Synthesis and Application of [1,2,5]Triazepane and [1,2,5]Oxadiazepane as Versatile Structural Units for Drug Discovery

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Seven-membered heterocyclic [1,2,5]triazepane and [1,2,5]-oxadiazepane derivatives were synthesized as candidate structures for application in drug discovery in place of conventional piperazine or morpholine moieties, offering multiple sites for modification with functional groups. We first synthesized the *N*-protected heterocycles, and then confirmed their utility by synthesizing analogues of the oxazolidinone antibacterial agent linezolid. The analogues exhibited potent *in vitro* and *in vivo* antibacterial activity. In particular, compound 10a exhibited good *in vivo* efficacy when administered intravenously in a murine model of systemic infection with methicillin-resistant *Staphylococcus aureus* SR3637. These seven-membered heterocycles are expected to be versatile structural units for drug discovery.

Key words seven-membered heterocycle; piperazine; morpholine; oxazolidinone; drug discovery; medicinal chemistry

Pharmacologically active low-molecular organic compounds generally consist of a core structural unit, known as the pharmacophore, linked to appropriate functional group(s). Six-membered saturated heterocycles represented by piperazine or morpholine have been widely applied as functional or linker units to develop antihistamines,[1,2] antipsychotics,[3,4] and antibacterial agents.[5,6] Two examples are shown in Fig. 1.[7,8]

In particular, the piperazine ring is found in the structures of various pharmacologically active compounds as a linker or terminal structural unit. Piperazine has two N atoms that can be readily functionalized and can be used to improve both lipophilicity[9] and hydrophilicity,[10] which in turn can improve bioavailability[11] and pharmaceutical formulation properties.[12] We thought that the seven-membered heterocycles [1,2,5]triazepane and [1,2,5]oxadiazepane, which could be considered homologues of piperazine, might be similarly useful (Fig. 2). Since [1,2,5]triazepane contains three N atoms, a wide range of chemical modifications should be available. Only a few monocyclic [1,2,5]triazepane-type compounds have been synthesized so far,[13] and no [1,2,5]oxadiazepane derivatives have been reported. Accordingly, we set out to synthesize several *N*-protected derivatives and to examine whether they might be useful in medicinal chemistry.

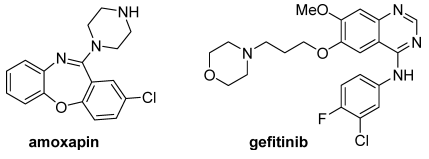


Fig. 1. Two Examples of Drugs Bearing a Six-Membered Heterocycle, Piperazine or Morpholine

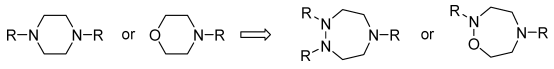
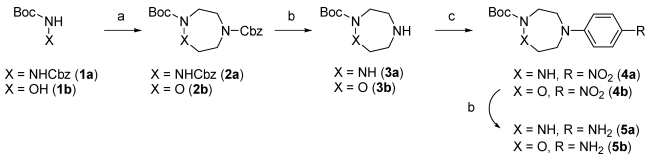


Fig. 2. Replacement of Six-Membered Heterocyclic Structures with Seven-Membered Heterocyclic Structures



Reagents and conditions: (a) NaH, bis(2-chloroethyl)carbamic acid benzyl ester, DMF, 60 °C; (b) 10% Pd/C, H_2, EtOH; (c) 4-fluoronitrobenzene, *i*-Pr_2NEt, CH_3CN.

Chart 1. Synthesis of [1,2,5]Triazepane and [1,2,5]Oxadiazepane Bearing a Boc Protecting Group at the 1-Position

First, we attempted to synthesize [1,2,5]triazepane and [1,2,5]oxadiazepane frameworks bearing *t*-butoxycarbonyl (Boc) protective groups. As shown in Chart 1, cyclization precursors, di-protected hydrazine **1a**[14] and bis(2-chloroethyl)carbamic acid benzyl ester,[15] were treated with NaH in *N*,*N*-dimethylformamide (DMF) to afford all *N*-protected [1,2,5]triazepane **2a** in good yield, followed by catalytic hydrogenation to obtain **3a** protected with a Boc group at the 1-position. The bulky Boc group at the 1-position is expected to decrease the basicity and nucleophilicity of the 2-position relative to the 5-position. As expected, selective arylation under basic conditions proceeded at the 5-position to afford nitrobenzene **4a**, and catalytic hydrogenation of **4a** provided aniline **5a** without cleavage of the N–N bond of the [1,2,5]triazepane framework. Compound **5a** should be a useful building block for *N*-aryl-type compounds. The [1,2,5]oxadiazepane derivative **5b** were similarly synthesized from commercially available **1b**.[16]

The triazepane protected with Boc groups at the 1- and 5-positions (**7**) was also synthesized *via* a similar procedure starting from **1a** and bis(2-chloroethyl)carbamic acid *t*-butyl ester (Chart 2).[17] This compound is also expected to be a versatile intermediate. For example, Pd-catalyzed *N*-arylation[18,19] of compound **3a** yielded a mixture of 2,5-diarylated compound **8a**, 5-arylated **8b**, and 2-arylated **8c**. However, arylation of compound **7** under the same conditions afforded 2-arylated compound **9** in good yield (Chart 3).

