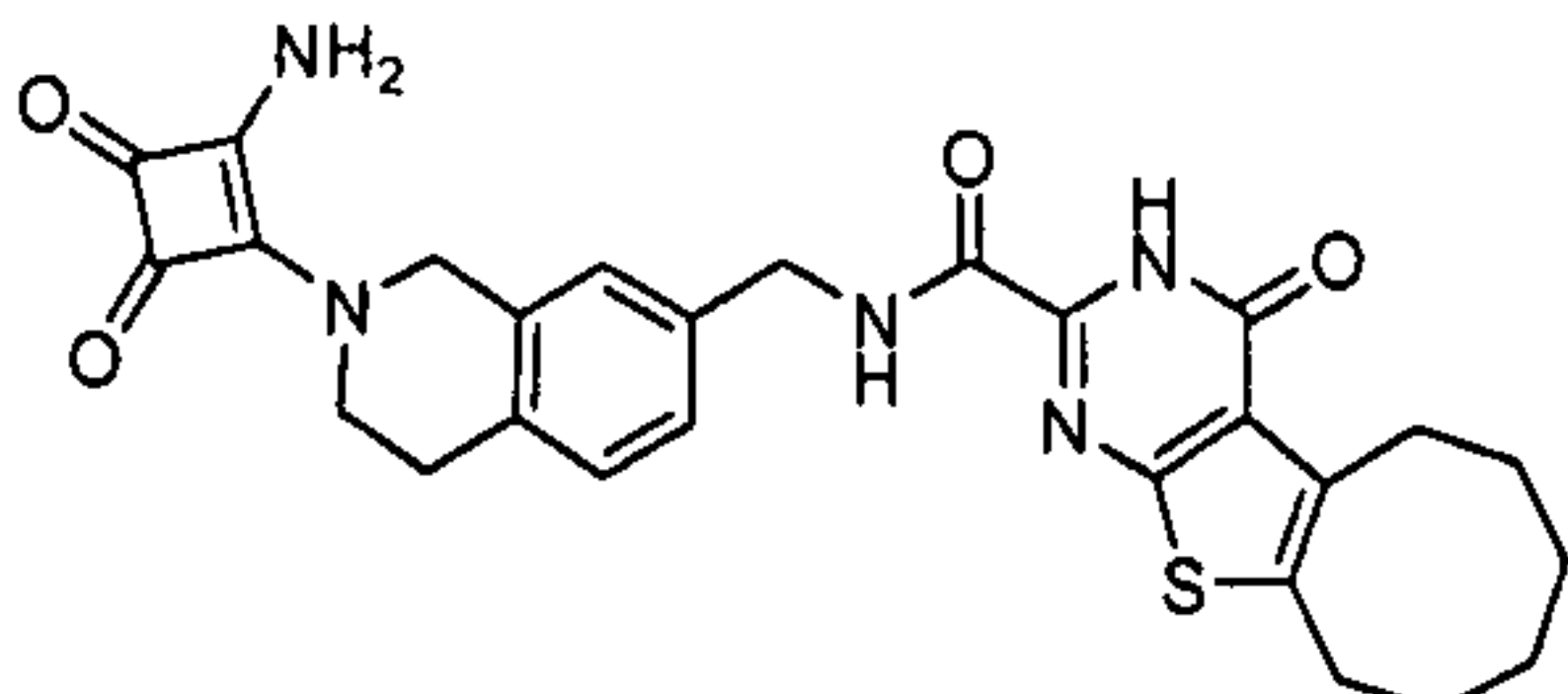
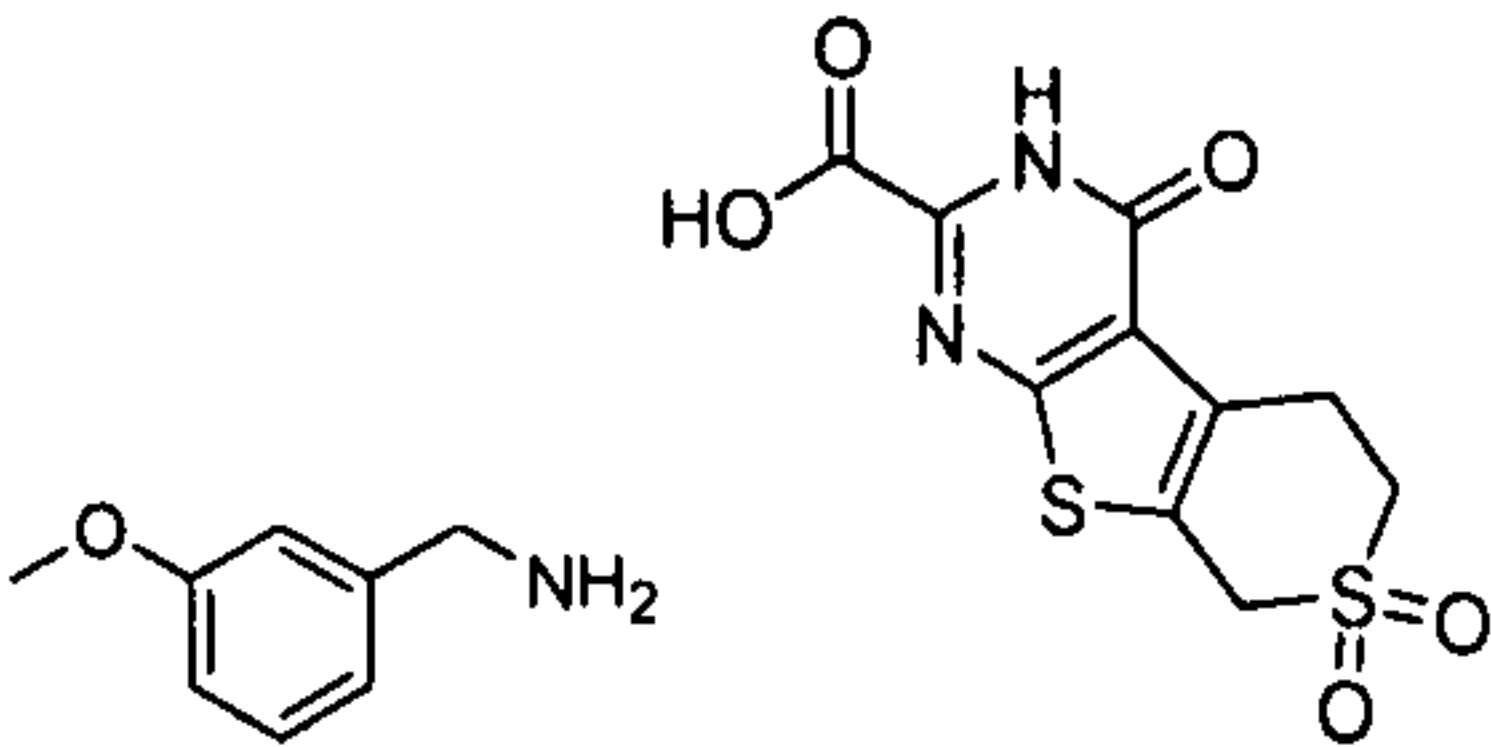
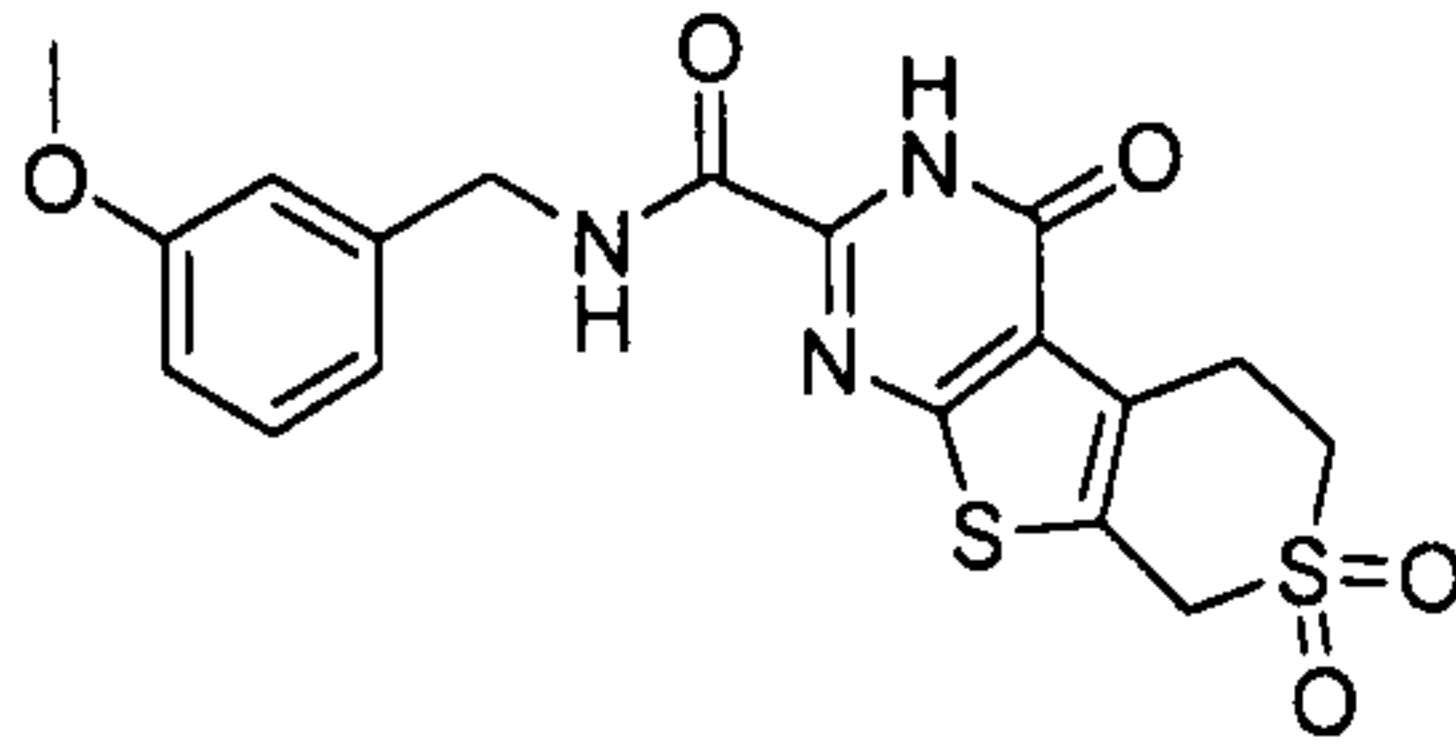
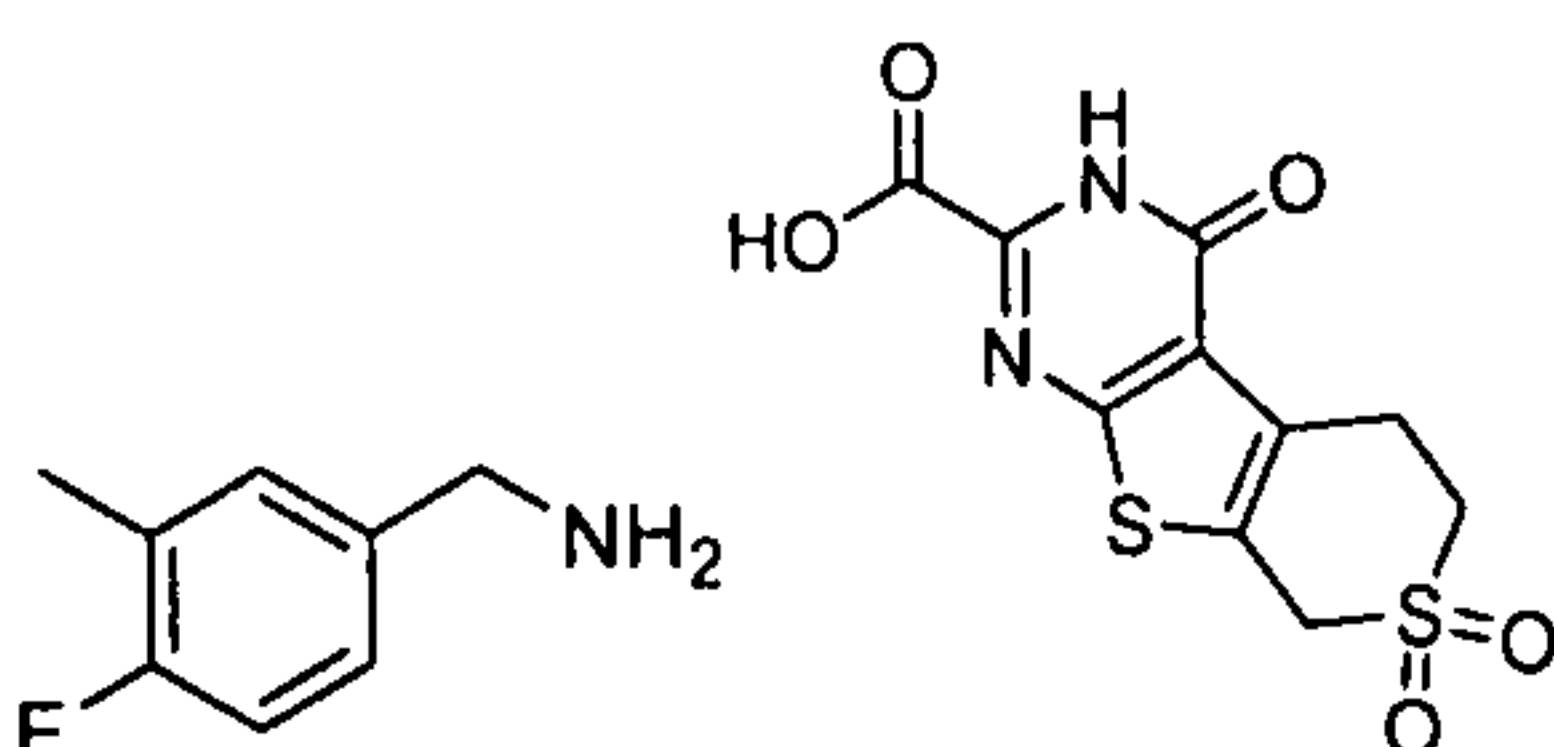
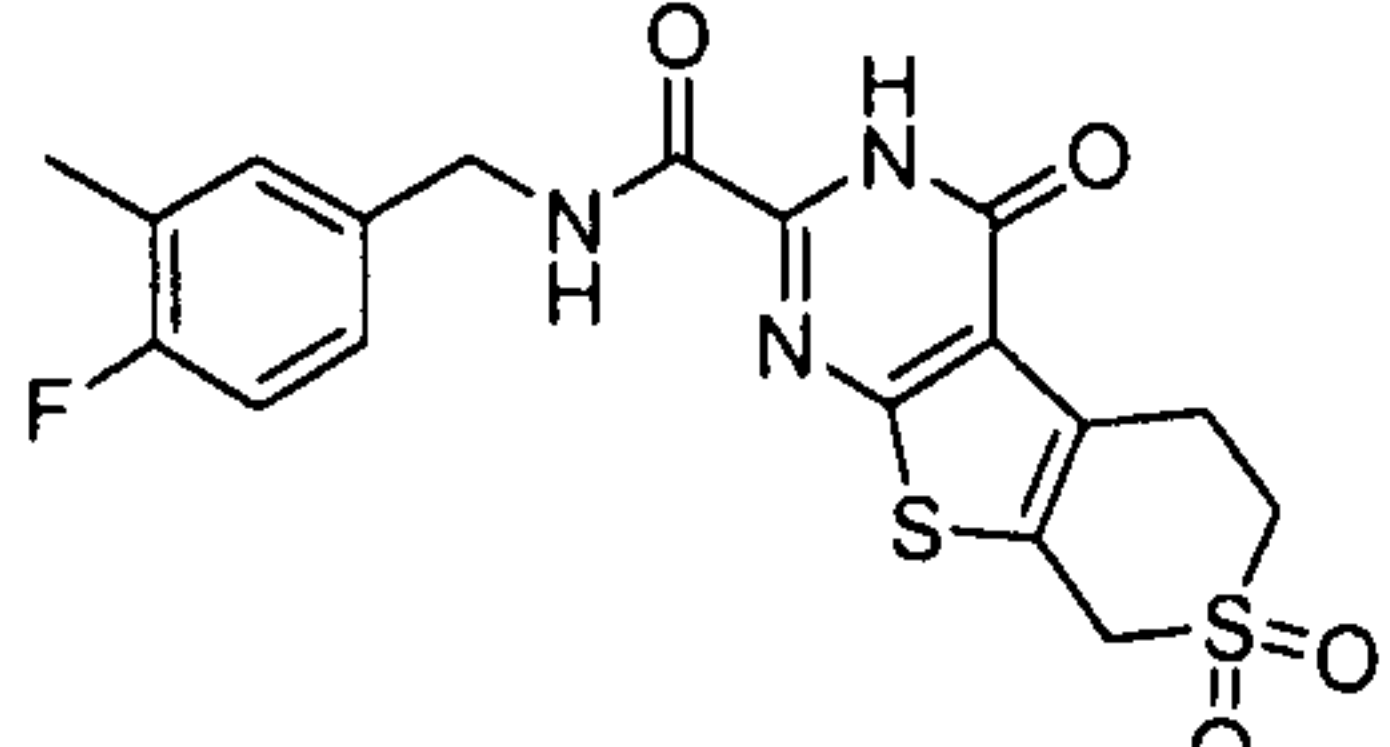
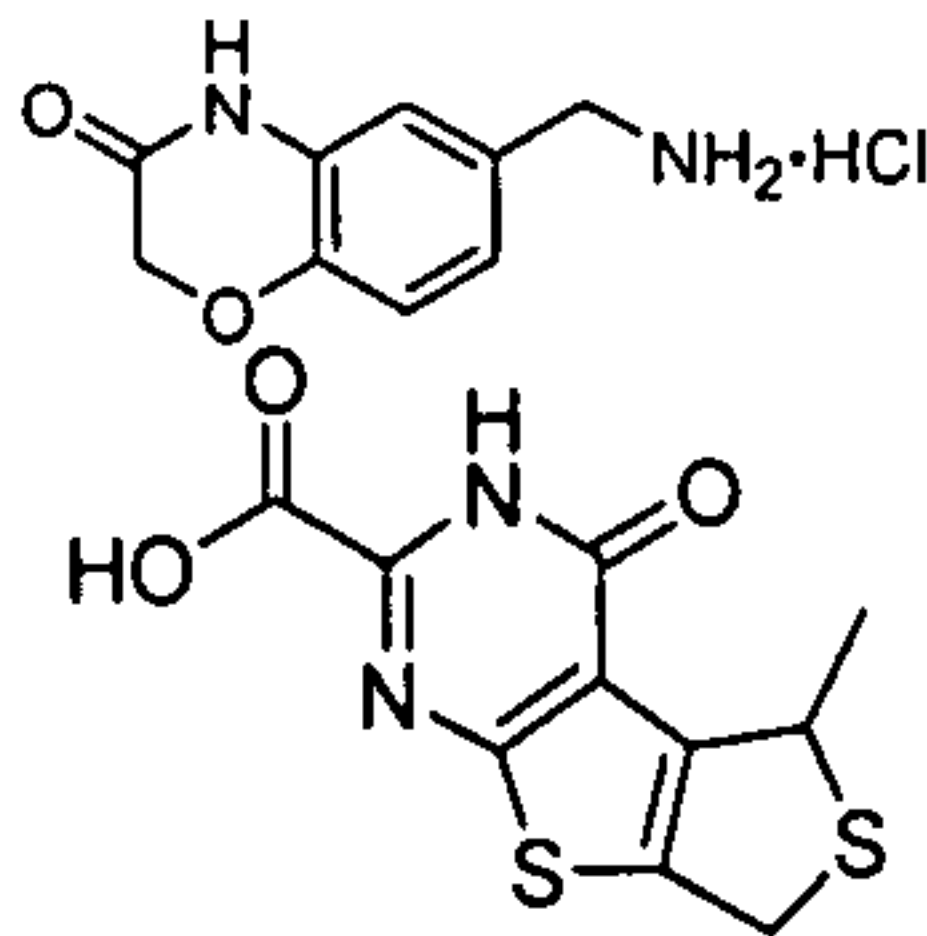
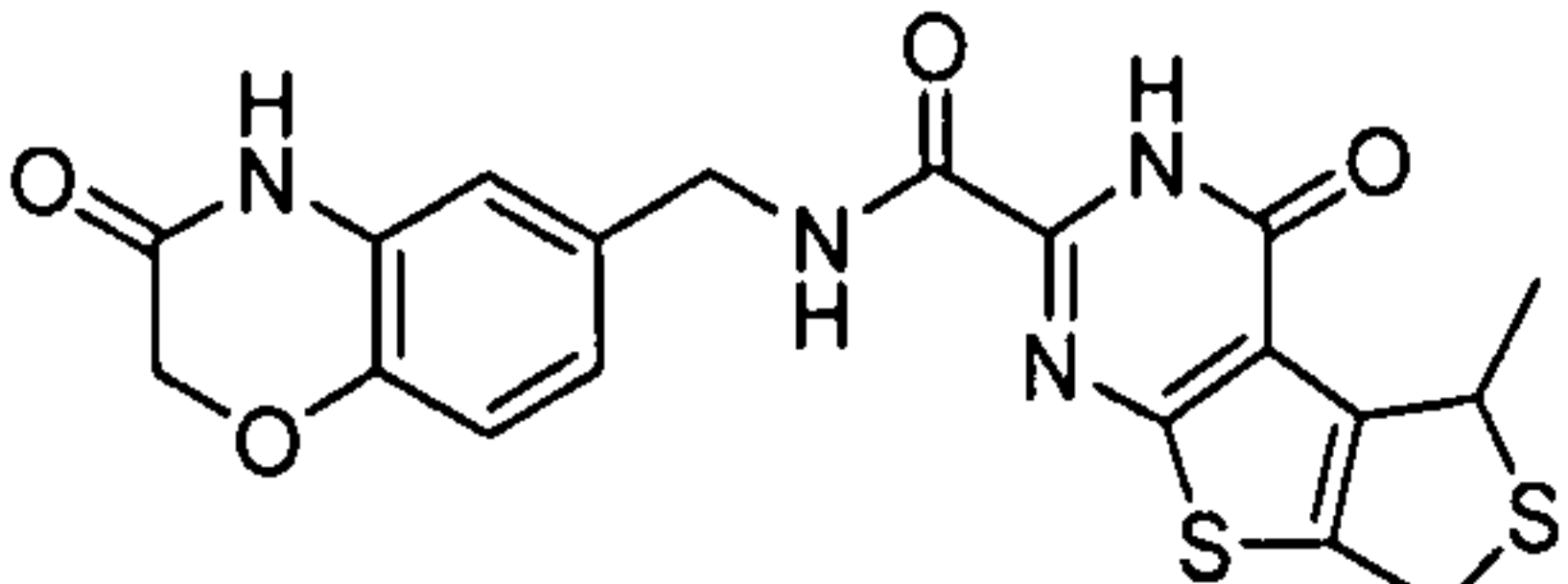
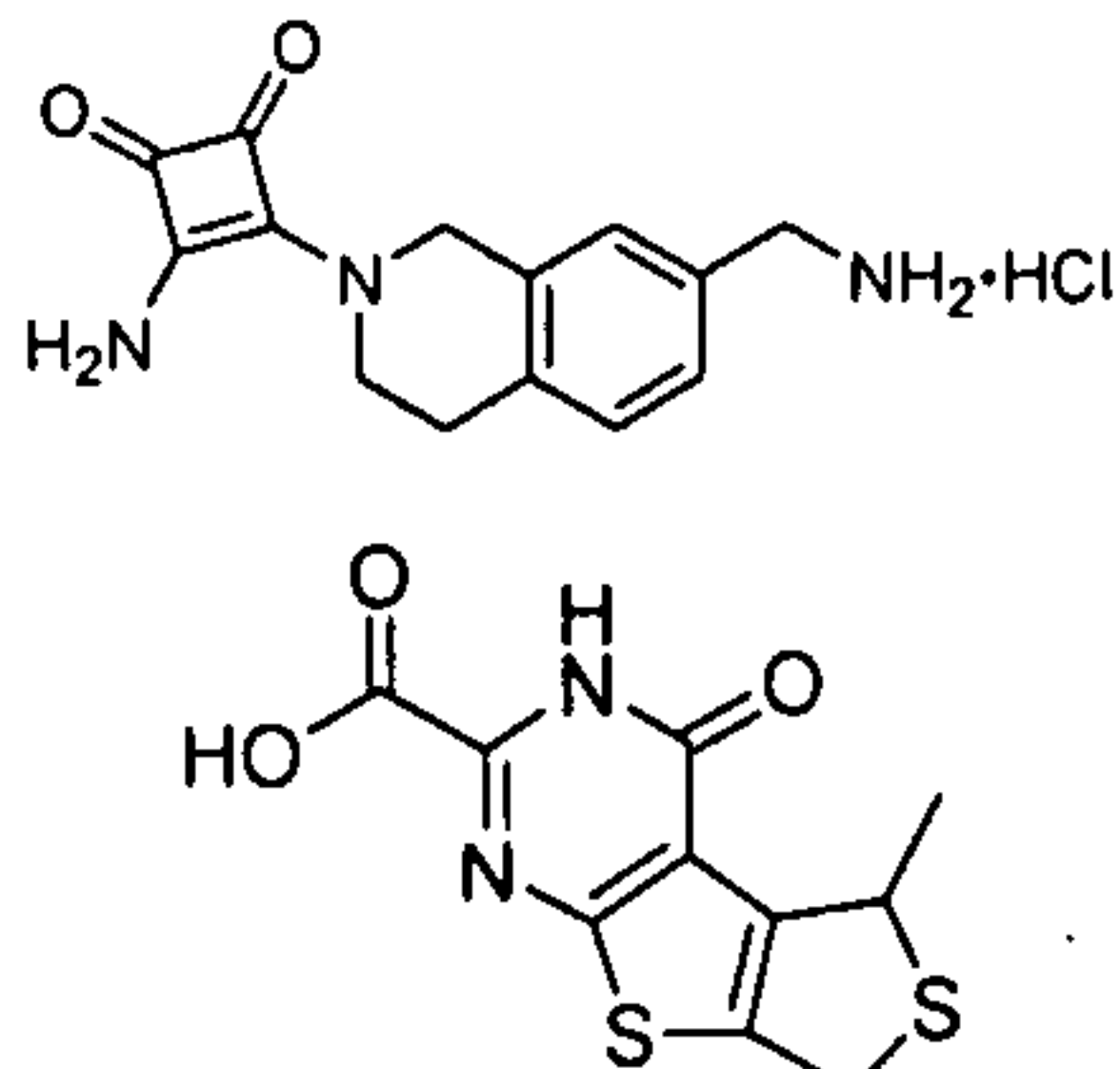
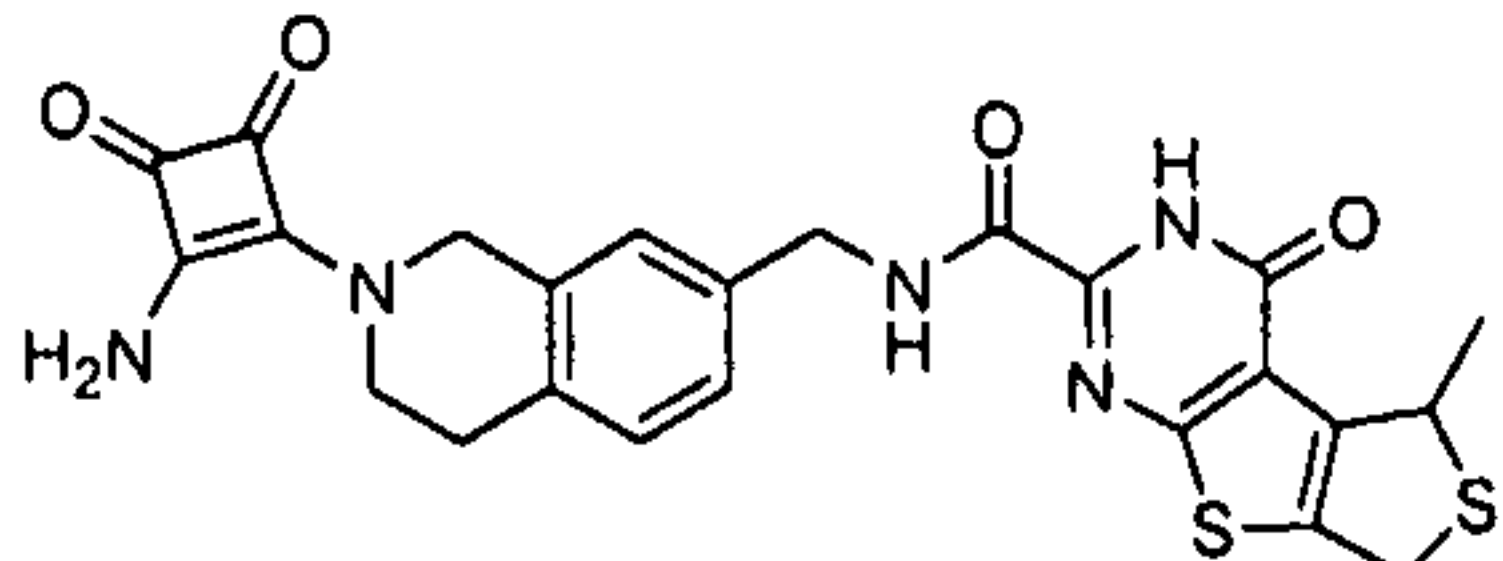
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/24  |   |  | A, 95%<br>[MH] <sup>+</sup> = 407  |
| 2/25  |  |  | A, 26%<br>[MH] <sup>+</sup> = 407  |
| 2/29  |  |  | A, 12%<br>[MH] <sup>+</sup> = 426  |
| 2/30  |  |  | A, n.d.<br>[MH] <sup>+</sup> = 426 |
| 2/33  |  |  | A, 29%<br>[MH] <sup>+</sup> = 411  |

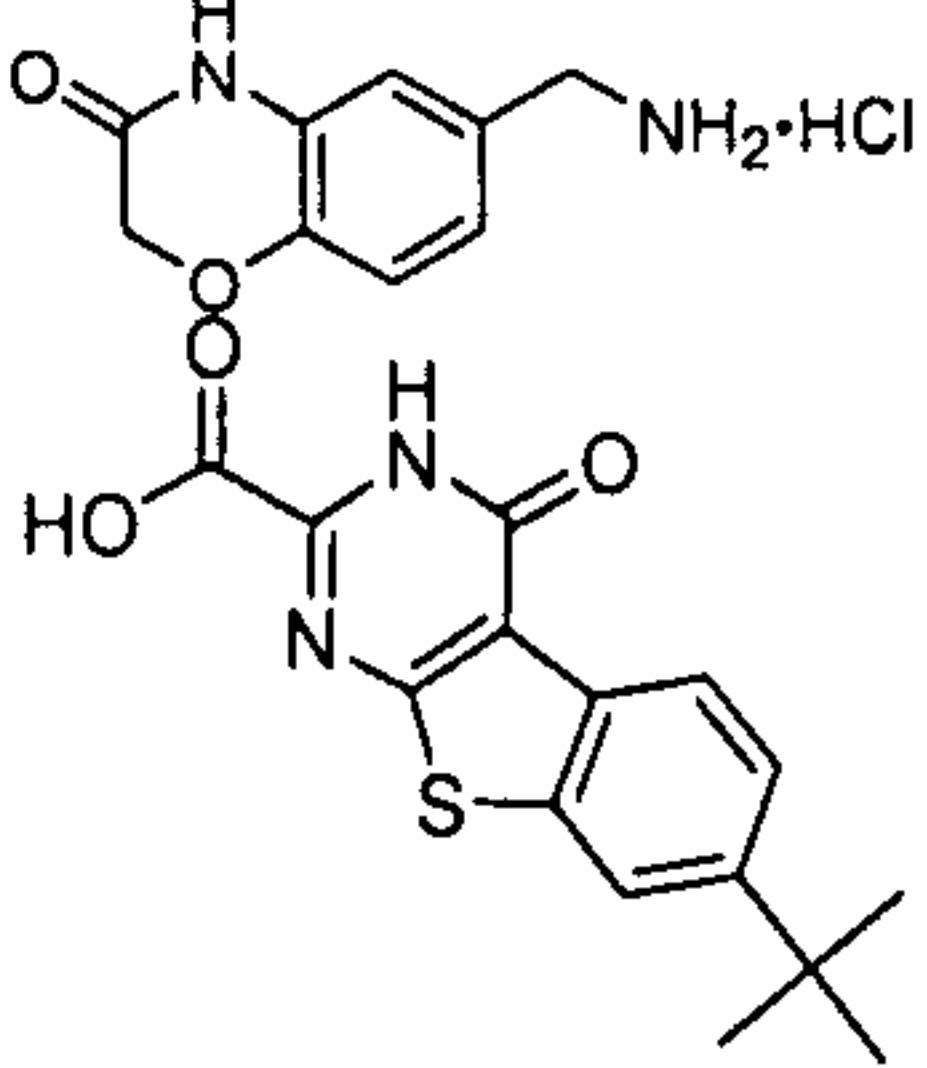
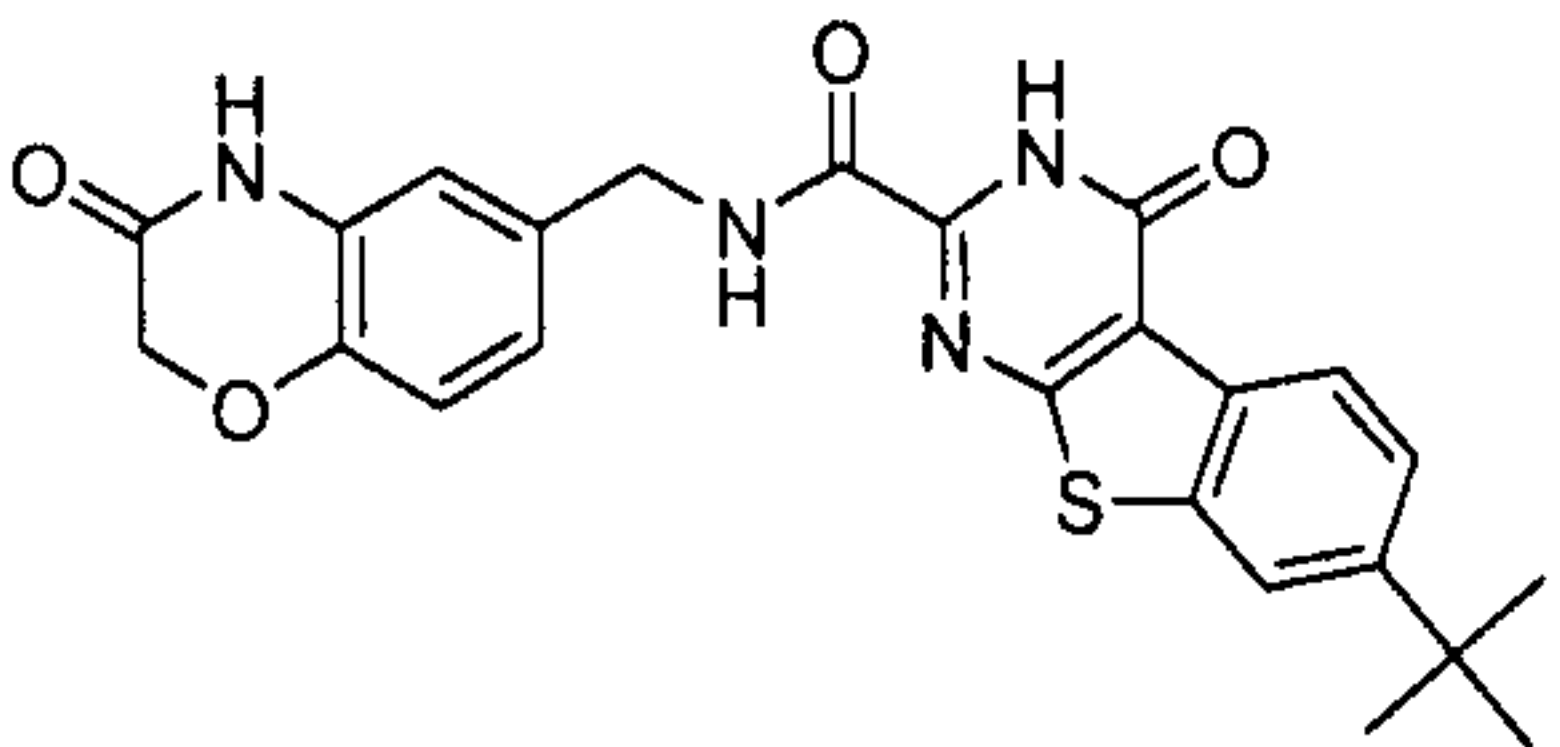
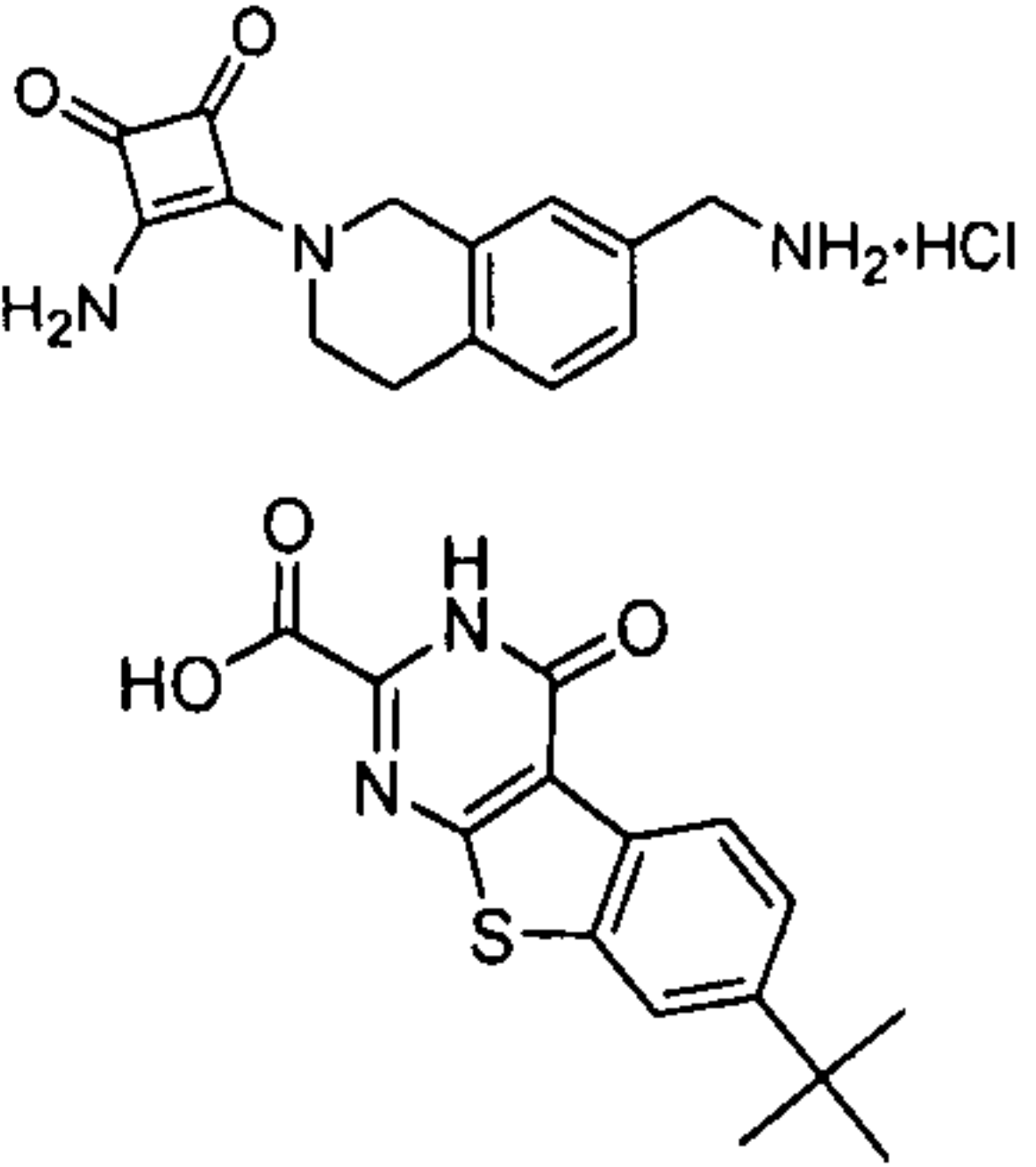
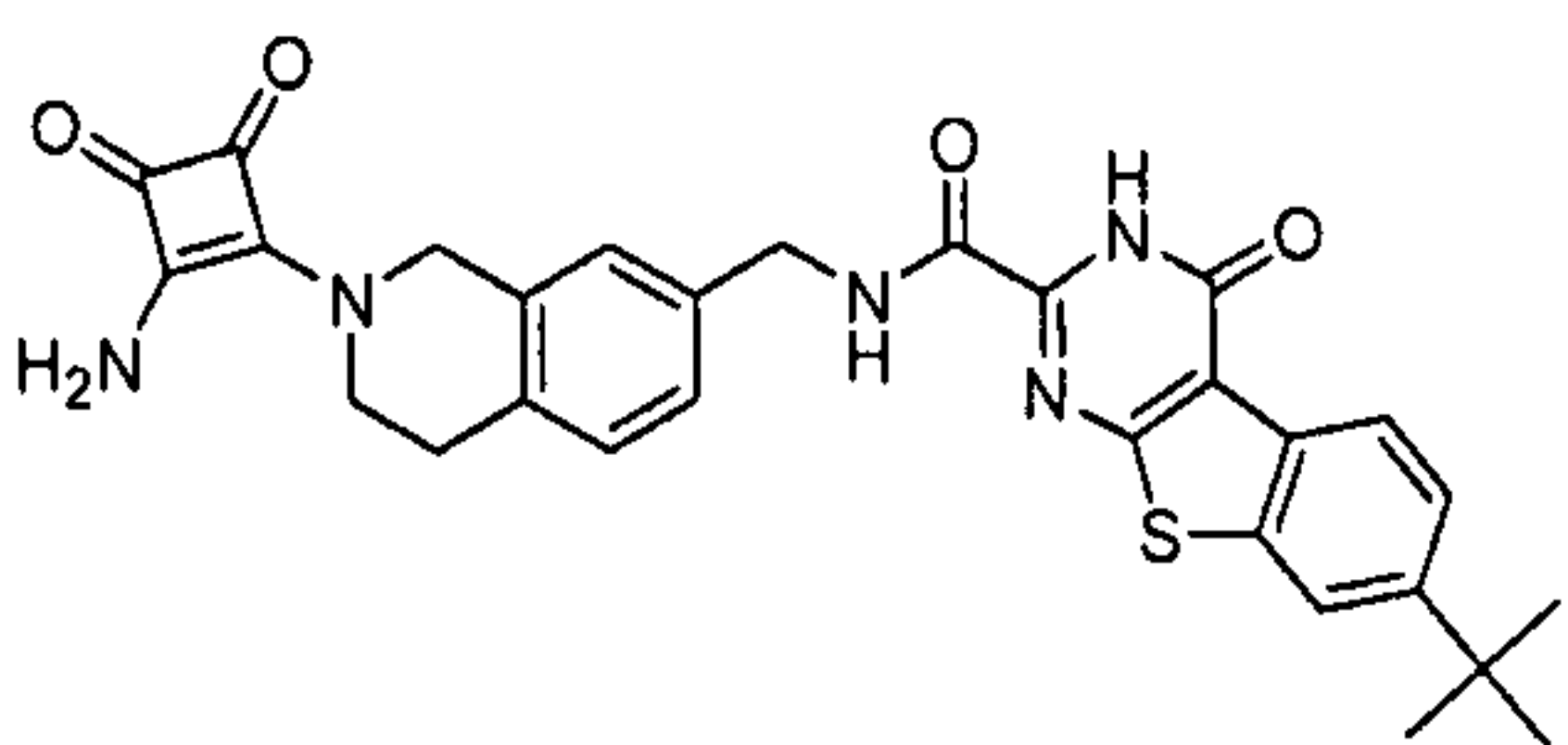
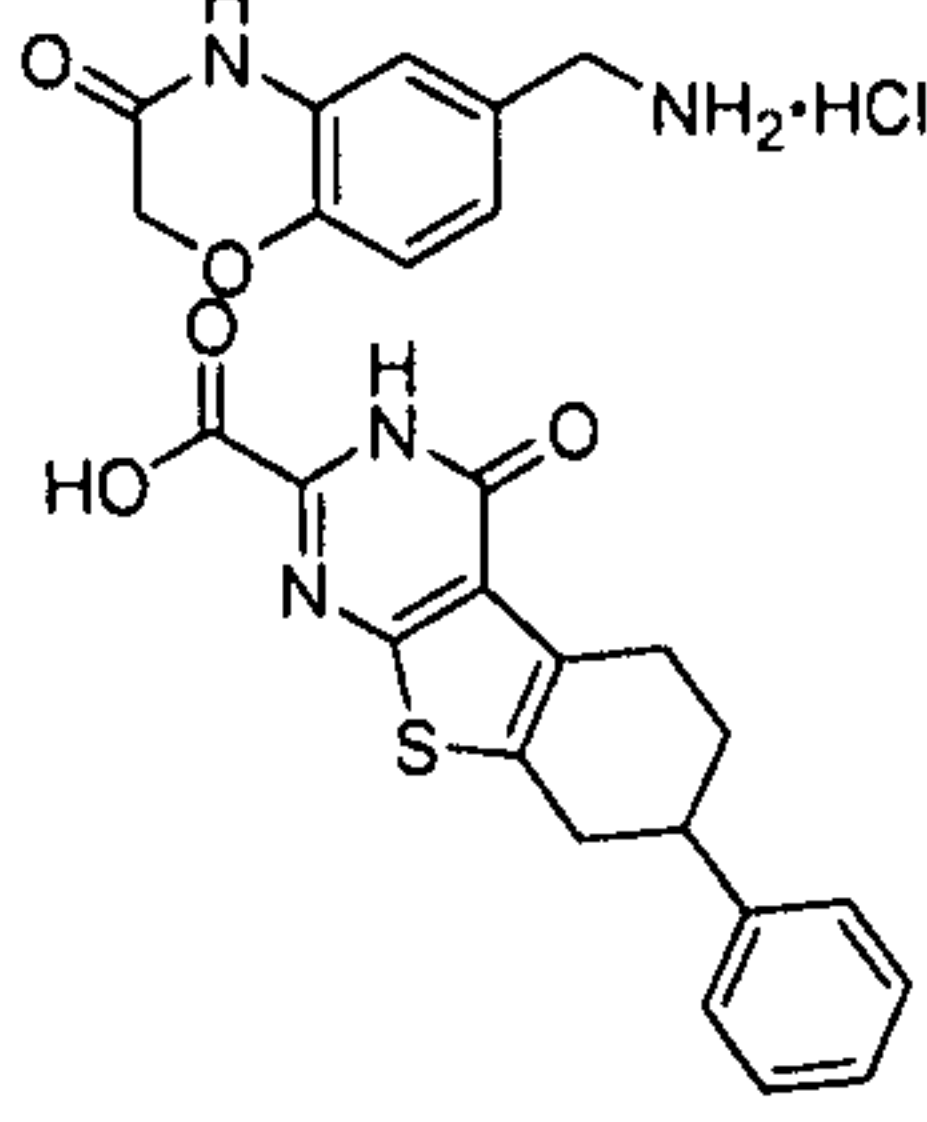
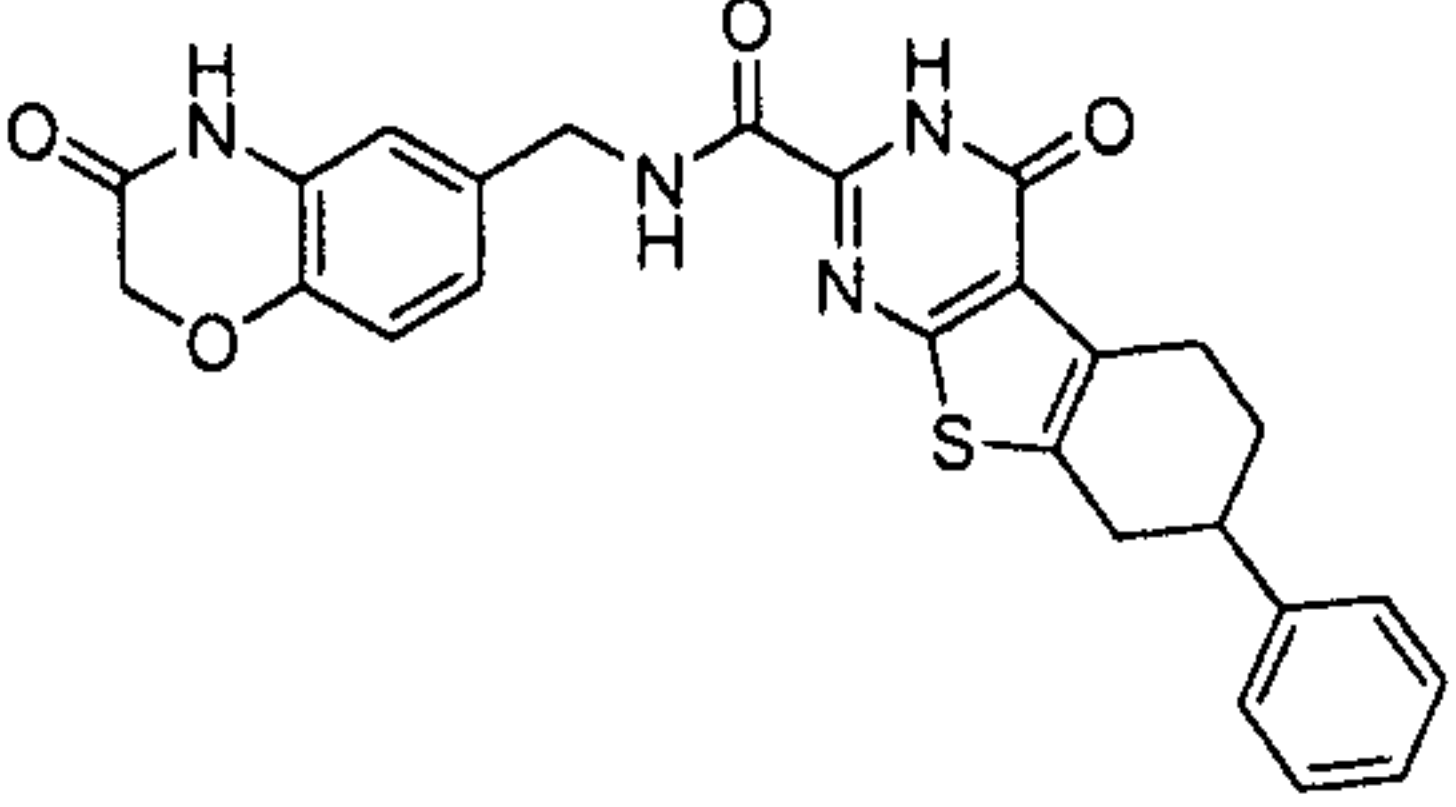
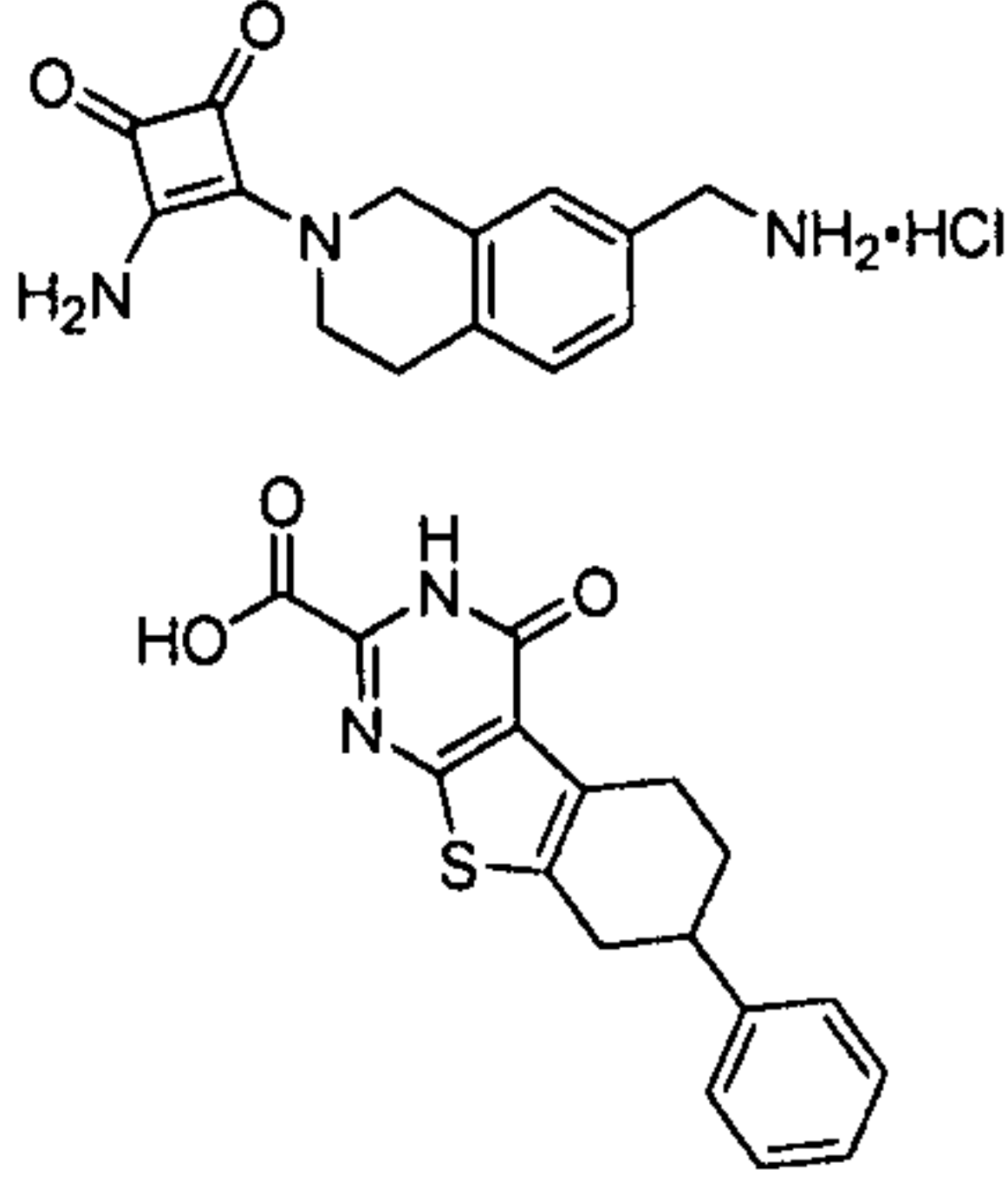
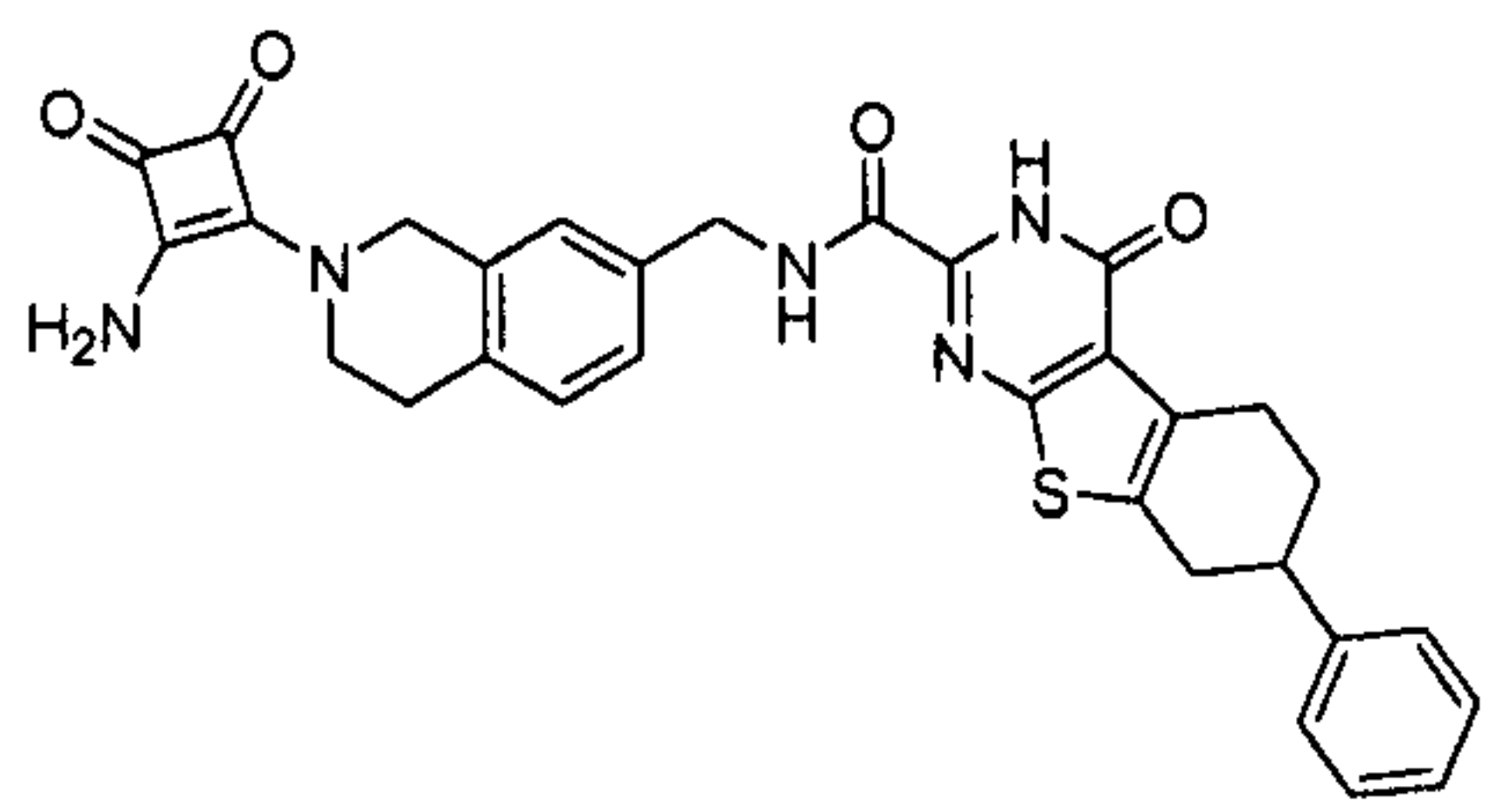
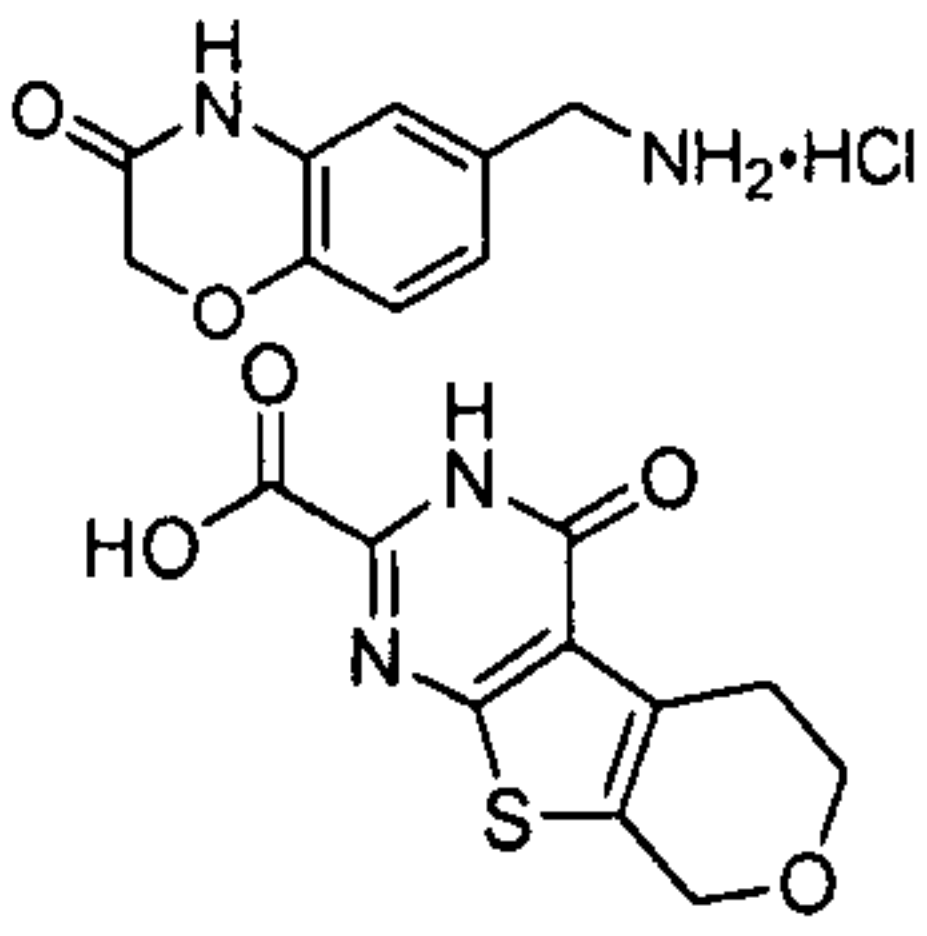
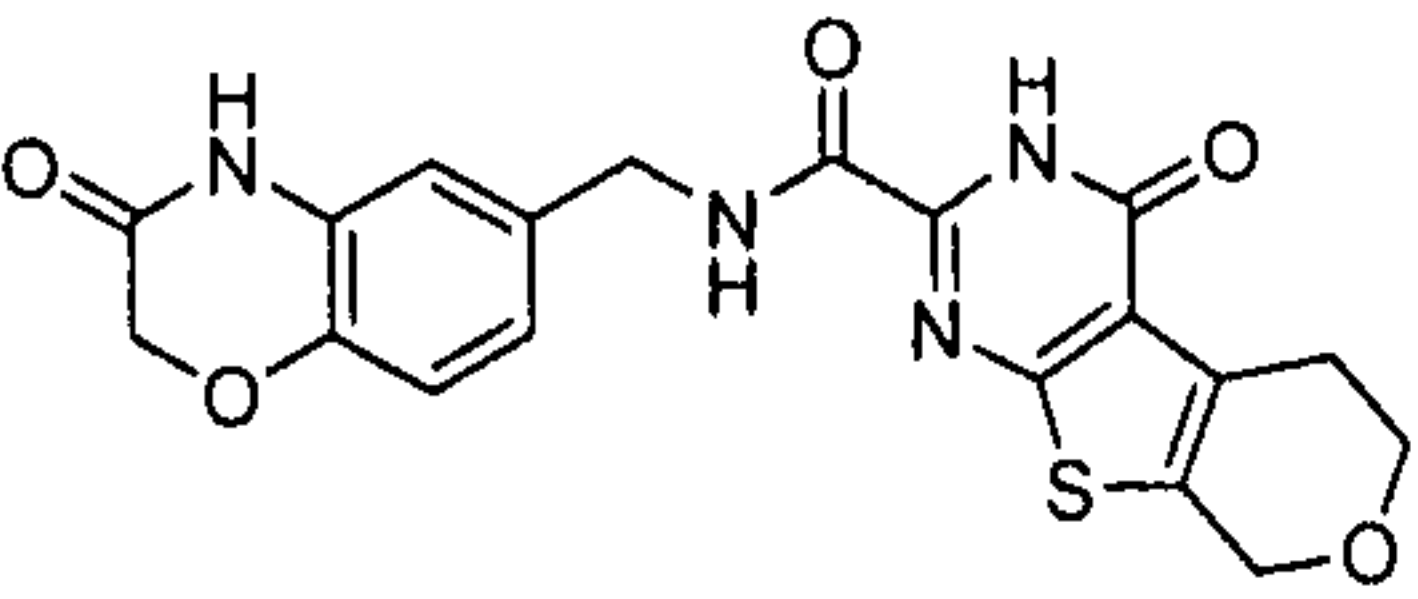
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/34  |    |    | A, 77%<br>[MH] <sup>+</sup> = 411 |
| 2/52  |   |   | A, 85%<br>[MH] <sup>+</sup> = 476 |
| 2/67  |  |  | A, 76%<br>[MH] <sup>+</sup> = 486 |
| 2/89  |  |  | A, 27%<br>[MH] <sup>+</sup> = 438 |
| 2/90  |  |  | A, 63%<br>[MH] <sup>+</sup> = 517 |

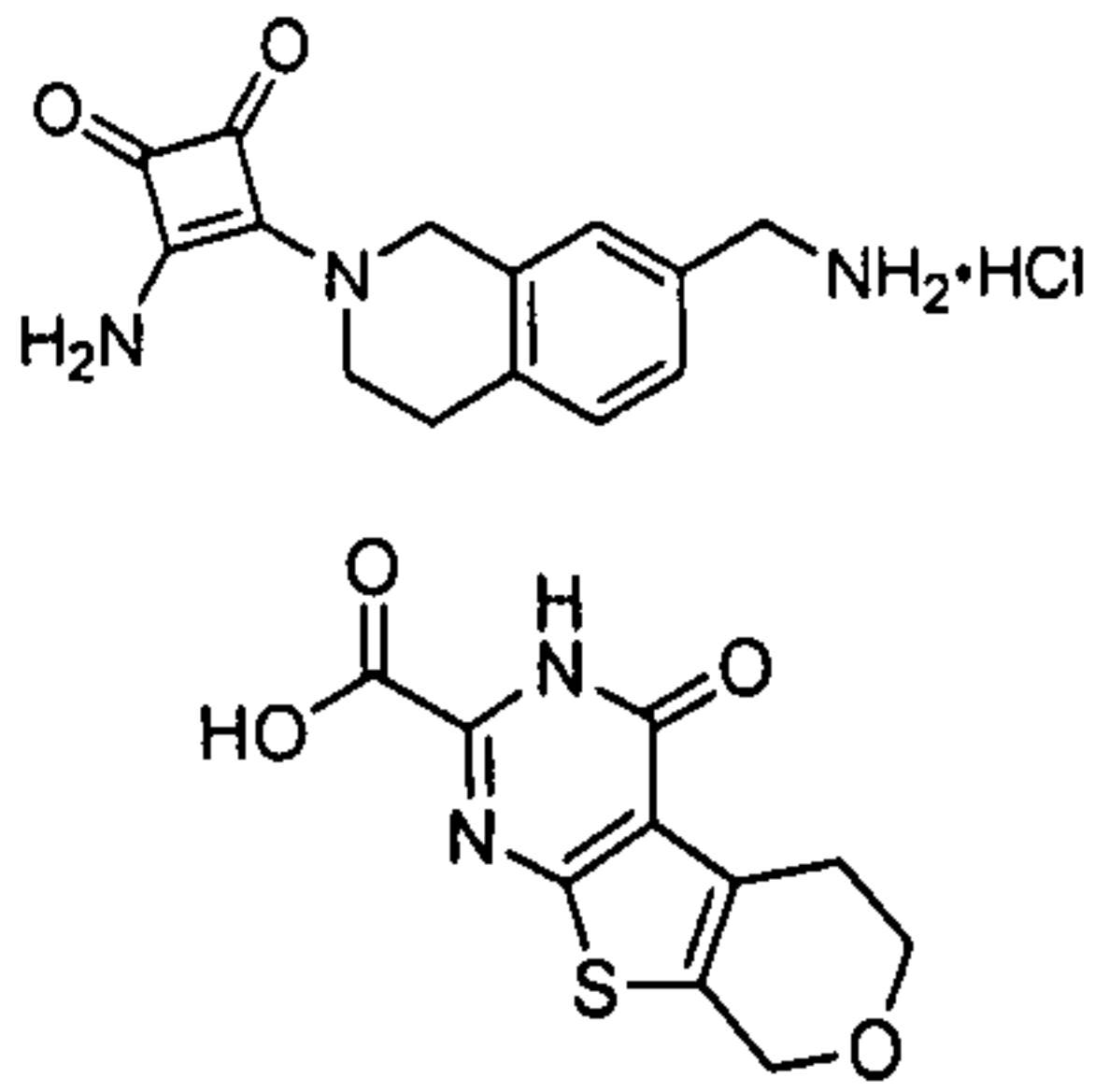
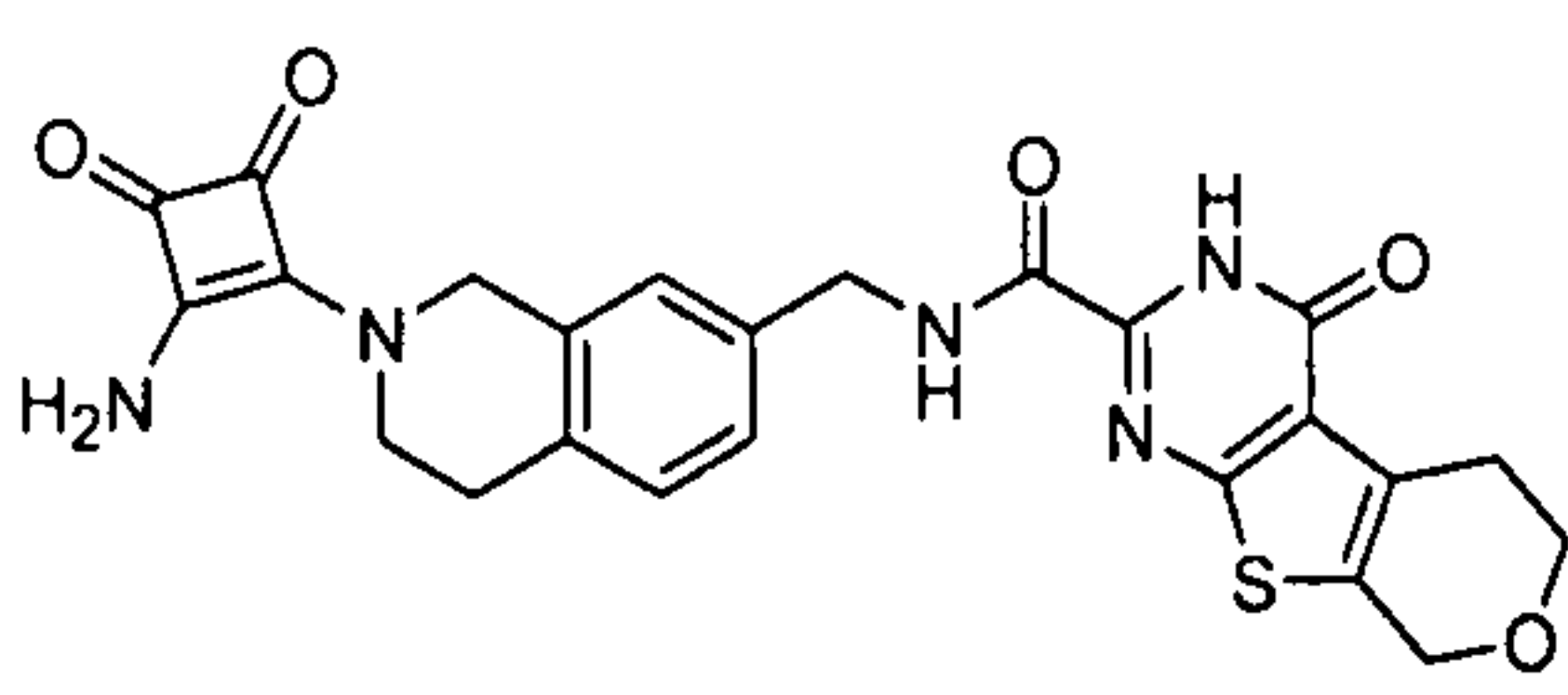
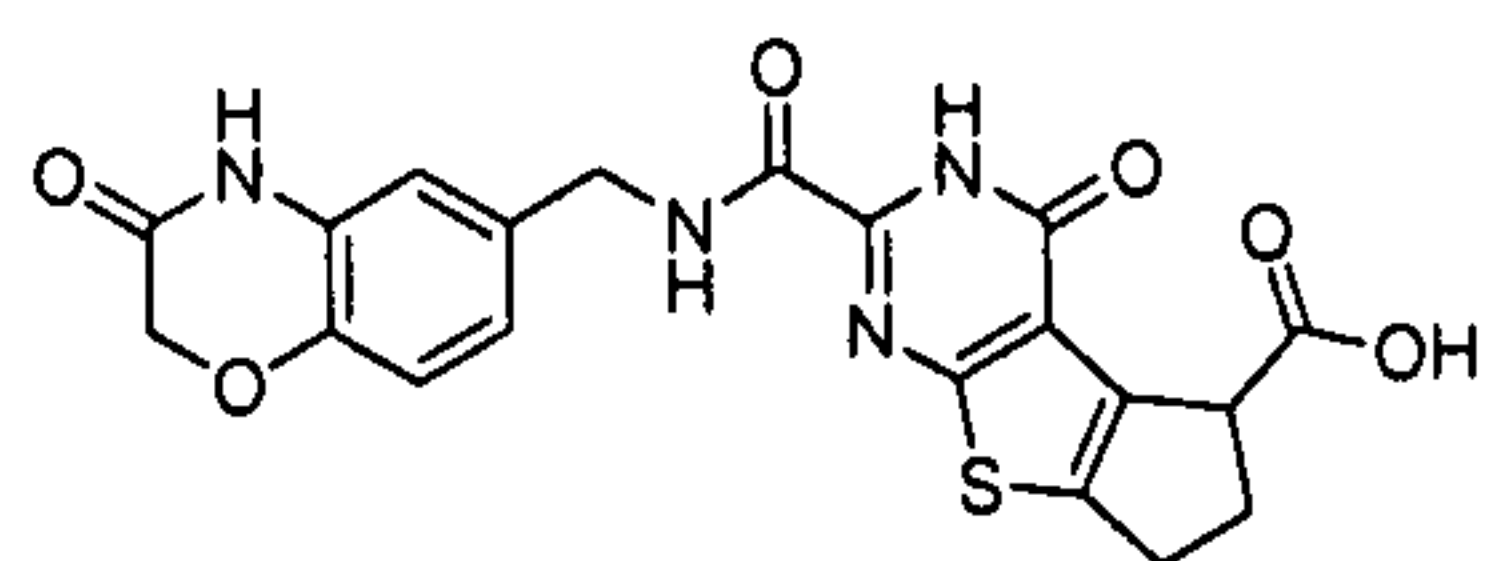
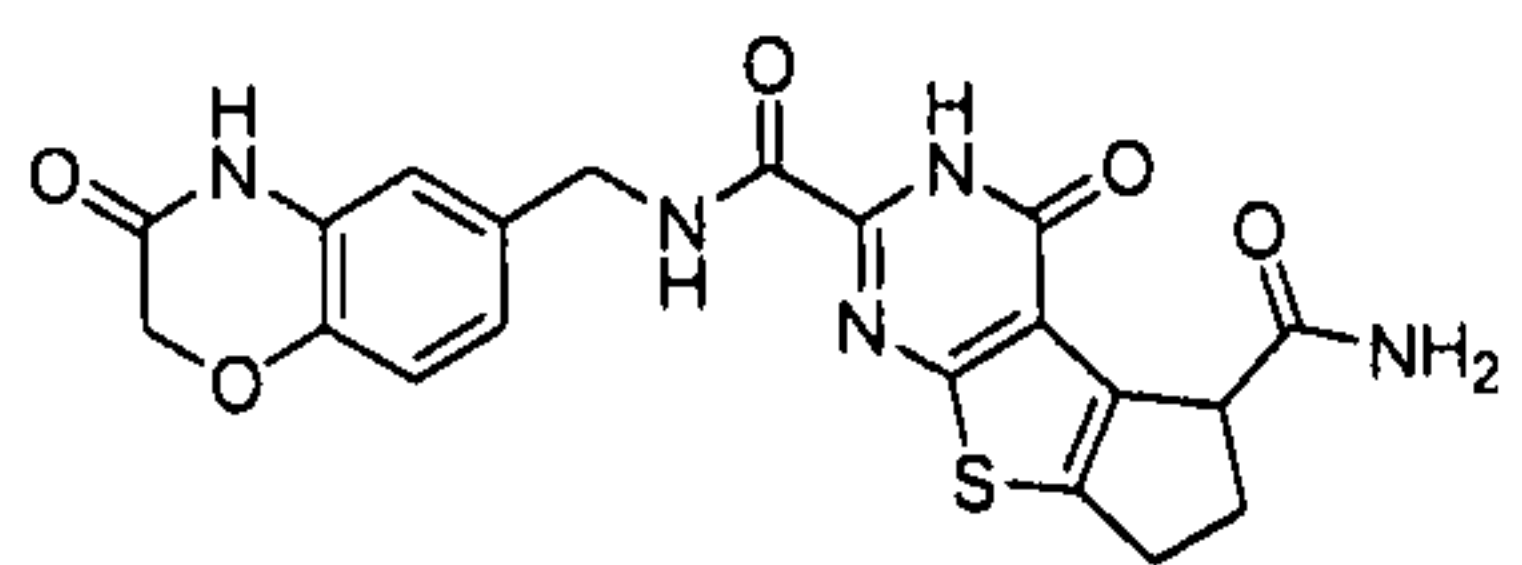
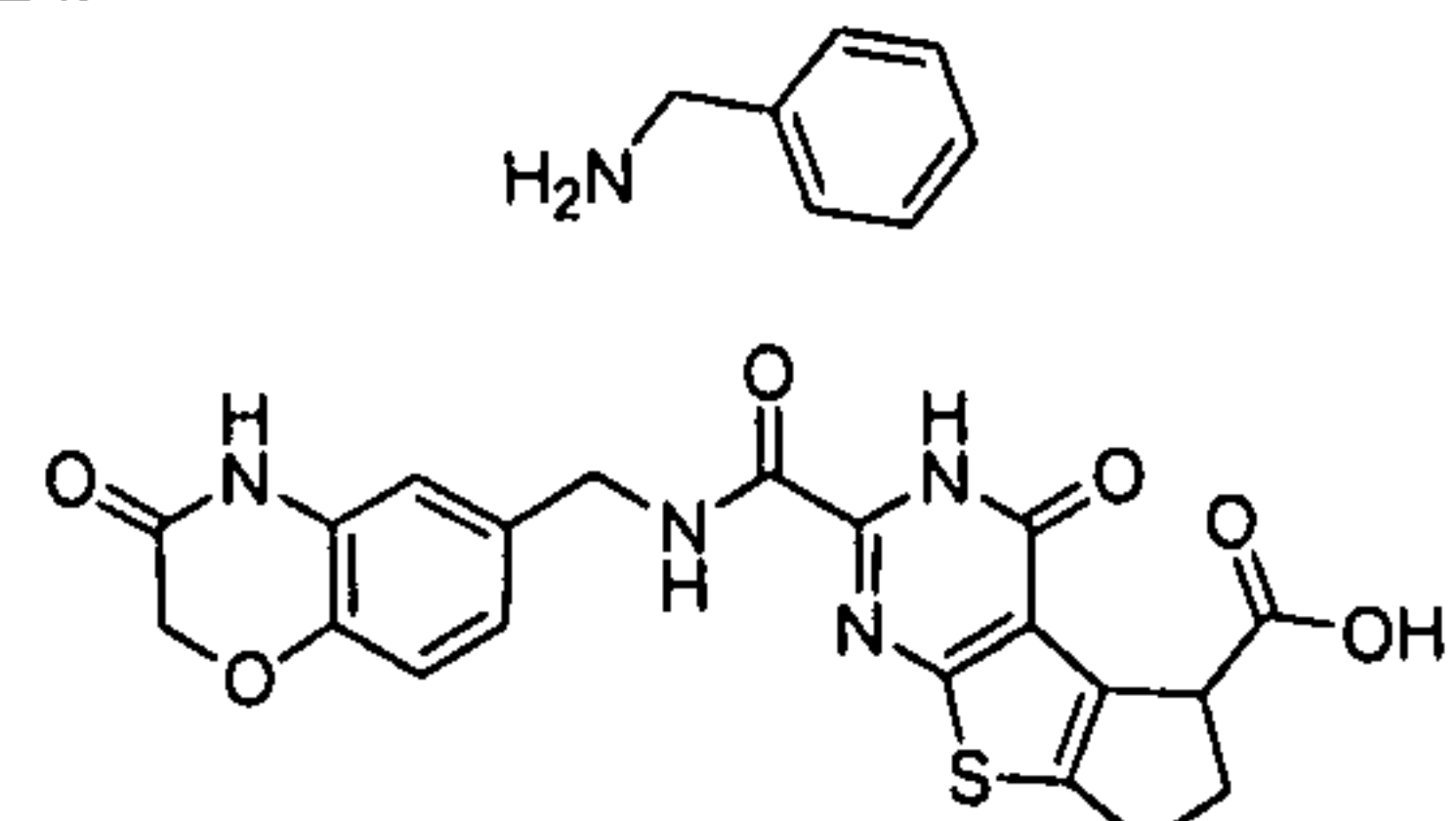
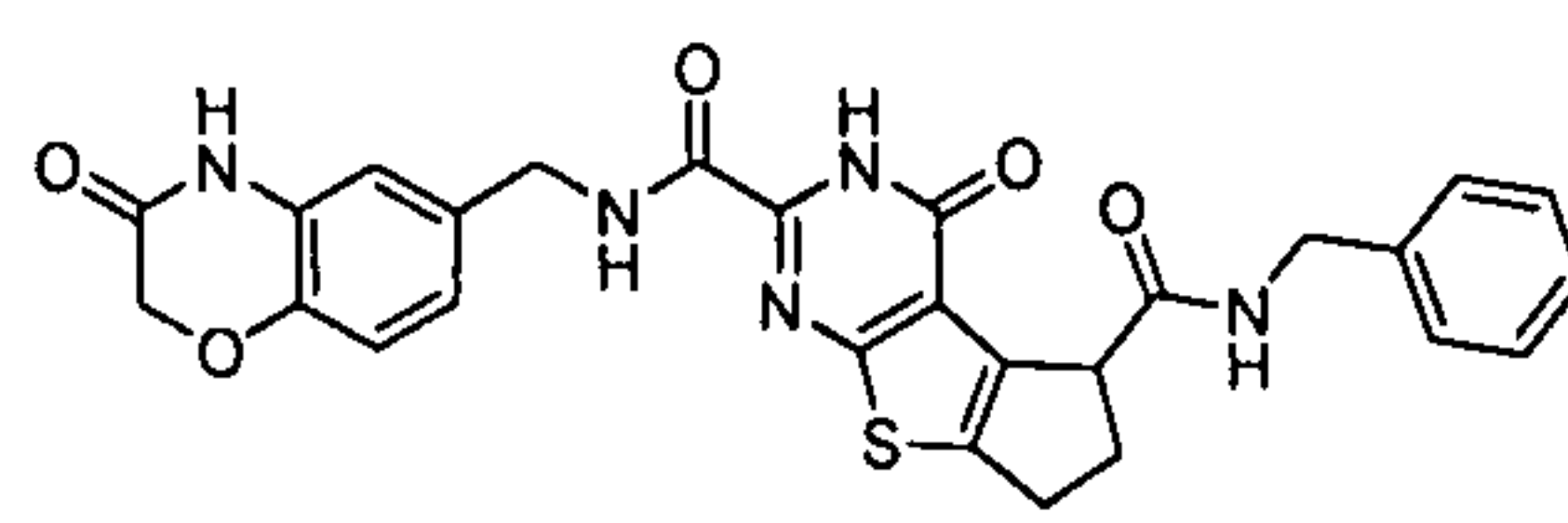
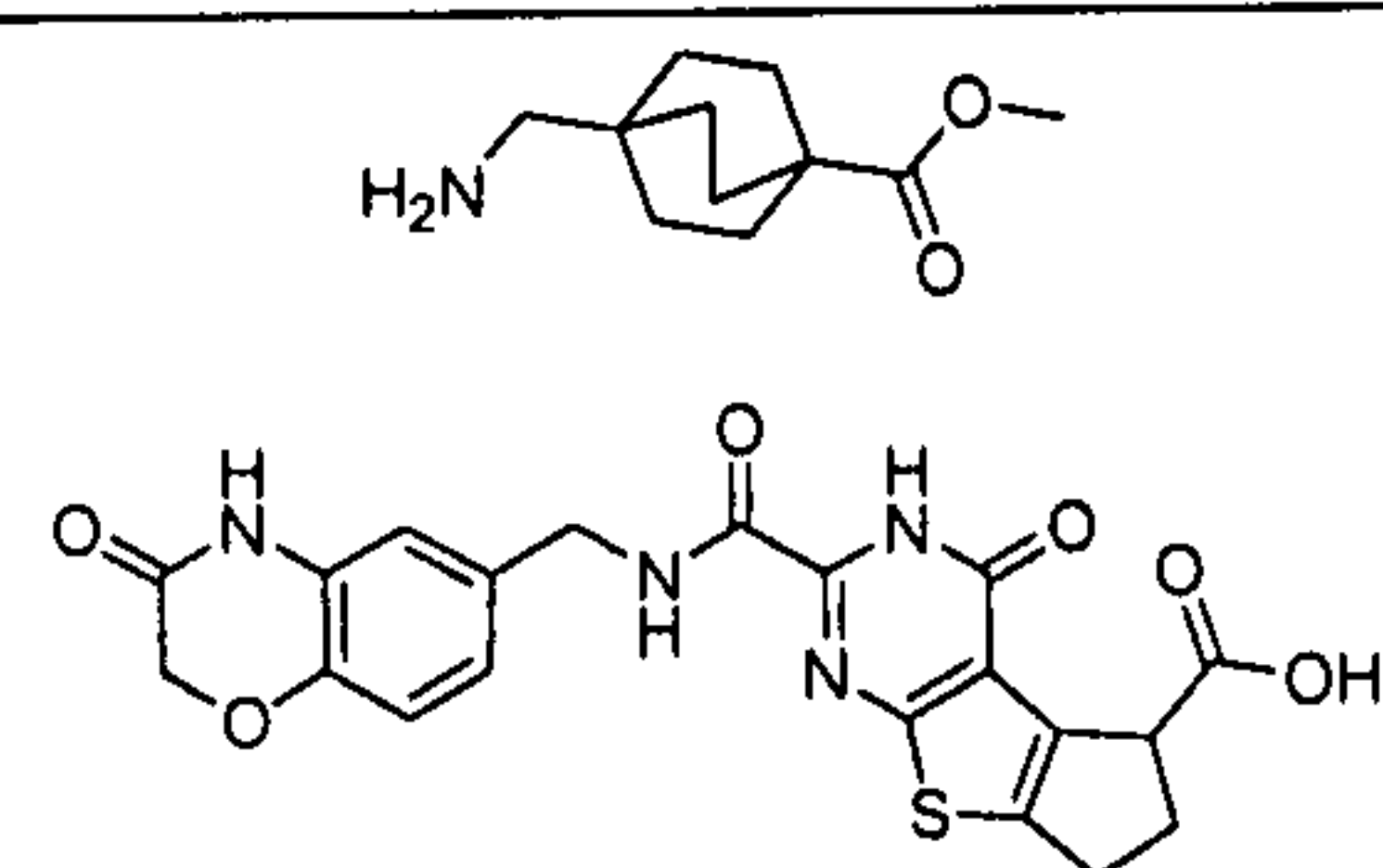
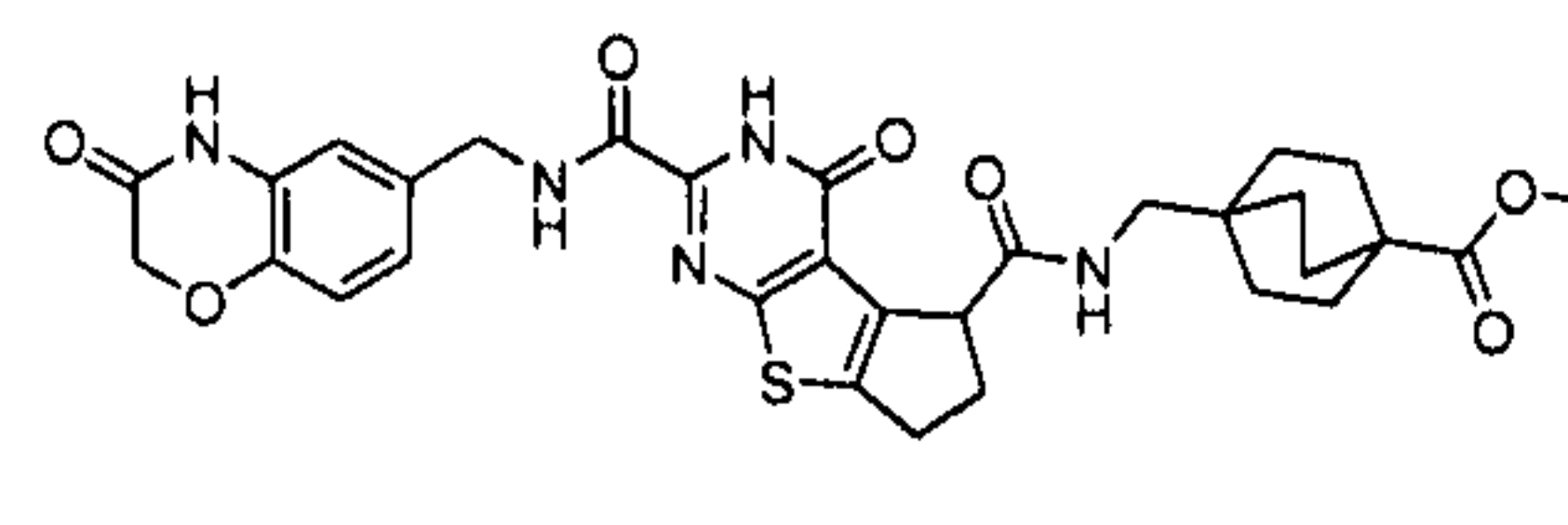
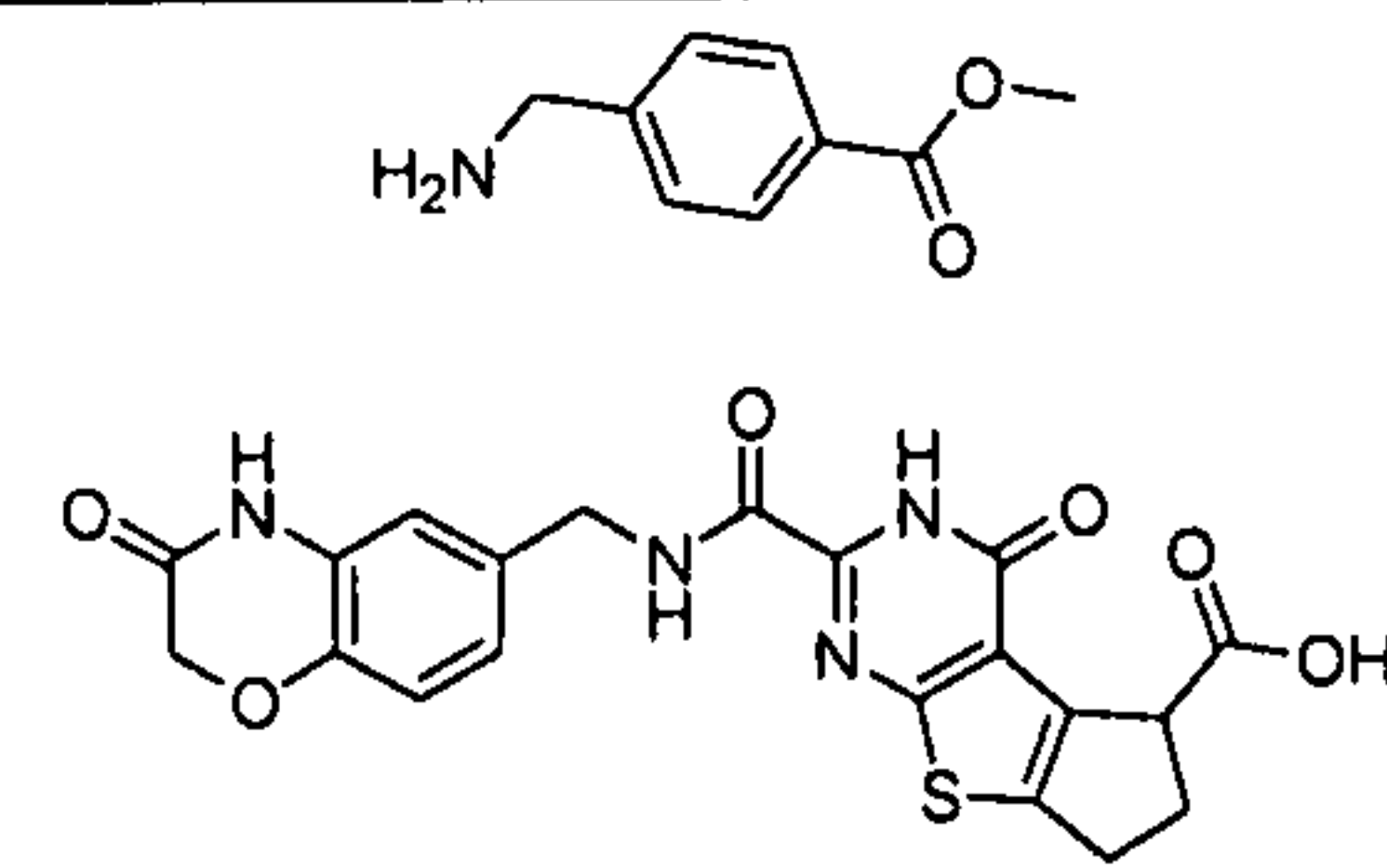
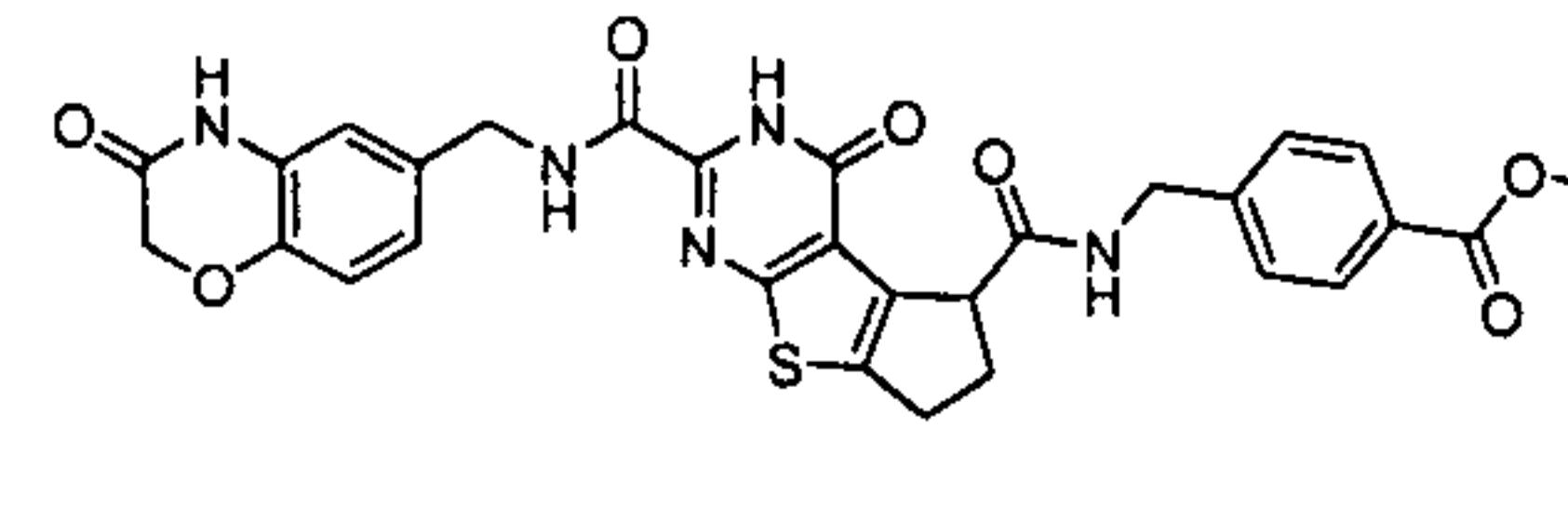
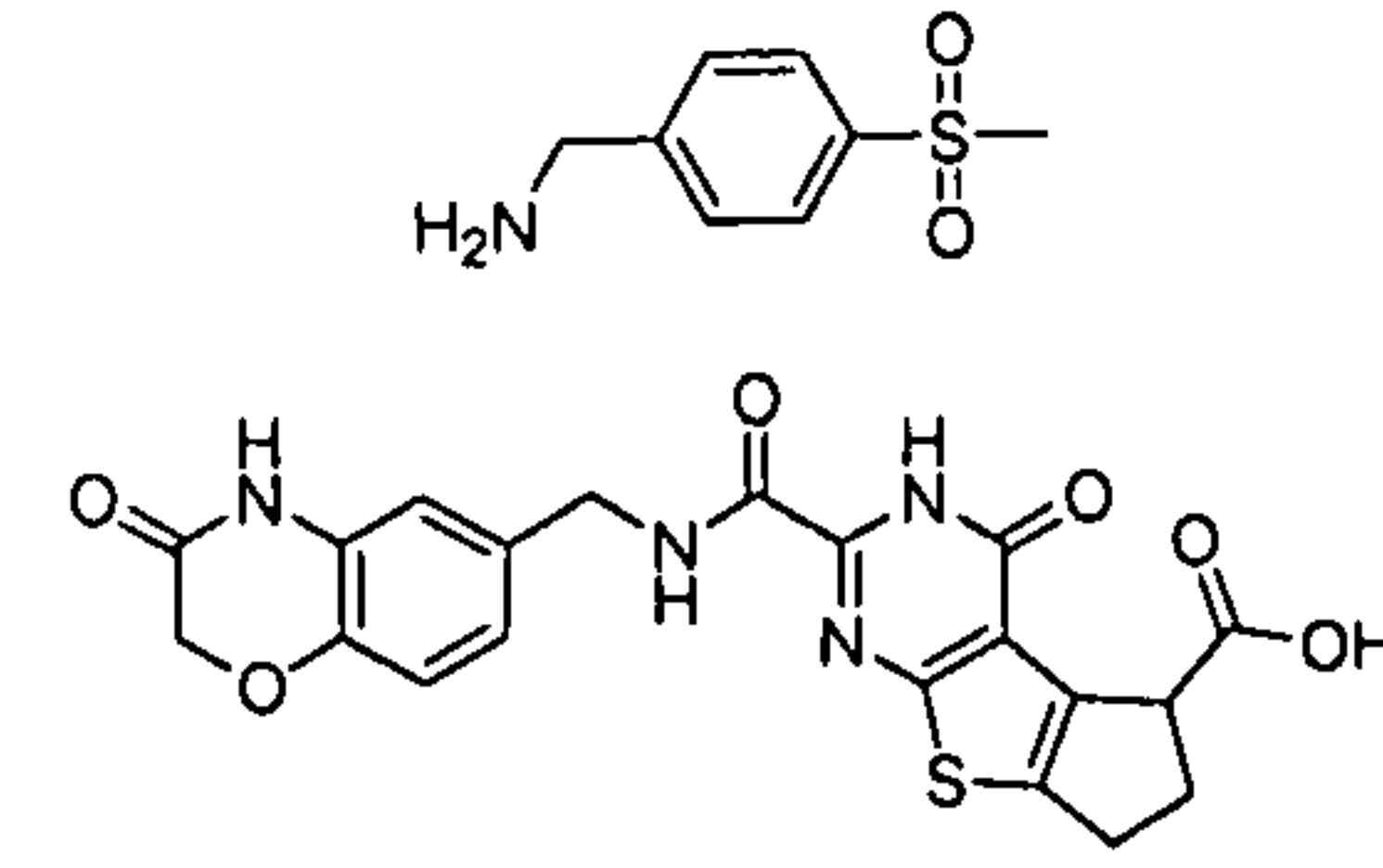
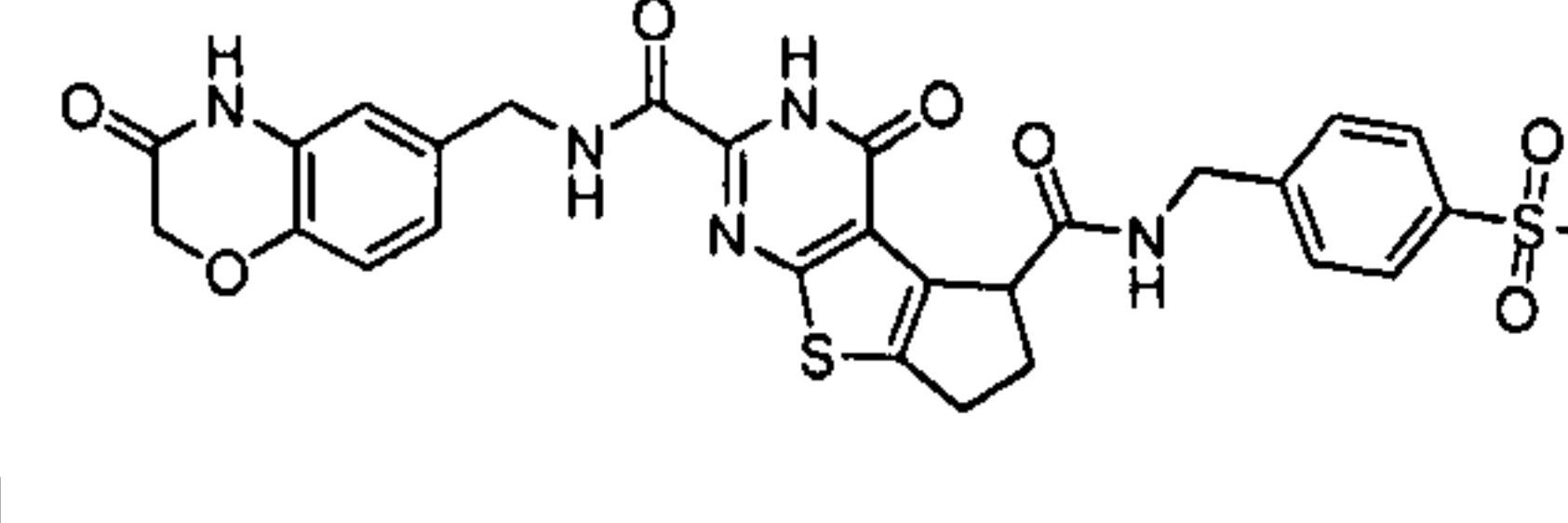
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/94  |    |    | A, 83%<br>[MH] <sup>+</sup> = 454 |
| 2/95  |   |  | A, 70%<br>[MH] <sup>+</sup> = 533 |
| 2/103 |  |  | A, 81%<br>[MH] <sup>+</sup> = 461 |
| 2/104 |  |  | A, 64%<br>[MH] <sup>+</sup> = 540 |
| 2/107 |  |  | A, 85%<br>[MH] <sup>+</sup> = 489 |

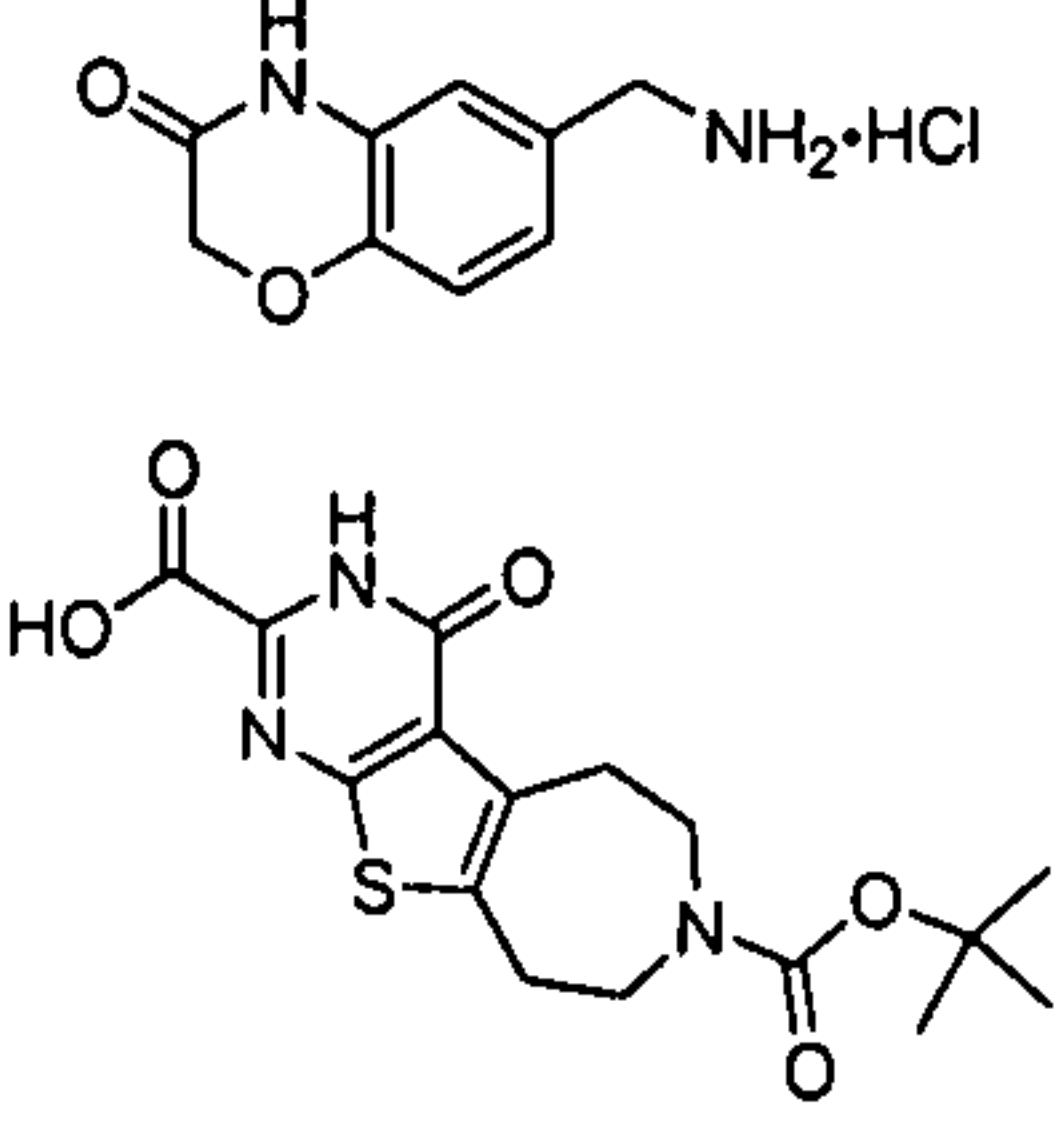
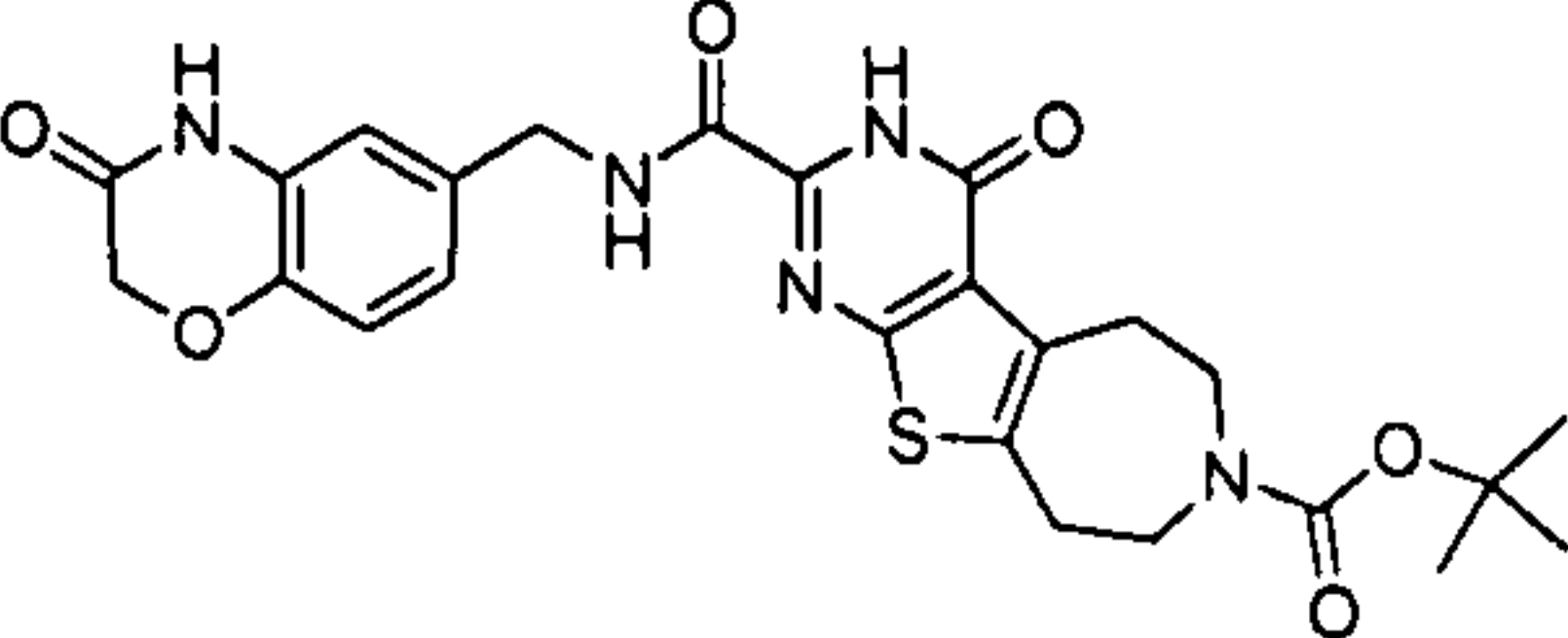
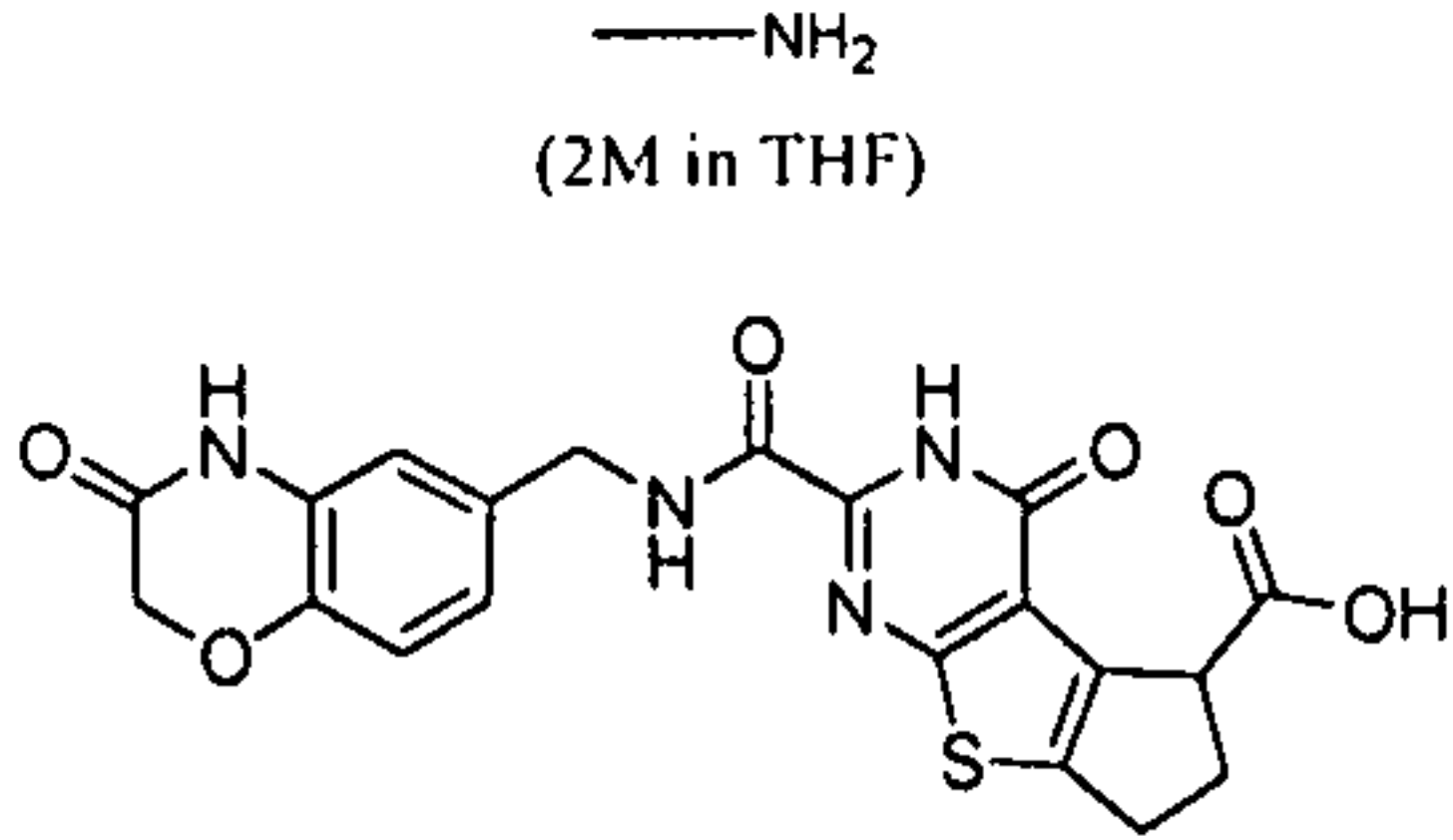
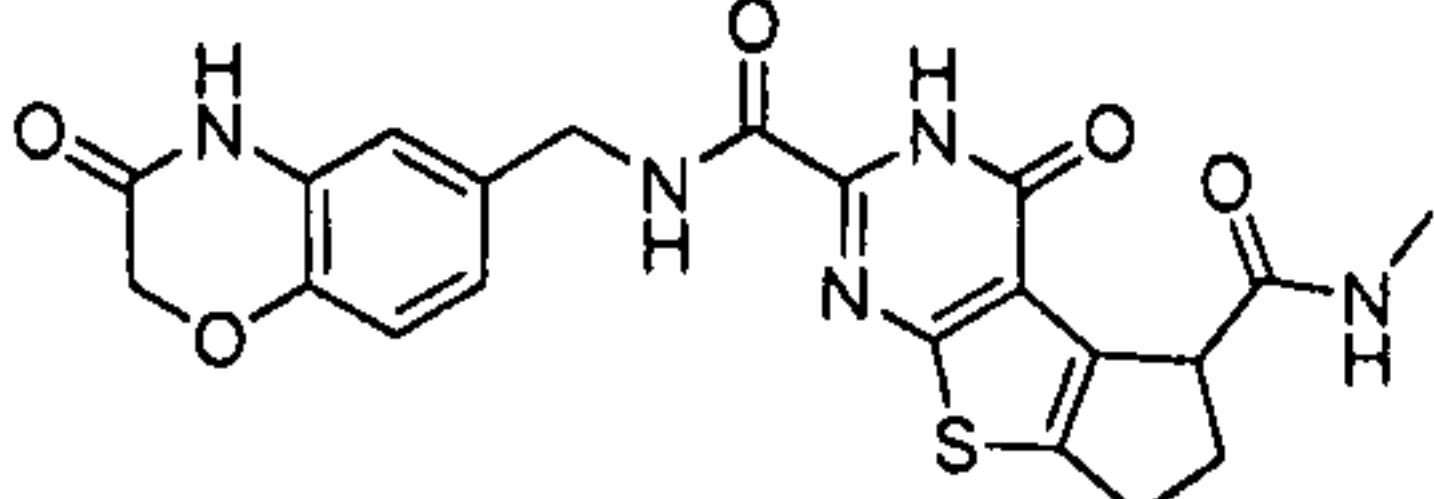
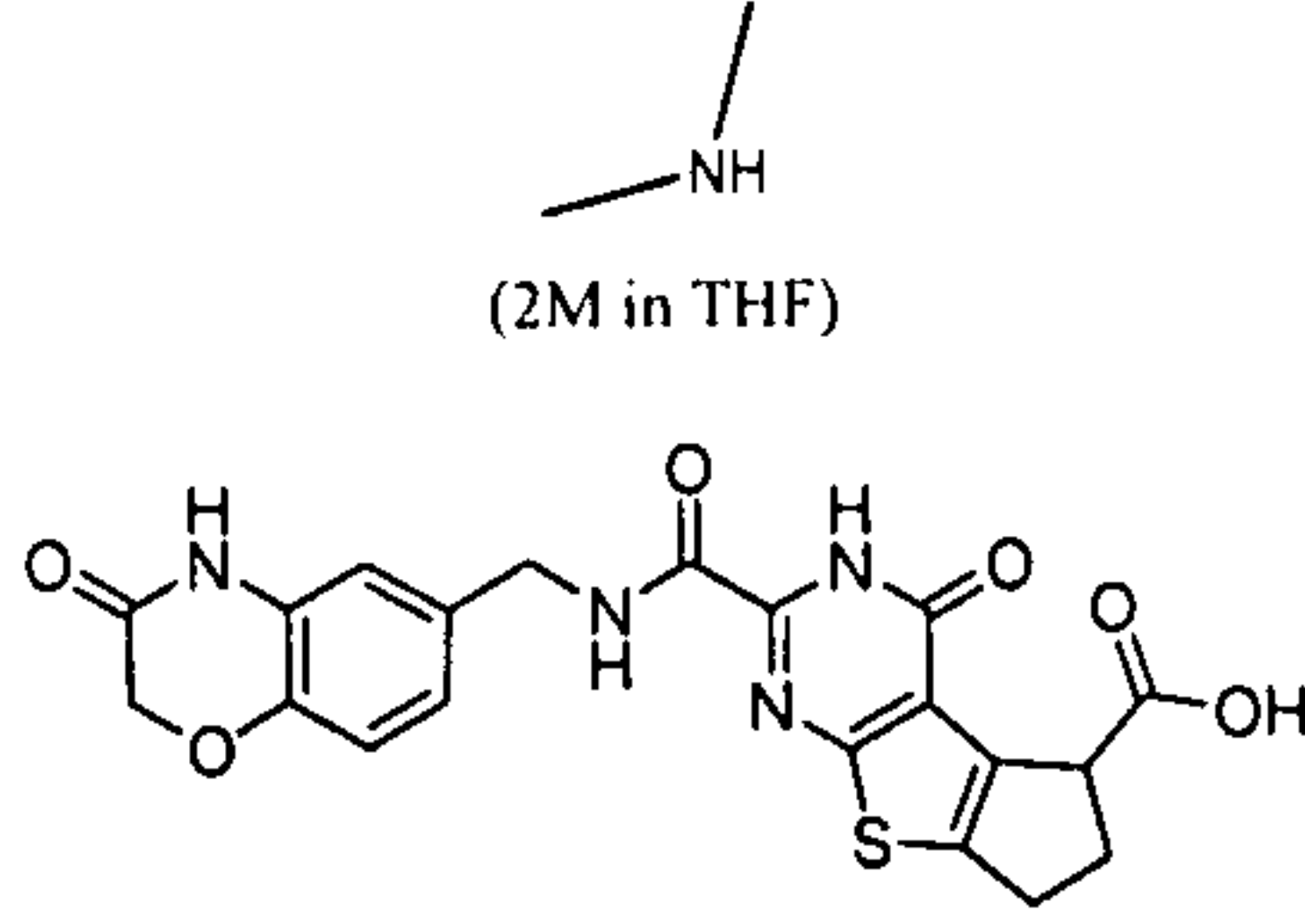
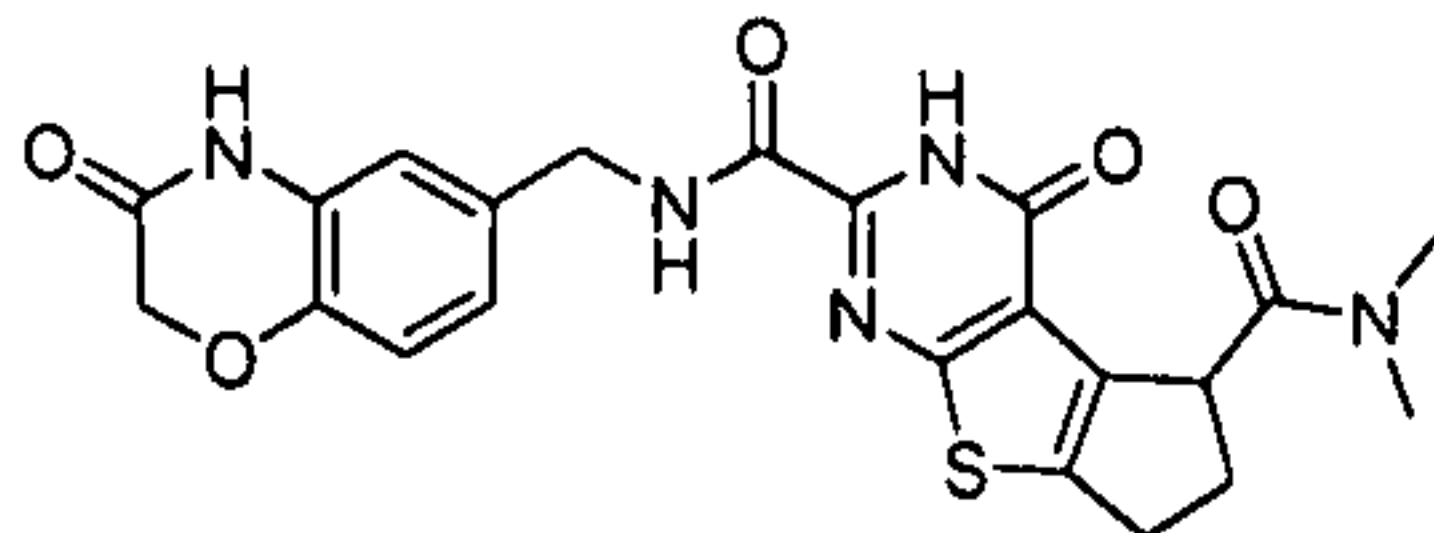
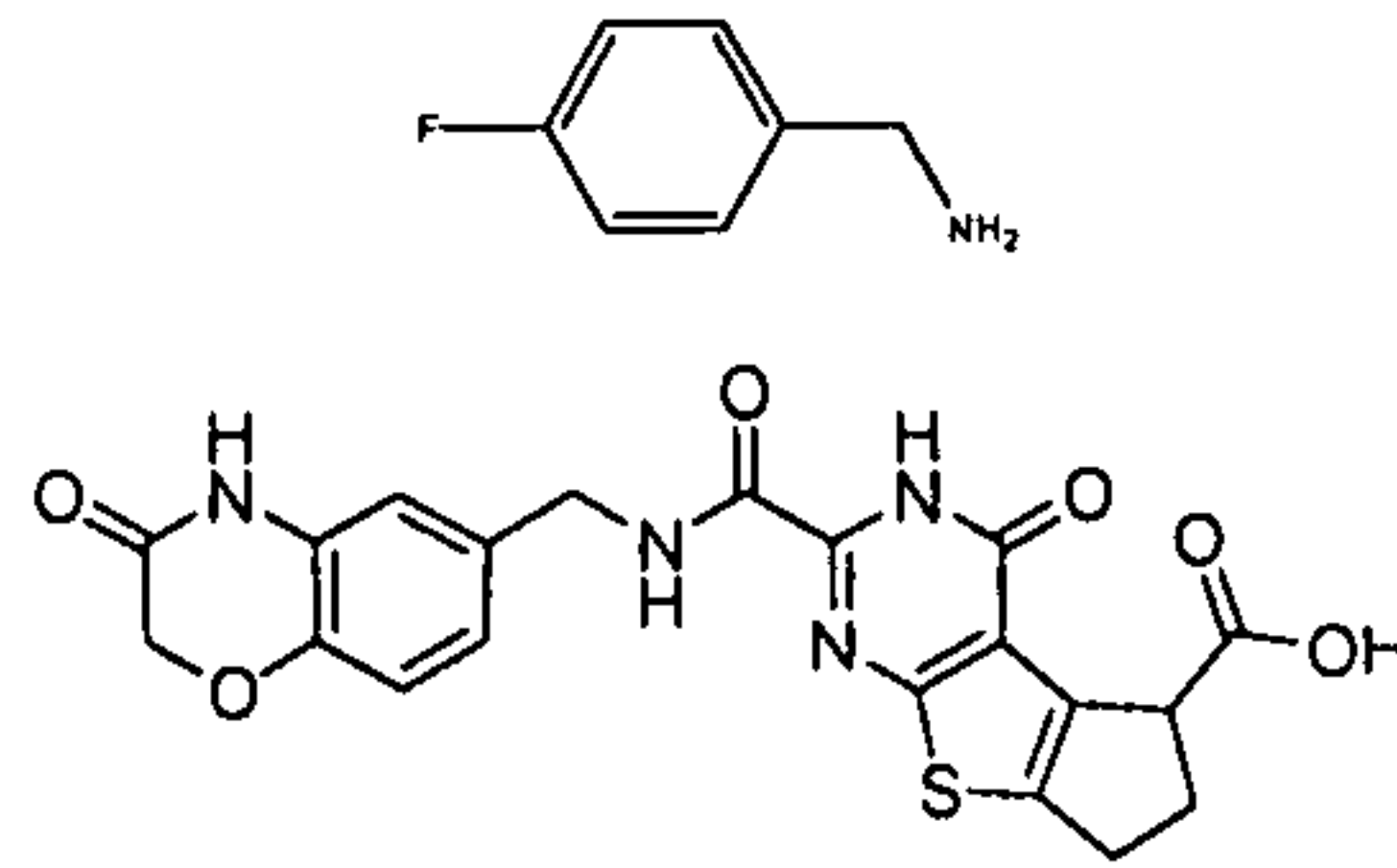
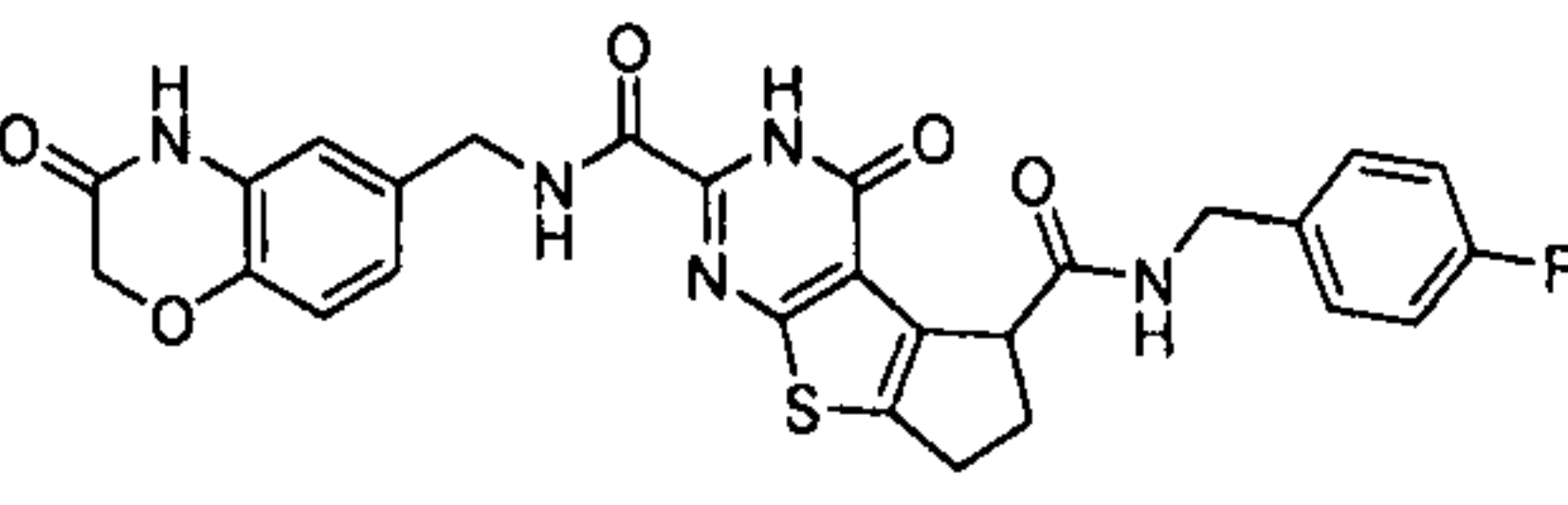
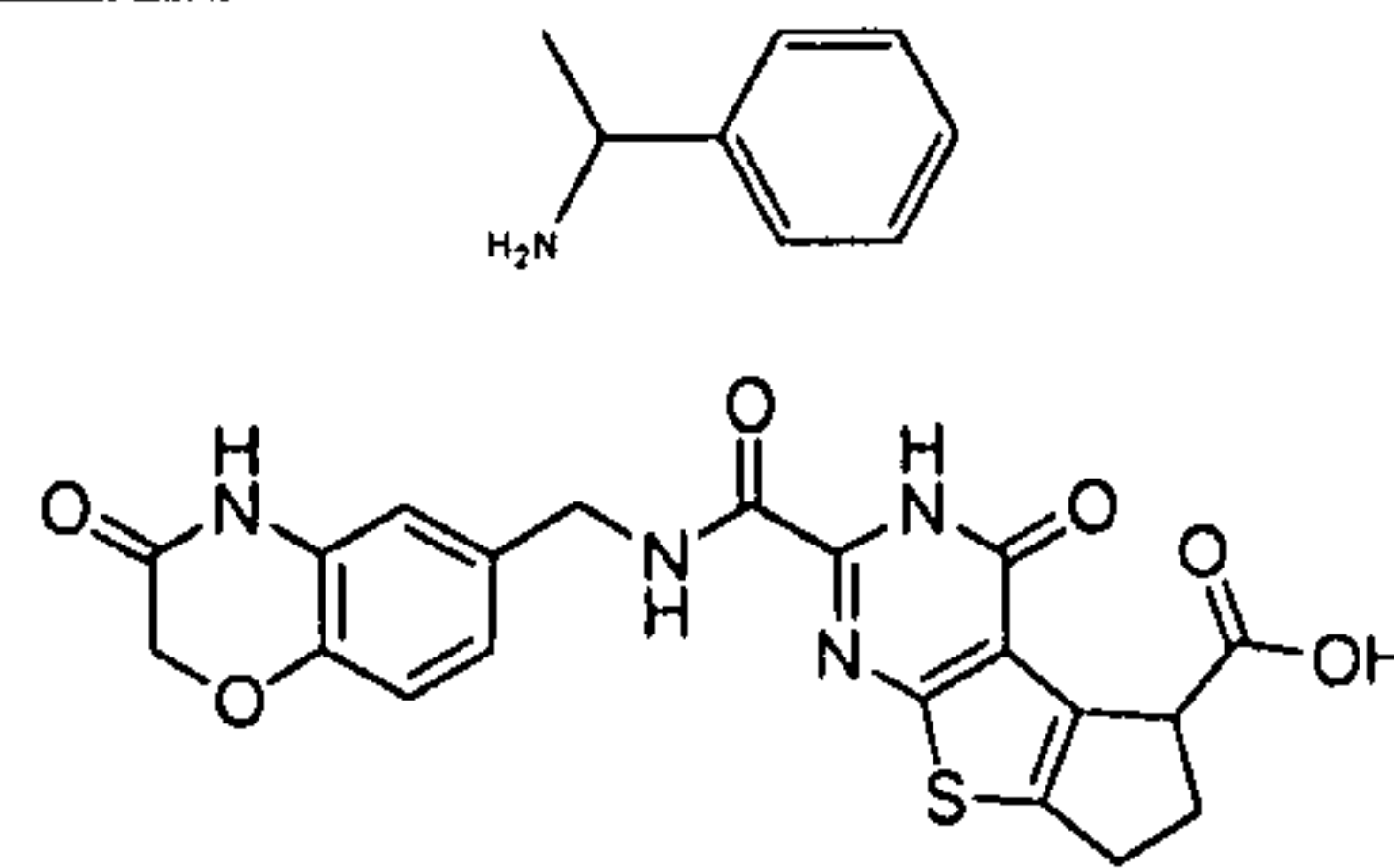
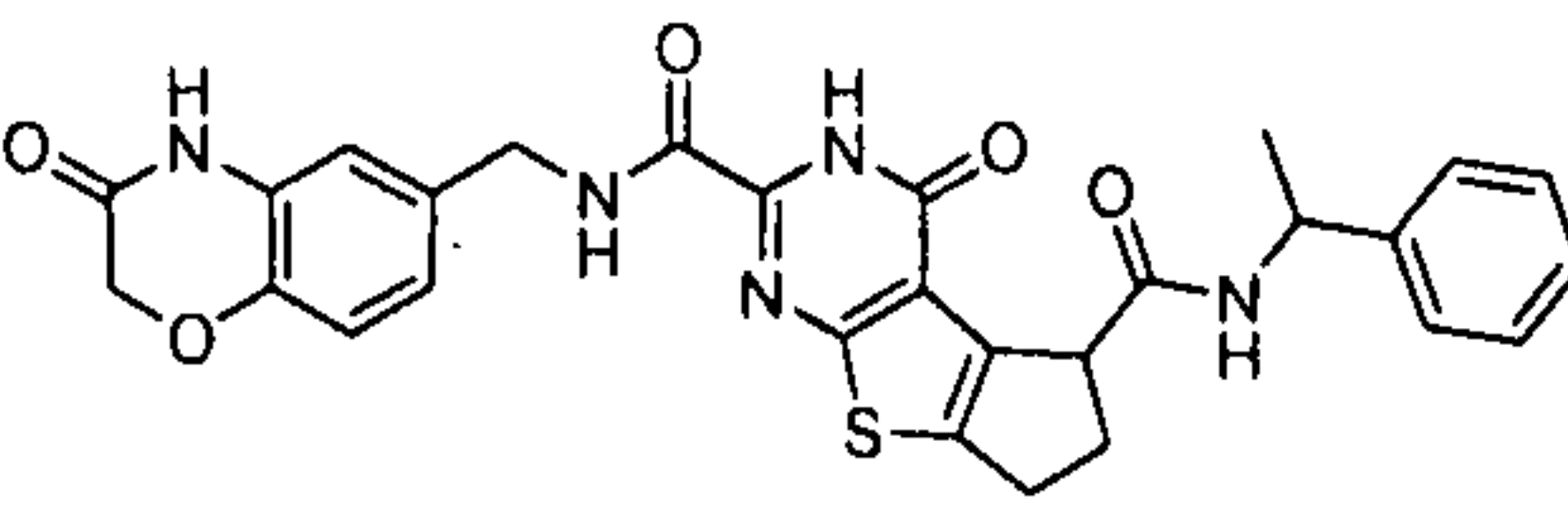
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                        |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------|
| 2/108 |    |    | A, quant.<br>[MH] <sup>+</sup> = 489 |
| 2/113 |  |  | A, 40%<br>[MH] <sup>+</sup> = 469    |
| 2/114 |  |  | A, 88%<br>[MH] <sup>+</sup> = 548    |
| 2/117 |  |  | A, 93%<br>[MH] <sup>+</sup> = 425    |
| 2/118 |  |  | A, 98%<br>[MH] <sup>+</sup> = 504    |

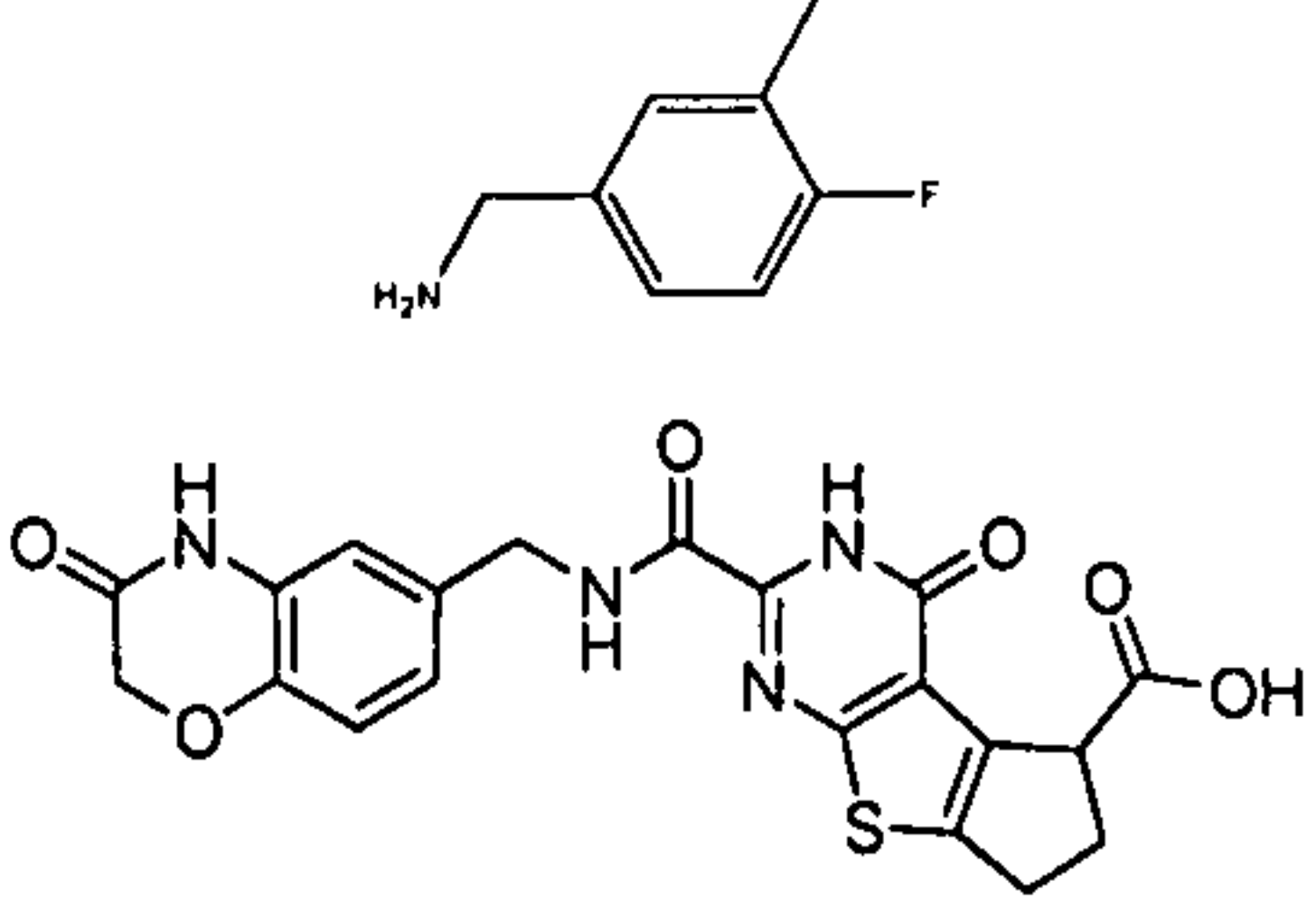
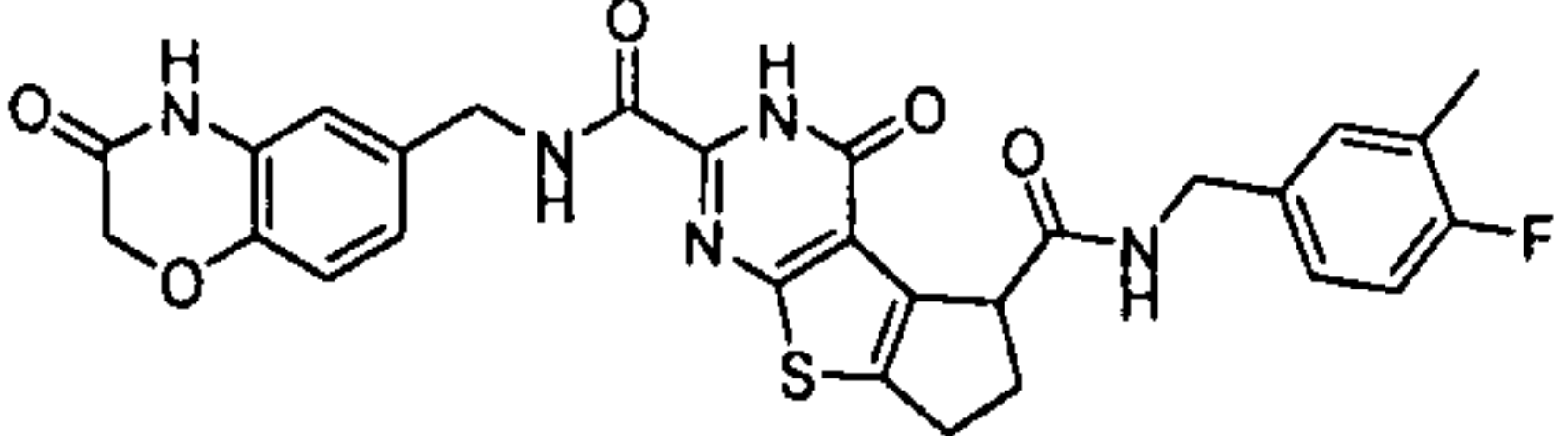
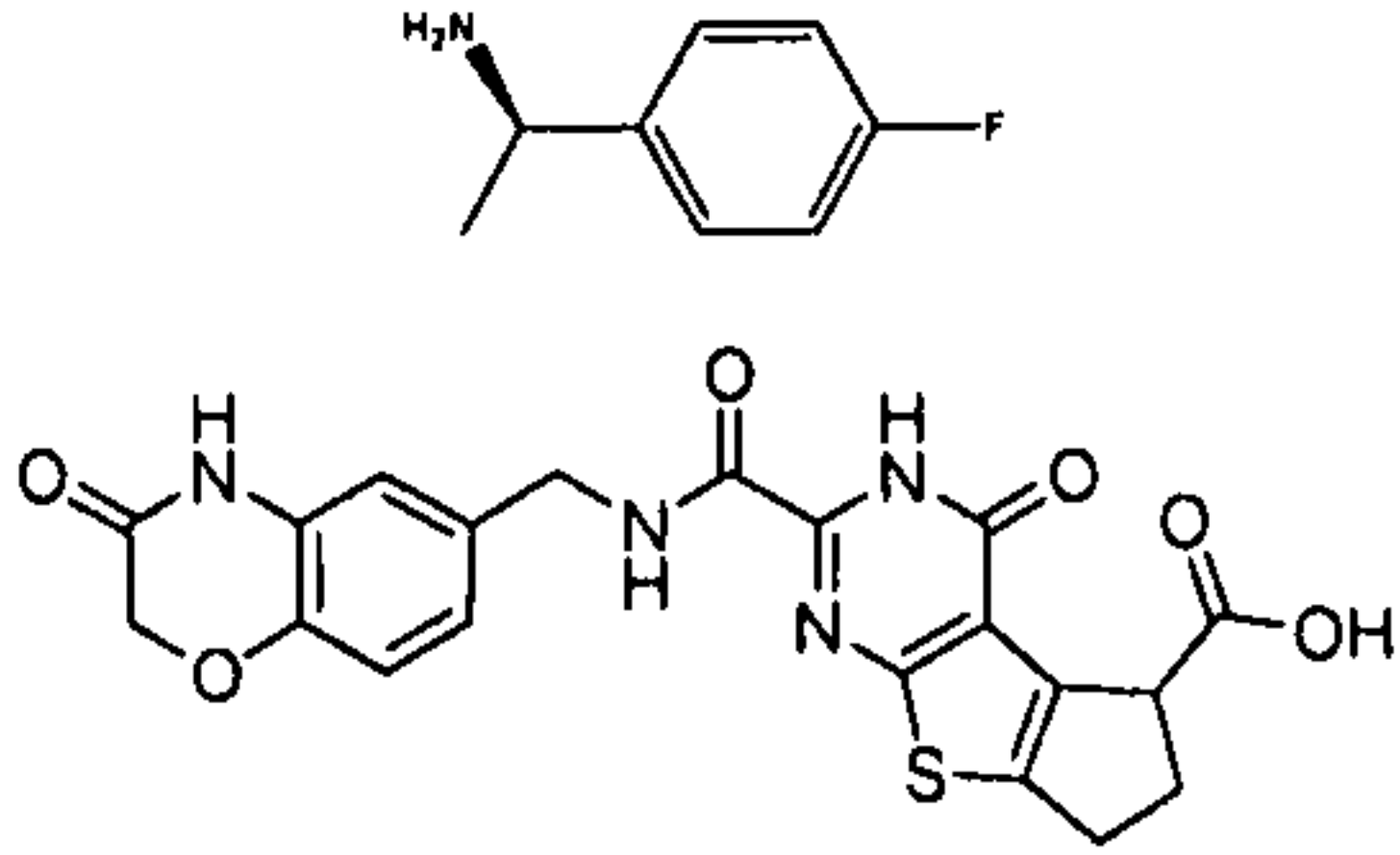
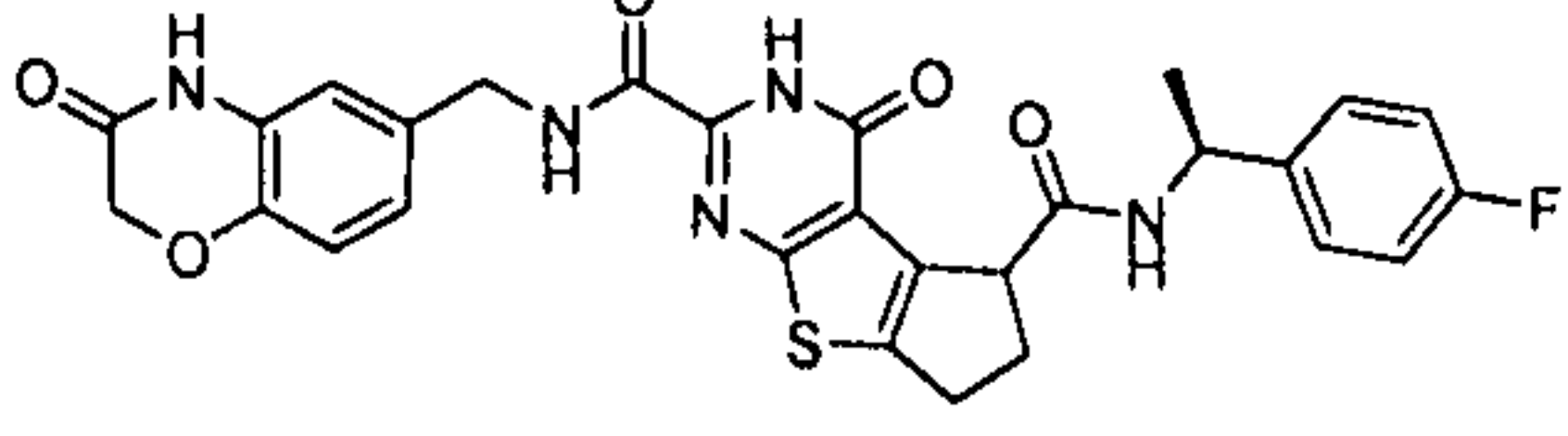
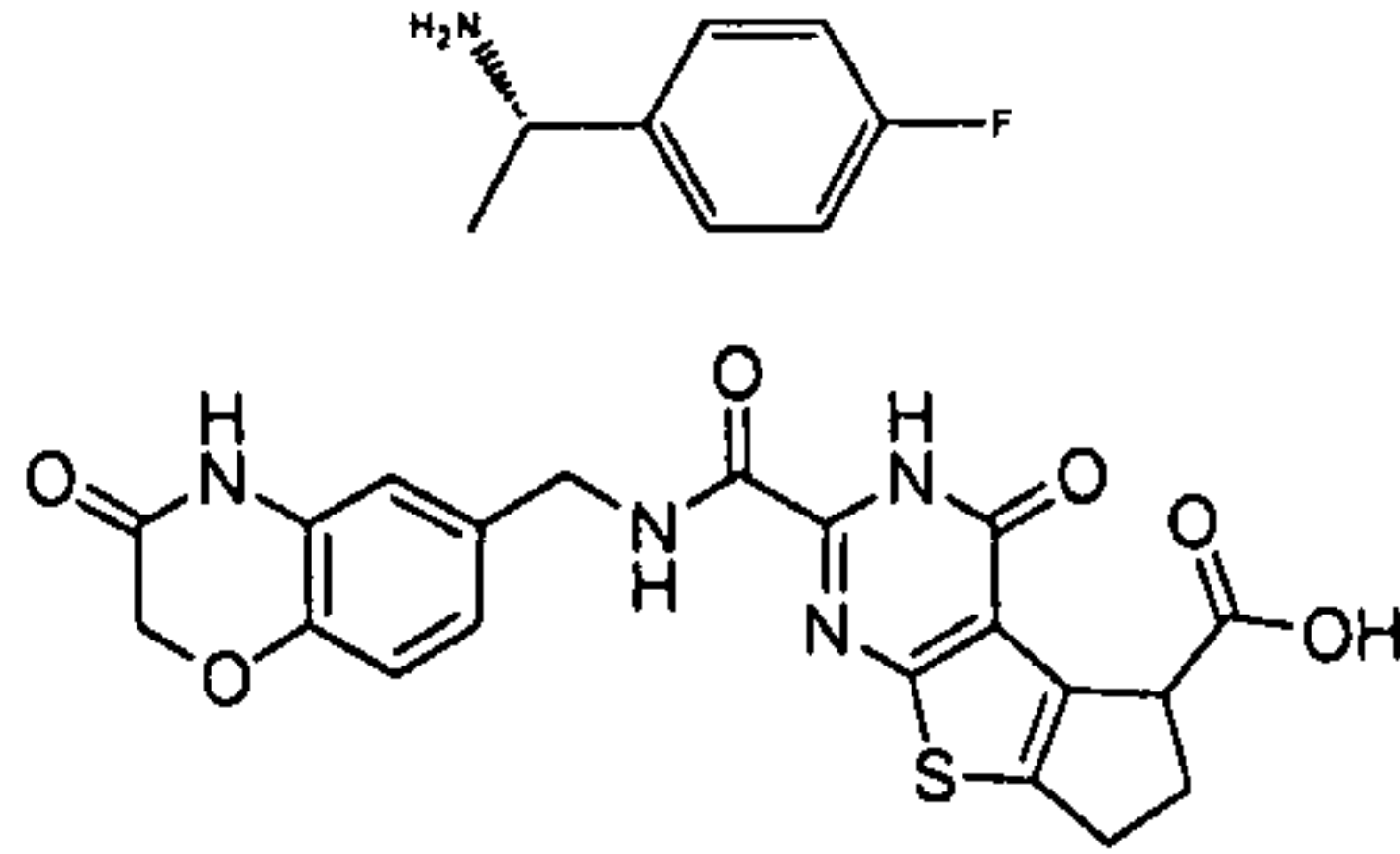
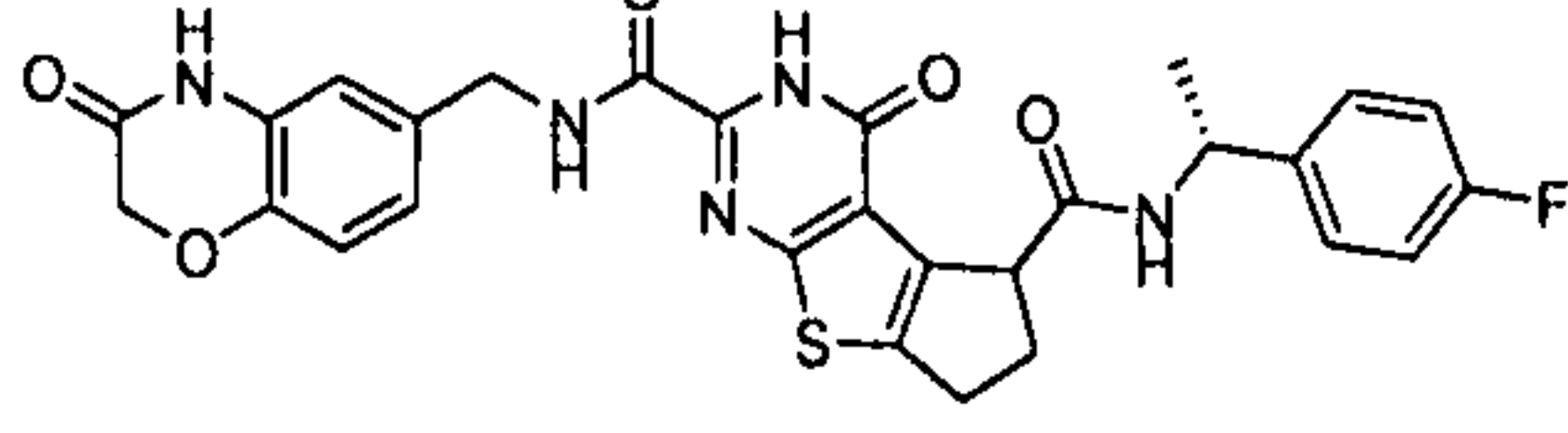
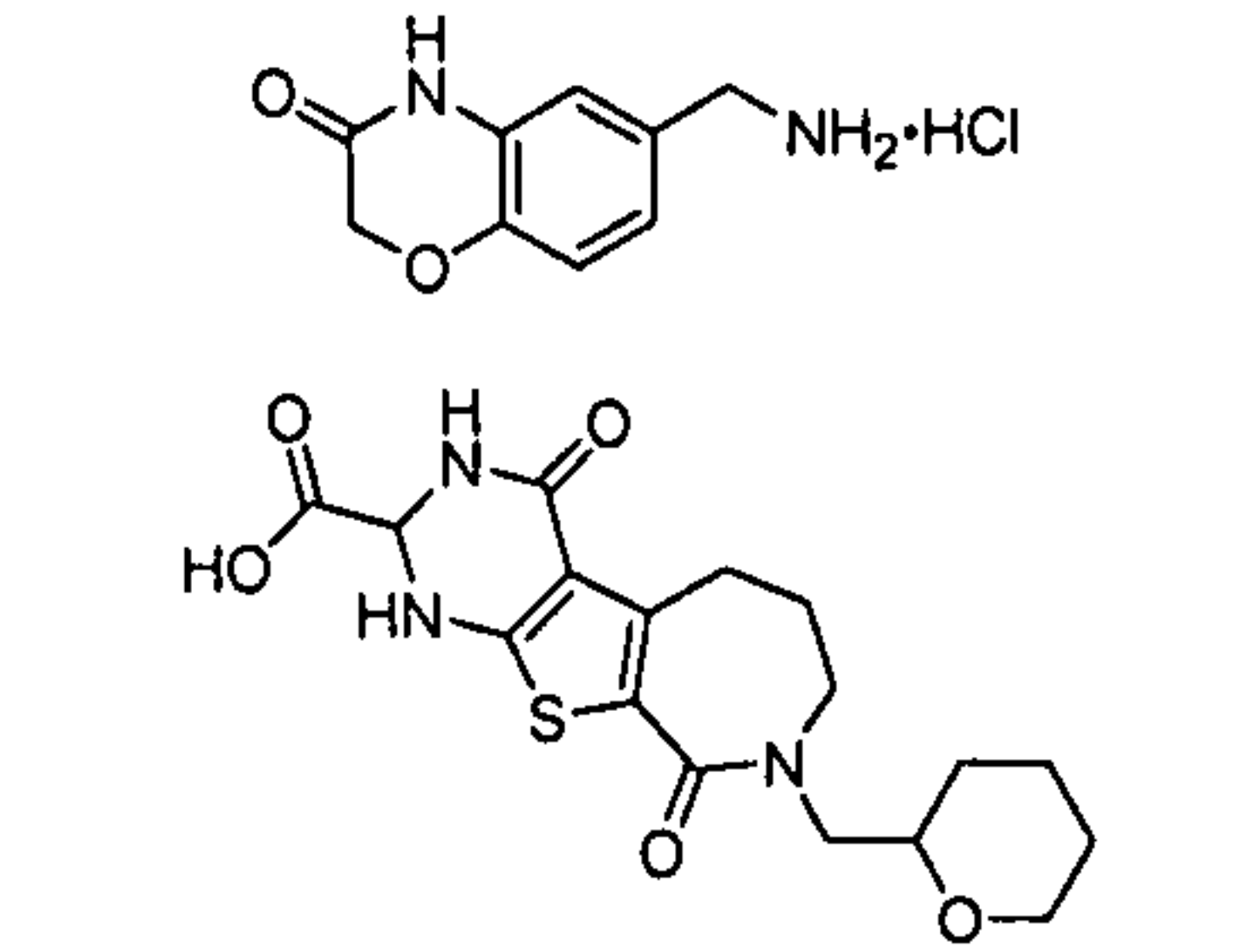
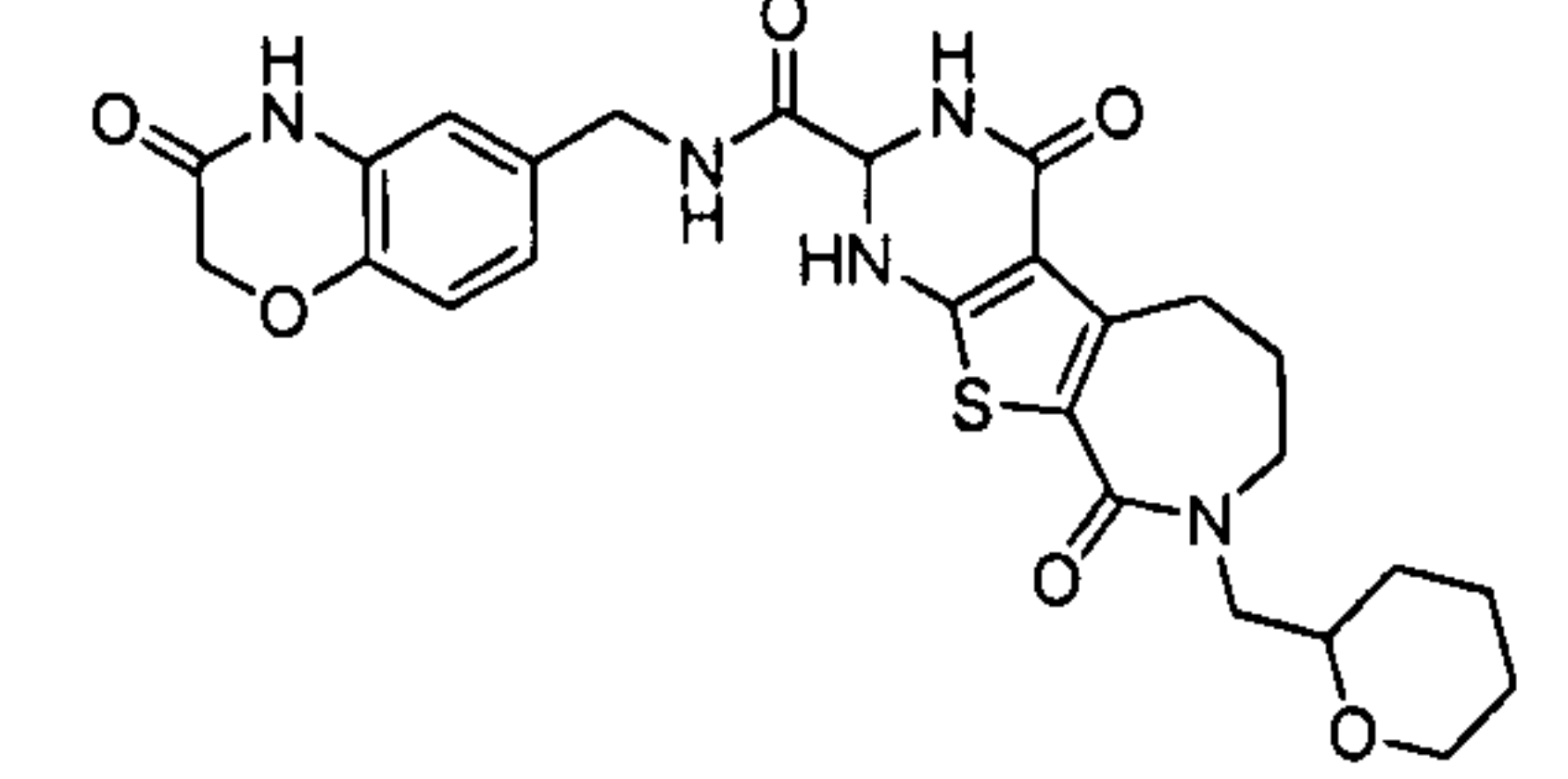
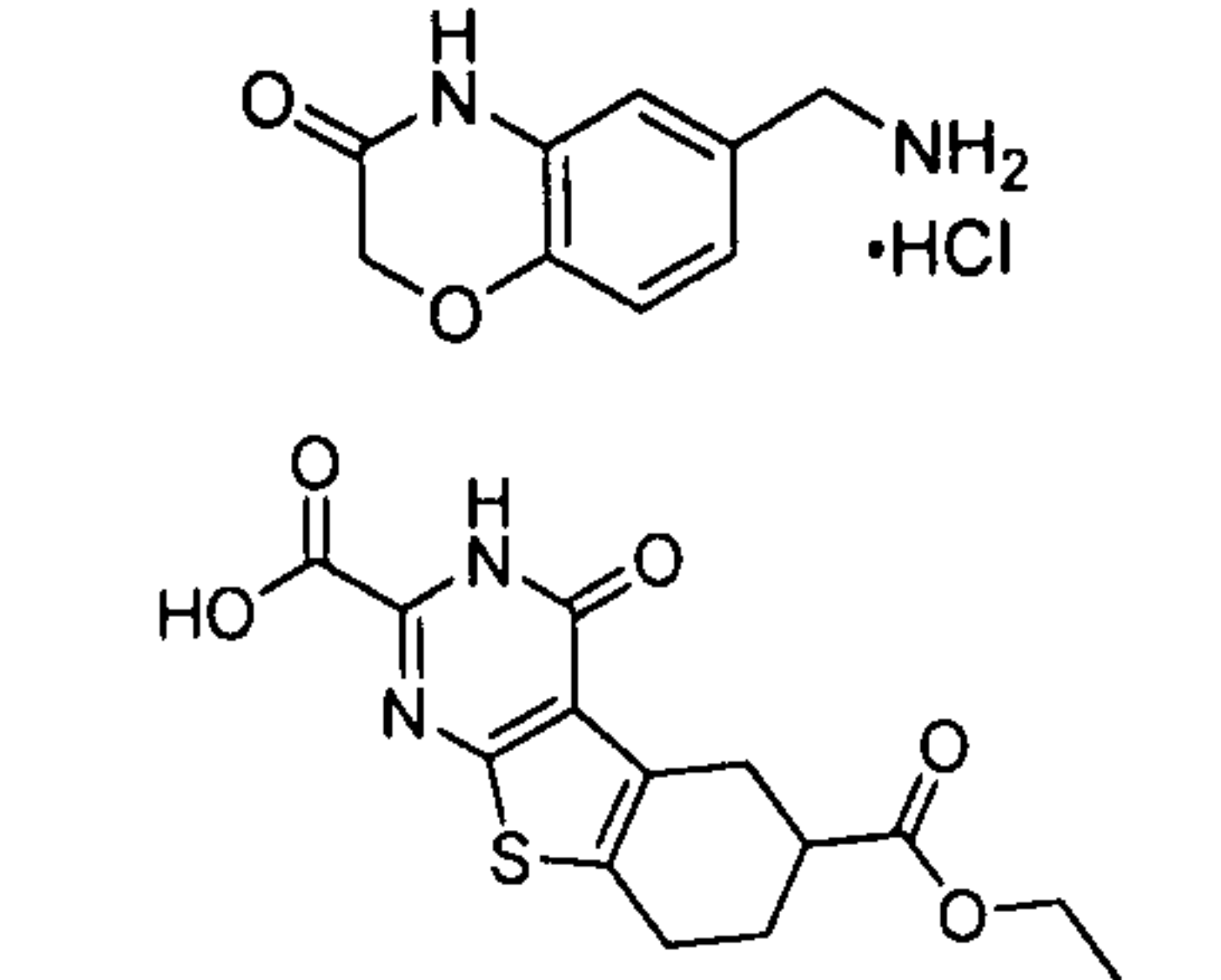
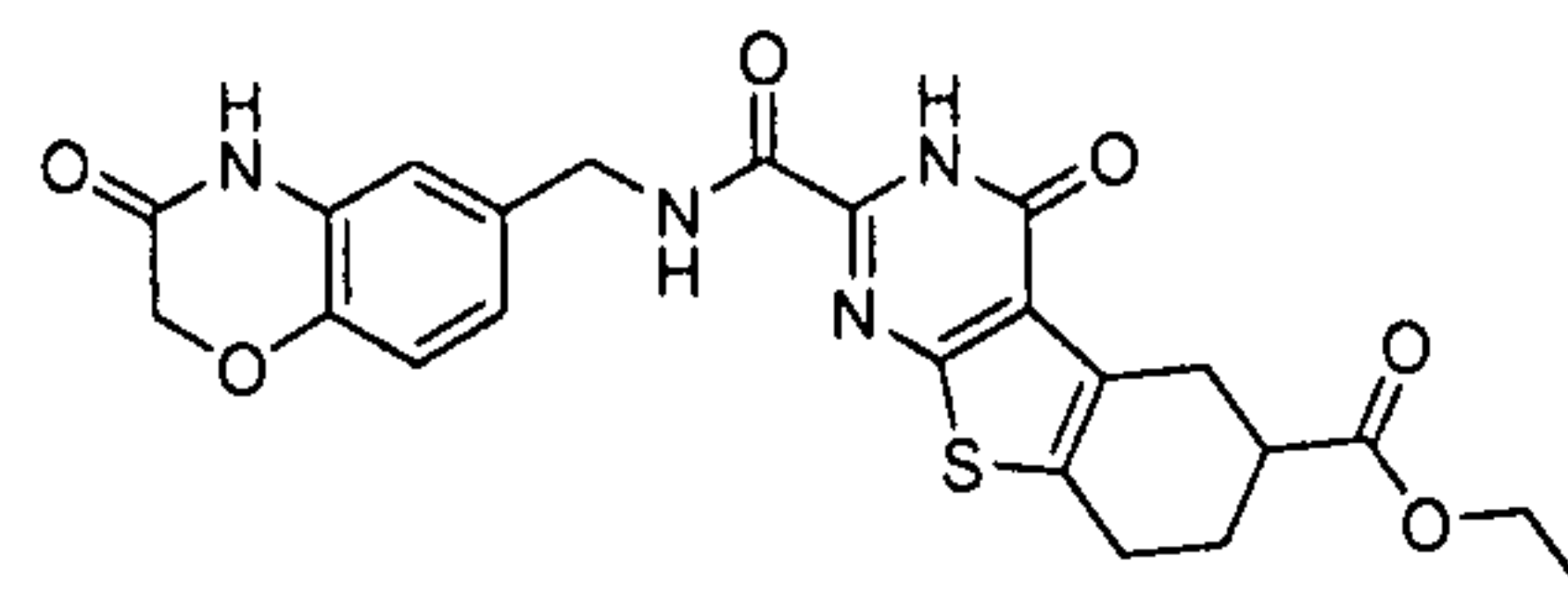
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/119 |    |    | A, 65%<br>[MH] <sup>+</sup> = 429 |
| 2/120 |   |  | A, 76%<br>[MH] <sup>+</sup> = 508 |
| 2/121 |  |  | A, 86%<br>[MH] <sup>+</sup> = 415 |
| 2/122 |  |  | A, 91%<br>[MH] <sup>+</sup> = 494 |
| 2/125 |  |  | A, 68%<br>[MH] <sup>+</sup> = 439 |

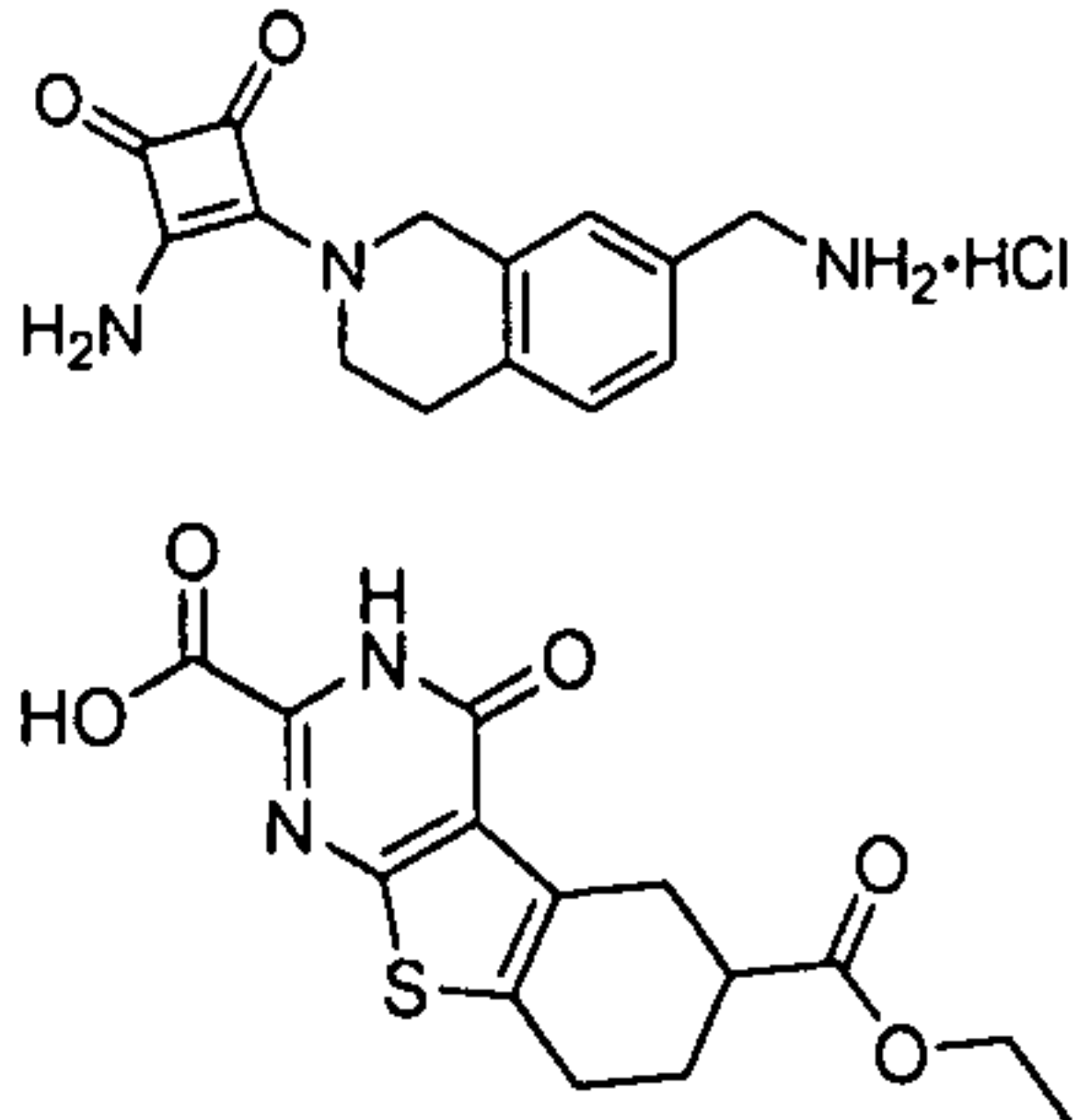
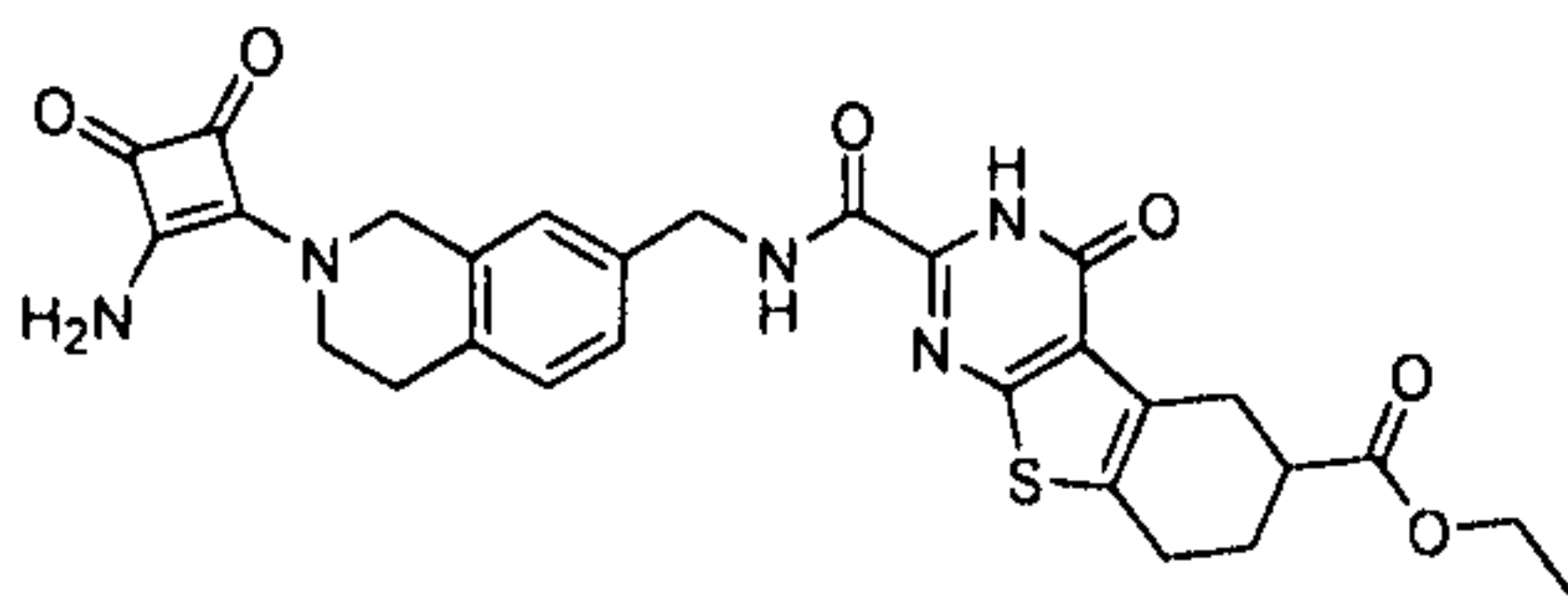
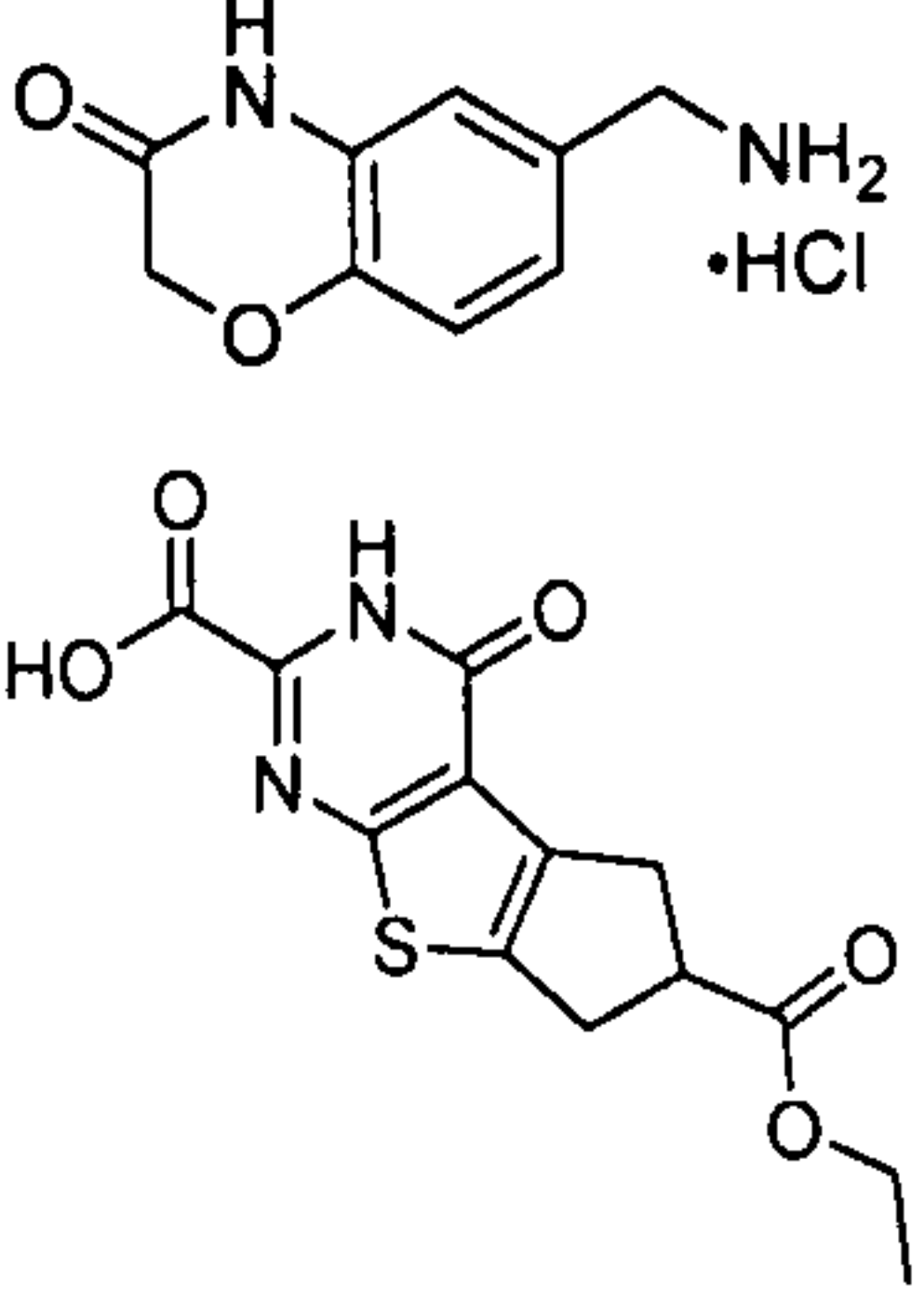
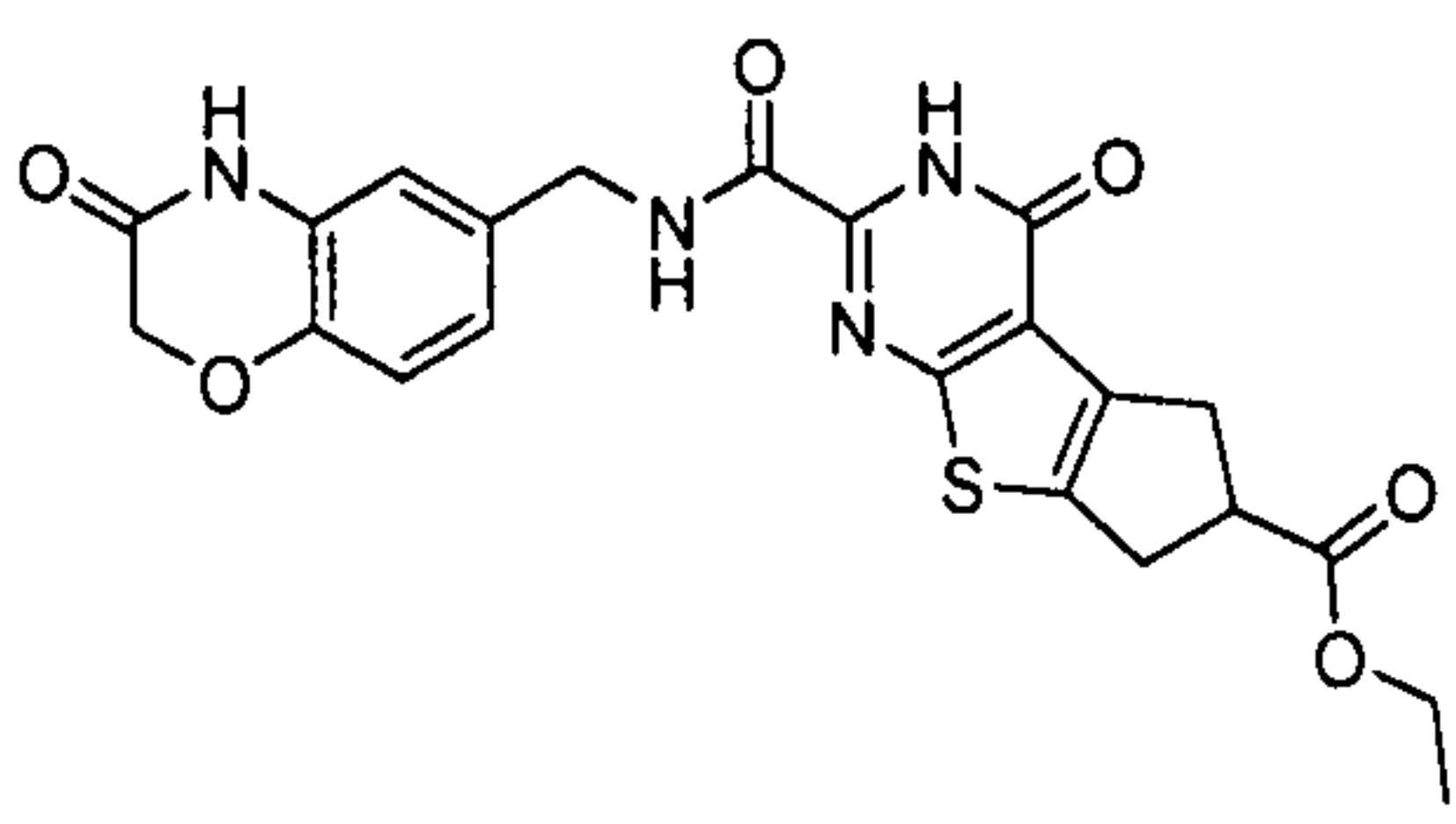
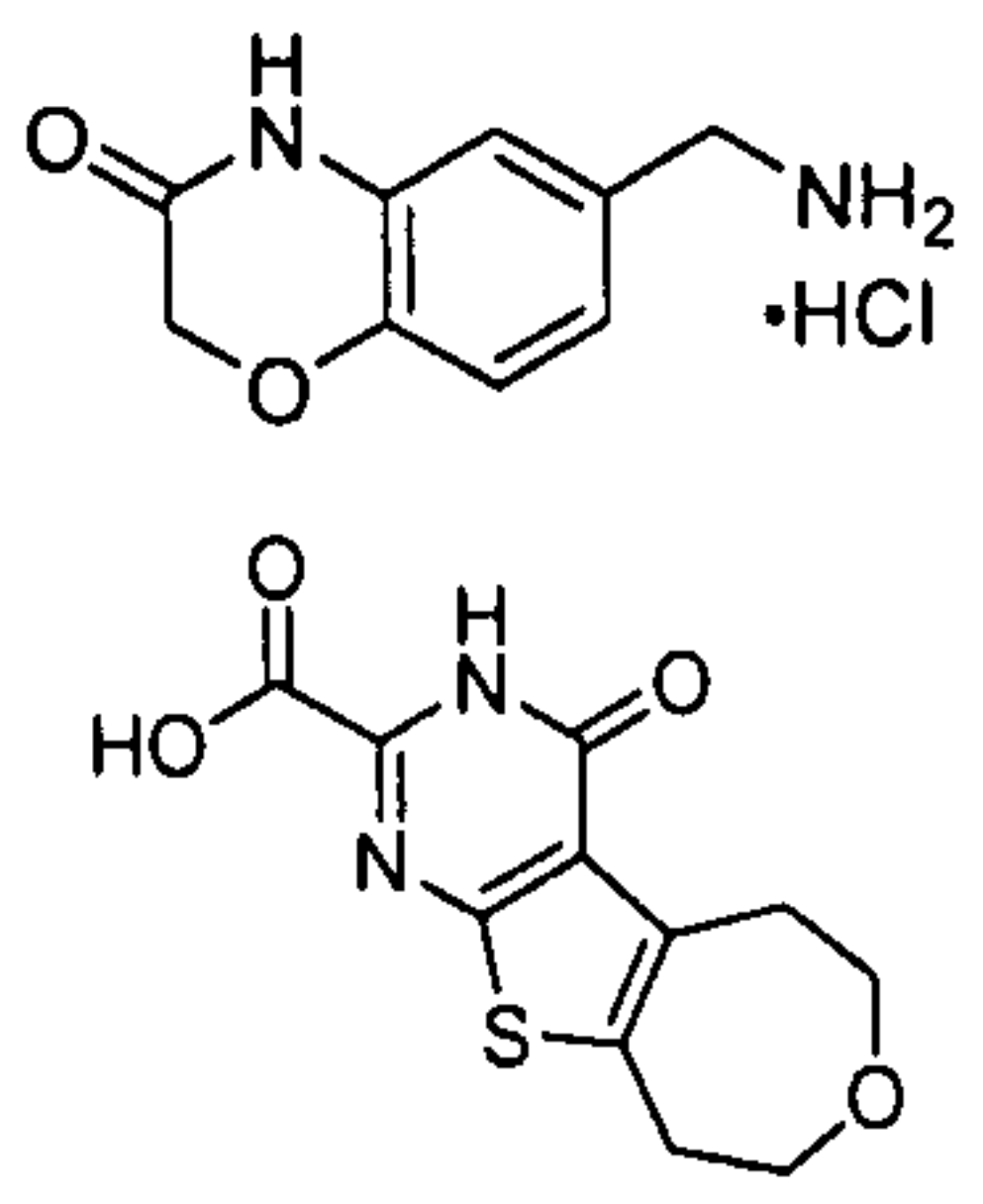
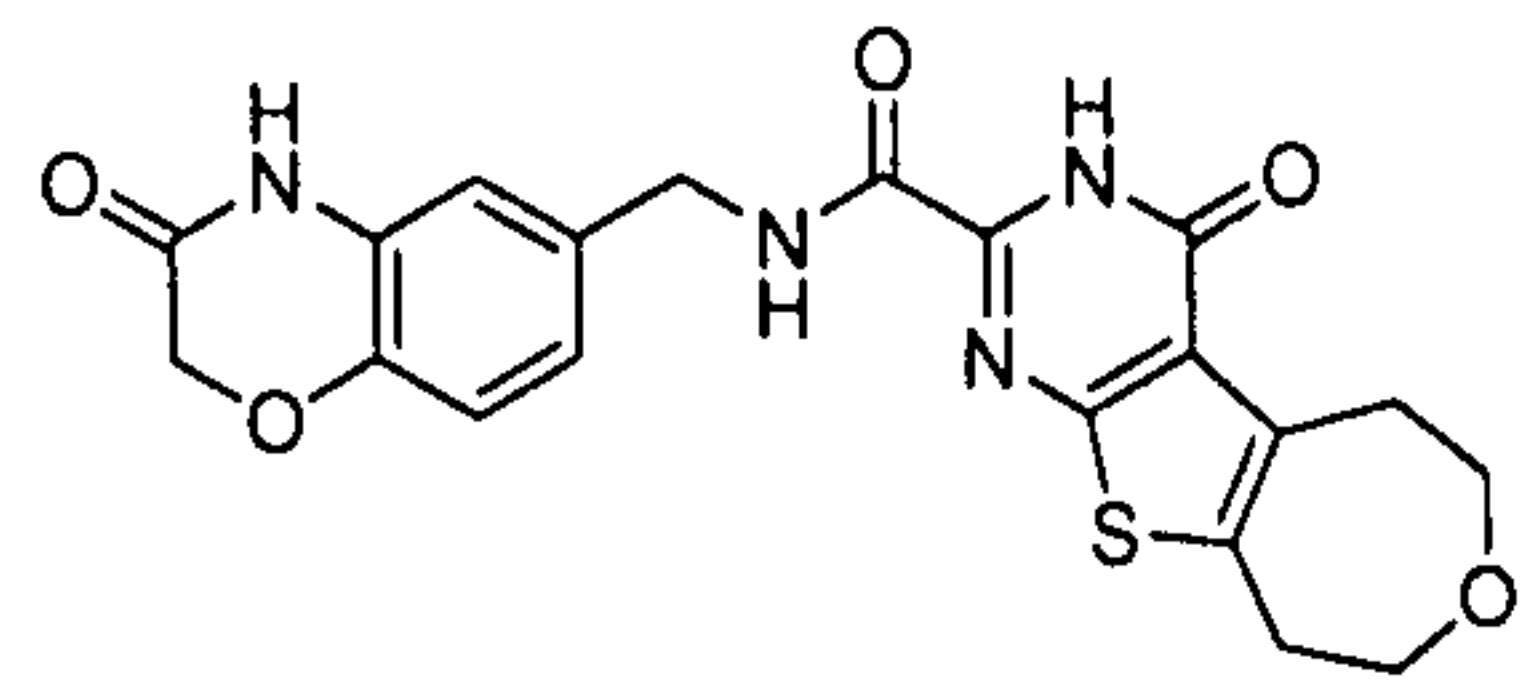
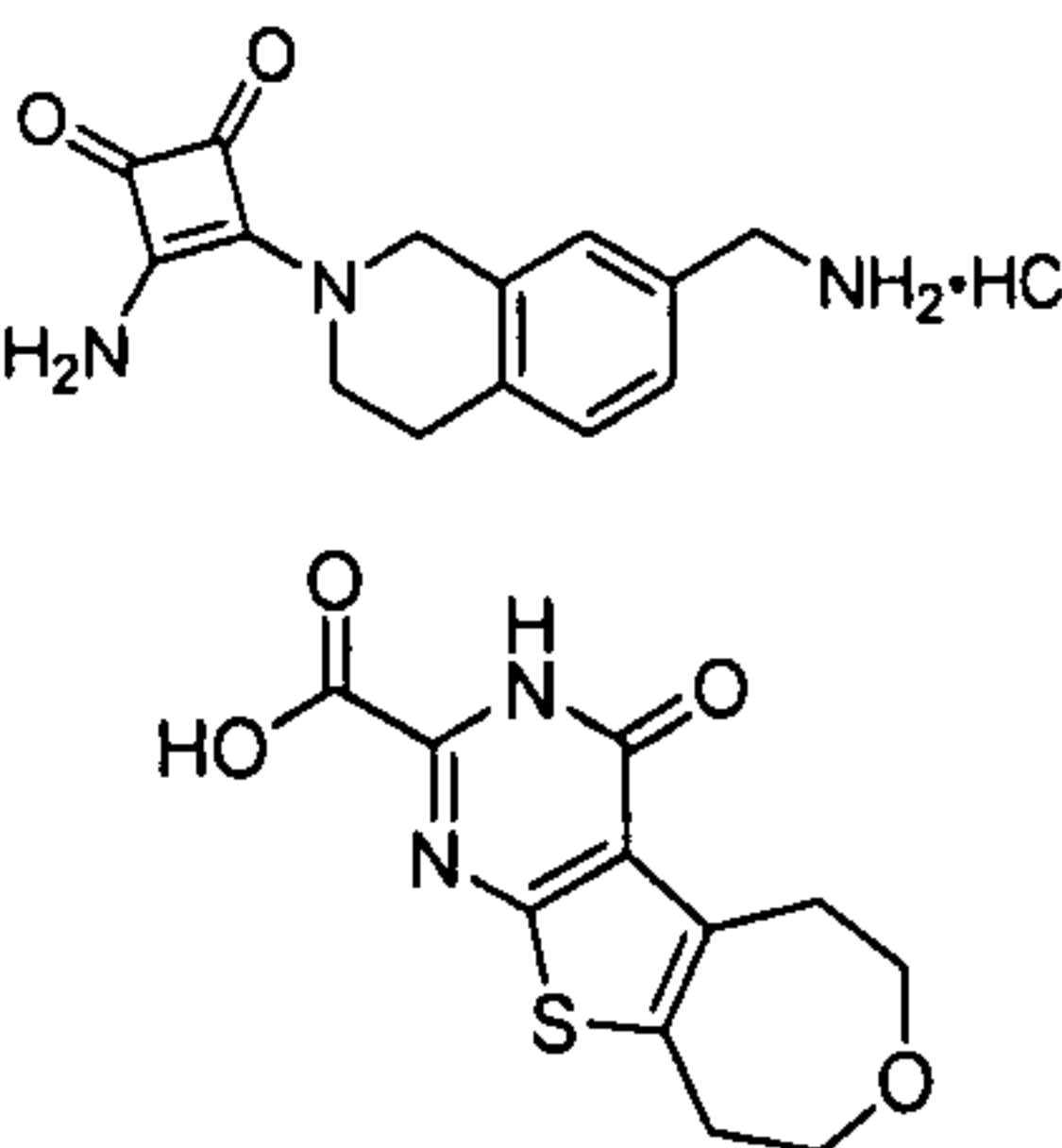
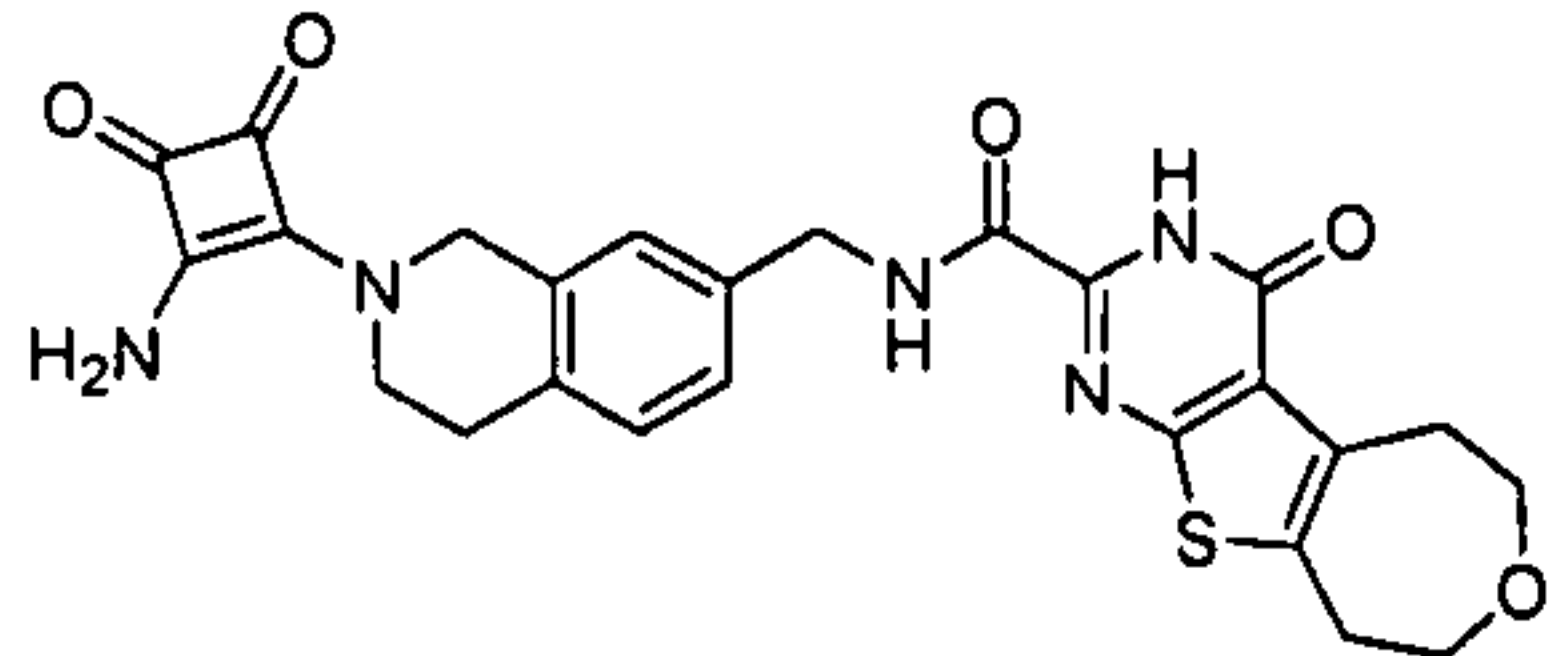
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/126 |     |    | A, 43%<br>[MH] <sup>+</sup> = 518 |
| 2/129 |  |  | A, 31%<br>[MH] <sup>+</sup> = 420 |
| 2/130 |  |  | A, 10%<br>[MH] <sup>+</sup> = 422 |
| 2/131 |   |  | A, 77%<br>[MH] <sup>+</sup> = 429 |
| 2/132 |   |  | A, 31%<br>[MH] <sup>+</sup> = 508 |

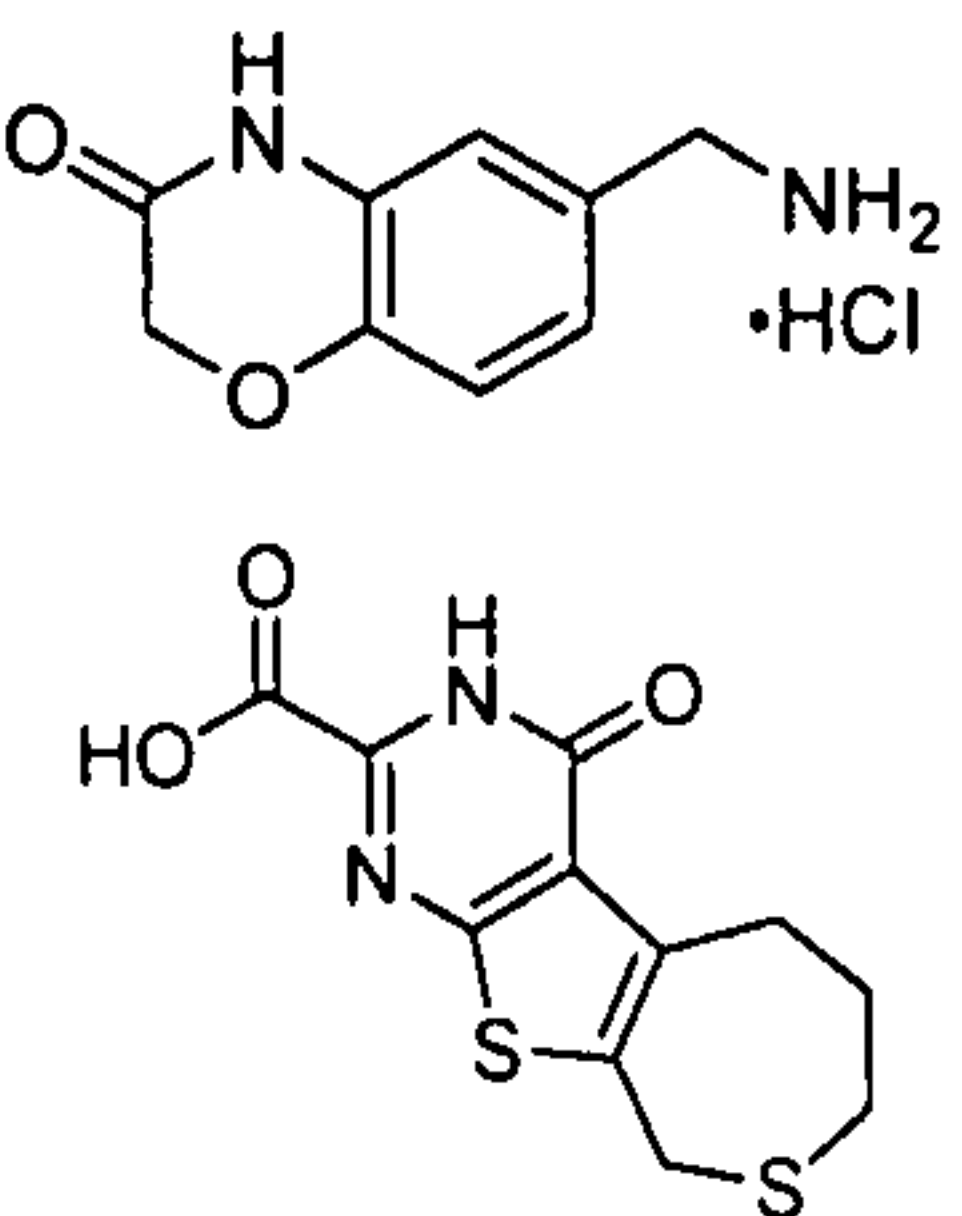
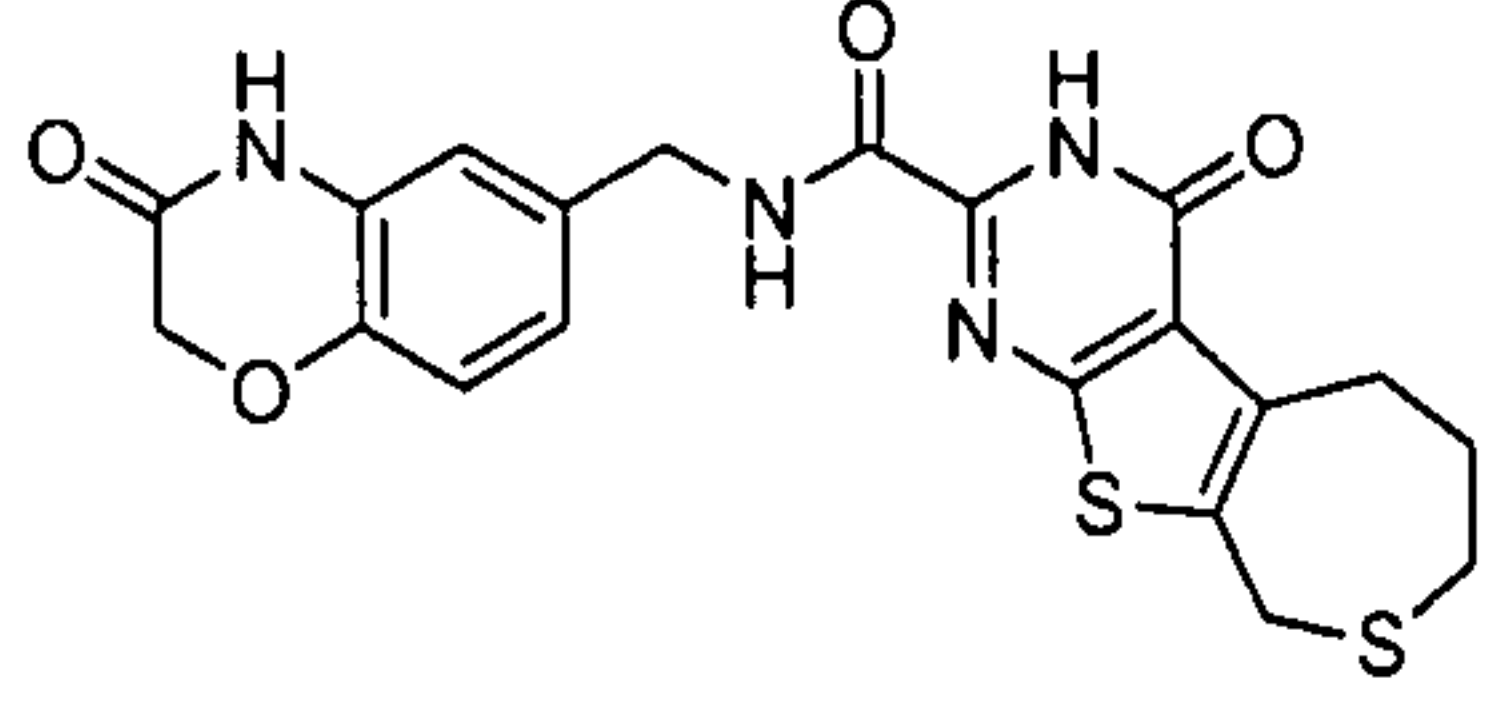
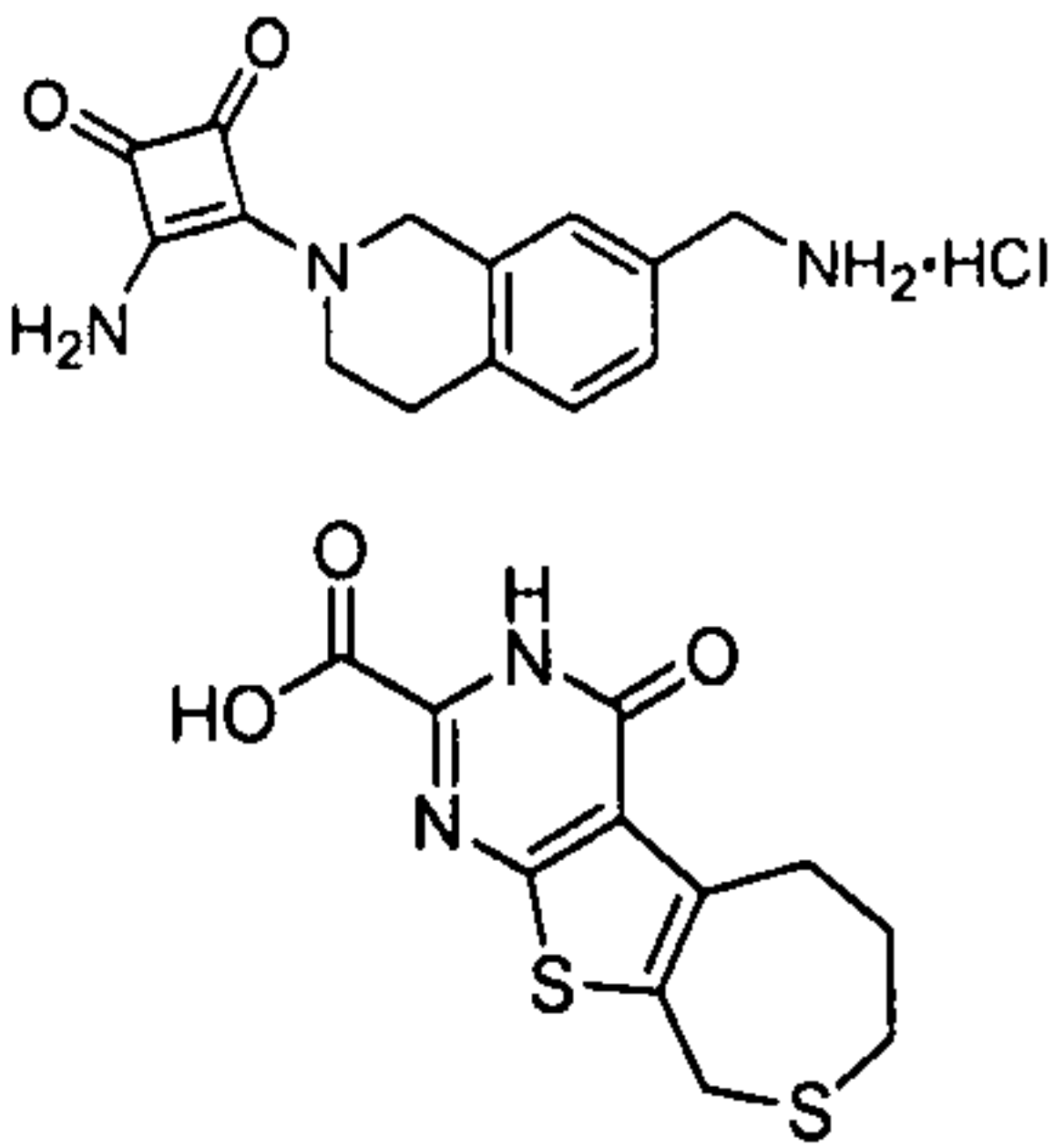
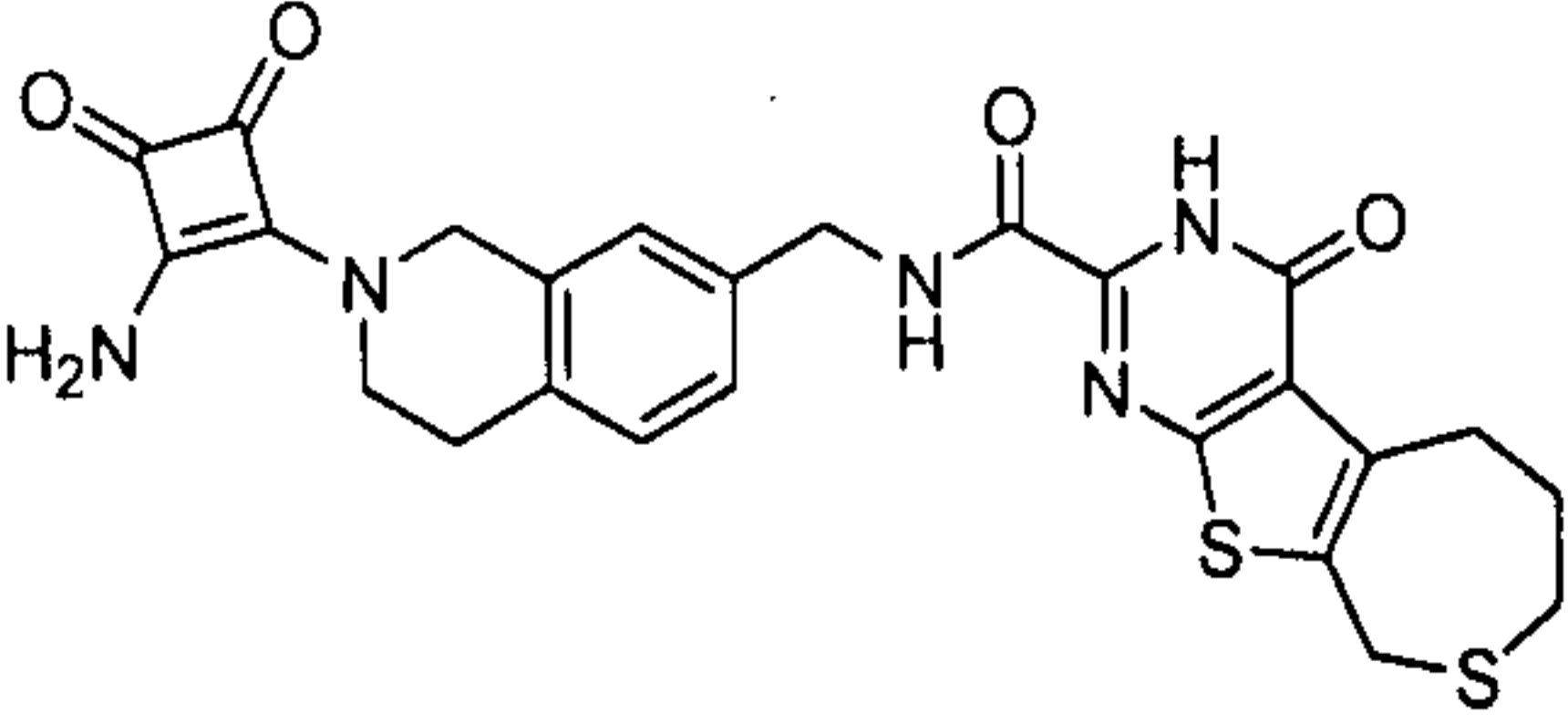
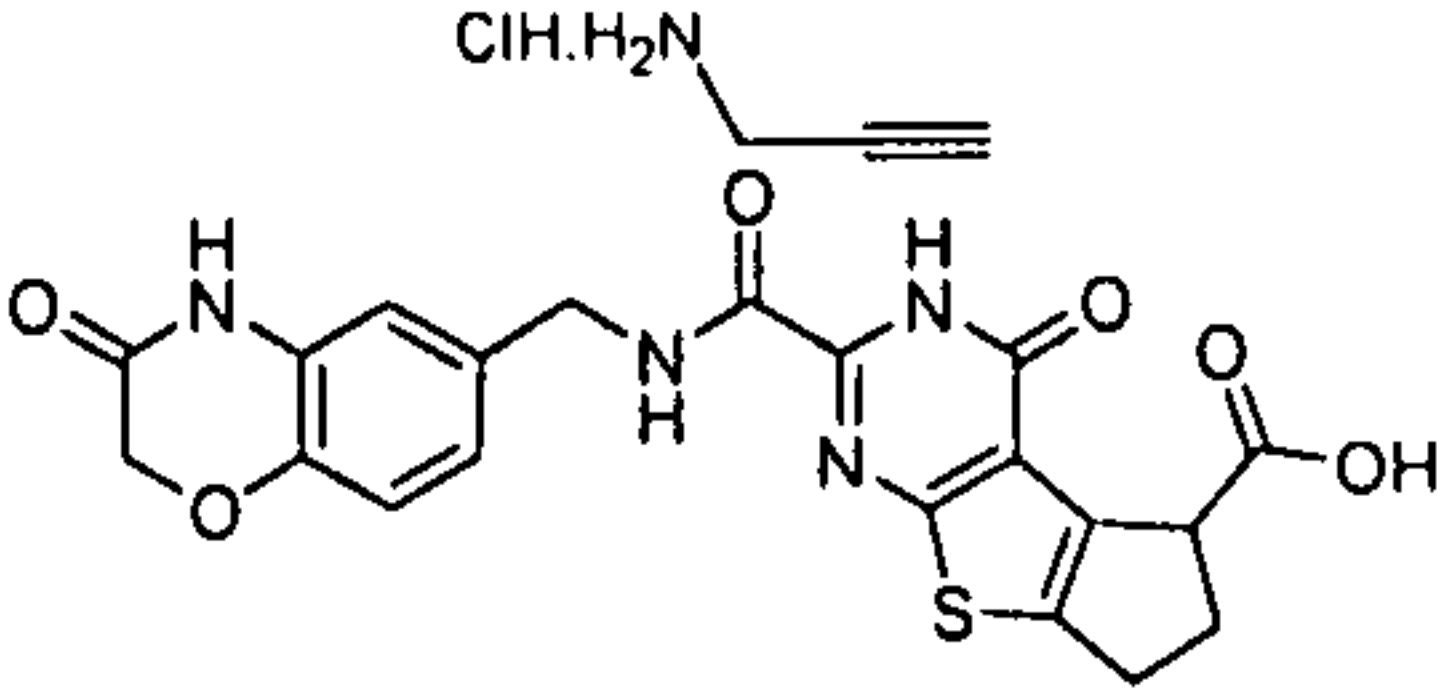
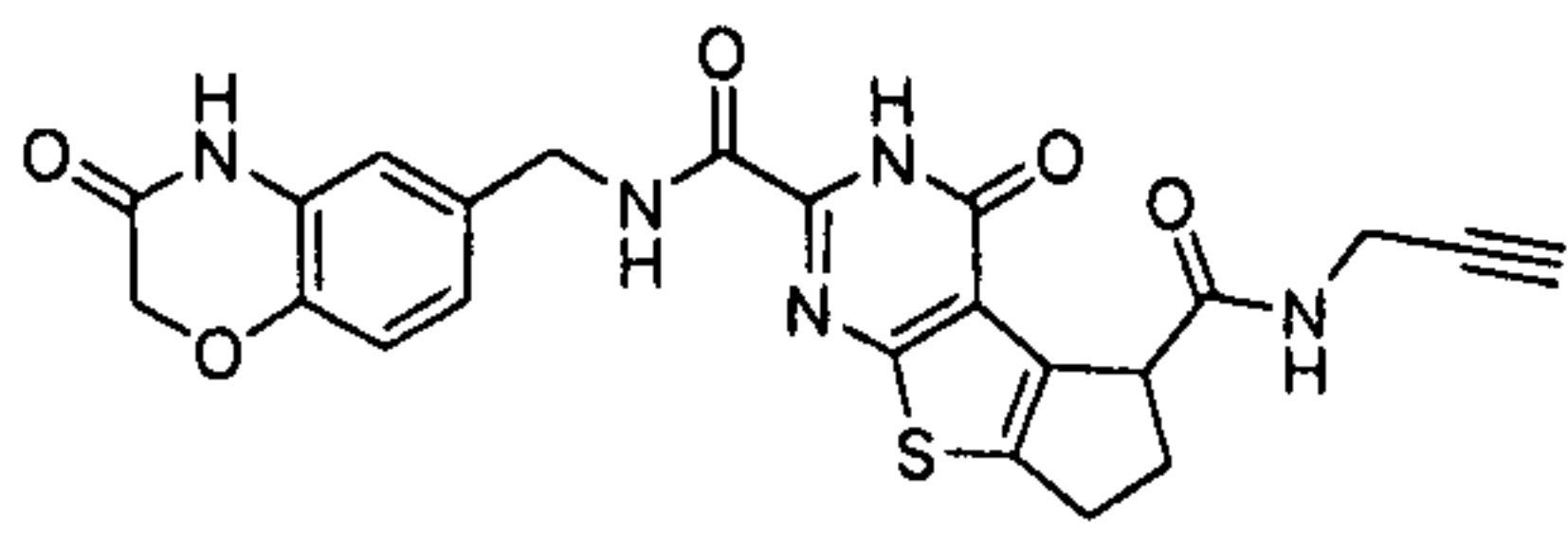
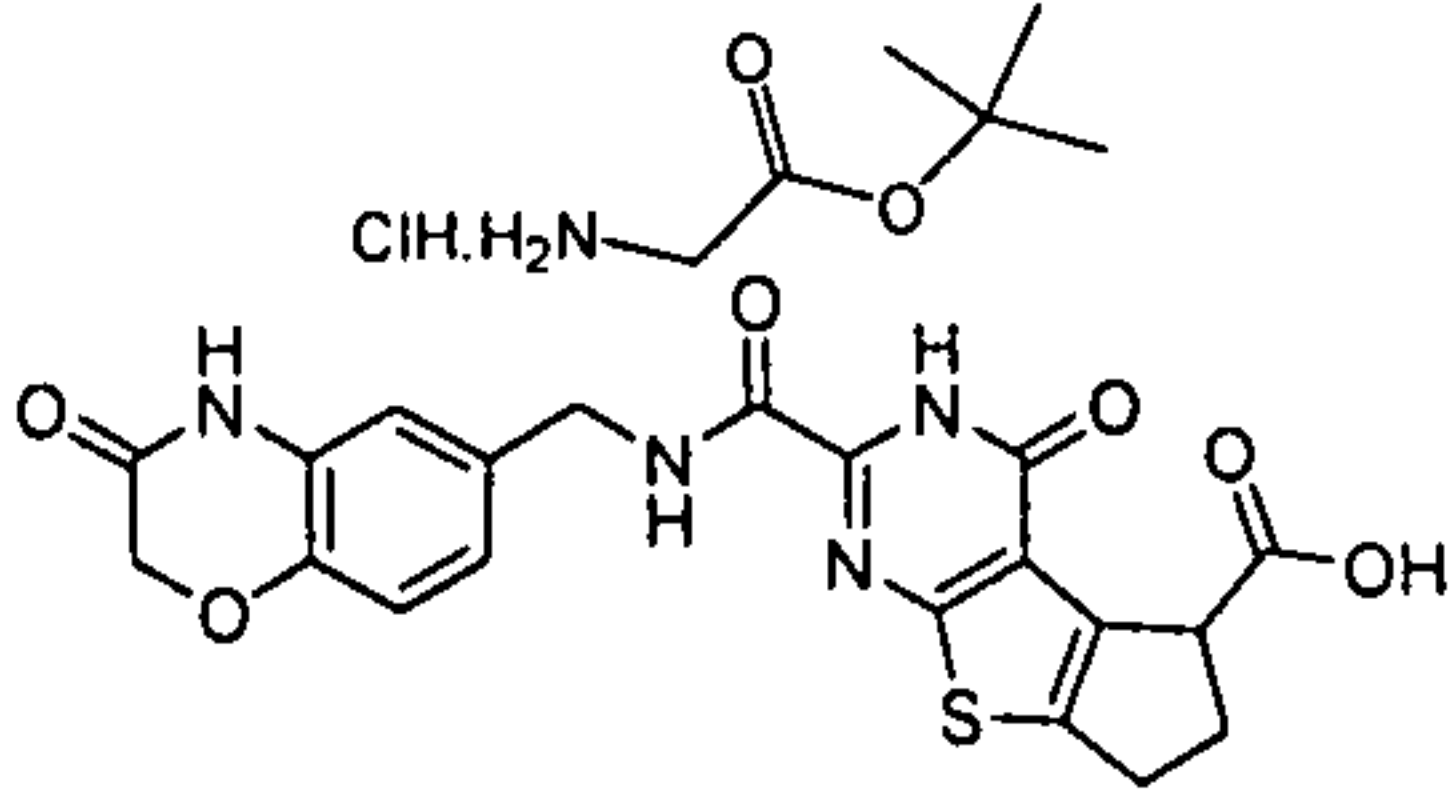
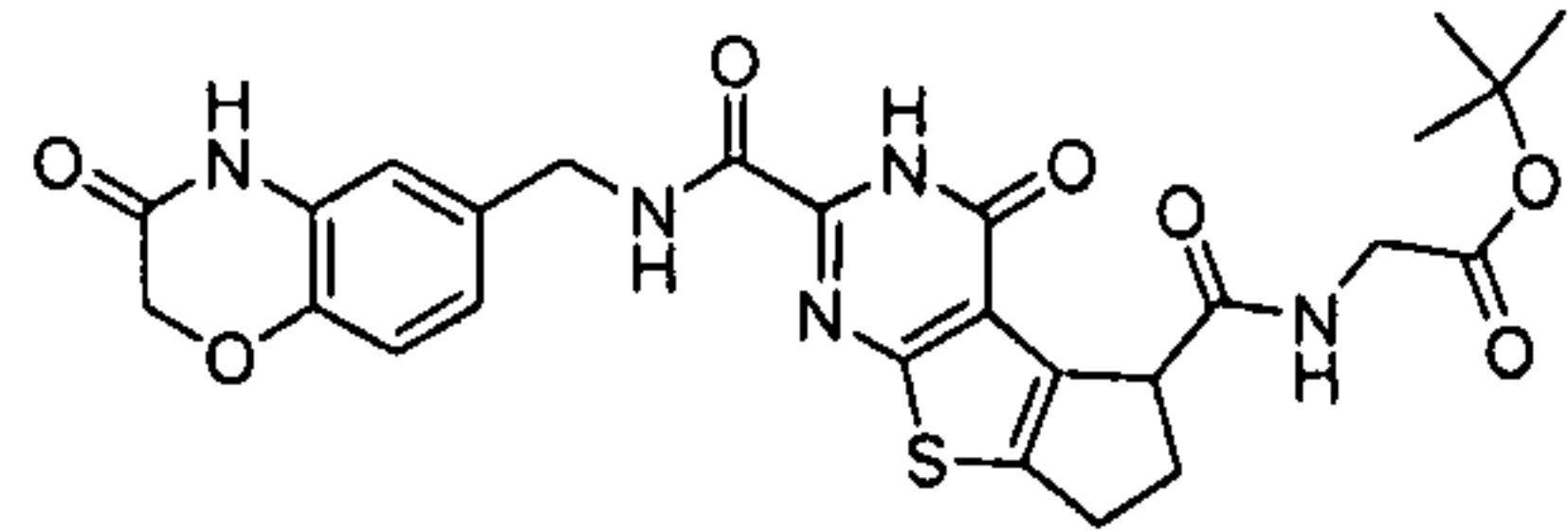
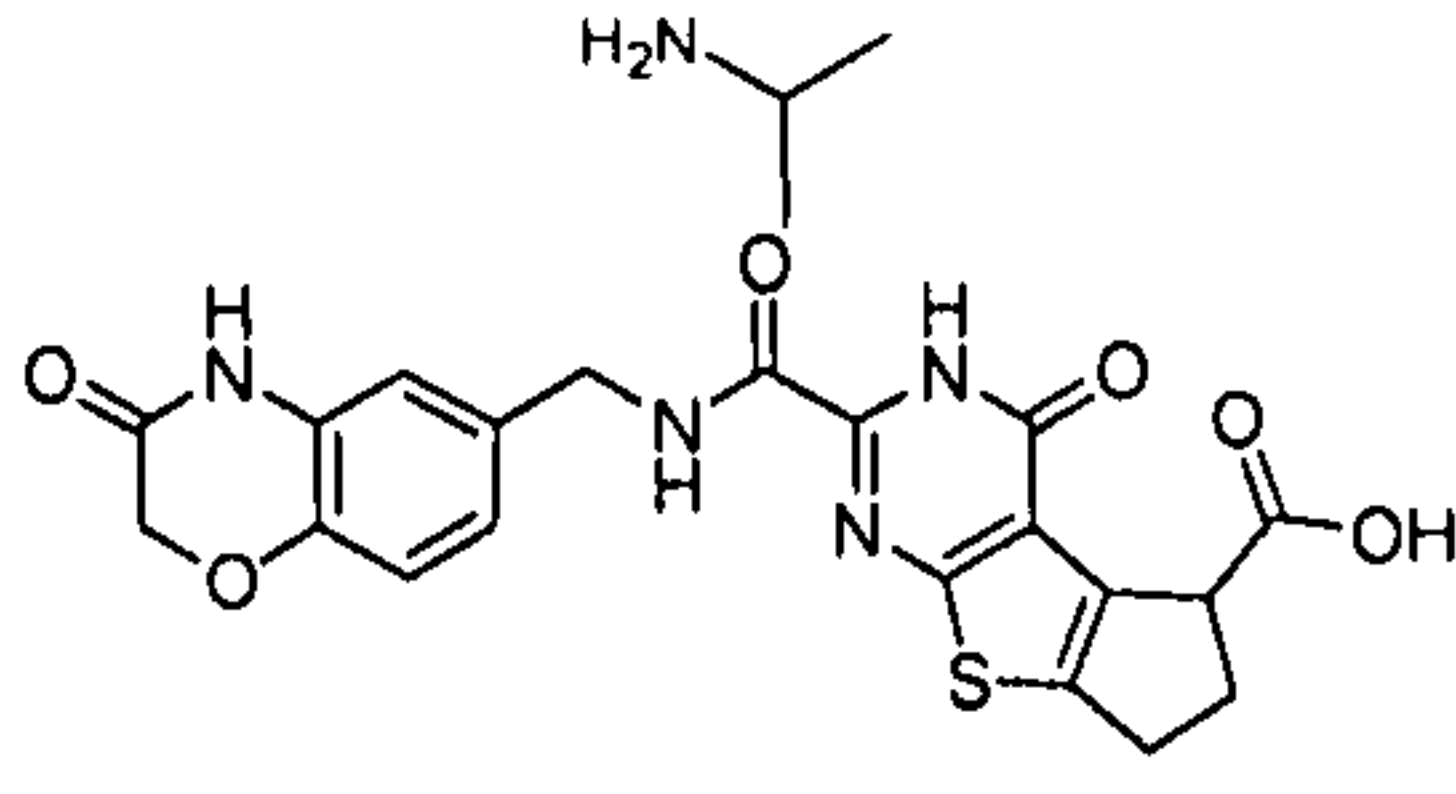
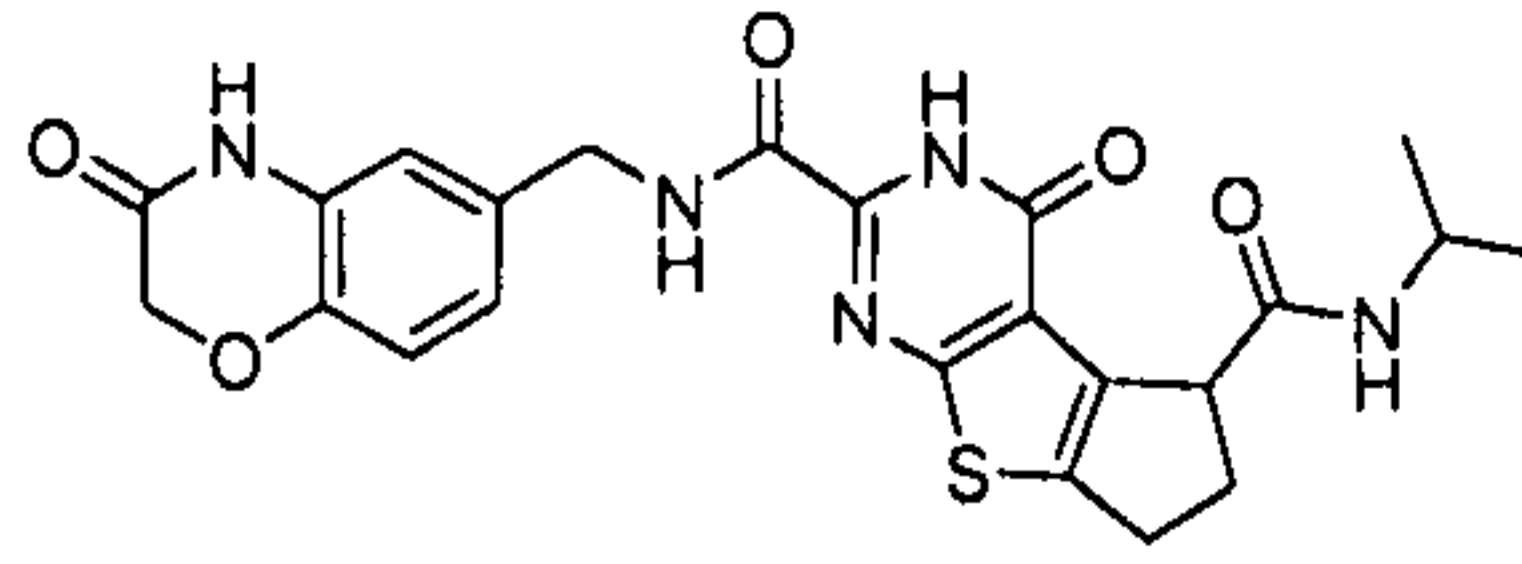
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/143 |    |    | A, 80%<br>[MH] <sup>+</sup> = 463 |
| 2/144 |   |  | A, 5%<br>[MH] <sup>+</sup> = 542  |
| 2/145 |  |  | A, 27%<br>[MH] <sup>+</sup> = 487 |
| 2/146 |  |  | A, 74%<br>[MH] <sup>+</sup> = 566 |
| 2/152 |  |  | A, 45%<br>[MH] <sup>+</sup> = 413 |

