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C07D 405/14 (2006.01)
C07D 413/14 (2006.01)

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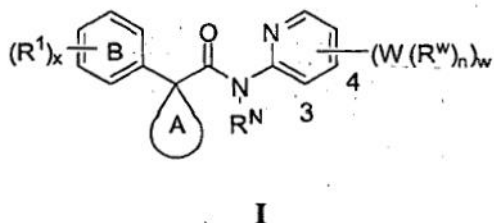
(54) Title **Pyridyl derivatives as CFTR modulators**

(56) References
Cited: WO-A-2005/075435
 WO-A-2007/056341
 WO-A-2008/141119
 US-A1- 2008 286 204

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (<http://worldwide.espacenet.com>) or via the search engine on our website here: <https://search.patentstyret.no/>

Patentkrav

1. Forbindelse ifølge formel **I**:



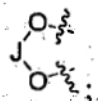
eller et farmasøytisk akseptabelt salt avledet derav, hvor:

5 R^N er H, alkyl, aryl, heteroaryl, aralkyl, sykloalkyl, eller heterosykloalkyl;

A er en monosyklisk ring med 3 substituenten;

B er alternativt festet til en ring med 5-7 substituenten valgt fra gruppen inneholdende :sykloalifatisk, aryl, heterosyklisk og heteroaryl;

R^1 er halo, alkyl, OH, alkoksy, thioalkyl, trifluorometoksy; eller to R^1 på



10 nærliggende atomer, sammen danner

hvor J velges fra gruppen inneholdende CH_2 , CF_2 , or $\text{C}(\text{CH}_3)_2$;

W er, uavhengig, en binding eller en (C1-C6) alkyliden kjede hvor opptil to metylen enheter av W er uavhengig byttet ut med -O-, -S-, -SO₂-, or -NR'-;

R' er uavhengig H, alkyl, aryl, heteroaryl, aralkyl, sykloalkyl, eller heterosyklisk;

15 R^w er uavhengig H, CN, NO₂, N(R)₂, CF₃, OCF₃, OH, OR, CO₂R, C(O)N(R)₂, -O(C1-C6)alkyliden-OR, -O(C1-C6)alkyliden-N(R)₂, -O(C1-C6)alkyliden-heterosyklisk eller en alifatisk, sykloalifatisk, aryl, aryloksy, heterosyklisk, eller heteroaryl, hvor, når substituert, R^w substituert med opp til to R²;

R^2 er halo, CN, NO_2 , CF_3 , OCF_3 , OR, $OC(O)R$, $OC(O)N(R)_2$, SR, $S(O)R$, SO_2R , $SO_2N(R)_2$, SO_3R , $C(O)R$, CO_2R , $C(O)N(R)_2$, $N(R)_2$, $NRC(O)R$, $NRCO_2R$, $NRC(O)N(R)_2$, $NRSO_2R$, $B(OR)_2$, eller $NRSO_2N(R)_2$;

R er uavhengig H, alkyl, sykloalkyl, heterosyklisk, aryl, eller heteroaryl;

5 n er 1 eller 2;

w er et heltall fra 0 til og med 4; and

x er et heltall fra 0 til og med 5 ;

betinget av at W er en binding og R^W er sykloalifatisk, heterosykloalifatisk, aryl, eller heteroaryl, $-W-R^W$ er festet til 3- eller 4-posisjon på pyridylringen.

10 2. Forbindelsen i krav 1, hvor J is CH_2 .

3. Forbindelsen i krav 1, hvor J er CF_2 .

4. Forbindelsen i krav 1, hvor R^N er H alkyl.

5. Forbindelsen i krav 1, hvor W er en binding.

6. Forbindelsen i krav 1, hvor W er en (C1-C6) alkyliden kjede.

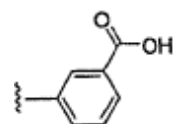
15 7. Forbindelsen i krav 1, hvor W er valgt fra gruppen bestående av $-CH_2-$, $-NH-$, $-O-$, and $-OCH_2-$.

8. Forbindelsen ifølge krav 1, hvor R^W er valgt fra gruppen bestående av H, OH, heterosyklisk, aryl, fenyl, heteroaryl, pyridyl, alkoksy, sykloalkyl, and sykloheksyl.

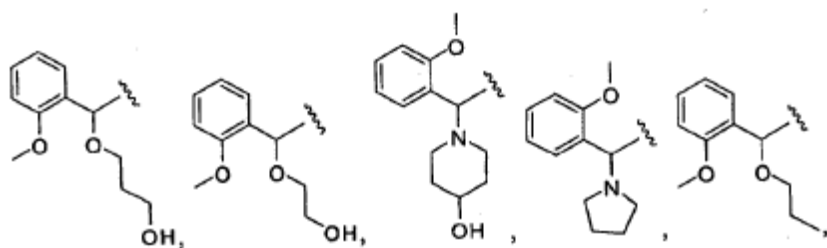
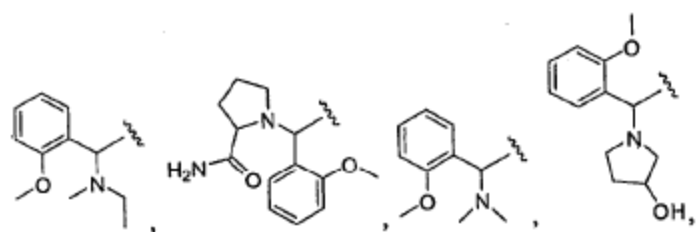
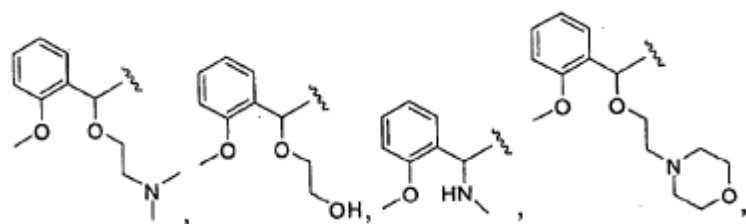
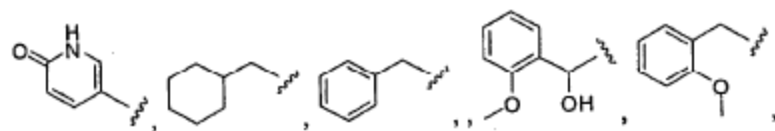
20 9. Forbindelsen ifølge krav 1, hvor $-W-R^W$ er asyklisk.

