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5-ARYL-β,γ BUTENOLIDE, A NEW CLASS OF ANTIBACTERIAL DERIVED FROM THE N-ARYL OXAZOLIDINONE DUP 721

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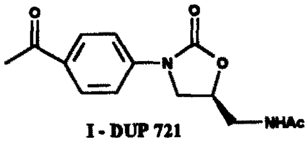
Abstract :

The synthesis of three heterocyclic analogues of DUP 721 is described. Replacement of the oxazolidinone ring of DUP 721 by a β, γ butenolide gives a compound with similar antibacterial activity.

The 3-aryloxazolidinones are a new class of synthetic antibacterial agents discovered by DuPont de Nemours [1a,b,c,d]. Different studies concerning the mechanism of action have shown that the oxazolidinones inhibit protein synthesis [2]. An improvement of the antibacterial and pharmacological profile has been achieved in this family by the synthesis of DUP 721 (figure 1).

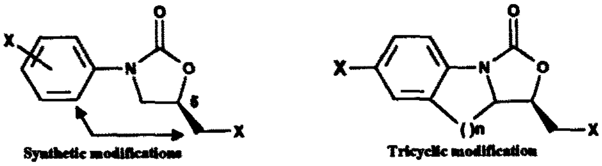
Figure 1 :



I - DUP 721

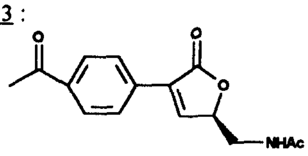
The *in vitro* spectrum of this compound includes activity against susceptible and resistant strains of staphylococci, streptococci, enterococci, anaerobic bacteria and mycobacteria [3]. Most of the synthetic modifications have been directed on two positions of the molecule : the aromatic ring [1] and the 5-methylene (figure 2). In a recent work, some interesting tricyclic modifications were also described (figure 2) [4] :

Figure 2 :

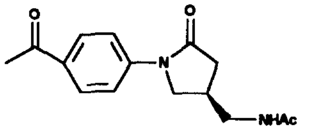


Surprisingly, the nature of the central heterocycle has never been explored. We speculated that the very flat oxazolidinone ring could be substituted by a β,γ butenolide ring, or by more flexible compound such as pyrrolidinone or pyrrolidine (figure 3).

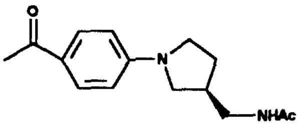
Figure 3 :



II



III



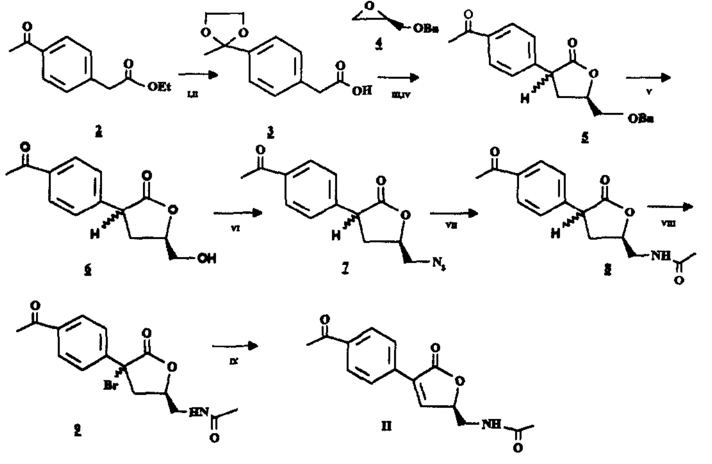
IV

We therefore decided to investigate the influence of these structural modifications on the antibacterial activity.

Synthesis :

Since chiral starting material was available for the synthesis of the lactone II, we chose to synthesize the chiral parent compound of DUP 721 (scheme 1). The synthesis started with the known p.acetylphenylethylacetate 2 [5] which was protected by a dioxolane ring and hydrolyzed to yield acid 3. The lithiated dianion of 3 was reacted with the commercial (S) benzyloxymethyloxirane 4 in THF at 0°C. The resulting γ hydroxy-acid was directly cyclized with simultaneous cleavage of the dioxolane ring by treatment of the crude product with p. toluene sulfonic acid in toluene in the presence of 4 Å molecular sieves. Lactone 5 was obtained in 65 % yield as a 1/1 diastereoisomeric mixture. The benzyl group was removed by hydrogen transfer reaction [6] to avoid reduction of the acetyl group (82 % yield). The N-acetyl function was then introduced using standard procedures : mesylation, nucleophilic substitution by NaN_3 and reduction with $P(OMe)_3$ [7] in 52 % overall yield. Bromination of 8 by NBS in CCl_4 gave only 20 % of the desired bromo compound 9 along with unchanged starting material which could be recycled.

