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GALE L. BOGER
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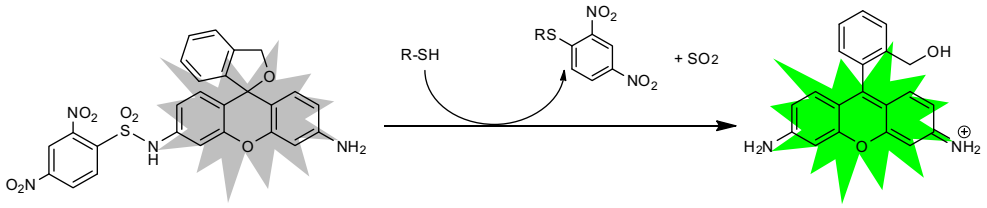
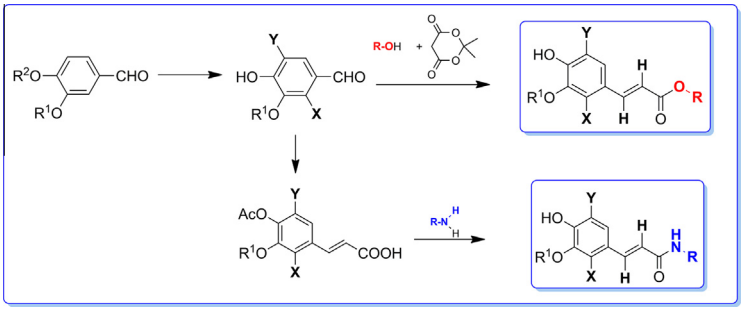
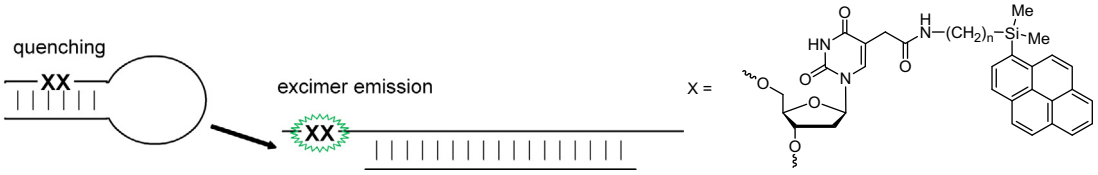
Contents

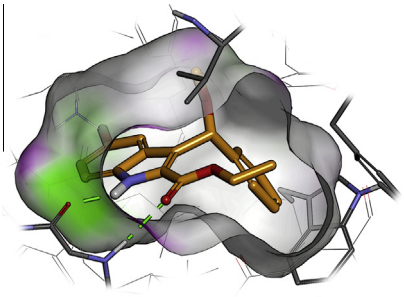
REGULAR ARTICLES

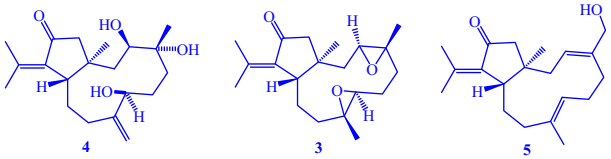




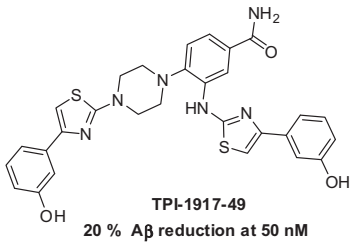
A series of feruloyl and caffeoyl derivatives from commercial vanillin and veratraldehyde were synthesized by two convenient methods. Most compounds demonstrated attractive cytotoxicity and several new compounds demonstrated significant antiproliferative and cytotoxic activities against HeLa and Bewo tumor cell lines.

