HU000031673T2

(19) **HU**

(11) Lajstromszám: **E 031 673**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 12 759136**
(22) A bejelentés napja: **2012. 09. 14.**

(96) Az európai bejelentés bejelentési száma:
EP 20120759136
(97) Az európai bejelentés közzétételi adatai:
EP 2755957 A1 **2013. 03. 21.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2755957 B1 **2016. 11. 02.**

(51) Int. Cl.: ***C07D239/47*** *(2006.01)*
A61K 31/519 *(2006.01)*
C07D239/69 *(2006.01)*
C07D405/12 *(2006.01)*
C07D487/04 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/EP 12/068068
(87) A nemzetközi közzétételi szám:
WO 13037942

(30) Elsőbbségi adatok:

11181280	**2011. 09. 14.**	**EP**
11188602	**2011. 11. 10.**	**EP**
11195581	**2011. 12. 23.**	**EP**

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(54) **Triazolopirimidin vegyületek szintézise**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 755 957 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
02.11.2016 Bulletin 2016/44

(21) Application number: **12759136.0**

(22) Date of filing: **14.09.2012**

(51) Int Cl.:
C07D 239/47 *(2006.01)* ***C07D 239/69*** *(2006.01)*
C07D 405/12 *(2006.01)* ***C07D 487/04*** *(2006.01)*
A61K 31/519 *(2006.01)*

(86) International application number:
PCT/EP2012/068068

(87) International publication number:
WO 2013/037942 (21.03.2013 Gazette 2013/12)

(54) SYNTHESIS OF TRIAZOLOPYRIMIDINE COMPOUNDS

SYNTHESE VON TRIAZOLPYRIMIDIN-VERBINDUNGEN

SYNTHÈSE DE COMPOSÉS DE TRIAZOLOPYRIMIDINES

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **14.09.2011 EP 11181280**
10.11.2011 EP 11188602
23.12.2011 EP 11195581

(43) Date of publication of application:
23.07.2014 Bulletin 2014/30

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(56) References cited:
WO-A1-01/36421 **WO-A1-2010/030224**
WO-A2-01/19826

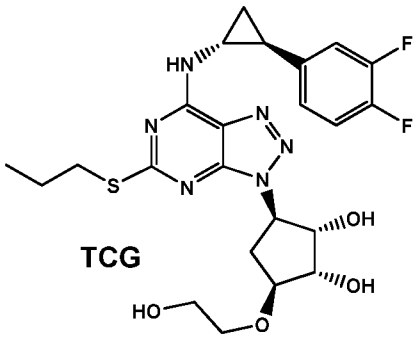
- **HONG YE ET AL: "Carba-nucleosides as Potent Antagonists of the Adenosine 5'-Diphosphate (ADP) Purinergic Receptor (P2Y12) on Human Platelets", CHEMMEDCHEM, vol. 3, no. 5, 19 May 2008 (2008-05-19), pages 732-736, XP055011415, ISSN: 1860-7179, DOI: 10.1002/cmdc.200700310**

EP 2 755 957 B1

Description

[0001] The present invention relates to the field of organic synthesis, in particular to the synthesis of specific triazolopyrimidine compounds and intermediates thereof as well as related derivatives.

[0002] An important triazolopyrimidine compound is ticagrelor (TCG; Brilinta®; 3-[7-[[(1*R*,2*S*)- 2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-(1*S*,2*S*,3*R*,5*S*)-1,2-cyclopentanediol) having the following structural formula.

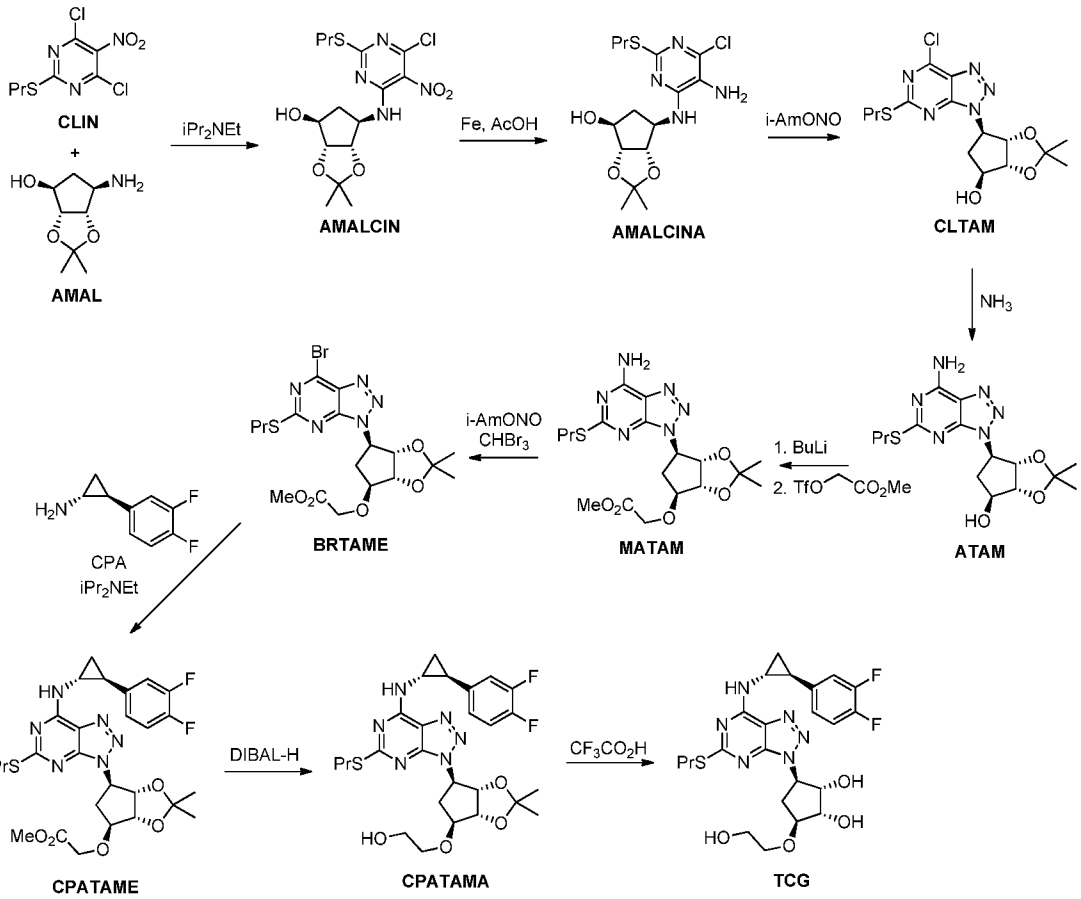


TCG

[0003] Ticagrelor shows pharmaceutical activity by functioning as a P2Y12 receptor antagonist and thus is indicated for the treatment or prevention of thrombotic events, for example stroke, heart attack, acute coronary syndrome or myocardial infection with ST elevation, other coronary artery diseases and arterial thrombosis as well as other disorders related to platelet aggregation (WO 00/34283).

[0004] The synthesis of ticagrelor **(TCG)** is demanding. There are five to six known synthetic variants, which are described in the basic patent application WO 00/34283, an improved one in patent application WO 01/92263, and a further improved one in patent application WO 10/030224 respectively derived from the originator AstraZeneca, while two are published in a "deutero" patent application WO 11/017108 of Auspex Pharmaceuticals. Further, there is one synthetic path published in a scientific journal (Bioorg. Med. Chem. Lett. 2007, 17,6013-6018).

[0005] The first synthesis of **TCG** as described in WO 00/34283 is depicted in scheme 1 below.



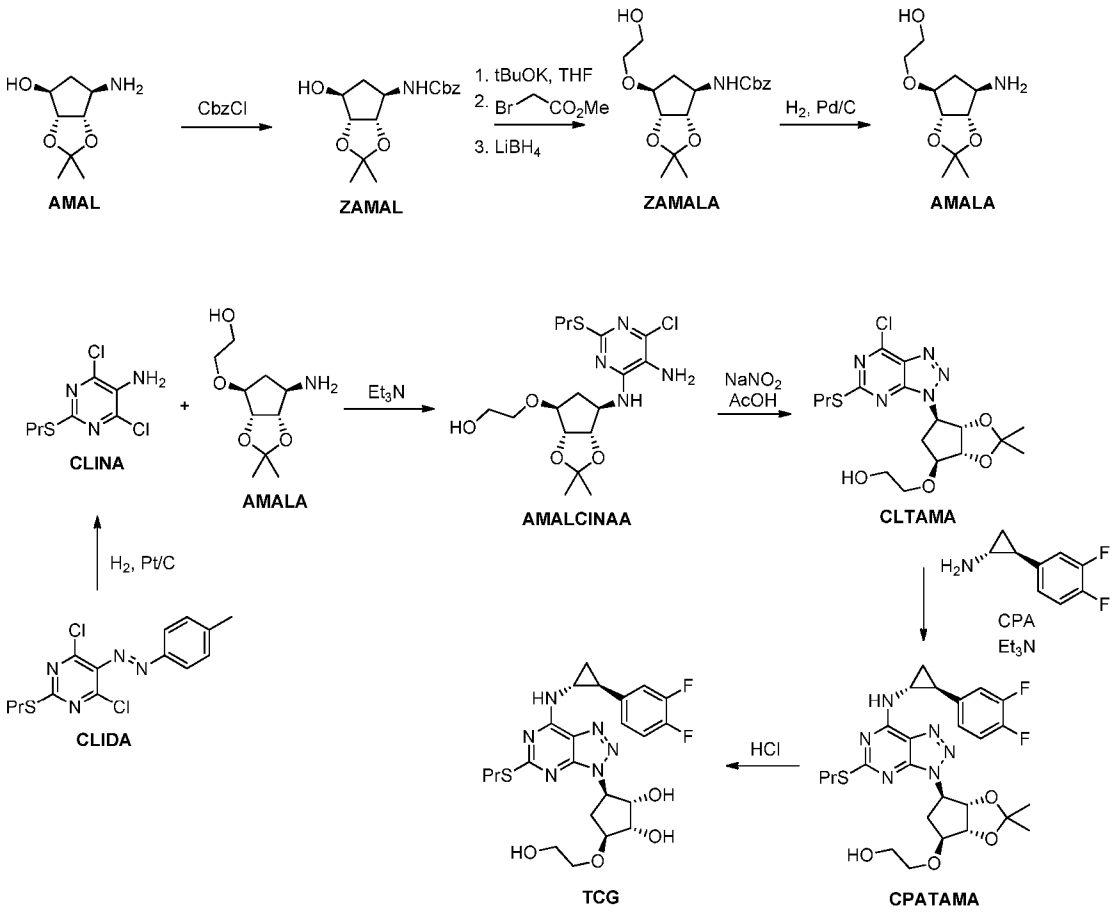
Scheme 1: Synthesis of ticagrelor (**TCG**) as described in WO 00/34283.

[0006] This nine step synthesis of ticagrelor **(TCG)** as described in WO 00/34283 (Scheme 1) starts with a reaction between **CLIN** and **AMAL.** In the presence of diisopropylethylamine (*i*Pr$_2$NEt) **AMALCIN** is formed, which is in then reduced with iron (Fe) in acetic acid to **AMALCINA.** In the next step **CLTAM** is formed using isopentyl nitrite (*i*AmONO). Next, **ATAM** was prepared using ammonia, and side chain was introduced **(MATAM)** using *n*-butyllithium and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acetate, which was previously prepared by reaction between methyl glycolate and triflic anhydride. In next step **BRTAME** is formed using *i*AmONO and $CHBr_3$, followed by the aromatic nucleophilic substitution of Br with **CPA** in the presence of *i*Pr$_2$NEt to form **CPATAME.** This is then reduced to **CPATAMA** using DIBAL-H. Deprotection of diol group in the presence of trifluoroacetic acid in the final step leads to **TCG.**

This synthetic path is very long (9 steps, not including reagents preparation) and uses toxic compounds like $CHBr_3$, triflic anhydride, and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acetate. The introduction of the methoxycarbonylmethyl group (reaction from **ATAM** to **MATAM**) is very difficult due to poor chemo-selectivity, as the amino group also reacts with 2-(((trifluoromethyl)sulfonyl)oxy)acetate.

An improved synthesis of ticagrelor **(TCG)** is described in WO 01/92263 (see Scheme 2). In this process the hydroxyethyl side chain is introduced at the beginning of the synthesis by a three step reaction path from **AMAL** to **AMALA,** which is then reacted with **CLINA** (prepared from **CLIDA**) in presence of triethylamine (Et_3N) to form **AMALCINAA.** The triazole ring of **CLTAM** is formed with $NaNO_2$ in acetic acid, and then Cl is exchanged with **CPA** to form **CPATAMA.** In the final step **TCG** is prepared via deprotection using HCl.

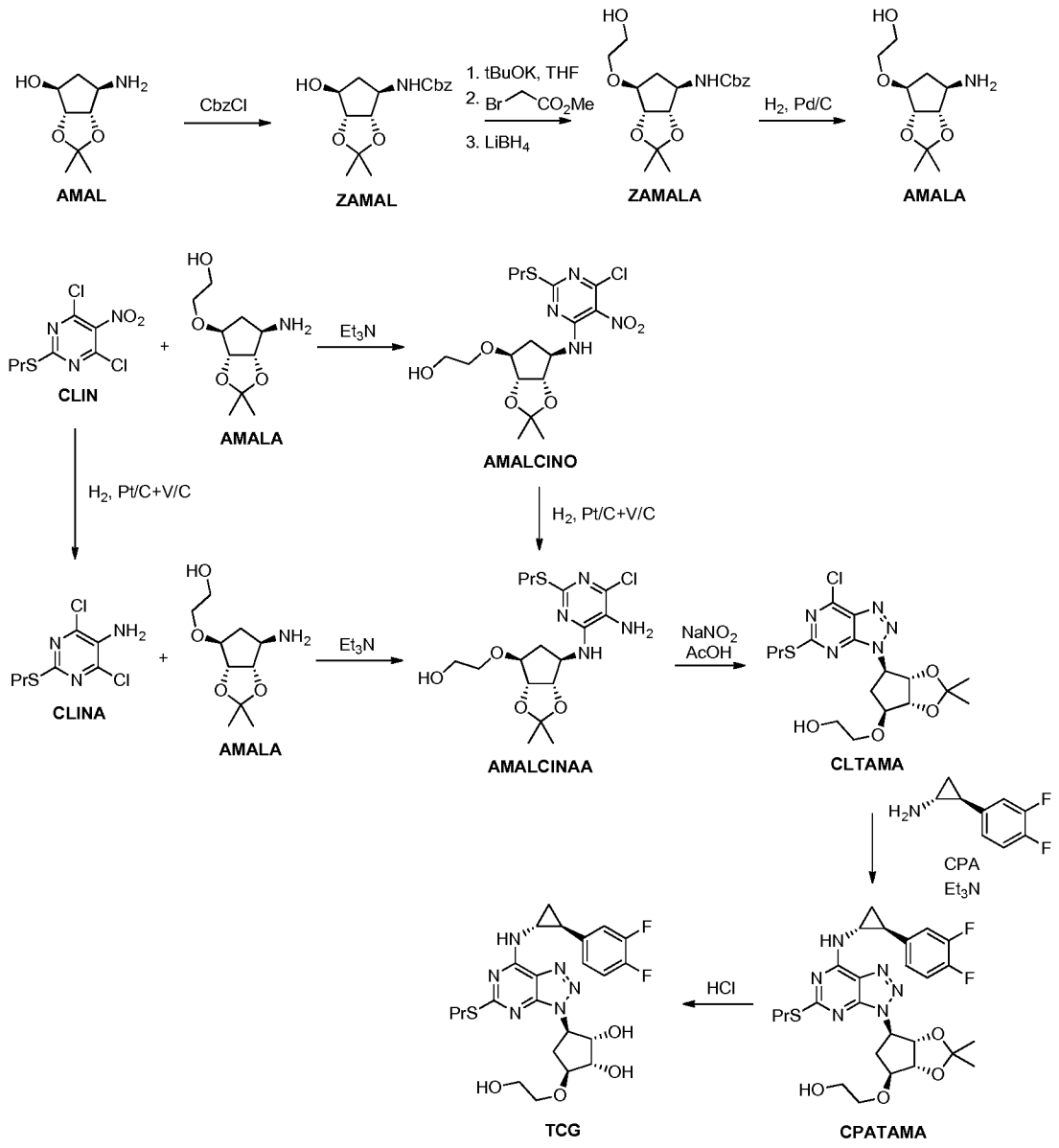
[0007] This improved process still has substantial length (7-8 steps). In **AMALA** synthesis the benzyloxycarbonyl protection (*Cbz*) is used, which is then removed in the third step using hydrogenation with Pd/C as a catalyst. Hydrogenation with Pt/C as a catalyst is also used in the reduction of **CLIDA** to **CLINA.**



Scheme 2: Synthesis of ticagrelor (**TCG**) as described in WO 01/92263.

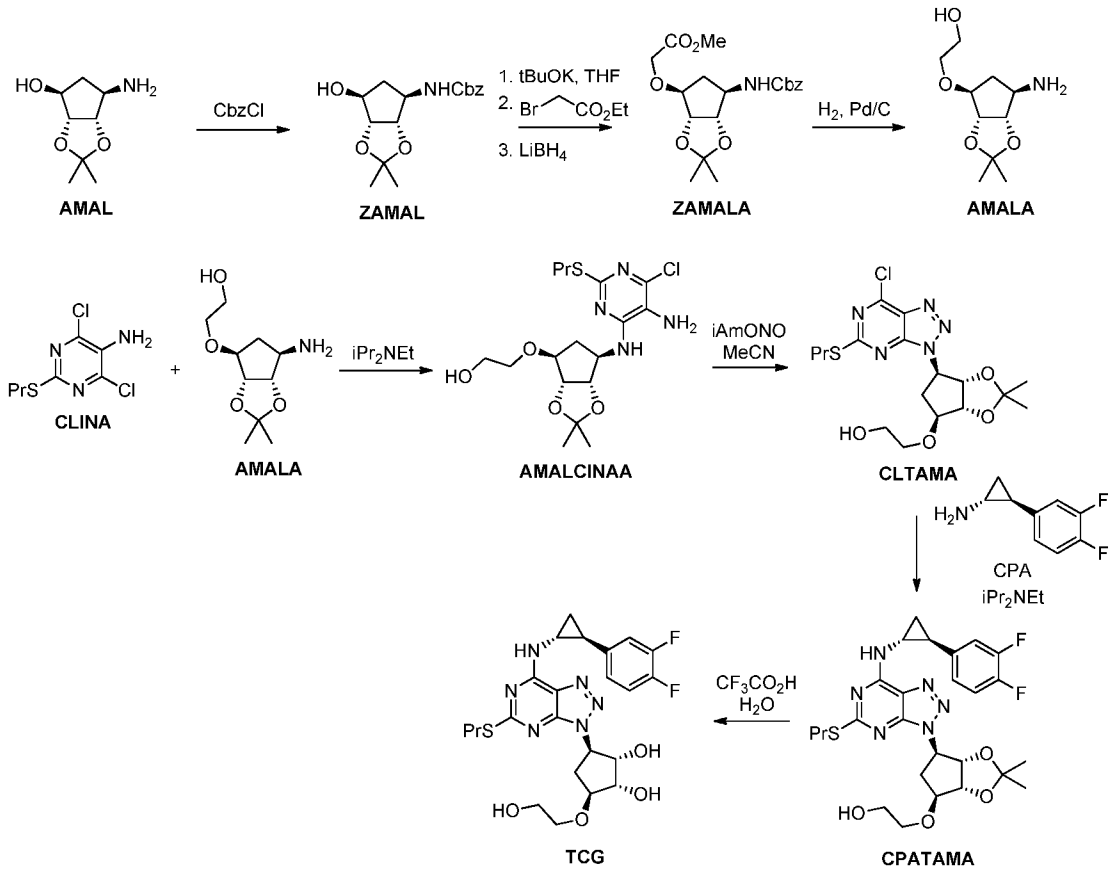
[0008] Another improved synthetic path is described in WO 10/030224 (Scheme 3). The key steps in this process are reduction of **CLIN** to **CLINA** or **AMALCINO** to **AMALCINAA** using hydrogen gas and platinum vanadium catalyst. The introduction of the hydroxyethyl side chain to **AMAL** to form **AMALA,** cyclization, substitution of Cl atom of **CLTAMA** with **CPA** and final acidic deprotection are the same as in WO 01/92263.

[0009] This further improved process to **TCG** has 8 reaction steps. Like in WO 01/92263, there are used the *Cbz* protecting group and heavy metals as catalysts like Pd, Pt and/or V.



Scheme 3: Syntheses of ticagrelor (**TCG**) as described in WO 10/030224.

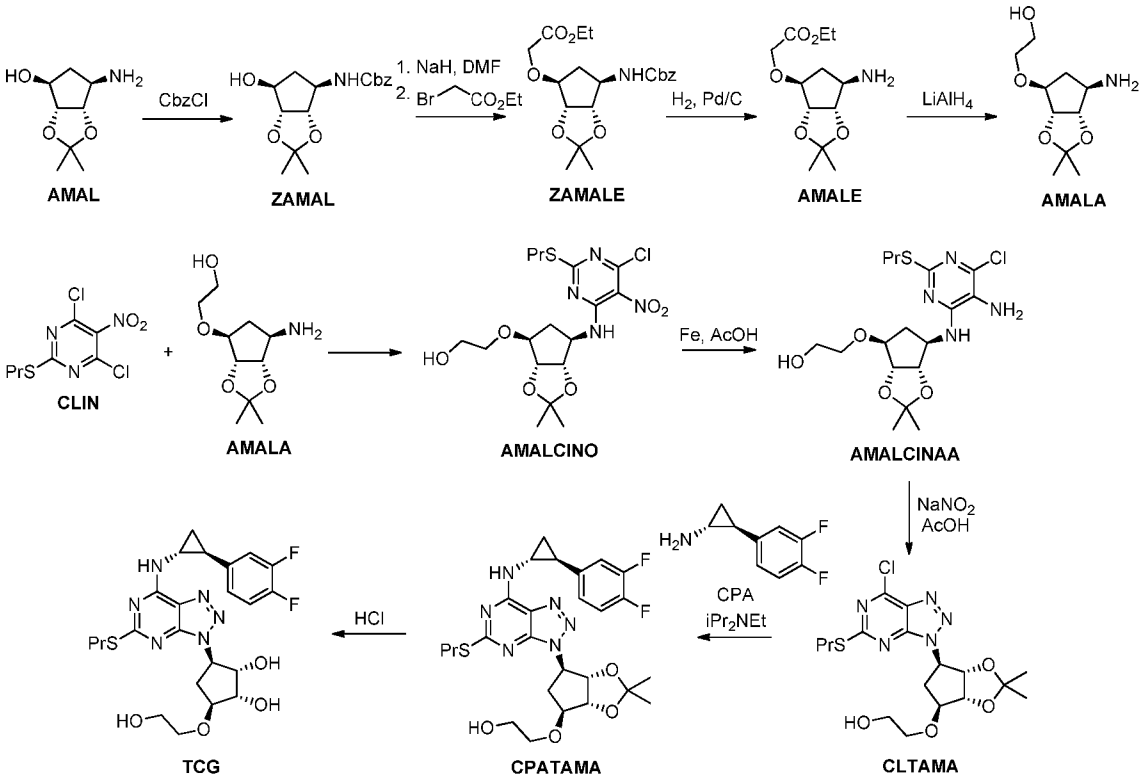
[0010] AstraZeneca published a synthetic path (Scheme 4) to ticagrelor **(TCG)** in Bioorg. Med. Chem. Lett. 2007, 17, 6013-6018. Intermediates in this process are similar to those described in WO 01/92263. There is difference in formation of triazolo ring of **CLTAMA** where *i*AmONO is used, and difference in deprotection in the last step.



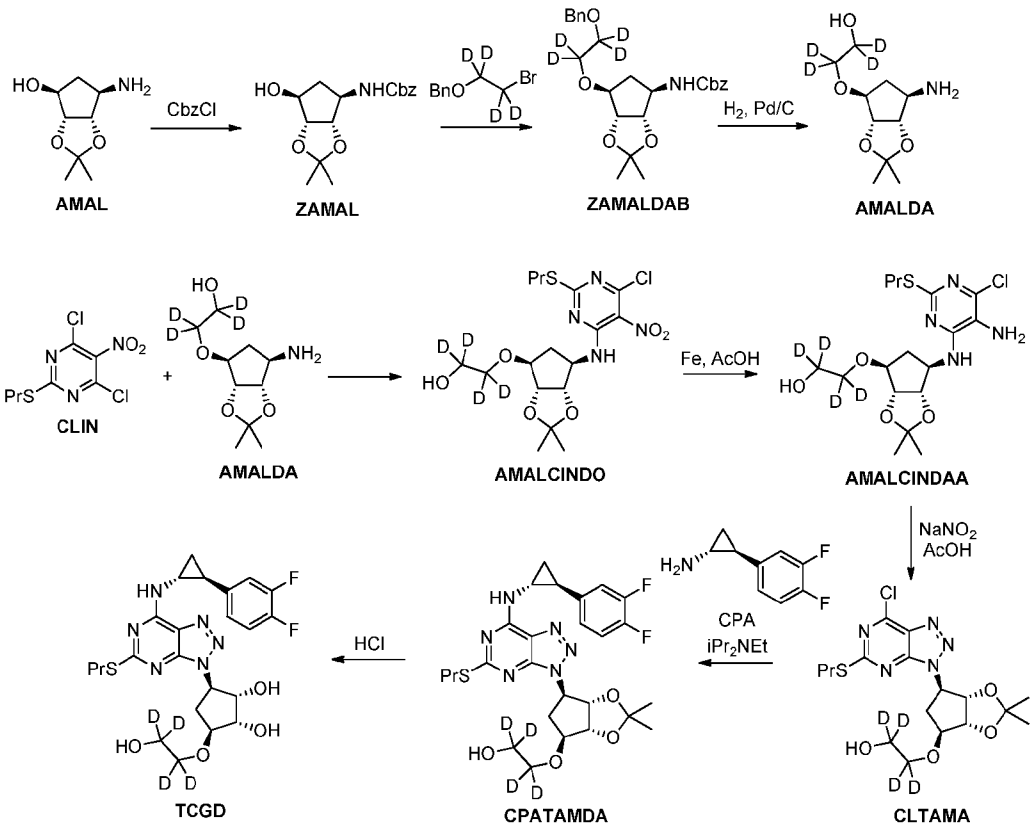
Scheme 4: Synthesis of ticagrelor (**TCG**) as described in *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6013–6018.

[0011] Another synthetic variant (Scheme 5) to ticagrelor **(TCG)** is described in WO 11/017108 by Auspex Pharmaceuticals. In nine step synthesis they prepared **AMALE** through deprotection of **ZAMALE** using hydrogen gas and Pd/C, which was then reduced to **AMALA** with $LiAlH_4$. **AMALCINO** was prepared without presence of base, further steps are similar to those published in WO 01/92263.

[0012] Still another synthetic variant (Scheme 6) to obtain ticagrelor with deuterated hydroxyethyl group **(TCGD)** is also described in WO 11/017108 by Auspex Pharmaceuticals.



Scheme 5: Synthesis of ticagrelor (**TCG**) as described in "deutero" patent WO 11/017108.



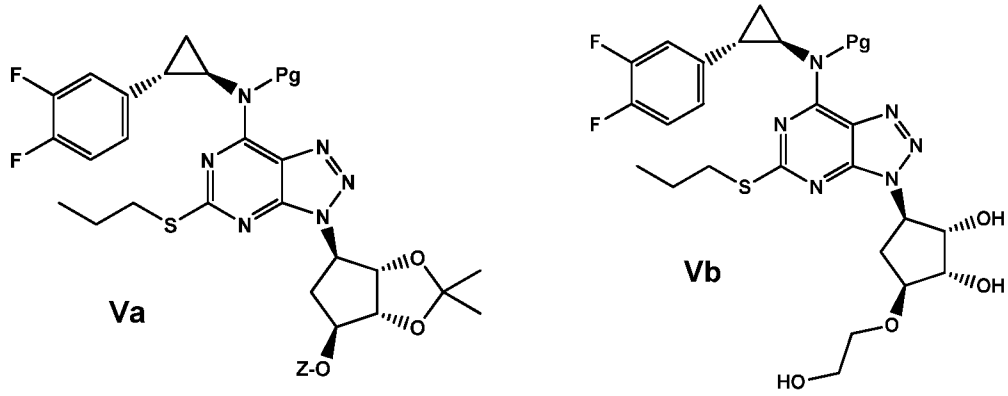
Scheme 6: Synthesis of ticagrelor with deuterated hydroxyethyl group (**TCGD**) as described in "deutero" patent WO 11/017108.

