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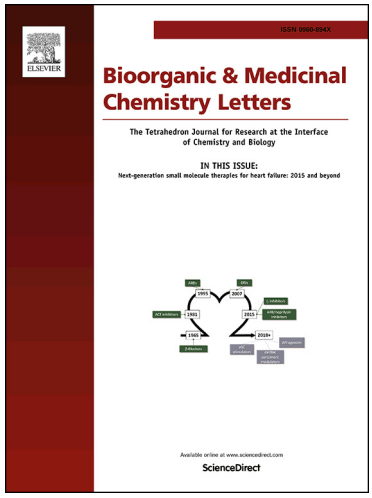

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Discovery of the Bifunctional Modulator of Angiotensin Ⅱ Type 1 Receptor (AT1R) and PPARγ derived from the AT1R Antagonist, Fimasartan

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Hypertension and Type 2 Diabetes (T2D) are known as common metabolic disorders among the population in the developed countries[1]. According to WHO[2], prevalence of hypertension in the developed countries is about 30% and T2D patients are consisted of nearly 10% of population, and 70% of which also suffer from hypertension and have very high risk of the fatal incidents such as stroke, heart failure, etc.

Particularly, among the patients with hypertension, 50% of them are known to proceed to the hyperglycemia sooner or later. According to the literature[3], the patients diagnosed with hypertension have the risk factor for developing hyperglycemia 1.6 times higher and the increased risk of fatal incidents mentioned above compared to those with normal blood pressure unless controlled timely and properly.

It is well known that the high probability of having multiple metabolic conditions simultaneously often causes difficulties in the patient's compliance of medication prescribed. Reducing the pill burden and inconvenience from differing dosing schedules for the individual drugs by providing fixed dose combo pills or multifunctional agents was considered to improve the medication compliance[4]. Accordingly, we reasoned a single molecule with bifunctional pharmacologies for the commonly accompanied metabolic conditions would have enhanced value in market, though more challenges in development. To this end, the feasibility to identify a dual-active molecule enabling to control blood pressure and hyperglycemia simultaneously has been explored[5].

Among the numerous ways to control hypertension[6], angiotensin Ⅱ type 1 receptor (AT1R) antagonists have been known to function by blocking vasoconstricting peptide angiotensin Ⅱ from activating the receptor[7]. There are many antihypertensive drugs of this kind dubbed as ARBs (angiotensin Ⅱ receptor blockers) approved for the clinical use including Losartan, Candersartan and Olmesartan among others (Figure 1). For treatment of T2D characterized by high blood sugar, insulin resistance, and relative lack of insulin, thiazolidinediones (TZDs) represented chiefly by Rosiglitazone and Pioglitazone have been widely used[8]. TZDs have insulin sensitizing effect by binding and activating nuclear receptor PPARγ to recover the proper blood glucose control.

Inspired by the well-known PPARγ partial agonism of ARBs represented by Telmisartan[9],