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Investigation on the oxidation of aryl oxiranylmethanols and the synthesis of 2-aryl-*N*-thiazolyl-oxirane-2-carboxamides as glucokinase activators

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ABSTRACT

$RuCl_3/NaIO_4$-initiated oxidation of oxiranemethanols was investigated, and two products, oxirane-2-carboxylic acid and (5′-oxotetrahydrofuran-3-yl)acetic acid, were obtained in variant ratios. The product structures were determined and a tentative mechanism involving oxidation-rearrangement-oxidation process was proposed. Glucokinase enzymatic assay revealed that oxiranecarboxamides **4a–c** retained moderate GK activation potency with amide **4a** showing an EC_{50} value of 584 nM and a high activation fold of 3.14. However, (5′-oxotetrahydrofuran-3-yl)acetamide **11a** is inactive. This study not only provided an alternative protocol to access (5′-oxotetrahydrofuran-3-yl)acetic acid analogs, but also yielded nanomolar GA activators (esp. **4a**) for further structure–activity relationship study.

By catalyzing the first step of glycolysis and phosphorylation of glucose to glucose 6-phosphate, glucokinase (GK), a unique isoform of the hexokinase enzymes, has emerged as a promising drug target for the type-II diabetes.[1] A growing number of small molecule glucokinase activators (GKAs) have been developed with the aim to activate this enzyme by interacting on its allosteric pocket to achieve anti-hyperglycemic effects.[2–7] Several such compounds have already approached in clinic, including the arylpropanamide **1**(PSN-GK1),[8–10] which was reported by OSI Pharmaceuticals and currently in phase I/II clinical trials (Fig. 1).

Based on the reported co-crystal structures of GK and its activators,[2,11] it was postulated that in GKAs like **1**, the backbone hydrogen and carbonyl oxygen of Arg^{63} anchor the thiazole nitrogen and amide NH through H-bonding, respectively, whereas the tetrahydro-2*H*-pryan-4-yl and the aryl are embedded in a lipophilic environment created by Met^{235}, Tyr^{214}, and Val^{62}. Therefore, much effort in the development of new GKAs currently focuses on optimization of these key pharmacophoric components.[2,3,11] We have also reported[12] a series of new GKAs bearing the propanamide skeleton by introducing diversified substituents to the aminothiazole C-4 or C-5 position, and identified several potent GKAs (e.g., **2**), with potency comparable to that of **1**.

In the meantime, a strategy to develop conformationally constrained propanamides has been reported as well. This was represented by cyclopropanecarboxamide **3**[3] (LY-2121260), a clinical GKA developed by Lilly Research Laboratories. Similar to **1**, this compound can stimulate insulin secretion in a glucose-dependent manner in pancreatic β-cells and increase glucose consumption in rat hepatocytes.[3] Encouraged by this result, we decided to explore the synthesis and GK activation of compounds **4a–c** containing an oxirane-2-carboxamide scaffold (Fig. 1). Herein, we report our synthesis and preliminary pharmacological investigations.

In the beginning, we decided to synthesize the target compounds **4a–c** by epoxidation of the key intermediate acrylic acid **5a**,[13,14] followed by amidation with appropriate aminothiazoles[12,15] (Scheme 1, path a). Although, this approach is straightforward, epoxidation of acid **5a** using *m*CPBA in CH_2Cl_2 at either rt or reflux only gave a complex mixture and no expected product was obtained. Esterification of acid **5a** followed by *m*CPBA-epoxidation gave no product as well. Changing to other oxidants including ^tBuOOH and H_2O_2, no reaction occurred. Based on these results, it is apparent that the failure of the epoxidation reaction is due to the electron-deficient property of acrylic acid **5a**, therefore, an alternative synthetic strategy was designed (path b, Scheme 1).

As described in Scheme 1, acid **5a** was first converted into the methyl ester and then subjected to reduction with DIBAL-H at −78 °C to afford allylic alcohol **7a** in 80% overall yield. Subsequent epoxidation[13] of alcohol **7a** with *m*CPBA in CH_2Cl_2 at 0 °C–rt went through smoothly, and the expected oxiran-2-ylmethanol **8a** was obtained in 90% yield. Oxidation of alcohol **8a** to acid **6a** was

