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A novel and practical synthesis of substituted 2-ethoxy benzimidazole: candesartan cilexetil

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ABSTRACT

A novel and practical synthetic route for the preparation of candesartan cilexetil from methyl 2-amino-3-nitrobenzoate is described. The key steps are the reaction of methyl 2-bromo-3-(diethoxymethyleneamino)benzoate with (2′-(1-trityl-1*H*-tetrazol-5-yl) biphenyl-4-yl) methanamine and the final formation of 2-ethoxy benzimidazole ring via intramolecular N-arylation. The final ring closure process could be utilized to prepare other 2-substituted benzimidazoles. The method is simple for operation and suitable for industrial production.

1. Introduction

The development of angiotensin receptor blockers (ARBs) is a major advance for the treatment of hypertension and potentially for other cardiovascular disorders.[1] Candesartan, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid, belongs to the class of ARBs and binds to angiotensin II receptor type 1 selectively and competitively, thus preventing actions of angiotensin II and decreasing the blood pressure levels.[2,3] Candesartan is administered as candesartan cilexetil, commonly known as (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate **1**, which has better bioavailability than candesartan. The prodrug is rapidly and completely hydrolyzed to candesartan during absorption by the gastrointestinal tract.[4,5] The antihypertensive effect of candesartan cilexetil has been documented in doses up to 16 mg/day in European studies[6] Receptor blockade by candesartan is more potent than that by valsartan[7] irbesartan[8] or losartan[9] in vitro and it has been shown that candesartan binds more tightly to and dissociates more slowly from the AT1-receptor than those other ARBs.[10] Candesartan cilexetil is indicated for the treatment of hypertension and also for the management of chronic heart failure.[11]

In recent years, extensive efforts have been drafted toward the convenient and efficient method for the synthesis of candesartan cilexetil **1** and several methods have been reported.[12–19] In general, these methods include three routes (Scheme 1): In route A[12–15], compound **4** was applied as the key intermediate. The N-alkylation of **3** with 5-(4′-(bromomethyl)biphenyl-2-yl)-1-trityl-1*H*-tetrazole and the formation of benzimidazole ring with tetraethoxymethane acted as the key elements. Route B[16,17] was similar to route A in which 4′-bromobiphenyl-2-carbonitrile was adopted in the N-alkylation of **3** instead of 5-(4′-(bromomethyl)biphenyl-2-yl)-1-trityl-1*H*-tetrazole, and then the tetrazole ring was formed with trimethyltin azide. In route C[18,19], 1-bromo-4-(bromomethyl) benzene was used in the N-alkylation of **3**, then the biphenyl tetrazole group was formed by Suzuki coupling reaction. All synthetic routes mentioned above involve methyl 2-(*tert*-butoxycarbonylamino)-3-nitrobenzoate **3**, which is obtained via Curtius rearrangement requiring closed and anhydrous condition, which is likely to result in an explosion and a low yield, respectively. In addition, some reagents are very expensive or unstable in storage, especially the reagent adopted in the formation of tetrazole group in method B is virulent, and a long reaction time is indispensable for this reaction. All of these obstacles prohibit the industrial production. Additionally, an approach for the substituted 2-ethoxy benzimidazole formed by introduction of chlorine at the 2-positon[15] was not possible for us to reproduce because it was too hard to prepare substituted 2-chloro benzimidazole. Namely, either the yield was rather low or the product unwanted. Therefore, the development of unique, concise and high yield approaches for candesartan cilexetil

