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Synthesis of new oxathiazinane dioxides and their in vitro cancer cell growth inhibitory activity

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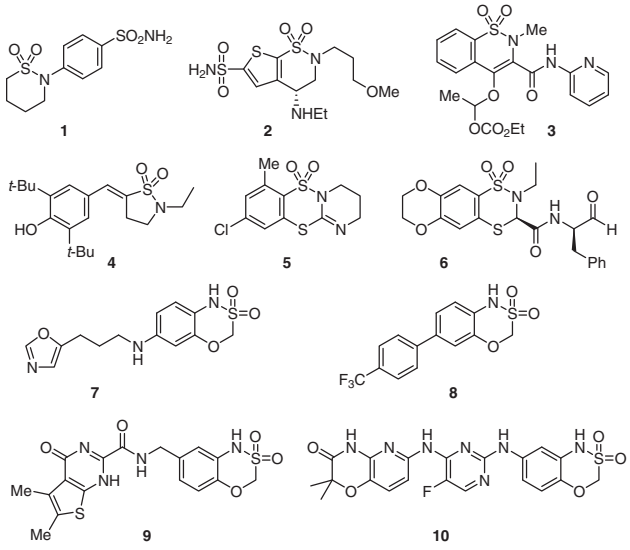
ABSTRACT

New oxathiazinane dioxides have been derived from D- and L-serine and tested for their in vitro cell growth inhibitory activity toward SKBR3 breast cancer cells. (5*R*)-5-(4-(4′-Bromomethyl)phenyl)benzyloxymethyl-[1,3,4]-oxathiazinane-3,3-dioxide showed a cytotoxicity of $IC_{50} \approx 10$ μM.

Sultams (cyclic sulfonamides) have shown potent biological activity.[1,2] For instance, sultam (**1**) is an antileptic agent,[3] brinzolamide (**2**) has been used for the treatment of glaucoma,[4] ampiroxicam (**3**),[5] and S-2474 (**4**) are COX-2 inhibitors,[6] benzodithiazine dioxide **5** has both antiviral and anticancer activities,[7] derivative **6** is a selective calpain I inhibitor,[8] **7** inhibits the binding of MIP-3β (macrophage inflammatory protein 3β) to CCR7 receptor,[9] **8** inhibits mitotic kinesin KSP (anti-cancer),[10] **9** is a metalloprotease inhibitor (can be use to inhibit tumor metastasis),[11] and **10** inhibits JAK kinase (can be used against solid and hematological malignancies such as leukemia and lymphomas).[12] Aminobenzosultams have been found to be lipoxygenase inhibitors[13] and other cyclic sulfonamides are herbicides.[14]

We report here the synthesis of new oxasultams of the type 5-hydroxymethyl-1,3,4-oxathiazinane-3,3-dioxide and disclose that some derivatives display in vitro growth inhibitory activity toward breast cancer (SKBR3) cell line. Our working hypothesis was that non-annulated oxathiazinane dioxides could imitate the polar moieties of anti-tumor compounds such as Edelfosine (**11**),[15] jaspine B (**12**),[16] or oleyl 2-acetamido-2-deoxy-α-D-glucopyranosides (e.g., **13**),[17] and that attaching a less polar side-chain through a 5-hydroxymethyl group could generate new cytotoxic agents.



Our scaffolds are chloromethanesulfonamide (*R*)-and (*S*)-**16** obtained from (*R*)- and (*S*)-**14**, both commercially available serine derivatives. Conversion of (*R*)-**14** into its methyl ester and subsequent reduction with $LiAlH_4$ in THF at 0 °C gave (*R*)-**15** in 94% and no epimerization (see below). Treatment of (*R*)-**15** with

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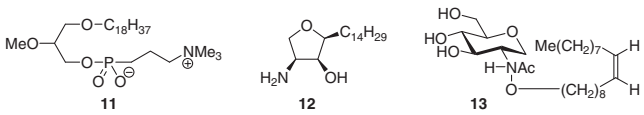


$ClCH_2SO_2Cl$ (1.2 equiv)/Et_3N (2 equiv) at 0 °C gave sulfonamide (*R*)-**16** in 63% yield. When stirred at 25 °C for several hours, (*R*)-**16** was converted into sultam (*R*)-**17**[18] (isolated in 28%) and polymeric material. As this latter base-induced HCl elimination was sluggish we protected the sulfonamide with a 4-methoxybenzyl group applying standard conditions. Thus (*R*)-**16** was treated with PMBBr (1.1 equiv) and K_2CO_3 (3 equiv) in DMF at 20 °C giving (*R*)-**18** in 73% yield. Heating (*R*)-**18** with Cs_2CO_3 (2 equiv) in DMF to 80 °C overnight produced sultam (*R*)-**19** (73%).

