Synthesis of Six New 2-Aryl-*N*-biphenyl Benzimidazoles and Crystal Structure of Methyl 4'-[(2-*p*-Chlorophenyl-1*H*-benzimidazole-1-yl)-methyl]biphenyl-2-carboxylate

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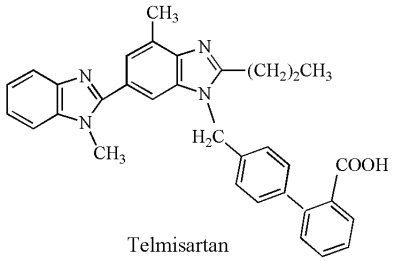
Received January 2, 2004

Six new 2-aryl-*N*-biphenyl benzimidazoles were designed and synthesized, starting with *O*-phenylenediamine and carboxylic acids *via* cyclization, followed by *N*-alkylation. All new compounds were identified by ^{1}H NMR, IR, MS spectra and elemental analysis. The crystal structure of methyl 4'-[(2- *p*-chlorophenyl-1*H* benzimidazole-1-yl)methyl]biphenyl-2-carboxylate (**4f**) was determined by single crystal X-raydiffraction.

J. Heterocyclic Chem., **41**, 621 (2004).

The renin-angiotensin system (RAS) plays an important role in the control of blood pressure and the regulation of volume and electrolyte homeostasis [1,2]. Angiotensin II (AII) is regarded as a major mediator of hypertensive disorders, including essential hypertension [3]. Despite the clinical efficacy of the angiotensin converting enzyme (ACE) inhibitors, these compounds induce side effects such as dry cough and angioedema, caused by potentiation of bradykinin, substance P and other active peptides, nonpeptide angiotensin II receptor antagonists are of interest [4-6]. The antihypertensive activity of nonpeptide angiotensin antagonist has been demonstrated in the clinic [7,8]. The antihypertensive activity of 2-alkyl-*N*-biphenyl fused benzimidazoles as angiotensin II receptor antagonists has already been established [9,10]. In the course of our study, we optimized the synthesis of Telmisartan (**I**) using a green catalytic procedure in higher overall yields. In order to examine the antihypertensive activity of 2-aryl-*N*-biphenylbenzimidazoles, which are unknown so far, we designed and synthesized six new 2-aryl-*N*-biphenyl benzimidazole derivatives.



Telmisartan

(**I**)

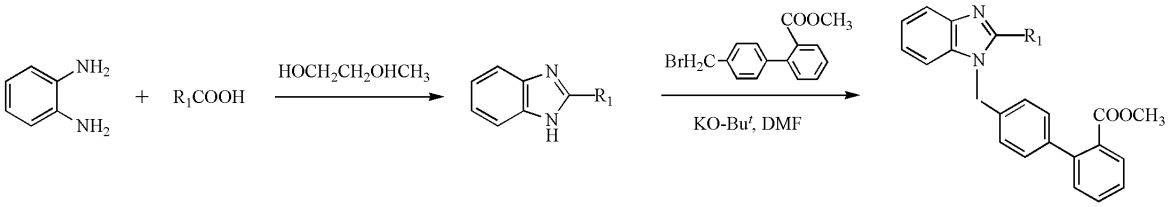
Treatment of *o*-phenylenediamine (**1**) with carboxylic acids (**2a**-**2f**) in propylene glycol at range 150-180 ºC for 10-18 hours led to benzimidazole derivatives (**3a**-**3f**) respectively, which in turn react with methyl 4-(bromomethyl)-biphenyl-2'-carboxylate in DMF to afford the 2-aryl-*N*-biphenylbenzimidazoles (**4a**-**4f**) respectively. The synthetic route is shown in Scheme I.

Benzimidazole heterocyclic derivatives were synthesized by condensation of *o*-phenylenediamine and carboxylic acids. The catalysts typically utilized for this reaction are hydrochloric acid, phosphonic acid and polyphosphonic acid [11-13], and new methods continued to be reported, such as these by propylene glycol [14] and *p*-toluenesulfonic acid [15].

During our study for the synthetic process of Telmisartan, the effects of different catalysts on the yield of the key intermediate of Telmisartan, 2-*n*-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazole, was investigated. Experimental results showed that the yield of the condensation step was 12.4% without catalyst, 25.6% with phosphonic acid, 53.2% with polyphosphonic acid and 71.2% with propylene glycol. Accordingly, propylene glycol was chosen as catalyst in the synthesis of 2-substituted benzimidazoles of interest.

