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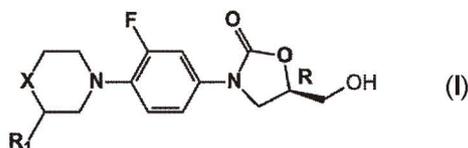
### (54) DERIVAT DE OXAZOLIDINONĂ CU ACTIVITATE ANTIMICROBIANĂ

#### (57) Rezumat:

Invenția se referă la derivați de oxazolidinonă cu activitate antimicrobiană, aceștia fiind utilizați în tratamentul infecțiilor cauzate de microorganisme gram-pozitive. Derivații de oxazolidinonă, conform invenției, sunt definiți de formula generală I:

în care  $R_1$  este metil sau hidrogen, X este oxigen sau CHR, și R este hidrogen sau metil.

Revendicări: 4

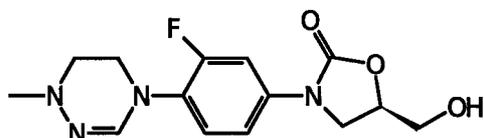




## Derivat de oxazolidinona cu activitate antimicrobiana

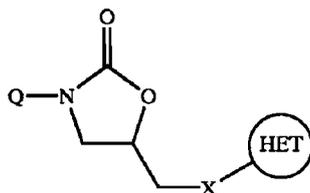
Inventia se refera la derivati de oxazolidinone si procedeu de preparare a acestora, utilizati ca substante cu activitate antimicrobiana fata de microorganisme Gram-pozitive (incluzand MRSA), Gram-negative anaerobe si *Mycobacterium tuberculosis*, sau ca intermediari in sinteza altor medicamente cu structura oxazolidinonica cu activitate antimicrobiana.

Se cunoaste din US 2013/0005967 un derivat de oxazolidinona (LCB01-0371) cu activitate antimicrobiana cu urmatoarea formula chimica



LCB01-0371

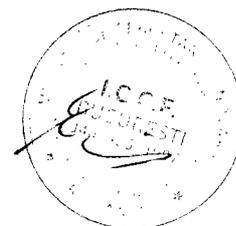
De asemenea se cunosc din US6617339 compusi cu urmatoarea formula:



in care substituentii au diferite semnificatii si care prezinta activitate antibacteriana

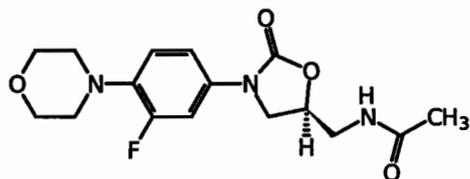
Problema tehnica pe care o rezolva inventia consta in identificarea unor derivati cu structura oxazolidinonica cu actiune antimicrobiana, cu randamente ridicate, printr-o tehnologie curata si usor accesibila.

Dezvoltarea rezistentei bacteriene la antibioticele utilizate in prezent in terapeutica medicala este o problema care afecteaza starea de sanatate a populatiei la nivel mondial. O preocupare deosebita o reprezinta bolile infectioase cauzate de bacterii Gram-pozitive cum ar fi :



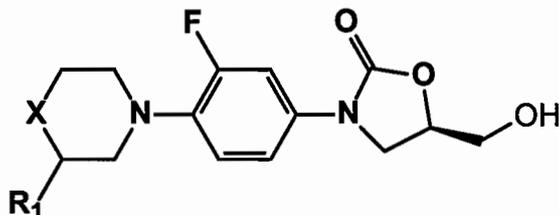
*Staphylococcus aureus* metilino rezistent (MRSA), *Streptococcus pneumoniae* penicilino rezistent (PRSP), *Enterococcus faecalis* vancomicino rezistent (VREF).

Succesul obtinut dupa descoperirea linezolidului [J. Med. Chem. 1996,39,673-679] a impulsat eforturile de a descoperi noi agenti cu activitate antimicrobiana din clasa oxazolidinonelor.



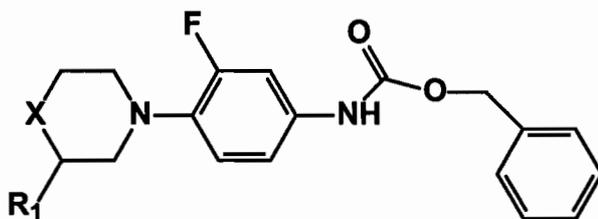
Linezolid

Prezenta inventie largeste gama derivatilor cu activitate antimicrobiana cu compusi care corespund formulei generale I:



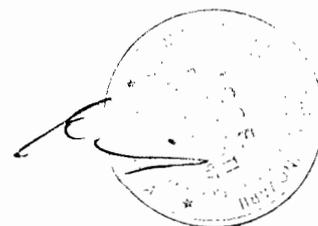
I

in care  $R_1$  este metil sau hidrogen, X este oxigen sau CHR iar R este hidrogen sau metil; si cu compusi care corespund formulei generale II:



II

in care  $R_1$  este metil sau hidrogen, X este oxigen sau CHR iar R este hidrogen sau metil.

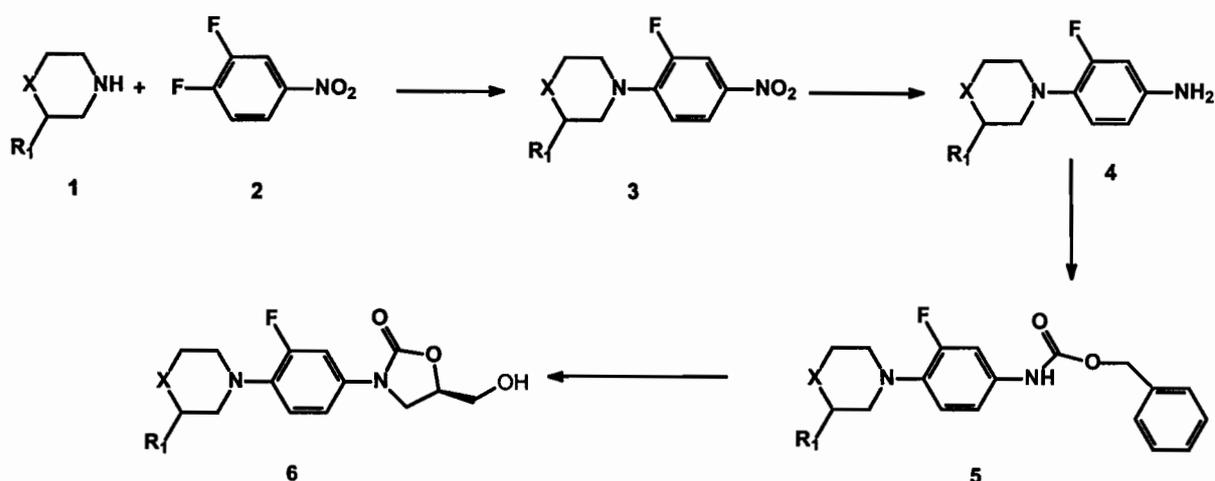


Procedeul de obtinere a derivatilor de oxazolidinona este reprezentat prin schema de reactii 1, schema ce implica uratoarele faze:

