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Microwave Synthesis of Chiral *N*-Benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin/thiazin-3(4*H*)-ones *via* Smiles Rearrangement and their Biological Evaluation

Li-juan Meng, Hua Zuo,† B. V. D. Vijaykumar, Gautam Dupati, Kyung-Min Choi, Kiwan Jang, Yong-Jin Yoon,‡ and Dong-Soo Shin*

Departments of Chemistry and Physics, Changwon National University, Changwon 641-773, Korea
**E-mail: dsshin@changwon.ac.kr*
†*College of Pharmaceutical Sciences, Southwest University, Chongqing 400716, China*
‡*Department of Chemistry, Gyeongsang National University, Chinju 660-701, Korea*
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Optically active *N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and *N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones with potential synthetic and pharmacological interest were prepared *via* Smiles rearrangement in conventional as well as microwave irradiation conditions in one-pot from inexpensive (*S*)-2-chloropropionic acid. Most of the compounds displayed good inhibition against Gram positive bacteria and fungi in the antibiotic test.

Key Words : Oxazinones, Thiazinones, Smiles rearrangement, Microwave irradiation, Antibiotic

Introduction

1,4-Benzoxazinones and 1,4-benzothiazinones are fascinating tools present in clinically significant pharmaceuticals and other biologically active molecules. Compounds containing 2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-one moiety are well known to show wide biological activities such as being antiulcer,[1] antihypertensive,[2] antifungal,[3,4] anticancer,[5] anti-inflammatory,[6,7] antimicrobial[8] and antithrombotic.[9] These are also known as 5-HT receptor antagonists,[10,11] bladder-selective potassium channel openers,[12] inhibitor of calcium channel,[13] Na^+/H^+ exchange inhibitor,[14] antidepressant,[15,16] dopamine D_2 receptor agonists and inhibitors of PI3Kinaseγ.[17-20] Some substituted [1,4]-oxazinones are also related to blocking the TXA_2 receptor and activate the PGI_2 receptor.[21] Certain kinds of benzo[1,4]oxazin-3(4*H*)-ones are photo chromic compounds[22,23] and some possess herbicidal activity.[24]

Benzo[*b*][1,4]thiazin-3(4*H*)-ones exhibit bacteriostatic,[25] antimicrobial,[26] antifungal,[27,28] Na^+/H^+ exchange system inhibitor,[29] calcium antagonist.[30,31] These are also useful as prophylactic drugs and/or therapeutic drugs in hyperlipemia, hyperglycemia, obesity, diseases attributable to sugar tolerance insufficiency, hypertension, osteoporosis, cachexia, and complications of diabetes such as retinopathy, nephrosis, neuropathy, cataract, coronary artery disease and arteriosclerosis.[32] Moreover, benzo[1,4]thiazin-3(*4H*)-ones are used as herbicide.[33]

The existing methods to furnish oxazinones and thiazinones involved substituted 2-aminophenol and 2-aminobenzenethiol as starting materials, but chiral benzo[1,4]-oxazinones/thiazinones are limited greatly due to the complicated methods or expensive materials. As a part of our continuing efforts to develop convenient synthetic methods to explore interesting heterocyclic systems,[34] we herein described a synthetic route for optically active benzo-fused [1,4]-oxazinones/thiazinones based on our previous study.[35,36] This method involved a Smiles rearrangement based one pot synthesis of optically active *N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin/thiazin-3(4*H*)-ones and their biological properties.

Experimental

Melting points were determined on a MEL-TEMP® capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph AUTOPOL IV digital polarimeter. Nuclear magnetic resonance (^1H and ^{13}C NMR spectra) were recorded in $CDCl_3$ (400 MHz for ^1H and 100 MHz for ^{13}C, respectively) with TMS as the internal reference on Bruker Advance 400 FT spectrometer. Chemicals shifts were reported in parts per million. Mass spectra (MS) were measured by the EI method. Silica gel (Merck D-6100, 70-230 mesh, ASTM) was used for flash column chromatography. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60F-254) with or without UV indicator. *N*,*N*-Dimethylformamide was distilled over anhydrous magnesium sulfate. All other reagents were commercially available (Acros, Aldrich) and were used without further purification. All microwave-assisted reactions were carried out on KMIC-1.5KW microwave reactor from Korea Microwave Instrument Company.

