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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF [6,5,5] AND [6,6,5] TRICYCLIC FUSED OXAZOLIDINONES

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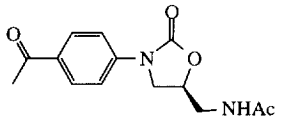
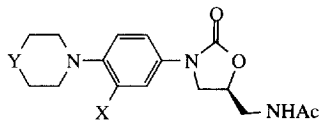
Abstract: A series of conformationally restricted, [6,5,5] and [6,6,5] tricyclic fused oxazolidinones were synthesized and tested for antibacterial activity. Several compounds in the *trans*-[6,5,5] series demonstrated potent *in vitro* and *in vivo* activity. This work provides valuable information regarding the preferred conformational orientation of the oxazolidinones at the binding site.

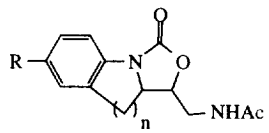
Introduction: Oxazolidinones are an exciting new class of antibacterial agents.[3,4] Key examples in this class are DuPont's seminal compound DuP 721 (**1**)[4] and Pharmacia & Upjohn's clinical candidates U-100592 (**2**) and U-100766 (**3a**).[3b,c] These compounds show promising activity against multiple antibiotic resistant strains of gram-positive bacteria *in vitro* and in animal models.



1 (DuP 721)



2: X=F, Y=NC(O)CH_2OH (U-100592)
3a: X=F, Y=O (U-100766)
3b: X=H, Y=O



4: n=1 ([6,5,5] series) or n=2 ([6,6,5] series) (where R is defined in Schemes 1-4)

We became interested in determining whether there was a preferred relative orientation of the aryl and oxazolidinone rings at the binding site. To answer this question a series of rigid oxazolidinone analogs were synthesized having the general structure **4**. These tricyclic fused oxazolidinones have the aryl and oxazolidinone rings joined together by either a one or two-carbon linker, giving rise to the [6,5,5] and [6,6,5] series, respectively.

Chemistry and Biology: The original racemic sytheses of the [6,5,5] and [6,6,5] frameworks are shown in Scheme 1.[3a,5] The two synthetic routes closely parallel each other; both involve the formation of a diastereomeric pair of cyanohydrins ((±)-**7** or (±)-**8**) which are separated and converted to either the *cis* or *trans* series of tricyclic oxazolidinones. The first tricyclic analogs to be made and tested were the four DuP 721 analogs (±)-**9b**, (±)-**10b**, (±)-**11b** and (±)-**12b**. The *trans*-[6,5,5] compound (±)-**10b** exhibited antibacterial potency approximately one-half that of the parent (±)-DuP 721 (Table 1). In contrast, (±)-**9b**, (±)-**11b** and (±)-**12b** were devoid of antibacterial activity at the concentrations tested.

Due to the promising activity of (±)-**10b**, we were encouraged to synthesize additional *trans*-[6,5,5] tricyclic analogs. Sulfonyl analogs were considered suitable targets since earlier work from DuPont had

