

(51) **International Patent Classification:**
A61K 9/00 (2006.01) A61K 31/5365 (2006.01)
A61K 9/20 (2006.01) A61P 31/18 (2006.01)
A61K 47/26 (2006.01) A61K 39/00 (2006.01)
A61K 47/34 (2017.01) C07K 16/10 (2006.01)
A61K 31/4985 (2006.01)

(21) **International Application Number:**
PCT/IB2020/061582

(22) **International Filing Date:**
07 December 2020 (07.12.2020)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
62/945,412 09 December 2019 (09.12.2019) US
62/982,305 27 February 2020 (27.02.2020) US

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

(84) **Designated States** (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) **Title:** PHARMACEUTICAL COMPOSITIONS COMPRISING CABOTEGRAVIR

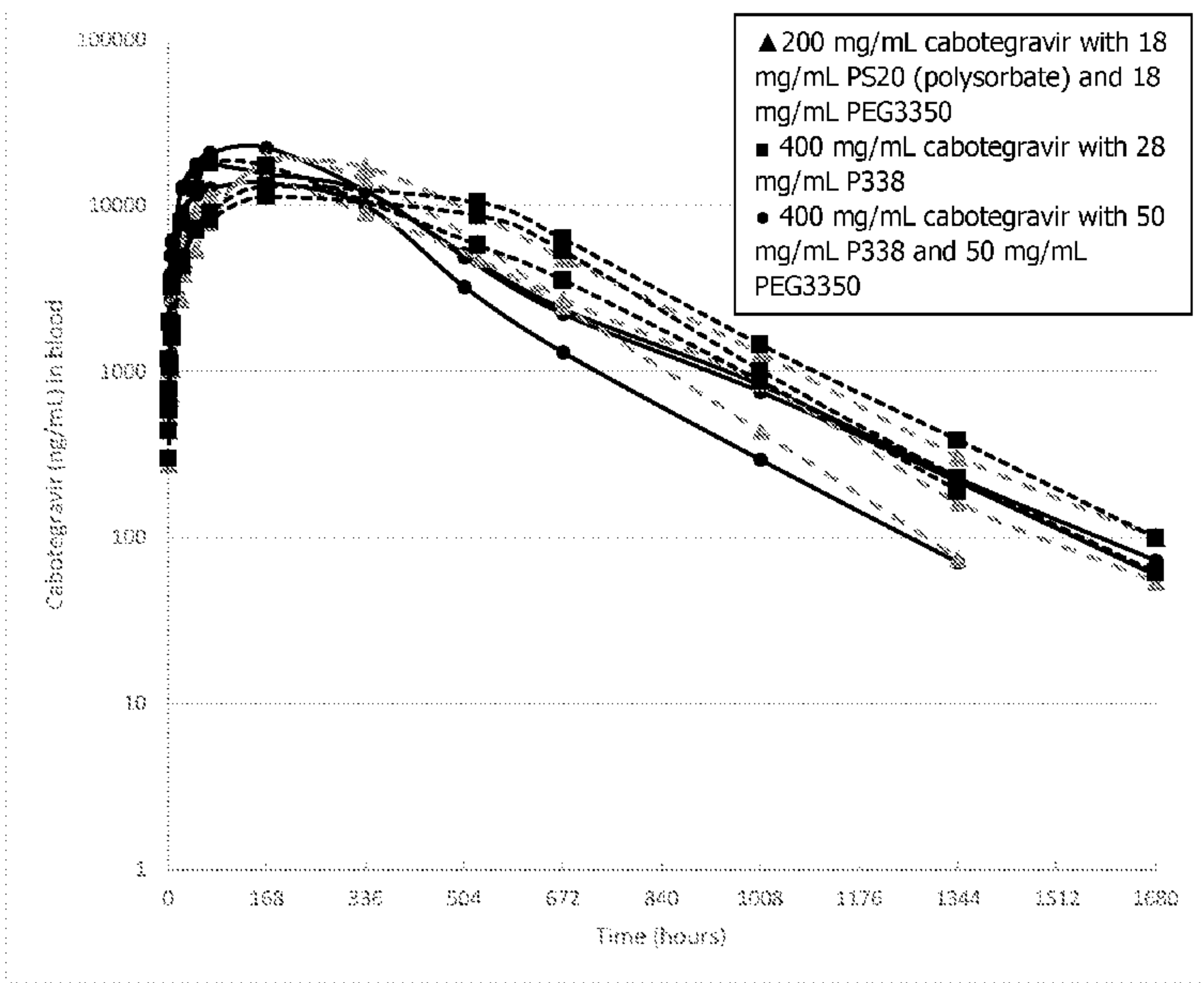


Figure 2

(57) **Abstract:** The present invention relates to Human Immunodeficiency Virus (HIV) treatment. In particular, the invention relates to a pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer useful as a long acting HIV treatment.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

PHARMACEUTICAL COMPOSITIONS COMPRISING CABOTEGRAVIR

FIELD OF THE INVENTION

The invention relates to Human Immunodeficiency Virus (HIV) treatment. In particular,
5 the invention relates to long acting treatment of HIV.

BACKGROUND TO THE INVENTION

Patients with HIV infection commonly undergo complex treatment regimens which involve
taking multiple pills at regular intervals each day. Patient non-compliance is a known problem
10 accompanying these complex HIV treatment regimens and can lead to the emergence of multiple-
drug resistant strains of HIV.

The application of long-acting parenterals has been established in clinical practice for
decades, notably in the areas of contraception, anti-psychotics and opiate addiction. More recently,
long-acting parenterals have been explored for use in the treatment and prevention of HIV. Long-
15 acting injectables have been proposed as a way of overcoming the non-compliance problem with
HIV treatment regimens. Long-acting injectable formulations are in clinical development and
clinical studies have demonstrated prolonged exposures (≥ 30 days) following injection, enabling
dosing at once-monthly intervals.

Achieving an injectable suspension with a high concentration of anti-HIV drug in order to
20 dose less frequently and overcome the non-compliance problem with HIV treatment regimens,
whilst keeping the same injection volume as previous HIV treatment regimens in order to maintain
patient experience is desirable. High concentration suspensions typically suffer from difficulty in
resuspension and particle size growth.

There is a need in the art for a long acting injectable to treat HIV that can be dosed at
25 fewer intervals whilst still achieving the same patient experience and overcoming known difficulties
with high concentration suspensions.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a pharmaceutical composition
30 comprising cabotegravir, or a pharmaceutically acceptable salt thereof, polyethylene glycol (PEG)
and poloxamer.

According to a second aspect of the invention, there is provided a method for the treatment
or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising
administering to said human a therapeutically effective amount of the pharmaceutical composition
35 as defined herein.

According to a third aspect of the invention, there is provided a pharmaceutical composition
as defined herein for use in the treatment or prevention of HIV.

According to a further aspect of the invention, there is provided a kit comprising
cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and a poloxamer.
40

The compositions of the invention may be advantageous in a number of respects. The
compositions of the invention allow a high concentration of cabotegravir to be present in the
composition. Currently there are no marketed suspensions with drug concentration higher than
312 mg/mL. When considering marketed suspensions for any pharmaceutical use, the suspensions
with the highest drug concentrations are ARISTADA INITIO (aripipazole lauroxil, used to treat
45 adults with schizophrenia) and INVEGA TRINZA (paliperidone palmitate, used to treat adults with
schizophrenia) which have solid drug concentrations of 281.25 mg/mL and 312 mg/mL

respectively. The compositions of the present invention enable up to 600 mg/mL of cabotegravir to be present in the composition (for example about 400 mg/mL).

The high concentration of cabotegravir allowed by the compositions of the present invention allows the concentrations to be administered to a patient less frequently than known HIV treatments. Compositions of the present invention also exhibit particle size stability and are able to achieve resuspension after storage.

DESCRIPTION OF DRAWINGS/FIGURES

Figure 1 shows a comparison of resuspension of two suspensions, Figure 1 A shows a suspension comprising cabotegravir, P338 (poloxamer) and PEG3350 (left) and Figure 1 B shows a suspension comprising cabotegravir, P338 and Kollidon 12 (polyvinylpyrrolidone) (right). The left vial shows a mostly clear vial bottom indicating that the suspension was resuspended and decanted. The right vial shows a vial bottom with suspension adhered to the bottom of the vial, indicating that resuspension was not achieved.

Figure 2 shows cabotegravir concentrations in blood of individual rats after a 10 mg/kg intramuscular administration of: a 200 mg/mL cabotegravir with 18 mg/mL PS20 (polysorbate) and 18 mg/mL PEG3350 (▲); 400 mg/mL cabotegravir with 28 mg/mL P338 (■); or 400 mg/mL cabotegravir with 50 mg/mL P338 and 50 mg/mL PEG3350 (●). Formulations also contained mannitol (14 to 30 mg/mL) for tonicity adjustment. 3 rats were used per formulation.

Figure 3 shows cabotegravir concentrations in blood of individual rats after a 10 mg/kg subcutaneous administration of 400 mg/mL cabotegravir with 50 mg/mL P338, 50 mg/mL PEG3350 and 30 mg/mL mannitol (●). 3 rats were used.

Figure 4 shows microscopy images of suspensions. Figure 4A (left) shows suspension 3a which was fully resuspended after storage for 6 months upright at 30°C/65%RH. Figure 4B (right) shows suspension 2a which was not resuspended after storage for 6 months upright at 30°C/65%RH.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term 'pharmaceutical composition' means a composition that is suitable for pharmaceutical use.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

Pharmaceutically acceptable salts include, amongst others, those described in Berge, J. Pharm. Sci., 1977, 66, 1-19, or those listed in P H Stahl and C G Wermuth, editors, *Handbook of Pharmaceutical Salts; Properties, Selection and Use, Second Edition* Stahl/Wermuth: Wiley-VCH/VHCA, 2011 (see <http://www.wiley.com/WileyCDA/WileyTitle/productCd-3906390519.html>). Suitable pharmaceutically acceptable salts can include acid or base addition salts. Suitable pharmaceutically acceptable salts of the invention include base addition salts.

Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (*N*-benzylphenethylamine), benzathine (*N,N'*-dibenzylethylenediamine), *bis*-(2-hydroxyethyl)amine, bismuth, calcium, chlorprocaine, choline, clemizole (1-*p* chlorobenzyl-2-pyrrolidyl)-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltri-amine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

As used herein, the term "treatment" or "treating" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression, invasion, or spread of the condition and reducing or delaying the reoccurrence of the condition in a previously afflicted subject.

As used herein, the term "prevention" or "preventing" refers to precluding the specified condition or symptoms of the condition.

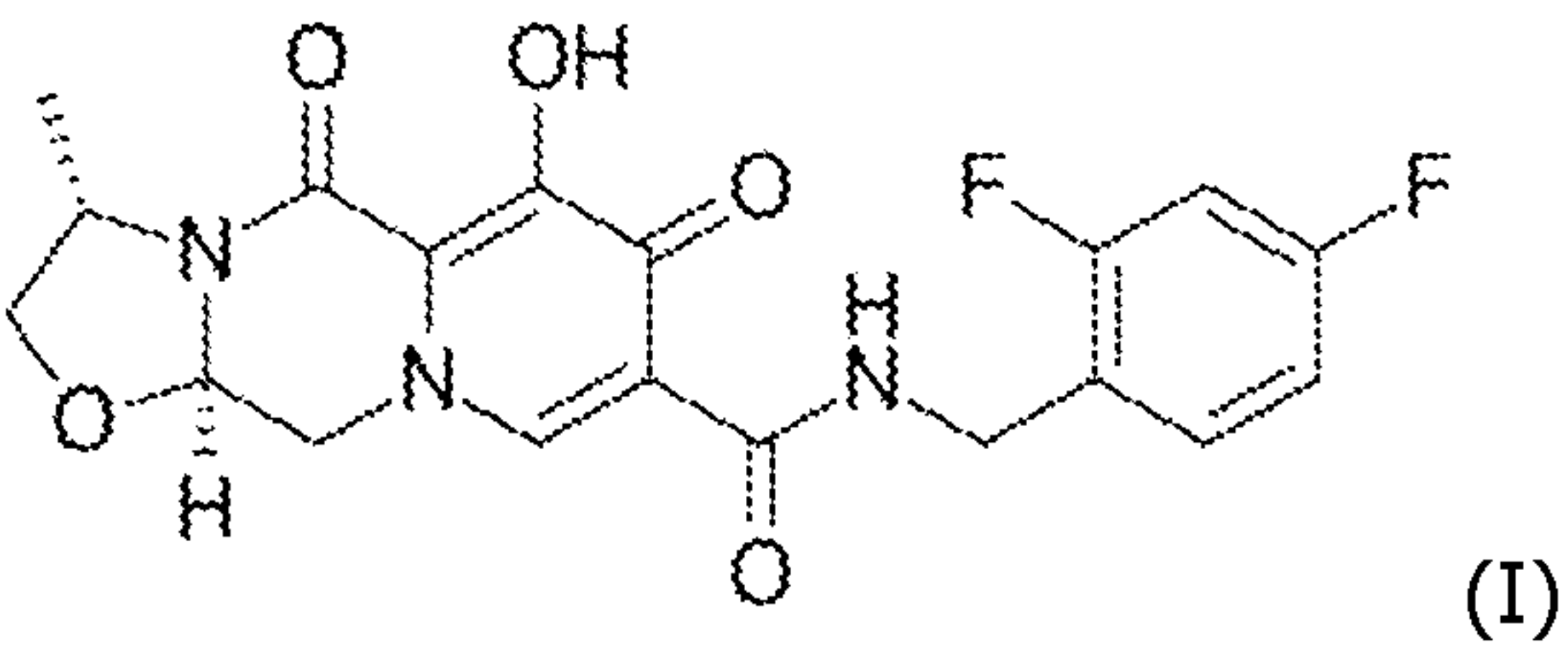
STATEMENT OF THE INVENTION

The present invention provides a pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

The pharmaceutical compositions described herein may be administered by any appropriate route. In a preferred embodiment, the compositions are administered parenterally (including subcutaneous, intramuscular, intravenous, or intradermal). In one embodiment the composition is administered intramuscularly. In another embodiment the composition is administered subcutaneously.

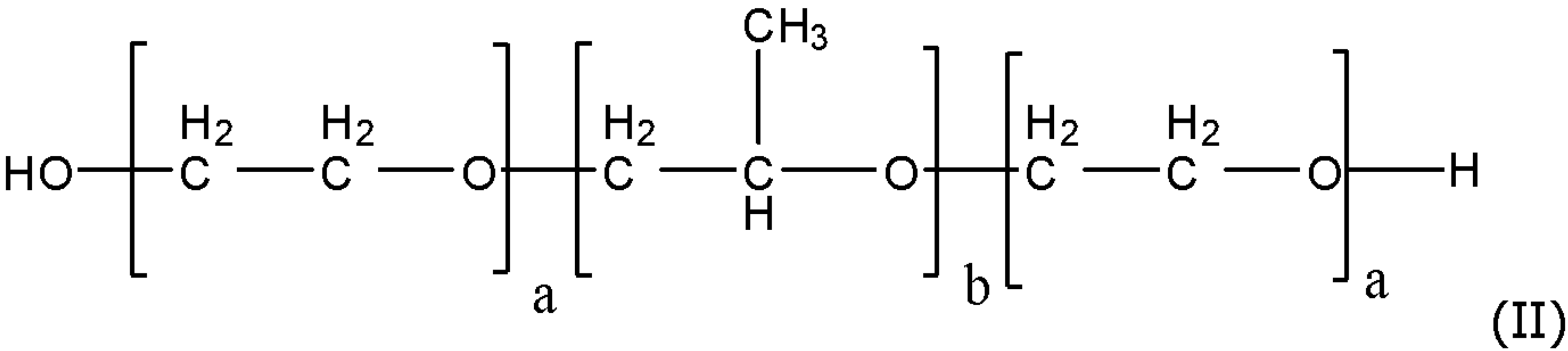
Cabotegravir (*N*-((2,4-Difluorophenyl)methyl)-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro(1,3)oxazolo(3,2-*a*)pyrido(1,2-*d*)pyrazine-8-carboxamide) is described in US 8,129,385 in example Z-1, which example is incorporated herein by reference. Cabotegravir is an integrase strand transfer inhibitor (INSTI) that exhibits subnanomolar potency and antiviral activity against a broad range of HIV-1 strains. Oral administration of Cabotegravir has exhibited acceptable safety and tolerability profiles, a long half-life, and few drug-drug interactions. Cabotegravir has been demonstrated to be efficacious in treatment and prevention of HIV both in oral and parenteral dosage forms, see for instance, Margolis DA, Brinson CC, Eron JJ, et al. 744 and Rilpivirine as Two Drug Oral Maintenance Therapy: LAI116482 (LATTE) Week 48 Results. 21st Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA, Margolis DA, Podzamczar D, Stellbrink H-J, et al. Cabotegravir + Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 48 Results. 21st International AIDS Conference; July 18-22, 2016; Durban, South Africa, Abstract THAB0206LB. Levin: Conference reports for National AIDS Treatment Advocacy Project (NATAP); 2016, and Markowitz M, Frank I, Grant R, et al. ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men. Abstract presented at: 23rd Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2016; Boston, MA.

Cabotegravir is represented by formula (I):



In an embodiment of the invention, cabotegravir is present in the pharmaceutical composition as the free acid.

5 The pharmaceutical compositions of the invention comprise a poloxamer. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (polyethylene glycol). Poloxamers are represented by Formula II. Poloxamers are also known by the trade names Synperonics, Pluronic, and Kolliphor. Poloxamers are commonly named with the letter "P" followed by three digits, the first two digits x 100 give the approximate molecular mass of the polyoxypropylene core, and the last digit x 10 gives the percentage polyoxyethylene content (e.g.,
10 P407 = Poloxamer with a polyoxypropylene molecular mass of 4,000 g/mol and a 70% polyoxyethylene content).



15 In an embodiment of the invention, the poloxamer may have a molecular mass of polyoxypropylene from 2000 to 5000 g/mol, and a polyoxyethylene content of 60% to 90%. In an embodiment of the present invention, the poloxamer may be P237, P338 or P407 (a and b values for these poloxamers can be seen in Table 1). P237, P338 and P407 are commercially available.

20

Poloxamer	a	b
P237	64	37
P338	141	44
P407	101	56

Table 1

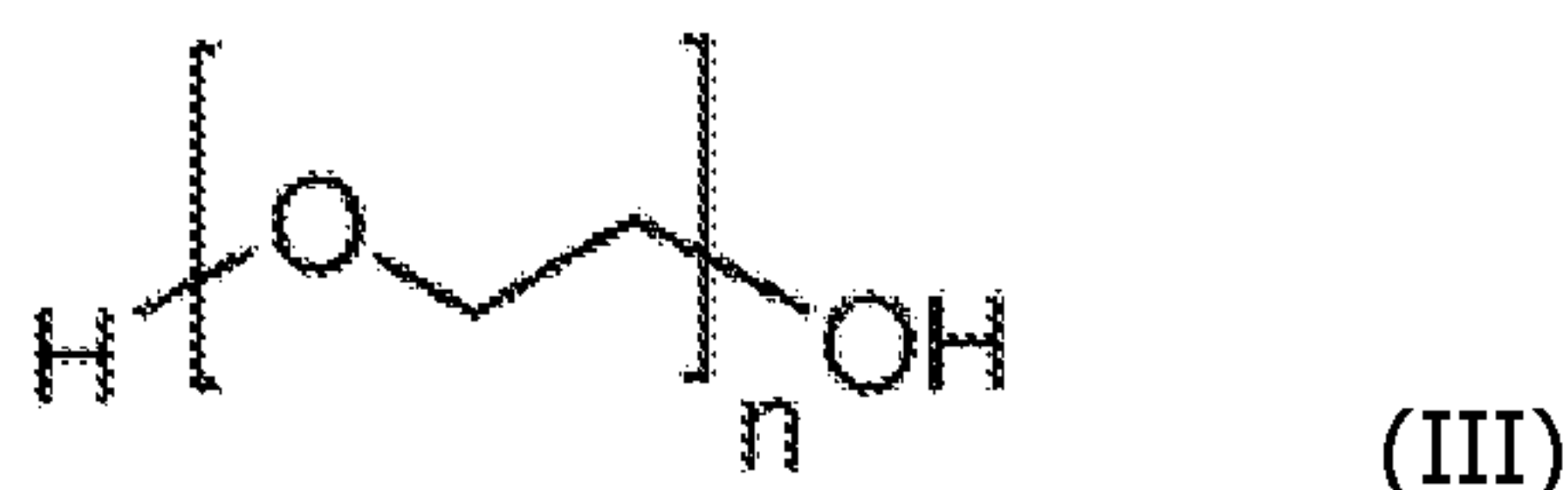
25 In an embodiment of the invention, the poloxamer is P237. In an embodiment the poloxamer is P407. In an embodiment the poloxamer is P338.

It is desirable to have a high concentration of cabotegravir in the composition (for example a cabotegravir concentration of around 400 or around 500 mg/mL). The inventors have found that the use of poloxamer in the composition allows a high concentration of cabotegravir to be present in the pharmaceutical composition. Cabotegravir is present in the composition in particle form. The
30 inventors have found that at high particle concentrations, there are more particle to particle interactions. These particle to particle interactions can lead to an unstable suspension. Poloxamer has both hydrophobic and hydrophilic chains. It is thought that the hydrophobic polyoxypropylene

chains of poloxamer adsorb onto the surface of the cabotegravir particles and thus provide steric hinderance between particles. This provides stabilization against particle aggregation or flocculation. It is thought that the polyethylene glycol chains provide stabilisation through steric hinderance, thus allowing a higher concentration of cabotegravir to be present in the overall composition and minimising the particle to particle interactions usually associated with high particle concentrations.

The inventors have found that the use of poloxamer P237, P407 or P338 gives enhanced physical stability to the pharmaceutical compositions of the invention. Without wishing to be bound by theory, it is thought this enhanced stability comes from the fact that P237, P407 and P338 comprise more polyethylene glycol chains than other commercially available poloxamers.

The pharmaceutical compositions of the invention also comprise polyethylene glycol (PEG). PEG is a polymer of ethylene oxide and is represented by formula (III):



In embodiments of the invention, n may be any suitable number. In an embodiment of the invention PEG has a number average mean molecular weight (M_n) of from 1000 to 8000 g/mol. In an embodiment of the invention PEG has an M_n of from 2500 to 5000 g/mol. In an embodiment of the invention PEG has an M_n of from 3000 to 4000 g/mol. In an embodiment of the invention PEG has an M_n of 3100 to 3700 g/mol. In an embodiment of the invention, PEG is PEG 3350 *i.e.* PEG has an M_n of 3350 g/mol. PEG3350 is commercially available.

Without wishing to be bound by theory, the inventors believe that PEG acts as a stabilizer in the compositions of the present invention, further stabilizing the cabotegravir alongside the PEG chains that are present in the poloxamer. As a non-adsorbing polymer, it is thought that PEG stabilizes the compositions of the present invention through increase in viscosity and providing steric repulsions between particles in the suspension.

The combination of PEG and poloxamer enables the high cabotegravir concentration described above to be achieved. This enables the composition of the invention to treat HIV in a patient for up to 6 months. In an embodiment the composition of the invention can treat HIV in a patient for up to 3 months, therefore enabling dosing once every month, 2 months or 3 months. In an embodiment about 1 mL to 3 mL of the pharmaceutical composition is delivered to a patient. In comparison with known and proposed cabotegravir compositions, the present invention allows for a higher dose to be delivered to the patient with less frequent dosing while keeping injection volume the same as for previous products.

In an embodiment of the invention the composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 407. In an alternative embodiment of the invention, the pharmaceutical composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 338. In an alternative embodiment of the invention, the pharmaceutical composition comprises cabotegravir, polyethylene glycol 3350 and poloxamer 237.

In an embodiment of the invention, the pharmaceutical composition comprises from 350 to 600 mg/mL of cabotegravir. In an embodiment of the invention, the pharmaceutical composition comprises from 350 to 500 mg/mL of cabotegravir. In another embodiment, the pharmaceutical composition comprises 380 to 420 mg/mL of cabotegravir. In another embodiment, the pharmaceutical composition comprises about 400 mg/mL of cabotegravir. In an alternative embodiment the pharmaceutical composition comprises about 500 mg/mL of cabotegravir

In an embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 4 to 50 mg/mL. In another embodiment the pharmaceutical composition comprises a poloxamer concentration of from 20 to 50 mg/mL. In an embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 30 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a poloxamer concentration of from 35 to 40 mg/mL.

As described above, the PEG chains in poloxamer provide stabilisation by steric hinderance, therefore it is possible that 0 mg/mL of PEG may be present in the composition. However, a composition comprising poloxamer and PEG provides additional stability to the composition, particularly particle size stability, and is preferred. A pharmaceutical composition comprising a polyethylene glycol concentration of 0 to 50 mg/mL. is disclosed herein.

In an embodiment of the invention, the pharmaceutical composition comprises a polyethylene glycol concentration of from more than 0 to 75 mg/mL. In another embodiment, the pharmaceutical composition comprises a PEG concentration of 5 to 50 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 20 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 30 to 40 mg/mL. In another embodiment, the pharmaceutical composition comprises a polyethylene glycol concentration of from 32 to 38 mg/mL.

In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer.

In an embodiment of the invention the pharmaceutical composition is as described in Table 2a:

Ingredient	Concentration (mg/mL)
Cabotegravir	About 400.0
Poloxamer 338	4 – 50
Polyethylene Glycol 3350	>0 – 75
Mannitol	20 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)

Table 2a

In an embodiment, the pharmaceutical composition is as described in Table 2b:

Ingredient	Concentration (mg/mL)	Lower allowed Concentration (mg/mL)	Higher allowed Concentration (mg/mL)
Cabotegravir	400	320	500
Poloxamer 338	38	30	47.5
Polyethylene Glycol 3350	35	28	43.7
Mannitol	20	16	25

Table 2b

In a further embodiment, the composition is as described in Table 2c:

Ingredient	Concentration (mg/mL)	
Cabotegravir	About 500.0	About 500.0
Poloxamer 338	35 – 50	--
Poloxamer 407	--	35 – 50
Polyethylene Glycol 3350	>0 – 75	>0 – 75
Mannitol	40 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)	40 (Adjusted to be isotonic within 285 – 310 mOsmol/kg)

Table 2c

5 The pharmaceutical composition of the present invention comprises particles of crystalline cabotegravir. In an embodiment the median particle diameter is from 0.1 μm to 10.0 μm. In another embodiment the median particle diameter is between 0.1 μm and 0.4 μm. In another embodiment the median particle diameter is from 0.15 μm to 0.25 μm. In another embodiment the median particle diameter is about 0.2 μm. The inventors have found that compositions with a median particle diameter of from 0.15 μm to 0.25 μm e.g. of about 0.2 μm have improved resuspension over compositions with larger particle sizes (as used here 'resuspension' means dispersion of sedimented product to a free-flowing suspension). The median particle diameter may be measured by any suitable method, for example, median particle diameter may be measured by laser diffraction (Malvern Mastersizer 3000) as described in the Examples section herein.

15 Pharmaceutical compositions of the present invention may retain their particle size over time. This is advantageous as increase in particle size can lead to poor resuspension. Poor resuspension can, for example, make it difficult for healthcare professionals to withdraw a pharmaceutical composition from, for example, a vial or flask. Particle size stability is believed to be important for resuspension of the composition over time and reduces the risk of changing pharmacokinetics.

20 In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer, wherein the median particle diameter of cabotegravir is from 0.1 μm to 10.0 μm.

25 In an embodiment, the pharmaceutical composition of the invention comprises cabotegravir or a pharmaceutically acceptable salt thereof, >0 to 75 mg/mL of PEG and 4 to 50 mg/mL of poloxamer, wherein the median particle diameter of cabotegravir is from 0.15 μm to 0.25 μm.

30 In an embodiment the composition of the invention further comprises a tonicity adjuster. The tonicity adjuster may be selected from any suitable tonicity adjuster. In an embodiment of the invention, the tonicity adjuster adjusts tonicity to be within 250 to 350 mOsmol/kg. In another embodiment the tonicity adjuster adjusts tonicity to be within 285 to 310 mOsmol/kg. In an embodiment mannitol is used as the tonicity adjuster. In an embodiment of the invention, the mannitol adjusts tonicity to be within 250 to 350 mOsmol/kg. In another embodiment the mannitol

adjusts tonicity to be within 285 to 310 mOsmol/kg. In an embodiment of the invention mannitol is present in the pharmaceutical composition at a concentration of 15 to 30 mg/mL.

In an embodiment the composition of the invention has a pH of about 4 or greater. A pH of about 4 or more reduces pain to the patient if the composition is administered via injection.

5 In an embodiment the pharmaceutical composition of the present invention further comprises at least one hyaluronidase. As used herein, the term 'hyaluronidase' refers to any enzyme of the family of hyaluronidases that catalyse the degradation of hyaluronic acid, a constituent of the extracellular matrix. Degradation of hyaluronic acid causes subcutaneous and intramuscular tissues to become more permeable allowing fluid or medication to diffuse into the
10 extracellular matrix and be taken up by the surrounding tissue more quickly. Without wishing to be bound by theory, it is thought that administering a pharmaceutical composition of the present invention in combination with a hyaluronidase may allow administration of a larger volume of the pharmaceutical composition thus allowing dosing frequency to be reduced. In addition, it is believed that the use of at least one hyaluronidase will provide an improved tolerability for the
15 pharmaceutical composition at the site of administration.

