Facile Synthesis of Novel Nonpeptide Angiotensin II Receptor Antagonists

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A series of Losartan analogues **1-12** with different functional groups were synthesized and characterized. In comparison with the previous reports, the synthetic procedures described in this paper have been optimized as follows below: 1) preparation of aromatic amine **15** and **18** through hydrogenation by employing Raney Ni and hydrazine as catalysts in place of palladium; 2) preparation of nitro-compound **17** by using pure fuming nitric acid at -20 - -15 °C; 3) alkylation of **21** with **22** or **23** in the presence of sodium hydride in place of potassium *tert*-butylate; 4) preparation of carboxylic acid **4** by ester cleavage rather than hydrolysis of cyano group.

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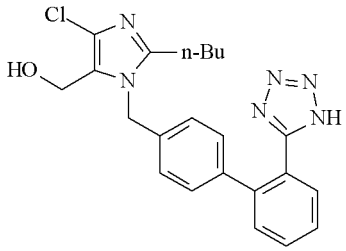
The rennin-angiotensin system (RAS) is known to play an important role in blood pressure regulation and electrolyte homeostasis [1]. Blockade of the RAS in antihypertensive therapy *via* angiotensin-converting enzyme (ACE) inhibitors, preventing the formation of A II from angiotensin I (A I), is well-documented. However, ACE also has kininase activity, and this lack of specificity has been implicated in the occasional side effects of ACE inhibitor such as dry cough and angioedema. So the pharmaceutical industry has devoted considerable effort to discovering nonpeptide rennin inhibitor [2] and A II receptor antagonists [3] as alternative means of blocking the RAS in a more specific way [4].

The discovery by Du Pont of the first orally active, nonpeptide, A II antagonist DuP 753 (Losartan) [5] (Figure 1), opened up an exciting new phase of research to investigate



DuP 753 (Losartan)

Figure 1

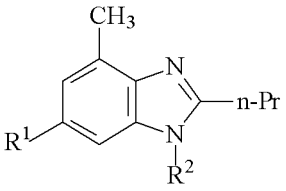
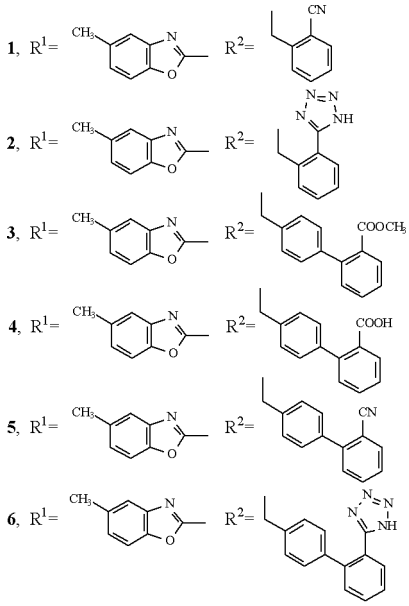
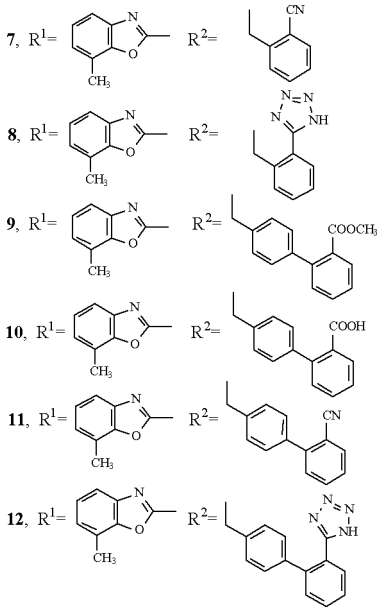


Figure 2





AT_1-selective [6] agents for the treatment of hypertensin. Since then, many other compounds structurally related to losartan have been synthesized [7]. However, the synthesis of these compounds suffered from their intrinsic drawbacks such as high cost, high toxicity, low activity, and complex purification. In this report, we describe the facile synthesis of novel well-designed substituted benzimidazole derivatives (**1-12**) with improved biological activity (Figure 2).