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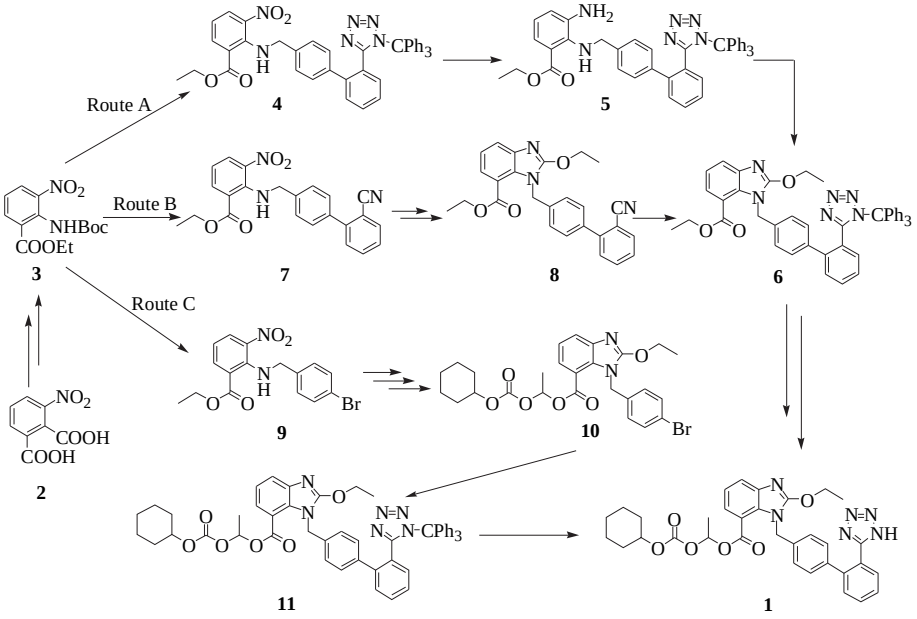
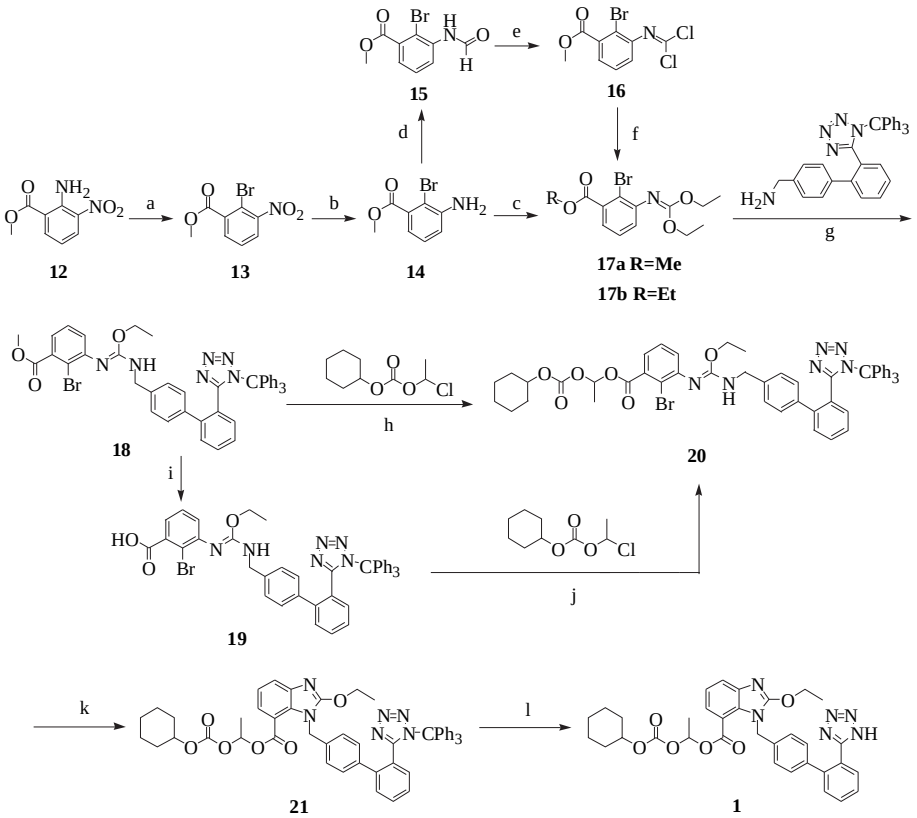
1 is requisite and significant. Here, we reported a novel and practical method for the synthesis of candesartan cilexetil **1** from methyl 2-amino-3-nitrobenzoate with readily available low cost raw material and reagents in good yields. This method surmounts many shortcomings concerning with the previous reports.

2. Results and discussion

The total synthesis of the target compound **1** was accomplished following the synthetic pathway described in Scheme 2. First, methyl 2-amino-3-nitrobenzoate **12** was converted to bromide **13**



Scheme 1. Available approaches for the synthesis of candesartan cilexetil 1.