In a second aspect, the present invention provides a method for the treatment or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising administering to said human a therapeutically effective amount of a pharmaceutical composition as defined herein.

20 In one embodiment the method comprises administering the pharmaceutical composition parenterally. In an embodiment the pharmaceutical composition is administered intramuscularly. In an embodiment the pharmaceutical composition is administered subcutaneously.

In an embodiment around 1mL to around 3 mL of the pharmaceutical composition is administered to the human. In an embodiment around 1mL of the pharmaceutical composition is
25 administered to the human. In another embodiment around 2 mL of the pharmaceutical composition is administered to the human. In an embodiment around 3 mL of the pharmaceutical composition is administered to the human.

In an embodiment the pharmaceutical composition is administered to the human once every 1, 2 or 3 months. In an embodiment the pharmaceutical composition is administered to the
30 human once every month. In an alternative embodiment, the pharmaceutical composition is administered once every 2 months. In an alternative embodiment the pharmaceutical composition is administered once every 3 months.

In one embodiment, the pharmaceutical composition is delivered to a patient once every month. The pharmaceutical composition may be administered by any suitable means. In one
35 embodiment, the pharmaceutical composition is self-administered by a patient. The term "self-administered", as used herein, means administration by someone other than a healthcare professional, for example, a patient may administer the pharmaceutical composition to themselves, or someone else, other than a healthcare professional may administer the pharmaceutical composition to the patient. In this embodiment the pharmaceutical composition may be
40 administered subcutaneously via injection. The subcutaneous injection may comprise 1 to 1.5 mL of the pharmaceutical composition. In one embodiment of the invention the pharmaceutical composition is self-administered once monthly by subcutaneous injection.

In an alternative embodiment the pharmaceutical composition is delivered to a patient once every three months. The pharmaceutical composition may be administered by any suitable
45 means. In one embodiment the pharmaceutical composition is administered intramuscularly via injection. In an embodiment the intramuscular injection is administered by a healthcare professional. The intramuscular injection may comprise 1 to 3 mL of the pharmaceutical

composition. In an embodiment of the invention the pharmaceutical composition is administered once every 3 months via intramuscular injection.

In an embodiment the pharmaceutical compositions of the present invention are administered in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

In an embodiment a pharmaceutical compound described herein is administered in combination with a broadly neutralising antibody. In an embodiment the neutralising antibody is N6-LS. N6-LS is a broadly neutralising antibody, which comprises (a) a heavy chain variable region (VH) comprising a heavy chain complementarity determining region (HCDR)1, a HCDR2, and a HCDR3 of the VH set forth as SEQ ID NO: 1; (b) a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1, a LCDR2, and a LCDR3 of the VL set forth as SEQ ID NO: 2 or a VL comprising an amino acid sequence at least 90 percent identical to one of SEQ ID NO: 2; or (c) a combination of (a) and (b); further comprising an IgG1 constant domain comprising M428L and N434S mutations; and wherein the antibody or antigen binding fragment specifically binds to HIV-1 gp120 and neutralizes HIV-1 infection.

SEQ ID NO: 1 is the amino acid sequence of the VH of the N6 mAb disclosed in patent application PCT/US2016/023145. SEQ ID NO: 2 is the amino acid sequence of the VL of the N6 mAb disclosed in patent application PCT/US2016/023145. SEQ ID NO: 1 and SEQ ID NO: 2 are described below:

SEQ ID NO 1:

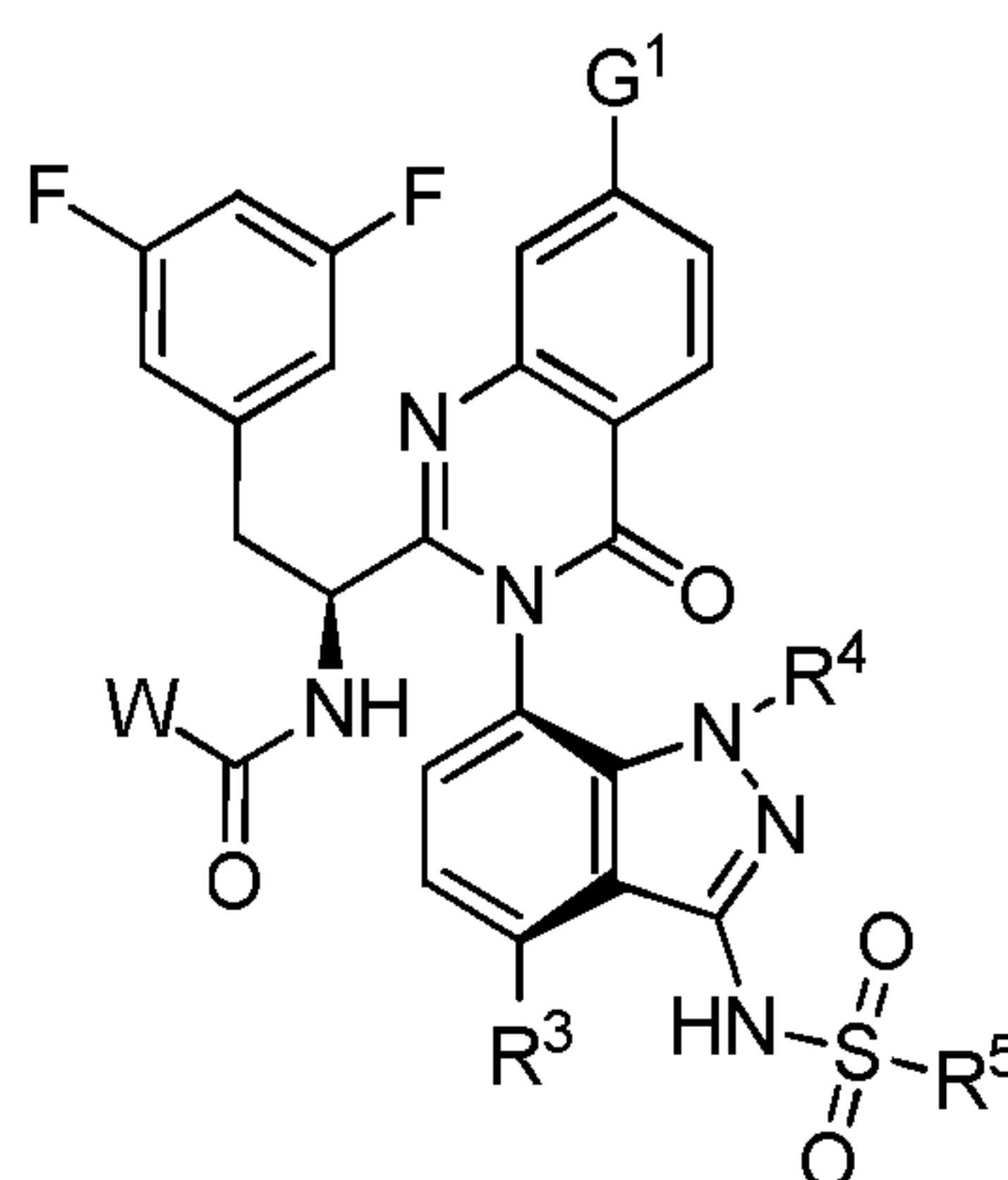
RAHLVQSGTAMKKPGASVRVSCQTSGYTFTAHLFWFRQAPGRGLEWVGWIKPQYGAVNFGGGFRDRVTL
TRDVYREIAYMDIRGLKPDDTAVYYCARDRSYGDSSWALDAWGQGTTVWSA

SEQ ID NO: 2:

YIHVTQSPSSLVSIGDRVTINCQTSQGVGSDLHWYQHKPGRAPKLLIHHTSSVEDGVPSRFSGSGFHTS
FNLTISDLQADDIATYYCQVLQFFGRGSRLHIK

In an embodiment, a pharmaceutical composition described herein is administered in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI).

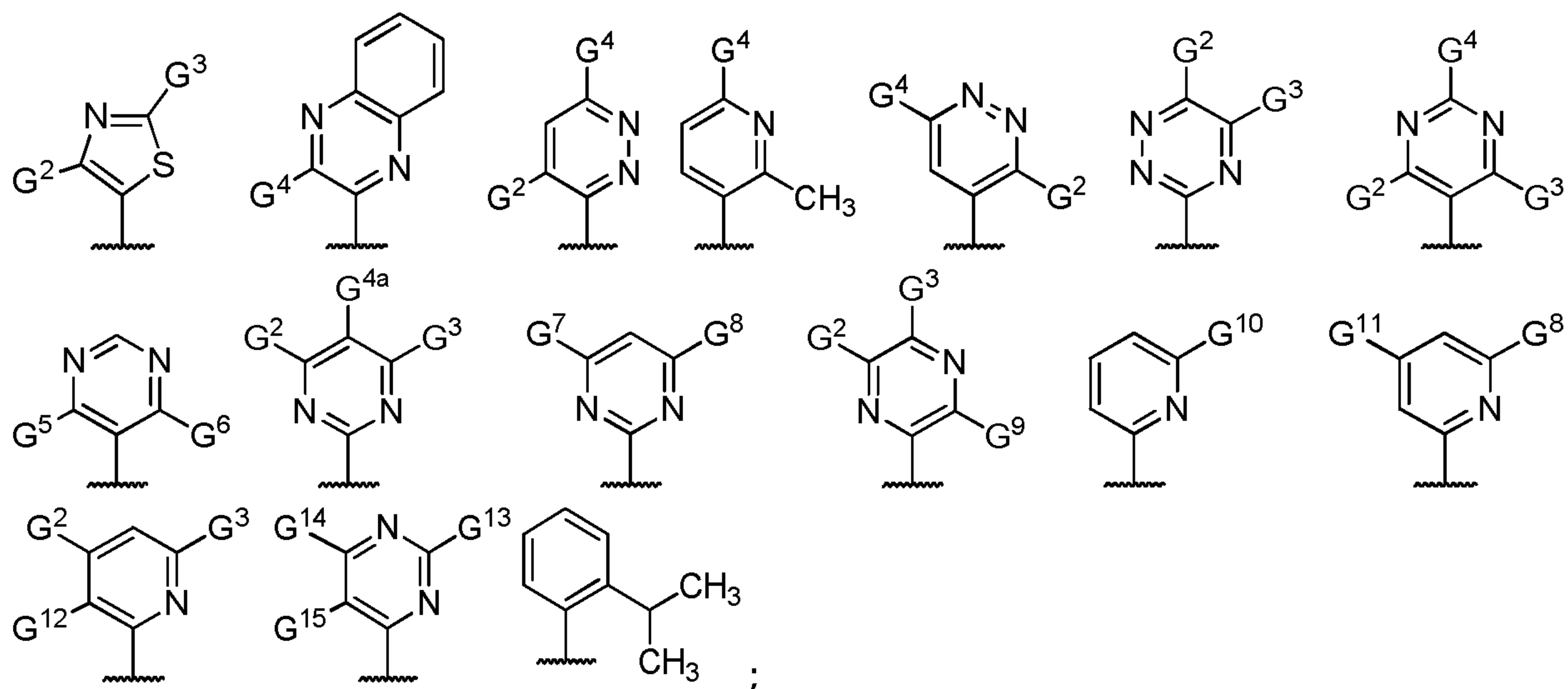
The pharmaceutical composition may be administered in combination with a capsid inhibitor. In an embodiment the capsid inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

G1 is phenyl substituted once with -N(CH₃)S(O₂)CH₃, -S(O₂)C(CH₃)₃, -CHF₂, -CF₃, -OCHF₂, -OCF₃, or -C(CH₃)₂OH, with the proviso that when G1 is -CHF₂ or CF₃, G1 is not in the para position or G1 is one of the following:



G² and G³ are independently selected from is H or -CH₃;

5 G⁴ is H, -CH₃, or -OCH₃;

G^{4a} is -CH₃, or -OCH₃;

G⁵ is -CH₃, or CH₂CH₃;

G⁶ is H, -CH₃, or CH₂CH₃;

G⁷ is ethyl, isopropyl, *tert*-butyl, -CHF₂, or -CF₃;

10 G⁸ is H, methyl, ethyl, -CHF₂, -CF₃, -OCH₃, or -OCH₂CH₃;

G⁹ is ethyl, isopropyl, cyclopropyl, -CH₂OH, -OCH₃;

G¹⁰ is ethyl, isopropyl, cyclopropyl, *tert*-butyl, -CHF₂, or -CF₃;

G¹¹ is methyl, -OCH₃, -CHF₂, -CF₃, -S(O₂)CH₃;

G¹² is F, -CH₃, -CHF₂, -CF₃, -OCH₃, -S(O₂)CH₃;

15 G¹³ is C₁-C₄alkyl, C₁-C₆cycloalkyl, -CH₂O(C₁-C₃alkyl);

G¹⁴ is H, C₁-C₄alkyl, -CHF₂, -CF₃, -O(C₁-C₃alkyl);

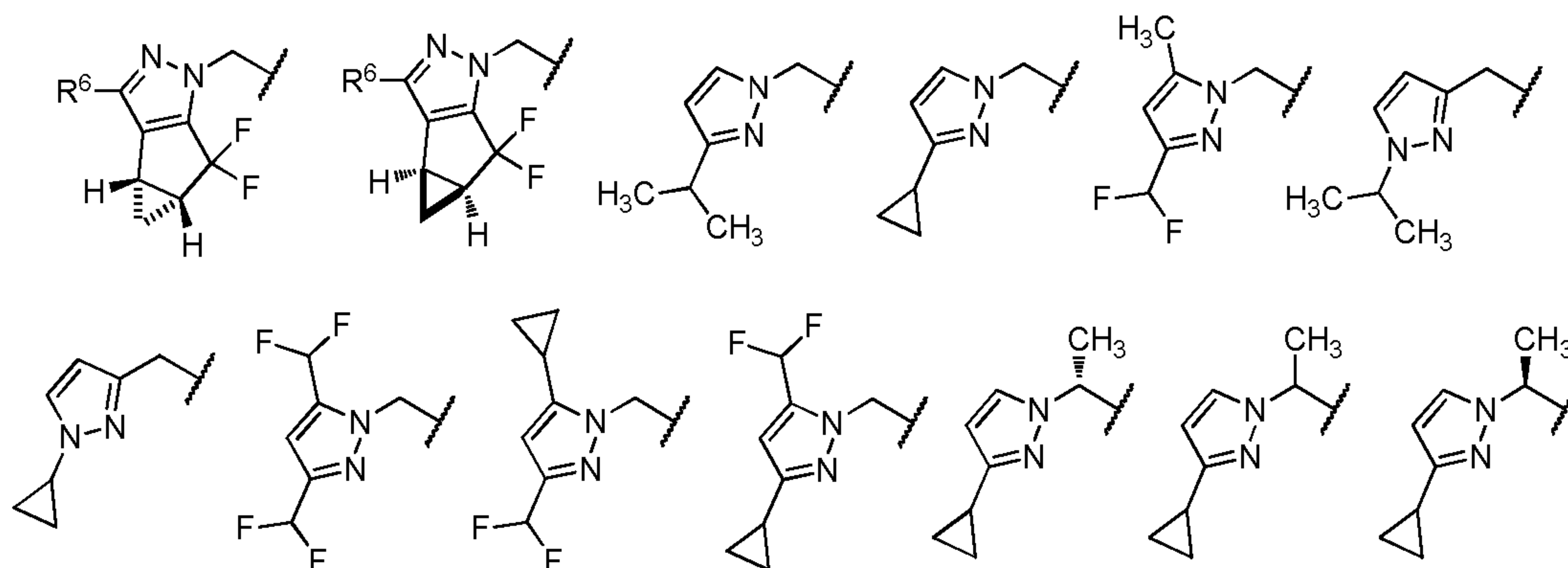
G¹⁵ is H, F, -CH₃, or OCH₃;

R³ is H, F, Cl, -CH₃, or -OCH₃;

R⁴ is H or C₁-C₃alkyl wherein C₁-C₃alkyl is optionally substituted with 1-3 fluorines;

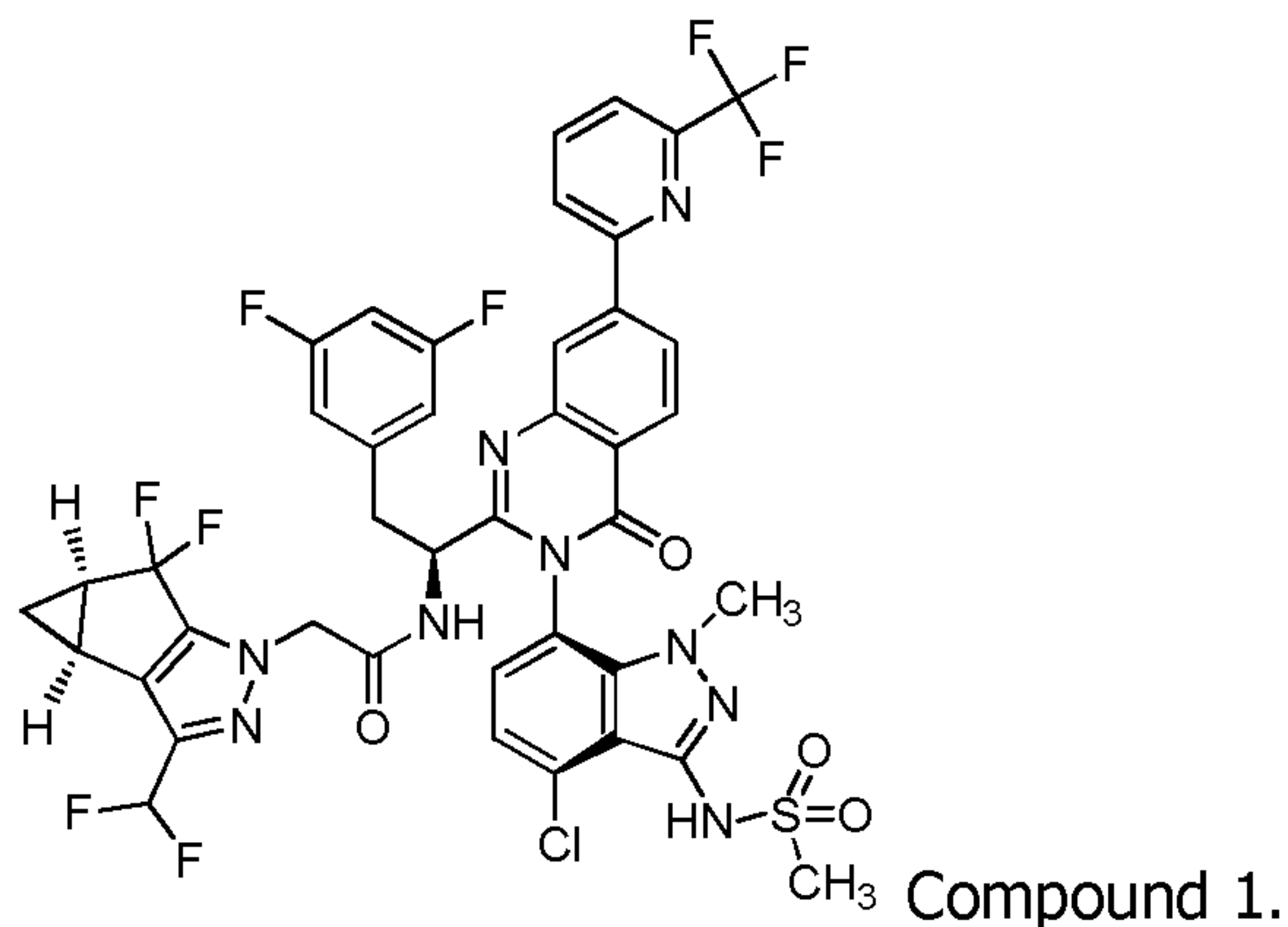
20 R⁵ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

W is selected from:



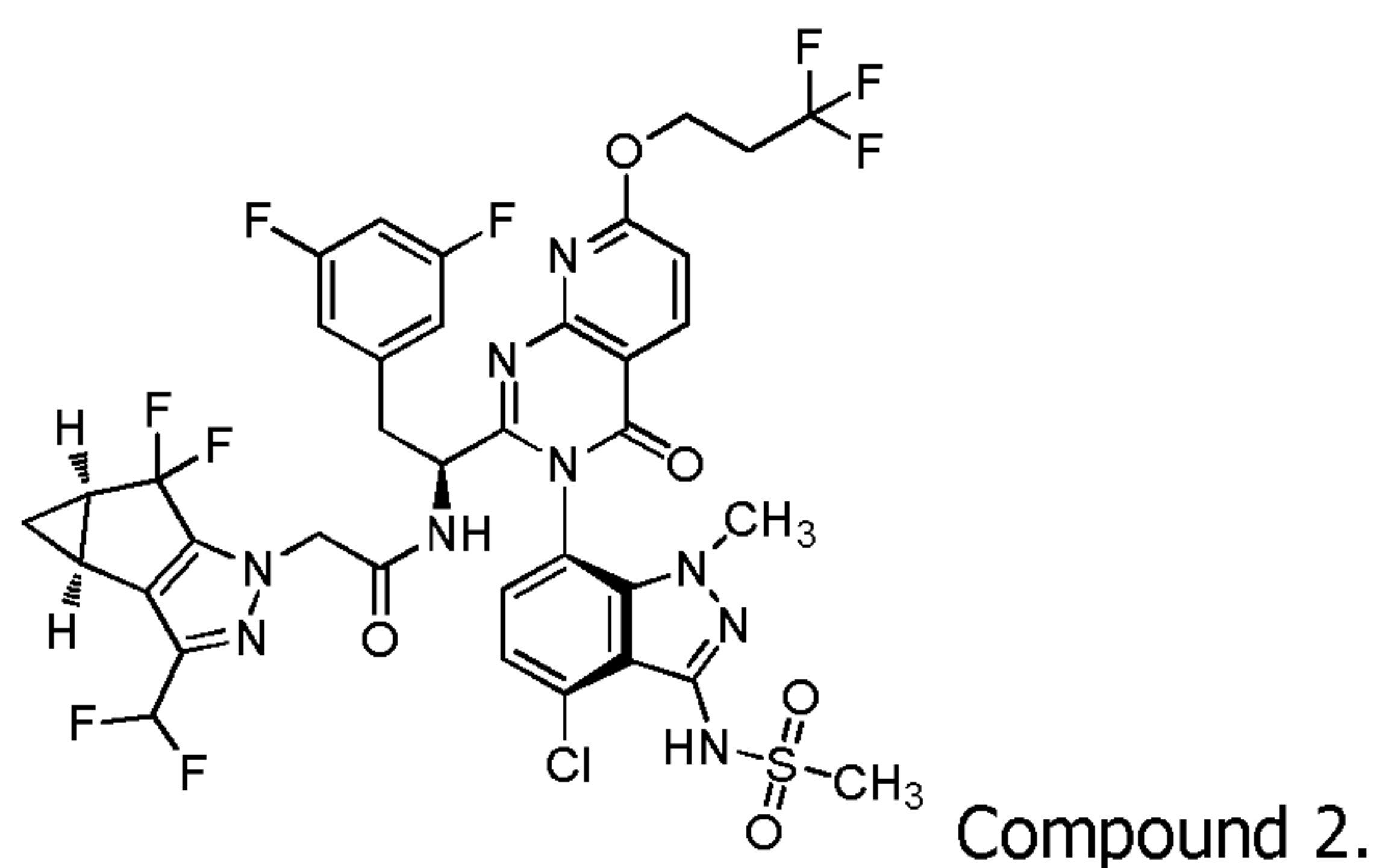
where R⁶ is methyl optionally substituted with 1 to 3 fluorines.

25 Compounds of Formula I are described in WO2020/084492 which is incorporated by reference. In an embodiment the capsid inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is described in WO 2020/084492 as Example 59 which example is incorporated herein by reference.



In an embodiment the capsid inhibitor is Compound 2 pharmaceutically acceptable salt thereof. Compound 2 is described in patent application number PCT/IB2020/055653 as Example 1, which example is incorporated herein by reference.

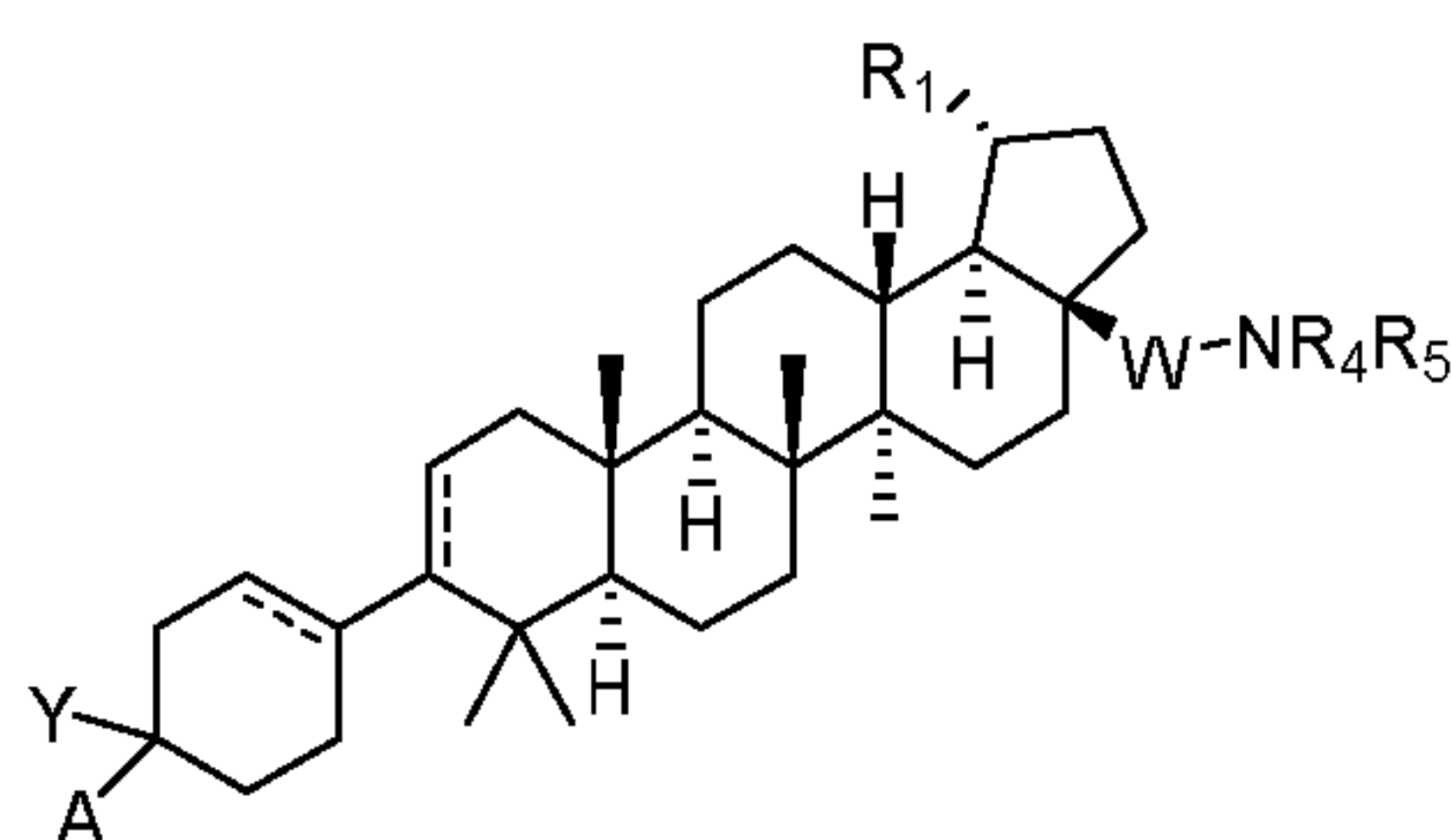
5



In an alternative embodiment, the capsid inhibitor is Lenacapavir.