Synthesis of (*S*)-*N*-benzyl-2-chloropropanamide (3). To a solution of (*S*)-2-chloropropanoic acid (1.0 g, 9.21 mmol) in dichloromethane was added DCC (2.28 g, 11.05 mmol) at 0 °C in several portions. The resulting mixture was stirred for 30 minutes at 0 °C, followed by the addition of benzyl amine (0.98 g, 9.21 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was filtered and the filtration cake was washed with dichloromethane carefully. The filtrate was concentrated to give the crude product.

Pure product was obtained by column chromatography using mixture of hexane and ethyl acetate as eluent (1.43 g, 79%).

A white solid; mp 79-80 °C; $[\alpha]_D^{20}$ –3.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (d, *J* = 6.8 Hz, 3H), 4.44-4.48 (m, 3H), 7.30-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.78, 43.90, 55.92, 127.70, 127.74, 128.84, 137.54, 169.54.

Typical Procedure for the Synthesis of (*R*)-4-benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones. The solution of aryl substituted 2-chlorophenols (2.40 mmol), (*S*)-*N*-benzyl-2-chloropropanamide (0.49 g, 2.40 mmol), Cs_2CO_3 (2.40 g, 7.36 mmol) in dry DMF was placed into microwave oven (KMIC-1.5kW) and irradiated at 130 °C (or heated conventionally at 130 °C) for the period listed in Table 1. The solvent was evaporated under reduced pressure. The residue was poured into water and was then extracted by ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product which was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate.

NMR, Mass, IR and Optical Data for Compounds 5a-d.

Compound 5a: A colorless oil; $[\alpha]_D^{20}$ –4.8 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 2996, 2935, 1684, 1582, 1494, 1392, 1293, 1095, 1000, 860, 785, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 6.8 Hz, 3H), 4.79 (q, *J* = 6.8 Hz, 1H), 5.14 (s, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 7.22-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.54, 45.31, 73.77, 116.22, 117.73, 122.60, 126.48, 127.60, 127.78, 128.82, 128.97, 135.74, 145.04, 166.57; MS (EI) *m/z*: 287 (M^+, 75%), 154 (10), 91 (100), 65 (6).

Compound 5b: A colorless oil; $[\alpha]_D^{20}$ –3.7 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 2991, 2935, 1684, 1582, 1494, 1392, 1289, 1095, 1002, 863, 779, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, *J* = 6.8 Hz, 3H), 4.75 (q, *J* = 6.8 Hz, 1H), 5.19 (s, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) *ä* 16.55 45.27, 73.78, 116.03, 116.63, 120.56, 125.54, 126.47, 127.62, 128.27, 128.98, 135.71, 145.17, 166.59; MS (EI) *m/z*: 330 (M^+, 75%), 198 (8), 91 (100), 65 (8).

Compound 5c: A colorless oil; $[\alpha]_D^{20}$ –3.9 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3365, 3034, 2935, 1688, 1582, 1509, 1407, 1300, 1118, 852, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 6.8 Hz, 3H), 4.79 (q, *J* = 6.8 Hz, 1H), 5.10 (d, *J* = 16 Hz, 1H), 5.15 (d, *J* = 16 Hz, 1H), 6.60-6.65 (m, 1H), 6.75-6.82 (m, 2H), 7.24-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.51, 45.46, 73.82, 105.41, 109.18, 116.08, 125.47, 126.49, 127.56, 128.96, 135.93, 145.34, 157.72, 166.44; MS (EI) *m/z*: 271 (M^+, 71%), 138 (9), 91 (100), 65 (6), 45 (19).

Compound 5d: A colorless oil; $[\alpha]_D^{20}$ +5.5 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3352, 3045, 2992, 1696, 1582, 1464, 1373, 1270, 1130, 883, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 6.8 Hz, 3H), 4.49 (q, *J* = 6.8 Hz, 1H), 5.38 (d, *J* = 15.6 Hz, 1H), 5.62 (d, *J* = 15.6 Hz, 1H), 6.91-7.01 (m, 3H), 7.14-7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.47, 47.34, 74.66, 115.86, 123.54, 125.36, 125.71, 126.94, 127.18, 127.80, 128.36, 136.60, 150.13, 169.19; MS (EI) *m/z*: 287 (M^+, 46%), 154 (13), 91 (100).

