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(71) Applicant: **DERMIRA, INC.** [US/US]; 275 Middlefield Road, Suite 150, Menlo Park, California 94025 (US).

(72) Inventors: **CEVIKBAS, Ferda**; c/o Dermira, Inc., 275 Middlefield Road, Suite 150, Menlo Park, California 94025 (US). **PEARSON, Christopher**; c/o Dermira, Inc., 275 Middlefield Road, Suite 150, Menlo Park, California 94025 (US). **GLEAVE, Laura**; c/o Dermira, Inc., 275 Middlefield Road, Suite 150, Menlo Park, California 94025 (US). **URSINYOVA, Nina Connelly**; c/o Dermira, Inc., 275 Middlefield Road, Suite 150, Menlo Park, California 94025 (US).

(74) Agent: **TSIMARAS, Michael J.**; 75 Main Street, Suite 203, Millburn, New Jersey 07041 (US).

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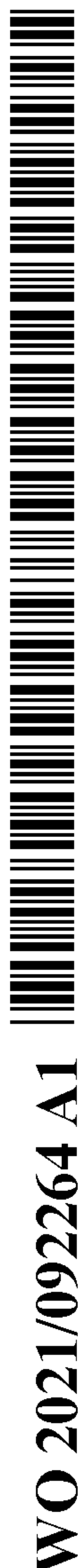
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(54) Title: MrgprX2 ANTAGONISTS AND USES THEREOF

(57) Abstract: The present disclosure is directed to use of MrgprX2 antagonists in the treatment of inflammatory disorders, e.g., inflammatory disorders of the skin. This invention is also directed to pharmaceutical compositions comprising a MrgprX2 antagonist and a pharmaceutically acceptable carrier for topical or oral administration.



MrgprX2 ANTAGONISTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Application Serial Nos. 62/931,186, filed on November 5, 2019, 62/931,576, filed on November 6, 2019, and 63/046,481, filed on June 30, 2020, the contents of each of which are hereby incorporated by reference in their entireties.

BACKGROUND

[0001] Atopic dermatitis (AD) is the most common inflammatory skin disease with an overall prevalence of 6% in adults in the US, and 1-3% of adults and 15-20% of children worldwide. 17.8 million Americans suffer from AD. The disease onset is typically in childhood, and skin manifestations are visible by the age of 1 year in 60% of the patients. Clinical manifestations are erythematous papules and plaques, oozing, crust, hypopigmentation and lichenification. The hallmark symptom of AD, however, is intense chronic itch that persists more than 6 weeks. Despite high prevalence of chronic itch in AD patients, there is no effective first-line treatment available with a good safety profile. Itch has a significant impact on the quality of life of these patients, including sleep impairment, ultimately leading to poor performance at work or school. Health-related quality of life in children is inversely correlated with the severity of the disease. Sleep is affected by persisting nocturnal pruritus.

[0002] Oral anti-histamines provide modest symptomatic relief due to their sedative effects without directly altering pruritus. Topical calcineurin inhibitors (TCI) as well as topical corticosteroids (TCS) might be helpful in reducing the pruritus. However, their adverse effects (skin atrophy, hypopigmentation, and telangiectasia in case of TCS, and the black box warning on TCI regarding skin cancer malignancies) makes them a less preferable treatment option for chronic use, particularly for young children. Hence there is a medical need to find new treatment options for itch is very high among patients and their families. In addition, relief of the chronic itch will disturb the itch-scratch cycle, which has secondary beneficial effects such as improving the skin barrier and may lead to improvement in skin lesions and erythema.

[0003] Finding both a cure and effective treatments for chronic itch in AD has been a significant challenge. Histamine is not a major pruritogen in AD, and thus histamine-blocking agents only work in AD patients through their sedative effects, particularly for nocturnal itch.

Proteases that are released from immune and skin cells of AD patients and act on GPCRs have been investigated as major pruritogenic contributors in AD. Cathepsin S has been described in the literature as a highly pro-inflammatory and itch-triggering protease. Overexpression of Cathepsin S results in an AD phenotype in mice with severe chronic itch. Recently, one group reported that Cathepsin S evokes itch via MrgprX2. Nevertheless, knowledge is limited regarding the key itch mediators in AD, although several have been identified and postulated to play a role.

[0004] Another pruritogenic neuropeptide is Substance P, released by neuronal and non-neuronal dermal cells, is a pro-inflammatory and vasoactive neuropeptide that also acts as a pruritogen. Hence, targeting its cognate receptor NK1 was considered as an ideal therapeutic approach and has been pursued with aprepitant. However, despite pre-clinical data in mice, the NK1R antagonist aprepitant failed to significantly block itch in humans.

[0005] MrgprX2 is a promising target due to its promiscuous ligand binding properties to various pruritic mediators. Multiple pruritic mediators known or speculated to be relevant players in the pathogenesis of AD appear to bind MrgprX receptor rather than the cognate receptors.

[0006] There is an unmet need for effective treatments for AD, and its symptoms. This invention is directed to this, as well as to other important ends.

SUMMARY

[0007] Described herein are topical and oral compositions comprising MrgprX2 antagonists and methods for using the MrgprX2 antagonists for the treatment of inflammatory conditions such as AD.

[0008] Therefore, in a first aspect, the present disclosure provides for compounds that are MrgprX2 antagonists.

[0009] In a second aspect, the present disclosure provides for topical and oral compositions comprising a MrgprX2 antagonist, and a pharmaceutically acceptable excipient.

[0010] In a third aspect, the present disclosure provides for a method for treating an inflammatory disorder, the method comprising administering to a subject in need thereof a topical or oral composition having a therapeutically effective amount of a MrgprX2 antagonist (e.g. a MrgprX2 antagonist according to the present disclosure); and a dermatologically or orally acceptable excipient.

[0011] In a fourth aspect, the present disclosure provides a method for reducing inflammation in mammalian skin, the method comprising administering to the mammalian skin an effective amount of a topical or oral composition including an MrgprX2 antagonist (e.g. a MrgprX2 antagonist according to the present disclosure) and a dermatologically or orally acceptable excipient to a subject in need thereof.

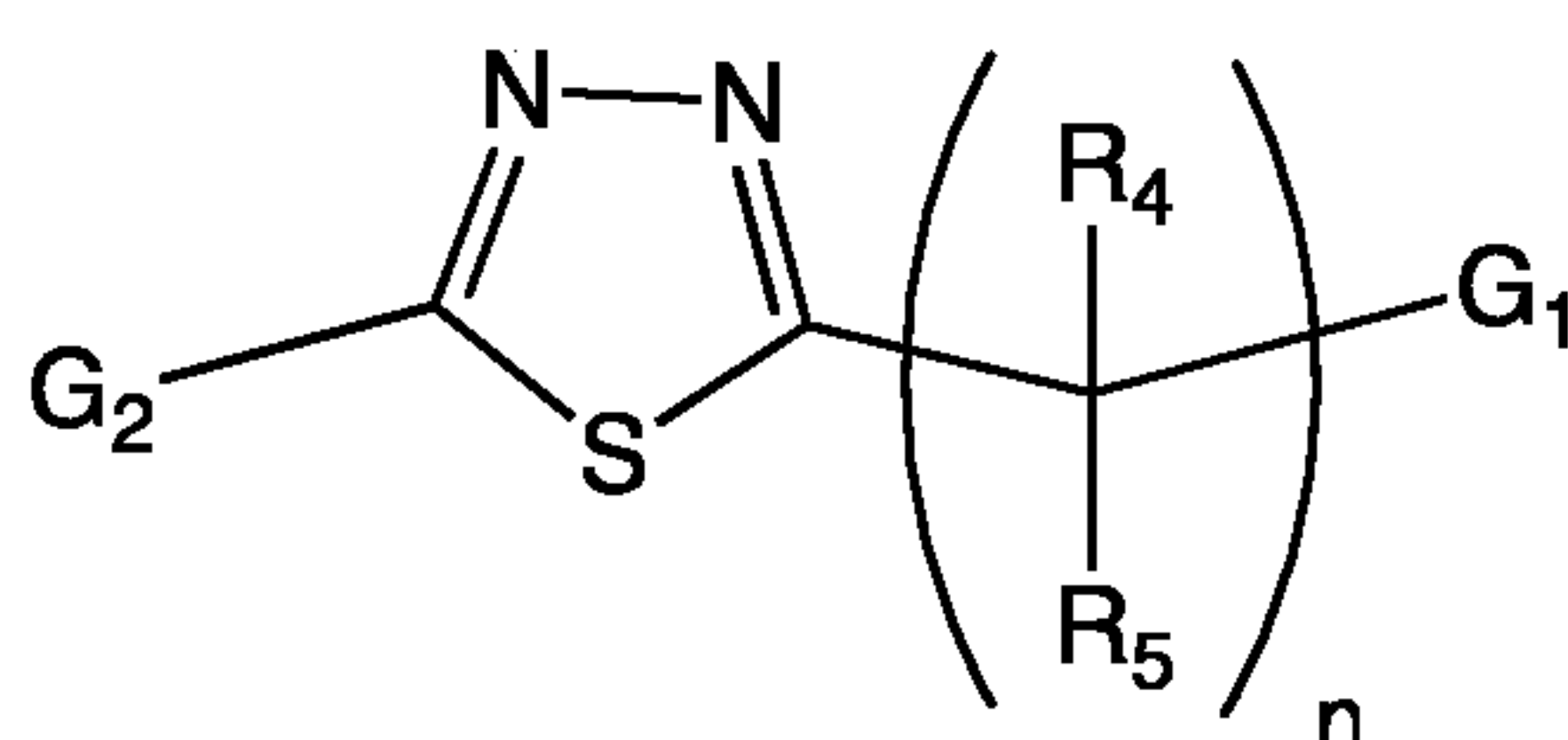
[0012] In a fifth aspect, the present disclosure provides a method for reducing the incidence of or severity of itch in a subject in need thereof, the method comprising administering a therapeutically effective amount of a topical or oral composition including a MrgprX2 antagonist (e.g. a MrgprX2 antagonist according to the present disclosure) to a subject in need thereof.

DETAILED DESCRIPTION

[0013] Provided herein are topical or oral compositions for treating inflammatory conditions, e.g., skin disorders characterized by inflammation. In particular, the pharmaceutical compositions include compounds that are antagonists of the Mas-related G protein-coupled receptor MrgprX2.

MrgprX2 Antagonists for use in the compositions and methods of the present disclosure

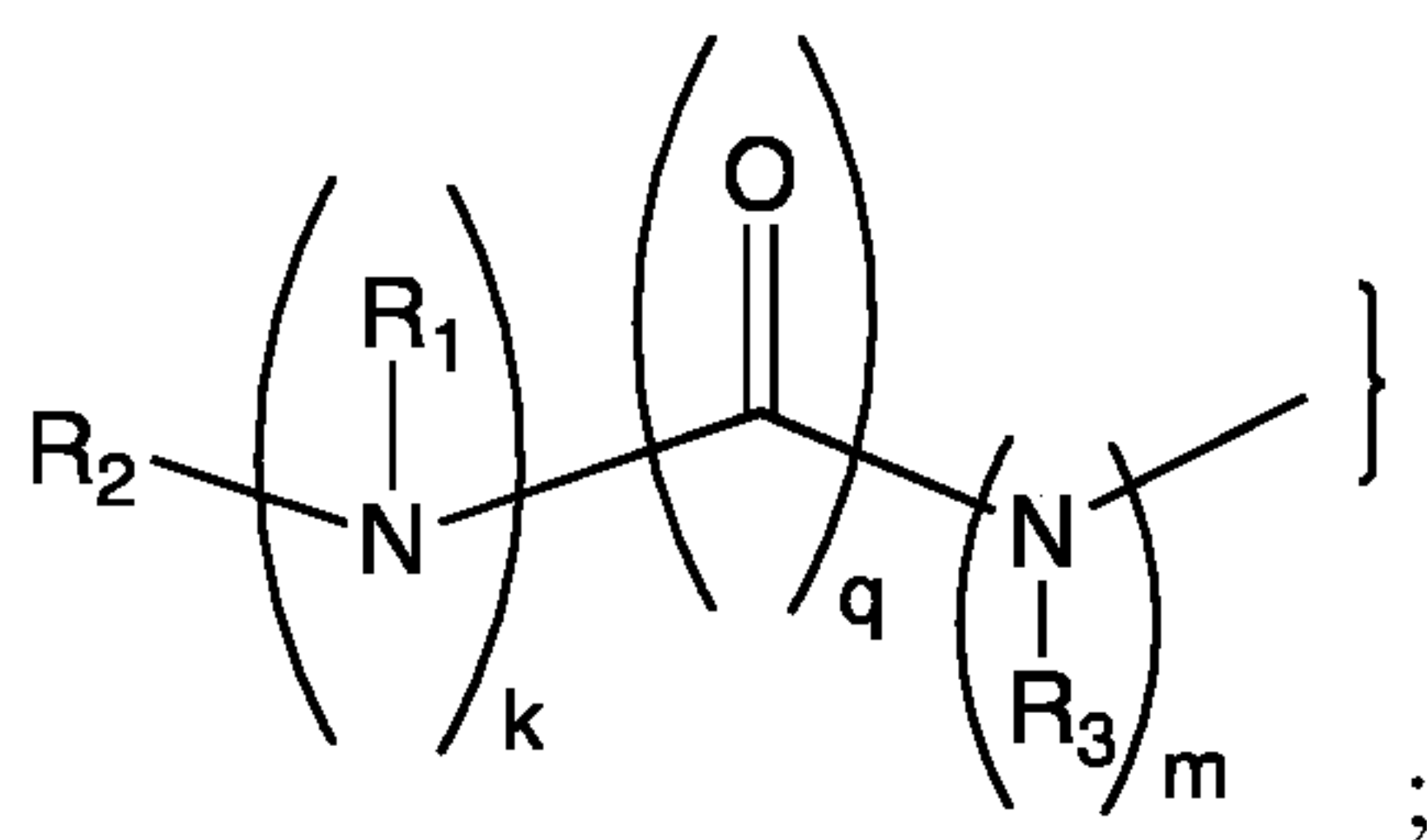
[0014] In several embodiments, the present disclosure provides for a Compound [Compound 1] that is a MrgprX2 antagonist having the Formula I:



Formula I

wherein:

G₂ is



q is 0 or 1;

m is 0 or 1;

n is 0, 1 or 2;

k is 0 or 1;

provided that k, q and m are not all 0;

provided that q is not 0 when m and k are each 1;

R₁ and R₂ are each independently H, C₁₋₆ alkyl; C₃₋₆ cycloalkyl; 5-10 member heterocycloalkyl having 1-3 ring heteroatoms independently selected from N, O and S; wherein each C₁₋₆ alkyl, C₃₋₆ cycloalkyl and 5-10 member heterocycloalkyl is optionally substituted with 1 to 3 R₂₀ groups;

provided that R₁ and R₂ are not simultaneously H;

each R₂₀ is independently selected from 1) hydroxy, 2) cyano, 3) C₁₋₃ alkyl, 4) C₁₋₃ alkoxy, 5) C₁₋₃ haloalkyl, 6) halogen, 7) C₁₋₃ alkyl, 8) C₃₋₆ cycloalkyl optionally substituted with 1-3 substituents selected from hydroxy, cyano, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and halogen, and 9) 5-10 member heterocycloalkyl having 1-3 ring heteroatoms independently selected from N, O and S optionally substituted with 1-3 substituents selected from hydroxy, cyano, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and halogen;

or R₁ and R₂ together with the nitrogen atom to which they are attached can form a 5 or 6 member saturated, partially unsaturated or aromatic heterocycle having 1-3 ring heteroatoms independently selected from N, O and S, which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, cyano and halogen;

R₃ is H or C₁₋₃ alkyl;

each R₄ and R₅ is independently H or C₁₋₃ alkyl;

G₁ is C₆₋₁₀ aryl; C₃₋₇ cycloalkyl; C₁₋₃ haloalkyl; C₁₋₃ alkyl and 5-10 member heteroaryl having 1-3 ring heteroatoms independently selected from N, O and S; wherein each of the C₆₋₁₀ aryl, C₃₋₇ cycloalkyl, C₁₋₃ haloalkyl and 5-10 member heteroaryl is optionally substituted with 1, 2 or 3 independently selected R₃₀ groups;

each R₃₀ is independently selected from halogen, cyano, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy optionally substituted with halogen, and hydroxy;

or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.

[0015] The present disclosure further provides compounds as follows:

- 1.1 Compound 1, wherein G₁ is optionally substituted C₆₋₁₀ aryl;
- 1.2 Compound 1, wherein G₁ is optionally substituted phenyl;
- 1.3 Compound 1 wherein G₁ is optionally substituted pyridyl;
- 1.4 Compound 1 wherein G₁ is optionally substituted C₃₋₆ cycloalkyl;
- 1.5 Compound 1 wherein G₁ is optionally substituted cyclopropyl or cyclohexyl;
- 1.6 Compound 1, wherein G₁ is phenyl optionally having one or two substituents;
- 1.7 Compound 1, wherein G₁ is phenyl optionally having one or two substituents;
- 1.8 Compound 1, wherein G₁ is phenyl substituted in the 3-position;
- 1.9 Compound 1, wherein G₁ is phenyl substituted in the 3-position and the 5-position;
- 1.10 Compound 1, wherein G₁ is phenyl substituted in the 2-position and the 5-position;
- 1.11 Compound 1, wherein G₁ is phenyl substituted in the 2-position and the 4-position;
- 1.12 Compound 1, wherein G₁ is phenyl substituted in the 2-position and the 3-position;
- 1.13 Compound 1, wherein G₁ is phenyl substituted in the 3-position and the 4-position;
- 1.14 Any of the preceding compounds, wherein each R₃₀ is independently selected from mono-, di- or trihalomethyl, fluorine, chlorine, methoxy, cyano and methyl;
- 1.15 Any of the preceding compounds, wherein each R₃₀ is independently selected from difluoromethyl, trifluoromethyl, fluorine, chlorine, methoxy, cyano and methyl;
- 1.16 Any of the preceding compounds, wherein each R₃₀ is independently selected from fluorine and chlorine;
- 1.17 Any of the preceding compounds, wherein each R₃₀ is fluorine;
- 1.18 Compound 1 wherein G₁ is C₁₋₃ haloalkyl;

- 1.19 Compound 1 wherein G_1 is trifluoromethyl;
- 1.20 Any of the preceding compounds, wherein n is 1;
- 1.21 Any of the preceding compounds, wherein n is 2;
- 1.22 Any of the preceding compounds, wherein m , k and q are each 1;
- 1.23 Any of the preceding compounds, wherein q and m are each 1, and k is 0;
- 1.24 Any of the preceding compounds, wherein m is 0; and k and q are each 1;
- 1.25 Any of the preceding compounds, wherein k is 0; and m and q are each 1;
- 1.26 Any of the preceding compounds, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups;
- 1.27 Any of the preceding compounds, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups independently selected from hydroxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, methoxy, halogen and cyano;
- 1.28 Any of the preceding compounds, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, cyano and halogen;
- 1.29 Any of the preceding compounds, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, cyano and halogen;
- 1.30 Any of the preceding compounds, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a C_{1-3} alkyl substituted with a ring selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine, tetrahydropyran, and C_{3-6} cycloalkyl, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, cyano and halogen;
- 1.31 Any of the preceding compounds, wherein R_1 and R_2 together with the nitrogen atom to which they are attached form a heterocycle selected from pyrrolidine,

tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, cyano and halogen;

- 1.32 Any of the preceding compounds, wherein the compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.

[0016] Also provided in accordance with the present disclosure is a topical or oral composition [Composition 1] comprising a MrgprX2 antagonist and a dermatologically or orally acceptable excipient. In some embodiments, the MrgprX2 antagonist is Compound I, having Formula I described above.

[0017] The present disclosure further provides compositions as follows:

- 1.1 Composition 1, wherein the MrgprX2 antagonist is Compound I, having Formula I described above;
- 1.2 Composition 1, wherein G₁ is optionally substituted C₆₋₁₀ aryl;
- 1.3 Composition 1, wherein G₁ is optionally substituted phenyl;
- 1.4 Composition 1 wherein G₁ is optionally substituted pyridyl;
- 1.5 Composition 1 wherein G₁ is optionally substituted C₃₋₆ cycloalkyl;
- 1.6 Composition 1 wherein G₁ is optionally substituted cyclopropyl or cyclohexyl;
- 1.7 Composition 1, wherein G₁ is phenyl optionally having one or two substituents;
- 1.8 Composition 1, wherein G₁ is phenyl optionally having one or two substituents;
- 1.9 Composition 1, wherein G₁ is phenyl substituted in the 3-position;
- 1.10 Composition 1, wherein G₁ is phenyl substituted in the 3-position and the 5-position;
- 1.11 Composition 1, wherein G₁ is phenyl substituted in the 2-position and the 5-position;
- 1.12 Composition 1, wherein G₁ is phenyl substituted in the 2-position and the 4-position;
- 1.13 Composition 1, wherein G₁ is phenyl substituted in the 2-position and the 3-position;
- 1.14 Composition 1, wherein G₁ is phenyl substituted in the 3-position and the 4-position;
- 1.15 Any of the preceding compositions, wherein each R₃₀ is independently selected from mono-, di- or trihalomethyl, fluorine, chlorine, methoxy, cyano and methyl;
- 1.16 Any of the preceding compositions, wherein each R₃₀ is independently selected from difluoromethyl, trifluoromethyl, fluorine, chlorine, methoxy, cyano and methyl;
- 1.17 Any of the preceding compositions, wherein each R₃₀ is independently selected from

fluorine and chlorine;

- 1.18 Any of the preceding compositions, wherein each R_{30} is fluorine;
- 1.19 Composition 1 wherein G_1 is C_{1-3} haloalkyl;
- 1.20 Composition 1 wherein G_1 is trifluoromethyl;
- 1.21 Any of the preceding compositions, wherein n is 1;
- 1.22 Any of the preceding compositions, wherein n is 2;
- 1.23 Any of the preceding compositions, wherein m , k and q are each 1;
- 1.24 Any of the preceding compositions, wherein q and m are each 1, and k is 0;
- 1.25 Any of the preceding compositions, wherein m is 0; and k and q are each 1;
- 1.26 Any of the preceding compositions, wherein k is 0; and m and q are each 1;
- 1.27 Any of the preceding compositions, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups;
- 1.28 Any of the preceding compositions, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups independently selected from hydroxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, methoxy, halogen and cyano;
- 1.29 Any of the preceding compositions, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, cyano and halogen;
- 1.30 Any of the preceding compositions, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, cyano and halogen;
- 1.31 Any of the preceding compositions, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a C_{1-3} alkyl substituted with a ring selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine, tetrahydropyran, and C_{3-6} cycloalkyl, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or

- trifluoromethyl, cyano and halogen;
- 1.32 Any of the preceding compositions, wherein R₁ and R₂ together with the nitrogen atom to which they are attached form a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, cyano and halogen;
- 1.33 Any of the preceding compounds, wherein the compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.
- 1.34 Any of the preceding compositions, wherein the composition is in an oral dosage form.
- 1.35 Any of the preceding compositions, wherein the composition is in the form of a cream, a gel, a spray or an ointment.
- 1.36 Any of the preceding compositions, wherein the MrgprX2 antagonist is present at a concentration of about 0.001 wt.% to about 10 wt.%, based on the total weight of the composition.
- 1.37 Any of the preceding compositions, wherein the MrgprX2 antagonist is present at a concentration of about 0.1 wt.% to about 5 wt.%, based on the total weight of the composition.
- 1.38 Any of the preceding compositions, further comprising a skin absorption enhancer.
- 1.39 Any of the preceding compositions, further comprising a skin absorption enhancer comprising one or more of mannitol, sulphoxides (e.g., dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (e.g., 2-pyrrolidone, 2P), alcohols and alkanols (e.g., ethanol, or decanol), glycols (e.g., propylene glycol, hexylene glycol, polyoxyethylene glycol, diethylene glycol), surfactants (also common in dosage forms) and terpenes.
- 1.40 Any of the preceding compositions, wherein the composition is applied to a patient's skin once daily.
- 1.41 Any of the preceding compositions, wherein the composition is applied to a patient's skin twice daily.
- 1.42 Any of the preceding compositions, wherein the composition is applied to a patient's

skin three times daily.

- 1.43 Any of the preceding compositions, wherein the composition is administered to a patient suffering from an inflammatory disorder.
- 1.44 The preceding composition, wherein the inflammatory disorder is a disorder of the skin.
- 1.45 The preceding composition, wherein the skin is human skin.
- 1.46 Any of compositions 1.64-1.66, wherein the inflammatory disorder activates or is consequent to activation, of MrgprX2.
- 1.47 The preceding composition, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, drug-adverse reactions.
- 1.48 Any of compositions 1.63-1.67, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis).
- 1.49 Any of compositions 1.63-1.66, wherein the inflammatory disorder is atopic dermatitis.
- 1.50 Any of the preceding compositions, wherein the subject is a human.
- 1.51 Any of the preceding compositions, wherein the mammalian skin is human skin.
- 1.52 Any one of the preceding compositions, wherein the composition is for oral administration.

[0018] As used herein, “topical composition” refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammalian skin, e.g., human skin. Such a medium includes all dermatologically acceptable carriers, diluents or excipients therefor.

[0019] “Stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[0020] “Solvate” refers to a form of a compound complexed by solvent molecules.

[0021] “Tautomers” refers to two molecules that are structural isomers that readily interconvert.

[0022] “Pharmaceutically acceptable salt” includes both acid and base addition salts.

[0023] “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

[0024] “Pharmaceutically acceptable base addition salt” refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine,

ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[0025] The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centres and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallisation. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC).

[0026] “Dermatologically acceptable excipient” includes without limitation any adjuvant, carrier, vehicle, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier, including those approved by the United States Food and Drug Administration as being acceptable for dermatological use on humans or domestic animals, or which are known, or are suitable for use in dermatological compositions.

[0027] “Optional” or “optionally” means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. When a functional group is described as “optionally substituted,” and in turn, substituents on the functional group are also “optionally substituted” and so on, for the purposes of this invention, such iterations are limited to three.

[0028] The term “alkyl” is intended to mean a straight or branched carbon radical containing the indicated number of carbon atoms. Some embodiments contain 1 to 5 carbons. Some

embodiments contain 1 to 4 carbons. Some embodiments contain 1 to 3 carbons. Some embodiments contain 1 or 2 carbons. Examples of alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, pentyl, isopentyl, *t*-pentyl, neopentyl, 1-methylbutyl [*i.e.*, -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [*i.e.*, -CH₂CH(CH₃)CH₂CH₃], *n*-hexyl, and the like.

[0029] The term “cycloalkyl” is intended to mean a saturated ring radical containing the indicated number of carbon atoms. Some embodiments contain 3 to 6 carbons. Some embodiments contain 3 to 5 carbons. Some embodiments contain 5 to 7 carbons. Some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[0030] The term “haloalkyl” is intended to mean a radical comprising an alkyl group having the indicated number of carbon atoms, substituted with one or more halogens. For example, C₁-C₆ haloalkyl may be fully substituted in which case it can be represented by the formula C_nL_{2n+1}, wherein L is a halogen and “n” is 1, 2, 3, 4, 5 or 6. When more than one halogen is present then they may be the same or different and selected from: fluorine, chlorine, bromine, and iodine. In some embodiments, haloalkyl contains 1 to 5 carbons. In some embodiments, haloalkyl contains 1 to 4 carbons. In some embodiments, haloalkyl contains 1 to 3 carbons. In some embodiments, haloalkyl contains 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, and the like. When used without a prefix indicating the number of halo substituents, “haloalkyl” groups contain 1, 2 or 3 halogen atoms.

[0031] The term “hydroxyalkyl” is intended to mean a radical comprising an alkyl group having the indicated number of carbon atoms, substituted with one or more hydroxy (*i.e.*, -OH) groups. When used without a prefix indicating the number of hydroxy substituents, “hydroxyalkyl” groups contain 1, 2 or 3 hydroxy groups.

[0032] The term “halogen” is intended to mean to a fluoro, chloro, bromo or iodo group.

[0033] The term “aryl” is intended to mean a ring system containing 6 to 10 carbon atoms, that may contain a single ring or two fused rings, and wherein at least one ring is aromatic. Examples include phenyl, indanyl, and naphthyl.

[0034] The term “heteroaryl” is intended to mean a ring system containing 5 to 14 ring atoms, that may contain a single ring, two fused rings or three fused rings, and wherein at least

one ring is aromatic and at least one ring atom is a heteroatom selected from, for example: O, S and N. Some embodiments contain 5 to 6 ring atoms for example furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, and the like. Some embodiments contain 8 to 14 ring atoms for example quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1*H*-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, isobenzofuran, 2,3-dihydrobenzofuranyl, 4*H*-benzo[1,3]dioxinyl, 3,4-dihydro-1*H*-isoquinolinyl, 1,4,6,7-tetrahydro-imidazo[4,5-*c*]pyridinyl, 7,8-dihydro-5*H*-[1,6]naphthyridinyl, 5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazinyl, benzo[1,3]dioxolyl, pyrazolo[1,5-*a*]pyrimidinyl, 1,2,3,4-tetrahydroquinolinyl, and the like.

[0035] The term “cyano” means a -CN group.

[0036] The term “alkoxy” means a group of formula -O-alkyl, having the indicated number of carbon atoms.

[0037] As used herein the term “heterocycloalkyl” is intended to mean a non-aromatic 3-6-membered heterocyclic ring optionally fused to a 3-6 member saturated, partially unsaturated, or aromatic aryl or heteroaryl ring. Examples non-aromatic 3-6-membered heterocyclic rings include oxirane, azinidine, oxetane, tetrahydrofuran, pyrrolidine, piperidine, tetrahydropyran, morpholine, piperazine, hexahydropyrimidine, hexahydropyridazine, and the like.

Heterocycloalkyl groups can contain one or more oxo (i.e. -C=O-) groups within the ring, and sulfur ring heteroatoms can be present as sulfur diones. Examples of such heterocycloalkyl rings include sulfolane, tetrahydro-2*H*-thiopyran-1,1,-dione, thiomorpholine 1,1-dioxide, 2-pyrrolidione, piperidin-2-one, piperazine-2-one, morpholine -3-one, and the like. Examples of heterocycloalkyls having a fused ring include dihydroindoles such as 1,3 dihydroindole.

[0038] The term “spiroalkyl” is intended to mean a structure of two or more rings in which two of the rings share one common atom, and wherein at least one of the rings is a cycloalkyl ring, containing the indicated number of carbon atoms. Examples include spirocyclopropane and spirocyclobutane.

Methods of Using the Compounds of the Invention

[0039] The Compounds of the Invention are useful in the treatment of inflammatory disorders, e.g., atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, and drug-adverse reactions. Therefore, administration or use of a preferred MrgprX2 antagonist as described herein, e.g., a MrgprX2 antagonist as hereinbefore described, e.g., a Compound of Formula I, provides a means to ameliorate symptoms of, and/or provide treatment for, various inflammatory diseases and disorders.

[0040] For example, in one embodiment the present disclosure provides for a method [Method 1] for treating an inflammatory disorder, the method comprising administering to a subject in need thereof a topical or oral composition comprising a therapeutically effective amount of a MrgprX2 antagonist (e.g. a MrgprX2 antagonist according to the present disclosure); and a dermatologically or orally acceptable excipient.

[0041] The present disclosure further provides further embodiments of Method 1 as follows:

- 1.1 Method 1, wherein the MrgprX2 antagonist is a compound according to Formula I described above;
- 1.2 Method 1.1, wherein the MrgprX2 antagonist is a compound according to any of Compounds 1.1-1.55 described above;
- 1.3 Any of the preceding methods, wherein the MrgprX2 antagonist is a compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof;
- 1.4 Any of the preceding methods, wherein the composition is in the form of a cream, a gel, a spray or an ointment.
- 1.5 Any of the preceding methods, wherein the MrgprX2 antagonist is present at a concentration of about 0.001 wt.% to about 10 wt.%, based on the total weight of the composition.
- 1.6 Any of the preceding methods, wherein the MrgprX2 antagonist is present at a concentration of about 0.1 wt.% to about 5 wt.%, based on the total weight of the composition.
- 1.7 Any of the preceding methods, further comprising a skin absorption enhancer.

- 1.8 Any of the preceding methods, further comprising a skin absorption enhancer comprising one or more of mannitol, sulphoxides (e.g., dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (e.g., 2-pyrrolidone, 2P), alcohols and alkanols (e.g., ethanol, or decanol), glycols (e.g., propylene glycol, hexylene glycol, polyoxyethylene glycol, diethylene glycol), surfactants (also common in dosage forms) and terpenes.
- 1.9 Any of the preceding methods, wherein the composition is applied to a patient's skin once daily.
- 1.10 Any of the preceding methods, wherein the composition is applied to a patient's skin twice daily.
- 1.11 Any of the preceding methods, wherein the composition is applied to a patient's skin three times daily.
- 1.12 Any of the preceding methods, wherein the composition is administered to a patient suffering from an inflammatory disorder.
- 1.13 The preceding methods, wherein the inflammatory disorder is a disorder of the skin.
- 1.14 The preceding methods, wherein the skin is human skin.
- 1.15 Any of methods 1.12-1.14, wherein the inflammatory disorder activates or is consequent to activation, of MrgprX2.
- 1.16 The preceding methods, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, or drug-adverse reactions.
- 1.17 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis).
- 1.18 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis.
- 1.19 Any of the preceding methods, wherein the subject is a human.
- 1.20 Any of the preceding methods, wherein the mammalian skin is human skin.
- 1.21 Any of the preceding methods, wherein the composition is for oral administration.

[0042] In another embodiment, the present disclosure provides a method [Method 2] for reducing inflammation in mammalian skin, the method comprising administering to the mammalian skin an effective amount of a topical or oral composition including a MrgprX2 antagonist according to the present disclosure and a dermatologically acceptable excipient to a subject in need thereof.

[0043] The present disclosure further provides further embodiments of Method 2 as follows:

- 2.1 Method 2, wherein the MrgprX2 antagonist is a compound according to Formula I described above;
- 2.2 Method 2 or 2.1, wherein the MrgprX2 antagonist is a compound according to any of Compounds 1.1-1.55 described above;
- 2.3 Any of the preceding methods, wherein the MrgprX2 antagonist is a compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof;
- 2.4 Any of the preceding methods, wherein the inflammation is consequent to activation of MrgprX2;
- 2.5 Any of the preceding methods, wherein the composition is in the form of a cream, a gel, a spray or an ointment.
- 2.6 Any of the preceding methods, wherein the MrgprX2 antagonist is present at a concentration of about 0.001 wt.% to about 10 wt.%, based on the total weight of the composition.
- 2.7 Any of the preceding methods, wherein the MrgprX2 antagonist is present at a concentration of about 0.1 wt.% to about 5 wt.%, based on the total weight of the composition.
- 2.8 Any of the preceding methods, further comprising a skin absorption enhancer.
- 2.9 Any of the preceding methods, further comprising a skin absorption enhancer comprising one or more of mannitol, sulphoxides (e.g., dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (e.g., 2-pyrrolidone, 2P), alcohols and alkanols (e.g., ethanol, or decanol), glycols (e.g., propylene glycol, hexylene glycol, polyoxyethylene glycol, diethylene glycol), surfactants (also common in dosage forms) and terpenes.
- 2.10 Any of the preceding methods, wherein the composition is applied to a patient's skin

once daily.

- 2.11 Any of the preceding methods, wherein the composition is applied to a patient's skin twice daily.
- 2.12 Any of the preceding methods, wherein the composition is applied to a patient's skin three times daily.
- 2.13 Any of the preceding methods, wherein the composition is administered to a patient suffering from an inflammatory disorder.
- 2.14 The preceding methods, wherein the inflammatory disorder is a disorder of the skin.
- 2.15 The preceding methods, wherein the skin is human skin.
- 2.16 Any of methods 1.12-1.14, wherein the inflammatory disorder activates or is consequent to activation, of MrgprX2.
- 2.17 The preceding methods, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, or drug-adverse reactions.
- 2.18 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis).
- 2.19 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis.
- 2.20 Any of the preceding methods, wherein the subject is a human.
- 2.21 Any of the preceding methods, wherein the mammalian skin is human skin.
- 2.22 Any of the preceding methods, wherein the composition is for oral administration.

[0044] A further embodiment provides a method [Method 3] for reducing the incidence of or severity of itch, the method comprising administering to the mammalian skin a therapeutically effective amount of a topical or oral composition according to any of Compositions 1 and 1.1-1.73.

[0045] The present disclosure further provides further embodiments of Method 3 as follows:

- 3.1 Method 3, wherein the severity of itch is reduced within 5 minutes of administration.
- 3.2 Method 3 or 3.1, wherein the severity of itch is reduced for a period of 6 hours from administration.
- 3.3 Method 3 or 3.1, wherein the severity of itch is reduced for a period of 12 hours from

- administration.
- 3.4 Method 3 or 3.1, wherein the severity of itch is reduced for a period of 18 hours from administration.
- 3.5 Method 3 or 3.1, wherein the severity of itch is reduced for a period of 24 hours from administration.
- 3.6 Any of the preceding methods, wherein the MgrprX2 antagonist is a compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.
- 3.7 Any of the preceding methods, wherein the composition is in the form of a cream, a gel, a spray or an ointment.
- 3.8 Any of the preceding methods, wherein the MgrprX2 antagonist is present at a concentration of about 0.001 wt.% to about 10 wt.%, based on the total weight of the composition.
- 3.9 Any of the preceding methods, wherein the MgrprX2 antagonist is present at a concentration of about 0.1 wt.% to about 5 wt.%, based on the total weight of the composition.
- 3.10 Any of the preceding methods, further comprising a skin absorption enhancer.
- 3.11 The preceding method, wherein the skin absorption enhancer comprises one or more of mannitol, sulphoxides (e.g., dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (e.g., 2-pyrrolidone, 2P), alcohols and alkanols (e.g., ethanol, or decanol), glycols (e.g., propylene glycol, hexylene glycol, polyoxyethylene glycol, diethylene glycol), surfactants (also common in dosage forms) and terpenes.
- 3.12 Any of the preceding methods, wherein the composition is applied to a patient's skin once daily.
- 3.13 Any of the preceding methods, wherein the composition is applied to a patient's skin twice daily.
- 3.14 Any of the preceding methods, wherein the composition is applied to a patient's skin three times daily.
- 3.15 Any of the preceding methods, wherein the composition is administered to a patient suffering from an inflammatory disorder.

- 3.16 Any of the preceding methods, wherein the inflammatory disorder is a disorder of the skin.
- 3.17 Any of the preceding methods, wherein the skin is human skin.
- 3.18 Any of methods 1.12-1.14, wherein the inflammatory disorder activates or is consequent to activation, of MrgprX2.
- 3.19 The preceding methods, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, or drug-adverse reactions.
- 3.20 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis).
- 3.21 Any of methods 1.12-1.16, wherein the inflammatory disorder is atopic dermatitis.
- 3.22 Any of the preceding methods, wherein the subject is a human.
- 3.23 Any of the preceding methods, wherein the mammalian skin is human skin.
- 3.24 Any of the preceding methods, wherein the composition is for oral administration.

[0046] “Atopic dermatitis” refers to a skin condition involving chronic inflammation, and symptoms of atopic dermatitis include a red, itchy rash. Atopic dermatitis may be present on the skin of any part of the body, but is common on the hands, feet, upper chest, and in the bends of elbows or knees. Additional symptoms of atopic dermatitis may include small raised bumps or thickened, scaly skin.

[0047] “Psoriasis” is a chronic skin condition related to an overactive immune response. Psoriasis may be present on may be present on the skin of any part of the body. Symptoms of psoriasis include local inflammation, skin flaking, and thick white or red patches of skin.

[0048] “Alopecia” is an autoimmune skin disease, causing hair loss on the scalp, face and sometimes on other areas of the body. In alopecia areata, for example, T cell lymphocytes cluster around affected follicles, causing inflammation and subsequent hair loss.

[0049] “Chronic Urticaria” (Hives) is a common skin rash triggered by many things including certain foods, medications, and stress. Symptoms can include itchy, raised, red, or skin-colored welts on the skin's surface. Given the role of mast cells in chronic idiopathic urticaria, MrgprX2

partakes a key function in the mast cell activation. Antimicrobial host defense peptides, neuropeptides, major basic protein, eosinophil peroxidase, and some FDA-approved peptidergic drugs activate human MrgprX2. Unique features of MrgprX2 that distinguish it from other GPCRs include their presence both on the plasma membrane and intracellular sites and their selective expression in MCs. Furthermore, small-molecule inhibitors of MrgprX2 could benefit the treatment of MC-dependent allergic and inflammatory disorders such as chronic urticaria which is currently treated by targeting the IgE axis of mast cell activity. However, a variety of MC-activity relies on ligand binding to MrgprX2 (Subramanian H et al., 2016, *The Journal of Allergy and Clinical Immunology*, 138(3), 700–710; <https://doi.org/10.1016/j.jaci.2016.04.051>) suggesting that targeting MRGPRX2 might indeed be a treatment option for IgE-independent and resistant chronic urticaria.

[0050] "Anaphylactic Shock" is an extreme, often life-threatening allergic reaction to an antigen to which the body has become hypersensitive. Mast cell activation via MrgprB2 has gained attention for its IgE independent mast cell activation and nonhistaminergic itch (Meixiong J. et al., 2019, *Immunity*, 50(5), 1163–1171.e5. <https://doi.org/10.1016/j.immuni.2019.03.013>). Activation of MrgprB2 by proadrenomedullin N-terminal peptide 9-20 (PAMP9-20) induced the release of multiple bioactive mediators from mast cells which in turn activated itch-sensing neurons suggesting the mast-cell specific MrgprB2 is key in mast-cell degranulation and related non-histaminergic itch. Mast cell MrgprB2 and MrgprX2 are activated by SP, compound 48/80 and pseudoallergy inducing drugs such as icatibant (McNeil, B.D. et al., 2015, *Nature*, 519(7542), 237–241; <https://doi.org/10.1038/nature14022>) placing MrgprX2 at the center stage of non-histaminergic mast cell activation and various allergic and nonallergic diseases as well as pseudoallergic reactions.

[0051] "Rosacea" is condition that causes redness and often small, red, pus-filled bumps on the face. MrgprX2 has also been identified as the receptor for endogenous host defense peptide, including cathelicidin (LL-37) and α -defensin (Subramanian, H. et al., 2011, *The Journal of Biological Chemistry*, 286(52), 44739–44749; <https://doi.org/10.1074/jbc.M111.277152> and Subramanian, H. et al., 2013, *Journal of Immunology (Baltimore, Md. : 1950)*, 191(1), 345–352; <https://doi.org/10.4049/jimmunol.1300023>) raising the possibility that mast-cell MrgprX2 could partake in antimicrobial host defense. Pituitary adenylate cyclase activating peptide (PACAP), an effective mast cell degranulator (Baun, M. et al., 2012, *Cephalalgia : An International Journal of*

Headache, 32(4), 337–345; <https://doi.org/10.1177/0333102412439354> and Seebeck, J. et al., 1998, *Annals of the New York Academy of Sciences*, 865, 141–146. <https://doi.org/10.1111/j.1749-6632.1998.tb11172.x>), has been shown to activate MrgprX2 (Tatemoto K. et al., 2006, *Biochemical and Biophysical Research Communications*, 349(4), 1322–1328; <https://doi.org/10.1016/j.bbrc.2006.08.177>; and McNeil, B.D. et al., 2015, *Nature*, 519(7542), 237–241; <https://doi.org/10.1038/nature14022>). These findings suggest that MrgprX2 may also function in innate immunity by regulating host defense responses. Given that MrgprX2 is activated by peptides such as LL-37 and the neuropeptide PACAP, both of which are crucially involved in rosacea and function as trigger peptides to affect mast cell activity and vasodilation. Together these findings suggest MrgprX2 as an emerging receptor in the pathophysiology of rosacea.

[0052] "Asthma" is a condition in which a person's airways become inflamed, narrow and swell, and produce extra mucus, which makes it difficult to breathe. Mast cells (MC), which also subside in close vicinity with smooth muscle, T cells and leukocytes, are important effector cells in airway hyperresponsiveness and inflammation, a phenomenon characteristic of asthma. Even though in healthy states only low amounts of transcripts are present, the levels of MrgprX2 transcripts increase in severe asthma which is characterized by a phenotypic switch of MCTC from MCT. In contrast to MCT, the mast cell MCTC population in severe asthma is expressing MrgprX2 (Fajt M. L. et al, 2013; *The Journal of Allergy and Clinical Immunology*, 131(6), 1504–1512; <https://doi.org/10.1016/j.jaci.2013.01.035> and Balzar, S. et al., 2011, *American Journal of Respiratory and Critical Care Medicine*, 183(3), 299–309; <https://doi.org/10.1164/rccm.201002-0295OC>). Given that the SP levels are increased in the lung of severe asthma patients which activates MrgprX2, the treatment with small molecule antagonists will benefit severe asthma patients (van Diest, SA. et al., 2012, *Biochimica et Biophysica Acta*, 1822(1), 74–84; <https://doi.org/10.1016/j.bbadis.2011.03.019>).

[0053] "Mammal" or "mammalian" includes humans and both domestic animals such as laboratory animals and household pets, (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[0054] "Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition. The amount of a compound of the invention which constitutes a

“therapeutically effective amount” will vary depending on the compound, the disease or condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure. Preferably, for purposes of this invention, a “therapeutically effective amount” is that amount of a compound of invention which is sufficient to inhibit inflammation of the skin.

[0055] “Treating” or “treatment”, as used herein, covers the treatment of the disease or condition of interest in a mammal, preferably a human, and includes:

- (i) preventing the disease or condition from occurring in the mammal;
- (ii) inhibiting the disease or condition in the mammal, *i.e.*, arresting its development;
- (iii) relieving the disease or condition in the mammal, *i.e.*, causing regression of the disease or condition; or
- (iv) relieving the symptoms of the disease or condition in the mammal, *i.e.*, relieving the symptoms without addressing the underlying disease or condition.

[0056] As used herein, the terms “disease,” “disorder,” and “condition” may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

[0057] In the present description, the term “about” means $\pm 20\%$ of the indicated range, value, or structure, unless otherwise indicated.

[0058] In some embodiments, the MrgprX2 antagonist (e.g. a MrgprX2 antagonist according to the present disclosure) is present in the topical or oral composition at a concentration of about 0.05% to about 5% by weight.

[0059] In certain embodiments, the pharmaceutical compositions described herein further include a dermatologically acceptable excipient. The dermatologically acceptable excipients may be one or more solvents that solubilize and/or stabilize the active ingredient (e.g., MrgprX2 antagonist) contained therein. The dermatologically acceptable excipients may also include skin penetration enhancers, preservatives, viscosity enhancers, pH adjusters, film forming agents and the like. Non-limiting examples of the suitable excipients include water, PEG 200, PEG 400, ethanol, glycerol, Transcutol P (diethylene glycol monoethyl ether), propylene glycol, 1,3-

dimethyl-2-imidazolidinone (DMI), sodium metabisulfite, butylated hydroxytoluene (BHT), benzyl alcohol, sodium benzoate, isopropyl myristate, diisopropyl adipate, crodamol OHS (ethylhexyl hydroxystearate), mineral oil, Betadex, TWEEN 20, Brij S20 (polyoxyethylene (20) stearyl ether).

[0060] More detailed description of certain suitable excipients is described below. As will be appreciated, components of the pharmaceutical formulations described herein can possess multiple functions. For example, a given substance may act as both a viscosity increasing agent and as an emulsifying agent.

[0061] The skin (especially stratum corneum) provides a physical barrier to the harmful effects of the external environment. In doing so, it also interferes with the absorption or transdermal delivery of topical therapeutic drugs. Thus, a suitable dermatologically acceptable excipient may include one or more penetration enhancers (or permeation enhancers), which are substances that promote the diffusion of the therapeutic drugs (e.g., the MrgprX2 antagonists described herein) through the skin barrier. They typically act to reduce the impedance or resistance of the skin to allow improved permeation of the therapeutic drugs. In particular, substances which would perturb the normal structure of the stratum corneum are capable of disrupting the intercellular lipid organization, thus reducing its effectiveness as a barrier. These substances could include any lipid material which would partition into the stratum corneum lipids causing a direct effect or any material which would affect the proteins and cause an indirect perturbation of the lipid structure. Furthermore, solvents, such as ethanol, can remove lipids from the stratum corneum, thus destroying its lipid organization and disrupting its barrier function.

[0062] Examples of penetration enhancers or barrier function disrupters include, but are not limited to, alcohol-based enhancers, such as alkanols with one to sixteen carbons, benzyl alcohol, butylene glycol, diethylene glycol, glycofurol, glycerides, glycerin, glycerol, phenethyl alcohol, polypropylene glycol, polyvinyl alcohol, and phenol; amide-based enhancers, such as N-butyl-N-dodecylacetamide, crotamiton, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformamide, and urea; amino acids, such as L- α -amino acids and water soluble proteins; azone and azone-like compounds, such as azacycloalkanes; essential oils, such as almond oil, amyl butyrate, apricot kernel oil, avocado oil, camphor, castor oil, 1-carvone, coconut oil, corn oil, cotton seed oil, eugenol, menthol, oil of anise, oil of clove, orange oil, peanut oil, peppermint oil, rose oil, safflower oil, sesame oil, shark liver oil (squalene), soybean oil, sunflower oil, and walnut oil;

vitamins and herbs, such as aloe, allantoin, black walnut extract, chamomile extract, panthenol, papain, tocopherol, and vitamin A palmitate; waxes, such as candelilla wax, carnauba wax, ceresin wax, beeswax, lanolin wax, jojoba oil, petrolatum; mixes, such as primary esters of fractionated vegetable oil fatty acids with glycerine or propylene glycol, and interesterified medium chain triglyceride oils; fatty acids and fatty acid esters, such as amyl caproate, butyl acetate, caprylic acid, cetyl ester, diethyl sebacate, dioctyl malate, elaidic acid ethyl caprylate, ethyl glycol palmitostearate, glyceryl behenate, glucose glutamate, isobutyl acetate, laureth-4, lauric acid, malic acid, methyl caprate, mineral oil, myristic acid, oleic acid, palmitic acid, PEG fatty esters, polyoxylene sorbitan monooleate, polypropylene glycols, propylene glycols, saccharose distearate, salicylic acid, sodium citrate, stearic acid, soaps, and caproic-, caprylic-, capric-, and lauric-triglycerides; macrocyclics, such as butylated hydroxyanisole, cyclopentadecanolide, cyclodextrins; phospholipid and phosphate enhancers, such as dialkylphosphates, ditetradecyl phosphate, lecithin, 2-pyrrolidone derivatives, such as alkyl pyrrolidone-5-carboxylate esters, pyroglutamic acid esters, N-methyl pyrrolidone, biodegradable soft penetration enhancers, such as dioxane derivatives and dioxolane derivatives; sulphoxide enhancers, such as dimethyl sulphoxide and decylmethyl sulphoxide; acid enhancers, such as alginic acid, sorbic acid, and succinic acid; cyclic amines; imidazolinones; imidazoles; ketones, such as acetone, dimethicone, methyl ethyl ketone, and pentanedione; lanolin derivatives, such as lanolin alcohol, PEG 16 lanolin, and acetylated lanolin; oxazolines; oxazolindinones; proline esters; pyrroles, urethanes; and surfactants, such as nonoxynols, polysorbates, polyoxylene alcohols, polyoxylene fatty acid esters, sodium lauryl sulfate, and sorbitan monostearate.

[0063] The topical compositions described herein typically contain one or more carriers, which preferably have a vapor pressure greater than or equal to 23.8 mm Hg at 25 °C. Preferred concentration range of a single carrier or the total of a combination of carriers can be from about 0.1 wt.% to about 10 wt. %, more preferably from about 10 wt. % to about 50 wt.%, more specifically from about 50 wt.% to about 95 wt.% of the dermatological composition. Non-limiting examples of the solvent include water (e.g., deionized water) and lower alcohols, including ethanol, 2-propanol and n-propanol.

[0064] A dermatological composition of the invention can contain one or more hydrophilic co-solvents, which are miscible with water and/or lower chain alcohols and preferably have a vapor pressure less than water at 25 °C (~ 23.8 mm Hg). The carrier typically has a vapor pressure greater

than or equal to the hydrophilic co-solvent as to concentrate the active ingredient (e.g., a MrgprX2 antagonist of the present disclosure) on the skin. A hydrophilic co-solvent may be a glycol, specifically propylene glycol. In particular, the propylene glycol can be from the class of polyethylene glycols, specifically polyethylene glycols ranging in molecular weight from 200 to 20000. Preferably, the solvent would be part of a class of glycol ethers. More specifically, a hydrophilic co-solvent of the invention would be diethylene glycol monoethyl ether (transcutol). As used herein, “diethylene glycol monoethyl ether” (“DGME”) or “transcutol” refers to 2-(2-ethoxyethoxy)ethanol {CAS NO 001893} or ethoxydiglycol. Another preferred co-solvent is 1,3-dimethyl-2-imidazolidinone (DMI).

[0065] The topical compositions described herein may also contain one or more “humectant(s)” used to provide a moistening effect. Preferably the humectant remains stable in the composition. Any suitable concentration of a single humectant or a combination of humectants can be employed, provided that the resulting concentration provides the desired moistening effect. Typically, the suitable amount of humectant will depend upon the specific humectant or humectants employed. Preferred concentration range of a single humectant or the total of a combination of humectants can be from about 0.1 wt.% to about 70 wt.%, more preferably from about 5.0 wt.% to about 30 wt.%, more specifically from about 10 wt.% to about 25 wt.% of the dermatological composition. Non-limiting examples for use herein include glycerin, polyhydric alcohols and silicone oils. More preferably, the humectant is glycerin, propylene glycol and/or cyclomethicone. Specifically, the filler would be glycerine and/or cyclomethicone.

[0066] In certain embodiments, the pharmaceutical compositions include a viscosity enhancing agent or an emulsifier. Gelling agents are used to increase the viscosity of the final composition. Emulsifiers are substances that stabilize an emulsion. The viscosity increasing agent can also act as an emulsifying agent. Typically, the concentration and combination of viscosity increasing agents will depend on the physical stability of the finished product. Preferred concentration range of a viscosity increasing agent can be from about 0.01 wt.% to about 20 wt.%, more preferably from about 0.1 wt.% to about 10 wt.%, more specifically from about 0.5 wt. % to about 5 wt.% of the dermatological composition. Non-limiting examples of viscosity increasing agents for use herein include classes of celluloses, acrylate polymers and acrylate crosspolymers, such as, hydroxypropyl cellulose, hydroxymethyl cellulose, Pluronic PF127 polymer, carbomer 980, carbomer 1342 and carbomer 940, more preferably hydroxypropyl cellulose, Pluronic PF127

carbomer 980 and carbomer 1342, more specifically hydroxypropyl cellulose (Klucel® EF, GF and/or HF), Pluronic PF127, carbomer 980 and/or carbomer 1342 (Pemulen® TR-1, TR-2 and/or Carbopol® ETD 2020). Examples of emulsifiers for use herein include polysorbates, laureth-4, and potassium cetyl sulfate.

[0067] The topical or oral compositions described herein may contain one or more anti-oxidants, radical scavengers, and/or stabilizing agents, preferred concentration range from about 0.001 wt.% to about 0.1 wt.%, more preferably from about 0.1 wt.% to about 5 wt.% of the dermatological composition. Non-limiting examples for use herein include butylatedhydroxytoluene, butylatedhydroxyanisole, ascorbyl palmitate, citric acid, vitamin E, vitamin E acetate, vitamin E-TPGS, ascorbic acid, tocophersolan and propyl gallate. More specifically the anti-oxidant can be ascorbyl palmitate, vitamin E acetate, vitamin E-TPGS, vitamin E or butylatedhydroxy toluene.

[0068] The topical or oral compositions described herein may also contain preservatives that exhibit anti-bacterial and/or anti-fungal properties. Preservatives can be present in a gelled dermatological composition of the invention to minimize bacterial and/or fungal over its shelf-life. Preferred concentration range of preservatives in a dermatological composition of the invention can be from about 0.001 wt.% to about 0.01 wt.%, more preferably from about 0.01 wt.% to about 0.5 wt.% of the dermatological composition. Non-limiting examples for use herein include diazolidinyl urea, methylparaben, propylparaben, tetrasodium EDTA, and ethylparaben. More specifically the preservative would be a combination of methylparaben and propylparaben.

[0069] The topical compositions described herein may optionally include one or more chelating agents. As used herein, the term “chelating agent” or “chelator” refers to those skin benefit agents capable of removing a metal ion from a system by forming a complex so that the metal ion cannot readily participate in or catalyze chemical reactions. The chelating agents for use herein are preferably formulated at concentrations ranging from about 0.001 wt.% to about 10 wt.%, more preferably from about 0.05 wt.% to about 5.0 wt.% of the dermatological composition. Non-limiting examples for use herein include EDTA, disodium edeate, dipotassium edeate, cyclodextrin, trisodium edetate, tetrasodium edetate, citric acid, sodium citrate, gluconic acid and potassium gluconate. Specifically, the chelating agent can be EDTA, disodium edeate, dipotassium edate, trisodium edetate or potassium gluconate.

[0070] The topical or oral compositions described herein may include one or more compatible cosmetically acceptable adjuvants commonly used, such as colorants, fragrances, emollients, and the like, as well as botanicals, such as aloe, chamomile, witch hazel and the like.

[0071] Alternatively, other pharmaceutical delivery systems may be employed for the pharmaceutical compositions of the invention. Liposomes and emulsions are well-known examples of delivery vehicles that may be used to deliver active compound(s) or prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) may also be employed.

[0072] The topical compositions described herein may be provided in any cosmetically suitable form, preferably as a lotion, a cream, or a ointment, as well as a sprayable liquid form (e.g., a spray that includes the MrgprX2 antagonist in a base, vehicle or carrier that dries in a cosmetically acceptable way without the greasy appearance that a lotion or ointment would have when applied to the skin).