Hydrogenolysis of the benzyl ether moiety with H_2/Pd–C (H-Cube, 50 °C, 30 bar) gave (*R*)-**20** (85%). The latter alcohol displaced *para*-phenylbenzyl bromide in the presence or 50% aqueous NaOH and Bu_4NI/CH_3CN at 20 °C furnishing (*R*)-**21** (65%). Selective hydrolysis of the PMB ether was induced with CF_3COOH/CH_2Cl_2 at −5 °C giving (*R*)-**22** (68%). Similarly (*R*)-**20** reacted with 4,4′-bis(bromomethyl)biphenyl in excess to give (*R*)-**23** that was deprotected into (*R*)-**24**[19] (Scheme 1).

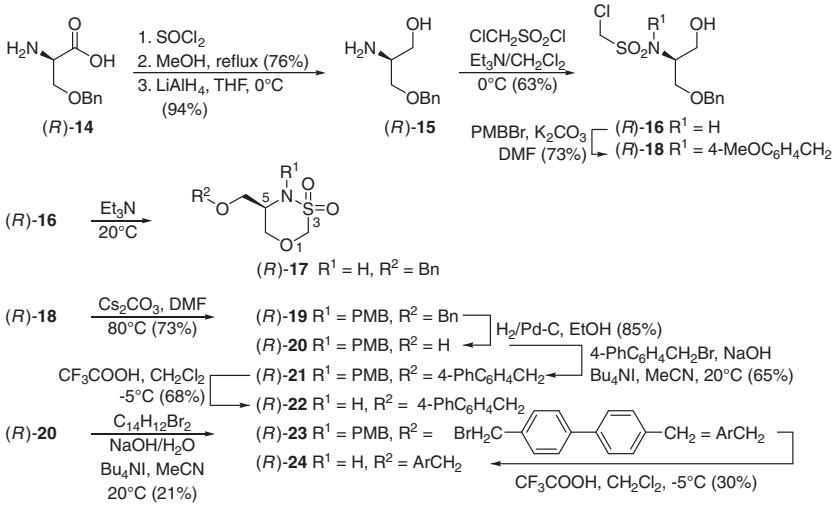
N-Benzyl derivatives were prepared as shown in Scheme 2. Treatment of (*R*)-**16** with $BnBr/K_2CO_3$/DMF at 23 °C gave a crude *N*-benzylsulfonamide that was heated to 80 °C in DMF containing 2 equiv of Cs_2CO_3. This provided sultam (*R*)-**25** in 45% (two steps). Selective hydrogenolysis of the benzyl ether moiety (H-Cube, EtOH, 45 °C, 40 bar) gave alcohol (*R*)-**26** (74%).[20] Debenzylation of (*R*)-**26** into (*R*)-**27** was very sluggish. On increasing H_2 pressure to 50 bar, no more than 10% of (*R*)-**27** was obtained. The latter was converted into oleyl ether (*R*)-**28** (34%) by reaction with oleyl methanesulfonate in excess at 23 °C (Bu_4NI 1 equiv, 50% aq NaOH, 15 h), into 4-fluorobenzyl ether (*R*)-**29** (86%) by reaction with 4-$FC_6H_4CH_2Br$ (same conditions), into 3-methoxybenzyl ether (*R*)-**30** (68%) by reaction with 3-$MeOC_6H_4CH_2Br$ (as above) and into benzoate (*R*)-**31** (73%) by reaction with BzCl in CH_2Cl_2 containing 2 equiv of DMAP (4-dimethylaminopyridine). Benzylamine derivative (*R*)-**32** (20%, two steps) was prepared by converting first alcohol (*R*)-**26** into its mesylate ($MeSO_2Cl/Et_3N/CH_2Cl_2$, 0 °C, 90 min) and reaction of the latter (crude) with an excess of benzylamine (MeCN, 60 °C, 15 h).