10. Forbindelsen ifølge krav 1, hvor $-W-R^W$ er an aryl, heteroaryl, sykloalifatisk, eller heterosykloalifatisk ring.

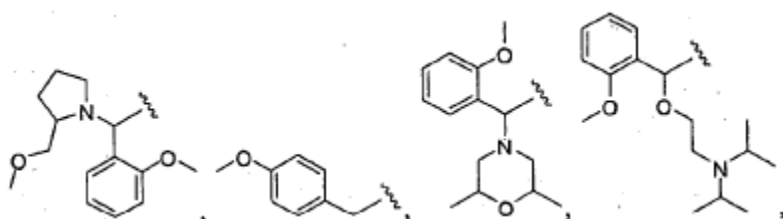
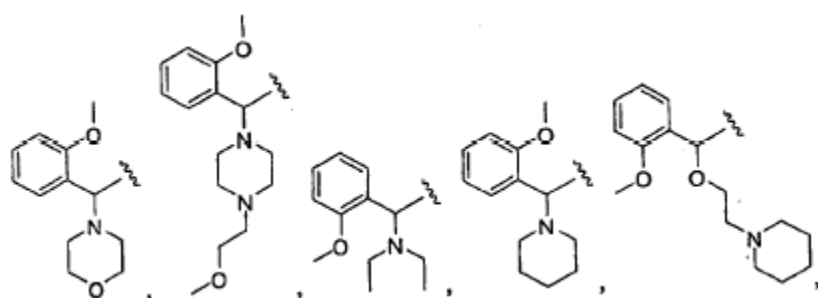
11. Forbindelsen ifølge krav 1, hvor $-W(R^W)_n$ er valgt fra følgende:

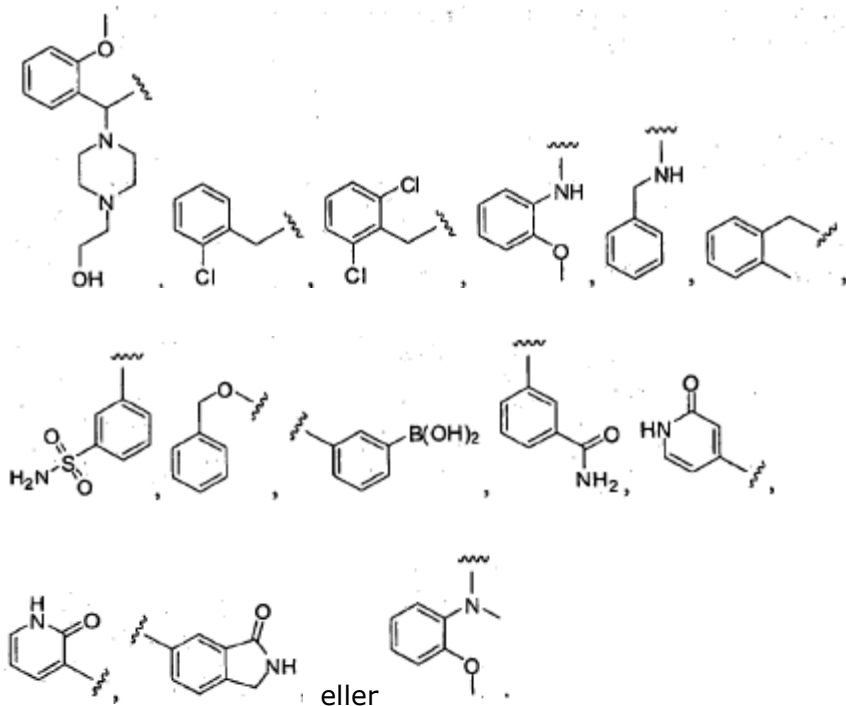


-F, -CH₃, -CH₂CH₃, -CN, -CF₃, -CONH₂, -CH₂CH(CH₃)₂,

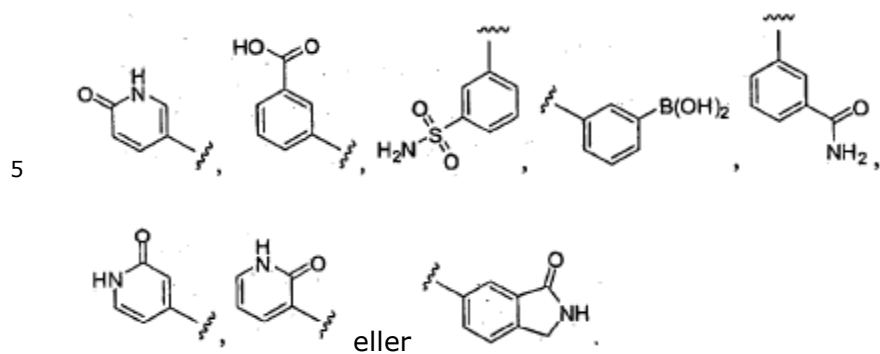


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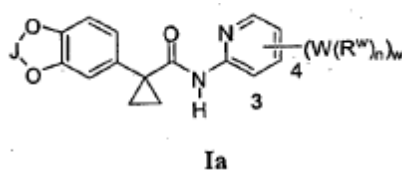