[0073] Any suitable amount of a MrgprX2 antagonist (e.g., a compound according to the present disclosure) can be employed in such dermatological compositions, provided the amount effectively reduces local inflammation and/or vascular dysfunction, and remains stable in the composition over a prolonged period of time. Preferably, the stability is over a prolonged period of time, e.g., up to about 3 years, up to 1 year, or up to about 6 months, which is typical in the manufacturing, packaging, shipping and/or storage of dermatologically acceptable compositions. A compound of the present disclosure can be in solution, partially in solution with an undissolved portion or completely undissolved suspension. A compound of the present disclosure can be present in a dermatological composition of the invention in a concentration range from about 0.001 wt.% to about 80 wt.%, from about 0.001 wt.% to about 50 wt.%, from about 0.001 wt.% to about 25 wt.%, or from about 0.001 wt.% to about 6 wt.% of the dermatological composition. In one embodiment, a compound of the present disclosure can be present in a concentration range of from about 0.001 wt.% to about 10 wt.%, from about 0.1 wt.% to about 10 wt.% or from about 1.0 wt.% to about 5.0 wt.% of the dermatological composition.

[0074] In treating the inflammatory disorders, e.g., atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, or

drug-adverse reactions, the topical composition comprising a compound of the present disclosure is preferably administered directly to the affected area of the skin (e.g., the skin that itches) of the human in need thereof. When such compositions are in use (e.g., when a dermatological composition comprising a compound of the present disclosure) and a dermatologically acceptable excipient is placed upon the skin of the human in need thereof, the MrgprX2 antagonist of is in continuous contact with the skin of the patient, thereby effecting penetration and treatment.

[0075] In topically administering the pharmaceutical compositions of the invention, the skin of the human to be treated can be optionally pre-treated (such as washing the skin with soap and water or cleansing the skin with an alcohol-based cleanser) prior to administration of the dermatological composition of the invention.

[0076] The pharmaceutical compositions of the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active compound(s). The topical composition described herein may also be provided in a patch with the topical composition on the side of the patch that directly contacts the skin. Dermatologically acceptable adhesives may be used to affix the patch to the skin for an extended period of time.

[0077] Oral Administration

[0078] In some embodiments, the pharmaceutical compositions herein are provided for oral administration. Thus, provided in accordance with the present disclosure are solid, semisolid, or liquid dosage forms for oral administration comprising a compound as described herein.

Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, pellets, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, enteric coatings, film coating agents, modified release agents, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[0079] Binders or granulators impart cohesiveness to a tablet to ensure that the tablet remains intact after compression. Suitable binders or granulators include, but are not limited to, starches,

such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, ethylcellulose, carboxymethylcellulose, methylcellulose, methyl paraben, polyalkyleneoxides, povidone, polyvinylpyrrolidone (PVP), crospovidones, Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxy ethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH- 103, AVICEL RC-581, AVICEL-PH- 105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0080] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, trehalose, lysine, leucine, lecithin, starch, kaolin, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[0081] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0082] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL[®] 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL[®] (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0083] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL[®] (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN[®] 20), polyoxyethylene sorbitan monooleate 80 (TWEEN[®] 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[0084] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0085] The pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed

tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0086] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0087] The pharmaceutical compositions provided herein may be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0088] The pharmaceutical compositions provided herein may be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in- water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

[0089] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[0090] The pharmaceutical compositions provided herein for oral administration may be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[0091] The pharmaceutical compositions provided herein may be provided as non- effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable

carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[0092] Coloring and flavoring agents can be used in all of the above dosage forms.

[0093] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms. Thus, in some preferred embodiments, the active ingredient(s) (i.e., the calcium channel blocker, or L-arginine, or a combination of a calcium channel blocker and L-arginine, or pharmaceutically acceptable salts, hydrates, solvates and prodrugs thereof), is administered in a pharmaceutical composition which is an immediate release oral dosage form, preferably but not necessarily including an enteric coating. In some preferred embodiments, the active ingredient(s) are administered in a pharmaceutical composition which is an extended release oral dosage form, preferably but not necessarily including an enteric coating. In further preferred embodiments, the active ingredients are administered in a pharmaceutical composition which contains both an immediate release dose and an extended release dose or pulsed release dose of the calcium channel blocker, preferably but not necessarily also including an enteric coating. Such dual release dosage forms achieve release of an initial dose of active ingredient, followed late in time by another pulsed release, or by a sustained release dose. Methodologies for preparing such dual release dosage forms are well known in the art.

[0094] In some embodiments, the active ingredients are formulated into a controlled release matrix tablet, which contains one or more polymeric matrix materials that promote the sustained, delayed or pulsed release profile. Non-limiting examples of such polymeric matrix materials include cellulosic materials as described above, and carbomers, for example those sold by Lubrizol Corporation under the name Carbopol[®], for example Carbopol[®] 71G NF, Carbopol[®] 971P NF and Carbopol[®] 974P NF polymers.

[0095] Some preferred examples of extended release compositions suitable for use in the methods and compositions of the invention include, for example and not limitation, extended release compositions found in nifedipine formulations such as Adalat CC[®], Procardia[®] XL, Afeditab[®] CR and Nifedical[®] XL; and in diltiazem formulations such as Cardizem[®] CD, Cardizem[®] LA, Cardizem[®] SR, Cartia[®] XT and Dilacor[®] XR.

[0096] In some embodiments, the present disclosure provides pharmaceutical compositions for oral administration, for use in treating the conditions and disorders described herein.

[0097] Dosages

[0098] The compositions provided herein contain therapeutically effective amounts of one or more of the compounds provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders described herein and a vehicle. Vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration, preferably topically, orally or via injection. In addition, the compounds may be formulated as the sole active ingredient in the composition or may be combined with other active ingredients.

[0099] The active compound is included in the vehicle in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be predicted empirically by testing the compounds in *in vitro* and *in vivo* systems well known to those of skill in the art and then extrapolated therefrom for dosages for humans. Human doses are then typically fine-tuned in clinical trials and titrated to response.

[00100] The concentration of active compound in the composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders as described herein.

[00101] In some embodiments, a therapeutically effective dosage should be from about 0.0001 mg to about 1000 mg per day. In some embodiments, 0.001-50 mg of active ingredient (MgrprX2 antagonist as described herein) per kilogram of body weight per day, delivered topically, orally or by injection as described herein. In some embodiments, the MgrprX2 antagonist is administered at a dosage of up to 1500 mg/day, for example 1200 mg/day, 900 mg/day, 850 mg/day, 800 mg/day, 750 mg/day, 700 mg/day, 650 mg/day, 600 mg/day, 550 mg/day, 500 mg/day, 450 mg/day, 400 mg/day, 350 mg/day, 300 mg/day, 250 mg/day, 200 mg/day, 150 mg/day, 100 mg/day, 50 mg/day, 25 mg/day, 10 mg/day, or 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.75, 0.5, 0.25, 0.10, 0.05 or 0.01 mg/day.

[00102] The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise

dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data or subsequent clinical testing. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00103] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from vehicle or carrier may be prepared. Methods for preparation of these compositions are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975 or later editions thereof.

[00104] Oral Dosage

[00105] The oral dosage forms of the invention that contain the MrgprX2 antagonists of the present disclosure will typically be administered at dosages described above.

[00106] In some preferred embodiments, the daily dose is administered once per day. In some embodiments, the dosage form is an extended release composition.

[00107] In some embodiments, the daily dose is administered in a single dose. In other embodiments, the daily dose is administered in smaller increments given multiple times per day, for example twice or three times per day, in amounts that combined equal the daily values above

[00108] In some preferred embodiments, the daily dose is administered in a single dose that provides efficacy for up to 12, up to 18, or up to 24 hours.

[00109] Topical Dosages

[00110] In some embodiments, topical formulations including the compounds of the present disclosure will contain the MrgprX2 antagonist at a concentration of from 0.001% to 20% by weight of the composition, for example 0.001%-10%, for example 0.001%-8%, for example 0.001%-5%, for example 0.001%-4%, for example 0.001%-3%, for example 0.001%-2%, for example 0.001%-1%, by weight of the of the composition.

[00111] The compounds or derivatives may be packaged as articles of manufacture containing packaging material, a compound or derivative thereof provided herein, which is effective for treatment, prevention or amelioration of one or more symptoms of the diseases or disorders, *supra*, within the packaging material, and a label that indicates that the compound or composition or derivative thereof, is used for the treatment, prevention or amelioration of one or more symptoms of the diseases or disorders, *supra*.

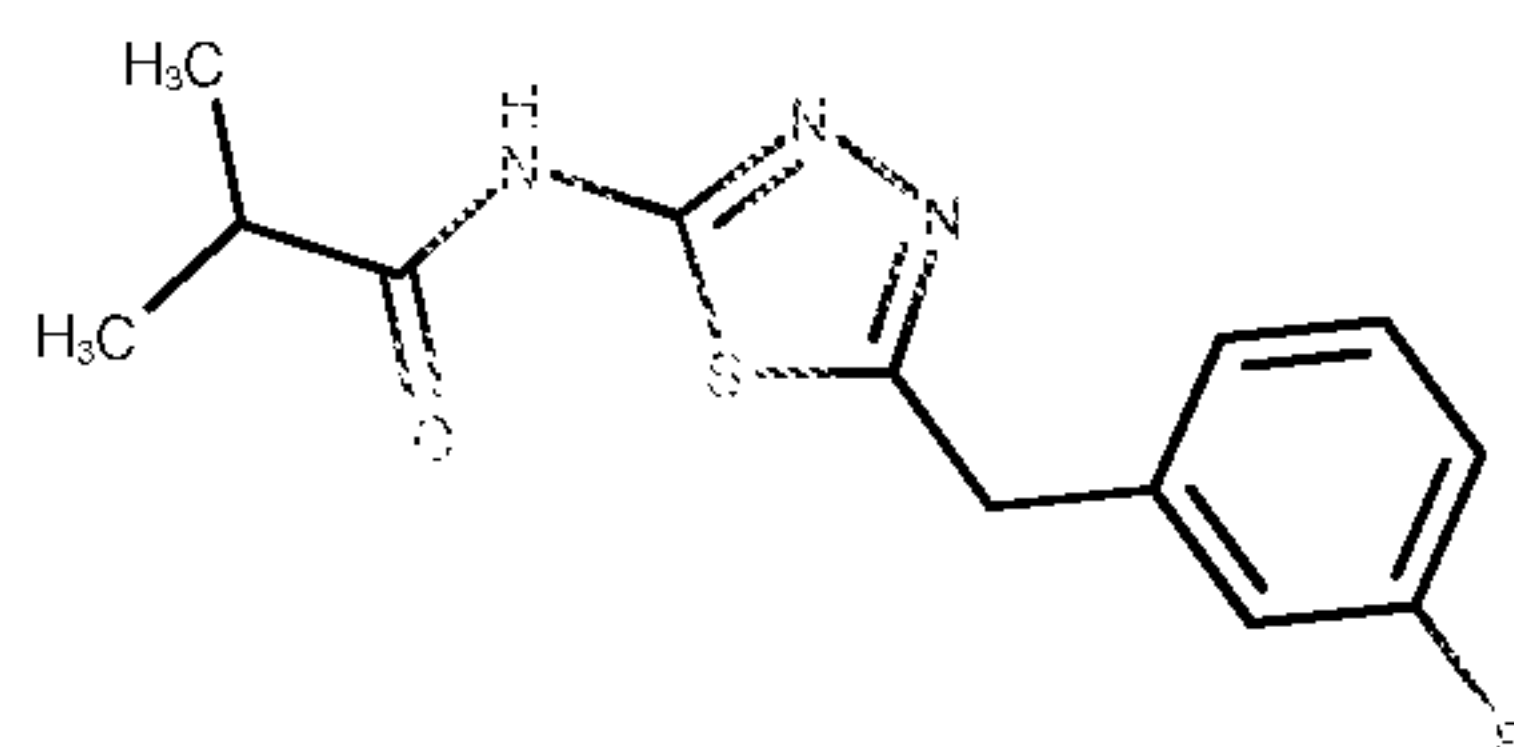
[00112] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of packaging materials include, but are not limited to, blister packs, bottles, tubes, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder described herein.

[00113] The following Examples may be used by one skilled in the art to determine the effectiveness of the compounds of the invention in treating a human having a dermatological condition characterized by inflammation.

[00114] Examples

Example 1 - Preparation of Compounds According to the Present Disclosure

Example E01



N-[5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-2-methyl-propanamide

[00115] Step1

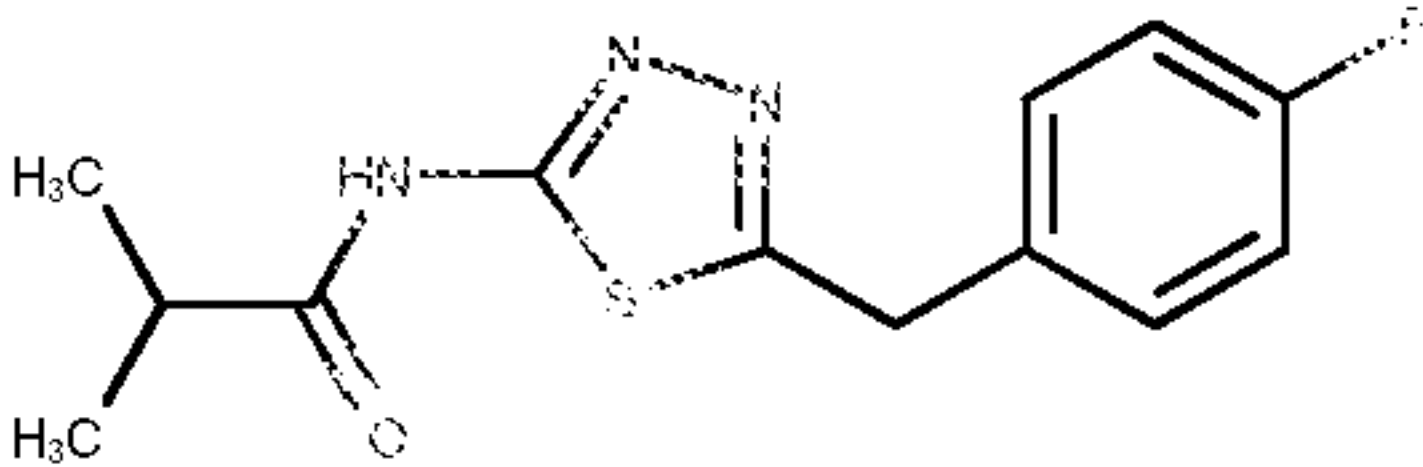
[00116] To a mixture of (3-fluorophenyl)acetic acid (497 g, 32.3 mmol) and sulfuric acid (8.8 mL, 0.161 mol) was added slowly hydrazinecarbothioamide (3000 mg, 32.3 mmol) and the

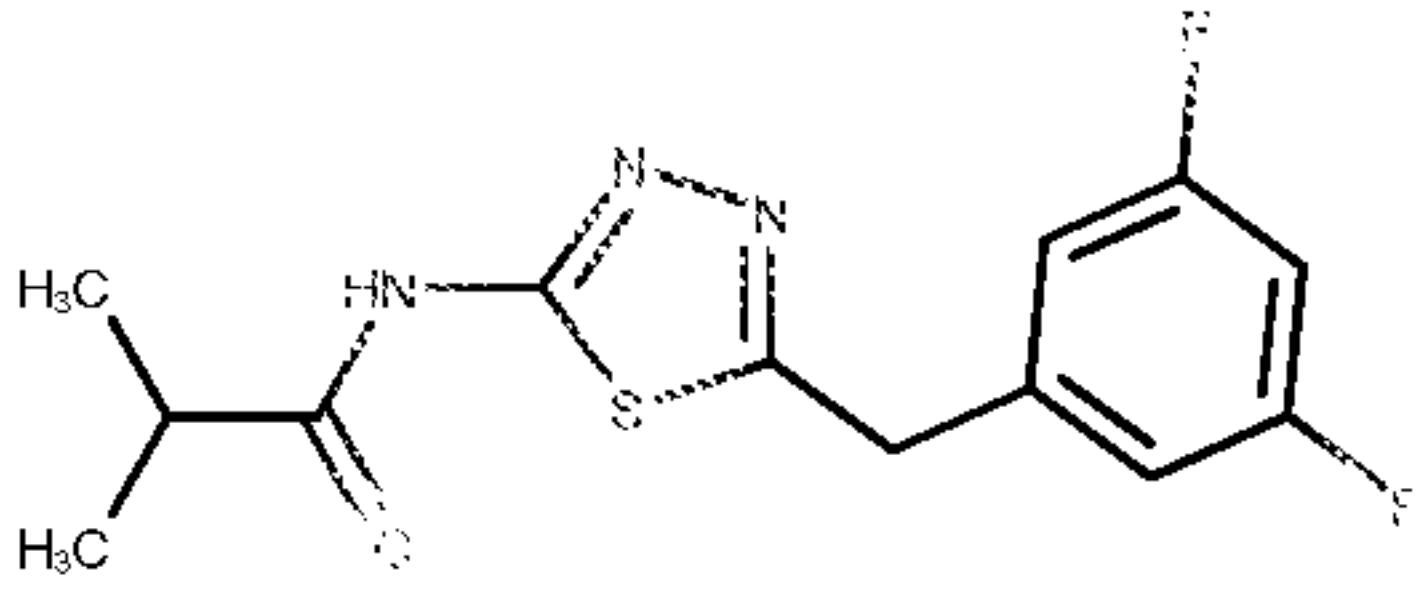
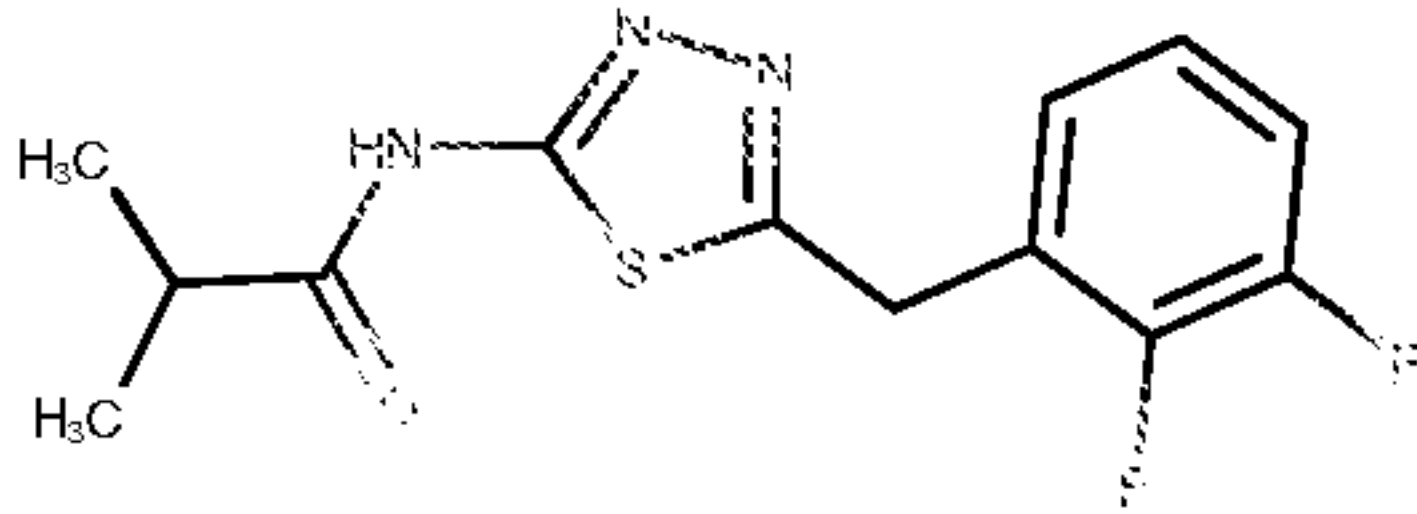
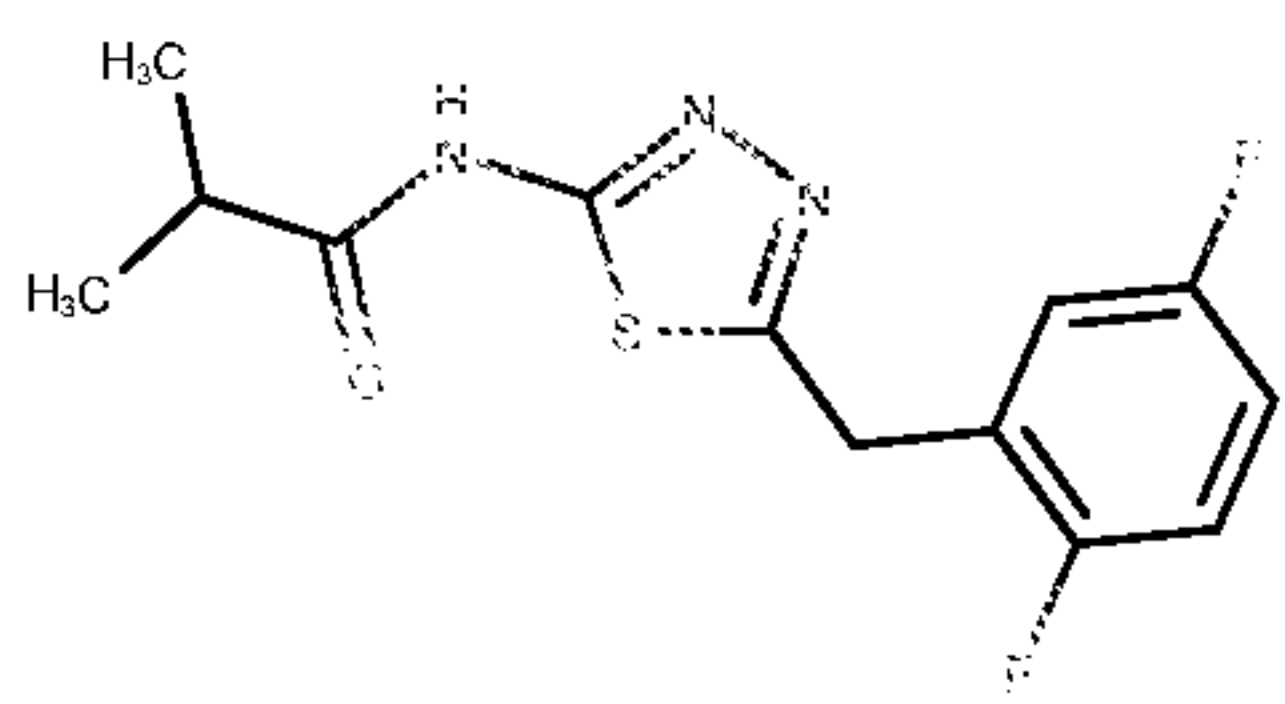
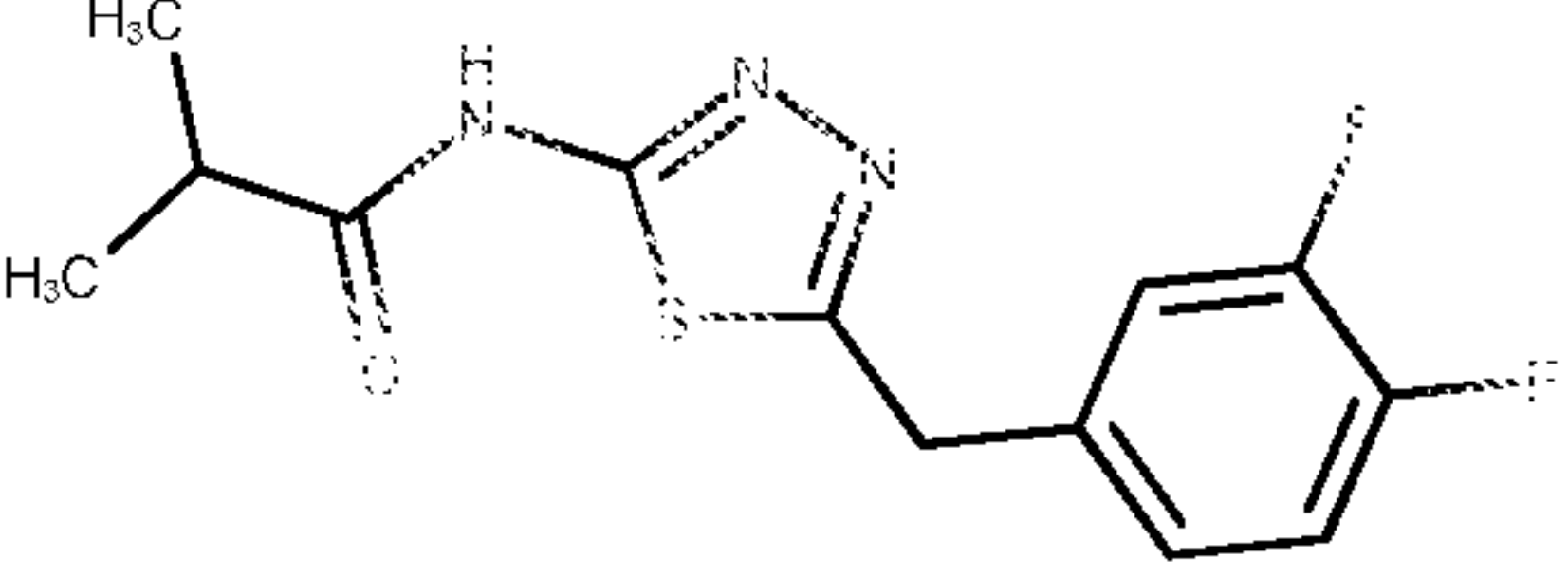
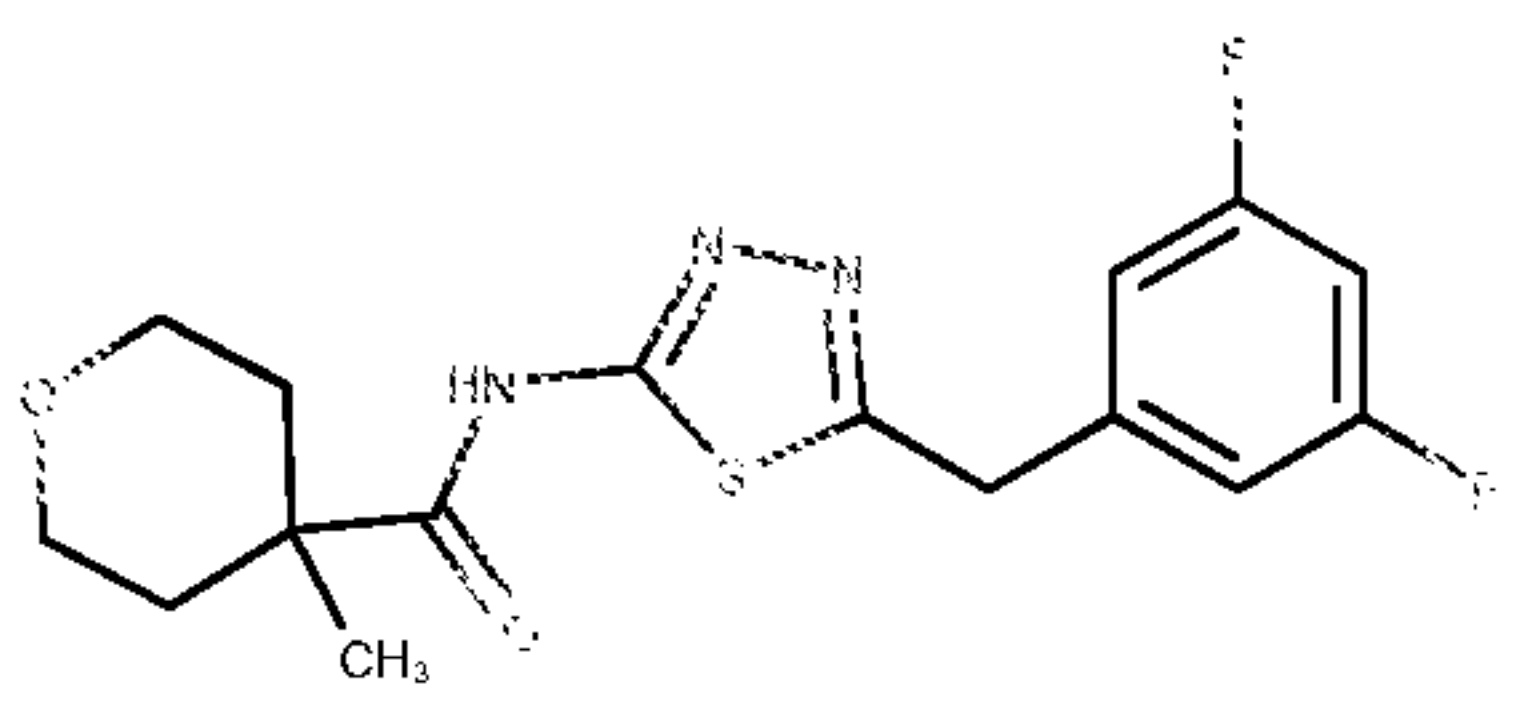
suspension heated at 80 °C for 2 h after which time the reaction mixture was cooled to RT and poured slowly onto a mixture of ice and sat aq NaHCO₃ (50 mL). The mixture was then basified to pH 9 with 37% ammonia in water. The resulting brown solution was filtered and the filtrate extracted with EtOAc (3 x 50 mL) and the combined organic extracts washed with brine (30 mL) and concentrated in vacuo. The crude was purified by FCC (KP Sil 25 g, 0-100% EtOAc in heptane, then 0-20% MeOH in EtOAc) to afford 5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine as a white solid (401 mg, 5% yield, 78% purity)

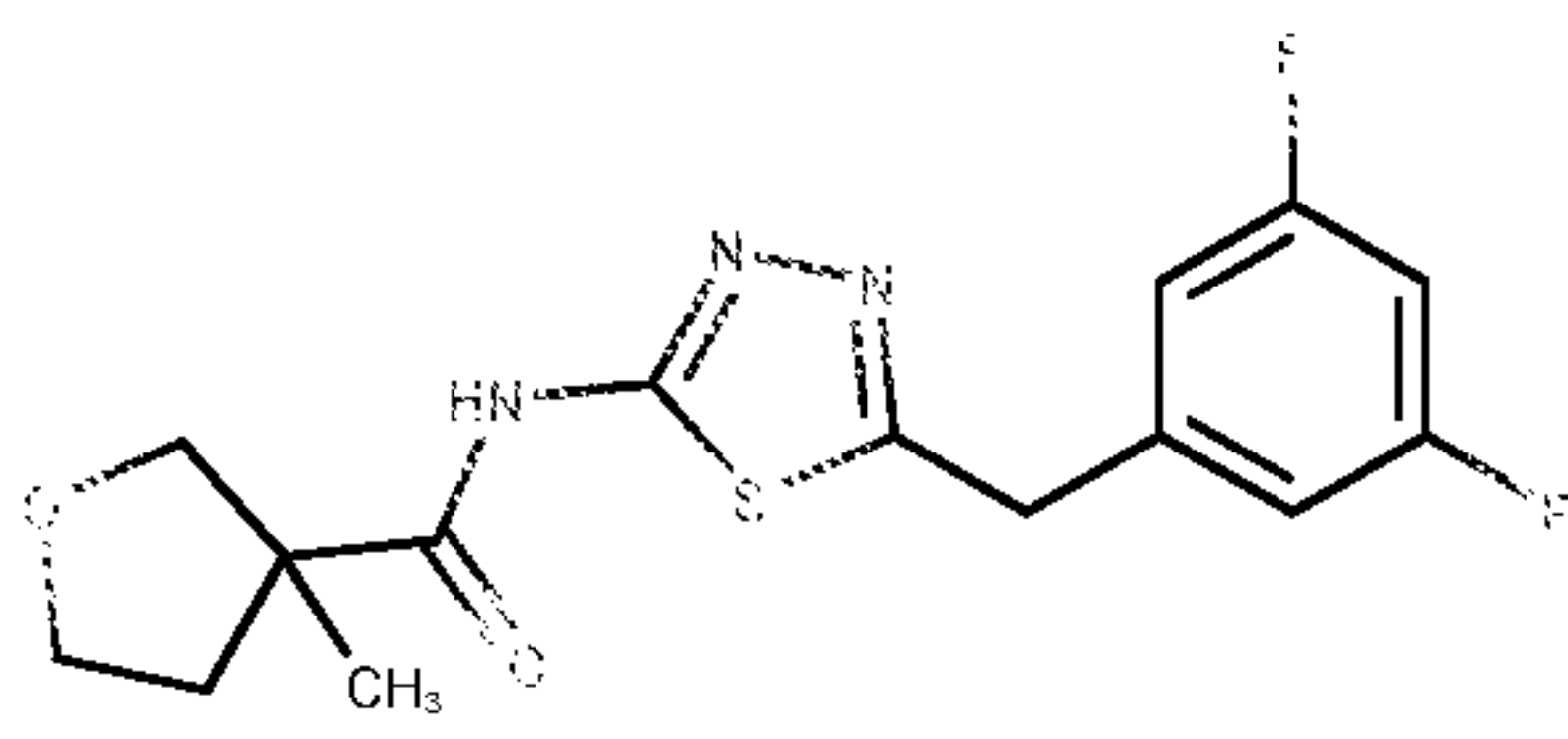
[00117] Step 2

[00118] To a solution of 5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine (78%, 75 mg, 0.280 mmol) and N-ethyl-N-isopropyl-propan-2-amine (98 uL, 0.559 mmol) in THF (2 mL) was added 2-methylpropanoyl chloride (35 uL, 0.335 mmol) with stirring at rt for 1 h after which time, MeOH (1 mL), 1M NaOH (1 mL) were added and the reaction mixture stirred at rt for 0.5 h. The reaction mixture was diluted with brine (5 mL) and extracted with EtOAc (2 x 5 mL) and the combined organic extracts washed concentrated in vacuo. The residue thus obtained was purified by column chromatography (Biotage Isolera 10 g SNAP Ultra, 0-60% EtOAc in heptane) to afford the title compound as a pale yellow solid (27 mg, 34%). ¹H NMR (400 MHz, DMSO-d₆) δ 12.39 (s, 1H), 7.44 – 7.34 (m, 1H), 7.22 – 7.13 (m, 2H), 7.10 (td, J = 8.5, 2.3 Hz, 1H), 4.37 (s, 2H), 2.74 (hept, J = 6.9 Hz, 1H), 1.09 (d, J = 6.9 Hz, 6H). LCMS m/z: 280.1 [M+H]⁺, RT = 2.82 (Method A)

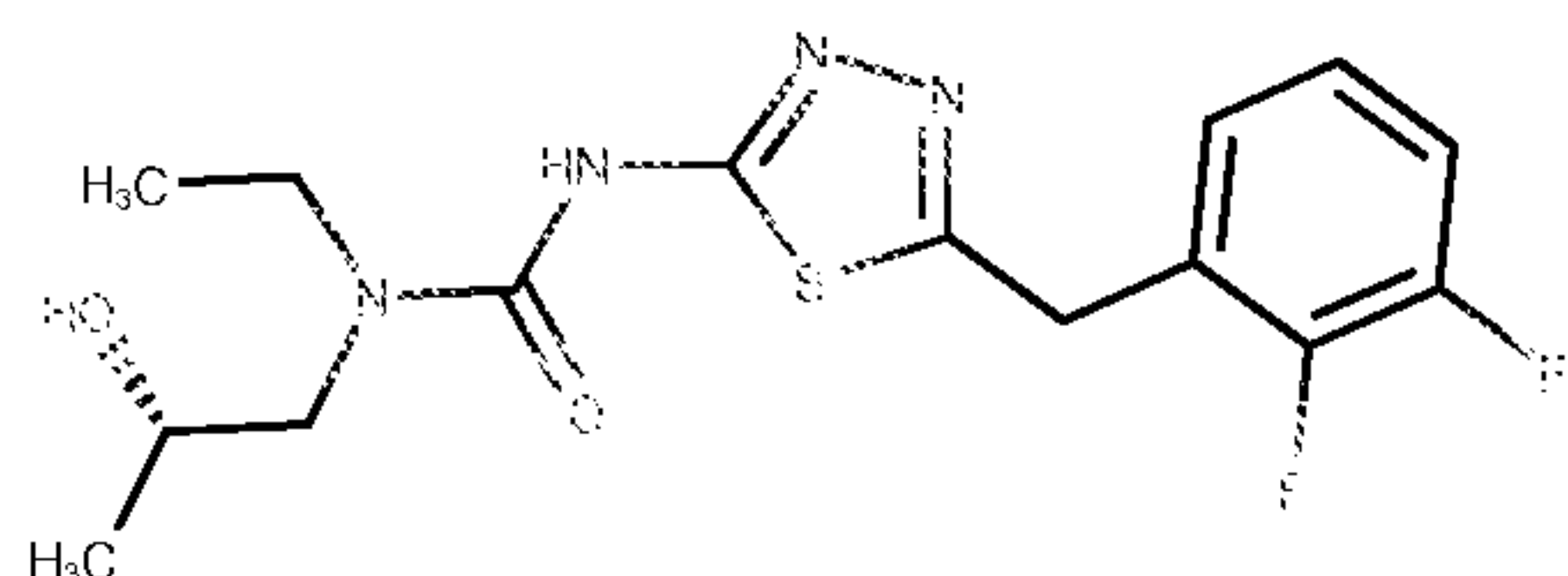
Table 1: The following compounds were synthesized using a similar method to that used in **Example E01**, or using the carboxylic acid in Step 2, in combination with a coupling agent such as HATU.

Example number	Structure	Analytical data	LCMS Method
E02		¹ H NMR (250 MHz, DMSO-d ₆) δ 12.38 (s, 1H), 7.47 – 7.29 (m, 2H), 7.27 – 7.01 (m, 2H), 4.34 (s, 2H), 2.74 (p, J = 6.8 Hz, 1H), 1.10 (d, J = 6.9 Hz, 6H). LCMS m/z: 280.1 [M+H] ⁺ , RT = 2.84	A

Example number	Structure	Analytical data	LCMS Method
E03		¹H NMR(400 MHz, DMSO-d₆) δ 12.42 (s, 1H), 7.21 – 6.98 (m, 3H), 4.39 (s, 2H), 2.73 (hept, J = 6.9 Hz, 1H), 1.10 (d, J = 6.9 Hz, 6H). LCMS m/z: 298.0 [M+H]⁺, RT = 2.94	A
E04		¹H NMR (500 MHz, DMSO-d₆) δ 12.44 (s, 1H), 7.43 – 7.34 (m, 1H), 7.28 – 7.12 (m, 2H), 4.53 – 4.37 (m, 2H), 2.74 (hept, J = 6.9 Hz, 1H), 1.10 (d, J = 6.9 Hz, 6H). LCMS m/z: 298.1 [M+H]⁺, RT = 2.92	A
E05		¹H NMR (400 MHz, DMSO-d₆) δ 12.42 (s, 1H), 7.36 – 7.24 (m, 2H), 7.24 – 7.16 (m, 1H), 4.44 – 4.31 (m, 2H), 2.74 (hept, J = 6.8 Hz, 1H), 1.10 (d, J = 6.9 Hz, 6H). LCMS m/z: 298.1 [M+H]⁺, RT = 2.89	A
E06		¹H NMR (400 MHz, Chloroform-d) δ 11.71 (s, 1H), 7.18 – 7.07 (m, 2H), 7.07 – 6.97 (m, 1H), 4.30 (s, 2H), 2.95 (hept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H). LCMS m/z: 298.1 [M+H]⁺, RT = 2.95	A
E07		¹H NMR (500 MHz, DMSO-d₆) δ 12.26 (s, 1H), 7.21 – 7.07 (m, 3H), 4.40 (s, 2H), 3.65 (dt, J = 11.5, 4.0 Hz, 2H), 3.38 (ddd, J = 11.7, 9.3, 2.6 Hz, 2H), 2.12 – 2.02 (m, 2H), 1.51 (ddd, J = 13.3, 9.1, 3.7 Hz, 2H), 1.26 (s, 3H). LCMS m/z: 354.1 [M+H]⁺, RT = 2.88	A

Example number	Structure	Analytical data	LCMS Method
E08		¹H NMR (500 MHz, Chloroform-d) δ 11.50 (s, 1H), 6.87 – 6.78 (m, 2H), 6.72 (tt, J = 8.9, 2.2 Hz, 1H), 4.31 (s, 2H), 4.26 (d, J = 9.3 Hz, 1H), 4.02 (td, J = 8.6, 5.8 Hz, 1H), 3.93 (td, J = 8.6, 6.6 Hz, 1H), 3.65 (d, J = 9.3 Hz, 1H), 2.51 (ddd, J = 13.0, 8.3, 6.7 Hz, 1H), 2.04 (ddd, J = 13.2, 8.4, 5.8 Hz, 1H), 1.52 (s, 3H). LCMS m/z: 340.1 [M+H]⁺, RT = 2.79	A

Example E09



3-[5-[(2,3-difluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-ethyl-1-[(2S)-2-hydroxypropyl]urea

[00119] Step 1

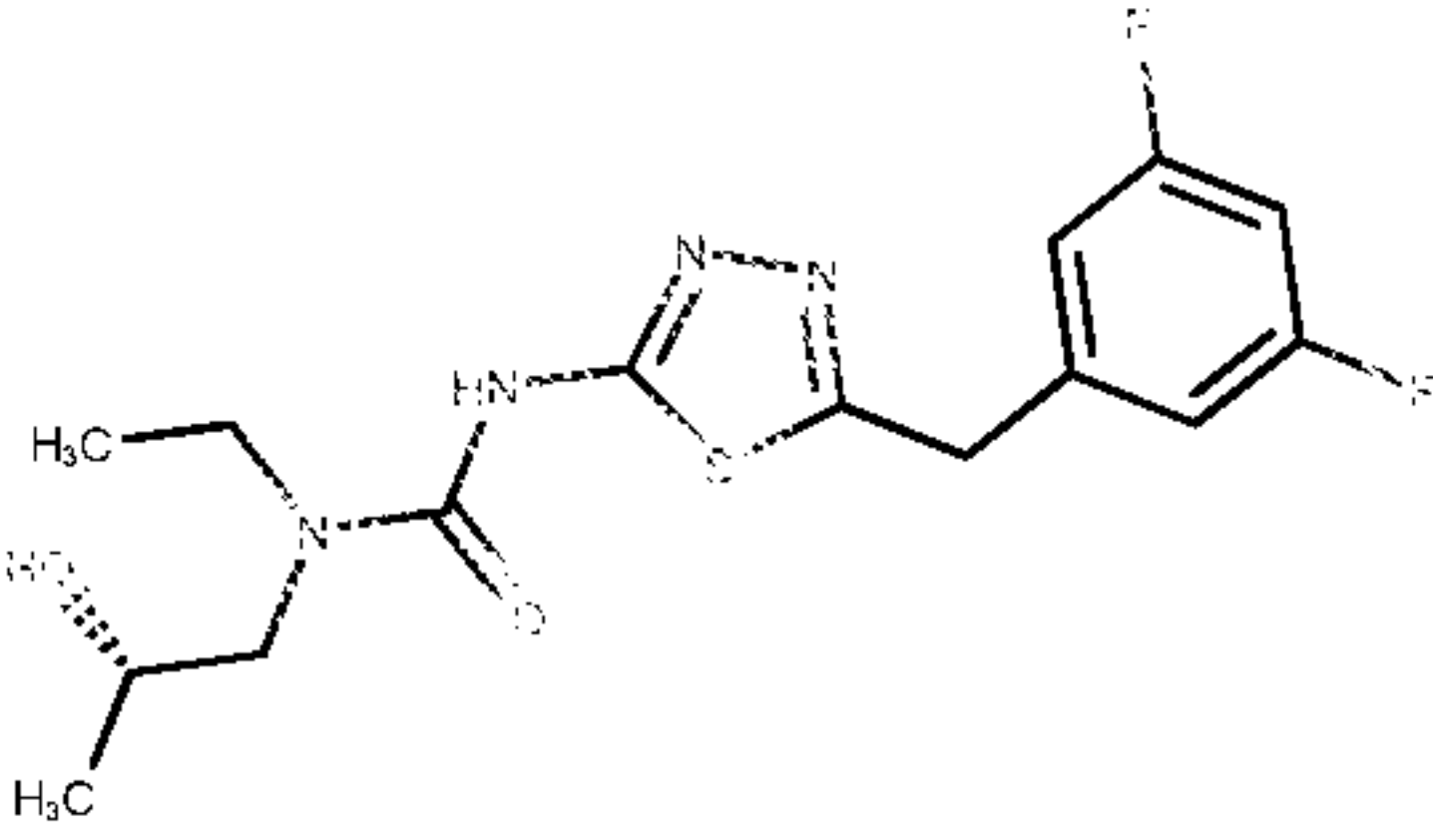
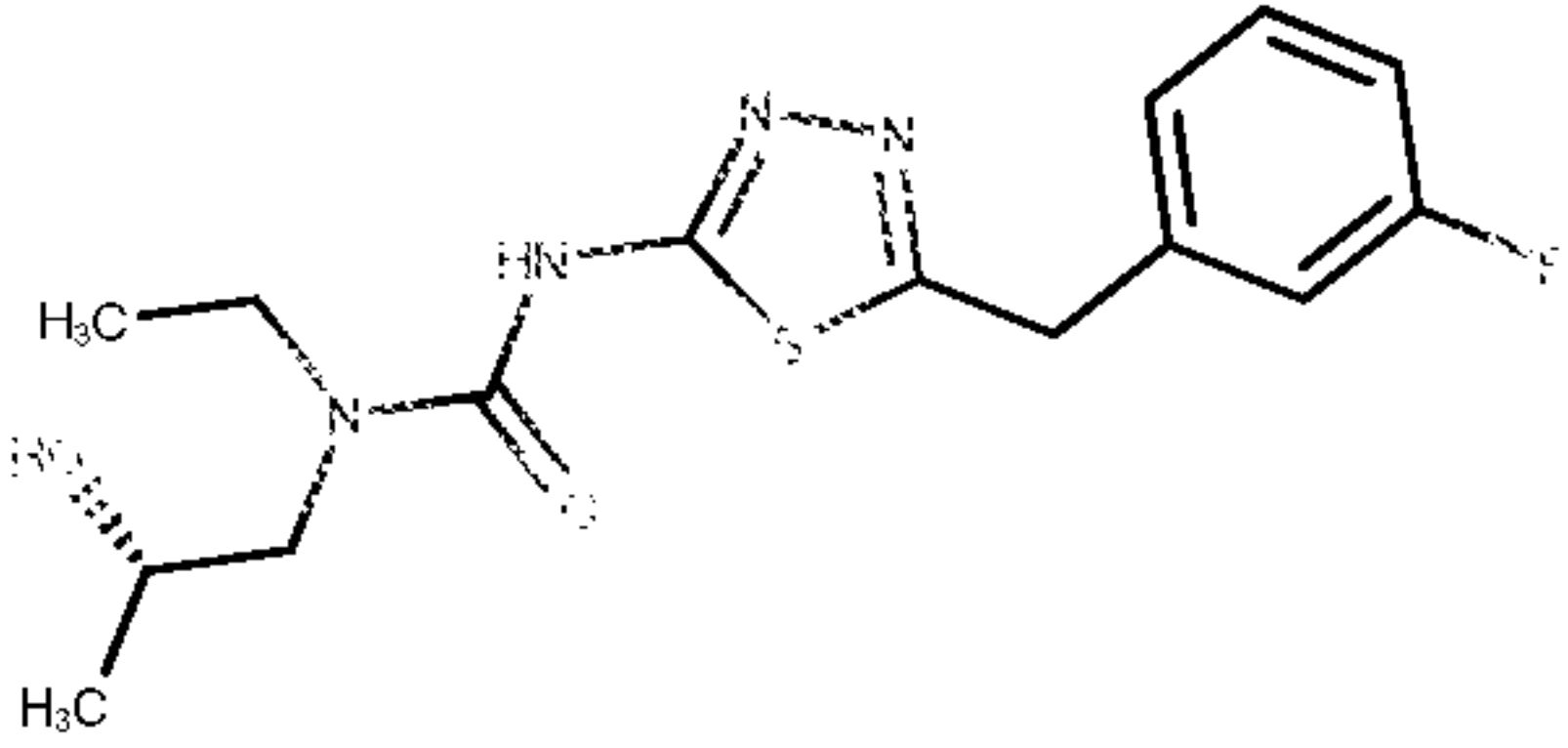
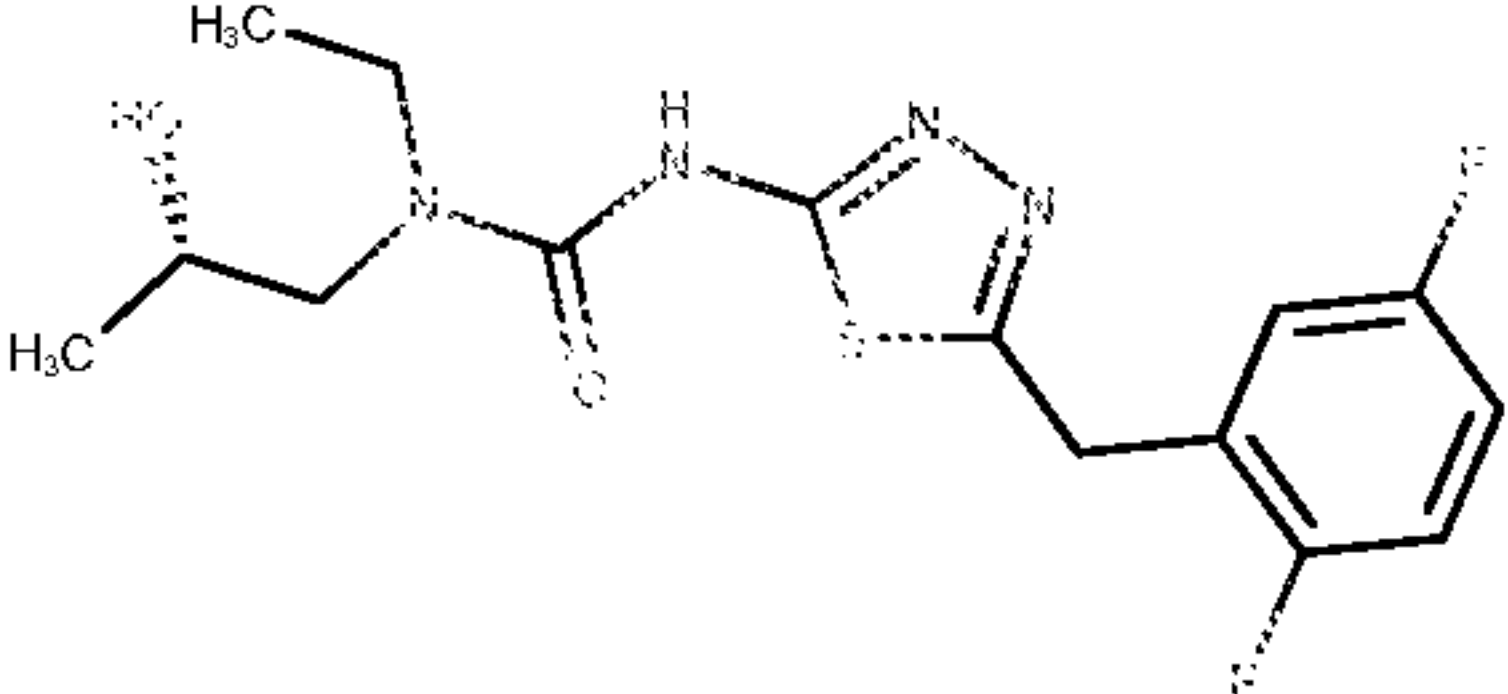
[00120] A stirred solution of aqueous ethanamine (70%, 5.5 mL, 68.9 mmol) was diluted with water (5 mL), cooled to 0 °C and a solution of (2S)-2-methyloxirane (1.00 g, 17.2 mmol) in water (2 mL) was added dropwise. The reaction mixture was allowed to warm up to RT and was stirred overnight. Solvent was then removed under reduced pressure to afford the title compound as a pale yellow liquid (1.35 g, 90% purity, 68% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 3.90 – 3.81 (m, 1H), 2.72 – 2.46 (m, 4H), 1.21 – 1.09 (m, 6H); NH and OH not observed

