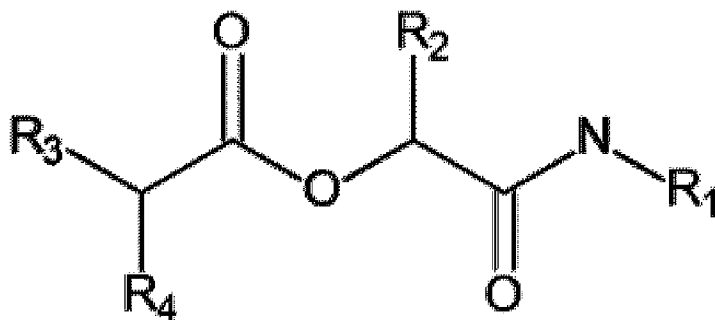




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(54) Titre : INHIBITEURS DE LA KALLICREINE 7
(54) Title: KALLIKREIN 7 INHIBITORS



Formula I

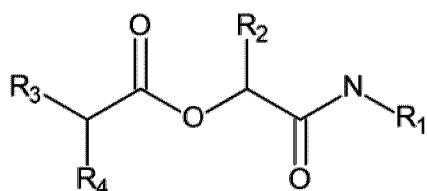
(57) **Abrégé/Abstract:**

The present invention relates to methods for inhibiting the activity of human kallikrein 7 (KLK7) (also known as serine protease stratum corneum chymotryptic enzyme, SCCE). The invention further relates to the use of KLK7 inhibitors of Formula I (see formula I) for the treatment and prevention of diseases, more specifically for the treatment and prevention of skin diseases. The invention also provides new compounds demonstrated to be inhibitors of KLK7.



ABSTRACT

The present invention relates to methods for inhibiting the activity of human kallikrein 7 (KLK7) (also known as serine protease stratum corneum chymotryptic enzyme, SCCE). The invention further relates to the use of KLK7 inhibitors of Formula I



Formula I

for the treatment and prevention of diseases, more specifically for the treatment and prevention of skin diseases. The invention also provides new compounds demonstrated to be inhibitors of KLK7.

KALLIKREIN 7 INHIBITORS

FIELD OF THE INVENTION

The present invention relates to methods for inhibiting the activity of human kallikrein 7 (KLK7) (also known as serine protease stratum corneum chymotryptic enzyme, SCCE). The invention further relates to the use of KLK7 inhibitors of Formula I for the treatment and prevention of diseases, more specifically for the treatment and prevention of skin diseases. The invention also provides new compounds demonstrated to be inhibitors of KLK7.

BACKGROUND

KLK7 (hK7, or stratum corneum chymotryptic enzyme (SCCE), Swissprot P49862) is a S1 serine protease of the kallikrein gene family displaying a chymotrypsin like activity. KLK 7 is mainly expressed in the skin and appears to play an important role in skin physiology (Egelrud. 1993. *Purification and preliminary characterization of stratum corneum chymotryptic enzyme: a proteinase that may be involved in desquamation*. J. Invest. Dermatol. 101, 200-204; Skytt *et al.* 1995. *Primary substrate specificity of recombinant human stratum corneum chymotryptic enzyme*. Biochem Biophys Res Commun 211, 586-589; Yousef *et al.* 2000. *The KLK7 (PRSS6) gene, encoding for the stratum corneum chymotryptic enzyme is a new member of the human kallikrein gene family - genomic characterization, mapping, tissue expression and hormonal regulation*. Gene 254, 119-1281).

KLK7 is involved in the degradation of the intercellular cohesive structure in cornified squamous epithelia in the process of desquamation. The desquamation process is well regulated and delicately balanced with the *de novo* production of corneocytes to maintain a constant thickness of the stratum corneum. In this regard, KLK7 is reported to be able to cleave the corneodesmosomal proteins corneodesmosin and desmocollin 1 (Simon *et al.* 2001. *Refined characterization of corneodesmosin proteolysis during terminal differentiation of human epidermis and its relationship to desquamation*. J. Biol. Chem. 276, 20292-20299; Caubet *et al.* 2004. *Degradation of corneodesmosome proteins by two serine proteases of the kallikrein family, SCTE/KLK5/hK5 and SCCE/KLK7/hK7*. J. Invest. Dermatol. 122, 1235-1244; Brattsand *et al.* 2005. *A proteolytic cascade of kallikreins in the stratum corneum*. J. Invest. Dermatol. 124, 198-203. In addition, it has been shown that the two lipid processing enzymes β -glucocerebrosidase and acidic sphingomyelinase can be degraded by KLK7

(Hachem *et al.* 2005. *Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity.* J. Invest. Dermatol. 125, 510-520). Both lipid processing enzymes are co-secreted with their substrates glucosylceramides and sphingomyelin and process these polar lipid precursors into their more non-polar products e.g. ceramides, which are subsequently incorporated into the extracellular lamellar membranes. The lamellar membrane architecture is critical for a functional skin barrier. Finally, KLK7 has been shown to activate the pro-inflammatory cytokine Pro-interleukin-1 β (IL-1 β) (Nylander-Lundqvist & Egelrud. 1997. *Formation of active IL-1 β from pro-IL-1 β catalyzed by stratum corneum chymotryptic enzyme in vitro.* Acta Derm. Venereol. 77, 203-206).

Several studies link an increased activity of KLK7 to inflammatory skin diseases like atopic dermatitis, psoriasis or Netherton syndrome. An increased KLK7 activity might lead to an uncontrolled degradation of corneodesmosomes resulting in a miss-regulated desquamation, an enhanced degradation of lipid processing enzymes resulting in a disturbed lamellar membrane architecture or an uncontrolled (in)activation of the pro-inflammatory cytokine IL-1 β . It have previously been demonstrated that this could lead to an impaired skin barrier function and inflammation (WO 2004/108139).

The KLK7 activity is controlled on several levels. Various factors might be responsible for an increased KLK7 activity in inflammatory skin diseases. Firstly, the amount of protease being expressed might be influenced by genetic factors. Such a genetic link, a polymorphism in the 3'-UTR in the KLK7 gene, has been described (Vasilopoulos *et al.* 2004. *Genetic association between an AACC insertion in the 3'UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis.* J. Invest. Dermatol. 123, 62-66.). The authors hypothesis that the described 4 base pair insertion in the 3'-UTR of the kallikrein 7 gene stabilizes the KLK7 mRNA and results in an overexpression of KLK7. Secondly, since KLK7 is secreted via lamellar bodies to the stratum corneum extracellular space as zymogen and it is not able to autoactivate, it needs to be activated by another protease e.g. kallikrein 5 (Caubet *et al. supra*). Uncontrolled activity of such an activating enzyme might result in an over-activation of KLK7. Thirdly, activated KLK7 can be inhibited by natural inhibitors like LEKTI, ALP or elafin (Schechter *et al.* 2005. *Inhibition of human kallikreins 5 and 7 by the serine protease inhibitor lympho-epithelial Kazal-type inhibitor (LEKTI).* Biol. Chem. 386, 1173-1184;

Franzke *et al.* 1996. *Antileukoprotease inhibits stratum corneum chymotryptic enzyme - Evidence for a regulative function in desquamation.* J. Biol. Chem. 271, 21886-21890). The decreased expression or the lack of such inhibitors might result in an enhanced KLK7 activity.

It has been found that mutations in the *spink* gene, coding for LEKTI, are causative for Netherton syndrome (Descargues *et al.* 2005. *Spink5- deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity.* Nat. Genet. 37, 56-65) and a single point mutation in the gene is linked to atopic dermatitis (Walley *et al.* 2001. *Gene polymorphism in Netherton and common atopic disease.* Nat. Genet. 29, 175-178; Nishio *et al.* 2003. *Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese.* Genes Immun. 4, 515-517). Finally, another level of controlling the activity of KLK7 is the pH. KLK7 has a neutral to slightly alkaline pH optimum and there is a pH gradient from neutral to acidic from the innermost to the outermost layers in the skin. Environmental factors like soap might result in a pH increase in the outermost layers of the stratum corneum towards the pH optimum of KLK7 thereby increasing the KLK7 activity.

The hypothesis that an increased activity of KLK7 is linked to inflammatory skin diseases is supported by the following studies: Firstly, Netherton syndrome patients show a phenotype dependent increase in serine protease activity, a decrease in corneodesmosomes, a decrease in the lipid processing enzymes β -glucocerebrosidase and acidic sphingomyelinase, and an impaired barrier function (Descargues *et al.* 2006. *Corneodesmosomal cadherins are preferential targets of stratum corneum trypsin- and chymotrypsin-like hyperactivity in Netherton syndrome.* J. Invest. Dermatol. 126, 1622-1632; Hachem *et al.* 2006. *Serine protease activity and residual LEKTI expression determine phenotype in Netherton syndrome.* J. Invest. Dermatol. 126, 1609-1621.). Secondly, a transgenic mice overexpressing human kallikrein 7 shows a skin phenotype similar to that found in patients with atopic dermatitis (Hansson *et al.* 2002. *Epidermal Overexpression of Stratum Corneum Chymotryptic Enzyme in Mice: A Model for Chronic Itchy Dermatitis.* J. Invest. Dermatol. 118, 444-449; Ny & Egelrud. 2003. *Transgenic mice over-expressing a serine protease in the skin: evidence of interferon gamma-independent MHC II expression by epidermal keratinocytes.* Acta Derm. Venereol. 83, 322-327; Ny & Egelrud. 2004. *Epidermal hyperproliferation and decreased skin barrier function in mice overexpressing stratum corneum chymotryptic enzyme.* Acta Derm. Venereol. 84, 18-22). Thirdly, in the skin of atopic dermatitis and psoriasis patients

elevated levels of KLK7 were described (Ekholm & Egelrud. 1999. *Stratum corneum chymotryptic enzyme in psoriasis*. Arch. Dermatol. Res. 291, 195-200). Therefore, KLK7 is considered to be a target for the treatment of inflammatory skin diseases like atopic dermatitis, psoriasis or Netherton syndrome and there is a need for specific inhibitors thereof.

WO 2004/108139 describes certain substituted benzoxazinone and thienoxazinone compounds as inhibitors of KLK7.

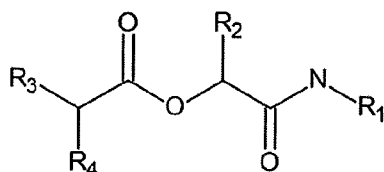
WO 2009/000878 describes substituted pyrrolidine-1,2-dicarboxamide compounds as inhibitors of KLK7.

WO 2009/024527 and WO 2009/024528 describe cyclic depsipeptides as inhibitors of KLK7.

DESCRIPTION OF THE INVENTION

The present inventors have now been found that the activity of KLK7 can be inhibited by compounds according to Formula I.

Accordingly, the present invention provides a compound according to Formula I



Formula I

wherein R₁ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
 R₂ is selected from hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl;
 R₃ is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -C₁-C₃-alkyl-R₅, wherein R₅ is selected from cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;
 R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and -NH-CO-R₆, wherein R₆ is selected from aryl, and substituted aryl, heteroaryl, and substituted heteroaryl;
 or a pharmaceutical acceptable salt thereof,

for use in medicine, more specifically for use in the prophylaxis, prevention and/or treatment of a skin disease.

Preferably, R₁ is selected from phenyl, substituted phenyl, isoxazolyl, substituted isoxazolyl and heteroaryl.

Preferably, R₂ is selected from hydrogen, -C₁-C₆-alkyl, C₁-C₃-alkyloxy-C₁-C₆-alkyl, and phenyl.

Preferably, R₃ is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, and -C₁-C₃-alkyl-R₅, wherein R₅ preferably is selected from cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl.

Preferably, R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and -NH-CO-R₆, wherein R₆ preferably is selected from aryl, and substituted aryl.

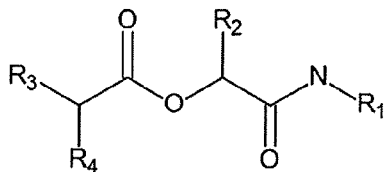
The stereochemical configuration around the carbon which is covalently bound to R₂ can be (S) or (R). Preferably, the stereochemical configuration around the carbon which is covalently bound to R₂ is (S).

The invention further relates to the use of a compound according to the Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a skin disease.

The skin disease may be an inflammatory skin disease. The skin disease can be selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.

The subject to be treated can be a mammal, such as a human, a dog, a cat, or a horse.

The present invention further provides a method for the prophylaxis, prevention and/or treatment of a skin disease which comprises the administration of a therapeutically active amount of a compound according to Formula I



Formula I

wherein R₁ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
 R₂ is selected from hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl;
 R₃ is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -C₁-C₃-alkyl-R₅, wherein R₅ is selected from cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;
 R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -NH-CO-R₆, wherein R₆ is selected from aryl, and substituted aryl, heteroaryl, and substituted heteroaryl;
 to a subject in need of such treatment.

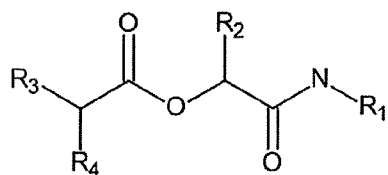
The skin disease may be an inflammatory skin disease. The skin disease can be selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.

The subject to be treated can be a mammal, such as a human, a dog, a cat, or a horse.

The present invention further provides a cosmetic or skin care composition comprising at least one compound with the Formula I, or a pharmaceutically acceptable salt thereof, said composition being in a form suitable for topical administration, and selected from the group consisting of a cream, an ointment, a lotion, a liniment, a gel, a paste, a stick, a spray, a shampoo, a soap, a hair conditioner and a powder.

The invention further provides the use of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, for treatment or prophylaxis of cosmetic skin conditions.

The present invention further provides compounds according to Formula I

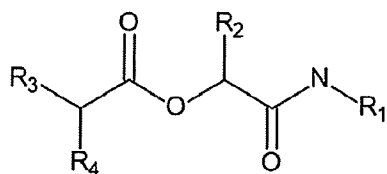


Formula I

wherein the compounds are selected from

- (1) [1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-chlorophenyl) acetate
- (3) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-chlorophenyl) acetate
- (7) [1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-methoxyphenyl) acetate
- (12) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-methoxyphenyl) acetate
- (14) [1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 3-cyclopentylpropanoate
- (15) [2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-methoxyphenyl)acetate
- (16) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 3-cyclopentylpropanoate
- (17) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-(4-chlorophenyl)acetate
- (20) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate
- (23) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate
- (26) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(1,3-benzodioxol-5-yl)acetate
- (36) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl) acetate
- (39) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(3,4-dichlorophenyl)acetate
- (41) 1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(3,4-dimethoxyphenyl)acetate
- (47) [1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2,2-diphenylacetate
- (49) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-benzamido-2-phenyl-acetate
- (52) [1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
- (54) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2,2-diphenylacetate
- (60) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
- (70) [2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-(4-chlorophenyl)acetate
- (72) [2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 3-cyclopentylpropanoate
- (75) [2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-benzamido-2-phenyl-acetate
- (79) [2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2,2-diphenylacetate
- (81) [2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-chlorophenyl)acetate
- (84) [2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-(4-methoxyphenyl)acetate

The present invention further provides compounds according to Formula I



Formula I

wherein the compounds are selected from

- (4) [2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-chlorophenyl)acetate
- (6) 1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate
- (8) 1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate
- (9) 1-(phenylcarbamoyl)propyl 2-(4-chlorophenyl)acetate
- (10) [2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 3-cyclopentylpropanoate
- (11) 1-[(4-methoxyphenyl)carbamoyl]propyl 3-cyclopentylpropanoate
- (13) [2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-chlorophenyl)acetate
- (19) [2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate
- (24) 1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate
- (25) 1-[(4-fluorophenyl)carbamoyl]propyl 3-cyclopentylpropanoate
- (30) 1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate
- (31) (2-anilino-1-methyl-2-oxo-ethyl) 3-cyclopentylpropanoate
- (32) (2-anilino-2-oxo-1-phenyl-ethyl) 2-(4-chlorophenyl)acetate
- (34) 1-(phenylcarbamoyl)propyl 2-(4-methoxyphenyl)acetate
- (35) [2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl)acetate
- (37) [2-(benzylamino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate
- (42) [2-(4-methoxyanilino)-2-oxo-ethyl] 2-(4-methoxyphenyl)acetate
- (43) 1-[(4-methoxyphenyl)carbamoyl]propyl 2,2-diphenylacetate
- (44) 1-[(4-fluorophenyl)carbamoyl]propyl 2,2-diphenylacetate
- (48) 1-(phenylcarbamoyl)propyl 2,2-diphenylacetate
- (59) [2-(4-methoxyanilino)-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
- (61) [2-(4-fluoroanilino)-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
- (62) (2-anilino-2-oxo-ethyl) 2-benzamido-2-phenyl-acetate
- (64) 1-[(4-methoxyphenyl)carbamoyl]propyl 2-benzamido-2-phenyl-acetate
- (65) 1-[(4-fluorophenyl)carbamoyl]propyl 2-benzamido-2-phenyl-acetate
- (66) (2-anilino-1-methyl-2-oxo-ethyl) 2-benzamido-2-phenyl-acetate
- (71) [2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate

- (76) (2-anilino-2-oxo-1-phenyl-ethyl) 2-benzamido-2-phenyl-acetate
- (78) [2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2,2-diphenylacetate
- (83) [2-(benzylamino)-1-methyl-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
- (91) [2-methyl-1-(phenylcarbamoyl)propyl] 2-(4-chlorophenyl)acetate
- (92) [1-[(4-methoxyphenyl)carbamoyl]-2-methyl-propyl] 2-(4-chlorophenyl)acetate
- (93) [2-methyl-1-(phenylcarbamoyl)propyl] 2-benzamido-2-phenyl-acetate
- (94) [2-methyl-1-(phenylcarbamoyl)propyl] 2-(4-methoxyphenyl)acetate
- (95) [1-[(4-methoxyphenyl)carbamoyl]-2-methyl-propyl] 2-benzamido-2-phenyl-acetate
- (96) [1-[(4-fluorophenyl)carbamoyl]-2-methyl-propyl] 2-benzamido-2-phenyl-acetate

The stereochemical configuration around the carbon which is covalently bound to R₂ of the compounds according to the invention can be (S) or (R). Preferably, the stereochemical configuration around the carbon which is covalently bound to R₂ of the compounds according to the invention is (S).