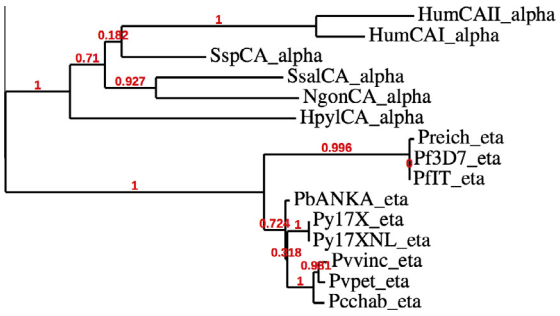


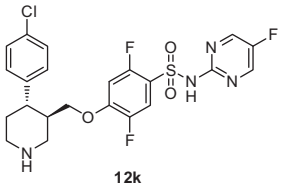




Anti-HIV activity EC_{50}	0.73μM	3.9μM	0.69 μM



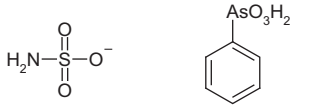




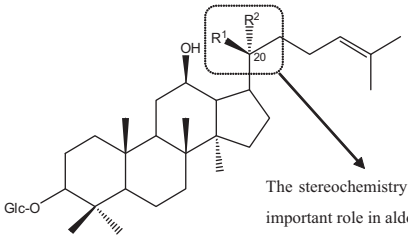
12k

$Na_v1.7$ IC_{50}: 11 nM

$Na_v1.5$ IC_{50}: > 10 μM

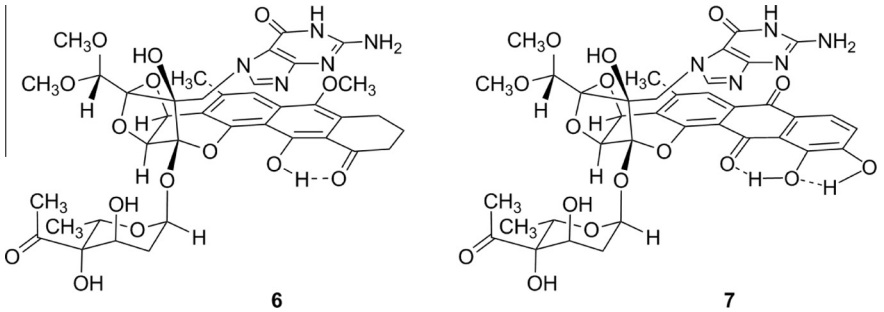


K_I (PgiCAb) = 60 μM K_I (PgiCAb) = 76 μM

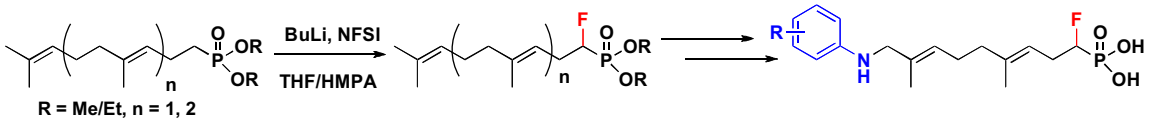


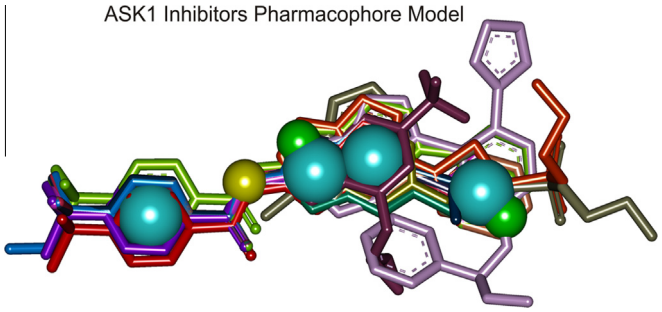
Ginsenoside	R^1	R^2
20(*S*)-Rh2	OH	CH_3
20(*R*)-Rh2	CH_3	OH

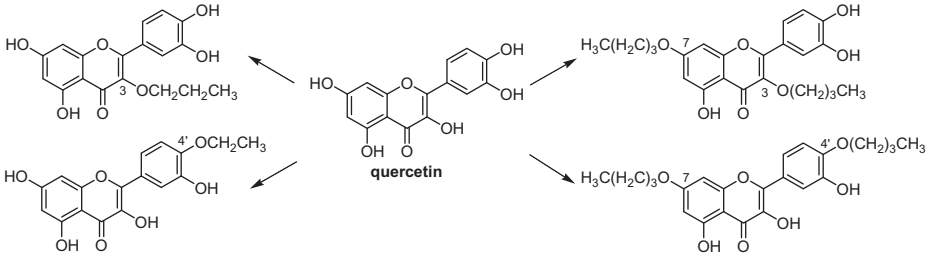
The stereochemistry of the hydroxyl group at C-20 may play an important role in aldose reductase inhibition