We next examined the potential of the new compounds for drug development. Oxazolidione antibacterial agents,[20] represented by linezolid[21] and eperezolid,[22] are a new class of antibacterial reagents effective against methicillin-resistant *Staphylococcus aureus* (MRSA)[23] or vancomycin-resistant *Enterococcus faecium* (VRE).[24] Since these compounds contain a six-membered saturated heterocycle (morpholine or piperazine), we examined the effect of replacing these rings with [1,2,5]triazepane and [1,2,5]oxadiazepane. The target compounds were synthesized from **3a** and **3b** *via* similar routes to those reported for the original compounds, respectively.[22,25] The new compounds **10a**[26] and **10b**[27] showed excellent *in vitro* antibacterial activity against MRSA or line-

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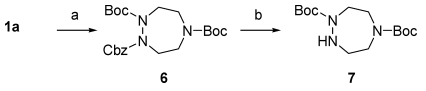
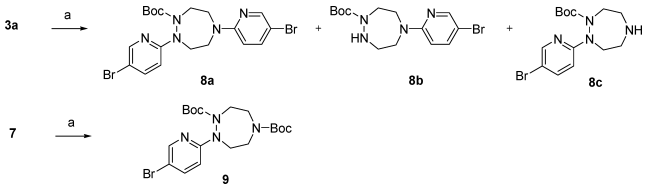


Reagents and conditions: (a) NaH, bis(2-chloroethyl)carbamic acid *t*-butyl ester, DMF, 60 °C; (b) 10% Pd/C, H_2, EtOH.

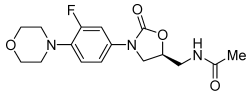
Chart 2. Synthesis of [1,2,5]Triazepane Protected with Boc Groups at the 1- and 5-Positions



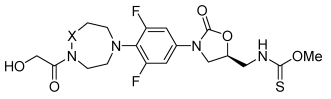
Reagents and conditions: (a) 2,5-dibromopyridine, $Pd_2(dba)_3$, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, *t*-BuONa, 1,4-dioxane, 80 °C.

Chart 3. Pd-Catalyzed *N*-Arylation of [1,2,5]Triazepanes **3a** and **7**

Table 1. Values of Minimum Inhibitory Concentration (MIC) of Oxazolidinone Derivatives **10a** and **10b**



linezolid



10a (X = NH)
10b (X = O)

Compound	MIC (μg/ml)			
	S. aureus SR3637	*S. aureus* NRS271	*E. faecium* SR27437	*S. pneumoniae* SR26180
linezolid	2	32	4	1
10a	0.25	2	0.25	0.125
10b	0.25	2	0.5	0.125

zolid-resistant *S. aureus*[28] in comparison with linezolid (Table 1). Furthermore, compound **10a** exhibited good *in vivo* efficacy when administered intravenously in a murine model of systemic infection, with MRSA SR3637 as the infectious organism.[29] Thus, [1,2,5]triazepane and [1,2,5]oxadiazepane appear to have great potential as structural units for drug development.

In summary, we synthesized seven-membered saturated heterocyclic [1,2,5]triazepane and [1,2,5]oxadiazepane derivatives as candidates for linker or terminal structural moieties for drug development. Introduction of these structures into oxazolidinone antibiotics in place of the original morpholine or piperazine moieties yielded novel active compounds. We consider that these heterocycles have great potential for structural variation and functionalization in drug development studies.