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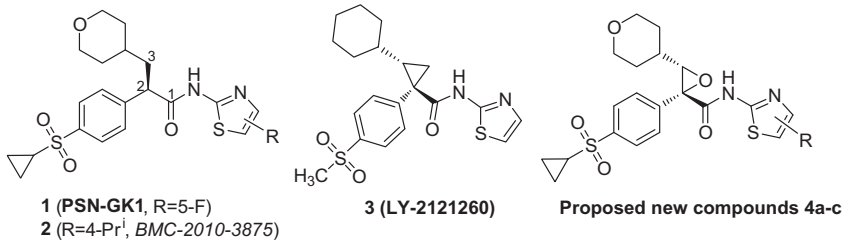
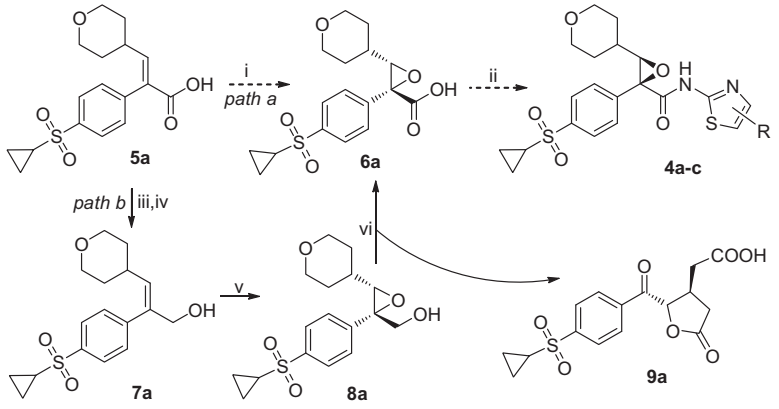


Figure 1. Reported GK activators and our proposed new analogs.



Scheme 1. Reagents and conditions: (i) 30% H_2O_2, 5% NaOH, CH_3CN, rt-60 °C or *m*CPBA, CH_2Cl_2, rt to reflux; (ii) an appropriate thiazole-2-amine, TBTU, Et_3N, DCM, rt; (iii) $SOCl_2$, MeOH, reflux; (iv) DIBAL-H, THF, −78 °C-rt; (v) *m*CPBA, CH_2Cl_2, 0 °C-rt; (vi) $NaIO_4$, $RuCl_3{\cdot}H_2O$, rt, MeCN:CCl_4:H_2O = 2:2:3.

conducted by following a procedure reported by Panek et al[16] using RuO_4 as the oxidant. It was found that the oxidation of **8a** with RuO_4, prepared in situ by mixing 5.0 equiv of $NaIO_4$ and a catalytic amount of $RuCl_3$ (10%), occurred very slowly, and an elongated time of 24 h was generally needed to complete the conversion. Although with careful column chromatography, the product obtained in 33% yield turned out to be a mixture on the basis of its NMR spectroscopic data with a ratio of 20:12. Fortunately, repetitive preparative TLCs allowed us to separate each component with sufficient amount for structural characterization.

The major component was confirmed to be the expected oxirane-2-carboxylic acid **6a** on the basis of its NMR spectra. Specifically, formation of the oxirane ring is ascertained by the existence of a doublet peak with chemical shift of 3.33 ppm and coupling constant of 9.0 Hz in the 300 M ^{1}H NMR, and the existence of a tertiary carbon at 67.3 ppm and a quaternary carbon at 61.7 ppm in the 400 M ^{13}C NMR. Quite surprisingly, all the diagnostical spectroscopic signals for the oxirane ring were not observed in the corresponding NMR spectra of the minor product. Moreover, the typical signals of tetrahydropyran ring, especially the two sets of proton peaks at 3.84 and 3.21 ppm and two secondary carbon signals at 66.6 and 66.1 ppm (–CH_2OCH_2–), also disappeared. All these results indicated that the second product does not contain the oxirane ring, and the tetrahydropyran ring has been destroyed. However, the exact structure of the second product could not be deduced at this time based on the available spectroscopic data, although it was determined as **9a** later.