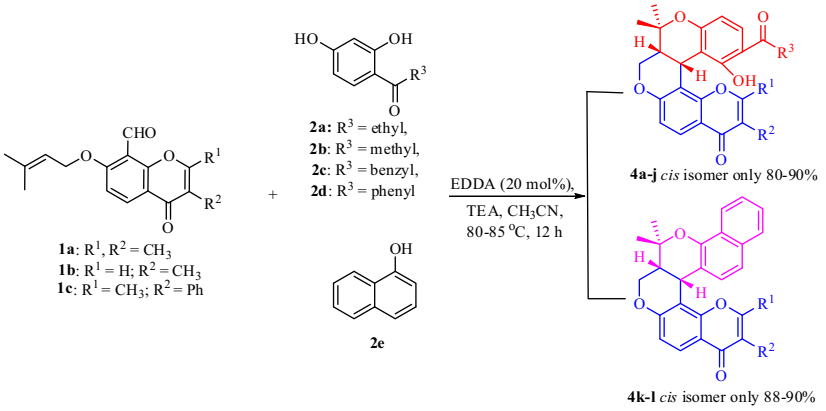


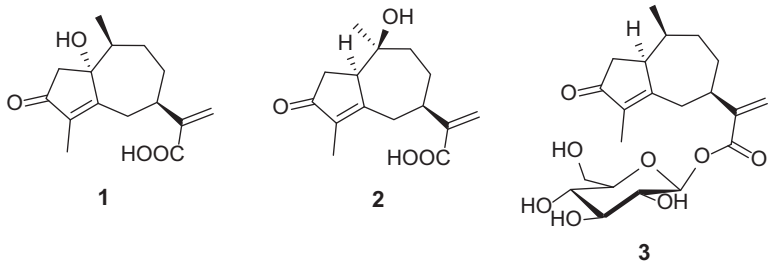
6 **7**

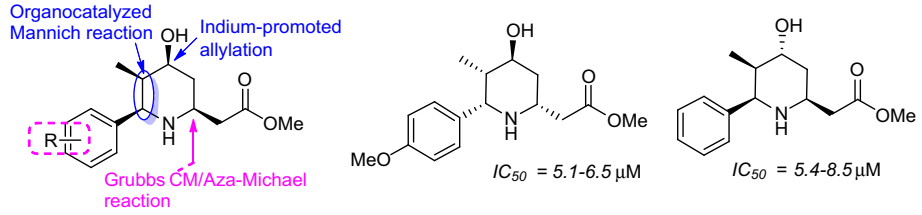


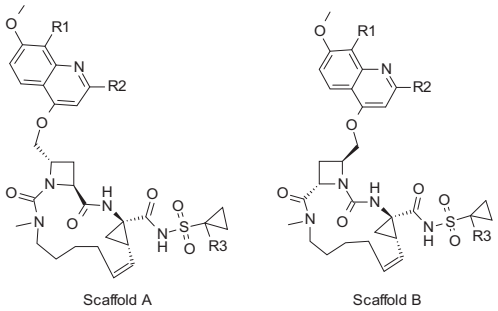


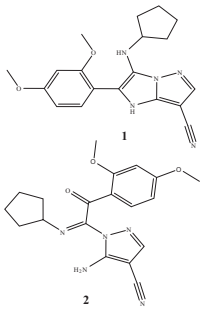


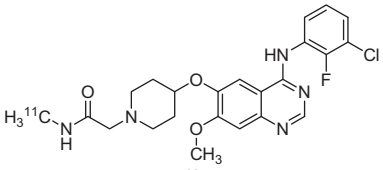




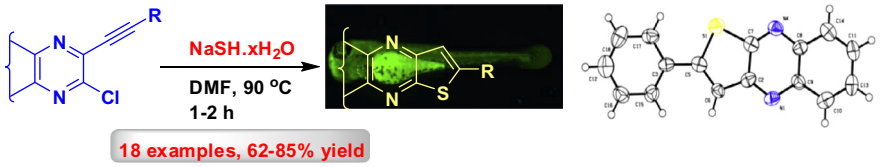




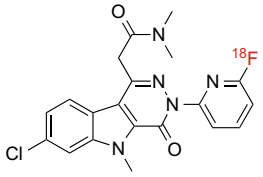




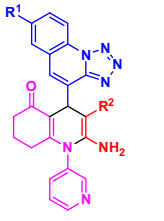
[^{11}C]AZD8931



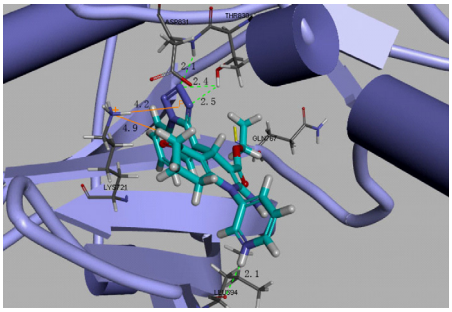
NaSH was used for the first time to construct the thiophene ring fused with N-heterocycles.



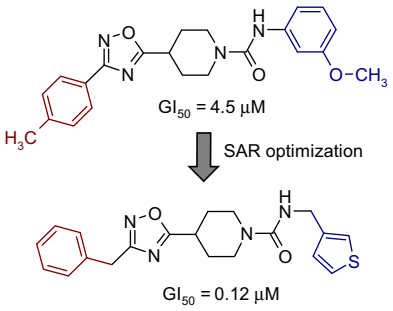
[^{18}F]-**14**

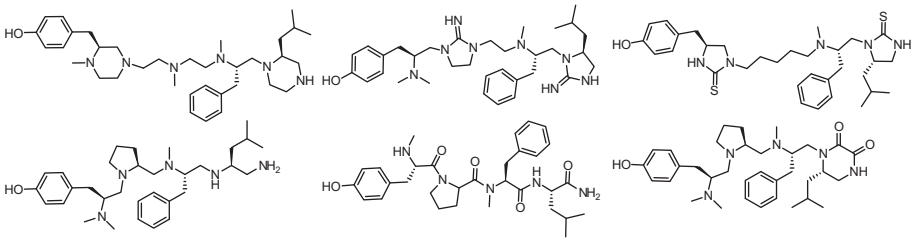


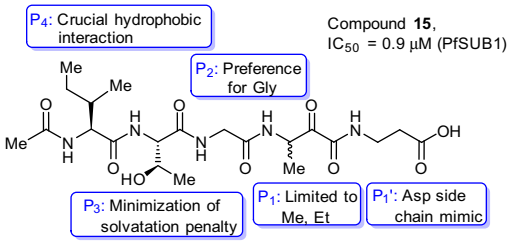
9a-l
R^1 = H, CH_3, OCH_3, Cl
R^2 = CN, COOMe, COOEt

