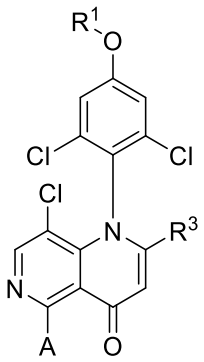
CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

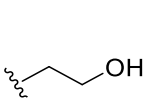
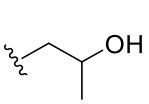
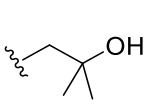
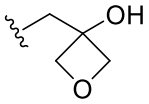
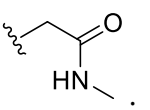
R^1 is (C_1-C_6)alkyl substituted with one or more substituents independently selected from -OH, -C(O)NHR^a and a 4- to 6-membered heterocycle which is optionally substituted with one or more -OH;

A is -OR^2 or (C_1-C_6)alkyl optionally substituted with one or more substituents independently selected from -SO_2(C_1-C_4)alkyl, -NHC(O)R^b, and -C(O)NHR^c;

R^2 is (C_1-C_6)alkyl substituted with one or more substituents independently selected from -NHC(O)R^d and -C(O)NHR^e, wherein the (C_1-C_6)alkyl is further optionally substituted with one or more substituents independently selected from halo, -OH and -CN;

R^a, R^b, R^c, R^d, and R^e are each independently selected from H and (C_1-C_6)alkyl optionally substituted with one or more -OH; and

R^3 is (C_1-C_4)alkyl.

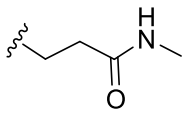
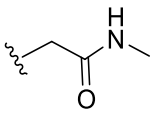
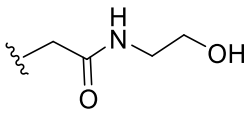
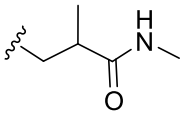
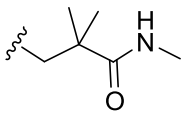
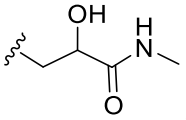
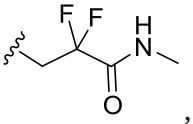
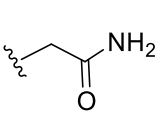
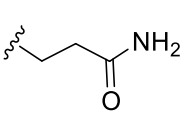
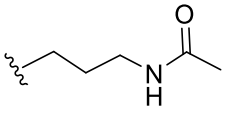
2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from , , , , and .

3. A compound according to claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein A is -OR^2.

4. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein R^e is selected from H and (C_1-C_4)alkyl optionally substituted with one or more -OH.

5. A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R^2 is (C_1-C_4)alkyl substituted with one or more substituents independently selected

from -NHC(O)CH_3, -C(O)NHCH_3, -C(O)NHCH_2CH_2OH, and -C(O)NH_2, and wherein the (C_1-C_4)alkyl is further optionally substituted with one or more substituents independently selected from halo, -OH and -CN.

6. A compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from , , , , , , , , , and .

7. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein R^3 is -CH_3.

8. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:
3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide;
2-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-(2-hydroxyethyl)acetamide;
3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide;
2-((8-chloro-1-(2,6-dichloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylacetamide;
2-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylacetamide;
(R)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxypropoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide;
(R)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N,2-dimethylpropanamide;
(S)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N,2-dimethylpropanamide;
N-(2-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)ethyl)acetamide;

(S)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxypropoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide;
3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N,2,2-trimethylpropanamide;
(R)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-2-hydroxy-N-methylpropanamide;
(S)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-2-hydroxy-N-methylpropanamide;
(S)-3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-2-hydroxy-N-methylpropanamide;
3-((8-chloro-1-(2,6-dichloro-4-((3-hydroxyoxetan-3-yl)methoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide;
3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-2,2-difluoro-N-methylpropanamide;
2-(4-(5-(2-amino-2-oxoethoxy)-8-chloro-2-methyl-4-oxo-1,6-naphthyridin-1(4H)-yl)-3,5-dichlorophenoxy)-N-methylacetamide;
3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)propanamide;
N-(3-(8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)propyl)acetamide;
8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-5-(2-(methylsulfonyl)ethyl)-1,6-naphthyridin-4(1H)-one;
8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-5-(2-(methylsulfonyl)propyl)-1,6-naphthyridin-4(1H)-one; and
8-chloro-1-(2,6-dichloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-2-methyl-5-(3-(methylsulfonyl)propyl)-1,6-naphthyridin-4(1H)-one.

9. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein the compound is 3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N,2,2-trimethylpropanamide.

10. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein the compound is 3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide.

11. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein the compound is 2-((8-chloro-1-(2,6-dichloro-4-(2- hydroxyethoxy)phenyl)-2-methyl- 4-oxo-1,4-dihydro-1,6- naphthyridin-5-yl)oxy)-N-methylacetamide.

12. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein the compound is N-(3-(8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)propyl)acetamide.

13. A compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein said compound is in a crystalline form selected from a free form, a hydrate, a solvate, a polymorph and a co-crystal thereof.

14. A compound according to claim 13, wherein said compound is 3-((8-chloro-1-(2,6-dichloro-4-(2-hydroxyethoxy)phenyl)-2-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)oxy)-N-methylpropanamide in any of the following crystalline forms:

(i) a free crystalline form named Modification A-1, characterized in that said crystalline form has an X-ray powder diffraction pattern comprising four or more 2θ values (± 0.1 degree), when measured using a CuKα radiation with a wavelength of 1.5418 Å at a temperature of about 22°C, selected from the 2θ values as set forth in the following table:

No.	Angle 2θ	d value Å	Relative Intensity %
1	7.7	11.47	99
2	11.3	7.86	5
3	15.4	5.74	10
4	16.4	5.40	32
5	17.7	5.00	9
6	21.2	4.19	19
7	22.7	3.91	9
8	23.3	3.81	43
9	24.0	3.70	100
10	26.4	3.37	12
11	27.2	3.28	23

(ii) a hydrate crystalline form named Modification A-2, characterized in that said crystalline form has an X-ray powder diffraction pattern comprising four or more 2θ values (± 0.1 degree), when measured using a CuKα radiation with a wavelength of 1.5418 Å at a temperature of about 22°C, selected from the 2θ values as set forth in the following table:

No.	Angle 2θ	d value Å	Relative Intensity %
1	7.6	11.62	17
2	10.7	8.30	3
3	15.2	5.81	4
4	16.9	5.24	27
5	21.4	4.15	17
6	24.0	3.70	100
7	25.8	3.45	3
8	27.4	3.26	17
9	30.7	2.91	2

(iii) a hydrate crystalline form named Modification A-3, characterized in that said crystalline form has an X-ray powder diffraction pattern comprising four or more 2θ values (± 0.1 degree), when measured using a CuKα radiation with a wavelength of 1.5418 Å at a temperature of about 22°C, selected from the 2θ values as set forth in the following table:

No.	Angle 2θ	d value Å	Relative Intensity %
1	7.6	11.55	23
2	15.3	5.78	9
3	17.0	5.22	18
4	20.7	4.29	5
5	21.4	4.14	8
6	22.2	3.99	33
7	25.9	3.44	20
8	29.1	3.07	10
9	32.3	2.77	12

(iv) a hydrate crystalline form named Modification A-4, characterized in that said crystalline form has an X-ray powder diffraction pattern comprising four or more 2θ values (± 0.1 degree), when measured

using a CuKα radiation with a wavelength of 1.5418 Å at a temperature of about 22°C, selected from the 2θ values as set forth in the following table:

No.	Angle 2θ	d value Å	Relative Intensity %
1	7.3	12.11	29
2	10.3	8.59	3
3	15.5	5.73	10
4	22.1	4.02	3
5	23.1	3.84	100
6	23.9	3.73	19
7	25.5	3.49	7
8	25.9	3.44	6
9	26.4	3.37	50
10	31.2	2.86	8