The result of the reaction between *o*-phenylenediamine and unsubstituted benzoic acid was shown in entry **3a** in

Scheme I



1 **2a~2f** **3a~3f** **4a~4f**

a: R_1=C_6H_5; **b**: R_1=*m*-$CH_3C_6H_5$; **c**: R_1=*p*-$CH_3C_6H_5$; **d**: R_1=*O*-ClC_6H_5; **e** : R_1= *m*-ClC_6H_5 **f**: R_1= *p*-ClC_6H_5

Table 1. When reacted at 160 ºC for 12 hours, 72.6% yield of 2-phenylbenzimidazole was obtained. Analogues of a reactant where the carboxylic group was deactivated by an electron-donating group (*m*-methyl, *p*-methyl) also led to moderate yields after a longer time (**3b**: 18 h, 78.5%; **3c**: 13 h, 78.8%). The carboxylic group can be activated by an electron-withdrawing group on the phenyl ring particularly those on the *meta*- and *para*-positions. This resulted in good yields of 2-substituted benzimidazoles using the same 12 h reaction time to give **3e**: 75.4% and **3f**: 71.6%. The field effect and steric hinderance that probably existed in the *ortho*-position reduced the yield of 2-substituted benzimidazole at the same reaction time (12h) (**3d**: 63.5%).

It was reported that the use of NaH and KO*t*-Bu were similar when used in the *N*-alkylation process [10,16]. However, hydrogen is generated during the reaction process when NaH is used, which is dangerous, thus KO*t*-Bu was chosen as the *N*-alkylation reagent.

As shown in Table 2, the product yield (**4a**) of the reaction between 2-unsubstitutedphenylbenzimidazole and methyl 4-(bromomethyl)biphenyl-2'- carboxylate at room temperature for 12 hours was 65.7% (Table 2, entry **4a**). It seems that the electron-donating group (methyl) on the 2-substituted phenyl ring of benzimidazole could increase electronic density on the nitrogen atom of the *N*-H group, which improves the nucleophilicity of the nitrogen atom, hence reaction time was reduced (**4b**: 8h; **4c**: 4h). The nucleophilicity of nitrogen atom could be activated by chlorine on the 2-substituted phenyl ring of benzimidazole, which was demonstrated by a shorter reaction time (8-10 h for **4d**-**4e**). The activating ability of the substituent group at different positions varied, the *ortho*-chlorine achieving the best result (**4d**: yield 85.9%).

Table 1
Results and Reaction Conditions of 2-Arylbenzimidzoles **3a**-**3f**

Entry	R_1	Time/h	Temp. (ºC)	Yield (%)	Mp / ºC
3a	C_6H_5	12	160	72.5	294~ 295(295)
3b	*m*- $CH_3C_6H_5$	18	170	78.5	218~ 220
3c	*p*- $CH_3C_6H_5$	13	160	78.8	286~ 288(270)
3d	*o*- ClC_6H_5	12	150	63.5	236~ 238(234)
3e	*m*- ClC_6H_5	12	170	75.4	238~ 240(238)
3f	*p*- ClC_6H_5	12	180	71.6	230~ 232(303)

A crystal of **4f** suitable for X-ray analysis was obtained by slow evaporation of AcOEt/CH_2Cl_2 solution. X-ray diffraction data were collected on a Rigaku RAXIS RAPID IP diffractometer, using graphite monochromated Mo Kα radiation (*l*=0.71073 Å). The structure was solved by direct method and refined by full-matrix least-squares methods using SHELXS98 program. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms attached to carbon atoms were placed at idealized positions, with C-H distances taken from the default settings of the refinement program. The drawing of the molecular structure and the higher occupancy in the three-dimensional packing arrangement are shown in Figures 1-3.

Table 2
Results and Reaction Conditions of 2-Aryl-*N*-biphenylbenzimidazoles **4a**-**4f**

Entry	R_1	Time/h.	Temp. (ºC)	Yield (%)	Mp/ºC
4a	C_6H_5	12	r. t.	65.7	120~ 122
4b	*m*- $CH_3C_6H_5$	8	r. t.	70.6	136~ 138
4c	*p*- $CH_3C_6H_5$	4	r. t.	77.5	148~ 150
4d	*o*- ClC_6H_5	10	r. t.	85.9	140~ 142
4e	*m*- ClC_6H_5	8	r. t.	75.7	116~ 118
4f	*p*- ClC_6H_5	9	r. t.	61.8	154~ 156

Single-crystal X-ray diffraction studies were performed on compound **4f**. Selected data are contained in Tables 3 to 5. An ORTEP drawing of **4f** showing the molecular conformation and atom-labeling scheme is depicted in Figure 1.