The invention further provides pharmaceutical compositions comprising a compound according to the invention in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The invention further provides a compound according to the invention for use in medicine.

The invention further provides a compound or a pharmaceutical composition according to the invention for use in prophylaxis, prevention and/or treatment of skin diseases. The skin disease can be an inflammatory skin disease. The inflammatory skin disease can be selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.

As will be understood, the compounds of Formula I described herein are effective KLK7 inhibitors. However, as some variation in the inhibition efficiency between the individual compounds of Formula I may be present, the inventors have provided suitable preliminary assays which can be used in order to assess the inhibition efficiency of the compounds of Formula I. For example, the "KLK7 Inhibitor Test" described in Example 1 herein is a simple test which may be performed to initially assess the potency of the compound. Accordingly, a

compound of Formula I which is preferred for the methods and uses disclosed herein, is a compound which, when assayed in the "KLK7 Inhibitor Test" described herein, has an IC_{50} value of less than 10 μM . More preferably, the compound has an IC_{50} value of less than 5 μM , even more preferably the compound has an IC_{50} value of less than 3 μM , still more preferably the compound has an IC_{50} value of less than 2 μM such as an IC_{50} value of less than 1 μM , most preferably the compound has an IC_{50} value of less than 0.5 μM , such as an IC_{50} value of less than 0.1 μM , when assayed in the "KLK7 Inhibitor Test" described herein.

LEGENDS TO FIGURES

Figure 1

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 4

Figure 2

1H -NMR spectra 400 MHz, DMSO- d_6) of compound 6

Figure 3

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 8

Figure 4

1H -NMR spectra (500 MHz, DMSO) of compound 9

Figure 5

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 10

Figure 6

1H -NMR spectra (400 MHz, DMSO- d_6 +CCl $_4$) of compound 11

Figure 7

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 13

Figure 8

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 14

Figure 9

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 15

Figure 10

1H -NMR spectra (400 MHz, DMSO- d_6) of compound 16

Figure 11

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 19

Figure 12

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 20

Figure 13

¹H-NMR spectra (400 MHz, DMSO-d₆+CCl₄) of compound 23

Figure 14

¹H-NMR spectra (500 MHz, DMSO) of compound 24

Figure 15

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 25

Figure 16

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 30

Figure 17

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 32

Figure 18

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 36

Figure 19

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 37

Figure 20

¹H-NMR spectra (400 MHz, DMSO-d₆) of compound 48

Figure 21

¹H-NMR spectra (500 MHz, DMSO) of compound 52

Figure 22

¹H-NMR spectra (500 MHz, CDCl₃) of compound 60

Definitions

The term "alkyl", as used herein, refers to saturated, straight- or branched-chain hydrocarbon radicals such as "C₁-C₃ alkyl", "C₁-C₆ alkyl," or "C₁-C₁₂ alkyl", containing between one and three, one and twelve, or one and six carbon atoms, respectively. Examples of C₁-C₃ alkyl radicals include methyl, ethyl, propyl and isopropyl radicals; examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, sec -butyl,

n-pentyl, neopentyl and n-hexyl radicals; and examples of C₁-C₁₂ alkyl radicals include, but are not limited to, ethyl, propyl, isopropyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl radicals and the like.

The term "substituted alkyl", as used herein, refers to an alkyl, such as a C₁-C₁₂ alkyl or C₁-C₆ alkyl group, substituted by one, two, three or more aliphatic substituents.

Suitable aliphatic substituents include, but are not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, aliphatic ethers, aromatic ethers, oxo, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen (such as perhaloalkyls), -C₂-C₁₂ alkenyl optionally substituted with halogen, -C₂-C₁₂ alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkynyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CO₂-heterocycloalkyl, -CO₂-C₁-C₁₂-alkyl, -CO₂-C₂-C₁₂-alkenyl, -CO₂-C₂-C₁₂-alkynyl, -CO₂-C₃-C₁₂-cycloalkyl, -CO₂-aryl, -CO₂-heteroaryl, -CO₂-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkynyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkynyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, -NHC(S)NH₂, -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NR-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkynyl, -NHC(NH)-C₃-C₁₂-

cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NR)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NR)NH-C₂-C₁₂-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls and the like can be further substituted.

The terms "C₂-C₁₂-alkenyl" or "C₂-C₆-alkenyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon atoms having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, alkadienes and the like.

The term "substituted alkenyl", as used herein, refers to a "C₂-C₁₂-alkenyl" or "C₂-C₆-alkenyl" group as previously defined, substituted by one, two, three or more aliphatic substituents.

The terms "C₂-C₁₂-alkynyl" or "C₂-C₆-alkynyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon atoms having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, and the like.

The term "substituted alkynyl", as used herein, refers to a "C₂-C₁₂-alkynyl" or "C₂-C₆-alkynyl" group as previously defined, substituted by one, two, three or more aliphatic substituents.

The terms "C₁-C₃-alkoxy" and "C₁-C₆-alkoxy", as used herein, refers to a C₁-C₃-alkyl group and C₁-C₆-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C₁-C₃-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy. Examples of C₁-C₆-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, neopentoxy and n-hexoxy.

The terms "halo" and "halogen", as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "aryl", as used herein, refers to a mono-or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like.

The term "substituted aryl", as used herein, refers to an aryl group, as previously defined, substituted by one, two, three or more aromatic substituents.

Aromatic substituents include, but are not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, aliphatic ethers, aromatic ethers, oxo, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen (such as perhaloalkyls), C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkynyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -CO₂-C₁-C₁₂-alkyl, -CO₂-C₂-C₁₂-alkenyl, -CO₂-C₂-C₁₂-alkynyl, -CO₂-C₃-C₁₂-cycloalkyl, -CO₂-aryl, -CO₂-heteroaryl, -CO₂-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkynyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-

C₂-C₁₂-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₁₂-alkynyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl-SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls and the like can be further substituted.

The term "arylalkyl", as used herein, refers to an aryl group attached to the parent compound via a C₁-C₃ alkyl or C₁-C₆ alkyl residue. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "substituted arylalkyl", as used herein, refers to an arylalkyl group, as previously defined, substituted by one, two, three or more aromatic substituents.

The term "heteroaryl", as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxaliny, and the like. The heteroaromatic ring may be bonded to the chemical structure through a carbon or hetero atom.

The term "substituted heteroaryl", as used herein, refers to a heteroaryl group as previously defined, substituted by one, two, three or four aromatic substituents.

The terms "cycloalkyl" or "C₃-C₁₂-cycloalkyl", as used herein, denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

The term "substituted C₃-C₁₂-cycloalkyl," as used herein, refers to a C₃-C₁₂-cycloalkyl group as previously defined, substituted by one, two, three or more aliphatic substituents.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to a benzene ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, and tetrahydrofuryl.

The term "substituted heterocycloalkyl", as used herein, refers to a heterocycloalkyl group, as previously defined, substituted by one, two, three or more aliphatic substituents.

The term "heteroarylalkyl", as used herein, to an heteroaryl group attached to the parent compound via a C₁-C₃ alkyl or C₁-C₆ alkyl residue. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "substituted heteroarylalkyl", as used herein, refers to a heteroarylalkyl group, as previously defined, substituted by independent replacement of one, two, or three or more aromatic substituents.

The term "C₁-C₃-alkylamino", as used herein, refers to one or two C₁-C₃-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C₁-C₃-alkylamino include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

The term "alkylamino" refers to a group having the structure- NH(C₁-C₁₂-alkyl) where C₁-C₁₂-alkyl is as previously defined.

The term "dialkylamino" refers to a group having the structure- N(C₁-C₁₂-alkyl) (C₁-C₁₂-alkyl), where C₁-C₁₂-alkyl is as previously defined. Examples of dialkylamino are, but not limited to, dimethylamino, diethylamino, methylethylamino, piperidino, and the like.

The term "alkoxycarbonyl" represents an ester group, i.e., an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

The term "carboxaldehyde", as used herein, refers to a group of formula- CHO.

The term "carboxy", as used herein, refers to a group of formula- COOH.

The term "carboxamide", as used herein, refers to a group of formula- C(O)NH(C₁-C₁₂-alkyl) or -C(O)N(C₁-C₁₂-alkyl) (C₁-C₁₂-alkyl), -C(O)NH₂, -NHC(O)(C₁-C₁₂-alkyl), (C₁-C₁₂-alkyl)C(O)(C₁-C₁₂-alkyl) and the like.

As used herein, the term “pharmaceutically acceptable salts” includes acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion using a suitable ion exchange resin.

In the context of the present specification, the term “treat” also includes “prophylaxis” unless there are specific indications to the contrary. The term “treat” within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring condition and continued therapy for chronic disorders.

The compounds of the present invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the present invention, the route of administration may be topical.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of the present invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in mixture with the finely divided compound of the present invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogenous mixture is then poured into conveniently sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous solutions for oral use can be made by dispersing the finely divided active

component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will according to one embodiment of the present invention include 0.05% to 99% weight (percent by weight), according to an alternative embodiment from 0.10 to 50% weight, of the compound of the present invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

The above-mentioned subject-matter for a pharmaceutical composition comprising a compound according to the present invention is applied analogously for a pharmaceutical composition comprising a combination according to the present invention.

Another object of the present invention is a compound as disclosed above for use in medicine.

Another object of the present invention is a pharmaceutical formulation comprising a compound as disclosed above in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

These, and other, embodiments of the invention will be better appreciated and understood when considered in conjunction with the following description and the accompanying drawings. It should be understood, however, that the following description, while indicating

various embodiments of the invention and numerous specific details thereof, is given by way of illustration and not of limitation. Many substitutions, modifications, additions and/or rearrangements may be made within the scope of the invention without departing from the spirit thereof, and the invention includes all such substitutions, modifications, additions and/or rearrangements.

EXAMPLES

KLK7 Inhibitor Test

Substrate: (MeO-Suc-Arg-Pro-Tyr-pNA), acetate salt, Peptide international, lot #906841, previously named S-2586

Enzyme: Active human KLK7 (SCCE) 0.62 mg/ml in 0.3 M NaCl, 10 mM NaAc, pH 4

Buffer: 10 mM NaPhosphate, 0.5 M NaCl, pH 7.2

150 µl of Substrate (2.5 mM) in Buffer was added to 96 wells plate (F8 Polysorp Unfra, Nunc cat. no. 469957). 10 µl of DMSO was added to the blank and control wells.

10 µl of substance in DMSO was added to wells giving final concentrations of 20 µM, 10 µM, 5 µM, 2.5 µM, 1.25 µM, 0.625 µM, 0.3125 µM, and 0.15625 µM .

40 µl of active KLK7 (SCCE) (diluted to 12,5 µg/ml in activity buffer) was added all wells except blank to which activity buffer was added.

Immediately after addition of SCCE the plate was transferred to a Spectramax 250 Microplate Reader (Molecular Devices) and enzyme activity (V) was measured as release of pNa measuring absorbance at 405 nm in 37 °C for 15 min with reading every 30 s.

The mean value V of each sample was calculated (n = 2 for the substances and n = 4 for the control). From the values of V the % of total activity was calculated as $(V_{\text{inhibitor}}/V_{\text{control (no inhibitor)}}) \times 100$.

Plotting and calculation was then done in originPro.

% of total activity (y) was plotted vs. log [inhibitor] (log x) and a function of dose response

$$y = A1 + (A2-A1)/(1 + 10^{((\text{LOG}(x0)-x)*p)})$$

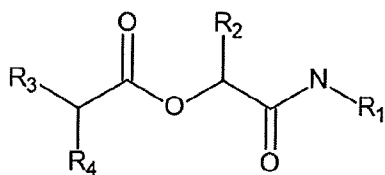
where A1 = Bottom platue, A2 = Top platue, x0 = EC₅₀ and p = Hill slope

was fitted to the curve. IC₅₀ concentration was calculated by setting y = 50 and solving for x.

The IC₅₀ values were used to identify KLK7 inhibitors according to the invention.

Results are presented in Table 1.

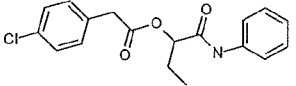
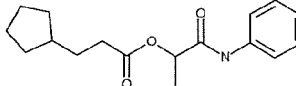
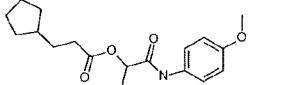
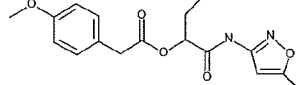
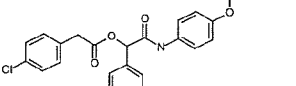
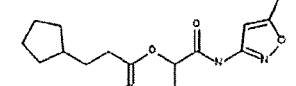
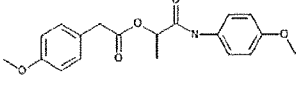
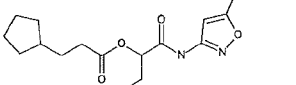
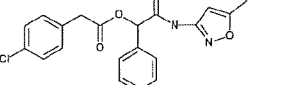
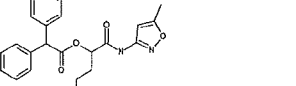
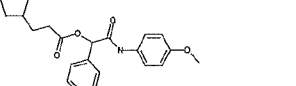
Table 1

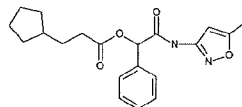
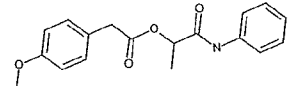
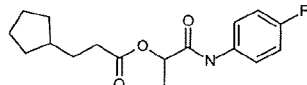
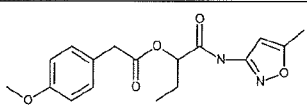
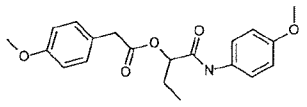
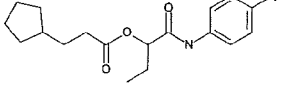
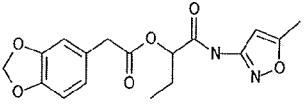
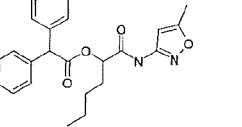
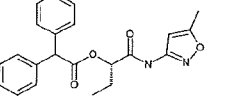
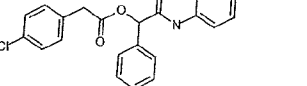
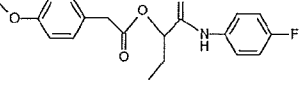
IC₅₀ values of compounds according to Formula I

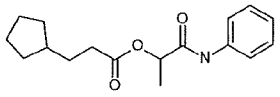
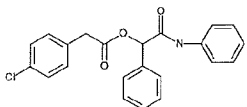
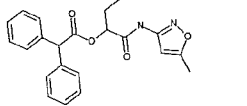
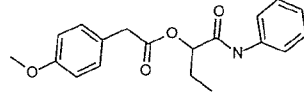
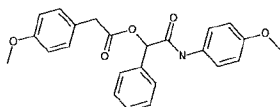
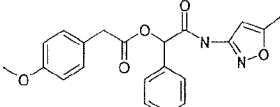
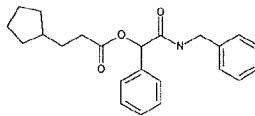
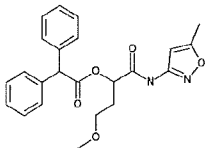
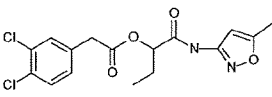
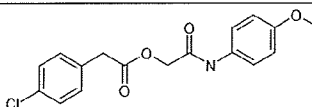
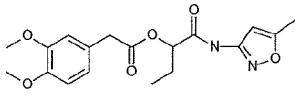
Formula I

wherein R₁, R₂, R₃ and R₄ are as defined in Table 1 below.