The pharmaceutical composition may be administered in combination with a maturation inhibitor. In an embodiment the maturation inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof:

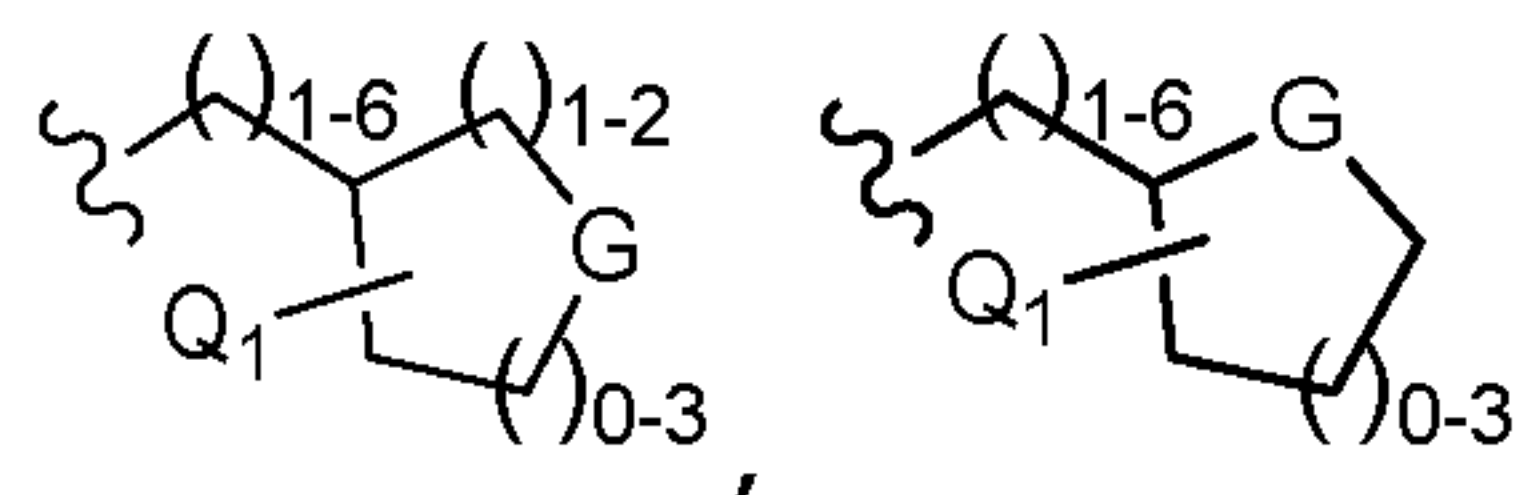
10



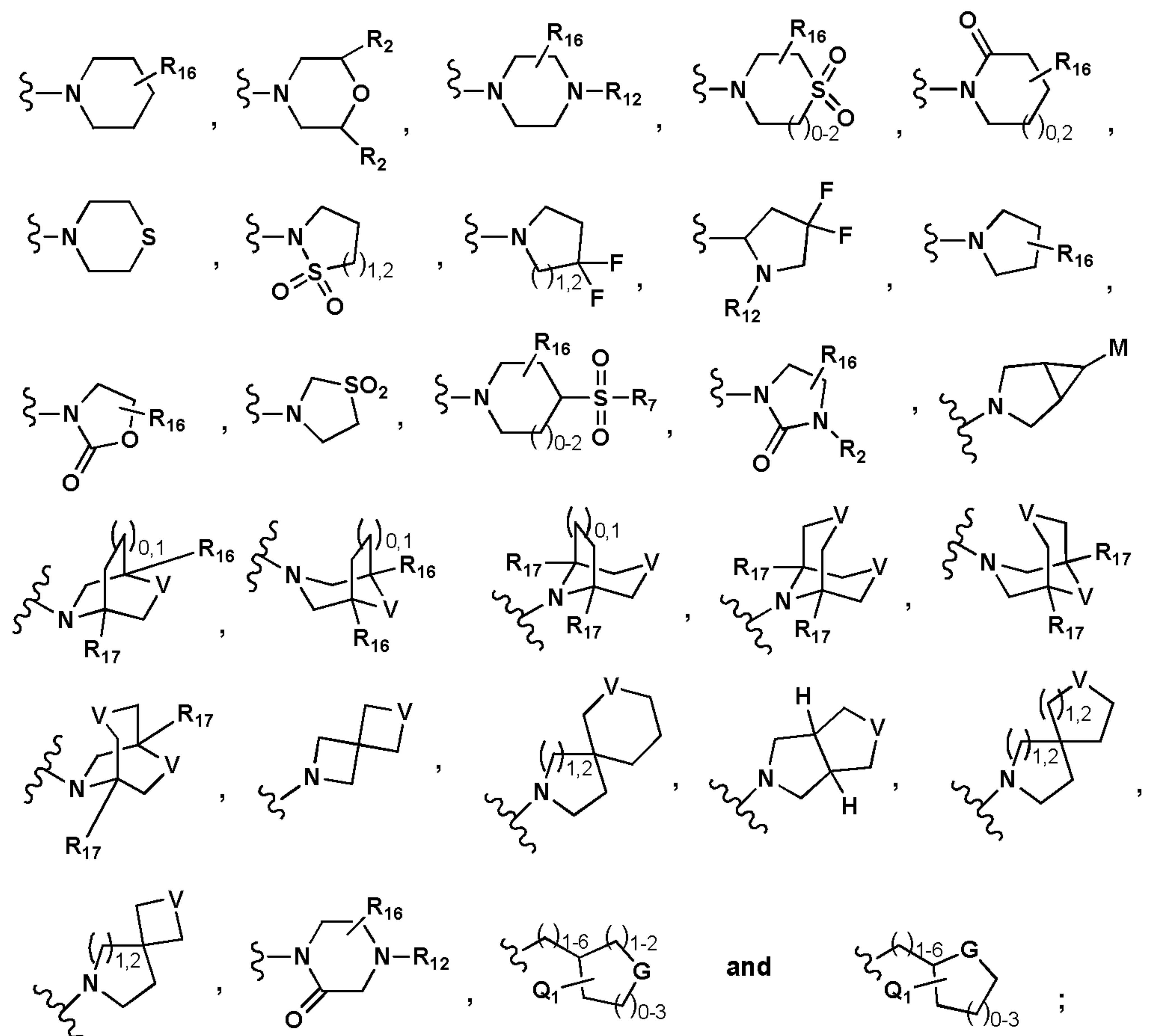
Formula II

- 15 wherein R_1 is isopropenyl or isopropyl;
 A is $-C_{1-6}$ alkyl- OR_0 ;
 wherein R_0 is heteroaryl- Q_0 ;
 Q_0 is selected from the group of $-H$, $-CN$, $-C_{1-6}$ alkyl, $-COOH$, $-Ph$, $-OC_{1-6}$ alkyl, $-halo$, $-CF_3$,
 Y is selected from the group of $-COOR_2$, $-C(O)NR_2SO_2R_3$, $-C(O)NHSO_2NR_2R_2$, $-$
 20 $SO_2NR_2C(O)R_2$, $-tetrazole$, and $-CONHOH$,
 wherein $n = 1-6$;
 R_2 is $-H$, $-C_{1-6}$ alkyl, $-alkylsubstituted\ C_{1-6}\ alkyl$ or $-arylsubstituted\ C_{1-6}\ alkyl$;
 W is absent, or is $-CH_2-$ or $-CO-$;
 R_3 is $-H$, $-C_{1-6}$ alkyl or $-alkylsubstituted\ C_{1-6}\ alkyl$;

R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ substituted -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁, aryl, heteroaryl, substituted heteroaryl, -COR₆, -SO₂R₇, -SO₂NR₂R₂, and



- 5 wherein G is selected from the group of -O-, -SO₂- and -NR₁₂-;
 wherein Q₁ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ fluoroalkyl, heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₈R₉ and -SO₂R₇;
 R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₃, -SO₂R₇ and -SO₂NR₂R₂;
 10 with the proviso that R₄ or R₅ is not -COR₆ when W is -CO-;
 with the further proviso that only one of R₄ or R₅ is selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;
 R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -
 15 NR₁₃R₁₄, and -OR₁₅;
 wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;
 R₇ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -CF₃, aryl, and heteroaryl;
 20 R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,
 or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:



M is selected from the group of $-R_{15}$, $-SO_2R_2$, $-SO_2NR_2R_2$, $-OH$ and $-NR_2R_{12}$;

V is selected from the group of $-CR_{10}R_{11}-$, $-SO_2-$, $-O-$ and $-NR_{12}-$;

with the proviso that only one of R_8 or R_9 can be $-COOR_3$;

R_{10} and R_{11} are independently selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl;

R_{12} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-alkylsubstituted\ C_{1-6}\ alkyl$, $-CONR_2R_2$, $-SO_2R_3$, and $-SO_2NR_2R_2$;

R_{13} and R_{14} are independently selected from the group of $-H$, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl- Q_3 , $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl- Q_3 , and C_{1-6} substituted alkyl- Q_3 ;

Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_2R_{12}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;

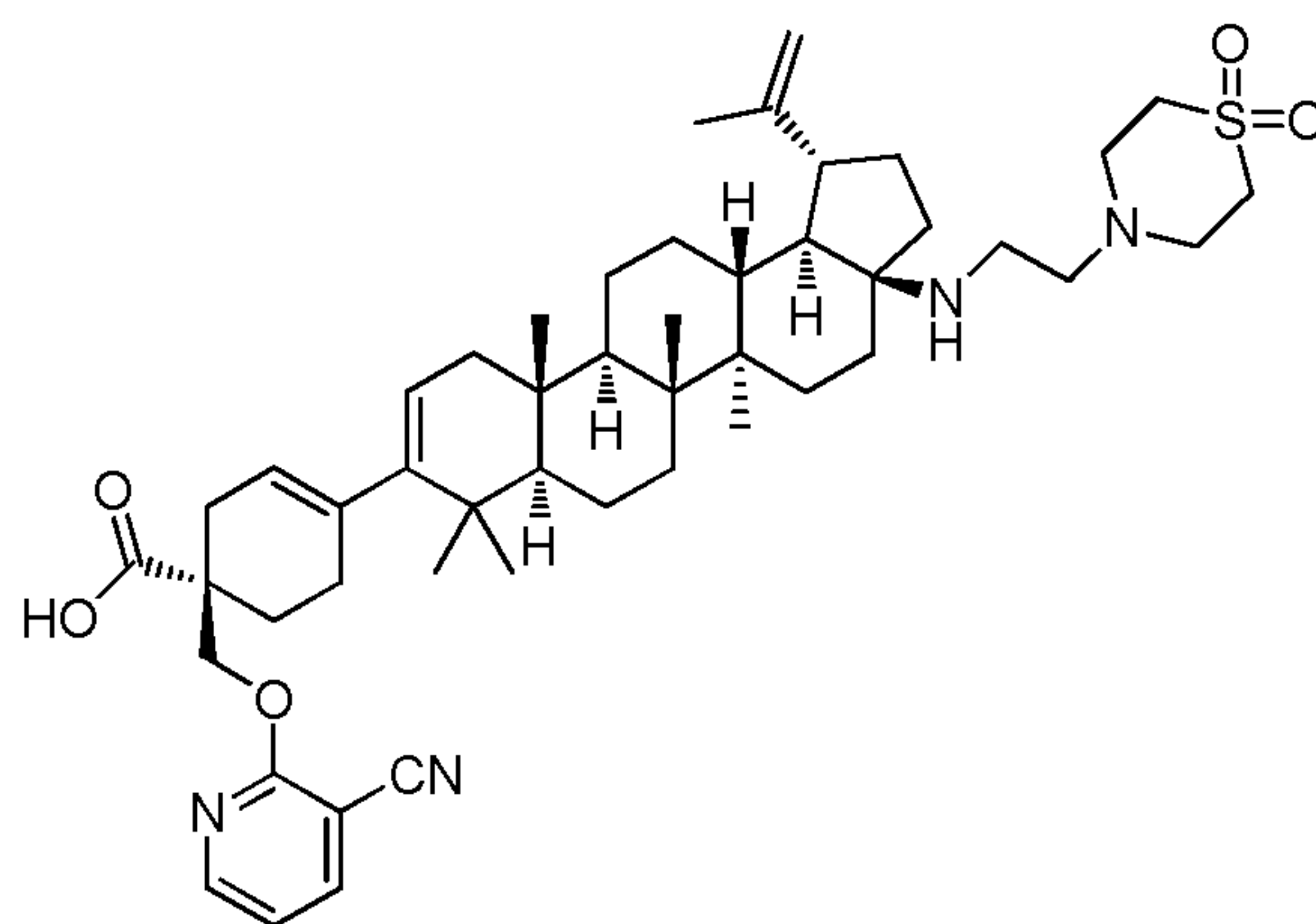
R_{15} is selected from the group of $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl- Q_3 , $-C_{1-6}$ alkyl- C_{3-6} cycloalkyl- Q_3 and $-C_{1-6}$ substituted alkyl- Q_3 ;

R_{16} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_2$;

with the proviso that when V is $-NR_{12}-$; R_{16} is not $-NR_2R_2$; and

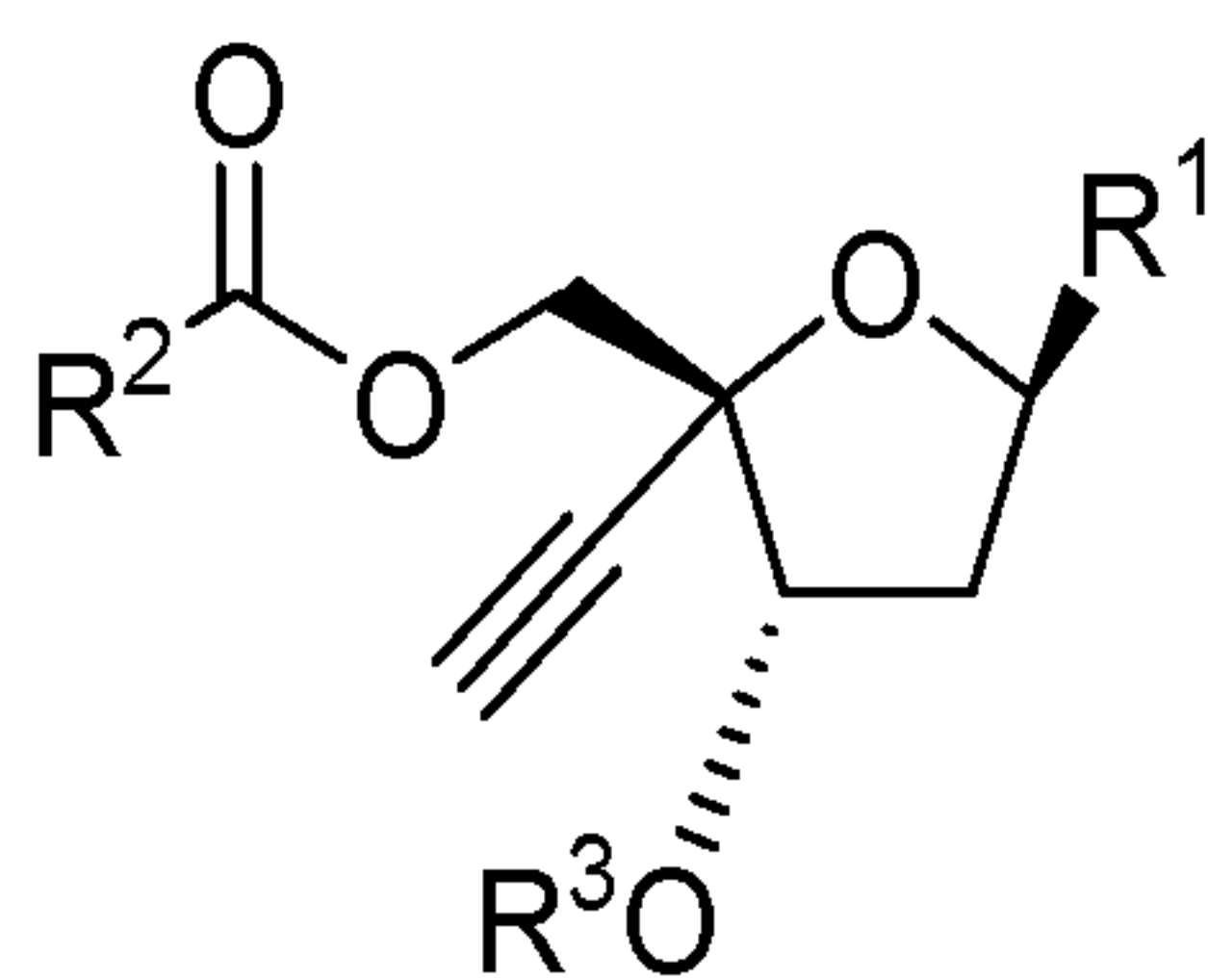
R_{17} is selected from the group of $-H$, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl.

Compounds of Formula II are described in WO 2017/134596 which is incorporated herein by reference. In an embodiment the maturation inhibitor is Compound 3. Compound 3 is described in WO 2017/134596 as Example 25 which example is incorporated herein by reference.



Compound 3.

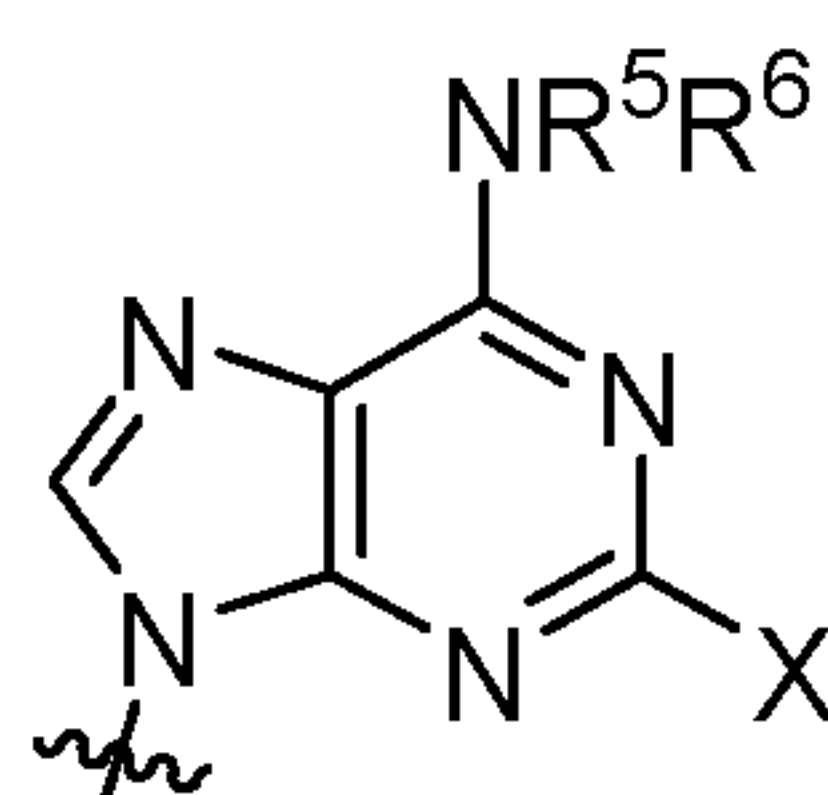
The pharmaceutical composition may be administered in combination with an NRTTI. In an embodiment the NRTTI is a compound of the formula 3:



Formula 3

wherein:

R^1 is:



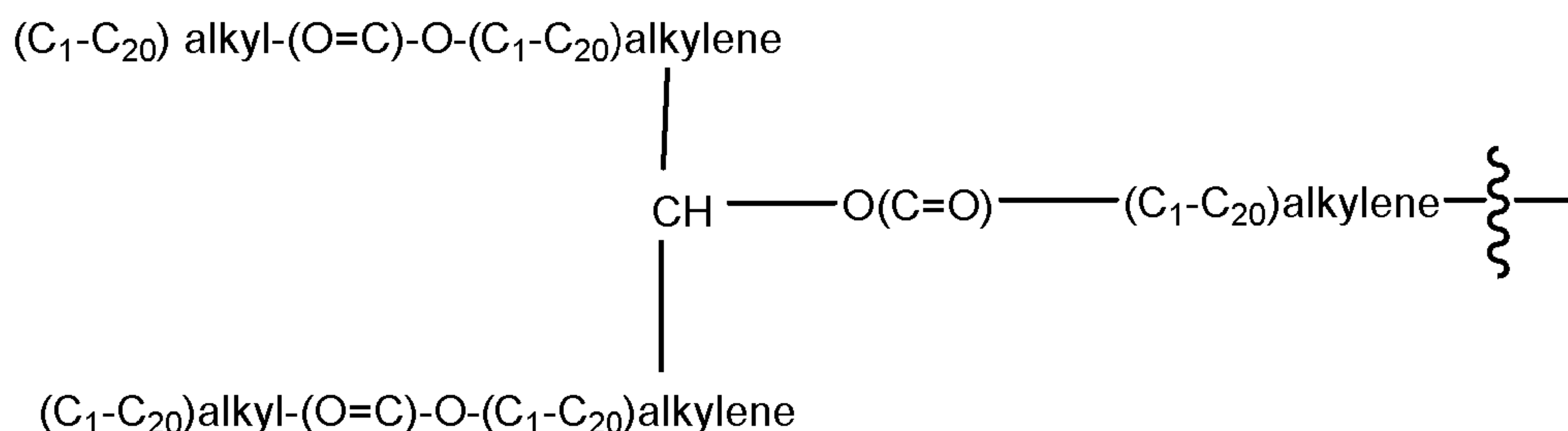
wherein:

X is selected from the group consisting of NH₂, F and Cl;

R⁵ is selected from the group consisting of H and (C₁-C₁₄) alkyl;

R⁶ is selected from the group consisting of H and -(C=O)-(C₁-C₁₄) alkyl;

R² is selected from the group consisting of (C₁-C₂₄) alkyl; (CH₂)_{n1}-O-(CH₂CH₂O)_{n2}-(C₁-C₁₄ alkyl) where n₁ and n₂ are integers independently selected from 1-4; -R⁷-NH-(C=O)-R⁸ wherein R⁷ may be (C₁-C₁₄) alkyl and R⁸ may be independently selected from H and (C₁-C₁₄) alkyl; -R⁹-(C₆-C₁₄) aryl, wherein R⁹ is a bond or (C₁-C₆) alkyl; -R¹⁰-(C₃-C₁₄) cycloalkyl, wherein R¹⁰ is a bond or (C₁-C₆) alkyl; -(C₁-C₂₀) alkylene-(C=O)-O-R¹¹ wherein R¹¹ may be selected from H and (C₁-C₂₀)alkyl;



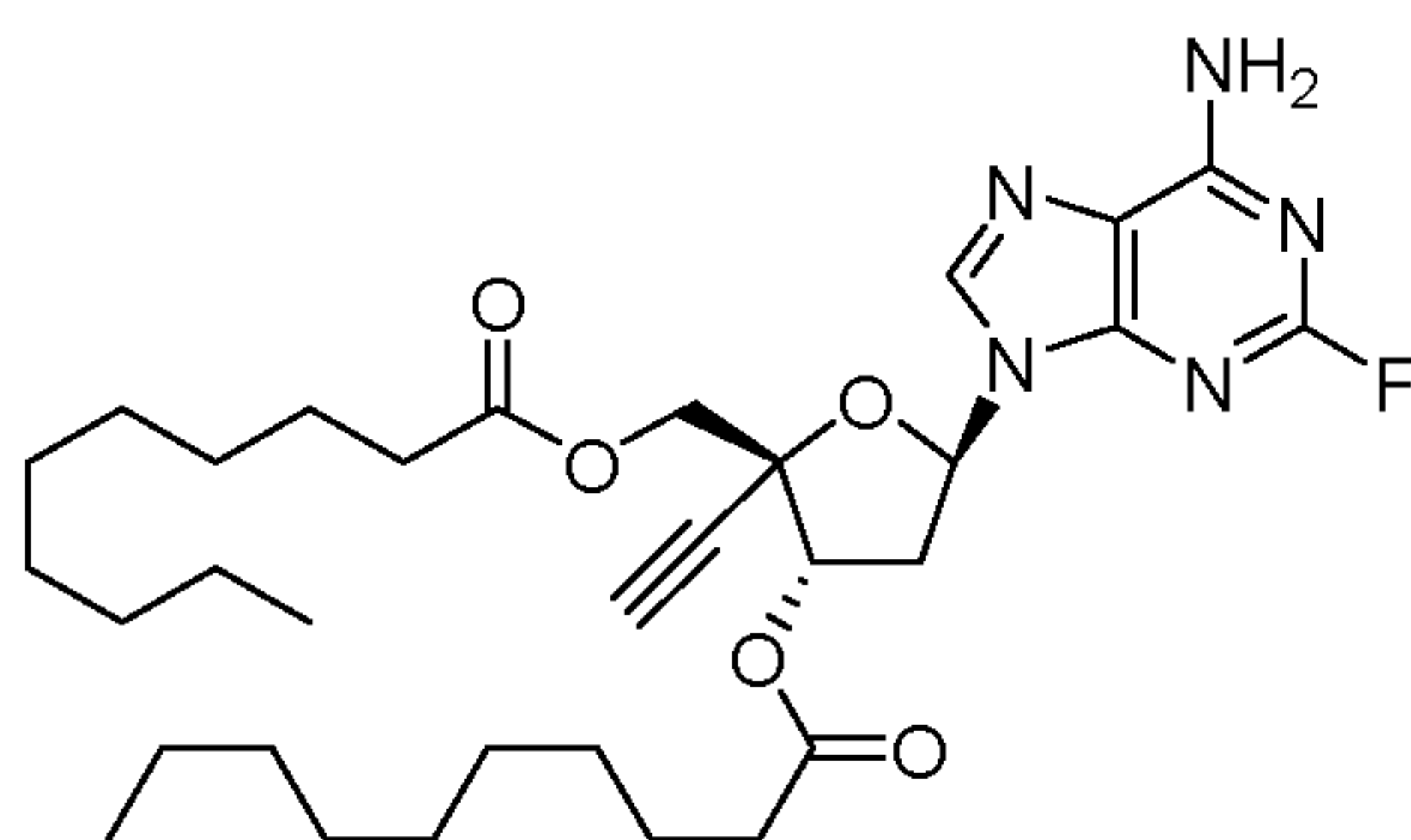
and;

R³ is selected from the group consisting of H, -(C=O)-(C₁-C₂₄) alkyl; -(C=O)-O-(C₁-C₂₄) alkyl; and C₃-C₁₄ cycloalkyl; or

R² and R³ join together to form a C₃ to C₂₈ cyclic structure; and

with the proviso that when R² is (C₁-C₁₄ alkyl) at least one of R³, R⁵ and R⁶ is not H.

Compounds of Formula 3 are disclosed in WO 2020/178767 which is incorporated by reference herein. In an embodiment a pharmaceutical composition of the invention is combined with Compound 4. Compound 4 is described in WO 2020/178767 as Example 18, which example is incorporated by reference herein.



Compound 4

In an alternative embodiment the NRTTI is Islatravir.

In an embodiment of the invention the pharmaceutical compositions of the present invention are administered in combination with hyaluronidase. In one embodiment the pharmaceutical compositions of the present invention and the hyaluronidase are administered sequentially. The hyaluronidase may be administered subcutaneously or intramuscularly via injection. In one embodiment the hyaluronidase is administered prior to the administration of the pharmaceutical composition. In this embodiment the pharmaceutical composition is administered as close as possible to the site of the injection of hyaluronidase. It is thought that the hyaluronidase increases the permeability of the injection site tissues to the pharmaceutical compositions.

In a third aspect, the present invention provides a pharmaceutical composition defined herein for use in the treatment or prevention of HIV.

In one embodiment, the pharmaceutical composition is suitable for use as an injectable composition. In one embodiment the use comprises administering the pharmaceutical composition

parenterally. In an embodiment the use comprises administering the pharmaceutical composition intramuscularly. In another embodiment the use comprises administering the pharmaceutical composition subcutaneously.

5 In an embodiment the use comprises administering around 1mL to around 3 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 1mL of the pharmaceutical composition to a patient. In another embodiment the use comprises administering around 2 mL of the pharmaceutical composition to a patient. In an embodiment the use comprises administering around 3 mL of the pharmaceutical composition to a patient.

10 In an embodiment the use comprises administering the pharmaceutical to a patient once every 1, 2 or 3 months. In an embodiment the use comprises administering the pharmaceutical composition to a patient once every month. In an alternative embodiment, the use comprises administering the pharmaceutical composition once every 2 months. In an alternative embodiment the use comprises administering the pharmaceutical composition once every 3 months.

15 In one embodiment, the use comprises delivering the the pharmaceutical composition to a patient once every month. In this embodiment, the pharmaceutical composition may be administered by any suitable means. The pharmaceutical composition may be self-administered by a patient. In this embodiment the pharmaceutical composition may be administered subcutaneously via injection. The subcutaneous injection may comprise 1 to 1.5 mL of the pharmaceutical composition. In one embodiment of the invention the pharmaceutical composition is self-administered once monthly by subcutaneous injection.