General Procedure for the Synthesis of (*R*)-4-benzyl-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones (5e to 5g). The solution of aryl substituted 2-chlorobenzenethiols (2.23 mmol), (*S*)-*N*-benzyl-2-chloropropanamide (0.44 g, 2.23 mmol), Cs_2CO_3 (2.18 g, 6.69 mmol) in dry DMF was placed into microwave oven (KMIC-1.5kW) and irradiated at 130 °C (or heated conventionally at 130 °C) for the period listed in Table 2. The solvent was evaporated under reduced pressure. The residue was poured into water and was then extracted by ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product which was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate.

NMR, Mass, IR and Optical Data for Compounds 5e-g.

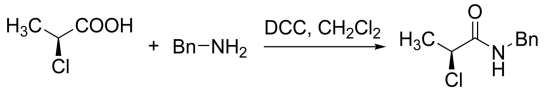
Compound 5e: A colorless oil; $[\alpha]_D^{20}$ –4.9 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3334, 3065, 2981, 1673, 1570, 1445, 1369, 1251, 1042, 777, 600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.8 Hz, 3H), 3.63 (q, *J* = 6.8 Hz, 1H), 5.23 (s, 2H), 6.93-6.95 (m, 1H) 7.03-7.11 (m, 2H), 7.19-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.13, 37.58, 49.27, 116.26, 123.52, 124.54, 126.20, 127.12, 127.36, 128.91, 132.73, 136.59, 140.38, 167.50 ; MS (EI) *m/z*: 303 (M^+, 76%), 247 (23), 184 (9), 170 (49), 91 (100), 65 (13), 45 (20).

Compound 5f: A colorless oil; $[\alpha]_D^{20}$ –5.1 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3331, 3034, 2935, 1670, 1570, 1480, 1365, 1216, 1106, 814, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 7.2 Hz, 3H), 3.64 (q, *J* = 7.2 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 5.21 (d, *J* = 16.4 Hz, 1H), 6.91 (d, *J* = 9.2 Hz, 1H), 7.06-7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 7.31-7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.28, 37.85, 48.76, 118.89, 124.41, 126.20, 127.18, 127.36, 128.21, 128.72, 128.91, 136.47, 137.81, 167.60; MS (EI) *m/z*: 303 (M^+, 78%), 247 (24), 170 (37), 91 (100), 65 (9), 45 (9).

Compound 5g: A colorless oil; $[\alpha]_D^{20}$ –5.7 (*c* 1.0, MeOH); IR (KBr) ν/cm^{-1}: 3083, 2981, 1658, 1574, 1414, 1357, 1210, 802, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.8 Hz, 3H), 3.62 (q, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 16.4 Hz, 1H), 5.23 (d, *J* = 16.4 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.20 (m, 2H), 7.27-7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.19, 37.81, 48.86, 118.03, 121.05, 123.62, 126.23, 127.43, 128.95, 129.47, 132.81, 136.31, 140.21, 167.67; MS (EI) *m/z*: 303 (M^+, 98%), 247 (32), 170 (50), 91 (100).

Results and Discussion

Our synthesis started with the preparation of optically active *N*-benzyl-(*S*)-2-chloropropanamide (**3**). In this purpose (*S*)-2-chloropropionic acid (**1**)[37] was coupled with benzyl amine (**2**) in presence of DCC to afford compound **3** (Scheme 1).



1 2 3

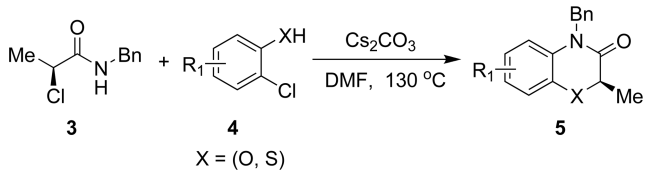
Scheme 1. Synthesis of *N*-benzyl-(*S*)-2-chloropropanamide (**3**).

