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Parallel Synthesis and Evaluation of *N*-(1-Phenylethyl)-5-phenyl-imidazole-2-amines as Na^+/K^+ ATPase Inhibitors

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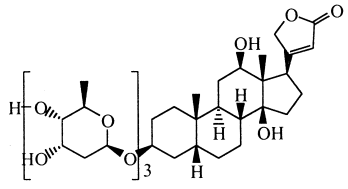
Abstract—A series of *N*-(1-phenylethyl)-5-phenyl-imidazole-2-amines was prepared using solution-phase, parallel synthesis and evaluated for Na^+/K^+ ATPase inhibition.

Congestive heart failure (CHF), a disease characterized by the failure of the heart to pump sufficient blood flow to meet the metabolic needs of the body,[1] affects 4.6 million Americans with an additional 400,000 new cases every year. The five-year mortality rate for CHF is nearly 50%,[2] and symptoms of the disease include peripheral edema, dyspnea, tachypnea, tachycardia, and decreased exercise capacity. Current treatment regimens for the disease include several different classes of drugs. Diuretics have been available since the 1950s and decrease the fluid load on the heart. Angiotensin converting enzyme (ACE) inhibitors were introduced in the 1980s, and have since been shown to increase life expectancy substantially. The oldest treatment for CHF, however, is the cardiac glycoside digoxin (**1**). Treatment of CHF with digoxin can be traced back to at least the 18th century, and has been shown to increase the exercise capacity of CHF patients.[3] This effect has been linked to the inhibition of myocardial Na^+/K^+ ATPase, which strengthens the heart's pumping action (positive inotropy). Digoxin plasma concentrations must be carefully maintained between 0.5 ng/mL to 2.0 ng/mL, as potentially life threatening effects begin to occur when plasma concentrations exceed 2.0 ng/mL. Treatment with digoxin is further complicated by high plasma protein binding and lipid solubility, which can greatly extend the time and dosing required to reach steady-state plasma concentrations (up to 2 weeks in some patients).[4] In an effort to develop positive inotropes with a more favorable therapeutic index, we examined a series of aminoimidazoles based on one of the few known nonsteriodal inotropes, BIIA (**2**). This imidazoisoquinoline is inotropic ($EC_{50} = 1.0\ \mu M$, guinea pig papillary muscle), and we believe that unlike digoxin, BIIA does not bind to the ouabain binding site. Instead, BIIA binds at a Na^+ site (the guanidine of BIIA acts as a sodium mimetic), blocking ion transport.[5] In an effort to develop more potent nonsteroidal inotropes, we prepared and examined a series of BIIA analogues using solution phase parallel synthesis methods.



Digoxin, 1

Our initial efforts to produce more efficacious analogues of BIIA focused on the preparation of des-B-ring compounds (e.g,. **3**). We believed that removal of the B-ring would permit greater conformational mobility, possibly allowing these analogues to adopt unique conformations that would enhance their interaction with the binding site of Na^+/K^+ ATPase, thereby increasing their potency. A retrosynthetic analysis suggested imidazole **4** as a central building block that could be elaborated with a combination of organometallic cross coupling chemistry and nucleophilic substitution reactions to establish the A-ring and the guanidine/D-ring, respectively. Imidazole **4** could in turn be prepared from an *N*-alkylated imidazole (**5**) by taking advantage of the difference in acidity between the 2- and 5-positions (Scheme 1).[6]

Installation of the desired functional groups was readily accomplished by selectively deprotonating *N*-methyl

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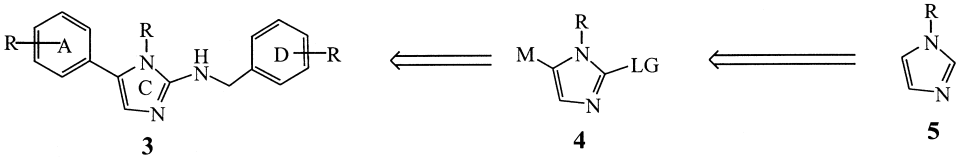
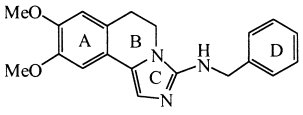


Scheme 1.

imidazole at the 2-position with *n*-BuLi and adding diphenyl disulfide. Further deprotonation of the 5-position with *n*-BuLi, followed by addition of iodine and oxidation with *m*CPBA in methylene chloride produced **6**.[7] The desired des-B-ring analogues of BIIA could then be approached by Suzuki coupling of **6** with phenyl boronic acid in aqueous dimethoxyethane in the presence of $Pd(PPh_3)_4$ and NaOH to produce **7**. Treatment of **7** with the lithium amide of α-methyl benzyl amine produced the desired product (**8**) in excellent yield.