The double bond was introduced by elimination of the bromine by treatment of 9 with 3.3 eq. of dry pyridine in toluene at 80°C. The (R) lactone II was obtained in 65 % yield, with a 80 % optical purity (determined by chiral HPLC : HSA 5 μ column, pH : 5 phosphate buffer).

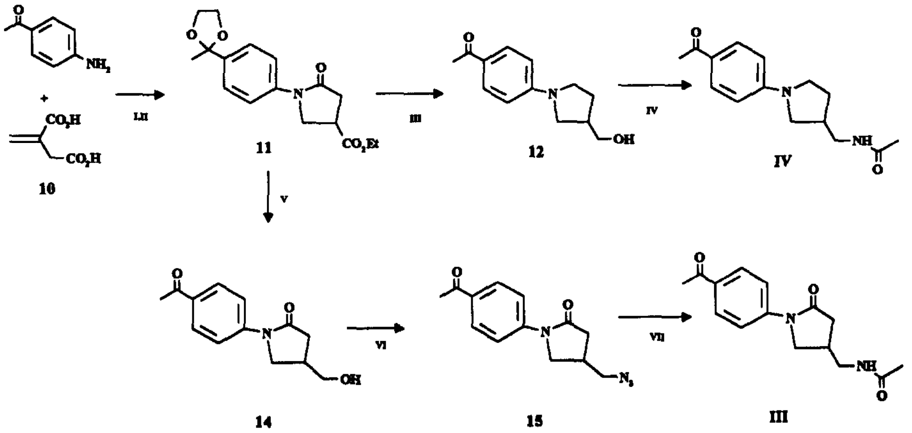


Scheme 1 : β,γ Butenolide synthesis

(I) $HO(CH_2)_2OH$, $HC(OEt)_3$, APTS cat., 50°C, 93%;(II) -a) NaOH 2N, EtOH, 50°C- b) AcOH, 5°C, 95%; (III) -a) LDA, THF, -5°C -b) 4, 0°to 24°C; (IV) APTS cat., toluene, 4A° molecular sieves, 65%; (V) $Pd(OH)_2$, cyclohexene, EtOH, Rfx., 82%; (VI) -a) CH_3SO_2Cl, Et_3N, CH_2Cl_2 -b) NaN_3, DMF, 80°C, 75%; (VII) -a) $P(OMe)_3$, $MeOCH_2OMe$, Rfx. -b) HCl 6N, Rfx. -c) NaOH 2N, Ac_2O, THF/H_2O, 69%; (VIII) NBS, $Ph(COO)_2$, CCl_4, Rfx., 20%; (IX) Pyridine, Toluene, 80°C, 65%.

The heterocycles III and IV were synthesized as racemates from itaconic acid 10 using described procedures [8] (scheme 2).

Fusion of p.acetylaniline with itaconic acid 10 followed by protection of the carbonyl, and esterification gave the carboxypyrrolidone 11 in 48 % yield. Reduction with $NaBH_4$ or $LiAlH_4$ provided pyrrolidinone 14 (96 % yield) and pyrrolidine 12 (97 % yield) respectively. Procedures analogous to the ones used for the lactone II led to the desired N-acetyl pyrrolidinone III in 58 % yield. Surprisingly, the azidomethyl pyrrolidine was directly reduced probably by thermal decomposition of the azido group during work up of the reaction. However, acetylation of the crude product gave the expected N-acetyl pyrrolidine IV in 25 % yield.



Scheme 2 : synthesis of pyrrolidone III and pyrrolidine IV

(I) -a) 140°C, neat -b) EtOH, CH_3COCl, Rfx, 48% ; (II) $HO(CH_2)_2OH$, $HC(OEt)_3$, APTS cat., 65°C, 100% ; (III) -a) $LiAlH_4$, THF, Rfx. -b) HCl 6N, 97% ; (IV) -a) CH_3SO_2Cl, Et_3N, CH_2Cl_2 -b) NaN_2, DMF, 85°C -c) Ac_2O, THF/H_2O, 24% ; (V) -a)$NaBH_4$, MeOH -b) HCl 6N, 76% ; (VI) -a) CH_3SO_2Cl, Et_3N, CH_2Cl_2 -b) NaN_3, DMF, 85°C, 81% ; (VII) $MeOCH_2OMe$, $P(OMe)_3$, Rfx. -d) HCl 6N, Rfx.
-e) NaOH 2N, Ac_2O, THF/H_2O, 72% .

Biological results :

The three compounds have been tested on both susceptible and resistant staphylococci and enterococci ; DUP 721 was used as a reference compound [9] (table 1).