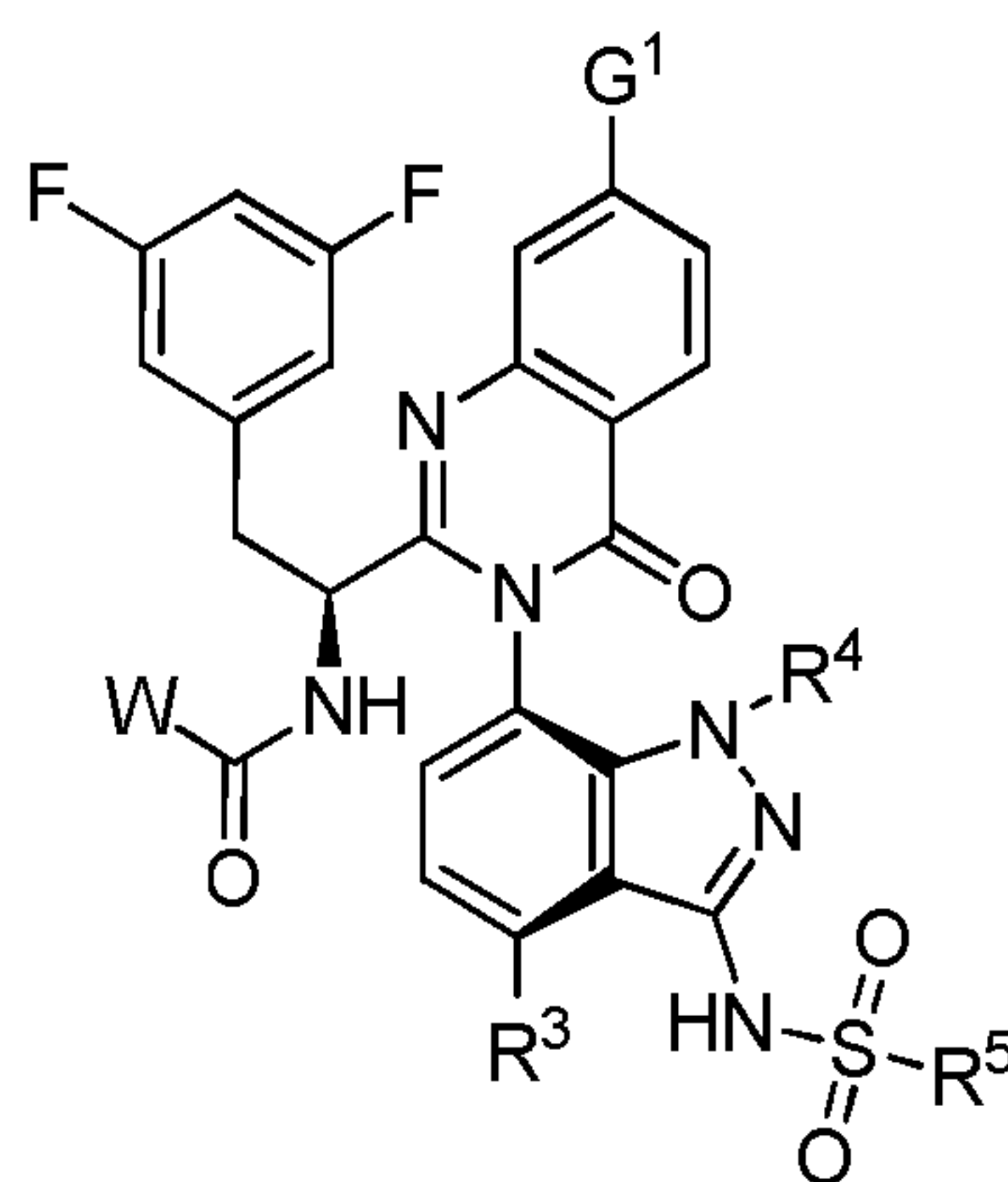
20 In an alternative embodiment the use comprises delivering the pharmaceutical composition to a patient once every three months. In this embodiment, the pharmaceutical composition may be administered by any suitable means. The pharmaceutical composition may be administered intramuscularly via injection. In an embodiment the intramuscular injection is administered by a healthcare professional. The intramuscular injection may comprise 2.5 to 3 mL of the pharmaceutical composition. In an embodiment of the invention the pharmaceutical composition is administered once every 3 months by intramuscular injection.

25 In an embodiment of the invention use comprises administering the pharmaceutical compositions of the present invention in combination with other pharmaceutical compositions as a component of a multi drug treatment regimen. In an embodiment, the other pharmaceutical compositions are drugs which treat or prevent HIV. Marketed medicines are currently available to treat HIV.

30 In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with N6-LS. N6-LS is described above.

In an embodiment the use comprises administering the pharmaceutical compositions of the present invention in combination with a capsid inhibitor, a maturation inhibitor or a nucleoside reverse transcriptase translocation inhibitor (NRTTI).

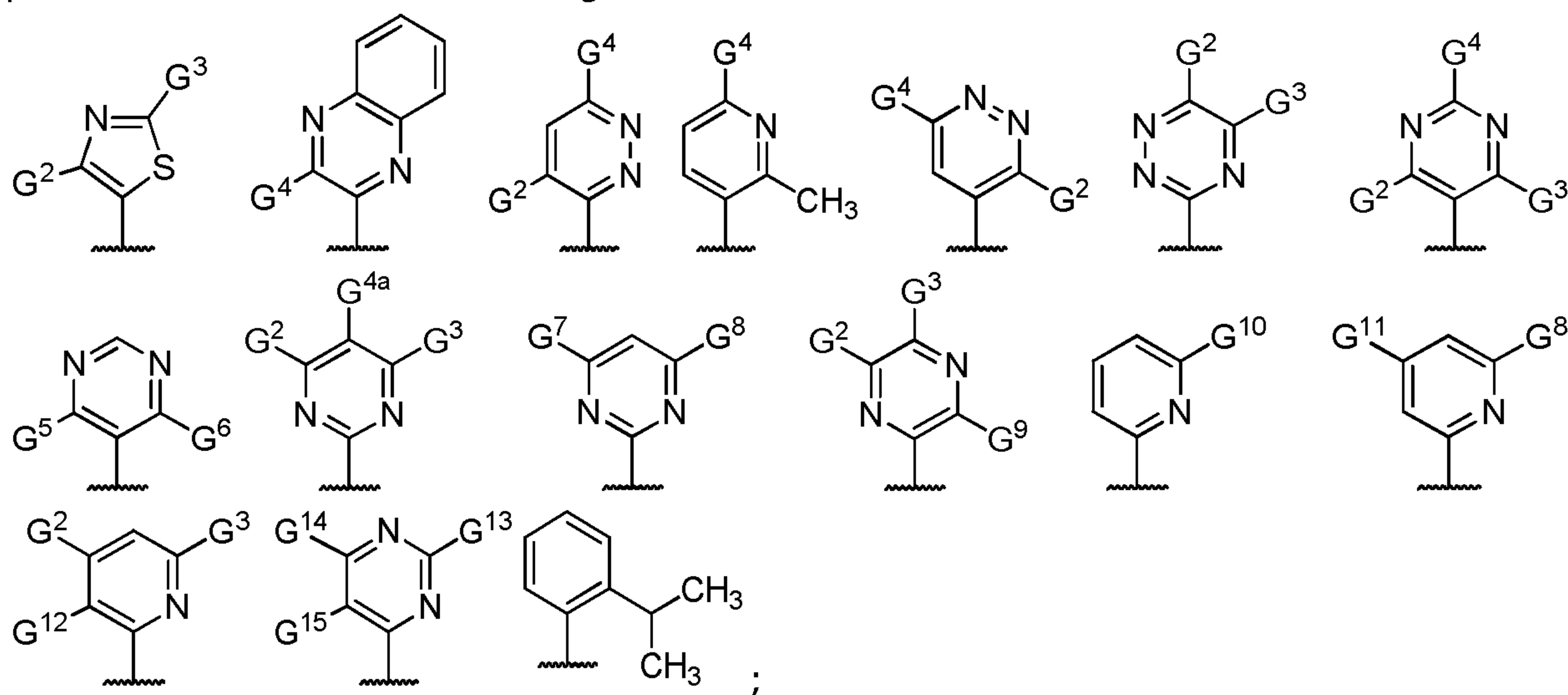
40 The pharmaceutical composition may be administered in combination with a capsid inhibitor. In an embodiment the capsid inhibitor is a compound of Formula I, or a pharmaceutically acceptable salt thereof:



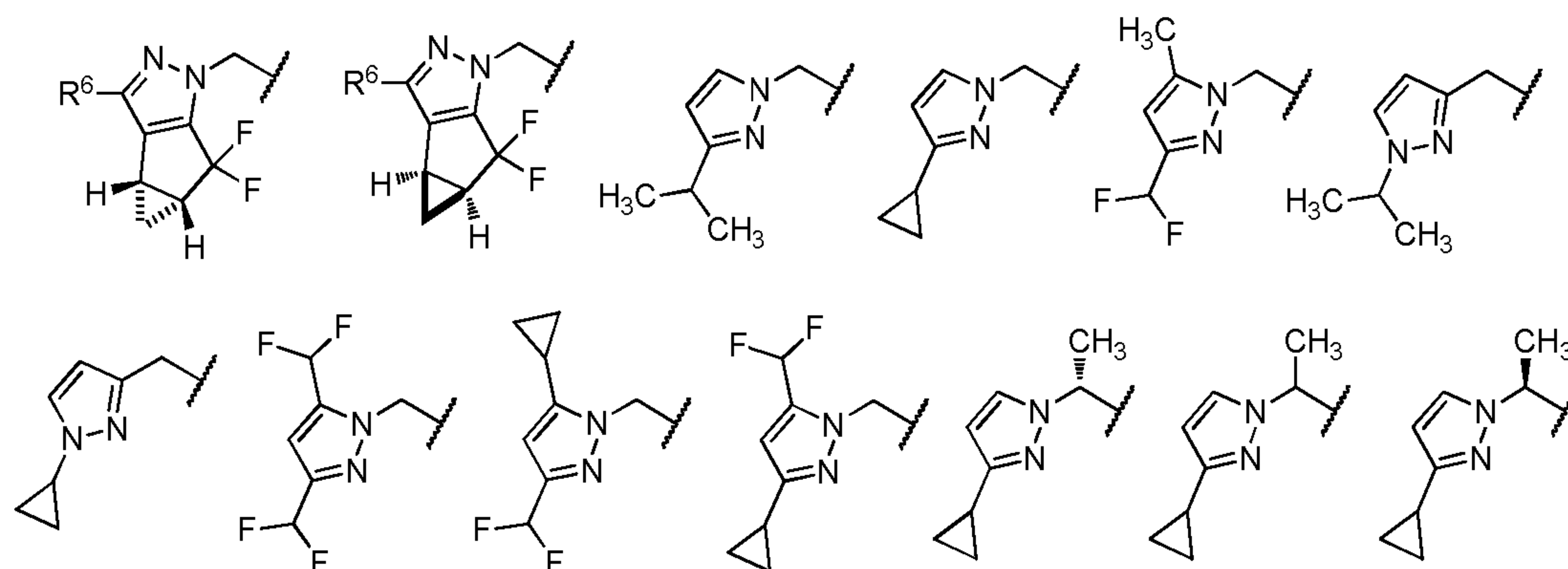
Formula I

wherein:

- G¹ is phenyl substituted once with -N(CH₃)S(O₂)CH₃, -S(O₂)C(CH₃)₃, -CHF₂, -CF₃, -OCHF₂, -OCF₃, or -C(CH₃)₂OH, with the proviso that when G¹ is -CHF₂ or CF₃, G¹ is not in the para position or G¹ is one of the following:

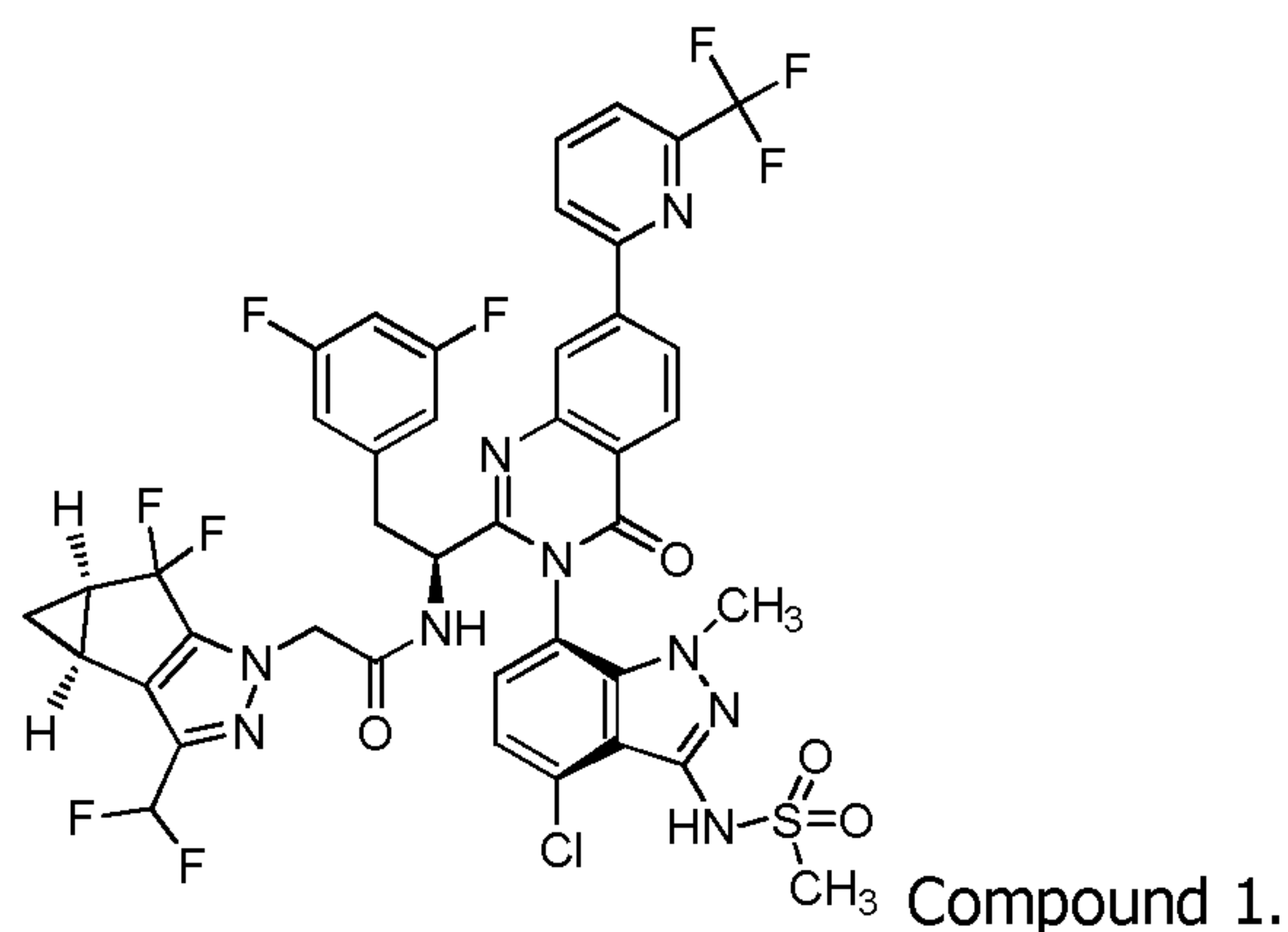


- G² and G³ are independently selected from is H or -CH₃;
 G⁴ is H, -CH₃, or -OCH₃;
 G^{4a} is -CH₃, or -OCH₃;
 G⁵ is -CH₃, or CH₂CH₃;
 G⁶ is H, -CH₃, or CH₂CH₃;
 G⁷ is ethyl, isopropyl, *tert*-butyl, -CHF₂, or -CF₃;
 G⁸ is H, methyl, ethyl, -CHF₂, -CF₃, -OCH₃, or -OCH₂CH₃;
 G⁹ is ethyl, isopropyl, cyclopropyl, -CH₂OH, -OCH₃;
 G¹⁰ is ethyl, isopropyl, cyclopropyl, *tert*-butyl, -CHF₂, or -CF₃;
 G¹¹ is methyl, -OCH₃, -CHF₂, -CF₃, -S(O₂)CH₃;
 G¹² is F, -CH₃, -CHF₂, -CF₃, -OCH₃, -S(O₂)CH₃;
 G¹³ is C₁-C₄alkyl, C₁-C₆cycloalkyl, -CH₂O(C₁-C₃alkyl);
 G¹⁴ is H, C₁-C₄alkyl, -CHF₂, -CF₃, -O(C₁-C₃alkyl);
 G¹⁵ is H, F, -CH₃, or OCH₃;
 R³ is H, F, Cl, -CH₃, or -OCH₃;
 R⁴ is H or C₁-C₃alkyl wherein C₁-C₃alkyl is optionally substituted with 1-3 fluorines;
 R⁵ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl;
 W is selected from:

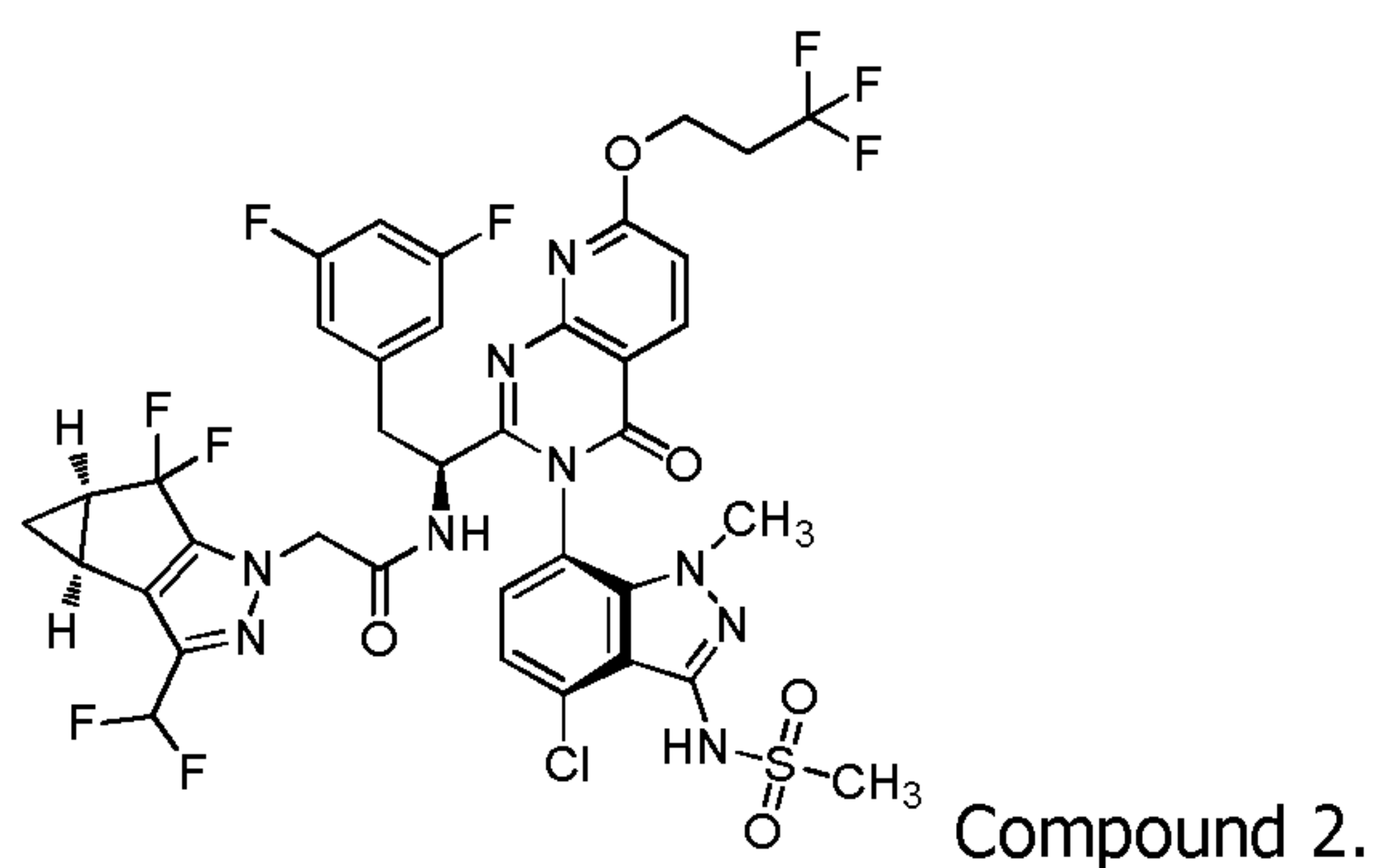


where R⁶ is methyl optionally substituted with 1 to 3 fluorines.

Compounds of Formula I are described in WO2020/084492 which is incorporated by reference. In an embodiment the capsid inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. Compound 1 is described in WO 2020/084492 as Example 59 which example is incorporated herein by reference.



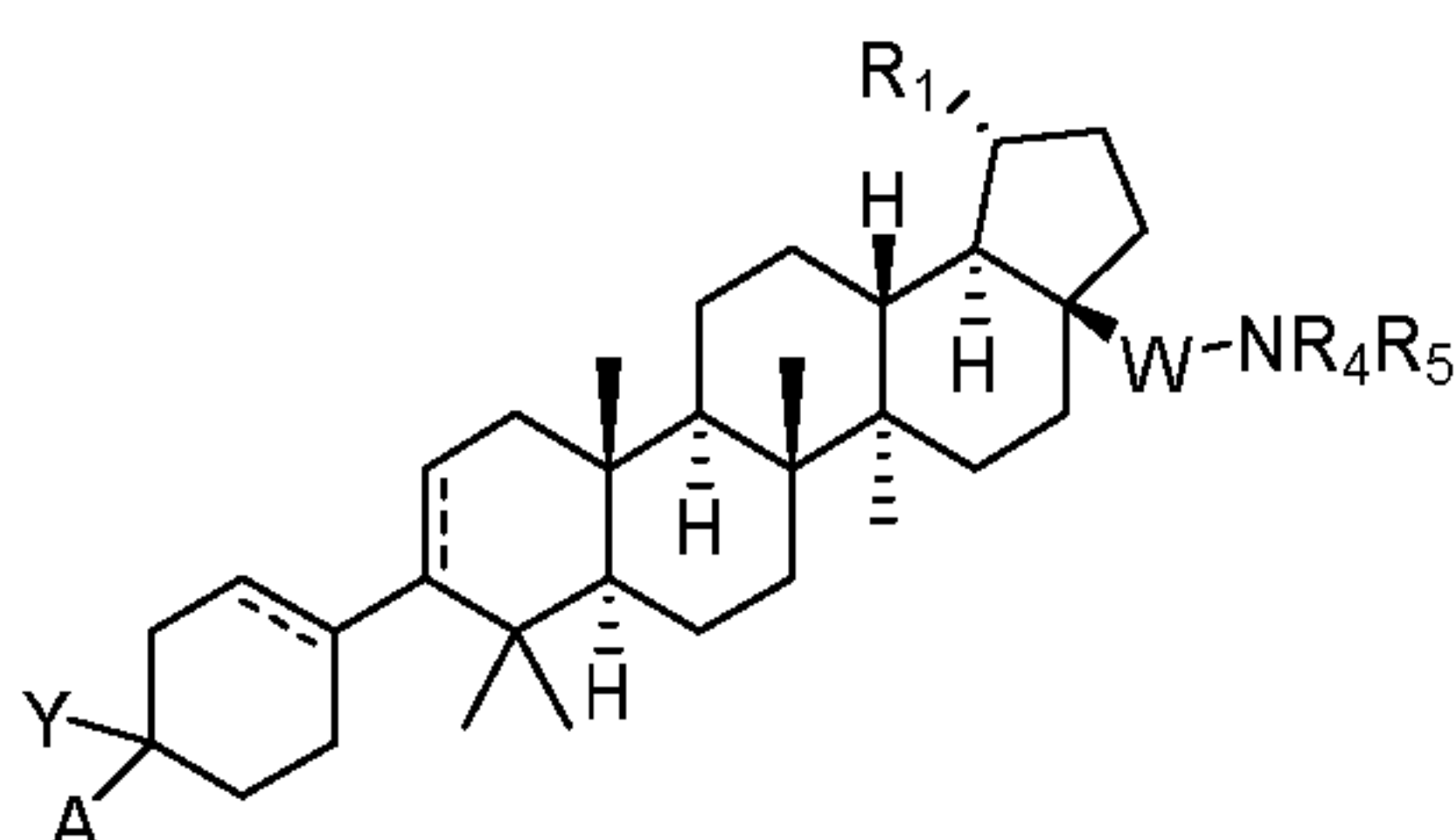
In an embodiment the capsid inhibitor is Compound 2 pharmaceutically acceptable salt thereof. Compound 2 is described in patent application number PCT/IB2020/055653 as Example 1, which example is incorporated herein by reference.



In an alternative embodiment the capsid inhibitor is lenacapavir.

The pharmaceutical composition may be administered in combination with a maturation inhibitor. In an embodiment the maturation inhibitor is a compound of Formula II or a pharmaceutically acceptable salt thereof:

5



Formula II

wherein R₁ is isopropenyl or isopropyl;

A is -C₁₋₆ alkyl-OR₀;

10 wherein R₀ is heteroaryl-Q₀;

Q₀ is selected from the group of -H, -CN, -C₁₋₆ alkyl, -COOH, -Ph, -OC₁₋₆ alkyl, -halo, -CF₃,

Y is selected from the group of -COOR₂, -C(O)NR₂SO₂R₃, -C(O)NHSO₂NR₂R₂, -SO₂NR₂C(O)R₂, -tetrazole, and -CONHOH,

wherein n = 1-6;

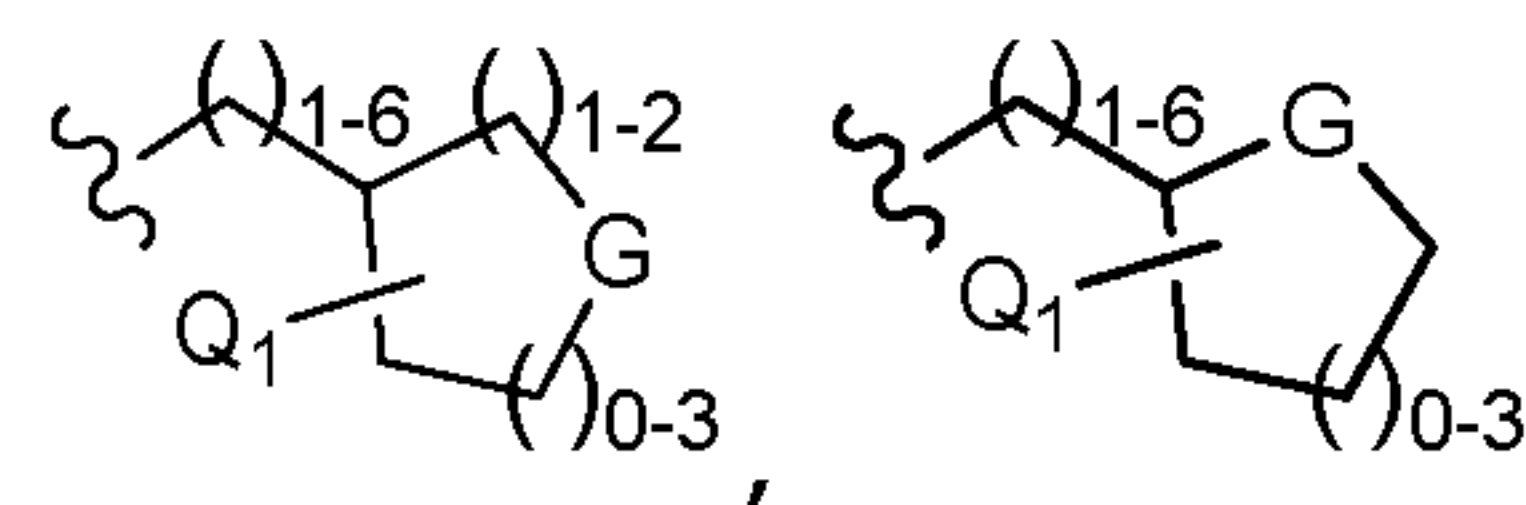
15 R₂ is -H, -C₁₋₆ alkyl, -alkylsubstituted C₁₋₆ alkyl or-arylsubstituted C₁₋₆ alkyl;

W is absent, or is -CH₂- or -CO-;

R₃ is -H, -C₁₋₆ alkyl or -alkylsubstituted C₁₋₆ alkyl;

R₄ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl, -C₁₋₆ substituted -C₁₋₆ alkyl, -C₁₋₆ alkyl-Q₁, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₁, aryl, heteroaryl, substituted heteroaryl, -COR₆, -

20 SO₂R₇, -SO₂NR₂R₂, and



wherein G is selected from the group of -O-, -SO₂- and -NR₁₂-;

wherein Q₁ is selected from the group of -C₁₋₆ alkyl, -C₁₋₆ fluoroalkyl, heteroaryl, substituted heteroaryl, halogen, -CF₃, -OR₂, -COOR₂, -NR₈R₉, -CONR₈R₉ and -SO₂R₇;

25 R₅ is selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ alkylsubstituted alkyl, -C₁₋₆ alkyl-NR₈R₉, -COR₃, -SO₂R₇ and -SO₂NR₂R₂;

with the proviso that R₄ or R₅ is not -COR₆ when W is -CO-;

with the further proviso that only one of R₄ or R₅ is selected from the group of -COR₆, -COCOR₆, -SO₂R₇ and -SO₂NR₂R₂;