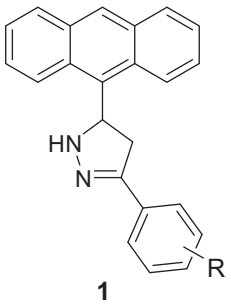


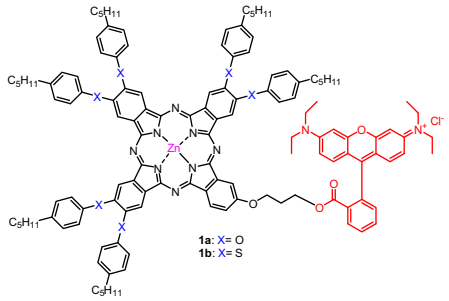
A new series of biquinoline–pyridine hybrids were designed and synthesized by a base-catalyzed cyclocondensation through one-pot multicomponent reaction. All compounds were tested for in vitro anticancer activities against two cancer cell lines A549 (adenocarcinomic human alveolar basal epithelial) and Hep G2 (liver cancer). Enzyme inhibitory activities of all compounds were carried out against EGFR and HER-2 kinase. Of the compounds studied, majority of the compounds showed effective anticancer activity against used cancer cell lines. Compound **9i** (IC_{50} = 0.09 μM) against EGFR and (IC_{50} = 0.2 μM) against HER-2 kinase displayed the most potent inhibitory activity as compared to other member of the series. In the molecular modelling study, compound **9i** was bound in to the active pocket of EGFR with four hydrogen bonds and two π–cation interactions having minimum binding energy ΔG_b = −54.4 kcal/mol.

