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The Conformation and Activity Relationship of Benzofuran Derivatives as Angiotensin II Receptor Antagonists

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Abstract—We have synthesized various benzofuran derivatives to study the relationship between the conformation and the angiotensin II type I receptor antagonistic activity. © 1997, Elsevier Science Ltd. All rights reserved.

Introduction

In our previous study, we tried to establish the three-dimensional arrangement of pharmacophoric elements for angiotensin II type I receptor antagonists with conformationally restricted derivatives of Dup753.[1] In the present study, as part of continuing efforts for this goal, we have synthesized various benzofuran derivatives and tried to define the structural and conformational requirement for the angiotensin II receptor antagonistic activity.

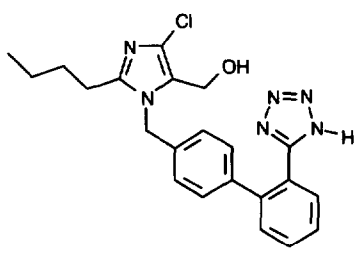
In the case of Dup753, a prototypic compound of angiotensin II type I receptor antagonists, it was proposed that there are three pharmacophoric elements in the molecule; a nitrogen atom in the imidazole ring, an alkyl side chain and an acidic moeity and these elements are connected through the biphenyl group as a spacer.[2]

Recently numerous compounds possessing various spacers have been introduced as new angiotensin II receptor antagonists,[3] including benzofuran derivatives developed by Glaxo.[4] We are specially interested in the benzofuran derivatives as a tool in our study because of availability of many attaching positions for the upper imidazole part and the lower tetrazole bearing part. Thus obtained regioisomers will provide various conformations which are certainly different in the aspect of the relative positions of pharmacophoric elements from those available in the biphenyl case. Especially, with an alternative type of benzofuran derivative, such as (a), where the imidazole upper part is connected to the furanyl part of benzofuran and the acid-carrying lower part is attached to the phenyl part of benzofuran, various conformations which are not available from the biphenyl and the Glaxo type benzofuran derivatives will be possible.

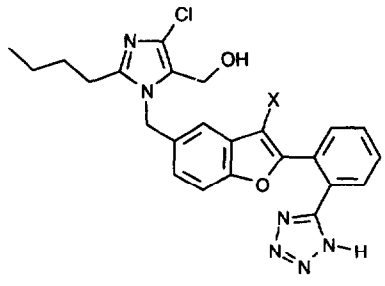
Results and Discussion

The syntheses of key intermediates for the bottom tetrazole-bearing benzofuranyl moiety and for the corresponding bromo-substituted intermediates are shown in Schemes 1–5. In the processes the trityl-protected phenyltetrazole unit is coupled to the benzofuranyl unit via a Pd(0) catalyzed coupling reaction.[5]

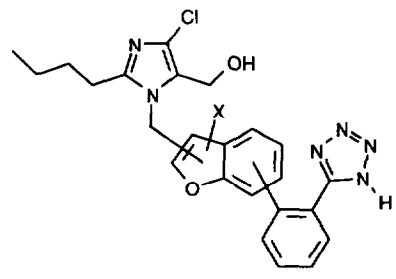
The processes for combining the upper imidazolyl aldehyde moiety[6] and the bottom benzofuranyl moiety, subsequent reductions and deprotection are shown in Schemes 6 and 7 to provide the final target compounds **44**, **47**, **50**, **52**, **55**, **57**, **59**, **62**, **64** and **66**.



Dup-753



X= H or Br
Glaxo



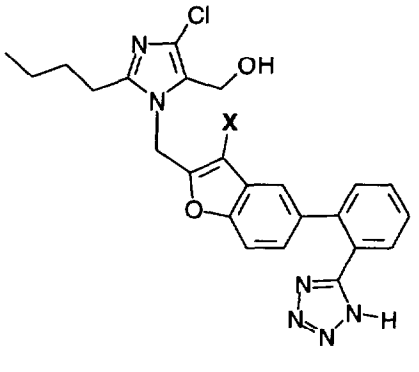
X= H or Br
A

The angiotensin II receptor antagonistic activity for these compounds was determined by the human recombinant angiotensin II receptor subtype with ^{125}I-[Sar1, Ile8]-angiotensin II as an agonist.

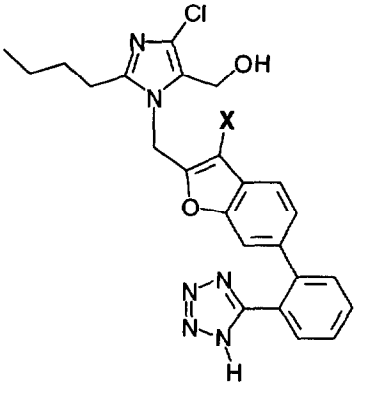
The conformational analysis on these compounds was carried out using molecular mechanic methods after generating the initial geometries by changing all rotatable bonds systematically. For analyzing pharmacophoric elements and finding the possibility of any correlations between the biological activity and the distances between key elements, we measured, with the lowest energy conformation of each compound, distances between the nitrogen atom, the center of the imidazole ring, the terminal methyl group of the butyl side chain, the hydroxyl group and the center of the tetrazole ring and designated them as *D*1, *D*2, *D*3, *D*4 and *D*5, respectively.

Table 1 shows the PIC_{50} values for the compounds in the angiotensin II type I receptor binding assay and distances defined previously in the lowest energy conformers from each compound. As can be seen from Table 1, the binding activities are generally low for these compounds and even the most active compound has its IC_{50} value in the micromolar range. As far as distances are concerned, one can anticipate that the distances *D*4 and *D*5 would be most important for determining biological activity based on the pharmacophoric elements for Dup753. The distance *D*2 could be used as an indicator for the relative orientation of the tetrazole ring against the butyl group.

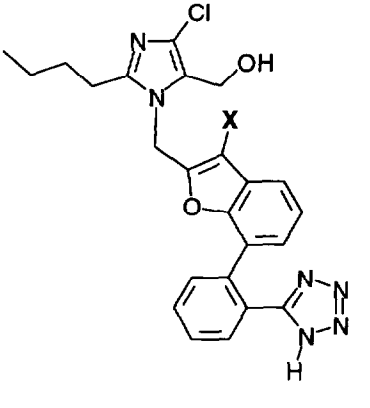
In order to establish the relationship, the biological activity, as PIC_{50}, was plotted against each distance, as in Figure 1. It is clear from Figure 1 that there are parabolic correlations between the biological activity and the distances *D*3 and *D*4, indicating that there are optimal distances for good activity. These distances in the compounds with lower activities are quite different from those with good activities. This indicates that the imidazole ring, especially the nitrogen atom, and the tetrazole group, which are points comprising the distances, *D*3 and *D*4, are important for a good receptor–ligand interaction. This result is similar to the finding with Dup753.[2] In the case of *D*5, the distance between the hydroxyl group and the tetrazole group, there is no apparent correlation, indicating that two points without the imidazole part are not sufficient for a good receptor–ligand interaction.



