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Parallel solid-phase synthesis of disubstituted 3-(1*H*-benzo[*d*]imidazol-2-yl) imidazolidine-2,4-diones and 3-(1*H*-benzo[*d*]imidazol-2-yl)-2-thioxoimidazolidin-4-ones

Sureshbabu Dadiboyena [a], Adel Nefzi [a,b,*]

[a] Torrey Pines Institute for Molecular Studies, 11350 SW Village Parkway, Port St. Lucie, FL 34987, USA
[b] Florida Atlantic University, Boca Raton, FL 33431, USA

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ABSTRACT

A multistep approach to construct novel 3-(1*H*-benzo[*d*]imidazol-2-yl)imidazolidine-2,4-diones and 3-(1*H*-benzo[*d*]imidazol-2-yl)-2-thioxoimidazolidin-4-ones from commercially available amino acids, amines, and carboxylic acids is described. Coupling of Fmoc-amino acid to resin-bound aminobenzimidazole provided following Fmoc elimination free amine. Treatment of the free amine with 1,1′-carbonyldiimidazole or 1,1′-thiocarbonyldiimidazole furnished the corresponding hydantoins and thiohydantoins via intramolecular cyclization. The desired aminobenzimidazole tethered hydantoins or thiohydantoins were isolated in good yields.

Solid phase organic synthesis (SPOS) is a powerful technique for the rapid synthesis of small molecules endowed with potential bioactive properties.[1–4] A recurring feature of this approach is the synthesis of substituted heterocycles of structural diversity which aroused greater attention and have proven to be broadly and economically useful as therapeutic agents.[4,5] Benzimidazoles are an important class of heterocycles displaying a wide variety of biological properties,[6–10] they represent a key structural motif in angiotensin-II-antagonists, anticoagulants, and gastric proton-pump inhibitors.[8–16] We previously reported the application of resin-bound amino-benzimidazoles as a template for the synthesis of a variety of heterocyclic compounds such as tetracyclic benzimidazoles,[13] triazino-benzimidazoles,[14] and branched thiohydantoin benzimidazoline-thiones.[16] In continuation of our efforts directed toward the synthesis of combinatorial libraries of heterocyclic compounds utilizing amino acids and benzimidazole scaffolds,[11–16] we describe herein a multistep approach for the parallel solid-phase synthesis of compounds containing amino-benzimidazole tethered to pharmacologically known hydantoin or thiohydantoin.

Hydantoins represent ubiquitous structural core sporadically found in a number of natural products **1**–**6**,[17,18] and bioactive heterocycles such as phenytoin **7** and mephenytoin **8**.[19–21] The high incidence of this pharmacophore in several drugs and drug-like candidates has resulted in the development of a plethora of methods to construct this valuable fragment.[18,22–30] In addition to hydantoins, thiohydantoins constitute analogous structural frameworks of synthetic and biomedical importance.[17,18,31–35] Due to aforementioned applications, the synthesis of hydantoins and thiohydantoins units has received greater attention and few reports representing pharmaceutical and medicinal applications of hydantoins and thiohydantoins (Fig. 1[36–42]).

We envisioned the preparation of hydantoins and thiohydantoin nuclei from the amino acid coupled benzimidazole precursor **11** following intramolecular cyclization. Aminobenzimidazoles **9** required for the synthesis are conveniently accessed in several steps from the corresponding resin bound 4-fluoro-3-nitrobenzoic acid.[11–16] The retrosynthetic rationale for the synthesis of aminobenzimidazole tethered hydantoins and thiohydantioins is illustrated in Scheme 1.

The synthesis of all compounds described was carried out utilizing the tea-bag technology, wherein the resin is packed within sealed polypropylene mesh packets.[15] This method is convenient and allow the parallel synthesis of a large number of compounds in a specified time period. Based on previous literature precedents,[13–15] we introduced the first position (R_1) of diversity with five different amines via nucleophilic substitution of 4-fluoro-3-nitrobenzoic acid, and the second position (R_2) of diversity was

* Corresponding author. Tel.: +1 (772) 345 4739; fax: +1 (772) 345 3649.
E-mail addresses: anefzi@tpims.org, adeln@tpims.org (A. Nefzi).

