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Solid-phase synthesis of benzimidazole libraries biased for RNA targets

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Abstract—An efficient and highly versatile synthesis of two libraries **1(x,y)** and **2-Ar(x,y,z)** or **2-R^2(x,y,w)** based on the *privileged* benzimidazole scaffold is described. Our design is aimed at obtaining molecules, biased for binding to RNA targets, by incorporating functionalities, which are frequently found in natural RNA-ligands. The library construction was realized with the use of SPOS in high average yields and purity. Monitoring and quantitation of intermediates and final products were performed by the use of NMR spectroscopy using DMFu as an internal standard.

The benzimidazole scaffold[1] has received extensive attention in medicinal chemistry, especially after the commercialization of the antihistamine Astemizole[2] and the antiulcerative Omeprazole (Fig. 1).[3] Benzimidazole's diverse portfolio of biological activities, including inhibition of phosphodiesterase IV,[4] antagonism of angiotensin 1,[5] neuropeptide Y binding,[6] inhibition of proton pumps,[7] antiarrythmic and antiviral indications,[8] as well as its close structural relationship to benzodiazepines,[9] suggested its inclusion in the general family of '*privileged structures*' (Fig. 1).[10]

Our focus on ribonucleic acids (RNA) and RNA-protein complexes as primordial targets for therapeutic intervention[11] led us to select the benzimidazole scaffold for the construction of a library of molecules biased for RNA-binding[11] for general screening in our areas of interest. The guidelines of our design are based on analyses of known RNA-binders, along with molecular modeling and chemoinformatics. Natural ligands that target RNAs have an increased number of hydrogen-bond donors/acceptors at the periphery of the molecule, as well as an increased rigidity, that would display those groups on a well-defined three-dimensional space.[11] Consequently, due to the increased polarity of these molecules and the anticipated difficulties in purification, solid phase organic synthesis

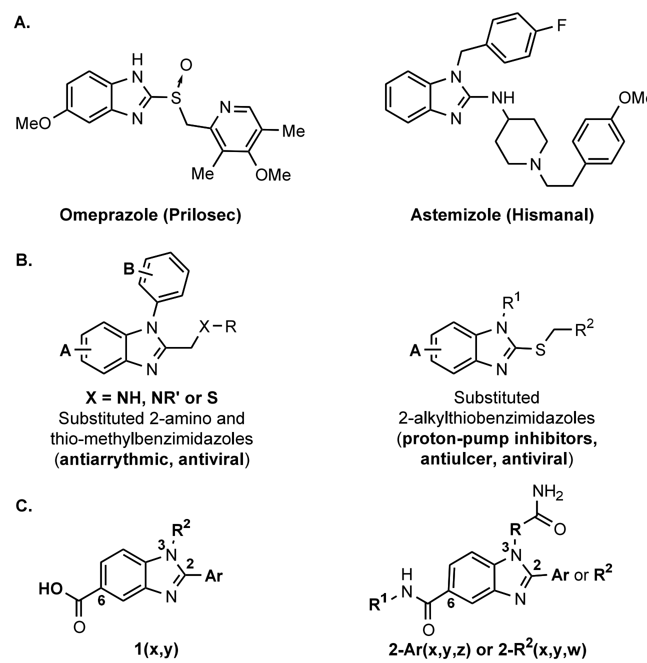

Figure 1. (A). Structures of drugs based on the benzimidazole scaffold; (B). Trisubstituted benzimidazoles and analogs with diverse biological activities; (C). Proposed structures for current work.

Keywords: benzimidazoles; privileged structures; RNA targets; NMR-quantitation.

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(SPOS) was selected as the method of choice for their construction.