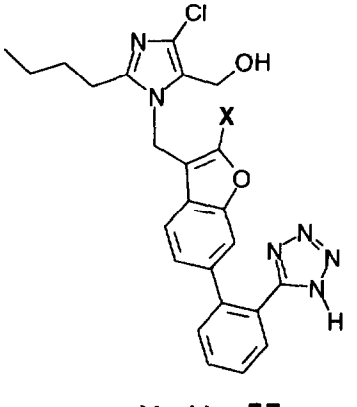
X= H **44**
X= Br **47**



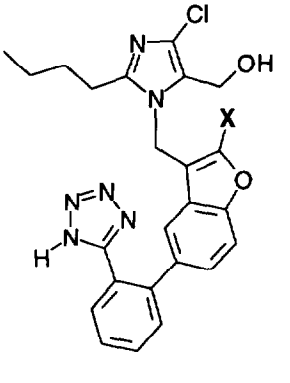
X= H **59**
X= Br **62**



X= H **64**
X= Br **66**



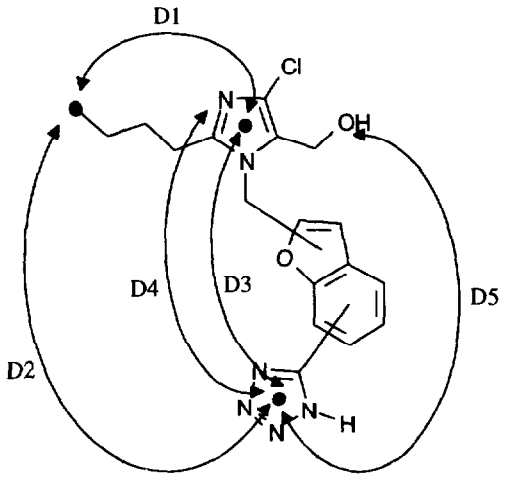
X= H **55**
X= Br **57**

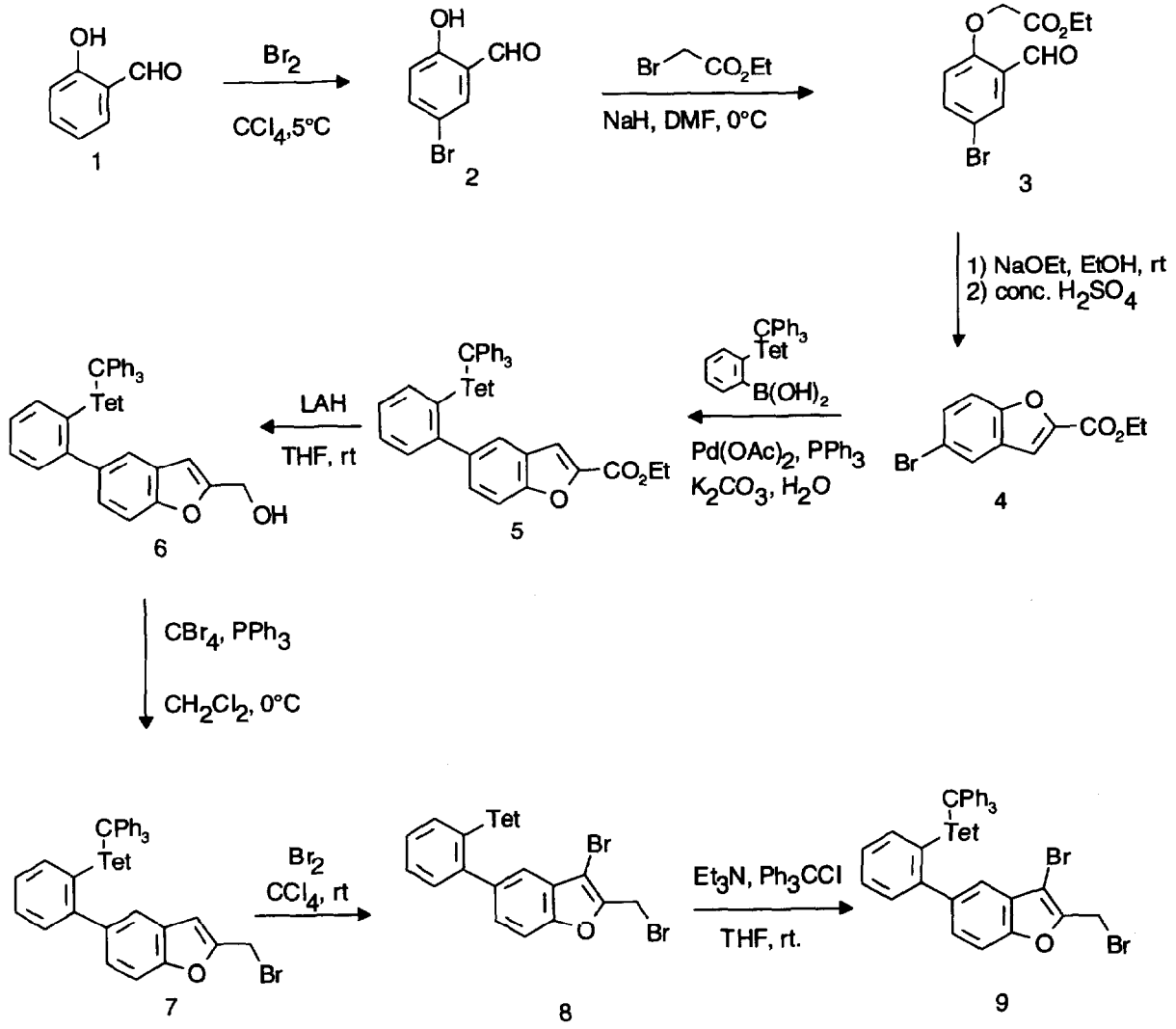


X= H **50**
X= Br **52**

In the graphs there are two compounds (**55** and **57**), which are actually much more active than the correlation curve predicts. This might suggest that an additional group, such as the hydroxyl group, possibly contribute somewhat to the receptor-ligand binding interaction.

In order to illustrate this analysis more effectively, the conformations from the most active compound and the least active compound are overlapped, using the nitrogen atom in the imidazole ring, the center of the tetrazole ring and the hydroxyl group for superimposition, with the most stable conformation of Dup753 and the Glaxo compound as shown in Figures 2 and 3, respectively. It is apparent from Figure 2 that there is overall similarity between the most active compound, (**55**), and Dup753, except there is some difference in the angle of the imidazole plane. On the other hand, the least active compound is quite different from Dup753, especially the locations of the tetrazole ring and the imidazole ring are notably different from each other. In the case of the comparison with the Glaxo compound (Fig. 3), there is more overall similarity between the most active compound (**55**) and the Glaxo compound, except some difference in the trajectory of the side alkyl chain. However, in the least active compounds the overall conformations are quite different from each other.





Scheme 1.

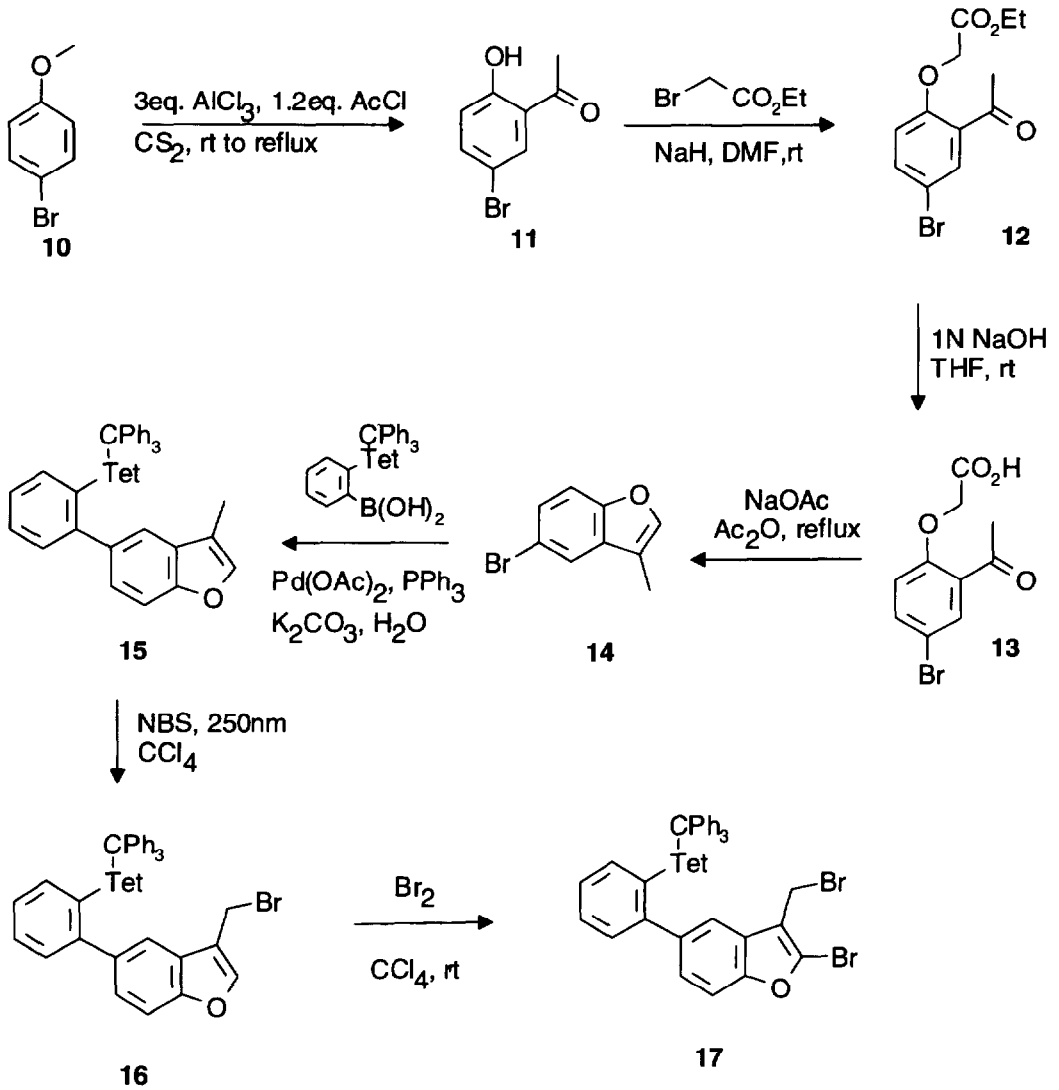
One significant difference between our benzofuran system and the Glaxo type benzofuran is in discrepancy of the binding activity between the hydrogen-substituted and the bromo-substituted analogues. Glaxo claimed that, in their compounds, the bromo-substituted analogue is much more active than the corresponding hydrogen-substituted analogue.[4c] They proposed that this difference might originate from the difference in the conformations. However, in our system we found that, in some isomers, the bromo-substituted analogues are less active than the corresponding hydrogen-substituted analogues (**44** versus **47**, **50** versus **52**, **55** versus **57**) and in other cases the opposite is true (**59** versus **62**, **64** versus **66**). Furthermore, we could not find any significant conformational differences between the hydrogen and the bromo analogues. Another possible explanation might be in the electronic nature of the bromo atom, however, it needs more studies since the bromo atom is located too far from the possible pharmacophoric elements to influence directly or indirectly. These remaining questions will be a subject for further studies.