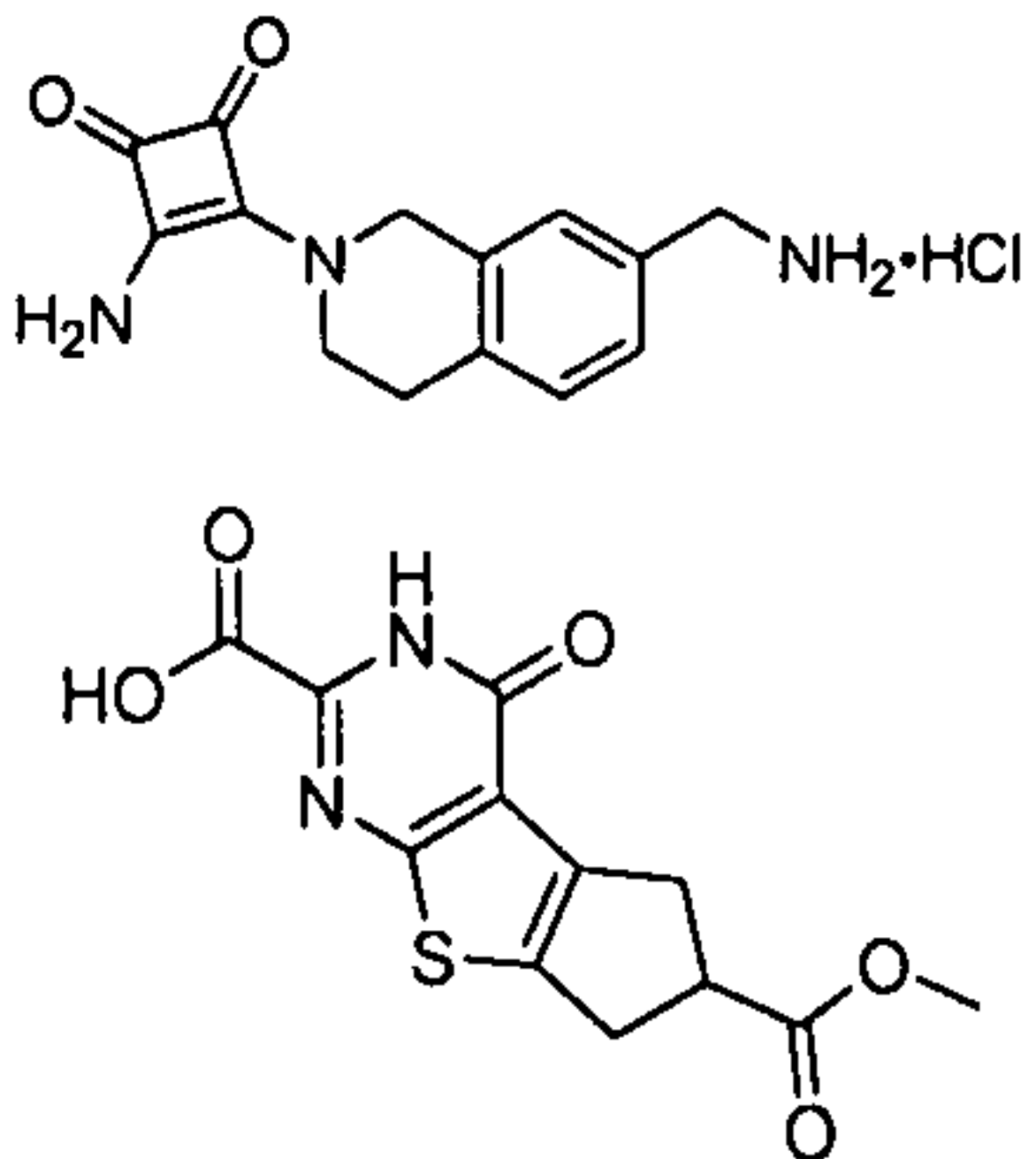
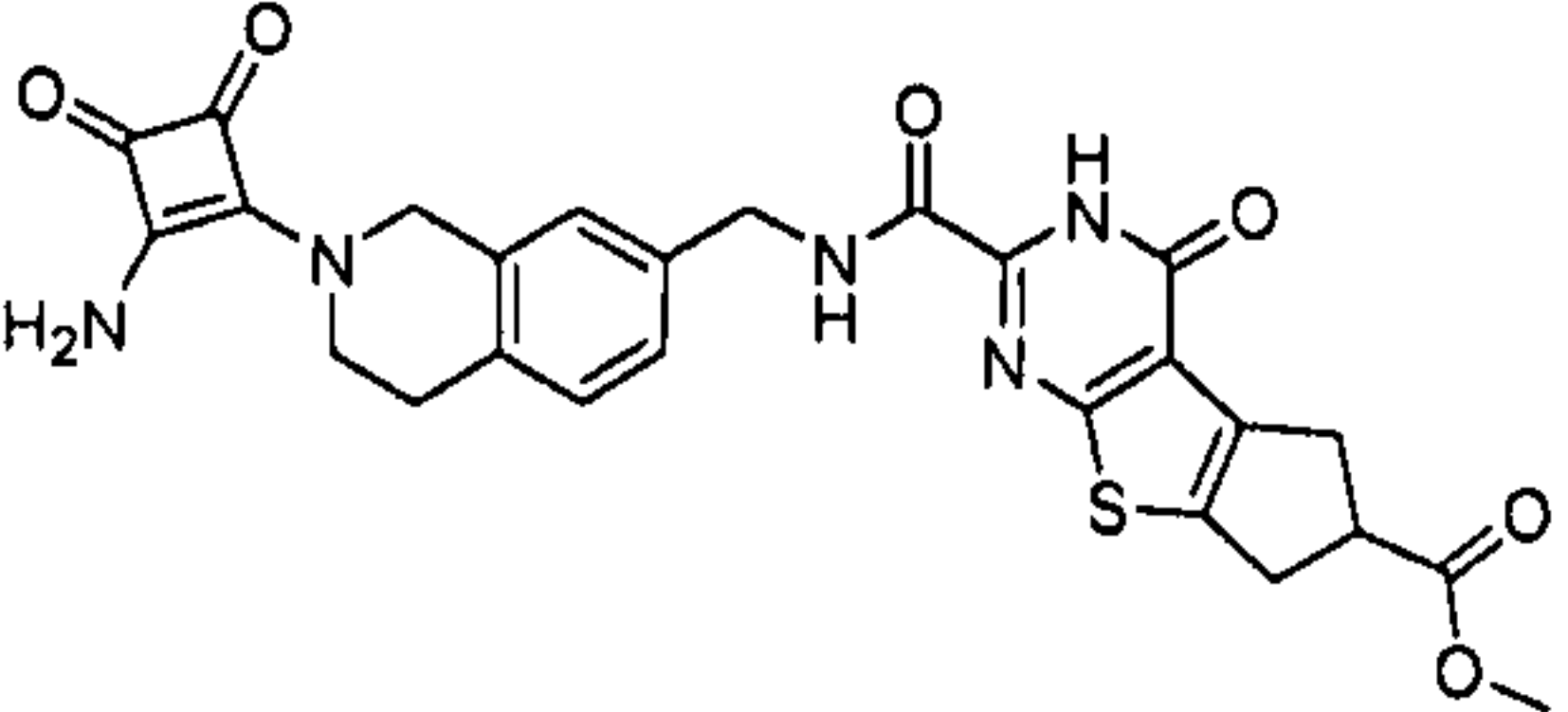
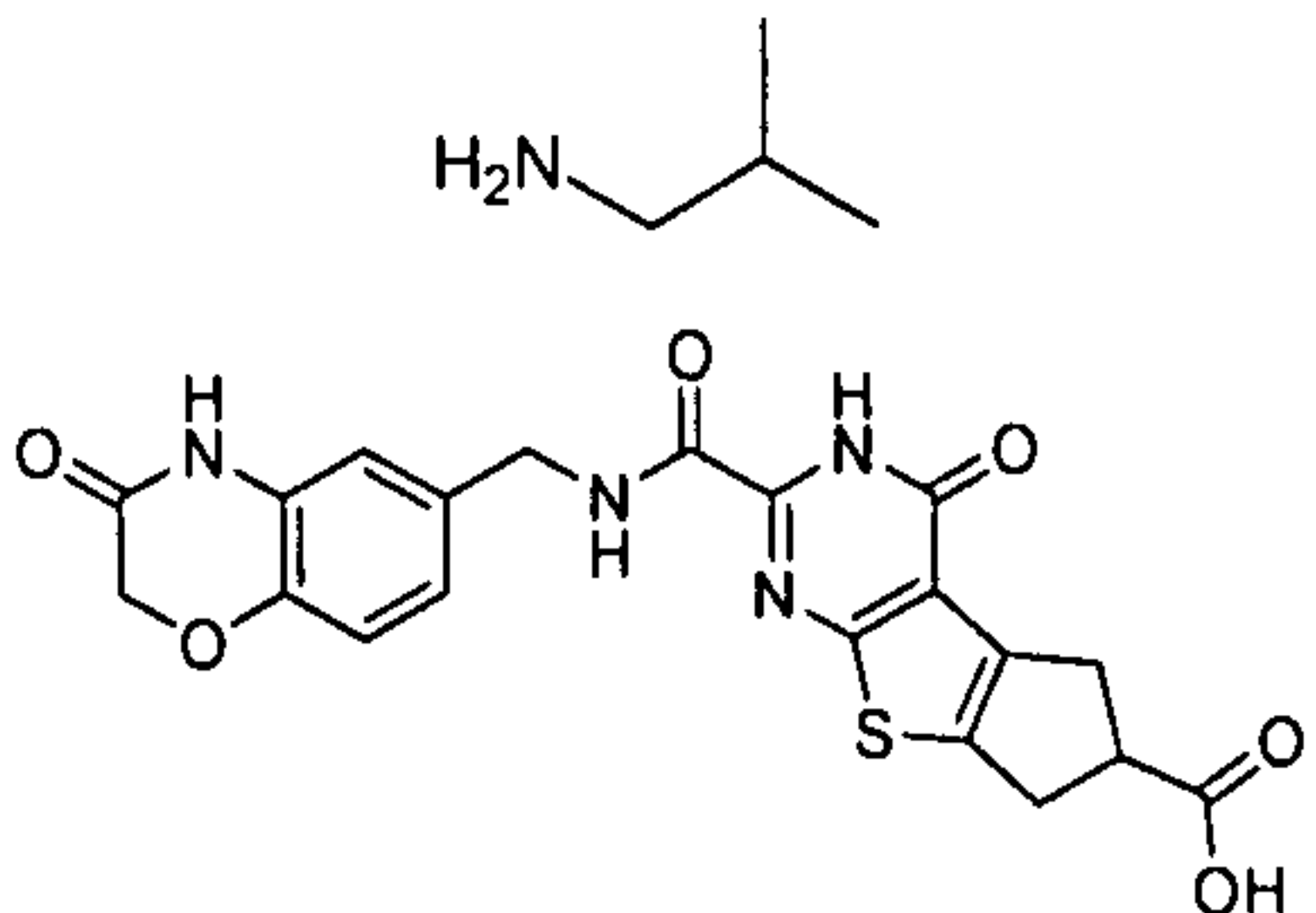
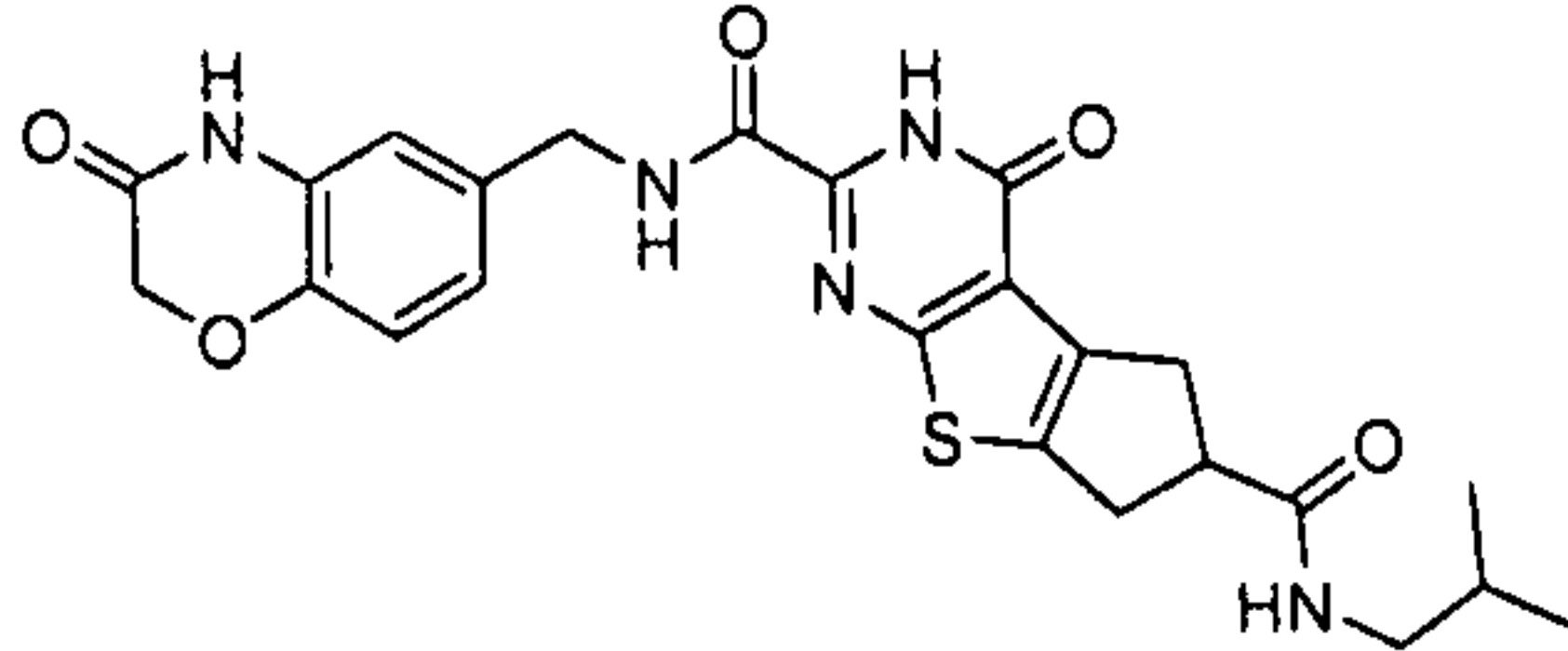
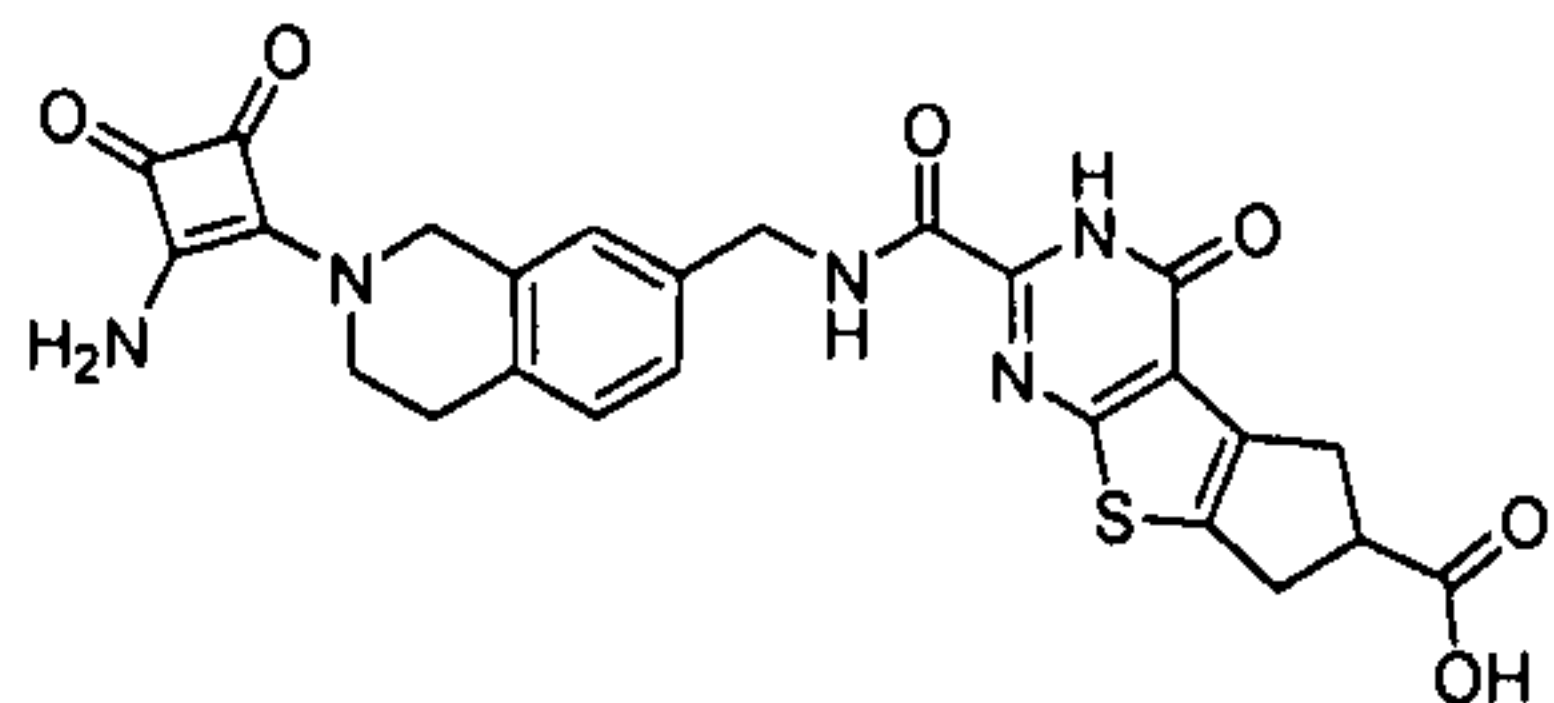
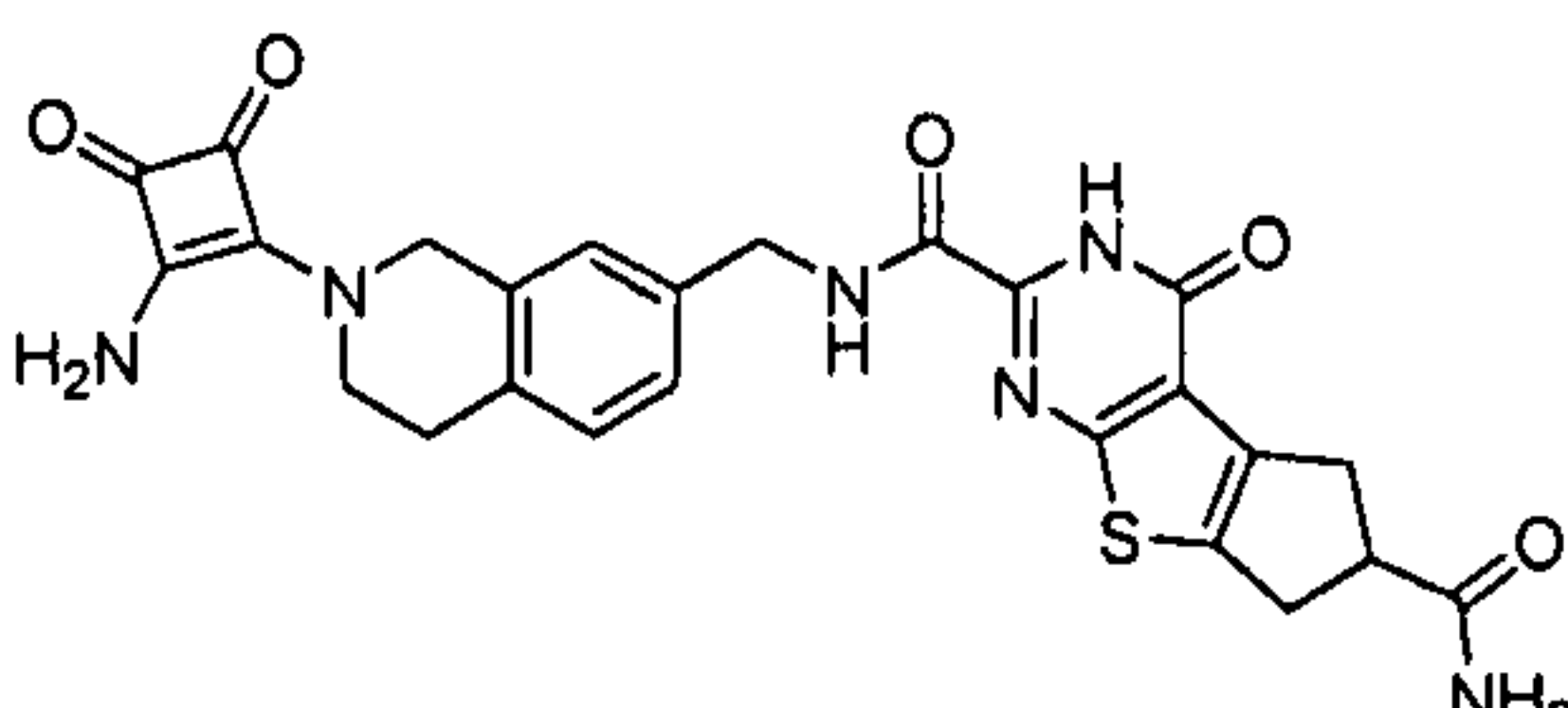
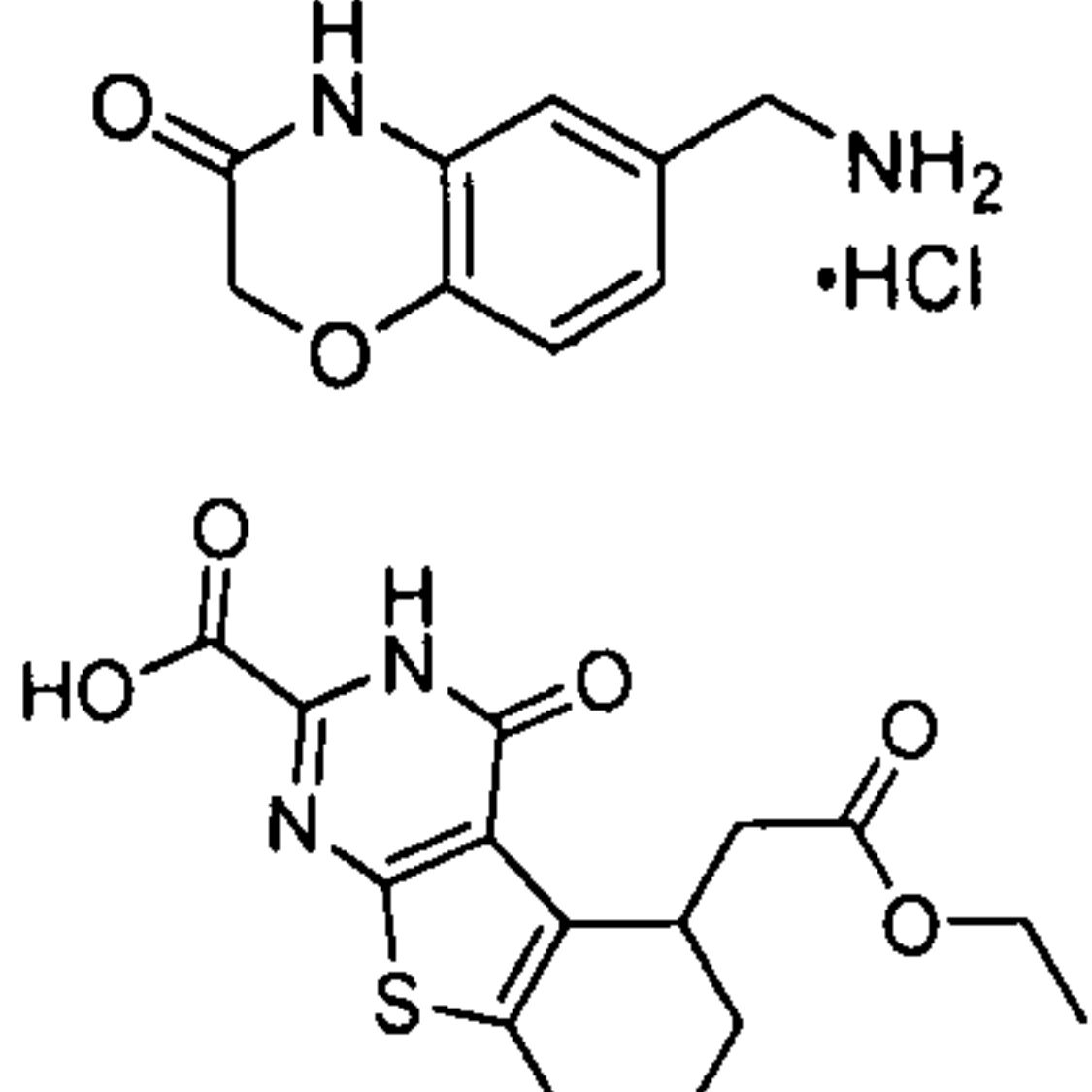
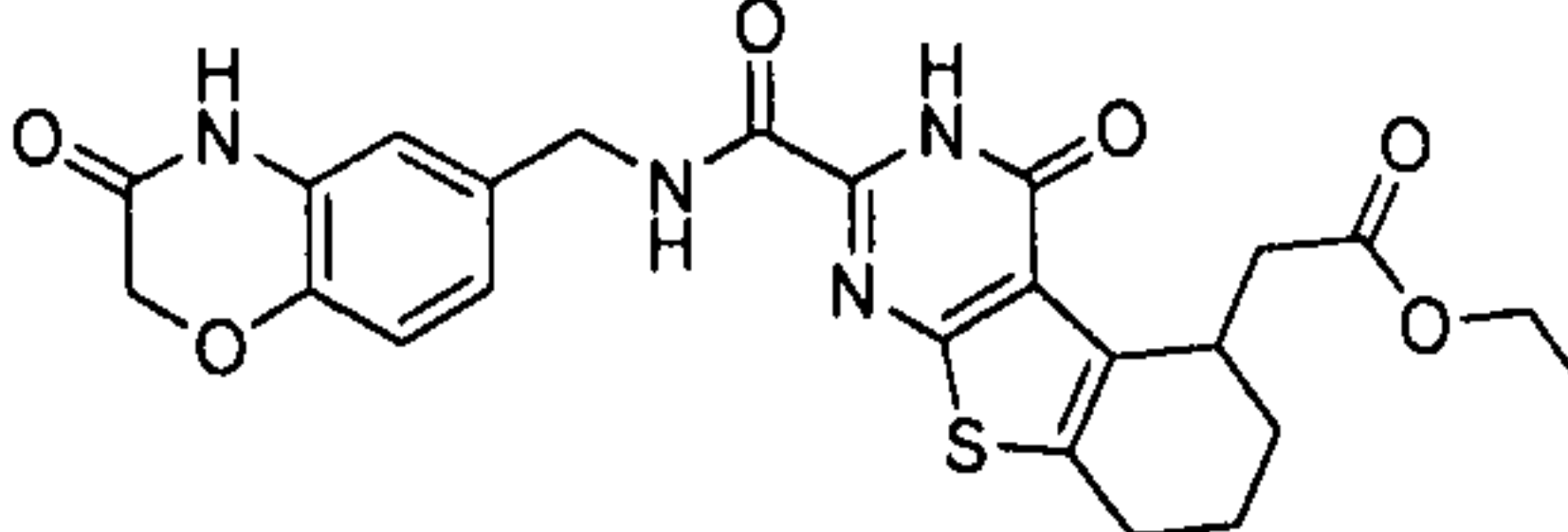
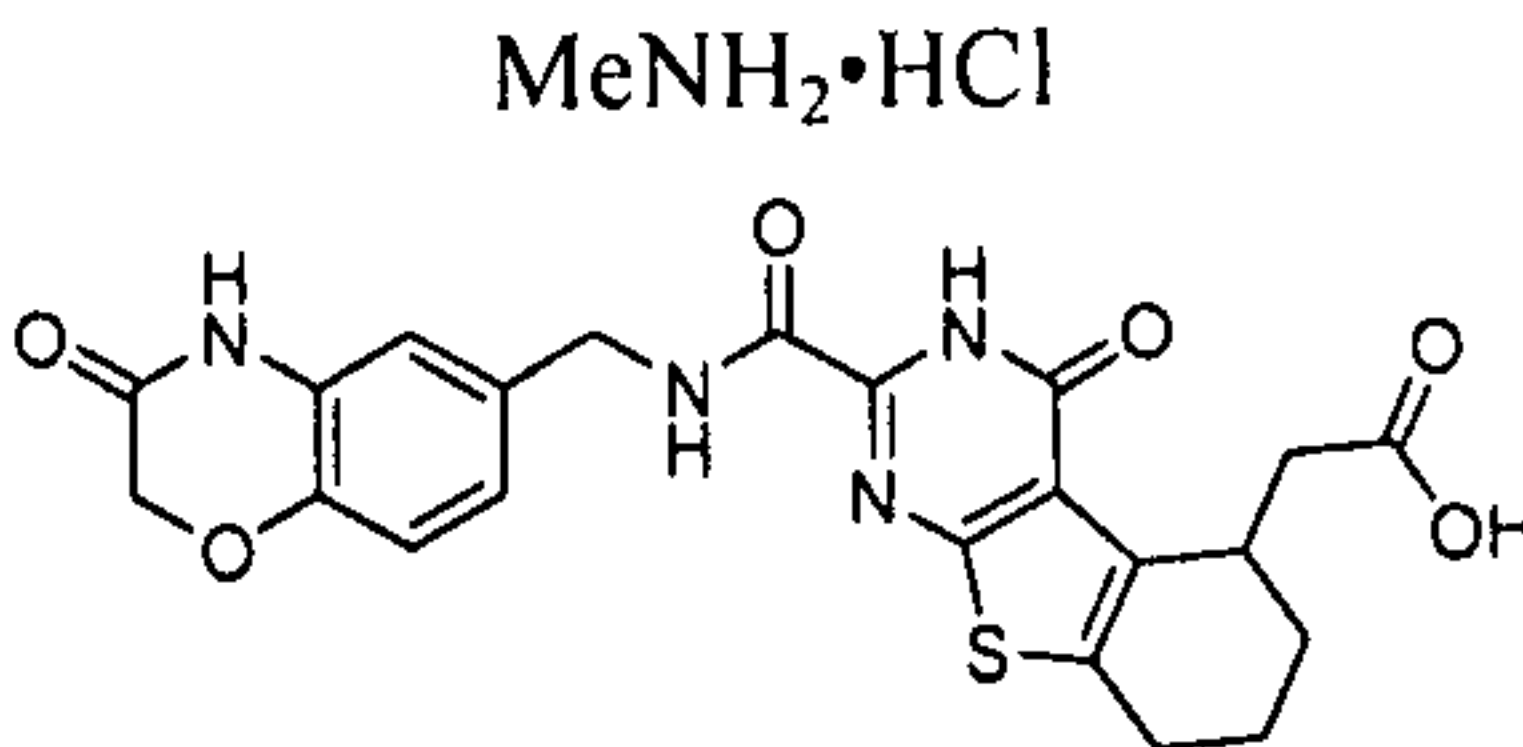
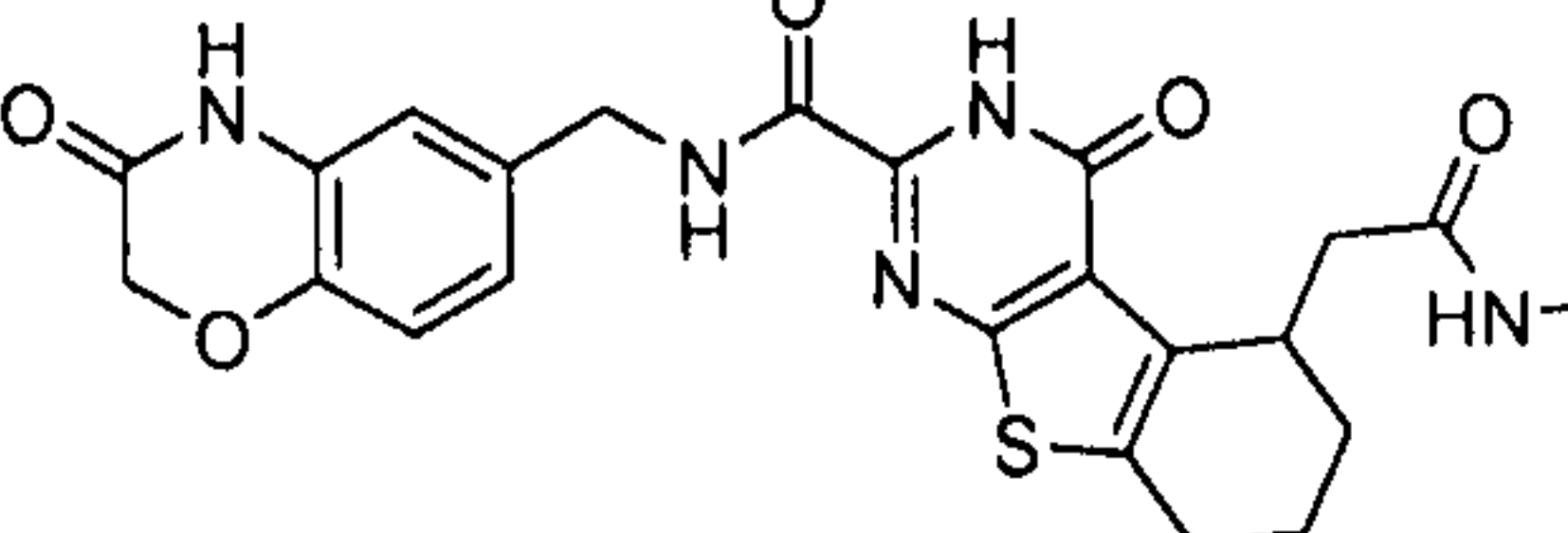
| Ex. # | amine, acid                                                                                                                  | product                                                                               | method, yield                     |
|-------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/153 |                                             |    | A, 60%<br>[MH] <sup>+</sup> = 492 |
| 2/166 | <p>NH<sub>3</sub> (0.5M in dioxane)</p>  |  | A, 75%<br>[MH] <sup>+</sup> = 440 |
| 2/167 |                                          |  | A, 99%<br>[MH] <sup>+</sup> = 530 |
| 2/168 |                                          |  | A, 40%<br>[MH] <sup>+</sup> = 620 |
| 2/169 |                                          |  | A, 34%<br>[MH] <sup>+</sup> = 587 |
| 2/170 |                                          |  | A, 50%<br>[MH] <sup>+</sup> = 608 |

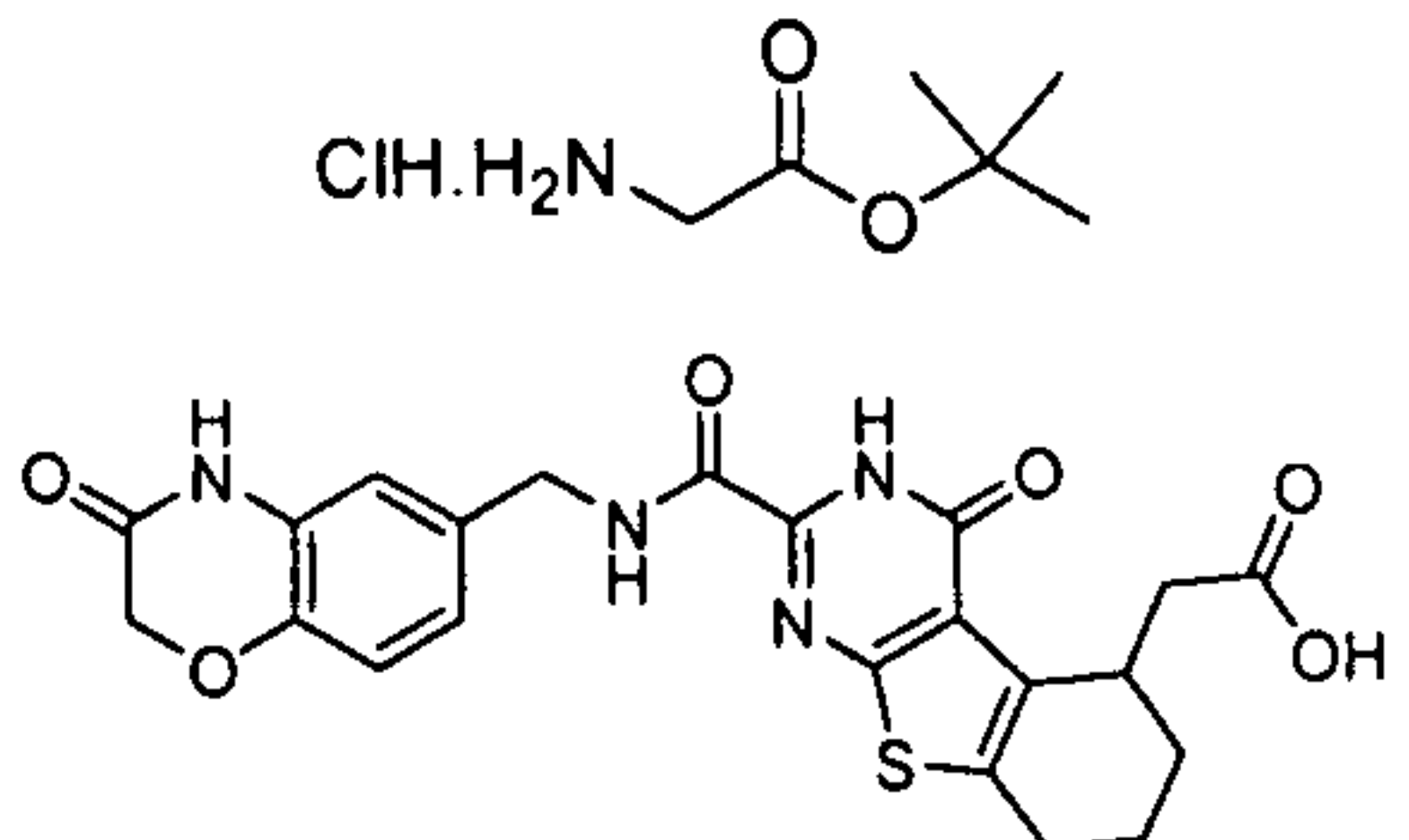
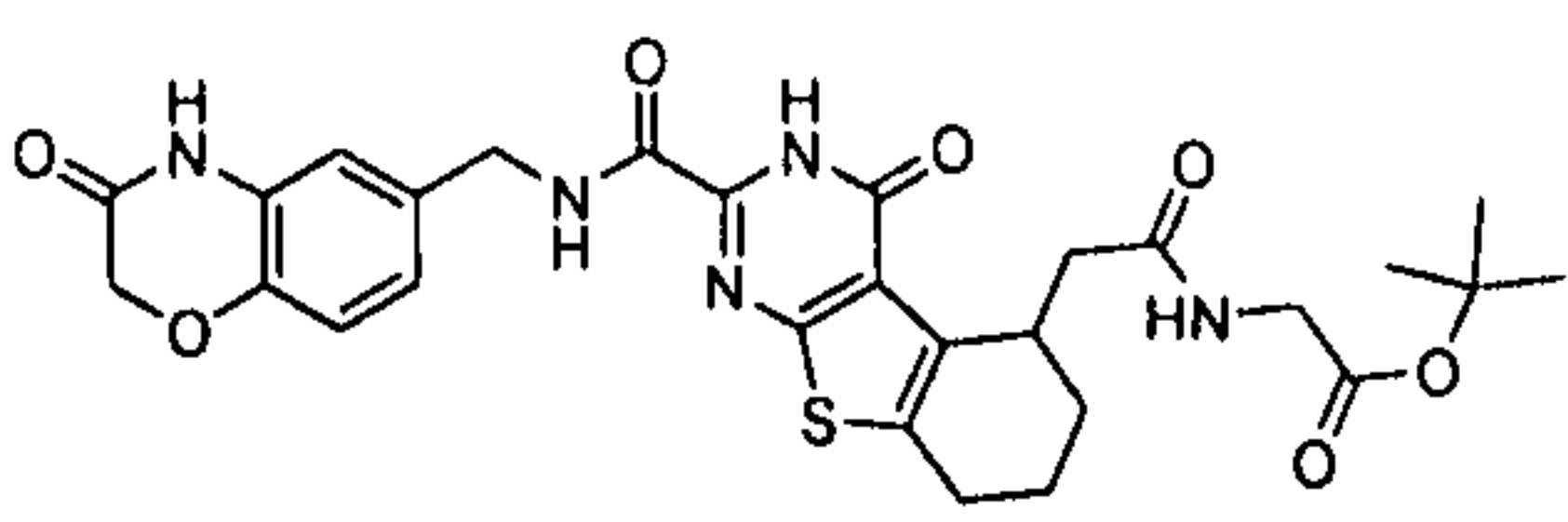
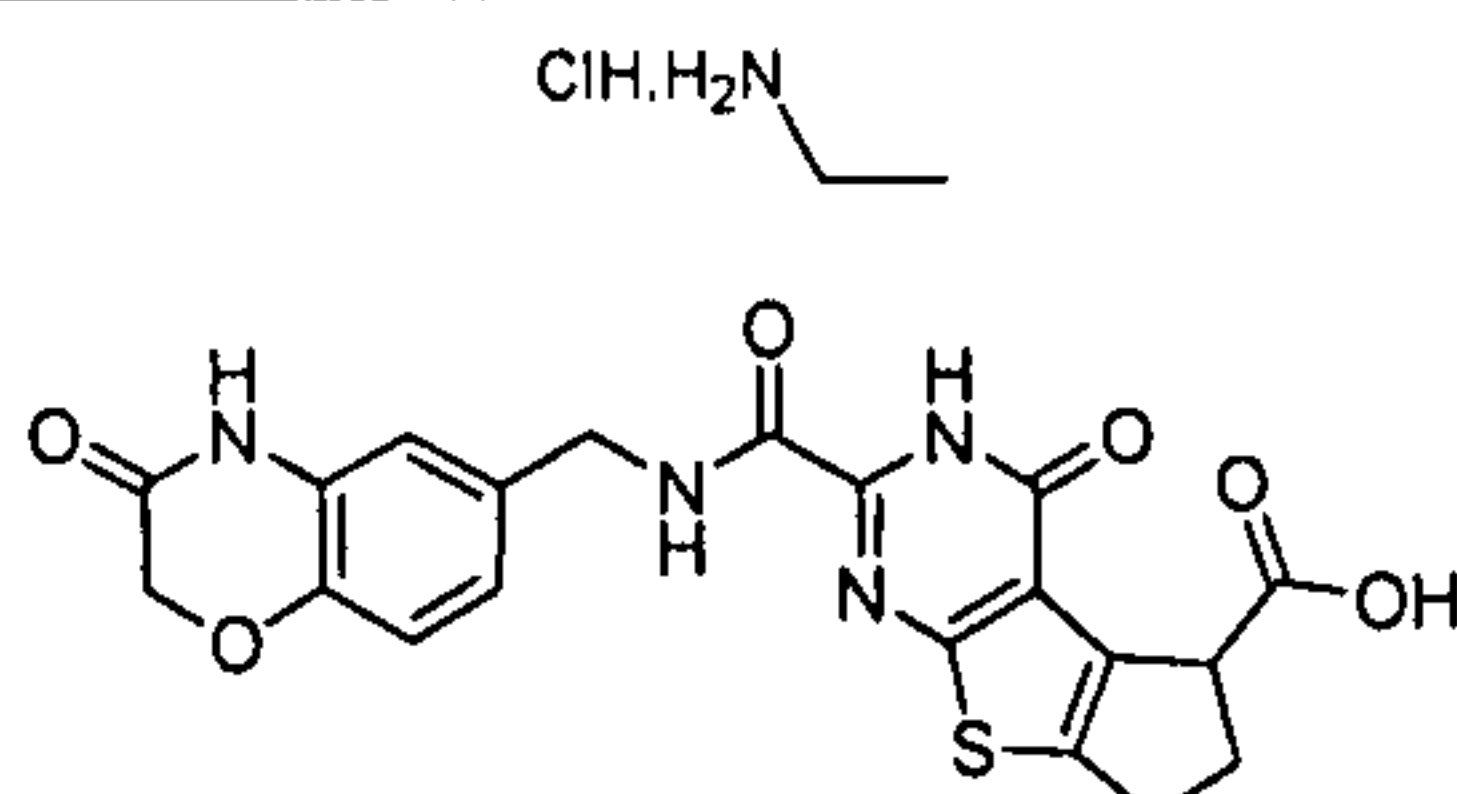
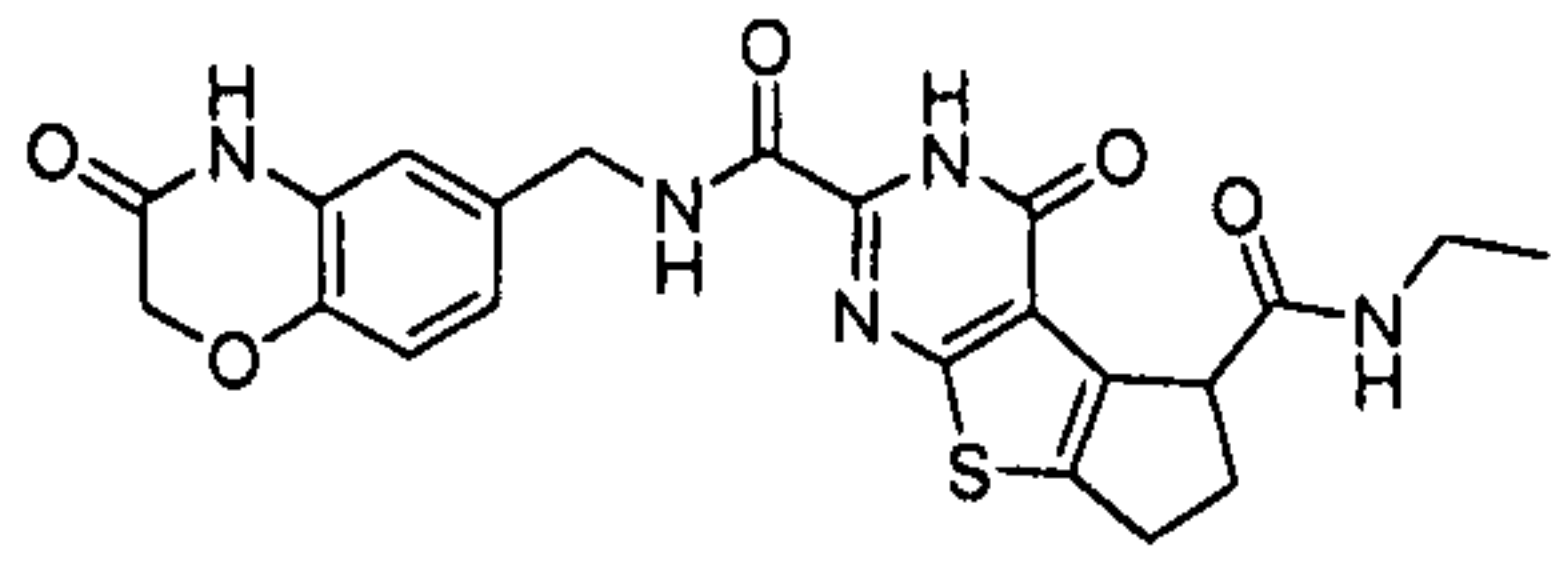
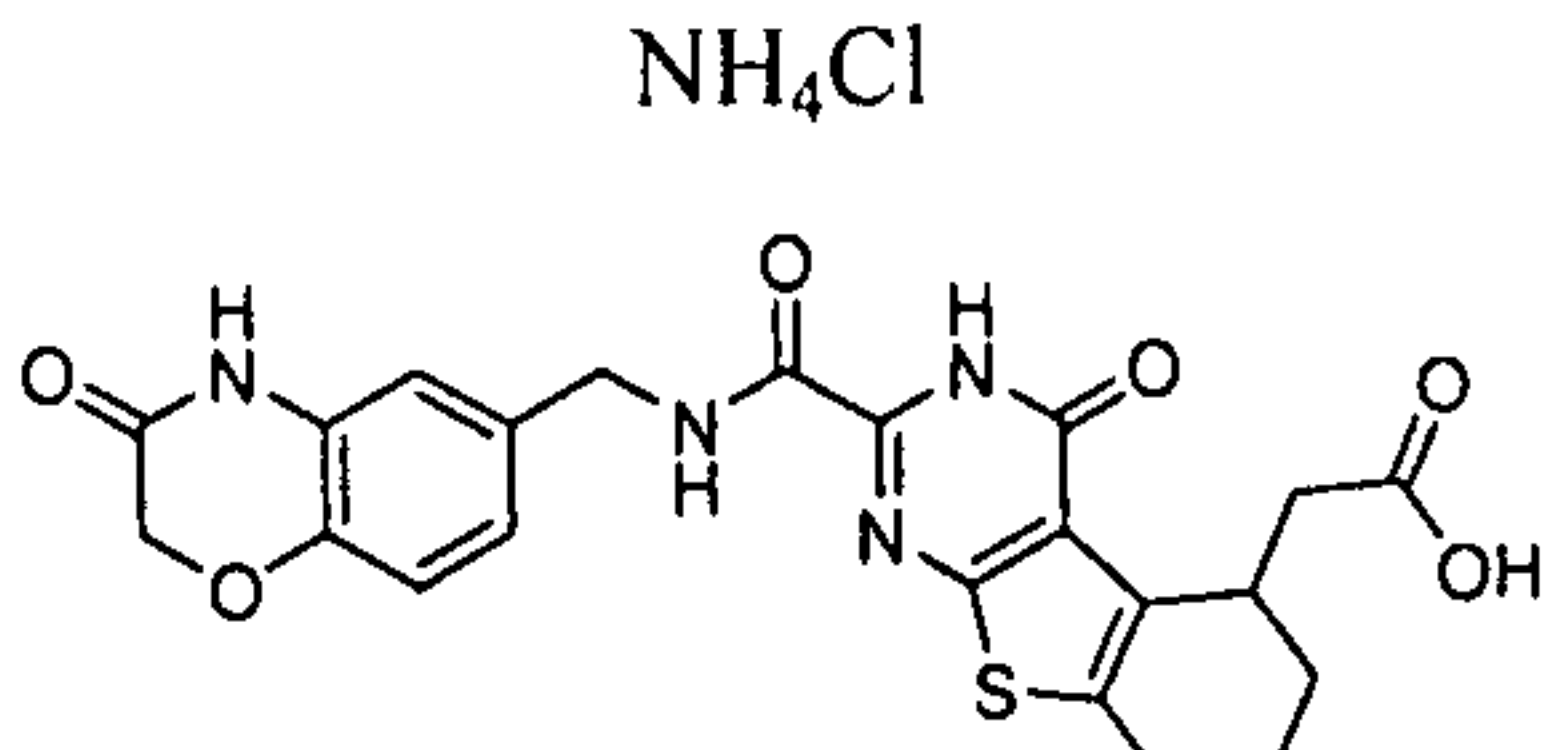
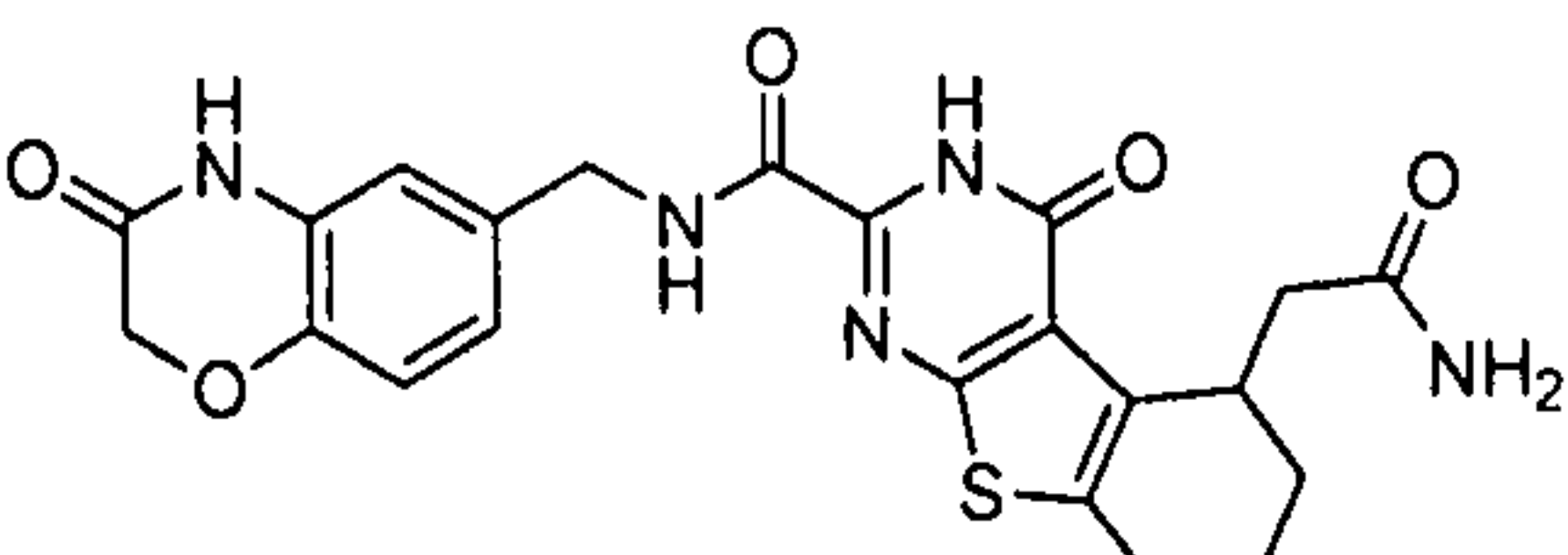
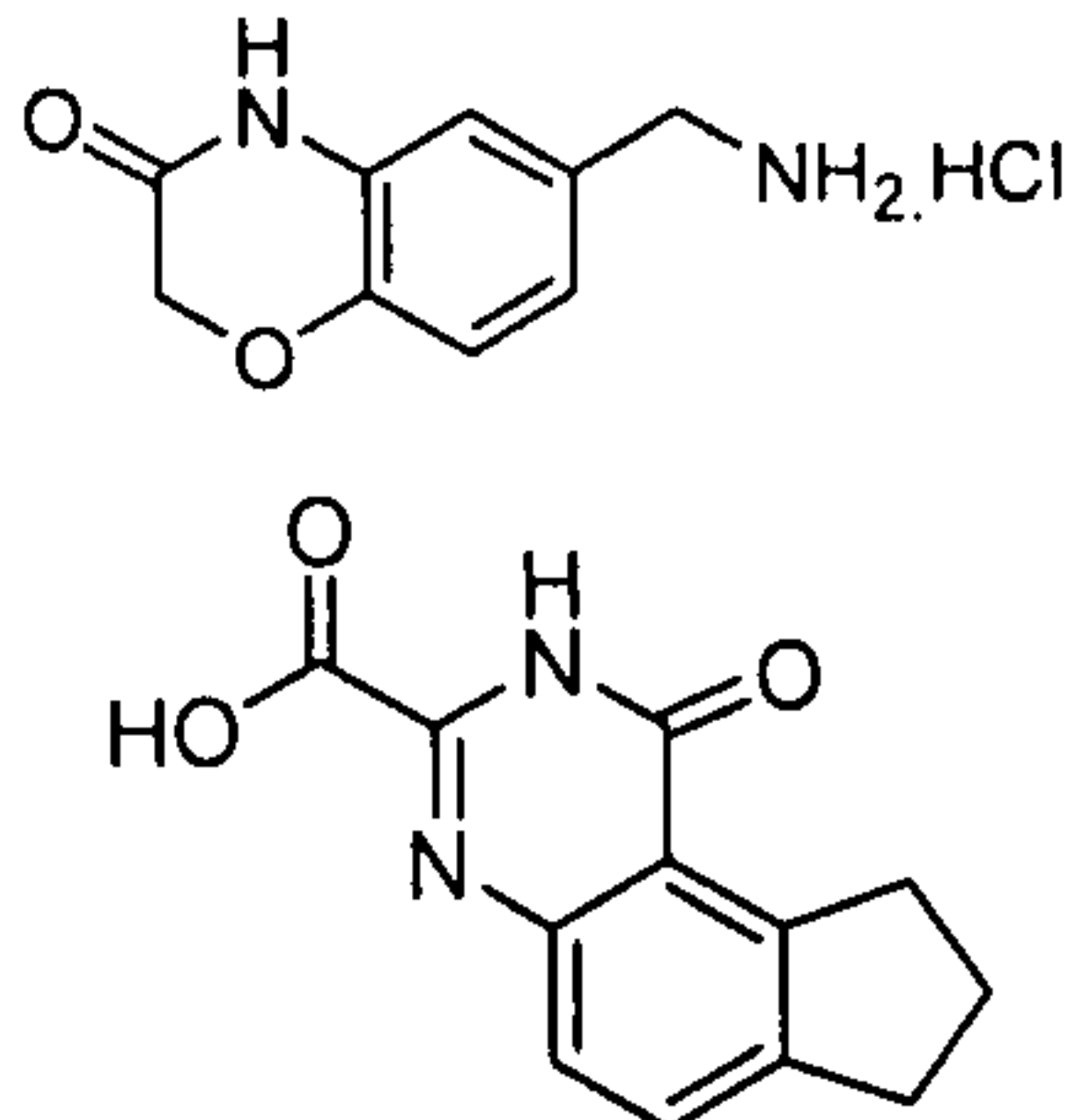
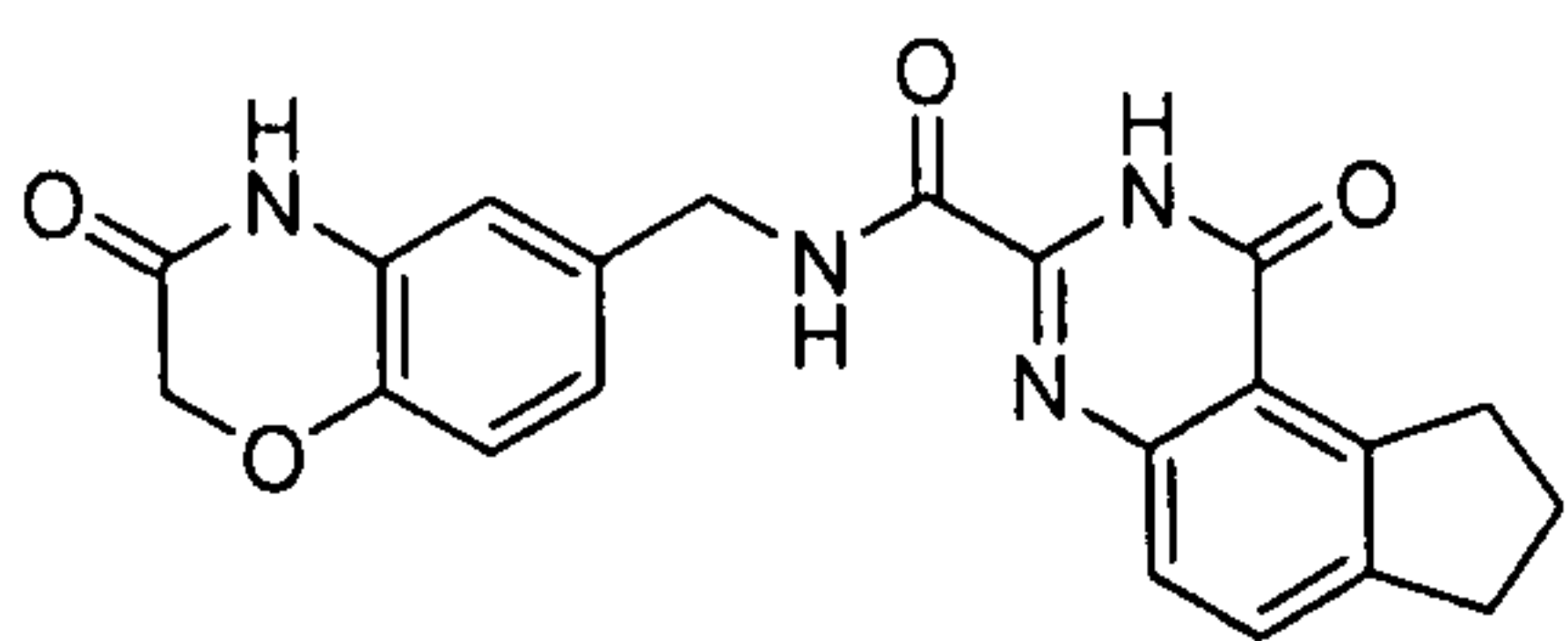
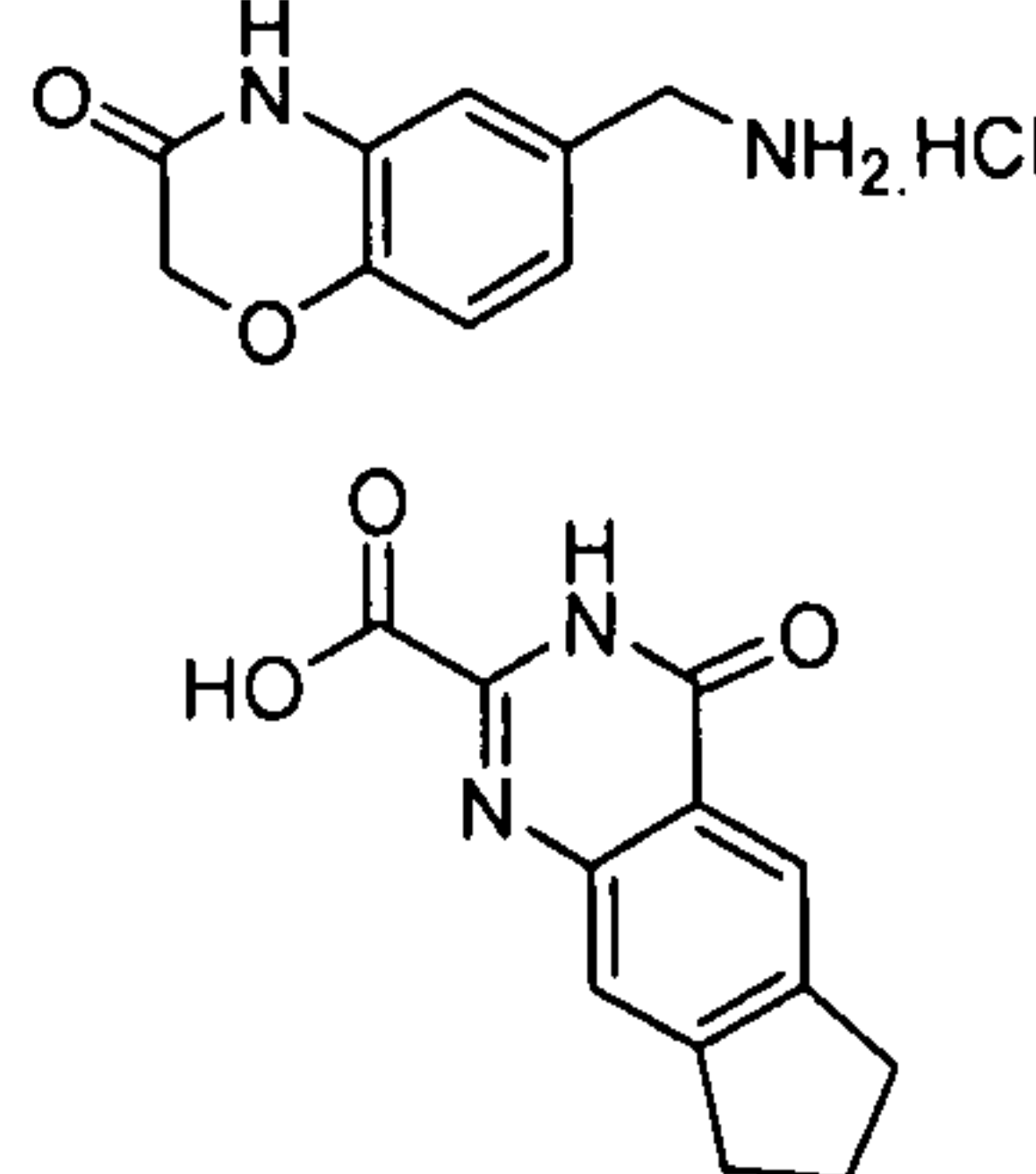
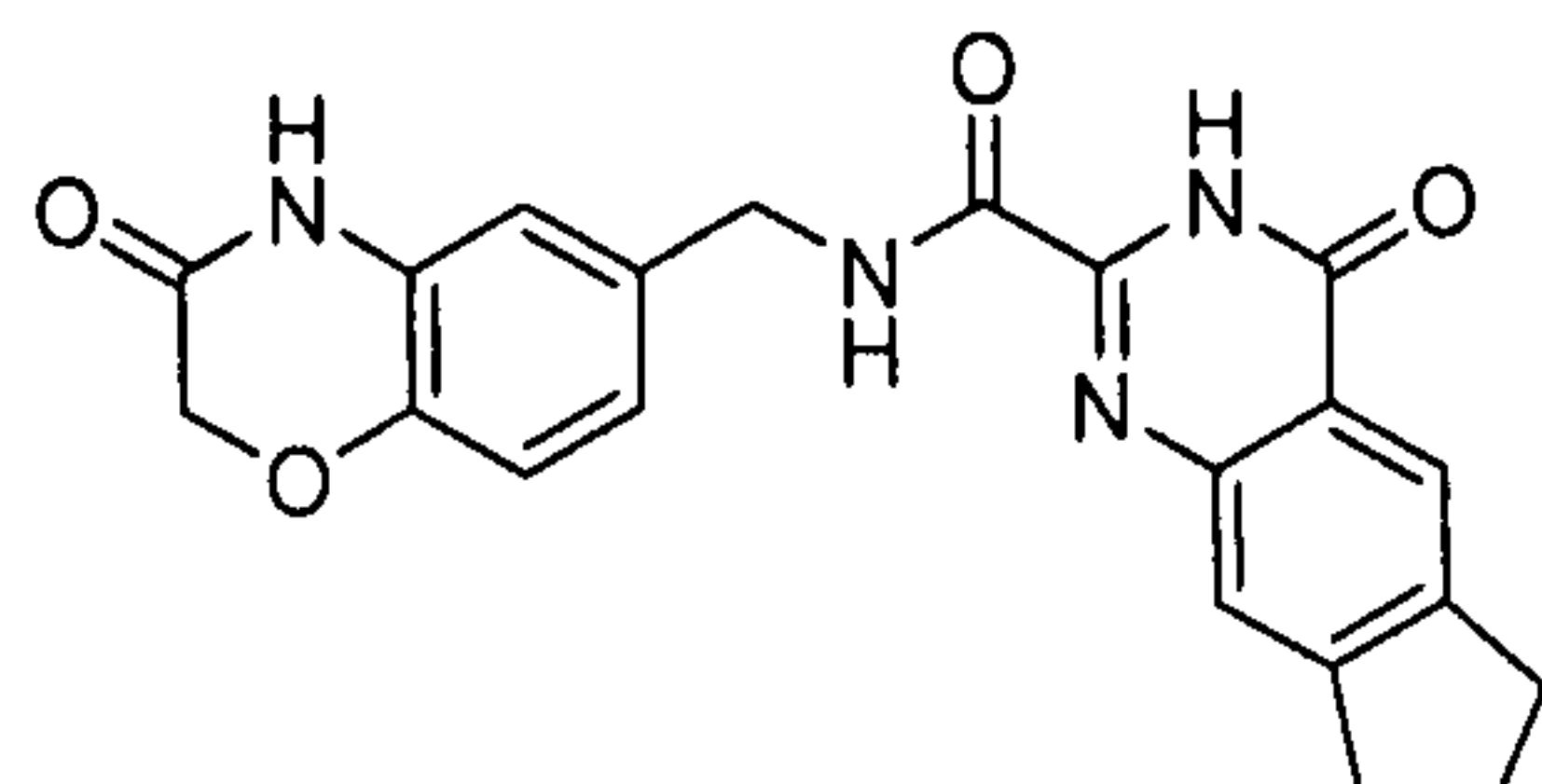
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/171 |     |    | A, 78%<br>[MH] <sup>+</sup> = 526 |
| 2/172 |   |  | A, 26%<br>[MH] <sup>+</sup> = 454 |
| 2/173 |  |  | A, 23%<br>[MH] <sup>+</sup> = 468 |
| 2/174 |  |  | A, 80%<br>[MH] <sup>+</sup> = 548 |
| 2/175 |  |  | A, 39%<br>[MH] <sup>+</sup> = 544 |

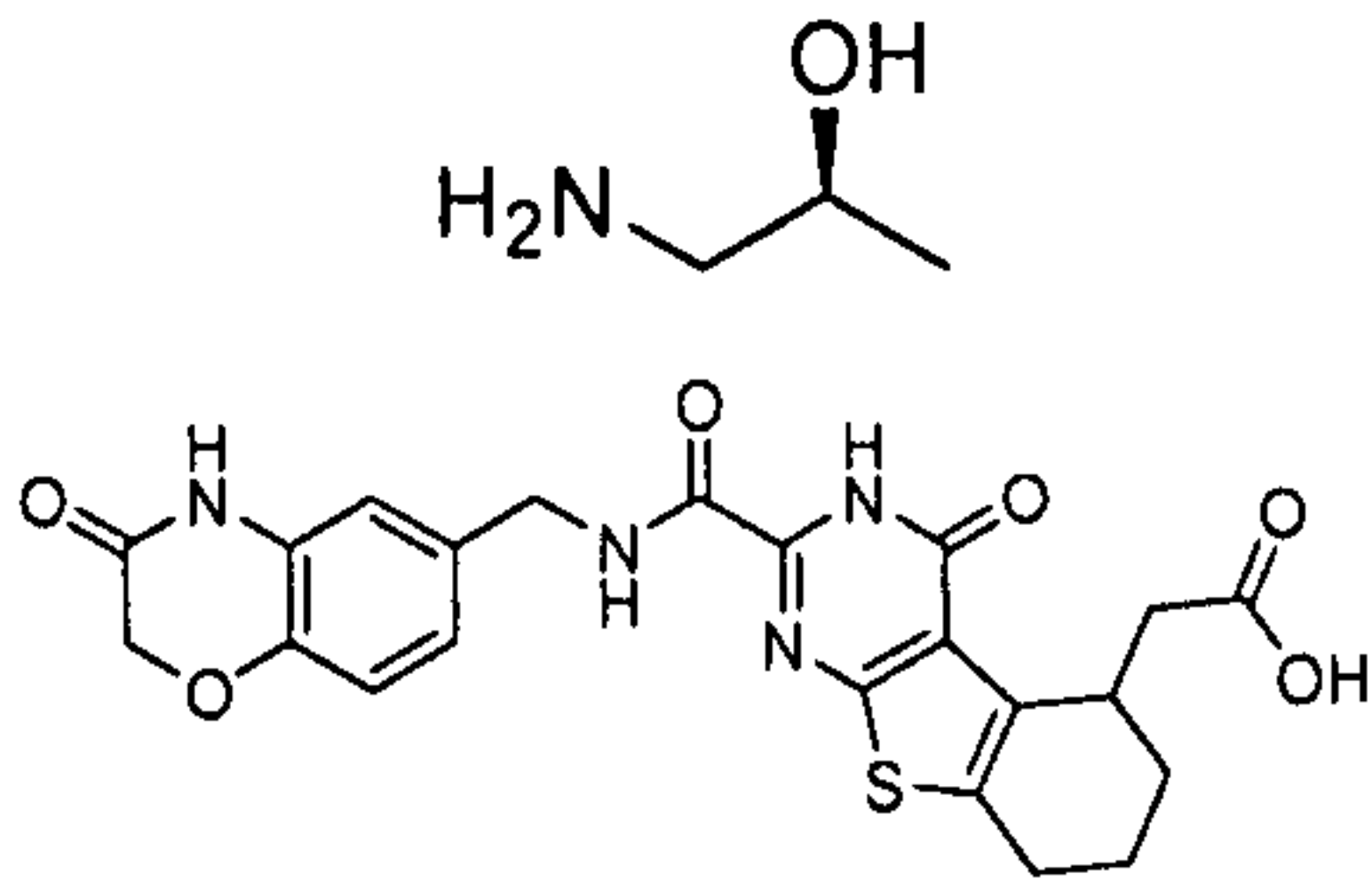
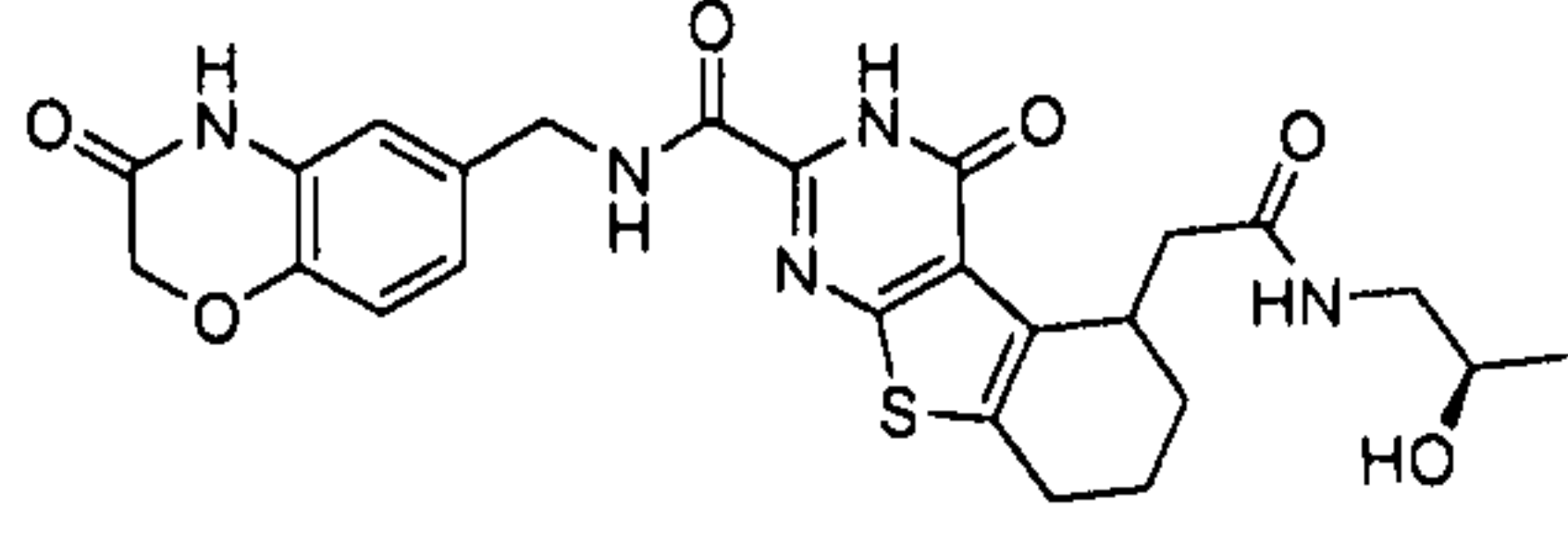
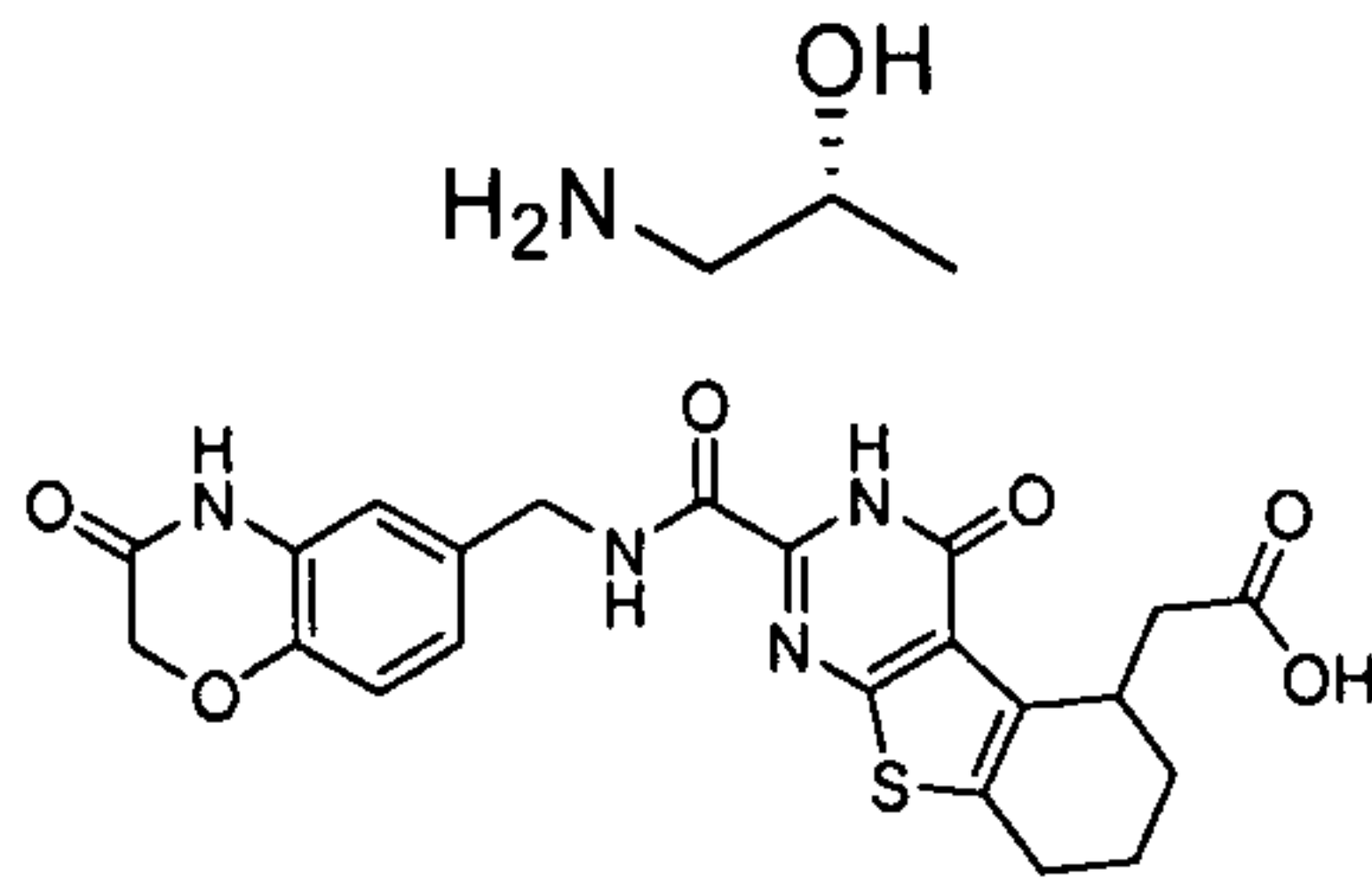
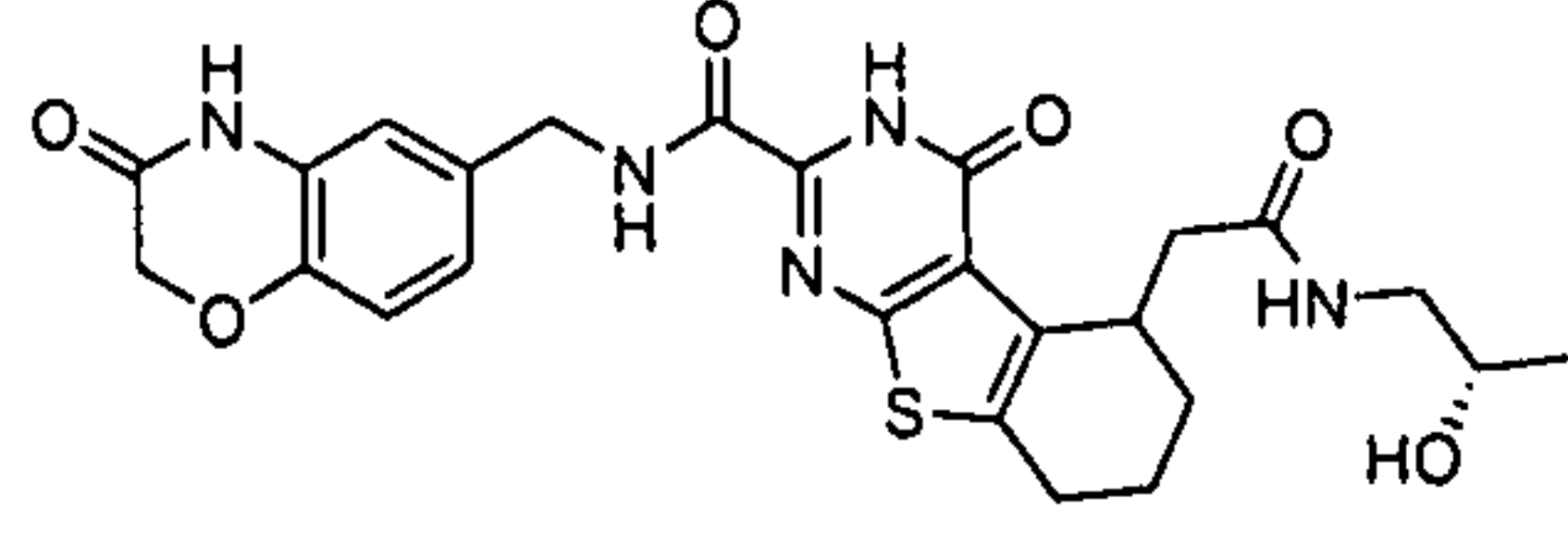
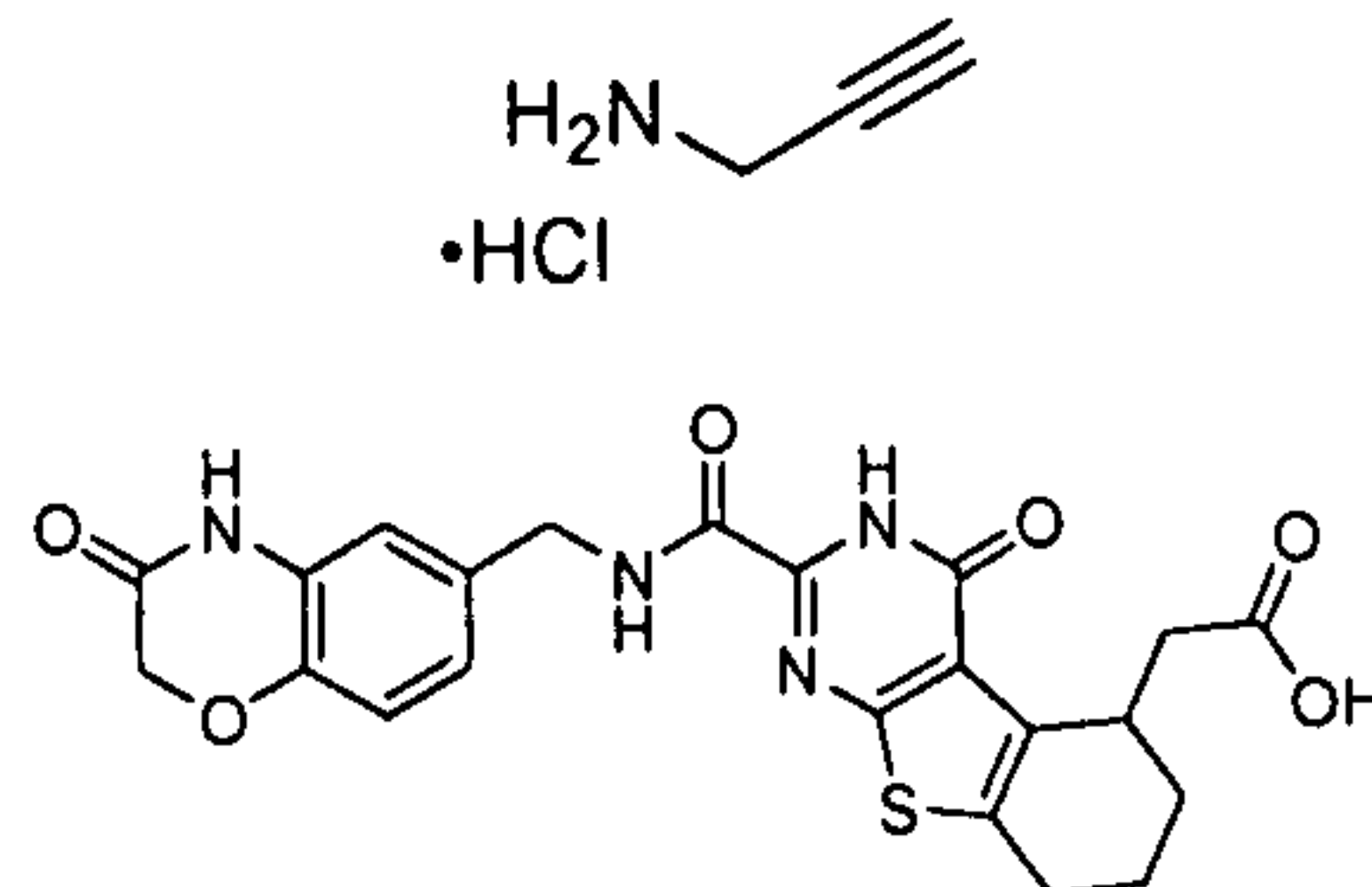
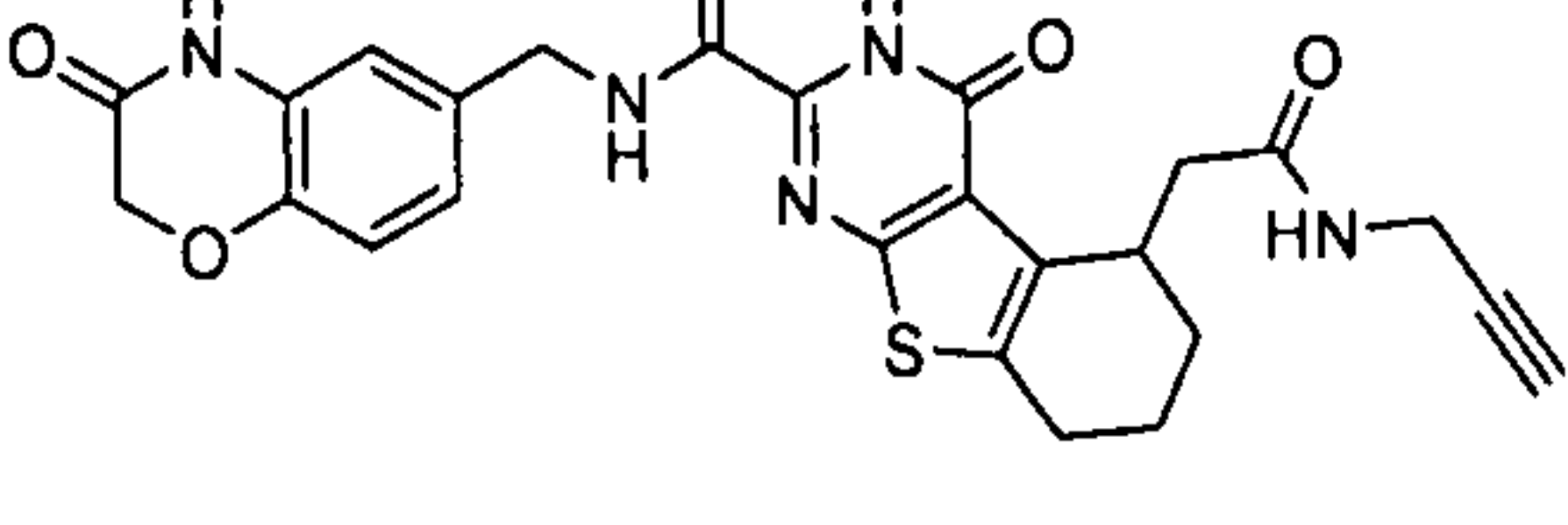
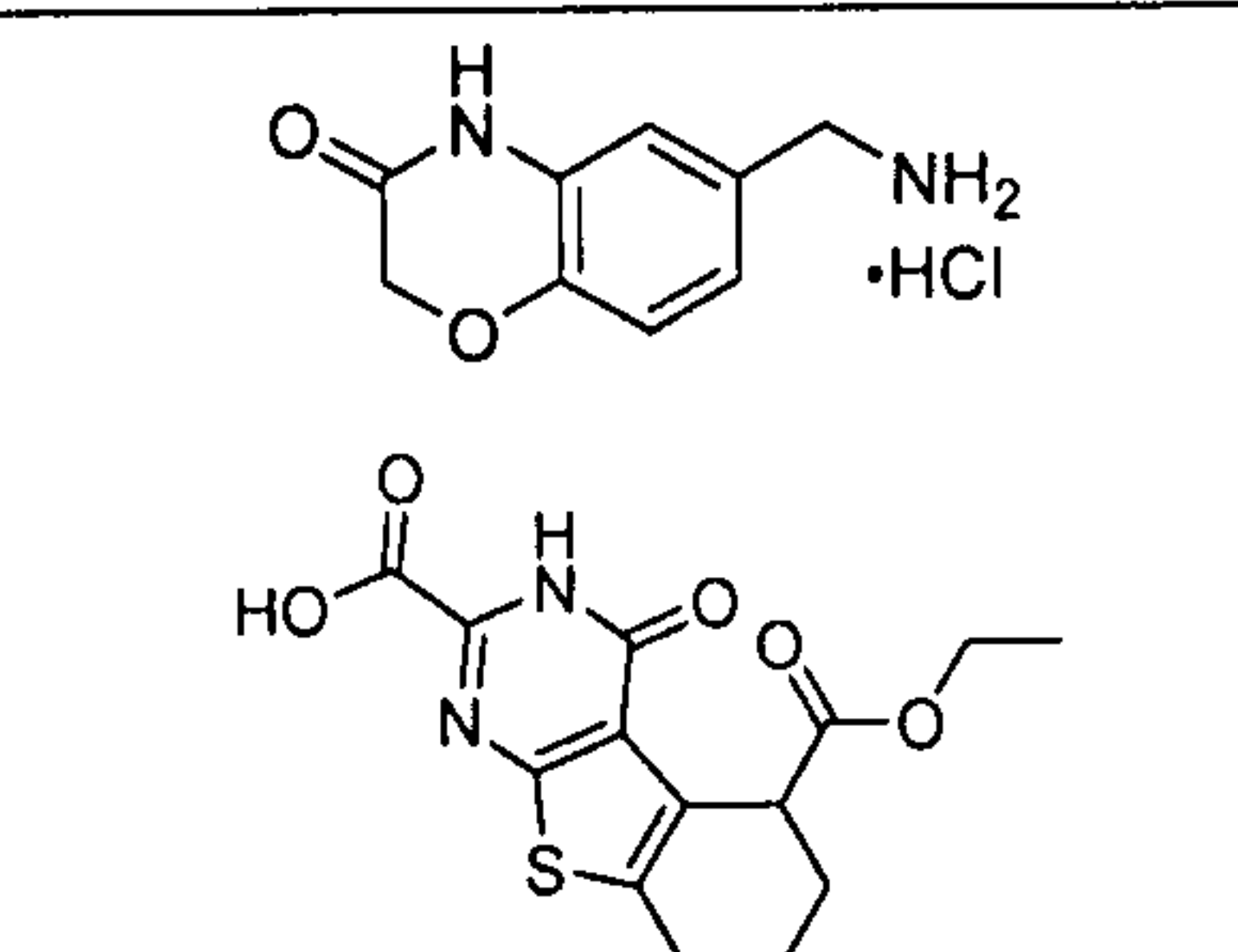
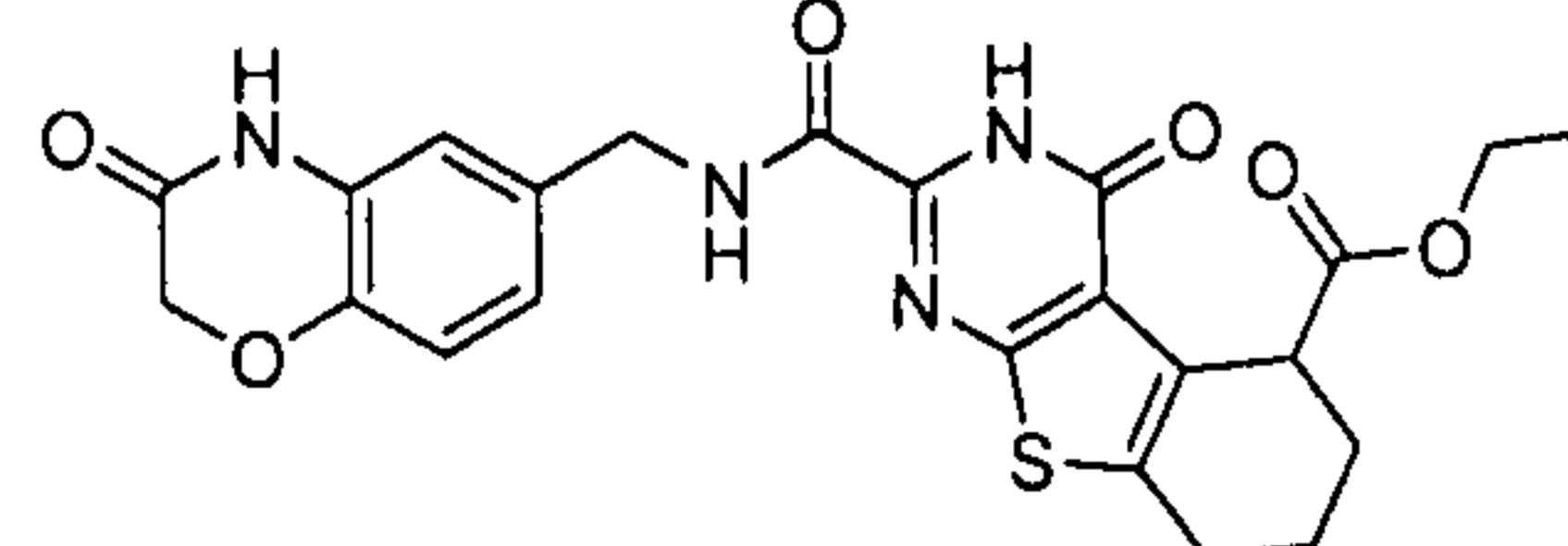
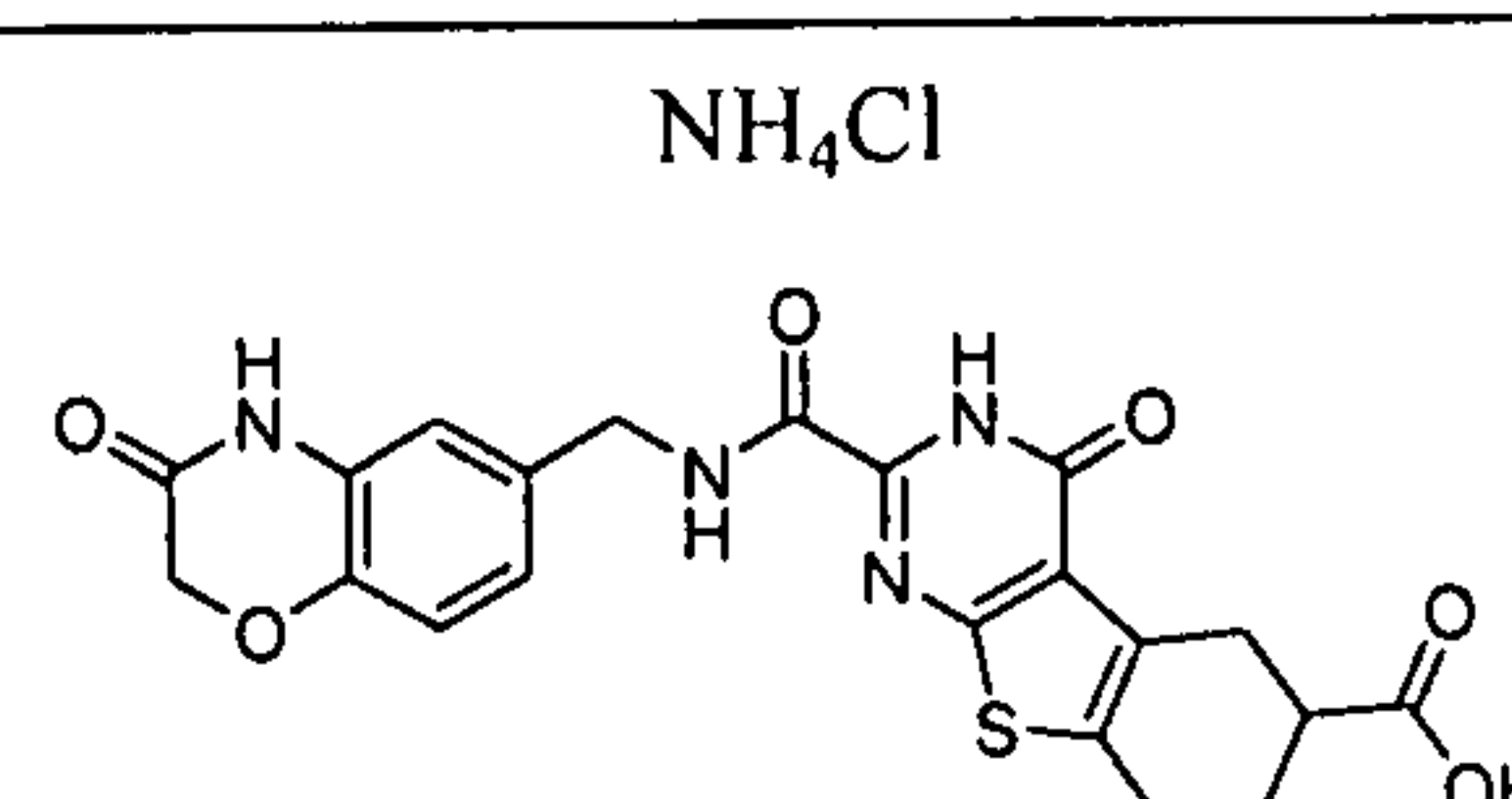
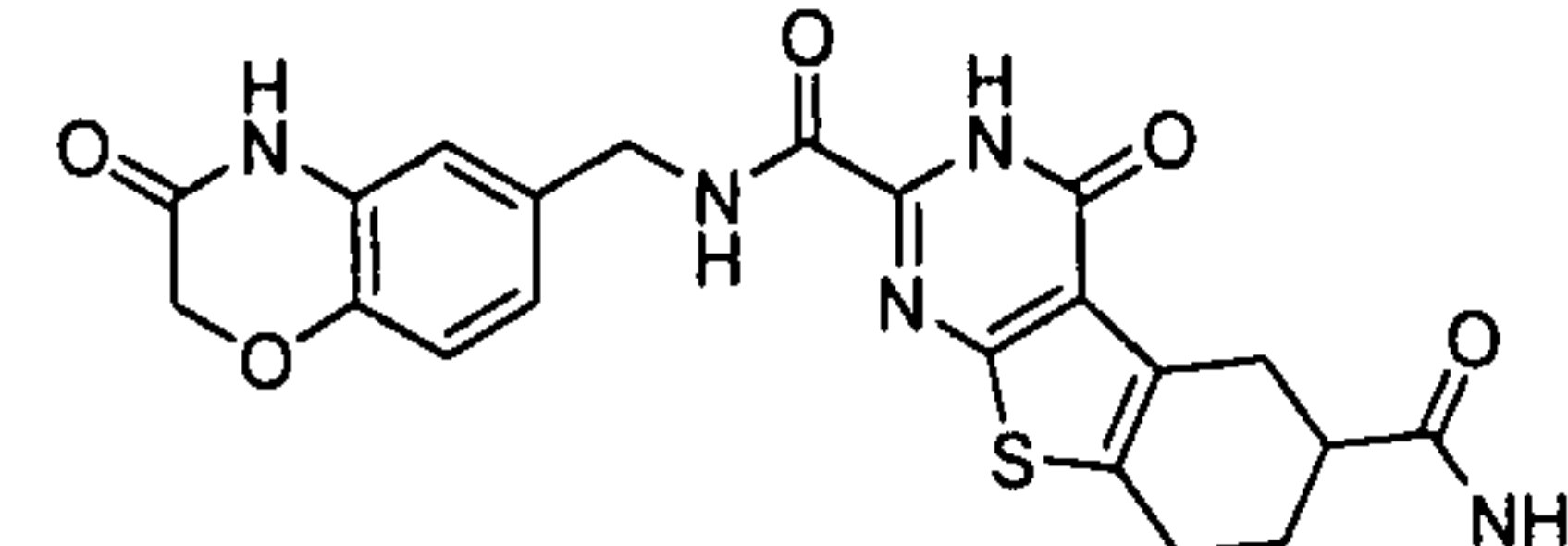
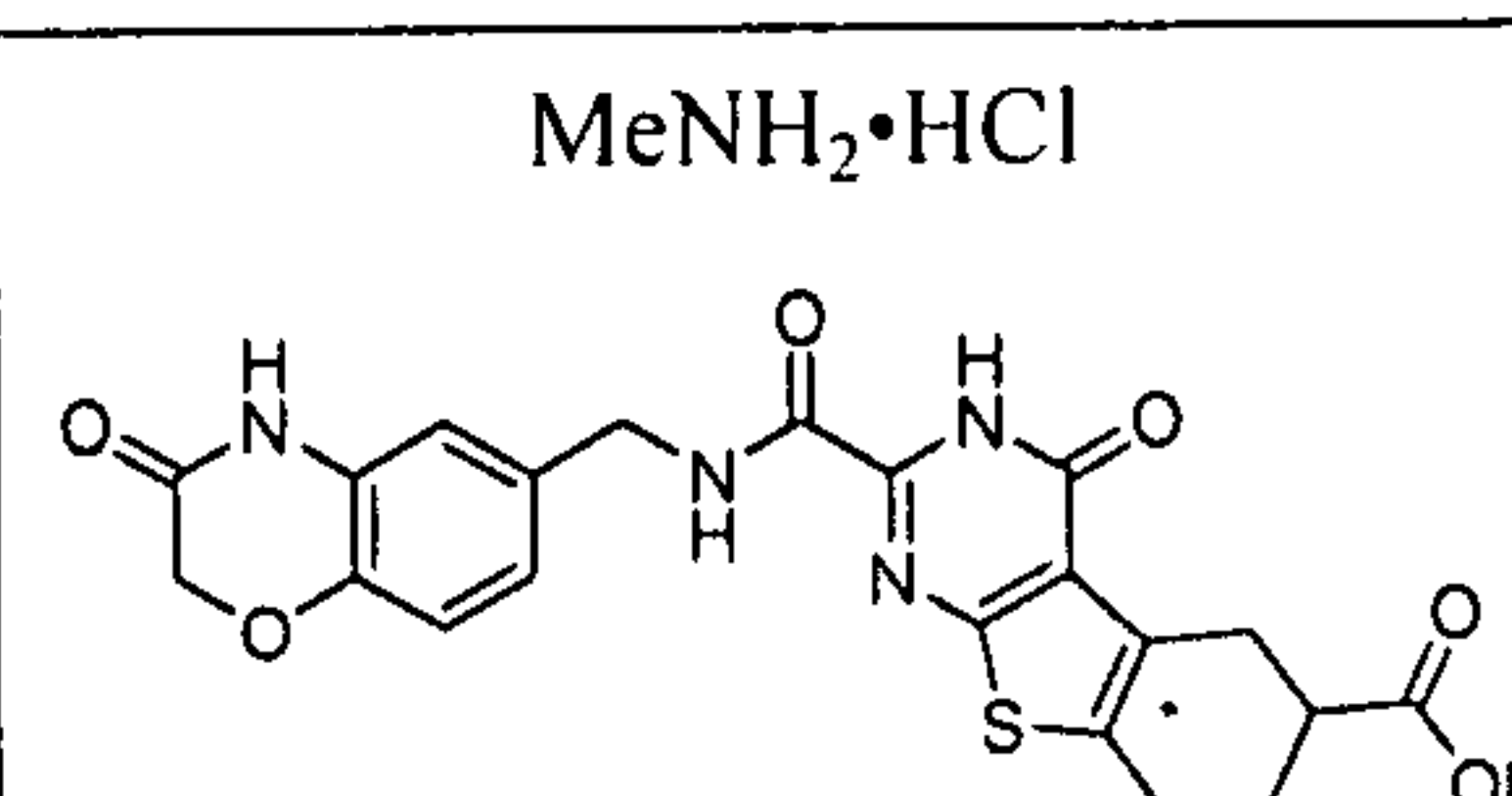
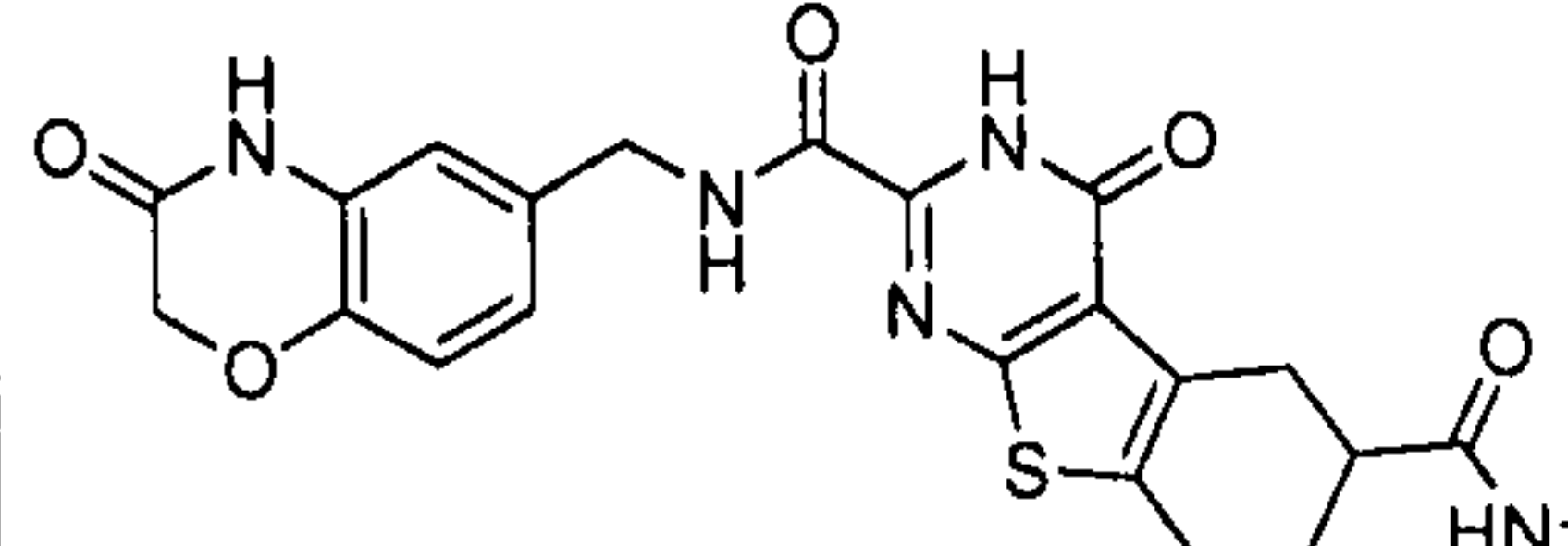
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                      |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/176 |    |    | A, 36%<br>[MH] <sup>+</sup> = 562  |
| 2/177 |   |  | A, 86%<br>[MH] <sup>+</sup> = 562  |
| 2/178 |  |  | A, 76%<br>[MH] <sup>+</sup> = 562  |
| 2/188 |  |  | A, n.d.<br>[MH] <sup>+</sup> = 538 |
| 2/208 |  |  | A, 25%<br>[MH] <sup>+</sup> = 483  |

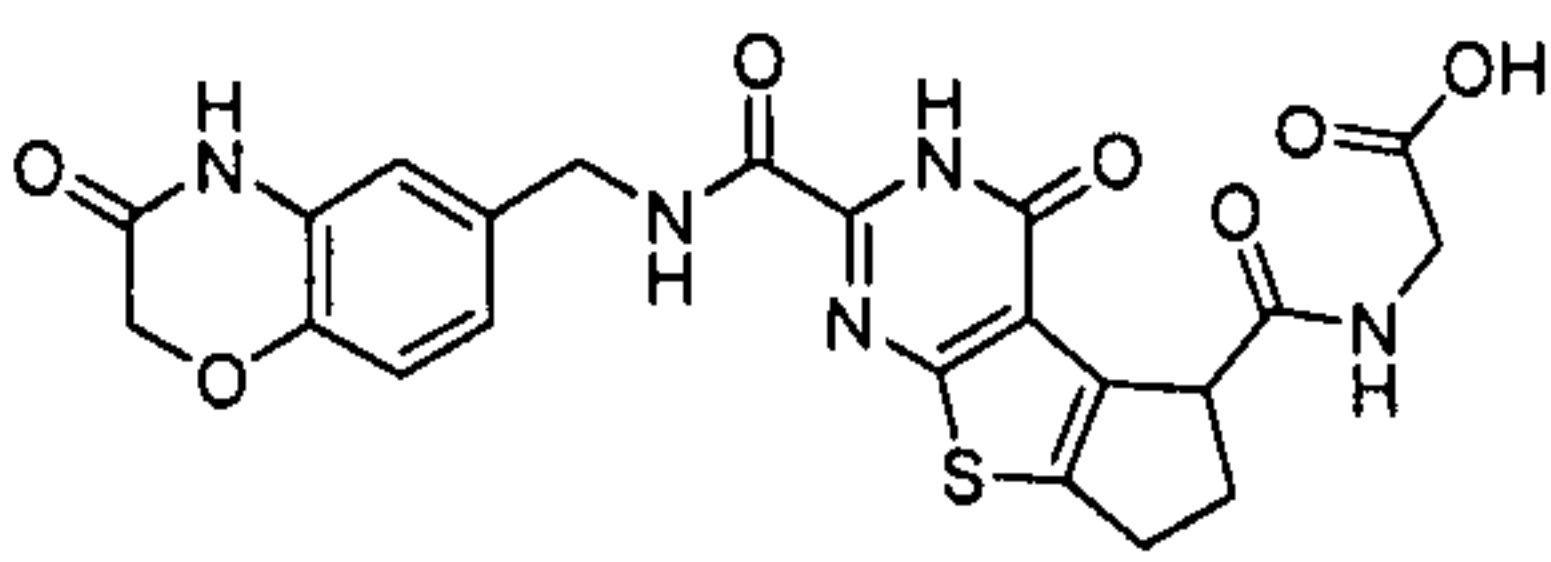
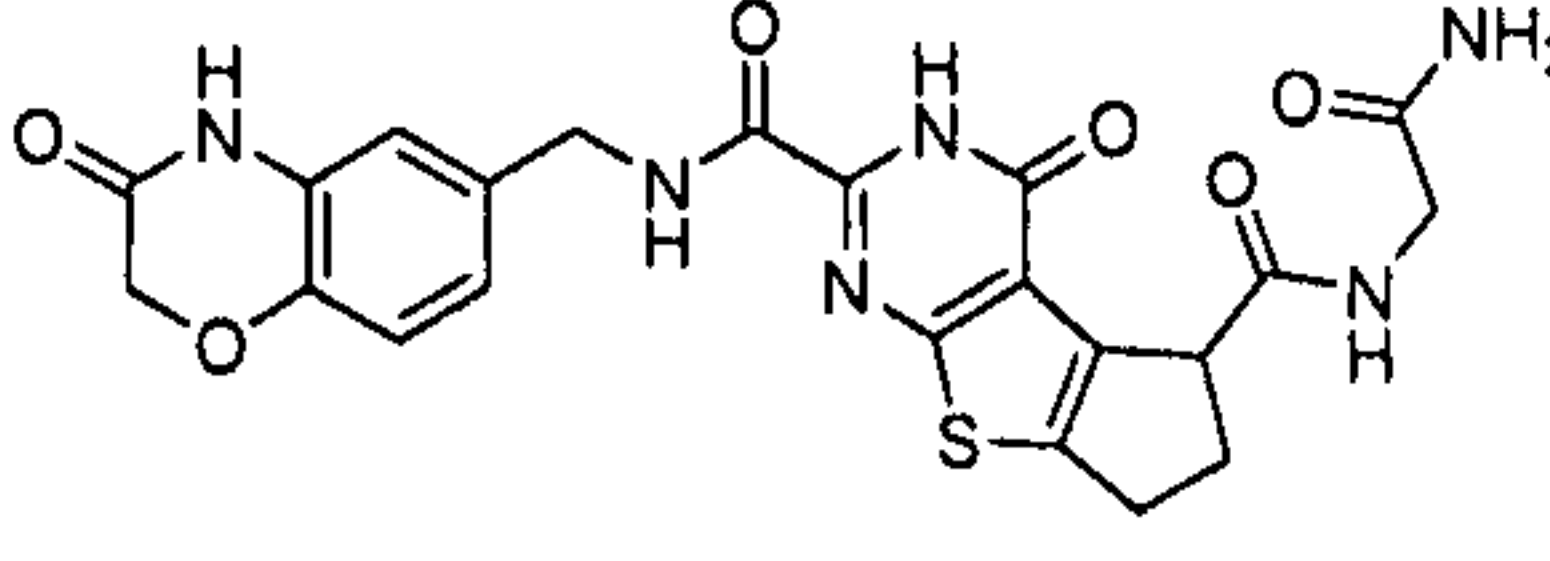
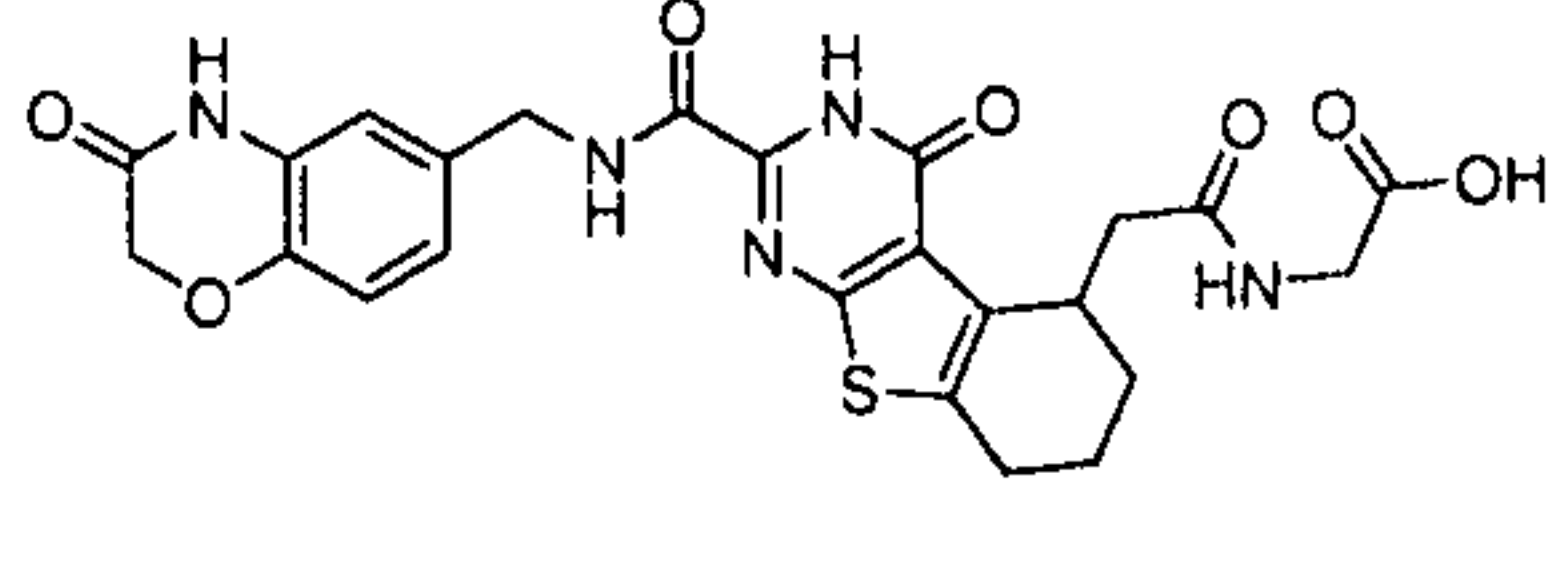
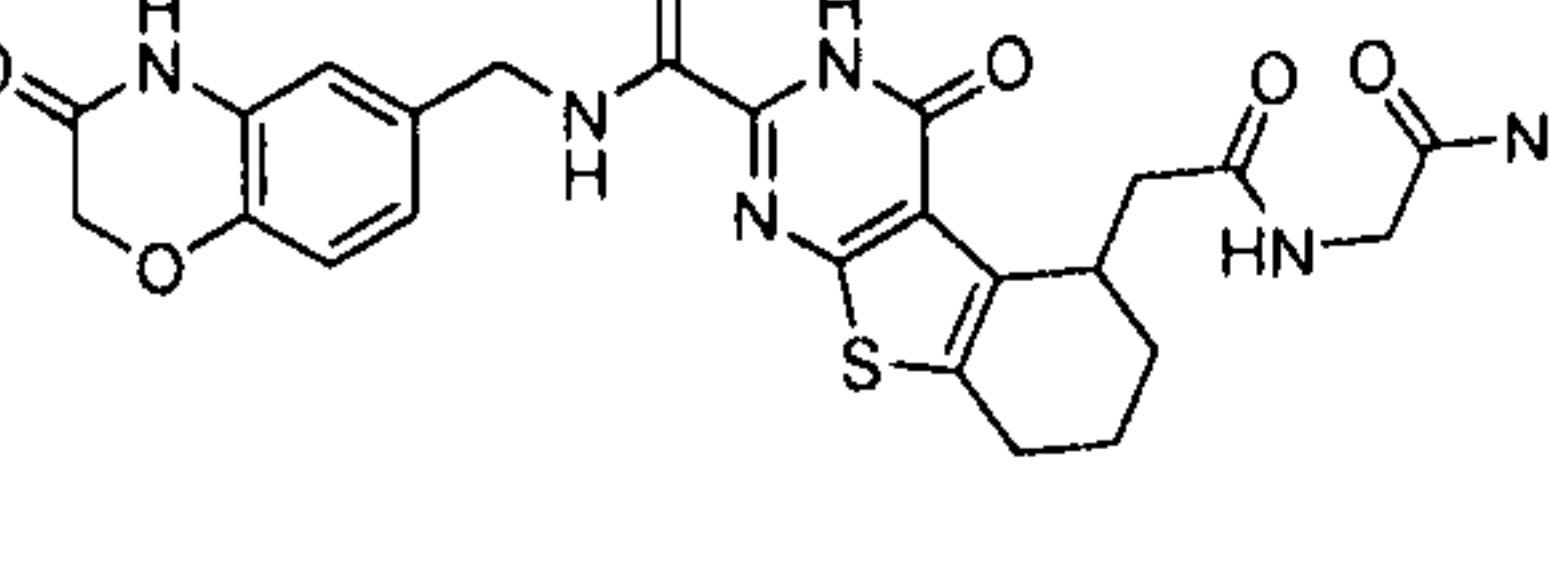
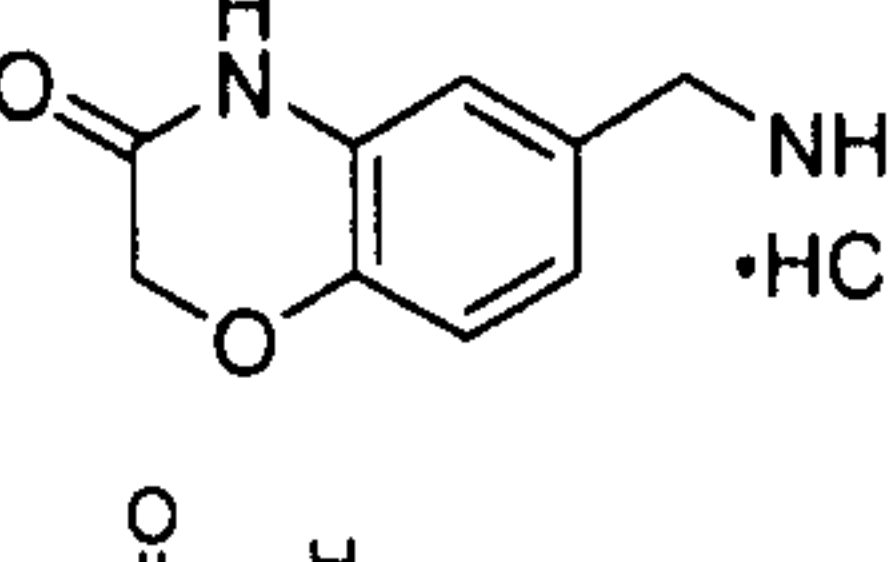
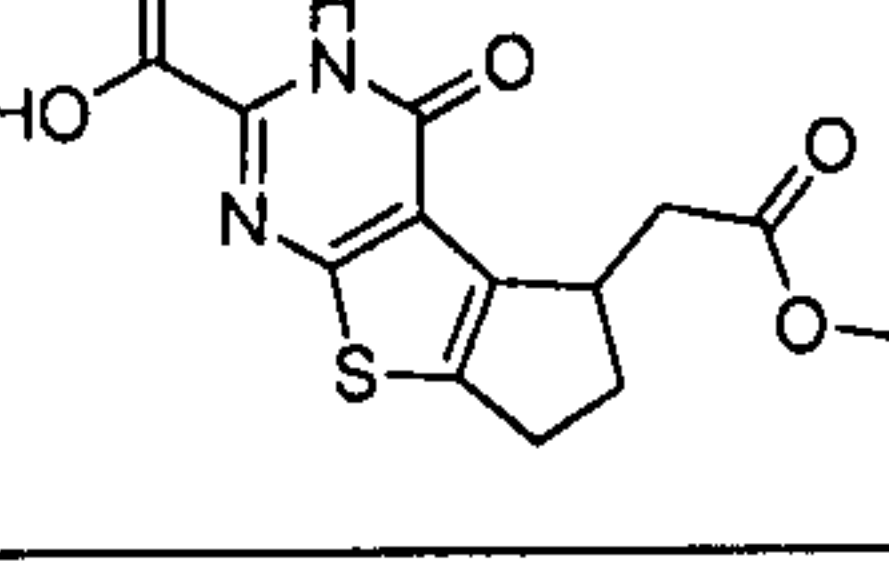
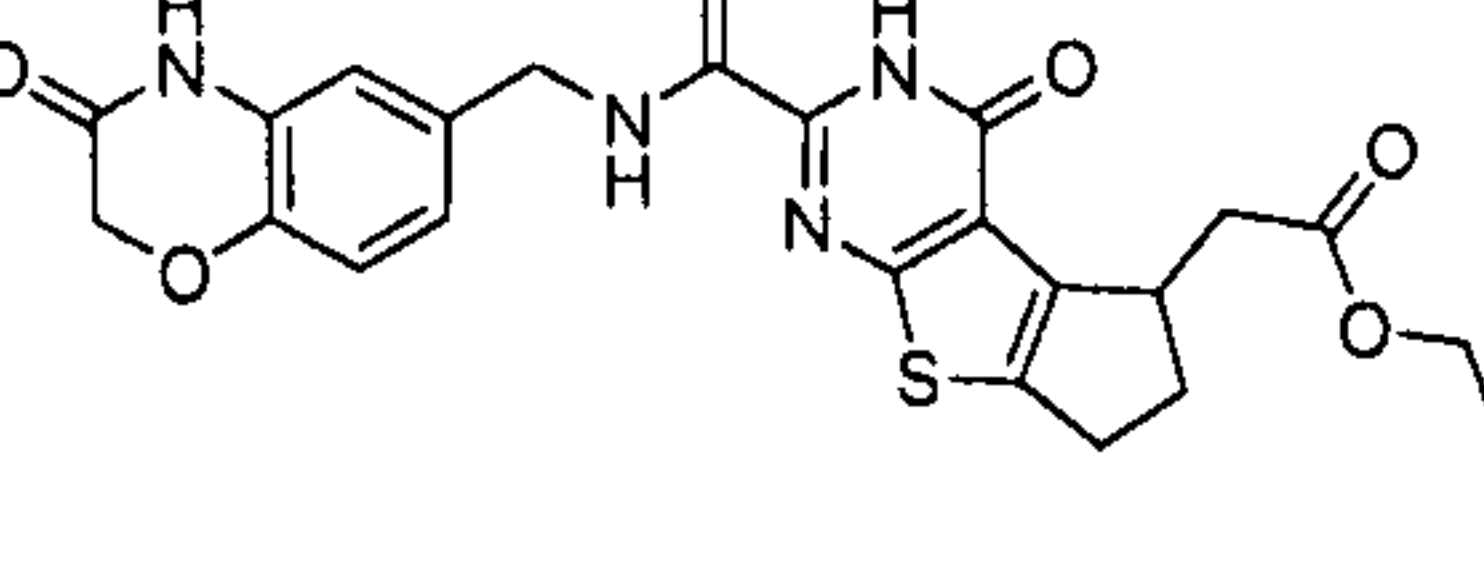
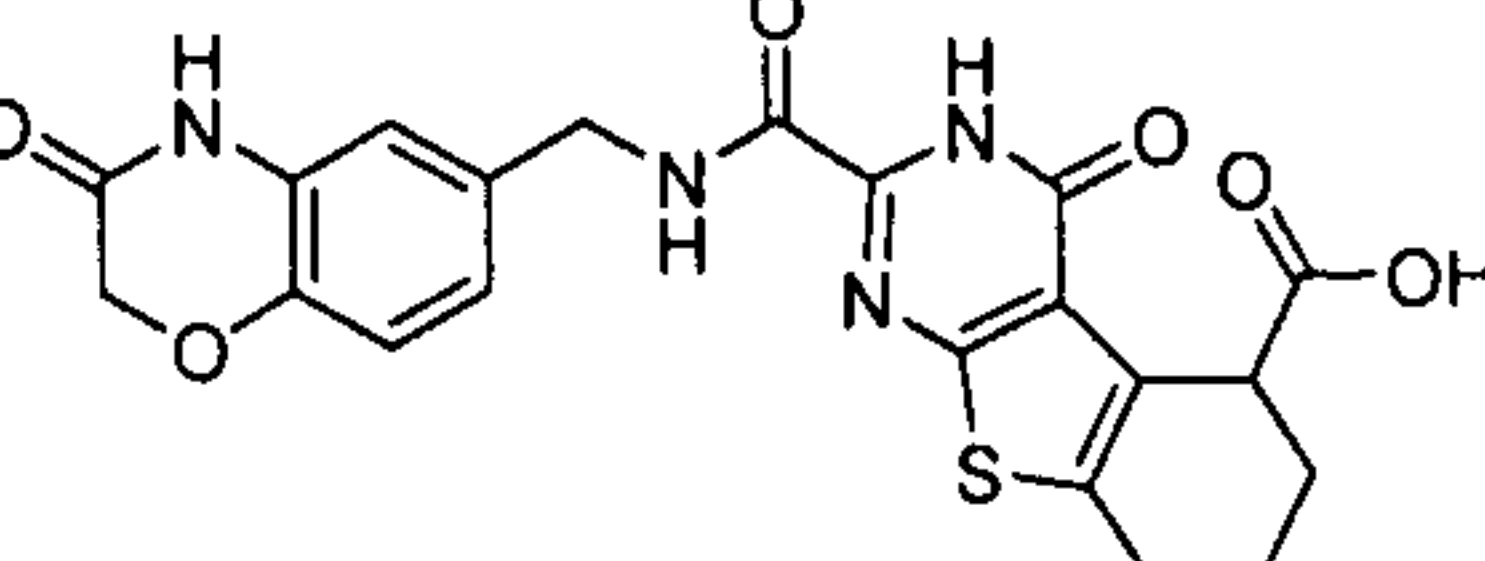
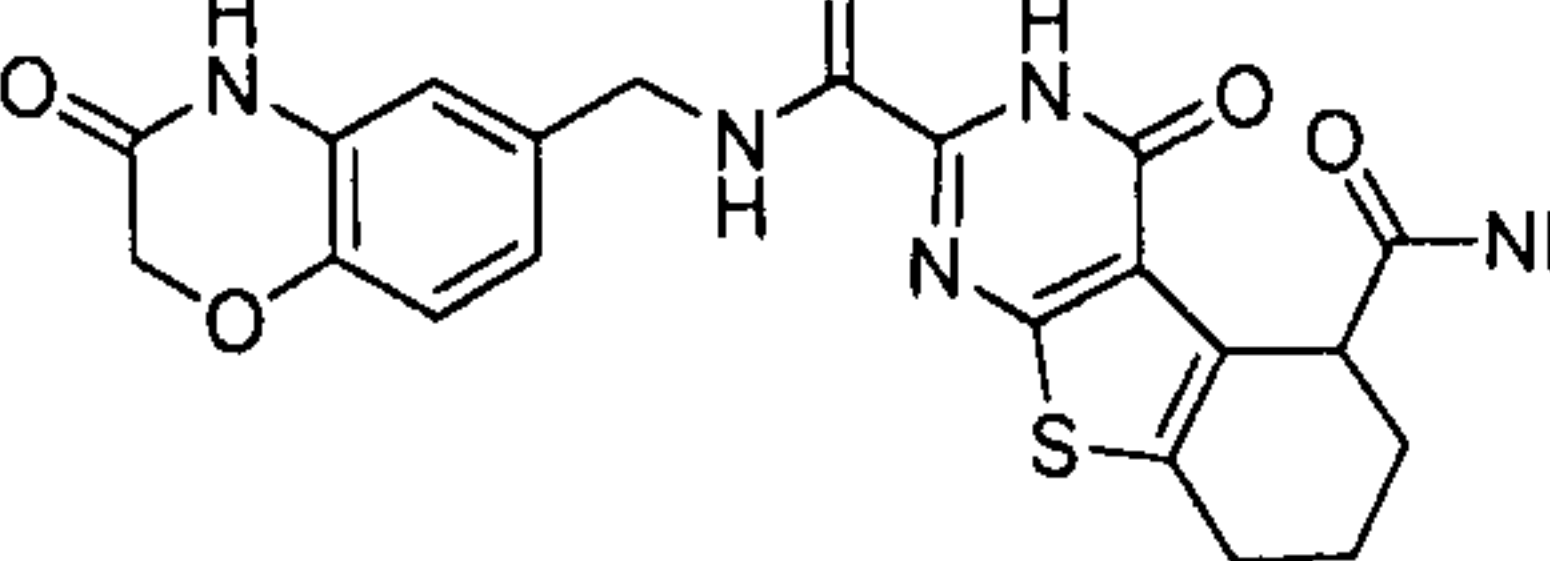
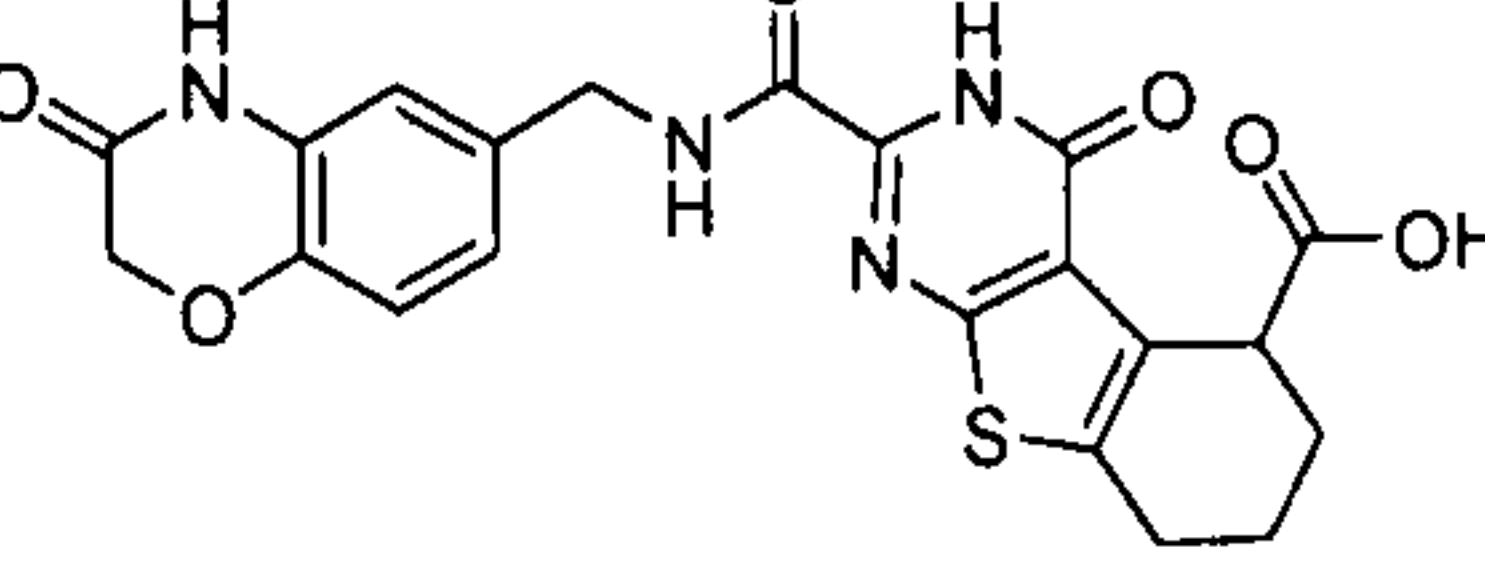
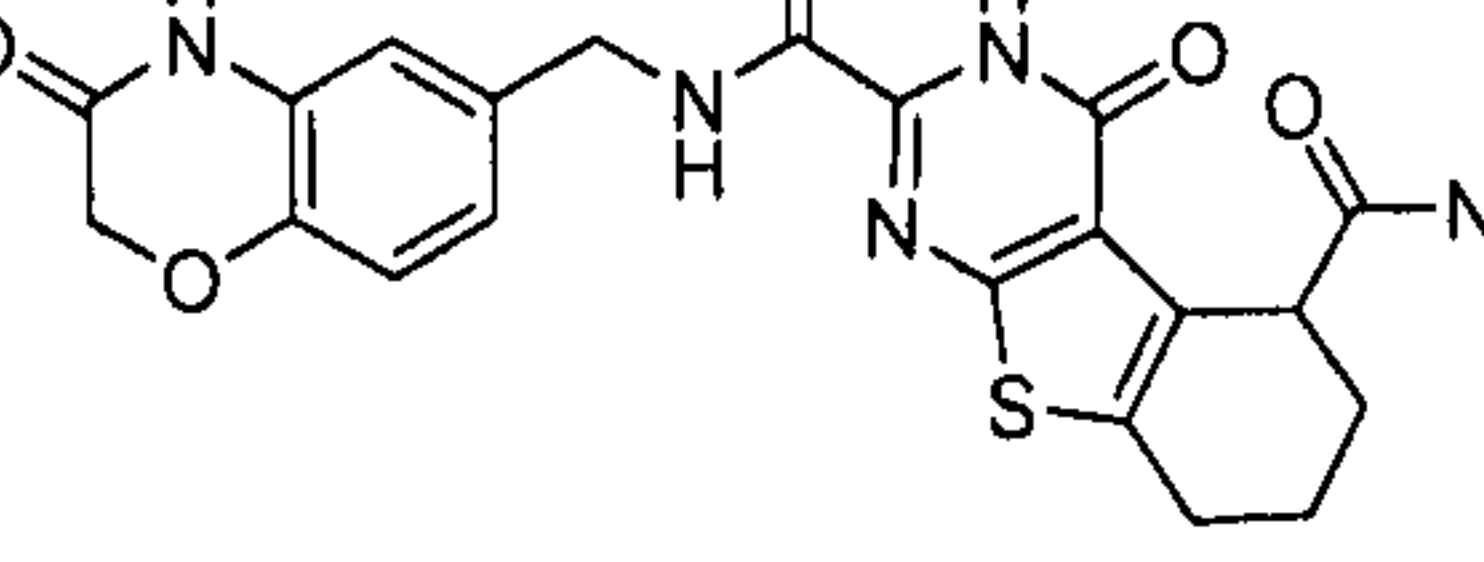
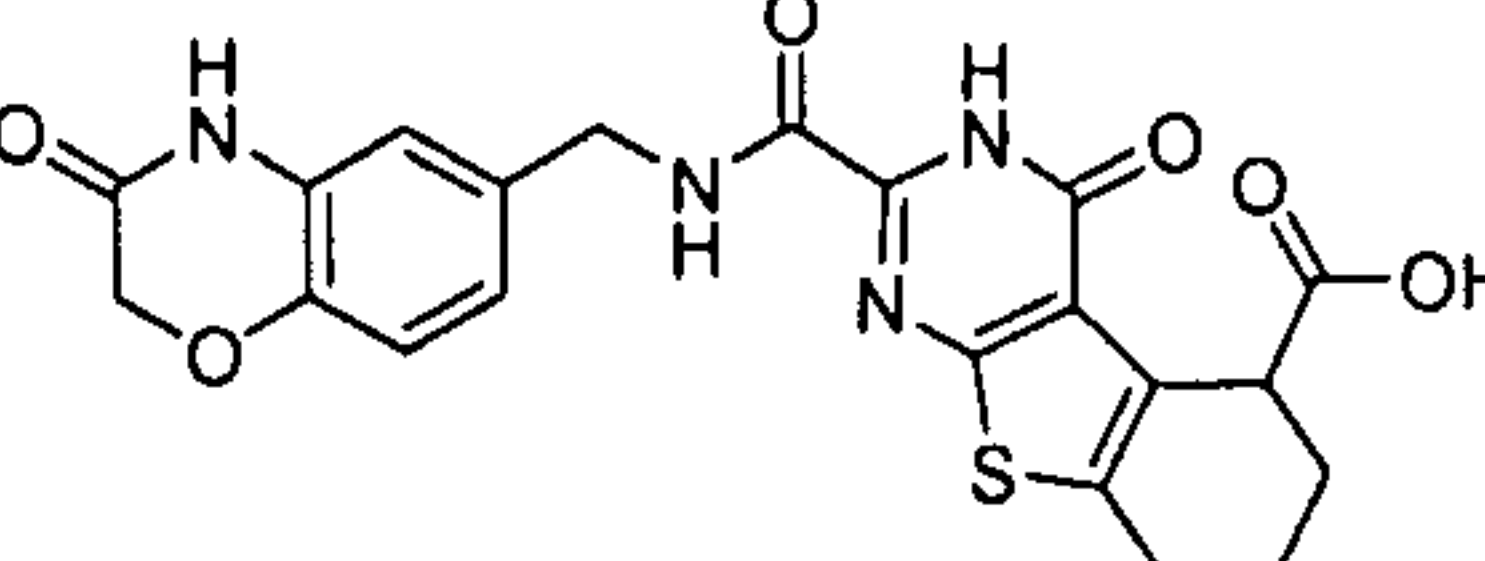
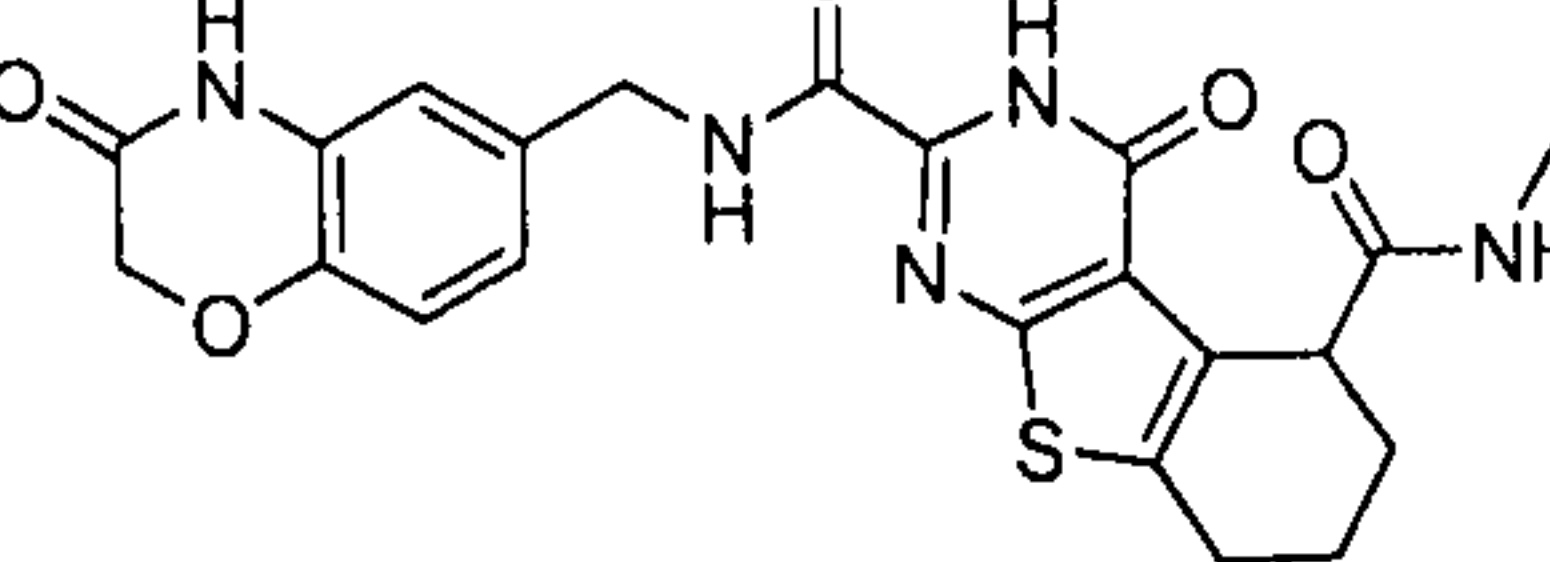
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                     |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/209 |    |    | A, 22%<br>[MH] <sup>+</sup> = 562 |
| 2/210 |  |  | A, 7%<br>[MH] <sup>+</sup> = 469  |
| 2/211 |  |  | A, 79%<br>[MH] <sup>+</sup> = 427 |
| 2/212 |  |  | A, 87%<br>[MH] <sup>+</sup> = 506 |

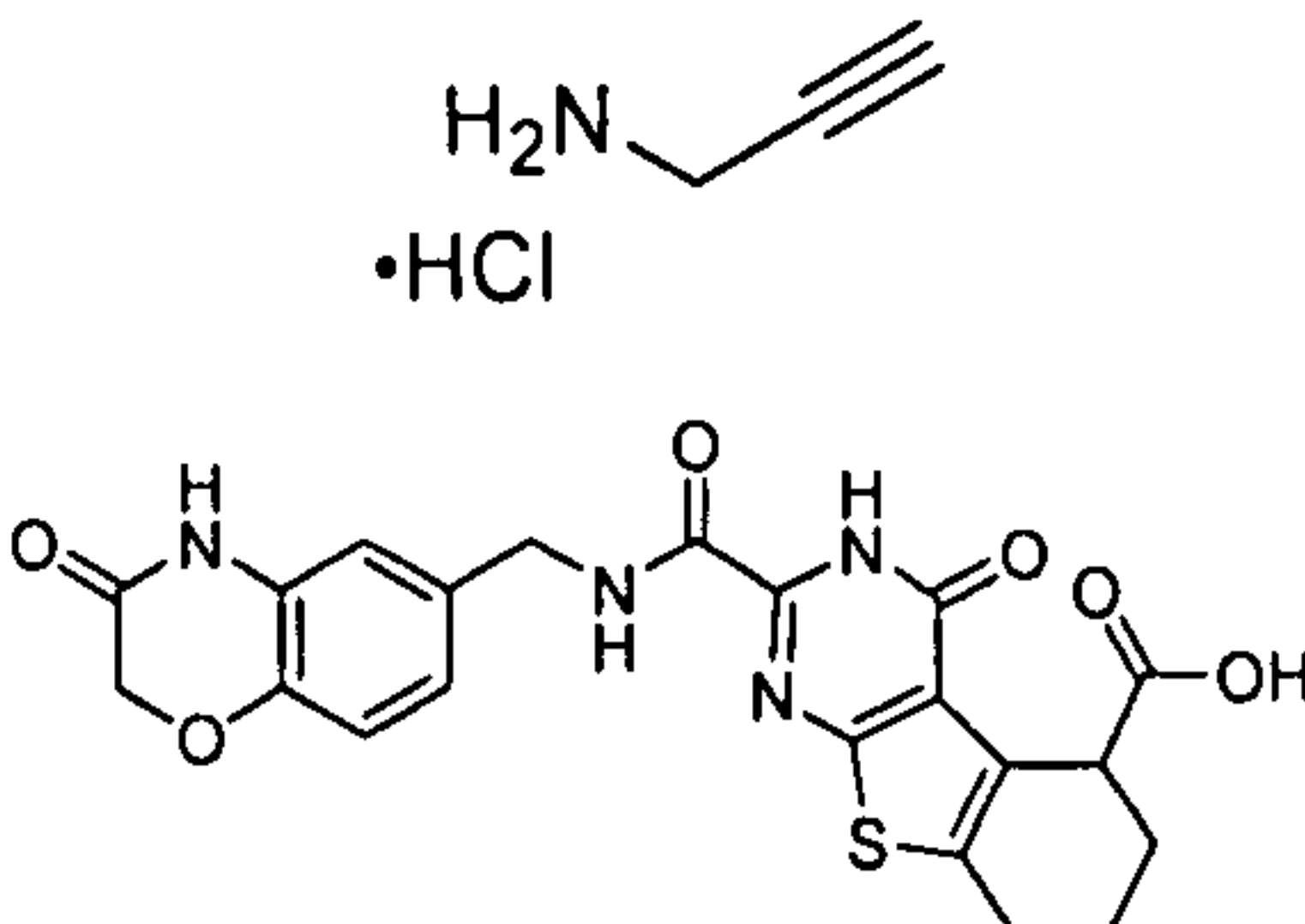
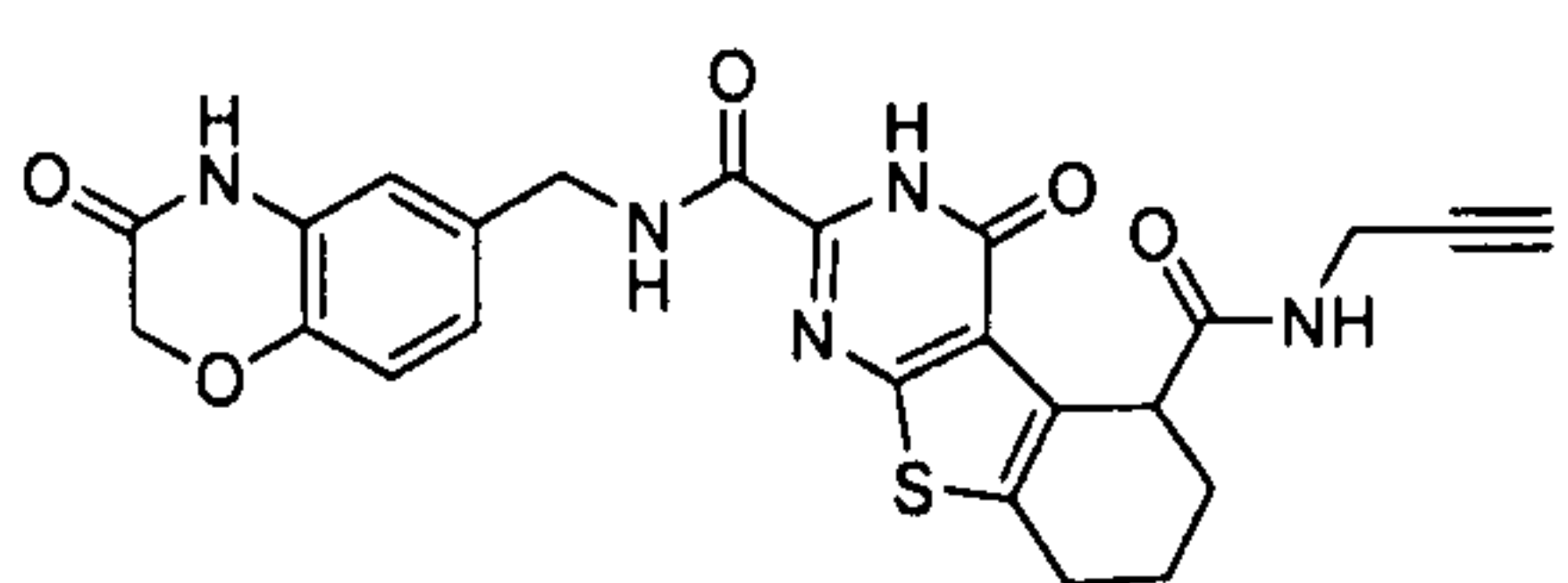
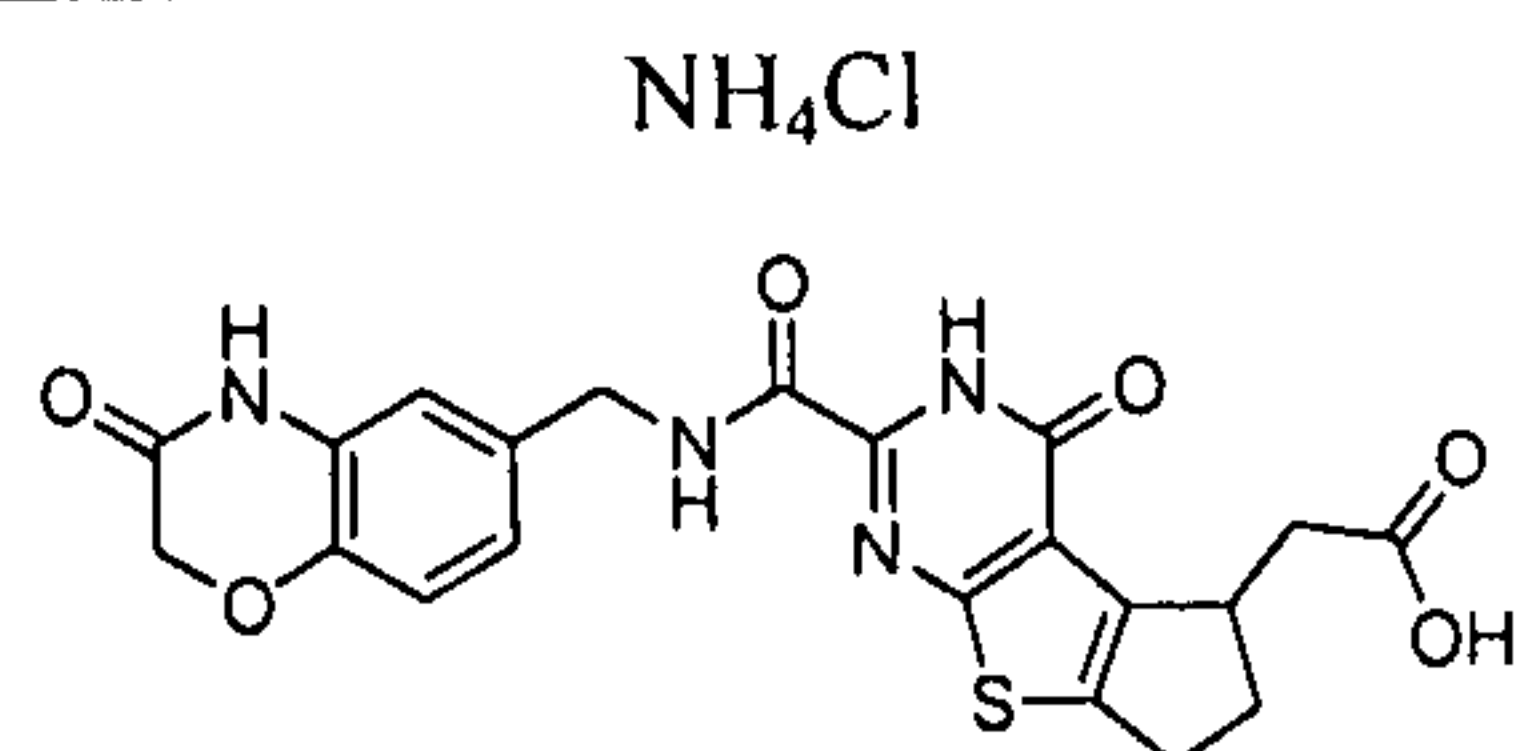
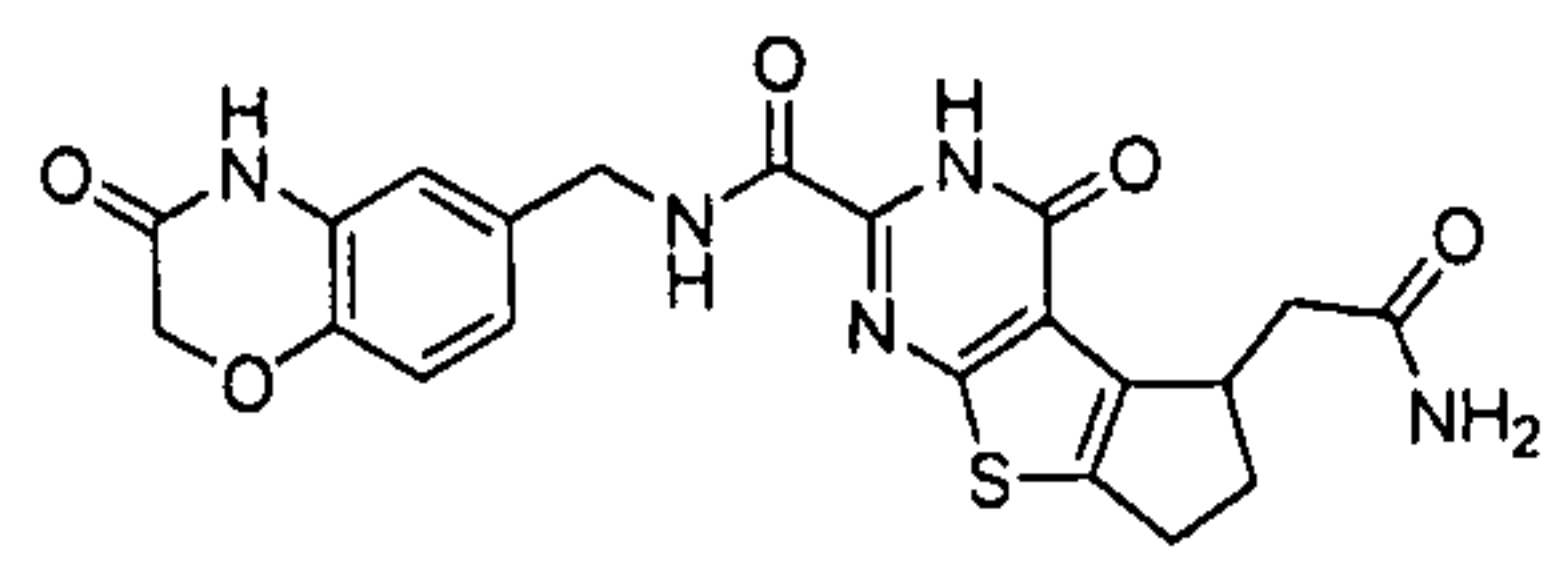
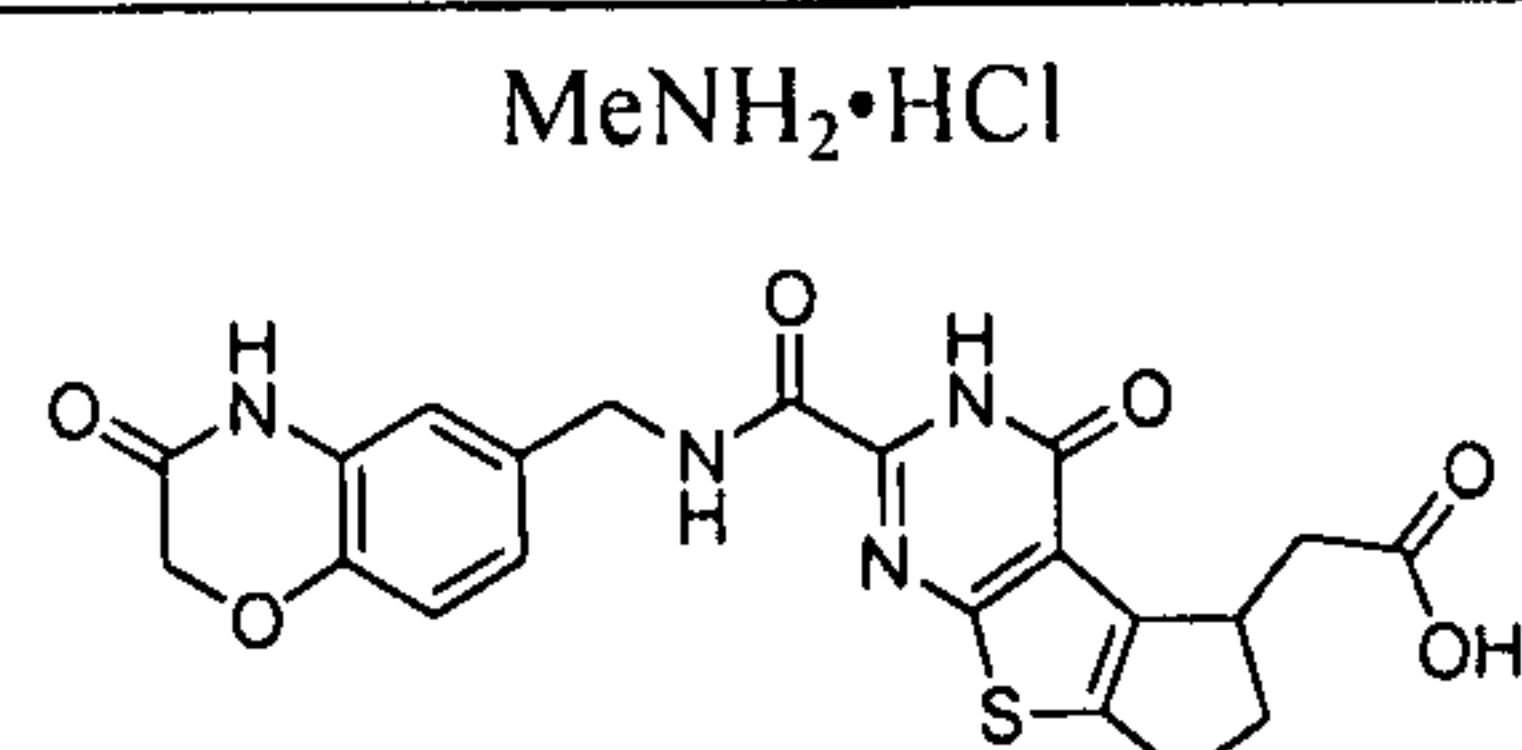
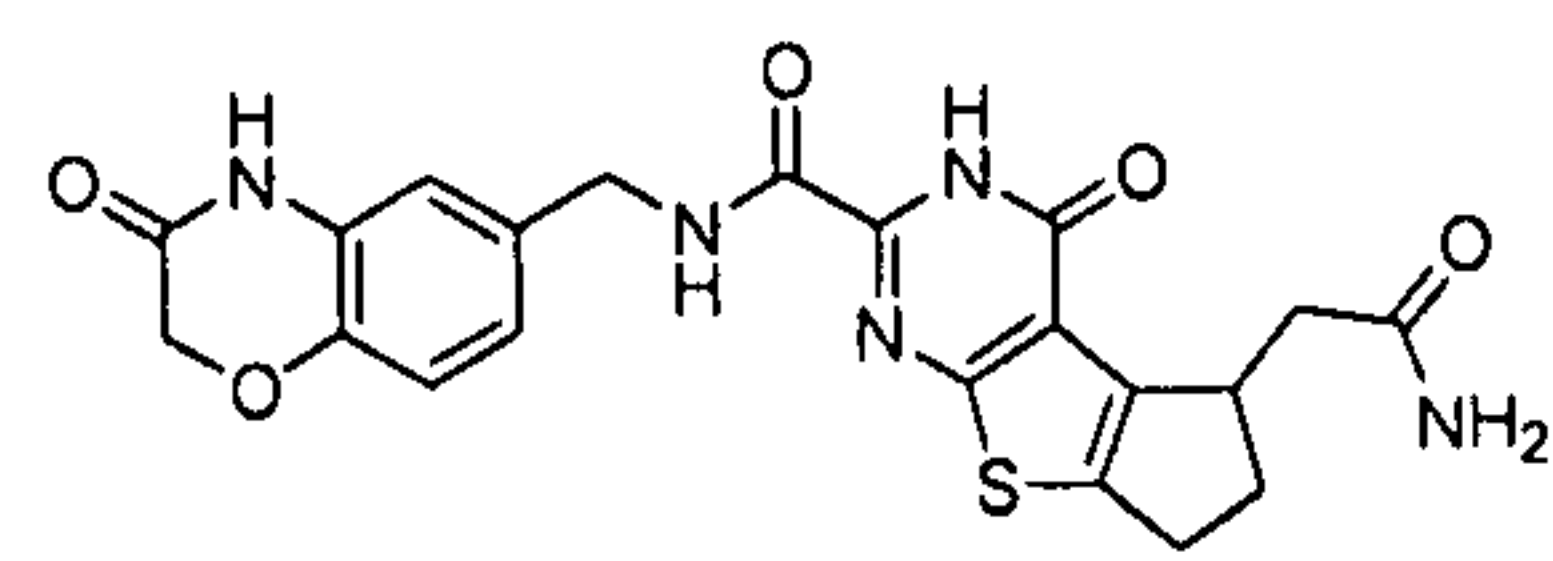
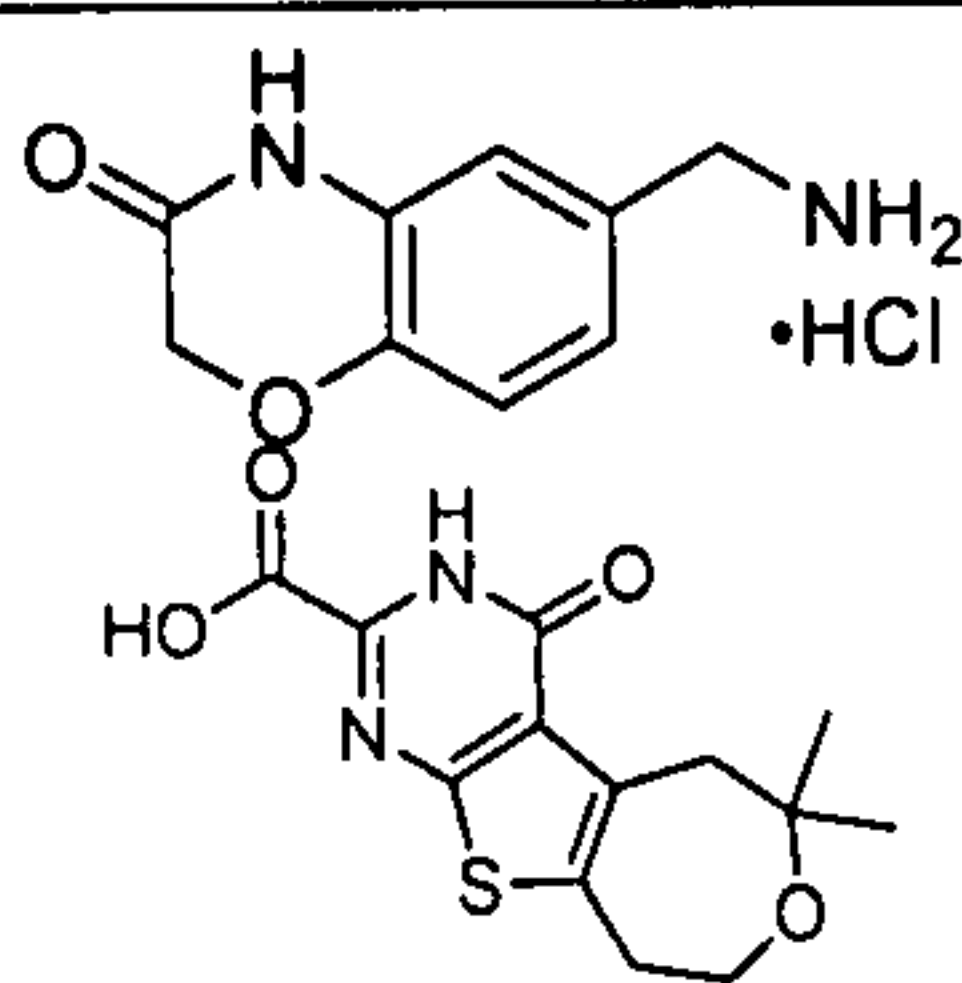
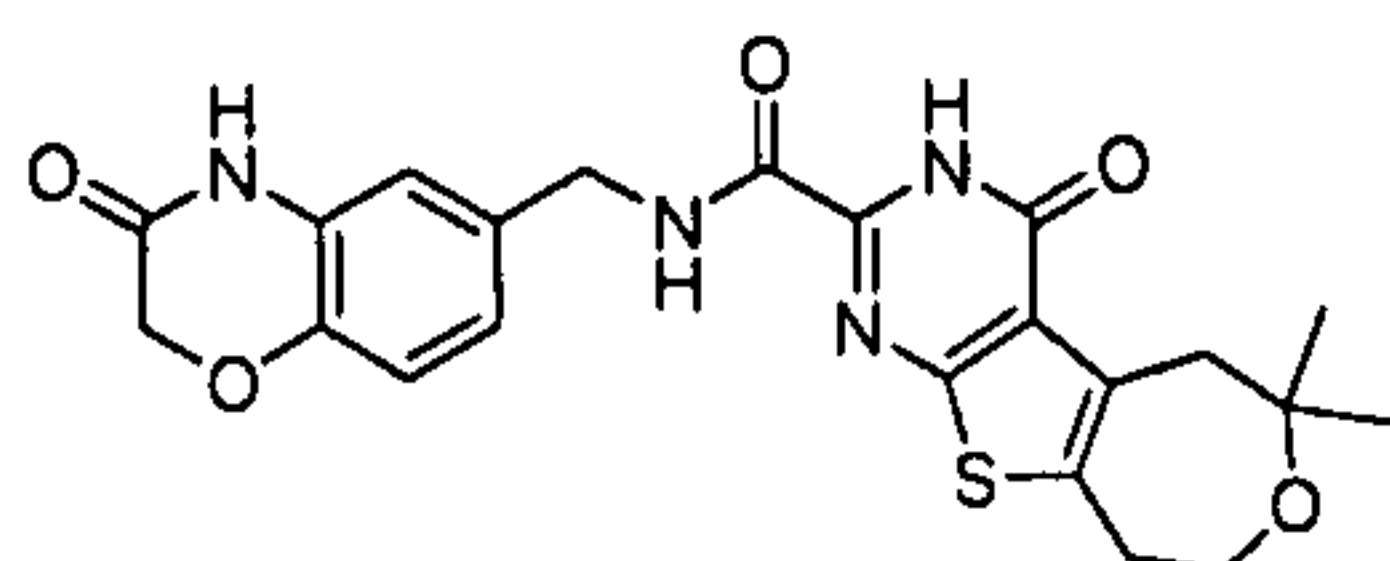
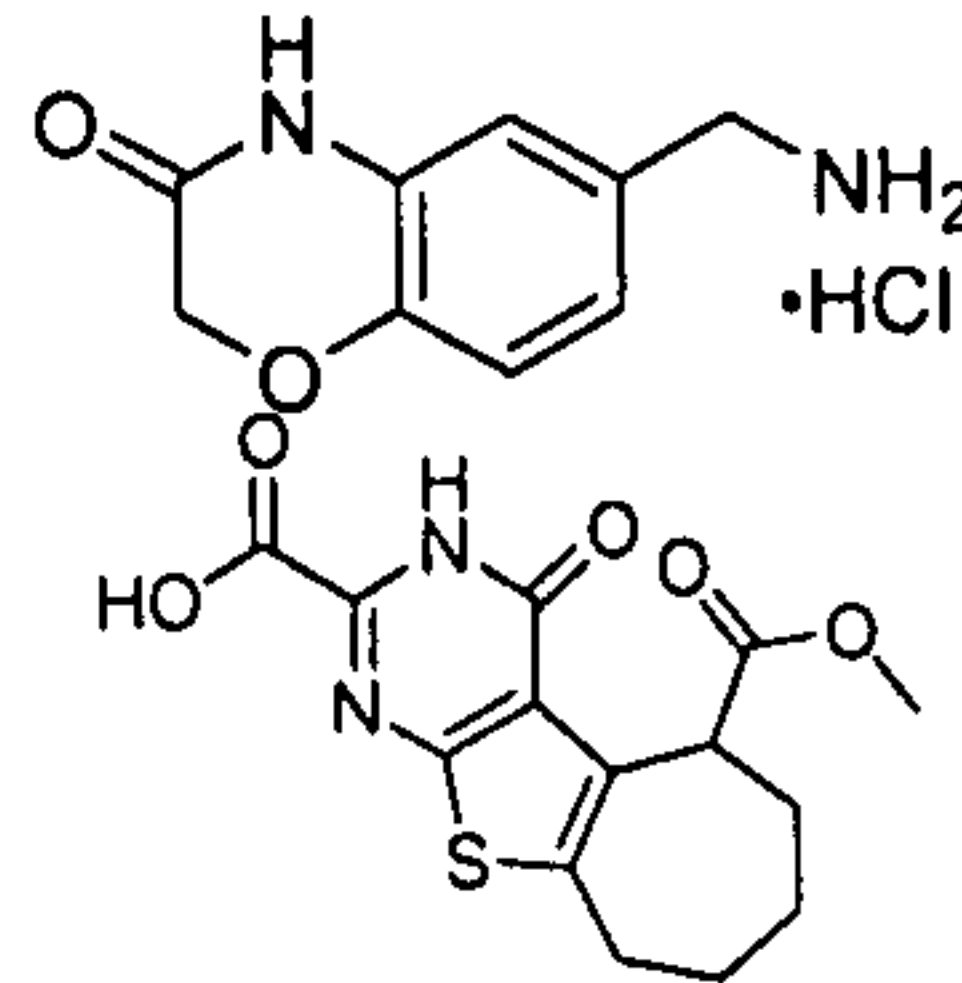
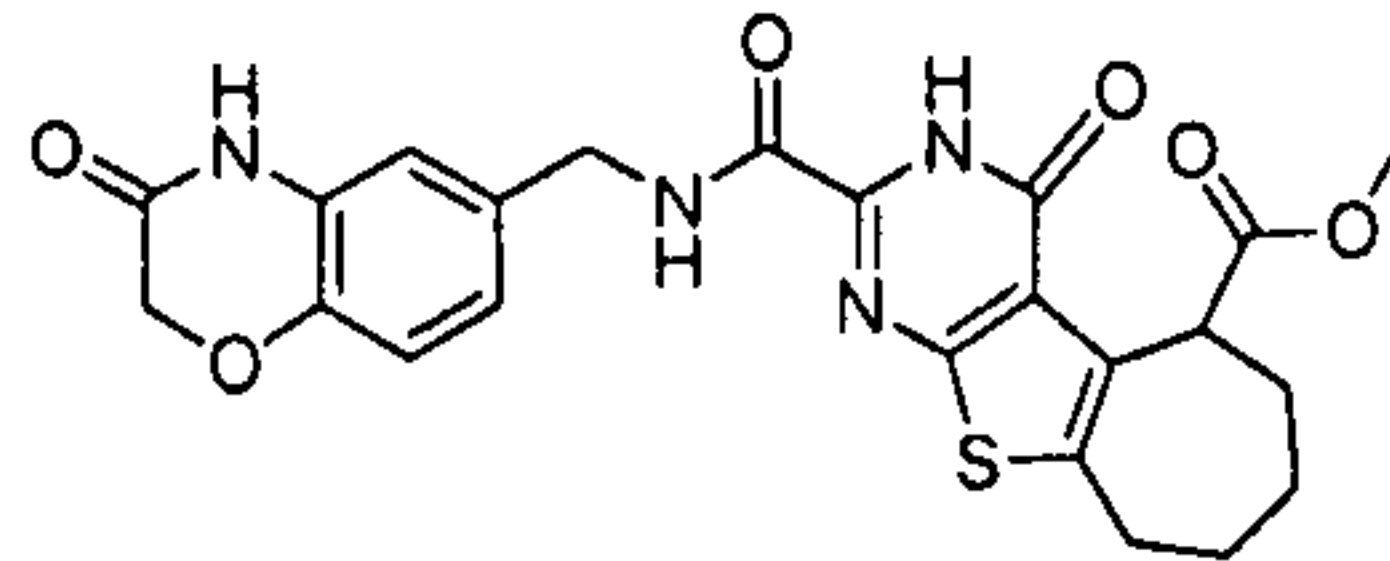
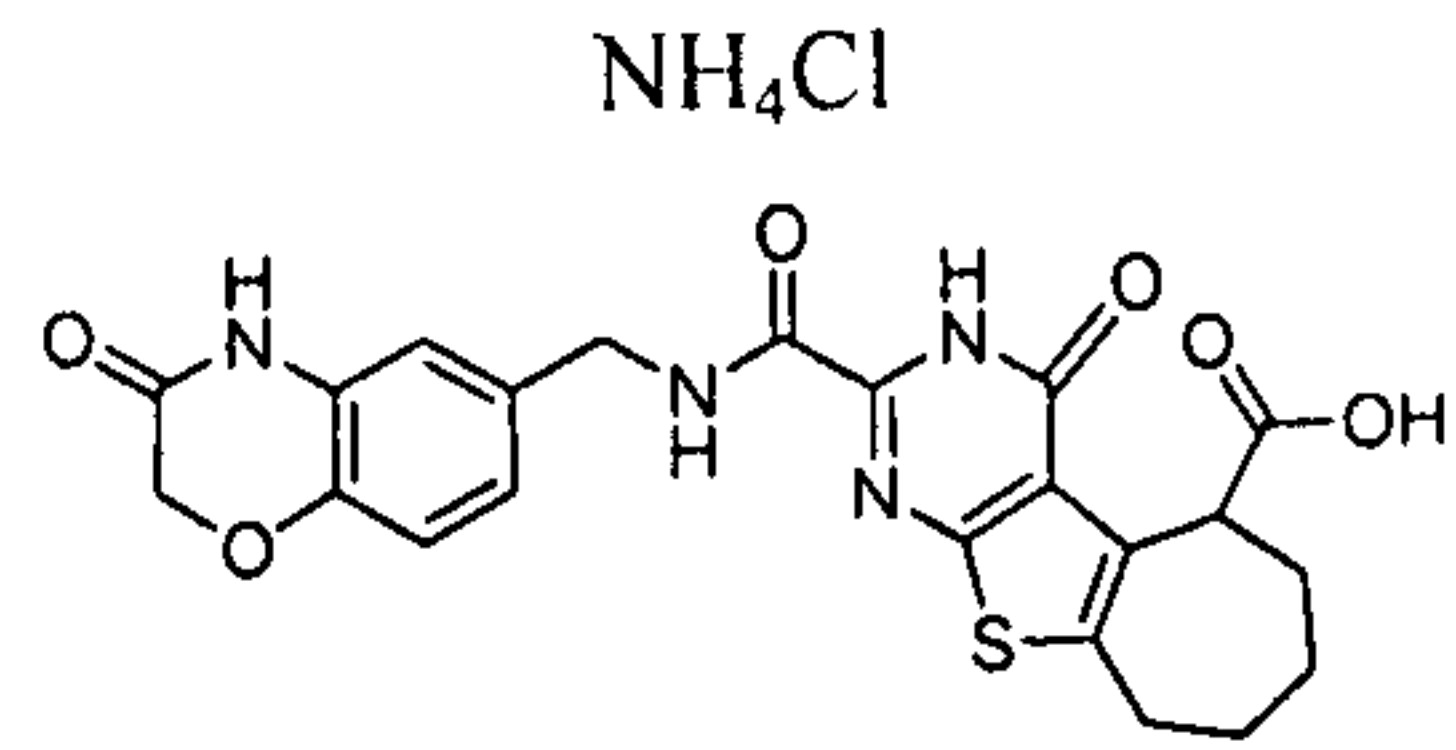
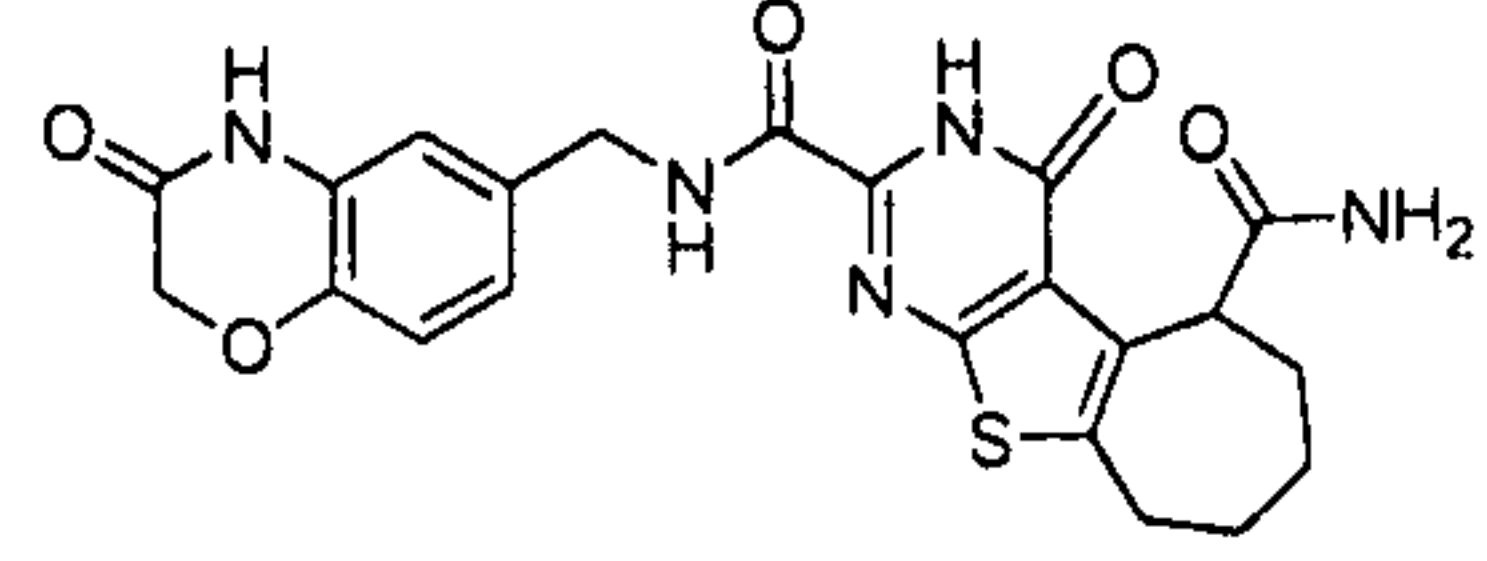
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/218 |     |    | A, 66%<br>[MH] <sup>+</sup> = 443 |
| 2/219 |   |  | A, 56%<br>[MH] <sup>+</sup> = 522 |
| 2/223 |  |  | A, 61%<br>[MH] <sup>+</sup> = 478 |
| 2/224 |  |  | A, 58%<br>[MH] <sup>+</sup> = 554 |
| 2/225 |  |  | A, 34%<br>[MH] <sup>+</sup> = 482 |

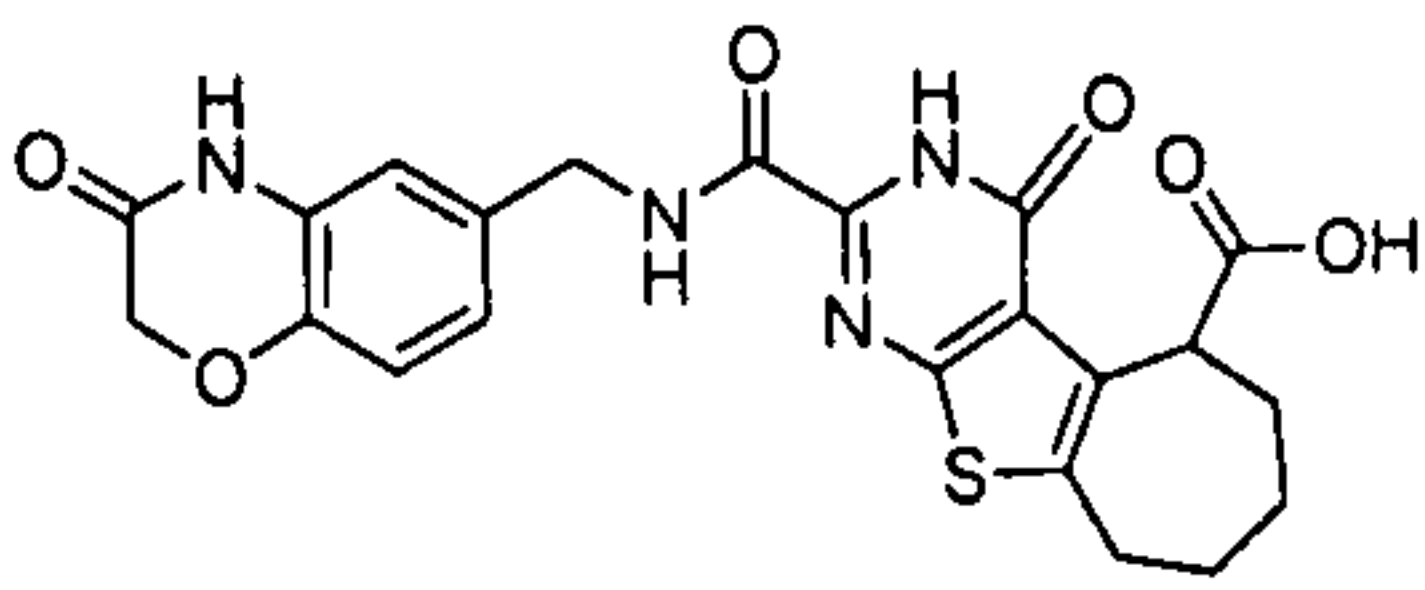
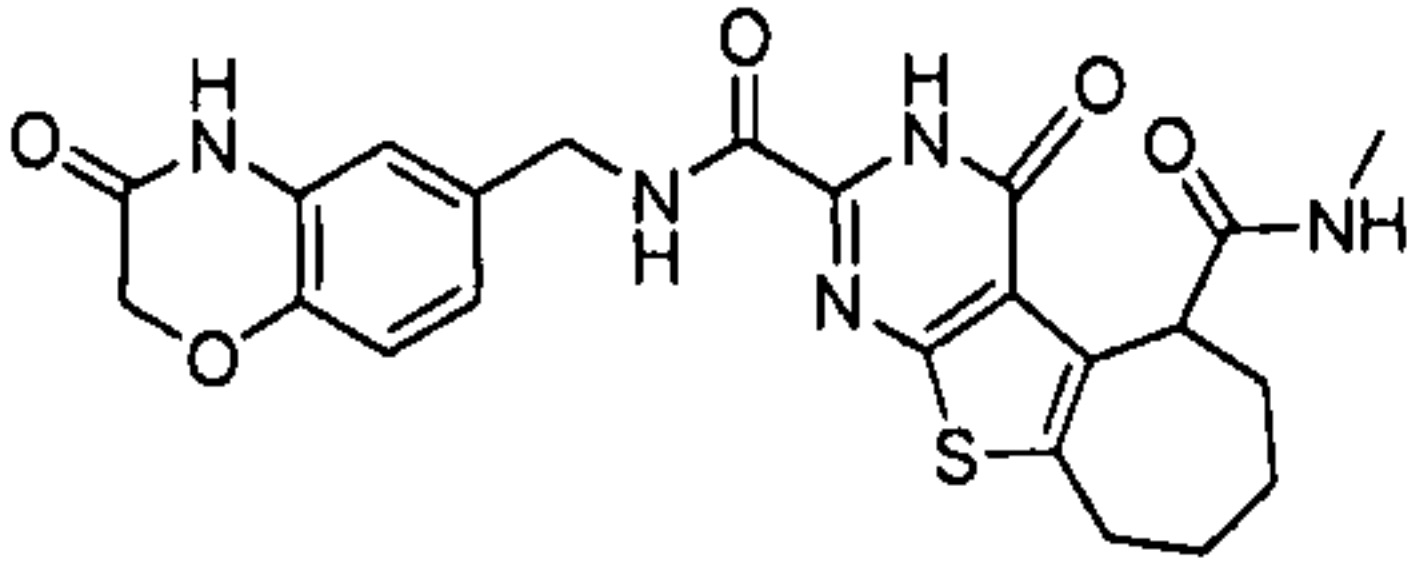
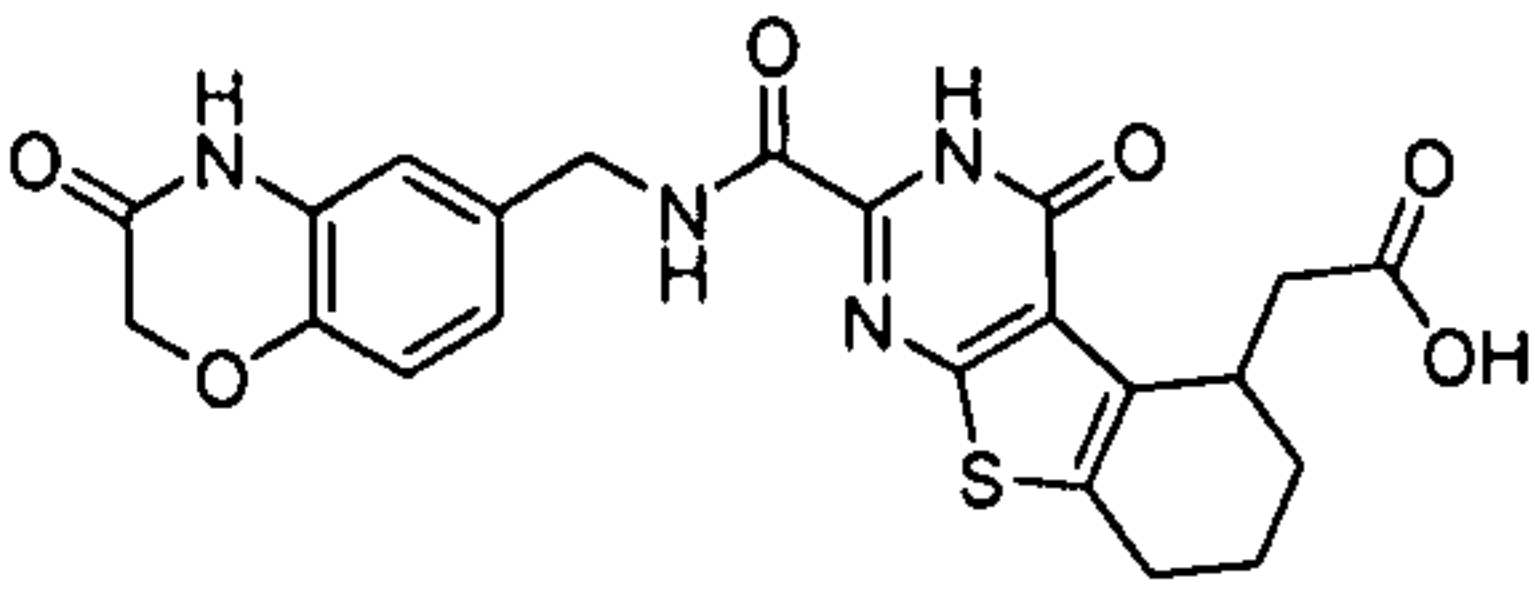
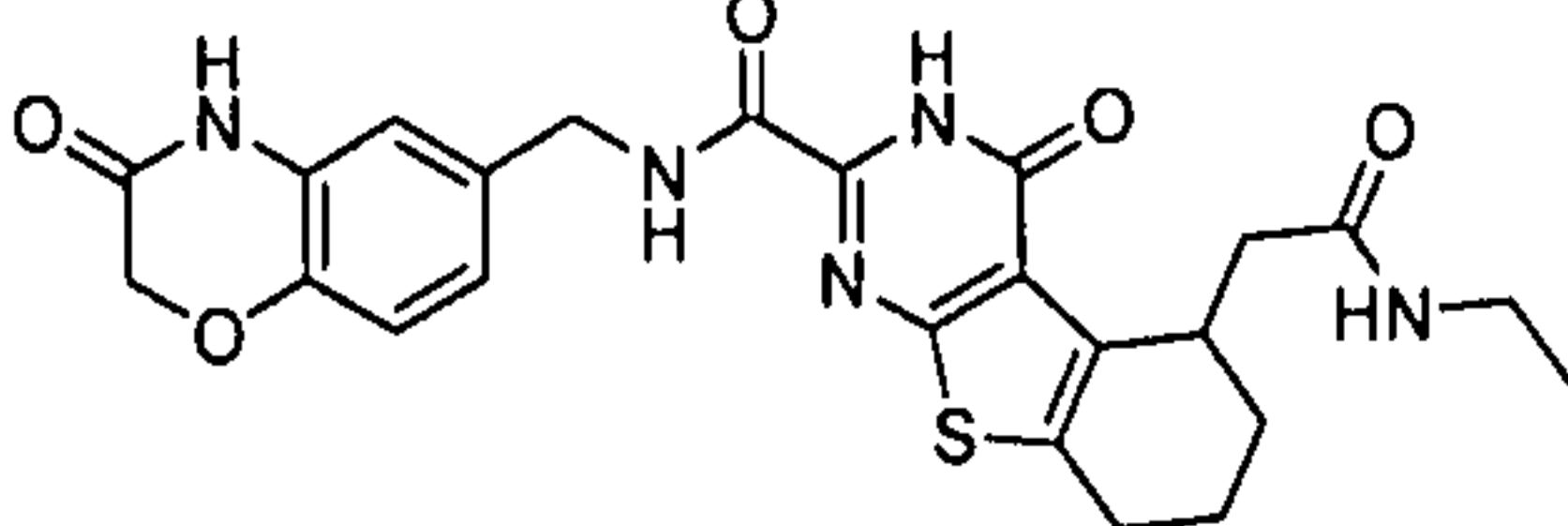
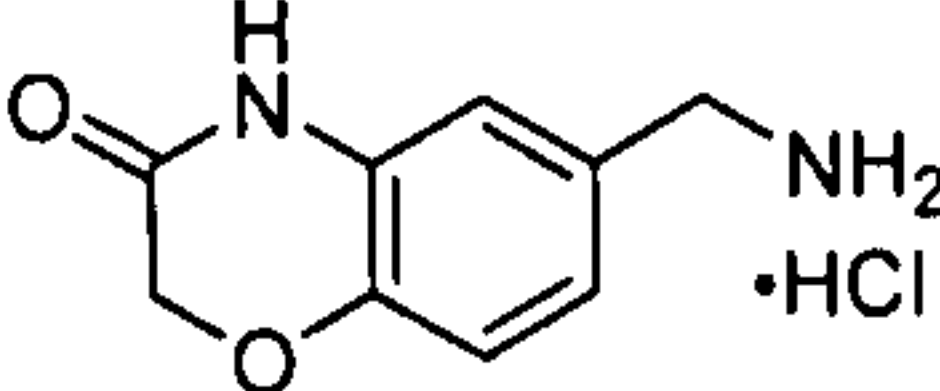
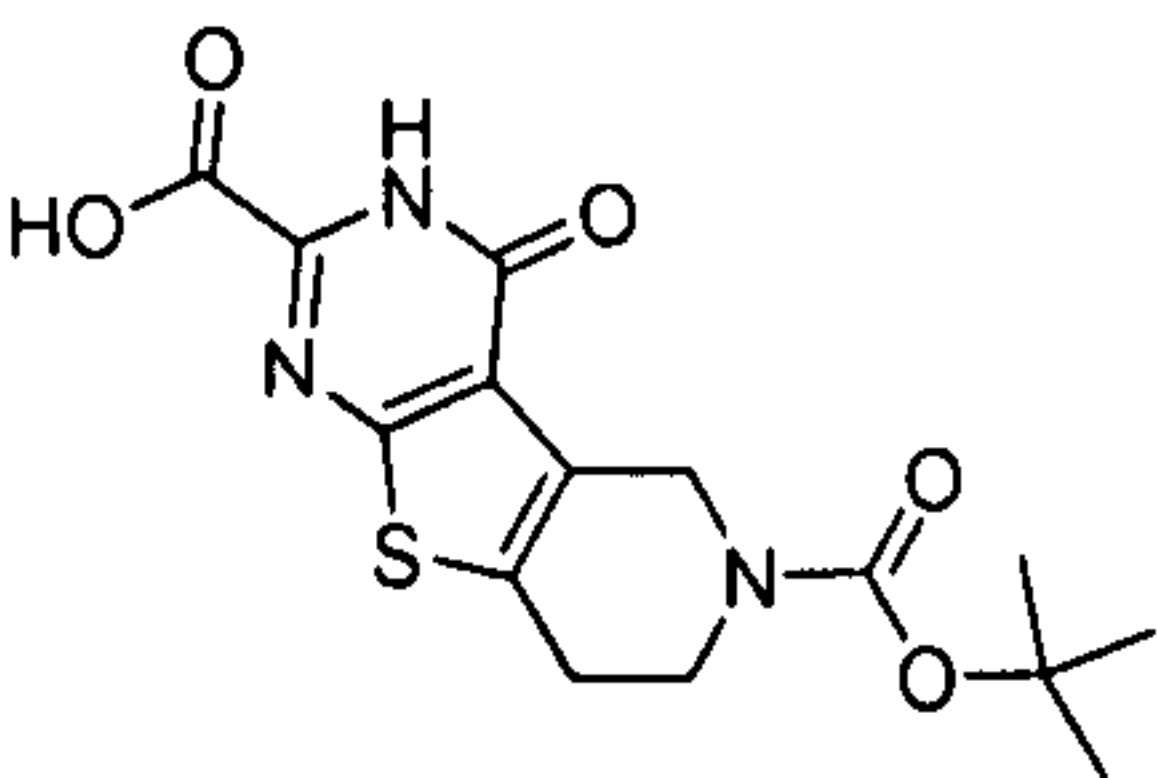
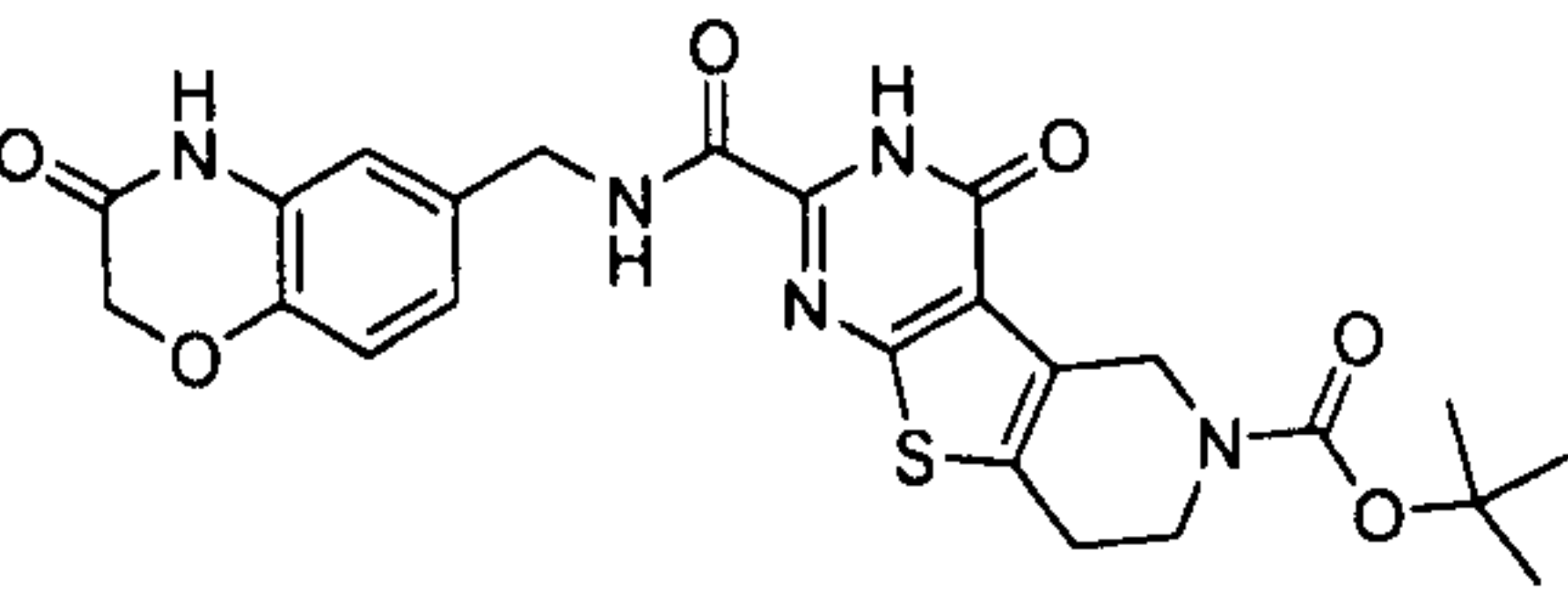
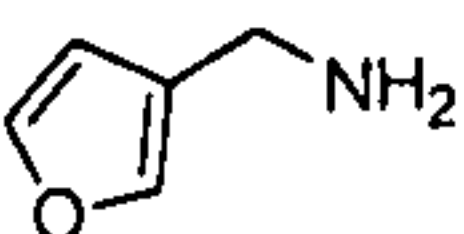
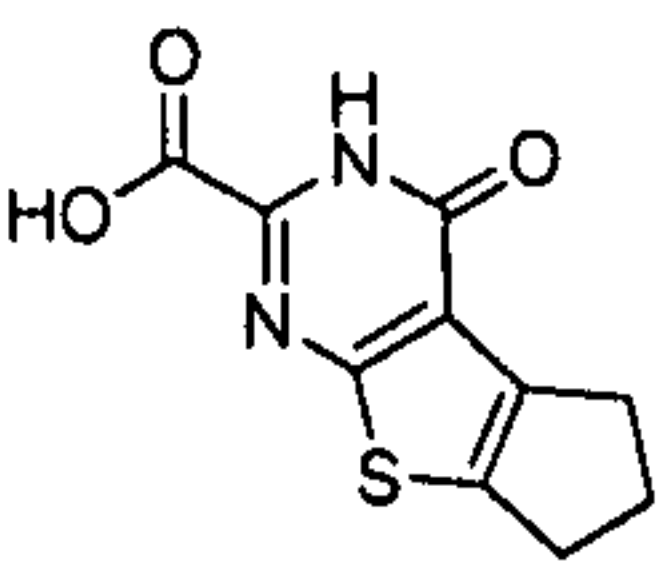
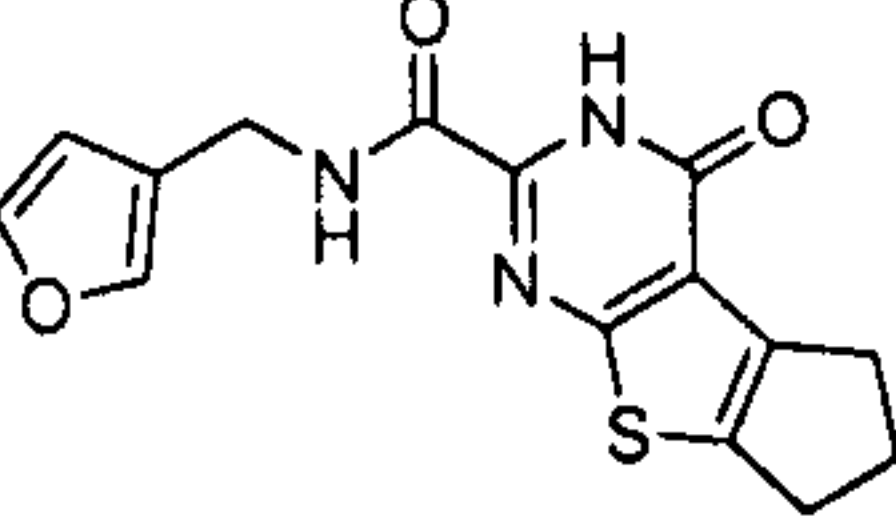
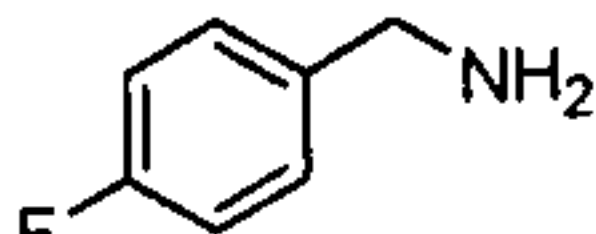
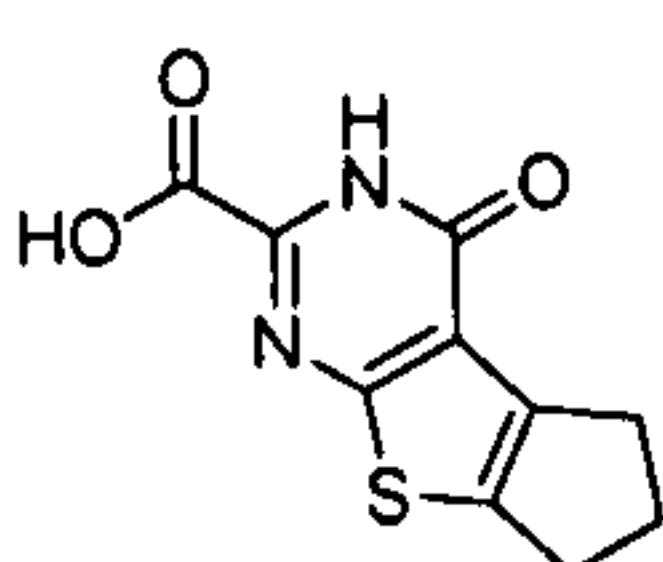
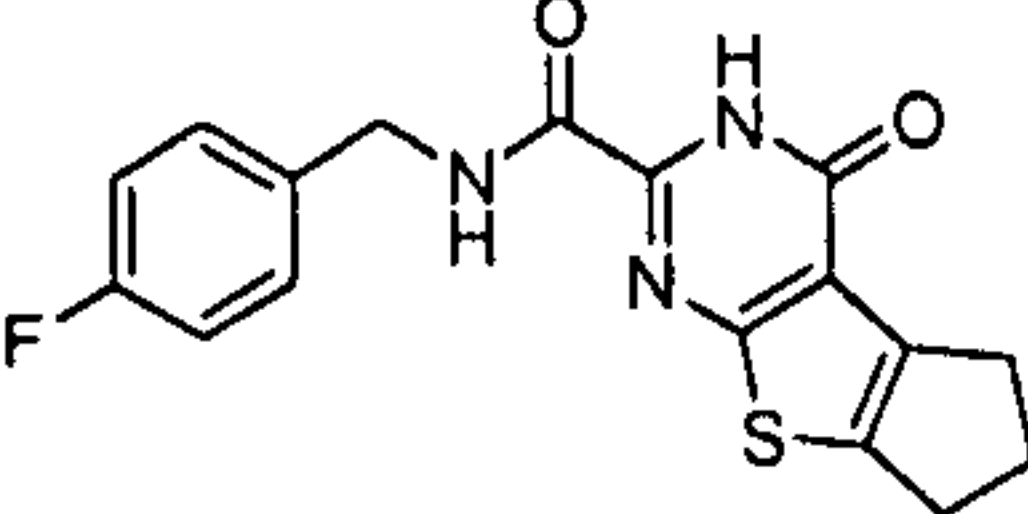
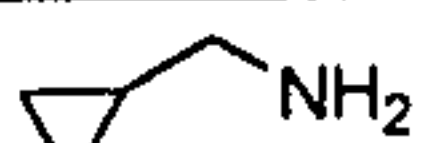
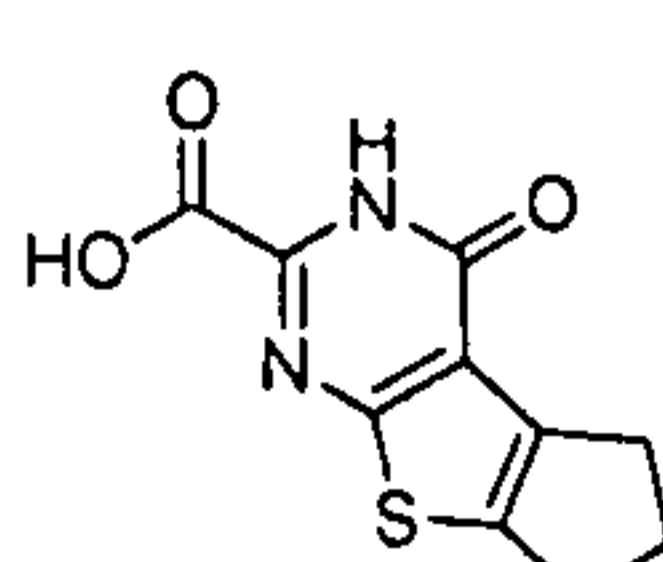
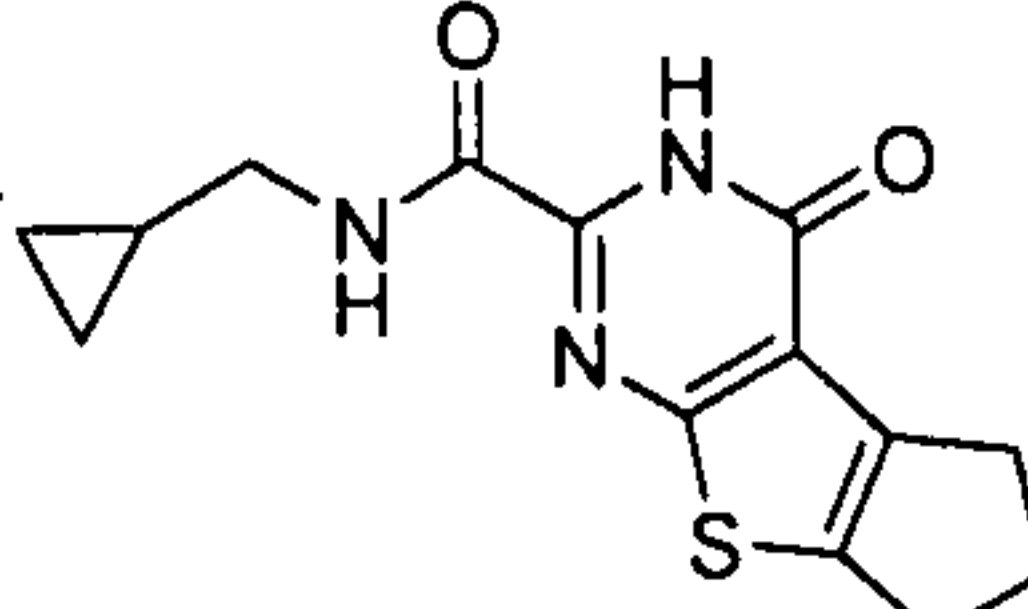
| Ex. # | amine, acid                                                                                                                    | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/230 |                                               |    | A, 48%<br>[MH] <sup>+</sup> = 534 |
| 2/231 |                                            |  | A, 87%<br>[MH] <sup>+</sup> = 496 |
| 2/232 |  <p>NH<sub>3</sub> (0.5 M in dioxanne)</p> |  | A, 70%<br>[MH] <sup>+</sup> = 519 |
| 2/236 |                                             |  | A, 98%<br>[MH] <sup>+</sup> = 497 |
| 2/237 |  <p>MeNH<sub>2</sub>·HCl</p>               |  | A, 78%<br>[MH] <sup>+</sup> = 482 |

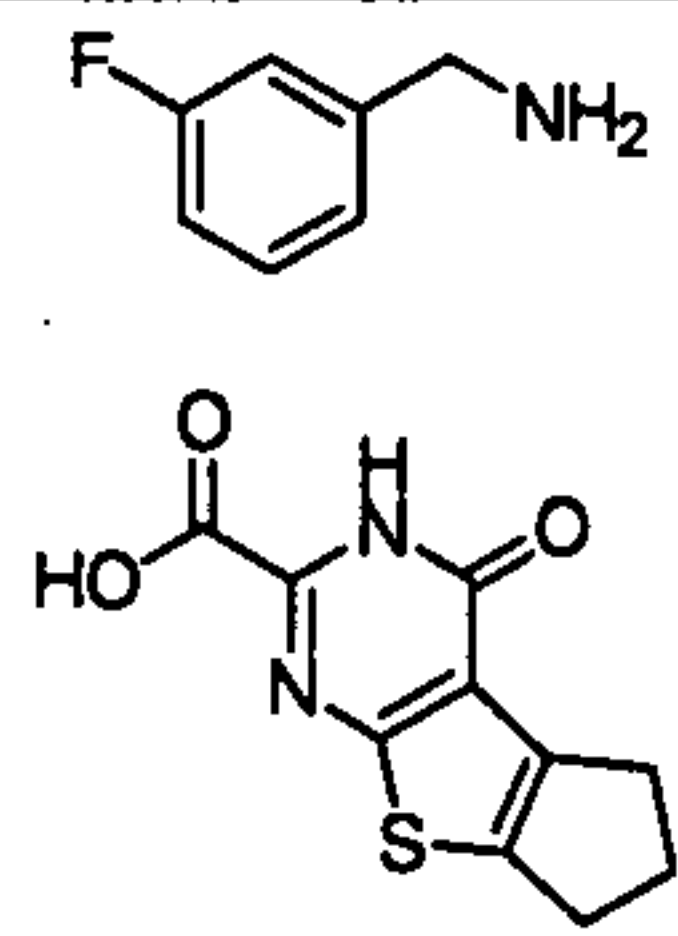
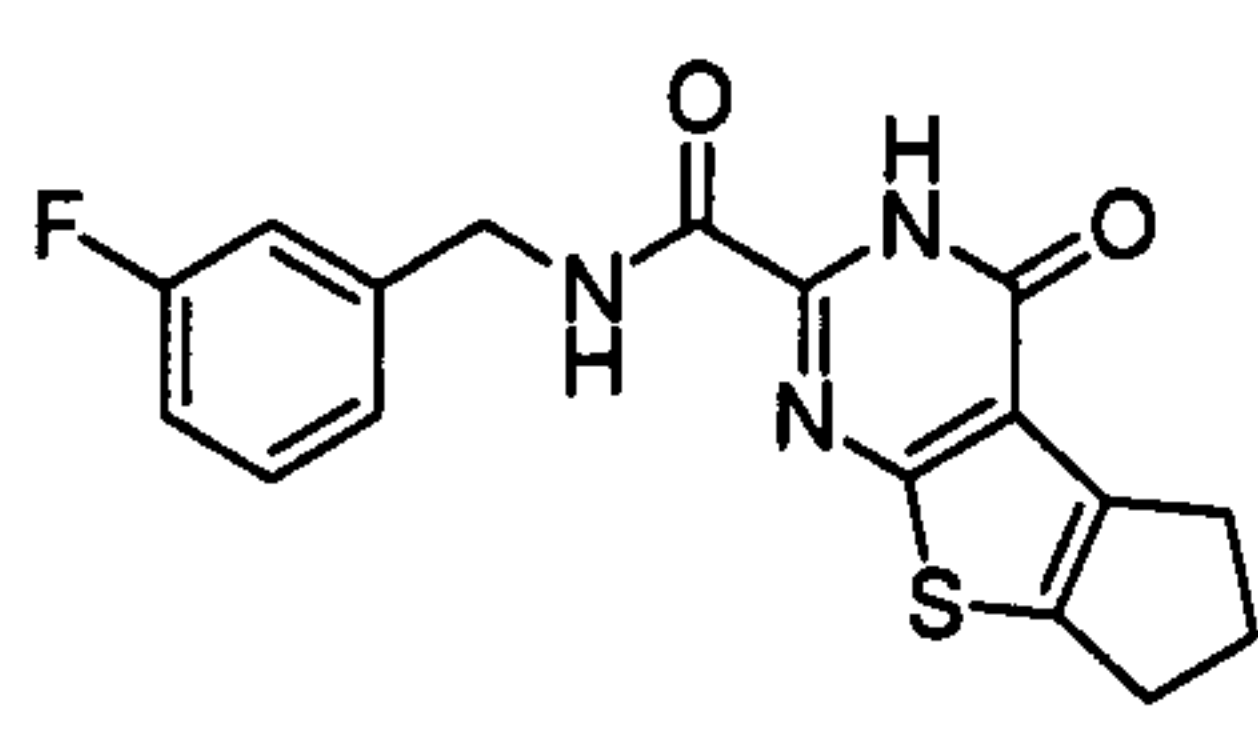
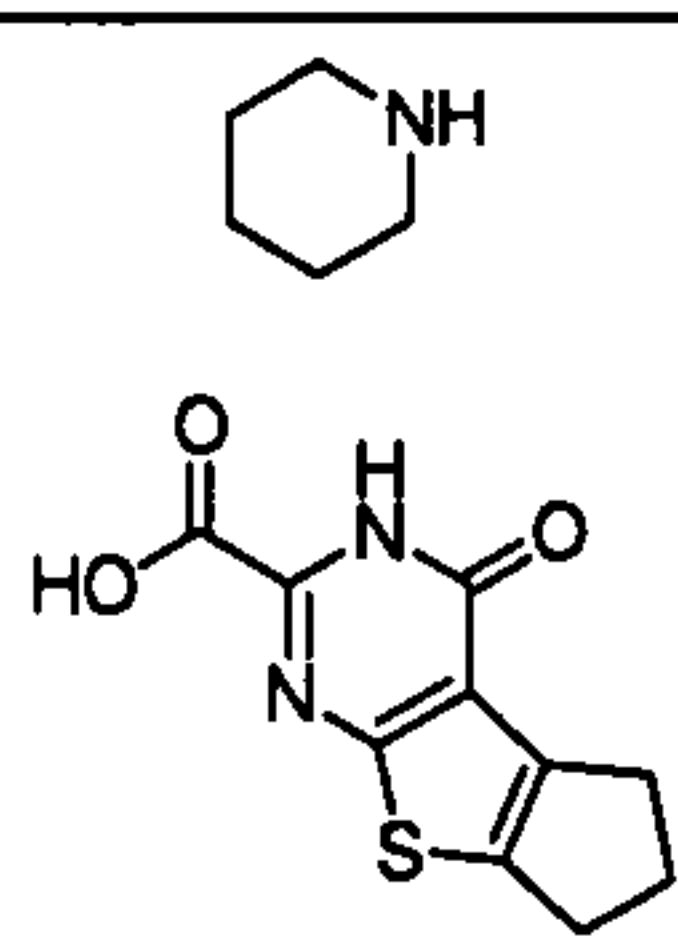
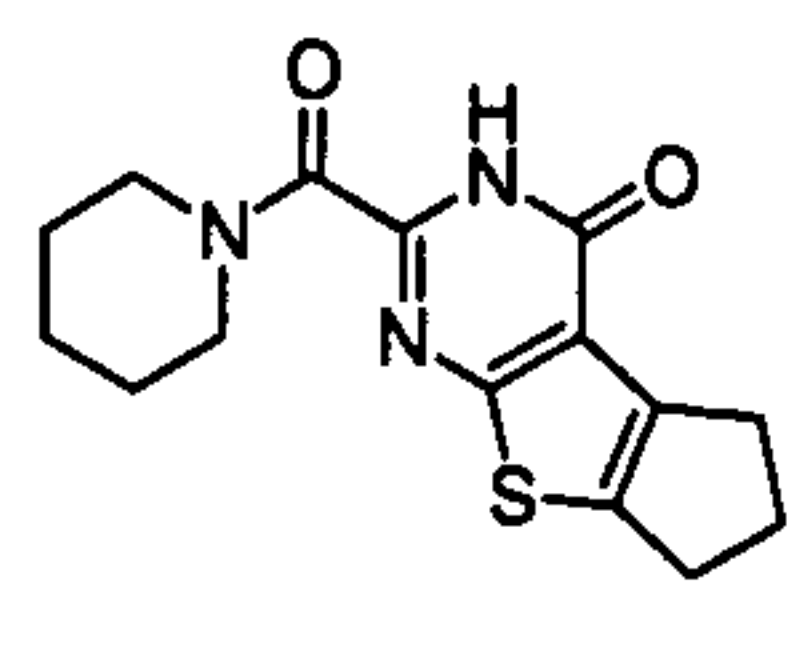
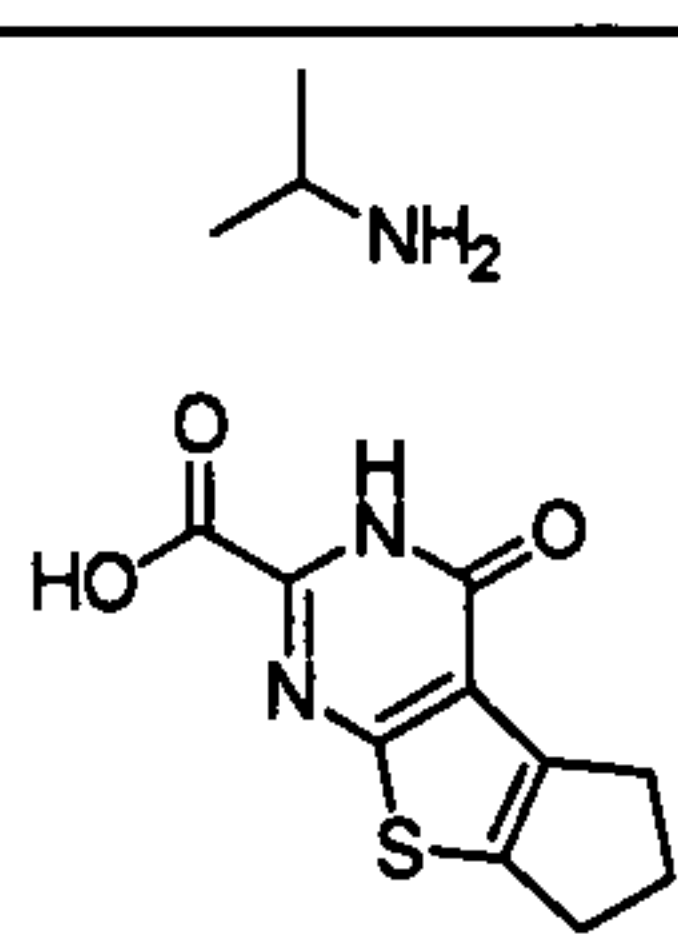
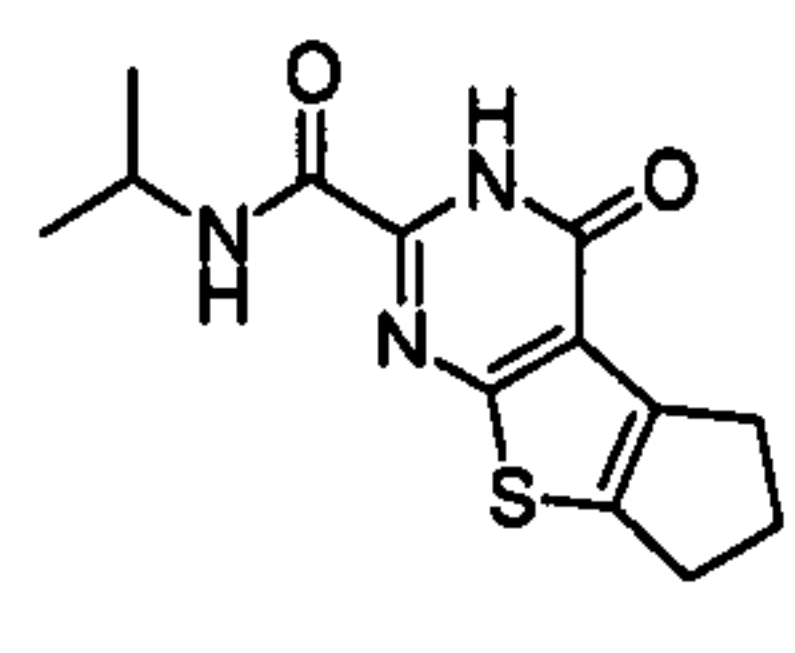
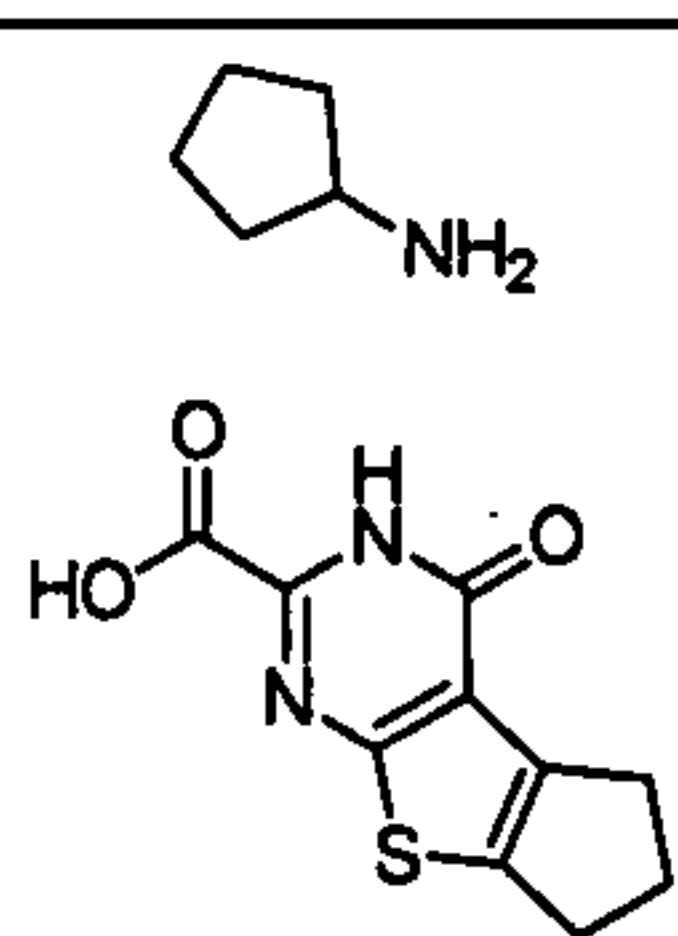
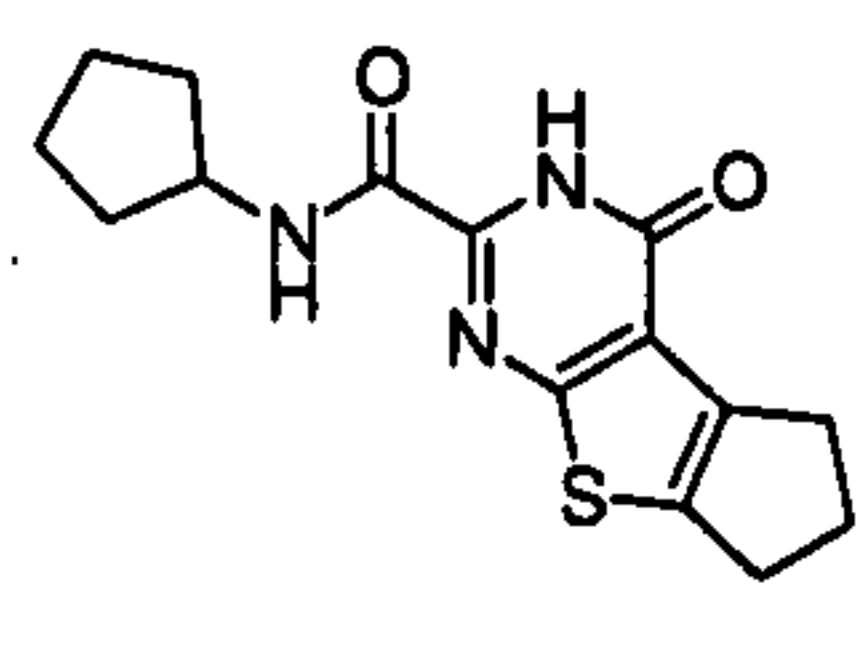
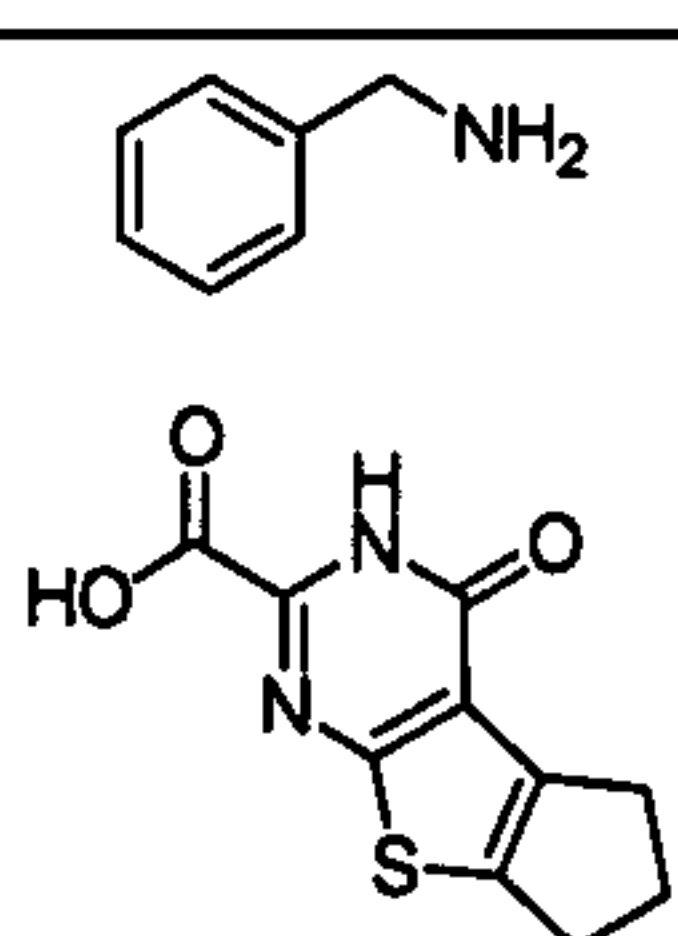
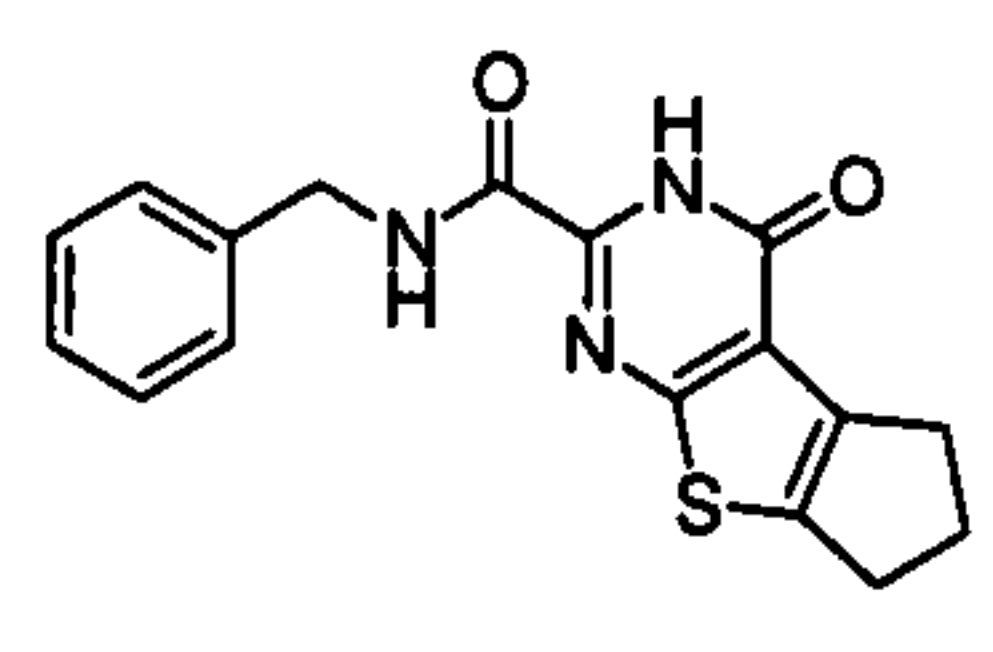
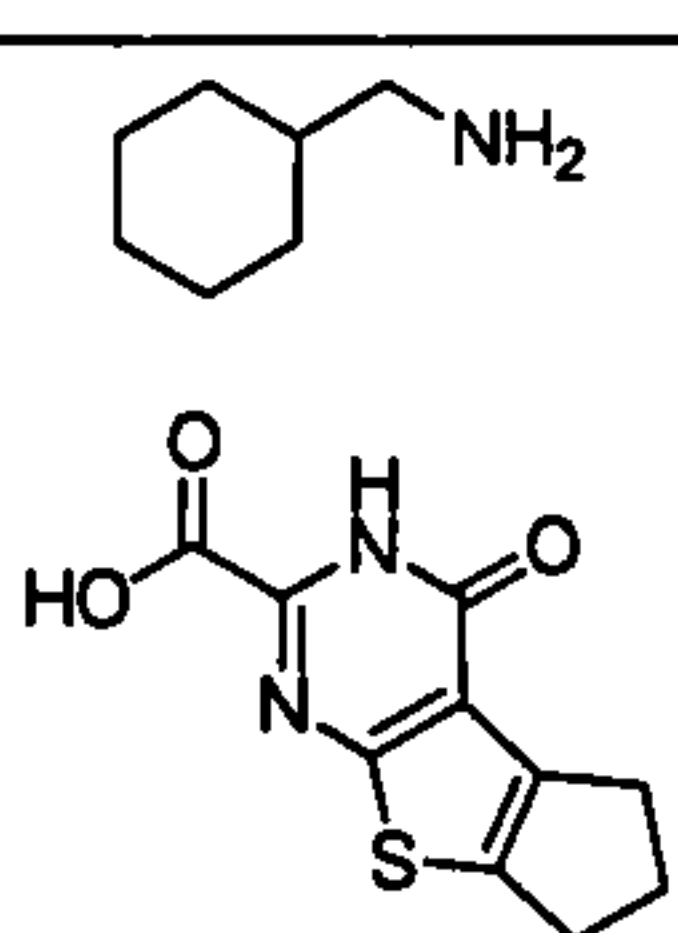
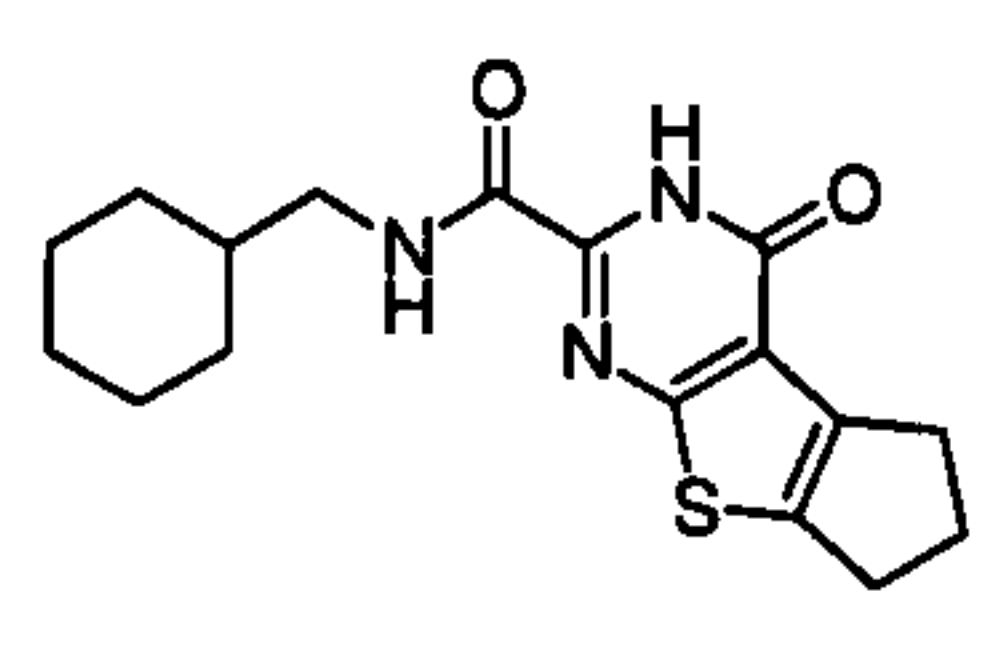
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/238 |    |    | A, 80%<br>[MH] <sup>+</sup> = 582 |
| 2/239 |    |   | A, 79%<br>[MH] <sup>+</sup> = 468 |
| 2/240 |  |  | A, 69%<br>[MH] <sup>+</sup> = 468 |
| 2/245 |   |  | A, 26%<br>[MH] <sup>+</sup> = 391 |
| 2/246 |   |  | A, 10%<br>[MH] <sup>+</sup> = 391 |