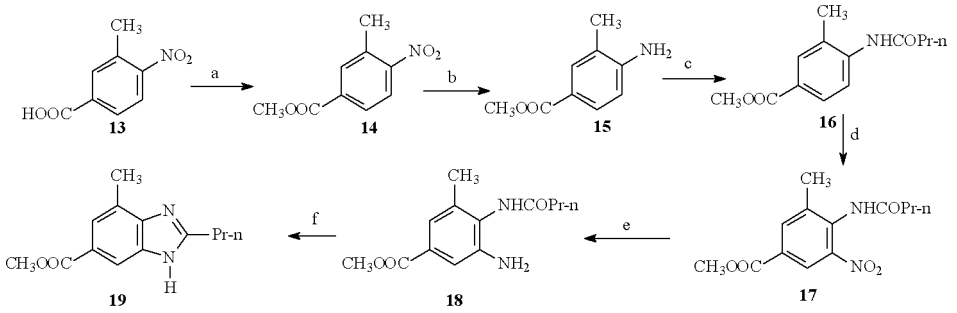
The target compounds own two distinct characteristics as follows: the *n*-propyl residue in position 2 of the benzimidazole can give higher receptor affinities than the other alkyl group [5]; the methyl group in position 4 has only a marginal effect on receptor affinity. It was introduced into these molecules for synthetic reasons in order to avoid isomeric mixtures in the alkylation reaction (step c and e in Scheme 2). The selectivity was attributed to the steric hindrance caused by the methyl group on the nearest nitrogen atom.

Synthesis of the benzimidazole (**19**) (Scheme 1) involved six steps. Esterification of 3-methyl-4-nitrobenzoic acid (**13**) gave the corresponding methyl benzoate (**14**), which was further hydrogenated using Raney nickel and hydrazine hydrate as catalysts to afford methyl 3-methyl-4-aminobenzoate (**15**). Then compound **15** was acylated, nitrated in position 5 followed by reduction and ring closure to yield the benzimidazole (**19**).

Zn/NaOH, Zn/NH_3 and Fe/HCl can catalytic hydrogenate nitro-compounds. However, many side reactions occurred under these conditions with low yields. Therefore, an improved method should be developed in order to shorten the reaction time and increase the yield.

It is well known that hydrazine hydrate in the presence of Raney Ni can convert aromatic nitro-compounds to amines quickly (about 2-3 hours) in high yield [8]. The order of charging-up was as follows: to the alcohol solution of nitro compounds was added hydrazine hydrate and then Raney Ni. This method had drawbacks such as the formation of many by-products and the difficulty to purify object product. It can be explained that the amide (main by-product) was obtained by the substitution of hydrazine hydrate to ester group in benzene ring. To obstruct the formation of amide, we successfully optimized the synthetic method through the change of charging-up order: to the alcohol solution of nitro compounds was added freshly prepared Raney Ni and then diluted hydrazine in small quantities at suitable intervals. After reacting for 2-4 h, TLC analysis revealed one spot with above 95% yield. These results were attributed to the fact that batch-wise small quantities of hydrazine first reacted with excessive Raney Ni, releasing hydrogen gas, which dramatically decreased the chance of the reaction of hydrazine and ester.

Scheme 1



a. CH_3OH/H_2SO_4; b. $NH_2NH_2H_2O$/Raney Ni; c. n-PrCOCl/$N(Et)_3$; d. HNO_3; e. $NH_2NH_2H_2O$/Raney Ni; f. HOAc

In the whole synthetic procedure of benzimidazole (**19**), the hydrogenation reaction played an important role, such as step b and e in Scheme 1. According to the literature [7], palladium (10% on carbon) was employed as catalyst for the catalytic hydrogenation of nitro-compounds. Considering the high cost of palladium, we used the homemade Raney Ni in place of palladium and obtained pure product. No matter what catalysts were employed (palladium or Raney Ni), the reaction time was very long *via* adding hydrogen gas to the reaction systems directly (*e.g.*, reducing 10 g of **14** by palladium needed about 3 days and by Raney Ni about 5 days). On the other hand, it was also reported that Zn/HCl,

In the nitration reaction (step d in Scheme 1), the amide was reacted with fuming nitric acid in sulfuric acid at 0 °C according to the literature [7], and the yield was low due to the influence of by-reaction. By accident, the amide was added directly to pure fuming nitric acid at –20 to -15 °C. It was interesting to find that under this reaction condition pure product was obtained in high yield (85%).