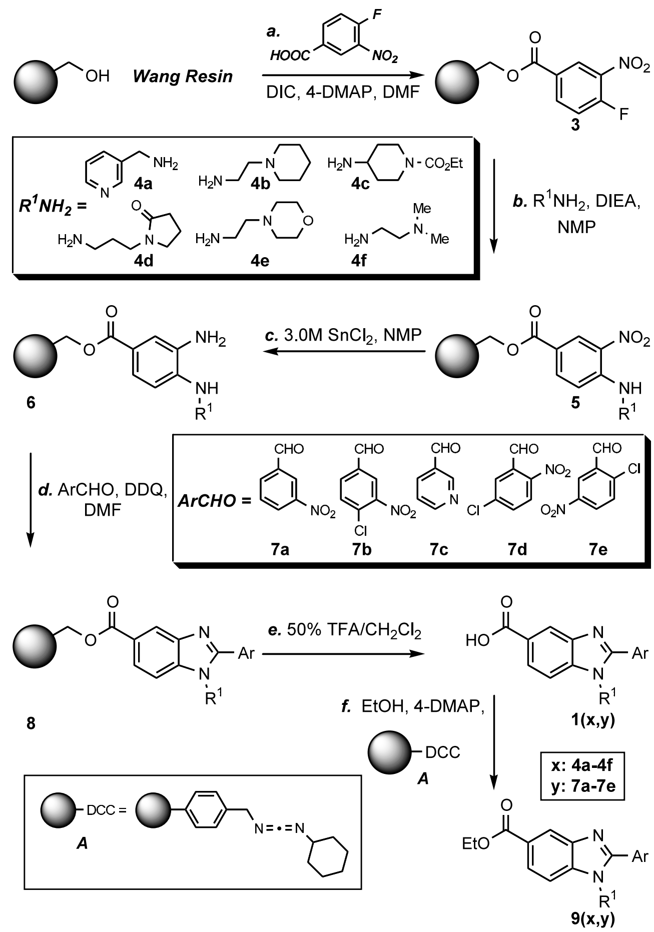
One important aspect of our operating strategy was the selection of NMR for quantitation of intermediates and final products, as well as partially accompanying LC–MS in the quality control process. This was accomplished by the use of 2,5-DiMethylFuran (DMFu) as an internal standard, in well defined concentrations within our NMR solvent (DMSO), as previously described.[12] We found the above method to be highly accurate and reliable, adding enormous flexibility to SPOS in terms of simultaneous quality and quantity control of the produced compounds.

In our work we focused on two libraries, namely **1** with two points of diversity at positions 2 and 3, and the more general **2** with three points of diversity at positions 2, 3 and 6 of the benzimidazole skeleton, respectively (Fig. 1).

The synthesis of **1(x,y)** (Scheme 1), emerged with the esterification of Wang resin (*p*-benzyloxybenzyl alcohol resin) with 4-fluoro-3-nitrobenzoic acid,[1d,i,j,l] using standard coupling conditions (DIC, 4-DMAP) to produce **3** in quantitative yield. Loading of the resin was verified after cleavage (50% TFA/CH_2Cl_2) by NMR quantitation with DMFu. Nucleophilic aromatic displacement (S_NAr) of the activated fluoride[1d,i,j,l,13] at the *ipso*-position with six commercially available amines (**4a**–**f**) furnished the corresponding nitroanilines **5** in almost quantitative yields.

These amines were selected to provide the additional required hydrogen-bond donors/acceptors and the reduced flexibility in most cases, represented by a maximum chain length of three carbons. Reduction of the nitro-functionality in **5** was accomplished by treatment with $SnCl_2$[14] in 1-methyl-2-pyrrolidinone (NMP), producing the desired *o*-phenylenediamines **6** in greater than 91% overall yield. The formation of the benzimidazole nucleus was accomplished by the treatment of anilines **6** with aromatic aldehydes **7a**–**e** in the presence of DDQ,[15] furnishing **8**. Later it was realized that inclusion of DDQ was not necessary[1m,n] and that exposure to air overnight was sufficient to induce the oxidative cyclocondensation, producing the desired benzimidazoles on solid phase. Cleavage from the solid support was performed by the use of a 50% trifluoroacetic acid (TFA) solution in CH_2Cl_2, furnishing benzimidazoles **1(x-y)** in 41% overall average yield and 94% average purity, as proven by LC–MS analysis and NMR quantitation of selected examples (see Supporting Information). Half of the amount of the resulting acids was further reacted with ethanol, in the presence of solid supported DCC (**A**) and 4-DMAP, to furnish ethyl esters **9(x-y)** in high yields, after filtration through a short pipette column (Scheme 1).