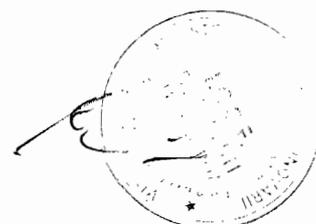
- Faza de obtinere nitroderivatilor (3) prin reactia 3,4-difluoro-nitrobenzenului (2) cu un heterociclu (1) in mediu de metanol la temperatura de 50°C, timp de 5 ore;
- Faza de obtinere a anilinei substituie (4) printr-o reactie de reducere;
- Faza de obtinere a carbamatilor (5) prin reactia anilinei substituie (4) cu cloroformiat de benzil;
- Faza de obtinere a alcoolilor (6) prin reactia carbamatului (5) cu (R) glicidil butiric, in prezenta de *n*-butil litiu, la -78°C, in mediu de tetrahidrofuran anh. si sub atmosfera de argon .

Prin aplicarea inventiei se obtin umatoarele avantaje:

- obtinerea de derivati de oxazolidinona cu formula I cu randamente ridicate, printr-o tehnologie curata si usor accesibila;
- obtinerea de derivati de oxazolidinona cu formula I, compusi cu activitate antimicrobiana fata de microorganisme Gram-pozitive, conform studiului experimental de testare a activitatii antimicrobiene;
- obtinerea de derivati de oxazolidinona cu formula I, intermediari cheie in sinteza unor compusi cu activitate antimicrobiana.



Schema de reactie 1

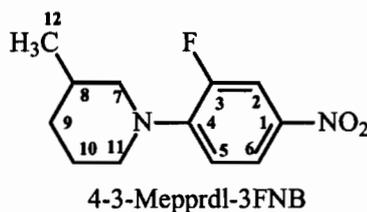


Inventia este ilustrata in continuare prin 4 exemple nelimitative:

### Exemplul 1

#### Sinteza 1-(2-fluoro-4-nitrofenil)-3-metil-piperidina

0,03 Moli (5 g) 3,4-difluoronitrobenzen se dizolva in 50 ml metanol, dupa care se adauga 0,075 moli (7.15 g) 3-metil-piperidina. Masa de reactie se mentine la temperatura de 50<sup>0</sup> timp de 5 ore, dupa care se raceste la 20<sup>0</sup>C si se concentreaza la evaporatorul rotativ. Reziduul obtinut se dizolva in 50 ml acetat de etil. Solutia obtinuta se spala de doua ori cu cate 50 ml de apa si apoi cu 50 ml solutie saturata de clorura de sodiu. Stratul organic separat se anhidrizeaza pe sulfat de sodiu anhidru apoi se concentreaza la rotavaporul rotativ. Produsul brut obtinut se purifica pe coloana cromatografica utilizand toluen-acetat: 1:1; Se obtin 6,43 g 1-(2-fluoro-4-nitrofenil)-3-metil-piperidina sub forma de ulei, rand. 90 % .



<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ ppm, J Hz): 7.94(dd, 1H, H-6, J(F-H<sup>6</sup>)= 2.2, <sup>4</sup>J(H<sup>5</sup>-H<sup>6</sup>)=8.8); 7.85(dd, 1H, H-2, <sup>4</sup>J(H<sup>2</sup>-H<sup>6</sup>)=2.5, <sup>4</sup>J(F-H<sup>2</sup>)=13.2); 6.90(t, 1H, H-5, J(F-H<sup>5</sup>)= <sup>3</sup>J(H<sup>5</sup>-H<sup>6</sup>)=8.8); 3.27(m, 4H, 2H-7, 2H-11, syst. A<sub>2</sub>B<sub>2</sub>); 1.60. 1.80(m, 6H, 2H-8, 2H-9, 2H-10).

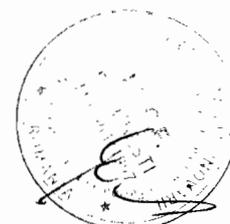
<sup>13</sup>C-NMR(CDCl<sub>3</sub>, δ ppm): 152.77(d, C-3, J(F-C<sup>3</sup>)=248.5 Hz); 146.46(d, C-1, <sup>3</sup>J(F-C<sup>1</sup>)=7.4 Hz); 139.56(d, C-4, J(F-C<sup>4</sup>)=8.0 Hz); 121.06(d, C-5, <sup>3</sup>J(F-C<sup>5</sup>)=2.9 Hz); 116.38(d, C-6, <sup>4</sup>J(F-C<sup>6</sup>)=4.3 Hz); 112.32(d, C-2, J(F-C<sup>2</sup>)=26.6 Hz); 51.00(d, C-7, C-11, <sup>4</sup>J(F-C<sup>7,11</sup>)=5.2 Hz); 25.81(C-8, C-10); 24.11(C-9).

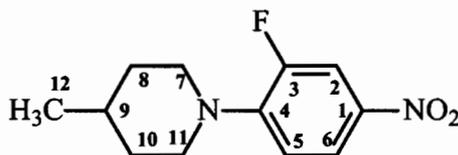
Prin acelasi procedeu au fost preparati umatorii compusi:

### Exemplul 1a

#### 1-(2-fluoro-4-nitrofenil)-4-metil-piperidina.

Produsul brut obtinut in urma prelucrarii masei de reactie se purifica pe coloana cromatografica utilizand toluen-acetat de etil: 3:1; Se obtin 6,07 g 1-(2-fluoro-4-nitrofenil)-4-metil-piperidina sub forma de ulei, rand. 85 %.





4-4-Mepprdl-3FNB

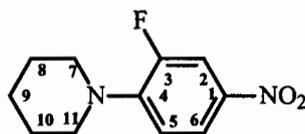
$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.94(dd, 1H, H-6,  $J(\text{F-H}^6)=2.2$ ,  $^4J(\text{H}^5-\text{H}^6)=8.8$ ); 7.85(dd, 1H, H-2,  $^4J(\text{H}^2-\text{H}^6)=2.5$ ,  $^4J(\text{F-H}^2)=13.2$ ); 6.90(t, 1H, H-5,  $J(\text{F-H}^5)=^3J(\text{H}^5-\text{H}^6)=8.8$ ); 3.88(m, 4H, H-7, H-11); 2.87(m, 2H, H-7, H-11); 1.77(m, 2H, H-8, H-10); 1.60(m, 1H, H-9); 1.39(m, 2H, H-8, H-10); 1.00(d, 3H, H-12, 6.6).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 152.75(d, C-3,  $J(\text{F-C}^3)=247.8$  Hz); 146.26(d, C-1,  $^3J(\text{F-C}^1)=7.9$  Hz); 139.66(d, C-4,  $J(\text{F-C}^4)=8.9$  Hz); 121.05(d, C-5,  $^3J(\text{F-C}^5)=2.9$  Hz); 117.06(d, C-6,  $^4J(\text{F-C}^6)=4.5$  Hz); 112.50(d, C-2,  $J(\text{F-C}^2)=27.8$  Hz); 50.34(d, C-7, C-11,  $J(\text{F-C}^7)=5.1$  Hz); 34.02(C-8, C-10); 31.65(C-9); 21.79(C-12).