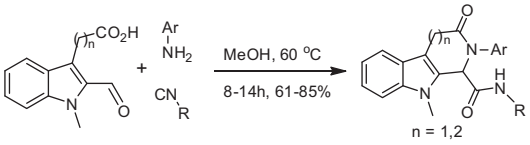


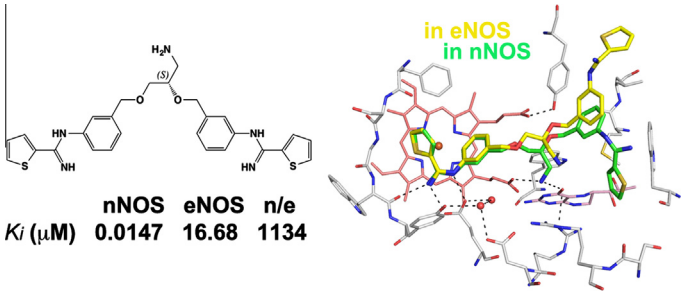


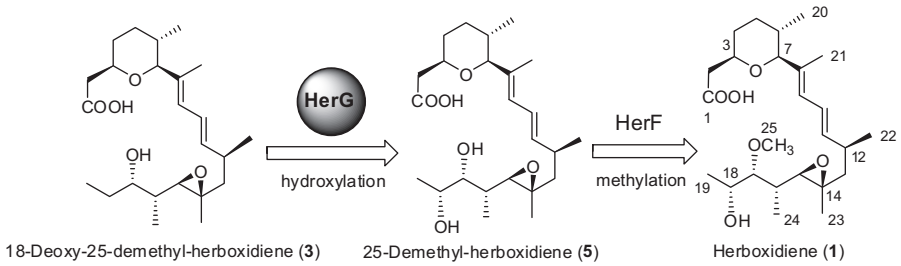


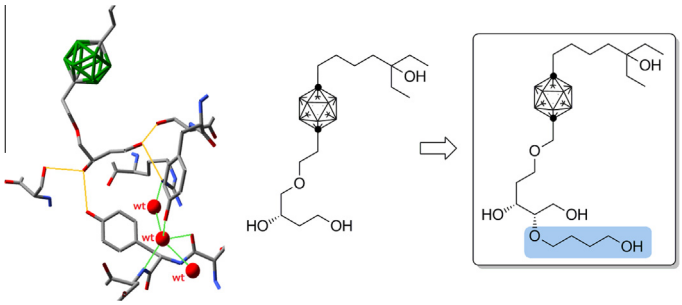


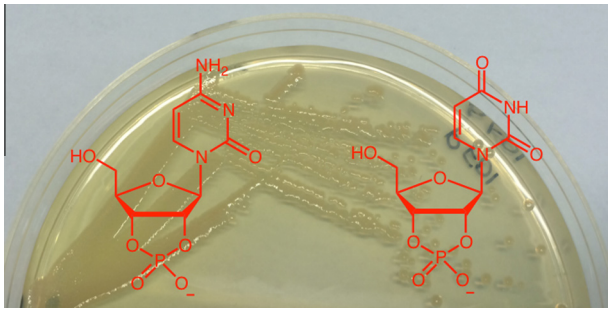


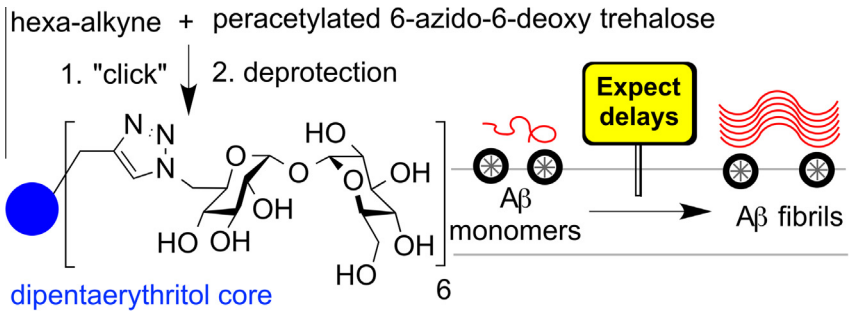


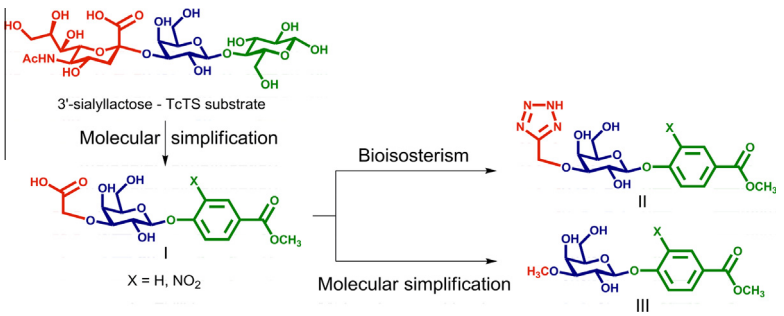


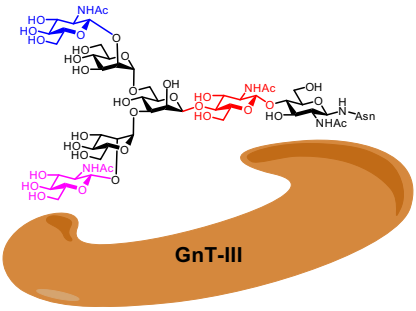


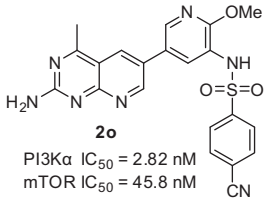


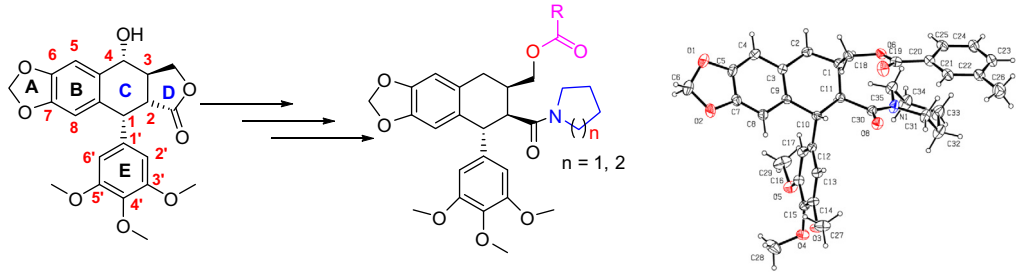


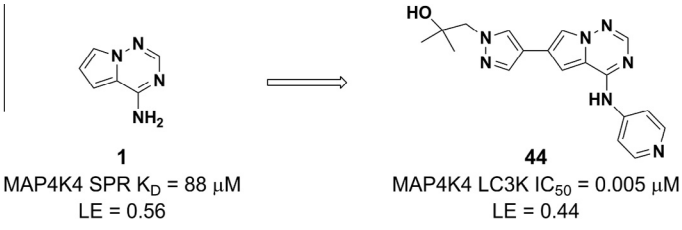


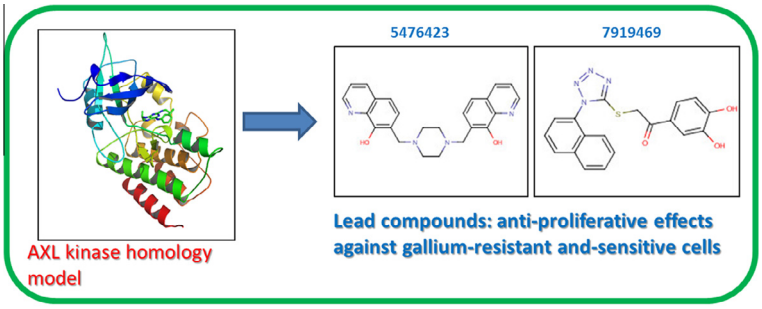


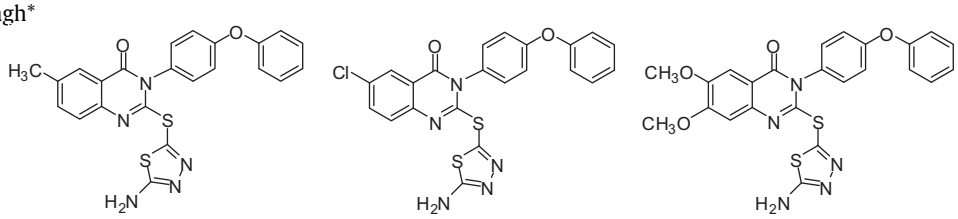






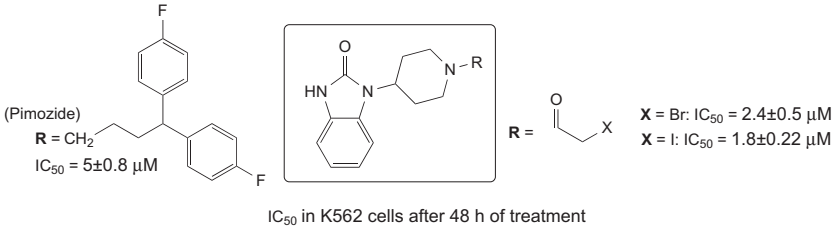


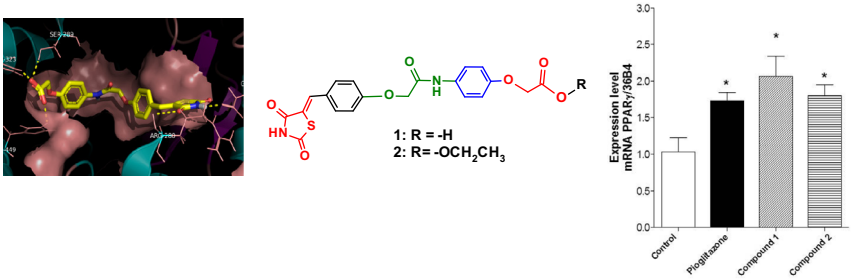


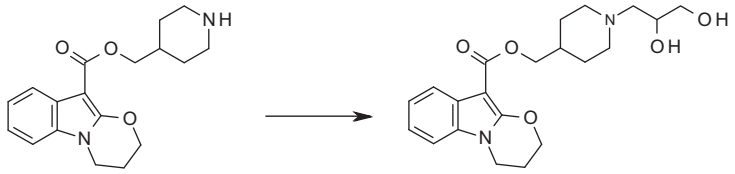


29, IC_{50} 0.1 μM **34**, IC_{50} 0.4 μM **39**, IC_{50} 0.6 μM

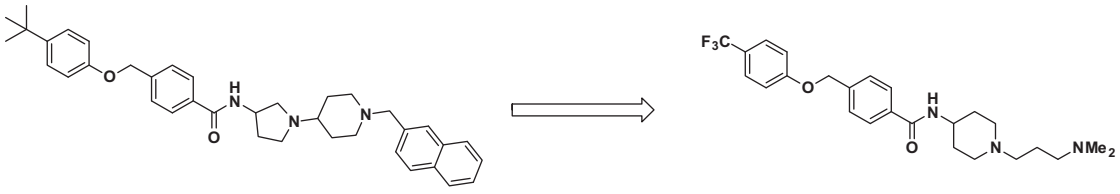
Compounds **29**, **34** and **39** showed DHFR inhibition (IC_{50} range of 0.1–0.6 μM). Recognition with key amino acids Glu30, Phe31 and Phe34 is essential for receptor binding.







5-HT$_4$ receptor antagonist
pK_i 10.1, pK_b 9.1
F 10.3%, hERG IC$_{50}$ 81μM



1
(human GlyT-2 IC$_{50}$ = 4040 nM)

20
(human GlyT-2 IC$_{50}$ = 15.3 nM)

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Illustrated is the workflow for a competitive ABPP platform to discover selective inhibitors of serine hydrolases. This platform was used to identify selective and cell-active carbamate inhibitors for the lipid hydrolase lipoprotein-associated phospholipase A2 (Lp-PLA2; accession number 3F96). See Nagano, J. M. et al. *Bioorg. Med. Chem. Lett.* **2013,** *23,* 839–843. Cover image designed and generated by Megan Blewett (TSRI).