Lactone II was as active as DUP 721 and exhibited a similar antimicrobial spectrum : active against Gram (+) strains (susceptible and resistant), MIC ≤ 2.5 - 5, inactive against Gram (-) strains, MIC > 40. III and IV were inactive.

Table 1 : In vitro antibacterial activity

MIC (µg/ml)	DUP 721	II	III	IV
Staphylococcus aureus SG 511 [b]	1.2	1.2	> 40	> 40
Staphylococcus aureus O11CB20 [c]	1.2	1.2	> 40	> 40
Staphylococcus epidermidis 012GO39 [c]	2.5	2.5	> 40	> 40
Streptococcus pyogenes 77A [b]	0.6	2.5	> 40	> 40
Streptococcus faecium M78L [b]	2.5	5	> 40	> 40
Streptococcus faecium 02D3IP1 [d]	< 1.2	2.5	> 40	> 40
Streptococcus faecalis 02D2DU17 [d]	2.5	2.5	> 40	> 40
Escherichia coli UC 1894	> 40	> 40	> 40	> 40

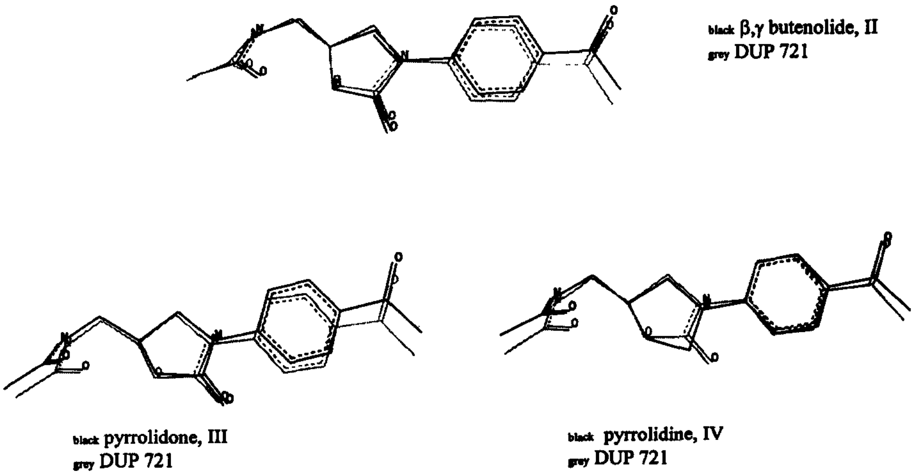
a Minimum Inhibitory Concentrations (MICs) were determined by a standard agar dilution method.
b Sensitive strains
c Oxacilline Resistant
d Vancomycin Resistant

A molecular modelling analysis (Discover ® Software) showed very good correlation between the three compounds and DUP 721 (figure 4). This confirmed the hypothesis of a requirement for coplanarity of the aromatic and the heterocyclic rings in the case of the active β, γ butenolide II.

The lack of activity of the aminoheterocycles could be better explained in terms of functional changes. Indeed, the more basic pyrrolidine IV is devoid of carbonyl and the amide function of the pyrrolidinone III is more polar than its carbamate or lactone counterpart in I or II.

These two examples illustrated the importance of the presence and the nature of the carbonyl group for the activity.

Figure 4 : Superposition of II, III, IV and DUP 721



black β,γ butenolide, II
grey DUP 721

black pyrrolidone, III
grey DUP 721

black pyrrolidine, IV
grey DUP 721

Conclusion :

This study demonstrates for the first time that the basic skeleton of the 3-aryl oxazolidinones antibiotics could be extended to a new structure : a 5-aryl-β,γ butenolide.

This lactone exhibits a similar antibiotic activity and offers an opportunity to further modifications in this protein synthesis inhibitor family.

Acknowledgment :

P. Brotto for Molecular Modelling.

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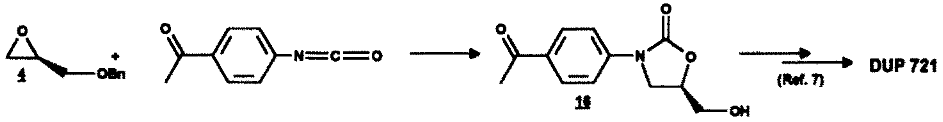
9) (S) DUP 721 was synthesized following a modified procedure of Wang et al. [7] (scheme 4) :

Scheme 4 :



The (S) glycidyl butyrate was replaced by the (S) benzyloxymethyloxirane 4, which was reacted with p. acetylisocyanate in xylene with LiBr, nBu_3PO at reflux in 98 % yield ; the benzyl group was then removed by treatment with $Pd(OH)_2$, cyclohexene in refluxing ethanol in 83 % yield to afford the described 5-hydroxymethylene oxazolidinone intermediate 16.

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