12. Forbindelsen ifølge krav 1, hvor $-W(R^w)_n$ valgt fra følgende:



13. Forbindelsen ifølge krav 1, med formel Ia:



eller et farmasøytisk akseptabelt salt derav, hvor:

10 J er CH_2 eller CF_2 ;

W er uavhengig en binding eller en (C1-C6) alkylidenkjede alternativt er substituert med R^2 hvor opp til to metylenenheter av W er uavhengig byttet ut av-O-, eller -NR'-;

R' uavhengig er H eller alkyl;

- 5 R^W uavhengig er H, CN, $N(R)_2$, CF_3 , OH, CO_2R , $C(O)N(R)_2$, -O(C1-C6)alkylidene-OR, -O(C1-C6)alkylidene- $N(R)_2$, -O(C1-C6)alkyliden-heterosyklisk, eller an alifatisk, sykloalifatisk, aryl, aryloksy, heterosyklisk, eller heteroaryl, hvor, når substituert, R^W er substituert med opp til to R^2 ;

R^2 er halo, OR, CO_2R , $C(O)N(R)_2$, $SO_2N(R)_2$, $B(OR)_2$, eller $N(R)_2$;

- 10 R er uavhengig H, alkyl, sykloalkyl, heterosyklisk, aryl, eller heteroaryl;

n er 1 eller 2; og

w er et heltall fra 0 til og med 4;

forutsatt at når W er en binding og R^W er sykloalifatisk, heterosykloalifatisk, aryl, eller heteroaryl, -W- R^W er festet til 3- eller 4-position på pyridyl ringen.

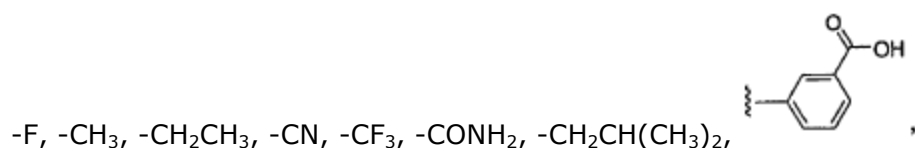
- 15 14. Forbindelsen ifølge krav 13, hvor J er CH_2 .

15. Forbindelsen ifølge krav 13, hvor J er CF_2 .

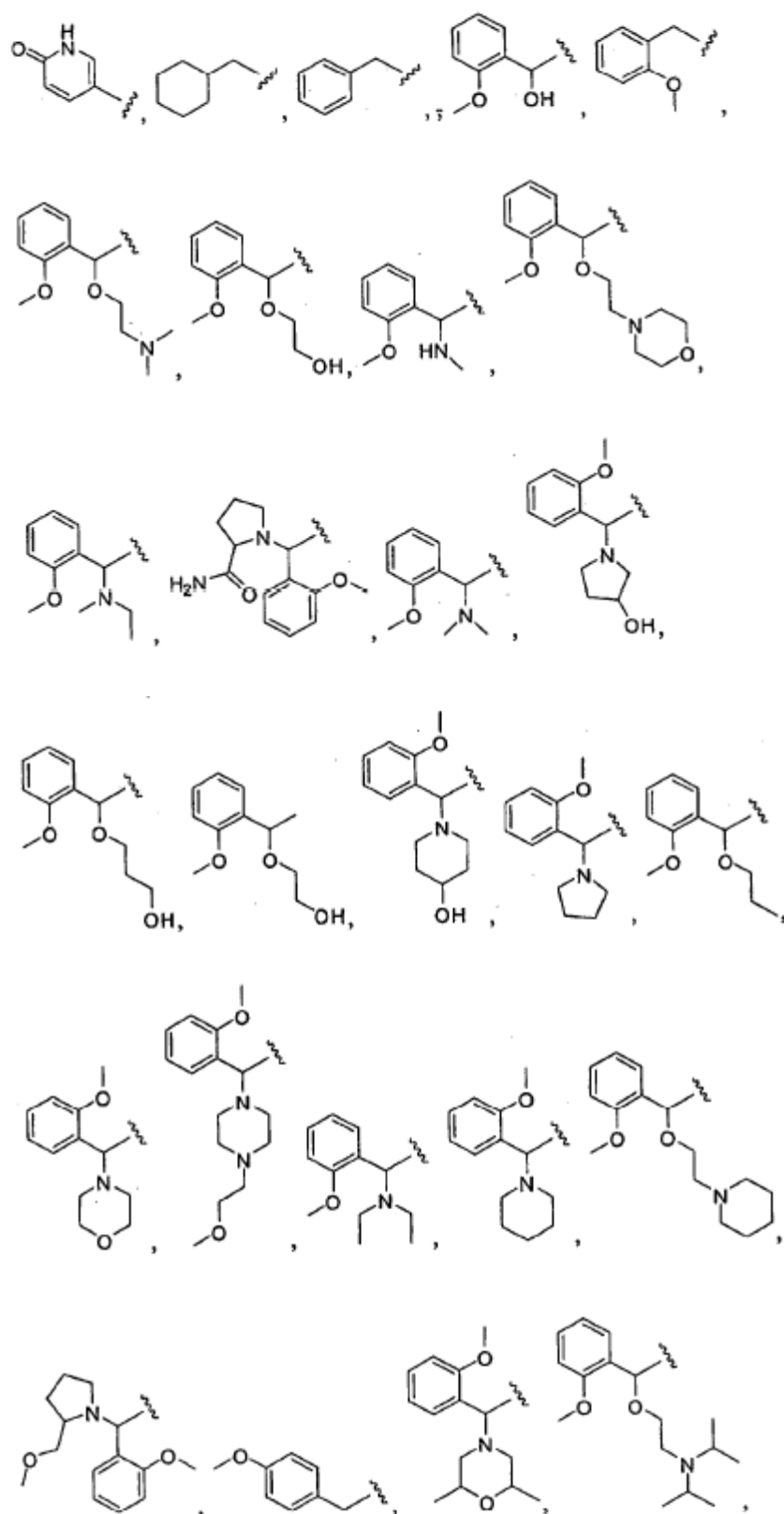
16. Forbindelsen ifølge krav 13, hvor -W- R^W er asyklisk.