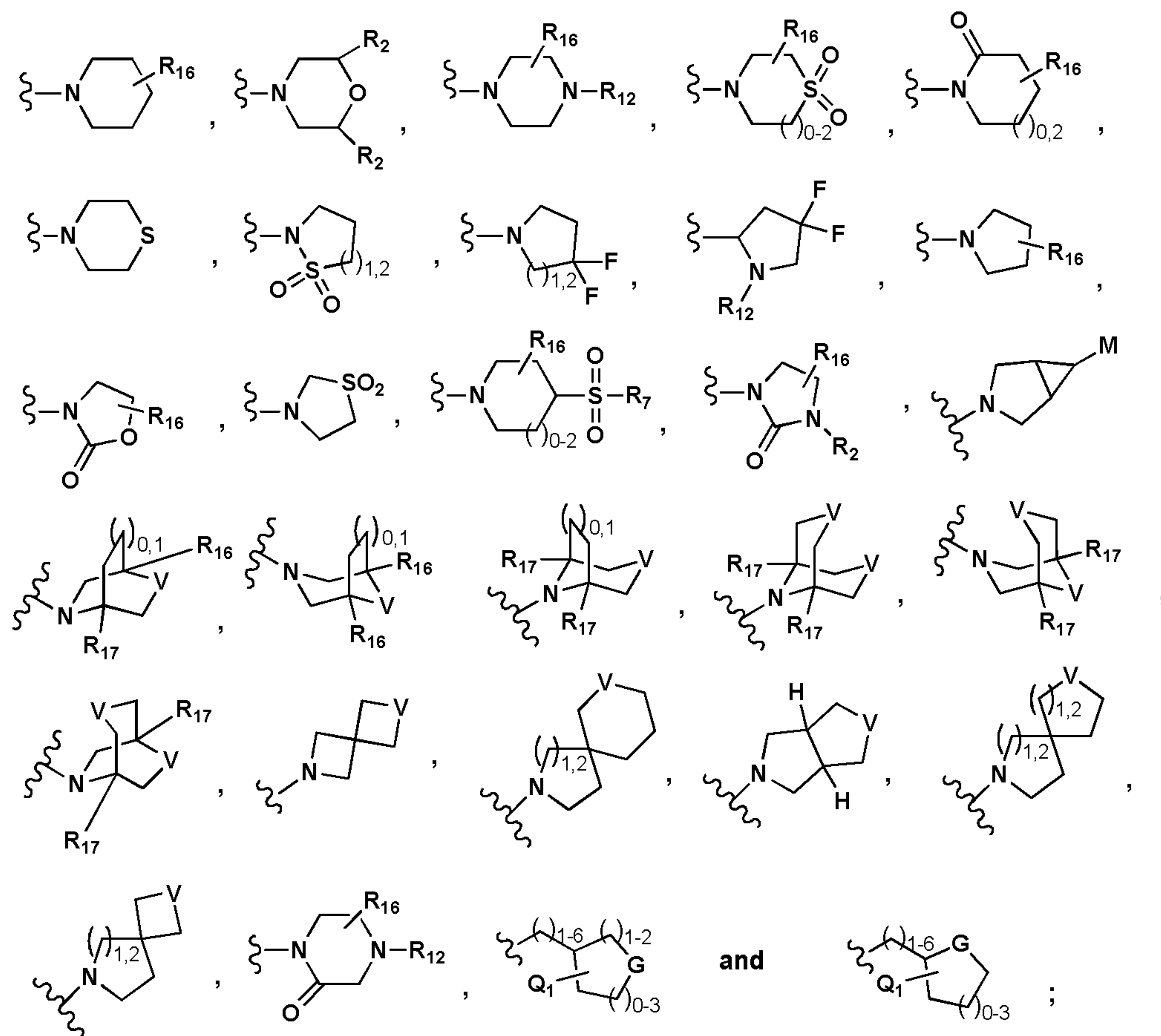
30 R₆ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ alkyl-substitutedalkyl, -C₃₋₆ cycloalkyl, -C₃₋₆ substitutedcycloalkyl-Q₂, -C₁₋₆ alkyl-Q₂, -C₁₋₆ alkyl-substitutedalkyl-Q₂, -C₃₋₆ cycloalkyl-Q₂, aryl-Q₂, -NR₁₃R₁₄, and -OR₁₅;

wherein Q₂ is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR₂, -COOR₂, -NR₈R₉, SO₂R₇, -CONHSO₂R₃, and -CONHSO₂NR₂R₂;

35 R₇ is selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, -C₃₋₆ cycloalkyl, -CF₃, aryl, and heteroaryl;

R₈ and R₉ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C₁₋₆ alkyl-Q₂, and -COOR₃,

or R₈ and R₉ are taken together with the adjacent N to form a cycle selected from the group of:



M is selected from the group of -R₁₅, -SO₂R₂, -SO₂NR₂R₂, -OH and -NR₂R₁₂;

V is selected from the group of -CR₁₀R₁₁-, -SO₂-, -O- and -NR₁₂-;

5 with the proviso that only one of R₈ or R₉ can be -COOR₃;

R₁₀ and R₁₁ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₁₋₆ substituted alkyl and -C₃₋₆ cycloalkyl;

R₁₂ is selected from the group of -H, -C₁₋₆ alkyl, -alkylsubstituted C₁₋₆ alkyl, -CONR₂R₂, -SO₂R₃, and -SO₂NR₂R₂;

10 R₁₃ and R₁₄ are independently selected from the group of -H, -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃, and C₁₋₆ substituted alkyl-Q₃;

Q₃ is selected from the group of heteroaryl, substituted heteroaryl, -NR₂R₁₂, -CONR₂R₂, -COOR₂, -OR₂, and -SO₂R₃;

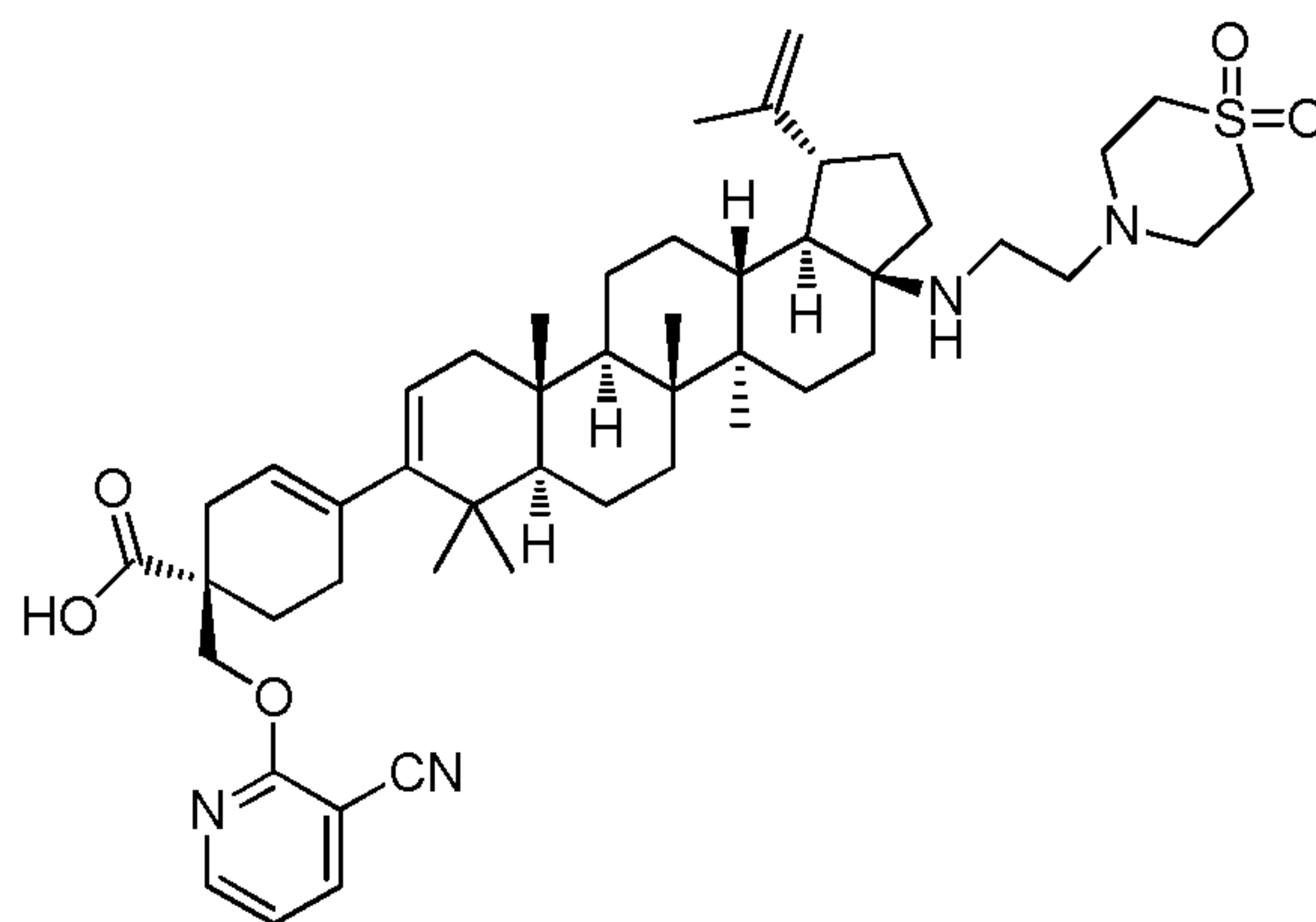
R₁₅ is selected from the group of -C₁₋₆ alkyl, -C₃₋₆ cycloalkyl, -C₁₋₆ substituted alkyl, -C₁₋₆ alkyl-Q₃, -C₁₋₆ alkyl-C₃₋₆ cycloalkyl-Q₃ and -C₁₋₆ substituted alkyl-Q₃;

15 R₁₆ is selected from the group of -H, -C₁₋₆ alkyl, -NR₂R₂, and -COOR₂;

with the proviso that when V is -NR₁₂-; R₁₆ is not -NR₂R₂; and

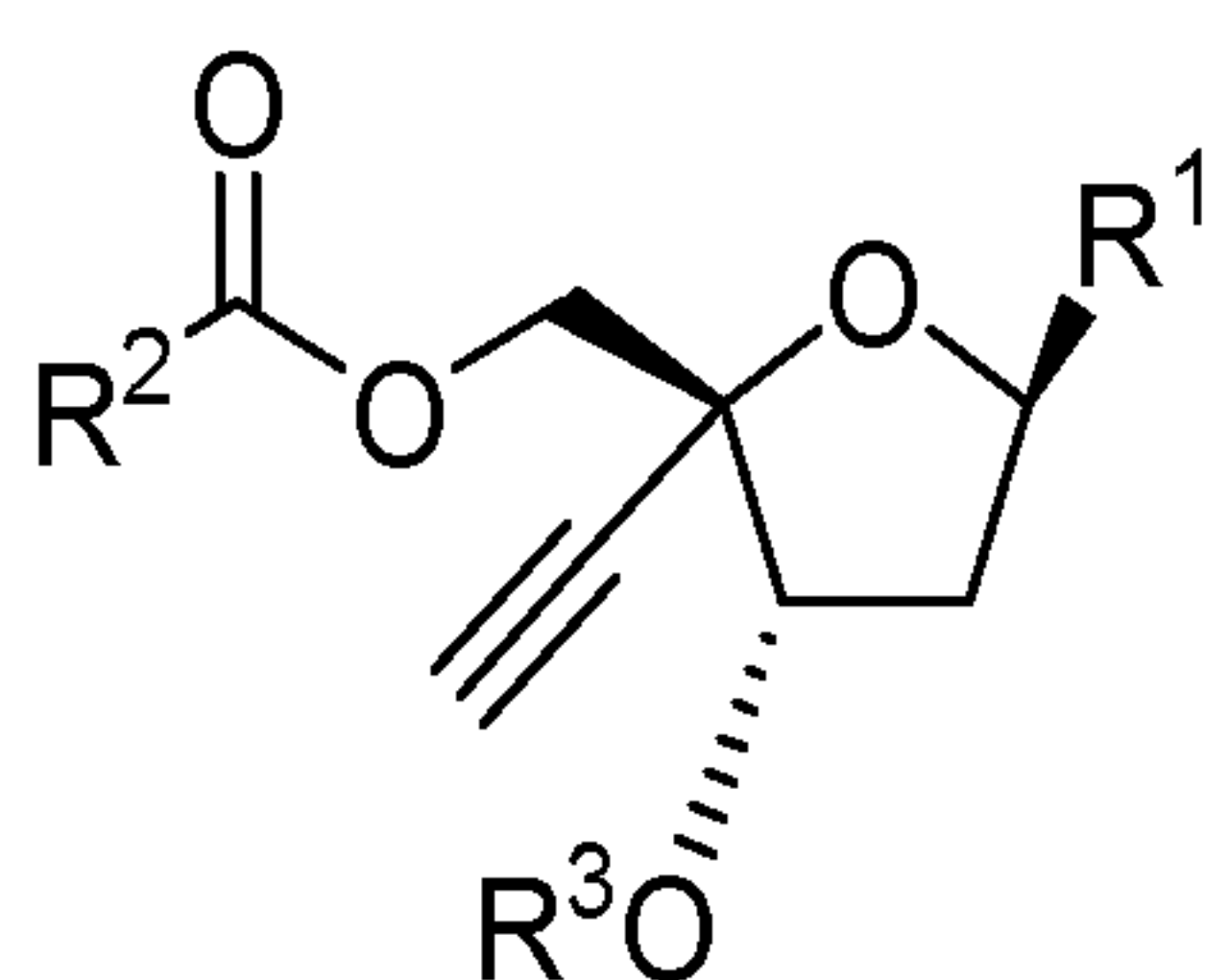
R₁₇ is selected from the group of -H, -C₁₋₆ alkyl, -COOR₃, and aryl.

Compounds of Formula II are described in WO 2017/134596 which is incorporated herein
20 by reference. In an embodiment the maturation inhibitor is Compound 3. Compound 3 is described
in WO 2017/134596 as Example 25 which example is incorporated herein by reference.



Compound 3.

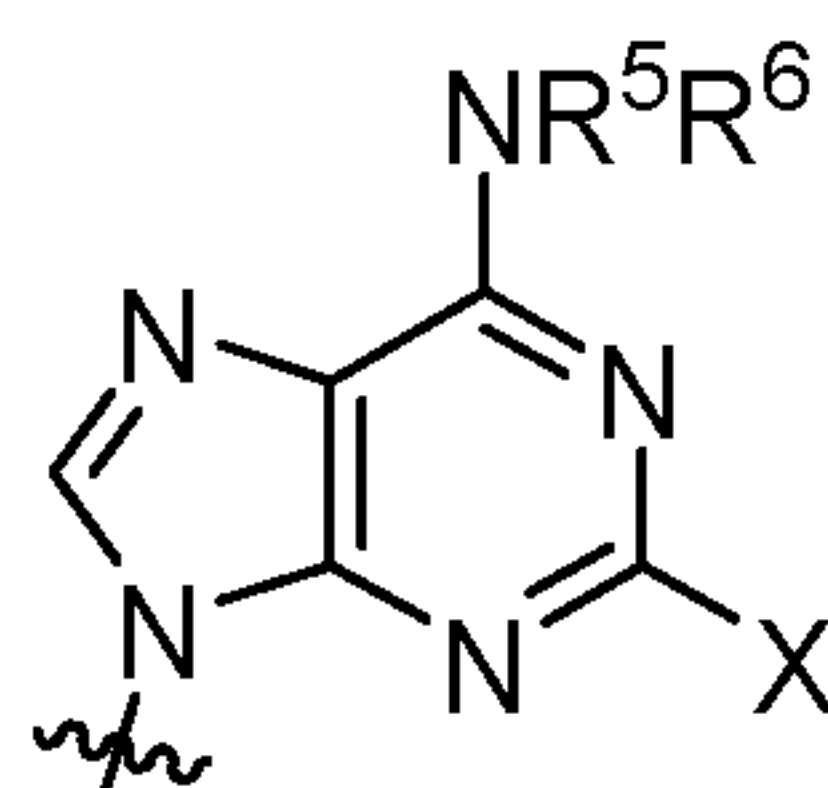
The pharmaceutical composition may be administered in combination with an NRTTI. In an embodiment the NRTTI is a compound of the formula 3:



Formula 3

wherein:

R¹ is:



wherein:

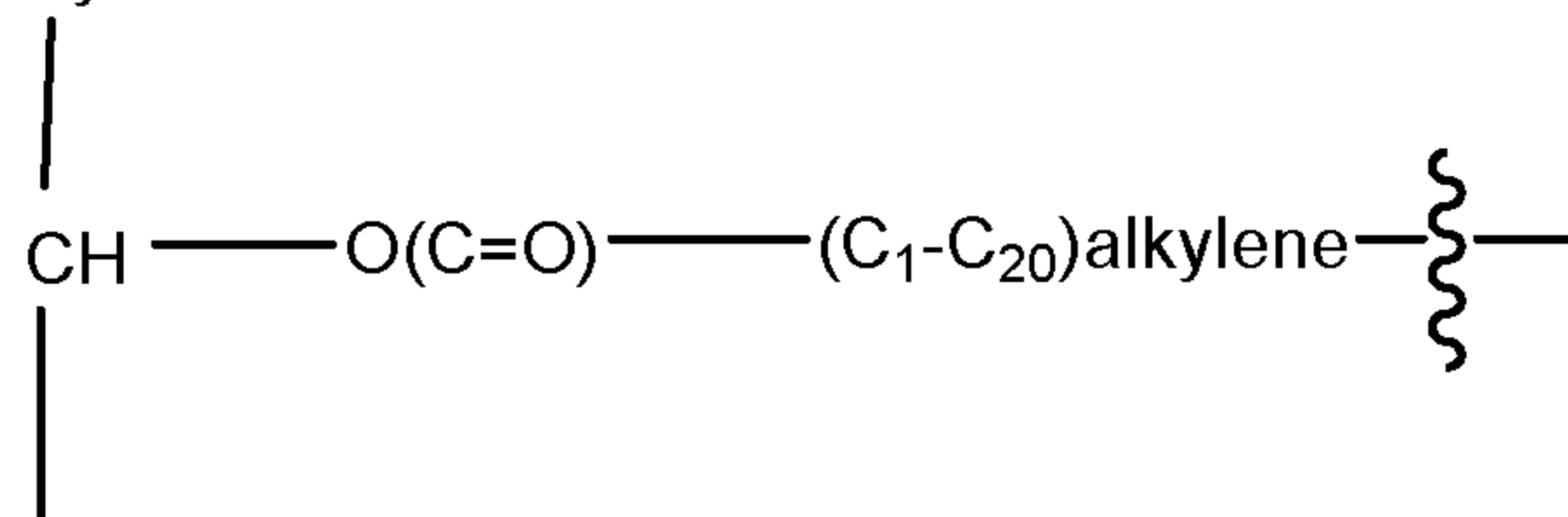
X is selected from the group consisting of NH₂, F and Cl;

R⁵ is selected from the group consisting of H and (C₁-C₁₄) alkyl;

R⁶ is selected from the group consisting of H and -(C=O)-(C₁-C₁₄) alkyl;

R² is selected from the group consisting of (C₁-C₂₄) alkyl; (CH₂)_{n1}-O-(CH₂CH₂O)_{n2}-(C₁-C₁₄ alkyl) where n₁ and n₂ are integers independently selected from 1-4; -R⁷-NH-(C=O)-R⁸ wherein R⁷ may be (C₁-C₁₄) alkyl and R⁸ may be independently selected from H and (C₁-C₁₄) alkyl; -R⁹-(C₆-C₁₄) aryl, wherein R⁹ is a bond or (C₁-C₆) alkyl; -R¹⁰-(C₃-C₁₄) cycloalkyl, wherein R¹⁰ is a bond or (C₁-C₆) alkyl; -(C₁-C₂₀) alkylene-(C=O)-O-R¹¹ wherein R¹¹ may be selected from H and (C₁-C₂₀)alkyl;

(C₁-C₂₀) alkyl-(O=C)-O-(C₁-C₂₀)alkylene

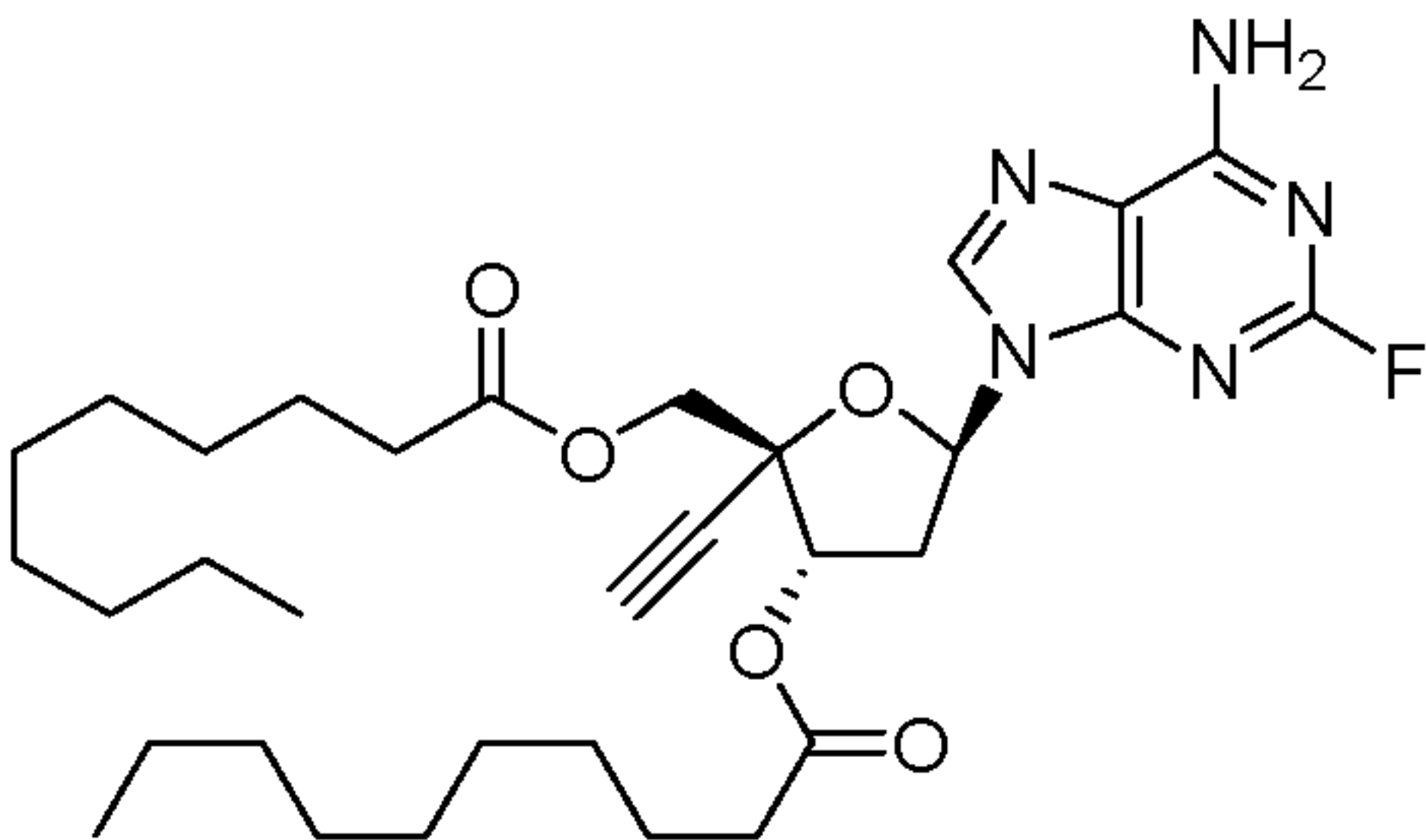


(C₁-C₂₀)alkyl-(O=C)-O-(C₁-C₂₀)alkylene

and;

R³ is selected from the group consisting of H, -(C=O)-(C₁-C₂₄) alkyl; -(C=O)-O-(C₁-C₂₄) alkyl; and C₃-C₁₄ cycloalkyl; or
R² and R³ join together to form a C₃ to C₂₈ cyclic structure; and
with the proviso that when R² is (C₁-C₁₄ alkyl) at least one of R³, R⁵ and R⁶ is not H.

Compounds of Formula 3 are disclosed in WO 2020/178767 which is incorporated by reference herein. In an embodiment a pharmaceutical composition of the invention is combined with Compound 4. Compound 4 is described in WO 2020/178767 as Example 18, which example is incorporated by reference herein.



Compound 4

In an alternative embodiment the NRTTI is Islatravir.
In a further embodiment the present invention provides a kit comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer. In an embodiment the kit comprises a syringe comprising a composition of the invention as well as a leaflet comprising use instructions.
The following non-limiting Examples illustrate the present invention.

EXAMPLES

Example 1: Composition of the invention

Ingredient	Concentration (mg/mL)
Cabotegravir	400.0
Poloxamer 338	38.0
Polyethylene Glycol 3350	35.0
Mannitol	20.0

Table 3

Table 3 shows an exemplary pharmaceutical composition of the invention (pharmaceutical compositions are also described in these examples as "suspensions") which was made using the following method.

A formulation vehicle was prepared by dissolving 9.5g Poloxamer 338 (BASF), 5.0g mannitol (Roquette Freres), and 8.7g PEG3350 (Clariant) in 164.2g water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired median particle diameter of 0.2 to 1.0 µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The resulting suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Example 2: Stability of a composition comprising Cabotegravir, Poloxamer 338 and PEG3350

A formulation vehicle was prepared by dissolving 7.5g Poloxamer 338 (BASF), 5.7g mannitol (Roquette Freres), and 7.5g PEG3350 (Clariant) in 166.7g water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 100g Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until a desired median particle diameter of 0.25µm was reached. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The milled suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy. Table 4 shows the suspension which was made.

Suspension 1	398 mg/mL cabotegravir (measured by HPLC)	30 mg/mL P338	30 mg/mL PEG3350	23 mg/mL mannitol
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Table 4

Suspension 1 was stored at ambient laboratory conditions for 3 months and then evaluated for resuspension using an automated vial shaker. Assessment of the time it took the suspension to resuspend was performed by using an automatic shaker to reduce variability in shaking (Glas-Col Benchtop Shaker). The vial comprising the composition was placed into a holder on the shaker and was shaken at 230 to 350 motor speed for 30 second intervals until the bottom of the vial was assessed through visual inspection to be clear of sedimented/caked suspension material. Figure 1 shows a micrograph of the bottom of a vial which contained Suspension 1 after 30 seconds of shaking by the automated shaker. Based on the microscopy images, Suspension 1 (left image in Figure 1) was superior in resuspension compared to Suspension 2 which is the same formulation, made using the method described above, but comprising Kollidon 12 (polyvinylpyrrolidone) instead of PEG3350. Suspension 1 (left image in Figure 1) shows a mostly clear vial bottom indicating that the suspension was resuspended and decanted. Suspension 2 shows a vial bottom with suspension (*i.e.* crystalline cabotegravir particles) adhered to the bottom of the vial, meaning that resuspension was not achieved. Both formulations were shaken using the automated shaker for 30 seconds, but Suspension 2 was hand shaken to try to further resuspend the product.

Particle size of Suspension 1 was measured after vials were stored in an upright position at accelerated (40°C/75%RH) and stressed (50°C/ambient) stability conditions. Particle size analysis for the particles in the suspension was performed using laser diffraction (Malvern Mastersizer 3000). This method generates particle size distributions for the samples. The instrument uses a proprietary algorithm to convert the 2-dimensional scattering pattern generated by the interaction of the laser with particles in the sample to a particle size distribution; the scattering pattern is dependent on the size distribution of the particles in the sample. Table 6 explains the definitions used reporting particle size distributions.

	Initial particle size			1 month 40°C/75%RH			1 month 50°C/ambient		
	x10	x50	x90	x10	x50	x90	x10	x50	x90
Suspension 1	0.07	0.15	0.37	0.07	0.16	0.39	0.08	0.18	0.45

Table 5

x50	Median particle diameter, μm ; here used on a volumetric basis, i.e. 50% by volume of the particles is smaller than this diameter and 50% is larger
x10	Particle diameter corresponding to 10% of the cumulative undersize distribution (here by volume), μm
x90	Particle diameter corresponding to 90% of the cumulative undersize distribution (here by volume), μm

Table 6

Table 5 shows minimal change in particle size of Suspension 1 over time and at varying conditions indicating stability of the suspension.

Example 3: 400 mg/mL Cabotegravir with Poloxamer 338 or 407

Injectable suspensions comprising about 400 mg/mL cabotegravir were prepared with Poloxamer 407 or 338. Mannitol was also added as a tonicity agent. The formulation vehicle was prepared by dissolving: 7.0g Poloxamer 338 and 3.5g mannitol in 177.0 g WFI (Suspension 4) or 7.5g P407 (BASF) and 4.7g mannitol (Roquette Freres) in 175.3g WFI (Suspension 3) and filtering the solution through a 0.2 μm filter. The formulation vehicle was added to 100g Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired mean particle diameter of around 0.2 μm was reached. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Table 7 shows the suspensions which were made. Each suspension was stored at 40°C/75%RH in an upright position. Initial particle size and particle size after 1 month was measured as an indicator of suspension stability. Table 8 shows the particle size in each suspension after 1 month. There was no change between initial particle size and particle size after 1 month. The lack of change in particle size is an indicator of stability of the suspensions.

Suspension 3	389 mg/mL cabotegravir (measured by HPLC)	30 mg/mL P407	19 mg/mL mannitol
Suspension 4	393 mg/mL cabotegravir (measured by HPLC)	28 mg/mL P338	14 mg/mL mannitol

Table 7

Suspension	Initial			1 month		
	X10 (μm)	X50 (μm)	X90 (μm)	X10 (μm)	X50 (μm)	X90 (μm)
Suspension 3	0.059	0.137	0.338	0.06	0.14	0.35
Suspension 4	0.12	0.28	0.74	0.12	0.28	0.75

Table 8

Example 4: Ability of compositions comprising Cabotegravir, Poloxamer 338 and PEG3350 to resuspend

Sixteen suspensions were made varying levels of PEG3350, p338 and particle size as shown in Table 9. All formulations were prepared using the above described methods *i.e.* by dissolving Poloxamer 338 (BASF), mannitol (Roquette Freres), and PEG3350 (Clariant) in water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to cabotegravir (free acid) to prepare an about 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until desired mean particle diameter of 0.2, 0.6 or 1.0 µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The filled suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy. The formulation was selected based on time to resuspension, particle size stability, viscosity and injection force. All suspensions made comprised about 400 mg/mL cabotegravir and about 30 mg/mL mannitol. The concentrations of P338 and PEG338 were varied. The suspensions made are listed below in Table 9.