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References and Notes

1) Buckle D. R., Outred D. R., Smith H., Spicer B. A., *J. Med. Chem.*, **27**, 1452—1457 (1984).
2) Ranise A., Bondavalli F., Bruno O., Schenone S., D'Amico M., Parrillo C., Marrazzo R., Rossi F., *Farmaco*, **47**, 1263—1283 (1992).
3) Bartl V., Svatek E., Dlabac A., *Collect. Czech. Chem. Commun.*, **49**, 1816—1826 (1984).
4) Scott M. K., Reitz A. B., Villani F. J. Jr., Rasmussen C. R., U.S. Patent 5332732 (1994).
5) Ziegler C. B. Jr., Bitha P., Kuck N. A., Fenton T. J., Peterson P. J., Lin Y., *J. Med. Chem.*, **33**, 142—146 (1990).
6) Dave C. G., Shah P. R., Pandya P. S., Shah G. K., *J. Indian Chem. Soc.*, **66**, 810—812 (1989).
7) Schmutz J., Künzle F., Hunziker F., Gauch R., *Helv. Chim. Acta*, **50**, 245—254 (1967).
8) Gibson K. H., U.S. Patent 5770599 (1998).
9) Valenta V., Prosek Z., Metysova J., Valchar M., Dlabac A., Protiva M., *Collect. Czech. Chem. Commun.*, **50**, 1070—1077 (1985).
10) Meanwell N. A., Hewawasam P., Thomas J. A., Wright J. J. K., Russell J. W., Gamberdella M., Goldenberg H. J., Seiler H. M., Zavoico G. B., *J. Med. Chem.*, **36**, 3251—3264 (1993).
11) Nonaka K., Ueno A., *Arzeim. Forsh.*, **35**, 1499—1502 (1985).
12) Selkirk A. B., Dey M. J., U.S. Patent 4973591 (1990).
13) Szotor K., *Diss. Pharm. Pharmacol.*, **24**, 385—388 (1972).
14) Dutta A. S., Morley J. S., *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1712—1720 (1975).
15) Amble E., Dale J., *Acta Chem. Scand. B*, **33**, 584—586 (1979).
16) Compounds **3a** and **3b** are available from Watanabe Chemical Industries, Ltd. as from April 5, 2010.
17) Chambers M. S., Baker R., Billington D. C., Knight A. K., Middlemiss D. N., Wong E. H., *J. Med. Chem.*, **35**, 2033—2039 (1992).
18) Yin J., Zhao M. M., Huffman M. A., McNamara J. M., *Org. Lett.*, **4**, 3481—3484 (2002).
19) Wolfe J. P., Buchwald S. L., *Org. Synth. Coll. Vol.*, **10**, 423 (2004).
20) Brickner S. J., *Curr. Pharm. Des.*, **2**, 175—194 (1996).
21) Clemett D., Markham A., *Drugs*, **59**, 815—827 (2000).
22) 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., Ford C. W., Zurenko G. E., *J. Med. Chem.*, **39**, 673—679 (1996).
23) Tomasz A. N., *Engl. J. Med.*, **330**, 1247—1251 (1994).
24) Dixson S., Brumfitt W., Hamilton-Miller J. M. T., *Eur. J. Clin. Microbiol.*, **4**, 19—23 (1985).
25) Tokuyama R., Takahashi Y., Tomita Y., Tsubouchi M., Iwasaki N., Kado N., Okezaki E., Nagata O., *Chem. Pharm. Bull.*, **49**, 361—367 (2001).
26) Data for **10a**. Colorless powder; mp 127—128 °C (EtOH); ^{1}H-NMR ($CDCl_3$) δ: 3.10—3.18 (2H, m), 3.25—3.32 (2H, m), 3.35—3.41 (2H, m), 3.74 (1H, t, J=6.1 Hz), 3.82 (1H, dd, J=7.1, 9.1 Hz), 3.85—3.91 (2H, m), 3.95—4.12 (2H, m), 4.01 (3H, s), 4.38 (2H, d, J=4.5 Hz), 4.87—4.97 (1H, m), 6.71 (1H, t, J=6.1 Hz), 7.11 (2H, d, J=10.7 Hz). ^{13}C-NMR ($CD_3OD/CDCl_3$=1/9) δ: 47.2, 47.3, 51.0, 51.6, 52.1, 55.4, 57.3, 60.3, 71.5, 102.5 (2C, d, J=29 Hz), 124.7 (t, J=15 Hz), 133.9 (t, J=13 Hz), 154.2, 158.2 (2C, dd, J=9, 244 Hz), 174.0, 192.6. EI-LR-MS m/z: 415 (M^+-CO_2), 355, 300, 169. *Anal.* Calcd for $C_{18}H_{23}F_2N_5O_5S$: C, 47.05; H, 5.05; N, 15.24. Found: C, 46.88; H, 5.00; N, 15.18.
27) Data for **10b**. Colorless powder; mp 176—177 °C (EtOH); ^{1}H-NMR ($CDCl_3$) δ: 3.41 (2H, t, J=4.8 Hz), 3.47 (2H, t, J=5.1 Hz), 3.82 (1H, dd, J=6.9, 9.0 Hz), 3.91—4.15 (5H, m), 4.01 (3H, s), 4.36 (2H, s), 4.88—4.98 (1H, m), 6.85 (1H, t, J=6.3 Hz), 7.11 (2H, d, J=10.5 Hz). ^{13}C-NMR ($CD_3OD/CDCl_3$=1/9) δ: 47.2, 47.3, 50.3, 51.9, 54.5, 57.3, 57.4, 59.5, 71.5, 102.3 (2C, d, J=30 Hz), 124.2 (t, J=14 Hz), 133.9 (t, J=14 Hz), 154.2, 157.9 (2C, dd, J=9, 244 Hz), 172.2, 192.7. EI-LR-MS m/z: 416 (M^+-CO_2), 355, 213, 169. *Anal.* Calcd for $C_{18}H_{22}F_2N_4O_6S$: C, 46.95; H, 4.82; N, 12.17. Found: C, 46.93; H, 4.83; N, 12.16.
28) Tsiodras S., Gold H., Sakoulas G., Eliopoulos G., Wennersten C., Venkataraman L., Moellering R., Ferraro M. Jr., *Lancet*, **358**, 207—208 (2001).
29) The ED_{50} value of compound **10a** was 0.77 mg/kg/dose (linezolid: 2.13 mg/kg/dose) for intravenous administration.