17. Forbindelsen ifølge krav 13, hvor -W- R^W er an aryl, heteroaryl, sykloalifatisk, or heterosykloalifatisk ring.

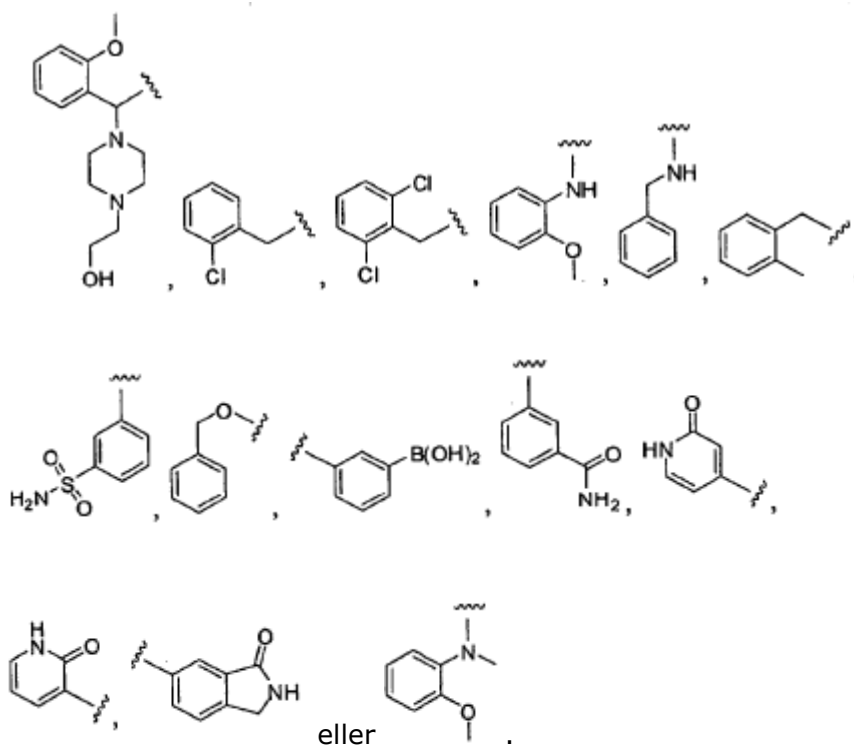
- 20 18. Forbindelsen ifølge krav 13, hvor -W(R^W)_n er valgt fra følgende:.



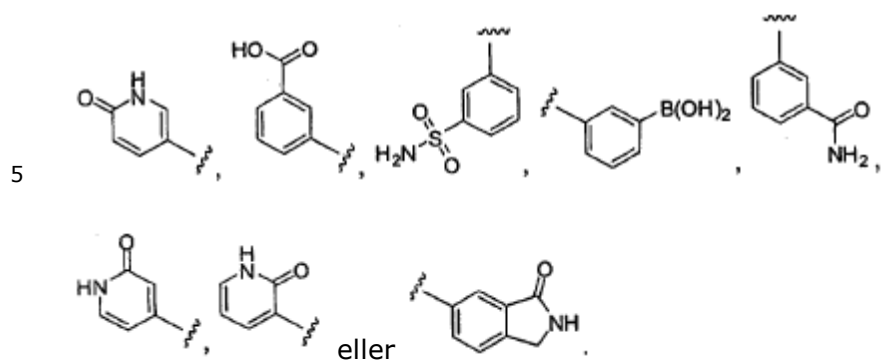
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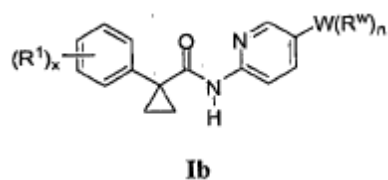
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19. Forbindelsen ifølge krav 13, hvor $-W(R^w)_n$ valgt fra følgende:



20. Forbindelsen ifølge krav 1, med formel Ib:



eller et farmasøytisk akseptabelt salt derav, hvor:

R^1 er halo, alkyl, OH, alkoksy, thioalkyl, trifluormetoksy; eller to R^1 på nærliggende

atomer, holdt sammen, danner 

hvor J er valgt fra gruppen bestående av CH_2 , CF_2 , eller $C(CH_3)_2$;

W er $-NR'$ eller $-CH_2-$;

- 5 R' er uavhengig H eller alkyl;

R^W er uavhengig H, CN, $N(R)_2$, CF_3 , OH, CO_2R , $C(O)N(R)_2$, $-O(C1-C6)$ alkyliden-OR, $-O(C1-C6)$ alkyliden- $N(R)_2$, $-O(C1-C6)$ alkyliden-heterosyklisk, eller en alifatisk, sykloalifatisk, aryl, aryloksy, heterosyklisk, eller heteroaryl, hvor, når substituert, R^W er substituert med opp til to R^2 ;

- 10 R^2 er halo, OR, CO_2R , $C(O)N(R)_2$, $SO_2N(R)_2$, $B(OR)_2$, eller $-N(R)_2$;

R er uavhengig H, alkyl, sykloalkyl, heterosyklisk, aryl, eller heteroaryl;

n er 1 eller 2;

w er et heltall fra 0 til og med 4; and

x er et heltall fra 0 til og med 5.