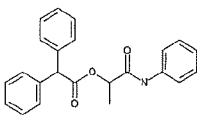
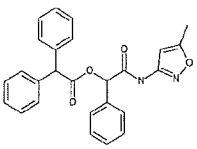
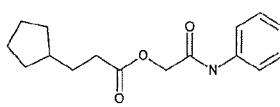
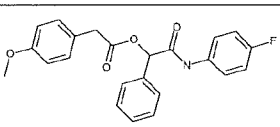
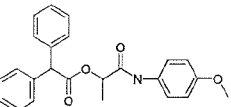
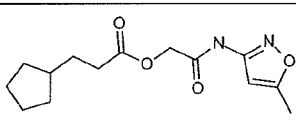
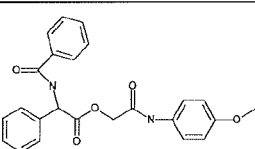
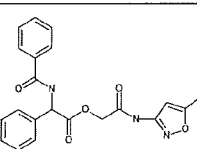
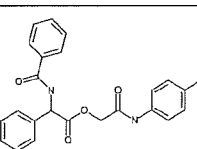
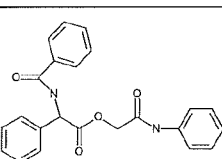
Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
1		5-methyl-3-isoxazolyl-	-methyl	4-chloro phenyl-	-H	0.039
2		4-fluoro phenyl-	-methyl	4-chloro phenyl-	-H	0.07
3		5-methyl-3-isoxazolyl-	-ethyl	4-chloro phenyl-	-H	0.08
4		4-methoxy phenyl-	-methyl	4-chloro phenyl-	-H	0.08
5		-phenyl	-methyl	4-chloro phenyl-	-H	0.09
6		4-methoxy phenyl-	-ethyl	4-chloro phenyl-	-H	0.12
7		5-methyl-3-isoxazolyl-	-methyl	4-methoxy phenyl	-H	0.13
8		4-fluoro phenyl-	-ethyl	4-chloro phenyl-	-H	0.14

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
9		-phenyl	-ethyl	4-chloro phenyl-	-H	0.15
10		4-methoxy phenyl-	-methyl	cyclopentyl methyl-	-H	0.15
11		4-methoxy phenyl-	-ethyl	cyclopentyl methyl-	-H	0.15
12		5-methyl-3- isoxazolyl-	-ethyl	4-methoxy phenyl	-H	0.15
13		4-methoxy phenyl-	-phenyl	4-chloro phenyl-	-H	0.17
14		5-methyl-3- isoxazolyl-	-methyl	cyclopentyl methyl-	-H	0.18
15		4-methoxy phenyl-	-methyl	4-methoxy phenyl	-H	0.18
16		5-methyl-3- isoxazolyl-	-ethyl	cyclopentyl methyl-	-H	0.19
17		5-methyl-3- isoxazolyl-	-phenyl	4-chloro phenyl-	-H	0.19
18		5-methyl-3- isoxazolyl-	-propyl	-phenyl	-phenyl	0.22
19		4-methoxy phenyl-	-phenyl	cyclopentyl methyl-	-H	0.23

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μ M)
20		5-methyl-3-isoxazolyl-	-phenyl	cyclopentyl methyl-	-H	0.23
21		-phenyl	-methyl	4-methoxy phenyl	-H	0.26
22		4-fluoro phenyl-	-methyl	cyclopentyl methyl-	-H	0.26
23		5-methyl-3-isoxazolyl-	-ethyl	4-methoxy phenyl	-H	0.27
24		4-methoxy phenyl-	-ethyl	4-methoxy phenyl	-H	0.28
25		4-fluoro phenyl-	-ethyl	cyclopentyl methyl-	-H	0.31
26		5-methyl-3-isoxazolyl-	-ethyl	1,3-benzo dioxolyl-	-H	0.32
27		5-methyl-3-isoxazolyl-	-butyl	-phenyl	-phenyl	0.33
28		5-methyl-3-isoxazolyl-	-ethyl	-phenyl	-phenyl	0.34
29		4-fluoro phenyl-	-phenyl	4-chloro phenyl-	-H	0.35
30		4-fluoro phenyl-	-ethyl	4-methoxy phenyl-	-H	0.36

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
31		-phenyl	-methyl	cyclopentyl methyl-	-H	0.37
32		-phenyl	-phenyl	4-chloro phenyl-	-H	0.38
33		5-methyl-3-isoxazolyl-	-ethyl	-phenyl	-phenyl	0.39
34		-phenyl	-ethyl	4-methoxy phenyl-	-H	0.39
35		4-methoxy phenyl-	-phenyl	4-methoxy phenyl-	-H	0.41
36		5-methyl-3-isoxazolyl-	-phenyl	4-methoxy phenyl-	-H	0.43
37		-phenyl	-phenyl	cyclopentyl methyl-	-H	0.46
38		5-methyl-3-isoxazolyl-	methoxy-propyl-	-phenyl	-phenyl	0.47
39		5-methyl-3-isoxazolyl-	-ethyl	3,4-dichloro phenyl-	-H	0.48
40		4-methoxy phenyl-	-H	4-chloro phenyl-	-H	0.55
41		5-methyl-3-isoxazolyl-	-ethyl	3,4-dimethoxy phenyl-	-H	0.58

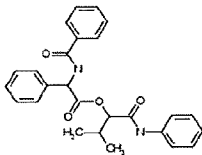
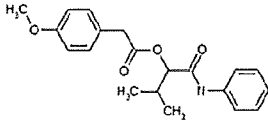
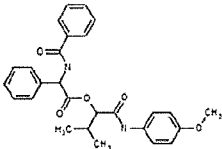
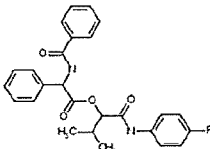
Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μ M)
42		4-fluoro phenyl-	-methyl	4-methoxy phenyl-	-H	0.59
43		4-methoxy phenyl-	-ethyl	-phenyl	-phenyl	0.63
44		4-fluoro phenyl-	-ethyl	-phenyl	-phenyl	0.64
45		5-methyl-3- isoxazolyl-	-ethyl	benzamido	-phenyl	0.66
46		4-methoxy phenyl-	-H	cyclopentyl methyl-	-H	0.69
47		5-methyl-3- isoxazolyl-	-methyl	-phenyl	-phenyl	0.74
48		-phenyl	-ethyl	-phenyl	-phenyl	0.76
49		5-methyl-3- isoxazolyl-	-phenyl	benzamido	-phenyl	0.78
50		4-fluoro phenyl-	-H	4-chloro phenyl-	-H	0.79
51		4-fluoro phenyl-	-H	cyclopentyl methyl-	-H	0.83
52		5-methyl-3- isoxazolyl-	-methyl	-benzamido	-phenyl	0.95

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μ M)
53		-phenyl	-methyl	-phenyl	-phenyl	1.10
54		5-methyl-3-isoxazolyl-	-phenyl	-phenyl	-phenyl	1.1
55		-phenyl	-H	cyclopentyl methyl-	-H	1.11
56		4-fluoro phenyl-	-phenyl	4-methoxy phenyl-	-H	1.17
57		4-methoxy phenyl-	-methyl	-phenyl	-phenyl	1.18
58		5-methyl-3-isoxazolyl-	-H	cyclopentyl methyl-	-H	1.20
59		4-methoxy phenyl-	-H	-benzamido	-phenyl	1.23
60		5-methyl-3-isoxazolyl-	-H	-benzamido	-phenyl	1.47
61		4-fluoro phenyl-	-H	-benzamido	-phenyl	1.51
62		-phenyl	-H	-benzamido	-phenyl	1.56

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
63		4-fluoro phenyl-	-methyl	-phenyl	-phenyl	1.62
64		4-methoxy phenyl-	-ethyl	-benzamido	-phenyl	1.7
65		4-fluoro phenyl-	-ethyl	-benzamido	-phenyl	1.79
66		-phenyl	-methyl	-benzamido	-phenyl	1.85
67		4-fluoro phenyl-	-H	4-methoxy phenyl-	-H	2.28
68		4-methoxy phenyl-	-H	4-methoxy phenyl-	-H	2.31
69		5-methyl-3- isoxazolyl-	-H	cyclopentyl methyl-	-H	2.7
70		5-methyl-3- isoxazolyl-	-isopropyl	4-chloro phenyl-	-H	2.7
71		4-methoxy phenyl-	-methyl	-benzamido	-phenyl	2.76
72		5-methyl-3- isoxazolyl-	-isopropyl	cyclopentyl methyl-	-H	2.78

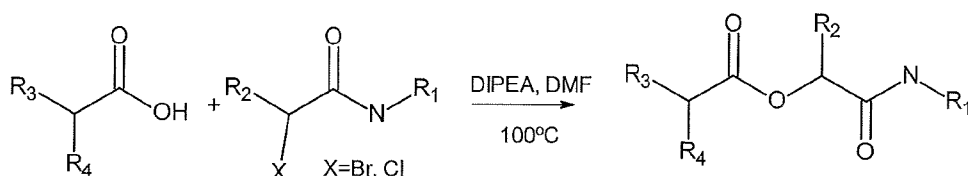
Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
73		5-methyl-3-isoxazolyl-	-H	4-chloro phenyl-	-H	2.9
74		5-methyl-3-isoxazolyl-	-H	4-methoxy phenyl-	-H	3.05
75		5-methyl-3-isoxazolyl-	-isopropyl	-benzamido	-phenyl	3.26
76		-phenyl	-phenyl	-benzamido	-phenyl	3.34
77		-phenyl	-H	4-methoxy phenyl-	-H	3.89
78		4-methoxy phenyl-	-phenyl	-phenyl	-phenyl	4.33
79		5-methyl-3-isoxazolyl-	-isopropyl	-phenyl	-phenyl	4.56
80		5-methyl-3-isoxazolyl-	-H	-phenyl	-phenyl	4.70
81		5-methyl-3-isoxazolyl-	-H	4-chloro phenyl-	-H	5.0
82		5-methyl-3-isoxazolyl-	-ethyl	-benzamido	2-methyl sulfanyl ethyl-	5.5

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μ M)
83		-phenyl	-methyl	-benzamido	-phenyl	5.89
84		5-methyl-3-isoxazolyl-	-isopropyl	4-methoxy phenyl-	-H	6.25
85		5-methyl-3-isoxazolyl-	-ethyl	-benzamido	-phenyl	6.43
86		5-methyl-3-isoxazolyl-	-H	-phenyl	-phenyl	6.64
87		4-methoxy phenyl-	-H	-phenyl	-phenyl	7.39
88		4-fluoro phenyl-	-H	-phenyl	-phenyl	8.49
89		5-methyl-3-isoxazolyl-	-ethyl	-benzamido	-iso butanyl	9.1
90		-phenyl	-H	-phenyl	-phenyl	11.2
91		-phenyl	-isopropyl	4-chloro phenyl-	-H	4.1
92		4-methoxy phenyl-	-isopropyl	4-chloro phenyl-	-H	3.8

Cmpd	Structure	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)
93		-phenyl	-isopropyl	-benzamido	-phenyl	2.3
94		-phenyl	-isopropyl	4-methoxy phenyl-	-H	3.6
95		4-methoxy phenyl-	-isopropyl	-benzamido	-phenyl	6.3
96		4-fluoro phenyl-	-isopropyl	-benzamido	-phenyl	3.7

General synthesis procedure

A round-bottomed flask was charged with the corresponding acid **A** (3.6 mmol), DIPEA (3.6 mmol) and DMF (1 mL). An appropriate 2-bromo- or 2-chloro-substituted acetamide **B** (3.0 mmol) was added under stirring. The resulting mixture was stirred at 100°C for 2h. Then it was cooled to ambient temperature and poured into solution of NaHCO₃ (2%, 7 mL). An oily product solidified after standing (2-5 h) at ambient temperature. A precipitate was filtered off, washed with solution of NaHCO₃ (2%, 2 x 7 mL), mixture of 2-propanol and water (1:1, 7 mL), water (7 mL) and dried. The crude material was re-crystallized from isopropanol.



Example 1

[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-chlorophenyl)acetate

¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 1.43 (3H, d, *J* = 6.4 Hz, CH₃), 2.38 (3H, s, CH₃), 3.69 (2H, m, CH₂), 5.09 (1H, q, *J* = 6.4 Hz, OCH), 6.60 (1H, s, isoxazole), 7.27 (4H, s, Ar), 10.89 (1H, br s, NH).

Example 3

1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-chlorophenyl)acetate

¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 0.92 (3H, t, *J* = 7.2 Hz, CH₃), 1.81 (2H, m, CH₂), 2.38 (3H, s, CH₃), 3.70 (2H, s, CH₂), 4.94 (1H, m, OCH), 6.61 (1H, s, isoxazole), 7.27 (4H, s, Ar), 10.93 (1H, br s, NH).

Example 4

[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-chlorophenyl)acetate

¹H-NMR (400 MHz, DMSO-d₆) Figure 1

Example 6

1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate

¹H-NMR (400 MHz, DMSO-d₆) Figure 2

Example 7

[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-methoxyphenyl) acetate

¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 1.42 (3H, d, *J* = 6.8 Hz, CH₃), 2.38 (3H, s, CH₃), 3.60 (2H, s, CH₂), 3.75 (3H, s, OCH₃), 5.05 (1H, q, *J* = 6.8 Hz, OCH), 6.61 (1H, s, isoxazole), 6.79 (2H, d, *J* = 8.4 Hz, Ar), 7.15 (2H, d, *J* = 8.4 Hz, Ar), 10.93 (1H, br s, NH).

Example 8**1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 3**Example 9****1-(phenylcarbamoyl)propyl 2-(4-chlorophenyl)acetate**¹H-NMR (500 MHz, DMSO) Figure 4**Example 10****[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 5**Example 11****1-[(4-methoxyphenyl)carbamoyl]propyl 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆+CCl₄) Figure 6**Example 13****[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-chlorophenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 7**Example 14****[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 8**Example 15****[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-methoxyphenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 9**Example 16****1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 10**Example 19****[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 11**Example 20****[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 12**Example 23****1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆+CCl₄) Figure 13

Example 24**1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate**¹H-NMR (500 MHz, DMSO) Figure 14**Example 25****1-[(4-fluorophenyl)carbamoyl]propyl 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 15**Example 30****1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 16**Example 32****(2-anilino-2-oxo-1-phenyl-ethyl) 2-(4-chlorophenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 17**Example 35****[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 3.65-3.75 (5H, m, CH₂, OCH₃), 3.76 (3H, s, OCH₃), 5.98 (1H, s, OCH), 6.76 (2H, d, *J* = 8.0 Hz, Ar), 6.81 (2H, d, *J* = 8.0 Hz, Ar), 7.21 (2H, d, *J* = 8.0 Hz, Ar), 7.26-7.38 (3H, m, Ar), 7.45 (2H, d, *J* = 8.0 Hz, Ar), 7.53 (2H, d, *J* = 6.8 Hz, Ar), 9.91 (1H, br s, NH).**Example 36****[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆) Figure 18**Example 37****[2-(benzylamino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate**¹H-NMR (400 MHz, DMSO-d₆) Figure 19**Example 42****[2-(4-methoxyanilino)-2-oxo-ethyl] 2-(4-chlorophenyl)acetate**¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 1.44 (3H, d, *J* = 6.8 Hz, CH₃), 3.63 (2H, m, CH₂), 3.75 (3H, s, OCH₃), 5.07 (1H, q, *J* = 6.8 Hz, CH), 6.80 (2H, d, *J* = 8.4 Hz, Ar), 6.96 (2H, m, Ar), 7.18 (2H, d, *J* = 8.4 Hz, Ar), 7.58 (2H, m, Ar), 9.74 (1H, br s, NH).**Example 44****1-[(4-fluorophenyl)carbamoyl]propyl 2,2-diphenylacetate**¹H-NMR (500 MHz, DMSO-d₆+CCl₄) δ ppm: 0.87 (3H, t, *J* = 7.5 Hz, CH₃), 1.82 (2H, m, CH₂), 4.97 (1H, m, OCH), 5.21 (1H, s, CH), 6.99 (2H, m, Ar), 7.18-7.38 (10H, m, Ar), 7.59 (2H, m, Ar), 9.87 (1H, br s, NH).

Example 47**[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2,2-diphenylacetate**

¹H-NMR (400 MHz, DMSO-d₆+CCl₄) δ ppm: 1.42 (3H, d, *J* = 6.8 Hz, CH₃), 2.39 (3H, s, CH₃), 5.11 (1H, q, *J* = 6.8 Hz, OCH), 5.16 (1H, s, CH), 6.64 (1H, s, isoxazole), 7.15-7.35 (10H, m, Ar), 11.01 (1H, s, NH).

