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Regioselective synthesis of 3-aryl-5-(1*H*-indole-3-carbonyl)-4-hydroxyfuroic acids as potential insulin receptor activators

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Abstract—3-Methoxy-4-aryl-furan-2,5-dicarboxylic acid (**8**) is selectively converted into its C-5 methylester (**6**) by treatment with methyl chloroformate followed by decarboxylation in one flask. Acylation of the resulting half ester with a 7-substituted indole was performed under mild conditions to afford 3-aryl-5-(1*H*-indole-3-carbonyl)-4-methoxy-2-furoic acid (**11**). The synthetic utility of the resulting furoic acids as a skeleton in the synthesis of potential insulin receptor activators is established.

Various approaches to develop an oral drug for the treatment of non-insulin dependent diabetes mellitus (NIDDM) have been developed in recent years.[1] Insulin receptor (IR) activators are fascinating because it is the primary interaction site relating to signal transduction of blood sugar metabolism. A dihydroxyquinone derivative, asterriquinone, discovered at Merck Co., has been identified as a potent and selective insulin receptor activator.[2] Further modification of the dihydroxyquinone derivative has led to a series of structurally related and simplified analogs.[2] More recently, a series of asterriquinone bioconversion products, 4-hydroxy-2-furoic acids, have been identified (Fig. 1).[3] They are active in the insulin receptor activation assay and had a significant glucose-lowering effect in an in vivo experiment conducted in db/db mice. However, the structure of 4-hydroxy-2-furoic acids is complicated, and has left a room for structure modification to develop simplified molecules possessing comparable activity. Preliminary biological data from Merck revealed that the activation of insulin receptor tyrosine kinase activity of 4-hydroxy-2-furoic acids depends critically on the terminal hydroxyl group of the C-7′ side chain on the C-5 indole ring.[3] Better activity is expected if a linear hydroxylalkyl chain mimics the C-7′ side chain of the lead molecule. Hence, the initial goal of this study is to synthesize various simplified analogs of the lead molecule, in which the C-3

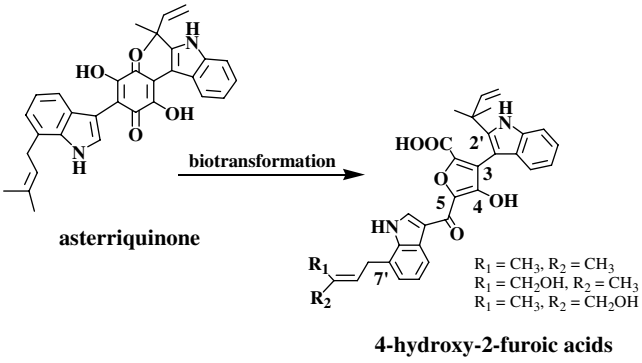

Figure 1. Biotransformation of asterriquinone.

and C-5 substituents are replaced with aryl and C-7′ hydroxyalkyl, and/or C-7′ carboxylalkyl substituents, respectively (Fig. 2).

The initial retroanalysis of furanindoles is shown in Figure 3.

Target **A** was planned to be prepared by the acylation of the half ester **C** with a C-7′ substituted indole **B**. Half ester **C** was planned to be prepared by selective hydrolysis of 3-methoxy-4-aryl-furan-2,5-dicarboxylic acid dimethyl ester **D**. The methyl ether was selected as a protecting group, because of its stability to both acidic and basic conditions in the subsequent steps. We selected compound **6** as the model molecule to explore

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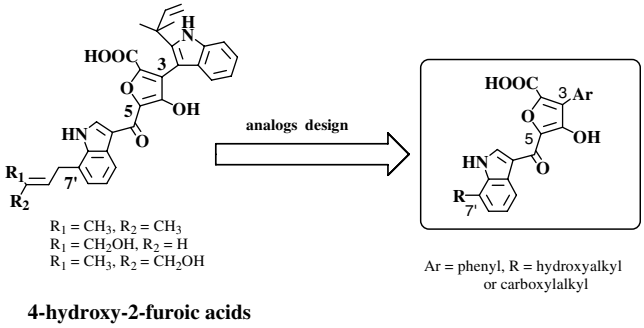


Figure 2. Rational design of 4-hydroxy-2-furoic acid derivatives as potential insulin receptor activators.

