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(54) Title **BILE ACID DERIVATIVES AS FXR/TGR5 AGONISTS**

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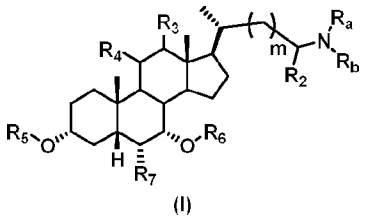
MACCHIARULO ET AL.: 'Probing the Binding Site of Bile Acids in TGR5.' MEDICINAL CHEMISTRY LETTERS vol. 4, no. 12, 2011, pages 1158 - 1162, XP055448079 Retrieved from the Internet: <URL:http://pubs.acs.org/doi/abs/10.1021/m1 400247k> [retrieved on 2016-01-07]

## Patentkrav

**1.** En forbindelse representert ved formel I, eller et farmasøytisk akseptabelt salt eller ester derav:




(I)

hvori:

$R_a$ er hydrogen eller substituert eller usubstituert-$C_1$-$C_8$-alkyl;

$R_b$ er valgt fra gruppen som består av:

-C(O)$NHSO_2R_1$ og -$SO_2R_1$;

$R_1$ er valgt fra gruppen som består av:

1) Halogen;
2) Hydroksyl;
3) Substituert eller usubstituert -$C_1$-$C_8$-alkyl;
4) Substituert eller usubstituert -$C_2$-$C_8$-alkenyl;
5) Substituert eller usubstituert -$C_2$-$C_8$-alkynyl;
6) Substituert eller usubstituert -$C_3$-$C_8$ sykloalkyl;
7) Substituert eller usubstituert aryl;
8) Substituert eller usubstituert arylalkyl;
9) Substituert eller usubstituert heterosykloalkyl;
10) Substituert eller usubstituert heteroaryl;
11) Substituert eller usubstituert heteroarylalkyl; og
12)-$NR_{10}R_{11}$;

$R_2$ er valgt fra gruppen som består av:

1)Hydrogen;
2)Substituert eller usubstituert -$C_1$-$C_8$-alkyl;
3)Substituert eller usubstituert -$C_2$-$C_8$-alkenyl;
4)Substituert eller usubstituert -$C_2$-$C_8$-alkynyl;

5) Substituert eller usubstituert arylalkyl; og

6) Substituert eller usubstituert aryl;

m er valgt fra 0, 1, 2 og 3;

R3 er hydrogen, hydroksyl, -$OSO_3H$, -$OSO_3$-, -OAc, -$OPO_3H_2$ eller -$OPO_{32}$-;

R4 er hydrogen, halogen, CN, $N_3$, hydroksyl, -$OSO_3H$, -$OSO_3$-, -OAc, -$OPO_3H_2$, - $OPO_3^2$-, -$SR_2$ eller -$NHR_2$, hvori $R_2$ er som definert tidligere;

Eller $R_3$ og $R_4$ tas sammen med karbonatomene som de er bundet til for å danne -CH = CH-, asykloalkylring eller en heterosykloalkylring;

$R_5$ og $R_6$ er uavhengig valgt fra hydrogen eller hydroksyl beskyttelsesgruppe $R_7$ er valgt fra gruppen bestående av:

1) Hydrogen;

2) Halogen;

3) Substituert eller usubstituert -$C_1$-$C_8$-alkyl;

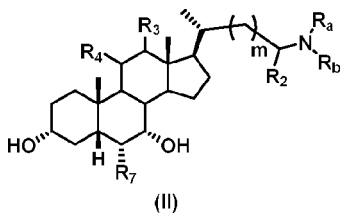
4) Substituert eller usubstituert -$C_2$-$C_8$-alkenyl;

5) Substituert eller usubstituert -$C_2$-$C_8$-alkynyl; og

6) Substituert eller usubstituert -$C_3$-$C_8$ sykloalkyl; og

$R_{10}$ og $R_{11}$ er hver uavhengig valgt fra hydrogen, substituert eller usubstituert -$C_1$-$C_8$-alkyl, substituert eller usubstituert -$C_2$-$C_8$-alkenyl, substituert eller usubstituert -$C_2$-$C_8$-alkynyl, substituert eller usubstituert -$C_3$-$C_8$-sykloalkyl, substituert eller usubstituert -$C_3$-$C_8$ heterosykloalkyl, eller $R_{10}$ og $R_{11}$ blir tatt sammen med nitrogenet de festet danner en heterosyklisk ring.

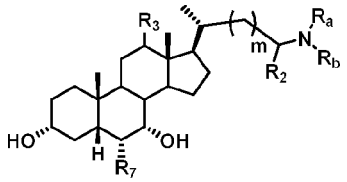
**2.** Forbindelsen ifølge patentkrav 1, representert ved formel II eller et farmasøytisk akseptabelt salt eller ester derav:




(II)

hvori $R_a$, $R_b$, $R_2$, $R_3$, $R_4$, $R_7$ og m er som definert i patentkrav 1.

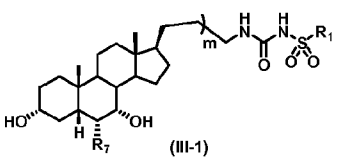
**3.** Forbindelsen ifølge patentkrav 1, representert ved formel III eller et farmasøytisk akseptabelt salt eller ester derav:



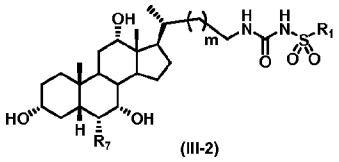
(III)

hvori $R_a$, $R_b$, $R_2$, $R_3$, $R_7$ og m er som definert i patentkrav 1.

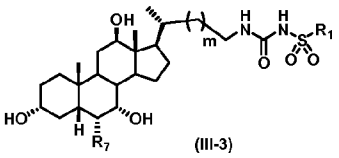
**4.** Forbindelsen ifølge patentkrav 1, representert ved en av formlene (III-1) til (III-12), eller et farmasøytisk akseptabelt salt eller ester derav, hvori $R_1$, $R_7$, $R_{10}$ og m er som definert i patentkrav 1:



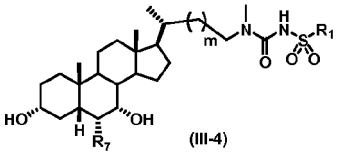
(III-1)



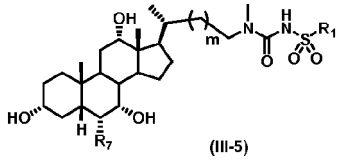
(III-2)



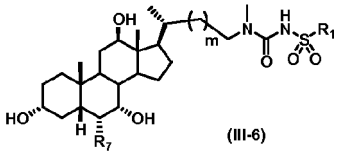
(III-3)



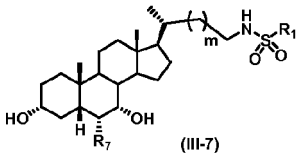
(III-4)



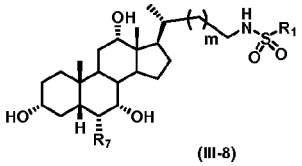
(III-5)



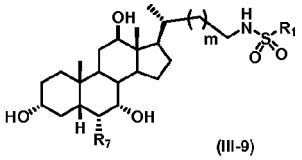
(III-6)



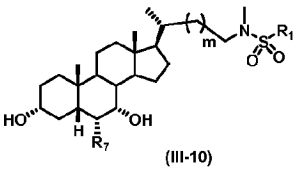
(III-7)



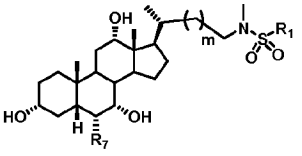
(III-8)