In the molecular structure of **4f**, all the five rings are planar, but the co-planarity among them is poor. The plane of the imidazole ring is deviated from the planes of the phenyl rings of the benzimidazolyl and 4-chlorophenyl moieties by 1.28(10)º and 45.40(10)º respectively. The deviation angle between the planes of the phenyl rings of the biphenyl moieties is 60.36(8)º. The angle doesn't agree well with those of related structures found in *N*-(4-biphenyl) urea [45.41(17)º] and 2,4-dicarbonitrile-biphenyl[44.1(1)º] [17, 18] maybe due to the co-effect of bulky 2- *p*-chlorophenylbenzimidazolyl and carboxylate. The plane of the phenyl ring of the benzimidazolyl moiety is deviated from that of the 4-chlorophenyl moiety is 46.65(9)º. In fact, the dihedral angle on the two phenyl rings of biphenyl moiety may be relevant to antihypertensive activity, but this needs to be confirmed by bio-activity screening.

The normal inter-ring bond distance for unsubstituted biphenyl is 1.507 Å, but for C (7)-C (8) in **4f** this value become 1.492(2) Å (Table 5), consistent with that of related structure in polychlorinatedbiphenyl [1.485(6) Å], 2-fluorobiphenyl [1.483(4) Å] and ethylbiphenyl [1.485(3) Å], and with the theoretically calculated value of 1.488Å between two sp^2-hybridized C atoms [17, 18].

An interesting aspect of the crystal structure here presented is the occurrence of two weak C-H···O interactions in **4f,** taking place among the neighboring molecules. The hydrogen bond distance of O2···C14H and O2···C28H is 2.541 Å and 2.512 Å respectively (Figure 3). The latter is shorter than that of the former, maybe due to the fact that two hydrogen bonds for the latter exist in adjacent two molecules other than a single one in the case of the former.

Table 3

Single Crystal X-Ray Crystallographic Analysis of **4f**

Formula	$C_{28}H_{21}ClN_2O_2$
Formula weight	452.92
Temperature, K	293(2)
Wavelength, Å	Mo Kα= 0.71073
Crystal system	Triclinic
Space group	P-1
a, Å	8.7001(17)
b, Å	10.681(2)
c, Å	12.929(3)
α, Å	99.62(3)
β, Å	106.66(3)
γ, Å	91.54(3)
V, Å^3	1131.2(4)
Z; density (calc), g/cm^3	2, 1.330
Crystal size, mm	0.45 x 0.35 x 0.35
F (000)	472
Absorption coef., mm^{-1}	0.198
Reflections collected	9465
Independent reflections	4951
R indices	$R^1 = 0.0694$, $wR^2 = 0.1430$
Largest diff. peak and hole, e/Å^{-3}	0.284 and -0.260

Table 4

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **4f**

Atom	x	y	z	U (eq)
Cl1	1287(1)	169(1)	3225(1)	81(1)
O1	-6591(2)	-7177(1)	-884(1)	64(1)
O2	-4261(2)	-6203(2)	-741(1)	84(1)
N1	1661(2)	-2809(1)	-1804(1)	44(1)
N2	2698(2)	-818(1)	-1711(1)	52(1)
C1	-5523(2)	-6709(2)	-1306(1)	45(1)
C2	-6124(2)	-6856(2)	-2524(1)	41(1)
C3	-7625(2)	-7520(2)	-3066(2)	54(1)
C4	-8289(2)	-7613(2)	-4180(2)	62(1)
C5	-7479(2)	-7044(2)	-4777(2)	59(1)
C6	-5977(2)	-6408(2)	-4256(1)	50(1)
C7	-5259(2)	-6314(2)	-3138(1)	40(1)
C8	-3604(2)	-5665(2)	-2679(1)	39(1)
C9	-3273(2)	-4420(2)	-2783(1)	41(1)
C10	-1708(2)	-3850(2)	-2396(1)	41(1)
C11	-443(2)	-4524(2)	-1913(1)	39(1)
C12	-776(2)	-5787(2)	-1836(2)	51(1)
C13	-2317(2)	-6342(2)	-2204(2)	51(1)
C14	1279(2)	-3964(2)	-1423(2)	46(1)
C15	2126(2)	-1600(2)	-1193(1)	44(1)
C16	1935(2)	-1219(2)	-96(1)	44(1)
C17	517(2)	-1521(2)	131(1)	44(1)
C18	293(2)	-1086(2)	1143(1)	47(1)
C19	1524(2)	-352(2)	1942(2)	52(1)
C20	2951(3)	-39(2)	1743(2)	63(1)
C21	3159(2)	-471(2)	729(2)	57(1)
C22	1981(2)	-2789(2)	-2793(2)	46(1)
C23	1797(2)	-3725(2)	-3702(2)	58(1)
C24	2228(3)	-3377(2)	-4569(2)	67(1)
C25	2819(3)	-2140(2)	-4534(2)	69(1)
C26	3017(2)	-1205(2)	-3623(2)	62(1)
C27	2608(2)	-1544(2)	-2726(2)	50(1)
C28	-6149(3)	-7054(2)	291(2)	69(1)