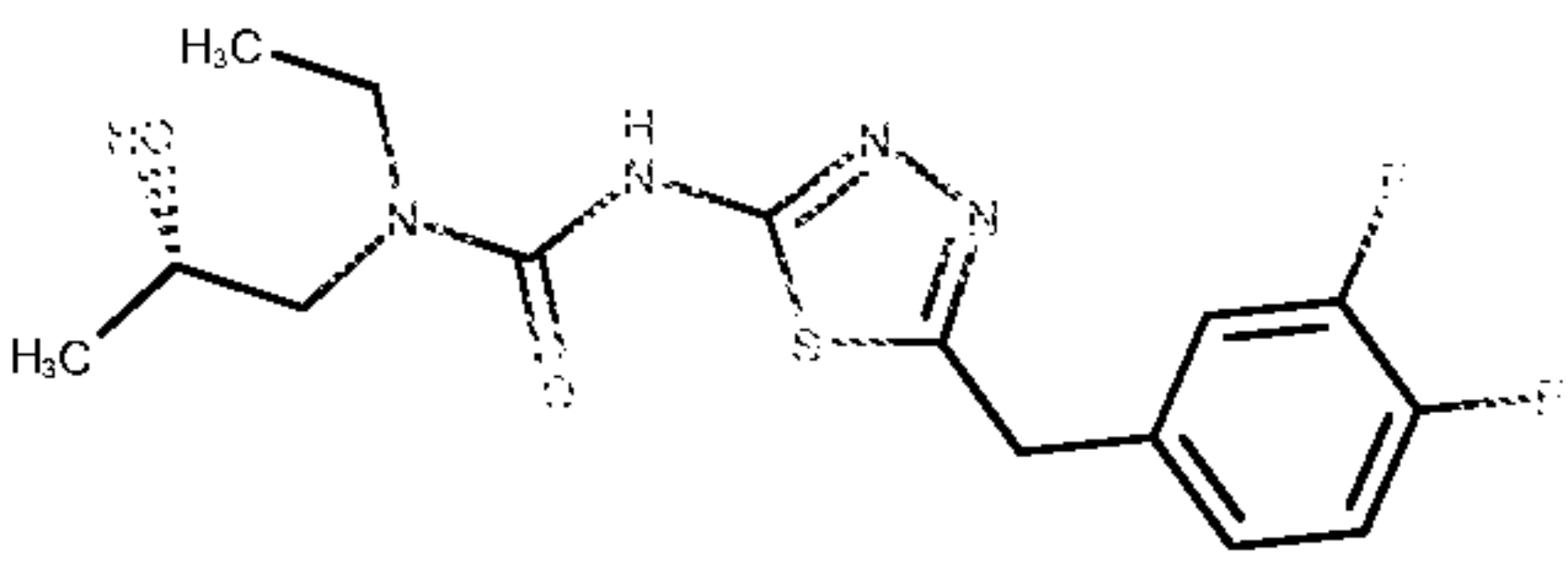
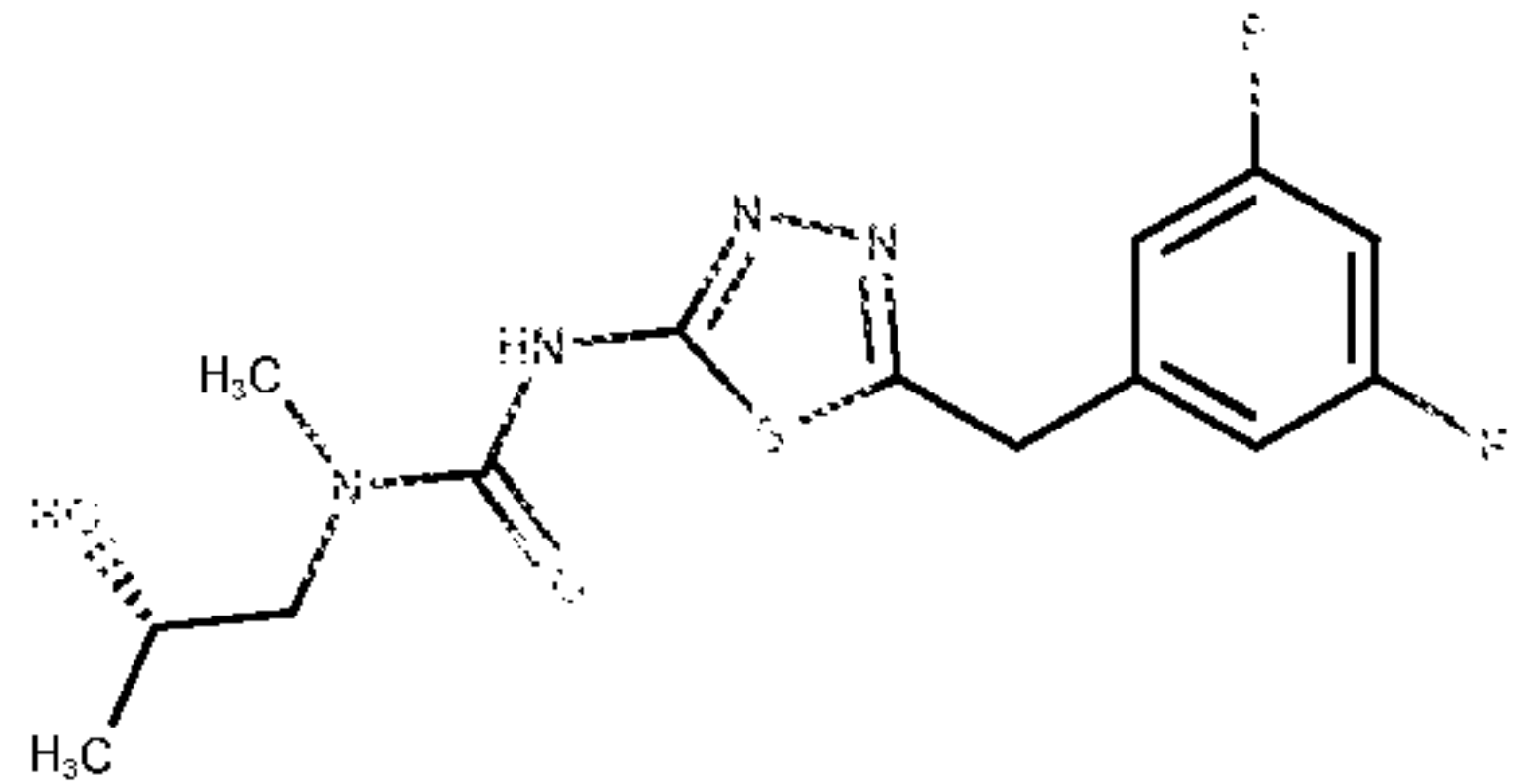
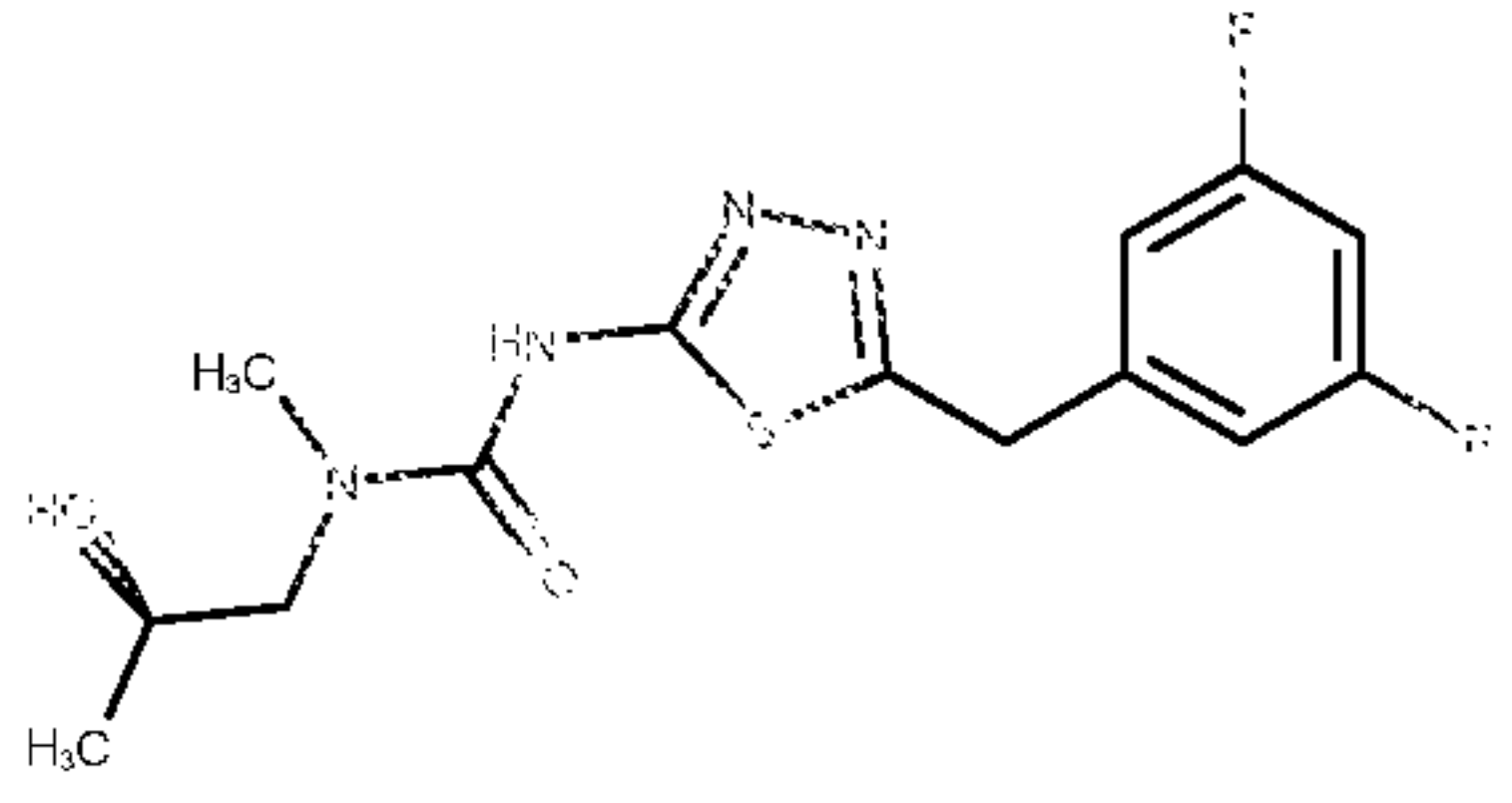
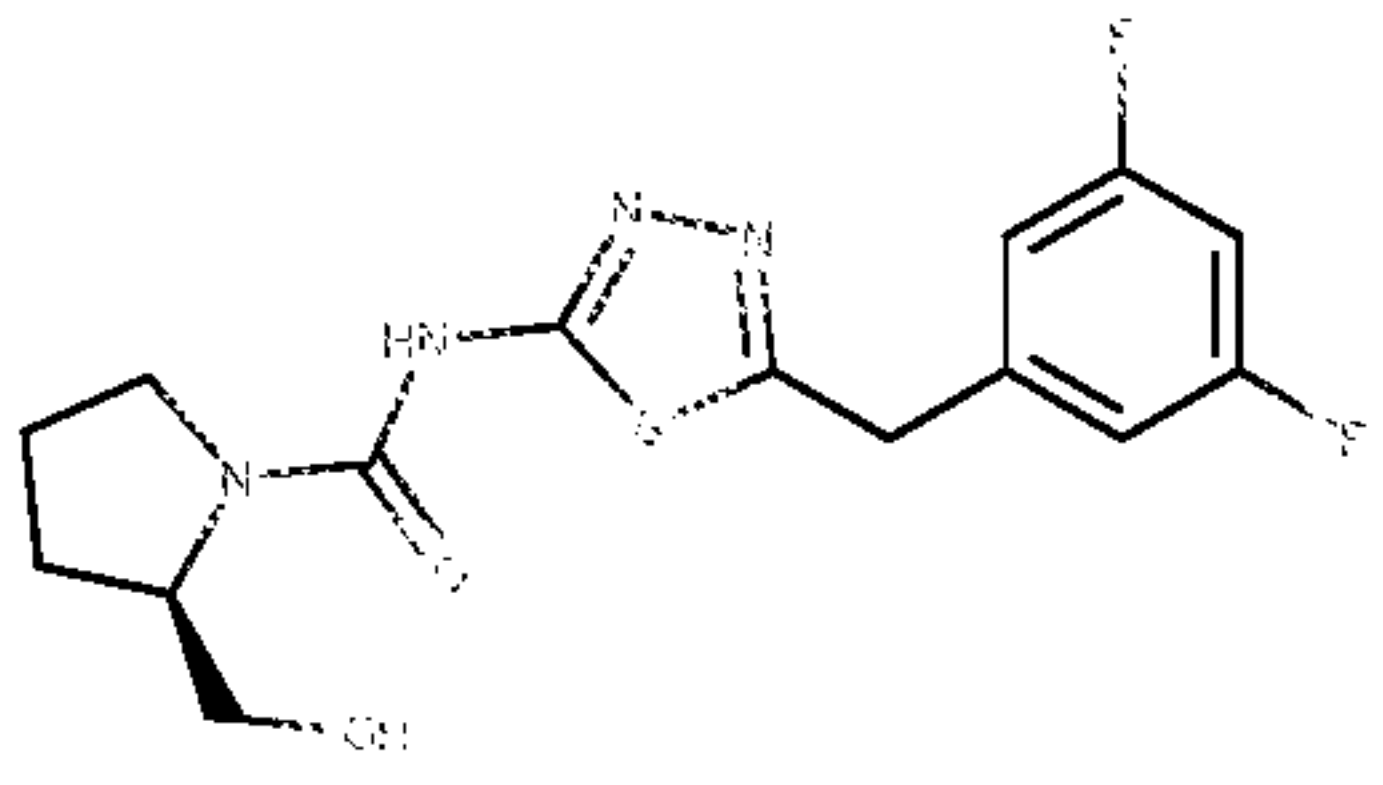
[00121] Step 2

[00122] To a solution of (4-nitrophenyl) carbonochloridate (59 mg, 0.290 mmol) in anhydrous THF (1 mL) was added a solution of 5-[(2,3-difluorophenyl)methyl]-1,3,4-thiadiazol-2-amine (synthesized using a similar method to E01 (step1), 60 mg, 0.264 mmol) and pyridine (23 uL, 0.290 mmol) in anhydrous THF (1 mL) and the reaction was stirred at RT for 20 minutes. (2S)-

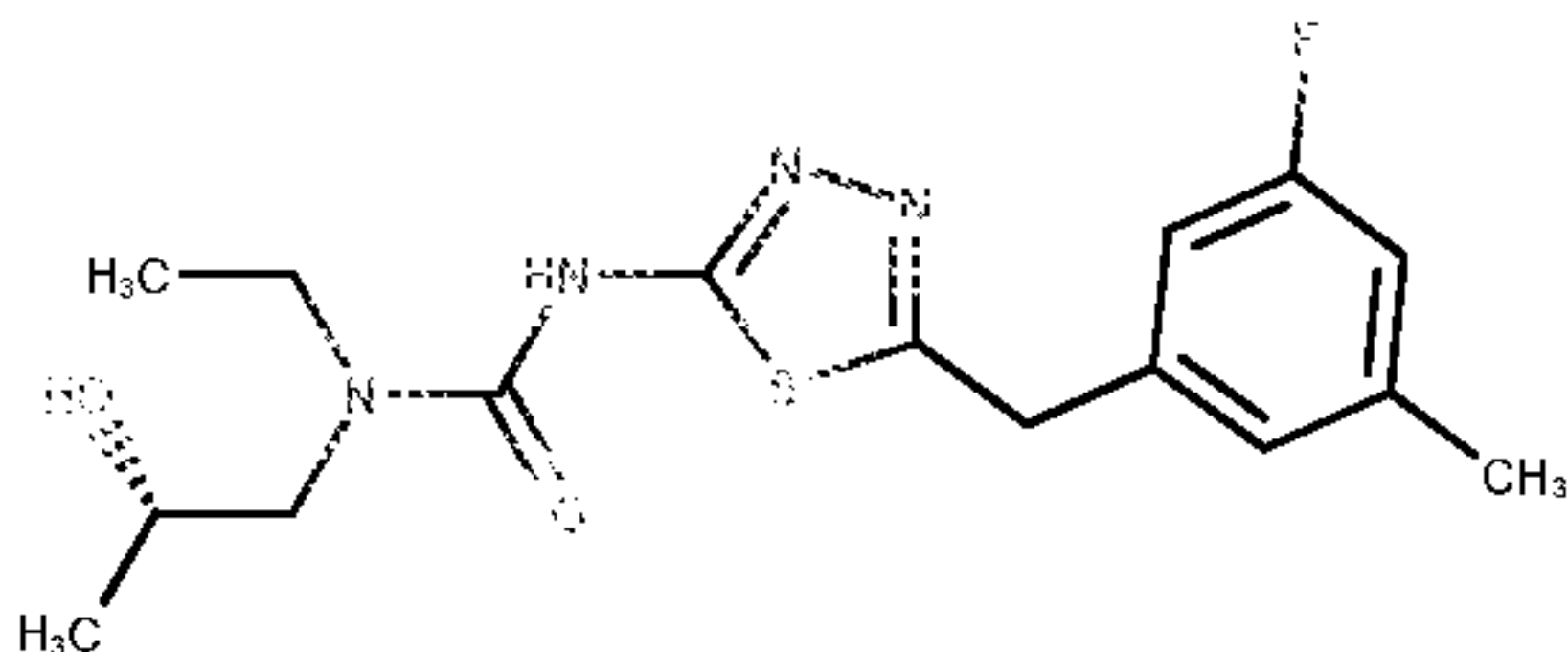
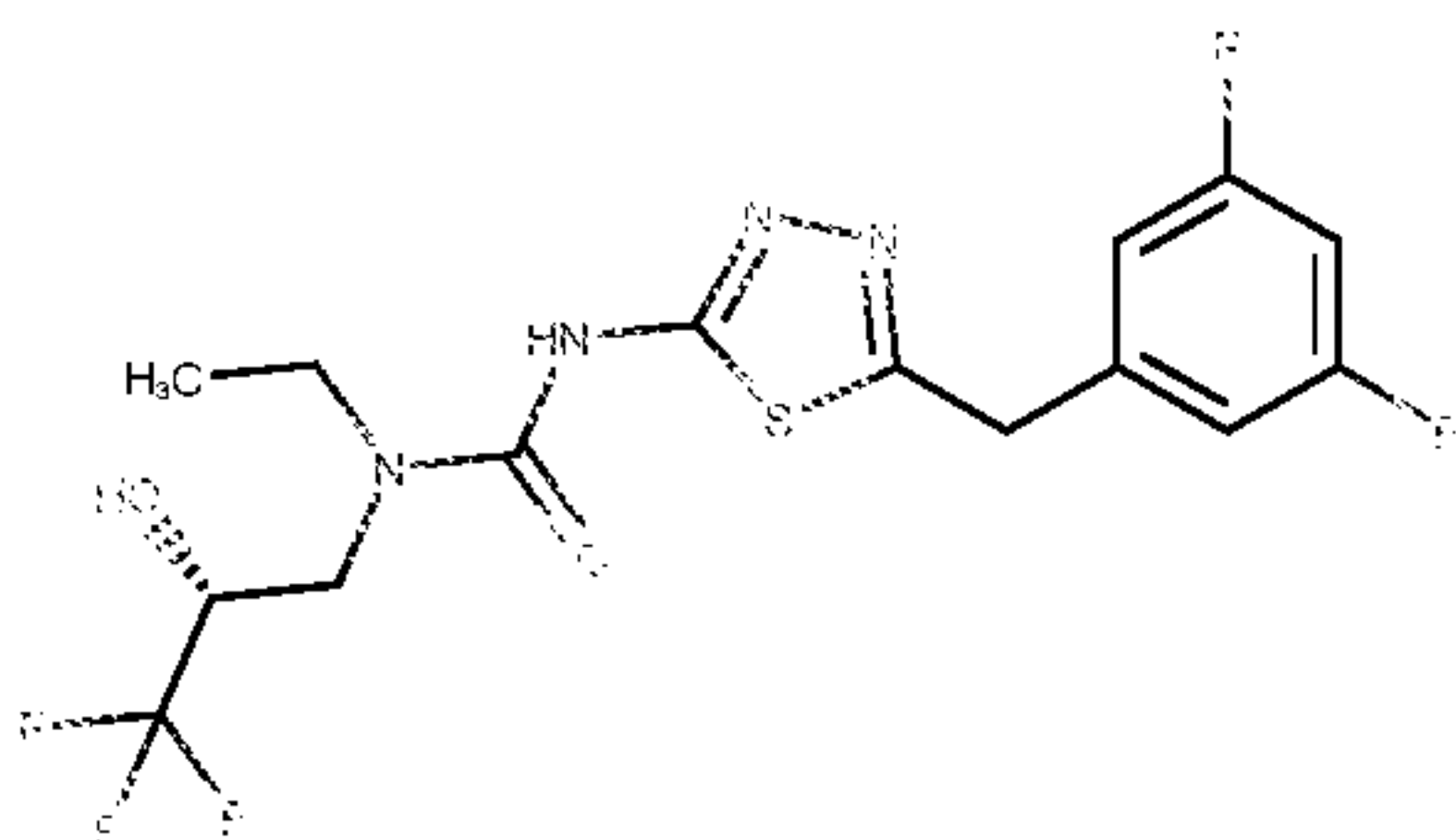
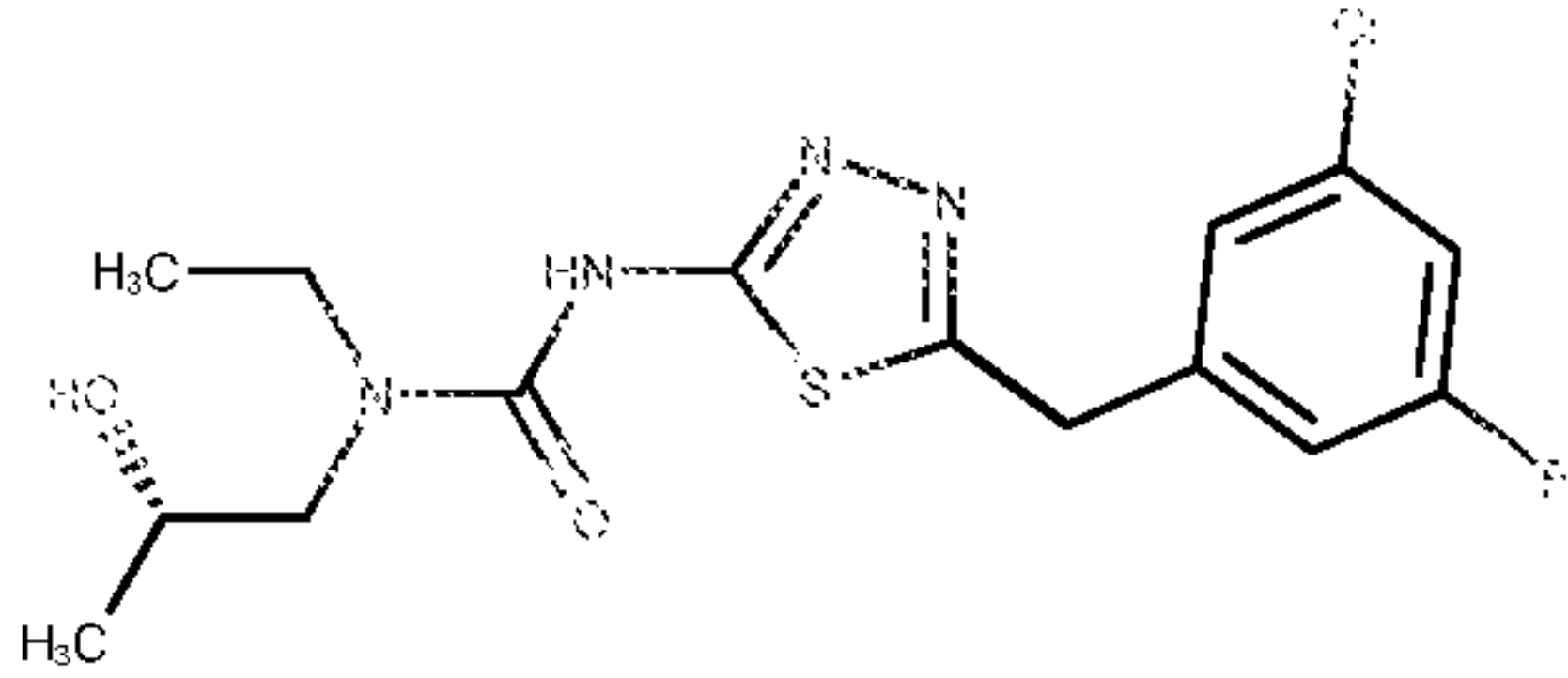
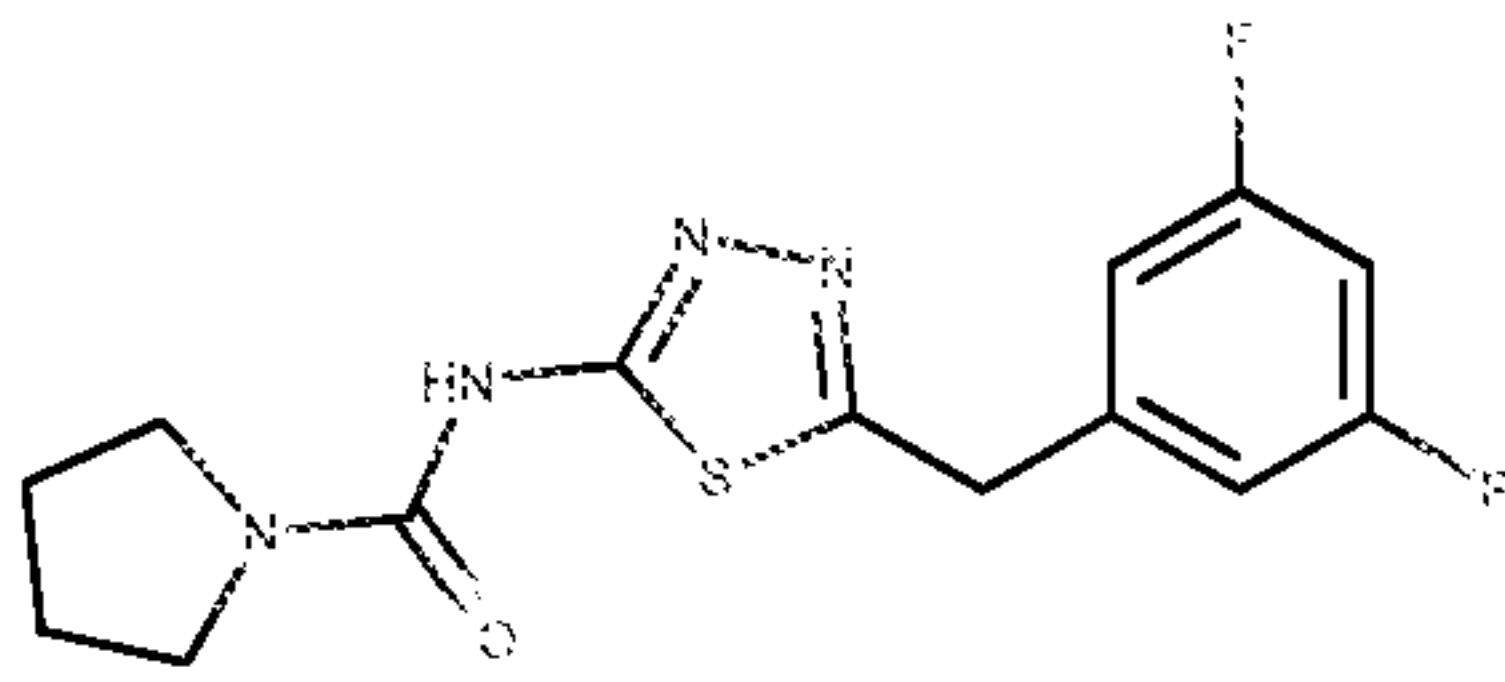
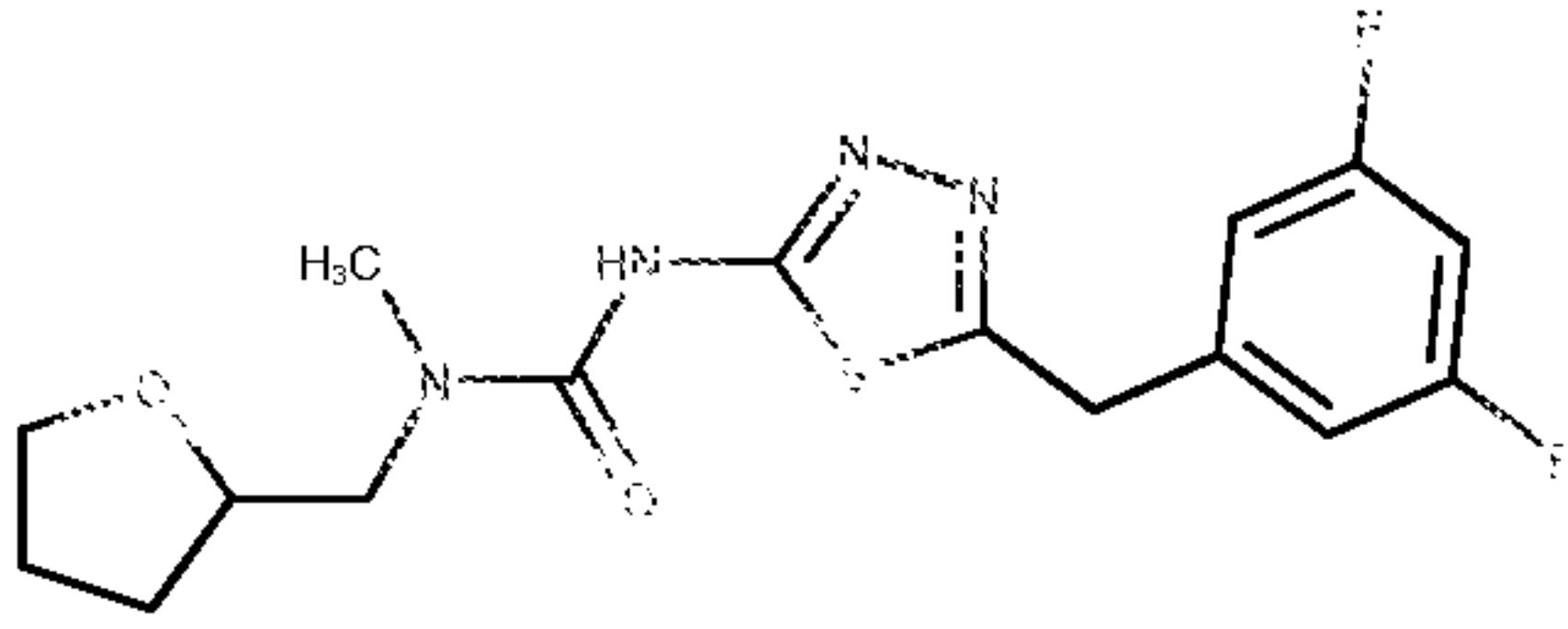
1-(ethylamino)propan-2-ol (39 mg, 0.343 mmol) and N-ethyl-N-isopropyl-propan-2-amine (69 μ L, 0.396 mmol) in anhydrous THF (1 mL) were then added and the reaction was stirred at RT for 15 minutes. It was then concentrated under reduced pressure and purified by prep HPLC (Method C) to afford the title compound as a white solid (64 mg). ^1H NMR (500 MHz, DMSO- d_6) δ 10.96 (s, 1H), 7.46 – 7.31 (m, 1H), 7.29 – 7.16 (m, 2H), 5.16 (s, 1H), 4.35 (s, 2H), 3.93 – 3.76 (m, 1H), 3.53 – 3.35 (m, 2H), 3.31 – 3.00 (m, 2H), 1.11 – 0.93 (m, 6H). LCMS m/z : 357.1 $[\text{M}+\text{H}]^+$, RT = 2.65 (Method A)

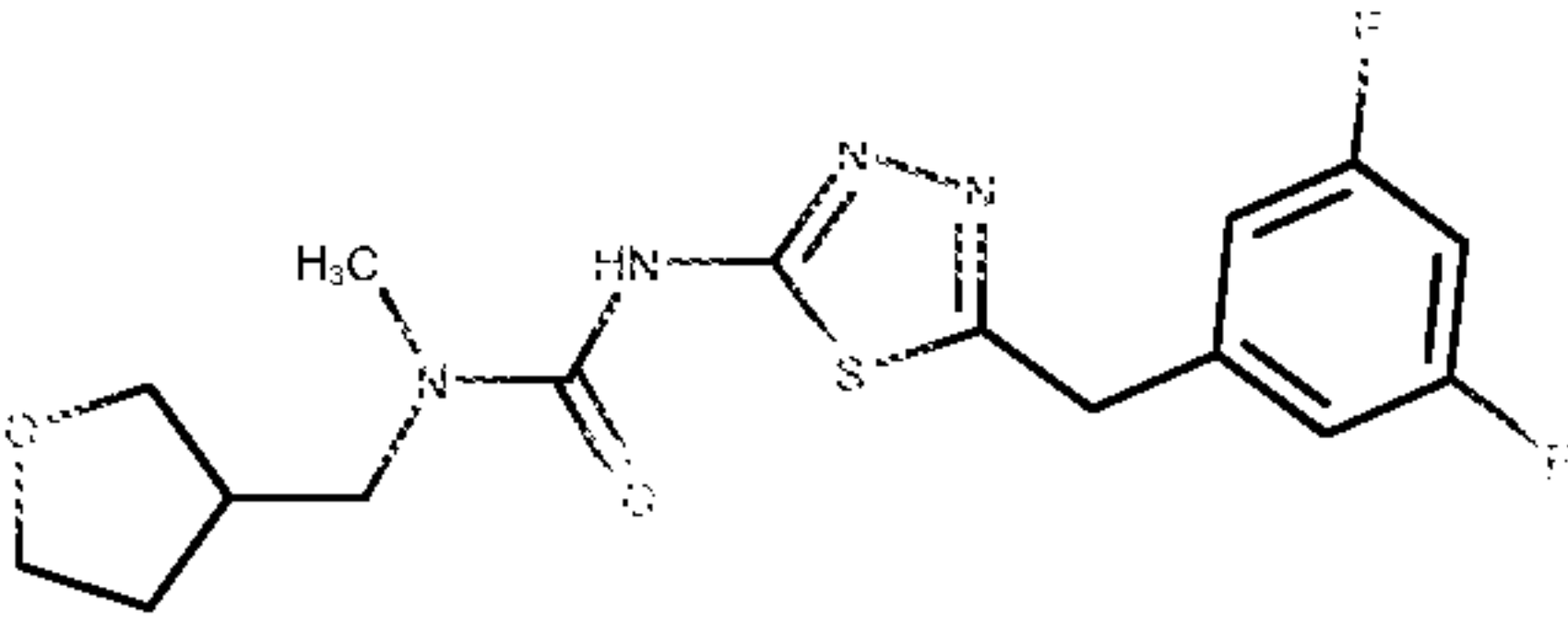
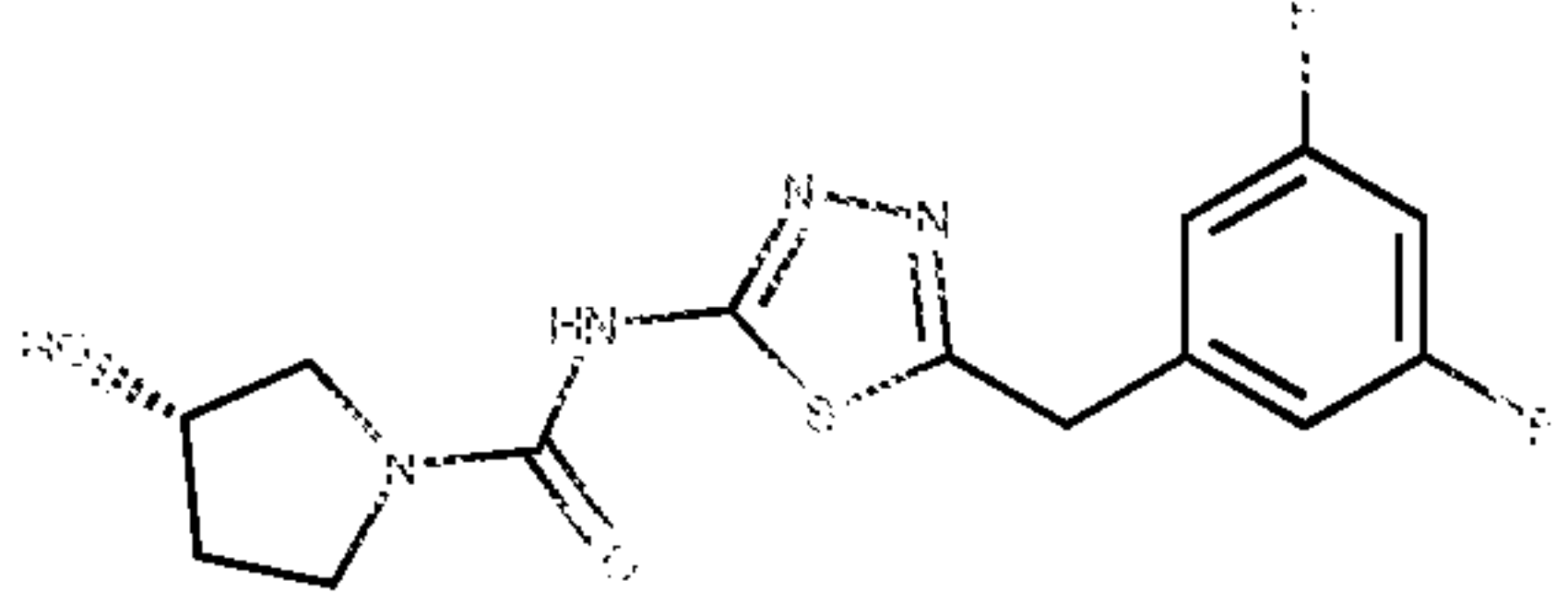
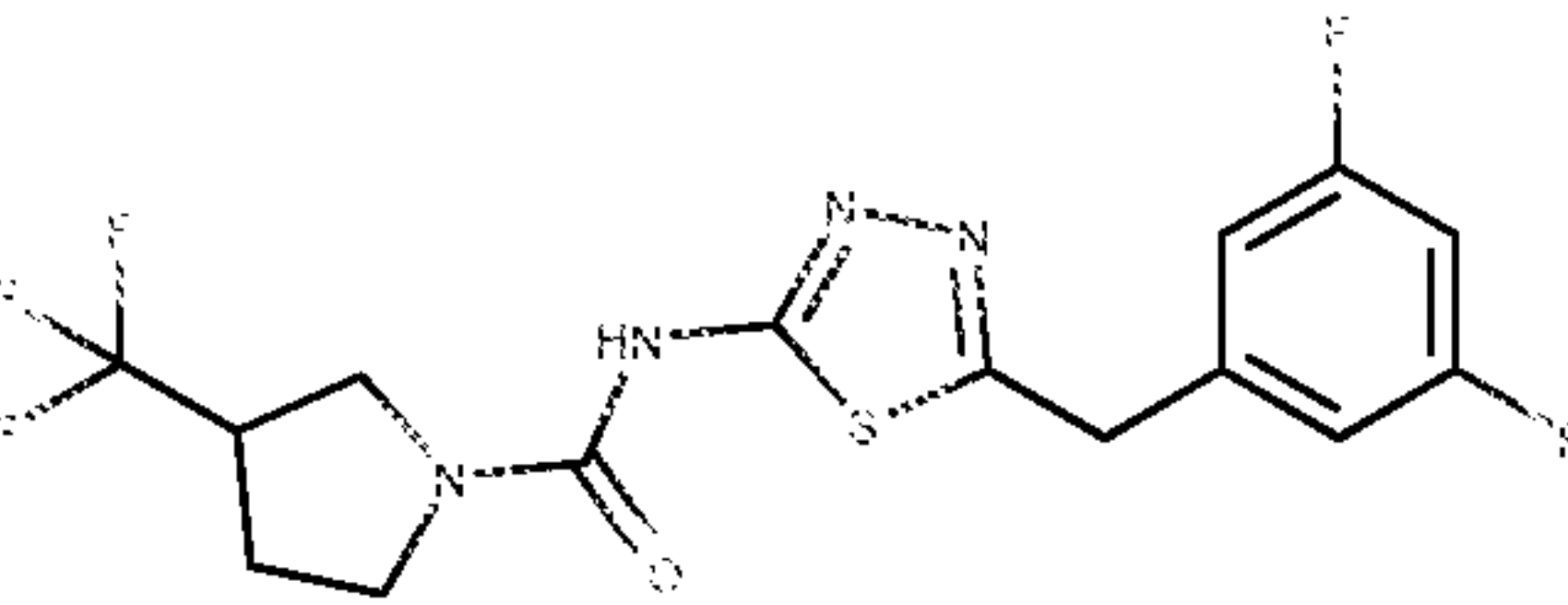
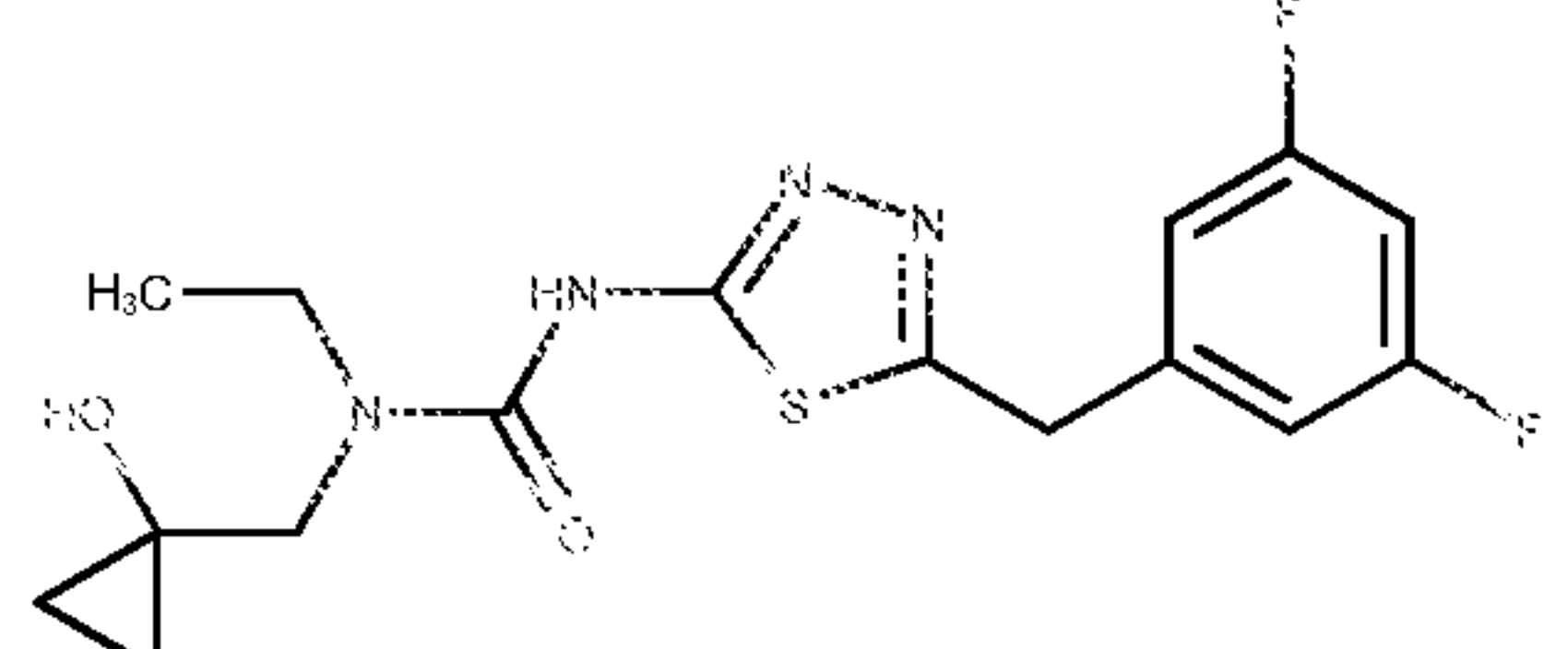
Table 2: The following compounds were synthesized using a similar method to that used in **Example E09**, using either commercial amines, or aminoalcohols synthesized using a similar method to Example E09, step 1.

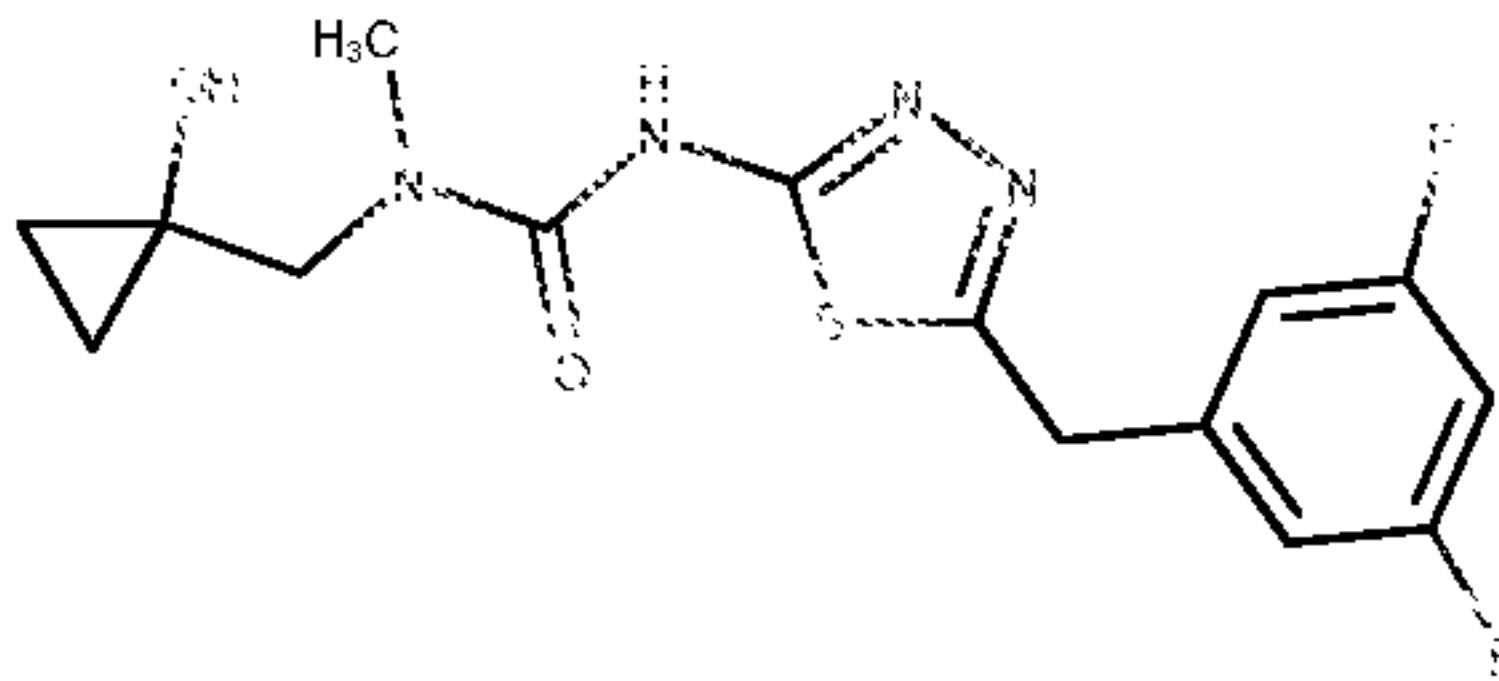
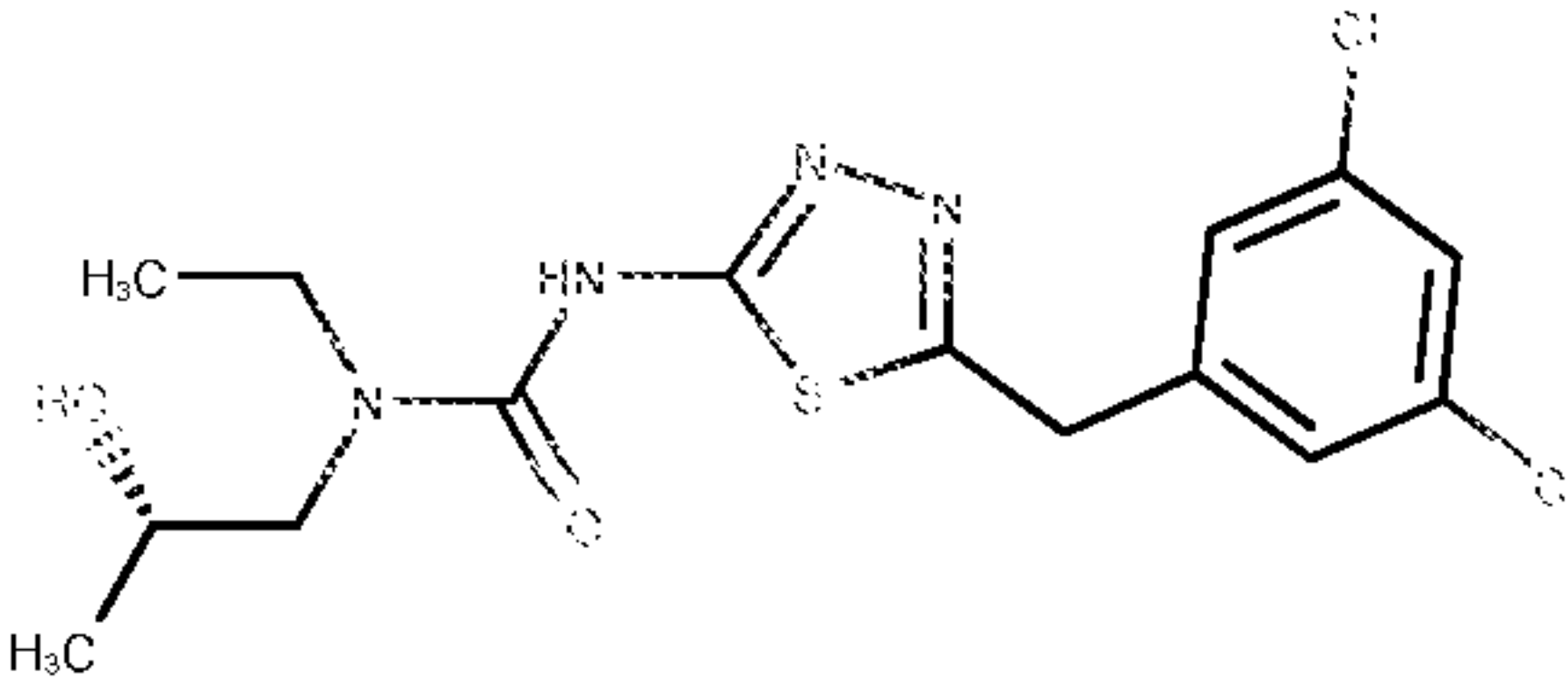
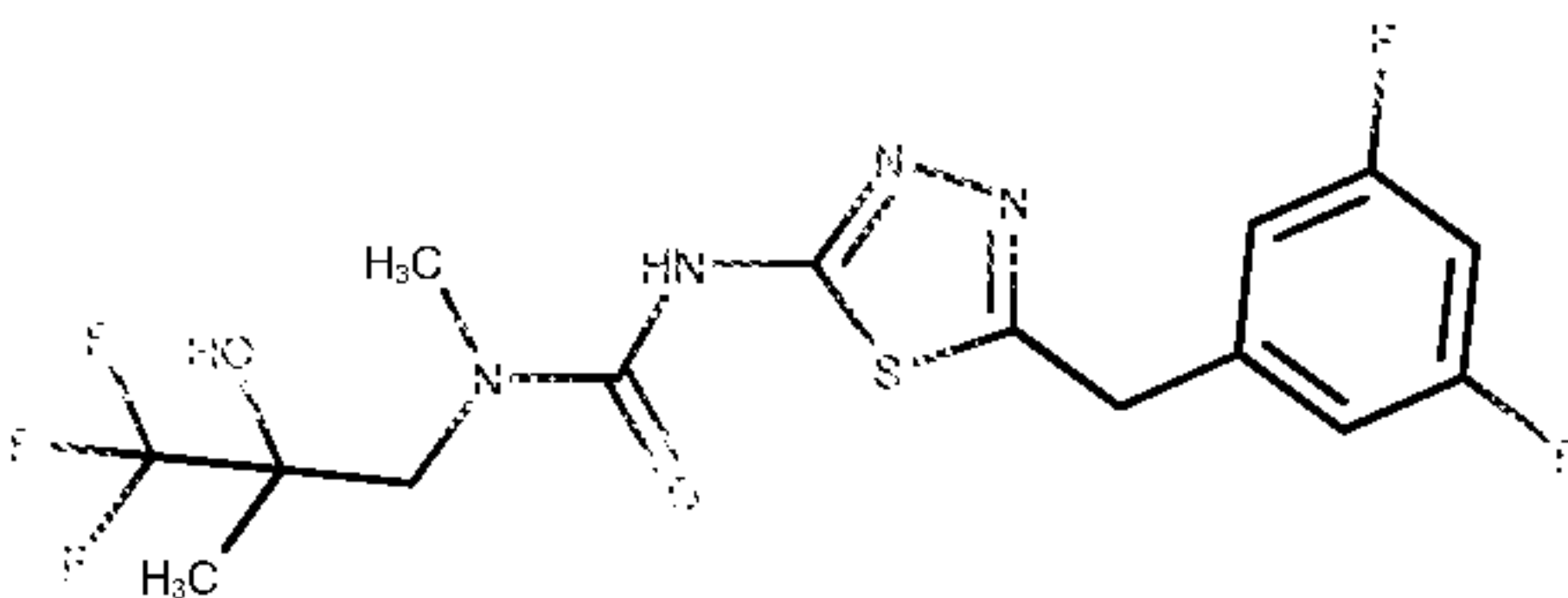
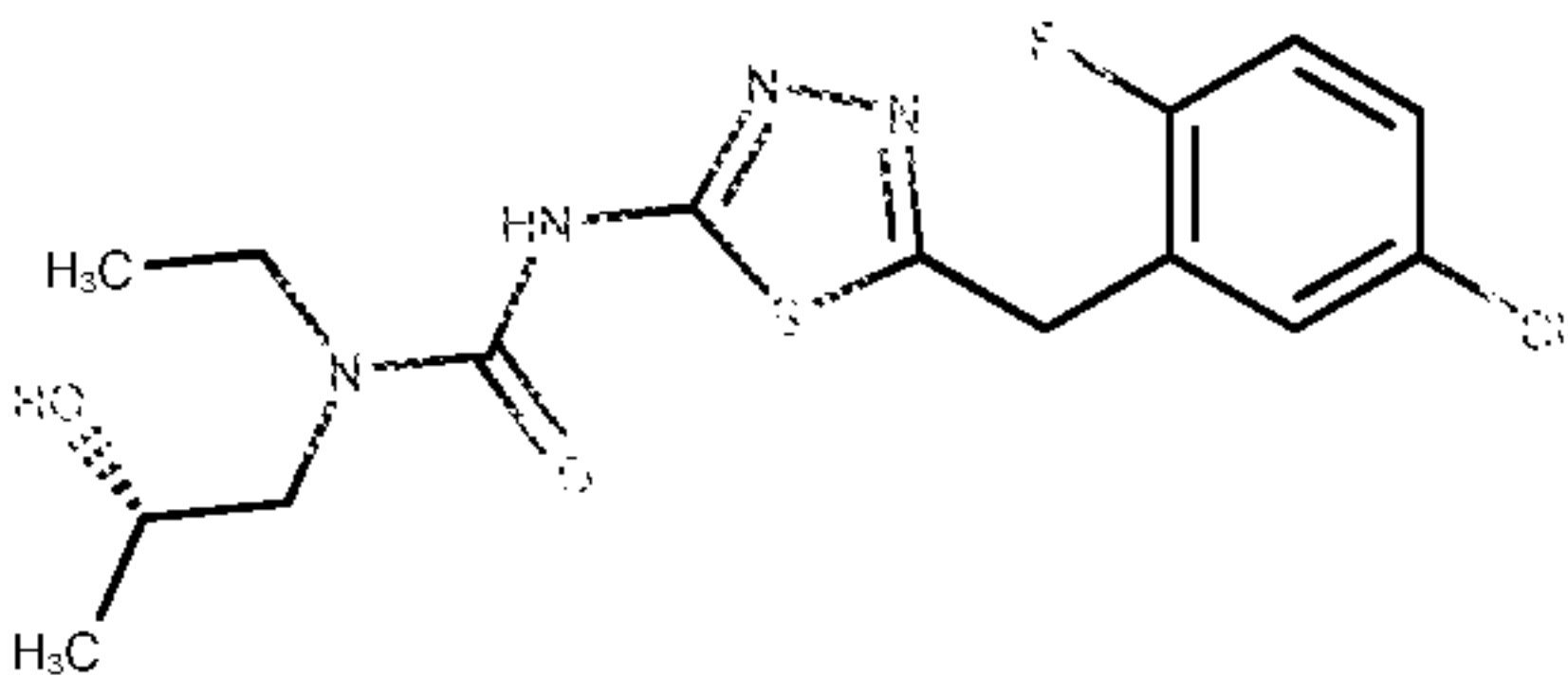
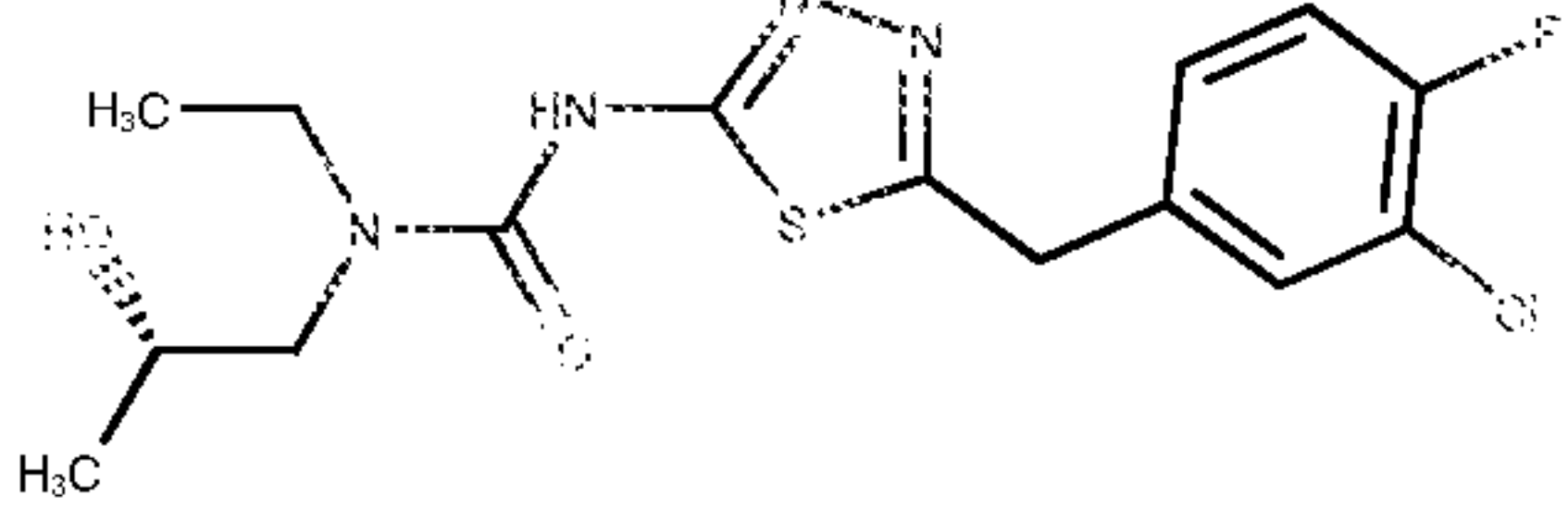
Example number	Structure	Analytical data	LCMS Method
E10		^1H NMR (400 MHz, DMSO- d_6) δ 10.98 (s, 1H), 7.14 (tt, J = 9.4, 2.4 Hz, 1H), 7.10 – 7.03 (m, 2H), 4.30 (s, 2H), 3.91 – 3.79 (m, 1H), 3.51 – 3.35 (m, 3H), 3.27 – 3.15 (m, 1H), 1.11 – 1.01 (m, 6H). LCMS m/z : 357.2 $[\text{M}+\text{H}]^+$, RT = 2.69	A
E11		^1H NMR (500 MHz, DMSO- d_6) δ 11.11 (s, 1H), 7.42 – 7.36 (m, 1H), 7.19 – 7.13 (m, 2H), 7.10 (td, J = 8.6, 2.4 Hz, 1H), 4.28 (s, 2H), 3.92 – 3.76 (m, 1H), 3.48 – 3.36 (m, 3H), 3.25 – 3.11 (m, 1H), 1.09 – 1.00 (m, 6H). LCMS m/z : 339.1 $[\text{M}+\text{H}]^+$, RT = 2.57	A
E12		^1H NMR (400 MHz, Chloroform- d) δ 7.06 – 6.90 (m, 3H), 4.28 (s, 2H), 4.26 – 4.16 (m, 1H), 3.54 – 3.35 (m, 3H), 3.29 (dd, J = 15.5, 2.1 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H). LCMS m/z : 357.2 $[\text{M}+\text{H}]^+$, RT = 2.62	A