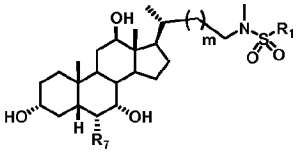
(III-9)



(III-10)

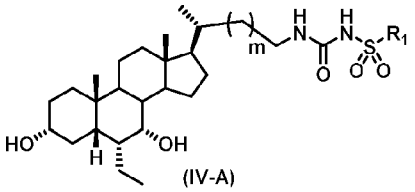


(III-11)

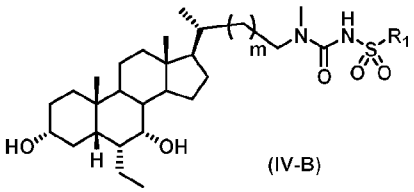


(III-12)

**5.** Forbindelsen ifølge patentkrav 1, representert ved formel IV-A eller formel IV-B eller et farmasøytisk akseptabelt salt eller ester derav:



(IV-A)

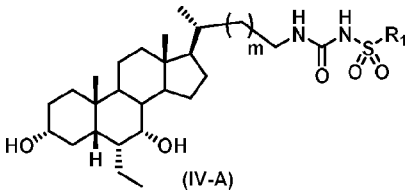


(IV-B)

hvori $R_1$ og m er som tidligere definert i patentkrav 1.

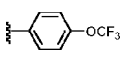
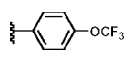
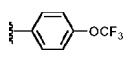
**6.** Forbindelsen ifølge patentkrav 1, valgt fra:

(A) Forbindelser ifølge formel IV-A hvori $R_1$ og m er avgrensbar for hver forbindelse i Tabell 1:

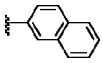
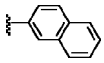
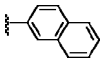



(IV-A)

**Tabell 1**

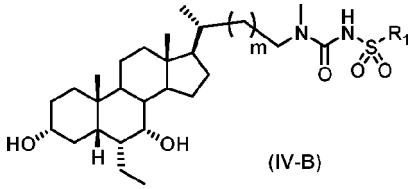
| Forbindelse | M | $R_1$ | Forbindelse | m | $R_1$ | Forbindelse | m | $R_1$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 | Metyl | 26 | 1 | Metyl | 51 | 2 | Metyl |
| 2 | 0 | Etyl | 27 | 1 | Etyl | 52 | 2 | Etyl |
| 3 | 0 | Klorprofam | 28 | 1 | Klorprofam | 53 | 2 | Klorprofam |
| 4 | 0 | Butyl | 29 | 1 | Butyl | 54 | 2 | Butyl |
| 5 | 0 | t-Butyl | 30 | 1 | t-Butyl | 55 | 2 | t-Butyl |
| 6 | 0 | Propyl | 31 | 1 | Propyl | 56 | 2 | Propyl |
| 7 | 0 | Benzyl | 32 | 1 | Benzyl | 57 | 2 | Benzyl |
| 8 | 0 | Vinyl | 33 | 1 | Vinyl | 58 | 2 | Vinyl |
| 9 | 0 | Allyl | 34 | 1 | Allyl | 59 | 2 | Allyl |
| 10 | 0 | CF3 | 35 | 1 | CF3 | 60 | 2 | CF3 |
| 11 | 0 |  | 36 | 1 |  | 61 | 2 |  |
| 12 | 0 |  | 37 | 1 |  | 62 | 2 |  |
| 13 | 0 |  | 38 | 1 |  | 63 | 2 |  |
| 14 | 0 |  | 39 | 1 |  | 64 | 2 |  |
| 15 | 0 |  | 40 | 1 |  | 65 | 2 |  |
| 16 | 0 |  | 41 | 1 |  | 66 | 2 |  |
| 17 | 0 | NH2 | 42 | 1 | NH2 | 67 | 2 | NH2 |
| 18 | 0 |  | 43 | 1 |  | 68 | 2 |  |
| 19 | 0 |  | 44 | 1 |  | 69 | 2 |  |
| 20 | 0 |  | 45 | 1 |  | 70 | 2 |  |

(fortsatt)

| Forbindelse | M | $R_1$ | Forbindelse | m | $R_1$ | Forbindelse | m | $R_1$ |
|---|---|---|---|---|---|---|---|---|
| 21 | 0 |  | 46 | 1 |  | 71 | 2 |  |
| 22 | 0 |  | 47 | 1 |  | 72 | 2 |  |
| 23 | 0 |  | 48 | 1 |  | 73 | 2 |  |
| 24 | 0 |  | 49 | 1 |  | 74 | 2 |  |
| 25 | 0 | F | 50 | 1 | F | 75 | 2 | F |

Og

(B) forbindelser ifølge formel IV-B hvori $R_1$ og m er avgrensbar for hvert eksempel i Tabell 2:

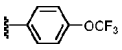
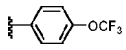
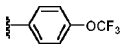
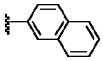
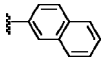
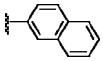



(IV-B)

**Tabell 2**

| Forbindelse | M | $R_1$ | Forbindelse | m | $R_1$ | Forbindelse | m | $R_1$ |
|---|---|---|---|---|---|---|---|---|
| 76 | 0 | Metyl | 101 | 1 | Metyl | 126 | 2 | Metyl |
| 77 | 0 | Etyl | 102 | 1 | Etyl | 127 | 2 | Etyl |
| 78 | 0 | Klorprofam | 103 | 1 | Klorprofam | 128 | 2 | Klorprofam |
| 79 | 0 | Butyl | 104 | 1 | Butyl | 129 | 2 | Butyl |
| 80 | 0 | t-Butyl | 105 | 1 | t-Butyl | 130 | 2 | t-Butyl |
| 81 | 0 | Propyl | 106 | 1 | Propyl | 131 | 2 | Propyl |
| 82 | 0 | Benzyl | 107 | 1 | Benzyl | 132 | 2 | Benzyl |
| 83 | 0 | Vinyl | 108 | 1 | Vinyl | 133 | 2 | Vinyl |
| 84 | 0 | Allyl | 109 | 1 | Allyl | 134 | 2 | Allyl |
| 85 | 0 | CF3 | 110 | 1 | CF3 | 135 | 2 | CF3 |
| 86 | 0 |  | 111 | 1 |  | 136 | 2 |  |
| 87 | 0 |  | 112 | 1 |  | 137 | 2 |  |
| 88 | 0 |  | 113 | 1 |  | 138 | 2 |  |

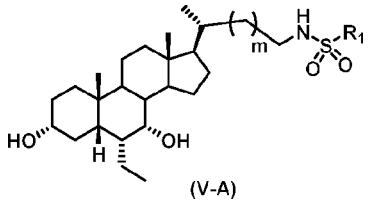
(fortsatt)

| Forbindelse | M | R1 | Forbindelse | m | R1 | Forbindelse | m | R1 |
|---|---|---|---|---|---|---|---|---|
| 89 | 0 |  | 114 | 1 |  | 139 | 2 |  |
| 90 | 0 |  | 115 | 1 |  | 140 | 2 |  |
| 91 | 0 |  | 116 | 1 |  | 141 | 2 |  |
| 92 | 0 | NH2 | 117 | 1 | NH2 | 142 | 2 | NH2 |
| 93 | 0 |  | 118 | 1 |  | 143 | 2 |  |
| 94 | 0 |  | 119 | 1 |  | 144 | 2 |  |
| 95 | 0 |  | 120 | 1 |  | 145 | 2 |  |
| 96 | 0 |  | 121 | 1 |  | 146 | 2 |  |
| 97 | 0 |  | 122 | 1 |  | 147 | 2 |  |
| 98 | 0 |  | 123 | 1 |  | 148 | 2 |  |
| 99 | 0 |  | 124 | 1 |  | 149 | 2 |  |
| 100 | 0 | F | 125 | 1 | F | 150 | 2 | F |

eller et farmasøytisk akseptabelt salt eller ester derav.