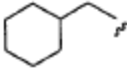
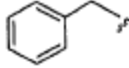
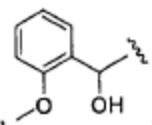
- 15 21. Forbindelsen i krav20, hvor to R^1 på nærliggende atomer, holdt sammen,

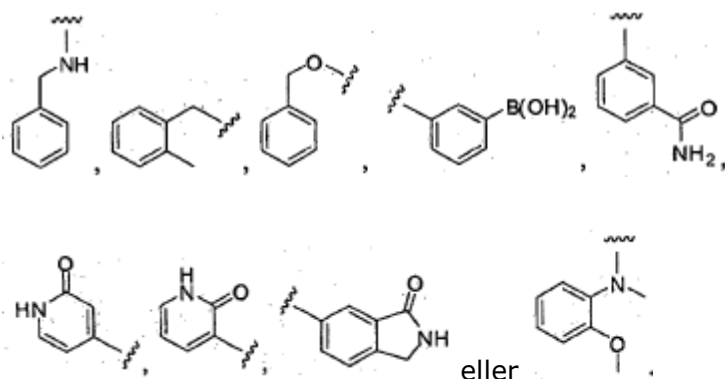
danner  and J er CH_2 .

22. Forbindelsen i krav20, hvor to R^1 på nærliggende atomer, holdt sammen,

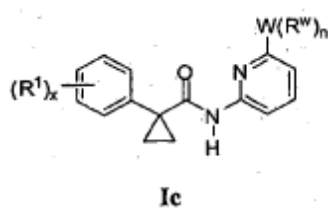
danner  og J er CF_2 .

23. Forbindelsen i krav20, hvor $-W(R^W)_n$ er valgt fra følgende:

- 20 $-CH_3$, $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, , , ,



24. Forbindelsen ifølge krav 1, med formel Ic:



5 eller et farmasøytisk akseptabelt salt derav, hvor:

R^1 er halo, alkyl, OH, alkoksy, thioalkyl, trifluorometoksy; eller to R^1 på

nærliggende atomer, holdt sammen, danner



hvor J er valgt fra gruppen bestående av CH_2 , CF_2 , eller $C(CH_3)_2$;

W er $-NR'$ eller $-CH_2-$;

10 R' er uavhengig H eller alkyl;

R^w er uavhengig H, CN, $N(R)_2$, CF_3 , OH, CO_2R , $C(O)N(R)_2$, $-O(C1-C6)$ alkyliden-OR, $-O(C1-C6)$ alkyliden- $N(R)_2$, $-O(C1-C6)$ alkyliden-heterosyklisk, eller an alifatisk, sykloalifatisk, aryl, aryloksy, heterosyklisk, eller heteroaryl, hvor, når substituert, R' er substituert med opp til to R^2 ;

15 R^2 er halo, OR, CO_2R , $C(O)N(R)_2$, $SO_2N(R)_2$, $B(OR)_2$, eller $N(R)_2$;

R er uavhengig H, alkyl, sykloalkyl, heterosyklisk, aryl, eller heteroaryl;

n er 1 eller 2;

w er et heltall fra 0 til og med 4; and

x er et heltall fra 0 til og med 5.

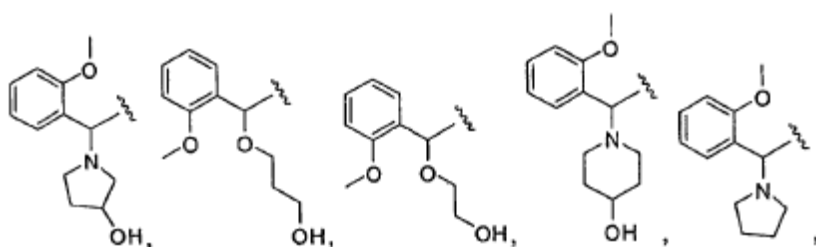
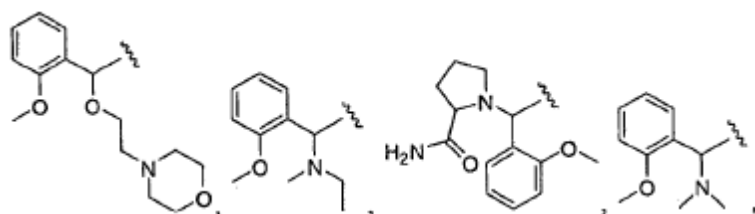
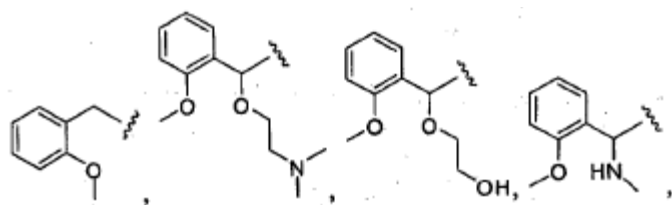
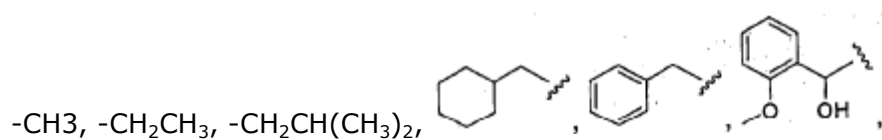
25. Forbindelsen i krav 24, hvor to R^1 på nærliggende atomer, holdt sammen,