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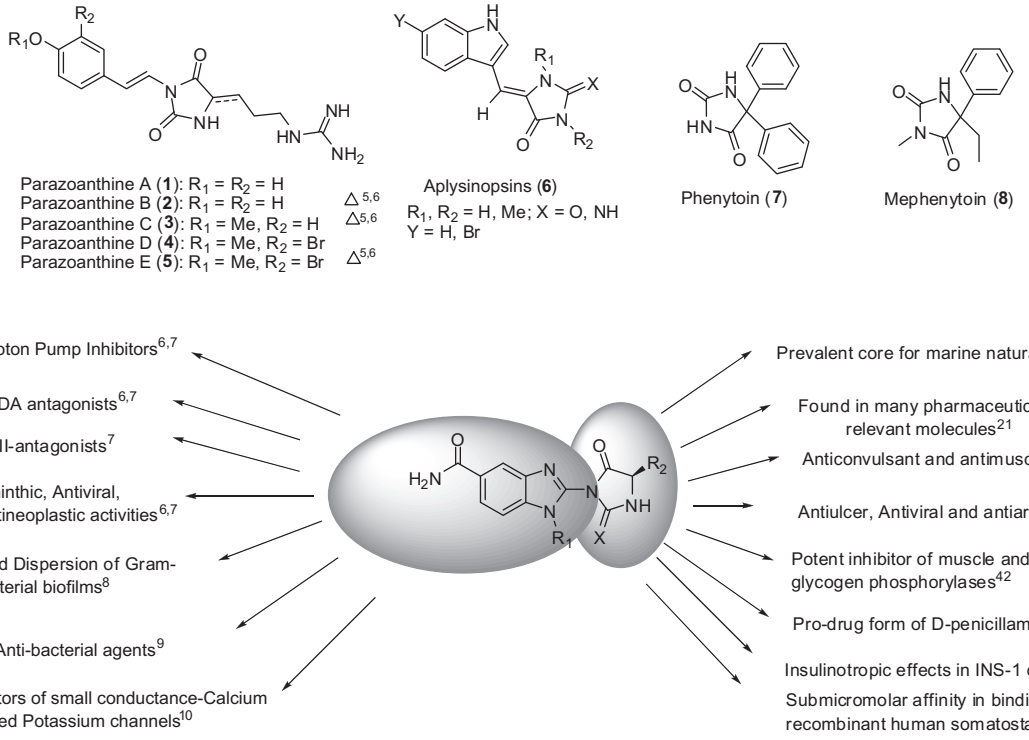
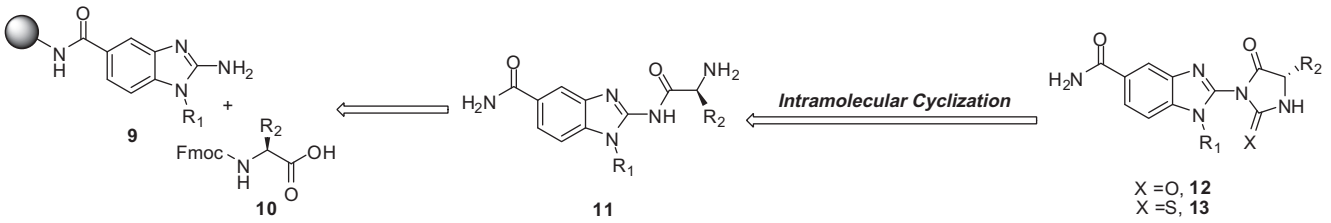
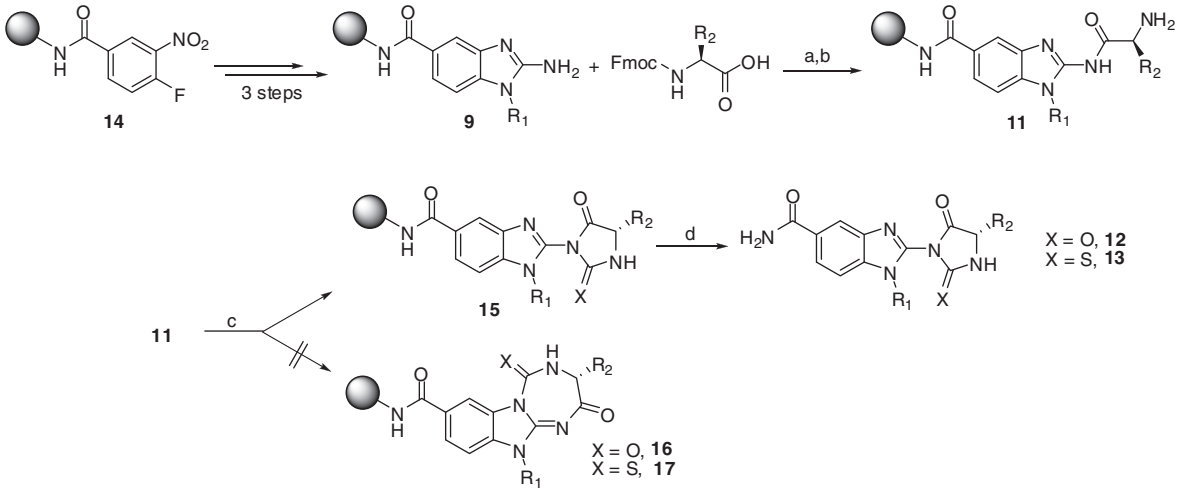


Figure 1. Natural and pharmaceutically occurring hydantoins and some reported bioactive properties of hydantoin/thiohydantoin structural motifs.