**7.** Forbindelsen ifølge patentkrav 1, valgt fra:

(A) Forbindelser ifølge formel V-A hvori $R_1$ og m er avgrensbar for hver forbindelse i Tabell 3:

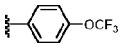
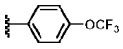
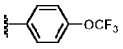
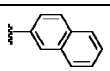
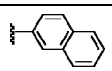
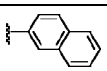



(V-A)

**Tabell 3**

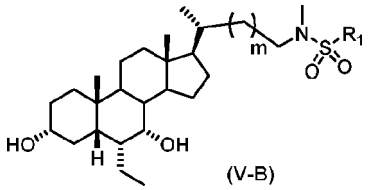
| Forbindelse | M | $R_1$ | Forbindelse | m | $R_1$ | Forbindelse | m | $R_1$ |
|---|---|---|---|---|---|---|---|---|
| 151 | 0 | Metyl | 176 | 1 | Metyl | 201 | 2 | Metyl |
| 152 | 0 | Etyl | 177 | 1 | Etyl | 202 | 2 | Etyl |
| 153 | 0 | Klorprofam | 178 | 1 | Klorprofam | 203 | 2 | Klorprofam |

(fortsatt)

| Forbindelse | M | R1 | Forbindelse | m | R1 | Forbindelse | m | R1 |
|---|---|---|---|---|---|---|---|---|
| 154 | 0 | Butyl | 179 | 1 | Butyl | 204 | 2 | Butyl |
| 155 | 0 | t-Butyl | 180 | 1 | t-Butyl | 205 | 2 | t-Butyl |
| 156 | 0 | Propyl | 181 | 1 | Propyl | 206 | 2 | Propyl |
| 157 | 0 | Benzyl | 182 | 1 | Benzyl | 207 | 2 | Benzyl |
| 158 | 0 | Vinyl | 183 | 1 | Vinyl | 208 | 2 | Vinyl |
| 159 | 0 | Allyl | 184 | 1 | Allyl | 209 | 2 | Allyl |
| 160 | 0 | $CF_3$ | 185 | 1 | $CF_3$ | 210 | 2 | $CF_3$ |
| 161 | 0 |  | 186 | 1 |  | 211 | 2 |  |
| 162 | 0 |  | 187 | 1 |  | 212 | 2 |  |
| 163 | 0 |  | 188 | 1 |  | 213 | 2 |  |
| 164 | 0 |  | 189 | 1 |  | 214 | 2 |  |
| 165 | 0 |  | 190 | 1 |  | 215 | 2 |  |
| 166 | 0 |  | 191 | 1 |  | 216 | 2 |  |
| 167 | 0 | $NH_2$ | 192 | 1 | $NH_2$ | 217 | 2 | $NH_2$ |
| 168 | 0 |  | 193 | 1 |  | 218 | 2 |  |
| 169 | 0 |  | 194 | 1 |  | 219 | 2 |  |
| 170 | 0 |  | 195 | 1 |  | 220 | 2 |  |
| 171 | 0 |  | 196 | 1 |  | 221 | 2 |  |
| 172 | 0 |  | 197 | 1 |  | 222 | 2 |  |
| 173 | 0 |  | 198 | 1 |  | 223 | 2 |  |
| 174 | 0 |  | 199 | 1 |  | 224 | 2 |  |
| 175 | 0 | F | 200 | 1 | F | 225 | 2 | F |

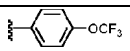
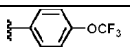
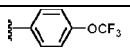
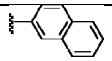
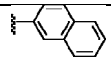
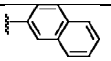
Og

(B) Forbindelser ifølge formel V-B hvori $R_1$ og m er avgrensbar for hver forbindelse i Tabell 4:




(V-B)

**Tabell 4**

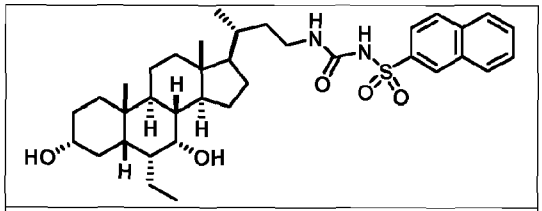
| Forbindelse | M | $R_1$ | Forbindelse | m | $R_1$ | Forbindelse | m | $R_1$ |
|---|---|---|---|---|---|---|---|---|
| 226 | 0 | Metyl | 251 | 1 | Metyl | 276 | 2 | Metyl |
| 227 | 0 | Etyl | 252 | 1 | Etyl | 277 | 2 | Etyl |
| 228 | 0 | Klorprofam | 253 | 1 | Klorprofam | 278 | 2 | Klorprofam |
| 229 | 0 | Butyl | 254 | 1 | Butyl | 279 | 2 | Butyl |
| 230 | 0 | t-Butyl | 255 | 1 | t-Butyl | 280 | 2 | t-Butyl |
| 231 | 0 | Propyl | 256 | 1 | Propyl | 281 | 2 | Propyl |
| 232 | 0 | Benzyl | 257 | 1 | Benzyl | 282 | 2 | Benzyl |
| 233 | 0 | Vinyl | 258 | 1 | Vinyl | 283 | 2 | Vinyl |
| 234 | 0 | Allyl | 259 | 1 | Allyl | 284 | 2 | Allyl |
| 235 | 0 | $CF_3$ | 260 | 1 | $CF_3$ | 285 | 2 | $CF_3$ |
| 236 | 0 |  | 261 | 1 |  | 286 | 2 |  |
| 237 | 0 |  | 262 | 1 |  | 287 | 2 |  |
| 238 | 0 |  | 263 | 1 |  | 288 | 2 |  |
| 239 | 0 |  | 264 | 1 |  | 289 | 2 |  |
| 240 | 0 |  | 265 | 1 |  | 290 | 2 |  |
| 241 | 0 |  | 266 | 1 |  | 291 | 2 |  |
| 242 | 0 | NH2 | 267 | 1 | NH2 | 292 | 2 | NH2 |
| 243 | 0 |  | 268 | 1 |  | 293 | 2 |  |
| 244 | 0 |  | 269 | 1 |  | 294 | 2 |  |
| 245 | 0 |  | 270 | 1 |  | 295 | 2 |  |
| 246 | 0 |  | 271 | 1 |  | 296 | 2 |  |
| 247 | 0 |  | 272 | 1 |  | 297 | 2 |  |
| 248 | 0 |  | 273 | 1 |  | 298 | 2 |  |

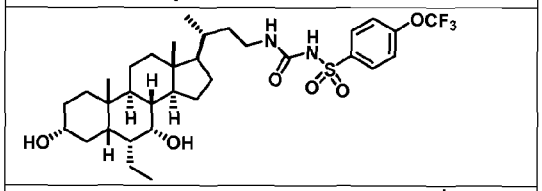
(fortsatt)

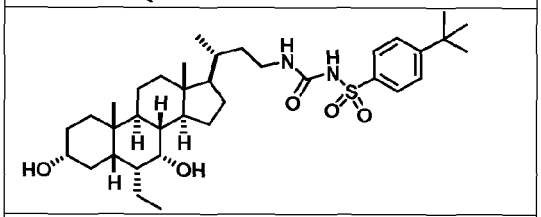
| Forbindelse | M | R1 | Forbindelse | m | R1 | Forbindelse | m | R1 |
|---|---|---|---|---|---|---|---|---|
| 249 | 0 |  | 274 | 1 |  | 299 | 2 |  |
| 250 | 0 | F | 275 | 1 | F | 300 | 2 | F |

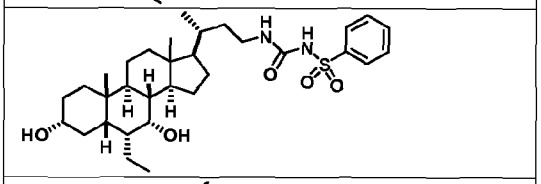
eller et farmasøytisk akseptabelt salt eller ester derav.