A number of *N*-methyl sultams were also prepared as shown in Scheme 3. Sulfonamide (*R*)-**16** was N-methylated first with MeI/K_2CO_3/DMF (23 °C, 10 h) and then treated with Cs_2CO_3/DMF (80 °C, 15 h) to give sultam (*R*)-**33** (48%, two steps). Hydrogenolysis of the benzyl ether (H-Cube, Pd–C/EtOH, 30 bar, 45 °C) provided alcohol (*R*)-**34**[21] in 85% yield. It was converted into its (*Z*)-oleyl ether (*R*)-**35** (57%), 4-phenylbenzyl ether (*R*)-**36** (52%) and β-naphthylmethyl ether (*R*)-**37** (75%) by treatment with (*Z*)-oleyl methanesulfonate (Bu_4NI, 50% aq NaOH, 23 °C, 15 h), with 4-$PhC_6H_4CH_2Br$ (Bu_4NI, MeCN, 50% aq NaOH, 23 °C, 15 h) and with 2-bromomethyl-naphthalene (Bu_4NI, 50% aq NaOH, 23 °C, 15 h), respectively.

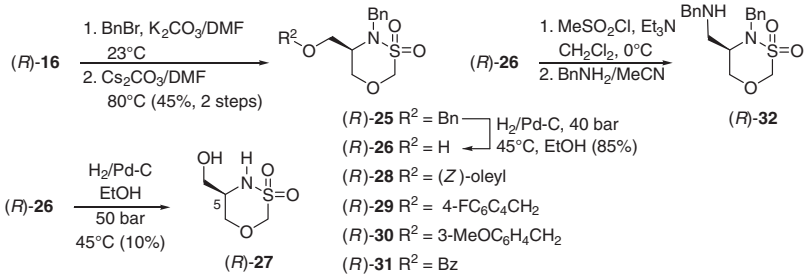
As we found that oxasultams (*R*)-**17** and (*R*)-**24** inhibited the growth of breast cancer cells (see below), we decided to prepare also a few (*S*)-derivatives. Thus following the route shown in Scheme 1, (2*S*)-2-amino-3-benzyloxypropane-1-ol ((*S*)-**15**) was treated with $ClCH_2SO_2Cl/Et_3N$ in CH_2Cl_2 to generate the corresponding sulfonamide (*S*)-**16**. On staying with Et_3N polymerization occurred together with the formation of (*S*)-**17** (33%). N-Benzylation of (*S*)-**16** followed by treatment with Cs_2CO_3/DMF gave (*S*)-**25** (45%, two steps). Selective hydrogenolysis of the benzyl ether of (*S*)-**25** furnished alcohol (*S*)-**26** that was converted into oleyl ether (*S*)-**28**. Protection of the sulfonamide group in (*S*)-**16** with PMB followed by treatment with Cs_2CO_3/DMF and selective hydrogenolysis of the benzyl group gave (*S*)-**20**. Alcohol (*S*)-**20** was transformed into 4-(4-bromomethylphenyl)benzyl ether (*S*)-**23** that was deprotected into (*S*)-**24**.

Mosher's ester of (*R*)-**26** and (*S*)-**26** obtained by reaction with (*R*)-(−)-α-methoxy-α-trifluoromethylacetyl chloride[22] gave esters with 98% and 95% ee, respectively (by ^{13}C–^{19}F satellites), thus demonstrated that less than 2.5% of our compounds have been epimerized.

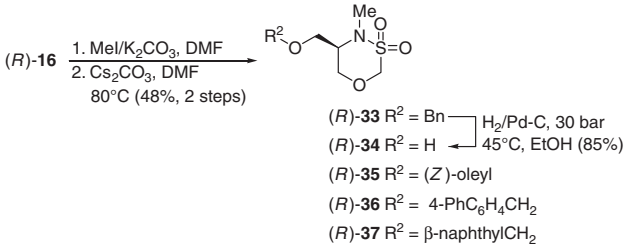
Compounds (*R*)-**17**, (*S*)-**17**, (*R*)-**22**, (*R*)-**24**, (*S*)-**24**, (*R*)-**25**, (*S*)-**25**, (*R*)-**28**, (*S*)-**28**, (*R*)-**29**, (*R*)-**30**, (*R*)-**31**, (*R*)-**33**, (*R*)-**35**, (*R*)-**36**, and (*R*)-**37** were submitted to the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium)/PMS(phenazine methosulfate: 5-methylphenazinium methylsulfate) assay to determine this inhibitory of the cell growth of SKBR3 cancer cells (breast cancer). Table 1 summarized our results and Figures 1 and 2 show concentration depending viability for selected oxasultams. The best cell growth inhibitory activities were observed for the free sulfonamides (no N-substituents). Interestingly (*S*)-**17** (5-benzyloxymethyl derivative) is slightly more active than its enantiomer (*R*)-**17** while (*S*)-**24** exhibits similar potency as its enantiomer (*R*)-**24**. These results suggest that the absolute configuration does not play a crucial role in the mode of action of these compounds. N-substitution of the oxasultams by benzyl or methyl