As becomes apparent from the above, a major drawback of the hitherto known synthesis schemes for the preparation of ticagrelor is that the synthesis is long.

Summary of the Invention

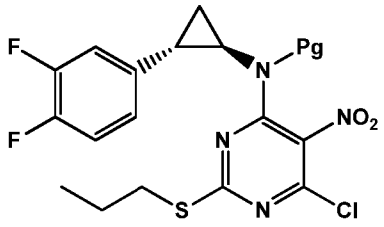
[0013] The object of the present invention was to provide an industrially applicable and economically improved process for obtaining ticagrelor.

[0014] The present invention provides a process for the preparation of a compound of formula **Va** or **Vb**



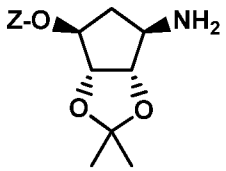
wherein Pg is an amino protecting group, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl, the process comprising the steps of:

(i) reacting a compound of formula **II'**

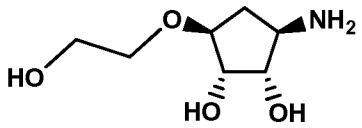


II'

wherein Pg is defined as above, with a compound of the formula **VI** or **VII**

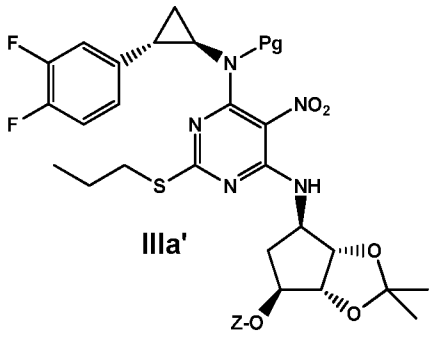


VI

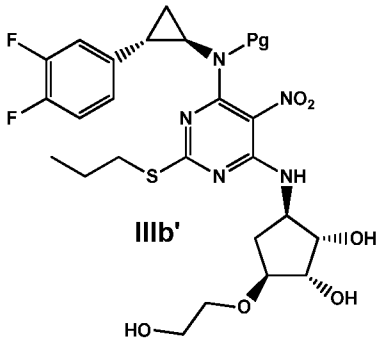


VII

wherein Z is defined as above, to obtain a compound of formula **III**a' or **IIIb',** respectively



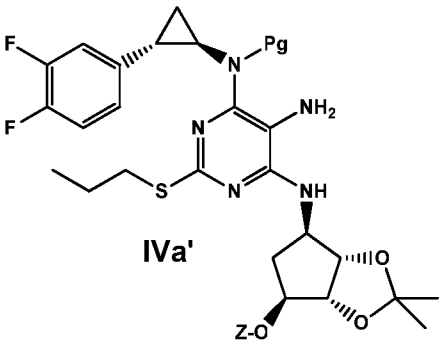
IIIa'



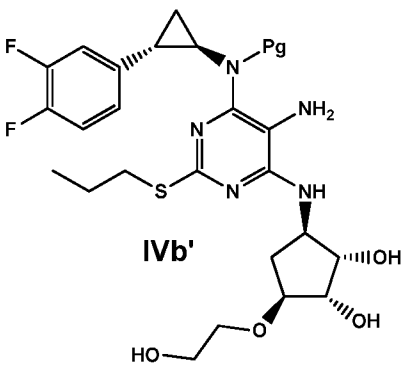
IIIb'

wherein Pg and Z are as defined above,

(ii) reducing the nitro group in the compound of formula **III**a' or **IIIb'** to an amino group to obtain a compound of formula **IVa'** or **IVb',** respectively, and



IVa'



IVb'

(iii) nitrosation of the compound of formula **IVa'** or **IVb'** to obtain the compound of formula **Va** or **Vb,** respectively.

[0015] The process defined above allows for preparation or synthesis of ticagrelor with an industrially applicable and economically improved process. Preferred embodiments will be described below. The present invention further provides novel compounds that are highly useful as key intermediates in the preparation or synthesis of ticagrelor.

Description of the Invention and of Preferred Embodiments

[0016] Aspects, advantageous features and preferred embodiments of the present invention will be described in further detail below, noting however that such aspects, advantages features as well as embodiments and examples are presented for illustrative purposes only and shall not limit the invention in any way.

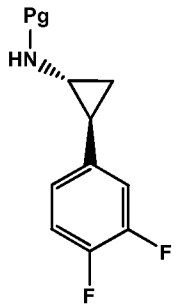
[0017] The introduction of a protective group on the amino group of the cyclopropane ring is a significant point of the present invention, which is a novel feature common to the key steps of the synthetic preparation as well as to the intermediate compounds mentioned above. This crucial point significantly distinguishes over every prior art synthesis in which a substitution reaction of the pyrimidine ring with cyclopentane is carried out first, and only then the triazole ring is created with a final substitution with the cyclopropane ring. This sequence of the reaction steps in the prior art solutions needs to be followed exactly, otherwise a selectivity of the triazole ring formation is eliminated, or wrong triazole systems are obtained. Introduction of the protective group on the amino group of cyclopropane ring according to the present invention however enables selectivity of the triazole ring formation regardless of the step conducted after the protective group is introduced. The synthesis and the special types of intermediate compounds are already suitably protected for the selective introduction of the cyclopentane ring and/or the selective introduction of the hydroxyethyl group.

[0018] In particular, the process according to the present invention reduces the number of the required reaction steps. It is possible to proceed in a short 3-4 step process, contrary to prior art processes requiring 7 steps or more. Further, while prior art syntheses use toxic or expensive reagents, and most of them require the use of hydrogen gas and heavy metals, it is possible according to the present invention to avoid the use of hydrogen gas, heavy metals and expensive reagents. Such avoidance of using hydrogen gas and/or heavy metals during the whole synthesis of ticagrelor, or in the preparation of precursor compounds disclosed herein, thus constitutes a preferred embodiment of the present invention.

[0019] A further significant advantage of the present invention resides in the possibility that several steps can be performed through one-pot conversions, without the need of isolation or separation of intermediate compounds, which one-pot system therefore constitutes a preferred embodiment of the present invention.

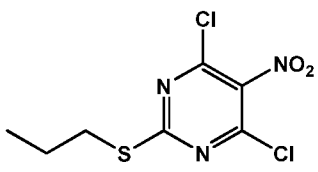
[0020] Accordingly, the possibility of reducing the number of required reaction steps, of increasing reaction selectivity, and of simplifying reactions respectively strongly contributes to provide an improved industrially applicable and economically beneficial process for obtaining triazolopyrimidine compounds and specifically ticagrelor.

[0021] According to a preferred embodiment, the compound of formula **II'** is prepared by comprising the steps of (0-1) providing a compound of formula **I**



I

wherein Pg is an amino protecting group, and
(0-2) reacting the compound of formula **I** with a compound of the formula

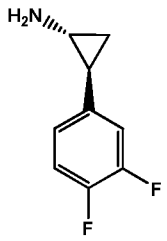


to obtain the compound of formula **II'.**

[0022] It has been found that various amino-protecting groups can be efficiently introduced at this early stage of the synthesis, wherein such amino protecting groups are particularly suited and consistent with the subsequent reaction steps, and allowing to increase reaction selectivity and making reaction simplifications through one-pot conversions possible.

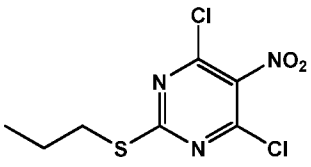
[0023] Alternatively, the compound of formula **II'** can be obtained by first carrying out a substitutional reaction with the pyrimidine ring and subsequently introducing the protecting group, by comprising the steps of:

(0-1') providing a compound of formula **Ia**

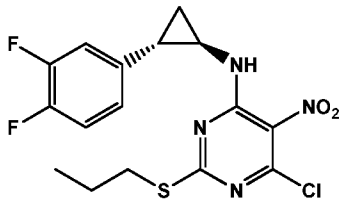


Ia

(0-2') reacting the compound of formula **Ia** with a compound of the formula



to obtain a compound of formula **IIa,**

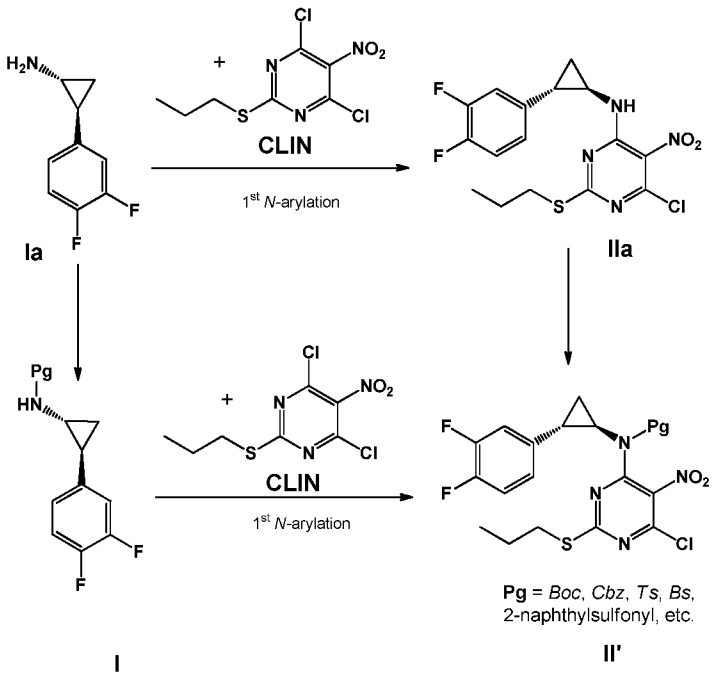


IIa

and

(0-3') introducing an amino protecting group Pg to obtain the compound of formula **II'.**

[0024] A summary of the afore-mentioned ways to prepare the compound of formula **II'** is shown in the following scheme 7 below.

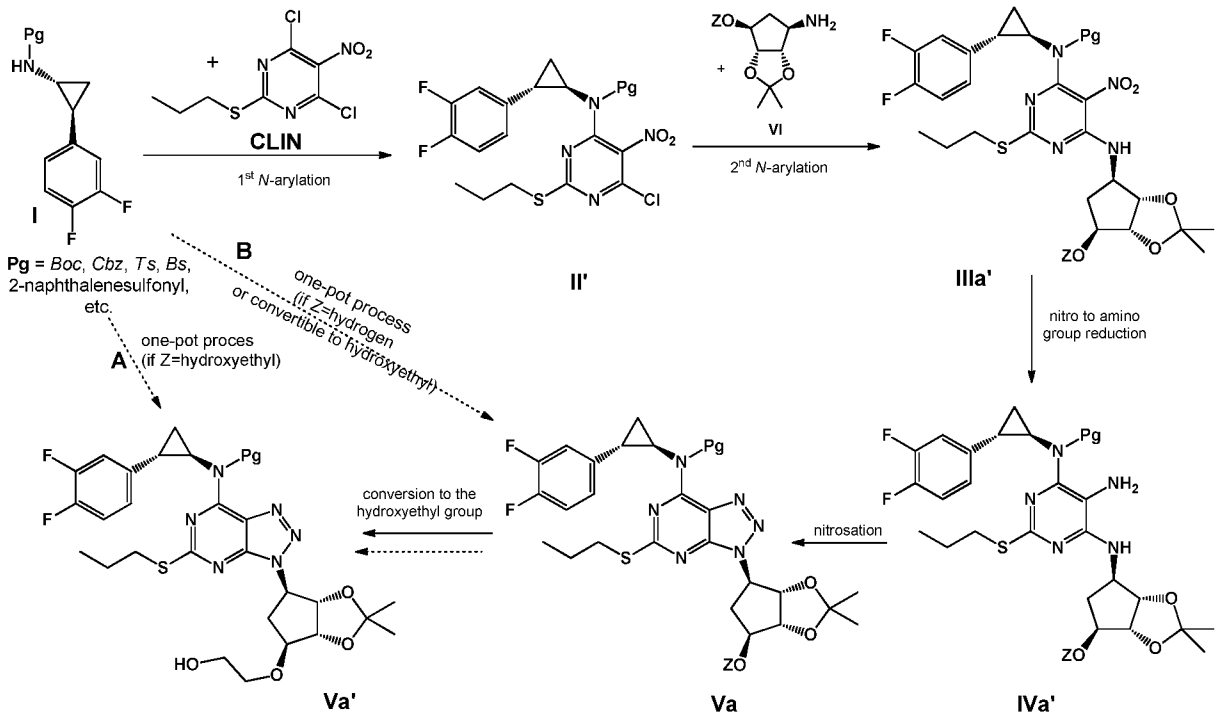


Scheme 7 showing process embodiments of the present invention.

[0025] As set forth above, it is possible and corresponds to a particularly preferred embodiment of the present invention, that steps (i) to (iii) specified above, and optionally also the preparation of the compound of formula **II',** are carried out in one pot. Thus, while of course separation or isolation of any of the intermediate compounds of formulae **IIIa'**, **IIIb', IVa', IVb'** and optionally of the compound of formula **II'** can be carried out to obtain such compounds as useful intermediate compounds, this can be beneficially dispensed with if desired. This preferred embodiment is not only economically beneficial by the feature that one-pot synthesis is made possible; it is especially advantageous due to the generally amorphous nature of the intermediate compounds, which would make the purification difficult using non-chromatographic means, while the use of chromatographic means would again render the whole process less economically acceptable. Furthermore, the protecting group "Pg" may be selected in such way that the intermediate of the critical isolable step is solid and recrystallizable, hence no need for using chromatography as a purification method exists anymore.

[0026] A further preferred embodiment, which is associated with additional advantages, is based on the beneficial possibility to carry out steps (i) and (ii), optionally also steps (0-1) to (0-2) or (0-1') to (0-3') generally under basic conditions in the presence of bases, which renders the synthetic steps consistent and further facilitates one-pot methodologies. More specifically, all chemical steps from the start shown above up to the compound of formula **IVa** are most efficient in the presence of bases of various strengths, more preferably in subsequent steps consistent with, or allowing, decreasing basicity. For example, a proper base, which can be used for the deprotonation of the compound of formula Ia is sodium hydride, while a suitable base which can be used as a hydrogen chloride scavenger in reaction step (i) (i.e. during the *N*-arylation of the compound of formula **VI**) can be selected from tertiary amines, alkali carbonates, or alkali phosphates, or from other poorly nucleophilic bases. Subsequently, mildly basic conditions, preferably using alkali carbonates, are well suited also for the nitro group reduction in step (ii), using for example sulphur-based reducing agents such as sodium dithionite or formamidine sulfinic acid (thiourea dioxide). Subsequently, and again consistent with a preferred one-pot methodology, the nitrosation step (iii) can be performed by shifting to mildly acidic conditions, suitably achieved for example by the addition of acetic acid, using appropriate nitrosating agents such as sodium nitrite, or it can be carried out as an alternative step by heating the solution of the crude product of the compound of formula **IVa** in the presence of an alkyl nitrite such as the readily available reagent isopentyl nitrite.

[0027] Further advantageous embodiments of the process according to the present invention are based on the synthetic possibility that useful synthetic options are allowed, depending on which cyclopentane substituent "Z" is used, and depending on what substituent "Z" is used at which stage of the synthesis. The possible synthetic options become more apparent by the illustrations of possible synthetic embodiments shown in the following scheme 8:



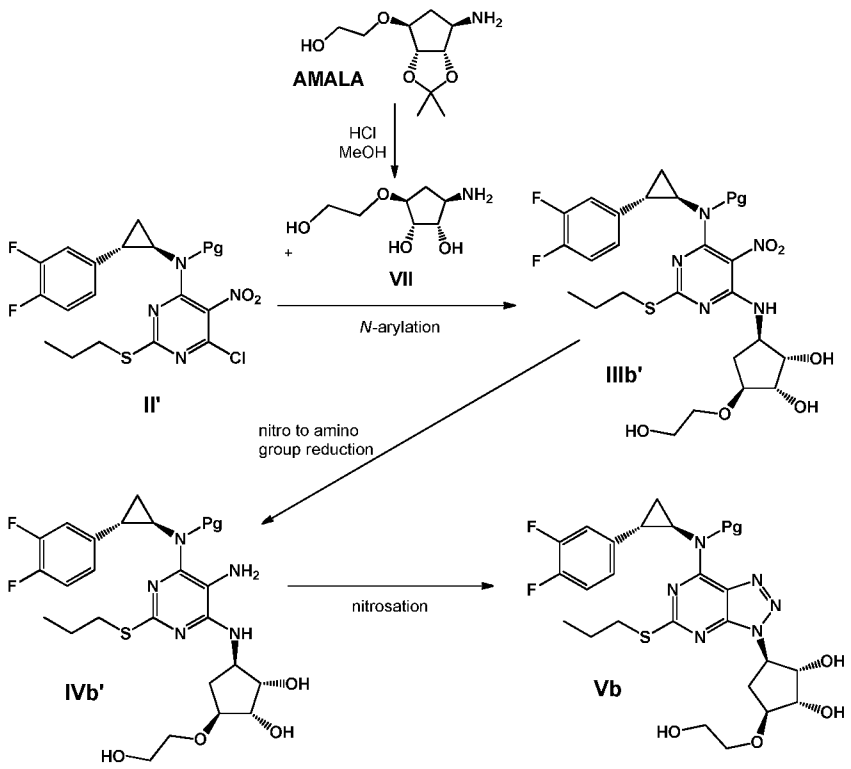
Scheme 8 showing process embodiments of the present invention.

[0028] More specifically, if the compound of formula **VI,** that is used in the reaction step (i) to be reacted with the compound of formula **II'**, already has a hydroxyethyl or a group convertible to hydroxyethyl as the group "Z", a one-pot process made feasible according to a preferred embodiment of the present invention already yields a desirable precursor compound of ticagrelor (see dashed arrow line A shown in reaction scheme 8), which precursor compound then only needs to be subjected to deprotection reactions for removing Pg and the vicinal hydroxyl protecting group at the cyclopentane ring, respectively. If, alternatively, "Z" in the compound of formula **VI** is hydrogen, then the molecular assembly sequence allows for a facilitated introduction of the hydroxyethyl group when it is done at a later stage of the synthesis, which is made possible because the described advantageous and preferred synthetic embodiments are still consistent with a one-pot process (see dashed arrow line B, and the subsequent conversion of the Z group in the compound of formula **Va** to the hydroxyethyl group as shown in scheme 8). Therefore, in the afore-mentioned alternative and economical routes to precursors of ticagrelor or ticagrelor itself, such preferred embodiments of the present invention constitute particularly suitable solutions for the synthetic challenge arising when the hydroxyethyl side chain is introduced at an early or at a later stage of the synthetic route.

[0029] Therefore, the advantageous possibility to join numerous steps into one-pot synthetic schemes is a surprising and unexpected effect of the present invention that results just from introducing the protective group to the amine moiety bound to the cyclopropane ring (denoted by the "Pg" protecting groups in the synthetic schemes), which protecting group "Pg" is present throughout the relevant intermediate compounds of formulae **Ia-Va'** (or as later shown in formulae **I-V).**

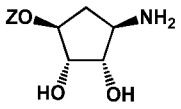
[0030] According to another embodiment, alternatively, a compound of formula **VII** can be added to the compound of formula **II'** to yield a compound of formula **IIIb'** (Scheme 9). **VII** already has a hydroxyethyl group, while the hydroxyl groups at the cyclopentane ring are not protected. From a compound of formula **IIIb',** a compound of formula **IVb'** can be obtained by reduction of the nitro group. As the hydroxyl groups at the cyclopentane ring are not protected, the nitrosation of **IVb'** yields directly a compound of formula **Vb.**

[0031] A compound of formula **VII,** another embodiment of the present invention, can be prepared for example by acid hydrolysis from **AMALA** (Scheme 9), which can be prepared as described in WO 01/92263.



Scheme 9 showing a specific embodiment of the present invention.

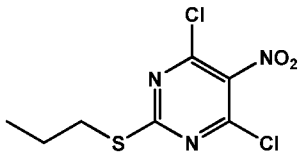
[0032] Alternatively, a compound of formula **VII'**



VII'

wherein Z is a group convertible to the hydroxyethyl group can be used instead of **VII** in a sequence of reactions presented in scheme 9. In the final step the group Z is converted to hydroxyethyl group by using methods known to the person skilled in the art as mentioned below.

[0033] According to the present invention, the group "Pg" can be selected from the group consisting of oxycarbonyl-type amino protecting groups and sulfonyl-type amino protecting groups, without being limited thereto. The group "Pg" as used in the present invention does not merely serve the purpose of protecting the amino group. It additionally provides for enhanced selectivity of the reactions into which the compounds of formula **II** enter. It was found that the selectivity for monosubstitution of the compound of formula



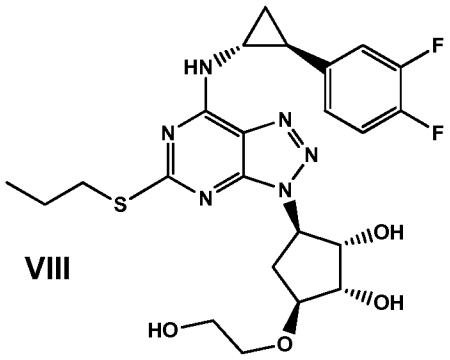
(CLIN)

is greatly enhanced by the reaction with the resulting carbamates or sulfamides when compared to the direct reaction between the compound of formula **Ia** (unprotected cyclopropane analogue) with CLIN. Yields are also improved. Moreover, the oxycarbonyl or sulfonyl N-substituents also allow for the regioselective triazole ring formation during the nitrosation step, and regioselective alkylation during the hydroxyethyl group introducing steps. According to preferred embodiments, Pg can be selected from the group consisting of *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), methanesulfonyl (Ms), benzenesulfonyl (Bs), *p*-toluenesulfonyl (Ts), and 2-naphthalenesulfonyl.

[0034] The group convertible to hydroxyethyl ("Z") according to the invention can be selected from the group consisting of: $-CH_2COOR_1$, wherein R_1, is selected from linear or branched C_1-C_6-alkyl or benzyl; cyanomethyl; $-CH_2CH(E_1R_2)(E_2R_3)$, wherein E_1 and E_2 are independently selected from a chalcogen element, preferably O or S, and R_2 and R_3 are the same or different, selected from C_1-C_4-alkyl, or together form C_2-C_4-alkylene or o-phenylene connection; or $-CH_2CH_2-OR_4$ wherein R_4 is a hydroxy protecting group, selected from tertiary alkyl group, preferably *tert*-butyl or trityl, arylmethyl group, preferably benzyl or para substituted benzyl, methoxy substituted C_1-C_2-alkyl group, preferably methoxymethyl (MOM), trisubstituted silyl group, preferably trimetylsilyl, *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl, acyl, preferably acetyl or benzoyl.

[0035] The group "Z" can be converted to the hydroxyethyl group by using methods known to the person skilled in the art, for instance $-CH_2COOR_1$ by reduction, cyanomethyl and $-CH_2CH(OR_2)(OR_3)$ by acid hydrolysis and reduction, silyloxyethyl groups by fluoride cleavage, *tert*-alkoxyethyl by acid cleavage, benzyloxyethyl by hydrogenation. In view of telescoping intermediates to the next step without isolation as described in route B in Scheme 8 it is preferable that the group is stable in all reactions of the one-step sequence, such as being stable in basic conditions. Most preferable groups are selected from $-CH_2COOMe$,$-CH_2COOEt$, *tert*-butoxyethyl, trityloxyethyl, and benzyloxyethyl.
Preferably, the groups Pg, R_4 and the glycol protection group are removed in one reaction step by acid cleavage. In this view *tert*-butoxyethyl group and trityloxyethyl group are the most preferable.

[0036] For preparing a ticagrelor **(TCG)** with the formula **VIII** shown below, the compound of formula **Va** or **Vb** as described above is subjected to the deprotection reaction(s) in order to remove Pg and in case of **Va** also the vicinal hydroxyl protecting group at the cyclopentane ring, respectively. The deprotection reaction(s) can proceed at the same time, to concurrently remove both "Pg" and the vicinal hydroxyl protecting group at the cyclopentane ring, for example using acids such as HCl or phosphoric acid in a suitable organic solvent, for example alcohols such as methanol or ethanol. If desired, a salt, a cocrystal or a complex of the compound of formula **VIII** (ticagrelor, **TCG**) can be optionally formed.



VIII

[0037] The ticagrelor compound prepared according to the invention may be used or administered on its own, preferably it is administered as a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable excipient and/or carrier. Further, the ticagrelor compound prepared according to the invention may be combined with other drugs, especially drugs having activity against platelet aggregation or thrombolytic events.

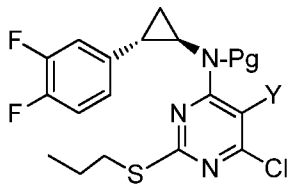
[0038] In a further aspect of the present invention, a pharmaceutical composition comprising the compound of formula **VIII** (ticagrelor, **TCG**) or a salt thereof is prepared by comprising the steps of preparing the compound of formula **VIII** or a salt thereof as described above, and mixing the compound of formula **VIII** or a salt thereof with a pharmaceutically acceptable carrier and/or excipient. The administration form can be suitably chosen, e.g. a form suitable for oral, parenteral, rectal administration and/or administration by inhalation, and the dosage form may be solid, liquid, or powdery. Therefore, the pharmaceutical composition comprising ticagrelor compound prepared according to the invention may suitably be in the form of tablets, pills, capsules, syrups, powders or granules for oral administration; or as sterile parenteral or subcutaneous solutions, suspensions for parenteral administration; or as suppositories for rectal administration.

[0039] Suitable excipients and/or carriers include, without being limited to, diluents, binders, disintegrants, lubricants, etc. For example, the compound or a finely divided form thereof, or particles comprising the compound, are mixed with a carrier or binder substance, e.g. a mono-, di- or polysaccharide such as sugars and starch, a sugar alcohol or another polyol. For example, lactose, saccharose, sorbitol, mannitol, starch, cellulose derivatives, a binder such as polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like are mixed, and then compressed into tablets. The compound or a finely divided form thereof or particles containing the same may be coated by another substance. The powder mixture or particles containing the compound may also be dispensed into capsules.

[0040] The pharmaceutical composition comprising ticagrelor prepared according to the invention in a desired dose

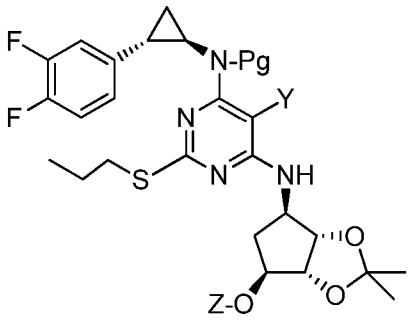
is generally suitable to treat a disease or condition of a patient in need thereof, specifically to display a desired activity against platelet aggregation, or in the treatment or prophylaxis of thrombolytic events.