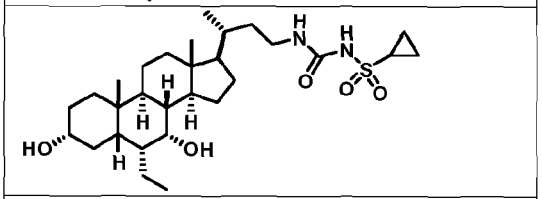
**8.** En forbindelse ifølge patentkrav 1, valgt fra forbindelsene angitt nedenfor, eller et farmasøytisk akseptabelt salt eller ester derav:

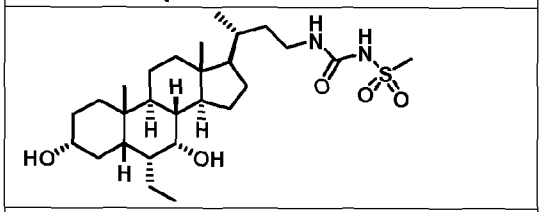


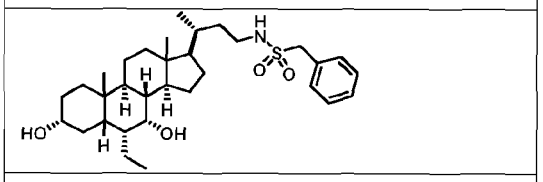


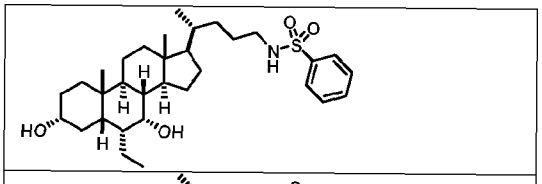


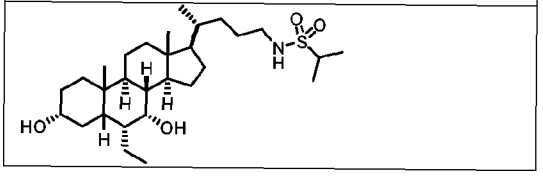


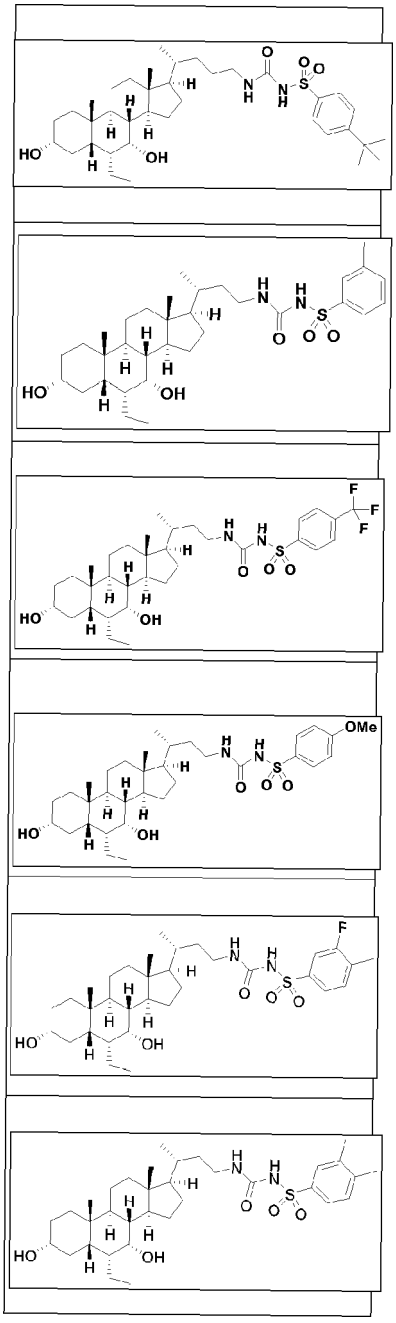


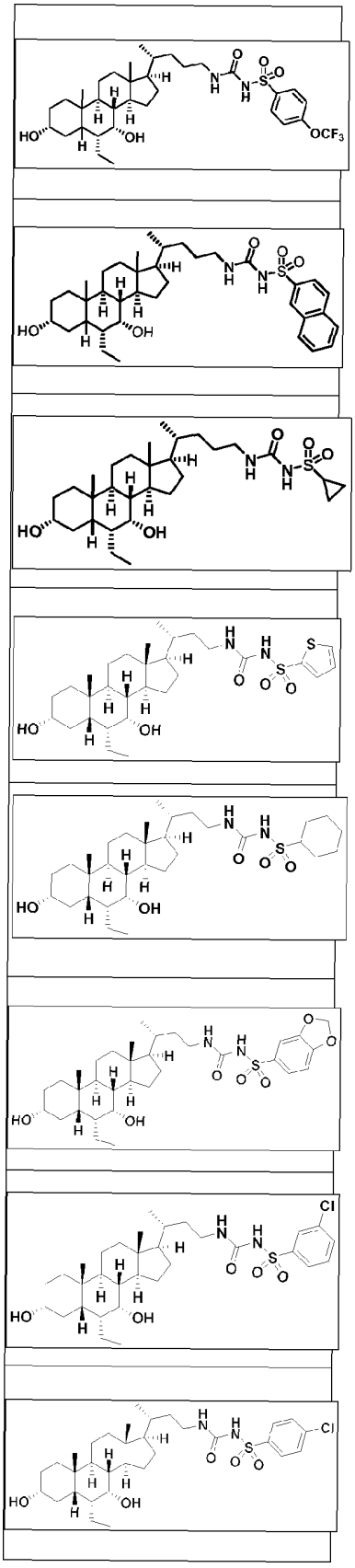


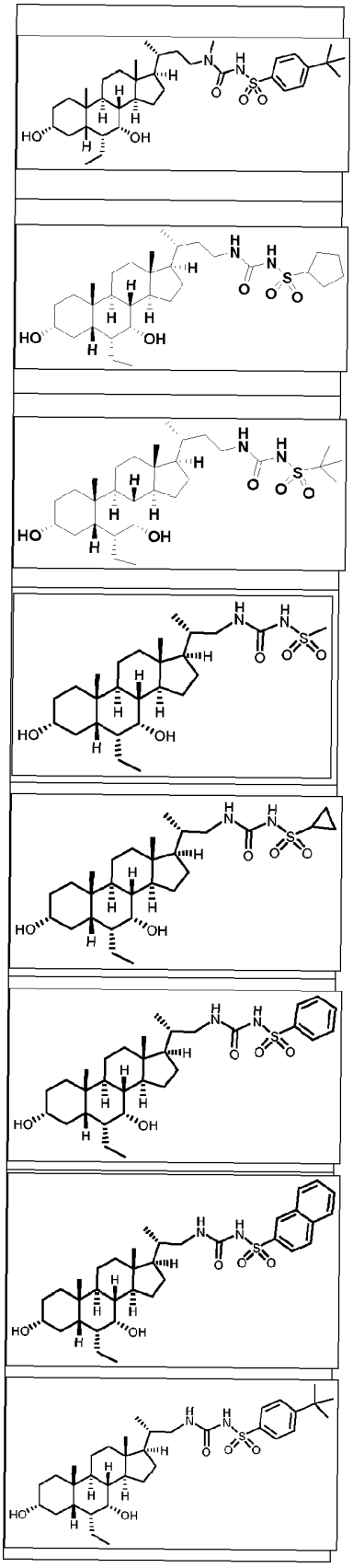


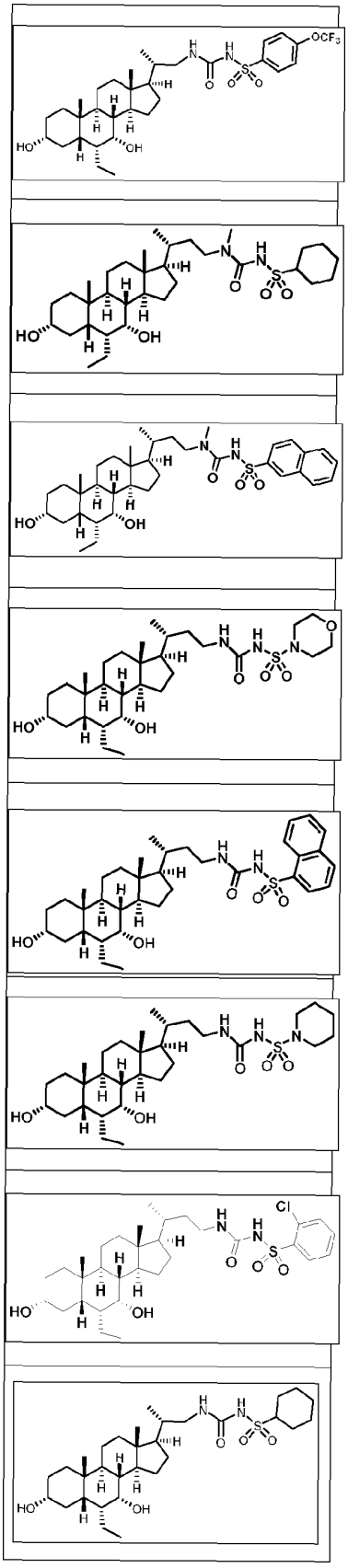


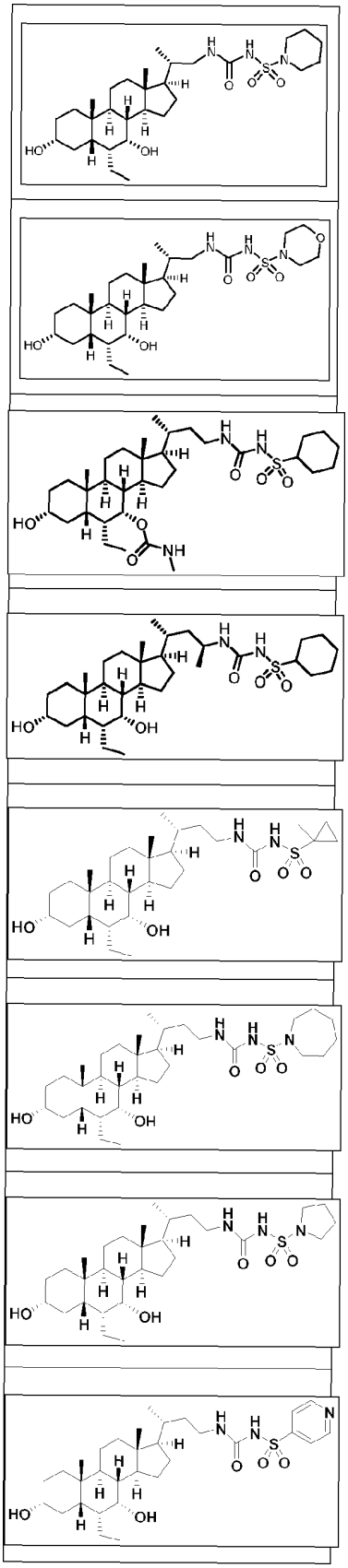


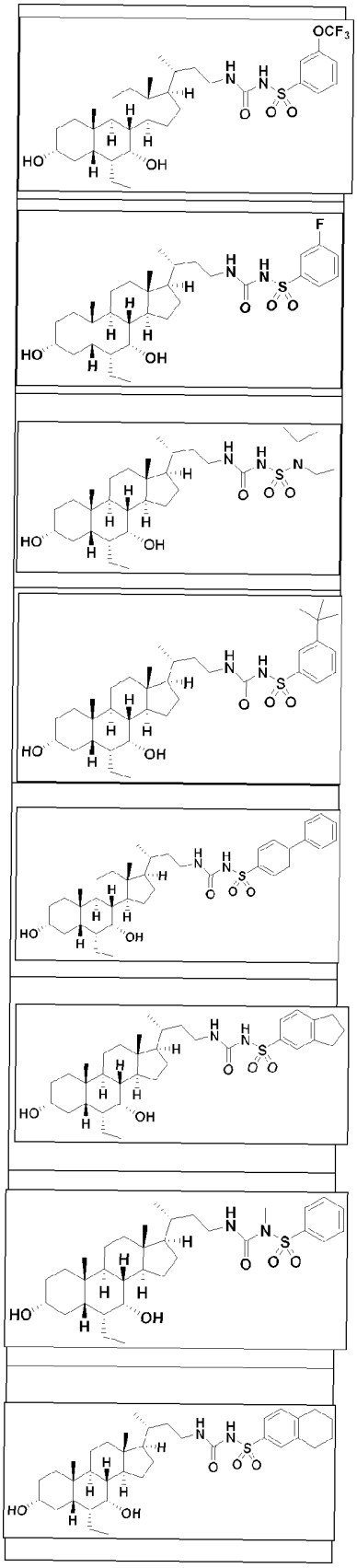


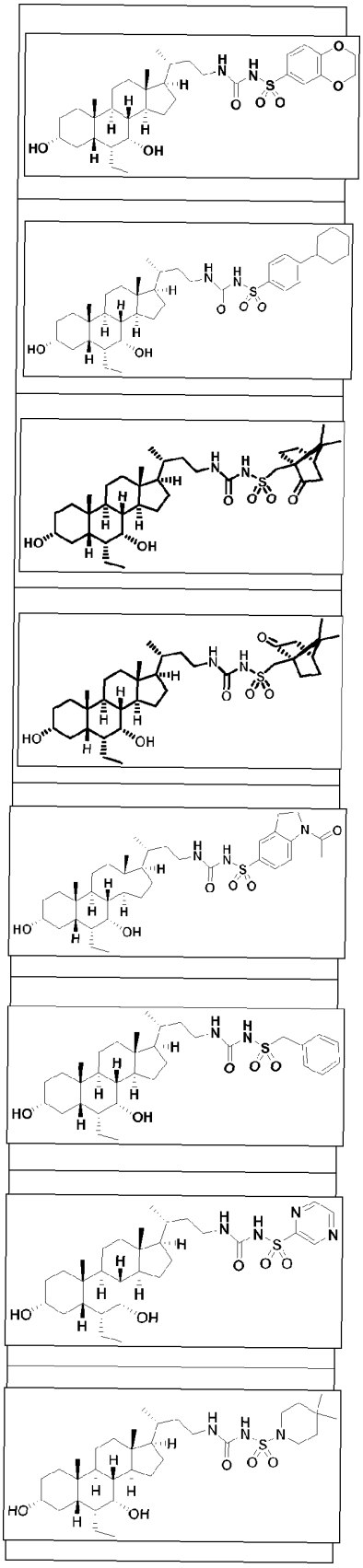


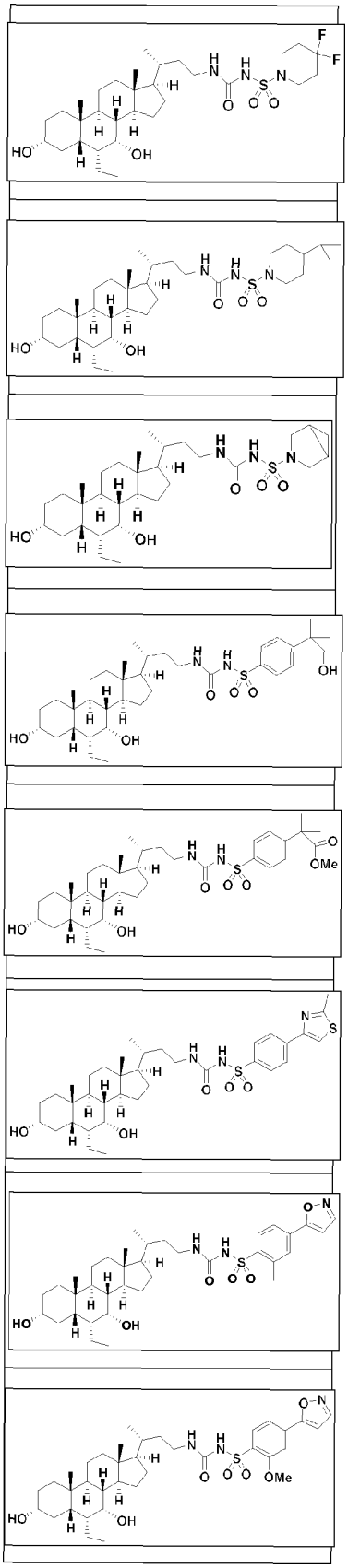


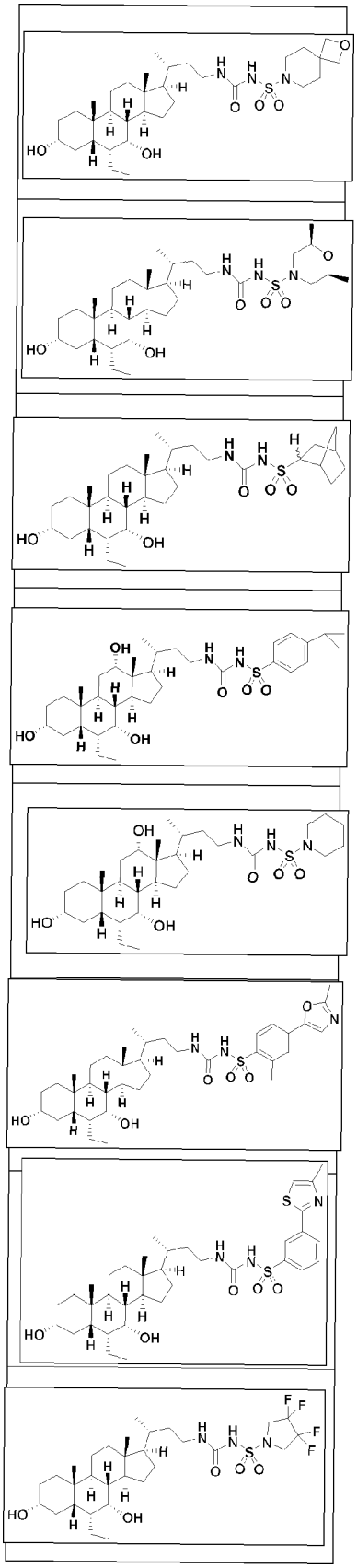


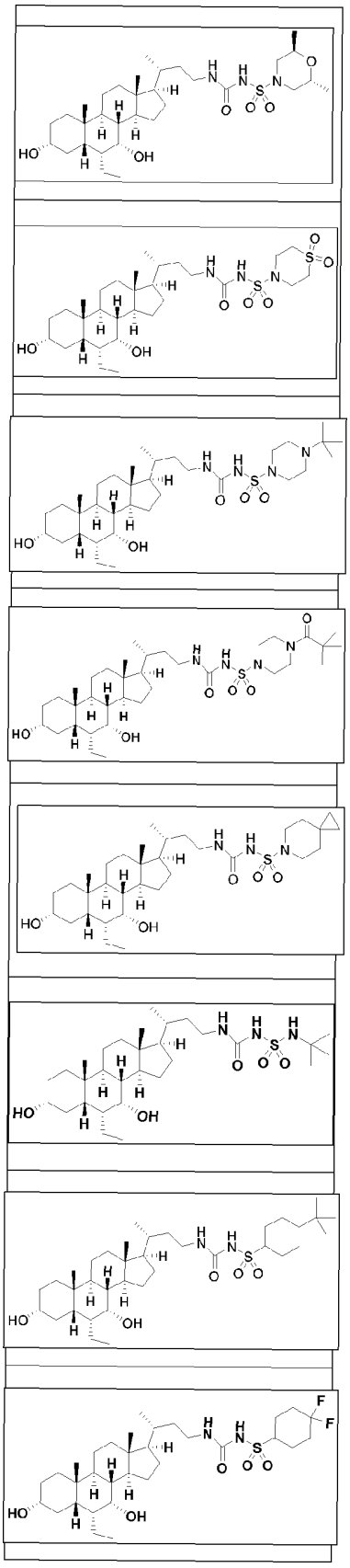


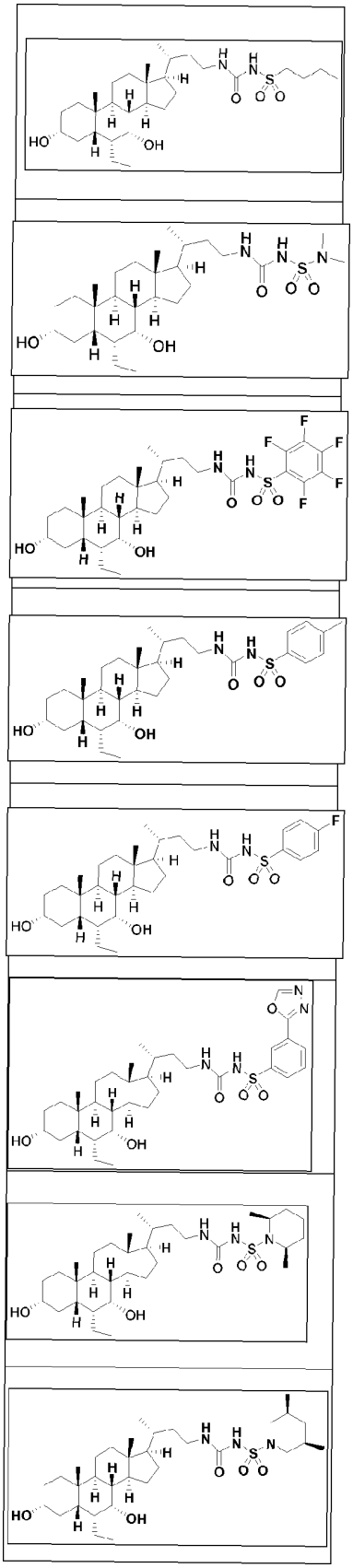


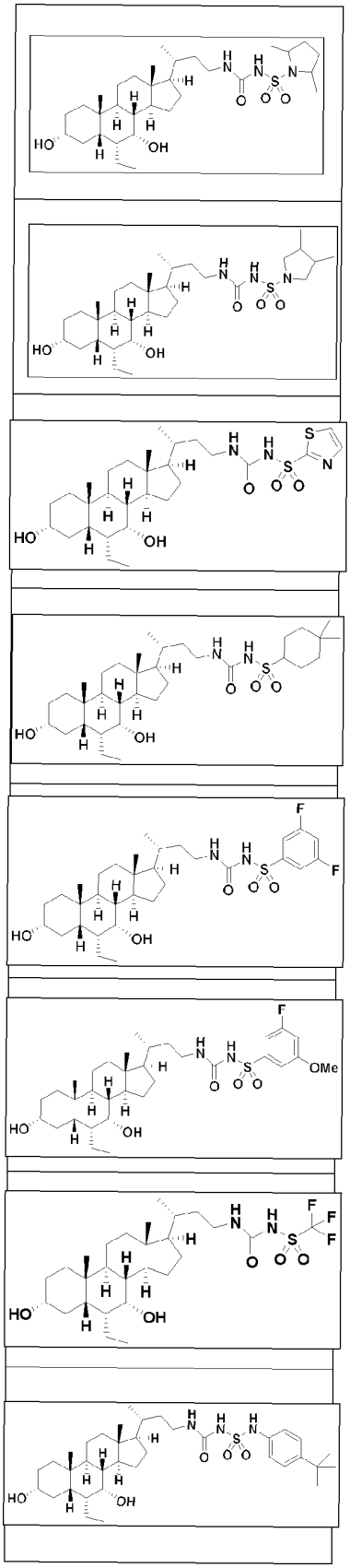


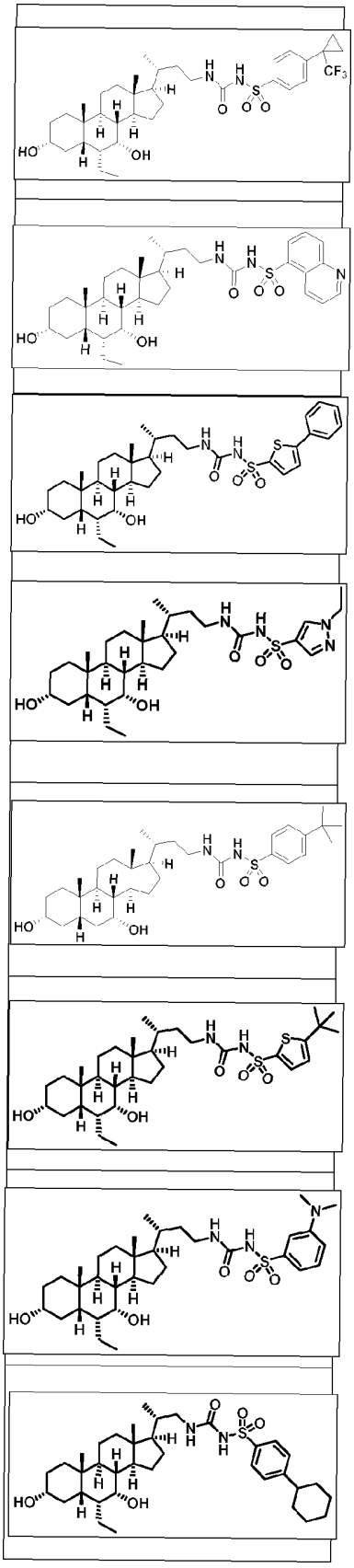


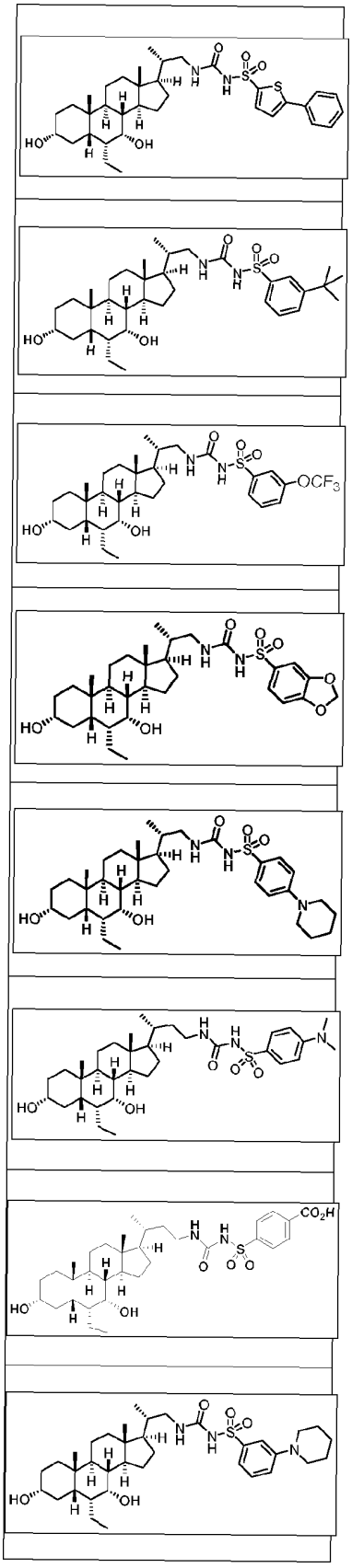