Scheme 1. Synthesis of benzyl- and (5*R*)-5-arylmethyloxymethyl[1,3,4]oxa-thiazinane-3,3-dioxides.



Scheme 2. Preparation of (5*R*)-4-benzyl-5-oxy- and -aminomethyl[1,3,4]oxathiazinane-3,3-dioxide derivatives.



Scheme 3. Preparation of (5*R*)-4-methyl-5-oxymethyl[1,3,4]oxathiazinane-3,3-dioxide derivatives.

group leads to lower inhibitory activity. The best compounds in our series are the two (4-bromomethylphenyl)-4-benzyloxymethyl derivatives (*R*)-**24** and (*S*)-**24** with a IC50 value of ca. 10 μM. Contrary to our initial working hypothesis (*R*)- and (*S*)-**28** with the long alkyl chain (oleyl) are not cytotoxic. The potential alkylation properties of (*R*)-**24** and (*S*)-**24** could be responsible of their cytotoxicity.

This work presents new monocyclic oxasultams with potential anti-cancer activities. They are obtained readily from D- or L-serine and their structures can be diversified widely. This should open the possibility to obtain new leads as anti-tumor agents. Work is underway with this objective in mind. We are pursuing studies to establish the biological targets of these compounds.

Table 1
Viability assays (MTS) on compounds (*R*)-**17**, (*S*)-**17**, (*R*)-**22**, (*R*)-**24**, (*S*)-**24**, (*R*)-**25**, (*S*)-**25**, (*R*)-**28**, (*S*)-**28**, (*R*)-**29**, (*R*)-**30**, (*R*)-**31**, (*R*)-**33**, (*R*)-**35**, (*R*)-**36**, and (*R*)-**37** toward SKBR3 (breast cancer) cell line

Product	%Viability				
	6.25 μM	12.5 μM	25 μM	50 μM	100 μM
(*R*)-**17**	100	100	100	80	16
(*S*)-**17**	100	94	78	51	22
(*R*)-**22**	75	75	75	44	46
(*R*)-**24**	66	34	10	10	10
(*S*)-**24**	99	81	26	18	20
(*R*)-**25**	89	82	88	83	82
(*S*)-**25**	81	80	82	87	96
(*R*)-**28**	100	100	99	100	100
(*S*)-**28**	71	81	81	82	96
(*R*)-**29**	93	86	88	99	96
(*R*)-**30**	100	100	100	96	89
(*R*)-**31**	81	98	88	89	100
(*R*)-**33**	85	81	88	83	82
(*R*)-**35**	72	71	65	65	65
(*R*)-**36**	89	66	60	61	52
(*R*)-**37**	81	82	73	74	74

Viability was determined after 72 h exposure.

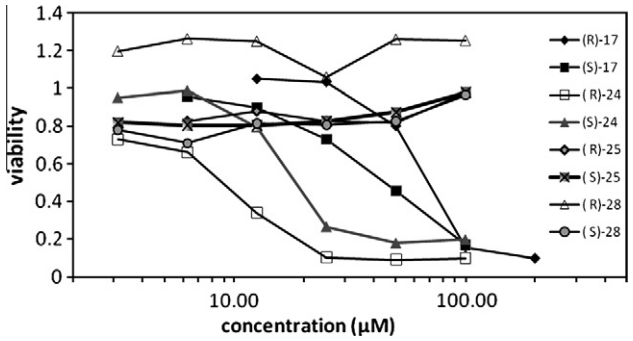


Figure 1. Plot of viability versus concentration for compounds (*R*)-**17**, (*S*)-**17**, (*R*)-**24**, (*S*)-**24**, (*R*)-**25**, (*S*)-**25**, (*R*)-**28**, and (*S*)-**28** toward SKBR3 (breast cancer) cell line. Viability was determined after 72 h exposure.