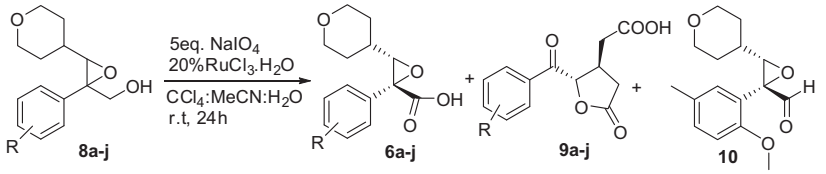
In order to improve the yield and selectivity, we next optimized the reaction conditions. First, we screened the loading of the oxidant. With 10% ruthenium chloride hydrate ($RuCl_3{\cdot}xH_2O$) as the catalyst, increasing (6.0 equiv) or decreasing (4.0 equiv) the oxidant $NaIO_4$ improved the yields of the products (Table 1, entries 2 and 3), but lower oxidant loading elevated the product ratio to 20:6 (entry 3). Higher temperature did not improve the reaction except producing a complex (entry 4). Variant amount of the catalyst was also explored (entries 5–7). It was found that higher

Table 1
Optimization of reaction conditions of oxiran-2-yl methanol **8a**[a]

Entry	Oxidant	$RuCl_3$ (%)	Solvent	*T*	**6**:**9**[b]	Yield (%)
1	**5eq** $NaIO_4$	10	CCl_4:MeCN:H_2O = 2:2:3	rt	20:12	33
2	**6eq** $NaIO_4$	10	CCl_4:MeCN:H_2O = 2:2:3	rt	20:12	38
3	**4eq** $NaIO_4$	10	CCl_4:MeCN:H_2O = 2:2:3	rt	20:6	48
4	**5eq** $NaIO_4$	10	CCl_4:MeCN:H_2O = 2:2:3	60 °C	—	—[c]
5	**5eq** $NaIO_4$	15	CCl_4:MeCN:H_2O = 2:2:3	rt	20:14	45
6	**5eq** $NaIO_4$	20	CCl_4:MeCN:H_2O = 2:2:3	rt	20:17	55
7	**5eq** $NaIO_4$	35	CCl_4:MeCN:H_2O = 2:2:3	rt	20:13	53
8	**5eq** NaClO	20 (py)	EA:MeCN:H_2O = 1:1:2		rt	—
9	**5eq** $KBrO_3$	20 (py)	EA:MeCN:H_2O = 1:1:2	rt	1:0	70
10	**5eq** NMO	20	CCl_4:MeCN:H_2O = 2:2:3	rt	—	—
11	**5eq Oxone**	20	CCl_4:MeCN:H_2O = 2:2:3	rt	1:0	61

[a] The reaction was conducted on 0.1 mmol scale, and was reacted for 24 h before workup.
[b] Determined by NMR spectra.
[c] The reaction produced a complex.

Table 2
Ruthenium-catalyzed oxidation of oxiran-2-yl methanols **8a–j**



No.	R	Product	(**6**:**9**) or (**6**:**10**)[a]	Yield[b] (%)
1 (**8a**)	4-Pr^{c}SO$_2$	**6a** + **9a**	20:17	55
2 (**8b**)	4-MeSO$_2$	**6b** + **9b**	20:12	50
3 (**8c**)	4-F	**6c** + **9c**	20:29	40
4 (**8d**)	4-I	**6d** + **9d**	20:5	71
5 (**8e**)	4-H	**6e**	1:0	36
6 (**8f**)	2-OMe,5-Me	**6f** + **10**	20:24	56
7 (**8g**)	4-(4-F-Ph)	**6g**	1:0	68
8 (**8h**)	4-CN	**6h** + **9h**	20:19	19
9 (**8i**)	4-Cl	**6i** + **9i**	20:20	62
10 (**8j**)	4-Br	**6j** + **9j**	20:10	73

[a] Determined by the ^{1}H NMR spectra.
[b] Isolated yields.

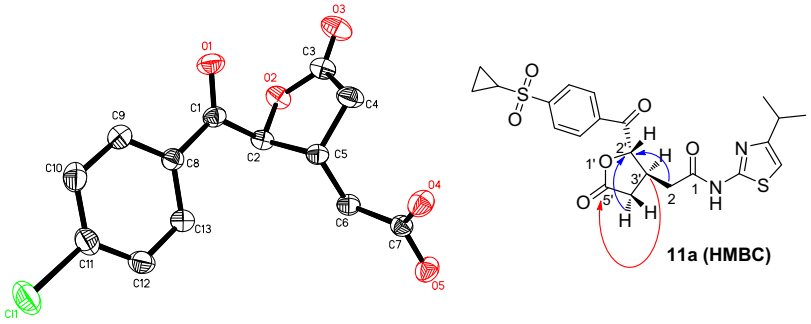


Figure 2. X-ray crystal of **9i** and HMBC analysis of **11a**.

loading of the catalyst generally increased the yield, but the ratios of the products (**6a:9a**) were not significantly changed. Changing $NaIO_4$ to other oxidants, including NaClO (entry 8) and NMO (entry 10) did not promote the reaction, while using $KBrO_3$ (entry 9) or Oxone (entry 11) as the oxidant, oxirane **6a** was obtained as the major product in 70% and 61% yield, respectively.