After ester hydrolysis the resulted benzimidazole carboxylic acid (**20**) was condensed with 2-amino-4-methylphenol in the presence of polyphosphorous acid to give the benzimidazole substituted by benzoxazole (**21**). Substitution of the benzimidazole (**21**) with **22** afforded

Table 1

Physical and Spectral Data for Compounds **1-12**

No.	Molecular Formula	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	MS	IR	^{1}H NMR Data	^{13}C NMR Data
1	$C_{28}H_{28}N_4O$	202-204	77.04 77.31	6.46 6.48	12.83 12.62	437 (M+ H^+, 100)	2963, 2932, 2872, 2222, 1599, 1455	8.13 (s, 1H, Ar-H), 7.98 (d, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.51 (m, 2H, Ar-H), 7.19 (d, 1H, Ar-H), 6.67(d, 1H, Ar-H), 5.88 (s, 2H, CH_2), 2.83 (t, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.76 (m, 2H, CH_2), 0.95 (t, 3H, CH_3)	163.7, 157.8, 148.8, 144.8, 142.3, 140.7, 135.5, 134.4, 134.3, 133.9, 129.4, 128.8, 126.5, 126.3, 121.7, 120.4, 119.6, 117.5, 110.4, 107.7, 45.3, 29.0, 21.4, 20.8, 16.7, 14.1
2	$C_{28}H_{29}N_7O$	194-196	70.12 70.34	6.09 6.11	20.44 20.20	480 (M+ H^+, 100)	3427, 2965, 1629, 1552, 1454	8.23 (s, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 8.07 (d, 1H, Ar-H), 7.57 (m, 2H, Ar-H), 7.53 (s, 1H, Ar-H), 7.47 (t, 1H, Ar-H), 7.21 (d, 1H, Ar-H), 6.82 (d, 1H, Ar-H) 6.28 (s, 2H, CH_2), 3.18 (t, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.75 (q, 2H, CH_2), 0.93 (t, 3H, CH_3)	163.0, 157.9, 156.1, 149.3, 142.5, 135.3, 135.0, 134.1, 132.3, 130.9, 129.3, 129.3, 128.0, 127.4, 127.1, 124.9, 123.6, 120.3, 47.0, 28.3, 21.9, 21.3, 17.4, 14.4
3	$C_{34}H_{31}N_3O_3$	182-184	77.13 77.30	5.86 5.66	7.94 8.00	530 (M+ H^+, 100), 531 (40)	3027, 2945, 1719, 1554	8.15 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.71 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H), 7.59 (t, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.47 (t, 2H, Ar-H), 7.39 (d, 1H, Ar-H), 7.26 (d, 2H, Ar-H), 7.19 (d, 1H, Ar-H), 7.14 (d, 2H, Ar-H), 5.70 (s, 2H, CH_2), 3.51 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.80 (q, 2H, CH_2), 0.98 (t, 3H, CH_3)	169.2, 164.4, 158.2, 149.3, 145.4, 142.9, 141.6, 140.6, 136.9, 136.0, 134.9, 132.3, 131.6, 131.3, 130.2, 129.8,129.5, 128.4, 127.0, 126.8, 122.0, 120.7, 120.1, 110.9,108.3, 52.6, 46.8, 29.6, 21.9, 21.4, 17.2, 14.7
4	$C_{33}H_{29}N_3O_3$	217-220	76.89 76.60	5.63 5.53	8.16 8.32	516 (M+ H^+, 100), 517 (40)	2964, 2869, 1697, 1556	8.17 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.44 (t, 1H, Ar-H), 7.37 (d, 1H, Ar-H), 7.34 (d, 2H, Ar-H), 7.28 (d, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 7.10 (d, 2H, Ar-H), 5.68 (s, 2H, CH_2), 2.89 (t, 2H, CH_2), 2.64 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.81 (q, 2H, CH_2), 0.98 (t, 3H, CH_3)	171.2, 164.4, 158.2, 149.3, 145.3, 142.9, 141.3, 140.4, 136.4, 136.0, 135.7, 134.9, 131.0, 130.6, 129.8, 129.7, 129.6, 127.9, 126.8, 126.7, 122.0, 120.8, 120.1, 110.9, 108.2, 46.8, 29.6, 21.9, 21.4, 17.3, 14.7