U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 5

Selected Bond Lengths (Å) and Angles (deg) for **4f**

Bonds	Distances	Bonds	Angles
Cl(1)-C(19)	1.7311(19)	C(1)-O(1)-C(28)	117.18(15)
O(1)-C(1)	1.330(2)	C(22)-N(1)-C(14)	125.00(14)
O(1)-C(28)	1.438(2)	C(3)-C(2)-C(7)	119.47(15)
O(2)-C(1)	1.186(2)	C(4)-C(5)-C(6)	119.82(17)
N(1)-C(15)	1.380(2)	C(6)-C(7)-C(8)	116.79(15)
C(1)-C(2)	1.490(2)	C(11)-C(10)-C(9)	120.42(15)
C(4)-C(5)	1.382(3)	N(2)-C(15)-C(16)	123.88(15)
C(6)-C(7)	1.385(2)	C(18)-C(19)-C(20)	121.04(17)
C(7)-C(8)	1.492(2)	C(23)-C(22)-C(27)	122.38(18)
C(22)-C(23)	1.377(3)	N(1)-C(22)-C(27)	105.99(15)
C(23)-C(24)	1.381(3)	C(25)-C(26)-C(27)	117.6(2)
C(24)-C(25)	1.394(3)	N(2)-C(27)-C(22)	109.89(16)
C(25)-C(26)	1.376(3)	N(2)-C(27)-C(26)	130.26(18)
C(26)-C(27)	1.405(3)	C(22)-C(27)-C(26)	119.85(18)

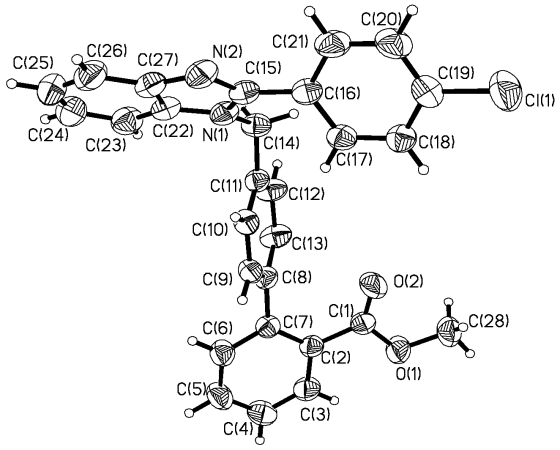


Figure 1. A perspective view of the molecular of **4f**.

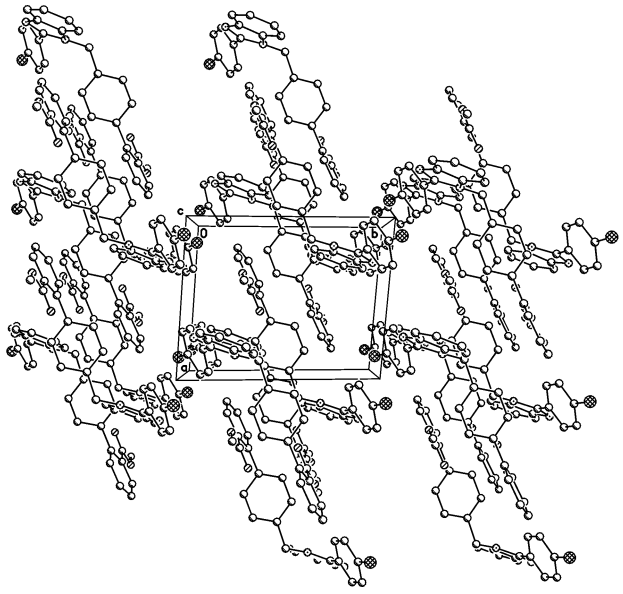


Figure 2. Packing of the molecule of compound **4f** in the unit cell showing its hydrogen network.