(v) a hydrate crystalline form named Modification A-5, characterized in that said crystalline form has an X-ray powder diffraction pattern comprising four or more 2θ values (± 0.1 degree), when measured using a CuKα radiation with a wavelength of 1.5418 Å at a temperature of about 22°C, selected from the 2θ values as set forth in the following table:

No.	Angle 2θ	d value Å	Relative Intensity %
1	5.0	17.84	47
2	9.9	8.93	14
3	14.9	5.96	21
4	15.9	5.58	39
5	17.7	5.01	14
6	19.8	4.47	87
7	24.0	3.71	84
8	25.5	3.49	68
9	27.2	3.28	23

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

16. The pharmaceutical composition according to claim 15, further comprising at least one additional pharmaceutically active agent selected from Class I antiarrhythmic agents, Class II antiarrhythmic agents, Class III antiarrhythmic agents, Class IV antiarrhythmic agents, Class V antiarrhythmic agents, cardiac glycosides and other drugs affecting atrial refractoriness; haemostasis modulators, antithrombotics; thrombin inhibitors; factor VIIa inhibitors; anticoagulants, factor Xa inhibitors, and direct thrombin inhibitors; antiplatelet agents, cyclooxygenase inhibitors, adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, glycoprotein IIB/IIA, adenosine reuptake inhibitors; anti-dyslipidemia agents, HMG-CoA reductase inhibitors, other cholesterol-lowering agents; bile acid sequestrants; cholesterol absorption inhibitors; cholesteryl ester transfer protein (CETP) inhibitors; inhibitors of the ileal bile acid transport system (IBAT inhibitors); bile acid binding resins; nicotinic acid and analogues thereof; anti-oxidants; omega-3 fatty acids; antihypertensive agents, including adrenergic receptor antagonists, beta blockers, alpha blockers, mixed alpha/beta blockers; adrenergic receptor agonists, alpha-2 agonists; angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers; angiotensin II receptor antagonists; aldosterone receptor antagonists; centrally acting adrenergic drugs, central alpha agonists; and diuretic agents; anti-obesity agents, pancreatic lipase inhibitors, microsomal transfer protein (MTP) modulators, diacyl glycerolacyltransferase (DGAT) inhibitors, cannabinoid (CBI) receptor antagonists; insulin and insulin analogues; insulin secretagogues; agents that improve incretin action, dipeptidyl peptidase IV (DPP-4) inhibitors, glucagon-like peptide- I (GLP-1) agonists; insulin sensitizing agents, peroxisome proliferator activated receptor gamma (PPARγ) agonists, agents that modulate hepatic glucose balance, fructose 1,6-bisphosphatase inhibitors, glycogen phosphorylase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators; agents designed to reduce/slow the absorption of glucose from the intestine, alpha-glucosidase inhibitors; agents which antagonize the actions of or reduce secretion of glucagon, amylin analogues; agents that prevent the reabsorption of glucose by the kidney, and sodium-dependent glucose transporter 2 (SGLT-2) inhibitors.

17. A compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 15 or claim 16 for use as a medicament.

18. Use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 15 or claim 16 in the manufacture of a medicament for treating a disease or disorder responsive to the inhibition of the GIRK1/4 receptor, wherein the disease or disorder responsive to the inhibition of the GIRK1/4 receptor is selected from cardiac arrhythmia, atrial fibrillation, bradyarrhythmia, bradycardia, heart block, sick sinus syndrome, parasympathetic hyperactivation, primary hyperaldosteronism, hypotension, and vasovagal syncope.

19. Use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition according to claim 15 or claim 16 in the manufacture of a medicament for use in a method for maintaining a sinus rhythm after cardioversion in a patient with persistent or recent onset of atrial fibrillation or preventing a recurrence in a patient with paroxysmal atrial fibrillation.

20. The use of claim 19, wherein the compound or the pharmaceutical composition is to be administered orally.