Example 48**1-(phenylcarbamoyl)propyl 2,2-diphenylacetate**

¹H-NMR (400 MHz, DMSO-d₆) Figure 20

Example 52**[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate**

¹H-NMR (500 MHz, DMSO) Figure 21

Example 60**[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate**

¹H-NMR (500 MHz, CDCl₃) Figure 22

Example 79**[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2,2-diphenylacetate**

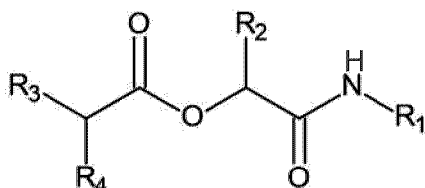
¹H-NMR (500 MHz, DMSO-d₆+CCl₄) δ ppm: 0.75 (3H, d, *J* = 6.5 Hz, CH₃), 0.78 (3H, d, *J* = 6.5 Hz, CH₃), 2.09 (1H, m, CH), 2.35 (3H, s, CH₃), 4.83 (1H, d, *J* = 5.0 Hz, OCH), 5.32 (1H, s, CH), 6.61 (1H, s, isoxazole), 7.20-7.39 (10H, m, Ar), 11.17 (1H, s, NH).

Example 94**[2-methyl-1-(phenylcarbamoyl)propyl] 2-(4-methoxyphenyl)acetate**

¹H-NMR (500 MHz, DMSO-d₆+CCl₄) δ ppm: 0.94 (6H, d, *J* = 6.5 Hz, CH₃), 2.19 (1H, m, CH), 3.66 (2H, m, CH₂), 3.76 (3H, s, OCH₃), 4.80 (1H, d, *J* = 5.5 Hz, OCH), 6.81 (2H, d, *J* = 8.5 Hz, Ar), 6.99 (1H, t, *J* = 7.3 Hz, Ar), 7.18-7.26 (4H, m, Ar), 7.56 (2H, d, *J* = 8.0 Hz, Ar), 9.66 (1H, s, NH).

CLAIMS

1. A compound according to Formula I



Formula I

wherein R₁ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R₂ is selected from hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl;

R₃ is selected from alkyl, , cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -C₁-C₃-alkyl-R₅, wherein R₅ is selected from cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl,;

R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and -NH-CO-R₆, wherein R₆ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

or a pharmaceutical acceptable salt thereof,

for use in the prophylaxis, prevention and/or treatment of a skin disease.

2. A compound according to claim 1

wherein R₁ is selected from phenyl, substituted phenyl, isoxazolyl, and substituted isoxazolyl;

R₂ is selected from hydrogen, -C₁-C₆-alkyl, C₁-C₃-alkyloxy-C₁-C₆-alkyl, and phenyl;

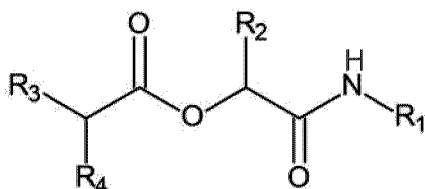
R₃ is selected from alkyl, , cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, and -C₁-C₃-alkyl-R₅, wherein R₅ is selected from cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl;

R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, and -NH-CO-R₆, wherein R₆ is selected from aryl, and substituted aryl;

or a pharmaceutical acceptable salt thereof,

for use in the prophylaxis, prevention and/or treatment of a skin disease.

3. A compound according to claim 1 or 2, or a pharmaceutical acceptable salt thereof, for use in the prophylaxis, prevention and/or treatment of an inflammatory skin disease.
4. A compound according to claim 1 or 2, or a pharmaceutical acceptable salt thereof, for use in the prophylaxis, prevention and/or treatment of a skin disease, wherein the skin disease is selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.
5. Use of a compound as defined in claim 1 or claim 2 for the manufacture of a medicament for the treatment of a skin disease.
6. A cosmetic or skin care composition comprising at least one compound with the Formula I,



Formula I

wherein R₁ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R₂ is selected from hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl;

R₃ is selected from alkyl, , cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -C₁-C₃-alkyl-R₅, wherein R₅ is selected from cycloalkyl, substituted cycloalkyl, aryl, and substituted aryl;

R₄ is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and -NH-CO-R₆, wherein R₆ is selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

or a pharmaceutically acceptable salt thereof,

said composition being in a form for topical administration, and selected from the group consisting of a cream, an ointment, a lotion, a liniment, a gel, a paste, a stick, a spray, a shampoo, a soap, a hair conditioner and a powder.

7. A compound selected from

[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-chlorophenyl) acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-chlorophenyl) acetate
[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-methoxyphenyl) acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-methoxyphenyl) acetate
[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 3-cyclopentylpropanoate
[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-methoxyphenyl)acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 3-cyclopentylpropanoate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-(4-chlorophenyl)acetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(1,3-benzodioxol-5-yl)acetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl) acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(3,4-dichlorophenyl)acetate
1-[(5-methylisoxazol-3-yl)carbamoyl]propyl 2-(3,4-dimethoxyphenyl)acetate
[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2,2-diphenylacetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2-benzamido-2-phenyl-acetate
[1-methyl-2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-1-phenyl-ethyl] 2,2-diphenylacetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-(4-chlorophenyl)acetate
[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 3-cyclopentylpropanoate
[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-benzamido-2-phenyl-acetate
[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2,2-diphenylacetate
[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethyl] 2-(4-chlorophenyl)acetate, and

[2-methyl-1-[(5-methylisoxazol-3-yl)carbamoyl]propyl] 2-(4-methoxyphenyl)acetate

8. A compound selected from

[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-(4-chlorophenyl)acetate

1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate

1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-chlorophenyl)acetate

1-(phenylcarbamoyl)propyl 2-(4-chlorophenyl)acetate

[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 3-cyclopentylpropanoate

1-[(4-methoxyphenyl)carbamoyl]propyl 3-cyclopentylpropanoate

[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-chlorophenyl)acetate

[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate

1-[(4-methoxyphenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate

1-[(4-fluorophenyl)carbamoyl]propyl 3-cyclopentylpropanoate

1-[(4-fluorophenyl)carbamoyl]propyl 2-(4-methoxyphenyl)acetate

(2-anilino-1-methyl-2-oxo-ethyl) 3-cyclopentylpropanoate

(2-anilino-2-oxo-1-phenyl-ethyl) 2-(4-chlorophenyl)acetate

1-(phenylcarbamoyl)propyl 2-(4-methoxyphenyl)acetate

[2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2-(4-methoxyphenyl)acetate

[2-(benzylamino)-2-oxo-1-phenyl-ethyl] 3-cyclopentylpropanoate

[2-(4-methoxyanilino)-2-oxo-ethyl] 2-(4-methoxyphenyl)acetate

1-[(4-methoxyphenyl)carbamoyl]propyl 2,2-diphenylacetate

1-[(4-fluorophenyl)carbamoyl]propyl 2,2-diphenylacetate

1-(phenylcarbamoyl)propyl 2,2-diphenylacetate

[2-(4-methoxyanilino)-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate

[2-(4-fluoroanilino)-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate

(2-anilino-2-oxo-ethyl) 2-benzamido-2-phenyl-acetate

1-[(4-methoxyphenyl)carbamoyl]propyl 2-benzamido-2-phenyl-acetate

1-[(4-fluorophenyl)carbamoyl]propyl 2-benzamido-2-phenyl-acetate

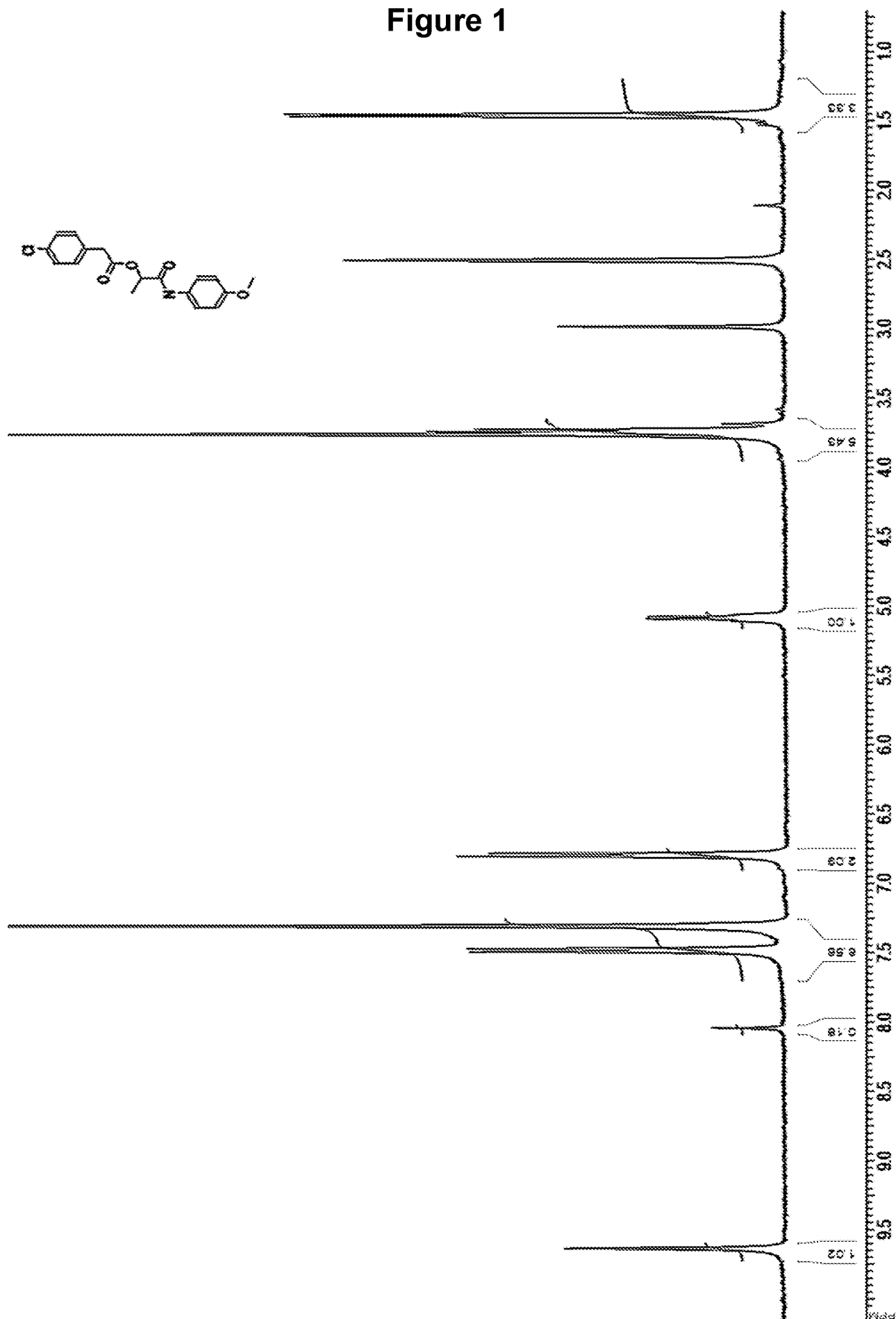
(2-anilino-1-methyl-2-oxo-ethyl) 2-benzamido-2-phenyl-acetate

[2-(4-methoxyanilino)-1-methyl-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate
 (2-anilino-2-oxo-1-phenyl-ethyl) 2-benzamido-2-phenyl-acetate
 [2-(4-methoxyanilino)-2-oxo-1-phenyl-ethyl] 2,2-diphenylacetate, and
 [2-(benzylamino)-1-methyl-2-oxo-ethyl] 2-benzamido-2-phenyl-acetate.
 [2-methyl-1-(phenylcarbamoyl)propyl] 2-(4-chlorophenyl)acetate
 [1-[(4-methoxyphenyl)carbamoyl]-2-methyl-propyl] 2-(4-chlorophenyl)acetate
 [2-methyl-1-(phenylcarbamoyl)propyl] 2-benzamido-2-phenyl-acetate
 [2-methyl-1-(phenylcarbamoyl)propyl] 2-(4-methoxyphenyl)acetate
 [1-[(4-methoxyphenyl)carbamoyl]-2-methyl-propyl] 2-benzamido-2-phenyl-acetate, and
 [1-[(4-fluorophenyl)carbamoyl]-2-methyl-propyl] 2-benzamido-2-phenyl-acetate

9. A pharmaceutical composition comprising a compound according to claim 7 or 8 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.
10. A compound according to claim 7 or 8 for use in medicine.
11. A compound according to claim 7 or 8 for use in prophylaxis, prevention and/or treatment of skin diseases.
12. The compound for use according to claim 11, wherein the skin disease is an inflammatory skin disease.
13. The compound for use according to claim 11, wherein the skin disease is selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.
14. The pharmaceutical composition according to claim 9 for use in medicine.

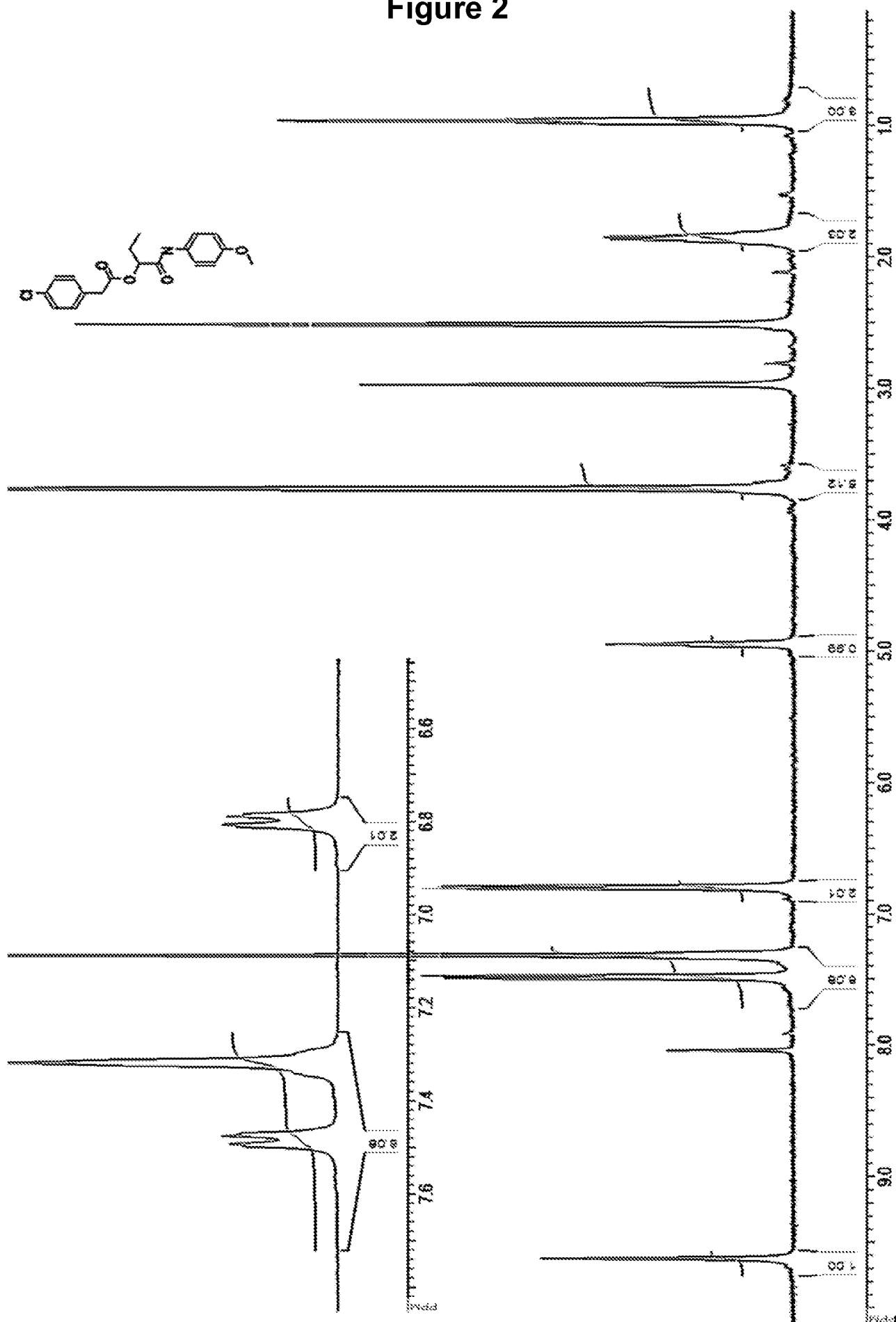
15. The pharmaceutical composition according to claim 9 for use in prophylaxis, prevention and/or treatment of skin diseases.
16. The pharmaceutical composition for use according to claim 15 wherein the skin disease is an inflammatory skin disease.
17. The pharmaceutical composition for use according to claim 15 wherein the skin disease is selected from Netherton syndrome, atopic dermatitis, contact dermatitis, eczema, psoriasis, acne, epidermal hyperkeratosis, acanthosis, epidermal inflammation, dermal inflammation and pruritus.
18. A cosmetic or skin care composition comprising at least one compound according to claim 7 or 8, or a pharmaceutically acceptable salt thereof, said composition being in a form for topical administration, and selected from the group consisting of a cream, an ointment, a lotion, a liniment, a gel, a paste, a stick, a spray, a shampoo, a soap, a hair conditioner and a powder.