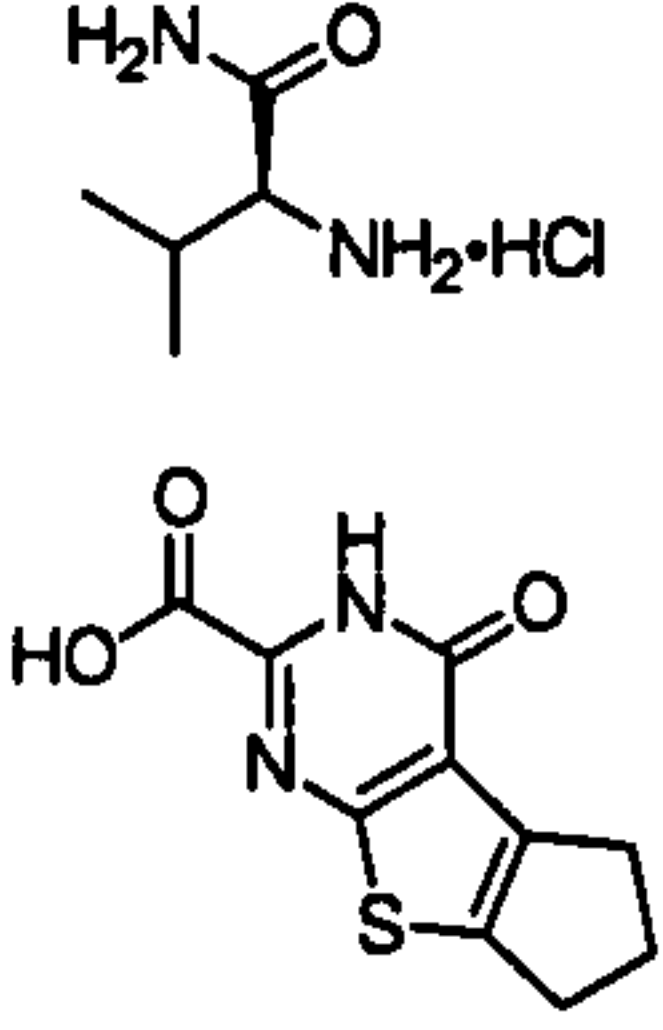
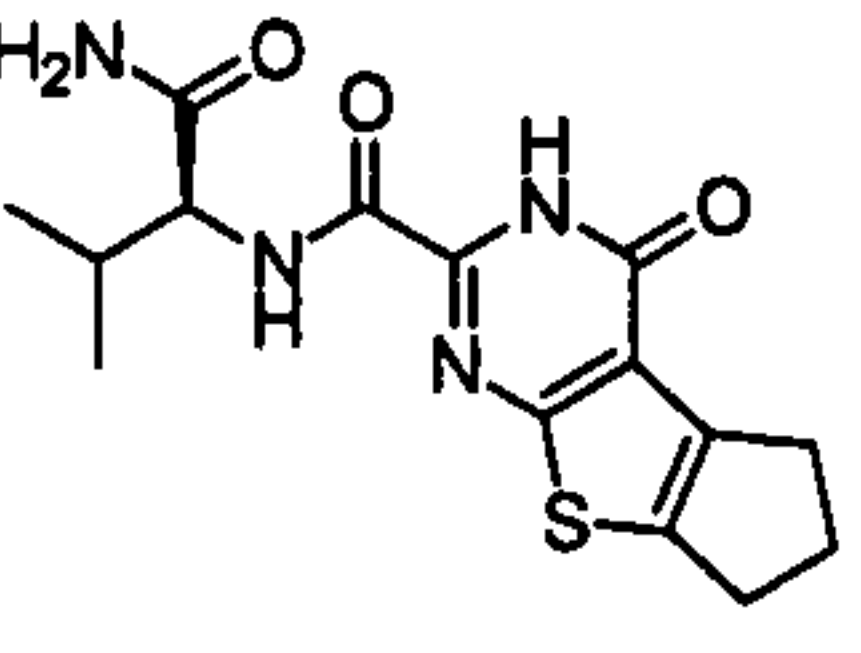
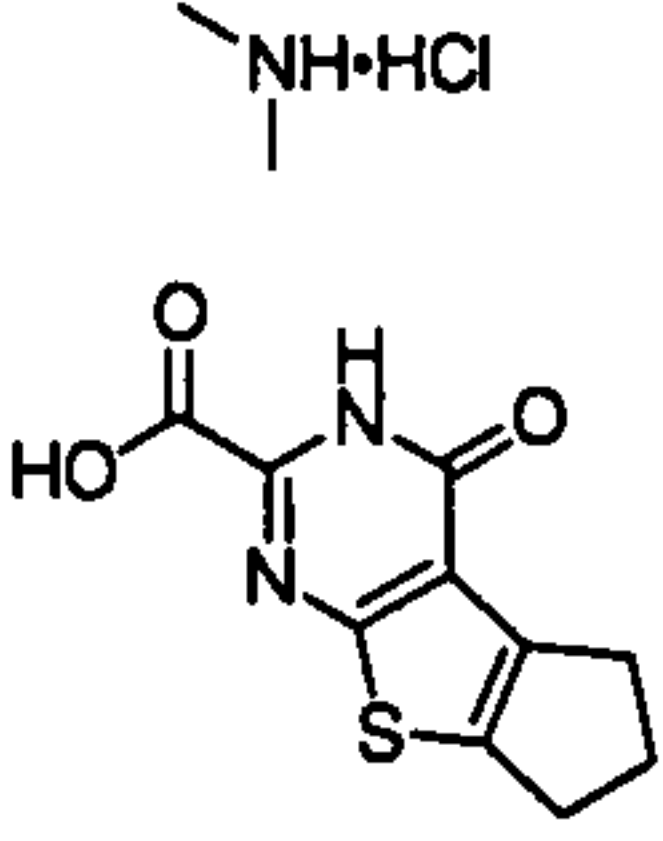
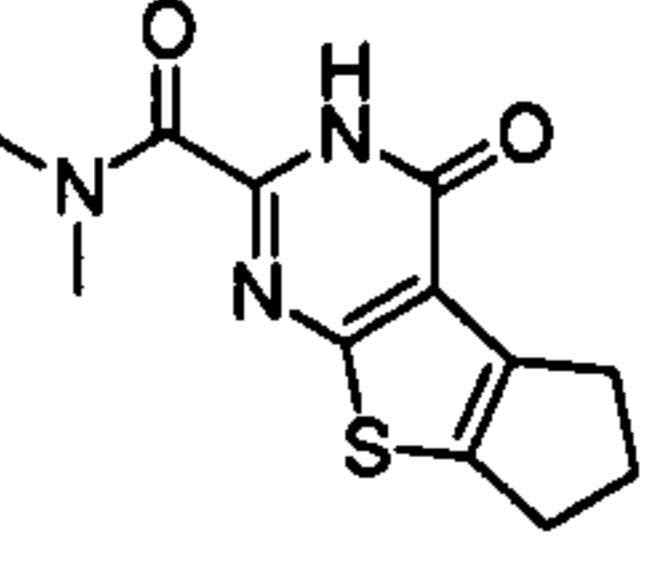
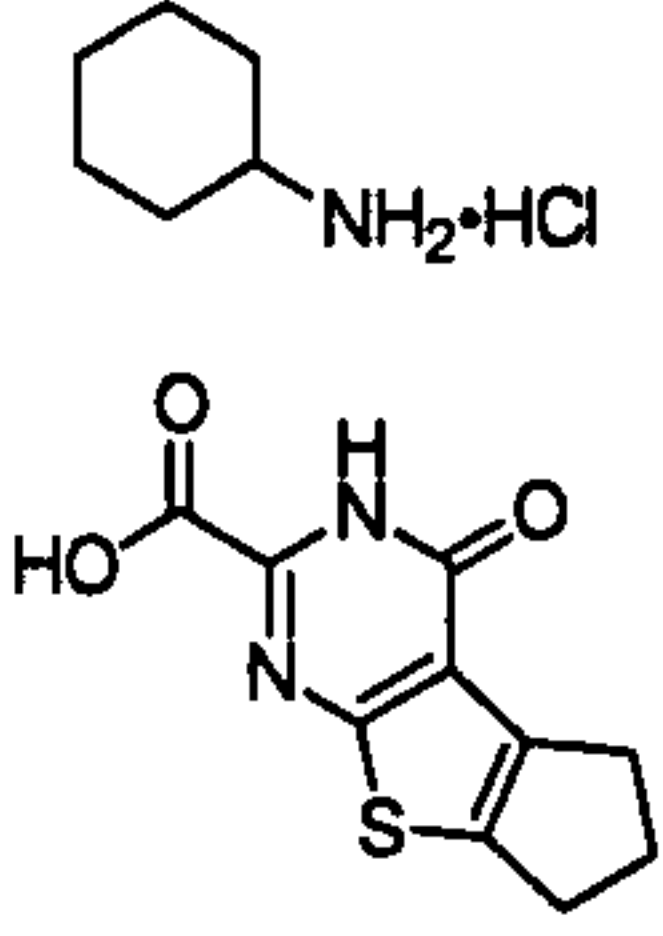
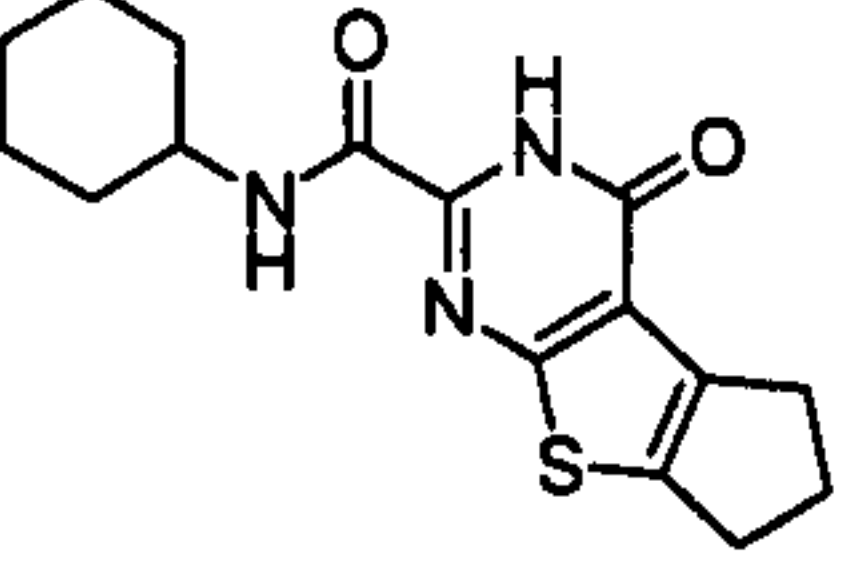
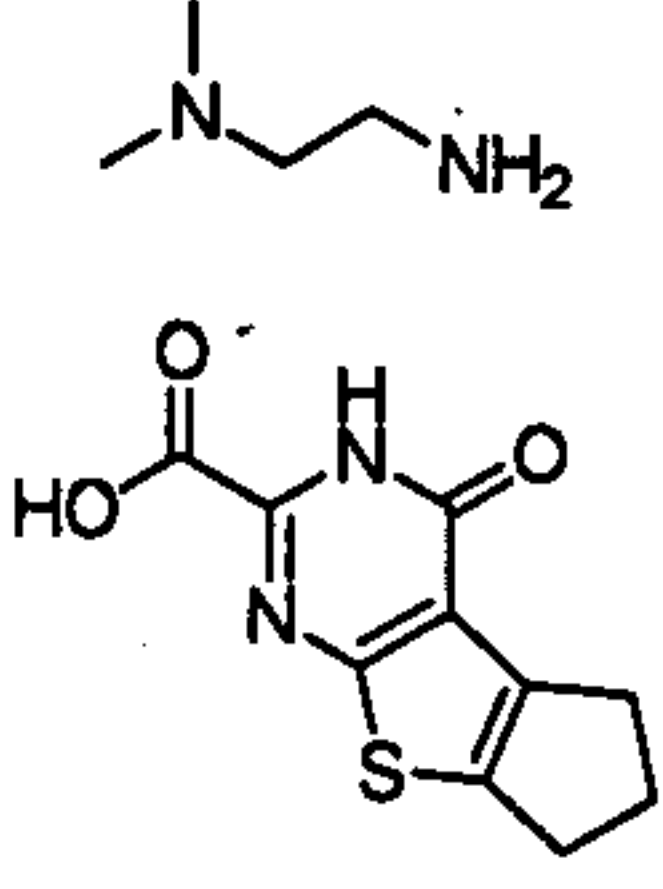
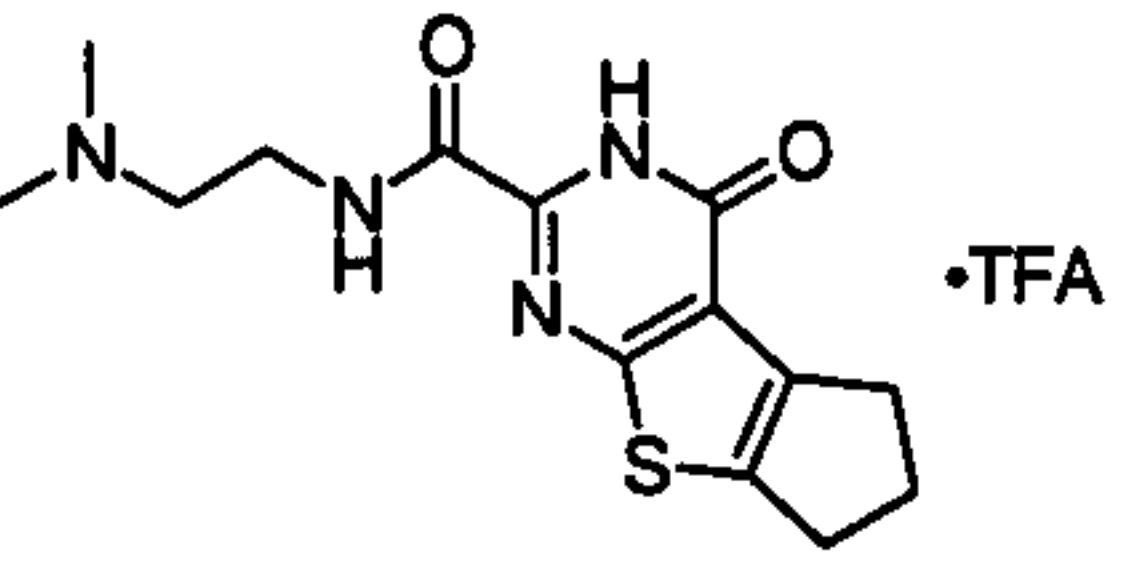
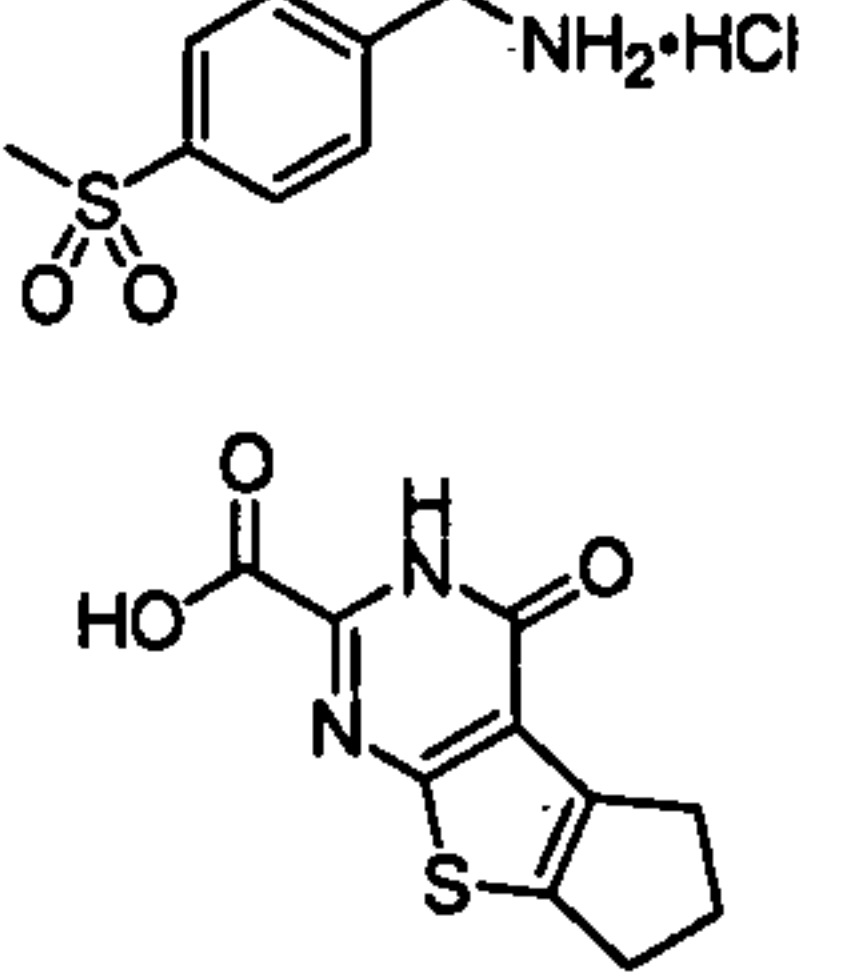
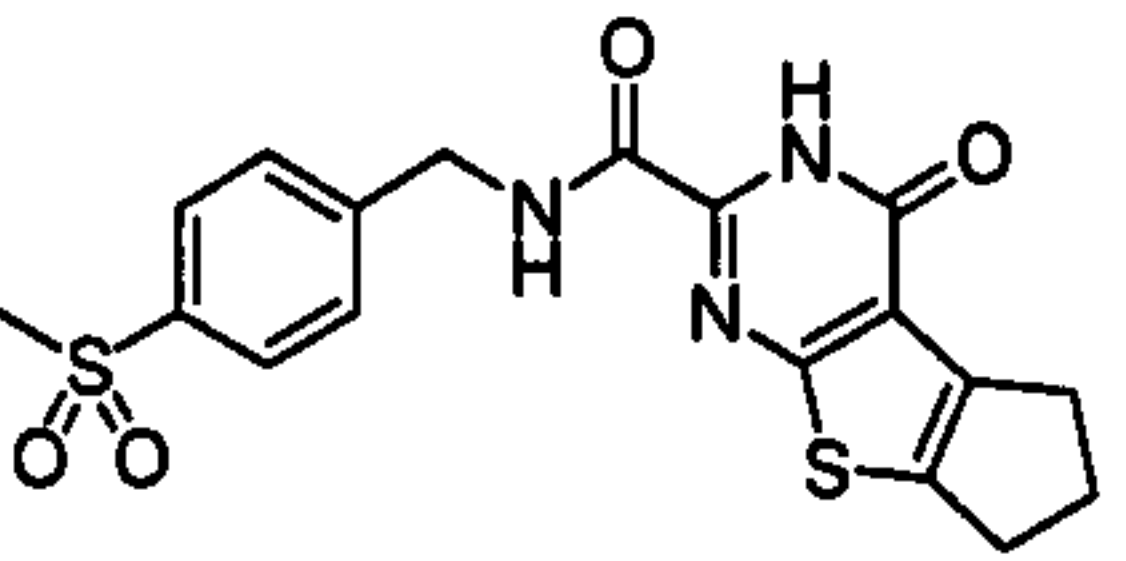
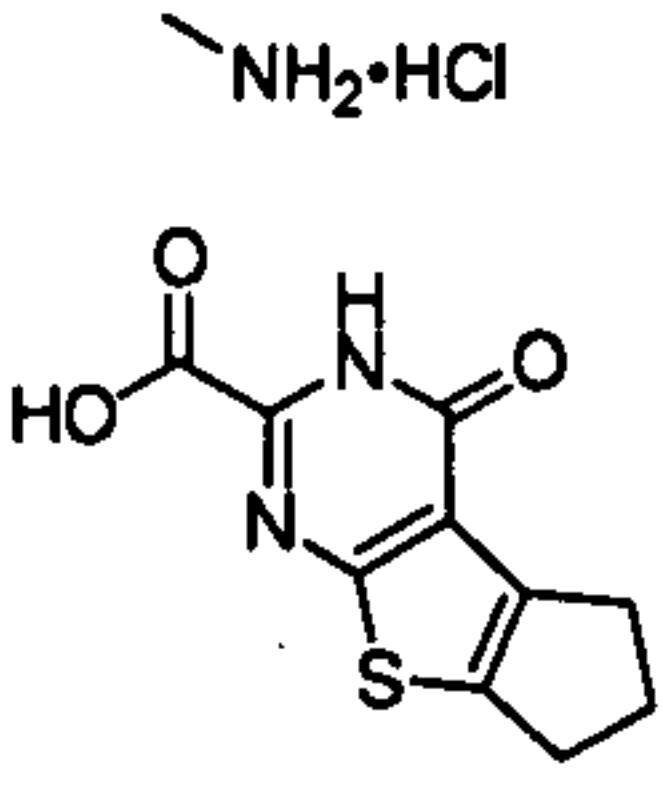
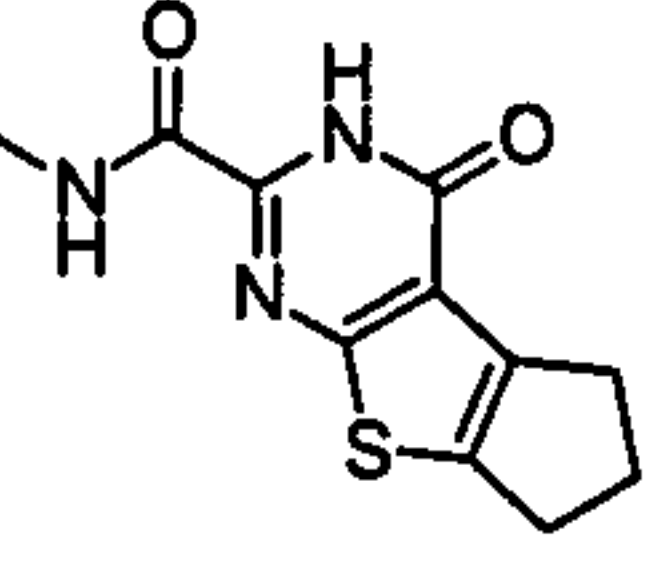
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/249 |    |    | A, 67%<br>[MH] <sup>+</sup> = 526 |
| 2/250 |   |  | A, 69%<br>[MH] <sup>+</sup> = 526 |
| 2/251 |  |  | A, 90%<br>[MH] <sup>+</sup> = 506 |
| 2/252 |  |  | A, 96%<br>[MH] <sup>+</sup> = 483 |
| 2/253 |  |  | A, 16%<br>[MH] <sup>+</sup> = 454 |
| 2/254 |  |  | A, 26%<br>[MH] <sup>+</sup> = 468 |

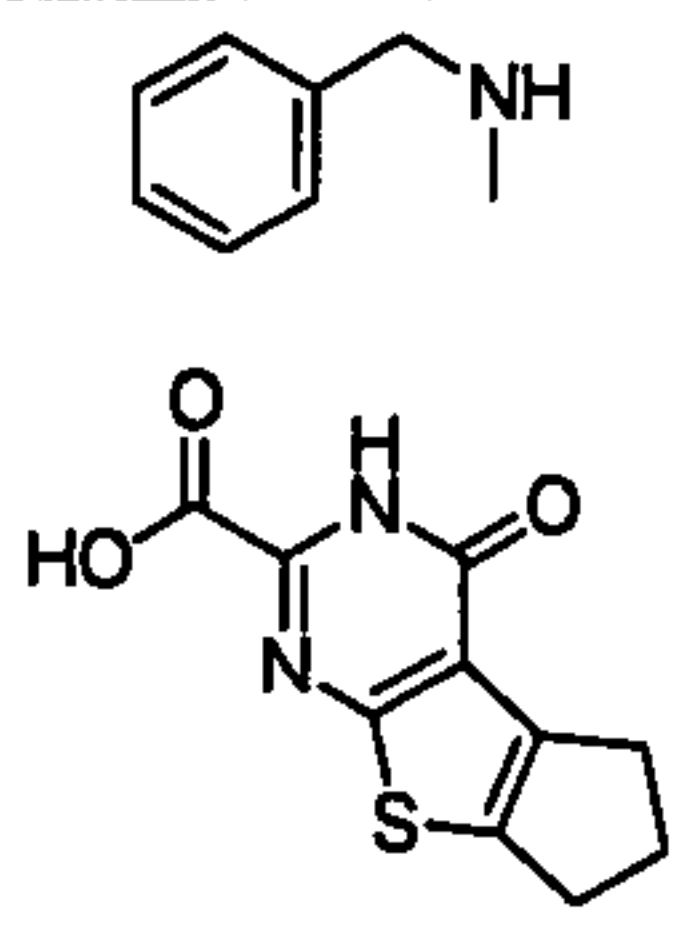
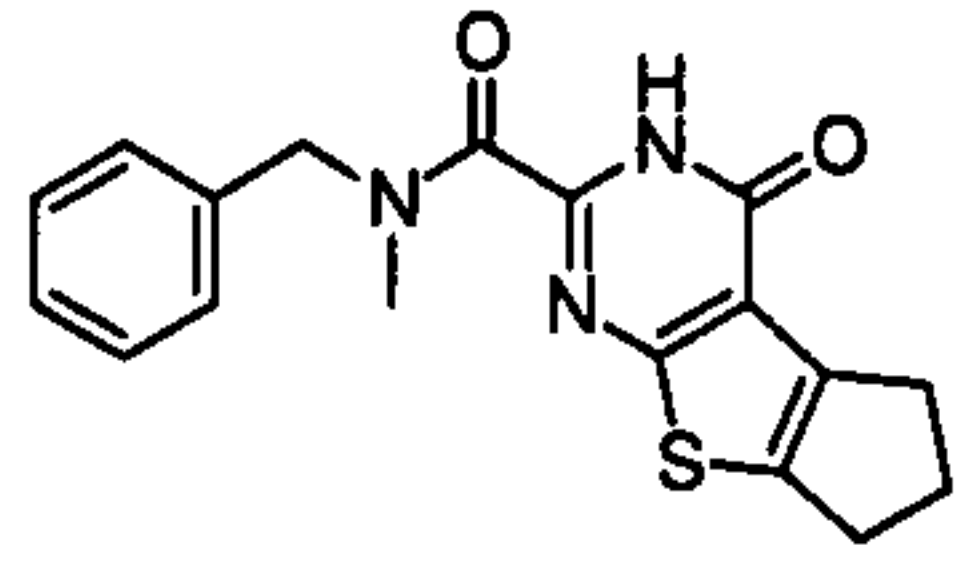
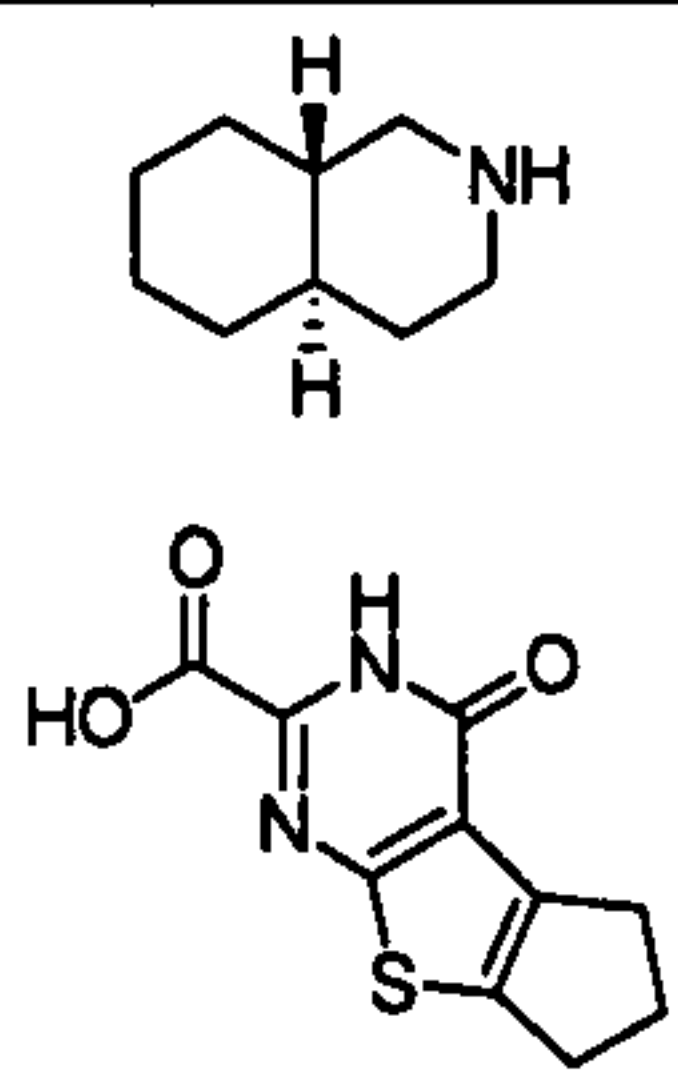
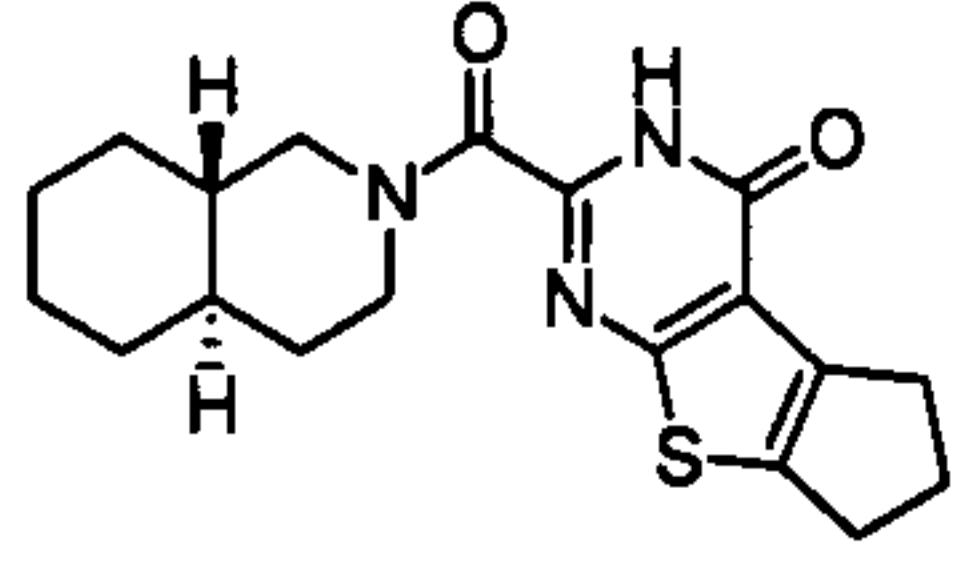
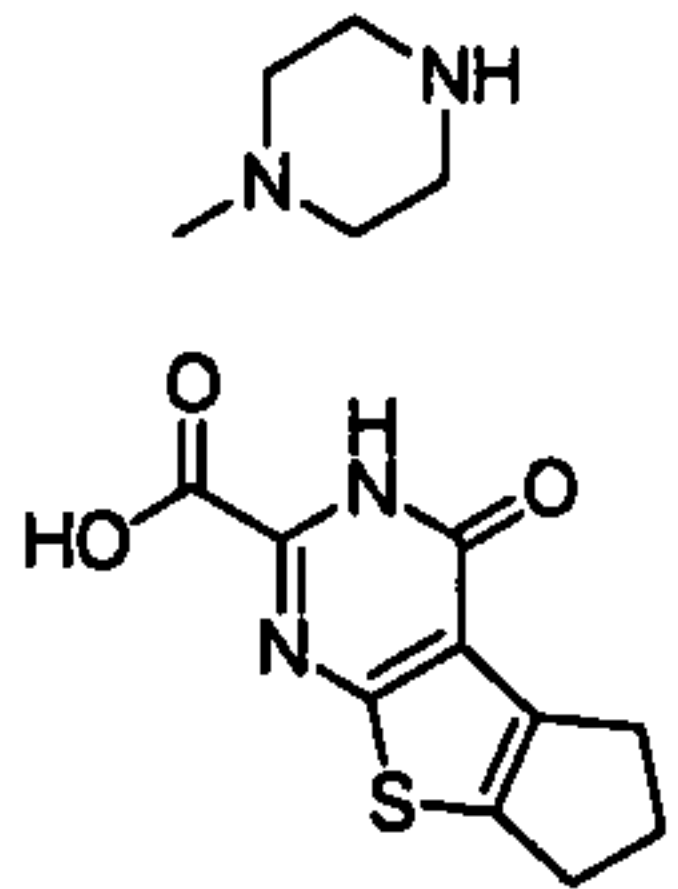
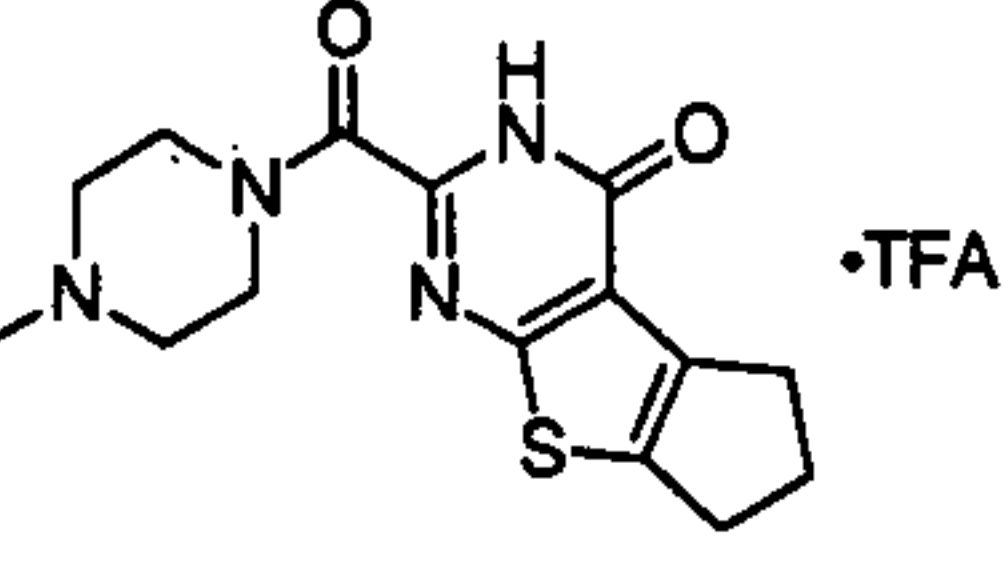
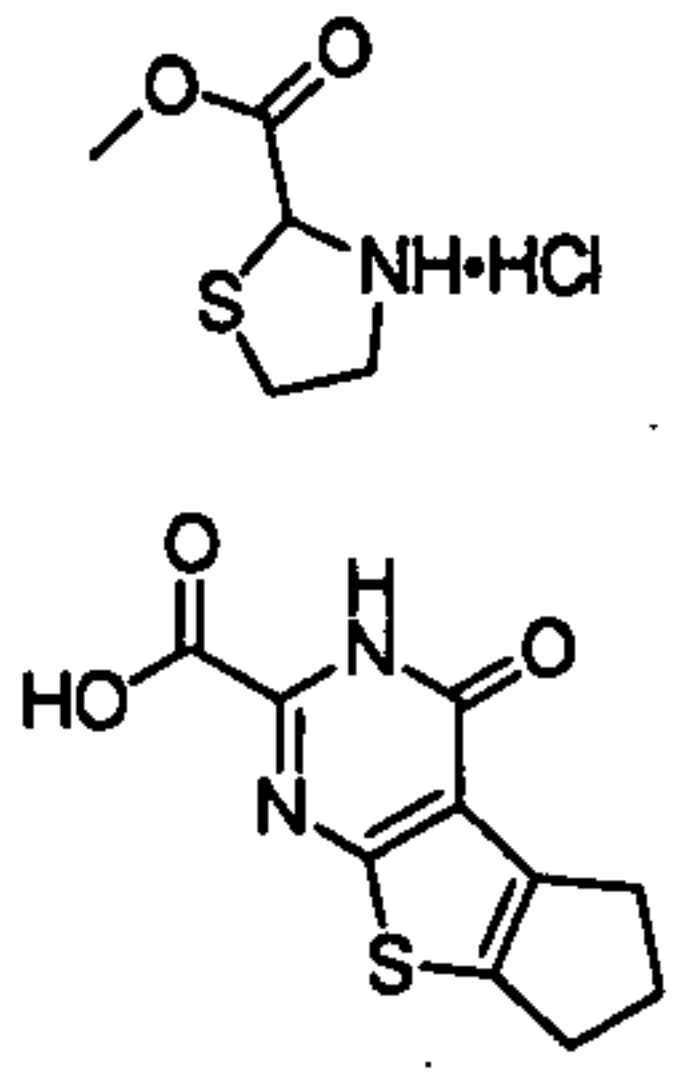
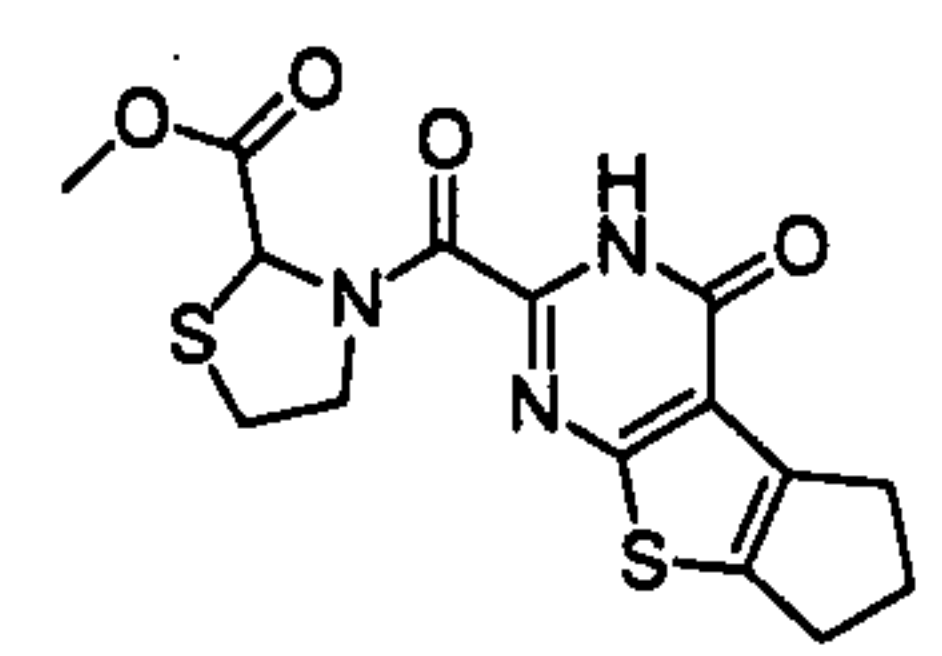
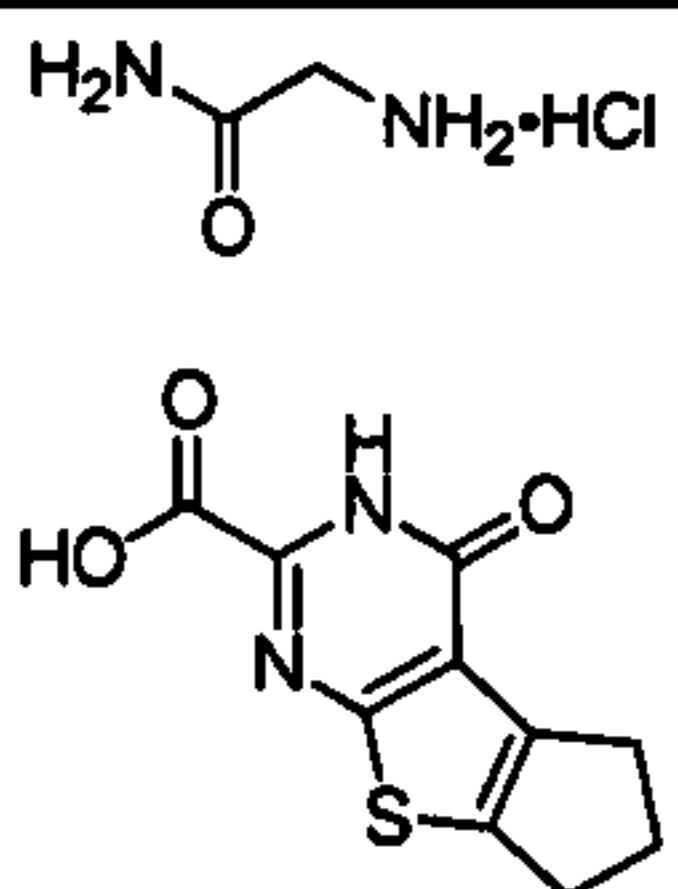
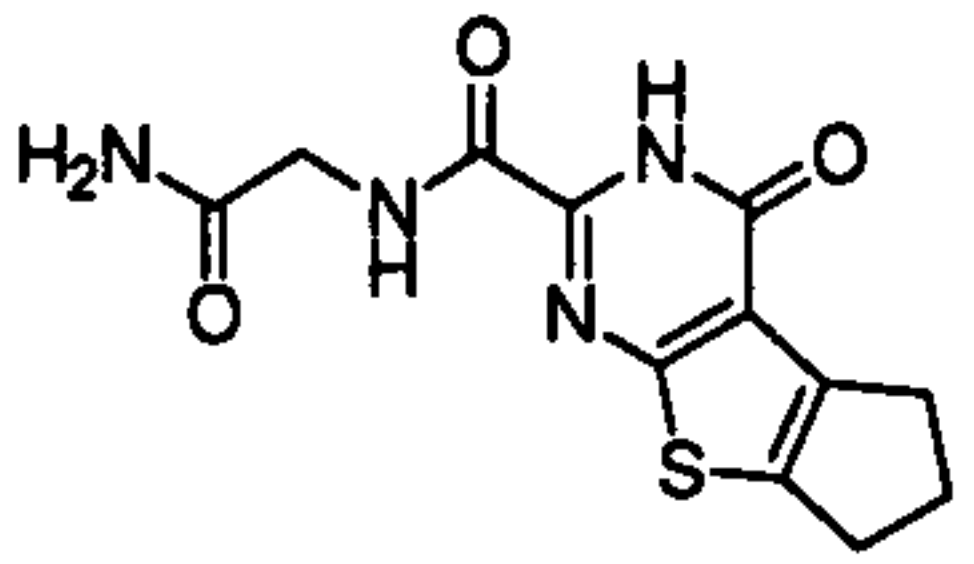
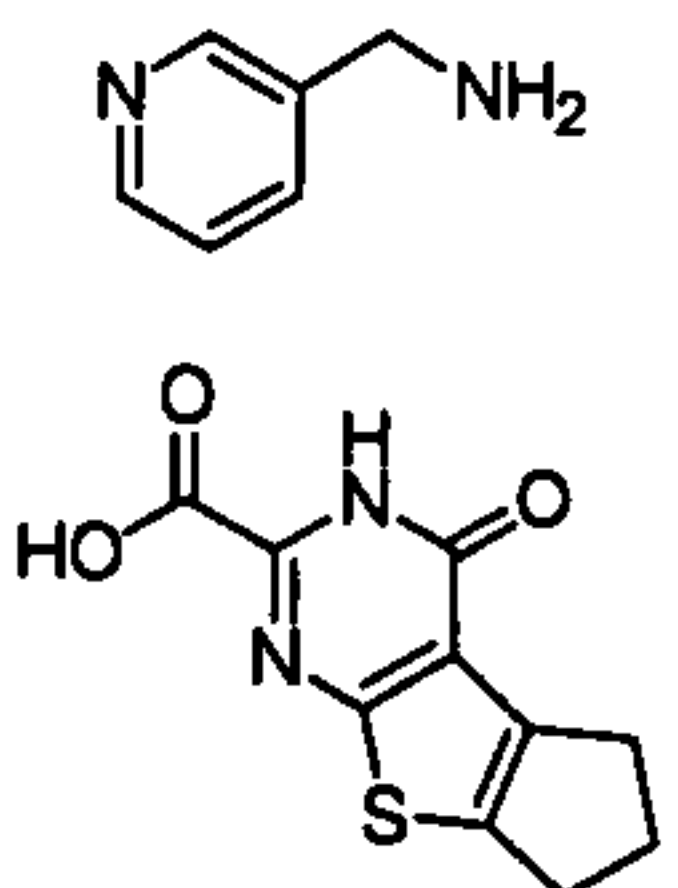
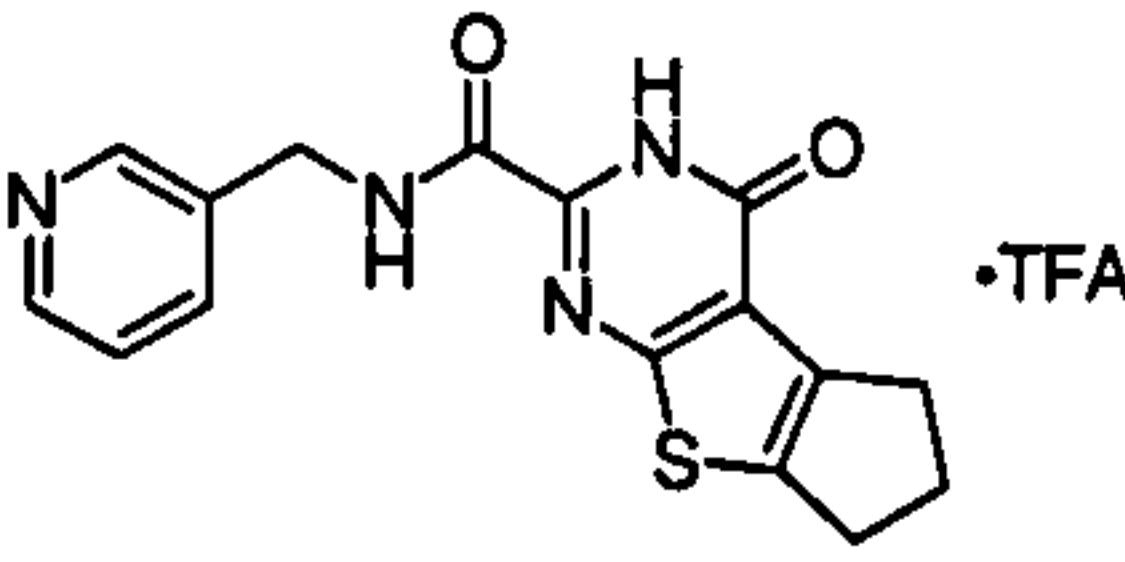
| Ex. # | amine, acid                                                                                                                                                                | product                                                                               | method, yield                     |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/255 | NH <sub>4</sub> Cl<br>                                                                   |    | A, 25%<br>[MH] <sup>+</sup> = 497 |
| 2/256 | NH <sub>4</sub> Cl<br>                                                                  |   | A, 86%<br>[MH] <sup>+</sup> = 525 |
| 2/257 | <br> |  | A, 85%<br>[MH] <sup>+</sup> = 483 |
| 2/258 | NH <sub>4</sub> Cl<br>                                                                 |  | A, 43%<br>[MH] <sup>+</sup> = 454 |
| 2/259 | MeNH <sub>2</sub> ·HCl<br>                                                             |  | A, 20%<br>[MH] <sup>+</sup> = 468 |
| 2/260 | EtNH <sub>2</sub> ·HCl<br>                                                             |  | A, 30%<br>[MH] <sup>+</sup> = 482 |

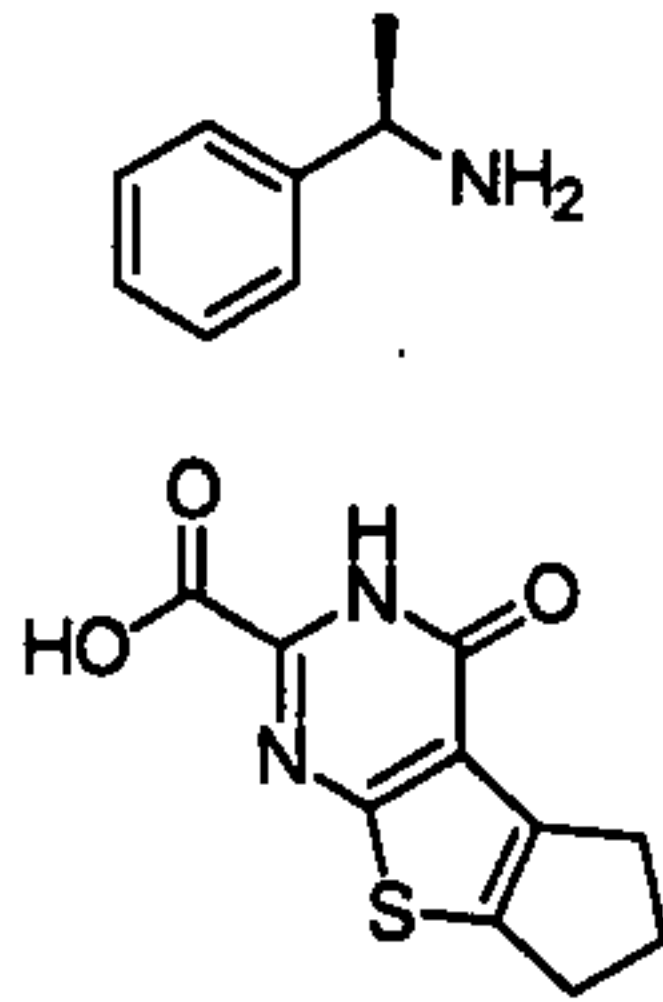
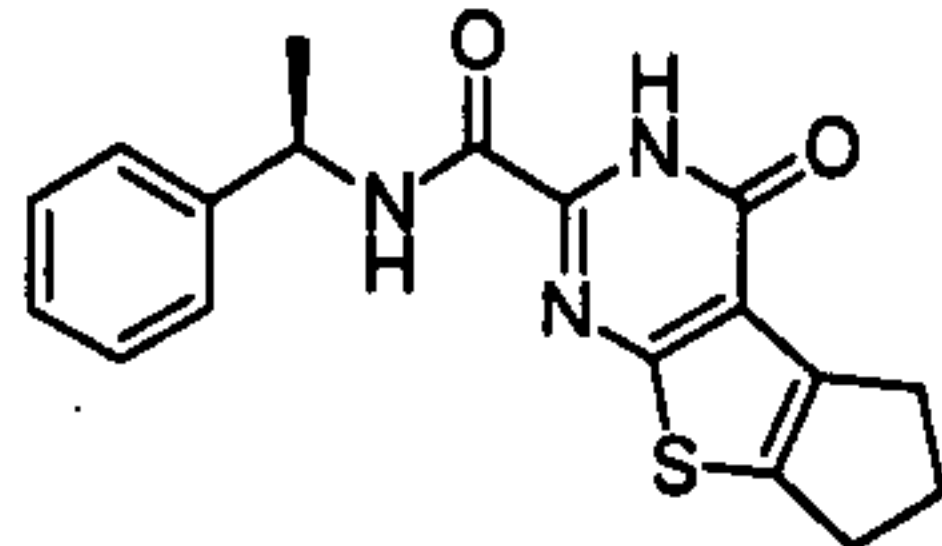
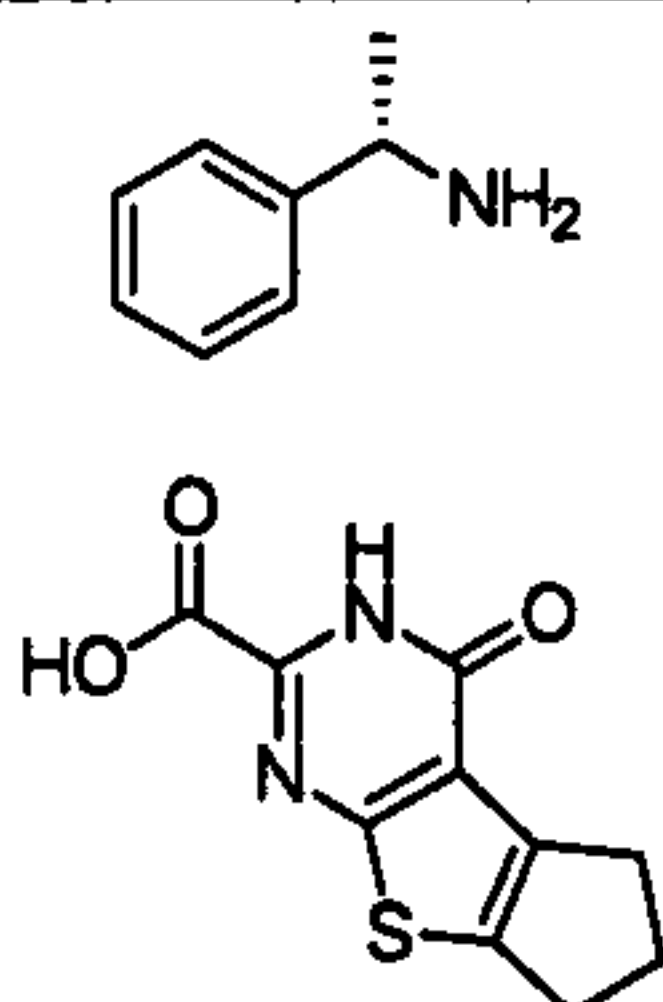
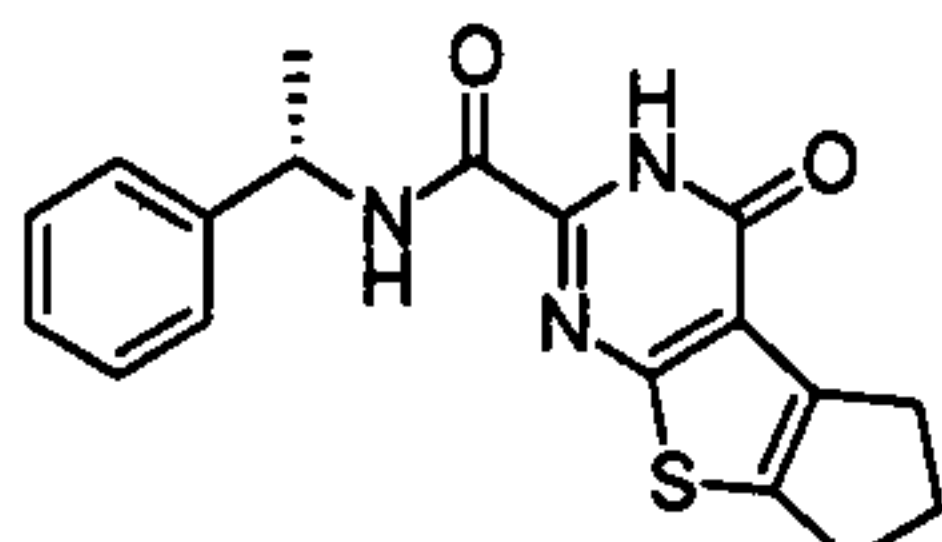
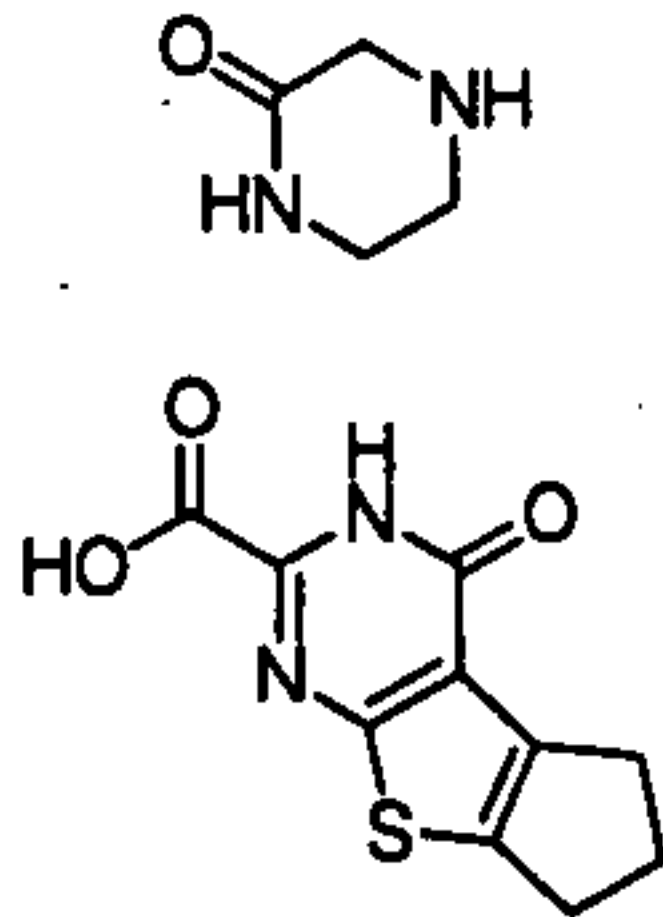
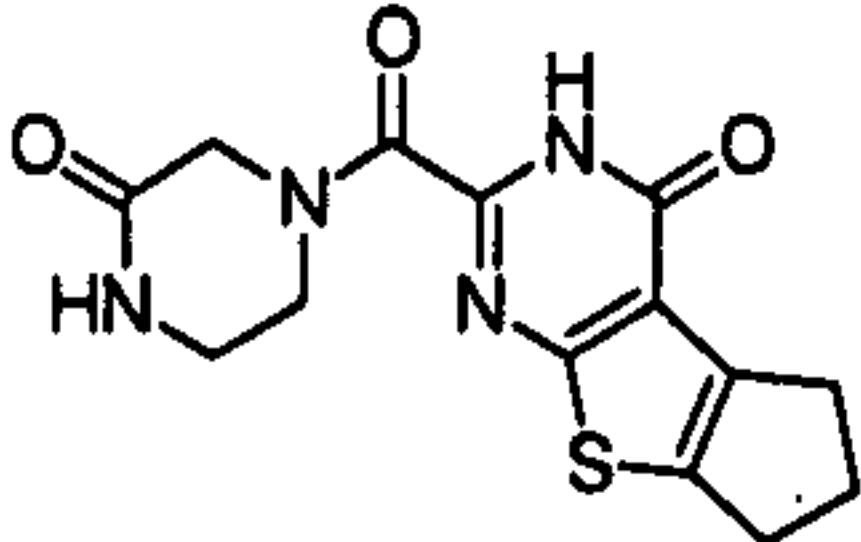
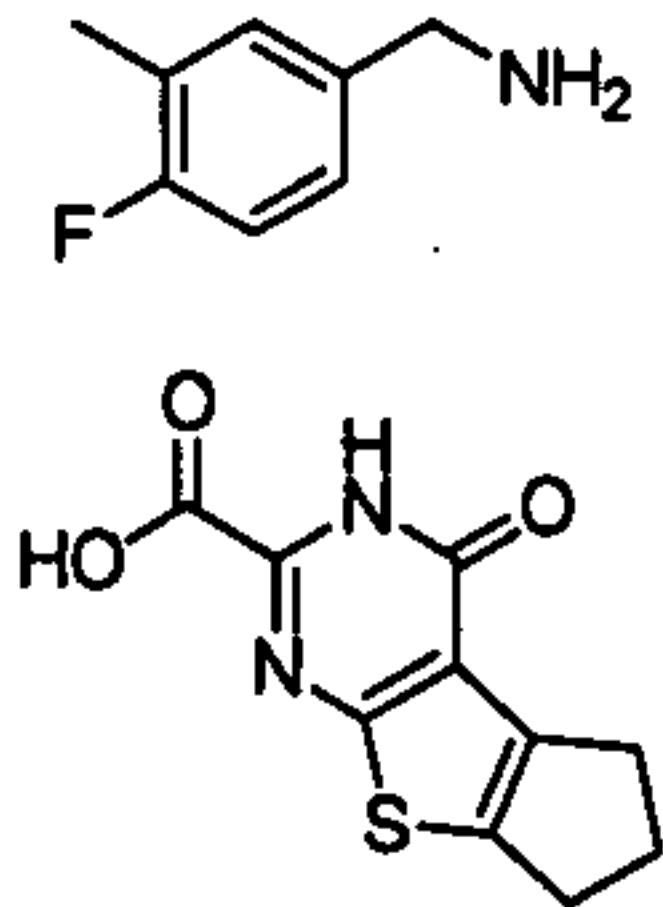
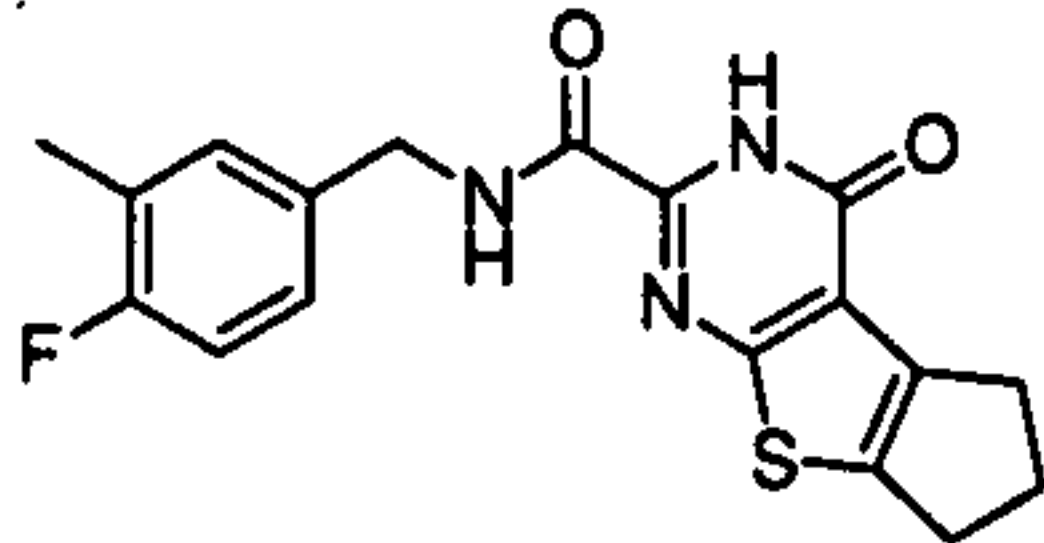
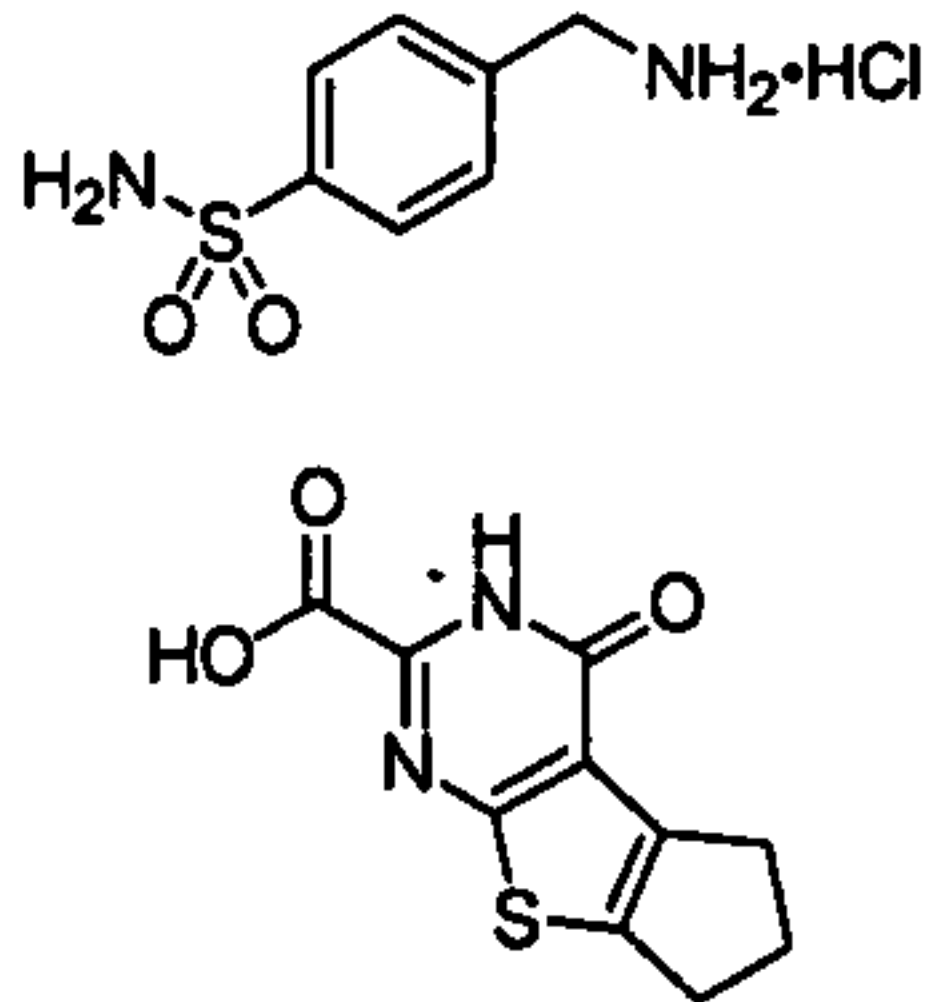
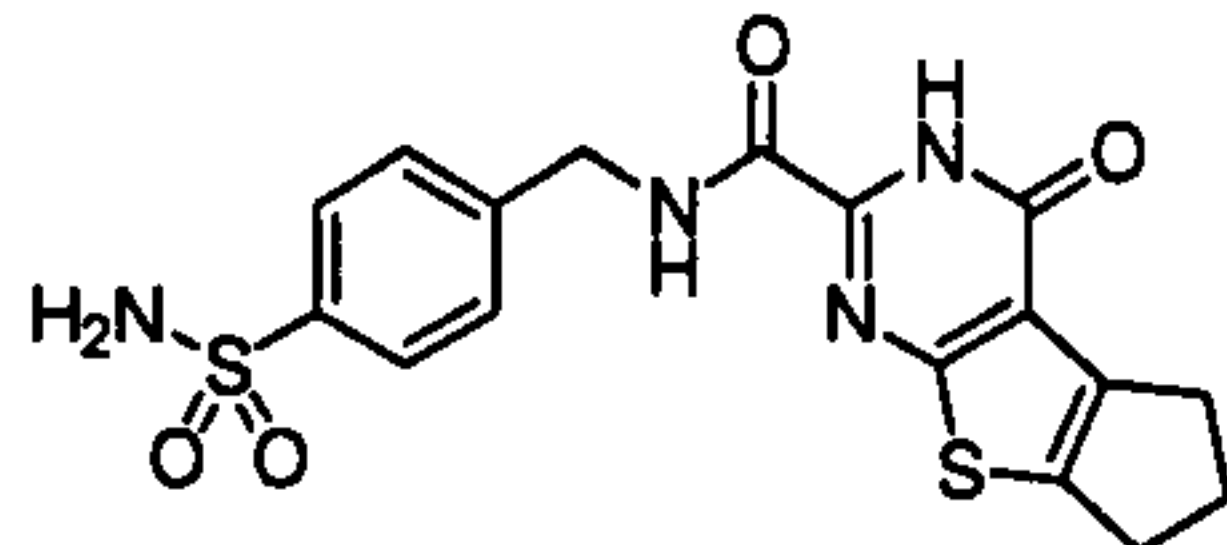
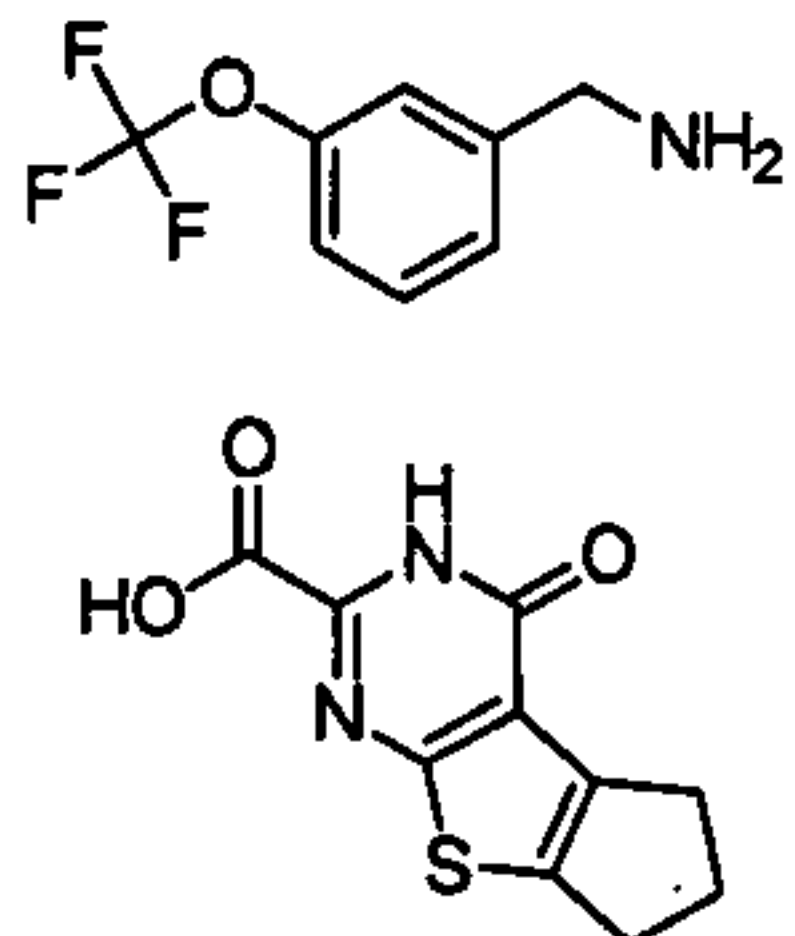
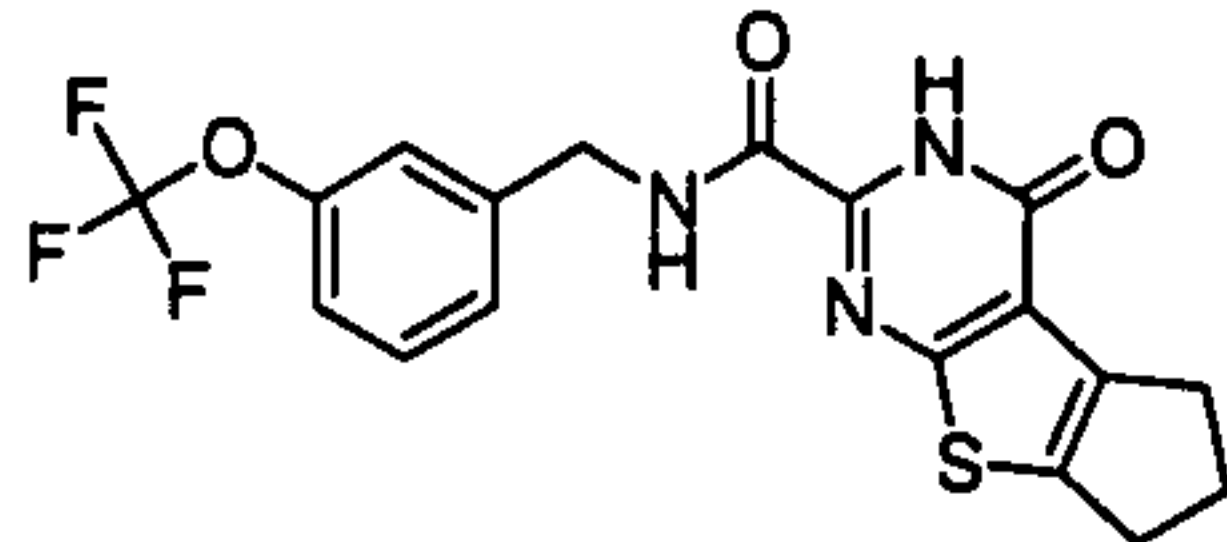
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                     |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------|
| 2/261 |    |    | A, 14%<br>[MH] <sup>+</sup> = 492 |
| 2/262 |   |   | A, 78%<br>[MH] <sup>+</sup> = 454 |
| 2/263 |  |  | A, 60%<br>[MH] <sup>+</sup> = 468 |
| 2/264 |   |  | A, 23%<br>[MH] <sup>+</sup> = 455 |
| 2/266 |   |  | A, 95%<br>[MH] <sup>+</sup> = 483 |
| 2/267 |  |  | A, 96%<br>[MH] <sup>+</sup> = 468 |

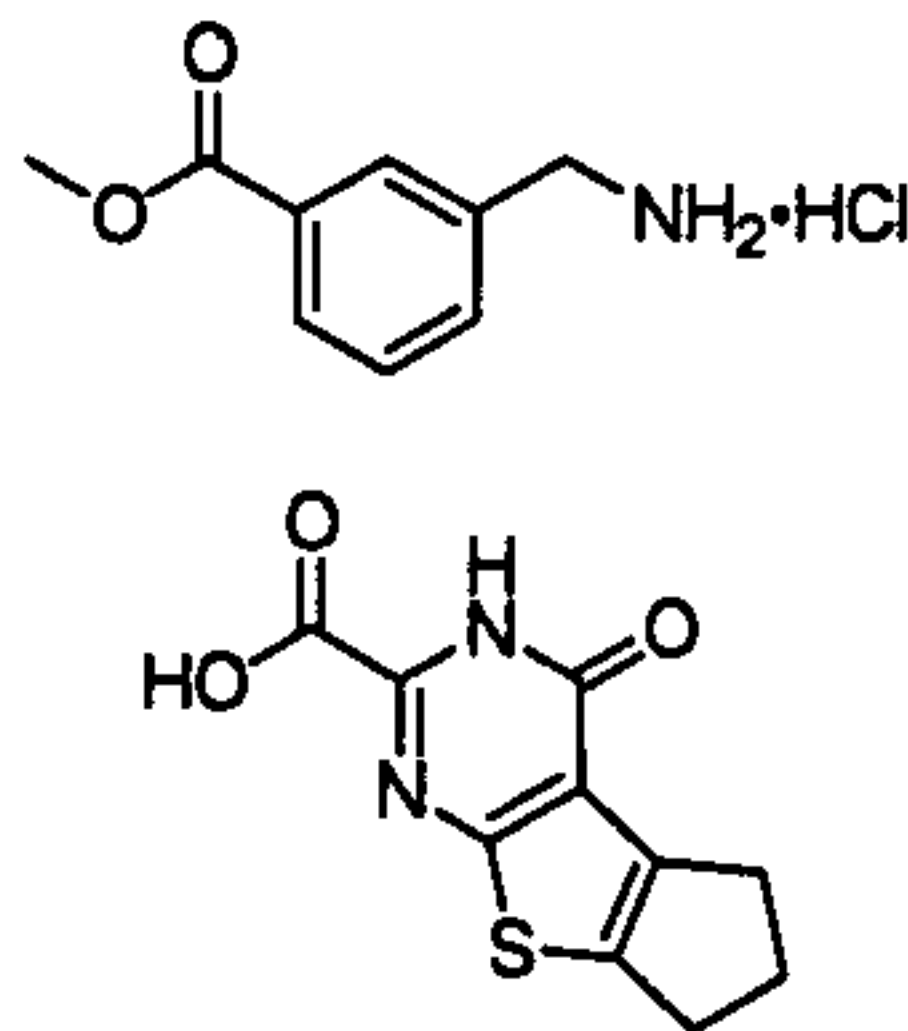
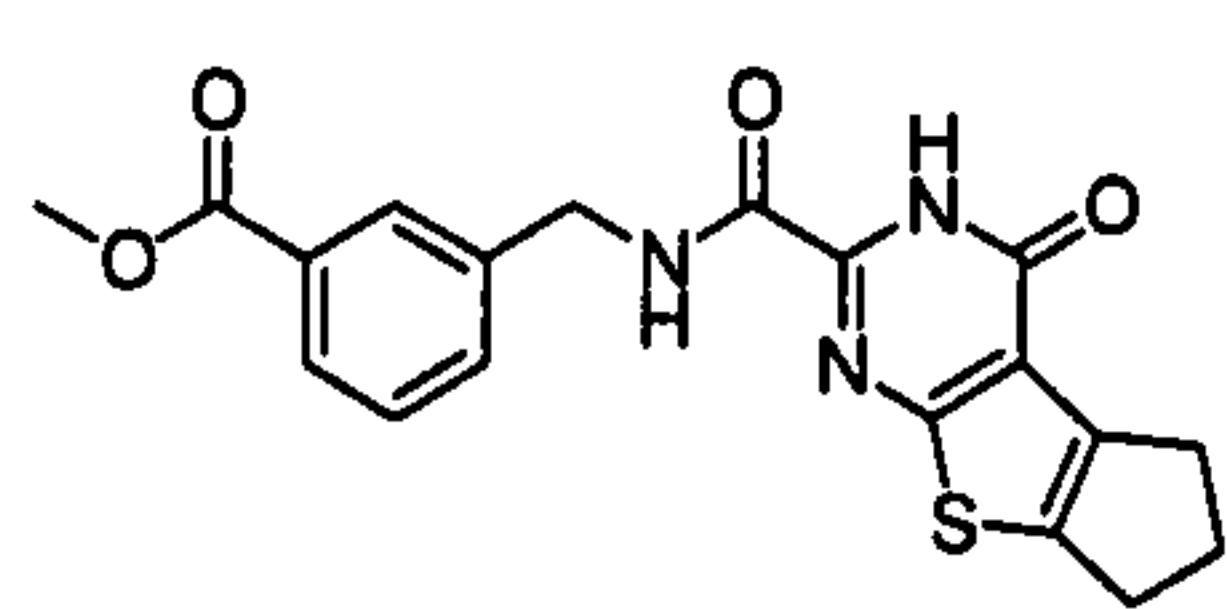
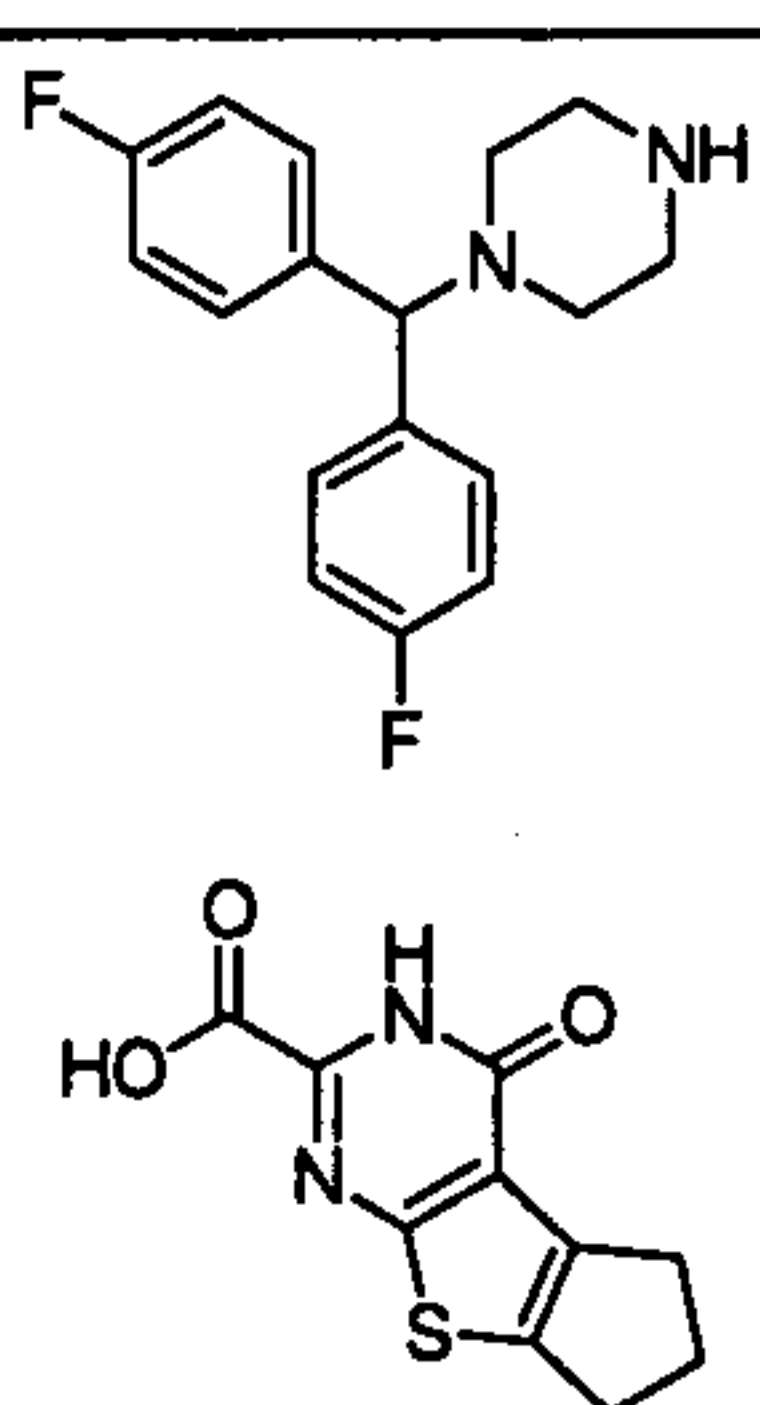
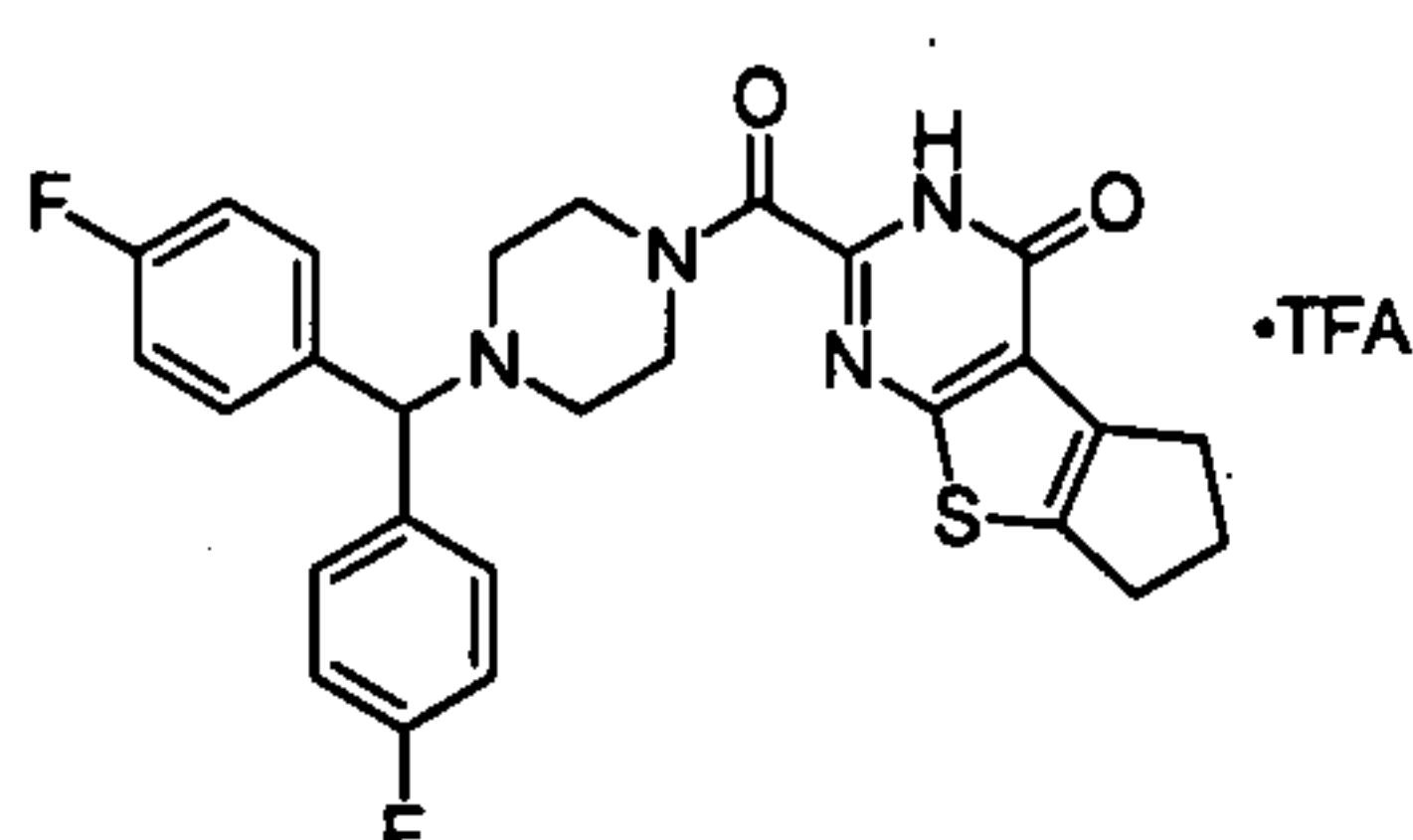
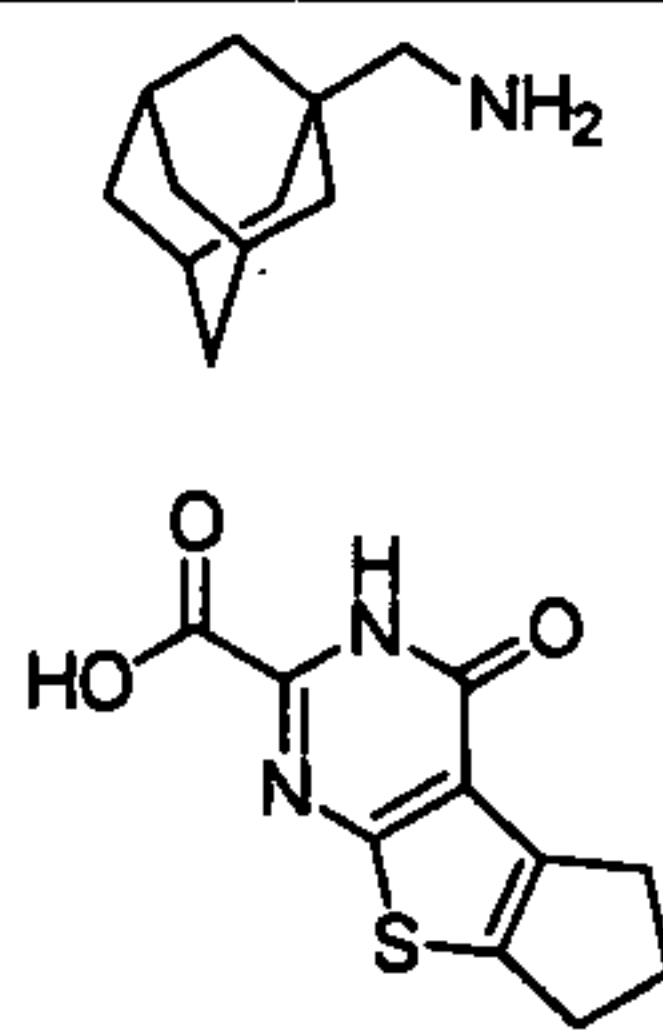
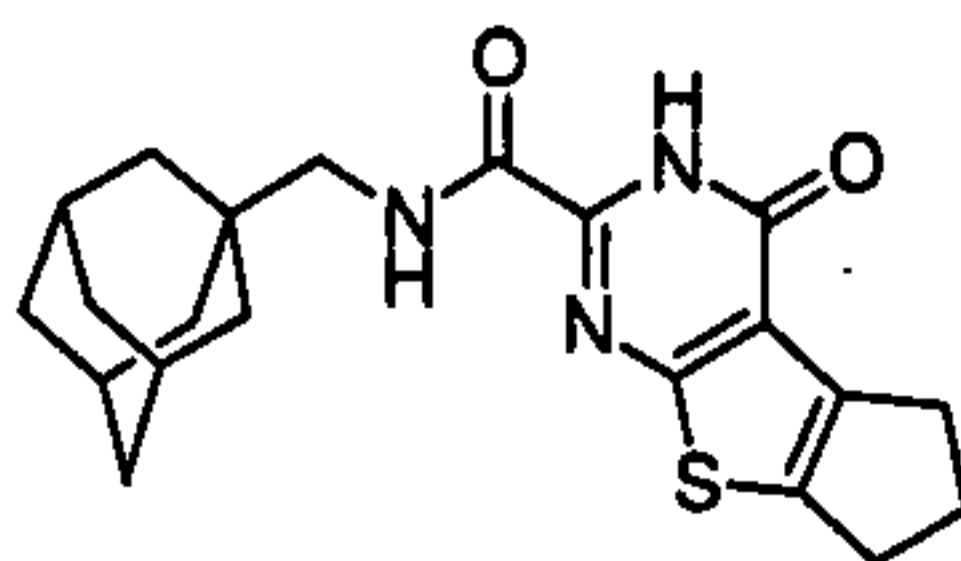
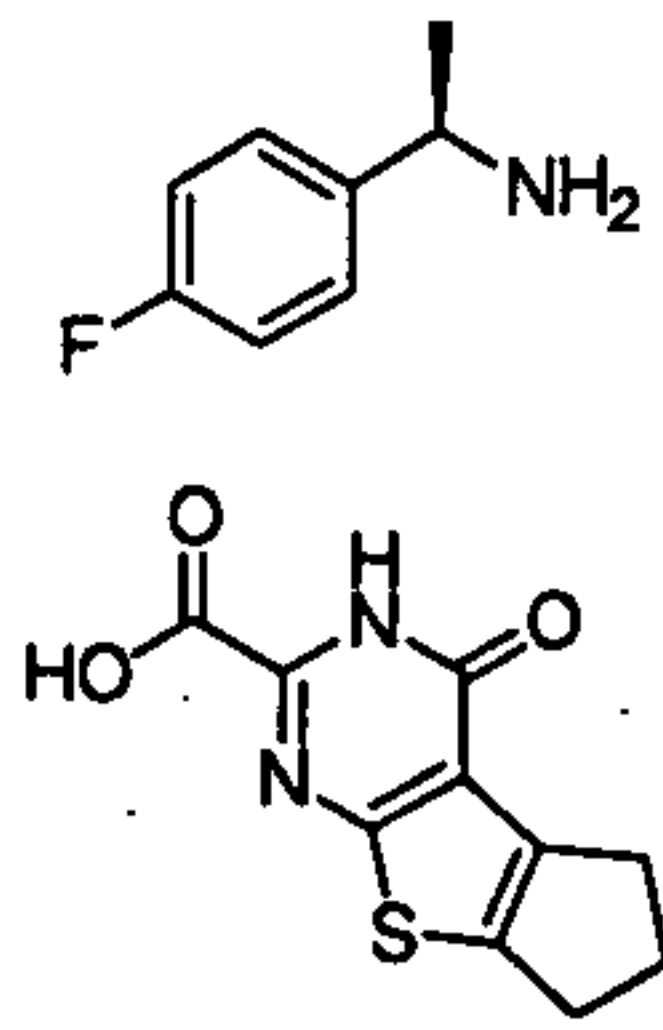
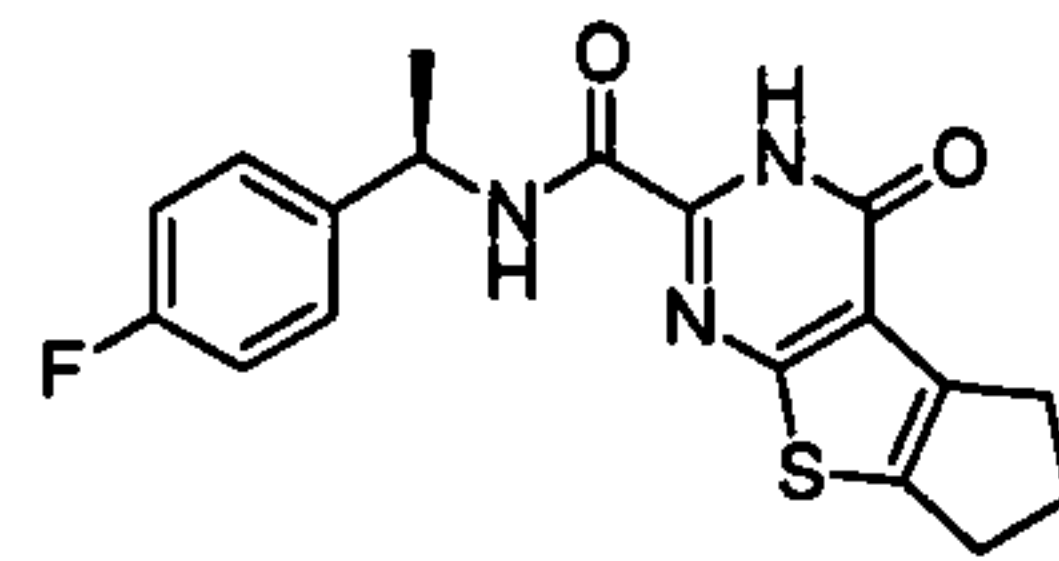
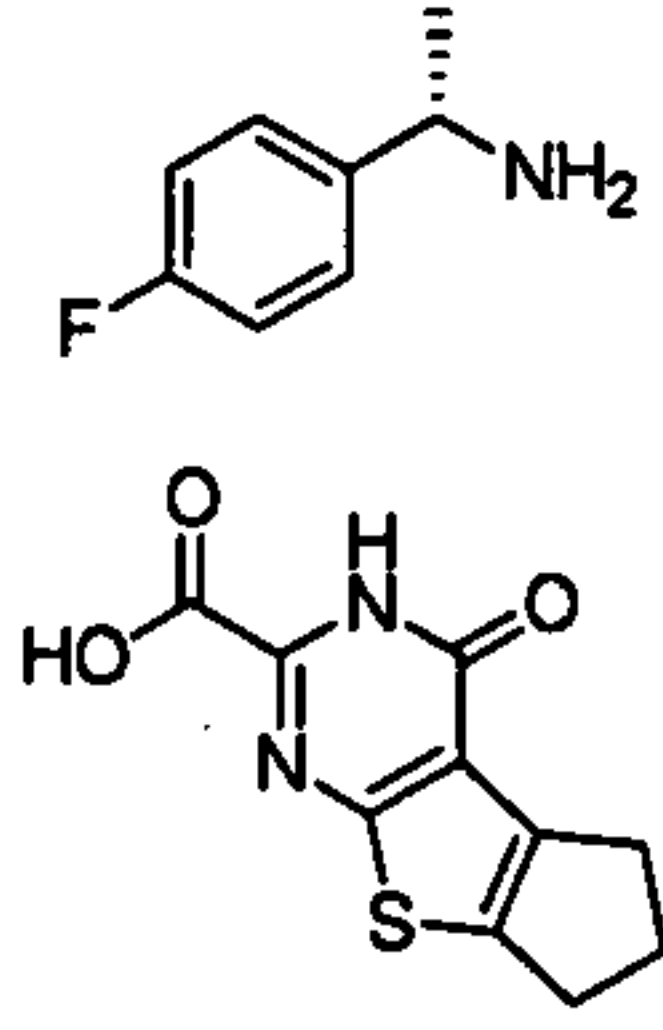
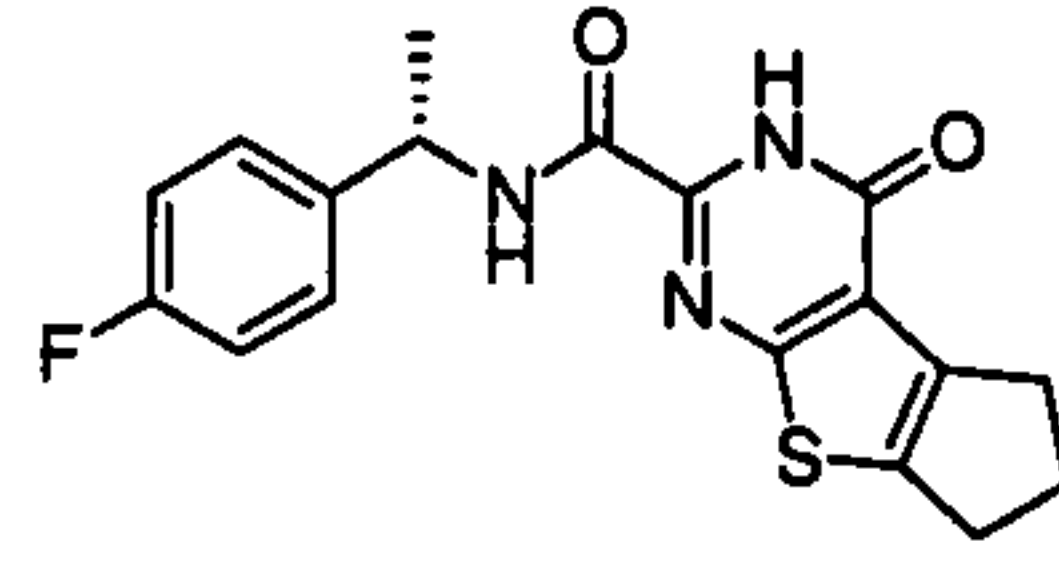
| Ex. # | amine, acid                                                                                                                                                                         | product                                                                               | method, yield                                |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------|
| 2/268 | <p>MeNH<sub>2</sub>·HCl</p>                                                                        |    | <p>A, 57%</p> <p>[MH]<sup>+</sup> = 482</p>  |
| 2/269 | <p>EtNH<sub>2</sub>·HCl</p>                                                                      |   | <p>A, 72%</p> <p>[MH]<sup>+</sup> = 496</p>  |
| 2/270 |  <p>·HCl</p>  |  | <p>A, 85%</p> <p>[MH]<sup>+</sup> = 512</p>  |
| 2/289 |               |  | <p>B, n.d.</p> <p>[MH]<sup>+</sup> = 315</p> |
| 2/290 |               |  | <p>B, n.d.</p> <p>[MH]<sup>+</sup> = 343</p> |
| 2/291 |               |  | <p>B, n.d.</p> <p>[MH]<sup>+</sup> = 289</p> |

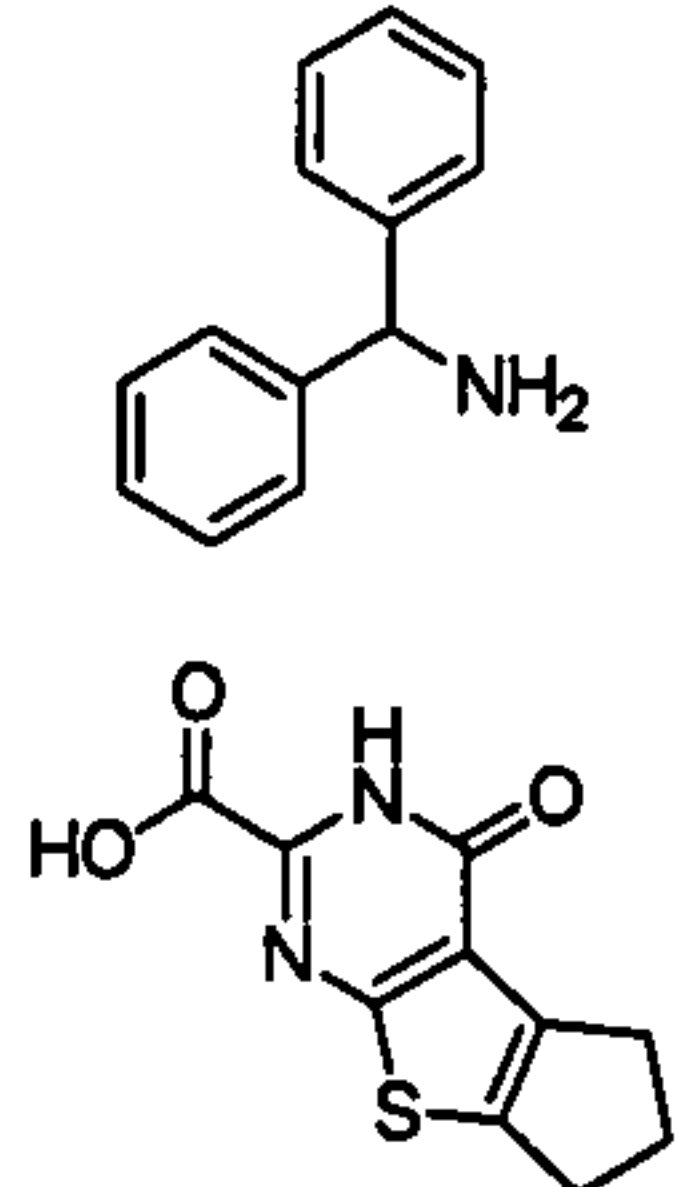
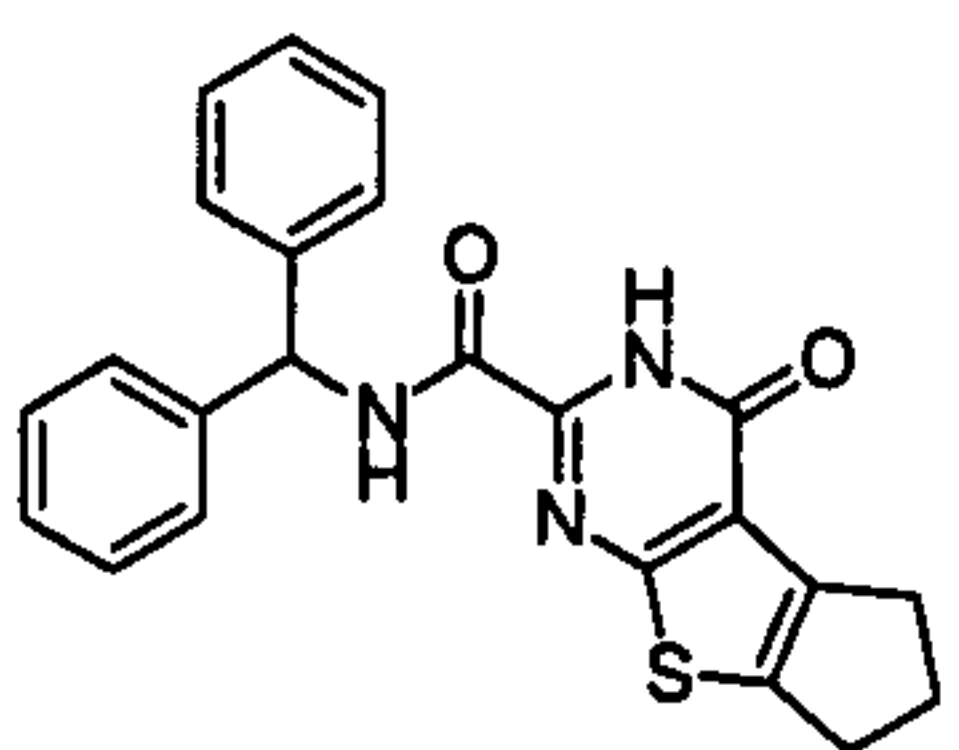
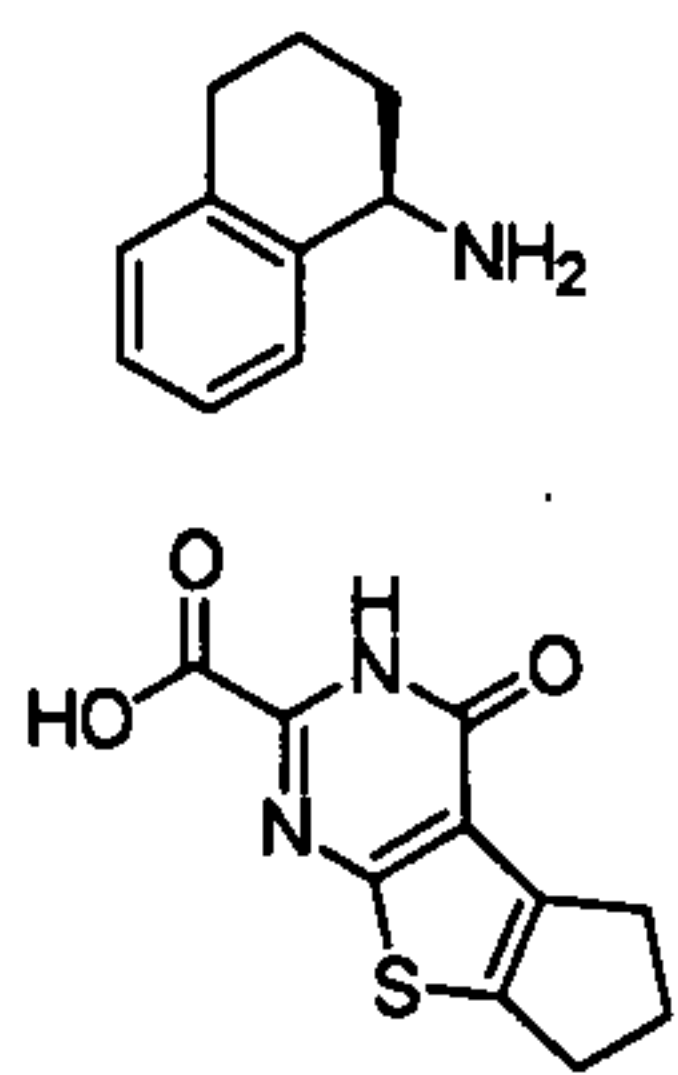
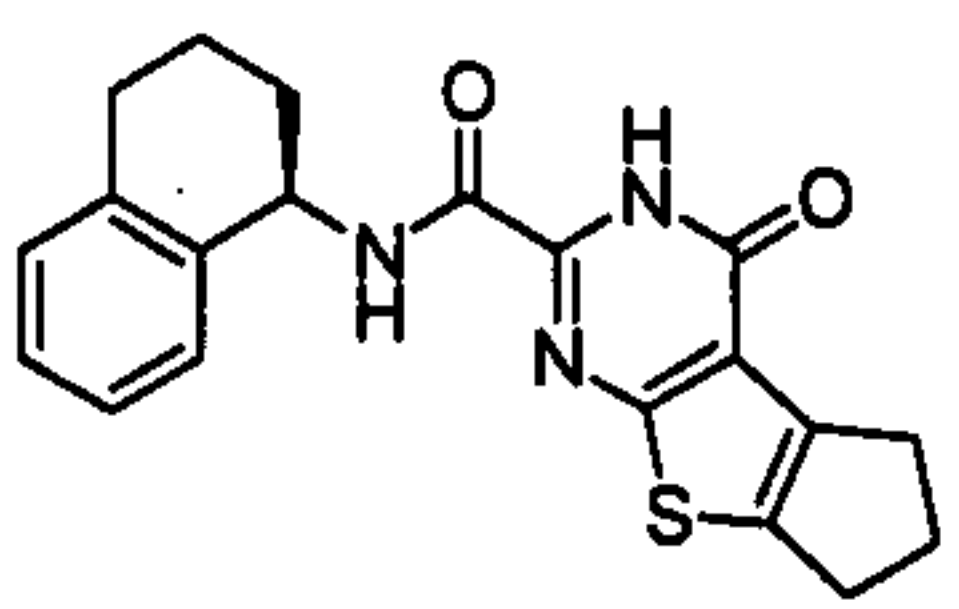
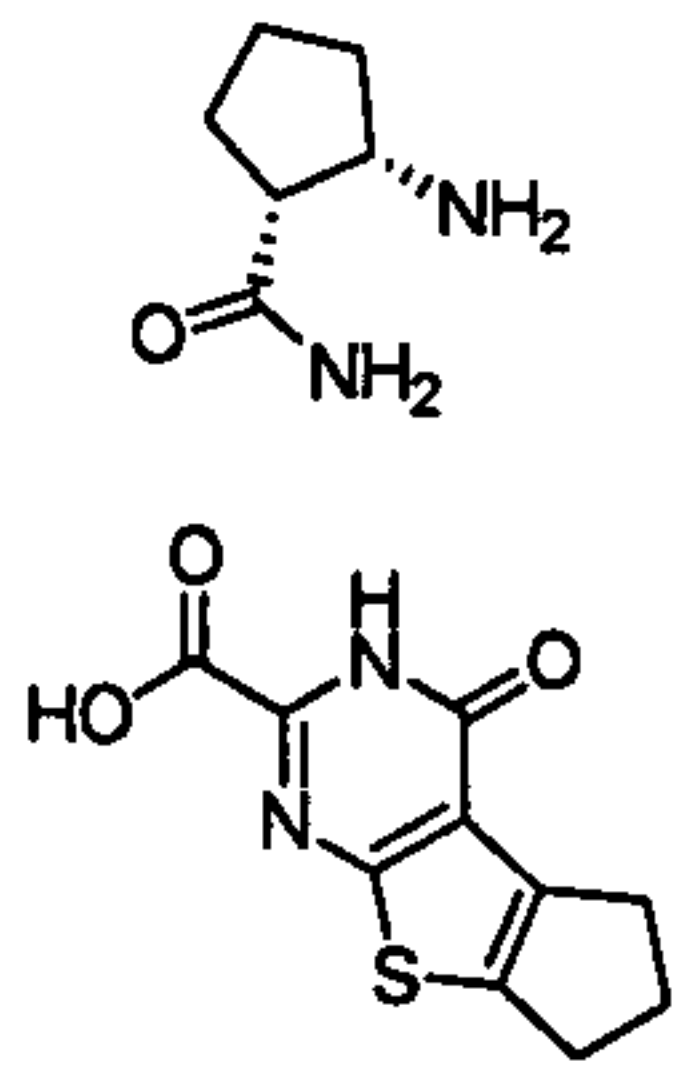
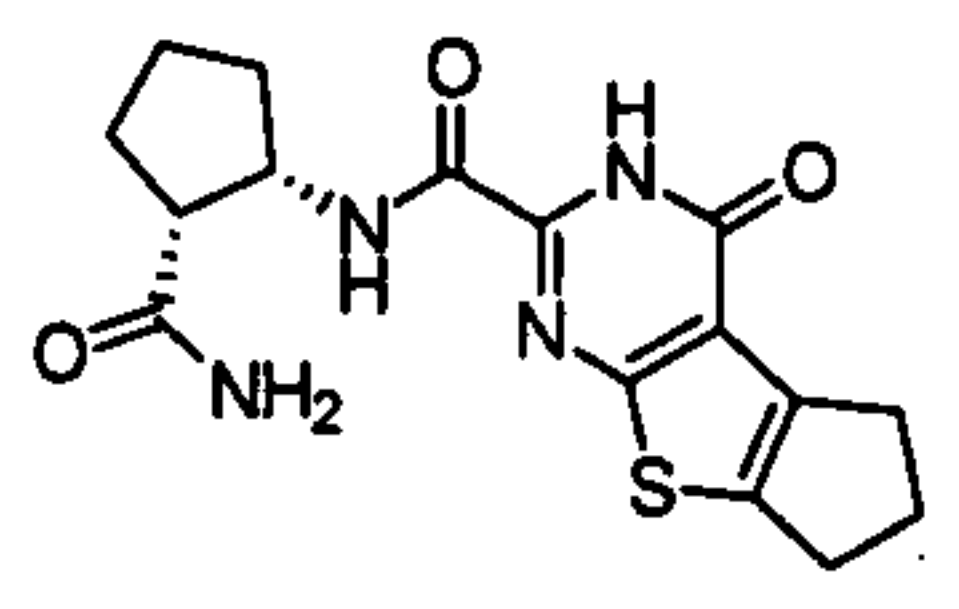
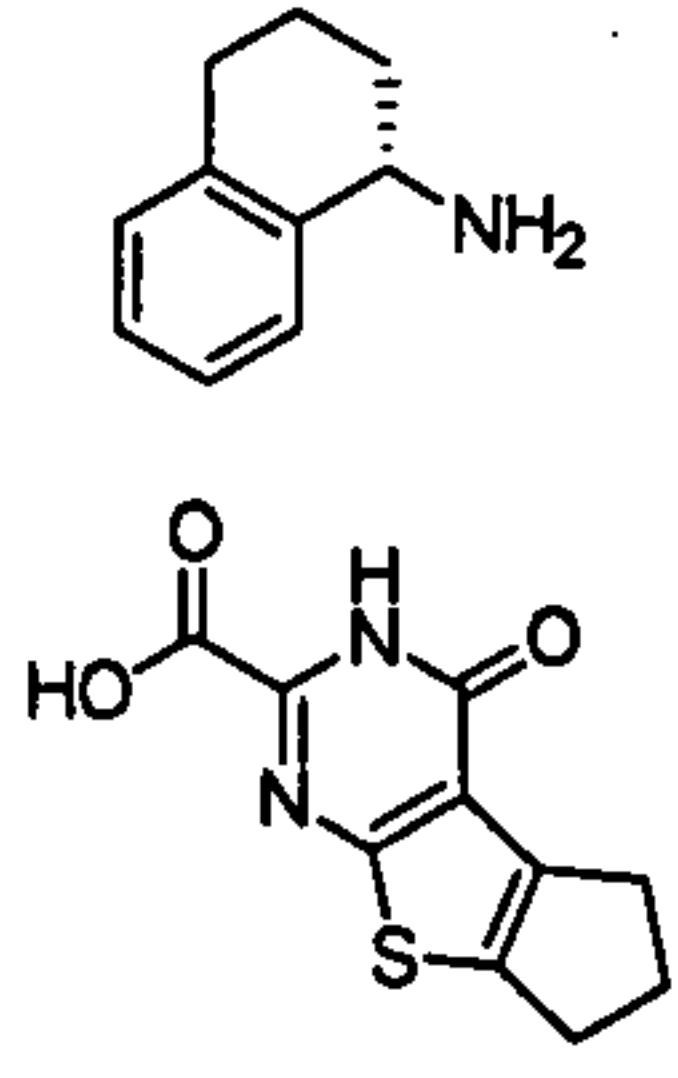
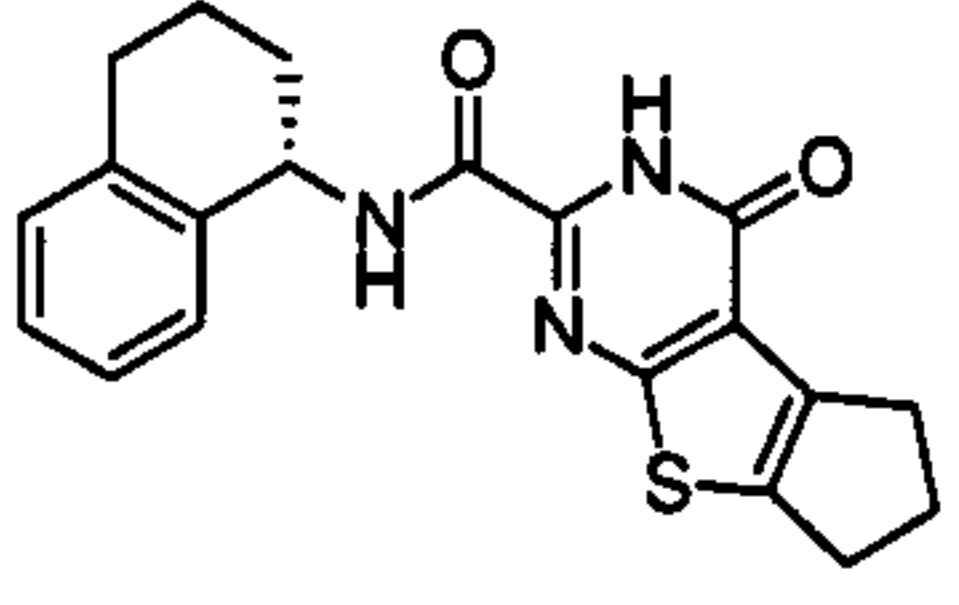
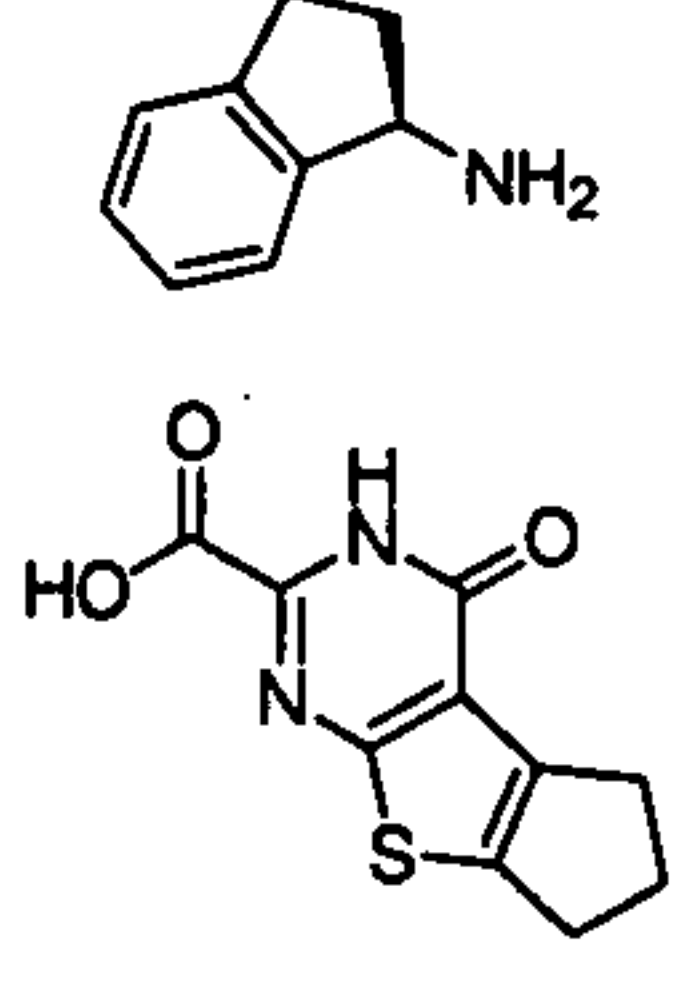
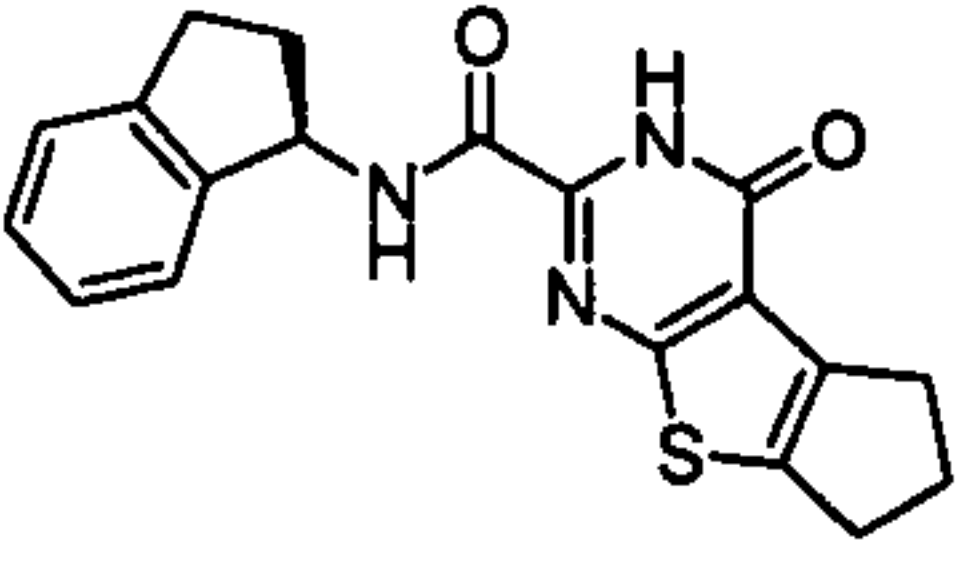
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/292 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 343 |
| 2/293 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 303 |
| 2/294 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 277 |
| 2/295 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 303 |
| 2/296 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 325 |
| 2/297 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 331 |

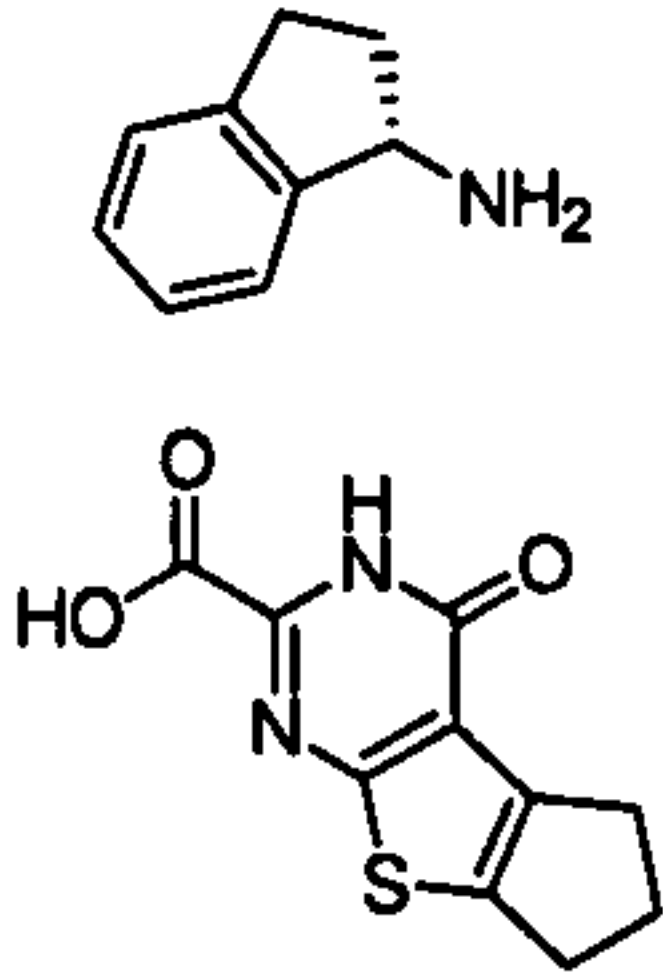
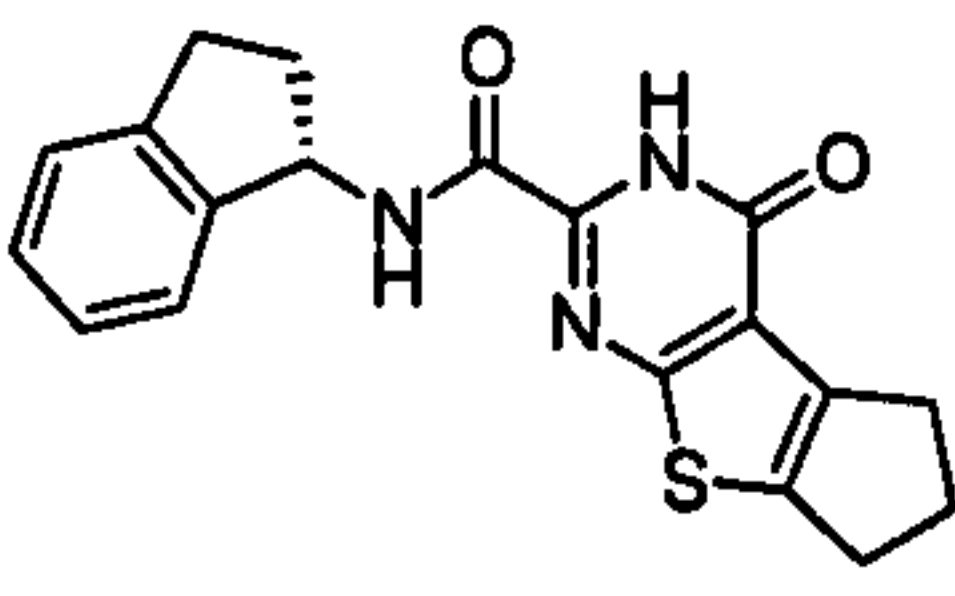
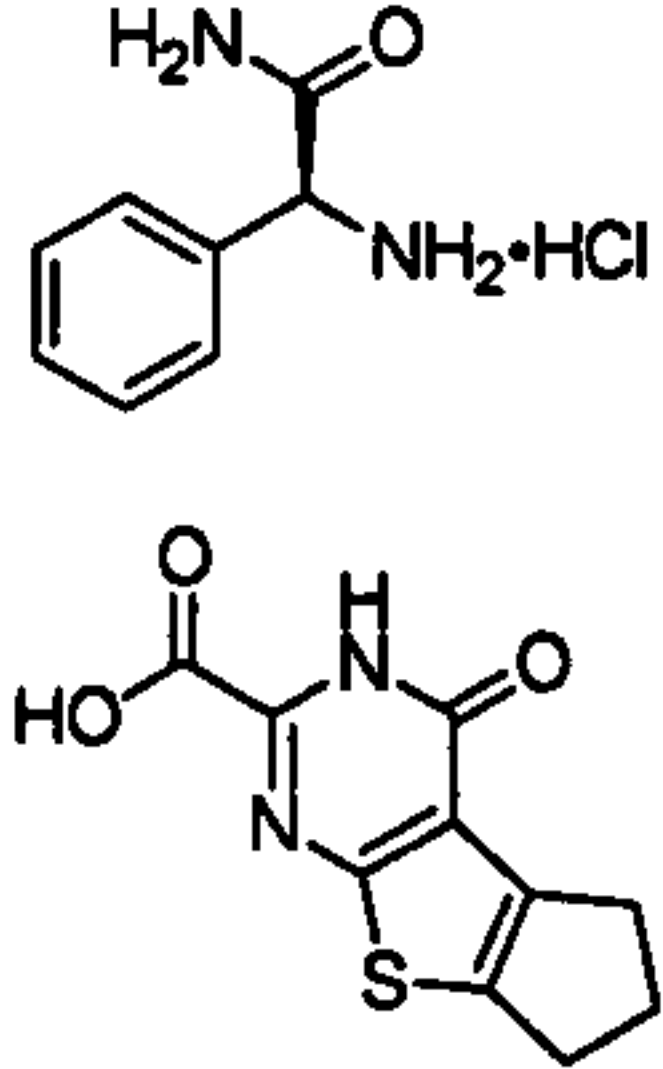
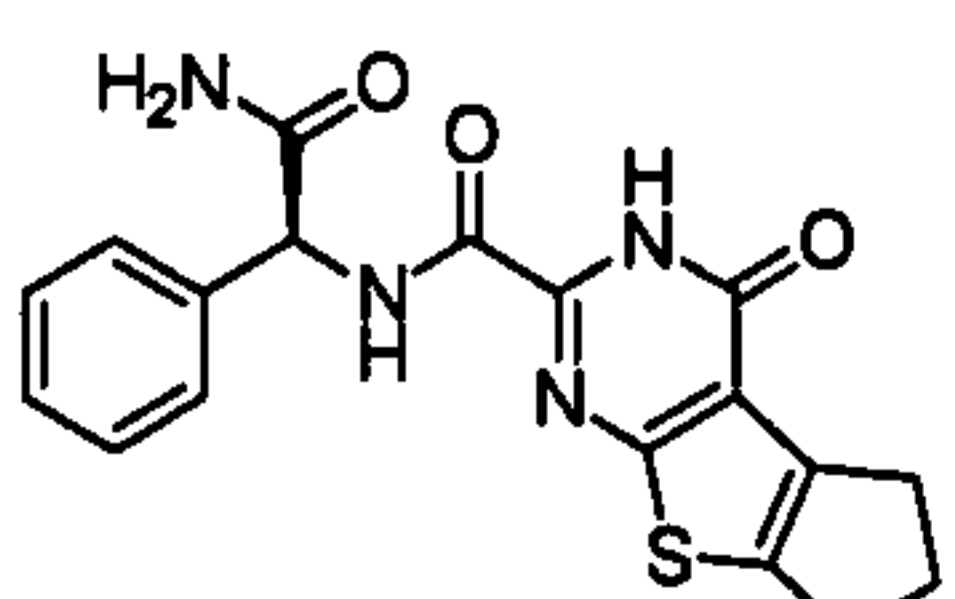
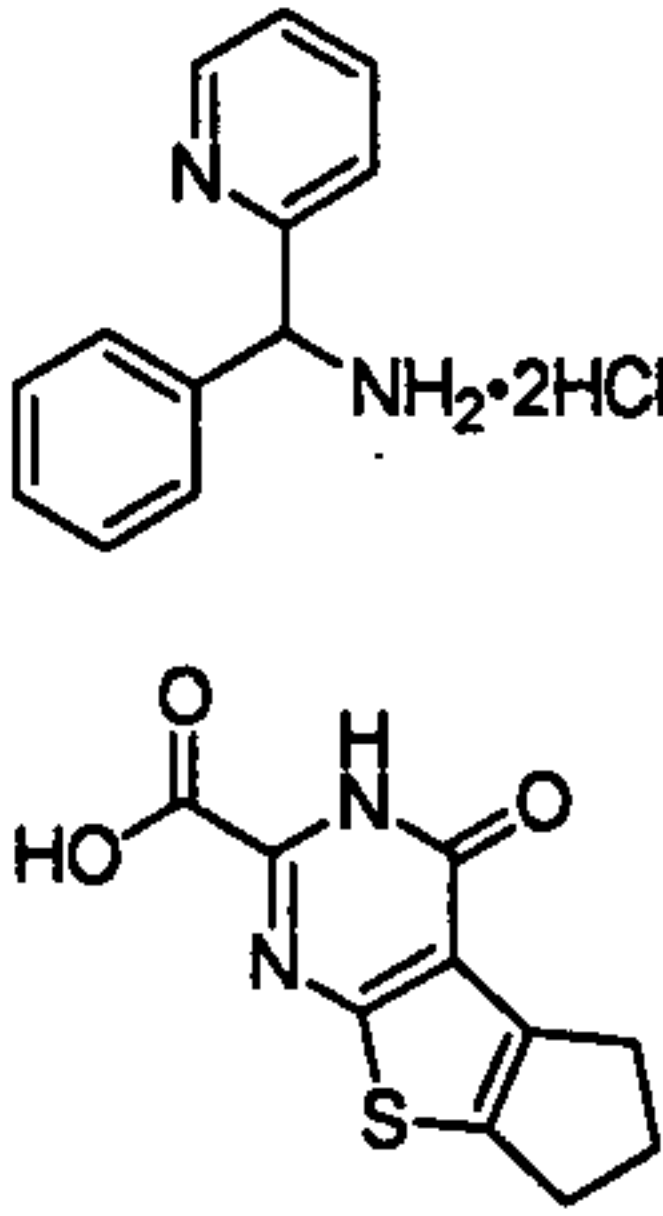
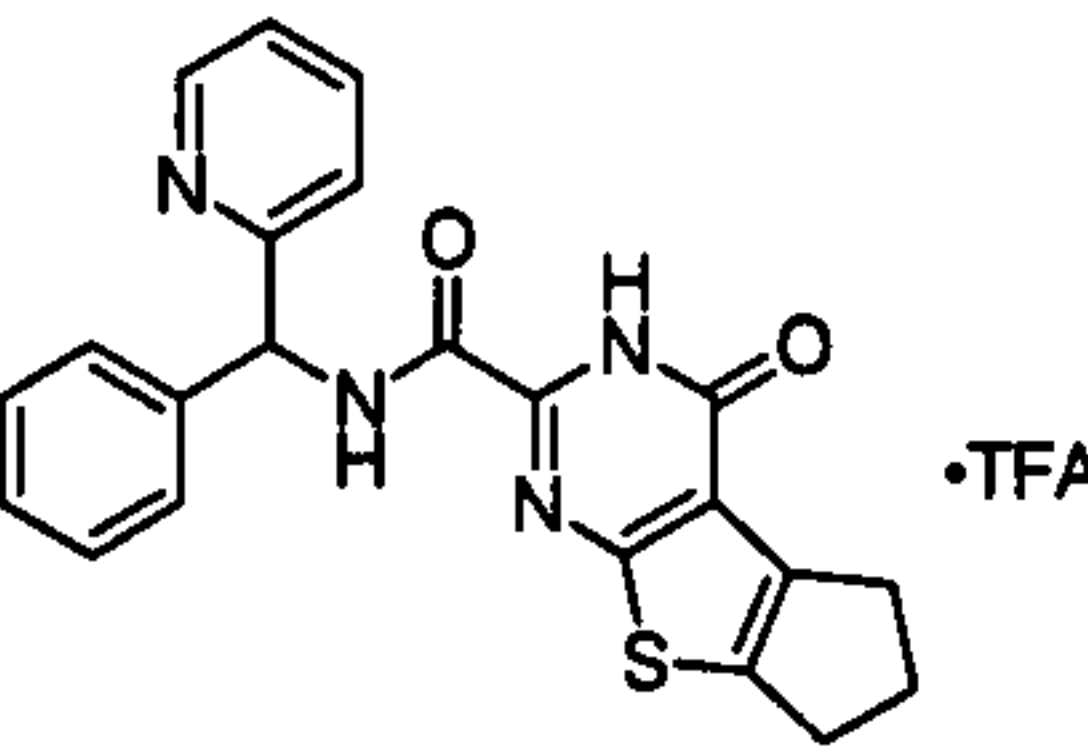
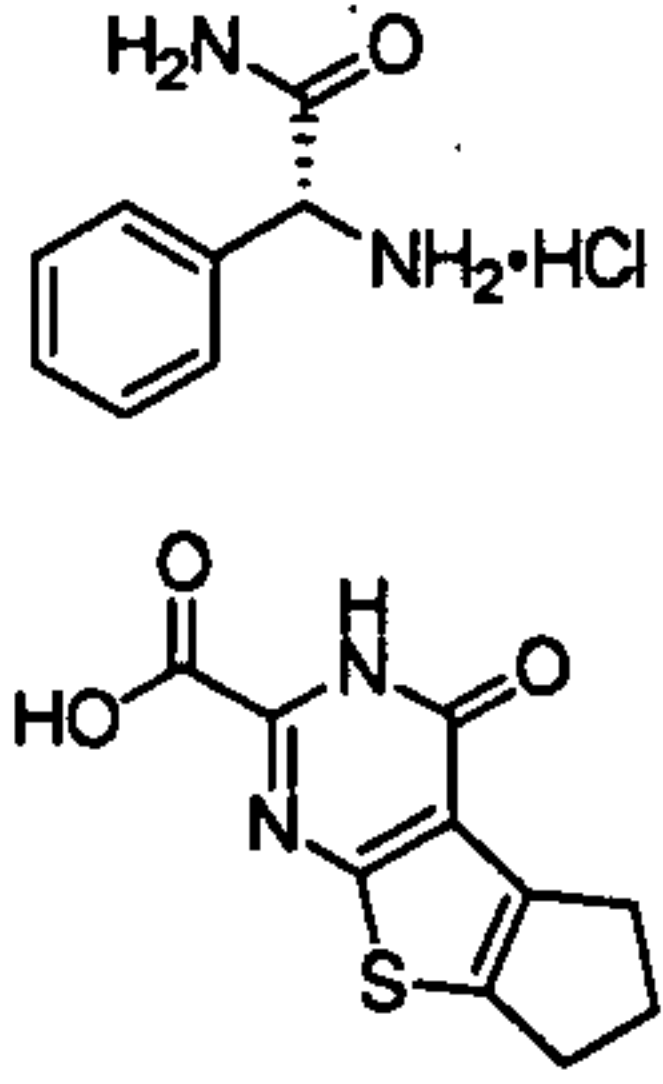
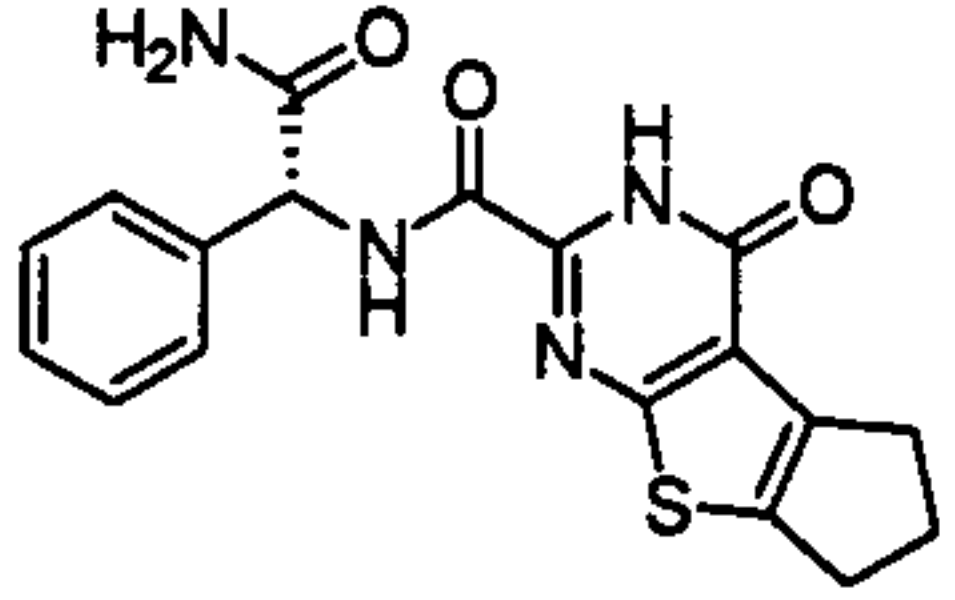
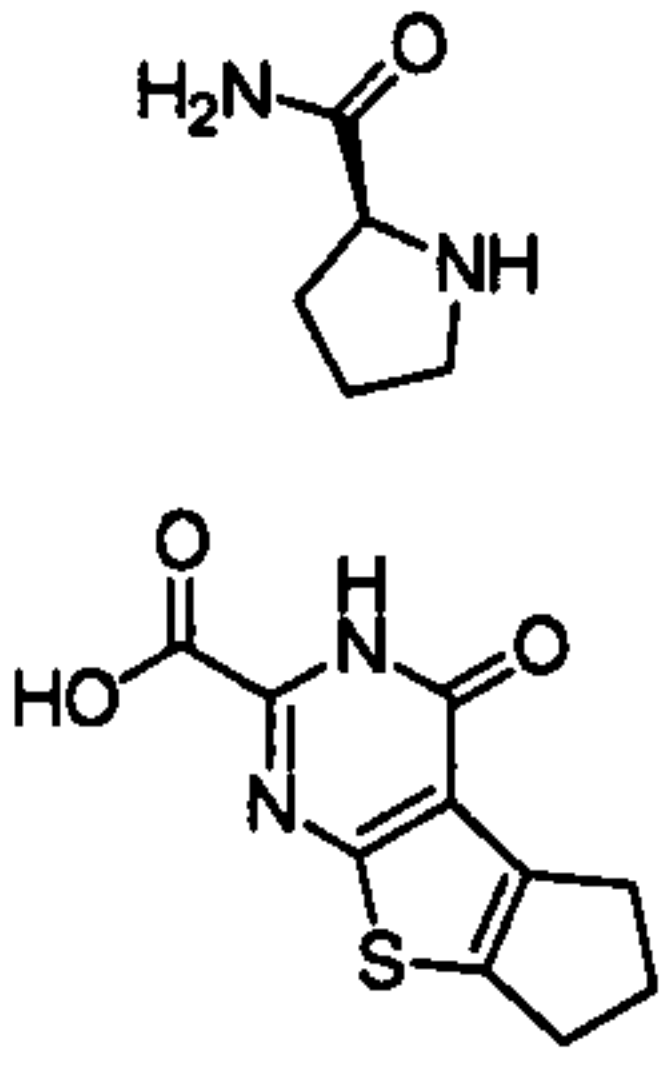
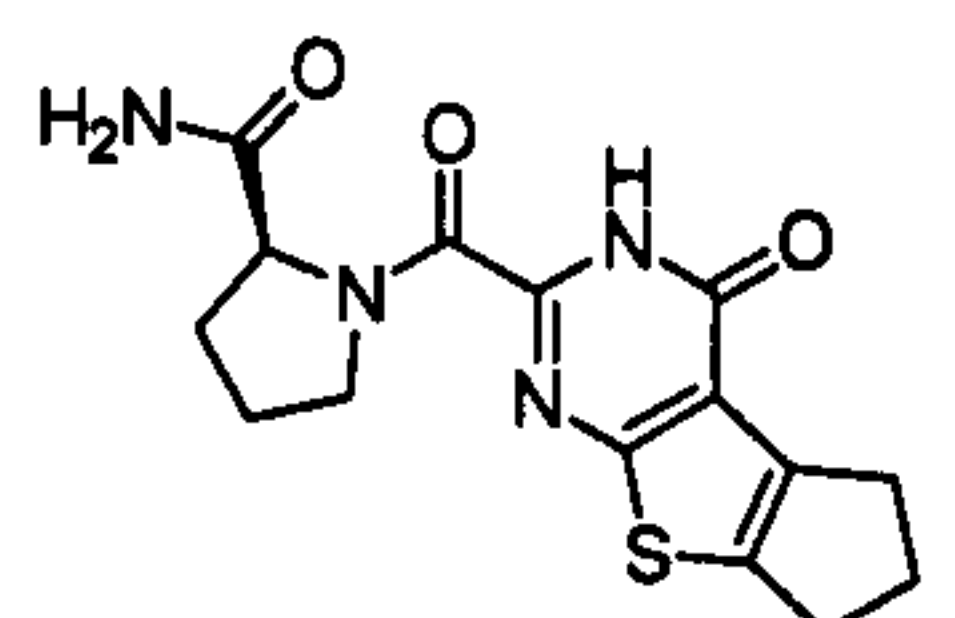
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/298 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 334    |
| 2/299 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 263    |
| 2/300 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 317    |
| 2/301 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 306 |
| 2/302 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 403    |
| 2/303 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 249    |

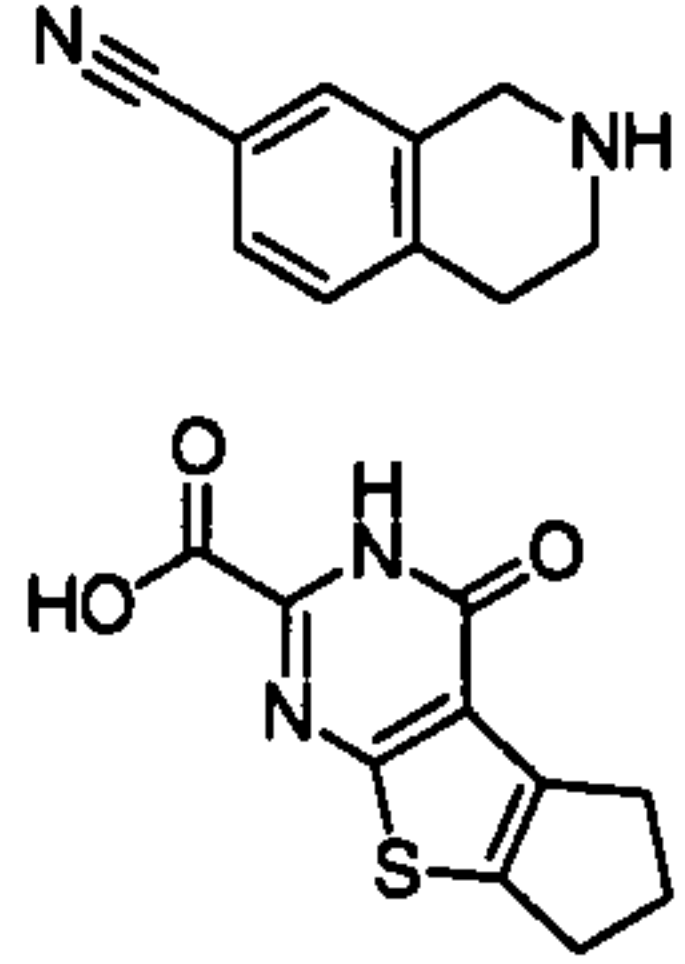
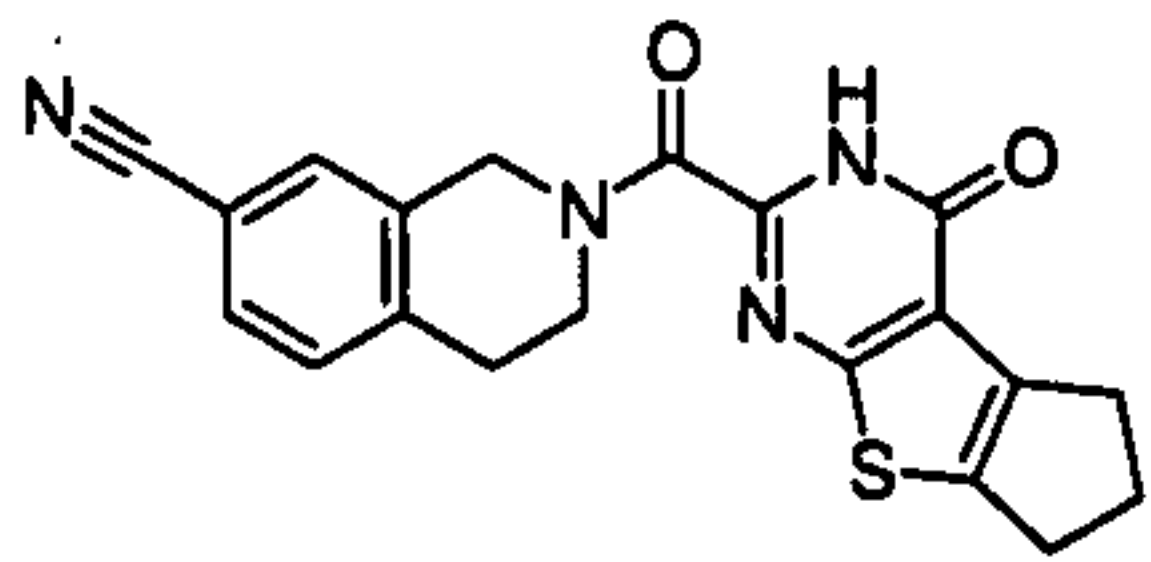
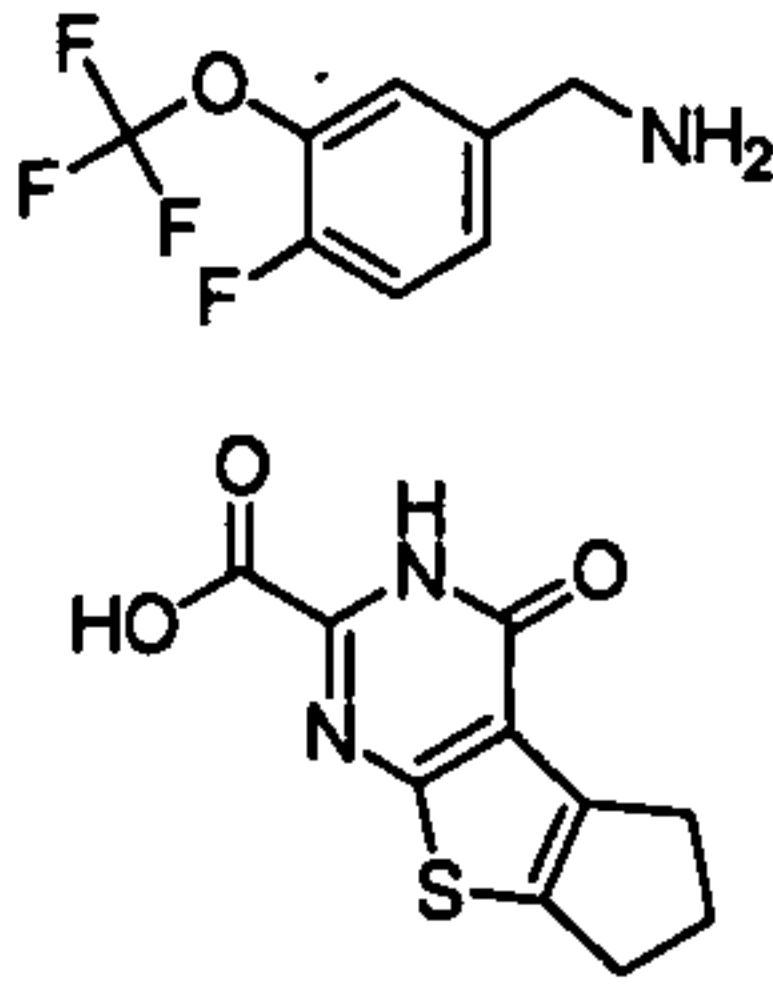
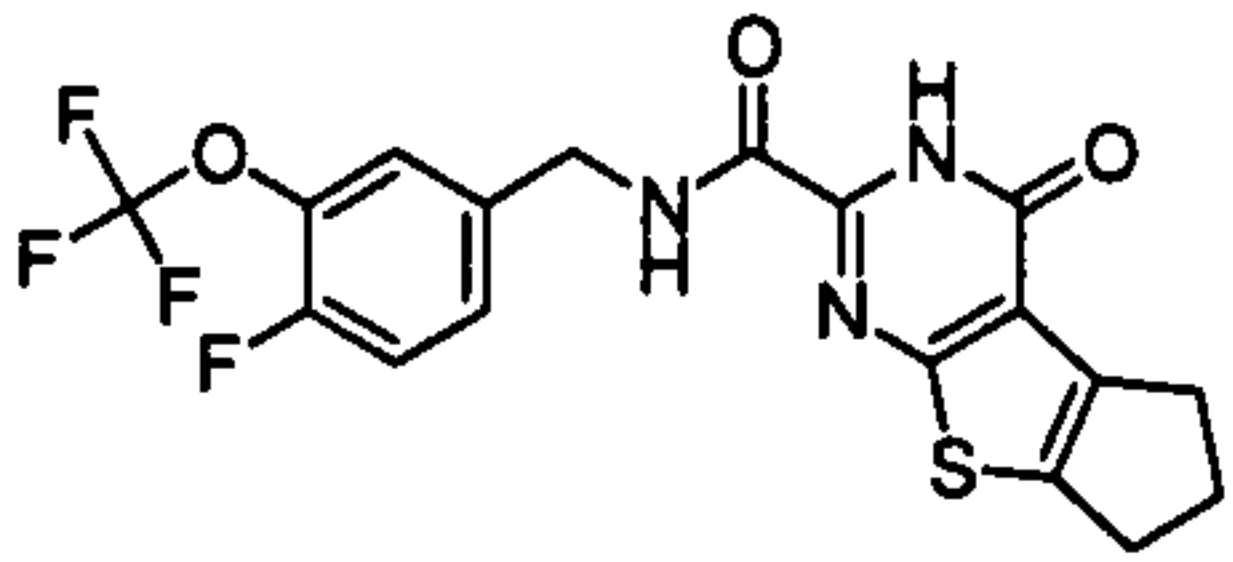
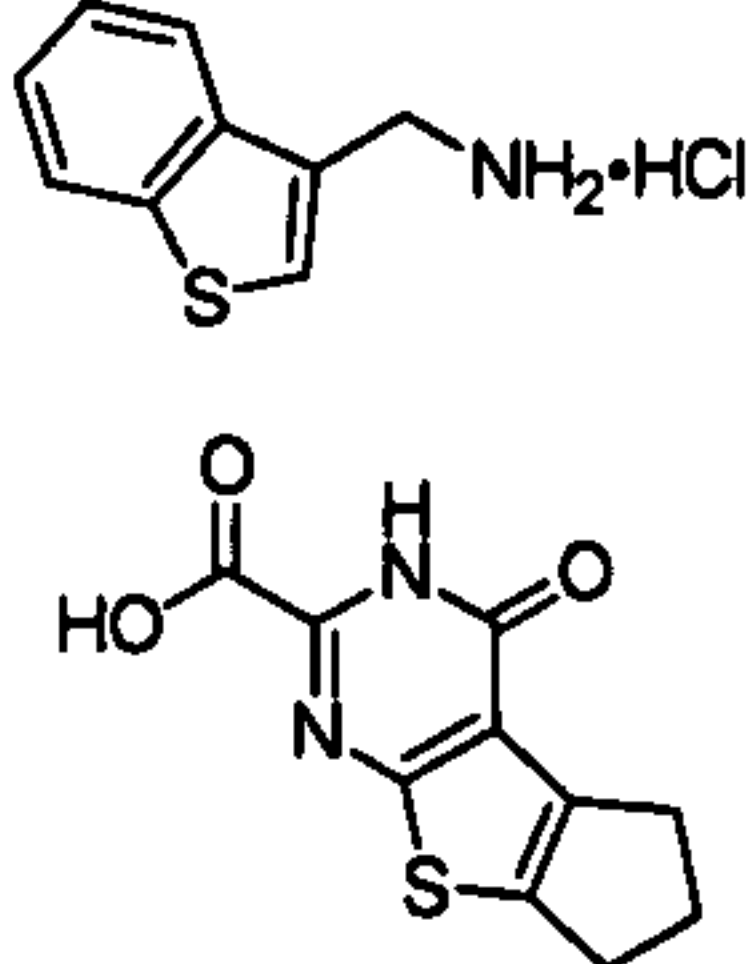
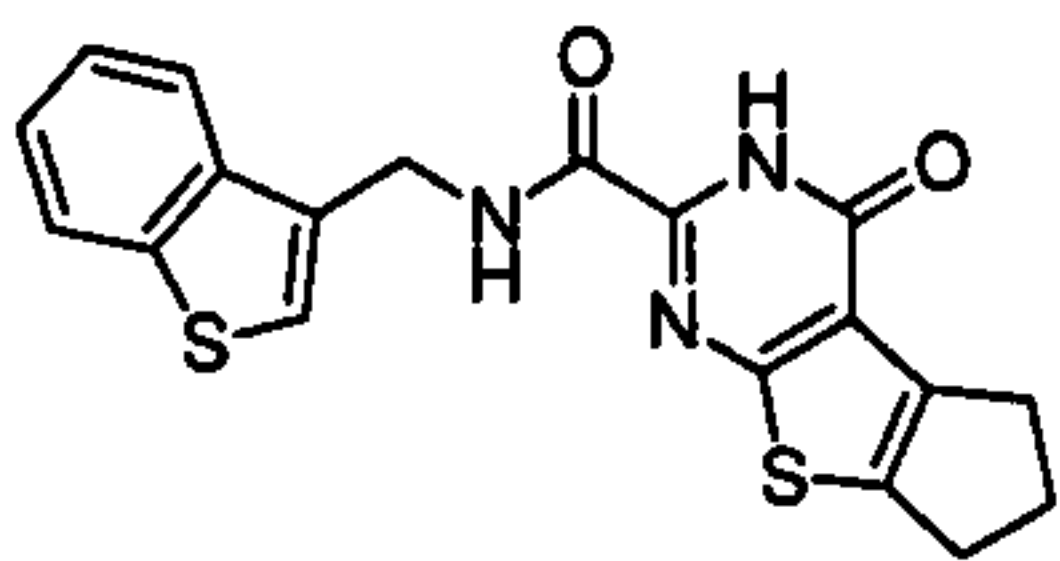
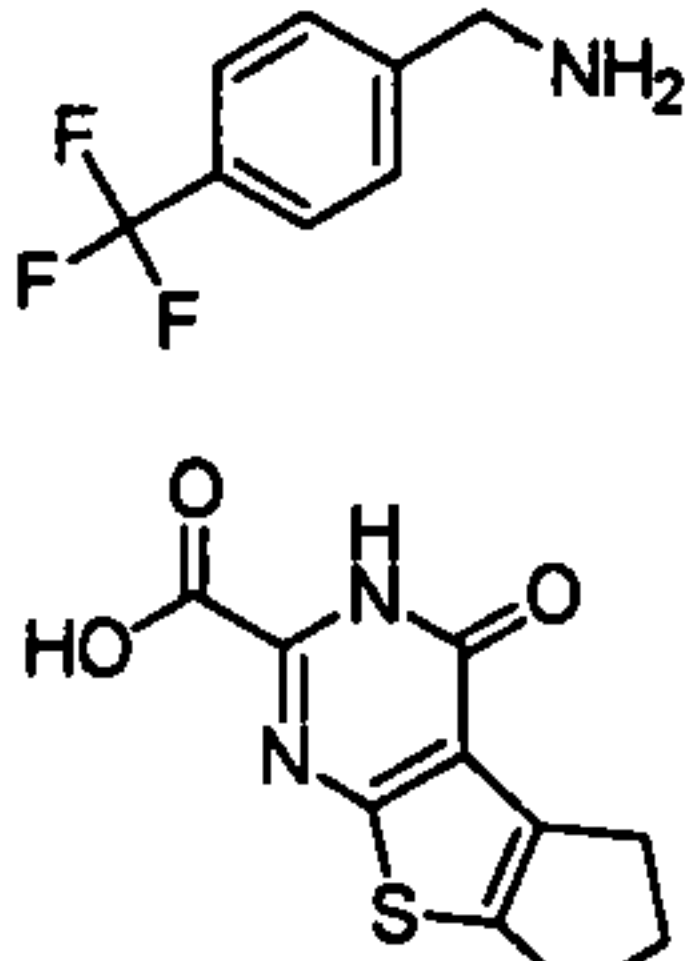
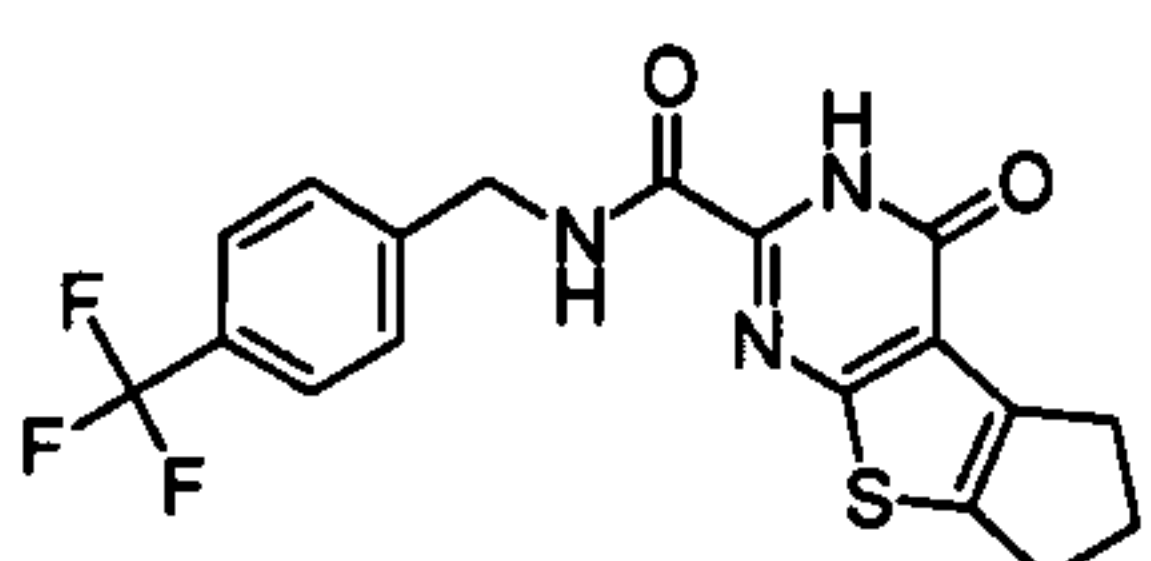
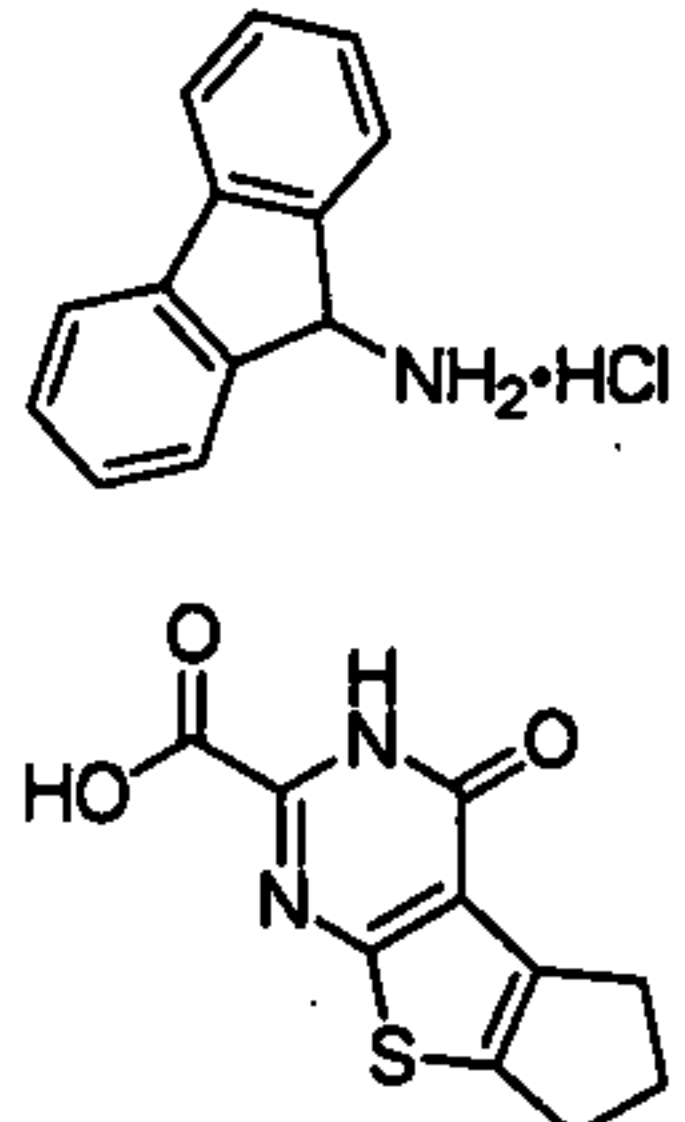
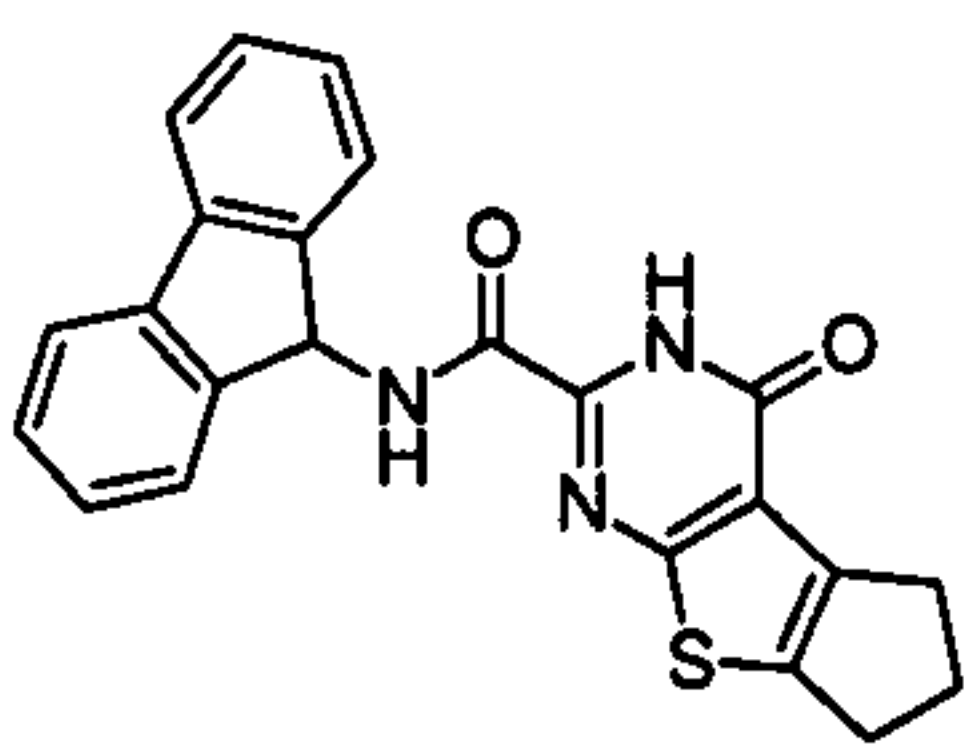
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/304 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 339    |
| 2/305 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 357    |
| 2/306 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 318 |
| 2/307 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 365    |
| 2/308 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 292    |
| 2/309 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 326 |

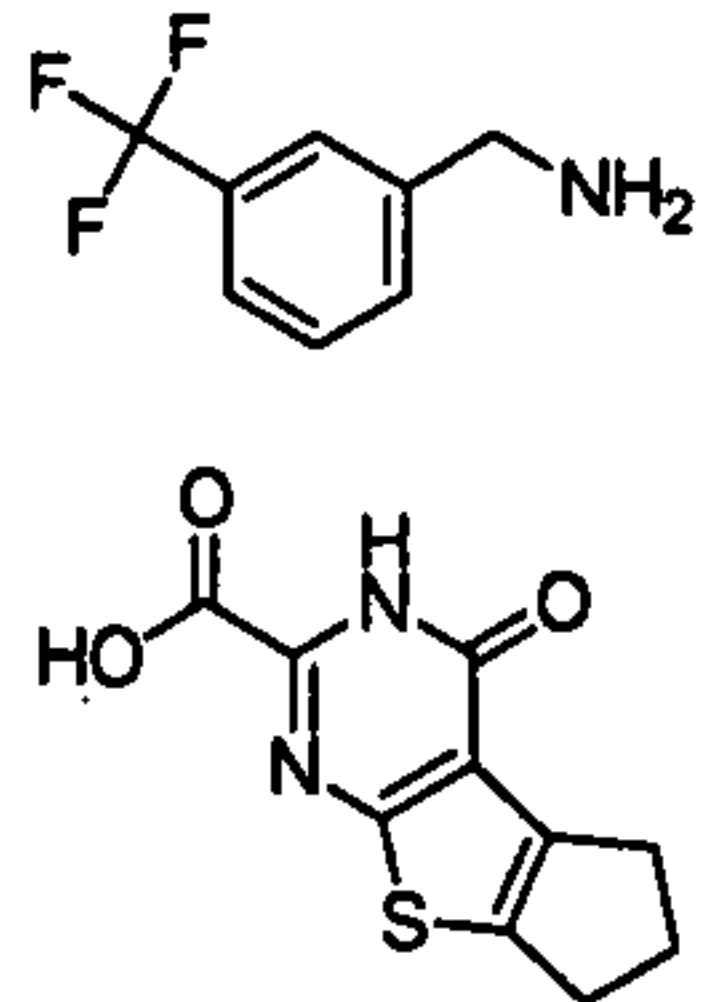
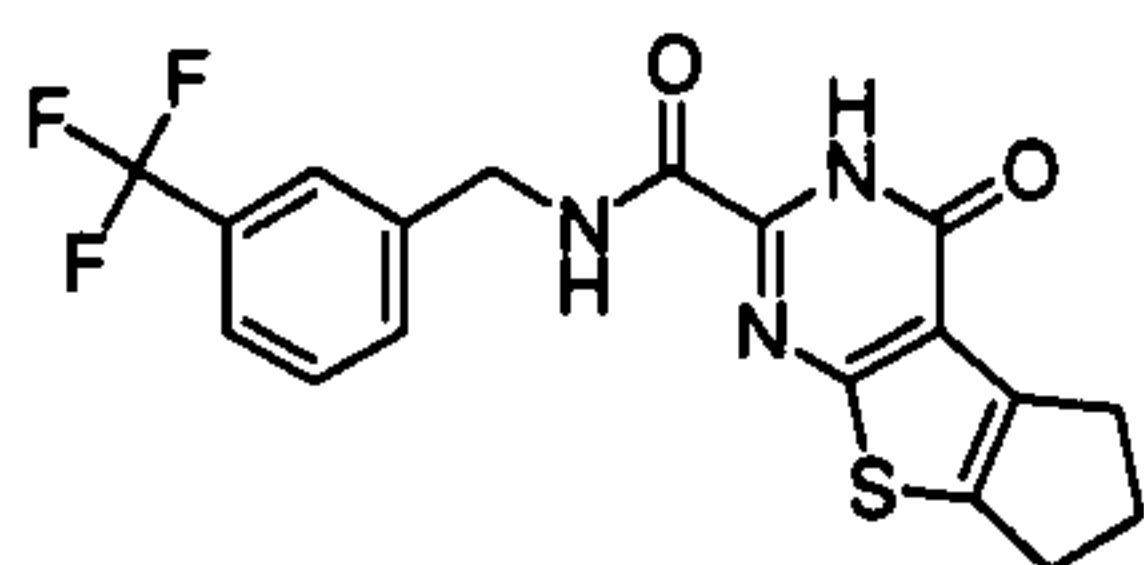
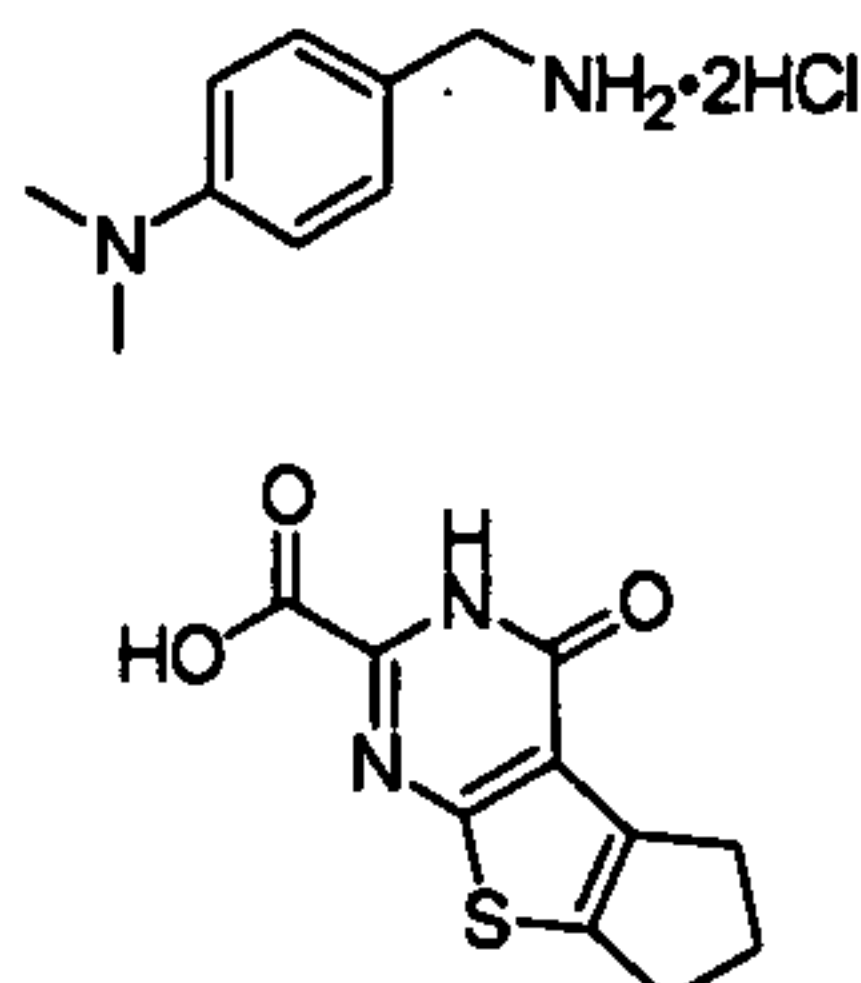
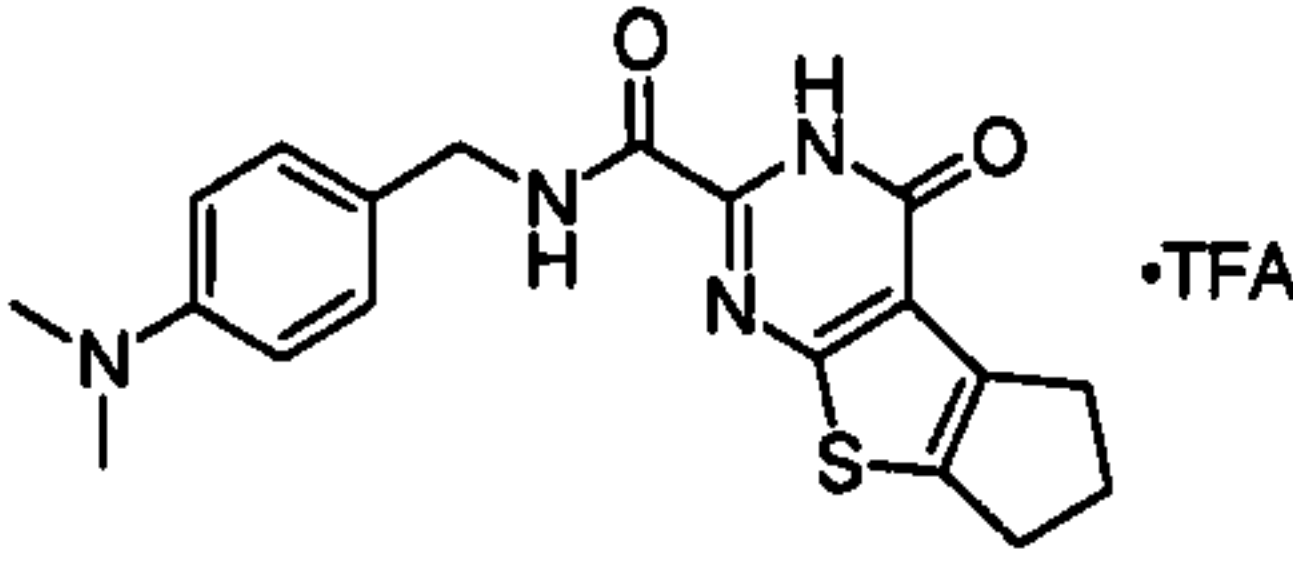
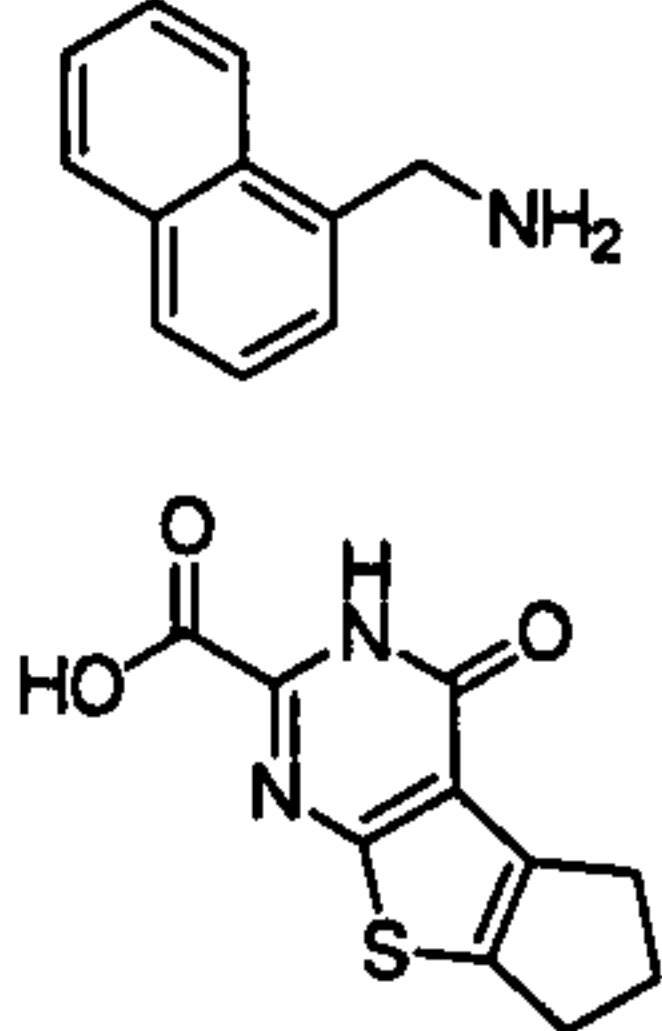
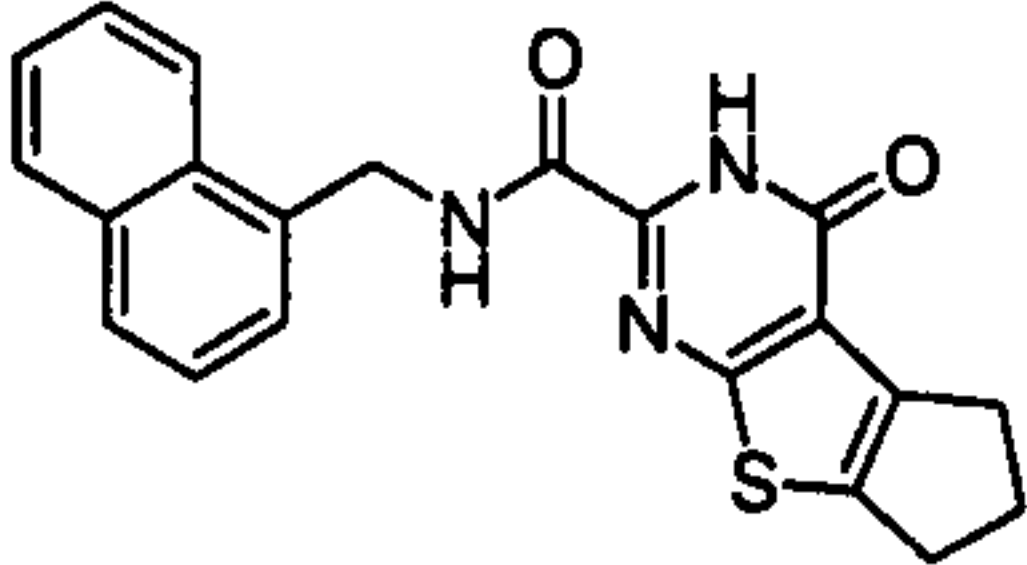
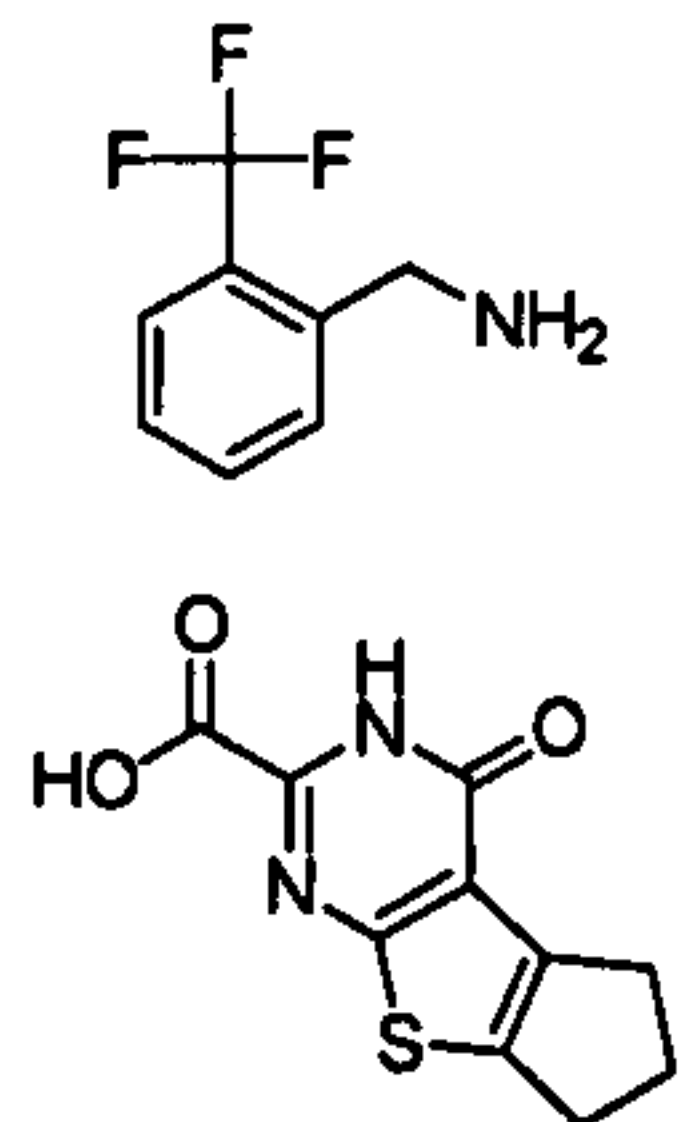
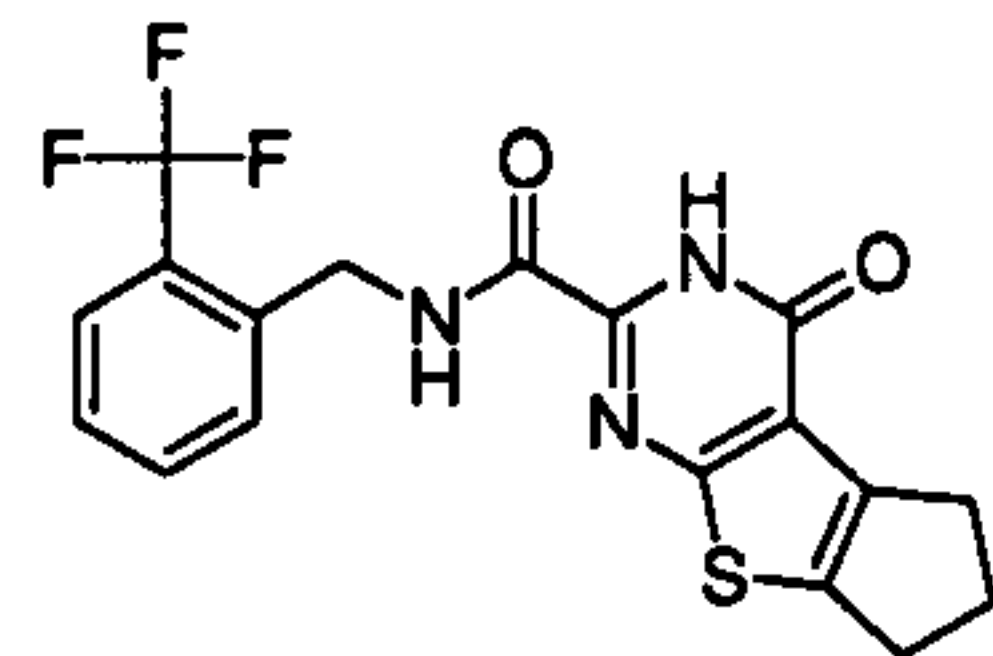
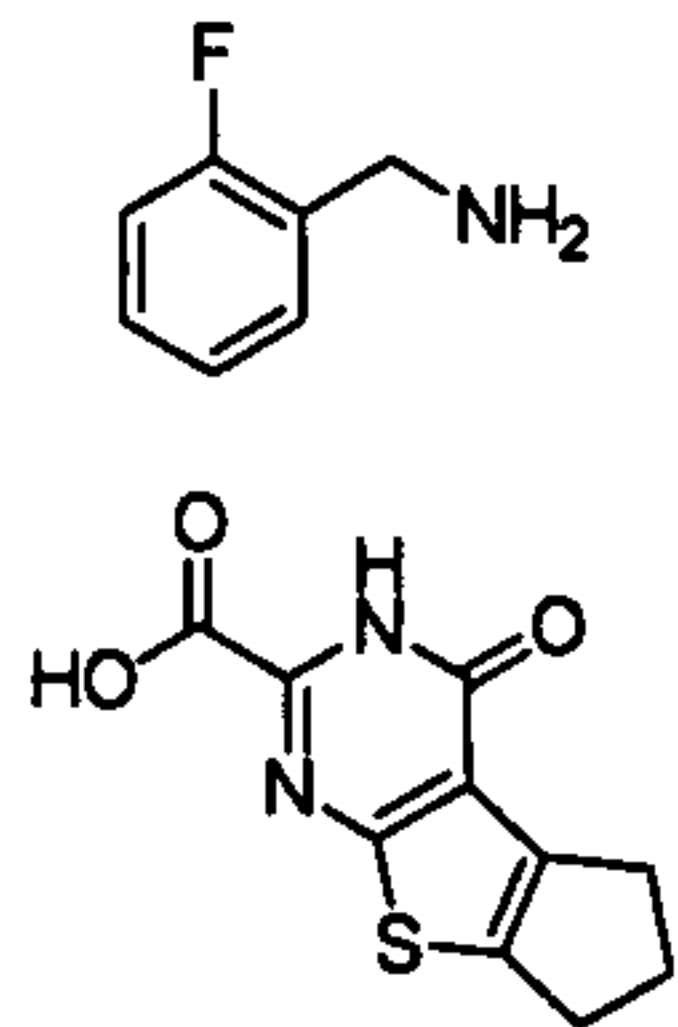
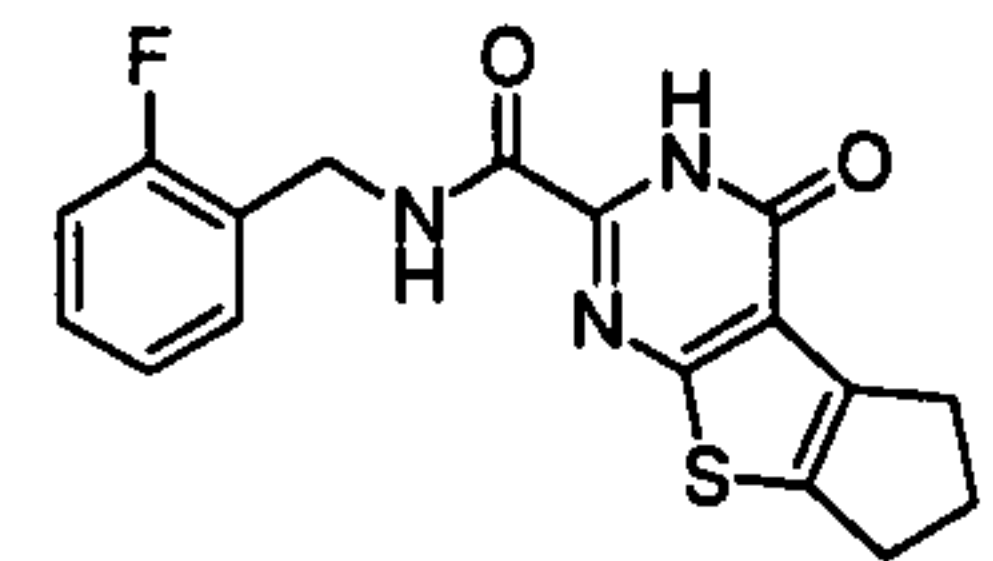
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/310 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 339 |
| 2/311 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 339 |
| 2/312 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 318 |
| 2/313 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 357 |
| 2/314 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 404 |
| 2/315 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 409 |

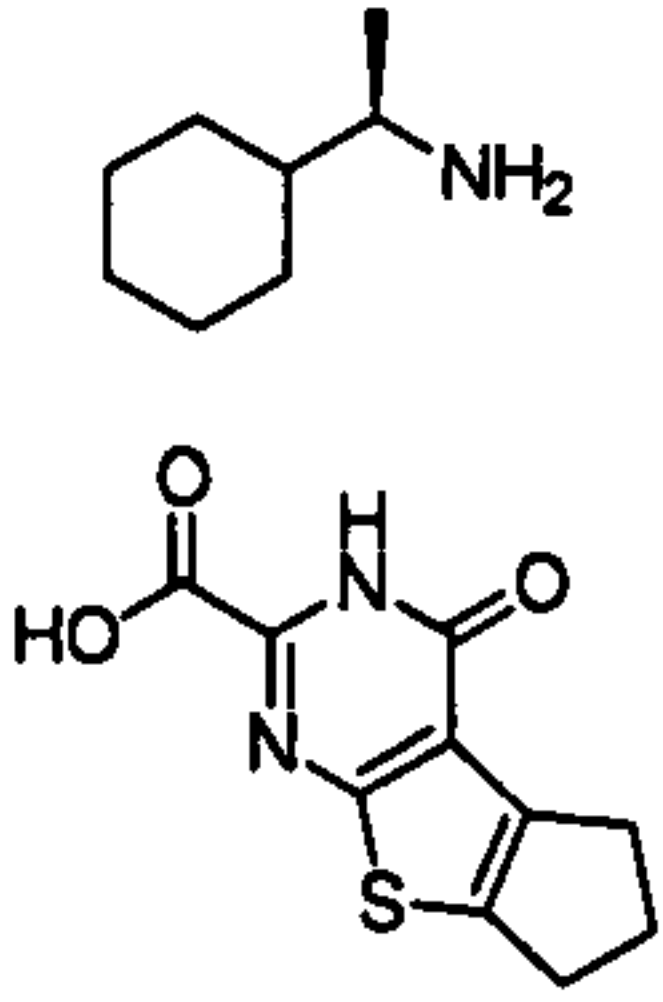
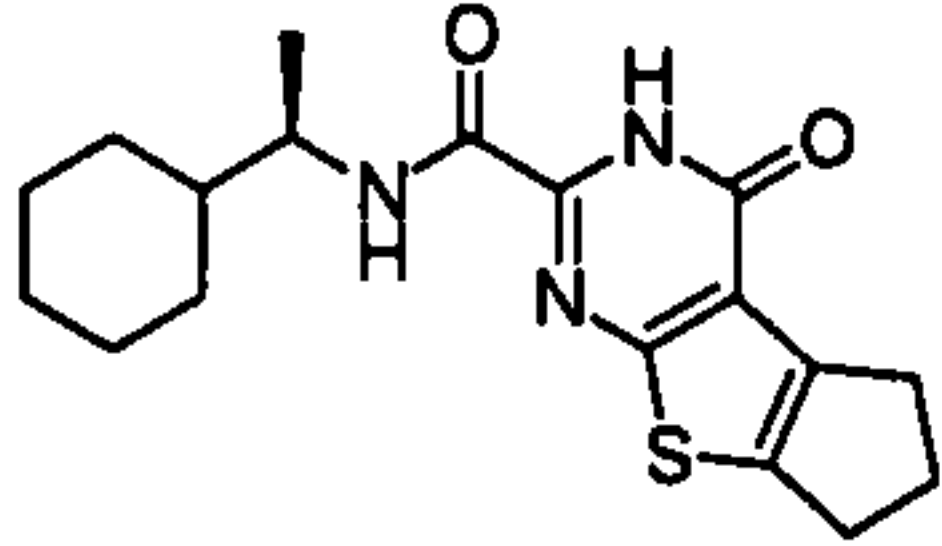
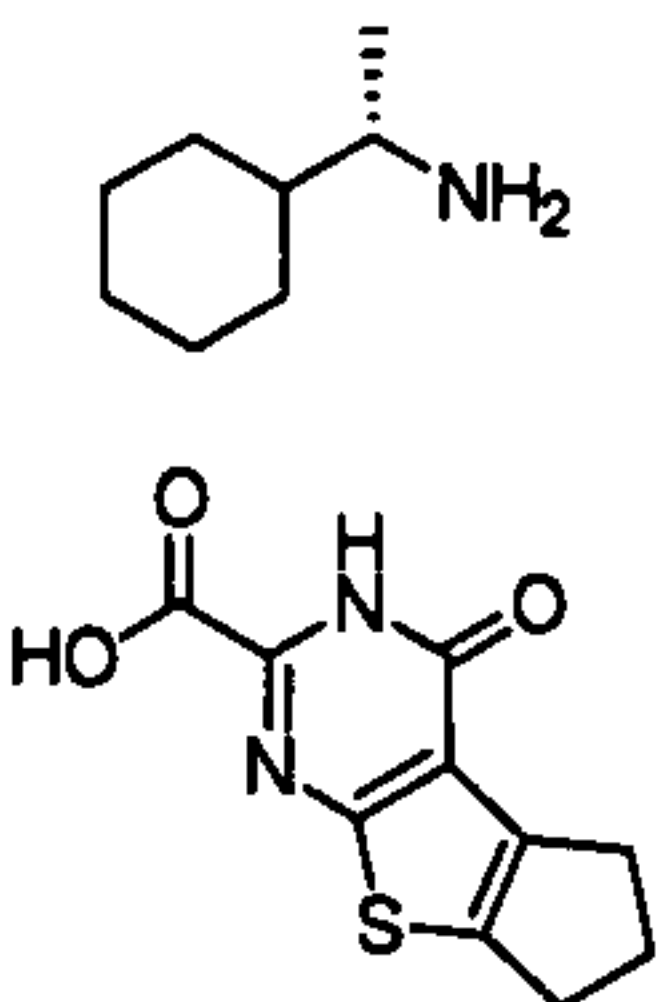
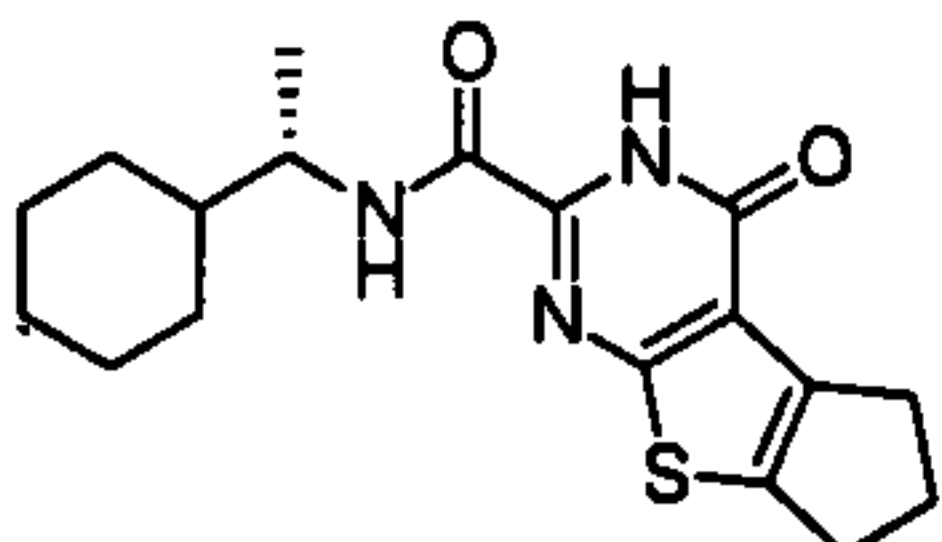
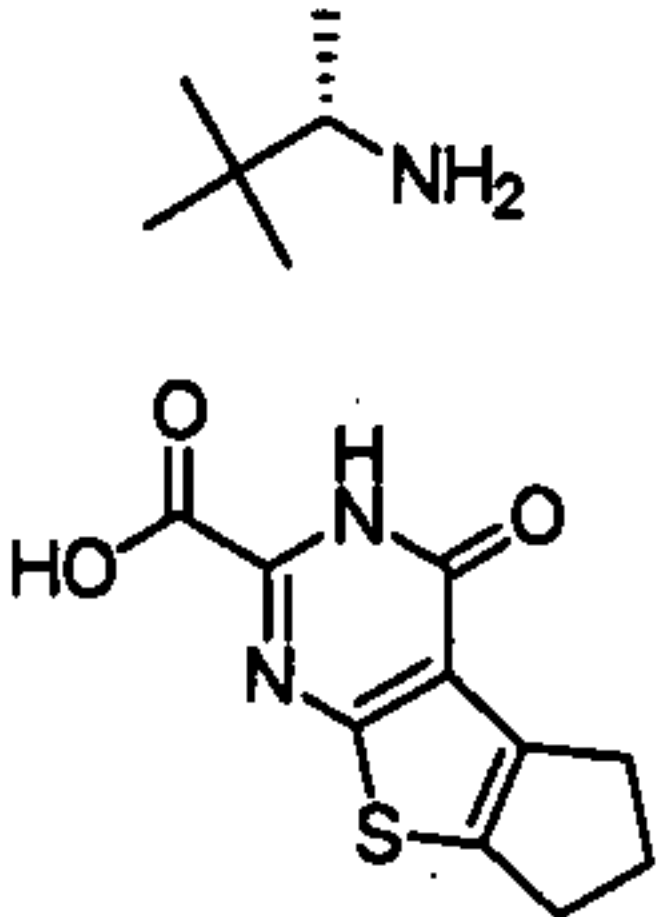
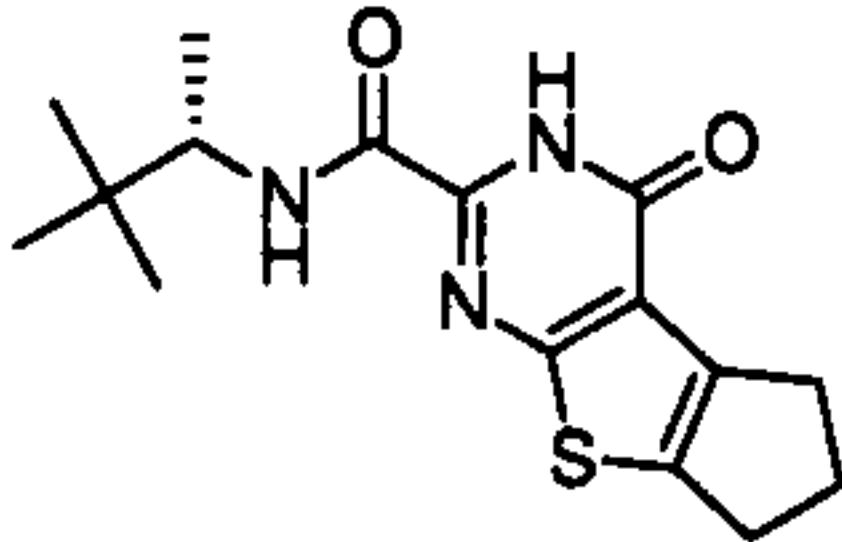
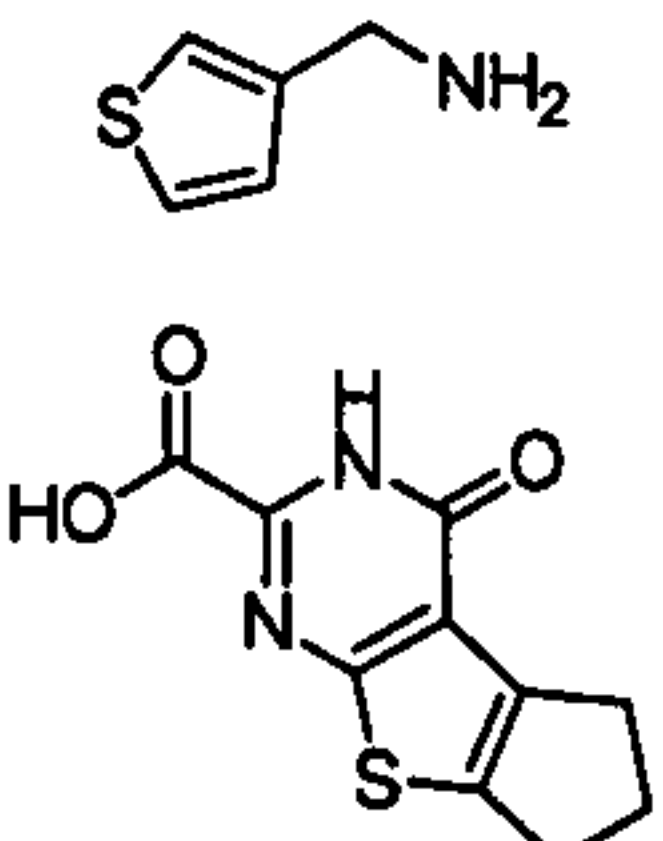
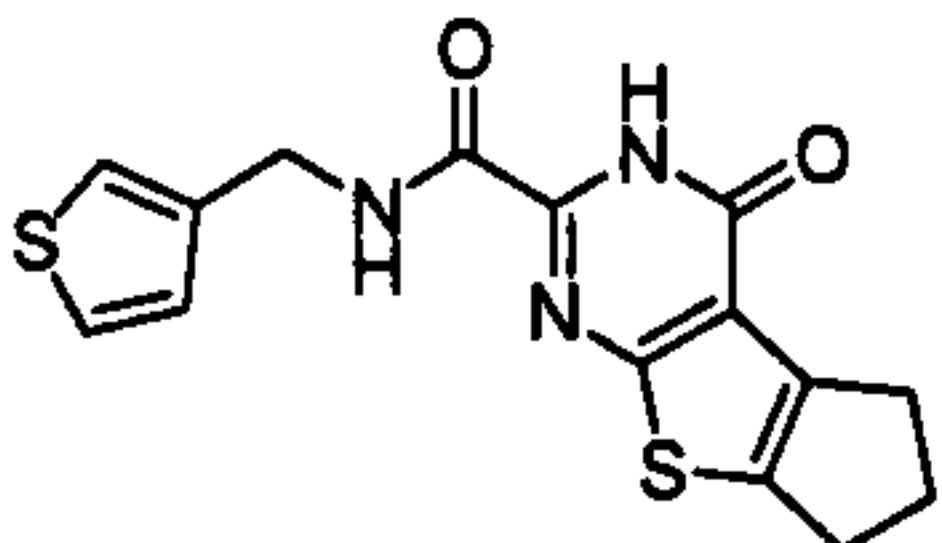
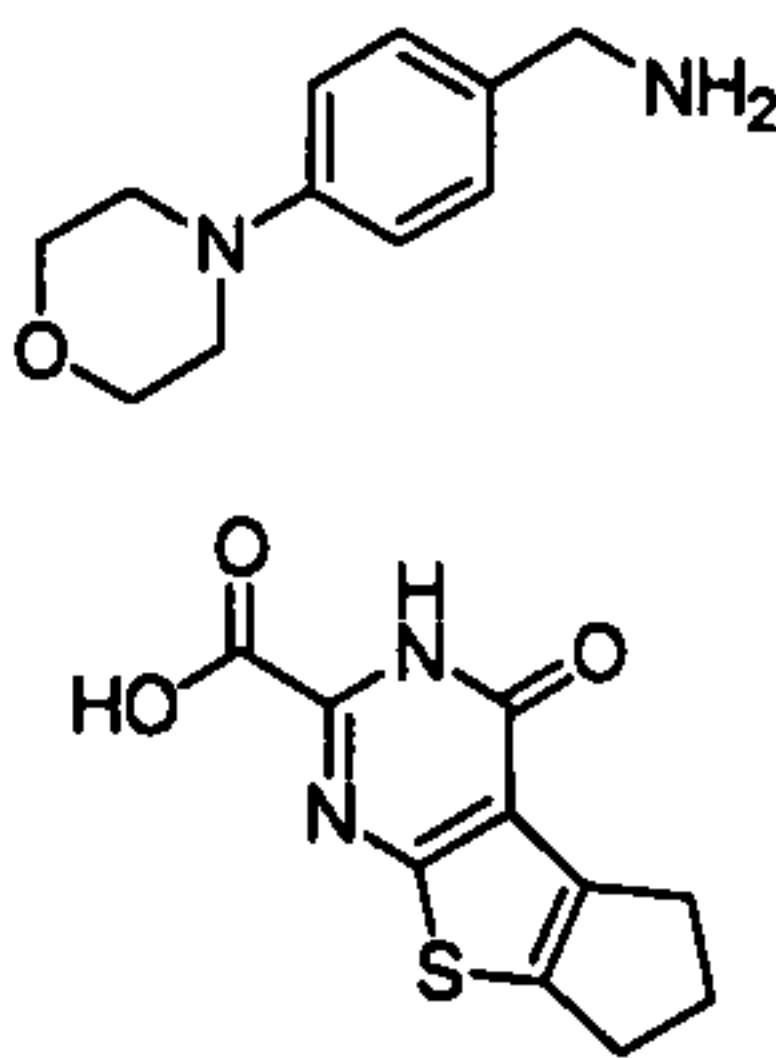
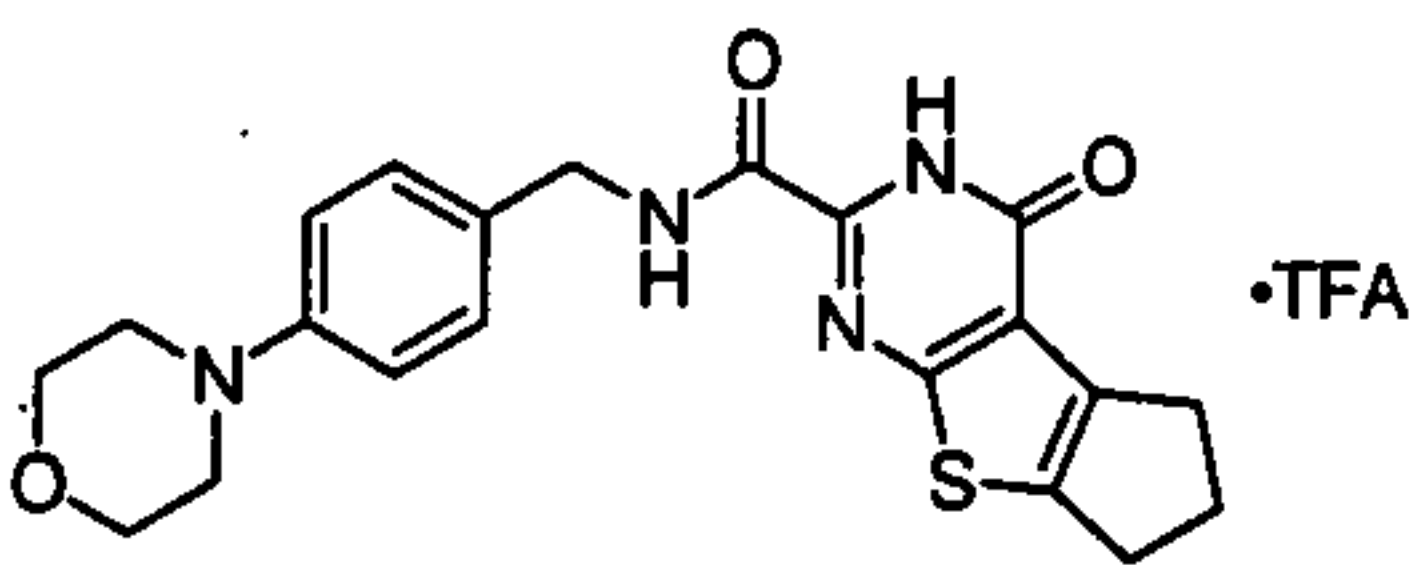
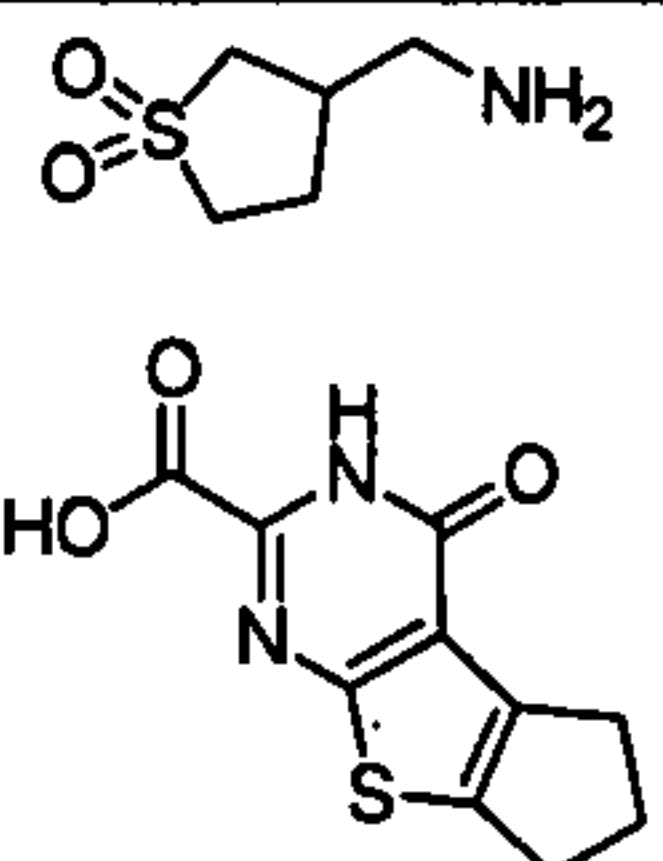
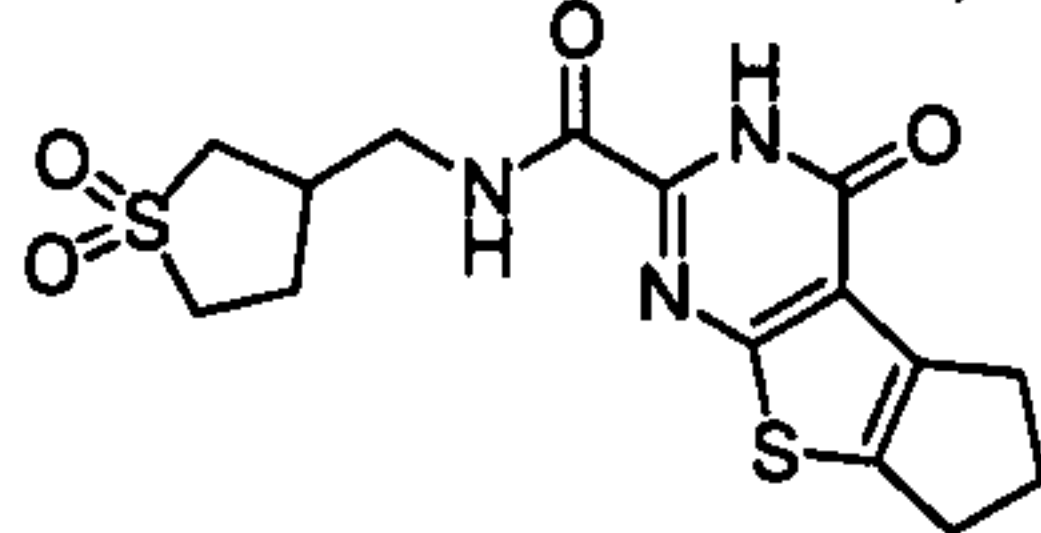
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/316 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 383    |
| 2/317 |   |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 506 |
| 2/318 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 383    |
| 2/319 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 357    |
| 2/320 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 357    |

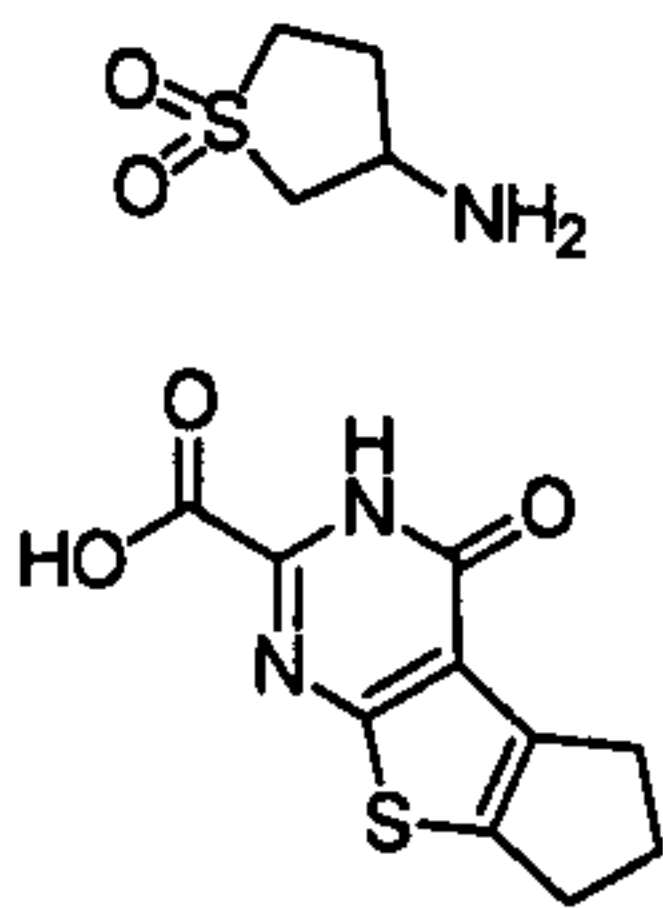
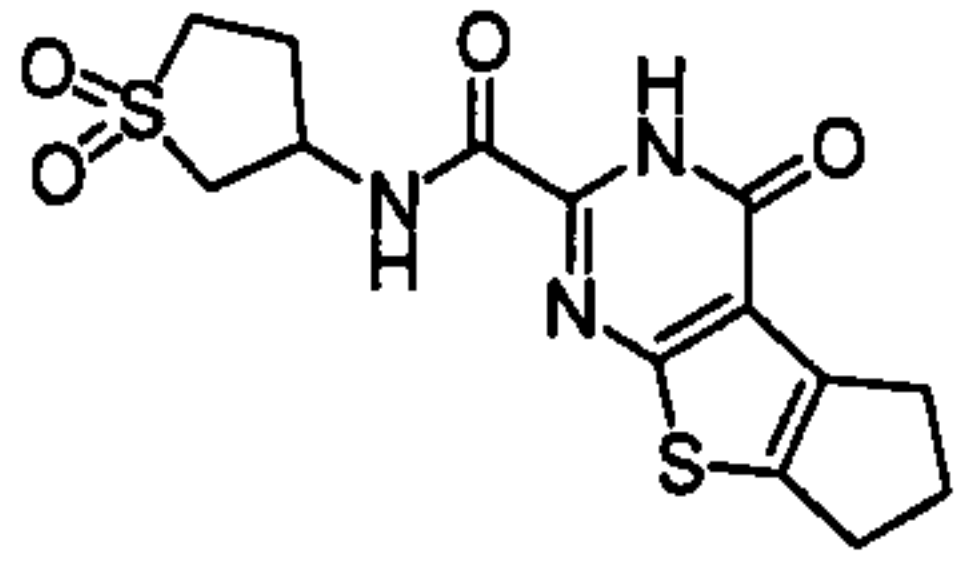
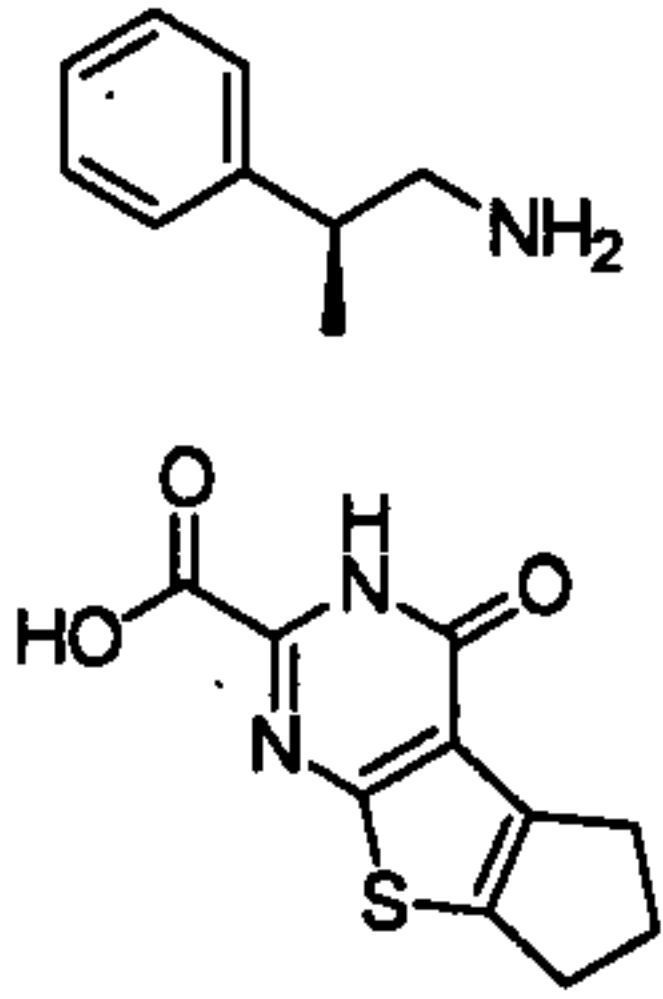
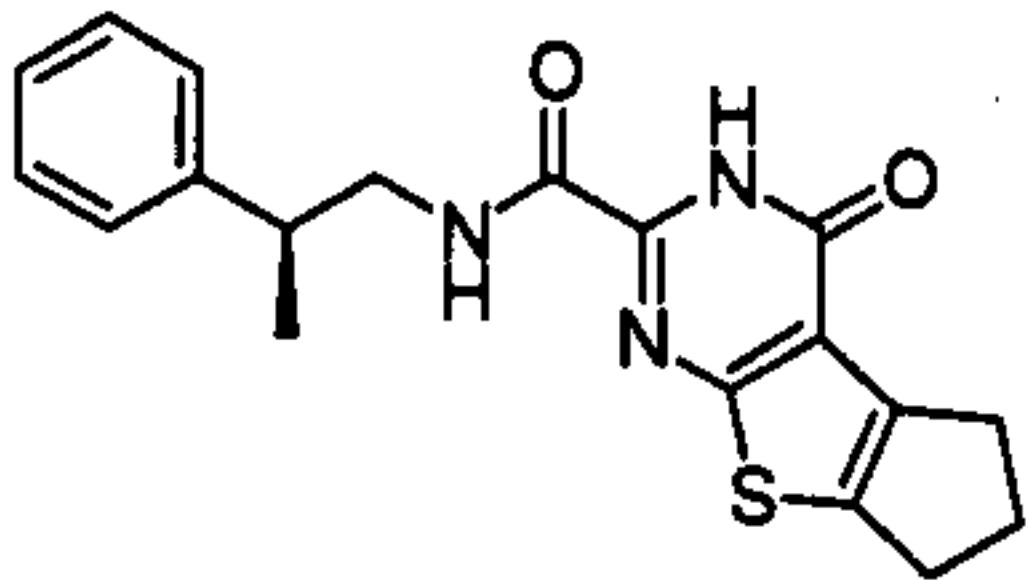
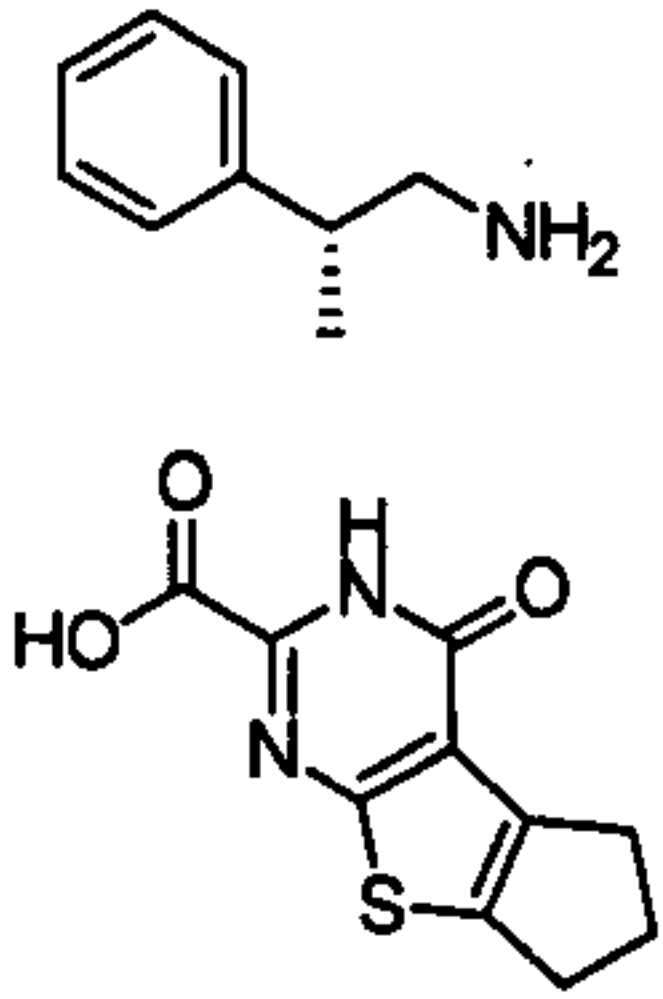
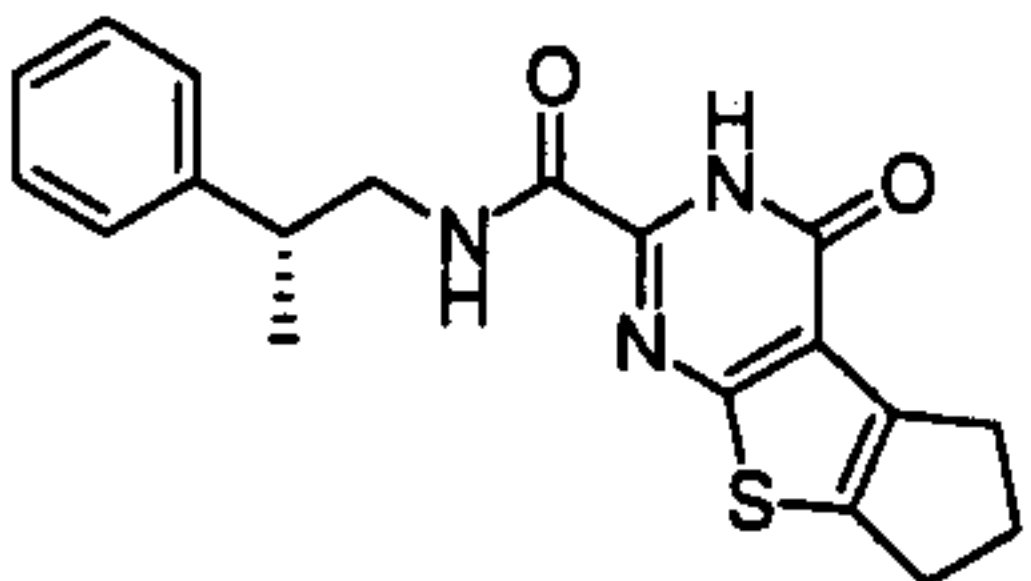
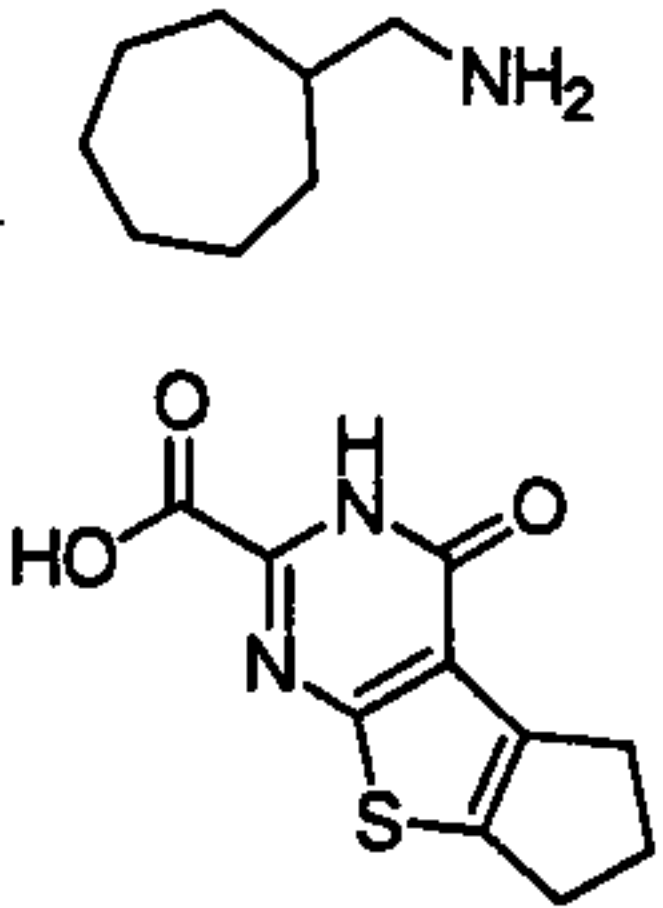
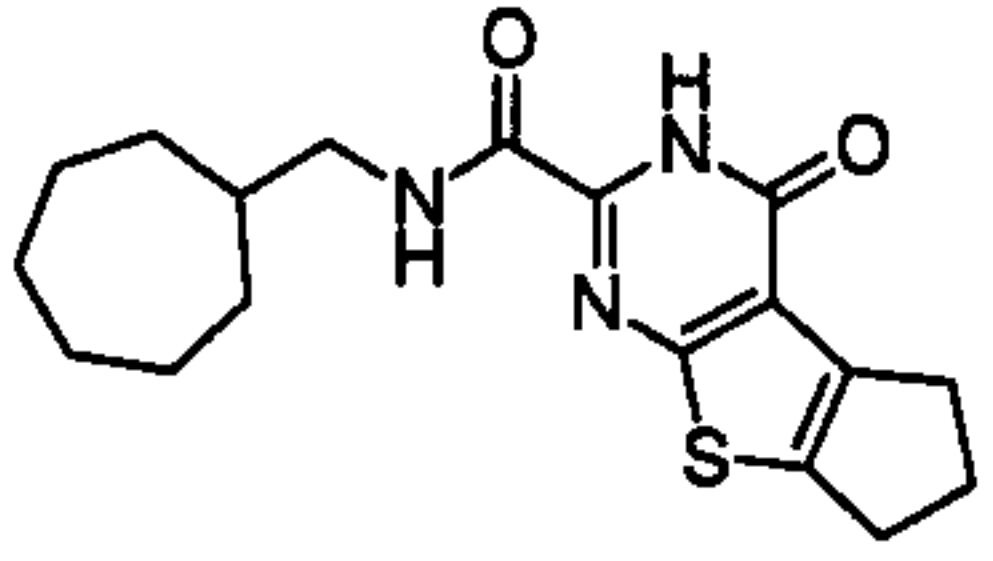
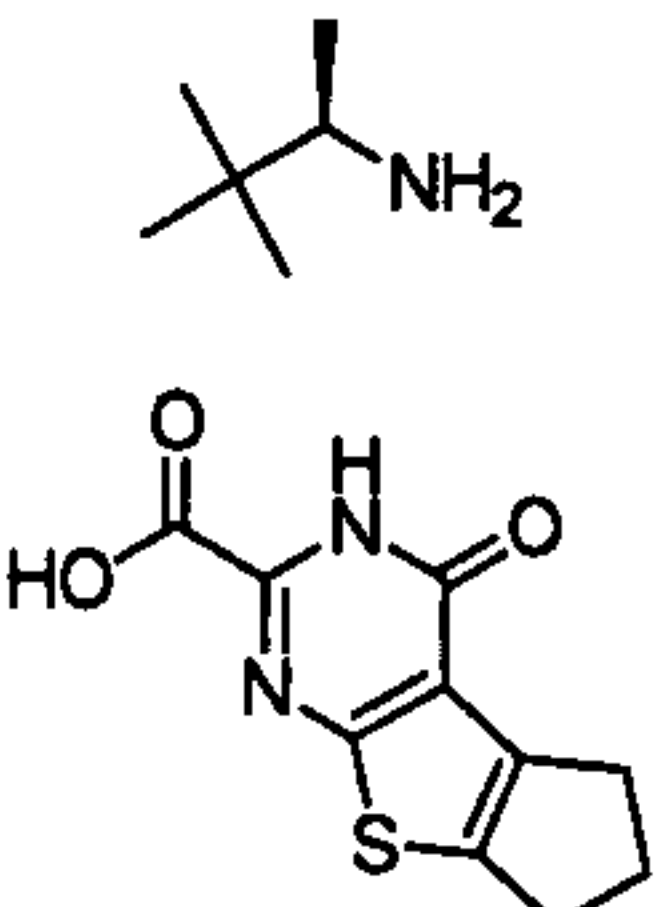
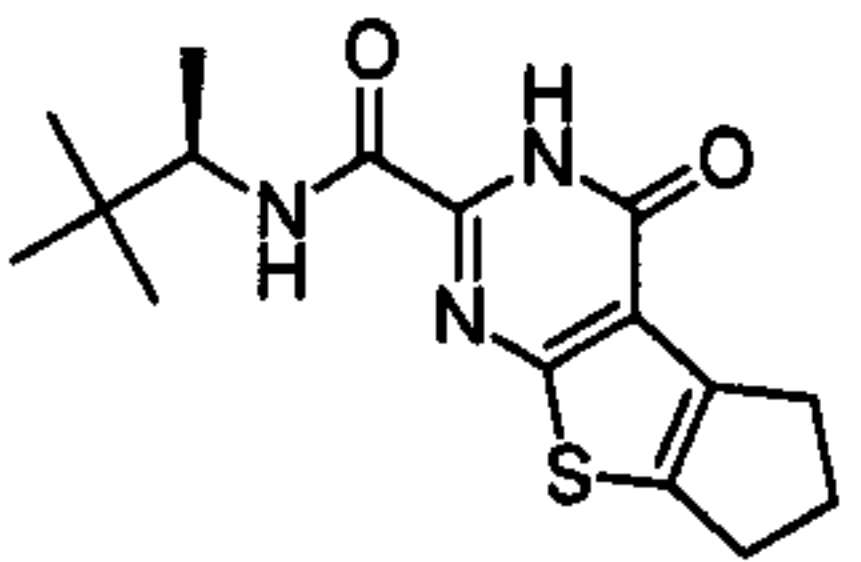
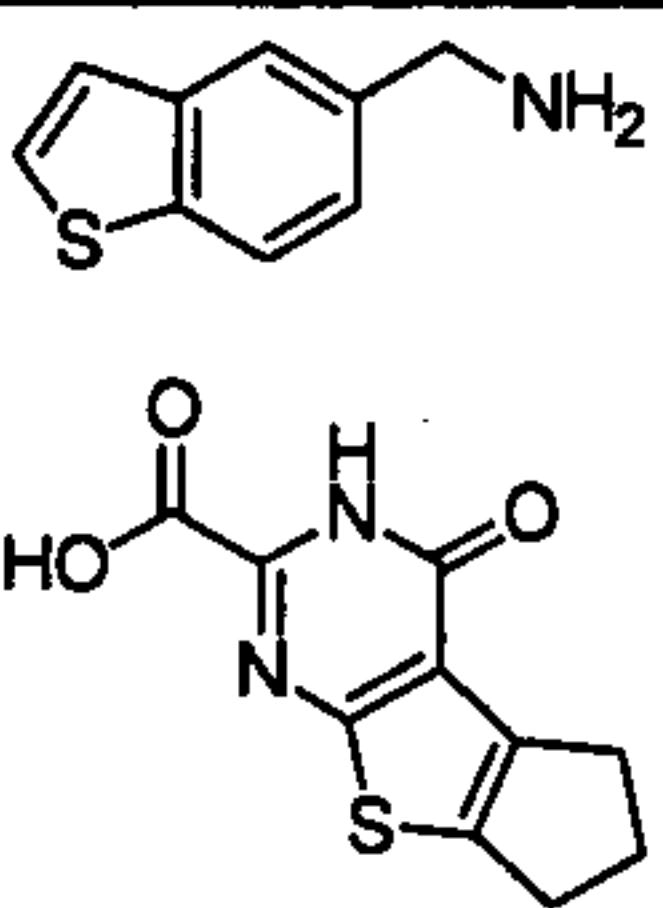
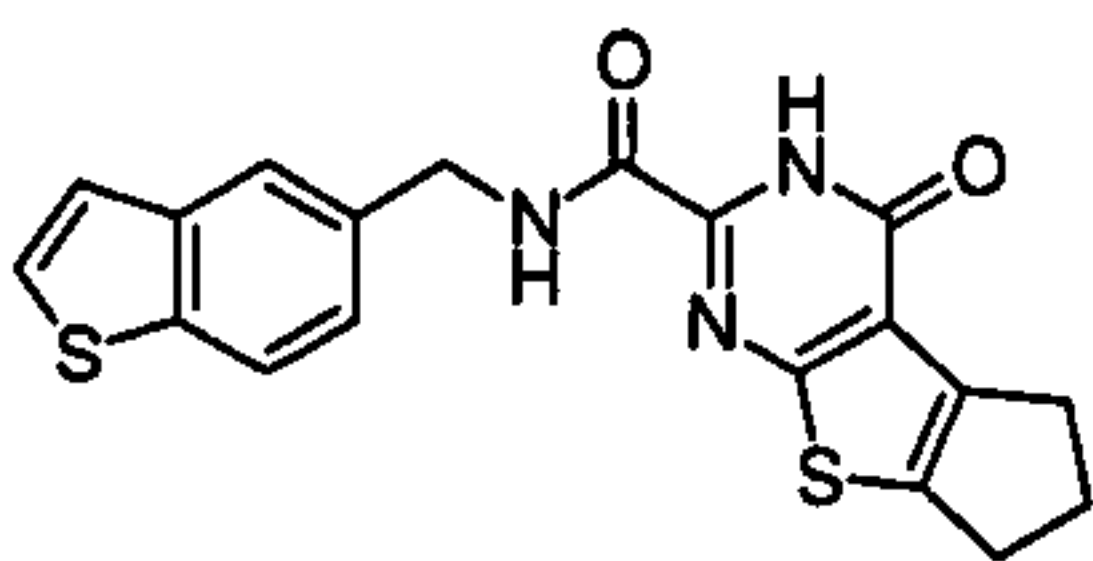
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/321 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 401 |
| 2/322 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 365 |
| 2/323 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 346 |
| 2/324 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 365 |
| 2/325 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 351 |

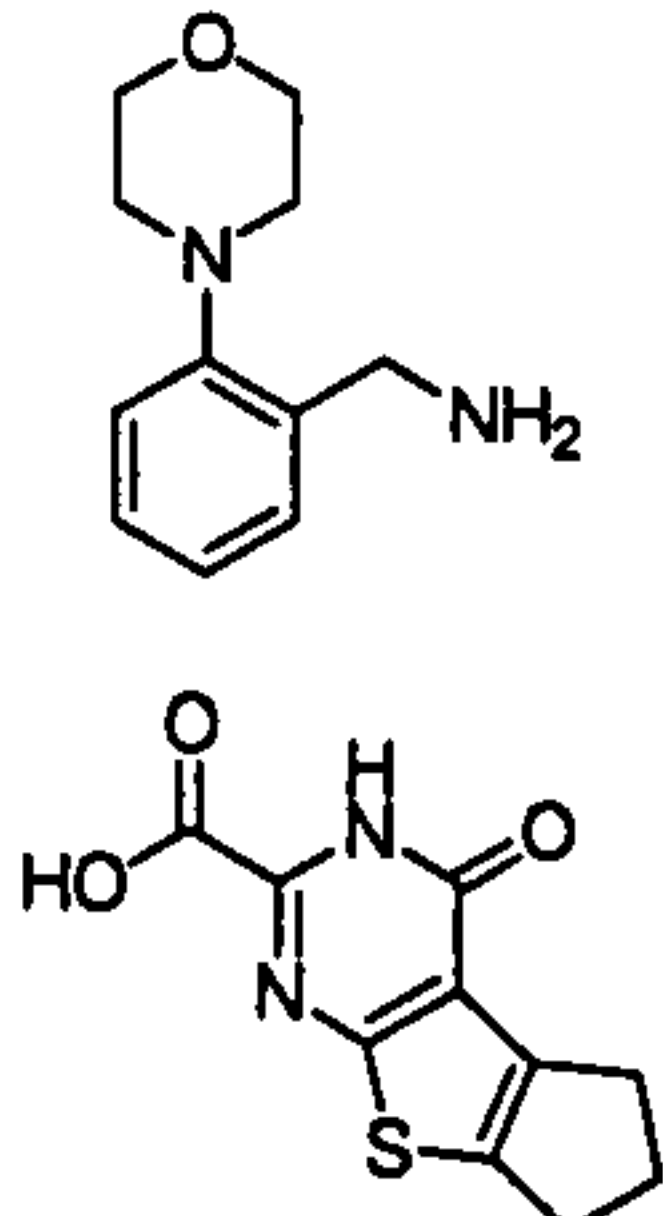
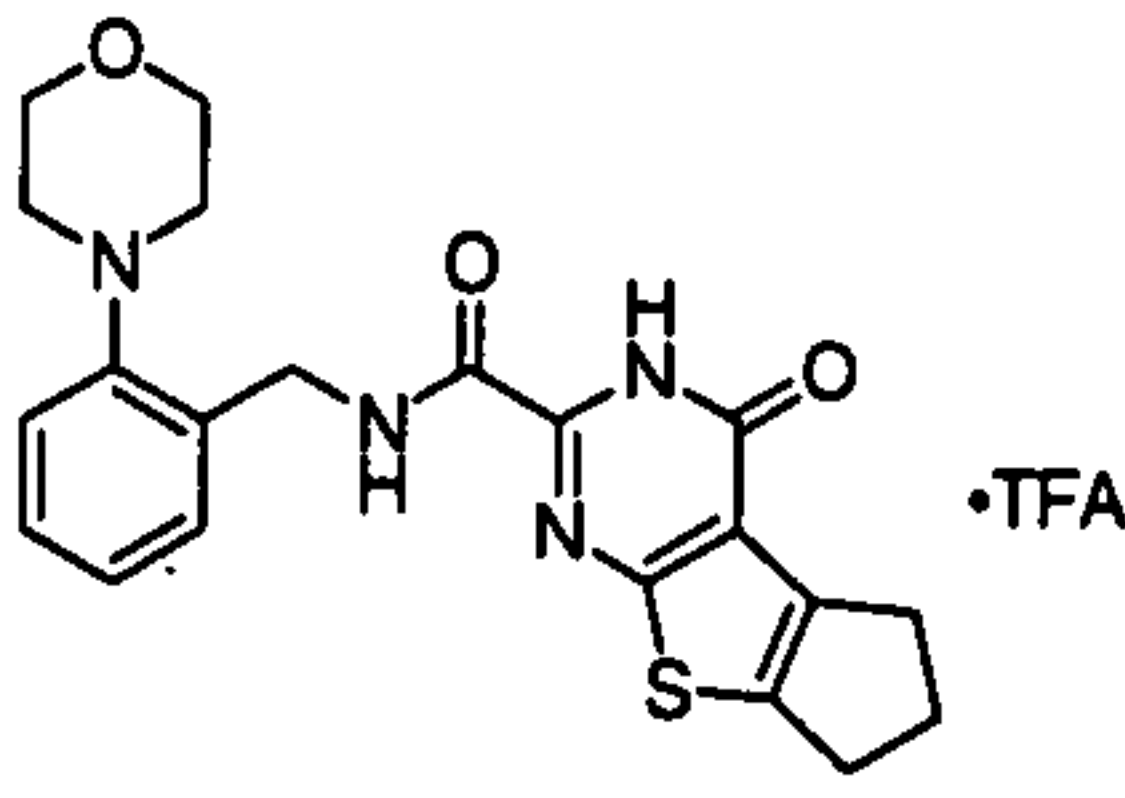
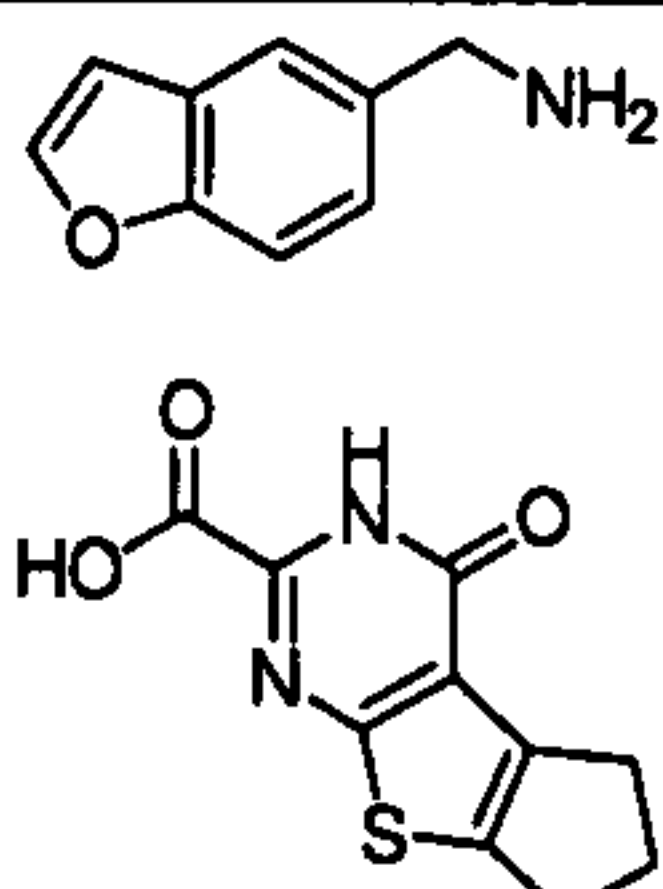
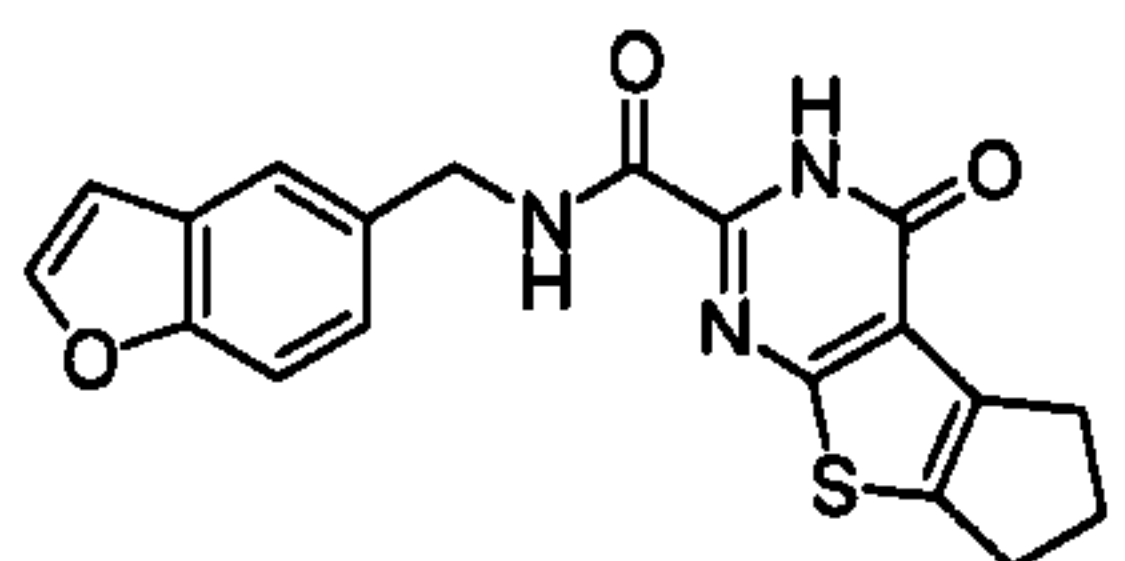
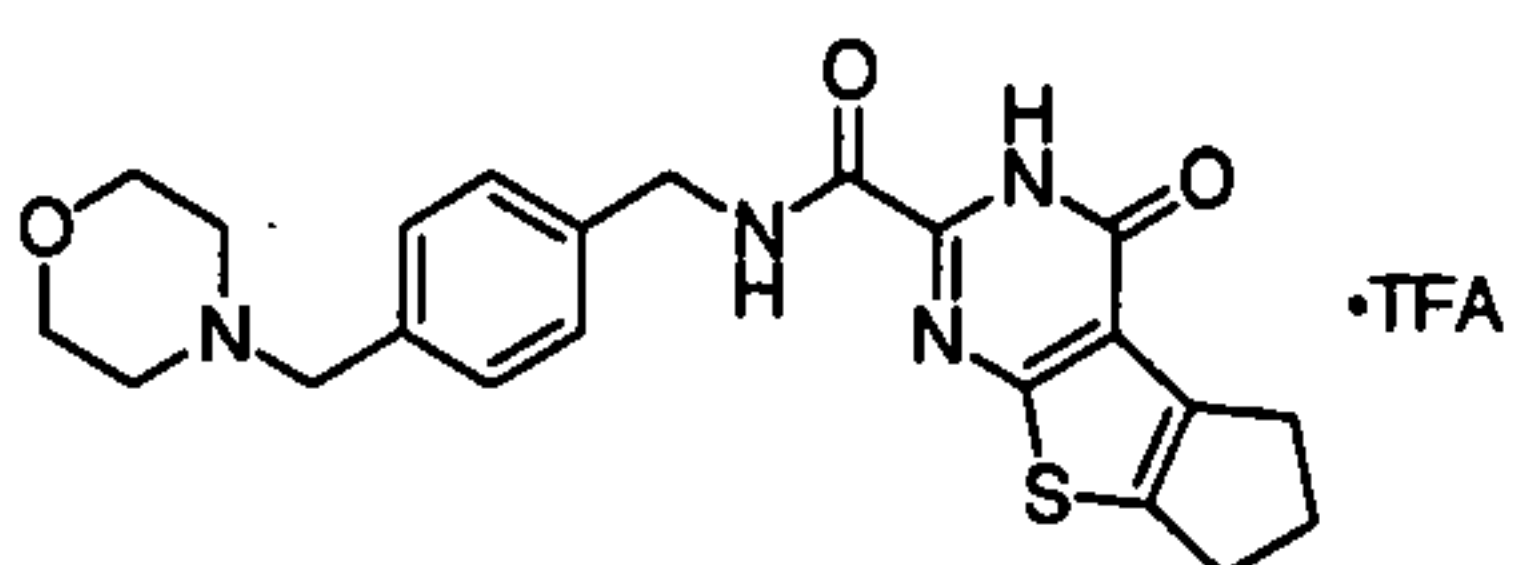
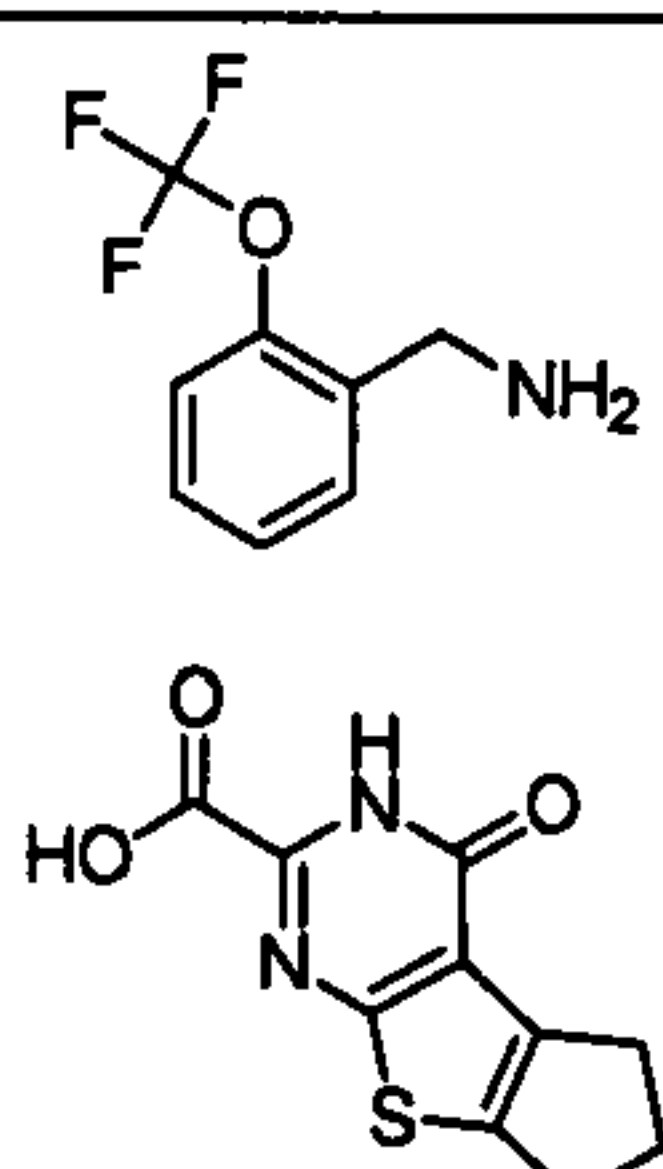
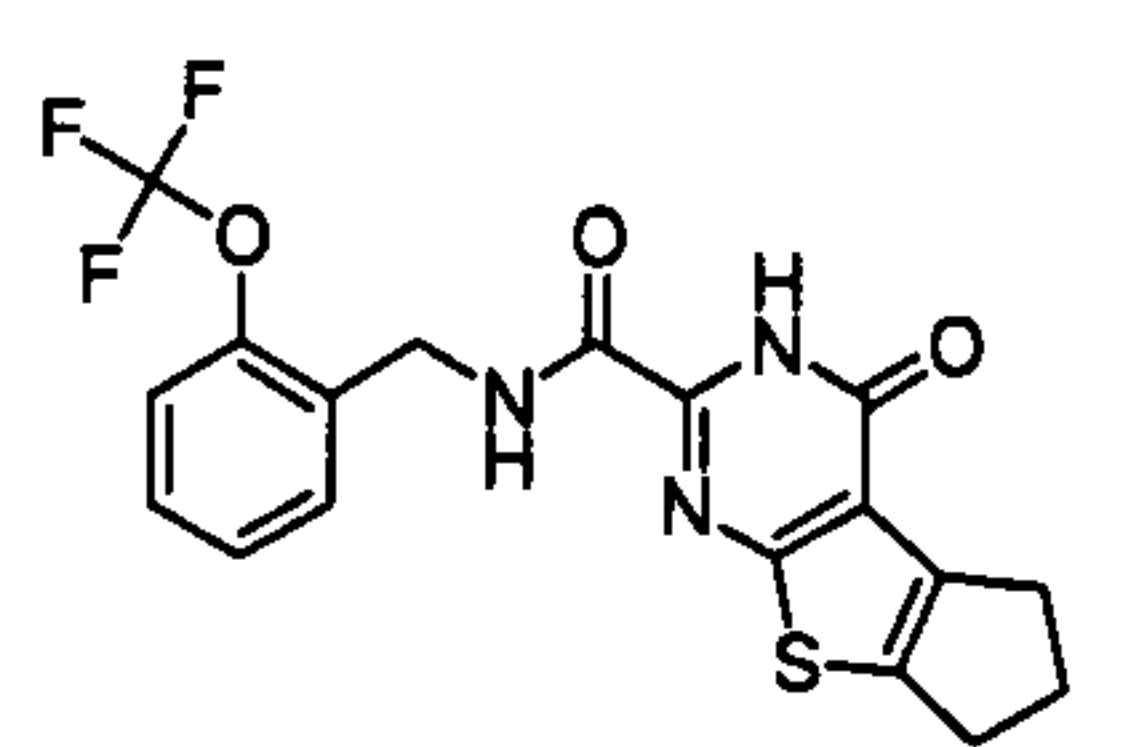
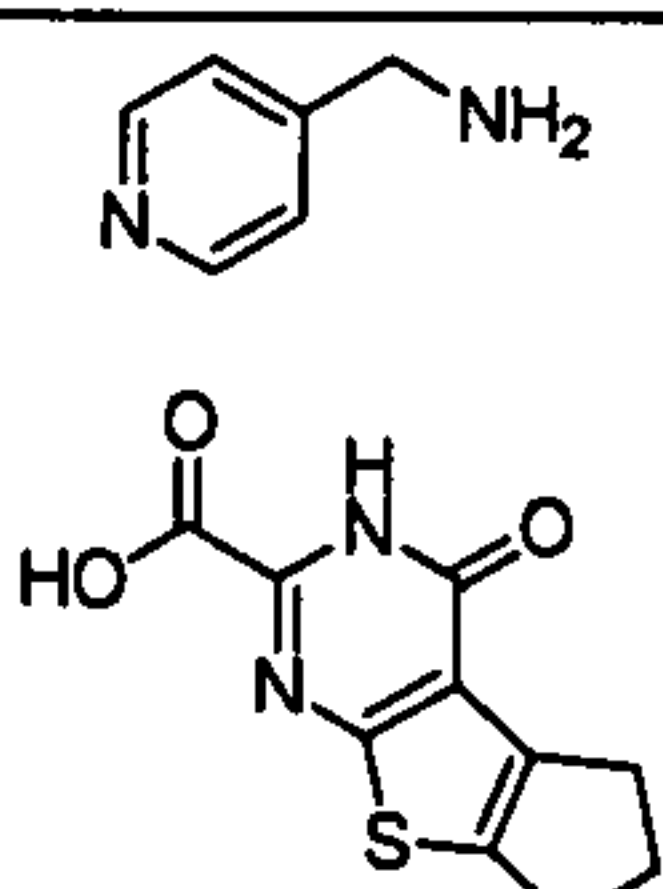
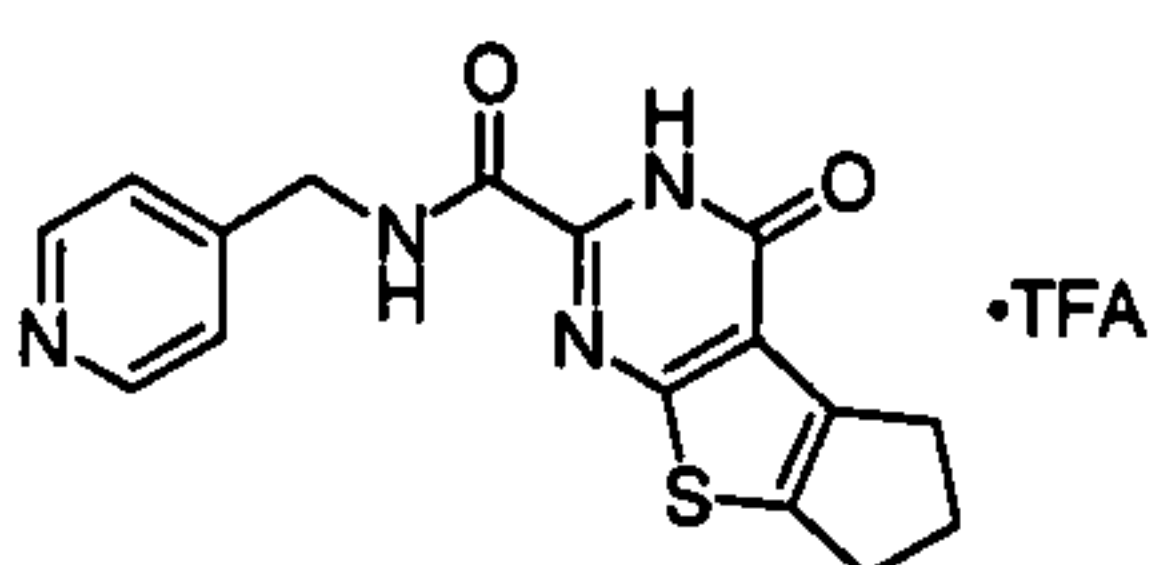
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/326 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 351    |
| 2/327 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 368    |
| 2/328 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 402 |
| 2/329 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 368    |
| 2/330 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 332    |