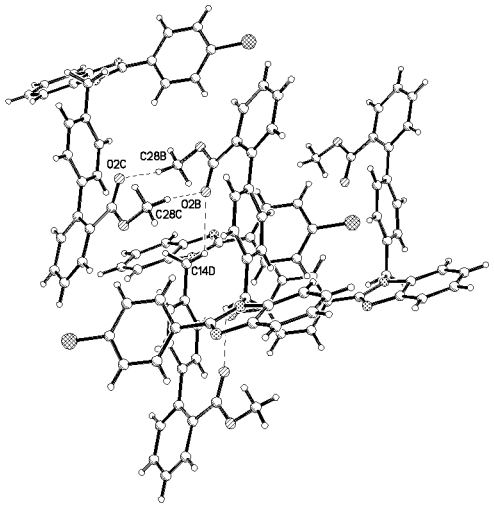


Figure 3. Hydrogen bond interaction of **4f**.

EXPERIMENTAL

General Methods.

Melting points were determinated using XT4 microscope melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet Magna IR 560 spectrophotometer and were run as KBr pellets unless otherwise indicated. ^{1}H NMR spectra (400MHz) were measured on an ARX400 instrument. Chemical shifts are reported in δ (ppm) relative to internal tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer using EI ionization. Elemental analyses were within ± 0.3% of theoretical values and were performed on an Elementar Vario EL.

2-Phenyl benzimidazole.

Under N_2 atmosphere, a mixture of benzoic acid (0.12 mol) and *o*-phenylenediamine (10.8 g, 0.1 mol) was heated at 160 ºC in 80 ml of propylene glycol for 12 h. Propylene glycol was removed by distillation under vacuum, then to the residue was added 50 mL alcohol and activated charcoal. After filtration, to the filtrate was added with 100 mL water to give a colorless solid, after collection by filtration the filter cake was washed by water to furnish white solid 2-phenyl benzimidazole (**3a**) 14.1 g (72.7%); mp 294-295 ºC (ref [12], 294.5-295.5ºC).

Compounds **3b**-**3f** were prepared using the procedure as described for 2-phenyl benzimidazole [19].

Methyl 4'-[(2-Phenyl-1*H*-benzimidazol-1-yl) methyl] biphenyl-2-carboxylate (**4a**).

To a solution of 1.0 g (5.37 mmol) of **3a** in 30 ml of DMF was added potassium *tert*-butylate 0.7 g (6.25 mmol), the mixture was stirred for 30 min at ambient temperature, and methyl 4-(bromomethyl)biphenyl-2'-carboxylate 1.65 g (5.40 mmol) was added. After stirring for 14 h the mixture was poured into water (120 ml) and extracted with ethyl acetate (3x50 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/light petroleum (30:70/v:v) to give **4a** (1.42 g, 66%)as a white solid: mp 120-122 ºC; ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 3H), 5.5 (s, 2H), 7.13 (d, J=8.2 Hz , 2H), 7.25-7.73 (m, 13H), 7.82 (d, J=7.8 Hz , 1H), 7.88 (d, J=8.0 Hz, 1H); ms: *m/z* 418 (M^+); IR(KBr): 3019, 2944, 1721, 1459, 1441, 1386, 1288, 1243, 1118, 760, 701cm^{-1}.

Anal. Calcd. for $C_{28}H_{22}N_2O_2$: C, 80.38; H, 5.26; N, 6.70. Found: C, 80.35; H, 5.30; N, 6.99.

Methyl 4'-[(2-*m*-Methylphenyl-1*H*-benzimidazole-1-yl)methyl]-biphenyl-2-carboxylate (**4b**).

This compound was prepared from compound **3b** using the procedure as described for compound **4a** in 70.6% yield, white solid, mp 136~ 138 ºC; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 3.60 (s, 3H), 5.50 (s, 2H), 7.14 (d, J=8.2 Hz, 2H), 7.24-7.53 (m, 11H), 7.60 (s, 1H), 7.82 (d, J=7.8 Hz, 1H), 7.87(d, J=7.9 Hz, 1H); ms: *m/z* 432 (M^+); IR (KBr): 3033, 2946, 1723, 1449, 1281, 1188, 742 cm^{-1}.