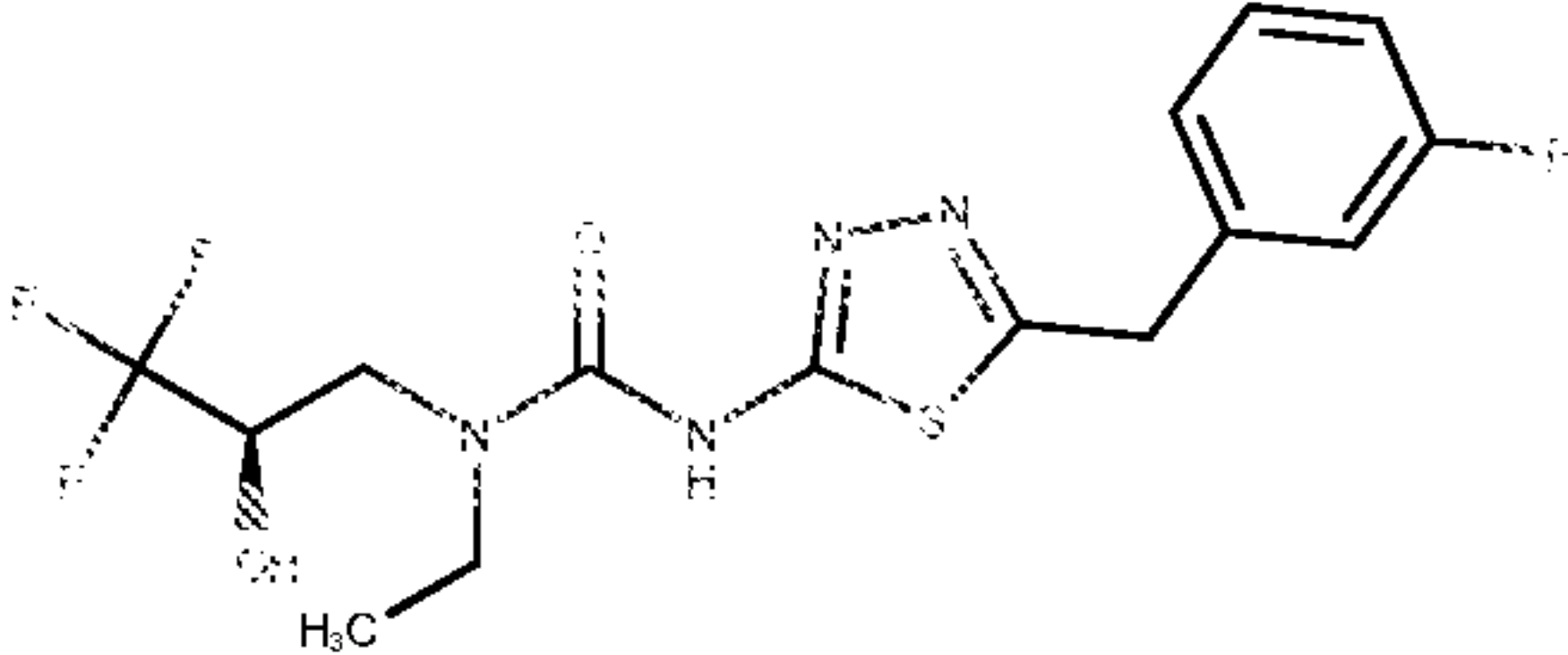
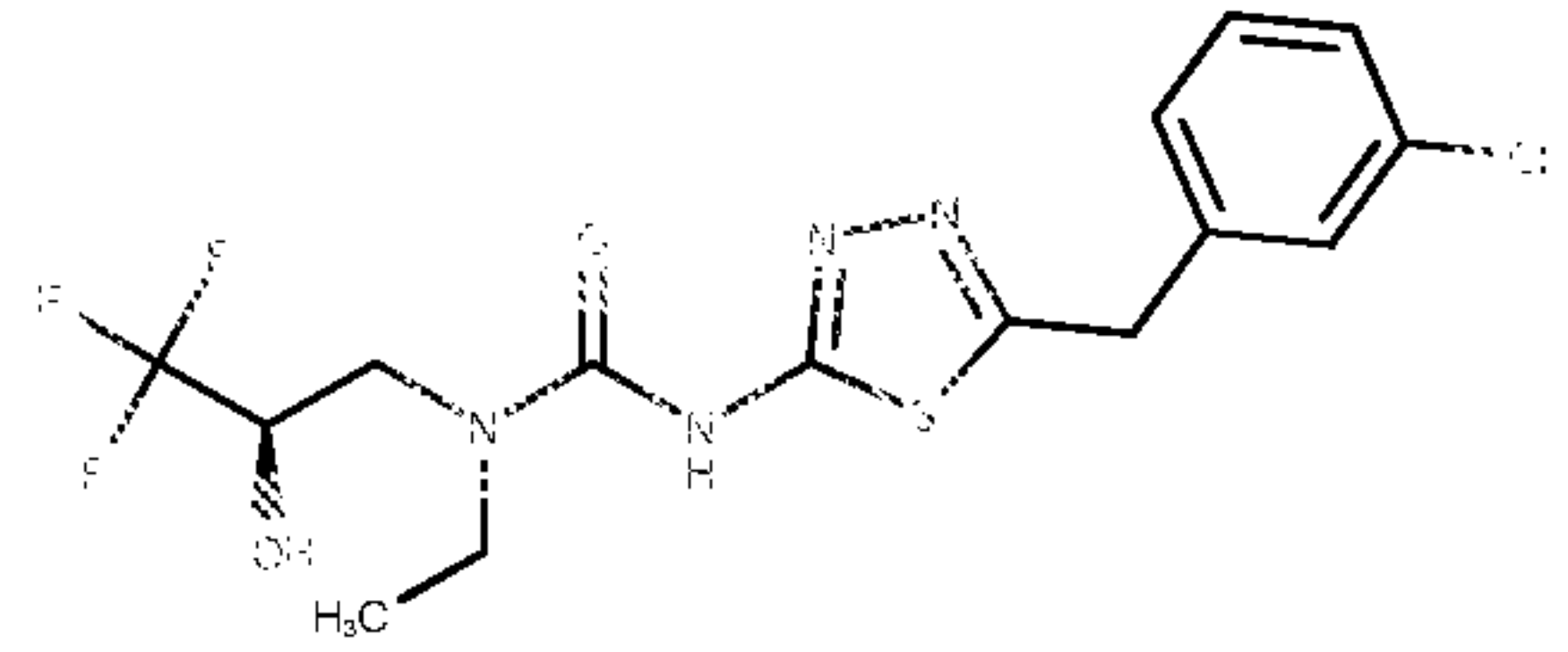
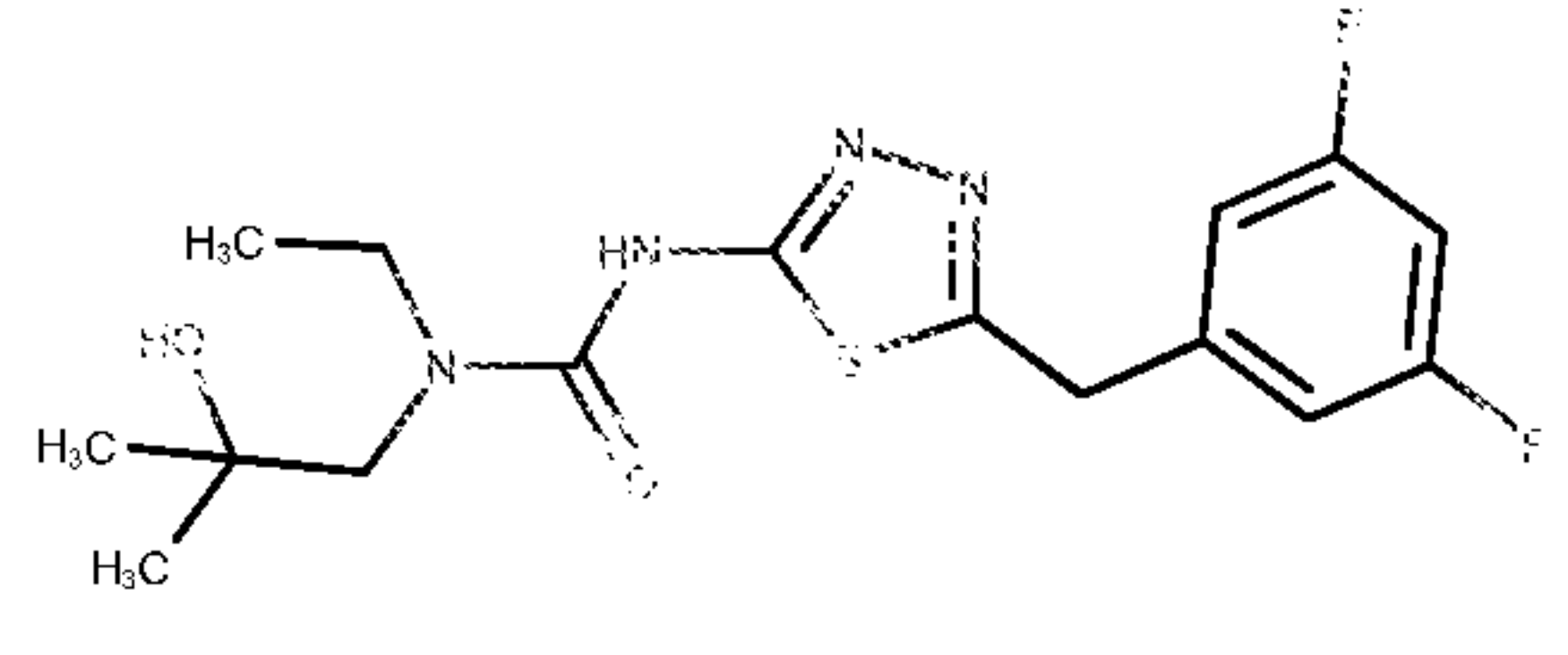
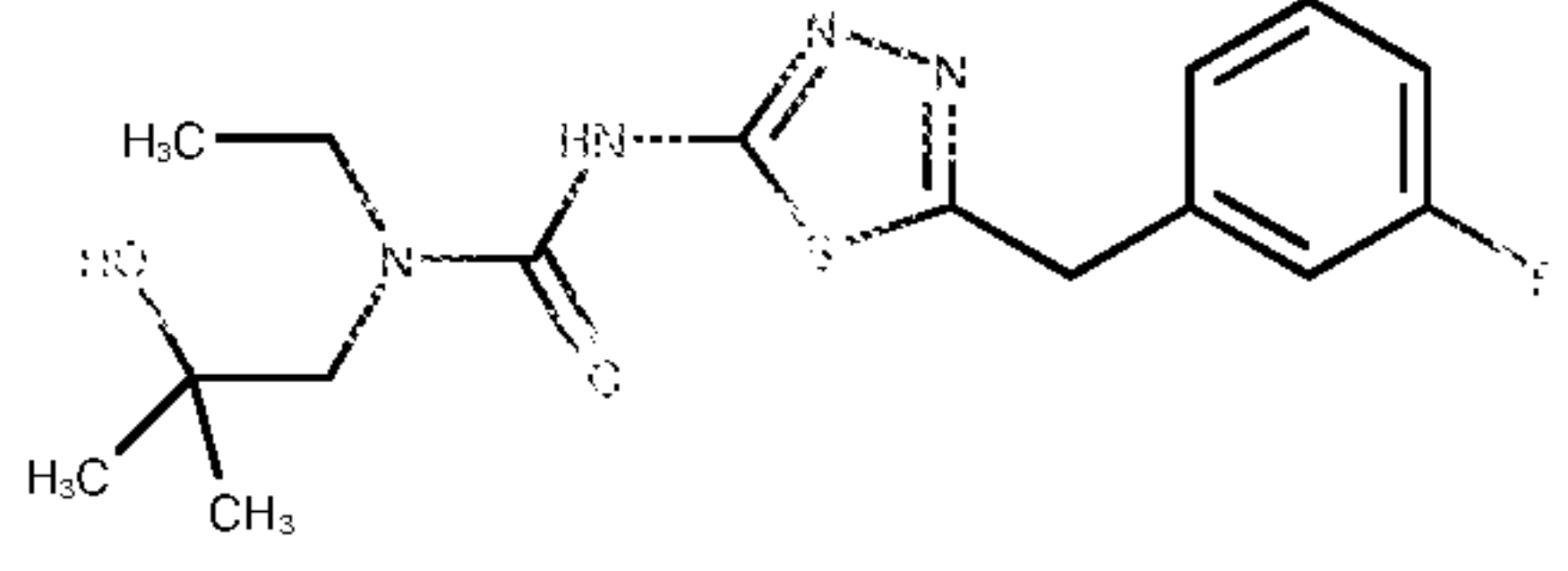
Example number	Structure	Analytical data	LCMS Method
E13		¹H NMR (400 MHz, Chloroform-d) δ 7.09 (dtd, J = 10.2, 5.2, 2.6 Hz, 2H), 7.04 – 6.95 (m, 1H), 4.23 (s, 3H), 3.54 – 3.33 (m, 3H), 3.29 (dd, J = 15.5, 1.8 Hz, 1H), 1.32 (d, J = 6.3 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H). LCMS m/z: 358.4 [M+H]⁺, RT = 2.68	A
E14		¹H NMR (400 MHz, DMSO-d₆) δ 10.93 (s, 1H, 15), 7.19 – 7.11 (m, 1H, 6), 7.11 – 7.04 (m, 2H, 2, 4), 4.95 (s, 1H, 23), 4.32 (s, 2H, 7), 3.94 – 3.78 (m, 1H, 21), 3.29 – 3.20 (m, 2H, 20), 2.99 (s, 3H, 19), 1.05 (d, J = 6.2 Hz, 3H, 22). LCMS m/z: 343.1 [M+H]⁺, RT = 2.36	A
E15		¹H NMR (400 MHz, DMSO-d₆) δ 11.05 (br s, 1H, 15), 7.19 – 7.11 (m, 1H, 6), 7.11 – 7.05 (m, 2H, 2, 4), 4.81 (br s, 1H, 23), 4.31 (s, 2H, 7), 3.90 – 3.78 (m, 1H, 21), 3.25 (m, 2H, 20), 2.99 (s, 3H, 19), 1.04 (d, J = 6.2 Hz, 3H, 22). LCMS m/z: 343.1 [M+H]⁺, RT = 2.36	A
E16		¹H NMR (500 MHz, DMSO-d₆) δ 10.20 (br s, 1H, 3), 7.19 – 7.11 (m, 1H, 14), 7.10 – 7.01 (m, 2H, 12, 16), 4.60 (br s, 1H, 24), 4.32 (s, 2H, 7), 3.95 (s, 1H, 22), 3.52 – 3.37 (m, 4H, 19, 23), 1.95 – 1.60 (m, 4H, 20, 21). LCMS m/z: 355.1 [M+H]⁺, RT = 2.46	A

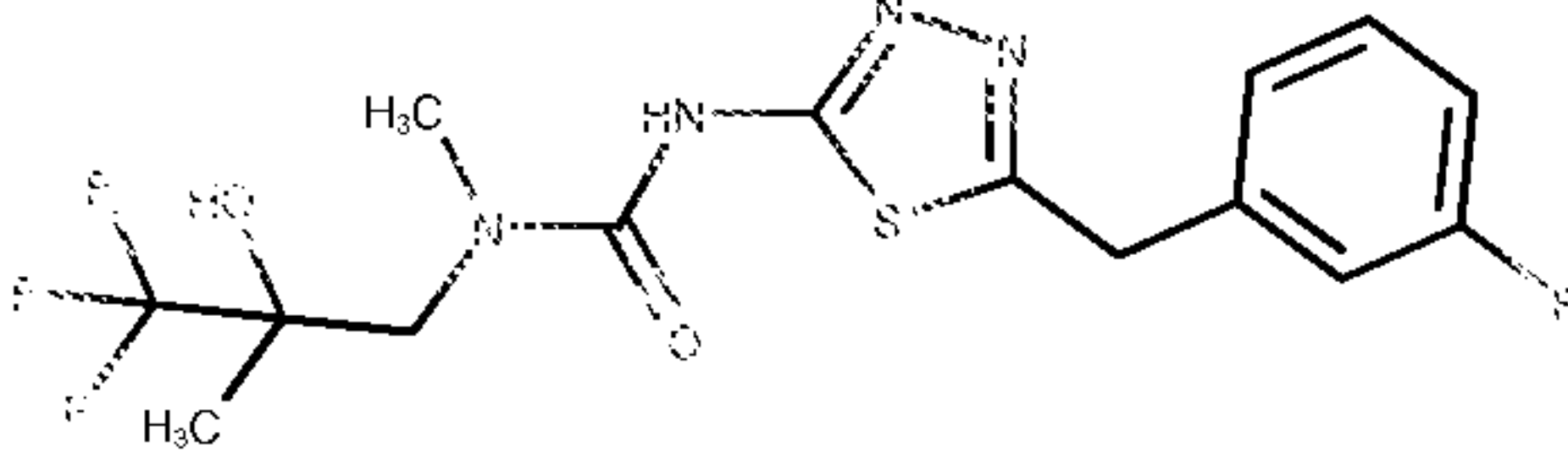
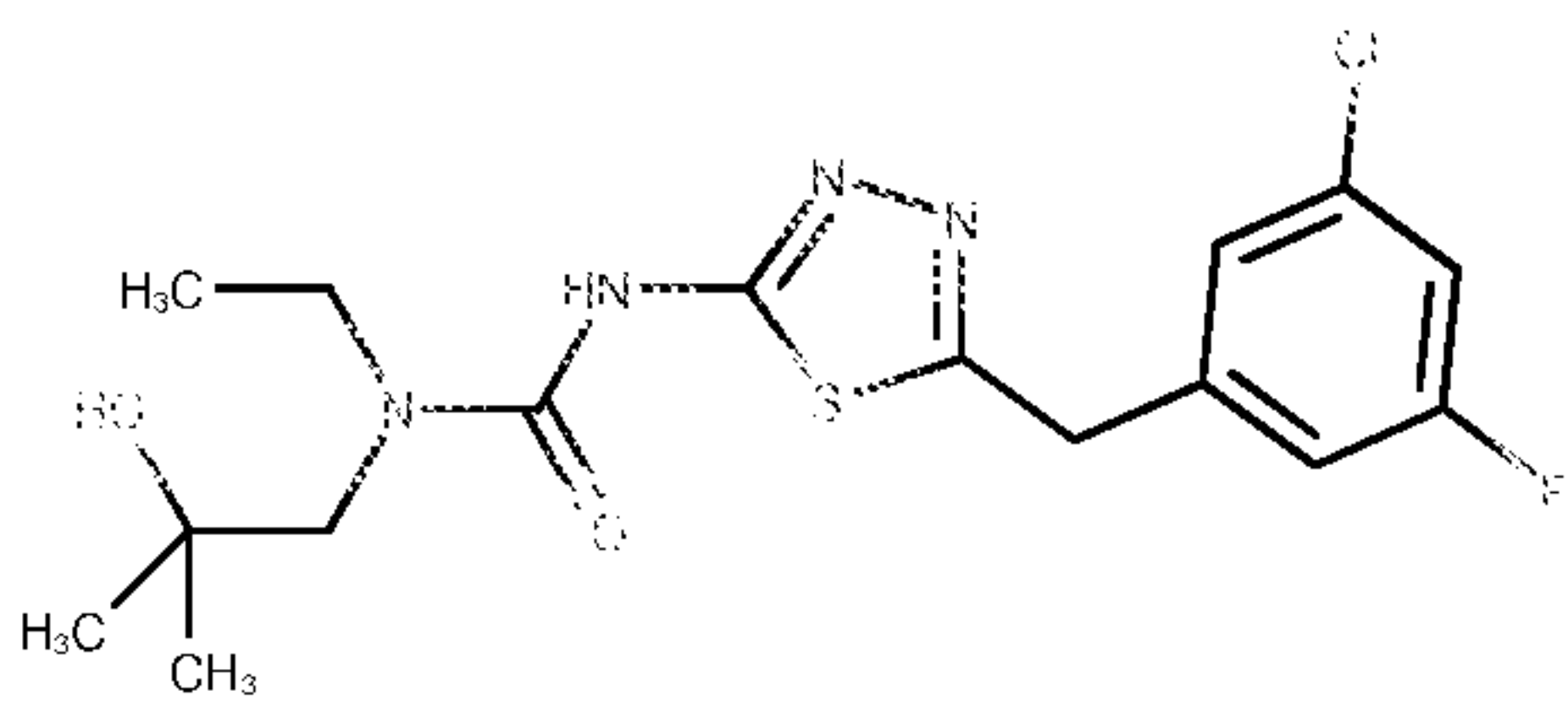
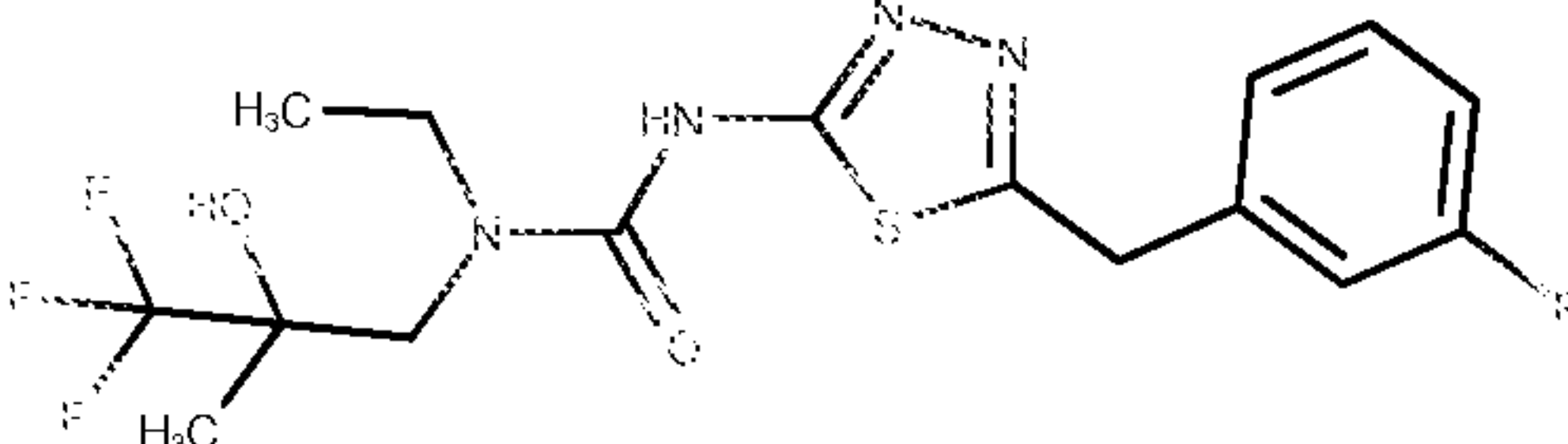
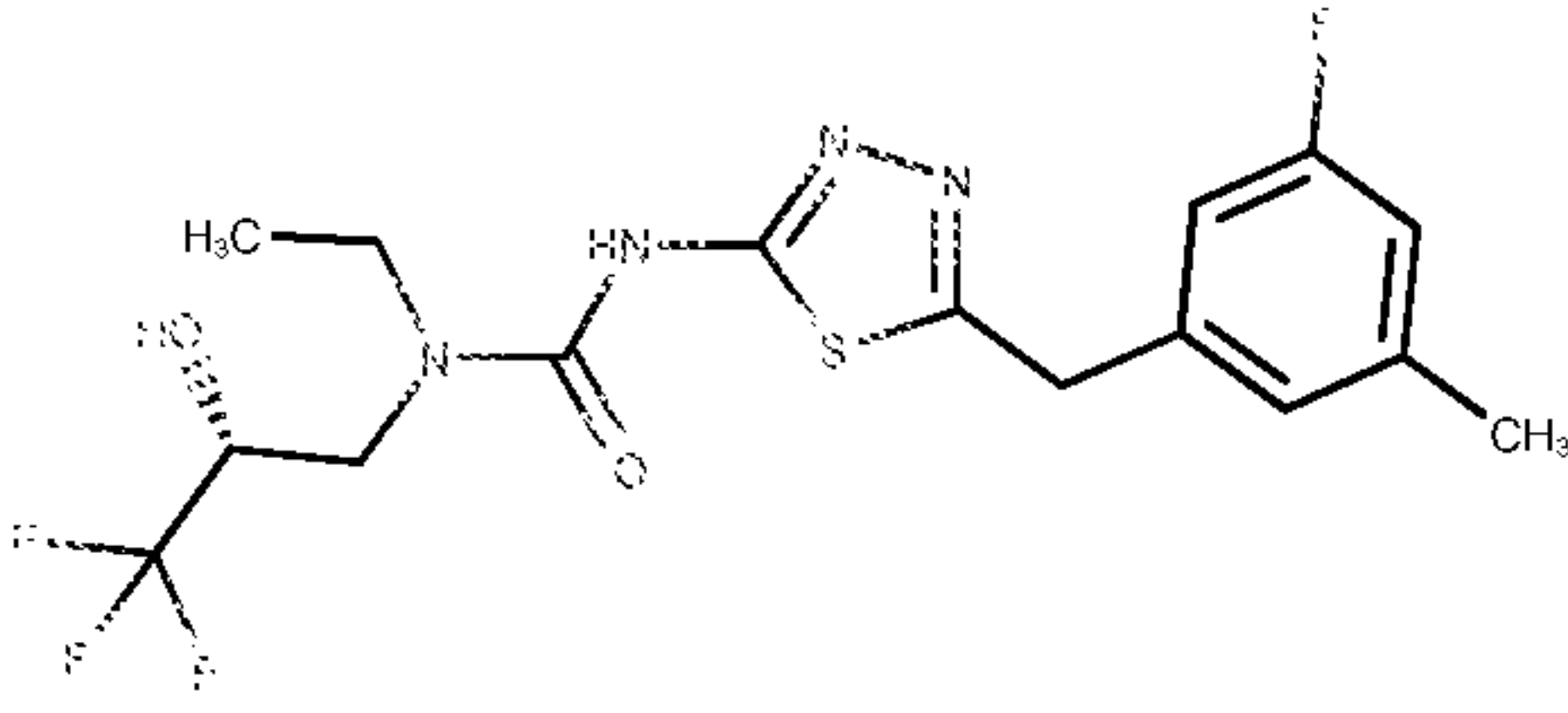
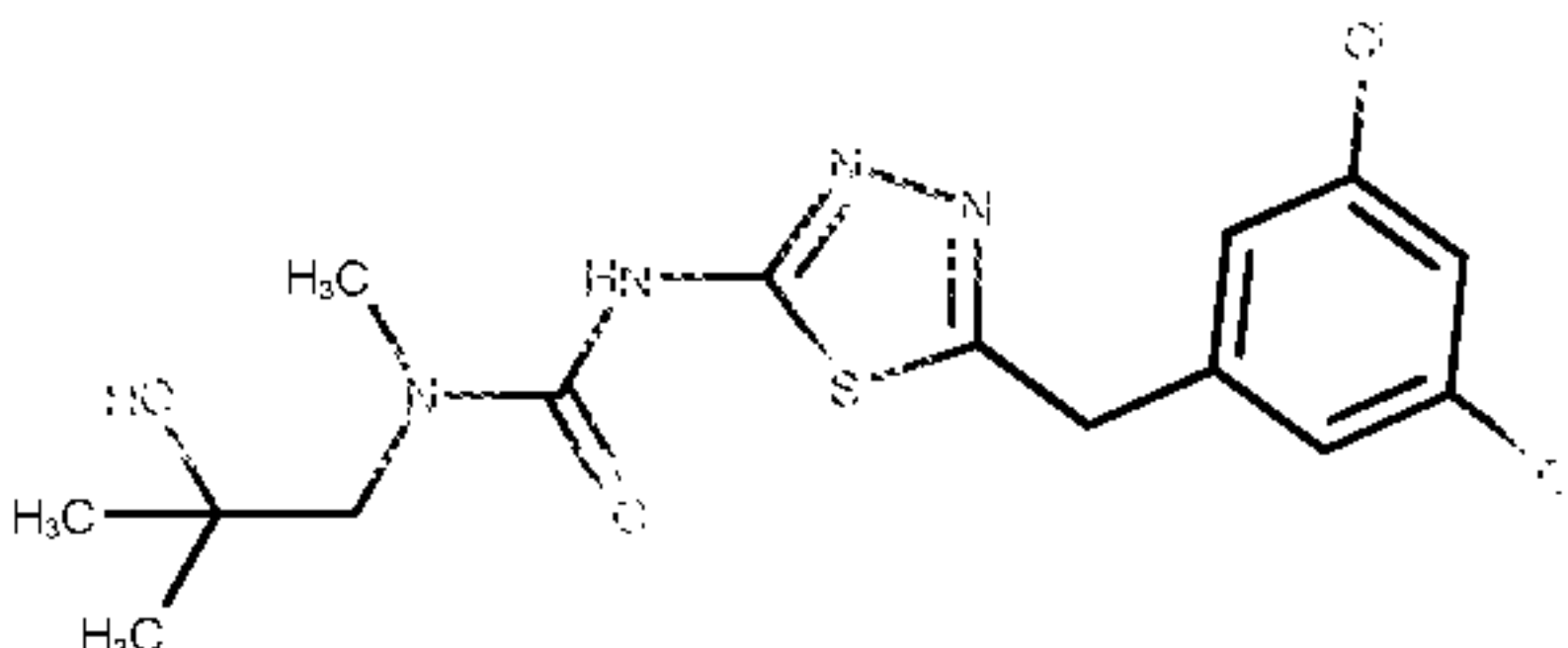
Example number	Structure	Analytical data	LCMS Method
E17		¹H NMR (400 MHz, DMSO-d₆) δ 10.94 (s, 1H), 7.14 (tt, J = 9.4, 2.4 Hz, 1H), 7.10 – 7.03 (m, 2H), 4.71 (s, 1H), 4.30 (s, 3H), 3.43 – 3.33 (m, 2H), 2.81 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H). LCMS m/z: 343.1 [M+H]⁺, RT = 2.29	A
E18		¹H NMR (500 MHz, DMSO-d₆) δ 11.39 (s, 1H), 7.15 (tt, J = 9.4, 2.3 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.88 – 5.97 (m, 1H), 4.29 (s, 2H), 4.25 – 4.17 (m, 1H), 3.68 (dd, J = 14.2, 3.2 Hz, 1H), 3.40 (s, 1H), 3.03 (d, J = 19.1 Hz, 3H). LCMS m/z: 397.1 [M+H]⁺, RT = 2.83	A
E19		¹H NMR (500 MHz, DMSO-d₆) δ 11.19 (s, 1H), 7.15 (tt, J = 9.4, 2.3 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.46 (s, 1H), 4.29 (s, 2H), 4.22 (s, 1H), 3.68 (d, J = 12.0 Hz, 1H), 3.40 (s, 1H), 3.05 (s, 3H). LCMS m/z: 397.1 [M+H]⁺, RT = 2.83	A
E20		¹H NMR (400 MHz, Chloroform-d) δ 6.86 – 6.77 (m, 2H), 6.70 (tt, J = 8.9, 2.3 Hz, 1H), 4.25 (s, 2H), 3.33 (s, 2H), 3.08 (s, 3H), 1.65 (s, 2H), 1.38 (s, 6H). LCMS m/z: 357.1 [M+H]⁺, RT = 2.62	A
E21		¹H NMR (400 MHz, Chloroform-d) δ 7.19 (t, J = 7.5 Hz, 1H), 7.10 – 7.03 (m, 3H), 4.29 – 4.22 (m, 1H), 4.22 (s, 2H), 3.57 – 3.24 (m, 4H), 2.31 (s, 3H), 1.32 (d, J = 6.3 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H), OH and NH not observed.	A

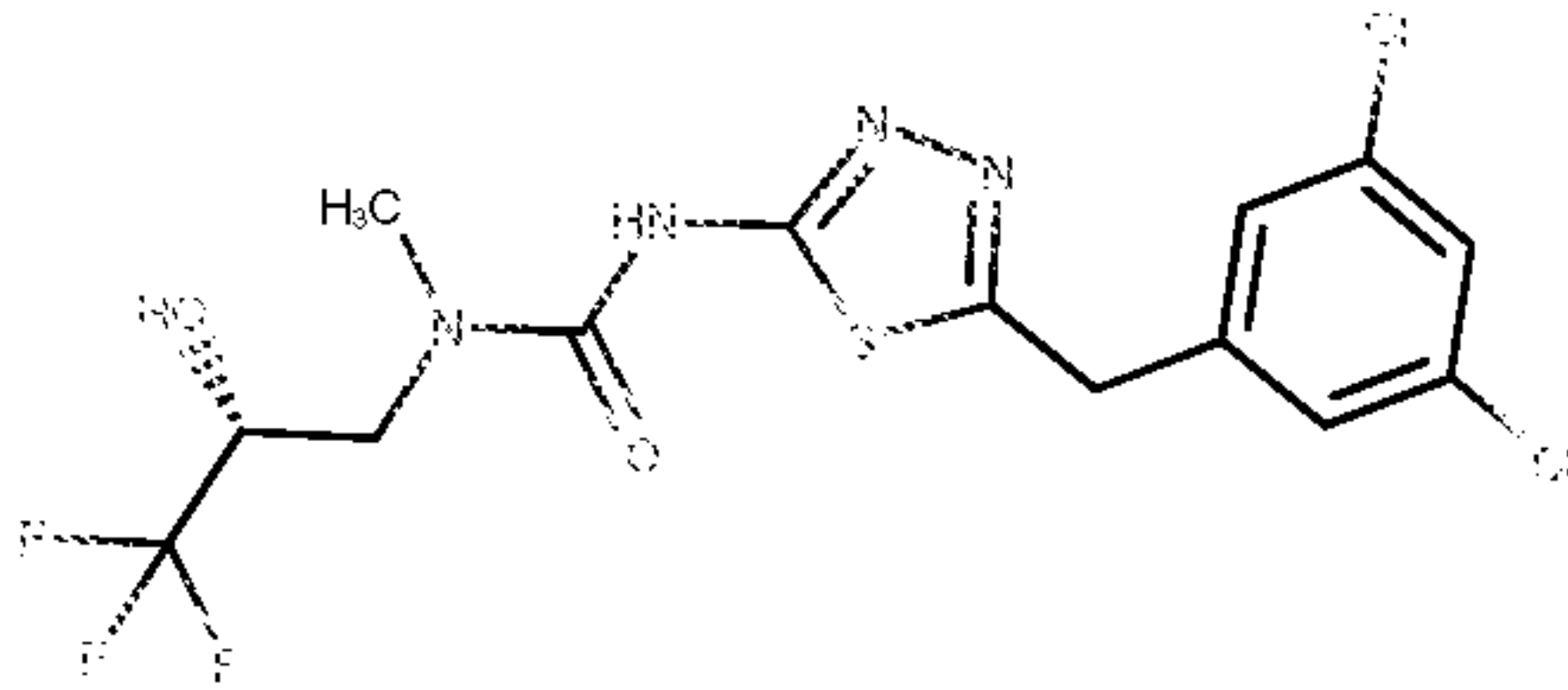
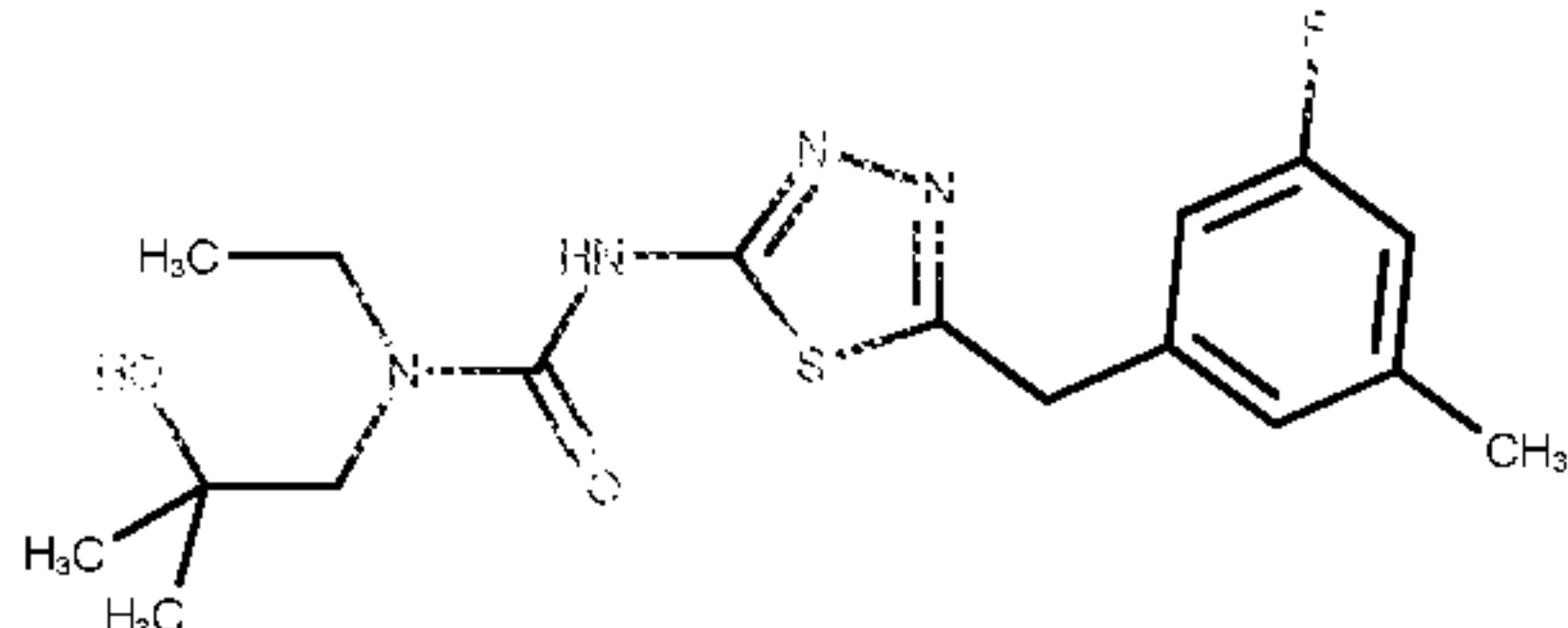
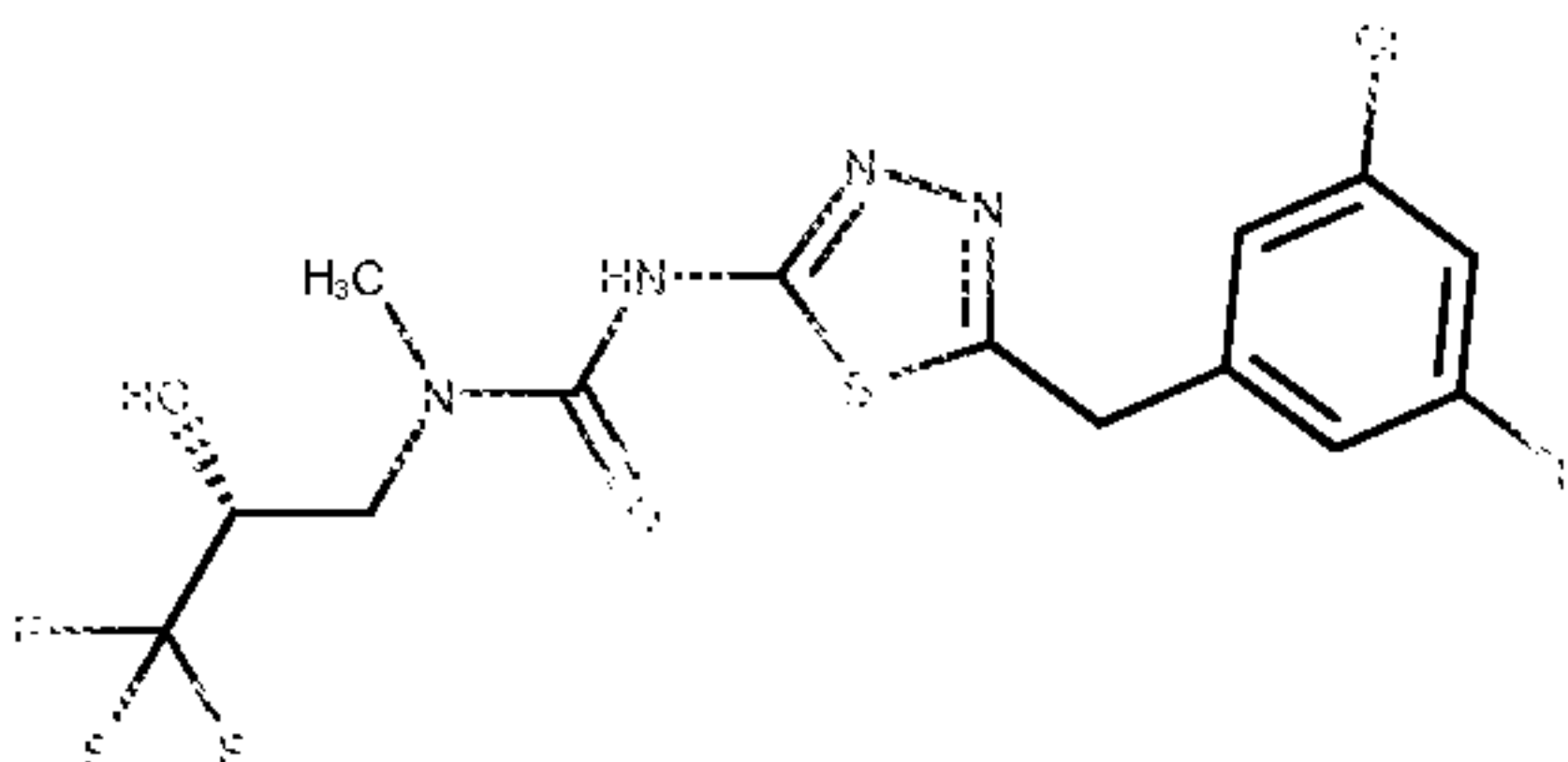
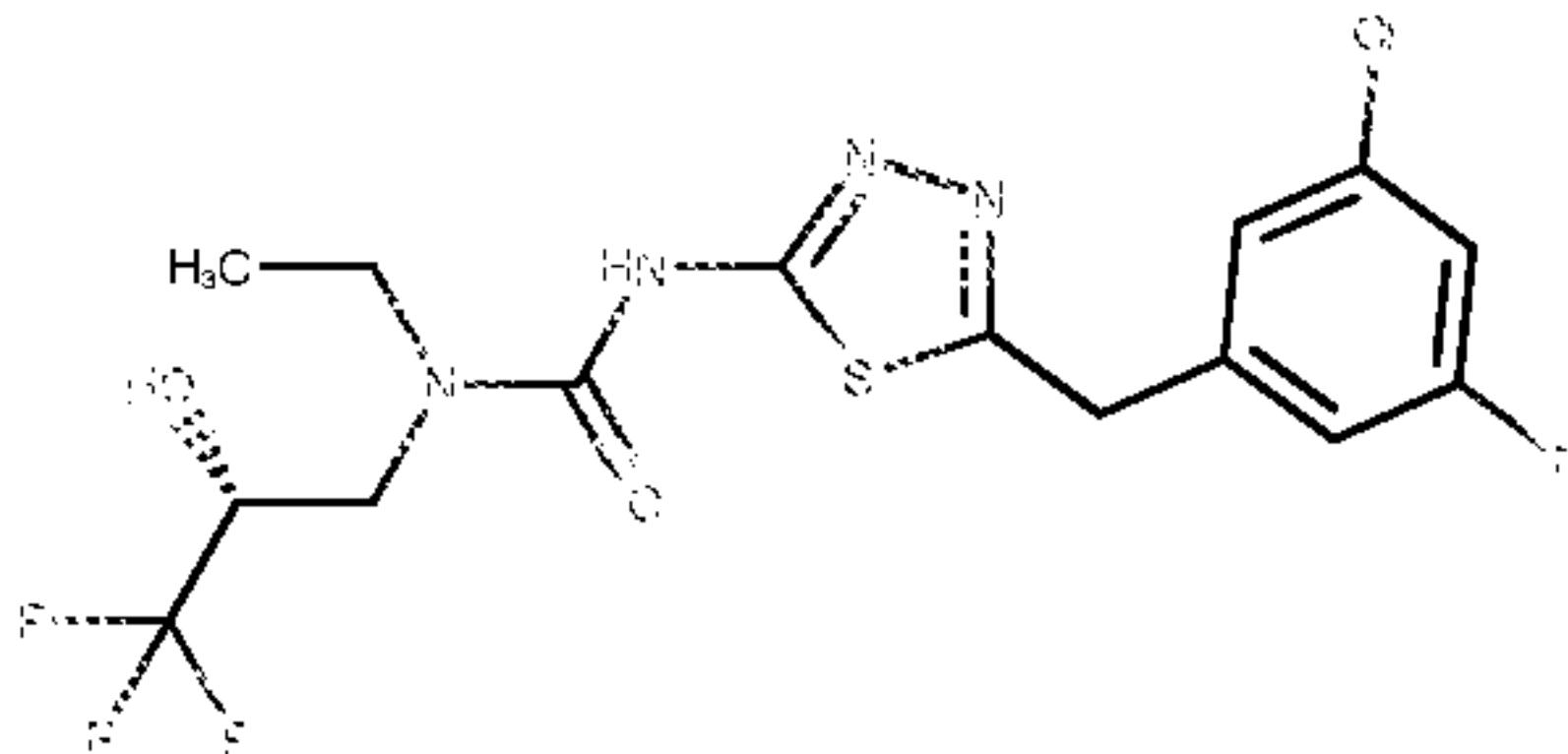
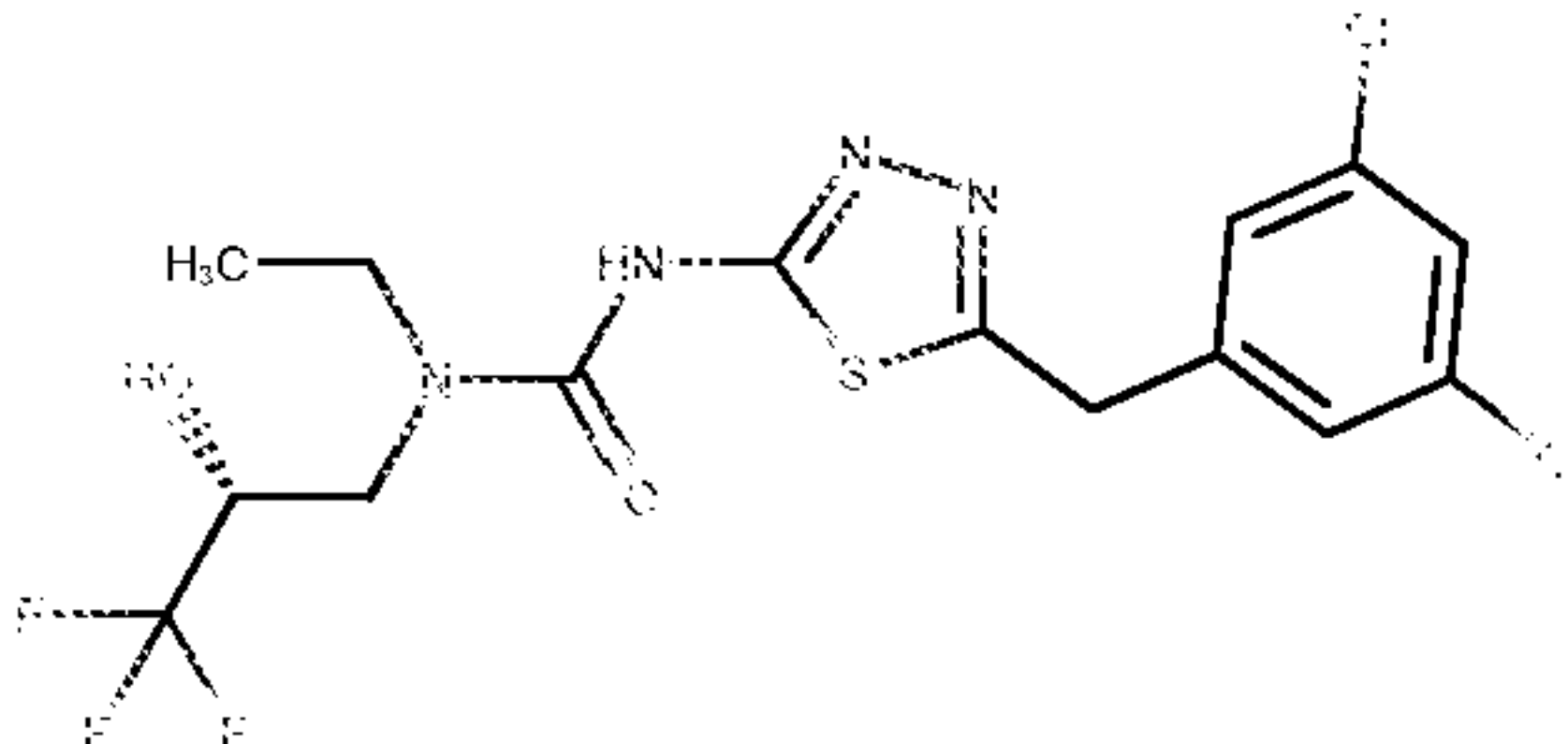
Example number	Structure	Analytical data	LCMS Method
		LCMS m/z: 335.1 [M+H] ⁺ , RT = 2.87	
E22		¹H NMR (500 MHz, DMSO-d₆) δ 11.18 (s, 1H), 6.99 – 6.89 (m, 3H), 5.03 (s, 1H), 4.22 (s, 2H), 3.92 – 3.78 (m, 1H), 3.33 – 3.11 (m, 2H), 2.29 (s, 3H), 1.17 – 0.93 (m, 6H), CH₂ under water peak. LCMS m/z: 353.2 [M+H]⁺, RT = 2.85	A
E23		¹H NMR (500 MHz, Chloroform-d) δ 6.82 – 6.77 (m, 2H), 6.74 – 6.69 (m, 1H), 4.37 – 4.29 (m, 1H), 4.22 (s, 2H), 3.80 – 3.73 (m, 1H), 3.61 – 3.52 (m, 1H), 3.50 – 3.39 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H). LCMS m/z: 411.1 [M+H]⁺, RT = 3.23	A
E24		¹H NMR (400 MHz, DMSO-d₆) δ 7.34 (dt, J = 8.8, 2.2 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.17 (m, 1H), 4.30 (s, 2H), 3.90 – 3.79 (m, 1H), 3.50 – 3.36 (m, 2H), 3.29 – 3.16 (m, 2H), 1.09 – 0.96 (m, 6H). LCMS m/z: 373.2 [M+H]⁺, RT = 2.59	B
E25		¹H NMR (400 MHz, Chloroform-d) δ 9.67 (s, 1H), 6.85 – 6.78 (m, 2H), 6.74 – 6.67 (m, 1H), 4.26 (s, 2H), 3.58 – 3.50 (m, 4H), 1.98 (s, 4H). LCMS m/z: 325.1 [M+H]⁺, RT = 2.66	A
E26		¹H NMR (500 MHz, DMSO-d₆) δ 11.12 (s, 1H), 7.15 (tt, J = 9.4, 2.4 Hz, 1H), 7.11 – 7.02 (m, 2H), 4.30 (s, 2H), 3.97 (dddd, J = 7.2, 7.2, 7.1, 3.9 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.68 – 3.56 (m, 1H), 3.56 – 3.42 (m,	A

Example number	Structure	Analytical data	LCMS Method
		1H), 2.99 (s, 3H), 2.01 – 1.67 (m, 3H), 1.56 – 1.36 (m, 1H). LCMS m/z: 369.3 [M+H] ⁺ , RT = 2.87	
E27		1H NMR (500 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 7.15 (tt, J = 9.4, 2.3 Hz, 1H), 7.11 – 7.04 (m, 2H), 4.29 (s, 2H), 3.74 (ddd, J = 8.1, 8.0, 5.4 Hz, 1H), 3.66 (dd, J = 8.3, 7.1 Hz, 1H), 3.63 – 3.56 (m, 1H), 3.46 – 3.35 (m, 2H), 2.97 (s, 3H), 1.96 – 1.79 (m, 1H), 1.60 – 1.41 (m, 1H); 2H under solvent peaks. LCMS m/z: 369.3 [M+H] ⁺ , RT = 2.61	A
E28		1H NMR (500 MHz, Chloroform-d) δ 9.53 (s, 1H), 6.88 – 6.76 (m, 2H), 6.76 – 6.68 (m, 1H), 4.58 (s, 1H), 4.26 (s, 2H), 3.79 – 3.48 (m, 4H), 2.13 – 1.94 (m, 2H). LCMS m/z: 341.1 [M+H] ⁺ , RT = 2.09	A
E29		1H NMR (500 MHz, Chloroform-d) δ 11.09 (s, 1H), 6.86 – 6.77 (m, 2H), 6.74 – 6.68 (m, 1H), 4.23 (s, 2H), 4.00 – 3.56 (m, 4H), 3.03 (s, 1H), 2.32 – 2.12 (m, 2H). LCMS m/z: 393.3 [M+H] ⁺ , RT = 3.13	A
E30		1H NMR (400 MHz, Chloroform-d) δ 6.86 – 6.78 (m, 2H), 6.74 (tt, J = 8.9, 2.3 Hz, 1H), 4.26 (s, 2H), 3.60 (q, J = 7.1 Hz, 2H), 3.53 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.95 – 0.90 (m, 2H), 0.65 – 0.60 (m, 2H). LCMS m/z: 369.2 [M+H] ⁺ , RT = 2.74	A

Example number	Structure	Analytical data	LCMS Method
E31		$^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 6.84 – 6.76 (m, 2H), 6.76 – 6.68 (m, 1H), 4.24 (s, 2H), 3.53 (s, 2H), 3.18 (s, 3H), 0.91 – 0.83 (m, 2H), 0.64 – 0.55 (m, 2H). LCMS m/z : 355.2 $[\text{M}+\text{H}]^+$, RT = 2.06	B
E32		$^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 11.03 (s, 1H), 7.52 (t, J = 1.9 Hz, 1H), 7.41 (d, J = 1.9 Hz, 2H), 5.11 (s, 1H), 4.30 (s, 2H), 3.91 – 3.78 (m, 1H), 3.55 – 3.34 (m, 2H), 3.31 – 3.08 (m, 2H), 1.10 – 0.99 (m, 6H). LCMS m/z : 389.2/391.2/393.2 $[\text{M}+\text{H}]^+$, RT = 3.22	A
E33		$^1\text{H NMR}$ (500 MHz, Chloroform- d) δ 6.82 (qd, J = 7.0, 2.3 Hz, 2H), 6.74 (tt, J = 8.9, 2.3 Hz, 1H), 4.25 (s, 2H), 3.85 (d, J = 15.3 Hz, 1H), 3.50 (s, 1H), 3.21 (s, 3H), 1.52 (s, 3H). LCMS m/z : 411.2 $[\text{M}+\text{H}]^+$, RT = 3.03	A
E34		$^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.26 (s, 1H), 7.21 (ddd, J = 8.7, 4.4, 2.7 Hz, 1H), 7.00 (t, J = 8.9 Hz, 1H), 4.27 (s, 2H), 4.24 – 4.18 (m, 1H), 3.54 – 3.35 (m, 3H), 3.29 (dd, J = 15.5, 2.0 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H). LCMS m/z : 373.2 $[\text{M}+\text{H}]^+$, RT = 2.86	A
E35		$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 7.56 (dd, J = 7.2, 2.1 Hz, 1H), 7.41 – 7.30 (m, 2H), 4.27 (s, 2H), 3.89 – 3.79 (m, 1H), 3.50 – 3.38 (m, 2H), 3.28 – 3.15 (m, 2H), 1.08 – 1.01 (m, 6H).	B

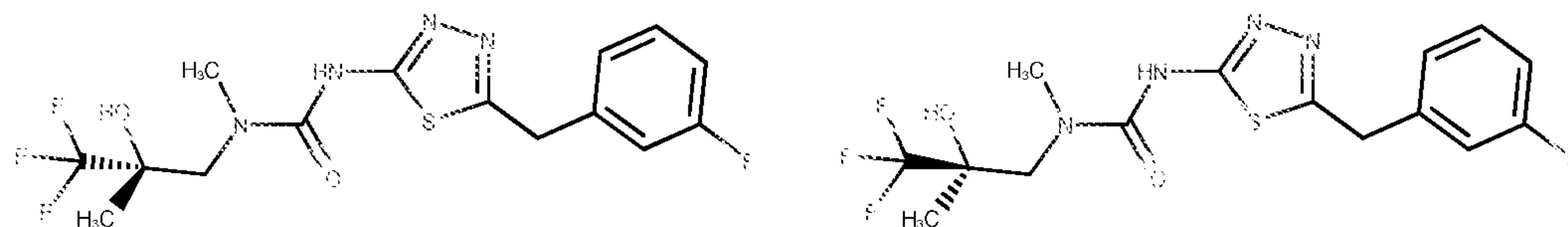
Example number	Structure	Analytical data	LCMS Method
		LCMS m/z: 373.2, 375.2 [M+H] ⁺ , RT = 2.60	
E36		¹ H NMR (500 MHz, Chloroform-d) δ 7.32 – 7.27 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.99 – 6.93 (m, 2H), 4.31 (q, J = 7.0 Hz, 1H), 4.24 (s, 2H), 3.77 (dd, J = 15.5, 9.2 Hz, 1H), 3.61 – 3.51 (m, 1H), 3.50 – 3.38 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). LCMS m/z: 393.2 [M+H] ⁺ , RT = 3.01	A
E37		¹ H NMR (500 MHz, Chloroform-d) δ 7.25 (dd, J = 4.9, 1.0 Hz, 3H), 7.18 – 7.12 (m, 1H), 4.31 (q, J = 6.9 Hz, 1H), 4.22 (s, 2H), 3.77 (dd, J = 15.5, 9.2 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.51 – 3.38 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H). LCMS m/z: 409.1 [M+H] ⁺ , RT = 3.22	A
E38		¹ H NMR (500 MHz, Chloroform-d) δ 6.86 – 6.80 (m, 2H), 6.72 (tt, J = 8.9, 2.3 Hz, 1H), 4.27 (s, 2H), 3.44 (d, J = 6.5 Hz, 2H), 3.32 (s, 2H), 1.40 (s, 6H), 1.20 (t, J = 7.0 Hz, 3H). LCMS m/z: 371.3 [M+H] ⁺ , RT = 2.97	A
E39		¹ H NMR (500 MHz, Chloroform-d) δ 7.30 – 7.24 (m, 1H), 7.11 – 7.03 (m, 1H), 7.01 – 6.97 (m, 1H), 6.97 – 6.88 (m, 1H), 4.27 (s, 2H), 3.51 – 3.34 (m, 2H), 3.29 (s, 2H), 1.37 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H): NH and OH not observed. LCMS m/z: 353.2 [M+H] ⁺ , RT = 2.85	A

Example number	Structure	Analytical data	LCMS Method
E40		¹H NMR (500 MHz, Chloroform-d) δ 7.34 – 7.29 (m, 1H), 7.09 – 7.05 (m, 1H), 6.99 (td, J = 8.8, 1.7 Hz, 2H), 4.27 (s, 2H), 3.85 (d, J = 15.4 Hz, 1H), 3.49 (s, 1H), 3.21 (s, 3H), 1.51 (s, 3H). LCMS m/z: 393.1 [M+H]⁺, RT = 2.93	A
E41		¹H NMR (400 MHz, DMSO-d₆) δ 7.34 (dt, J = 8.8, 2.1 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.16 (m, 1H), 4.31 (s, 2H), 3.45 – 3.35 (m, 2H), 3.29 – 3.26 (m, 2H), 1.14 (s, 6H), 1.05 (t, J = 7.0 Hz, 3H). LCMS m/z: 387.2, 389.2 [M+H]⁺, RT = 3.22	A
E42		¹H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.29 (m, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.99 (t, J = 8.2 Hz, 2H), 4.26 (s, 2H), 3.81 (d, J = 15.5 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.38 (d, J = 15.7 Hz, 1H), 3.25 (s, 1H), 1.55 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H). LCMS m/z: 407.1 [M+H]⁺, RT = 3.21	A
E43		¹H NMR (500 MHz, Chloroform-d) δ 6.87 (s, 1H), 6.80 (dd, J = 8.7, 6.4 Hz, 2H), 4.39 – 4.28 (m, 1H), 4.20 (s, 2H), 3.80 (dd, J = 15.5, 9.2 Hz, 1H), 3.58 (dq, J = 14.3, 7.1 Hz, 1H), 3.52 – 3.38 (m, 2H), 2.34 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). LCMS m/z: 407.1 [M+H]⁺, RT = 3.23	A
E44		¹H NMR (400 MHz, Chloroform-d) δ 7.25 (d, J = 1.9 Hz, 1H), 7.18 (d, J = 1.8 Hz, 2H), 4.24 (s, 2H), 3.34 (s, 2H), 3.09 (s, 3H), 1.37 (s, 6H).	A

Example number	Structure	Analytical data	LCMS Method
		LCMS m/z: 389.2, 391.1, 393.1 [M+H] ⁺ , RT = 3.14	
E45		¹ H NMR (500 MHz, Chloroform-d) δ 7.28 (t, J = 1.8 Hz, 1H), 7.16 (d, J = 1.8 Hz, 2H), 4.29 (q, J = 6.7 Hz, 1H), 4.20 (s, 2H), 3.82 (dd, J = 15.3, 8.9 Hz, 1H), 3.56 (d, J = 14.8 Hz, 1H), 3.18 (s, 3H). LCMS m/z: 429.1, 431.1, 433.1 [M+H] ⁺ , RT = 3.30	A
E46		¹ H NMR (400 MHz, Chloroform-d) δ 6.87 (s, 1H), 6.82 – 6.72 (m, 2H), 4.21 (s, 2H), 3.41 (q, J = 6.8 Hz, 2H), 3.30 (s, 2H), 2.30 (s, 3H), 1.37 (s, 6H), 1.17 (t, J = 7.0 Hz, 3H). LCMS m/z: 367.3 [M+H] ⁺ , RT = 2.89	B
E47		¹ H NMR (400 MHz, Chloroform-d) δ 7.07 (s, 1H), 7.01 (dt, J = 8.5, 2.1 Hz, 1H), 6.93 – 6.86 (m, 1H), 4.34 – 4.23 (m, 1H), 4.22 (s, 2H), 3.87 – 3.76 (m, 1H), 3.56 (d, J = 14.6 Hz, 1H), 3.18 (s, 3H). LCMS m/z: 413.1 [M+H] ⁺ , RT = 2.40	B
E48		¹ H NMR (400 MHz, DMF-d ₇) δ 7.35 (dt, J = 8.8, 2.1 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.16 (m, 1H), 4.31 – 4.16 (m, 3H), 3.70 – 3.41 (m, 4H), 1.06 (t, J = 7.0 Hz, 3H). LCMS m/z: 427.2 [M+H] ⁺ , RT = 2.57	B
E49		¹ H NMR (500 MHz, DMSO-d ₆) δ 7.53 (t, J = 1.9 Hz, 1H), 7.42 (d, J = 1.9 Hz, 2H), 4.27 (s, 2H), 4.24 – 4.18 (m, 1H), 3.67 (d, J = 13.8 Hz, 1H), 3.60 – 3.40 (m, 3H), 1.06 (t, J = 7.0 Hz, 3H).	B

Example number	Structure	Analytical data	LCMS Method
		LCMS m/z: 443.1 and 445.1 [M+H] ⁺ , RT = 2.90	

Example E50 and E51



Single unknown enantiomers of 3-[5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)urea

[00123] 3-[5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)urea (Example E40) was separated to give two single enantiomers.