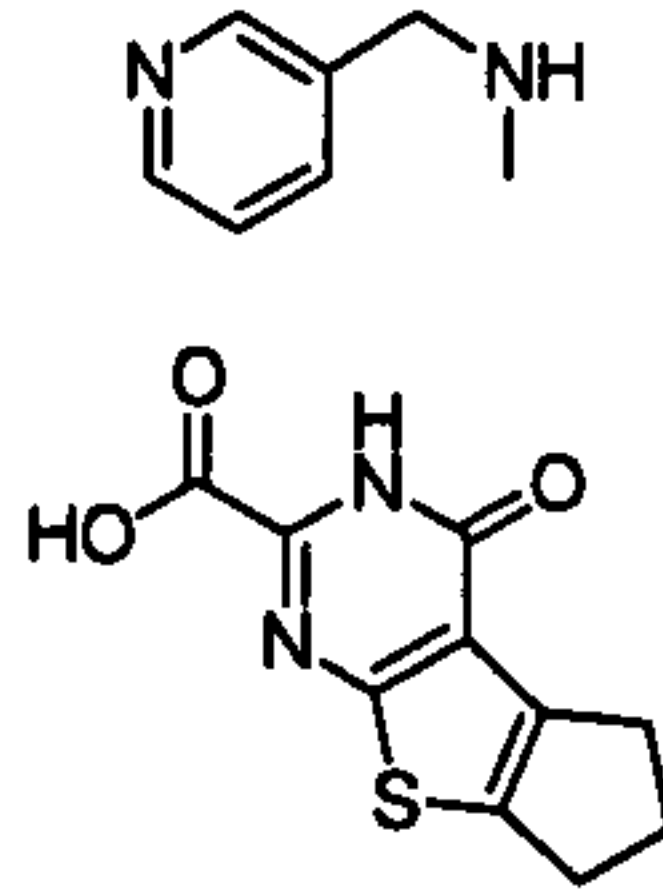
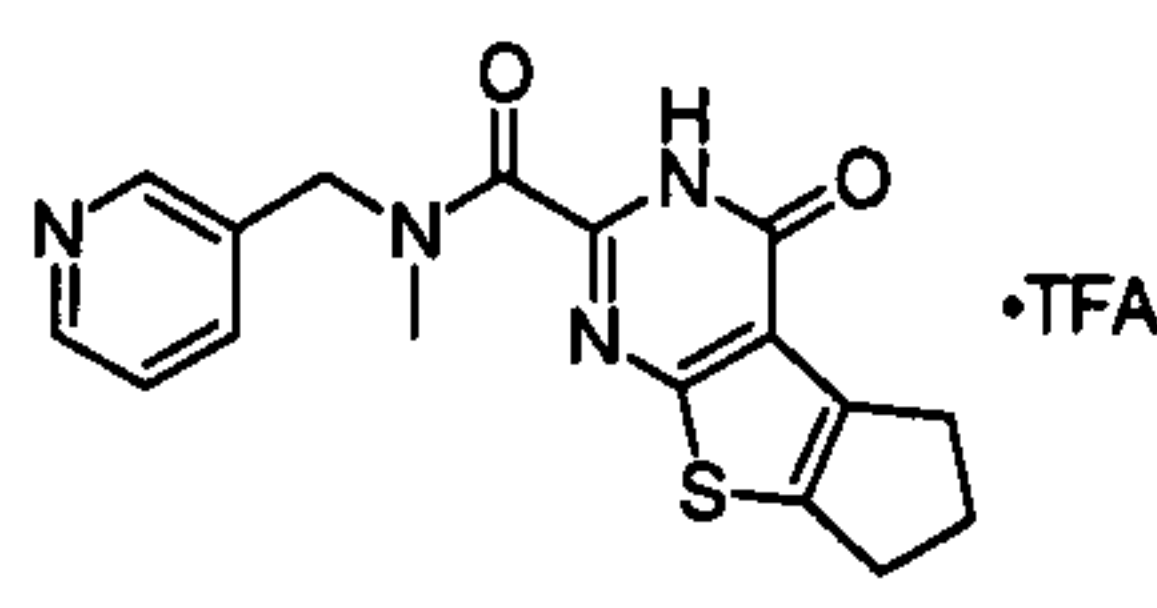
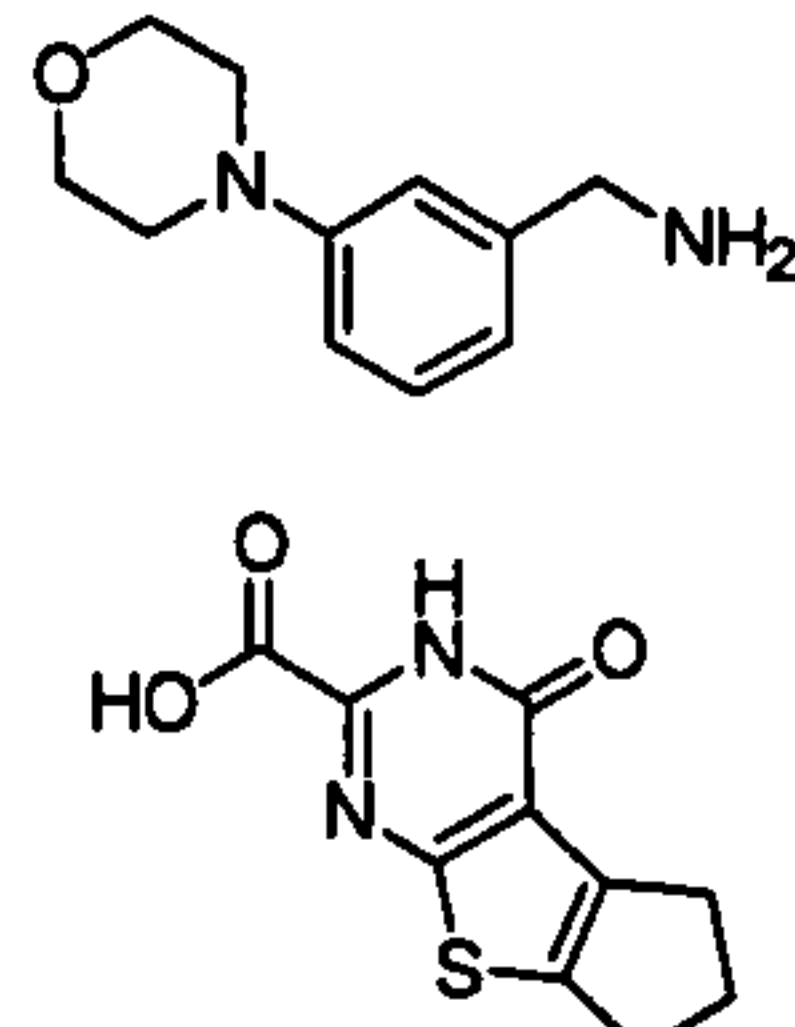
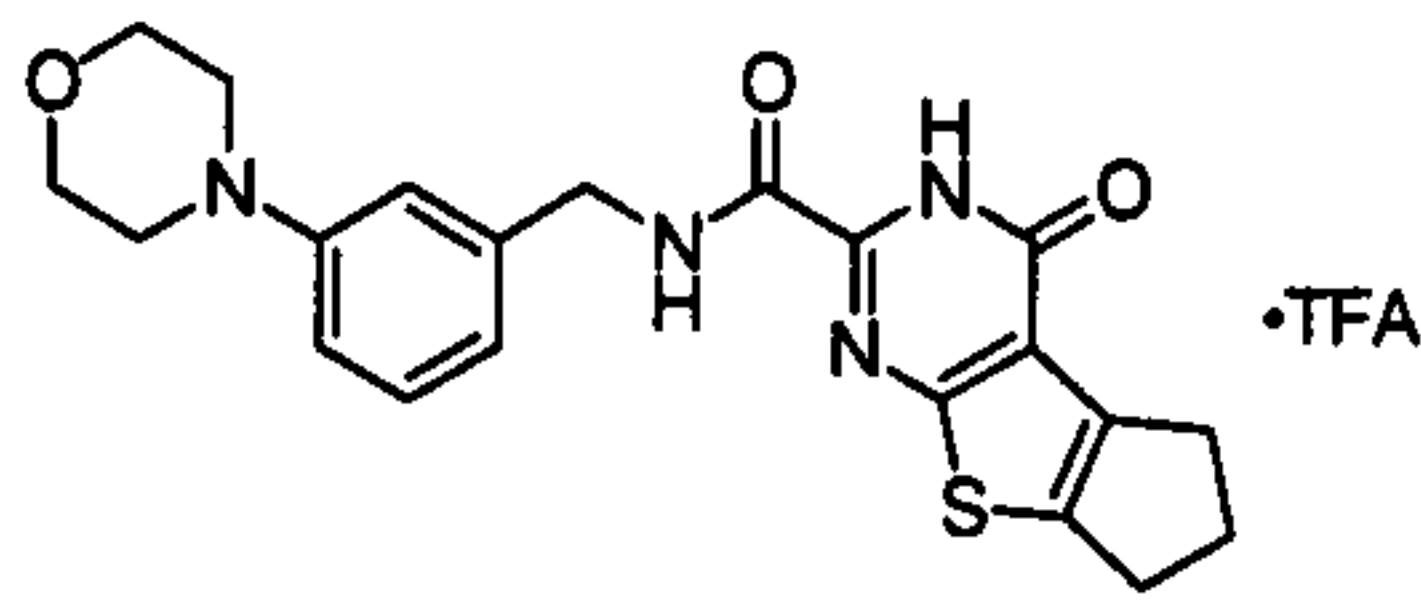
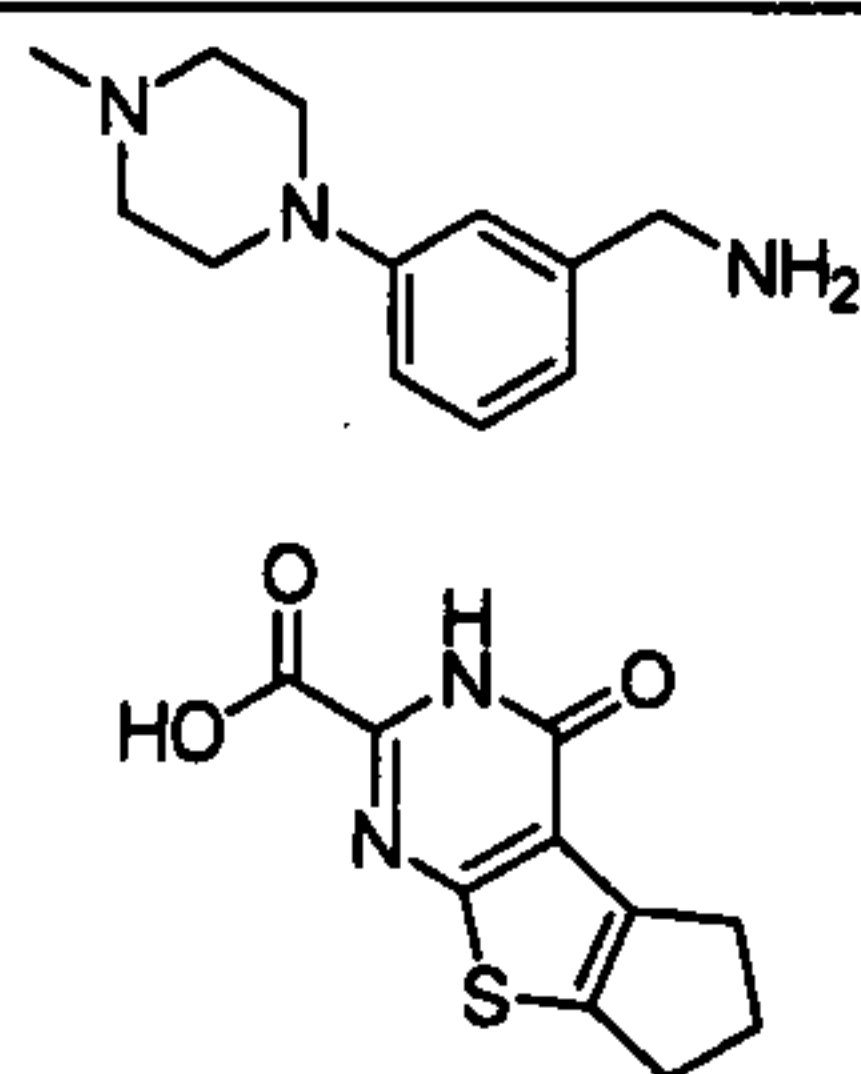
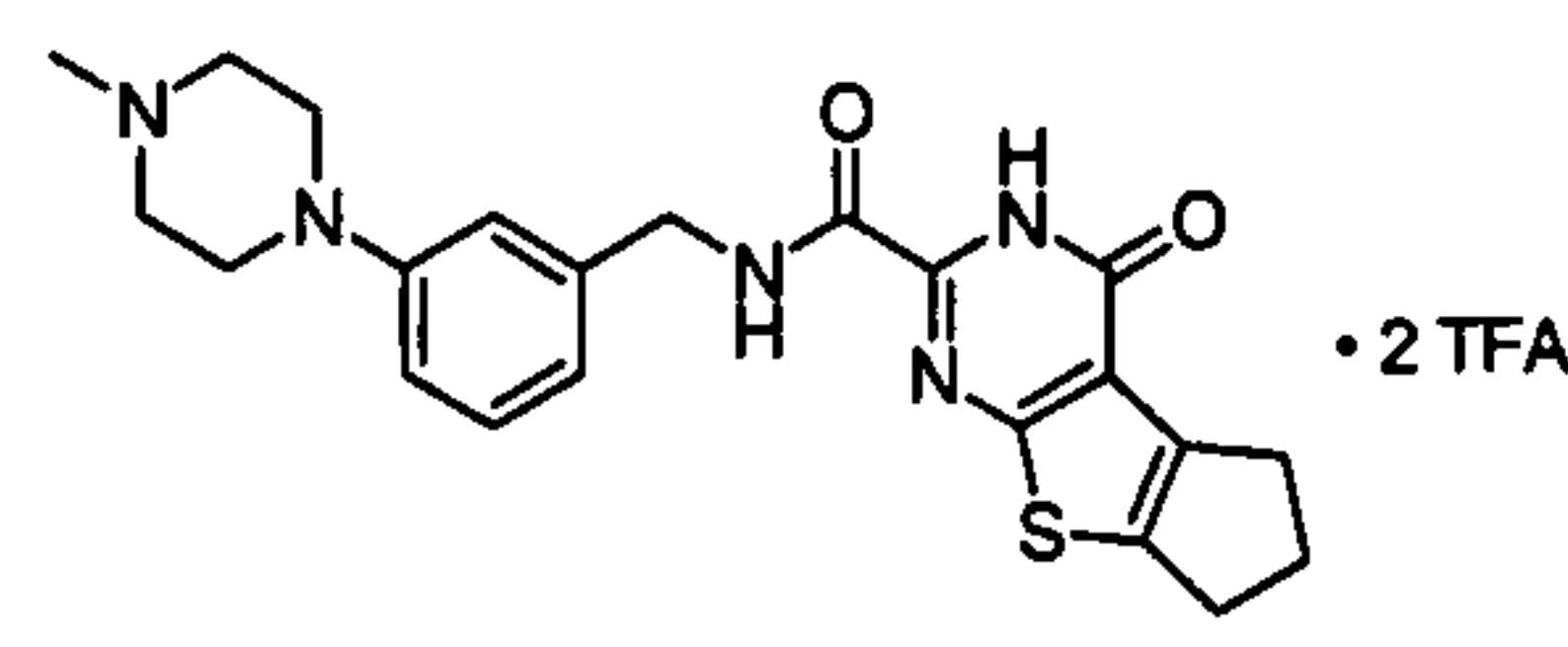
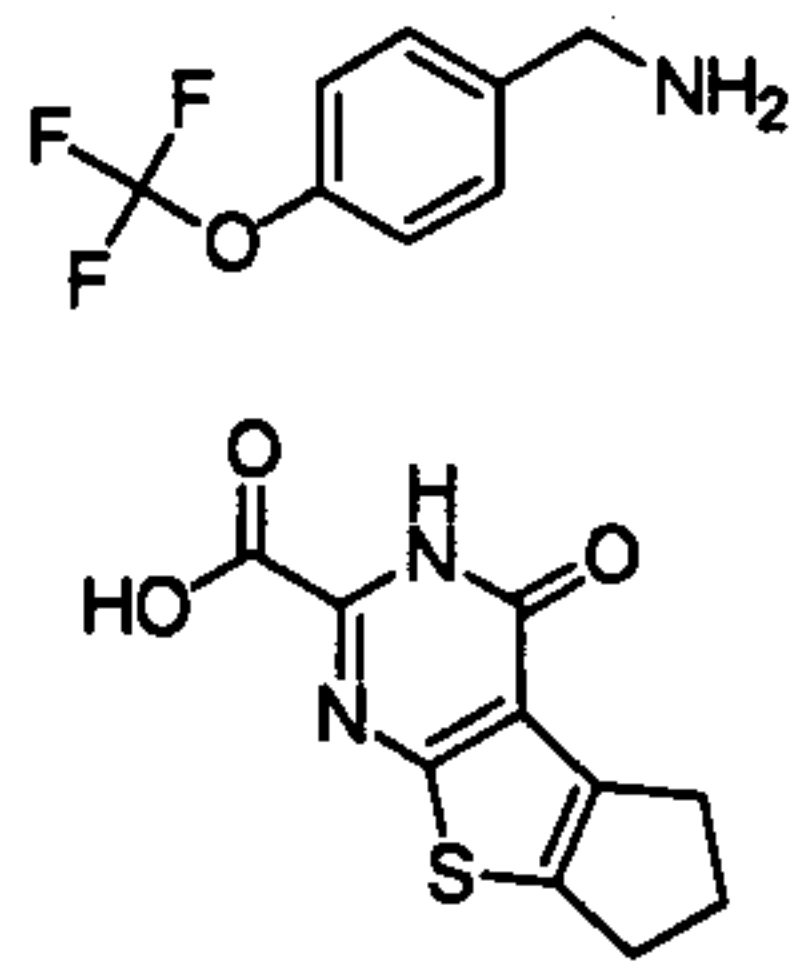
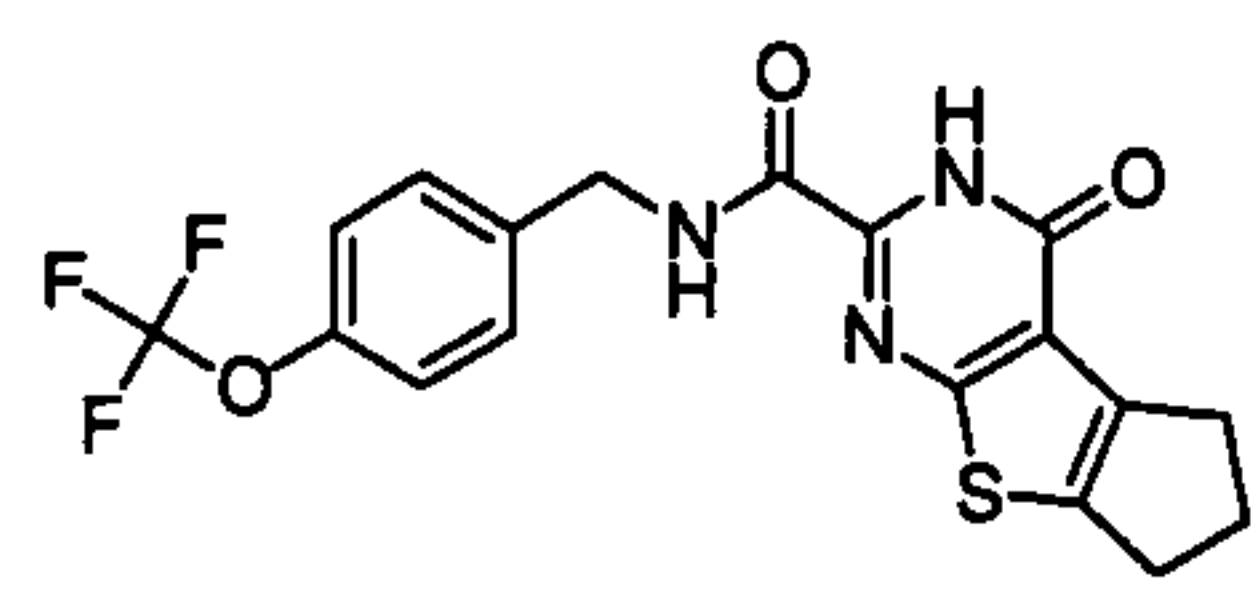
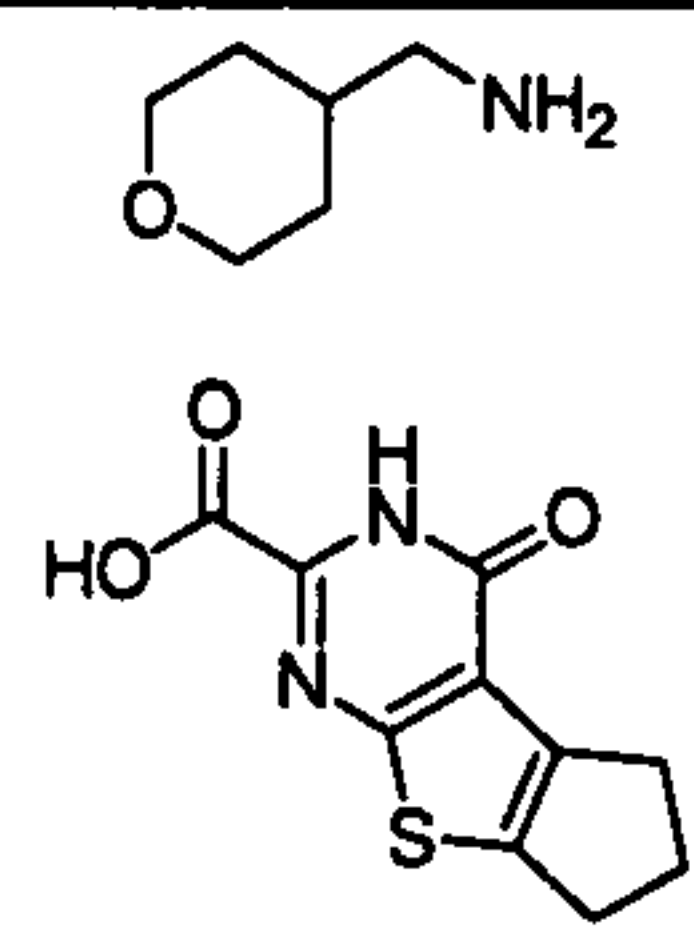
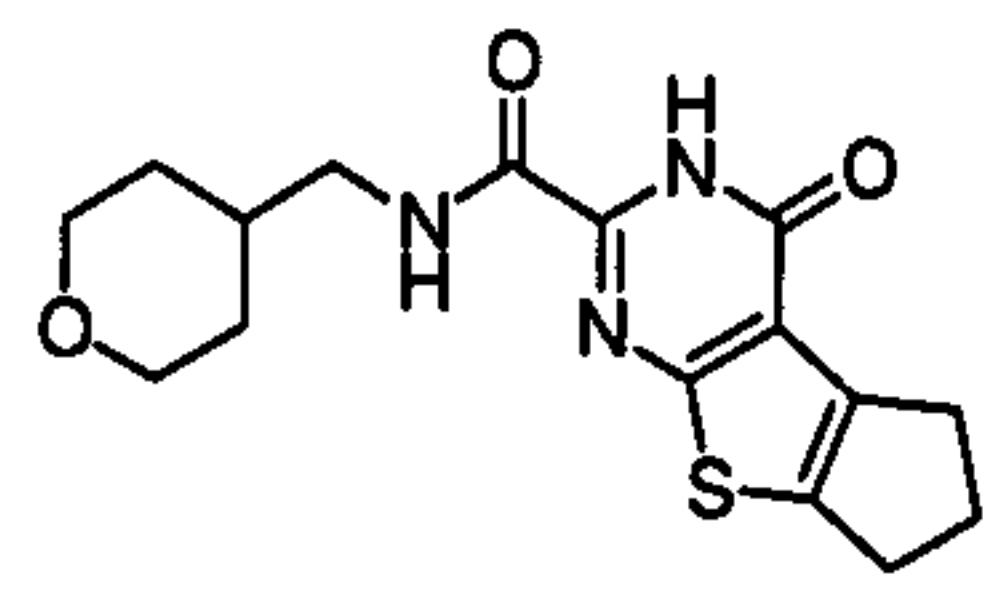
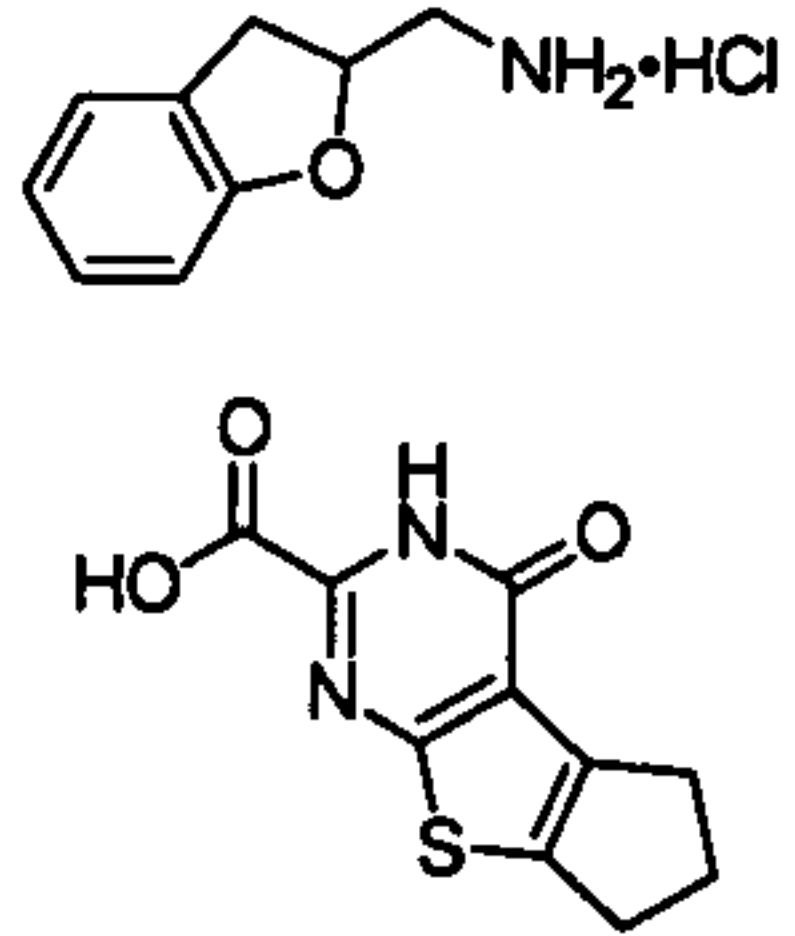
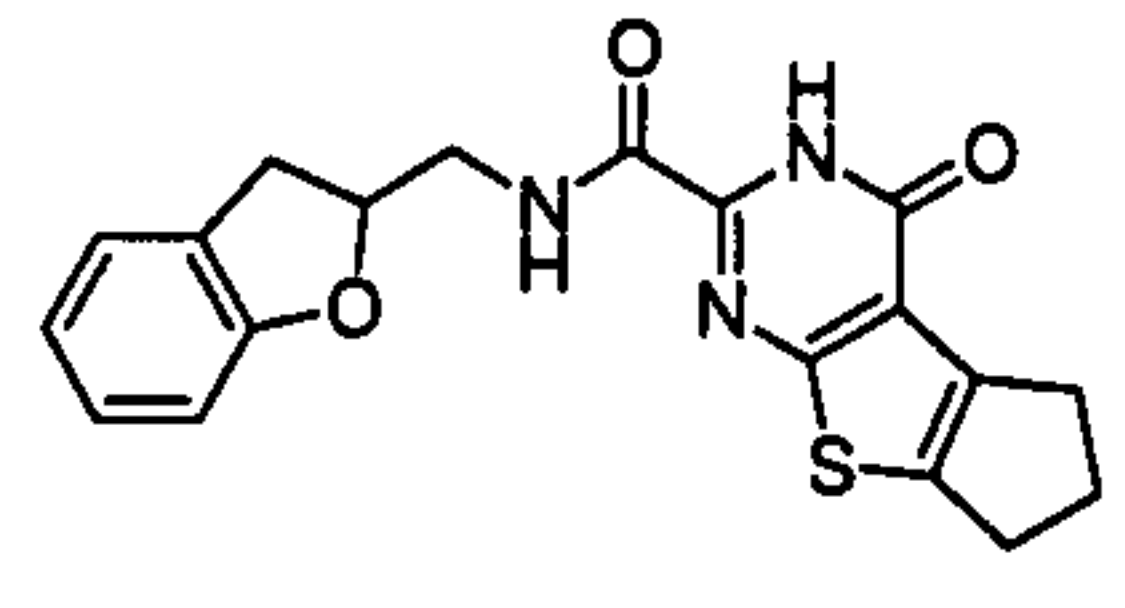
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/331 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 376 |
| 2/332 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 427 |
| 2/333 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 381 |
| 2/334 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 393 |
| 2/335 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 399 |

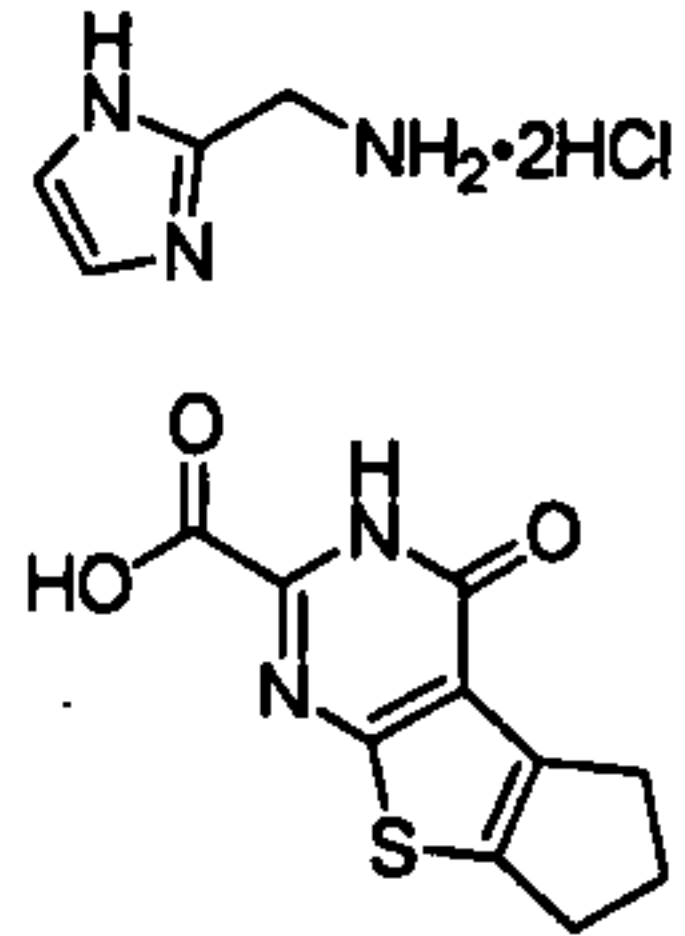
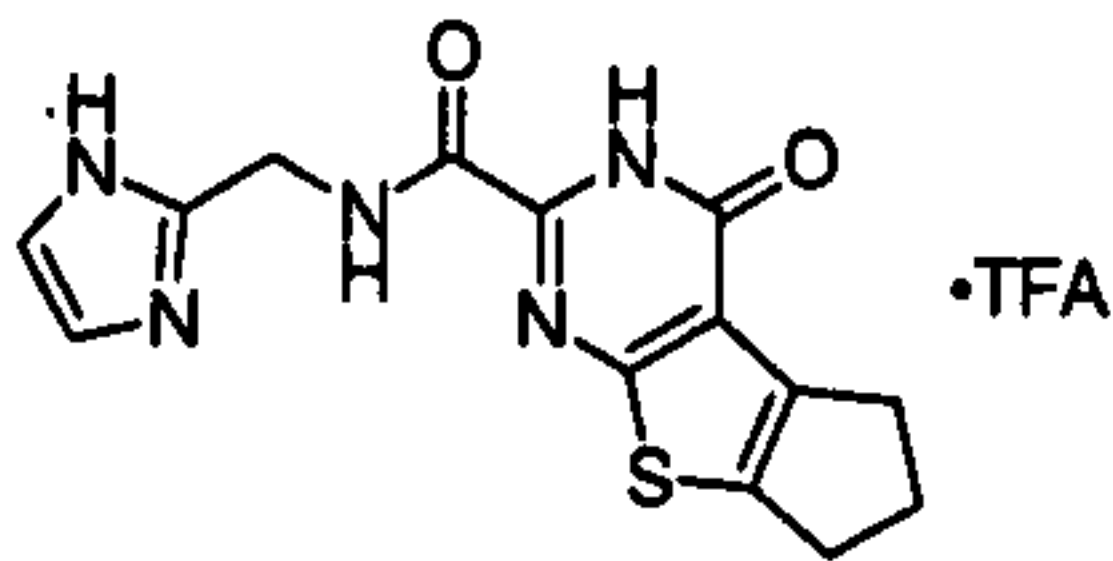
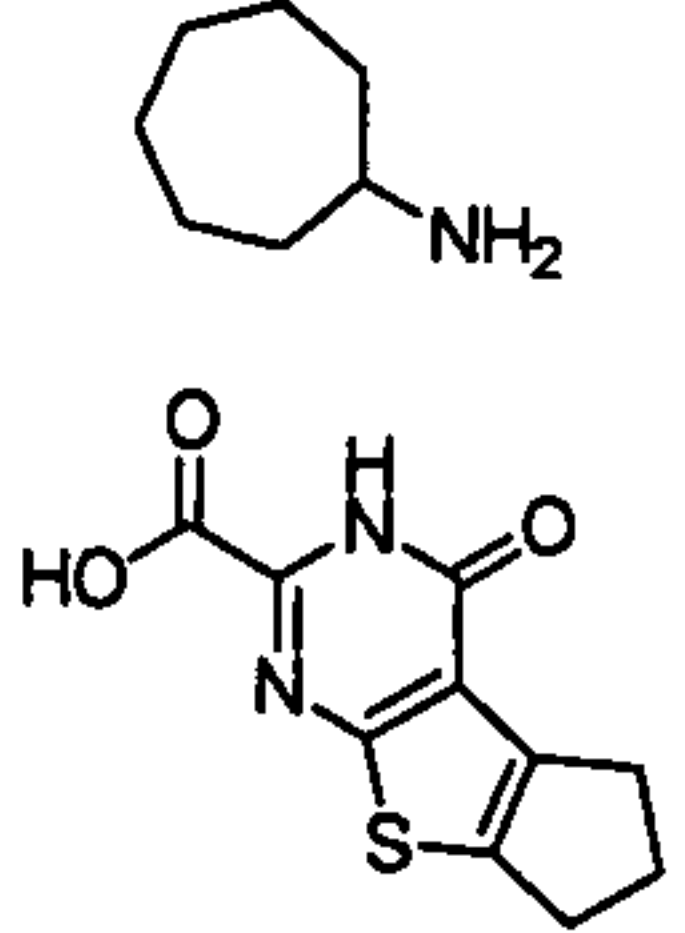
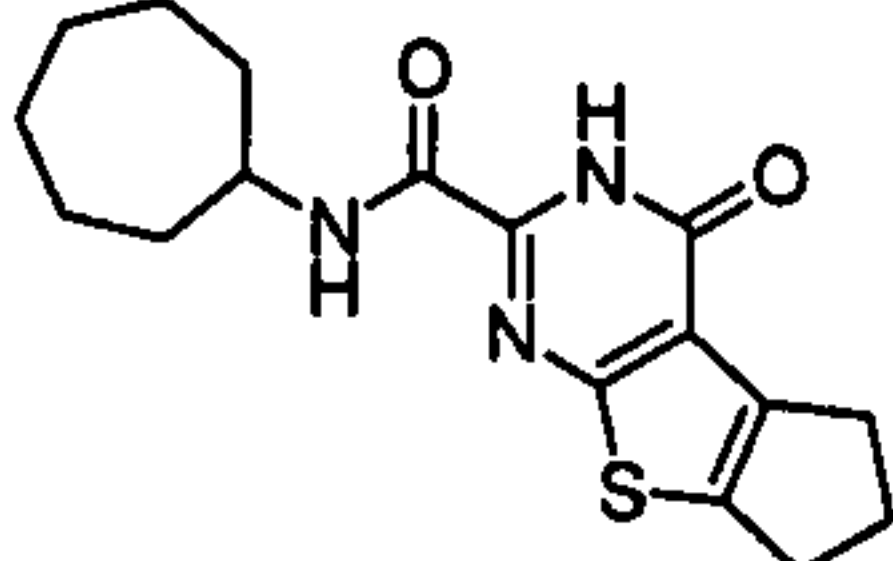
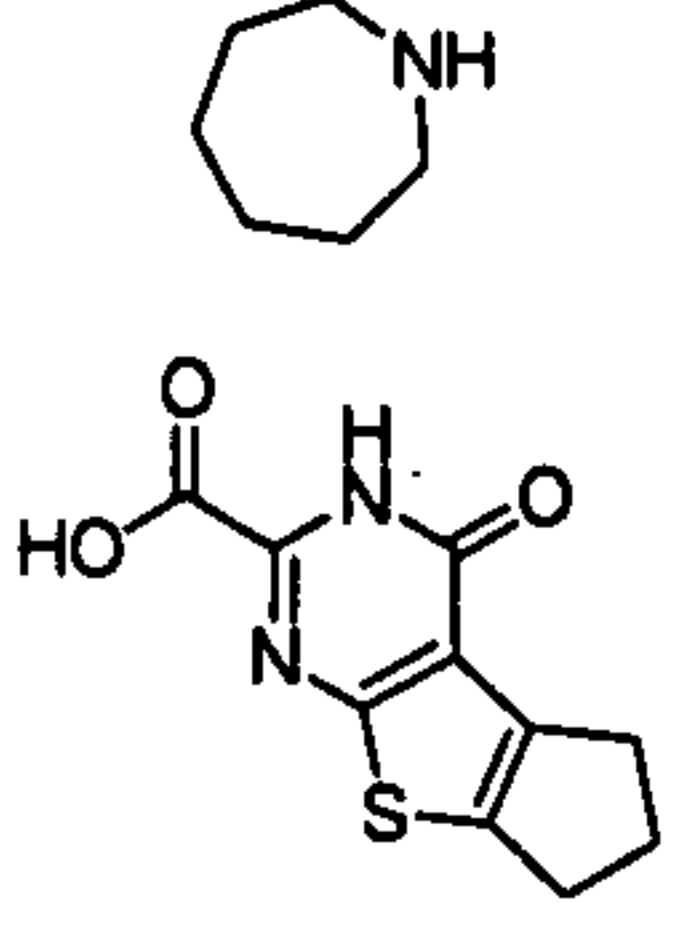
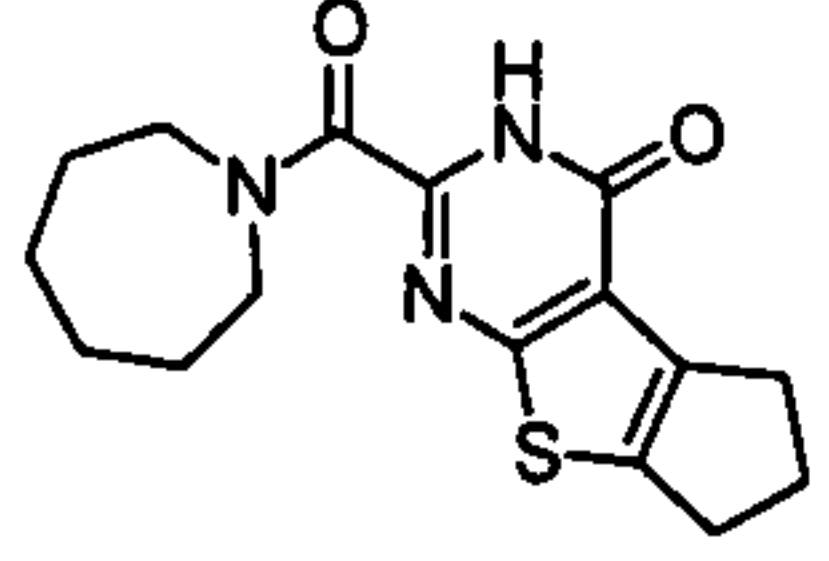
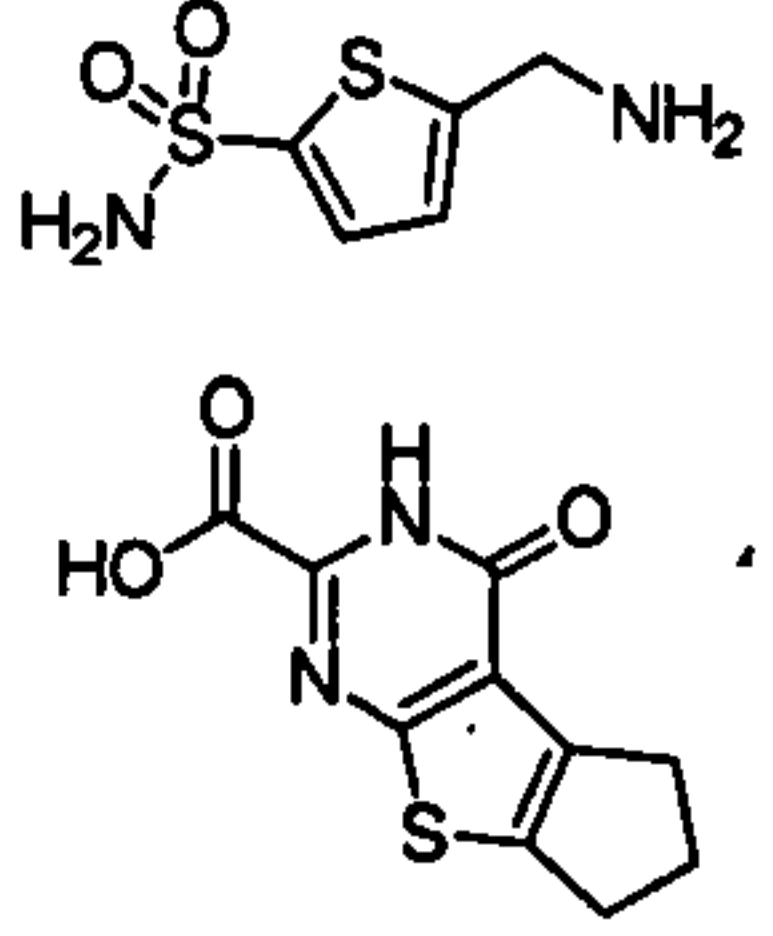
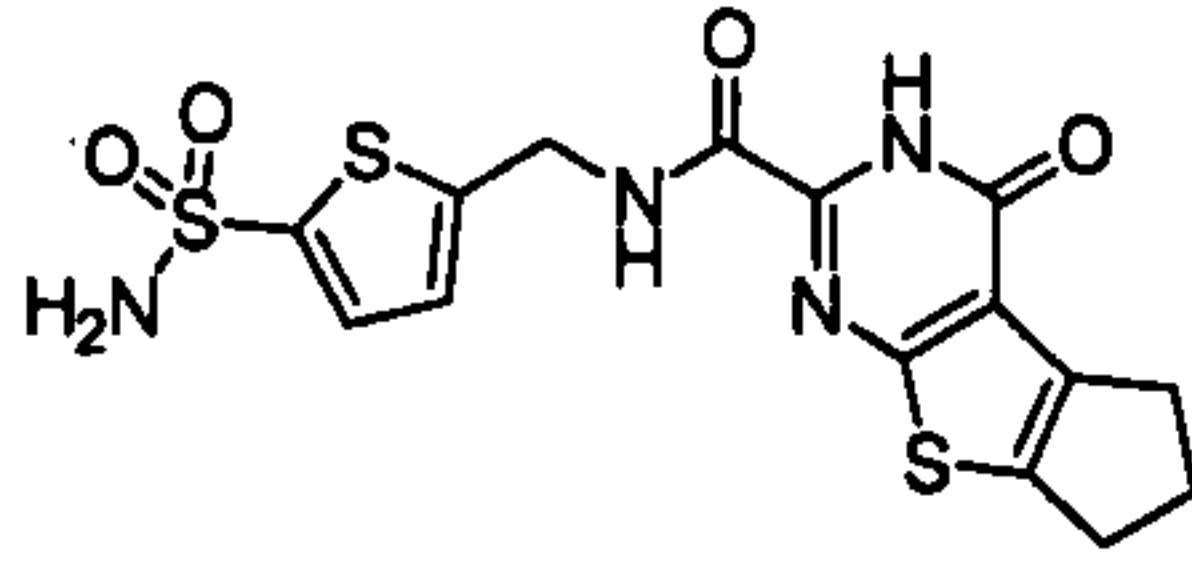
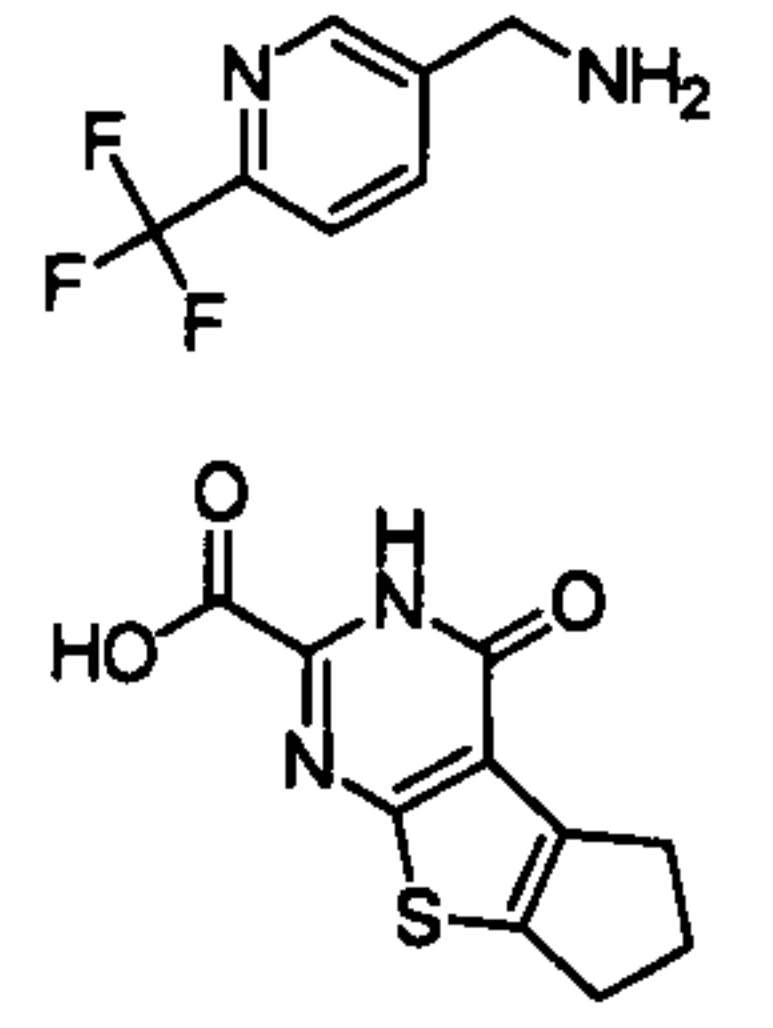
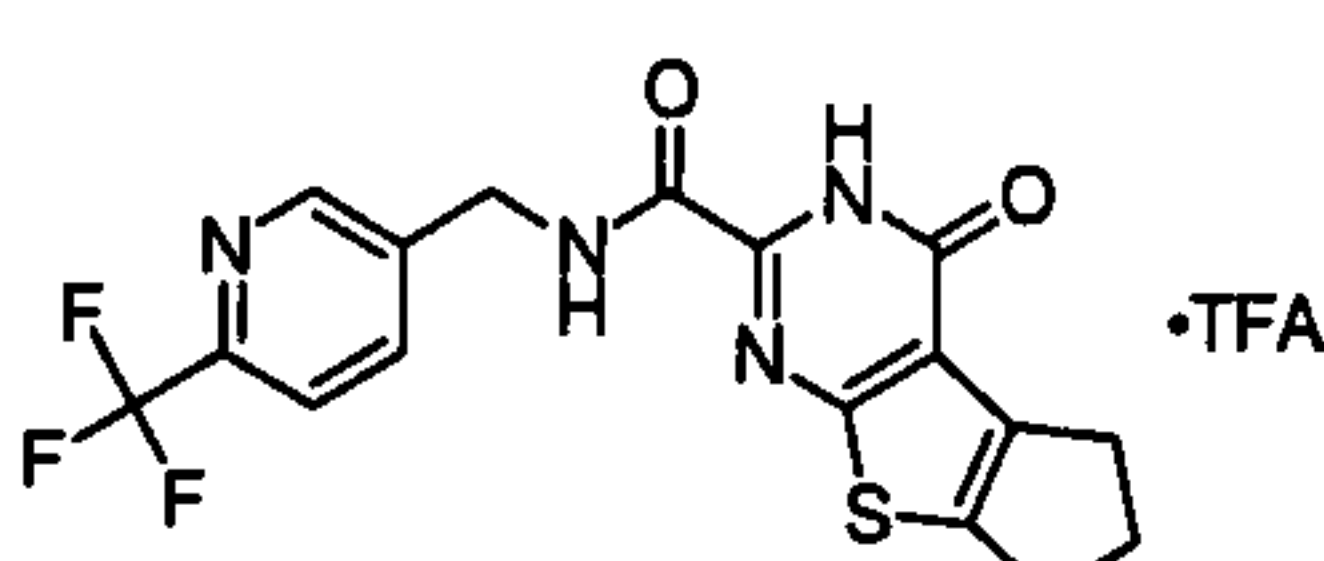
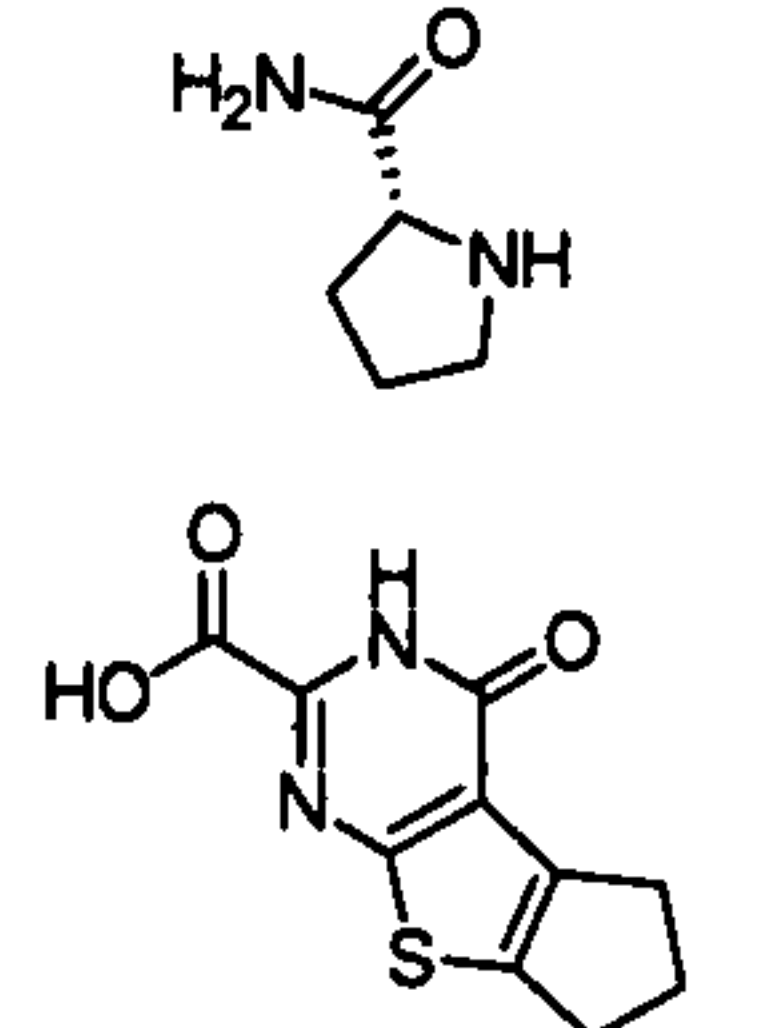
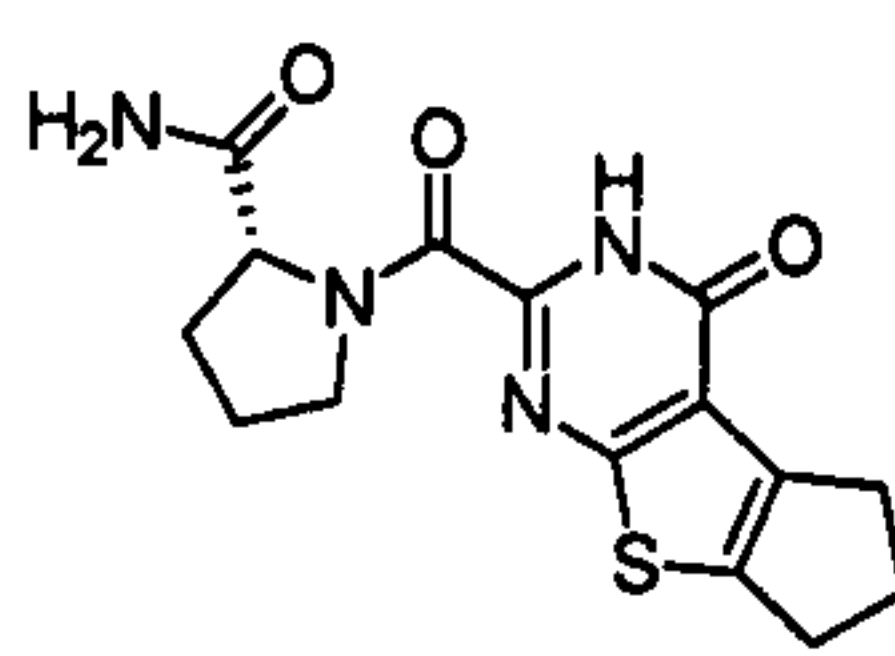
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/336 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 393    |
| 2/337 |   |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 368 |
| 2/338 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 375    |
| 2/339 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 393    |
| 2/340 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 343    |

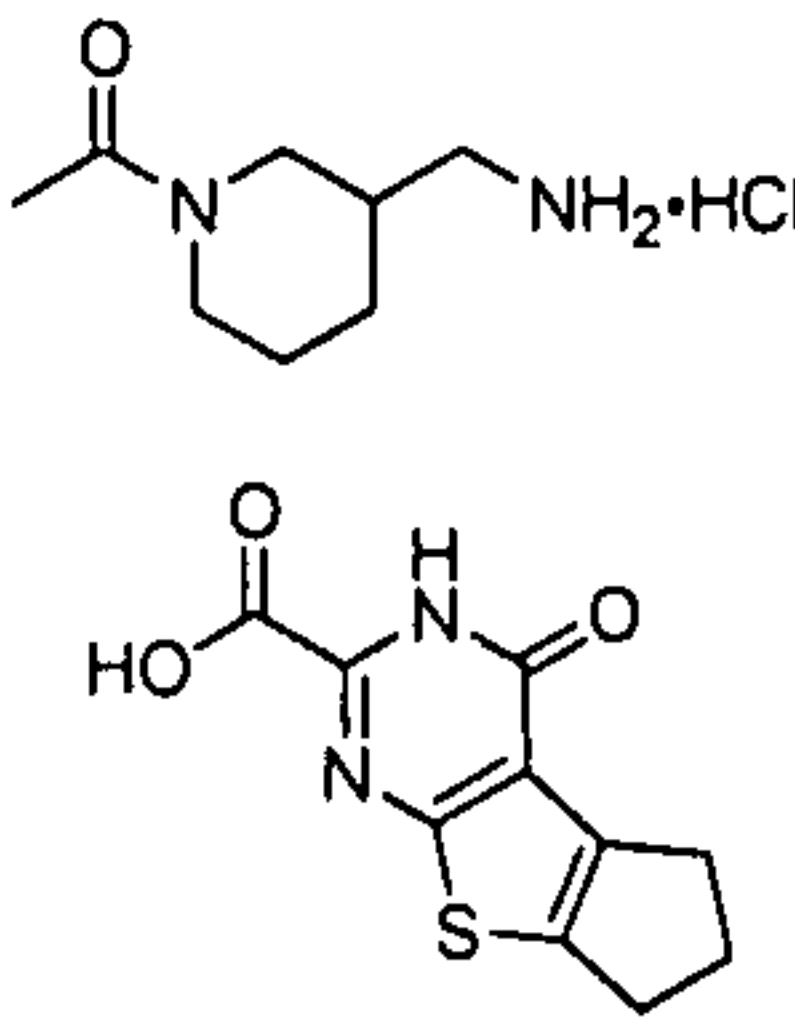
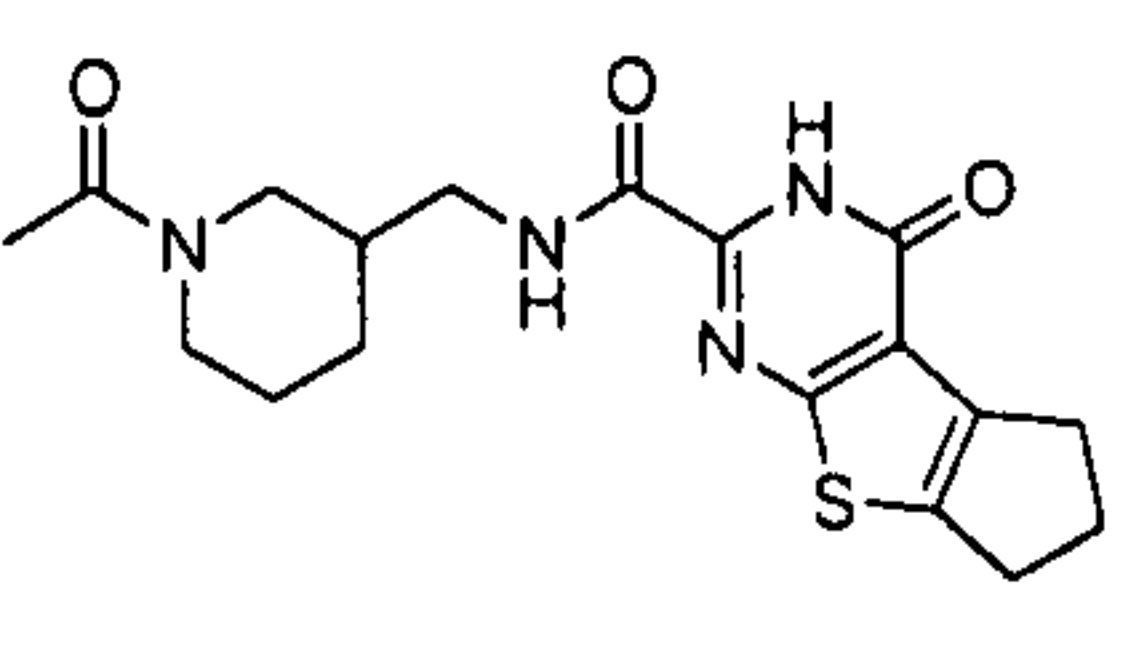
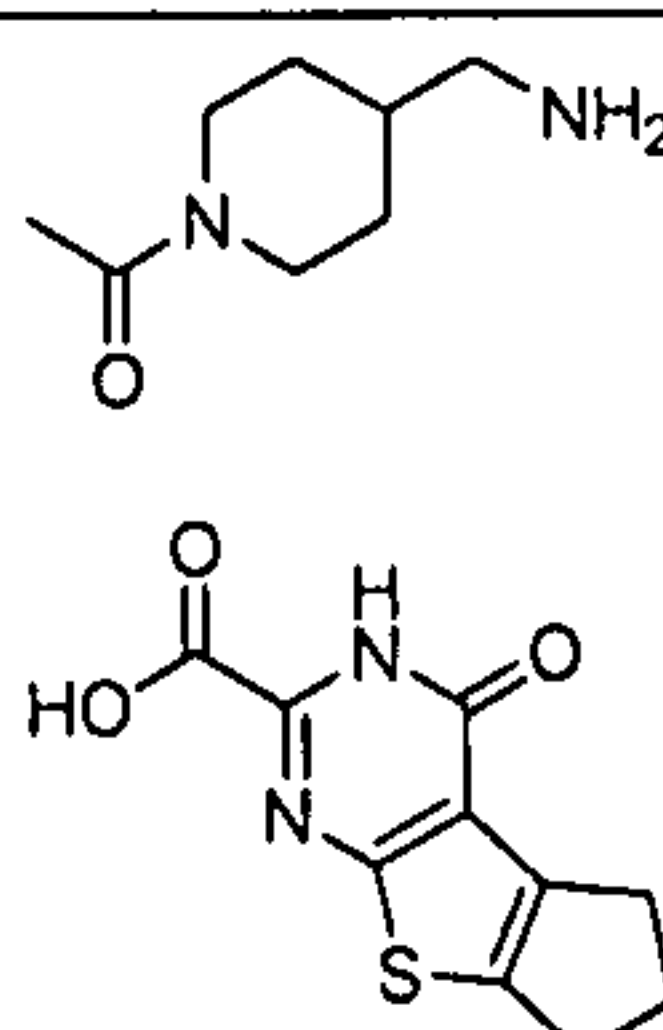
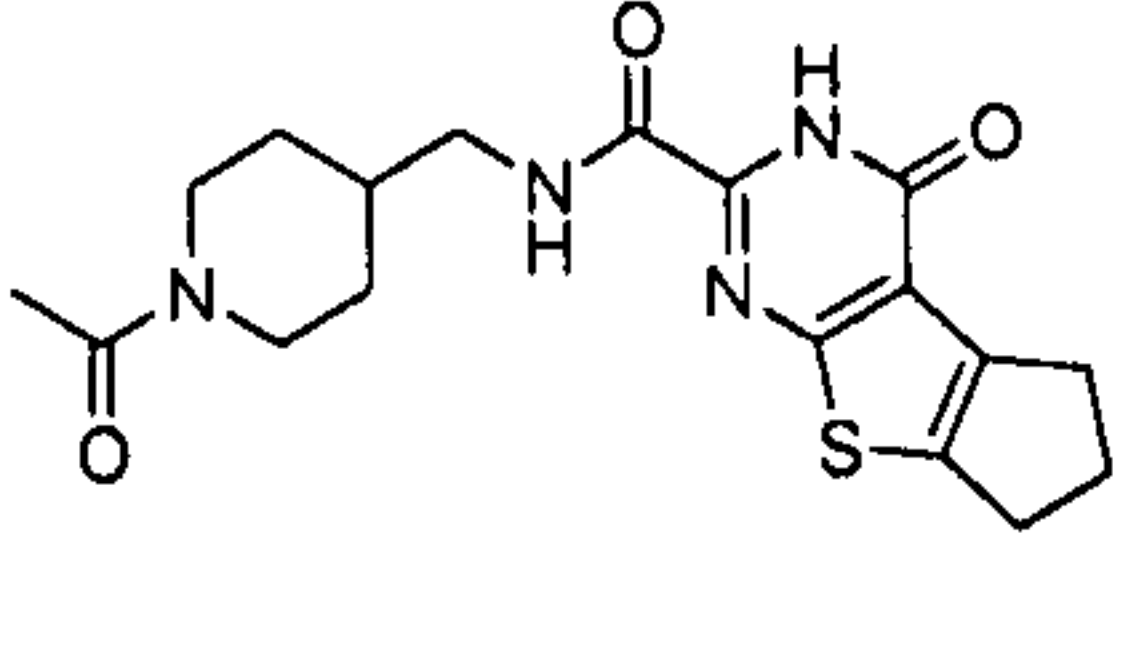
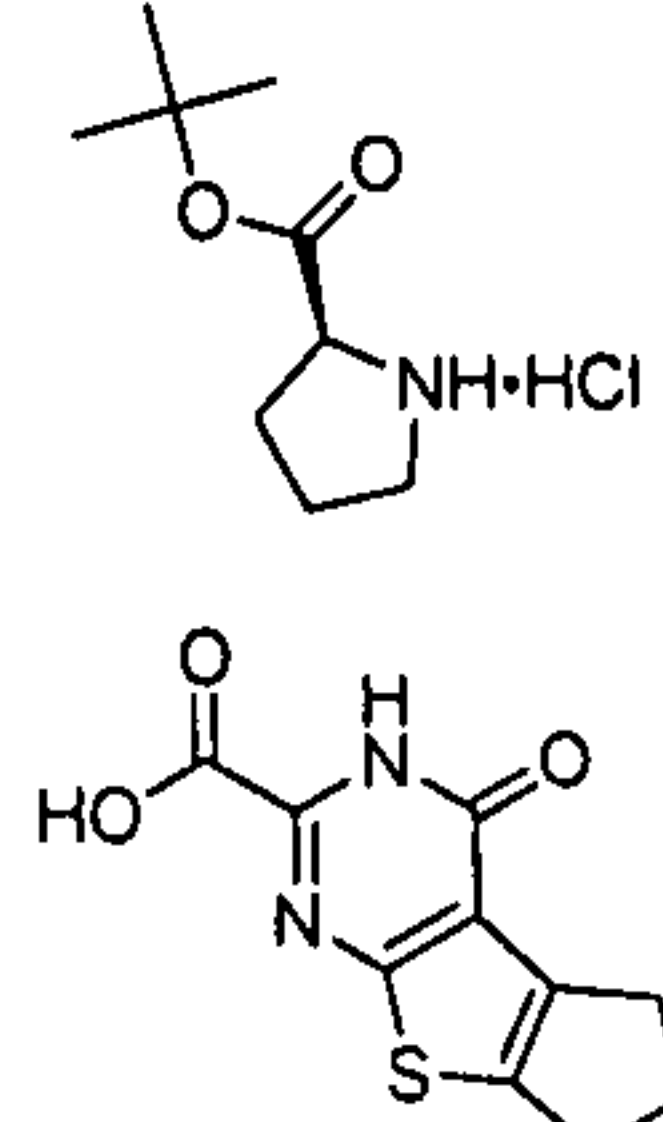
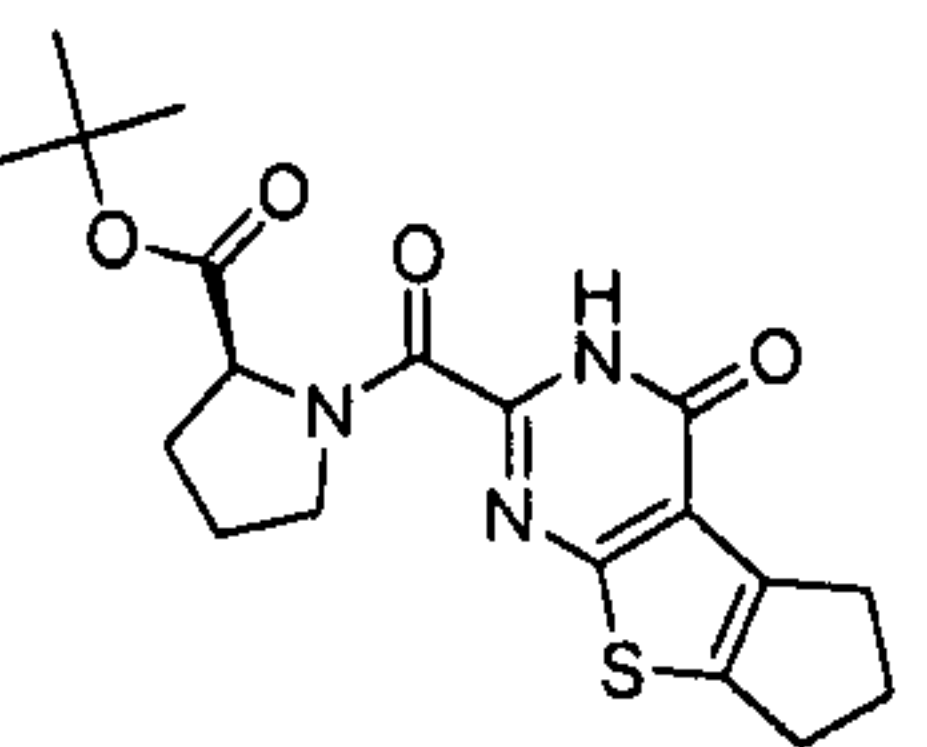
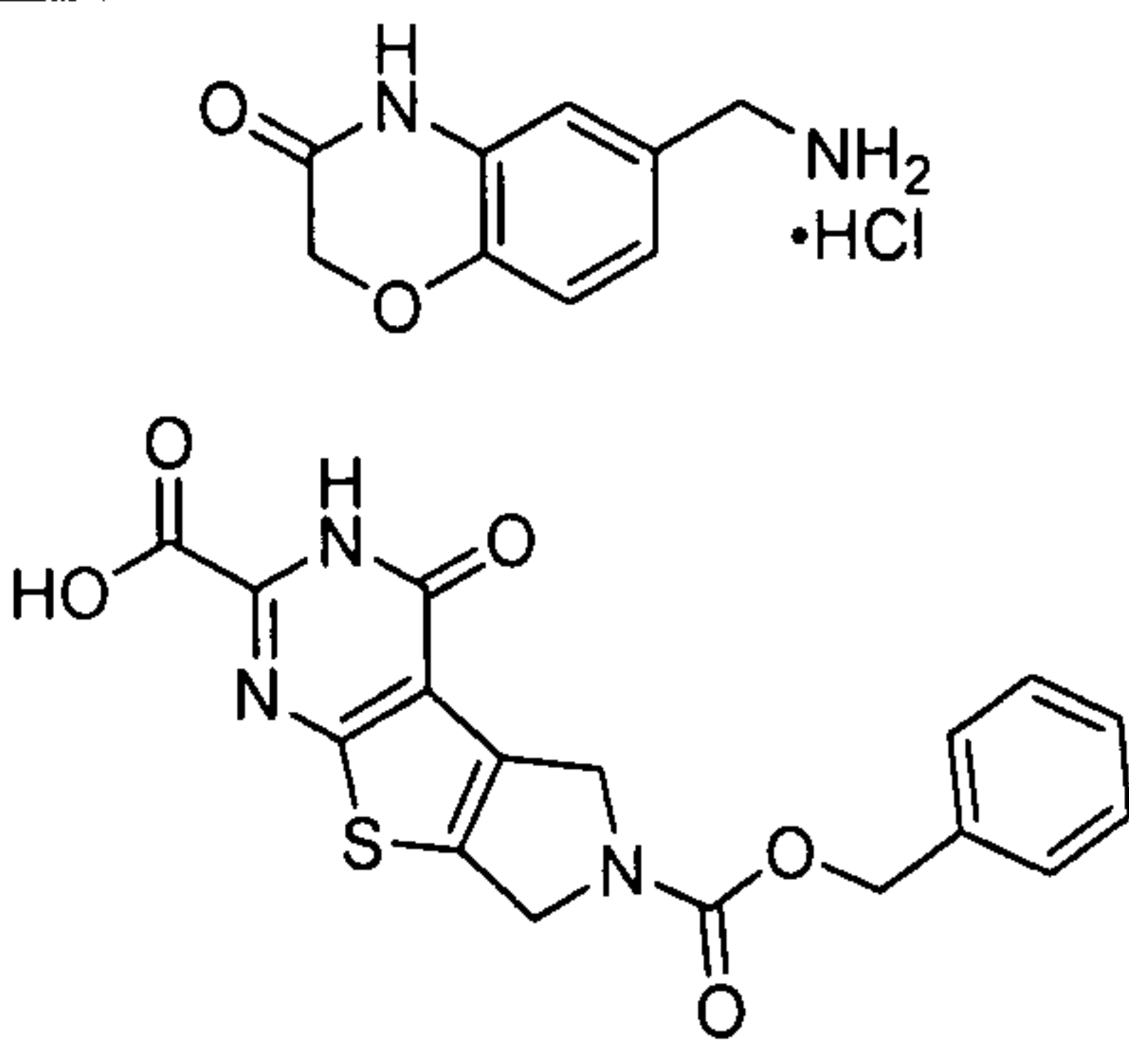
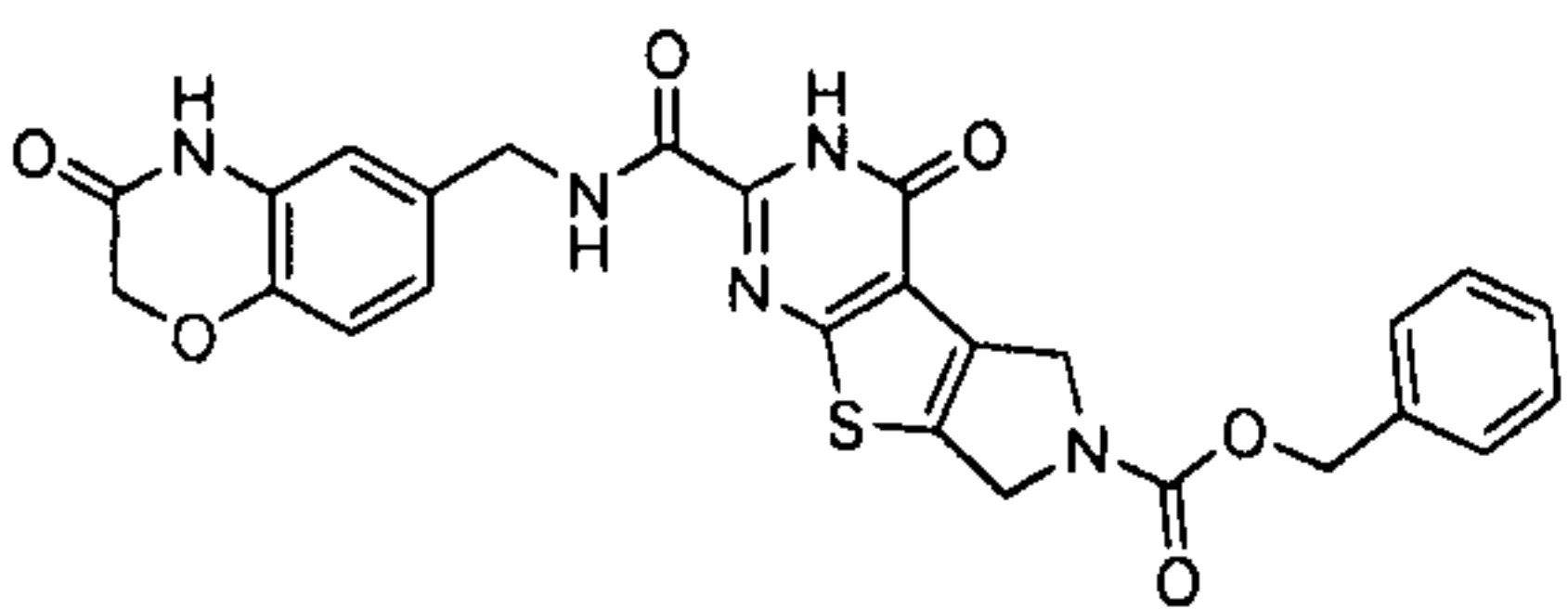
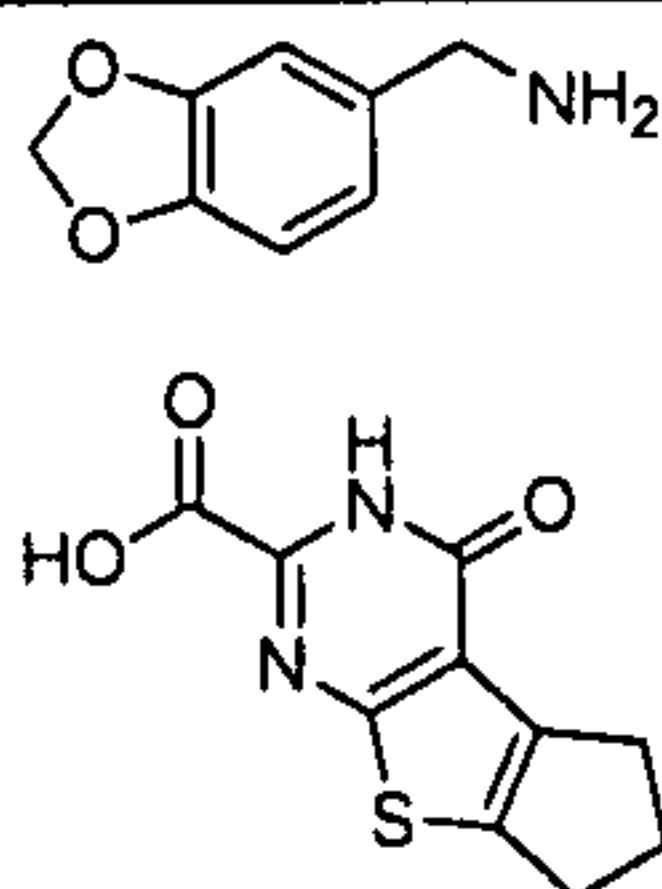
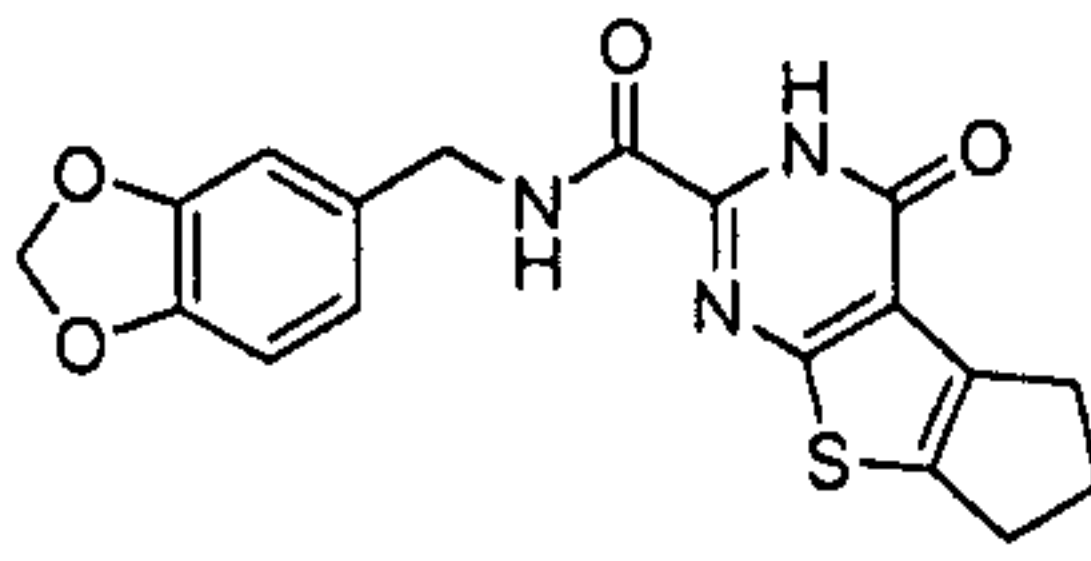
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/341 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 345    |
| 2/342 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 345    |
| 2/343 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 319    |
| 2/344 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 331    |
| 2/345 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 410 |
| 2/346 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 367    |

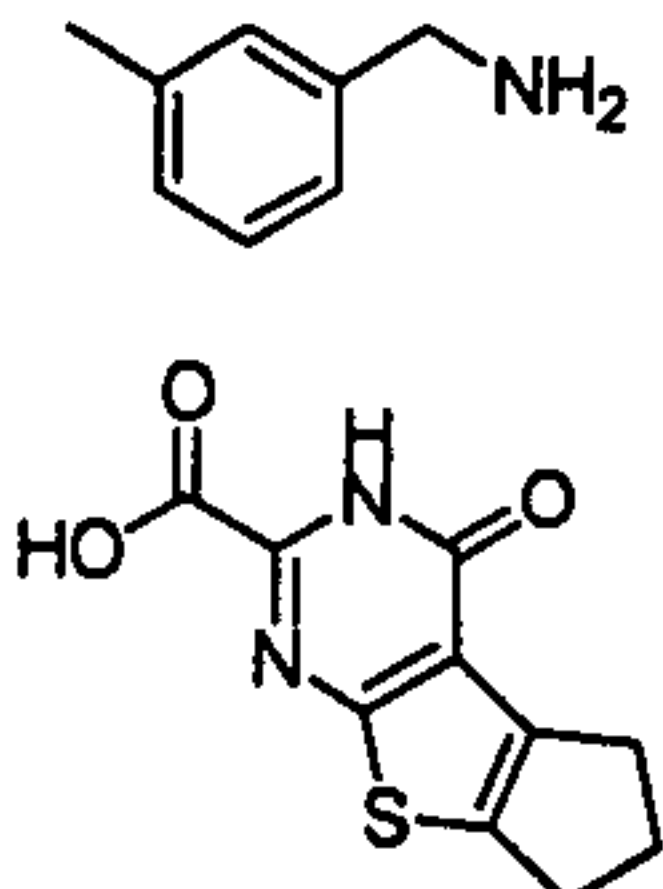
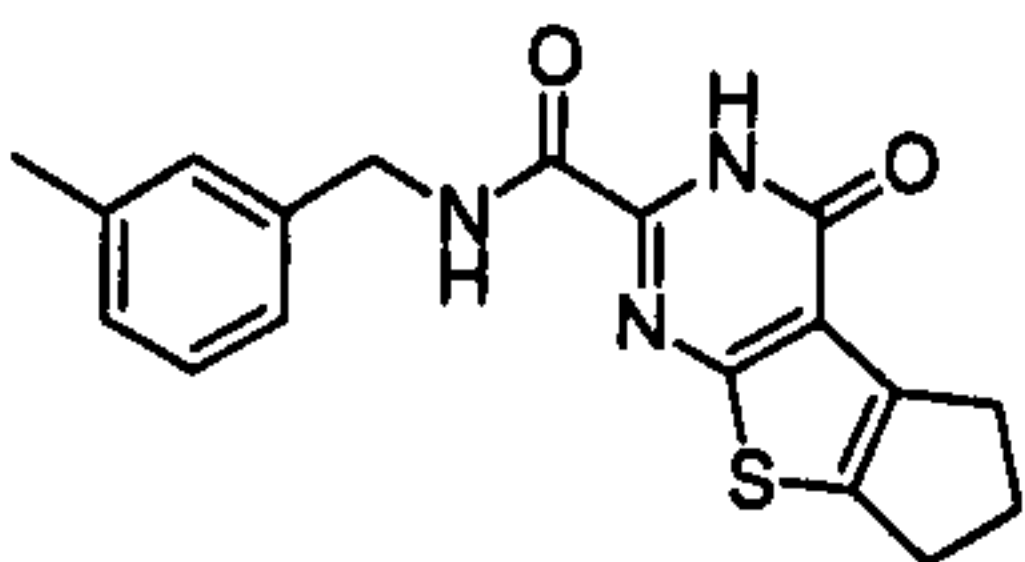
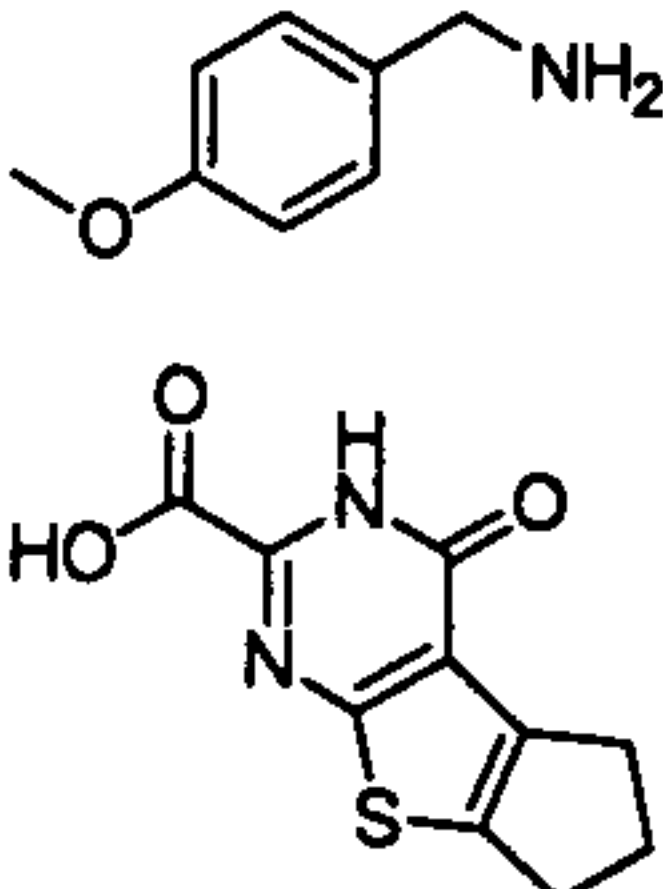
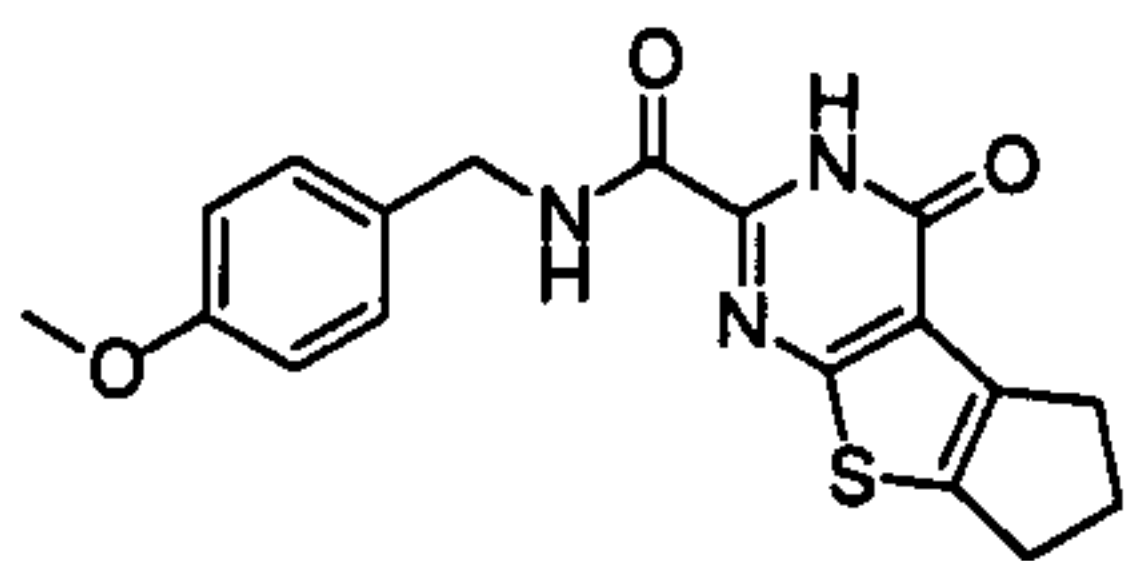
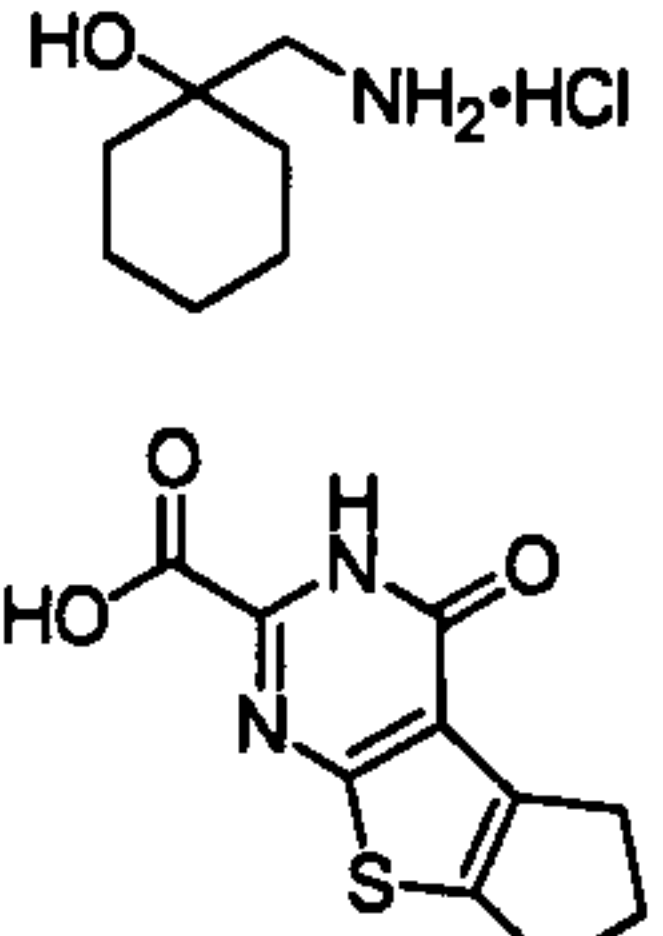
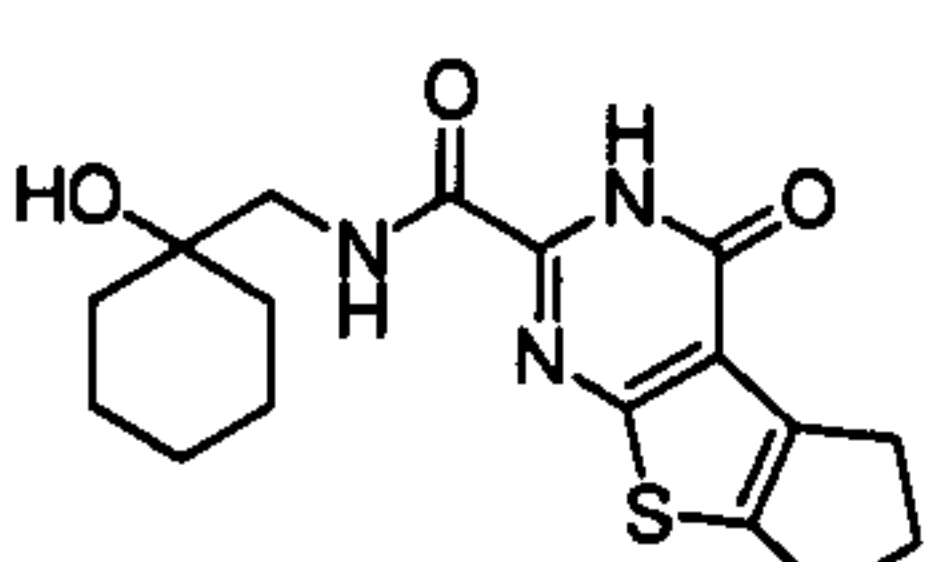
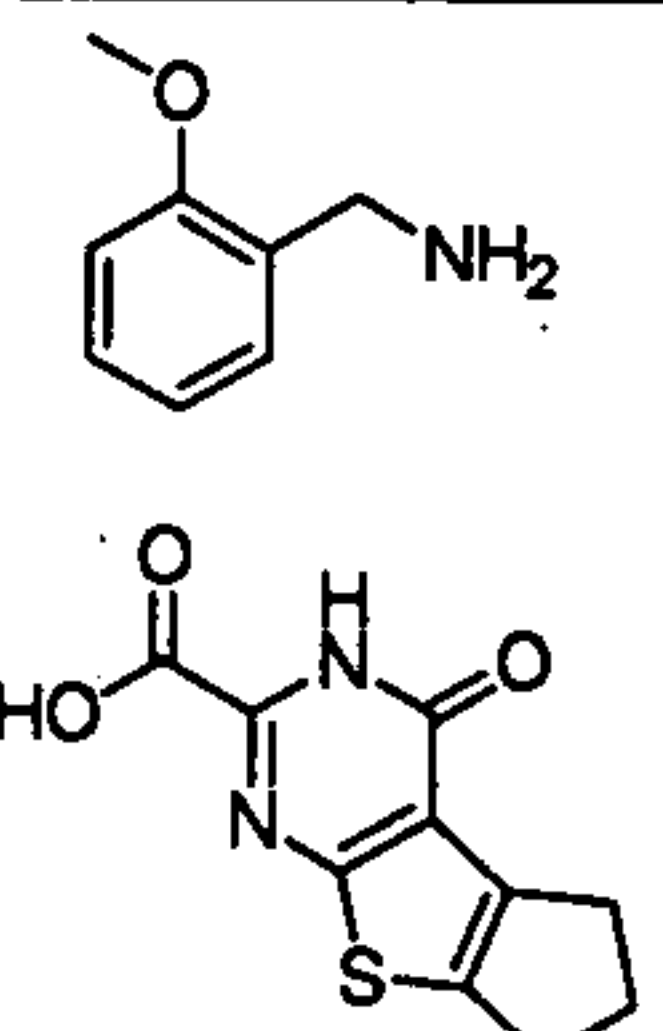
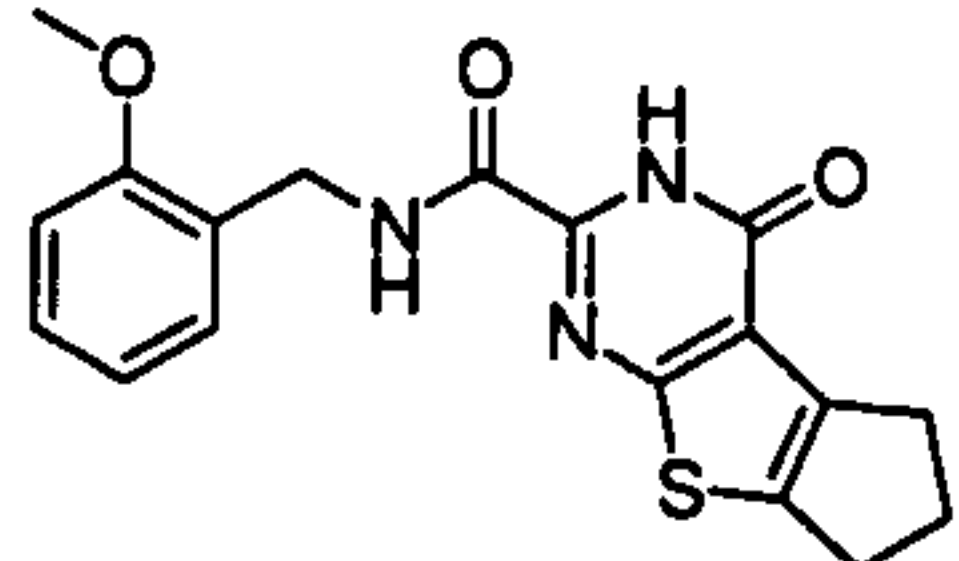
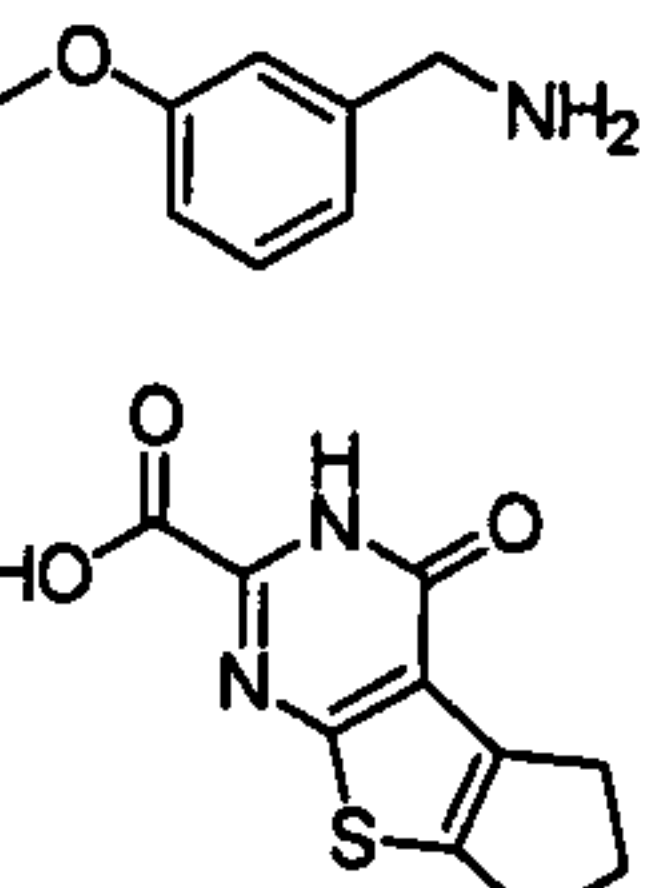
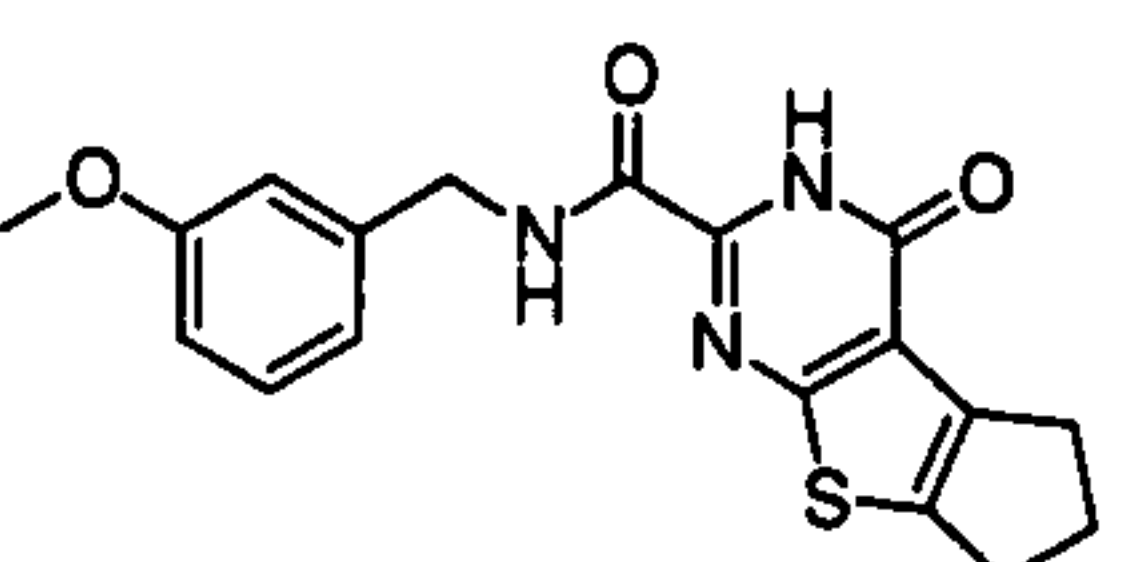
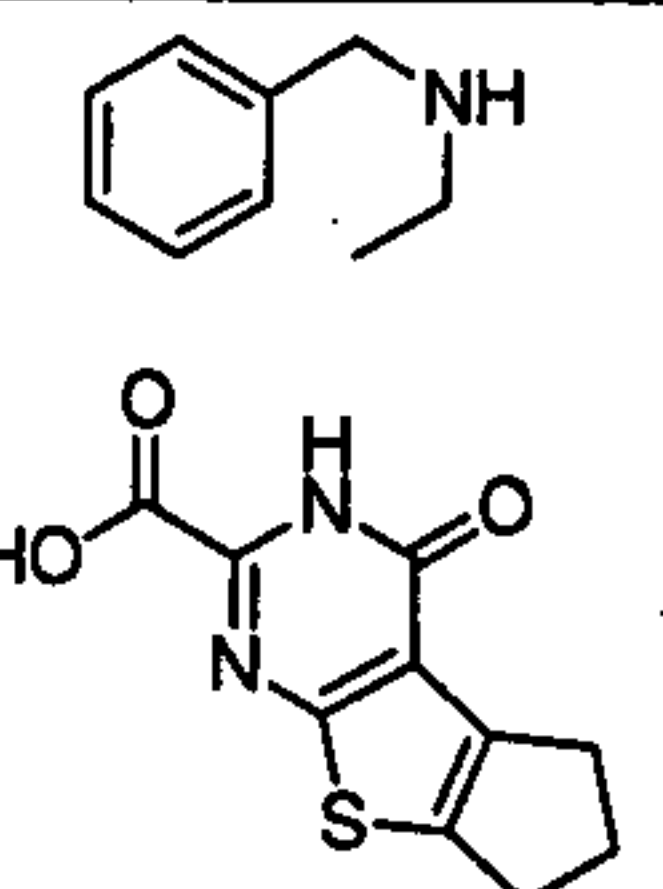
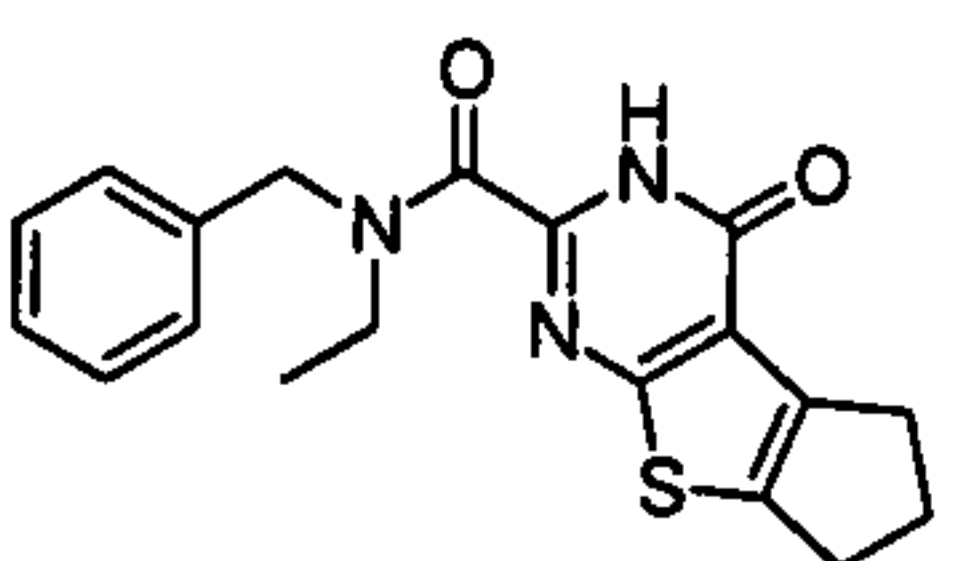
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/347 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 353 |
| 2/348 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 353 |
| 2/349 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 353 |
| 2/350 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 345 |
| 2/351 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 319 |
| 2/352 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 381 |

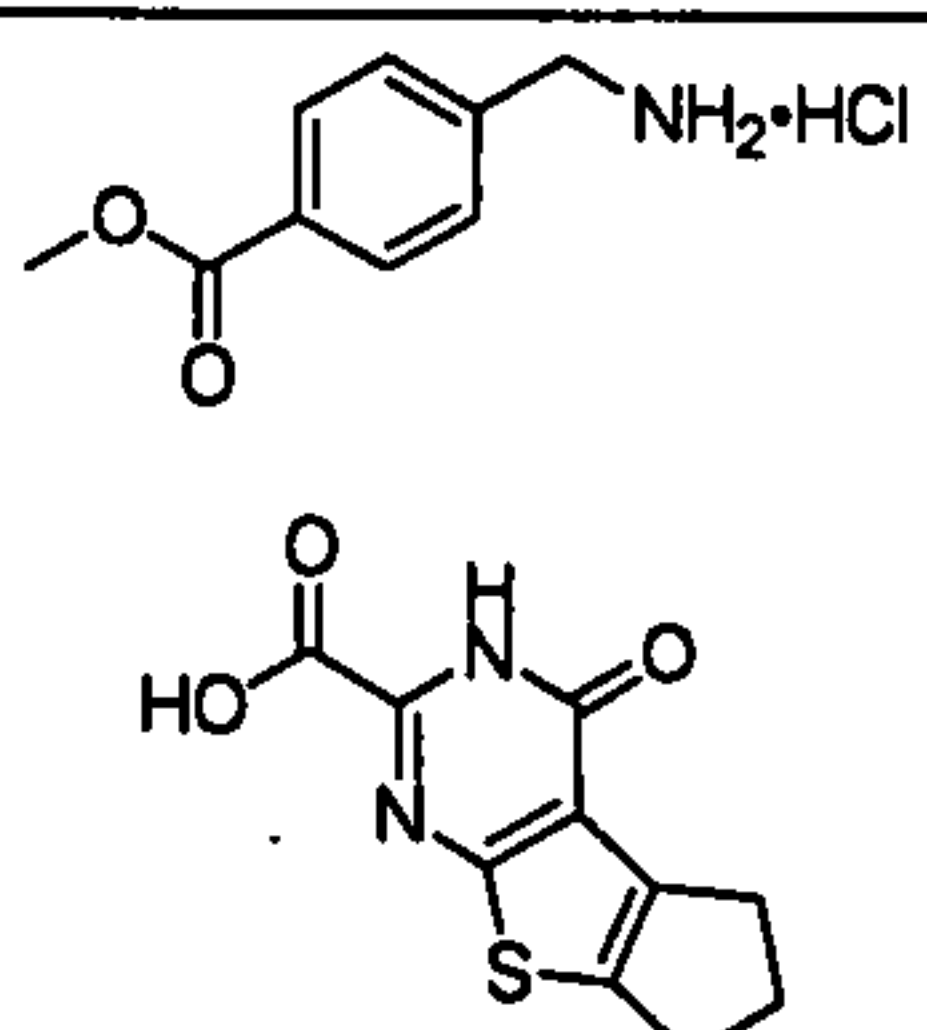
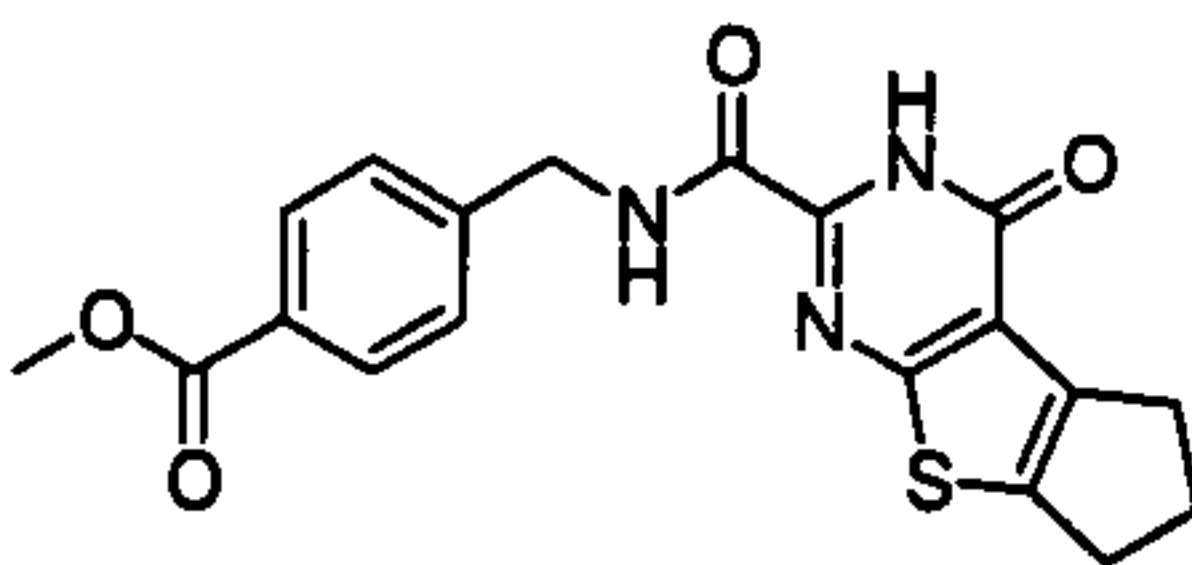
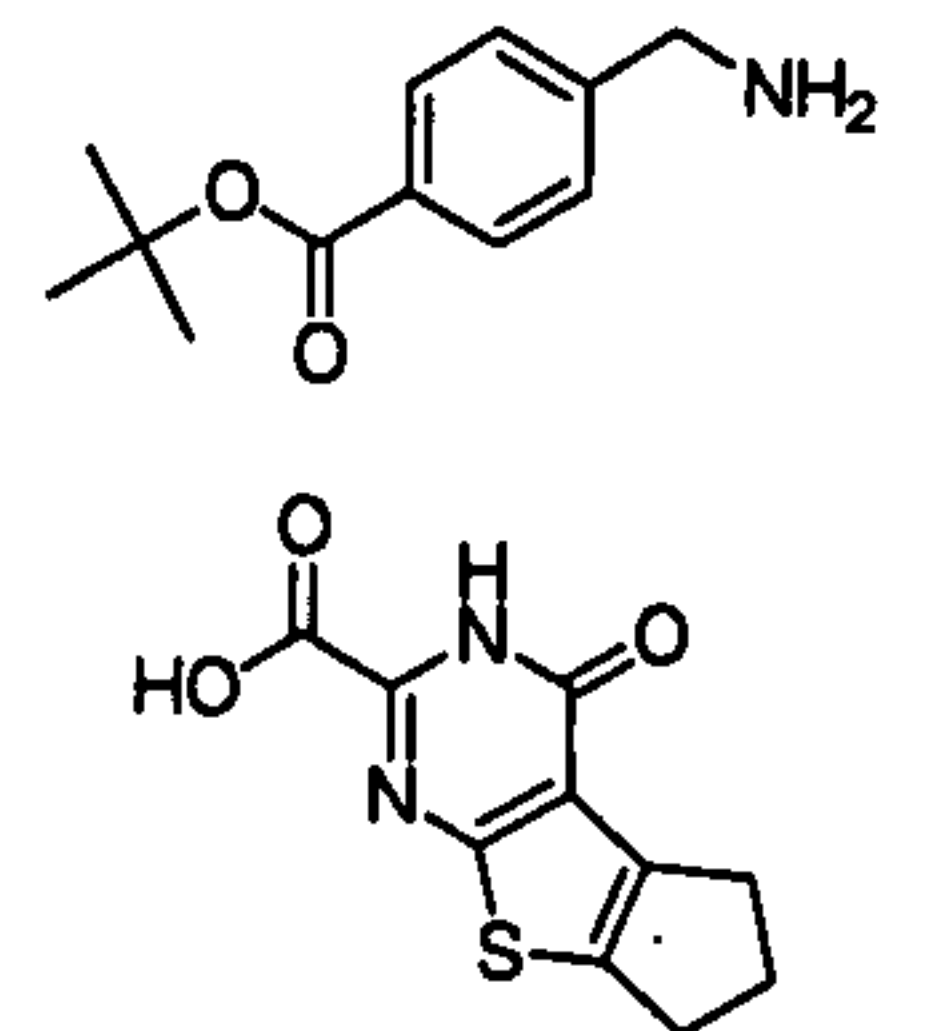
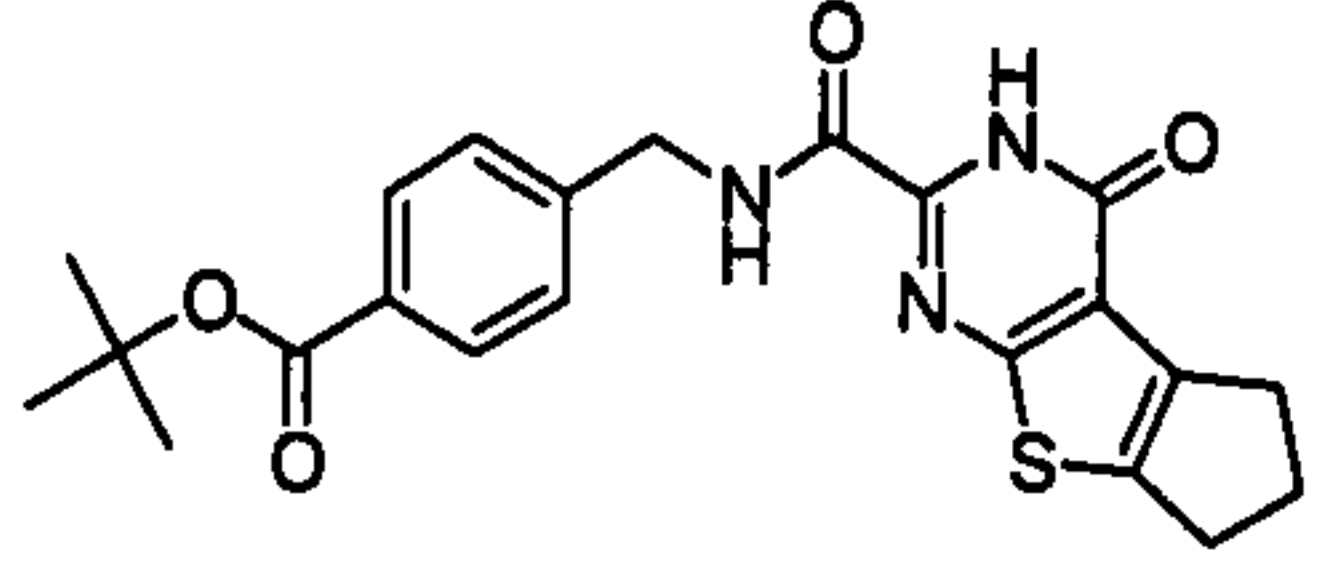
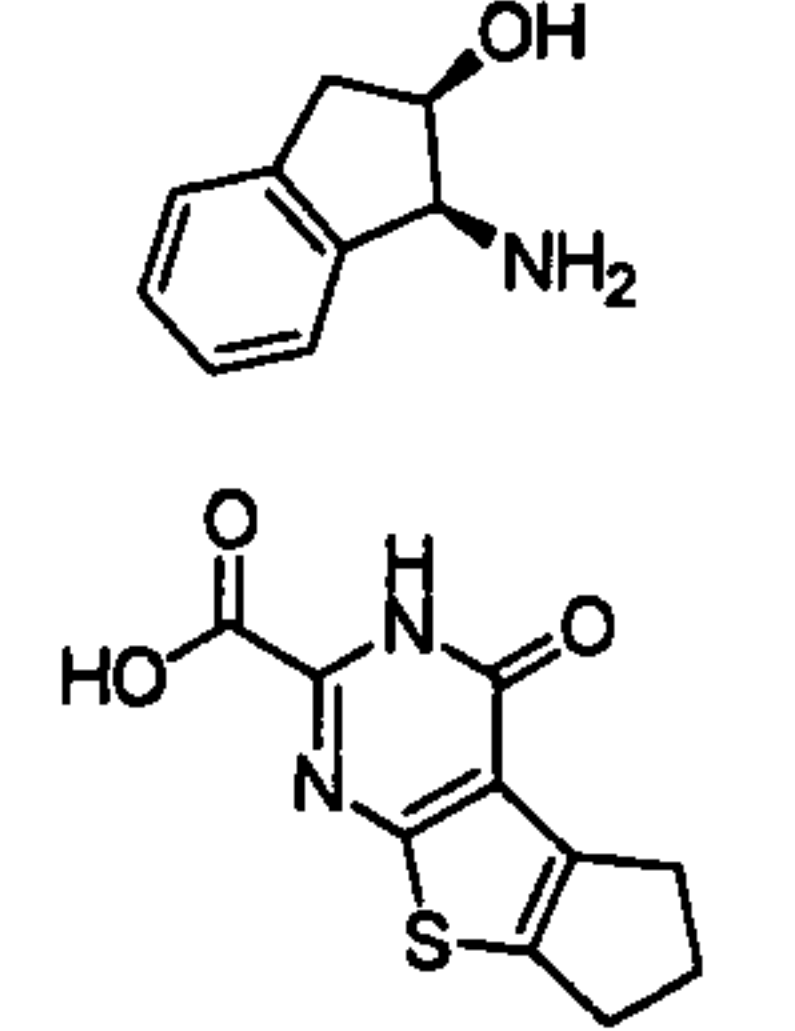
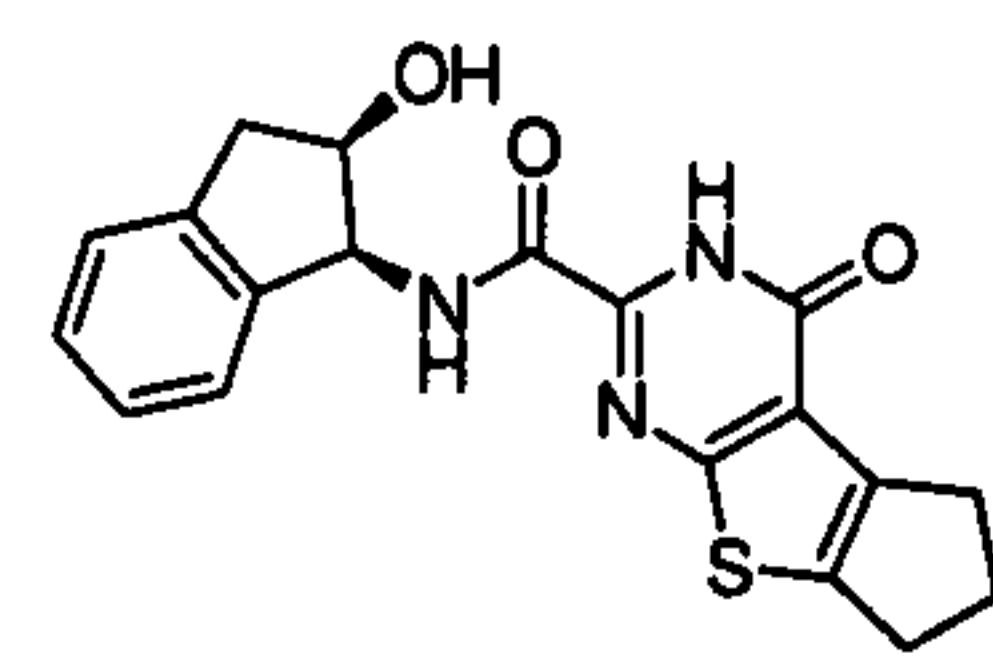
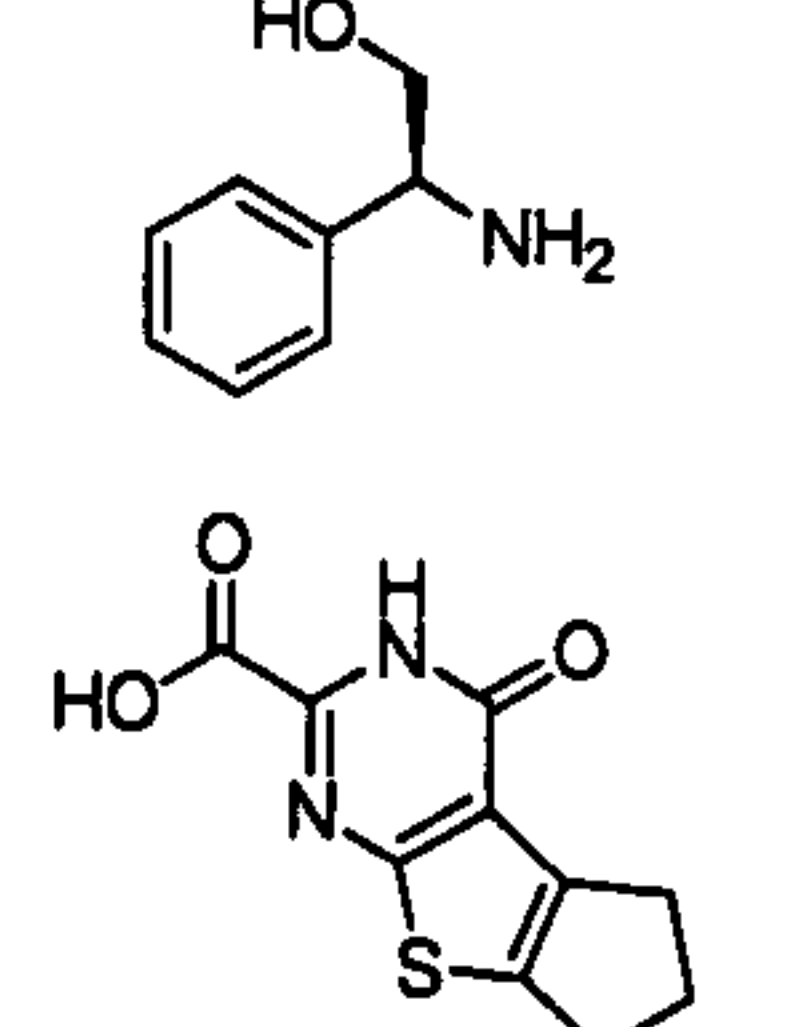
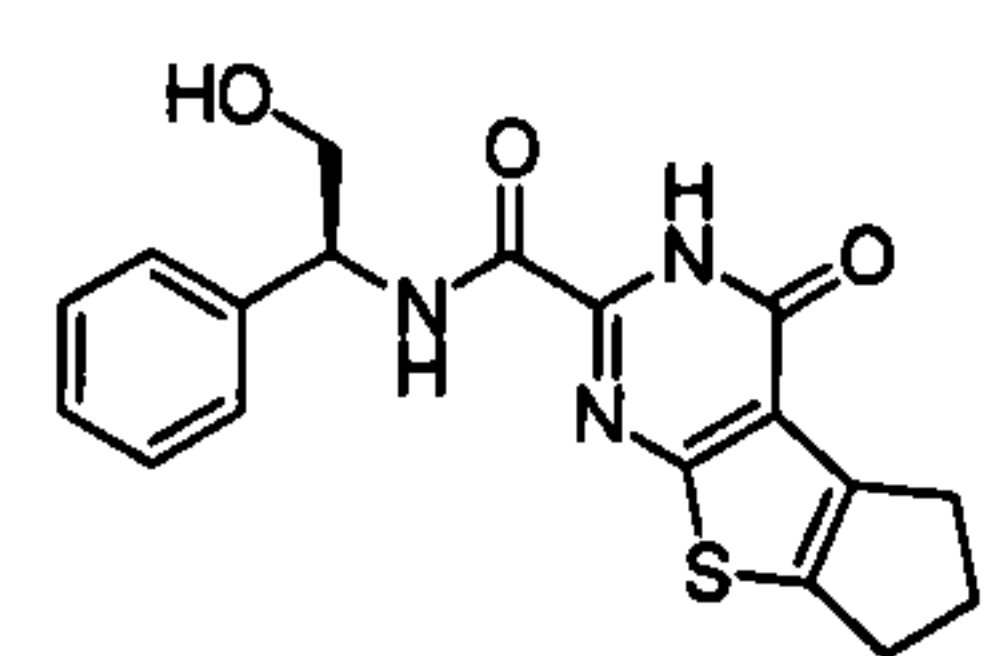
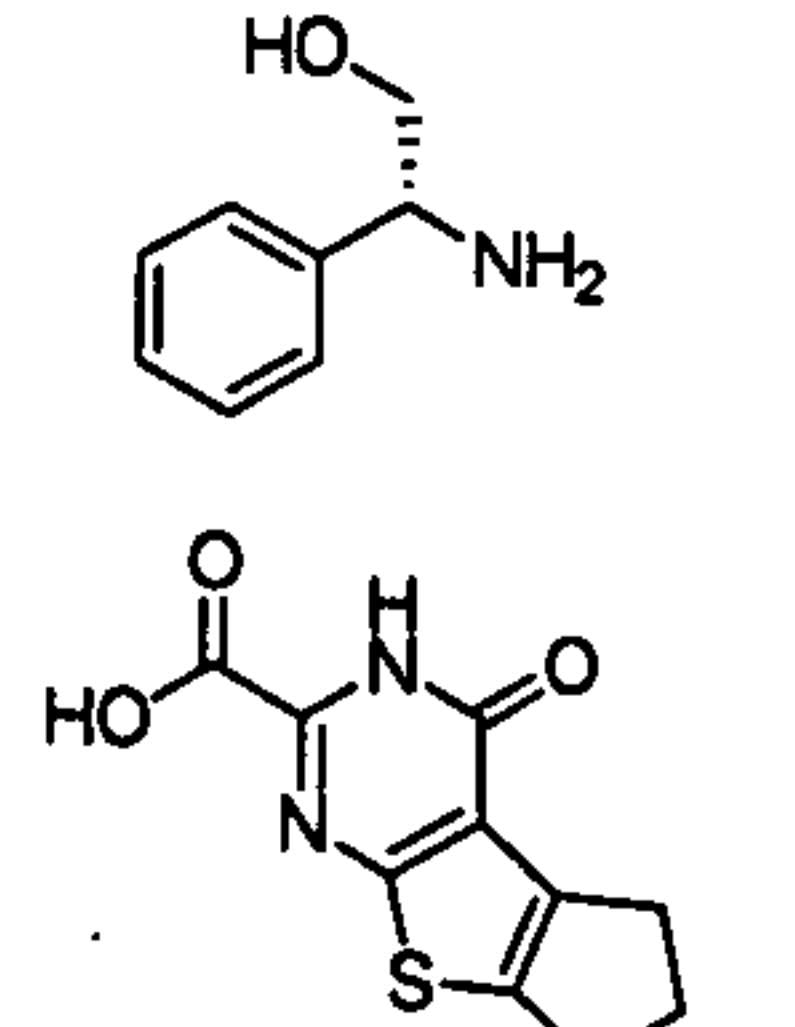
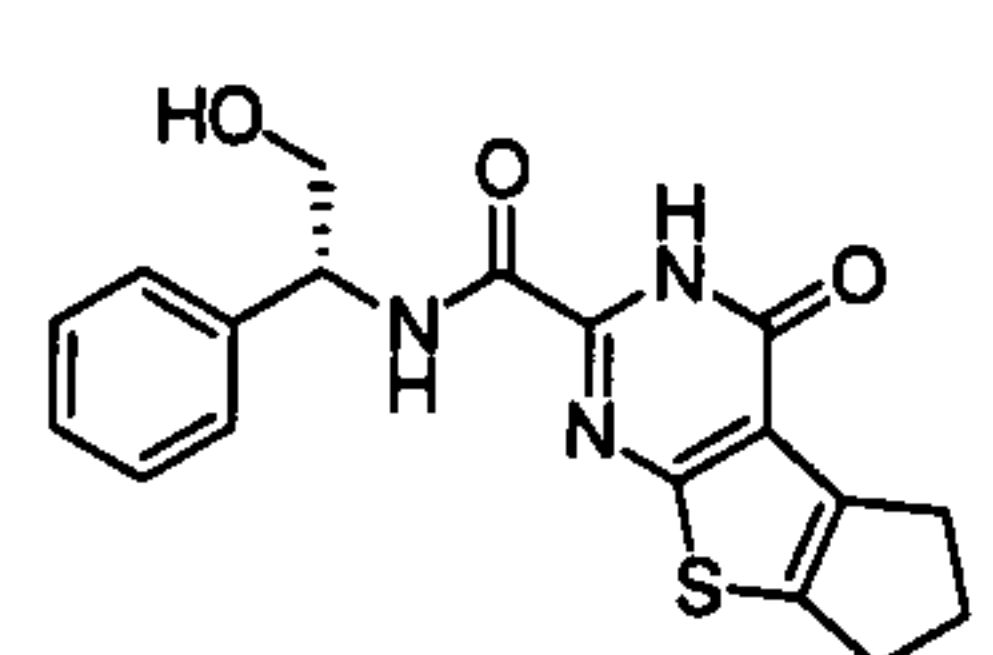
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 2/353 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 410 |
| 2/354 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>365    |
| 2/355 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 424 |
| 2/356 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>409    |
| 2/357 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 326 |

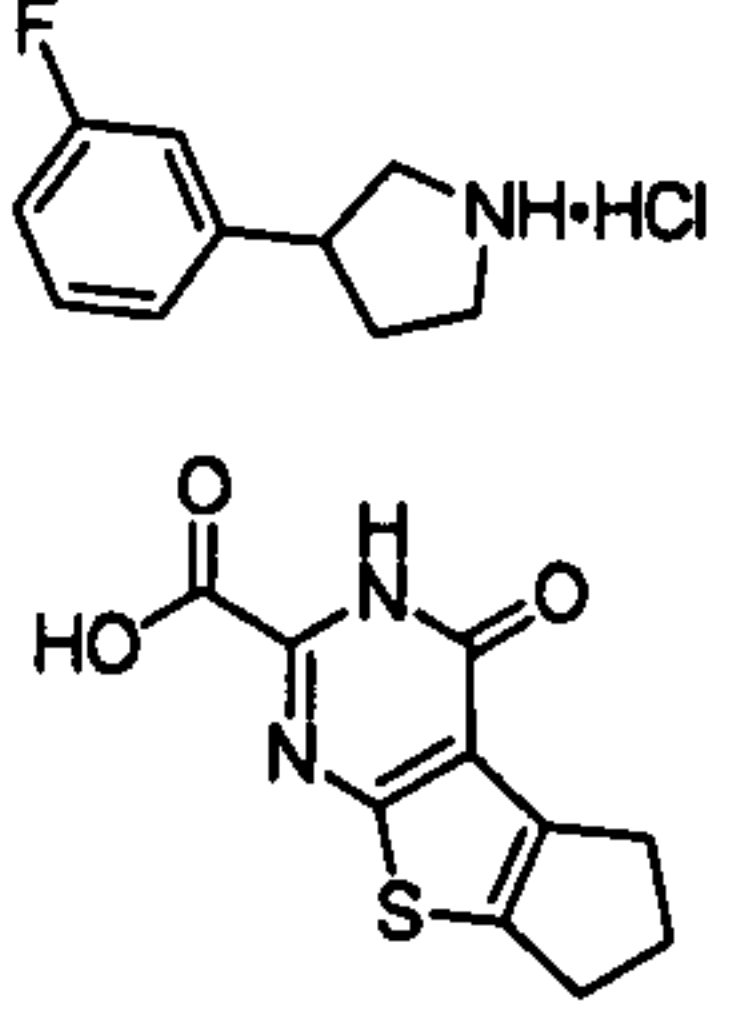
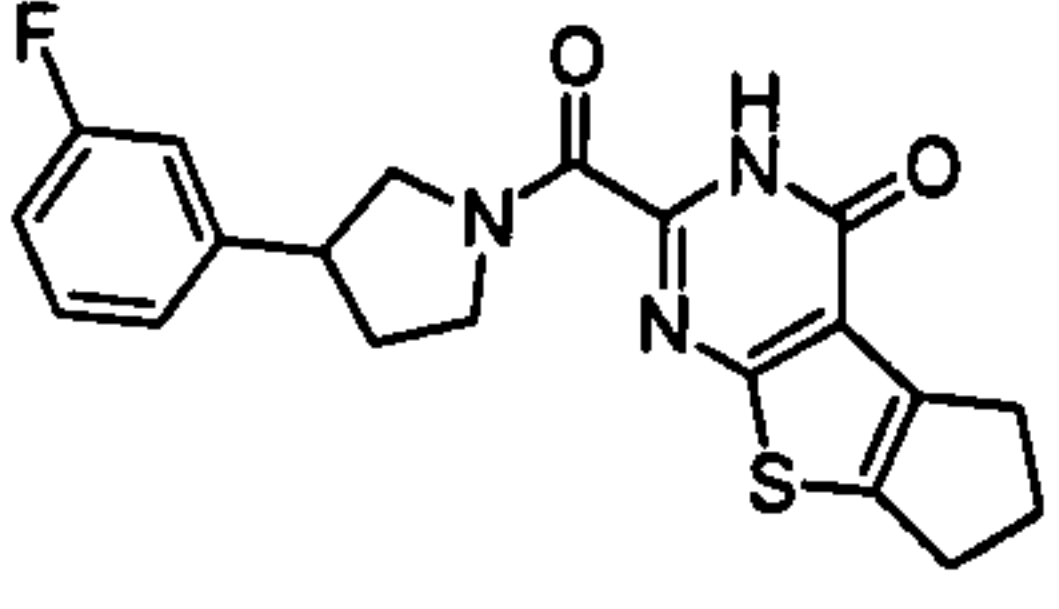
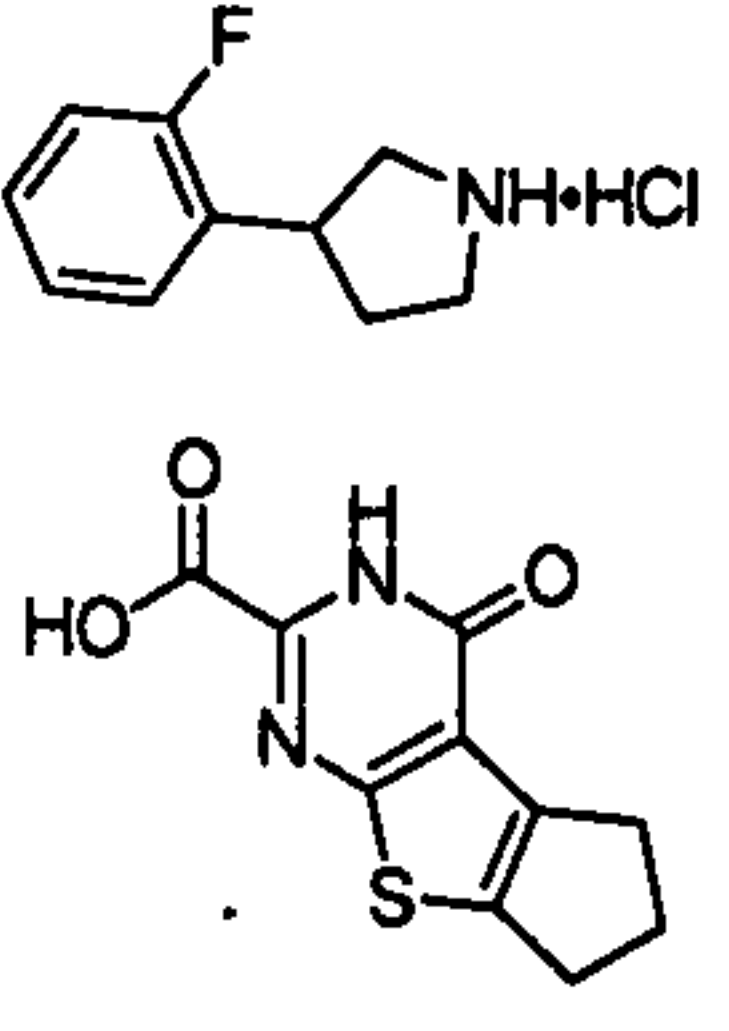
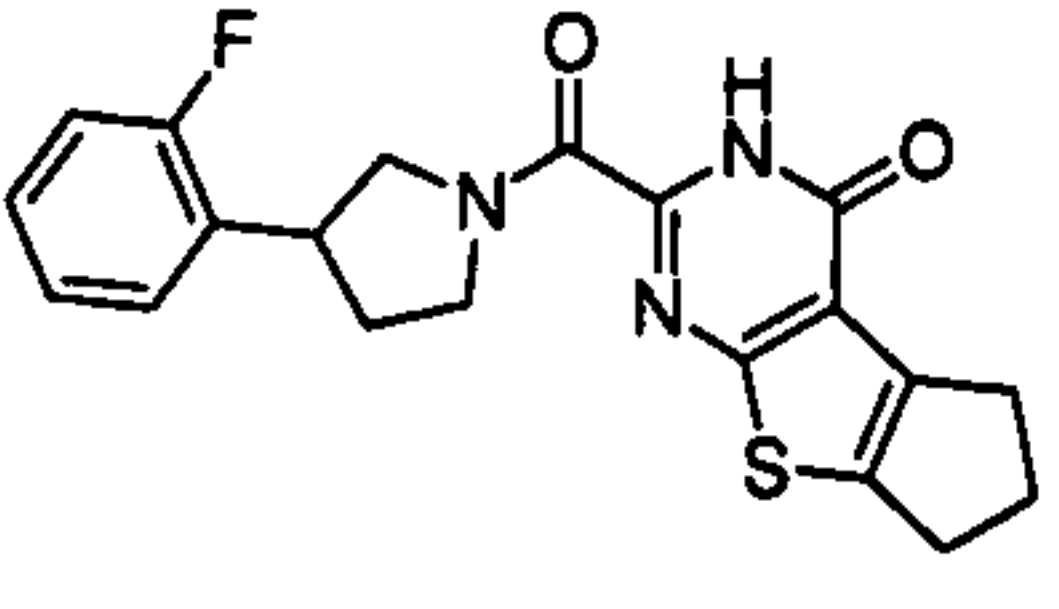
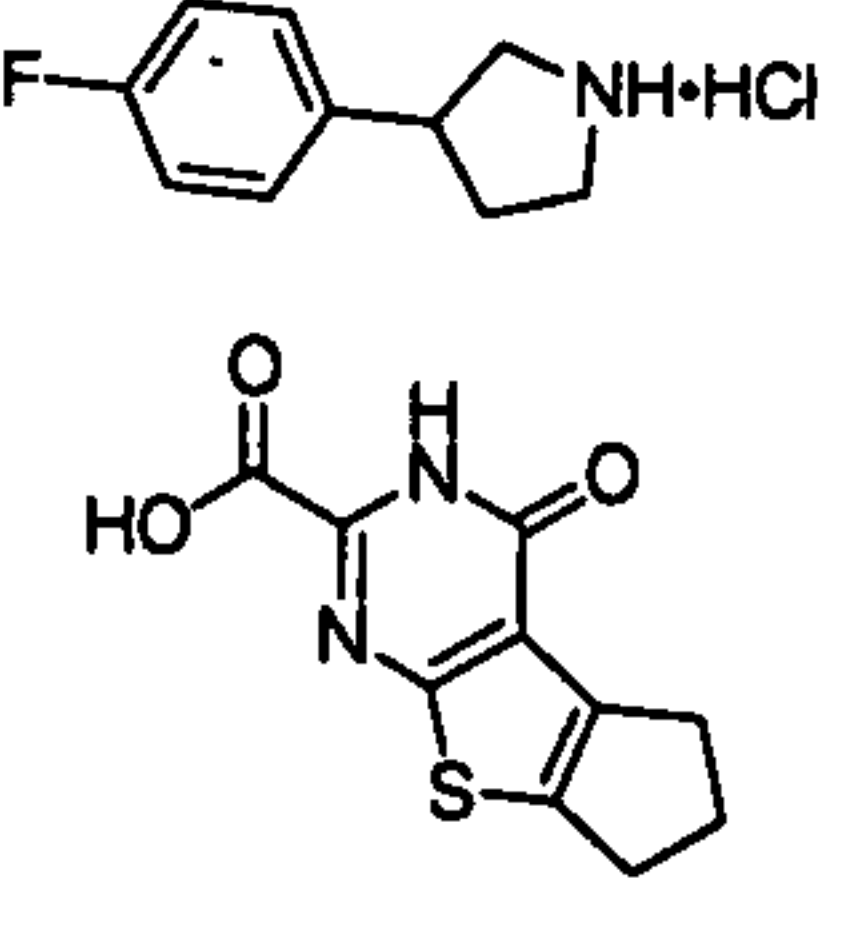
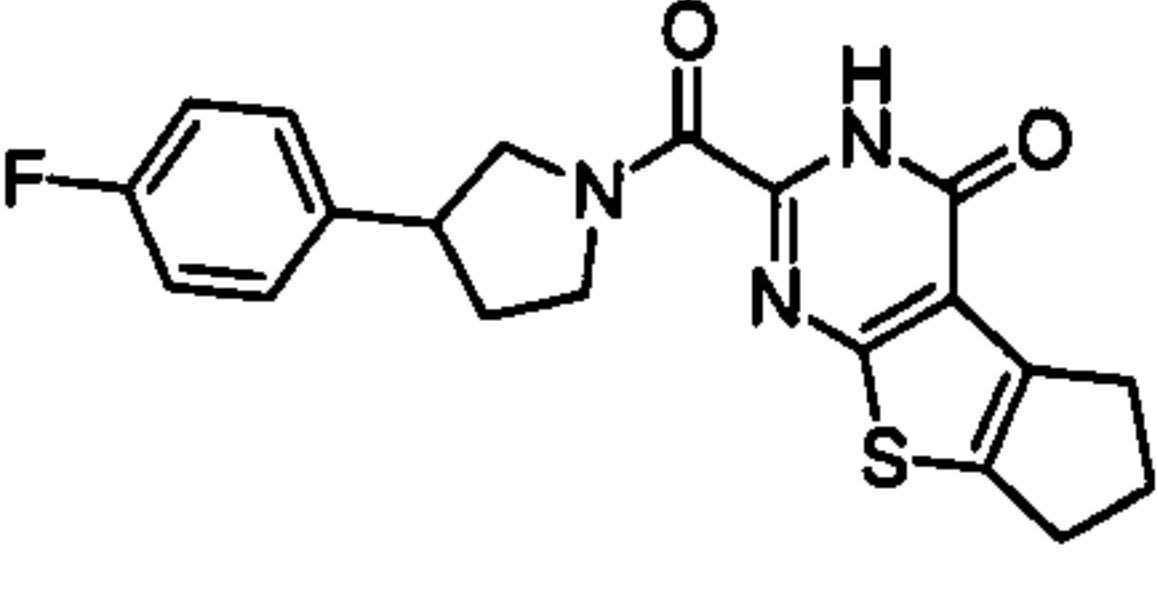
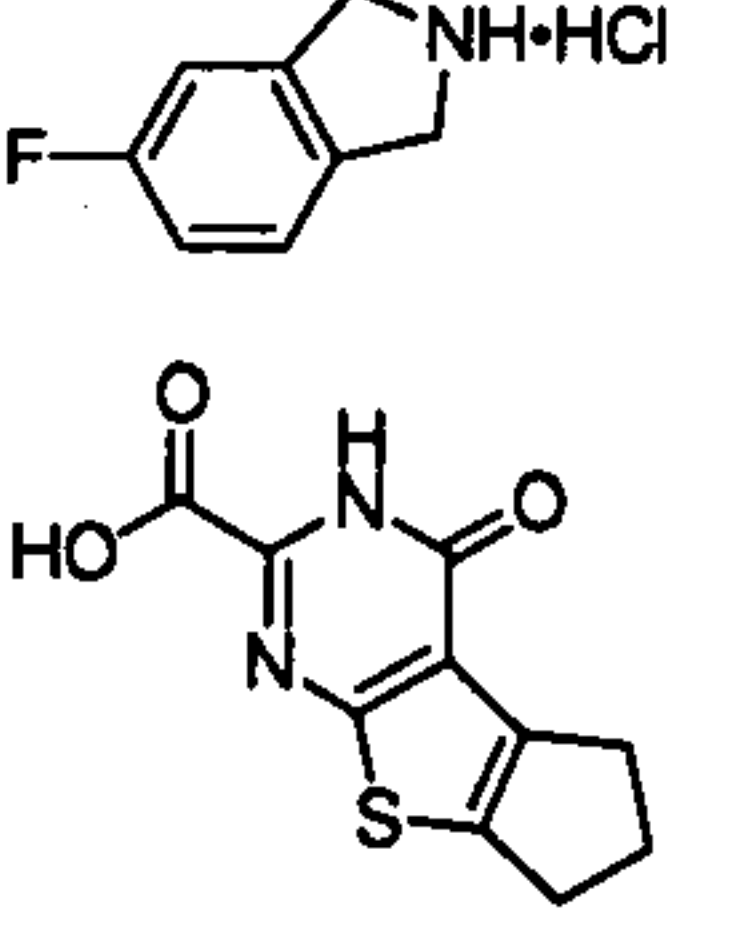
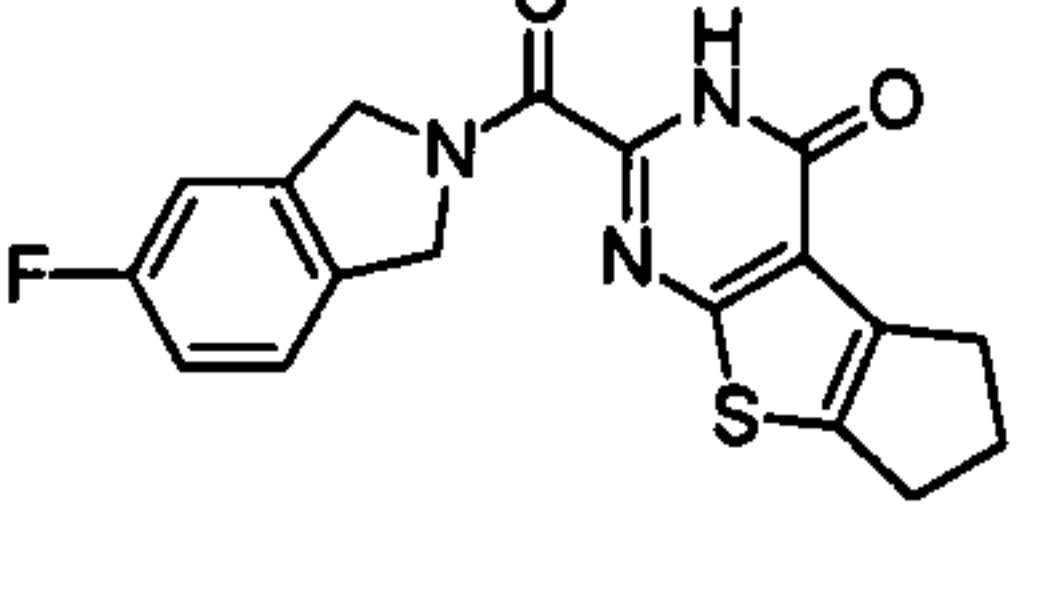
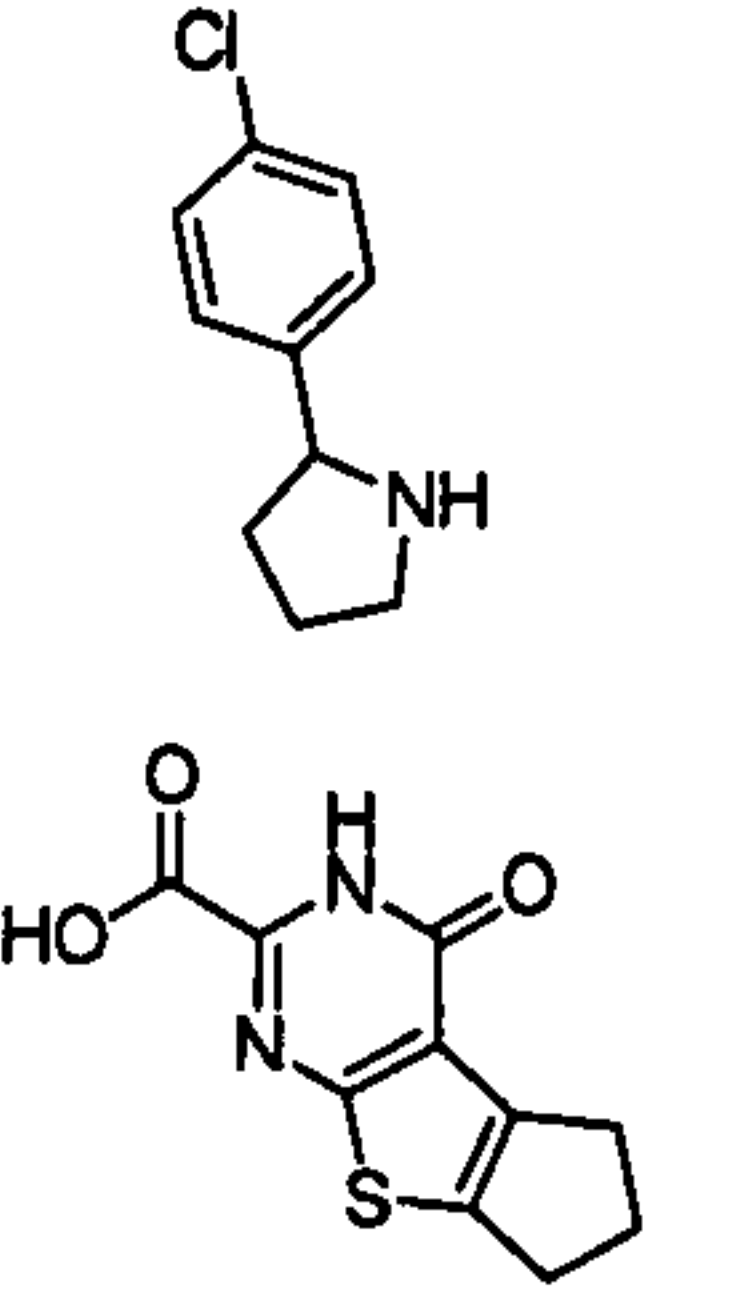
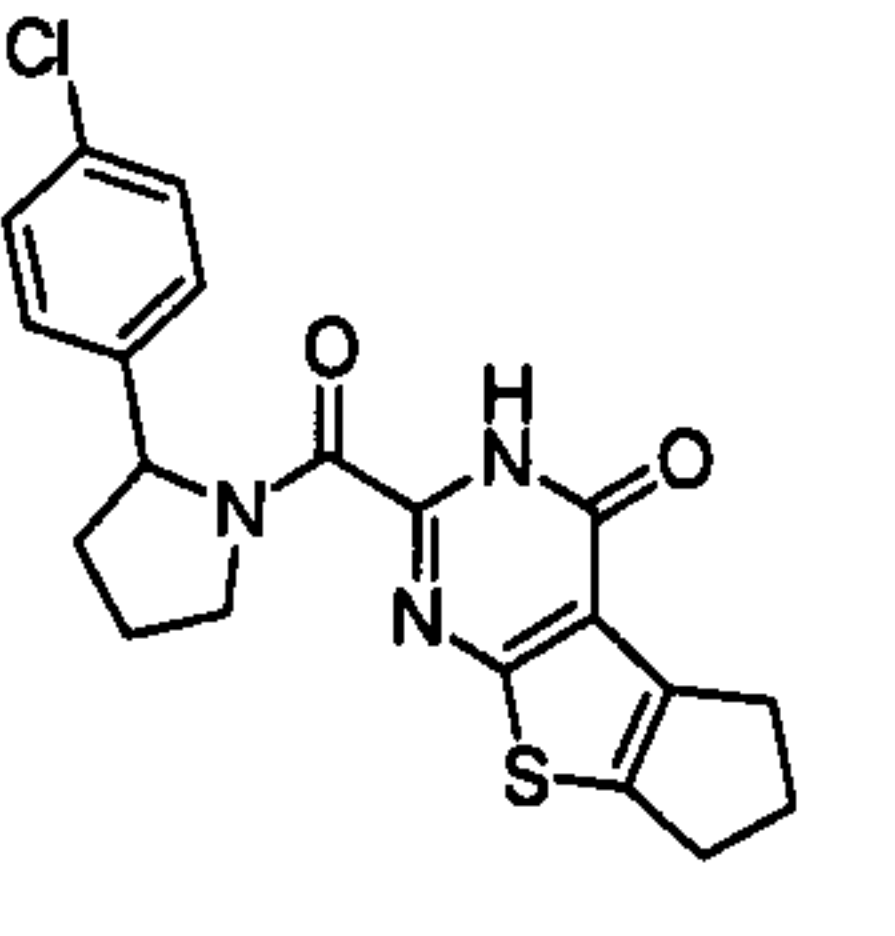
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------|
| 2/358 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 340              |
| 2/359 |   |   | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 410              |
| 2/360 |  |  | B, n.d.<br>[M-(TFA) <sub>2</sub> ] <sup>+</sup> = 423 |
| 2/361 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 409                    |
| 2/362 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 333                    |
| 2/363 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 367                    |

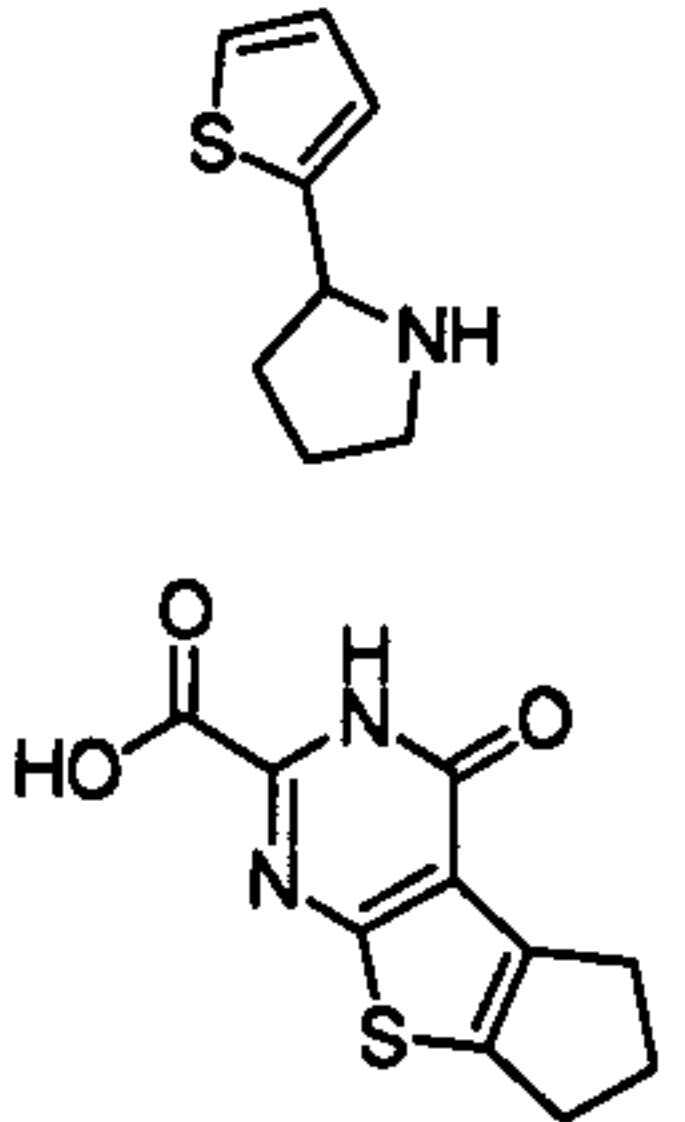
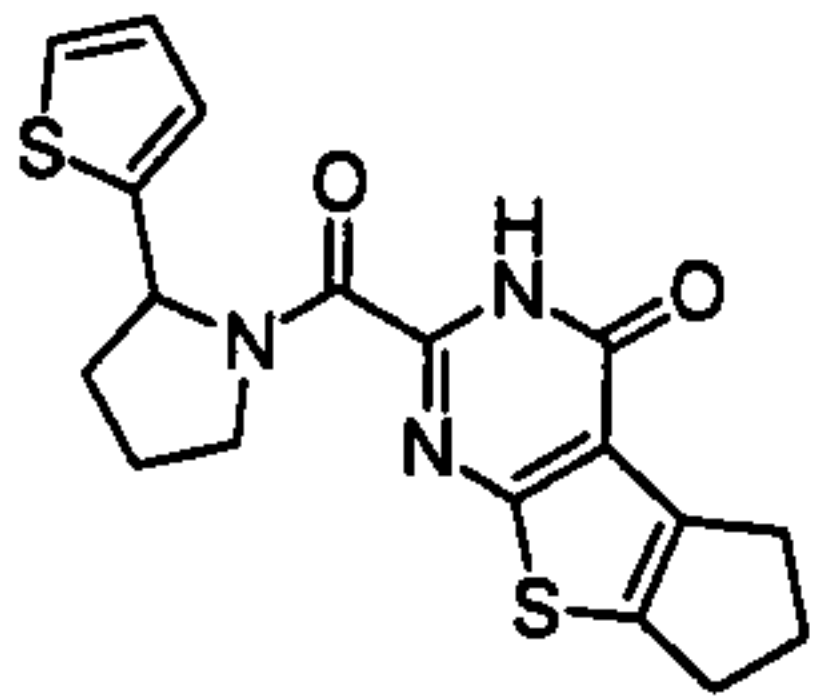
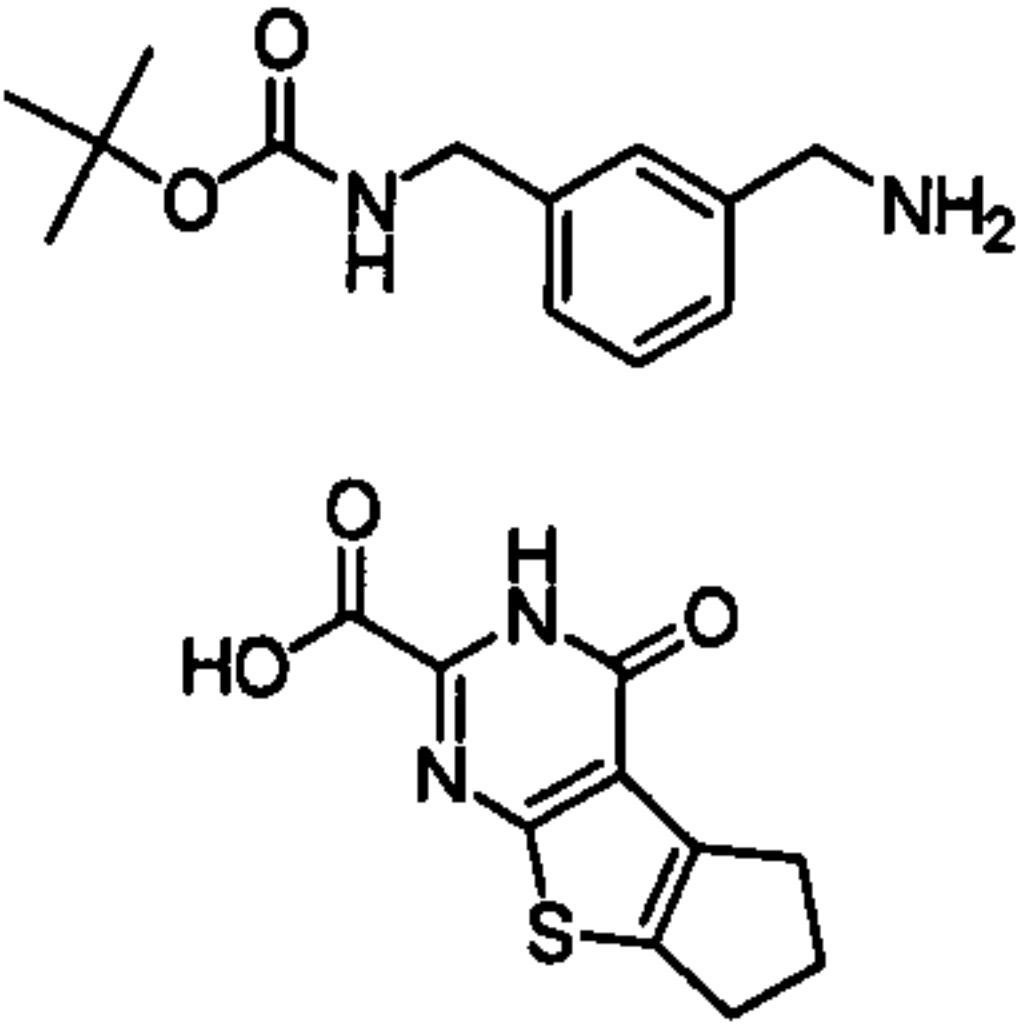
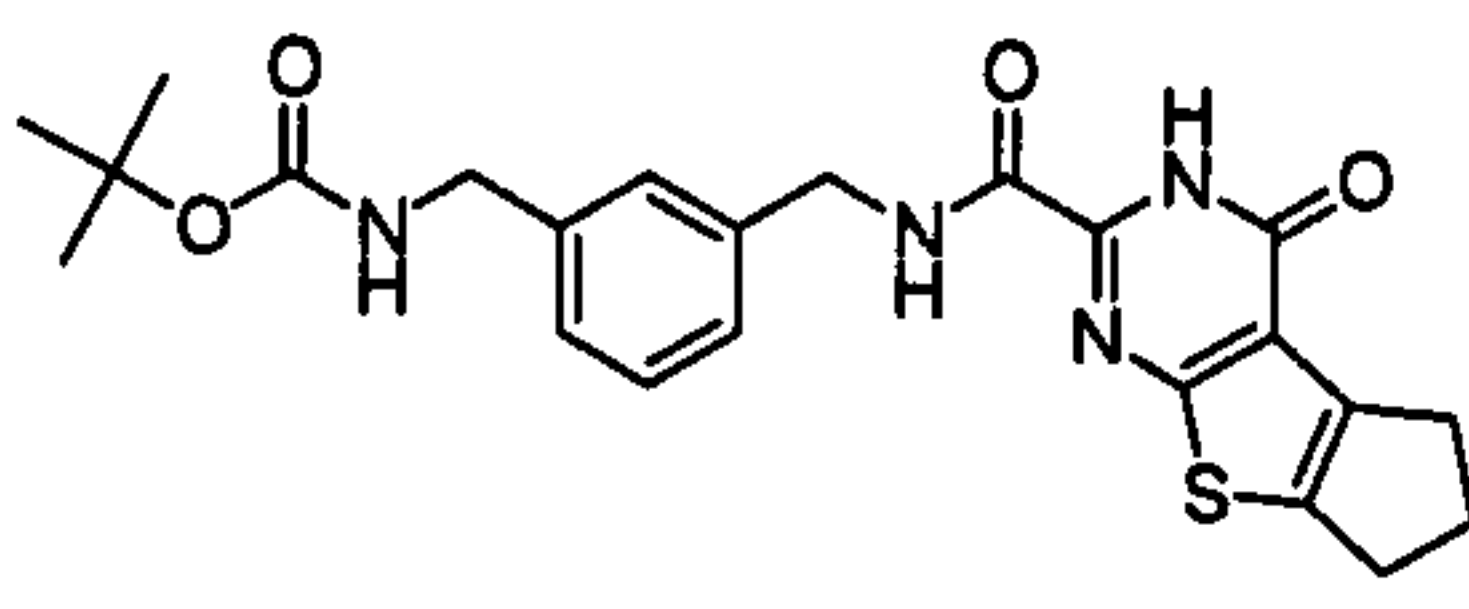
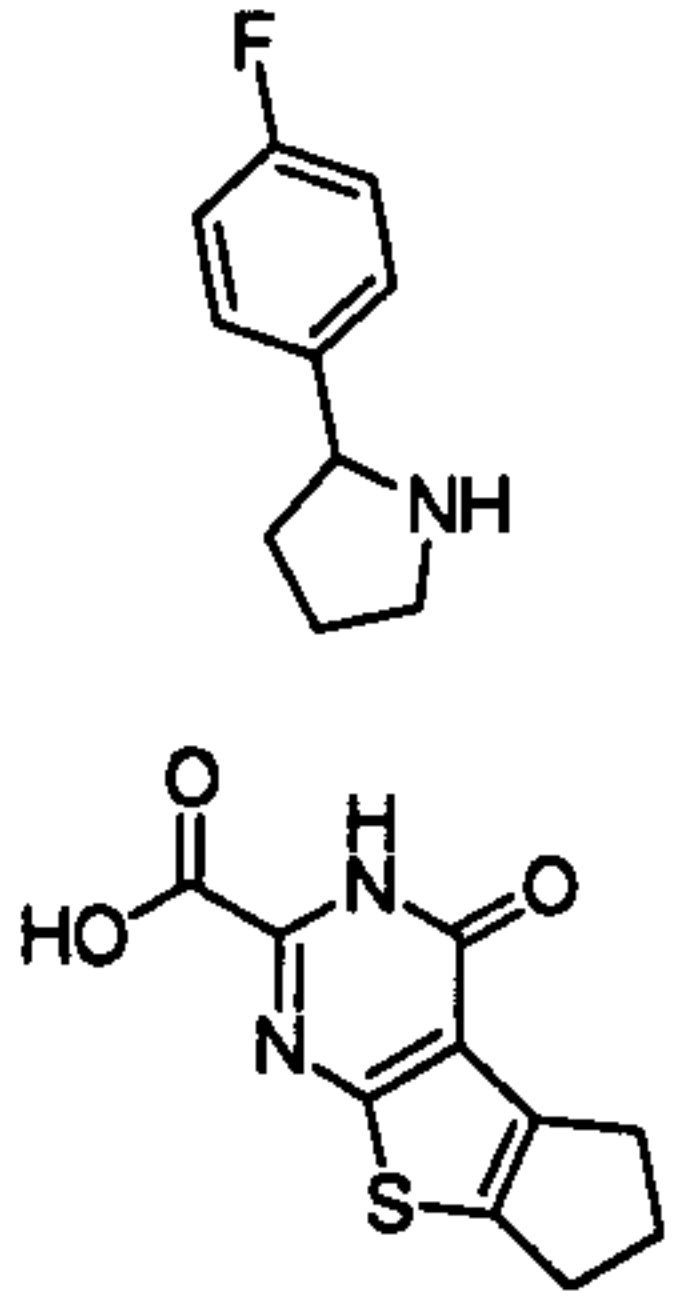
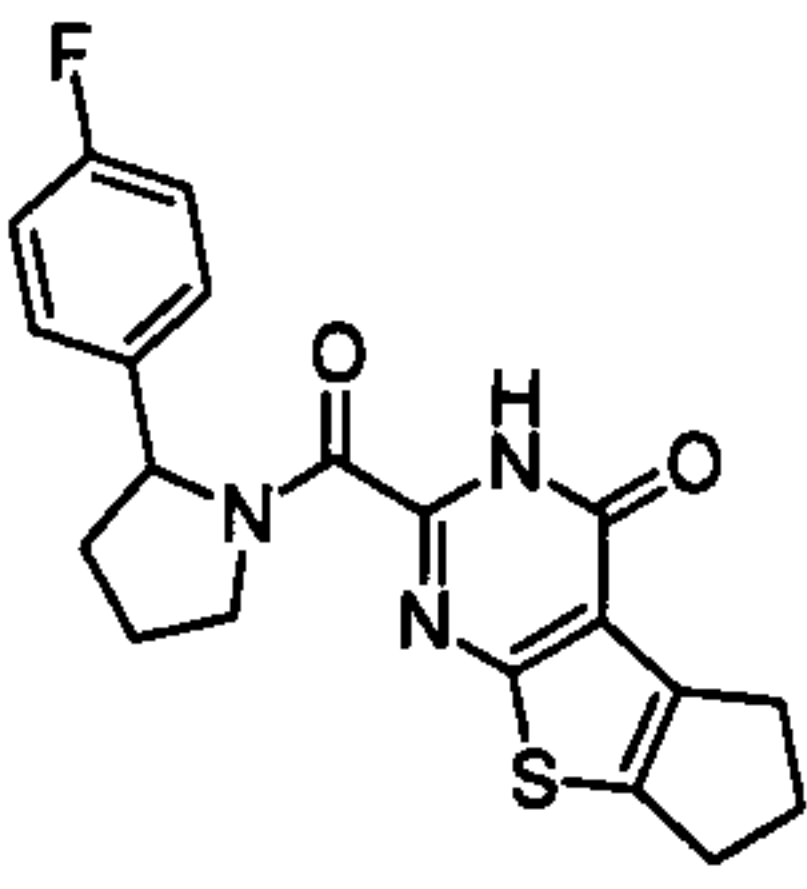
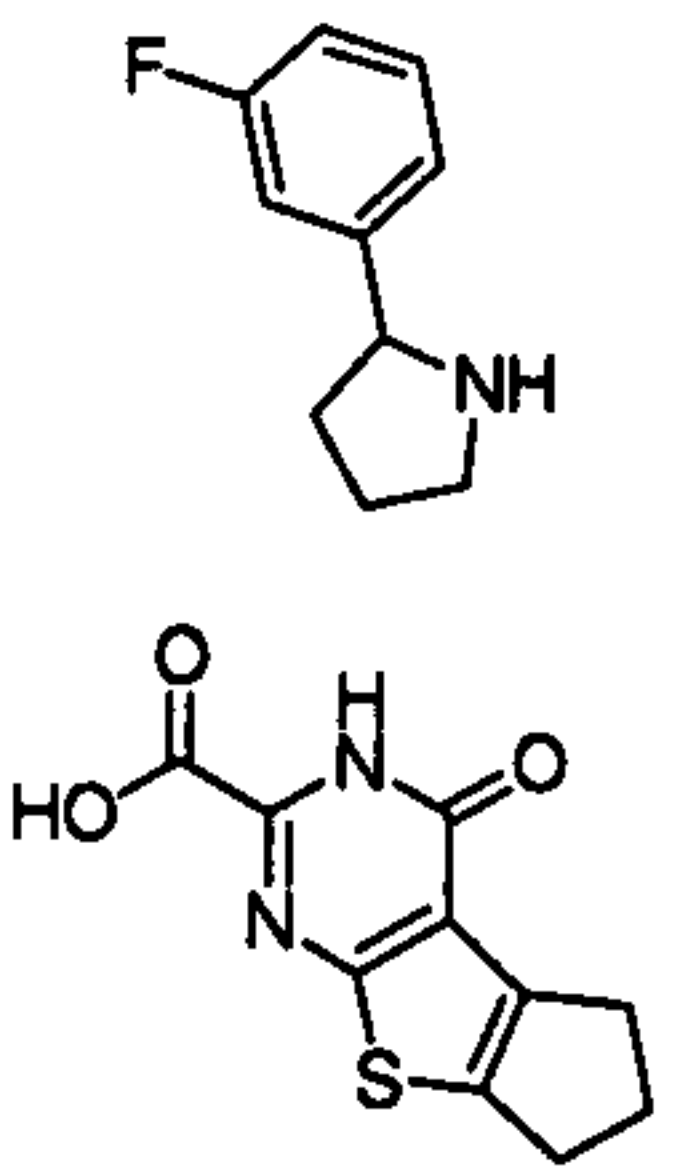
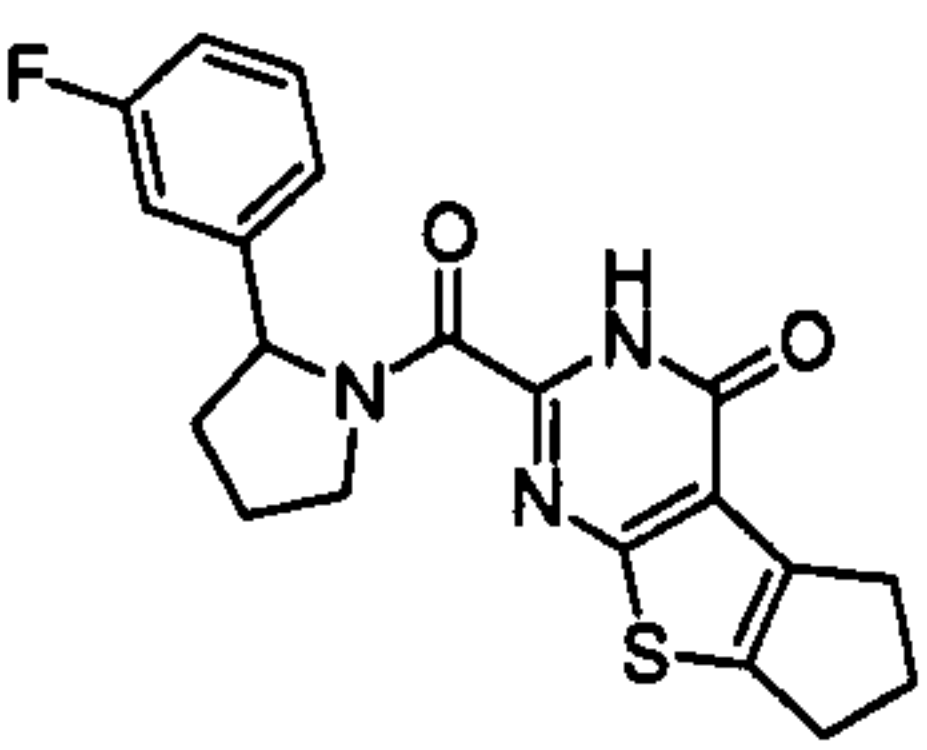
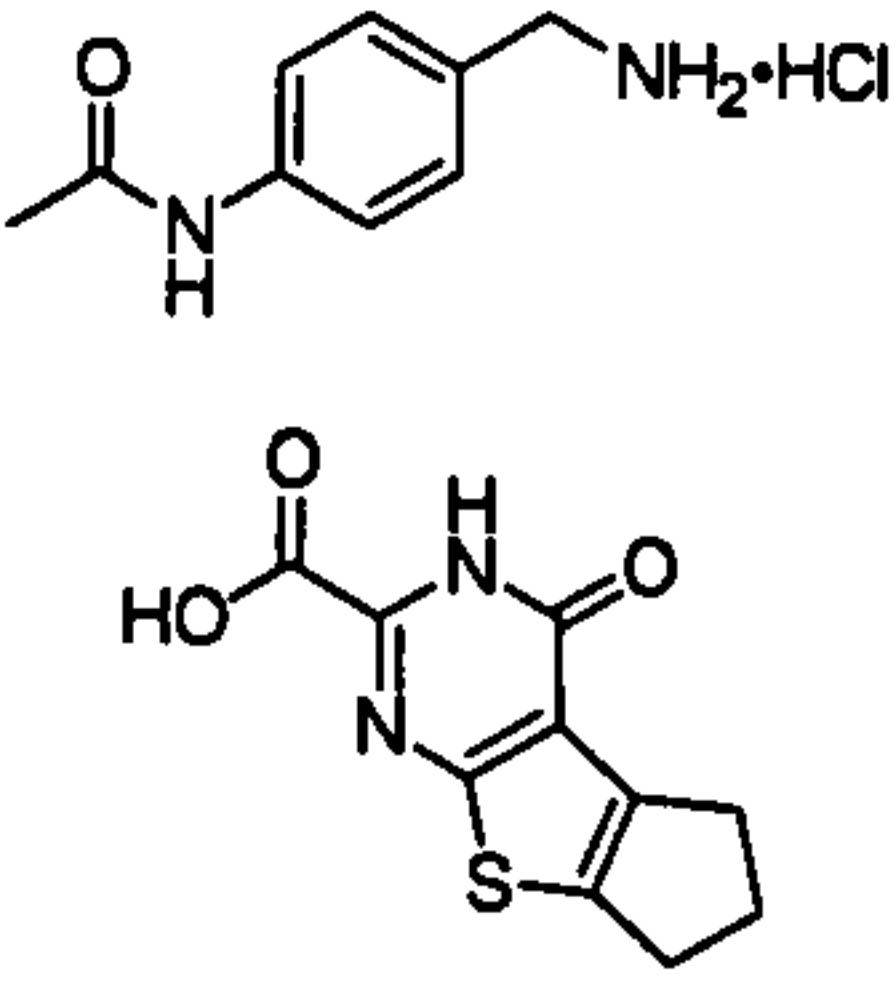
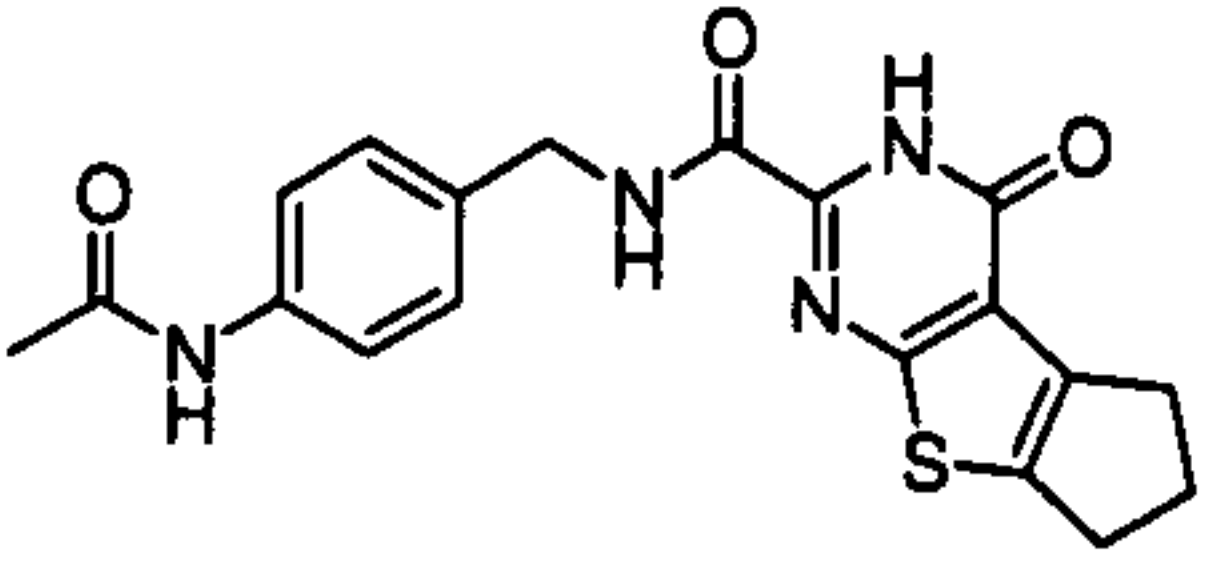
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 2/364 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 315 |
| 2/365 |   |   | B, n.d.<br>[MH] <sup>+</sup> =<br>331    |
| 2/366 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>317    |
| 2/367 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>410    |
| 2/368 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 394 |
| 2/369 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>332    |

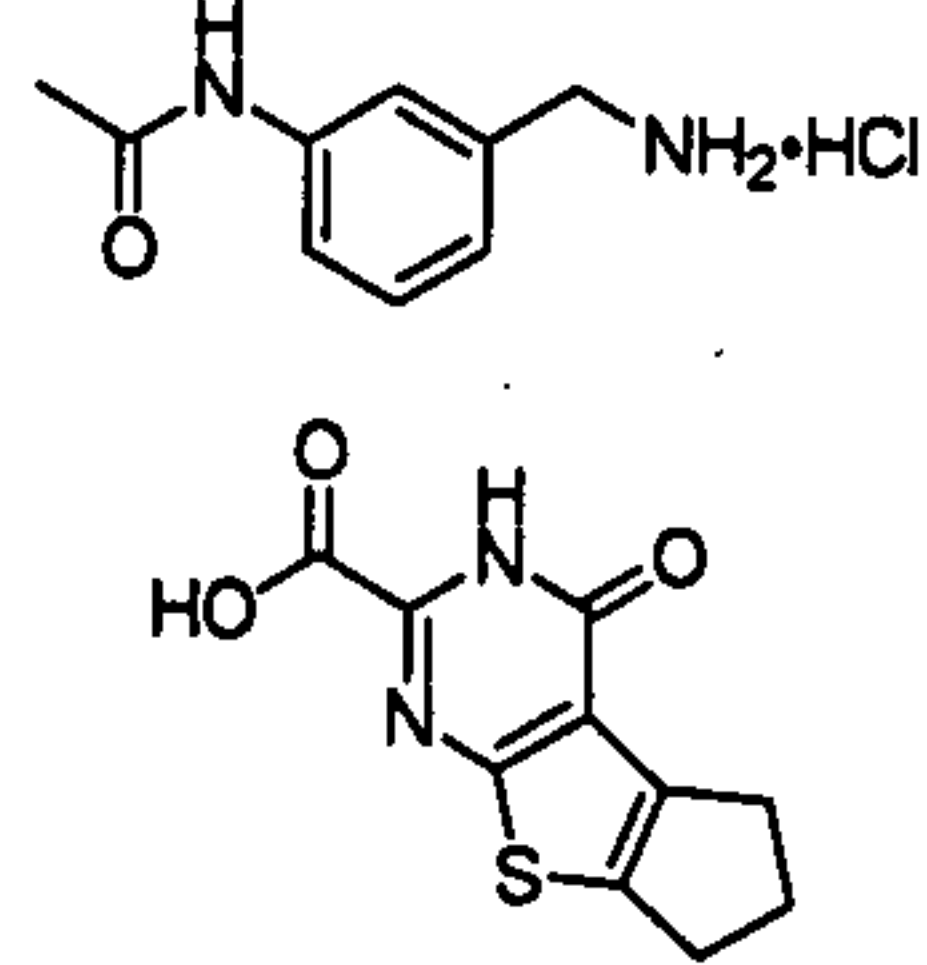
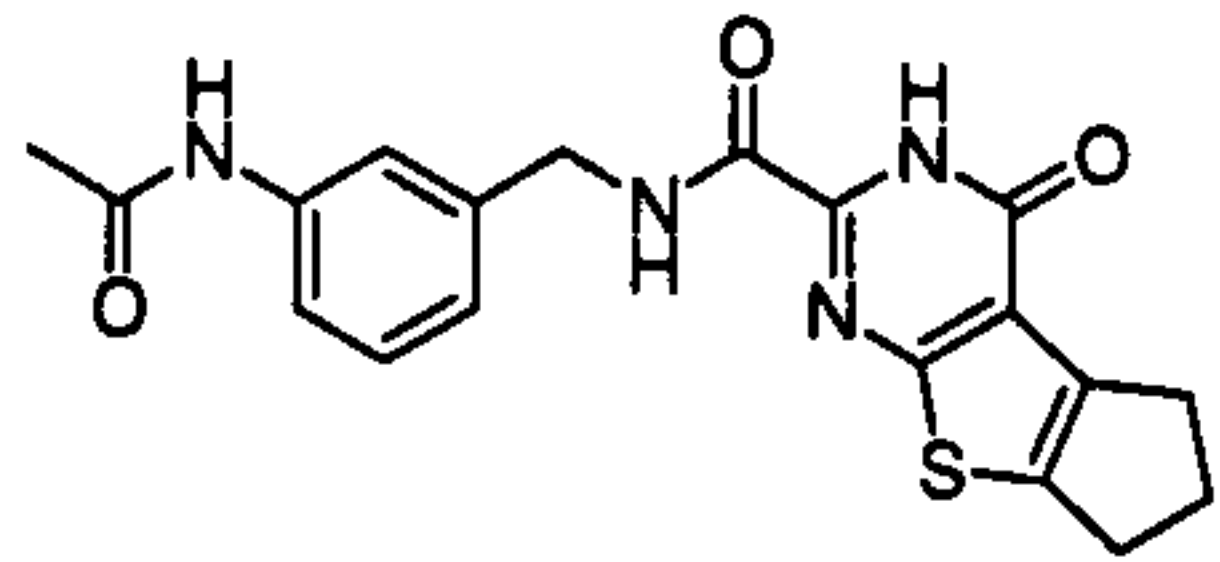
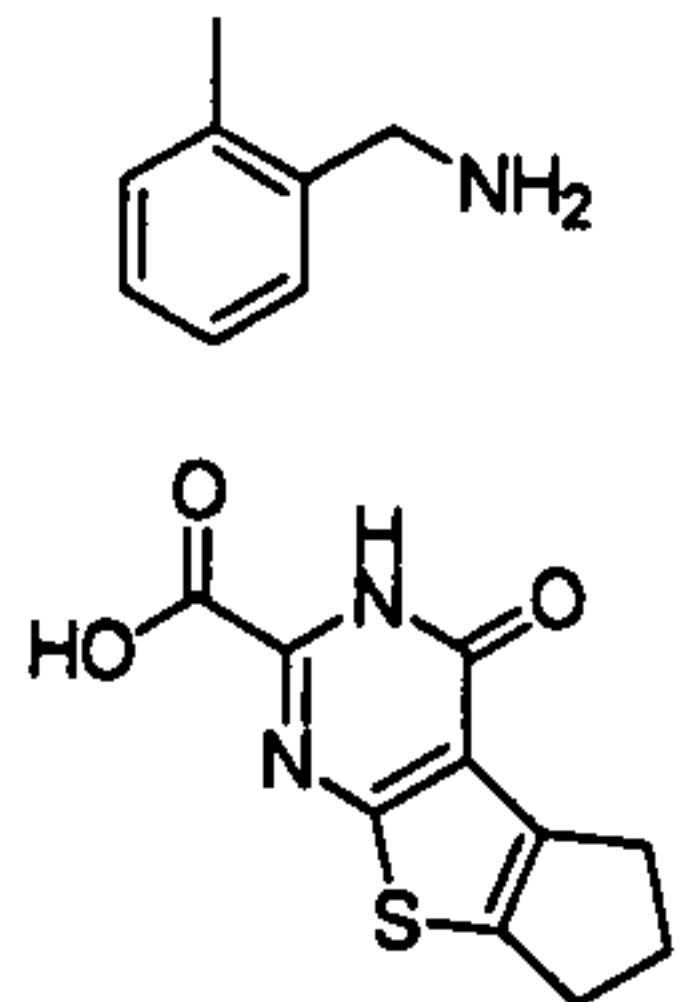
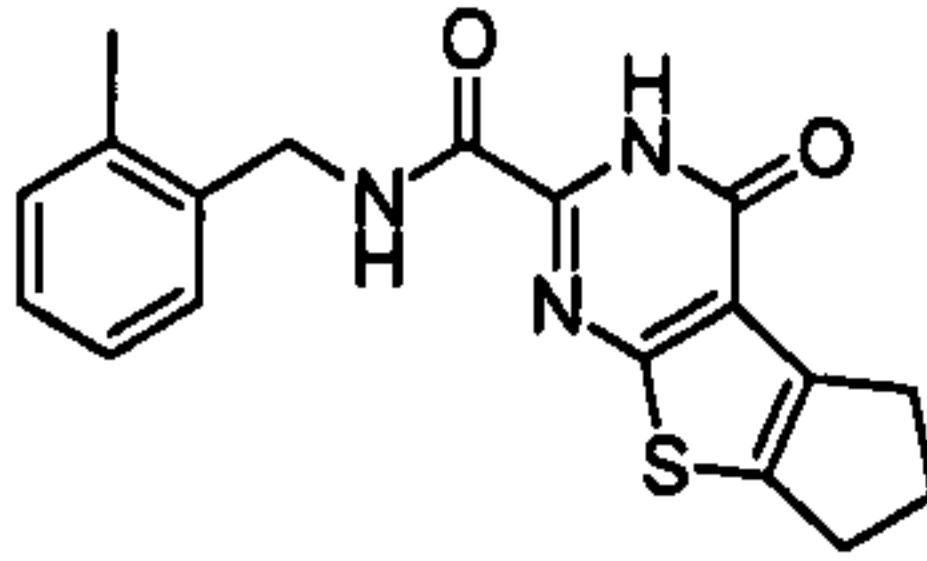
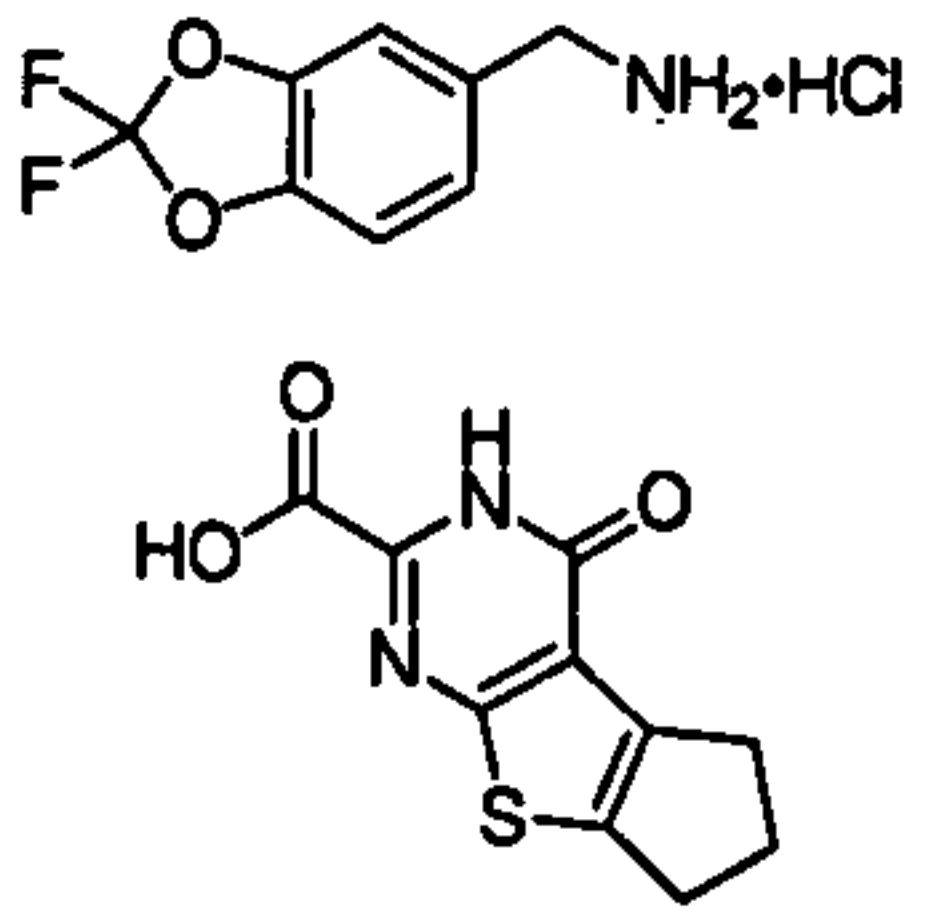
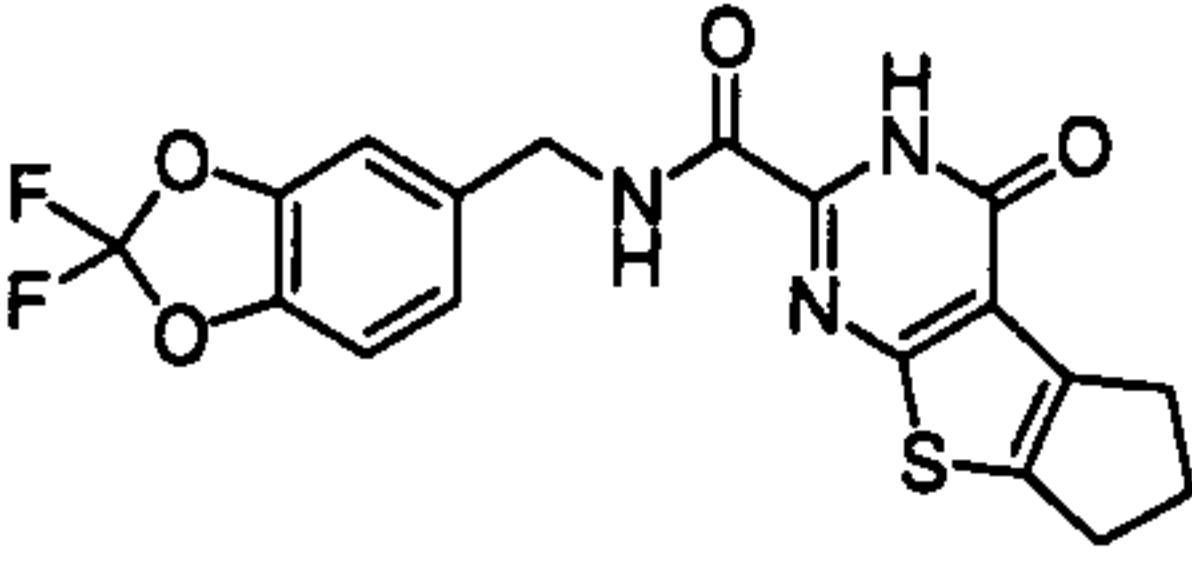
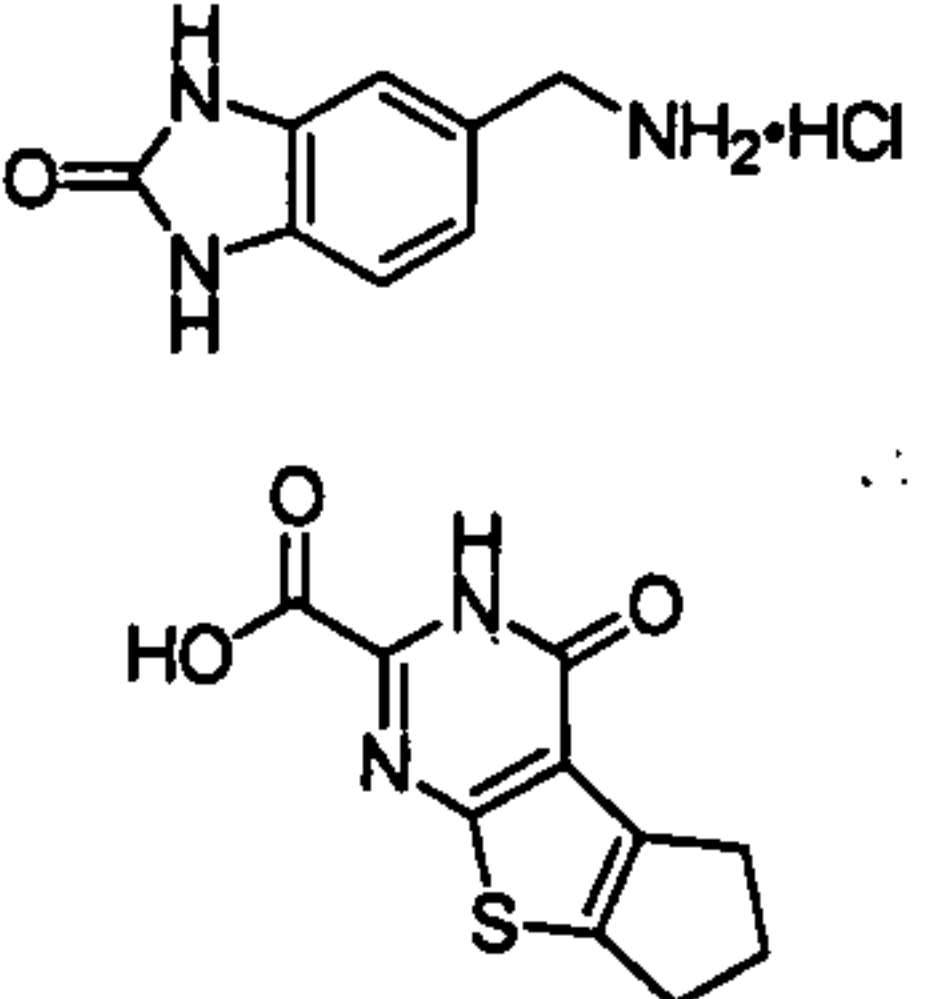
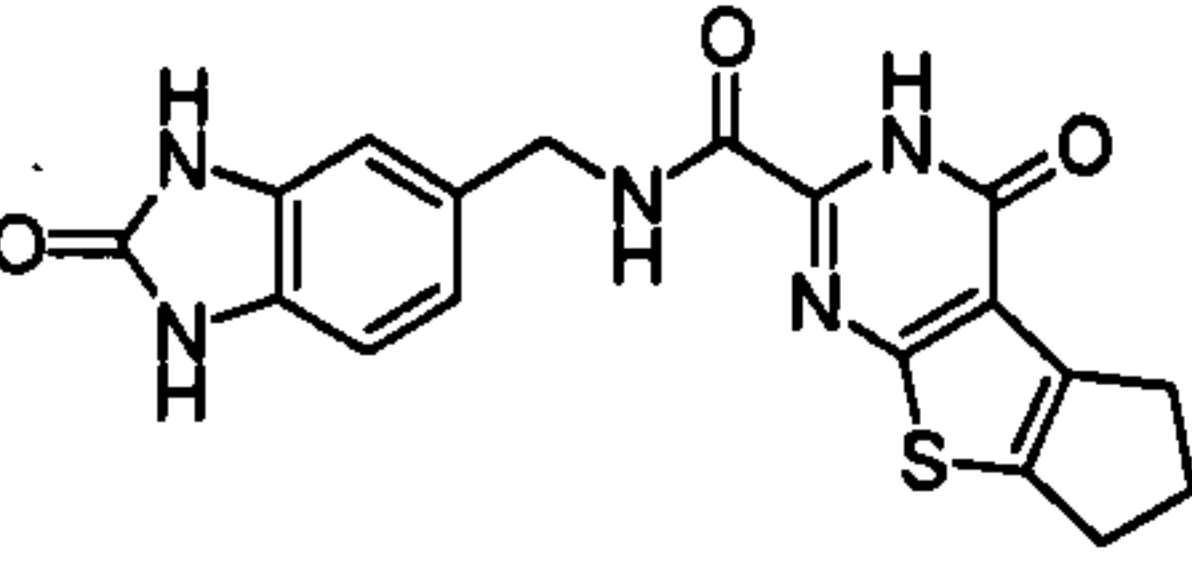
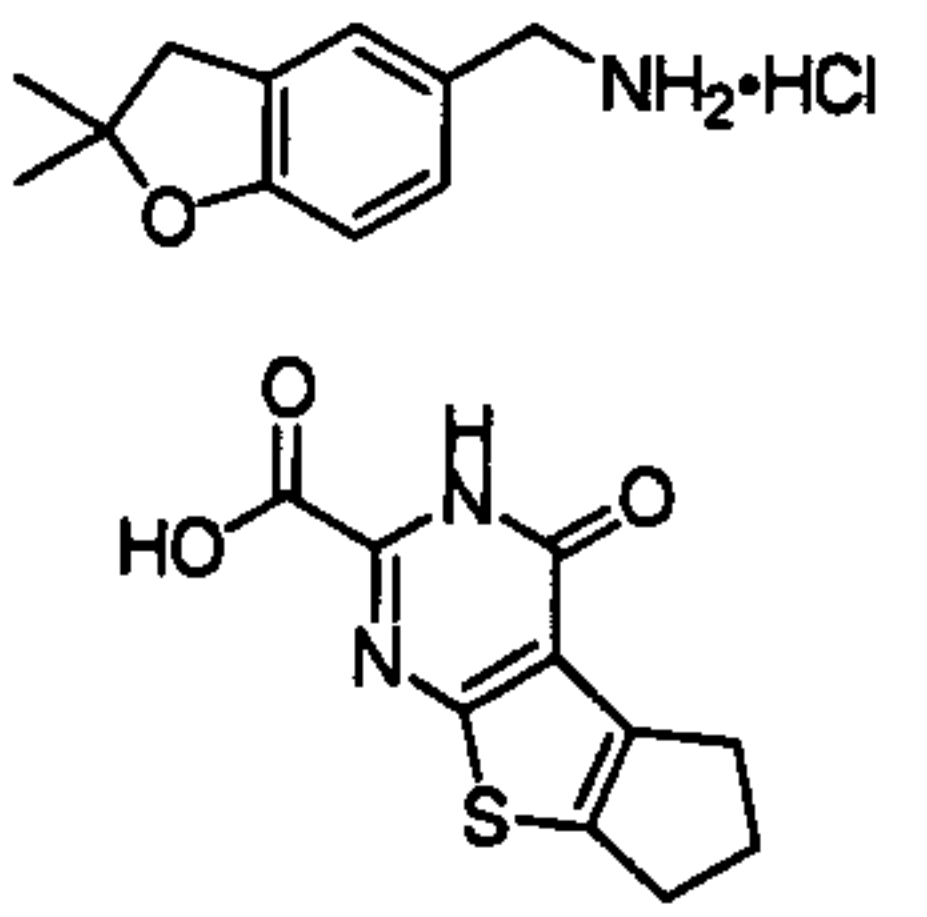
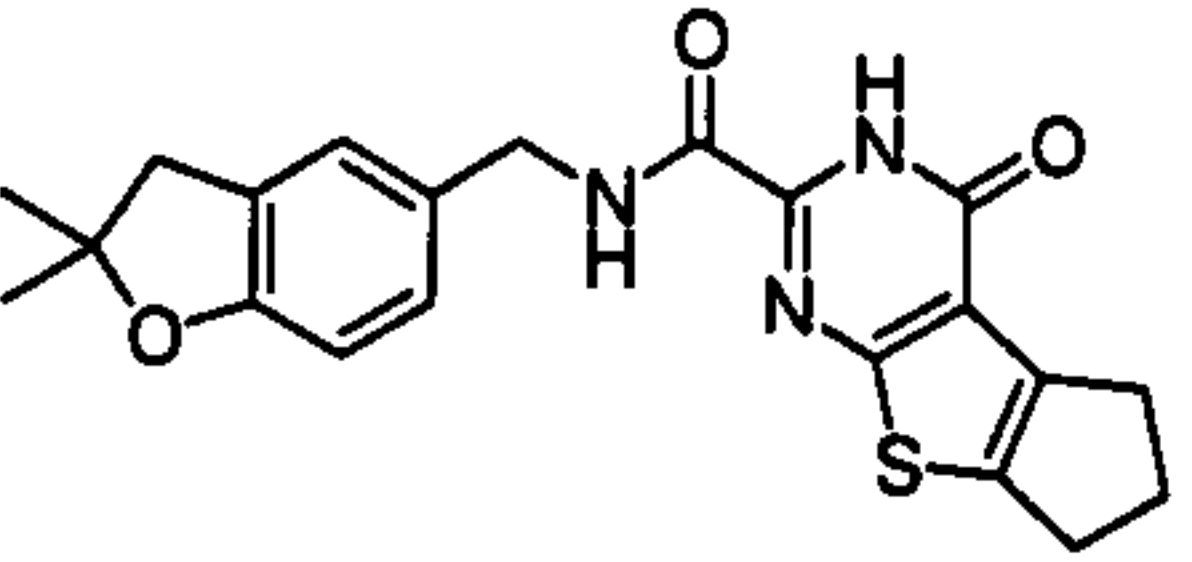
| Ex. # | amine, acid                                                                          | product                                                                               | method, yield                      |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/370 |     |    | B, n.d.<br>[MH] <sup>+</sup> = 374 |
| 2/371 |    |  | B, n.d.<br>[MH] <sup>+</sup> = 374 |
| 2/372 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 389 |
| 2/376 |  |  | A, 87%<br>[MH] <sup>+</sup> = 532  |
| 2/382 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 370 |

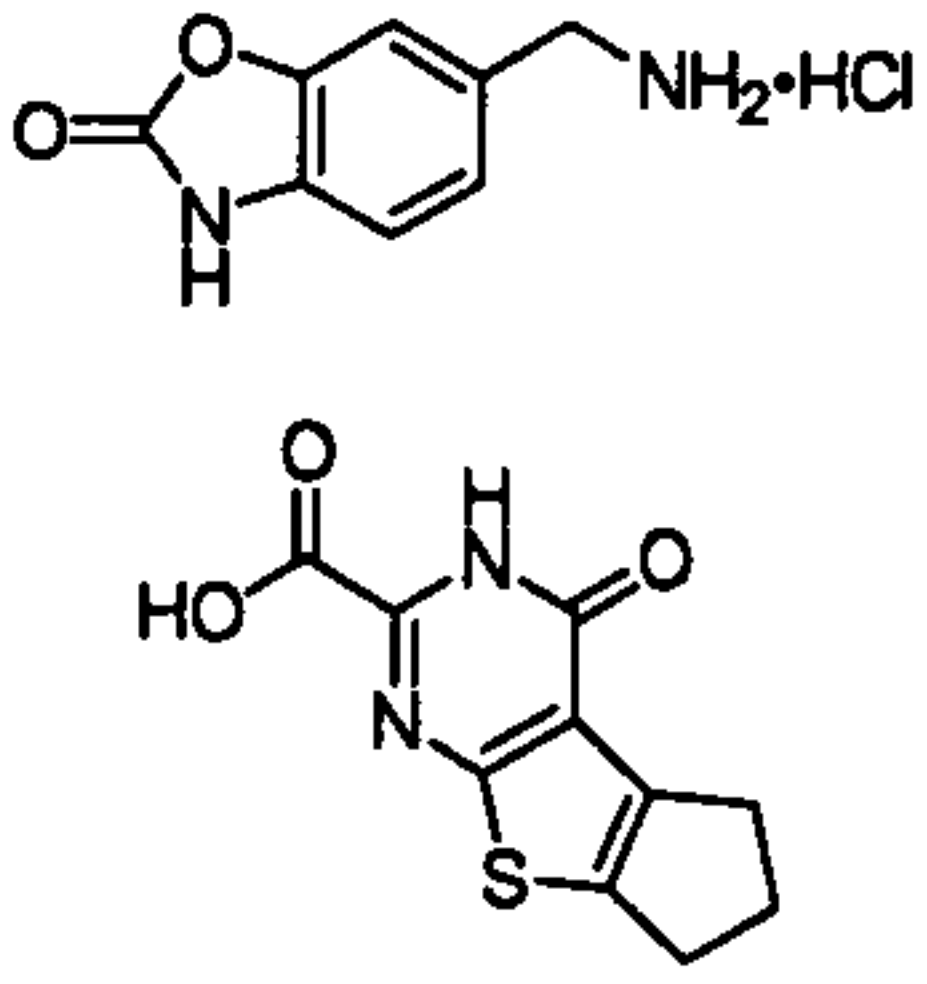
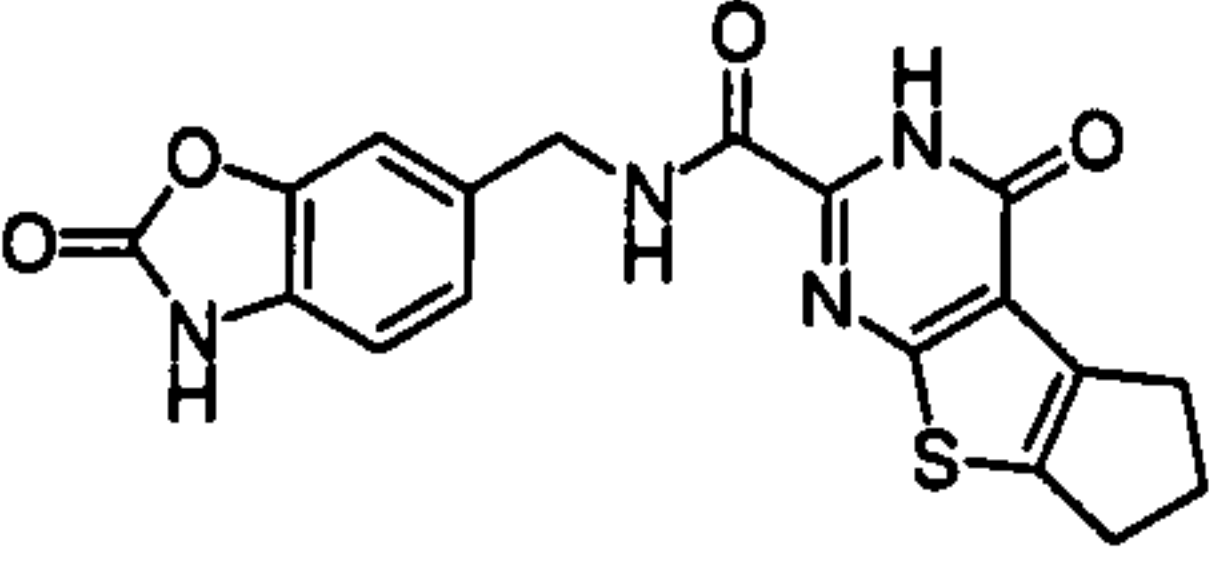
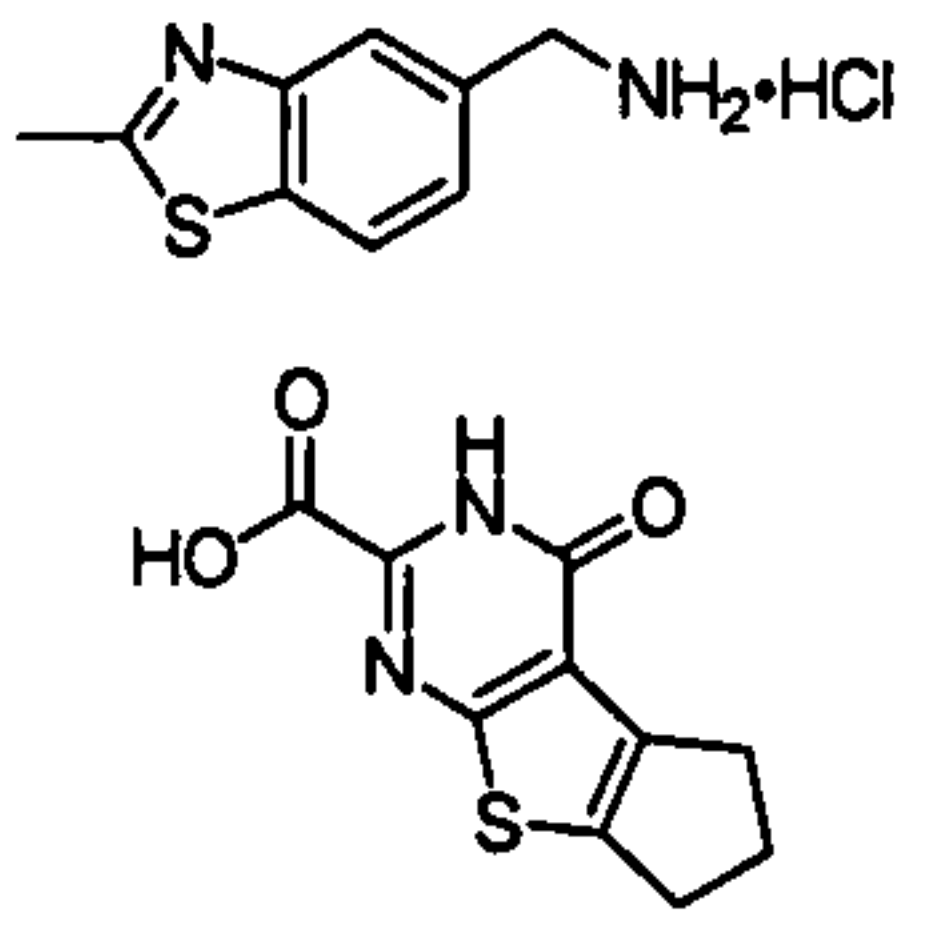
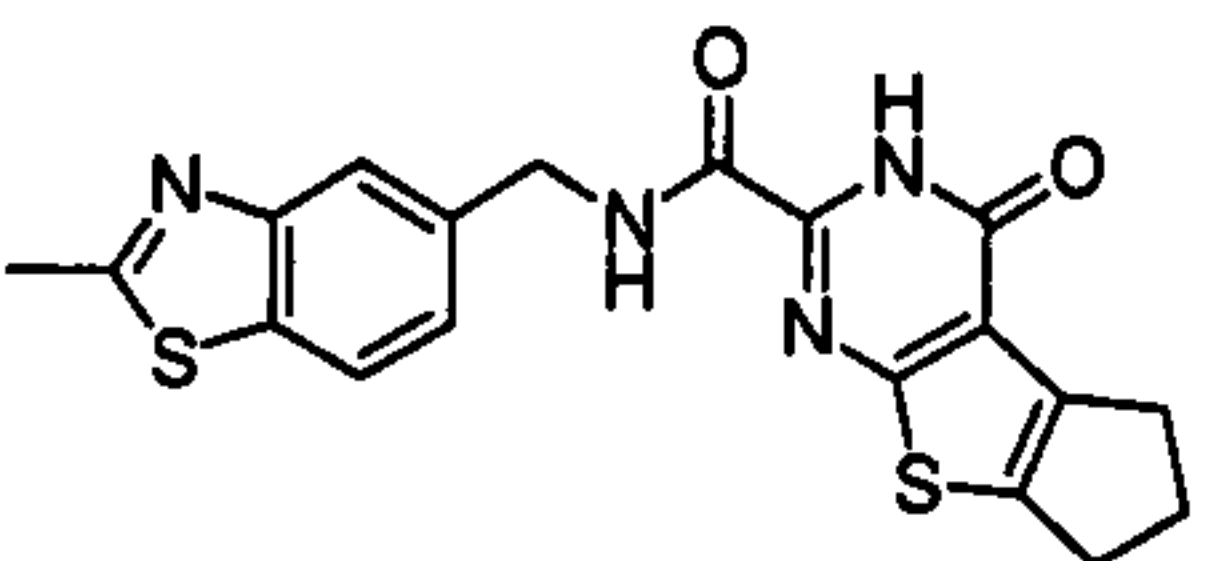
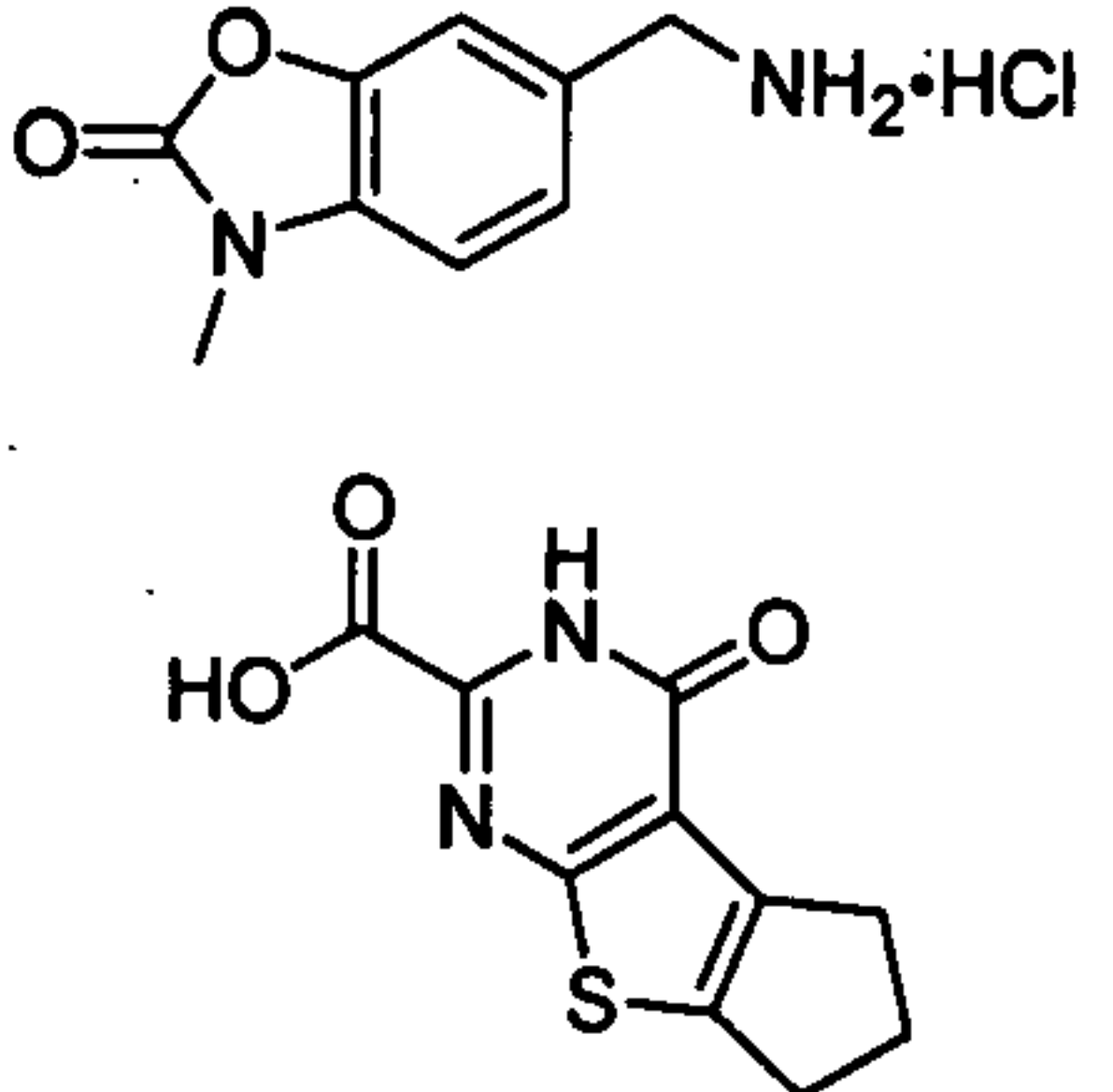
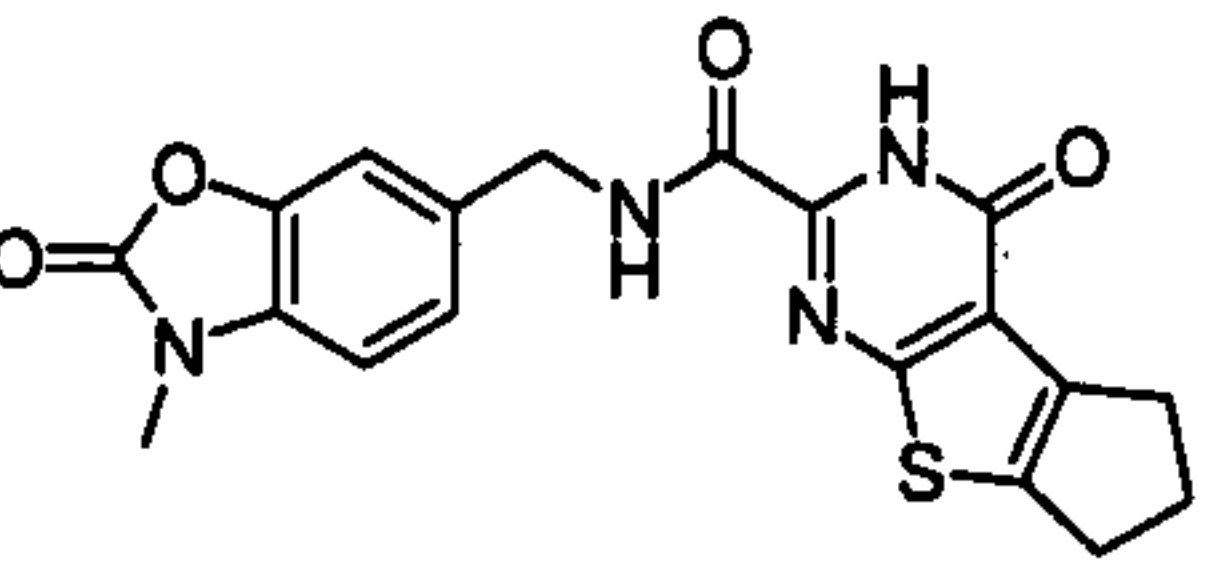
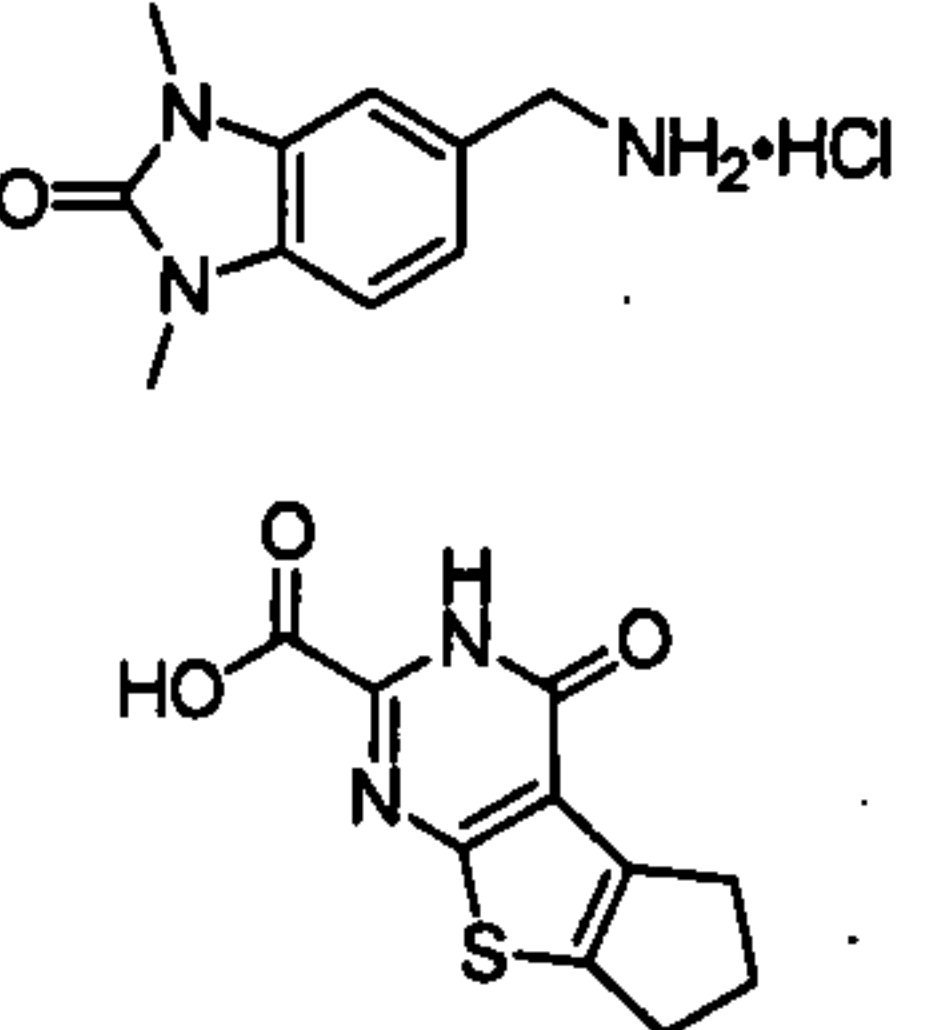
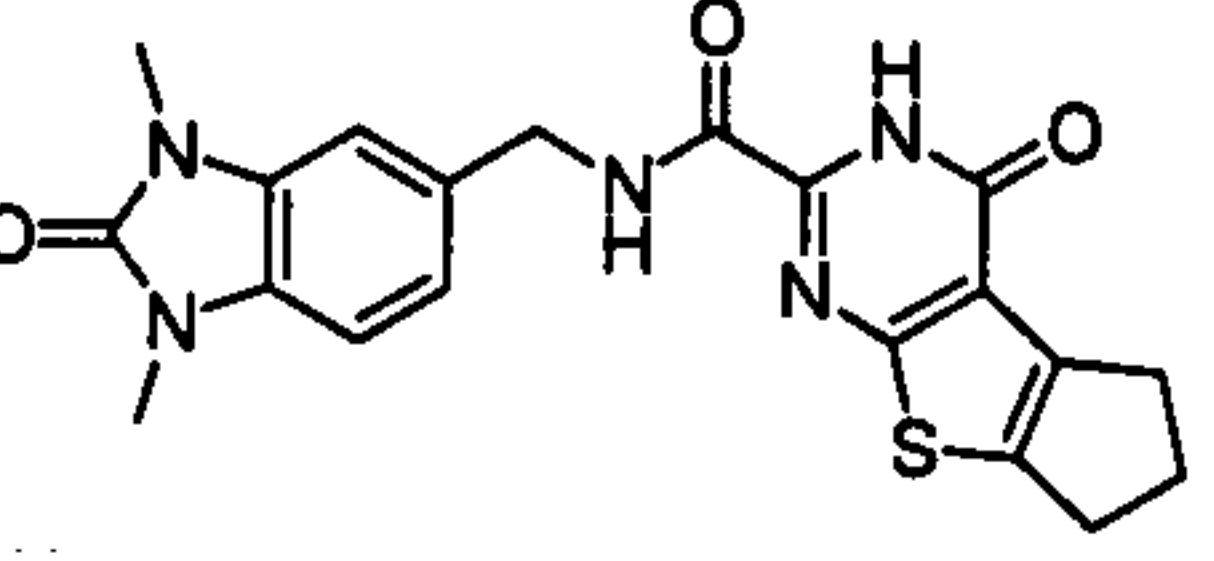
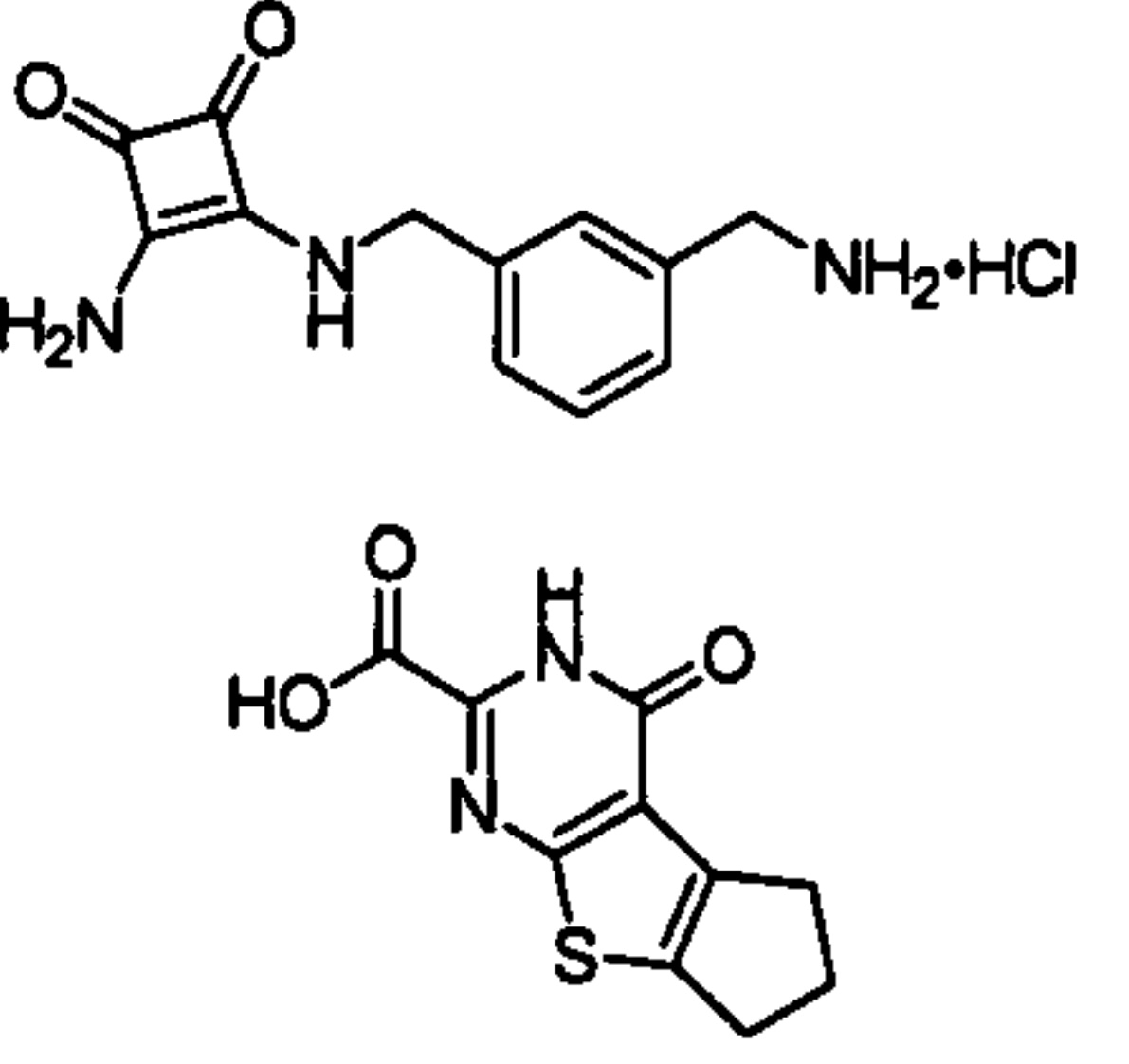
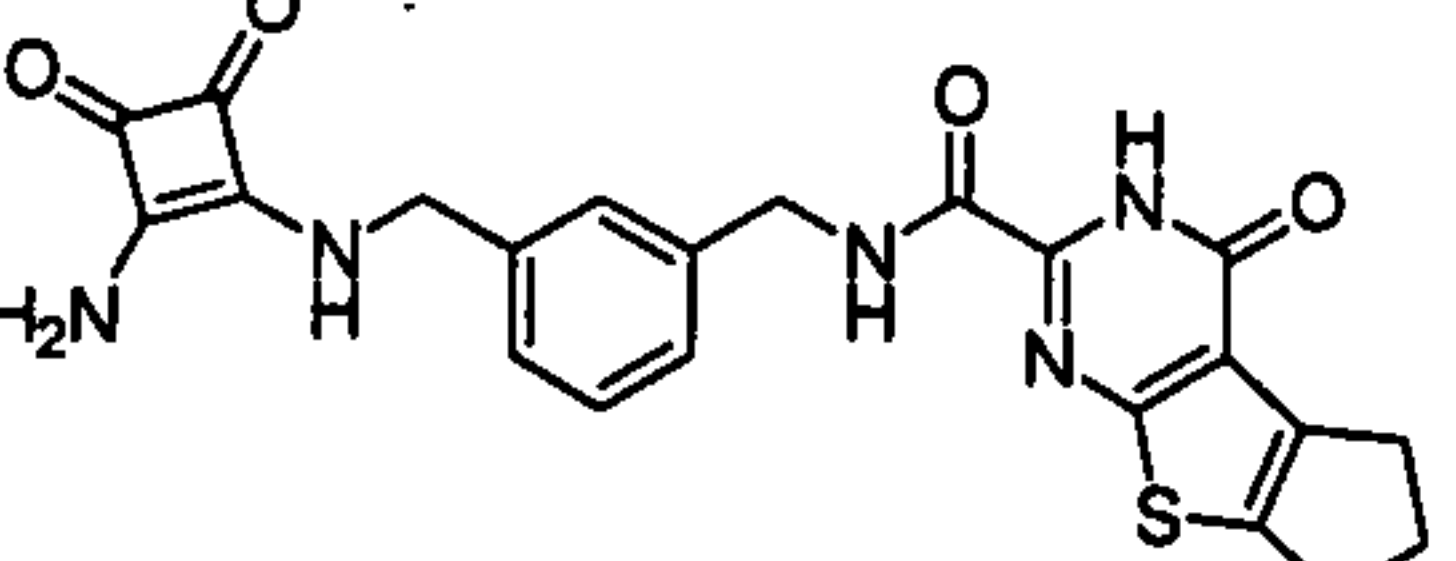
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/383 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 340 |
| 2/384 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 356 |
| 2/385 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 348 |
| 2/386 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 356 |
| 2/387 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 356 |
| 2/388 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 354 |

