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SYNTHESIS OF NEW 3-THIOSUBSTITUTED CARBACEPHEM ANTIBIOTICS AND THEIR ACTIVITY AGAINST PENICILLIN RESISTANT *STREPTOCOCCUS PNEUMONIAE*

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Abstract: The synthesis of a series of 3-thiosubstituted carbacephem derivatives is described. The compounds were assayed against penicillin susceptible, intermediate and resistant strains of *Streptococcus pneumoniae*. Several analogs displayed potent in vitro activity against these organisms.
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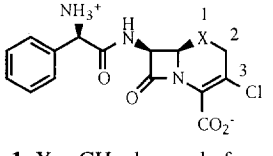
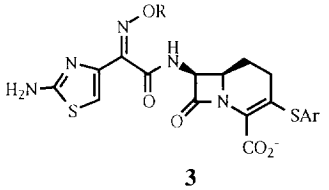
The emergence of microbial drug resistance has spurred a resurgence in the development of new antimicrobial agents to counter the specter of this evolving global public health threat.[1] The most frequent grounds for the administration of an antibiotic are diseases of the respiratory tract, and *Streptococcus pneumoniae* remains the major human pathogen responsible for such infections. Recently, there has been an alarming increase in the prevalence of *S. pneumoniae* strains with diminished susceptibility to penicillin and other clinically useful chemotherapeutic agents including macrolides, quinolones, and other β-lactams.[2] We now wish to report a new series of carbacephem antibiotics several of which possess potent activity in vitro against penicllin-resistant *S. pneumoniae* (PRSP).



1 X = CH_2 loracarbef
2 X = S cefaclor

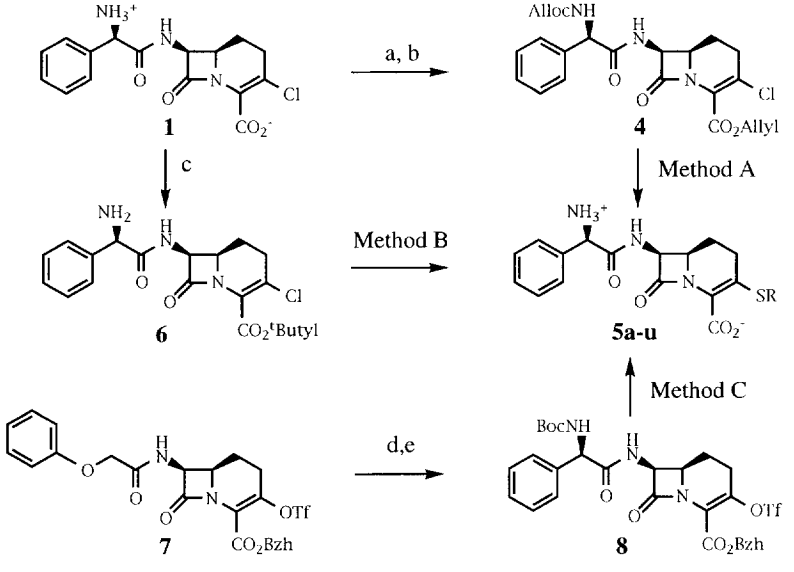


3

The carbacephems, exemplified by the prototypical commercial agent loracarbef **1**, are a novel class of β-lactam antibiotics that are distinguished from their cephalosporin counterparts (e.g., cefaclor **2**) in that the sulfur atom in the 1-position is replaced by a methylene group.[3] This, seemingly minor, modification confers some unique properties to the carbacephem skeleton, most notably increased stability relative to the corresponding cephalosporin nucleus. The remarkable stability of the carbacephems has been demonstrated in the synthesis of several 3-thiosubstituted carbacephems bearing a (D)-phenylglycine side chain at the 7-amino position.[4] In contrast to the corresponding cephalosporin analogs which had half-lives of less than one hour at pH 6.6, the carbacephems proved to be chemically robust. The enhanced chemical stability of the carbacephems has recently been further exploited to provide a series of 3-thiocarbacephem derivatives bearing aminothiazole alkoxime side chains (i.e., **3**).[5] Several of the resultant compounds showed impressive activity in vitro against methicillin resistant *Staphylococcus aureus*

(MRSA). Inspired by the enhanced potency of these compounds towards MRSA, we turned our attention to the possibility of exploring a complementary structure-activity relationship based on an analogous modification of loracarbef with the goal of improving activity against PRSP.