[0041] Further aspects of the present invention reside in the provision of valuable intermediate compounds useful in the synthesis of a compound of formula **VIII** (ticagrelor, **TCG**), which intermediate compounds respectively have in common the amino group protecting group Pg:

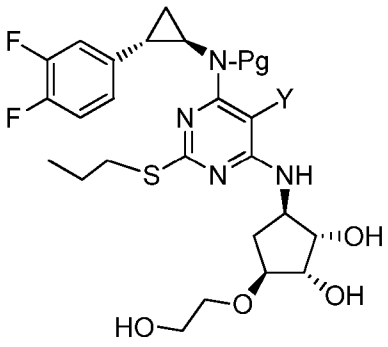


II

(Pg is an amino protecting group, and Y is NO_2 or NH_2)

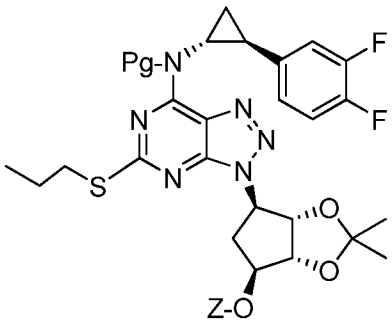


IVa



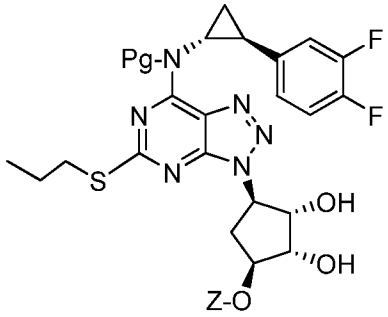
IVb

(Pg is an amino protecting group, Y is NO_2 or NH_2, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl)



Va

(Pg is an amino protecting group, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl)

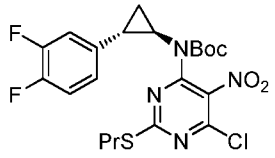
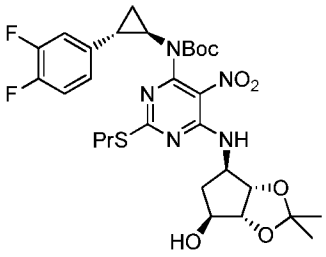
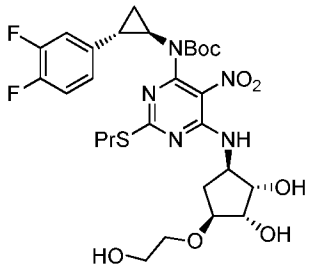
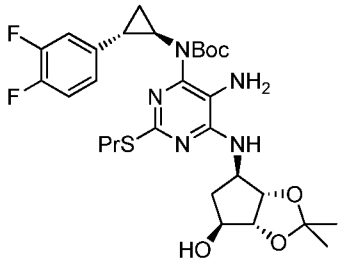


Vb

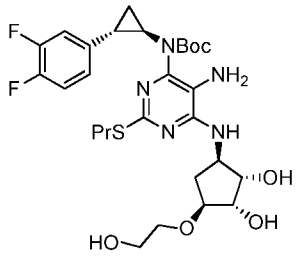
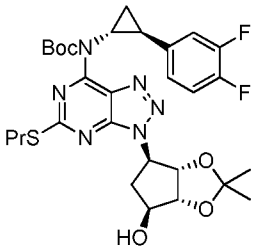
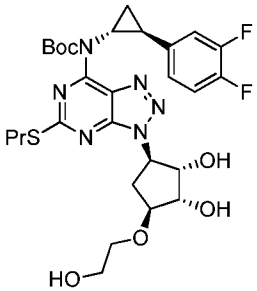
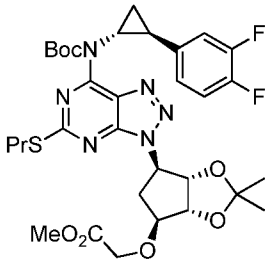
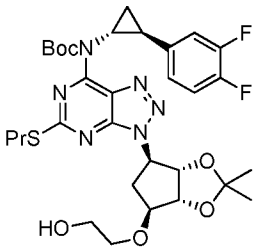
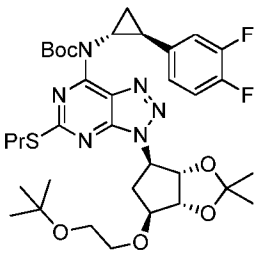
(Pg is an amino protecting group, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl)

[0042] As to the definition of "Pg" and "Z", reference is made to the descriptions elsewhere in the present specification.

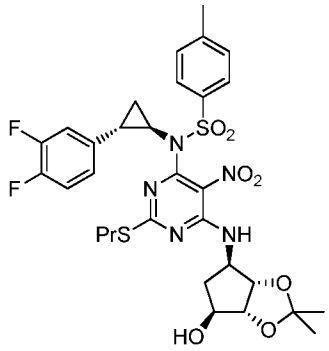
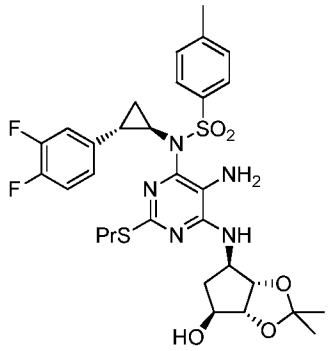
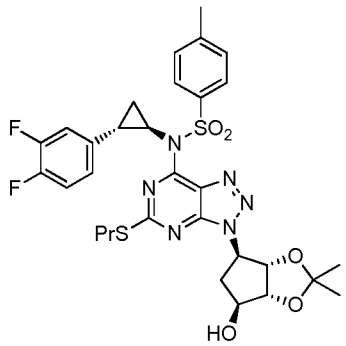
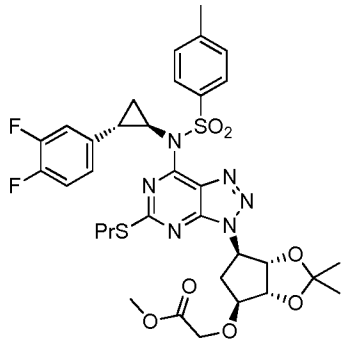
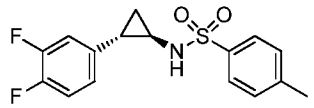
[0043] Particular examples of such useful intermediate compounds are listed by their respective formulas below (in these formulas, "Pr" denotes "propyl"):

Formula	Chemical name
	*tert*-butyl (6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl) ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate
	*tert*-butyl((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)carbamate
	*tert*-butyl((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(6-(((1*R*,2*S*,3*S*,4*S*)-2,3-dihydroxy-4-(2-hydroxyethoxy)cyclopentyl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)carbamate
	*tert*-butyl (5-amino-6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-2-(propylthio)pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate

(continued)

Formula	Chemical name
	*tert*-butyl (5-amino-6-(((1*R*,2*S*,3*S*,4*S*)-2,3-dihydroxy-4-(2-hydroxyethoxy)cyclopentyl)amino)-2-(propylthio)pyrimidin-4-yl) ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate
	*tert*-butyl((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)carbamate
	*tert*-butyl((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((1*R*,2*S*,3S,4S)-2,3-dihydroxy-4-(2-hydroxyethoxy)cyclopentyl)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)carbamate
	methyl2-(((3a*R*,4*S*,6*R*,6a*S*)-6-(7-((*tert*-butoxycarbonyl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy)acetate
	*tert*-butyl((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((3a*S*,4*R*,6*S*,6a*R*)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)carbamate
	*tert*-butyl(3-((3a*S*,4*R*,6*S*,6a*R*)-6-(2-(*tert*-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate

(continued)

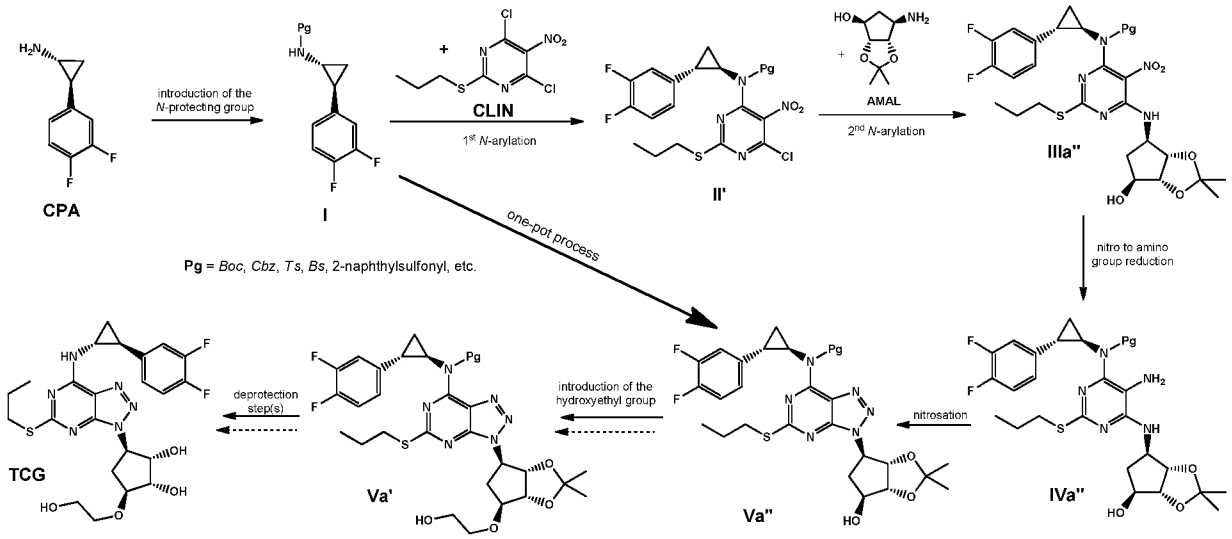
Formula	Chemical name
	*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-N-(6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)-4-methylbenzenesulfonamide
	*N*-(5-amino-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-*N*-(6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-2-(propylthio)pyrimidin-4-yl)-4-methylbenzenesulfonamide
	*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-N-(3-((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-4-methylbenzenesulfonamide
	methyl 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-(7-(*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-4-methylphenylsulfonamido)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy)acetate
	*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-4-methylbenzenesulfonamide

[0044] In the above particularly exemplified compounds, "Pg" is represented by *tert*-butyloxycarbonyl (Boc)-group and p-toluenesulfonyl (Ts) group, but it should be apparent that analogous useful and further specifically exemplified inter-

mediate compounds correspond to those listed above, wherein the specific protecting group, Boc or Ts, is replaced by other amino group protecting groups, e.g. carbobenzyloxy (Cbz), *p*-toluenesulfonyl (Ts) group, benzenesulfonyl (Bs), methanesulfonyl (Ms), or 2-naphthalenesulfonyl.

[0045] Specific embodiments representing the basic synthetic concept of the present invention are further described below. More specifically, in an illustrative but non-limiting example, scheme 10 below illustrates a concept of the molecular assembly of ticagrelor **(TCG),** while noting that this scheme is by no means limiting with respect to the specific nature of transformation, reactions, conditions protecting groups, methods and reagents, which can be used.

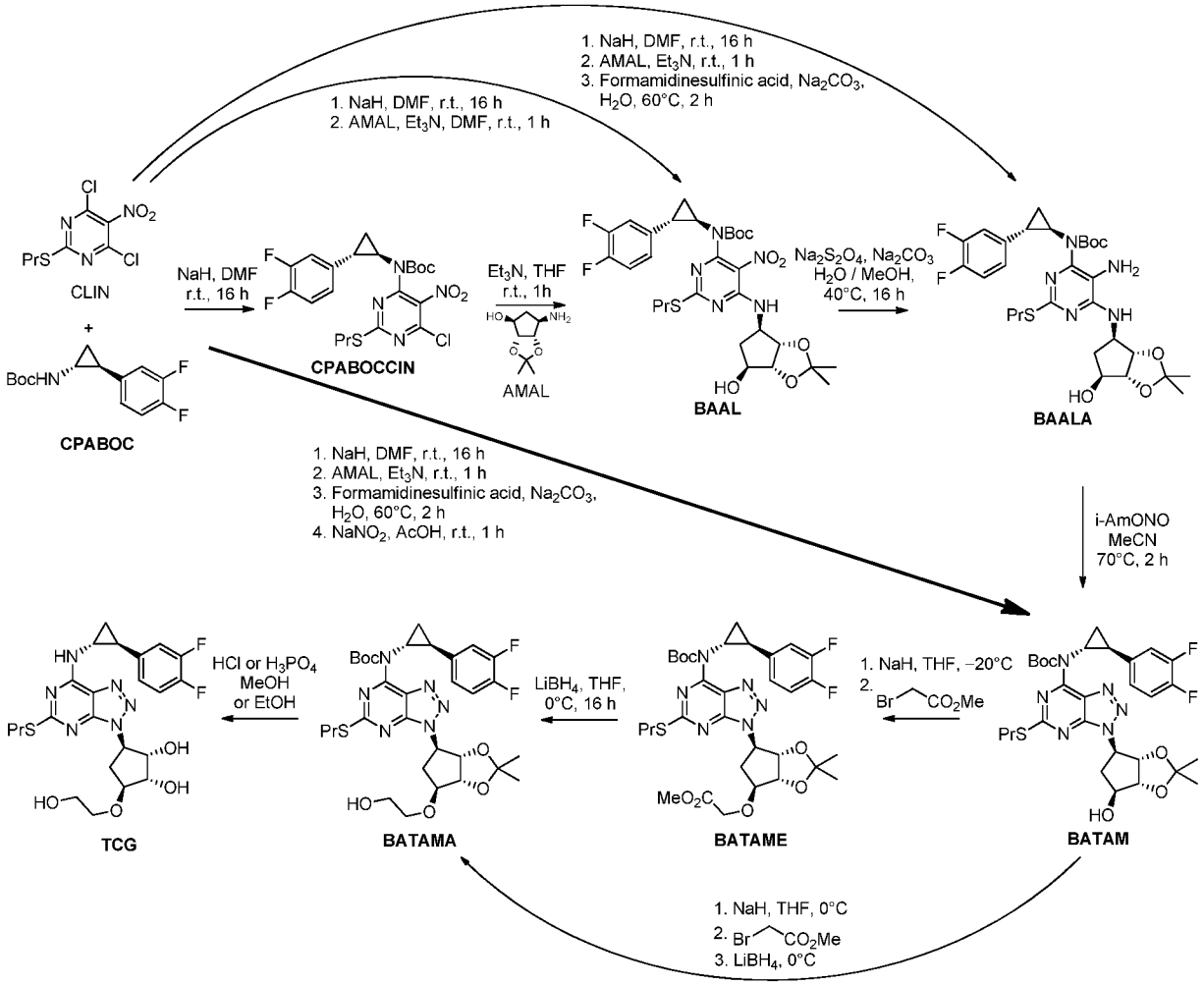
[0046] This illustration of the general synthetic route first includes a substitution of the amino group of the **CPA** with an electron withdrawing group, for example of the oxycarbonyl or sulfonyl type, in order to increase the acidity of the N-H bond. It was found that the selectivity for monosubstitution at **CLIN** is greatly enhanced if in the reaction of *N*-arylation a carbamate, sulfonamide or other amide derivative of **CPA** is reacted with **CLIN,** compared to direct reaction between **CPA** and **CLIN.** The obtained *N*-protected intermediates of the structural type **II** are then used to arylate **AMAL** to give intermediates **IIIa.** The nitro group is then reduced to give the diamines **IVa** which can be nitrosated to affect the formation of the triazole ring of intermediates **Va.** The protecting group introduced in the first step allows for the regioselective triazole ring formation during the nitrosation step. Compound **Va** is already suitably protected for the selective introduction of the hydroxyethyl group on the secondary alcohol group. The hydroxyethylation process and the later deprotection steps to give ticagrelor **(TCG)** can be performed by various methodologies known to those skilled in the art, such as an *O*-alkylation with an alkyl haloacetate, ester group reduction and deprotection under acidic conditions.



Scheme 10: Illustration of the basic synthetic concept of the invention.

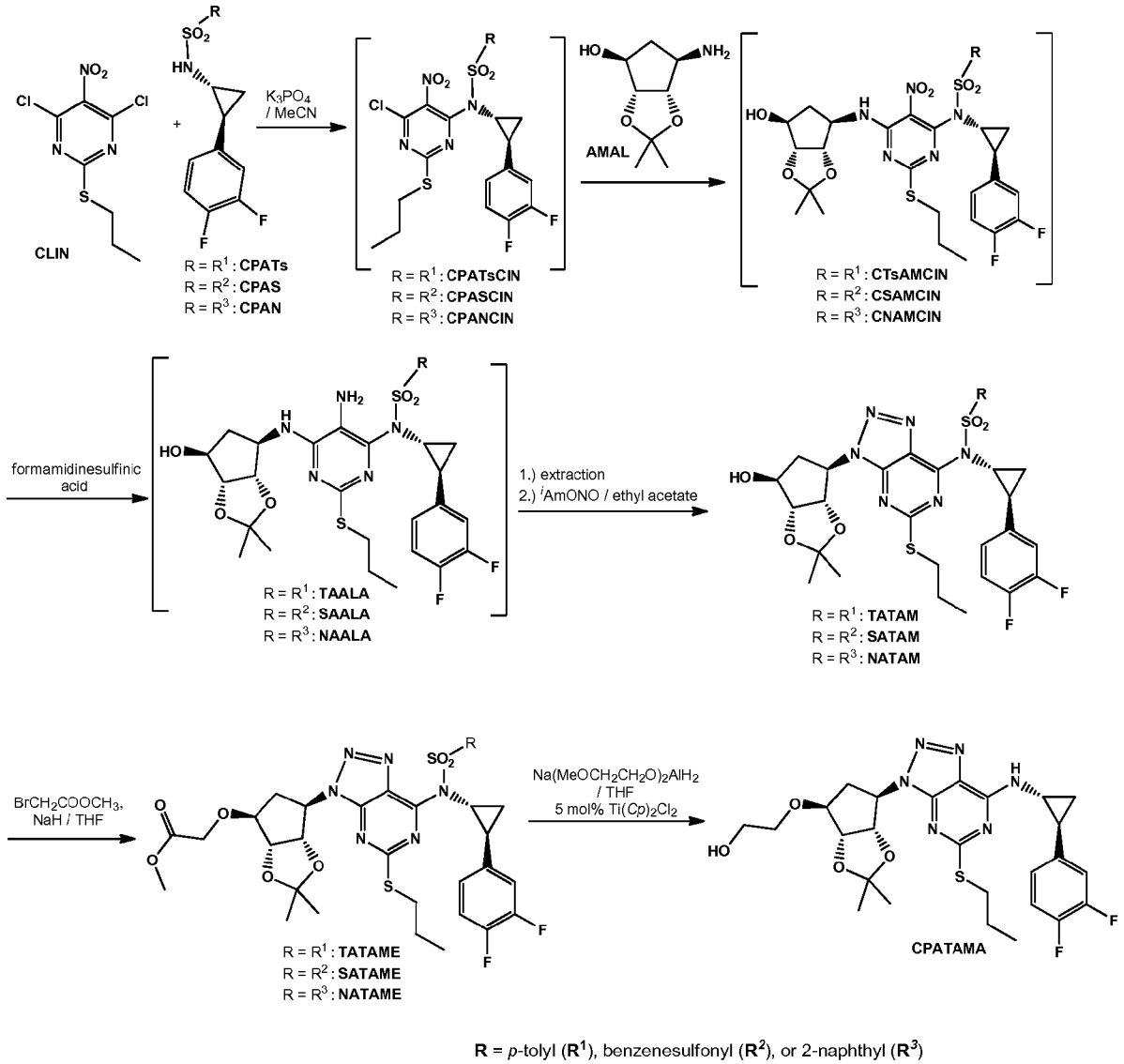
[0047] In a more specific example of ticagrelor synthesis, the embodiment of the invention is represented by the use of the *tert*-butoxycarbonyl (*Boc*) protected **CPA** derivative **CPABOC** (Scheme 11). This is deprotonated with sodium hydride in order to be *N*-arylated with **CLIN.** This gives **CPABOCCIN** with good selectivity and yields. This product is then used for the *N*-arylation of **AMAL,** preferably in the presence of a base such as triethylamine or alkali carbonates, to give **BAAL.** The next reaction steps include the reduction of the nitro group to give **BAALA** and its nitrosation to give **BATAM.** This is a key intermediate for use in the subsequent hydroxyethylation and deprotection steps which can be implemented using numerous synthetic approaches. Specifically, this can be achieved by alkylation with methyl bromoacetate to give **BATAME,** its reduction with lithium borohydride to give **BATAMA,** and finally the one step deprotection of the acetonide and *Boc* protecting groups under acidic conditions to give ticagrelor **(TCG).**

[0048] This synthetic route was found particularly advantageous for the application of one-pot methodologies. Specifically, the synthesis can be efficiently carried from **CPABOC** to **BATAM** in a one-pot procedure comprised of four chemical steps (Scheme 11).



Scheme 11: Synthesis of ticagrelor representing the embodiment of the invention.

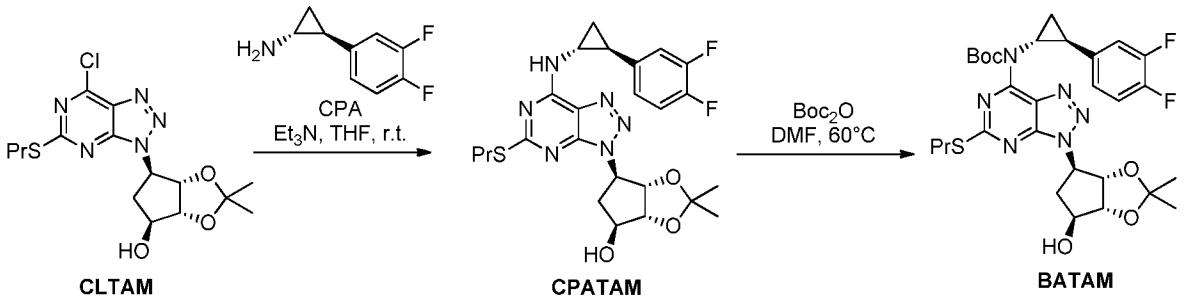
[0049] Protecting groups other than *Boc* may also be suitable. For example, the sulfonyl protecting groups, such as the *p*-toluenesulfonyl (*Ts*), benzenesulfonyl (Bs) or the 2-naphthalenesulfonyl group, were found to be suitable for the one pot synthesis of intermediates of type **V** directly from **CPA** derived sulfonamides **CPATs, CPAS** or **CPAN** correspondingly (Scheme 12). The increased acidity of these sulfonamides in comparison to the less acidic carbamate **CPABOC** allows for the use of more practical bases than sodium hydride. Tripotassium phosphate in acetonitrile was found particularly suitable for this first chemical step, as well as for the subsequent two chemical steps comprising the one-pot process toward **TAALA, SAALA or NAALA.** The triazole ring formation is suitably carried out by extracting the water diluted reaction mixture with ethyl acetate, phase separation, addition of isopentyl nitrite to the organic phase and mild heating. The intermediates **TAALA, SAALA** and **NAALA** thus need not be isolated in this process.



Scheme 12: One-pot synthesis of sulfonyl protected triazoles without the isolation of intermediates and further transformation to CPATAMA.

[0050] The compounds **TATAM, SATAM, NATAM,** or related sulfonamides, corresponding to intermediates of type **Va,** can then be used for the introduction of the hydroxyethyl ether side chain on their hydroxy group and further transformations toward ticagrelor. In particular, the hydroxyethyl group introduction can be performed by alkylation with methyl bromoacetate to give the ester intermediate which can then be reduced to the alcohol using the sodium bis(2-methoxyethoxy)aluminumhydride while at the same time catalytic amounts of titanocene dichloride promote the reductive cleavage of the sulfonyl protecting groups. Thus, the final intermediate **CPATAMA** can be obtained in two reaction steps from **TATAM** or other such sulfonamides. This new method for sulfonyl group deprotection employing the titanocene catalysis was developed specifically for the purpose of being applicable during the ester group reduction in order to perform both functional group transformations concurrently. **CPATAMA** is then hydrolysed to ticagrelor in acidic media according to prior art.

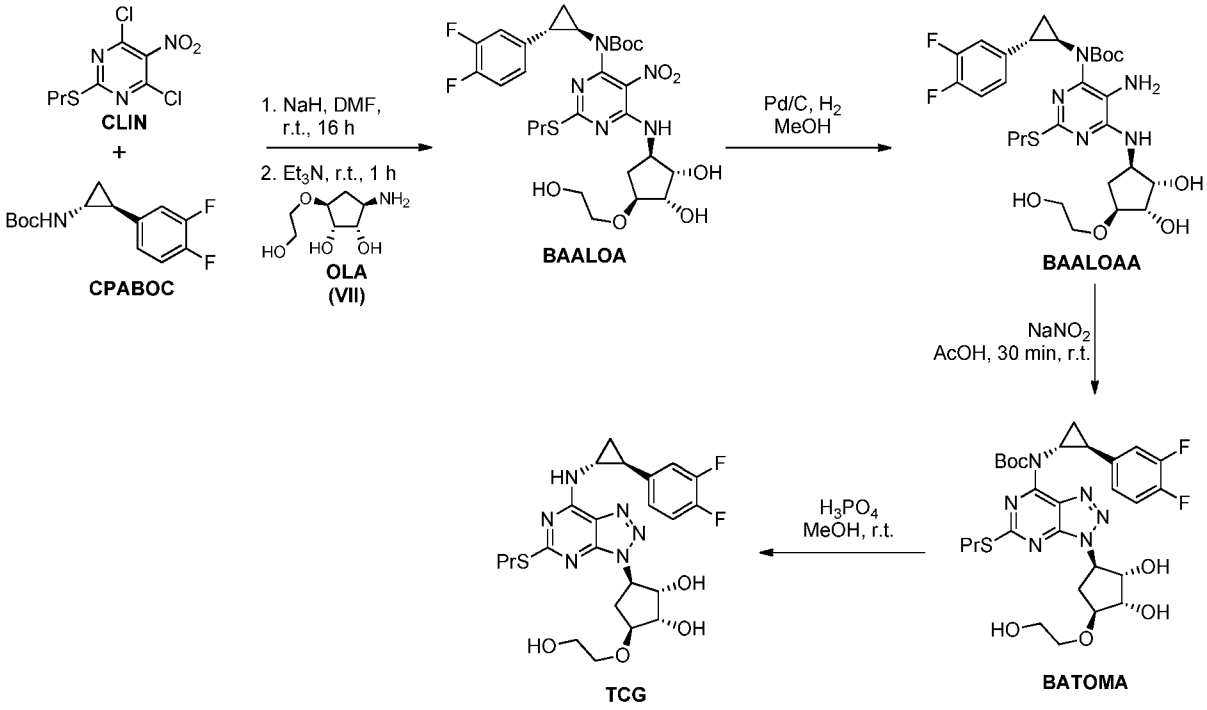
[0051] In another embodiment the key intermediate **BATAM** can be prepared from **CPATAM,** which can be derived from **CLTAM** as shown in scheme 13. The analogous sulfonyl protected intermediate **TATAM** can be prepared by the N-arylation of **CLTAM** with **CPATs** in acetonitrile and K_3PO_4 as a base. **CLTAM** can be prepared as described in WO 00/34283 (Scheme 1).



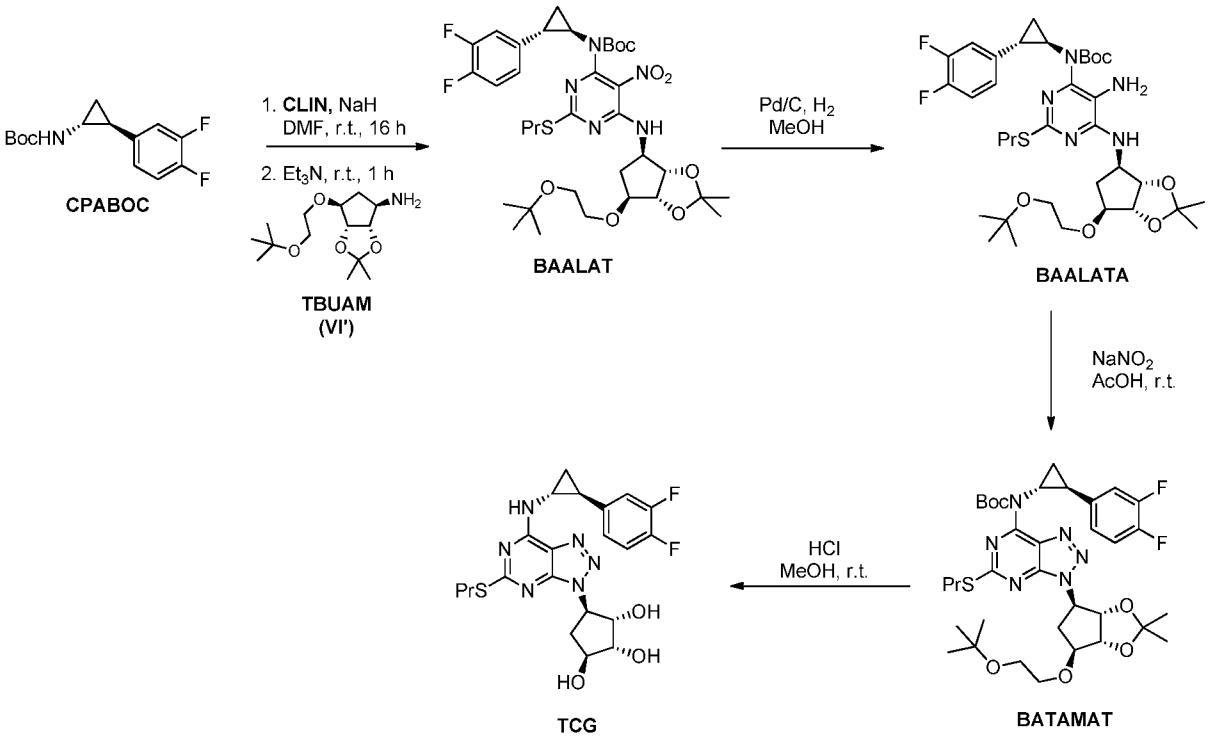
Scheme 13: Synthesis of **BATAM** from **CLTAM** via **CPATAM**.