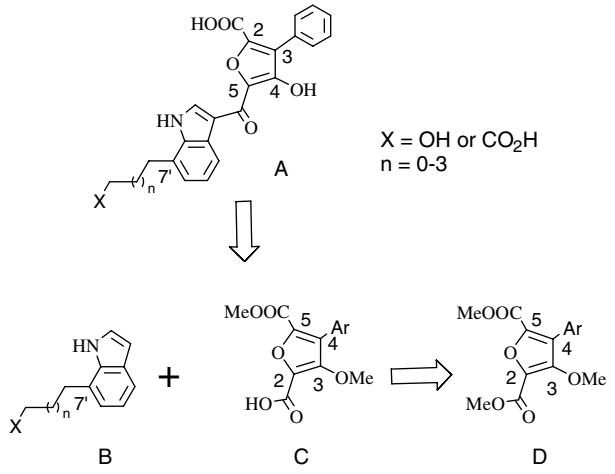
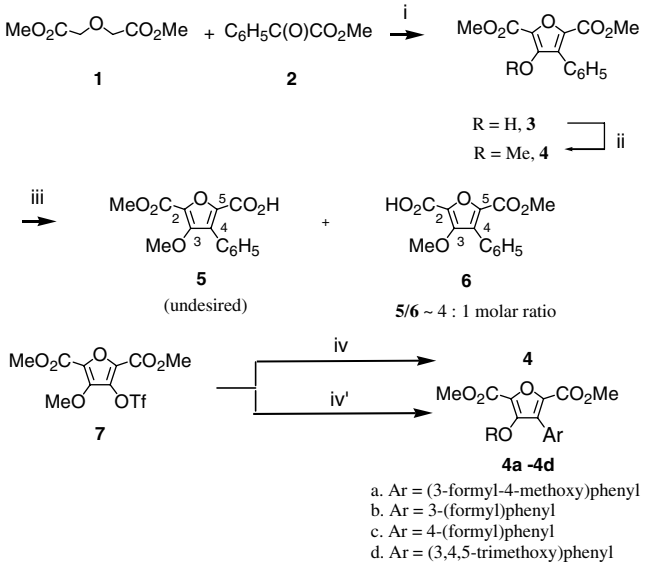


Figure 3. Retroanalysis of 4-hydroxy-furoic acid derivatives.

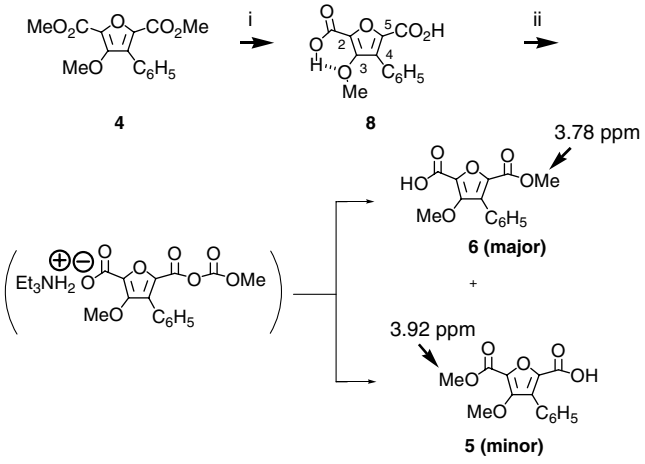
the synthetic pathway of half ester **C** (Scheme 1). The furan skeleton, 3-methoxy-4-phenyl-furoic 2,5-dicarboxylic acid dimethyl ester **4**, was prepared by adding a mixture of dimethyl diglycolate **1** and arylglyoxalate **2** (1.5:2 molar ratio) to a refluxing suspension of *t*-BuOK (2.7 M equiv vs dimethyl diglycolate, prepared from potassium and equal molar amounts of *t*-BuOH) in refluxing benzene, and the resulting **3** was immediately protected by methylation to provide **4** without isolation. A related synthetic method of **3** and a synthetic useful mixed ester has been described recently.[4]

Alternatively, **4** and various nuclear substituted analogues (**4a**–**d**) can be prepared by the palladium-catalyzed cross-coupling of the self-prepared triflate **7** with a commercial boronic acid in good yield. Our next effort is to selectively hydrolyze the less hindered C-2 ester of **4**, and then acylating that site to introduce the indole ring. However, the resonance-stabilizing effect of the 3-OMe group was most probably responsible for the reluctance of C-2 ester hydrolysis, despite the fact that the C-2 ester was less hindered than the C-5 ester. The undesired isomer **5** was formed as a major product (**5**/**6** ~ 4:1 molar ratio). Given the resonance effect of the 3-OMe group, this work suggests that the desired half ester **6** can be prepared by the selective methylation of the corresponding diacid **8**. Since the C-2 carboxylic acid of **8** is conjugated with an electron-donating group (3-



Scheme 1. Preparation of diester **4** and half esters **5** and **6**. Reagents and conditions: (i) *t*-BuOK, benzene, reflux; (ii) MeI, K_2CO_3, DMF, 45.0% (two steps); (iii) LiOH (~100 mol %), MeOH, H_2O, 95.0%; (iv) $C_6H_5B(OH)_2$ (1.2 equiv), Na_2CO_3 (3.0 equiv), $PdCl_2(PPh_3)_2$, DMF, 90 °C, 80.4% and (iv′) $ArB(OH)_2$ (1.2 equiv), Na_2CO_3 (3.0 equiv), $PdCl_2$ $(PPh_3)_2$, DMF, 90 °C, 55.5–74.3%.

