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A novel series of indazole-/indole-based glucagon receptor antagonists

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This publication is dedicated to Professor Iwao Ojima on the occasion of his 70th birthday

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ABSTRACT

A novel, potent series of glucagon receptor antagonists (GRAs) was discovered. These indazole- and indole-based compounds were designed on an earlier pyrazole-based GRA lead MK-0893. Structure–activity relationship (SAR) studies were focused on the C3 and C6 positions of the indazole core, as well as the benzylic position on the *N*-1 of indazole. Multiple potent GRAs were identified with excellent in vitro profiles and good pharmacokinetics in rat. Among them, GRA **16d** was found to be orally active in blunting glucagon induced glucose excursion in an acute glucagon challenge model in glucagon receptor humanized (hGCGR) mice at 1, 3 and 10 mg/kg (mpk), and significantly lowered acute glucose levels in hGCGR ob/ob mice at 3 mpk dose.

Type 2 Diabetes Mellitus (T2DM) is a growing worldwide epidemic currently affecting an estimated 300 million people.[1] Despite a number of diabetic therapies available nowadays, there remains a significant unmet medical need for additional therapies.[2] T2DM is partially characterized by elevated and dysregulated hepatic glucose production (HGP). Glucagon is a 29-amino acid peptide that acts as a major counter-regulatory hormone to insulin, and stimulates gluconeogenesis and glycogenolysis in liver and thus increasing HGP.[3] Studies in type 2 diabetic subjects have demonstrated a causal role for glucagon in promoting excessive glucose production.[4] An inappropriately high rate of HGP is the predominant cause of fasting hyperglycemia and a major contributor to the postprandial hyperglycemia characteristic of T2DM.[5] It is therefore postulated that blocking the action of the glucagon receptor would lead to improved glycemic control in T2DM patients.[6]

With this, there have been many Letters detailing efforts to identify both small and large molecule glucagon receptor antagonists (GRAs) as potential treatments for T2DM over the last two decades.[6,7] Clinical data on one of the early GRAs, Bay 27-9955 (**1**) was reported and an acute effect was observed with the compound in blocking glucagon-induced glucose increase in healthy volunteers.[8] A series of β-alanine acid containing urea based GRAs such as NNC 25-0926 (**2**) was later reported by Novo-Nordisk.[9–11] Various scaffold changes replacing the urea core while keeping the β-alanine moiety by many groups have since been reported in patent applications[7] and literature (e.g., GRA **3** reported by Pfizer[12]). Prominent examples of this include several GRA clinical candidates, such as MK-0893 (**4**, Merck)[13] and likely LY2409021 (Eli Lilly).[14]

With the continued interest in the area of developing novel GRAs as a potential treatment for T2DM, we designed a novel series of GRAs possessing an indazole or an indole/azaindole core (**5**, Fig. 1) as intrigued by the presence of a unique 5-naphthylpyrozole moiety in the core structure of MK-0893. In this Letter, we would like to discuss the synthesis and the structure–activity relationship (SAR) studies of this series of GRAs, leading to the identification of several potent compounds which demonstrated excellent in vitro and in vivo profiles.

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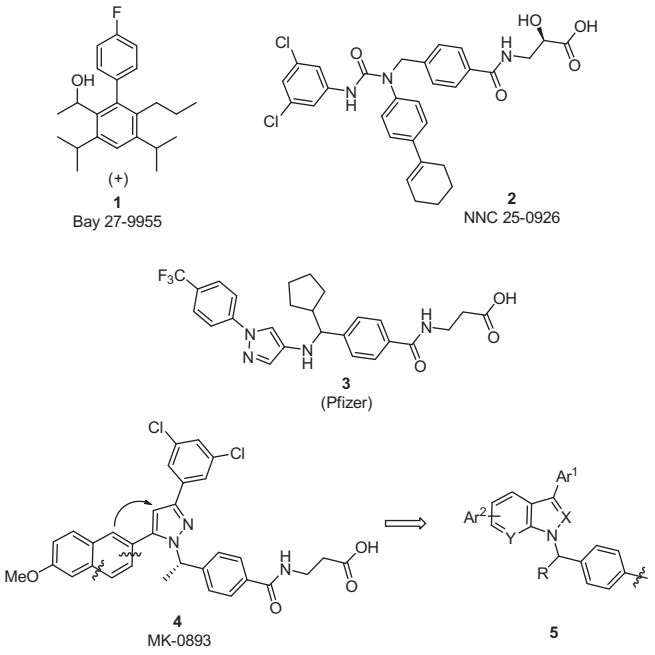
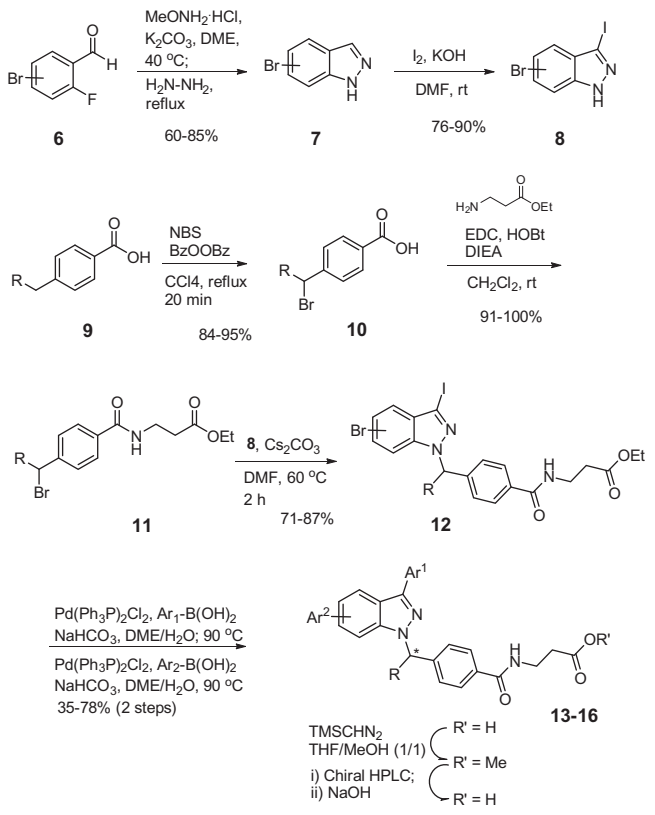