Scheme 2. Reagents and conditions: (a) (i), 40% BrH, $NaNO_2$, $H_2O/C_4H_8O_2$, 0 °C; (ii), CuBr/40% BrH reflux, 0.5 h, 60%; (b) Fe, NH_4Cl/H_2O, DMF, 100 °C, 1 h, 88%; (c) $(CH_3CH_2O)_4C$, HOAc catalyzed, 120 °C, 1.5 h, 75%; (d) 98% HCOOH, reflux, 2.5 h, 90%; (e) SO_2Cl_2, $SOCl_2$, rt, 24 h, 80%; (f) NaOEt, EtOH, rt, 24 h, 80%; (g) $C_6H_5CH_3$, 100 °C, 3 h, 65%; (h) NaOH, DMF, rt, 5 h, then 70 °C, 8 h, 70%; (i) NaOH, DMF, rt, 5 h, 92%; (j) NaOH, DMF, 70 °C, 8 h, 75%; (k) CuI, K_2CO_3, L-proline, DMSO, 70 °C, 3 h, 75%; (l) $C_6H_5CH_3$, CH_3OH, reflux, 10 h, 75%.

via a Sandmeyer reaction.[20] The reduction of the nitro group of bromide **13** with iron gave the corresponding 3-amino derivative **14** in 88% yield.[21] Compound **14** could transform into compound **17a** directly via reacting with tetraethoxymethane[22], however, tetraethoxymethane is an expensive reagent. Due to its high cost, we developed another approach. Refluxing compound **14** in formic acid afforded formamide **15**, which was sufficiently pure for the next step without further purification. The formamide **15** was treated with sulfuryl chloride in thionyl chloride at room temperature to give compound **16**, followed by substitution with sodium ethoxide in anhydrous ethanol to generate compound **17b**. In the reaction, transesterification made the product to be **17b** rather than **17a** as we expected initially. Fortunately, ethyl ester group of **17b** had no influence on next steps comparing with carbomethoxy group of **17a**. The coupling reaction of **17a** with (2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-yl) methanamine in toluene at 100 °C afforded **18** in 65% yield. We have tried other conditions as shown in Table 1 to enhance the yield, but none of them turned out to be ideal. That is, under such conditions, the yield is rather low. The compound **18** was saponified to corresponding free acid **19**, which was esterified with 1-chloroethyl cyclohexyl carbonate in DMF at 70 °C to give ester **20** in 75% yield. Remarkably, the ester **20** could also be obtained from compound **18** in one pot with the same result.

Table 1
Synthetic yield of **19** under various conditions

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield[b] (%)
1	Toluene	NC[a]	100	3	65
2	Toluene	NH_4Cl	100	2.5	28
3	Toluene	HOAc	80	2	32
4	Toluene	$(CH_3)_3CCOOH$	80	2.5	30
5	Toluene	Silica gel	100	3	57
6	Dioxane	$(CH_3)_3CCOOH$	80	3.5	36
7	Chloroform	KOAc	60	5	50
8	DMF	NC[a]	70	4.5	23
9	THF	NC[a]	65	5	40

[a] No catalyst.
[b] Isolated yield.

Significantly, although C–N bond formation has been well explored for the construction of various heterocycles, there is no report for the preparation of substituted 2-oxide benzimidazoles via intramolecular cyclization. On the basis of the synthesis of 2-mercapto benzimidazoles[23], substituted benzimidazoles[24] and dimeric dicopper(I) complexes[25], the substituted 2-ethoxy benzimidazole **21** was obtained by reaction of compound **20** in DMSO in the presence of copper(I) iodide, potassium carbonate and L-proline at 70 °C with the yield of 75%. Additionally, the intramolecular N-arylation of compound **20** was also accomplished with 6 equiv sodium hydride and a catalytic amount of copper (I) iodide[26] in refluxing THF. Although sodium hydride is dangerous and to be avoided in industrial production, it is worth noting that in our approach the above compounds are produced simultaneously. Finally, the deprotection of trityl group of ester **21** was accomplished in refluxing mixture of methanol and toluene to afford the target compound **1** with the yield of 75%.

3. Conclusion

In summary, we have presented a novel and practical method for the total synthesis of candesartan cilexetil **1** from methyl 2-amino-3-nitrobenzoate with readily available low cost raw material and reagents in good yields. Furthermore, a Cu-catalyzed intramolecular N-arylation process to synthesize substituted 2-ethoxy benzimidazole is described. It is expected that other 2-substituted benzimidazoles may also be prepared by this strategy.