5	$C_{33}H_{28}N_4O$	185-187	79.84 79.74	5.65 5.80	11.29 11.50	497 (M+ H^+, 100), 498 (35), 519 (M+ Na^+, 10)	2963, 2223, 1558	8.19 (s, 1H, Ar-H), 7.93 (d, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.76 (t, 1H, Ar-H), 7.59 (m, 6H, Ar-H), 7.24 (d, 2H, Ar-H), 7.19 (d, 1H, Ar-H), 5.77 (s, 2H, CH_2), 2.91 (t, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 1.80 (m, 2H, CH_2), 0.98 (t, 3H, CH_3)	164.3, 158.3, 149.3, 145.4, 144.9, 142.9, 138.6, 137.9, 136.0, 134.9, 134.7, 134.4, 130.9, 130.1, 129.9, 129.1, 127.4, 126.8,122.0, 120.8, 120.1, 119.3, 111.0, 110.9, 108.3, 46.7, 29.6, 21.9, 21.4, 17.3, 14.7
6	$C_{33}H_{29}N_7O$	180-182	73.47 73.60	5.38 5.20	18.18 18.40	539 (M^+, 40), 538 (100)	3431, 2965, 1559	8.37 (s, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 7.66 (m, 3H, Ar-H), 7.57 (d, 2H, Ar-H), 7.51 (d, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.15 (m, 2H, Ar-H), 7.11 (m, 2H, Ar-H), 5.84 (s, 2H, CH_2), 3.05 (t, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 1.72 (m, 2H, CH_2), 0.96 (t, 3H, CH_3)	167.0, 163.0, 156.9, 155.0, 148.5, 146.0, 141.8, 140.9, 138.9, 135.0, 134.3, 133.5, 131.1, 130.6, 130.0, 129.3, 127.9, 126.4, 123.4, 119.4, 117.5, 115.0, 111.0, 110.2, 108.6, 46.6, 27.7, 21.0, 20.5, 16.5, 13.6
7	$C_{28}H_{28}N_4O$	196-198	77.04 77.25	6.46 6.58	12.83 13.05	437 (M+ H^+, 100)	2222, 1623, 1509	8.13 (s, 1H, Ar-H), 7.98 (d, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.62 (t, 1H,Ar-H), 7.54 (m, 2H, Ar-H), 7.27 (t, 1H, Ar-H), 7.21 (d, 1H, Ar-H), 6.77 (d, 1H, Ar-H), 5.88 (s, 2H, CH_2), 2.85 (t, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 1.77 (m, 2H, CH_2), 0.96 (t, 3H, CH_3)	163.4, 157.8, 150.0, 144.8, 141.7, 140.7, 135.5, 134.3, 134.0, 129.4, 126.9, 126.2, 125.0, 121.6, 121.0, 120.5, 117.5, 117.1, 110.5, 107.8, 45.4, 29.1, 20.8, 16.7, 15.2, 14.2
8	$C_{28}H_{29}N_7O$	238-240	70.12 70.19	6.09 6.30	20.44 20.63	480 (M+ H^+, 100)	3422, 2966, 2872, 1557, 1455	8.07 (s, 1H, Ar-H), 7.96 (m, 2H, Ar-H), 7.53 (m, 2H, Ar-H), 7.47 (t, 2H, Ar-H), 7.25 (t, 1H, Ar-H), 7.18 (d, 1H, Ar-H), 6.65 (d, 1H, Ar-H), 6.09 (s, 2H, CH_2), 2.90 (t, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 1.76 (q, 2H, CH_2), 0.93 (t, 3H, CH_3),	162.9, 157.6, 155.6, 149.6, 141.6, 135.7, 134.8, 131.7, 130.4, 128.7, 128.5, 126.5, 126.3, 124.9, 123.0, 122.4, 121.3, 121.0, 117.1, 108.0, 45.7, 28.6, 20.8, 16.8, 15.2, 14.1
9	$C_{34}H_{31}N_3O_3$	157-158	77.13 77.00	5.86 5.84	7.94 7.98	530 (M+ H^+, 100), 552 (M+ Na^+, 35)	2960, 2929, 1724, 1551	8.20 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.47 (t, 1H, Ar-H), 7.39 (d, 1H, Ar-H), 7.27 (m, 3H, Ar-H), 7.20 (d, 1H, Ar-H), 7.17 (d, 2H, Ar-H), 5.71 (s, 2H, CH_2), 3.51 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.79 (q, 2H, CH_2), 0.98 (t, 3H, CH_3)	169.2, 164.0, 158.3, 150.2, 145.4, 142.2, 141.6, 140.6, 136.9, 136.1, 132.4, 131.6, 131.3, 130.2, 129.8, 129.5, 128.4, 127.1, 126.7, 125.4, 121.9, 121.6, 120.8, 117.6, 108.4, 52.6, 49.9, 29.6, 21.4, 17.2, 15.7, 14.7