[0052] In another special embodiment ticagrelor is prepared from the protected cyclopropylamine derivative **CPABOC.** First step of the synthesis is a one-pot reaction of heteroarylation in basic conditions and condensation with the unprotected cyclopentane derivative **OLA (VII),** followed by reduction of nitro group to amino group yielding the intermediate **BAALOAA,** which is further converted to benzotriazole **BATOMA.** Deprotecting of **BATOMA** gives ticagrelor in high yield. Again the conversion of a simple starting compound such as **CLIN** to ticagrelor needs only four technological steps, even with no need for additional protection of cyclopentane hydroxy groups (Scheme 14).

[0053] In a further special embodiment presented in Scheme 15 ticagrelor is prepared from the protected cyclopropylamine derivative **CPABOC** using intermediates with a group convertible to the hydroxyethyl group **(TBUAM (VI')).** In the first step the molecule **BAALAT** is constructed of three constituted parts **CPABOC, TBUAM** and **CLIN** in one step. The intermediate is further transformed by reduction of nitro group and diazotisation to the triazolo derivative **BATAMAT,** which is finally deprotected by simultaneous cleavage of Boc, *tert*-butoxy and isopropylidene groups in acidic methanol solution to give ticagrelor. In spite of the additional conversion to the hydroxy group the process keeps a reduced number of steps by triple deprotection in one step.



Scheme 14: Synthesis of ticagrelor using unprotected cyclopentane derivative.



Scheme 15: Synthesis of ticagrelor using triple cleavage of protecting group in one step.

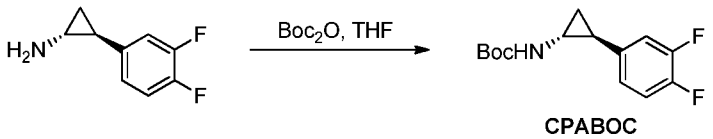
[0054] In the following the present invention will be described in further detail by illustrative, non-limiting examples.

Examples

Example 1: Preparation of *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamte

[0055]

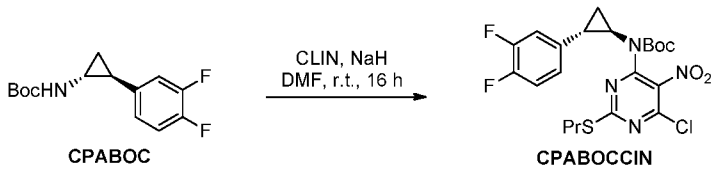
(**CPABOC**)



[0056] To a solution of *trans*-(1*R*,2*S*)-2-(2,3-difluorophenyl)cyclopropylamine (26.4 g, 156 mmol) (24 mL, 172 mmol) in THF (100 mL) was slowly added a solution of BOC_2O in THF (100 mL). The resulting reaction mixture was stirred at room temperature for 1 h, then concentrated. After addition of water (200 mL), the white precipitate was filtered off, washed with water (3 x 100 mL), and dried to afford 42.0 g (99% yield) of title compound as white powder. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.16 (m, 2H), 1.45 (s, 9H), 2.01 (m, 1 H), 2.31 (m, 1 H), 2.64 (m, 1 H), 4.91 (br s, 1 H), 6.88 (m, 1 H), 6.95 (m, 1 H), 7.03 (m, 1 H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.3 (m, 1 F), -142.8 (m, 1F); MS (ESI) *m/z:* 270 $[MH]^+$.

Example 2: Preparation of *tert*-butyl (6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(CPABOCCIN)**

[0057]

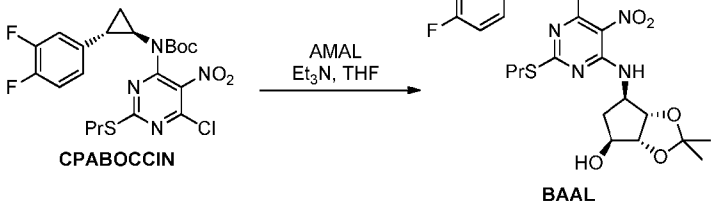


CPABOC CPABOCCIN

[0058] A mixture of **CPABOC** (0.20 g, 0.74 mmol), **CLIN** (0.20 g, 0.74 mmol) and NaH (60% in oil, 36 mg, 0.74 mmol) in dry DMF (2 mL) was stirred at room temperature for 16 hours, then acetic acid (0.5 mL) and water (10 mL) were added. After extraction with diisopropyl ether (3x10 mL), the combined organic layers were dried over $MgSO_4$, and concentrated. Purification by chromatography (SiO_2 hexane:EtOAc) afforded title compound as yellow oil (0.23 g, 62% yield).^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, J = 7.3 Hz, 3H), 1.22 (m, 1 H), 1.29 (q, J = 6.6 Hz, 1H), 1.36 (s, 9H), 1.66 (m, 2H), 2.17 (m, 1H), 2.94 (m, 1H), 3.03 (m, 1 H), 3.08 (m, 1 H), 6.58 (m, 1 H), 6.94 (m, 1 H), 7.01 (m, 1 H).

Example 3: Preparation of *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*]-[1,3]dioxol-4-yl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)carbamate **(BAAL)**

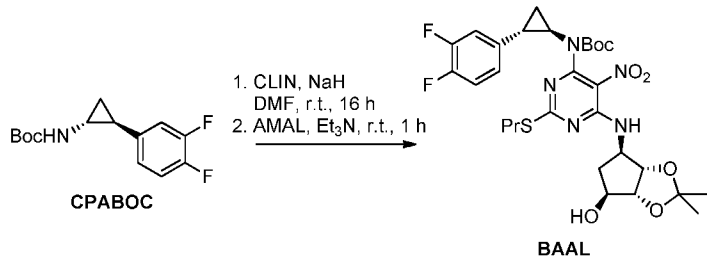
[0059]



CPABOCCIN BAAL

[0060] To a solution of **CPABOCCIN** (0.20 g, 0.40 mmol) and triethylamine (0.061 mL, 0.44 mmol) in dry THF (2 mL) was added **AMAL** (76 mg, 0.44 mmol). The resulting reaction mixture was stirred at room temperature for 1 h, then water was added (10 mL), and the product was extracted to THF (3x5 mL). Combined organic layers were dried over $MgSO_4$, and then concentrated. Purification by chromatography (SiO_2 hexane:EtOAc) afforded the title compound as a yellow oil (0.24 g, 93% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, J = 7.3 Hz, 3H), 1.19 (s, 3H), 1.27 (m, 2H), 1.31 (s, 9H), 1.36 (s, 3H), 1.69 (m, 2H), 1.77 (m, 1 H), 2.19 (br s, 1 H), 2.26 (m, 1 H), 2.67 (m, 1 H), 2.91-3.08 (m, 3H), 4.29 (m, 1 H), 4.46 (m, 1 H), 4.52 (m, 1 H), 4.68 (m, 1 H), 6.88 (m, 1 H), 6.94-7.01 (m, 2H), 8.64 (d, J = 8.0 Hz, 1 H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.4 (m, 1F),-142.6(m, 1F); MS (ESI) *m/z:* 638 $[MH]^+$.

[0061] **BAAL** was also prepared through one-pot reaction starting from **CPABOC.**

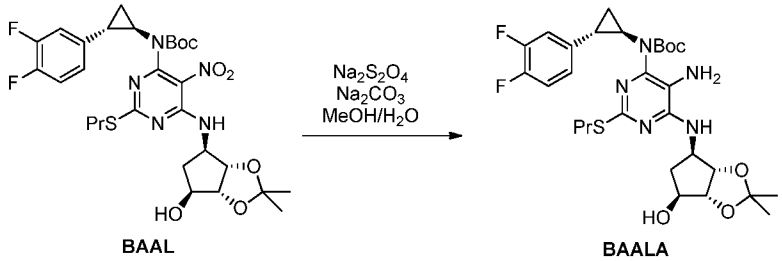


CPABOC BAAL

[0062] A mixture of **CPABOC** (1.0 g, 3.71 mmol), **CLIN** (1.0 g, 3.71 mmol) and NaH (60% in oil, 0.16 g, 4.08 mmol) in dry DMF (8 mL) was stirred at room temperature for 16 hours, then triethylamine (0.57 mL, 4.08 mmol) and **AMAL** (0.71 g, 4.08 mmol) were added at room temperature, and the resulting reaction mixture was stirred at room temperature for 1 h. Water (50 mL) was slowly added and product was extracted to diisopropyl ether (3 x 30 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellow oil (1.94 g, 82% yield).

Example 4: Preparation of *tert*-butyl (5-amino-6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-2-(propylthio) pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(BAALA)**

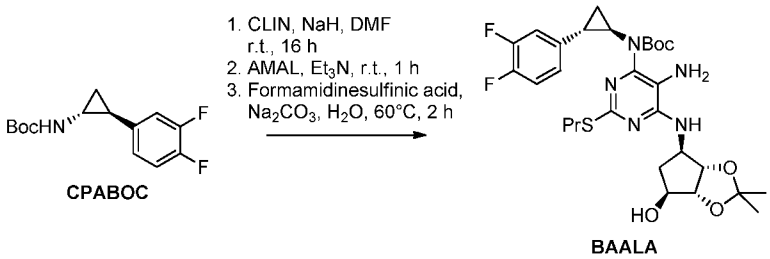
[0063]



BAAL BAALA

[0064] A solution of **BAAL** (0.64 g, 1.0 mmol) in MeOH (2 mL) was added to a mixture of sodium dithionite (0.57 g, 3.3 mmol), Na_2CO_3 (0.35 g, 3.3 mmol), water (1 mL) and MeOH (1 mL). Resulting reaction mixture was stirred at 40°C for 16 h, then water was added (30 mL), and product was extracted to EtOAc (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to give a crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as an orange oil (0.41 g, 68% yield). ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.4 (m, 1F), -142.7 (m, 1F); MS (ESI) *m/z:* 608 $[MH]^+$.

[0065] **BAALA** was also prepared through a one-pot reaction starting from **CPABOC.**

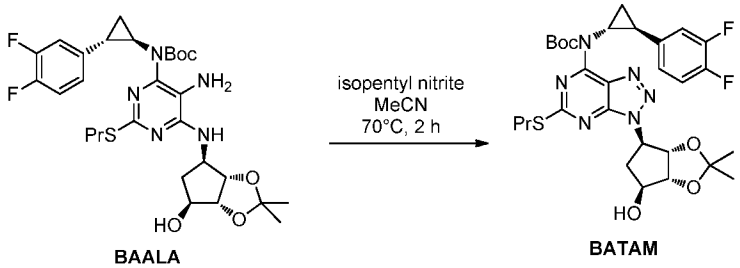


CPABOC BAALA

[0066] A mixture of **CPABOC** (1.0 g, 3.71 mmol), **CLIN** (1.0 g, 3.71 mmol) and NaH (60% in oil, 0.16 g, 4.08 mmol) in dry DMF (8 mL) was stirred at room temperature for 16 hours, then triethylamine (0.57 mL, 4.08 mmol) and **AMAL** (0.64 g, 3.71 mmol) were added at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. Then water (1 mL), Na_2CO_3 (1.29 g, 12.2 mmol) and formamidinesulfinic acid (1.32 g, 12.2 mmol) were added, and the resulting reaction mixture was stirred at 60°C for 2 h. Water (100 mL) was added and the product was extracted to 2-methyltetrahydrofuran (3 x 30 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to give a crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as a orange oil (1.42 g, 63% yield).

Example 5: Preparation *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((3a*S*,4*R*, 6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)carbamate **(BATAM)**

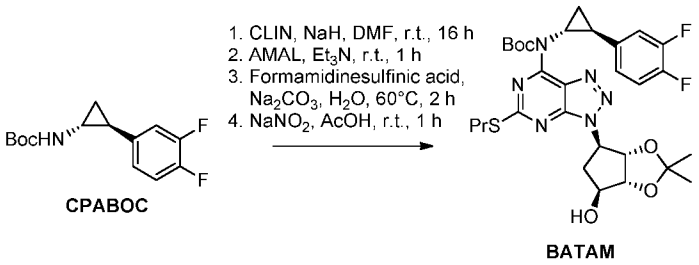
[0067]



BAALA BATAM

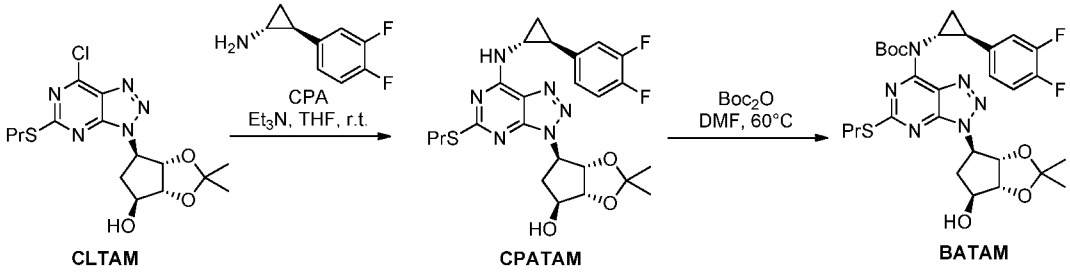
[0068] The title compound was prepared using the method described in WO 00/34283.
A solution of **BAALA** (0.40 g, 0.66 mmol) and isopentyl nitrite (0.13 mL, 1.0 mmol) in acetonitrile (4 mL) was stirred for 2 h at 70 °C. Volatile components were then evaporated, and crude product was purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as a yellow oil (0.40 g, 98% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, J = 7.3 Hz, 3H), 1.22 (m, 1 H), 1.25 (s, 3H), 1.38 (m, 1 H), 1.42 (s, 9H), 1.47 (s, 3H), 1.72 (m, 2H), 2.12 (m, 1 H), 2.23 (m, 1 H), 2.84 (m, 1 H), 2.99-3.05 (m, 1 H), 3.07-3.14 (m, 1H), 3.17 (m, 1H), 4.28 (m, 1H), 4.36 (m, 1H), 4.72 (m, 1H), 4.86 (m, 1H), 5.30 (m, 1H), 6.90 (m, 1H), 6.98-7.04 (m, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.1 (m, 1F), -142.3 (m, 1F); MS (ESI) *m/z:* 619 $[MH]^+$.

[0069] **BATAM** was also prepared through a one-pot reaction starting from **CPABOC.**



[0070] A mixture of **CPABOC** (10.0 g, 37.1 mmol), **CLIN** (9.95 g, 37.1 mmol) and NaH (60% in oil, 1.63 g, 40.8 mmol) in dry DMF (50 mL) was stirred at room temperature for 16 hours, then triethylamine (5.69 mL, 40.8 mmol), and **AMAL** (6.43 g, 37.1 mmol) were slowly added at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h, then water (20 mL), Na_2CO_3 (12.9 g, 122 mmol) and formamidinesulfinic acid (13.2 g, 122 mmol) were added, and the resulting reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was then cooled to 0°C. Acetic acid (50 mL) was added dropwise over 2 h. $NaNO_2$ (3.84 g, 55.7 mmol) was then added and resulting reaction mixture was stirred at room temperature for 1 h. Water was added (500 mL), product was extracted to 2-methyltetrahydrofuran (3 x 100 mL), combined organic phases were dried over $MgSO_4$, then concentrated to afford crude product, which was purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as yellow oil (12.0 g, 52% yield).

[0071] **BATAM** was also prepared from **CLTAM** via **CPATAM.**

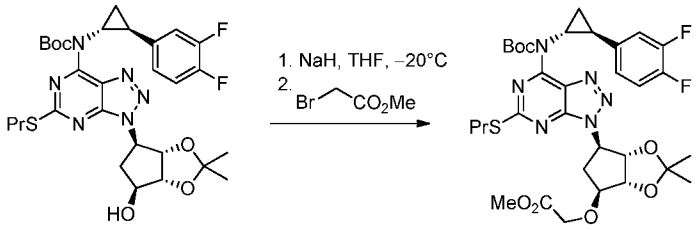


[0072] To a solution of **CLTAM,** which was prepared using the method described in WO 00/34283 (2.0 g, 5.18 mmol) and Et_3N (0.13 mL, 1.0 mmol) in dry THF (7 mL) was slowly added at room temperature a solution of **CPA** in dry THF (3 mL). The resulting reaction mixture was stirred for 1 h, then salts were filtered off, and the filtrate was concentrated. **CPATAM** was then crystallized from hexane/diisopropyl ether mixture to afford a white powder (2.29 g, 85% yield). Mp 108°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, J = 7.2 Hz, 3H), 1.31 (s, 3H), 1.35-1.44 (m, 2H), 1.53 (s, 3H), 1.67 (m, 2H), 1.92 (m, 1H), 2.15 (m, 1H), 2.23 (m, 1H), 2.92 (m, 1H), 3.00 (m, 1H), 3.09 (m, 1H), 3.15 (m, 1H), 4.44 (m, 1H), 4.83 (m, 1H), 4.89 (m, 1H), 5.35 (d, J=8.4Hz, 1H), 5.46 (m, 1H), 7.00 (m, 1 H), 7.07-7.13 (m, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.0 (m, 1F), -142.3 (m, 1 F); MS (ESI) m/z: 519 $[MH]^+$.

[0073] A solution of **CPATAM** (2.0 g, 3.86 mmol) and Boc_2O (0.93 g, 4.26 mmol) in DMF (10 mL) was stirred at 60°C until TLC and HPLC analysis showed total conversion (several days). Then water (100 mL) was added, and product was extracted to 2-methyltetrahydrofuran (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated to give a crude product, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford a yellowish oil (0.82 g, 34% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, J = 7.3 Hz, 3H), 1.22 (m, 1 H), 1.25 (s, 3H), 1.38 (m, 1 H), 1.42 (s, 9H), 1.47 (s, 3H), 1.72 (m, 2H), 2.12 (m, 1H), 2.23 (m, 1H), 2.84 (m, 1H), 2.99-3.05 (m, 1H), 3.07-3.14 (m, 1H), 3.17 (m, 1H), 4.28 (m, 1 H), 4.36 (m, 1 H), 4.72 (m, 1 H), 4.86 (m, 1 H), 5.30 (m, 1 H), 6.90 (m, 1 H), 6.98-7.04 (m, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.1 (m, 1 F), -142.3 (m, 1 F); MS (ESI) m/z: 619 $[MH]^+$.

Example 6: Preparation of methyl 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-(7-((*tert*-butoxycarbonyl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*] pyrimidin-3-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy) acetate **(BATAME)**

[0074]

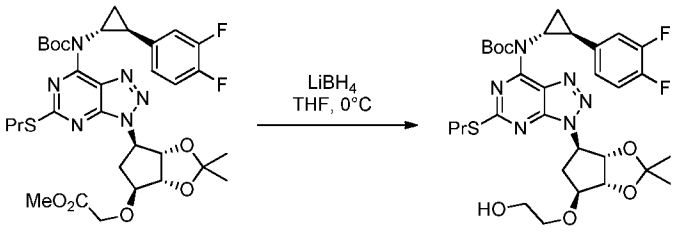


BATAM **BATAME**

[0075] To a solution of **BATAM** (1.79 g, 2.89 mmol) in dry THF (10 mL) NaH (0.13 g, 3.18 mmol) was added at-20°C and stirred for 1 h, then methyl bromoacetate (0.30 mL, 3.18 mmol) was added at -20°C. The resulting reaction mixture was stirred at -20°C for 16 h. Acetic acid (5 mL) was added slowly, then water (50 mL) was added, and the product was extracted to 2-methyltetrahydrofuran (3 x 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ (3x10 mL), dried over $MgSO_4$, and concentrated to give a crude product, which was then purified by chromatography (SiO_2, hexane:EtOAc). Colorless oil (1.60 g, 80% yield). ^1H NMR ($CDCl_3$, 500 MHz) (δ 0.99 (t, J = 7.3 Hz, 3H), 1.21 (m, 1 H), 1.28 (s, 3H), 1.36 (m, 1 H), 1.40 (s, 9H), 1.48 (s, 3H), 1.73 (m, 2H), 2.14 (m, 1 H), 2.68 (m, 2H), 3.00-3.11 (m, 2H), 3.18 (m, 1H), 3.65 (s, 3H), 4.01-4.10 (m, 3H), 4.76 (dd, J = 6.8, 2.5 Hz, 1 H), 5.11 (m, 1 H), 5.42 (dd, J = 6.8, 3.7 Hz, 1 H), 6.91 (m, 1 H), 6.97-7.05 (m, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.4 (m, 1 F), - 142.5 (m, 1F); MS (ESI) *m/z*: 691 $[MH]^+$.

Example 7: Preparation of *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((3a*S*,4*R*,6*S*,6a*R*)-6-(2-hydroxyethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3] dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)carbamate **(BATAMA)**

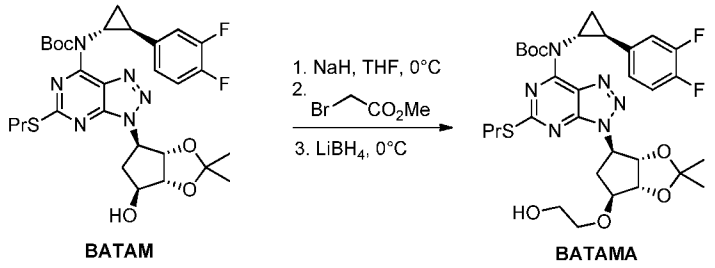
[0076]



BATAME **BATAMA**

[0077] To a solution of **BATAME** (1.79 g, 2.89 mmol) in dry THF (10 mL) at 0°C $LiBH_4$ (0.10 g, 4.63 mmol) was added and stirred for 16 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (5 mL). Water was added (50 mL), product was extracted to MeTHF (3 x 30 mL), combined organic phases were dried over $MgSO_4$, then concentrated to give a crude product, which was purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as a colorless oil (1.20 g, 78% yield).^1H NMR ($CDCl_3$, 500 MHz) (δ 1.07 (t, J = 7.3 Hz, 3H), 1.29 (m, 1 H), 1.37 (s, 3H), 1.43 (q, J = 6.9 Hz, 1 H), 1.48 (s, 9H), 1.56 (s, 3H), 1.80 (m, 2H), 2.21 (m, 1 H), 2.26 (m, 1 H), 2.56 (m, 1 H), 2.70 (m, 1 H), 3.07-3.20 (m, 2H), 3.26 (m, 1 H), 3.49 (m, 1 H), 3.52-3.66 (m, 3H), 4.05 (m, 1 H), 4.87 (d, J = 6.4 Hz, 1 H), 5.22 (m, 1 H), 5.53 (m, 1 H), 6.98 (m, 1 H), 7.04-7.12 (m, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ-139.3 (m, 1F),-142.4 (m, 1F); MS (ESI) *m/z:* 663 $[MH]^+$.

[0078] **BATAMA** was also prepared through a one-pot reaction starting from **BATAM.**

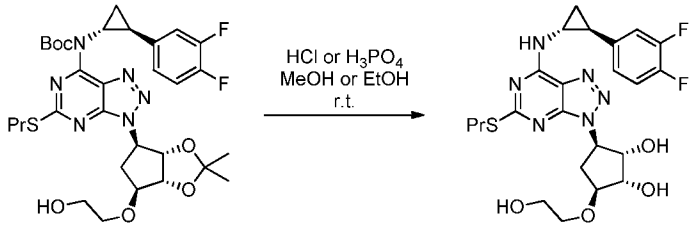


BATAM BATAMA

[0079] To a solution of **BATAM** (2.0 g, 3.23 mmol) in dry THF (10 mL) NaH (60% in oil, 0.14 g, 3.56 mmol) was added at 0 °C and stirred for 15 min, then methyl bromoacetate (0.36 mL, 3.80 mmol) was added, and the resulting reaction mixture was stirred at 0 °C for 2 h. Then $LiBH_4$ (0.14 g, 6.46 mmol) was added at 0°C and stirred for 2 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (5 mL). Water was added (20 mL), product was extracted to MeTHF (3x10 mL), combined organic phases were dried over $MgSO_4$, then concentrated to give a crude product, which was purified by chromatography (SiO_2, hexane:EtOAc) to afford the title compound as colorless oil (0.42 g, 20% yield).

Example 8: Preparation of (1*S*,2*S*,3*R*,5*S*)-3-(7-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl) amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy) cyclopentane-1,2-diol **(TCG,** ticagrelor)

[0080]

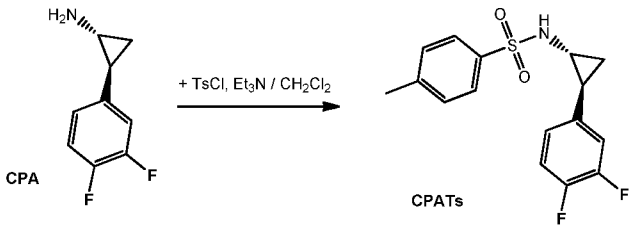


BATAMA TCG

[0081] To a solution of **BATAMA** (0.25 g, 0.38 mmol) in EtOH (10 mL) at room temperature *ortho*-phosphoric acid (85%, 1.5 mL) was slowly added. The resulting reaction mixture was stirred at room temperature for 24 h. Water was then added (20 mL) and the reaction mixture neutralized with 1 M NaOH. The product was extracted to ethyl acetate (5 x 10 mL), the combined organic phases were dried over Na_2SO_4, then concentrated to give a crude product, which was purified by chromatography (SiO_2, EtOAc) to afford title compound as a white powder (0.17 g, 87% yield). ^{19}F NMR (CD_3OD, 470.5 MHz) δ -141.9 - -142.1 (m, 1 F), -145.6 - -145.9 (m, 1 F); MS (ESI) *m/z*: 523 $[MH]^+$.

Example 9: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-4-methylbenzene sulfonamide **(CPATs)**

[0082]



CPA CPATs

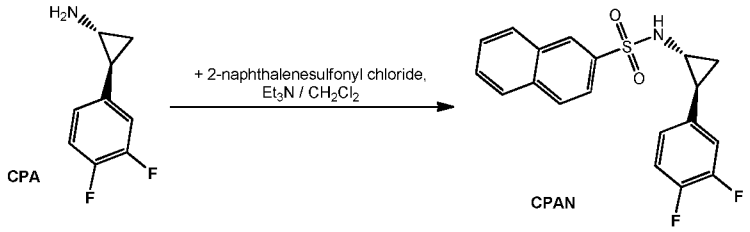
[0083] To a solution of **CPA** (16.92 g, 100 mmol) and triethylamine (17.4 mL, 125 mmol) in dichloromethane (140 mL) stirring in an ice bath was drop-wise added a solution of *p*-toluenesulfonyl chloride (20.02 g, 105 mmol) in dichloromethane (50 mL) in the course of 30 min. After 1 h reaction time there was added NH_3(aq) (25%, 10 mL), the mixture was left stirring for additional 10 min and then washed with water (300 mL), 1 M HCl (aq) (150 mL), water (300 mL) and evaporated under reduced pressure to give a white solid (31.45 g, 97% yield): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (q, *J* = 6.8 Hz, 1 H), 1.26 (m, 1 H), 2.11 (m, 1 H), 2.31 (m, 1 H), 2.43 (s, 3H), 5.33 (s, 1 H), 6.74 (m, 2H), 7.02 (m, 1 H), 7.29 (d, *J* = 8.0

Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ-138.89 (m, 1F),-142.17(m, 1 F).