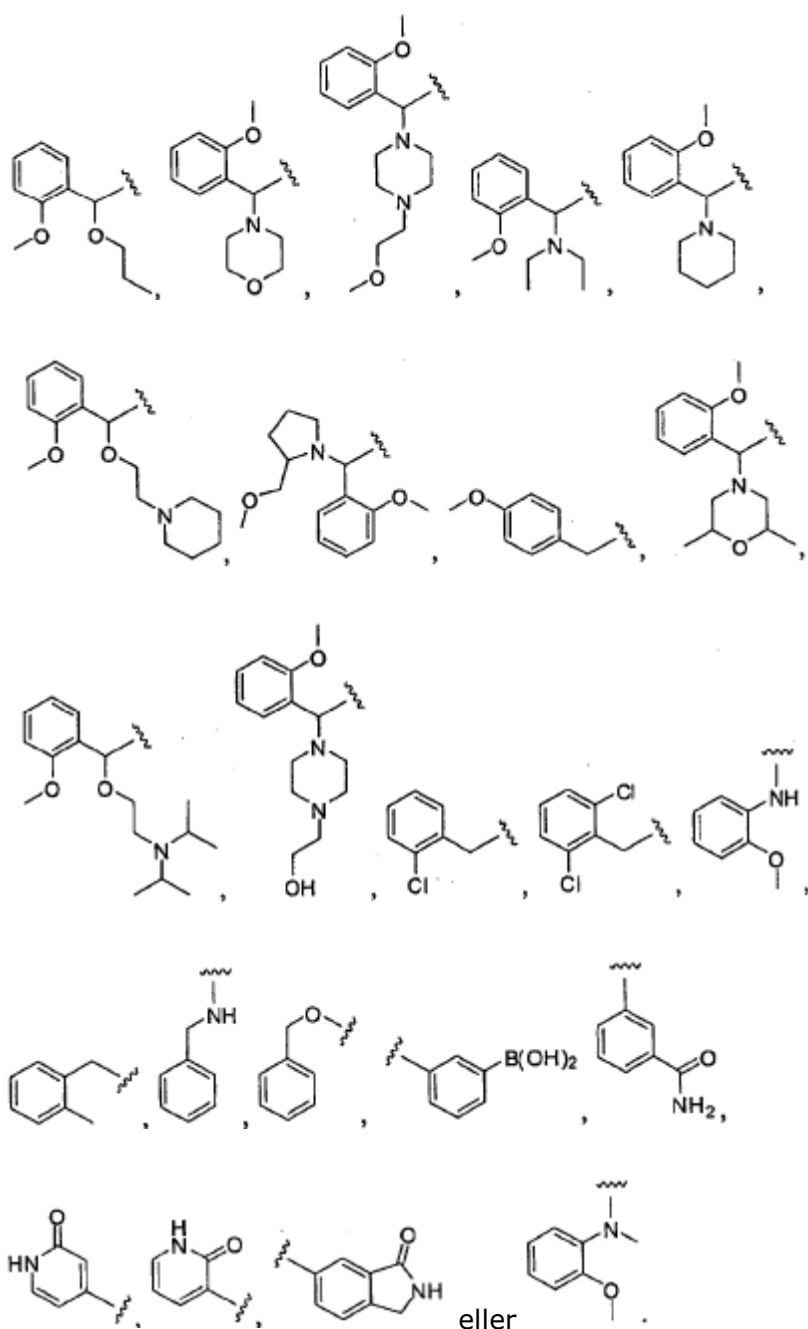
danner  and J er CH_2 .

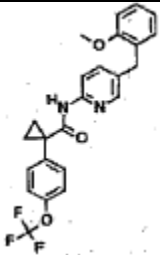
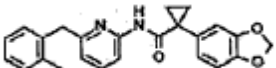
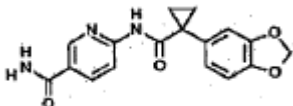
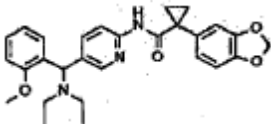
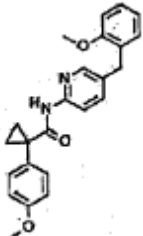
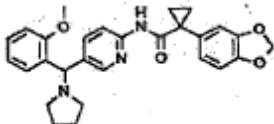
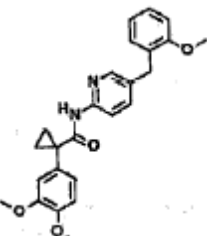
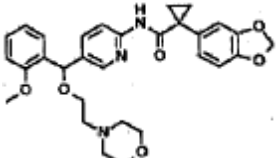
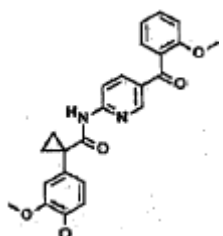
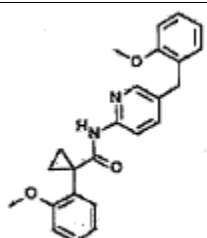
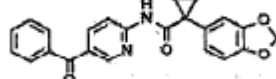
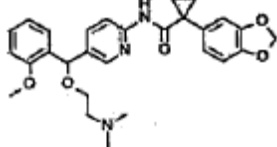
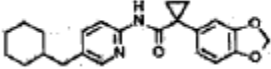
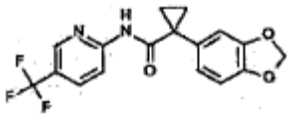
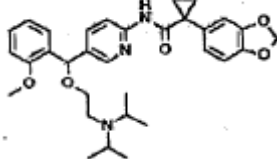
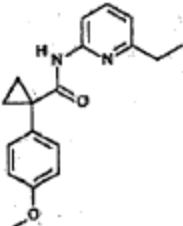
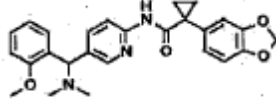
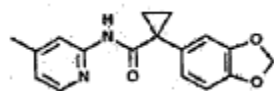
5 26. Forbindelsen i krav 24, hvor to R^1 på nærliggende atomer, holdt sammen,