Table 1 (continued)

No.	Molecular Formula	Mp (°C)	Elemental Analysis Calcd./Found C	H	N	MS	IR	^{1}H NMR Data	^{13}C NMR Data
10	$C_{33}H_{29}N_3O_3$	147-150	76.89 76.79	5.63 5.70	8.16 8.20	516 (M+ H^+, 100), 517 (35)	3422, 2964, 1698, 1557	8.22 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.46 (m, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.34-7.29 (m, 4H, Ar-H), 7.20 (d, 1H, Ar-H), 7.12 (d, 2H, Ar-H), 5.69 (s, 2H, CH_2), 2.88 (t, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.80 (m, 2H, CH_2), 0.98 (t, 3H, CH_3)	170.8, 164.0, 158.2, 150.2, 145.4, 142.3, 141.2, 140.7, 136.5, 136.1, 134.9, 131.1, 130.9, 129.8, 129.7, 128.0, 127.7, 126.8, 126.7, 125.4, 121.9, 121.6, 120.8, 117.6, 108.3, 46.9, 29.6, 21.4, 17.2, 15.8, 14.7
11	$C_{33}H_{28}N_4O$	217-219	79.84 79.80	5.65 5.70	11.29 11.50	497 (M+ H^+, 100), 498 (40)	2964, 2222, 1557	8.22 (s, 1H, Ar-H), 7.94 (m, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.76 (m, 1H, Ar-H), 7.60-7.55 (m, 6H, Ar-H), 7.26 (d, 2H, Ar-H), 7.20 (d, 1H, Ar-H), 5.76 (s, 2H, CH_2), 2.90 (t, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 1.80 (m, 2H, CH_2), 0.97 (t, 3H, CH_3)	164.0, 158.3, 150.2, 145.4, 144.8, 142.2, 138.6, 137.9, 136.1, 134.7, 134.4, 130.9, 130.1, 129.9, 129.1, 127.5, 126.7, 125.5, 122.0, 121.6, 120.9, 119.3, 117.6, 111.0, 108.3, 46.8, 29.6, 21.4, 17.3, 15.8, 14.7
12	$C_{33}H_{29}N_7O$	210-212	73.47	5.38	18.18	540 (M+ H^+, 100)	3431, 2965, 2850, 1559	8.20 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 7.60 (m, 1H, Ar-H), 7.55-7.45 (m, 6H, Ar-H), 7.20 (d, 1H, Ar-H), 7.17 (d, 2H, Ar-H), 5.71 (s, 2H, CH_2), 2.90 (t, 2H, CH_2), 2.66 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.79 (m, 2H, CH_2), 0.98 (t, 3H, CH_3)	169.2, 163.0, 158.3, 150.2, 145.4, 141.0, 140.9, 140.6, 136.8, 135.2, 132.4, 131.5, 131.0, 130.2, 129.8, 129.5, 127.5, 127.1.126.7, 125.5, 121.9, 121.7, 120.0, 116.6, 108.9, 46.6, 27.8, 20.1, 19.0, 16.5, 13.4

the benzimidazole (**5**), which was further treated with sodium azide and ammonium chloride at 140 °C to yield the tetrazole (**6**). Alkylation of **21** with **23** followed by ester cleavage yielded the carboxylic acid (**4**). As described above, the 4-methyl group directed the biphenylmethyl group into the benzimidazole at position 1 to give the requisite regioisomer in large excess. The other analogues **1**, **2**, and **7-12** were prepared in a similar manner.

According to the literature [7], the alkylation of **21** with **22** or **23** employed potassium *tert*-butylate as dehydrogenation reagent for the 14 h reaction time. After repeating exploration, it was interesting to find that when we adopted sodium hydride, which owned strong ability of dehydrogenation, in place of potassium *tert*-butylate, the reaction time was shortened to about 4 h with the approximately the same yield.