Example 10: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)naphthalene-2-sulfonamide

[0084]

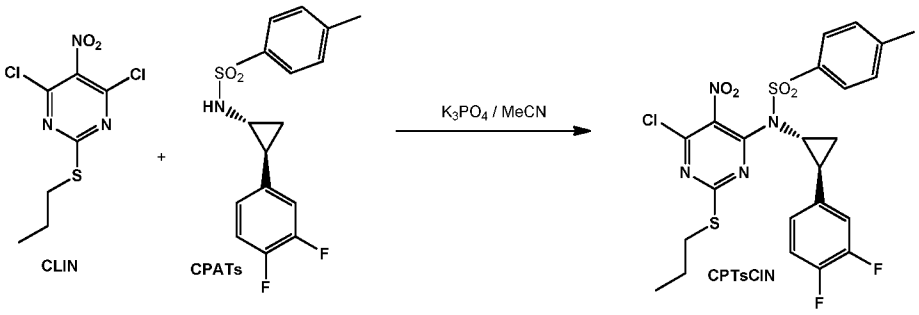
(**CPAN**)



[0085] Prepared in the same manner as **CPATs** (Example 9) by using 2-naphthalenesulfonyl chloride (11.90 g, 52.5 mmol) giving **CPAN** as a white solid (17.43 g, 97% yield): ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ-138.78 (m, 1F),-142.11 (m, 1 F).

Example 11: Preparation of *N*-(6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-4-methylbenzenesulfonamide **(CPTsCIN)**

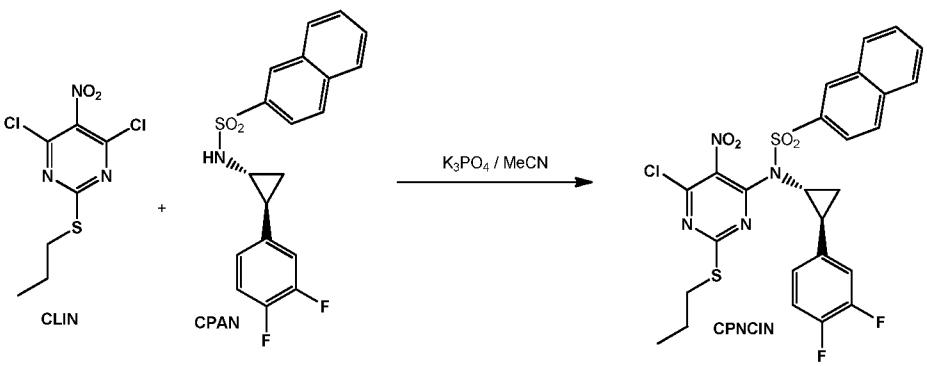
[0086]



[0087] To a solution of **CPATs** (1.29 g, 4 mmol) and **CLIN** (1.07 g, 4 mmol) in acetonitrile (15 mL) was added anhydrous K_3PO_4 (1.27 g, 6 mmol) and the mixture stirred for 24 h at 25°C. The reaction mixture was then diluted with water (50 mL), extracted with diisopropyl ether (50 mL), the extract washed with water (2 x 50 mL) and evaporated under reduced pressure. The crude product was purified with flash chromatography to give a brownish resin (1.08 g, 49% yield): MS (ESI) *m/z:* 555 $[MH]^+$; ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ-138.43 (m, 1F),-141.32 (m, 1 F).

Example 12: Preparation of *N*-(6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)naphthalene-2-sulfonamide **(CPNCIN)**

[0088]



[0089] To a solution of **CPAN** (1.44 g, 4 mmol) and **CLIN** (1.07 g, 4 mmol) in acetonitrile (15 mL) was added anhydrous K_3PO_4 (1.27 g, 6 mmol) and the mixture stirred for 48 h at 25°C. The reaction mixture was then diluted with water (50 mL), extracted with diisopropyl ether (50 mL), the extract washed with water (2 x 50 mL) and evaporated under reduced pressure. The crude product was purified with flash chromatography to give a brownish resin (1.56 g, 67% yield): MS (ESI) *m/z:* 591 $[MH]^+$.

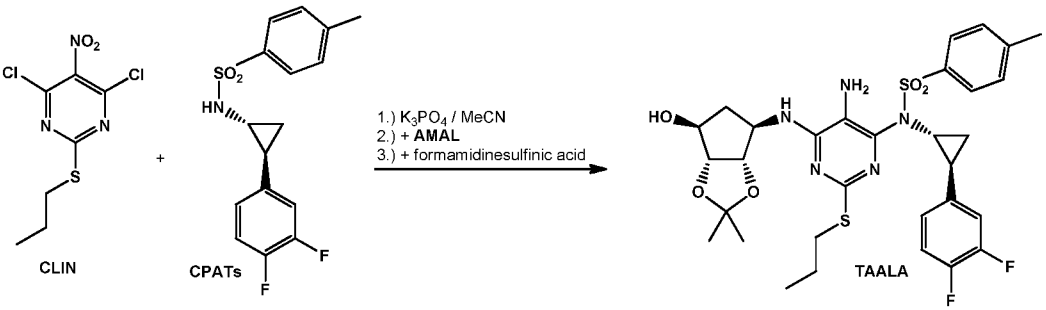
Example 13: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-*N*-(6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)-4-methylbenzenesulfonamide **(CTsAMCIN)**

[0090]

[0091] To a solution of **CPATs** (1.29 g, 4 mmol) and **CLIN** (1.07 g, 4 mmol) in acetonitrile (15 mL) was added anhydrous K_3PO_4 (1.27 g, 6 mmol) and the mixture stirred for 24 h at 25°C. **AMAL** (0.66 g, 3.8 mmol) was then added and stirring continued for additional 2 h. The reaction mixture was then diluted with water (50 mL), extracted with diisopropyl ether (50 mL), the extract washed with water (2 x 50 mL) and evaporated under reduced pressure. The crude product was purified with flash chromatography to give an amorphous solid (2.14 g, 77% yield): 95 area% HPLC; MS (ESI) m/z: 692 $[MH]^+$; ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ-138.93 (m, 1 F), -141.97 (m, 1 F).

Example 14: Preparation of *N*-(5-amino-6-(((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro -3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-2-(propylthio)pyrimidin-4-yl)-*N*-((1*R*,2*S*) -2-(3,4-difluorophenyl)cyclopropyl)-4-methylbenzenesulfonamide **(TAALA)**

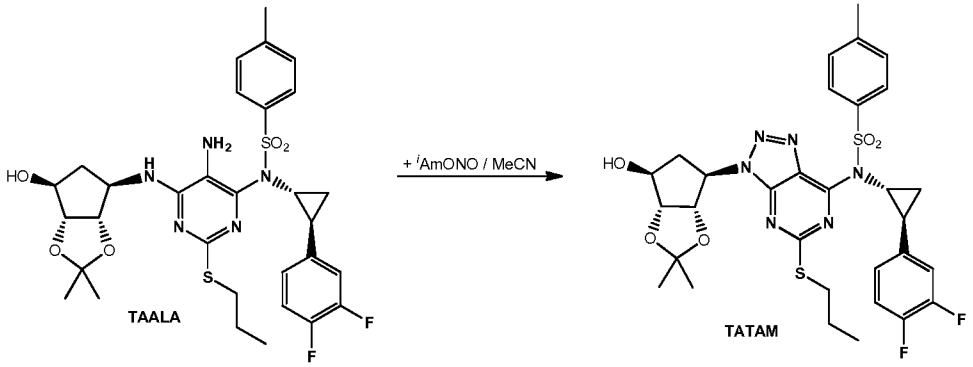
[0092]



[0093] A mixture of **CLIN** (0.96 g, 3.6 mmol), **CPATs** (1.29 g, 4 mmol) and K_3PO_4 (2.29 g, 10.8 mmol) in acetonitrile (15 mL) was stirred for 120 min at 25°C. **AMAL** (0.66 g, 3.8 mmol) was added and the mixture stirred for additional 2 hours. At this point formamidinesulfinic acid (1.36 g, 12.6 mmol) was added and the reaction temperature increased to 60 °C. After 24 hours, the mixture was diluted with water (75 mL), extracted with with ethyl acetate (50 mL), the extract washed with 0.1 M HCl(aq) (50 mL) and evaporated on a rotavapor to give a pale orange amorphous solid which was further purified by flash chromatography with hexane / ethyl acetate eluent (gradient from 4 : 1 to 1 : 1) to give **TAALA** as an light brown amorphous powder (1.20 g, 50% yield): MS (ESI) *m/z:* 662 $[MH]^+$.

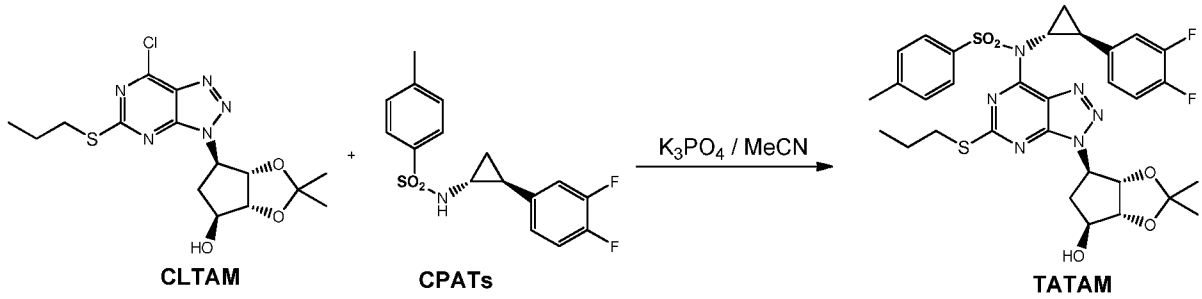
Example 15: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-*N*-(3-((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)-4-methylbenzenesulfonamide **(TATAM)**

[0094]



[0095] To a solution of **TAALA** (500 mg, 0.75 mmol) in acetonitrile (5 mL) was added isopentyl nitrite (0.13 mL, 0.94 mmol) and the mixture stirred for 2 h at 60°C. The reaction mixture was then diluted with water (50 mL), extracted with diisopropyl ether (30 mL), the extract washed with water (2 x 50 mL) and evaporated under reduced pressure to give an off-white amorphous powder (450 mg, 89% yield): 97 area% HPLC; MS (ESI) *m/z:* 673 $[MH]^+$.

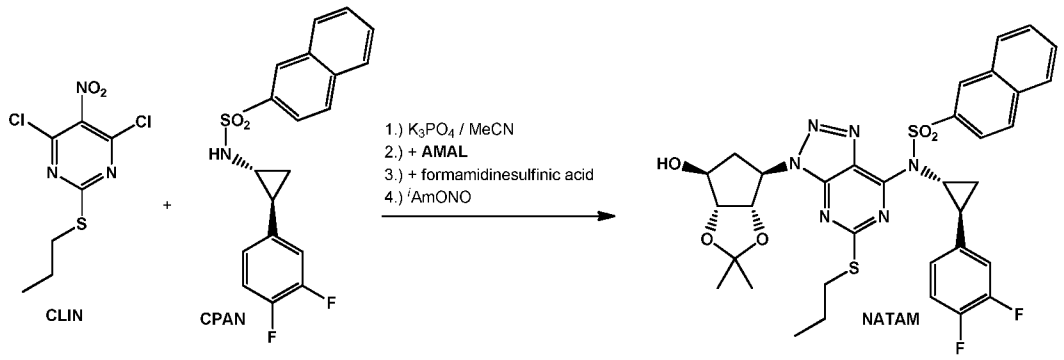
[0096] **TATAM** was also prepared from **CLTAM** via **CPATs.**



[0097] To a solution of **CLTAM** (1.16 g, 3 mmol), which was prepared using the method described in WO 00/34283, and **CPATs** (0.97 g, 3 mmol) in acetonitrile (20 mL) was added anhydrous K_3PO_4 (0.96 g, 4.5 mmol). After stirring for 24 h at 25°C, the mixture was diluted with water (80 mL) and extracted with diisopropyl ether (50 mL). The extract was washed with water (80 mL) and evaporated under reduced pressure to give a resinous crude product which was purified by flash chromatography to afford **TATAM** as an amorphous powder (1.52 g, 75% yield).

Example 16: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-*N*-(3-((3a*S*,4*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)naphthalene-2-sulfonamide **(NATAM)**

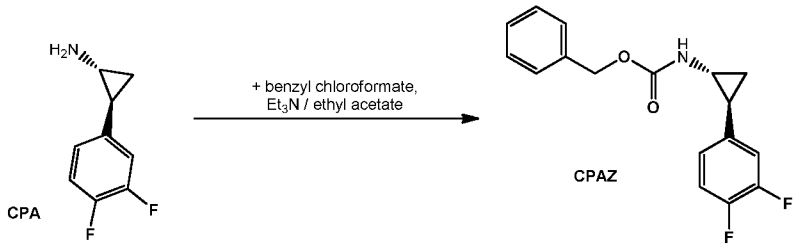
[0098]



[0099] A mixture of **CLIN** (1.27 g, 4.75 mmol), **CPAN** (1.80 g, 5 mmol) and K_3PO_4 (3.03 g, 14.25 mmol) in acetonitrile (20 mL) was stirred for 150 min at 25°C. **AMAL** (0.78 g, 4.5 mmol) was added and the mixture stirred for additional 2 hours. At this point formamidinesulfinic acid (2.05 g, 19 mmol) was added and the reaction temperature increased to 60°C. After 18 hours, the mixture was diluted with water (100 mL), extracted with ethyl acetate (60 mL), the extract washed with 0.1 M HCl(aq) (60 mL) and evaporated under reduced pressure to give a brown resin (3.18 g). This was dissolved in ethyl acetate (30 mL), isopentyl nitrite (0.76 mL, 5.63 mmol) was added and the solution stirred for 1 h at 60°C. The brown solution was concentrated and the product isolated using flash chromatography with hexane / ethyl acetate eluent (gradient from 5 : 1 to 2 : 1). **NATAM** was thus obtained as a beige powder (1.86 g, 58% yield).

Example 17: Preparation of benzyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(CPAZ)**

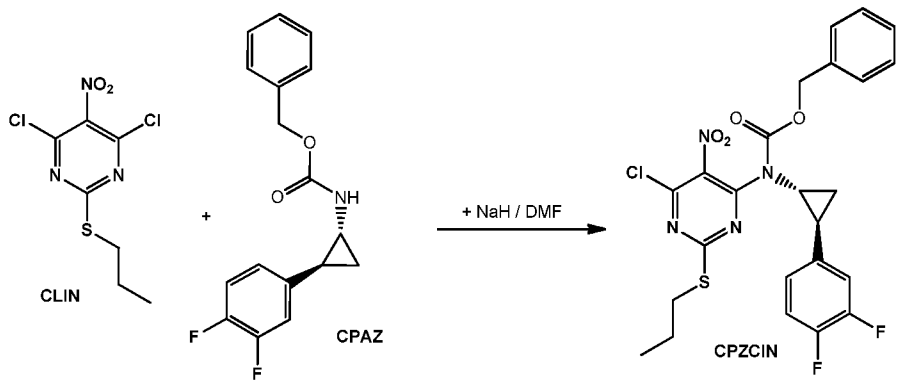
[0100]



[0101] To a solution of **CPA** (11.84 g, 70 mmol) and triethylamine (12.2 mL, 87.5 mmol) in ethyl acetate (80 mL) stirring in an ice bath was drop-wise added a solution of benzyl chloroformate (11.0 mL, 77 mmol) in ethyl acetate (40 mL) at such a rate to maintain the reaction temperature bellow 15°C. After 1 h stirring in the ice bath, water (120 mL) was added and the mixture kept stirring for additional 30 min. The organic phase was separated, washed with 0.2 M HCl(aq) (200 mL), water (2 x 100 mL) and evaporated on a rotavapor. There was obtained a white solid (22.28 g) which was recrystallized from cyclohexane to give the product as a white crystalline solid (19.62 g, 92% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) (δ1.17 (m, 2H), 2.07 (m, 1 H), 2.71 (m, 1H), 5.15 (s, 2H), 5.35 (bs, 1H), 6.70-7.10 (m, 3H), 7.33-7.42 (m, 5H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ -139.10 (m, 1F),-142.53(m, 1 F).

Example 18: Preparation of benzyl (6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(CPZCIN)**

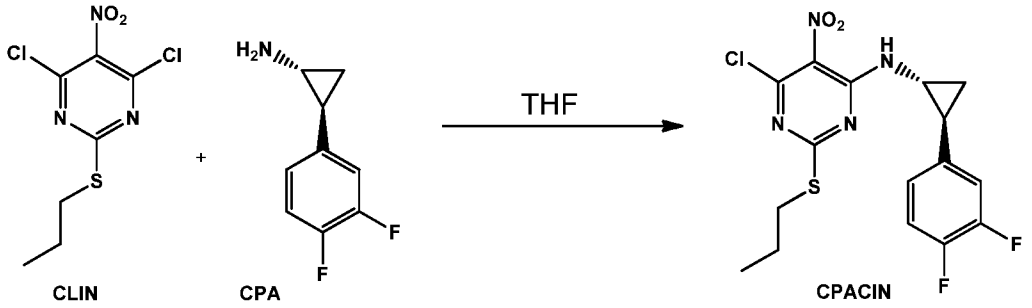
[0102]



[0103] To a solution of **CPAZ** (4.85 g, 16 mmol) and **CLIN** (5.35 g, 20 mmol) in DMF (75 mL) stirring under a nitrogen atmosphere on an ice-bath was added 60% sodium hydride in oil (0.80 g, 20 mmol). After 1 h in an ice-bath, the reaction is stirred for 19 h at 25°C. The mixture is then diluted with 1% aqueous acetic acid (300 mL), extracted with ethyl acetate (200 mL), the extract washed with water (3 x 300 mL) and evaporated under reduced pressure. The crude product was purified by flash chromatography to give a yellow resin (5.31 g, 62% yield).

Example 19: Preparation of 6-chloro-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-5-nitro-2-(propylthio)pyrimidin-4-amine **(CPACIN)**

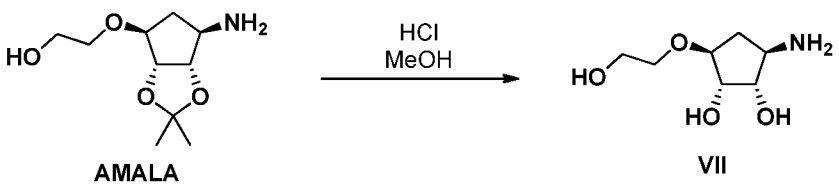
[0104]



[0105] To a solution of **CLIN** (13.4 g, 50 mmol) in THF (150 mL) was added a solution of **CPA** (8.50 g, 50 mmol) at an addition rate of 10 mL/h while maintaining the reaction temperature at 0°C. After the addition, the reaction mixture was then stirred at 25 °C for 4 days. *n*-Hexane (200 mL) was then added and the mixture diluted with water (500 mL). The organic phase was then washed with water and evaporated under reduced pressure to give a crude product which was purified by flash chromatography to afford **CPACIN** as a crystalline product (12.2 g, 61% yield): MS (ESI) *m/z:* 401 $[MH]^+$.

Example 20: Preparation of (1*S*,2*S*,3*R*,5*S*)-3-amino-5-(2-hydroxyethoxy)cyclopentane-1,2-diol **(OLA = VII)**

[0106]

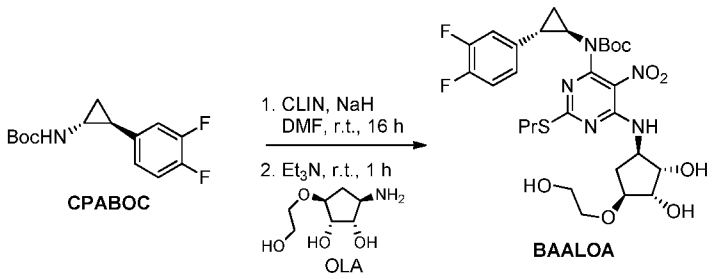


[0107] **AMALA** was prepared according to the process described in WO01/92263.
A solution of **AMALA** (1.0 g, 4.60 mmol) and 3 M HCl (5 mL) in MeOH (15 mL) was stirred at room temperature for 24 hours. Solvents were then evaporated to dryness. 2-Propanol (20 mL) and Na_2CO_3 (2.0 g) was added to the residue. The resulting mixture was stirred at room temperature for 24 h. Insoluble salts were then filtered off and filtrate was

concentrated to afford title compound as a colorless oil (0.57 g, 80% yield): ^{1}H NMR (DMSO-d_6) δ = 1.07 (m, 1 H), 2.19 (m, 1 H), 2.87 (dd, J = 14.7, 7.8 Hz, 1 H), 3.00-3.60 (m, 10H), 3.53 (m, 1 H), 3.74 (dd, J = 5.4, 3.4, 1 H); ^{13}C NMR (DMSO-d_6) δ = 36.4, 55.0, 60.4, 70.7, 75.1, 78.7, 83.3; MS (ESI) m/z: 178 $[MH]^+$.

Example 21: Preparation of *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(6-(((1*R*,2*S*,3*S*,4*S*)-2,3-dihydroxy-4-(2-hydroxyethoxy)cyclopentyl)amino)-5-nitro-2-(propylthio)pyrimidin-4-yl)carbamate **(BAALOA)**

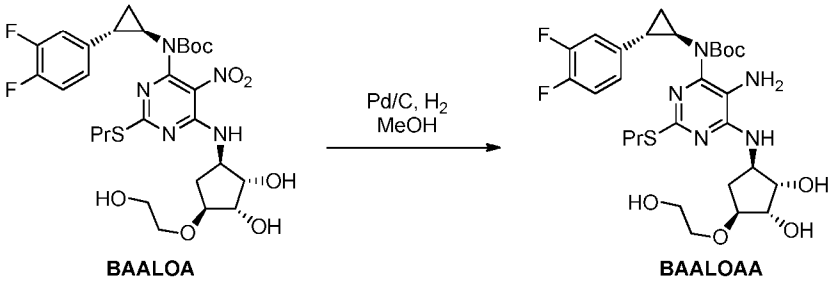
[0108]



[0109] A mixture of **CPABOC** (1.31 g, 4.87 mmol), **CLIN** (1.30 g, 3.71 mmol) and NaH (60% in oil, 0.21 g, 5.36 mmol) in dry DMF (10 mL) was stirred at room temperature for 16 hours, then triethylamine (0.75 mL, 5.36 mmol) and **OLA** (0.90 g, 5.08 mmol) were added at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. Water (70 mL) was slowly added and product was extracted to MeTHF (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellow oil (2.53 g, 81% yield). MS (ESI) m/z: 642 $[MH]^+$.

Example 22: Preparation of *tert*-butyl (5-amino-6-(((1*R*,2*S*,3*S*,4*S*)-2,3-dihydroxy-4-(2-hydroxy ethoxy)cyclopentyl)amino)-2-(propylthio)pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(BAALOAA)**

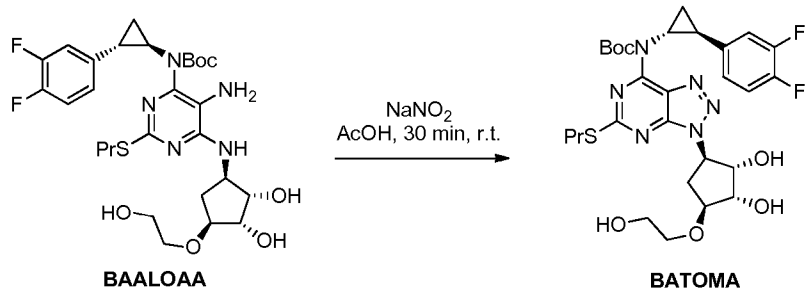
[0110]



[0111] A mixture of **BAALOA** (0.66 g, 1.03 mmol) and Pd/C (5%, 70 mg) in MeOH (7 mL) was hydrogenated under 10 bar H_2 for 16 h. Catalyst was then filtered off and filtrate was concentrated to afford title compound as yellow syrup (0.56 g, 89% yield). MS (ESI) m/z: 612 $[MH]^+$.

Example 23: Preparation *tert*-butyl ((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)(3-((1*R*,2*S*,3*S*, 4*S*)-2,3-dihydroxy-4-(2-hydroxyethoxy)cyclopentyl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)carbamate **(BATOMA)**

[0112]

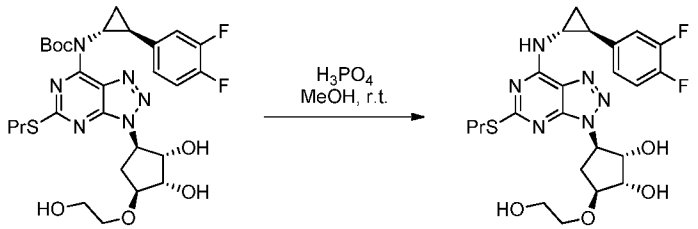


BAALOAA **BATOMA**

[0113] To a solution of **BAALOAA** (0.60 g, 0.98 mmol) in AcOH (5 mL) was added $NaNO_2$ (81 mg, 1.18 mmol). Resulting reaction mixture was stirred for 30 min at room temperature. Water (50 mL) was added and product was extracted to MeTHF (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellowish syrup (0.58 g, 96% yield). MS (ESI) m/z: 623 $[MH]^+$.

Example 24: Preparation of (1*S*,2*S*,3*R*,5*S*)-3-(7-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl) amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy) cyclopentane-1,2-diol **(TCG)**

[0114]

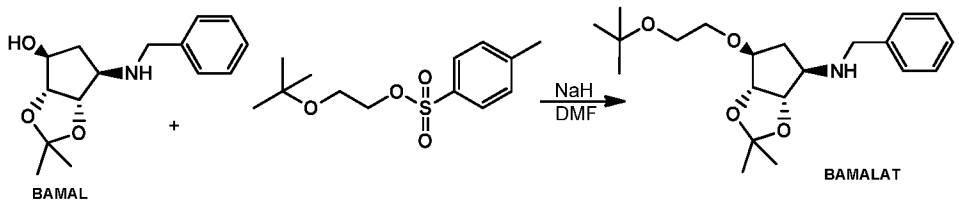


BATOMA **TCG**

[0115] To a solution of **BATOMA** (0.10 g, 0.15 mmol) in MeOH (4 mL) at room temperature ortho-phosphoric acid (85%, 1.5 mL) was added. Resulting reaction mixture was stirred at room temperature for 24 h, then water was added (10 mL), and reaction mixture was neutralized with 1 M NaOH. The product was extracted to EtOAc (5 x 5 mL), combined organic phases were dried over Na_2SO_4, and then concentrated to afford crude product, which was purified by chromatography (SiO_2, EtOAc) to afford title compound as a white powder (66 mg, 84% yield). MS (ESI) m/z: 523 $[MH]^+$.

Example 25: Preparation of (3a*S*,4*R*,6*S*,6a*R*)-*N*-benzyl-6-(2-*tert*-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-amine **(BAMALAT)**

[0116]



BAMAL **BAMALAT**

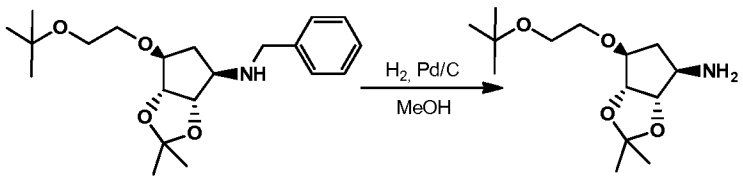
[0117] A solution of 10 g (38 mmol) of (3a*R*,4*S*,6*R*,6a*S*)-6-(benzylamino)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (**BAMAL,** prepared according to J. Org. Chem. 70, 6884 (2005)) in dry DMF (100 mL) under nitrogen atmosphere was cooled at 0°C followed by addition of NaH (60 %, 1.8 g, 46 mmol). After stirring for 30 min at 0°C, 2-(*tert*-butoxy)ethyl 4-methylbenzenesulfonate (10.3 g, 38 mmol) was added and the reaction mixture was allowed to warm at room temperature. After stirring for 4 hours, the reaction mixture was quenched with water (100 mL). The mixture was extracted 3 x 100 mL of n-hexane. The combined organic phases were dried over $MgSO_4$, filtered and evaporated to the dryness.