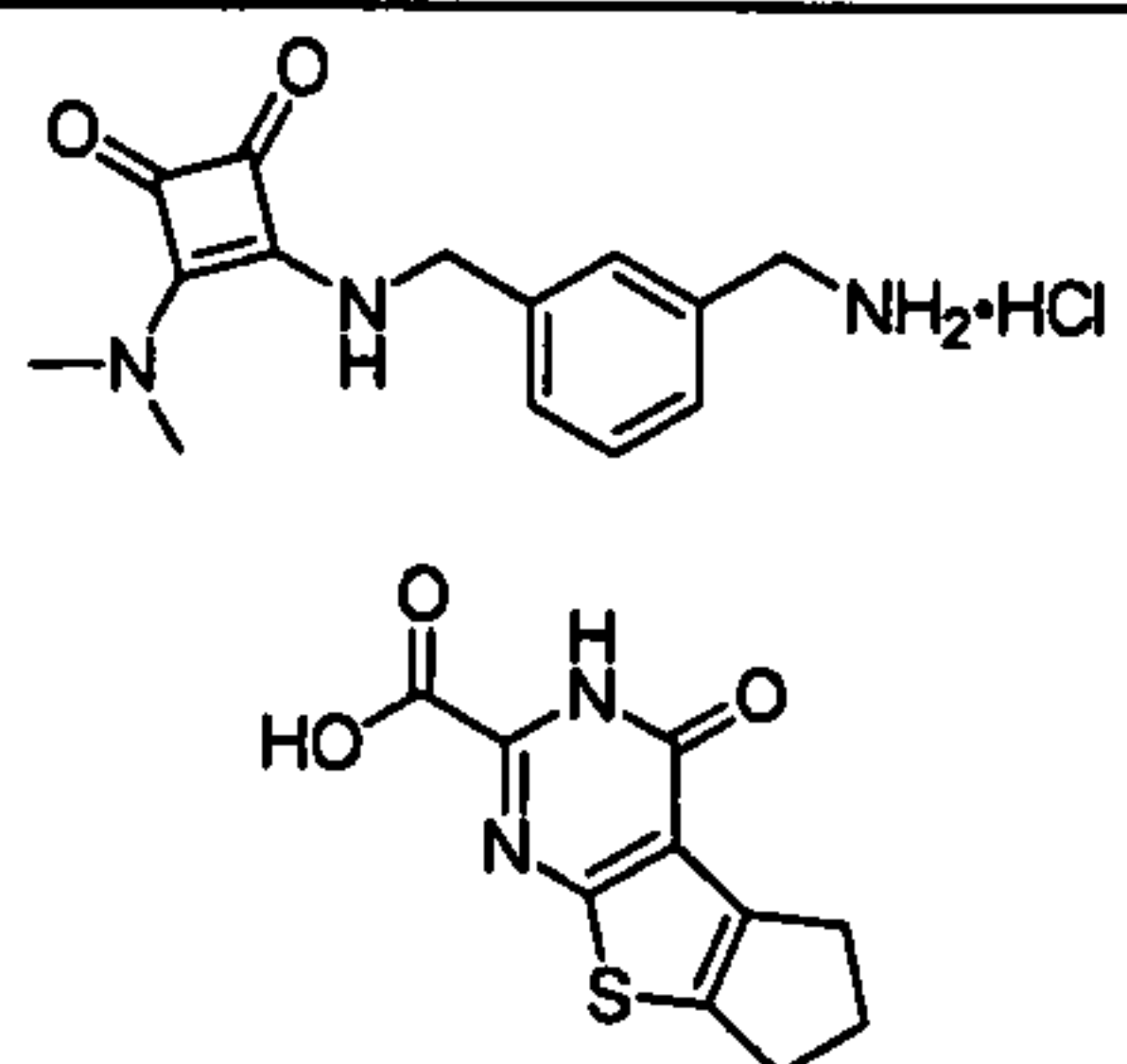
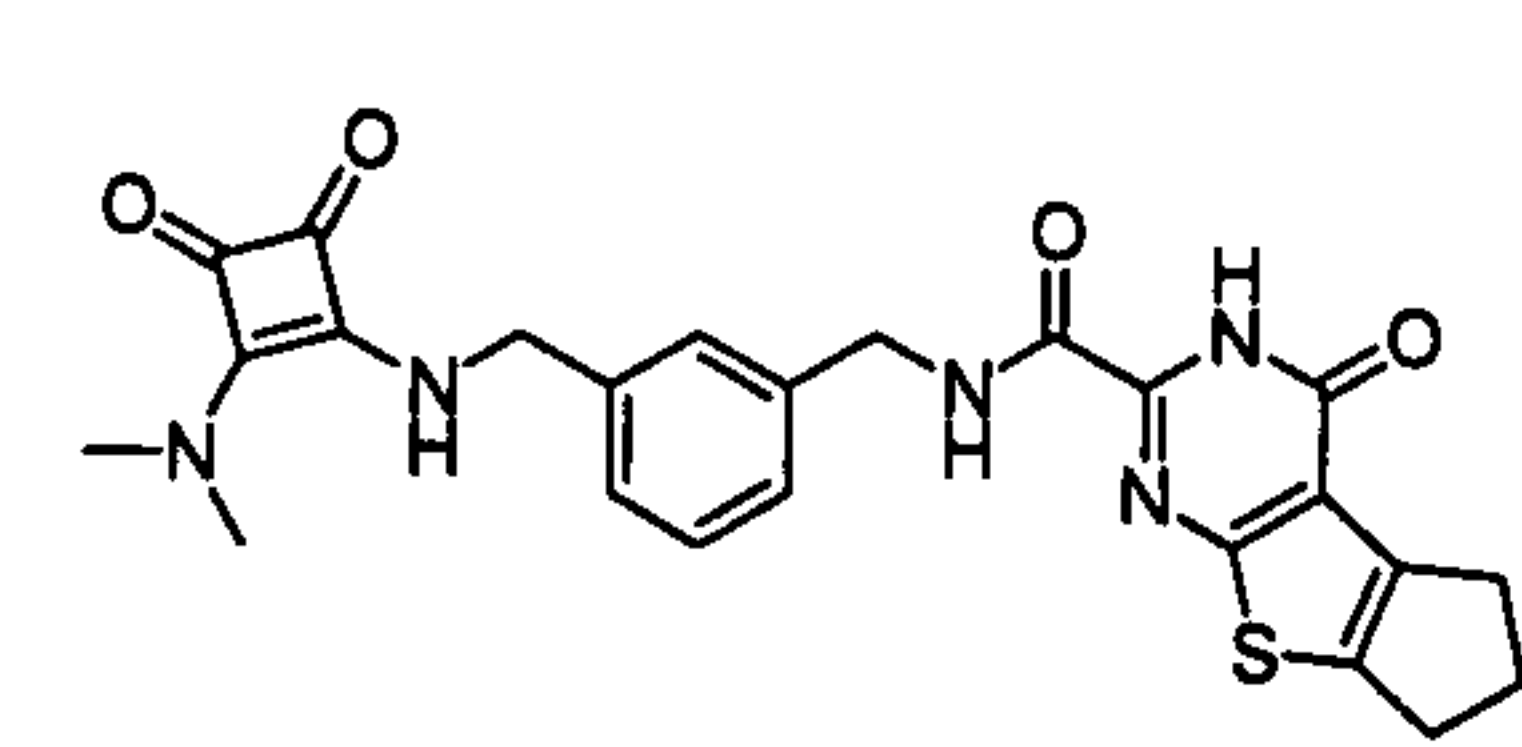
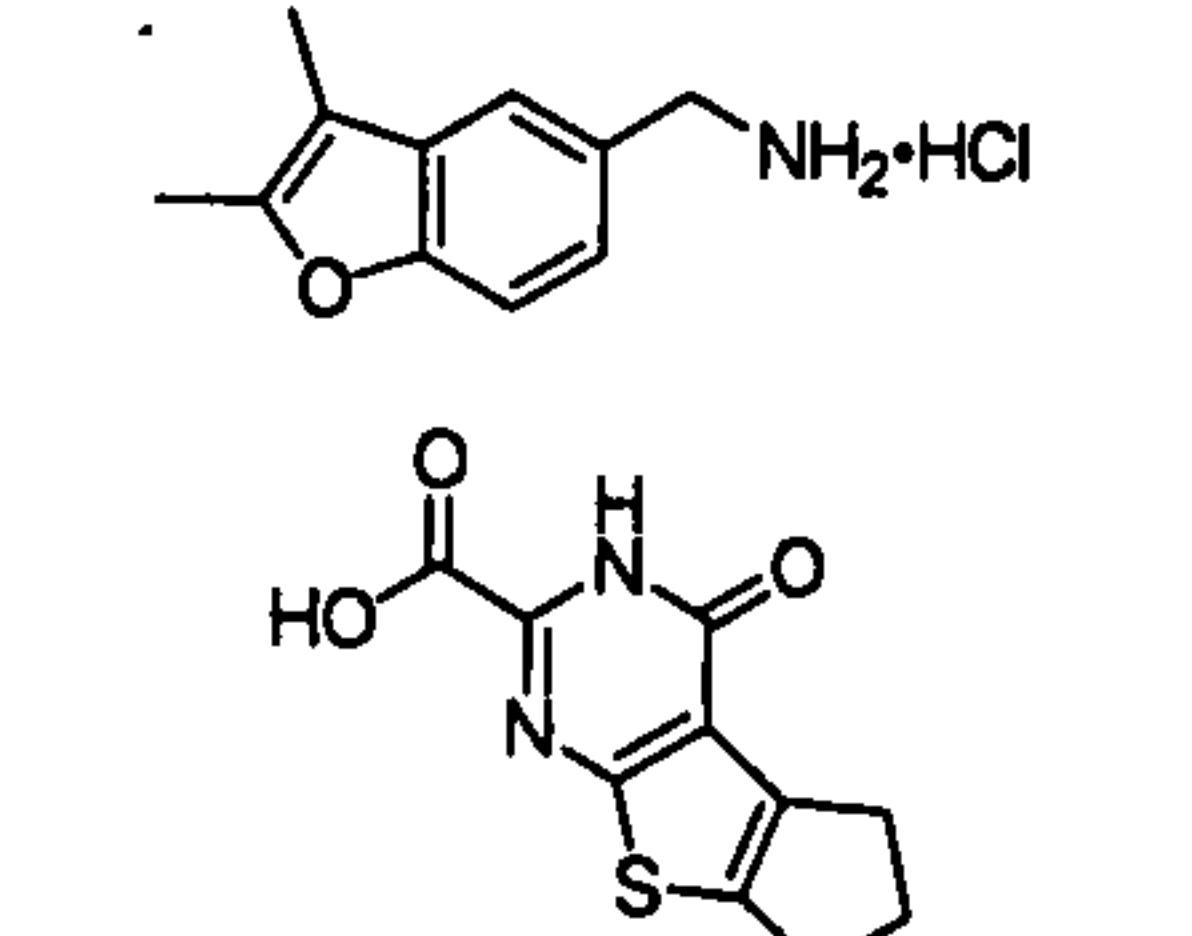
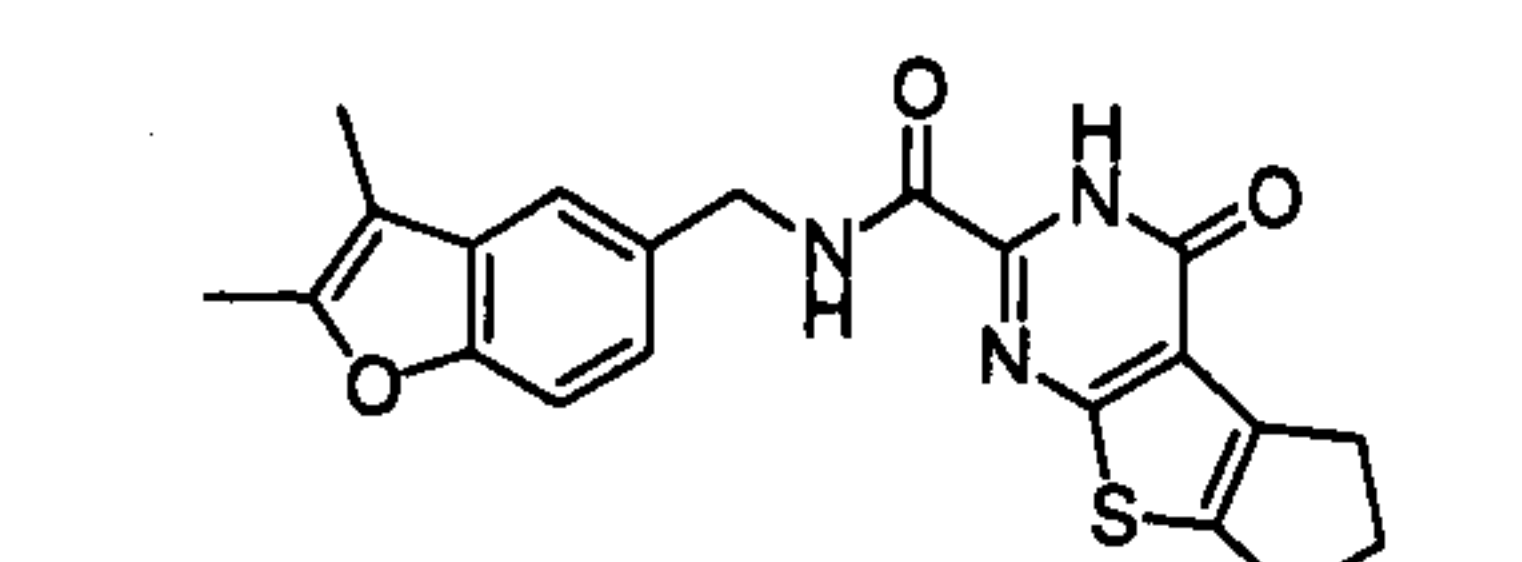
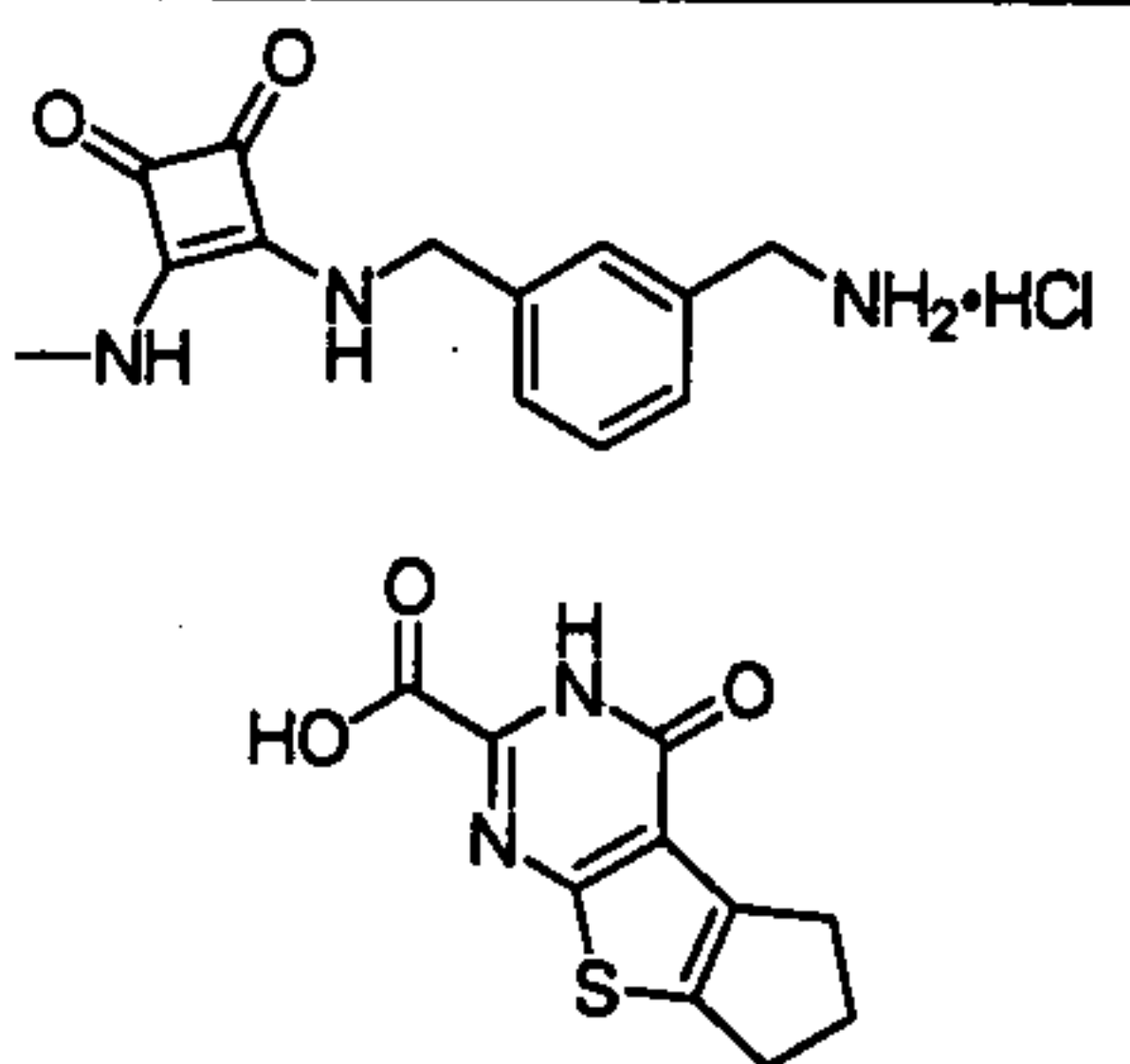
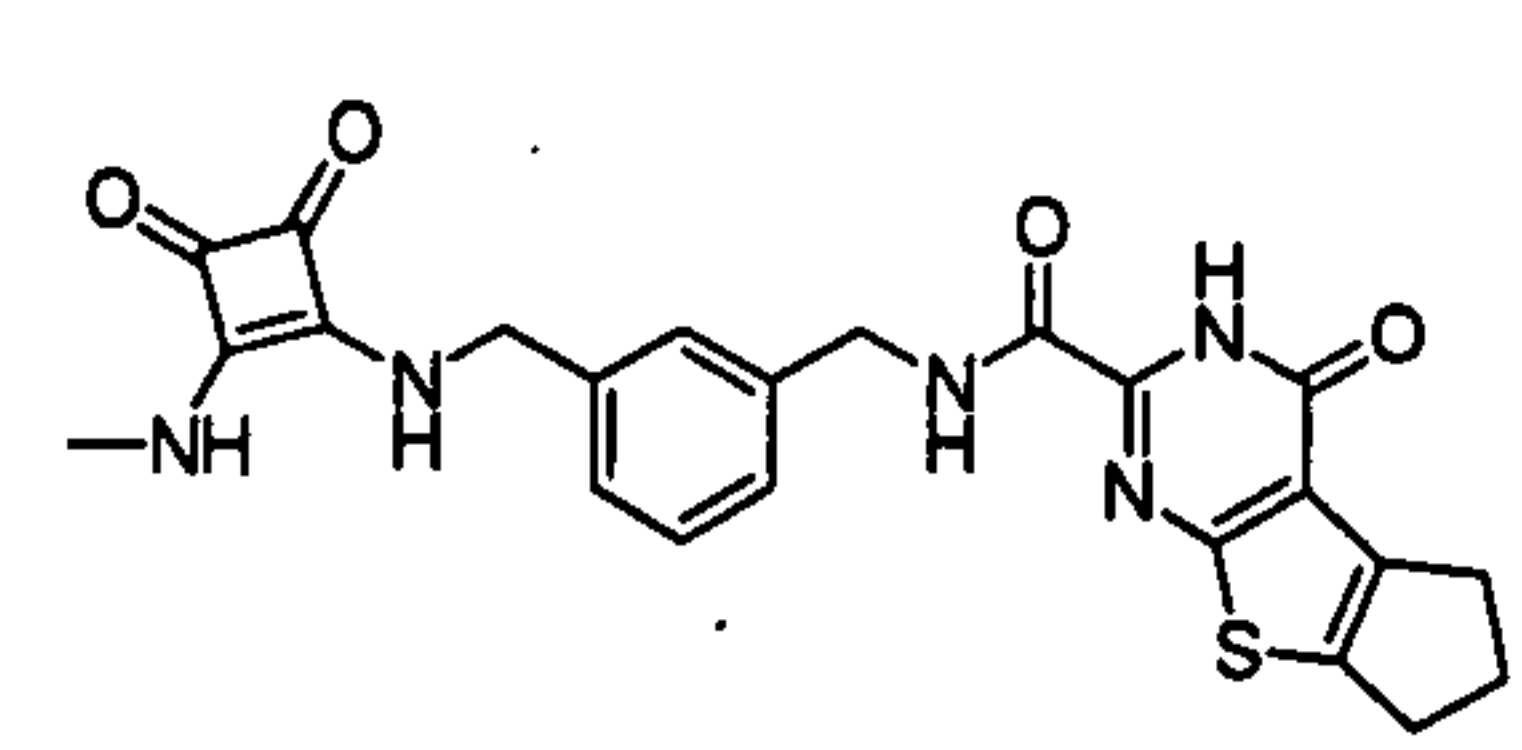
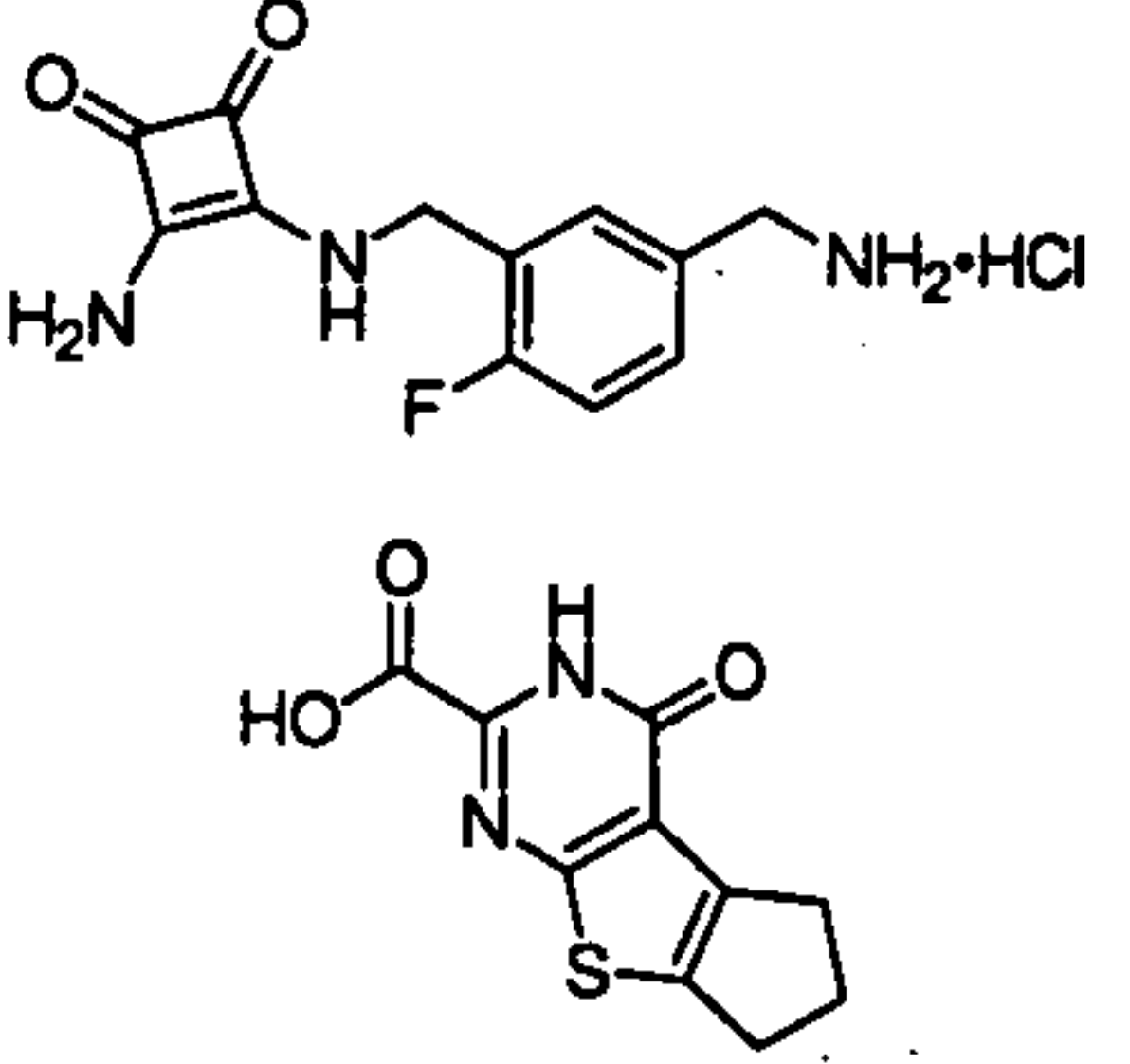
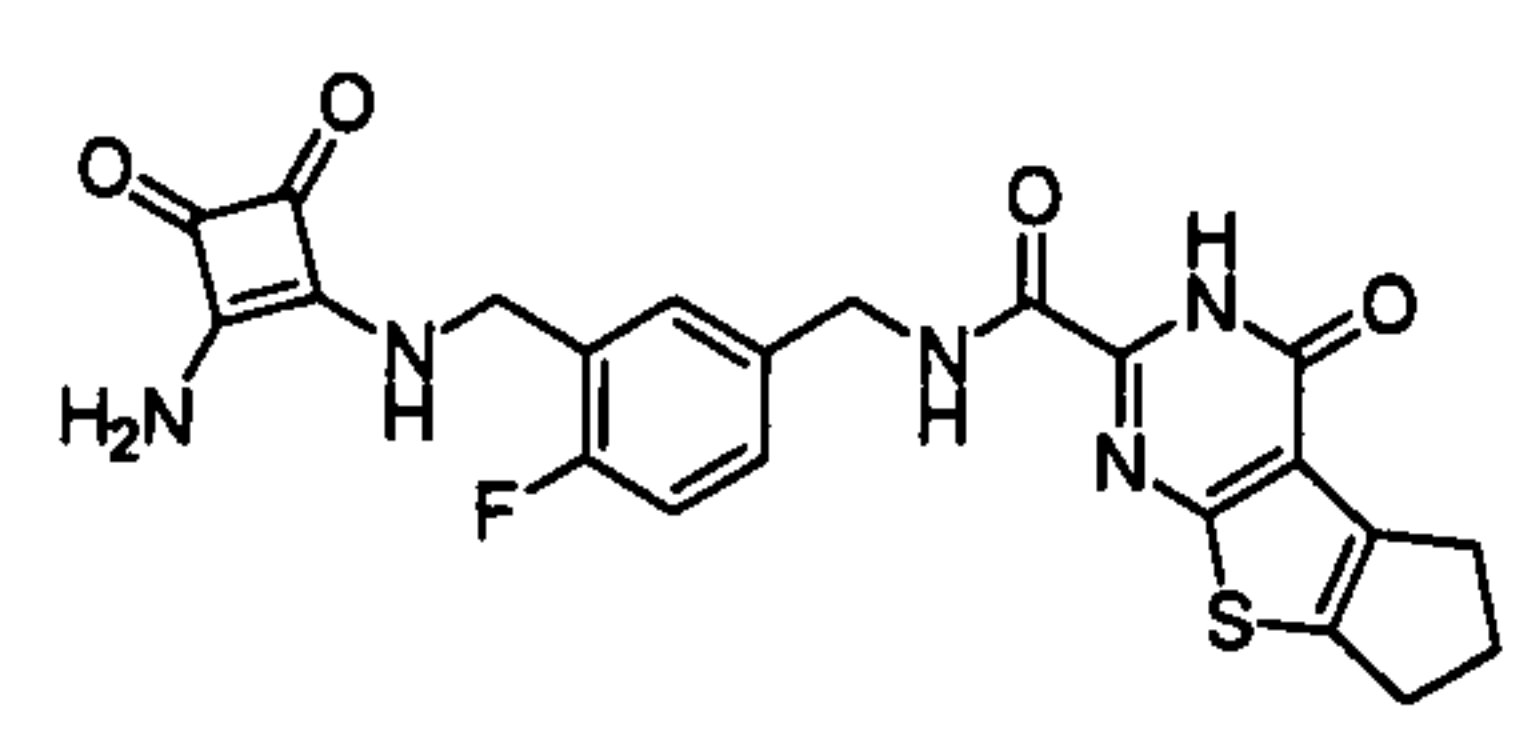
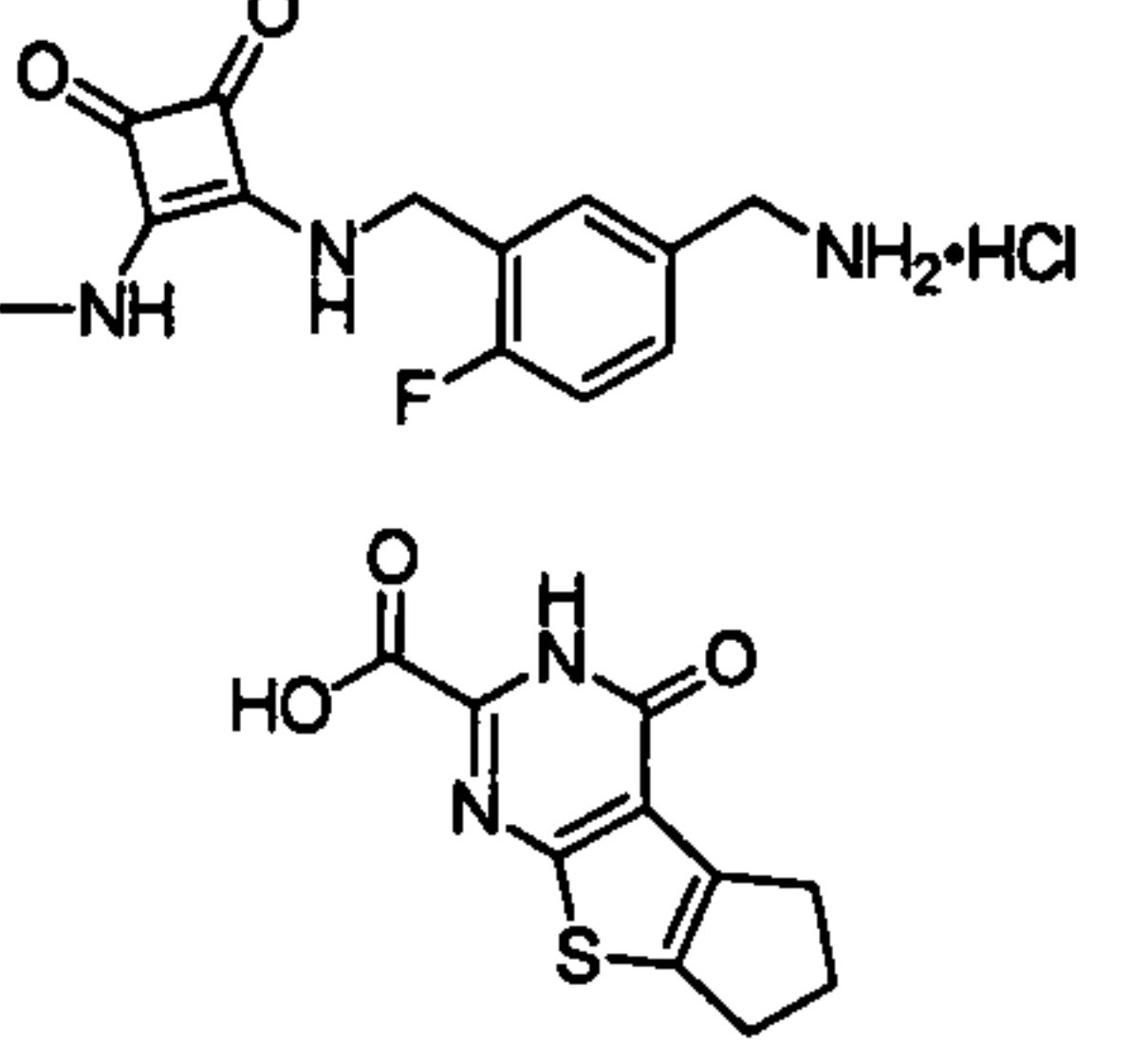
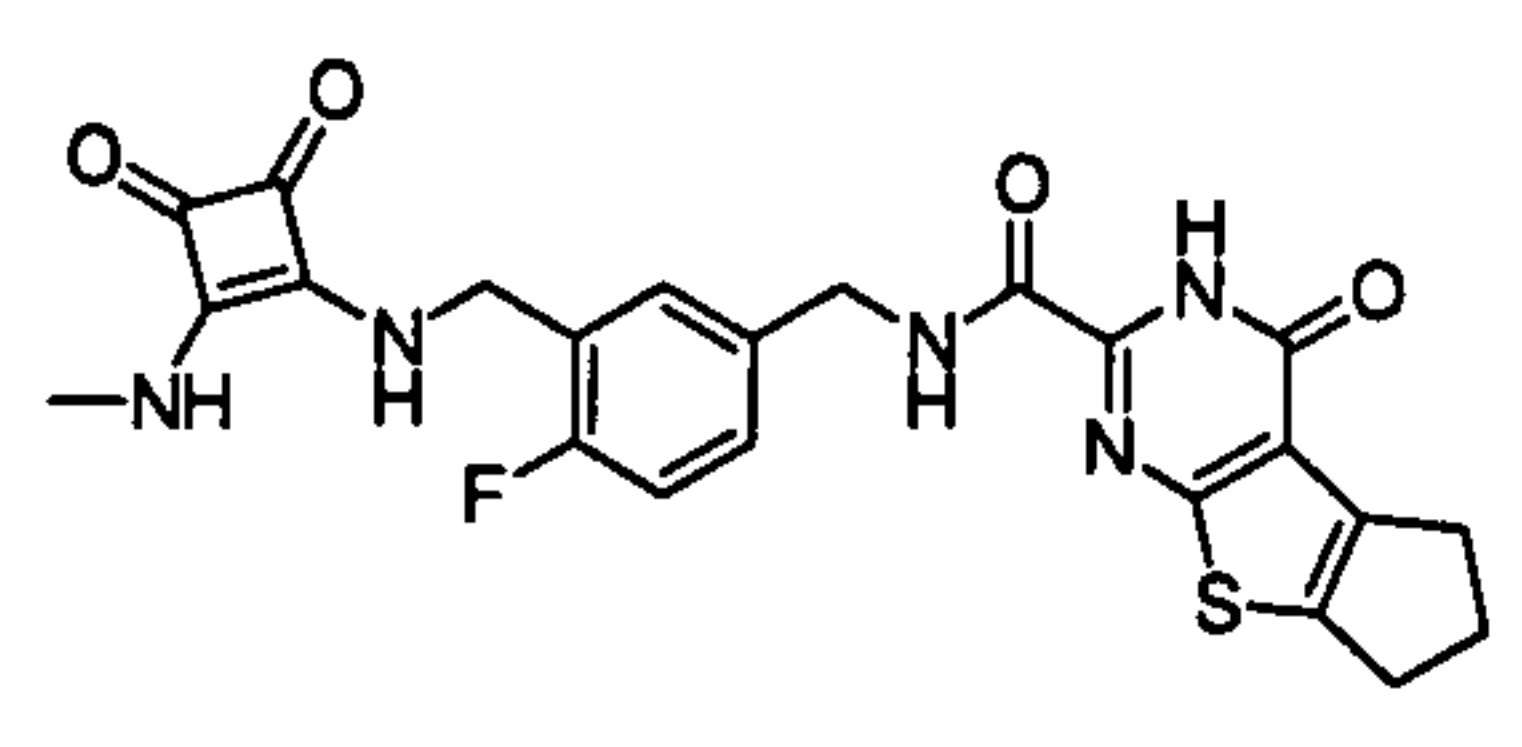
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/389 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/390 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 426 |
| 2/391 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 368 |
| 2/392 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 356 |
| 2/393 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 356 |

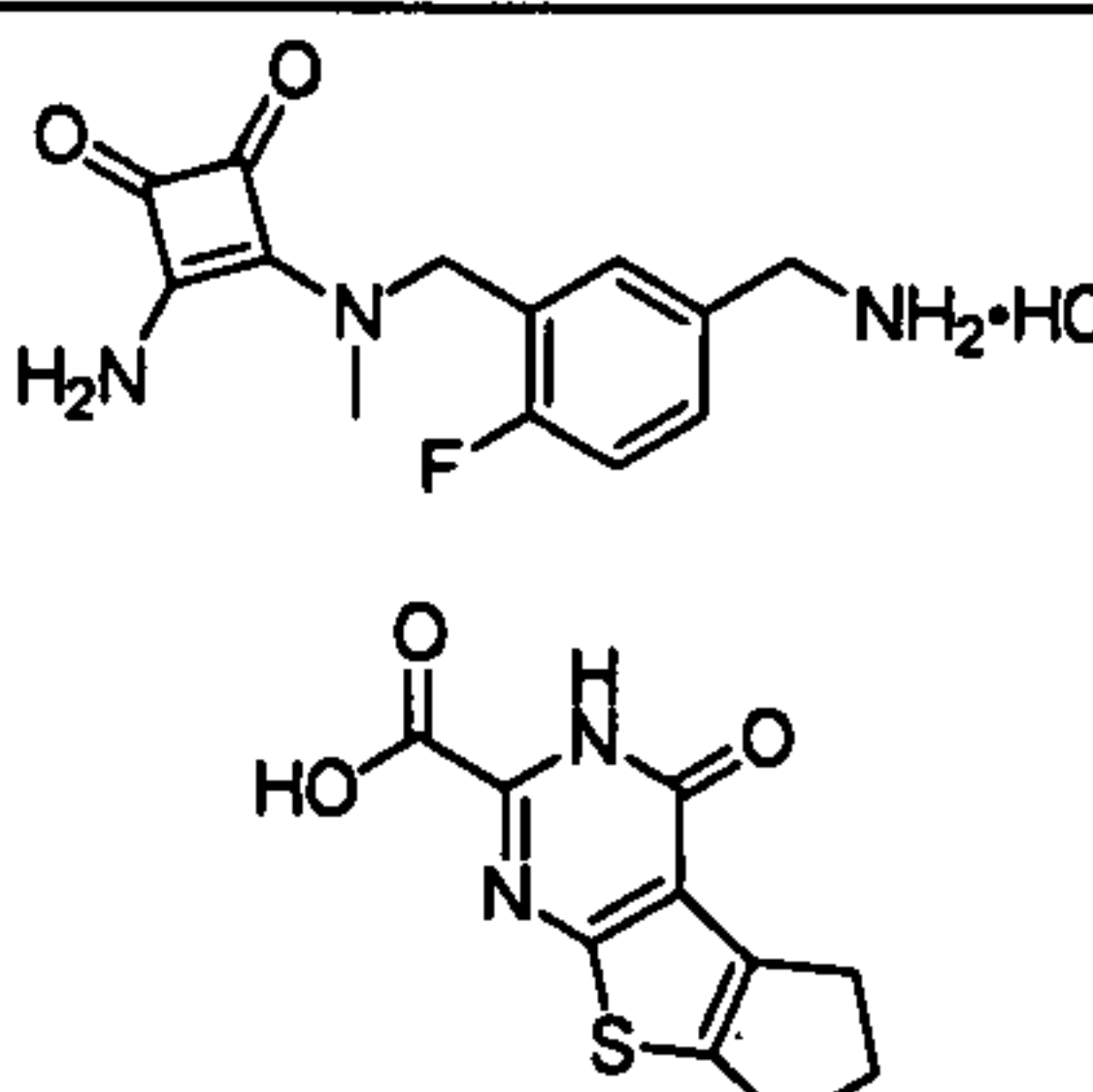
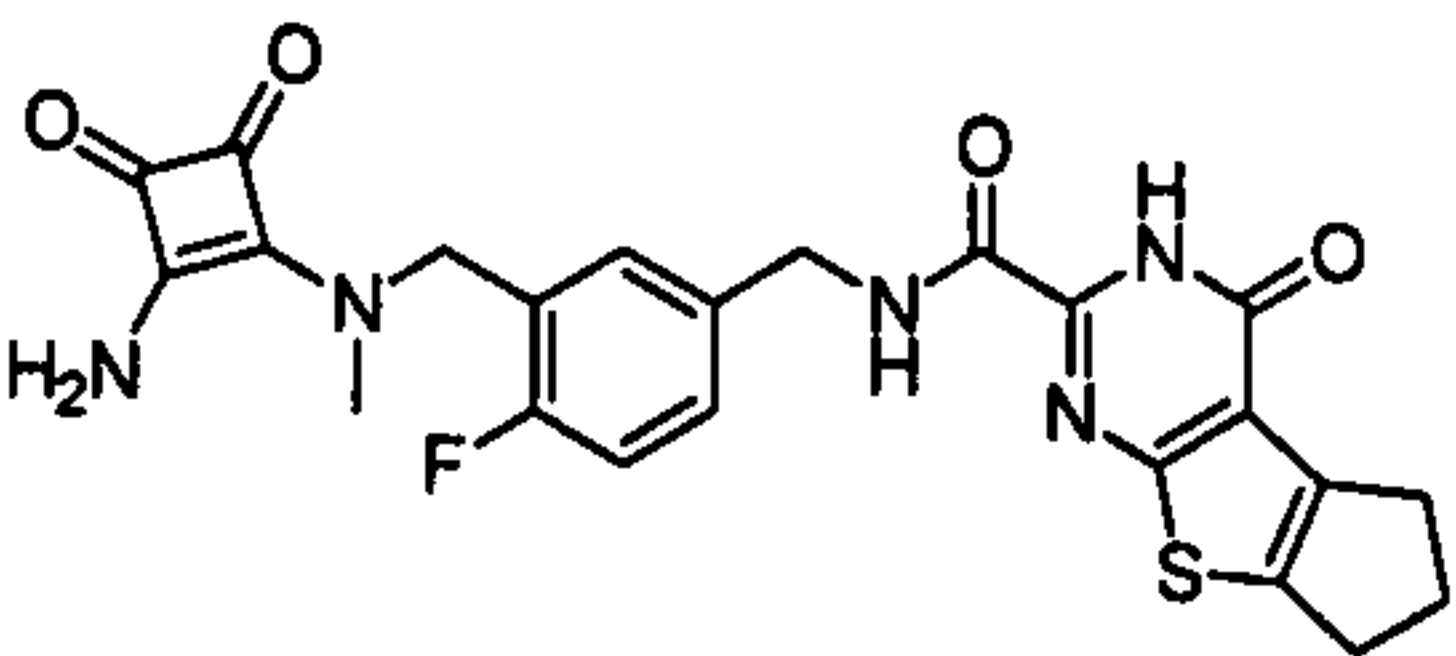
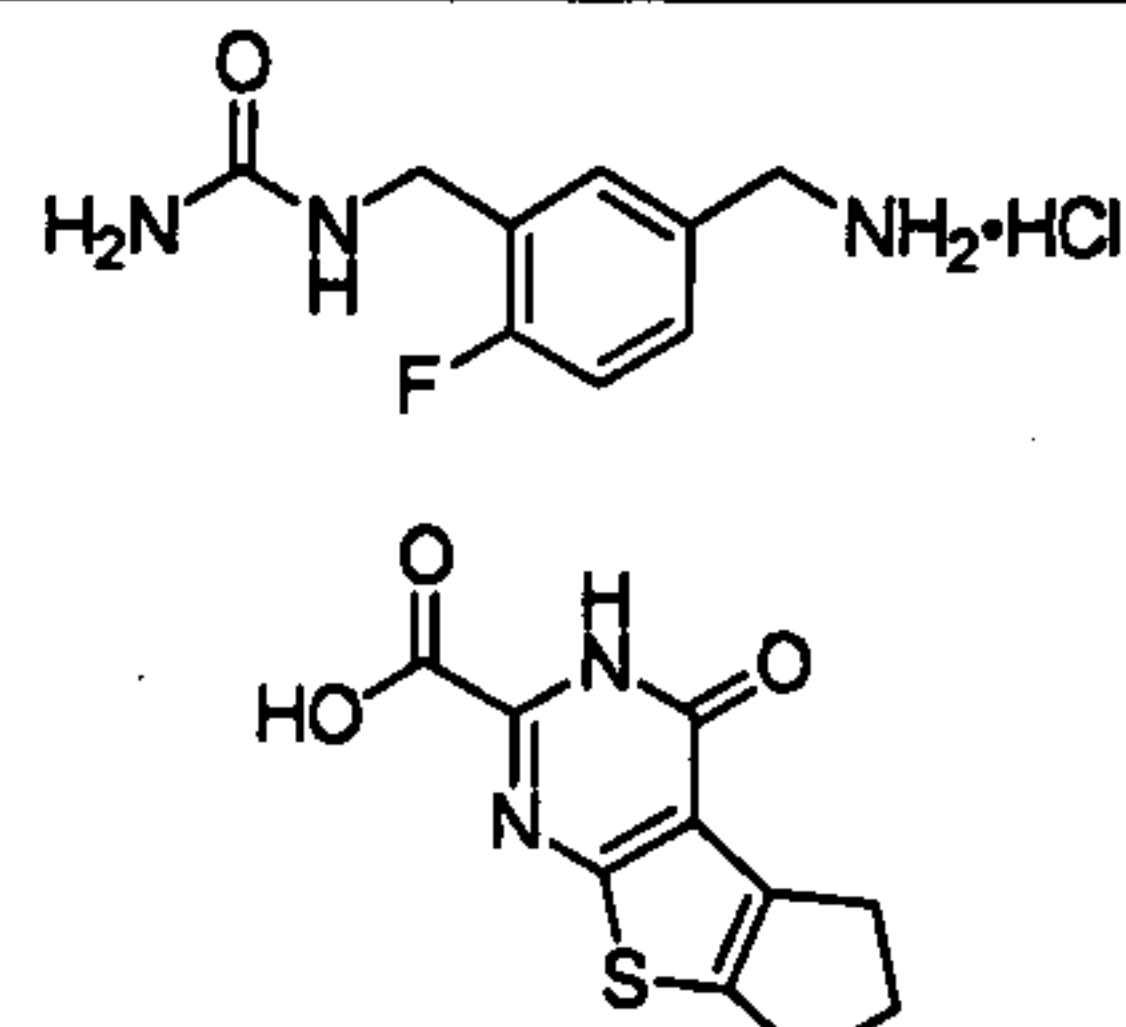
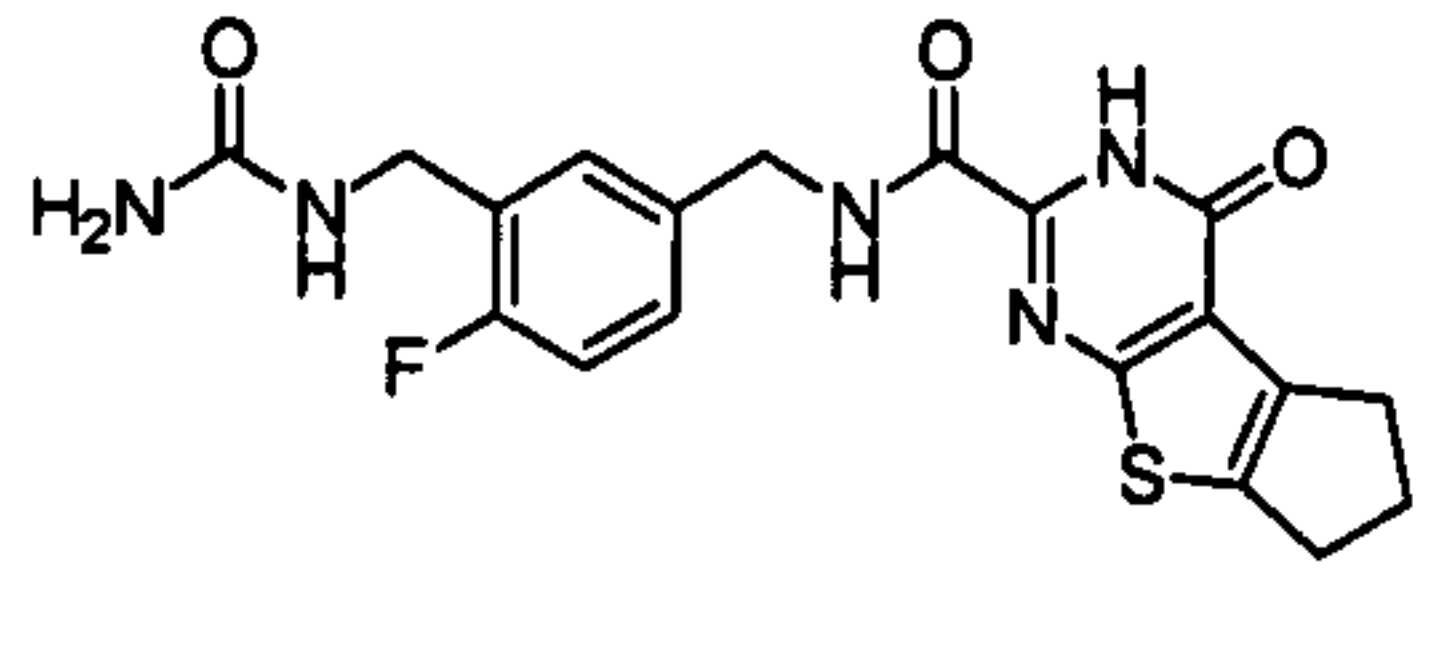
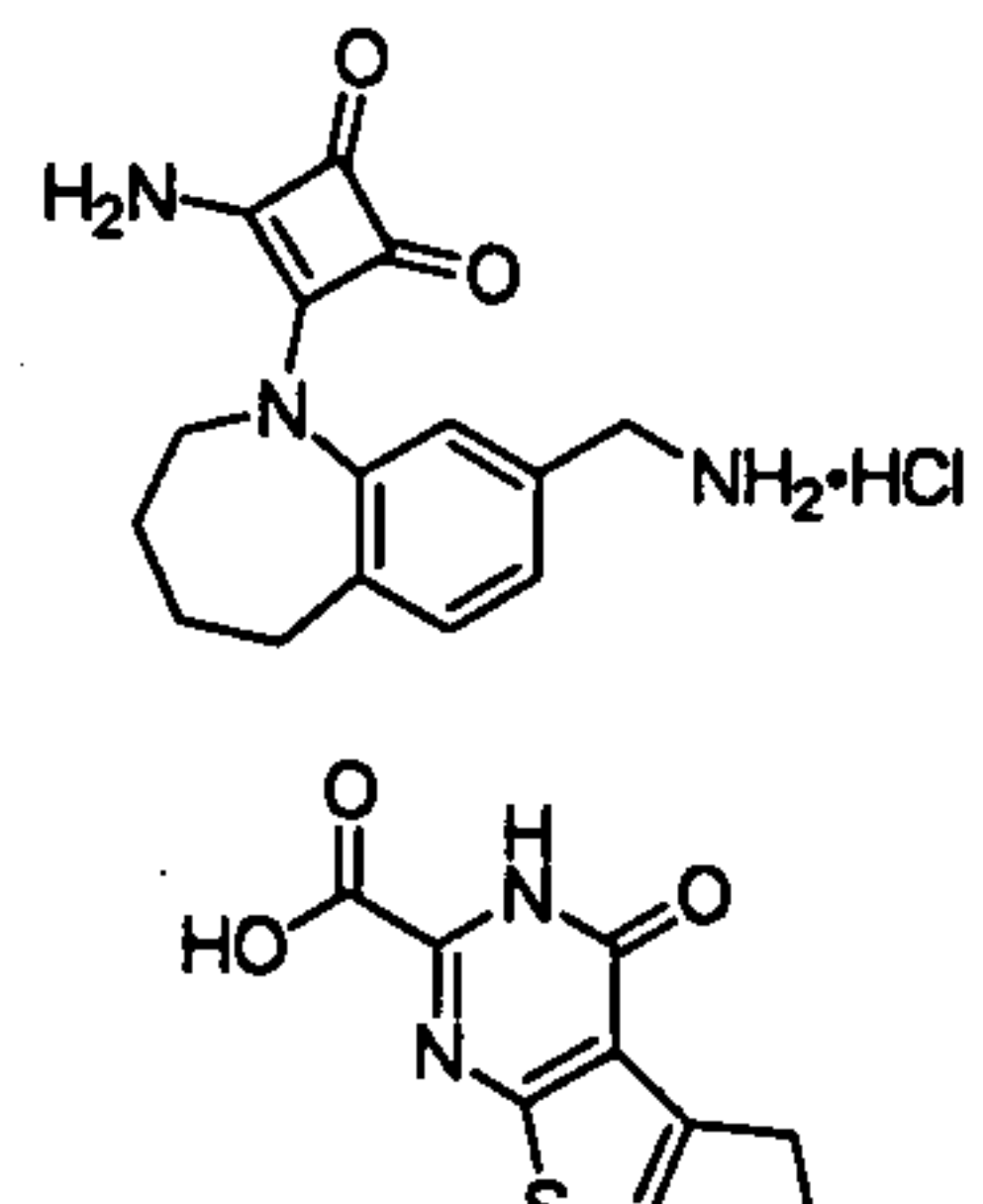
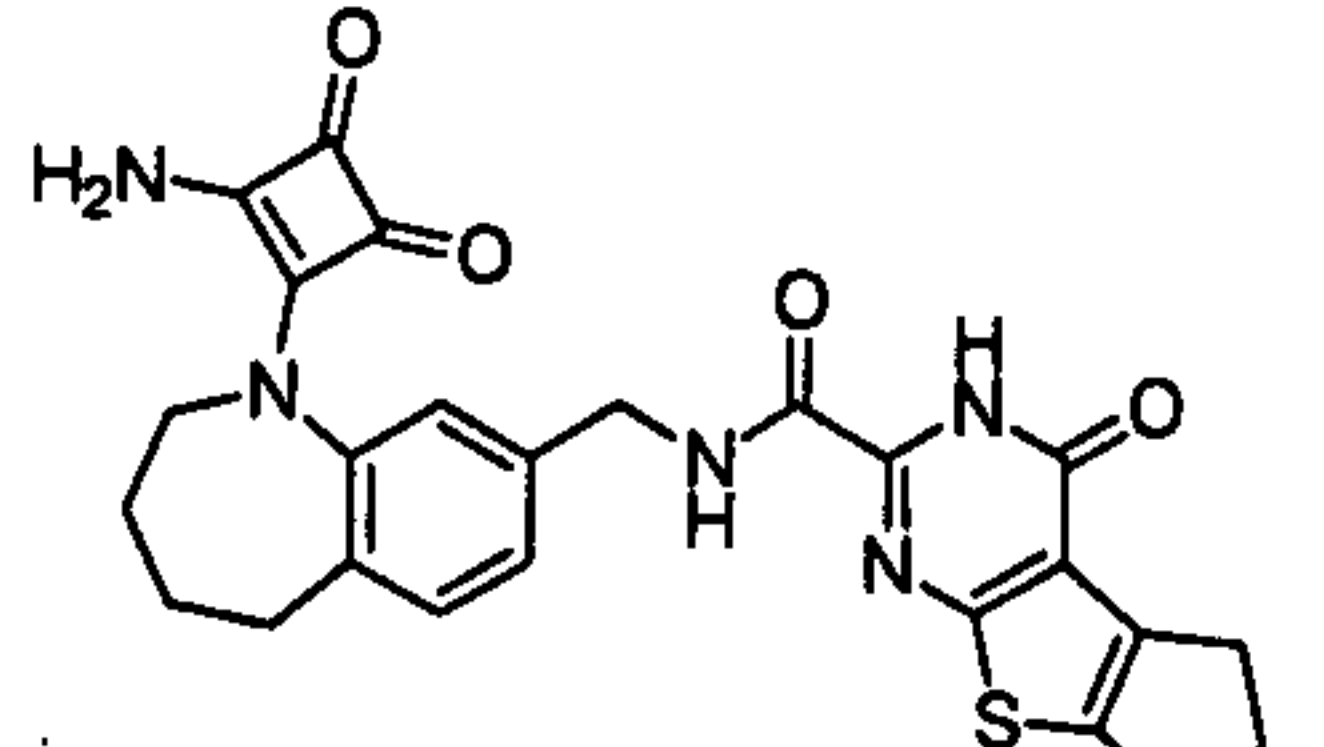
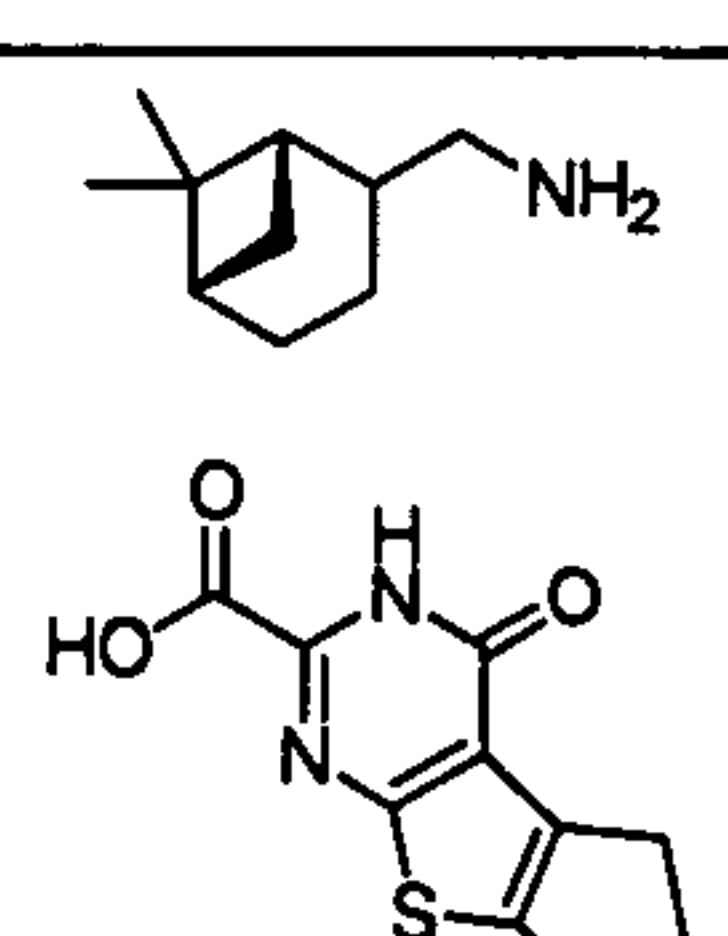
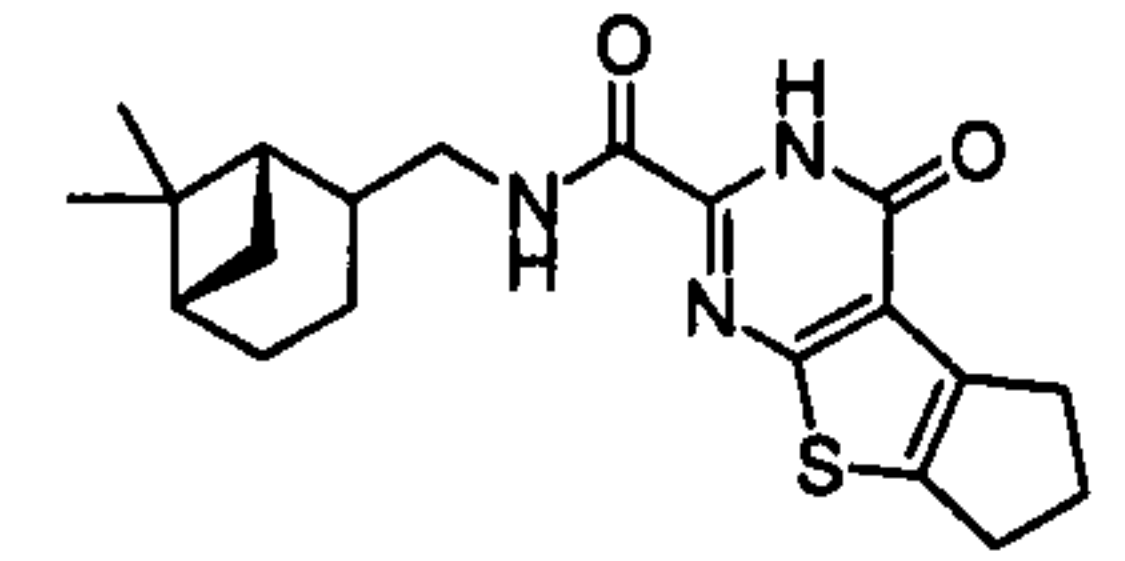
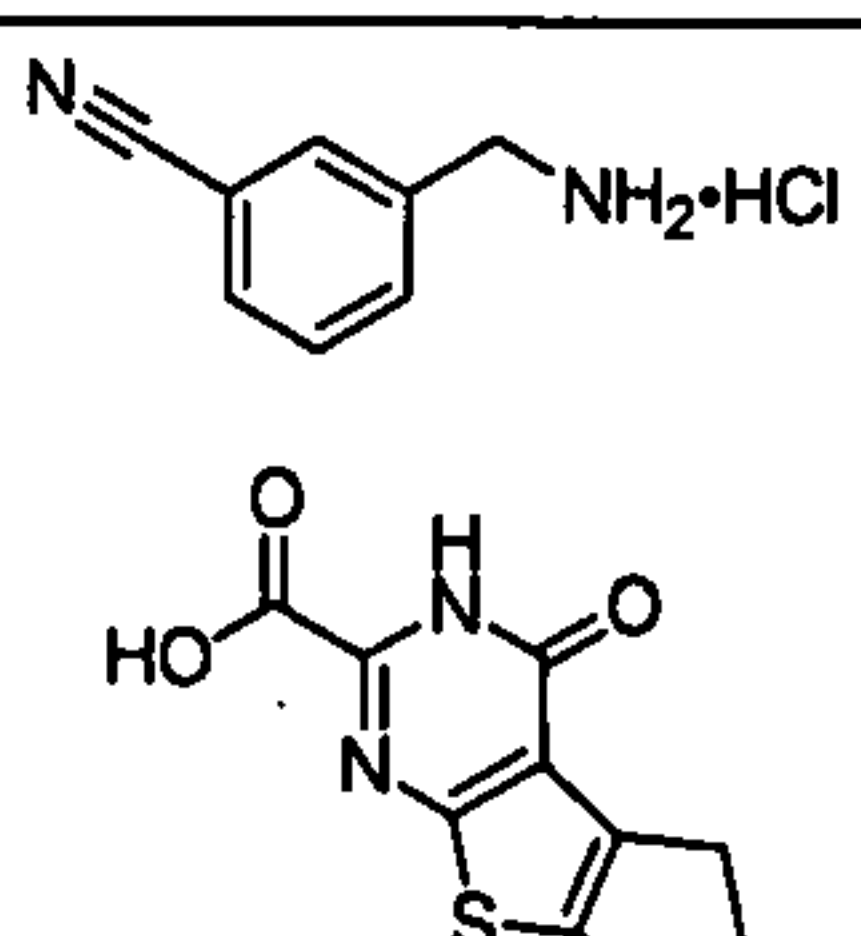
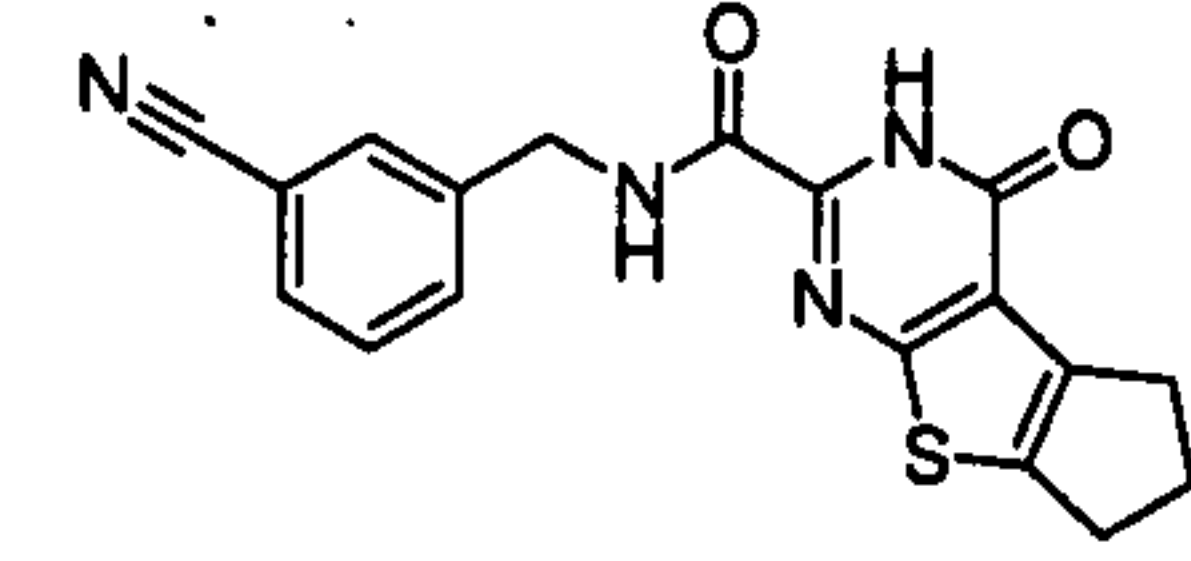
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/394 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/395 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/396 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/397 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 356 |
| 2/398 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 400 |

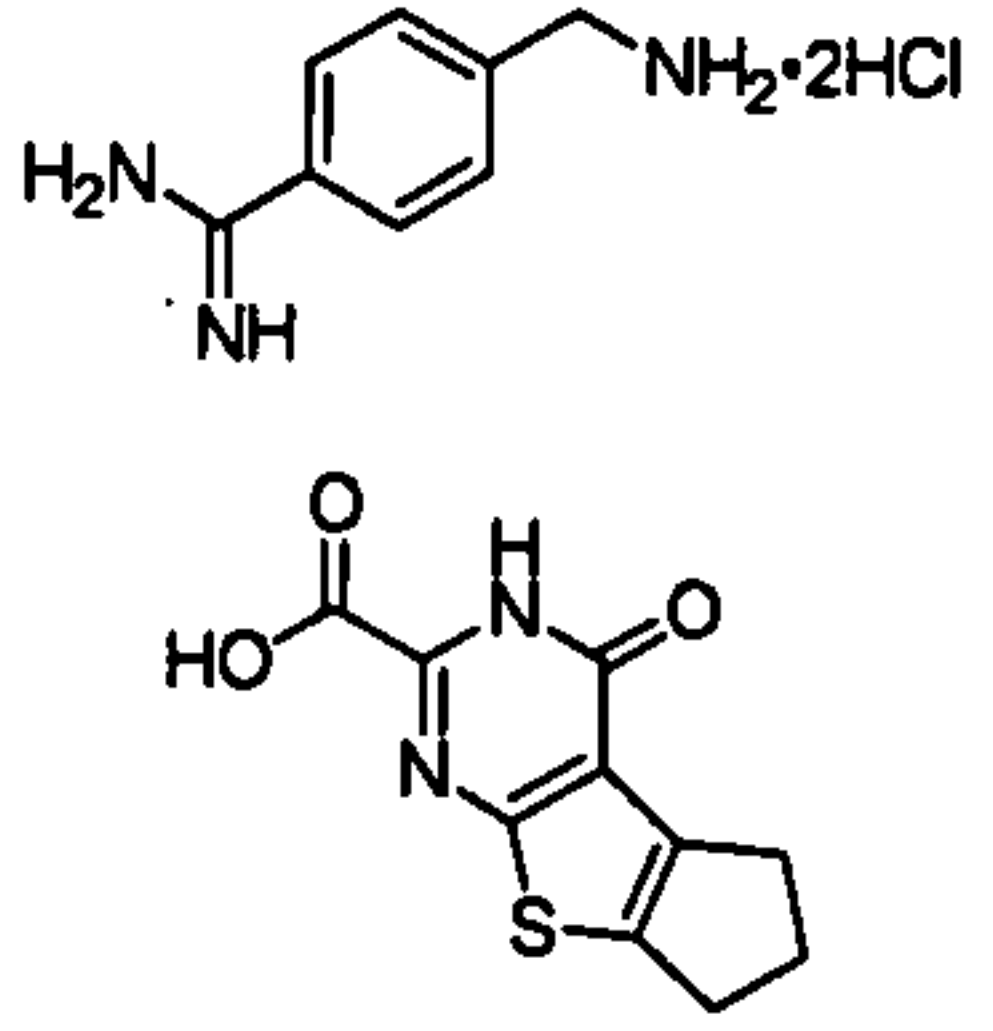
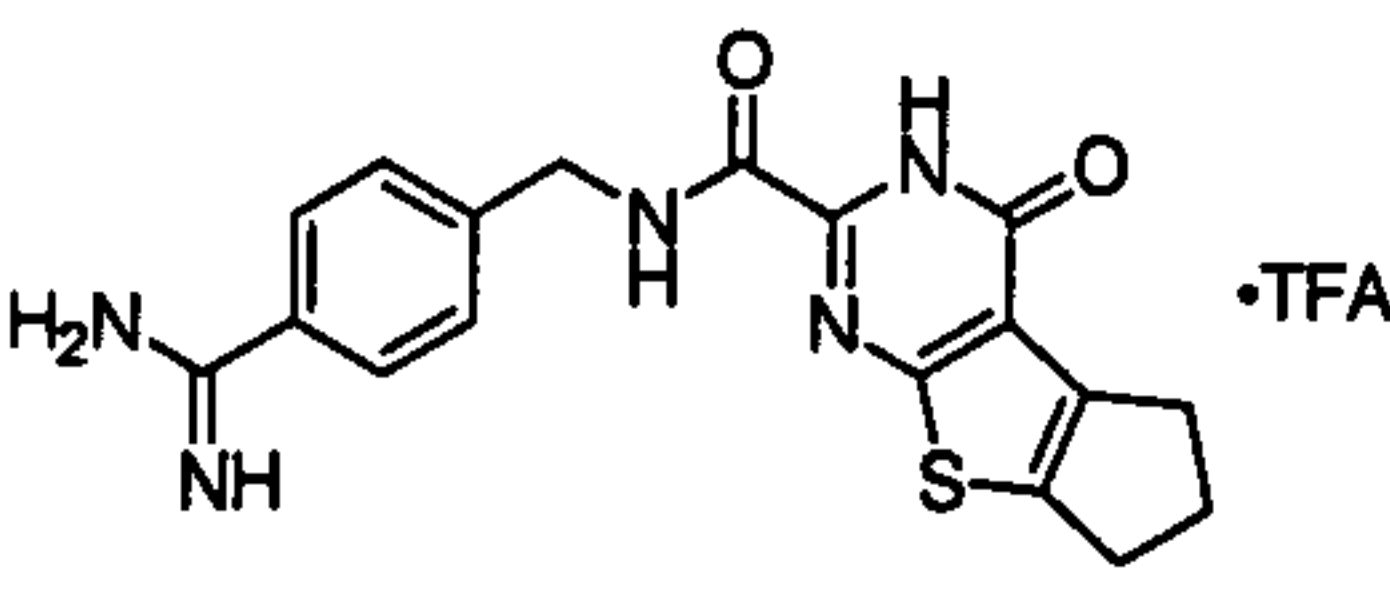
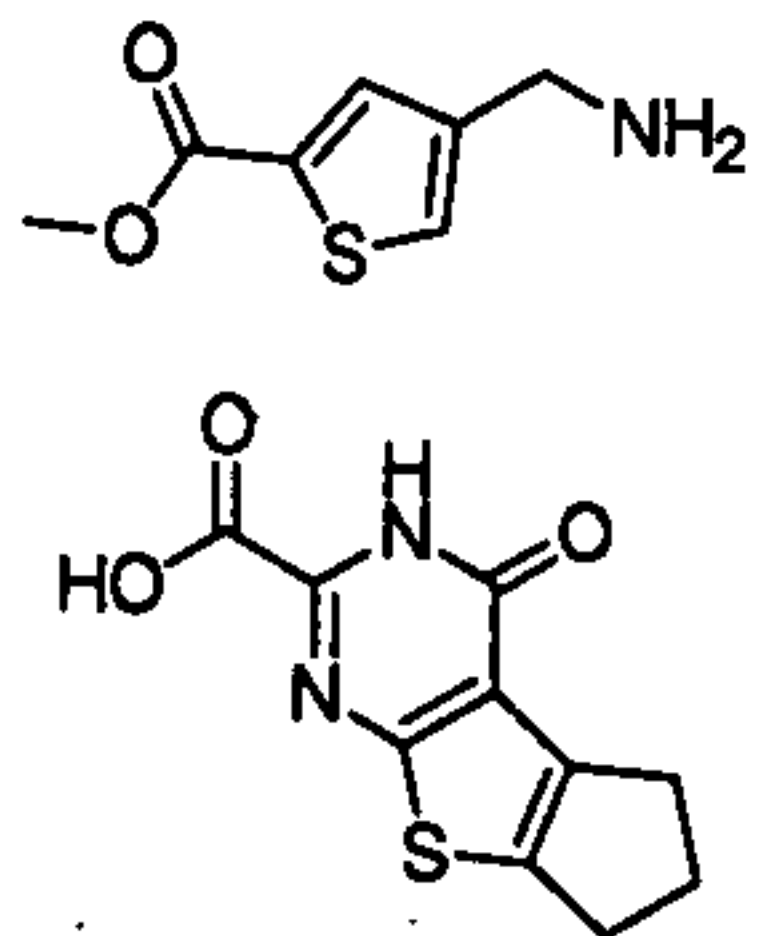
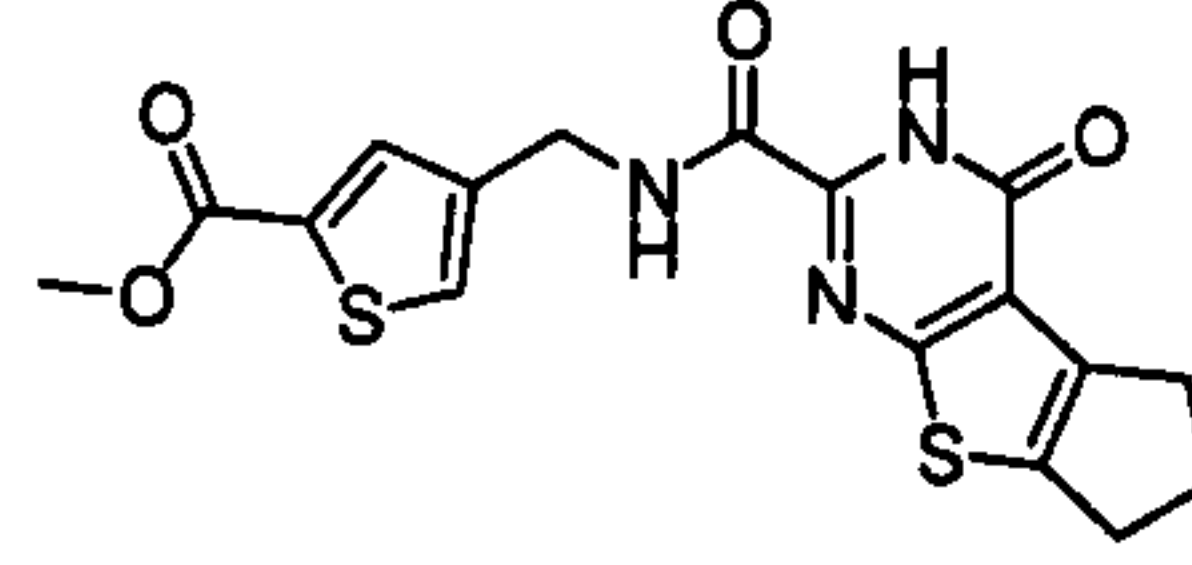
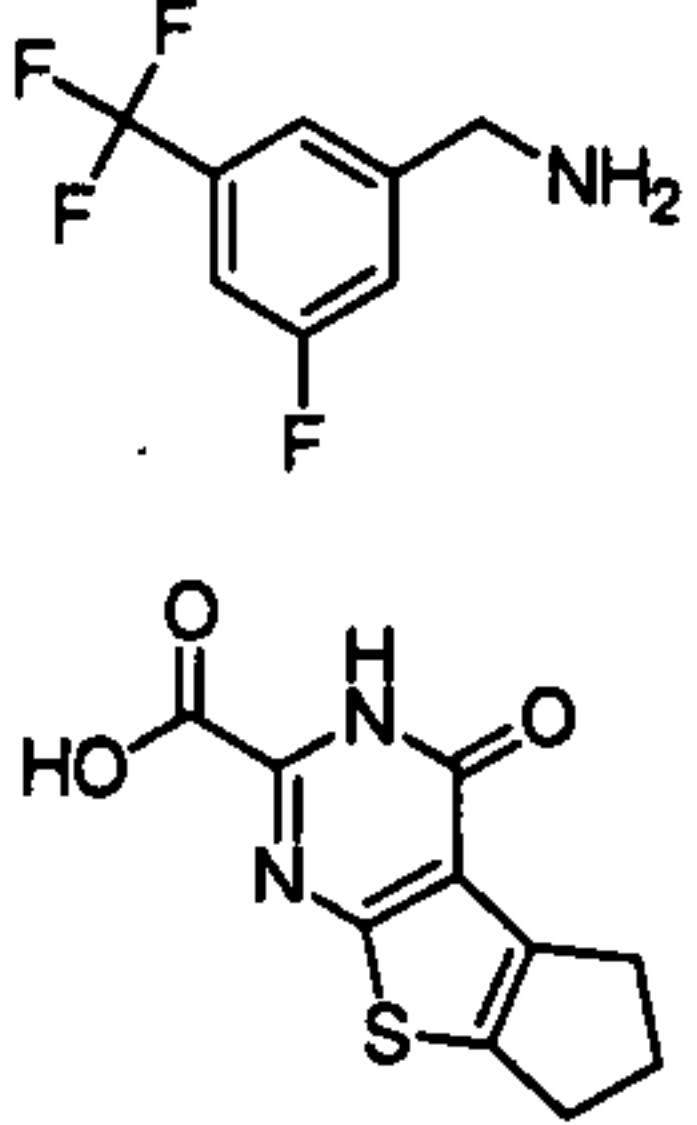
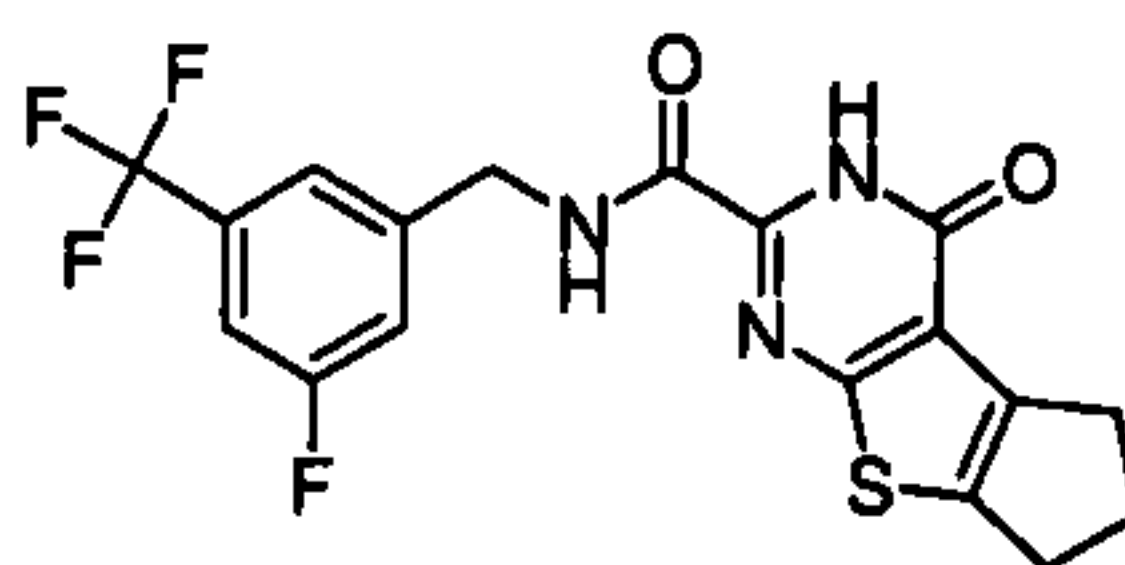
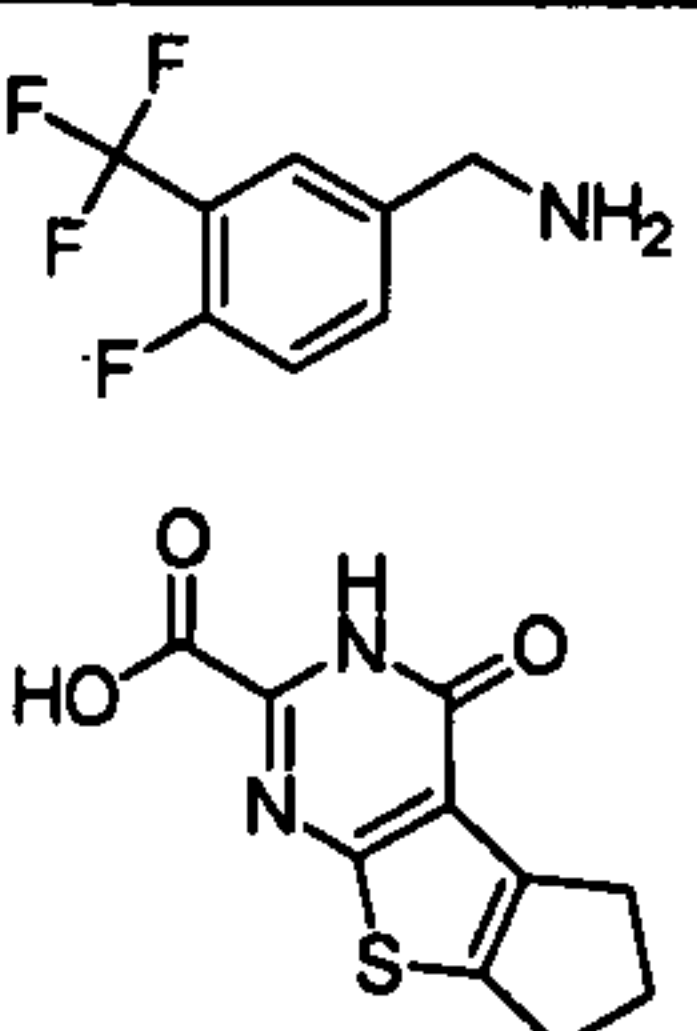
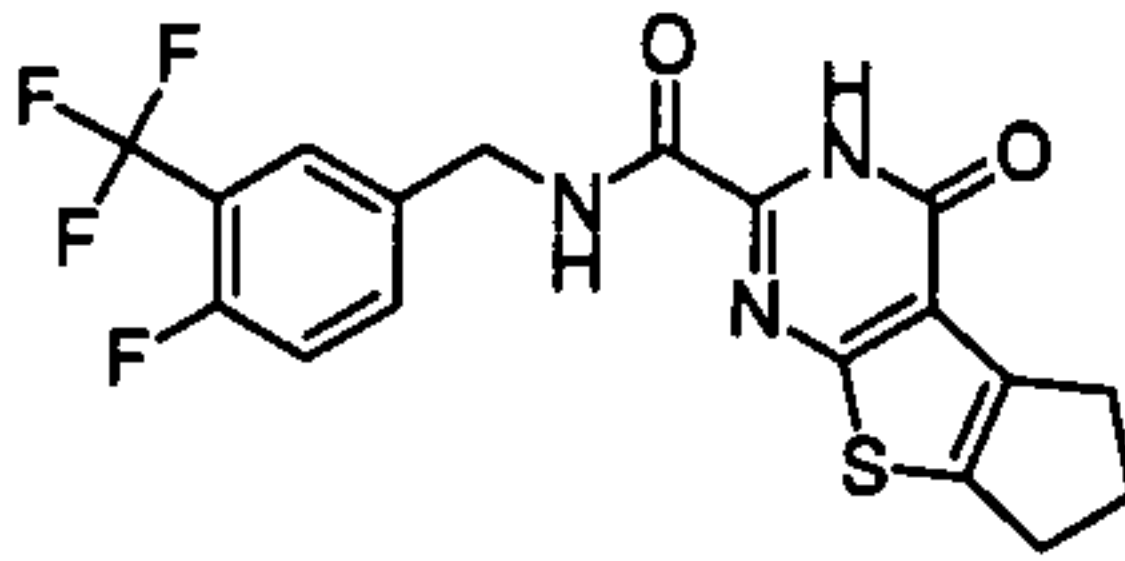
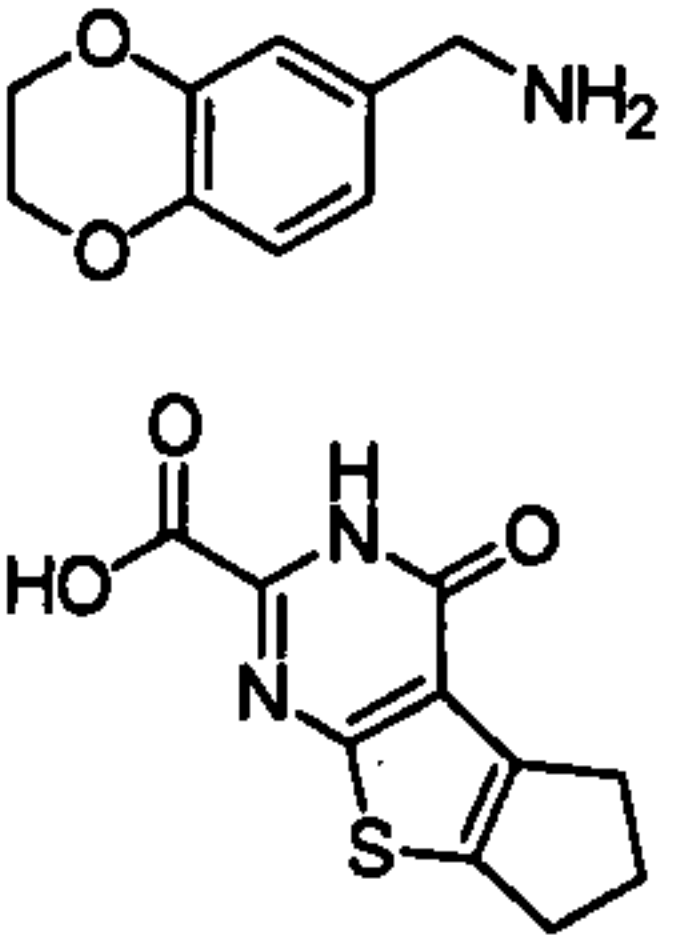
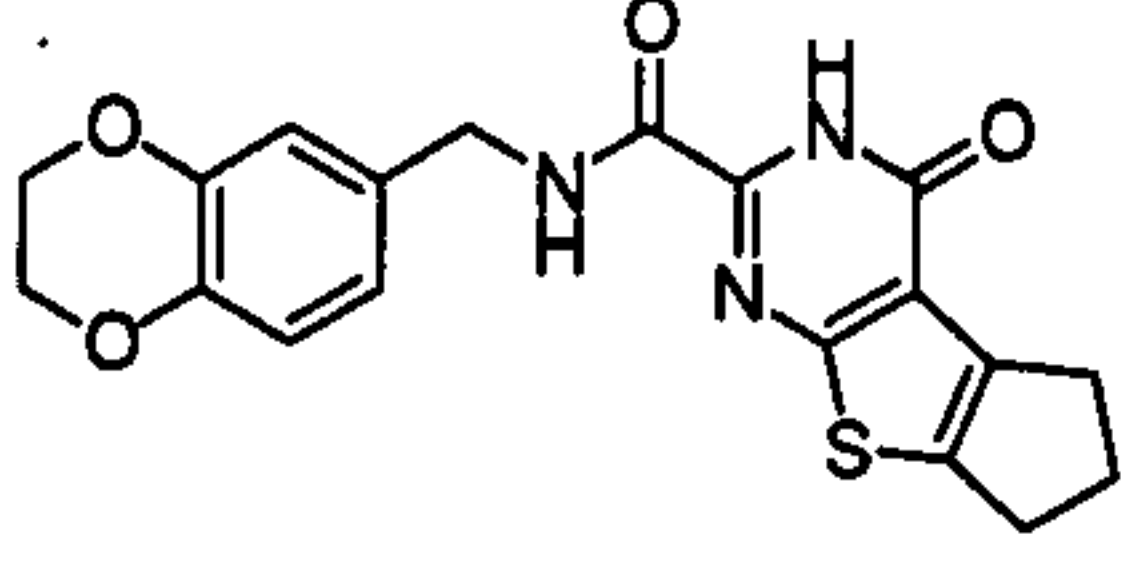
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/399 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 372 |
| 2/400 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 455 |
| 2/401 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/402 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/403 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 383 |

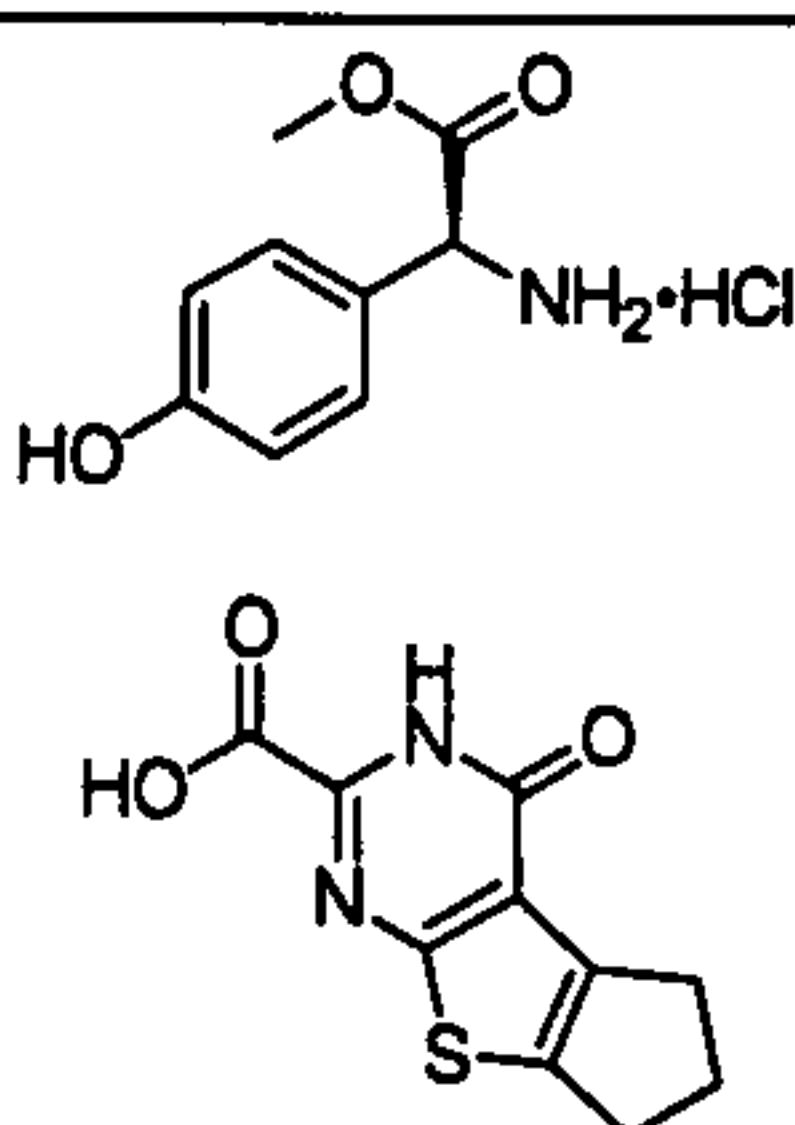
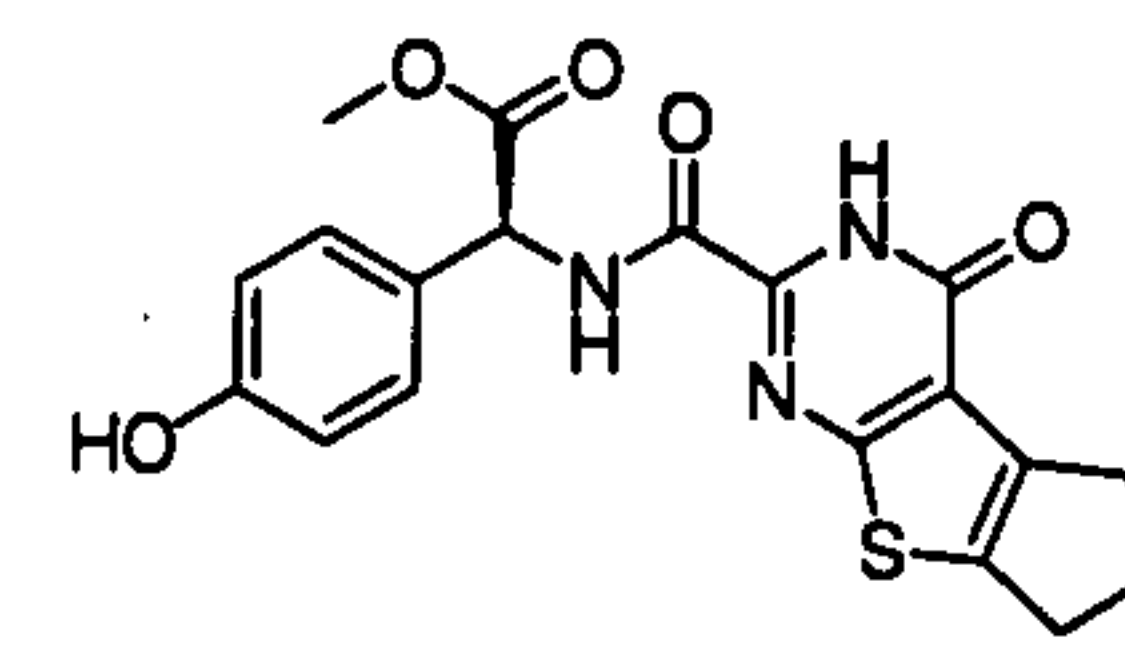
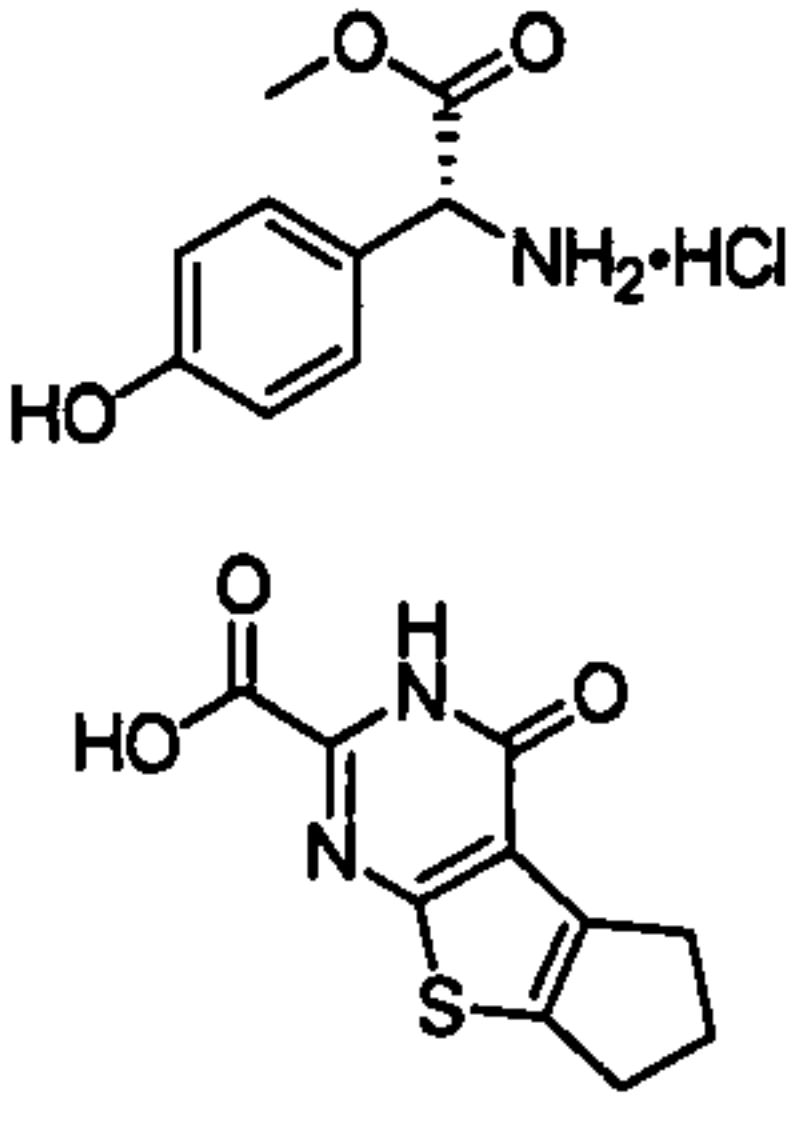
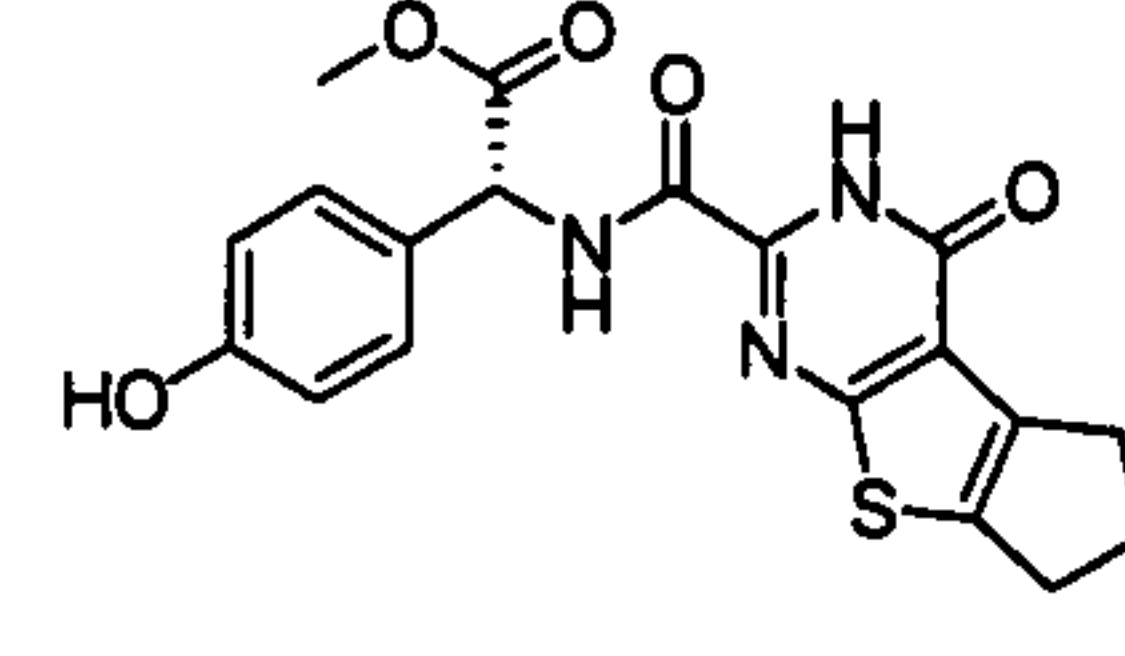
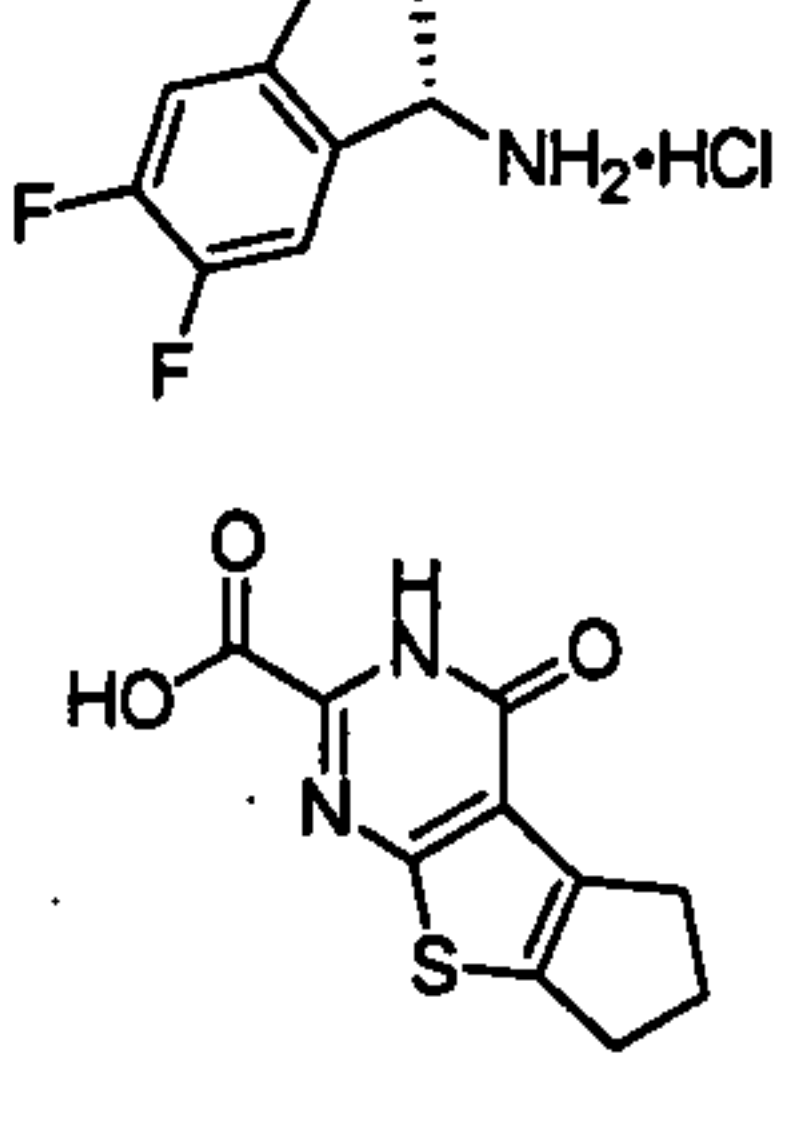
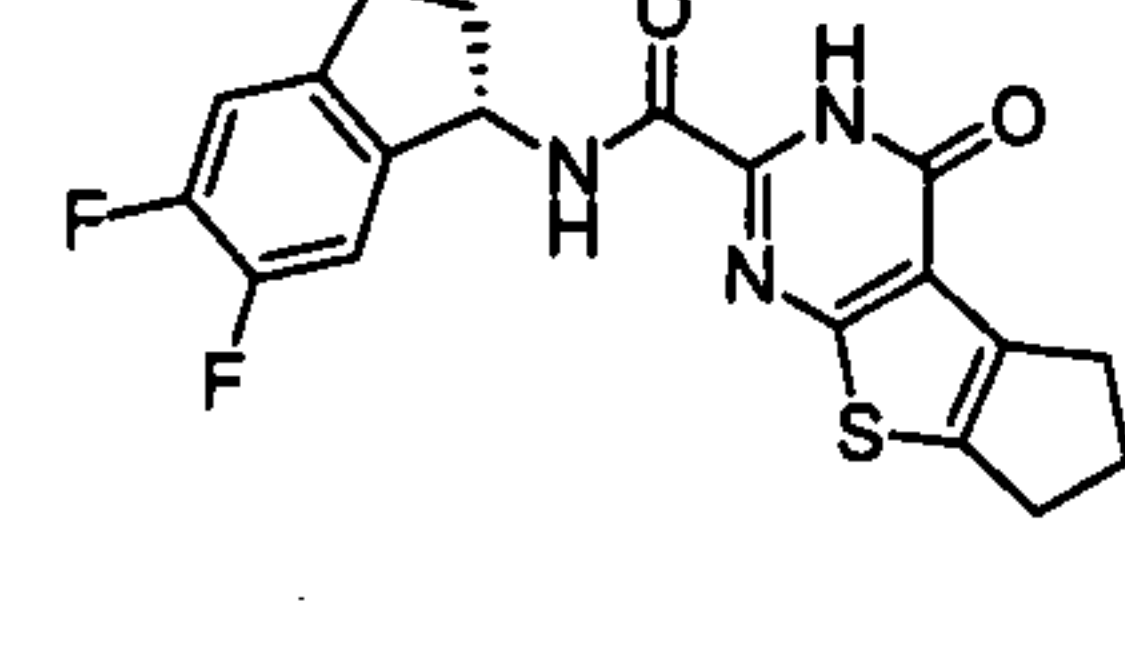
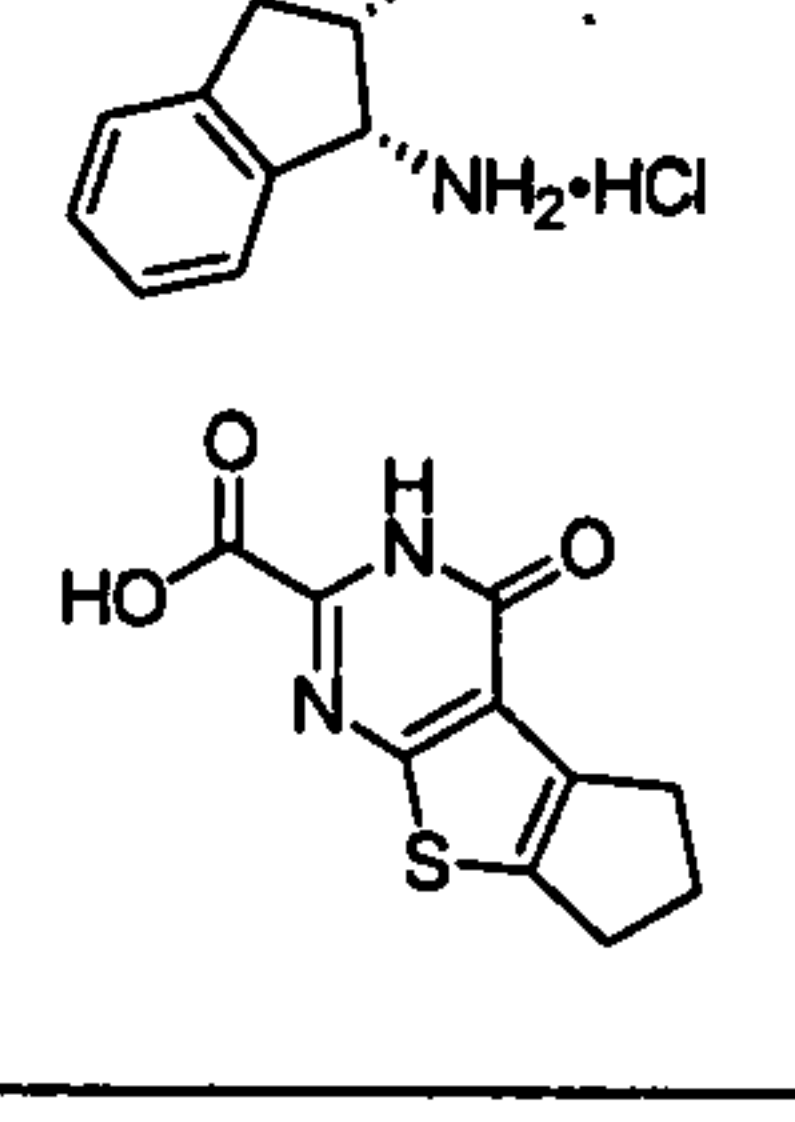
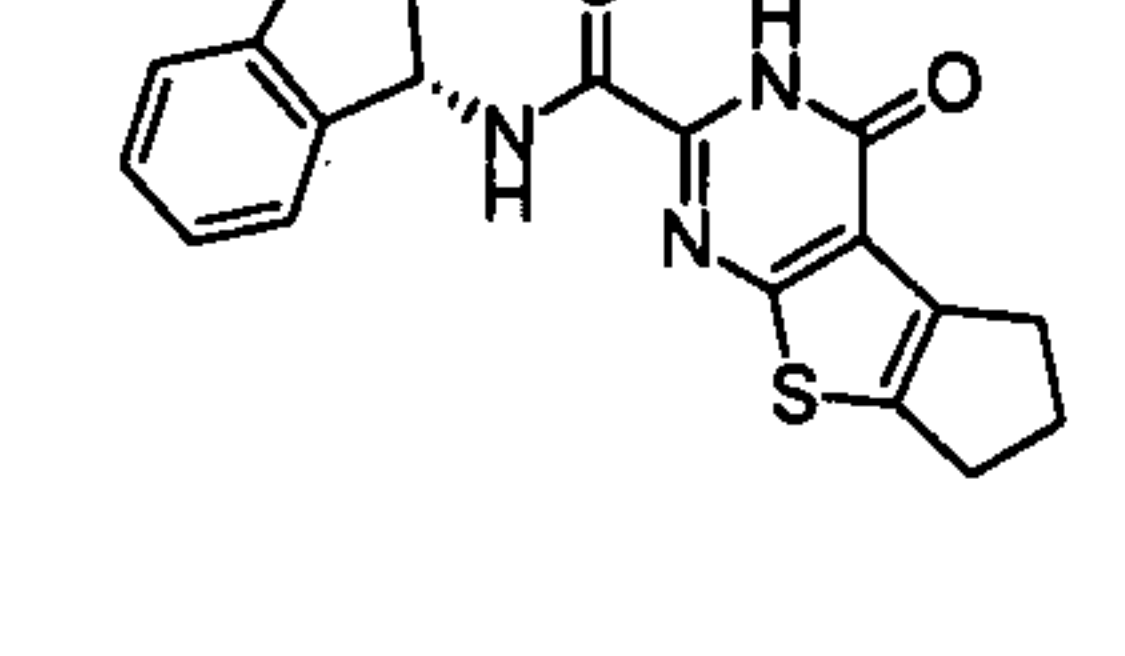
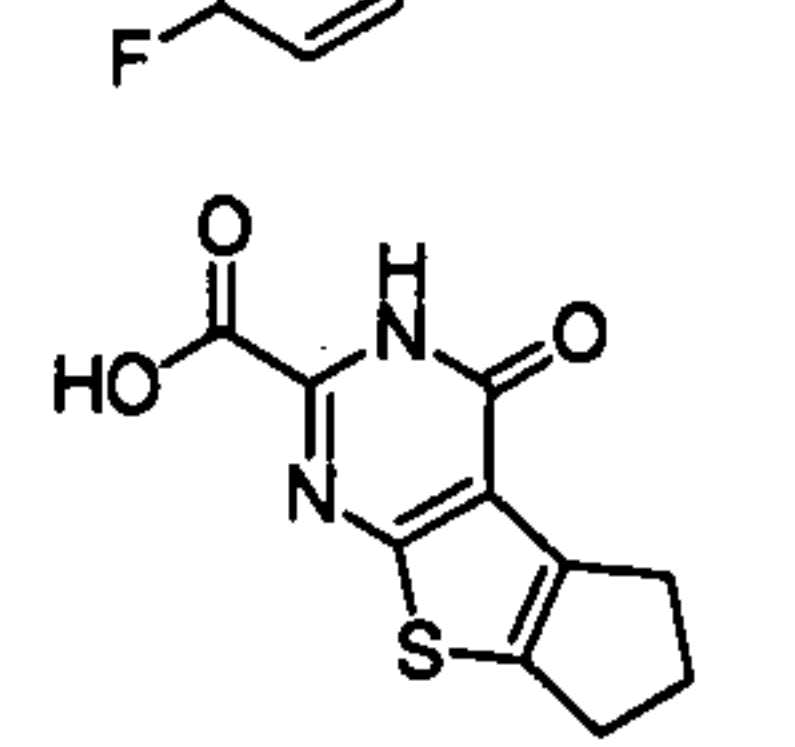
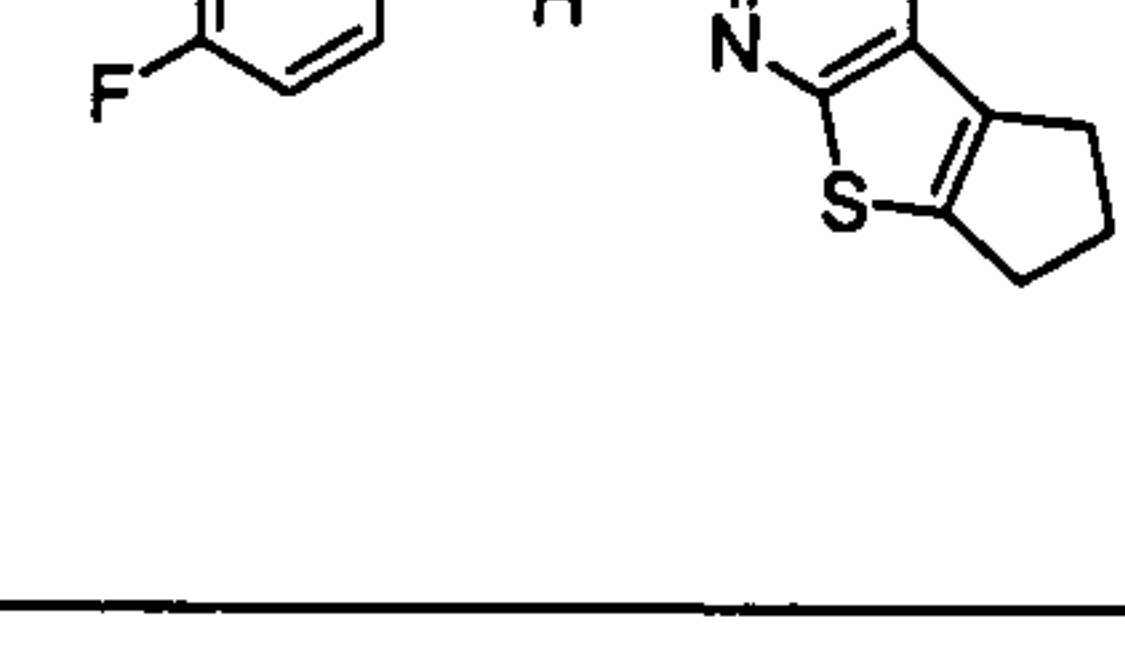
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/404 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 383 |
| 2/405 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 340 |
| 2/406 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 406 |
| 2/407 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 382 |
| 2/408 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 396 |

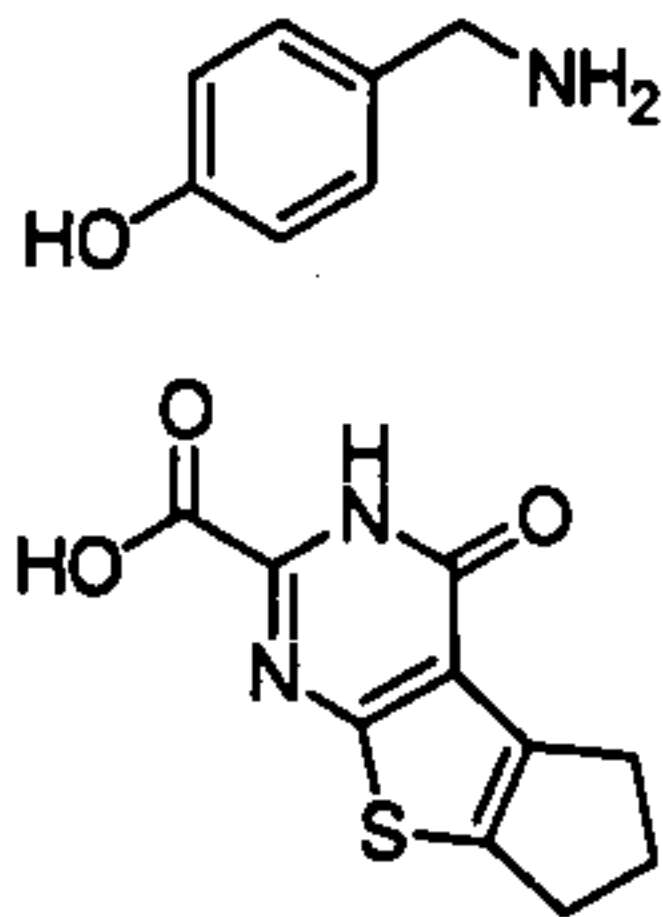
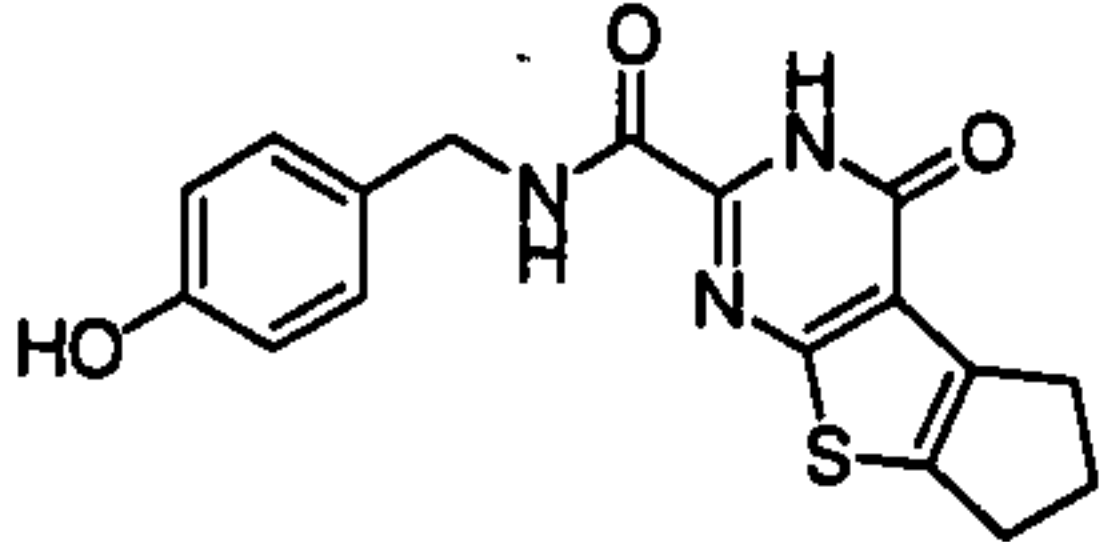
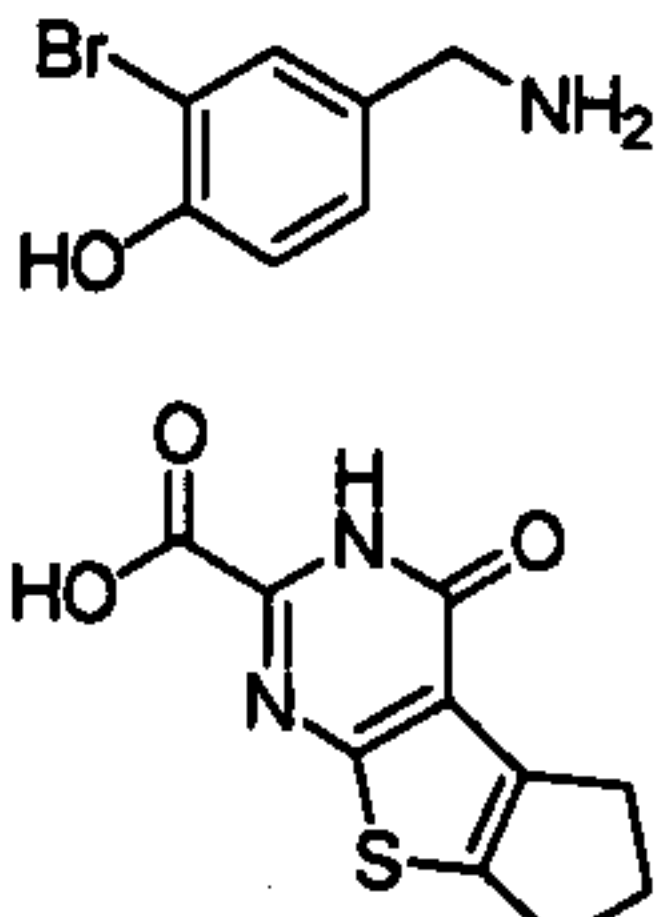
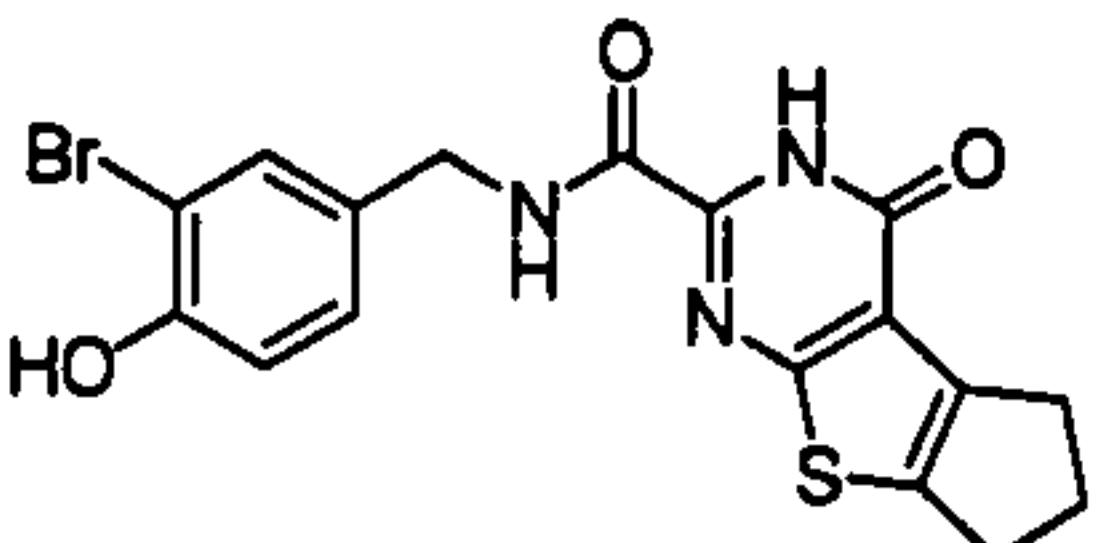
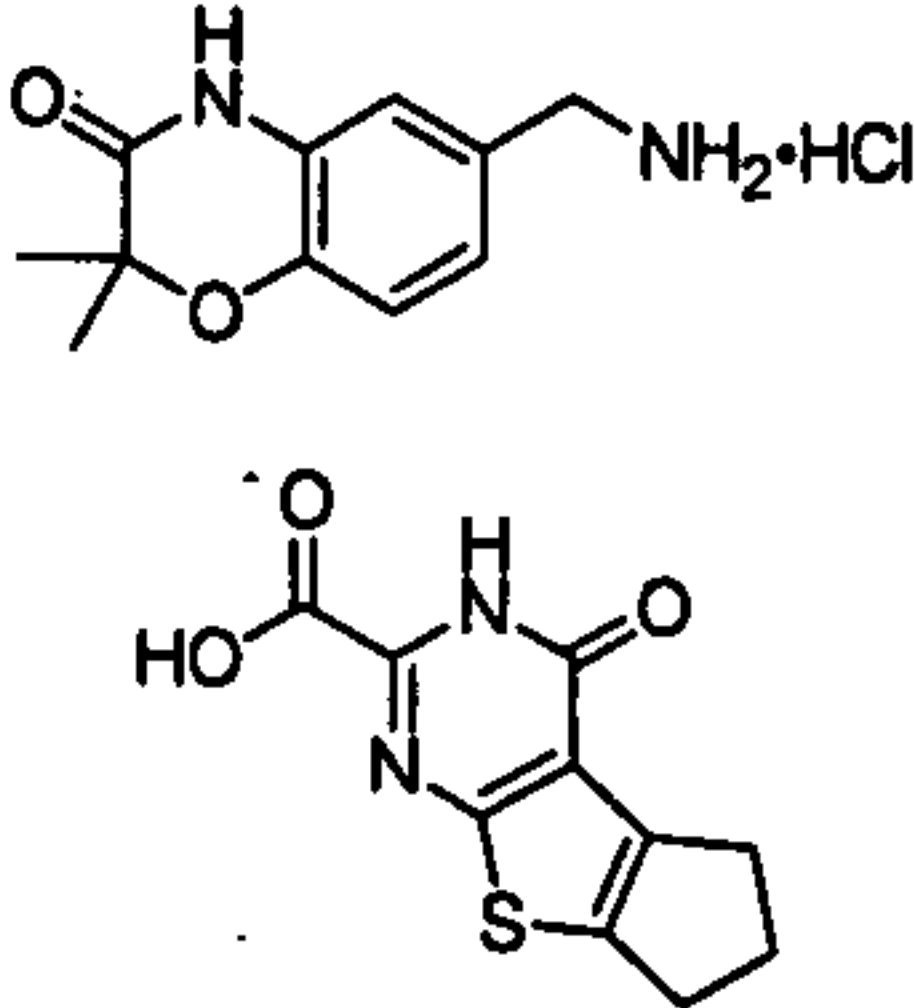
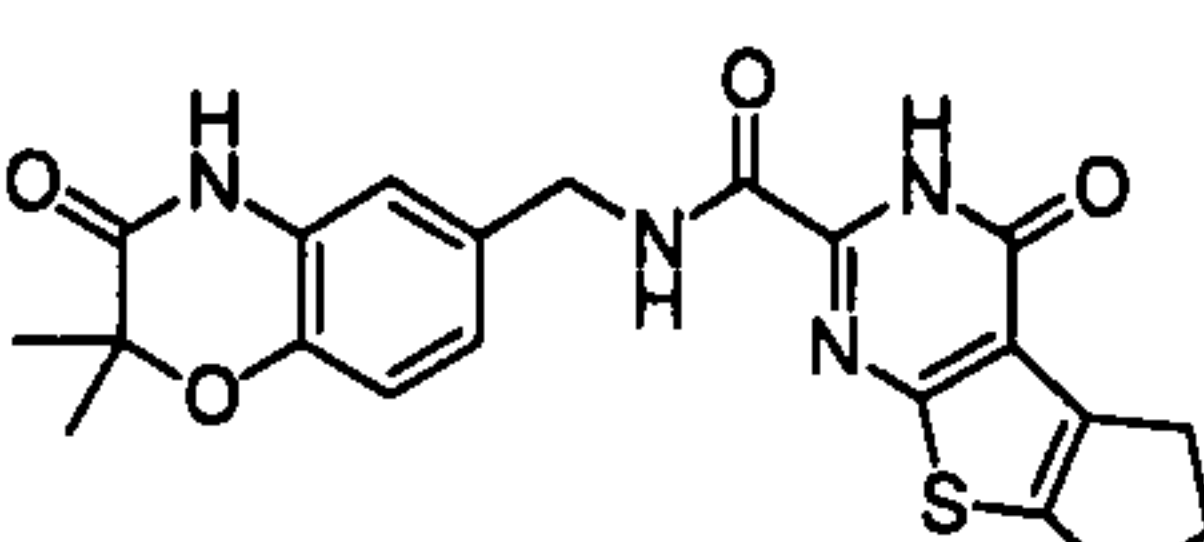
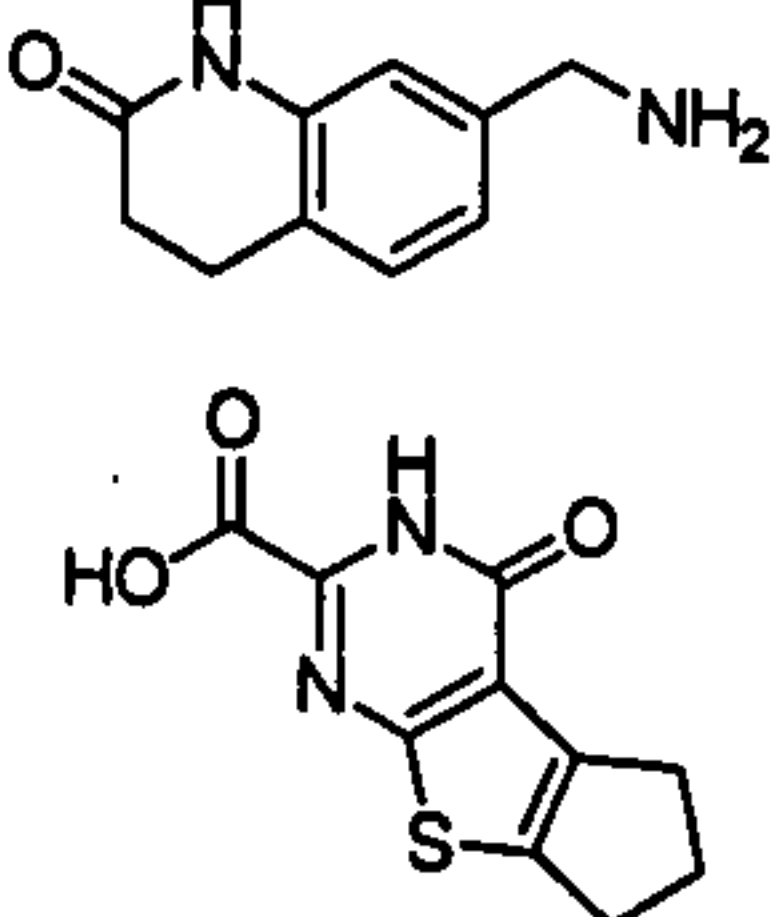
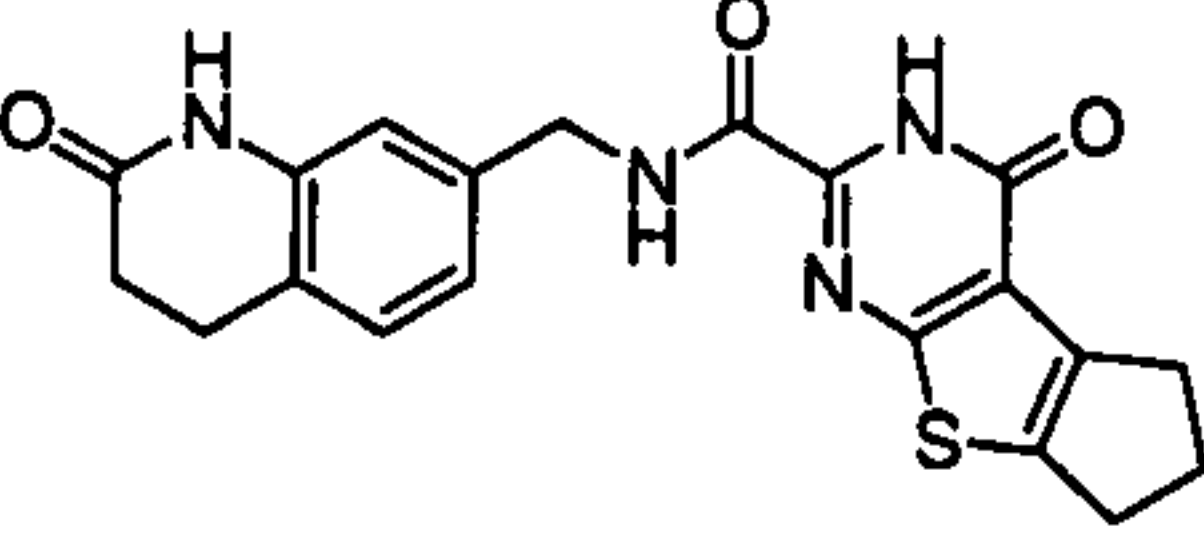
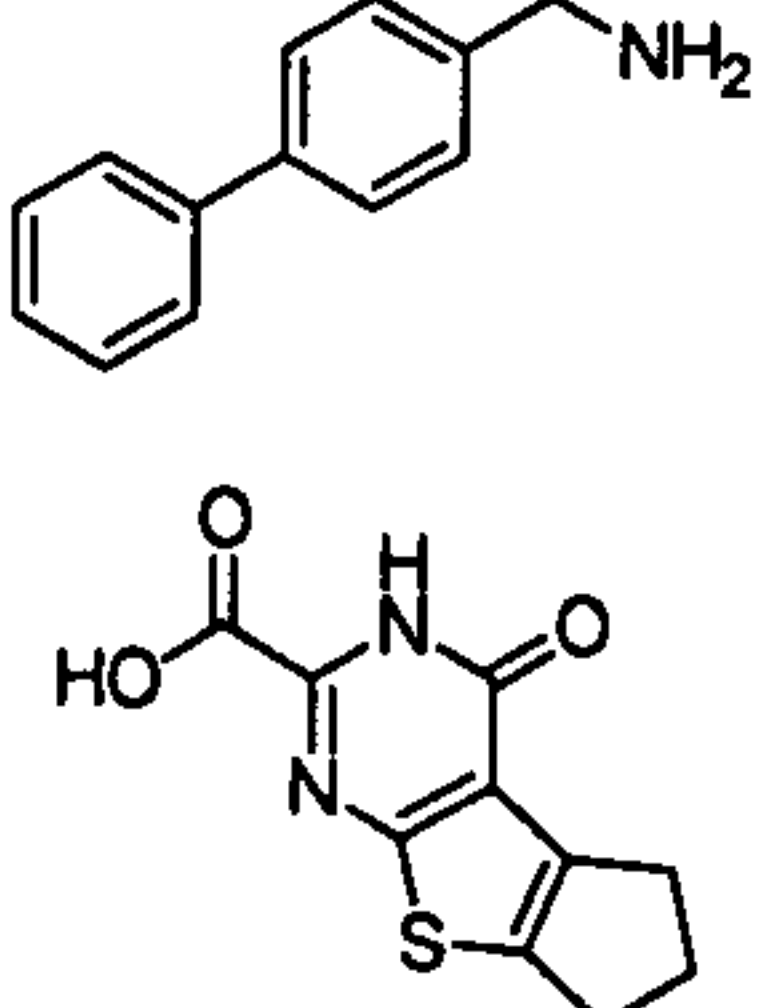
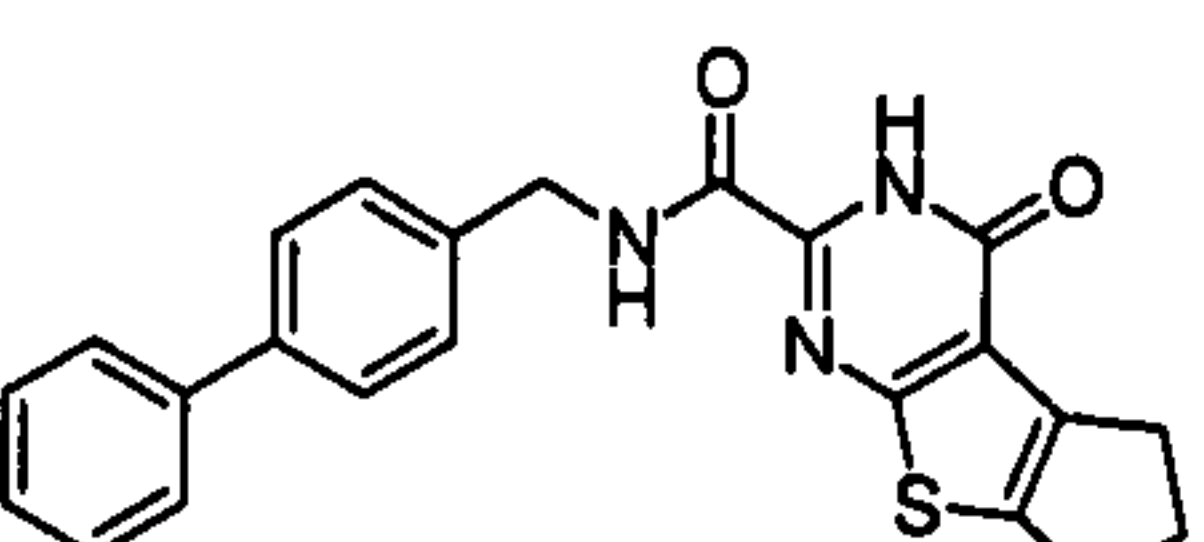
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/409 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 383 |
| 2/410 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 397 |
| 2/411 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 397 |
| 2/412 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 410 |
| 2/413 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 450 |

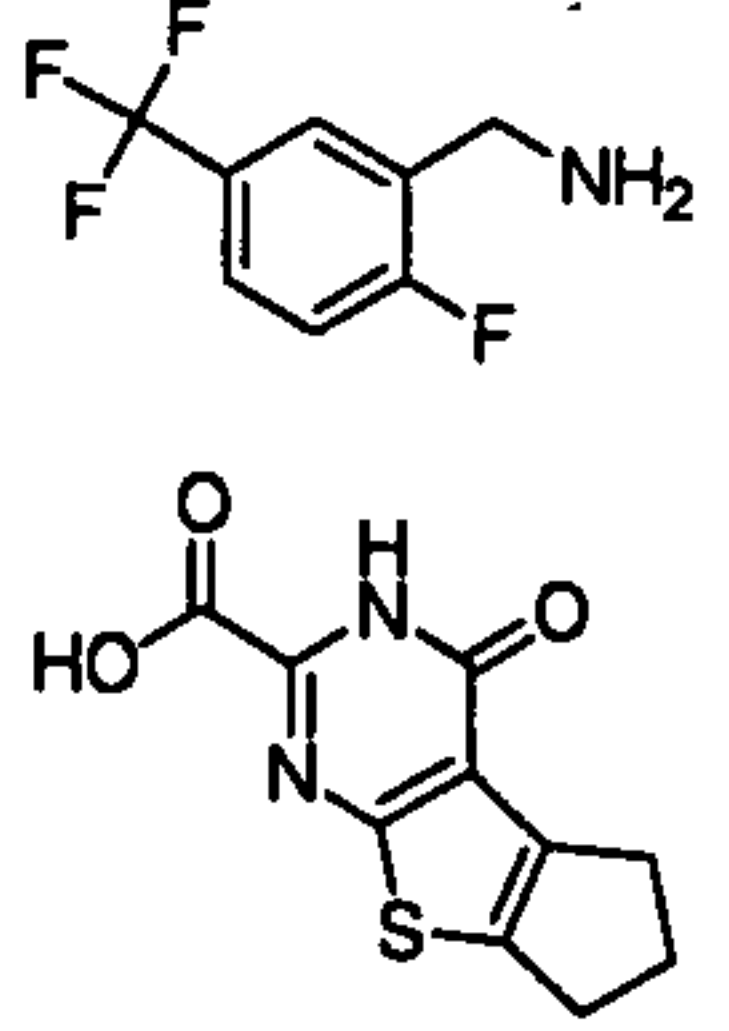
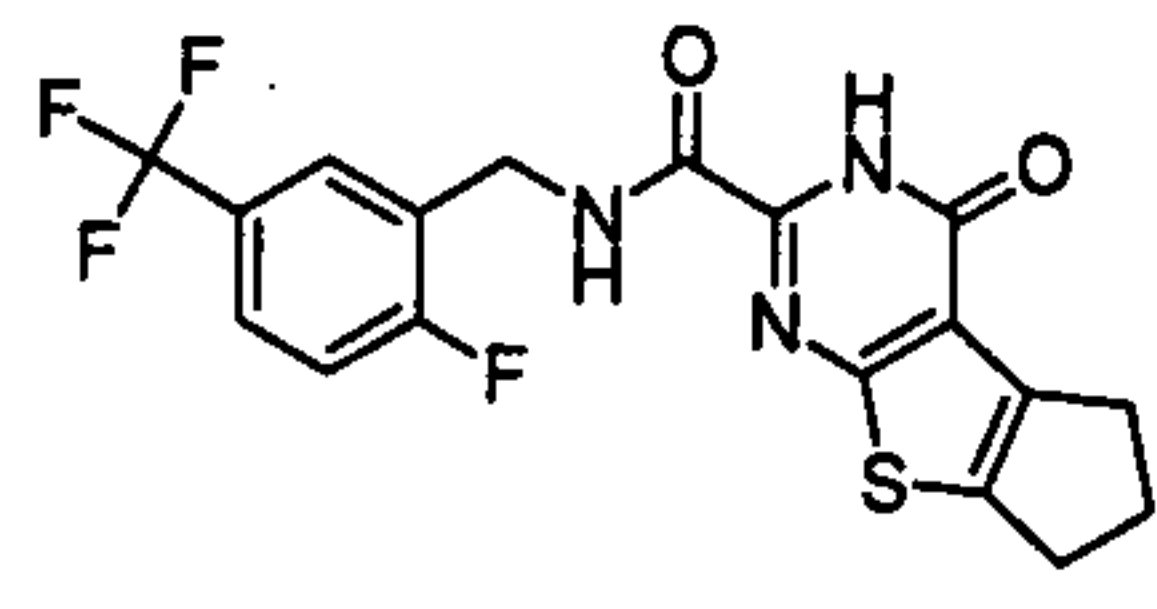
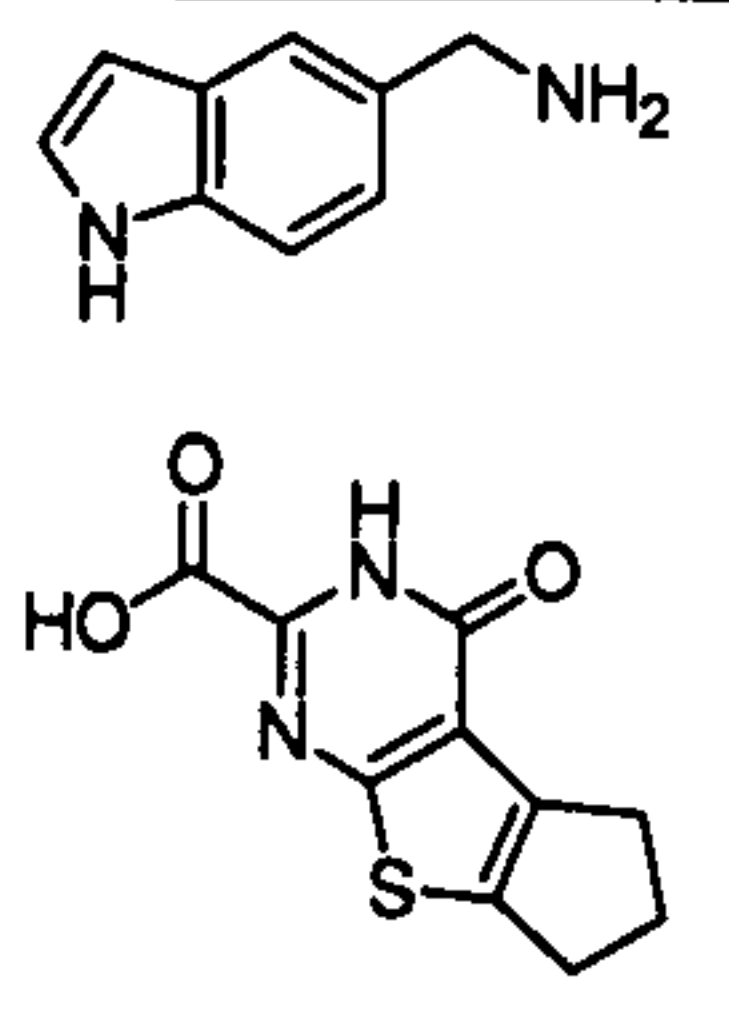
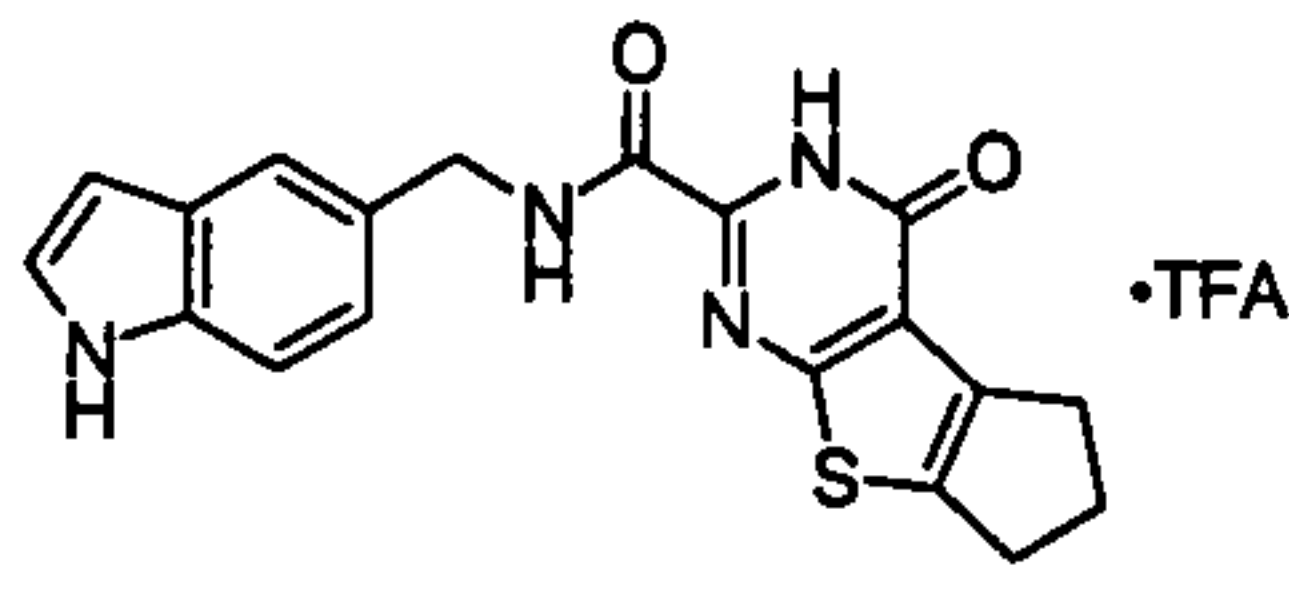
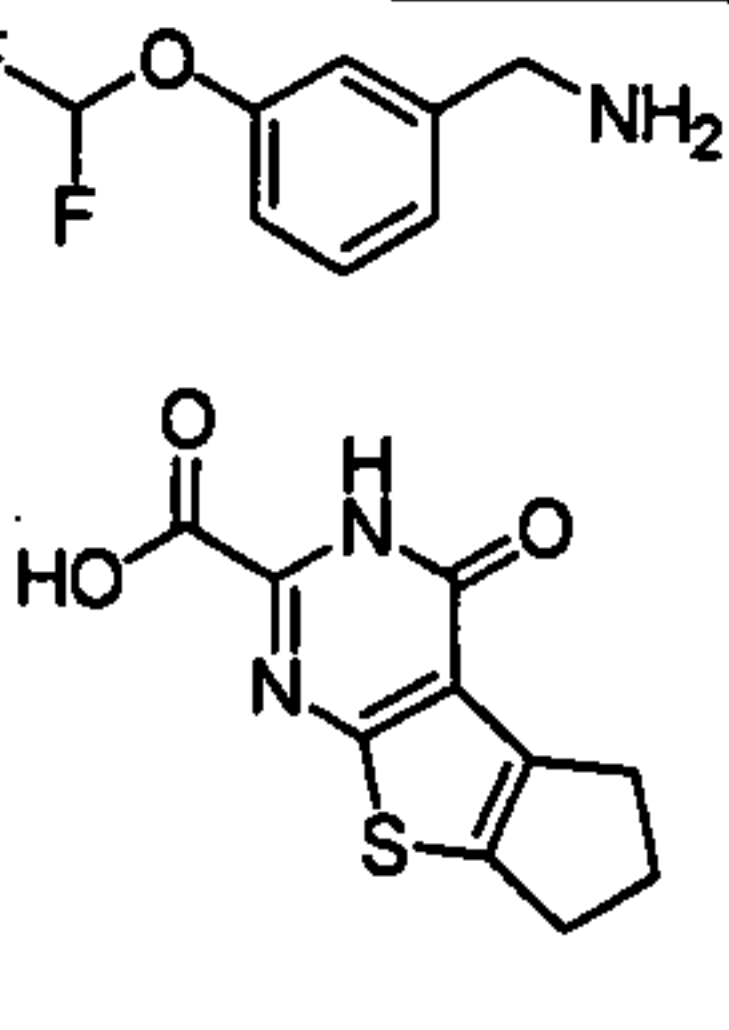
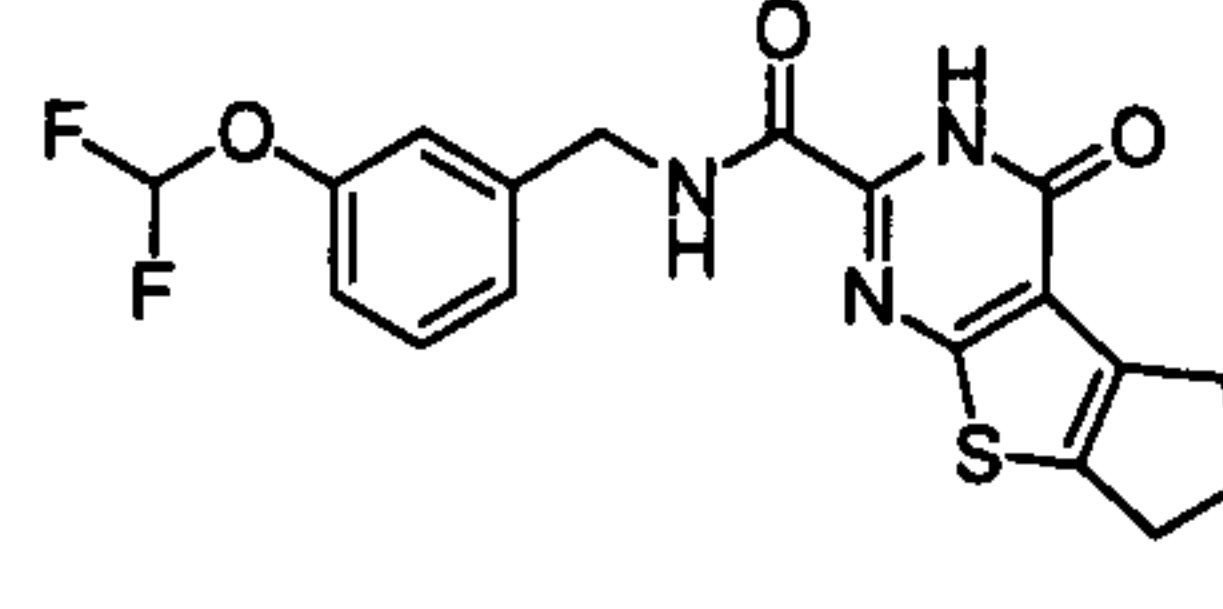
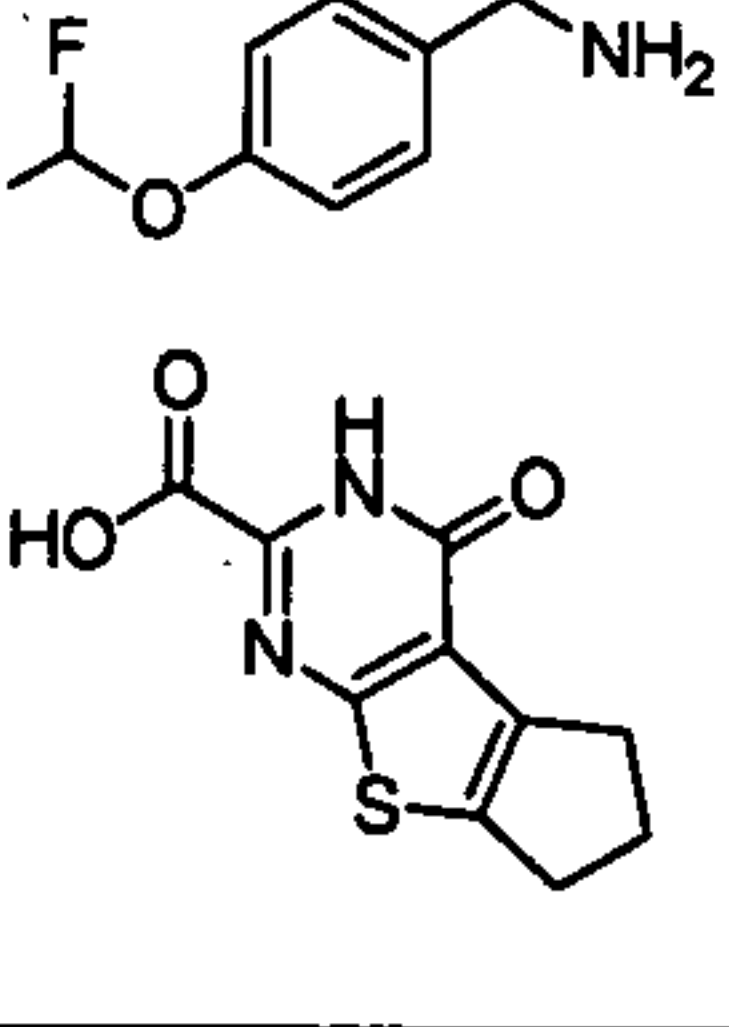
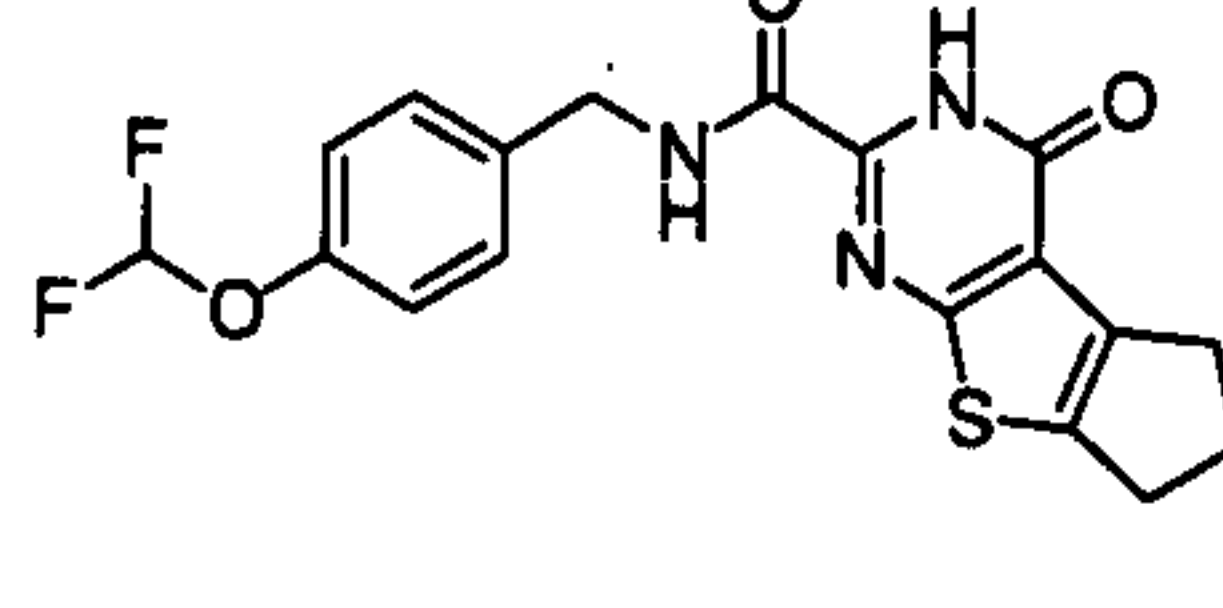
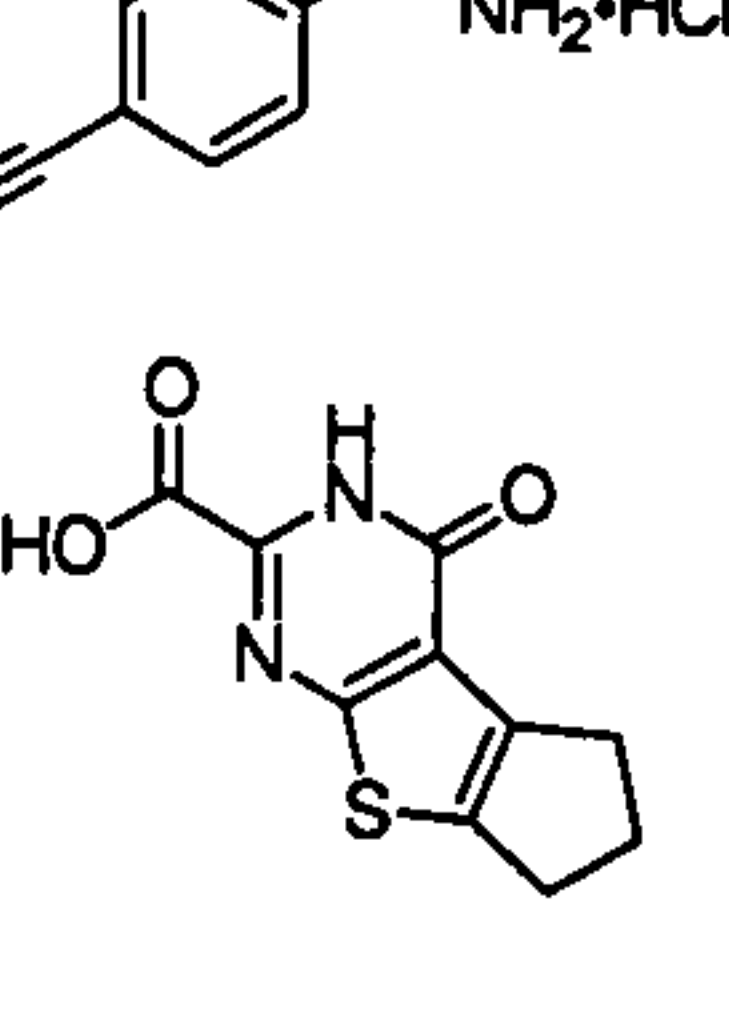
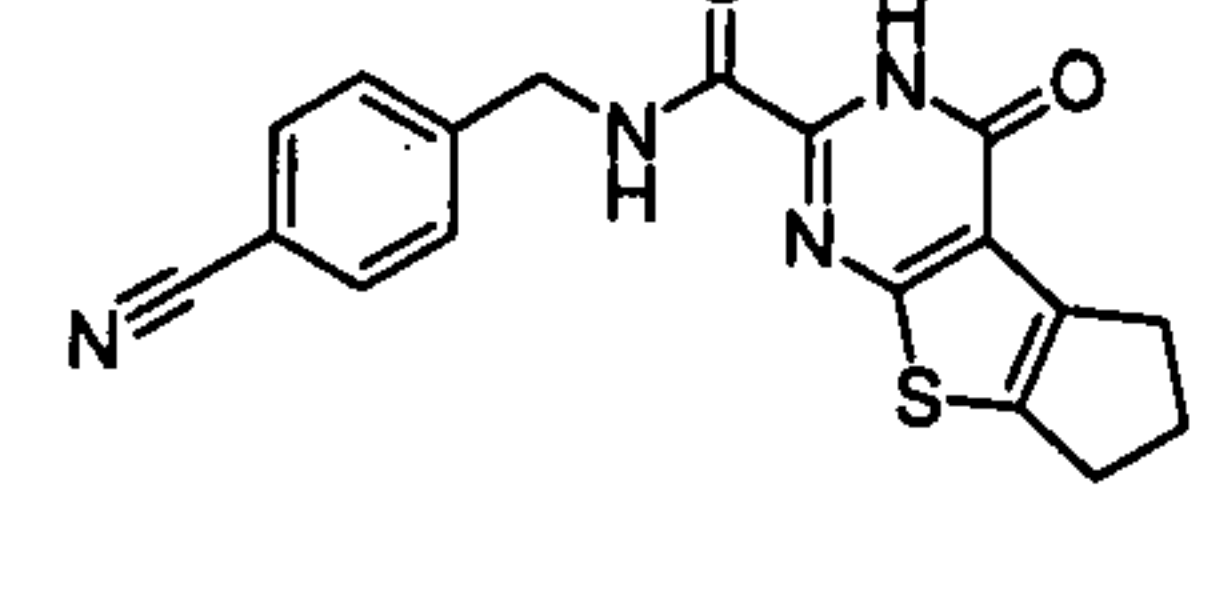
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/414 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 478 |
| 2/415 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 394 |
| 2/416 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 464 |
| 2/417 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 468 |
| 2/418 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 482 |

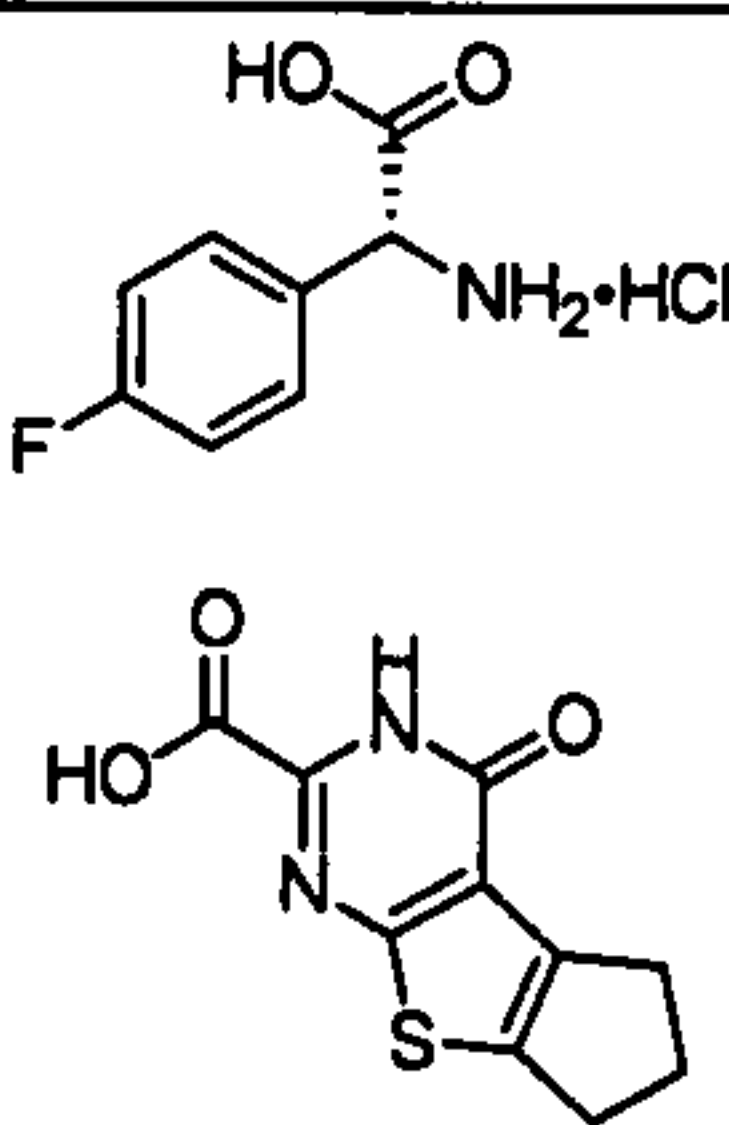
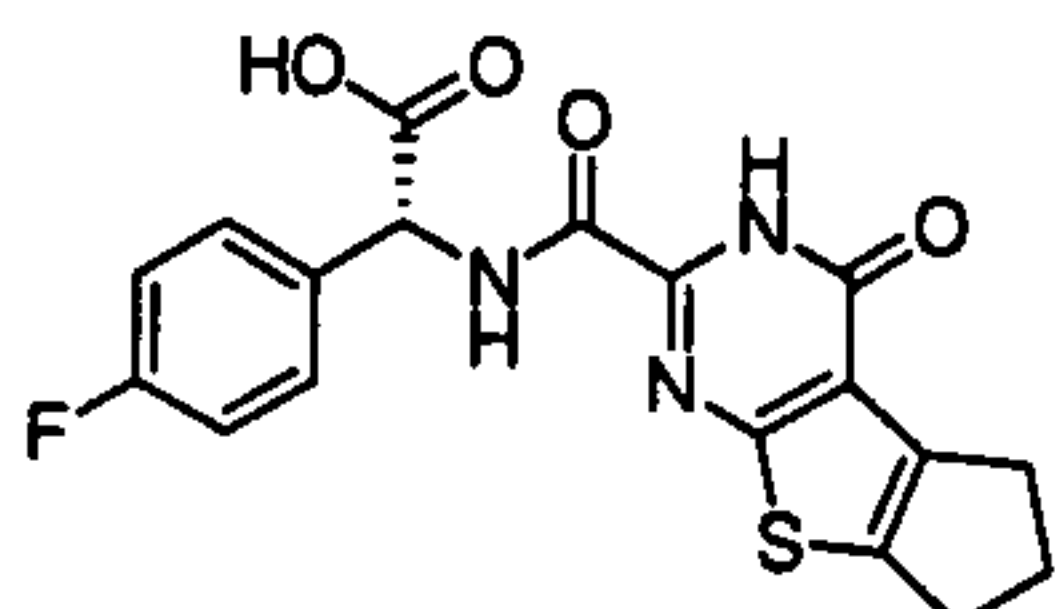
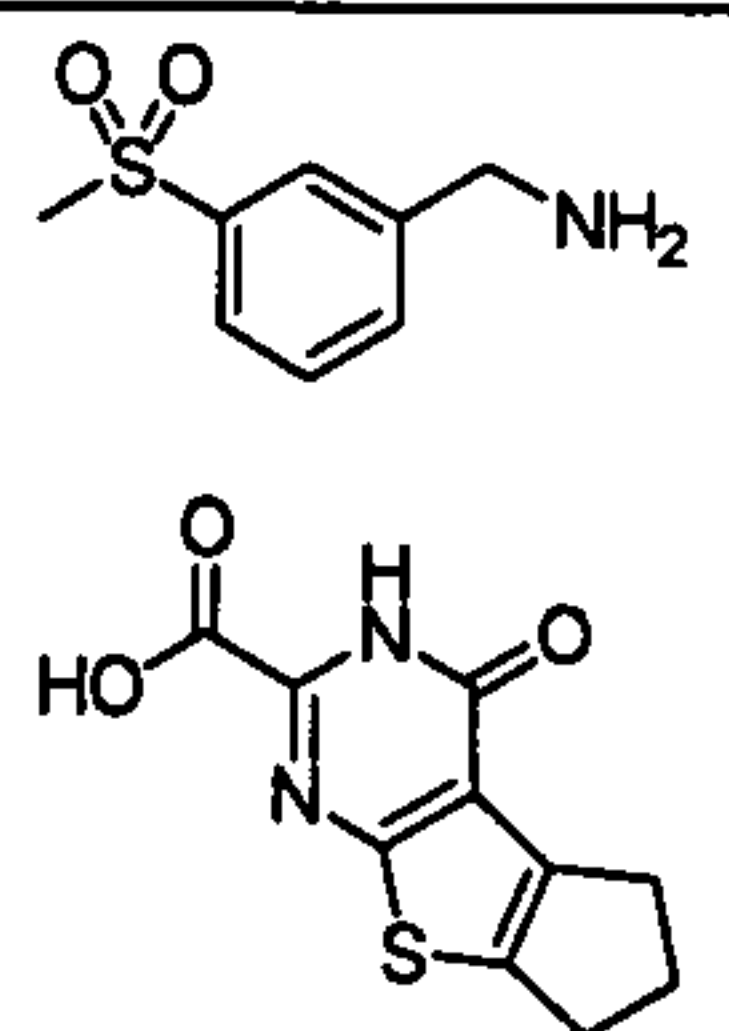
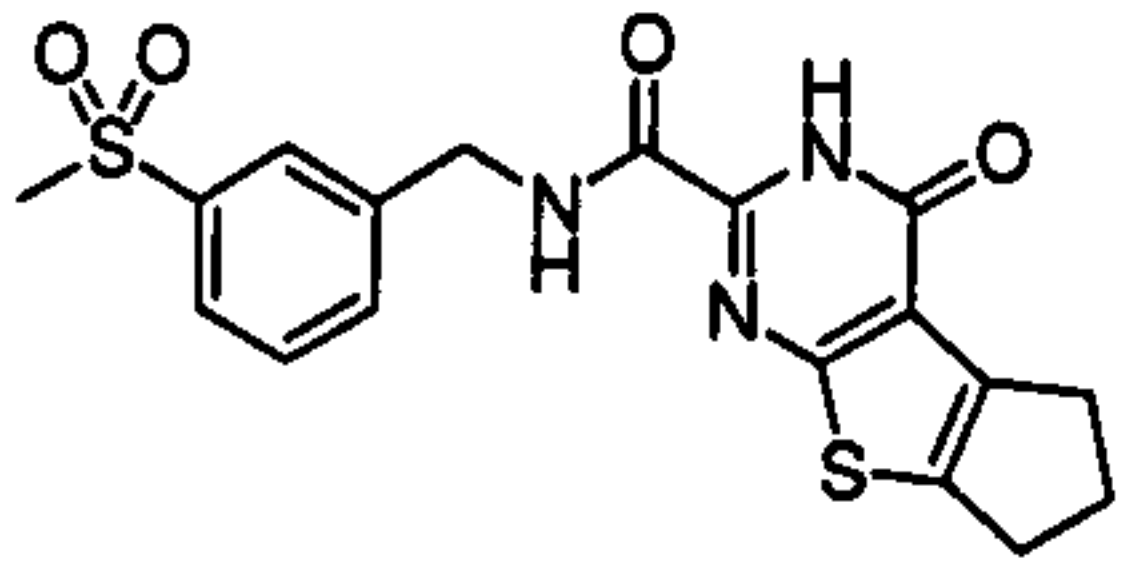
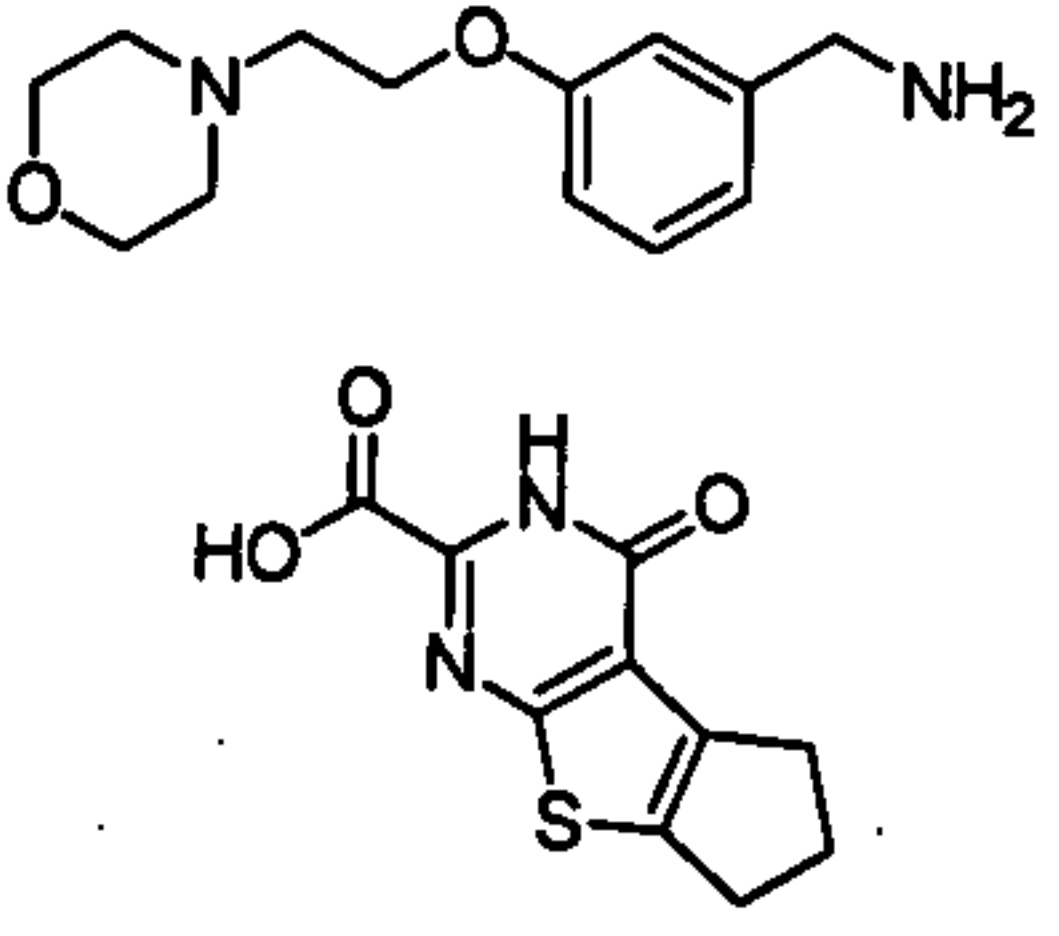
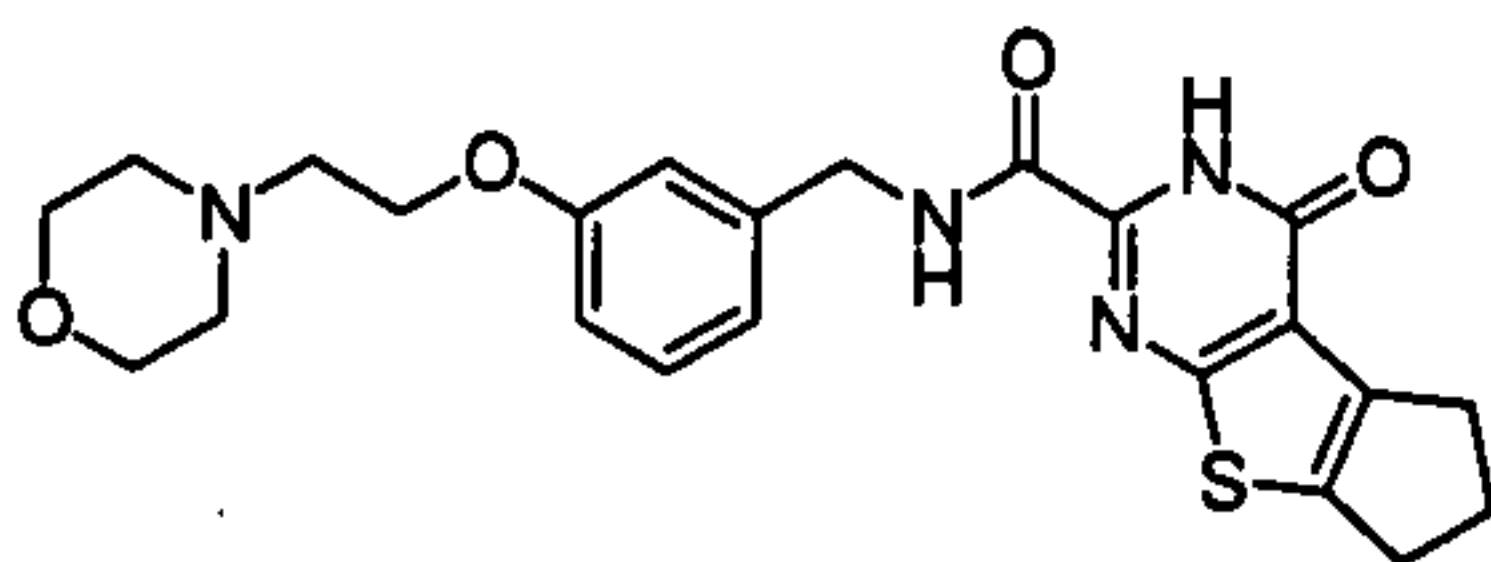
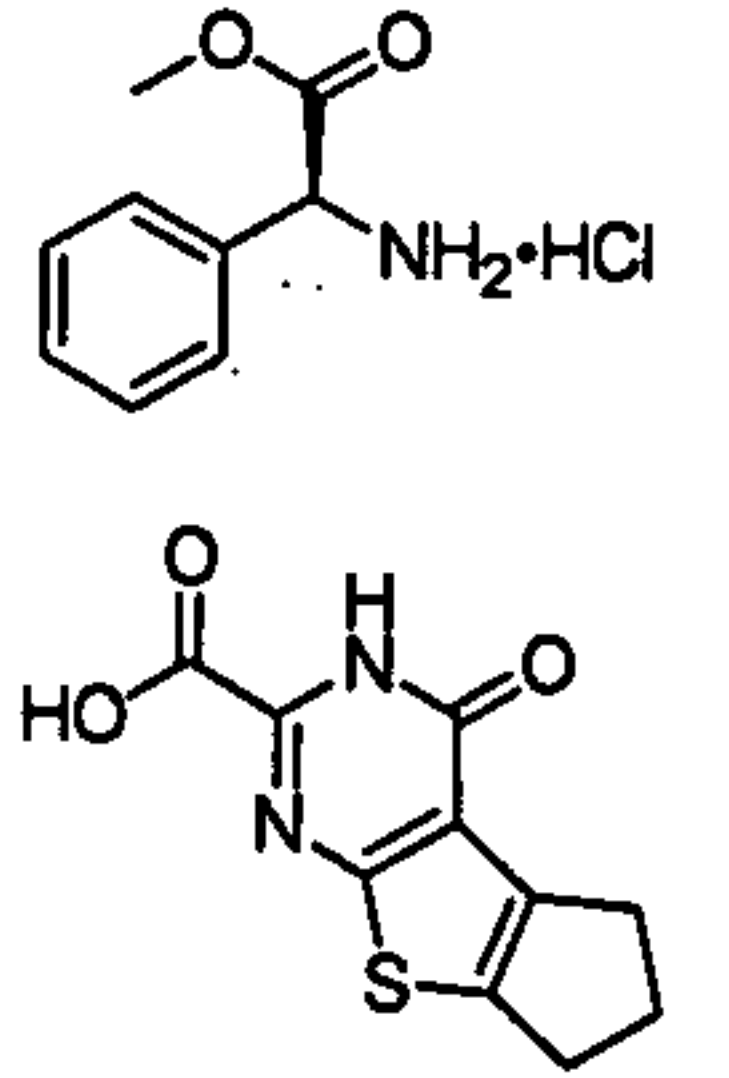
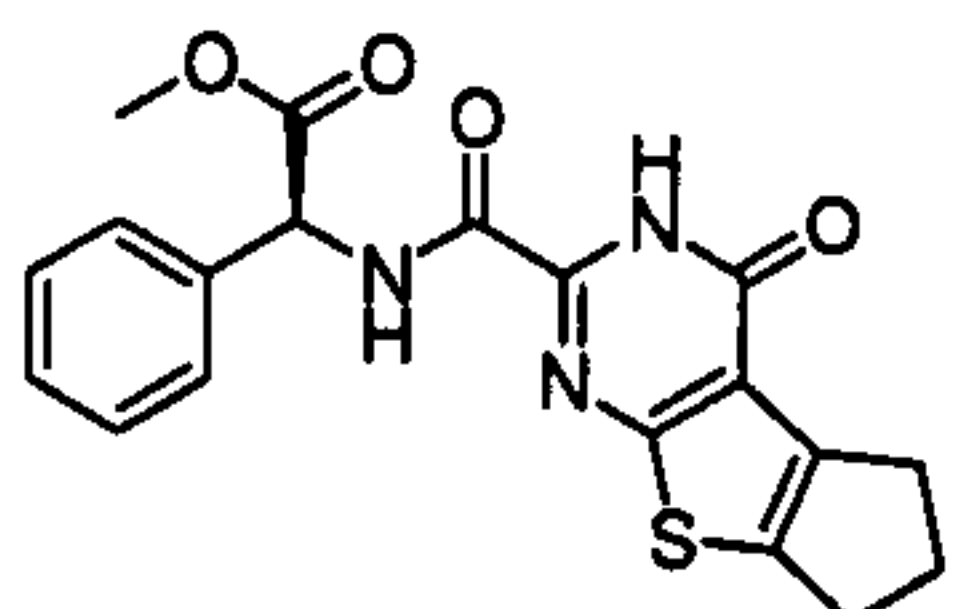
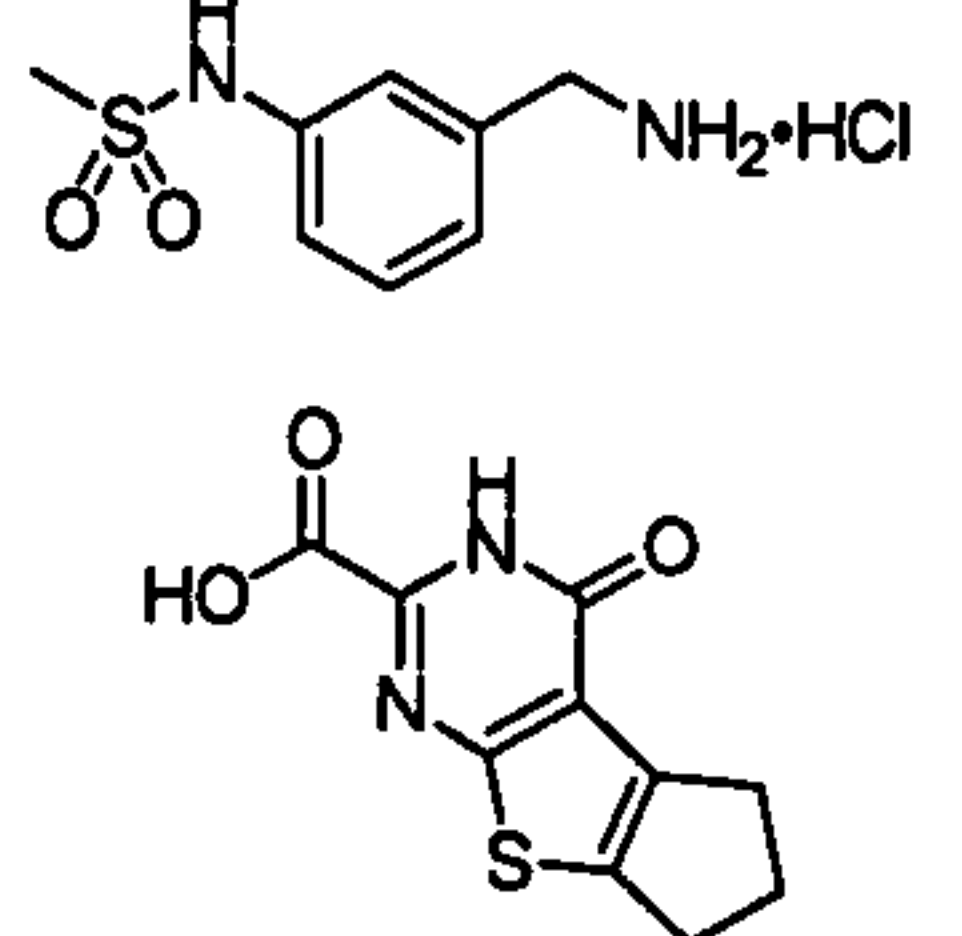
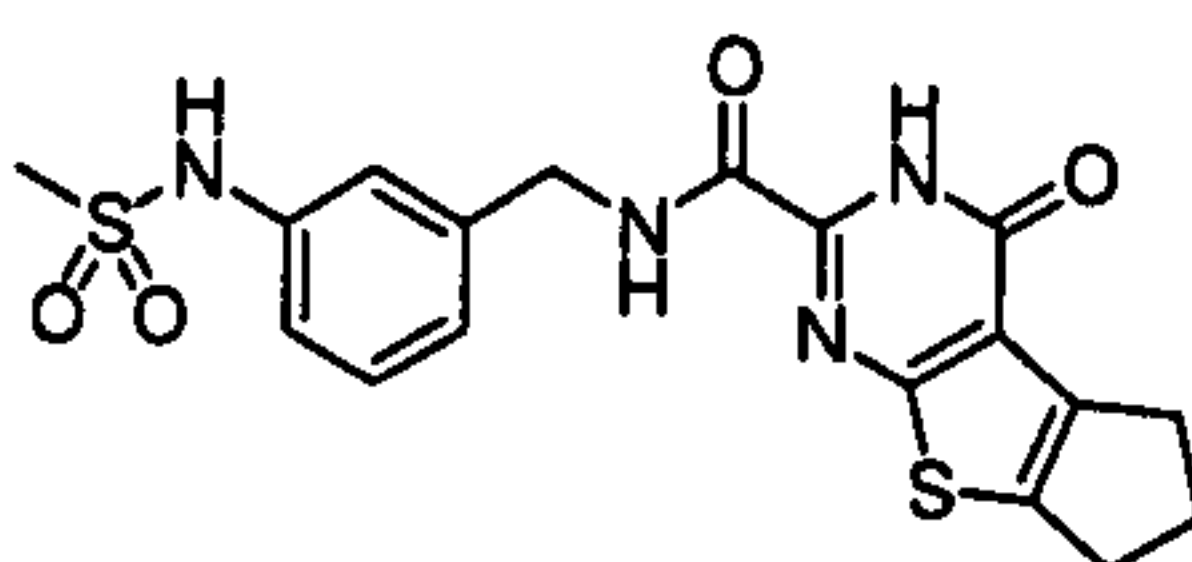
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/419 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 482 |
| 2/420 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 416 |
| 2/421 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 490 |
| 2/422 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 372 |
| 2/423 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 351 |

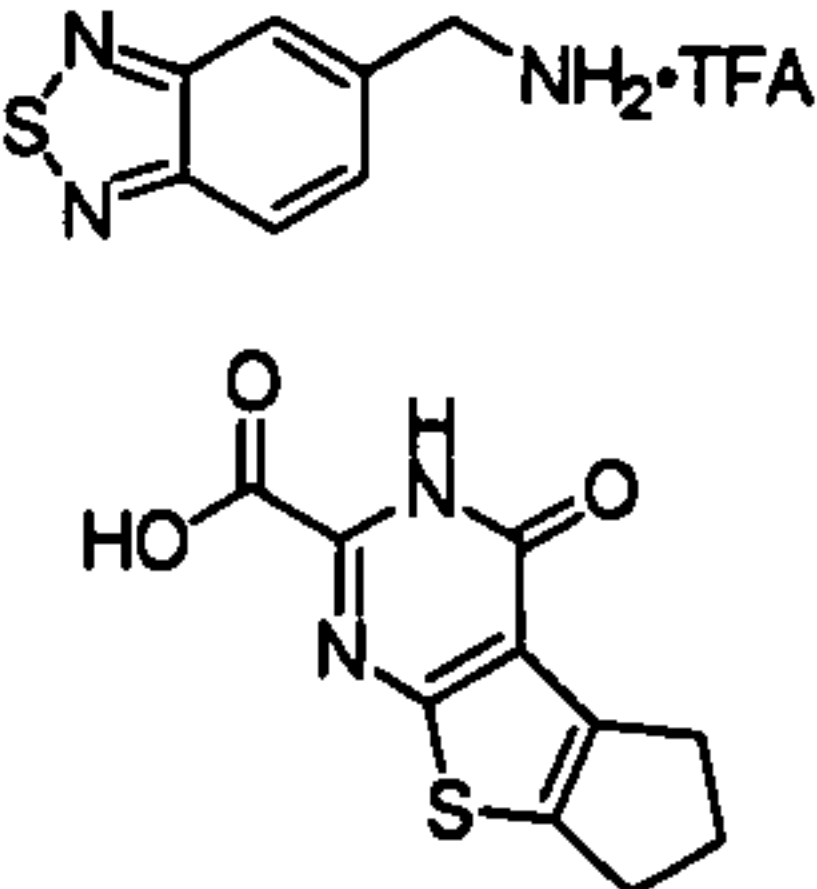
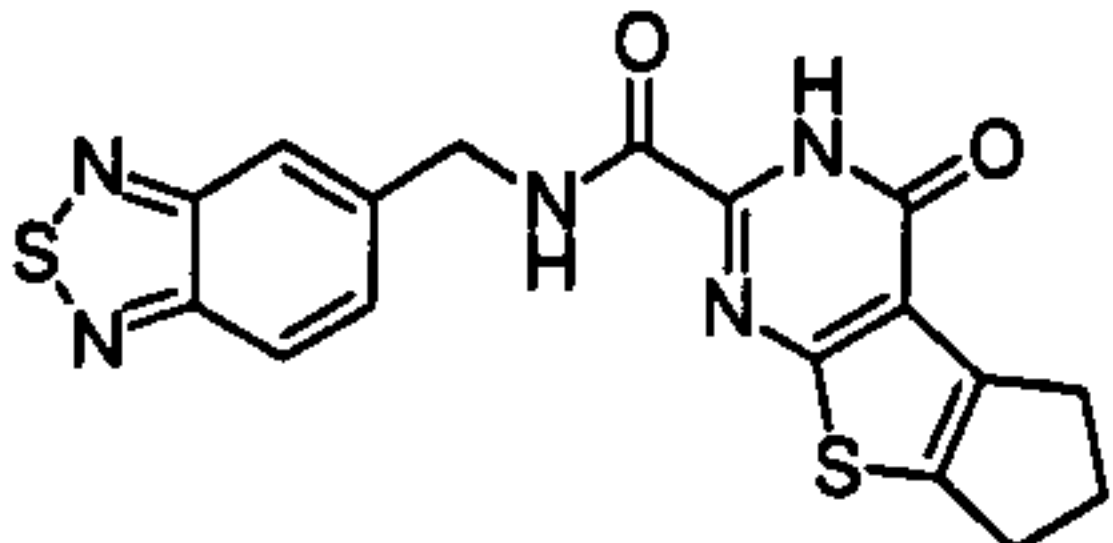
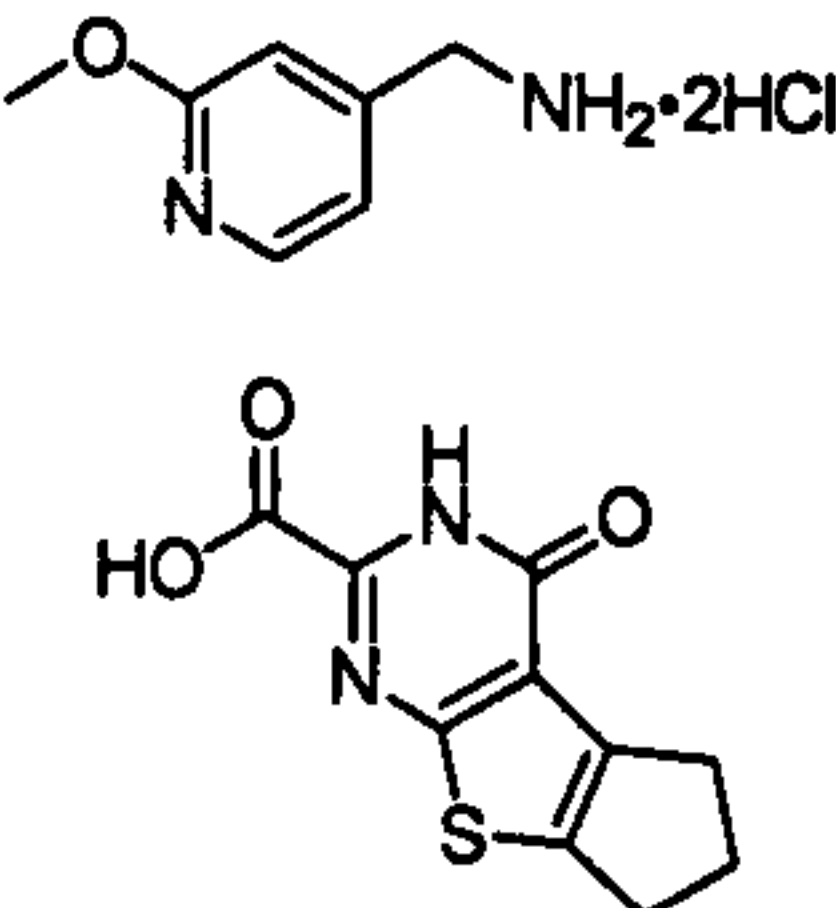
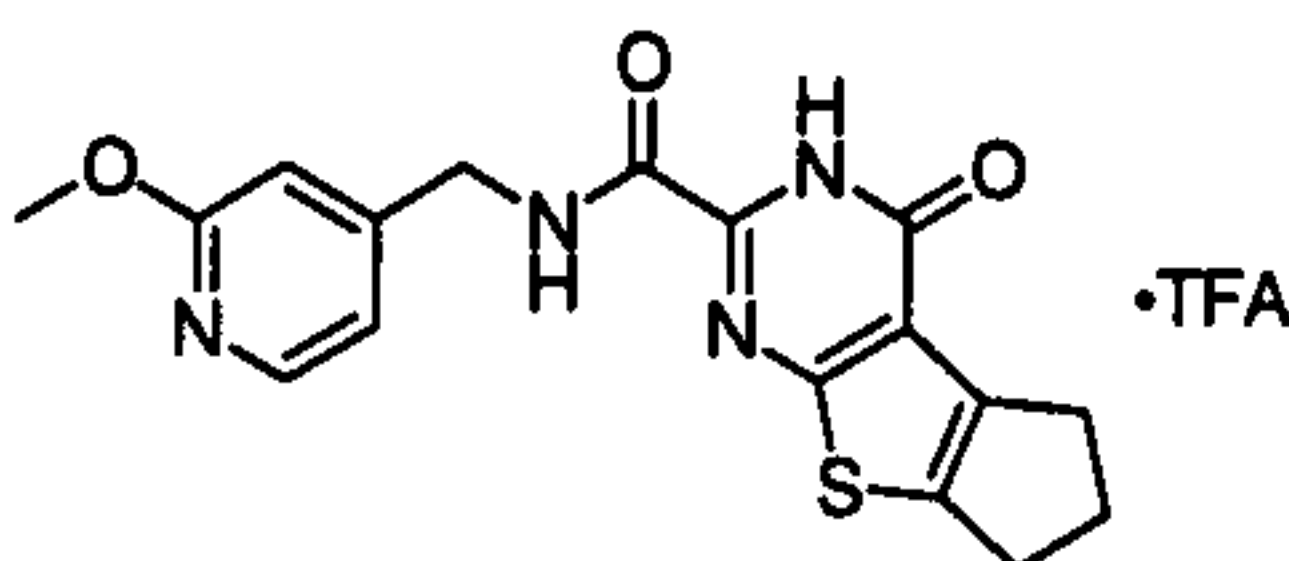
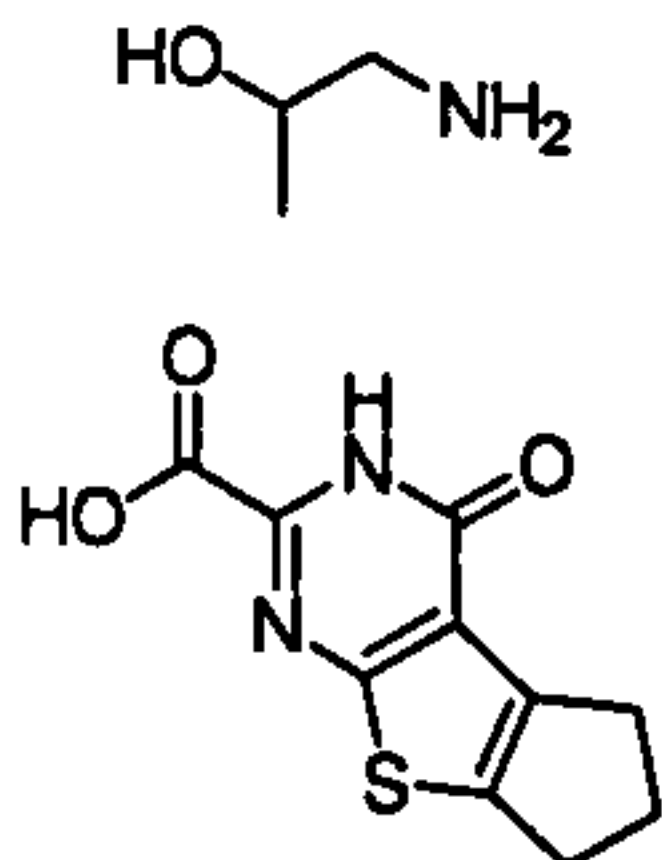
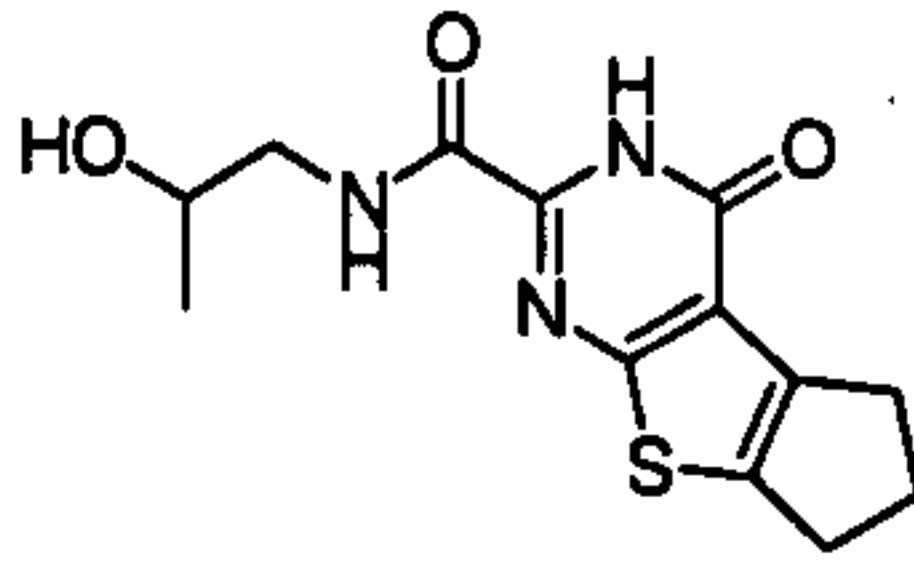
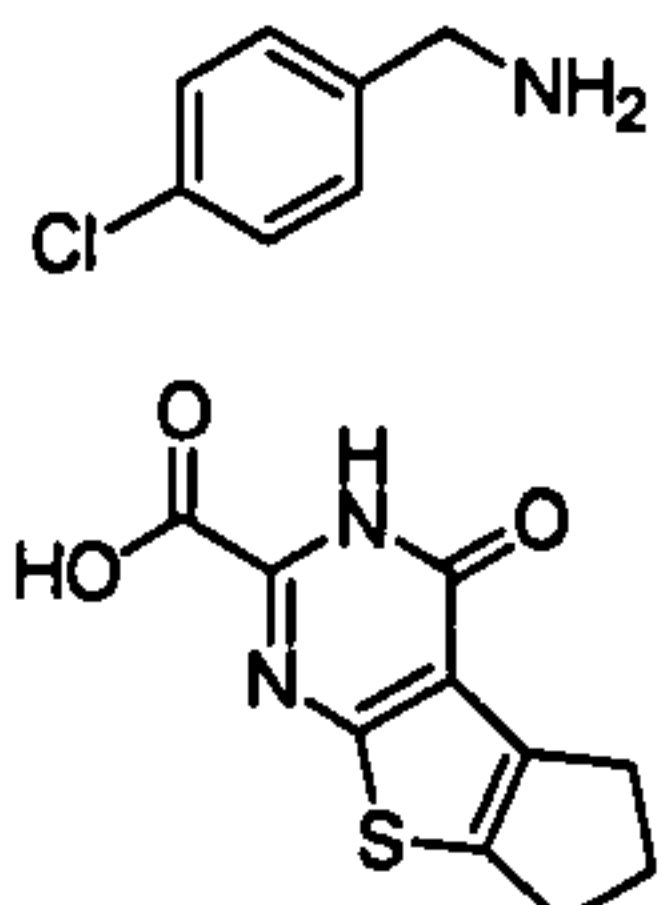
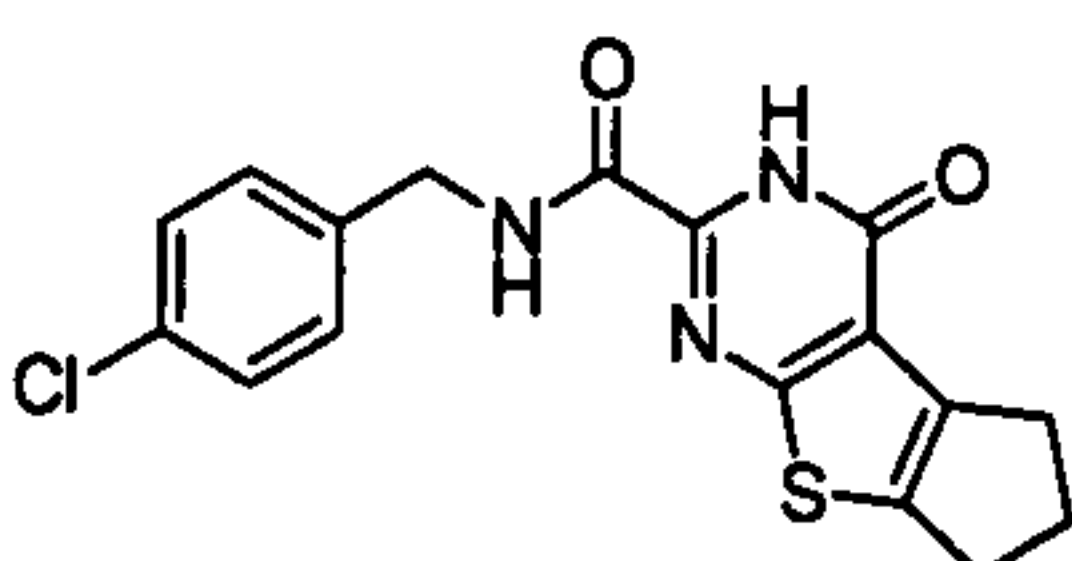
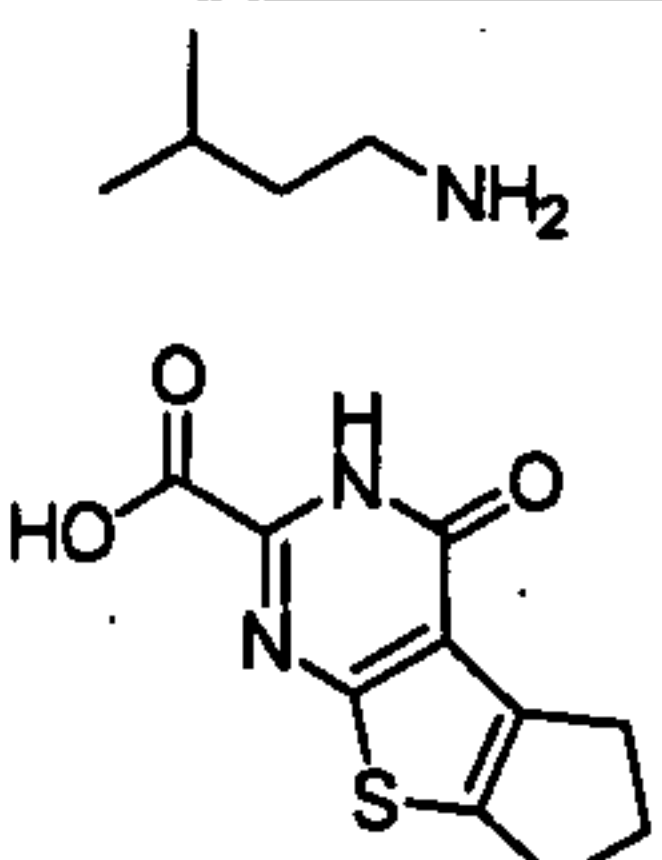
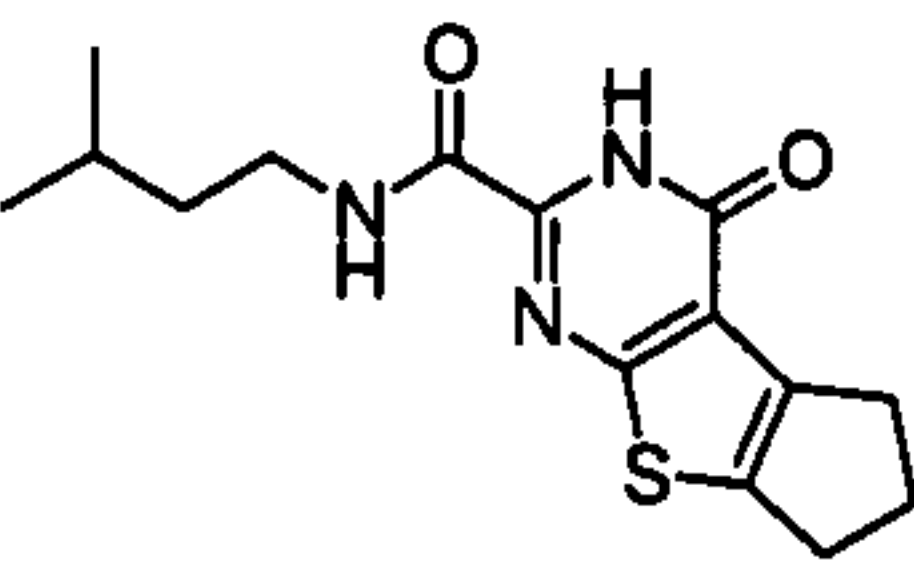
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 2/424 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 368 |
| 2/425 |   |  | B, n.d.<br>[MH] <sup>+</sup> =<br>390    |
| 2/426 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>412    |
| 2/427 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>412    |
| 2/428 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>384    |

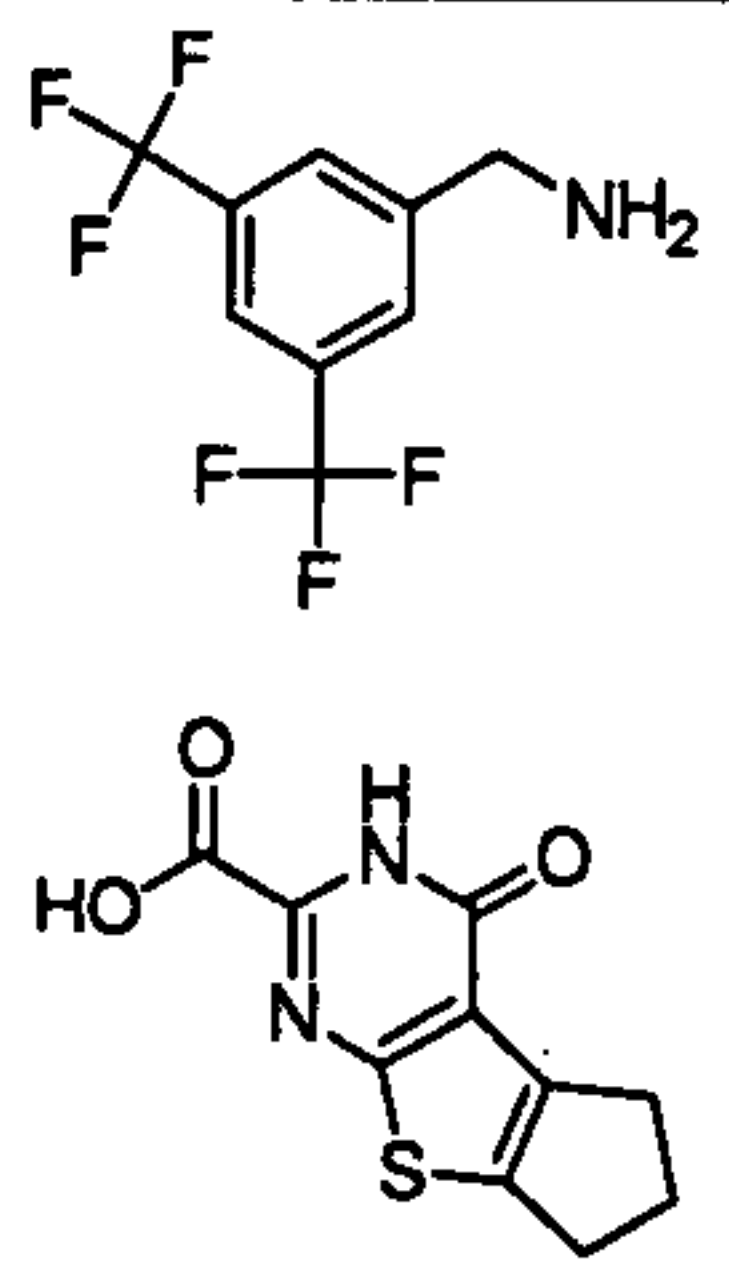
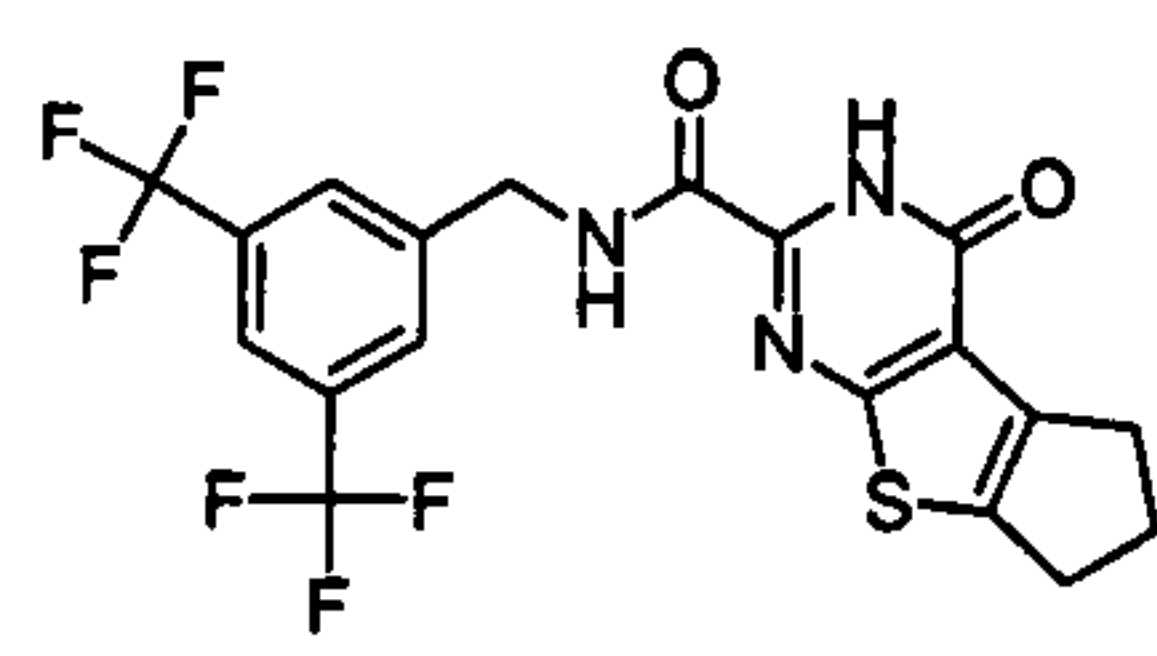
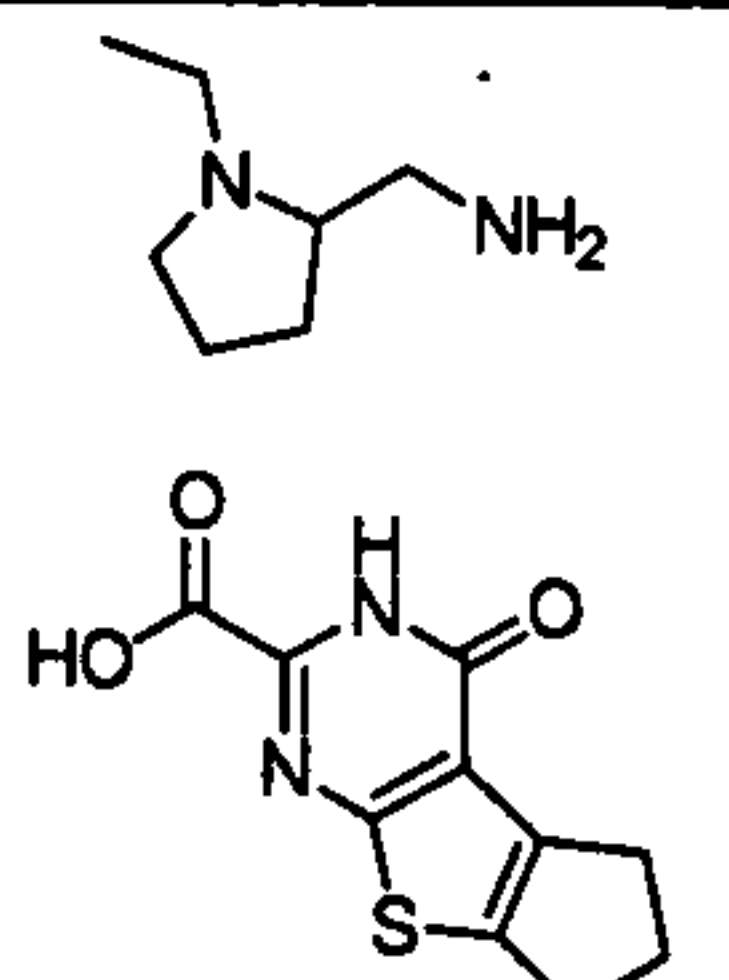
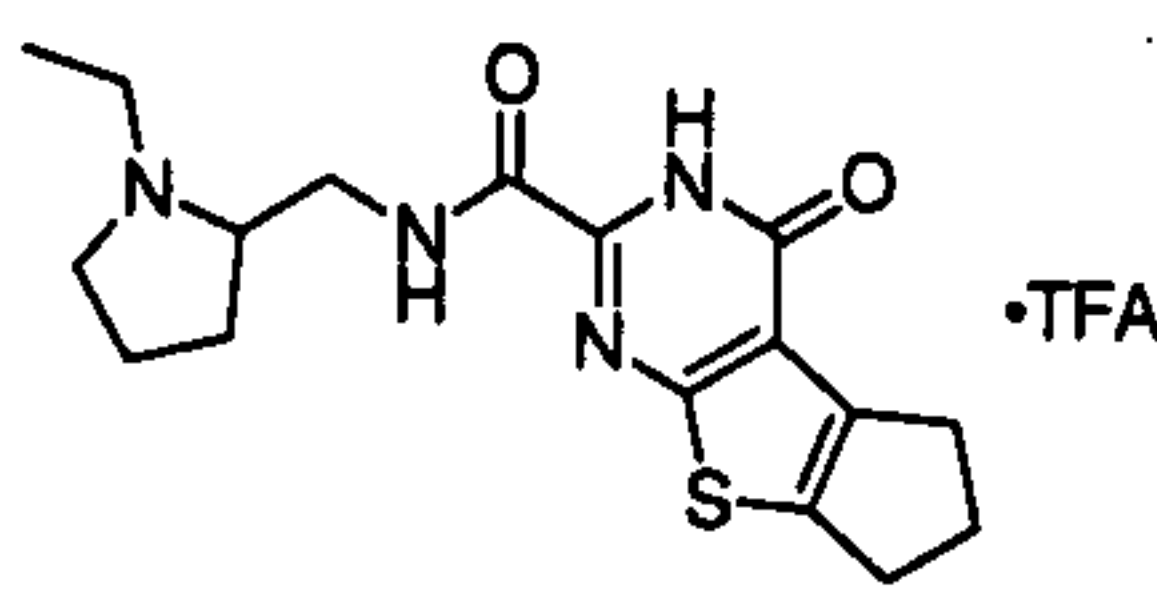
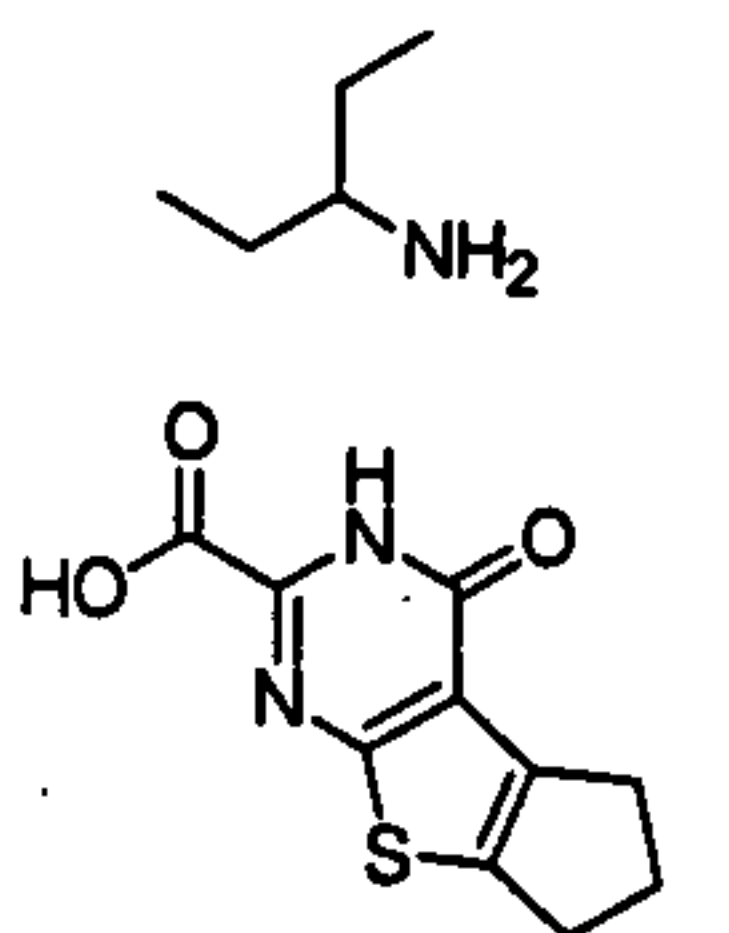
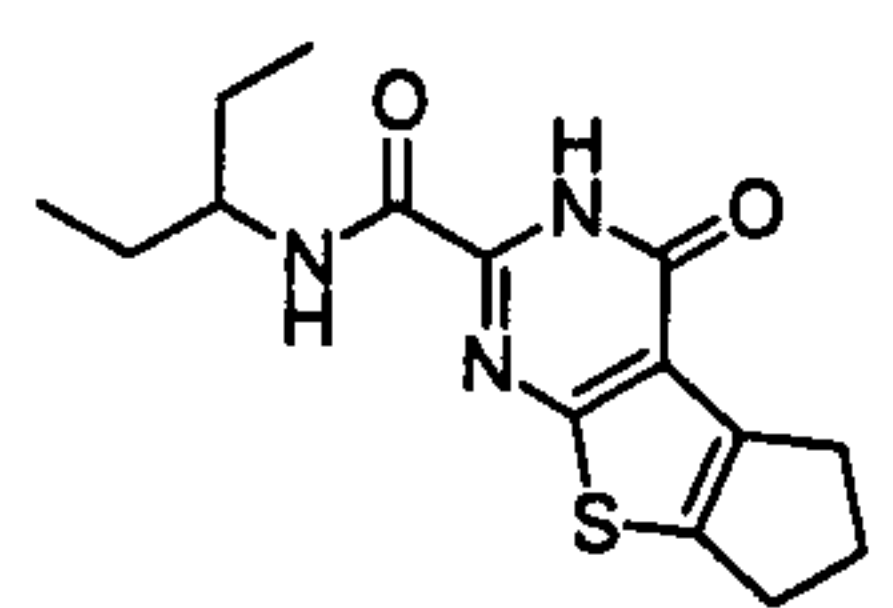
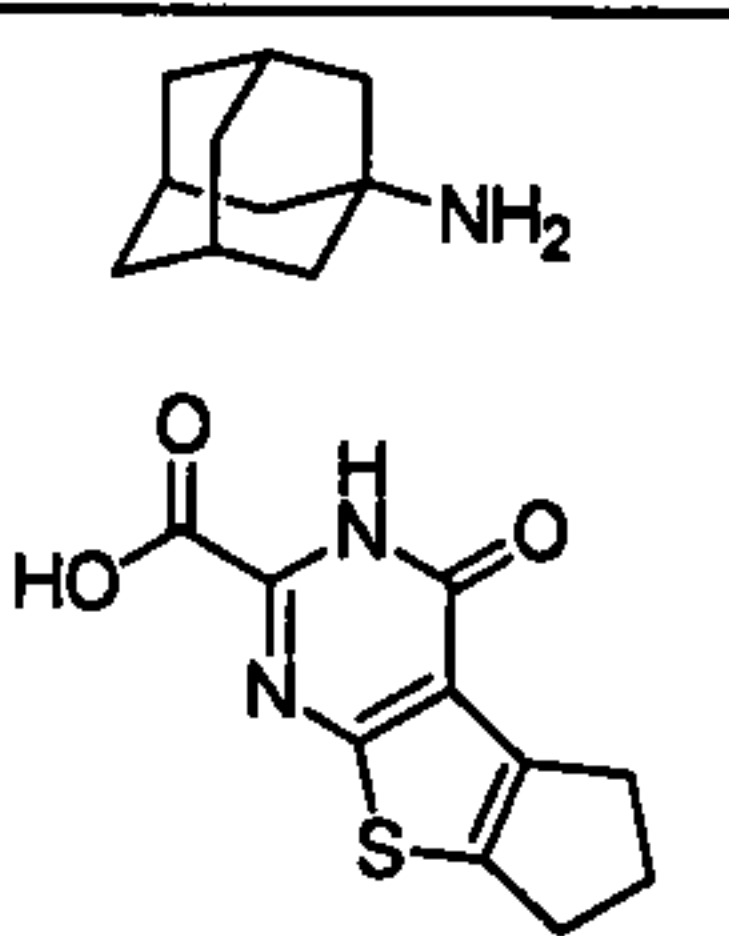
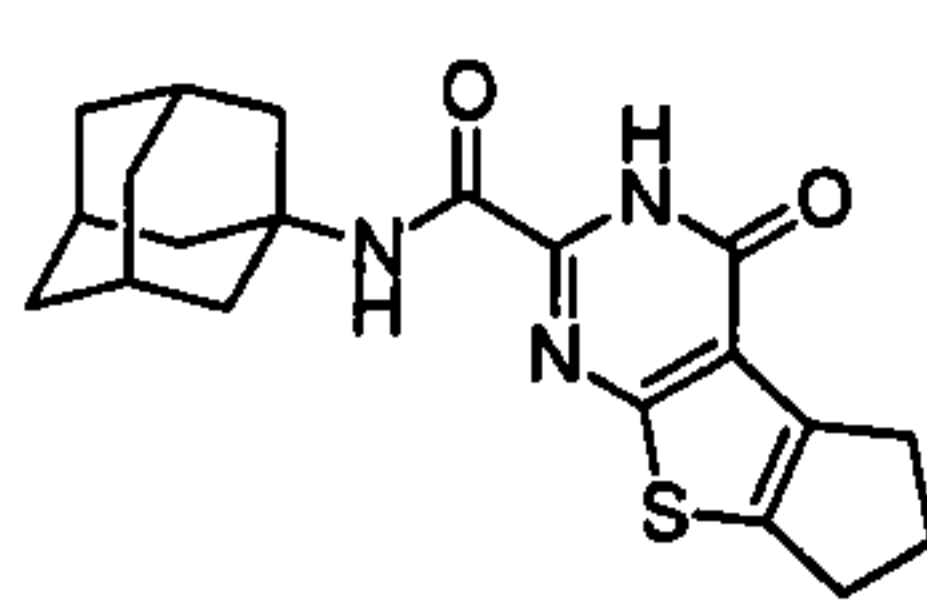
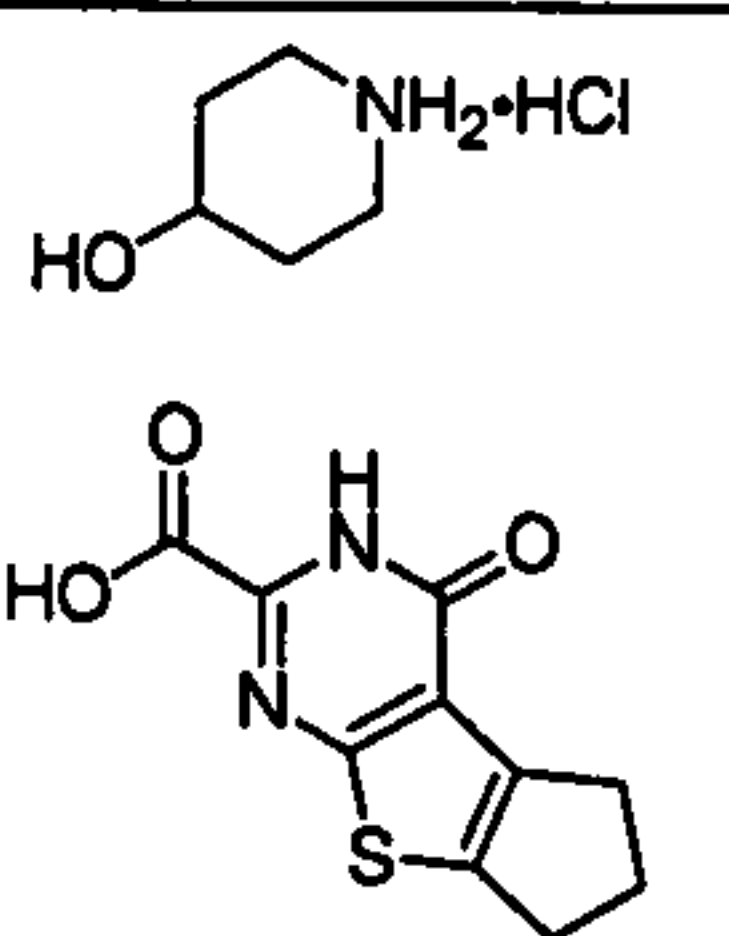
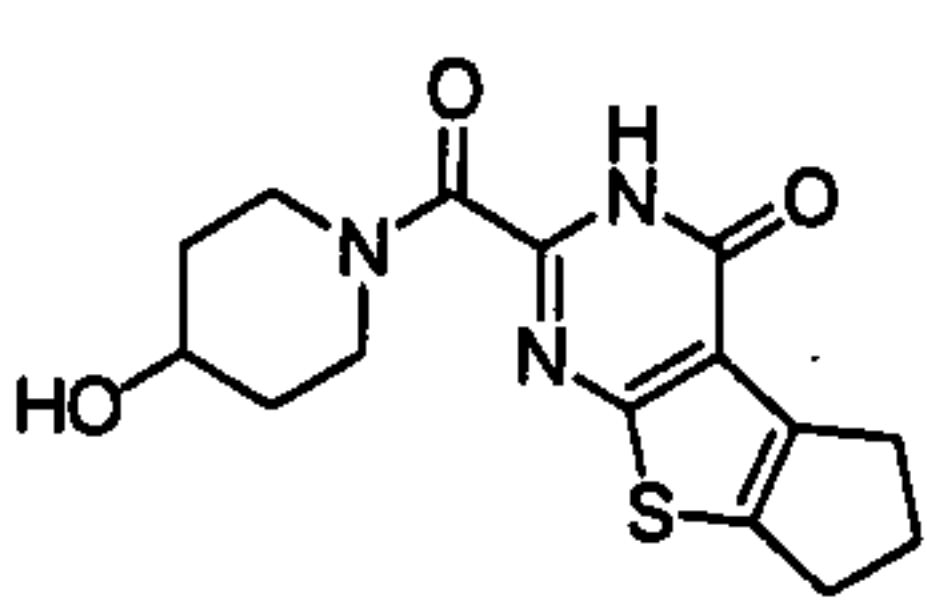
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/429 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 400 |
| 2/430 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 400 |
| 2/431 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 388 |
| 2/432 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 368 |
| 2/433 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 378 |

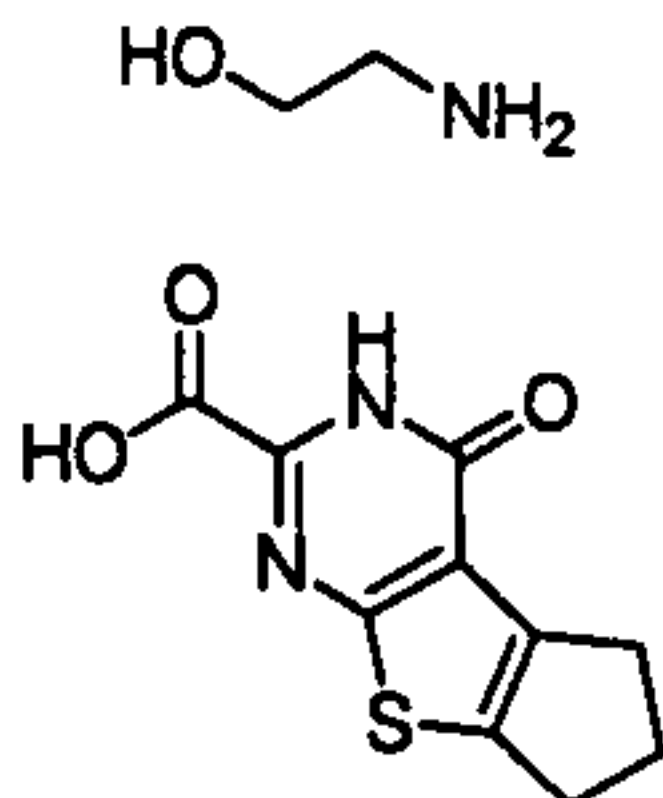
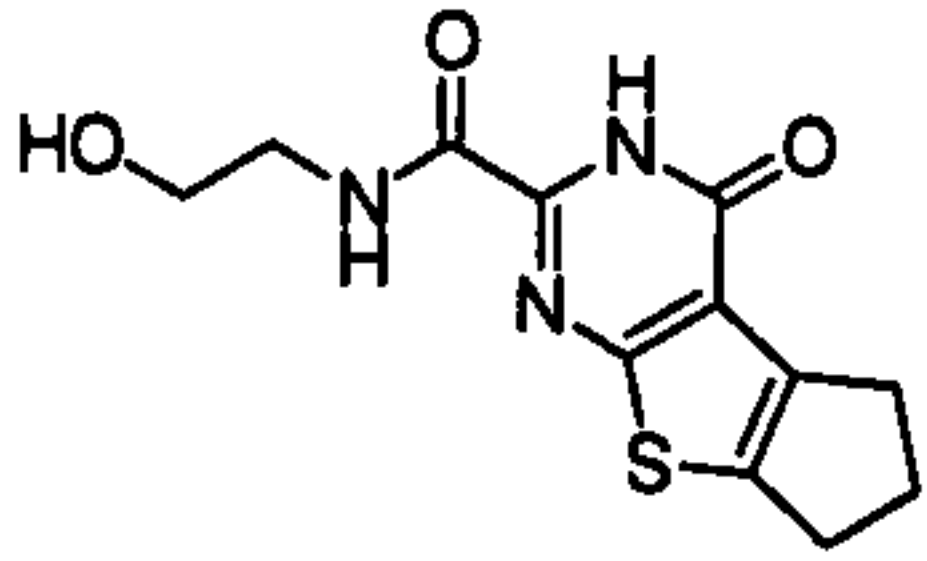
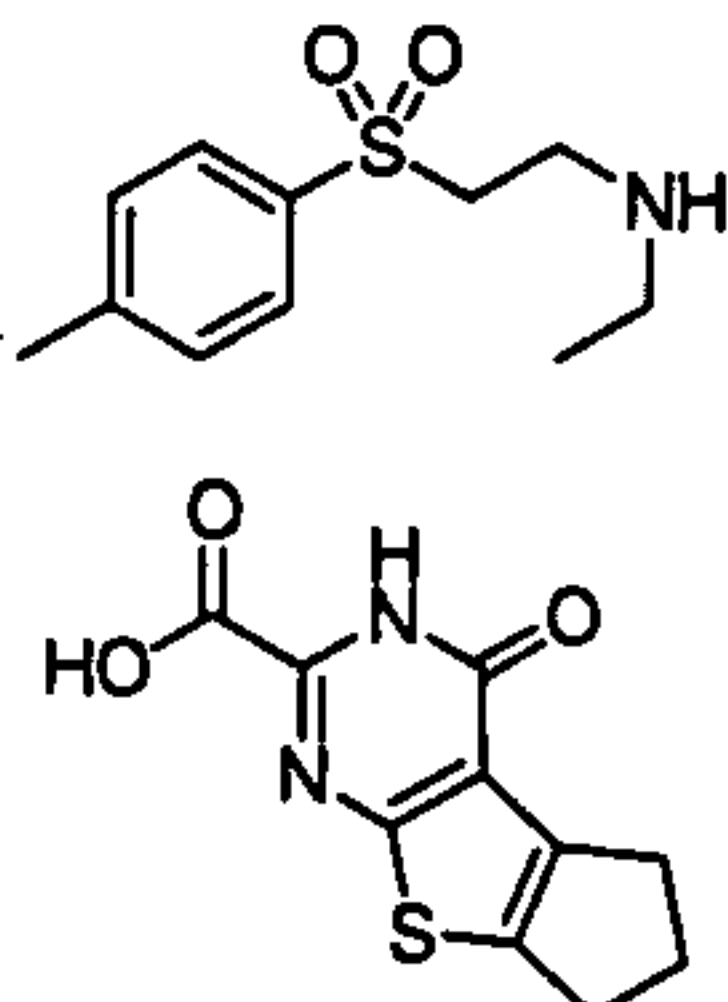
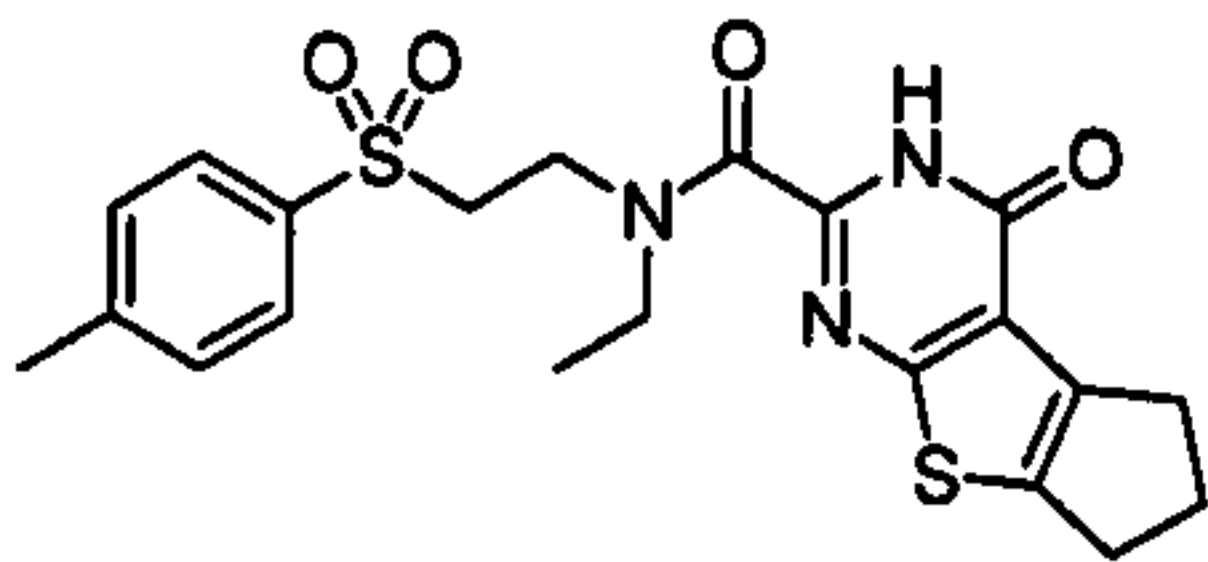
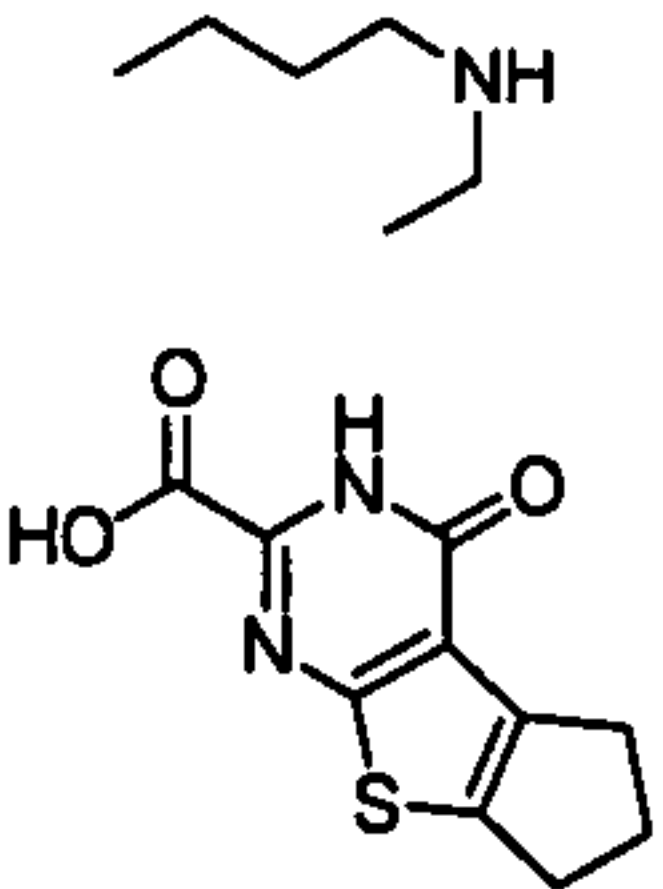
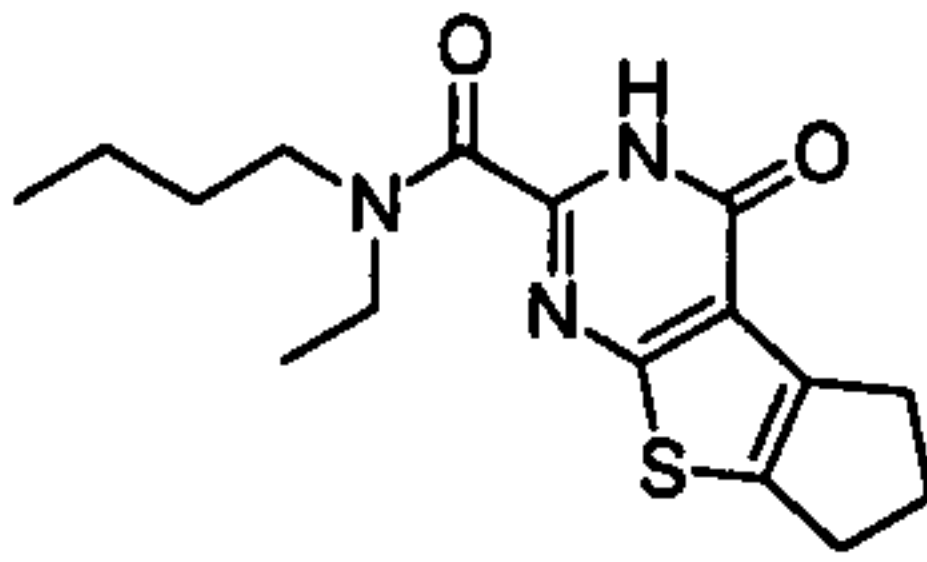
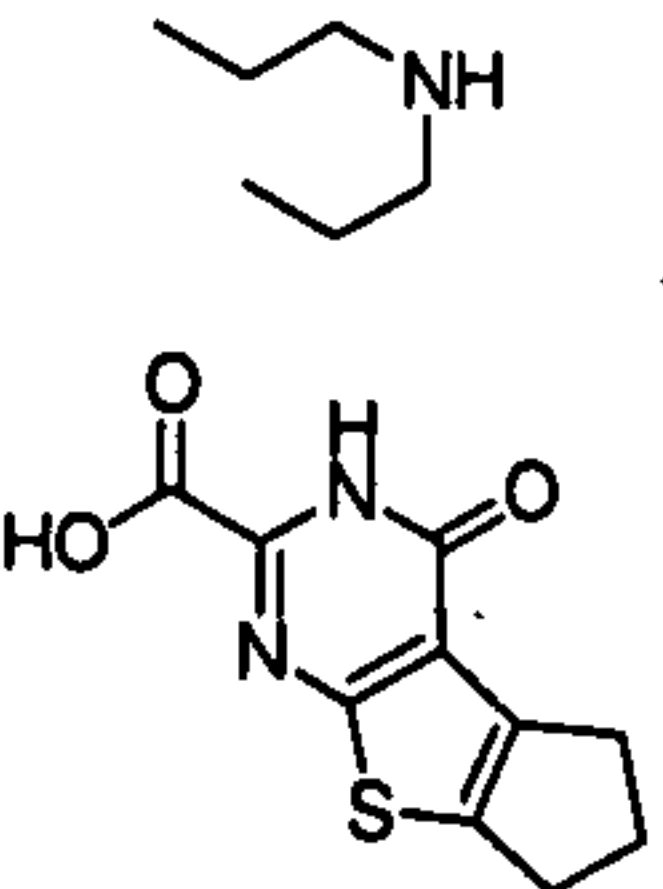
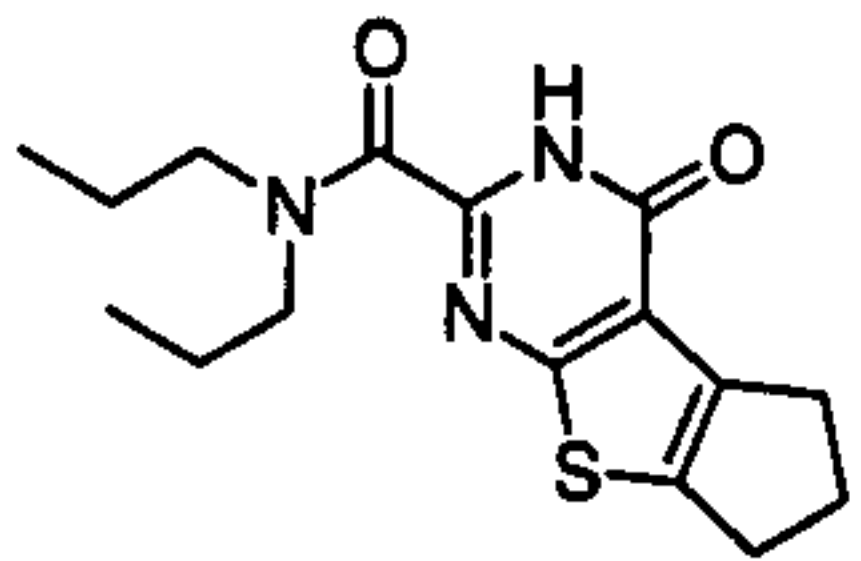
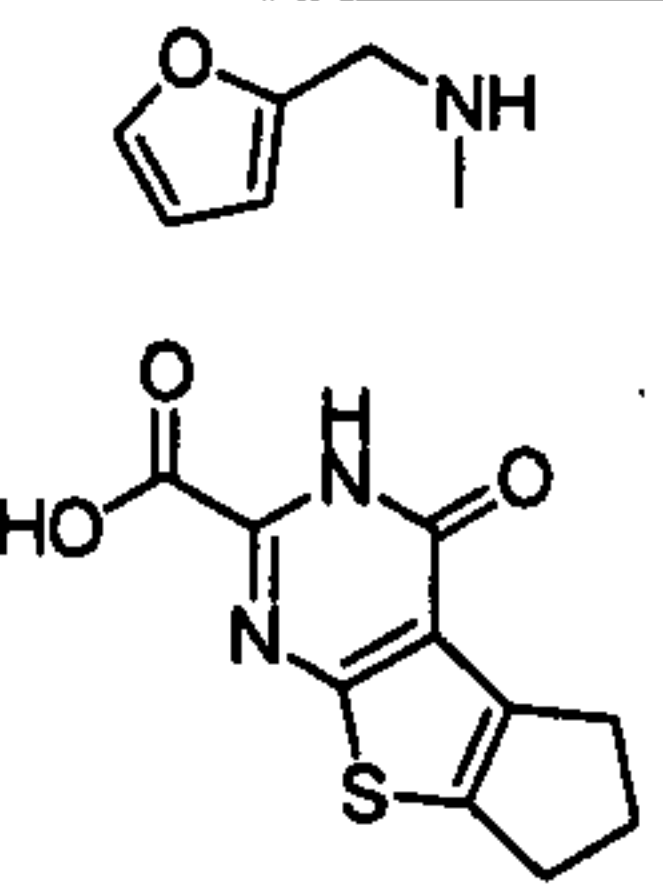
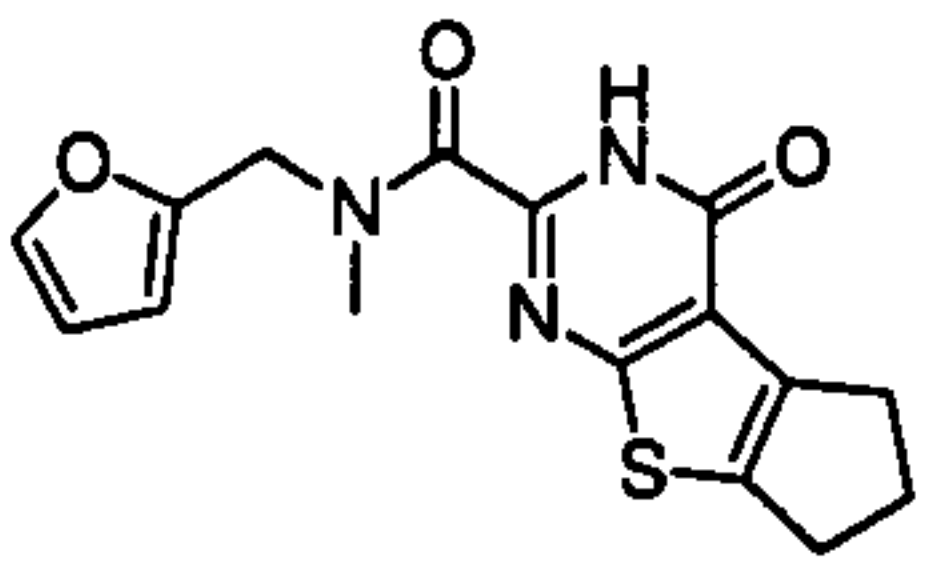
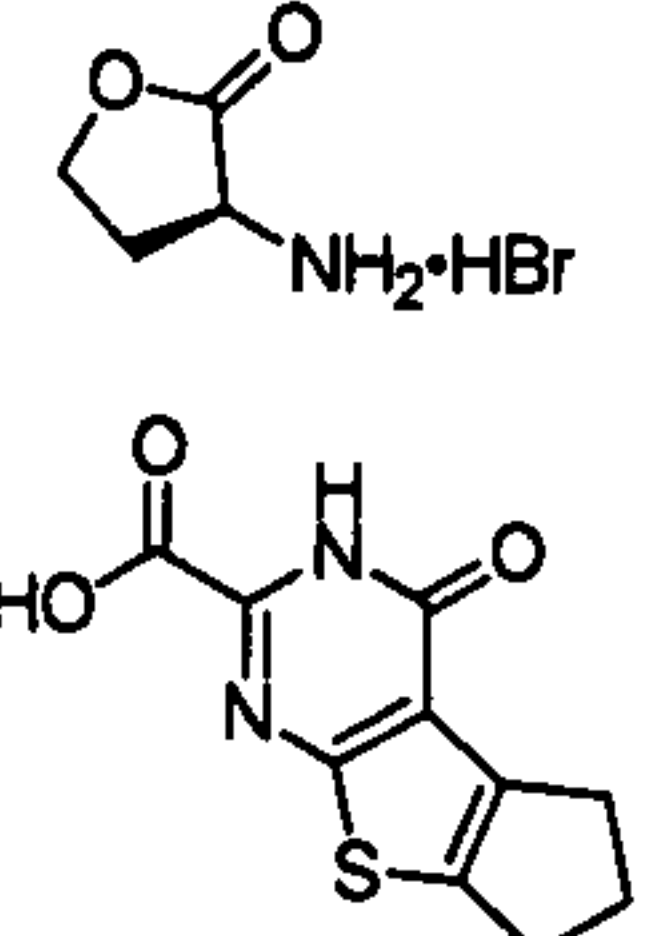
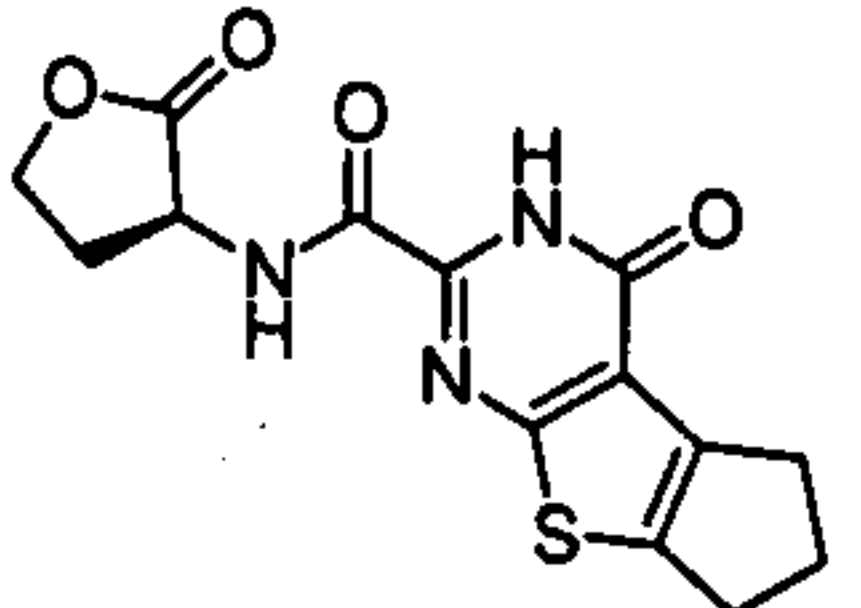
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                          |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------|
| 2/434 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 342     |
| 2/435 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 420/422 |
| 2/436 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 425     |
| 2/437 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 395     |
| 2/438 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 402     |