Experimental

General procedure

Anhydrous solvents were freshly distilled under nitrogen as follows : THF from sodium and benzophenore; CH_2Cl_2 from CaH_2. All reactions were monitored by TLC precoated silica gel 60-F254 glass-backed (E. Merck). Materials were detected by visualization under a UV lamp (254 nm). Flash column chromatogrphy was conducted using silica gel (E. Merck, 230–400 mesh. ASTM). ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer or Bruker AM 300 spectrometer using tetramethylsilane as an interal standand. 13C NMR spectra were taken in DMSO-d_6 or CD_3OD solution on a Bruker AMX 500 spectrometer. MS spectra were obtained with a JEOL JMS-DX 303 mass spectrometer.

5-Bromo-2-hydroxybenzaldehyde (2). To a solution of 300 mL of CS_2 and 30 g (0.24 mol) of salicyl aldehyde at 50 °C, was added dropwise 47 g (0.29 mol) of Br_2 in 20 mL of CS_2. The solid was then collected by filtration



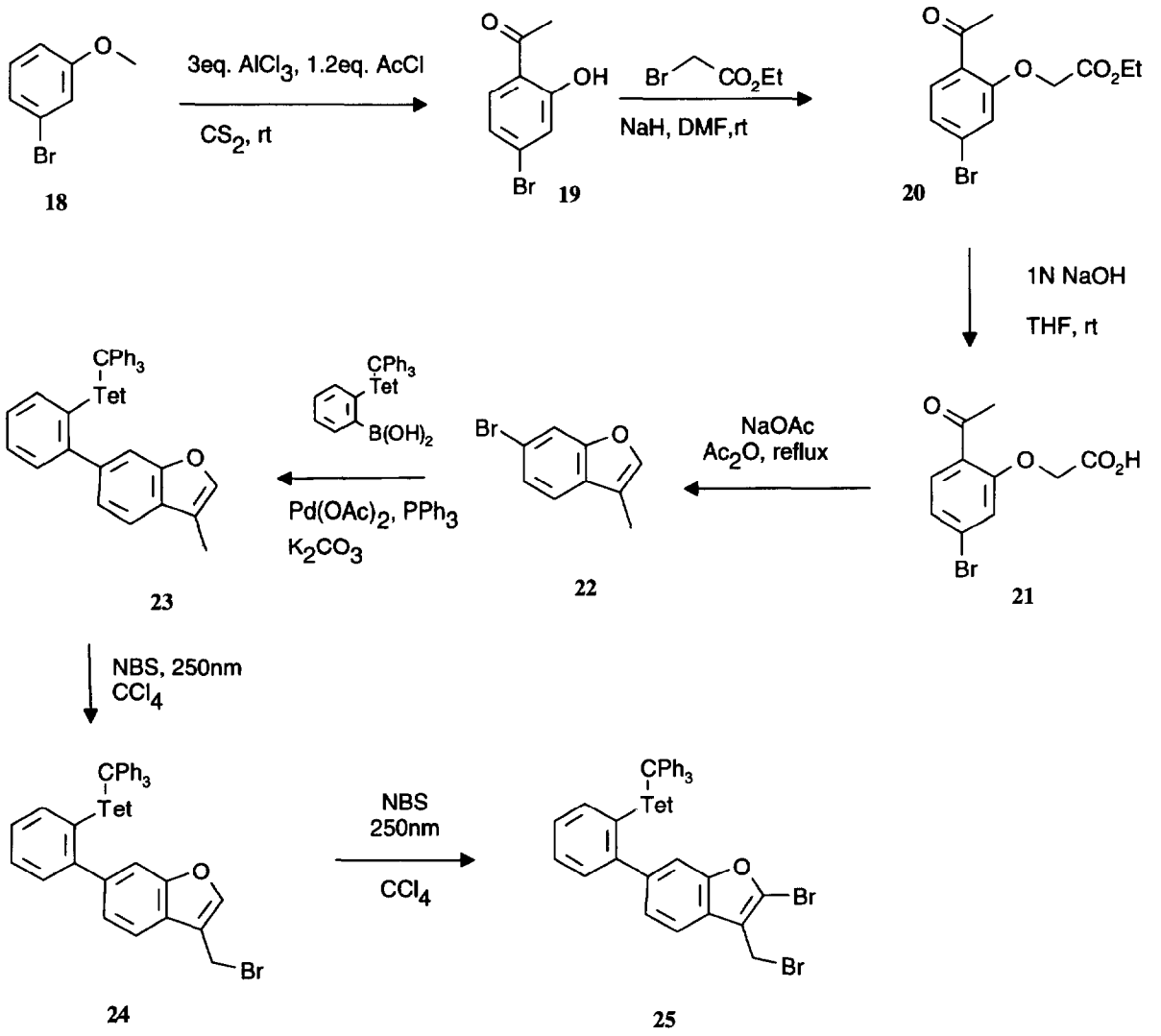
Scheme 2.

and washed with *n*-hexane to obtain the desired product (39 g, 79.3%). ^{1}H NMR (CDCl3, 200 MHz): δ 6.90–6.95 (1H, d), 7.58–7.70(2H, t) 9.85 (1H, s), 10.97 (1H, s).

(4-Bromo-2-formylphenoxy)-acetic acid ethyl ester (3). To the solution of **2** (34 g, 0.17 mol) in 300 mL of DMF was added 6.116 g (0.25 mol) of NaH with ice cooling and the solution was stirred for 30 min. To the solution was added 28 mL (0.25 mol) of ethyl bromoacetate dropwise over 30 min. After the solution was stirred for 2 h, the reaction was quenched by adding ice and 100 mL of 1 N HCl. The reaction mixture was then extracted with ethyl acetate and the organic layer was washed with water, dried with anhyd $MgSO_4$, and concentrated to give the crude product which was purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give pure **3** (39 g, 78%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26–1.33 (3H, t), 4.21–4.31 (2H, q), 4.72 (2H, s), 6.75–6.80 (1H, d), 7.59–7.62 (1H, dd), 7.95 (1H, d), 10.48 (1H, s).

5-Bromobenzofuran-2-carboxylic acid ethyl ester (4). A mixture of **3** (25 g, 0.08 mol) and 1 N sodium ethoxide (125 mL, 0.125 mL) in 200 mL of abs ethanol was refluxed for 3 hrs. After small amount of concd H_2SO_4 was added, the reaction mixture was refluxed for an additional 1 h. After the reaction mixture was cooled to rt, it was diluted with 100 mL of water and neutralized with 6 N NaOH solution. The reaction mixture was then extracted with ethyl acetate and the organic layer was washed with water, dried with anhyd $MgSO_4$, and concentrated to give the crude product which was purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give pure **4** as a solid (13 g, 55%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.39–1.45 (3H, t), 4.39–4.50 (2H, q), 7.41–7.56 (3H, m), 7.81 (1H, d).

5-[2-(1-Trityl-1*H*-tetrazol-5-yl)phenyl]benzofuran-2-carboxylic acid ethyl ester (5). To a degassed solution of $Pd(OAc)_2$ (0.04 g, 0.18 mmol) and triphenylphosphine (0.195 g, 0.743 mmol) in 16 ml of ethylene glycol dimethyl ether and 4 ml of THF, was added 5-[2-(1-trityl-1H-tetrazol-5-yl)-phenyl]boronic acid (0.965 g,