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20(*S*)-Ginsenoside Rh2 as aldose reductase inhibitor from *Panax ginseng*

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Ginsenoside
Aldose reductase inhibitor

ABSTRACT

The root of *Panax ginseng* C. A. Meyer (Araliaceae) is a well-known herbal medicine in East Asia. The major bioactive metabolites in this root are commonly identified as ginsenosides. A series of ginsenosides were determined for in vitro human recombinant aldose reductase. This Letter aims to clarify the structural requirement for aldose reductase inhibition. We discovered that only ginsenoside 20(*S*)-Rh2 showed potent against aldose reductase, with an IC_{50} of 147.3 μM. These results implied that the stereochemistry of the hydroxyl group at C-20 may play an important role in aldose reductase inhibition. An understanding of these requirements is considered necessary in order to develop a new type of aldose reductase inhibitor. Furthermore, *P. ginseng* might be an important herbal medicine in preventing diabetic complications.

Diabetes Mellitus is a complex and chronic metabolic disease characterized by hyperglycemia. As one of the most prevalent metabolic syndromes worldwide, this disease is very common around the world and has major effect on public health. Hyperglycemia is the condition in which significant part of the glucose enters into polyol pathway which is measured as the main cause of pathogenesis of long-term diabetic complications, including neuropathy, retinopathy, nephropathy, and cataract.[1–4]

Aldose reductase (ALR2, EC 1.1.1.21) is a member of aldo–keto reductase superfamily and the first enzyme which catalyzes the NADPH-dependent reduction of glucose to sorbitol in the rate determining step of polyol pathway.[5,6] The sorbitol accumulation together with imbalance of NADPH/$NADP^+$ and NAD^+/NADH cofactors and following oxidative stress within the cells are considered to be key causes of cellular damage that raise diabetic complications. Because of this reason, ALR2 inhibitors can be alternative to prevent and delay the development of diabetic complications.[7] Furthermore many compounds have been isolated from medicinal plants[8–13] and also have been synthesized to obtain active ALR2 inhibitors.[14–16]

Ginseng, the root of *Panax ginseng* C. A. Meyer (Araliaceae), has been used as traditional medicines in Korea, China and other East Asia countries for thousands of years. Many of medicinal effects of ginseng are recognized to the main active constituents of ginseng which are known as ginsenosides (triterpene glycosides). More than 50 ginsenosides have been clarified. Generally ginsenosides are divided into three types; first type is protopanaxadiol type ginsenosides (PPD) including Ra_1–Ra_3, Rb_1–Rb_3, etc. Second type is protopanaxatriol type ginsenosides (PPT) such as Re, Rg_1, Rg_2, etc. Third type is oleanonic acid type such as ginsenoside Ro.[17] Many of the pharmacological effects of ginseng, including antitumor activities,[18] anti-oxidant and oxidative stress,[19–22] anti hyperalgesic,[23] etc.

Ginseng has been reported to be effective in the prevention and treatment of diabetic complications such as nephropathy.[24,25] Recently, it was also reported that after eight weeks of hydrolyzed ginseng extract supplementation on diabetic participants were significantly reduced fasting plasma glucose and postprandial glucose compared to the placebo group. Furthermore, there is no clinically significant changes in any safety parameter were observed.[26] These scientific evidences have been proved that ginseng can be used as potential supplement to reduce the risk of diabetic complications. Therefore, in the course of our studies on compounds made from natural products for anti diabetic complication agents, we have determined ginsenosides isolated from *P. ginseng* against aldose reductase.

In the current study, we determine aldose reductase inhibition of ginsenoside 20(*S*)-Rh2, ginsenoside 20(*R*)-Rh2, ginsenoside 20(*RS*)-Rh2, ginsenoside 20(*S*)-Rg3, ginsenoside 20(*R*)-Rg3, ginsenoside 20(*S*)-Rg2, ginsenoside 20(*S*)-Rh1, ginsenoside Compound K and quercetin as positive control. From our experiment, all

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ginsenosides did not show any inhibition up to 200 μM except ginsenoside 20(*S*)-Rh2. Only ginsenoside 20(*S*)-Rh2 showed active inhibition among these ginsenosides with IC_{50} value of 147.3 μM and compare to quercetin with IC_{50} value of 2.9 μM (Table 1). The only different between ginsenoside 20(*S*)-Rh2 and ginsenoside 20(*R*)-Rh2 is hydroxyl position of carbon-20 (Fig. 1). As a result, we can bring to a close that the stereospecificity of the hydroxyl group at the carbon-20 of ginsenosides 20(*R*)-Rh2 plays a important role in aldose reductase inhibition.

The preceding studies from our laboratory revealed that the hydroxyl group at 20(*R*)-ginsenoside Rh2 is selective osteoclastogenesis inhibitor without any cytotoxicity and proved to show proliferation inhibition on androgen-dependent and -independent prostate cancer cells.[27,28] Moreover, recent paper reported that in type 2 insulin-resistant diabetic nephropathy animal models, 20(*S*)-ginsenoside Rg3 decreased the high blood glucose and proteinuria and augmented creatinine clearance in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF). Furthermore, the elevated serum glucose, glycosylated protein, and thiobarbituric acid-reactive substance levels in diabetic rats were also significantly reduced by the 20(*S*)-ginsenoside Rg3 administrations.[29,30] In our experiment, 20(*S*)-ginsenoside Rg3 did not show any aldose reductase inhibition up to 200 μM, but the interesting point is the hydroxyl group position at carbon-20 is important substituent, not only diabetic nephropathy in vivo but also for aldose reductase inhibition in vitro.