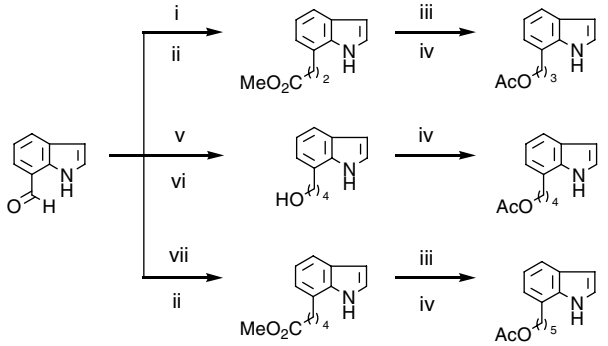
OMe), the electron density around the acidic proton is higher than that of C-2 carboxylic acid for resonance effect; moreover, the acidic proton is locked intramolecularly by the 3-OMe group. Therefore, the C-2 carboxylic acid should be relatively less easily deprotonated and thus less easily acylated in comparison with C-5 carboxylic acid during treatment with methyl chloroformate and a weak base, such as triethylamine. Precedent showed that mixed anhydride might undergo decarboxylation into ester in the presence of tertiary amines.[5] Accordingly, we proposed that the desired half ester **6** could be selectively prepared from **8** by the mixed anhydride method.



Scheme 2. Regioselective synthesis of **6**: Reagents and conditions: (i) OH^-, MeOH, H_2O, 90.0% and (ii) $ClCO_2Me$, NEt_3, then DMAP (cat.), 59.0% (**6**/**5** = 4.8:1 molar ratio).

The route to the desired half ester **6** is achieved regioselectively from the furoic dimethyl ester **4** (Scheme 2). Hydrolysis of **4** provided diacid **8**. Upon treatment of **8** with 1.0–2.5 M equiv of weak base, such as triethylamine, and methyl chloroformate, the kinetic C-5 carboxylate is preferentially acylated to yield an unstable mixed anhydride, which is then decarboxylated into the half ester **6** in the presence of a catalytic amount of tertiary amine, such as DMAP. We proposed that even a small amount of methanol formed by decarboxylation of the mixed anhydride could catalyze the formation of methylester. The regiochemistry is elucidated by ^{1}H NMR, the methyl ester protons of the desired isomer exhibit an upper chemical shift than that of the undesired isomer for the shielding effect of the aryl ring. The presented approach is employed to prepare related half esters from the respective diacids with a similar regio-selectivity (Table 1).

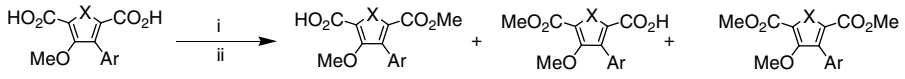
The 7-substituted indole intermediates were prepared from 7-formyl indole by a variety of chain extension reactions; such as by the Wittig reaction, which involves condensation with ylids, or Horner–Emmons reaction, which involves condensation with trimethylphosphonoacetate. Various linear carbon chains with hydrophilic groups (e.g., OH or CO_2H) were prepared (Scheme 3).



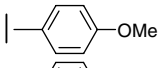
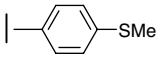
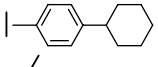
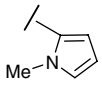
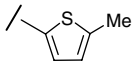
Scheme 3. Preparation of the C-7 substituted indoles: Reagents and conditions: (i) $(MeO)_2P(O)CH_2CO_2Me$, NaH, DME, 92.3%; (ii) H_2, Pd–C; ~95.0%; (iii) $NaBH_4$, MeOH, THF, reflux, 65.3–75.3%; (iv) Ac_2O, NEt_3, $CHCl_3$, ~90.0%; (v) $(C_6H_5)_3P{=}CH(CH_2)_3OTHP$, 65.4%; (vi) H_3O^+, 50.3% and (vii) $(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH, THF, 85.3%.