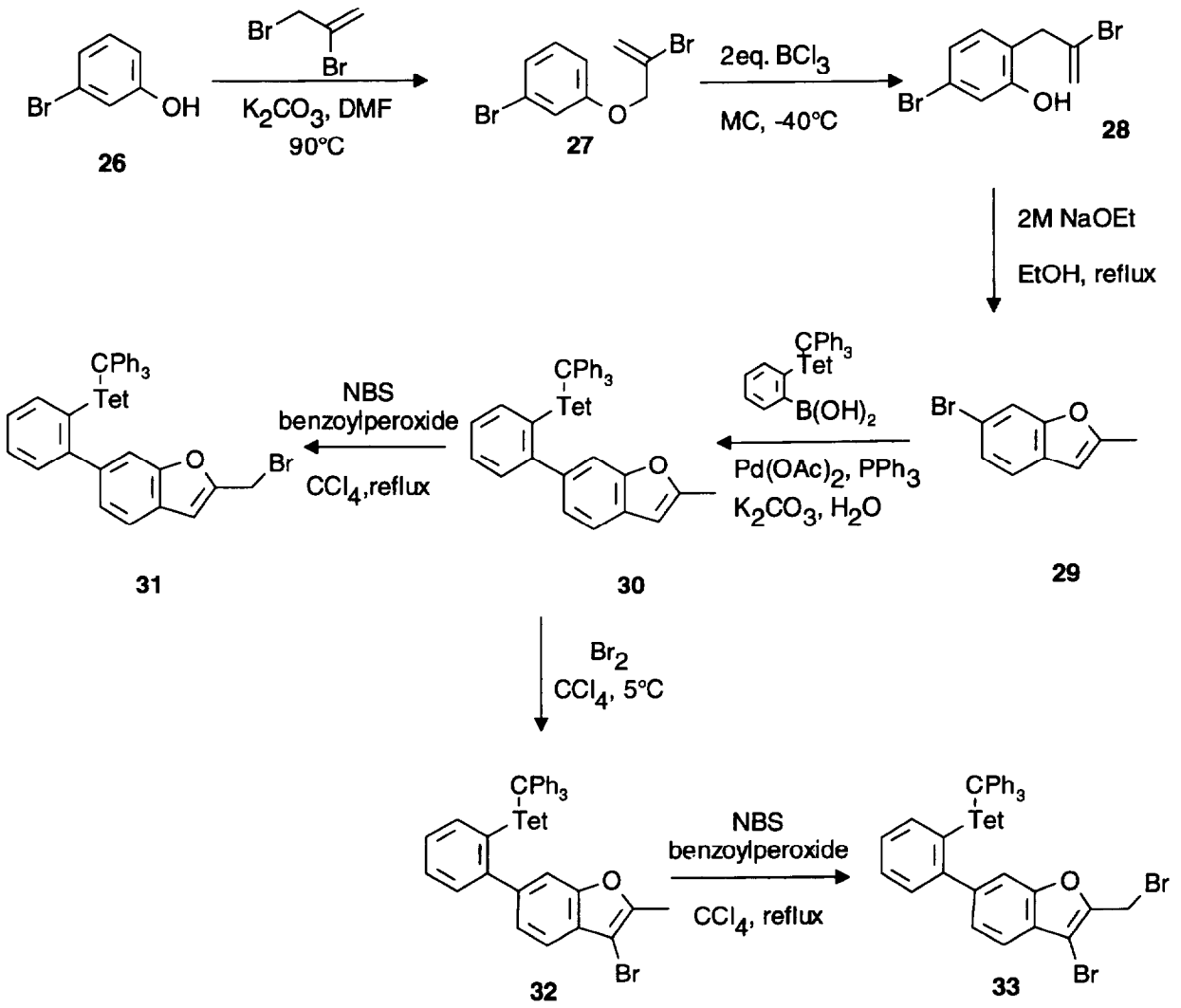
Scheme 3.

2.23 mmol). After the mixture was stirred for 30 min, 0.08 mL of water was added and the reaction mixture was stirred for another 30 min. To the reaction mixture was then added 0.5 g (1.85 mmol) of **4** and 0.64 g (4.64 mmol) of K_2CO_3 and then the reaction mixture was refluxed for 5 h under nitrogen atmosphere. The reaction mixture was then cooled to rt and a small amount of water was added, which was then extracted with ethyl acetate and the organic layer was washed with water, dried with anhyd $MgSO_4$, and concentrated to give the crude product, which was purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give pure **5** (1 g, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.41–1.49 (3H, t), 4.41–4.52 (2H, q), 6.80–6.85 (6H, m), 7.23–7.30 (4H, m), 7.32 (1H, s), 7.39–7.51 (5H, m), 8.00–8.04 (1H, m).

{5-[2-(1-Trityl-1*H*-tetrazol-5-yl)phenyl]benzofuran-2-yl}methanol (6). To a solution of 1 g (1.7 mmol) of **5** in 20 mL of THF was added 0.098 g (2.6 mmol) of $LiAlH_4$. After 30 min of refluxing, the reaction mixture was quenched with satd NH_4Cl solution. The reaction mixture was then extracted with ethyl acetate and the organic layer was washed with water, dried with anhyd $MgSO_4$, and concentrated to give the crude product which was purified by column chromatography (silica gel, *n*-hexane:EtOAc 7:3) to give pure **6** (0.71 g, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.75–4.77 (2H, d), 6.49 (1H, s), 6.81–6.84 (6H, dd), 6.99–6.70 (1H, dd), 7.12–7.20 (7H, m), 7.24–7.29 (3H, m), 7.33 (1H, d), 7.43–7.48 (3H, m), 7.92–7.95 (1H, m).

5-[2-(2-Bromomethylbenzofuran-5-yl)phenyl]-1-trityl-1*H*-tetrazole (7). To a solution of **6** (0.71 g, 1.32 mmol) in 14 mL of CH_2Cl_2, was added, with ice-cooling, 0.65 g (1.99 mmol) of CBr_4 and 0.52 g (1.99 mmol) of triphenylphosphine. After stirring for 40 min, the reaction mixture was concentrated to give the crude product which was purified by column chromatography (silica gel, *n*-hexane:EtOAc 7:3) to give pure **7**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (2H, s), 6.66 (1H, s), 6.81–6.83 (6H, m), 7.03 1H, dd), 7.11–7.51 (14H, m), 7.94–7.98 (1H, m).

5-[2-(3-Bromo-2-bromomethylbenzofuran-5-yl)phenyl]-1*H*-tetrazole (8). To a solution of 7 (0.5 g, 0.83 mmol) in 4 mL of $CHCl_3$ and 4 mL of CCl_4 was added dropwise 0.05 mL (1 mmol) of bromine in 1 mL of



Scheme 4.

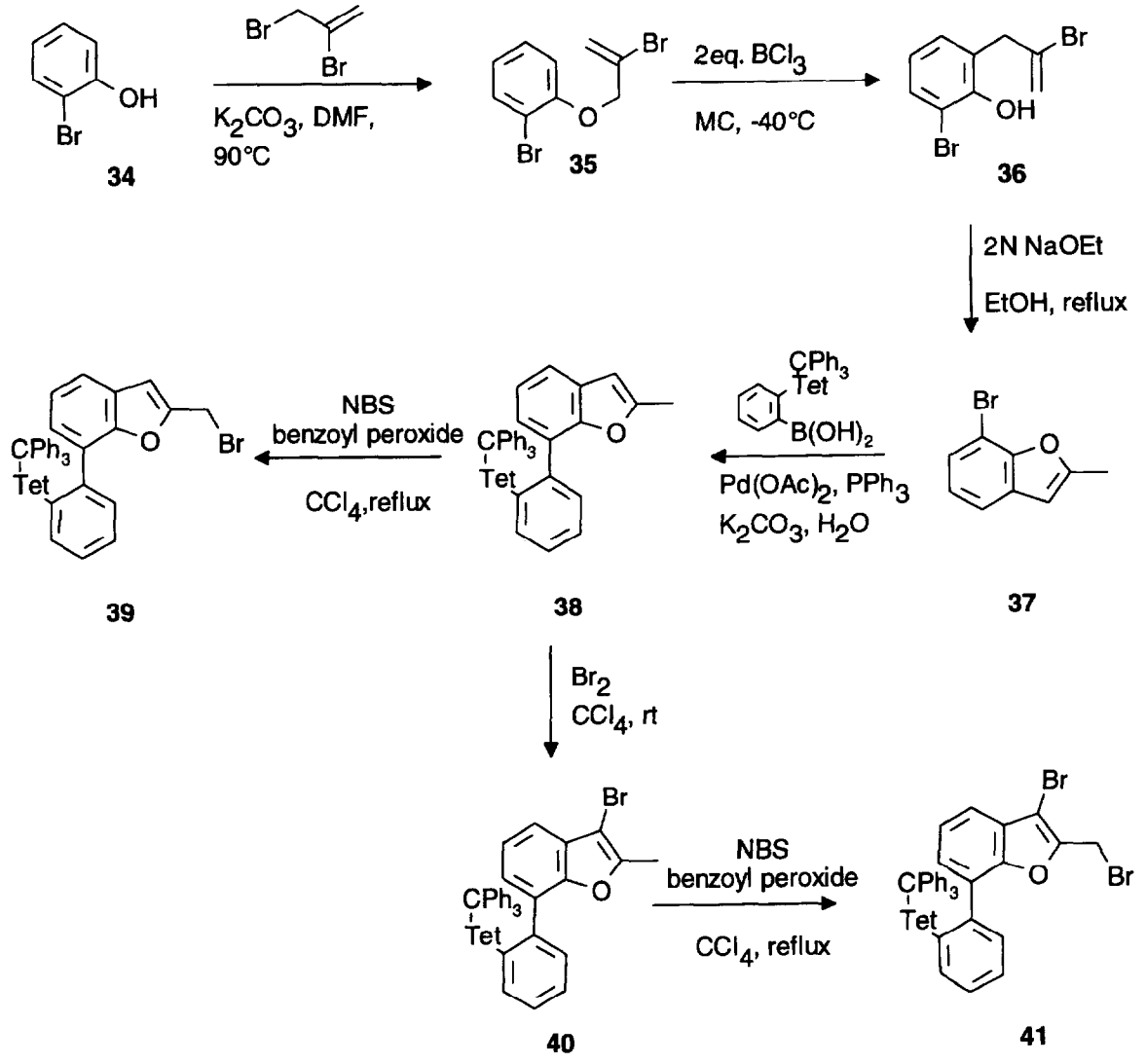
CCl_4. After stirring for 24 h, the solid was collected to give the desired product (0.22 g, 63%).