Figure 1

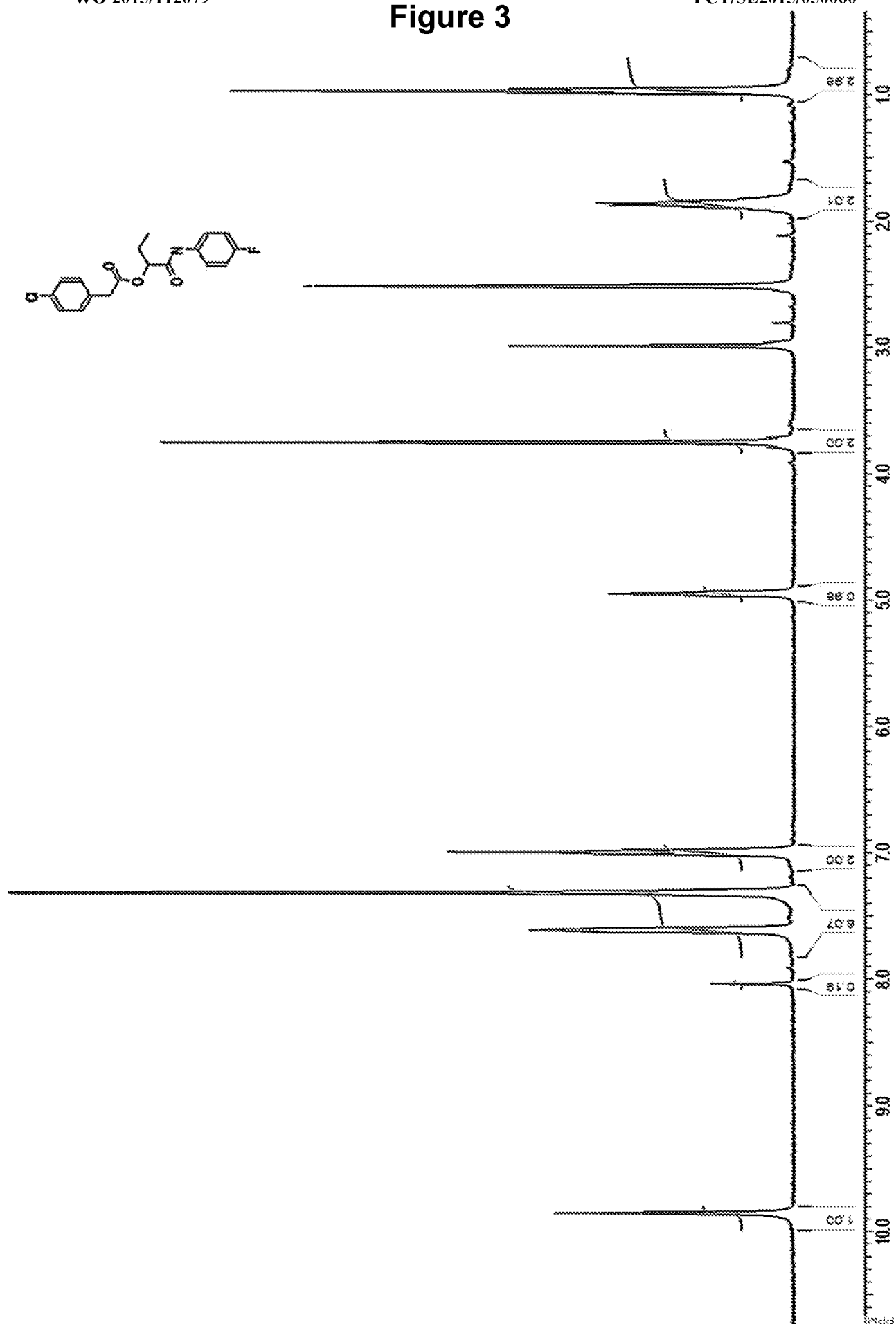


SUBSTITUTE SHEET (Rule 26)

Figure 2



SUBSTITUTE SHEET (Rule 26)

Figure 3

[illegible]

Figure 5

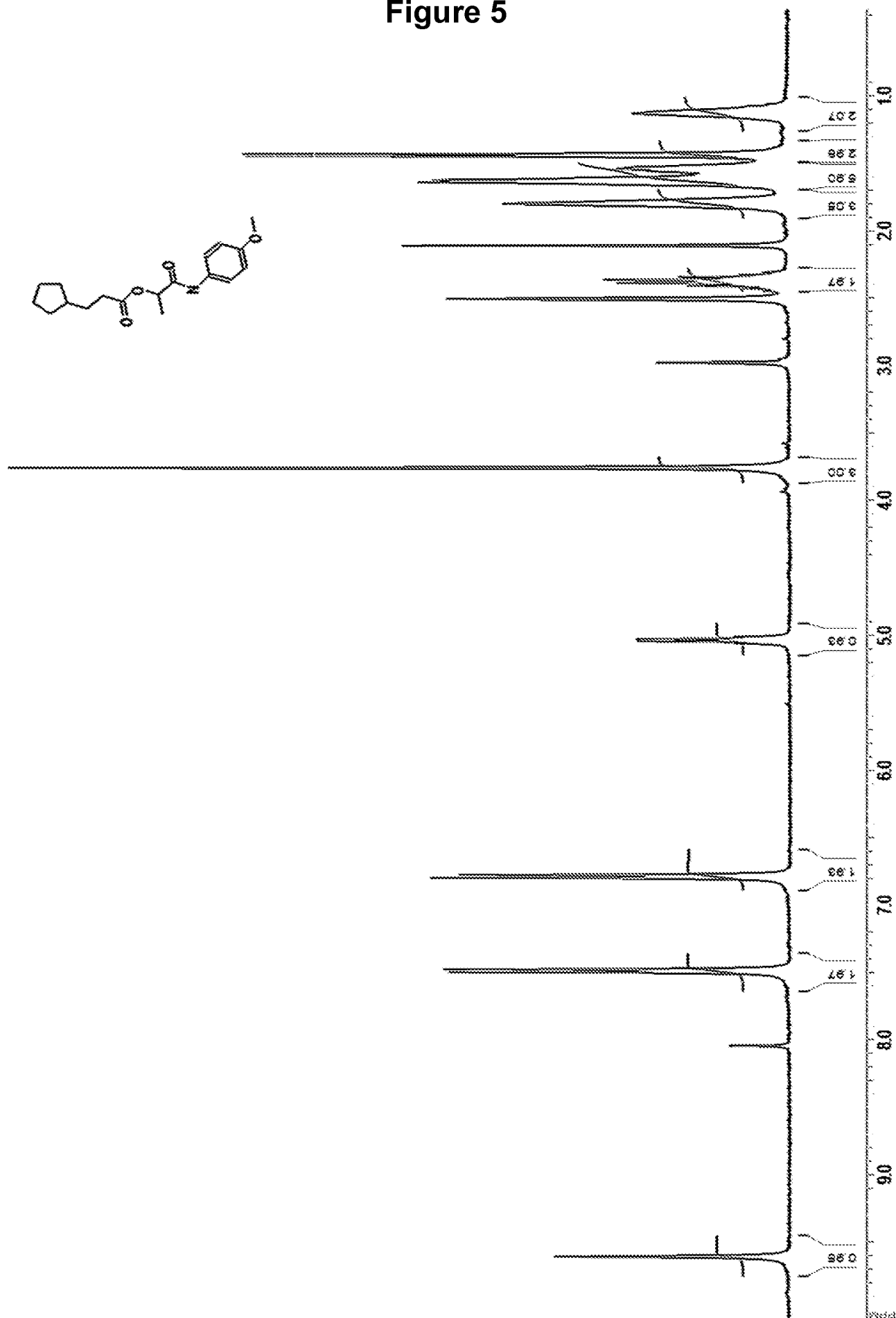


Figure 6

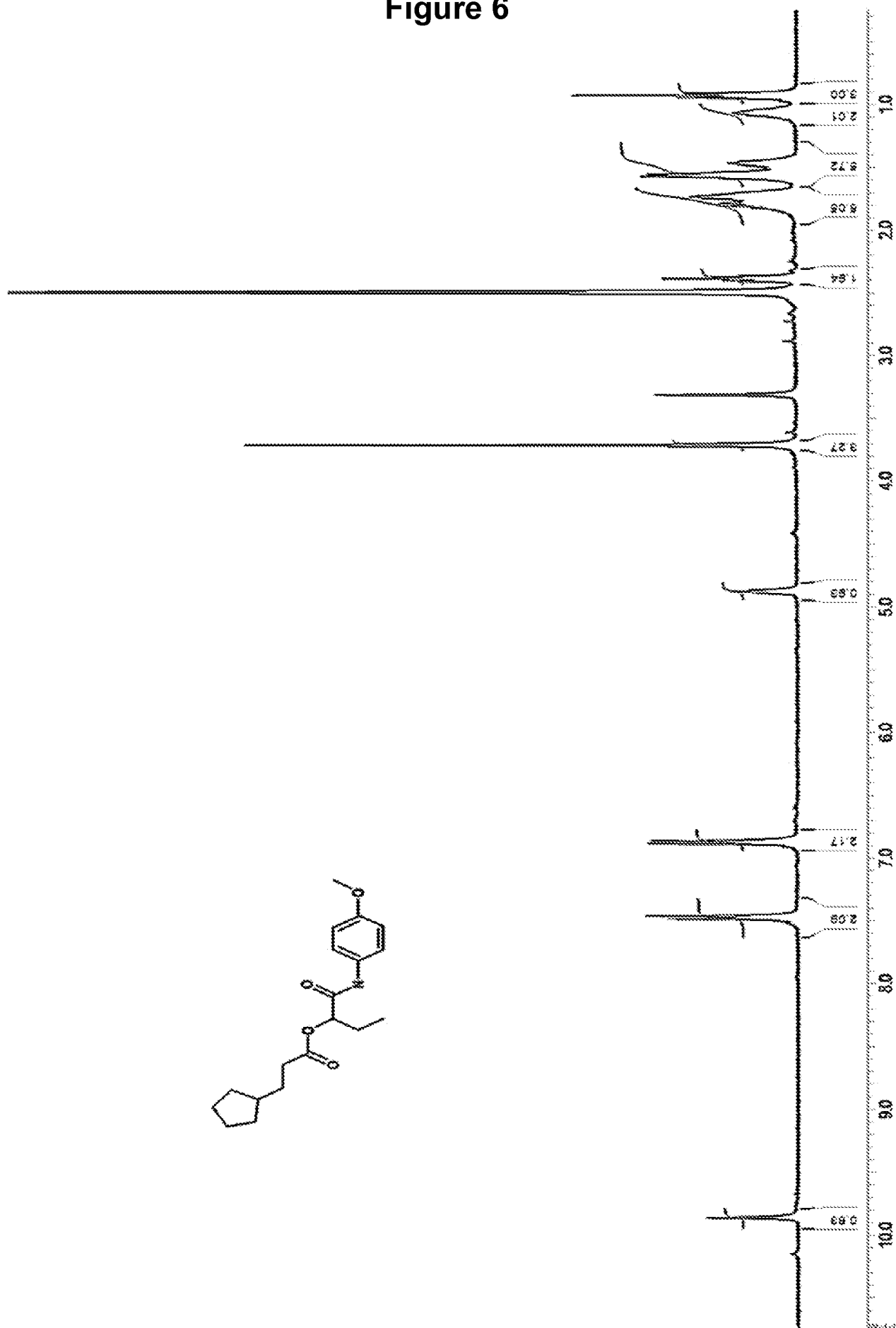


Figure 7

O=C(NC1=CC=C(C=C1)C2=CC=CC=C2)C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5C6=CC=C(C=C6)C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9

Chemical structure of compound 10 is shown. The spectrum displays peaks corresponding to the structure, with integration values provided for several regions: 0.98, 4.97, 7.92, 2.26, 4.18, 7.01, 2.00, 0.98, 0.07, and 0.98.