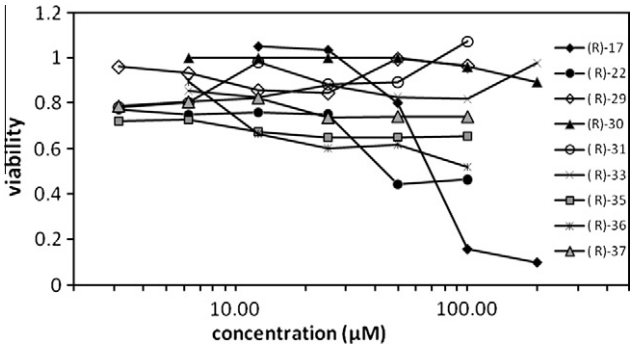


Figure 2. Plot of viability versus concentration for compounds (*R*)-**17**, (*R*)-**22**, (*R*)-**29**, (*R*)-**30**, (*R*)-**31**, (*R*)-**33**, (*R*)-**35**, (*R*)-**36**, and (*R*)-**37** toward SKBR3 (breast cancer) cell line. Viability was determined after 72 h exposure. Data for (*R*)-**17** appear again here as a reference.

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Supplementary data

Experimental details and spectroscopic characterization of new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.09.019.

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18. *Data of* (*R*)-**17**: $[\alpha]_{405}^{25} = -6$ (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H: 7.38–7.32 (m, 4H), 5.09 (d, ^3J = 8.9, 1H), 4.57–4.49 (m, 4H), 3.91 (m, 1H), 3.75 (m, 3H), 3.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C: 137.0 (s), 128.6, 128.1, 127.8 (3d), 73.6, 69.1, 56.5 (3t), 55.1 (d), 44.8 (6).
19. *Data of* (*R*)-**24**: $[\alpha]_{405}^{25} = -20$ (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H: 7.35–7.61 (m, 8H), 4.76 (m, 2H), 4.58 (m, 4H), 4.45 (d, ^3J = 11.6, 1H), 4.04 (m, 1H), 3.98 (dd, ^3J = 12.2, 3.1, 1H), 3.73 (br t, ^3J = 14.4, 1H), 3.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C: 140.7, 140.6, 137.0, 136.1 (4s), 129.5, 129.2, 129.1, 128.4, 127.5, 127.4, 127.3, 127.2 (8d), 82.0, 73.4, 68.9, 68.0 (4t), 56.4 (d), 33.2 (t).
20. *Data of* (*R*)-**26**: $[\alpha]_{405}^{25} = 20$ (*c* 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H: 7.38–7.33 (m, 4H, H arom.) 4.69 (d, ^2J = 11.3, 1H, *H*HC(2)) 4.67 (d, ^2J = 14.8, 1H, N-CH*H*-Ph) 4.55 (d, ^2J = 11.3, 1H, H*H*C(2)) 4.31 (d, ^2J = 14.8, 1H, N-C*H*H-Ph) 4.04 (m, 1H, CH_2-C(5)), 3.97 (m, 1H, H_2C(7)) 3.91 (dd, ^2J = 12.4, ^3J = 1.9, 1H, *H*HC(6)) 3.58 (dd, ^2J = 12.4, ^3J = 3.0 , 1H, H*H*C(6)) 3.41 (m, 1H, CH-N) 2.42 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C: 135.68 (s, C arom.) 128.86 (d, ^1J = 161.3, CH arom.) 128.50 (d, ^1J = 157.6, CH arom.) 128.23 (d, ^1J = 167.0, CH arom.) 82.57 (t, ^1J = 154.8, C(2)) 66.29 (t, ^1J = 146.4, C(7) or CH_2(6)) 60.50 (d, ^1J = 140.3, C(5)) 60.10 (t, ^1J = 145.0, C(7) or CH_2(6)) 50.39 (t, ^1J = 140.3, N-CH_2-Ph).
21. *Data of* (*R*)-**34**: $[\alpha]_{405}^{25} = -34$ (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H: 4.60 (m, 2H), 4.06 (dd, ^3J = 11.6, 6.5, 1H, 3.94 (m, 3H), 3.61 (m, 1H), 2.96 (s, 3H).
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