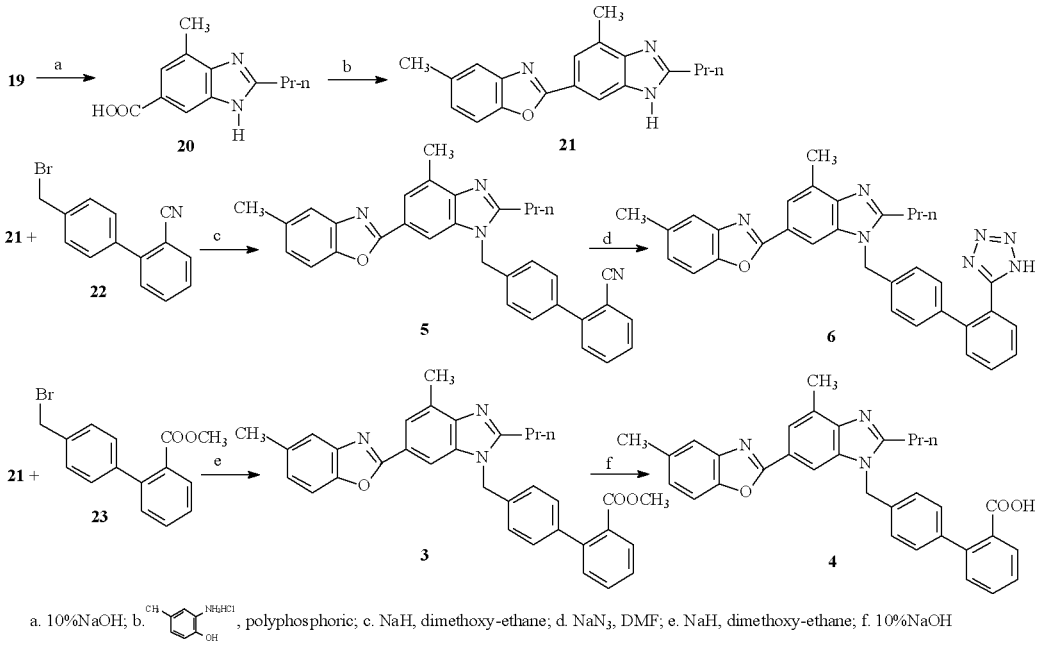
In the course of our study for the synthesis of compounds **4**, at first we employed the synthetic route in Scheme 3 and hoped that compound **5** can transform directly to compound **4** in order to simplify synthetic steps. Unfortunately, TLC revealed several spots, which indicated the formation of by-products. Although the detailed mechanism of this reaction remains unclear at this stage, a tentative explanation was that the heterocycle part would decompose under strong basic condition because the transformation of cyano group to carboxyl group required a long reaction time (about 24 hours). In order to overcome this drawback, we use ester group to replace cyano group (Scheme 2), which could greatly shorten the reaction time. As expected, TLC revealed one spot after reacting for about 3 hours with high yield, indicating that the heterocycle part shouldn't decompose due to the short reacting time of the transformation of ester group to carboxyl group.

In conclusion, we have greatly simplified the conventional synthetic procedures for Losartan analogues with the advantages of low cost, high yields, facile purification, and high activity in four different aspects. With the optimized procedure, a series of Losartan analogues **1-12** with different functional groups were synthesized and characterized. Details of the biological activities of these compounds are currently underway and will be reported in due time.

EXPERIMENTAL

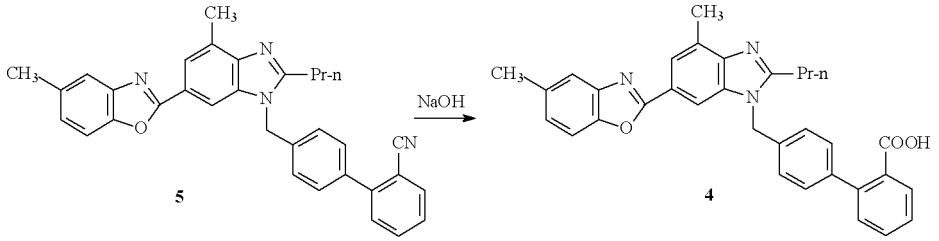
All Melting points were determined on an RY-1 melting point apparatus and are not corrected. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H nmr spectra were measured on a Brucker-500 (500 MHz) spectrometer. ^{13}C nmr spectra were measured on a Brucker-500 (125 MHz) spectrometer. Chemical shifts were given in δ values (ppm) using TMS as an internal standard, and coupling constants (J) were given in Hz. Mass spectra were recorded on HP1100 HPLC-MSD mass spectrometer.

Scheme 2



a. 10%NaOH; b. , polyphosphoric; c. NaH, dimethoxy-ethane; d. NaN_3, DMF; e. NaH, dimethoxy-ethane; f. 10%NaOH

Scheme 3



Methyl 3-Methyl-4-nitrobenzoate (**14**).

A mixture of **13** (1.81 g) and methanol (5 mL) was added concentrated sulfuric acid (0.5 mL) under stirring. The resulting mixture was heated to reflux for about 2 h and yellow solid precipitated upon cooling. The solid was recrystallized from methanol to give **14** (0.15 g, 74.3%) as light yellow needles. mp 78-79 °C; ^{1}H nmr ($CDCl_3$): δ 8.03 (br, 1H, Ar-H), 7.98 (m, 2H, Ar-H), 3.97 (s, 3H, C*H*$_3$O), 2.63 (s, 3H, PhC*H*$_3$); ir (KBr): 3005,1740, 1620, 1590, 1520, 1350 cm^{-1}.