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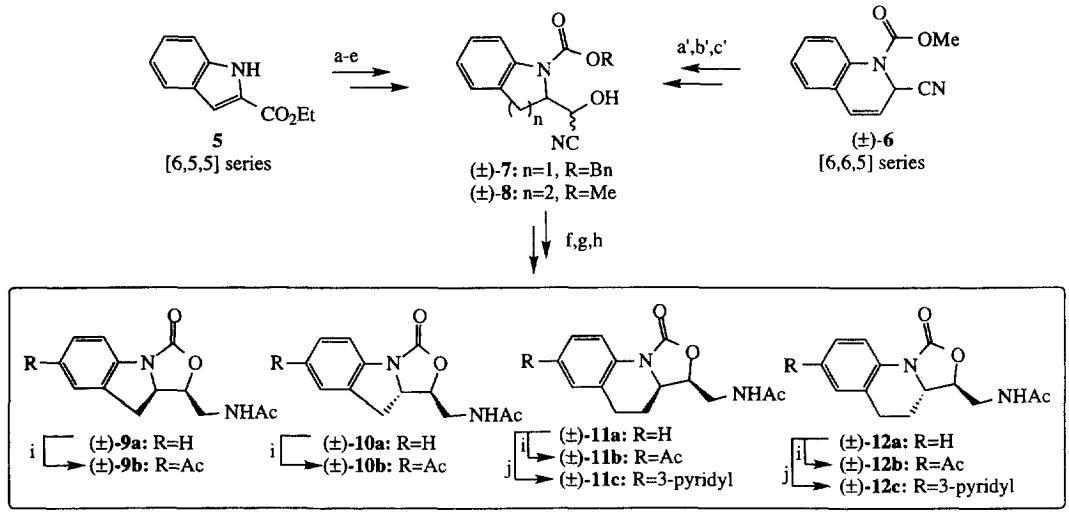
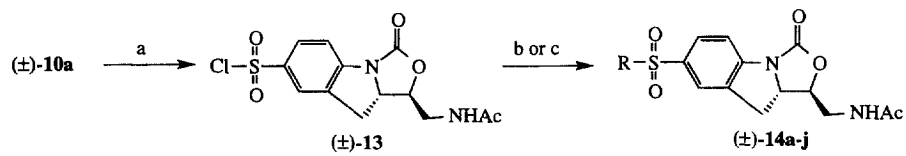
shown that some compounds of this type demonstrate good activity.[4] The chlorosulfonyl [6,5,5] tricyclic oxazolidinone (±)-**13** was synthesized from the parent (±)-**10a** by treatment with chlorosulfonic acid (Scheme 2). This compound was then used as an intermediate in the synthesis of the methanesulfonyl analog (±)-**14a** and nine sulfonamides ((±)-**14b-j**). (±)-**14a** and the N,N-dimethylsulfonamide (±)-**14b** exhibited only weak *in vitro* antibacterial activity (Table 1). None of the other sulfonyl analogs exhibited antibacterial activity at the levels tested.

Scheme 1



(a) Mg, MeOH, 92%; (b) CBZCl, $NaHCO_3$, 90%; (c) $LiBH_4$, 75%; (d) oxalyl chloride, DMSO, 94%; (e) $(CH_3)_2C(CN)OH$, K_2CO_3, 75%; (a') H_2, Pd/C, 99%; (b') Ra-Ni, NaH_2PO_2, 79%; (c') TMSCN (f) BH_3.DMS; (g) Ac_2O; (h) K_2CO_3, CH_3CN. 41% for **9a** (3 steps: f,g and h). 40% for **10a** (3 steps). 37% for **11a** (4 steps: c',f,g and h). 43% for **12a** (4 steps). (i) Ac_2O, MsOH, Ms_2O, 55% for **9b**, 67% for **10b**, 87% for **11b**, 79% for **12b**. (j) NBS, benzoyl peroxide then $ArB(OMe)_2$, $Pd(PPh_3)_4$, K_2HPO_4. 64% for **11c**. 55% for **12c**.

Scheme 2

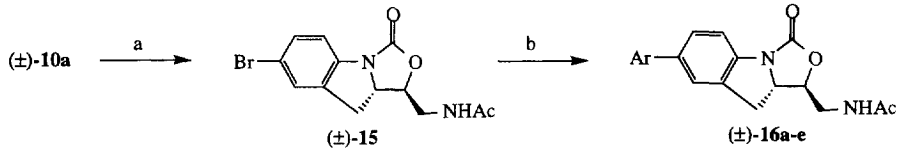


(a) $ClSO_2OH$, 72%; (b) (i) Na_2SO_3, $NaHCO_3$ (ii) MeI; (c) R_1R_2NH, Et_3N. R groups (yield from **10a**): **14a**, Me (28%); **14b**, NMe_2 (87%); **14c**, *c*-C_5H_9NH (89%); **14d**, EtNH (37%); **14e**, $PhCH_2NH$ (36%); **14f**, PhNH (50%); **14g**, $O(CH_2CH_2)_2N$ (25%); **14h**, $CH_2(CH_2CH_2)_2N$ (64%); **14i**, $HO(CH_2)_3NMe$ (82%); **14j**, NH_2 (65%).