### Exemplul 1b

#### *1-(2-fluoro-4-nitrofenil)-piperidina.*

Produsul brut obtinut in urma prelucrarii masei de reactie se purifica pe coloana cromatografica utilizand toluen-acetat de etil : 1:1; Se obtin 6,25 g 1-(2-fluoro-4-nitrofenil)-piperidina sub forma de ulei, rand. 93 %.



4-pprdl-3FNB

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.94(dd, 1H, H-6,  $J(\text{F-H}^6)=2.2$ ,  $^4J(\text{H}^5-\text{H}^6)=8.8$ ); 7.85(dd, 1H, H-2,  $^4J(\text{H}^2-\text{H}^6)=2.5$ ,  $^4J(\text{F-H}^2)=13.2$ ); 6.90(t, 1H, H-5,  $J(\text{F-H}^5)=^3J(\text{H}^5-\text{H}^6)=8.8$ ); 3.27(m, 4H, 2H-7, 2H-11, syst.  $\text{A}_2\text{B}_2$ ); 1.60. 1.80(m, 6H, 2H-8, 2H-9, 2H-10).

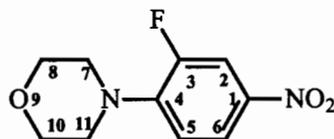
$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 152.77(d, C-3,  $J(\text{F-C}^3)=248.5$  Hz); 146.46(d, C-1,  $^3J(\text{F-C}^1)=7.4$  Hz); 139.56(d, C-4,  $J(\text{F-C}^4)=8.0$  Hz); 121.06(d, C-5,  $^3J(\text{F-C}^5)=2.9$  Hz); 116.38(d, C-6,  $^4J(\text{F-C}^6)=4.3$  Hz); 112.32(d, C-2,  $J(\text{F-C}^2)=26.6$  Hz); 51.00(d, C-7, C-11,  $^4J(\text{F-C}^{7,11})=5.2$  Hz); 25.81(C-8, C-10); 24.11(C-9).

### Exemplul 1c

#### *1-(2-fluoro-4-nitrofenil)-morfolina*

Produsul brut obtinut in urma prelucrarii masei de reactie se purifica prin recristalizare din metanol. Se obtin 6,38 g 1-(2-fluoro-4-nitrofenil)-morfolina, p.t. 108,5110,90C, rand. 94 %.





4-morfolinil-3FNB

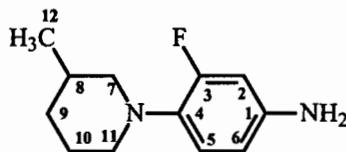
$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.99(dd, 1H, H-6,  $^4J(\text{F-H}^6)=2.2$ ,  $^4J(\text{H}^5-\text{H}^6)=8.8$ ); 7.91(dd, 1H, H-2,  $^4J(\text{H}^2-\text{H}^6)=2.5$ ,  $J(\text{F-H}^2)=13.2$ ); 6.93(t, 1H, H-5,  $^5J(\text{F-H}^5)=^3J(\text{H}^5-\text{H}^6)=8.8$ ); 3.88(m, 4H, H-8, H-10, syst.  $\text{A}_2\text{B}_2$ ); 3.29(m, 4H, H-7, H-11, syst.  $\text{A}_2\text{B}_2$ ).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 153.12(d, C-3,  $J(\text{F-C}^3)=249.7$  Hz); 145.49(d, C-1,  $^3J(\text{F-C}^1)=7.6$  Hz); 140.86(d, C-4,  $J(\text{F-C}^4)=9.8$  Hz); 120.99(d, C-5,  $^3J(\text{F-C}^5)=2.9$  Hz); 116.88(d, C-6,  $^4J(\text{F-C}^6)=4.0$  Hz); 112.61(d, C-2,  $J(\text{F-C}^2)=26.4$  Hz); 66.58(C-8, C-10); 49.89(d, C-7, C-11,  $J(\text{F-C}^{7,11})=5.2$  Hz).

## Exemplul 2

### Sinteza 3-Fluoro-4-(3-metil-piperidin-1-il)-anilinei

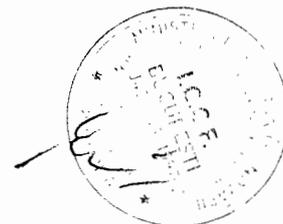
La o solutie formata din 0,03 Moli (7,12 g) 1-(2-fluoro-4-nitrofenil)-3-metil-piperidina si 100 ml acetona se adauga 0,09 Moli format de amoniu si 0,712 g Pd/C si se agita apoi la  $50^\circ\text{C}$  timp de 6 ore. La finalul regimului de reactie, pus in evidenta prin cromatografie pe strat subtire: sistem de eluare: tetrahidrofuran :dioxan:amoniac conc. : 20:60:30 (v/v/v), suport Silica gel 60F 254 (s-a umarit disparitia spotului cracteristic nitroderivatului), se raceste masa de reactie la temperatura camerei si se filtreaza. Solutia acetonica, care contine 3-Fluoro-4-(3-metil-piperidin-1-il)-anilina se concentreaza la vid redus si se dizolva in 50 ml acetat de etil. Solutia obtinuta se spala cu apa (2 x 50 ml) apoi cu 50 ml solutie saturata de clorura de sodium. Dupa anhidrizare pe sulfat de sodiu anh. se concentreaza la presiune redusa. Produsul brut obtinut se purifica pe coloana cromatografica utilizand toluen-acetat de etil: 3:1; Se obtin 5,0 g 3-Fluoro-4-(3-metil-piperidin-1-il)-anilina sub forma de ulei, rand. 80 %.



4-3-Mepr-3FNB-anilina

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 6.81(t, 1H, H-5,  $^4J(\text{F-H}^5)=^3J(\text{H}^5-\text{H}^6)=8.9$ ); 6.45÷6.35(m, 2H, H-2, H-6); 3.51(bs, 2H,  $\text{NH}_2$ ); 3.18(m, 4H, 2H-7, 2H-11); 2.44(m, 1H, H-8); 2.19(t, 1H, H-9); 1.83÷1.75(m, 3H, H-9, 2H-10); 0.92(d, 3H, H-12, 6.5).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 156.72(d, C-3,  $J(\text{F-C}^3)=244.7$  Hz); 142.21(d, C-1,  $^3J(\text{F-C}^1)=10.3$  Hz); 133.10(d, C-4,  $J(\text{F-C}^4)=10.3$  Hz); 120.58(d, C-5,  $^3J(\text{F-C}^5)=4.2$  Hz); 110.56(d, C-6,  $^4J(\text{F-C}^6)=4.0$  Hz).