Method: Chiralpak AD-H, 10 x 250mm, 5 um column eluting with 10% IPA : 90%CO₂ at a flow rate of 15 ml/min.

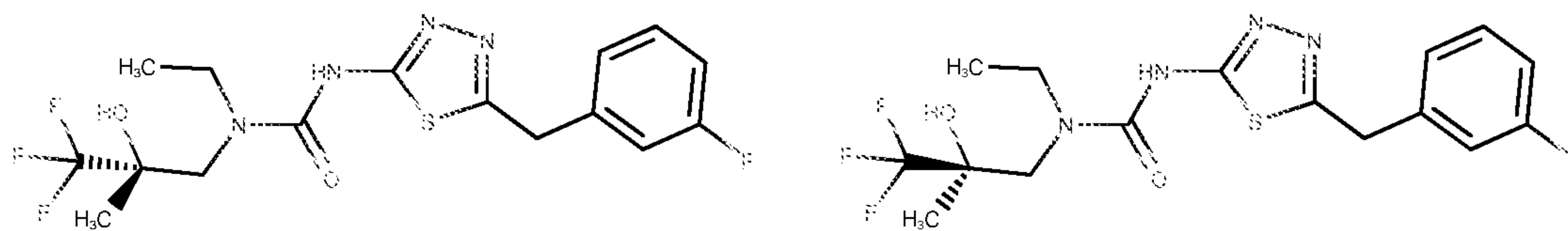
Example E50 (first eluting):

[00124] ¹H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.20 (m, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.89 (t, J = 7.9 Hz, 2H), 4.17 (s, 2H), 3.80 (d, J = 15.2 Hz, 1H), 3.34 (s, 1H), 3.10 (s, 3H), 1.44 (s, 3H). LCMS m/z: 393.2 [M+H]⁺, RT = 2.93 (Method A)

Example E51 (second eluting):

[00125] ¹H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.20 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 8.0 Hz, 2H), 4.17 (s, 2H), 3.79 (d, J = 15.9 Hz, 1H), 3.35 (s, 1H), 3.10 (s, 3H), 1.44 (s, 3H). LCMS m/z: 393.2 [M+H]⁺, RT = 2.93 (Method A)

Example E52 and E53



Single unknown enantiomers of 1-ethyl-3-[5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)urea

[00126] 1-ethyl-3-[5-[(3-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)urea (Example E42) was separated to give two enantiomers. Method: Chiralpak AD-H, 10 x 250mm, 5 um column eluting with 15% IPA: 85%CO₂ at a flow rate of 15 ml/min.

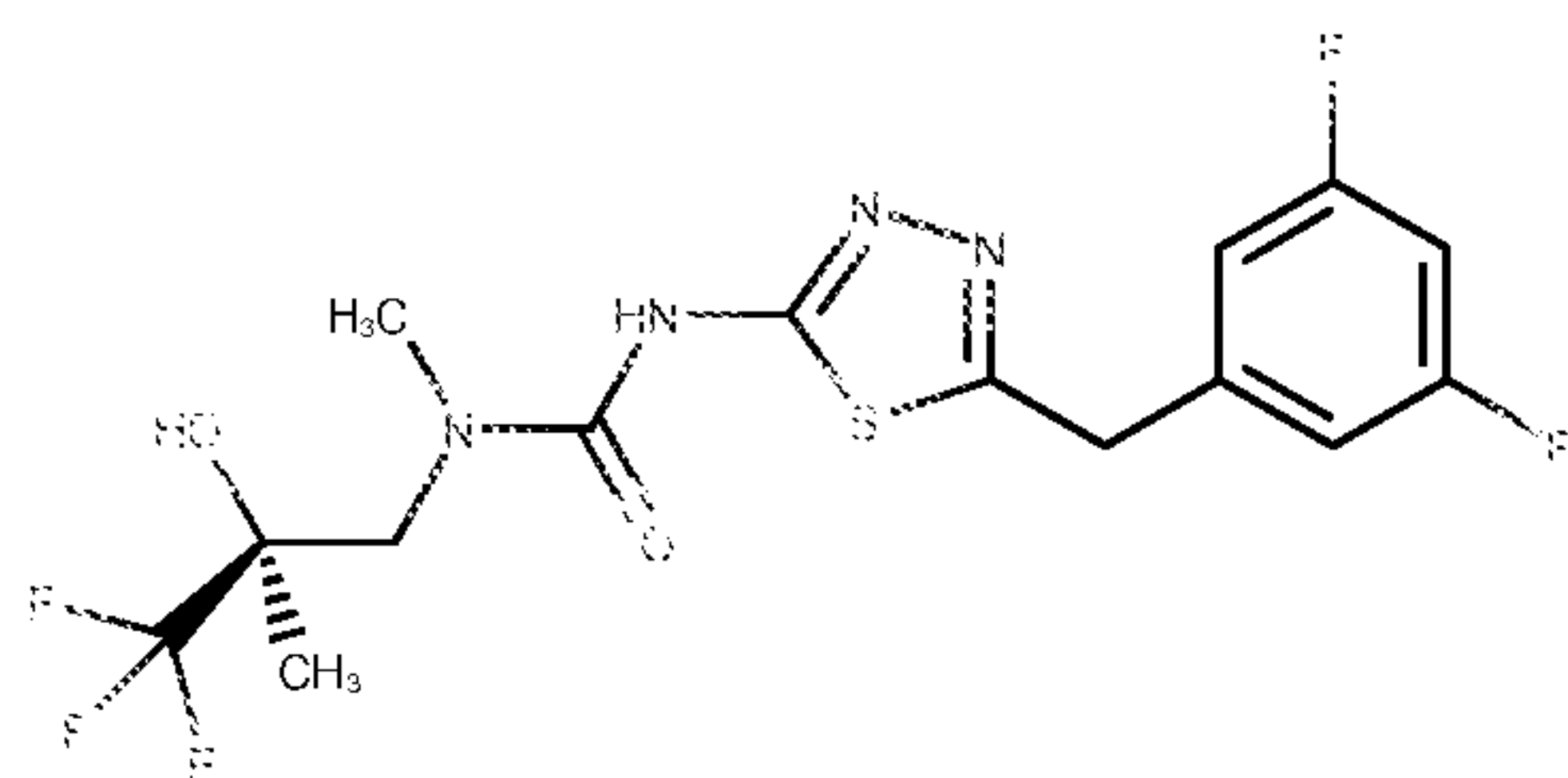
Example E52 (first eluting)

[00127] ¹HNMR(400 MHz, Chloroform-d) δ 7.25 – 7.20 (m, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.89 (t, J = 8.2 Hz, 2H), 4.16 (s, 2H), 3.81 – 3.65 (m, 2H), 3.25 (d, J = 15.4 Hz, 1H), 3.07 (s, 1H), 1.48 (s, 3H), 1.13 (t, J = 7.0 Hz, 3H). LCMS m/z: 407.2 [M+H]⁺, RT = 3.21 (Method A)

Example E53 (second eluting)

[00128] ¹HNMR(400 MHz, Chloroform-d) δ 7.25 – 7.20 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 8.3 Hz, 2H), 4.16 (s, 2H), 3.79 – 3.65 (m, 2H), 3.24 (d, J = 15.2 Hz, 1H), 3.07 (s, 1H), 1.48 (s, 3H), 1.13 (t, J = 7.0 Hz, 3H). LCMS m/z: 407.3 [M+H]⁺, RT = 3.24 (Method A)

Example E54



3-[5-[(3,5-difluorophenyl)methyl]-1,3,4-thiadiazol-2-yl]-1-methyl-1-[(2S)-3,3,3-trifluoro-2-hydroxy-2-methyl-propyl]urea

[00129] Step 1

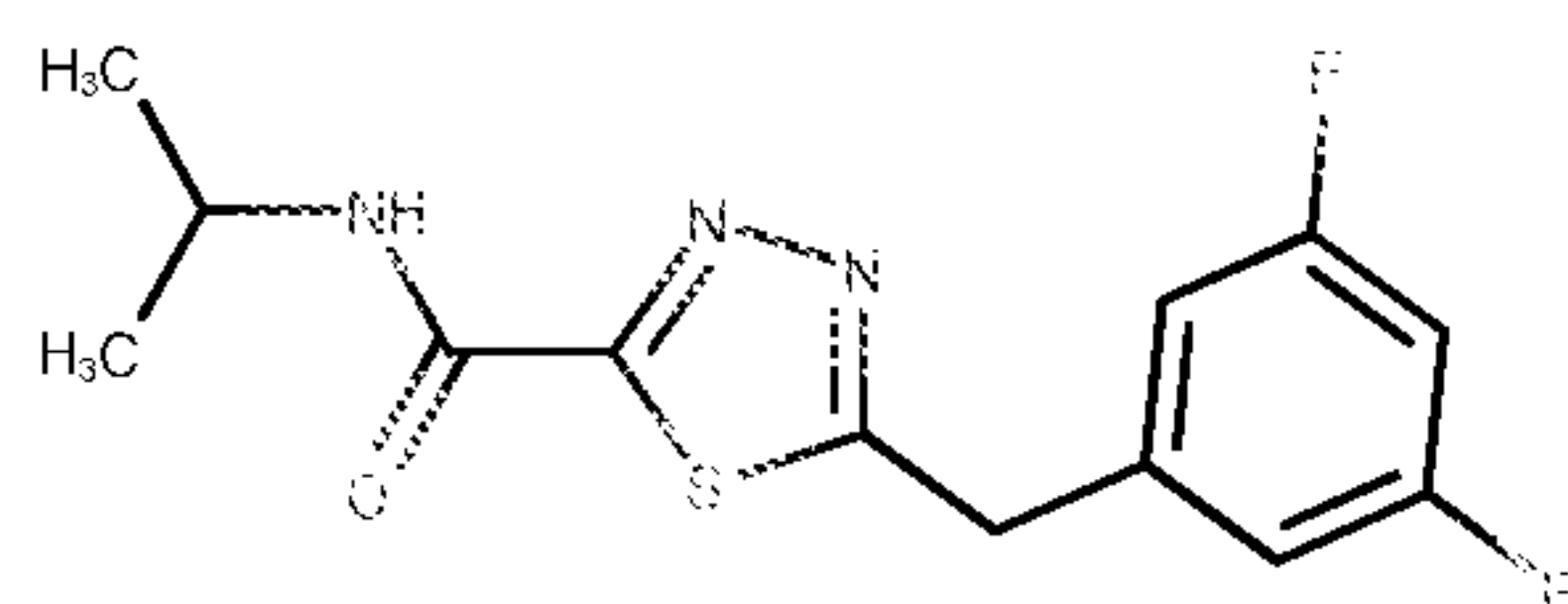
[00130] To a three-necked RBF under N₂ was added (2S)-2-(trifluoromethyl)oxirane (200 mg, 1.78 mmol) followed by THF-Anhydrous (8 mL) and the stirred solution was cooled to -100 °C with a Et₂O/dry ice bath. 1.6 M butyllithium (1.2 mL, 1.96 mmol) was then added dropwise followed by stirring at this temperature for 10 minutes. Iodomethane (0.17 mL, 2.68 mmol) was then added and the reaction was stirred for 2 h at this temperature, warmed up to ~ 0 °C with an ice bath and to this was added 2 M methanamine (3.6 mL, 7.14 mmol) and the reaction was allowed to warm up to RT and was stirred overnight. It was then quenched by addition of sat. aq. NH₄Cl (5 mL) and volatiles were then removed under reduced pressure (pressure at 100 mbar). The residue was loaded onto a SCX-2 cartridge (5 g, washing with MeOH, eluting with 3.5N NH₃/MeOH). The MeOH fraction was concentrated under reduced pressure to afford (2S)-1,1,1-trifluoro-2-methyl-3-(methylamino)propan-2-ol as an orange liquid (750 mg, 30% purity). ¹H NMR (500 MHz, Methanol-d₄) δ 3.38 (d, J = 13.2 Hz, 1H), 3.23 (d, J = 13.2 Hz, 1H), 2.77 (s, 3H), 1.54 – 1.46 (m, 3H), NH and OH not observed.

[00131] Step 2

[00132] A solution of (4-nitrophenyl) carbonochloridate (49 mg, 0.245 mmol) in anhydrous THF (1 mL) was cooled with an ice bath. While stirring, to this was added a solution of 5-[(3,5-difluorophenyl)methyl]-1,3,4-thiadiazol-2-amine (synthesized using a similar method to Example E01 (step 1), 55 mg, 0.223 mmol) and pyridine (0.020 mL, 0.245 mmol) in anhydrous THF (1 mL) and the reaction was warmed up to RT and stirred at RT for 30 minutes. (2S)-1,1,1-trifluoro-2-methyl-3-(methylamino)propan-2-ol (95 mg, 0.181 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.058 mL, 0.334 mmol) in anhydrous THF (1 mL) were then added and the reaction was stirred at RT for 15 minutes. It was then diluted with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was dried over MgSO₄, filtered, concentrated under reduced pressure and purified by prep HPLC (Method C) to afford the title compound as a white solid (24 mg). ¹H NMR (500 MHz, DMSO-d₆) δ 11.10 (s, 1H), 7.15 (tt, J = 9.4, 2.4 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.21 (s, 1H), 4.29 (s, 2H), 4.07 – 3.73 (m, 1H), 3.08 (s, 3H), 1.19 (s, 3H); 1H under water peak. LCMS m/z: 411.2 [M+H]⁺, RT = 3.06 (Method A)

Table 3: The following compounds were synthesized using a similar method to that used in **Example E54**.

Example number	Structure	Analytical data	LCMS Method
E55		$^1\text{H NMR}$ (500 MHz, Chloroform-d) δ 6.83 (tt, J = 6.7, 3.5 Hz, 2H), 6.74 (tt, J = 8.9, 2.3 Hz, 1H), 4.28 – 4.22 (m, 2H), 3.90 (d, J = 13.6 Hz, 1H), 3.42 (s, 1H), 3.20 (s, 3H), 1.55 (s, 3H). LCMS m/z : 411.1 $[\text{M}+\text{H}]^+$, RT = 3.24	A
E56		$^1\text{H NMR}$ (500 MHz, Chloroform-d) δ 10.04 (s, 1H), 7.07 (s, 1H), 7.00 (dt, J = 8.4, 2.0 Hz, 1H), 6.92 – 6.86 (m, 1H), 4.22 (d, J = 2.6 Hz, 2H), 3.89 (d, J = 14.0 Hz, 1H), 3.39 (s, 1H), 3.18 (s, 3H), 1.54 (s, 3H). LCMS m/z : 427.2, 429.2 $[\text{M}+\text{H}]^+$, RT = 3.28	A
E57		$^1\text{H NMR}$ (500 MHz, Chloroform-d) δ 6.89 – 6.82 (m, 1H), 6.82 – 6.73 (m, 2H), 4.22 – 4.15 (m, 2H), 3.84 (s, 1H), 3.42 (s, 1H), 3.17 (s, 3H), 2.32 (s, 3H), 1.49 (s, 3H). LCMS m/z : 407.2 $[2\text{M}+\text{H}]^+$, RT = 3.20	A

Example E58**5-[(3,5-difluorophenyl)methyl]-N-isopropyl-1,3,4-thiadiazole-2-carboxamide****[00133]** Step 1

[00134] Hydrazine hydrate (0.64 mL, 13.0 mmol) was added to a stirred solution of ethyl 2-(3,5-difluorophenyl)acetate (1.12 g, 5.6 mmol) in MeOH (10mL). The reaction was stirred at

70°C for 4 hrs, then stirred at room temp overnight. The reaction was concentrated under vacuum to yield difluorophenyl)acetohydrazide (1.21 g) as an off white solid.

[00135] Step 2

[00136] Ethyl 2-chloro-2-oxo-acetate (800 uL, 7.16 mmol) was added dropwise to a stirred solution of 2-(3,5-difluorophenyl)acetohydrazide (1.21 g, 6.50 mmol) and triethylamine (1.1 mL, 7.89 mmol) in DCM-Anhydrous (15 mL) at 0°C forming a yellow solution. After 15mins the ice bath was removed and the reaction stirred at room temp for 30 minutes. The reaction was diluted with water (10 mL) and extracted into DCM (3x20mL). A white solid was present and so the layers were filtered to give a white solid. The DCM layers were combined, dried over MgSO₄, filtered and concentrated under vacuum to yield a yellow solid. The solids were combined and dissolved in EtOAc and the aqueous was further extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated to yield ethyl 2-[2-(3,5-difluorophenyl)acetyl]hydrazino]-2-oxo-acetate (1.92 g, 80% purity) as a yellow solid.

[00137] Step 3

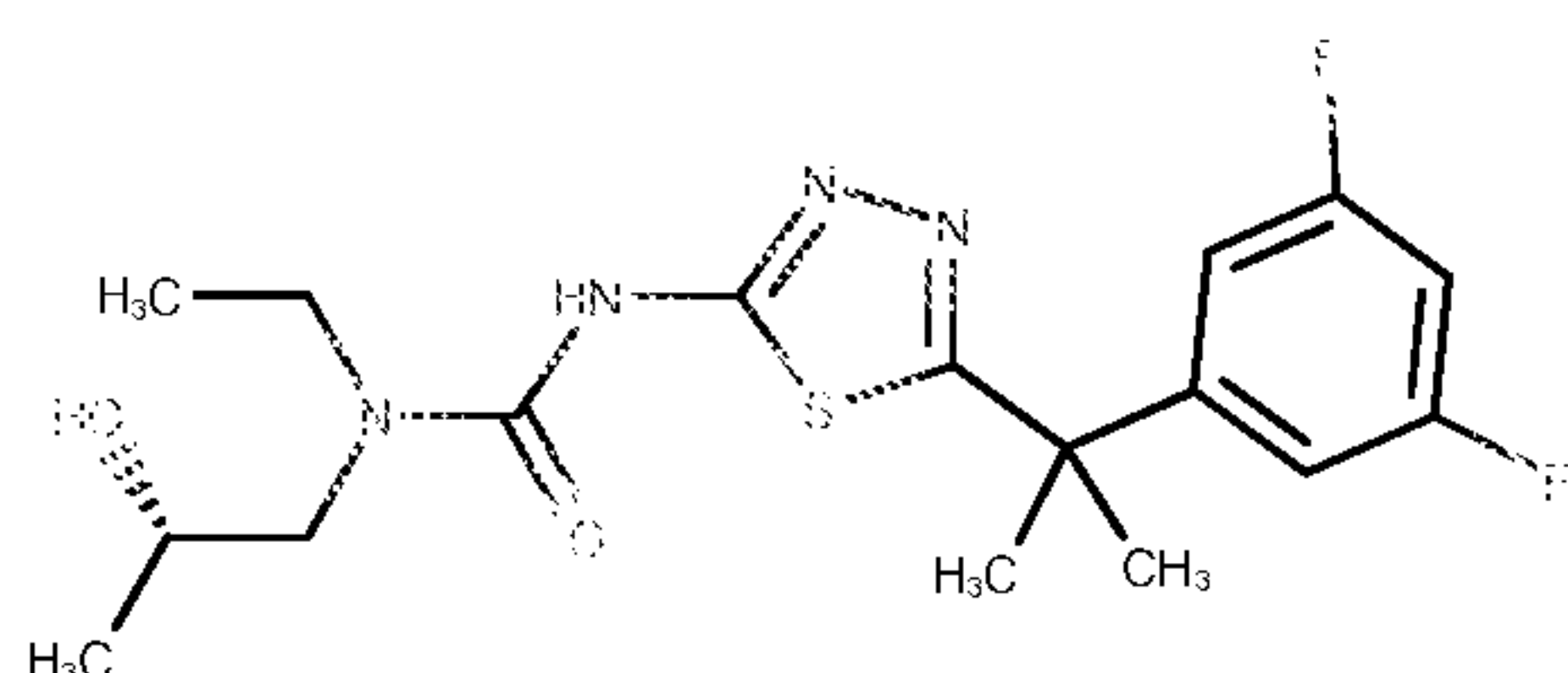
[00138] Ethyl 2-[2-[2-(3,5-difluorophenyl)acetyl]hydrazino]-2-oxo-acetate (80%, 100 mg, 0.279 mmol) and Lawessons reagent (71 mg, 0.176 mmol) were stirred in THF (1mL) in a pressure vial at 50°C for a total of 3 hours to give a pale yellow solution. Water (4mL) was added and the mixture extracted with EtOAc (4x 3mL). The organics were combined and concentrated. The crude product was purified by FCC (Biotage SNAP KP-Sil 10g) eluting with 0-25% EtOAc in Heptane, then flushing with 25-100% EtOAc in heptane to afford ethyl 5-[(3,5-difluorophenyl)methyl]-1,3,4-thiadiazole-2-carboxylate (45 mg, 54% Yield). ¹H NMR (500 MHz, Chloroform-d) δ 6.85 (qd, J = 7.3, 2.3 Hz, 2H), 6.76 (tt, J = 8.9, 2.3 Hz, 1H), 4.53 – 4.48 (m, 2H), 4.47 (s, 2H), 1.44 (t, J = 7.1 Hz, 3H).

[00139] Step 4

[00140] In a 1.5mL vial with septum, ethyl 5-[(3,5-difluorophenyl)methyl]-1,3,4-thiadiazole-2-carboxylate (96%, 45 mg, 0.152 mmol) was dissolved in Methanol-Anhydrous (0.5 mL) and propan-2-amine (13 uL, 0.152 mmol) was added and the solution turned yellow (after 5 mins the reaction became green then turned yellow). The sealed reaction was heated at 80°C for 1 hour.

Further propan-2-amine (100 uL, 1.16 mmol) was added and the reaction was heated at 80°C for 1 hour. The reaction was concentrated and purified by prep HPLC (Method D) to afford the title compound (32 mg, 70% Yield) as an off white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.03 (d, J = 8.1 Hz, 1H), 7.18 (tt, J = 9.6, 2.4 Hz, 1H), 7.13 (dd, J = 8.4, 2.0 Hz, 2H), 4.57 (s, 2H), 4.14 – 4.01 (m, 1H), 1.17 (d, J = 6.6 Hz, 6H). LCMS m/z: 298.1 [M+H]⁺, RT = 3.11 (Method A)

Example E59



3-[5-[1-(3,5-difluorophenyl)-1-methyl-ethyl]-1,3,4-thiadiazol-2-yl]-1-ethyl-1-[(2S)-2-hydroxypropyl]urea

[00141] Step 1

[00142] Sodium hydroxide (214 mg, 5.22 mmol) was dissolved in warm water (0.3 mL). (3,5-difluorophenyl)acetonitrile (200 mg, 1.31 mmol) in DMSO (1.2 mL) was added to the warmed mixture and stirred in a cool water bath (~10°C). Iodomethane (0.33 mL, 5.22 mmol) was added dropwise and then stirred at room temperature for 1 hour. Water (2 mL) was added and the mixture extracted into EtOAc (3 x 3 mL) and combined organics concentrated under vacuum to afford 2-(3,5-difluorophenyl)-2-methyl-propanenitrile (275 mg).

[00143] Step 2

[00144] Sodium hydroxide (1.28 g, 31.9 mmol) was added to a stirred solution of 2-(3,5-difluorophenyl)-2-methyl-propanenitrile (85% purity, 2.27 g, 10.6 mmol) in methanol (2 mL) and water (5 mL). The reaction was stirred at 90°C overnight (~20 hrs) then stirred at room temp for approximately 46 hrs. The reaction was diluted with water (5 mL) and extracted into EtOAc

(3x 10mL), organics dried over MgSO₄, filtered and concentrated under vacuum to yield 2-(3,5-difluorophenyl)-2-methyl-propanoic acid (2.28 g).

[00145] Step 3

[00146] 5-[1-(3,5-difluorophenyl)-1-methyl-ethyl]-1,3,4-thiadiazol-2-amine was synthesized using a similar method to that used in Example E01 (step 1).

¹H NMR (400 MHz, Chloroform-d) δ 6.95 – 6.79 (m, 2H), 6.68 (tt, J = 8.7, 2.3 Hz, 1H), 4.97 (s, 2H), 1.78 (s, 6H).

[00147] Step 4

[00148] The title compound was synthesized using a similar method to that used in Example E09 (step 2). ¹H NMR (400 MHz, Chloroform-d) δ 6.90 – 6.76 (m, 2H), 6.66 (tt, J = 8.7, 2.3 Hz, 1H), 4.30 – 4.16 (m, 1H), 3.57 – 3.45 (m, 1H), 3.45 – 3.27 (m, 3H), 1.80 (s, 6H), 1.32 (d, J = 6.3 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H). LCMS m/z: 385.3 [M+H]⁺, RT = 2.96 (Method B)

HPLC Methods

Analytical LCMS

[00149] Method A

[00150] Analytical uHPLC-MS were performed on a Waters Acquity uPLC system using a Phenomenex Kinetex-XB C18 column (2.1 mm x 100 mm, 1.7 μ M; temperature: 40 °C) and a gradient of 5-100% B (A = 0.1% formic acid in H₂O; B = 0.1% formic acid in ACN) over 5.3 min then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 μ L at flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity PDA detector spectrum range: 200-400 nm, ELS data was collected using a Water Acquity ELS detector (where fitted) were reported. Mass

spectra were obtained using a Waters SQD (MSQ1) or Waters Acquity QDA (MSQ2). Data were integrated and reported using Waters MassLynx and OpenLynx software.

[00151] Method B

[00152] Analytical uPLC-MS were performed on a Waters Acquity uPLC system using a Waters UPLC® BEH™ C18 column (2.1 mm x 100mm, 1.7µm column; temperature: 40°C) and a gradient of 5-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = ACN) over 5.3 min then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 µL and at flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector Spectrum range: 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE mass detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Preparative HPLC Methods

[00153] Purification methods are as follows:

[00154] Method C: ACIDIC METHOD

[00155] Purifications were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm x 100 mm, 10 µM; temperature: r.t.) and a gradient of 10-95% B (A= 0.1% formic acid in H₂O; B= 0.1% formic acid in ACN) over 14.44 min then 95% B for 2.11 min. A second gradient of 95-10% B was then applied over 0.2 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

[00156] Method D: BASIC METHOD

[00157] Purifications were performed on a Gilson LC system using a Waters X-Bridge C18 column (30 mm x 10 mm, 10 µM; temperature: r.t.) and a gradient of 30-95% B (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in ACN) over 11.00 min then 95% B for 2.10 min. A second gradient of 95-30% B was then applied over 0.21 min with an

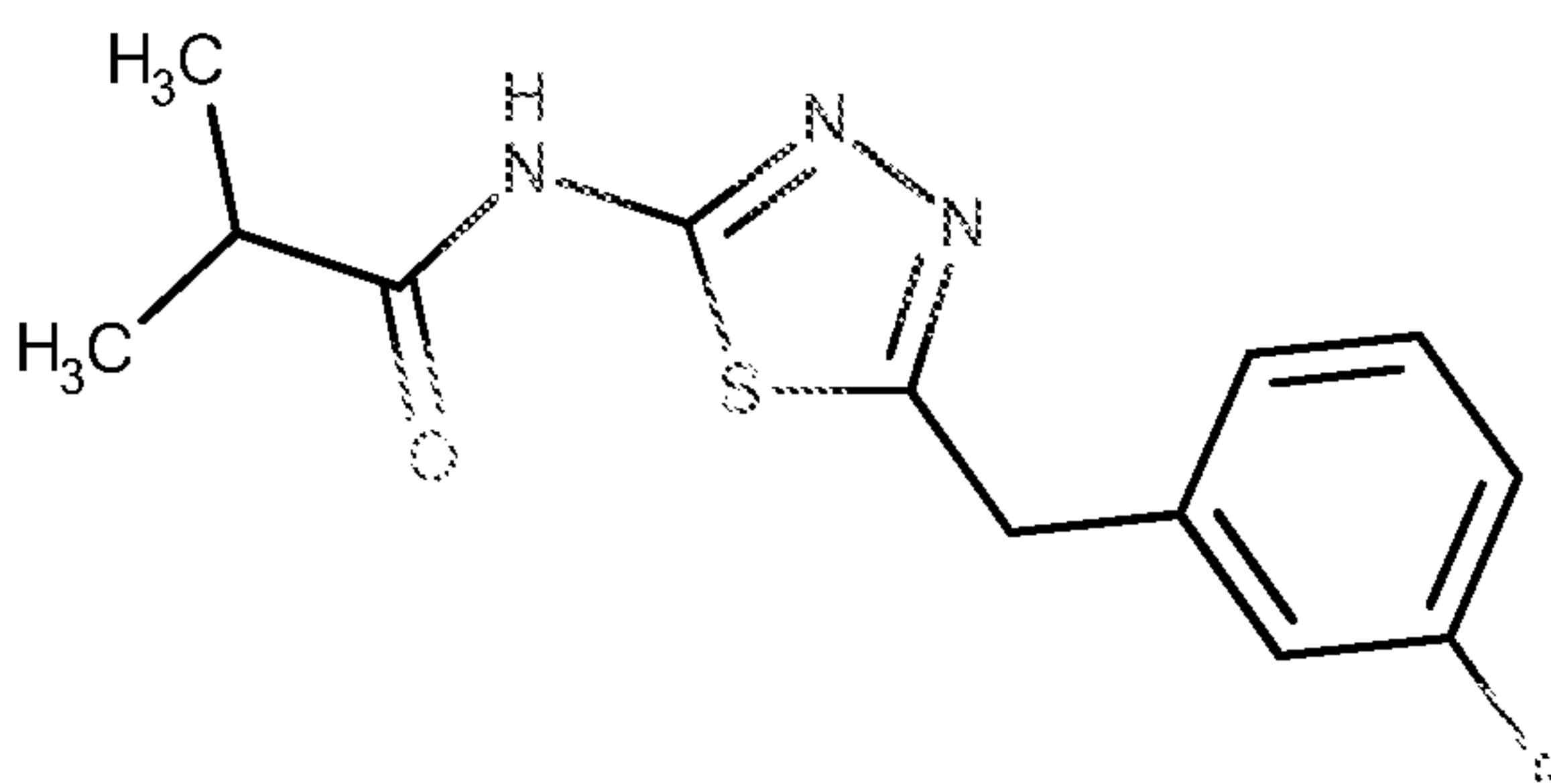
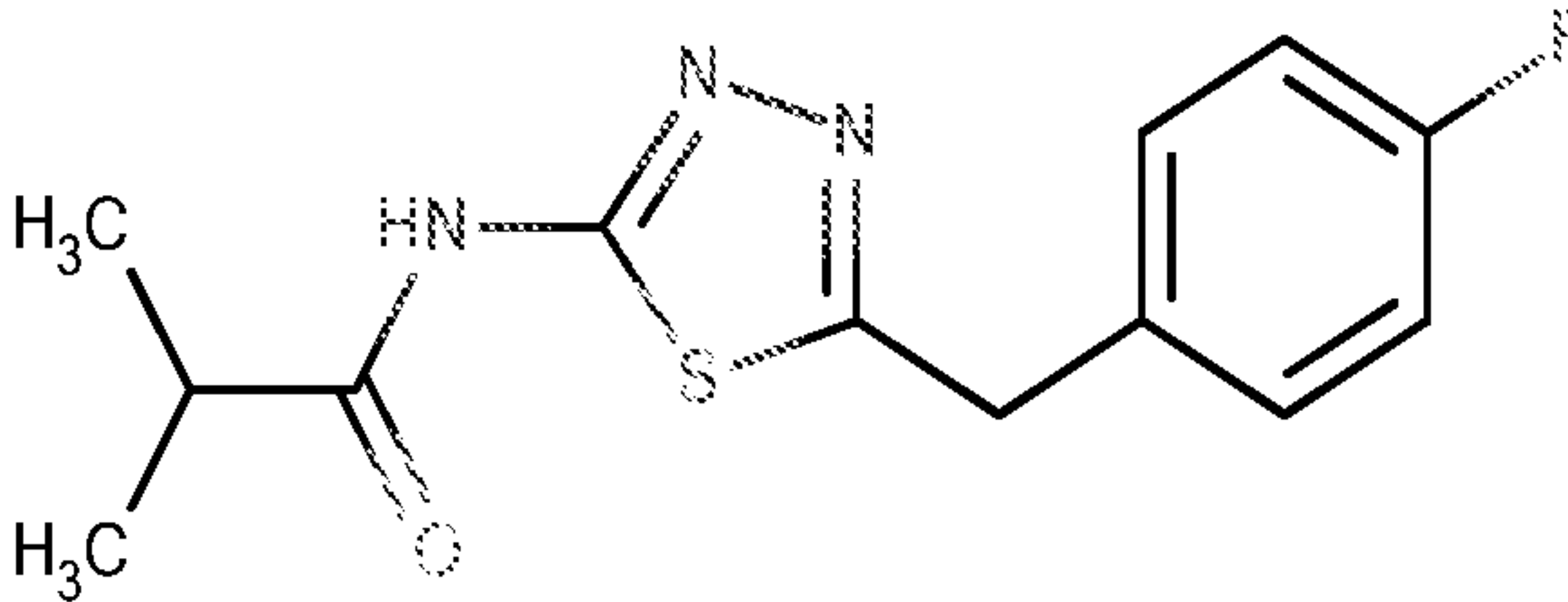
injection volume of 1500 μ L at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

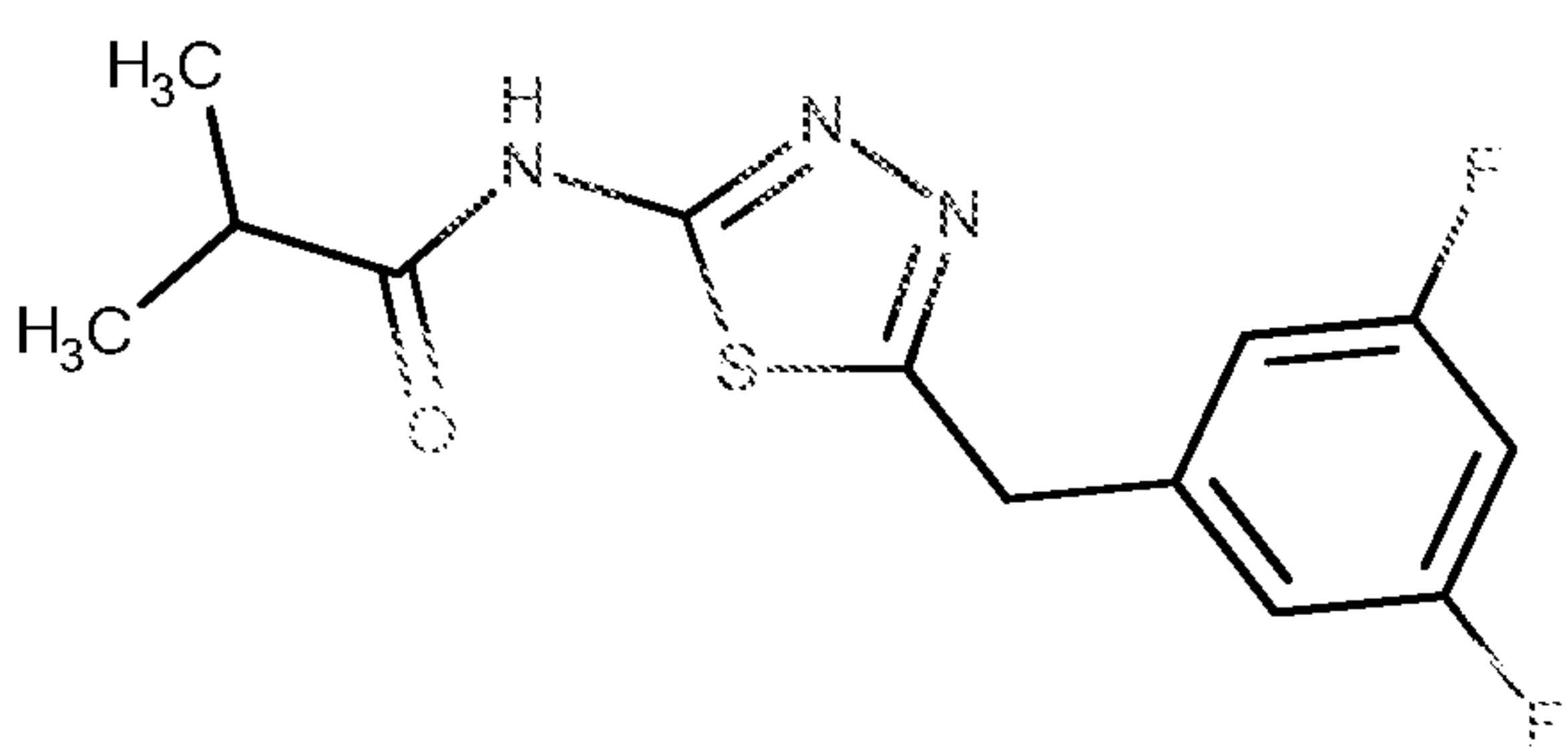
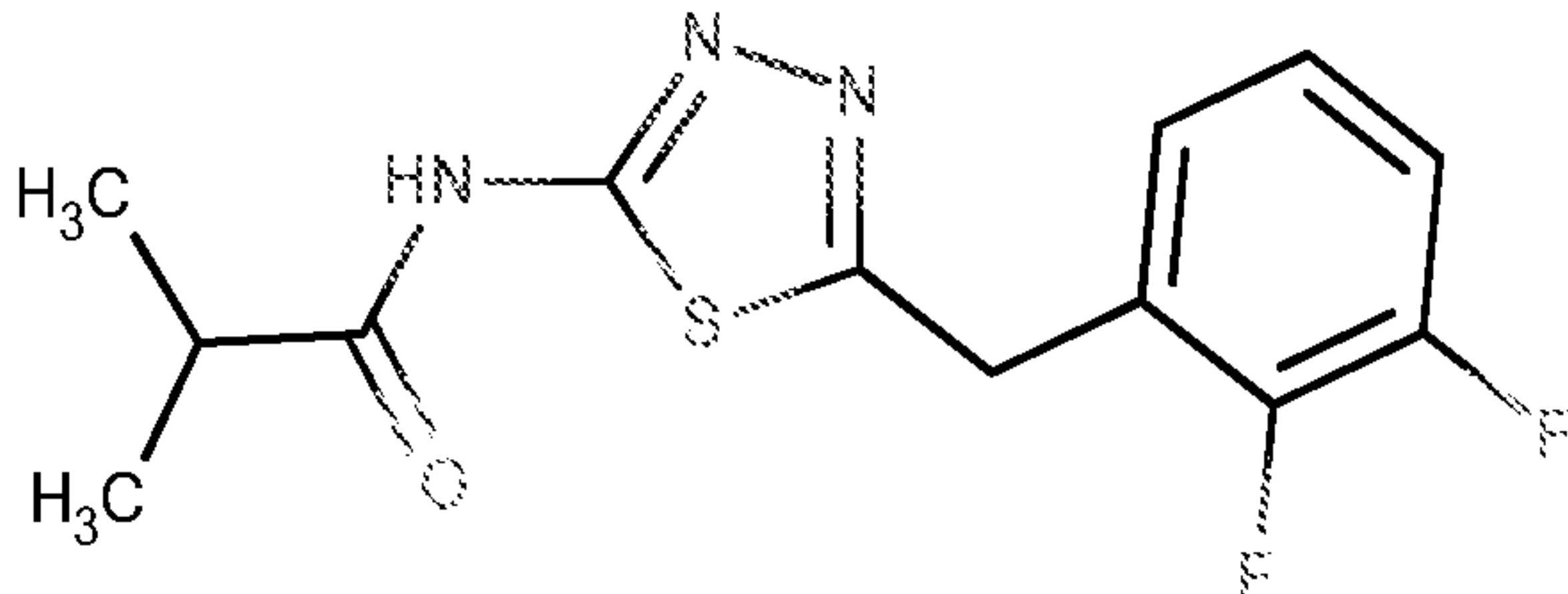
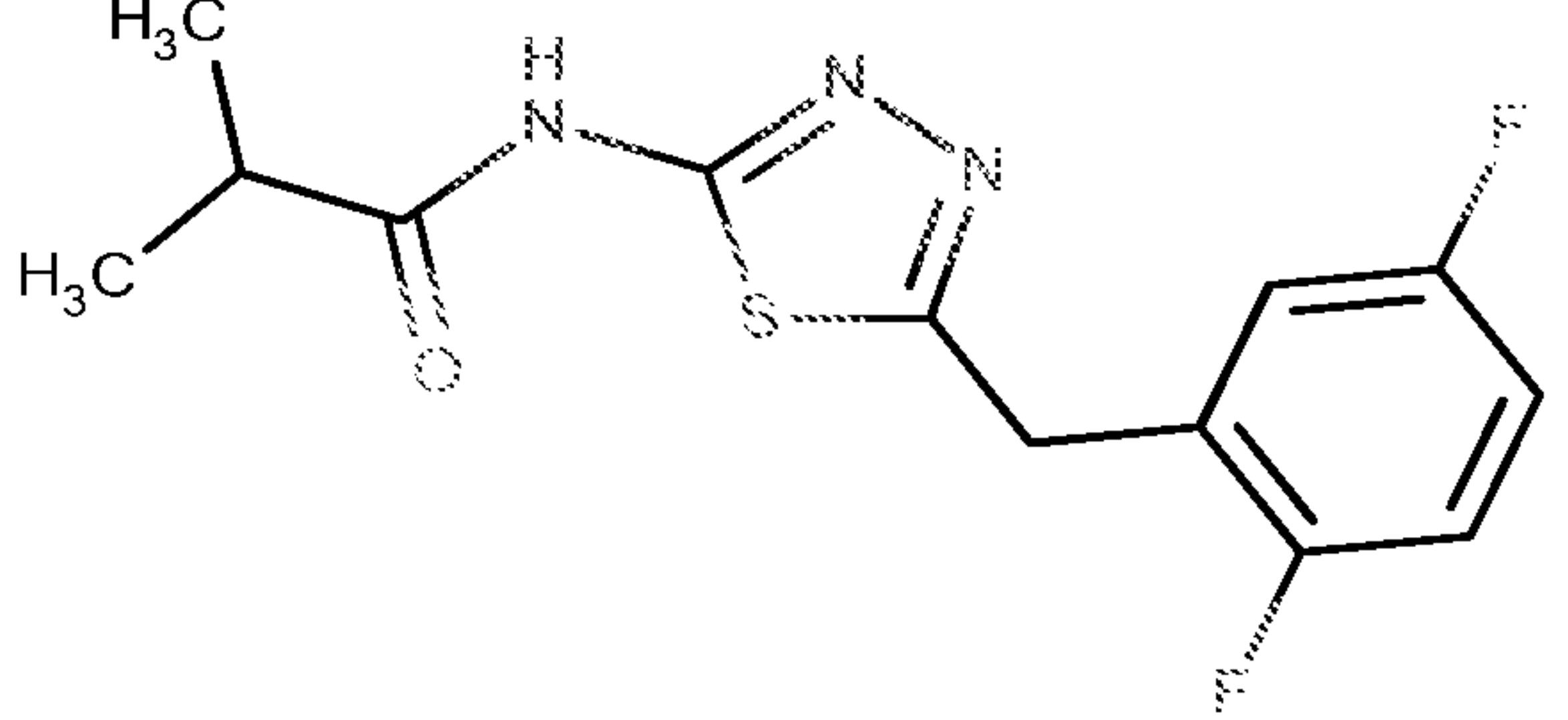
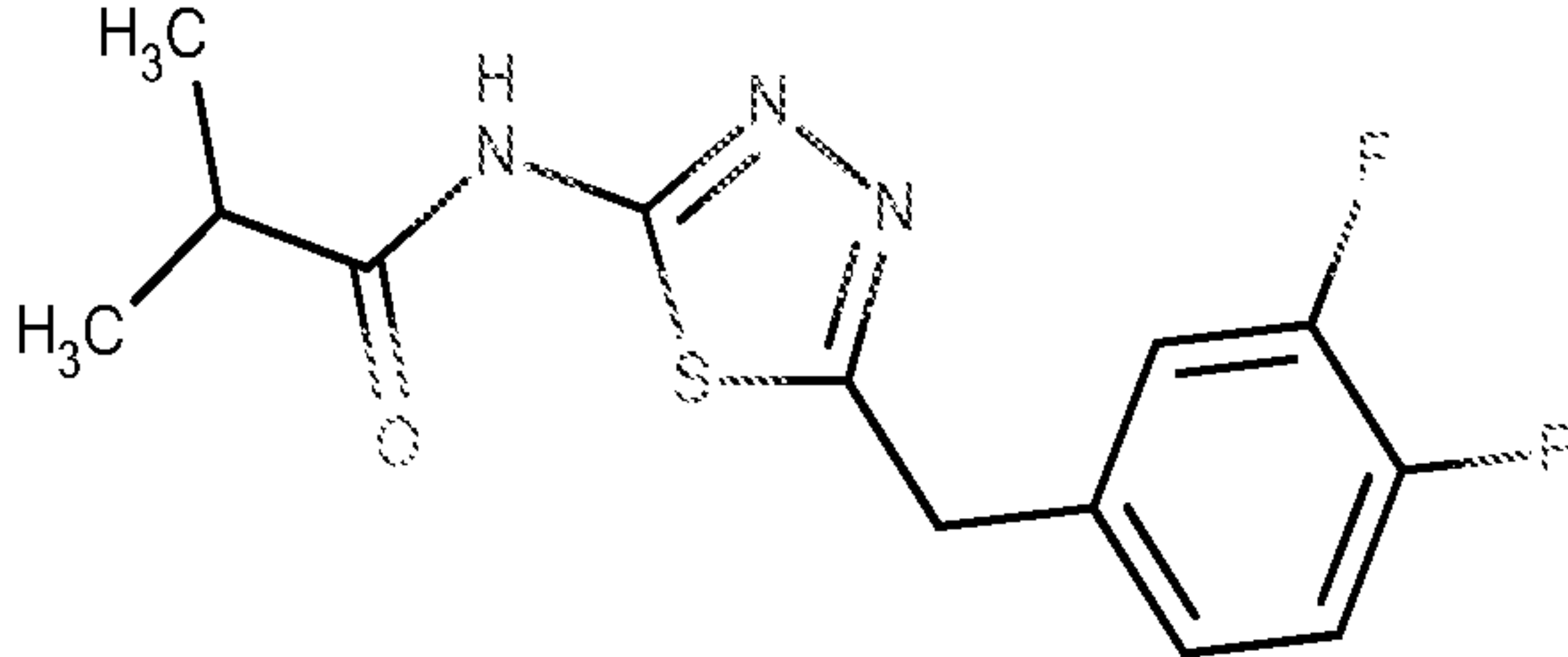
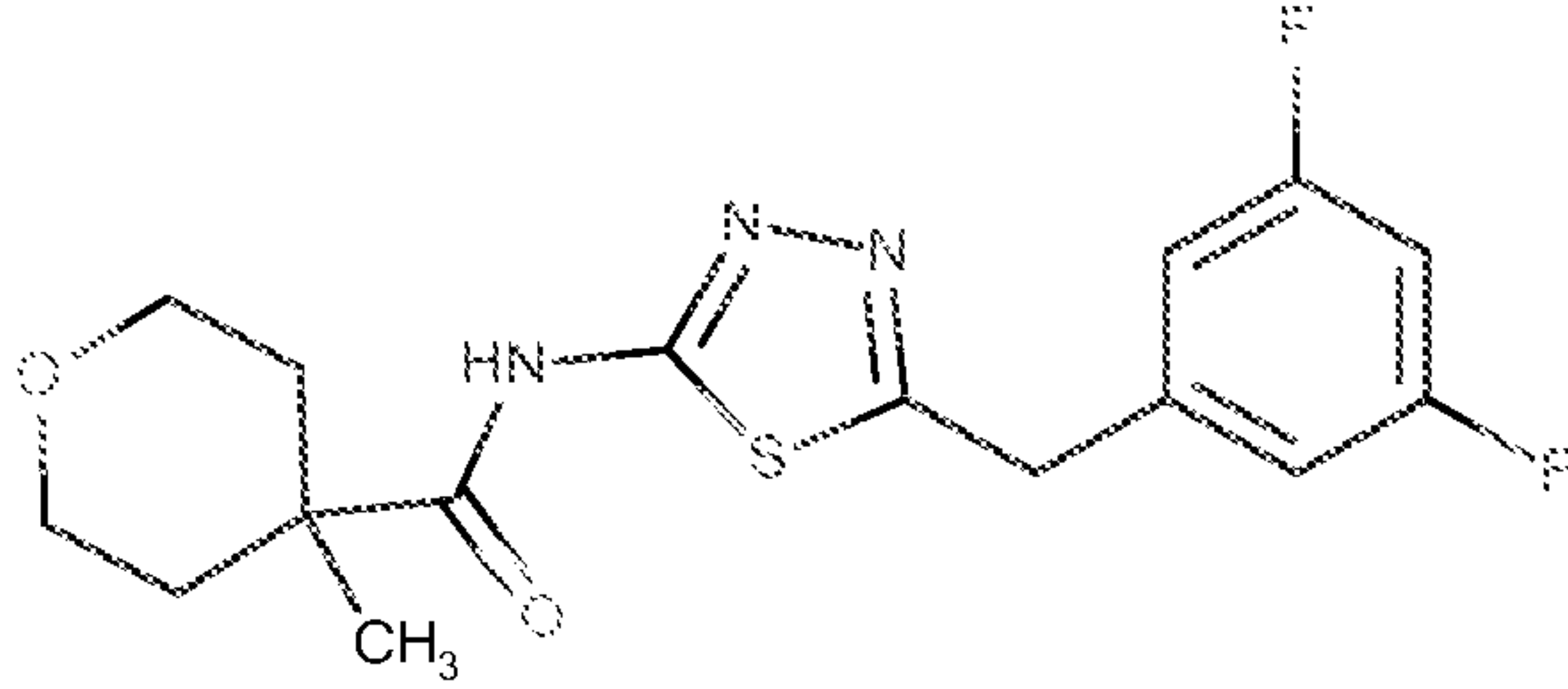
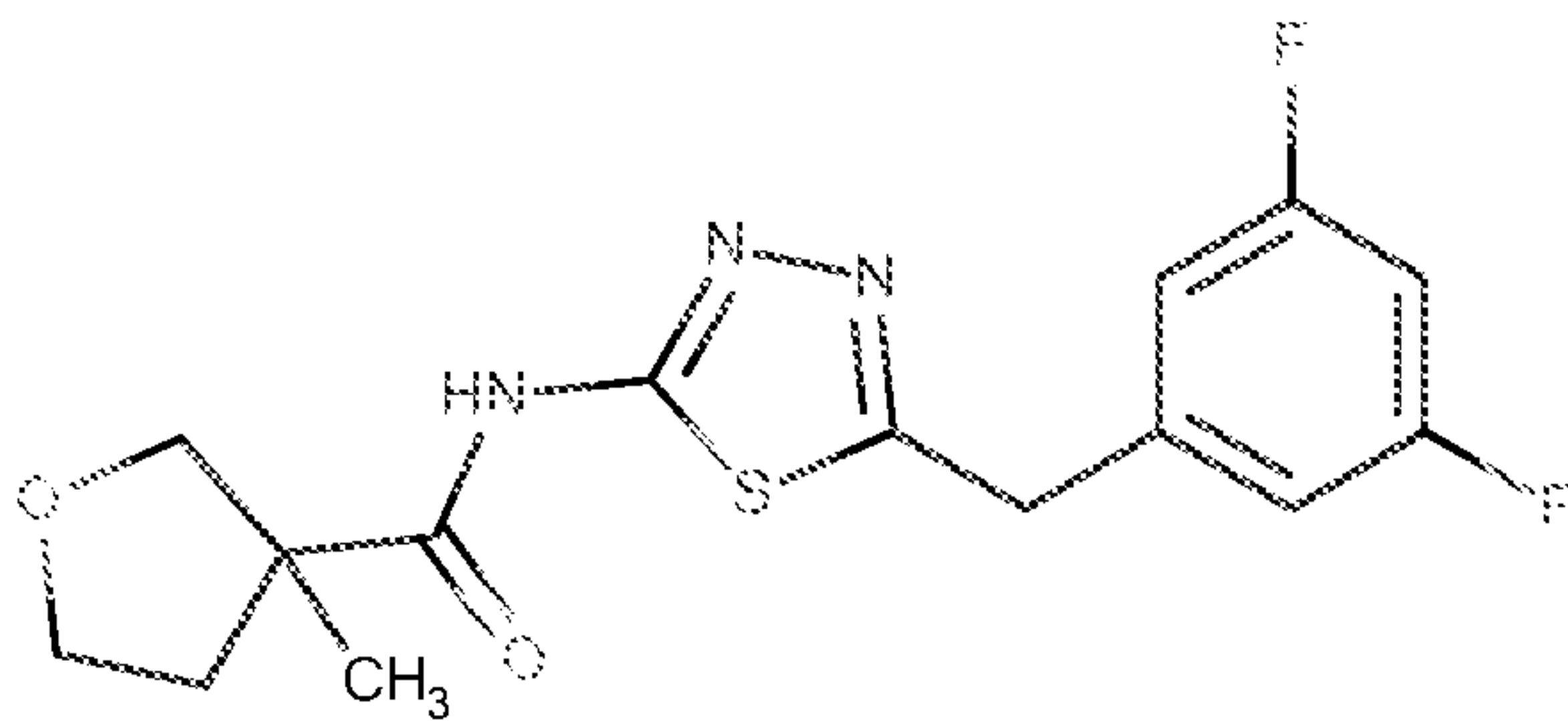
Example 2 - Screening of Compounds