A 1990 DuPont patent disclosed a variety of 3-phenyl-5-acetamidomethyl oxazolidinones having potent antibacterial activities, wherein aromatic and heteroaromatic moieties were coupled at the para position of the phenyl ring.[6] The most active analogs reported were those having 3-pyridyl, 4-pyridyl and 4-cyanophenyl substituents. We wished to explore the utility of these and related groups appended to the *trans*-[6,5,5] tricyclic

oxazolidinone framework. The parent tricyclic oxazolidinone (±)-**10a** was selectively brominated upon treatment with NBS and benzoyl peroxide to give aryl bromide (±)-**15** (Scheme 3). A series of racemic aryl- and heteroaryl-substituted [6,5,5] tricyclic oxazolidinones ((±)-**16a-e**) were synthesized by treating (±)-**15** with various aryl boronic acids under Suzuki palladium-catalyzed cross coupling conditions.[7] The *cis*- and *trans*- 3-pyridyl [6,6,5] tricyclic oxazolidinones (±)-**11c** and (±)-**12c** were synthesized in an analogous manner (Scheme 1).

Scheme 3

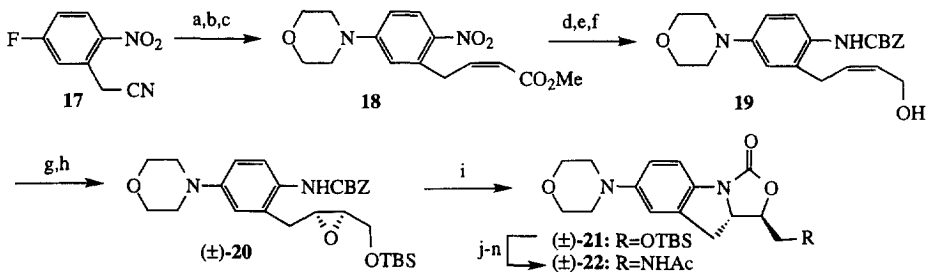


(a) NBS, benzoyl peroxide, 98%; (b) $ArB(OH)_2$, $(Ph_3P)_4Pd$, $KHPO_4$. Ar groups (yield from **10a**): **16a**, Ph (36%); **16b**, 3-pyridyl (45-65%); **16c**, 4-pyridyl (55%); **16d**, 4-cyanophenyl (80%); **16e**, 5-pyrimidyl (40%).

Several of the *trans*-[6,5,5] analogs (**16a-e**) had very potent antibacterial activity (Table 1); the most potent being the 3-pyridyl compound (±)-**16b**. This compound had *in vitro* antibacterial activity approximately twice as potent as (±)-DuP 721. Unfortunately, (±)-**16b** was found to elicit toxic effects in the rat when administered orally at 100 mg/kg b.i.d. for 30 days.[8] Interestingly, the *trans*-3-pyridyl [6,6,5] tricyclic oxazolidinone (±)-**12c** also demonstrated weak antibacterial activity (Table 1).

An asymmetric synthesis of the parent *trans*-[6,5,5] tricyclic molecule (±)-**10a** was developed so that we would have access to these active [6,5,5] tricyclic analogs in enantiomerically enriched form.[9] (-)-**10a** (98.8% ee) was converted into the optically active DuP 721 analog (+)-**10b** using the same conditions employed in the racemic series (Scheme 1). (+)-**10b** was at least twice as potent *in vitro* as the racemate (Table 1). This indicates that the enantiomer having the 5-(S)-acetamidomethyl side chain is responsible for biological activity which is in accord with earlier findings, in the non-tricyclic series, at DuPont.[4]

Scheme 4



(a) Morpholine, MeCN, 93%; (b) DIBALH, $PhCH_3$, 46%; (c) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, THF, 76%; (d) DIBALH, $PhCH_3$, 91%; (e) $SnCl_2.H_2O$, EtOH, 93%; (f) CBZCl, $NaHCO_3$, 76%; (g) m-CPBA, $CHCl_3$, $NaHCO_3$, 76%; (h) TBSCl, imidazole, DMF, 62%; (i) LHMDS, THF, 70%; (j) Bu_4NF, THF, 82%; (k) MsCl, Et_3N, CH_2Cl_2, 95%; (l) NaN_3, DMF, 94%; (m) H_2, Pd/C, MeOH, 100%; (n) Ac_2O, pyridine, 76%.