4. Experimental

4.1. General

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker AMX 400-MHz spectrometer in $CDCl_3$, if not noted otherwise, chemical shifts are indicated in parts per million with TMS as an internal standard. High-resolution mass spectra (HRMS) were measured on Bruker micro TOF-Q 10165 instrument with positive-ion electrospray ESI (+) using internal mass references. Infra-red spectra were recorded using a Jasco IR700 Infrared spectrophotometer, as KBr pellets. Flash column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates with petroleum ether/ethyl acetate. All chemicals and solvents were purchased from commercial supplier and used without further purification.

*4.1.1. Methyl 2-bromo-3-nitrobenzoate (**13**).* To a solution of methyl 2-amino-3-nitrobenzoate **12** (5 g, 25.9 mmol) in a mixture of water (20 ml) and 1,4-dioxane (20 ml) was added dropwise 40% hydrobromic acid (12 ml, 83 mmol) at room temperature and stirred for 30 min. After cooling the mixture to 0 °C, a solution of sodium nitrite (1.93 g, 28 mmol) in water (5 ml) was added dropwise over a 15 min period, and then the reaction mixture was stirred for 30 min at 0 °C. Then a fresh solution of copper(I) bromide (5.5 g, 38.5 mol) in 40% hydrobromic acid (6 ml) was added quickly, the reaction mixture was stirred for 30 min at 0 °C, then heated to reflux for 30 min. After cooling, the mixture was diluted with water and extracted with ethyl acetate (150 ml×3). The combined organic layer was washed with water (100 ml×2), satd $NaHCO_3$ solution (100 ml×2) and brine (100 ml), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford bromide **13** (3.99 g, 60%) as colorless crystals; mp: 78–79 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.98 (s, 3H, OCH_3), 7.53 (t, J=8.0 Hz, 1H, ArH), 7.76 (dd, J=8.0 Hz, J=1.6 Hz, 1H, ArH), 7.86 (dd, J=8.0, 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.1, 112.9, 126.7, 128.2, 133.1, 135.9, 152.1, 165.6; IR (film, cm^{-1}): 3424, 3029, 2925, 1730, 1666, 1646, 1457, 1381, 1333, 1239, 1191, 1059, 1033, 755, 703; HRMS (ESI): calcd for $C_8H_7BrNO_4$ $[M+H]^+$: 259.9553, found 259.9555.

*4.1.2. Methyl 3-amino-2-bromobenzoate (**14**).* To a solution of bromide **13** (6.1 g, 23.5 mmol) in DMF (15 ml) was added a solution of ammonium chloride (7.54 g, 140 mmol) in water (15 ml) and iron powder reduced (3.95 g, 70 mmol). The mixture was vigorously stirred and heated to 100 °C for 1 h. After cooling, the mixture was diluted with water and extracted with ethyl acetate (150 ml×3). The combined organic layer was washed with water (100 ml×2), satd $NaHCO_3$ solution (100 ml×2) and brine (100 ml), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to give compound **14** (4.77 g, 88%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.90(s, 3H, OCH_3), 4.36 (br s, 2H, NH_2), 6.85 (dd, J=7.6 Hz, J=1.6 Hz, 1H, ArH), 7.06 (dd, J=7.6, 1.6 Hz, 1H, ArH), 7.12 (t, J=7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.5, 107.2, 118.1, 119.9, 127.7, 133.4, 145.4, 167.5; IR (film, cm^{-1}): 3472, 3374, 2951, 2361, 1725, 1616, 1450, 1326, 1265, 1203, 1156, 1107, 1021, 801, 754; HRMS (ESI): calcd for $C_8H_9BrNO_2$ $[M+H]^+$: 229.9811, found 229.9811.

*4.1.3. Methyl 2-bromo-3-formamidobenzoate (**15**).* The compound **14** (4.6 g, 20 mmol) was dissolved in 98% formic acid (20 ml) and heated to reflux for 2.5 h. The formic acid was removed in vacuo then the residue was slowly poured into ice-cold water (100 ml) with stirring. The white solid was collected by filtration and washed

by cold water and dried to give formamide **15** (4.6 g, 90%), which was used for next step without further purification; mp: 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.94(s, 3H, OCH_3), 7.37–7.39 (m, 2H, ArH), 7.50–7.55 (m, 1H, ArH), 8.03 (br s, 1H, NH), 8.54–8.56 (m, 1H, NCOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.7, 112.1, 124.8, 126.5, 128.1, 133.2, 135.9, 159.1, 166.6; HRMS (ESI): calcd for $C_9H_8BrNNaO_3$ $[M+Na]^+$: 279.9580, found 279.9589.