5-[2-(3-Bromo-2-bromomethylbenzofuran-5-yl)phenyl]-1-trityl-1*H*-tetrazole (9). The reaction mixture of **8** (0.22 g, 0.5 mmol), of triphenylmethyl chloride (0.2 g, 0.6 mmol) and triethylamine (0.08 mL, 0.6 mmol) in 5 mL of THF was stirred for 30 min. The solid was filtered off and the filtrate was concentrated and the residue was purified by column chromatography (silica gel, *n*-hexane:EtOAc 9.5:0.5) to obtain the desired product **9** (0.23 g, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.66 (2H, s), 6.83–6.86 (6H, m), 7.04 (1H, dd), 7.07–7.52 (14H, m), 7.99–8.02 (1H, m).

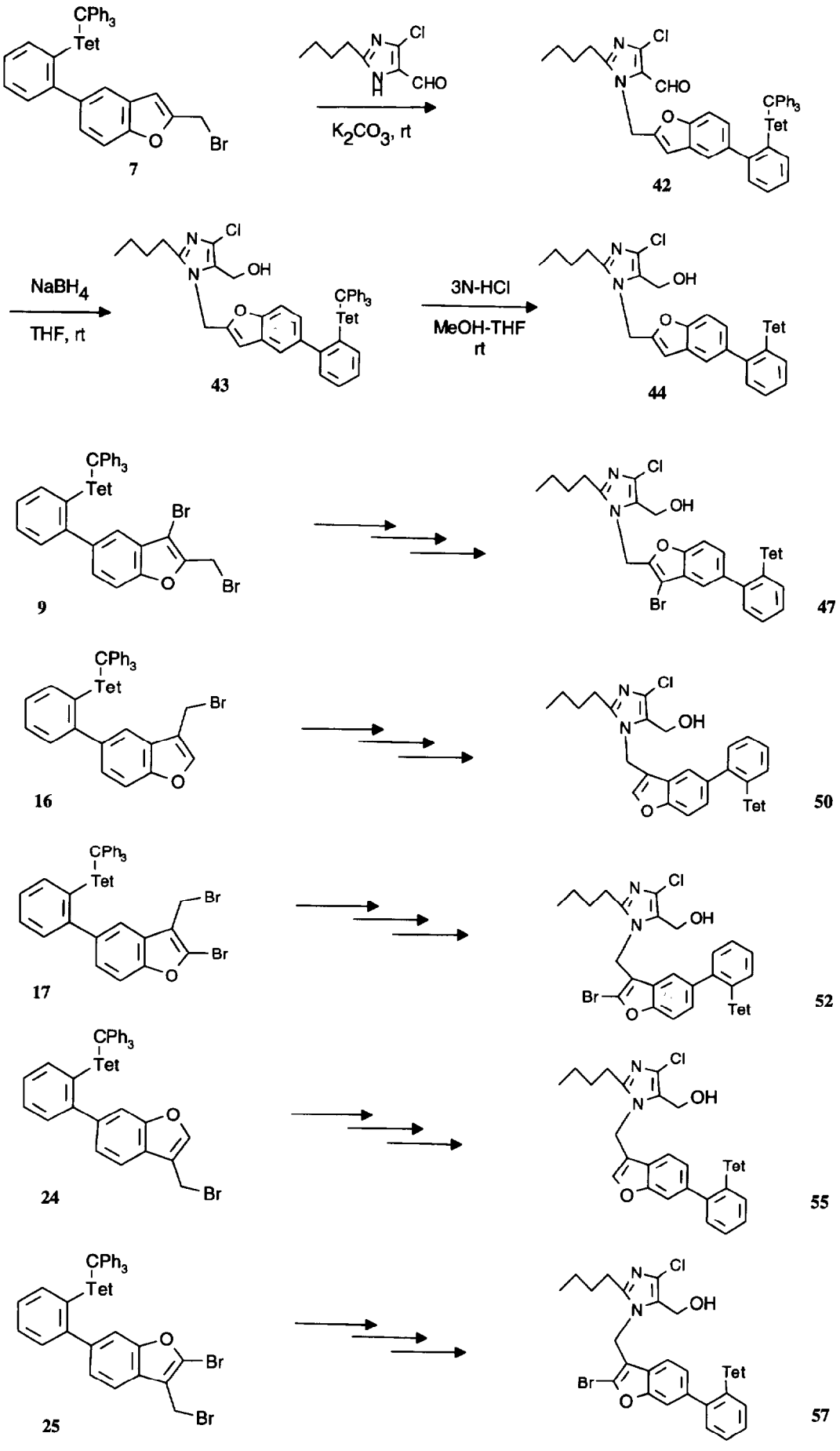
1-(5-Bromo-2-hydroxyphenyl)ethanone (11). The mixture of 4-bromoanisole (2 g, 10.7 mmol), aluminum chloride (4.2 g, 32 mmol) and acetyl chloride (0.9 ml, 12.8 mmol) in 30 mL of CS_2 was refluxed for 2.5 h. The reaction was quenched with ice and 6 N HCl solution, the reaction mixture was extracted with ethyl acetate and the organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give **11** (1 g, 43%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.30 (3H, s), 6.83–6.88 (1H, d), 7.50–7.58 (1H, dd), 7.81 (1H, d), 12.15 (1H, s).

(2-Acetyl-4-bromophenoxy)acetic acid ethyl ester (12).[7] A solution of 11 (4.8 g, 12.6 mmol) in 24 mL of DMF was treated with NaH (0.16 g, 6.7 mmol) and then with bromoethyl acetate (1.1 g, 6.7 mmol) and the reaction mixture was stirred at rt for 4 h. The mixture was diluted with water and then pH of the solution was adjusted to 5 with 1 N HCl soln. The reaction product was extracted with ethyl acetate and the organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (*n*-hexane:EtOAc 9:1) to give **12** (6 g, 87%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22–1.31 (3H, t), 2.67 (3H, s), 4.20–4.31 (2H, q), 4.69 (2H, s), 6.69–6.74 (1H, d), 7.46–7.54 (1H, dd), 7.82 (1H, d).

(2-Acetyl-4-bromophenoxy)acetic acid (13).[7] A mixture of **12** (6 g, 20 mmol) and 1 N NaOH (24 mL) in 60



Scheme 5.

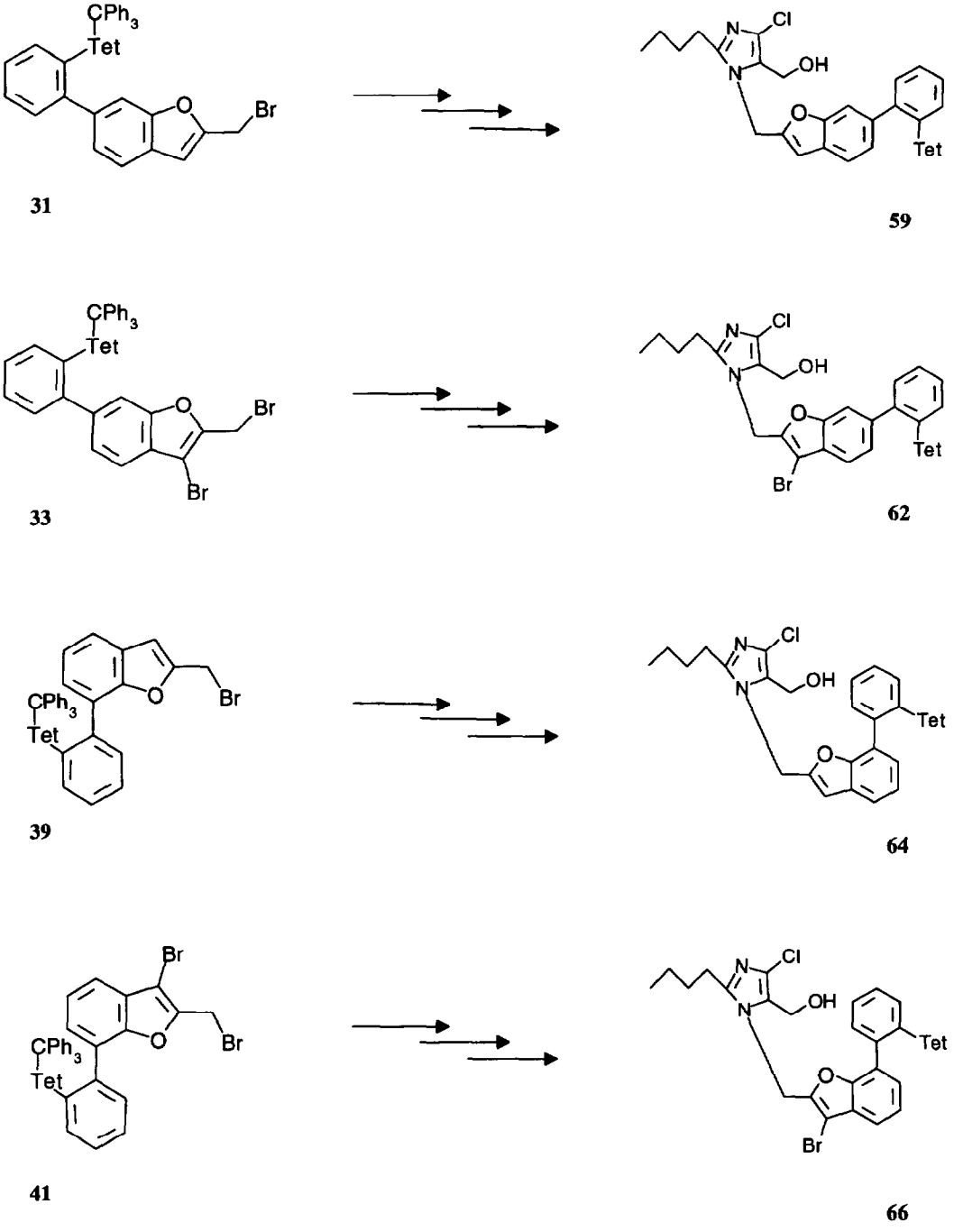

CPh3
Tet
Br
7
Cl
N
N
H
CHO
K2CO3, rt
42
NaBH4
THF, rt
OH
43
3N-HCl
MeOH-THF
rt
44
9
47
16
50
17
52
24
55
25
57

Scheme 6.

mL of THF was stirred for 3.5 h. The solution was adjusted to pH 3 with 1 N HCl and the product was collected by filtration and dried to give **13** (4 g, 73%). ^{1}H NMR ($CDCl_3$+CD_3OD, 200 MHz): δ 2.60 (3H, s), 4.42 (2H, s), 6.78–6.85 (1H, d), 7.40–7.50 (1H, dd), 7.70 (1H, d).