The morpholino tricyclic molecule **22** (Scheme 4) was chosen as a synthetic target. *A priori* it was anticipated that this molecule would have good antibacterial activity. It is the tricyclic des-fluoro equivalent of the current clinical candidate U-100766 (**3a**). Previous work in our laboratories and at DuPont suggests that a fluorine substituent provides only a modest potency enhancement compared to the corresponding des-fluoro compounds. Earlier, more direct attempts at synthesizing **22** from the parent **10a** or the aryl bromide **15** had proved unsuccessful[10] and so an independent synthesis was developed. A strategy similar to that used in the asymmetric synthesis of (-)-**10a** was chosen.[9] A key reaction in the synthesis was a novel intramolecular lithio-carbamate/epoxide cyclization (**20** to **21**). This led to the formation of both five membered rings of the tricyclic oxazolidinone in one step with complete regiochemical control. Surprisingly, (±)-**22** exhibited poor antibacterial activity (Table 1).

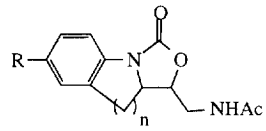
Discussion: A novel series of [6,5,5] and [6,6,5] tricyclic oxazolidinones has been prepared and examined for antibacterial activity. All *cis* analogs tested were inactive. In the *trans* series the [6,5,5] compounds proved much more potent than the corresponding [6,6,5] compounds. Many of the *trans*-[6,5,5] analogs had potent activity (i.e. (±)-**11b** and (±)-**16a-e**), similar to that of their non-tricyclic counterparts. The most potent was the 3-pyridyl analog (±)-**16b**. Some *trans*-[6,5,5] tricyclic analogs did not follow this trend and had surprisingly poor antibacterial activity (i.e. (±)-**14a-j** and (±)-**22**). To account for some of these observations, molecular modeling studies were performed.

Energy minimization calculations (MM2) performed on DuP 721 (**1**) showed that a negative torsional angle between the aryl and oxazolidinone rings is favored (-29° calculated for 'average' low energy conformations).[11] This is comparable to that found in the analogous *trans*-[6,5,5] compound (±)-**10b** (-24° calculated) but opposite to that found in the *cis* compound (±)-**9b** (+21° calculated).[12] The activity of (±)-**10b** (*ca.* half that of (±)-**1**) and the inactivity of (±)-**9b** suggest that (±)-**1** and related compounds may bind to their receptor *via* a low energy conformation in which the torsional angle about the aryl-N bond adopts a value roughly similar to that found in (±)-**10b** and other *trans* analogs.

A comparison of the energy minimized structures of **10b** and DuP 721 (**1**) (Figure 1A) reveals a disparity in the orientation of the aryl ring attached to the oxazolidinone nitrogen in each of these two compounds. This difference arises in part from bond angle distortions introduced by the presence of a second five-member ring in **10b**. Despite this difference *trans*-[6,5,5] compounds, such as **10b**, are still able to bind to the receptor, as evidenced by the high potency of **10b** and the aryl series of compounds (±)-**16a-e**. This trend does not hold true for the sulfonyl analogs (±)-**14a-j** or for the morpholino analog (±)-**22** which have much weaker activity. It is assumed that the small size of the acyl substituent in **10b** and the planarity of the aryl substituents in (±)-**16a-e** enable those tricyclic compounds to still comfortably fit the receptor. This is not the case when the bulkier morpholino group is attached to the tricyclic framework or when a sulfonyl substituent is used. Clearly, subtle forces are in effect, and it is hoped that the synthesis and testing of additional *trans*-[6,5,5] tricyclic analogs will provide further enlightenment.

Figure 1B illustrates that in *trans*-[6,6,5] analogs such as (±)-**12b** the position of the aryl ring more closely approximates the position of the aryl ring found in active non-tricyclic oxazolidinones such as (±)-**1**. *A priori* it was therefore predicted that *trans*-[6,6,5] analogs would have potent antibacterial activity. This proved not to be the case. Their lack of activity is assumed to be due to the additional steric bulk imparted by the ethylene linker.