From the results above, it is in general that by using 4.0 equiv of $NaIO_4$, or switching to other oxidants, the oxidation product **6a** could be obtained as the dominant product in moderate yield. The lower yield is likely due to the existence of high amount of inorganic salts and the difficulty in isolating the products. Since the structure of the minor product **9a** had not been settled yet, we decided to choose 5.0 equiv $NaIO_4$ and 20% of $RuCl_3{\cdot}xH_2O$ with the solvent mixture of CCl_4/MeCN/H_2O (2:2:3) as the optimal reaction condition (Table 1, entry 5) to prepare both products for further investigation.

As shown in Table 2, a small class of oxiran-2-ylmethanols **8b–j** were prepared following a similar procedure as that of preparation of **8a**, and subjected to the oxidation reaction subsequently. It was found that all the oxiran-2-ylmethanol substrates went through the oxidation and afforded two products in 19–73% yields, with **6a–j**/**9a–j** ratios of nearly 1:1, except in cases of 4-iodophenyl-(**8d**), non-substituted phenyl- (**8e**), and 4-fluorobiphenyl-(**8g**) substituted oxiranemethanols where the corresponding oxirane acids were produced as the major products. It is of note that in the case of 2-methoxy-5-methyl substituted substrate (entry 6), the oxidation intermediate oxiranecarbaldehyde **10** was obtained as the side product.

Although most of side products **9a–j** were obtained as powder, we managed to achieve the X-ray crystals of **9i** from the mixture of chloroform and methanol, and secured its structure as 2-(2-(4-chlorobenzoyl)-5-oxotetrahydrofuran-3-yl)acetic acid. As shown in Figure 2, the benzoyl and acetamide moieties are in trans-configuration. The structures of **9a–d**, as well as **9h** and **9j** were deduced by analogy.

In spite of the wide use[17] of ruthenium (VIII) tetroxide (RuO_4), in the oxidation of alkenes, alcohols, amines, amides, β-lactams,

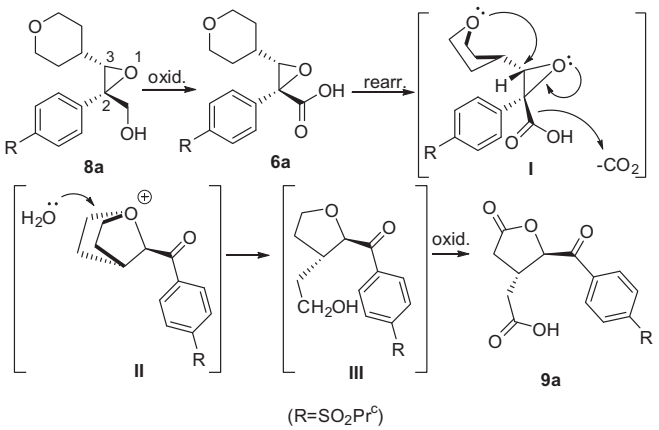
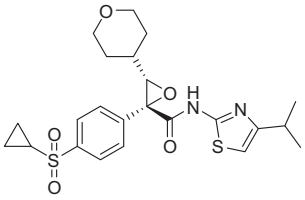
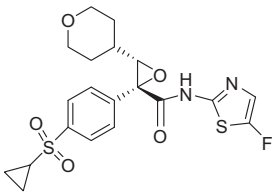
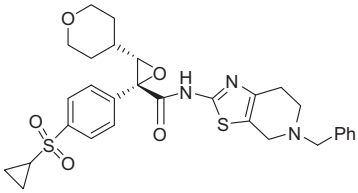
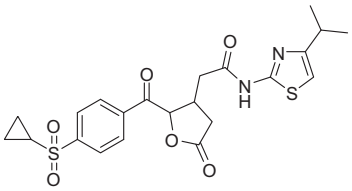


Figure 3. Proposed mechanism.