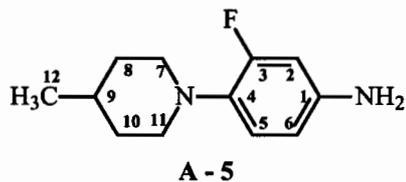


$C^6$ )=2.9 Hz); 103.87(d, C-2,  $J(F-C^2)$ =24.4 Hz); 60.17(d, C-7 or C-11,  $J(F-C^7)$ =2.5 Hz); 52.37(d, C-7 or C-11,  $J(F-C^7)$ =2.3 Hz); 32.81(C-9 or C-10); 31.43(C-8); 25.87(C-9 or C-10); 19.56(C-12).

### Exemplul 2a

#### 3-Fluoro-4-(4-metil-piperidin-1-il)-anilina

Produsul brut obtinut in urma prelucrării masei de reacție se purifica pe coloana cromatografica utilizand toluen-acetat de etil: 1:1; Se obtin 4,96 g 3-Fluoro-4-(4-metil-piperidin-1-il)-anilinei sub forma de ulei, rand. 79 %.



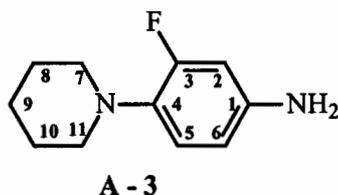
$^1H$ -NMR( $CDCl_3$ ,  $\delta$  ppm,  $J$  Hz): 6.81(t, 1H, H-5,  $^4J(F-H^5)$ =  $^3J(H^5-H^6)$ =9.1); 6.44÷6.35(m, 2H, H-2, H-6); 3.50(bs, 2H,  $NH_2$ , deuterable); 3.23(m, 2H, H-7<sub>eq</sub>, H-11<sub>eq</sub> or H-7<sub>ax</sub>, H-11<sub>ax</sub>); 2.57(m, 2H, H-7<sub>eq</sub>, H-11<sub>eq</sub> or H-7<sub>ax</sub>, H-11<sub>ax</sub>); 1.70(m, 2H, H-8<sub>eq</sub>, H-10<sub>eq</sub> or H-8<sub>ax</sub>, H-10<sub>ax</sub>); 1.38÷1.44(m, 3H, H-8<sub>eq</sub>, H-10<sub>eq</sub> or H-8<sub>ax</sub>, H-10<sub>ax</sub>, H-9); 0.98(d, 3H, H-12, 5.5).

$^{13}C$ -NMR( $CDCl_3$ ,  $\delta$  ppm): 156.72(d, C-3,  $J(F-C^3)$ =242.6 Hz); 142.25(d, C-1,  $^3J(F-C^1)$ =10.5 Hz); 132.99(d, C-4,  $J(F-C^4)$ =10.0 Hz); 120.52(d, C-5,  $^3J(F-C^5)$ =4.4 Hz); 110.56(d, C-6,  $^4J(F-C^6)$ =2.9 Hz); 103.38(d, C-2,  $J(F-C^2)$ =22.5 Hz); 52.31(d, C-7, C-11,  $J(F-C^{7,11})$ =2.0 Hz); 34.61(C-8, C-10); 30.57(C-9); 11.97(C-12).

### Exemplul 2b

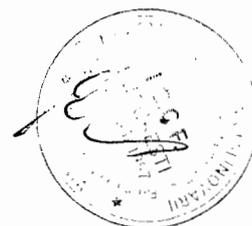
#### 3-Fluoro-4-(piperidin-1-il)-anilina

Produsul brut obtinut in urma prelucrării masei de reacție se purifica pe coloana cromatografica utilizand toluen-acetat: 1:1; Se obtin 5,4 g 3-Fluoro-4-(piperidin-1-il)-anilinei sub forma de ulei, rand. 92,7 %.



$^1H$ -NMR( $CDCl_3$ ,  $\delta$  ppm,  $J$  Hz): 6.81(t, 1H, H-5,  $^4J(F-H^5)$ =  $^3J(H^5-H^6)$ =9.2); 6.44÷6.35(m, 2H, H-2, H-6); 3.51(bs, 2H,  $NH_2$ , deuterable); 2.89(t, 4H, H-7, H-11, 5.5); 1.71(qv, 4H, H-8, H-10, 5.5); 1.52(m, 2H, H-9).

$^{13}C$ -NMR( $CDCl_3$ ,  $\delta$  ppm): 156.73(d, C-3,  $J(F-C^3)$ =242.5 Hz); 142.25(d, C-1,  $^3J(F-C^1)$ =10.2 Hz); 133.24(d, C-4,  $J(F-C^4)$ =9.5 Hz); 120.51(d, C-5,  $^3J(F-C^5)$ =4.5 Hz); 110.55(d, C-6,  $^4J(F-$

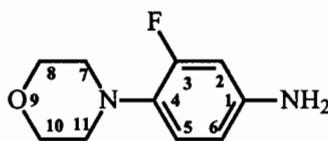


$C^6=3.4$  Hz); 103.86(d, C-2,  $J(F-C^2)=23.9$  Hz); 52.97(d, C-7 and C-11,  $^4J(F-C^{7,11})=2.5$  Hz); 26.31(C-8, C-10); 24.18(C-9).

### Exemplul 2c

#### 3-Fluoro-4-(morfolin-1-il)-anilina

Produsul brut obtinut in urma prelucrarii masei de reactie se purifica prin recristalizare din acetona. Se obtin 5,6g 3-Fluoro-4-(morfolin-1-il)-anilinei, p.t. 120,2-122,2°C, rand. 95 %.



4-morfolinil-3FNB-anilina

$^1H$ -NMR( $CDCl_3$ ,  $\delta$  ppm,  $J$  Hz): 6.79(t, 1H, H-5,  $^4J(F-H^5)=^3J(H^5-H^6)=9.2$ ); 6.46÷6.38(m, 2H, H-2, H-6); 3.84(m, 4H, H-8, H-10, syst.  $A_2B_2$ ); 2.95(m, 4H, H-7, H-11, syst.  $A_2B_2$ ).

$^{13}C$ -NMR( $CDCl_3$ ,  $\delta$  ppm): 156.70(d, C-3,  $J(F-C^3)=244.8$  Hz); 143.20(d, C-1,  $^3J(F-C^1)=10.6$  Hz); 131.32(d, C-4,  $J(F-C^4)=10.0$  Hz); 120.18(d, C-5,  $^3J(F-C^5)=4.6$  Hz); 110.56(d, C-6,  $^4J(F-C^6)=2.8$  Hz); 103.73(d, C-2,  $J(F-C^2)=23.5$  Hz); 67.08(C-8, C-10); 51.72(d, C-7, C-11,  $J(F-C^{7,11})=2.0$  Hz).