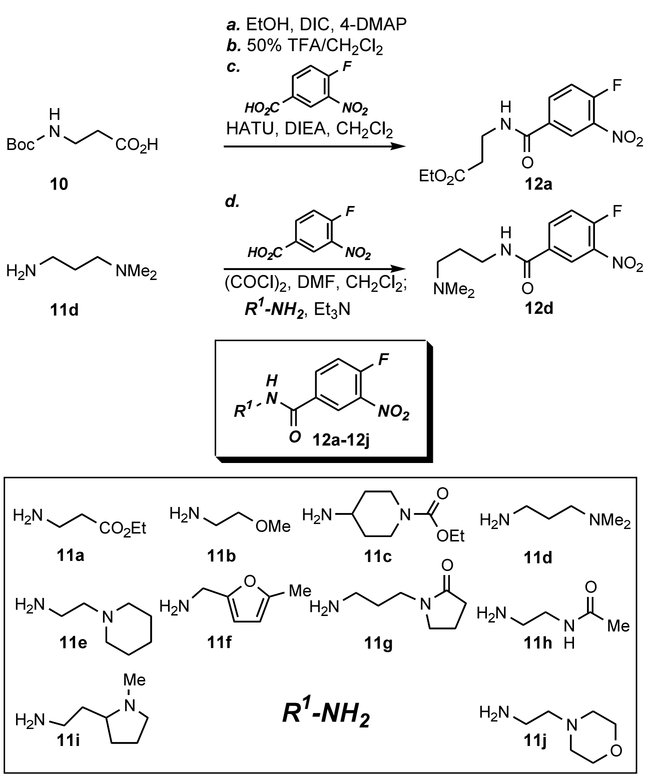
For the synthesis of benzimidazole libraries **2-Ar(x,y,z)** and **2-R²(x,y,w)** with three points of diversity, we utilized again 4-fluoro-3-nitrobenzoic acid. Ten amines (**11a**–**j**) were selected for coupling with the acid, including **11a**, synthesized from **10** through an esterification–deprotection sequence (Scheme 2). The coupling was performed by two different methods, either through HATU mediation[16] or through the formation of the highly reactive acyl chloride. The results of the coupling are summarized in Scheme 2.