Suspension	Cabotegravir (mg/mL) by HPLC	pH (duplicate measurements)	P338 (mg/mL)	PEG3350 (mg/mL)	Target x50 (µm)
1a	402	4.6, 4.5	26	20	0.2
2a	404	4.3, 4.5	26	50	0.2
3a	405	5.2, 5.3	38	35	0.2
4a	396	4.4, 4.1	50	0	0.2
5a	406	4.3, 4.3	50	20	0.2
6a	406	4.8, 4.8	50	50	0.2
7a	403	4.9, 4.8	26	35	0.6
8a	397	4.8, 4.7	38	20	0.6
9a	394	4.0, 4.3	38	35	0.6
10a	401	5.0, 4.9	38	50	0.6
11a	398	5.1, 4.7	50	35	0.6
12a	401	4.4, 4.6	26	20	1.0
13a	402	5.0, 5.1	26	50	1.0
14a	400	4.9, 4.8	38	35	1.0
15a	402	4.1, 4.4	50	20	1.0
16a	402	5.0, 5.2	50	50	1.0

Table 9

Each suspension was tested for its ability to resuspend. Vials were stored in an upright position prior to testing. The vials were then inserted into the holder of a benchtop shaker (Glas-Col) so that the vials were at an angle of approximately 45° (1 and 2 months) to the ground with the top of the vial facing downwards, or 0° (3 and 6 months) to the ground. The vials were shaken for 30 seconds at a motor speed setting of 230 to 250. After shaking, the samples were visually

inspected to see if the suspension had resuspended. Resuspension was determined visually as absence of product caked to the bottom of the vial. If the bottom of the vial was transparent to light, it was determined that the suspension had resuspended. If the product had not yet resuspended, it was shaken for another 30 seconds and the bottom of the vial was checked again.

Shaking and visual inspection were continued until the product visually appeared resuspended after a maximum of 4 shaking increments (up to 3 months) or a maximum of 5 shaking increments at 6 months.

The shaking angle of the test was changed from 45° to 0° after 2 months to improve resuspension because the majority of suspensions did not resuspend after 2 months at 30°C/65%RH. The 45° angle is not as representative of human shaking as the 0° angle when Instruction for Use (IFU) instructions for suspension redispersion prior to administration are followed. At 2 months, samples were noted with an asterisk if the vials were not fully resuspended by visual observation. At 3 and 6 months, microscope images were used to determine whether product was fully resuspended; samples containing residual product on the vial bottom were noted with an asterisk. An example of suspensions considered to be fully resuspended (A) and not resuspended (B) are in Figure 4.

Table 10 shows resuspension data after 2 months upright storage at 30°C/65%RH. The number of 30-second shaking intervals to resuspend 3 vials per suspension is shown. The automated shaker was used to reduce the variability in force and torque experienced by the vial during shaking.

Suspension 3a required the lowest number of shaking intervals to resuspend the vials. The three suspensions which required the least number of shaking intervals were all 0.2 µm formulations indicating that this particle size allows for good resuspension.

Table 11 shows resuspension data after 3 and 6 months upright storage at 30°C/65%RH. The number of 30-second shaking intervals to resuspend 3 vials per suspension is shown. Suspension 3a continued to require a lower number of 30 sec increments of shaking on the benchtop shaker per vial for product resuspension after 6 months compared to most of the other formulations.

Suspension	P338 (mg/mL)	PEG3350 (mg/mL)	Target Size (µm)	# of 30 second shaking intervals (3 replicates)			Total
3a	38	35	0.2	2	2	2	6
4a	50	0	0.2	3	2	2	7
1a	26	20	0.2	2	3	3	8
6a	50	50	0.2	3	3	3	9
9a	38	35	0.6	4	4	4	12
16a	50	50	1	4	4	4	12
2a	26	50	0.2	4	4	4	*12
5a	50	20	0.2	4	4	4	*12
11a	50	35	0.6	4	4	4	*12
14a	38	35	1	4	4	4	*12
13a	26	50	1	4	4	4	*12
15a	50	20	1	4	4	4	*12

12a	26	20	1	4	4	4	*12
8a	38	20	0.6	4	4	4	*12
7a	26	35	0.6	4	4	4	*12
10a	38	50	0.6	4	4	4	*12

Table 10 - *indicates that suspensions were not fully resuspended after 4 shakes per vial

Suspension	3 months 30°C/65%RH		6 months 30°C/65%RH	
	Total	Avg/Vial	Total	Avg/Vial
1a	5	1.7	6	2.0
2a	12	4.0*	15	5.0*
3a	5	1.7	6	2.0
4a	3	1.0	3	1.0
5a	6	2.0	6^	3.0
6a	7	2.3	9	3.0
7a	6	2.0	7	2.3
8a	6	2.0	7	2.3
9a	8	2.7	15	5.0
10a	6	2.0	15	5.0
11a	6	2.0	15	5.0
12a	12	4.0*	15	5.0*
13a	9	3.0	15	5.0
14a	5	1.7	6	2.0
15a	3	1.0	6	2.0
16a	6	2.0	14	4.7

Table 11 - * indicates that suspensions were not fully resuspended after 4 or 5 shakes per vial via evaluation using a light microscope. ^indicates that only 2 vials were tested. 3 vials were tested for all other conditions.

5 Example 5: Particle size and viscosity of compositions comprising Cabotegravir, Poloxamer 338 and PEG3350

10 The viscosity of each of the suspensions made in Table 9 in Example 4 was measured initially after they were made. The particle size of the suspensions was also measured initially after they were made as well as after 2, 3 and 6 months of storage at 40°C/75%RH. Results are shown in Table 12 and 13. Across all suspensions, there was minimal change in particle size after storage under accelerated conditions. Viscosity differed across suspensions. Suspensions with a target x50 of 0.2µm and 50 mg/mL P338 had the highest viscosities. The shear viscosity of the suspensions was measured using a Malvern Kinexus Pro rheometer equipped with a roughened cone and plate. Data was gathered at 20 °C with data collection at 10 points per decade across a shear rate range
15 from 0.1 s⁻¹ to 10 s⁻¹.

Suspensions			Initial			2 MN 40°C/75%RH		
	Visc @ 0.1 s ⁻¹ (cP)	Visc @ 10 s ⁻¹ (cP)	X10 (µm)	X50 (µm)	X90 (µm)	X10 (µm)	X50 (µm)	X90 (µm)
1a	24	18	0.09	0.2	0.5	0.11	0.23	0.54

2a	38	24	0.1	0.23	0.54	0.12	0.26	0.59
3a	116	43	0.07	0.17	0.39	0.08	0.17	0.4
4a	406	76	0.09	0.21	0.59	0.1	0.24	0.79
5a	763	95	0.1	0.22	0.55	0.73	0.24	0.58
6a	392	79	0.09	0.2	0.51	0.11	0.24	0.57
7a	83	25	0.21	0.6	1.60	0.28	0.70	2.0
8a	50	28	0.23	0.66	1.90	0.27	0.71	2.1
9a	92	31	0.18	0.61	1.7	0.26	0.68	2.0
10a	132	40	0.23	0.66	1.90	0.34	0.76	2.3
11a	124	44	0.24	0.69	2.00	0.33	0.78	2.3
12a	17	11	0.33	0.96	2.6	0.43	1.0	2.7
13a	32	16	0.57	1.3	3.0	0.6	1.4	3.1
14a	54	24	0.49	1.2	3.0	0.52	1.2	3.0
15a	37	15	0.74	1.6	3.3	0.73	1.6	3.4
16a	92	55	0.61	1.4	3.1	0.6	1.4	3.2

Table 12

	3 months 40°C/75%RH			6 months 40°C/75%RH		
Suspension	x10 (µm)	x50 (µm)	x90 (µm)	x10 (µm)	x50 (µm)	x90 (µm)
1a	0.1	0.22	0.53	0.09	0.21	0.57
2a	0.11	0.26	0.62	0.10	0.24	0.63
3a	0.07	0.16	0.4	0.07	0.16	0.4
4a	0.08	0.22	0.83	0.09	0.23	0.8
5a	0.08	0.2	0.54	0.09	0.21	0.53
6a	0.1	0.23	0.58	0.09	0.24	0.71
7a	0.16	0.63	1.7	0.19	0.67	1.9
8a	0.15	0.67	1.8	0.21	0.67	1.9
9a	0.22	0.67	2.0	0.20	0.66	1.9
10a	0.19	0.69	2.0	0.21	0.73	2.0
11a	0.18	0.73	2.1	0.21	0.77	2.1
12a	0.41	1.0	2.7	0.35	0.99	2.6
13a	0.6	1.4	3.1	0.6	1.4	3.1
14a	0.52	1.2	3.0	0.54	1.3	3.0
15a	0.71	1.6	3.3	0.69	1.6	3.3
16a	0.6	1.4	3.2	0.6	1.4	3.2

Table 13 - No major changes observed in particle size after 6 months at 40°C/75%RH.Example 6: 12-month stability of suspension 6a

5 A suspension with the P338 and PEG3350 composition and target size of suspension 6a was manufactured for a non-clinical safety study and monitored on stability for 12 months. The data is shown in Table 14. No changes in content, impurities or particle size were observed. A drop in pH was observed, but the pH is still within the acceptable pH range for injection.

Storage Condition/ Orientation	Storage Time (Months)	Cabotegravir Content by HPLC (mg/mL)	Drug Related Impurities (% area)	pH	Particle Size (µm)		
					X ₁₀	X ₅₀	X ₉₀
Initial	Initial	398.8	0.05	5.6, 5.5	0.05	0.12	0.28
30°C/65%RH /Inverted	2	400.0	0.05	4.8, 4.8	0.05	0.14	0.36
	3	401.2	0.05	4.8, 4.6	0.05	0.13	0.29
	6	398.0	0.05	4.6, 4.7	0.06	0.14	0.31
	9	401.6	0.05	4.5, 4.7	0.06	0.13	0.31
	12	396.0	0.05	4.5, 4.7	0.05	0.12	0.29

Table 14Example 7: Pharmacokinetics

The pharmacokinetics of cabotegravir suspensions were evaluated in male Sprague Dawley rats. Three suspensions were tested: (i) 200 mg/mL cabotegravir with PS20 and PEG3350; (ii) 400 mg/mL cabotegravir with P338; (iii) and 400 mg/mL cabotegravir with P338 and PEG3350. The suspensions tested are shown in Table 15.

Suspension	Cabotegravir (mg/mL) by HPLC	Excipients	Size (x10) in µm	Size (x50) in µm	Size (x90) in µm
i	195	18 mg/mL PS20, 18 mg/mL PEG3350, 31 mg/mL mannitol	0.07	0.17	0.51
ii	393	28 mg/mL P338, 14 mg/mL mannitol	0.12	0.28	0.74
iii	399	50 mg/mL P338, 50 mg/mL PEG3350, 30 mg/mL mannitol	0.05	0.12	0.28

Table 15

Rats were administered the cabotegravir suspensions by intramuscular injection in the right gastrocnemius muscle or subcutaneous injection at 200 or 400 mL/kg (rats weighed just prior to dosing) to achieve a target dose of 10 mg/kg/dose. A total of three rats were used per suspension. Blood samples were collected into 500 µL K₂EDTA tubes via lateral tail vein or tail tip amputation. 75 µL of whole blood was then transferred to a new matrix tube, combined with 75 µL of sterile water, vortexed and stored on dry ice. Samples were stored at -80°C for drug concentration analysis. Blood concentrations of cabotegravir were determined using an analytical method based on protein precipitation, followed by UHPLC/MS/MS analysis. Using a 25 µL aliquot of sample, the lower limit of quantification (LLQ) for cabotegravir was 50 ng/mL. The computer systems that were used on this study to acquire and quantify data included Analyst Version 1.6.1 and SMS2000 Version 3.1.

Figure 2 shows cabotegravir concentration in blood of individual rats after intramuscular administration of suspension i, ii or iii. Overall, the pharmacokinetic profiles for all three suspensions were found to be similar. In particular, the slopes for the terminal phase, representing absorption rates for long acting formulations under the assumption of 'flip-flop kinetics', overlap for all formulations tested. This suggests that the long-acting profile for cabotegravir is maintained for the 400 mg/mL suspensions compared to the 200 mg/mL suspension.

Figure 3 shows cabotegravir concentrations in blood after a 10 mg/kg subcutaneous administration of 400 mg/mL cabotegravir with 50 mg/mL P338, 50 mg/mL PEG3350 and 30 mg/mL mannitol. 3 rats were used. Each line represents the blood concentration of a separate rat. Subcutaneous administration resulted in detectable blood cabotegravir concentrations out to 12 weeks.

Example 8: Comparison with a suspension comprising 400 mg/mL Cabotegravir with Polysorbate 20 (PS20) and Polyethylene Glycol 3350 (PEG3350)

A long acting suspension comprising 200 mg/mL cabotegravir, 20 mg/mL PS20 and 20 mg/mL PEG3350 was investigated to test stability when the cabotegravir concentration was increased to 400 mg/mL.

The suspension was prepared in a 250mL batch using a Netzsch miniCer and 0.3mm YTZ grinding beads. A range of excipient concentrations were explored.

The formulation vehicle was prepared by dissolving Polysorbate 20 (Croda), Polyethylene Glycol 3350 (Clariant), and mannitol (Roquette Freres) in water for injection (WFI) and filtering the solution through a 0.2µm filter. The formulation vehicle was then added to Cabotegravir (free acid) to prepare a 400 mg/ml coarse suspension. The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired median particle diameter of less than 0.25µm was reached as measured by laser diffraction. The wet bead mill was cooled to maintain a temperature between 1 and 25°C. The suspension was then filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The filled suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

30 mg/mL PS20, 30 mg/mL PEG3350 and 19 mg/mL mannitol with 400 mg/mL cabotegravir was prepared. The gamma irradiated suspension in vials was set down in the upright position and stored at 40°C/75%RH. After 1 month and 3 months of storage, suspensions were tested for stability. Table 16 shows particle size after formulation and after 1 month of storage at 40°C/75%RH for the 400 mg/mL cabotegravir formulation with 30 mg/mL PS20, 30 mg/mL PEG3350, 19 mg/mL mannitol. At 1 month, the particle size had increased compared to the initial time point (Table 13 and Figure 3). At 3 months, the suspension had become an unrecoverable gel which could not be removed from the vial with a syringe.

Time	x10	x50	x90
Initial	0.07	0.17	0.61
1 month	0.14	0.41	3.2

Table 16

Further suspensions comprising cabotegravir, PS20 and PEG3350 were prepared with the concentrations shown in Table 17. Experiments 1, 2 and 5 were prepared using the method described above for 20 mg/mL PS20 and PEG3350. In experiment 3, the suspension was first milled with PS20 (no PEG3350), and then PEG3350 was added, here 400 mg/mL cabotegravir was milled with 30 mg/mL PS20. After milling, a concentrated solution (400 mg/mL) of PEG3350 was added to dilute the 400 mg/mL suspension to 360 mg/mL cabotegravir, 27 mg/mL PS20, 27 mg/mL mannitol. Compositions were all prepared on a 250mL batch scale using the Netzsch miniCer with 0.3mm YTZ grinding beads.

Experiment Number	PS20 (mg/mL)	PEG3350 (mg/mL)
1	40.0	40.0
2	30.0	40.0
3	27*	40.0
4	20	20.0
5	20	0

Table 17

*400 mg/mL was diluted down by 10%, resulting in 360 mg/mL cabotegravir and 27 mg/mL PS20

In Experiments 1, 2, 4 and 5 during wet bead milling on the miniCer, the suspension thickened into a paste and was not recoverable. In Experiment 3, within 5 minutes of adding the 400 mg/mL PEG3350 solution, the suspension thickened and could no longer be stirred. The combination of PS20 and PEG3350 with 400 mg/mL cabotegravir did not produce a physically stable suspension.

Example 9: 500 mg/mL Cabotegravir with Poloxamer 338 or 407

Injectable suspensions comprising about 500 mg/mL cabotegravir were prepared with Poloxamer 407 or Poloxamer 338. Mannitol was also added as a tonicity agent. The formulation vehicle was prepared by dissolving: 8.8g Poloxamer 338 and 7.0g mannitol in 159.3 g WFI (Suspension 4); 9.7g P338 (BASF) and 11.1g mannitol (Roquette Freres) in 159.3g WFI (Suspension 5); and 9.7g P407 (BASF) and 11.1g mannitol (Roquette Freres) in 159.3g WFI (Suspension 6) and filtering the solution through a 0.2µm filter. The formulation vehicle was added to 125g Cabotegravir (free acid) to prepare a 500 mg/ml coarse suspension (Suspension 4) or 138.8g Cabotegravir (free acid) to prepare a 555 mg/mL coarse suspension (Suspensions 5 & 6). The coarse suspension, while stirred, was circulated through a wet bead mill set at 29.7Hz (Netzsch MiniCer) containing 0.30mm YTZ grinding beads (Nikkato Corp) at 73 – 145 ml/min until the desired mean particle diameter of around 0.2µm was reached. The wet bead mill was cooled to maintain a temperature between 1 to 25°C. In the case of Suspensions 5 & 6, the milled suspension was diluted with concentrated PEG3350 solutions to produce final suspension compositions of 500 mg/mL Cabotegravir, 35 mg/mL P338 or P407, 40 mg/mL mannitol, and 0-40 mg/mL PEG3350. The suspension was filled into Type I glass vials, flushed with nitrogen, stoppered (FM457 stopper) and sealed. The resulting suspension was terminally sterilized by gamma irradiation at a minimum dose of 25kGy.

Table 18 shows the suspensions which were made. Each suspension was stored at 40°C/75%RH in an upright position. Initial particle size and particle size after 1 month was measured as an indicator of suspension stability. Table 19 shows the particle size in each suspension after 1 month. There was no change between initial particle size and particle size after 1 month. The lack of change in particle size is an indicator of stability of the suspensions.

The viscosity of each of the suspensions made in Table 18 was measured initially after they were made. The particle size of the suspensions was also measured initially after they were made as well as after 1 month of storage at 50°C. Results are shown in Table 19. Across all suspensions, there was minimal change in particle size after storage under accelerated conditions. The viscosity of Suspension 4 is within the range of viscosities observed in the Cabotegravir 400 mg/mL compositional DoE and is modestly higher than the viscosity of Suspension 3a (discussed above), which has a similar P338 composition and similar size target x50 of 0.2µm. The shear

viscosity of the suspensions was measured using a Malvern Kinexus Pro rheometer equipped with a roughened cone and plate. Data was gathered at 20 °C with data collection at 10 points per decade across a shear rate range from 0.1 s⁻¹ to 10 s⁻¹.

Suspension 4	497 mg/mL cabotegravir (measured by HPLC)	35 mg/mL P338	40 mg/mL mannitol	0 mg/mL PEG
Suspension 5	500 mg/mL cabotegravir (theoretical)	35 mg/mL P338	40 mg/mL mannitol	0-40 mg/mL PEG3350
Suspension 6	500 mg/mL cabotegravir (theoretical)	35 mg/mL P407	40 mg/mL mannitol	0-40 mg/mL PEG3350

Table 18

Suspension	Visc @ 0.1 s ⁻¹ (cP)	Visc @ 10 s ⁻¹ (cP)	Initial			1 month @ 50°C/ambient RH		
			X10 (um)	X50 (um)	X90 (um)	X10 (um)	X50 (um)	X90 (um)
Suspension 4	197.016	61.419	0.07	0.22	0.72	0.09	0.24	0.69
Suspension 5	NT	NT	0.07	0.17	0.42	-		
Suspension 6	NT	NT	0.09	0.21	0.51	-		

Table 19

Example 10: Wettability study to define limits of Cabotegravir suspension strength

Wettability of Cabotegravir in 38 mg/mL P338, 35 mg/mL PEG3350, and 20 mg/mL mannitol was assessed to estimate the approximate concentration limit for Cabotegravir suspension in this vehicle. This was performed by adding increasing amounts of Cab to 5g of vehicle until a gross change in coarse suspension properties was observed. The results are summarized in Table 20 and show that the upper boundary of Cabotegravir solid suspension concentration in this vehicle is 600 mg/mL or less.

mg/mL Cabotegravir	Cababotegravir (g)	Vehicle* (g)	Gross viscosity
396	2.63	5	Similar to water
500	3.57	5	Similar to water
565†	4.33	5	Similar to water
580†	4.50	5	Boundary of thickening
600†	4.81	5	Thicker, but flowable
635†	5.28	5	Slightly paste-like

Table 20

*38 mg/mL P338, 35 mg/mL PEG3350, 20 mg/mL mannitol

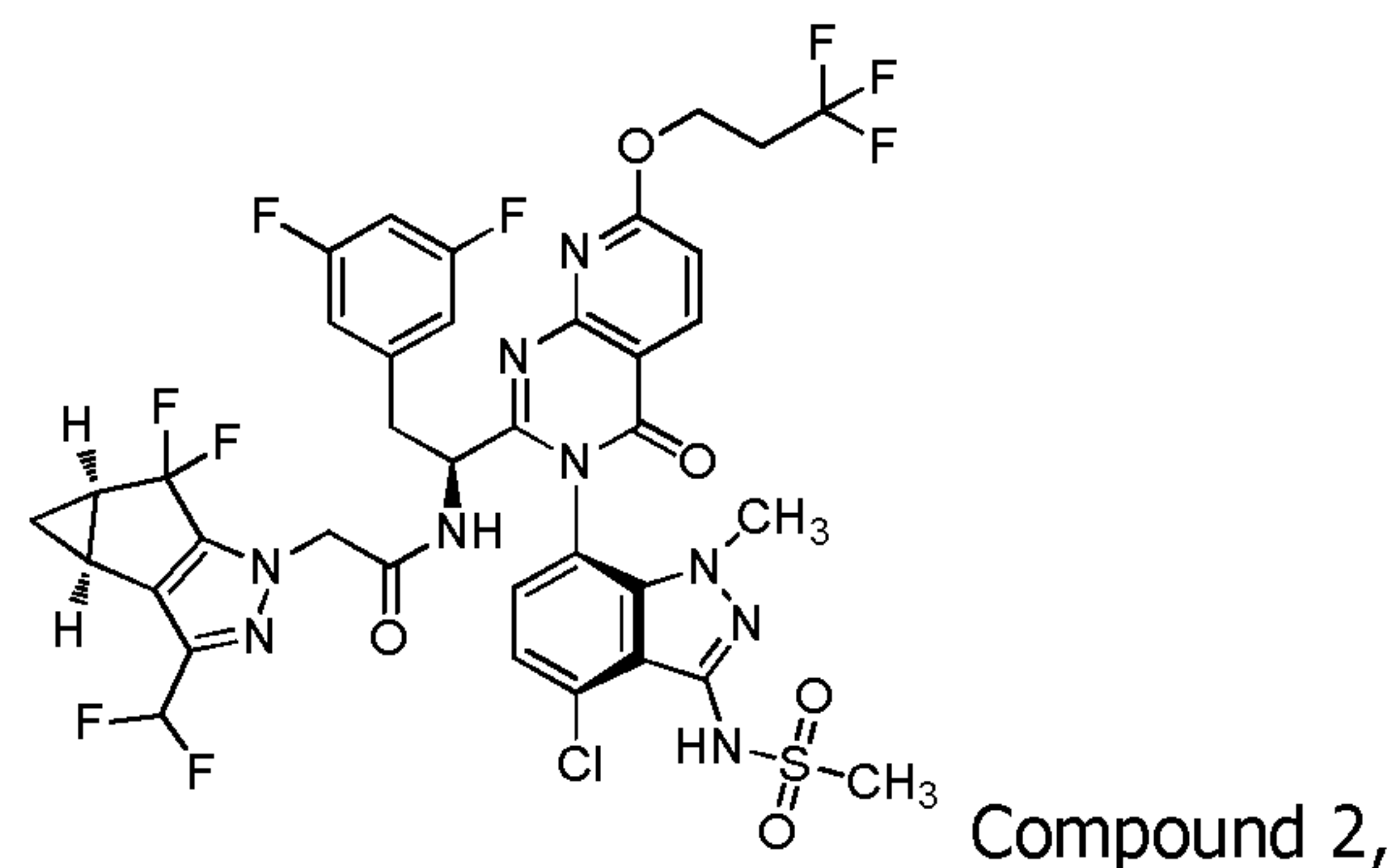
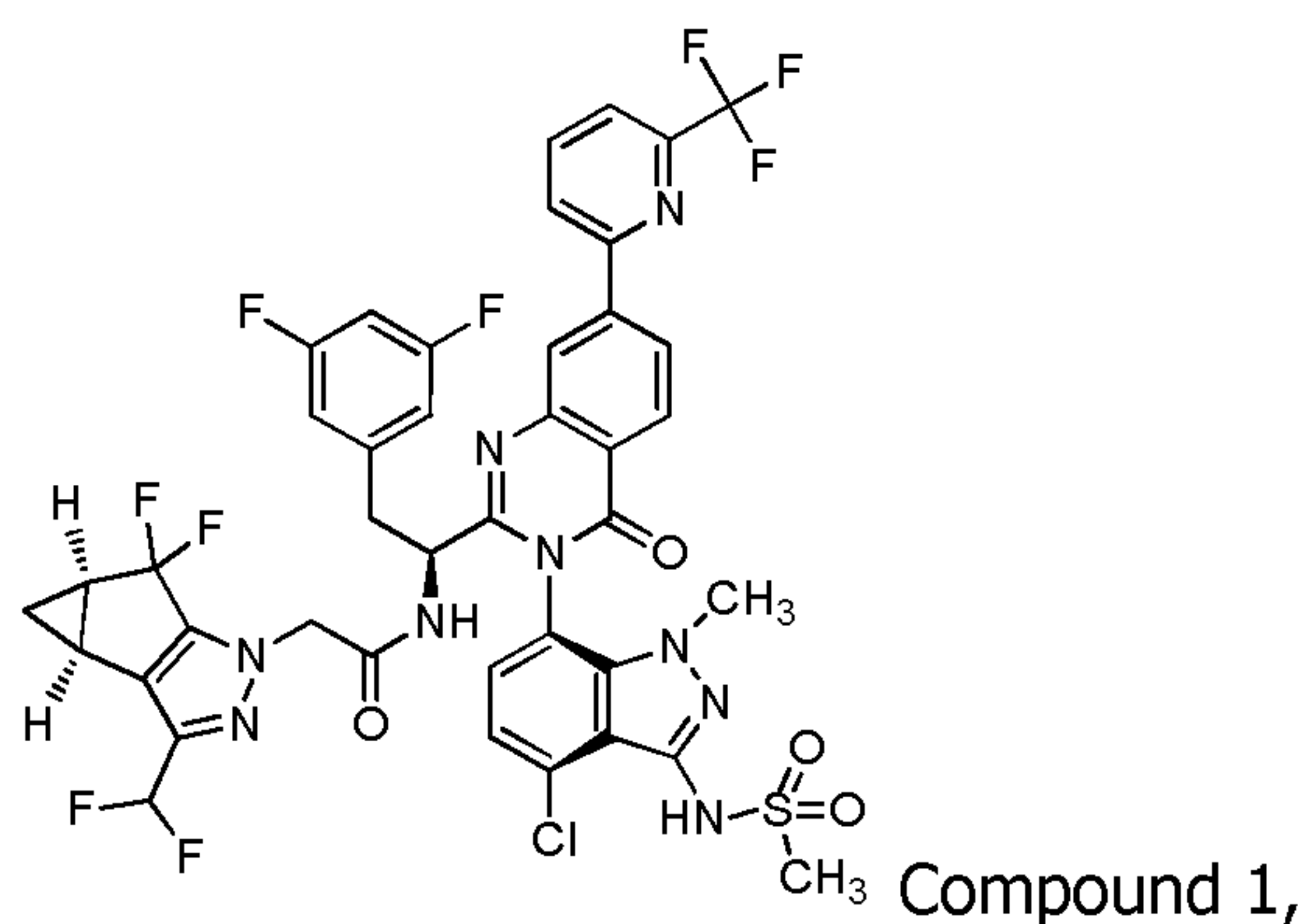
†These values were calculated using densities approximated from lower concentrations

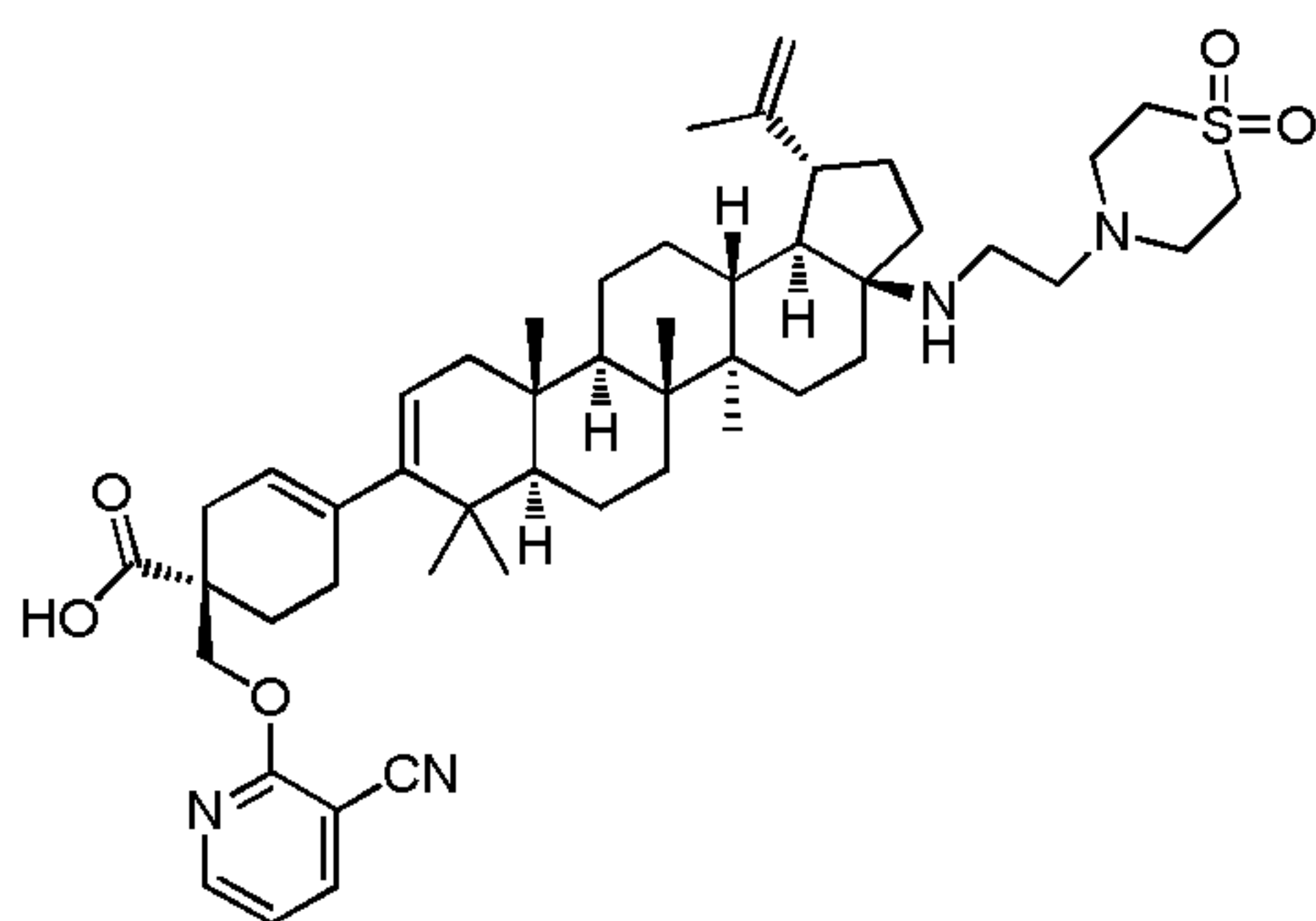
- 5 It will be understood that the present invention has been described above purely by way of example, and modification of detail can be made within the scope of the invention. Each feature disclosed in the description, and where appropriate the claims and drawings may be provided independently or in any appropriate combination.