### Exemplul 3

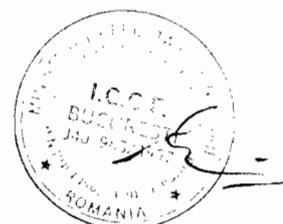
#### Sinteza N-Benziloxicarbonil-3-fluoro-4-(3-metil-piperidinil)-anilinei

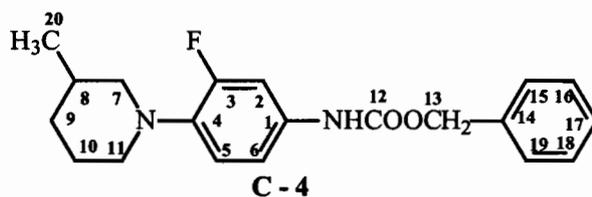
Peste un amestec format din 0,027 moli (5,32g) 3-Fluoro-4-(3-metil-piperidin-1-il)-anilina, 0,065 moli (5,4 g) carbonat acid de sodiu, 100 ml acetona si 50 ml apa , racit la 0-5°C, se aduga prin picurare 0,033 moli (5,63 g) cloroformiat de benzil. Dupa adaugarea intregii cantitati de cloroformiat de benzil, se ridica temperatura masei de reactie la temperatura camerei si se agita in continuare la aceeasi temperatura timp de 4 ore. Apoi se toarna masa de reactie peste un amestec format din apa si gheata. Dupa 6 ore se filtreaza precipitatul format. Dupa spalare cu apa si uscare s-au obtinut 8,13 g, spot unic (CSS: sistem de eluare: tetrahidrofuran :dioxan:amoniac conc. : 20:60:30 (v/v/v), suport Silica gel 60F 254 ), rand. 88%, p.t. 109,3-111,6°C.

$C_{20}H_{23}FN_2O_2$ : M= 342,41 g/mol

Valori teoretice: C: 70,15% H: 6,77% N:8,18%

Valori gasite : C : 70,22% H: 6,91% N:8,22%





$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.41÷7.33(m, 6H, H-2,  $\text{H}^{15}\div\text{H}^{19}$ ); 6.94(dd, 1H, H-6, 2.2, 8.8); 6.88(t, 1H, H-5,  $^4J(\text{F-H}^5)=^3J(\text{H}^5\text{-H}^6)=8.8$ ); 6.58(bs, NH); 3.27(m, 2H, H-7<sub>ax</sub>, H-11<sub>ax</sub> or H-7<sub>eq</sub>, H-11<sub>eq</sub>); 2.53(m, 1H, H-8); 5.18(s, 2H, H-13); 2.23(m, 2H, H-7<sub>eq</sub>, H-11<sub>eq</sub> or H-7<sub>ax</sub>, H-11<sub>ax</sub>); 1.85÷1.72(m, 4H, H-9, H-10); 0.92(d, 3H, H-20, 6.4).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 155.72(d, C-3,  $J(\text{F-C}^3)=245.4$  Hz); 153.37(C-12); 137.40(d, C-1,  $^3J(\text{F-C}^1)=9.7$  Hz); 132.36(d, C-4,  $J(\text{F-C}^4)=10.2$  Hz); 135.97(C-14); 128.63(C-16, C-18); 28.34(C-17); 128.33(C-15, C-19); 119.50(d, C-5,  $^3J(\text{F-C}^5)=4.4$  Hz); 114.38(d, C-6,  $^4J(\text{F-C}^6)=3.4$  Hz); 107.58(d, C-2,  $J(\text{F-C}^2)=22.7$  Hz); 67.06(C-12); 59.43(C-7 or C-11); 51.79(C-7 or C-11); 32.76(C-9 or C-10); 31.29(C-9 or C-10); 25.68(C-8); 19.89(C-20).

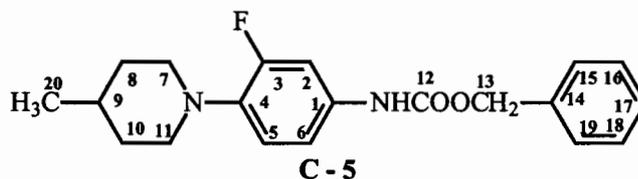
### Exemplul 3a

N-Benziloxicarbonil-3-fluoro-4-(4-metil-piperidini)-anilina: rand. 97%, p.t. 121,5-123,4°C

$\text{C}_{20}\text{H}_{23}\text{FN}_2\text{O}_2$ : M= 342,41 g/mol

Valori teoretice: C: 70,15% H: 6,77% N:8,18%

Valori gasite : C : 70,17% H: 6,70% N:8,33%



$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.42÷7.34(m, 6H, H-2,  $\text{H}^{15}\div\text{H}^{19}$ ); 6.94(dd, 1H, H-6, 2.2, 8.8); 6.88(t, 1H, H-5,  $^4J(\text{F-H}^5)=^3J(\text{H}^5\text{-H}^6)=8.8$ ); 6.61(bs 1H, HN); 5.18(s, 2H, H-13); 3.33(m, 2H, H-7<sub>eq</sub>, H-11<sub>eq</sub> or H-7<sub>ax</sub>, H-11<sub>ax</sub>); 2.60(m, 2H, H-7<sub>eq</sub>, H-11<sub>eq</sub> or H-7<sub>ax</sub>, H-11<sub>ax</sub>); 1.76÷1.36(m, 5H, H-8, H-9, H-10); 0.99(d, 3H, H-20, 5.5).

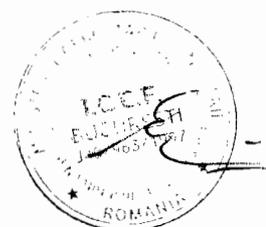
$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 156.02(d, C-3,  $J(\text{F-C}^3)=244.7$  Hz); 154.06(C-12); 137.35(d, C-1,  $^3J(\text{F-C}^1)=10.1$  Hz); 132.31(d, C-4,  $J(\text{F-C}^4)=10.4$  Hz); 135.97(C-14); 128.62(C-16, C-18); 128.38(C-17); 128.33(C-15, C-19); 119.43(d, C-5,  $^3J(\text{F-C}^5)=4.4$  Hz); 114.33(d, C-6,  $^4J(\text{F-C}^6)=3.4$  Hz); 107.59(d, C-2,  $J(\text{F-C}^2)=22.7$  Hz); 67.06(C-13); 51.69(C-7, C-11); 34.44(C-8, C-10); 30.58(C-9); 21.94(C-20).