Figure 1. Structures of several key glucagon receptor antagonists.

The synthesis of the indazole-based GRAs is shown in Scheme 1. Treatment of 5-bromo-, 4-bromo-, or 3-bromo-2-fluorobenzaldehydes **6** with methoxyamine in the presence of K_2CO_3, followed by refluxing with hydrazine in DME afforded corresponding 5-, 6-, or 7-bromoindazoles **7** in good yields. Iodination of **7** with iodine/KOH in DMF provided 3-Iodoindazoles **8** in excellent yields.



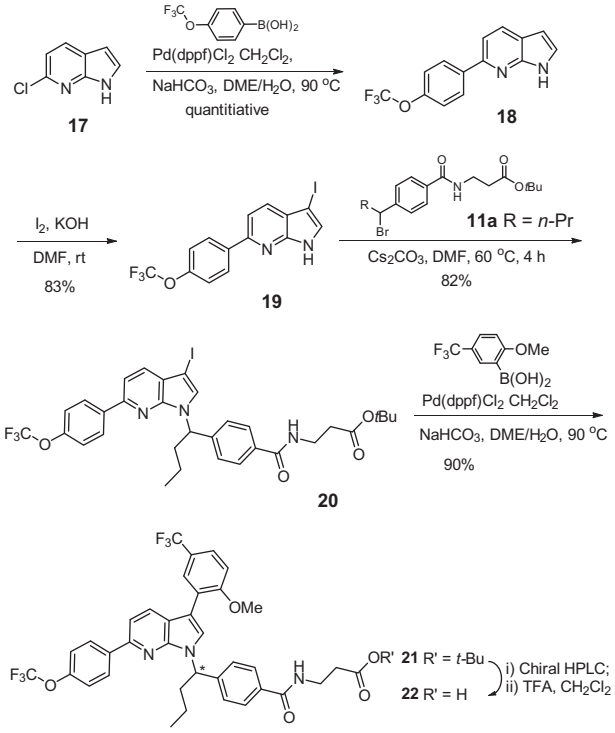
Scheme 1. Synthesis of indazole GRAs **13–16**.

Bromination at the benzylic position of 4-alkylbenzoic acids **9** was achieved with NBS and benzoyl peroxide, and the resulting **10** was coupled with β-alanine ethyl ester to afford amides **11**. Indazoles **8** were then alkylated at the *N*-1 position with benzylbromides **11** in the presence of Cs_2CO_3 in DMF to provide **12**. Suzuki couplings of **12** with $Ar^1B(OH)_2$ catalyzed by $Pd(Ph_3P)_2Cl_2$ preferentially at the 3-postion of the indazole (resulted in the partial hydrolysis of ethyl ester), followed by a second Suzuki coupling with $Ar^2B(OH)_2$ at the 5-, 6-, or 7-position of the indazole core under similar conditions were then performed. The sequential Suzuki couplings provided desired bis-substituted indazoles **13–16** in moderate to good yields over two steps. To facilitate the chiral resolution of the racemic compounds, the acids were converted to methyl esters by simple treatment with $TMSCHN_2$ in MeOH/THF, and re-hydrolyzed back to acids after chiral separation.[15]

To synthesize the 7-azaindole based compound **22**, Suzuki coupling of 6-chloro-7-azaindole **17** with 4-CF_3O-phenylboronic acid was carried out in the presence of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ to supply biaryl **18** in quantitative yield (Scheme 2). Iodination at the C-3 position resulted 3-iodo-7-azaindazole **19**. Alkylation of the *N*-1 position of **19** with bromide **11a**, prepared similarly to **11** as shown in Scheme 1, provide iodide **20** in 82% yield. Suzuki coupling of **20** with 5-trifluoromethyl-2-methoxyphenylboronic acid afforded *tert*-butyl ester **21** in high yield, which was hydrolyzed to provide desired acid **22** after chiral resolution.[16]

Similarly, synthesis of indole-based compound **30** is shown in Scheme 3. Briefly, 6-bromoindole **23** was alkylated at the *N*-1 position with bromide **24**, and the resulting indole **25** was iodinated at the C-3 position to afford **26**. Suzuki coupling of **26** with 5-trifluoromethyl-2-methoxyphenylboronic acid afforded methyl eater **27**, which was hydrolyzed to acid **28**, and coupled with β-alanine ethyl ester to provide **29**. The second Suzuki coupling of **29** with substituted phenylboronic acids followed by ester saponification afforded desired compounds **30**.

The compounds thus synthesized were first evaluated in vitro using both binding and functional assay formats.[13] The binding



Scheme 2. Synthesis of azaindole GRA **22**.