Methyl 3-Methyl-4-aminobenzoate (**15**).

To compound **14** (0.20 g) dissolved in methanol (1.95 mL) and containing approximately 0.1 g of freshly prepared Raney Ni was added diluted hydrazine (65% aqueous hydrazine in twice its volume of methanol) in small quantities at suitable intervals at room temperature stirring for 2-4 h. After separation of the Raney Ni and methanol was removed under vacuum, the white solid (**15**) was obtained (0.15 g, 92.1%). mp 181-121 °C; ^{1}H nmr ($CDCl_3$): δ 7.76 (s, 1H, Ar-H), 7.74 (d, J=8.2 Hz, 1H, Ar-H), 6.64 (d, J=8.2 Hz, 1H, Ar-H), 4.15 (br, 2H, N*H*$_2$), 3.85 (s, 3H, C*H*$_3$O), 2.17 (s, 3H, PhC*H*$_3$); ir (KBr): 3470, 3380, 1700 cm^{-1}.

Methyl 4-(*n*-Butyrylamino)-3-methylbenzoate (**16**).

A mixture of **15** (1.65 g), dichloromethane (7 mL) dried by anhydrous $MgSO_4$ and freshly redistilled triethylamine was added butyryl chloride (4.3 mL) at 8-10 °C and then stirred for 1 h at room temprature. After filtration, the resulting solution was washed with water (1.5 mLx2), saturated $NaHCO_3$ solution (1.5 mL) and water (1.0 mLx2), and dried over anhydrous $MgSO_4$. Through removal of solvent, a white solid was obtained. This solid was purified *via* recrystallization from ethyl acetate to give 16 (1.87 g, 79.6%). mp 125-127 °C; ^{1}H nmr ($CDCl_3$): δ 8.37 (br, 1H, N*H*), 7.88 (m, 2H, Ar-H), 7.09 (s, 1H, Ar-H), 3.89 (s, 3H, C*H*$_3$O), 2.41 (t, J=7.3 Hz, 2H, C*H*$_2$CH$_2$CH$_3$), 2.31 (s, 3H, PhC*H*$_3$), 1.78 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 1.04 (t, J=7.4 Hz, 3H, CH$_2$C*H*$_3$); ir (KBr): 3300, 2950, 1730, 1670, 1530 cm^{-1}.

Methyl 4-(*n*-Butyrylamino)-3-methyl-5-nitrobenzoate (**17**).

To fuming nitric acid (3 mL) was added compound **16** (1 g) in small quantities at –20 °C to -15 °C. After stirring for about 1.5 h the resulting solution was poured 7 g ice and precipitated solid. This solid was washed with icy water (2 mLx2), saturated $NaHCO_3$ (1 ml), and water (2 mLx2), and recrystallized from ethyl acetate to obtain light yellow needles (0.9 g, 75.6%). mp 163-164 °C; ^{1}H nmr ($CDCl_3$): δ 8.57 (br, 1H, N*H*), 8.52 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 3.98 (s, 3H, C*H*$_3$O), 2.47 (t, J=7.5 Hz,

2H, CH_2CH$_2$CH$_3$), 2.39 (s, 3H, PhCH_3), 1.81 (m, 2H, CH$_2$CH_2CH$_3$), 1.06 (t, J=7.4 Hz, 3H, CH$_2$CH_3); ir (KBr): 3480, 2950, 1740, 1670, 1550, 1520 cm^{-1}.

Methyl4-(*n*-Butyrylamino)-3-methyl-5-aminoobenzoate (**18**).

Compound **17** (0.28 g) was reduced with Raney Ni (0.2 g) and hydrazine in methanol by the same procedure as described for the preparation of compound **15** to obtain pure product **18** (0.23 g, 92%). Ir (KBr): 3440, 3360, 2975, 1720, 1660, 1517 cm^{-1}.

2-*n*-Propyl-4-methyl-6-(methoxycarbonyl)benzimidazole (**19**).

Compound **18** (1.0 g) was dissolved in the glacial acetic acid and heated under reflux for 2 h. After evaporation of the acetic acid water was added and the pH was adjusted to 9 by addition of concentrated ammonia. This solution was extracted with ethyl acetate (10 mLx3), and the combined organic layers were washed with aqueous $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent the yellow solid **19** was obtained (0.85 g, 90%). mp 139-143 °C; ^{1}H nmr (DMSO): δ 12.40 (br, 1H, N*H*), 7.80 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 3.77 (s, 3H, CH_3O), 2.70 (t, J=7.4 Hz, 2H, CH_2CH$_2$CH$_3$), 2.40 (s, 3H, PhCH_3), 1.70 (m, 2H, CH$_2$CH_2CH$_3$), 0.90 (t, J=7.3 Hz, 3H, CH$_2$CH_3); ir (KBr): 3400, 1720, 1627 cm^{-1}.