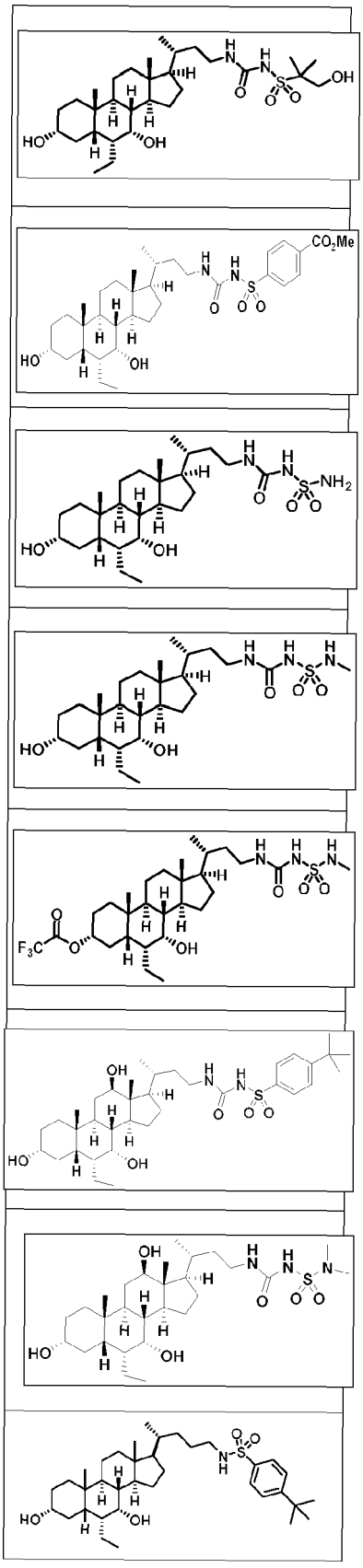


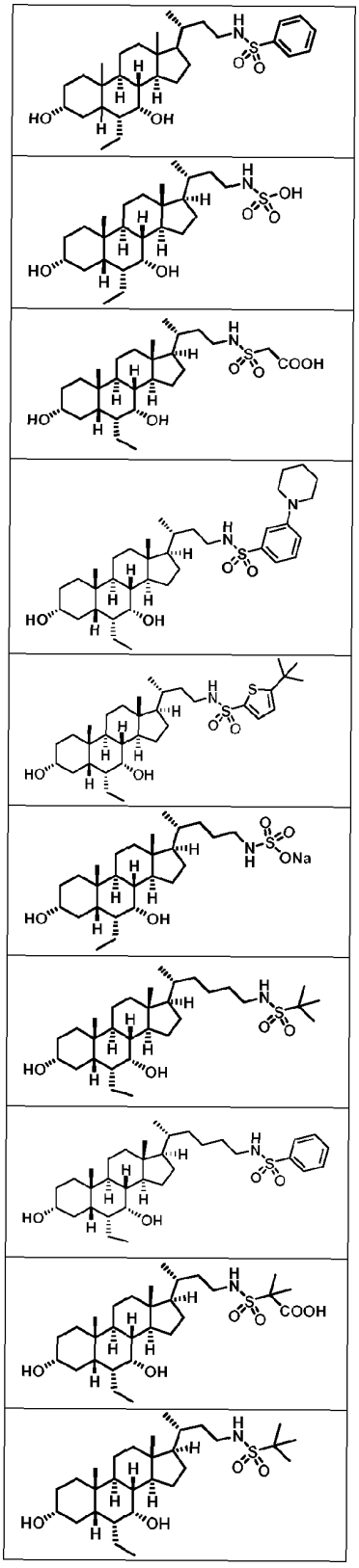


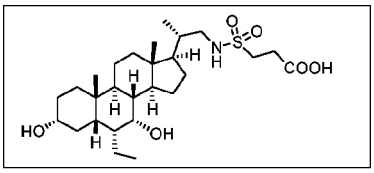


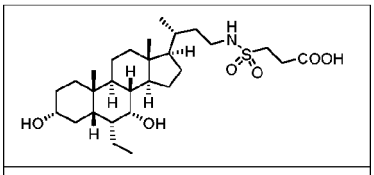


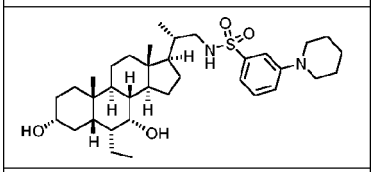


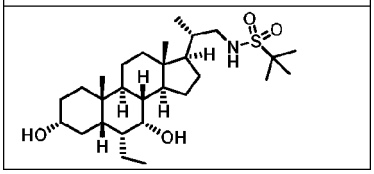




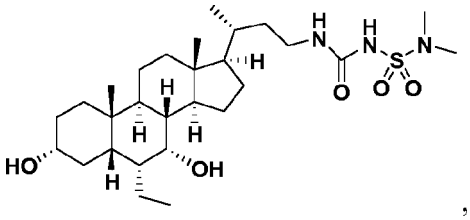








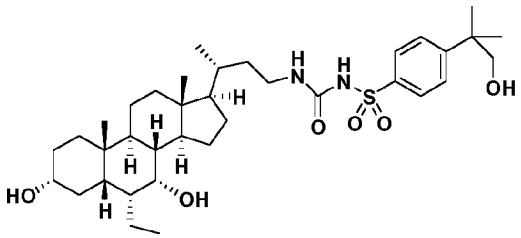
**9.** Forbindelsen ifølge patentkrav 8, som har strukturen



,

eller et farmasøytisk akseptabelt salt eller ester derav.

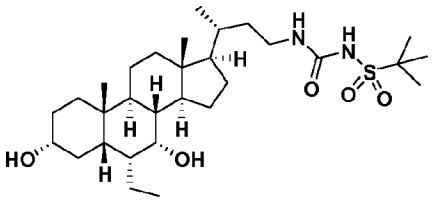
**10.** Forbindelsen ifølge patentkrav 8, som har strukturen



,

eller et farmasøytisk akseptabelt salt eller ester derav.

**11.** Forbindelsen ifølge patentkrav 8, som har strukturen



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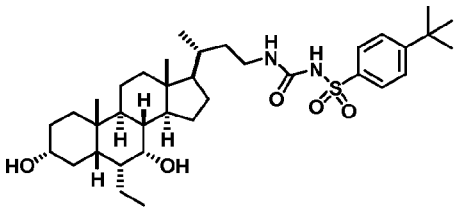
eller et farmasøytisk akseptabelt salt eller ester derav.