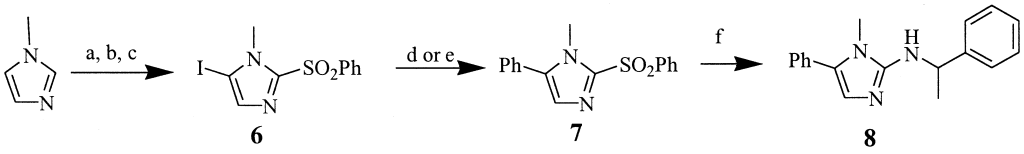
BIIA, 2

Biological screening of **8** in an isolated enzyme assay revealed that the desired activity had been maintained (ATPase activity was measured by monitoring the release of inorganic phosphate by colorimetric determination; myocardial Na^+/K^+ ATPase was isolated from canine cardiac sarcolema).[8,9] Therefore, we turned our attention to the preparation of directed libraries of analogous compounds. Libraries exploring the ramifications of modifying the D-ring were produced by condensing **7** with a series of amines as their lithium amides. The desired products were isolated by column chromatography and tested in the isolated enzyme assay. Some representative examples are shown in Table 1, entries 2–7. Modification of the A-ring was also accomplished by preparation of solution-phase libraries, but by a slightly different method. The number of commercially available aryl boronic acids is relatively small, and we felt that we could produce a much larger library of compounds by inverting the positions of the metal and halide by employing Stille rather than Suzuki chemistry. Starting with *N*-methyl imidazole, selective deprotonation in the 2-position, followed by addition of diphenyl disulfide and *m*CPBA oxidation in methylene chloride provided the necessary electrophile in the 2-position. Further deprotonation with *n*-BuLi and addition of tributyltin chloride produced **9** in good yield (Scheme 3). Installation of the tin functionality on the imidazole ring allowed us to explore a wide range of commercially available aryl bromides as potential coupling partners. The des-B-ring analogues of BIIA were then prepared by a two-step, one-pot procedure. Stille coupling of **9** with an aryl bromide was performed in refluxing 1,4 dioxane in the presence of BHT and $Pd(PPh_3)_4$. When

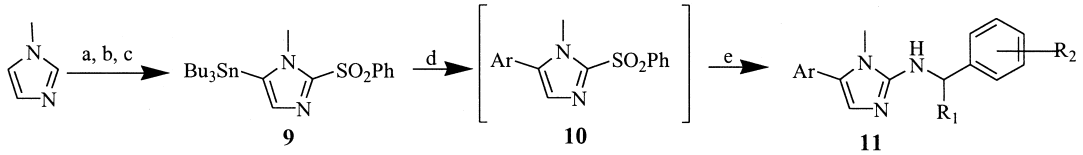
Table 1. Representative examples of des-B-ring analogues of BIIA (**11**) and isolated enzyme activity

Entry	Ar	R_1	R_2	Yield	IC_{50} (μM)[c]
1	Ph	CH_3	H	[a]	38
2	Ph	(*R*)-CH_3	H	63%	10
3	Ph	(*S*)-CH_3	H	72%	61
4	Ph	CH_3	4-Cl	62%	1.3
5	Ph	CH_3	4-F	70%	10
6	Ph	*sec*-Butyl	H	67%	77
7	Ph	CH_2CH_3	4-Cl	82%	0.8
8	2-Napthyl	CH_3	H	29%[b]	2.1
9	3-Biphenyl	CH_3	H	57%[b]	14
10	4-CF_3O-Ph	CH_3	H	41%[b]	33
11	3,5-di-F-Ph	CH_3	H	29%[b]	52
12	3,5-di-CF_3-Ph	CH_3	H	40%[b]	88
13	3,4-di-CH_3O-Ph	CH_3	H	45%[b]	99

[a]See Scheme 2 for yields.
[b]Yield over two steps.
[c]Compounds were evaluated once over a 2 log range. Digoxin $IC_{50} = 30$ nM.