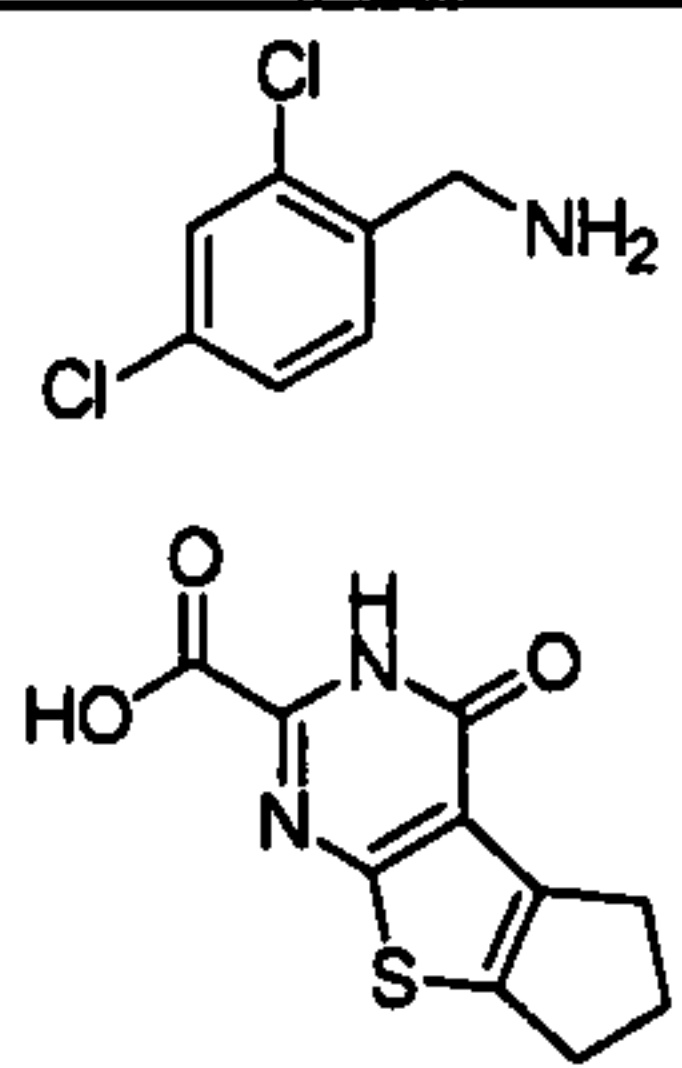
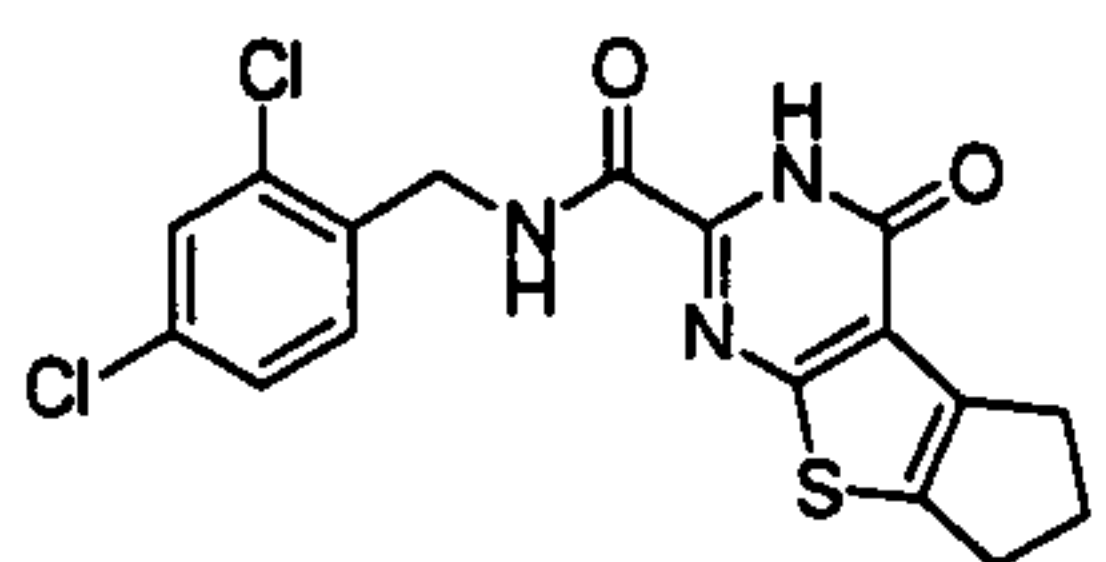
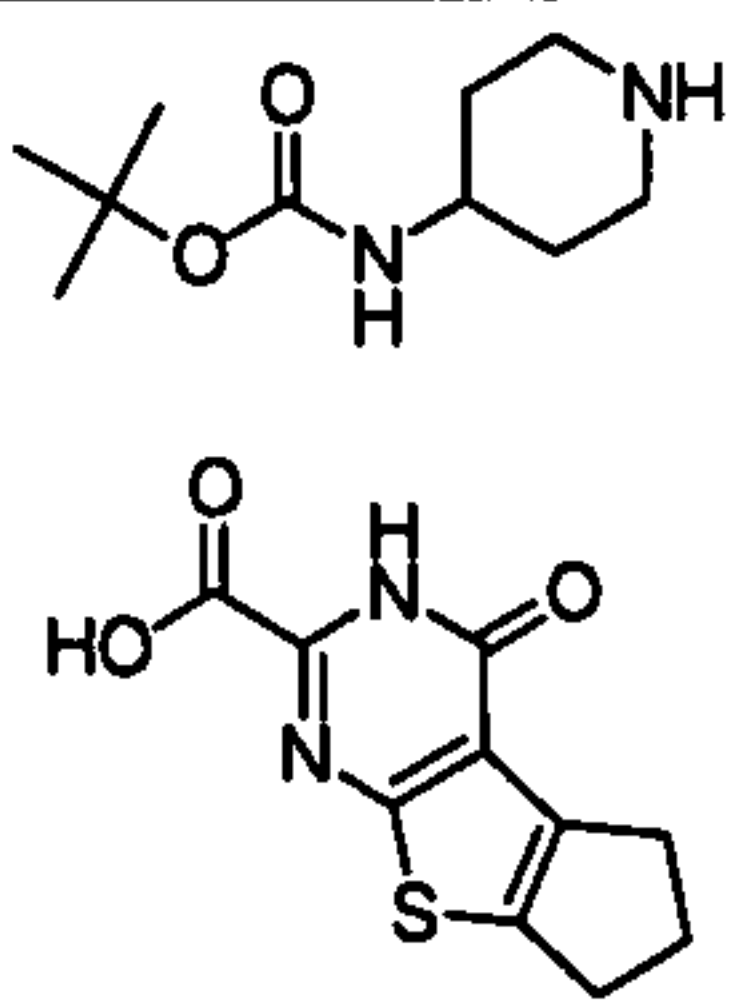
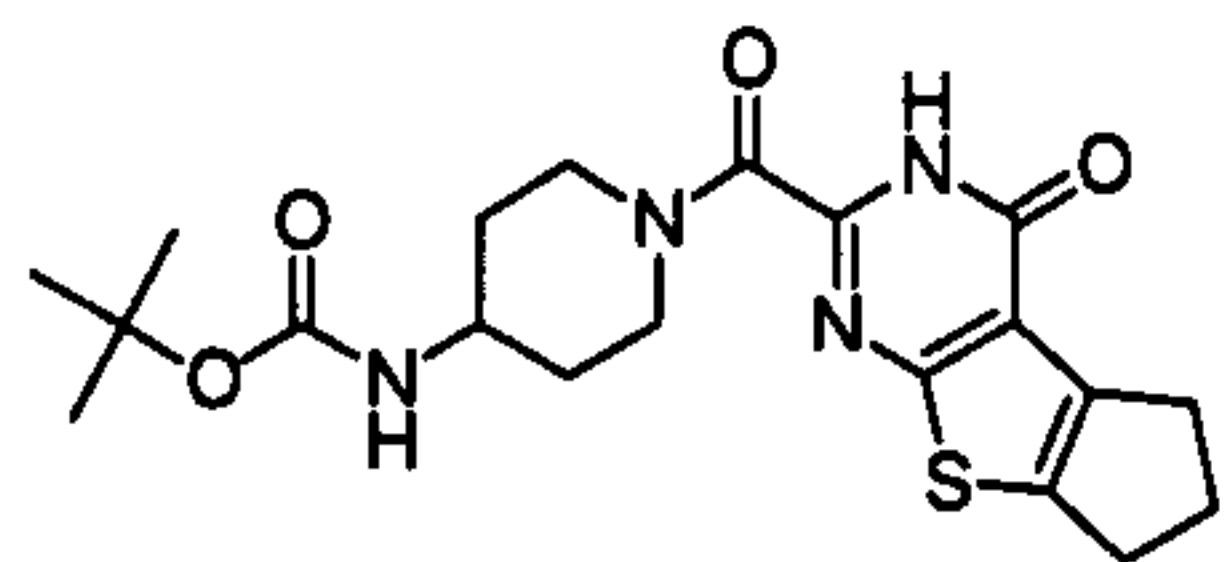
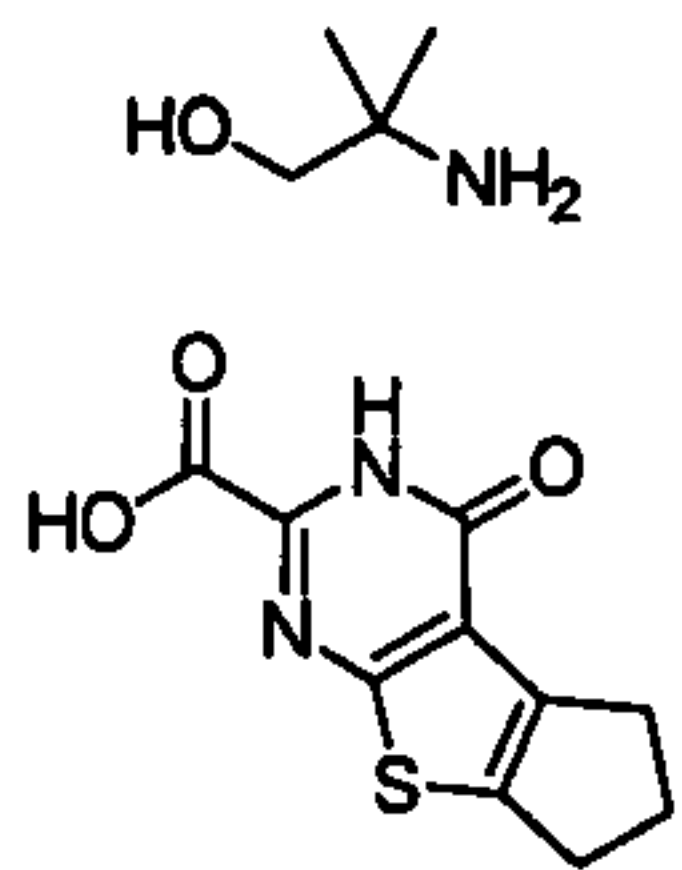
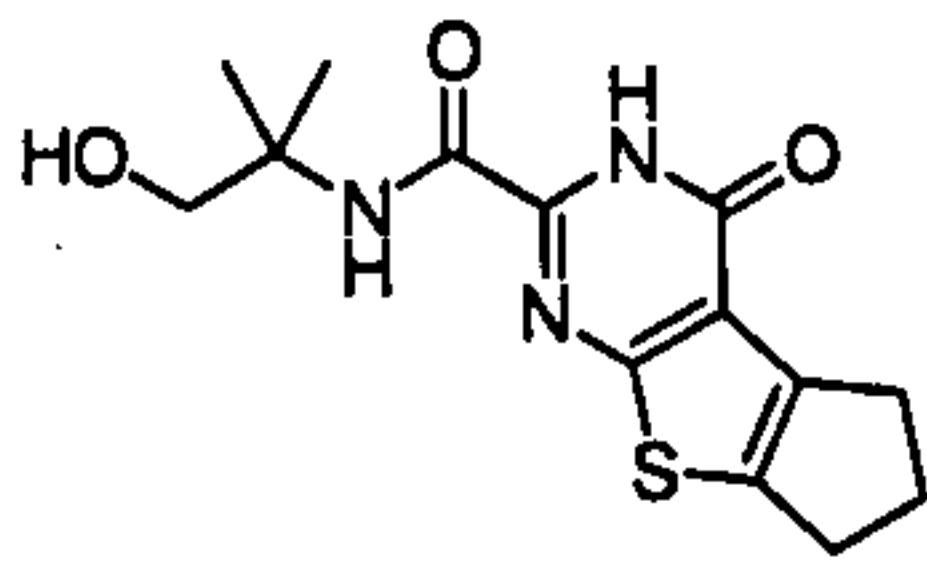
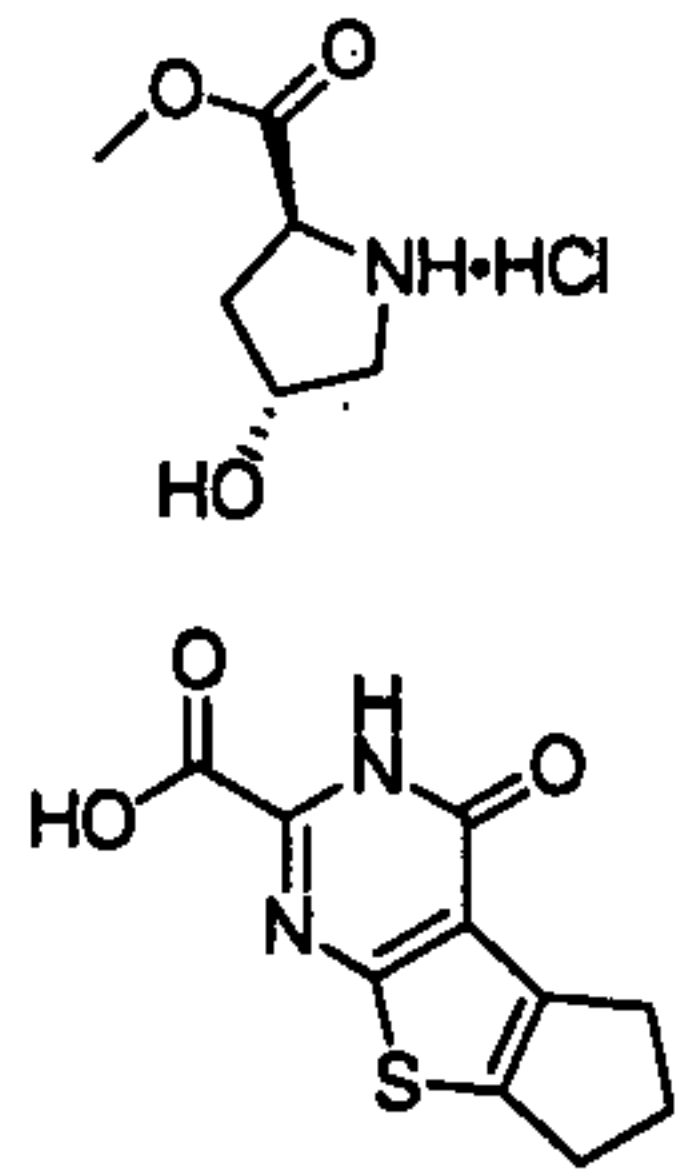
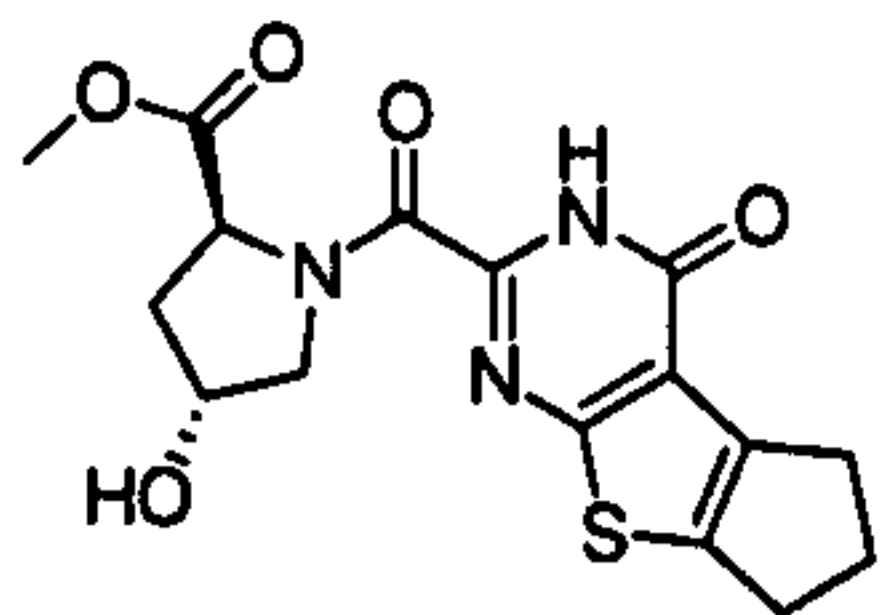
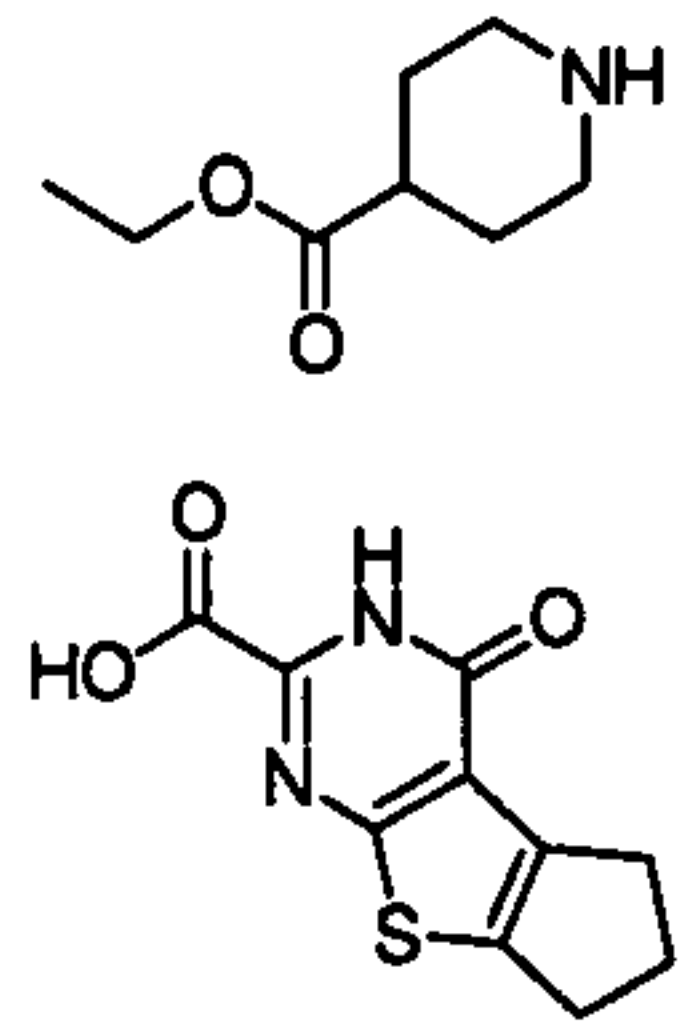
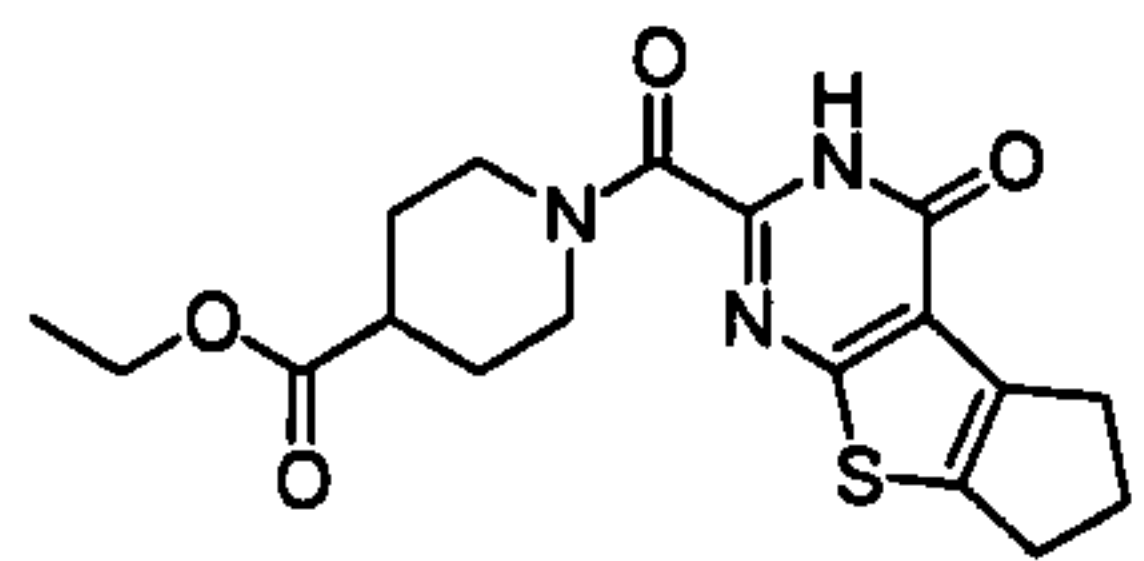
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/439 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 412    |
| 2/440 |   |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 365 |
| 2/441 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 392    |
| 2/442 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 392    |
| 2/443 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 351    |

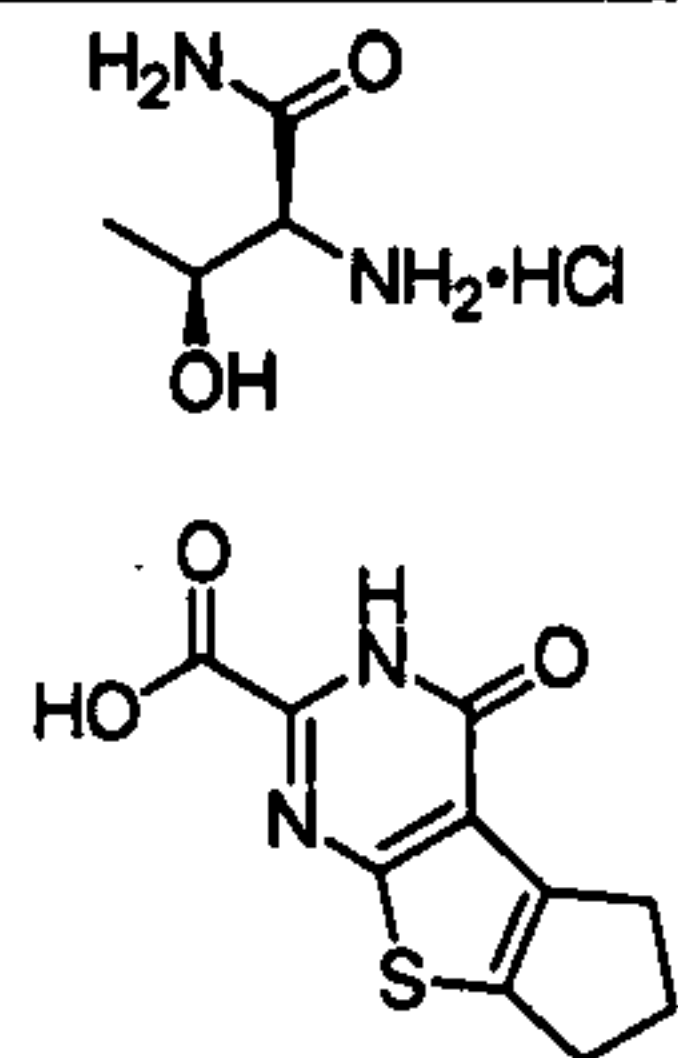
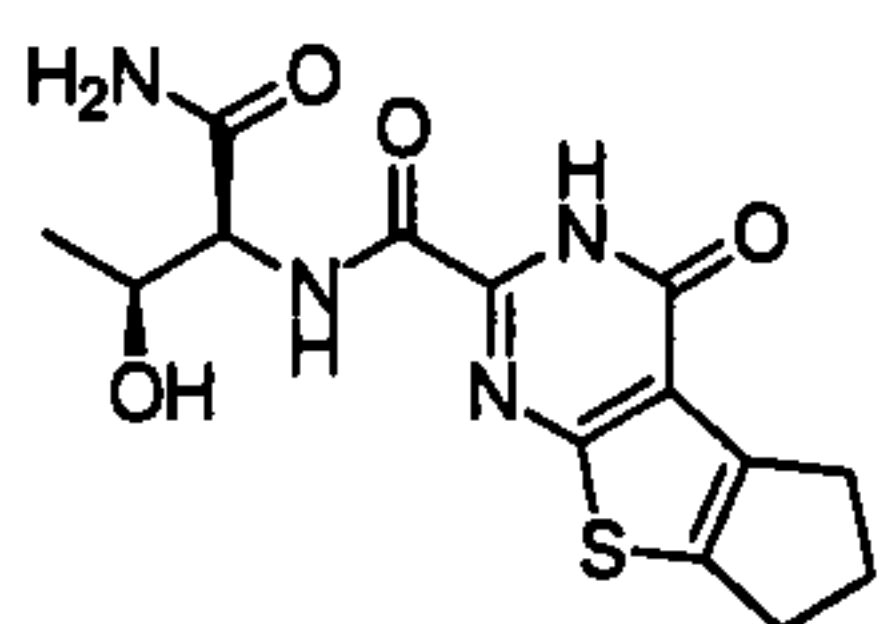
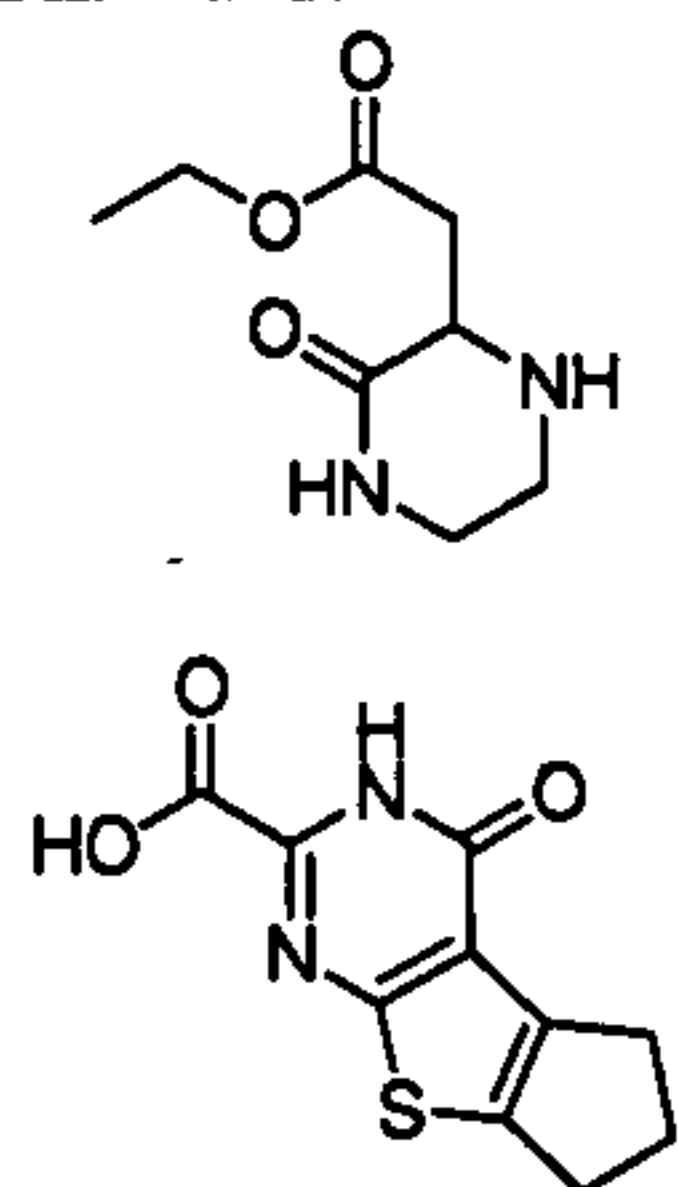
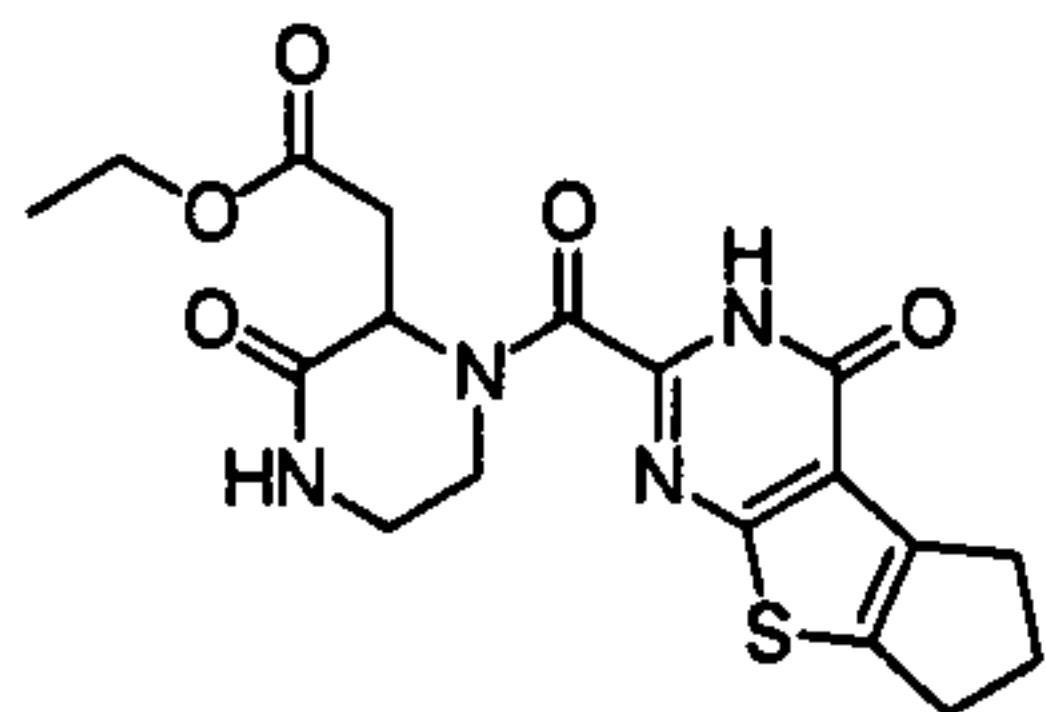
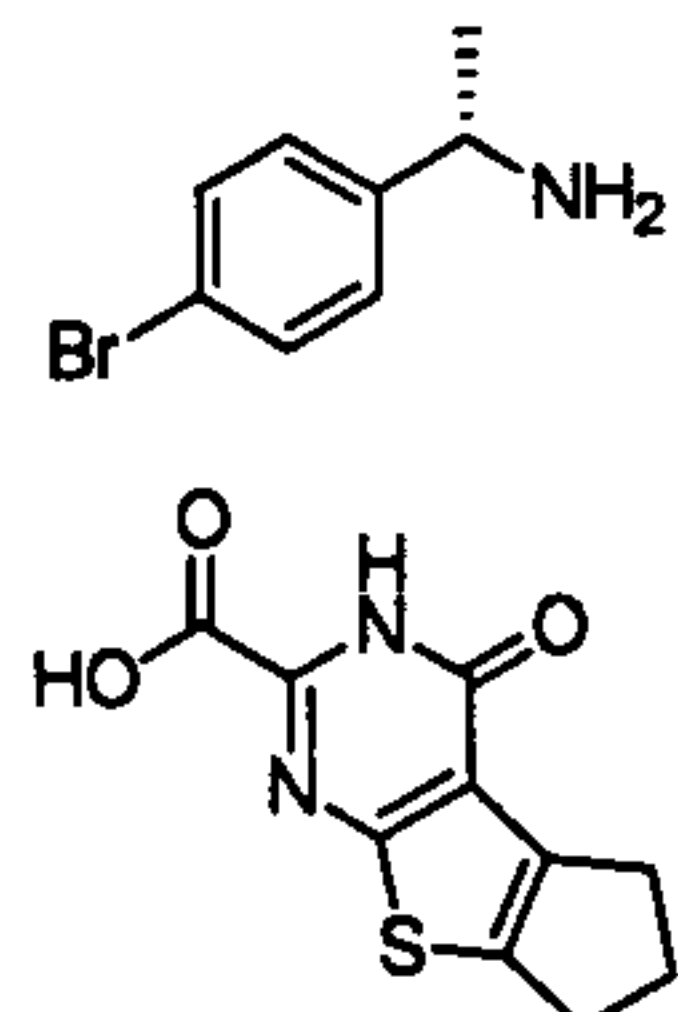
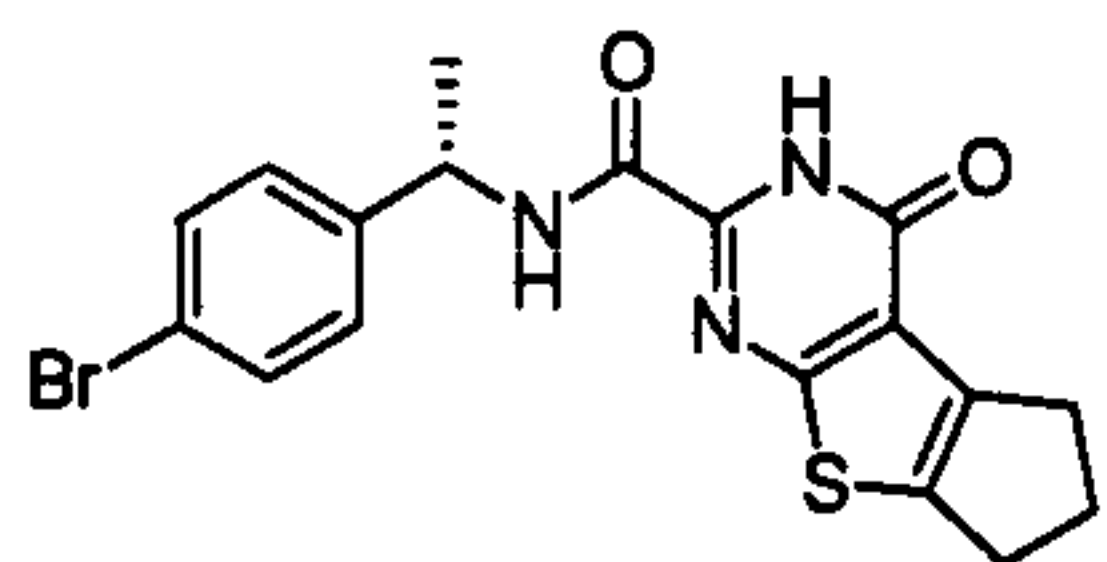
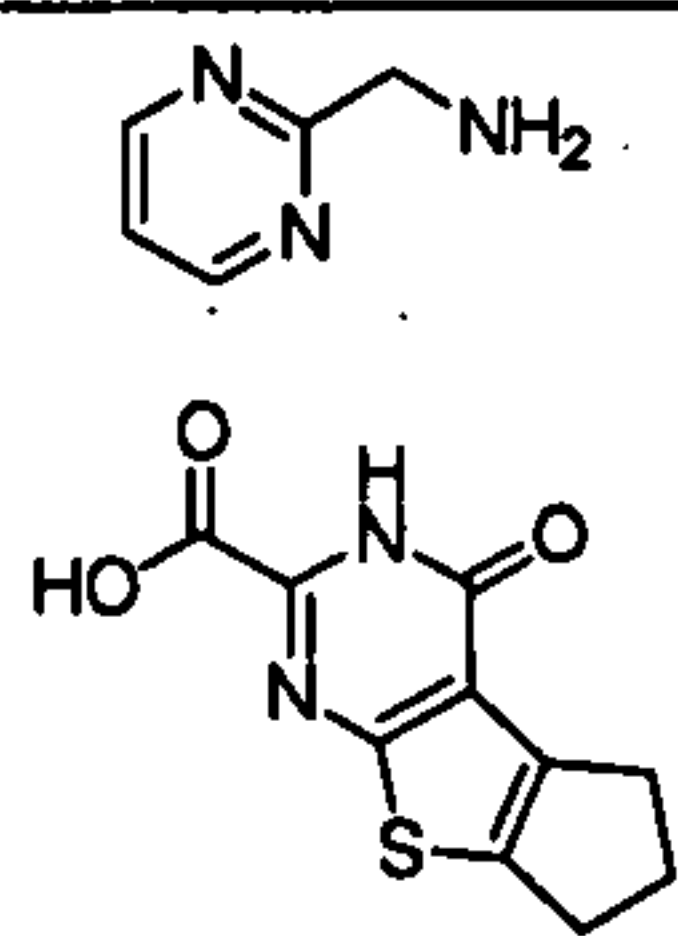
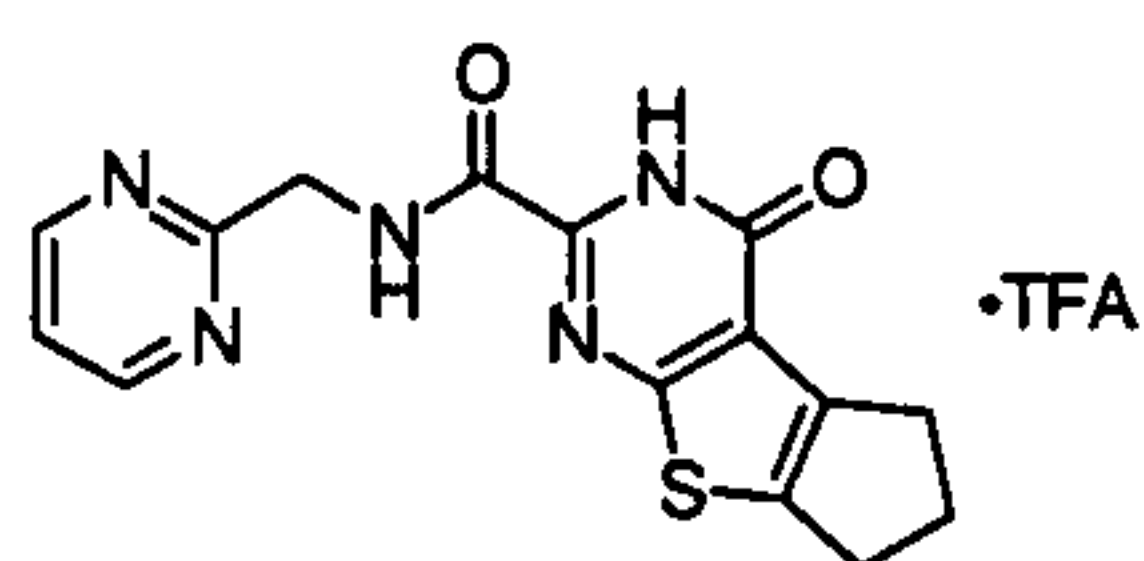
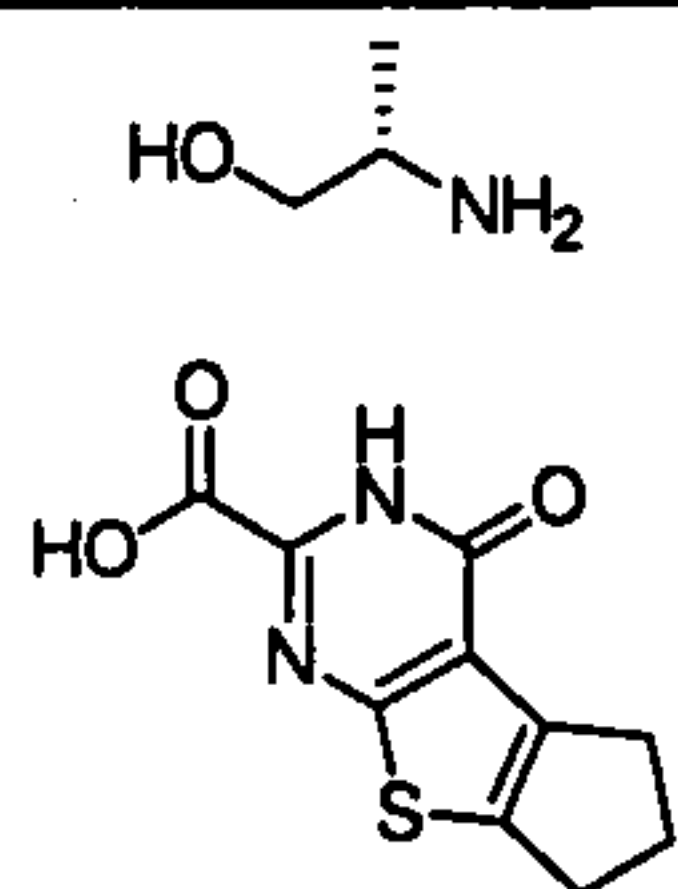
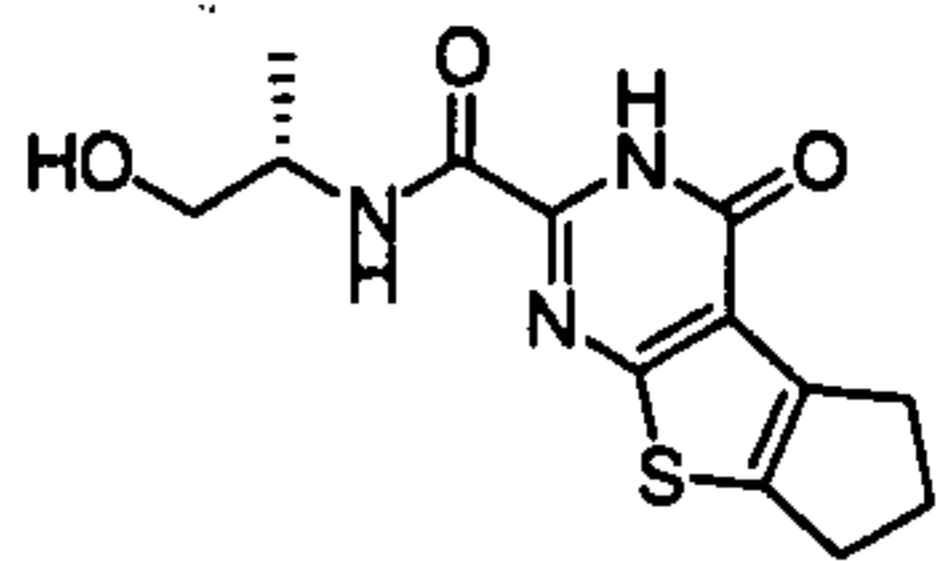
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/444 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 388 |
| 2/445 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 404 |
| 2/446 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 455 |
| 2/447 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 384 |
| 2/448 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 419 |

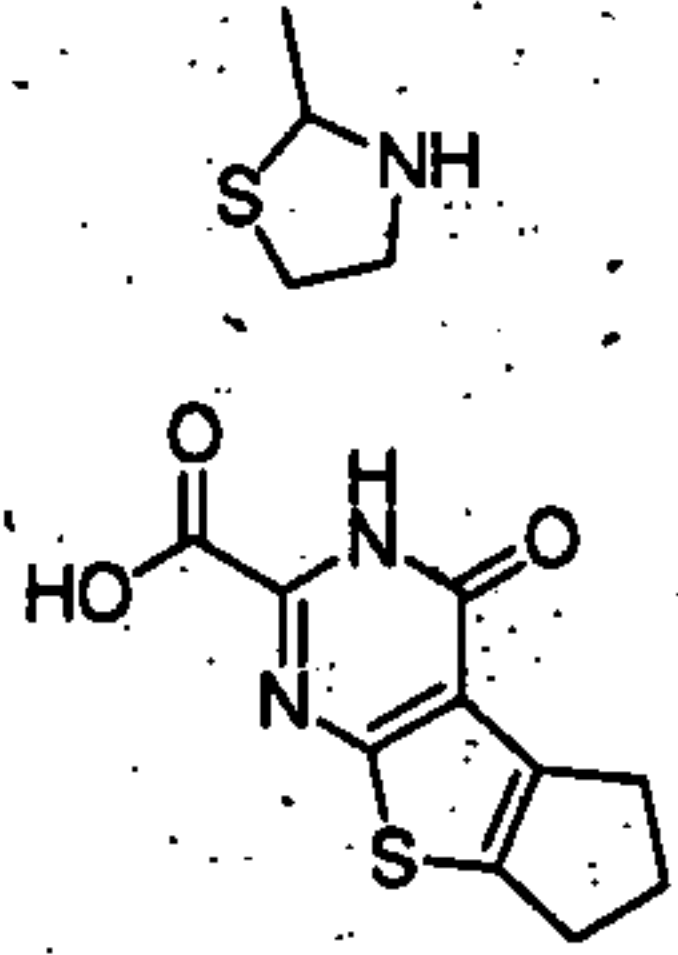
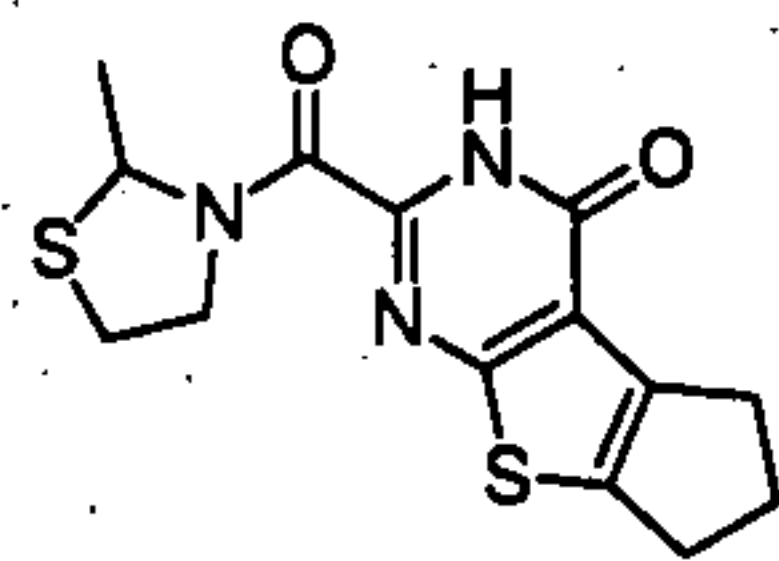
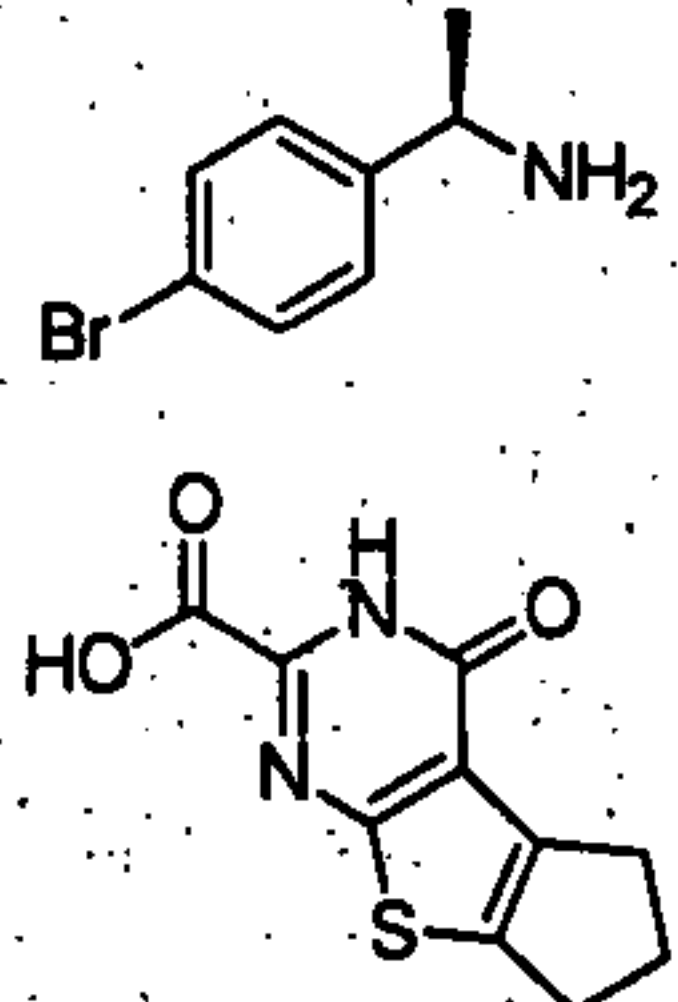
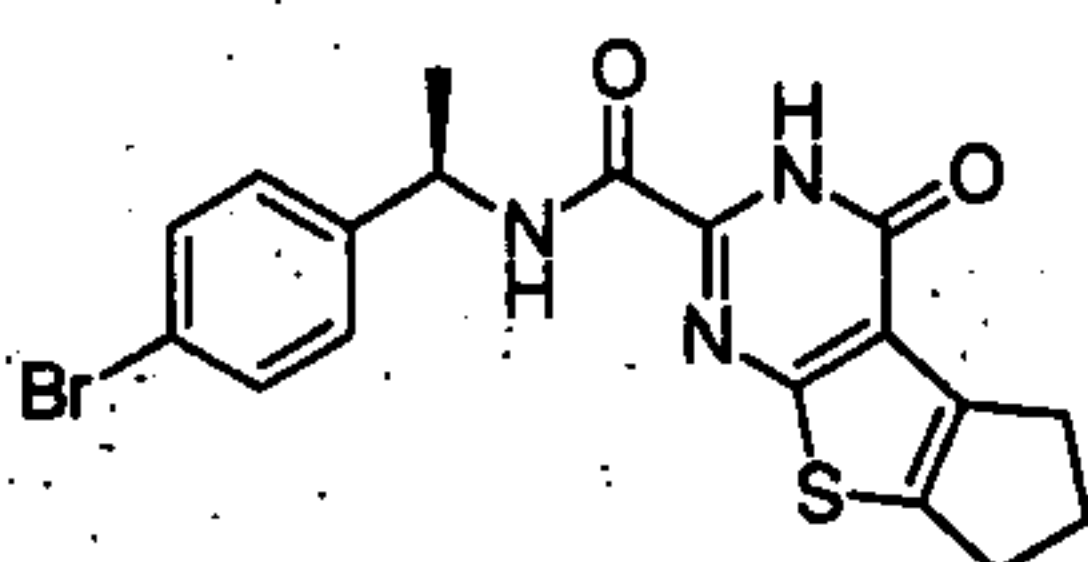
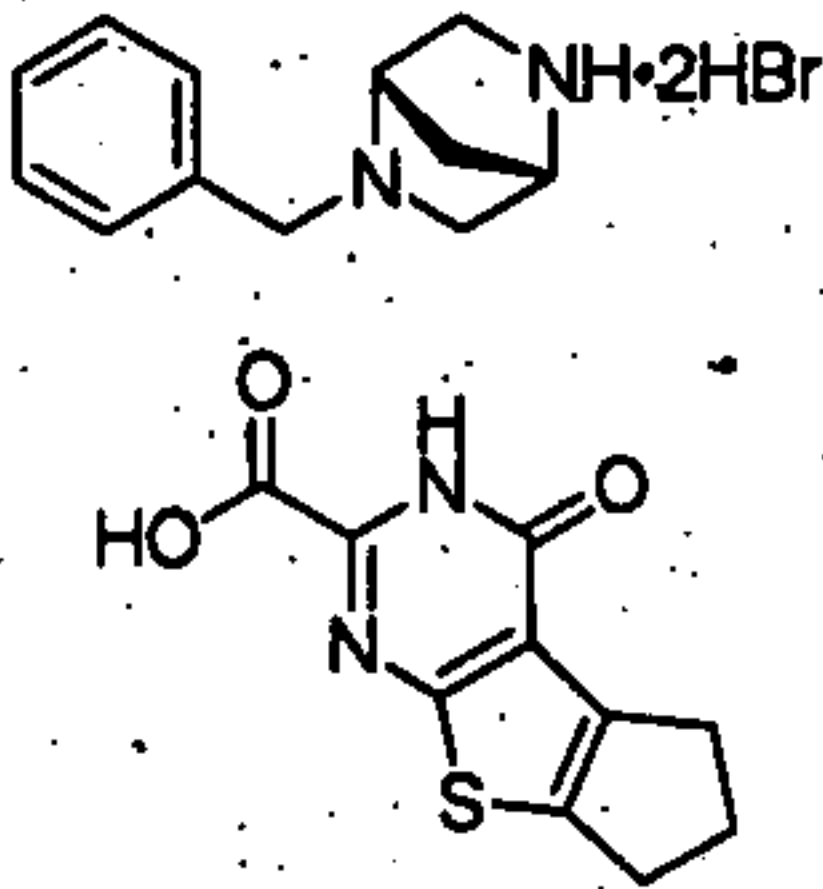
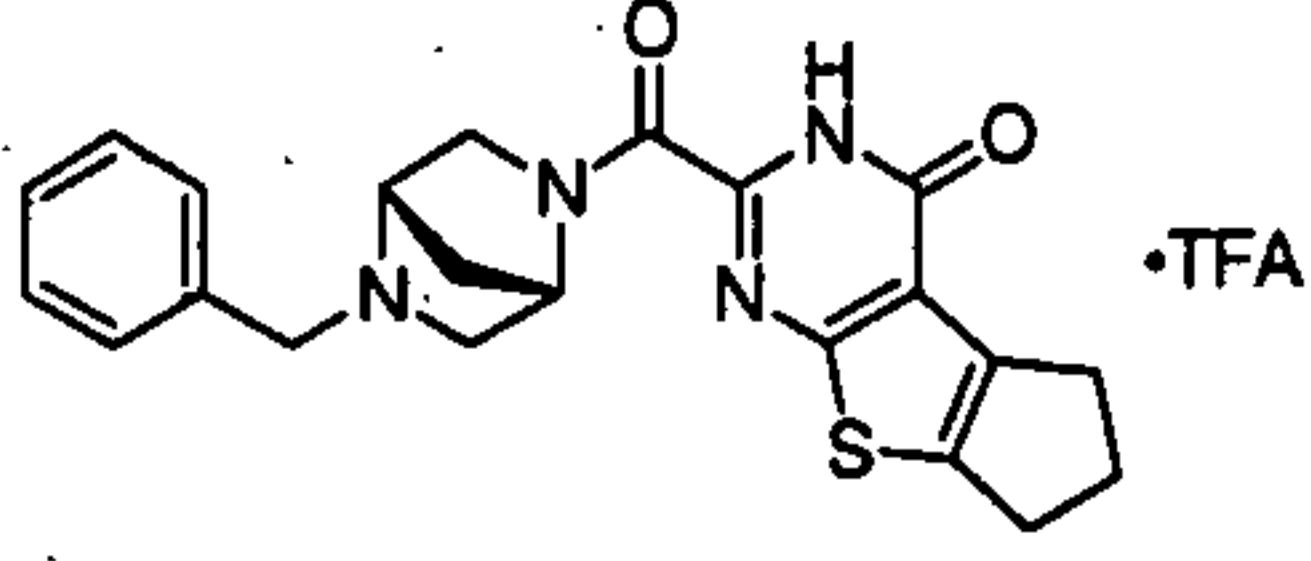
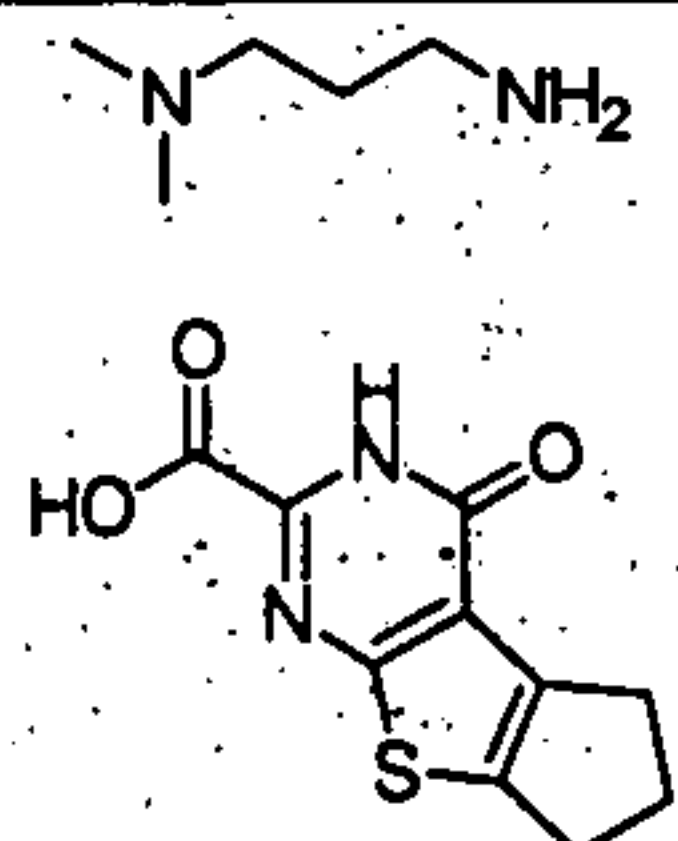
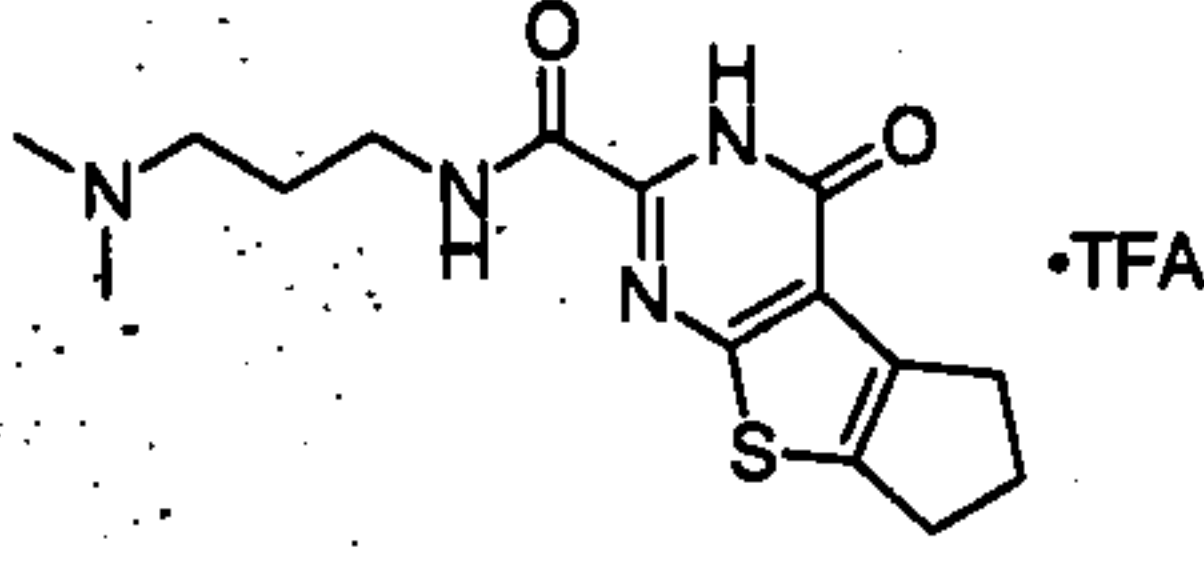
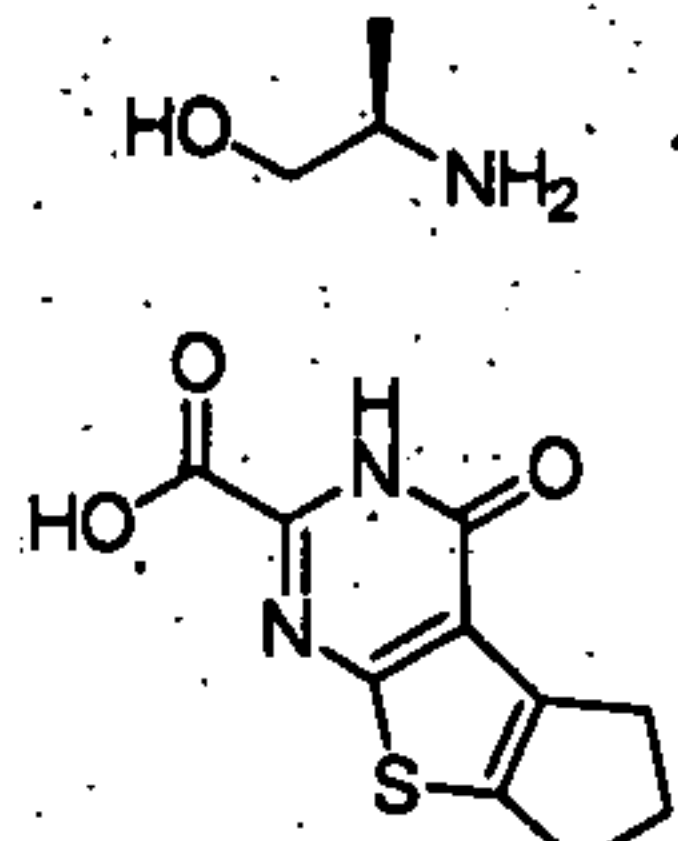
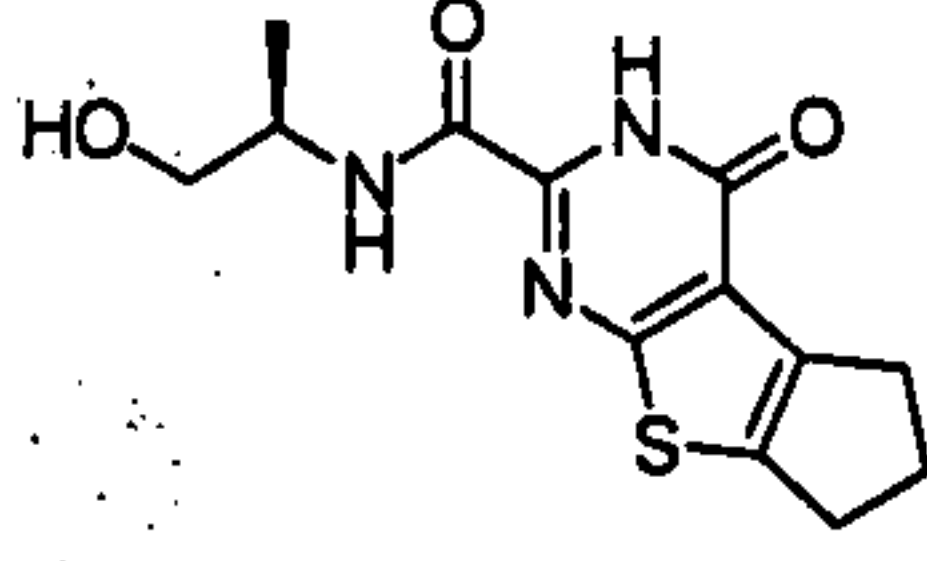
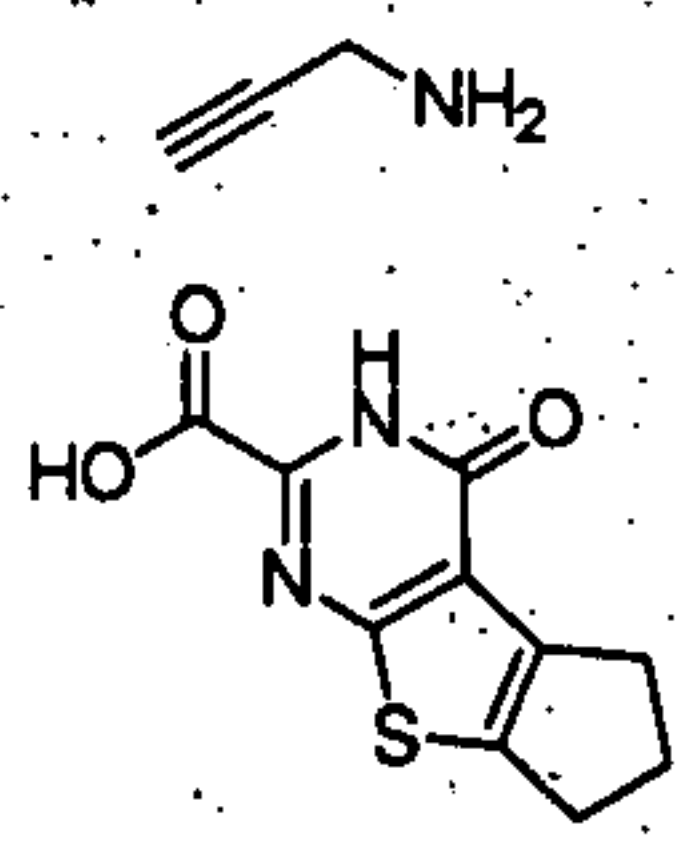
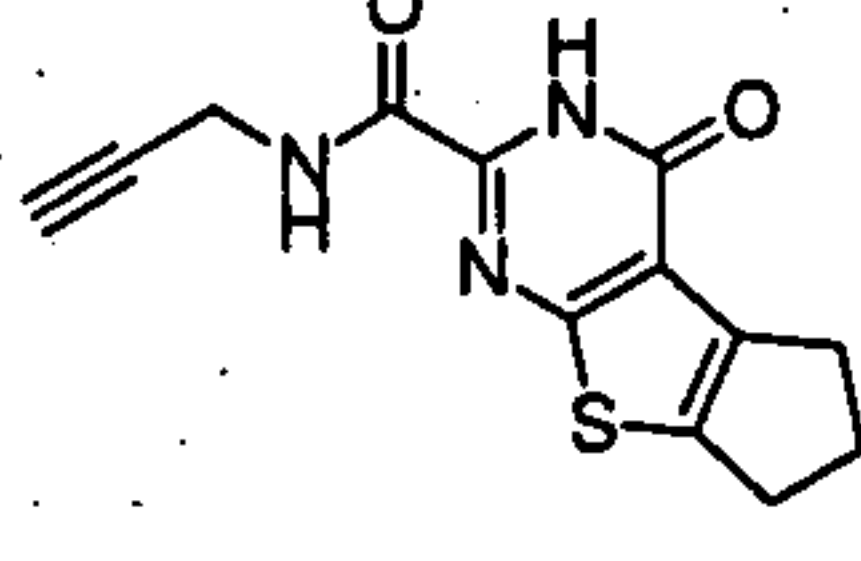
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/449 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 384    |
| 2/450 |   |   | B, n.d.<br>[M-TFA] <sup>+</sup> = 357 |
| 2/451 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 294    |
| 2/452 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 360    |
| 2/453 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 306    |

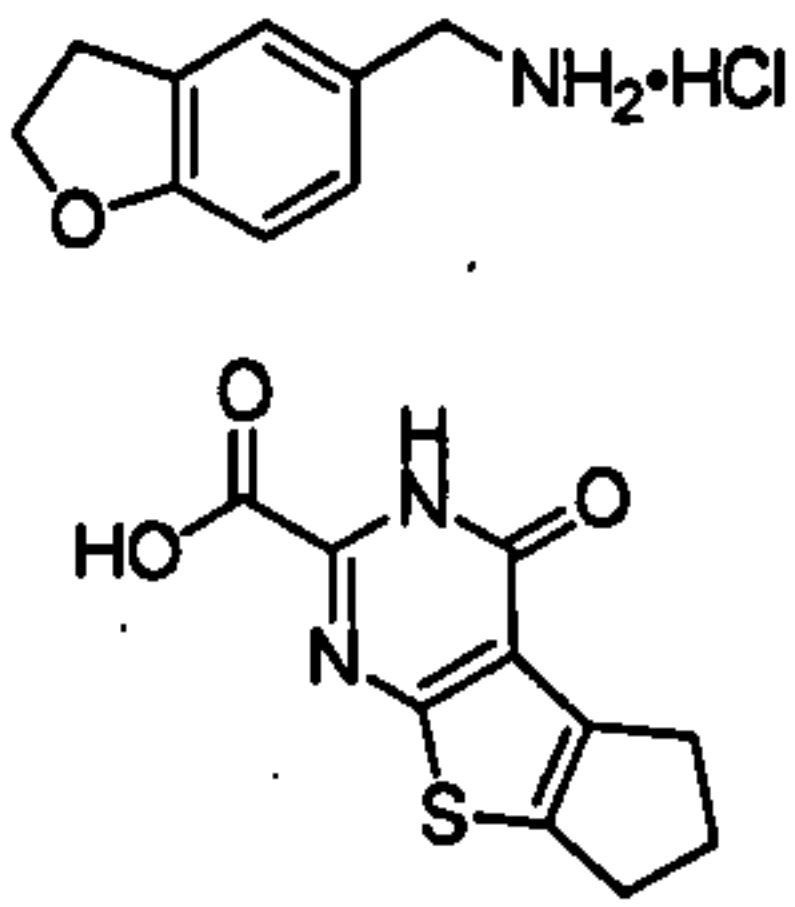
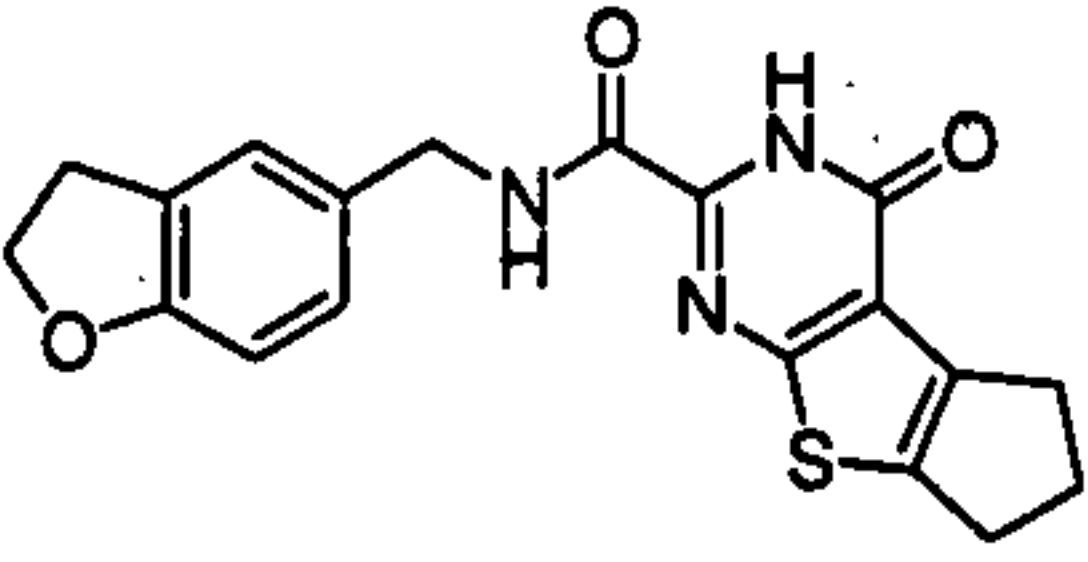
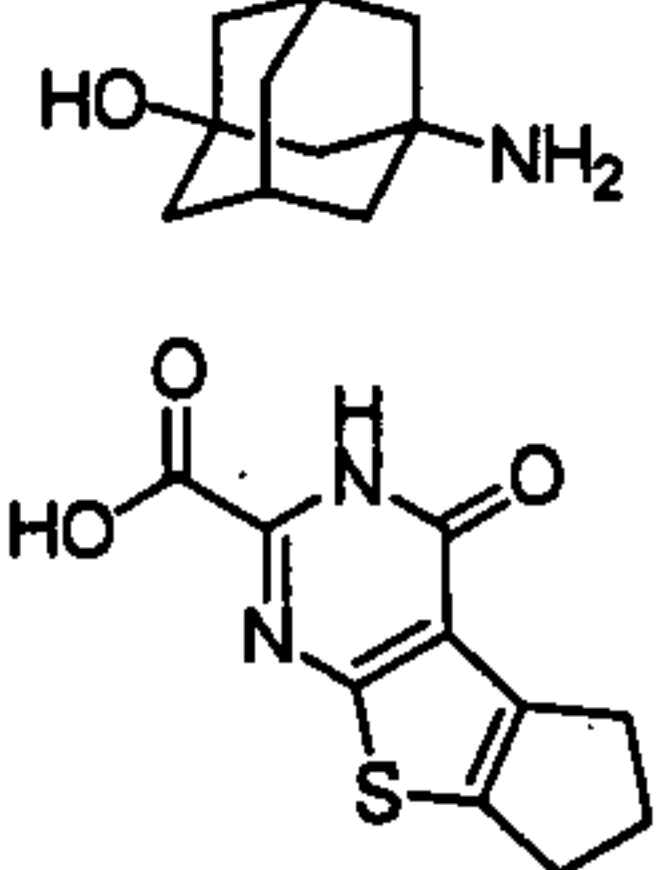
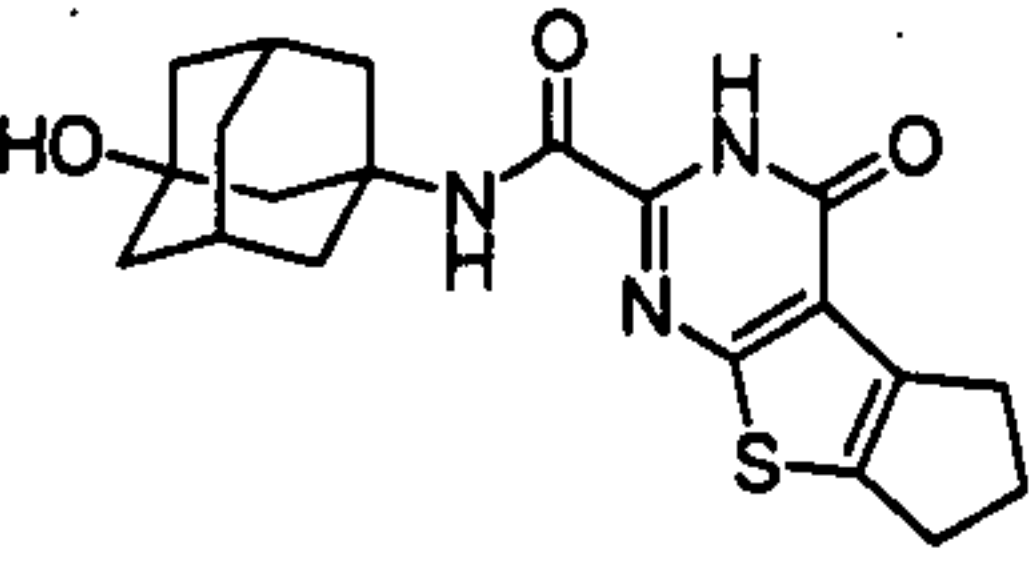
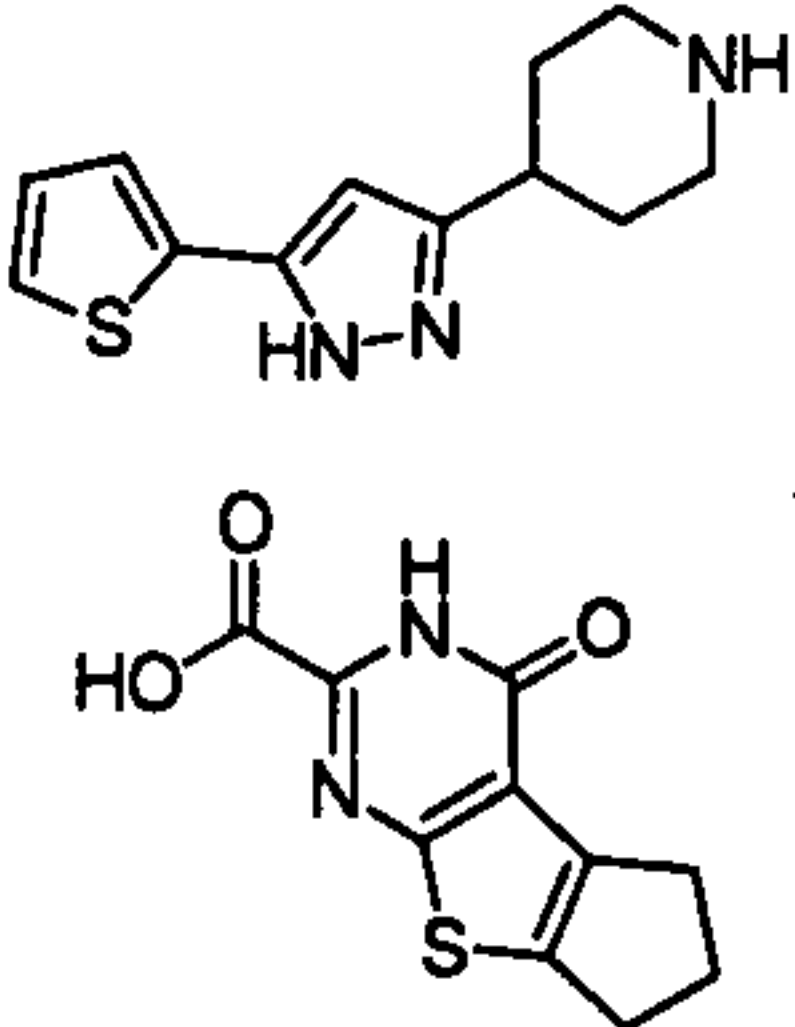
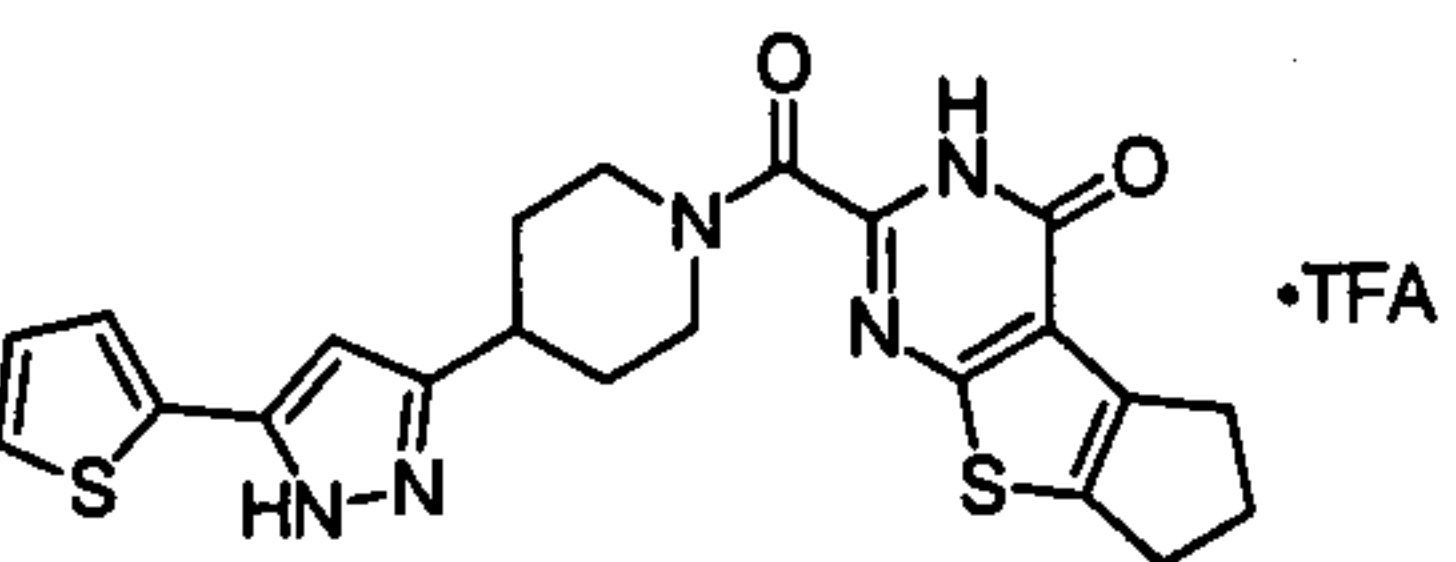
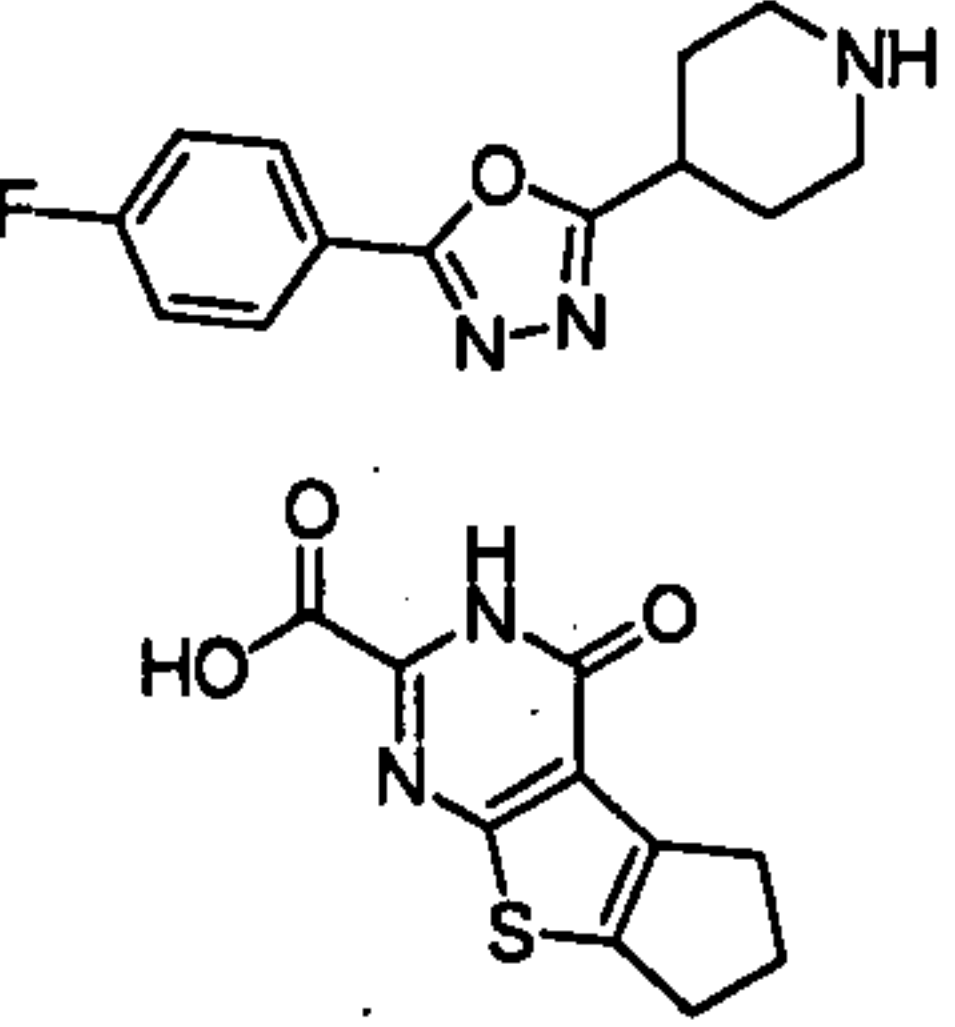
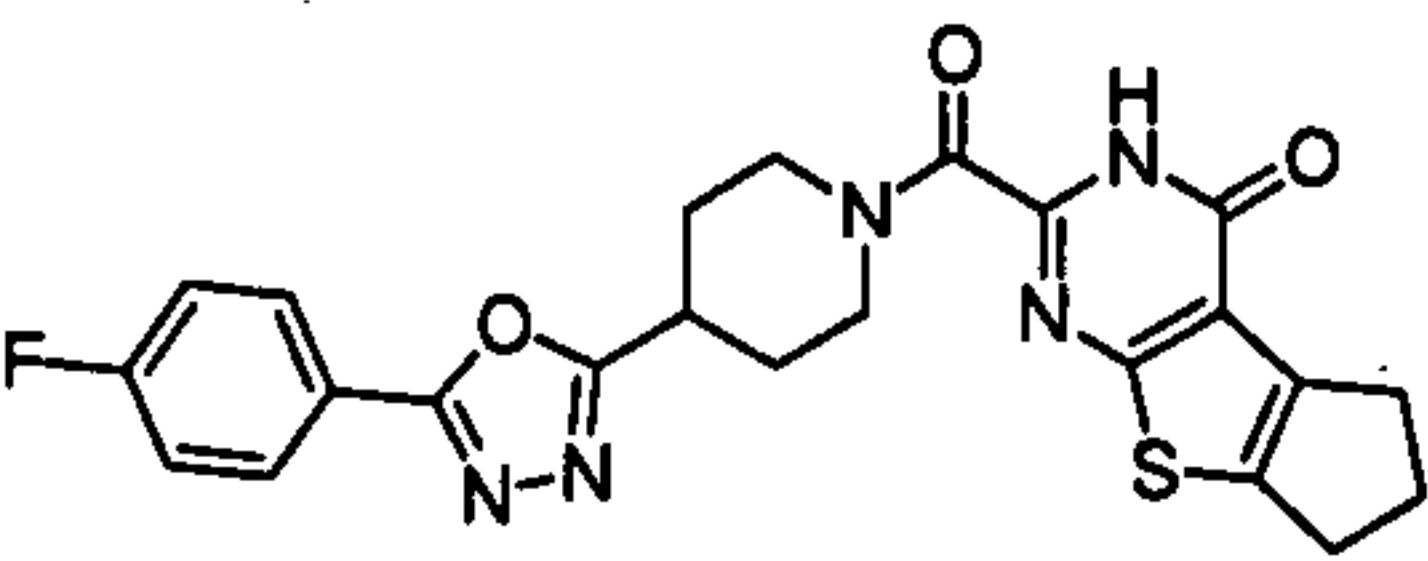
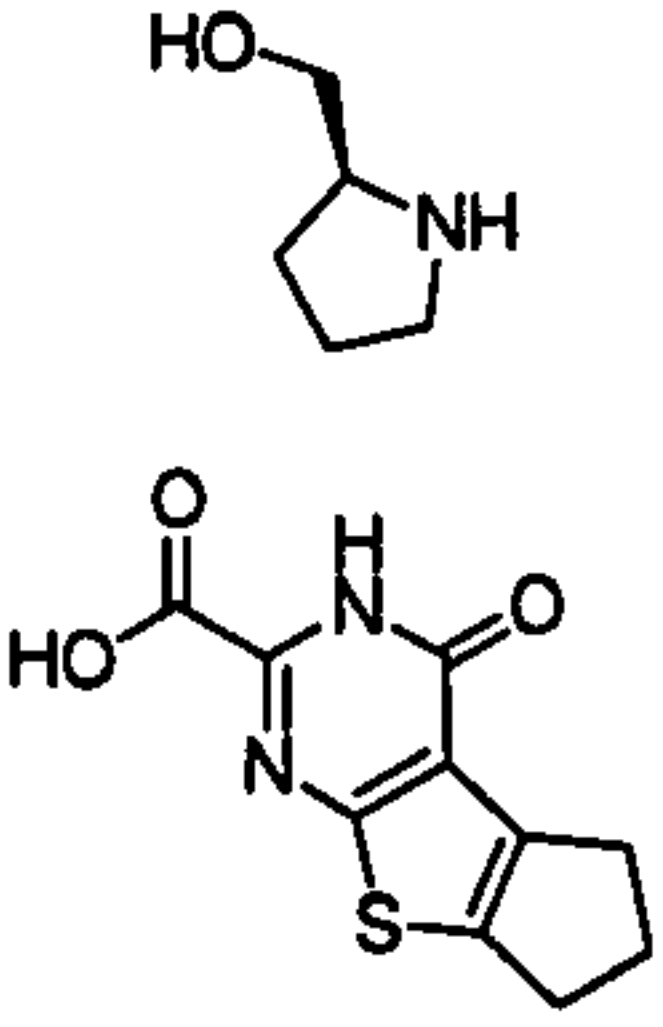
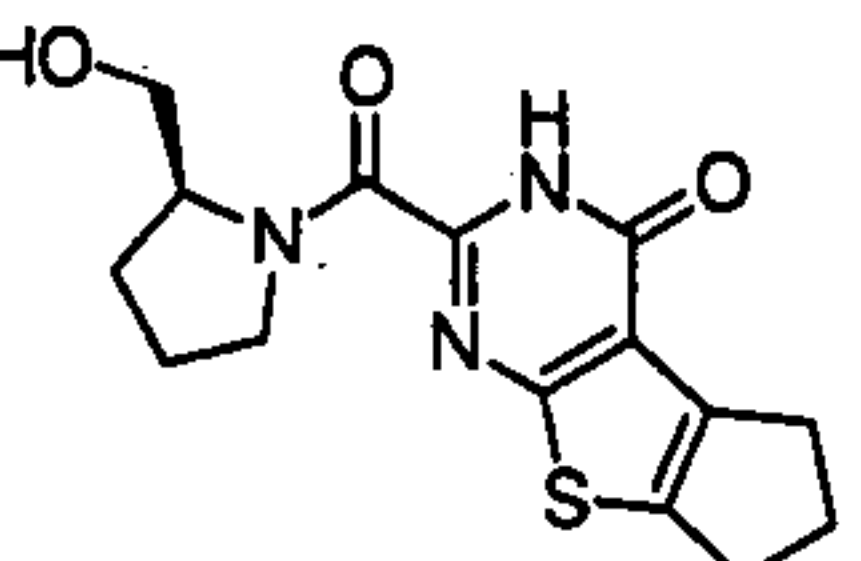
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/454 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 462    |
| 2/455 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 347 |
| 2/456 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 306    |
| 2/457 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 370    |
| 2/458 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 320    |

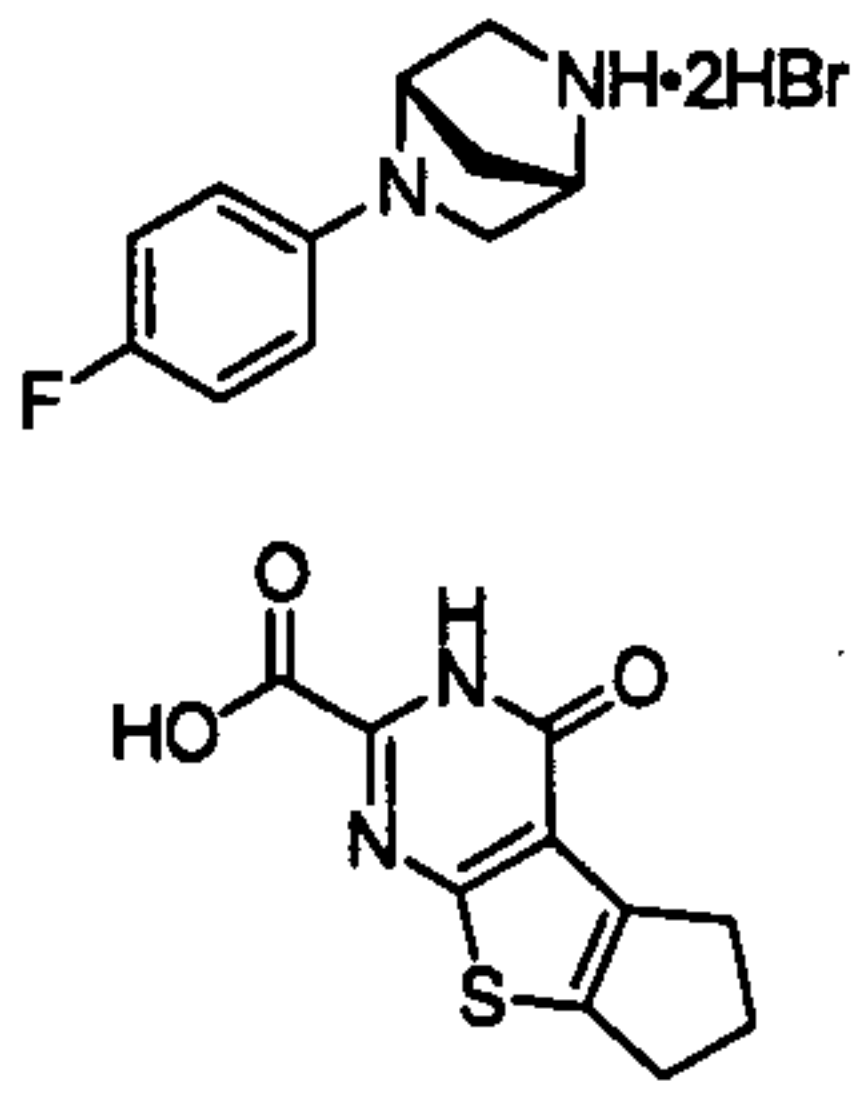
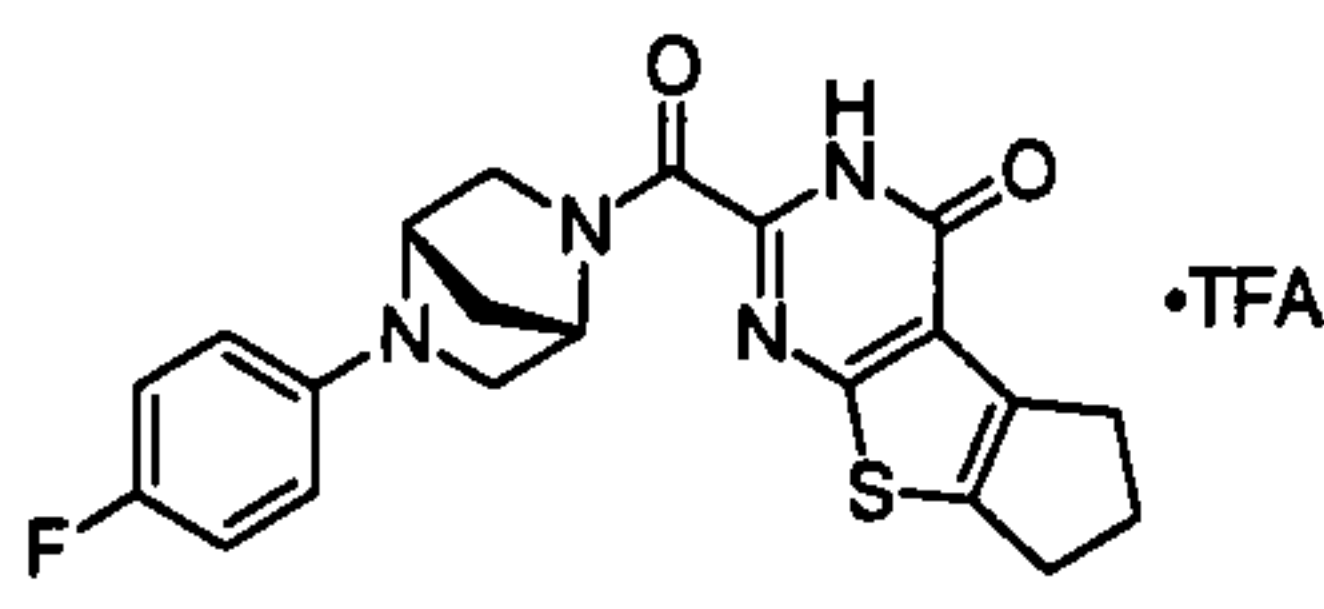
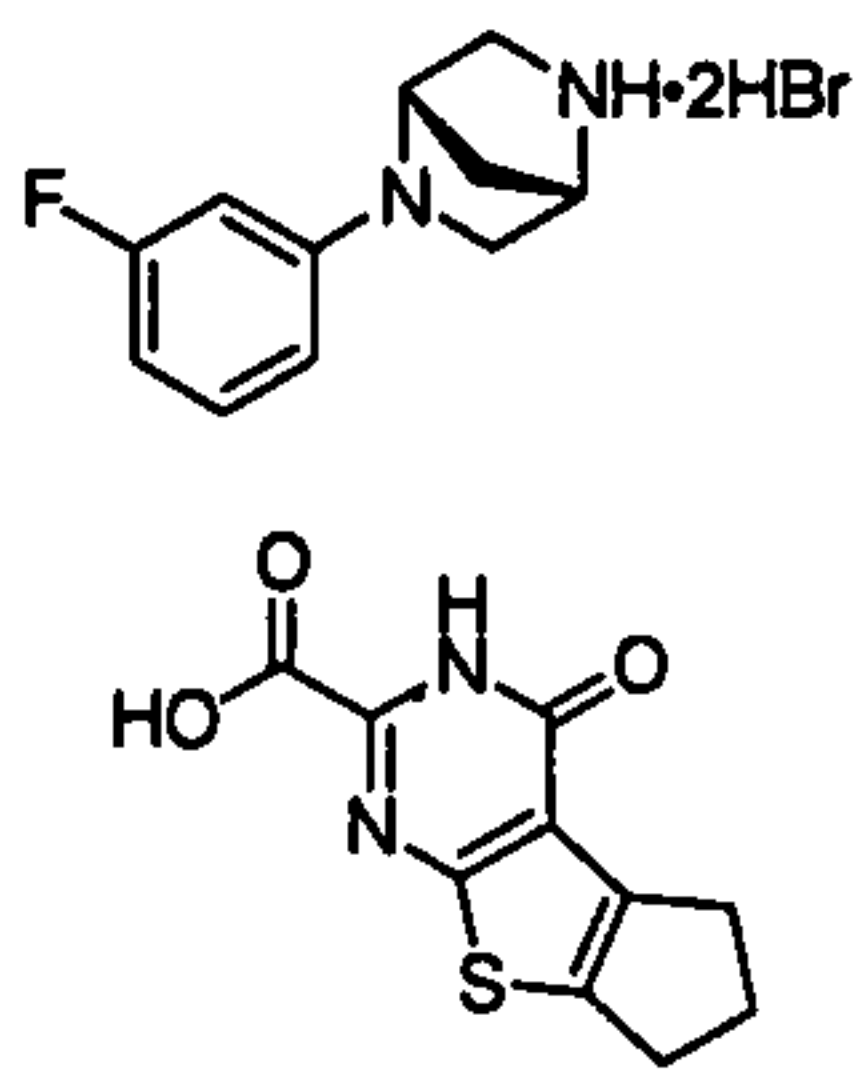
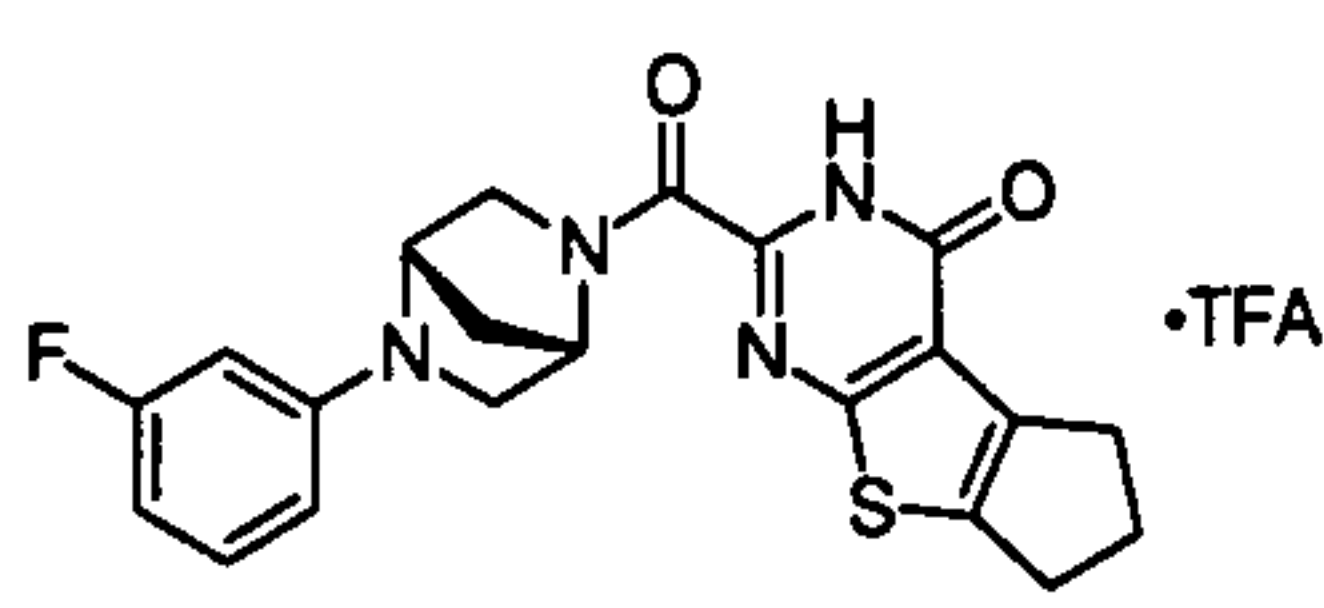
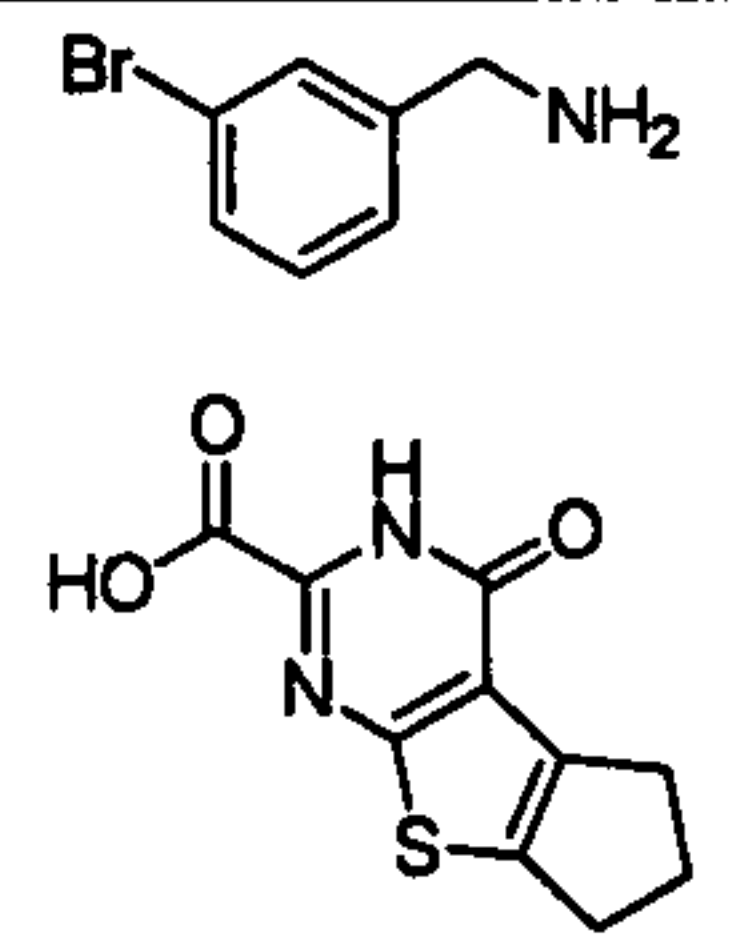
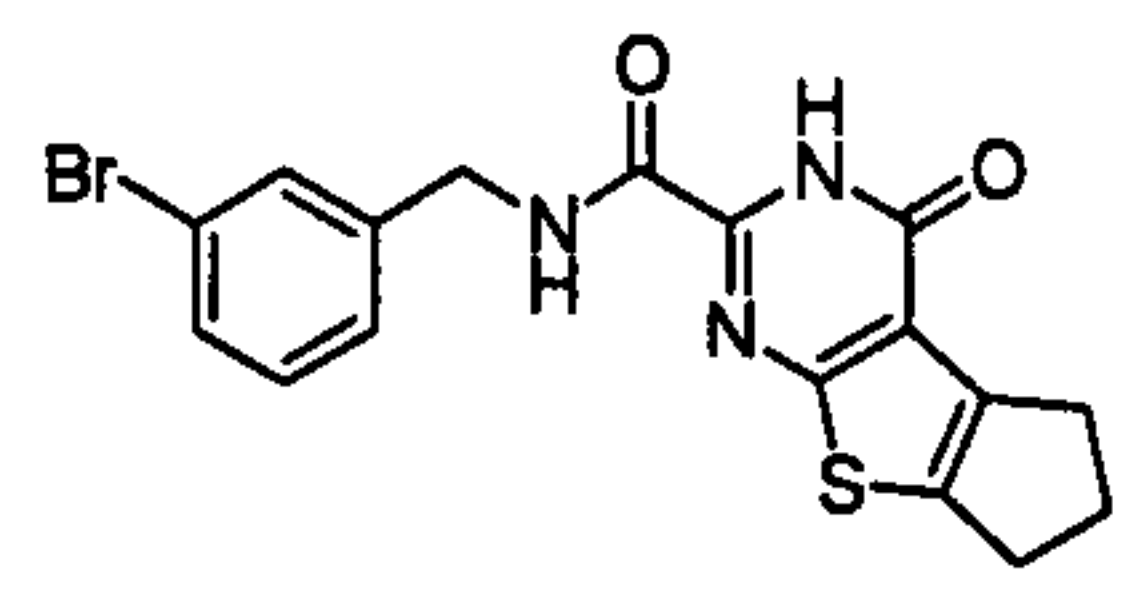
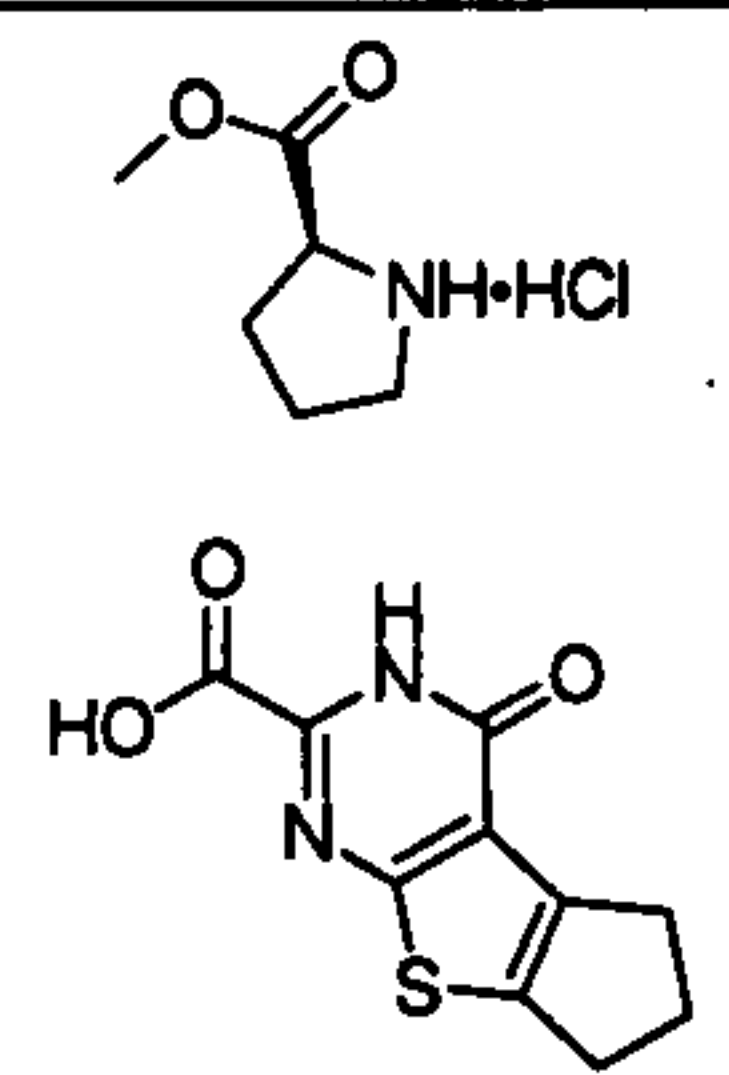
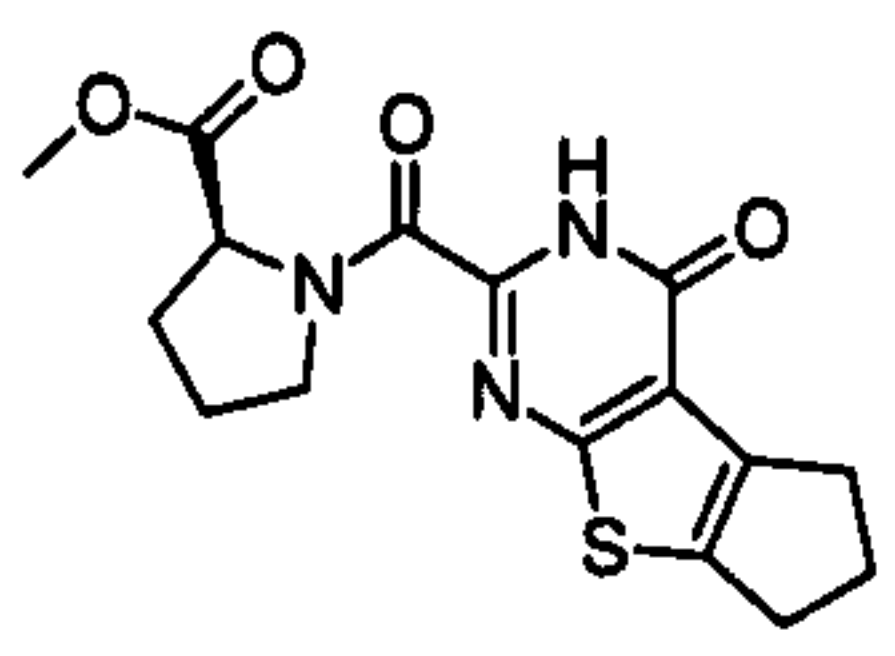
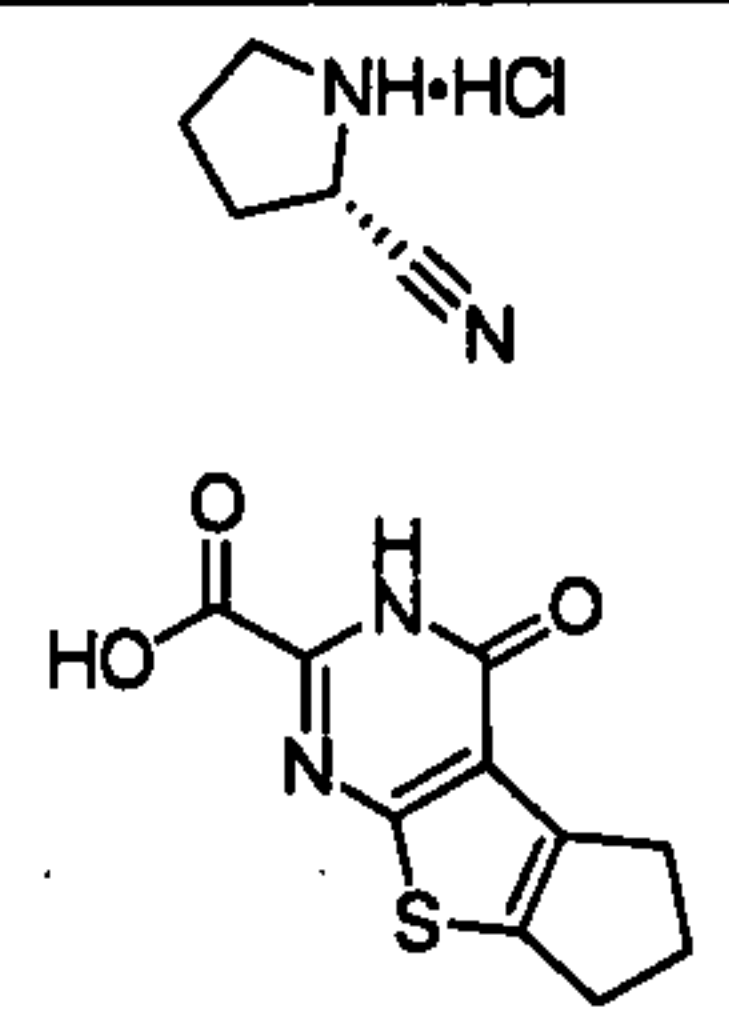
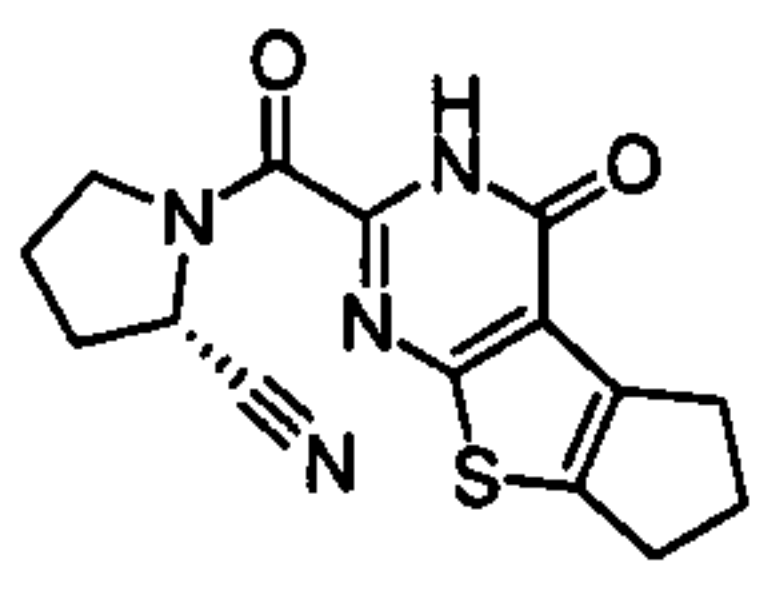
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/459 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 280 |
| 2/460 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 446 |
| 2/461 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 320 |
| 2/462 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 320 |
| 2/463 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 330 |
| 2/464 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 320 |

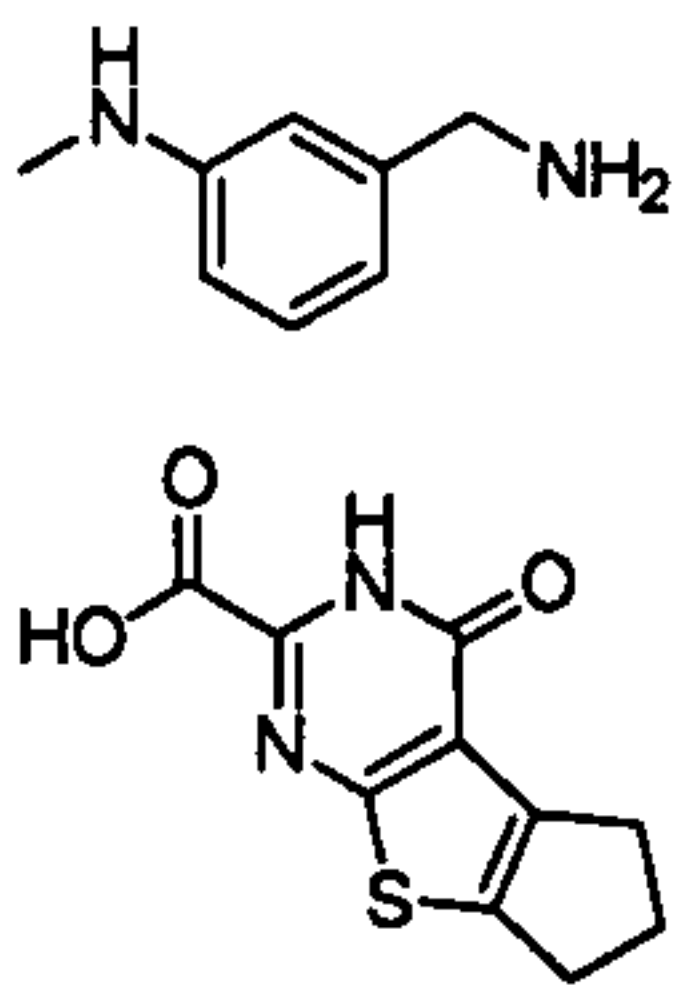
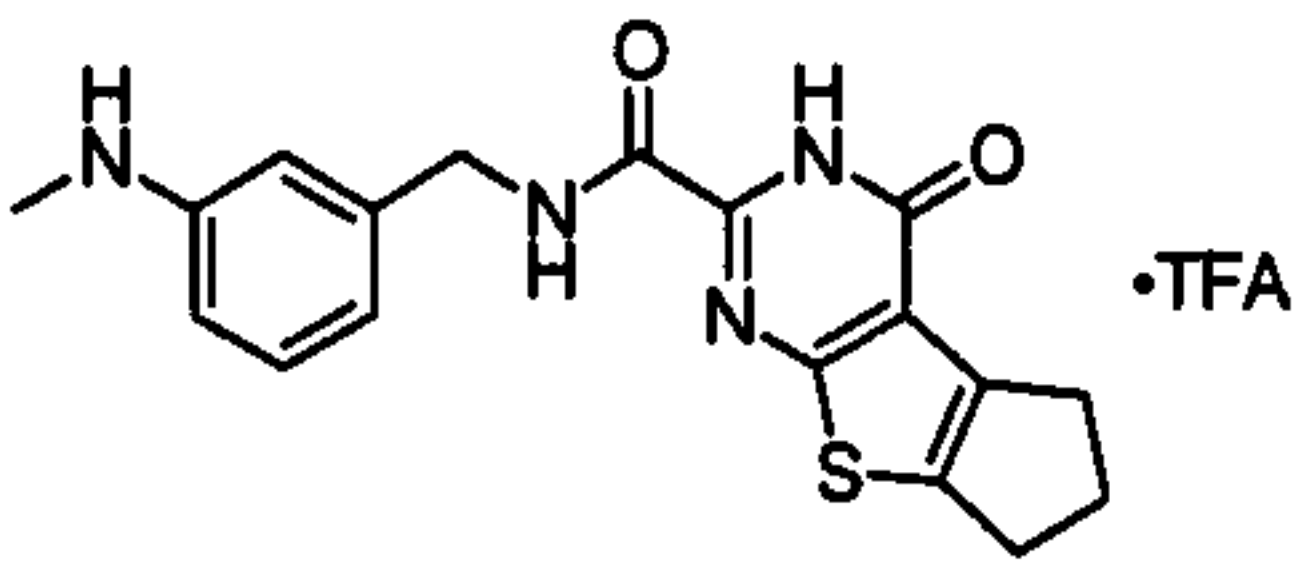
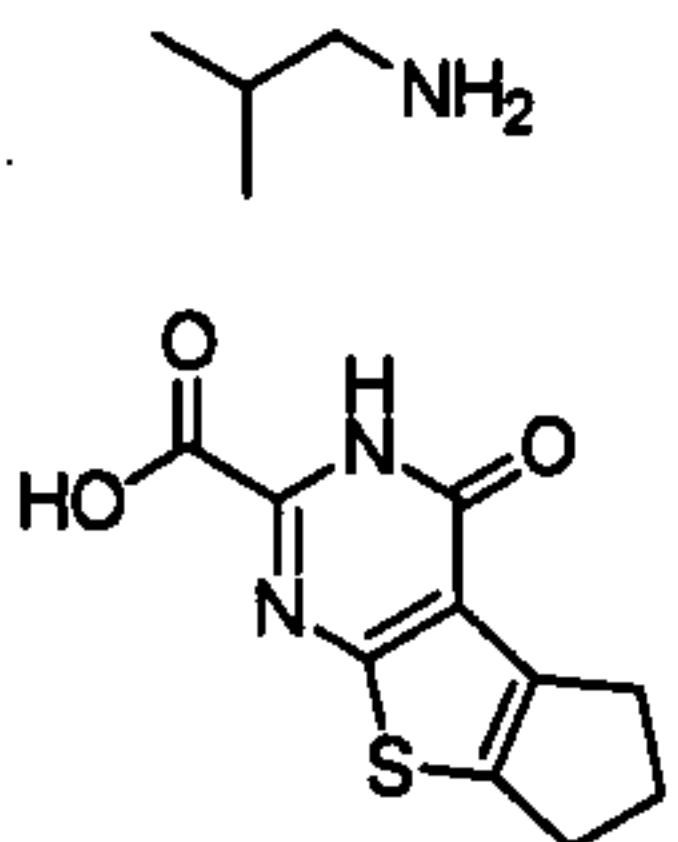
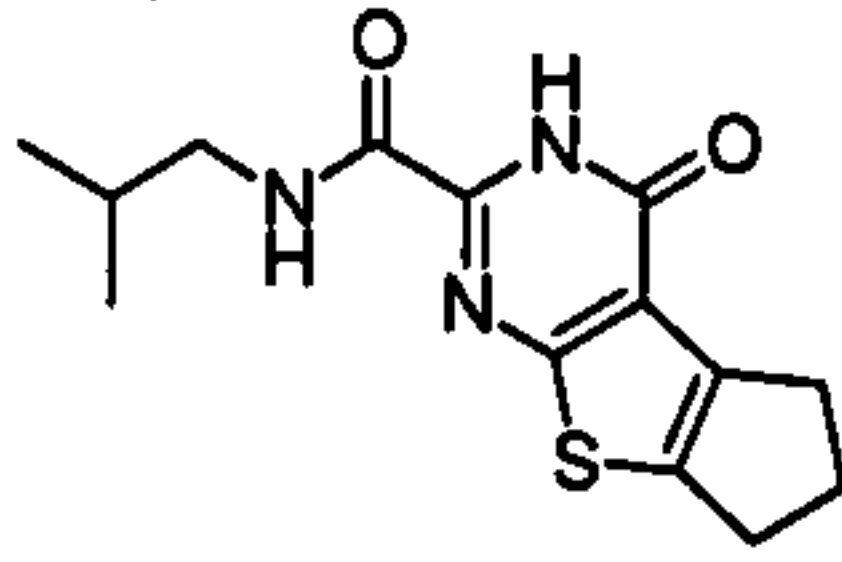
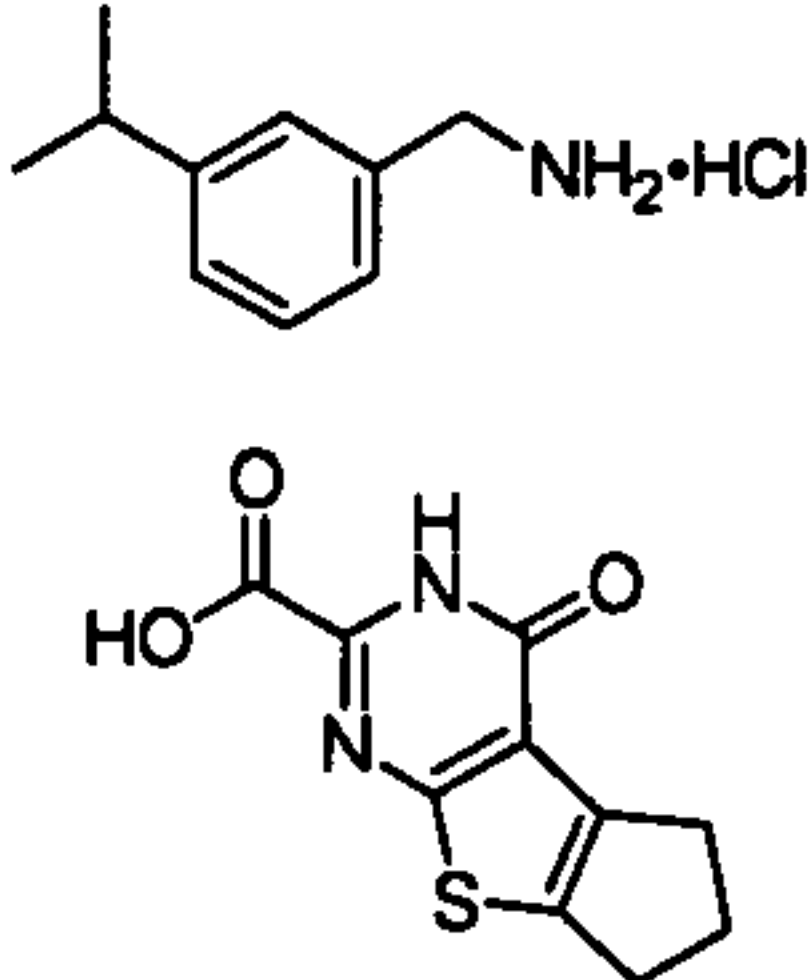
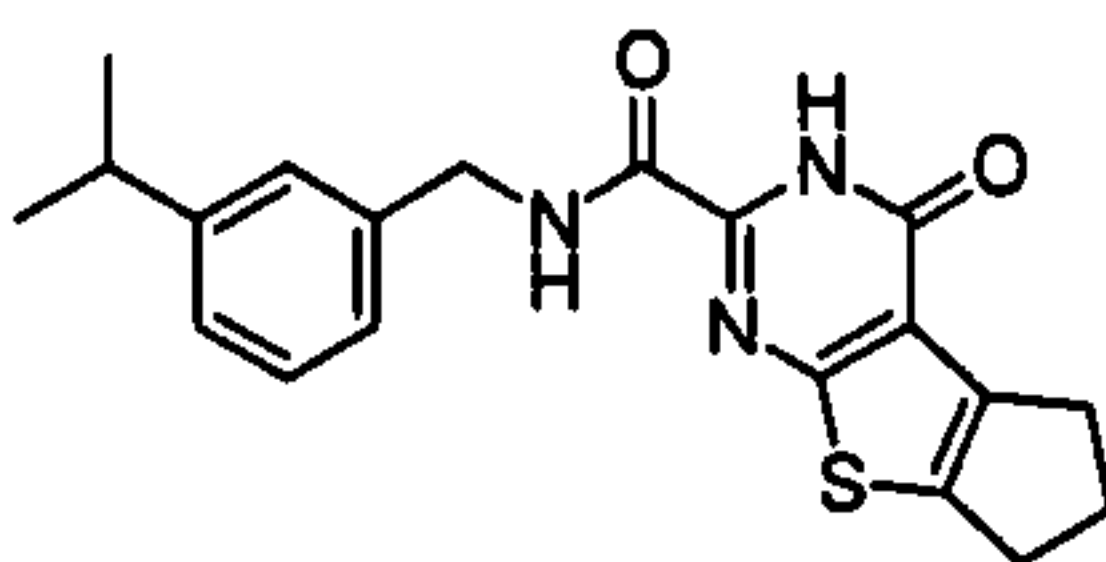
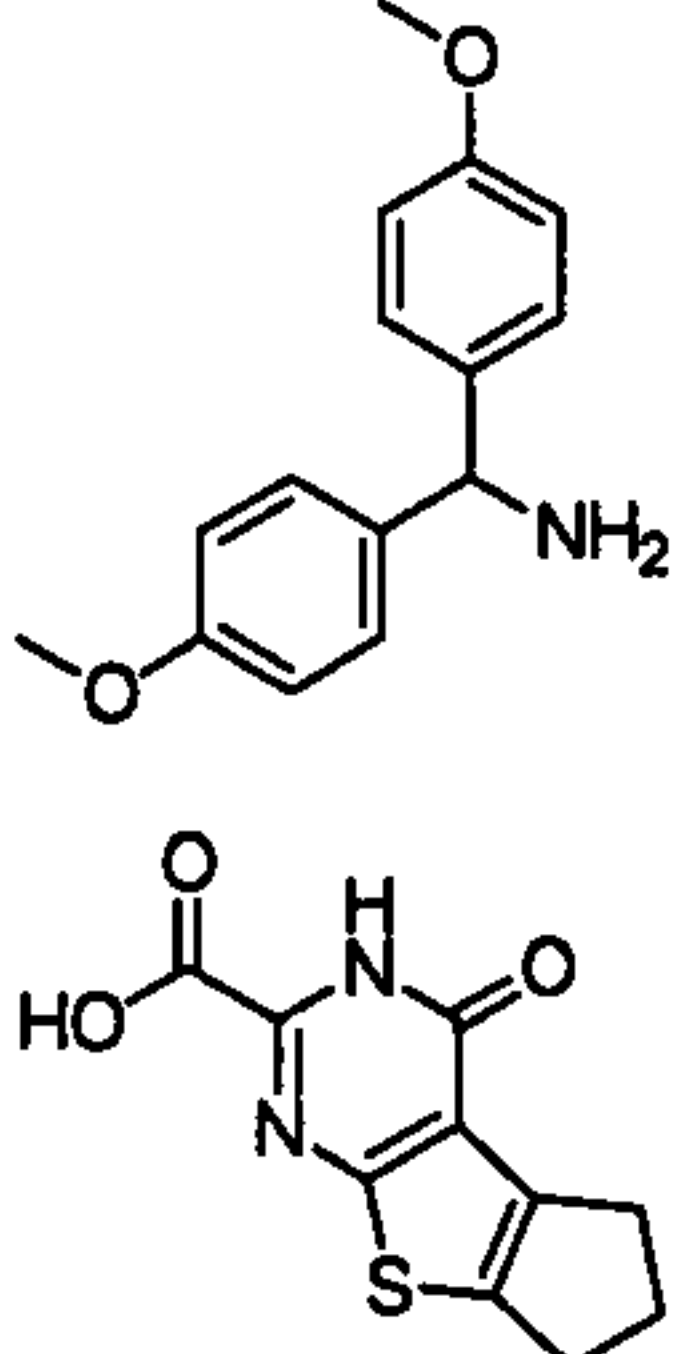
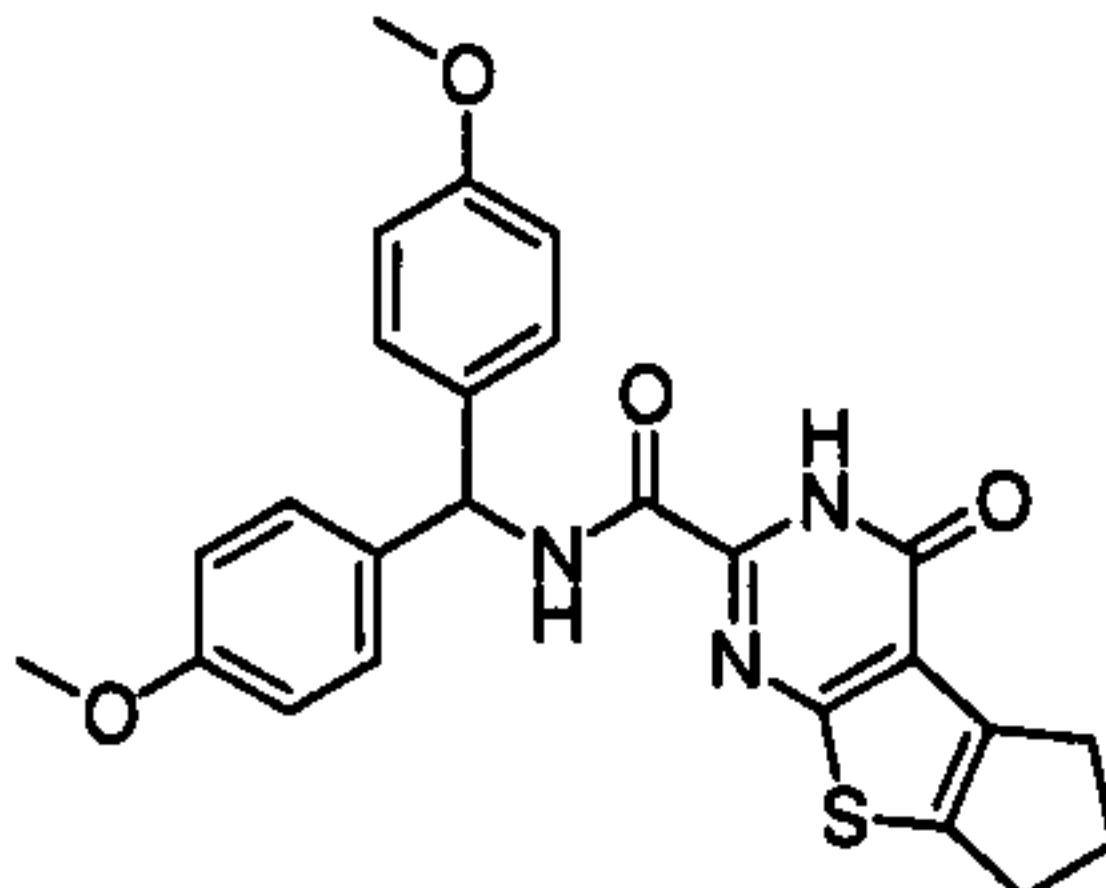
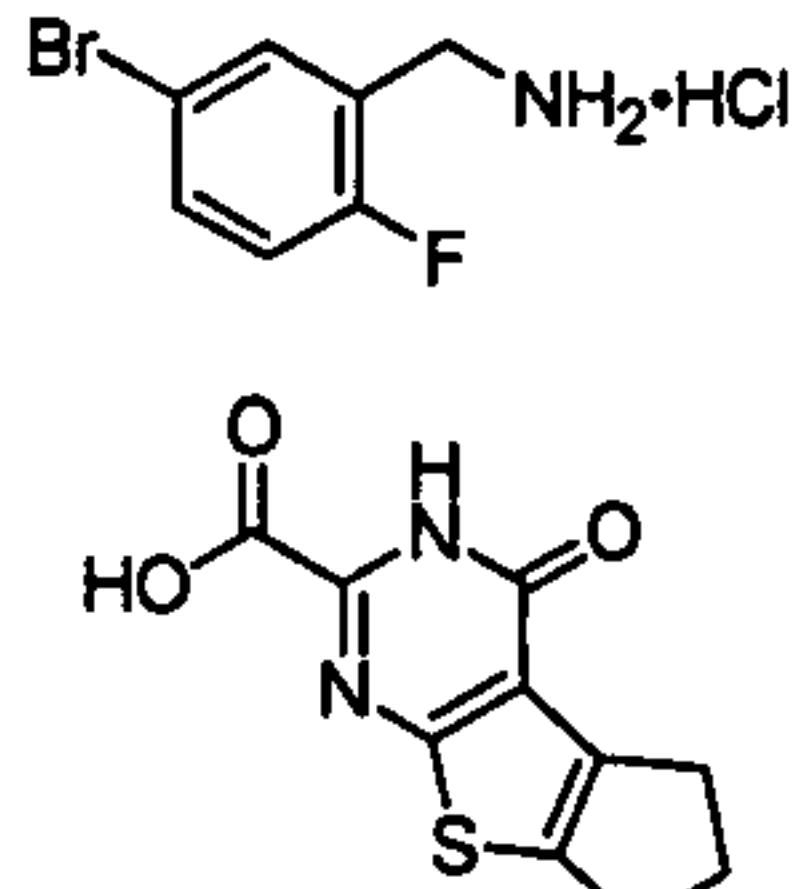
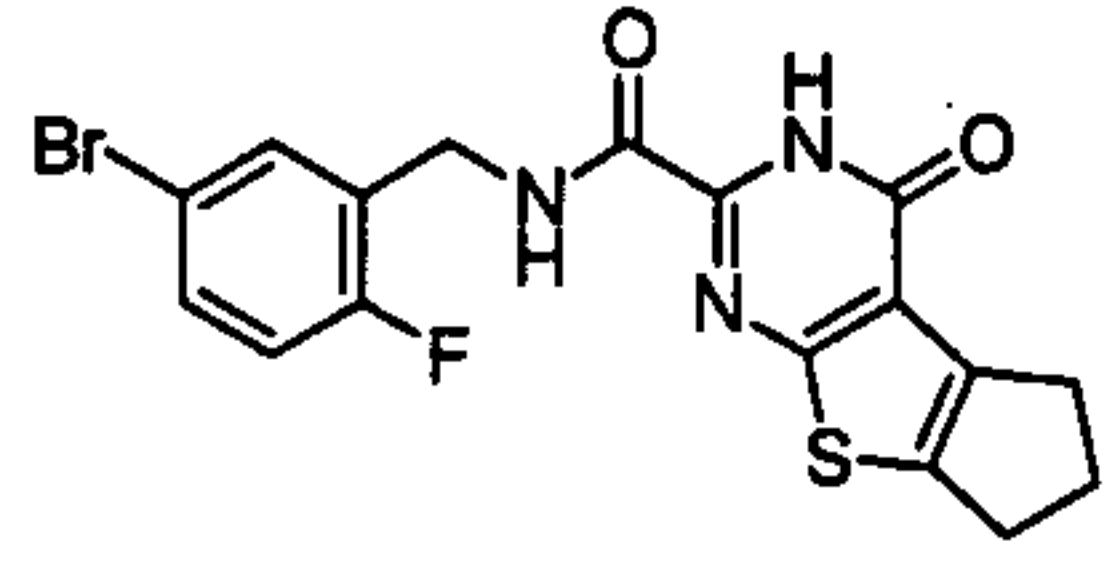
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/465 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 394 |
| 2/466 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 419 |
| 2/467 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 308 |
| 2/468 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 364 |
| 2/469 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 376 |

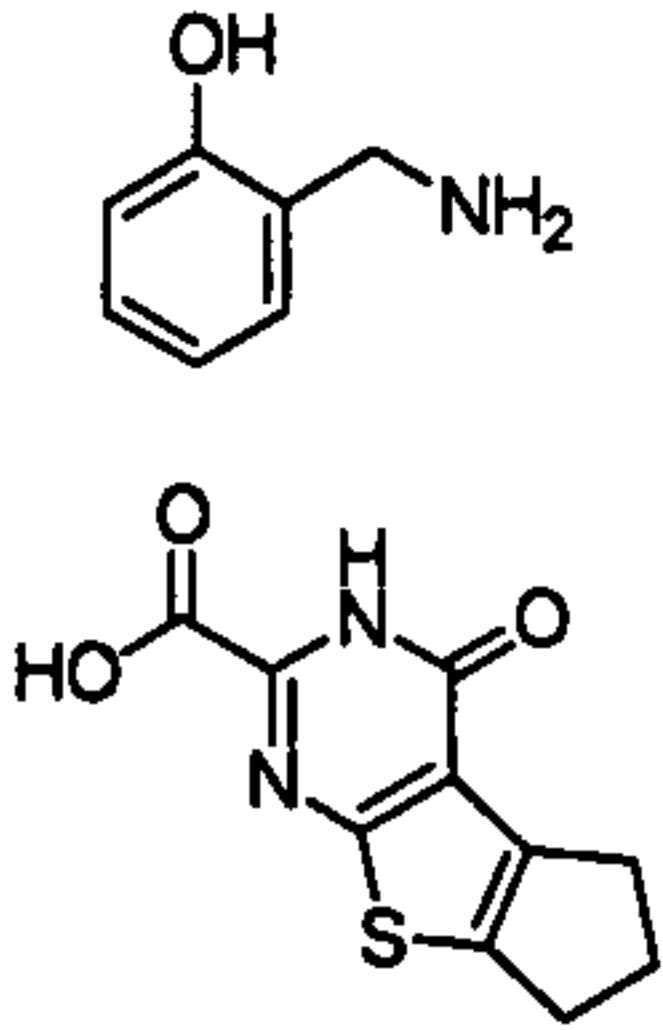
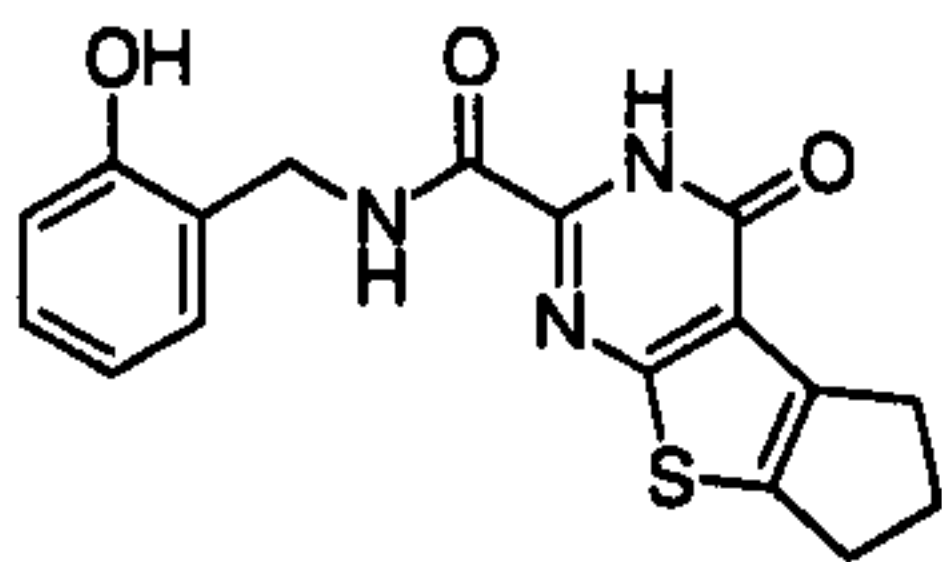
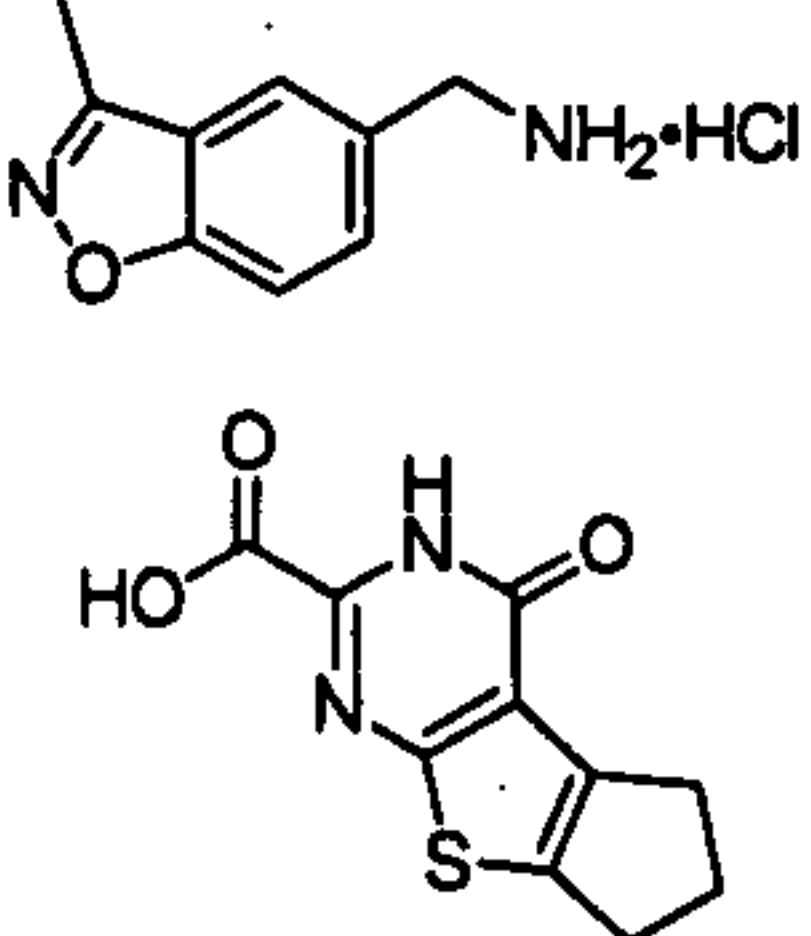
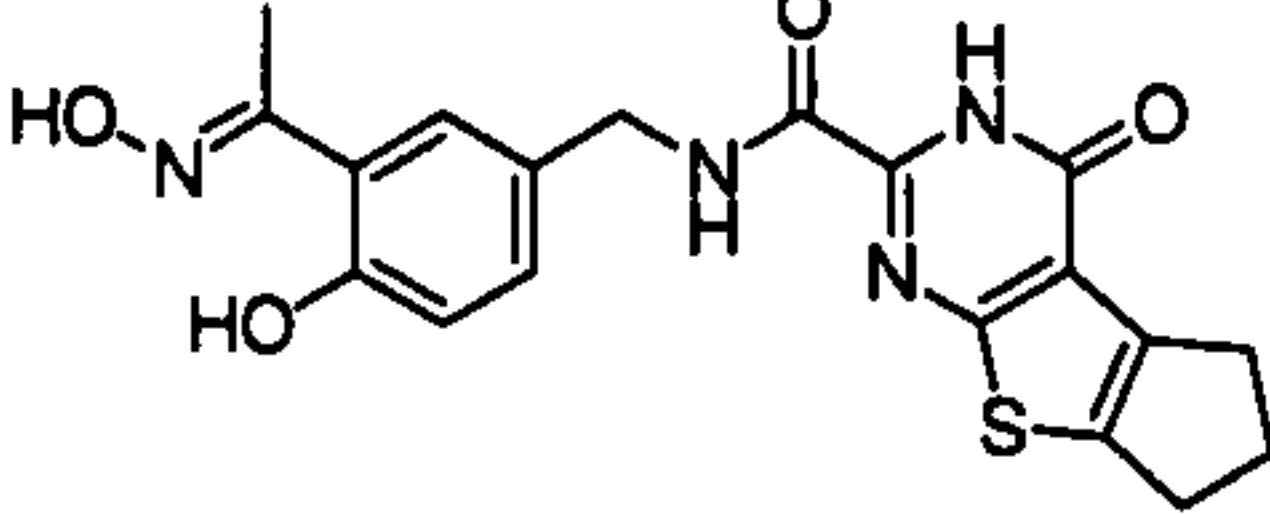
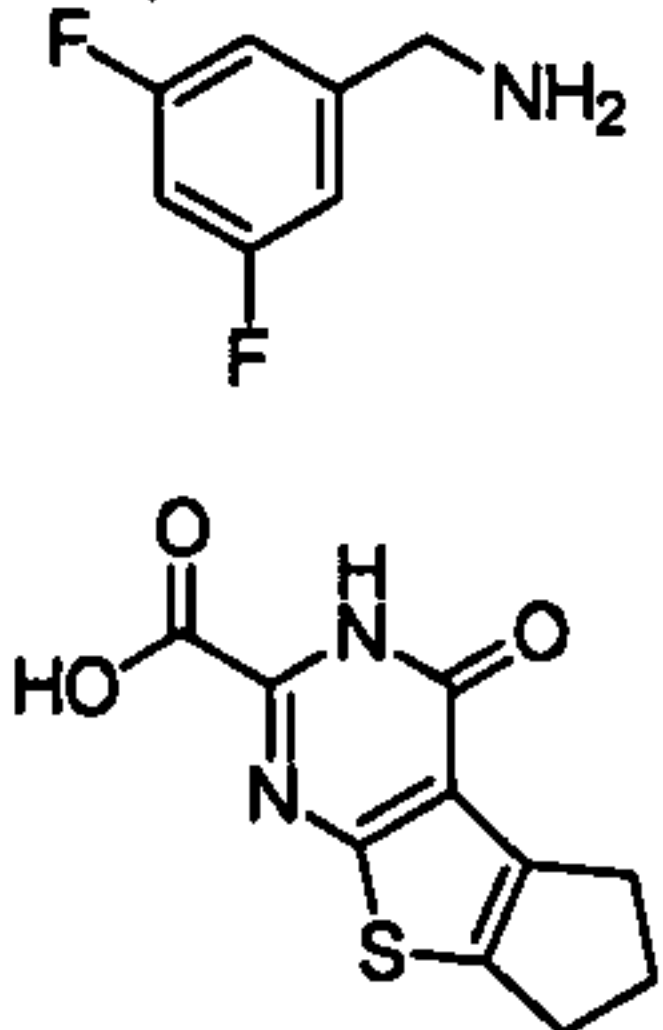
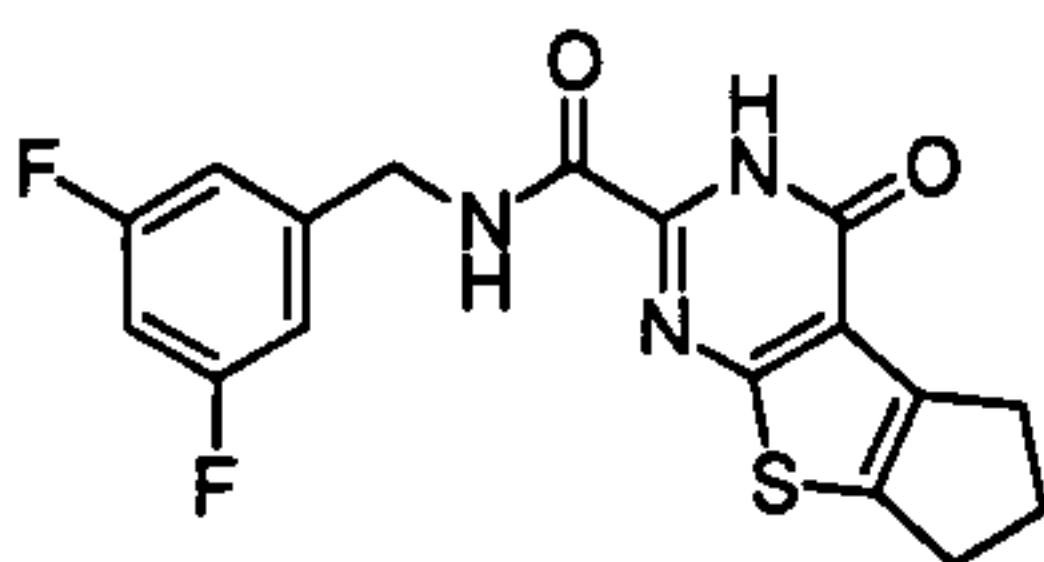
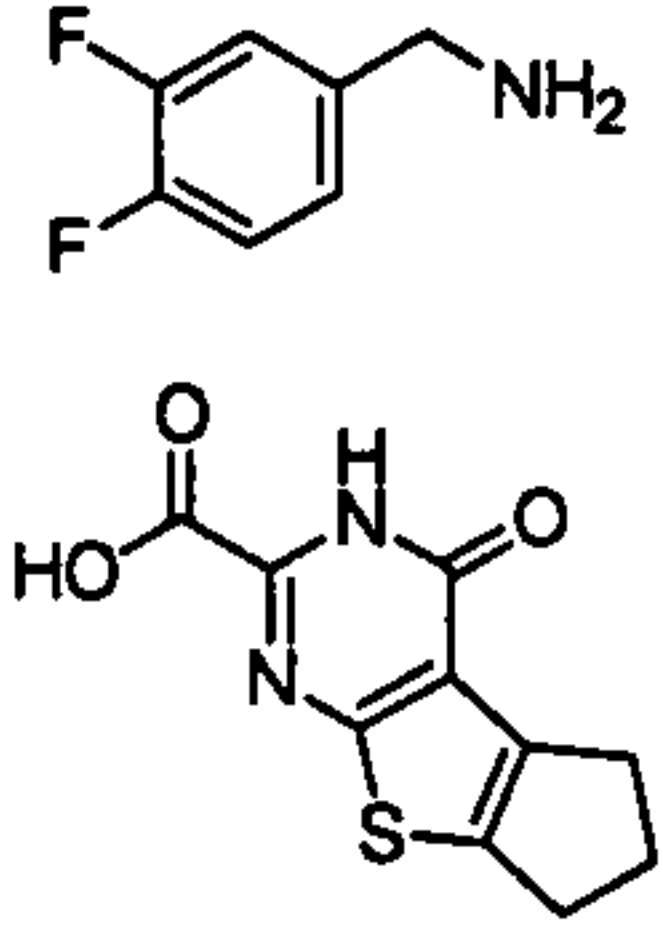
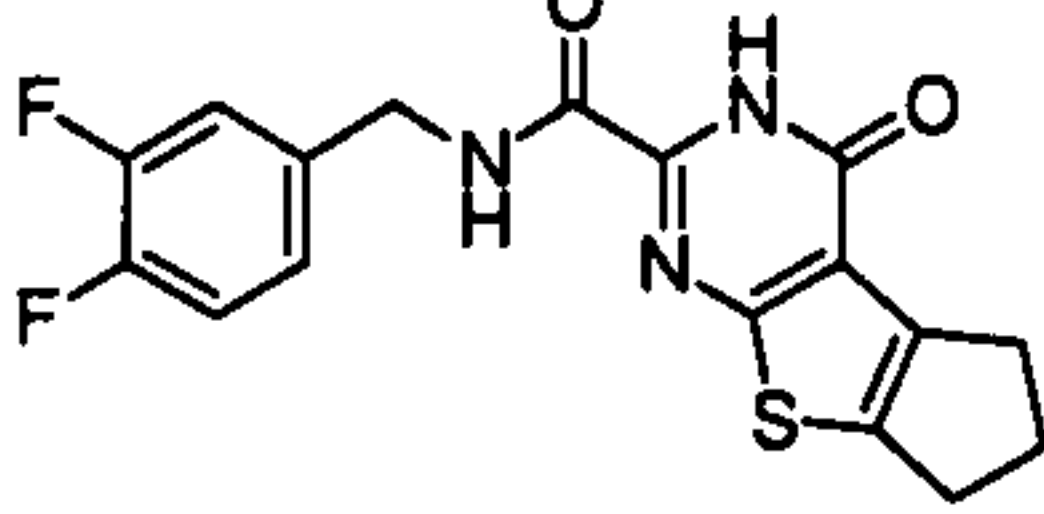
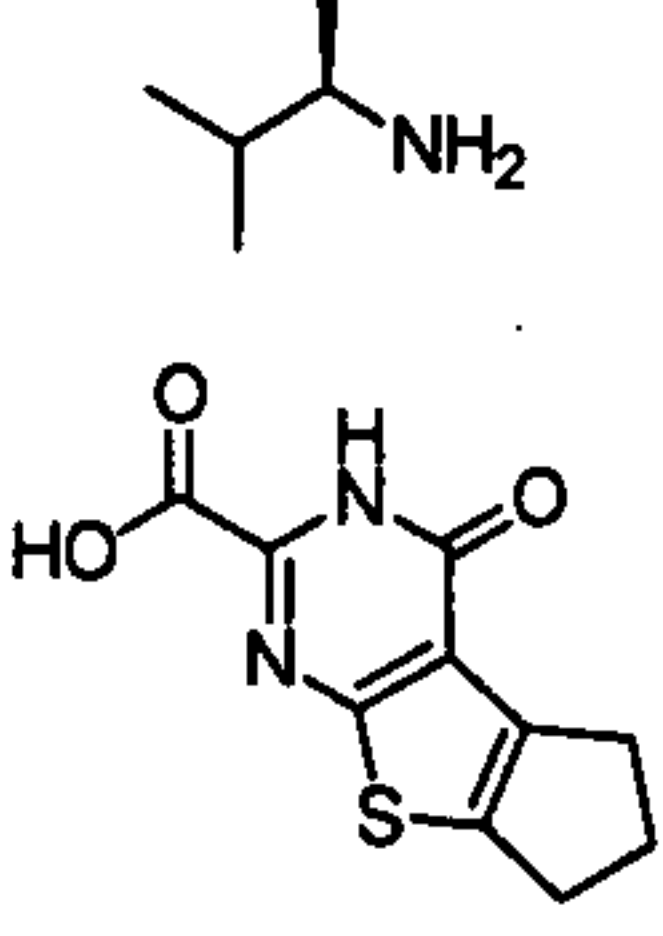
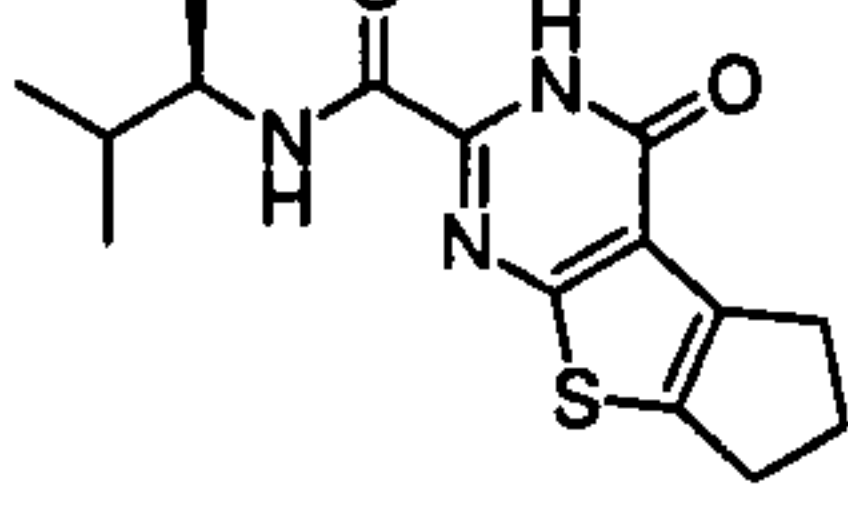
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                          |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------|
| 2/470 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 337     |
| 2/471 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 405     |
| 2/472 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 418/420 |
| 2/473 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 328  |
| 2/474 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 294     |

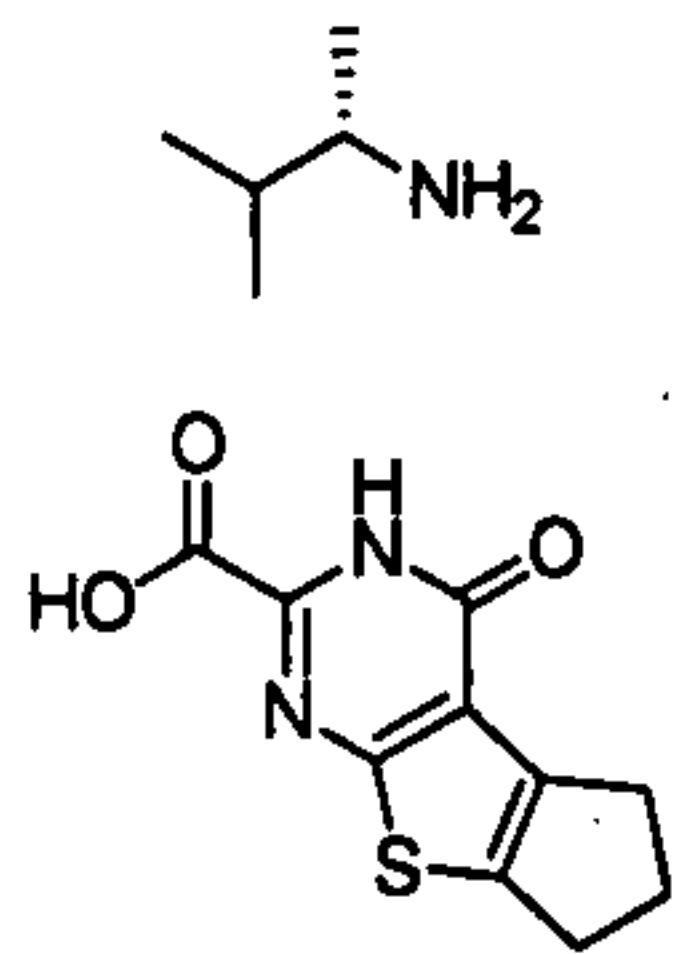
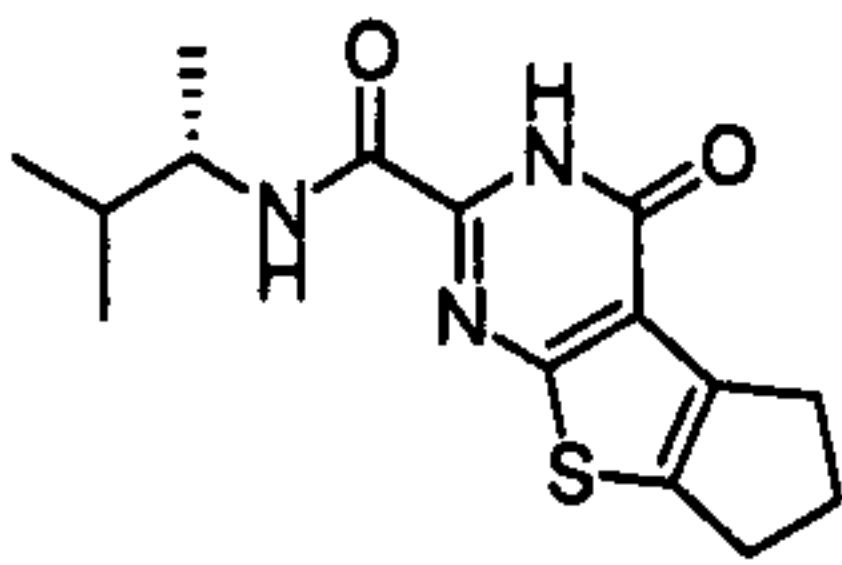
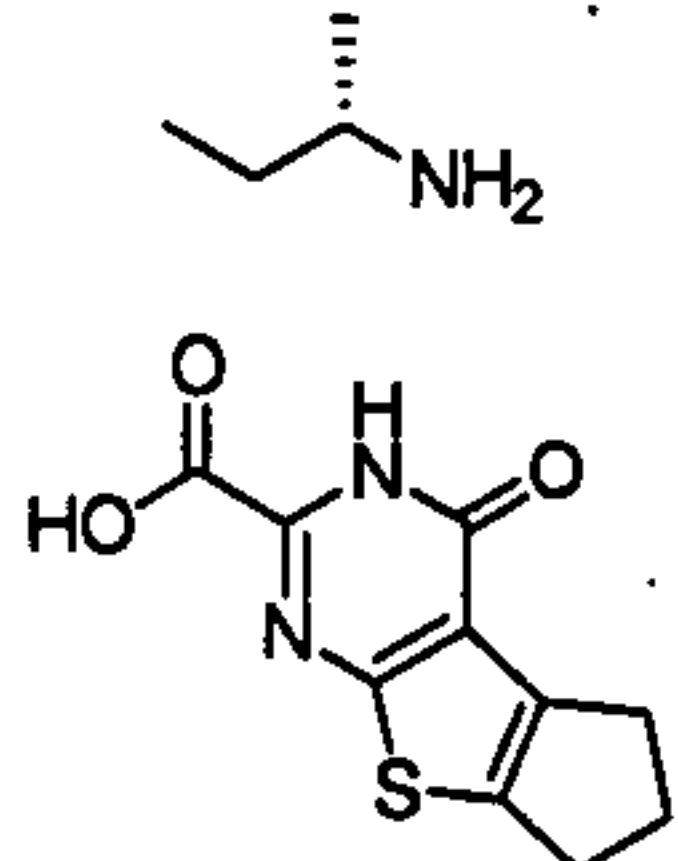
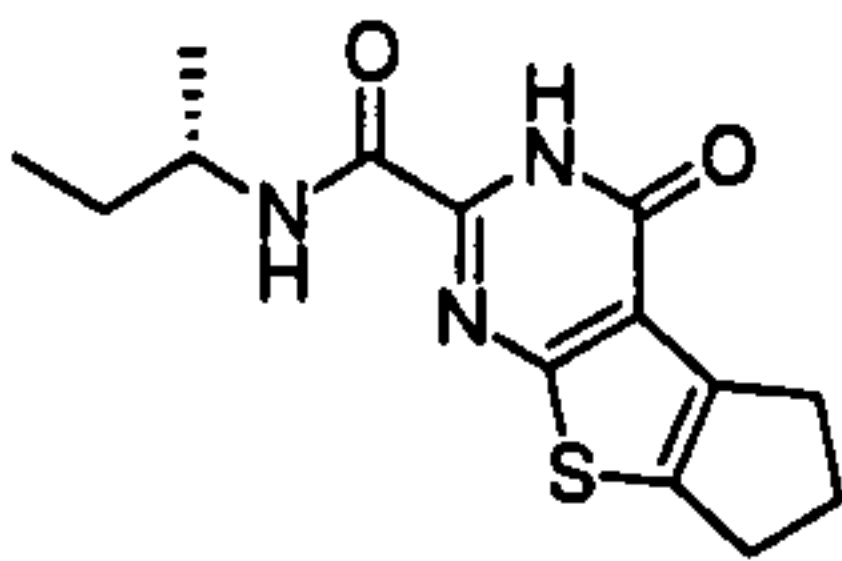
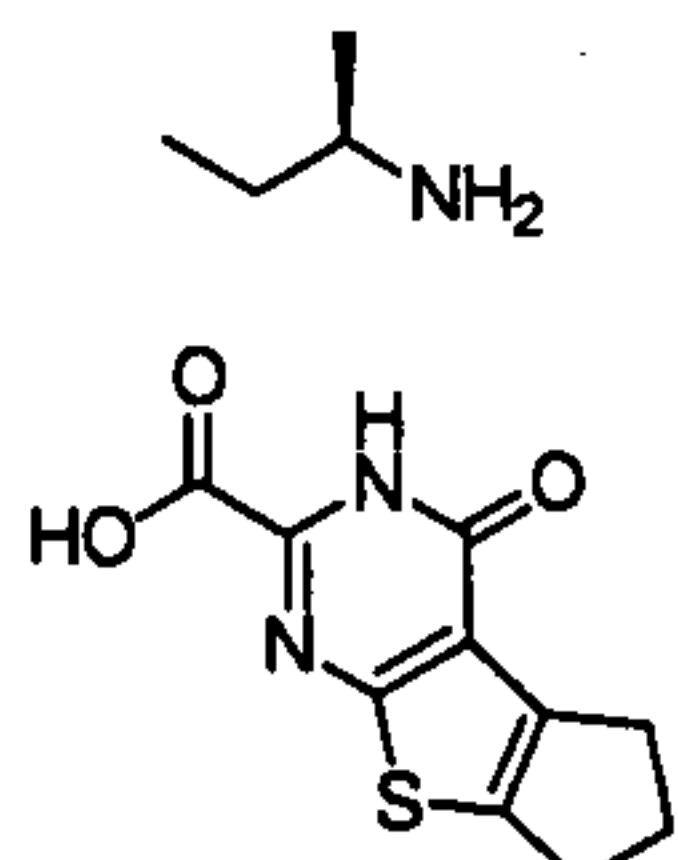
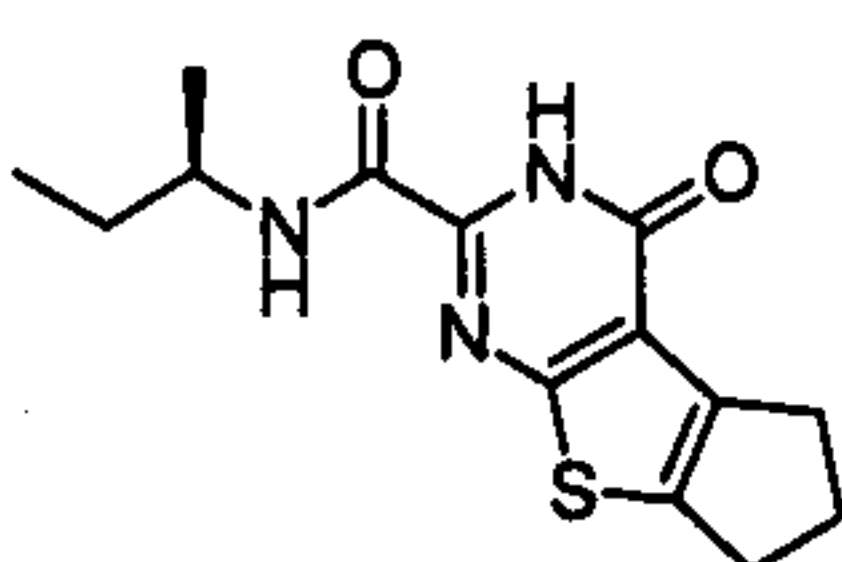
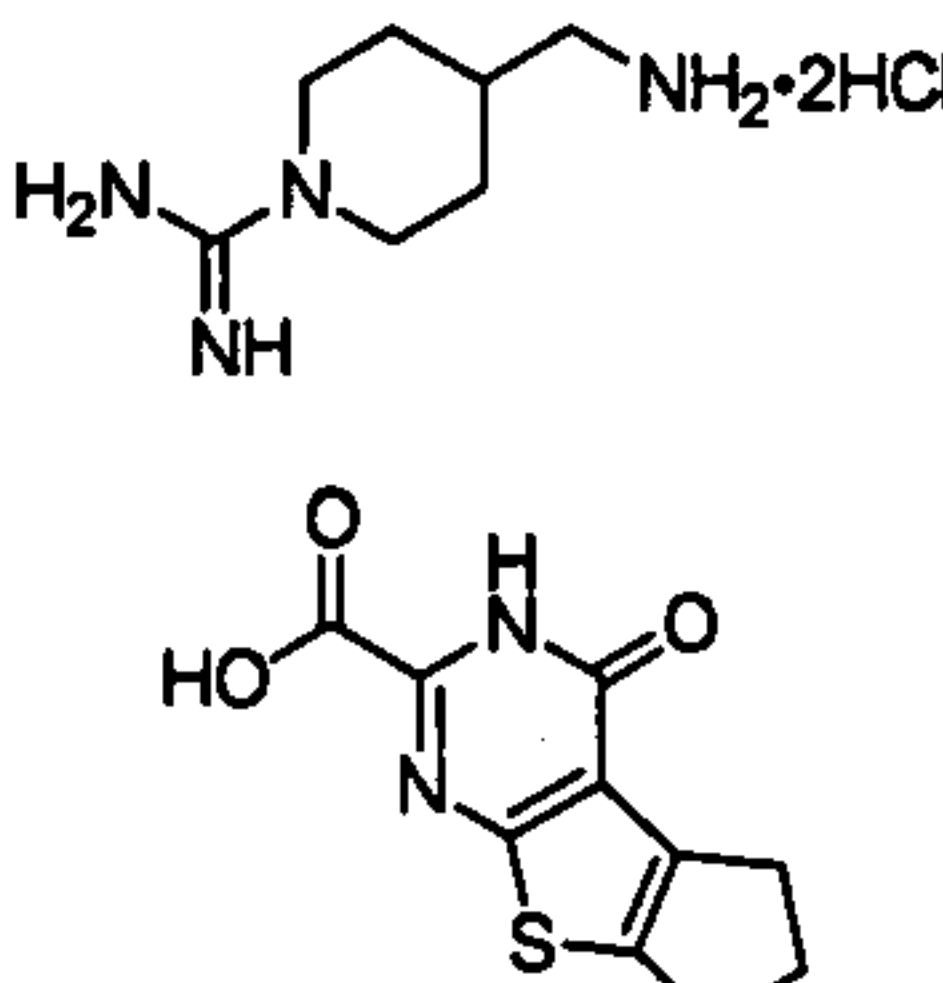
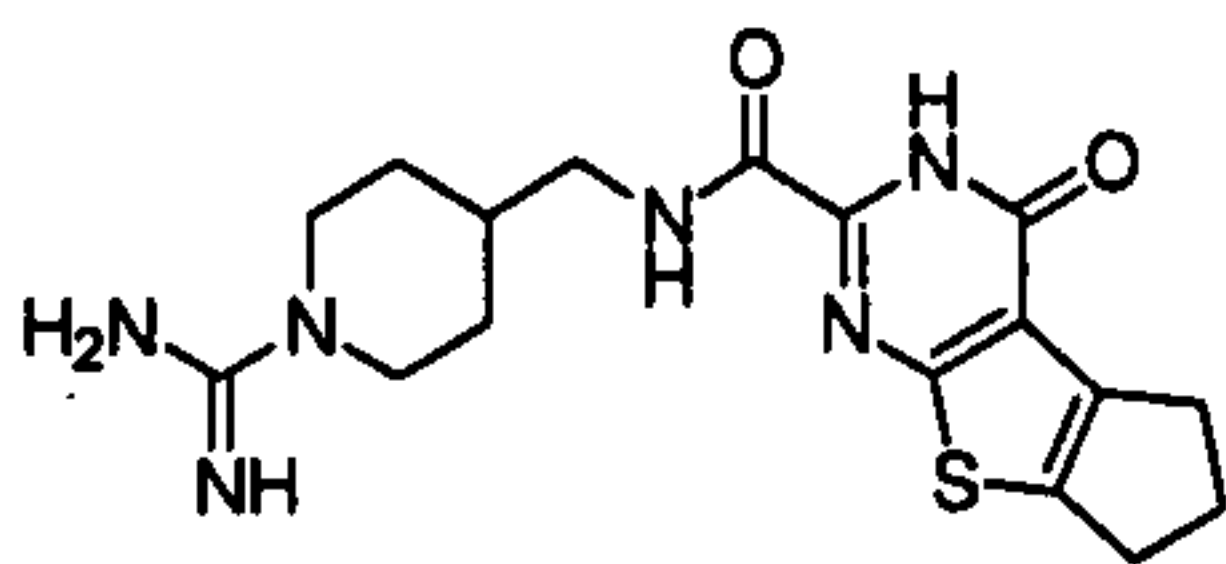
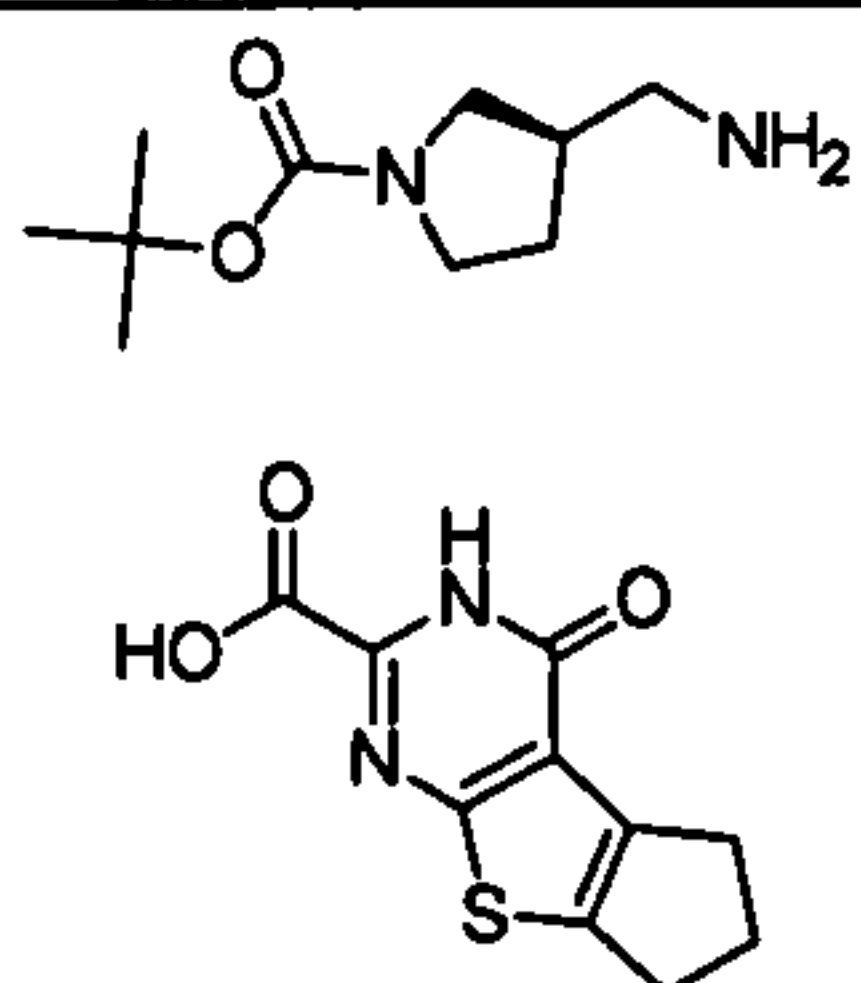
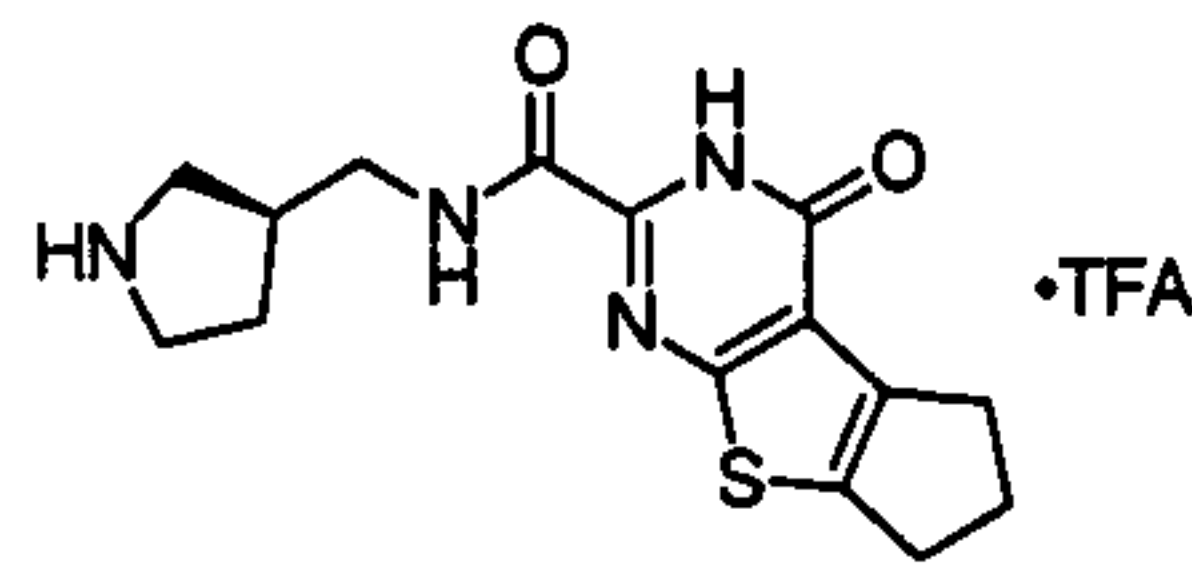
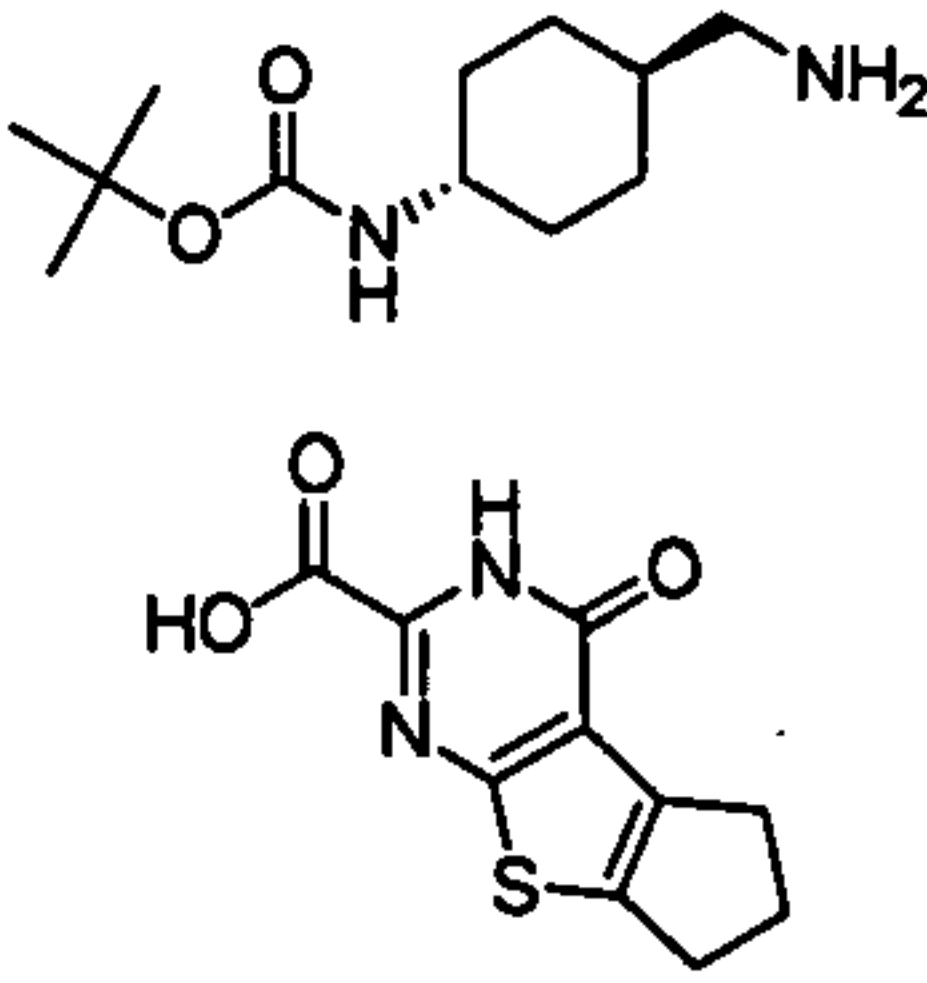
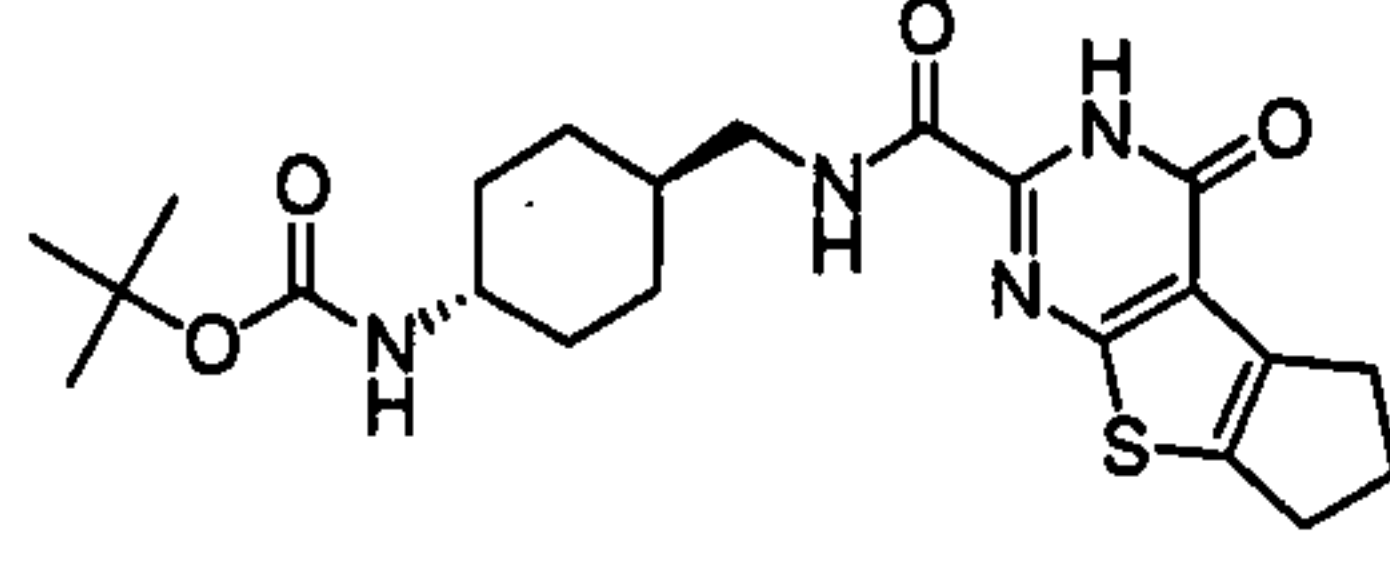
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                          |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------|
| 2/475 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 322     |
| 2/476 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 418/420 |
| 2/477 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 407  |
| 2/478 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 321  |
| 2/479 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 294     |
| 2/480 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 274     |

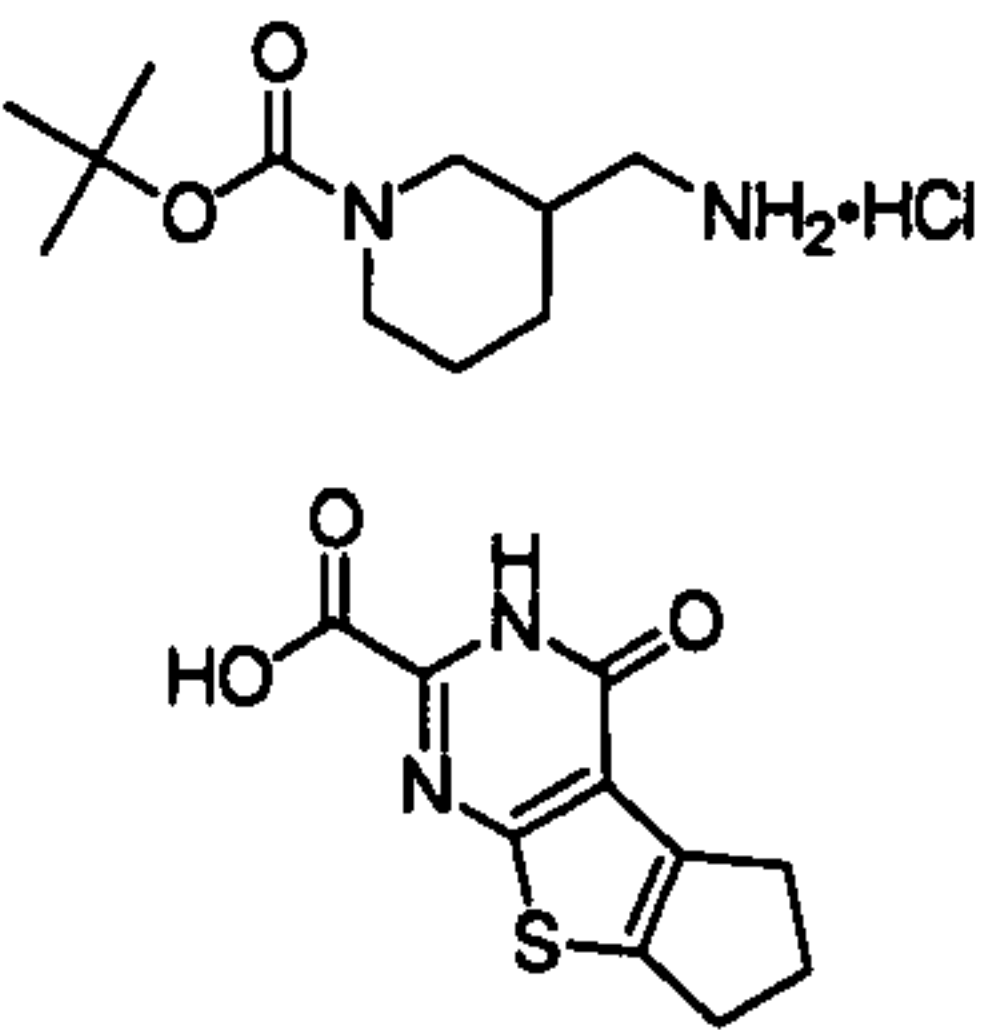
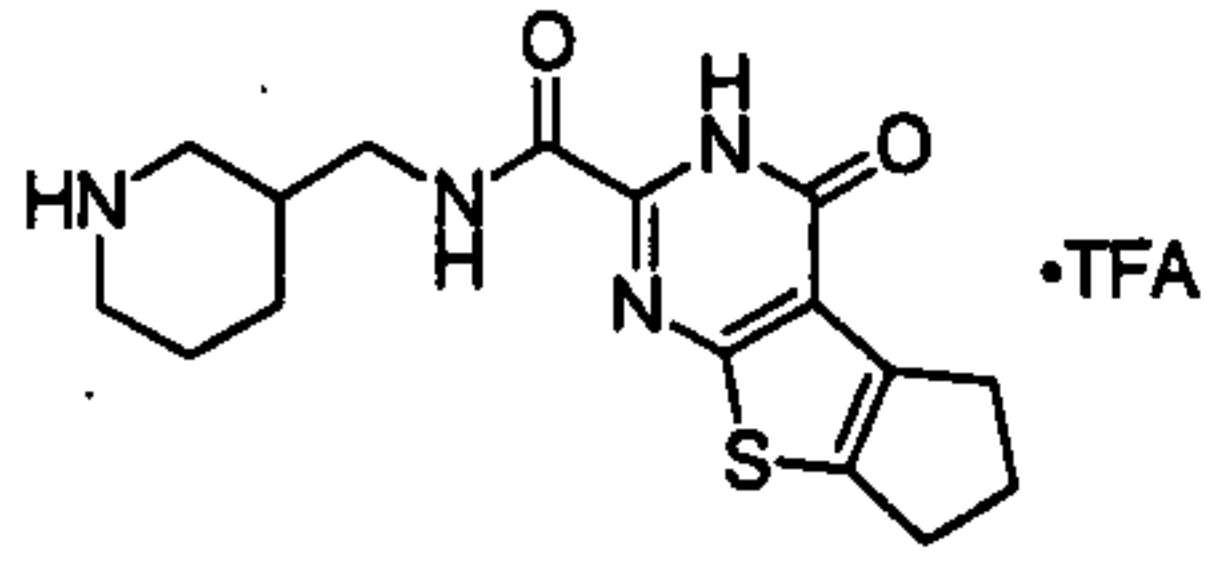
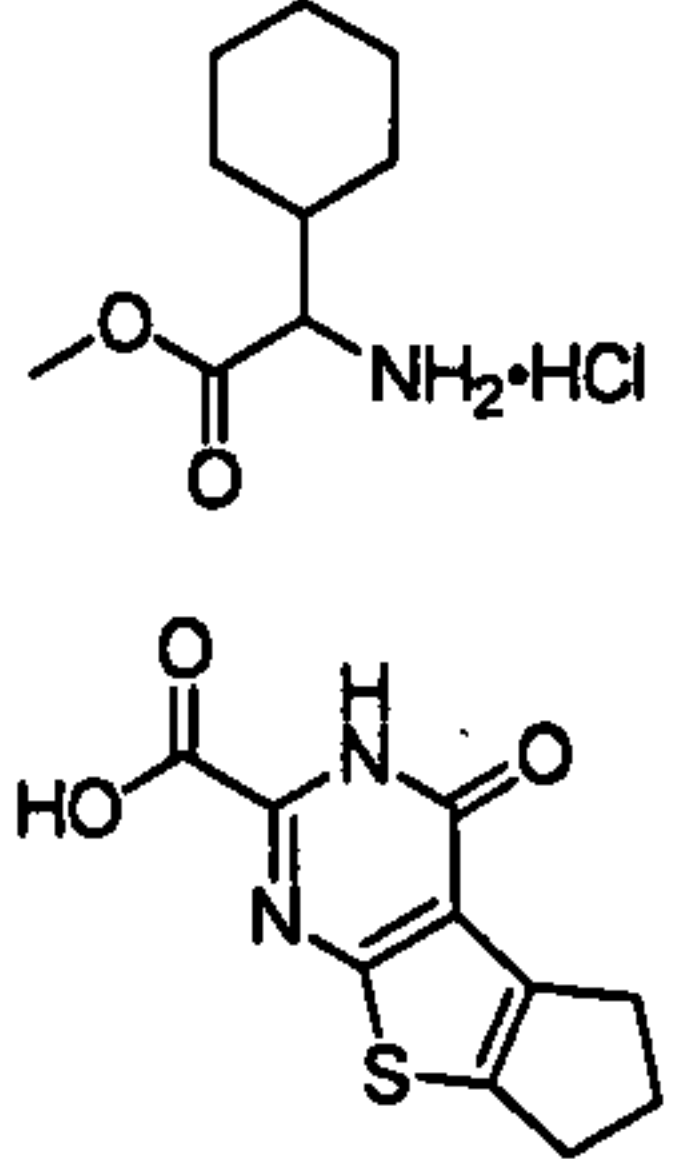
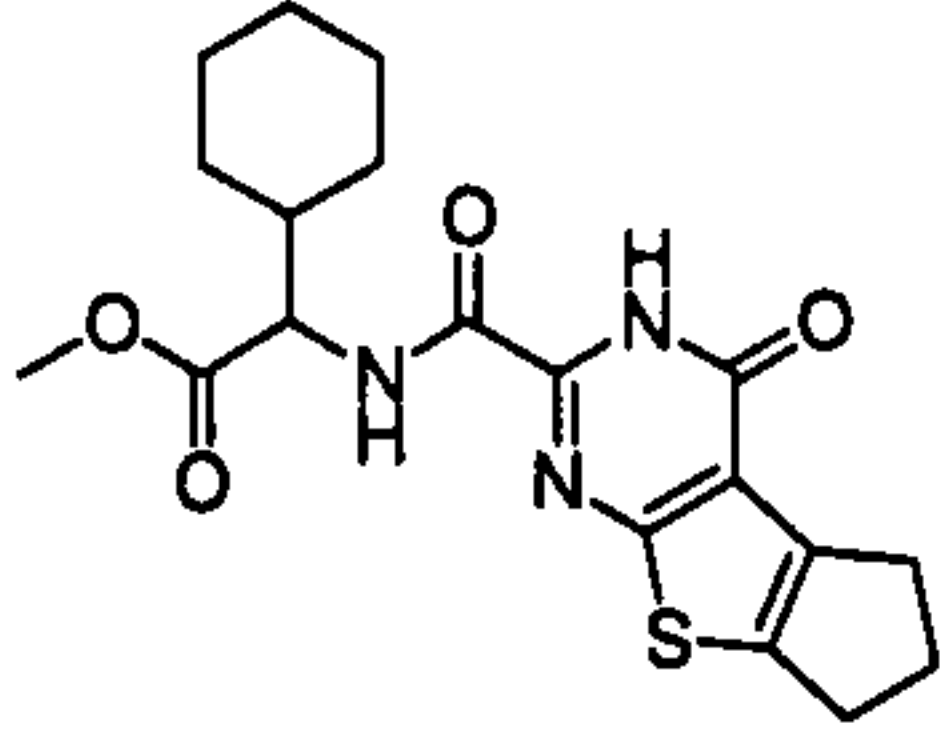
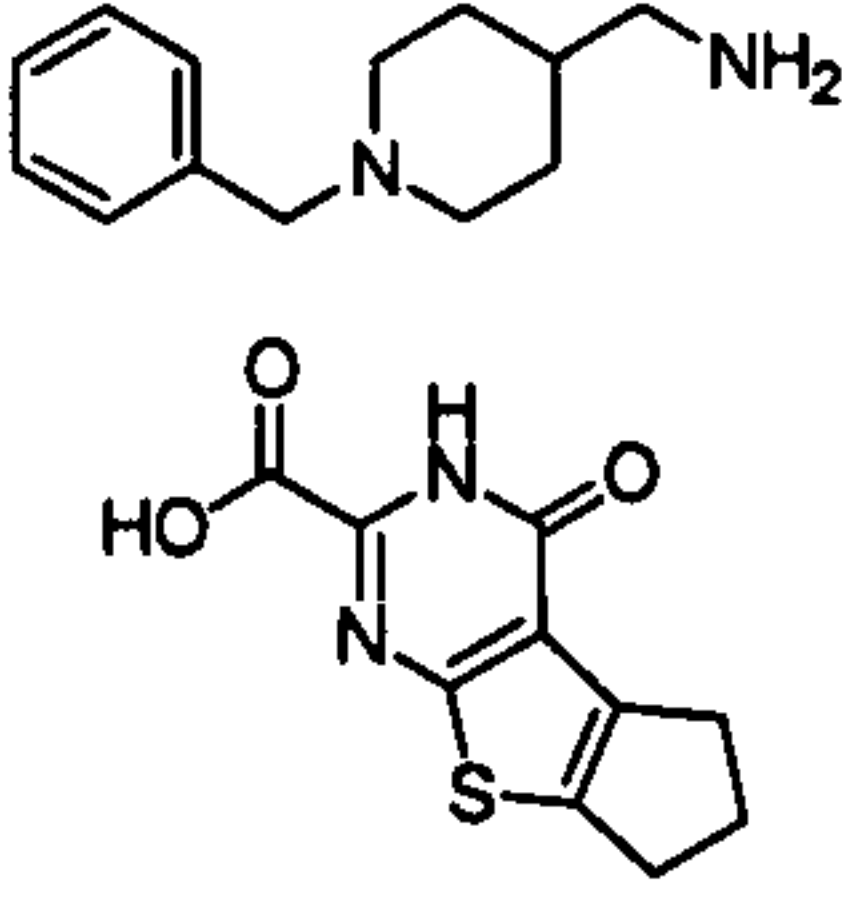
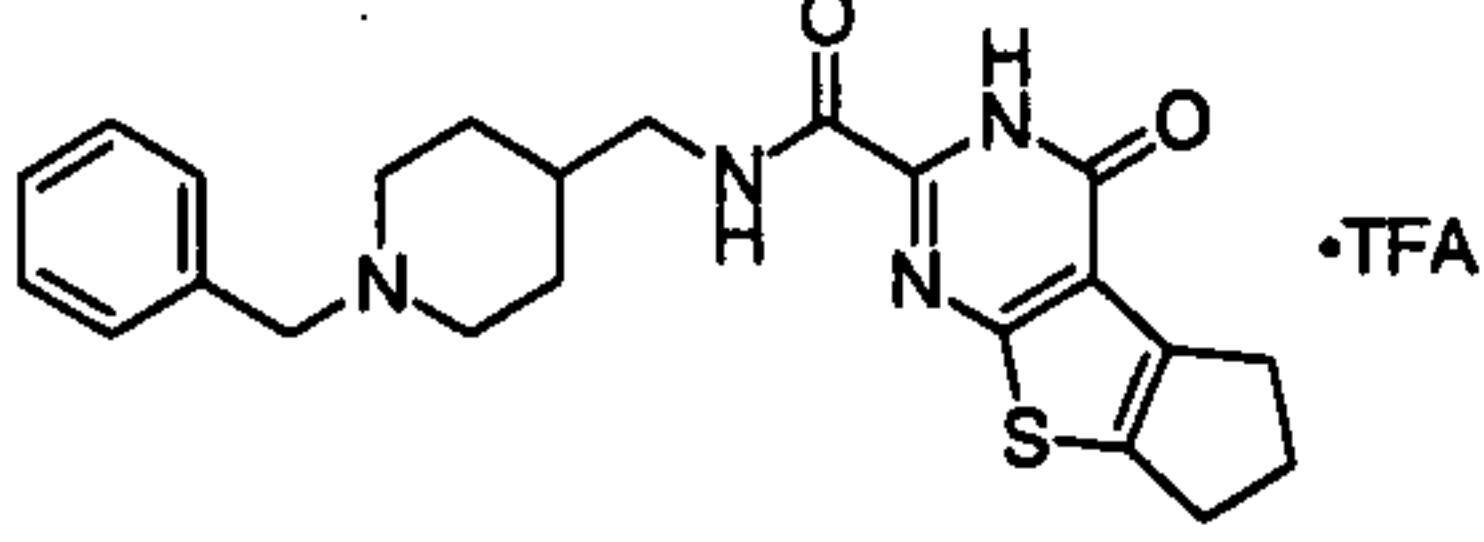
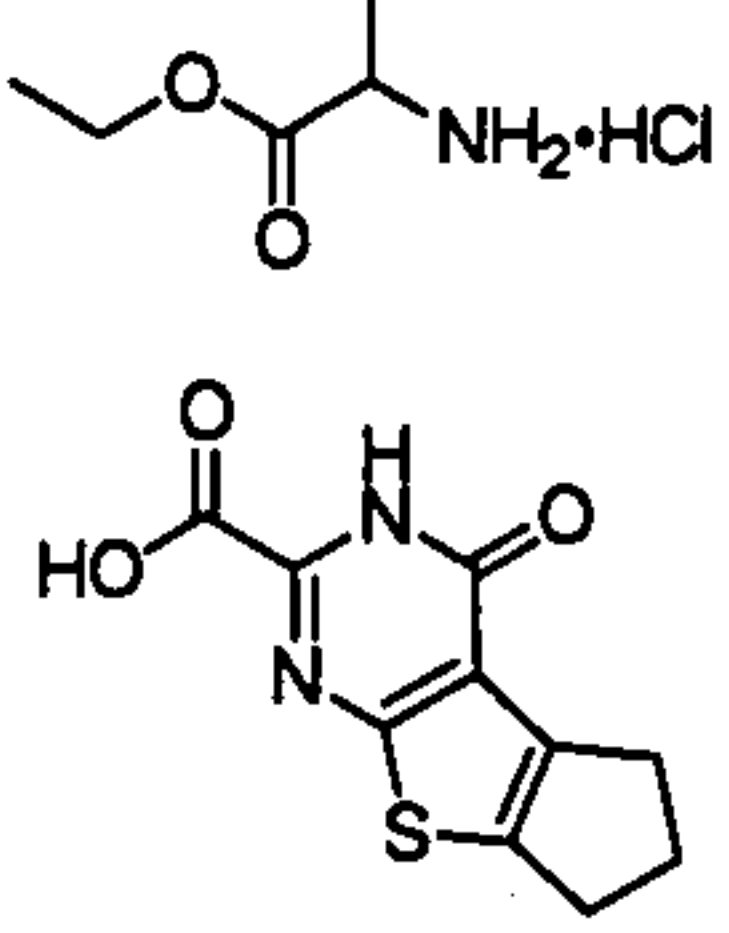
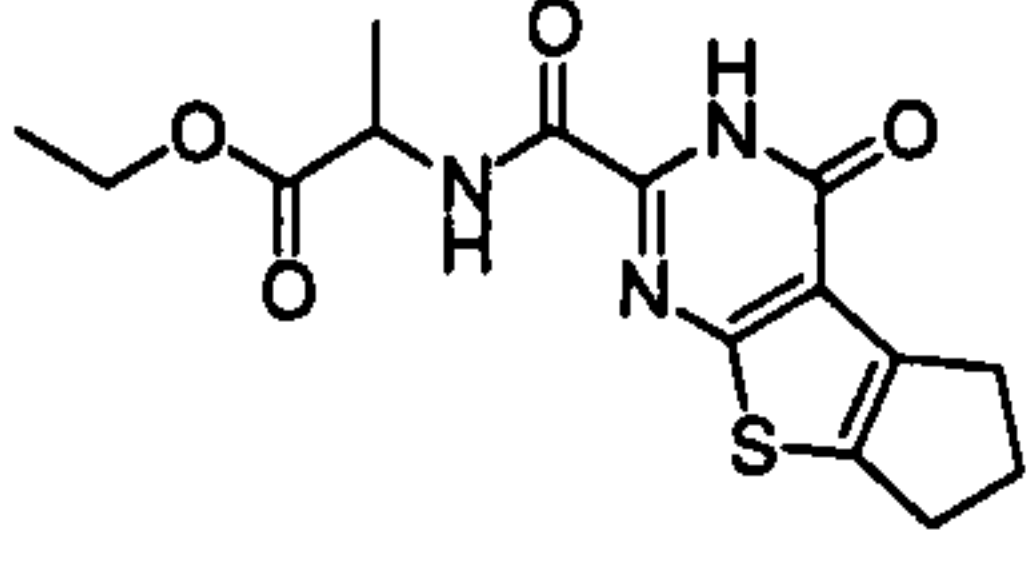
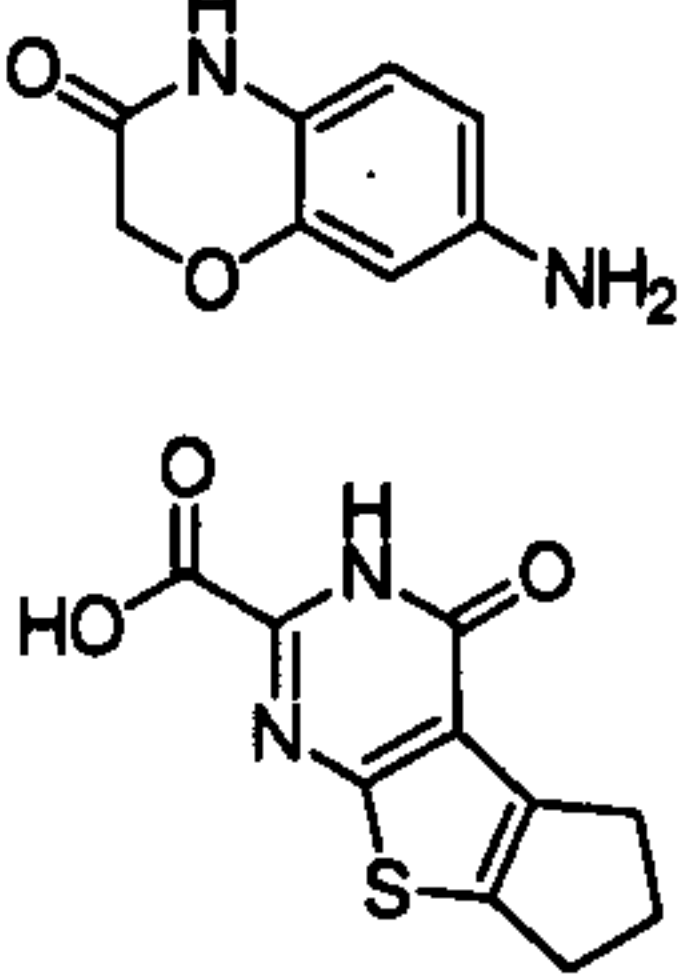
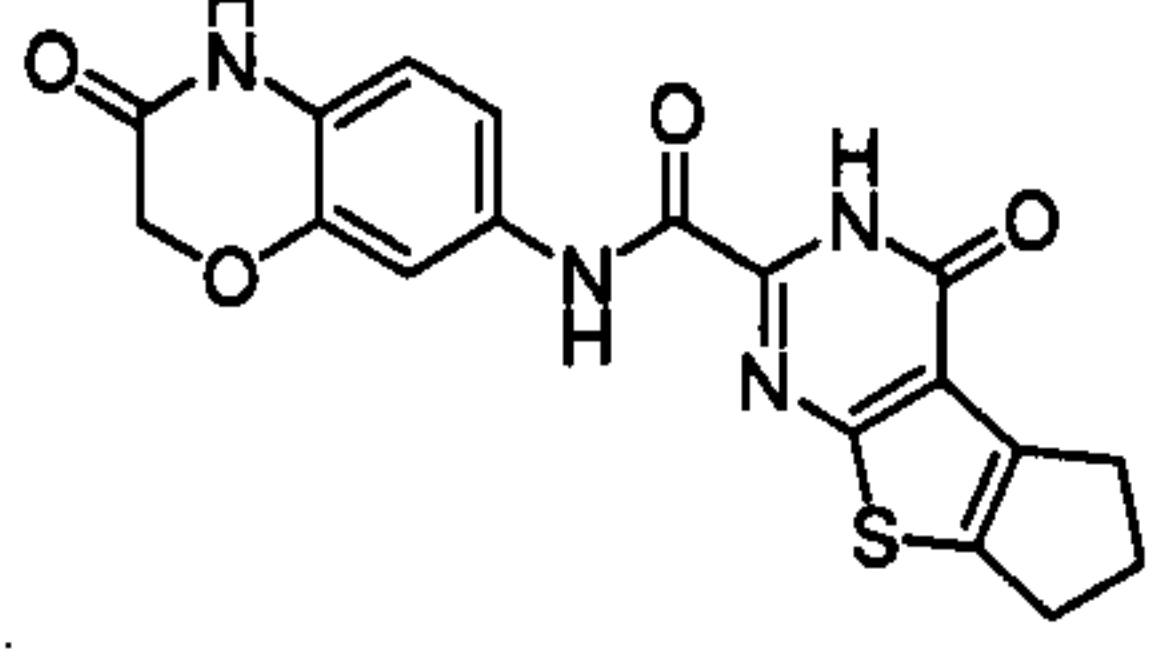
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/481 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 368    |
| 2/482 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 386    |
| 2/483 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 452 |
| 2/484 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 466    |
| 2/485 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 320    |

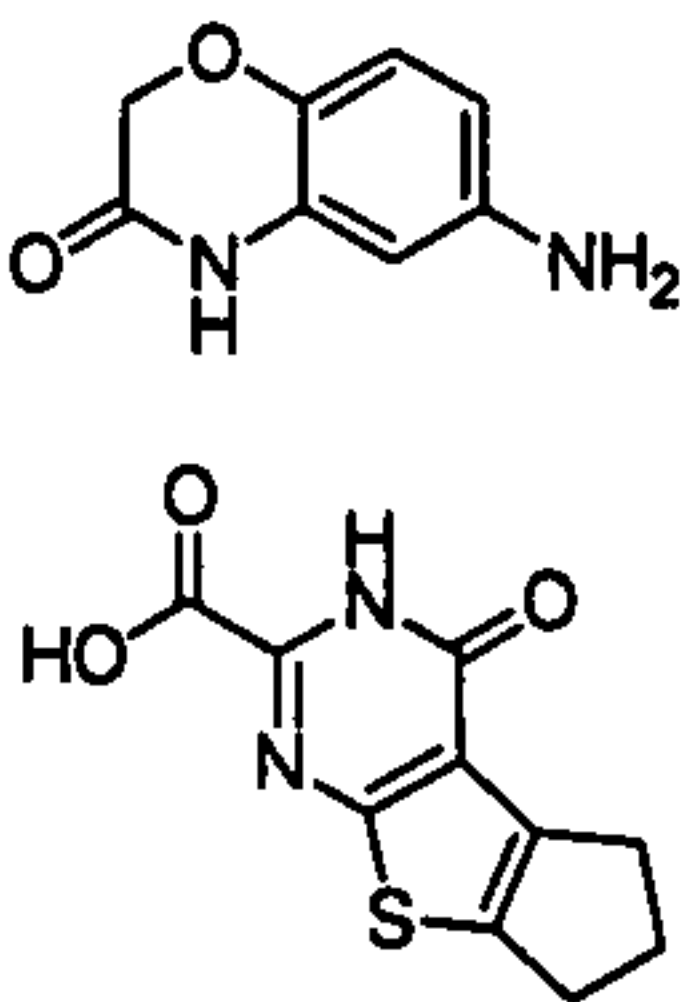
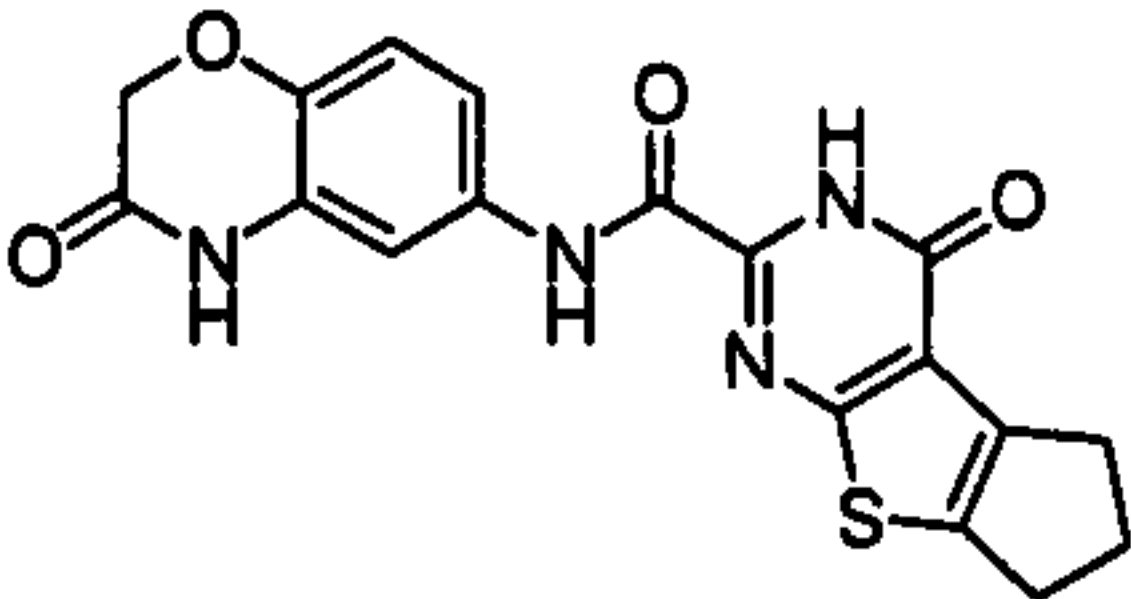
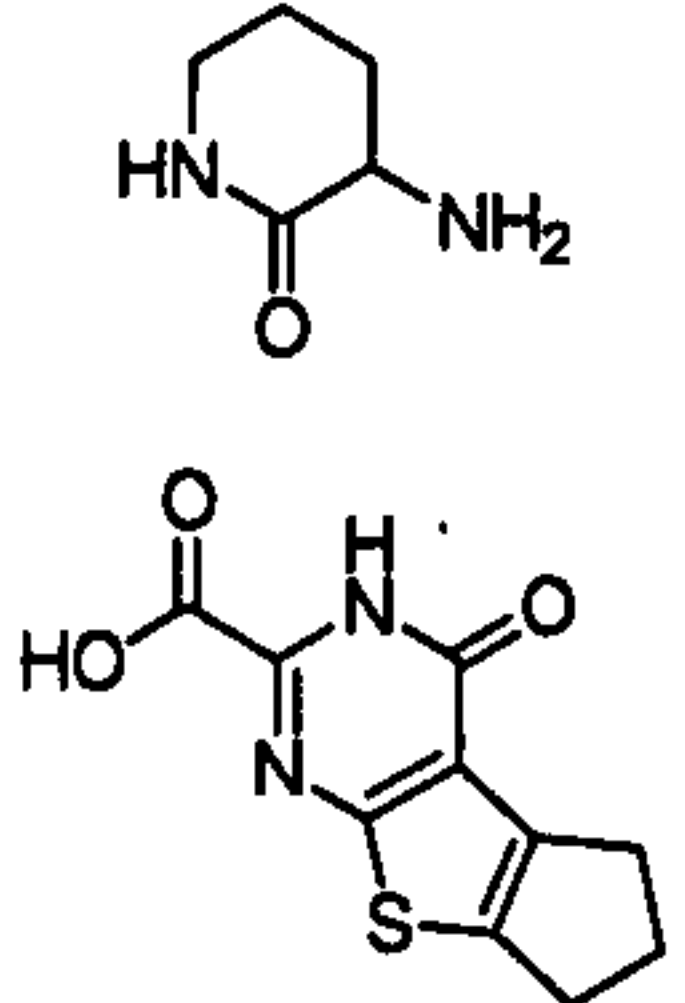
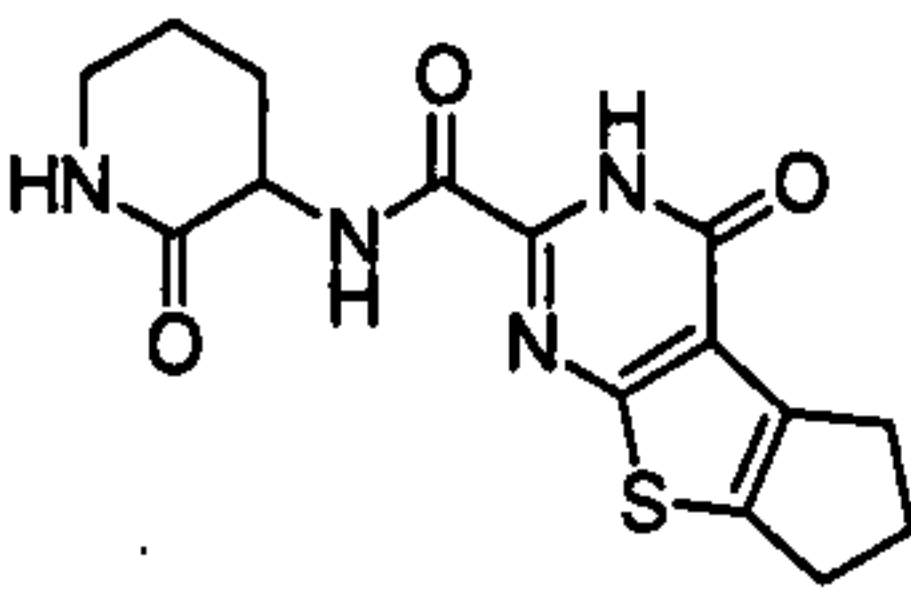
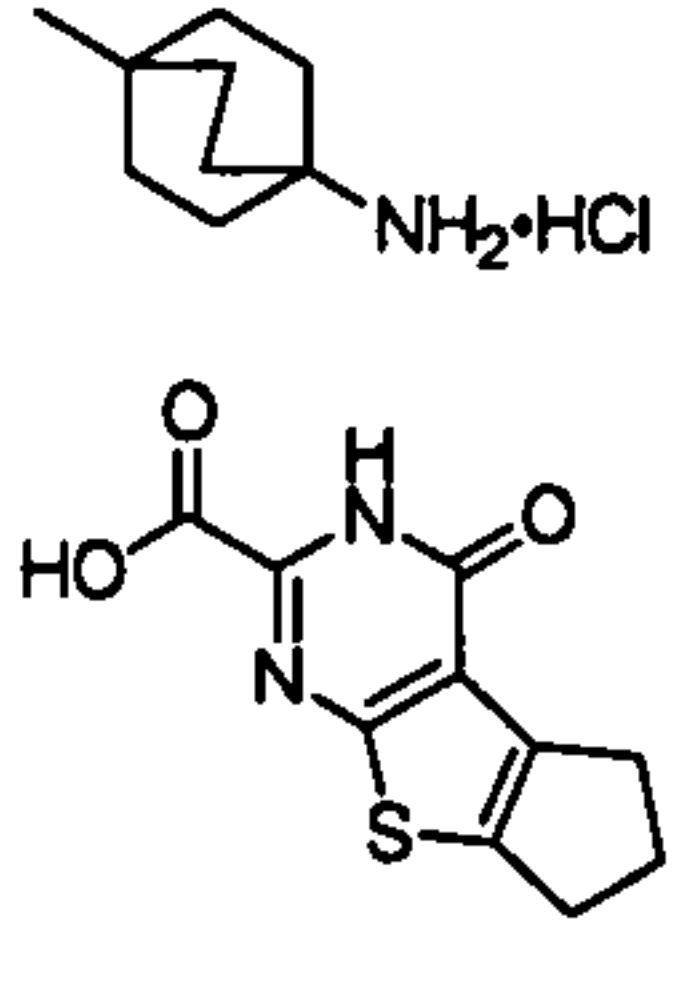
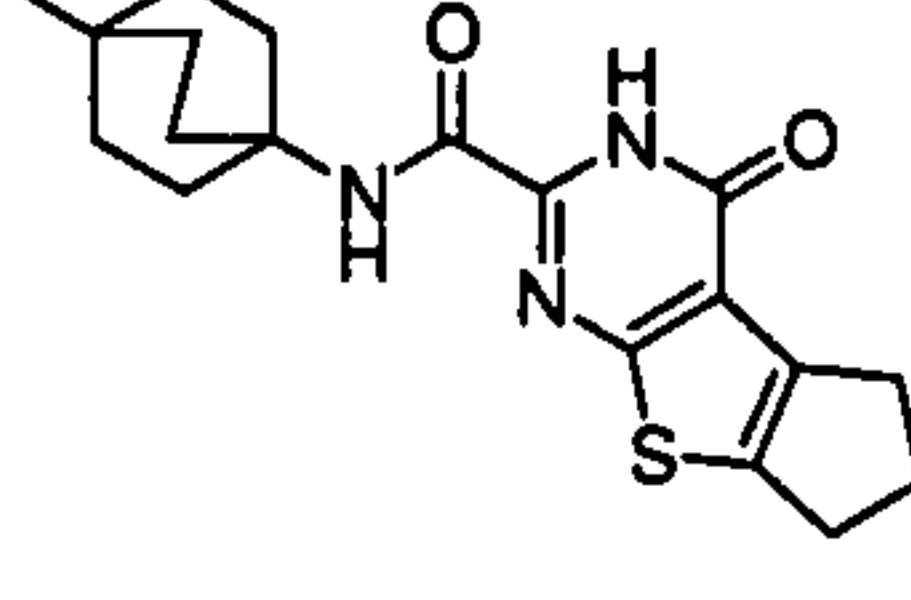
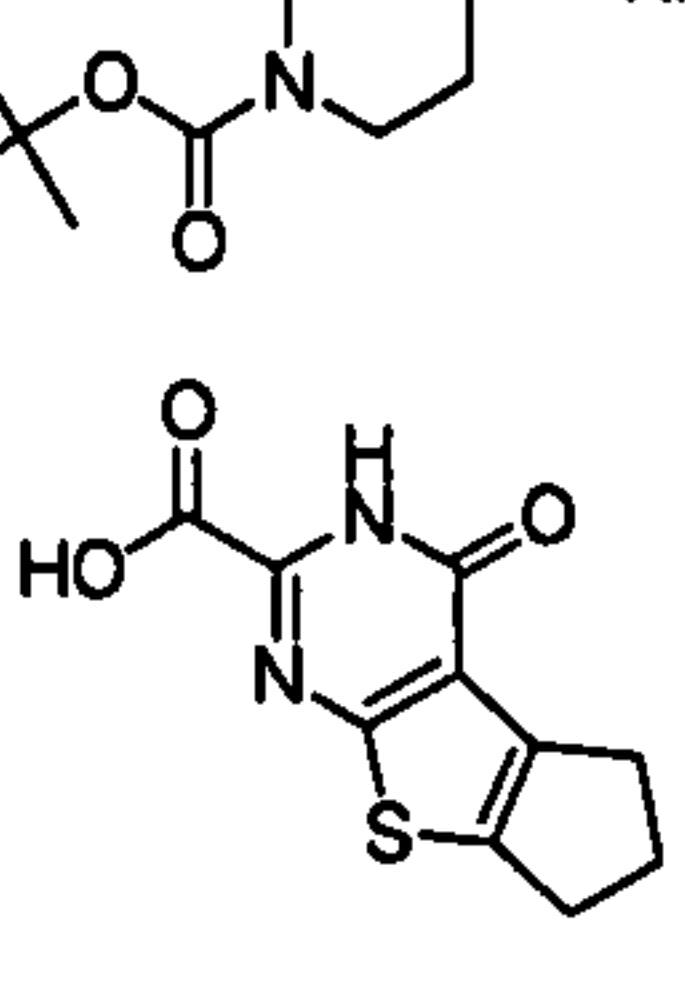
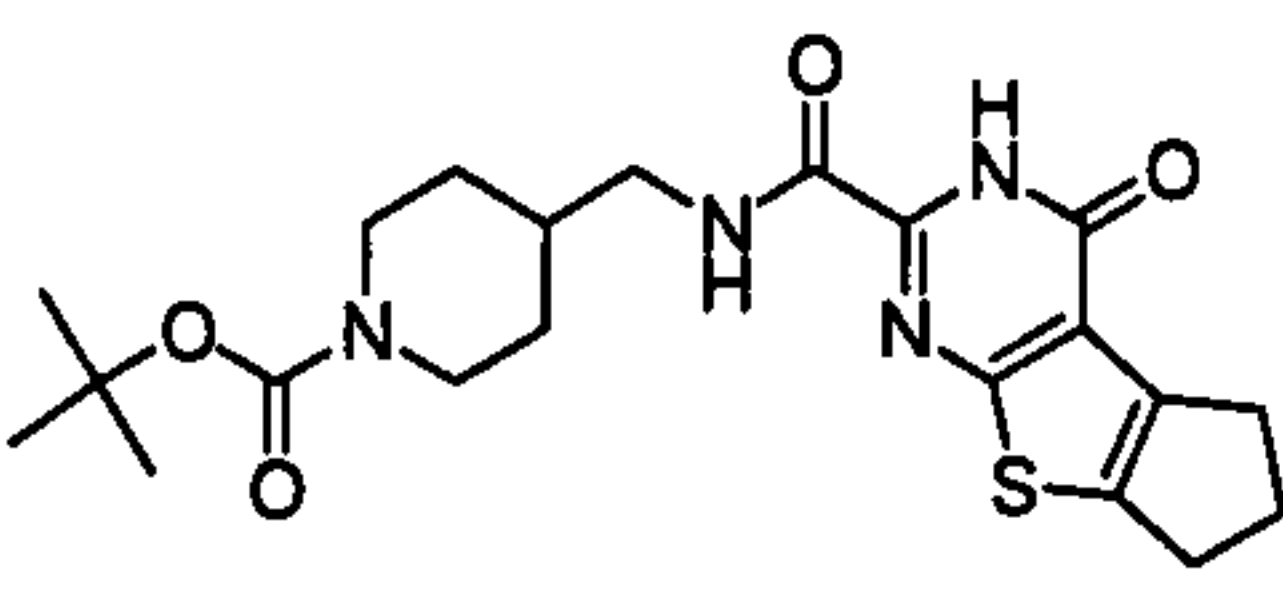
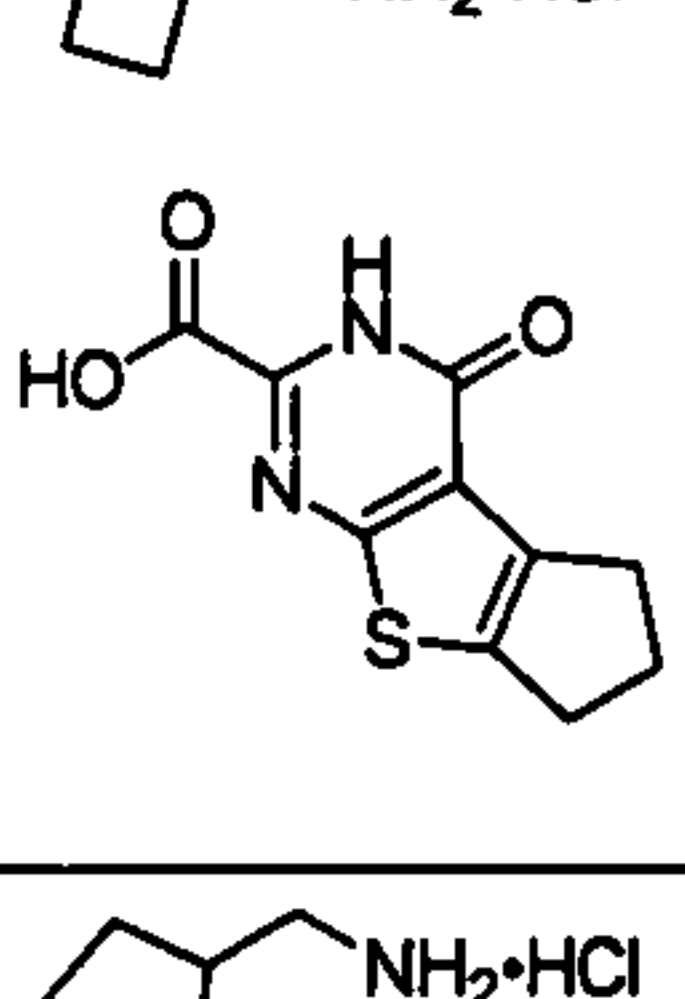
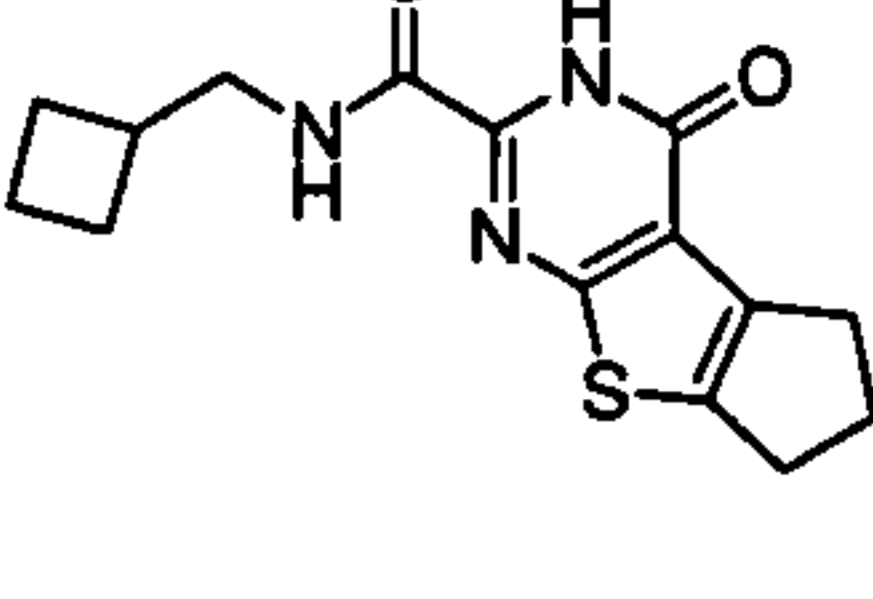
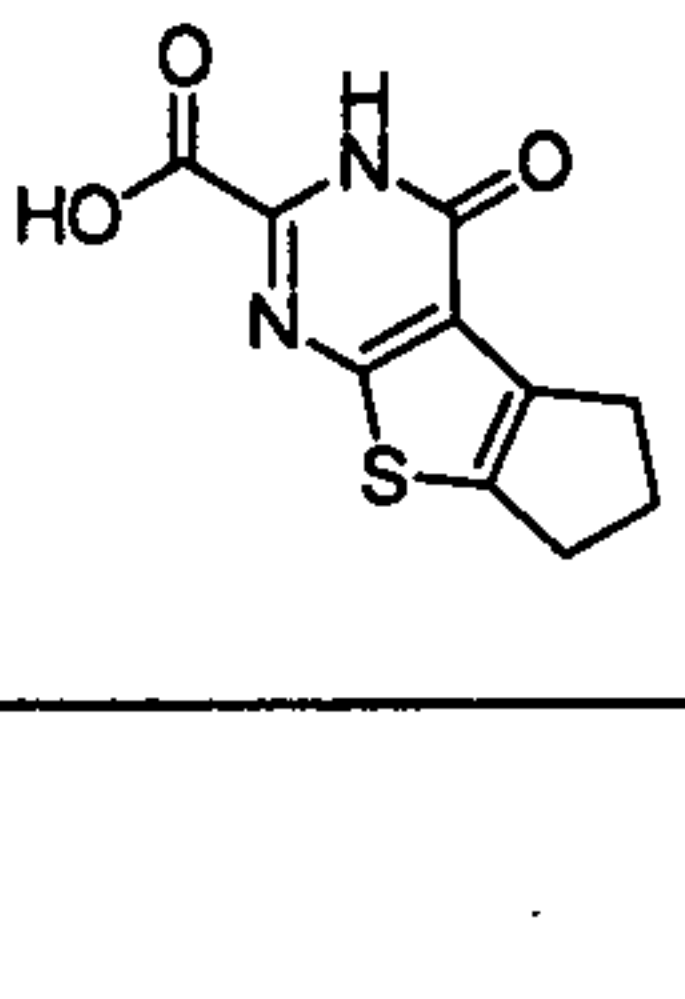
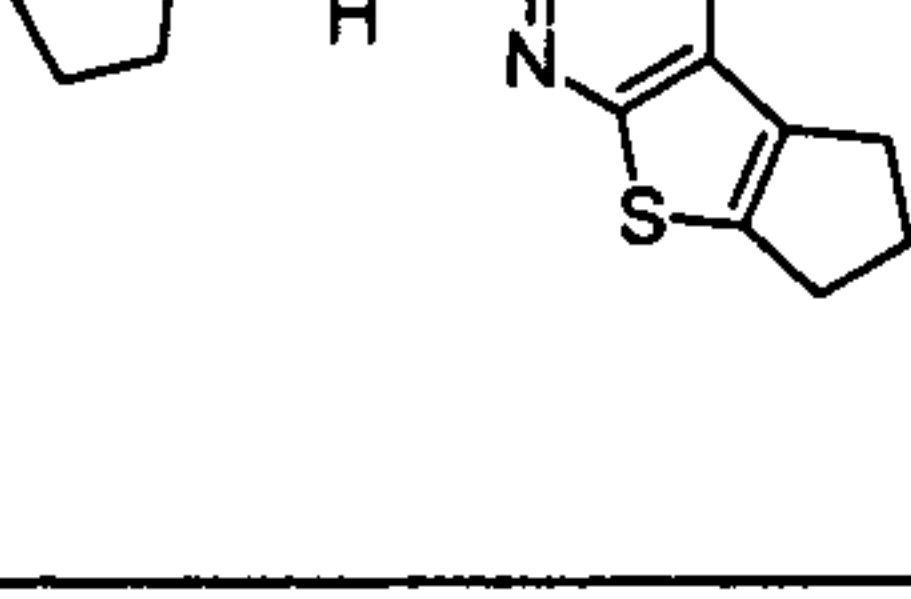
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                             |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------|
| 2/486 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 411  |
| 2/487 |   |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 411  |
| 2/488 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>404/406 |
| 2/489 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>348     |
| 2/490 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>315     |