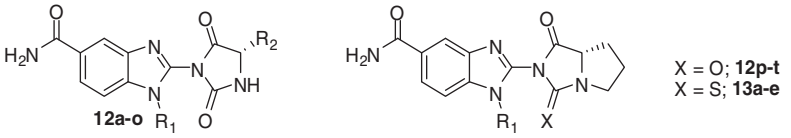


Scheme 1. Retrosynthetic illustration of synthetic work to construct hydantoins and thiohydantoins.



Scheme 2. Parallel solid-phase synthesis of hydantoin and thiohydantoin derivatives. Reagents and condtions: (a) PyBOP (8 equiv, 0.5 M anhyd. DMF), HOBt (8 equiv), DIEA (8 equiv), 12 h, rt; (b) 20% piperidine/DMF, 20 min (2×), rt; (c) 1,1′-carbonyldiimidazole (or) 1,1′-thiocarbonyldiimidazole, anhyd. DMF, 80 °C, 12 h; (d) HF/anisole (99:1), 0 °C, 90 min.

Table 1
Hydantoins and thiohydantoins isolated from intramolecular cyclization



Entry	R_1	R_2 (amino acid)	Mass calcd/found (MH^+)	Yields[a] (%)
12a	Cyclopentyl	Phe	417.4/418.2	71
12b	*n*-Butyl	Phe	405.4/406.3	92
12c	Cyclohexanemethyl	Phe	445.5/446.3	93
12d	*i*-Butyl	Phe	405.4/406.2	89
12e	3-(trifluoromethyl)benzyl	Phe	507.5/508.3	85
12f	Cyclopentyl	Leu	383.4/384.2	81
12g	*n*-Butyl	Leu	371.4/372.3	83
12h	Cyclohexanemethyl	Leu	411.5/412.2	96
12i	*i*-Butyl	Leu	371.4/372.2	74
12j	3-(Trifluoromethyl)benzyl	Leu	473.4/474.1	98
12k	Cyclopentyl	Tyr	433.4/434.3	81
12l	*n*-Butyl	Tyr	421.4/422.2	72
12m	Cyclohexanemethyl	Tyr	461.5/462.3	91
12n	*i*-Butyl	Tyr	421.4/422.2	95
12o	3-(Trifluoromethyl)benzyl	Tyr	523.5/524.3	77
12p	Cyclopentyl	Pro	367.4/368.4	92
12q	*n*-Butyl	Pro	355.4/356.4	95
12r	Cyclohexanemethyl	Pro	395.4/386.2	81
12s	*i*-Butyl	Pro	355.4/356.4	91
12t	3-(Trifluoromethyl)benzyl	Pro	457.4/458.2	73
13a	Cyclopentyl	Pro	383.5/384.3	91
13b	*n*-Butyl	Pro	371.5/372.3	88
13c	Cyclohexanemethyl	Pro	411.5/413.4	92
13d	*i*-Butyl	Pro	371.5/372.2	89
13e	3-(Trifluoromethyl)benzyl	Pro	473.5/474.4	65

The products were run on a Vydac column, gradients 5–95% formic acid in ACN in 7 min.
[a] The yields are based on the weight of purified products and are relative to the initial loading of the resin. (The purity of the purified compounds is higher than 95% for all the compounds.)

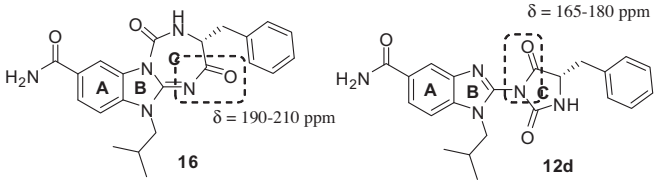


Figure 2. ^{13}C NMR based structural assignment of hydantoin nuclei.

introduced by coupling resin-bound aminobenzimidazole **9** with four different amino acids using PyBOP in anhydrous DMF conditions. The protected Fmoc group was later deprotected using 20% piperidine to afford the free amine **11**. Treatment of the amine **11** with 1,1′-carbonyldiimidazole or 1,1′-thiocarbonyldiimidazole generated an intermediate isocyanate or isothiocyanate which, later underwent intramolecular cyclization pathway and furnished the corresponding hydantoins or thiohydantoins, respectively.[43] The synthetic protocol for the parallel solid-phase synthesis of hydantoins is outlined in Scheme 2.