5-Bromo-3-methylbenzofuran (14).[7] A mixture of **13** (4 g, 14.6 mmol) and sodium acetate (2.4 g, 29 mmol) in 70 mL of acetic anhydride was refluxed for 17 h. The mixture was diluted with 30 ml of benzene and neutralized with 6 N NaOH soln. The mixture was then extracted with ethyl ether and the organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane) to give **14** (2.2 g, 71%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20 (3H, s), 7.32 (1H, s), 7.33–7.34 (1H, d), 7.37–7.40 (1H, d), 7.63–7.64 (1H, d).

5-[2-(3-Methylbenzofuran-5-yl)phenyl]-1-trityl-1*H*-tetrazole (15). The product **15** was obtained (1.1 g, 89%) from **14** (0.5 g, 2.3 mmol) as described in the preparation of **5**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (3H, d), 6.79–6.87 (6H, m), 6.95–7.01 (1H, dd), 7.08–7.50 (15H, m), 7.92–8.00 (1H, m).



Scheme 7.

5-[2-(3-Bromomethylbenzofuran-5-yl)phenyl]-1-trityl-1*H*-tetrazole (16). A mixture of 15 (0.8 g, 1.54 mmol) and *N*-bromosuccinimide (0.3 g, 1.7 mmol) in 17 mL of CCl_4 was irradiated with light. The solid was removed and the filtrate was concentrated and purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give **16** (0.4 g, 34%).^{1}H NMR (CDCl3, 300 MHz): δ 4.44 (2H, s), 6.82–6.85 (6H, m), 7.06–7.31 (11H, m), 7.45–7.51 (3H, m), 7.68 (1H, s), 7.99–8.01 (1H, m).

5-[2-(2-Bromo-3-bromomethylbenzofuran-5-yl)phenyl]-1-trityl-1*H*-tetrazole (17). To a solution of **16** (0.13 g, 0.21 mmol) in 2 mL of CCl_4 was added bromine (68.8 mg, 0.43 mmol) dropwise. The solution was stirred at rt for 5 h and the product was collected by filtration to give **17** (0.07 g, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.34 (2H, s), 6.82–6.86 (6H, m), 7.05–7.29 (13H, m), 7.41–7.42 (1H, m), 7.50–7.51 (1H, m), 8.01–8.04 (1H, m).

1-(4-Bromo-2-hydroxyphenyl)ethanone (19). The product **19** was obtained (2 g, 11%) from 3-bromoanisole (1.5 g, 80 mmol) as described in the preparation of **11**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.60 (3H, d), 6.82–6.90 (1H, dd), 7.52–7.60 (1H, dd), 7.80 (1H, d), 12.17 (1H, s).

Ethyl-(2-acetyl-5-bromophenoxy)acetate (20).[7] The product **20** was obtained (2 g, 67%) from **19** (2 g, 9.3 mmol) as described in the preparation of 12. ^{1}H NMR (CDCl3, 200 MHz): δ 1.20–1.30 (3H, t), 2.67 (3H, s), 4.20–4.31 (2H, q), 4.67 (2H, s), 6.68–6.72 (1H, d), 7.46–7.52 (1H, dd), 7.82 (1H, d).

(2-Acetyl-5-bromophenoxy)acetic acid (21).[7] The product **21** was obtained (1.77 g, 97%) from **20** (2 g, 6.64 mmol) as described in the preparation of **13**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.60 (3H, s), 4.78 (2H, s), 7.13–7.18 (2H, m), 7.50–7.56 (1H, d).

6-Bromo-3-methylbenzofuran (22).[7] The product **22** was obtained (1.2 g, 77%) from **21** (2 g, 7.23 mmol) as

Table 1.

Compound	PIC_{50}	*D*1	*D*2	*D*3	*D*4	*D*5
44	4.97	5.98	3.89	7.98	7.84	9.23
47	4.85	5.99	4.02	8.85	8.74	11.11
50	4.43	6.01	8.82	4.48	4.97	3.27
52	3.40	5.98	8.32	4.49	4.90	3.26
55	6.15	5.99	8.67	7.70	8.22	8.23
57	6.10	5.99	8.63	7.79	8.34	8.27
59	4.52	5.99	4.16	8.53	8.43	10.86
62	5.13	5.99	4.22	6.44	6.27	7.21
64	3.36	6.01	7.08	3.66	4.01	3.49
66	4.00	5.99	7.31	3.86	4.32	3.25

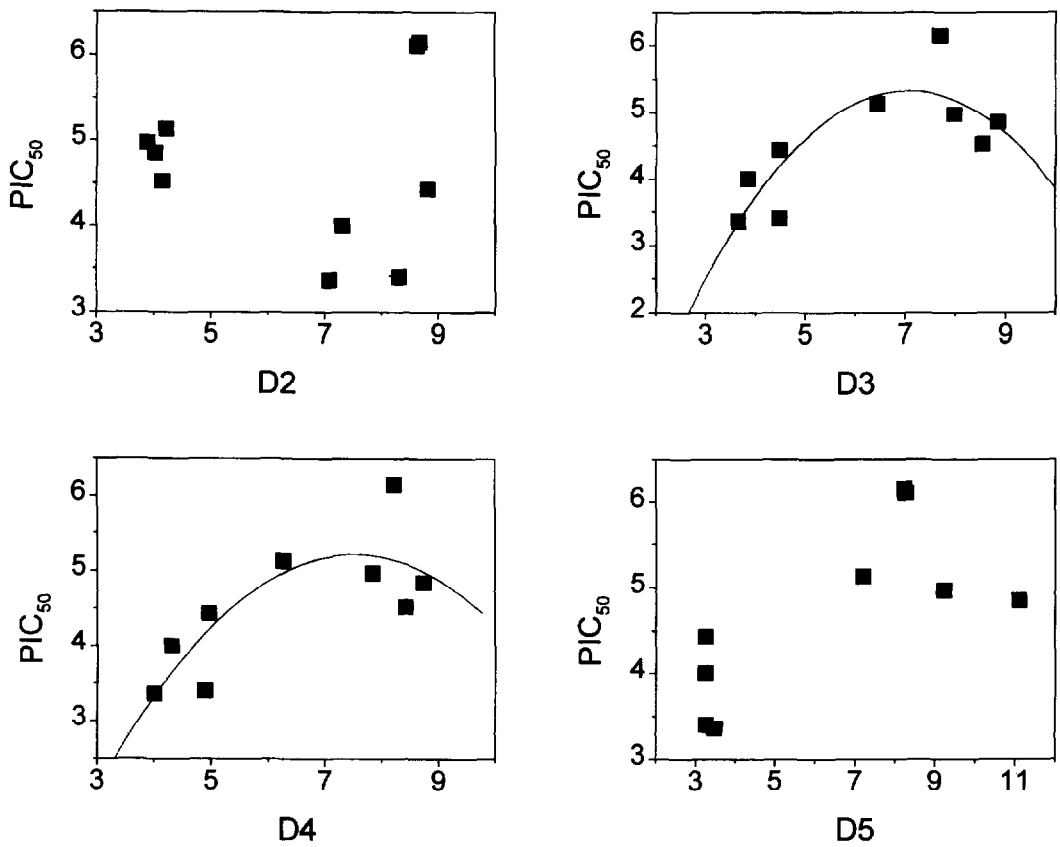
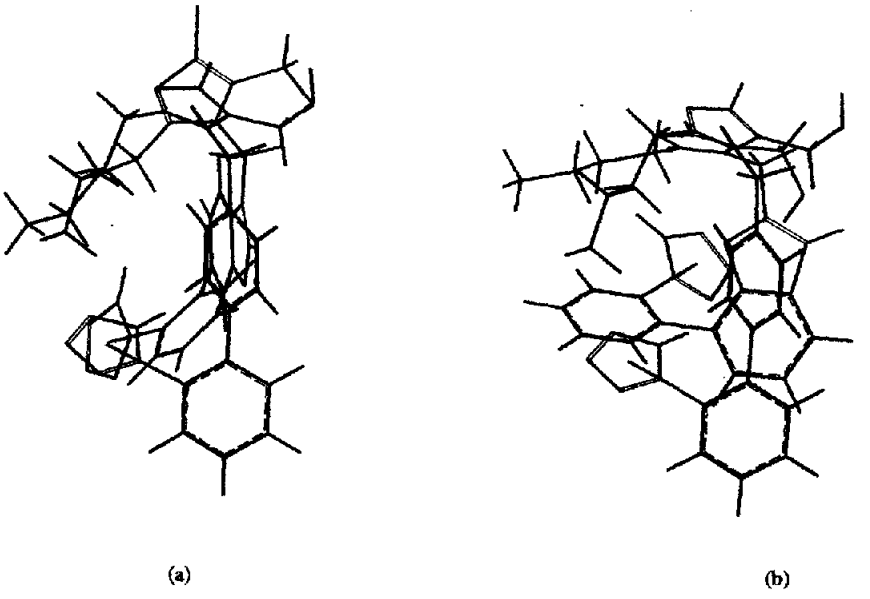