The synthetic route of 3-aryl-5-(1*H*-indole-3-carbonyl)-4-hydroxy-2-furoic acids **11** is illustrated in Scheme 4.

Table 1. Selective methylation of **8**



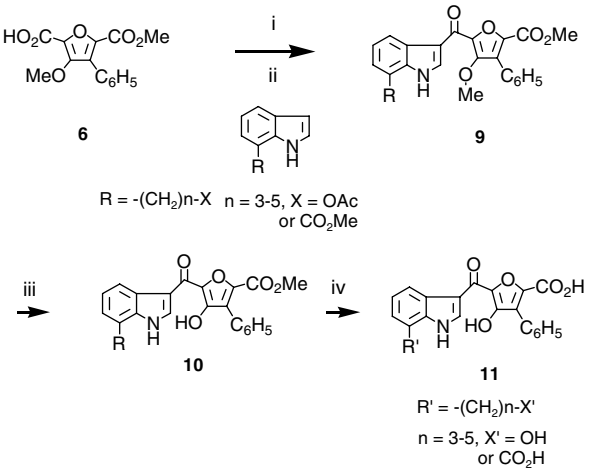
8 **6** **5** **4**

Entry	X	Ar	NEt_3 (M equiv)	$ClCO_2Me$ (M equiv)	Recovery of **8** (%)	Isolated yield of **4** (%)	Isolated yield of **5** and **6**[a] (%)	Selectivity **6**:**5**[b]
1	O		1.0	1.0	20.7	10.6	50.7	1.9:1
2	O		1.5	1.0	8.0	12.6	59.0	4.8:1
3	O		2.0	1.0	10.6	17.7	45.7	4.1:1
4	O		1.5	1.0	7.5	20.2	44.0	6.3:1
5	O		1.5	1.0	9.6	11.6	59.7	2.2:1
6	O		1.5	1.0	7.0	19.8	45.7	3.8:1
7	O		1.5	1.0	9.1	22.1	40.1	3.5:1
8	O		1.5	1.0	9.3	18.5	46.8	3.7:1
9	O		1.5	1.0	10.7	17.7	45.7	2.5:1
10	S		1.5	1.0	9.7	14.8	54.7	3.2:1
11	S		2.0	1.0	9.8	14.5	52.9	3.7:1
12	S		2.5	1.0	4.5	8.6	71.5	2.4:1

Reagents and conditions: (i) $ClCO_2Me$, CH_2Cl_2, NEt_3, 0 °C and (ii) DMAP (cat.), 0 °C to rt.

[a] For typical procedure, see Supplementary data.

[b] Determined by HPLC analysis.



Scheme 4. Synthesis of **11**. Reagents and conditions: (i) oxalyl chloride, CH_2Cl_2, DMAP (cat.); (ii) Et_2AlCl, $CHCl_3$, −10 °C–rt, 60.5–65.3% (two steps); (iii) BCl_3, CH_2Cl_2, 85.5–90.5% and (iv) OH^-, 70.0–75.0%.

The acylation of half ester **6** with 7-substituted indoles was performed under mild conditions, using dialkyl aluminium chloride as the catalyst.[6,7] The acylation intermediates **9** were deprotected under mild reaction conditions using excessive amounts of boron trichloride (~2–20 M equiv) to give 4-hydroxyfurans **10** in good yields. Conversion of compounds **6**–**10** could also be accomplished in one flask without isolation of intermediate **9**. Finally, the hydrolysis of the furan ester and the deprotection of the indole C-7 side chain were performed simultaneously to provide target molecules **11**.

In conclusion, this study presented a methodology for synthesizing 3-aryl-5-(1*H*-indole-3-carbonyl)-4-hydroxy-2-furoic acids.[8] The core structure, 3-methoxy-4-aryl-2,5-furanoic dicarboxylic dimethyl ester, can be prepared by either condensation or metal-catalyzed cross coupling reaction. Regioselective esterification of 3-methoxy-4-aryl-2,5-furanoic acid was conducted by the mixed anhydride method, allowing various aryl groups to be introduced into the furan ring with the desired regiochemistry. Additionally, both the acylation of the desired half ester **6** and the demethylation of the resulting furan indole intermediate **9** can be conducted under mild conditions. This study also proposed a model for synthesizing a novel furandiindole skeleton in which the aryl group (Ar) could be replaced with an indole ring.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.076.

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7. Notably, the complete removal of superfluous oxalyl chloride before acylation is key to the success of this step, for typical procedure see Supplementary data.
8. Efficacies of compounds on cell-based insulin receptor tyrosine kinase activity will be reported elsewhere.