The competitive reaction leading to the formation of the fused tricyclic diketo-triazepines **16** and **17** was not observed. The structural assignment of hydantoin was identified based upon the unique nature of the ^{13}C chemical shift of the –(CO)NH joining the amino acid and benzimidazole. The carbonyl in diketotriazepine **16** or **17**, is in conjugation with the imine C=N bond, and would tend to exhibit ^{13}C chemical shift greater than 200 ppm. However, in case of hydantoin, the two carbonyls are attached to same nitrogen, and the ^{13}C chemical shift for those compounds would be ~165–180 ppm, which is in accordance with our experimental data (Fig. 2).[43] All of these intramolecular cyclizations leading to the formation of hydantoins or thiohydantoins occurred in good isolated yields and the results are shown in Table 1.

In summary, we have developed an efficient solid-phase synthesis of aminobenzimidazole tethered hydantoins and thiohydantoins via intramolecular cyclization as an essential step. The coupling of resin-bound aminobenzimidazoles[13–16] with several amino acids led to the formation of benzimidazole coupled amino acid residues. Following Fmoc elimination, the free amino group was used as the precursor to prepare a library of hydantoins and thiohydantoins tethered benzimidazole.[43]

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43. *General procedure for the solid-phase synthesis of amino-benzimidazole tethered hydantoins and thiohydantoins*: *p*-Methylbenzhydrylamine (MBHA) resin (100 mg, 1.10 mequiv/g, 100–200 mesh) was sealed inside a polypropylene mesh packet. Polypropylene bottles were used for all of the reactions. Resin bound amino-benzimidazoles were synthesized according to a previous literature.[13–16] Fmoc-amino acid (8 equiv, 0.2 M in anhyd DMF) was coupled to MBHA resin bound benzimidazole for 12 h at room temperature using the coupling reagent PyBOP (8 equiv, 0.2 M), DIEA (8 equiv, 0.2 M) followed by washes with DMF (3×) and DCM (3×). Following Fmoc deprotection with a solution of 20% piperidine in DMF, the resin-bound *N*-terminal amino acid residue was treated with 1,1′-carbonyldiimidazole (1,1′-thiocarbonyldiimidazole) in anhydrous DMF (0.2 M) at 80 °C for 12 h. The reaction mixture was decanted, and the resulting resin-bound hydantion (thiohydantoin) product was washed with DMF (3×) and DCM (3×). The resin was cleaved with HF/anisole for 90 min at 0 °C, and the desired hydantoin (thiohydantoin) was obtained following extraction with 95% AcOH in H_2O and lyophilization as a white powder. The final products were purified by preparative reverse-phase HPLC. NMR data for entry **12b**: ^{1}H NMR (DMSO-d_6): δ 0.75 (m, 3H), 0.92 (t, J = 7.5 Hz, 2H), 1.23 (s, 1H), 1.30–1.35 (m, 2H), 3.12 (br s, 2H), 3.67–3.75 (m, 1H), 4.89 (br s, 1H), 7.27–7.38 (m, 6H), 7.63–7.65 (m, 1H), 7.87 (d, J = 10 Hz, 1H), 7.98–8.01 (m, 1H), 8.22 (s, 1H), 8.98 (br s, 1H); ^{13}C NMR: δ 13.5, 19.0, 43.0, 58.0, 110.7, 119.2, 123.0, 127.1, 128.3, 128.8, 130.0, 139.6, 140.0, 153.5, 168.0; LC–MS *m/z* data calcd for $C_{22}H_{23}N_5O_3$ (MH^+): 405.4; found: 406.3; NMR data for entry **12d**: ^{1}H NMR (DMSO-d_6): δ 0.50–78 (m, 4H), 0.91 (d, J = 7 Hz, 2H), 1.23 (s, 1H), 3.12–3.13 (m, 2H), 3.67 (m, 1H), 3.91 (d, J = 7.5 Hz, 1H), 4.90 (br s, 1H), 7.18 (d, J = 5 Hz, 1H), 7.28–7.38 (m, 6H), 7.67–7.72 (m, 1H), 7.87 (d, J = 9.8 Hz, 1H), 7.98–8.02 (m, 1H), 8.22 (br s, 1H), 8.97 (br s, 1H); ^{13}C NMR: δ 19.5, 27.1, 50.2, 58.1, 111.0, 119.1, 123.0, 128.1, 128.4, 128.8, 128.9, 130.0, 139.92, 139.98, 153.5, 168.0; LC–MS *m/z* data calcd for $C_{22}H_{23}N_5O_3$ (MH^+): 405.4; found: 406.3.