CLAIMS

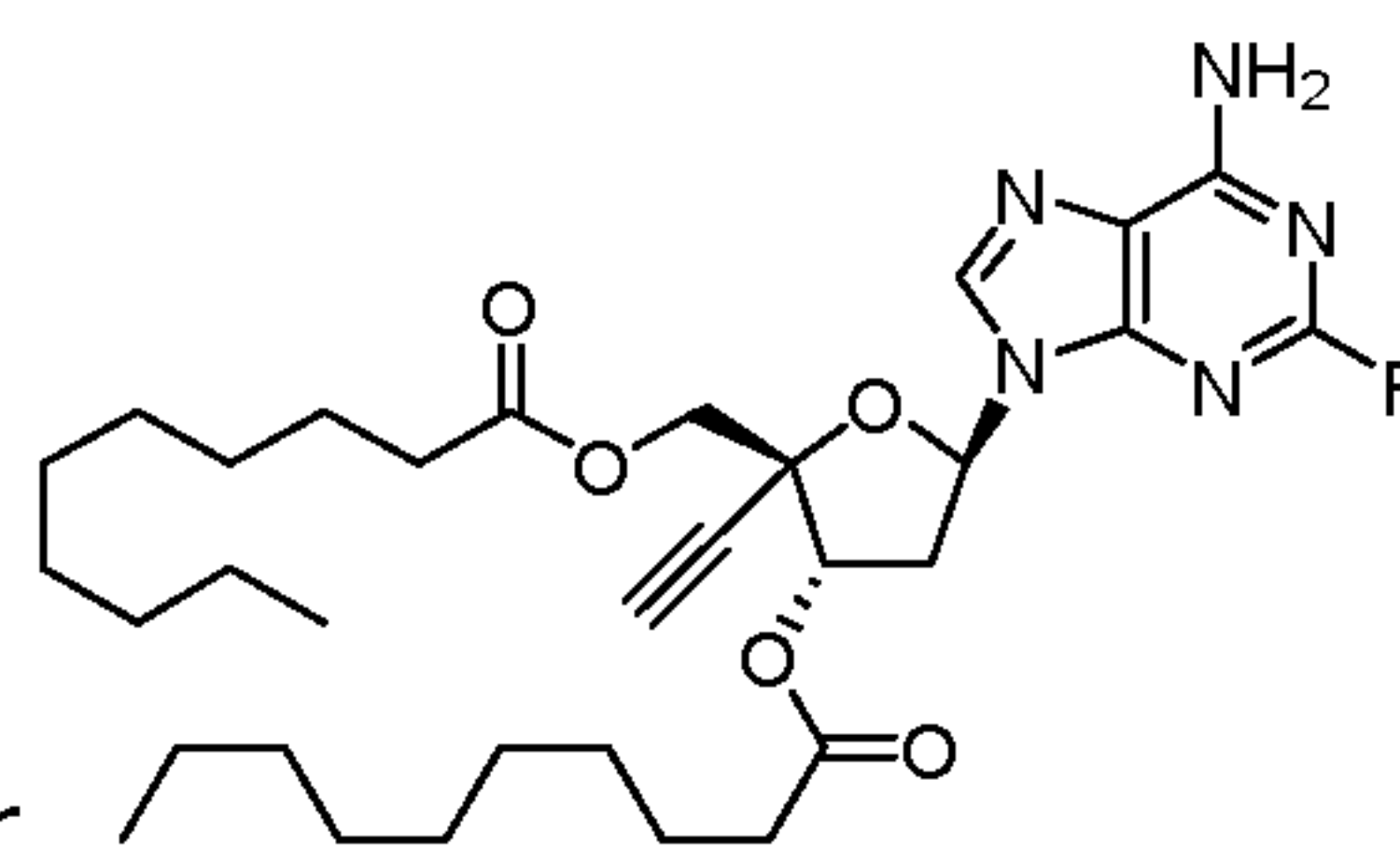
1. A pharmaceutical composition comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.
- 5 2. The pharmaceutical composition according to Claim 1, wherein the polyethylene glycol is polyethylene glycol 3350.
3. The pharmaceutical composition according to Claim 1 or Claim 2, wherein the poloxamer is poloxamer 407, poloxamer 237 or poloxamer 338.
- 10 4. The pharmaceutical composition according to Claim 3, wherein the poloxamer is poloxamer 407 or poloxamer 338.
- 15 5. The pharmaceutical composition according to any preceding claim wherein the polyethylene glycol is polyethylene glycol 3350 and the poloxamer is poloxamer 407.
6. The pharmaceutical composition according to any of Claims 1 to 4, wherein the polyethylene glycol is polyethylene glycol 3350 and the poloxamer is poloxamer 338.
- 20 7. The pharmaceutical composition according to any preceding claim, wherein the cabotegravir is present in the form of particles with a median particle diameter of about 0.1 to 10 μm .
- 25 8. The pharmaceutical composition according to Claim 7, wherein the cabotegravir is present in the form of particles with a median particle diameter of above 0.15 to 0.25 μm .
9. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition further comprises mannitol.
- 30 10. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a cabotegravir concentration of 350 to 600 mg/mL.
- 35 11. The pharmaceutical composition according to Claim 10, wherein the pharmaceutical composition comprises a cabotegravir concentration of 350 to 500 mg/mL.
12. The pharmaceutical composition according to Claim 11, wherein the pharmaceutical composition comprises a cabotegravir concentration of 380 to 420 mg/mL.
- 40 13. The pharmaceutical composition according to Claim 12, wherein the pharmaceutical composition comprises a cabotegravir concentration of about 400 mg/mL.
14. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a poloxamer concentration of 4 to 50 mg/mL.
- 45 15. The pharmaceutical composition according to any preceding claim, wherein the pharmaceutical composition comprises a polyethylene glycol concentration of 5 to 50 mg/mL.

16. The pharmaceutical composition according to any preceding claim, wherein the composition is a parenteral pharmaceutical composition.
- 5 17. The pharmaceutical composition according to any preceding claim wherein the composition is suitable for use as an injectable composition.
- 10 18. A method for the treatment or prevention of human immunodeficiency virus (HIV) in a human in need thereof comprising administering to said human a therapeutically effective amount of a pharmaceutical composition as defined in any one of Claims 1 to 17.
19. The method according to Claim 18, wherein the method comprises a step of administering the pharmaceutical composition subcutaneously or intramuscularly.
- 15 20. The method according to Claim 18 or 19, wherein about 1 mL to about 3 mL of the pharmaceutical composition is administered to the human.
- 20 21. The method according to any of Claims 18 to 20, wherein the method comprises administering the pharmaceutical composition to the human once every month, once every 2 months or once every 3 months.
22. The method according to any of Claims 18 to 20, wherein the method comprises administering 1 to 1.5 mL of the pharmaceutical composition subcutaneously to a human once every month.
- 25 23. The method according to any of Claims 18 to 20, wherein the method comprises administering 2.5 to 3mL of the pharmaceutical composition intramuscularly to the human once every 3 months.
- 30 24. The method according to any of Claims 18 to 23, wherein the method comprises administering the pharmaceutical composition in combination with N6-LS,





Compound 3 or



Compound 4.

25. A pharmaceutical composition defined in any of Claims 1 to 17 for use in the treatment or prevention of HIV.

26. The pharmaceutical composition for use according to Claim 25, wherein the pharmaceutical composition is administered to a human intramuscularly or subcutaneously.

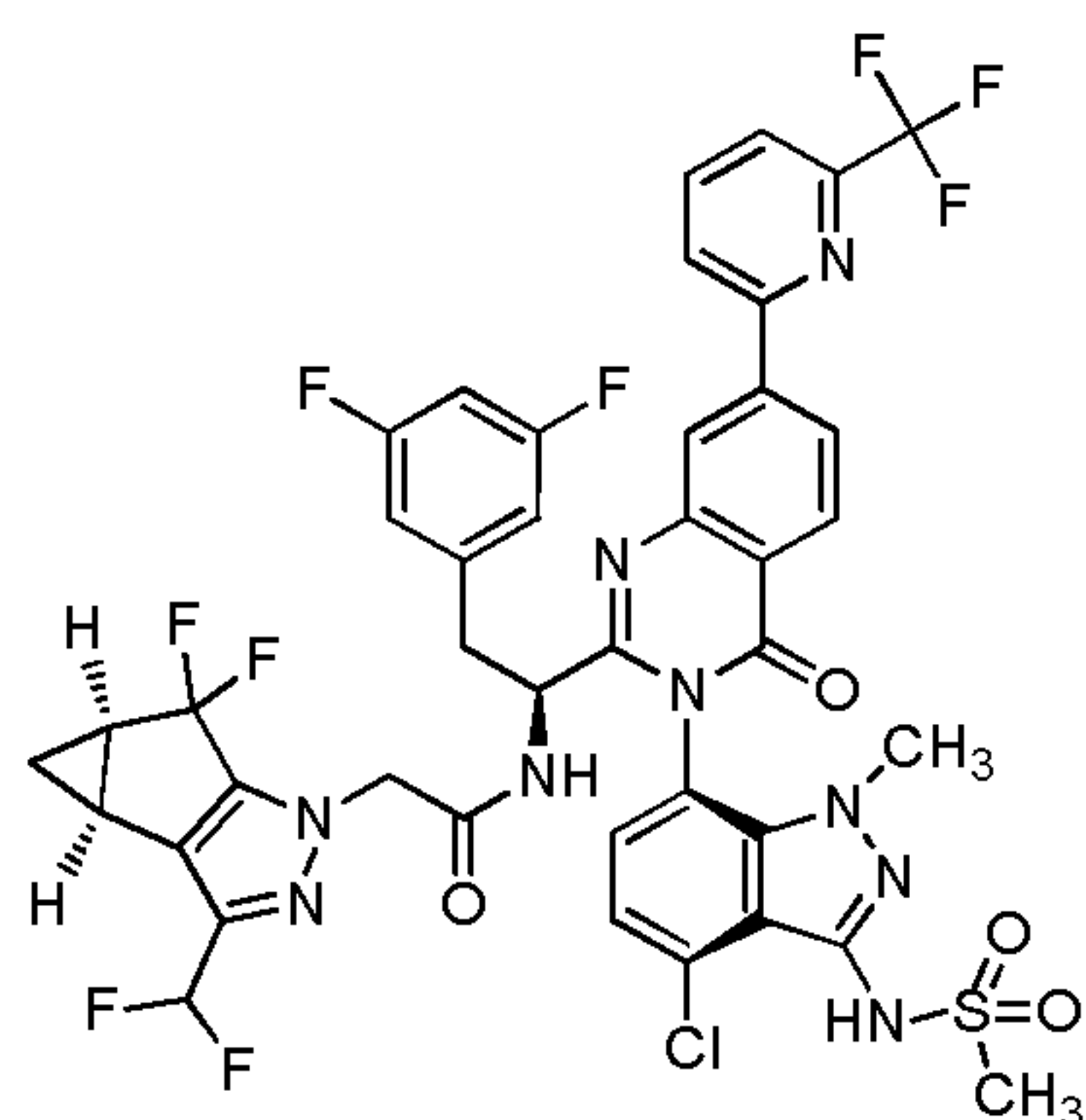
27. The pharmaceutical composition for use according to either Claim 25 or Claim 26, wherein about 1 mL to about 3 mL of the pharmaceutical composition is administered to a human.

28. The pharmaceutical composition for use according to any of Claims 25 to 27, wherein the pharmaceutical composition is administered once every month, once every 2 months or once every 3 months.

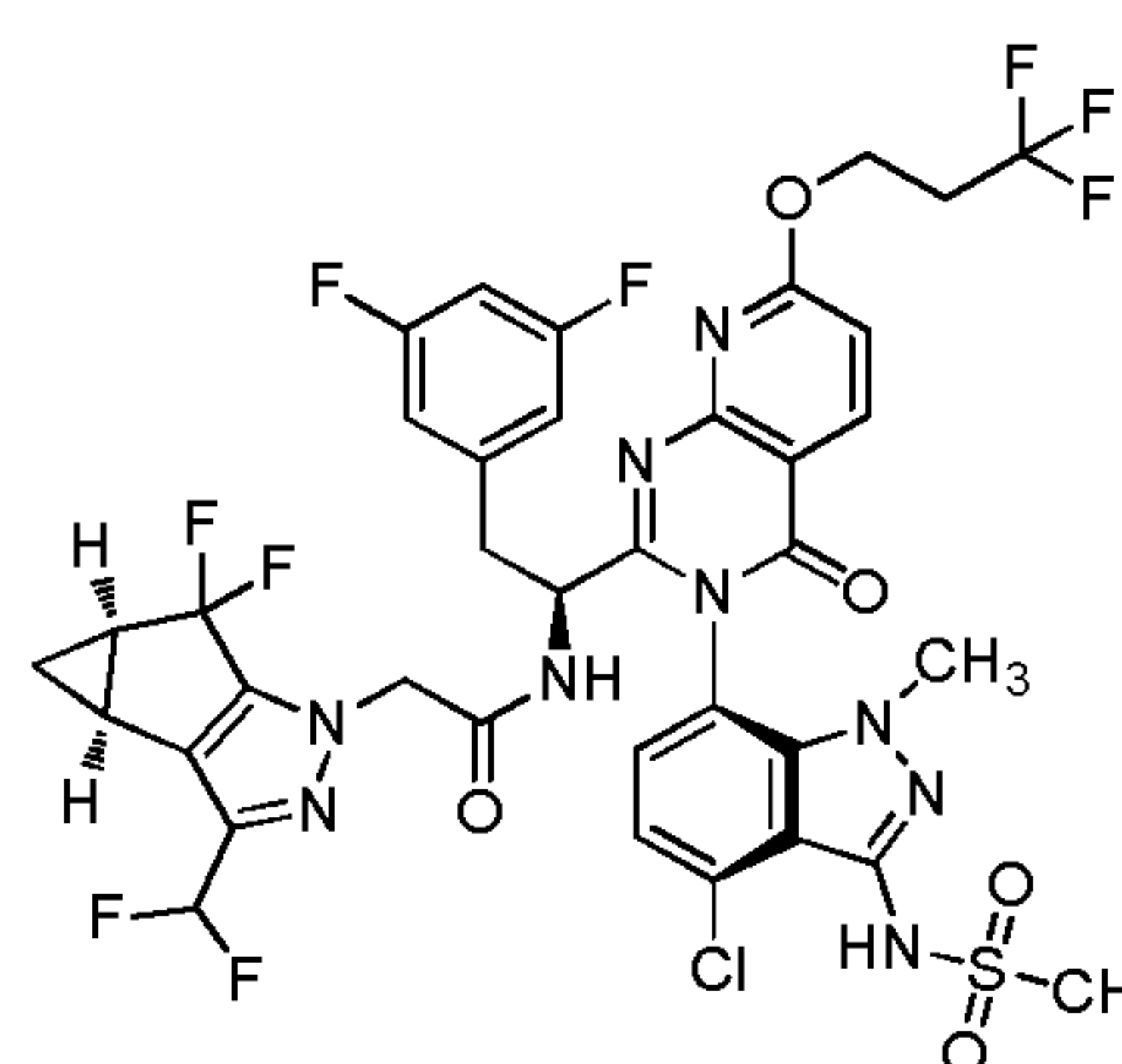
29. The pharmaceutical composition for use according to any of Claims 25 to 28, wherein 1 to 1.5 mL of the pharmaceutical composition is administered subcutaneously once every month.

30. The pharmaceutical composition for use according to any of Claims 25 to 29, wherein 2.5 to 3mL of the pharmaceutical composition is administered intramuscularly once every 3 months.

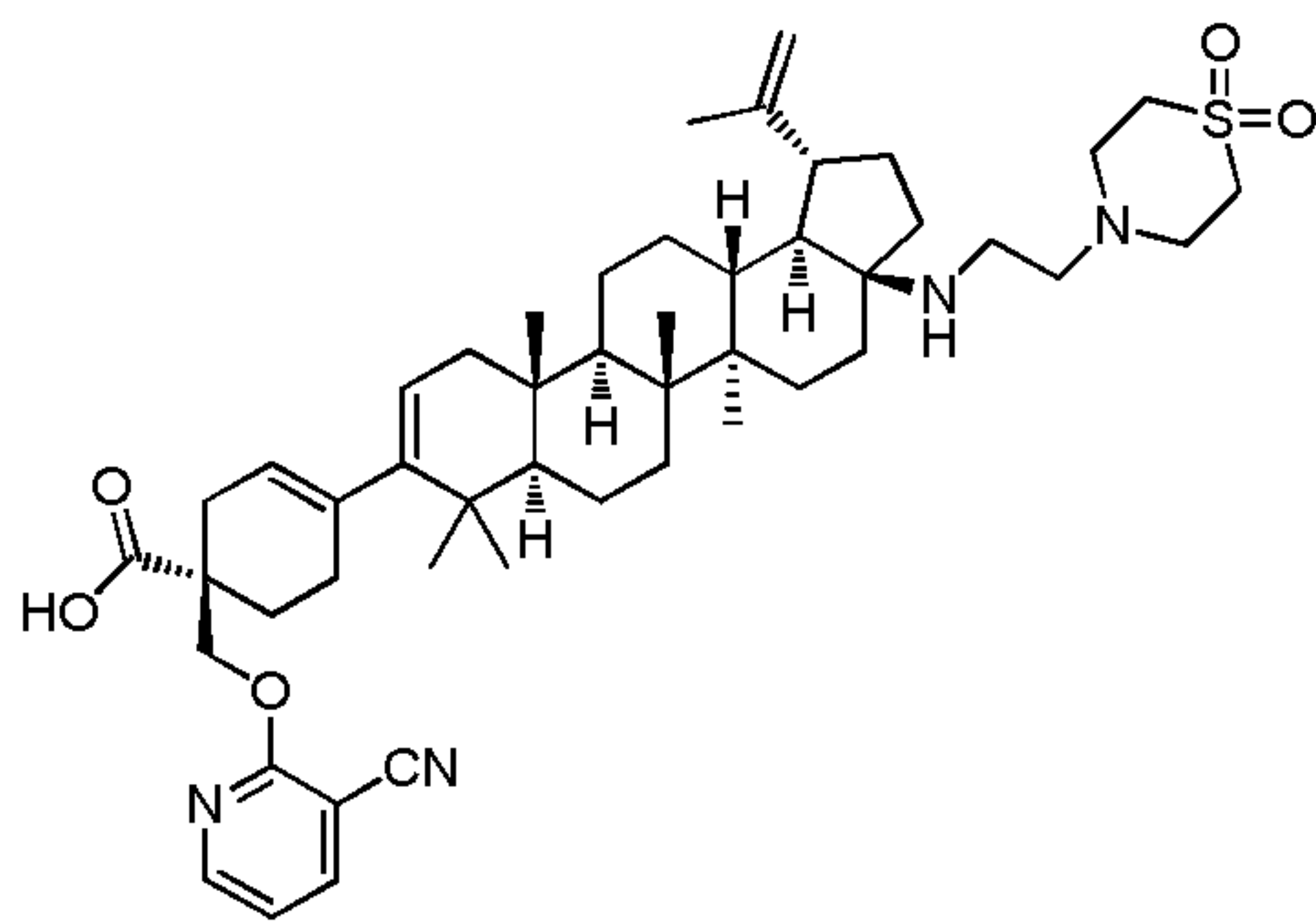
31. The pharmaceutical composition for use according to any of Claims 25 to 30, wherein the pharmaceutical composition is administered in combination with N6-LS,



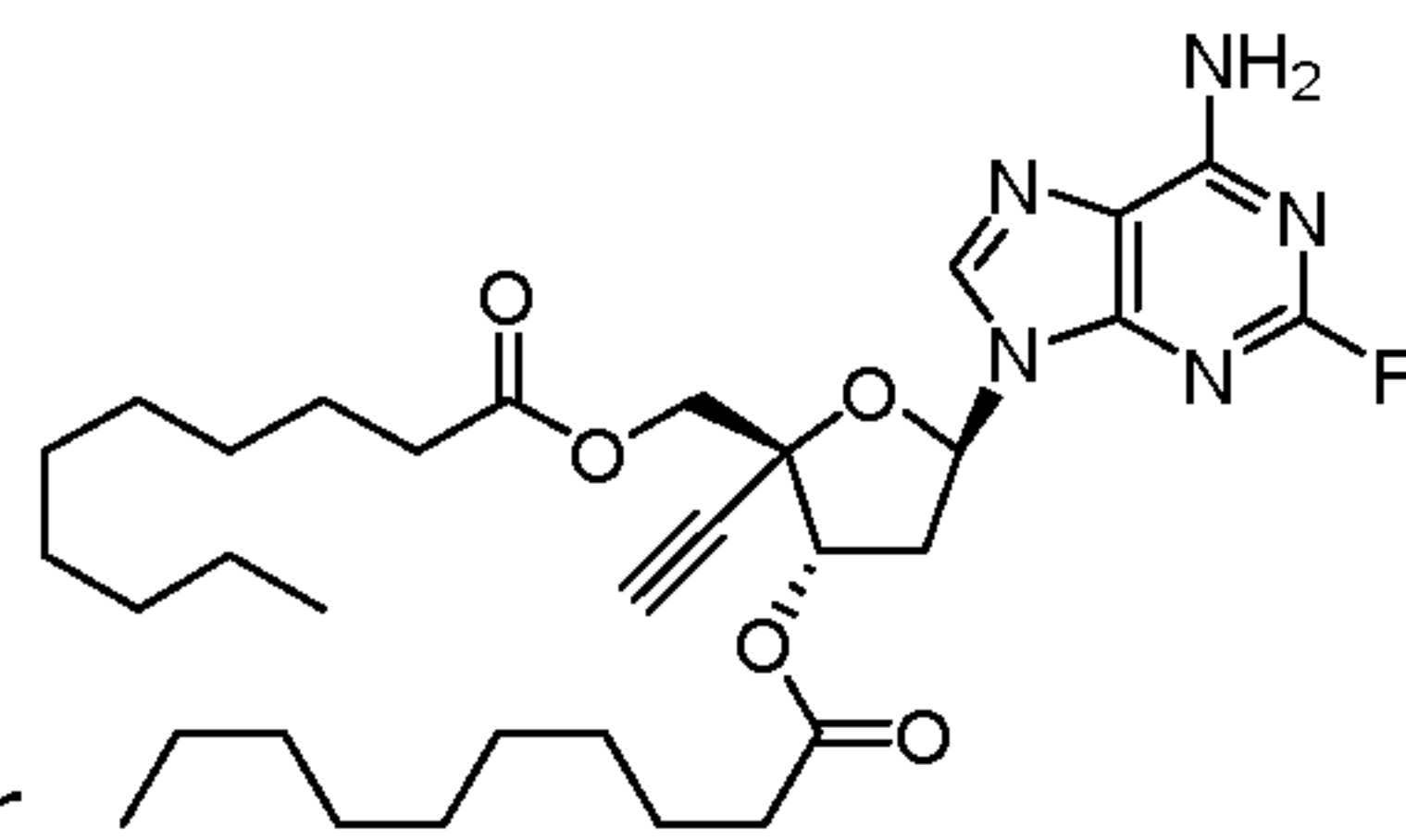
Compound 1,



Compound 2,



Compound 3 or



Compound 4.

- 5 32. A method of making a pharmaceutical composition according to any of Claims 1 to 17, wherein the method comprises contacting cabotegravir or a pharmaceutically acceptable salt thereof with polyethylene glycol and poloxamer.
33. A kit comprising cabotegravir or a pharmaceutically acceptable salt thereof, polyethylene glycol and poloxamer.