Figure 1. The fitting lines were from polynomial regression ($PIC_{50}=A+B1*X+B2*X^2$). The parameters from each data set were $A=-3.21288$, $B1=2.42189$, $B2=-0.17153$ for *D*3 and $A=-3.44856$, $B1=2.30483$, $B2=-0.15314$ for *D*4. The R^2 values were 0.68956 for *D*3 and 0.64755 for *D*4, respectively.



(a) (b)

Figure 2. (a) Superimposition of the most active compound (**55**, blue) and the DuP753 compound (black); (b) Superimposition of the least active compound (**64**, blue) and the DuP753 compound (black).

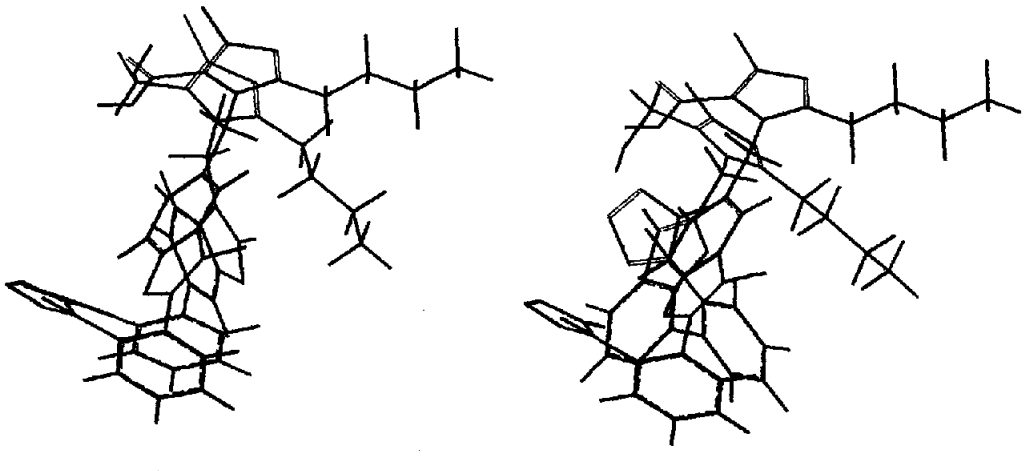
described in the preparation of **14**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.20 (3H, d), 7.35 (3H, d), 7.61 (1H, d).

5-[2-(3-Methylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (23). The product **23** was obtained (0.32 g, 67%) from **22** (0.2 g, 0.94 mmol) as described in the preparation of 15. ^{1}H NMR (CDCl3, 300 MHz): 2.18 (3H, d), 6.80–6.94 (7H, m), 7.10–7.30 (12H, m), 7.38–7.51 (3H, m), 7.90–7.96 (1H, m).

5-[2-(3-Bromomethylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (24). The product **24** was obtained (0.32 g, 32%) from **23** (0.86 g, 0.19 mmol) as described in the preparation of **16**. ^{1}H NMR ($CDCl_3$, 300 MHz) d 4.57 (2H, s), 6.82–6.85 (6H, m), 7.02–7.05 (1H, dd), 7.14–7.31 (11H, m), 7.36–7.50 (3H, m), 7.67 (1H, s), 7.94–7.95 (1H, m).

5-[2-(2-Bromo-3-bromomethylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (25). A mixture of **24** (0.1 g, 0.19 mmol), *N*-bromosuccinimide (51 mg, 0.28 mmol) and benzoyl peroxide (50 mg) in 4 mL of CCl_4 was refluxed for 17 h. The solid was removed by filtration, the filtrate was concentrated and the residue was purified by column chromatography (silica gel, *n*-hexane: EtOAc 9:1) to give **25** (0.09 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.49 (2H, s), 6.82–6.85 (6H, m), 7.05–7.08 (1H, dd), 7.16–7.52 (14H, m), 7.98–8.01 (1H, m).

1-Bromo-3-(2-bromo-allyloxy)-benzene (27). The reaction mixture of 3-bromophenol (10 g, 57 mmol), 2,3-dibromoethene (17.32 g, 86.7 mmol) and K_2CO_3 (15 g) in 100 mL of DMF was heated at 90 °C for 4 h. The reaction mixture was cooled to rt, diluted with 50 mL of water and extracted with ether. The organic



(a) (b)

Figure 3. (a) Superimposition of the most active compound (**55**, blue) and the Glaxo compound (black); (b) Superimposition of the least active compound (**64**, blue) and the Glaxo compound (black).

layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane) to give 27 (16 g, 96%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.60 (2H, s), 5.65 (1H, s), 5.98 (1H, d), 6.80–6.90 (1H, m), 7.04–7.18 (3H, m).

5-Bromo-2-(2-bromo-allyl)-phenol (28). A solution of 27 (10 g, 34 mmol) in 200 ml of CS_2 was cooled to −40 °C and 68 mL of 1 N BCl_3 was added slowly. After the solution was warmed to rt and stirred for 1 h. The reaction was quenched with 6 N HCl solution and the product was extracted with ether. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give **28** (6 g, 60%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.70(2H, s), 5.08 (1H, s), 5.52–5.60 (2H, m), 6.98 (1H, s), 7.05 (2H, d).

6-Bromo-2-methylbenzofuran (29). To a solution of **28** (12.6 g, 43 mmol) in 120 mL of ethanol was added 100 ml of 2 M sodium ethoxide. The mixture was refluxed for 5 h, cooled to rt and concentrated. The residue was diluted with water and extracted with ether. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane) to give **29** (6.5 g, 71%).^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (3H, s), 6.33 (1H, d), 7.30 (2H, d), 7.56 (1H, s).

5-[2-(2-Methylbenzofuran-6-yl)phenyl]-1-trityl-1H-tetrazole (30). The product **30** was obtained (2.18 g, 88%) from 29 (1 g, 2.3 mmol) as described in the preparation of **5**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.44 (1H, d), 6.31 (1H, d), 6.83–6.90 (6H, m), 6.92 (1H, dd), 7.14–7.20 (7H, m), 7.25–7.45 (5H, m), 7.45–7.48 (3H, m), 7.89–7.92 (1H, m).

5-[2-(2-Bromomethylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (31). The reaction mixture of **30** (0.8 g, 1.54 mmol) and *N*-bromosuccinimide (0.3 g, 1.69 mmol) in 16 mL of CCl_4 was irradiated with light for 2.5 h. The solid was removed by filtration, the filtrate was concentrated and the residue was purified by column chromatography (silica gel, *n*-hexane:EtOAc 9:1) to give **31** (1.1 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.60 (2H, d), 6.70 (1H, d), 6.82–6.98 6H. m), 7.15 (12H, m), 7.40–7.55 (3H, m), 7.92–8.00 (1H, m).

5-[2-(3-Bromo-2-methylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (32). The product **32** was obtained (0.62 g, 74%) from **30** (0.73 g, 1.4 mmol) as described in the preparation of 8. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.44 (3H, s), 6.82–6.85 (6H, m), 6.99 (1H, dd), 7.10–7.42 (11H, m), 7.45–7.47 (3H, m), 7.95–7.98 (1H, m).

5-[2-(3-Bromo-2-bromomethylbenzofuran-6-yl)phenyl]-1-trityl-1*H*-tetrazole (33). The product **33** was obtained (1 g, 95%) from **32** (0.93 g, 1.55 mmol) as described in the preparation of 31.^{1}H NMR ($CDCl_3$, 300 MHz); δ 4.63 (2H, s), 6.82–6.85 (6H, m), 6.99 (1H, dd), 7.09–7.32 (11H, m), 7.40 (1H, m), 7.48–7.50 (2H, m), 7.99–8.02 (1H, m).

1-Bromo-2-(2-bromoallyloxy)benzene (35). The product **35** was obtained (9.6 g, 96%) from 2-bromophenol (5 g, 28.9 mmol) as described in the preparation of 27.^{1}H NMR (CDCl3, 200 MHz): δ 4.68 (2H, t), 5.80 (1H, q), 6.12 (1H, q), 6.82–6.90 (2H, m), 7.20–7.30 (1H, m), 7.51–7.58 (1H, dd).