*4.1.4. Methyl 2-bromo-3-(dichloromethyleneamino)benzoate (**16**).* Under a blanket of argon, sulfuryl chloride (4 g, 30 mmol) was added to a solution of formamide **15** (2.58 g, 10 mmol) in thionyl chloride (10 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. After removal of the solvent under reduced pressure, the residue was slowly poured into ice-cold water and extracted with ethyl acetate (100 ml×2). The combined organic layer was washed with water, satd $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford **16** (2.48 g, 80%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (s, 3H, OCH_3), 7.00 (dd, J=1.6, 8.0 Hz, 1H, ArH), 7.39 (t, J=8.0 Hz, 1H, ArH), 7.58 (dd, J=1.6, 5.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.7, 113.2, 123.1, 127.8, 127.9, 131.5, 134.2, 146.0, 166.5; HRMS (ESI): calcd for $C_9H_6BrCl_2NNaO_2$ $[M+Na]^+$: 331.8851, found 331.8857.

*4.1.5. Methyl 2-bromo-3-(diethoxymethyleneamino)benzoate (**17a**).* The mixture of **14** (1.38 g, 6 mmol), tetraethoxymethane (1.73 g, 9 mol), and a drop of acetic acid was stirred and heated to 120 °C for 1.5 h, meanwhile the by-product (ethanol) was removed. After cooling, the mixture was diluted with water and extracted with ethyl acetate (50 ml×2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford **17a** (1.5 g, 75%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32–1.35 (m, 6H, $2CH_3$), 3.91 (s, 3H, OCH_3), 4.24–4.28 (m, 4H, $2OCH_2$), 7.06 (dd, J=8.0, 1.6 Hz, 1H, ArH), 7.21 (t, J=7.6 Hz, 1H, ArH), 7.30 (dd, J=7.6, 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6 (2C), 52.4 (2C), 64.7, 116.6, 124.3, 126.4, 127.1, 133.9, 147.2, 151.0, 167.7; IR (film, cm^{-1}): 2988, 2920, 2364, 2328, 1736, 1682, 1575, 1444, 1405, 1372, 1309, 1196, 1145, 1076, 1034, 810, 761, 718; HRMS (ESI): calcd for $C_{13}H_{16}BrNNaO_4$ $[M+Na]^+$: 352.0155, found 352.0159.

*4.1.6. Ethyl 2-bromo-3-(diethoxymethyleneamino)benzoate (**17b**).* Under a blanket of argon, sodium ethoxide (2.04 g, 30 mmol) was added to a solution of **16** (3.1 g, 10 mmol) in anhydrous ethanol (10 ml) at room temperature and stirred for 24 h. the mixture was diluted with water and extracted with ethyl acetate (100 ml×2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford **17b** (2.9 g, 83%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30–1.34 (m, 6H, $2CH_3$), 1.39 (t, J=7.2 Hz, 3H, CH_3), 4.25–4.30 (m, 4H, $2OCH_2$), 4.39 (t, J=7.2 Hz, 3H, CH_3), 7.04(d, J=6.8 Hz, 1H, ArH), 7.20 (t, J=7.6 Hz, 1H, ArH), 7.27 (d, J=6.8 Hz, 1H, ArH).