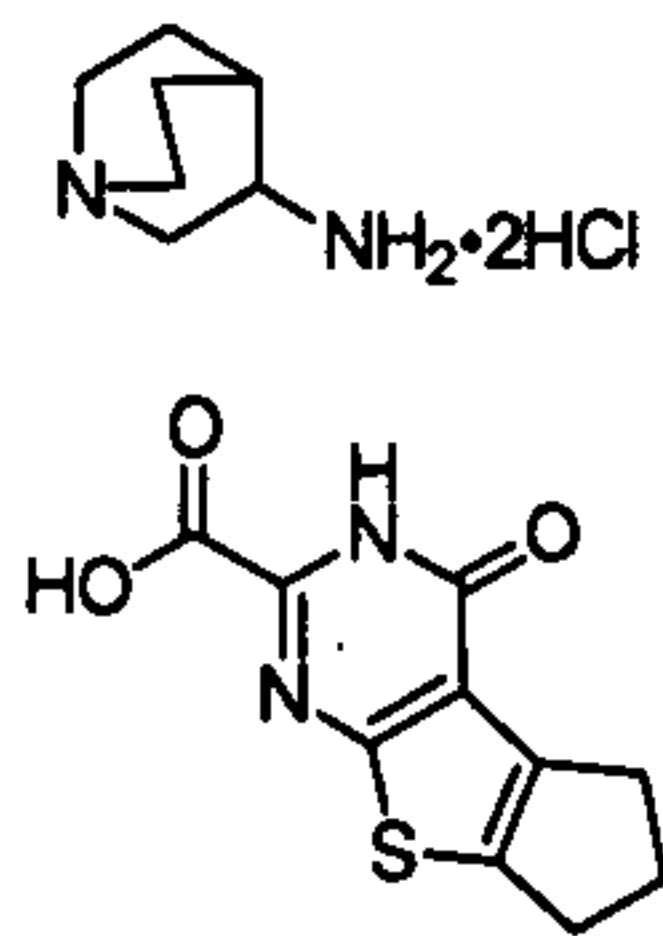
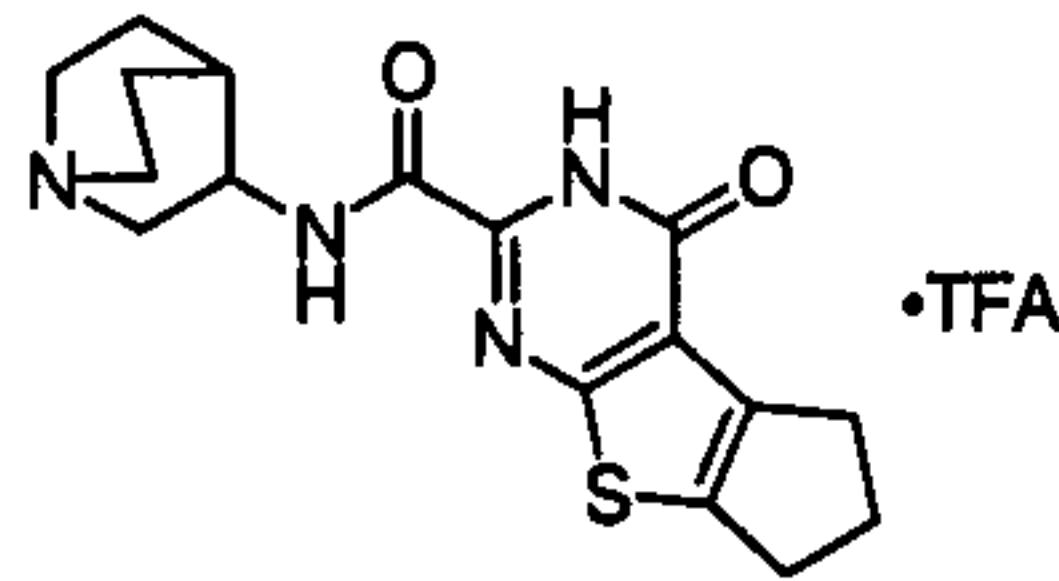
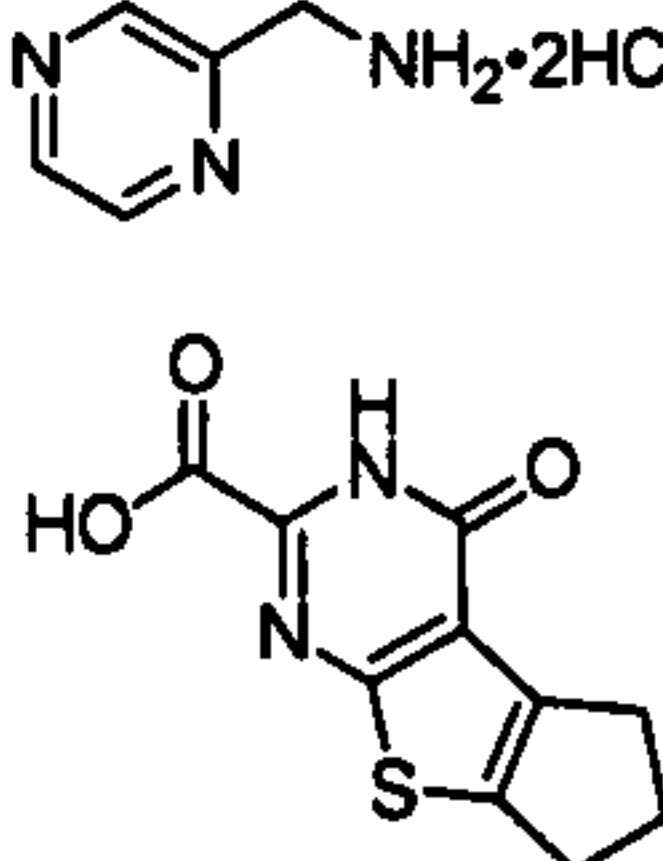
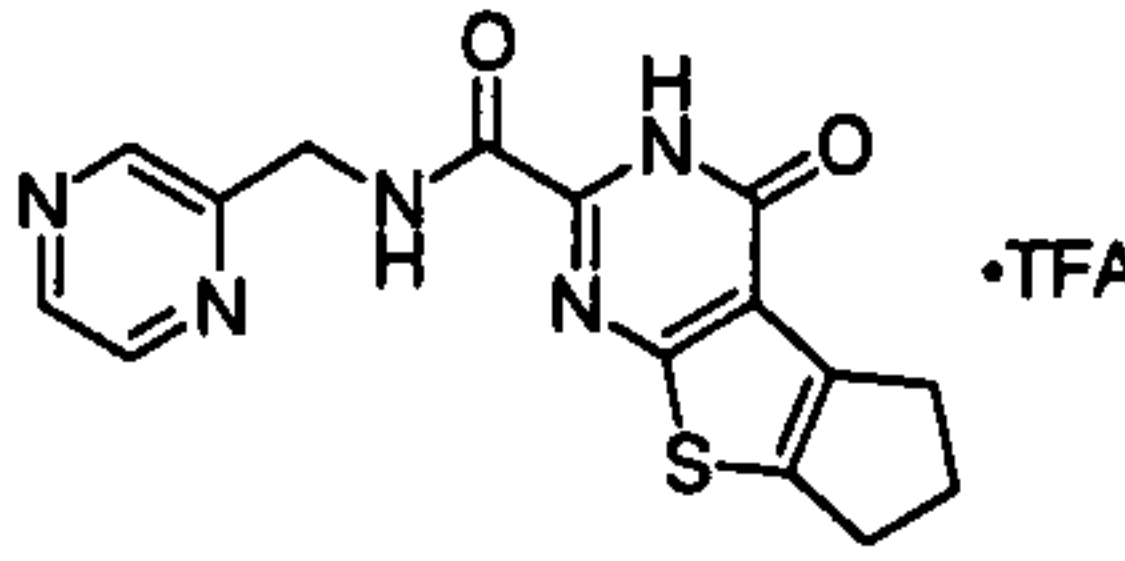
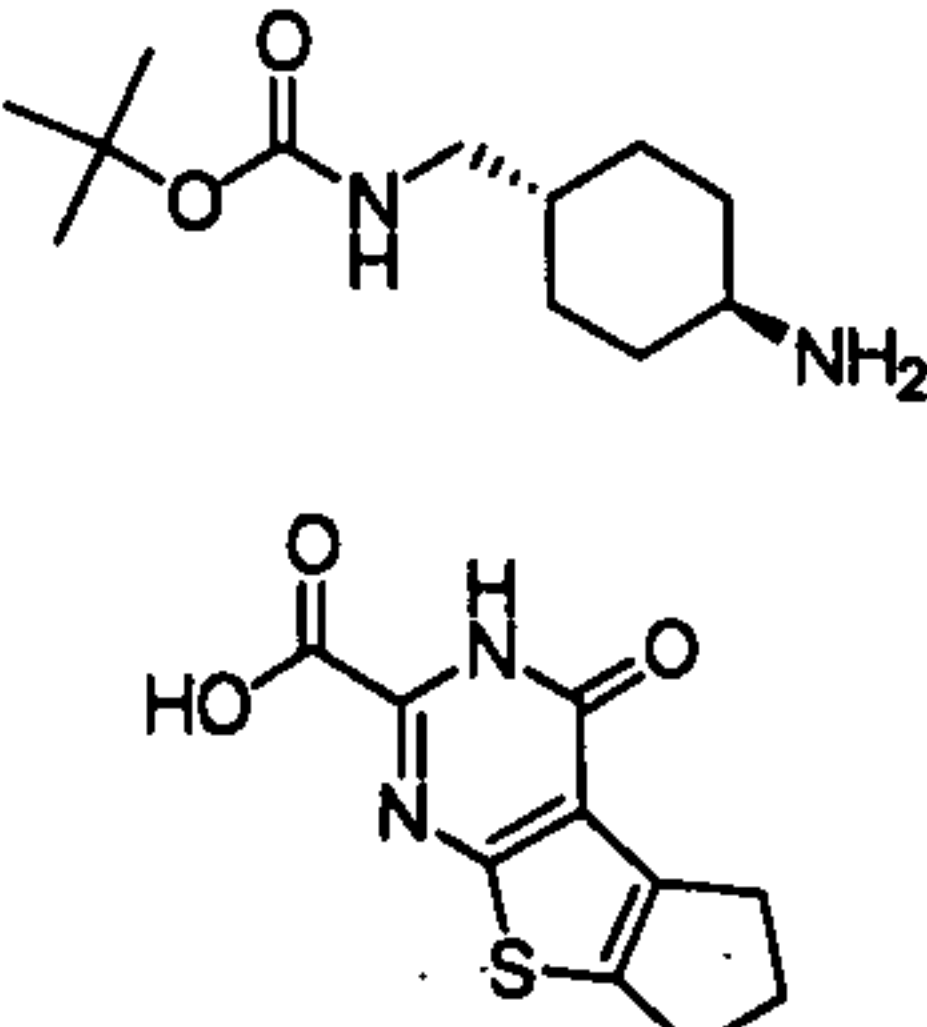
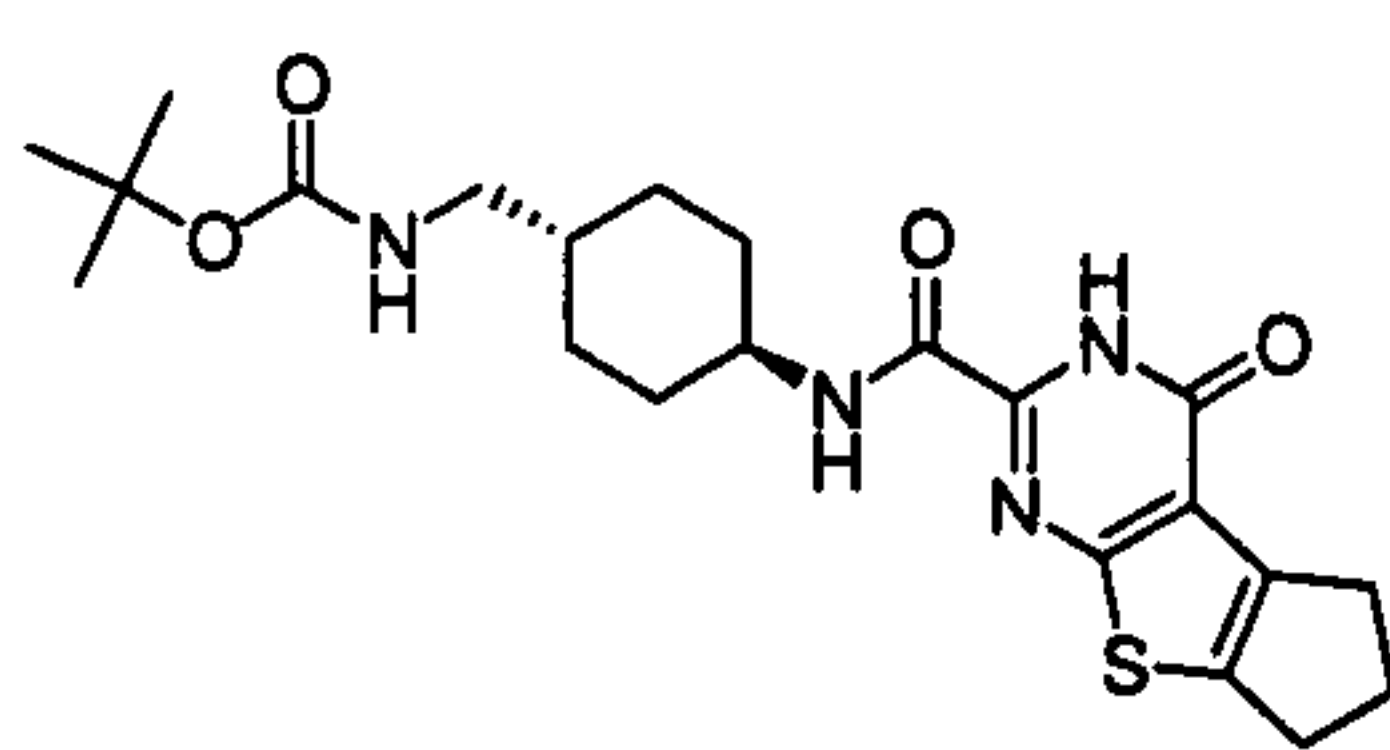
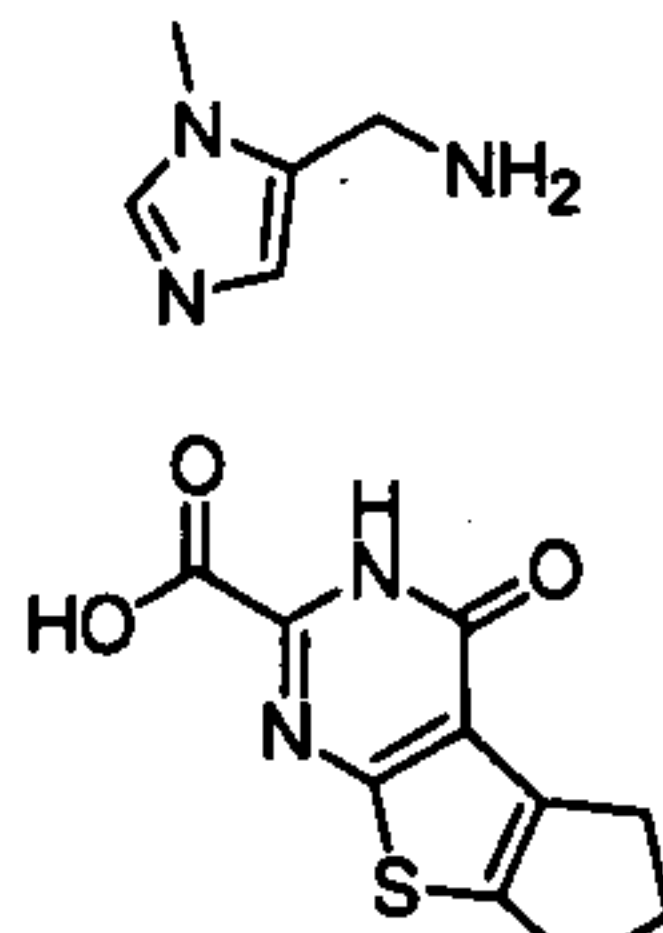
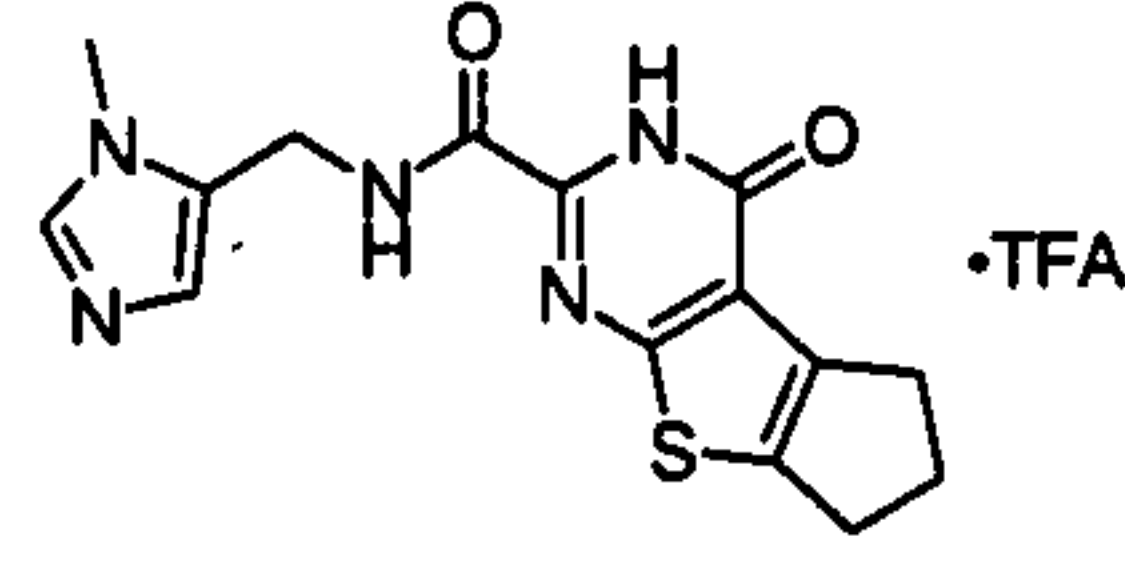
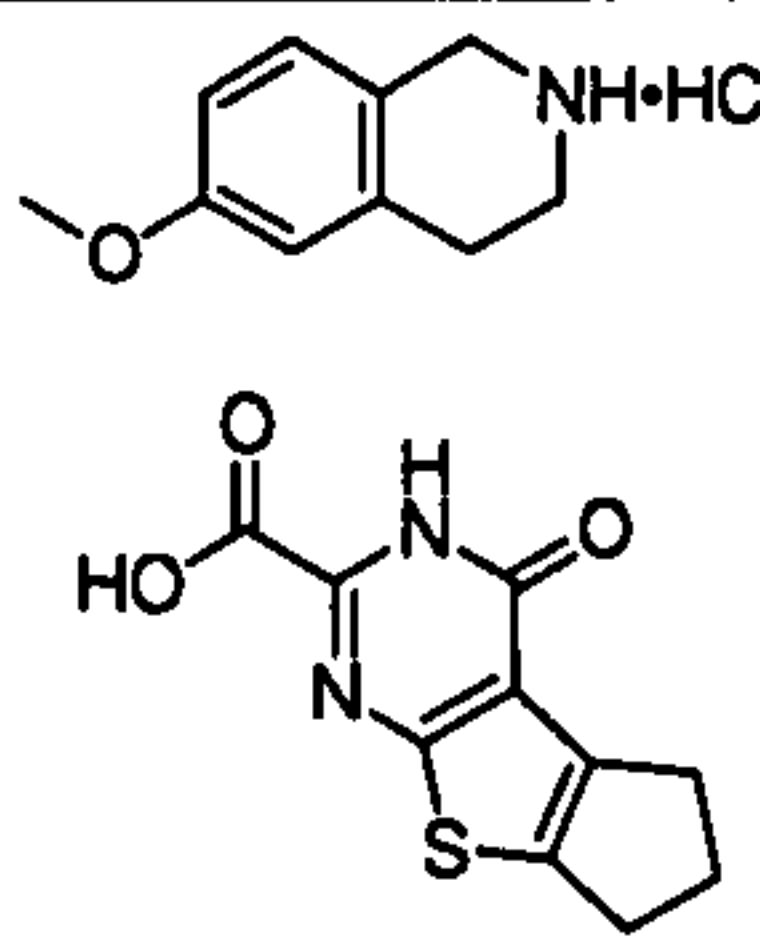
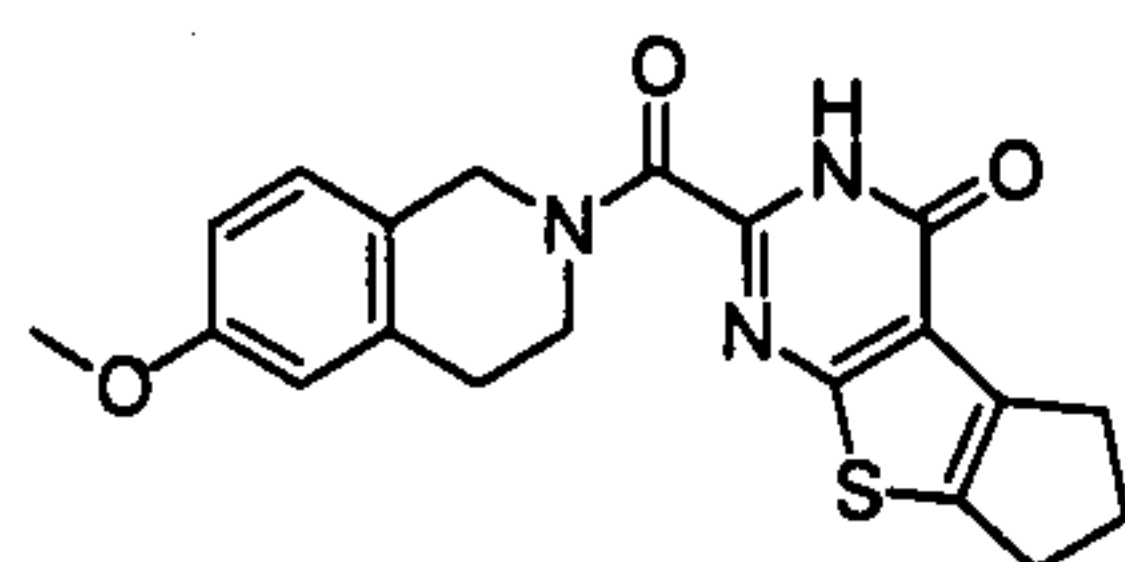
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                             |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------|
| 2/491 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 355  |
| 2/492 |   |  | B, n.d.<br>[MH] <sup>+</sup> =<br>292     |
| 2/493 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>368     |
| 2/494 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>462     |
| 2/495 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>422/424 |

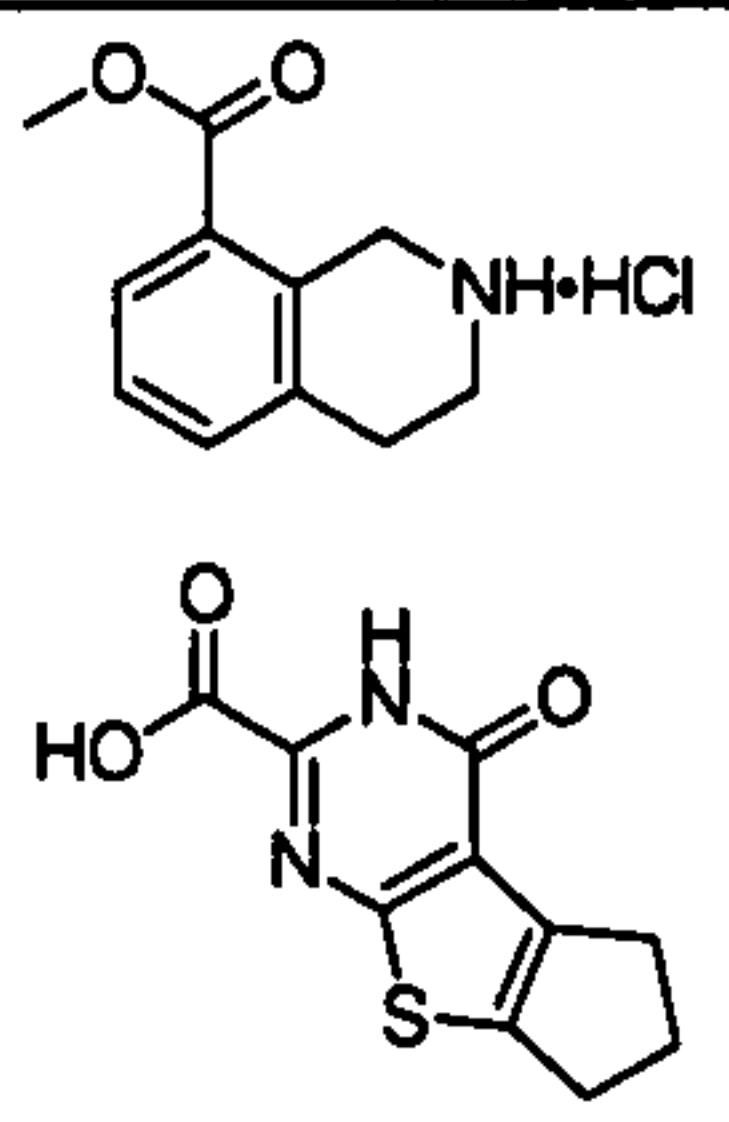
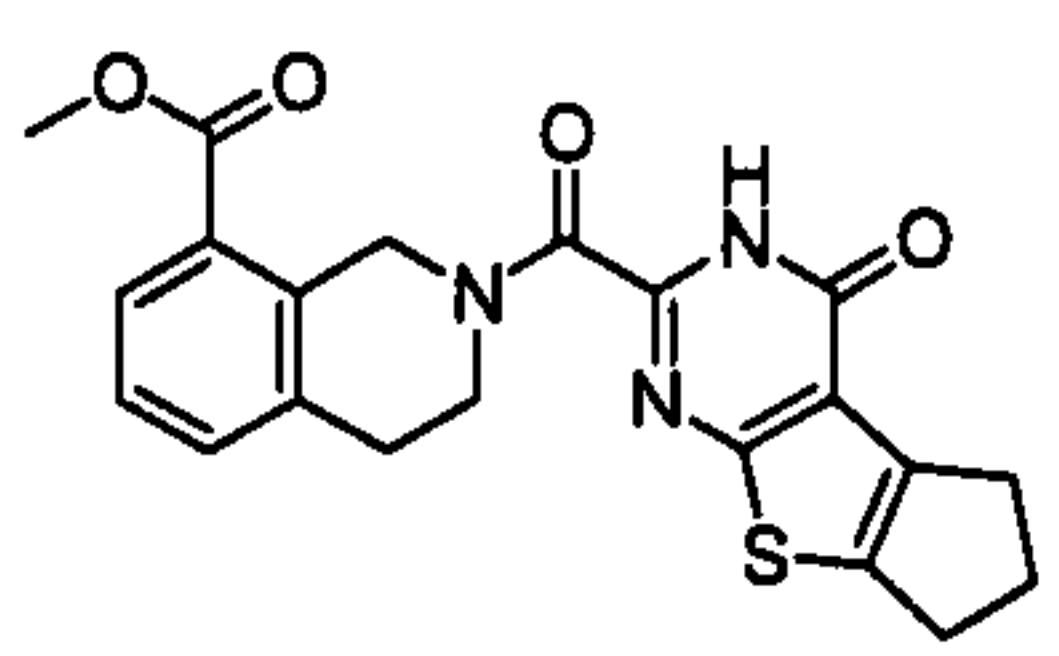
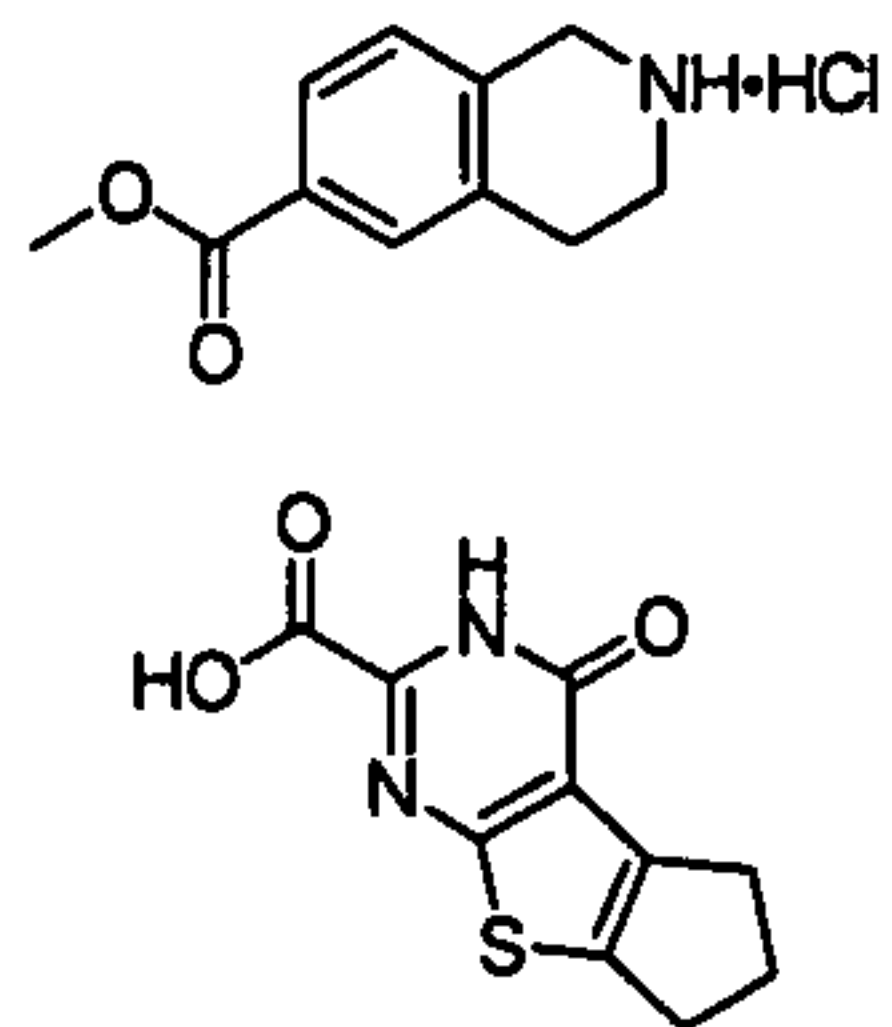
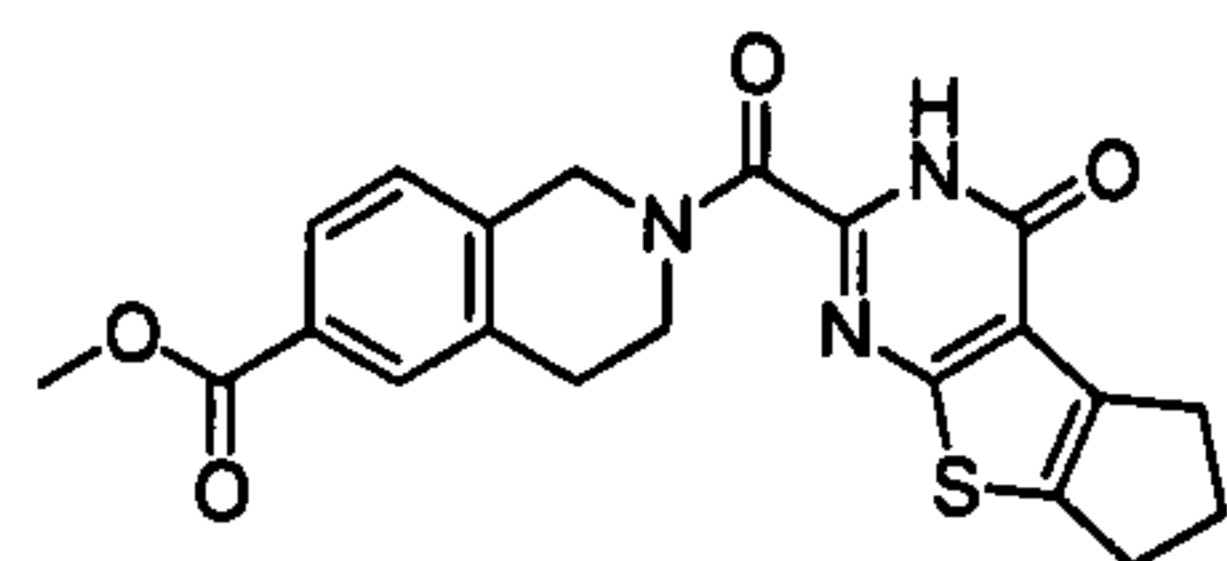
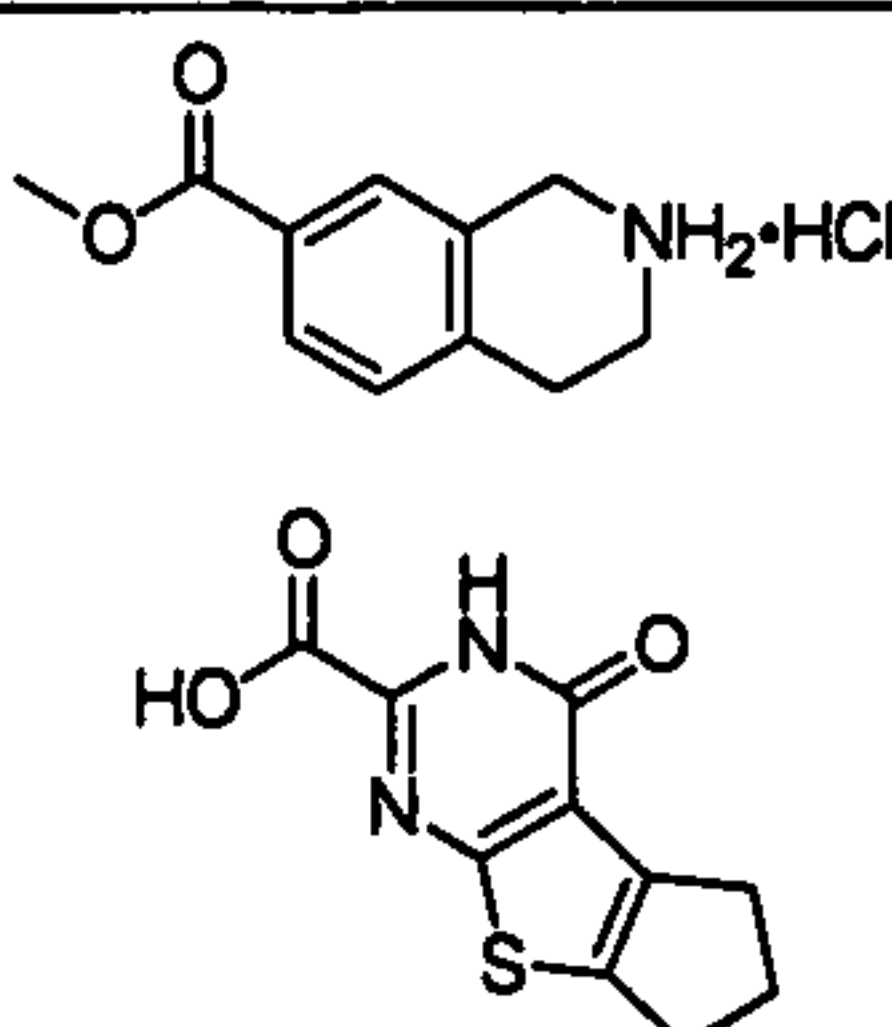
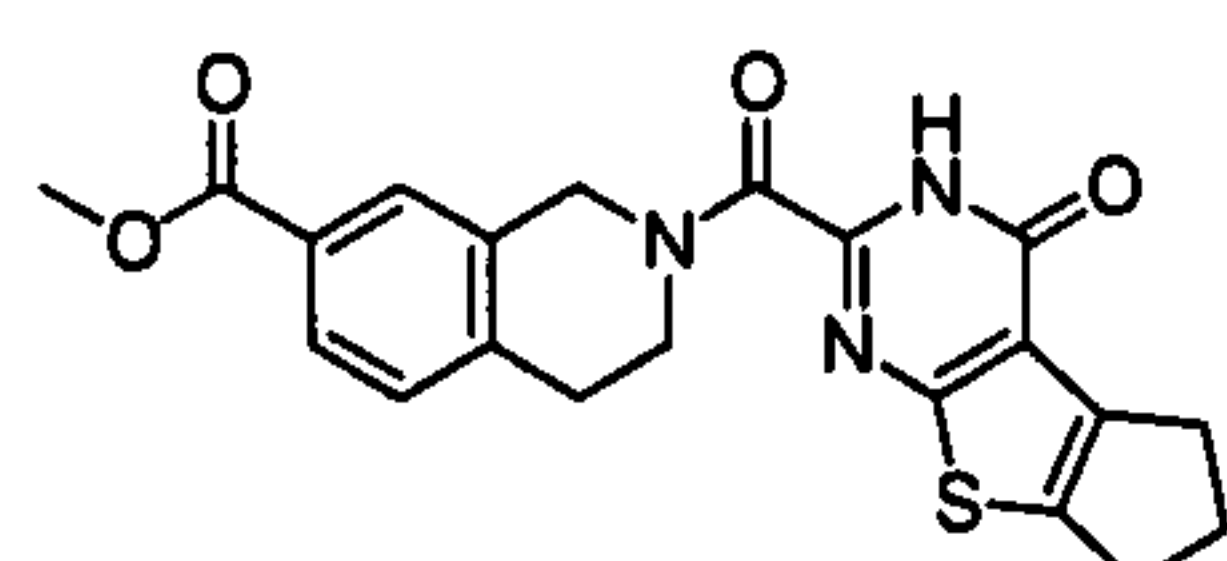
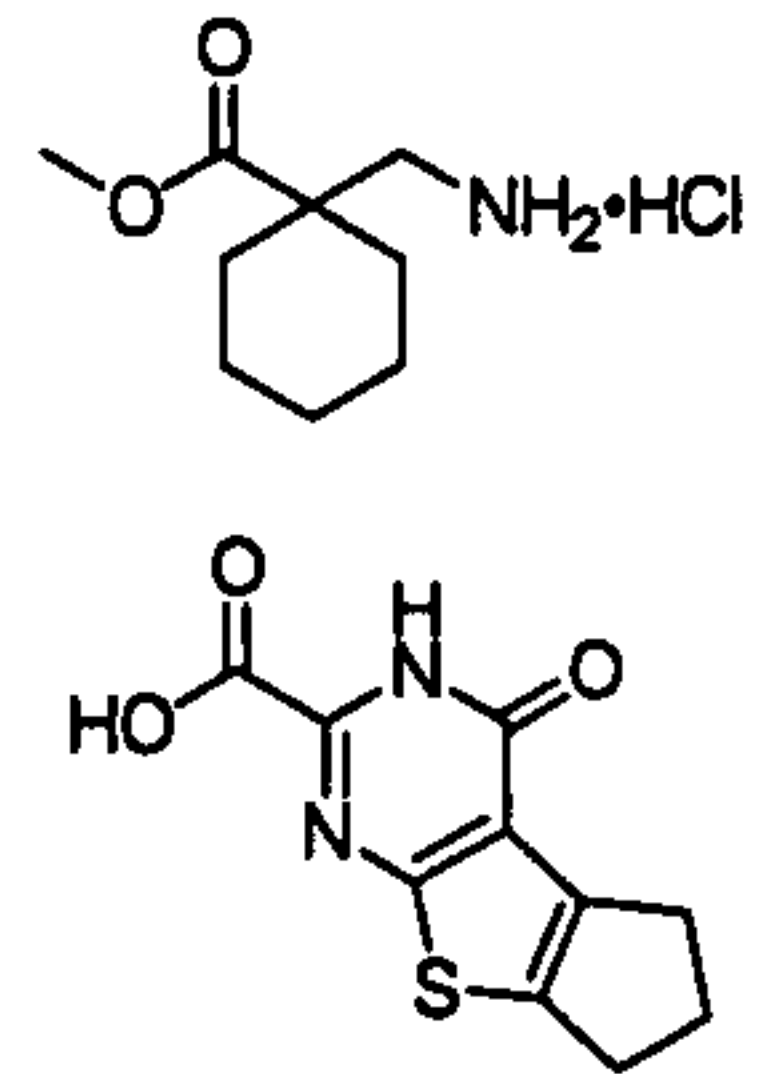
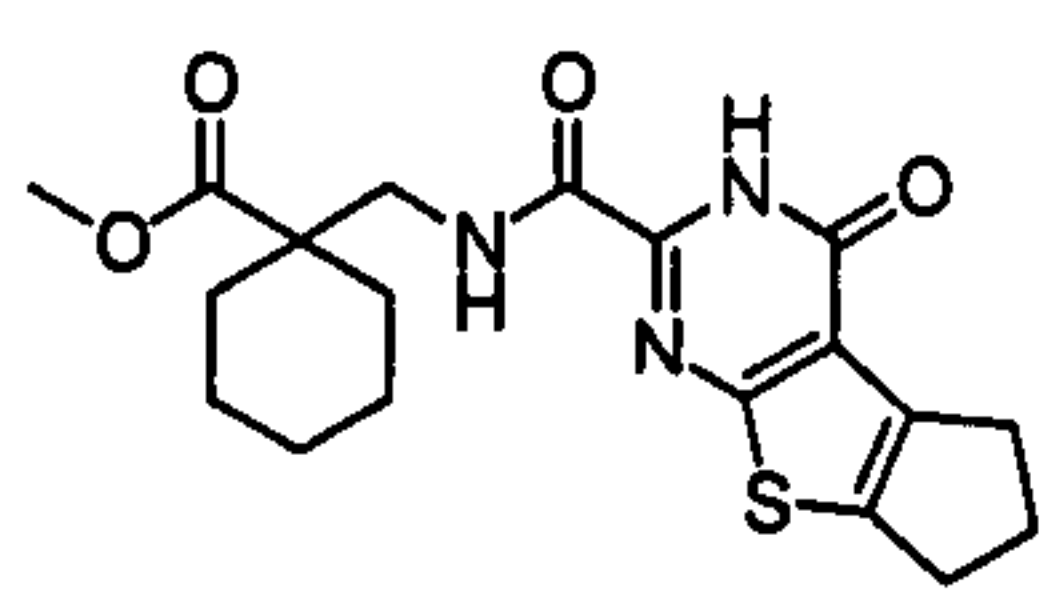
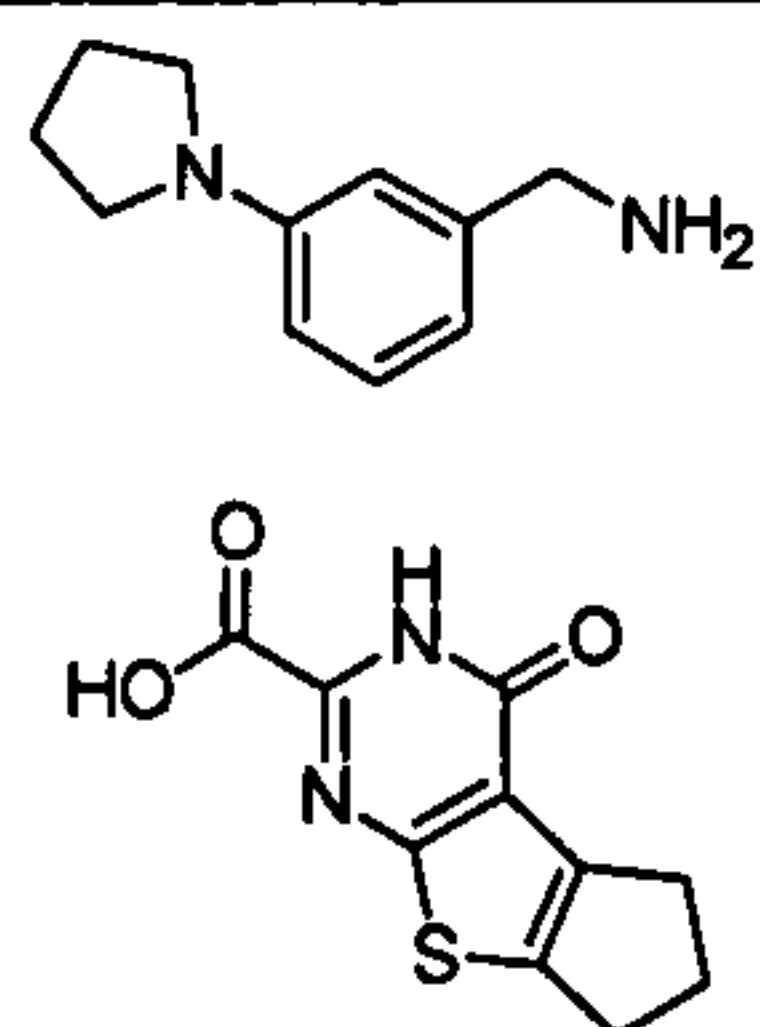
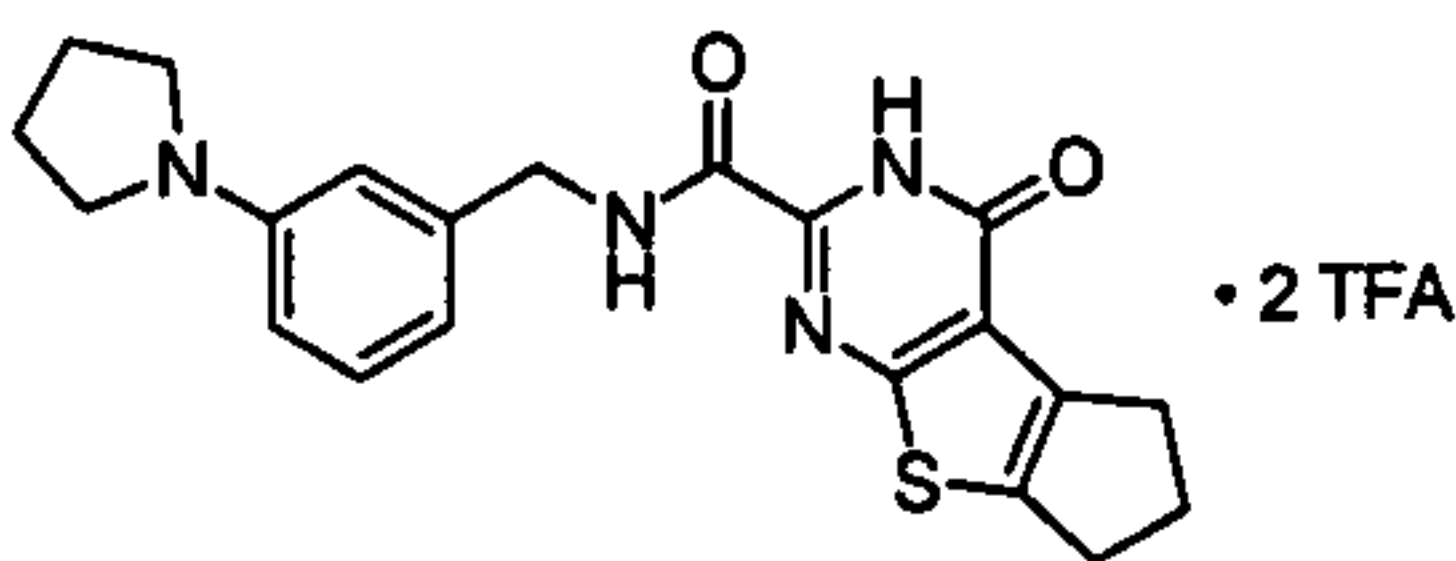
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/496 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 342 |
| 2/497 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 399 |
| 2/498 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 362 |
| 2/499 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 362 |
| 2/500 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 306 |

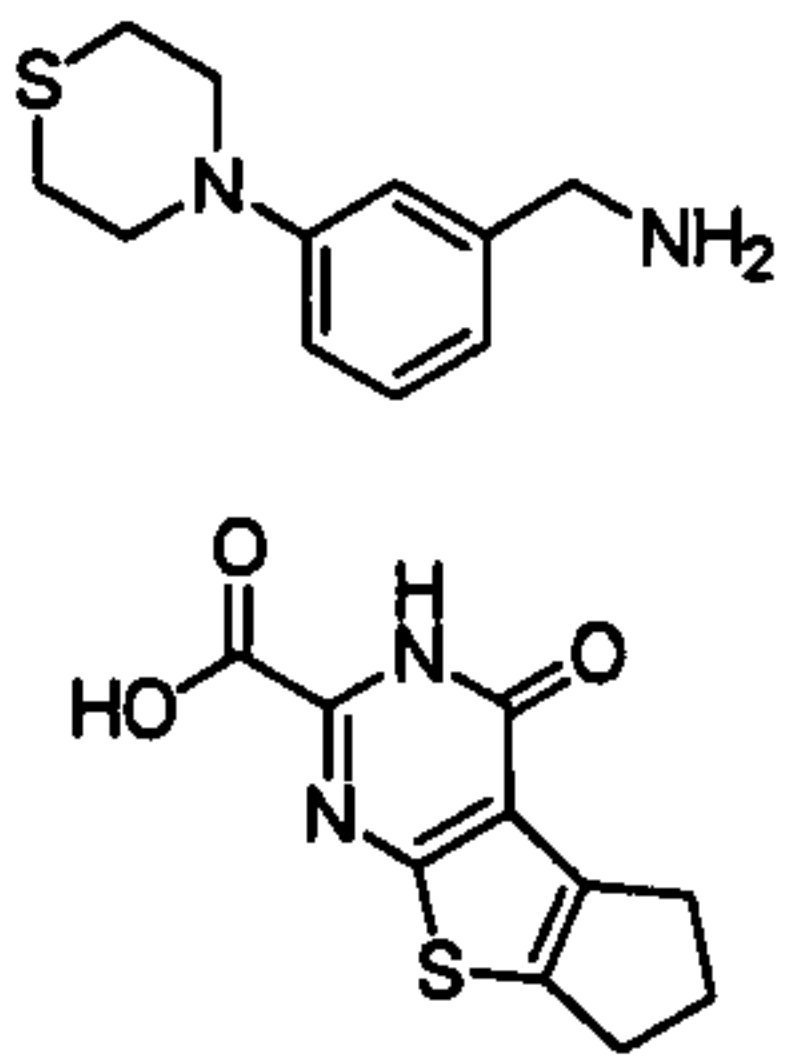
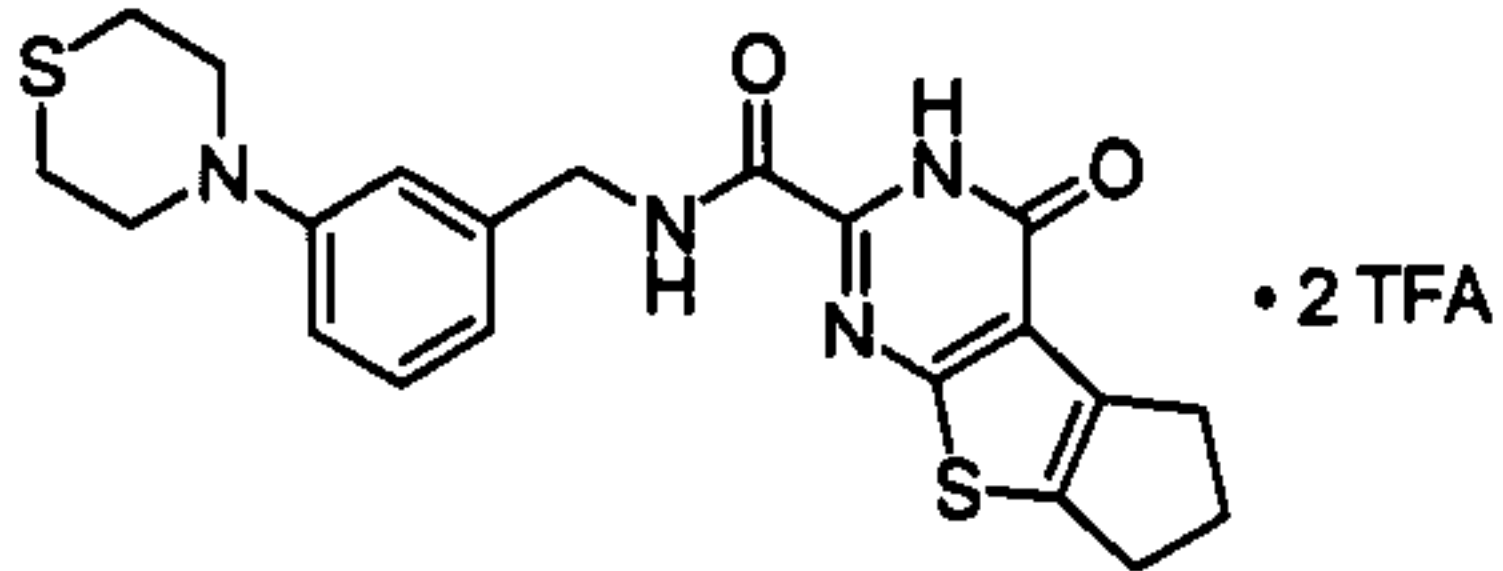
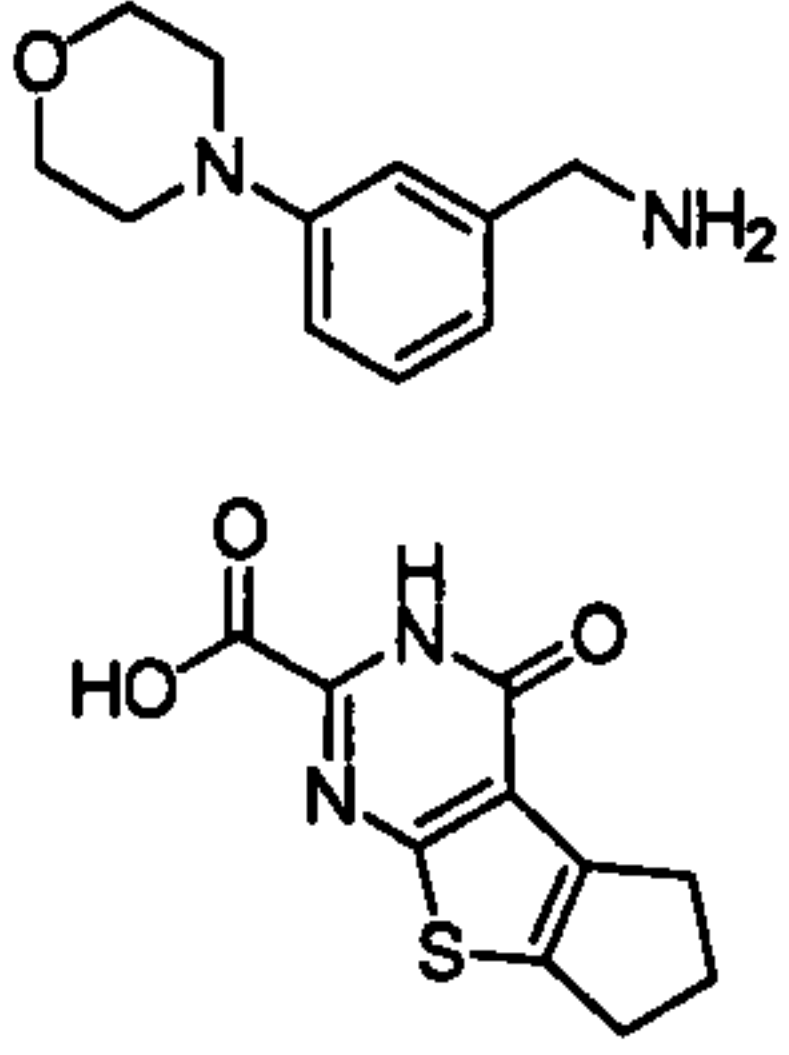
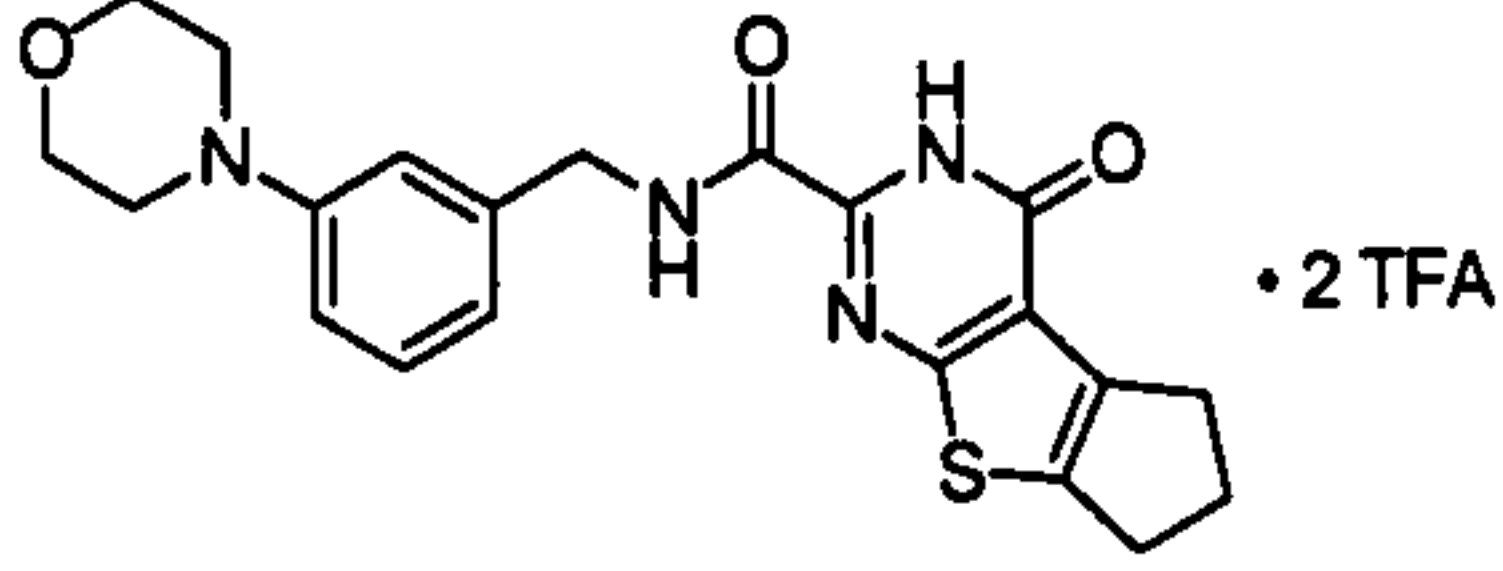
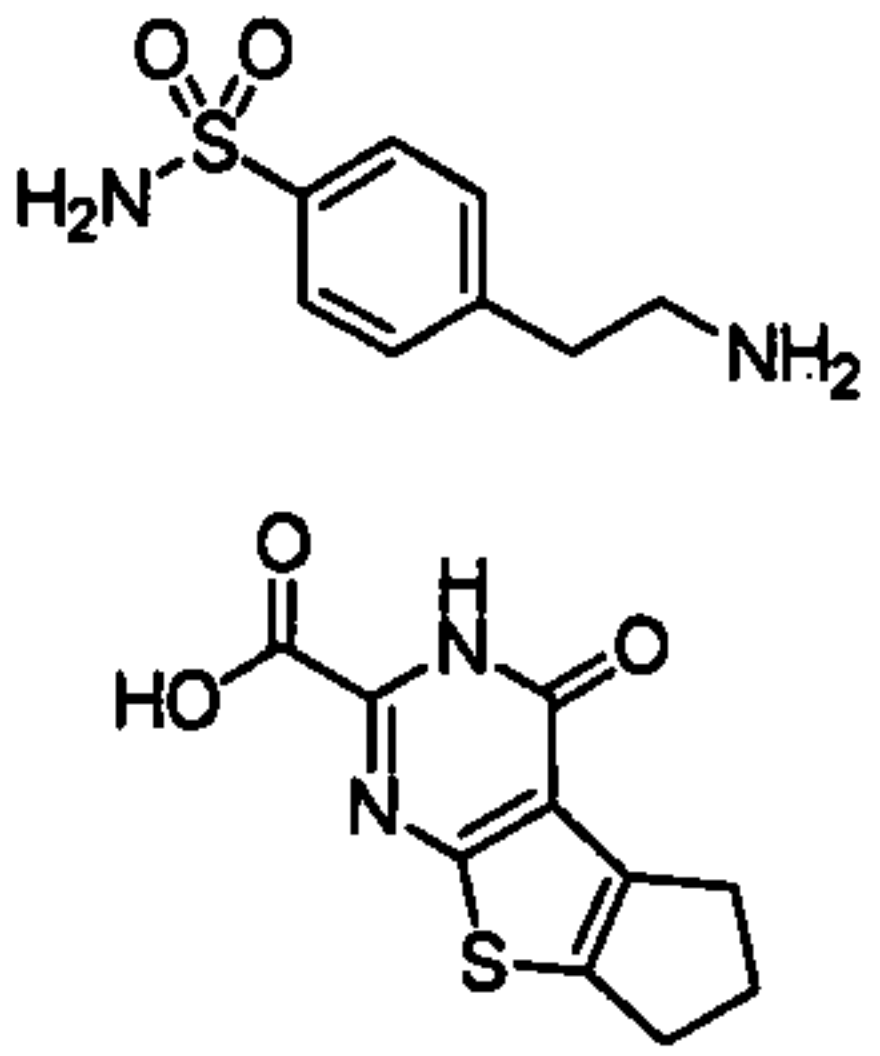
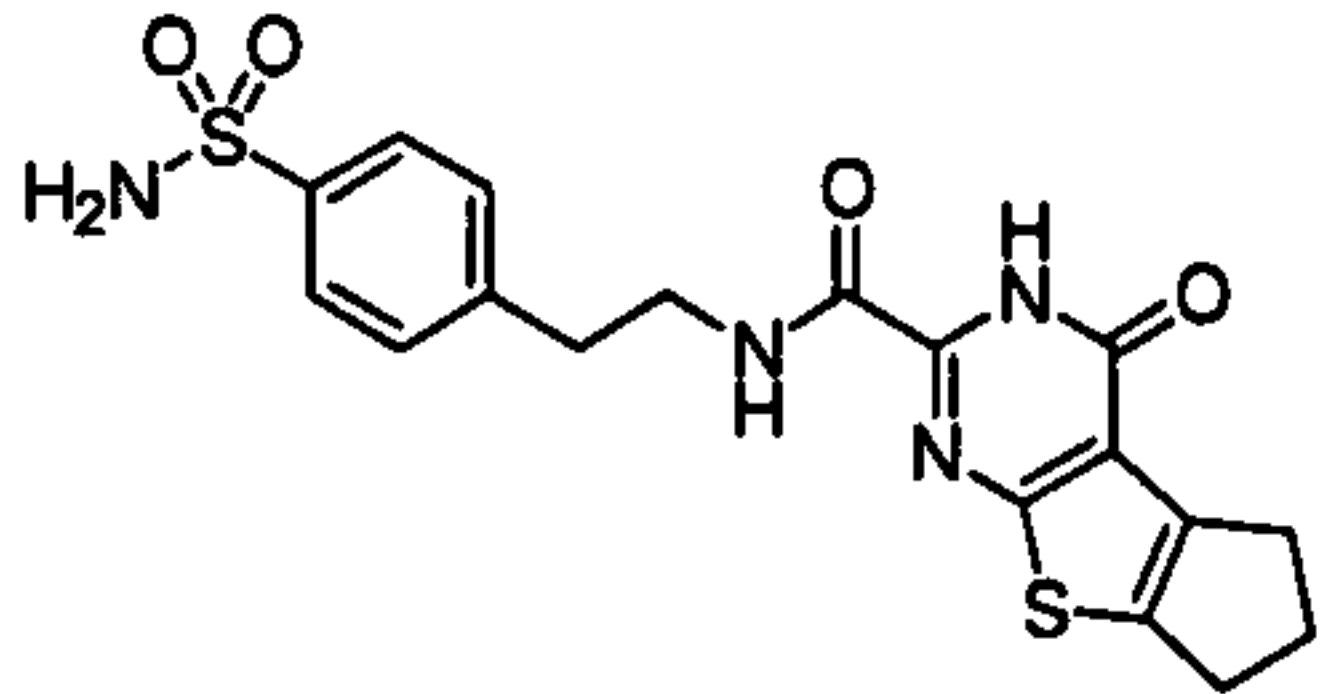
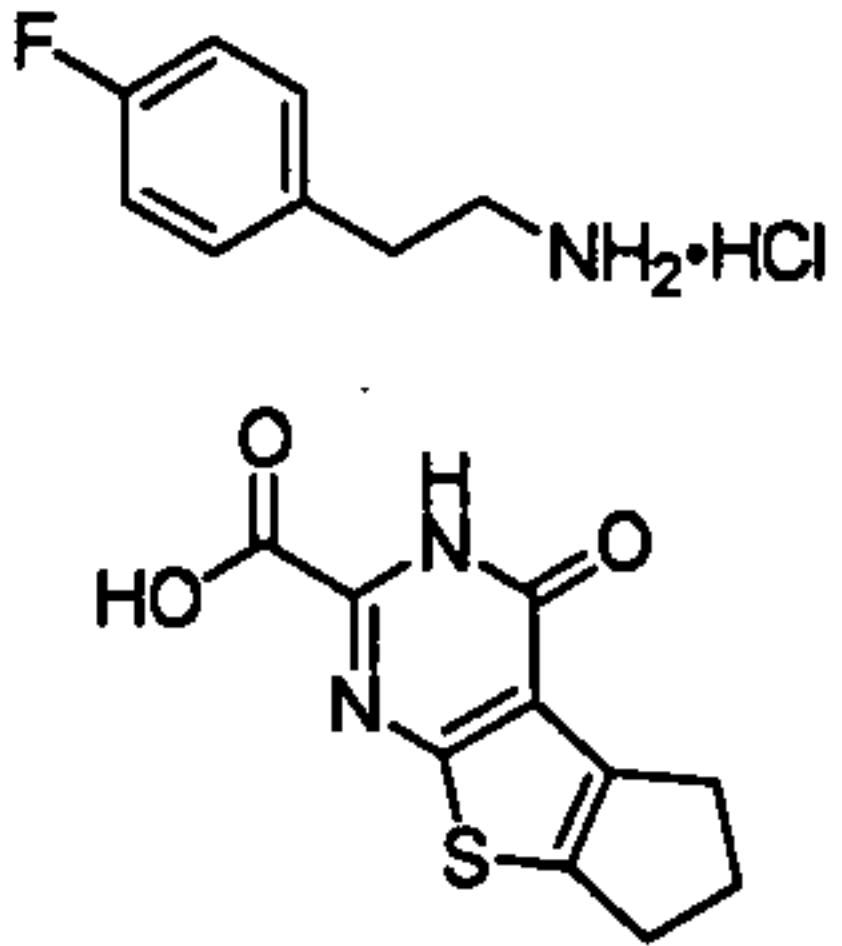
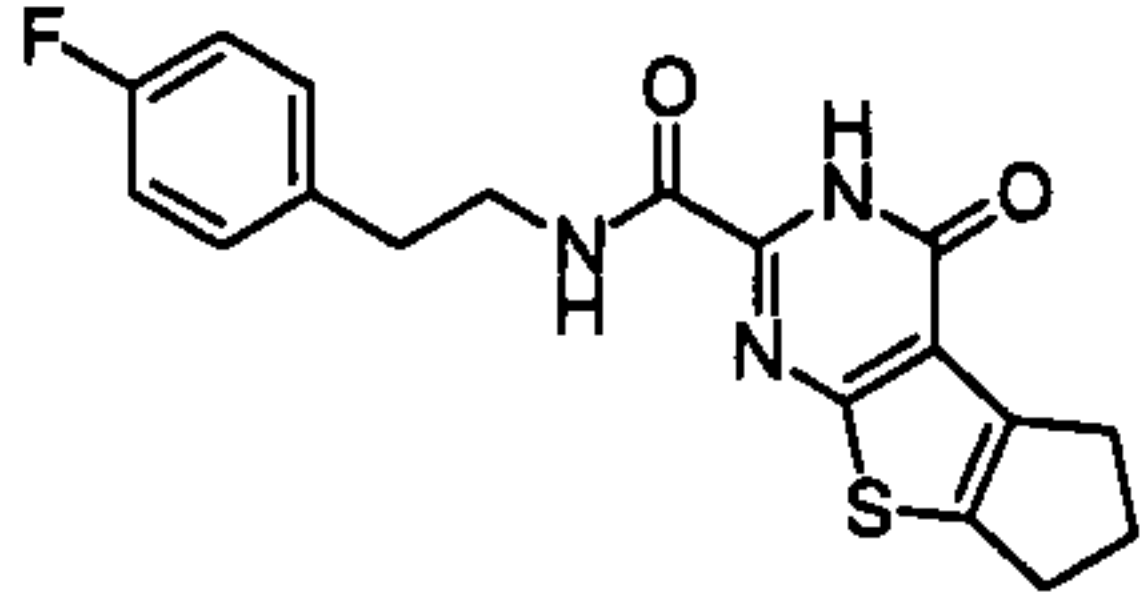
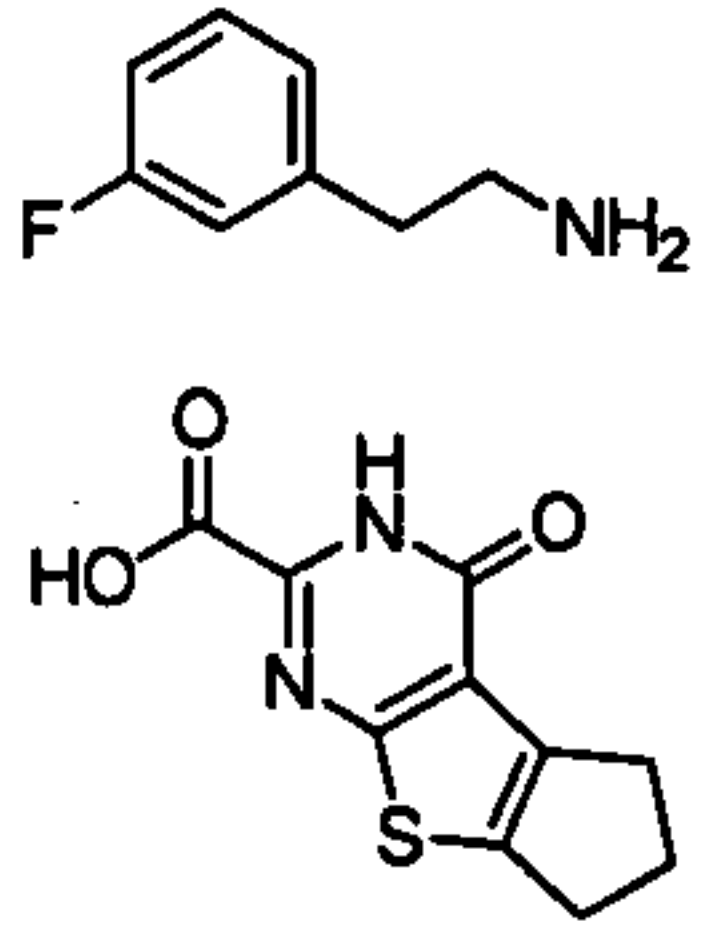
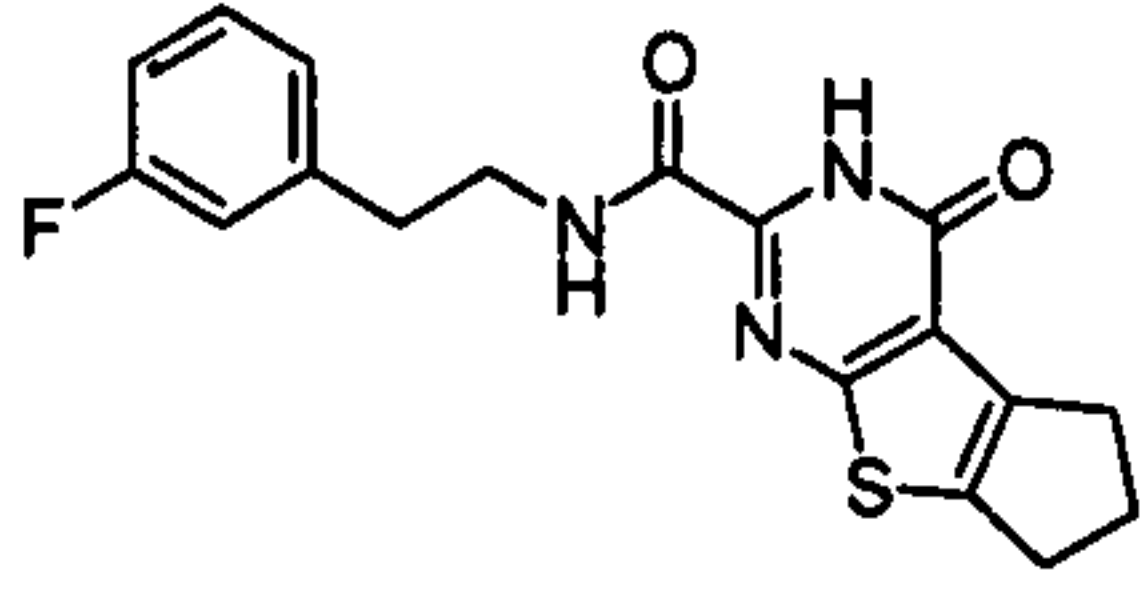
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/501 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 306    |
| 2/502 |   |   | B, n.d.<br>[MH] <sup>+</sup> = 292    |
| 2/503 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 292    |
| 2/504 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 375 |
| 2/505 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 319 |
| 2/506 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 447    |

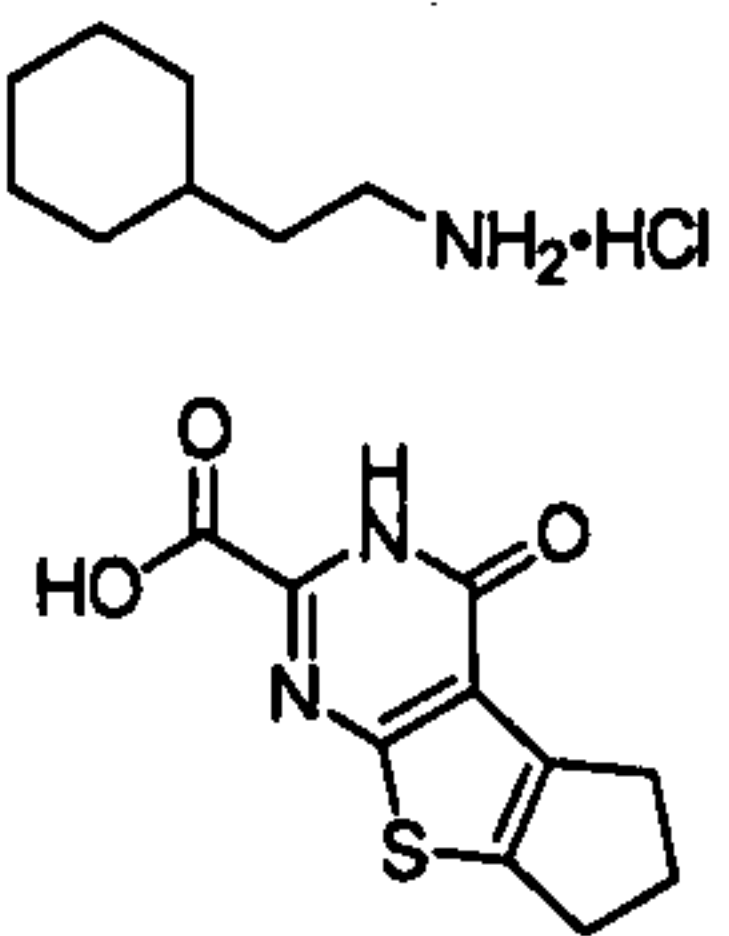
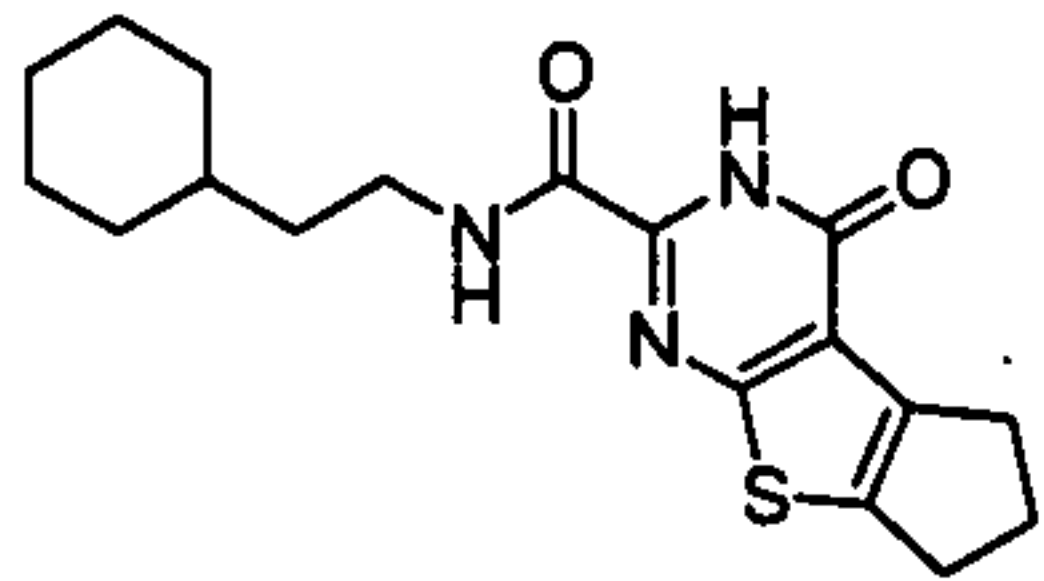
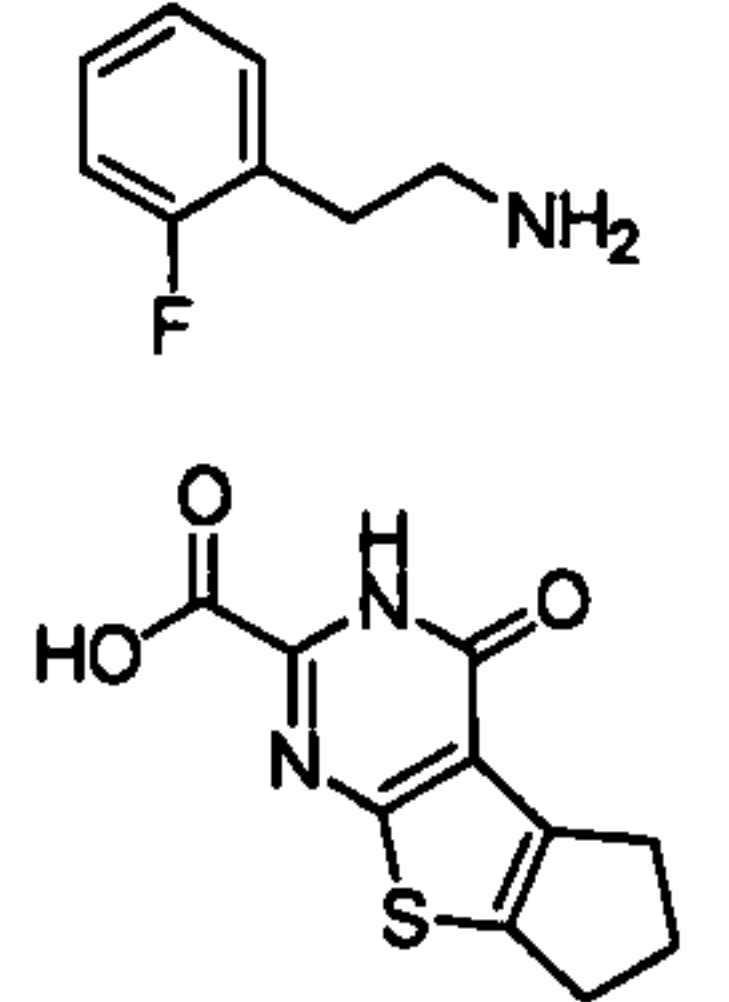
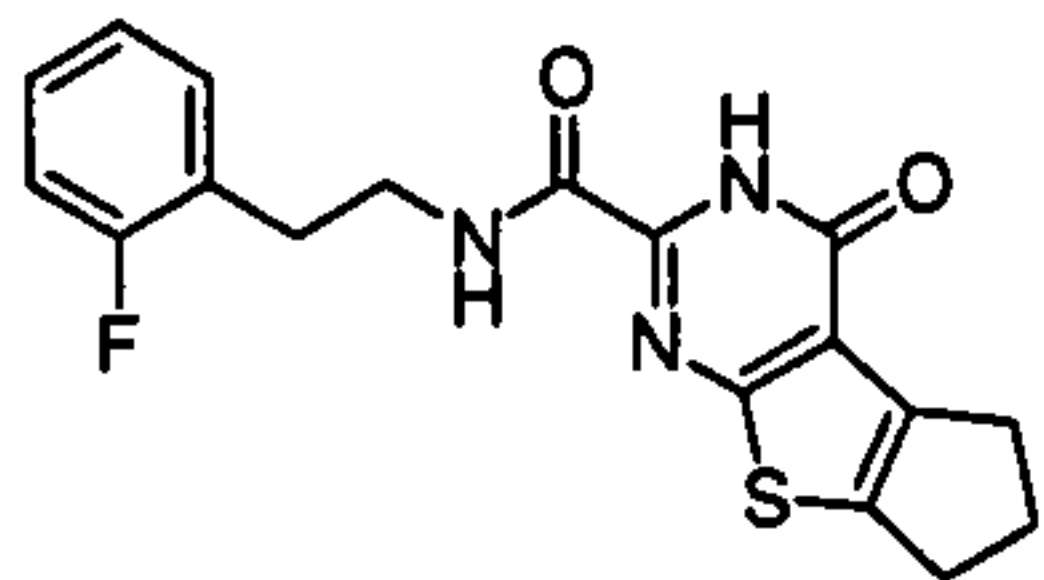
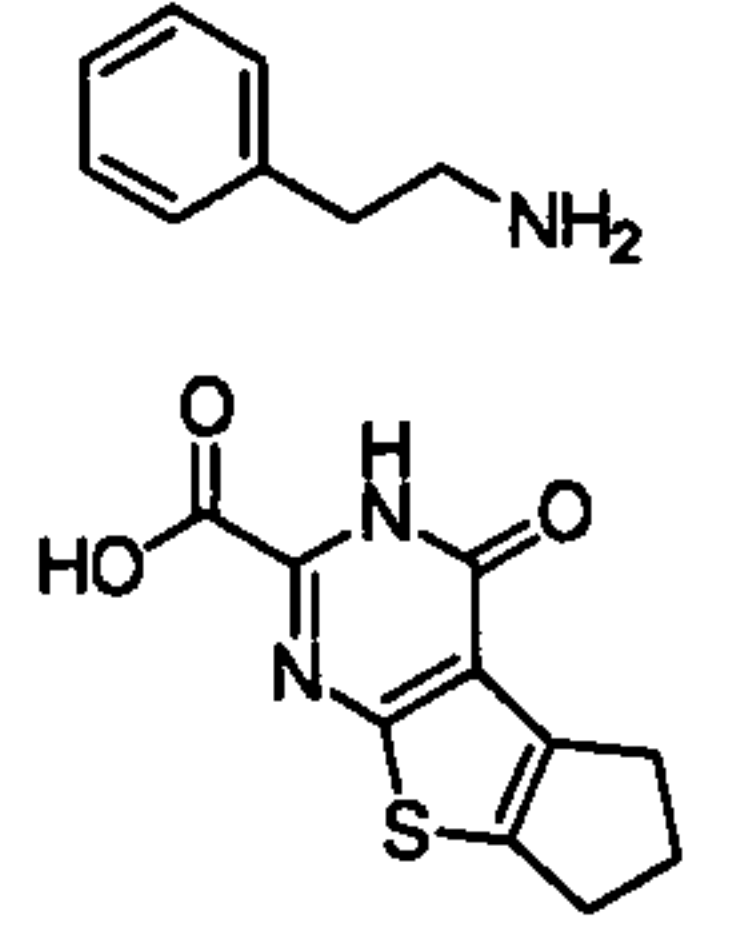
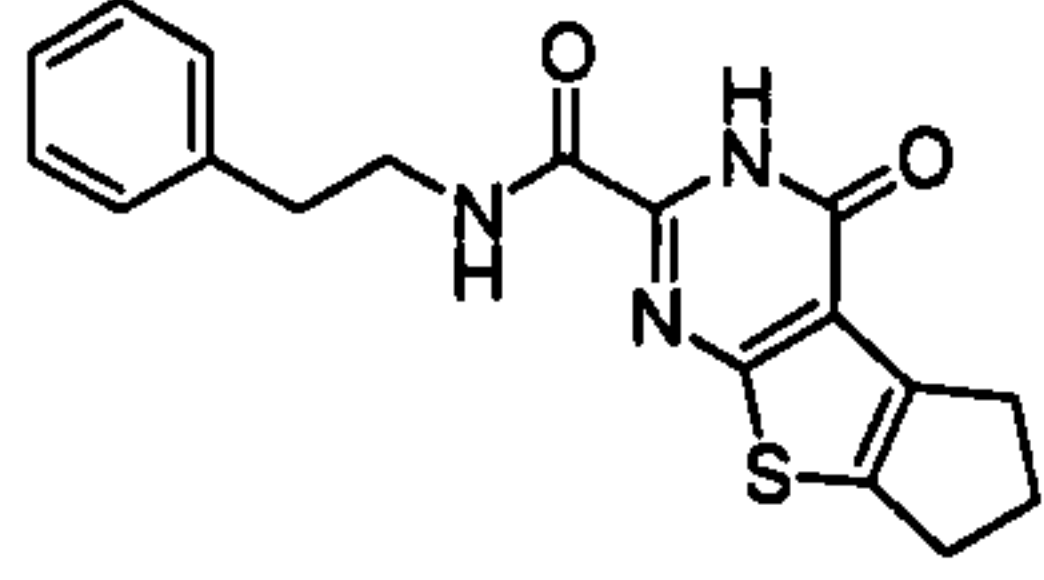
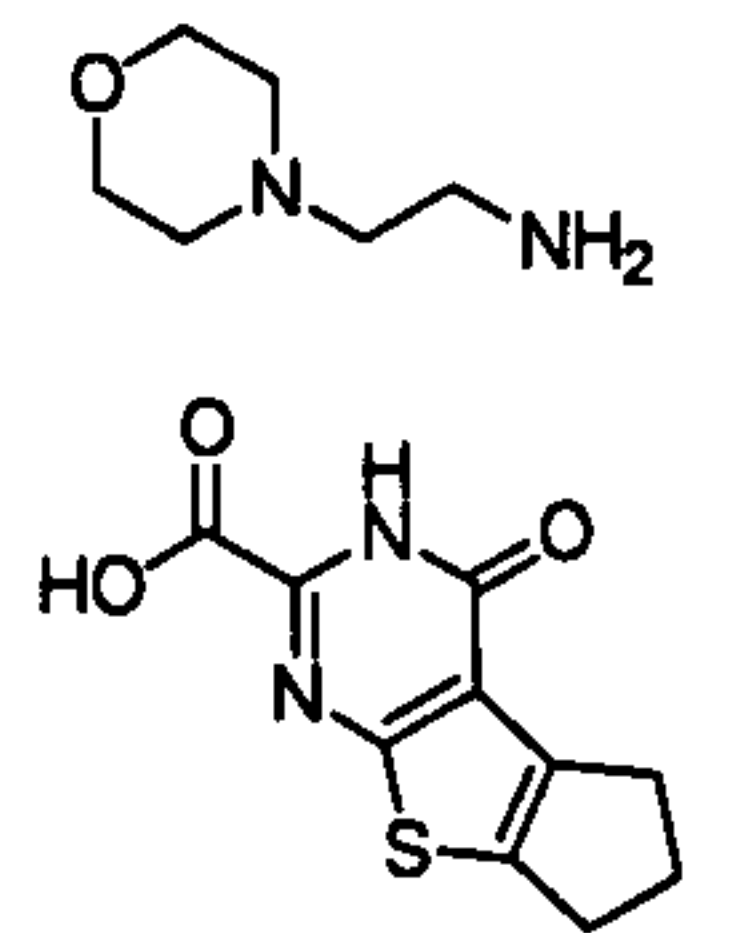
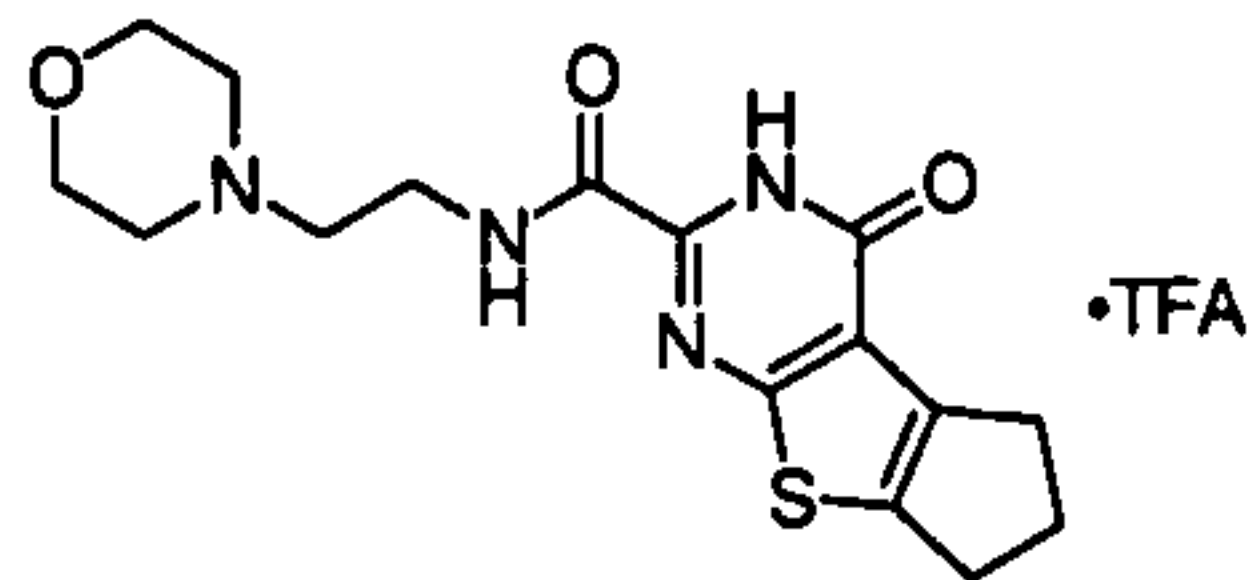
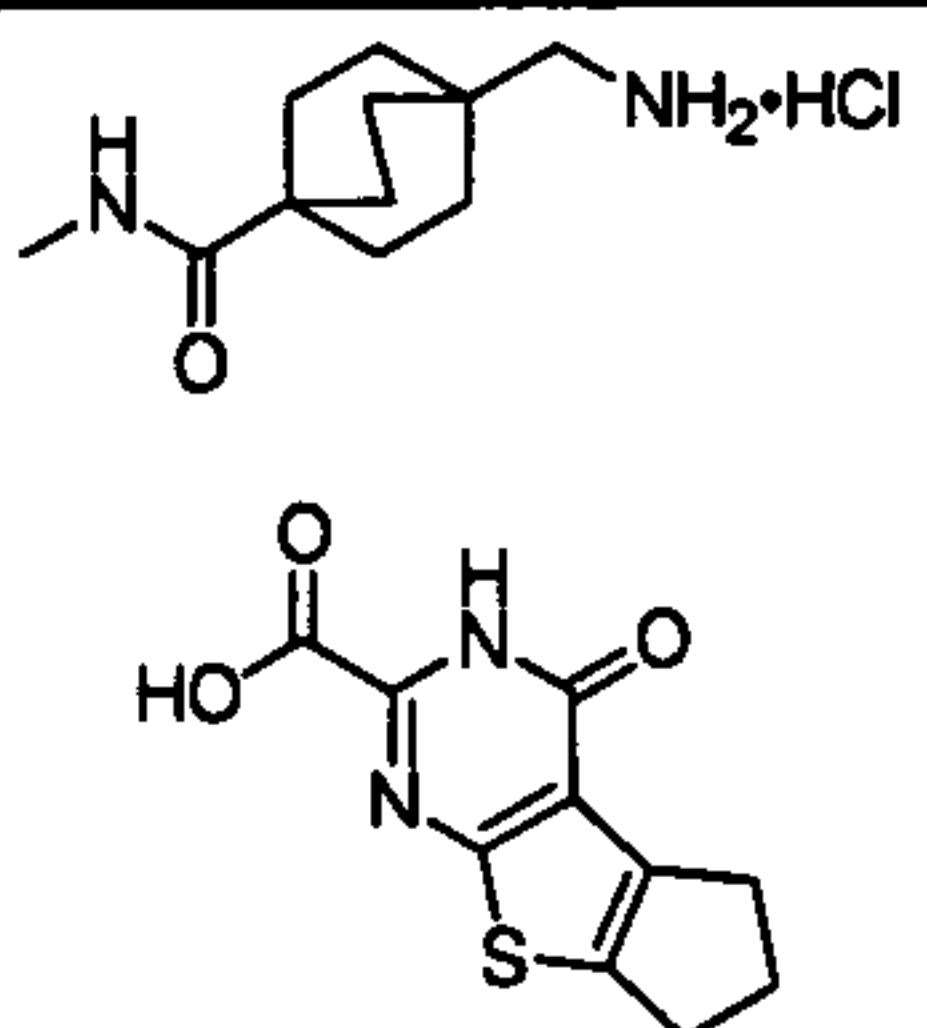
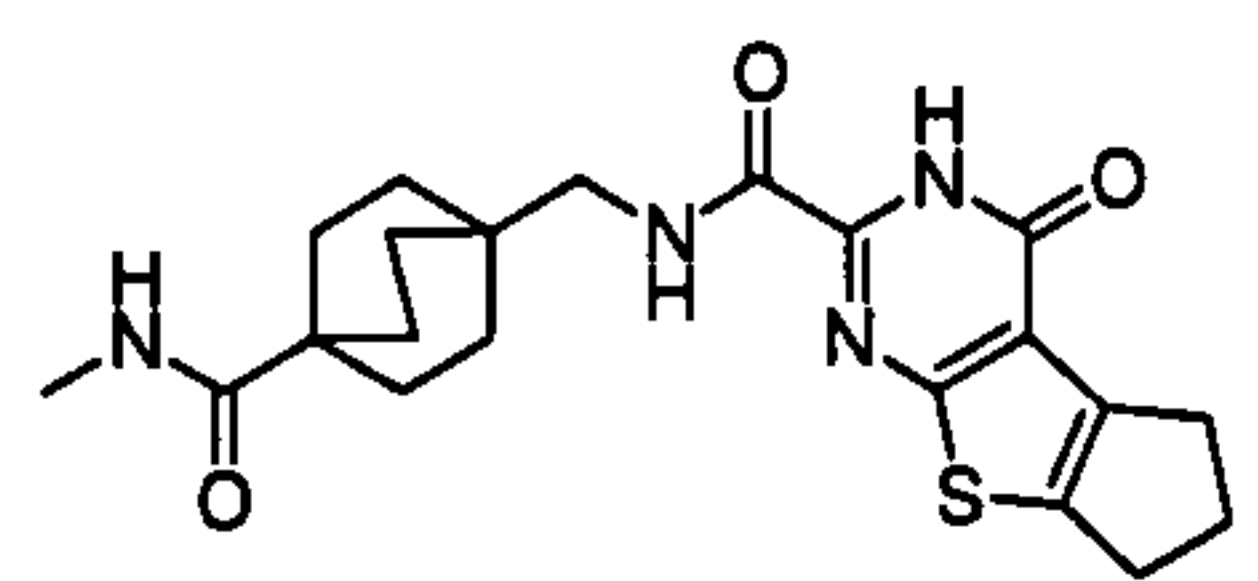
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 2/507 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 333 |
| 2/508 |   |  | B, n.d.<br>[MH] <sup>+</sup><br>= 390    |
| 2/509 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 423 |
| 2/510 |  |  | B, n.d.<br>[MH] <sup>+</sup><br>= 336    |
| 2/511 |  |  | B, n.d.<br>[MH] <sup>+</sup><br>= 383    |

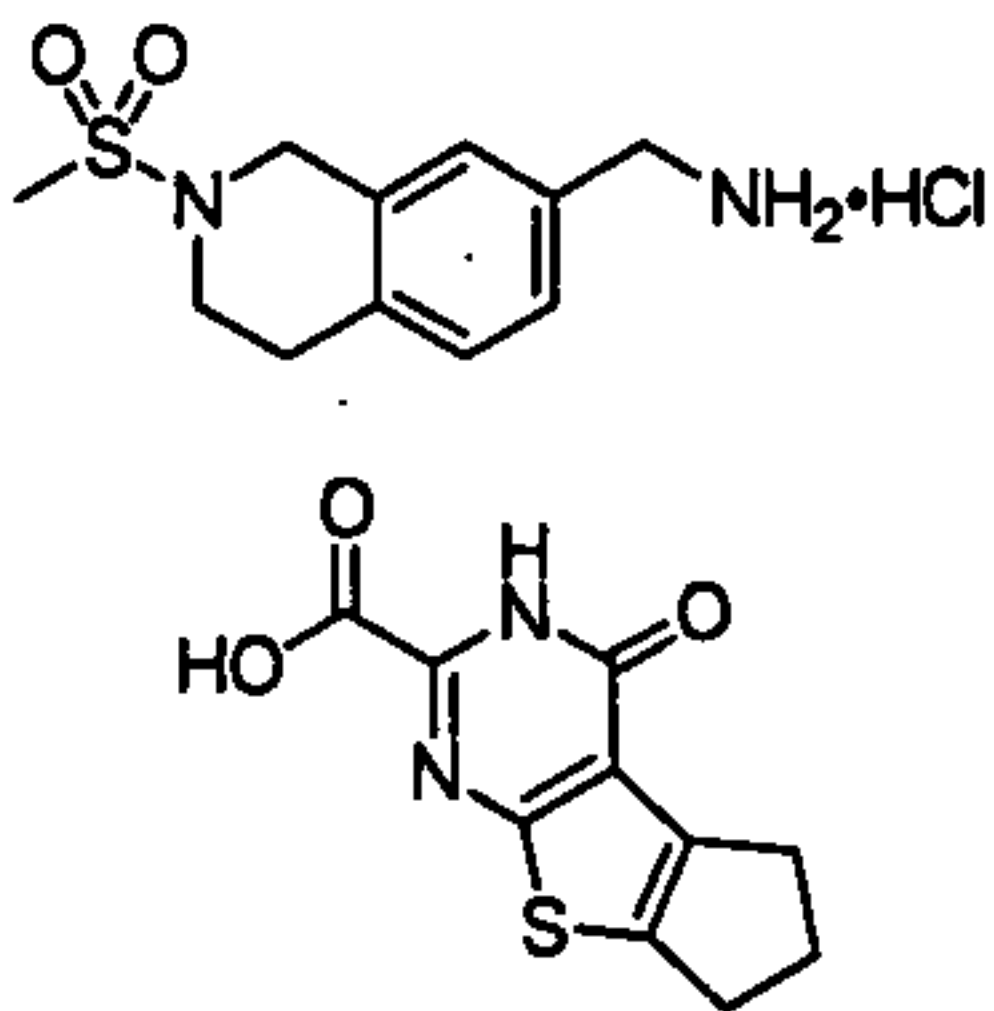
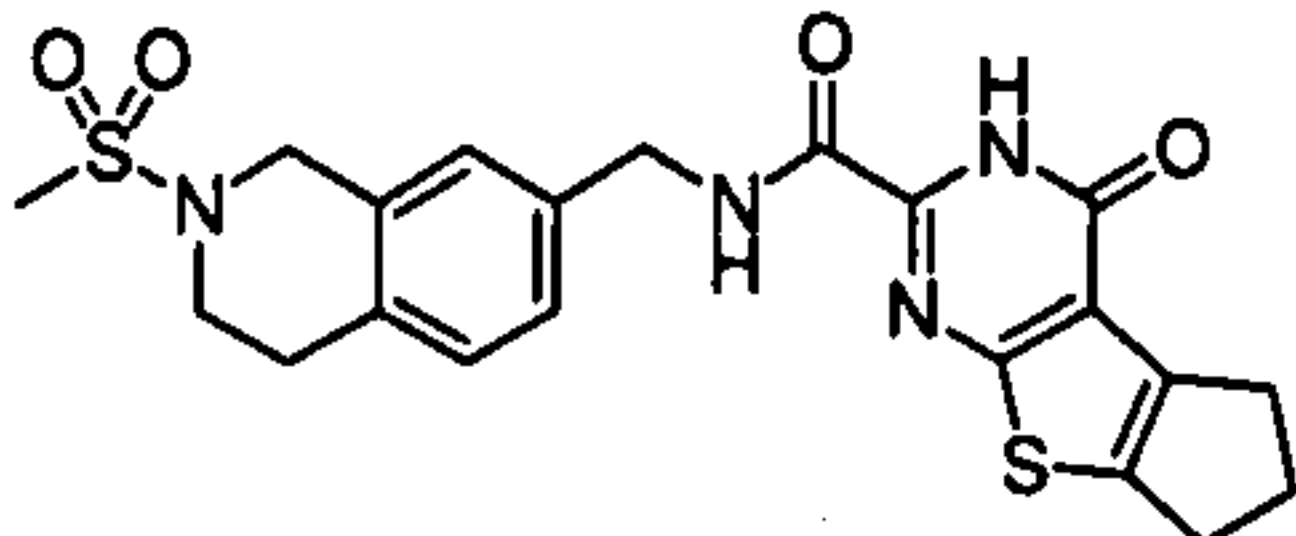
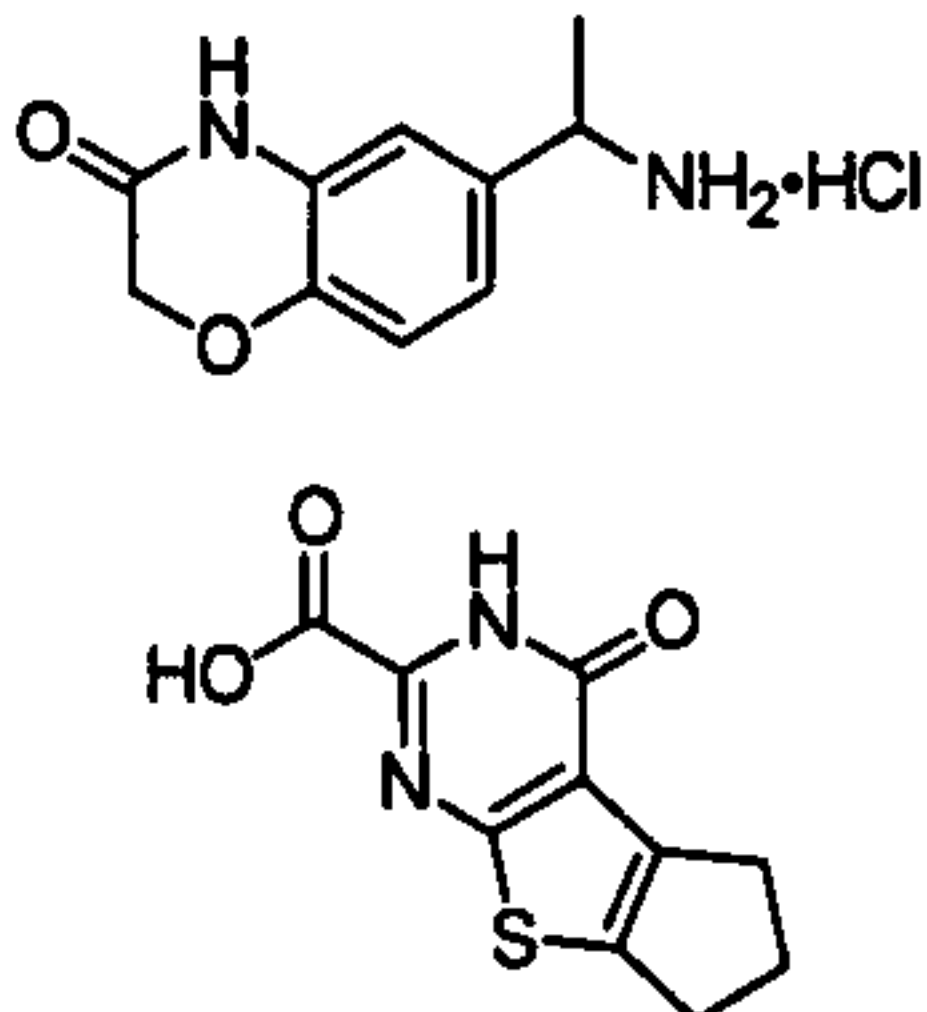
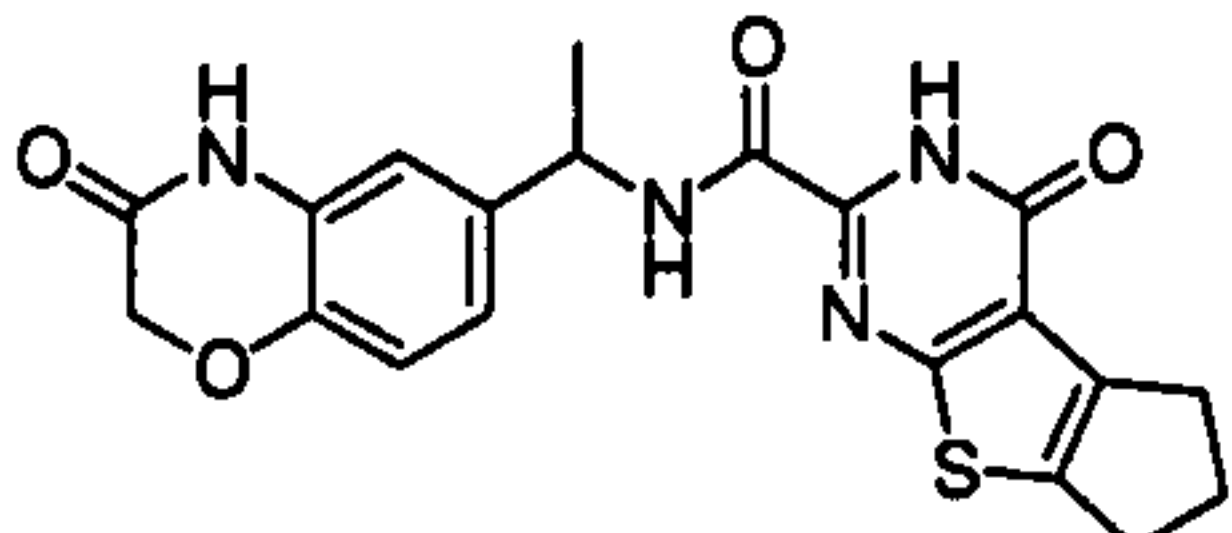
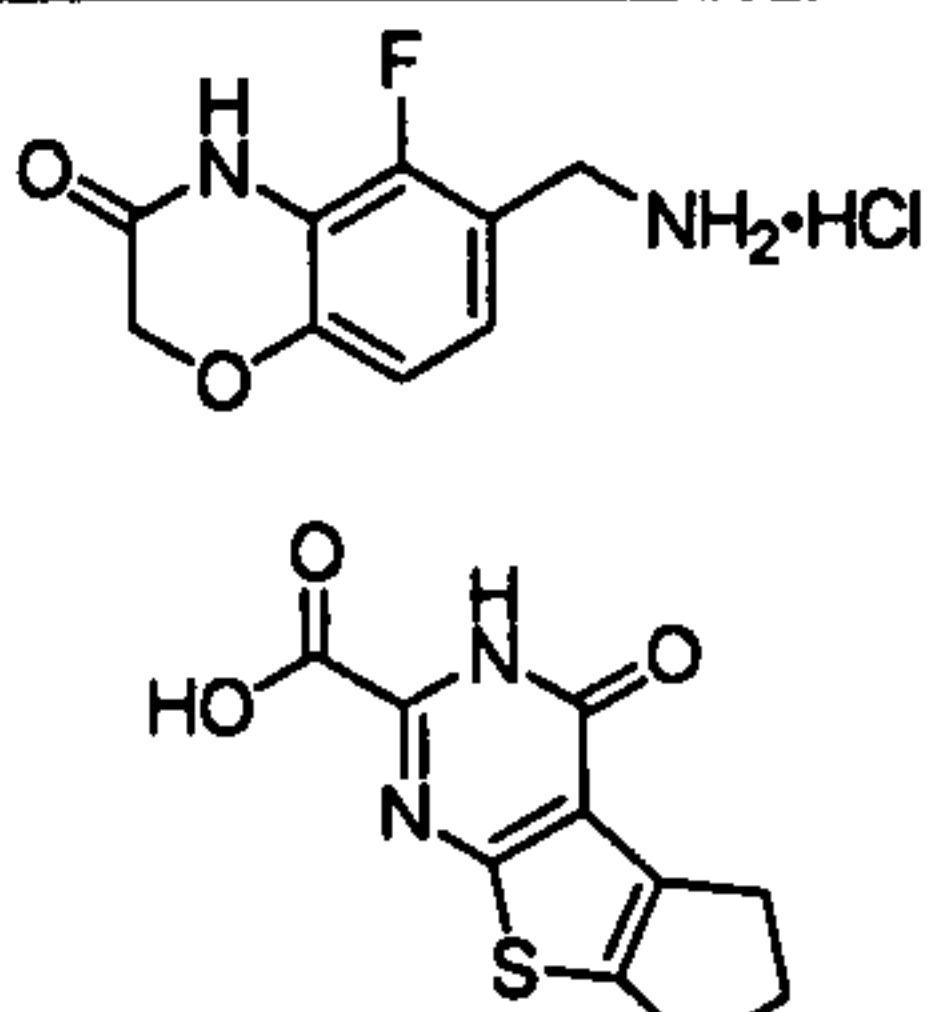
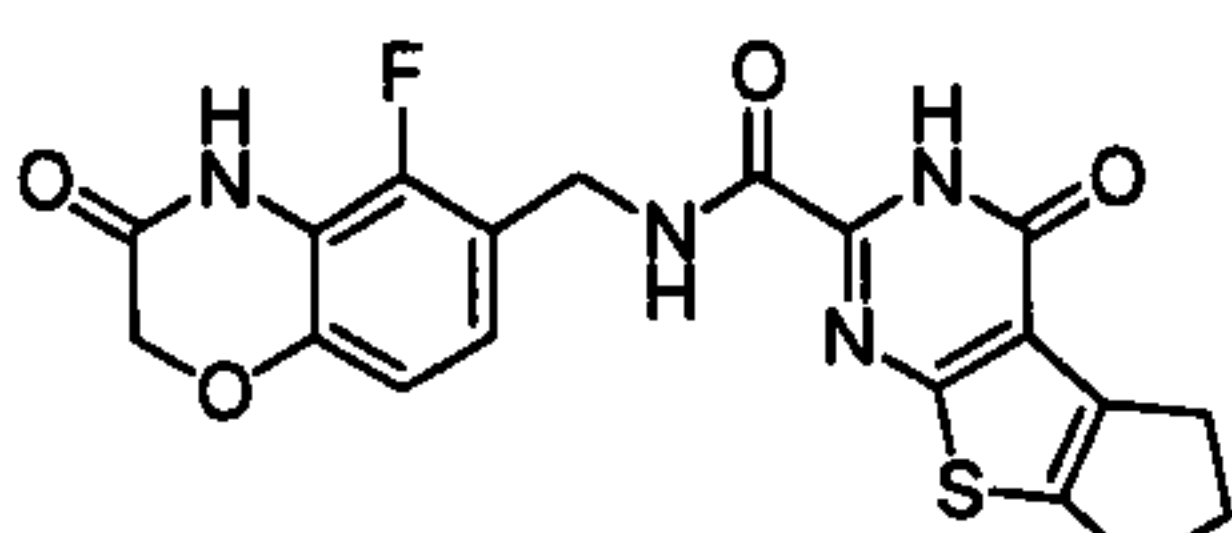
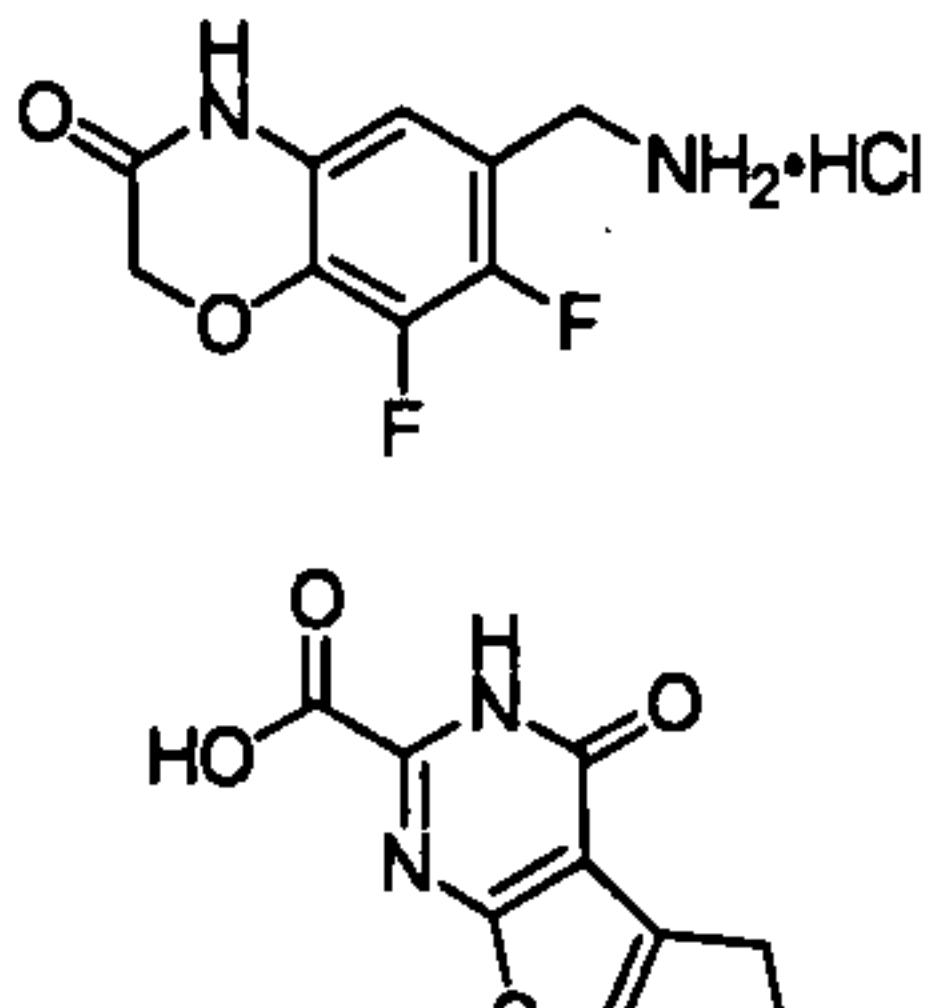
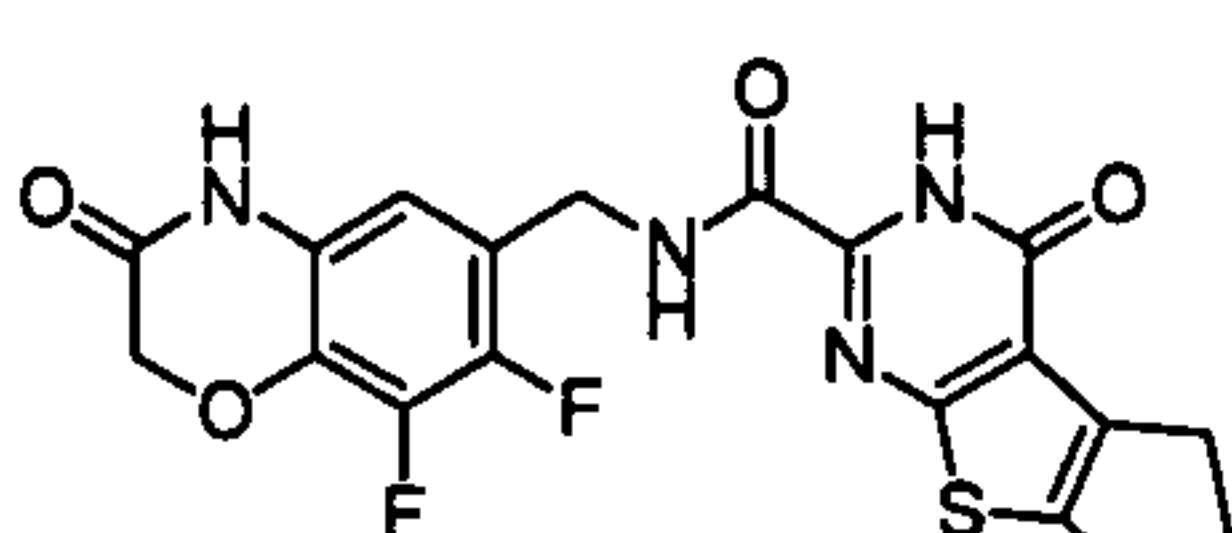
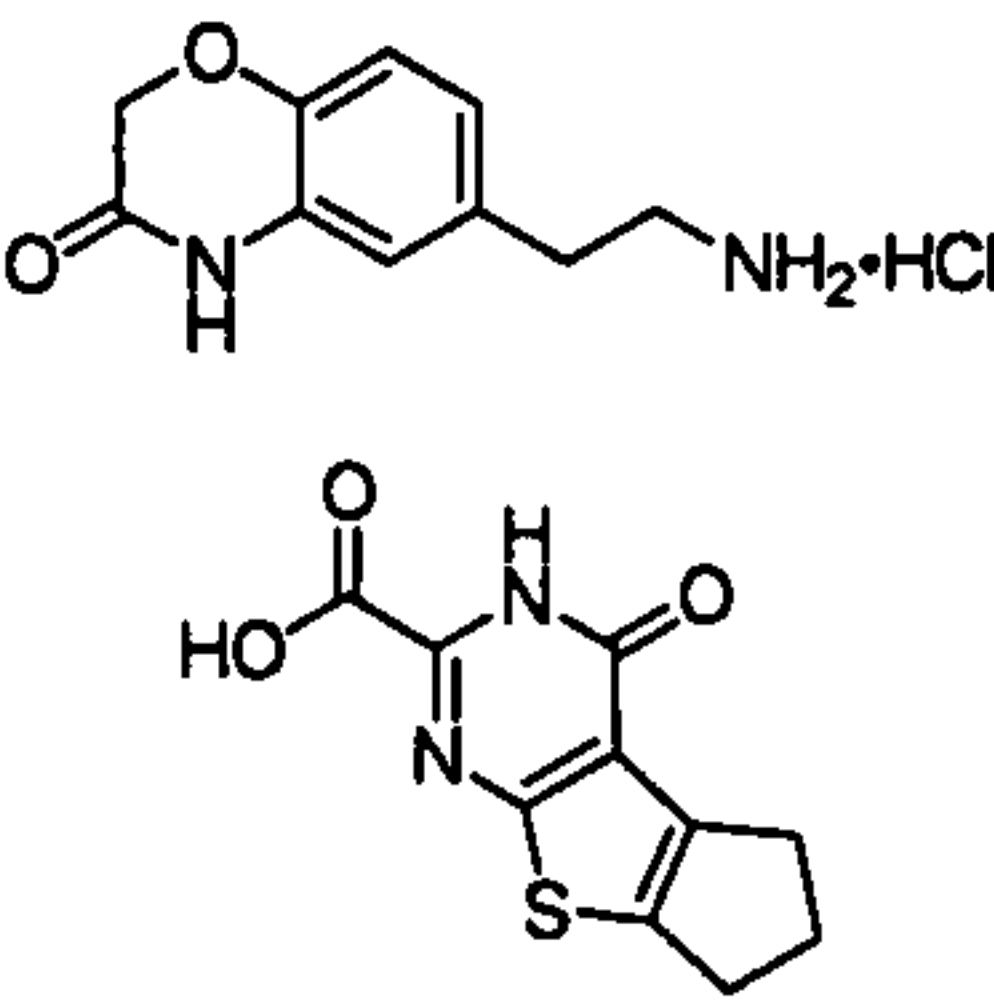
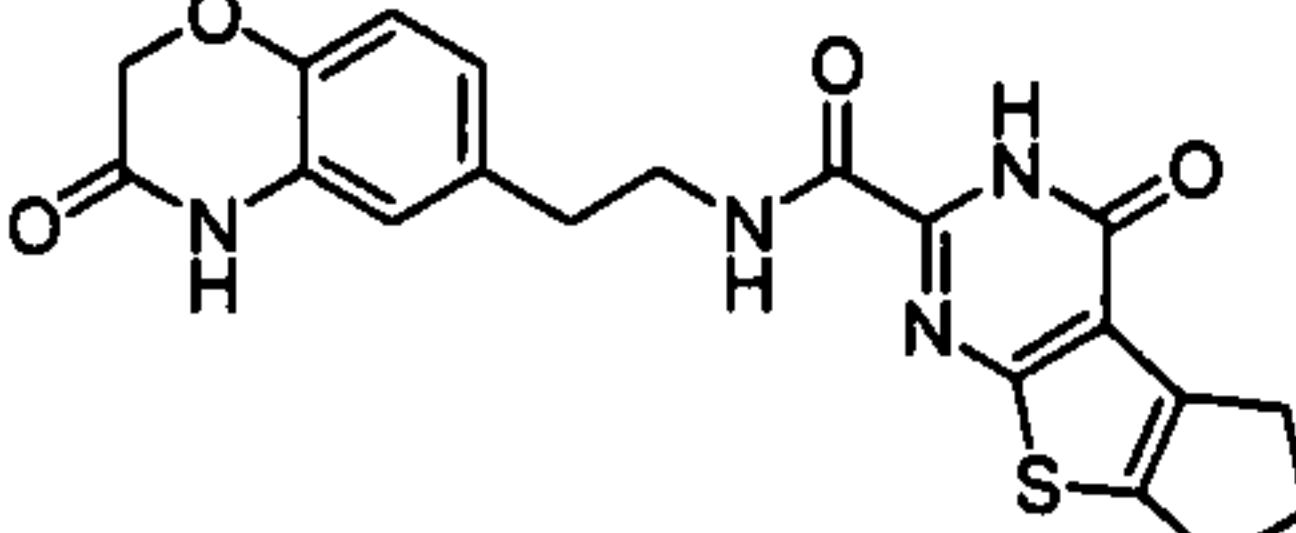
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/512 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 383 |
| 2/513 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 333 |
| 2/514 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 358 |
| 2/515 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 433 |
| 2/516 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 304 |
| 2/517 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 318 |

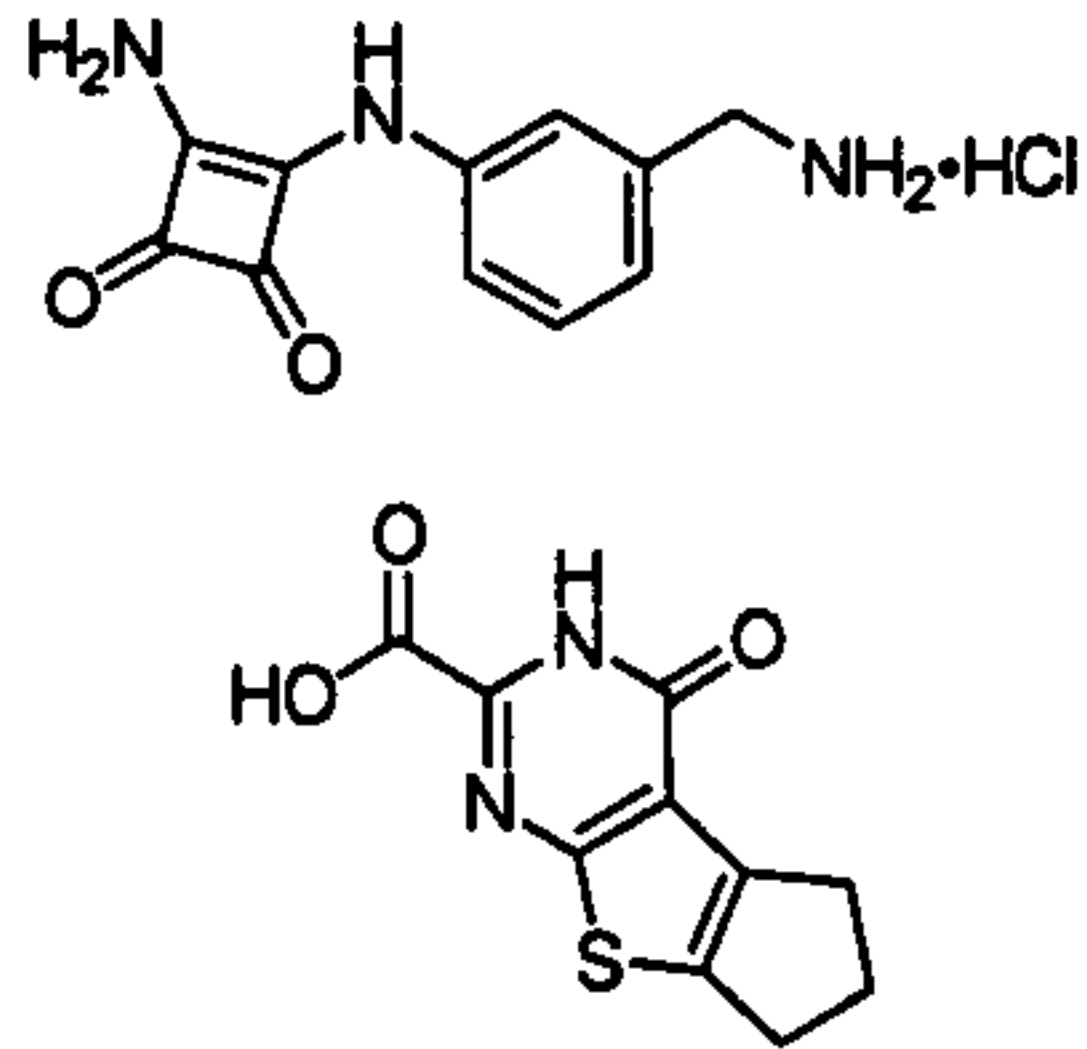
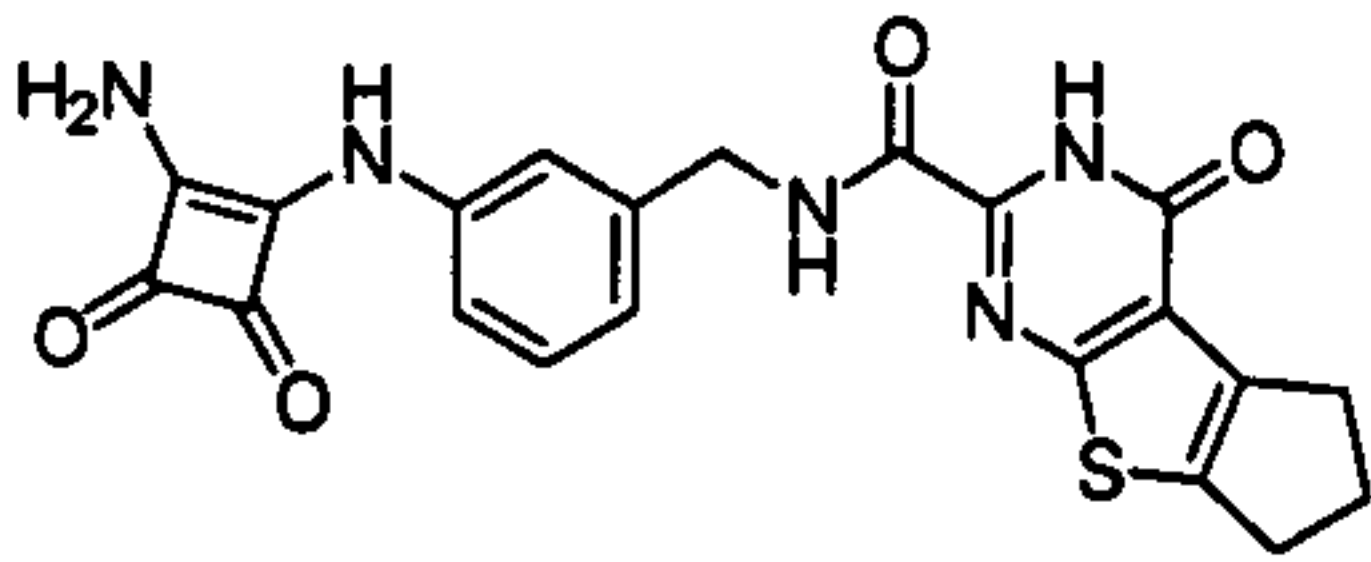
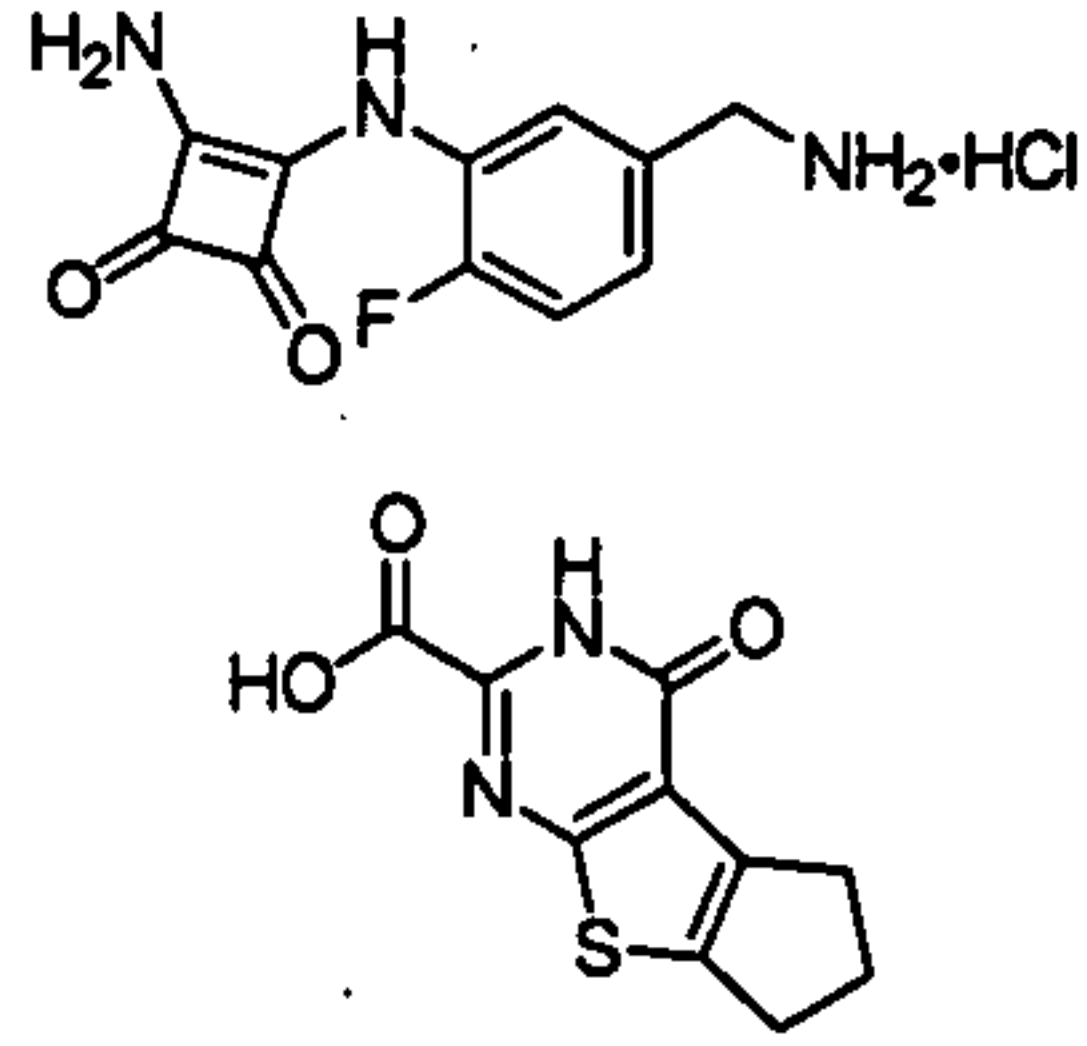
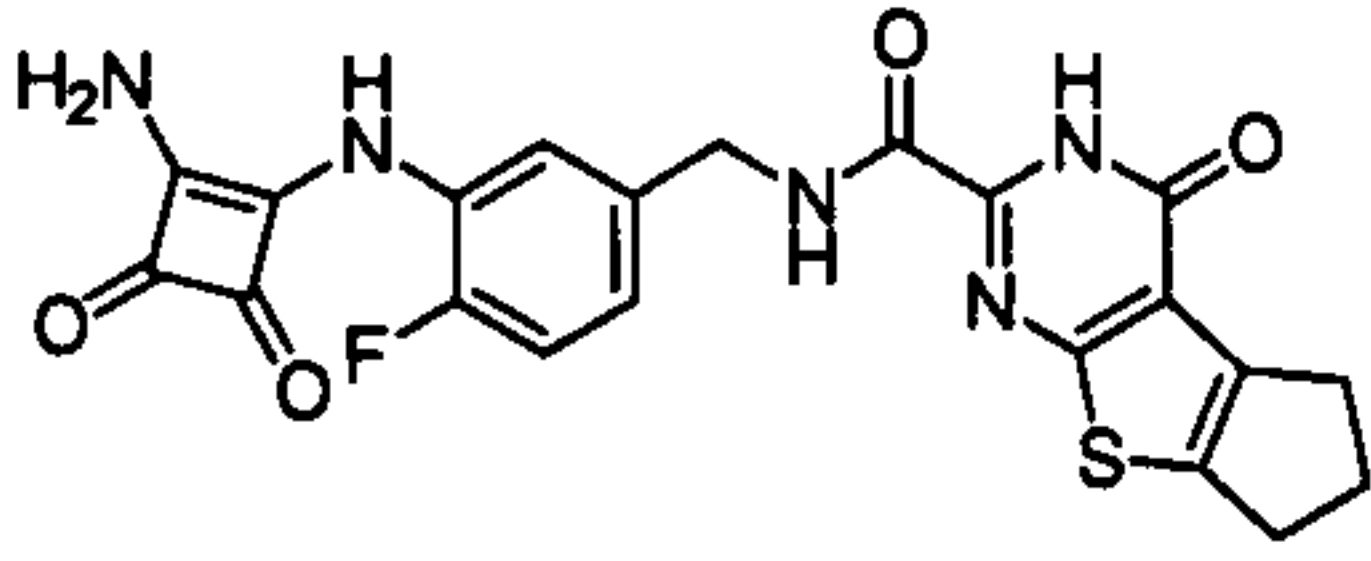
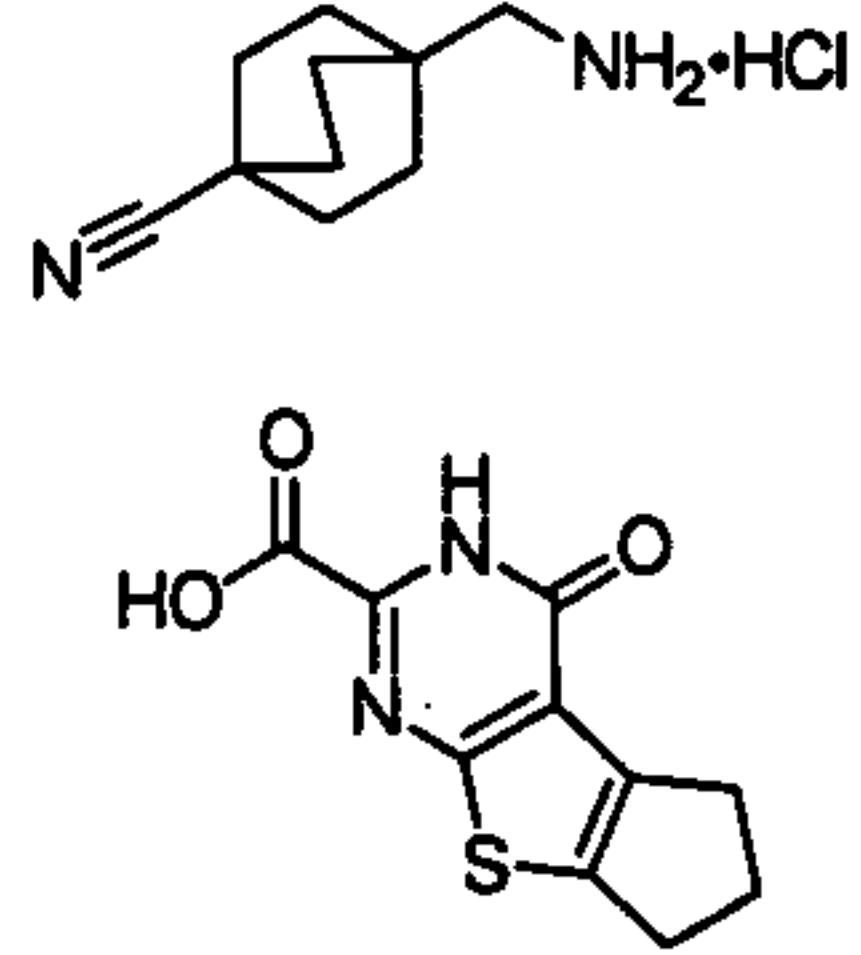
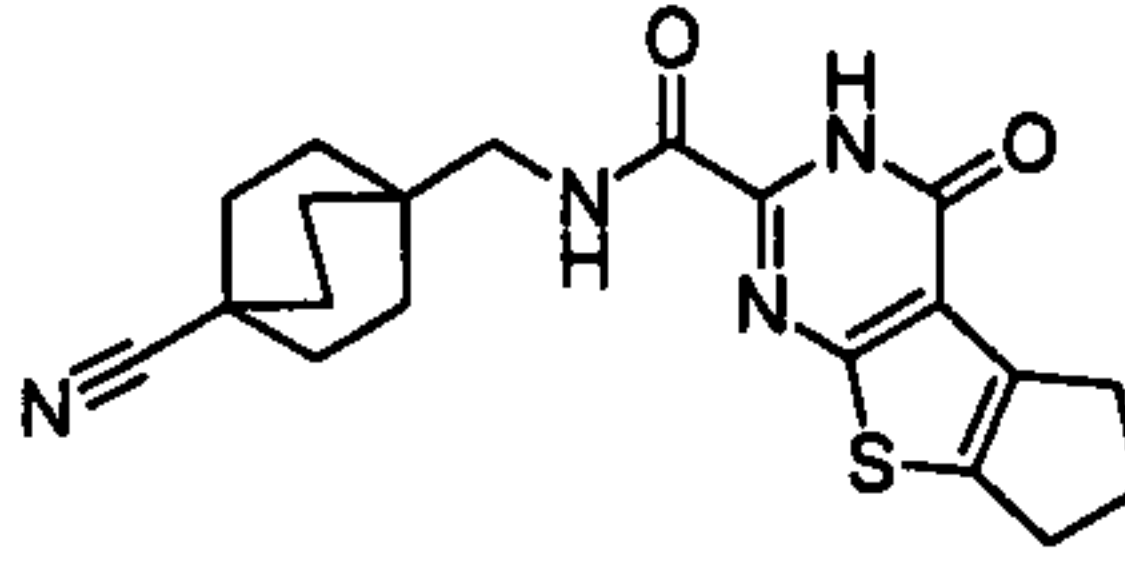
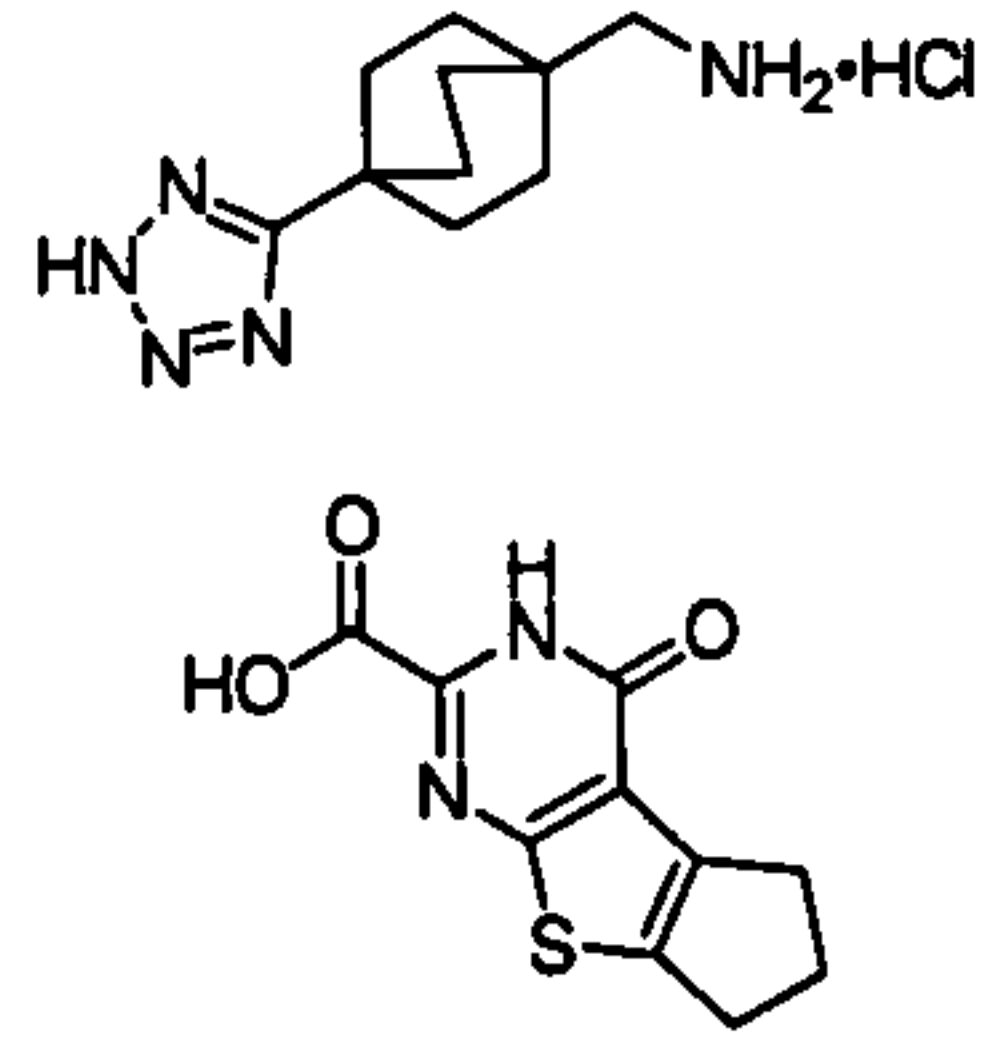
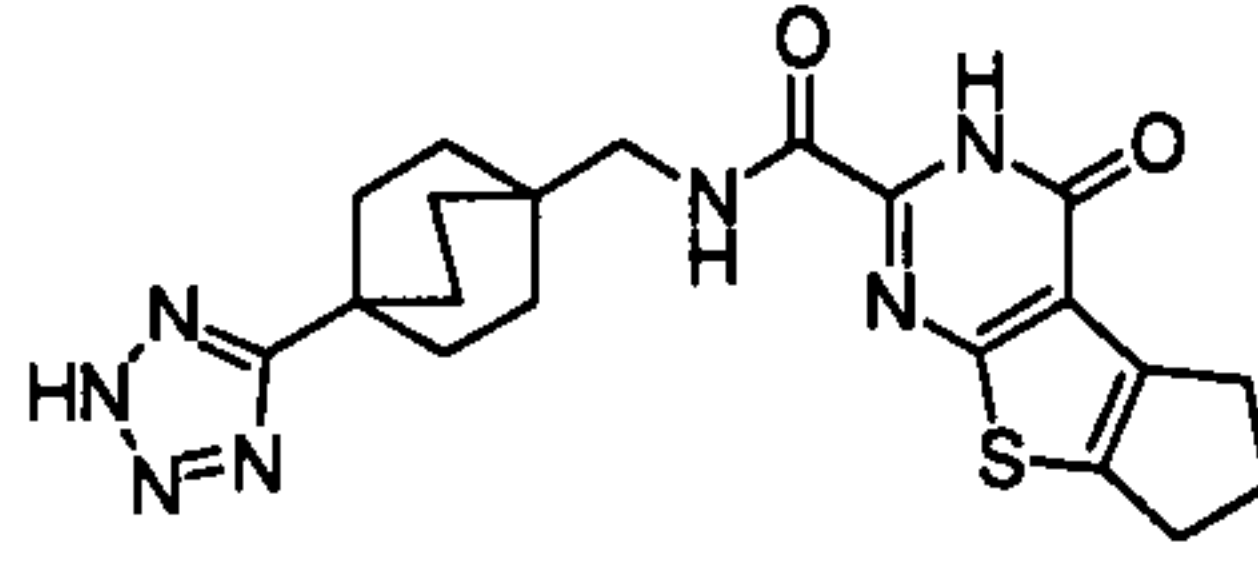
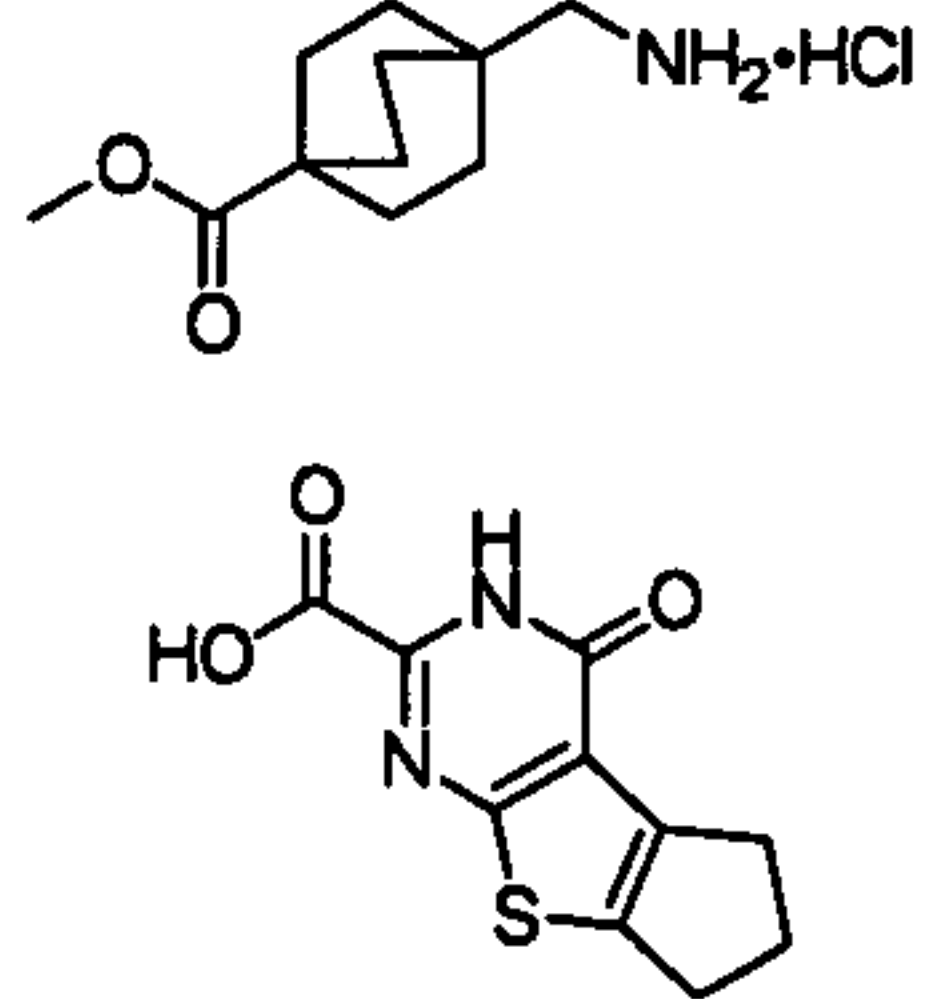
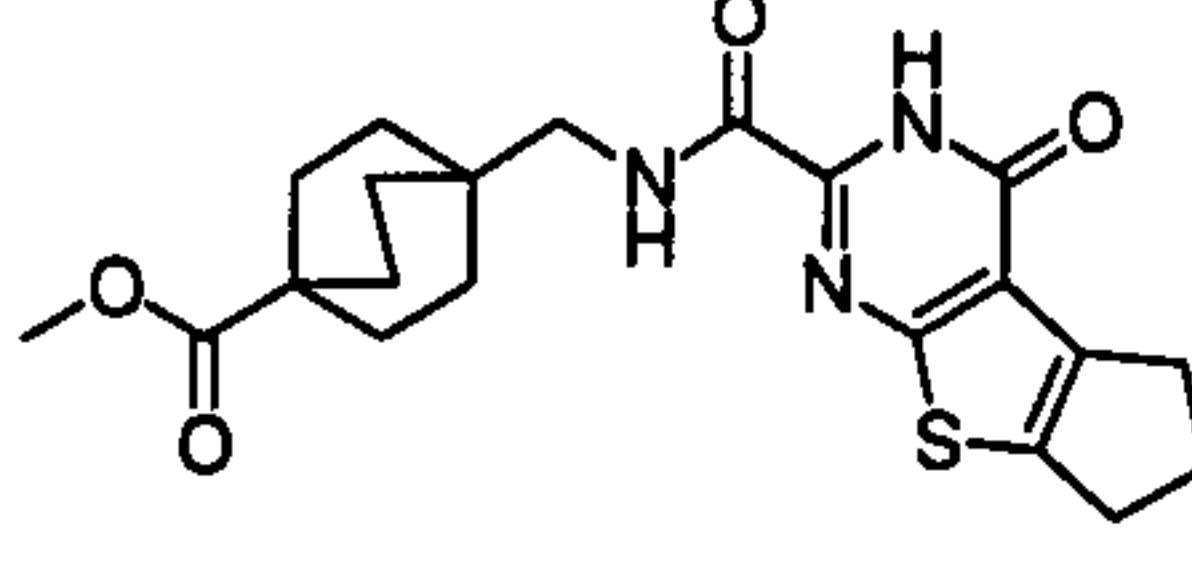
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                            |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|
| 2/518 |    |    | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 345 |
| 2/519 |   |   | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 328 |
| 2/520 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>447    |
| 2/521 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup><br>= 330 |
| 2/522 |  |  | B, n.d.<br>[MH] <sup>+</sup> =<br>382    |

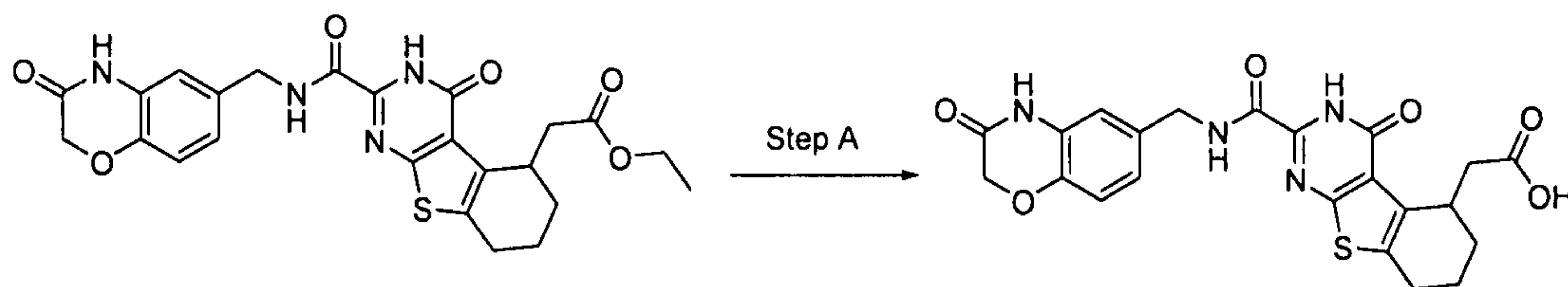
| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------|
| 2/523 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 410                    |
| 2/524 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 410                    |
| 2/525 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 410                    |
| 2/526 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 390                    |
| 2/527 |  |  | B, n.d.<br>[M-(TFA) <sub>2</sub> ] <sup>+</sup> = 396 |

| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------|
| 2/528 |    |    | B, n.d.<br>[M-(TFA) <sub>2</sub> ] <sup>+</sup> = 428 |
| 2/529 |   |  | B, n.d.<br>[M-(TFA) <sub>2</sub> ] <sup>+</sup> = 412 |
| 2/530 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 419                    |
| 2/531 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 358                    |
| 2/532 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 358                    |

| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                         |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------|
| 2/533 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 346    |
| 2/534 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 358    |
| 2/535 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 340    |
| 2/536 |  |  | B, n.d.<br>[M-TFA] <sup>+</sup> = 349 |
| 2/537 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 415    |

| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/538 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 459 |
| 2/539 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 411 |
| 2/540 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 415 |
| 2/541 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 433 |
| 2/542 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 411 |

| Ex. # | amine, acid                                                                         | product                                                                               | method, yield                      |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------|
| 2/543 |    |    | B, n.d.<br>[MH] <sup>+</sup> = 436 |
| 2/544 |   |  | B, n.d.<br>[MH] <sup>+</sup> = 454 |
| 2/545 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 383 |
| 2/546 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 426 |
| 2/547 |  |  | B, n.d.<br>[MH] <sup>+</sup> = 416 |

**Example 3****Step A**

To a solution of the title compound from Step A above (200 mg) in THF (3 mL) was added 1M aqueous LiOH (1.2 mL). The resulting mixture was stirred at room temperature 3h, concentrated and suspended in 1M aqueous HCl. The residue was filtered off and used without further purification (150 mg, 80%).  $[MH]^+ = 469$ .

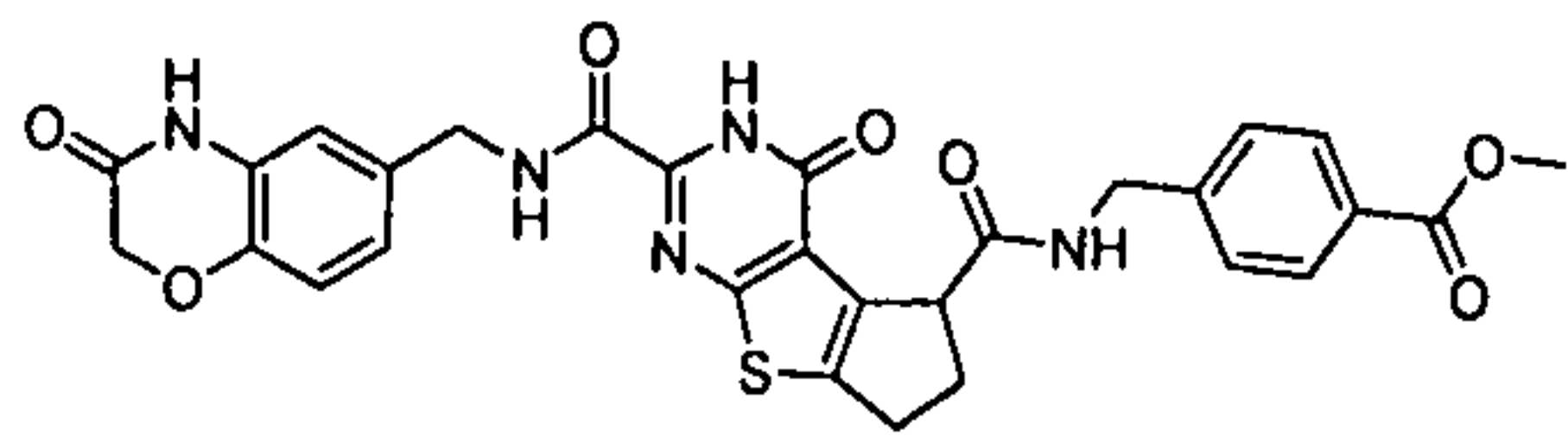
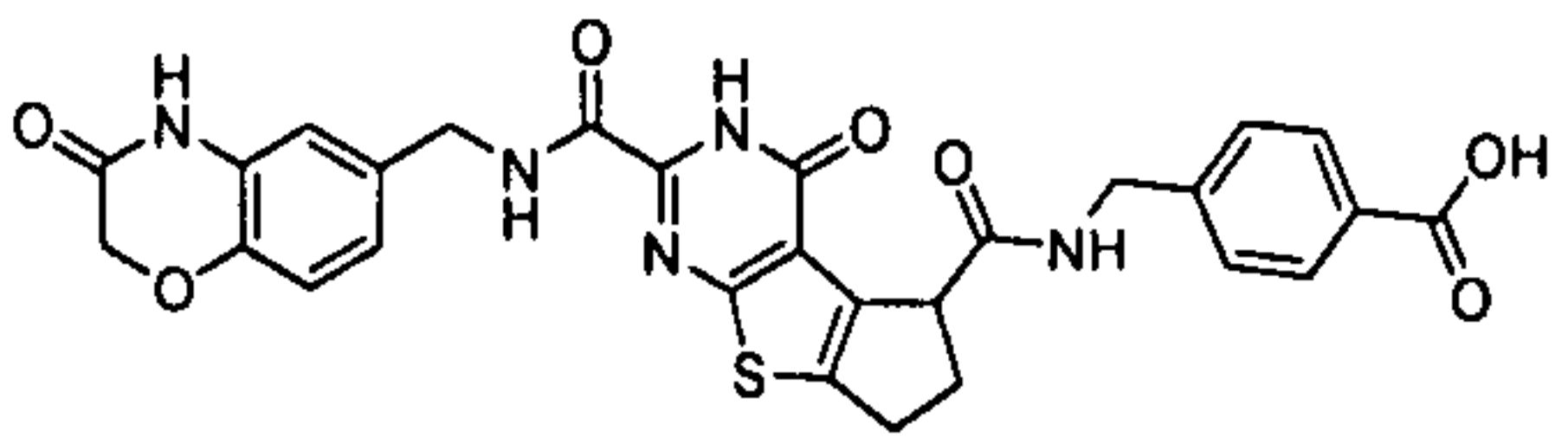
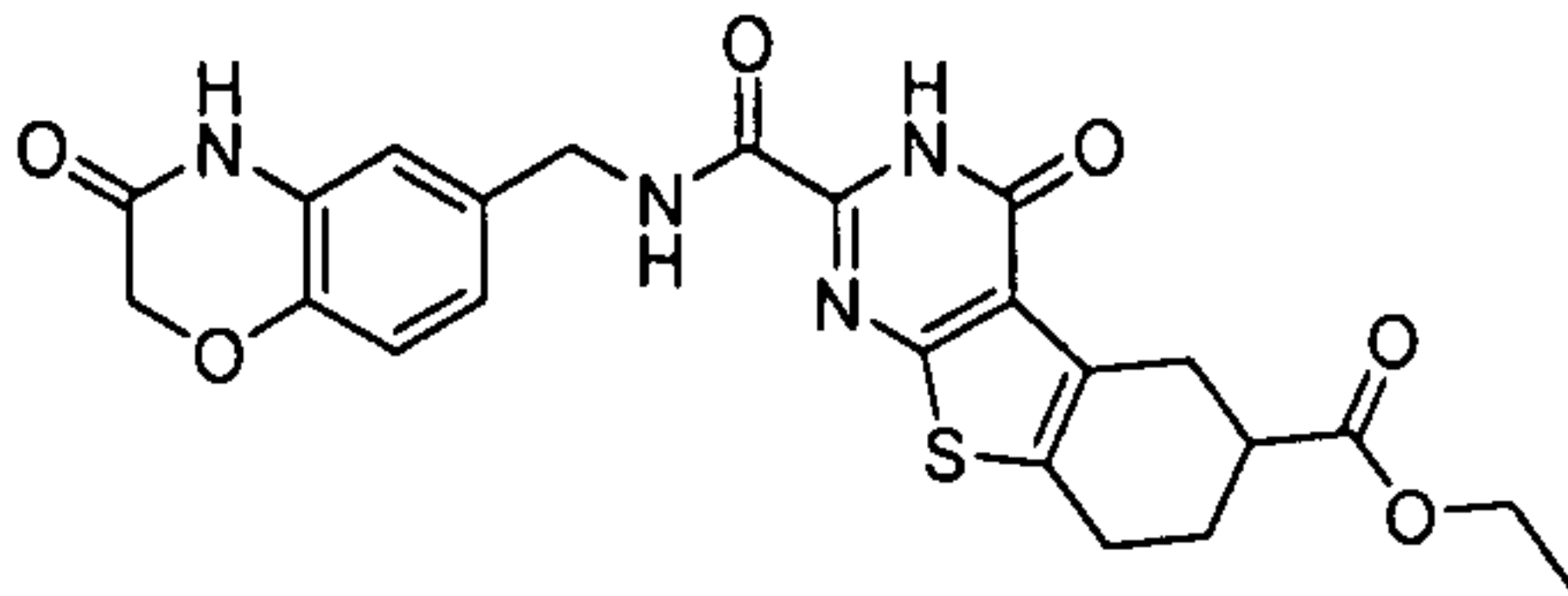
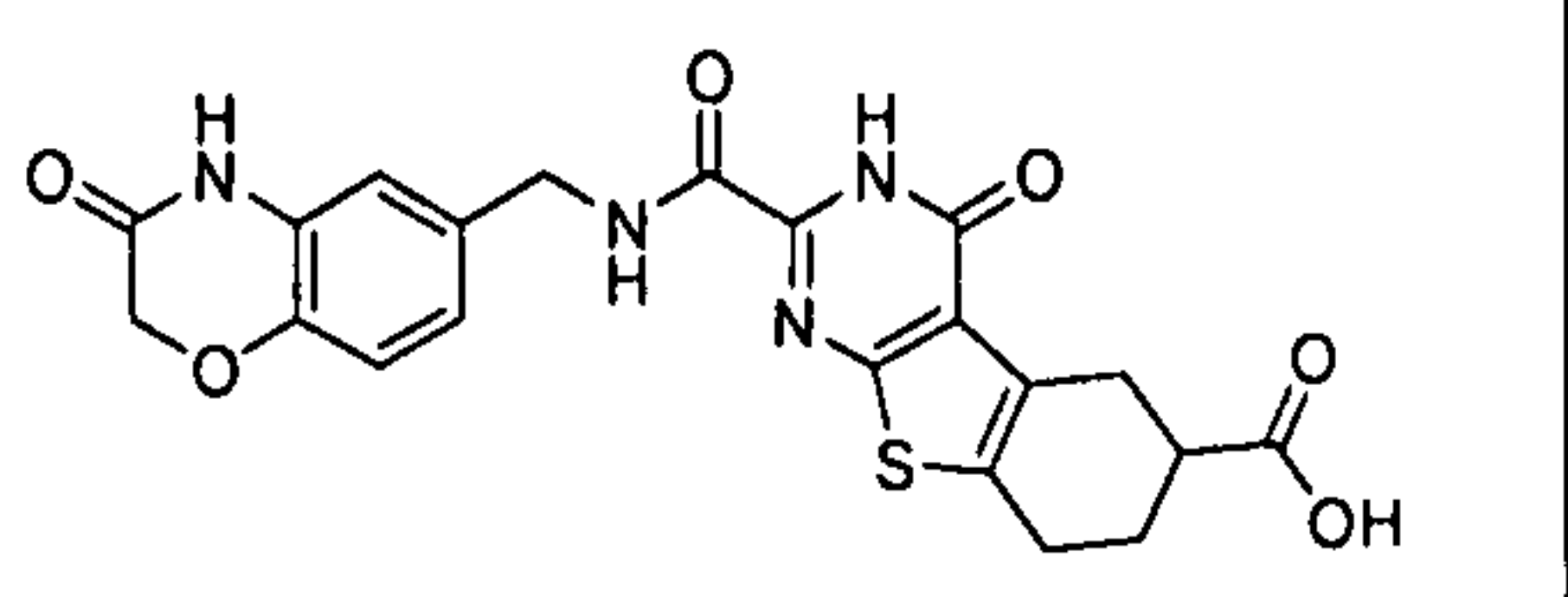
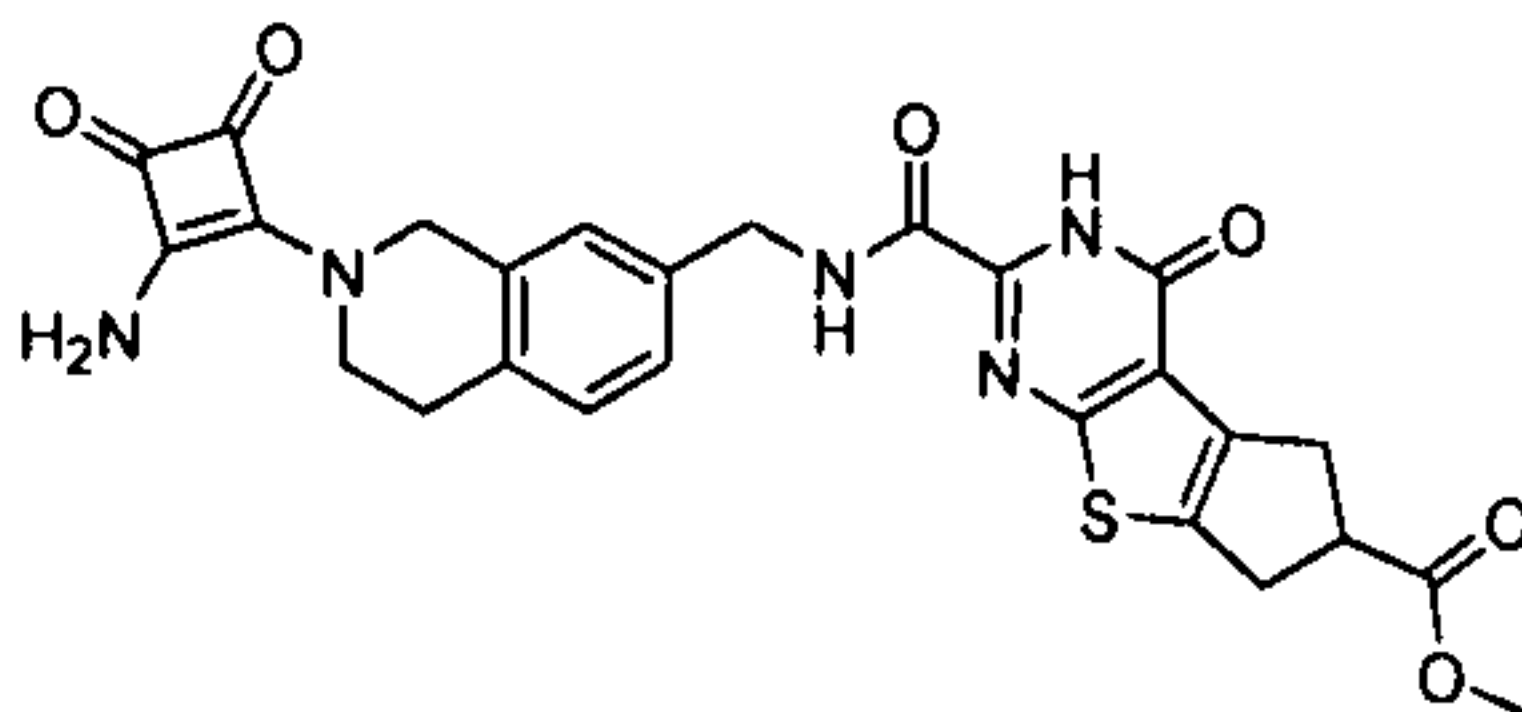
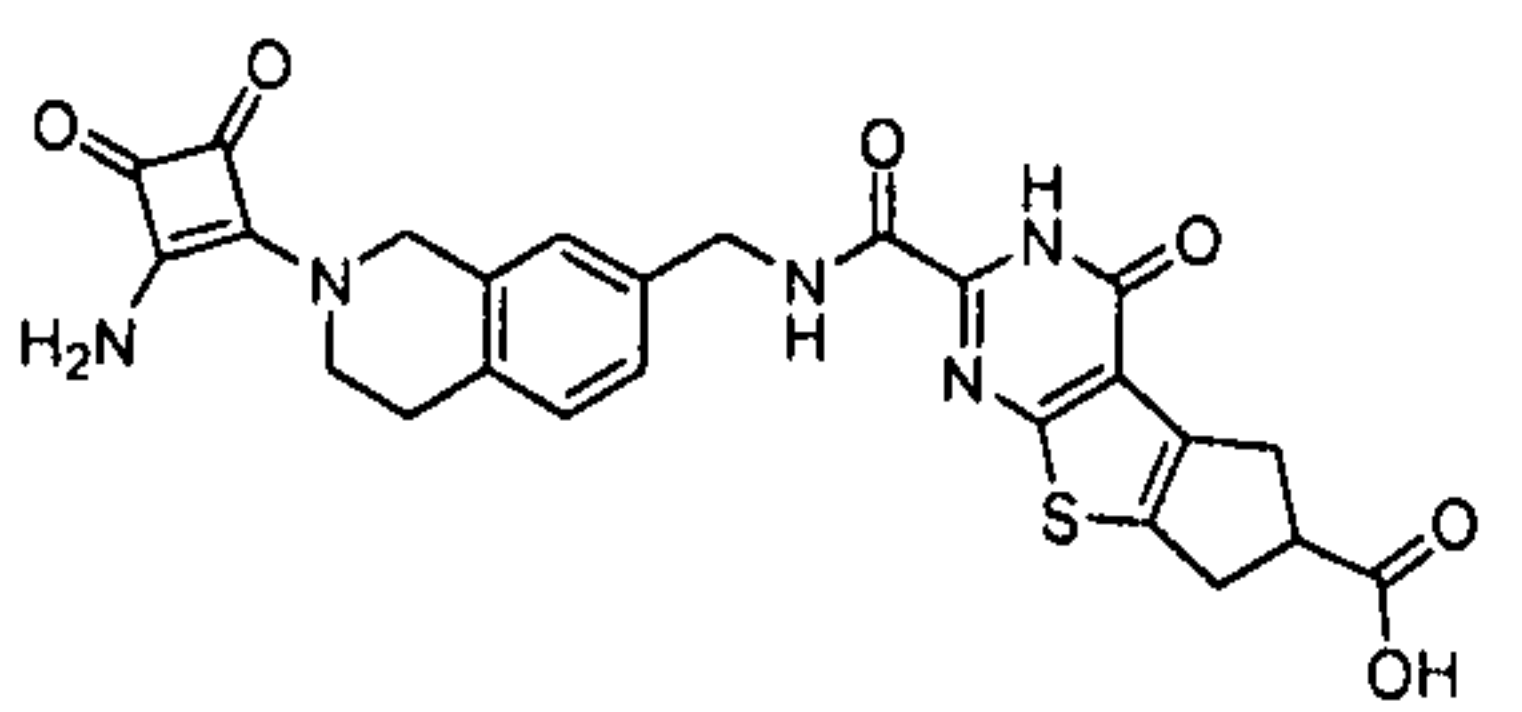
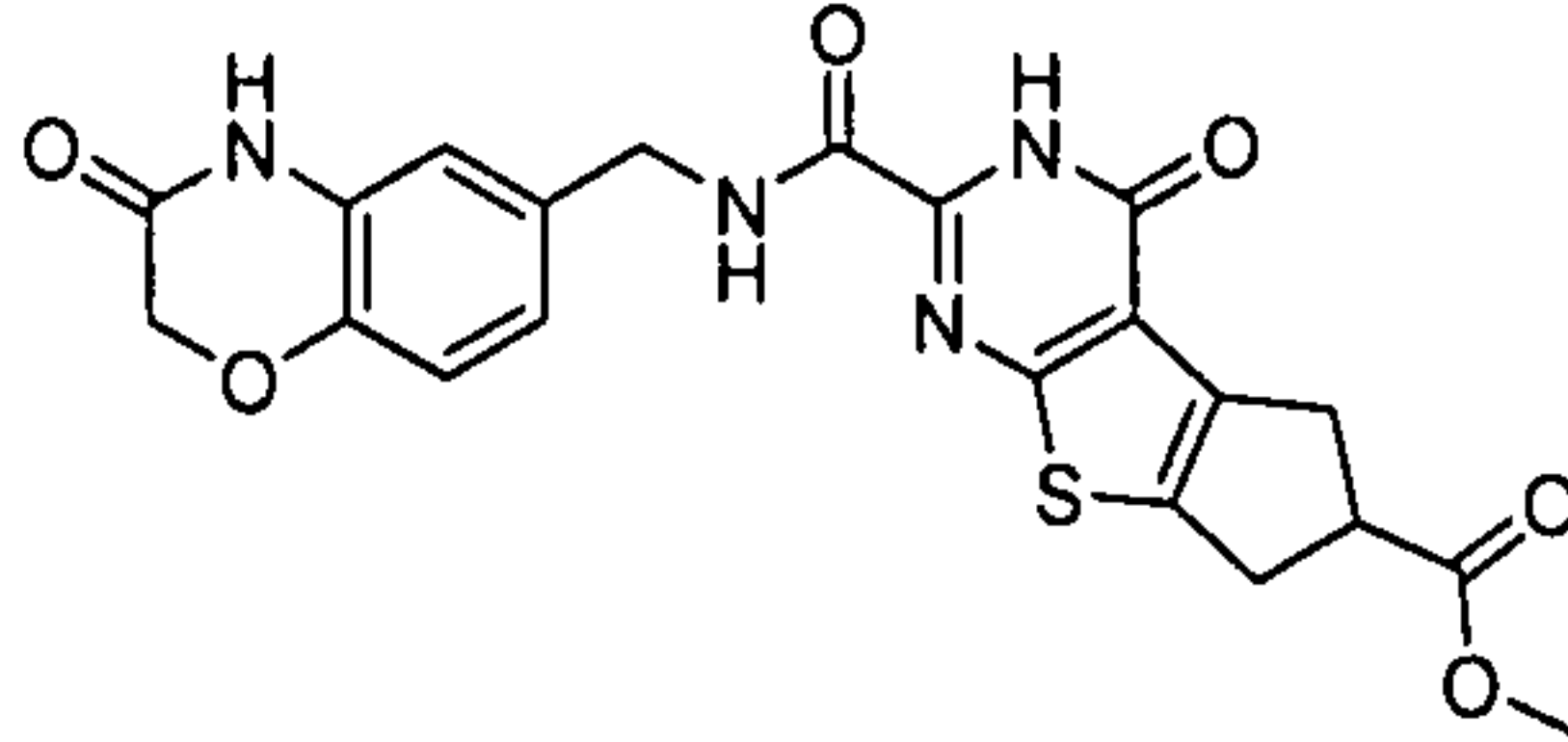
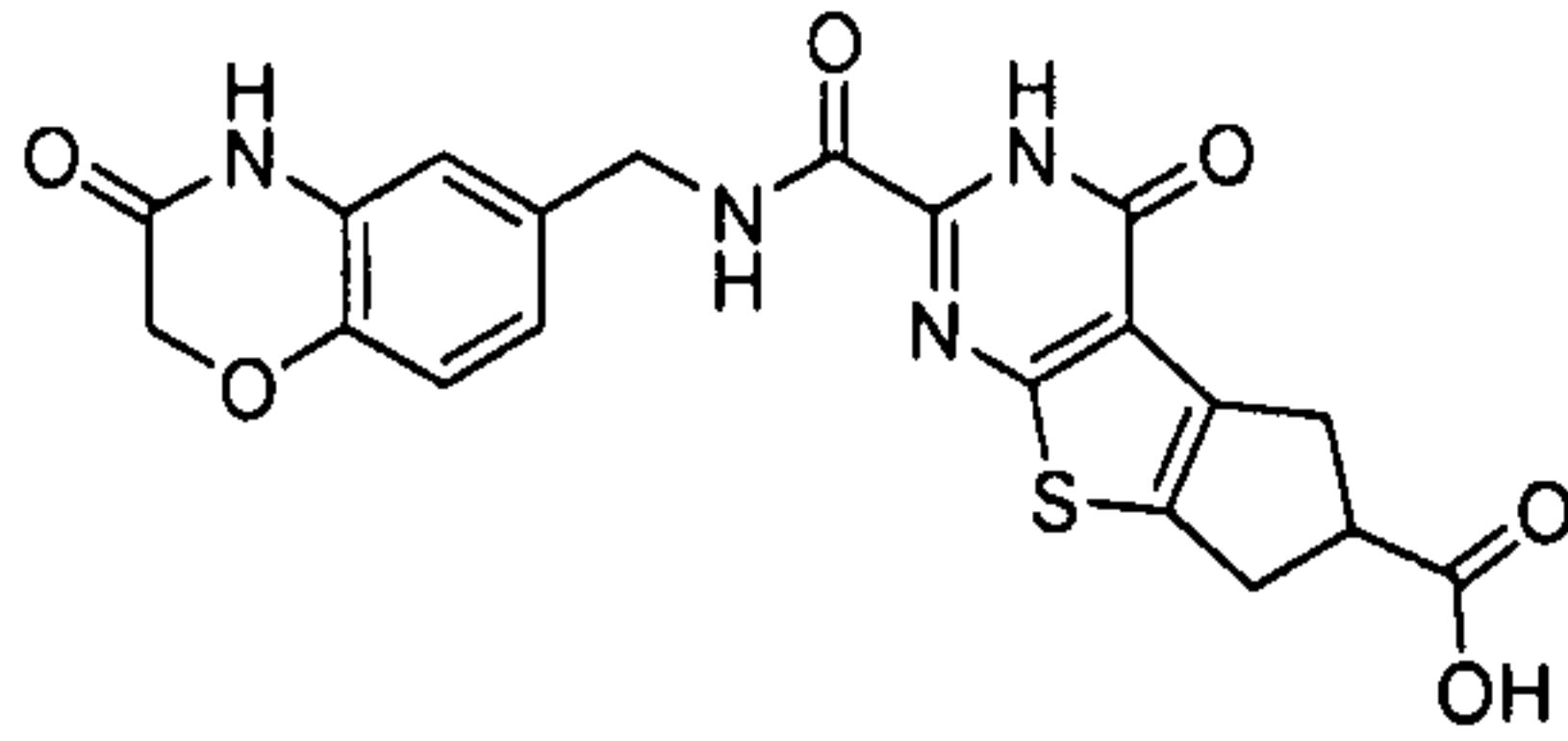
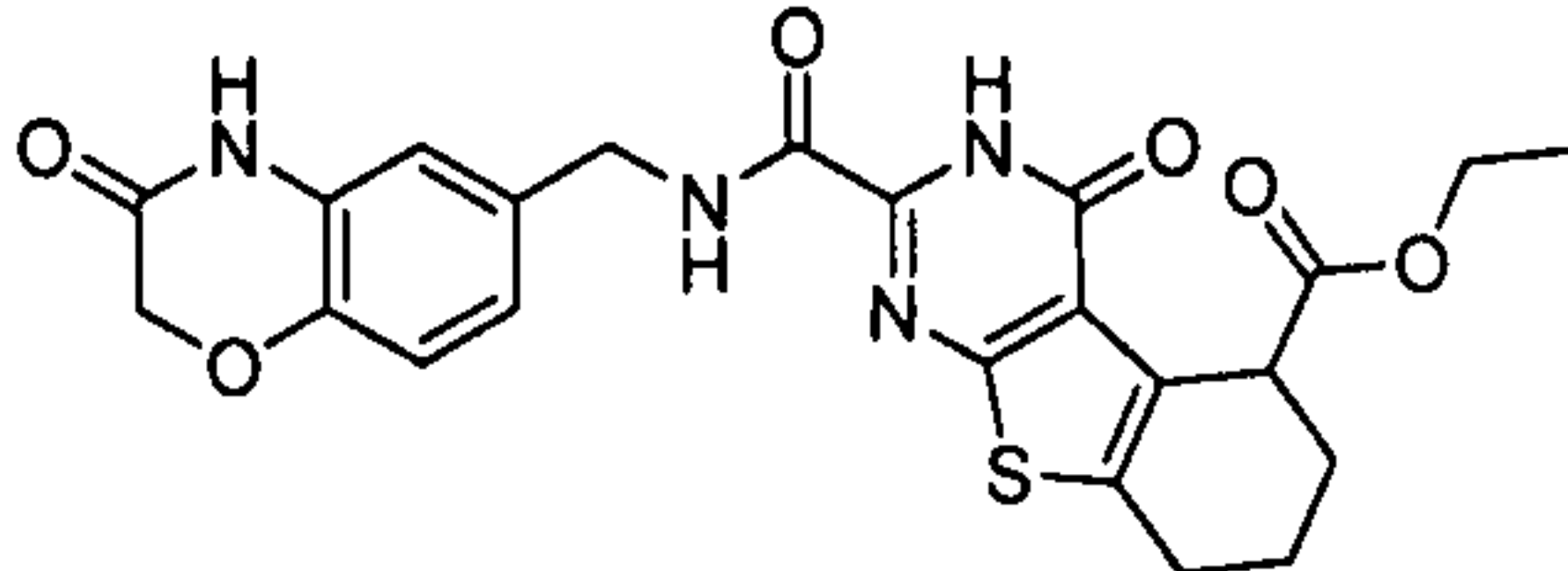
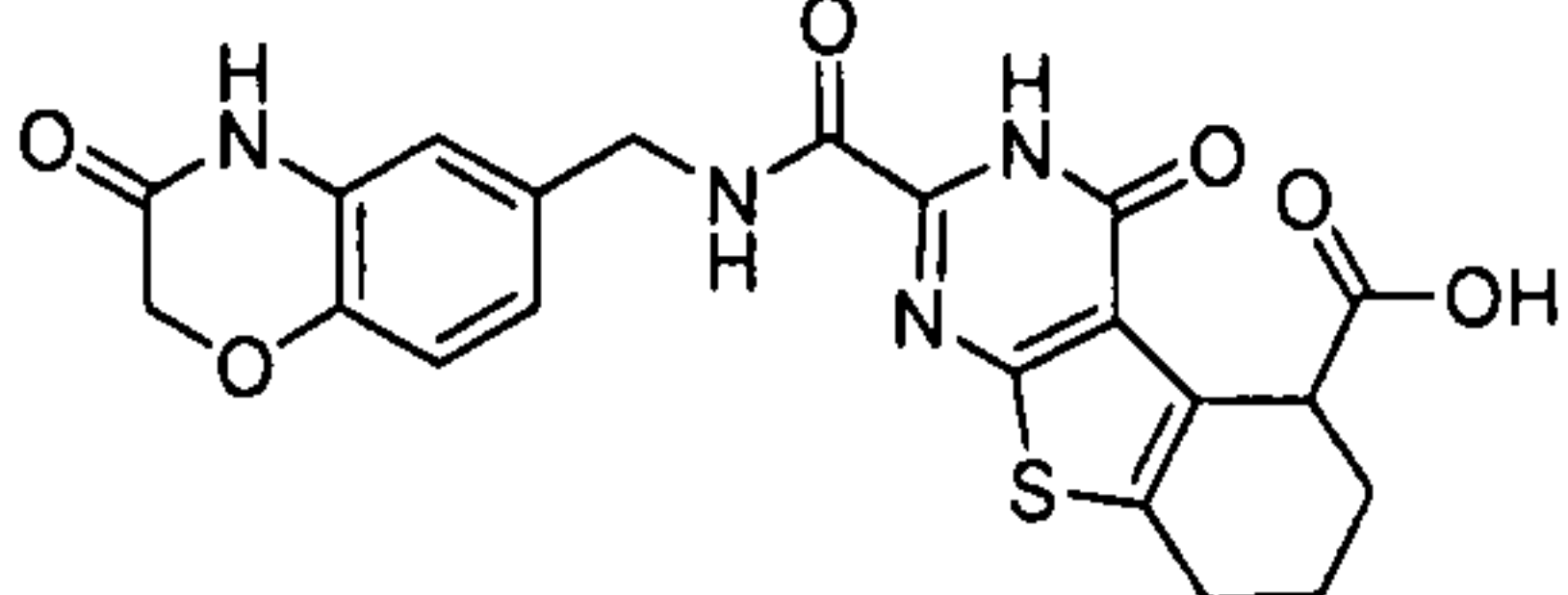
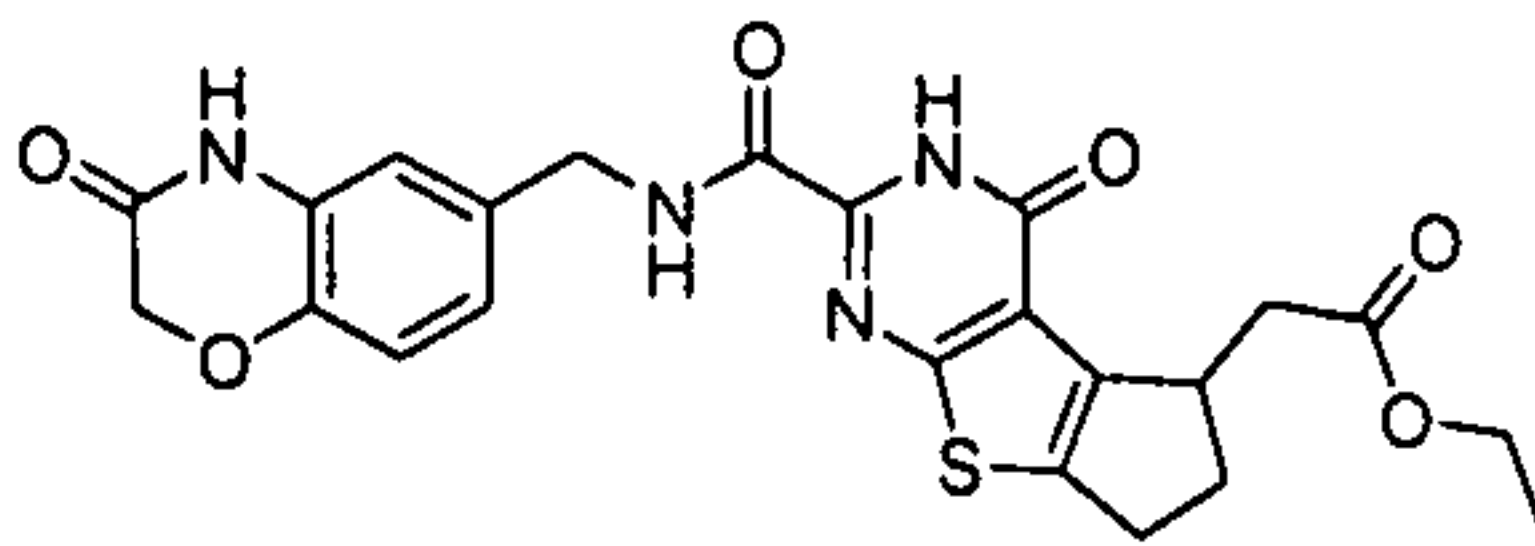
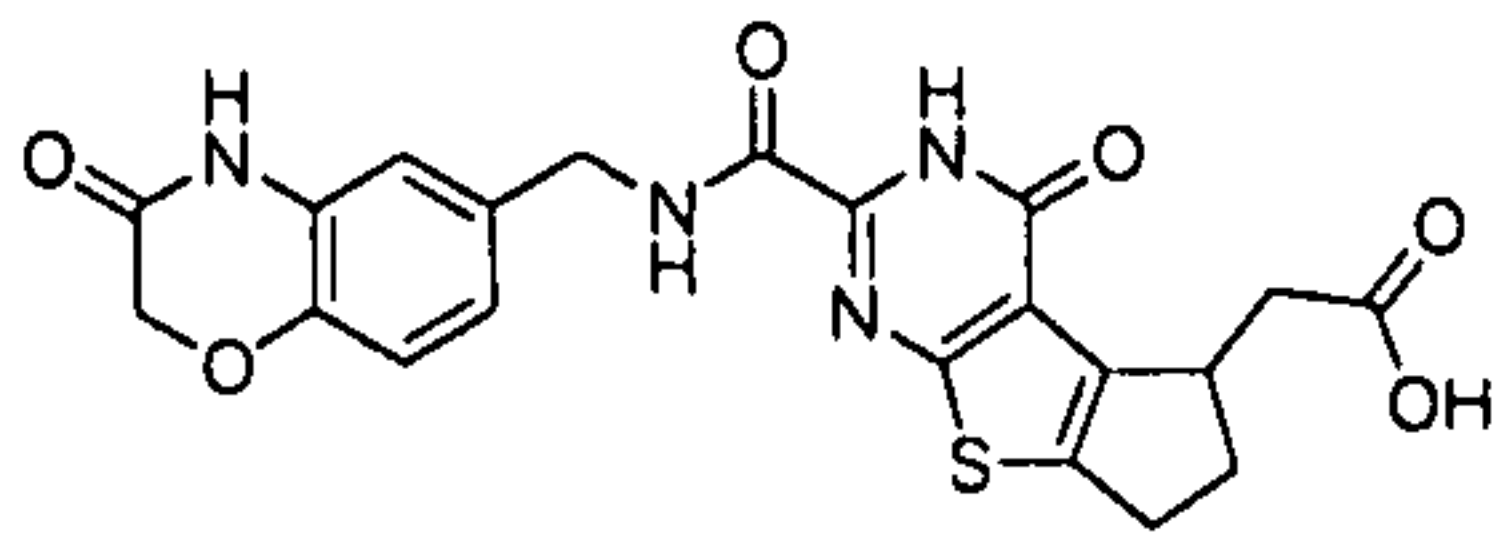
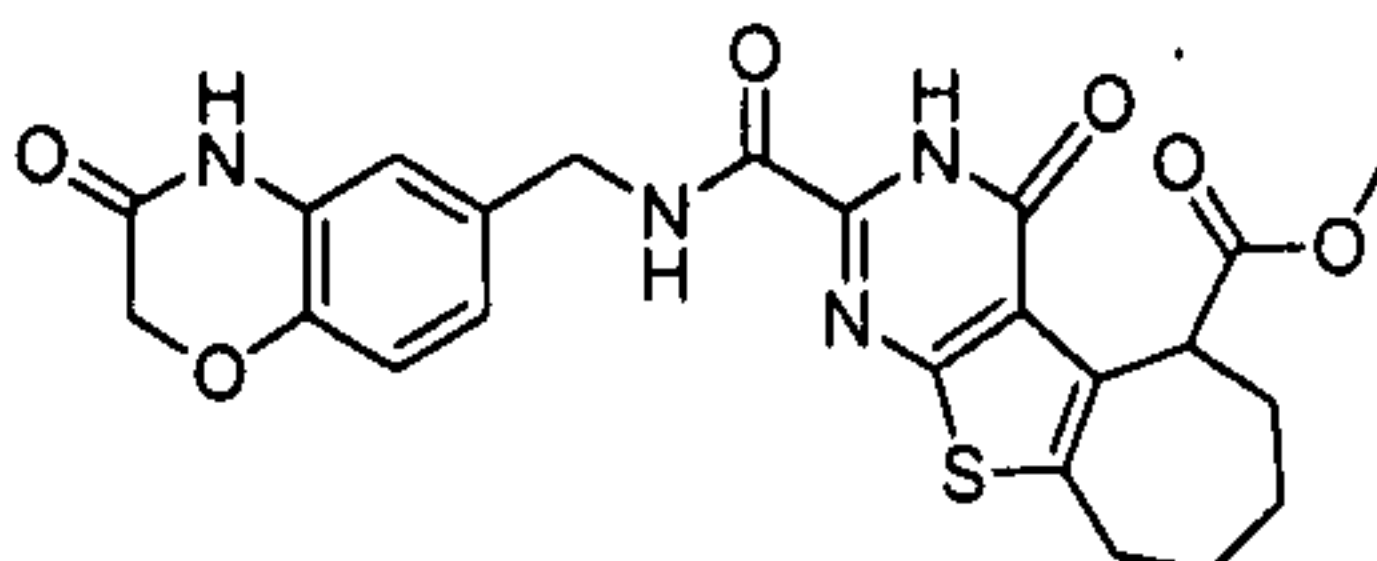
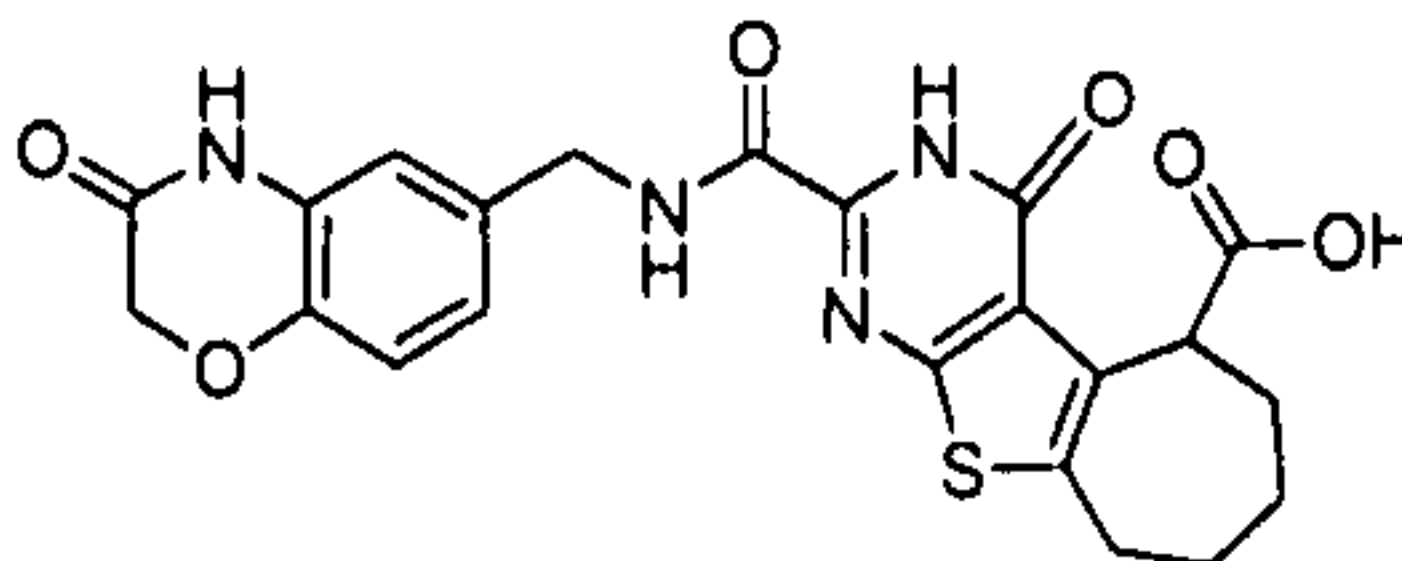
10

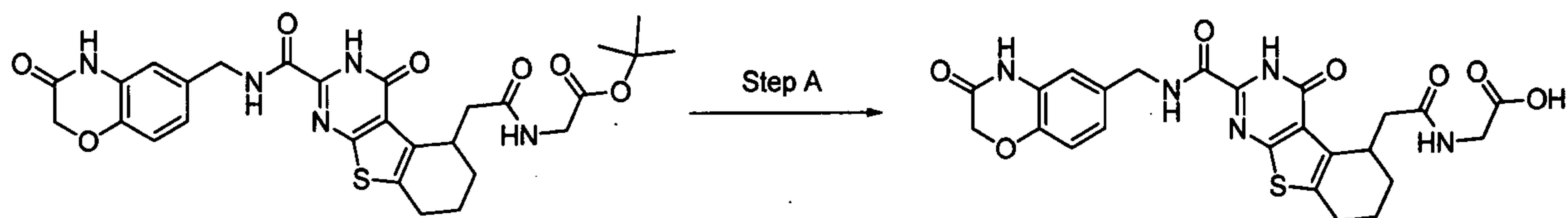
**Examples 4/4-4/19**

Following a similar procedure as described in Example 3, except using the ester indicated in Table II.2 below, the following compounds were prepared.

**Table II.2**

| Ex. # | Ester | Product | yield                 |
|-------|-------|---------|-----------------------|
| 4/4   |       |         | 70%<br>$[MH]^+ = 441$ |
| 4/9   |       |         | 66%<br>$[MH]^+ = 606$ |

| Ex. # | Ester                                                                                | Product                                                                               | yield                          |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------|
| 4/10  |    |    | 68%<br>[MH] <sup>+</sup> = 574 |
| 4/11  |    |    | 99%<br>[MH] <sup>+</sup> = 455 |
| 4/14  |   |   | 65%<br>[MH] <sup>+</sup> = 520 |
| 4/15  |  |  | 65%<br>[MH] <sup>+</sup> = 441 |
| 4/17  |  |  | 40%<br>[MH] <sup>+</sup> = 455 |
| 4/18  |  |  | 72%<br>[MH] <sup>+</sup> = 455 |
| 4/19  |   |  | 66%<br>[MH] <sup>+</sup> = 467 |

**Example 15****Step A**

- 5 To the title compound from Step A above (55 mg) was added a 4M solution of HCl in 1,4-dioxane (3 mL). The reaction mixture was stirred at room temperature overnight and concentrated to afford the title compound (29 mg, 58%).  $[MH]^+ = 526$ .

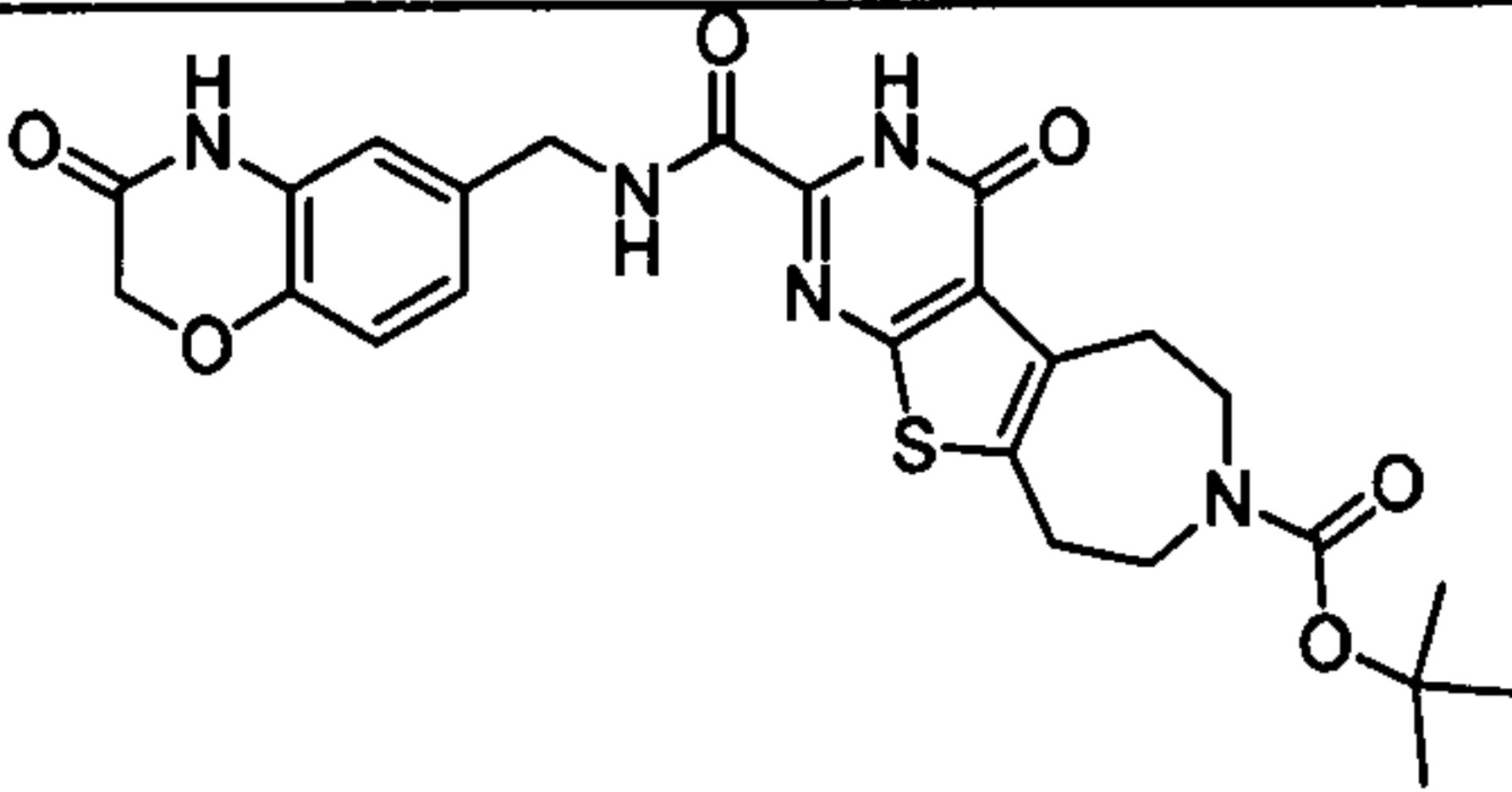
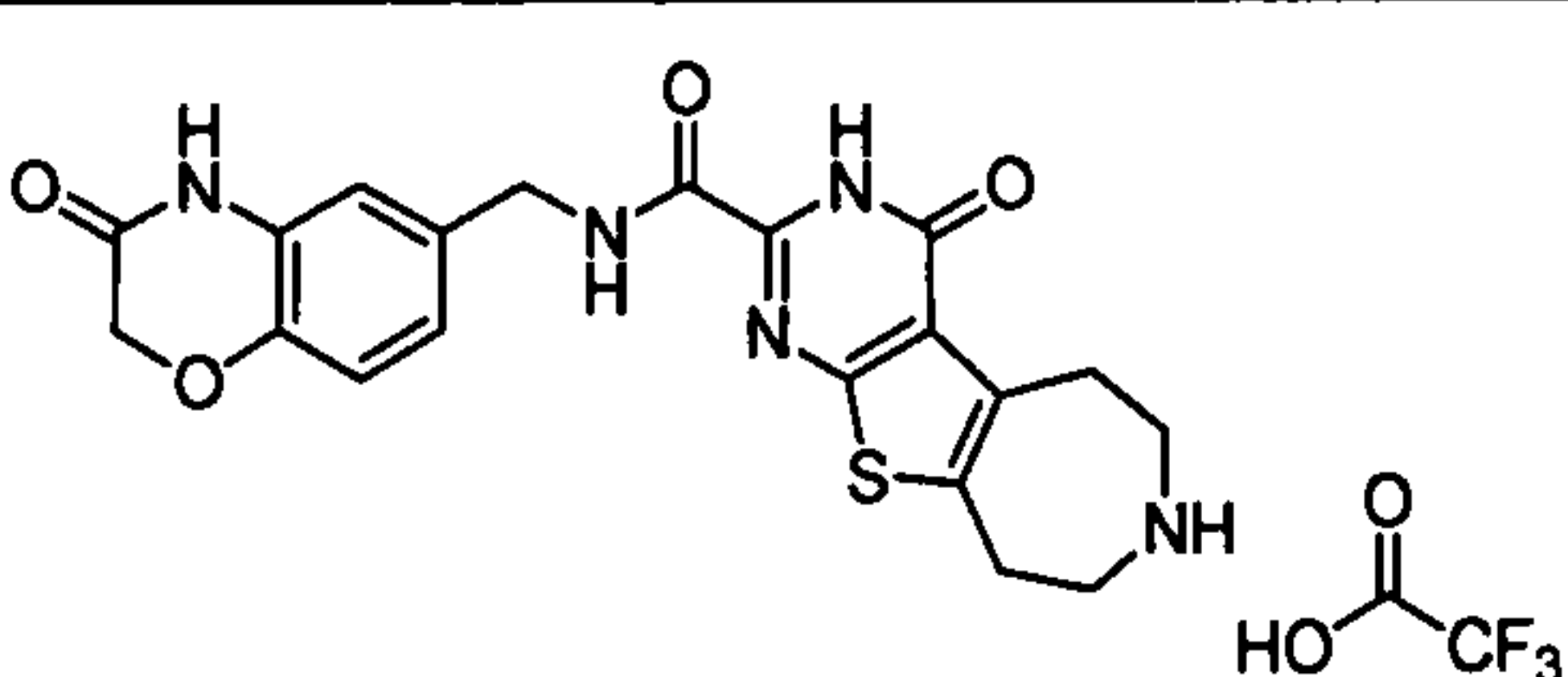
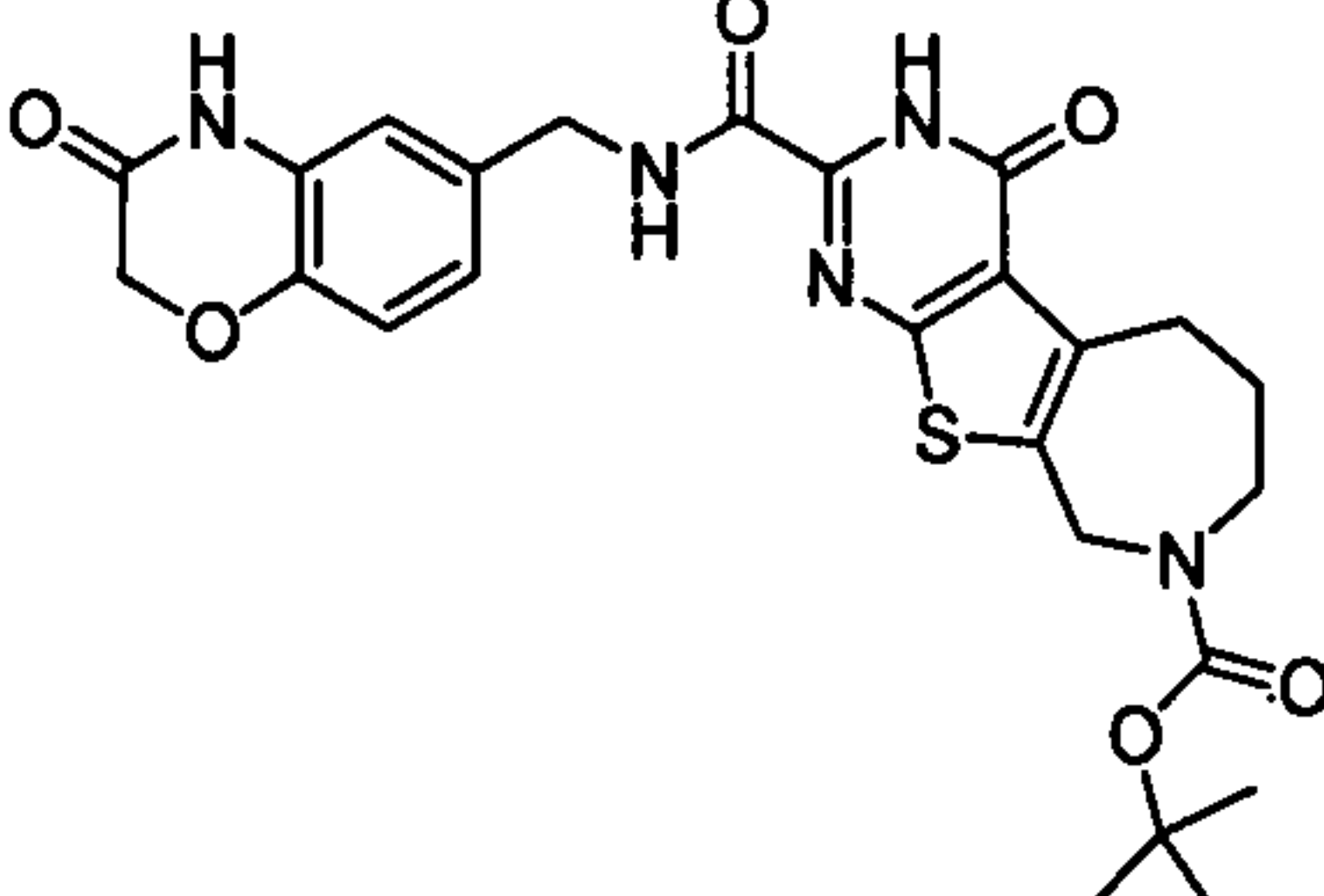
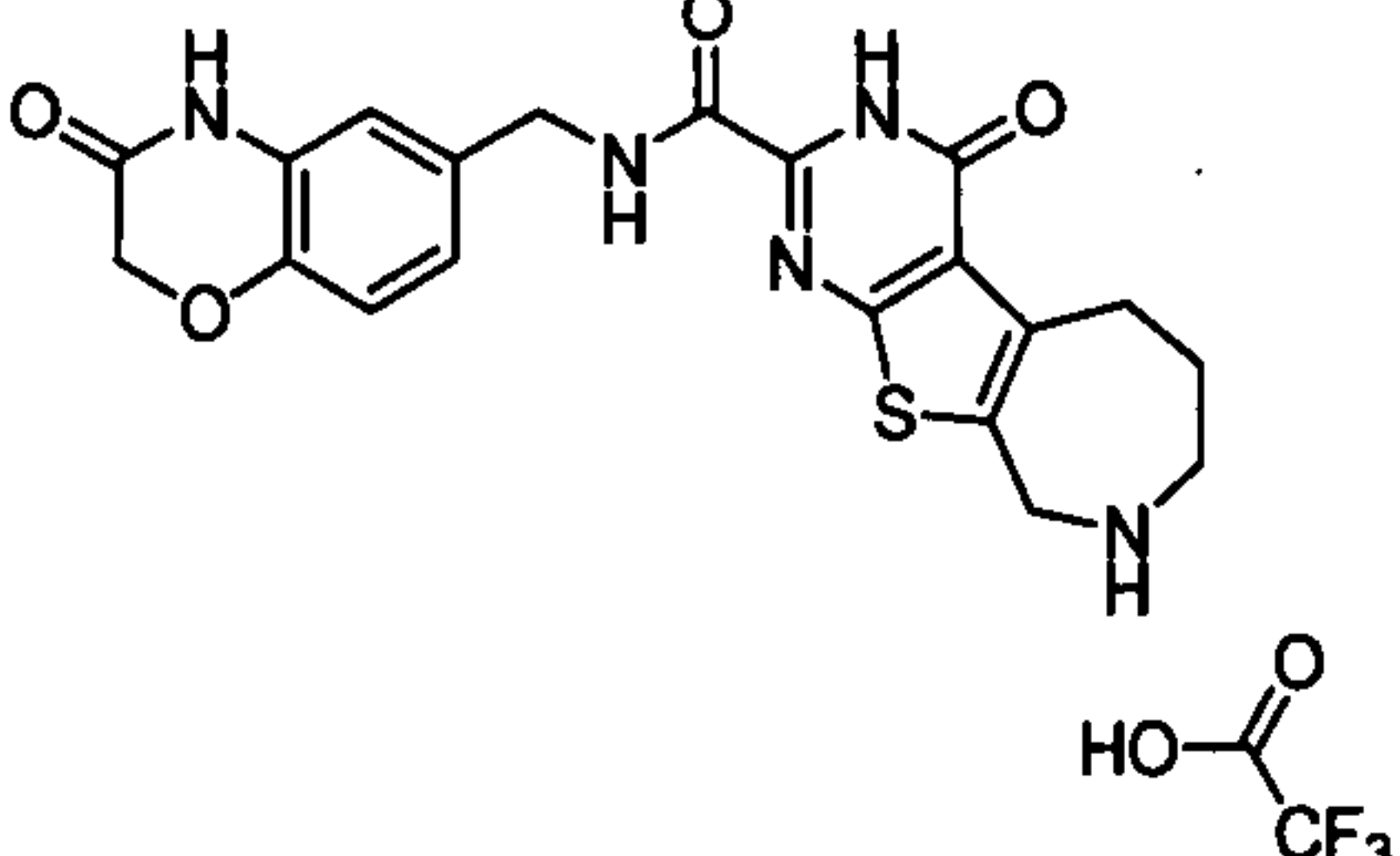
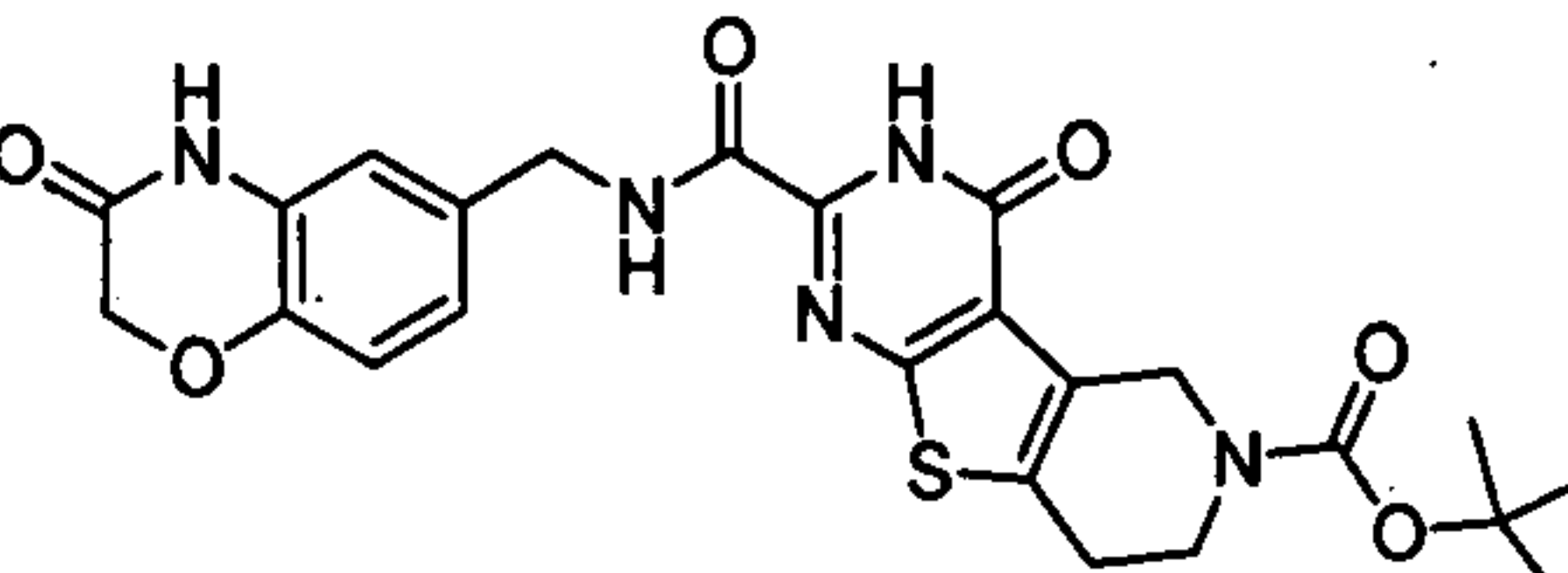
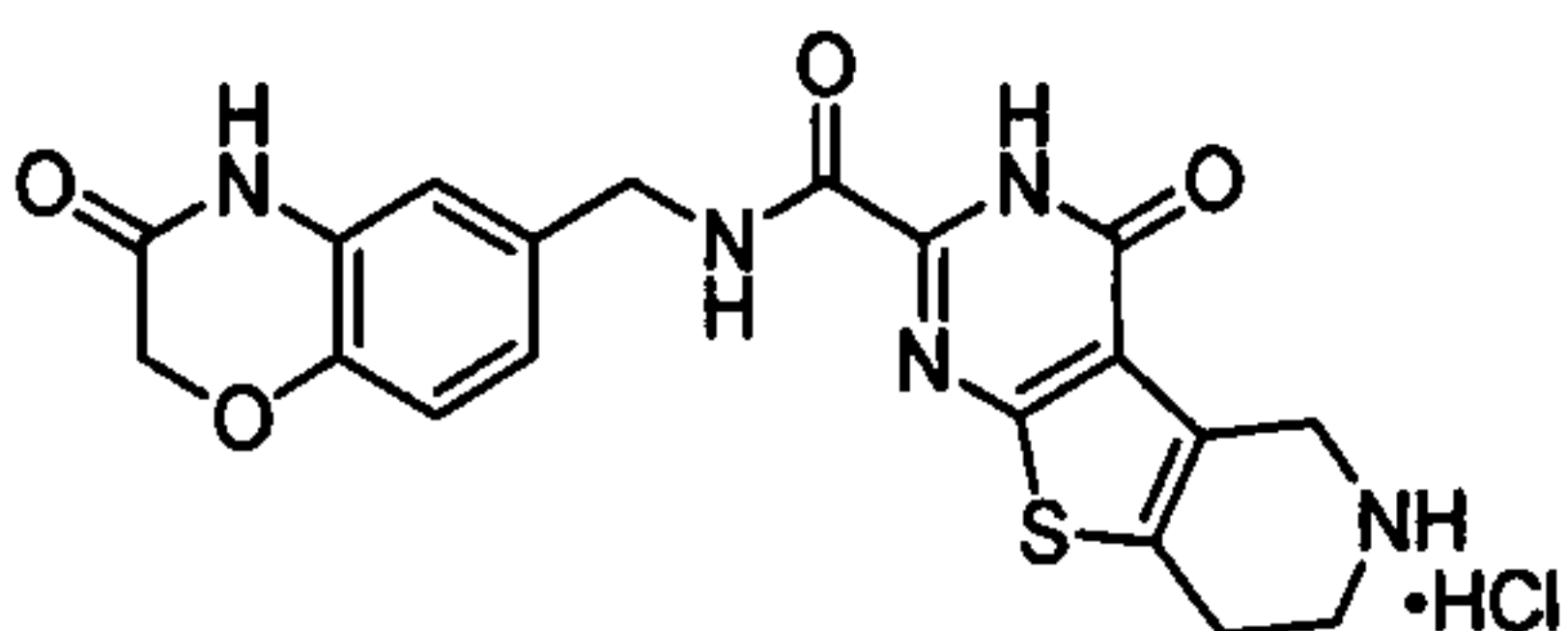
10

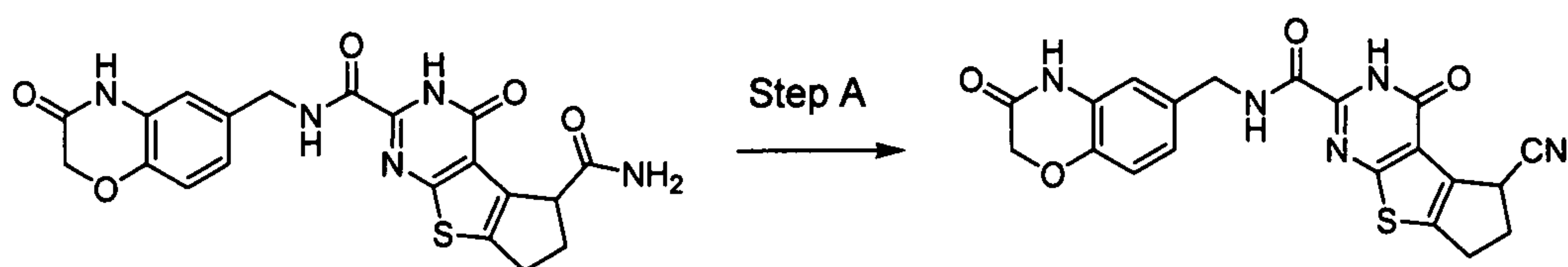
**Examples 15/2 – 15/5**

Following a similar procedure as described in the Example 15, except using the protected product indicated in Table II.7 below, the following compounds were prepared.

**Table II.7**

| Ex. # | educt | product | Yield                     |
|-------|-------|---------|---------------------------|
| 15/2  |       |         | 50%<br><br>$[MH]^+ = 498$ |

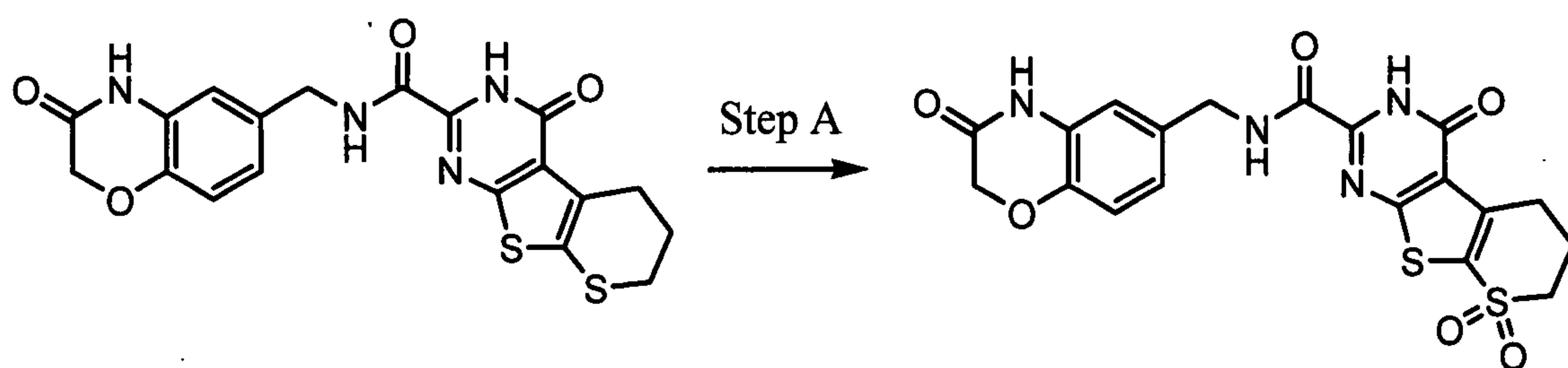
| Ex. # | educt                                                                                | product                                                                               | Yield                          |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------|
| 15/3  |    |    | 16%<br>[MH] <sup>+</sup> = 426 |
| 15/4  |    |   | 69%<br>[MH] <sup>+</sup> = 426 |
| 15/5  |  |  | 46%<br>[MH] <sup>+</sup> = 412 |

**Example 19****Step A**

- 5 To DMF (5 mL) was added 2M oxalylchloride in dichloromethane (250  $\mu$ L) at 0 °C. Then a solution of the title compound from Example 2/166. (200 mg) in DMF (2 mL) was added and the mixture was stirred for 6h at 0 °C. After adding pyridine (150  $\mu$ L) the mixture was stirred for additional 2h at room temperature. The mixture was concentrated and the remaining residue was

suspended in 1M HCl and filtered to afford the title compound as an off white solid (192 mg, 99%).  $[MH]^+ = 422$ .

### Example 22



5

#### Step A

The title compound from example 2/119 (9 mg) was placed in a mixture acetic acid/acetic acid anhydride (1:1). Hydrogen peroxide (6  $\mu$ L) was added and the reaction mixture was heated at 100°C for 4h and then stirred at room temperature overnight. After evaporation, water was added and the residual product was filtrated and dried to afford the title compound (7 mg, 72%).  $[MH]^+ = 461$ .

10

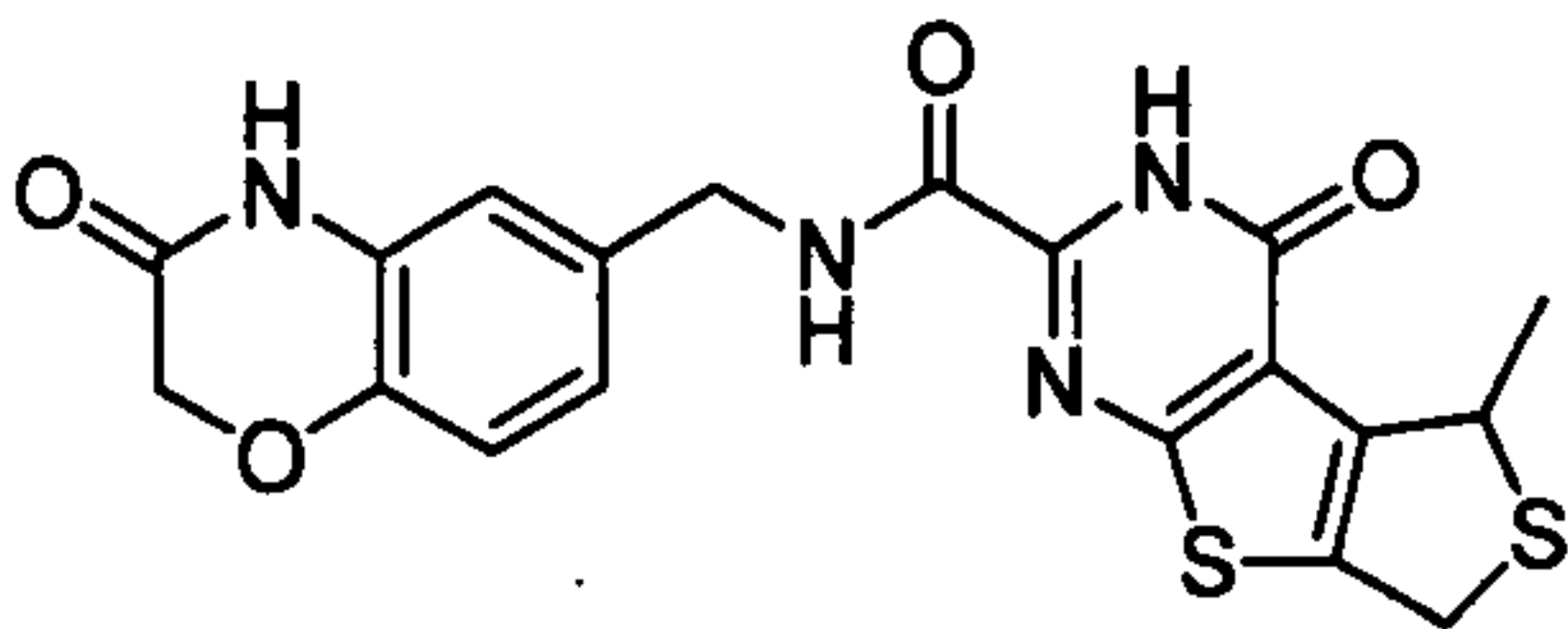
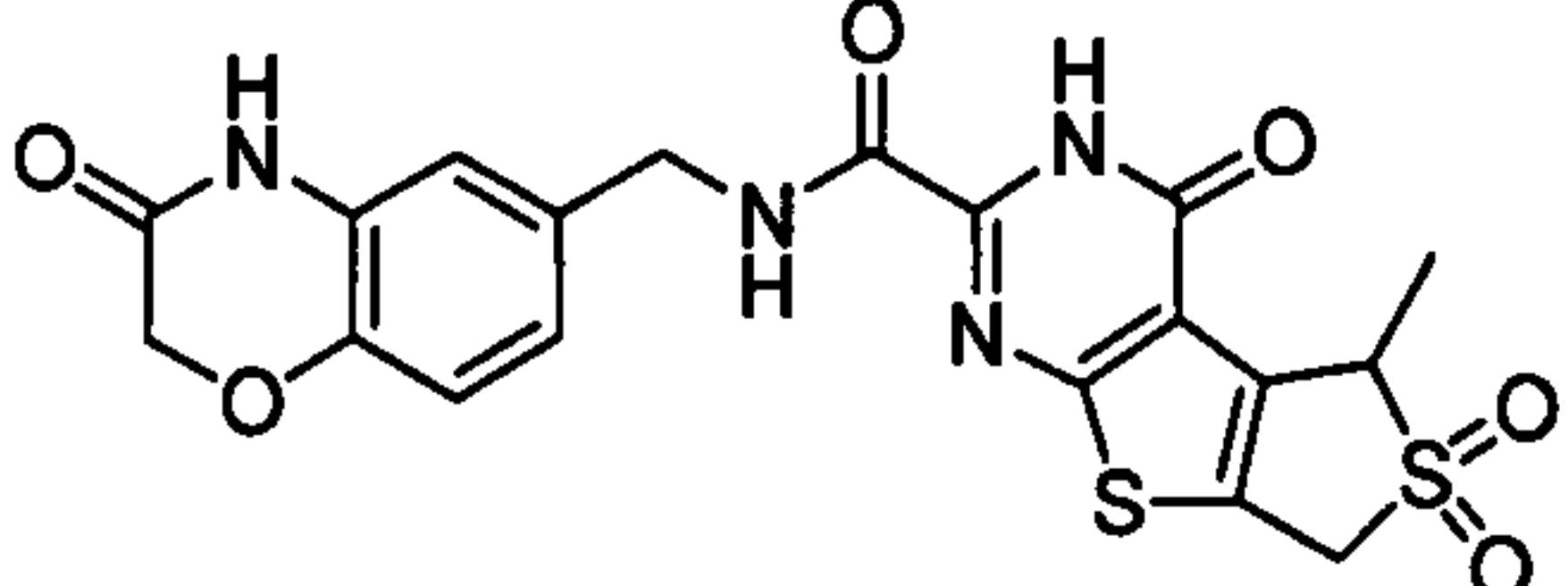
### Example 22/1 and 22/2

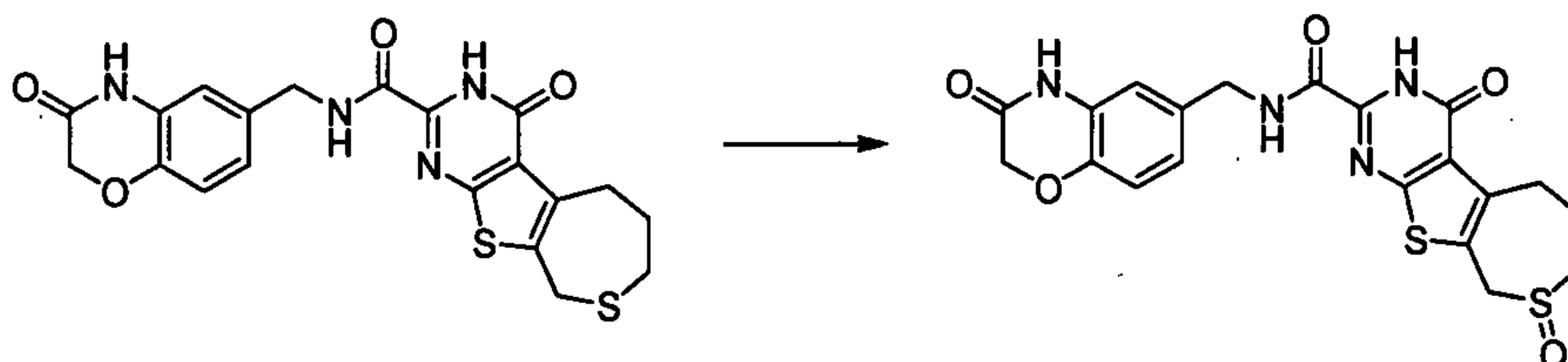
Following a similar procedure as described in Example 22, except using the educt indicated in Table II.9 below, the following compounds were prepared.

15

**Table II.9**

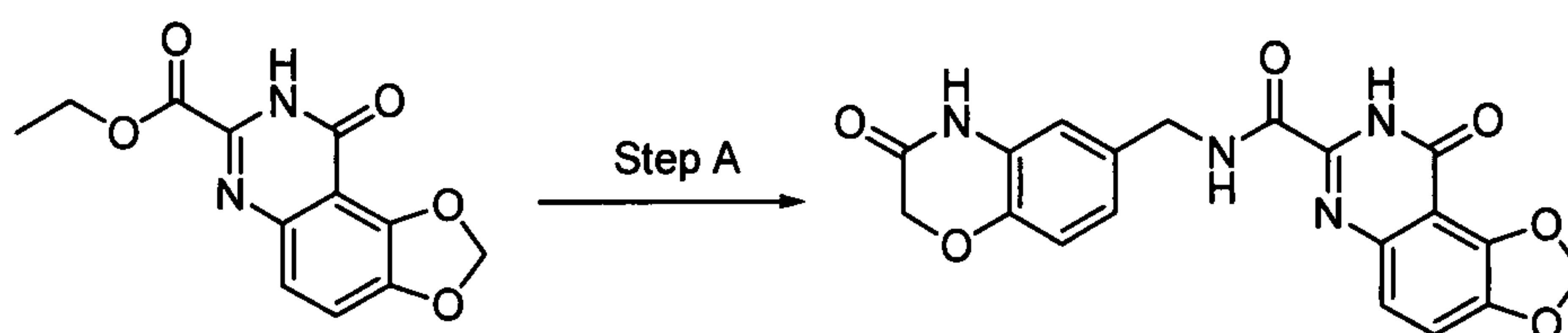
| Ex. # | educt | product | Yield                 |
|-------|-------|---------|-----------------------|
| 22/1  |       |         | 80%<br>$[MH]^+ = 475$ |

| Ex. # | educt                                                                              | product                                                                             | Yield                          |
|-------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------|
| 22/2  |  |  | 89%<br>[MH] <sup>+</sup> = 461 |

**Example 26****Step A**

- 5 The title compound from Example 2/218 (15.8 mg) was dissolved in DMSO, then H<sub>2</sub>O<sub>2</sub> (~ 1 mL) was added and the mixture was stirred at room temperature for 3 h, evaporated, slurried with water and filtered to afford the title compound (13.8 mg, 84%) as a colourless solid. [MH]<sup>+</sup> = 459.