Figure 8

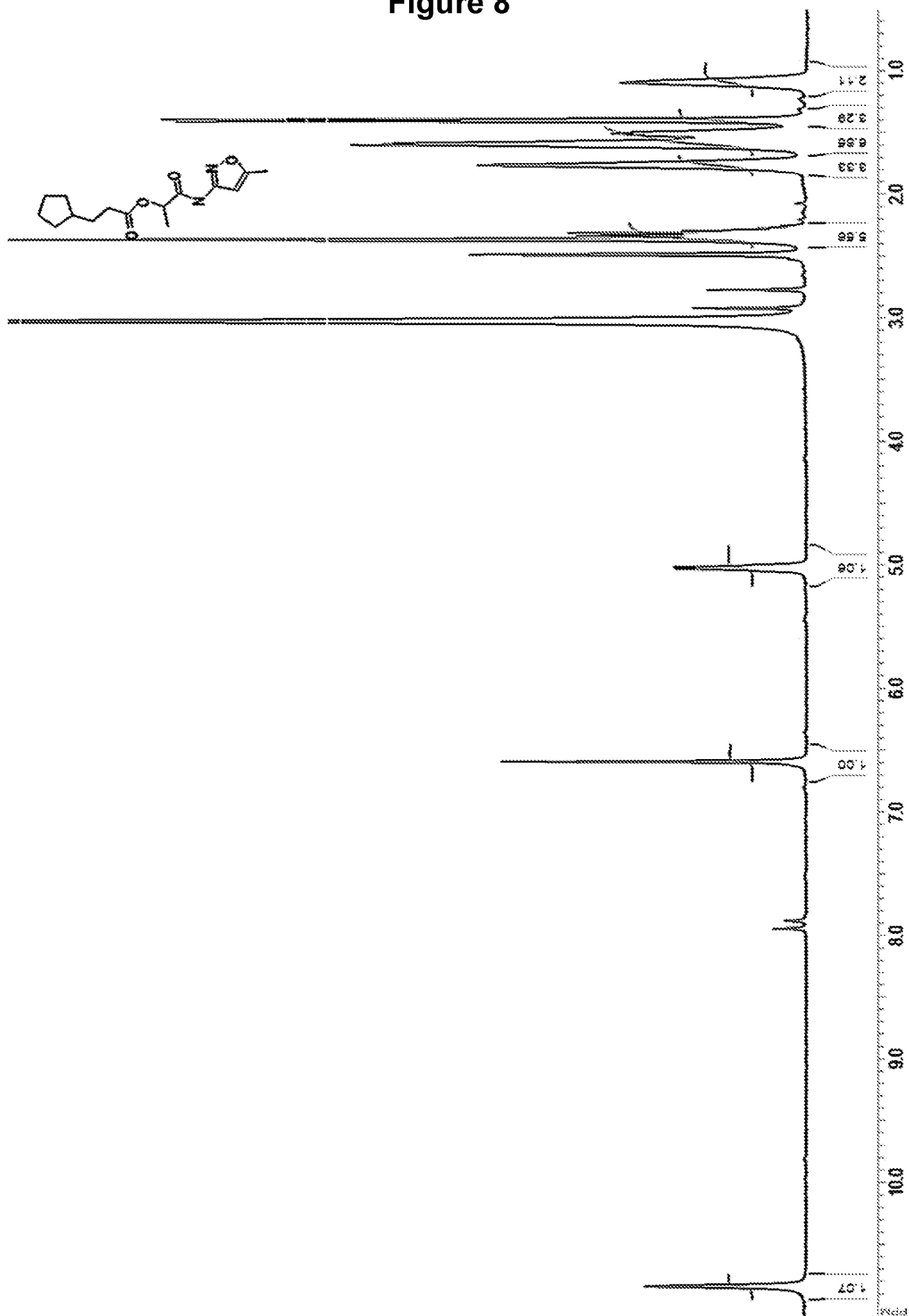


Figure 9

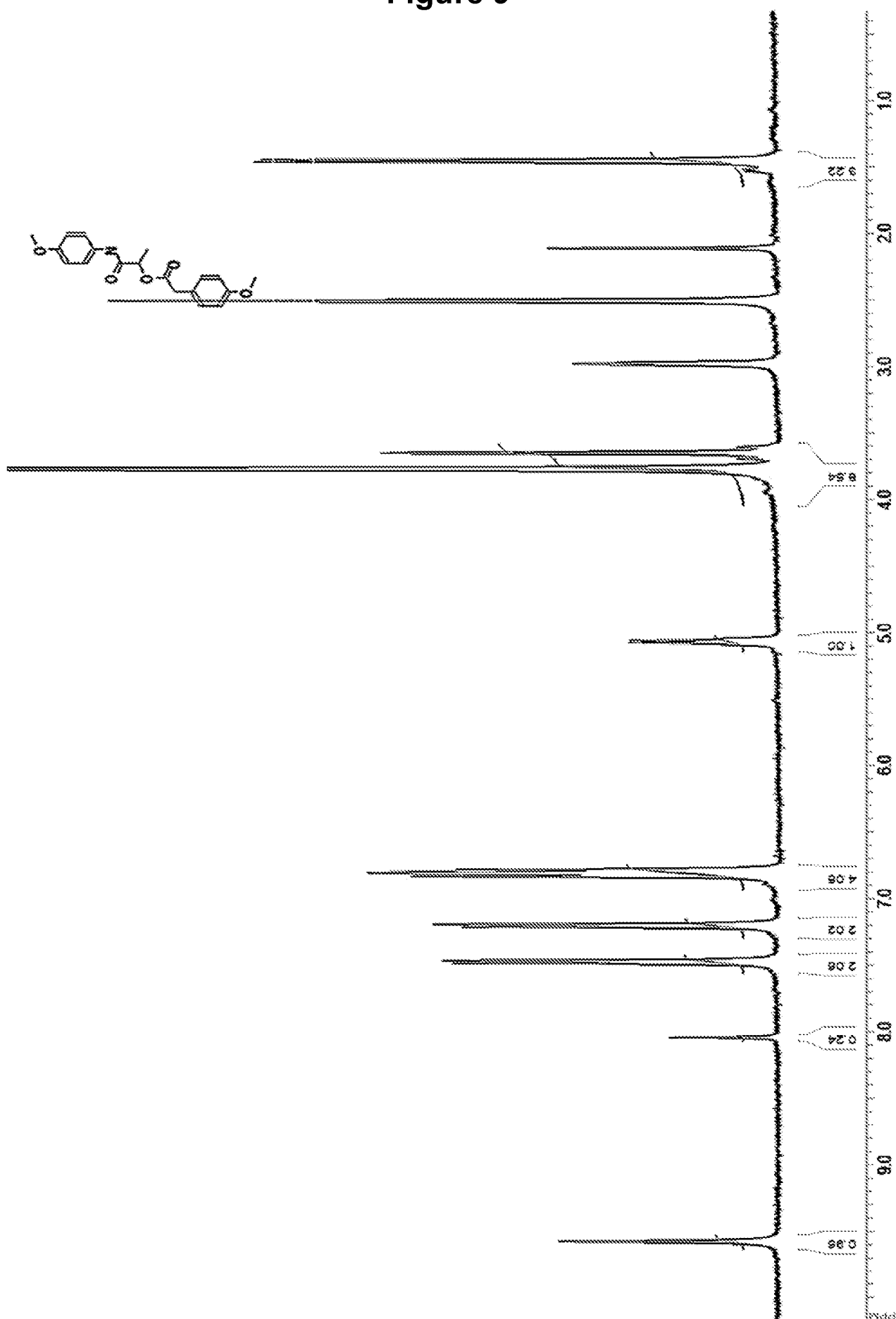


Figure 10

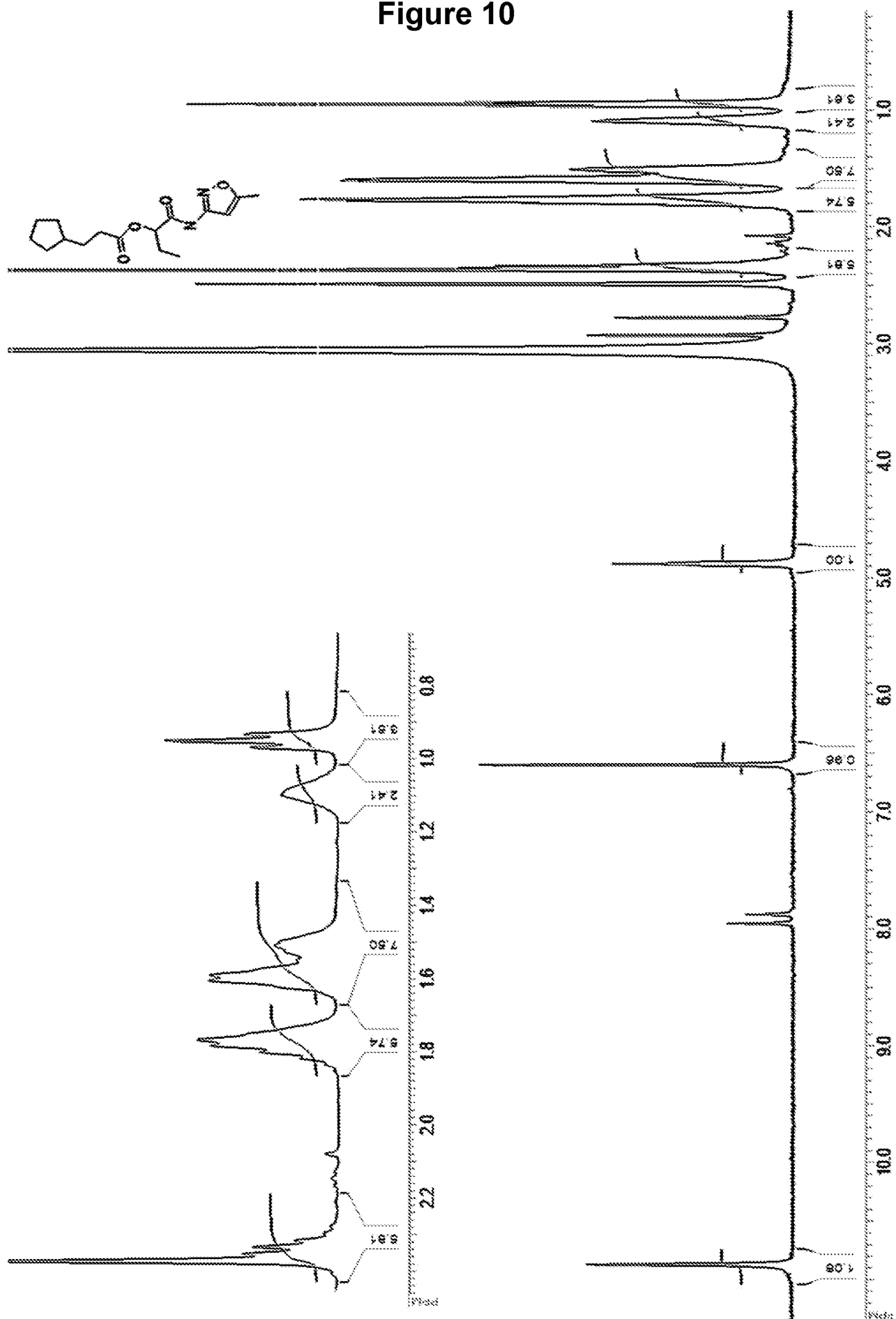


Figure 11

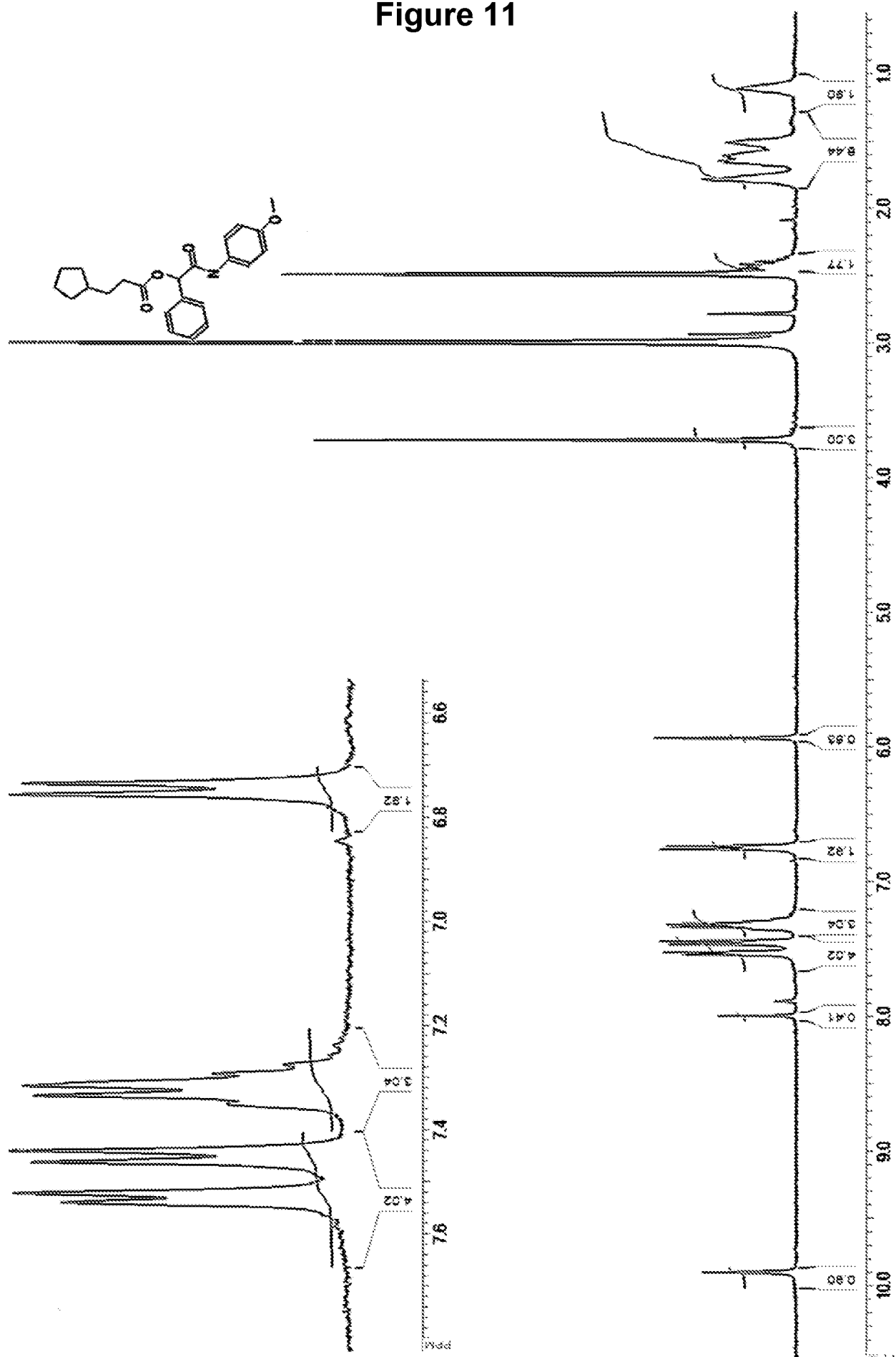
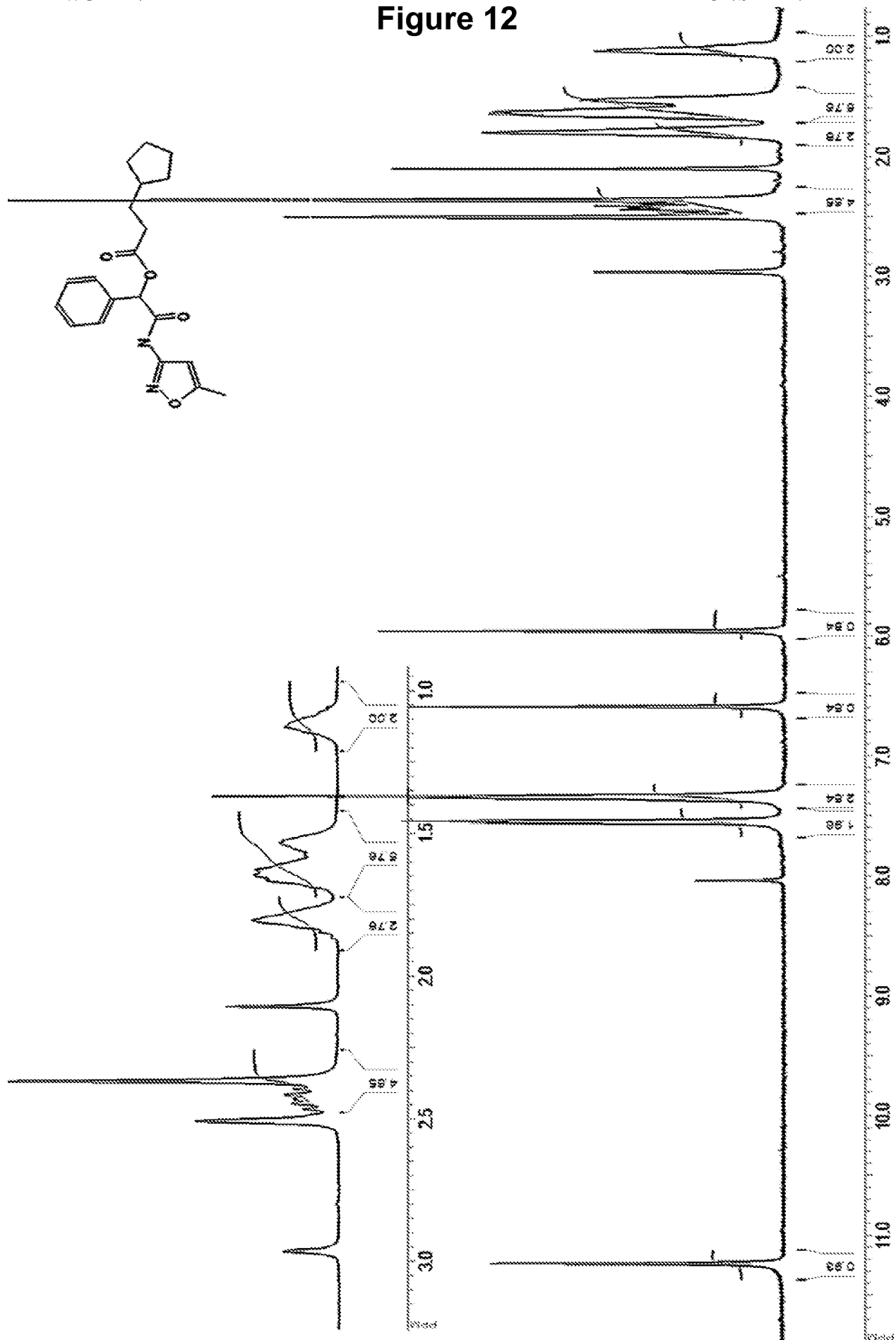


Figure 12



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Figure 13

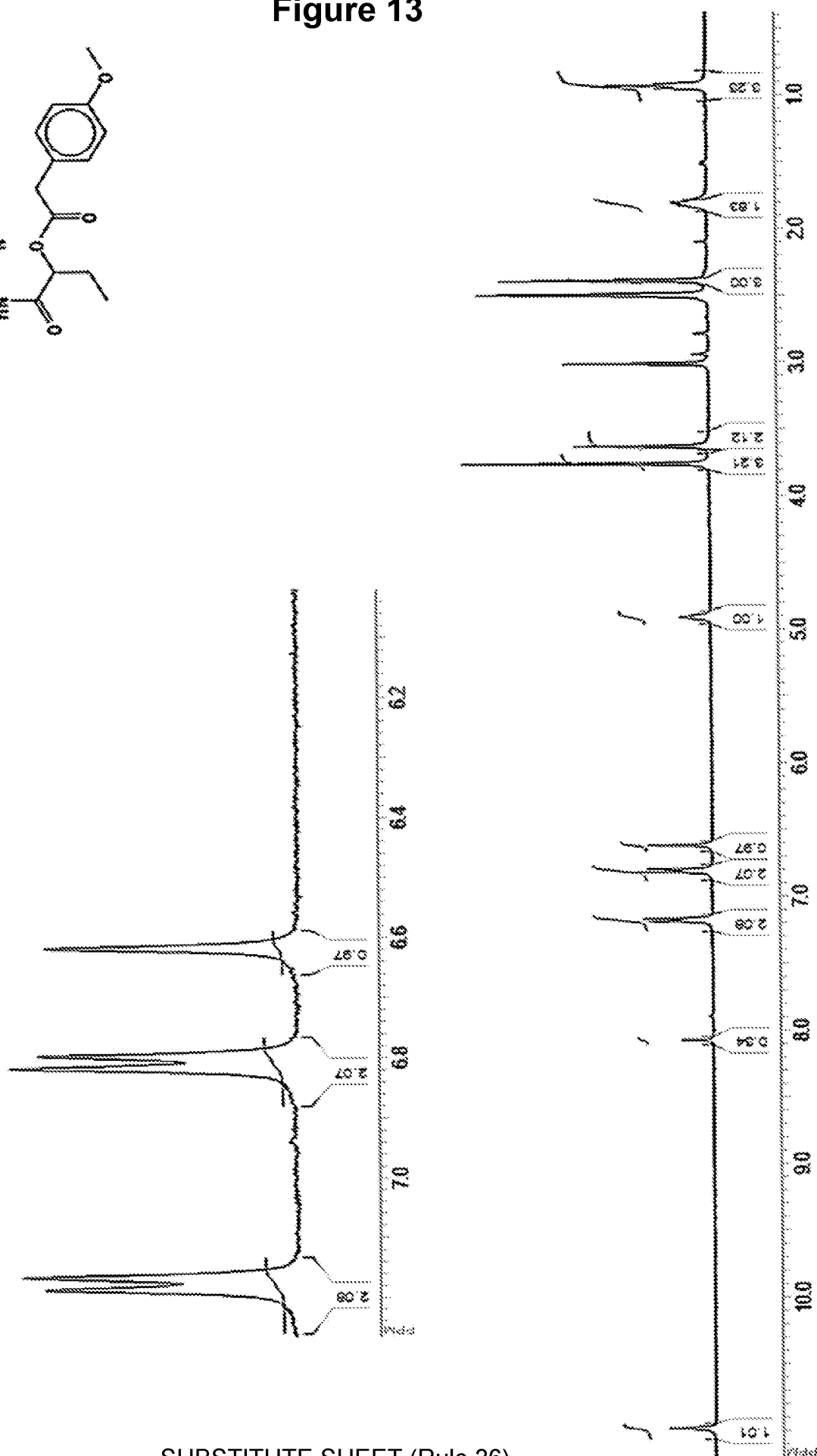
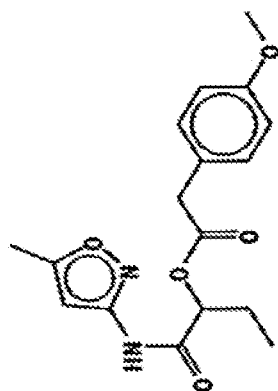