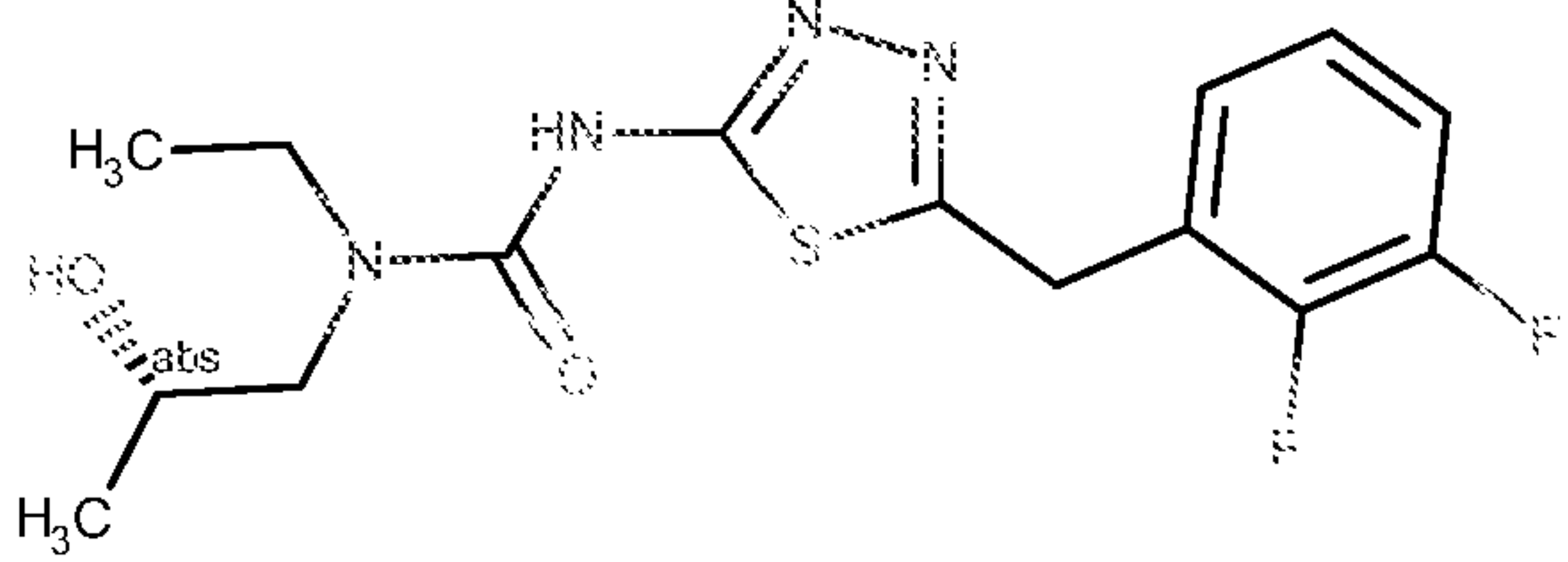
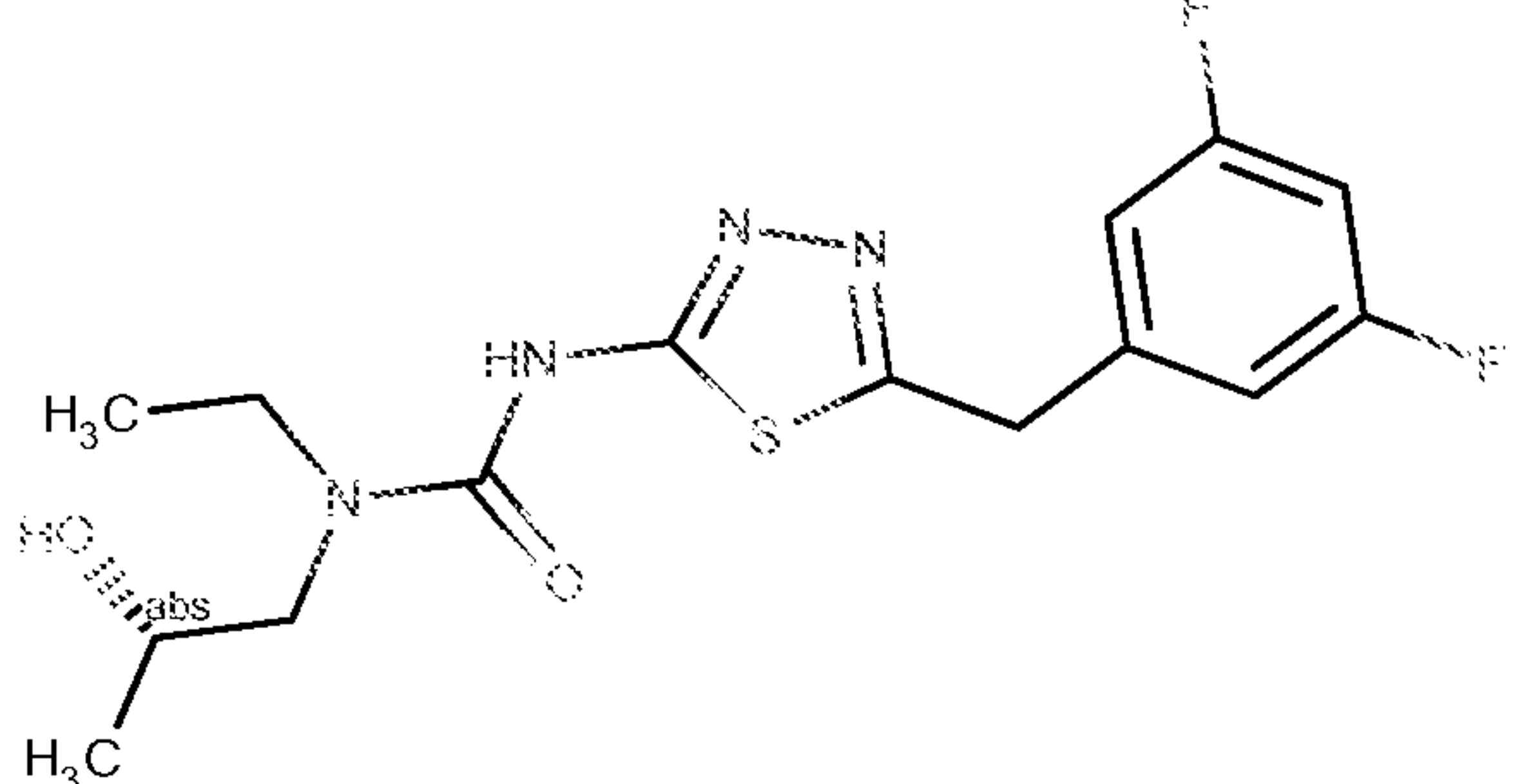
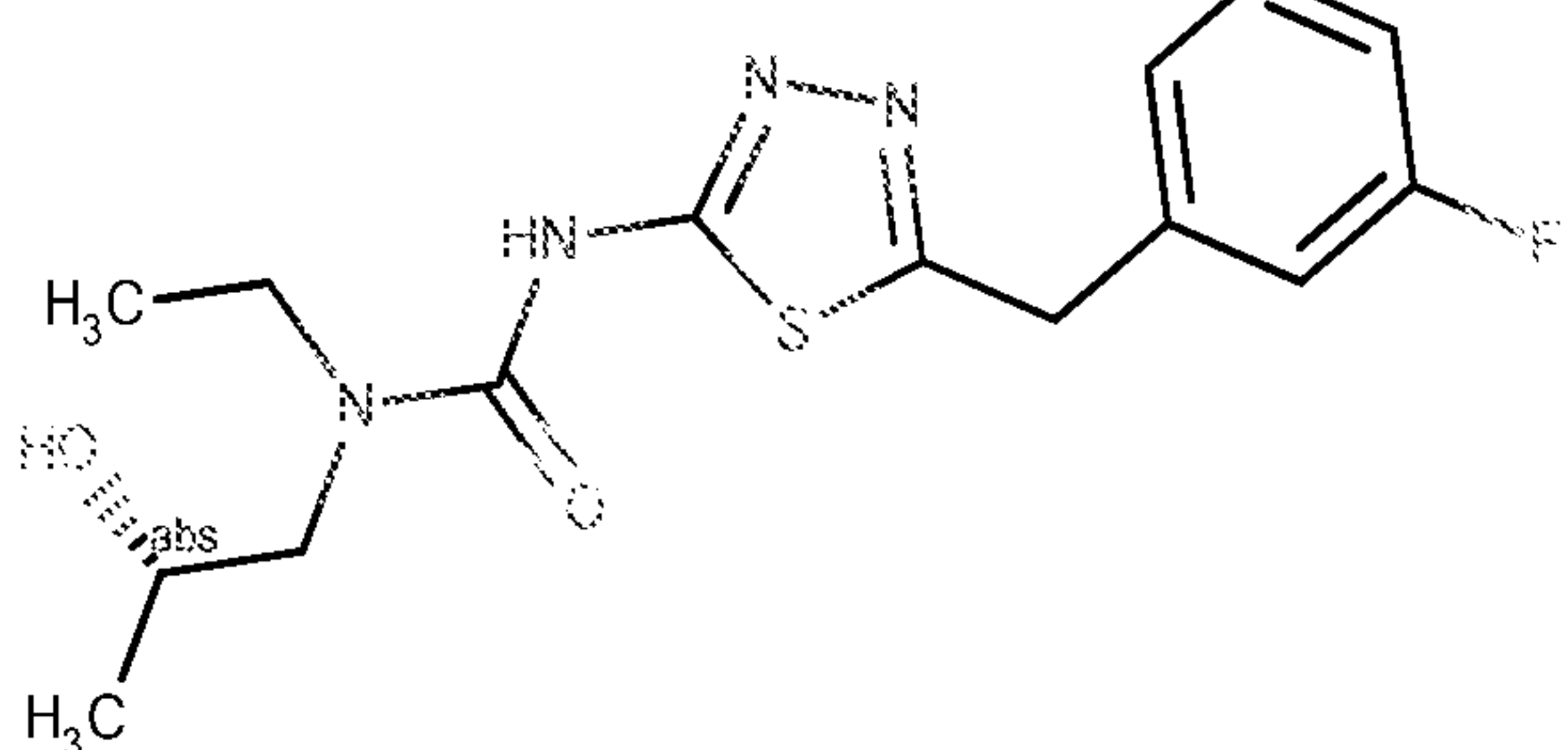
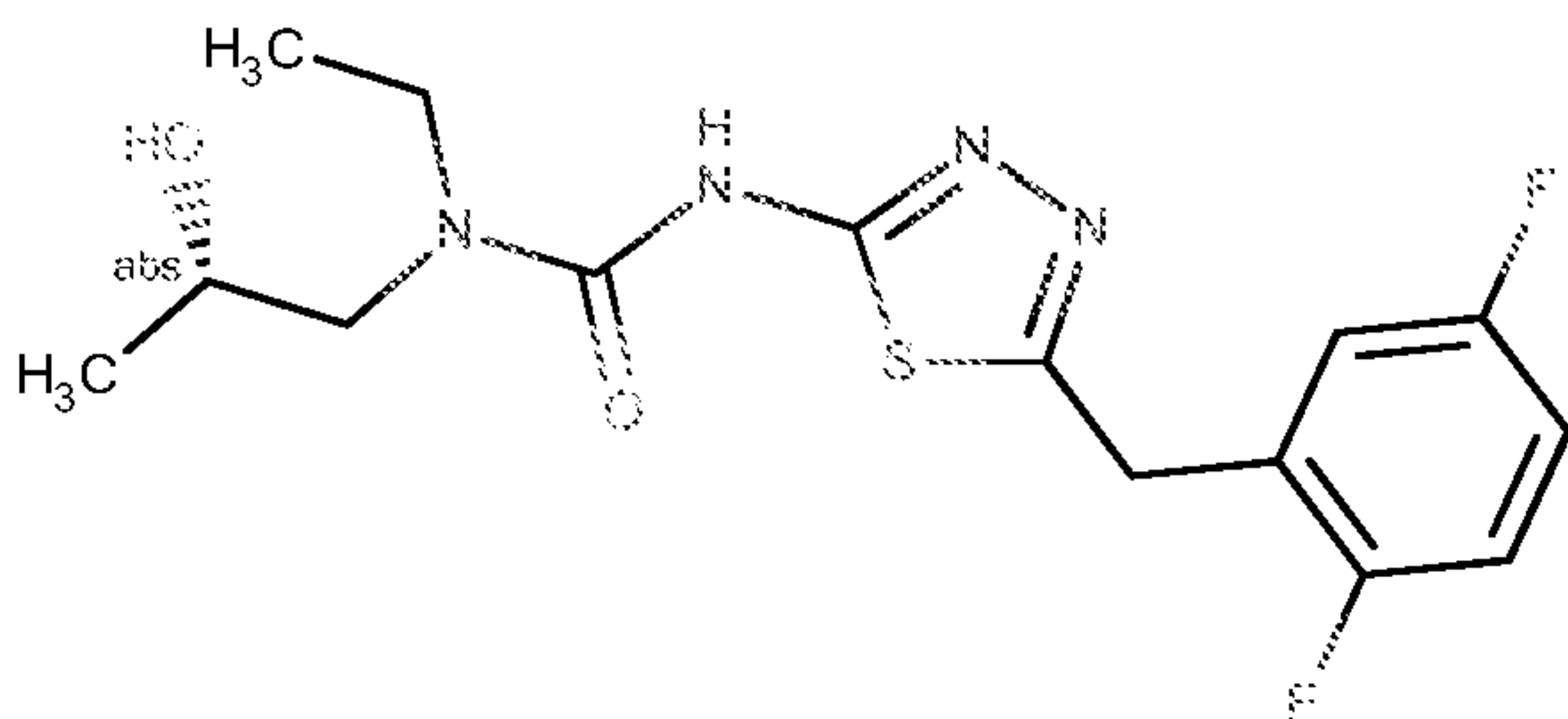
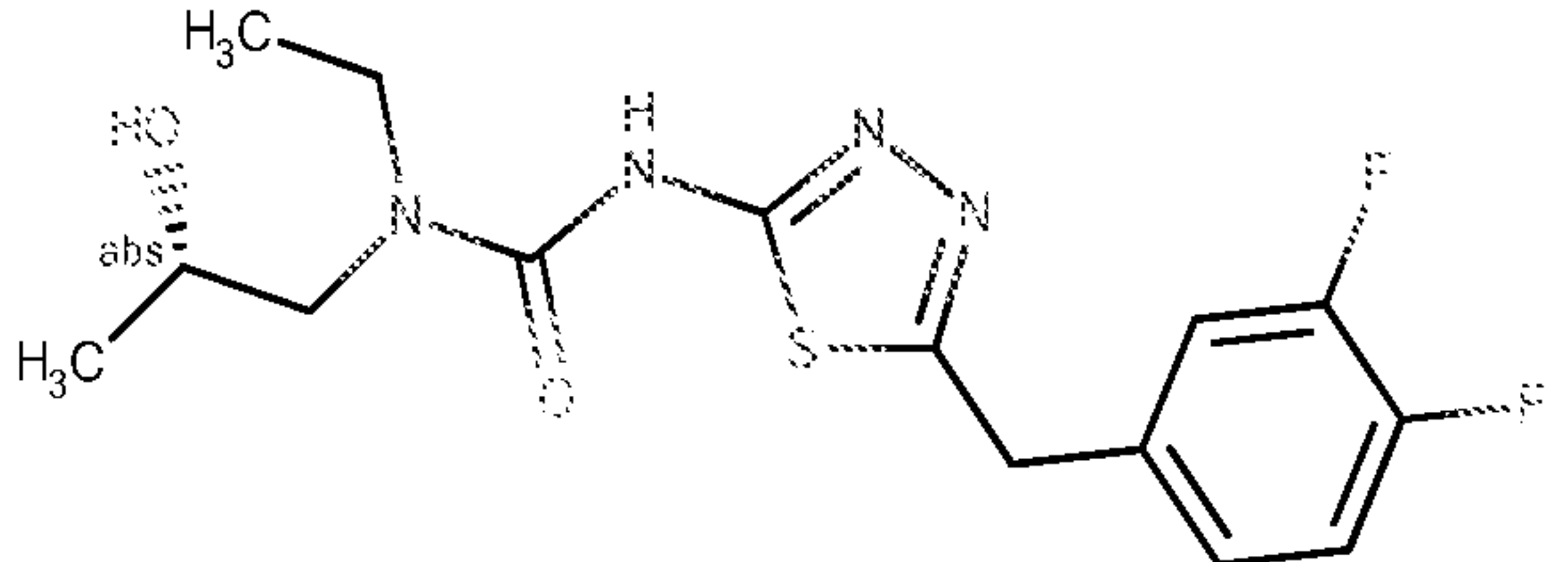
[00158] Potent and selective hMrgpMRGPRX2 compounds have been generated from compounds identified during a high throughput screening (HTS) campaign and followed up with cycles of structure activity based medicinal chemistry efforts. These compounds were characterized in recombinant hMrgpMRGPRX2 expressing cells for their antagonist activity and the potency was confirmed in the human mast cell line LAD-2, where the target is endogenously expressed. The assays used to determine potencies are functional read-out looking at intracellular calcium mobilization using the FLIPR™ technology. In these FLIPR assays, we test the identified compounds using recombinant cellular systems expressing mouse MrgprB2, mouse MrgprA1, gerbil MrgpMRGPRX2 orthologue, Chinese hamster MrgpMRGPRX2 orthologue and cynomolgus monkey MrgpMRGPRX2 orthologue, respectively for orthologue activity.

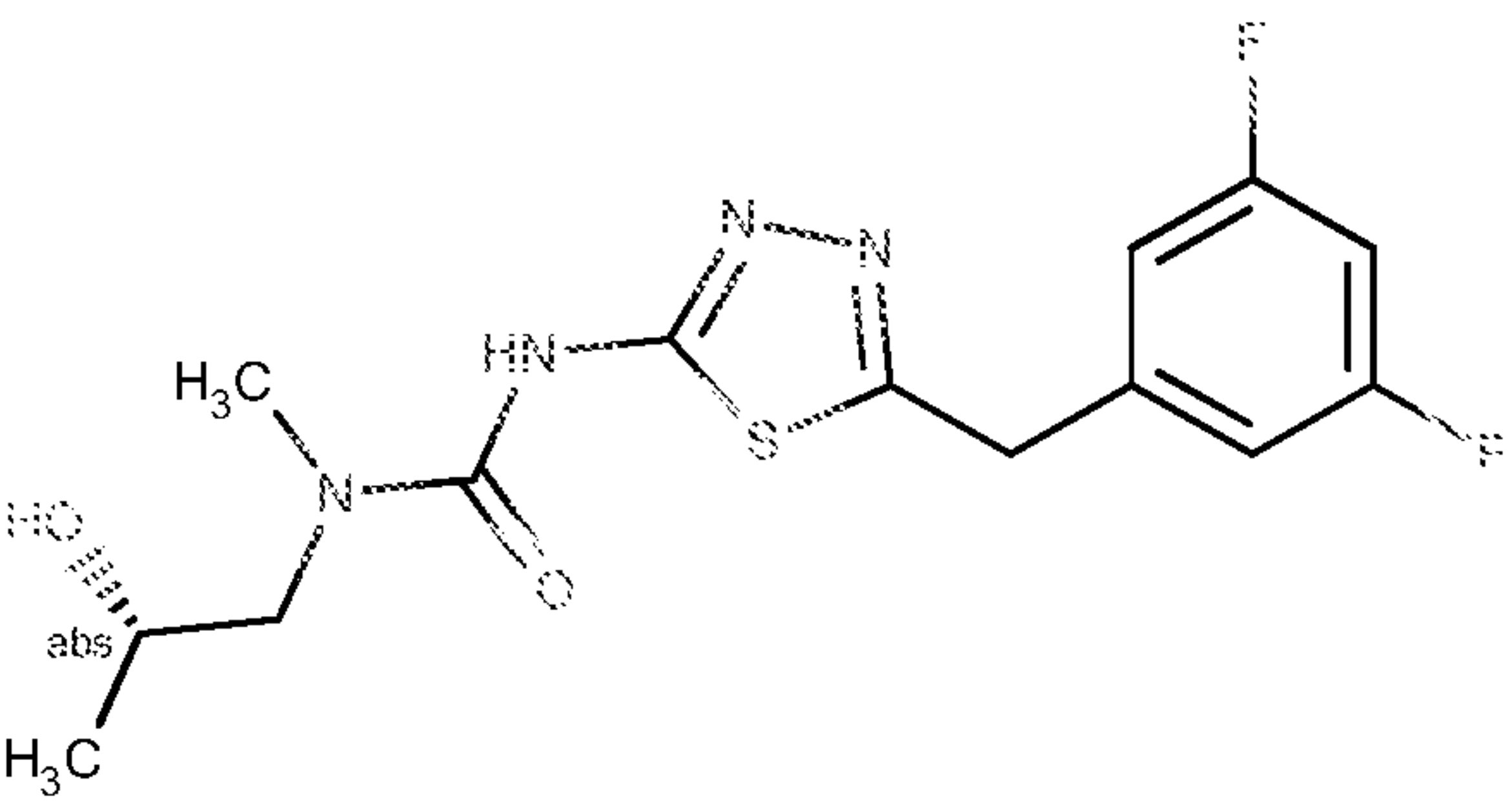
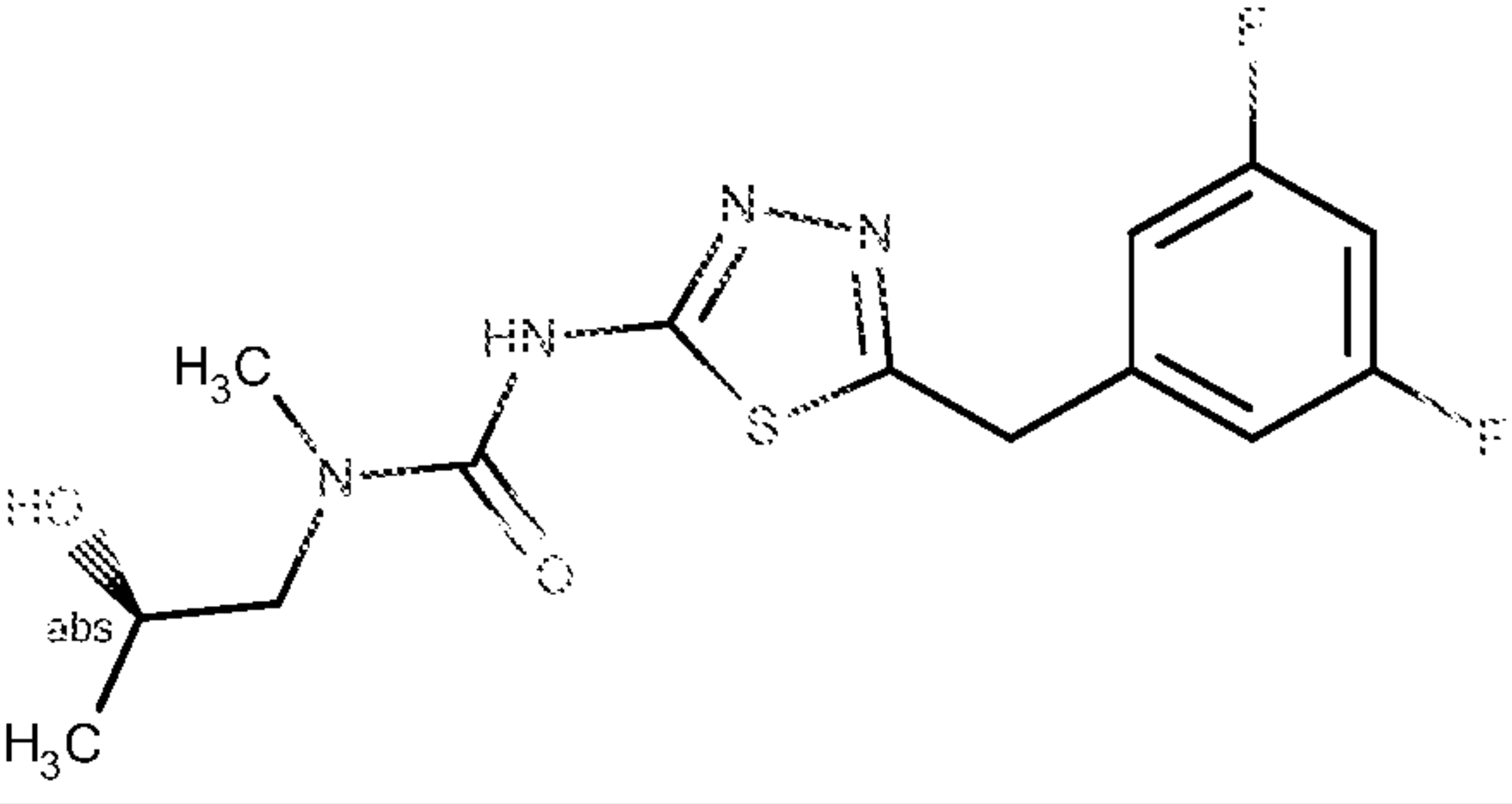
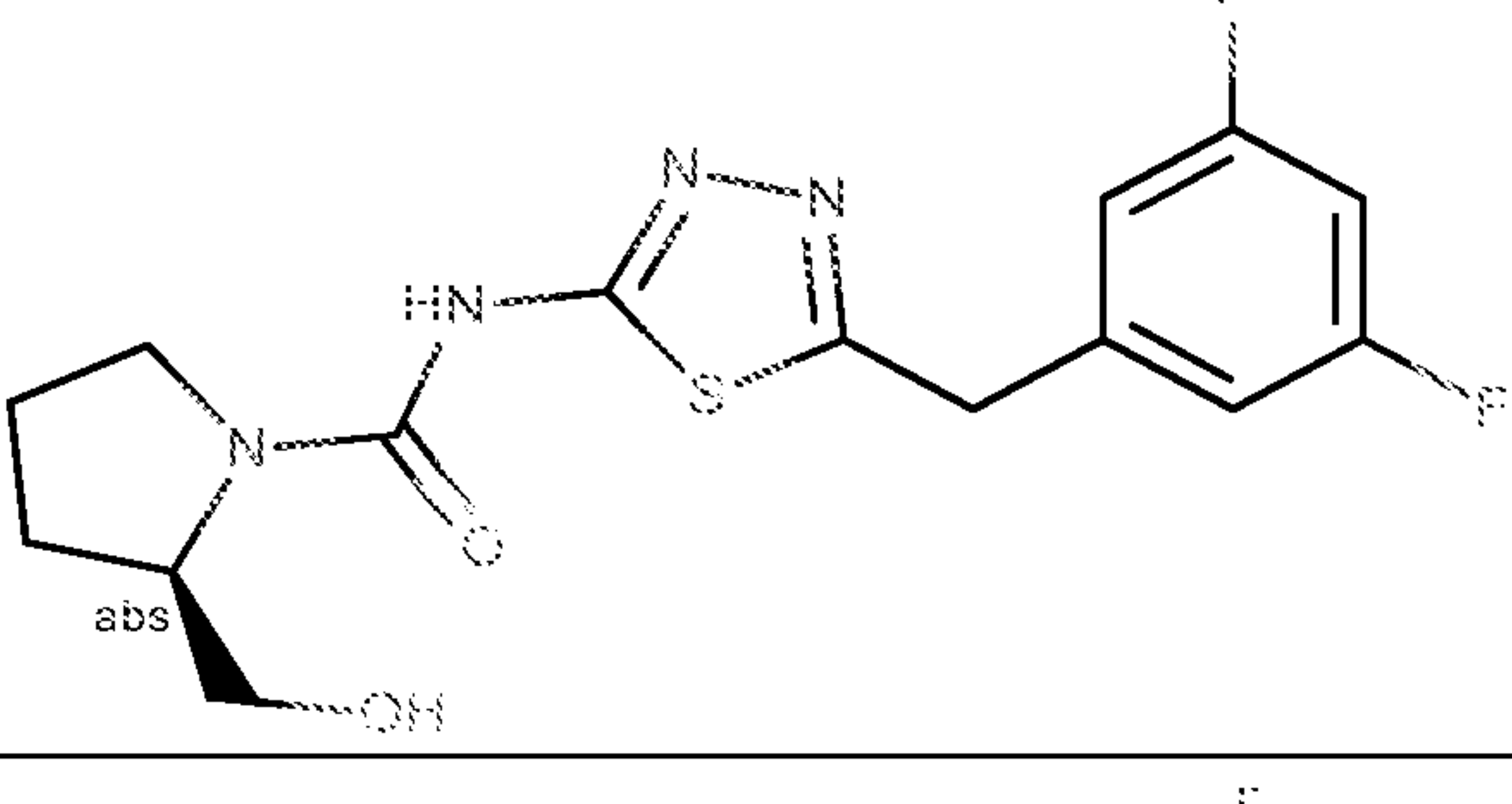
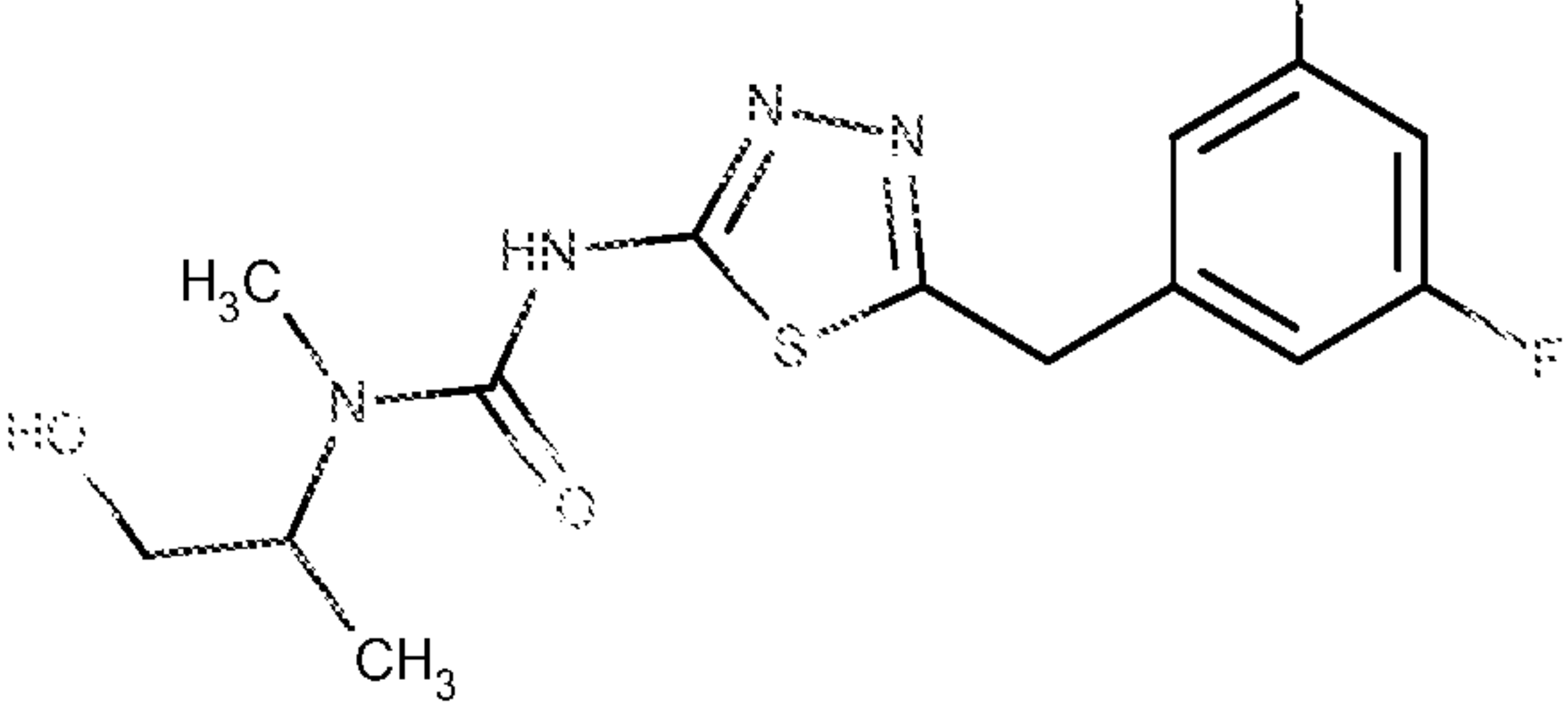
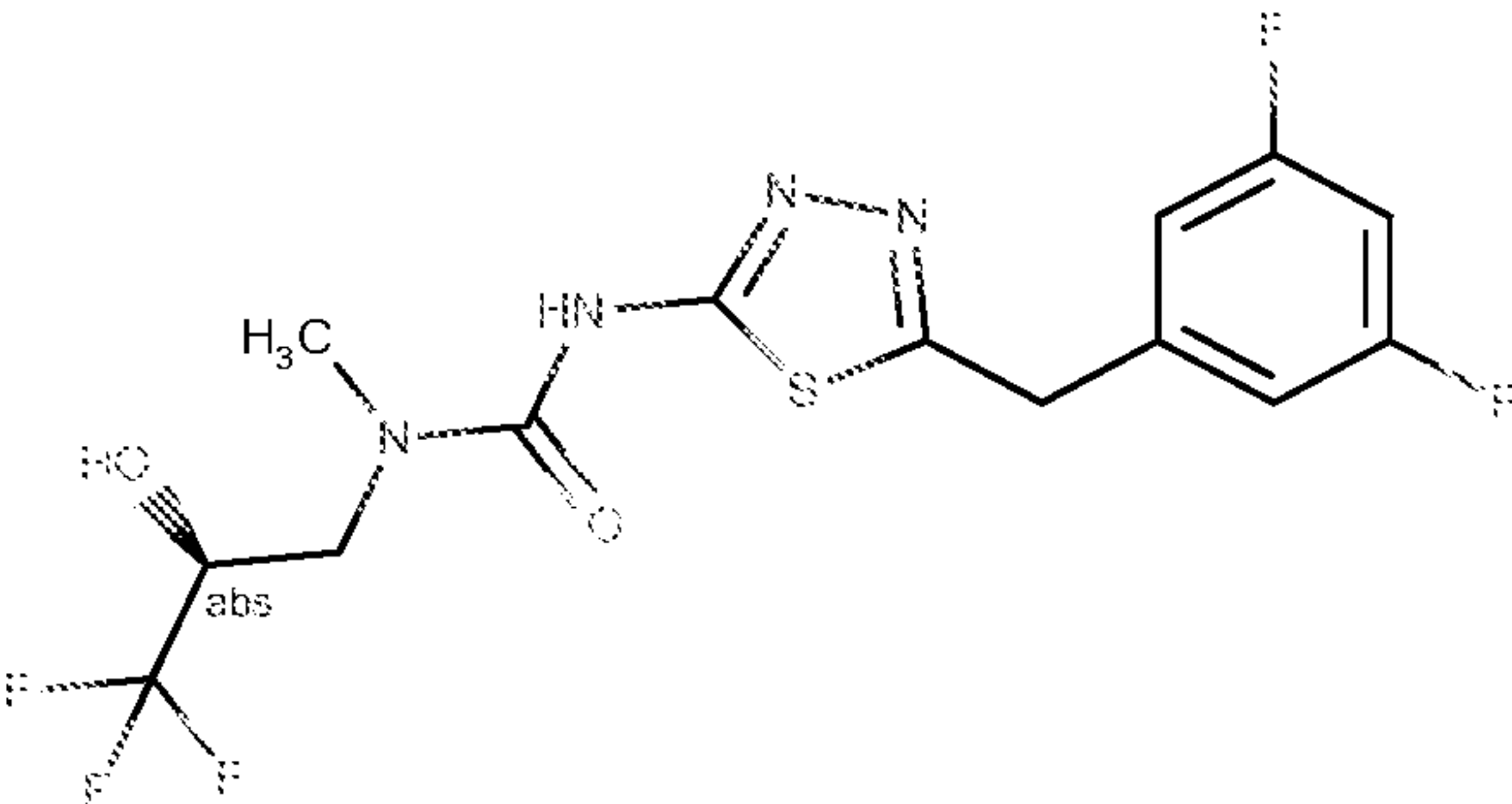
[00159] Results are summarized below in Table 4.

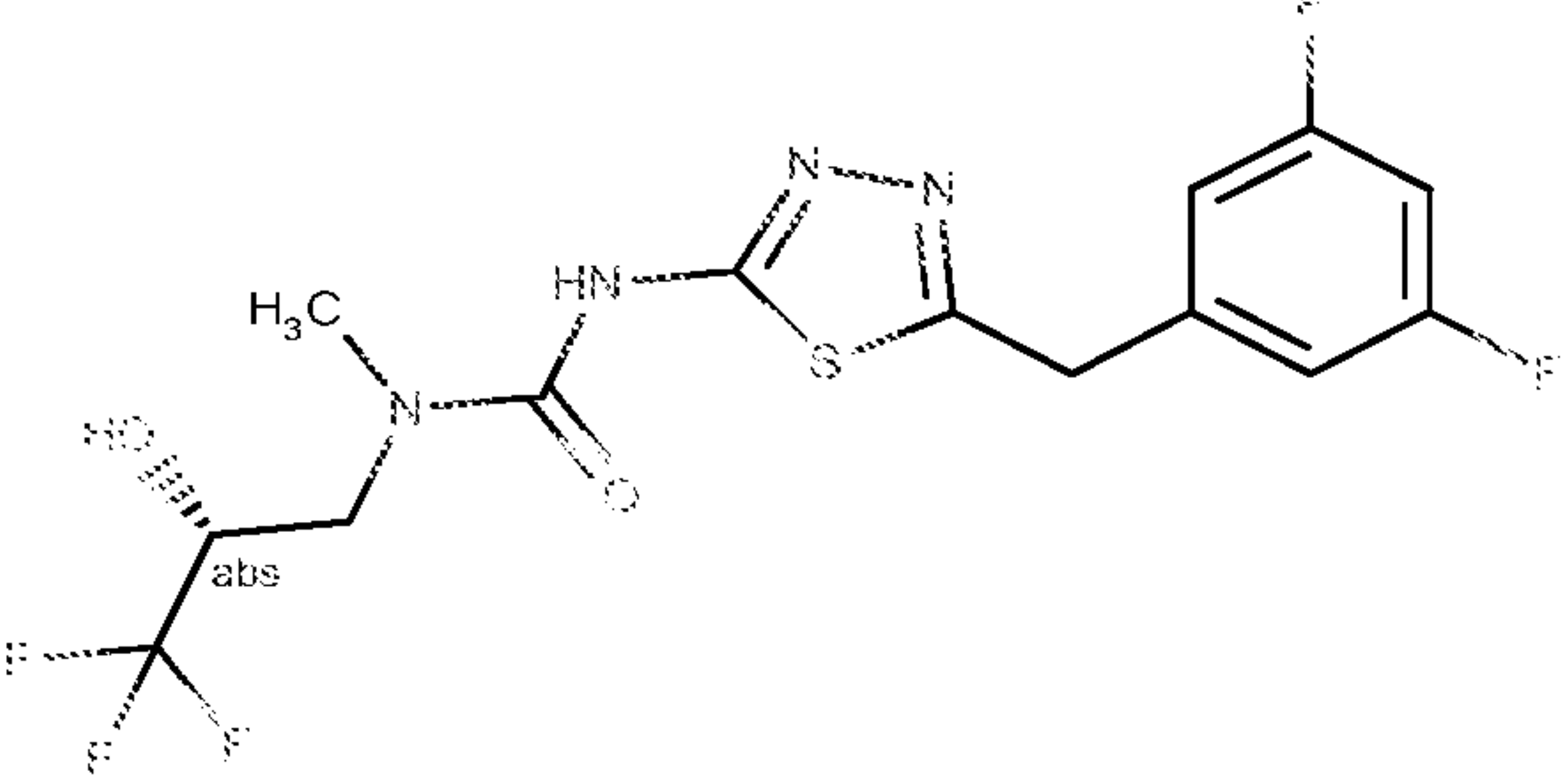
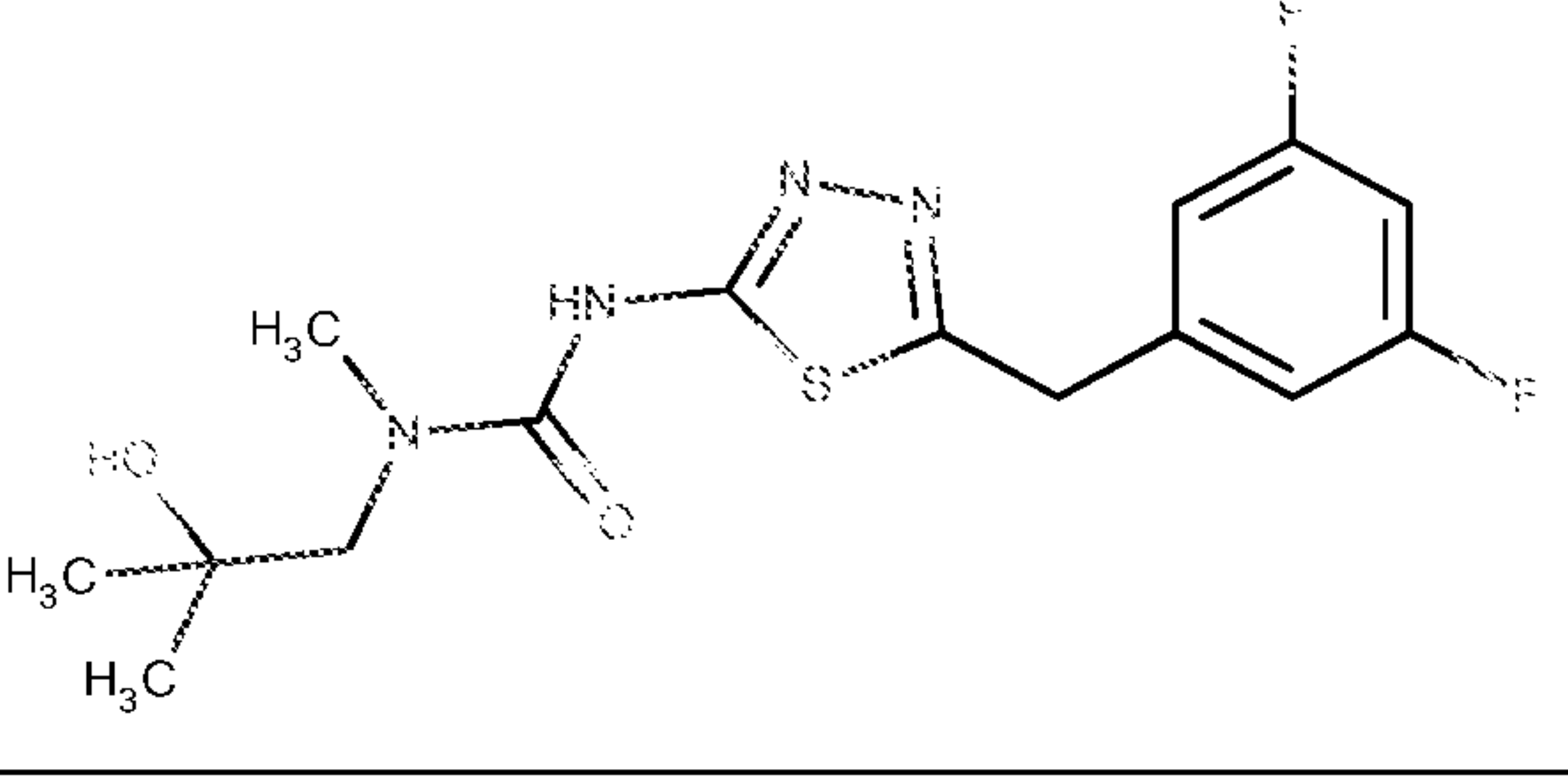
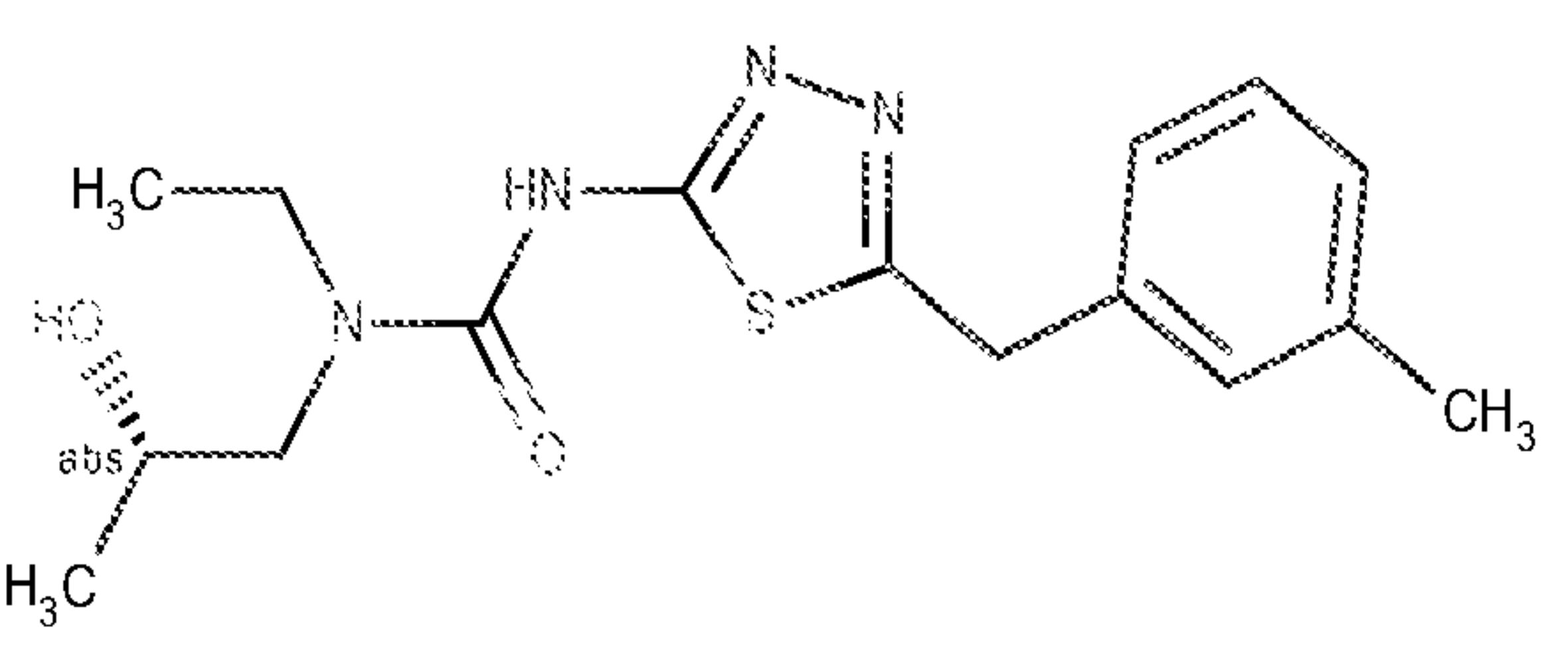
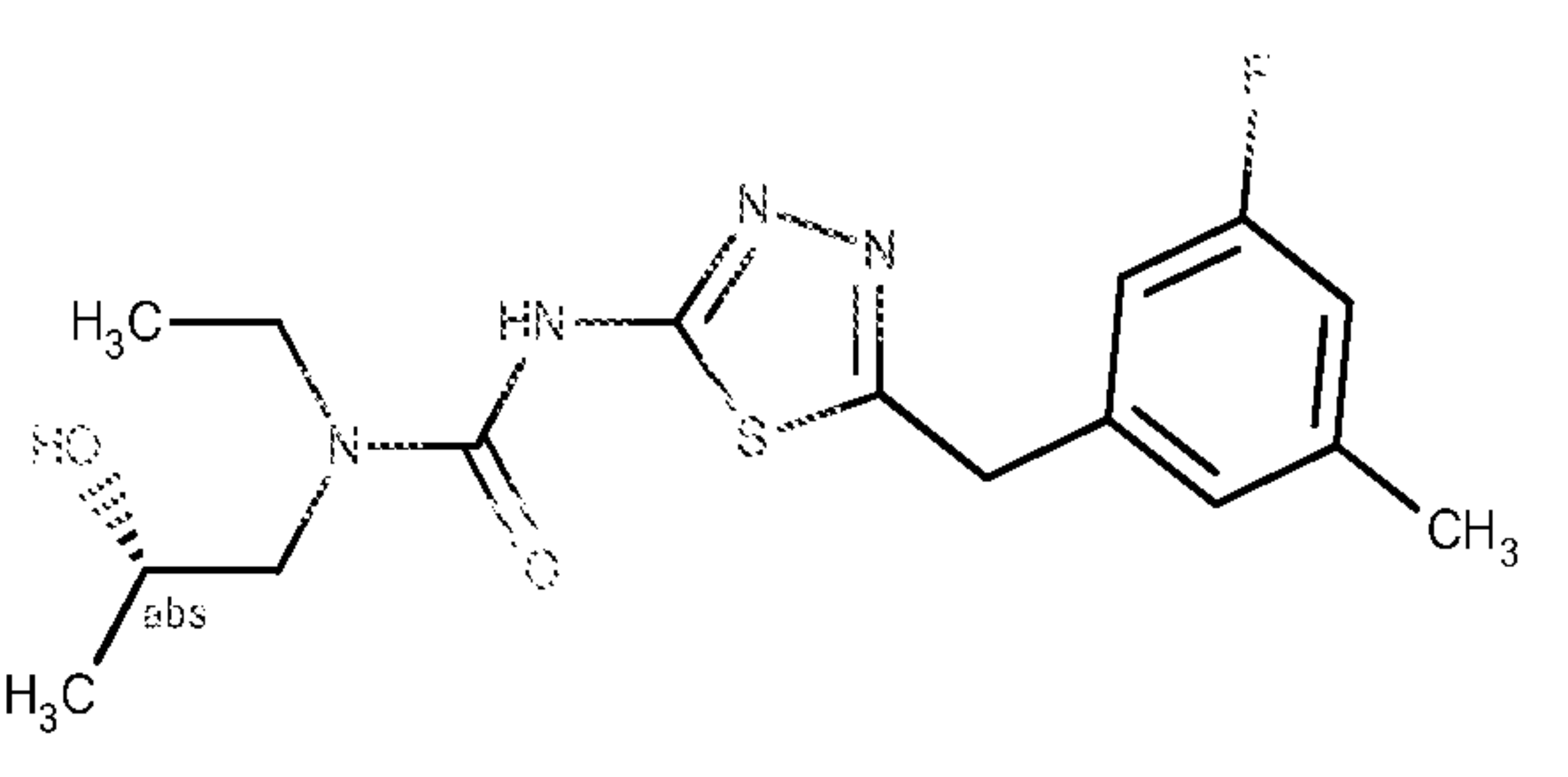
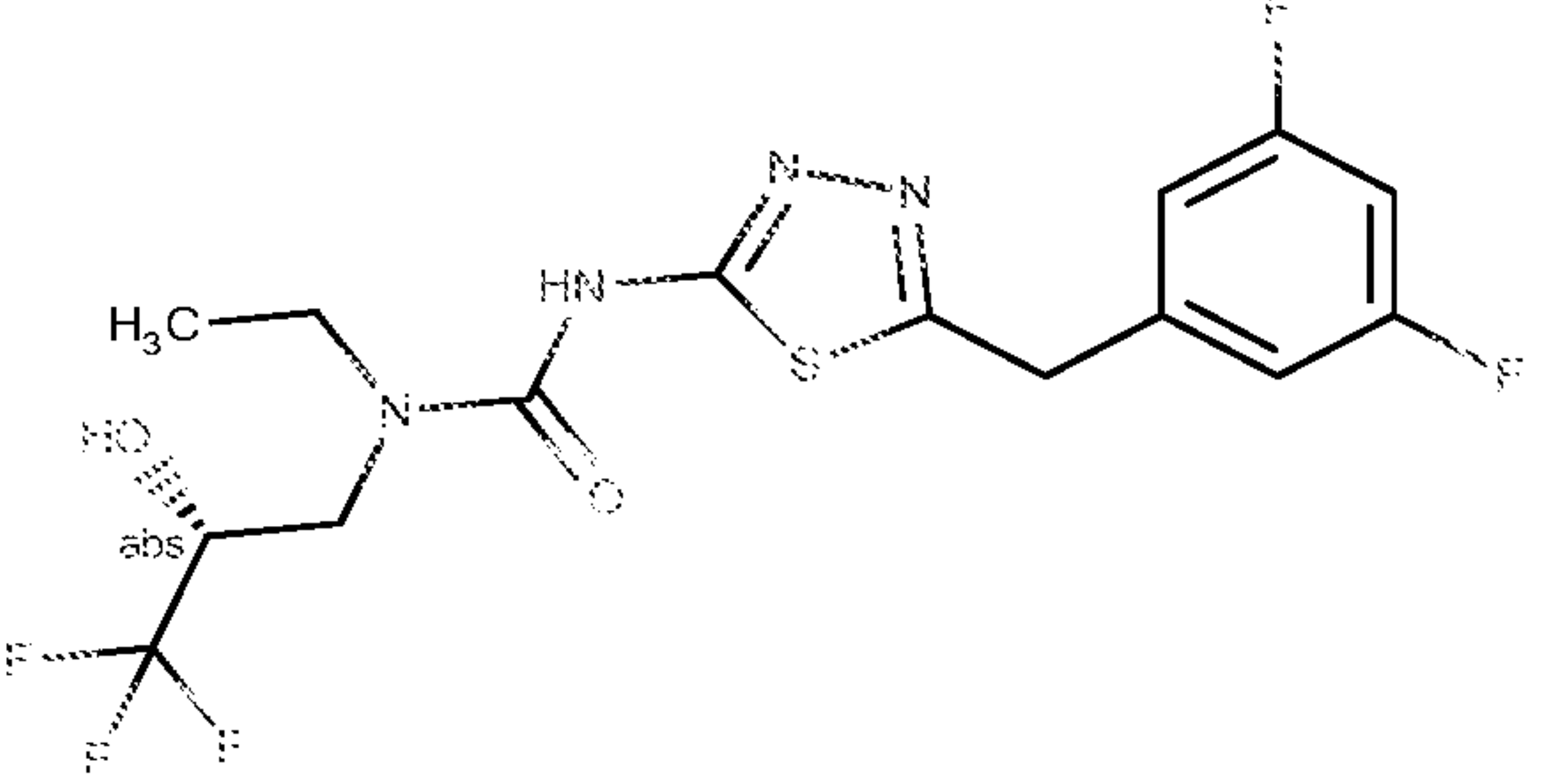
Table 4