Table 1. Antibacterial Activity of [6,5,5] and [6,6,5] Fused Tricyclic Oxazolidinones



			MIC (μg/mL)[a]						ED_{50}[b]
Cmpd[c]	n	R	*S.a.*1[d]	*S.a.*2[e]	*S.e.*[f]	*E.f.*[g]	*S.p.*[h]	*B.f.*[i]	*S.a.*1
9a	1	H	>32	>32	>32	>32	>32	>32	-
10a	1	H	>32	>32	>32	>32	>32	>32	-
11a	2	H	>64	>64	>64	>64	>64	>32	-
12a	2	H	>64	>64	>64	>64	>64	>32	-
9b	1	Ac	>16	>16	>16	>16	>16	>16	-
11b	2	Ac	>16	>16	>16	>16	>16	>16	-
12b	2	Ac	>16	>16	>16	>16	>16	>16	-
10b	1	Ac	8	-	8	16	-	-	39.5[j] (1.8)[j,k]
(+)-**10b**	1	Ac	4	4	2	4	4	4	-
14a	1	SO_2Me	64	32	64	64	16	>32	-
14b	1	SO_2NMe_2	64	64	64	>64	64	>32	-
14c-j	1	$SO_2NR_1R_2$	>64	>64	>64	>64	>64	>32	-
16a	1	Ph	-	-	2	4	-	32	>25[j] (2.2)[j,k]
16b	1	3-pyridyl	4	2	2	2	-	2	9.4 (2.9)[k] 4.4[j] (1.1)[j,k]
16b.HCl	1	3-pyridyl.HCl	2	2	1	2	0.5	4	6.0 (1.8)[k]
16c	1	4-pyridyl	4	2	2	2	-	8	6.1 (2.1)[k] 16.5[j] (5.9)[j,k]
16d	1	4-cyanophenyl	4	4	2	2	2	32	17.1 (2.5)[k]
16e	1	5-pyrimidyl	8	4	4	4	-	8	11.4 (2.5)[k]
11c	2	3-pyridyl	>64	>64	>64	>64	>64	>32	-
12c	2	3-pyridyl	32	16	16	32	16	>32	-
22	1	morpholino	64	64	32	128	32	>16	>20 (2.2)[l]
Comparator drugs									
DuP 721 ((±)-**1**)	0	Ac	2-4	4	4	8	2	8-16	9.4 (4.8)[k] 18.1[j] (7.9)[j,k]
U-100766 ((-)-**3a**)	0	morpholino	2-4	4	1	2	0.5	4	2.0-15
(-)-**3b**	0	morpholino	4	4	2	4	1	4	-
vancomycin	-	-	0.5	0.5	0.5	4	0.5	>16	1.1-4.8

[a]Minimum inhibitory concentration: lowest concentration of drug that inhibits visible growth of the organism. [b]Effective dose50: amount of drug required (mg/kg body weight/dose) to cure 50% of infected mice subjected to a lethal systemic infection (drug administered orally). [c]Data is for racemic material unless otherwise noted. [d]*Staphylococcus aureus* UC (Upjohn Culture) 9213 (methicillin susceptible). [e]*Staphylococcus aureus* UC12673 (methicillin resistant). [f]*Staphylococcus epidermidis* UC 30031. [g]*Enterococcus faecalis* UC9217. [h]*Streptococcus pneumoniae* UC9912. [i]*Bacteroides fragilis* UC12199. [j]These values are for *Staphylococcus aureus* UC9271. [k]Figures in parenthesis are for the vancomycin control. [l]Figure in parenthesis is for the U-100592 control, which is equipotent to vancomycin.

Overall, these studies demonstrate the feasibility of preparing active oxazolidinone antibacterial agents which are conformationally constrained by a linker between the oxazolidinone ring and an attached phenyl group. The comparative SAR of these compounds and their non-tricyclic counterparts provides a number of interesting insights concerning the structural requirements for antibacterial activity.