### Exemplul 3b

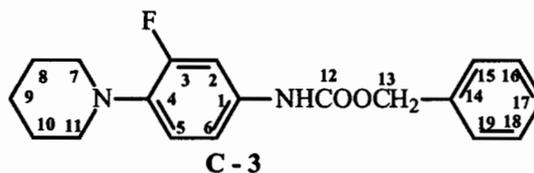
N-Benziloxicarbonil-3-fluoro-4-piperidini-anilina: rand. 68,2%, p.t. 116,4-118,5°C.

$\text{C}_{19}\text{H}_{21}\text{FN}_2\text{O}_2$ : M= 328,39 g/mol

Valori teoretice: C: 69,49% H: 6,45% N:8,53%



Valori gasite : C : 69,60% H: 6,30% N:8,49%



$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.40÷7.32(m, 6H, H-2,  $\text{H}^{15}\div\text{H}^{19}$ ); 6.95(dd, 1H, H-6, 2.1, 8.8); 6.87(t, 1H, H-5,  $^4J(\text{F-H}^5)=^3J(\text{H}^5\text{-H}^6)=8.8$ ); 6.63(bs, 1H, NH); 5.18(s, 2H, H-13); 2.95(t, 4H, H-7, H-11, 5.4); 1.72(qv, 4H, H-8, H-10, 5.4); 1.56(m, 2H, H-9).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 155.70(d, C-3,  $J(\text{F-C}^3)=244.6$  Hz); 153.33(C-12); 137.42(d, C-1,  $^3J(\text{F-C}^1)=9.3$  Hz); 132.34(d, C-4,  $J(\text{F-C}^4)=10.8$  Hz); 135.97(C-14); 128.62(C-16, C-18); 128.37(C-17); 128.32(C-15, C-19); 119.39(d, C-5,  $^3J(\text{F-C}^5)=4.4$  Hz); 114.41(d, C-6,  $^4J(\text{F-C}^6)=3.4$  Hz); 107.55(d, C-2,  $J(\text{F-C}^2)=22.7$  Hz); 67.05(C-12); 52.34(C-7, C-11); 26.16(C-8, C-10); 14.17(C-9).

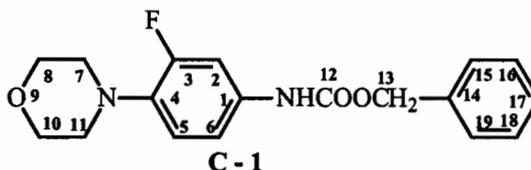
### Exemplul 3c

N-Benziloxicarbonil-3-fluoro-4-morfolinil-anilina: rand. 96,6%, p.t. 123-123,7°C.

$\text{C}_{18}\text{H}_{19}\text{FN}_2\text{O}_3$ ;  $M=330,36$  g/mol

Valori teoretice: C: 65,44% H: 5,80% N:8,48%

Valori gasite : C : 65,51% H: 5,90% N:8,51%



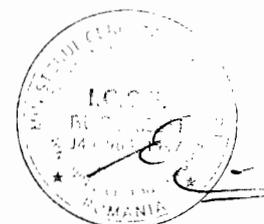
$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.41÷7.33(m, 6H, H-2,  $\text{H}^{15}\div\text{H}^{19}$ ); 6.97(dd, 1H, H-6, 2.1, 8.8); 6.86(t, 1H, H-5,  $^4J(\text{F-H}^5)=^3J(\text{H}^5\text{-H}^6)=8.8$ ); 6.69(bs, 1H, HN); 5.19(s, 2H, H-13); 3.86(m, 4H, H-8, H-10); 3.02(m, 4H, H-7, H-11).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 155.66(d, C-3,  $J(\text{F-C}^3)=244.8$  Hz); 153.28(C-12); 135.87(d, C-1,  $^3J(\text{F-C}^1)=9.3$  Hz); 133.01(d, C-4,  $J(\text{F-C}^4)=10.8$  Hz); 118.96(d, C-5,  $^3J(\text{F-C}^5)=4.1$  Hz); 114.47(d, C-6,  $^4J(\text{F-C}^6)=3.4$  Hz); 108.01(d, C-2,  $J(\text{F-C}^2)=23.1$  Hz); 135.90(C-14); 128.64(C-16, C-18); 128.43(C-17); 128.35(C-15, C-19); 67.13(C-13); 67.00(C-8, C-10); 51.13(d, C-7, C-11,  $^4J(\text{F-C}^{7,11})=2.9$  Hz).

### Exemplul 4

Sinteza (R)-[N-3-(3-fluoro-4-(3-metil-piperidini)fenil)-2-oxo-5-oxazolidinil]metanolului

La o solutie de 0,0207 moli (7,08 g) de N-Benziloxicarbonil-3-fluoro-4-(3-metil-piperidini)-anilina in 200 ml tetrahidrofuran anh. sub atmosfera de argon, la o temperature de -78°C se aduga 0,207 moli (8,4 ml) nBuLi 2,5 M/hexan, in decurs de 20-30 min. Se agita in continuare la aceeasi temperature timp de 35 minute, apoi se aduga 0,021 moli (3,05 g) de

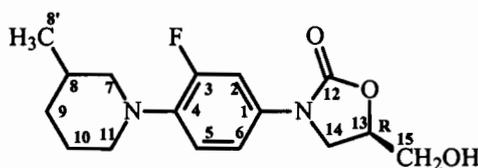


glicidil butirat prin picurare timp de 40 minute. Se ridica apoi temperatura masei de reactie la temperatura camerei. Se agita la aceeasi temperatura timp de 48 de ore. Reactia se stinge cu o solutie saturate de clorura de amoniu, dupa care se adauga 60 ml de acetat de etil si 20 ml de apa. Se separa straturile. Stratul apos se extrage cu 3 x 30 ml acetat de etil. Straturile organice reunite se usuca pe sulfat de sodiu anhidru. Prin concentrare la presiune redusa se obtine un produs brut, care se recrystalizeaza din acetat de etil si hexan. Se obtin 5,0 g, spot unic (CSS: sistem de eluare: tetrahidrofuran :dioxan:amoniac conc. : 20:60:30 (v/v/v), suport Silica gel 60F 254 ), rand. 78%, p.t.98,6-101,3°C.

**C<sub>16</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub> : M= 308,35 g/mol**

Valori teoretice: C: 62,32% H: 6,86% N:9,09%

Valori gasite : C : 62,19% H: 7,00% N:9,27%



alcool - 4

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ ppm, J Hz): 7.38(dd, 1H, H-2, <sup>4</sup>J(H<sup>6</sup>-H<sup>2</sup>)= 2.1, <sup>4</sup>J(F-H<sup>2</sup>)=14.4);7.10(dd, 1H, H-6, <sup>5</sup>J(F-H<sup>6</sup>)= 2.1, <sup>4</sup>J(H<sup>5</sup>-H<sup>6</sup>)=9.1);6.93(t, 1H, H-5, <sup>3</sup>J(H<sup>5</sup>-H<sup>6</sup>)=9.1, J(F-H<sup>5</sup>)=9.1);4.72(m, 1H, H-13);4.00(d, 1H, H-15A, 8.7); 3.94(dd, 1H, H-15B, 8.7, 6.8); 3.96(d, 1H, H-14A, 12.6); 3.74(dd, 1H, H-14B, 12.6, 4.2);3.30(m, 2H, H-11); 2.70(bs, 1H, OH); 2.55(m, 1H, H-7); 2.26(m, H-7); 1.97(m, 5H, H-8, 2H-9, 2H-10); 0.93(d, 3H, H-8', 5.9).