Reaction of *N*-benzyl-(*S*)-2-chloropropanamide (**3**) with variously substituted 2-chlorophenols and 2-chlorobenzenethiols gave the corresponding (*R*)-*N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and (*R*)-*N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones *via* Smiles rearrangement[38] in one pot. The reaction proceeded smoothly in DMF at 130 °C under conventional heating.

The same reaction was then tried under microwave irradiation instead of conventional heating and was complete within 15-35 min to afford the desired product in 72-85% yield (Table 1). Investigation on reaction time, yield and purification procedure showed that the synthesis under microwave irradiation was much more efficient method. All reactions that took 8-12 hours under conventional heating method were completed within minutes under microwave irradiation giving moderate to excellent yields.

The GC-MS spectra clearly indicated the formation of the corresponding products. IR, ^{1}H NMR and ^{13}C NMR spectra further confirmed the structures of oxazinones and thiazinones.

A mechanistic rationalization for this reaction is provided in Scheme 3. The presence of Cs_2CO_3 facilitates the formation of *O*- or *S*-alkylated product **6** by displacement of chlorine. The cyclization of *O* or *S*-alkylated product by Smiles rearrangement occurred *via* two steps; the spiro-type intermediate was formed in the first step, and was rearranged in the second step with the loss of HCl yielding compound **5**. The presence of optical activity in the final products indicates that the initial *O*- or *S*- alkylation takes place by S_N2 process.

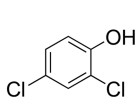
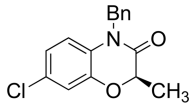
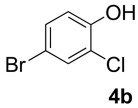
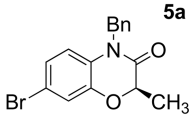
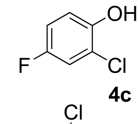
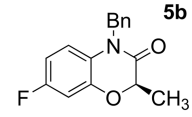
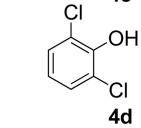
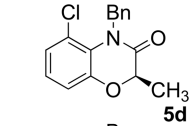
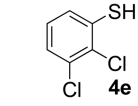
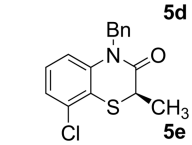
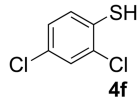
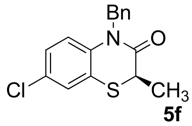
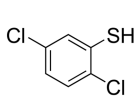
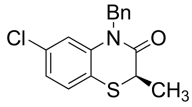


3 4 5

X = (O, S)

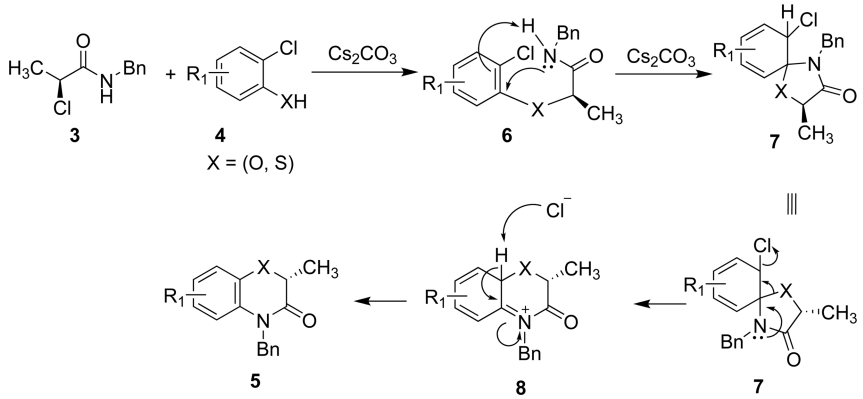
Scheme 2. Synthesis of **5** using Smiles rearrangement.