[0118] Obtained **BAMALAT** was isolated from the reaction mixture by salt formation with fumaric acid. The solution of reaction mixture of **BAMALAT** (contained about 60% of **BAMALAT**) in 2-butanone was warmed to 50°C. 1 eq of fumaric acid (calculated to amount of **BAMALAT**) was added and reaction mixture was stirred at 50 °C until fumaric acid dissolution. The reaction mixture was allowed to cool at room temperature followed by addition of *n*-hexane. After overnight stirring at room temperature, the precipitated white salt of **BAMALAT** was sucked off, washed with *n*-hexane and dried under reduce pressure at 40°C.

[0119] Fumarate salt of **BAMALAT** was suspended in EtOAc and 5% aqueous solution of $NaHCO_3$ was added to the suspension. The mixture was stirred vigorously at room temperature for an hour. The two clear phases were separated and organic phase was washed with water, dried over $MgSO_4$ and evaporated to the dryness to provide pure **BAMALAT.**
^1H NMR ($CDCl_3$) δ = 1.14 (s, 9H), 1.30 (s, 3H), 1.40 (s, 3H), 1.88 (d, 1H), 2.10 (m, 1H), 3.14 (m, 1H), 3.45 (m, 2H), 3.59 (m, 2H), 3.80-3.90 (m, 3H), 4.62 (m, 2H), 7.22-7.35 (m, 5H) ppm.
13C NMR (CDCl3) δ = 24.0, 26.4, 27.4, 33.8, 51.7, 60.1, 63.1, 69.1, 72.9, 83.9, 84.6, 84.8 110.2, 126.7, 128.1, 128.2, 140.3 ppm.

Example 26: (3a*S*,4*R*,6*S*,6a*R*)-6-(2-(*tert*-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-amine **(TBUAM)**

[0120]

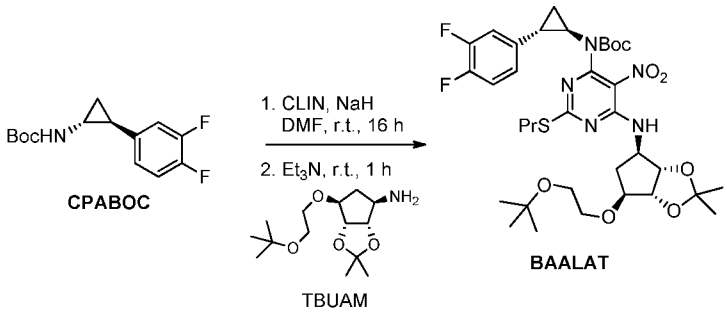


BAMALAT **TBUAM**

[0121] The solution of **BAMALAT** (6.0 g, 16.5 mmol) in MeOH (50 mL) was hydrogenated at 5 bar of hydrogen for 16 hours at 50°C in the presence of Pd/C (10%, 0.6 g). The reaction mixture was passed through the pad of Celite and evaporated to the dryness to provide **TBUAM.**
^1H NMR ($CDCl_3$) δ = 1.13 (s, 9H), 1.23 (s, 3H), 1.36 (s, 3H), 1.74 (d, 1 H), 2.06 (m, 1 H), 3.25 (d, 1 H), 3.43 (m, 2H), 3.55 (m, 2H), 3.81 (d, 1 H), 4.38 (d, 1 H), 4.61 (d, 1 H) ppm.
^{13}C NMR ($CDCl_3$) δ = 23.8, 26.2, 27.4, 35.2, 57.8, 60.8, 68.8, 72.8, 84.0, 85.1, 88.5, 109.8 ppm.

Example 27: Preparation of *tert*-butyl (6-(((3a*S*,4*R*,6*S*,6a*R*)-6-(2-(*tert*-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-5-nitro-2-(propyl thio)pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(BAALAT)**

[0122]

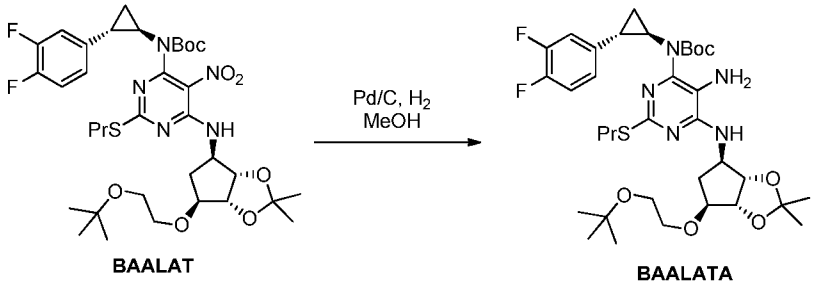


CPABOC TBUAM **BAALAT**

[0123] A mixture of **CPABOC** (1.06 g, 3.95 mmol), **CLIN** (1.06 g, 3.95 mmol) and NaH (60% in oil, 0.17 g, 4.35 mmol) in dry DMF (10 mL) was stirred at room temperature for 16 hours, then triethylamine (0.61 mL, 4.35 mmol) and **TBUAM** (1.08 g, 3.95 mmol) were added at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. Water (70 mL) was slowly added and product was extracted to MeTHF (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellow oil (2.13 g, 73% yield).

Example 28: Preparation of *tert*-butyl (5-amino-6-(((3a*S*,4*R*,6*S*,6a*R*)-6-(2-(tert-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)amino)-2-(propylthio) pyrimidin-4-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)carbamate **(BAALATA)**

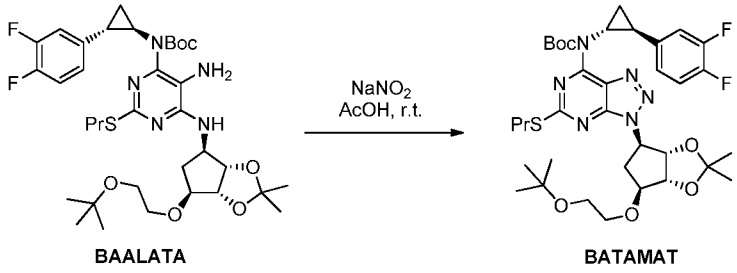
[0124]



[0125] A mixture of **BAALAT** (0.50 g, 1.03 mmol) and Pd/C (5%, 50 mg) in MeOH (5 mL) was hydrogenated under 10 bar of hydrogen for 16 h. Catalyst was then filtered off and filtrate was concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellow oil (0.44 g, 92% yield). MS (ESI) m/z: 708 $[MH]^+$.

Example 29: Preparation *tert*-butyl (3-((3a*S*,4*R*,6*S*,6a*R*)-6-(2-(*tert*-butoxy)ethoxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl) carbamate **(BATAMAT)**

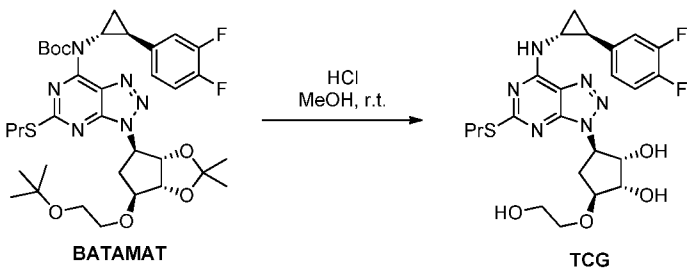
[0126]



[0127] To a solution of **BAALATA** (0.35 g, 0.49 mmol) in AcOH (5 mL) was added $NaNO_2$ (41 mg, 0.59 mmol). Resulting reaction mixture was stirred for 1 h at room temperature. Water (50 mL) was added and product was extracted to MeTHF (3 x 10 mL). Combined organic phases were dried over $MgSO_4$, then concentrated to afford crude compound, which was then purified by chromatography (SiO_2, hexane:EtOAc) to afford title compound as yellow oil (0.33 g, 95% yield). MS (ESI) m/z: 719 $[MH]^+$.

Example 30: Preparation of (1*S*,2*S*,3*R*,5*S*)-3-(7-(((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl) amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxy ethoxy)cyclopentane-1,2-diol **(TCG)**

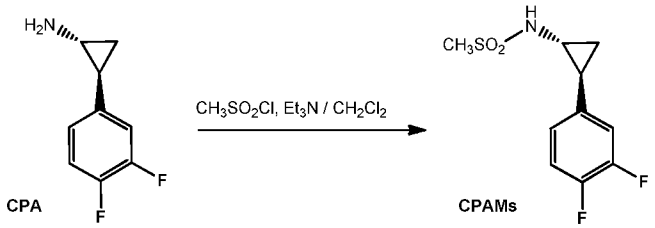
[0128]



[0129] To a solution of **BATAMAT** (0.10 g, 0.14 mmol) in MeOH (4 mL) at room temperature 37% HCl (1 mL) was added. Resulting reaction mixture was stirred at room temperature and monitored by TLC and HPLC. After total conversion (several days) water was added (10 mL), and reaction mixture was neutralized with 1 M NaOH. The product was extracted to EtOAc (5x5 mL), combined organic phases were dried over Na_2SO_4, and then concentrated to afford crude product, which was purified by chromatography (SiO_2, EtOAc) to afford title compound as a white powder (50 mg, 63% yield). MS (ESI) m/z: 523 $[MH]^+$.

Example 31: Preparation of *N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)methanesulfonamide **(CPAMs)**

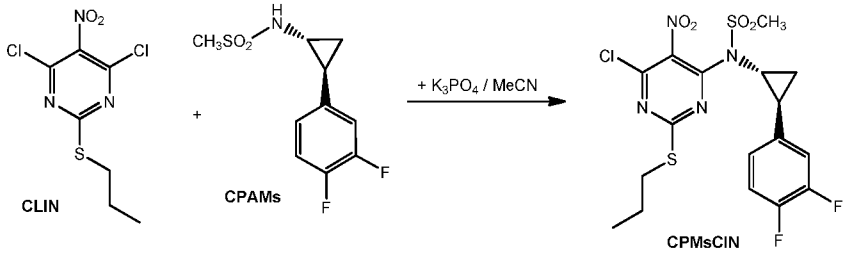
[0130]



[0131] To a solution of **CPA** (6.77 g, 40 mmol) and triethylamine (6.70 mL, 50 mmol) in dichloromethane (60 mL) at 0°C was slowly added a solution of methanesulfonyl chloride (3.87 mL, 50 mmol) in dichloromethane (20 mL) in the course of 3 h. After two additional hours of stirring, the reaction mixture was washed with 1 M HCl (aq) (60 mL) and water (60 mL), and then evaporated under reduced pressure to give a crude product (9.89 g) which was recrystallized from an ethanol / water mixture to give the title compound as a white crystalline product (7.60 g, 77% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.24 (m, 1 H), 1.38 (m, 1 H), 2.31 (m, 1H), 2.70 (m, 1H), 3.05 (s, 3H), 4.85 (s, 1H), 6.90 (m, 1H), 6.96 (m, 1H), 7.10 (m, 1H); ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ = -141.67 (m, 1 F), -138.46 (m, 1 F).

Example 32: Preparation of *N*-(6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl)-*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)methanesulfonamide **(CPMsCIN)**

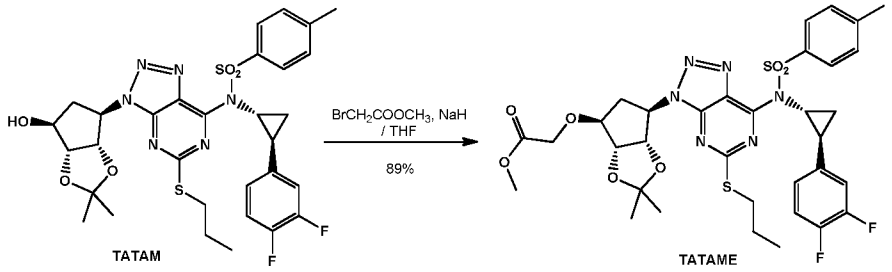
[0132]



[0133] To a solution of **CPAMs** (1.98 g, 8 mmol) and **CLIN** (2.14 g, 8 mmol) in acetonitrile (30 mL) was added anhydrous K_3PO_4 (3.40 g, 16 mmol) and the mixture stirred for 24 h at 25°C. The reaction mixture was then diluted with water (100 mL), extracted with diisopropyl ether (50 mL), the extract washed with water (2 x 100 mL) and evaporated under reduced pressure. The crude product was purified with flash chromatography to give a yellowish resin (2.32 g, 61% yield): ^{19}F NMR ($CDCl_3$, 470.5 MHz) δ = -140.83 (m, 1F),-138.14(m, 1 F).

Example 33: Preparation of methyl 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-(7-(*N*-((1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl)-4-methylphenylsulfonamido)-5-(propylthio)-3*H*-[1,2,3]triazolo [4,5-*d*]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-oxy)acetate **(TATAME)**

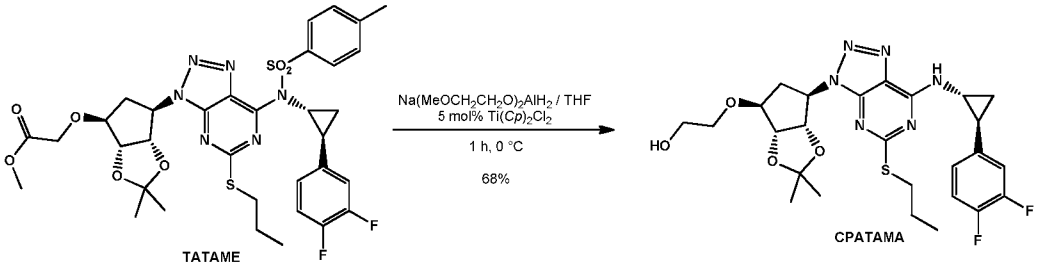
[0134]



[0135] To a solution of **TATAM** (3.31 g, 5 mmol) in dry THF (20 mL) 60% NaH (0.35 g, 8.75 mmol) was added at -20°C and stirred for 20 min, then methyl bromoacetate (0.83 mL, 8.75 mmol) was added. The resulting reaction mixture was stirred at -20°C for 18 h. Acetic acid (0.5 mL) was added slowly followed by water (50 mL). The product was extracted with MTBE (50 mL), extract washed with water (3 x 50 mL) and and concentrated to give a crude product, which was then purified by chromatography (SiO_2, hexane:EtOAc) to give the title compound as an amorphous solid (3.30 g, 89% yield): ^{19}F NMR ($CDCl_3$) δ = -141.83 (m, 1F), -138.9 (m,1F).

Example 34: Preparation of 2-(((3a*R*,4*S*,6*R*,6a*S*)-6-(7-(((1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)oxy)ethanol **(CPATAMA)**

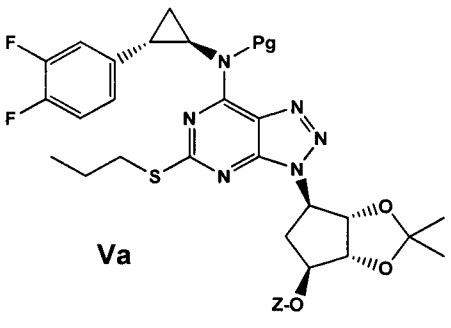
[0136]

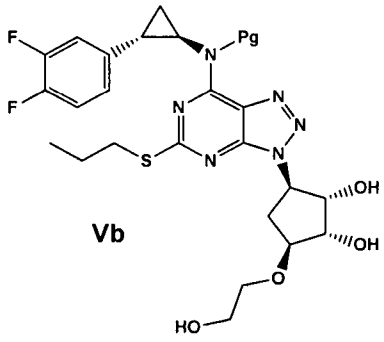


[0137] To a solution of **TATAME** (370 mg, 0.5 mmol) and titanocene dichloride (6 mg, 5 mol%) in THF (5 mL) stirring on an ice bath was added sodium bis(2-methoxyethoxy)aluminumhydride (3.5 M solution in toluene, 0.36 mL, 1.25 mmol). The mixture was stirred for 1 h in an ice bath and then 2 h at about 25°C. The reaction mixture was poured into 0.1 M NaOH(aq) (50 mL), extracted with MTBE (50 mL), the extract washed with water (2 x 50 mL), concentrated and the residue purified by chromatography (SiO_2, hexane:EtOAc) to give the title compound as a resinous product (0.19 g, 68% yield).

Claims

1. A process for the preparation of a compound of formula **Va** or **Vb**

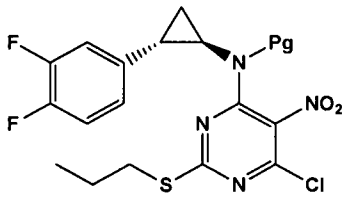




wherein Pg is an amino protecting group, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl,

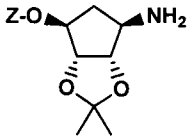
the process comprising the steps of:

(i) reacting a compound of formula **II'**

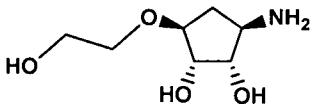


II'

wherein Pg is defined as above, with a compound of the formula **VI** or **VII**

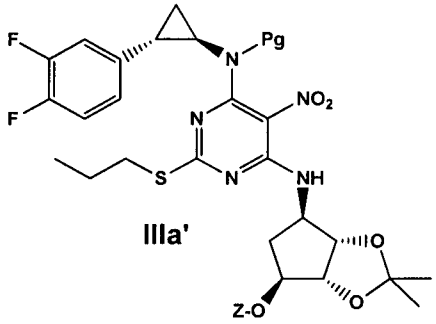


VI

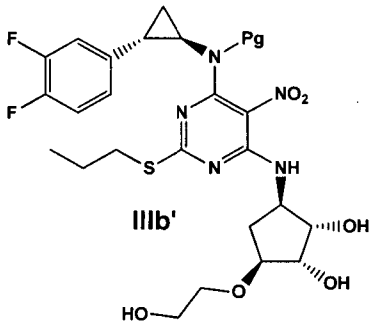


VII

wherein Z is defined as above, to obtain a compound of formula **IIIa'** or **IIIb',** respectively



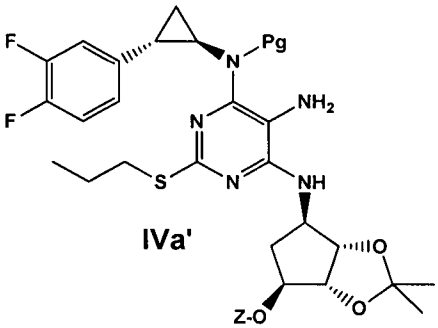
IIIa'



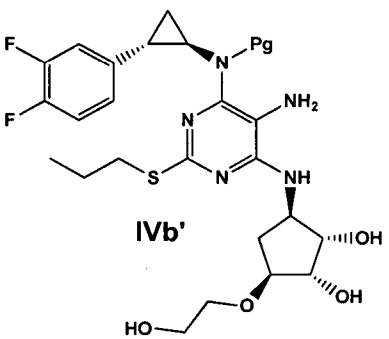
IIIb'

wherein Pg and Z are as defined above,

(ii) reducing the nitro group in the compound of formula **IIIa'** or **IIIb'** to an amino group to obtain a compound of formula **IVa'** or **IVb',** respectively,



IVa'



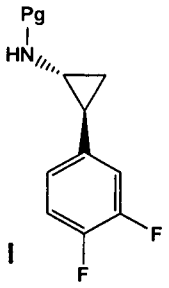
IVb'

and

(iii) nitrosation of the compound of formula **IVa'** or **IVb'** to obtain the compound of formula **Va** or **Vb,** respectively.

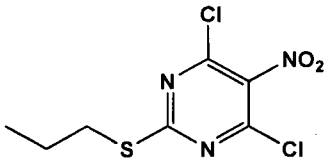
2. The process according to claim 1, wherein the compound of formula **II'** is prepared by comprising the steps of either

(0-1) providing a compound of formula **I**

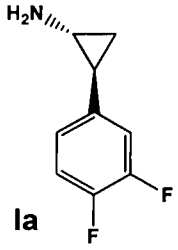


I

wherein Pg is an amino protecting group, and
(0-2) reacting the compound of formula **I** with a compound of the formula

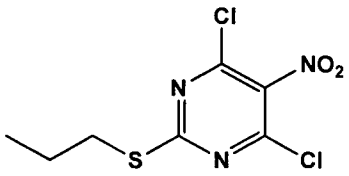


to obtain the compound of formula **II'**;
or
(0-1') providing a compound of formula **Ia**

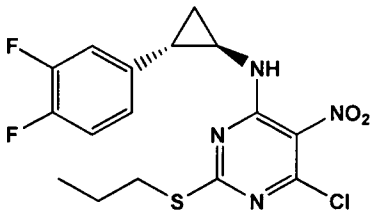


Ia

(0-2') reacting the compound of formula **Ia** with a compound of the formula



to obtain a compound of formula **IIa,**



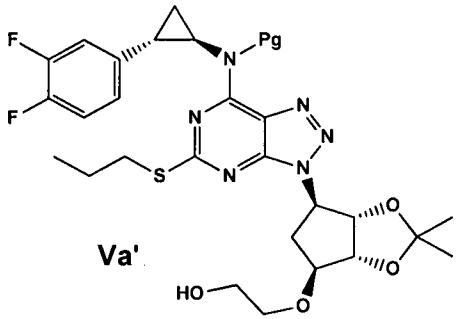
IIa

and
(0-3') introducing an amino protecting group Pg to obtain the compound of formula **II'.**

3. The process according to claim 1 or 2, wherein the steps (i) to (iii), optionally also the preparation of the compound of formula **II',** are carried out in one pot.

4. The process according to any one of the preceding claims, wherein steps (i) and (ii), optionally also steps (0-1) to (0-2) or (0-1') to (0-3'), are carried out under basic conditions in the presence of bases, and/or step (iii) is carried out under acidic conditions.

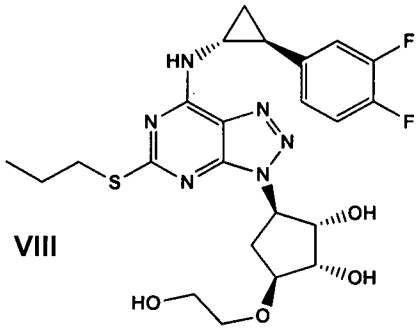
5. The process according to any one of the preceding claims, wherein Z is hydrogen or a group convertible to hydroxyethyl, and after the preparation of the compound of formula **Va,** a hydroxyethyl group is introduced to obtain a compound of formula **Va'**



Va'

6. The process according to any one of the preceding claims, wherein Pg is selected from the group of oxycarbonyl-type amino protecting groups, carbamate-type amino protecting groups and sulfonyl-type amino protecting groups, preferably Pg is selected from the group consisting of *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), methanesulfonyl (Ms), benzenesulfonyl (Bs), p-toluenesulfonyl (Ts), and 2-naphthalenesulfonyl.

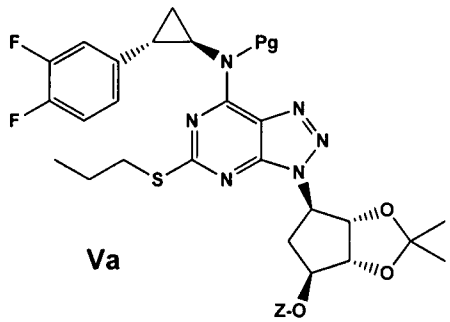
7. Process for the preparation of a compound of formula **VIII** or a salt thereof



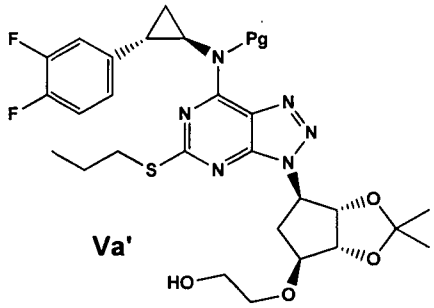
VIII

comprising the steps of:

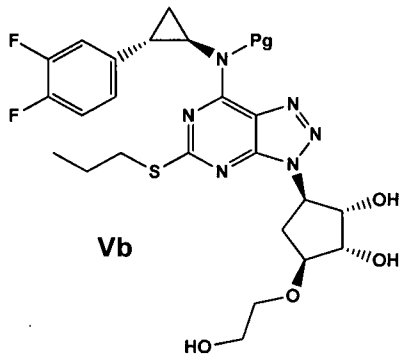
(i) preparing a compound of formula **Va, Va'** or **Vb** according to any one of claims 1 to 6



Va



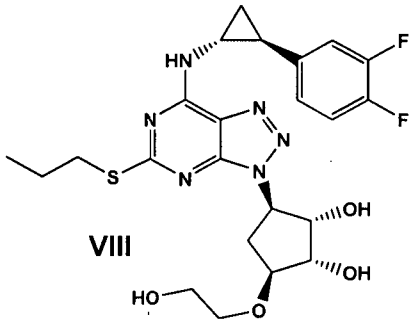
Va'



Vb

wherein Pg and Z are as defined above, wherein if Z in the compound of formula **Va** is hydrogen or a group convertible to hydroxyethyl, a hydroxyethyl group is introduced to obtain a compound of formula **Va'**,
(ii) carrying out deprotection reaction(s) to remove Pg and in the compound of formula **Va** or **Va'** deprotection reaction(s) of the vicinal hydroxyl protecting group at the pentane ring, respectively,
(iii) optionally forming a salt of the compound of formula **VIII.**

8. Process for the preparation of a pharmaceutical composition comprising a compound of formula **VIII** or a salt thereof

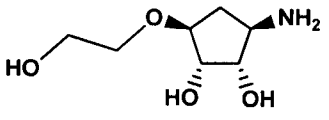


VIII

comprising the steps of:

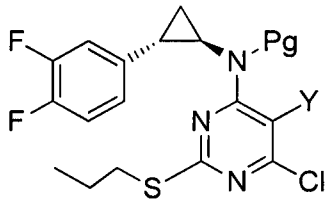
(i) preparing a compound of formula **VIII** or a salt thereof according to claim 7, and
(ii) mixing the compound of formula **VIII** or a salt thereof with a pharmaceutically acceptable carrier and/or excipient.

9. A compound of the following formula **VII**



VII

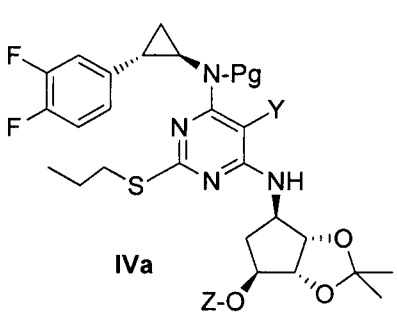
10. A compound of the following formula **II**



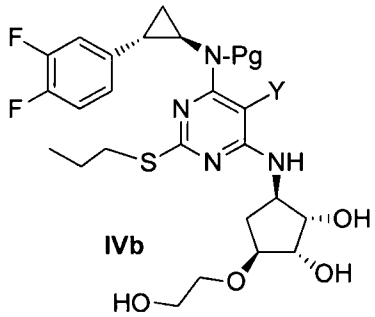
II

wherein Pg is an amino protecting group selected from the group consisting of oxycarbonyl-type amino protecting groups and sulfonyl-type amino protecting groups, preferably Pg is selected from the group consisting of *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), methanesulfonyl (Ms), benzenesulfonyl (Bs), *p*-toluenesulfonyl (Ts), and 2-naphthalenesulfonyl, and Y is NO_2 or NH_2.