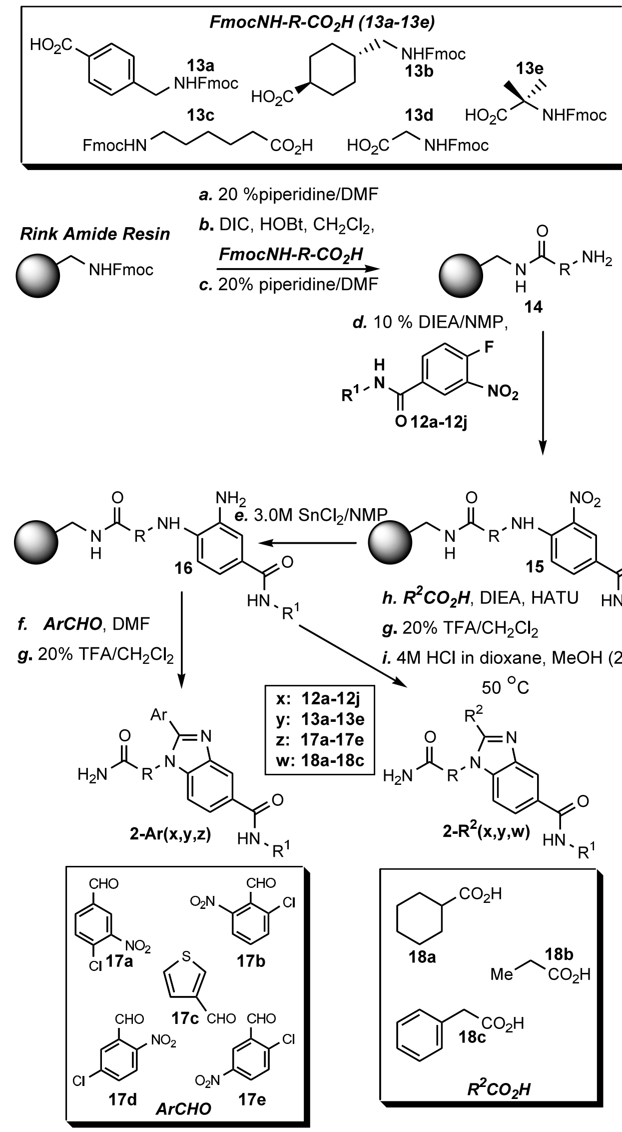
Scheme 1. *Reagents and conditions*: (a) 5.0 equiv. of 4-fluoro-3-nitrobenzoic acid, 5.0 equiv. of DIC, 0.1 equiv. of 4-DMAP, DMF (0.25 M), 16 h, 23°C, quantitative; (b) 5.0 equiv. of R^1NH_2 (**4a**–**f**), 10% v/v DIEA in NMP (0.2 M), 18 h, 23°C; (c) 3 M $SnCl_2$ in NMP, 16 h, 23°C, >91% for two steps; (d) 5.0 equiv. of ArCHO (**7a**–**e**), 2.0 equiv. of DDQ, DMF (0.2 M), 18 h, 23°C; (e) 50% TFA in CH_2Cl_2, 30 min, 23°C, average yield of 41% overall; (f) 100 equiv. of EtOH, 4.0 equiv. of solid supported carbodiimide **A**, 0.1 equiv. of 4-DMAP, 16 h, 23°C, average yield of 92%. DIC = 1,3-Diisopropylcarbodiimide; 4-DMAP = 4-(Dimethylamino)pyridine; DMF = *N*,*N*-Dimethylformamide; DIEA = *N*,*N*-Diisopropylethylamine; NMP = 1-Methyl-2-pyrrolidinone; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; TFA = Trifluoroacetic acid.

Rink amide resin was selected[1d,j] due to its high acid sensitivity in the final cleaving step. Thus, after removing the Fmoc functionality by treatment with 20% piperidine in DMF, five Fmoc-*N*-protected amino acids **13a**–**e**[17] were loaded on the resin under standard conditions (DIC, HOBt) to produce amides **14** on solid phase (Scheme 3).

Cleavage from the solid support, followed by NMR quantitation with DMFu indicated quantitative loading for all five amino acids. Removal of the Fmoc-protecting group was again accomplished with 20% piperidine/DMF. The liberated amine nucleophilicly displaced the fluorine atom from the previously synthesized **12a–j**, furnishing the corresponding nitroanilines **15** in high yields for all cases except **15e**. In that case steric hindrance of the geminal dimethyl functionality prevented the desired reaction. Thus, only **13e** was obtained after the cleavage reaction. Consequently, amino acid **13e** was excluded from further experimentation. Reduction of the nitro group with $SnCl_2$ produced the desired *o*-phenylenediamines **16**, which were further reacted with five aromatic aldehydes, **17a–e**, of various substitutions.[1b,i,k,m,18] Cleavage with 20% TFA/CH_2Cl_2 afforded the desired benzimidazoles **2-Ar(x,y,z)**, in an average yield of 42% for all monomers, exhibiting satisfactory LC–MS spectra throughout (93% average purity).