*4.1.7. (E)-Methyl 2-bromo-3-(ethoxy((2′-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl)methylamino)methyleneamino)benzoate (**18**).* The mixture of **17a** (1.98 g, 6 mmol) and (2′-(1-trityl-1*H*-tetrazol-5-yl) biphenyl-4-yl)methanamine (2.47 g, 5 mmol) in toluene (5 ml) was stirred and heated to 100 °C for 3 h. The mixture was diluted with water and extracted with ethyl acetate (100 ml×2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to give compound **18** (2.52 g, 65%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, J=6.8 Hz, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (d, J=5.6 Hz, 1H, NH), 4.21 (d, J=5.6 Hz, 2H, NCH_2), 4.38(q, J=6.8 Hz, 2H, OCH_2), 6.87–6.89 (m, 6H, ArH), 6.97–7.00 (m, 3H, ArH), 7.07 (d, J=8 Hz, 2H, ArH), 7.18–7.31 (m, 11H, ArH), 7.34–7.38 (m, 1H, ArH), 7.43–7.47 (m, 2H, ArH), 7.91 (dd, J=1.2, 7.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 45.1, 52.5, 63.0, 82.9, 116.9, 124.3, 126.4, 126.5, 127.5, 127.6, 128.0, 128.2, 128.5, 129.4, 129.9, 130.2, 130.3, 130.6, 134.9, 137.5, 140.2, 141.2, 141.8, 148.2, 152.4, 164.0, 167.7; IR (film, cm^{-1}) ν_{max}=3424, 3029, 2924, 1732, 1654, 1458, 1333, 1291, 1241, 1192, 1143, 1064, 1028, 816, 754, 702; HRMS (ESI): calcd for $C_{44}H_{38}BrN_6O_3$ $[M+H]^+$: 777.2183, found 777.2207.

*4.1.8. (E)-2-Bromo-3-(ethoxy((2′-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methylamino)methyleneamino)benzoic acid (**19**).* To a solution of **18** (1 g, 1.29 mmol) in DMF (5 ml) was added powdered sodium hydroxide (0.3 g, 7.5 mmol) at room temperature and stirred for 5 h. The mixture was acidified with acetic acid. After stirring for further 15 min, the reaction mixture was extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to give **19** (0.9 g, 92%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, J=6.8 Hz, 3H, CH_3), 4.15 (s, 2H, NCH_2), 4.44 (q, J=6.8 Hz, 2H, OCH_2), 6.87–6.88 (m, 6H, ArH), 6.92–7.10 (m, 6H, ArH), 7.18–7.35 (m, 11H, ArH), 7.44–7.45 (m, 2H, ArH), 7.87 (d, J=7.2 Hz, 1H, ArH).

*4.1.9. (±)-1-(Cyclohexyloxycarbonyloxy)ethyl 2-bromo-3-(ethoxy ((2′-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methylamino)methyleneamino)benzoate (**20**). Method A*: To a solution of **19** (1 g, 1.31 mmol) in DMF (5 ml) was added powdered sodium hydroxide (0.052 g, 1.31 mmol) at room temperature and stirred for 30 min, 1-chloroethyl cyclohexyl carbonate (0.54 g, 2.62 mmol) was added and the mixture was heated to 70 °C for 8 h. The mixture was diluted with water and extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford colorless oil **20** (0.92 g, 75%).

Method B: To a solution of **18** (1 g, 1.29 mmol) in DMF (5 ml) was added powdered sodium hydroxide (0.1 g, 2.5 mmol) at room temperature and stirred for 5 h, 1-chloroethyl cyclohexyl carbonate (0.53 g, 2.58 mmol) was added and the mixture was heated to 70 °C for 8 h. The mixture was diluted with water and extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford colorless oil **20** (0.84 g, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25–1.38 (m, 5H, CH_2 and CH_3), 1.44–1.53 (m, 4H, $2CH_2$), 1.68 (d, J=5.6 Hz, 3H, CH_3), 1.72–1.73 (m, 2H, CH_2), 1.90–1.93 (m, 2H, CH_2), 3.93–3.95 (m, 1H, OCH), 4.21 (d, J=5.6 Hz, 2H, NCH_2), 4.38 (q, J=6.8 Hz, 2H, OCH_2), 4.64–4.67 (m, 1H, OCH), 6.88–6.90 (m, 6H, ArH), 6.96–7.01(m, 4H), 7.06–7.08 (m, 2H, ArH), 7.15–7.49 (m, 14H, ArH), 7.92 (d, J=7.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 19.6, 23.6, 25.2, 29.7, 31.4, 31.5, 45.1, 63.0, 77.6, 82.9, 92.1, 117.3, 124.8, 126.4, 126.6, 127.1, 127.5, 127.6, 128.0, 128.2, 129.4, 130.2, 130.3, 130.6, 133.6, 137.5, 140.2, 141.2, 141.8, 152.4, 152.5, 164.0, 164.8; IR (film, cm^{-1}) ν_{max}=3421, 3028, 2927, 2365, 2329, 1756, 1656, 1456, 1288, 1239, 1070, 912, 754, 703; HRMS (ESI): calcd for $C_{52}H_{50}BrN_6O_6$ $[M+H]^+$: 933.2970, found 933.2941.