11. A compound of the following formula **IVa** or **IVb**



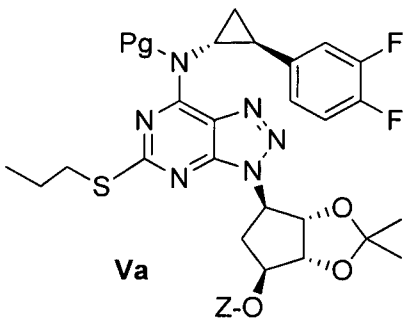
IVa



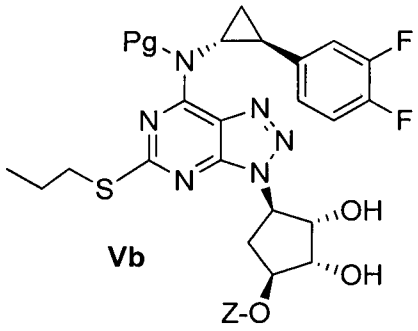
IVb

wherein Pg is an amino protecting group selected from the group consisting of oxycarbonyl-type amino protecting groups and sulfonyl-type amino protecting groups, preferably Pg is selected from the group consisting of *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), methanesulfonyl (Ms), benzenesulfonyl (Bs), *p*-toluenesulfonyl (Ts), and 2-naphthalenesulfonyl, Y is NO_2 or NH_2, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl.

12. A compound of the following formula **Va** or **Vb**



Va



Vb

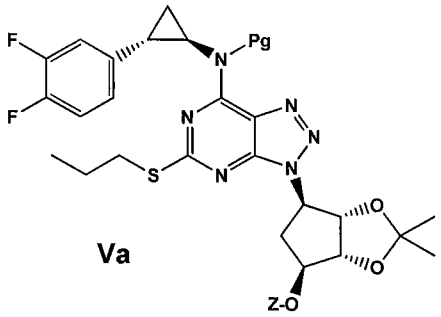
wherein Pg is an amino protecting group selected from the group consisting of oxycarbonyl-type amino protecting groups and sulfonyl-type amino protecting groups, preferably Pg is selected from the group consisting of *tert*-butyloxycarbonyl (Boc), carbobenzyloxy (Cbz), methanesulfonyl (Ms), benzenesulfonyl (Bs), *p*-toluenesulfonyl (Ts), and 2-naphthalenesulfonyl, and Z is hydrogen, hydroxyethyl or a group convertible to hydroxyethyl.

13. The compound as defined in any one of claims 11 to 12, wherein Z is selected from hydrogen, hydroxyethyl and $-CH_2-CO-OCH_3$.

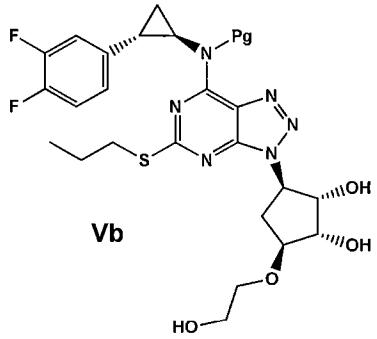
14. Use of a compound as defined in any one of claims 9 to 13 in the preparation of ticagrelor.

Patentansprüche

1. Ein Verfahren zur Herstellung einer Verbindung der Formel **Va** or **Vb**



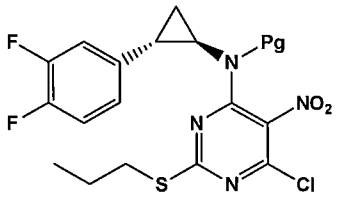
Va



Vb

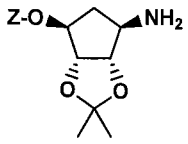
wobei Pg eine Aminoschutzgruppe ist und Z Wasserstoff, Hydroxyethyl oder eine in Hydroxyethyl konvertierbare Gruppe ist,
umfassend folgende Schritte:

(i) Umsetzen einer Verbindung der Formel **II'**

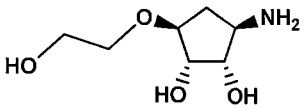


II'

wobei Pg wie oben definiert ist, mit einer Verbindung der Formel **VI** or **VII**

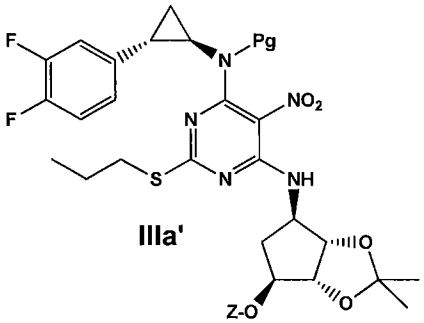


VI

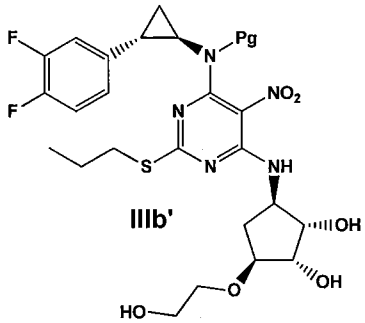


VII

wobei Z wie oben definiert ist, um eine Verbindung der Formel **IIIa'** bzw. **IIIb'**

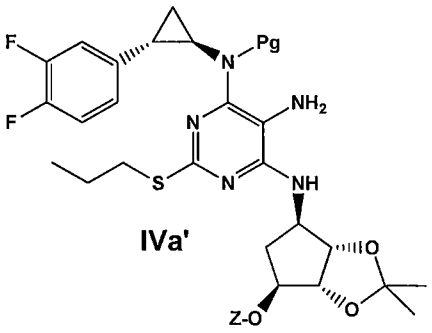


IIIa'

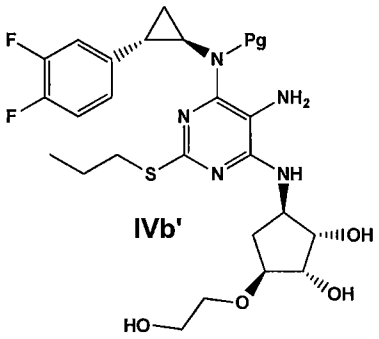


IIIb'

zu erhalten, wobei Pg und Z wie oben definiert sind,
(ii) Reduzieren der Nitrogruppe in der Verbindung der Formel **IIIa'** oder **IIIb'** zu einer Aminogruppe, um eine Verbindung der Formel **IVa'** bzw. **IVb'**



IVa'

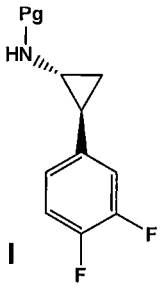


IVb'

zu erhalten,
und
(iii) Nitrosierung der Verbindung der Formel **IVa'** oder **IVb',** um die Verbindung der Formel **Va** bzw. **Vb** zu erhalten.

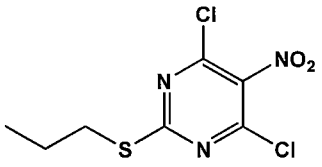
2. Das Verfahren gemäß Anspruch 1, wobei die Verbindung der Formel **II'** hergestellt wird durch Einbeziehen folgender Schritte
entweder

(0-1) Bereitstellen einer Verbindung der Formel **I**

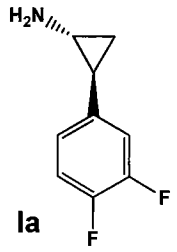


I

wobei Pg eine Aminoschutzgruppe ist, und
(0-2) Umsetzen der Verbindung der Formel **I** mit einer Verbindung der Formel

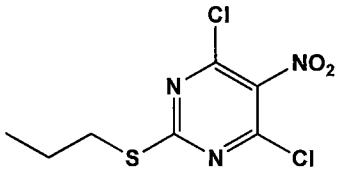


um die Verbindung mit der Formel **II'** zu erhalten;
oder
(0-1') Bereitstellen einer Verbindung der Formel **Ia**

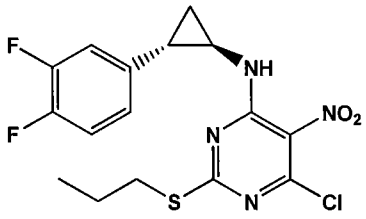


Ia

(0-2') Umsetzen der Verbindung der Formel **Ia** mit einer Verbindung der Formel



um eine Verbindung der Formel **IIa**



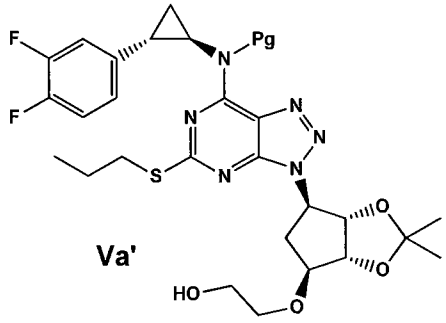
IIa

zu erhalten,
und
(0-3') Einführen einer Aminoschutzgruppe Pg, um die Verbindung mit der Formel **II'** zu erhalten.

3. Das Verfahren gemäß Anspruch 1 oder 2, wobei die Schritte (i) bis (iii), optional auch die Herstellung der Verbindung der Formel **II',** im Eintopfverfahren ausgeführt werden.

4. Das Verfahren gemäß einem der vorstehenden Ansprüche, wobei die Schritte (i) und (ii), optional auch die Schritte (0-1) bis (0-2) oder (0-1') bis (0-3'), unter basischen Bedingungen in der Anwesenheit von Basen durchgeführt werden, und/oder der Schritt (iii) unter sauren Bedingungen ausgeführt wird.

5. Das Verfahren gemäß einem der vorstehenden Ansprüche, wobei Z Wasserstoff oder eine in Hydroxyethyl konvertierbare Gruppe ist, und nach der Herstellung der Verbindung der Formel **Va** eine Hydroxyethylgruppe eingeführt wird, um eine Verbindung der Formel **Va'**

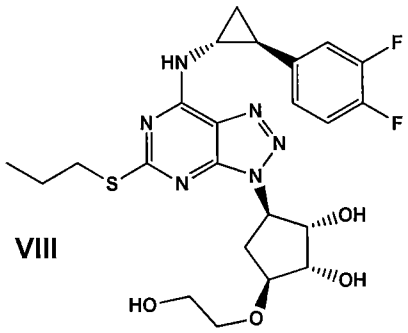


Va'

zu erhalten.

6. Das Verfahren gemäß einem der vorstehenden Ansprüche, wobei Pg aus der Gruppe der Aminoschutzgruppen vom Oxycarbonyl-Typ, der Aminoschutzgruppen vom Carbamat-Typ und der Aminoschutzgruppen vom Sulfonyl-Typ ausgewählt wird, wobei Pg bevorzugt aus der Gruppe bestehend aus *tert*-Butyloxycarbonyl (Boc), Carbobenzoxy (Cbz), Methansulfonyl (Ms), Benzolsulfonyl (Bs), p-Toluolsulfonyl (Ts) und 2-Naphthalinsulfonyl ausgewählt wird.

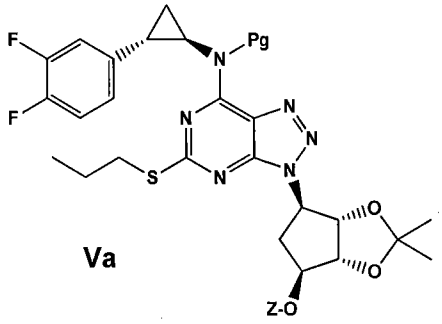
7. Verfahren zur Herstellung einer Verbindung der Formel **VIII** oder eines Salzes davon



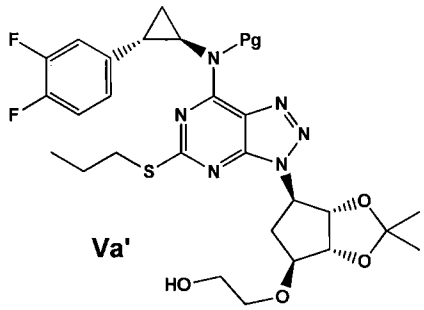
VIII

umfassend folgende Schritte:

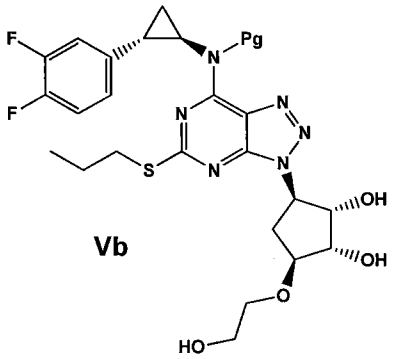
(i) Herstellen einer Verbindung der Formel **Va, Va'** oder **Vb** gemäß einem der Ansprüche 1 bis 6



Va



Va'



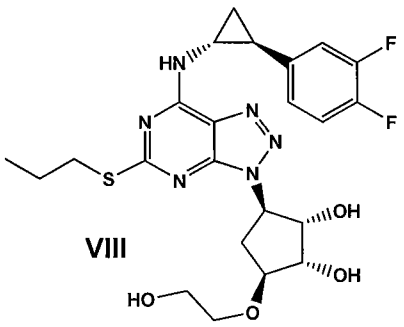
Vb

wobei Pg und Z wie oben definiert sind, wobei dann, wenn Z in der Verbindung der Formel **Va** Wasserstoff oder eine in Hydroxyethyl konvertierbare Gruppe ist, eine Hydroxyethylgruppe eingeführt wird, um eine Verbindung der Formel **Va'** zu erhalten,

(ii) Durchführen einer Entschützungsreaktion oder von Entschützungsreaktionen, um Pg zu entfernen, und jeweils in der Verbindung der Formel **Va** oder **Va'** Durchführen einer Entschützungsreaktion oder von Entschützungsreaktionen der Schutzgruppe der vicinalen Hydroxylgruppen am Pentanring,

(iii) optional Bilden eines Salzes der Verbindung der Formel **VIII.**

8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung umfassend eine Verbindung der Formel **VIII** oder eines Salzes davon

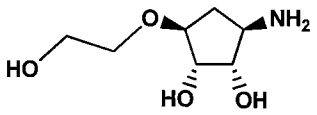


VIII

umfassend folgende Schritte:

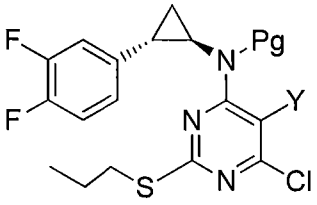
(i) Herstellen einer Verbindung der Formel **VIII** oder eines Salzes davon gemäß Anspruch 7 und
(ii) Mischen der Verbindung der Formel **VIII** oder eines Salzes davon mit einem pharmazeutisch akzeptierbaren Träger und/oder Hilfsstoff.

9. Eine Verbindung der folgenden Formel **VII**



VII

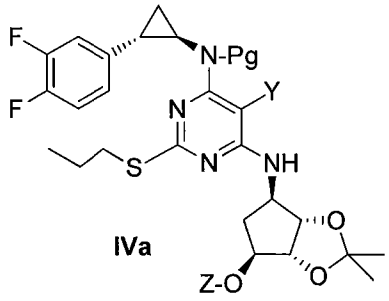
10. Eine Verbindung der folgenden Formel **II**



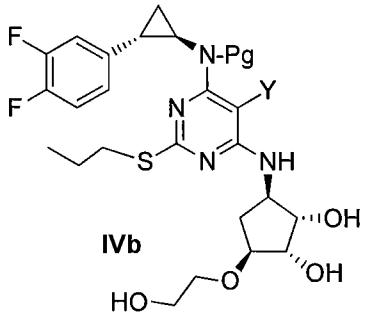
II

wobei Pg eine aus der Gruppe bestehend aus Aminoschutzgruppen vom Oxycarbonyl-Typ und Aminoschutzgruppen vom Sulfonyl-Typ ausgewählte Aminoschutzgruppe ist, wobei Pg bevorzugt aus der Gruppe bestehend aus *tert*-Butyloxycarbonyl (Boc), Carbobenzoxy (Cbz), Methansulfonyl (Ms), Benzolsulfonyl (Bs), p-Toluolsulfonyl (Ts) und 2-Naphthalinsulfonyl ausgewählt ist und Y NO_2 oder NH_2 ist.

11. Eine Verbindung der folgenden Formel **IVa** oder **IVb**



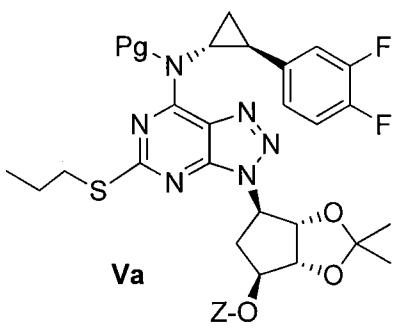
IVa



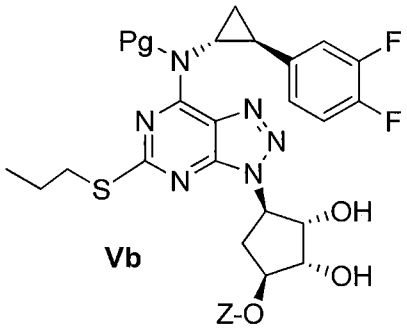
IVb

wobei Pg eine aus der Gruppe bestehend aus Aminoschutzgruppen vom Oxycarbonyl-Typ und Aminoschutzgruppen vom Sulfonyl-Typ ausgewählte Aminoschutzgruppe ist, wobei Pg bevorzugt aus der Gruppe bestehend aus *tert*-Butyloxycarbonyl (Boc), Carbobenzoxy (Cbz), Methansulfonyl (Ms), Benzolsulfonyl (Bs), p-Toluolsulfonyl (Ts) und 2-Naphthalinsulfonyl ausgewählt ist, Y NO_2 oder NH_2 ist und Z Wasserstoff, Hydroxyethyl oder eine in Hydroxyethyl konvertierbare Gruppe ist.

12. Eine Verbindung der folgenden Formel **Va** oder **Vb**



Va



Vb

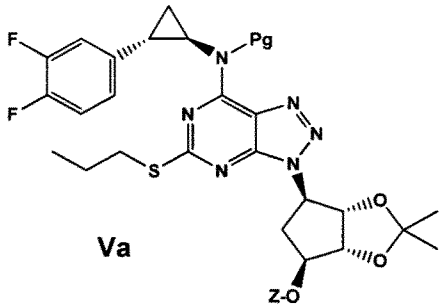
wobei Pg eine aus der Gruppe bestehend aus Aminoschutzgruppen vom Oxycarbonyl-Typ und Aminoschutzgruppen vom Sulfonyl-Typ ausgewählte Aminoschutzgruppe ist, wobei Pg bevorzugt aus der Gruppe bestehend aus *tert*-Butyloxycarbonyl (Boc), Carbobenzoxy (Cbz), Methansulfonyl (Ms), Benzolsulfonyl (Bs), p-Toluolsulfonyl (Ts) und 2-Naphthalinsulfonyl ausgewählt ist, und Z Wasserstoff, Hydroxyethyl oder eine in Hydroxyethyl konvertierbare Gruppe ist.

13. Die Verbindung gemäß einem der Ansprüche 11 bis 12, wobei Z ausgewählt ist aus Wasserstoff, Hydroxyethyl oder $-CH_2-CO-OCH_3$.

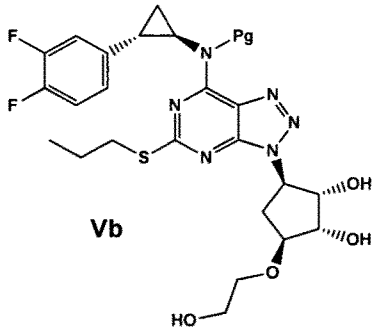
14. Verwendung einer Verbindung gemäß einem der Ansprüche 9 bis 13 in der Herstellung von Ticagrelor.

Revendications

1. Procédé pour la préparation d'un composé de formule Va ou de formule Vb



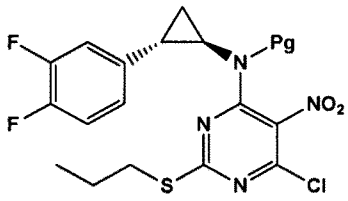
Va



Vb

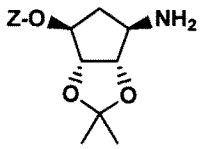
dans lesquelles Pg est un groupe amino-protecteur, et Z représente un hydrogène, un hydroxyéthyle ou un groupe convertible en un hydroxyéthyle,
le procédé comprenant les étapes de :

(I) faire réagir un composé de formule II'

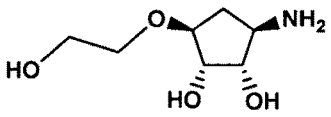


II'

dans laquelle Pg est défini comme ci-dessus, avec un composé de formule VI ou de formule VII

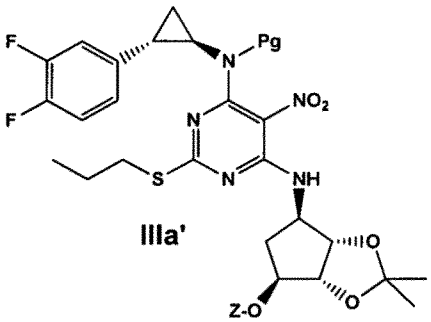


VI

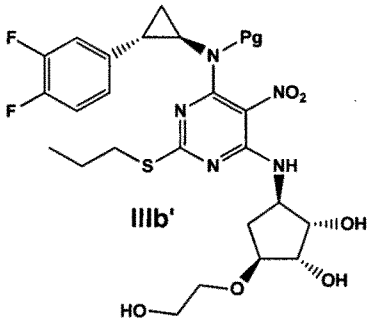


VII

dans lesquelles Z est défini comme ci-dessus, pour obtenir un composé de formule IIIa' ou de formule IIIb', respectivement

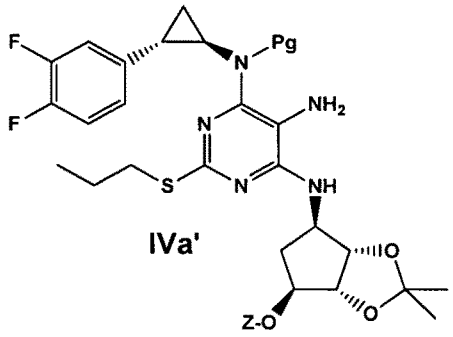


IIIa'

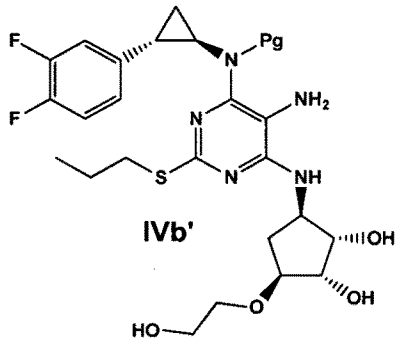


IIIb'

dans lesquelles Pg et Z sont tels que définis ci-dessus,
(ii) réduire le groupe nitro dans le composé de formule IIIa' ou de formule IIIb' en un groupe amino pour obtenir un composé de formule IVa' ou de formule IVb', respectivement,



IVa'



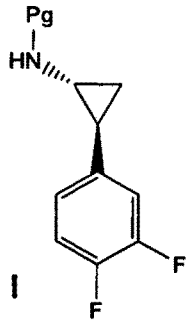
IVb'

et

(Iii) nitroser le composé de formule IVa' ou de formule IVb' pour obtenir le composé de formule Va ou de formule Vb, respectivement.

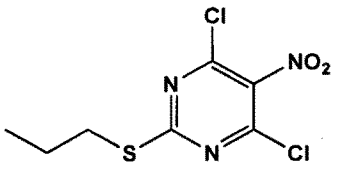
2. Procédé selon la revendication 1, dans lequel le composé de formule II' est préparé selon les étapes de soit

(0-1) fournir un composé de formule I



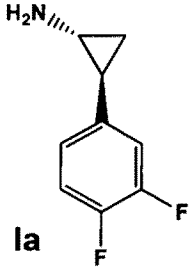
I

dans laquelle Pg est un groupe amino-protecteur, et
(0-2) faire réagir le composé de formule I avec un composé de formule



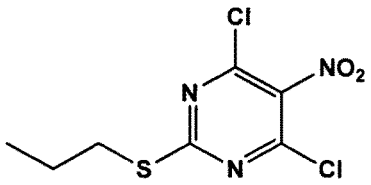
pour obtenir le composé de formule II' ;
soit

(0-1') fournir un composé de formule Ia

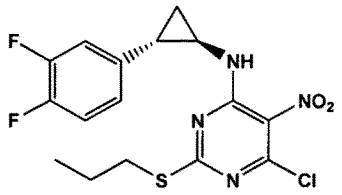


Ia

(0-2 ') faire réagir le composé de formule Ia avec un composé de formule



pour obtenir un composé de formule IIa,



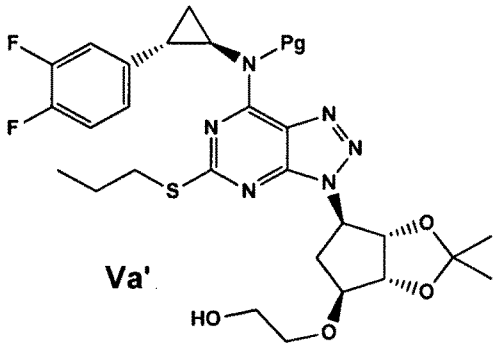
IIa

et
(0-3 ') introduire un groupe amino-protecteur Pg pour obtenir le composé de formule II'.

3. Procédé selon la revendication 1 ou 2, dans lequel les étapes (i) à (iii), également optionnellement la préparation du composé de formule II', sont effectuées dans de manière monotope.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel les étapes (i) et (ii), également optionnellement les étapes (0-1) à (0-2) ou (0-1') à (0-3'), sont effectuées dans des conditions basiques en présence de bases, et/ou l'étape (iii) est effectuée dans des conditions acides.

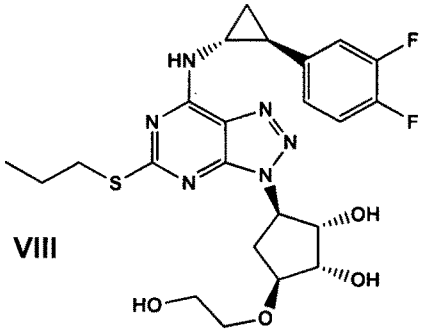
5. Procédé selon l'une quelconque des revendications précédentes, dans lequel Z représente un hydrogène ou un groupe convertible en un hydroxyéthyle, et après la préparation du composé de formule Va, un groupe hydroxyéthyle est introduit pour obtenir un composé de formule Va'



Va'

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel Pg est sélectionné dans le groupe constitué par les groupes amino protecteurs de type oxycarbonyle, les groupes amino protecteurs de type carbamate et les groupes amino protecteurs de type sulfonyle, de préférence Pg est choisi dans le groupe constitué par le *tert*-butyloxycarbonyle (Boc), le carbobenzyloxy (Cbz), le méthanesulfonyle (Ms), le benzènesulfonyle (Bs), le p-toluènesulfonyle (Ts) et le 2-naphtalènesulfonyle.

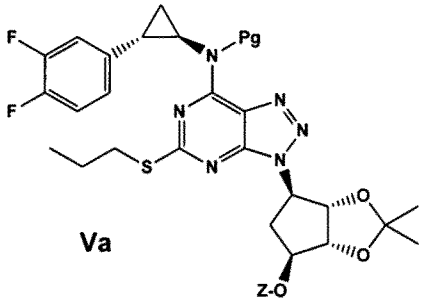
7. Procédé de préparation d'un composé de formule VIII ou un sel de celui-ci



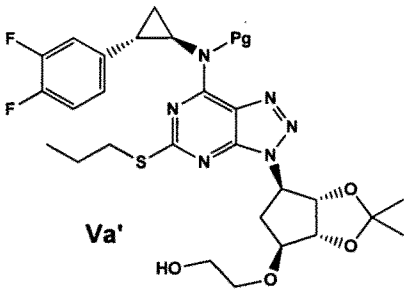
VIII

comprenant les étapes de :

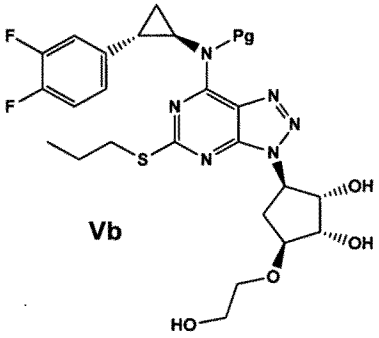
(i) préparation d'un composé de formule Va, de formule Va' ou de formule Vb selon l'une quelconque des revendications 1 à 6,



Va



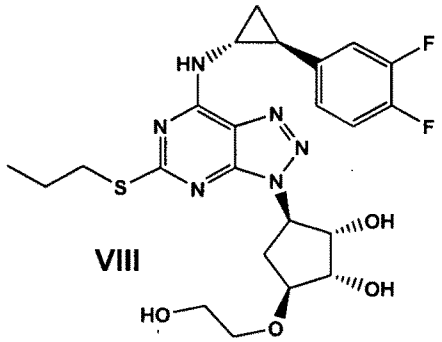
Va'



Vb

dans lesquelles Pg et Z sont tels que définis ci-dessus,
dans lequel si Z dans le composé de formule Va est un hydrogène ou un groupe convertible en un hydroxyéthyle, un hydroxyéthyle est introduit pour obtenir un composé de formule Va',
(ii) réalisation de la ou des réaction(s) de dé-protection pour retirer Pg et dans le composé de formule Va ou de formule Va' de la ou des réaction(s) de dé-protection du groupe protecteur d'hydroxyle vicinal sur le cycle pentane,
respectivement,
(iii) optionnellement formation d'un sel du composé de formule VIII.