Table 1. Comparison between conventional heating (C.H.) and microwave irradiation (M.W.) of Smiles rearrangement (Scheme 2)

Entry	4	Products	C.H **4a-g** to **5a-g**		M.W **4a-g** to **5a-g**	
			Time (h)	Yield (%)[a]	Time[a] (min)	Yield (%)[b]
1	 **4a**	 **5a**	12	83	15	85
2	 **4b**	 **5b**	8	80	30	78
3	 **4c**	 **5c**	10	70	20	75
4	 **4d**	 **5d**	14	80	35	72
5	 **4e**	 **5e**	10	75	35	75
6	 **4f**	 **5f**	10	78	30	80
7	 **4g**	 **5g**	8	80	20	78

[a]The microwave-assisted reaction time is the hold time at final temperature (reaction temperature). [b]Yields refer to the isolated pure compounds after column chromatography.

Compounds **5a-g** were synthesized according to the above procedure and screened for the *anti*-microbial activity. The



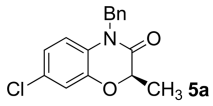
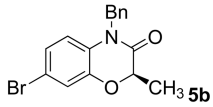
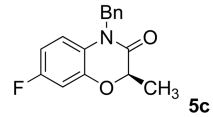
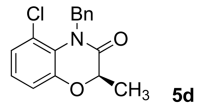
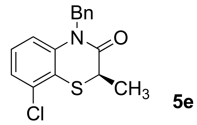
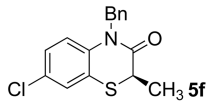
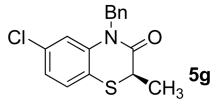
3 4 6 7

X = (O, S)

5 8 7

Scheme 3. Proposed mechanism for the formation of (*R*)-*N*-benzyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin/thiazin-3(4*H*)-ones **5**.

Table 2. Antibacterial activity of **5a-g** expressed as MIC μg/mL

Entry	Products	Microorganisms[a]				
		Gram-positive		Gram-negative		Fungi[b]
		B. S.	S. A.	E. C.	M. L.	C. A.
9	 **5a**	256	4	1	8	0.5
10	 **5b**	32	2	256	128	128
11	 **5c**	8	32	>256	1	1
12	 **5d**	0.25	256	0.25	256	-
13	 **5e**	>256	4	>256	>256	2
14	 **5f**	0.25	256	0.25	1	-
15	 **5g**	4	256	256	128	256
16	Metronidazole	0.25	256	0.25	1	-
17	Ampicillin Sodium	4	256	256	128	256

[a]Gram positive bacteria: B.S., Bacillus subtilis CMCC 63501; S.A., Stapylococcus aureus CMCC 26003; Gram negative bacteria E.C.; Escherichia coli CMCC 44102; M.L., Micrococcus luteus CNCC 28001. [b]Fungi: C.A., Candida albicans CMCC 98001.

antimicrobial activity was assayed *in vitro* by the twofold broth dilution technique (Ericcsson, H. M. *et al*., 1971; Stalons, D. R. *et al*., 1975) against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram negative bacteria (*Escherichia coli*, *Micrococcus luteus*), and fungi (*Candida albicans*). The minimal inhibitory concentrations (MIC, μg/mL) were defined as the lowest concentrations of compound that inhibited the growth of each strain. Ampicillin and Metronidazole were used as reference antibacterial and antifungal substances, respectively. The results of antimicrobial activities were summarized in Table 2.

Most of the compounds displayed good inhibition of the growth of Gram positive and Gram positive bacteria, including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Micrococcus luteus* and *Candida albicans*. Some of the novel oxazinones and thiazinones exhibit excellent activity (compound **5d** and **5f**), which was very close to the reference drugs Ampicillin and Metronidazole. On the other hand, with regard to the influence of the substitution at the benzene ring fluorine atom enhancing the activity against Gram positive and Gram negative bacteria compared with chlorine or bromine atom. Excellent activities shown by **5a**, **5c**, **5e** against *Candida albicans* can be explained by the position of halogen atom on the aromatic ring where **5b** showed moderate activity. Further studies including other biological activities and expansion of derivatives are currently under progress in our laboratory.

Conclusion

A one-pot microwave assisted synthesis of optically active *N*-benzylated-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ones and *N*-benzylated-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones has been described with potential synthetic and pharmacological interest using Smiles rearrangement as a key step.

The antibacterial test showed most of the compounds display good inhibition of the growth of Gram positive, Gram positive bacteria and fungi which encourage us to explore diversity of compounds of this class.

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