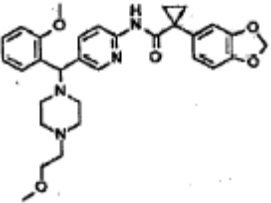
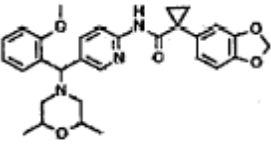
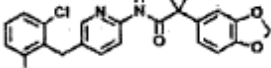
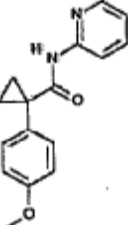
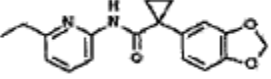
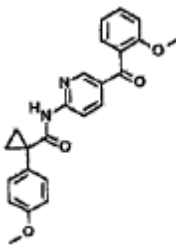
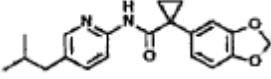
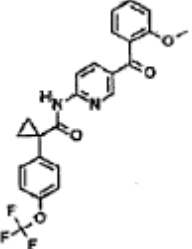
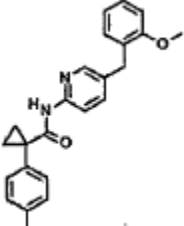
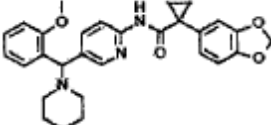
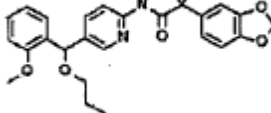
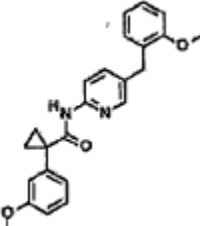
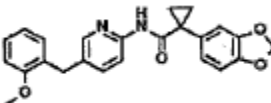
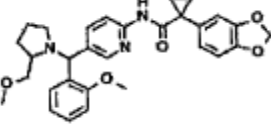
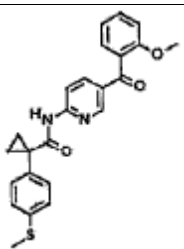
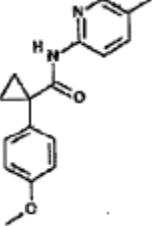
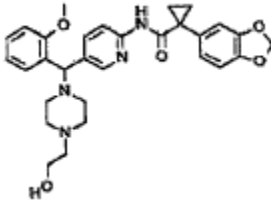
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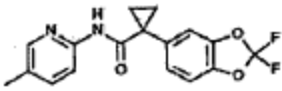
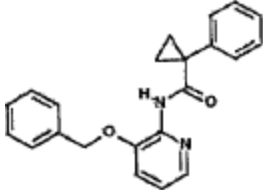
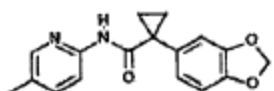
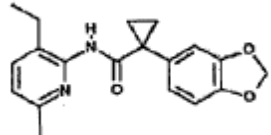
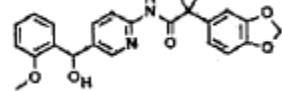
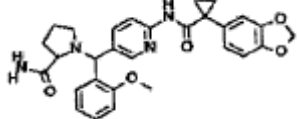
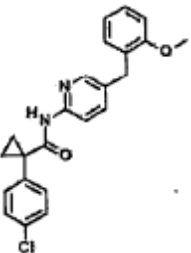
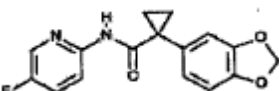
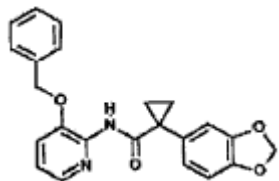
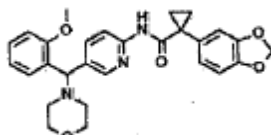
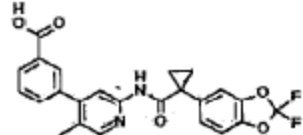
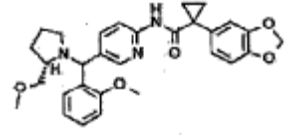
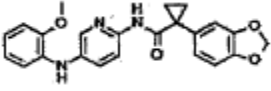
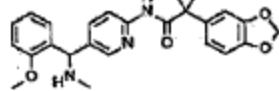
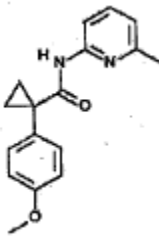
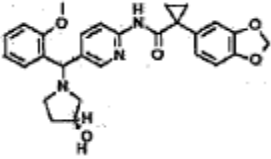
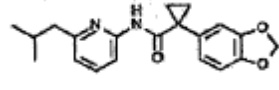
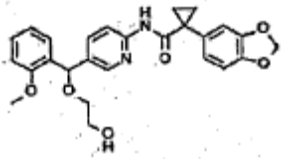
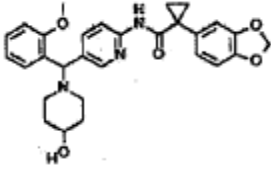
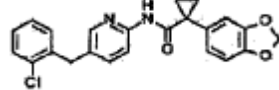
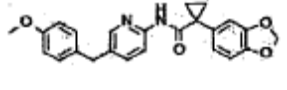
27. Forbindelsen i krav 24, hvor $-W(R^w)_n$ er valgt fra følgende:

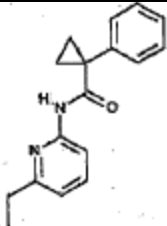
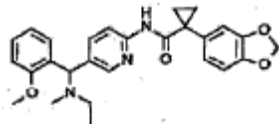
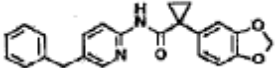
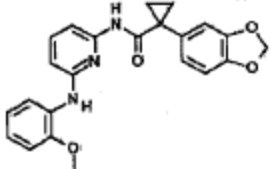
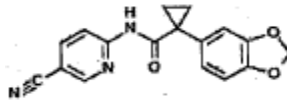
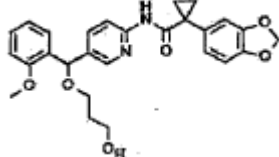
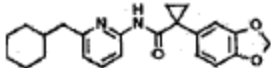
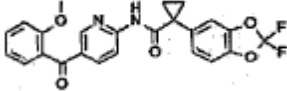
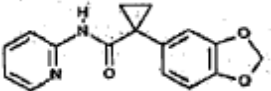
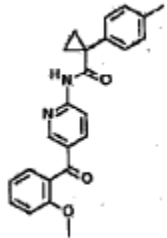
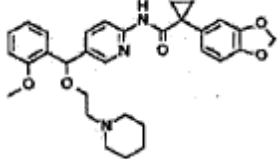
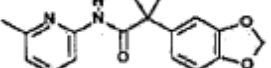
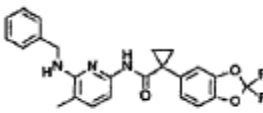
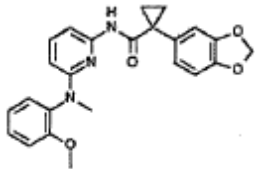
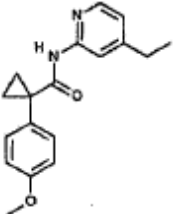
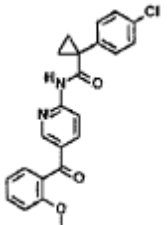
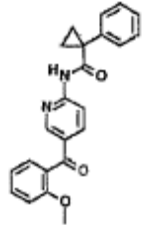
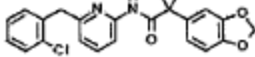




		
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29. En farmasøytisk sammensetning omfattende (i) en forbindelse ifølge krav 1; og (ii) en farmasøytisk akseptabel bærer.

30. Sammensetning ifølge krav 29, videre omfattende ytterligere en agent valgt fra en mucolytisk agent, bronchodialator, en anti-biotisk, en anti-infektiv agent, en anti-inflammatorisk agent, CFTR modulator annet enn en forbindelse ifølge krav 1, og en næringsagent.
- 5 31. Sammensetning ifølge krav 30, hvor ytterligere agenten er N-(5-hydroksy-2,4-ditert-butyl-fenyl)-4-okso-1 H-quinoline-3-karboksamid.
32. In vitro metode for modulering av ABC transportører i en cellemembran, omfattende de ulike steg for å tilføre nevnte celle en forbindelse ifølge krav 1.
33. In-vitro metode ifølge krav 31, hvor ABC transportørene er CFTR.
- 10 34. Forbindelse I følge ethvert av kravene 1 til 28 eller en farmasøytisk sammensetning ifølge krav 29 til 31 for bruk i behandling av en tilstand, sykdom, eller forstyrrelse valgt fra cystisk fibrose, arvelig emfysema, arvelig hemokromatose, koagulering-fibrinolyse mangler slik som protein C mangel, Type 1
- 15 hereditært angioødem, fettprosseseringsmangler, slik som familiær hyperkolesterolemi, Type 1 chylomicronemi, abetalipoproteinemi, lysosomal avleiringssykdommer, slik som Icell sykdom/pseudo-Hurler, mukoliposakkaridoser, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendokrinopati/hyperinsulinemi, diabetes mellitus, Laron dvergvekst, myeloperoksidase mangel, primær
- 20 hypoparathyrose, melanoma, glycanose CDG type I, arvelig emfysem, medfødt hypertyreose, osteogenesis imperfecta, arvelig hypofibrinogenemi, ACT mangel, diabetes insipidus (DI), nevrohypofysal DI, nefrogenisk DI, Charcot-Marie Tooth syndrom, Pelizaeus-Merzbacher sykdom, nevrodegenerative sykdommer slik som Alzheimer, Parkinson, amyotropisk lateral sklerose, progressive supranukleær lammelse, Picks sykdom, flere polyglutamine nevrologiske forstyrrelser som
- 25 Huntington, spinocerebellar ataxi type I, spinal og bulbar muskelatrofi, dentatorubral pallidoluysian atrofi, og myotonisk dystrofi, og også spongiform encefalopatier, slik som arvelig Creutzfeldt-Jakob sykdom, Fabry sykdom, Gerstmann- Sträussler-Scheinker syndrom, COPD, tørre øyer and Sjogrens sykdom.
- 30 35. Forbindelse ifølge ethvert av kravene 1 til 28 eller en farmasøytisk sammensetning ifølge ethvert av kravene 29 to 31 for bruk i behandlingen av cystisk fibrose.

36. Utstyr for måling av aktivitet av ABC transportører eller et fragment derav i en biologisk prøve in vitro eller in vivo, omfattende:

(i) første sammensetning omfattende forbindelse ifølge krav 1; og

(ii) instruksjoner for:

5 a) administrere sammensetningen til den biologiske prøven;

b) måle aktiviteten til omtalte ABC transportører eller et fragment derav.