*4.1.10. (±)-1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-3-((2′-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-3H-benzo[d]imidazole-4-carboxylate (**21**).* Under a blanket of argon, the mixture of **20** (3.5 g, 3.75 mmol), copper iodide (0.35 g, 1.88 mmol), potassium carbonate (0.1 g, 7.25 mmol), and L-proline (0.45 g, 3.75 mmol) in DMSO (20 ml) was stirred and heated to 70 °C for 3 h. The mixture was diluted with water and extracted with ethyl acetate (150 ml×2). The combined organic layer was washed with water

and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford compound **21** (2.4 g, 75%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.19–1.51 (m, 12H), 1.67–1.71 (m, 2H), 1.91 (m, 2H, CH_2), 4.61–4.63 (m, 3H, NCH_2 and OCH), 5.56 (q, 2H, J=16 Hz, OCH_2), 6.76–6.99 (m, 11H), 7.16–7.33 (m, 11H, ArH), 7.30–7.46 (m, 2H, ArH), 7.56 (d, J=8.0 Hz, 1H, ArH), 7.75 (d, J=8.4 Hz, 1H, ArH), 7.86 (d, J=6.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 19.5, 23.6, 25.1, 31.4, 47.0, 66.7, 77.5, 82.2, 91.7, 114.8, 120.8, 122.5, 124.0, 126.2, 126.3, 127.4, 127.6, 128.2, 129.4, 129.8, 130.2, 130.3, 130.6, 135.7, 140.0, 141.2, 141.8, 142.0, 152.5, 158.7, 163.9, 164.0; IR (film, cm^{-1}) ν_{max}=2926, 2855, 1760, 1613, 1550, 1423, 1352, 1281, 1244, 1077, 1036, 991, 912, 912, 871, 748, 693; HRMS (ESI): calcd for $C_{52}H_{49}N_6O_6$ $[M+H]^+$: 853.3708, found 853,3747.

*4.1.11. (±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate (**1**).* Compound **21** (3.5 g, 4.1 mmol) was dissolved in a mixture of methanol (15 ml) and toluene (5 ml) with stirring. The reaction mixture was then heated at refluxed temperature for 10 h before being cooled to room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate (150 ml×2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was applied to flash column chromatography (silica gel) to afford the final product **1** (1.88 g, 75%) as white solid; mp: 128–129 °C; ^1H NMR (400 MHz, DMSO-*d*) δ: 1.18–1.32 (m, 4H), 1.35–1.47 (m, 8H), 1.61–1.65 (m, 2H), 1.79–1.82 (m, 2H), 4.55–4.63 (m, 3H, OCH_2, and OCH), 5.51 (d, J=20 Hz, 2H, NCH_2), 6.79 (q, J=5.6 Hz, 1H, –O–CH(CH_3)–O–), 6.90 (d, J=8.0 Hz, 2H, ArH), 7.00 (d, J=8.0 Hz, 2H, ArH), 7.21 (t, J=8.0 Hz, 1H, ArH), 7.45–7.48 (m, 2H, ArH), 7.55–7.57 (m, 1H, ArH), 7.62–7.64 (m, 2H, ArH), 7.74 (dd, J=8.0, 1.0 Hz, 1H, ArH), 16.2 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d*) δ: 14.8, 19.6, 23.4 (2C), 25.0, 31.2 (2C), 46.7, 67.2, 77.3, 92.4, 113.5, 113.7, 121.2, 122.8, 123.8, 127.0, 128.2, 128.9, 129.5, 130.6, 131.0, 131.1, 131.5, 136.8, 138.6, 141.5, 152.4, 155.4, 158.2, 163.9; IR (film, cm^{-1}) ν_{max}=3418, 2941, 2862, 1755, 1718, 1615, 1551, 1477, 1431, 1282, 1244, 1077, 1037, 994, 910, 870, 750; HRMS (ESI): calcd for $C_{33}H_{34}N_6NaO_6$ $[M+Na]^+$: 633.2432, found 633.2456.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.037. These data include MOL files and InChIKeys of the most important compounds described in this article.

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