8. Procédé pour la préparation d'une composition pharmaceutique comprenant un composé de formule VIII ou un sel de celui-ci

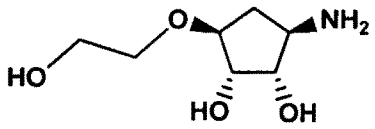


VIII

comprenant les étapes de :

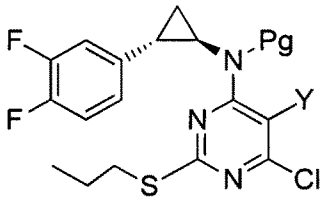
(i) préparation d'un composé de formule VIII ou un sel de celui-ci selon la revendication 7, et
(ii) mélange du composé de formule VIII ou d'un sel de celui-ci avec un véhicule et/ou excipient pharmaceutiquement acceptable

9. Composé de formule VII suivante



VII

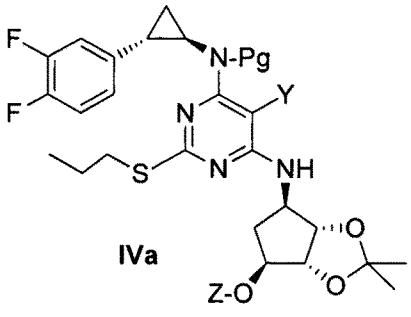
10. Composé de formule II suivante



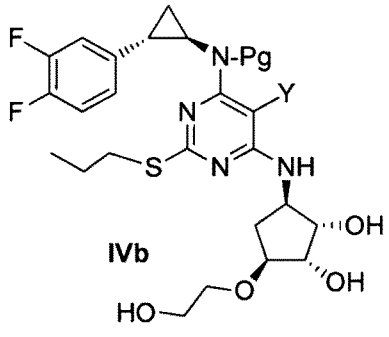
II

dans laquelle Pg est un groupe amino-protecteur choisi dans le groupe constitué par les groupes amino-protecteurs de type oxycarbonyle et les groupes amino-protecteurs de type sulfonyle, de préférence Pg est choisi dans le groupe constitué par le *tert*-butyloxycarbonyle (Boc), le (Cbz), méthanesulfonyle (Ms), le benzènesulfonyle (Bs), le *p*-toluènesulfonyle (Ts), et le 2-naphtalènesulfonyle, et Y représente NO_2 ou NH_2.

11. Composé de formule IVa ou de formule IVb suivantes



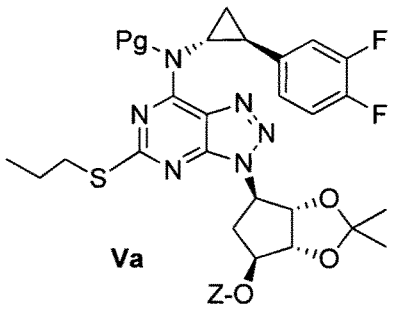
IVa



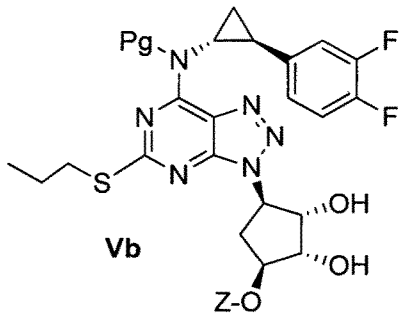
IVb

dans laquelle Pg est un groupe amino-protecteur choisi dans le groupe constitué par les groupes amino-protecteurs de type oxycarbonyle et les groupes amino-protecteurs de type sulfonyle, de préférence Pg est choisi dans le groupe constitué par le *tert*-butyloxycarbonyle (Boc}, le carbobenzyloxy (Cbz), le méthanesulfonyle (Ms), le benzènesulfonyle (Bs), le *p*-toluènesulfonyle (Ts), et le 2-naphtalènesulfonyle, Y représente NO_2 ou NH_2 et Z représente un hydrogène, un hydroxyéthyle ou un groupe convertible en un hydroxyéthyle.

12. Composé de formule Va ou de formule Vb suivantes



Va



Vb

dans lesquelles Pg est un groupe amino-protecteur choisi dans le groupe constitué par les groupes amino-protecteurs de type oxycarbonyle et les groupes amino-protecteurs de type sulfonyle, de préférence Pg est choisi dans le groupe constitué par le *tert*-butyloxycarbonyle (Boc), le carbobenzyloxy (Cbz), le méthanesulfonyle (Ms), le benzènesulfonyle (Bs), le *p*-toluènesulfonyle (Ts), et le 2-naphtalènesulfonyle, et Z représente un hydrogène, un hydroxyéthyle ou un groupe convertible en un hydroxyéthyle.

13. Composé tel que défini dans l'une quelconque des revendications 11 à 12, dans lequel Z est choisi parmi un hydrogène, un hydroxyéthyle et $-CH_2-CO-OCH_3$.

14. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 9 à 13 dans la préparation de ticagrelor.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 0034283 A **[0003] [0004] [0005] [0006] [0051] [0068] [0072] [0097]**
- WO 0192263 A **[0004] [0006] [0008] [0009] [0010] [0011] [0031] [0107]**
- WO 10030224 A **[0004] [0008]**
- WO 11017108 A **[0004] [0011] [0012]**

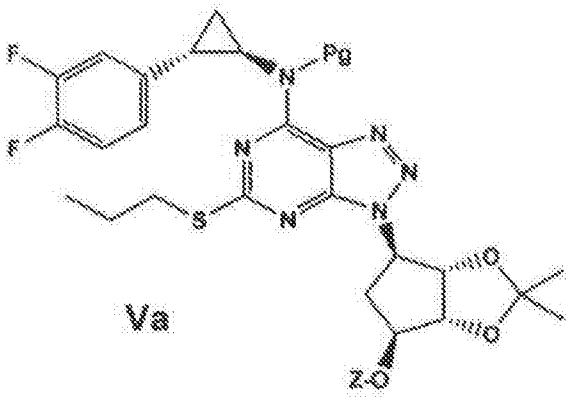
Non-patent literature cited in the description

- *Bioorg. Med. Chem. Lett.,* 2007, vol. 17, 6013-6018 **[0004] [0010]**
- *J. Org. Chem.,* 2005, vol. 70, 6884 **[0117]**

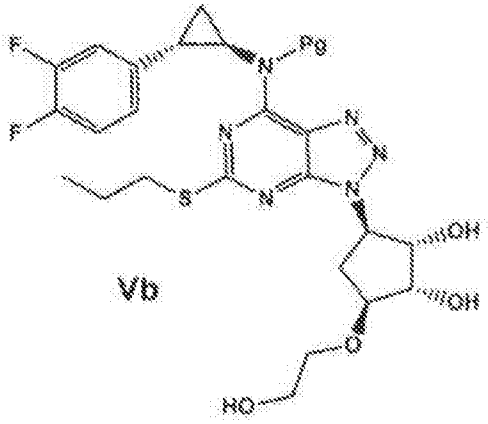
Triazolopirimidin vegyületek szintézise

Szabadalmi igénypontok

1. Eljárás egy Va vagy Vb:



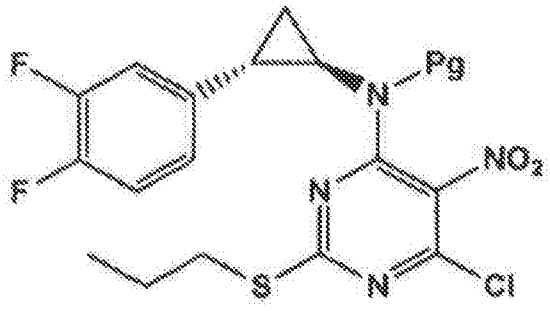
Va



Vb

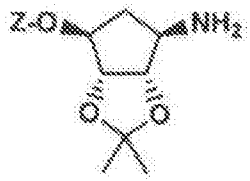
képletű vegyület előállítására, ahol Pg egy amino-védőcsoport, és Z hidrogénatom, hidroxietilcsoport, vagy egy hidroxietilcsoporttá alakítható csoport, melynek során:

(i) egy II':

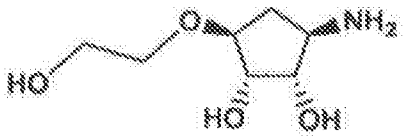


II'

képletű vegyületet, ahol Pg a fent megadott, egy VI vagy VII:

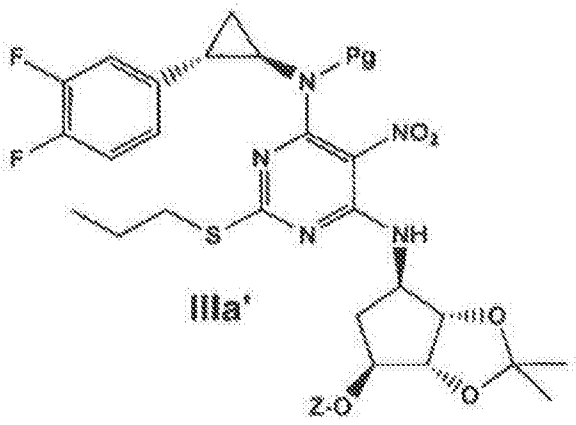


VI

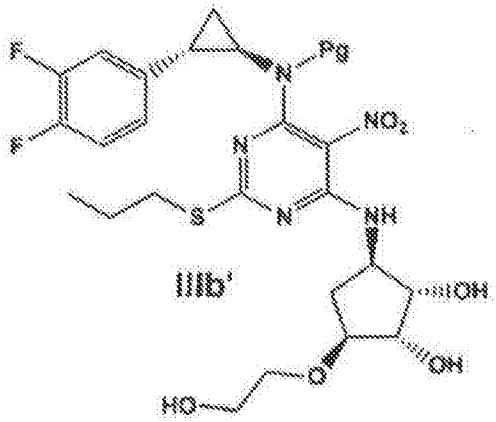


VII

képletű vegyülettel reagáltatunk, ahol Z a fent megadott, egy IIIa' illetve IIIb':

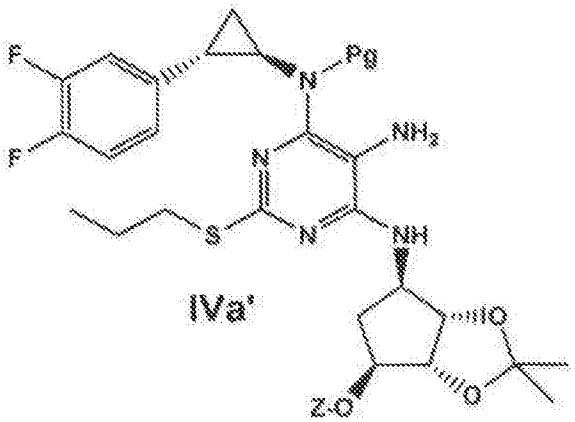


IIIa'

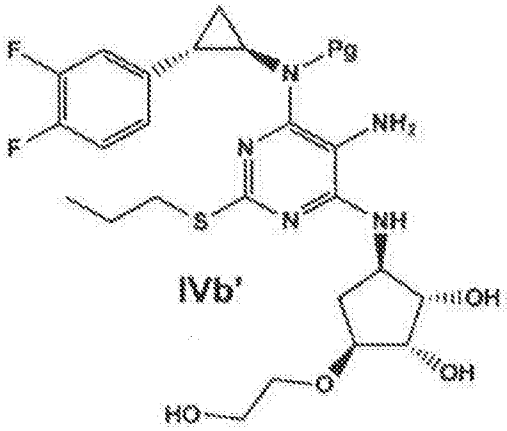


IIIb'

képletű vegyület előállítására, ahol Pg és Z a fent megadott,
(ii) a IIIa' vagy IIIb' képletű vegyületekben a nitrocsoportot egy aminocsoporttá redukáljuk, a IVa' illetve IVb':



IVa'

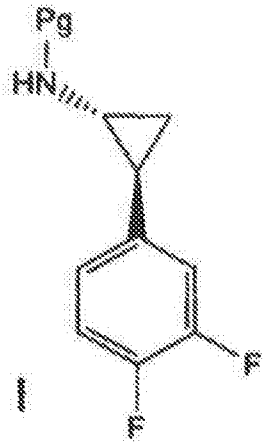


IVb'

képletű vegyület előállítására, és
(iii) a IVa' vagy IVb' képletű vegyületet nitrozáljuk, az Va illetve Vb képletű vegyület előállítására.

2. Az 1. igénypont szerinti eljárás, ahol a II' képletű vegyületet úgy állítjuk elő, hogy vagy

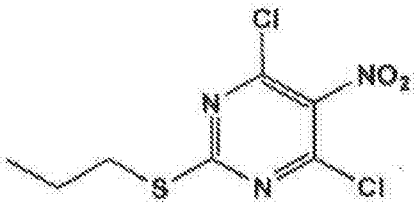
(0-1) egy I:



I

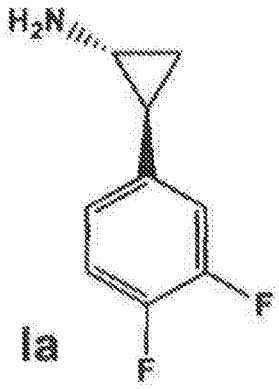
képletű vegyületet biztosítunk, ahol Pg egy amino-védőcsoport, és

(0-2) az I képletű vegyületet egy



képletű vegyülettel reagáltatjuk, a II' képletű vegyület előállítására; vagy

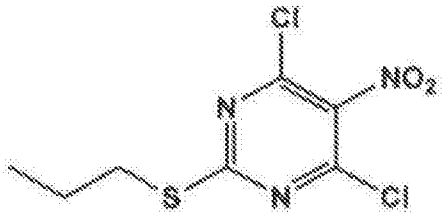
(0-1') egy Ia:



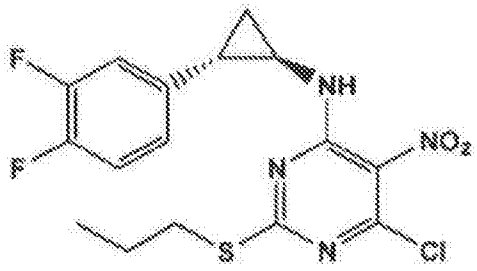
Ia

képletű vegyületet biztosítunk,

(0-2') az Ia képletű vegyületet egy



képletű vegyülettel reagáltatjuk, egy IIa:



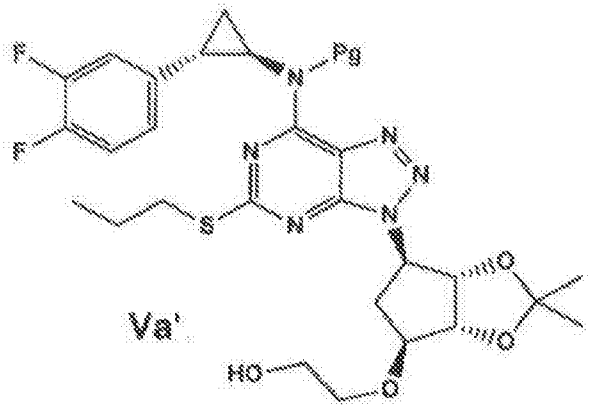
IIa

képletű vegyület előállítására, és
(0-3') egy Pg amino-védőcsoportot viszünk be, a II' képletű vegyület előállítására.

3. Az 1. vagy 2. igénypont szerinti eljárás, ahol az (i) - (iii) lépéseket, adott esetben a II' képletű vegyület előállítását is egy edényben végezzük.

4. Az előző igénypontok bármelyike szerinti eljárás, ahol az (i) és (ii) lépéseket, adott esetben a (0-1) - (0-2) vagy (0-1') - (0-3') lépéseket is bázikus körülmények között, bázis jelenlétében végezzük, és/vagy a (iii) lépést savas körülmények között végezzük.

5. Az előző igénypontok bármelyike szerinti eljárás, ahol Z hidrogénatom vagy egy hidroxietilcsoporttá alakítható csoport, és az Va képletű vegyület előállítását követően egy hidroxietilcsoportot vezetünk be az Va':

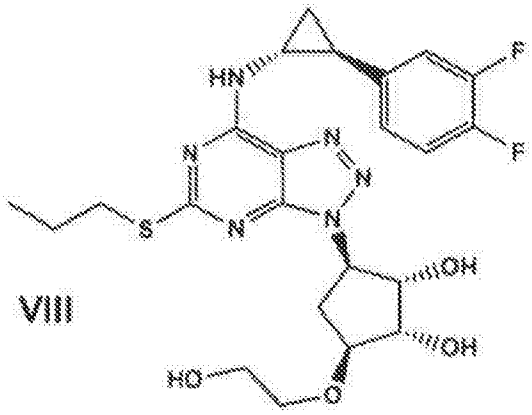


Va'

képletű vegyület előállítására.

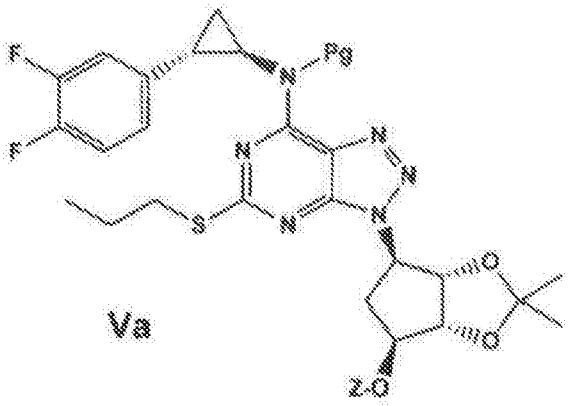
6. Az előző igénypontok bármelyike szerinti eljárás, ahol Pg oxikarbonil-típusú amino-védőcsoportok, karbamát-típusú amino-védőcsoportok és szulfonil-típusú amino-védőcsoportok közül választott, előnyösen Pg *terc*-butiloxikarbonil (Boc), karbobenziloxi (Cbz), metánszulfonil (Ms), benzolszulfonil (Bs), p-toluolszulfonil (Ts), és 2-naftalinszulfonilcsoportok közül választott.

7. Eljárás egy VIII:

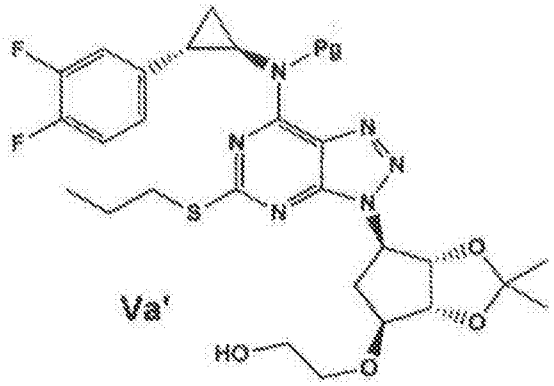


VIII

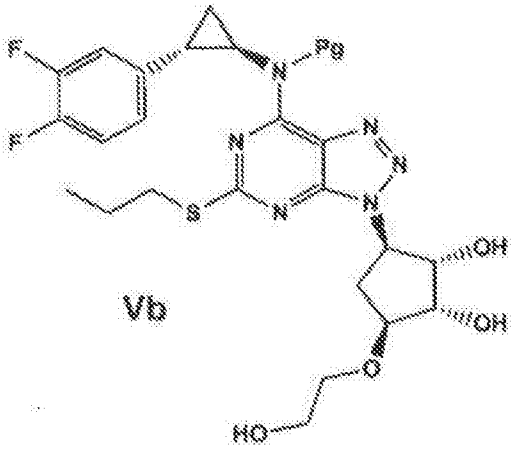
képletű vegyület vagy sója előállítására, melynek során:
(i) egy 1-6. igénypontok bármelyike szerinti Va, Va' vagy Vb:



Va



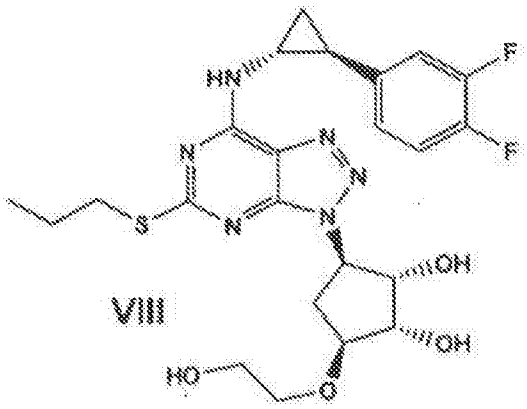
Va'



Vb

képletű vegyületet állítunk elő, ahol Pg és Z a fentiekben megadott, ahol ha az Va képletű vegyületben Z hidrogénatom vagy hidroxietilcsoporttá alakítható csoport, egy hidroxietilcsoportot viszünk be az Va'képletű vegyület előállítására,
(ii) védőcsoport-eltávolítási reakció(ka)t végzünk el a Pg csoport eltávolítására, illetve az Va vagy Va' képletű vegyületekben a pentángyűrűn levő vicinális hidroxi-védőcsoportok eltávolítására,
(iii) adott esetben a VIII képletű vegyület sóját képezzük.

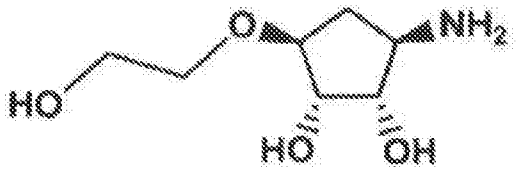
8. Eljárás egy VIII:



VIII

képletű vegyületet vagy egy sóját tartalmazó gyógyászati készítmény előállítására, melynek során:
(i) a 7. igénypont szerint VIII képletű vegyületet vagy sóját állítunk elő, és
(ii) a VIII képletű vegyületet vagy sóját egy gyógyászatilag elfogadható hordozóval és/vagy segédanyaggal keverjük.

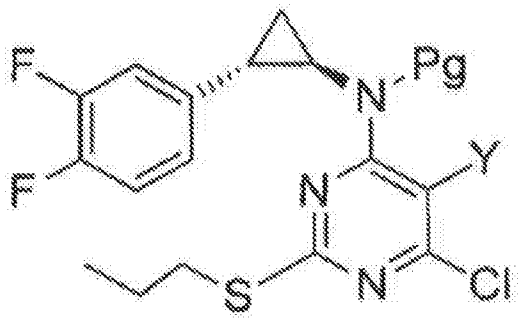
9. Egy VII:



VII

képletű vegyület.

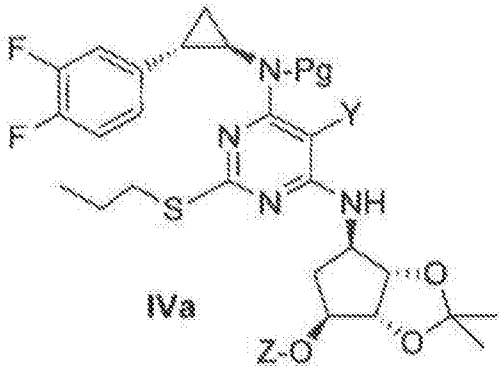
10. Egy II:



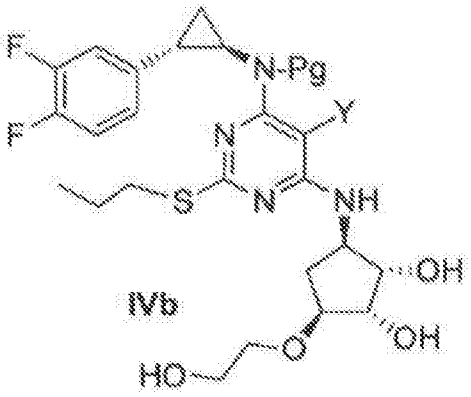
II

képletű vegyület, ahol Pg egy oxikarbonil-típusú amino-védőcsoportok és szulfonil-típusú amino-védőcsoportok közül választott amino-védőcsoport, előnyösen Pg *terc*-butiloxikarbonil (Boc), karbobenziloxi (Cbz), metánszulfonil (Ms), benzolszulfonil (Bs), p-toluolszulfonil (Ts), és 2-naftalinszulfonilcsoportok közül választott, és Y NO_2 vagy NH_2.

11. Egy IVa vagy IVb:



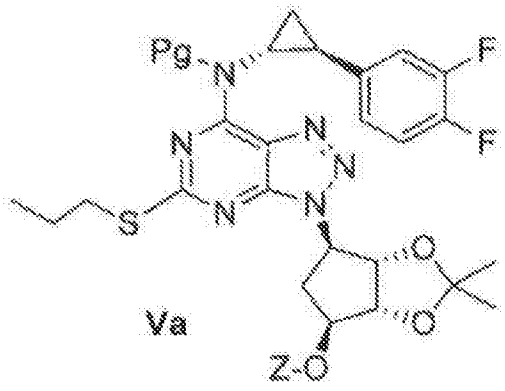
IVa



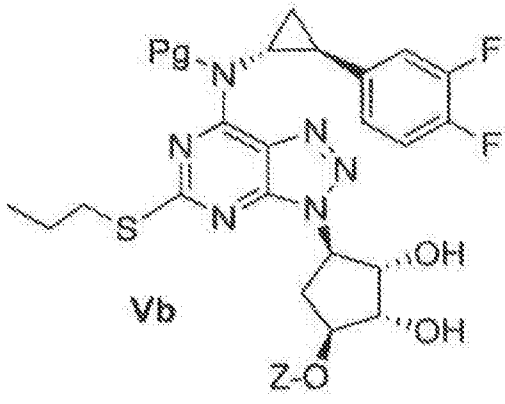
IVb

képletű vegyület, ahol Pg egy oxikarbonil-típusú amino-védőcsoportok és szulfonil-típusú amino-védőcsoportok közül választott amino-védőcsoport, előnyösen Pg *terc*-butiloxikarbonil (Boc), karbobenziloxi (Cbz), metánszulfonil (Ms), benzolszulfonil (Bs), p-toluolszulfonil (Ts), és 2-naftalinszulfonilcsoportok közül választott, Y NO_2 vagy NH_2, és Z hidrogénatom, hidroxietil vagy hidroxietilcsoporttá alakítható csoport.

12. Egy Va vagy Vb:



Va



Vb

képletű vegyület, ahol Pg egy oxikarbonil-típusú amino-védőcsoportok és szulfonil-típusú amino-védőcsoportok közül választott amino-védőcsoport, előnyösen Pg *terc*-butiloxikarbonil (Boc), karbobenziloxi (Cbz), metánszulfonil (Ms), benzolszulfonil (Bs), p-toluolszulfonil (Ts), és 2-naftalinszulfonilcsoportok közül választott, és Z hidrogénatom, hidroxietil vagy hidroxietilcsoporttá alakítható csoport.

13. A 11. vagy 12. igénypontok bármelyike szerinti vegyület, ahol Z hidrogénatom, hidroxietil és $-CH_2-CO-OCH_3$ csoportok közül választott.

14. A 9-13. igénypontok bármelyike szerinti vegyület alkalmazása ticagrelor előállításában.