2-*n*-Propyl-4-methyl-6-carboxybenzimidazole (**20**).

To a solution of 0.69 g of **19** in methanol was added a solution of 10% NaOH, and the mixture was heated under reflux for 2 h. After evaporation of methanol, water (3.5 mL) was added to the residue and the pH was adjusted to 5 by addition of aqueous citric acid (30%). The precipitated solid was collected by filtration, washed with water, and dried to yield compound **20** (0.54 g, 82.3%). mp 298-300 °C; ^{1}H nmr (DMSO): δ 12.70 (br, 2H, N*H* and COO*H*), 8.81 (s, 1H, Ar-H), 7.79(s, 1H, Ar-H), 3.04 (t, J=7.3 Hz, 2H, CH_2CH$_2$CH$_3$), 2.73 (s, 3H, PhCH_3), 2.00 (m, 2H, CH$_2$CH_2CH$_3$), 1.20 (t, J=7.1 Hz, 3H, CH$_2$CH_3); ir (KBr): 3200-2500, 1680, 1580, 1420-1340 cm^{-1}.

2-*n*-Propyl-4-methyl-6-(5-methylbenzoxazole-2-yl)benzimidazole (**21**).

Compound **20** (1.13 g) was dissolved in polyphosphoric acid (9.4 mL) at 120 °C, and *p*-methyl-*o*-aminophenol hydrochloride (0.88 g) was added in small portions. After stirring at 160 °C for 20 h the mixture was allowed to cool and then poured into water. The pH was adjusted to 9 by addition of concentrated ammonia (ice cooling). The precipitated solid was collected by filtration, dried, recrystallized twice with ethyl acetate and ethanol respectively to give white solid **21** (1.05 g, 67.1%). mp 208-210 °C; ^{1}H nmr (DMSO): δ 8.10 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.63 (d, J=8.2 Hz, 10H, Ar-H), 7.56 (s, 1H, Ar-H), 7.20 (d, J=8.2 Hz, 1H, Ar-H), 2.85 (t, J=7.5 Hz, 2H, CH_2CH$_2$CH$_3$), 2.59 (s, 3H, PhCH_3), 2.44 (s, 3H, PhCH_3), 1.83 (m, 2H, CH$_2$CH_2CH$_3$), 0.98 (t, J=7.4 Hz, 3H, CH$_2$CH_3); ir (KBr): 1600, 1559, 1455 cm^{-1}.

4'-[[2-*n*-Propyl-4-methyl-6-(5-methylbenzoxazole-2-yl)-benzimidazol-1-yl]methyl]-2-cyanobiphenyl (**5**).

To a solution of **21** (1 g) in dimethoxy ethane (3.5 mL) was added NaH (0.34 g) at 0 °C, the mixture was stirred for 1 h at ambient temperature, and **22** (1.5 g) was added. After stirring for 4 h the solid was collected by filtration, washed with petroleum ether (5 mLx3) and water (5 mLx3), dried to give white solid **5** (1.73 g, 86.5%).

4'-[[2-*n*-Propyl-4-methyl-6-(5-methylbenzoxazole-2-yl)-benzimidazol-1-yl]methyl]-2-(1*H*-tetrazol-5-yl)biphenyl (**6**).

To a solution of **5** (1 g) in DMF were added sodium azide (1.73 g) and ammonium chloride (1.40 g), and the mixture was heated at 140 °C for 18 h. After cooling, water (15 mL) was added, and the precipitated solid was collected by filtration, dried and purified by recrystallization from methanol to give 6 (0.87 g, 80%).

4'-[[2-*n*-Propyl-4-methyl-6-(5-methylbenzoxazole-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylate (**3**).

The title compound was prepared from **21** and **23** by the same procedure described for the preparation of **5** (84.7%).

4'-[[2-*n*-Propyl-4-methyl-6-(5-methylbenzoxazole-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (**4**).

To a solution of **3** (1.06 g) in methanol was added 10% NaOH solution (4 mL) at refluxing. The mixture was stirred for 3 h and poured on water (6 mL). The pH was adjusted to 5 by addition of glacial acetic acid, and the solid was collected by filtration and dried to give **4** (0.86, 83.5%) as a white solid.

Compounds **1**, **2**, and **7-12** were prepared in a similar manner.

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