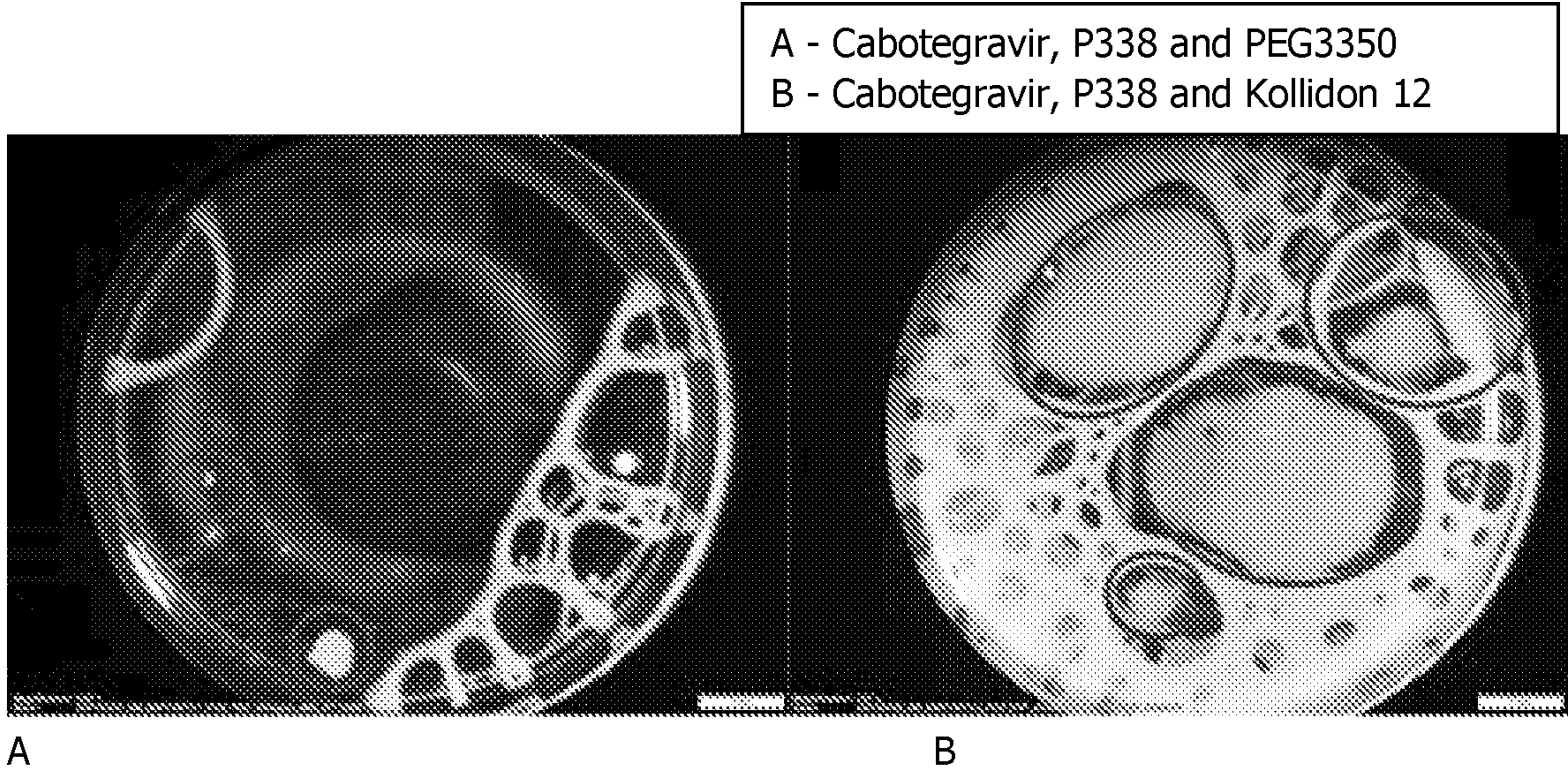


Figure 1

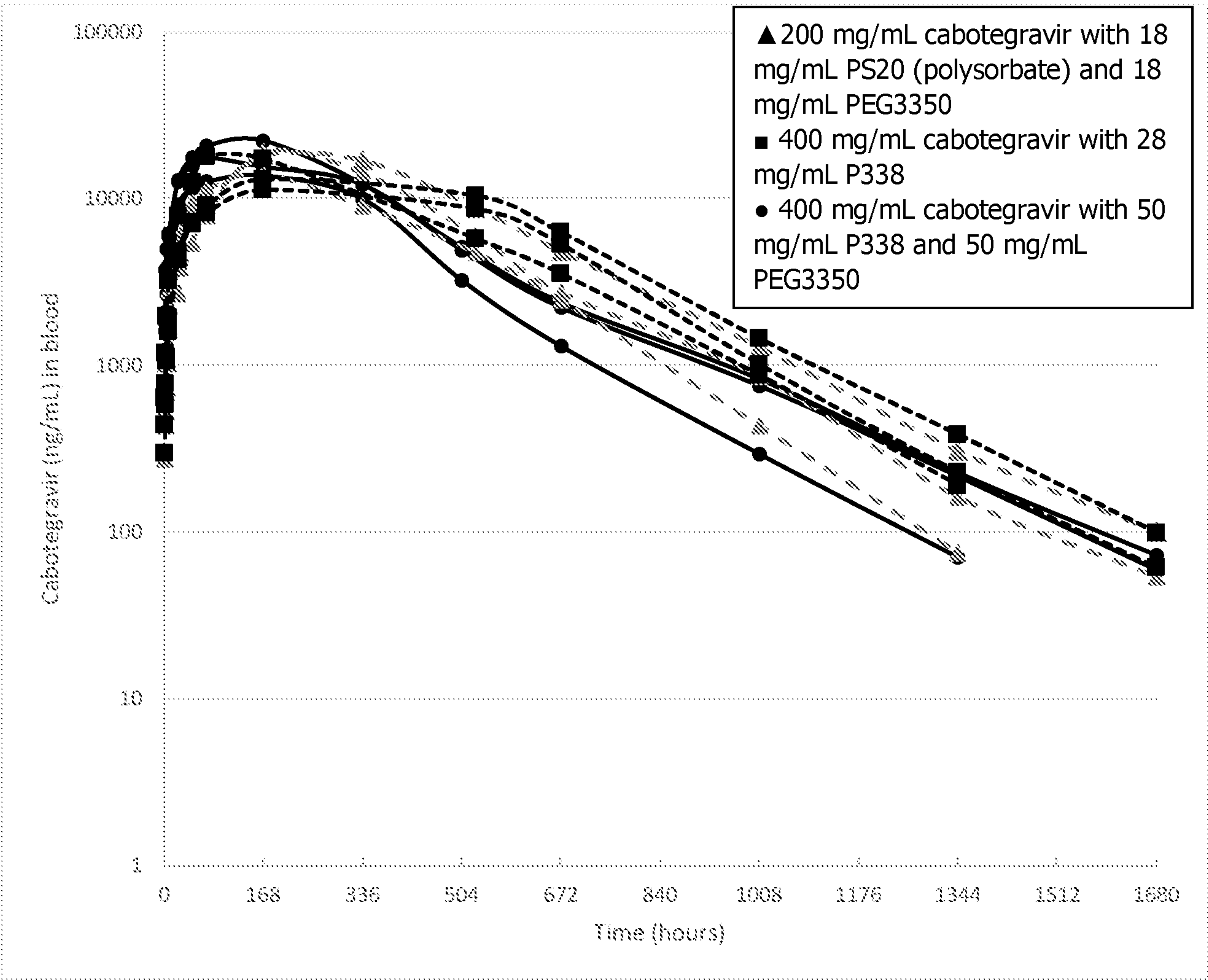


Figure 2

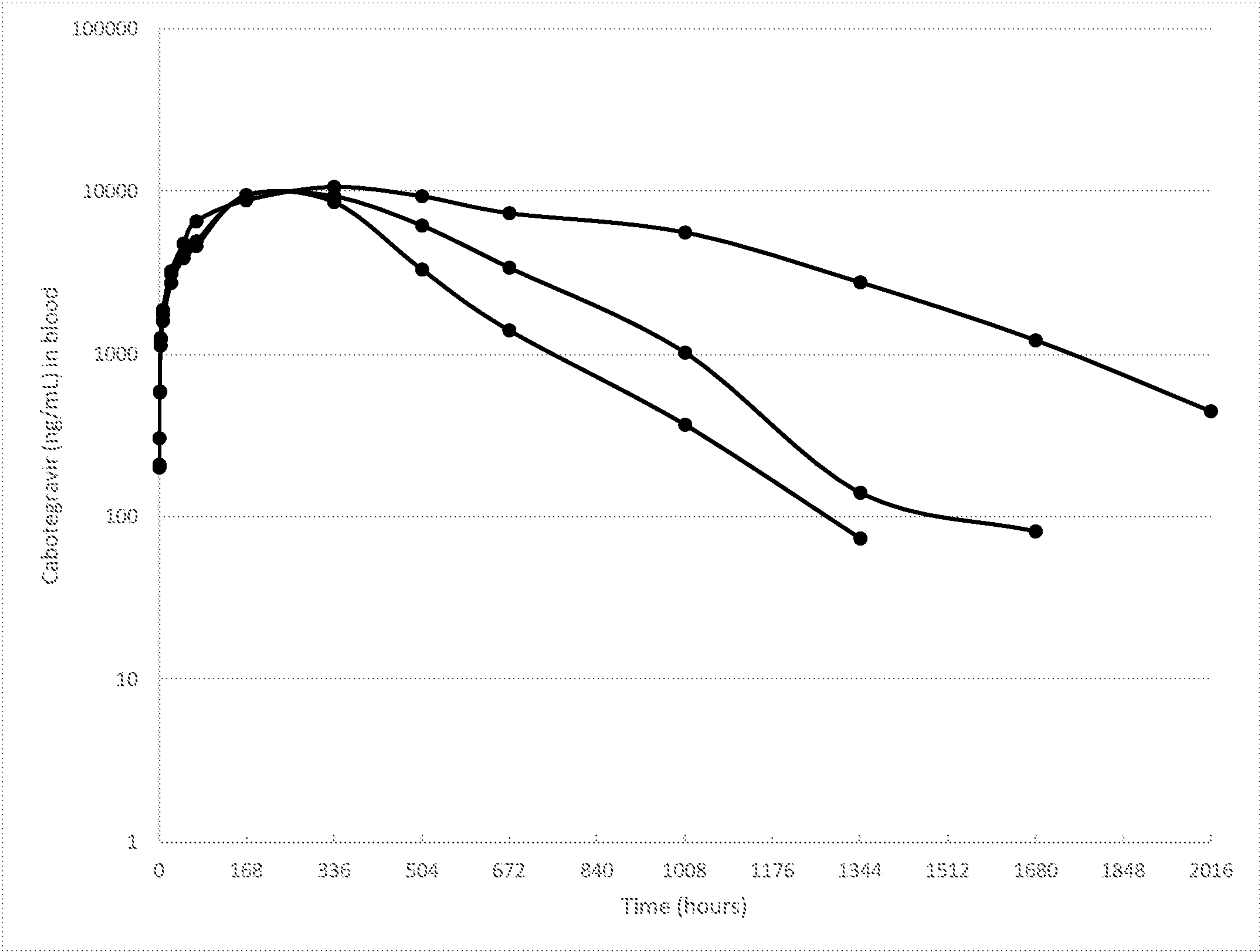


Figure 3

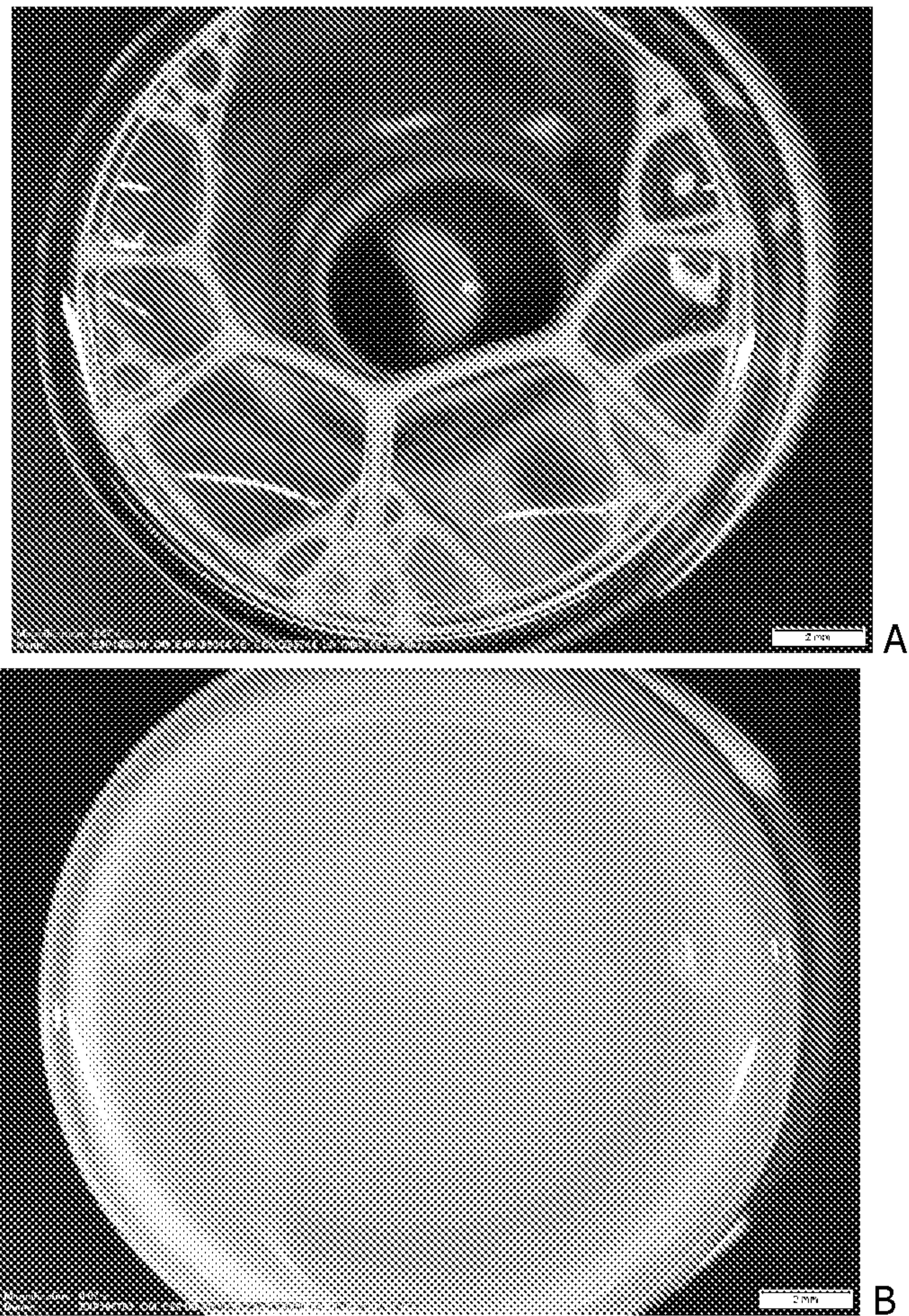


Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K9/20 A61K47/26 A61K47/34 A61K31/4985 A61K31/5365 A61P31/18 A61K39/00 C07K16/10 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) A61K A61P C07K 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, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2020/112931 A1 (UNIV NEBRASKA [US]) 4 June 2020 (2020-06-04) page 26, line 23; claims 1,5, 12-14,23-31,35 pages 9,14, 20 - page 22; example 2 page 25 - page 27 -----	1-33
X, P	WO 2020/018459 A1 (GILEAD SCIENCES INC [US]) 23 January 2020 (2020-01-23) page 30 - page 36; claims 1,17,43-45,81,93-94 page 129 - page 139 -----	1-33
Y	WO 2017/223280 A2 (VIIV HEALTHCARE CO [US]; UNIV NEBRASKA [US]) 28 December 2017 (2017-12-28) pages 17,20 - page 22; claims 13,21 page 27 ----- - / - -	1-33
☒ 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 21 April 2021		Date of mailing of the international search report 10/05/2021
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 Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/046786 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]) 31 March 2016 (2016-03-31)	1-9, 16-19, 25,26, 32,33
Y	paragraph [0046] - paragraphs [0048], [0060]; claims 1-5,9,12,13,16,17 paragraph [0094] - paragraph [0095]; examples -----	1-33
X	WO 2015/127437 A1 (UNIV NEBRASKA [US]) 27 August 2015 (2015-08-27)	1,3,4,9, 16-20, 25,26, 32,33
Y	pages 11,12,17 - page 19; claims 1,8,21; figures; examples -----	1-33
X	WO 2012/037320 A2 (GLAXOSMITHKLINE LLC [US]; MUNDHRA DEEPAK B [US]; PAN RENNAN [US]) 22 March 2012 (2012-03-22)	1-9, 15-20, 25-27,33
Y	pages 3,4; claim 1; figures 1,2; examples -----	1-33
A	ZHOU TIAN ET AL: "Creation of a nanoformulated cabotegravir prodrug with improved antiretroviral profiles", BIOMATERIALS, ELSEVIER, AMSTERDAM, NL, vol. 151, 15 October 2017 (2017-10-15), pages 53-65, XP085235415, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2017.10.023 page 57, left-hand column page 61, right-hand column -----	1,18,25
X	Tian Zhou: "Next Generation of Translational Long-Acting Cabotegravir", Theses & Dissertations, 1 May 2018 (2018-05-01), XP055708824, University of Nebraska Medical Center Omaha, Nebraska Retrieved from the Internet: URL:https://digitalcommons.unmc.edu/cgi/vi ewcontent.cgi?article=1261&context=etd [retrieved on 2020-06-25]	1-5, 15-18, 25,26
Y	page 29 - page 31; figures 2.1, 2.2, 2.6 page 44 - page 51; figures 2.11, 2.12; table 2.3 -----	1-33
X,P	WO 2020/222108 A1 (VIVV HEALTHCARE UK NO 5 LTD [GB]) 5 November 2020 (2020-11-05) claims -----	1,24,31
-/--		

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International application No

PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Cabotegravir Crystalline Form", RESEARCH DISCLOSURE, KENNETH MASON PUBLICATIONS, HAMPSHIRE, UK, GB, vol. 633, no. 64, 1 January 2017 (2017-01-01), page 109, XP007145401, ISSN: 0374-4353 [retrieved on 2016-12-19] the whole document -----	1,25,33
A	WO 2019/198024 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 17 October 2019 (2019-10-17) claims 1,9,12,18,19,22,24; examples 107, 168, 170, 173, 181, 185 -----	1,24,31
E	WO 2020/254985 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 24 December 2020 (2020-12-24) page 43, line 23 - line 30; claims 1,2,11,12 page 6 -----	1,24,31
X,P	WO 2020/157692 A1 (VIIV HEALTHCARE UK LTD [GB]) 6 August 2020 (2020-08-06) page 41; claims 6,10,11; example 1 -----	1,24,31
A	WO 2018/203235 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 8 November 2018 (2018-11-08) page 10, line 24 - line 25; claims 1,5,7,8,12,14 -----	1,24,31
X	WO 2019/207460 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 31 October 2019 (2019-10-31) page 7 -----	1,24,31
Y	MENDES E ET AL: "Synthesis, stability and in vitro dermal evaluation of aminocarbonyloxymethyl esters as prodrugs of carboxylic acid agents", BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 10, no. 3, 1 March 2002 (2002-03-01), pages 809-816, XP002296488, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(01)00336-4 page 809 - page 810; table 1 -----	1,24,31
X	WO 2017/134596 A1 (VIIV HEALTHCARE UK LTD [GB]) 10 August 2017 (2017-08-10) cited in the application page 43 -----	1,24,31
A	WO 2015/157483 A1 (SQUIBB BRISTOL MYERS CO [US]) 15 October 2015 (2015-10-15) page 46; claims 1,13,16,17 -----	1,24,31
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2021/050961 A1 (SCRIPPS RESEARCH INST [US]) 18 March 2021 (2021-03-18) page 4; claims 2,6,12-14,21,23-25; table 1 -----	1,24,31
Y	WO 2019/171285 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]; VIIV HEALTHCARE CO [US]) 12 September 2019 (2019-09-12) page 19, line 9 - line 10; claims 7,9,13,14; table 1 page 31 - page 35 page 21, line 21 -----	1,24,31
Y	MASAYUKI KAGEYAMA ET AL: "Enantioselective Total Synthesis of the Potent Anti-HIV Nucleoside EFdA", ORGANIC LETTERS ., vol. 13, no. 19, 7 October 2011 (2011-10-07), pages 5264-5266, XP055582155, US ISSN: 1523-7060, DOI: 10.1021/o1202116k page 5264; figure 1; compound 1 -----	1,24,31
Y	US 2018/002366 A1 (GIRIJAVALLABHAN VINAY M [US] ET AL) 4 January 2018 (2018-01-04) paragraphs [0147], [0148], [0163] - paragraph [0165]; claims 69,71 -----	1,24,31
A	Harper Rachel: "Broadly neutralising antibody to be developed for HIV-1 treatment", European Pharmaceutical Review, 25 November 2019 (2019-11-25), pages 1-2, XP055795889, Retrieved from the Internet: URL:https://www.europeanpharmaceuticalrevi ew.com/news/106488/investigational-broadly -neutralising-antibody-hiv-treatment/ [retrieved on 2021-04-15] the whole document -----	1,24,31
Y	GROBBEN MARLOES ET AL: "The potential of engineered antibodies for HIV-1 therapy and cure", CURRENT OPINION IN VIROLOGY, vol. 38, 1 October 2019 (2019-10-01), pages 70-80, XP055795898, United Kingdom ISSN: 1879-6257, DOI: 10.1016/j.coviro.2019.07.007 table 1 -----	1,24,31
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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) for Viral Suppression in Adults Living With HIV-1", ClinicalTrials.gov v Identifier: NCT03739996, 14 November 2018 (2018-11-14), pages 1-14, XP055795915, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NC T03739996 [retrieved on 2021-04-15] the whole document	1,24,31
Y	----- US 2017/232020 A1 (MALHOTRA GEENA [IN] ET AL) 17 August 2017 (2017-08-17) paragraphs [0062], [0066]; claims 1,4,19	1,24,31
Y	----- WO 2018/002902 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY LTD [GB]) 4 January 2018 (2018-01-04) page 17 - page 19; table 2 page 33, line 28 - page 34, line 4 pages 35,39 - page 43	1,24,31
Y	----- JUCKER BEAT M ET AL: "Multimodal imaging approach to examine biodistribution kinetics of Cabotegravir (GSK1265744) long acting parenteral formulation in rat", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 268, 16 October 2017 (2017-10-16), pages 102-112, XP085300178, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2017.10.017 page 103, right-hand column	1-31
Y	----- Rowe R. C. ET AL: "Poloxamer" In: "Handbook of Pharmaceutical Excipients", 1 January 2009 (2009-01-01), Pharmaceutical Press, UK, XP055629883, ISBN: 978-0-85369-792-3 pages 506-509, 651-6, page 506 - page 509 ----- -/--	1-33

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061582

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Raymond C. Rowe Et Al: "Polyethylene Glycol" In: "Handbook of Pharmaceutical Excipients", 1 January 2006 (2006-01-01), Pharmaceutical Press [u.a.], London [u.a.] 031835, XP055399278, ISBN: 978-1-58212-058-4 pages 545-550, page 545 - page 550 -----	1-33
Y	US 2004/265388 A1 (ZHANG ZHONG [US] ET AL) 30 December 2004 (2004-12-30) paragraph [0130] - paragraph [0131]; claims 1,3,4 -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/061582

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.:

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: 1-23, 25-30, 32, 33(completely); 24, 31(partially)

Pharmaceutical composition comprising cabotegravir as the sole active ingredient for the treatment and prevention of HIV-1

2. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a Compound 1 or 2 for the treatment and prevention of HIV-1

3. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a penta-fused Compound 3 for the treatment and prevention of HIV-1

4. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and a purine Compound 4 for the treatment and prevention of HIV-1.

5. claims: 24, 31(all partially)

Pharmaceutical composition comprising a drug combination of cabotegravir and the broadly neutralising antibody (bNAb) N6LS for the treatment and prevention of HIV-1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/061582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020112931	A1	04-06-2020	NONE
WO 2020018459	A1	23-01-2020	AU 2019307500 A1 28-01-2021 CA 3103522 A1 23-01-2020 CN 112423750 A 26-02-2021 KR 20210033492 A 26-03-2021 TW 202033196 A 16-09-2020 US 2020038389 A1 06-02-2020 WO 2020018459 A1 23-01-2020
WO 2017223280	A2	28-12-2017	EP 3474857 A2 01-05-2019 JP 2019524670 A 05-09-2019 WO 2017223280 A2 28-12-2017
WO 2016046786	A1	31-03-2016	AU 2015323321 A1 13-04-2017 BR 112017006005 A2 19-12-2017 CA 2961528 A1 31-03-2016 CL 2017000714 A1 03-11-2017 CN 106999425 A 01-08-2017 CR 20170113 A 26-05-2017 DO P2017000086 A 30-06-2017 EA 201790495 A1 29-09-2017 EP 3197430 A1 02-08-2017 JP 2017528497 A 28-09-2017 KR 20170056702 A 23-05-2017 PE 20170691 A1 13-06-2017 SG 11201702379T A 27-04-2017 US 2017246118 A1 31-08-2017 WO 2016046786 A1 31-03-2016 ZA 201702086 B 26-06-2019
WO 2015127437	A1	27-08-2015	EP 3110422 A1 04-01-2017 US 2017165271 A1 15-06-2017 WO 2015127437 A1 27-08-2015
WO 2012037320	A2	22-03-2012	AU 2011302030 A1 04-04-2013 BR 112013005907 A2 07-06-2016 CA 2810524 A1 22-03-2012 CL 2013000715 A1 05-07-2013 CN 103547266 A 29-01-2014 CY 1118279 T1 28-06-2017 DK 2616076 T3 24-10-2016 EA 201390233 A1 31-03-2014 EP 2616076 A2 24-07-2013 ES 2594557 T3 21-12-2016 HR P20161280 T1 18-11-2016 HU E031336 T2 28-07-2017 IL 225028 A 30-04-2017 JP 6231385 B2 15-11-2017 JP 2014500849 A 16-01-2014 KR 20130116254 A 23-10-2013 LT 2616076 T 10-10-2016 ME 02520 B 20-02-2017 MX 346193 B 10-03-2017 PL 2616076 T3 31-07-2017 PT 2616076 T 30-09-2016 SM T201600350 B 10-11-2016 TW 201223529 A 16-06-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/061582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		UA 108250 C2	10-04-2015
		US 2013171214 A1	04-07-2013
		US 2017027933 A1	02-02-2017
		WO 2012037320 A2	22-03-2012
		ZA 201301766 B	30-11-2016

WO 2020222108	A1	05-11-2020	NONE

WO 2019198024	A1	17-10-2019	EP 3774775 A1
		US 2021024503 A1	28-01-2021
		WO 2019198024 A1	17-10-2019

WO 2020254985	A1	24-12-2020	NONE

WO 2020157692	A1	06-08-2020	TW 202045502 A
		UY 38559 A	31-07-2020
		WO 2020157692 A1	06-08-2020

WO 2018203235	A1	08-11-2018	EP 3619205 A1
		JP 2020518601 A	25-06-2020
		TW 201906834 A	16-02-2019
		US 10954252 B1	23-03-2021
		UY 37710 A	30-11-2018
		WO 2018203235 A1	08-11-2018

WO 2019207460	A1	31-10-2019	EP 3784349 A1
		WO 2019207460 A1	31-10-2019

WO 2017134596	A1	10-08-2017	AR 107512 A1
		AU 2017215529 A1	23-08-2018
		BR 112018015629 A2	26-12-2018
		CA 3013417 A1	10-08-2017
		CL 2018002084 A1	21-09-2018
		CN 109153700 A	04-01-2019
		CO 2018008157 A2	21-08-2018
		CR 20180387 A	20-09-2018
		DK 3411381 T3	06-04-2021
		DO P2018000174 A	15-07-2019
		EA 201891649 A1	28-02-2019
		EP 3411381 A1	12-12-2018
		HK 1256866 A1	04-10-2019
		IL 260741 A	30-04-2020
		JP 6735837 B2	05-08-2020
		JP 2019504104 A	14-02-2019
		KR 20180105229 A	27-09-2018
		MA 43960 B1	26-02-2021
		PE 20181355 A1	22-08-2018
		PT 3411381 T	18-03-2021
		RU 2018130181 A	05-03-2020
		SG 11201806388X A	30-08-2018
		TW 201739757 A	16-11-2017
		US 2019031709 A1	31-01-2019
		US 2019359647 A1	28-11-2019
		UY 37109 A	29-09-2017
		WO 2017134596 A1	10-08-2017
		ZA 201805044 B	26-08-2020

WO 2015157483	A1	15-10-2015	AR 101077 A1
			23-11-2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/061582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		AU 2015243500 A1	27-10-2016	
		CA 2944778 A1	15-10-2015	
		CL 2016002528 A1	23-06-2017	
		CN 106604909 A	26-04-2017	
		CR 20160472 A	10-03-2017	
		DK 3129392 T3	19-10-2020	
		DO P2016000277 A	28-02-2017	
		EA 201691760 A1	28-02-2017	
		EP 3129392 A1	15-02-2017	
		EP 3750910 A1	16-12-2020	
		HR P20201645 T1	25-12-2020	
		HU E051719 T2	29-03-2021	
		IL 248053 A	30-04-2020	
		JP 6568202 B2	28-08-2019	
		JP 2017510659 A	13-04-2017	
		KR 20160147809 A	23-12-2016	
		LT 3129392 T	10-11-2020	
		MA 39374 A1	29-06-2018	
		PE 20161391 A1	10-01-2017	
		PH 12016501951 A1	09-01-2017	
		PT 3129392 T	30-10-2020	
		SG 10201709017P A	29-11-2017	
		SG 11201608041Q A	28-10-2016	
		SI 3129392 T1	30-11-2020	
		TW 201623324 A	01-07-2016	
		UA 120927 C2	10-03-2020	
		US 2015291655 A1	15-10-2015	
		US 2017056420 A1	02-03-2017	
		US 2017340650 A1	30-11-2017	
		US 2019151336 A1	23-05-2019	
		US 2020360404 A1	19-11-2020	
		UY 36070 A	30-10-2015	
		WO 2015157483 A1	15-10-2015	
		ZA 201606748 B	30-05-2018	

WO 2021050961	A1	18-03-2021	WO 2021050956 A1	18-03-2021
			WO 2021050961 A1	18-03-2021

WO 2019171285	A1	12-09-2019	EP 3762396 A1	13-01-2021
			US 2020407393 A1	31-12-2020
			WO 2019171285 A1	12-09-2019

US 2018002366	A1	04-01-2018	AR 099788 A1	17-08-2016
			AU 2015236018 A1	06-10-2016
			AU 2017225090 A1	28-09-2017
			CA 2943792 A1	01-10-2015
			CL 2016002414 A1	05-05-2017
			CN 106795199 A	31-05-2017
			CR 20160451 A	06-12-2016
			DO P2016000265 A	30-04-2017
			EA 201691931 A1	28-02-2017
			EC SP16085206 A	31-08-2017
			EP 3122752 A1	01-02-2017
			GE P20197009 B	12-08-2019
			GT 201600201 A	18-12-2018
			IL 247923 A	31-01-2021
			JO 3636 B1	27-08-2020
			JP 6182680 B2	16-08-2017

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/061582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 2017512797 A	25-05-2017
		KR 20160128437 A	07-11-2016
		MD 20160117 A2	28-02-2017
		MX 367058 B	02-08-2019
		NI 201600145 A	27-10-2016
		NZ 724343 A	28-02-2020
		PE 20170197 A1	22-03-2017
		PH 12016501897 A1	19-12-2016
		SG 11201608031P A	28-10-2016
		SV 2016005290 A	03-05-2018
		TW 201619180 A	01-06-2016
		UA 120758 C2	10-02-2020
		US 2015274767 A1	01-10-2015
		US 2018002366 A1	04-01-2018
		WO 2015143712 A1	01-10-2015
		WO 2015148746 A1	01-10-2015

US 2017232020	A1	17-08-2017	
		AU 2017218800 A1	27-09-2018
		BR 112018016517 A2	19-03-2019
		CA 3014411 A1	17-08-2017
		CN 109195633 A	11-01-2019
		EP 3413913 A1	19-12-2018
		JP 2019504869 A	21-02-2019
		RU 2018132408 A	12-03-2020
		US 2017232020 A1	17-08-2017
		US 2021038619 A1	11-02-2021
		WO 2017138022 A1	17-08-2017

WO 2018002902	A1	04-01-2018	
		EP 3478324 A1	08-05-2019
		JP 2019524687 A	05-09-2019
		TW 201811376 A	01-04-2018
		US 2019328900 A1	31-10-2019
		WO 2018002902 A1	04-01-2018

US 2004265388	A1	30-12-2004	
		AU 2005208869 A1	11-08-2005
		EP 1708719 A2	11-10-2006
		JP 5668004 B2	12-02-2015
		JP 2007519732 A	19-07-2007
		JP 2012140451 A	26-07-2012
		US 2004265388 A1	30-12-2004
		US 2009093549 A1	09-04-2009
		WO 2005072343 A2	11-08-2005