Figure 14

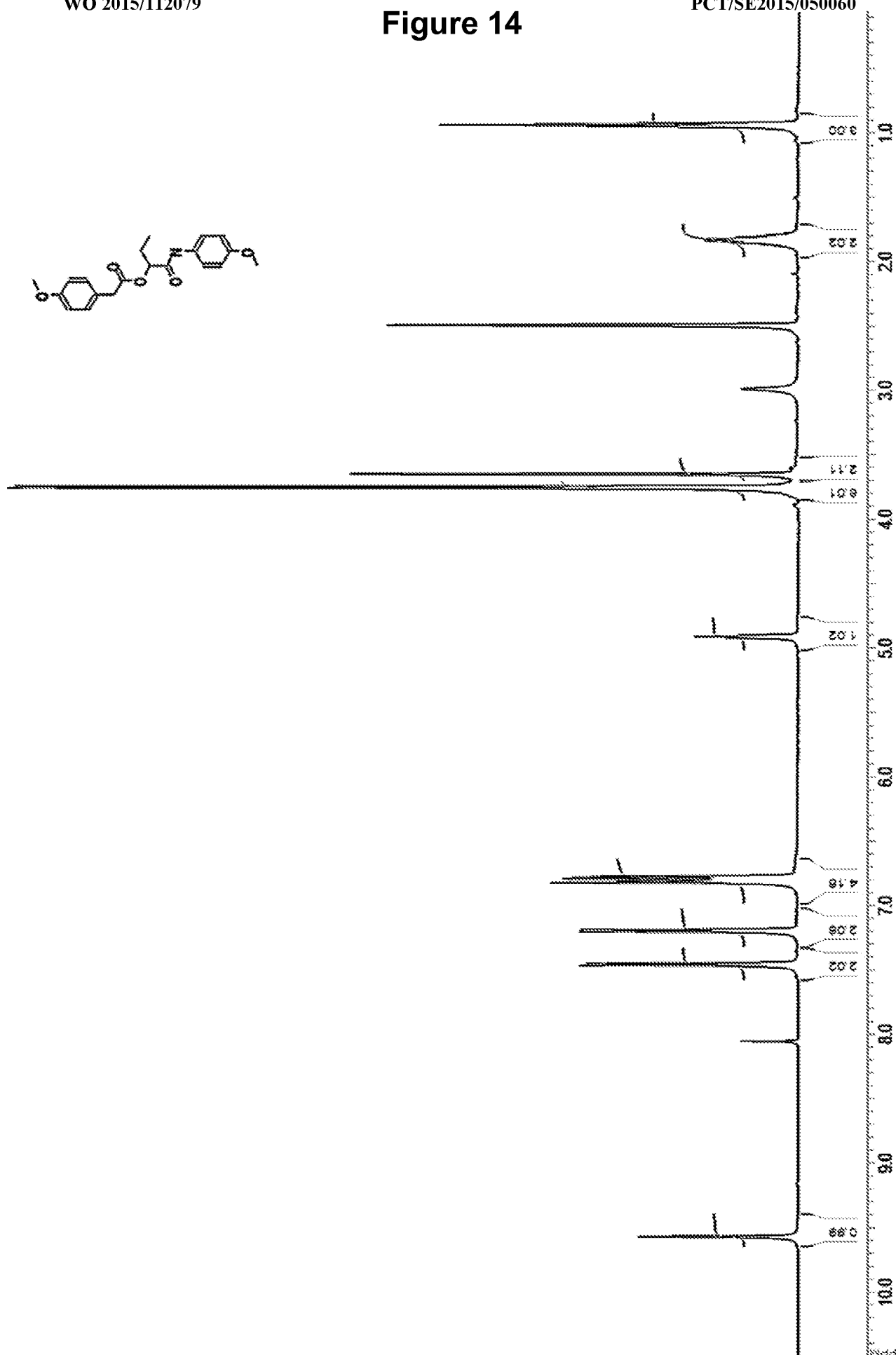


Figure 15

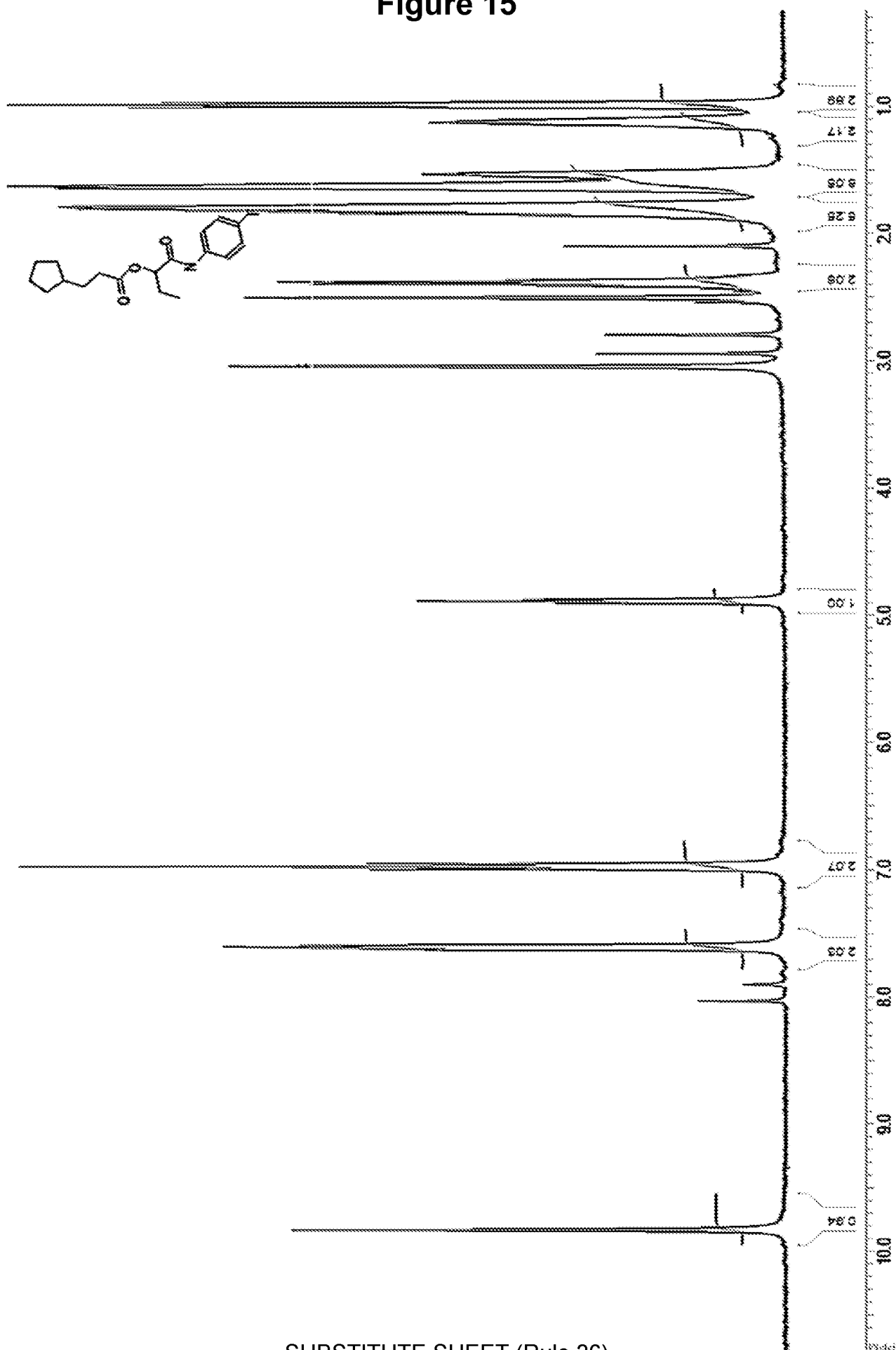
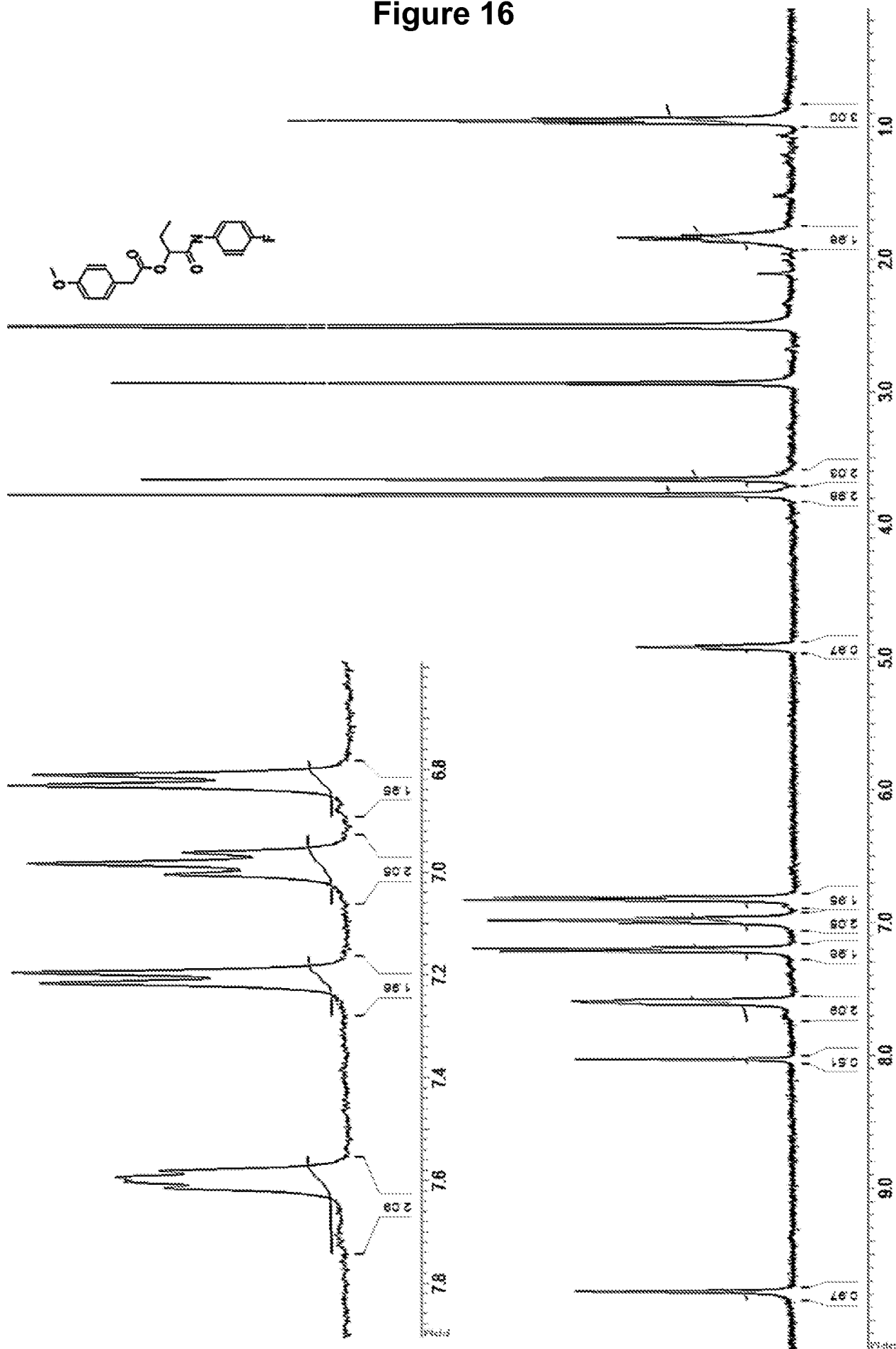