Scheme 1

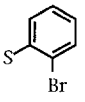
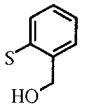
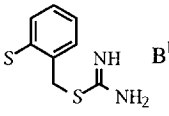
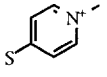
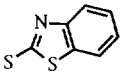
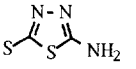
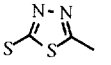
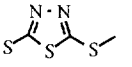
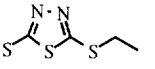
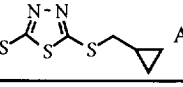


Reagents: (a) AllocCl, H_2O, Me_2CO, pH 8.5 ; (b) allyl bromide, Na_2CO_3, DMF; (c) isobutylene, H_2SO_4, dioxane; (d) PCl_5, Py, ^tBuOH; (e), Boc-(D)-phenylglycine, HBTU, DIPA then recrystalization from $CHCl_3$. Method A: (i) RSNa, DMF; (ii) $Pd(PPh_3)_4$, sodium 2-ethylhexanoate. Method B: (i) RSNa, DMF; (ii) TFA, CH_2Cl_2. Method C : (i) RSNa, DMF; (ii) TFA, triethylsilane, CH_2Cl_2

Chemistry

Previously reported routes to carbacephems bearing a sulfide at the 3-position employed thiolate displacement of the corresponding enol mesylate[4] or enol triflate.[5] In order to circumvent the multistep synthesis necessary to secure an alkyl sulfonate derivative of **1** we elected, initially, to explore displacement of the corresponding chloride present in loracarbef, available in bulk quantities as a consequence of its commercial manufacture. In the first instance, the protected loracarbef derivative **4** was examined wherein the 11-amino group is masked as its alloc derivative and the carboxylic acid is blocked as the corresponding allyl ester. Treatment of **4** with moderately nucleophilic thiolate salts, derived from a series of heterocyclic thiols via treatment with sodium hydride, gave rise to the corresponding sulfides in moderate yields. In certain sluggish cases gentle heating of the reaction mixture was necessary. Palladium(0) mediated deprotection followed by HPLC purification then afforded the desired 3-thiosubstituted analogs in a form suitable for antimicrobial evaluation.

Table 1. Antibacterial activity of 3-thiocarbacephems against *Streptococcus pneumoniae* strains

Compd	SR	Synthesis	MIC (μg/mL)[a] susc(3)	Int(3)	Res(5)
1	loracarbef	—	2	8	>16
5a	SMe	B	1	8	>16
5b		B	0.06	1	4
5c		B	0.06	0.25	2
5d		B	0.06	2	4
5e		B[b]	0.02	0.25	0.5
5f		A	0.06	1	2
5g		C	0.12	0.25	4
5h		C[c]	0.25	1	4
5i		A	0.12	0.5	4
5j		A	0.5	4	8
5k		B	0.25	2	16
5l		A	1	8	>16
5m		A	0.12	2	4
5n		A	0.5	4	>16
5o		A	0.06	0.25	1
5p		A	0.06	0.25	1
5q		A	0.06	0.5	2
5r		A	0.03	1	1
5s		A	<0.03	0.06	0.25
5t		A	0.03	0.25	0.5
5u		A	<0.03	0.06	0.25

[a]Minimum inhibitory concentration determined by broth microdilution method according to NCCLS (ref 6). Table values are modal MIC for the tested strains (numbers of strains in parentheses).

[b]synthesized from **5d** *t*-butyl ester with 11-amino Boc protection in a manner analogous to that reported in ref 7.

[c]synthesized from **5g**

When **4** was exposed to more nucleophilic alkyl and aryl thiolate salts complex mixtures resulted, presumably due to premature protecting group cleavage. To address this issue, recourse was made to the corresponding *t*-butyl ester derivative **5** in which the 11-amino group is not protected. Gratifyingly, **5** afforded clean reaction with alkyl and aryl thiolate salts even at low temperature. Several heteroaryl thiolates proved inert towards the chloride **4** and thus the more reactive trifflate **8** was synthesized from the previously reported phenoxyacetyl protected intermediate **7**[8] as outlined in Scheme 1.

Biological Evaluation

The antibacterial activity of the 3-thiosubstituted derivatives in vitro versus penicillin susceptible, intermediate and resistant *Streptococcus pneumoniae* strains as determined by broth microdilution MIC (μg/mL; number of strains in parentheses) is summarized in Table 1.[6] In general, alkyl thioethers, as exemplified by **5a,** offered no improvement in activity relative to loracarbef. A significant increase in potency was observed however in the aryl thioether analogs **5b-d**. The isothiourea containing side chain present in **5e** has been reported to improve activity against Gram positive organisms when appended to a cephalosporin nucleus[8] and indeed proved to be the most active member of the aryl thioethers examined in this series. Entries **5f-i** incorporating pyridine and pyrimidine derived thioethers proved to be generally equipotent to the arylthioethers. Compounds **5g**, **5h**, **5o**, **5q**, and **5r** have been disclosed previously,[4] although their activity against PRSP was not described, and were resynthesized for comparison using the methods described above. Derivatives **5j-m** employing benzothiazole, thiophene, N-methyl imidazole and N-methyl triazole thioethers respectively showed a diminution in activity relative to the 6-membered heterocyclic analogs described above. The greatest increase in activity was observed with the thiadiazole analogs. Entries **5o-r** were similar in activity and comparable to the more potent aryl thioether and 6-membered heteroaryl thioethers. However, appending a thioalkyl group at 2-position of the 1,3,4-thiadiazole moiety resulted in compounds **5s-u** having excellent activity (0.25 - 0.5 μg/mL) against PRSP and activities <0.03 μg/mL versus the penicillin susceptible strains. The expanded antimicrobial spectrum of the compounds described herein and their properties in vivo will be disclosed in a subsequent publication.

References and Notes

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