**12.** Forbindelsen ifølge patentkrav 8, som har strukturen



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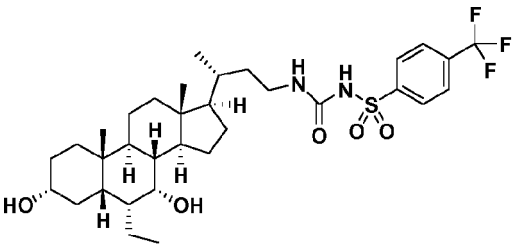
eller et farmasøytisk akseptabelt salt eller ester derav.

**13.** Forbindelsen ifølge patentkrav 8, som har strukturen



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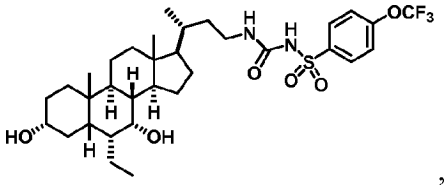
eller et farmasøytisk akseptabelt salt eller ester derav.

**14.** Forbindelsen ifølge patentkrav 8, som har strukturen



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eller et farmasøytisk akseptabelt salt eller ester derav.

**15.** Forbindelsen ifølge hvilket som helst av patentkravene 1 til 14 for anvendelse for å forhindre eller behandle en FXR-mediert sykdom eller tilstand.

**16.** Forbindelsen for anvendelse ifølge patentkrav 15, hvor den FXR-medierte sykdommen eller tilstanden er valgt fra gruppen bestående av kronisk leversykdom, gastrointestinal sykdom, nyresykdom, kardiovaskulær sykdom og metabolsk sykdom.