Table 3
In vitro activation of GK by compounds **4a–c** and **11a**

Compound	Structure	EC_{50} (nM)	Activation fold*
1	–	62 (130[2])	2.59
2	–	125	
4a		584	3.14
4b		444	1.85
4c		1230	1.08
11a		>10,000	1.28

phenols, and inactivated hydrocarbons, oxidation of (3-(tetrahydro-2*H*-pyran-4-yl)oxiran-2-yl)methanol to (5′-oxotetrahydrofuran-3-yl)acetic acid has never been reported before. Therefore, a tentative oxidation-rearrangement-oxidation reaction mechanism was proposed. Since both acids **6a** and **9a** were obtained in most cases, we believed that acid **9** was produced from **6**. As demonstrated in Figure 3, oxirane-2-carboxylic acid **6a** first underwent decarboxylation, followed by oxirane ring-opening and nucleophilic attack of oxirane C-3 by the oxygen atom of tetrahydropyran to form an oxonium intermediate **II**. Nucleophilic attack of species **II** by water should generate tetrahydrofuran **III**. This intermediate would readily undergo a second oxidation to afford acid **9a**. It should be mentioned that $RuCl_3$-catalyzed oxidation of tetrahydropyrans or tetrahydrofurans to corresponding lactones has been reported in the literature long time ago.[18–26] Although several other mechanisms may exist, the key elements involving oxidation, rearrangement, and re-oxidation should be the same.

The structures of **9a–j** are rare, and the available synthesis is very limited. In 2005, Tomoda and co-workers[27] reported the isolation of two natural products, named as phenatic acids A and B, from the culture of *Streptomyces* sp. K03-0132. These are the earliest structural examples containing (2′-benzoyl-5′-oxotetrahydrofuran-3-yl)acetic acid scaffold, similar to that in compound **9i**. Total synthesis of these compounds was achieved recently by Fernandes et al[28] through 11–12 steps. Therefore, our study provided an alternative to access this class of compounds, although further work is needed to improve the yield.

Although glucokinase activators (GKAs) generally are benzamide or arylacetamide analogs, we decided to convert both acids **6a–j** and **9a–j** into corresponding *N*-heteroaryl amides. To quickly validate the effects of these new compounds, amides **4a–c** and **11a** were prepared following a similar procedure we reported before by coupling of acid **6a** or **9a** with an appropriate thiazole. Amide **11a** was further confirmed by all the spectroscopic data, especially by its COSY, HSQC, and HMBC (Fig. 2).

All these new compounds were tested in an enzymatic glucokinase (GK) assay using purified recombinant human islet GK following a similar procedure as we reported earlier.[12,15] The GK activity of each compound was evaluated in six different concentrations and was reported as EC_{50} value and maximum activation fold (versus control level). Clinical compound **1**(PSN-GK1) and our earlier lead **2** were also evaluated in current assays for side-by-side comparison.

From the results in Table 3, conformationally constrained arylacetamides **4a–c** retained moderate GK potency with EC_{50} values of 444–1230 nM, 4–10 fold less potent than our earlier lead **2** and much less potent than the clinical compound **1**. The substituent in the aminothiazole component did not impact the EC_{50} values significantly, whereas an appreciable discrepancy in activation fold was observed. Compound **4a** possesses an EC_{50} value of 584 nM with a high activation fold of 3.14, while compound **4b** has a slightly higher potency (EC_{50}, 444 nM) but with a much lower activation fold of 1.85. The piperidine-fused aminothiazole **4c** showed negligible activation potency. Quite disappointingly, amide **11a** is nearly invalid in GK activation, indicating that the 5′-oxotetrahydrofuran-3-yl)acetyl moiety in **11a** may not interact with the lipophilic environment proposed[2,11] for the tetrahydopyran moiety in **1** and **2**.

In summary, $RuCl_3$-catalyzed oxidation of oxiranemethanols was investigated, and two products, oxirane-2-carboxylic acid and

(5′-oxotetrahydrofuran-3-yl)acetic acid, were obtained in variant ratios. The product structures were determined and a tentative mechanism was proposed involving oxidation-rearrangement-oxidation process. Coupling of the resulting acids with aminothiazoles produced amides **4a–c** and **11a**. Glucokinase enzymatic assay revealed that oxirane-carboxamides **4a–c** retained moderate GK activation potency with amide **4a** showing an EC_{50} value of 584 nM and a high activation fold of 3.14. However, (5′-oxotetrahydrofuran-3-yl)acetamide **11a** is inactive. This study not only provided an alternative protocol to access (5′-oxotetrahydrofuran-3-yl)acetic acid analogs, but also yielded nanomolar GA activators (esp. **4a**) for further structure–activity relationship study.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.111.

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