In conclusion, it is the first time that aldose reductase inhibition of 20(*S*)-ginsenoside Rh2 was found. We revealed that the stereospecificity of the hydroxyl group at the carbon-20 of ginsenosides plays an important role in aldose reductase inhibition. Even though more studies are required to determine the more specific structural necessities for aldose reductase inhibitors, the present results should provide an approach in the development of an optimally active ginseng compound to improve a new type of anti diabetic complications agents especially for aldose reductase inhibitor.

The chemicals used were human recombinant aldose reductase and dl-glyceraldehyde (Wako Pure Chemical Industries, Ltd, Osaka, Japan). Quercetin is kind of property from laboratory of systematic forest and forest product science, Kyushu University (Fukuoka, Japan) and β-NADPH from Oriental Yeast Co., Ltd (Osaka, Japan). Dimethyl sulfoxide, phosphate buffer and all the other chemicals were of analytical grade (Wako Pure Chemical Industries, Ltd, Osaka, Japan). The ginsenosides were isolated as previously reported by Jin et al.[31]

Aldose reductase assay: Aldose reductase activity was determined spectrophotometrically on a JASCO V-530 UV/vis spectrophotometer. The reaction mixture contained 0.15 mM β-NADPH, 10 mM DL-glyceraldehyde, 5 μl of HRAR and 100 μl of test sample solution or dimethyl sulfoxide (DMSO) in a total volume of 1.0 ml of 100 mM sodium phosphate buffer (pH 6.2). After the reaction mixtures were incubated at 25 °C for 5 min in advance, the reaction was initiated by adding the enzyme, and then the decrease of absorbance was measured at 340 nm for 10 min using a JASCO V-530 UV/vis spectrophotometer. The inhibitory activity (%) was estimated as follows: [1 − (Δ*A* sample/min − Δ*A* control/min)] × 100. Δ*A* sample/min showed a decrease of absorbance for 1 min with a sample and Δ*A* control/min with DMSO instead of a sample.[32]

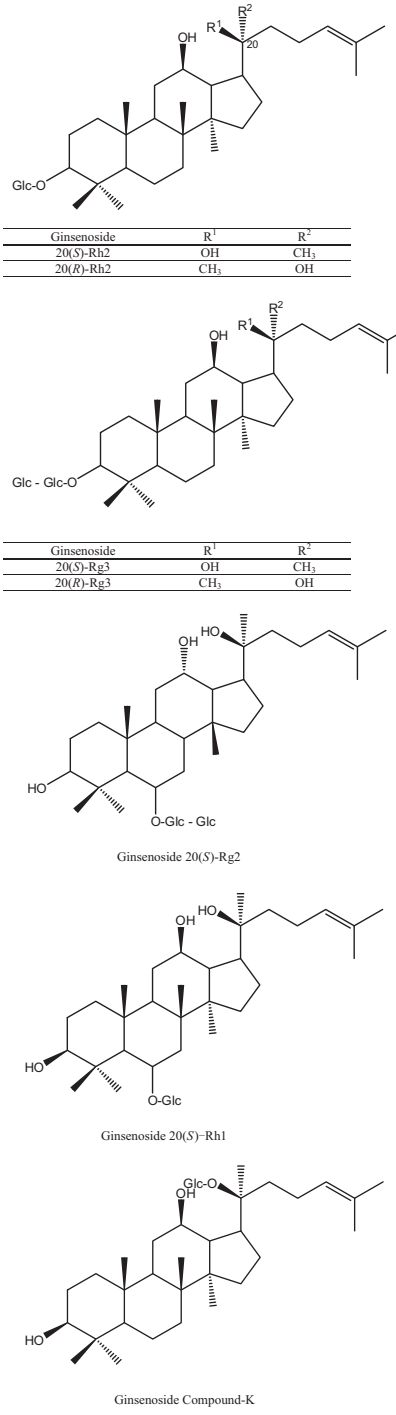

Figure 1. The chemical structures of ginsenoside 20(*S*)-Rh2, 20(*R*)-Rh2, 20(*RS*)-Rh2, 20(*S*)-Rg3, 20(*R*)-Rg3, 20(*S*)-Rg2, 20(*S*)-Rh1 and compound K.

Table 1
Aldose reductase inhibitory of the ginseng compounds

Compounds	IC_{50} (μM)
Ginsenoside 20(*S*)-Rh2	147.3
Ginsenoside 20(*R*)-Rh2	>200
Ginsenoside 20(*RS*)-Rh2	>200
Ginsenoside 20(*S*)-Rg3	>200
Ginsenoside 20(*R*)-Rg3	>200
Ginsenoside 20(*S*)-Rg2	>200
Ginsenoside 20(*S*)-Rh1	>200
Ginsenoside compound K	>200
Quercetin	2.9

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