**17.** Forbindelsen for anvendelse ifølge patentkrav 16, hvori den FXR-medierte sykdommen eller tilstanden er en kronisk leversykdom valgt fra gruppen bestående av primær biliær kolangitt, cerebrotendinøs xantomatose, primær skleroserende kolangitt, medikamentindusert kolestase, intrahepatisk svangerskapskolestase, parenteral ernæringsassosiert kolestase, bakteriell gjengroing eller sepsisassosiert kolestase, autoimmun hepatitt, kronisk viral hepatitt, alkoholisk leversykdom, ikke-alkoholisk fettleversykdom, ikke-alkoholisk steatohepatitt, levertransplantasjon assosiert transplantat versus vertssykdom, levende donortransplantasjon leverregenerering, medfødt leverfibrose, koledokolitiase, granulomatøs leversykdom, intra- eller ekstrahepatisk malignitet, Sjøgrens syndrom, sarkoidose, Wilsons sykdom, Gauchers sykdom, hemokromatose og alfa 1-antitrypsinmangel.

**18.** Forbindelsen for anvendelse ifølge patentkrav 16, hvor den FXR-medierte sykdommen eller tilstanden er

(a) en nyresykdom valgt fra gruppen bestående av diabetisk nefropati, fokal segmentell

glomerulosklerose, hypertensiv nefrosklerose, kronisk glomerulonefritt, kronisk transplantasjonsglomerulopati, kronisk interstitiell nefritt og polycystisk nyresykdom;

(b) en hjerte- og karsykdom valgt fra gruppen bestående av aterosklerose, arteriosklerose, dyslipidemi, hyperkolesterolemi og hypertriglyseridemi; eller

(c) en metabolsk sykdom valgt fra gruppen bestående av insulinresistens, diabetes type 1 og type 2 og fedme.

**19.** Forbindelsen for anvendelse ifølge patentkrav 15, karakterisert ved at den FXR-medierte sykdommen eller tilstanden er ikke-alkoholisk fettleversykdom, ikke-alkoholisk steatohepatitt eller primær biliær kolangitt.

**20.** En farmasøytisk sammensetning som omfatter forbindelsen ifølge hvilket som helst av patentkravene 1-14 og en farmasøytisk akseptabel bærer.