<sup>13</sup>C-NMR(CDCl<sub>3</sub>, δ ppm): 155.46(d, C-3, J(F-C<sup>3</sup>)=243.2 Hz);154.64(C-12);137.81(d, C-4, J(F-C<sup>4</sup>)=9.3 Hz); 132.89(d, C-1, J(F-C<sup>4</sup>)=10.3 Hz); 119.25(d, C-5, J(F-C<sup>5</sup>)=3.8 Hz); 113.87(d, C-6, J(F-C<sup>6</sup>)=3.7 Hz); 107.32(d, C-2, J(F-C<sup>2</sup>)=26.3 Hz); 72.83(C-13); 62.75(C-15);46.49(C-14);59.28(C-11); 51.65(d, C-7, C-11, J(F-C<sup>7,11</sup>)=3.2 Hz); 32.77(C-10); 31.26(C-8); 25.64(C-9); 19.48(C-8').

#### Exemplul 4a

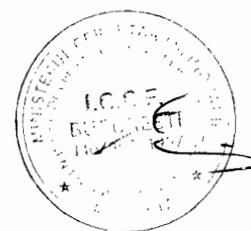
*(R)-[N-3-(3-fluoro-4-(4-metil-piperidinil)fenil)-2-oxo-5-oxazolidinil]metanol*

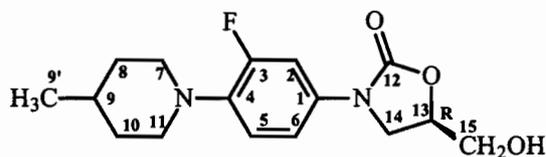
rand. 75%, p.t.121.5-123,4°C.

**C<sub>16</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub> : M= 308,35 g/mol**

Valori teoretice: C: 62,32% H: 6,86% N:9,09%

Valori gasite : C : 62,37% H: 6,80% N:9,23%





alcool - 5

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$ , Hz): 7.38(dd, 1H, H-2,  $^4J(\text{H}^6\text{-H}^2)=1.9$ ,  $^4J(\text{F-H}^2)=14.4$ ); 7.08(dd, 1H, H-6,  $^5J(\text{F-H}^6)=1.9$ ,  $^4J(\text{H}^5\text{-H}^6)=9.1$ ); 6.93(t, 1H, H-5,  $^3J(\text{H}^5\text{-H}^6)=8.7$ ,  $J(\text{F-H}^5)=9.1$ ); 4.70(m, 1H, H-13); 3.99(m, 1H, H-15A,  $J(\text{A-B})=16.9$ ,  $J(\text{H}^{15\text{A}}\text{-H}^{13})=8.7$ ); 3.93(m, 1H, H-15B,  $J(\text{A-B})=16.9$ ,  $J(\text{H}^{15\text{B}}\text{-H}^{13})=8.7$ ); 3.92(m, 1H, H-14A); 3.72(dd, 1H, H-14B,  $J(\text{A-B})=12.6$ ,  $J(\text{H}^{13}\text{-H}^{14\text{B}})=3.9$ ); 3.35(m, 2H, H-7eq, H-11eq or H-7ax, H-11ax); 3.13(bs, 1H, OH); 2.62(m, 2H, H-7eq, H-11eq or H-7ax, H-11ax); 1.73(m, 2H, H-8eq, H-10eq or H-8ax, H-10ax); 1.32÷1.48(m, 3H, H-13, H-8eq, H-10eq or H-8ax, H-10ax); 0.98(d, 3H, H-9', 5.8). Se poate scrie și ca interval: 4.01÷3.89(m, 3H, H-14A, H-15A, H-15B);

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 155.42(d, C-3,  $J(\text{F-C}^3)=245.1$  Hz); 154.73(C-12); 137.56(d, C-4,  $J(\text{F-C}^4)=8.8$  Hz); 132.46(d, C-1,  $J(\text{F-C}^4)=10.3$  Hz); 119.25(d, C-5,  $J(\text{F-C}^5)=4.5$  Hz); 113.86(d, C-6,  $J(\text{F-C}^6)=3.3$  Hz); 107.31(d, C-2,  $J(\text{F-C}^2)=26.1$  Hz); 72.92(C-13); 62.66(C-15); 51.57(C-7, C-11); 46.51(C-14); 34.41(C-8, C-10); 30.59(C-9); 21.93(C-9').

#### Exemplul 4b

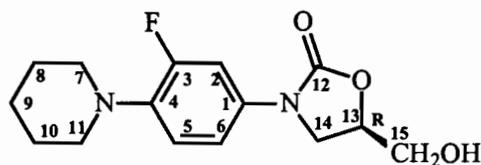
*(R)*-[*N*-3-(3-fluoro-4-(piperidinilfenil))-2-oxo-5-oxazolidinil]metanol:

rand. 77%, p.t.116,4-118,5 $^{\circ}\text{C}$ .

$\text{C}_{15}\text{H}_{19}\text{FN}_2\text{O}_3$ ;  $M=294,33$  g/mol

Valori teoretice: C: 61,21% H: 6,51% N:9,52%

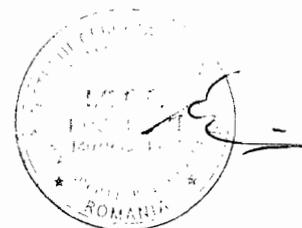
Valori gasite : C : 61,02% H: 6,70% N:9,50%



alcool - 3

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm,  $J$  Hz): 7.38(dd, 1H, H-2,  $^4J(\text{F-H}^2)=2.1$ ,  $^4J(\text{H}^6\text{-H}^2)=14.4$ ); 7.10(dd, 1H, H-6,  $^5J(\text{F-H}^6)=2.1$ ,  $^4J(\text{H}^5\text{-H}^6)=9.1$ ); 6.93(t, 1H, H-5,  $^3J(\text{H}^5\text{-H}^6)=9.1$ ,  $J(\text{F-H}^5)=9.1$ ); 4.72(m, 1H, H-13); 4.00(d, 1H, H-15A, 8.7); 3.92(dd, 1H, H-15B, 8.7, 6.8); 3.96(d, 1H, H-14A, 12.6); 3.74(dd, 1H, H-14B, 12.6, 4.2); 2.98(m, 4H, H-7, H-11); 2.70(bs, 1H, OH); 1.70(qv, 4H, H-8, H-10, 5.6); 1.58(m, 2H, H-9).