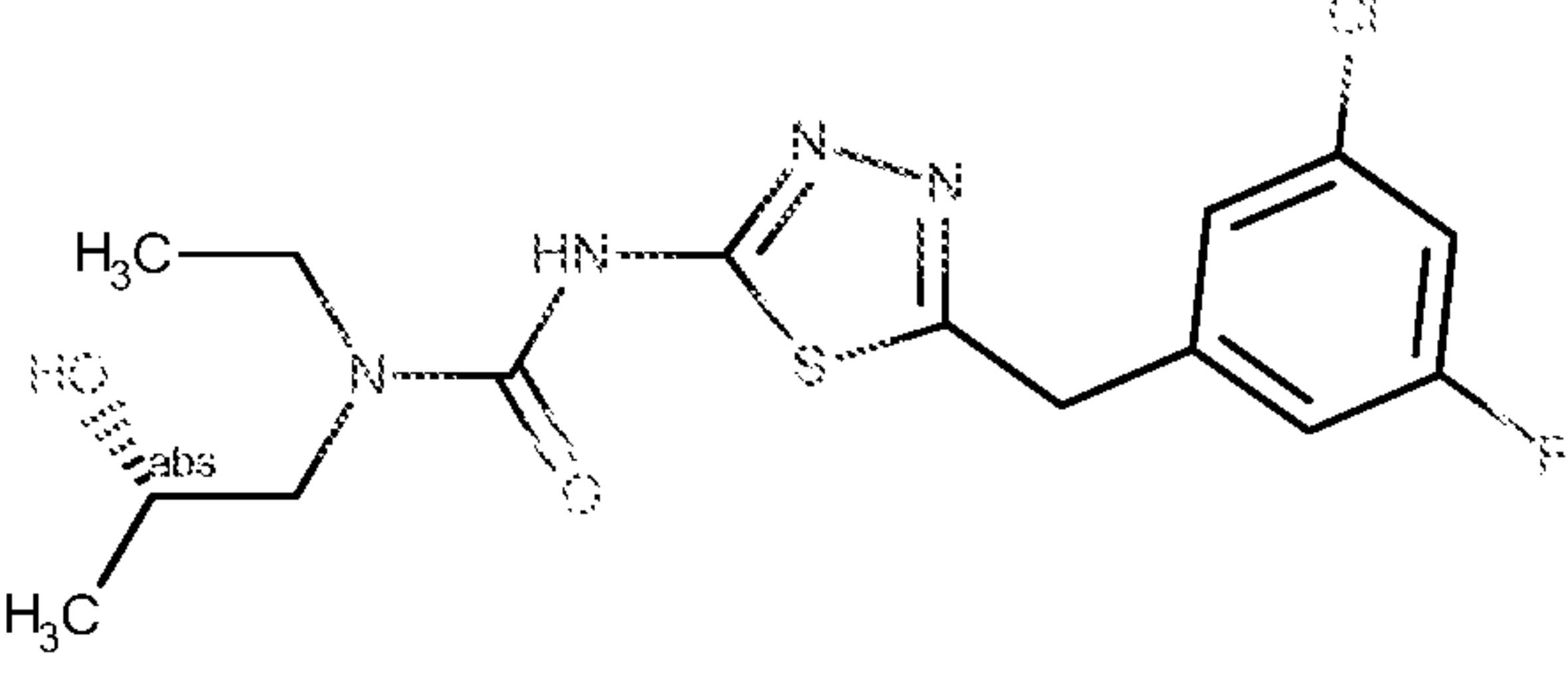
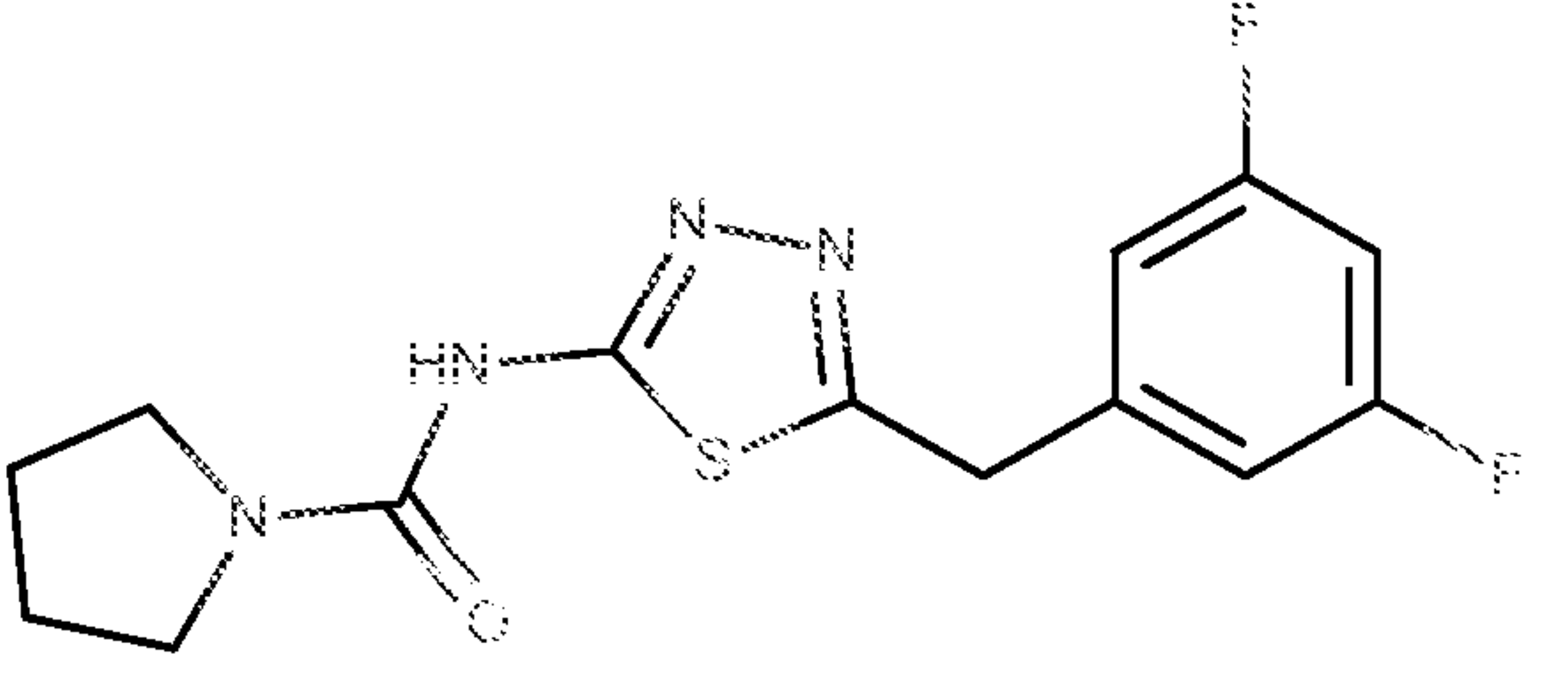
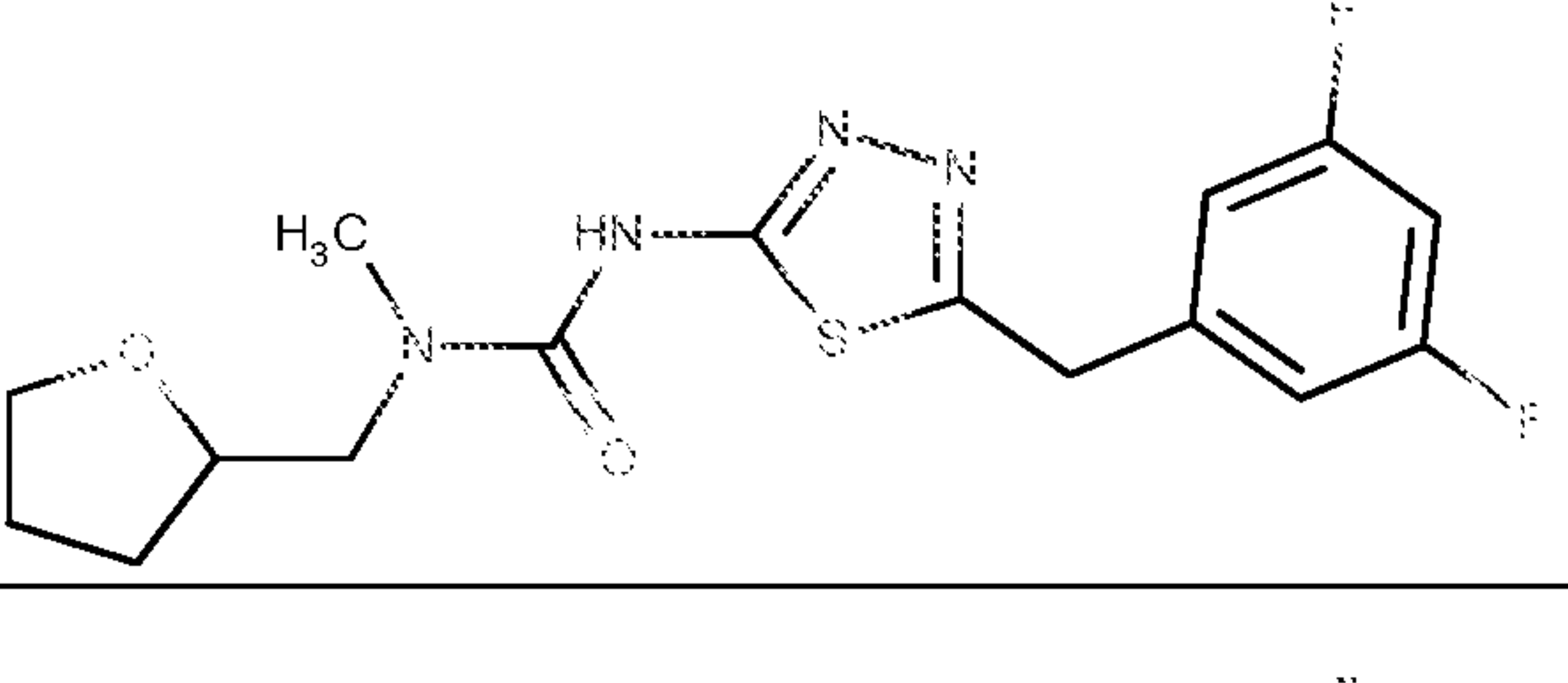
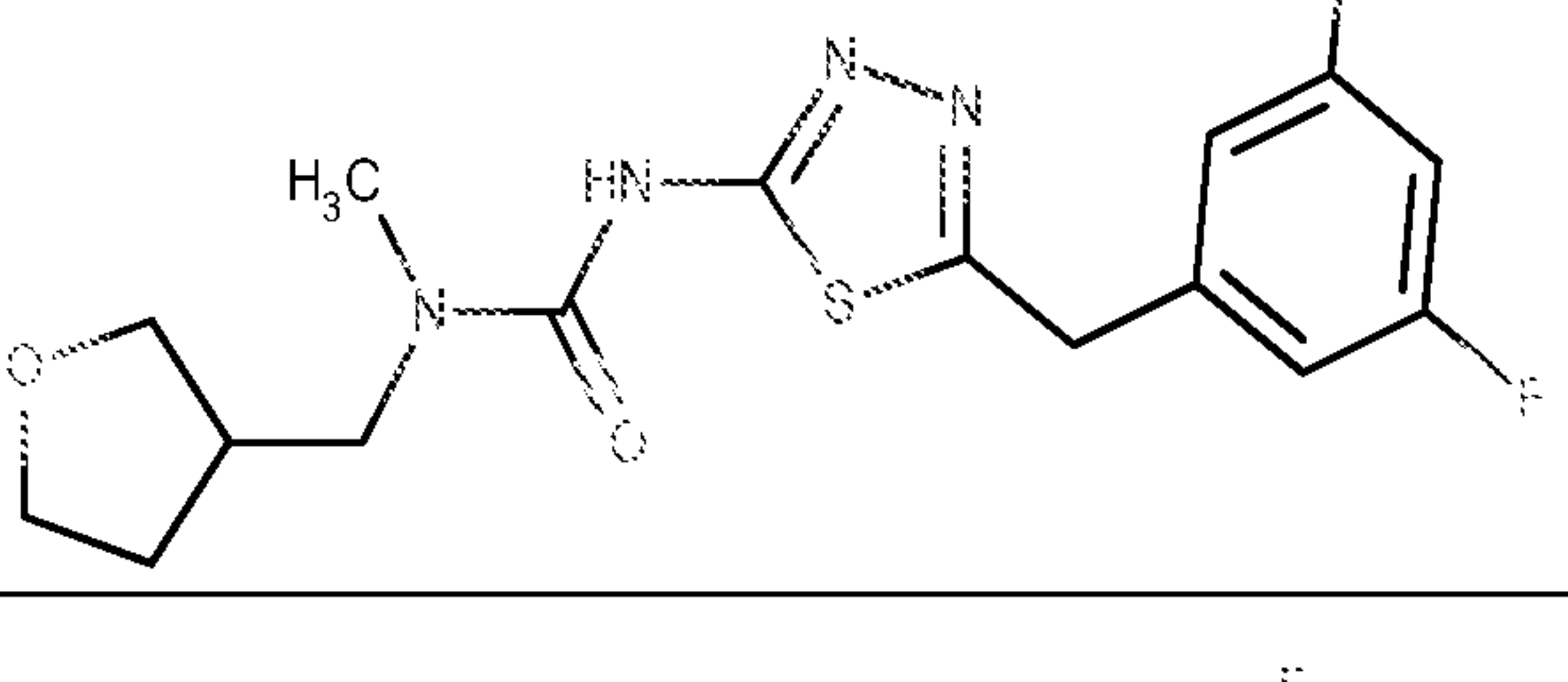
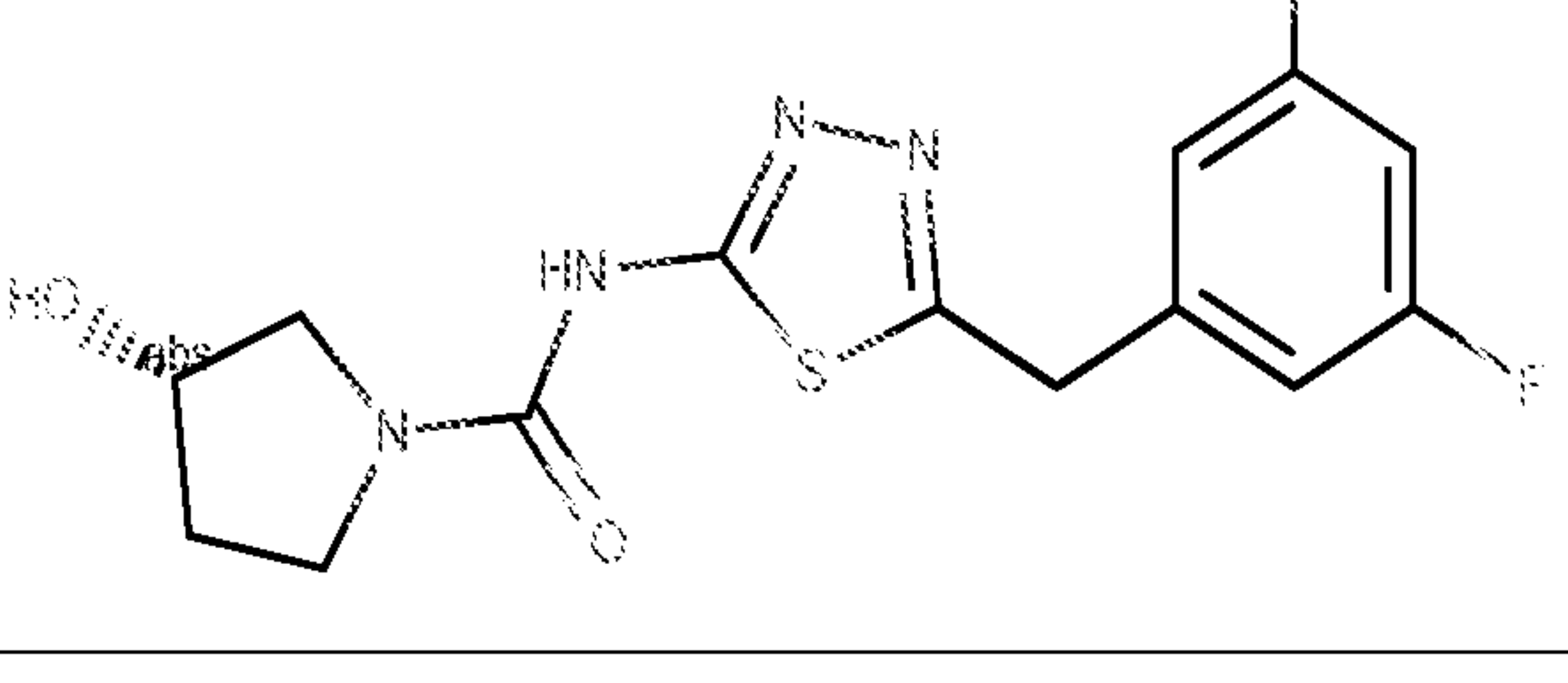
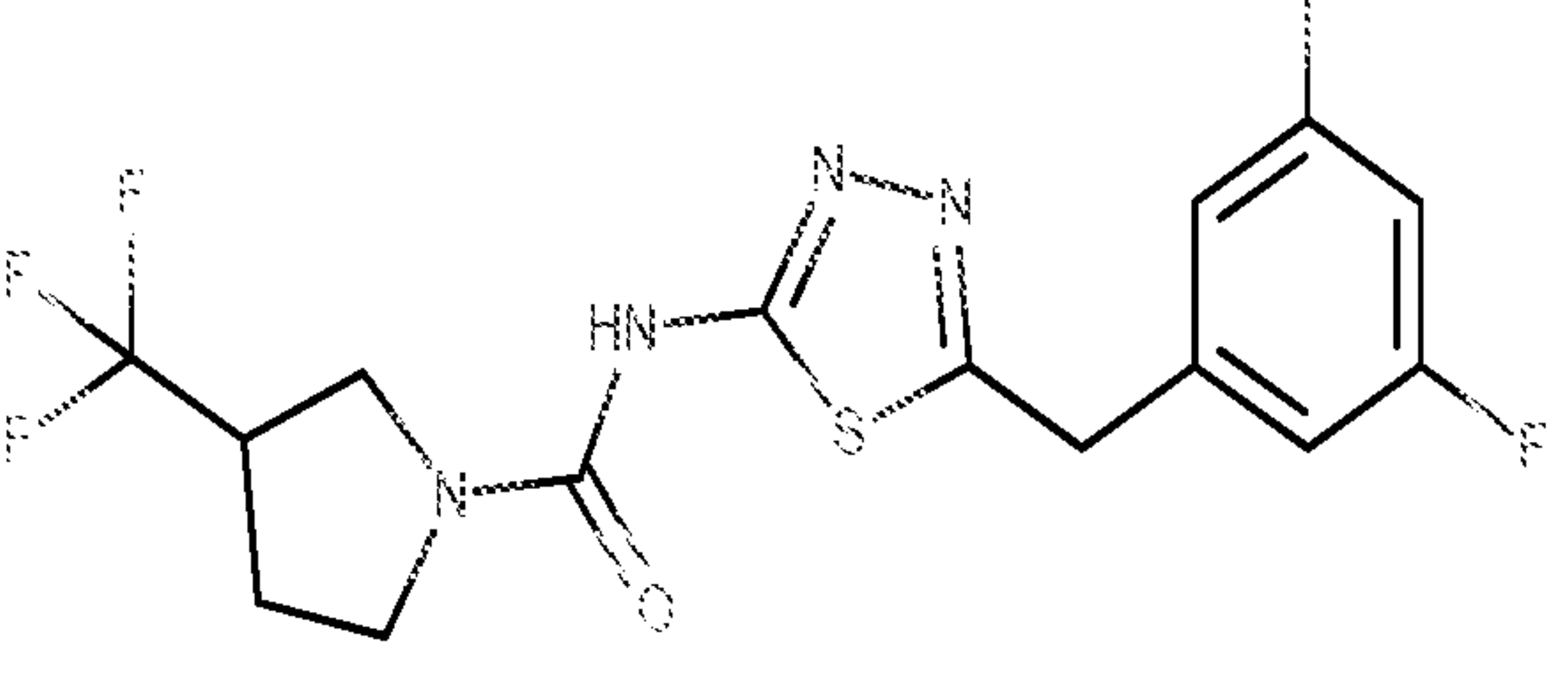
Compound	Structure	Human MrgprX2 Antagonist pIC50
E01		5.6
E02		5.1

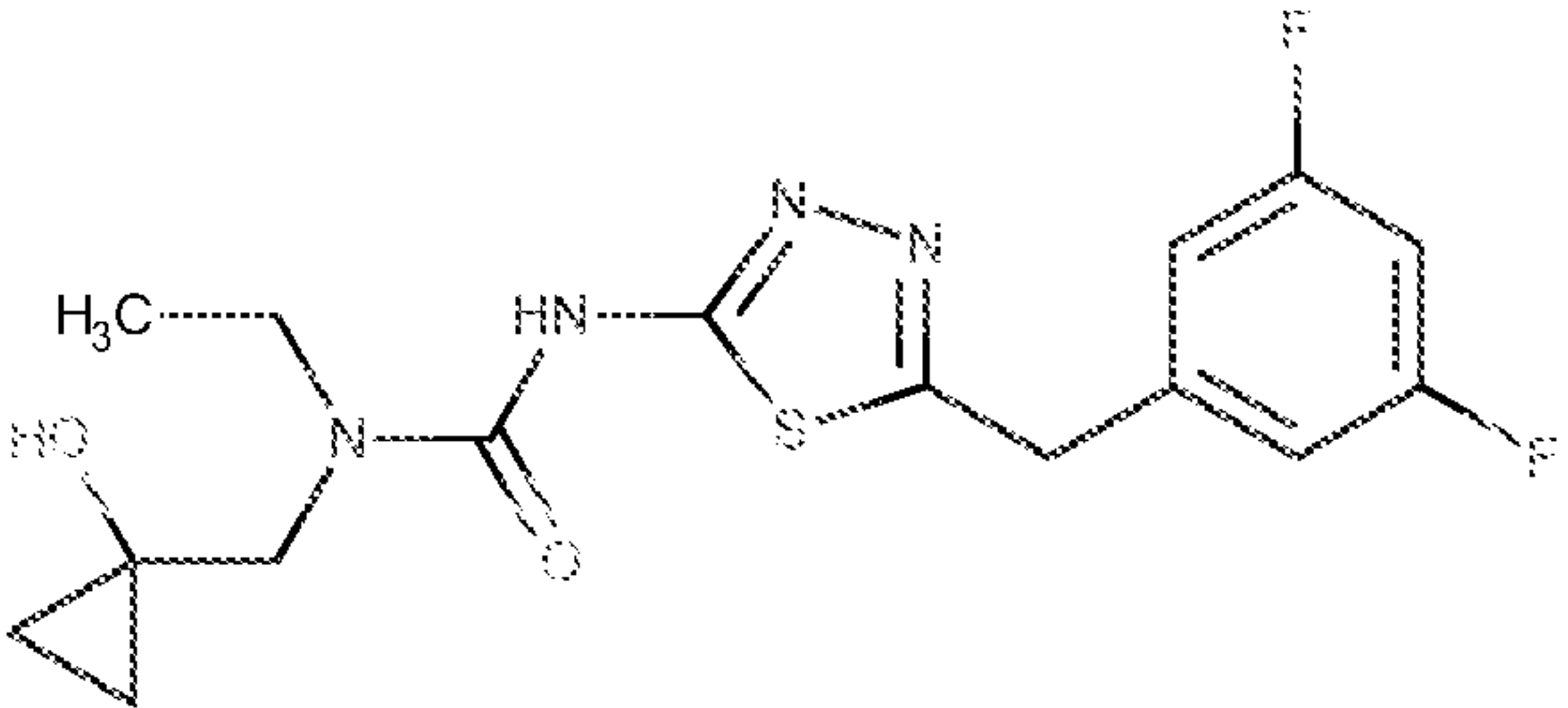
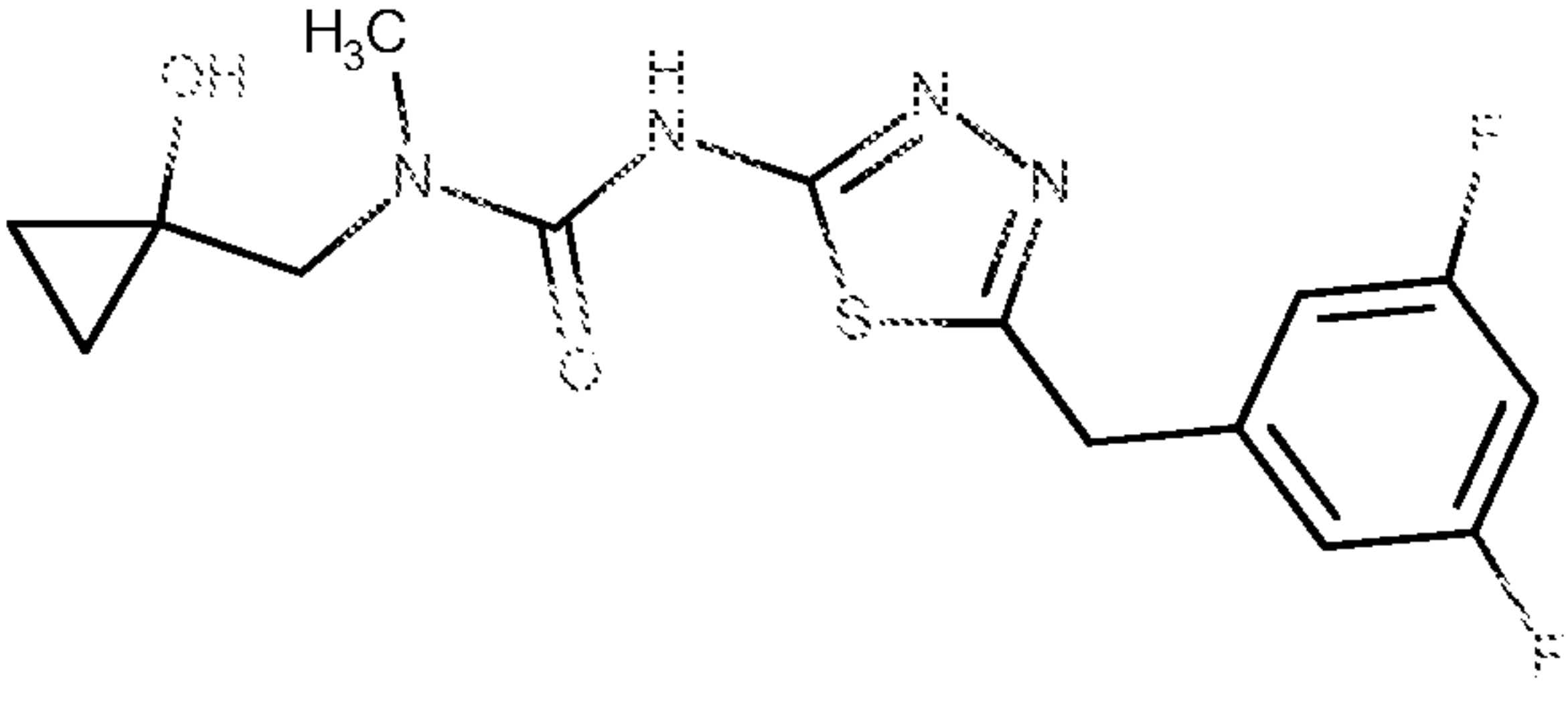
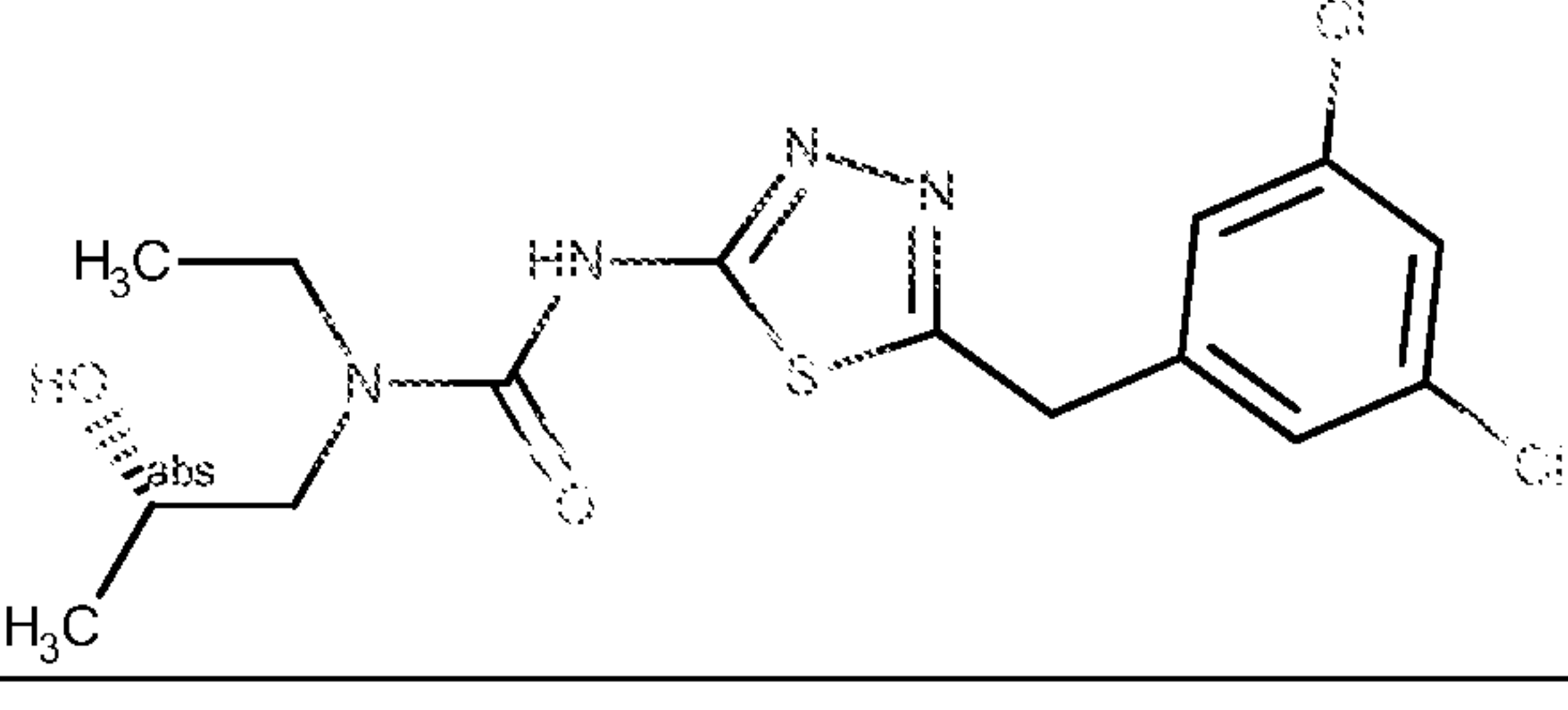
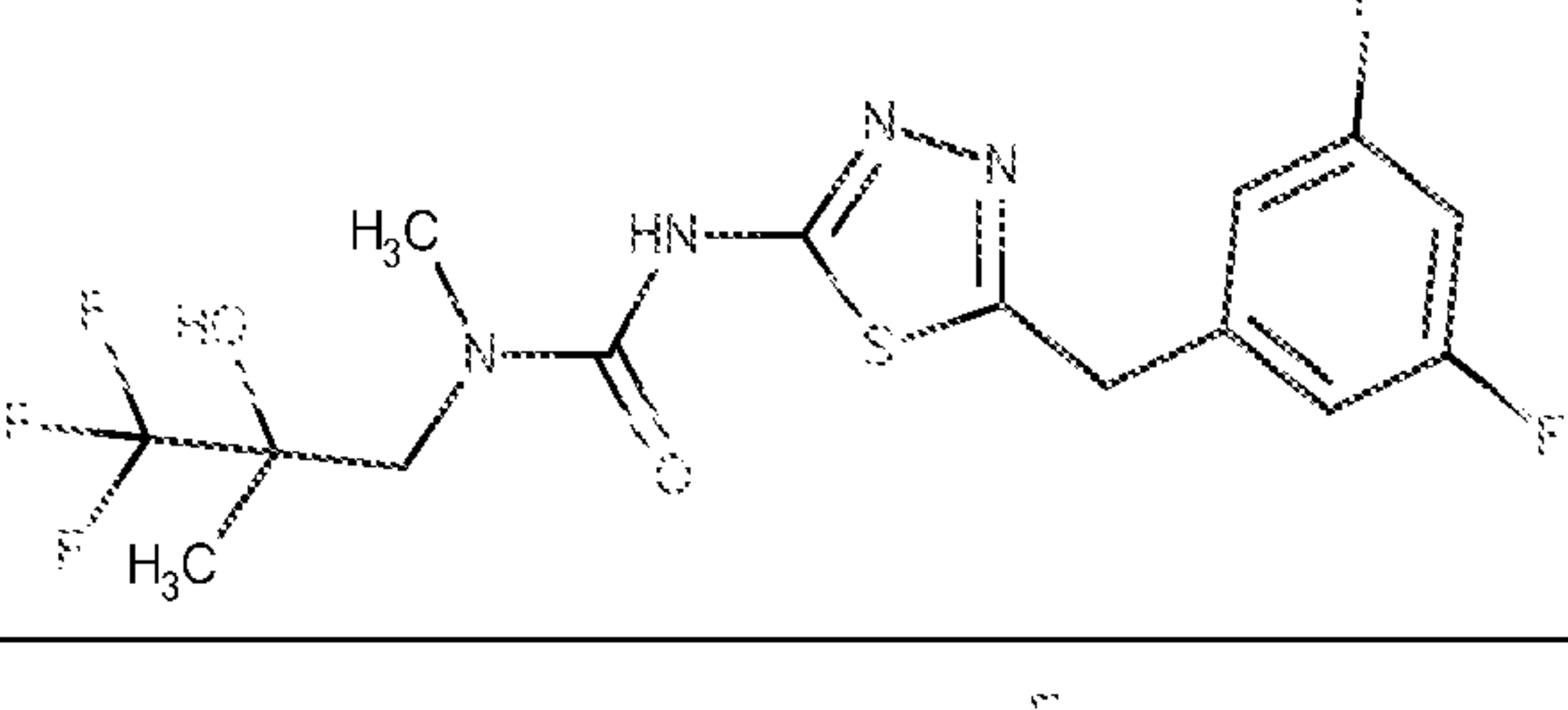
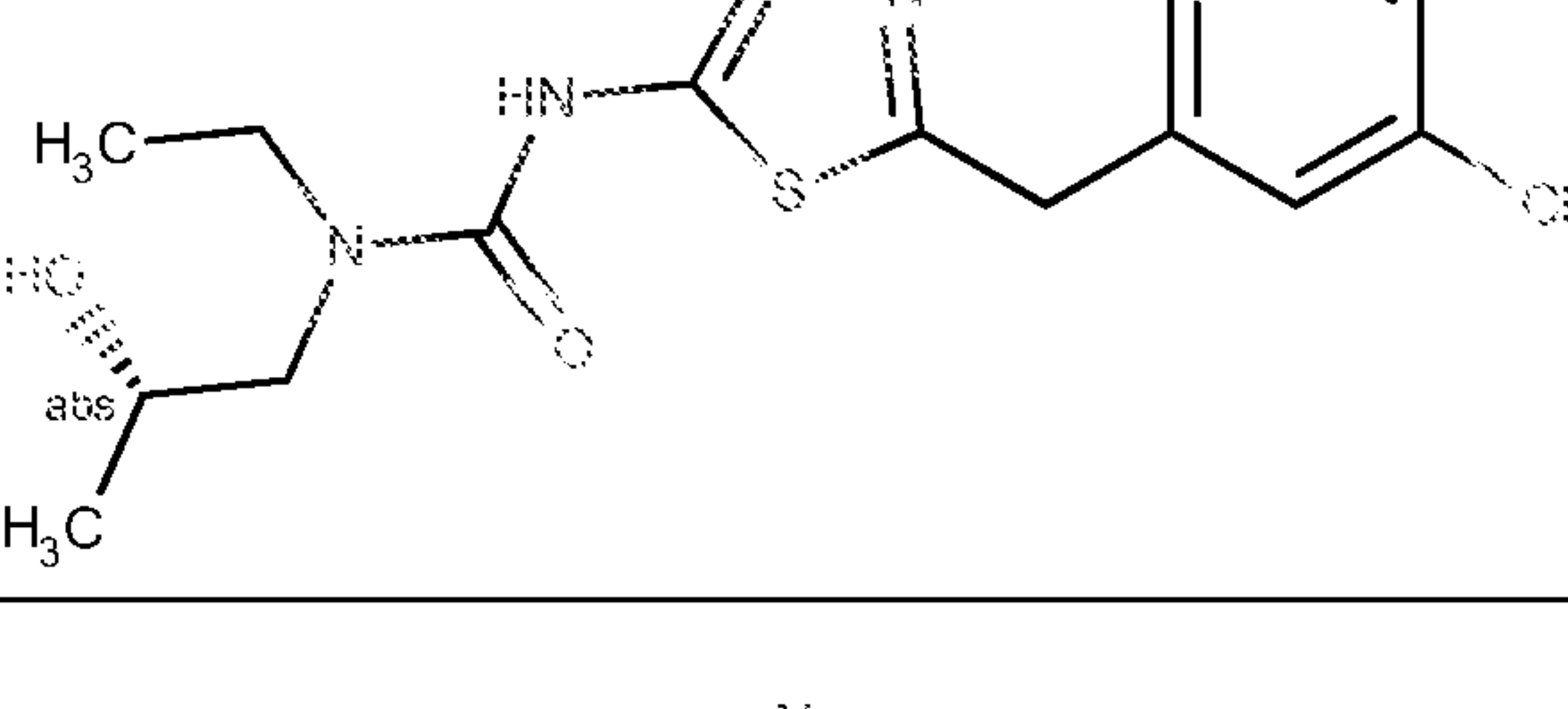
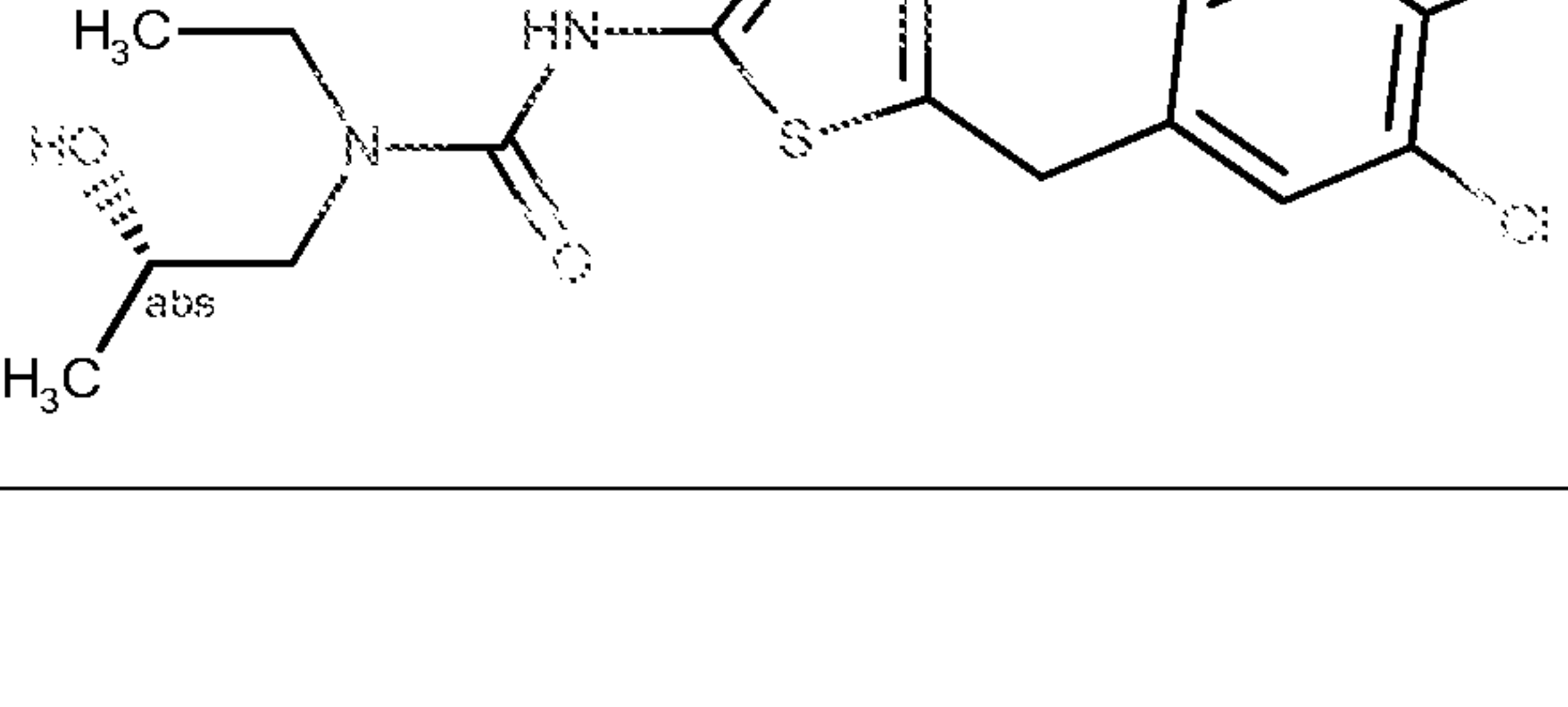
E03		6.6
E04		5.9
E05		5.6
E06		5.8
E07		6.0
E08		5.7

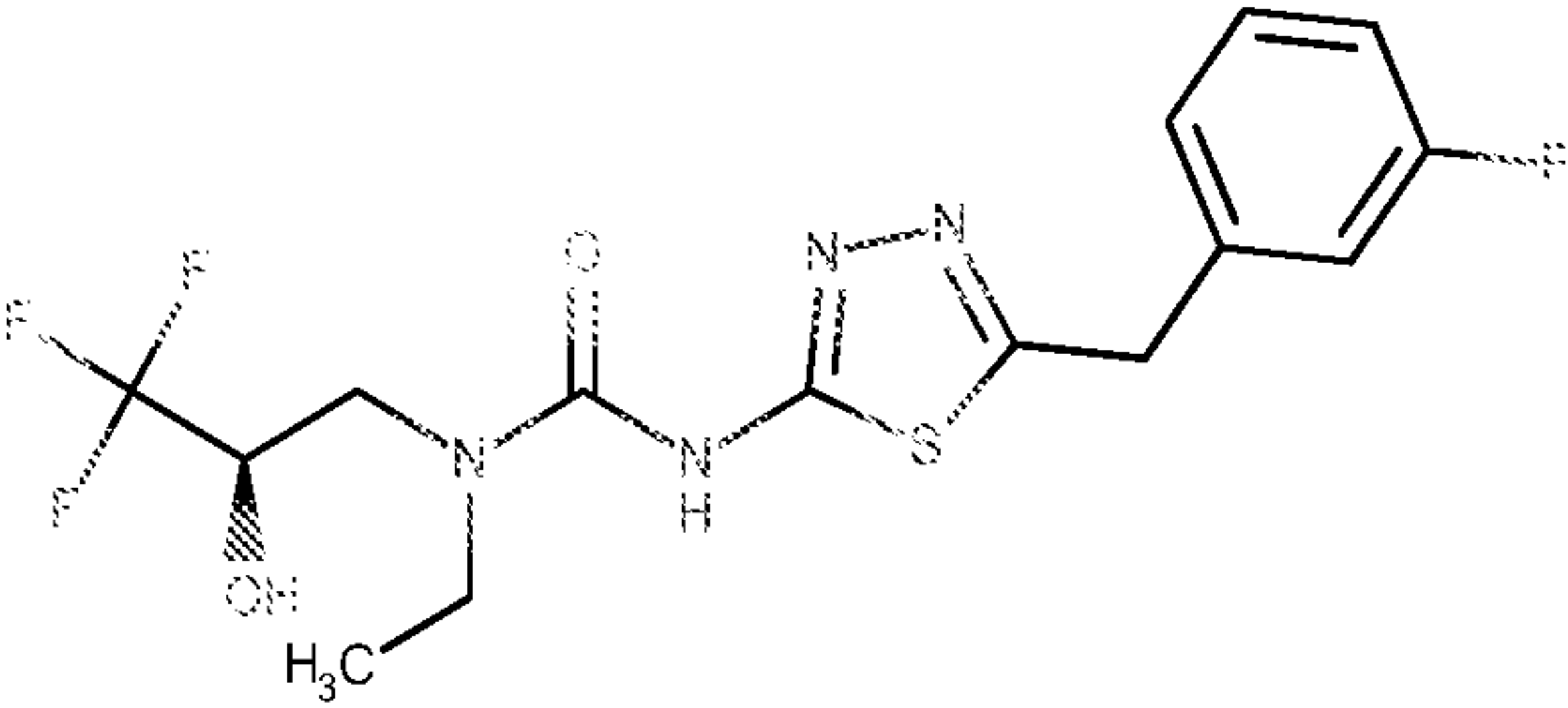
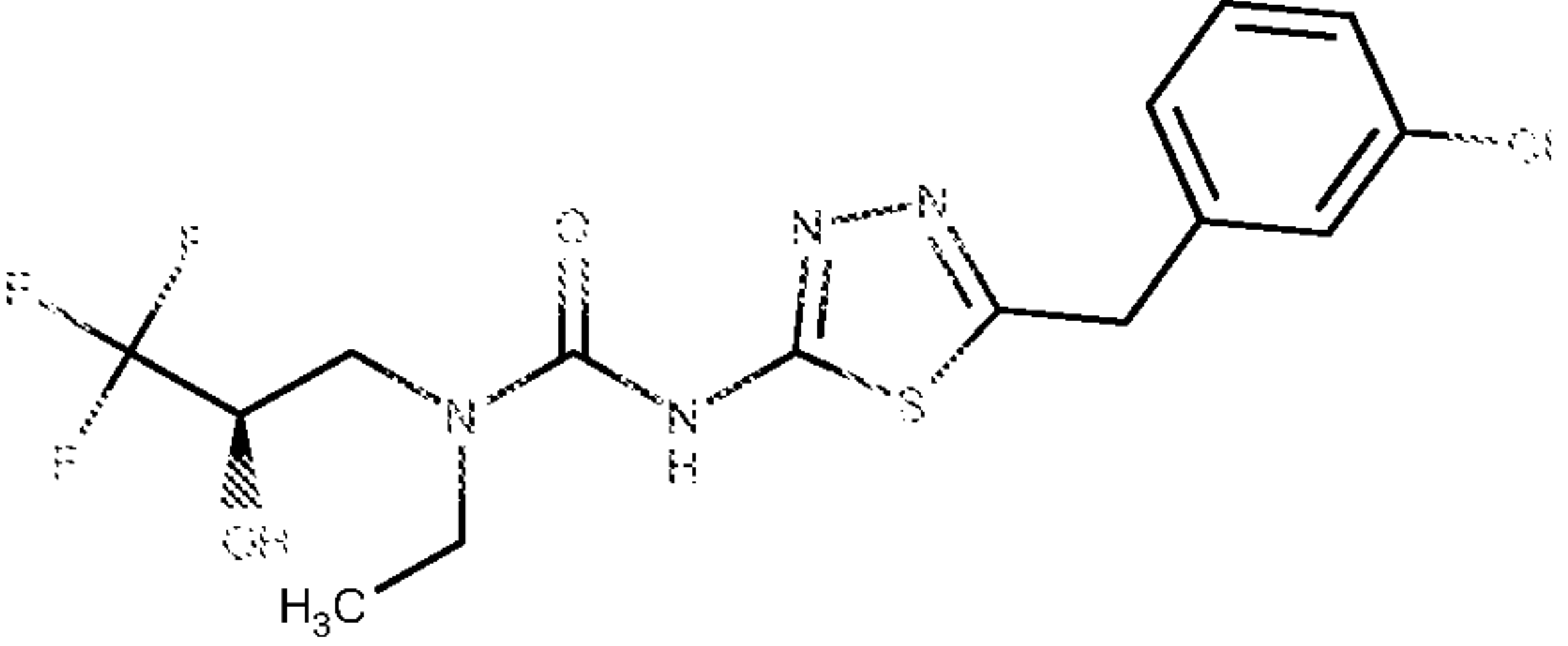
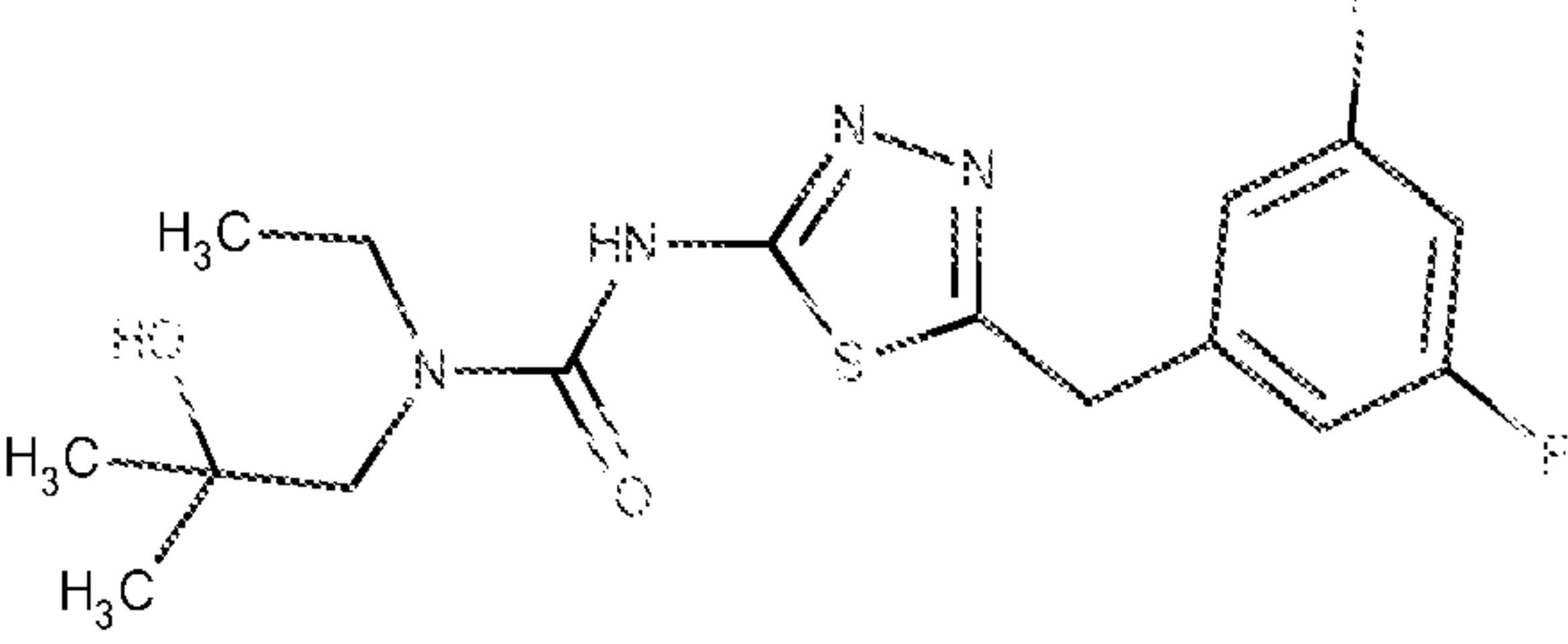
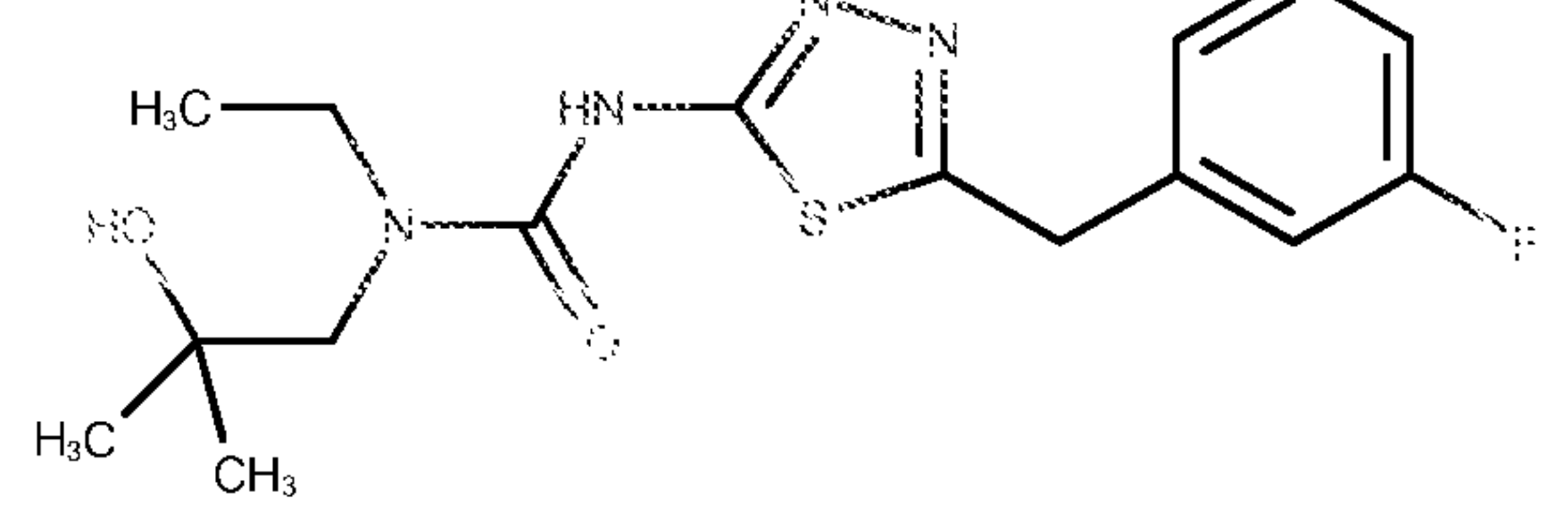
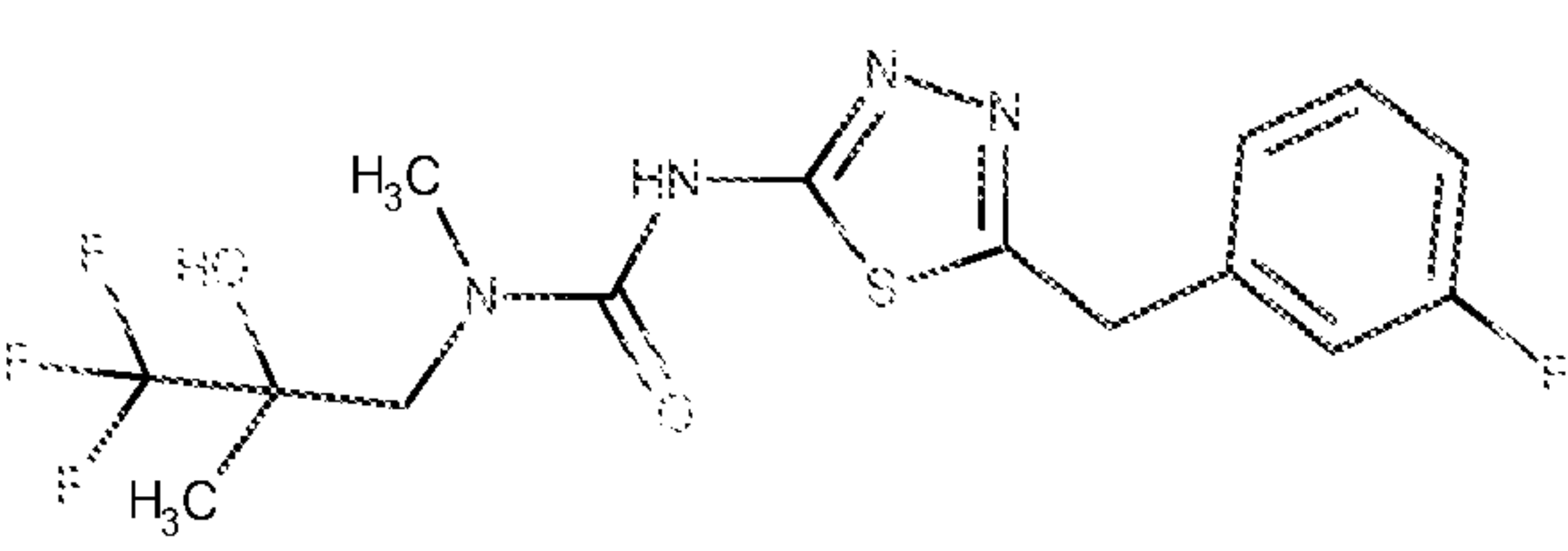
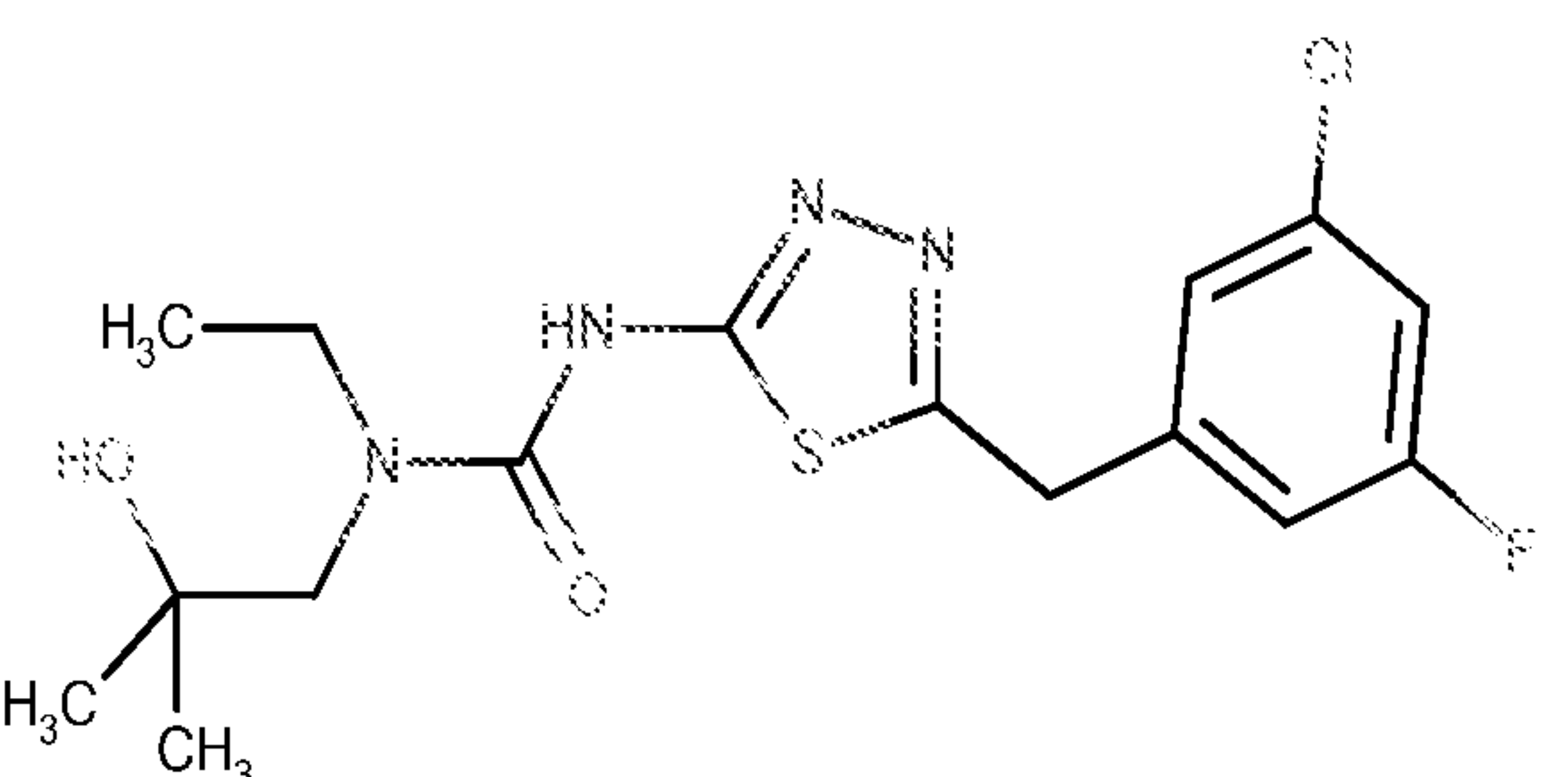
E09		5.8
E10		6.6
E11		5.5
E12		5.7
E13		5.7