Figure 16



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Figure 17

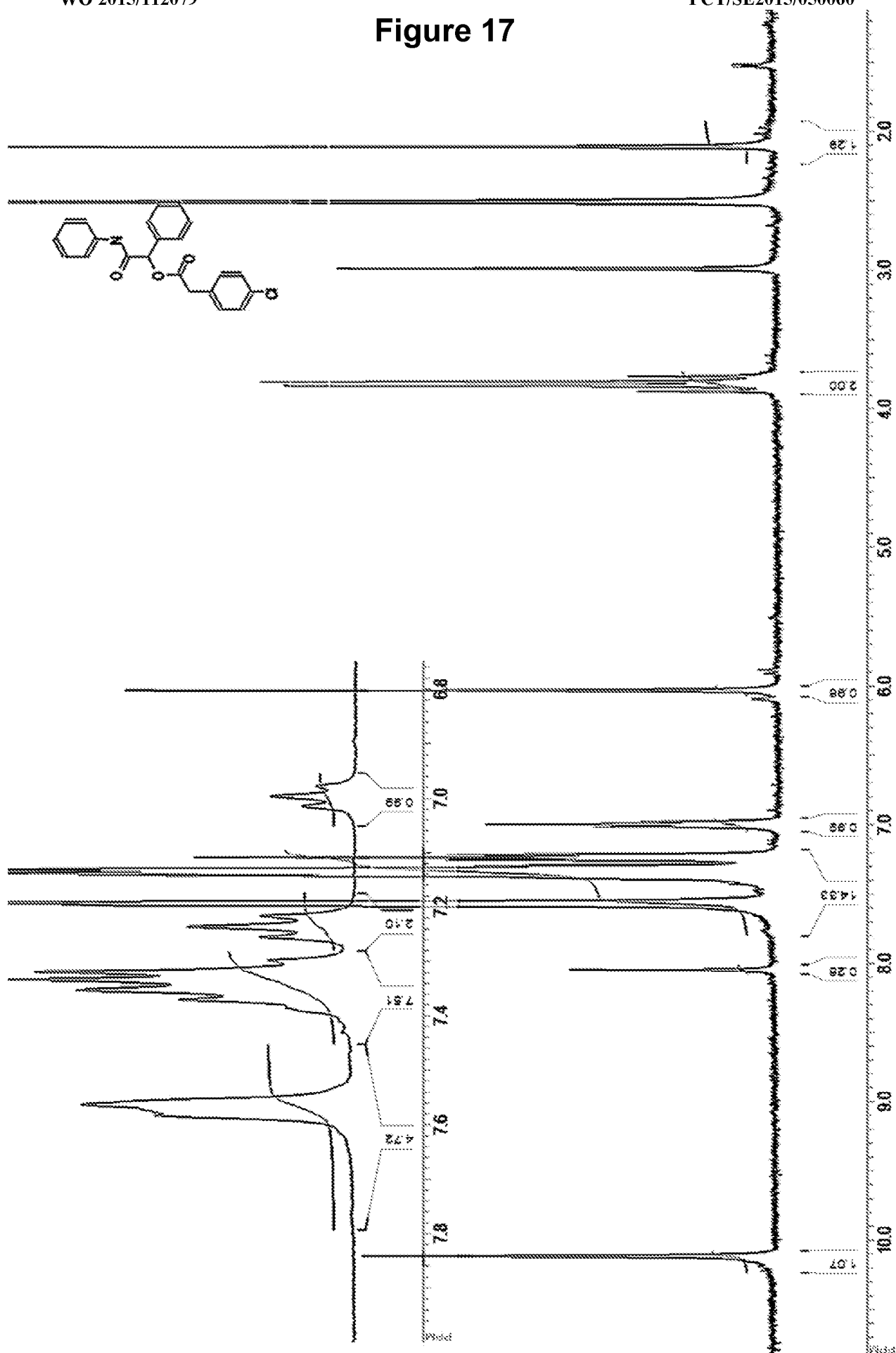
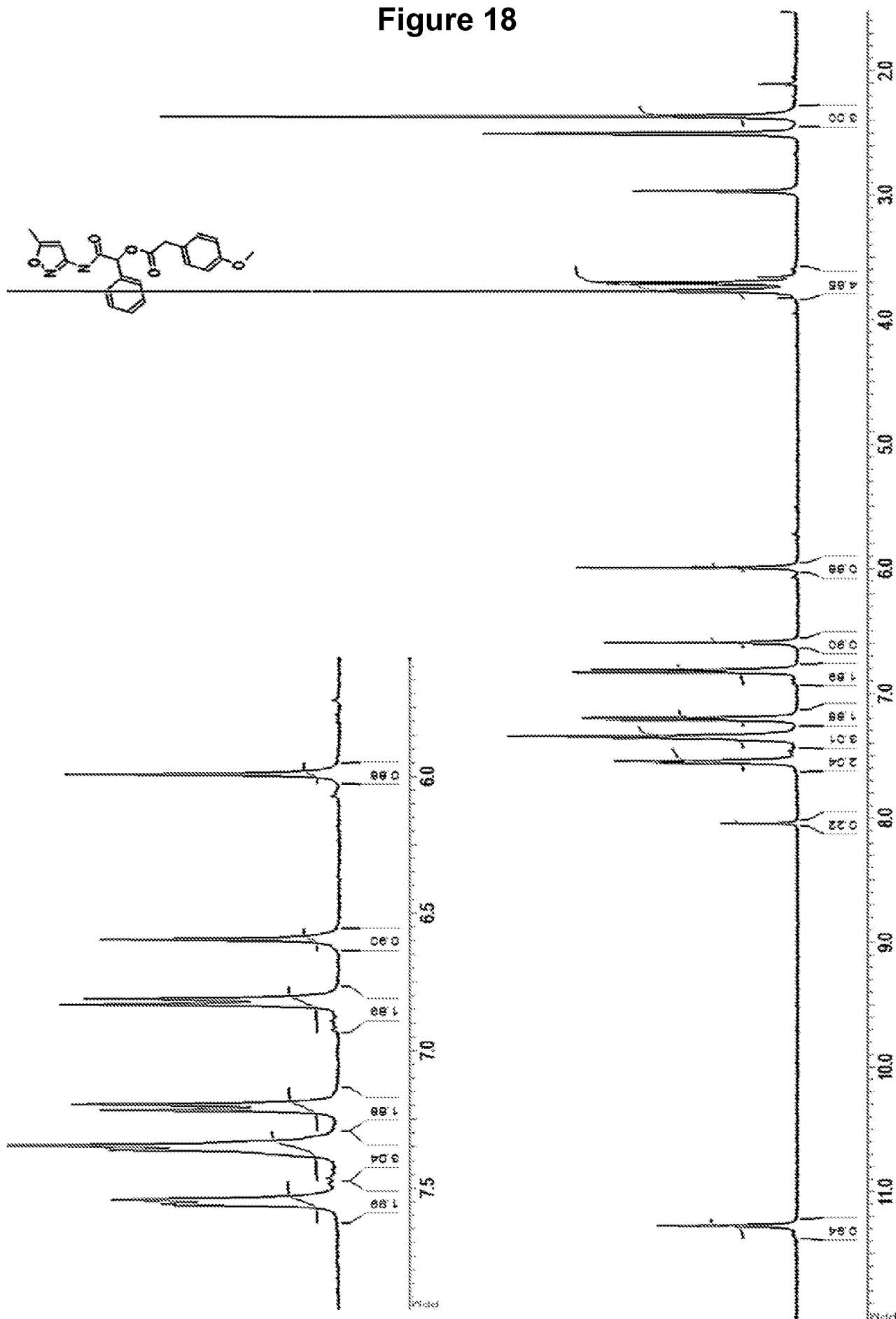


Figure 18



Chemical structure of compound 10 is shown in the top right corner. The structure is a complex molecule with a central benzene ring, a cyclohexyl group, a carboxylic acid group, and a phenyl group.

The ^1H NMR spectrum shows the following peaks and integrations:

- 0.5 ppm (2.08)
- 1.0 ppm (5.74)
- 1.5 ppm (9.26)
- 2.0 ppm (9.26)
- 2.5 ppm (4.06)
- 4.0 ppm (2.00)
- 5.5 ppm (0.90)
- 6.5 ppm (0.92)
- 7.0 ppm (4.98)
- 8.0 ppm (0.92)

Figure 20

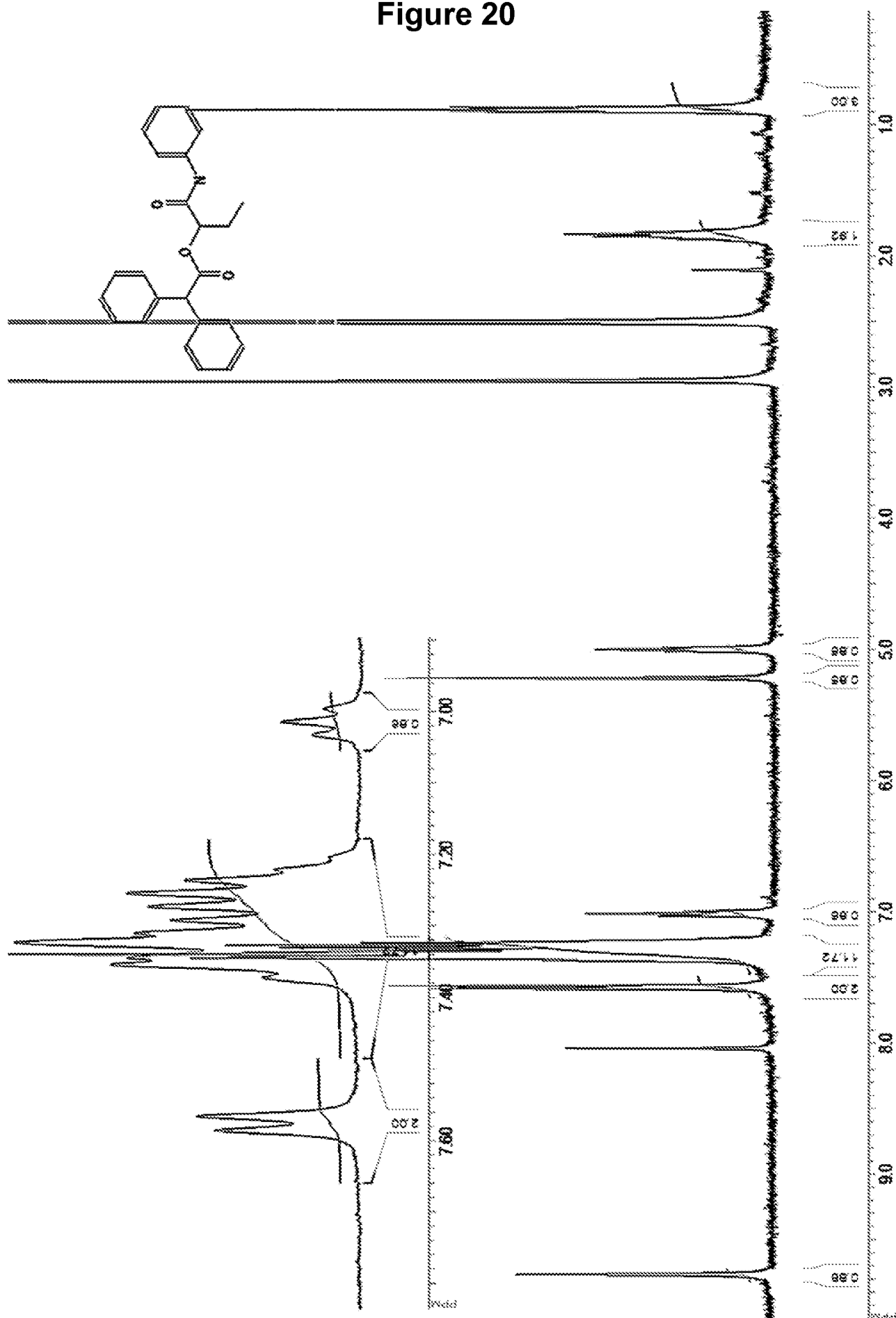


Figure 21

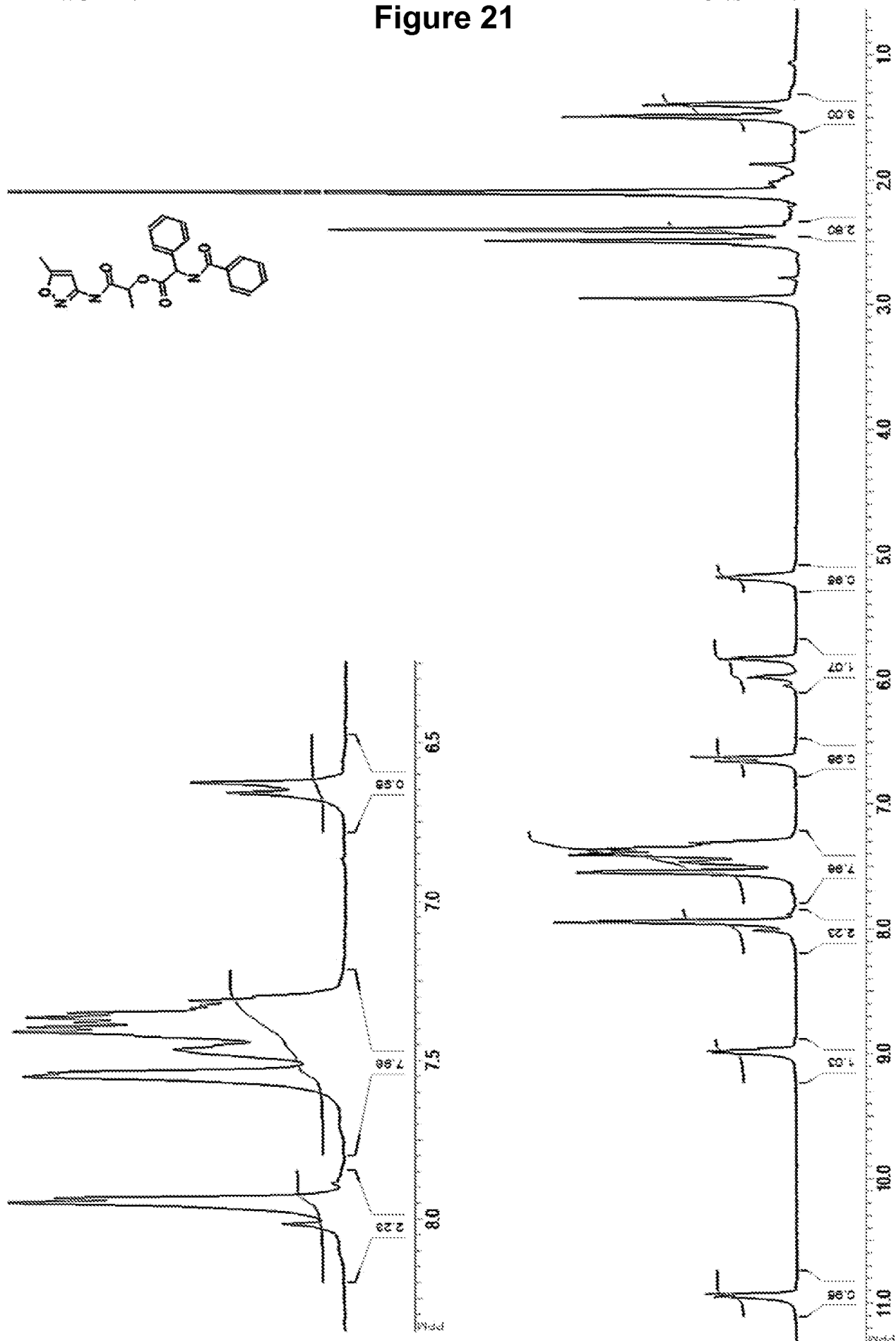
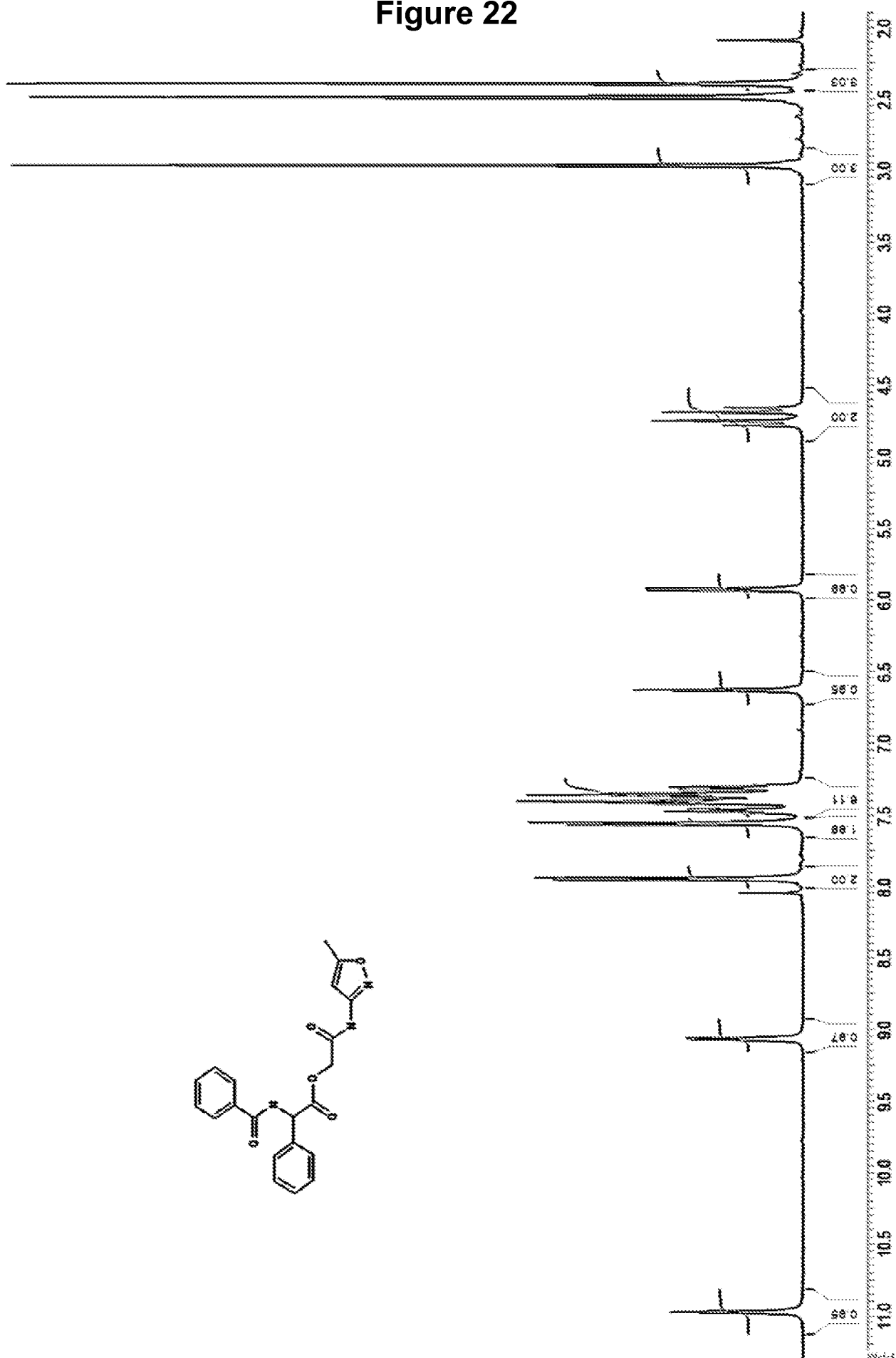
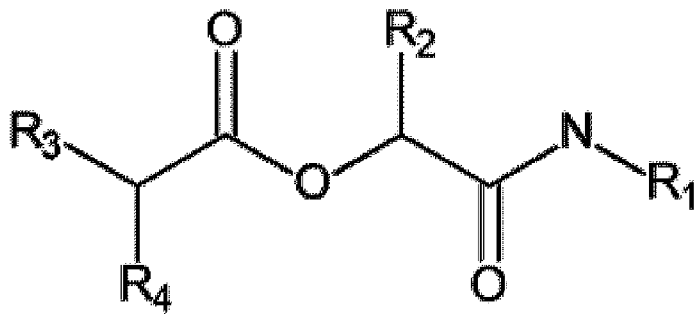


Figure 22





Formula I