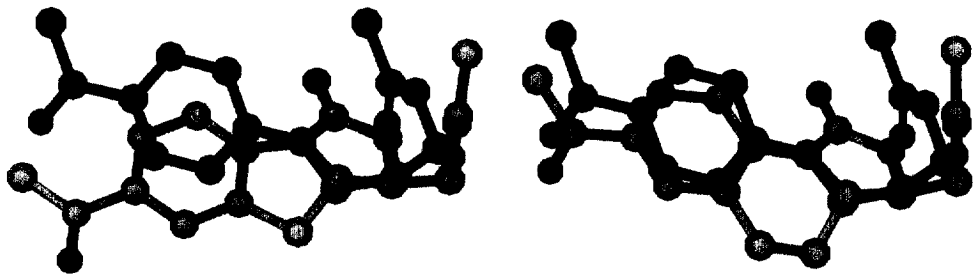


Figure 1: Superimposition of DuP 721 (**1**) with: (**A**) *trans*-[6,5,5] tricyclic analog **10b** and (**B**) *trans*-[6,6,5] tricyclic analog **12b**.

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References and Notes:

1. Current address: NeoRx Corporation, 410 W. Harrison, Seattle, WA 98119.
2. Current address: Central Research, Pfizer, Inc, Groton, CT 06340.
3. (a) Brickner, S.J. *Current Pharmaceutical Design* **1996**, *2*, 175; (b) Brickner, S.J.; Hutchinson, D.K.; Barbachyn, M.R.; Manninen, P.R.; Ulanowicz, D.A.; Garmon, S.A.; Grega, K.C.; Hendges, S.K.; Toops, D.S.; Zurenko, G.E.; Ford, C.W. *J. Med. Chem.* **1996**, *39*, 673; (c) Barbachyn, M.R.; Hutchinson, D.K.; Brickner, S.J.; Cynamon, M.H.; Kilburn, J.O.; Klemens, S.P.; Glickman, S.E.; Grega, K.C.; Hendges, S.K.; Toops, D.S.; Ford, C.W.; Zurenko, G.E. *J. Med. Chem.* **1996**, *39*, 680. (d) Shinabarger, D.L.; Marotti, K.R.; Murray, R.W.; Lin, A.H.; Melchior, E.P.; Swaney, S.M.; Dunyak, D.S.; Demyan, W.F.; Buysse, J.M. *Antimicrob. Agents Chemother.* **1997**, *41*, 2132.
4. Gregory, W.A.; Brittelli, D.R.; Wang, C.-L.J.; Wuonola, M.A.; McRipley, R.J.; Eustice, D.C.; Eberley, V.S.; Bartholomew, P.T.; Slee, A.M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
5. (a) Brickner, S.J.; Manninen, P.R.; Ulanowicz, D.A.; Lovasz, K.D.; Rohrer, D.C. 206th ACS National Meeting, Chicago, IL. August 22-27, **1993**. *Abst. Pap. Am. Chem. Soc.* 206 (1-2); (b) Brickner, S.J.; Manninen, P.R.; Ulanowicz, D.A.; Zurenko, G.E.; Schaadt, R.D.; Yagi, B.H.; Lovasz, K.D. 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, **1993**, paper 72.
6. Carlson, R.K.; Park, C.-H.; Gregory, W.A. US Patent 4,948,801 Aug. 14, 1990.
7. Yanagi, T.; Miyaura, N.; Suzuki, A. *Synth. Comm.* **1981**, *11*, 513.
8. Unpublished results of Palmer, J.R.; Piper, R.C. and Platte, T.F. Pharmacia & Upjohn.
9. Gleave, D.M.; Brickner, S.J. *J. Org. Chem.* **1996**, *61*, 6470.
10. More recently, conditions have been found whereby the parent **10a** can be selectively nitrated. This potentially provides an alternative, more direct, route to the morpholino and other amino analogs.
11. The lowest energy conformation was obtained by employing the MM2 potential. A conformational space search was then performed to locate a large population of low energy conformations. These were grouped and analyzed to evaluate conformational populations and geometric parameters. An average torsional angle was calculated for the largest population of low energy conformations.
12. Corresponding values for (±)-**11b** and (±)-**12b** are +15° and -19° respectively.