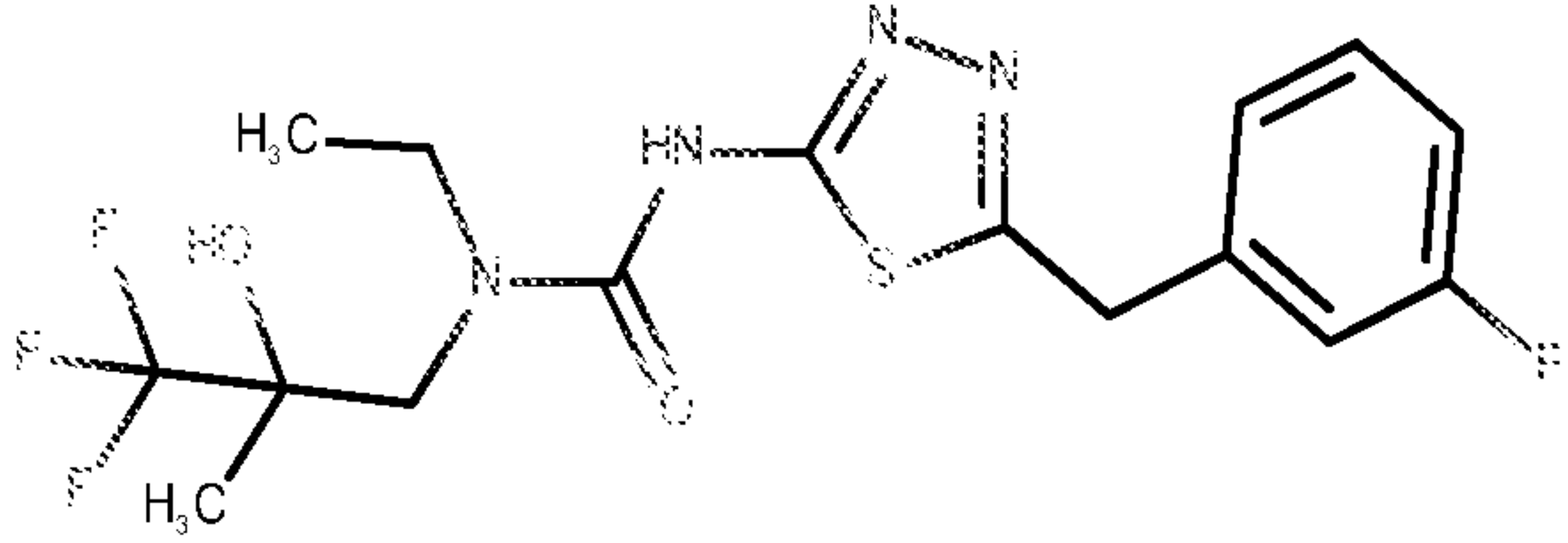
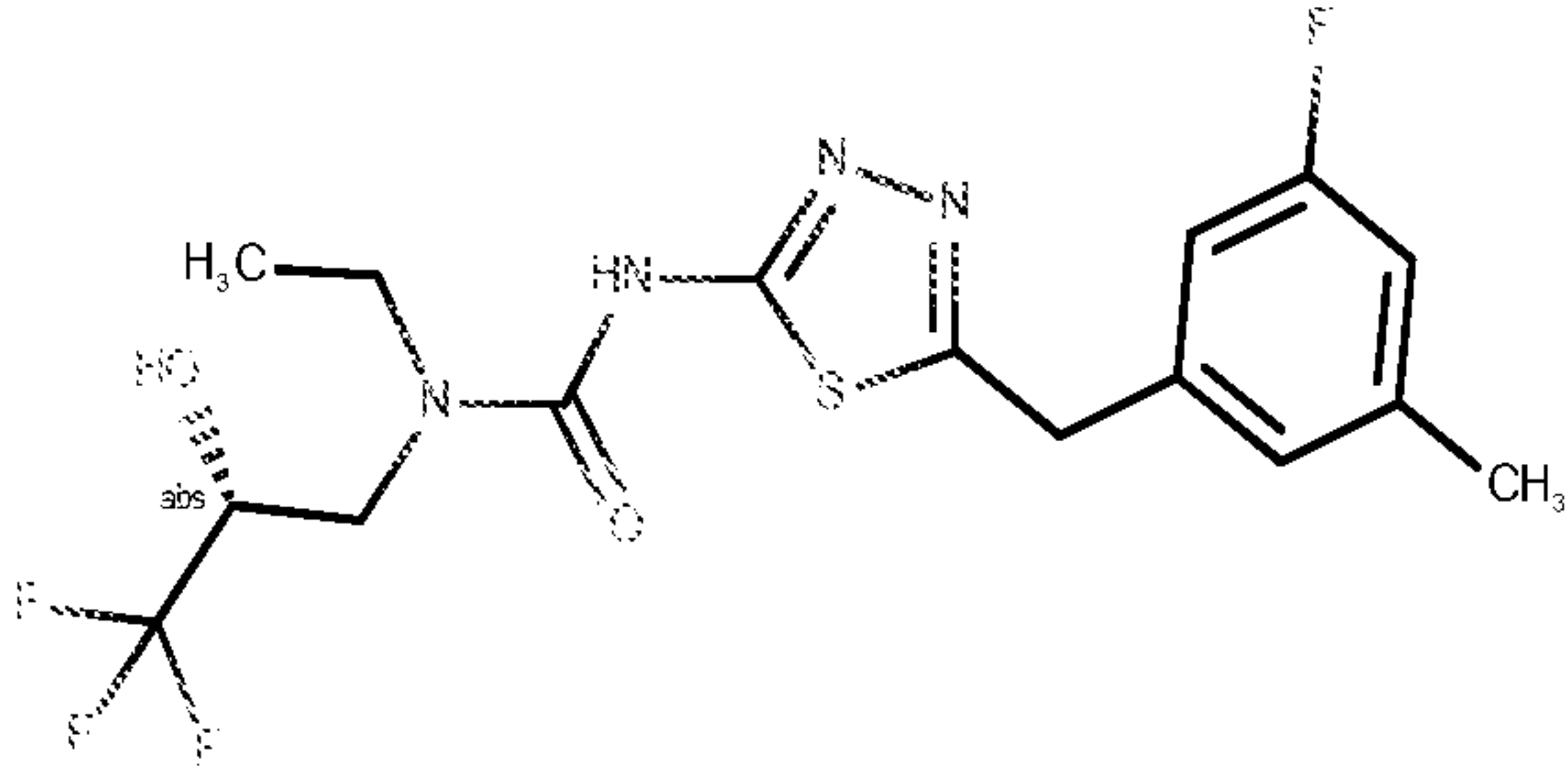
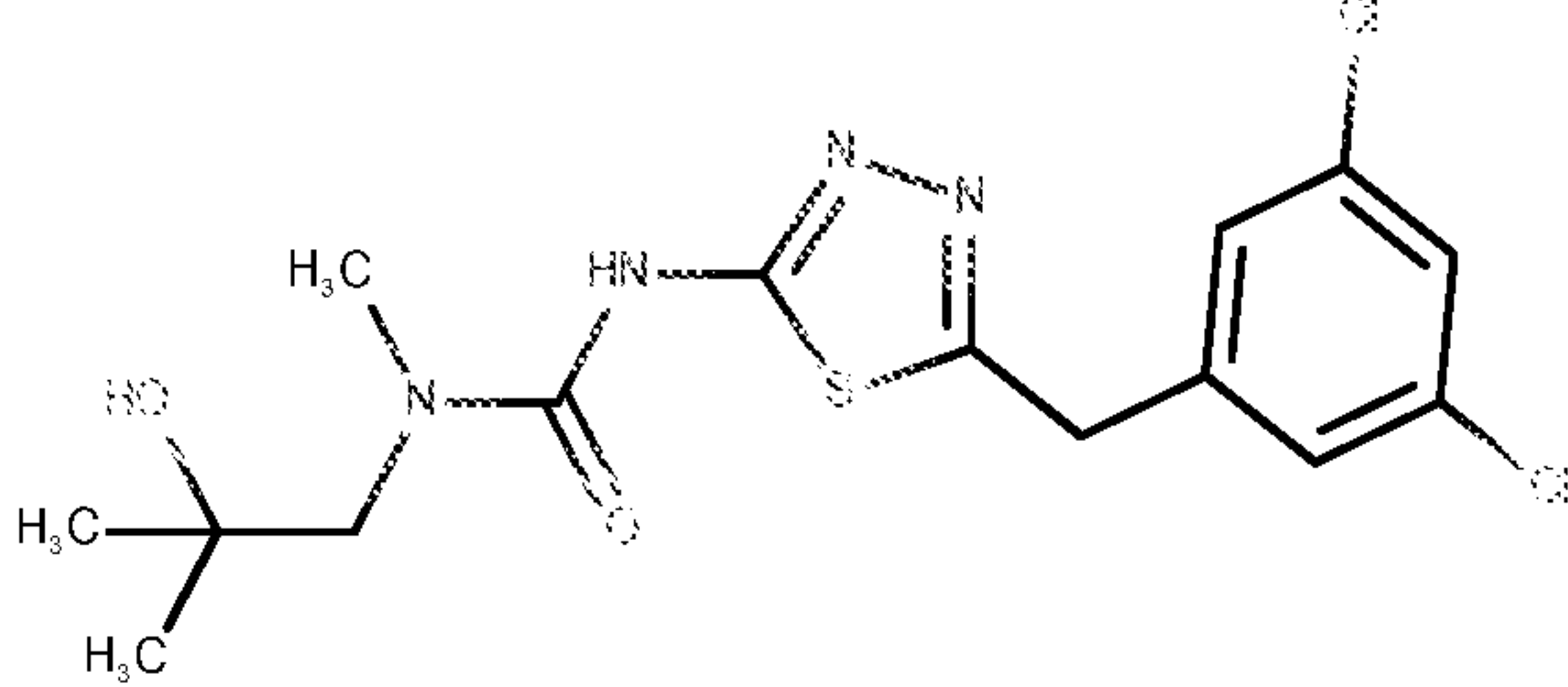
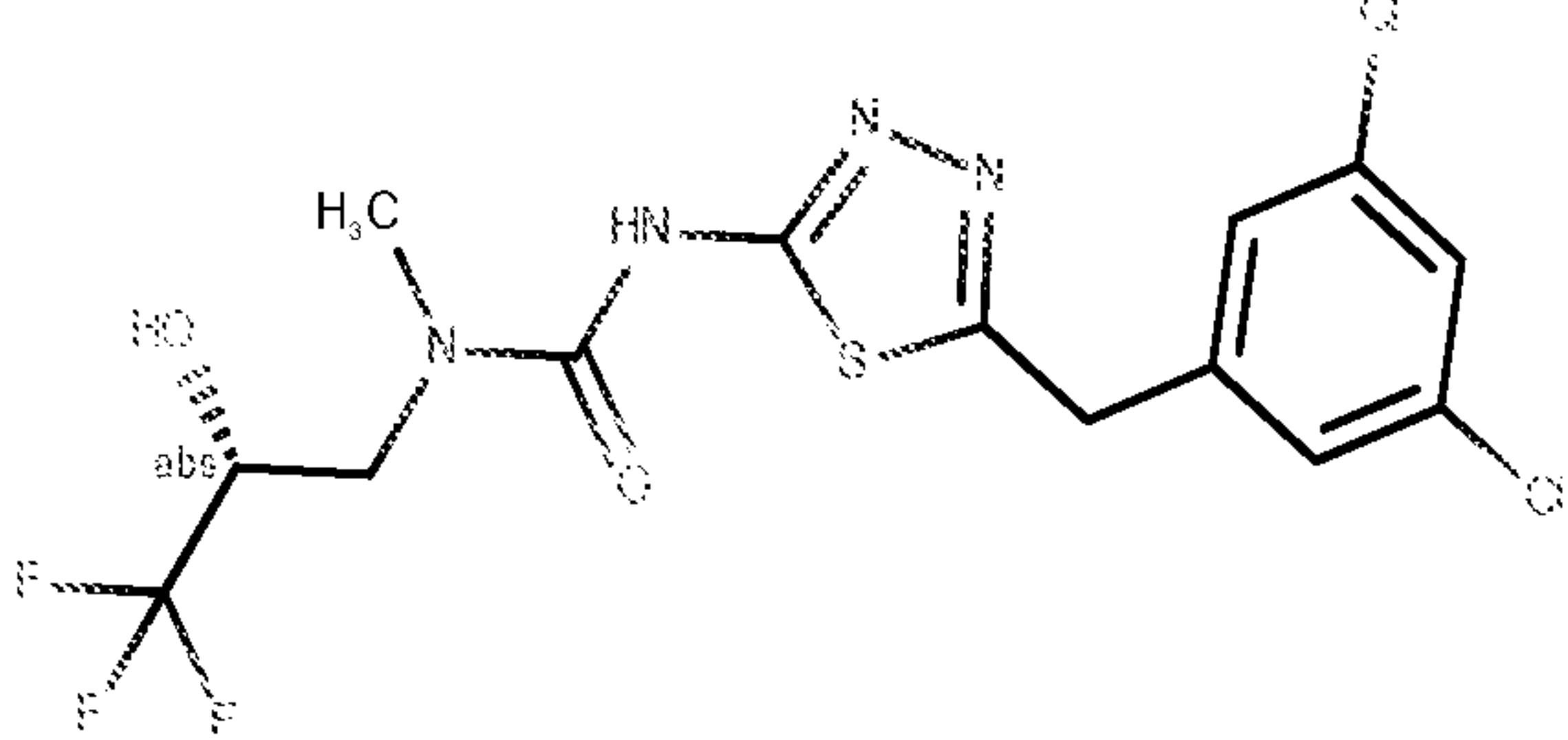
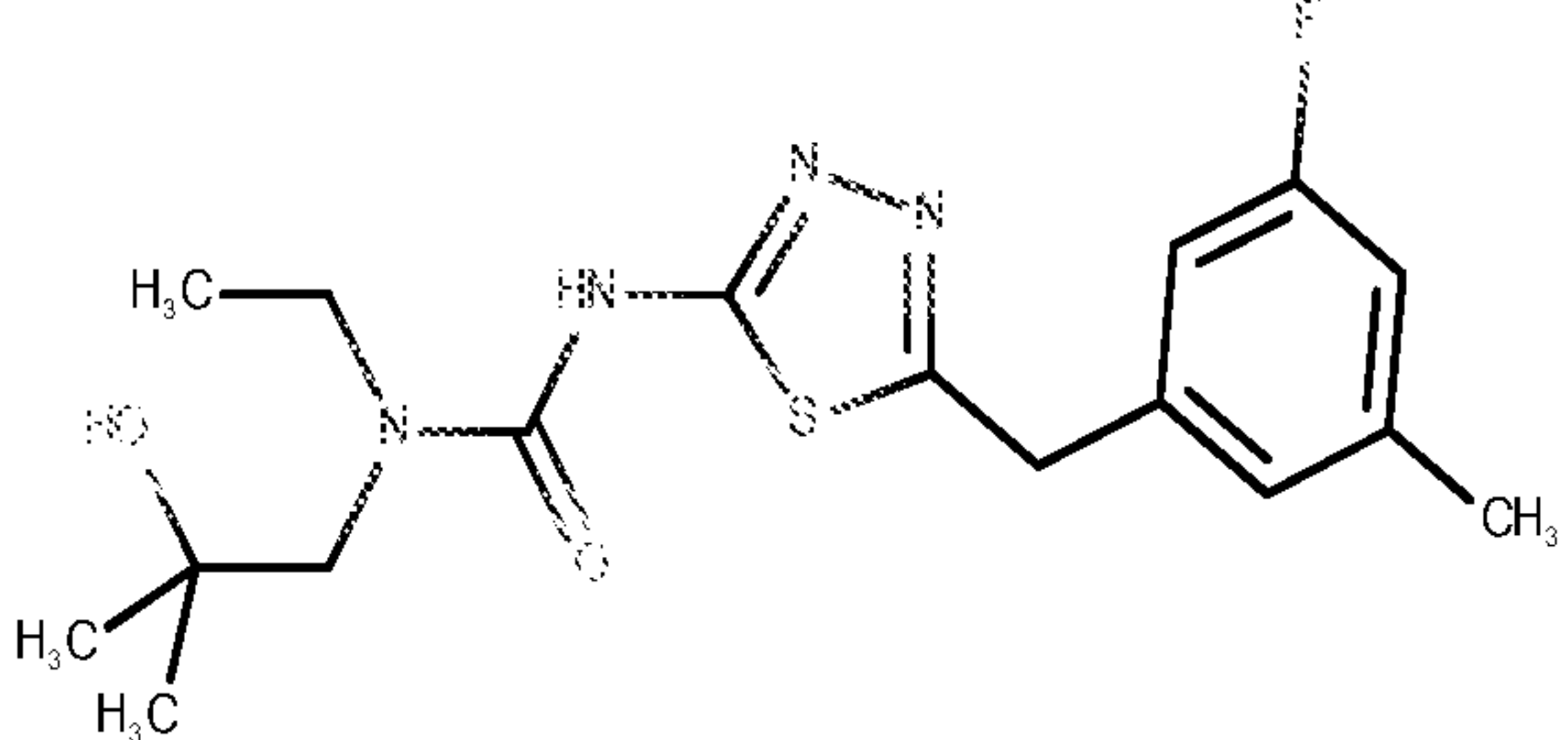
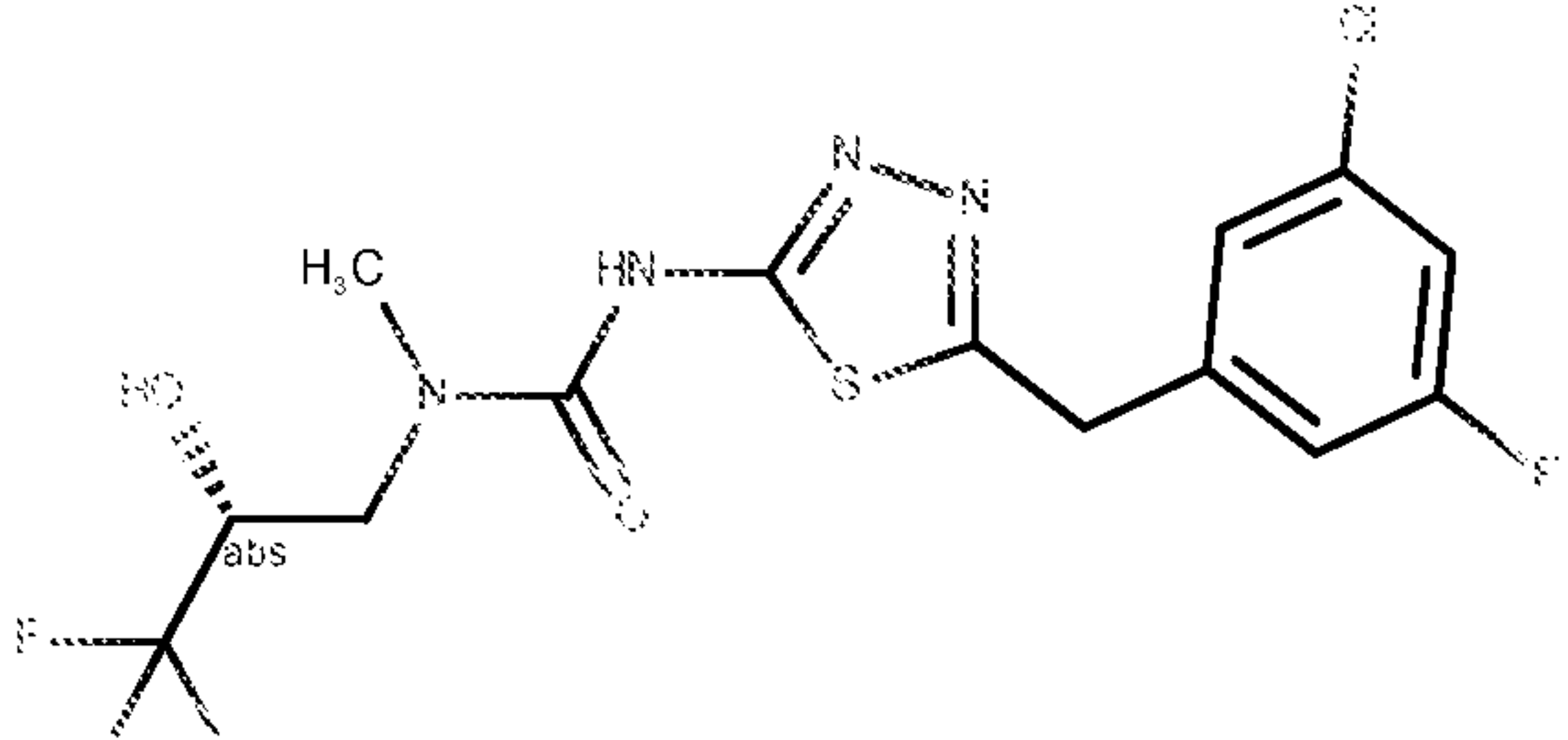
E14		5.6
E15		5.4
E16		5.7
E17		5.4
E18		6.0

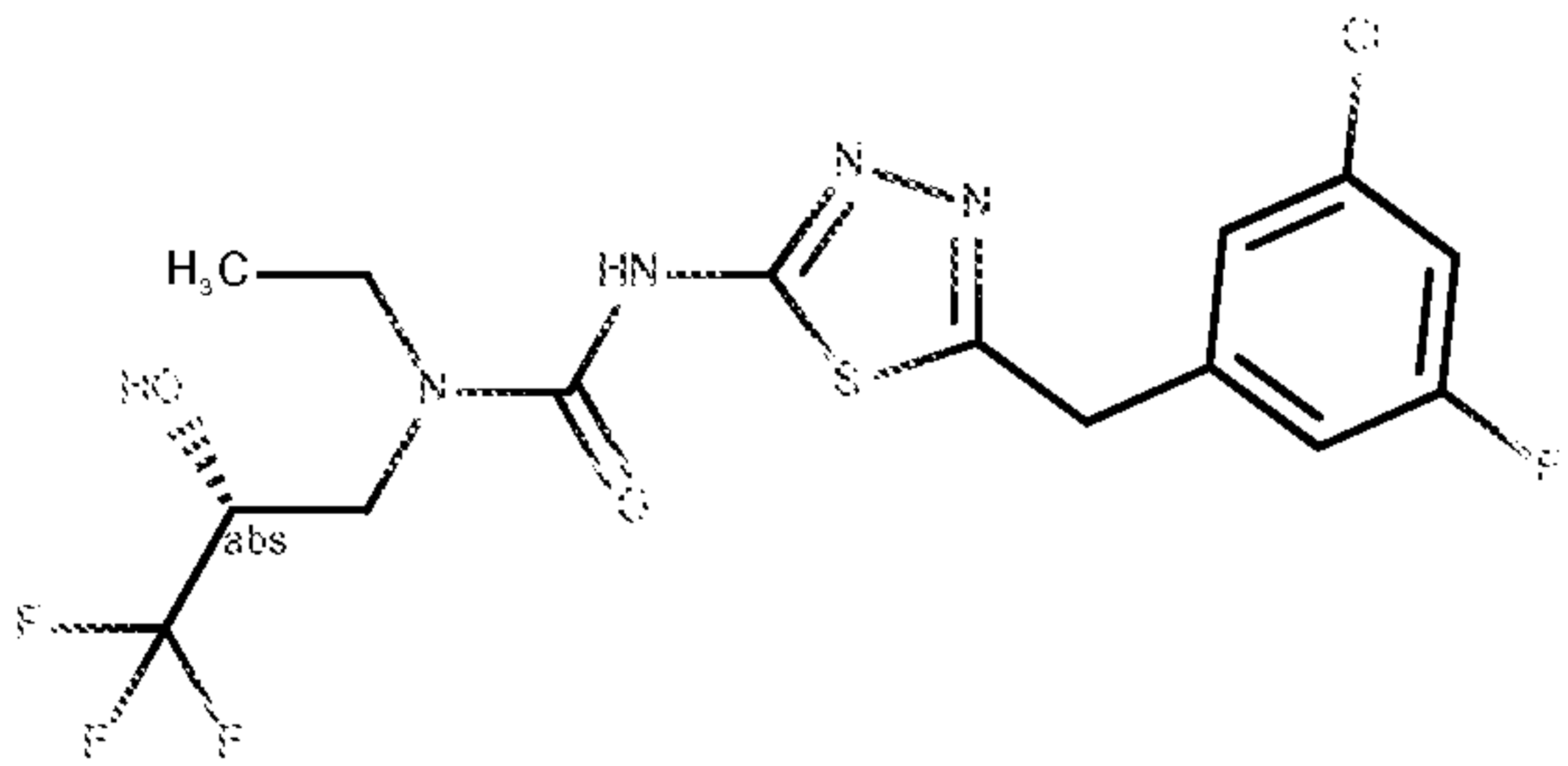
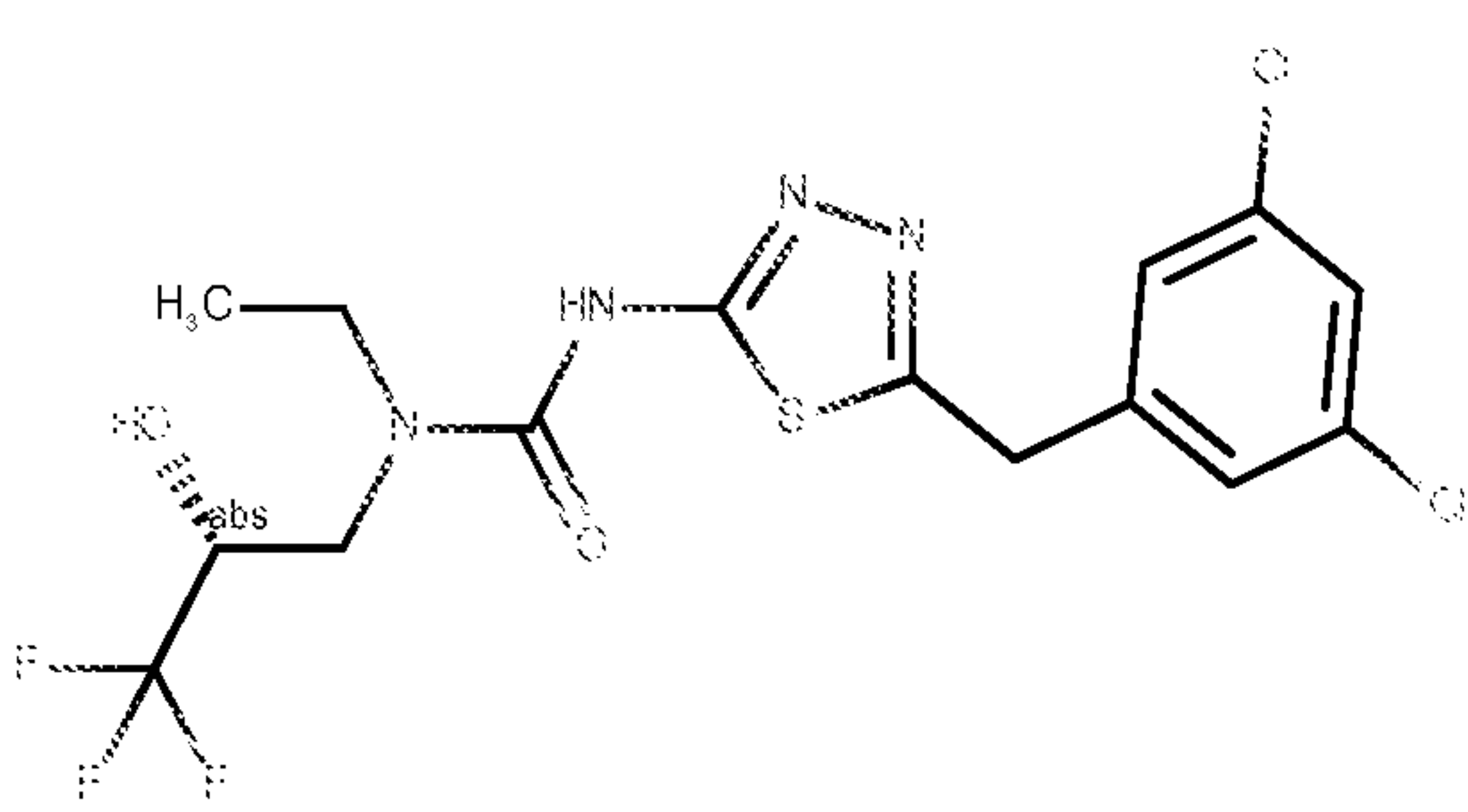
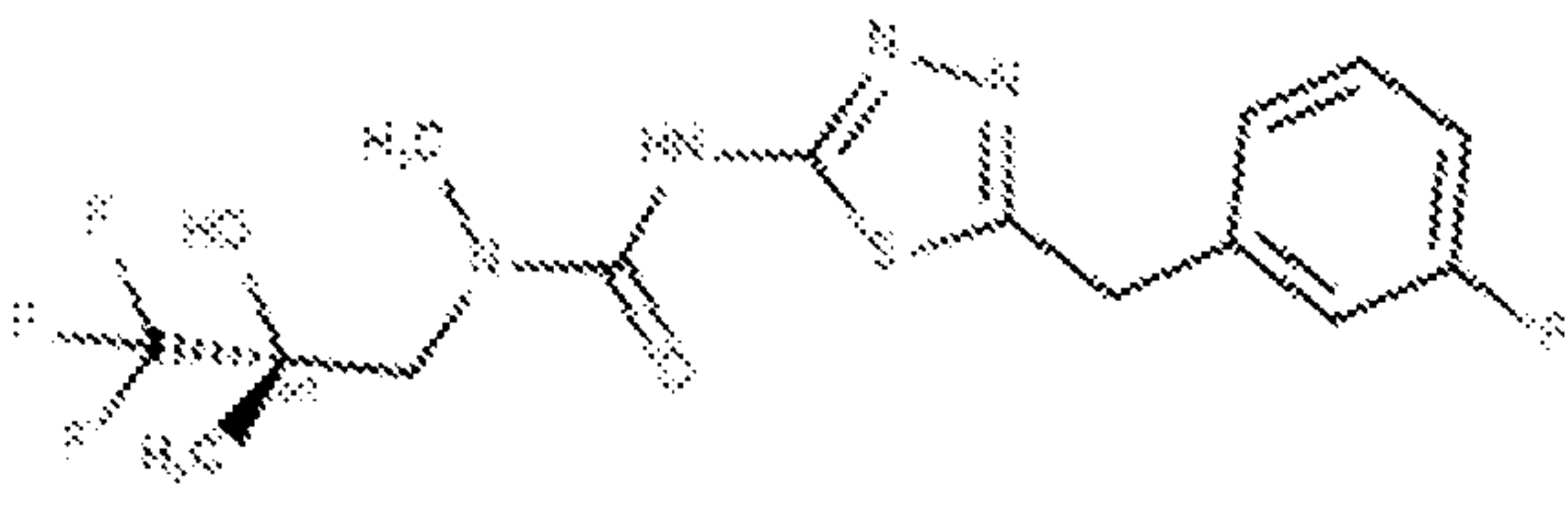
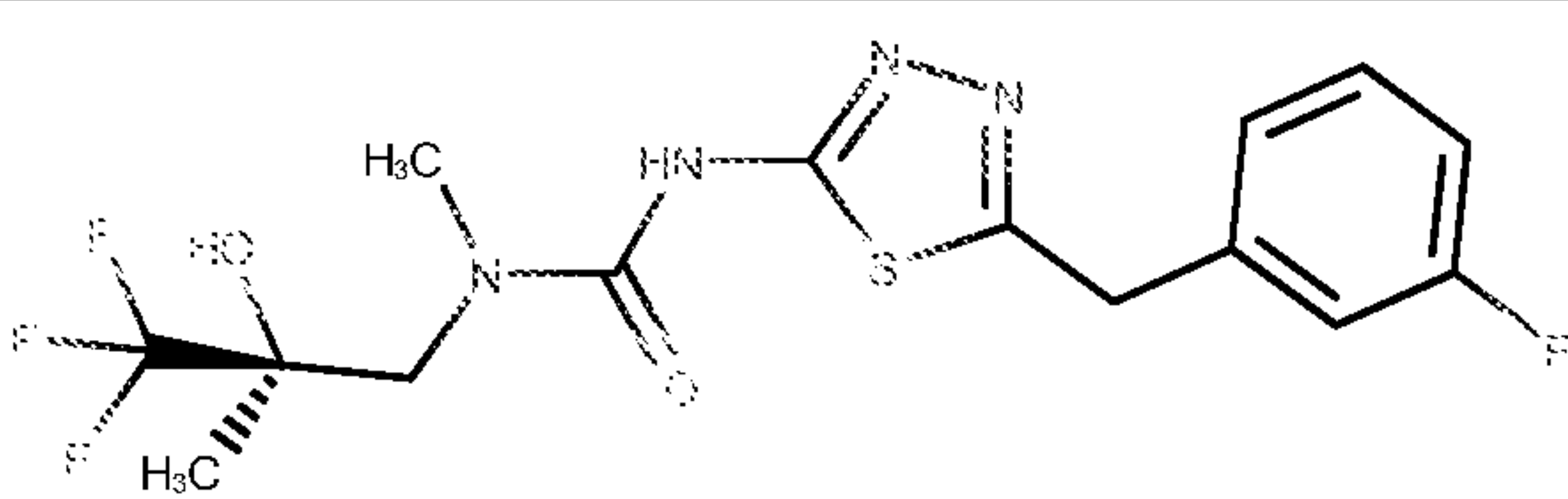
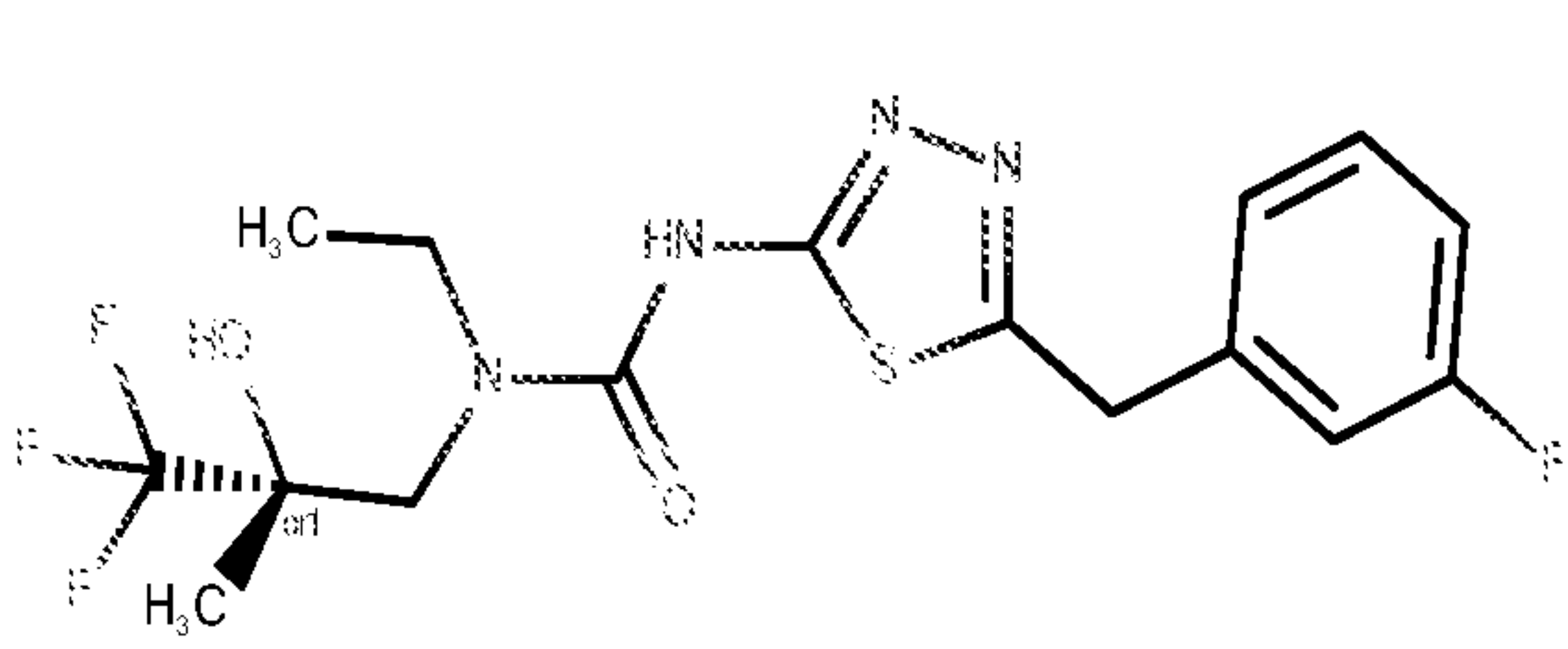
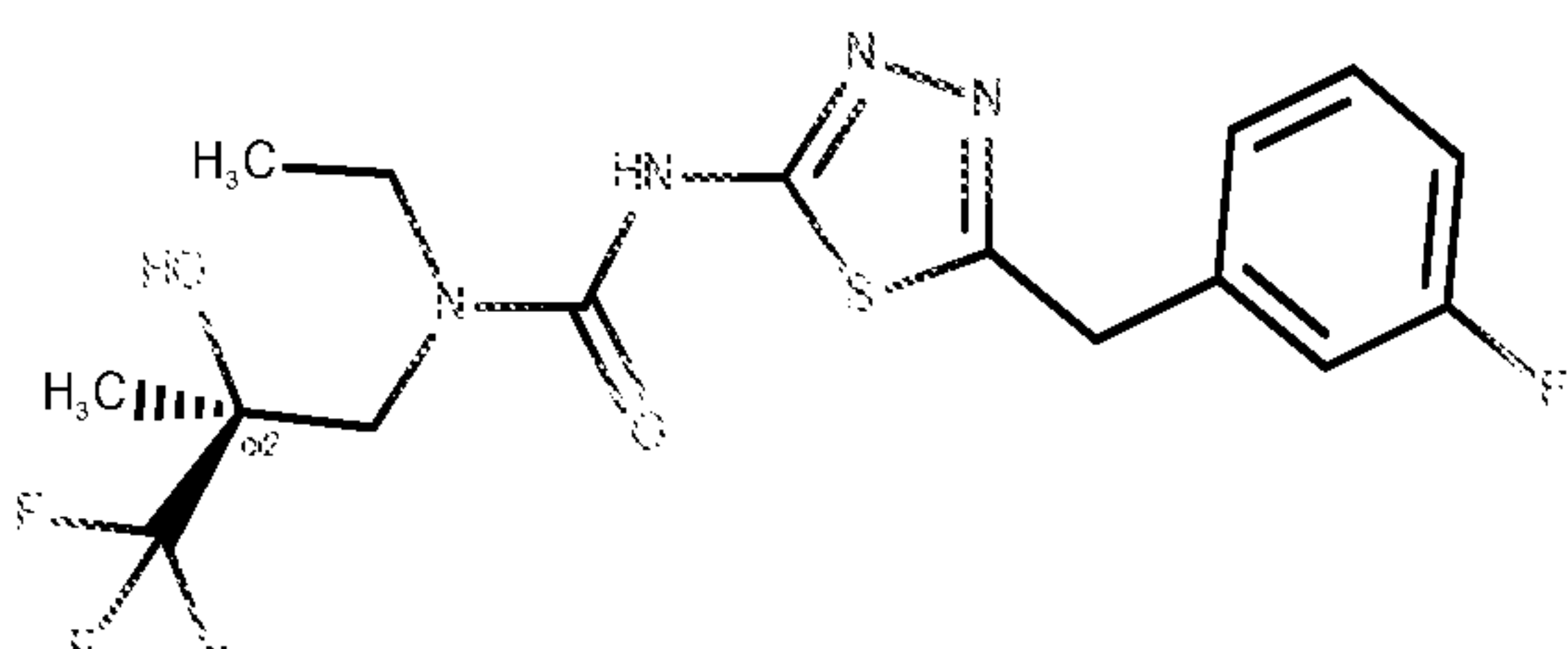
E19	 <chem>CC(C(C(F)(F)F)CC)N(C)C(=O)Nc1nc(Cc2cc(F)c(F)cc2)s1</chem>	7.1
E20	 <chem>CC(C(C)C)N(C)C(=O)Nc1nc(Cc2cc(F)c(F)cc2)s1</chem>	6.7
E21	 <chem>CC(C(C)C)N(C)C(=O)Nc1nc(Cc2ccc(C)cc2)s1</chem>	5.1
E22	 <chem>CC(C(C)C)N(C)C(=O)Nc1nc(Cc2cc(C)c(F)cc2)s1</chem>	6.1
E23	 <chem>CC(C(C(C(F)(F)F)CC)CC)N(C)C(=O)Nc1nc(Cc2cc(F)c(F)cc2)s1</chem>	8.1

E24		7.0
E25		5.1
E26		5.9
E27		5.2
E28		5.3
E29		6.2

E30		7.1
E31		5.9
E32		6.8
E33		7.8
E34		5.4
E35		6.1

E36		6.7
E37		6.8
E38		7.4
E39		6.14
E40		6.5
E41		7.78

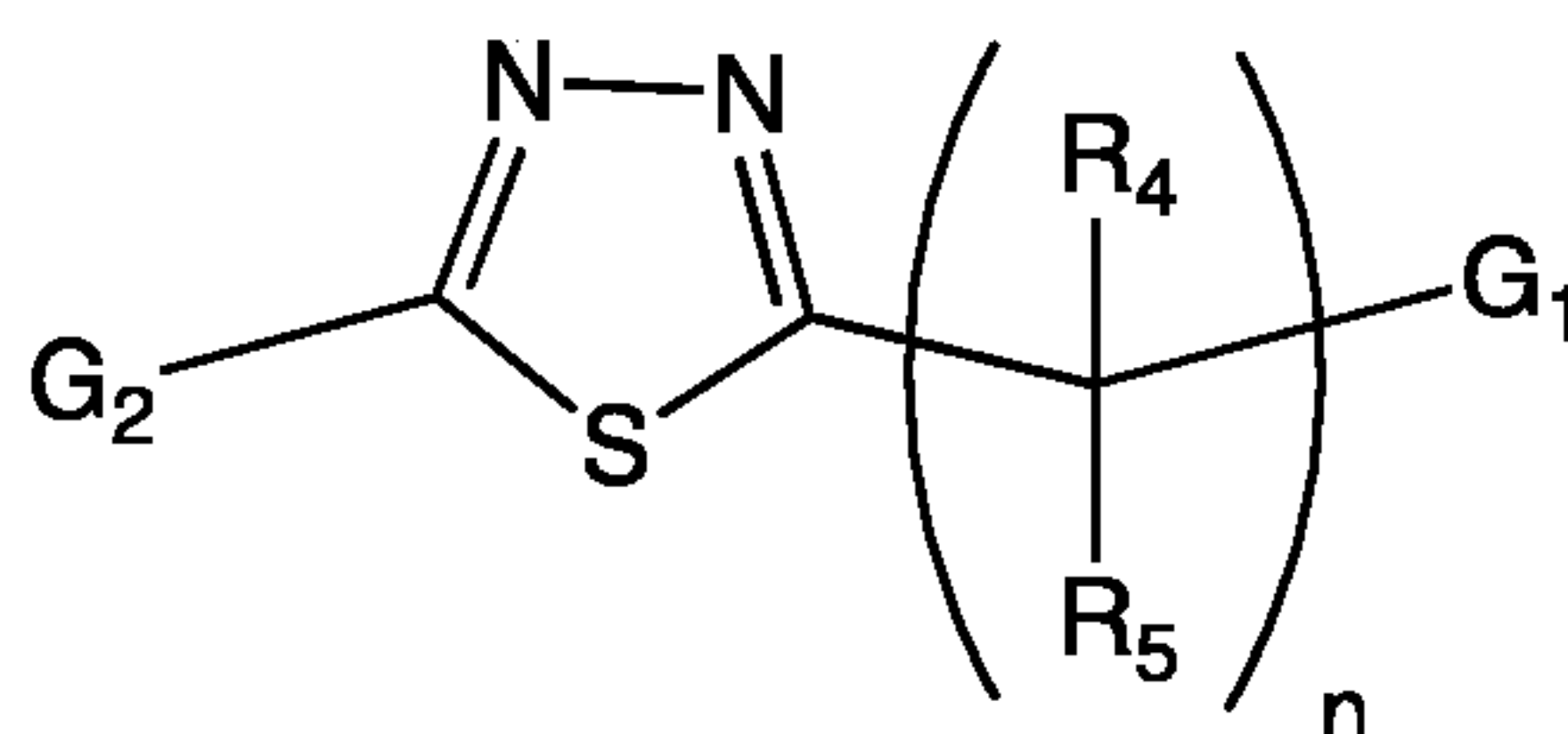
E42		7.32
E43		7.16
E44		6.79
E45		6.54
E46		6.43
E47		6.87

E48		7.85
E49		7.42
E50		6.53
E51		5.0
E52		7.3
E53		5.47

E54		6.9
E55		8.0
E56		7.79
E57		7.07
E58		5.5
E59		5.6

WHAT IS CLAIMED IS:

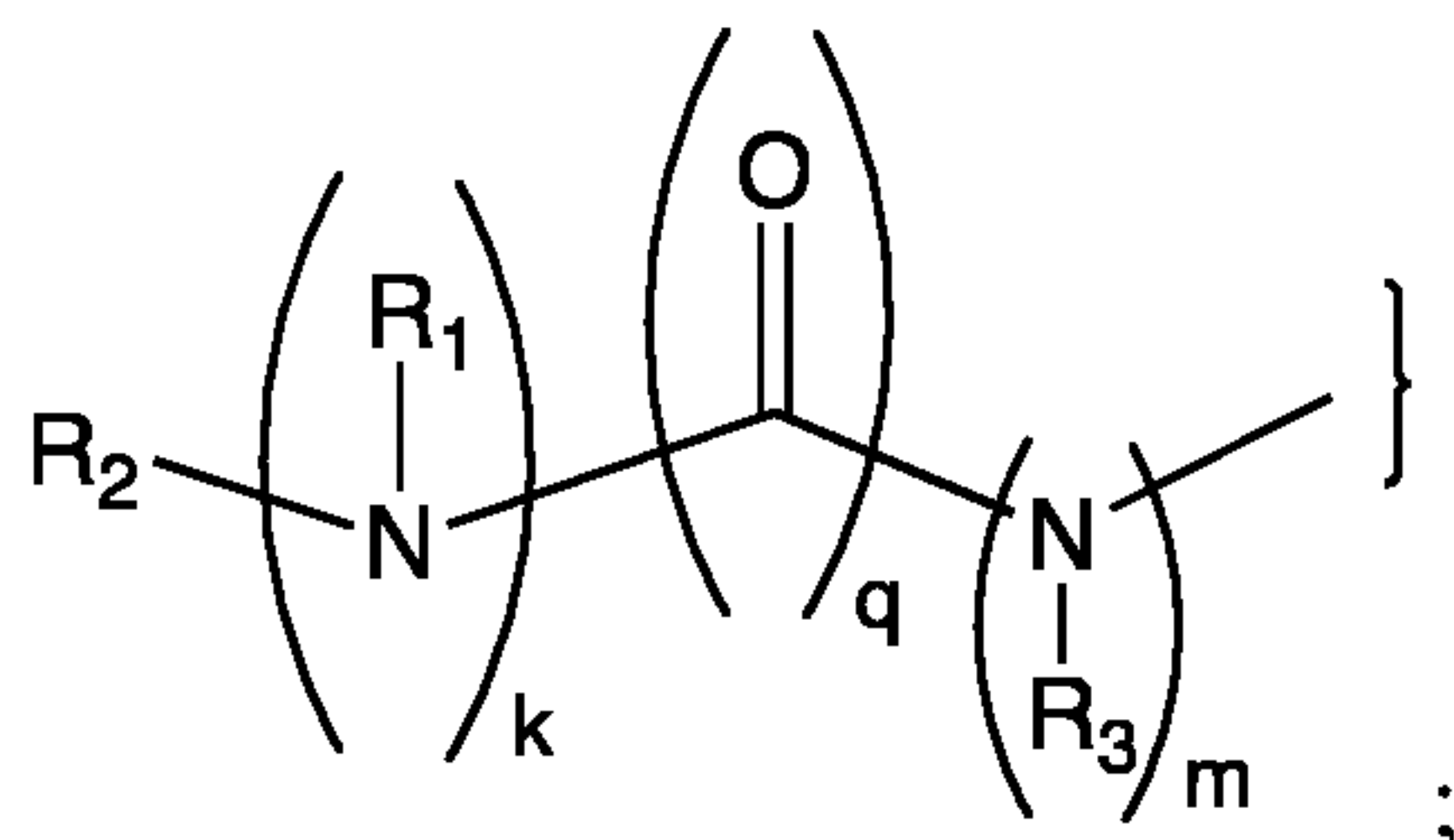
1. A compound having the Formula I:



Formula I

wherein:

G₂ is



q is 0 or 1;

m is 0 or 1;

n is 0, 1 or 2;

k is 0 or 1;

provided that k, q and m are not all 0;

provided that q is not 0 when m and k are each 1;

R₁ and R₂ are each independently H, C₁₋₆ alkyl; C₃₋₆ cycloalkyl; 5-10 member heterocycloalkyl having 1-3 ring heteroatoms independently selected from N, O and S; wherein each C₁₋₆ alkyl, C₃₋₆ cycloalkyl and 5-10 member heterocycloalkyl is optionally substituted with 1 to 3 R₂₀ groups;

provided that R₁ and R₂ are not simultaneously H;

each R₂₀ is independently selected from 1) hydroxy, 2) cyano, 3) C₁₋₃ alkyl, 4) C₁₋₃ alkoxy, 5) C₁₋₃ haloalkyl, 6) halogen, 7) C₁₋₃ alkyl, 8) C₃₋₆ cycloalkyl optionally substituted with 1-3 substituents selected from hydroxy, cyano, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and halogen, and 9) 5-10 member heterocycloalkyl having 1-3 ring heteroatoms independently selected from N, O and S optionally substituted with 1-3 substituents selected from hydroxy, cyano, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl and halogen;

or R₁ and R₂ together with the nitrogen atom to which they are attached can form a 5 or 6 member saturated, partially unsaturated or aromatic heterocycle having 1-3 ring heteroatoms independently selected from N, O and S, which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C₁₋₃ alkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, cyano and halogen;

R₃ is H or C₁₋₃ alkyl;

each R₄ and R₅ is independently H or C₁₋₃ alkyl;

G₁ is C₆₋₁₀ aryl; C₃₋₇ cycloalkyl; C₁₋₃ haloalkyl; C₁₋₃ alkyl and 5-10 member heteroaryl having 1-3 ring heteroatoms independently selected from N, O and S; wherein each of the C₆₋₁₀ aryl, C₃₋₇ cycloalkyl, C₁₋₃ haloalkyl and 5-10 member heteroaryl is optionally substituted with 1, 2 or 3 independently selected R₃₀ groups;

each R₃₀ is independently selected from halogen, cyano, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy optionally substituted with halogen, and hydroxy;

or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein G₁ is optionally substituted C₆₋₁₀ aryl.
3. The compound of claim 1, wherein G₁ is optionally substituted phenyl.
4. The compound of claim 1, wherein G₁ is optionally substituted pyridyl.
5. The compound of claim 1, wherein G₁ is optionally substituted C₃₋₆ cycloalkyl.
6. The compound of claim 1, wherein G₁ is optionally substituted cyclopropyl or cyclohexyl.
7. The compound of claim 1, wherein G₁ is phenyl optionally having one or two substituents.

8. The compound of claim 1, wherein G_1 is phenyl optionally having one or two substituents.
9. The compound of claim 1, wherein G_1 is phenyl substituted in the 3-position.
10. The compound of claim 1, wherein G_1 is phenyl substituted in the 3-position and the 5-position.
11. The compound of claim 1, wherein G_1 is phenyl substituted in the 2-position and the 5-position.
12. The compound of claim 1, wherein G_1 is phenyl substituted in the 2-position and the 4-position;
13. The compound of claim 1, wherein G_1 is phenyl substituted in the 2-position and the 3-position;
14. The compound of claim 1, wherein G_1 is phenyl substituted in the 3-position and the 4-position;
15. The compound of any of the preceding compounds, wherein each R_{30} is independently selected from mono-, di- or trihalomethyl, fluorine, chlorine, methoxy, cyano and methyl;
16. The compound of any of the preceding compounds, wherein each R_{30} is independently selected from difluoromethyl, trifluoromethyl, fluorine, chlorine, methoxy, cyano and methyl;
17. The compound of any of the preceding claims, wherein each R_{30} is independently selected from fluorine and chlorine;
18. The compound of any of the preceding compounds, wherein each R_{30} is fluorine;
19. The compound of claim 1, wherein G_1 is C_{1-3} haloalkyl;
20. The compound of claim 1, wherein G_1 is trifluoromethyl;
21. Any of the preceding compounds, wherein n is 1;
22. The compound of any of the preceding claims, wherein n is 2;
23. The compound of any of the preceding claims, wherein m , k and q are each 1;
24. The compound of any of the preceding claims, wherein q and m are each 1, and k is 0;
25. The compound of any of the preceding claims, wherein m is 0; and k and q are each 1;
26. The compound of any of the preceding claims, wherein k is 0; and m and q are each 1;
27. The compound of any of the preceding claims, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups;

28. The compound of any of the preceding claims, wherein R_1 and R_2 are each independently C_{1-3} alkyl optionally substituted with 1 to 3 R_{20} groups independently selected from hydroxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, methoxy, halogen and cyano;
29. The compound of any of the preceding claims compounds, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, cyano and halogen;
30. The compound of any of the preceding claims, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, cyano and halogen;
31. The compound of any of the preceding claims, wherein R_1 is H or C_{1-3} alkyl, and R_2 is a C_{1-3} alkyl substituted with a ring selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine, tetrahydropyran, and C_{3-6} cycloalkyl, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, methyl, hydroxymethyl, hydroxyethyl, methoxy, di- or trihalomethyl for example difluoromethyl or trifluoromethyl, cyano and halogen;
32. The compound of any of the preceding claims, wherein R_1 and R_2 together with the nitrogen atom to which they are attached form a heterocycle selected from pyrrolidine, tetrahydrofuran, morpholine, piperidine and tetrahydropyran, each of which is optionally substituted with 1, 2 or 3 groups selected from hydroxy, C_{1-3} alkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, cyano and halogen;
33. The compound of any of the preceding claims, wherein the compound selected from the Compounds in Table 1 herein, or a stereoisomer, solvates, tautomers, or pharmaceutically acceptable salts thereof.
34. A method for treating an inflammatory disorder, the method comprising administering to a subject in need thereof a topical or oral composition comprising a therapeutically

- effective amount of compound of claim 1, and a dermatologically or orally acceptable excipient.
35. The method of claim 34, wherein the composition is in the form of a cream, a gel, a spray or an ointment, or is a dosage form for oral administration, for example a tablet or capsule.
 36. The method of claim 34, wherein the MrgprX2 antagonist is present at a concentration of about 0.001 wt.% to about 10 wt.%, based on the total weight of the composition.
 37. The method of claim 34, wherein the MrgprX2 antagonist is present at a concentration of about 0.1 wt.% to about 5 wt.%, based on the total weight of the composition.
 38. The method of claim 34, wherein the composition further comprises a skin absorption enhancer.
 39. The method of claim 34, wherein the composition further comprises a skin absorption enhancer comprising one or more of mannitol, sulphoxides (e.g., dimethylsulphoxide, DMSO), Azones (e.g. laurocapram), pyrrolidones (e.g., 2-pyrrolidone, 2P), alcohols and alkanols (e.g., ethanol, or decanol), glycols (e.g., propylene glycol, hexylene glycol, polyoxyethylene glycol, diethylene glycol), surfactants (also common in dosage forms) and terpenes.
 40. The method of any of claims 34-39, wherein the composition is applied to a patient's skin once daily.
 41. The method of any of claims 34-39, wherein the composition is applied to a patient's skin twice daily.
 42. The method of any of claims 34-39, wherein the composition is applied to a patient's skin three times daily.
 43. The method of any of claims 34-42, wherein the composition is administered to a patient suffering from an inflammatory disorder.
 44. The method of any of claims 34-43, wherein the inflammatory disorder is a disorder of the skin.
 45. The method of any of claims 34-44, wherein the skin is human skin.
 46. The method of any of claims 43-45 wherein the inflammatory disorder activates or is consequent to activation, of MrgprX2.

47. The method of any of claims 43-46, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis), chronic urticaria, pseudo-allergic reactions triggered by small molecules for example anaphylactoid drug reactions, anaphylactic shock, rosacea, asthma, systemic itch such as cholestatic or uremic itch, chronic itch triggered by systemic diseases, or drug-adverse reactions.
48. The method of any of claims 43-47, wherein the inflammatory disorder is atopic dermatitis (e.g., Asian atopic dermatitis, European atopic dermatitis).
49. The method of any of claims 43-48, wherein the subject is a human.
50. The method of any of claims 43-48 wherein the mammalian skin is human skin.

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D285/12 A61K31/433 C07D285/135 C07D417/12
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/089415 A2 (NOVO NORDISK AS [DK]; KAMPEN GITA CAMILLA TEJLGAARD [DK] ET AL.) 21 October 2004 (2004-10-21) Claim 8, page 218, lines 3 and 21; page 59, lines 16,34; claims 1,4-46 -----	1-3,7-9, 14-17, 21,27, 28,34, 35,43-50
X	US 2009/163545 A1 (GOLDFARB DAVID SCOTT [US]) 25 June 2009 (2009-06-25) Compounds with RN: 303096-15-3, 342590-74-3, 600149-89-1, 331618-96-3, 310458-29-8, 600141-20-6; paragraphs [0042], [0049], [0050]; claim 1; table 1 -/-	1-3,7-9, 14-16, 21,28, 34,35, 43-50



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

15 February 2021

Date of mailing of the international search report

16/04/2021

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Rufet, Jacques

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2009, GOLDFARB, DAVID SCOTT: "Method using lifespan-altering compounds for altering the lifespan of eukaryotic organisms, and screening for such compounds", XP055775928, retrieved from STN Database accession no. 2009:846112 abstract & GOLDFARB, DAVID SCOTT: "Method using lifespan-altering compounds for altering the lifespan of eukaryotic organisms, and screening for such compounds", U.S. PAT. APPL. PUBL., 57PP. CODEN: USXXCO, 2009, -----	1-3,7-9, 14-16, 21,28, 34,35, 43-50
X	----- US 4 158 659 A (ROSS WILLIAM J ET AL) 19 June 1979 (1979-06-19) column 2, line 48 - column 4, line 5; examples 8-19,22,35,36 -----	1,34-43, 47,49,50
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KHODAKOVSKIY PAVEL ET AL: "Noncatalytic Electrophilic Alkylation of 1H-Indole with 2-Trifluoroacetyl-1,3-heterazoles", SYNTHESIS, vol. 2010, no. 06, 4 January 2010 (2010-01-04), pages 967-970, XP055775321, STUTTGART, DE. ISSN: 0039-7881, DOI: 10.1055/s-0029-1219219 Retrieved from the Internet: URL:https://www.thieme-connect.com/product s/ejournals/pdf/10.1055/s-0029-1219219.pdf > compound 6	1-3,28
X	----- WO 2018/160878 A1 (ASSEMBLY BIOSCIENCES INC [US]) 7 September 2018 (2018-09-07) page 221; compound 65 -----	1-3,28

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.

☐

Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2.

☐

Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.

☐

Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.

☐

As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.

☐

As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.

☐

As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.

☒

No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

25(completely); 1-22, 27-50(partially)

Remark on Protest

- ☐

The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 25(completely); 1-22, 27-50(partially)

A compound of formula (I) wherein G2 is attached to the thiadiazolyl ring via a -C(0)- group; i.e. $m = 0$ and $Q = 1$

2. claims: 23, 24, 26(completely); 1-22, 27-50(partially)

A compound of formula (I) wherein G2 is attached to the thiadiazolyl ring via a nitrogen atom; i.e. $m = 1$

INTERNATIONAL SEARCH REPORT

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International application No

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