10

**Example 28****Step A**

- To a solution of 9-oxo-8,9-dihydro-1,3-dioxo-6,8-diazacyclopenta[a]naphthalene-7-carboxylic acid ethyl ester (32 mg) in ethanol (1 mL) were added triethyl amine (40 μL) and the title compound from the Preparative
- 15

Example 13 (30 mg). The mixture was heated at 180°C in a microwave oven for 1 h and then concentrated. The remaining residue was purified by silica gel chromatography (10% methanol in methylene chloride) to give a yellow solid (45 mg, 95%).  $[MH]^+ = 395$ .

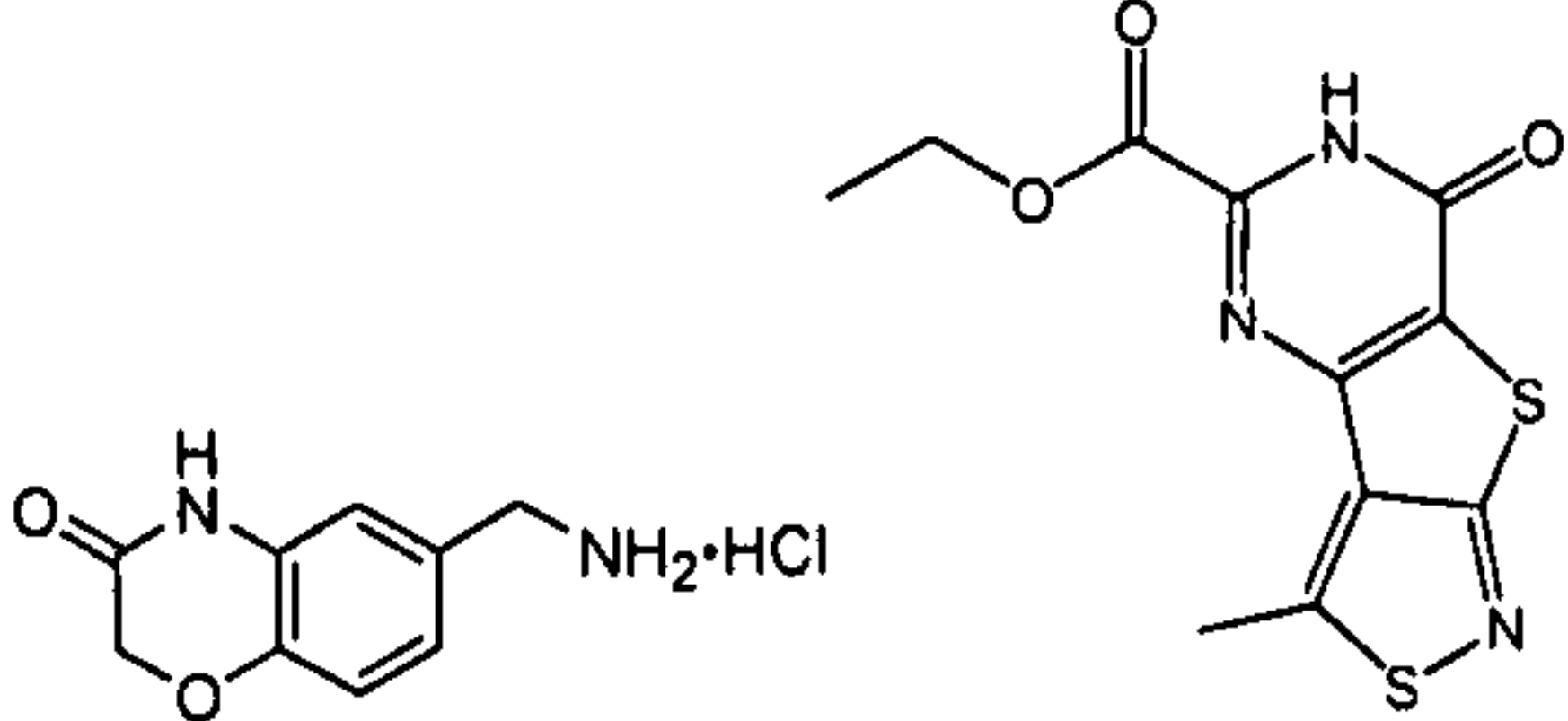
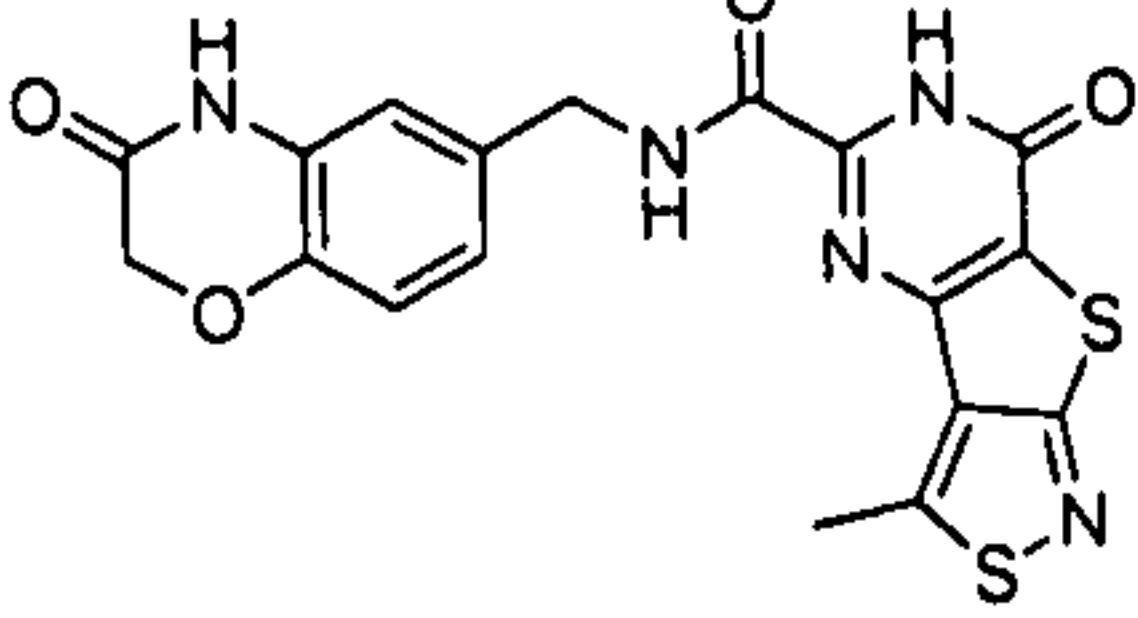
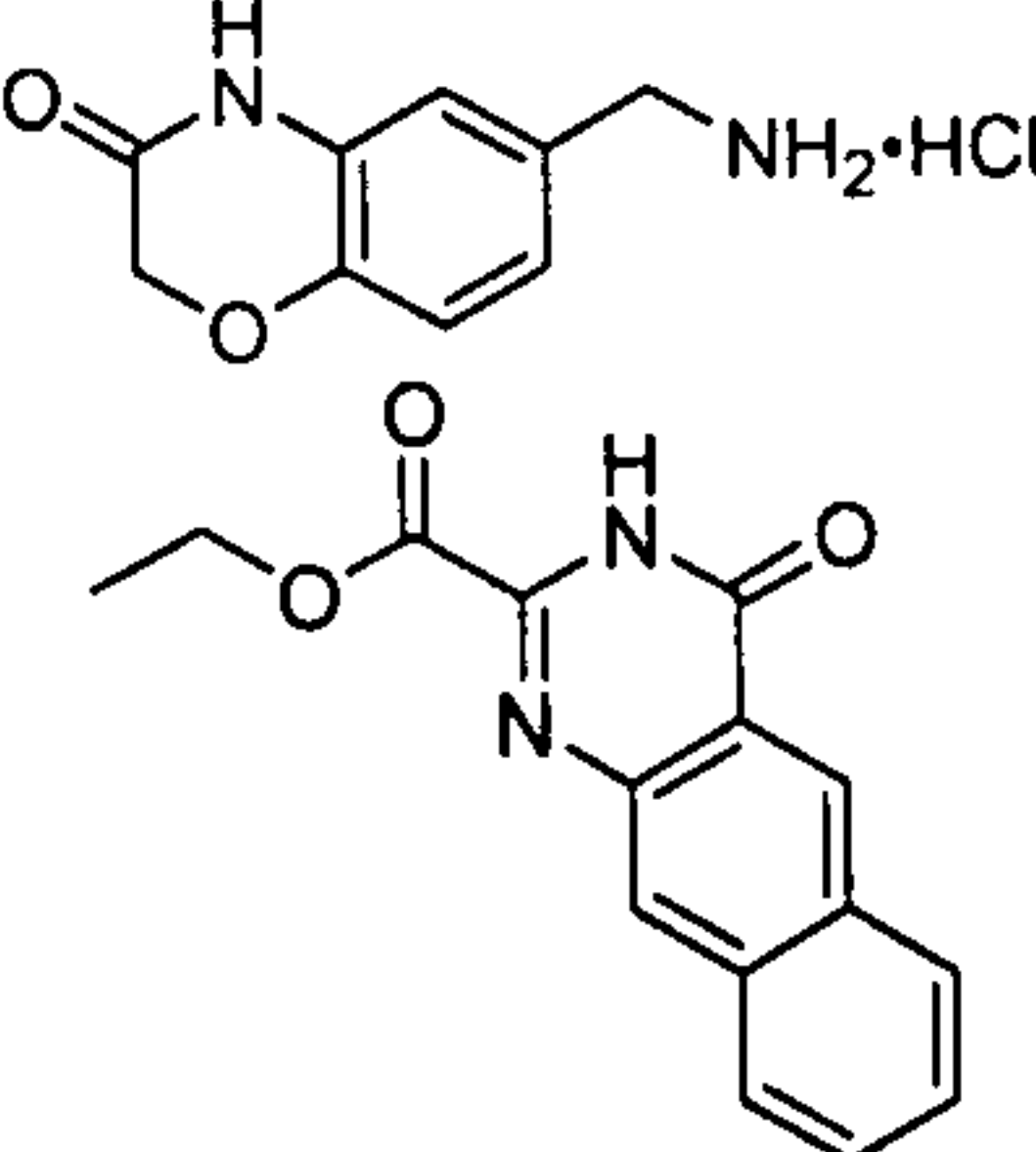
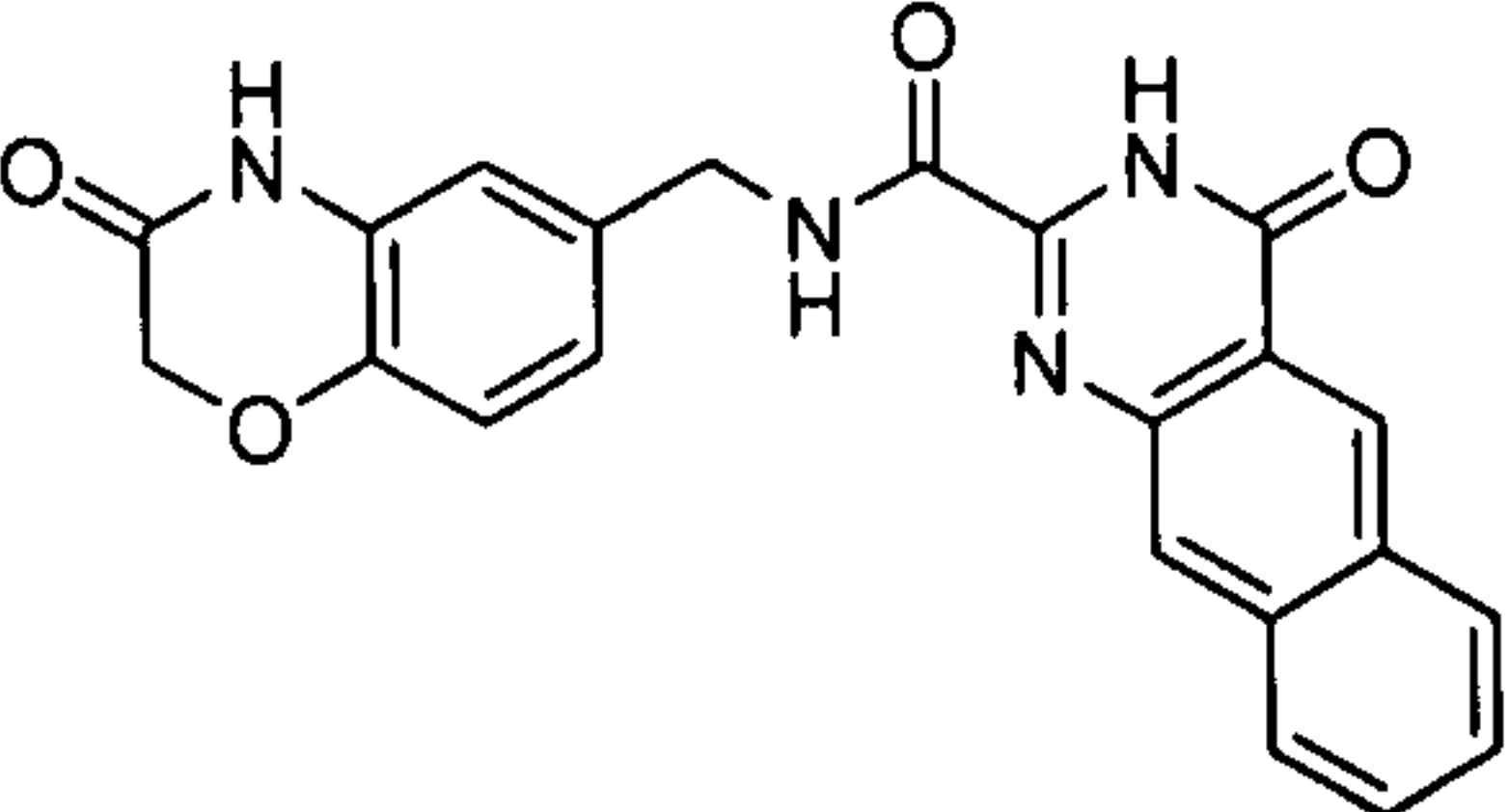
5

### Example 39/7 and 39/20

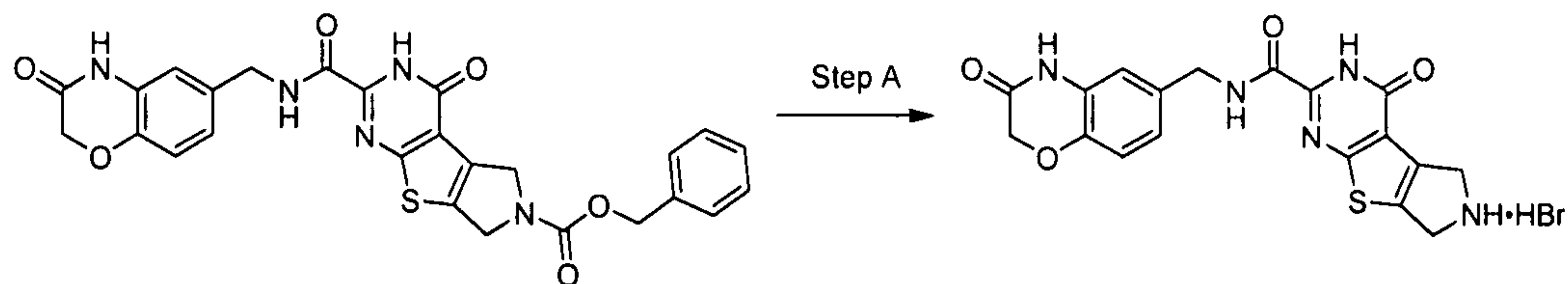
Following similar procedures as described in Examples 28 except using the amines and the ester indicated in Table II.14 below, the following compounds were prepared.

10

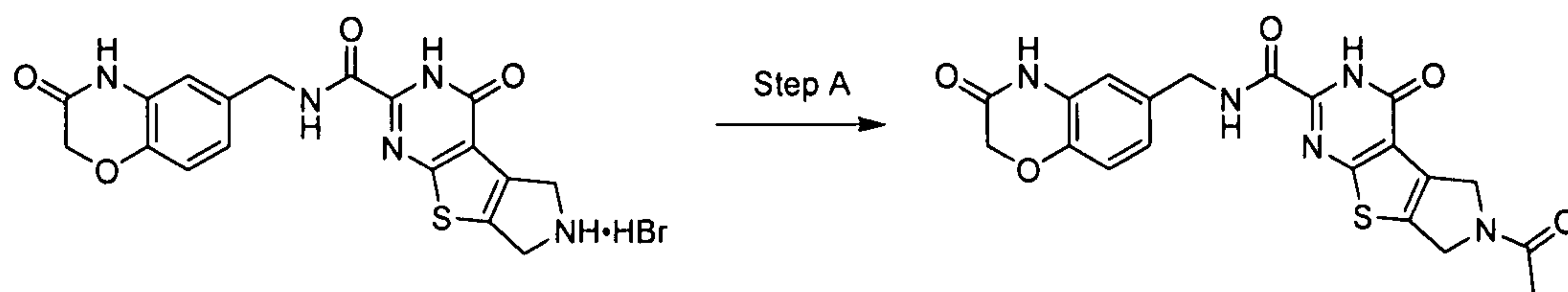
**Table II.14**

| Ex. # | amine; ester                                                                         | product                                                                               | Yield                 |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| 39/7  |  |  | 20%<br>$[MH]^+ = 428$ |
| 39/20 |   |  | 19%<br>$[MH]^+ = 401$ |

### Example 41

Step A

The title compound from Example 2/376 above was stirred in a solution of HBr in glacial acid (33wt%) at room temperature for 2 h. Evaporation afford the  
 5 title compound.  $[MH]^+ = 398$ .

Example 42Step A

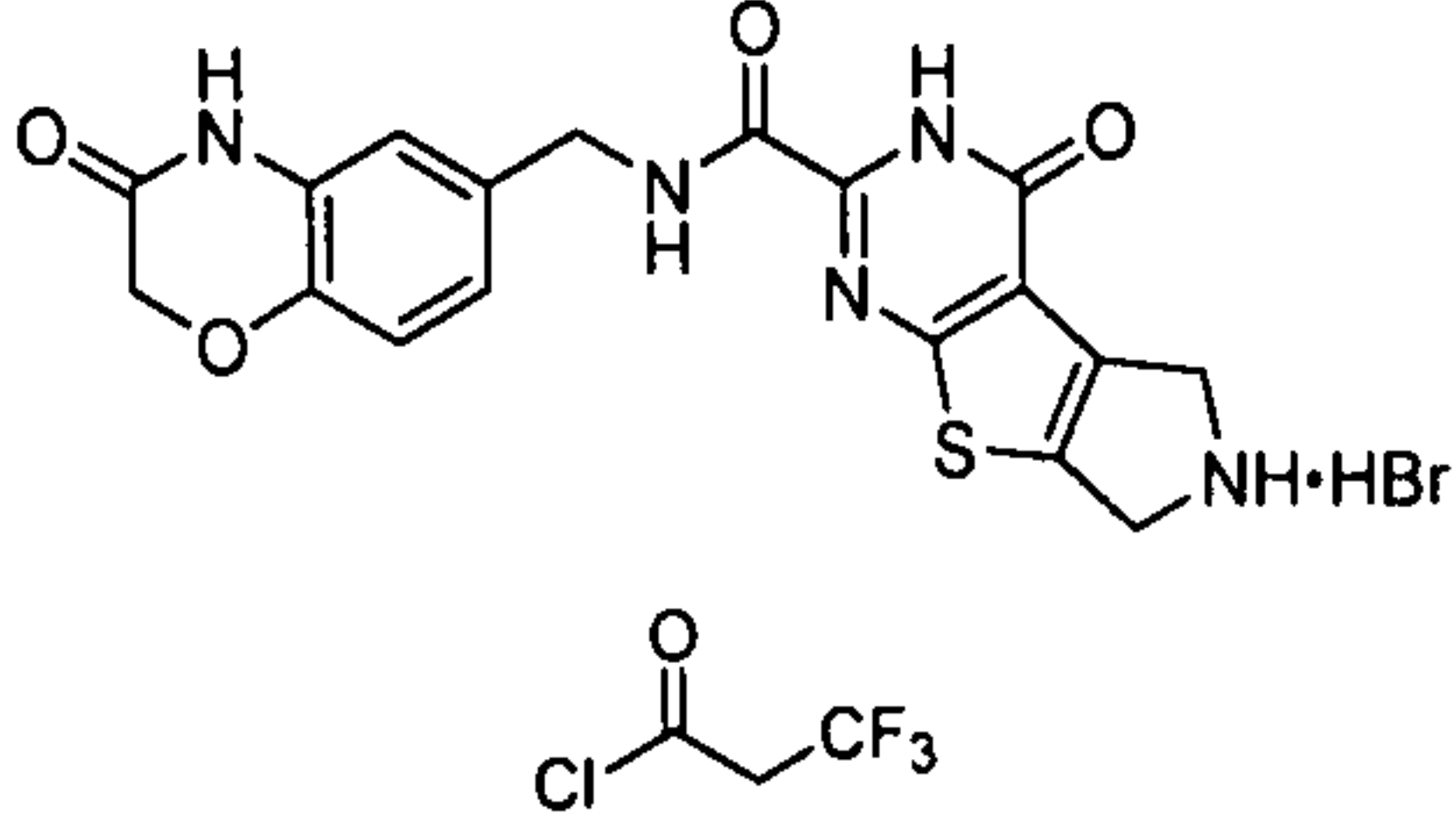
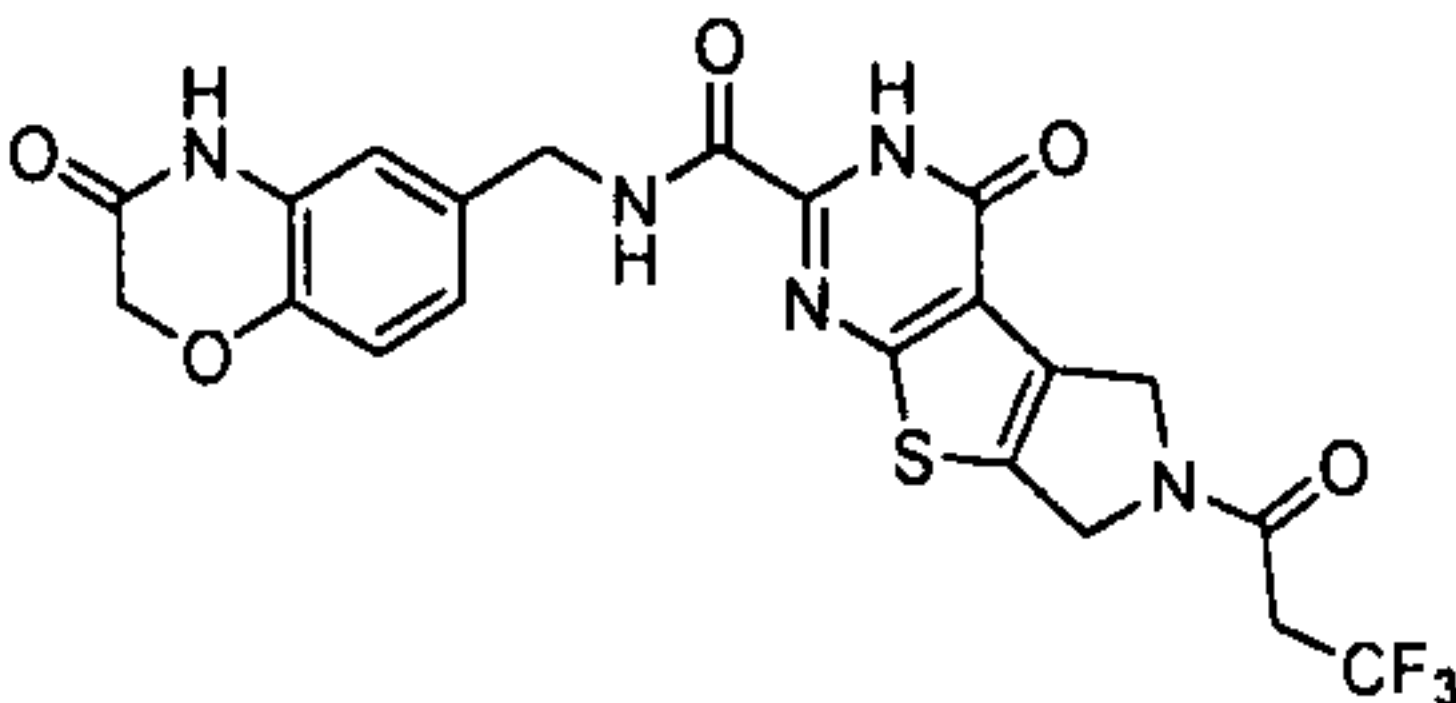
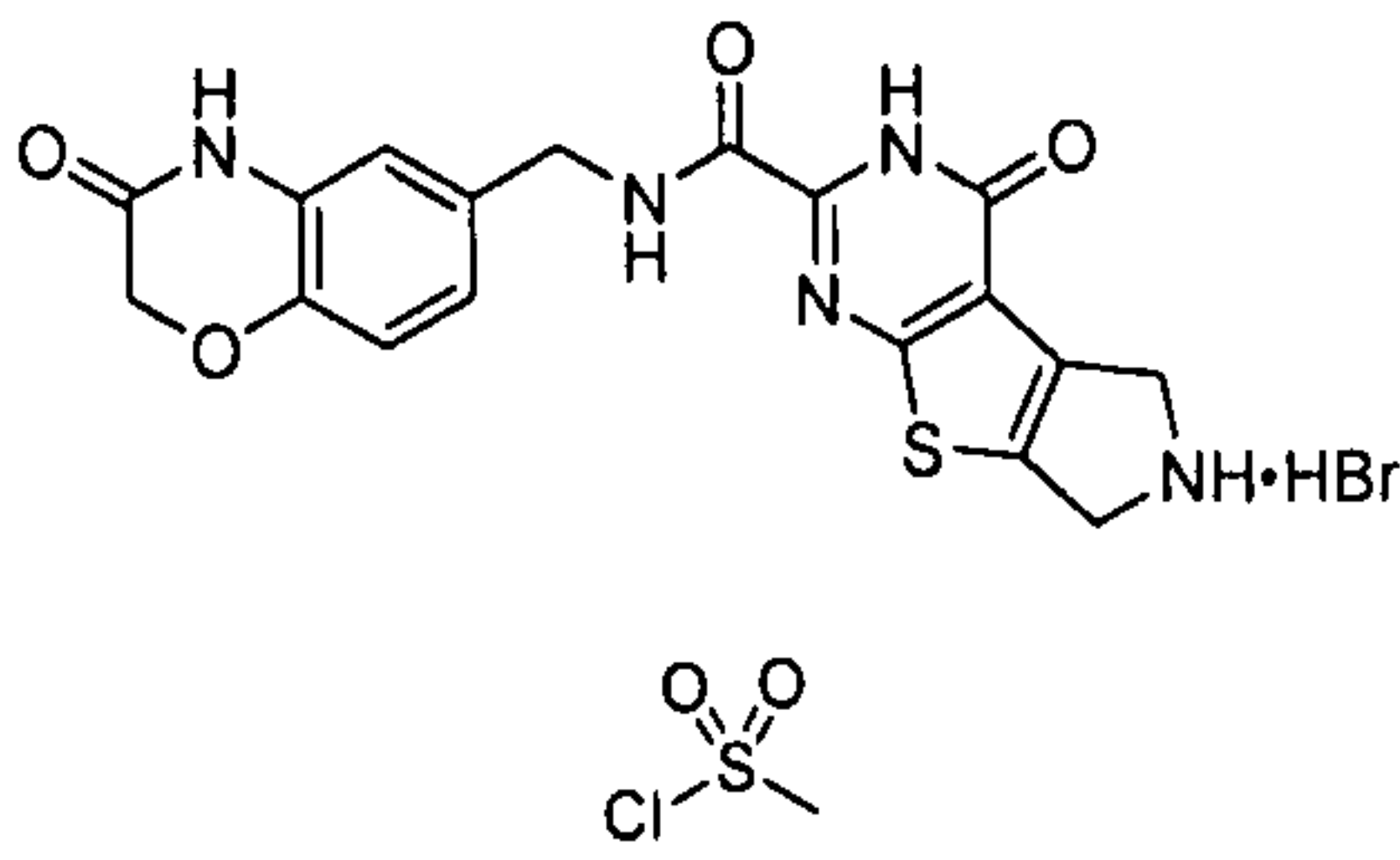
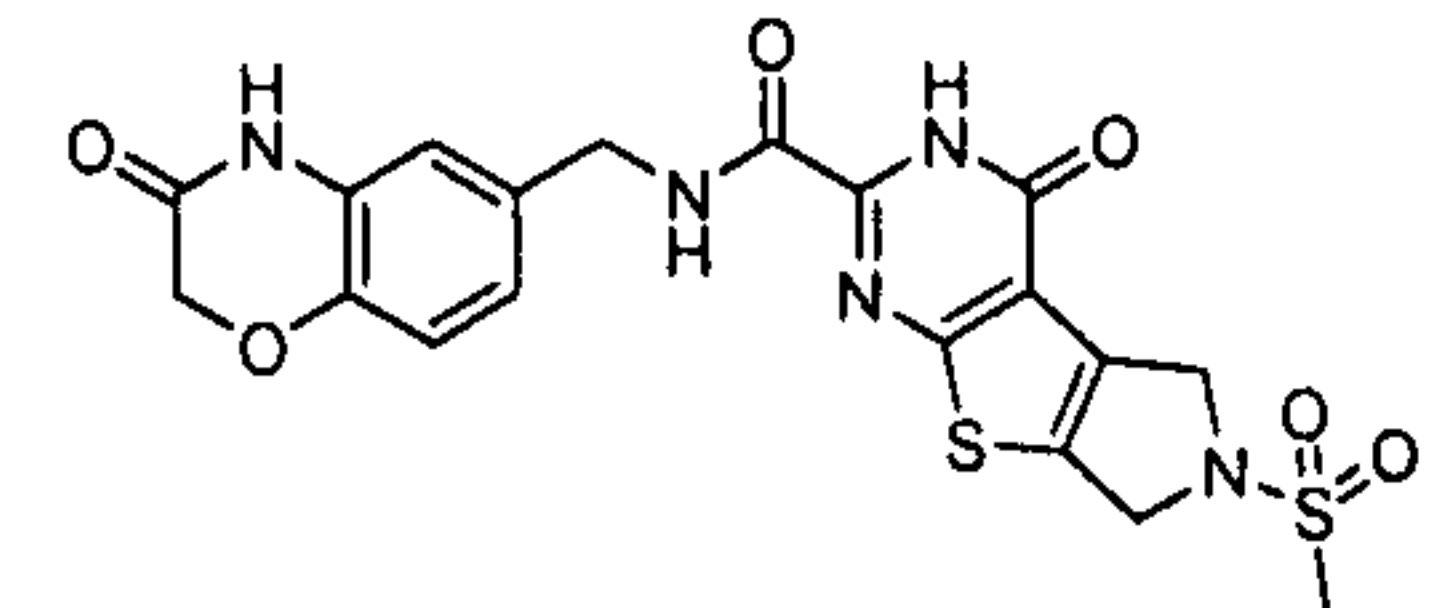
10 To a solution of the title compound from Example 41 (9.6 mg) in pyridine (200 $\mu$ L) was added acetyl chloride (3  $\mu$ L) at room temperature. The mixture was stirred for 2 h at room temperature and evaporated. The resulting residue was purified by HPLC to afford the title compound. (2.2 mg; 25%,  $[MH]^+ = 440$ ).

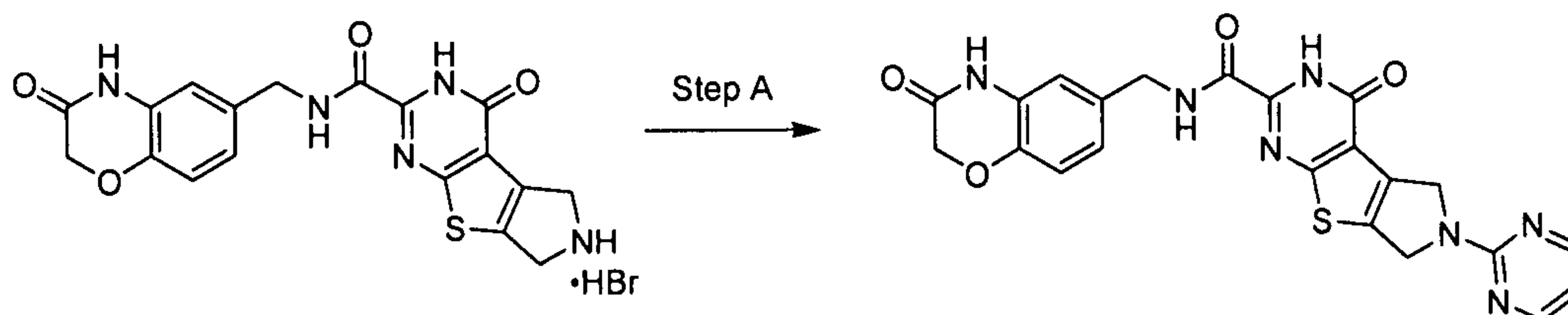
15

Example 42/1 and 42/2

Following a similar procedure as described in Example 42 above, except using amines and acid chlorides as indicated in the Table II.15 below, the following compounds were prepared.

**Table II.15**

| Ex. # | amine; acid chloride                                                                | product                                                                               | Yield                          |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------|
| 42/1  |   |    | 9%<br>[MH] <sup>+</sup> = 508  |
| 42/2  |  |  | 29%<br>[MH] <sup>+</sup> = 476 |

**Example 43****5 Step A**

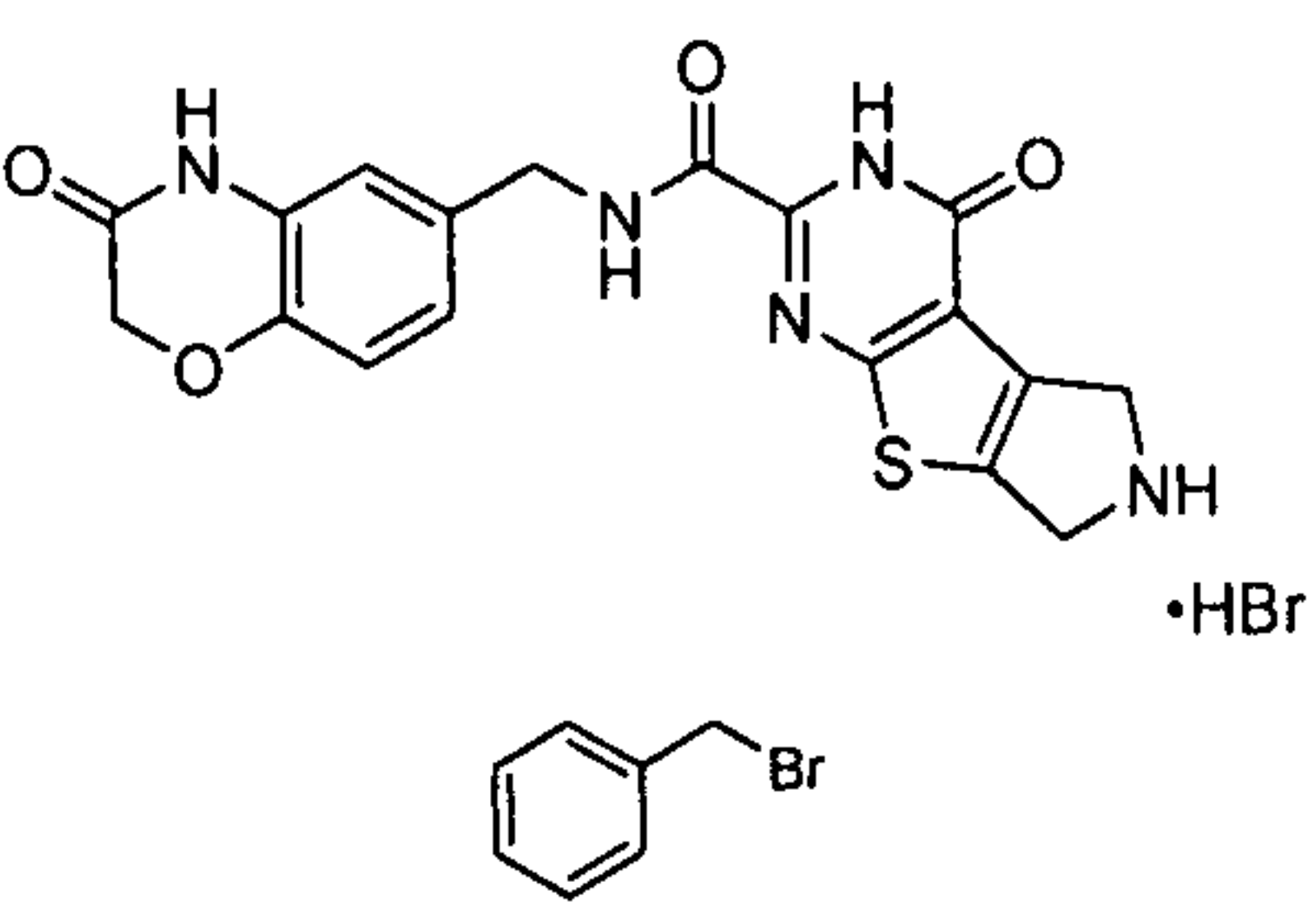
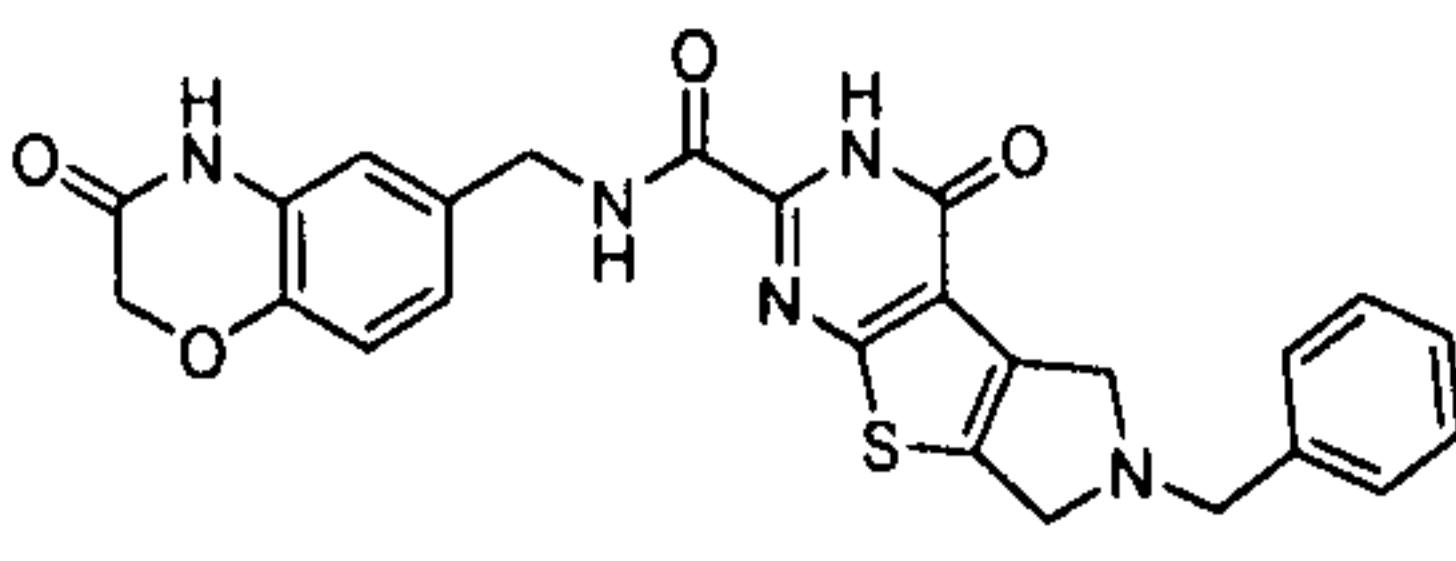
To a solution of the title compound from Example 41 (15 mg) above in DMA (500μL) was added 2-bromo-pyrimidine (10 mg). The mixture was heated in a sealed tube at 100°C (microwave) for 5 min. Purification by HPLC afforded the title compound. (6.1 mg; 33%, [MH]<sup>+</sup> = 476).

**Example 43/1**

Following a similar procedure as described in Example 43 above, except using amine and benzyl bromide as indicated in the Table II.16 below, the following compound was prepared.

5

**Table II.16**

| Ex. # | amine; benzyl bromide                                                               | product                                                                               | yield                 |
|-------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| 43/1  |  |  | 14%<br>$[MH]^+ = 488$ |

**Example 1700****Assay for Determining MMP-13 Inhibition**

The typical assay for MMP-13 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50  $\mu$ L aliquots. 10  $\mu$ L of a 50 nM stock solution of catalytic domain of MMP-13 enzyme (produced by Alantos or commercially available from Invitek (Berlin), Cat.# 30100812) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40  $\mu$ L of a 12.5  $\mu$ M stock solution of MMP-13 fluorescent substrate (Calbiochem, Cat. No. 444235). The time-dependent increase in fluorescence is measured at the 320 nm excitation and 390 nm emission by automatic plate multireader. The IC<sub>50</sub> values are calculated from the initial reaction rates.

**Example 1701****Assay for Determining MMP-3 Inhibition**

The typical assay for MMP-3 activity is carried out in assay buffer  
5 comprised of 50 mM MES, pH 6.0, 10 mM CaCl<sub>2</sub> and 0.05% Brij-35. Different  
concentrations of tested compounds are prepared in assay buffer in 50 µL aliquots.  
10 µL of a 100 nM stock solution of the catalytic domain of MMP-3 enzyme  
(Biomol, Cat. No. SE-109) is added to the compound solution. The mixture of  
enzyme and compound in assay buffer is thoroughly mixed and incubated for  
10 10 min at room temperature. Upon the completion of incubation, the assay is  
started by addition of 40 µL of a 12.5 µM stock solution of NFF-3 fluorescent  
substrate (Calbiochem, Cat. No. 480455). The time-dependent increase in  
fluorescence is measured at the 330 nm excitation and 390 nm emission by an  
automatic plate multireader. The IC<sub>50</sub> values are calculated from the initial  
15 reaction rates.

**Example 1702****Assay for Determining MMP-8 Inhibition**

The typical assay for MMP-8 activity is carried out in assay buffer  
20 comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-  
35. Different concentrations of tested compounds are prepared in assay buffer in  
50 µL aliquots. 10 µL of a 50 nM stock solution of activated MMP-8 enzyme  
(Calbiochem, Cat. No. 444229) is added to the compound solution. The mixture of  
enzyme and compound in assay buffer is thoroughly mixed and incubated for  
25 10 min at 37°C. Upon the completion of incubation, the assay is started by  
addition of 40 µL of a 10 µM stock solution of OmniMMP fluorescent substrate  
(Biomol, Cat. No. P-126). The time-dependent increase in fluorescence is

measured at the 320 nm excitation and 390 nm emission by an automatic plate multireader at 37°C. The IC<sub>50</sub> values are calculated from the initial reaction rates.

### **Example 1703**

#### **5                      Assay for Determining MMP-12 Inhibition**

The typical assay for MMP-12 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 µL aliquots. 10 µL of a 50 nM stock solution of the catalytic domain of  
10    MMP-12 enzyme (Biomol, Cat. No. SE-138) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40 µL of a 12.5 µM stock solution of OmniMMP fluorescent substrate (Biomol, Cat. No. P-126). The time-dependent increase in  
15    fluorescence is measured at the 320 nm excitation and 390 nm emission by automatic plate multireader at 37°C. The IC<sub>50</sub> values are calculated from the initial reaction rates.

### **Example 1704**

#### **20                      Assay for Determining Aggrecanase-1 Inhibition**

The typical assay for aggrecanase-1 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 µL aliquots. 10 µL of a 75 nM stock solution of aggrecanase-1 (Invitek) is  
25    added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed. The reaction is started by addition of 40 µL of a 250 nM stock solution of aggrecan-IGD substrate (Invitek) and incubation at 37°C for exact 15 min. The reaction is stopped by addition of EDTA and the samples

are analysed by using aggrecanase ELISA (Invitex, InviLISA, Cat. No. 30510111) according to the protocol of the supplier. Shortly: 100  $\mu$ L of each proteolytic reaction are incubated in a pre-coated micro plate for 90 min at room temperature. After 3 times washing, antibody-peroxidase conjugate is added for 90 min at room temperature. After 5 times washing, the plate is incubated with TMB solution for 3 min at room temperature. The peroxidase reaction is stopped with sulfurous acid and the absorbance is read at 450 nm. The IC<sub>50</sub> values are calculated from the absorbance signal corresponding to residual aggrecanase activity.

10

### **Example 1705**

#### **Assay for Determining Inhibition of MMP-3 Mediated Proteoglycan Degradation**

The assay for MMP-3 activity is carried out in assay buffer comprised of 50 mM MES, pH 6.0, 10 mM CaCl<sub>2</sub> and 0.05 % Brij-35. Articular cartilage is isolated fresh from the first phalanges of adult cows and cut into pieces (~3 mg). Bovine cartilage is incubated with 50 nM human MMP-3 (Chemikon, cat.# 25020461) in presence or absence of inhibitor for 24 h at 37°C. Sulfated glycosaminoglycan (aggrecan) degradation products (sGAG) are detected in supernatant, using a modification of the colorimetric DMMB (1,9-dimethylmethylen blue dye) assay (Billinghurst et al., 2000, Arthritis & Rheumatism, 43 (3), 664). 10  $\mu$ L of the samples or standard are added to 190  $\mu$ L of the dye reagent in microtiter plate wells, and the absorbance is measured at 525 nm immediately. All data points are performed in triplicates.

25

### **Example 1706**

#### **Assay for Determining Inhibition of MMP-3 mediated Pro-Collagenase 3 Activation**

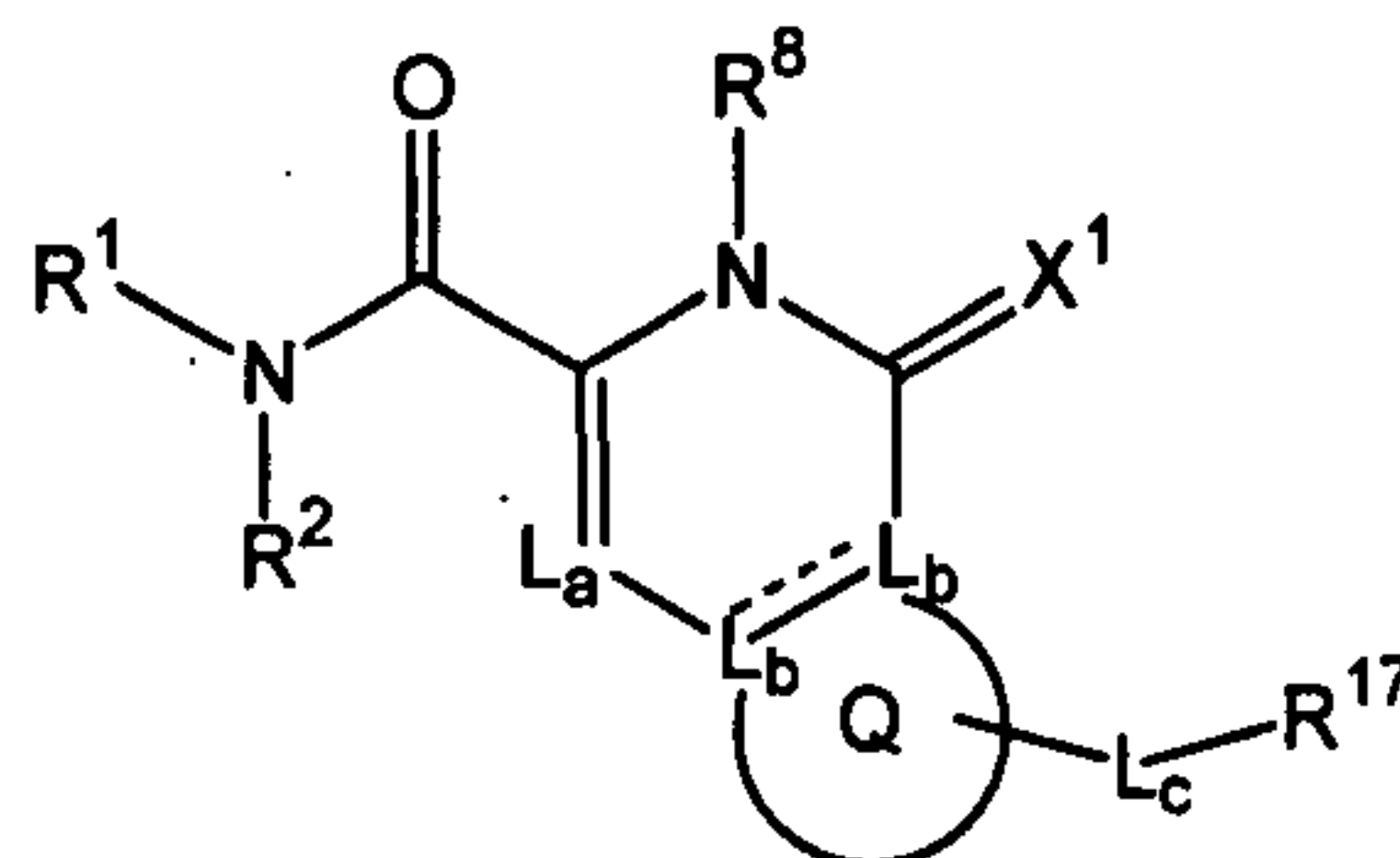
The assay for MMP-3 mediated activation of pro-collagenase 3 (pro-MMP-13) is carried out in assay buffer comprised of 50 mM MES, pH 6.0, 10 mM CaCl<sub>2</sub> and 0.05% Brij-35 (Nagase; *J. Biol. Chem.* 1994 Aug 19;269(33):20952-7).

5 Different concentrations of tested compounds are prepared in assay buffer in 5  $\mu$ L aliquots. 10  $\mu$ L of a 100 nM stock solution of trypsin-activated (Knäuper V., et al., 1996 *J. Biol. Chem.* 271 1544-1550) human pro-MMP-3 (Chemicon; CC1035) is added to the compound solution. To this mixture, 35  $\mu$ L of a 286 nM stock solution of pro-collagenase 3 (Invitek; 30100803) is added to the mixture of  
10 enzyme and compound. The mixture is thoroughly mixed and incubated for 5 h at 37°C. Upon the completion of incubation, 10  $\mu$ L of the incubation mixture is added to 50  $\mu$ L assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-35 and the mixture is thoroughly mixed.

The assay to determine the MMP-13 activity is started by addition of  
15 40  $\mu$ L of a 10  $\mu$ M stock solution of MMP-13 fluorogenic substrate (Calbiochem, Cat. No. 444235) in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM CaCl<sub>2</sub> and 0.05% Brij-35 (Knäuper, V., et al., 1996. *J. Biol. Chem.* 271, 1544-1550). The time-dependent increase in fluorescence is measured at 320 nm excitation and 390 nm emission by an automatic plate multireader at room  
20 temperature. The IC<sub>50</sub> values are calculated from the initial reaction rates.

**What is claimed:**

1. A compound having Formula (I):



Formula (I)

5 wherein

$R^1$  in each occurrence is independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl,

wherein  $R^1$  is optionally substituted one or more times, or

15 wherein  $R^1$  is optionally substituted by one  $R^{16}$  group and optionally substituted by one or more  $R^9$  groups;

$R^2$  is selected from hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or  $R^1$  and  $R^2$  when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O,  $S(O)_x$ , or  $NR^{50}$  and which is optionally substituted one or more times;

$R^4$  in each occurrence is independently selected from  $R^{10}$ , hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl,  $CF_3$ ,  $(C_0-C_6)$ -alkyl-COR<sup>10</sup>,  $(C_0-C_6)$ -alkyl-OR<sup>10</sup>,  $(C_0-C_6)$ -alkyl-NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-NO<sub>2</sub>,  $(C_0-C_6)$ -alkyl-CN,  $(C_0-C_6)$ -alkyl-S(O)<sub>y</sub>OR<sup>10</sup>,  $(C_0-C_6)$ -alkyl-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-NR<sup>10</sup>CONR<sup>11</sup>SO<sub>2</sub>R<sup>30</sup>,  $(C_0-C_6)$ -alkyl-S(O)<sub>x</sub>R<sup>10</sup>,  $(C_0-C_6)$ -alkyl-OC(O)R<sup>10</sup>,  $(C_0-C_6)$ -alkyl-OC(O)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-C(=NR<sup>10</sup>)NR<sup>10</sup>R<sup>11</sup>,  $(C_0-C_6)$ -alkyl-

NR<sup>10</sup>C(=NR<sup>11</sup>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>,  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)-NR<sup>11</sup>-CN, O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
 C(O)NR<sup>10</sup>R<sup>11</sup>, S(O)<sub>x</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)OR<sup>10</sup>, S(O)<sub>x</sub>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>R<sup>11</sup>,  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(O)NR<sup>10</sup>-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)R<sup>10</sup>,  
 5 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-C(O)-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
 NR<sup>10</sup>-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>-S(O)<sub>y</sub>R<sup>10</sup>, O-(C<sub>0</sub>-C<sub>6</sub>)-alkyl-aryl and O-  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-heteroaryl,

wherein each R<sup>4</sup> group is optionally substituted one or more times, or

wherein each R<sup>4</sup> group is optionally substituted by one or more R<sup>14</sup> groups,

10 or

wherein optionally two R<sup>4</sup> groups, when taken together with the nitrogen  
 or carbon to which they are attached complete a 3- to 8-membered saturated ring  
 or multicyclic ring or unsaturated ring containing carbon atoms and optionally  
 containing one or more heteroatom independently selected from O, S(O)<sub>x</sub>, N, or

15 NR<sup>50</sup> and which is optionally substituted one or more times, or

optionally two R<sup>4</sup> groups together at one saturated carbon atom form =O,  
 =S, =NR<sup>10</sup> or =NOR<sup>10</sup>;

R<sup>5</sup> is independently selected from hydrogen, alkyl, C(O)NR<sup>10</sup>R<sup>11</sup>, aryl,  
 arylalkyl, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and C(O)OR<sup>10</sup> wherein alkyl, aryl and arylalkyl are

20 optionally substituted one or more times;

R<sup>8</sup> is independently selected from hydrogen, alkyl, cycloalkyl,  
 heterocycloalkyl, aryl, heteroaryl, R<sup>10</sup> and NR<sup>10</sup>R<sup>11</sup> wherein alkyl, cycloalkyl,  
 heterocycloalkyl, aryl, and heteroaryl is optionally substituted one or more times;

R<sup>9</sup> in each occurrence is independently selected from R<sup>10</sup>, hydrogen, alkyl,  
 25 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF<sub>2</sub>, CF<sub>3</sub>, OR<sup>10</sup>, SR<sup>10</sup>,  
 COOR<sup>10</sup>, CH(CH<sub>3</sub>)CO<sub>2</sub>H, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-COR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-OR<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-  
 alkyl-NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NO<sub>2</sub>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-CN, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>y</sub>OR<sup>10</sup>,  
 (C<sub>0</sub>-C<sub>6</sub>)-alkyl-P(O)<sub>2</sub>OH, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>y</sub>NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
 NR<sup>10</sup>CONR<sup>11</sup>SO<sub>2</sub>R<sup>30</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-S(O)<sub>x</sub>R<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-OC(O)R<sup>10</sup>, (C<sub>0</sub>-C<sub>6</sub>)-  
 30 alkyl-OC(O)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-C(=NR<sup>10</sup>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-  
 NR<sup>10</sup>C(=NR<sup>11</sup>)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-NR<sup>10</sup>C(=N-CN)NR<sup>10</sup>R<sup>11</sup>, (C<sub>0</sub>-C<sub>6</sub>)-alkyl-

$C(=N-CN)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}C(=N-NO_2)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(=N-NO_2)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}SO_2R^{11}$ ,  $C(O)NR^{10}-(C_0-C_6)$ -alkyl-heteroaryl,  $C(O)NR^{10}-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-heteroaryl,  
 5  $S(O)_2NR^{10}$ -alkyl,  $S(O)_2-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2-(C_0-C_6)$ -alkyl-heteroaryl,  $(C_0-C_6)$ -alkyl- $C(O)-NR^{11}-CN$ ,  $O-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}-(C_0-C_6)$ -alkyl- $NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)R^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)-NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-S(O)_yNR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl-  
 10  $NR^{10}-S(O)_yR^{11}$ ,  $O-(C_0-C_6)$ -alkyl-aryl and  $O-(C_0-C_6)$ -alkyl-heteroaryl,

wherein each  $R^9$  group is optionally substituted, or

wherein each  $R^9$  group is optionally substituted by one or more  $R^{14}$  groups;

$R^{10}$  and  $R^{11}$  in each occurrence are independently selected from hydrogen,

alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, bicycloalkyl,

15 heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, fluoroalkyl,

heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl,

heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl,

bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, heterocycloalkyl,

fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl,

20 heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or

$R^{10}$  and  $R^{11}$  when taken together with the nitrogen to which they are attached

complete a 3- to 8-membered ring containing carbon atoms and optionally

containing a heteroatom selected from O,  $S(O)_x$ , or  $NR^{50}$  and which is optionally

substituted one or more times;

25  $R^{14}$  is independently selected from hydrogen, alkyl, arylalkyl,

cycloalkylalkyl, heteroarylalkyl, heterocyclalkyl and halo, wherein alkyl,

arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclalkyl are optionally

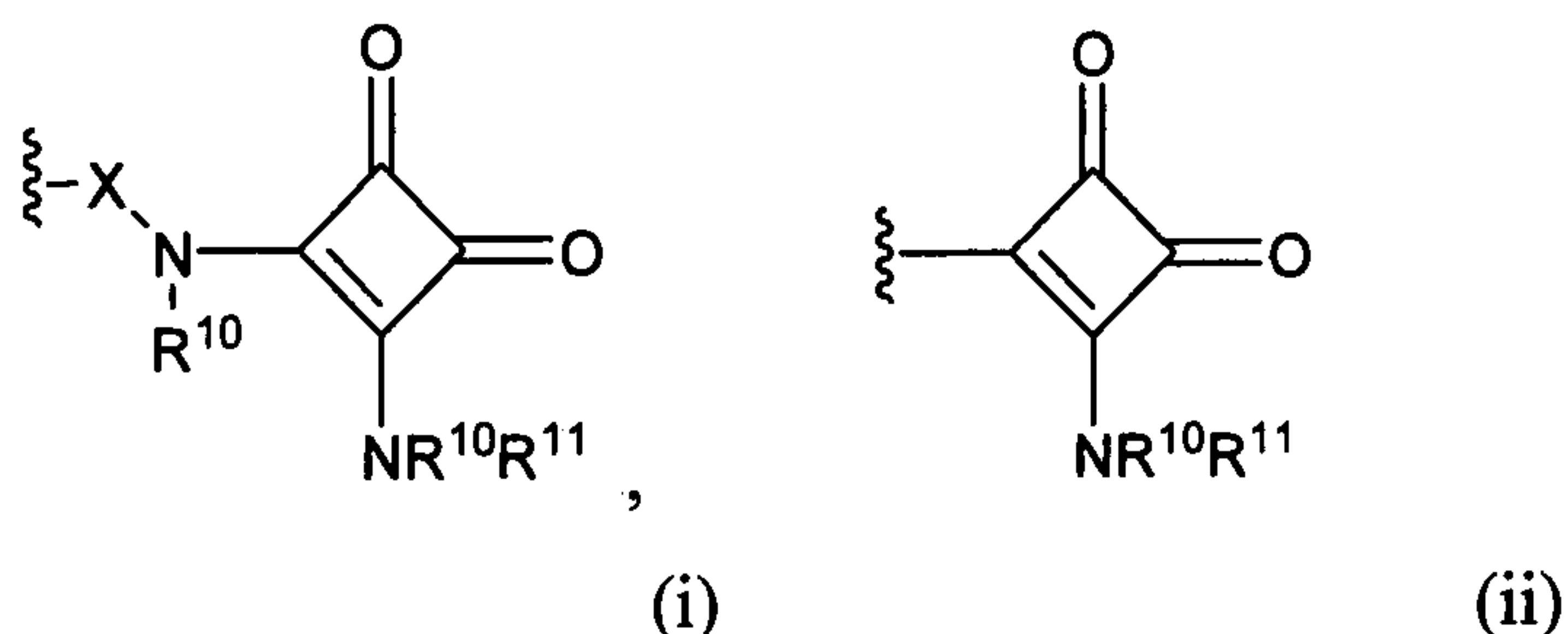
substituted one or more times.

$R^{16}$  is selected from cycloalkyl, heterocycloalkyl, bicycloalkyl,

30 heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused

aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl

fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, heterocycloalkyl fused heteroarylalkyl, (i) and  
 5 (ii):



wherein cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused  
 10 aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more  
 15 times;

$R^{17}$  is selected from  $R^1$ ,  $R^4$  and  $R^{21}$ ;

$R^{21}$  is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and

wherein  $R^{21}$  is optionally substituted one or more times, or

20 wherein  $R^{21}$  is optionally substituted by one or more  $R^9$  groups;

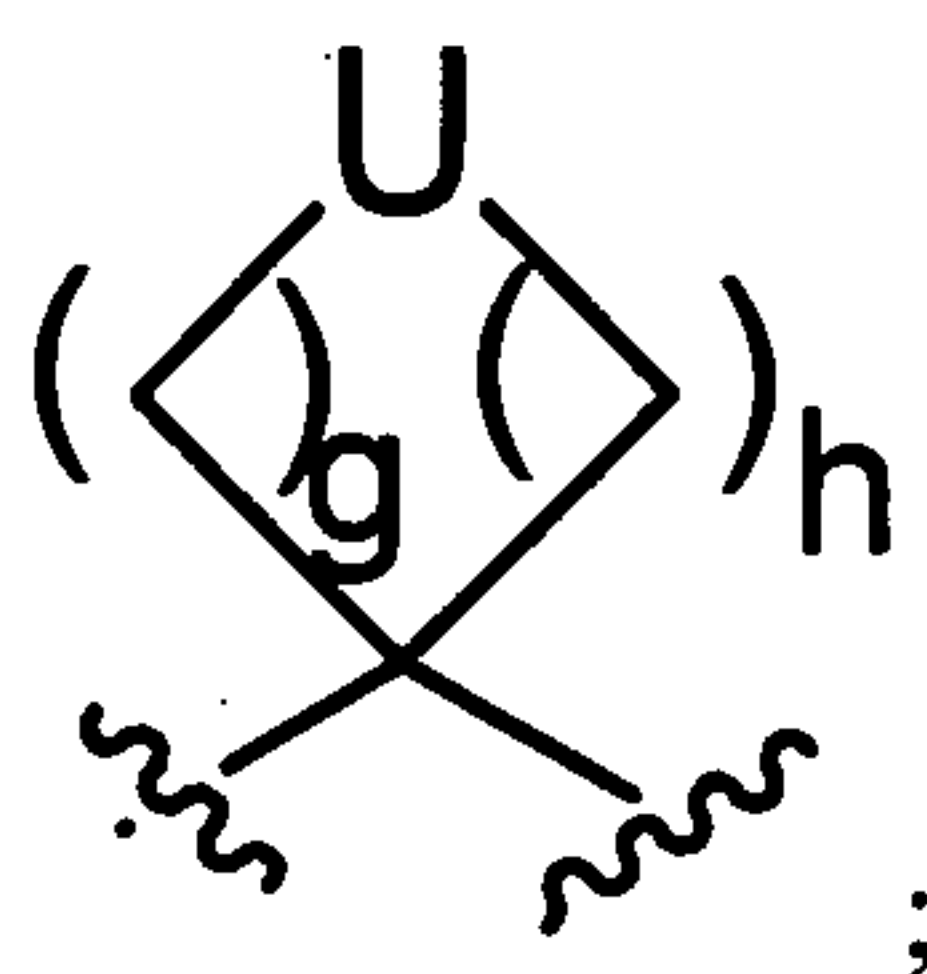
$R^{30}$  is selected from alkyl and  $(C_0-C_6)$ -alkyl-aryl, wherein alkyl and aryl are optionally substituted;

$R^{50}$  in each occurrence is independently selected from hydrogen, alkyl, aryl, heteroaryl,  $C(O)R^{80}$ ,  $C(O)NR^{80}R^{81}$ ,  $SO_2R^{80}$  and  $SO_2NR^{80}R^{81}$ , wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;  
 25

$R^{80}$  and  $R^{81}$  in each occurrence are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl,

heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or  
 5  $R^{80}$  and  $R^{81}$  when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O,  $S(O)_x$ , -NH, and -N(alkyl) and which is optionally substituted one or more times;

E is selected from a bond,  $CR^{10}R^{11}$ , O,  $NR^5$ , S, S=O,  $S(=O)_2$ , C(=O),  
 10  $N(R^{10})(C=O)$ ,  $(C=O)N(R^{10})$ ,  $N(R^{10})S(=O)_2$ ,  $S(=O)_2N(R^{10})$ , C=N-OR<sup>11</sup>,  
 $-C(R^{10}R^{11})C(R^{10}R^{11})-$ ,  $-CH_2-W^1-$  and



$L_a$  is independently selected from  $CR^9$  and N;

$L_b$  is independently selected from C and N with the proviso, that both  $L_b$   
 15 are not N, and that the bond between  $L_b$  and  $L_b$  is optionally a double bond only if both  $L_b$  are C;

$L_c$  is selected from a single bond or an acyclic, straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 10 carbon atoms, optionally containing 1 to 3 groups independently selected from -S-, -O-,  $NR^{10}-$ , -  
 20  $NR^{10}CO-$ ,  $-CONR^{10}-$ ,  $-S(O)_x-$ ,  $-SO_2NR^{10}-$ ,  $-NR^{10}SO_2-$ ,  $NR^{10}SO_2NR^{10}-$ , -  
 $NR^{10}CONR^{10}-$ ,  $-OC(O)NR^{10}-$ ,  $-NR^{10}C(O)O-$ , which replace a corresponding number of non-adjacent carbon atoms, and wherein the hydrocarbon chain is optionally substituted one or more times;

Q is a 4- to 8-membered ring selected from cycloalkyl, heterocycloalkyl or  
 25 a 5- or 6-membered ring selected from aryl and heteroaryl,  
 wherein Q is optionally substituted one or more times, or  
 wherein Q is optionally substituted one or more times with  $R^4$ , or

wherein Q is fused via two of its adjacent atoms, which are selected from N and C with a further cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl and heteroaryl system, which is optionally independently substituted one or more times;

5 U is selected from  $C(R^5R^{10})$ ,  $NR^5$ , O, S, S=O and  $S(=O)_2$ ;

$W^1$  is selected from O,  $NR^5$ , S, S=O,  $S(=O)_2$ ,  $N(R^{10})(C=O)$ ,  $N(R^{10})S(=O)_2$  and  $S(=O)_2N(R^{10})$ ;

X is selected from a bond and  $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$ ;

10  $X^1$  is independently selected from O, S,  $NR^{10}$ , N-CN,  $NCOR^{10}$ , N- $NO_2$ , or N- $SO_2R^{10}$ ;

g and h are independently selected from 0-2;

w is selected from 0-4;

x is selected from 0 to 2;

y is selected from 1 and 2;

15 the dotted line optionally represents a double bond; and

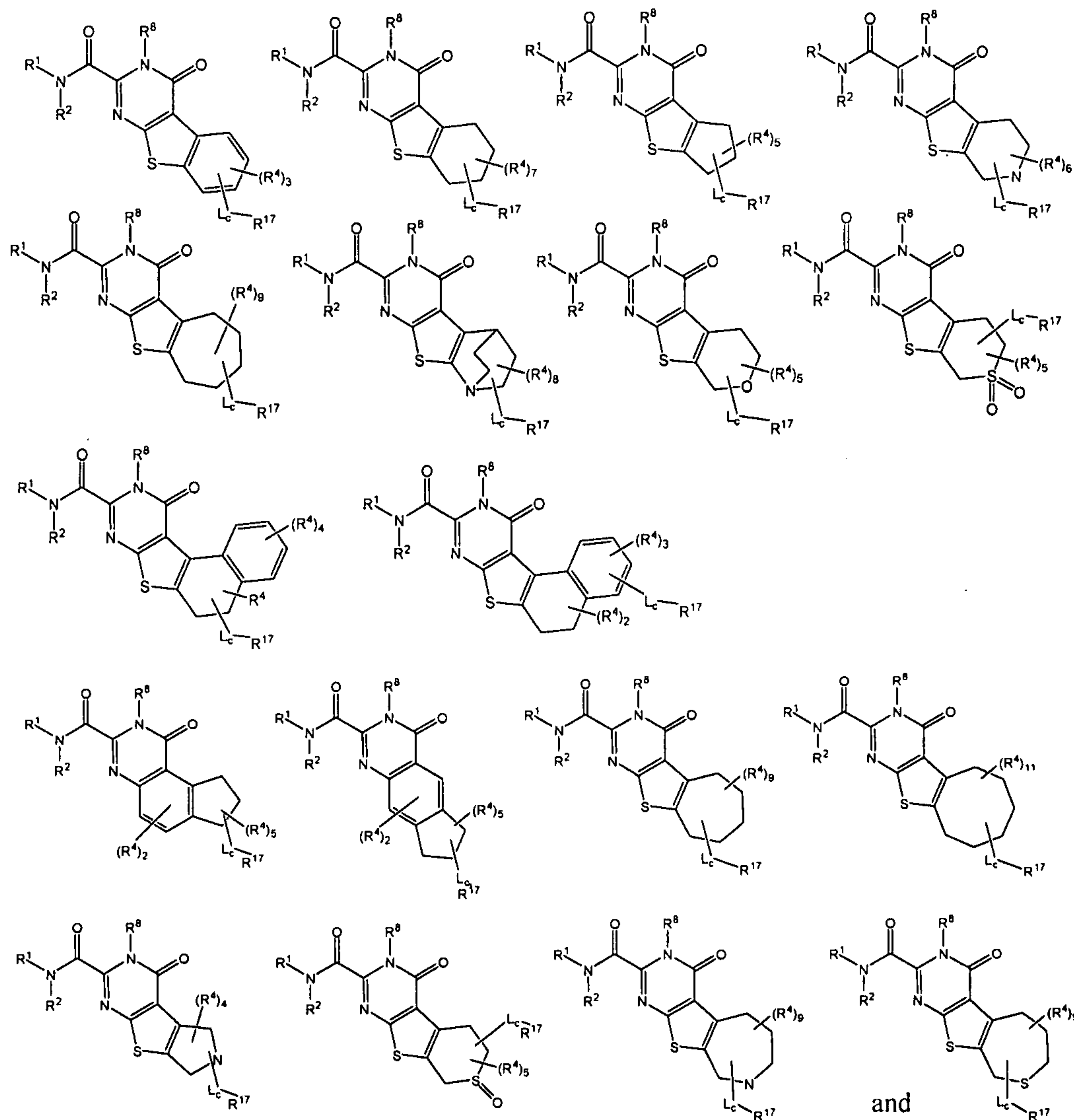
N-oxides, pharmaceutically acceptable salts, prodrugs, formulations, polymorphs, tautomers, racemic mixtures and stereoisomers thereof.

2. A compound according to claim 1, wherein Q is phenyl or thiophene that  
20 is fused via two of its adjacent atoms with a further cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, aryl and heteroaryl system, which is optionally independently substituted one or more times.

3. A compound according to claim 2, wherein  $L_a$  is N.  
25

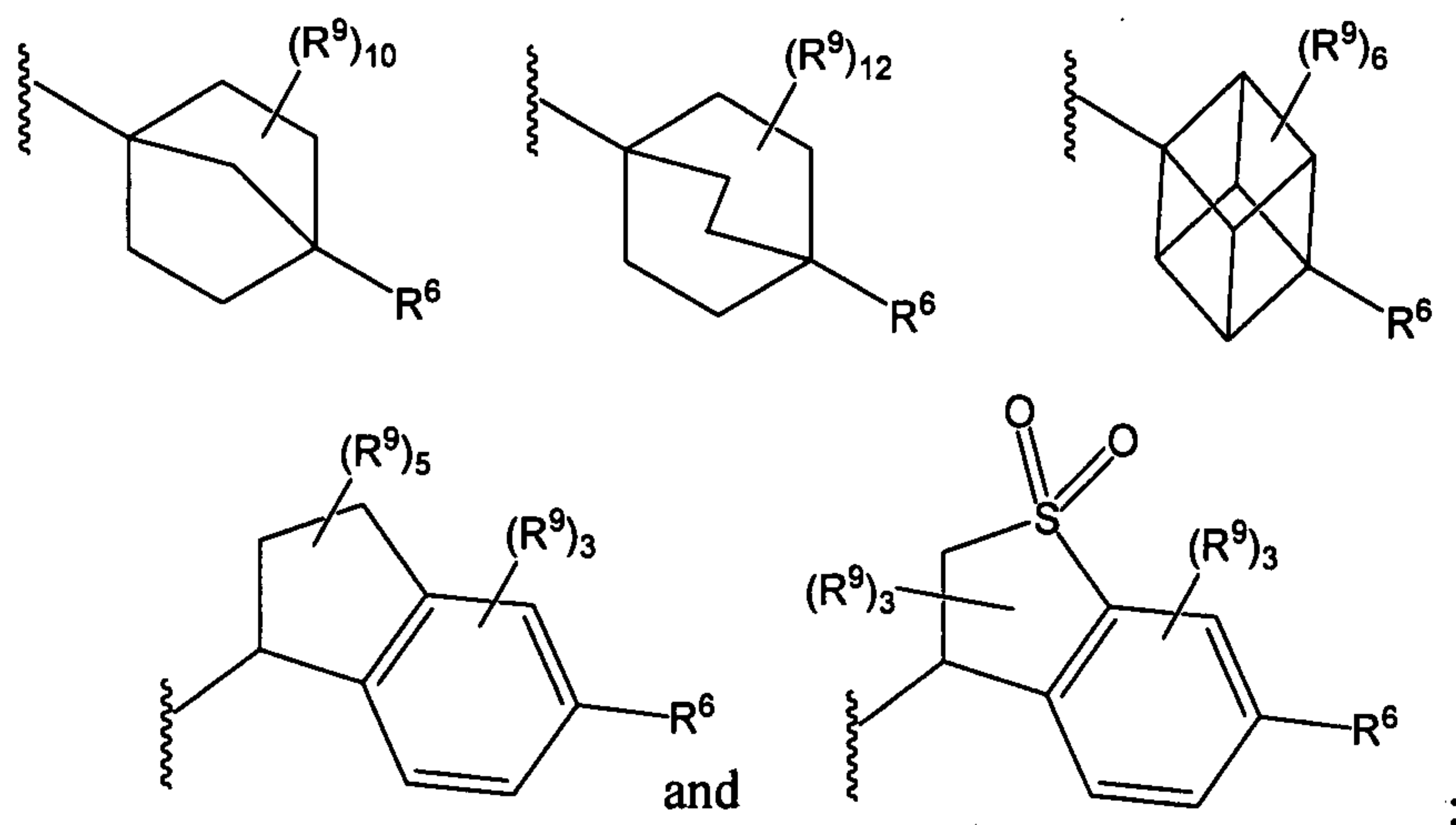
4. A compound according to claim 2, wherein:  
 $L_a$  is N; and  
 $L_b$  is C.

5. A compound according to claim 1, selected from:



6. A compound according to claim 5, wherein  $R^8$  is H.

7. A compound according to claim 5, wherein  $R^{17}$  is selected from

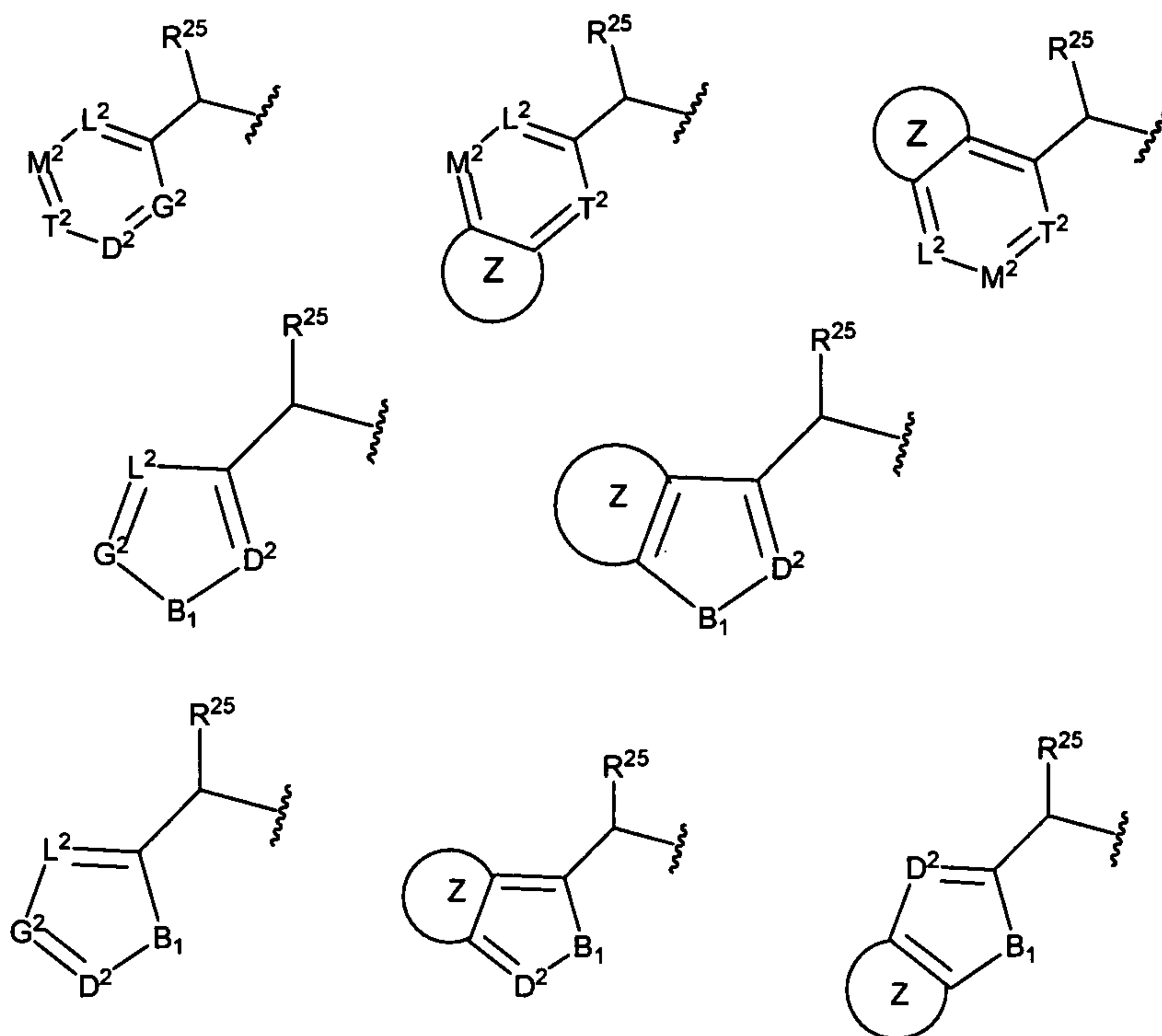


wherein:

$R^6$  is selected from  $R^9$ , cycloalkyl, heterocycloalkyl, aryl, heteroaryl,  $C(O)OR^{10}$ ,  $CH(CH_3)CO_2H$ ,  $(C_0-C_6)$ -alkyl- $COR^{10}$ ,  $(C_0-C_6)$ -alkyl- $OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NO_2$ ,  $(C_0-C_6)$ -alkyl-CN,  $(C_0-C_6)$ -alkyl- $S(O)_yOR^{10}$ ,  $(C_0-C_6)$ -alkyl- $P(O)_2OH$ ,  $(C_0-C_6)$ -alkyl- $S(O)_yNR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}CONR^{11}SO_2R^{30}$ ,  $(C_0-C_6)$ -alkyl- $S(O)_xR^{10}$ ,  $(C_0-C_6)$ -alkyl- $OC(O)R^{10}$ ,  $(C_0-C_6)$ -alkyl- $OC(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(=NR^{10})NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}C(=NR^{11})NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}C(=N-CN)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(=N-CN)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}C(=N-NO_2)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(=N-NO_2)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}SO_2R^{11}$ ,  $C(O)NR^{10}-(C_0-C_6)$ -alkyl-heteroaryl,  $C(O)NR^{10}-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2NR^{10}-(C_0-C_6)$ -alkyl-heteroaryl,  $S(O)_2NR^{10}$ -alkyl,  $S(O)_2-(C_0-C_6)$ -alkyl-aryl,  $S(O)_2-(C_0-C_6)$ -alkyl-heteroaryl,  $(C_0-C_6)$ -alkyl- $C(O)-NR^{11}-CN$ ,  $O-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)OR^{10}$ ,  $S(O)_x-(C_0-C_6)$ -alkyl- $C(O)NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $C(O)NR^{10}-(C_0-C_6)$ -alkyl- $NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)R^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)OR^{10}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-C(O)-NR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-S(O)_yNR^{10}R^{11}$ ,  $(C_0-C_6)$ -alkyl- $NR^{10}-S(O)_yR^{11}$ ,  $O-(C_0-C_6)$ -alkyl-aryl and  $O-(C_0-C_6)$ -alkyl-heteroaryl, wherein each  $R^6$  group is optionally substituted by one or more  $R^{14}$  groups;

$R^9$  is independently selected from hydrogen, alkyl, halo,  $CHF_2$ ,  $CF_3$ ,  $OR^{10}$ ,  $NR^{10}R^{11}$ ,  $NO_2$ , and CN, wherein alkyl is optionally substituted one or more times;

8. A compound according to claim 5, wherein  $R^1$  is selected from:



wherein:

- $R^{18}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

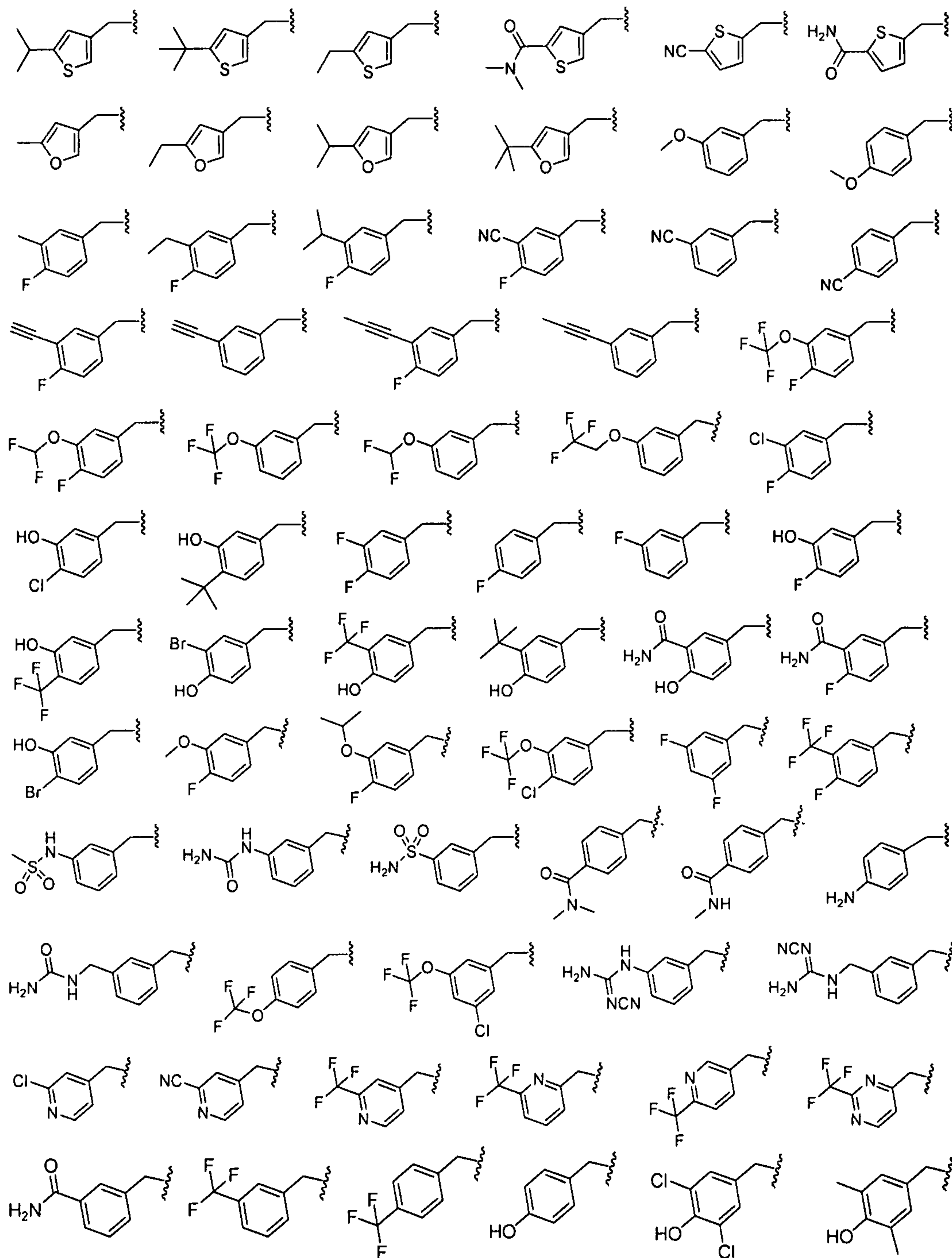
- $R^{25}$  is selected from hydrogen, alkyl, cycloalkyl,  $C(O)NR^{10}R^{11}$  and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

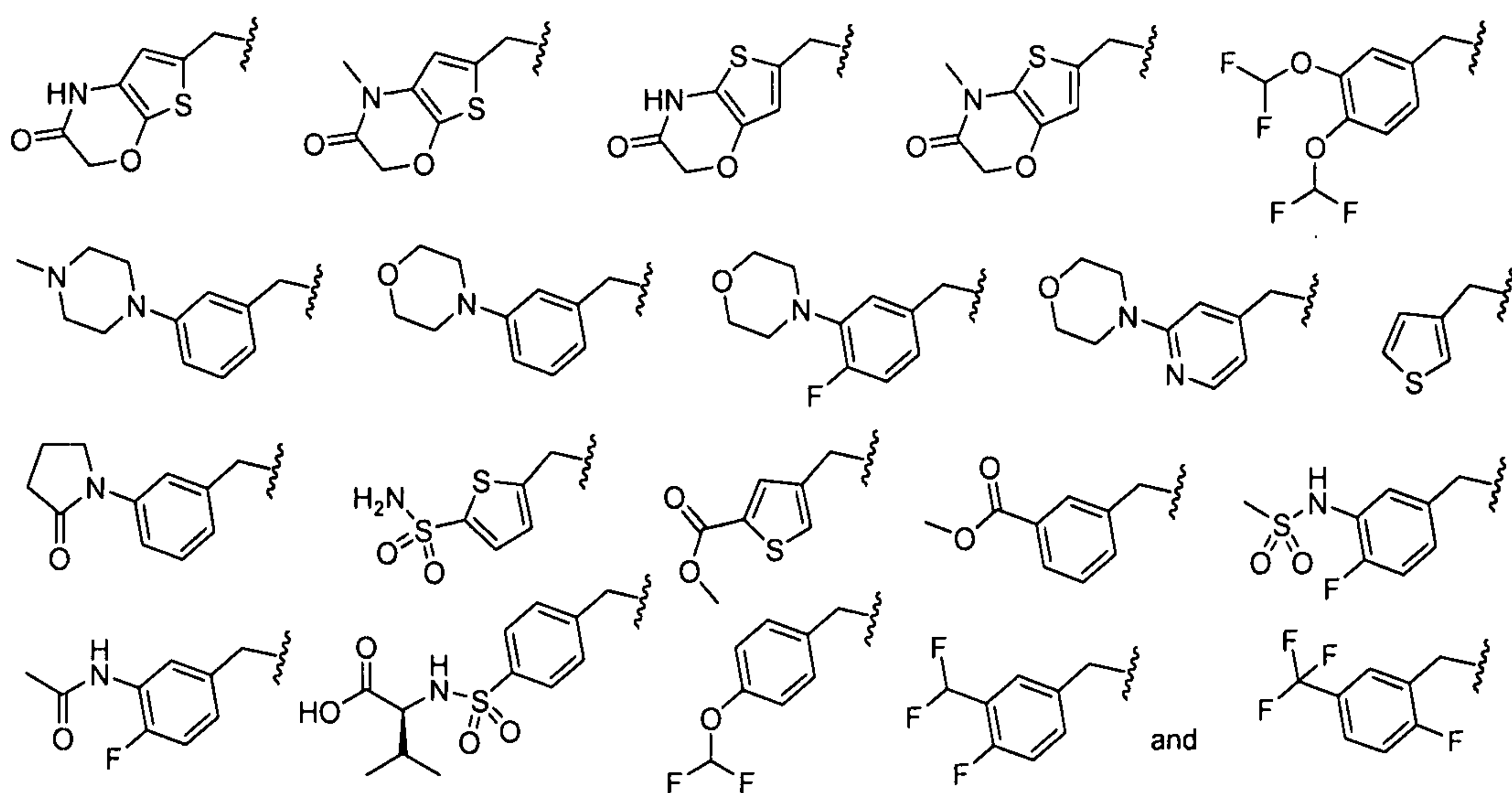
$B_1$  is selected from  $NR^{10}$ , O and S;

$D^2$ ,  $G^2$ ,  $L^2$ ,  $M^2$  and  $T^2$  are independently selected from  $CR^{18}$  and N; and

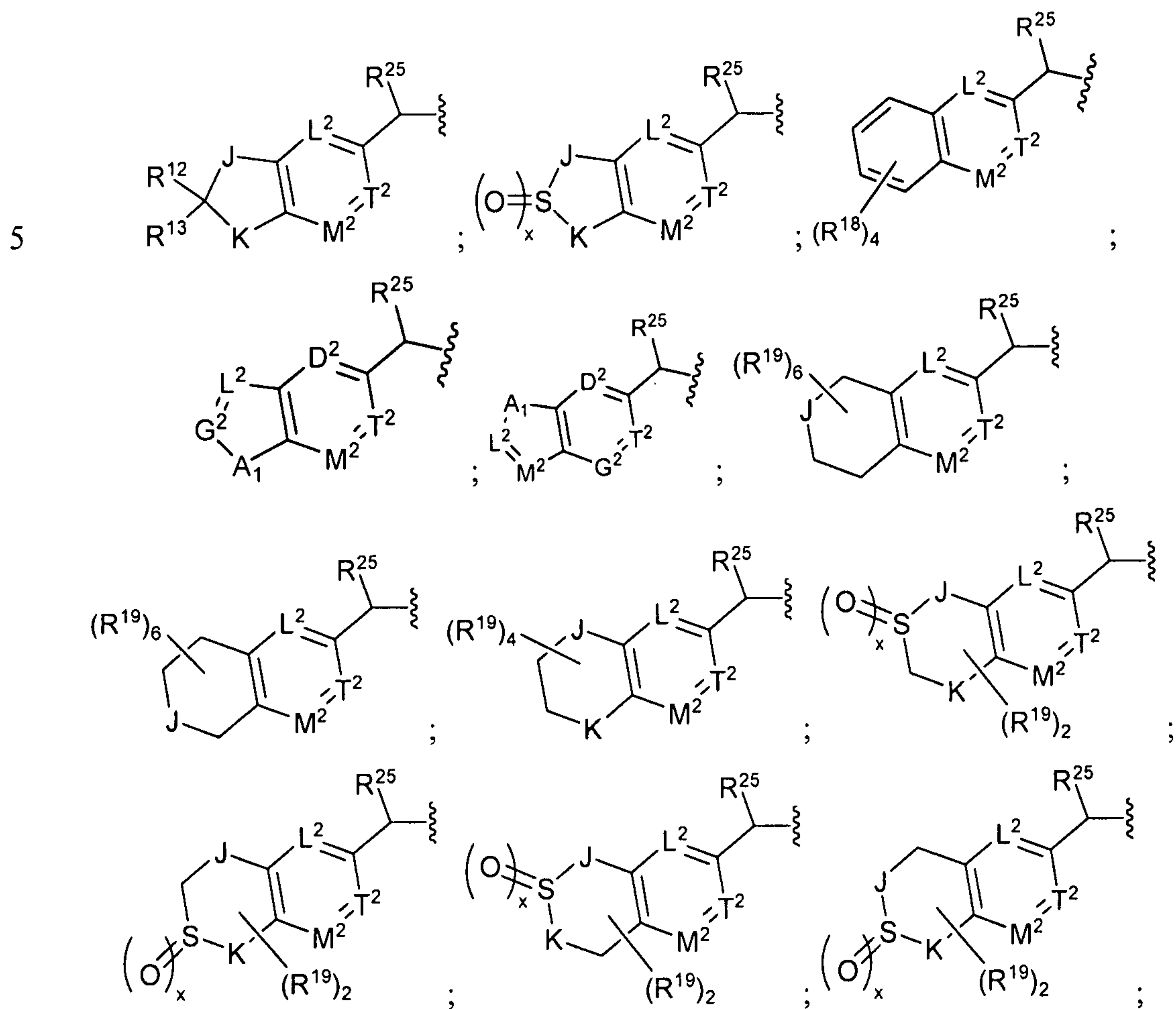
- $Z$  is a 5- to 8-membered ring selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

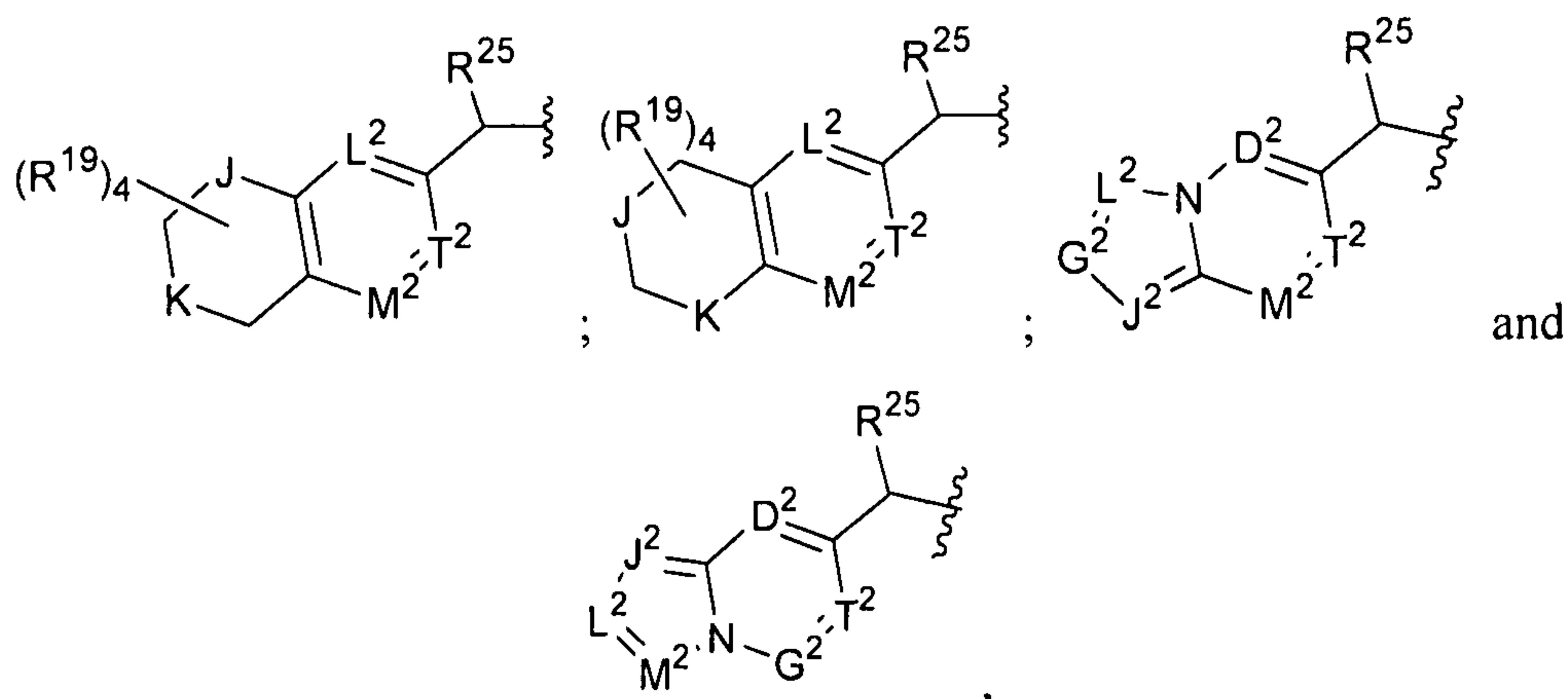
9. The compound according to claim 6, wherein R<sup>1</sup> is selected from:





10. A compound according to claim 5, wherein  $R^1$  is selected from:





wherein:

R<sup>12</sup> and R<sup>13</sup> are independently selected from hydrogen, alkyl and halo,  
 5 wherein alkyl is optionally substituted one or more times, or optionally R<sup>12</sup> and R<sup>13</sup> together form =O, =S, =NR<sup>10</sup> or =NOR<sup>10</sup>;

R<sup>18</sup> is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, C(O)NR<sup>10</sup>R<sup>11</sup>, CO<sub>2</sub>R<sup>10</sup>, OR<sup>10</sup>, OCF<sub>3</sub>, OCHF<sub>2</sub>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>COR<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>,  
 10 NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and NR<sup>10</sup>R<sup>11</sup>, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R<sup>19</sup> is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, C(O)NR<sup>10</sup>R<sup>11</sup>, CO<sub>2</sub>R<sup>10</sup>,  
 15 OR<sup>10</sup>, OCF<sub>3</sub>, OCHF<sub>2</sub>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>COR<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and NR<sup>10</sup>R<sup>11</sup>, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R<sup>19</sup> groups together at one carbon atom form =O, =S, =NR<sup>10</sup> or =NOR<sup>10</sup>;

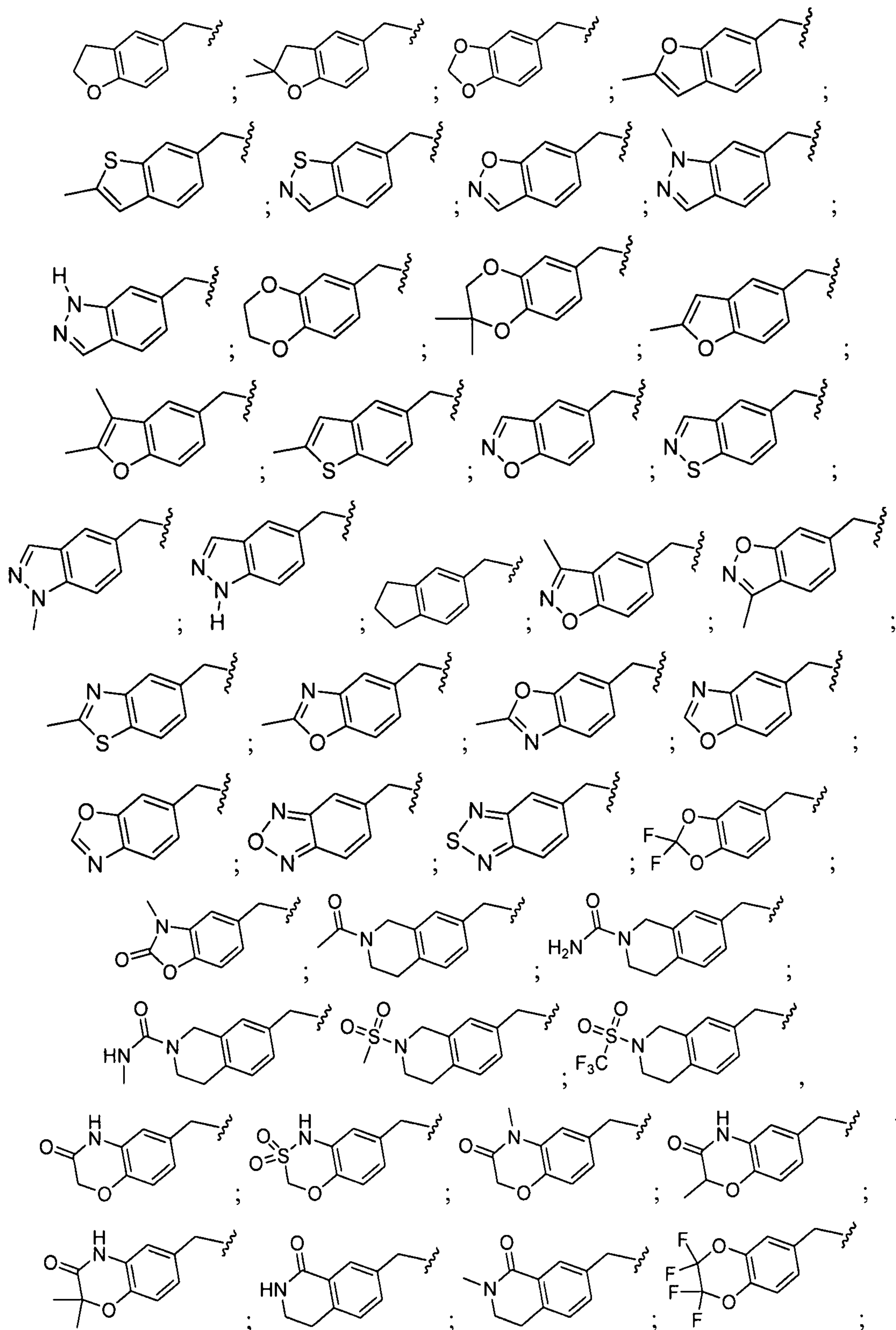
20 R<sup>25</sup> is selected from hydrogen, alkyl, cycloalkyl, C(O)NR<sup>10</sup>R<sup>11</sup> and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

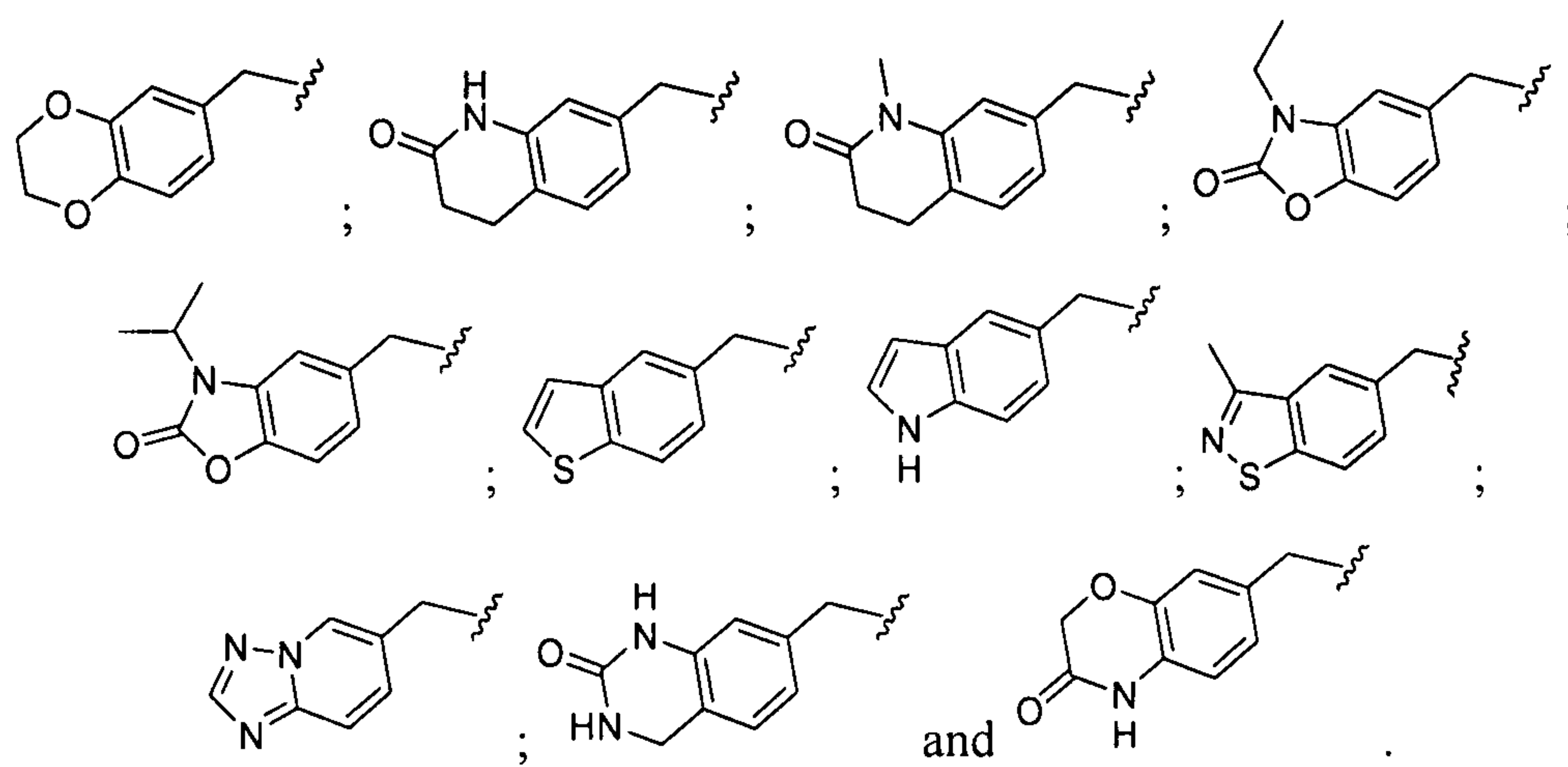
J and K are independently selected from CR<sup>10</sup>R<sup>18</sup>, NR<sup>10</sup>, O and S(O)<sub>x</sub>;

A<sub>1</sub> is selected from NR<sup>10</sup>, O and S(O)<sub>x</sub>; and

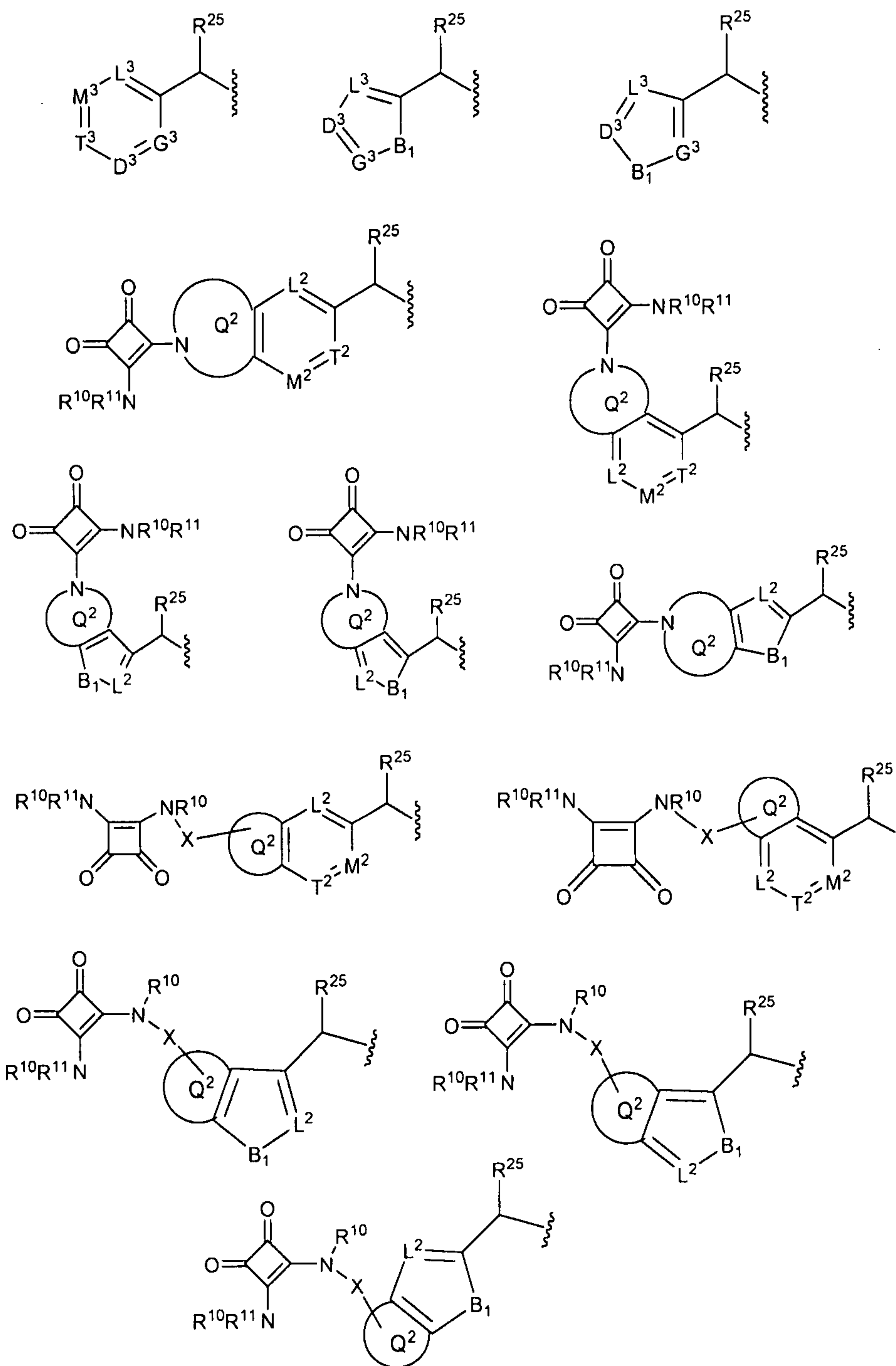
25 D<sup>2</sup>, G<sup>2</sup>, J<sup>2</sup>, L<sup>2</sup>, M<sup>2</sup> and T<sup>2</sup> are independently selected from CR<sup>18</sup> and N.

10





- 5 12. A compound according to claim 5, wherein R<sup>1</sup> is selected from:



wherein:

R<sup>18</sup> is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, C(O)NR<sup>10</sup>R<sup>11</sup>, CO<sub>2</sub>R<sup>10</sup>,  
 5 OR<sup>10</sup>, OCF<sub>3</sub>, OCHF<sub>2</sub>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>COR<sup>11</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>11</sup>,  
 NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup> and NR<sup>10</sup>R<sup>11</sup>, wherein alkyl, haloalkyl, cycloalkyl,

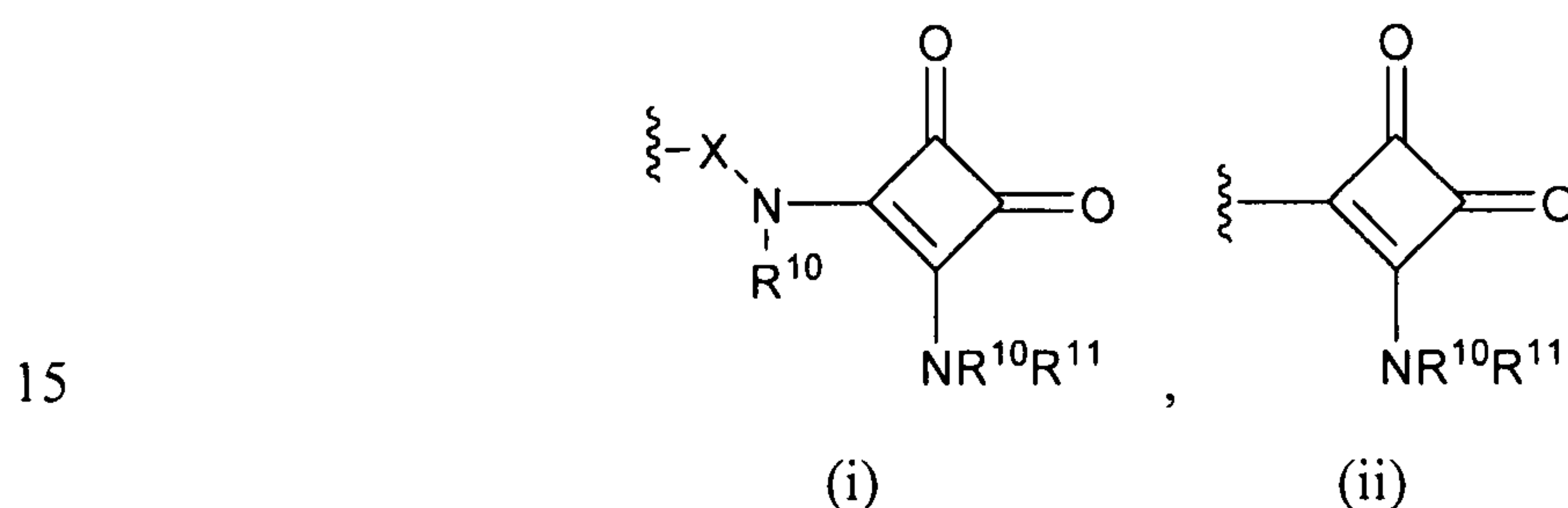
heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

$R^{19}$  is independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN,  $C(O)NR^{10}R^{11}$ ,  $CO_2R^{10}$ ,  
 5  $OR^{10}$ ,  $OCF_3$ ,  $OCHF_2$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}COR^{11}$ ,  $NR^{10}SO_2R^{11}$ ,  
 $NR^{10}SO_2NR^{10}R^{11}$ ,  $SO_2NR^{10}R^{11}$  and  $NR^{10}R^{11}$ , wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two  $R^{19}$  groups together at one carbon atom form  $=O$ ,  $=S$ ,  $=NR^{10}$  or  $=NOR^{10}$ ;

10  $R^{25}$  is selected from hydrogen, alkyl, cycloalkyl,  $CONR^{10}R^{11}$  and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

$L^2$ ,  $M^2$ , and  $T^2$  are independently selected from  $CR^{18}$  and N;

$D^3$ ,  $G^3$ ,  $L^3$ ,  $M^3$ , and  $T^3$  are independently selected from N,  $CR^{18}$ , (i) and (ii)

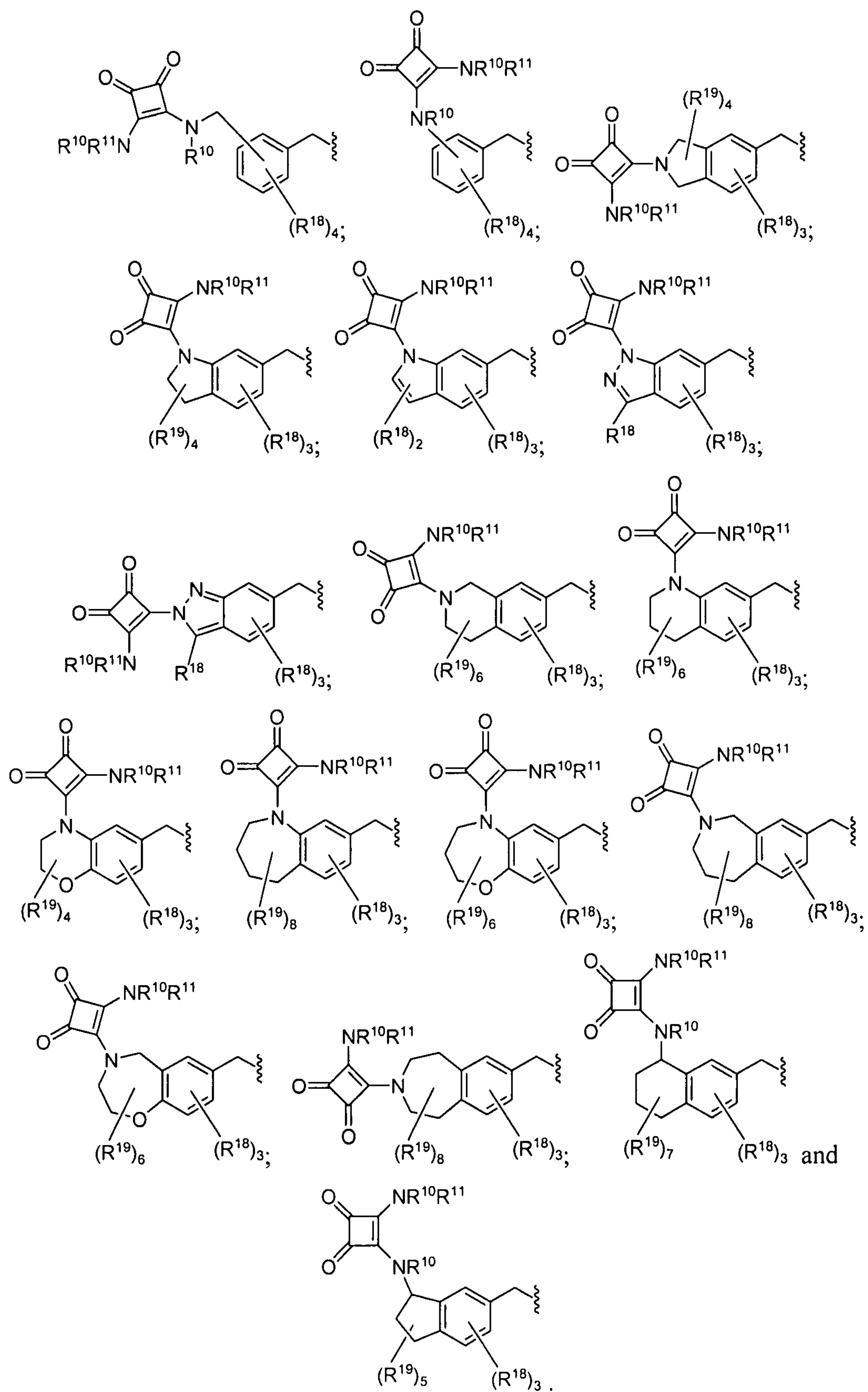


with the proviso that one of  $L^3$ ,  $M^3$ ,  $T^3$ ,  $D^3$ , and  $G^3$  is (i) or (ii);

$B_1$  is selected from the group consisting of  $NR^{10}$ , O and  $S(O)_x$ ; and

20  $Q^2$  is a 5- to 8-membered ring selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, which is optionally substituted one or more times with  $R^{19}$ .

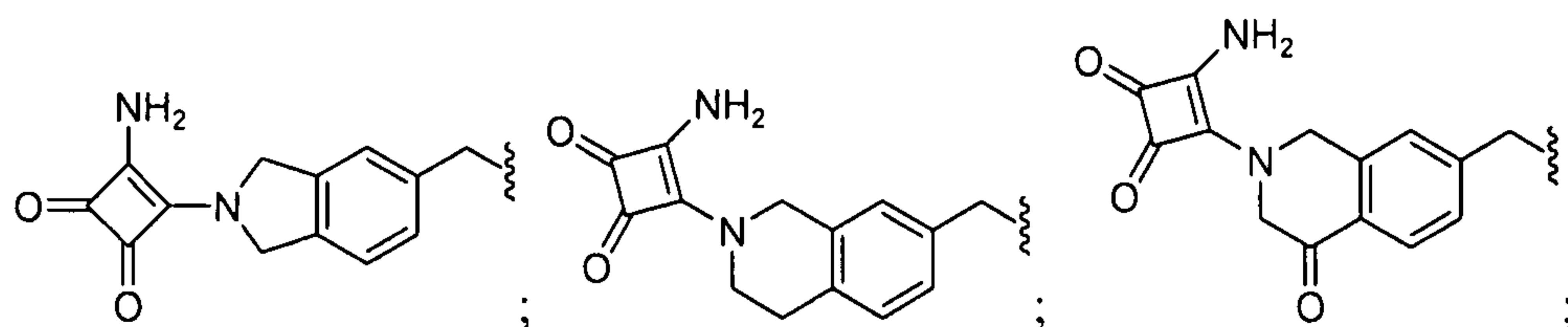
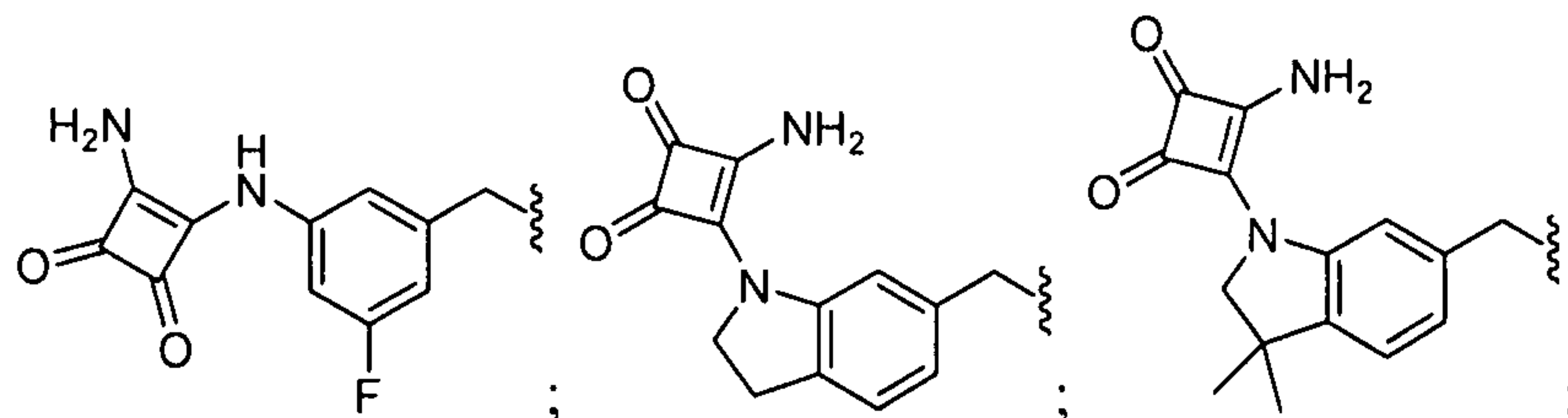
13. A compound according to claim 6, wherein  $R^1$  is selected from:



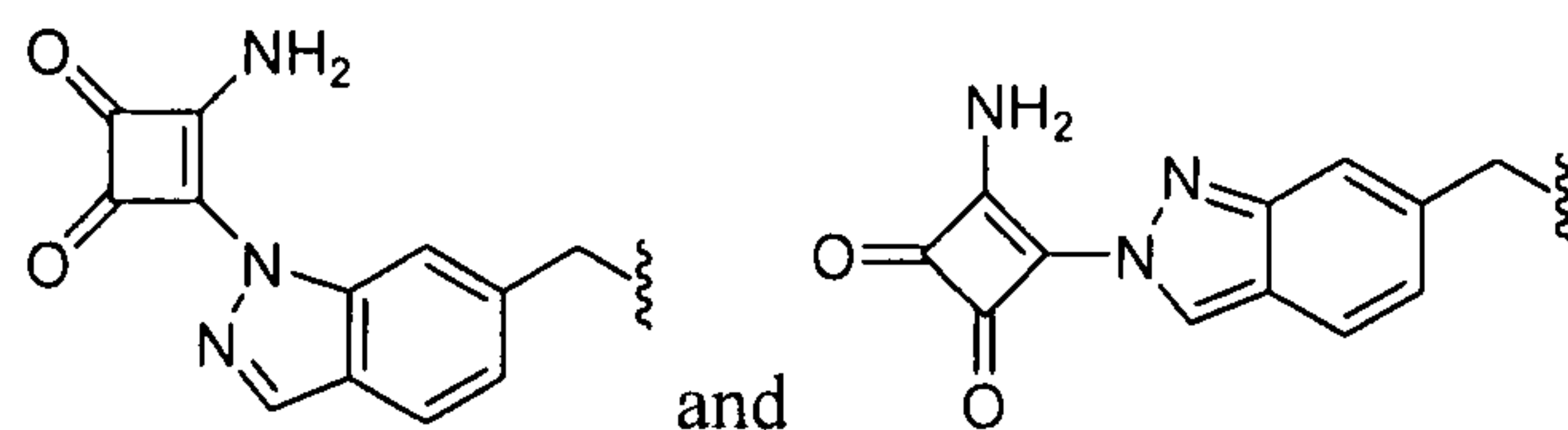
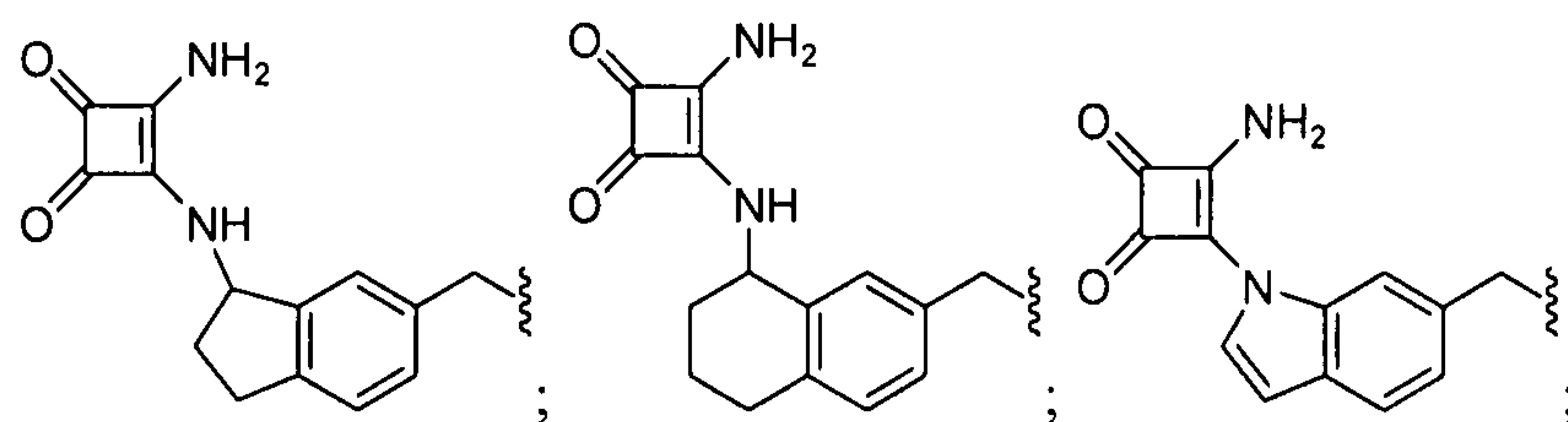
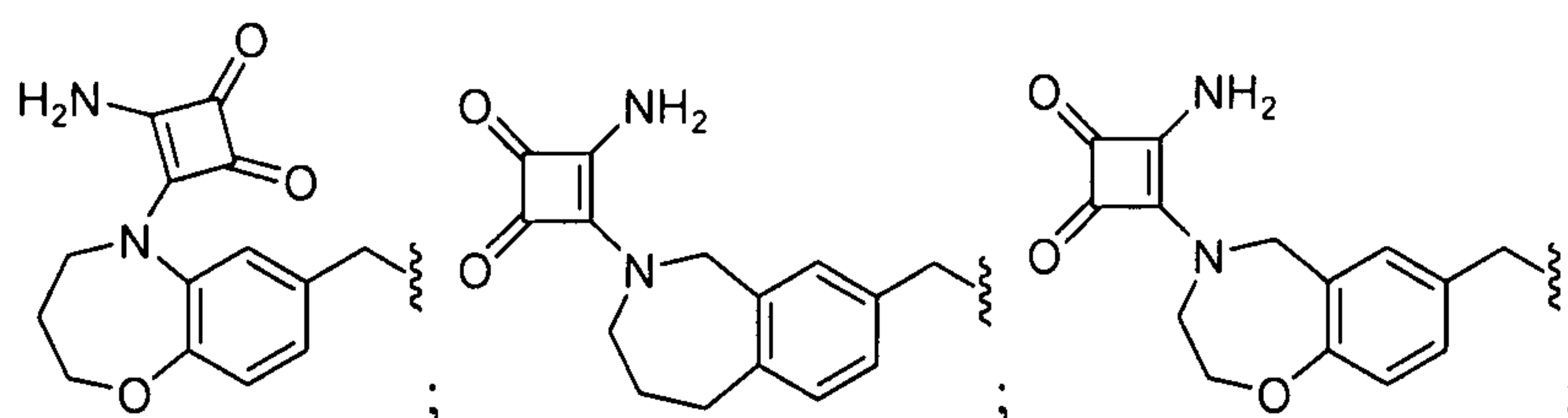
5





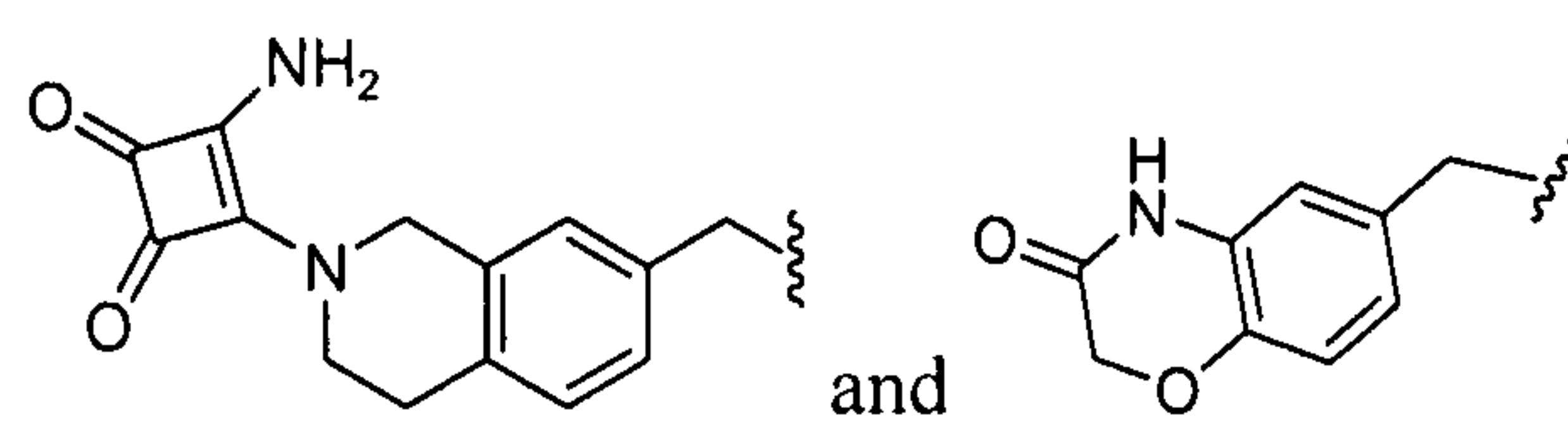


Chemical structures 1-4 are shown, each featuring a benzene ring substituted with a wavy line (representing a substituent) and a heterocyclic system. Structure 1 is a 2,2-difluoro-1,2,3,4-tetrahydroquinoline derivative. Structure 2 is a 1,2,3,4-tetrahydroquinoline derivative. Structure 3 is a 2,3-dihydro-1,4-benzodioxine derivative. Structure 4 is a 1,2,3,4-tetrahydroquinoline derivative with a different heterocyclic system.



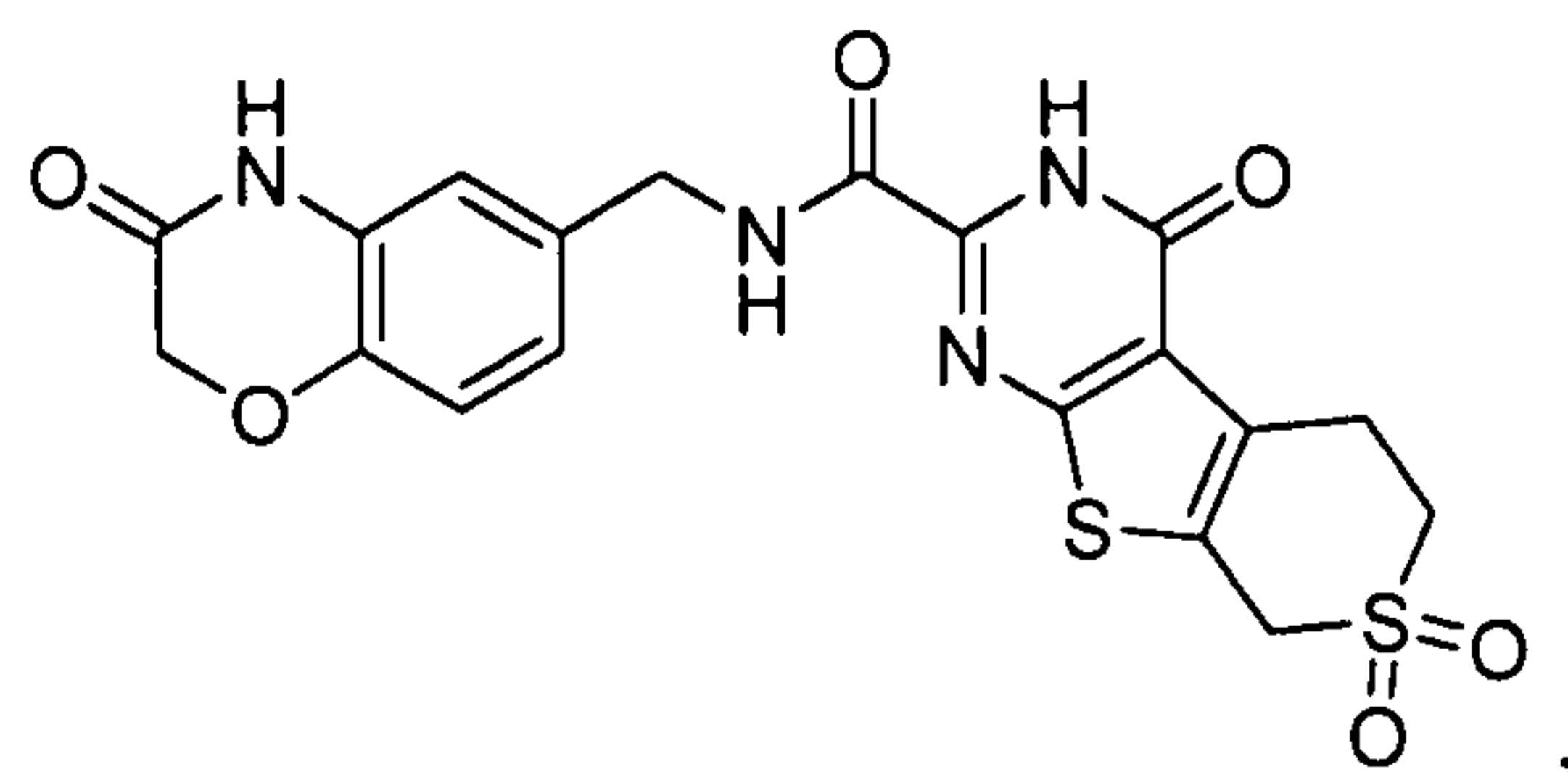
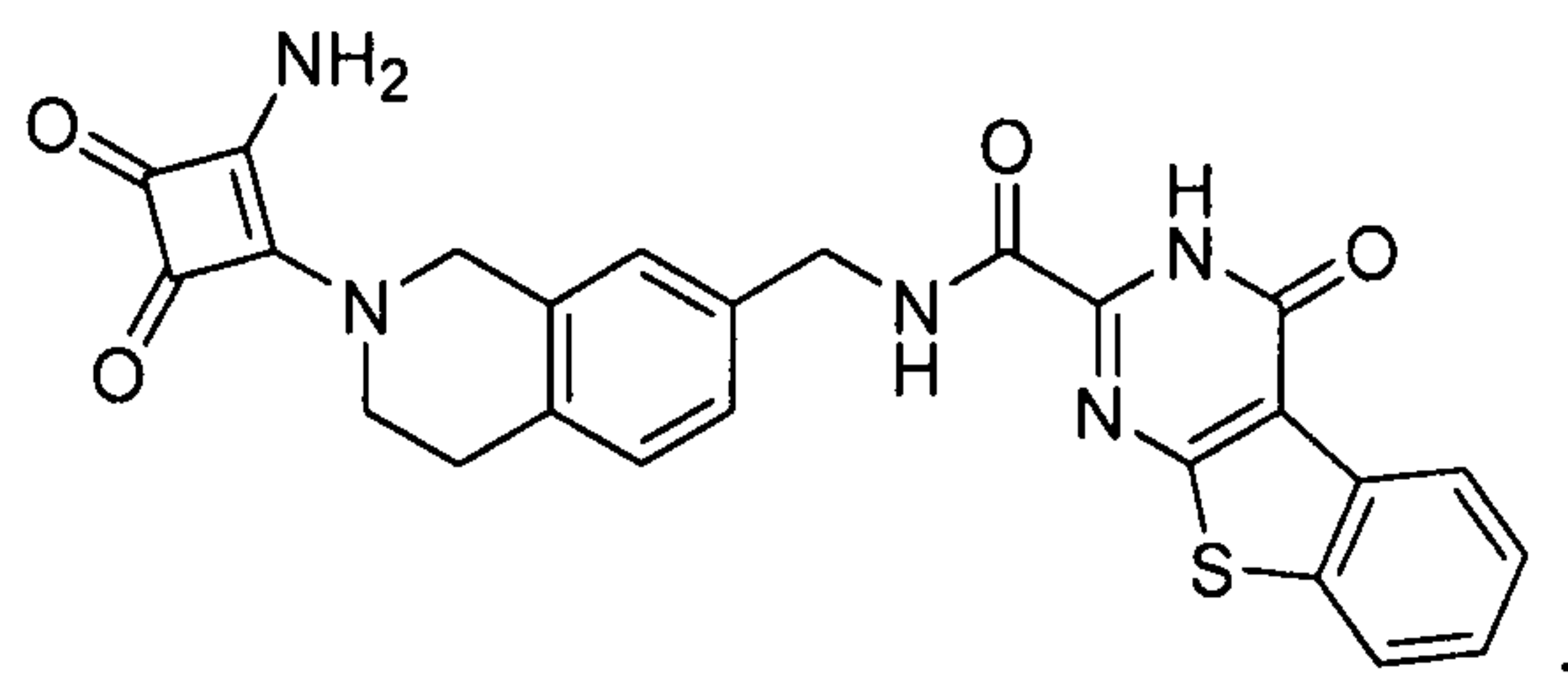
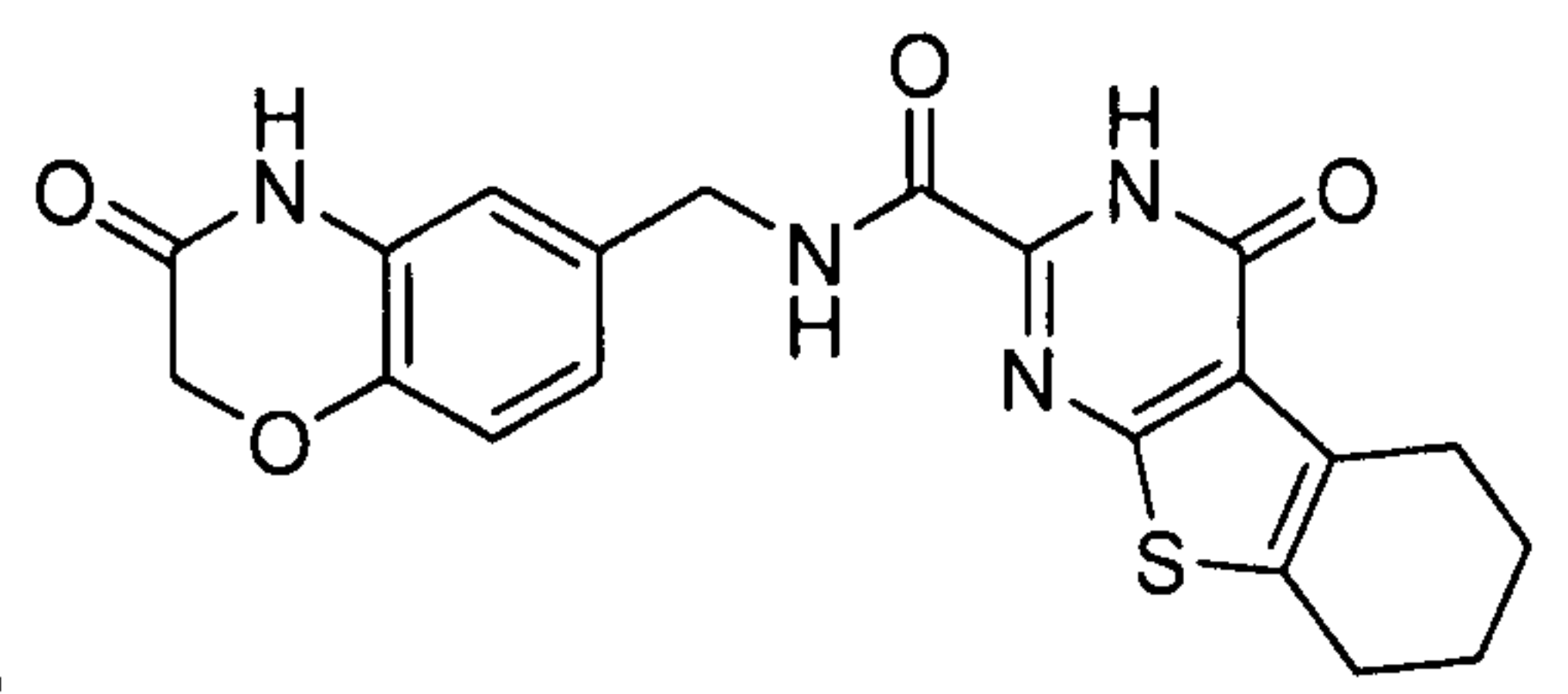
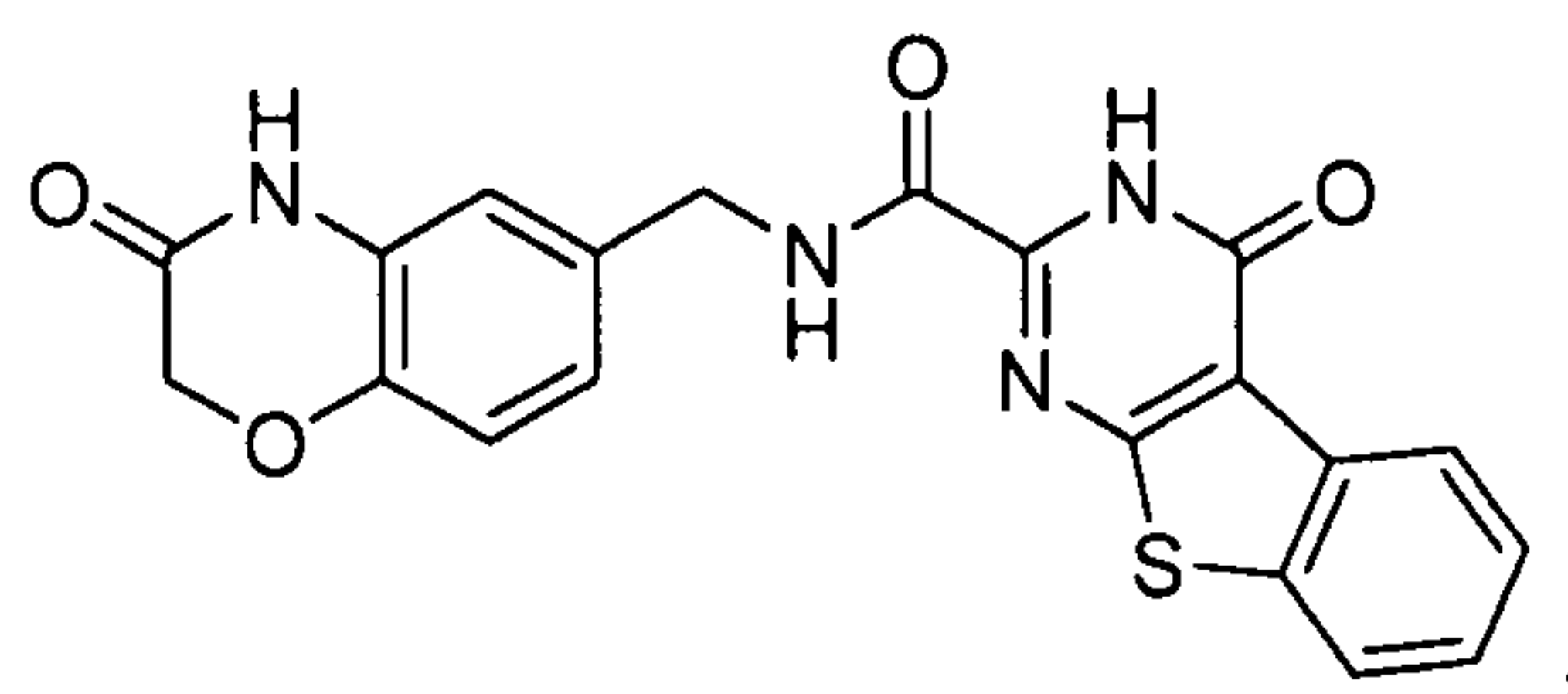
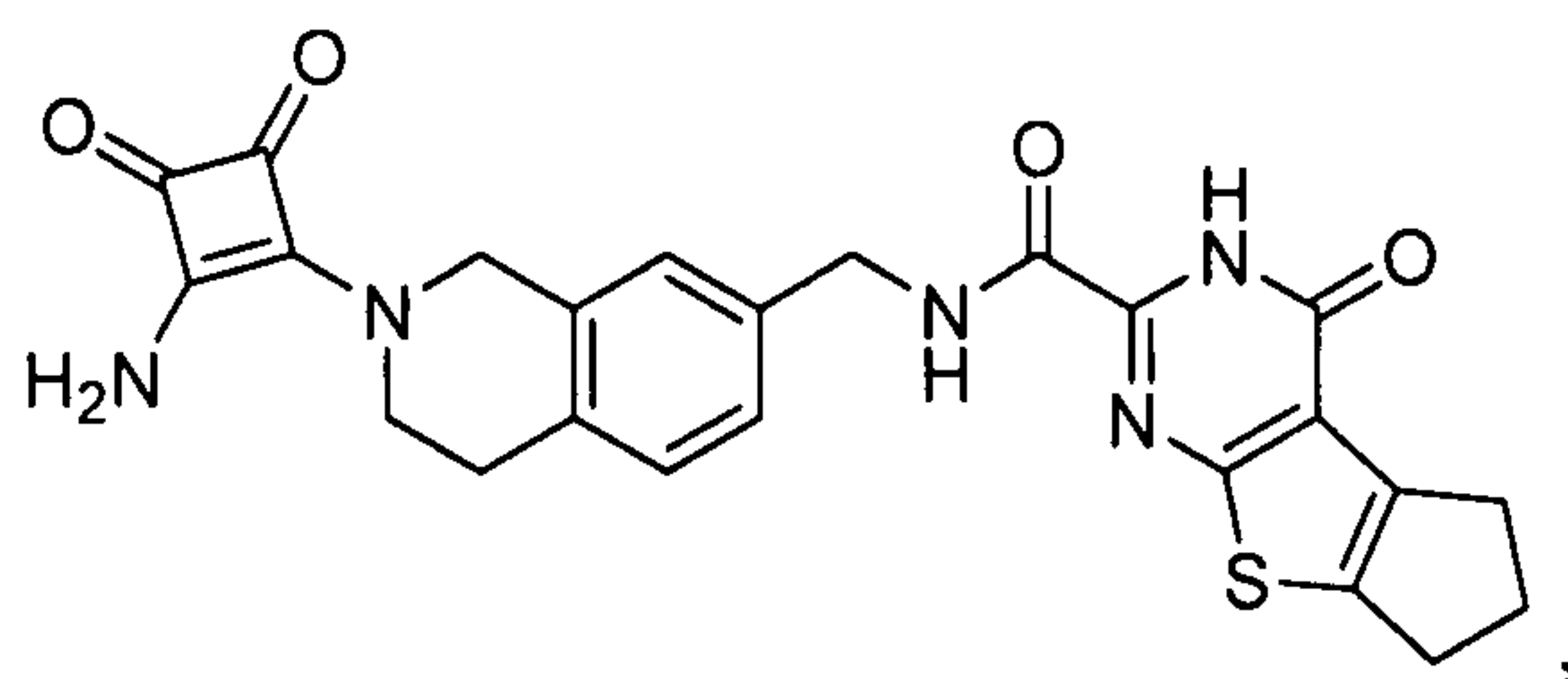
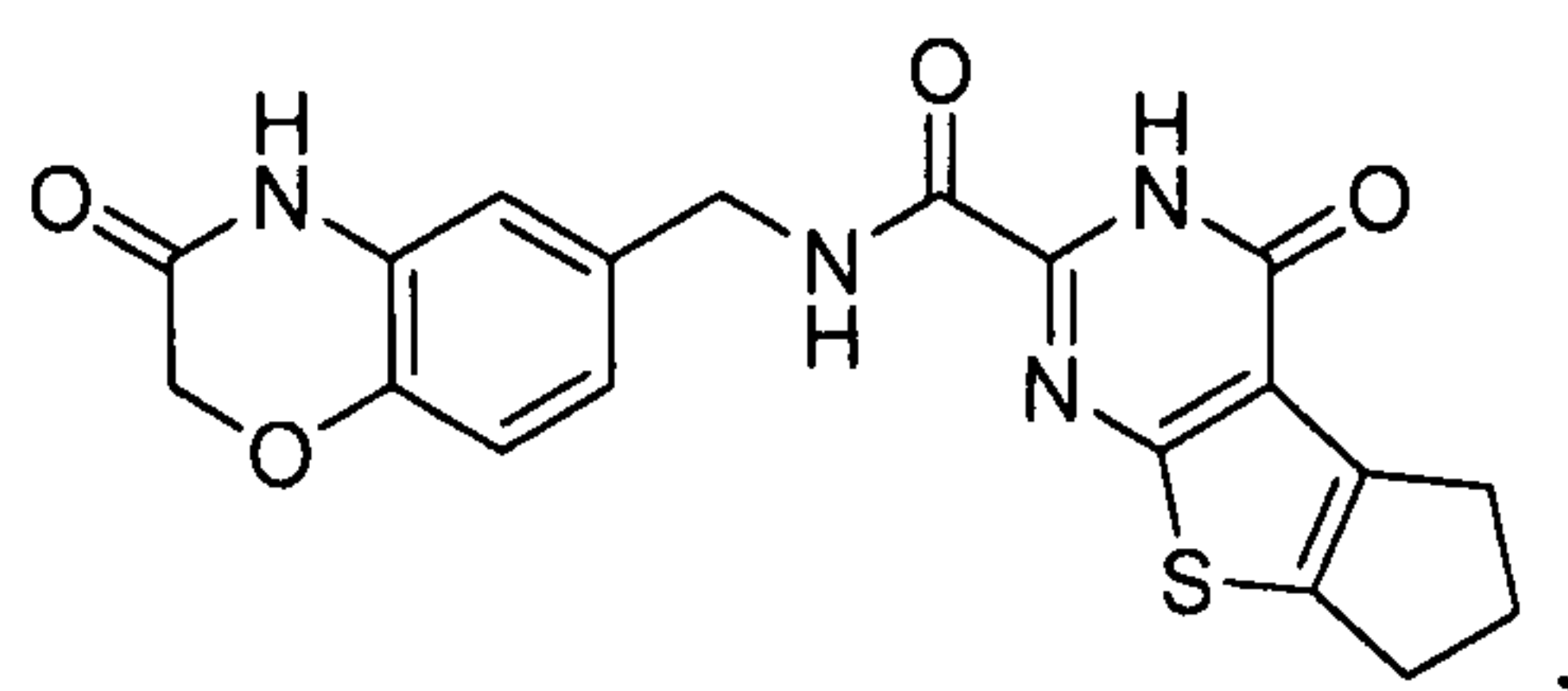
and

15. A compound according to claim 6, wherein R<sup>1</sup> is selected from:

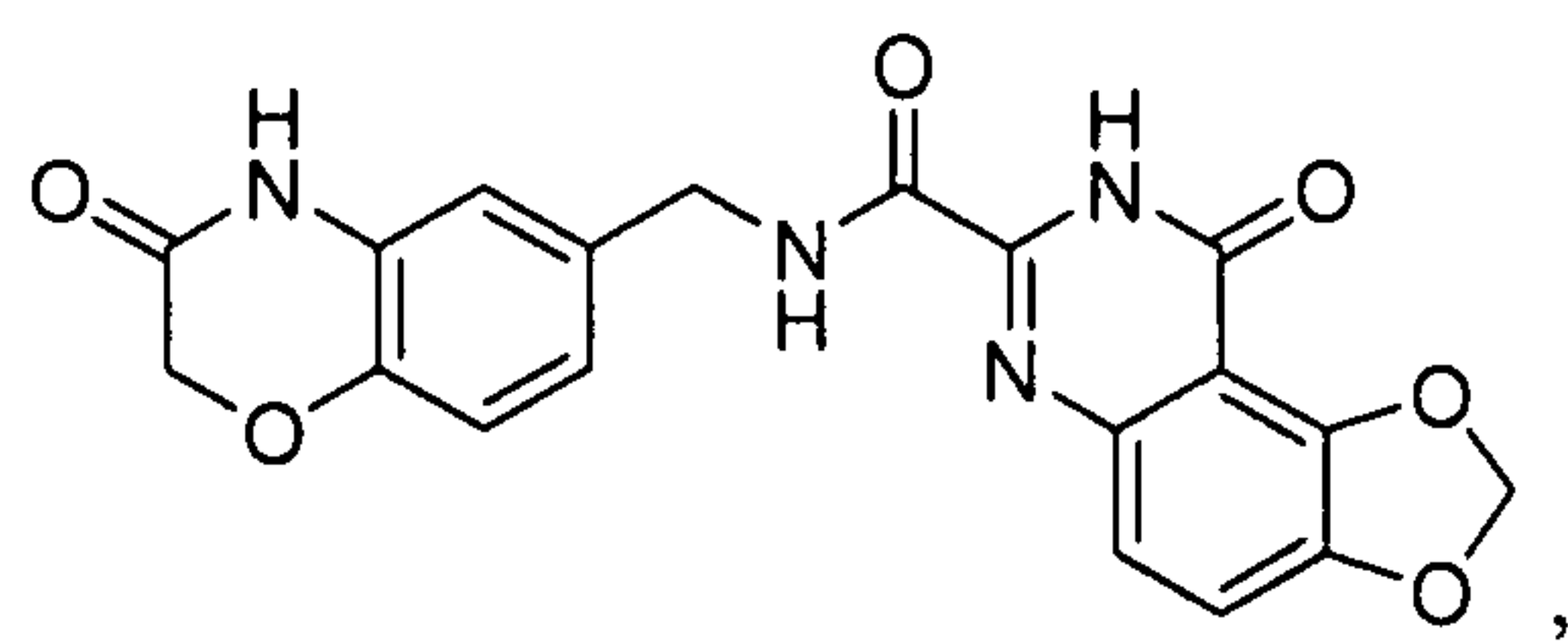
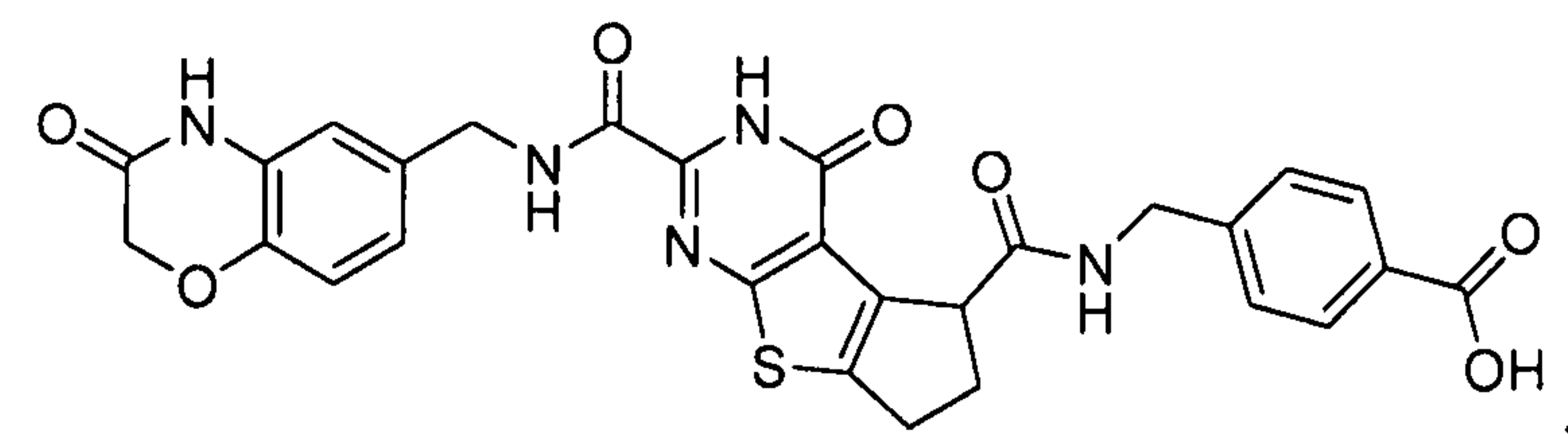
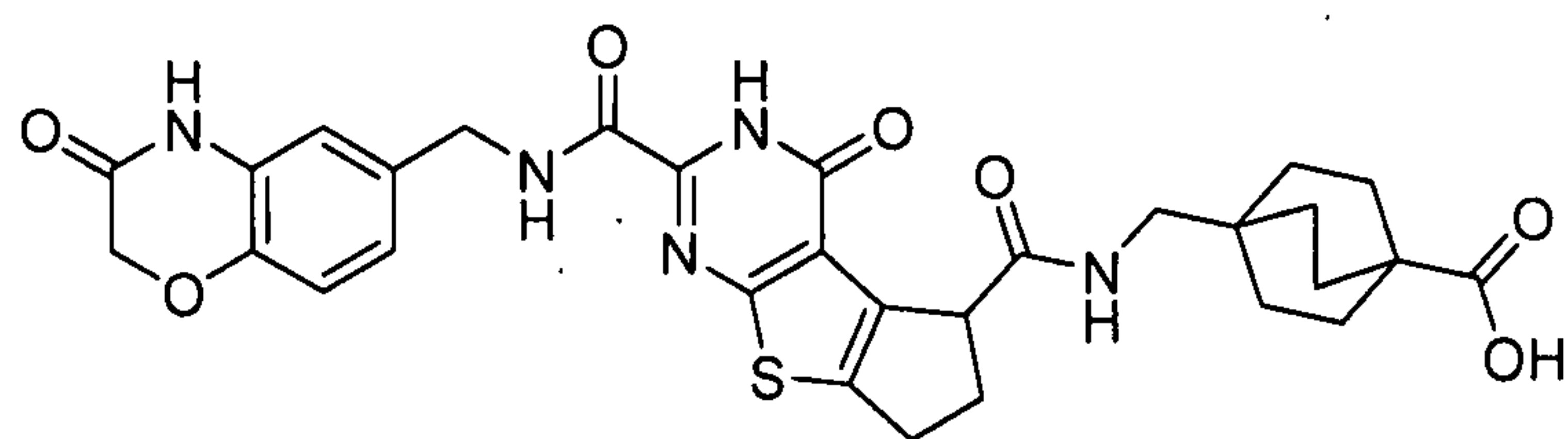
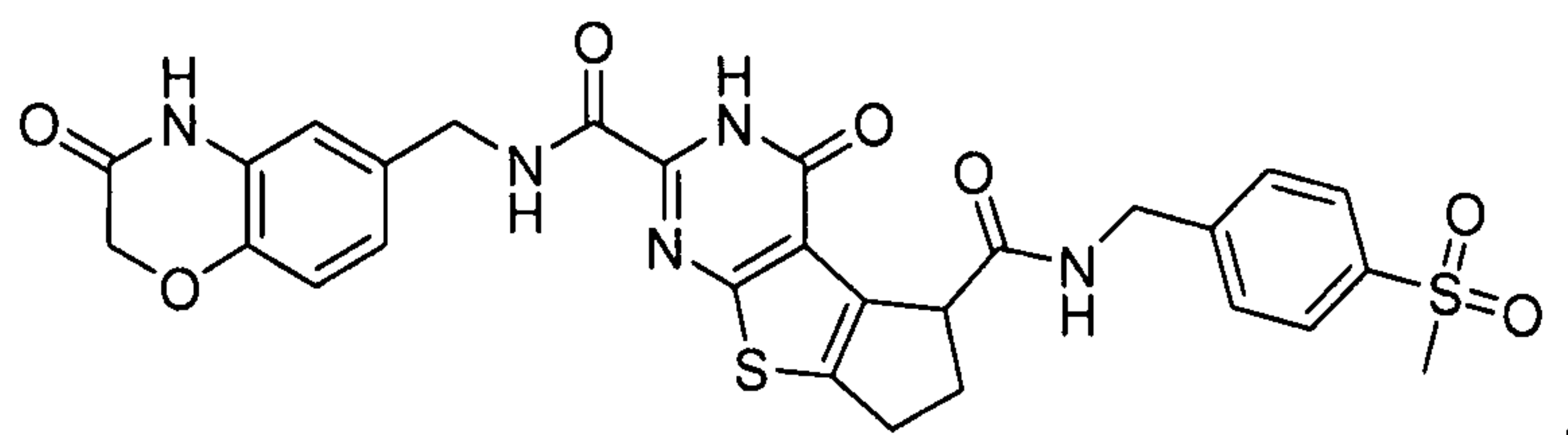
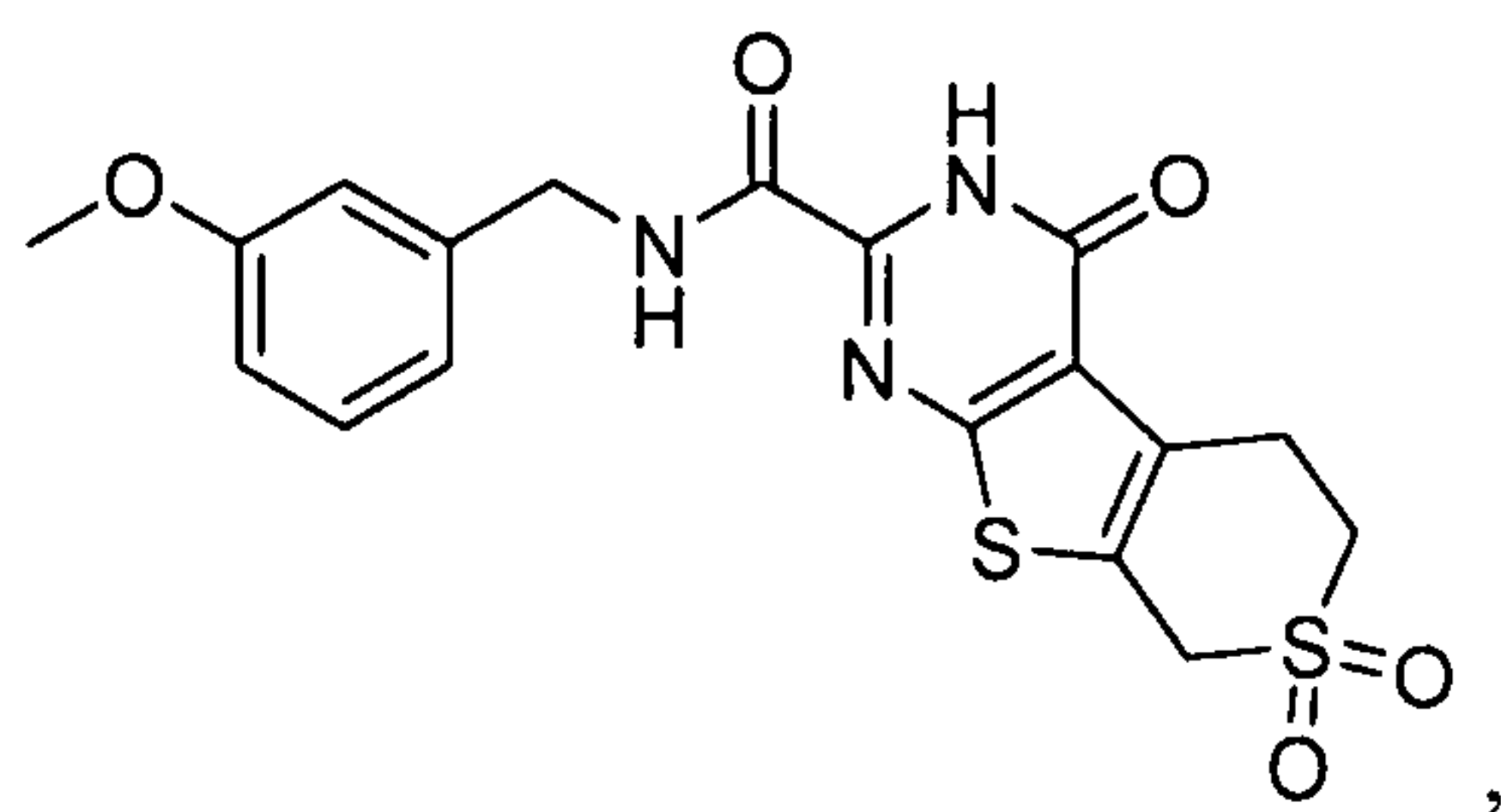
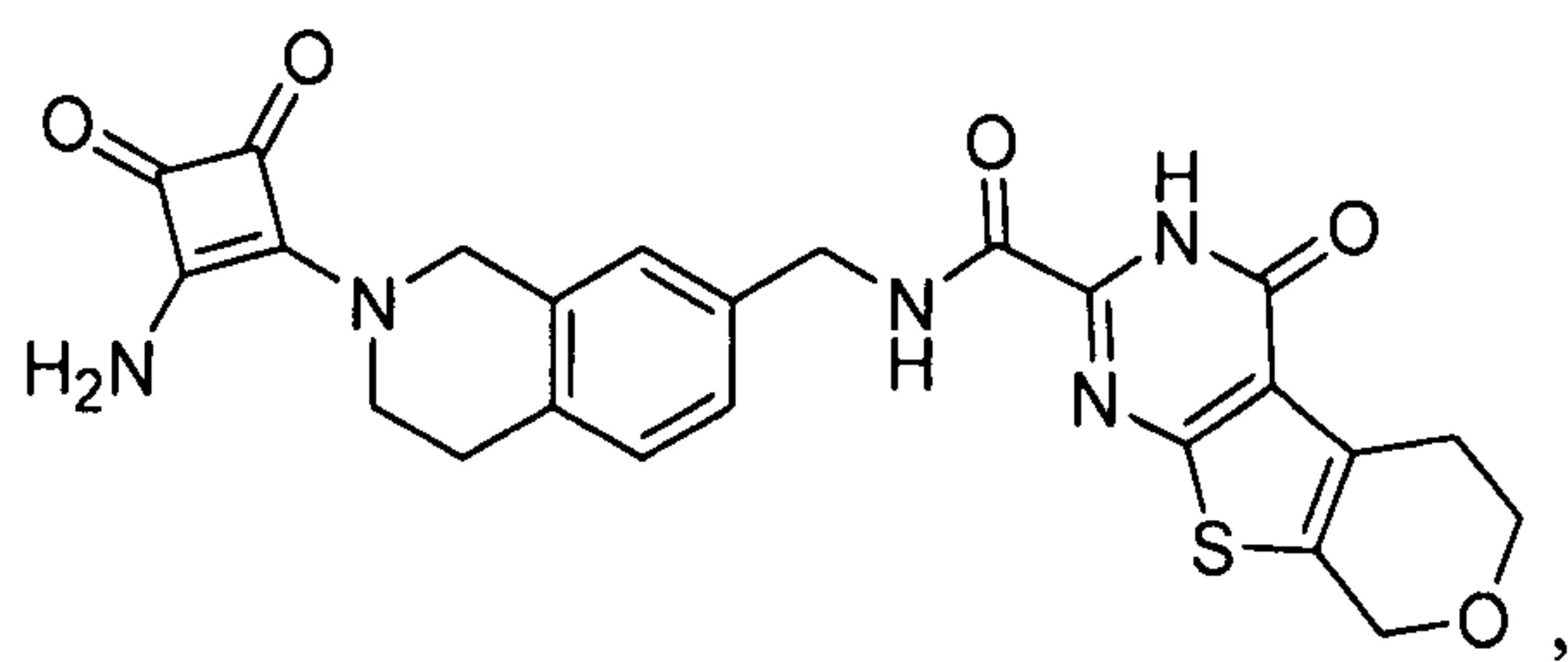
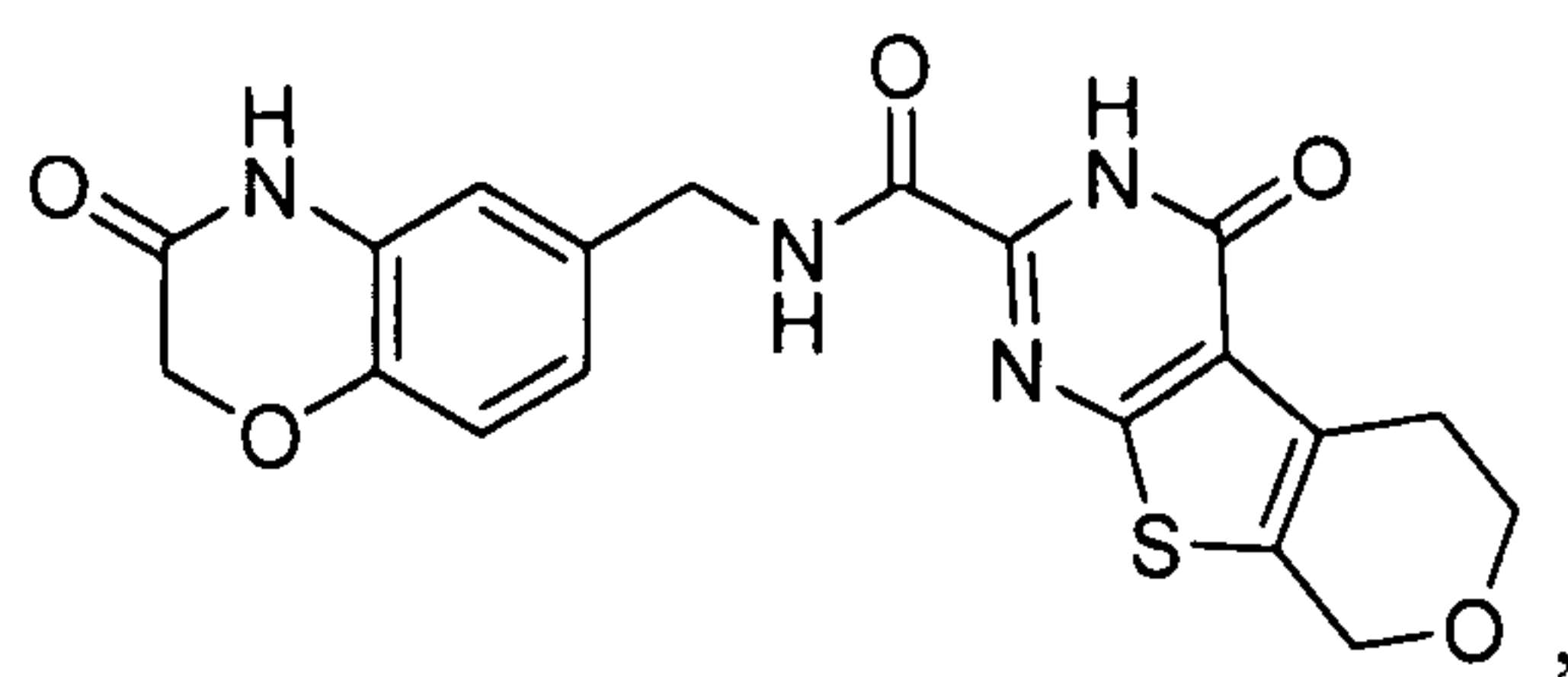


16. A compound according to claim 1, having the structure:

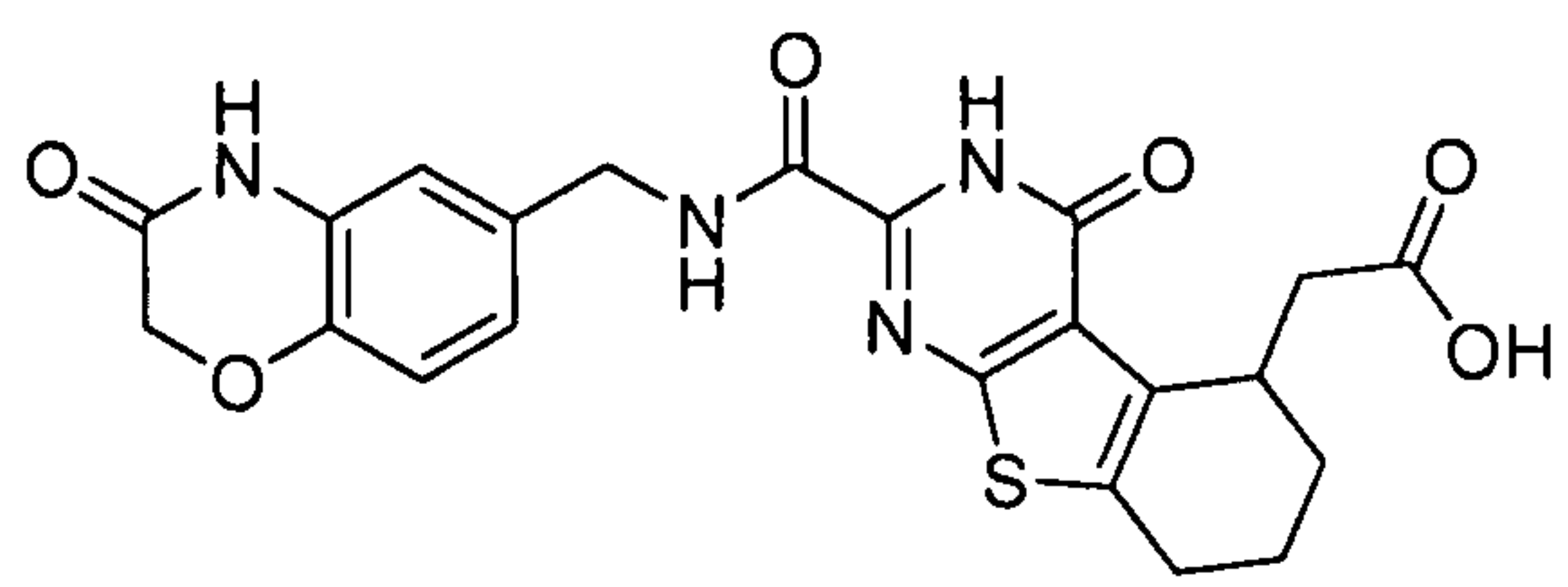
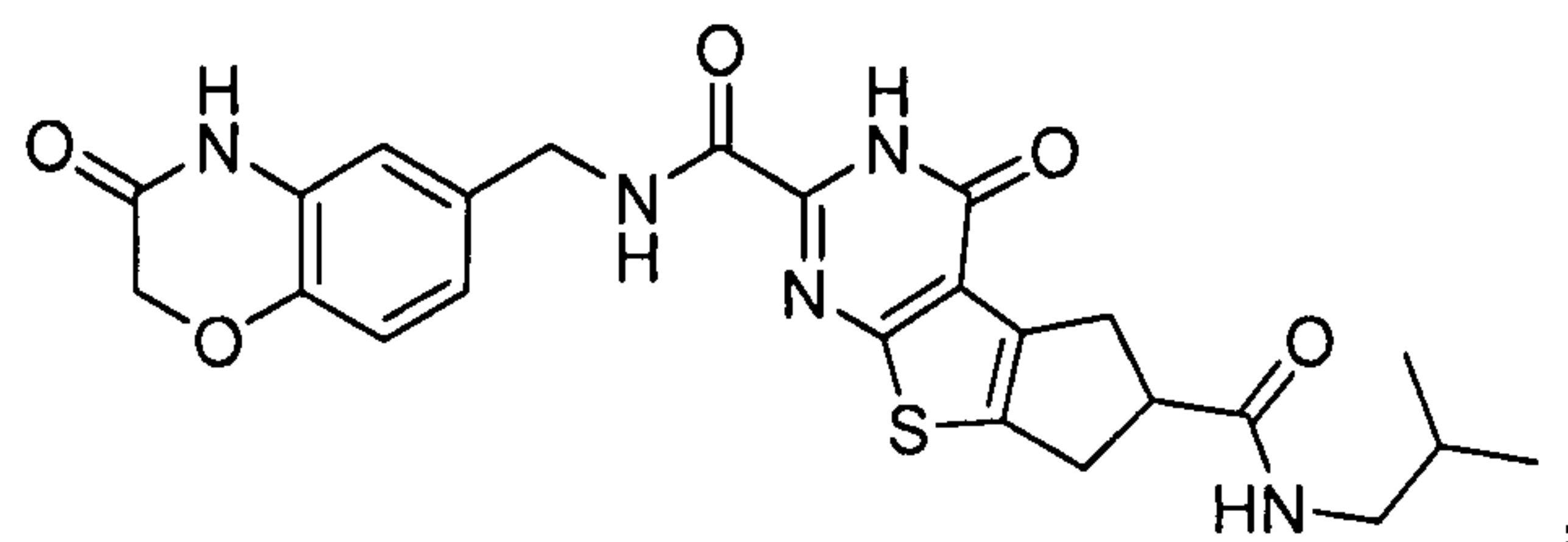
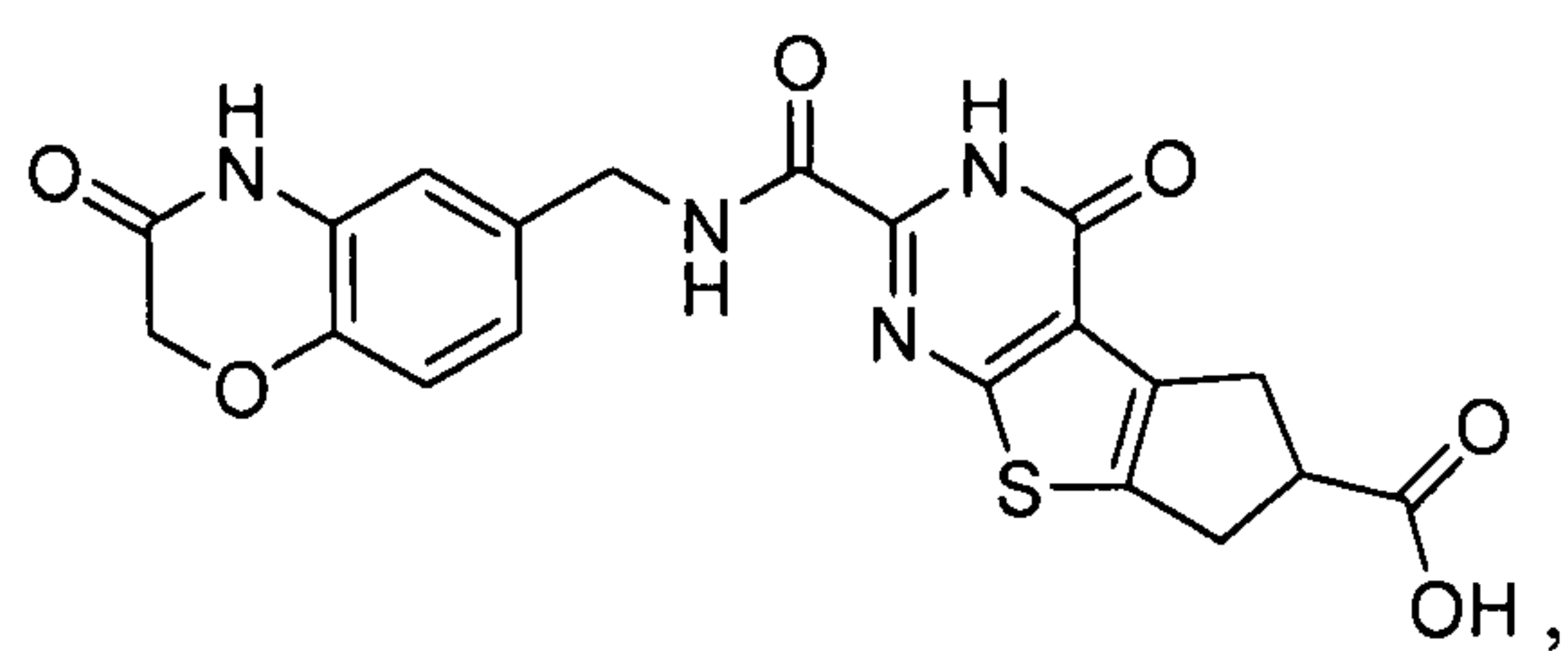
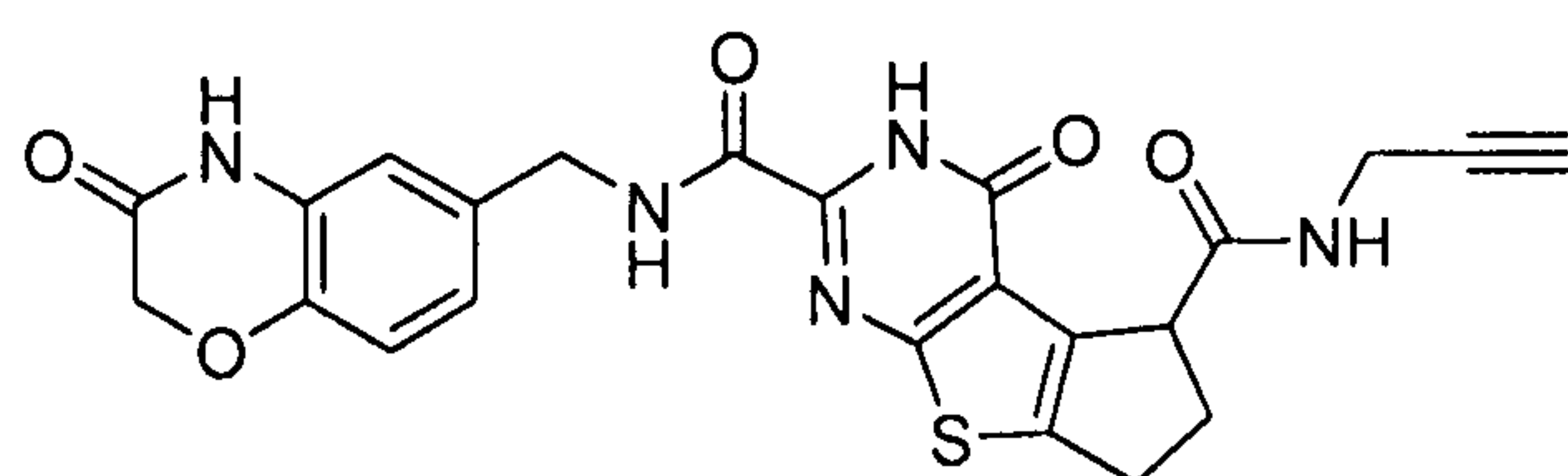
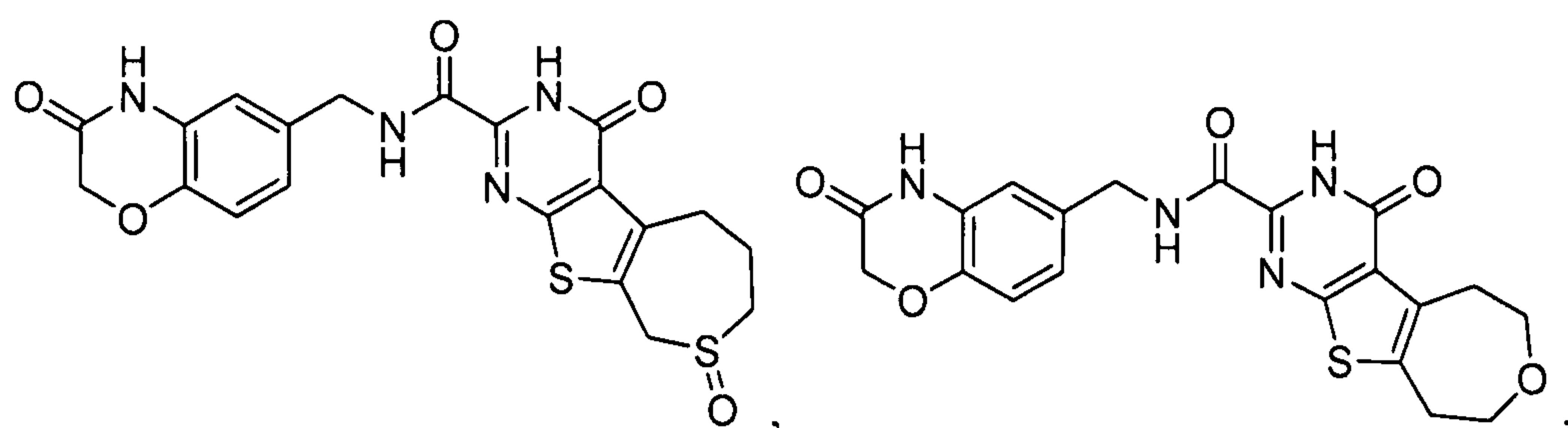
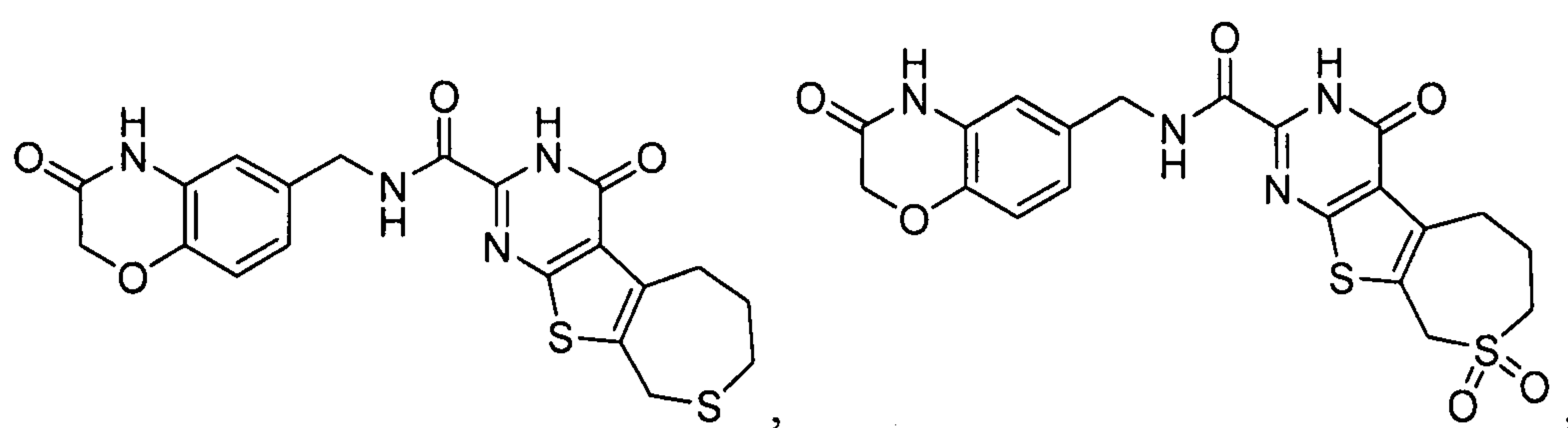
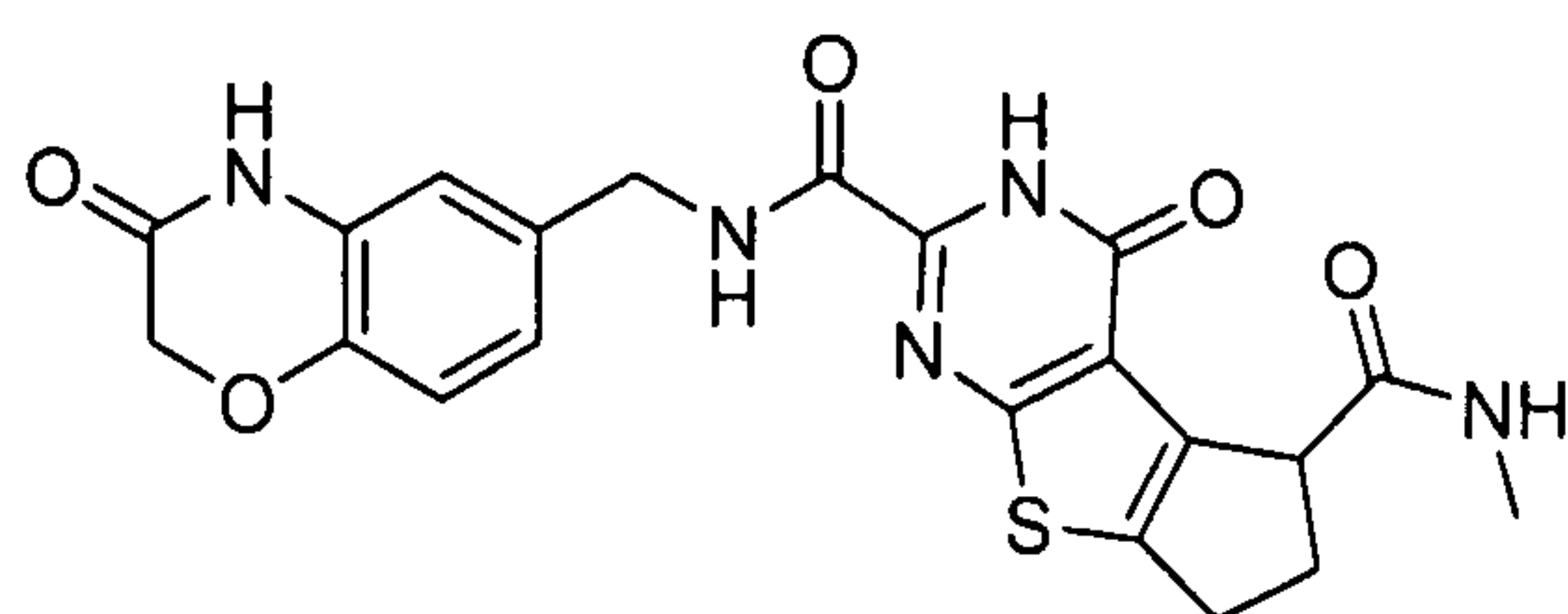
5



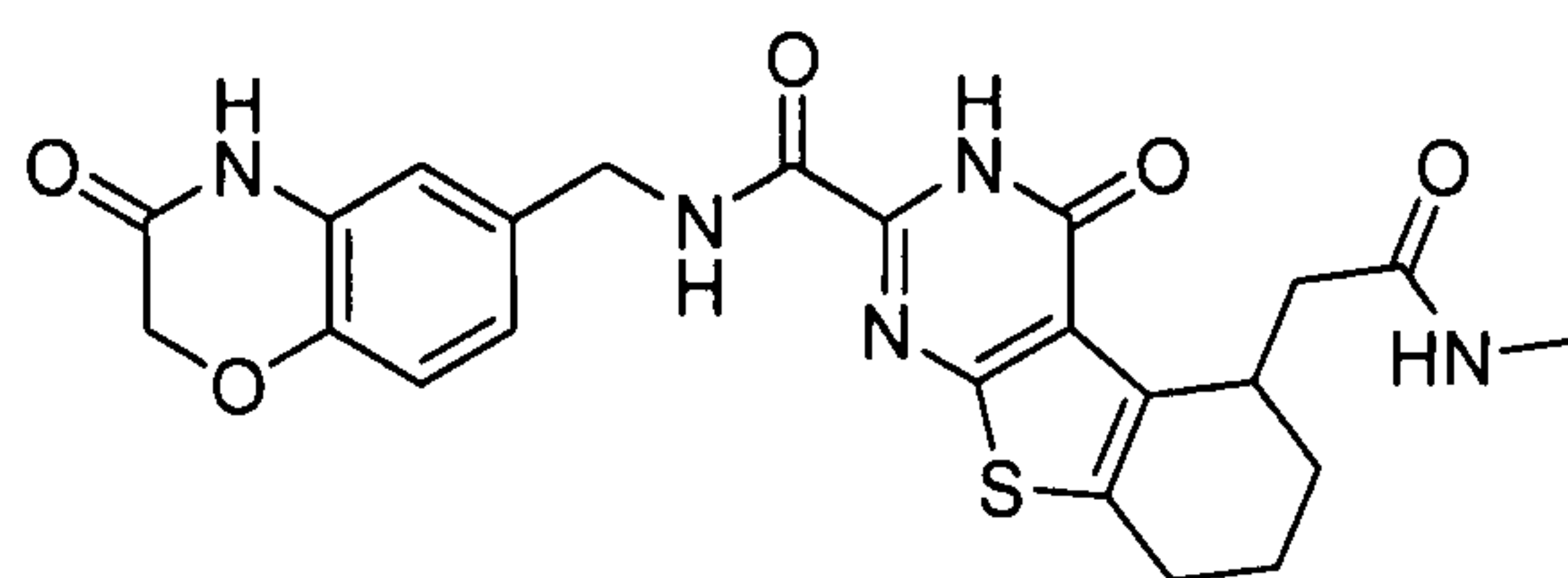




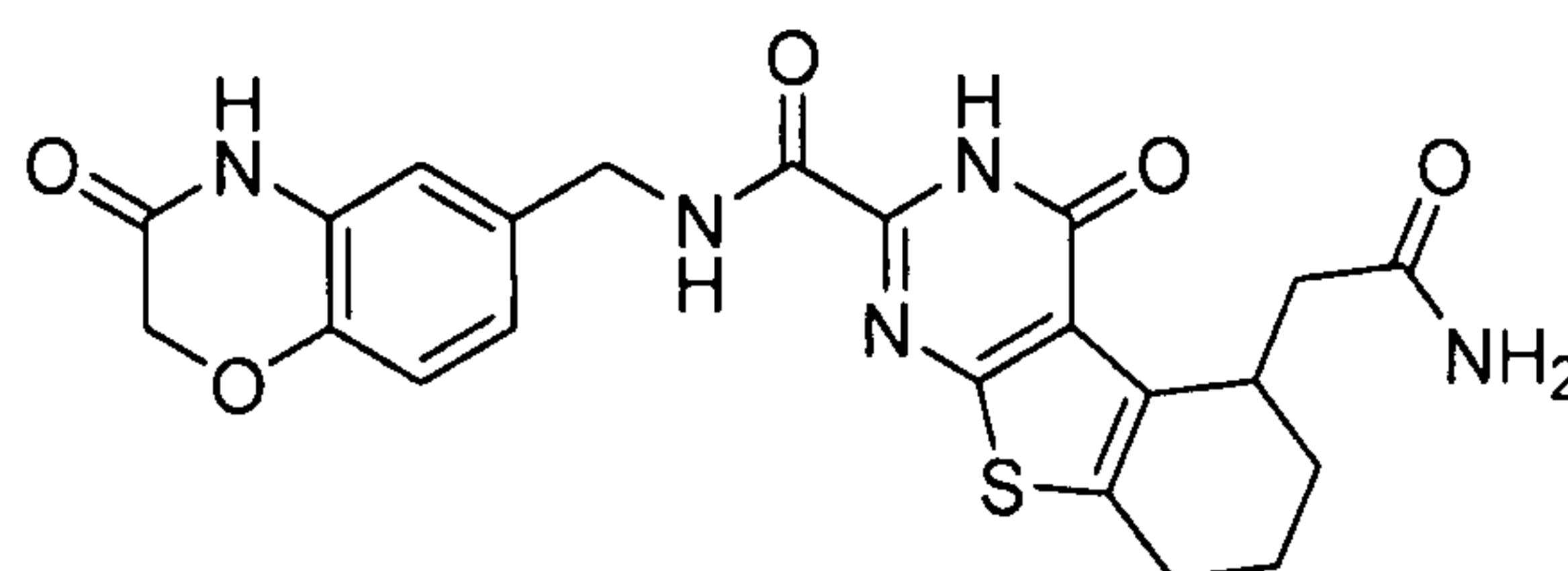
5



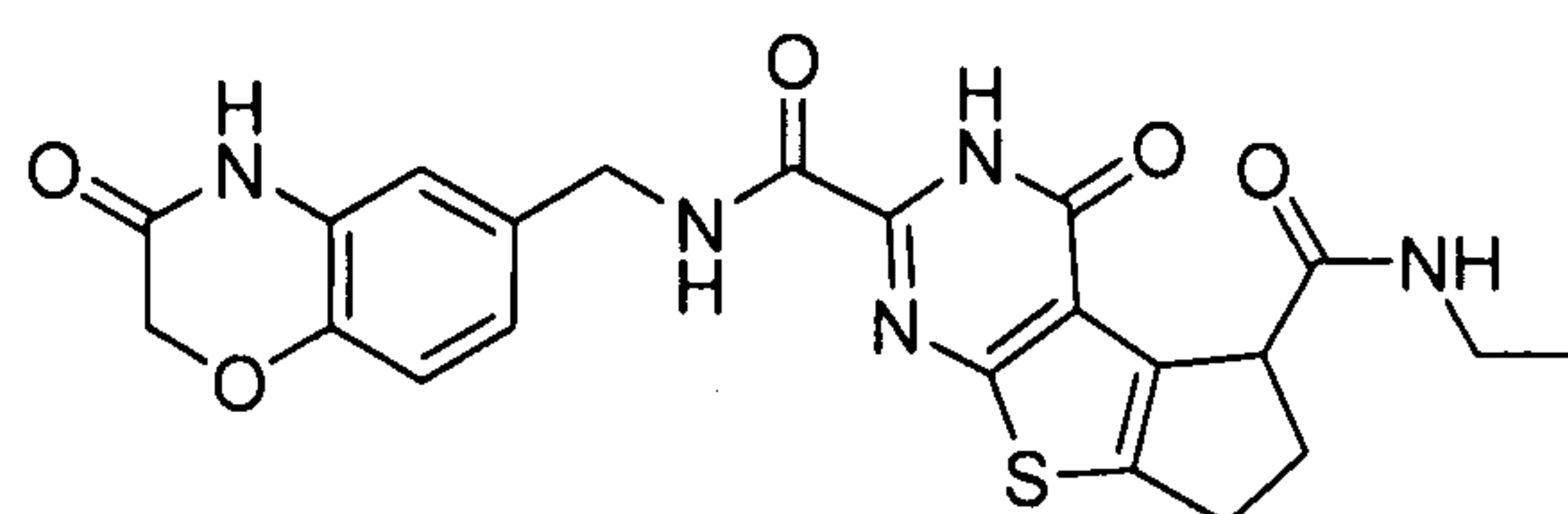
5



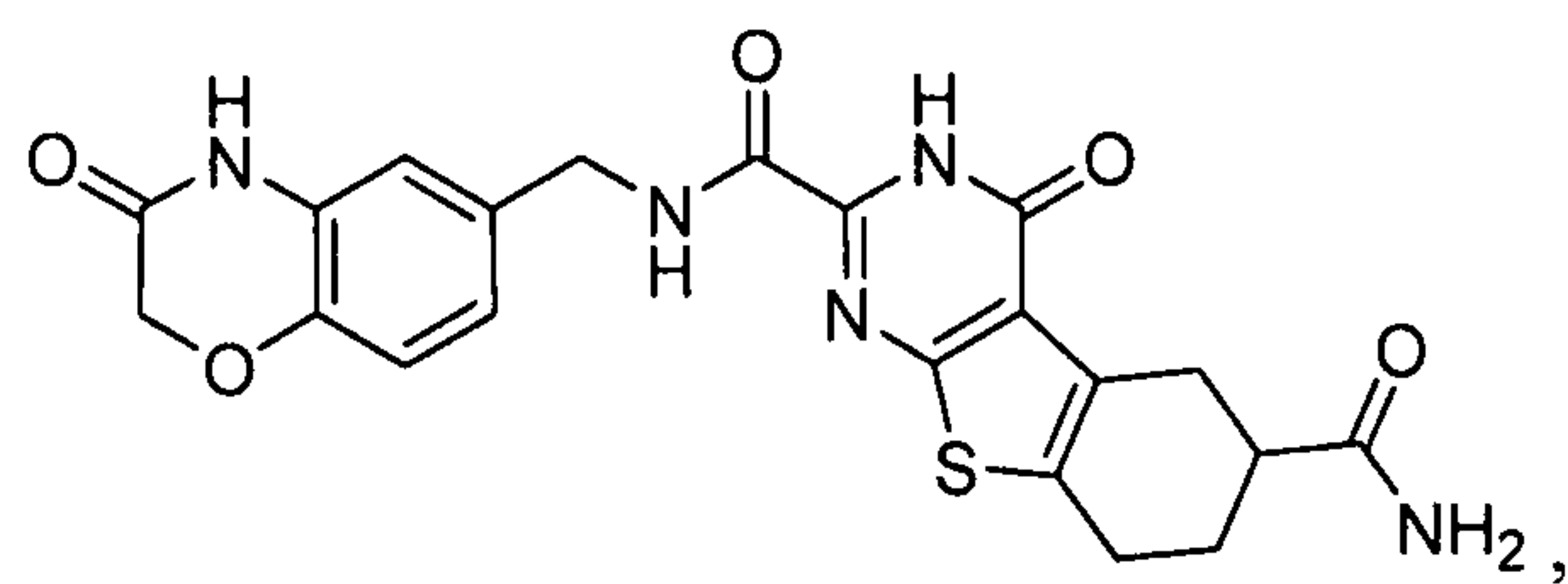
,



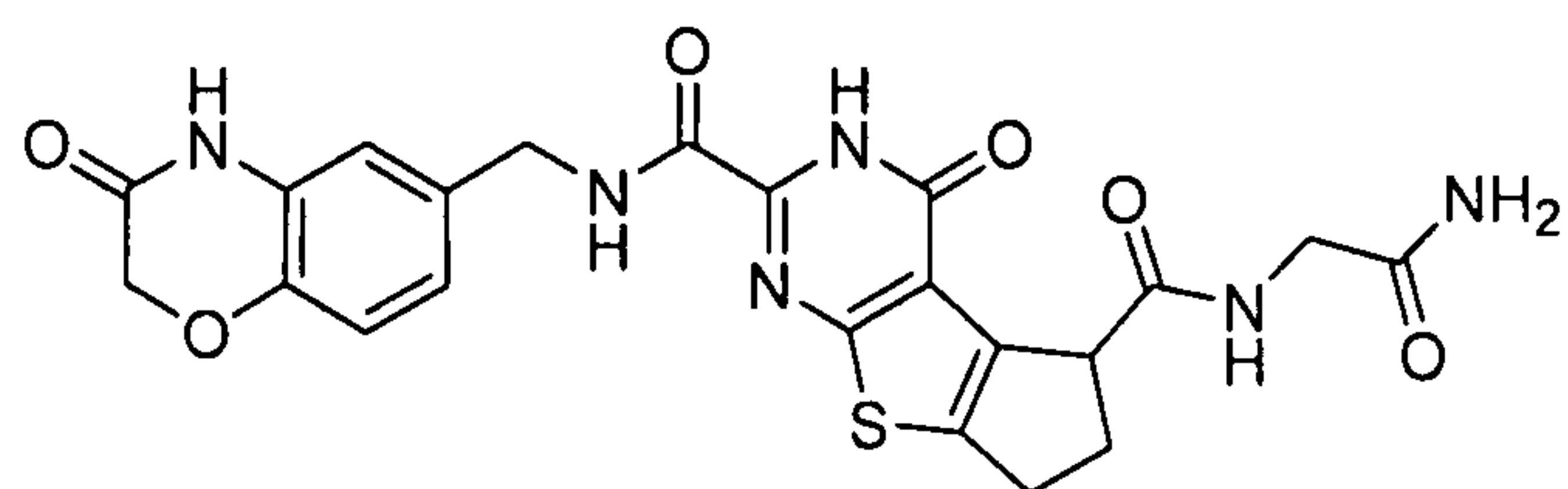
,



,

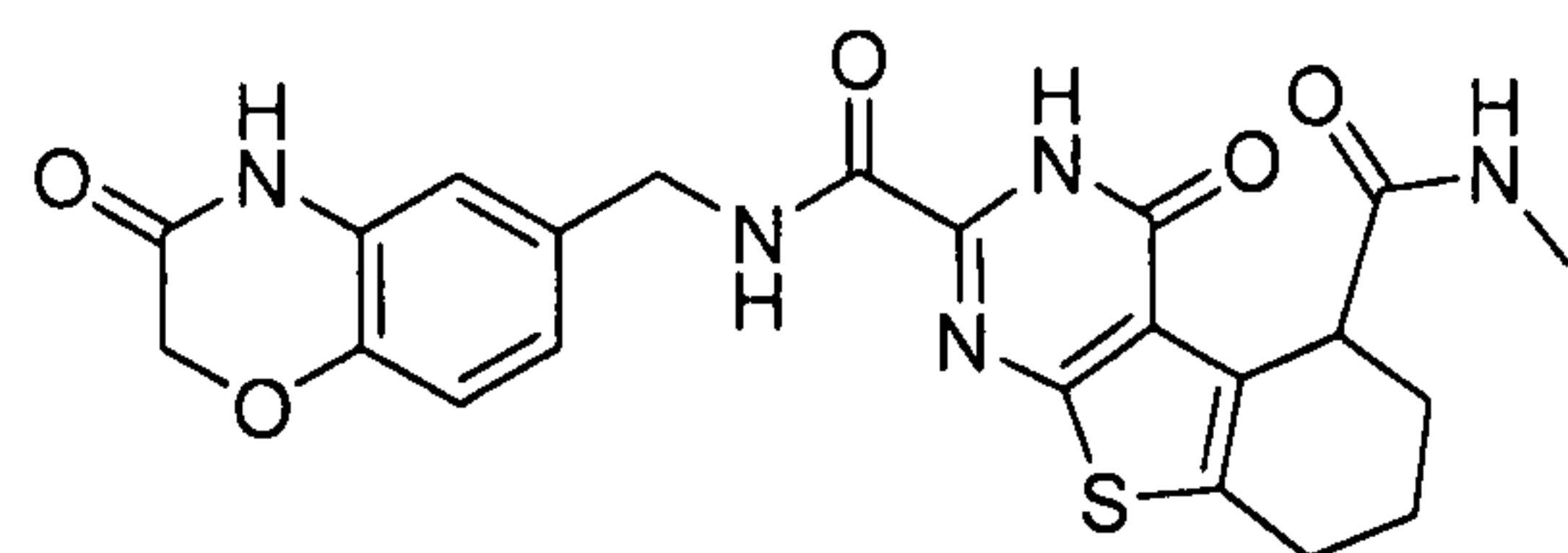


,

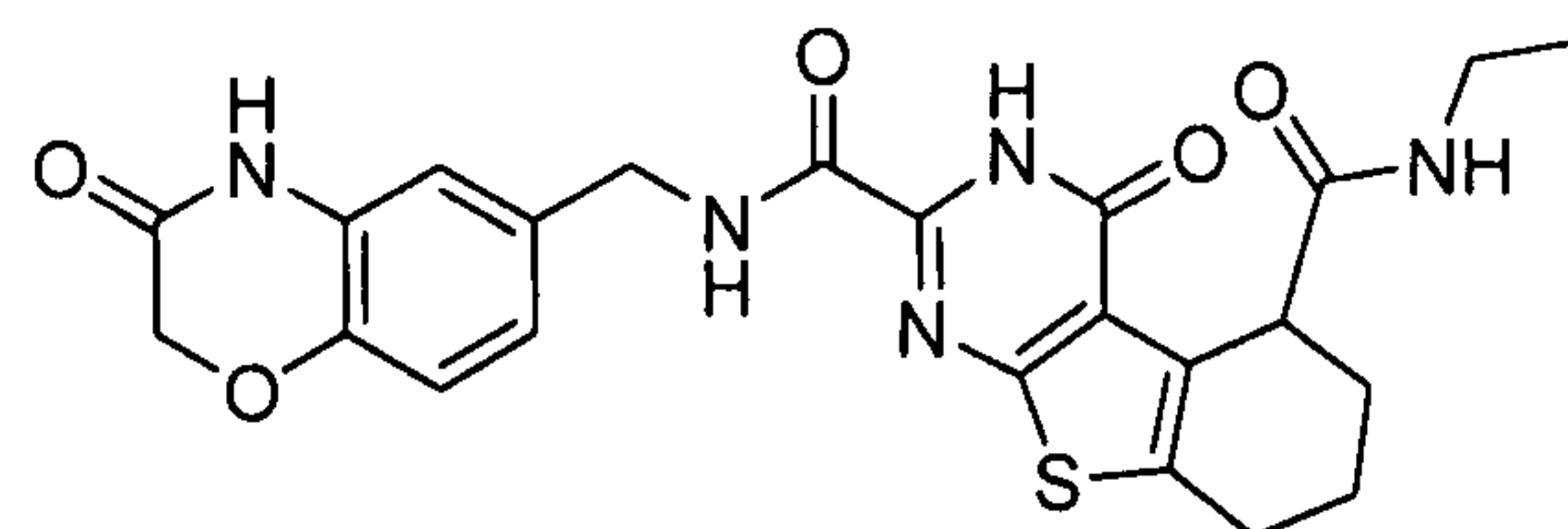


,

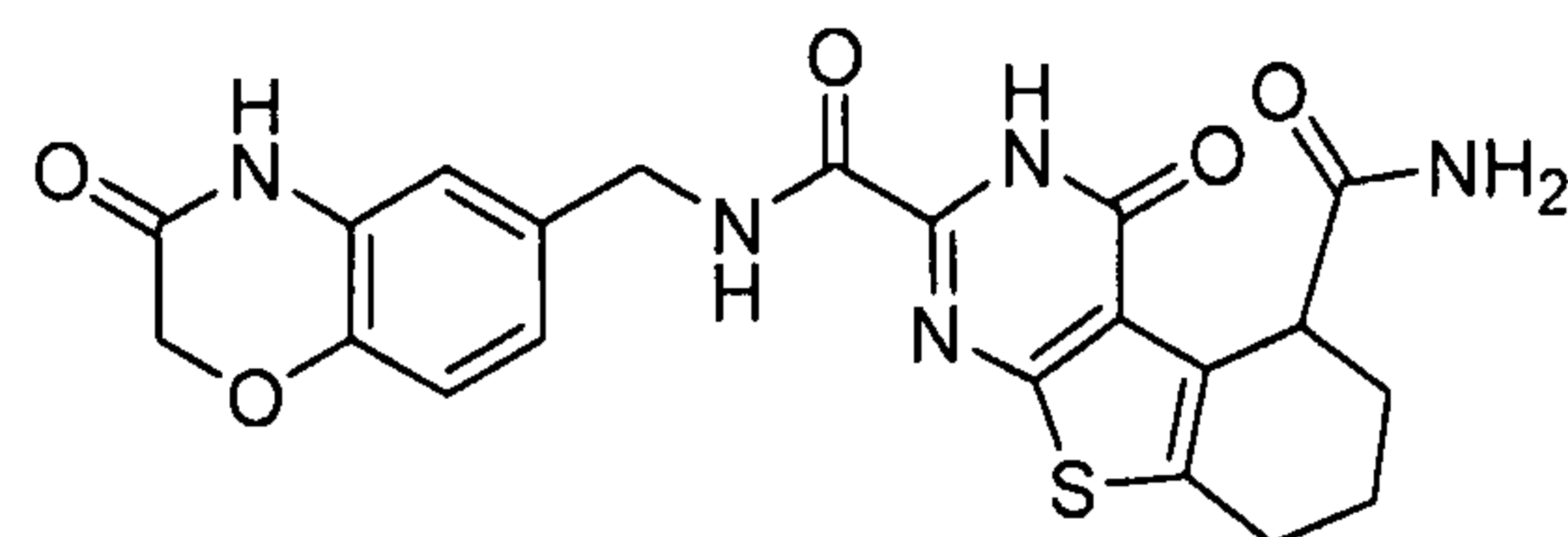
5



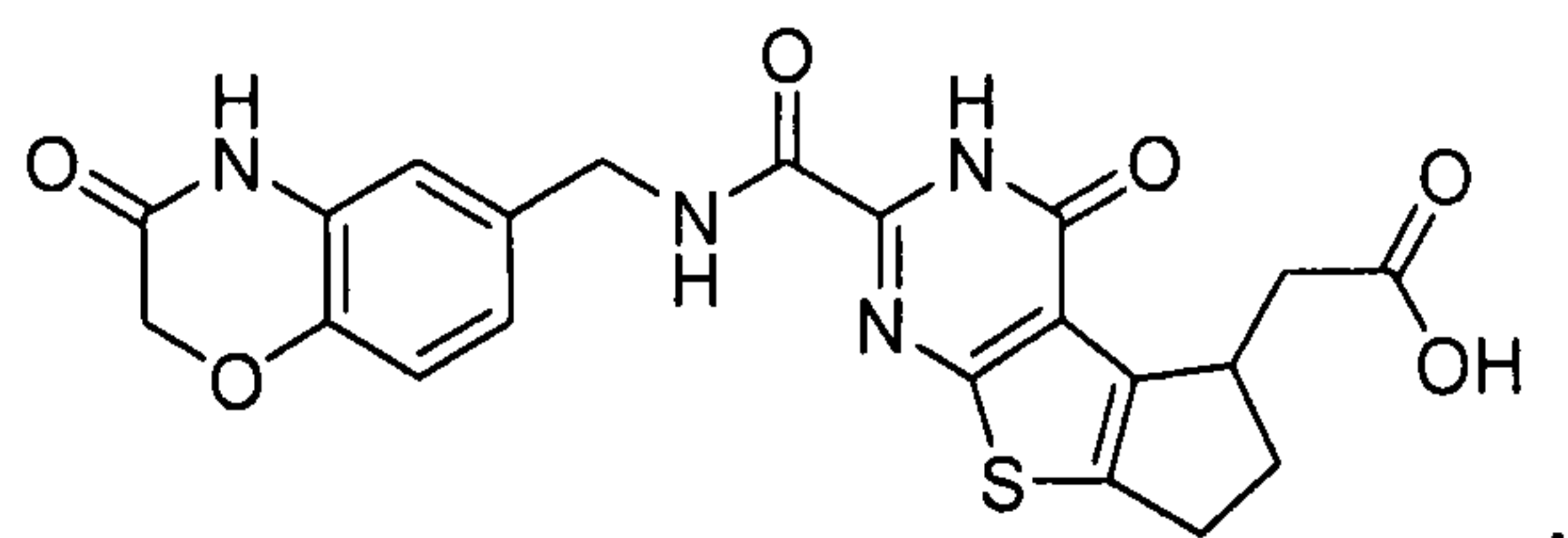
,



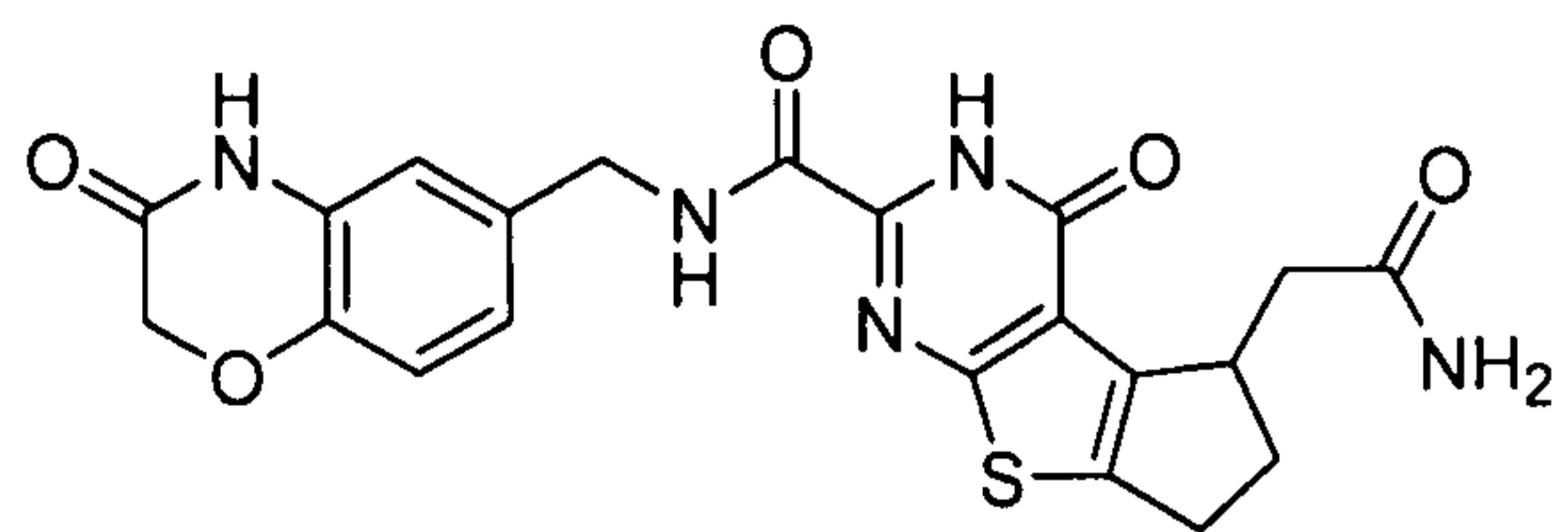
,



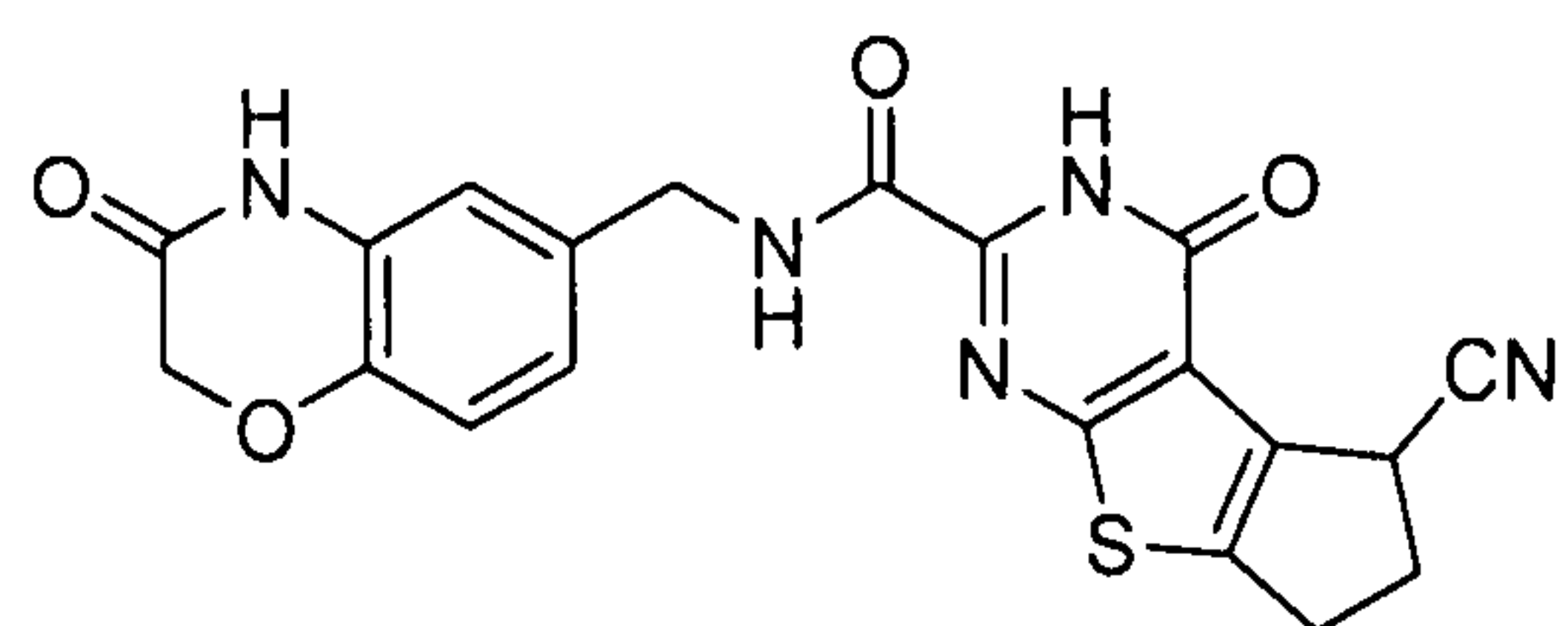
,



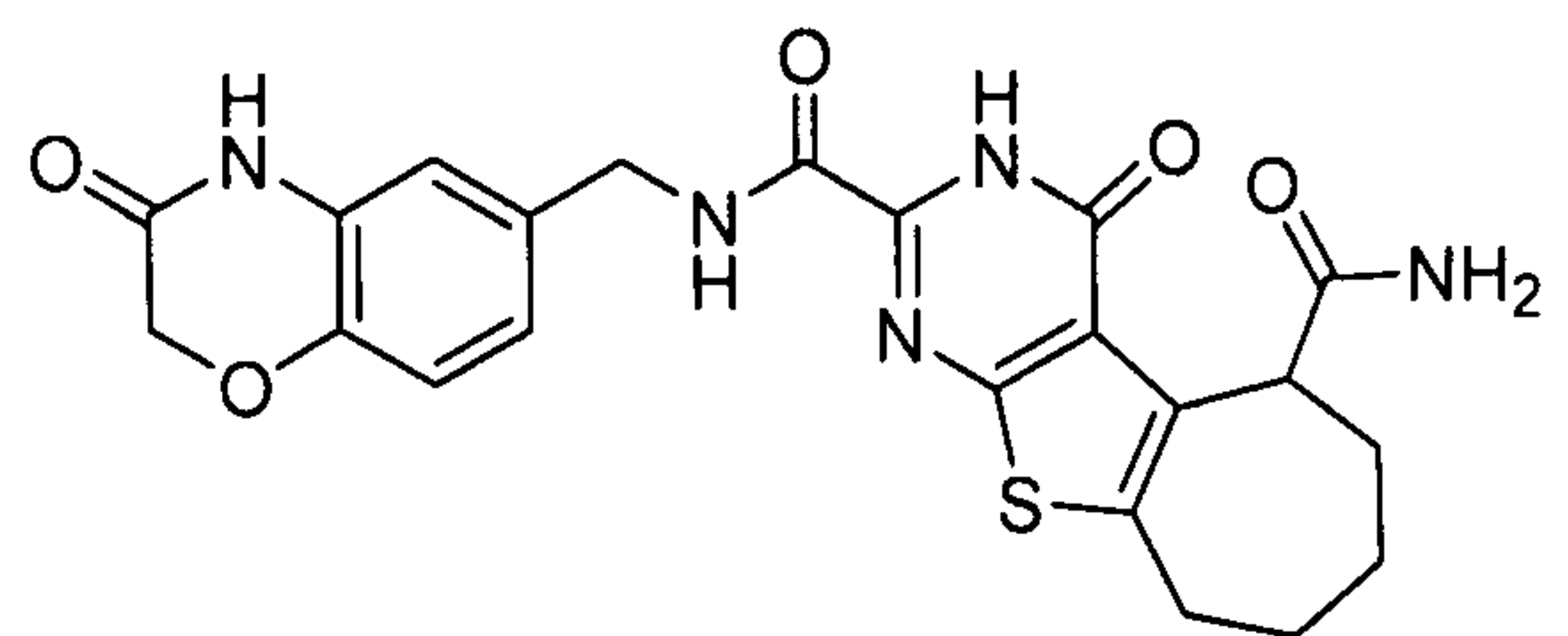
,



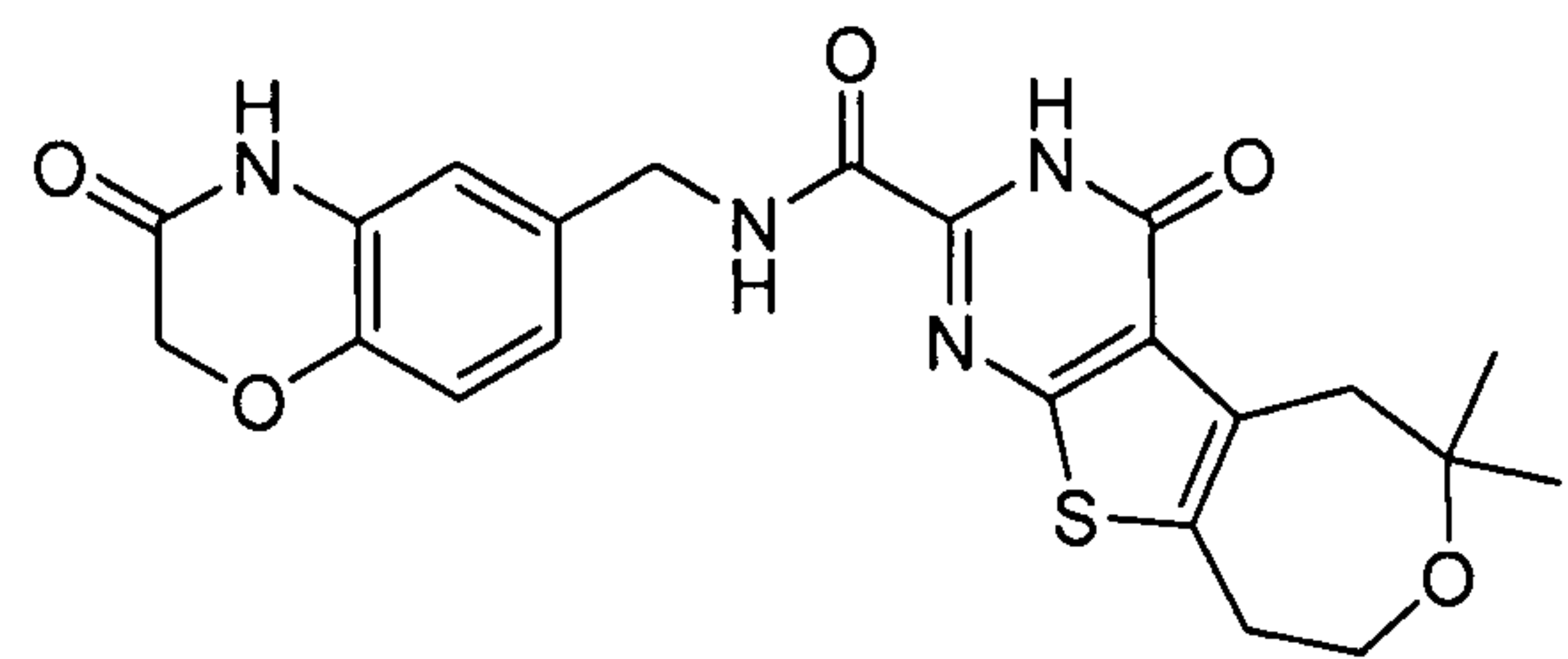
,



,

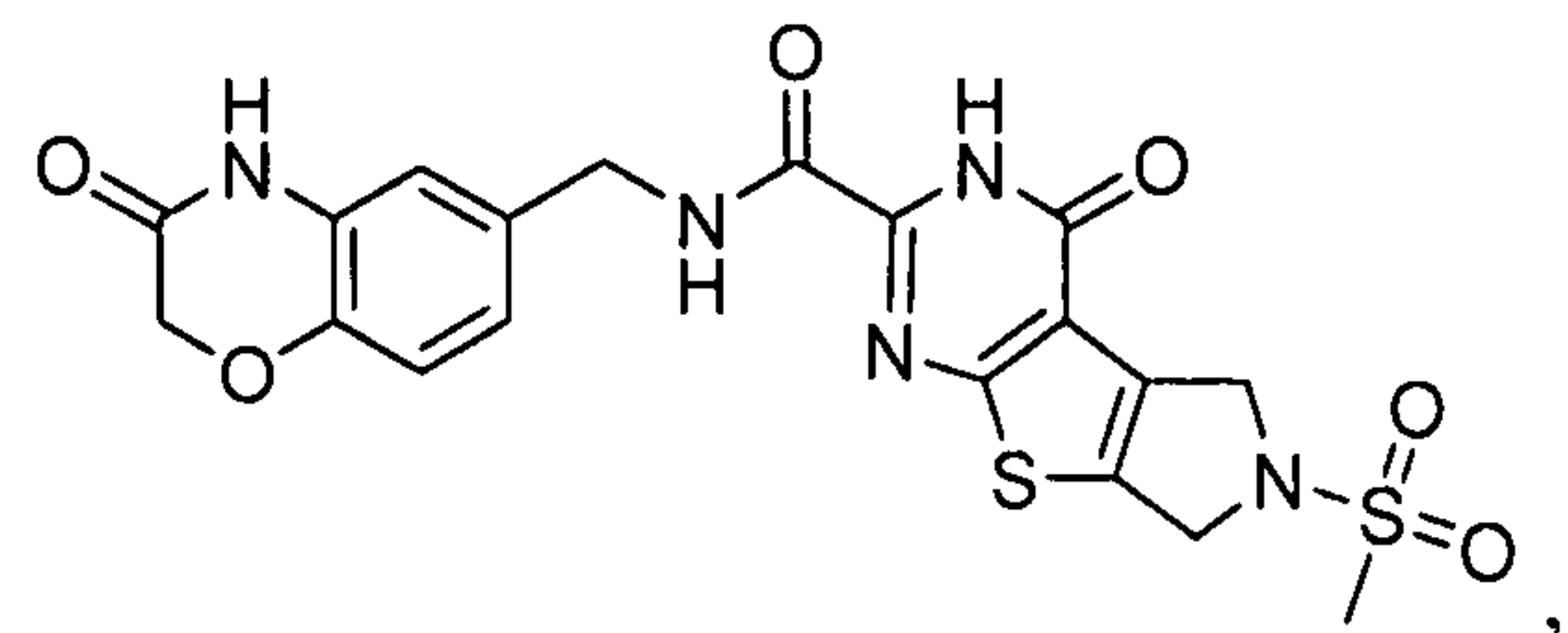


,

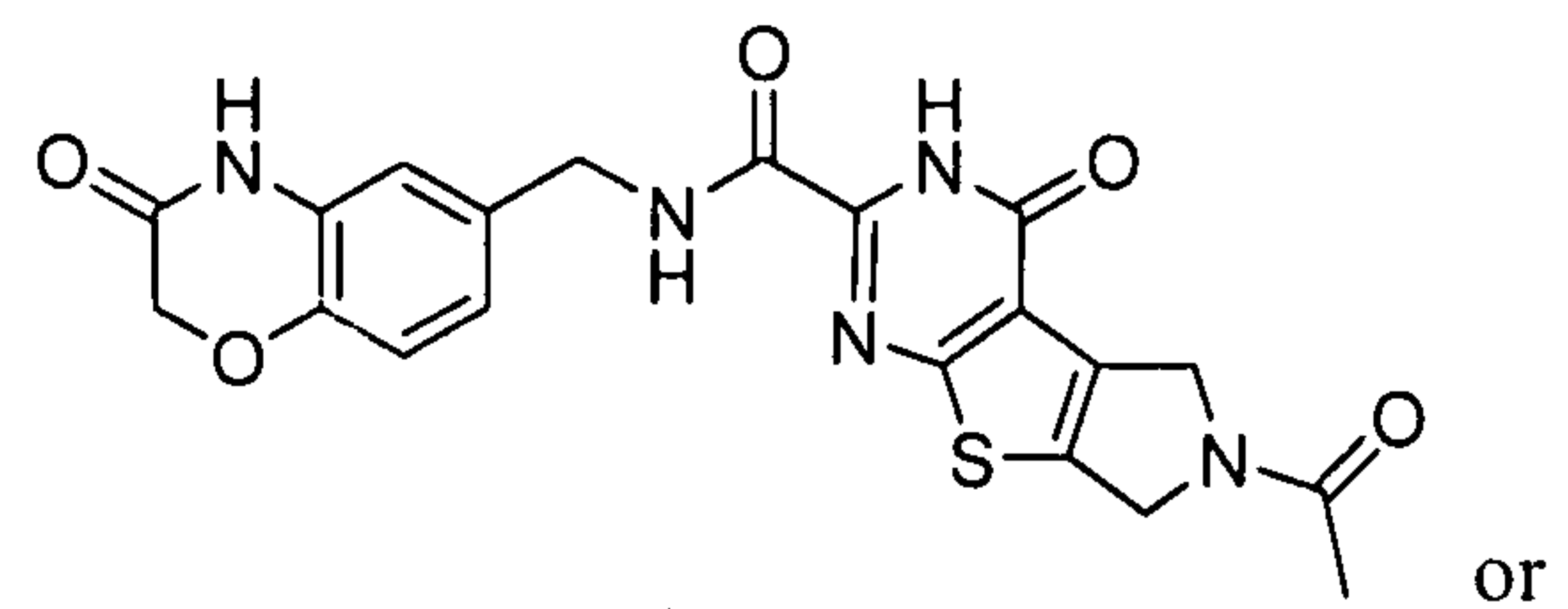


,

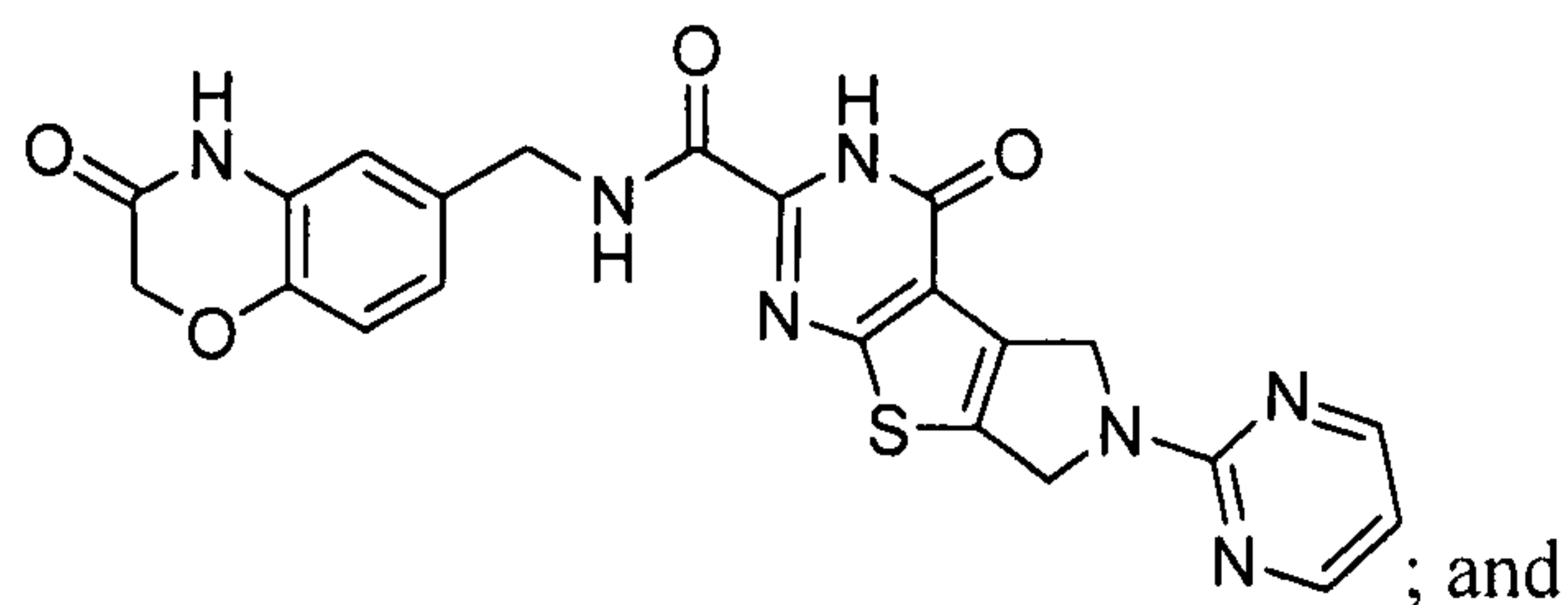
5



,



or



N-oxides, pharmaceutically acceptable salts, prodrugs, formulations, polymorphs, tautomers, racemic mixtures and stereoisomers thereof.

- 5 17. A pharmaceutical composition comprising an effective amount of a compound according to claim 1.
18. The use of a compound according to claim 1 in the manufacture of a medicament for the treatment of a metalloprotease mediated disease.
- 10 19. The use according to claim 18, wherein the disease is selected from rheumatoid arthritis, osteoarthritis, inflammation, atherosclerosis and multiple sclerosis.
20. A pharmaceutical composition comprising:
  - 15 A) an effective amount of a compound selected from: a compound according to claim 1;
  - B) a pharmaceutically acceptable carrier; and
  - C) a drug, agent or therapeutic selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid;
  - 20 (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.