Scheme 2. *Reagents and conditions*: (a) EtOH (1.0 M) as solvent, 2.0 equiv. of DIC, 0.1 equiv. of 4-DMAP, 16 h, 23°C, 95% after purification (20% EtOAc/hexanes); (b) 50% TFA in CH_2Cl_2, 3 h, 23°C; (c) 1.0 equiv. of 4-fluoro-3-nitrobenzoic acid, 2.0 equiv. of HATU, 3.0 equiv. of DIEA, CH_2Cl_2 (0.2 M), 16 h, 23°C, 92% for **12a**, 87% for **12b**, 74% for **12c**; (d) 2.0 equiv. of DMF, −20°C, 2.0 equiv. of $(COCl)_2$, 10 min; then 1.0 equiv. of 4-fluoro-3-nitrobenzoic acid, 30 min; then 1.0 equiv. of **11d–j**, 3.0 equiv. of Et_3N, 1 h, 23°C, 97% for **12d**, 99% for **12e**, 85% for **12f**, 98% for **12g**, 84% for **12h**, 98% for **12i**, 99% for **12j**. HATU = *O*-(7-Azabenzotriazole-1-yl)-*N*,*N*,*N′*,*N′*-tetramethyluronium hexafluorophosphate; for reagent abbreviations see also legend of Scheme 1.



Scheme 3. *Reagents and conditions*: (a) 20% piperidine in DMF, 3 h, 25°C, quantitative; (b) 3.0 equiv. of FmocNH-R-CO_2H (**13a–e**), 5.0 equiv. of DIC, 5.0 equiv. of HOBt, CH_2Cl_2 (0.25 M), 16 h, 25°C, quantitative; (c) 20% piperidine in DMF, 3 h, 25°C, quantitative; (d) 5.0 equiv. of **12a–j**, 10% v/v DIEA in NMP (0.3 M), 18 h, 25°C; (e) 3.0 M $SnCl_2$ in NMP, 16 h, 25°C, >91% for two steps; (f) 5.0 equiv. of ArCHO (**17a–e**), DMF (0.3 M), 18 h, 25°C; (g) 20% TFA in CH_2Cl_2, 30 min, 25°C, average yield of 42% overall for **2-Ar(x,y,z)**; (h) 5.0 equiv. of R^2CO_2H (**18a–c**), 5.0 equiv. of HATU, 15 equiv. of DIEA, DMF (0.2 M), 18 h, 25°C; (i) 4 M HCl in dioxane/MeOH (2:1), 16 h, 50°C, average yield of 38% overall. HOBt = 1-Hydroxybenzotriazole; for reagent abbreviations see also legends of Schemes 1 and 2.

The same intermediate diaminobenzenes **16** were coupled with three aliphatic acids **18a–c**,[1j,l,m,19] furnishing after a cleavage/cyclization (TFA) and dehydration (HCl) sequence the desired benzimidazoles **2-R²(x,y,w)** in an average of 38% overall yield and high purity (LC–MS).

In conclusion, we have described the synthesis of two libraries containing molecules biased for RNA-binding, **1(x,y)** and **2-Ar(x,y,z)** or **2-R^2(x,y,w)**, based on the *privileged* benzimidazole scaffold. Careful design allowed the introduction of a variety of polar groups on the periphery of the molecules. Library synthesis was realized with the use of SPOS in high average yields and purity. Intermediates and final products were monitored and quantitated by NMR spectroscopy utilizing DMFu as an internal standard. Biological screening against a variety of different bacterial and viral RNA-targets is currently under investigation.

Supplementary material

^{1}H NMR data for randomly selected examples from **1(x,y)** (three compounds) and **9(x,y)** (three compounds), **2-Ar(x,y,z)** (25 compounds), and **2-R^2(x,y,w)** (eight compounds).

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