Anal. Calcd. for $C_{29}H_{24}N_2O_2$: C, 80.56; H, 5.56; N, 6.48. Found: C, 80.52; H, 5.55; N, 6.49.

Methyl 4'-[(2-*p*-Methylphenyl-1*H*-benzimidazole-1-yl)methyl]-biphenyl-2-carboxylate (**4c**).

This compound was prepared from compound **3c** using the procedure as described for compound **4a** in 77.5% yield as white solid: mp 148-150 ºC; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.60 (s, 3H), 5.47 (s, 2H), 7.13 (d, J=8.1 Hz, 2H), 7.22-7.34 (m, 8H), 7.39 (dt, J=7.6 Hz, J=1.2 Hz, 1H), 7.50 (dt, J=7.5 Hz, J=1.3 Hz, 1H), 7.60 (d, J=8.1 Hz, 2H), 7.82 (dd, J=7.7 Hz, J=1.3 Hz, 1H), 7.86 (d, J=8.1 Hz, 1H); ms: *m/z* 432 (M^+); IR (KBr): 3030, 2944, 1730, 1473, 1457, 1287, 1246, 1184, 1088, 829, 762, 738 cm^{-1}.

Anal. Calcd. for $C_{29}H_{24}N_2O_2$: C, 80.56; H, 5.56; N, 6.48. Found: C, 80.53; H, 5.54; N, 6.47.

Methyl 4'-[(2-*o*-Chlorophenyl-1*H*-benzimidazole-1-yl)methyl]-biphenyl-2-car-boxylate (**4d**).

This compound was prepared from compound **3d** using the procedure as described for compound **4a** in 85.9% yield as a white solid: mp 140-142 ºC ; ^{1}H NMR ($CDCl_3$): δ 3.57 (s, 3H), 5.30 (s, 2H),7.0 (d, J=8.3 Hz , 2H), 7.15-7.89 (m, 14H); ms: *m/z* 452 (M^+); IR (KBr): 3051, 2945, 1719, 1441, 1389, 1287, 1241, 1117, 1045, 762 cm^{-1}.

Anal. Calcd. for $C_{28}H_{21}ClN_2O_2$: C, 74.25; H, 4.64; N, 6.18. Found: C, 74.22; H, 4.62; N, 6.20.

Methyl 4'-[(2-*m*-Chlorophenyl-1*H*-benzimidazole-1-yl)methyl]-biphenyl-2-carboxylate (**4e**).

This compound was prepared from compound **3e** using the procedure as described for compound **4a** in 75.7% yield as a white solid: mp 118-120 ºC; ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 3H), 5.48 (s, 2H), 7.11 (d, J=8.1 Hz, 2H), 7.25-7.74 (m, 11H), 7.73 (s, 1H), 7.82 (d, J=7.8 Hz, 1H), 7.87 (d, J=7.9 Hz, 1H); ms: *m/z* 452 (M^+); IR (KBr): 3034, 2940, 1721, 1442, 1376, 1281, 1251, 1063, 761 cm^{-1}.

Anal. Calcd. for $C_{28}H_{21}ClN_2O_2$: C, 74.25; H, 4.64; N, 6.18. Found: C, 74.26; H, 4.65; N, 6.18.

Methyl 4'-[(2-*p*-Chlorophenyl-1*H*-benzimidazole-1-yl)methyl]-biphenyl-2-carboxylate (**4f**).

This compound was prepared from compound **3f** using the procedure as described for compound **4a** in 61.8% yield as a white solid: mp 154-156 ºC; ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H), 5.49 (s, 2H), 7.11 (d, J=7.8 Hz, 2H), 7.27-7.54 (m,10 H), 7.66 (d,

J=7.9 Hz, 2H), 7.84 (d, J=7.7 Hz, 1H), 7.89 (d, J=7.8 Hz, 1H); ms: *m/z* 452 (M^+); IR (KBr): 3033, 2935, 1728, 1454, 1249, 1094, 843, 752, 704 cm^{-1}.

Anal. Calcd. for $C_{28}H_{21}ClN_2O_2$: C, 74.25; H, 4.64; N, 6.18. Found: C, 74.24; H, 4.63; N, 6.18.

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