Scheme 2. Reagents: (a) (i) *n*-BuLi, THF, −78 °C; (ii) Ph_2S_2, THF, 73%; (b) (i) *n*-BuLi, THF −78 °C; (ii) I_2, THF, 96%; (c) *m*CPBA, CH_2Cl_2, 83%; (d) $PhB(OH)_2$, $Pd(PPh_3)_4$, NaOH, DME, H_2O, reflux, 73%; (e) $PhSnMe_3$, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C, 62%; (f) α-methyl benzyl amine, *n*-BuLi, 0 °C, 76%.



Scheme 3. Reagents: (a) (i) *n*-BuLi, THF, −78 °C; (ii) Ph_2S_2, THF, 73%; (b) *m*CPBA, CH_2Cl_2, 97%; (c) (i) *n*-BuLi, THF −78 °C; (ii) $SnBu_3Cl$, THF, 89%; (d) ArBr, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 24 h; (e) RNH_2, *n*-BuLi, 0 °C, 76%.

the reaction was complete, a solution of the lithium salt of the desired benzyl amine in THF was added. The desired products were isolated by column chromatography and tested in the isolated enzyme assay. Representative examples from this library are also shown in Table 1 (entries 8–13).[9]

The results shown in Table 1 lead to several conclusions about the nature of the binding of BIIA to myocardial Na^+/K^+ ATPase. First, the B-ring is clearly not a required aspect of the pharmacophore, as its removal does not appear to dramatically decrease the range of observed activity. Second, binding is sensitive to changes in the chiral center of the benzyl amine/D-ring portion of the compound, as indicated by the difference in activity observed in entries 1–3 of Table 1. Third, the A-ring is probably associated with a hydrophobic pocket of the binding site of Na^+/K^+ ATPase. This is suggested by the nearly 50-fold increase in activity between entries 8 and 13, as well as the overall trend of entries 8–13.

In summary, we have developed a series of des-B-ring analogues of BIIA (**2**), which are potent inhibitors of myocardial Na^+/K^+ ATPase using solution-phase, parallel-synthesis methods.

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9. Typical library preparation: Bromobenzene (76 mg, 50.6 uL, 0.48 mmol), imidazole **9** (225 mg, 0.44 mmol), and 0.5 mg of BHT were dissolved in 1.5 mL of 1.4 dioxane, and 9 mg of $Pd(PPh_3)_4$ was added. The reaction was heated to reflux for 24 h and is then cooled to 12 °C. Separately, 0.55 mL of *n*-BuLi (2.4 M in hexane) was added to a 12 °C solution of α-methyl benzylamine (180 mg, 0.17 mL, 1.49 mmol) in 2.0 mL of 1.4 dioxane. After 30 min, the lithium amide solution was added to the imidazole solution in a dropwise fashion, and the reaction was allowed to warm to room temperature. After 15 h, the reaction was quenched with 10 mL of $NaHCO_3$, and the solution was extracted with EtOAc (3×10 mL). The combined EtOAc was washed with aqueous KF (10 mL), dried over $MgSO_4$, filtered and stripped of solvents to yield a yellow solid. Chromatography with 1:1 hexane:EtOAc provided 92.6 mg (76 %) of the desired product as a pale-yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (10H, m), 6.81 (1H, s), 5.08 (1H, m, $J=9.6$ Hz), 3.87 (1H, bs), 3.38 (3H, t), 1.64 (3H, t, $J=9.6$ Hz), ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 150.3, 144.9, 130.9, 129.9, 128.9, 128.8, 127.9, 127.4, 127.1, 126.5, 123.4, 53.6, 30.4, 23.4. IR 3010, 2980, 1550, 1225, 1175, 925 cm^{-1}. Mass spectrum m/z (%): 278 (M + 1, 100%).