$^{13}\text{C-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$  ppm): 155.46(d, C-3,  $J(\text{F-C}^3)=243.2$  Hz); 154.64(C-12); 137.81(d, C-4,  $J(\text{F-C}^4)=9.3$  Hz); 132.89(d, C-1,  $J(\text{F-C}^4)=10.3$  Hz); 119.22(d, C-5,  $J(\text{F-C}^5)=3.8$  Hz); 113.86(d, C-6,  $J(\text{F-C}^6)=3.7$  Hz); 107.32(d, C-2,  $J(\text{F-C}^2)=26.3$  Hz); 72.83(C-13); 62.75(C-15); 52.22(d, C-7, C-11,  $J(\text{F-C}^{7/11})=3.2$  Hz); 46.48(C-14); 26.14(C-8, C-10); 24.19(C-9).



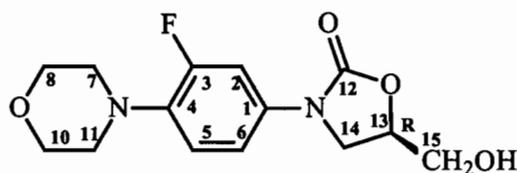
**Exemplul 4b***(R)-[N-3-(3-fluoro-4-morfolinilfenil)-2-oxo-5-oxazolidini]metanol:*

rand. 75 %, p.t.111,7-112,5°C.

**C<sub>15</sub>H<sub>19</sub>FN<sub>2</sub>O<sub>3</sub>: M= 294,33 g/mol**

Valori teoretice: C: 61,21% H: 6,51% N:9,52%

Valori gasite : C : 61,02% H: 6,70% N:9,50%



alcool - 1

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ ppm, *J* Hz): 7.43(dd, 1H, H-2, <sup>4</sup>*J*(F-H<sup>2</sup>)= 1.9, <sup>4</sup>*J*(H<sup>6</sup>-H<sup>2</sup>)=14.4); 7.10(dd, 1H, H-6, <sup>5</sup>*J*(F-H<sup>6</sup>)= 1.9, <sup>4</sup>*J*(H<sup>5</sup>-H<sup>6</sup>)=9.1); 6.91(t, 1H, H-5, <sup>3</sup>*J*(H<sup>5</sup>-H<sup>6</sup>)=8.7, *J*(F-H<sup>5</sup>)=8.7); 3.86(m, 4H, H-8, H-10, syst. A<sub>2</sub>B<sub>2</sub>); 3.14(bs, 1H, HO); 3.04(m, 4H, H-7, H-11, syst. A<sub>2</sub>B<sub>2</sub>); 4.73(m, 1H, H-13); 3.99(d, 1H, H-15A, syst. AB, 8.6); 3.94(dd, 1H, H-15B, syst AB, 8.6, *J*(H<sup>15B</sup>-H<sup>13</sup>)=6.8 Hz); 3.97(bd, 1H, H-14A, 11.4); 3.73(bd, 1H, H-14B, syst. AB, 11.4).

<sup>13</sup>C-NMR(CDCl<sub>3</sub>, δ ppm): 155.34(d, C-3, *J*(F-C<sup>3</sup>)=244.4 Hz); 154.71(C-12); 136.25(d, C-4, *J*(F-C<sup>4</sup>)=9.1 Hz); 133.11(d, C-1, *J*(F-C<sup>4</sup>)=10.5 Hz); 118.73(d, C-5, *J*(F-C<sup>5</sup>)=4.1 Hz); 113.86(d, C-6, *J*(F-C<sup>6</sup>)=3.7 Hz); 107.40(d, C-2, *J*(F-C<sup>2</sup>)=26.1 Hz); 72.95(C-13); 62.60(C-15); 46.39(C-14); 66.91(C-8, C-10); 50.97(d, C-7, C-11, *J*(F-C<sup>7,11</sup>)=2.9 Hz).

*Determinarea activitatii antimicrobiene*

S-a determinat activitatea biologica *in vitro* pentru compuşii prezentati la exemplele 4, 4a, 4b si 4c. Testarea activităţii antibacteriene s-a făcut pe o serie de microorganisme: *E. Coli* ATCC 8739, *S.aureus* ATCC 6548.

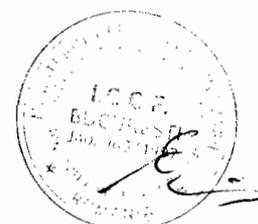
Exemplu	Concentratia minima inhibitorie (µg/ml)	
	<i>E.coli</i> ATCC 8739	<i>S.aur</i> ATCC 6548
Exemplu 4	>128	64
Exemplu 4a	>128	128
Exemplu 4b	>128	128
Exemplu 4c	>128	128

Compusii testati au prezentat o activitate antimicrobiana fata de microorganisme gram-pozitive (*St. Aur.*)



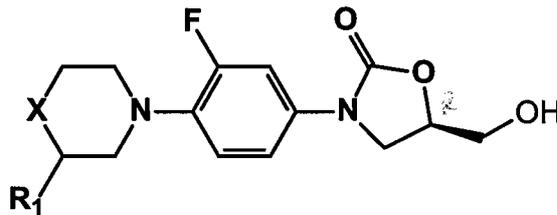
*Concluzie*

Au fost obtinuti derivati de oxazolidinone cu randamente ridicate si cu puritate corespunzatoare, printr-o tehnologie curata si usor accesibila. Derivatii de oxazolidinone prezinta activitate antimicrobiana fata de microorganisme gram-pozitive (*St. Aur.*).



## REVENDICARI

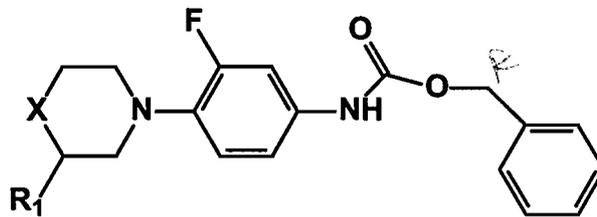
1. Derivati de oxazolidinona, caracterizati prin aceea ca prezinta umatoarea structura chimica corespunzatoare formulei generale I



I

in care R<sub>1</sub> este metil, X este CHR iar R este metil.

2. Derivati de anilina caracterizati prin aceea ca prezinta umatoarea structura chimica corespunzatoare formulei generale II



II

in care R<sub>1</sub> este metil, X este CHR iar R este metil.

3. Derivat oxazolidinona, conform revendicarii 1, caracterizat prin aceea ca, este *(R)-[N-3-(3-fluoro-4-(3-metil-piperidinil)fenil)-2-oxo-5-oxazolidinil]metanol*

4. Derivat de anilina, conform revendicarii 2, caracterizat prin aceea ca, este *N-Benziloxicarbonil-3-fluoro-4-(3-metil-piperidinil)-anilina*