2-Bromo-6-(2-bromoallyl)phenol (36). The product **36** was obtained (2.1 g, 21%) from **35** (9.6 g, 32.8 mmol) as described in the preparation of 28. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81 (2H, s), 5.51–5.52 (1H, q), 5.56–5.57 (1H, q), 5.62 (1H, d), 6.77–6.82 (1H, t), 7.13–7.16 (1H, dd), 7.37–7.41 (1H, dd).

7-Bromo-2-methylbenzofuran (37). The product **37** was obtained (0.66 g, 69%) from **36** (1.3 g, 4.467 mmol) as described in the preparation of 29. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.50 (3H, d), 6.43–6.44 (1H, q), 7.02–7.07 (1H, t), 7.36–7.38 (1H, dd), 7.40–7.41 (1H, dd).

5-[2-(2-Methylbenzofuran-7-yl)phenyl]-1-trityl-1*H*-tetrazole (38). The product **38** was obtained (0.66 g, 69%) from **37** (1 g, 4.73 mmol) as described in the preparation of **5**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.20 (3H, s), 6.22 (1H, s), 6.75–6.80 (6H, m), 7.15–7.45 (12H, m), 7.54–7.60 (3H, m), 8.10–8.18 (1H, m).

5-[2-(2-Bromomethylbenzofuran-7-yl)phenyl]-1-trityl-1*H*-tetrazole (39). The product **39** was obtained (0.6 g, 34%) from **38** (1.5 g, 2.89 mmol) as described in the preparation of **38**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27 (2H, s), 6.59 (1H, s), 6.75–6.79 (6H, m), 7.11–7.30 (11H, m), 7.40–7.43 (1H, m), 7.52–7.55 (3H, m), 8.12–8.14 (1H, m).

5-[2-(3-Bromo-2-methylbenzofuran-7-yl)phenyl]-1-trityl-1*H*-tetrazole (40). The product **40** was obtained (0.31 g, 53%) from **38** (0.5 g, 0.96 mmol) as described in the preparation of **32**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.12 (3H, s), 6.72–6.75 (6H, m), 7.07–7.28 (12H, m), 7.45–7.47 (3H, m), 8.09–8.12 (1H, m).

5-[2-(3-Bromo-2-bromomethylbenzofuran-7-yl)phenyl]-1-trityl-1*H*-tetrazole (41). The product **41** was obtained (0.11 g, 88%) from **40** (0.11 g, 0.18 mmol) as described in the preparation of **33**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.32 (2H, s), 6.74–6.77 (6H, m), 7.16–7.34 (12H, m), 7.45–7.50 (1H, m), 7.55–7.58 (2H, m), 8.17–8.19 (1H, m).

2-Butyl-5-chloro-3-{5-[2-(1-trityl-1*H*-tetrazol-5-yl)-phenyl]-benzofuran-2-ylmethyl}-3*H*-imidazole-4-carbaldehyde (42). The reaction mixture of 7 (0.3 g, 0.5 mmol), 2-*n*-butyl-4-chloro-1*H*-imidazol-5-carboxaldehyde (0.08 g, 0.45 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in 6 ml of DMF was refluxed for 3 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (anhyd

$MgSO_4$), concentrated and purified by column chromatography (silica gel, *n*-hexane:EtOAc 7:3) to give **42** (0.26 g, 73%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95 (3H, t), 1.47 (2H, m), 1.85 (2H, m), 2.90 (2H, t), 5.61 (2H, s), 6.60 (1H, s), 6.80 (6H, d), 6.95–7.50 (15H, m), 7.93 (1H, m), 9.70 (1H, s).

{2-Butyl-5-chloro-3-{5-[2-(1-trityl-1*H*-tetrazol-5-yl)-phenyl]benzofuran-2-ylmethyl}3*H*-imidazole-4-yl}-methanol (43). The solution of **42** (0.20 g, 0.28 mmol) in THF (8 mL) was treated with sodium borohydride (0.02 g, 0.56 mmol) for 1 h at rt. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography to give **43** (0.15 g, 75%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93 (3H, t), 1.40 (2H, m), 1.80 (2H, m), 2.85 (2H, t), 4.60 (2H, s), 5.57 (2H, s), 6.58 (1H, s), 6.80–7.90 (22H, m).

{2-Butyl-5-chloro-3-{5-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-2-ylmethyl}-3*H*-imidazole-4-yl}methanol (44). The reaction mixture of **43** (0.13 g, 0.18 mmol) in methanol and THF was treated with 3 N HCl for 17 h. The solution was diluted with water and the pH for the solution was adjusted to 3–4 with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried (anhyd $MgSO_4$), concentrated and purified by column chromatography to give the final compound **44** (0.07 g, 86%). ^{1}H NMR ($CDCl_3$:CD_3OD 9:1, 200 MHz): δ 0.85 (3H, t), 1.32 (2H, m), 1.60 (2H, m), 2.62 (2H, t), 4.55 (2H, s), 5.25 (2H, s), 6.44 (1H, s), 6.95 (1H, dd), 7.20–7.60 (5H, m), 7.70 (1H, d). (CD_3OD, 500 MHz): δ 14.09, 23.31, 27.27, 42.38, 53.07, 106.25, 111.98, 122.97, 125.25, 126.68, 127.18, 127.44, 128.75, 129.51, 131.60, 132.17, 136.27, 150.16, 154.41, 155.95, 157.43. FABMS(Ar):463(M^+).

{3-{3-Bromo-5-[2-(1*H*-tetrazol-5-yl)phenyl]benzofuran-2-ylmethyl}-2-butyl-5-chloro-3*H*-imidazol-4-yl}-methanol (47). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **47** was obtained in 35% overall yield from 9. ^{1}H NMR (CD_3OD, 300 MHz): δ 0.85–0.90 (3H, t), 1.31–1.39 (2H, m), 1.54–1.61 (2H, m), 2.73–2.79 (2H, t), 4.66 (2H, s), 5.51 (2H, s), 7.10–7.14 (1H, dd), 7.28 (1H, d), 7.39–7.42 (1H, dd), 7.57–7.61 (2H, m), 7.66–7.71 (2H, m). ^{13}C NMR (CD_3OD, 500 MHz): δ 14.10, 23.37, 27.47, 30.99, 40.76, 53.11, 97.60, 112.70, 121.39, 126.88, 127.50, 128.74, 128.93, 129.18, 131.66, 132.20, 132.56, 140.32, 142.93, 150.27, 150.46, 154.81, 156.83. FABMS(Ar):543(M+2).

{2-Butyl-5-chloro-3-{5-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-3-ylmethyl}-3*H*-imidazol-4-yl}methanol (50). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **50** was obtained in 35% overall yield from 16. ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ 0.82–0.87 (3H, t), 1.27–1.34 (2H, m), 1.56–1.61 (2H, m), 2.61–2.66 (2H, t), 4.51 (2H, s), 5.32 (2H, s), 7.02–7.05 (1H, d), 7.24 (1H, s), 7.36-7.39 (1H, d), 7.42 (1H, s), 7.51–7.53 (2H, m), 7.60–7.62 (1H, d), 7.65–7.68 (1H, d). ^{13}C NMR ($CDCl_3$+CD_3OD, 500 MHz): δ 14.01, 23.24, 27.41, 30.99, 40.08, 53.07, 112.29, 118.39, 121.07, 126.54, 126.81, 127.35, 127.53, 128.66, 131.64, 132.06, 136.58, 143.47, 144.71, 149.98, 156.35. FABMS(Ar): 463(M^+).

{3-{2-Bromo-5-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-3-ylmethyl}-2-butyl-5-chloro-3*H*-imidazol-4-yl}-methanol (52). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **52** was obtained in 62% overall yield from **17**. ^{1}H NMR (CD_3OD, 300 MHz): δ 0.78–0.85(3H, t), 1.22–1.32 (2H, m), 1.44–1.52 (2H, m), 2.55–2.60 (2H, t), 4.50 (2H, s), 5.33 (2H, s), 6.91–6.96 (2H, m), 7.29–7.32 (1H, d), 7.35–7.38 (1H, dd), 7.46–7.62 (3H,m). ^{13}C NMR (CD_3OD, 500 MHz): δ 14.00, 23.25, 27.70, 30.85, 40.75, 53.20, 111.30, 115.94, 120.26, 127.27, 127.60, 127.90, 128.40, 129.97, 130.49, 131.63, 138.41, 142.85, 150.38, 155.86.

{2-Butyl-5-chloro-3-{6-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-3-ylmethyl}-3*H*-imidazol-4-yl}methanol (55). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **55** was obtained in 43% overall yield from **24**. ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ 0.85–0.89 (3H, t), 1.27–1.326 (2H, m), 1.56–1.64 (2H, m), 2.63–2.68 (2H, t), 4.53 (2H, s), 5.34 (2H, s), 6.99–7.03 (1H, dd), 7.26–7.35 (3H, m), 7.50–7.66 (4H, m). ^{13}C NMR ($CDCl_3$+CD_3OD, 500 MHz): δ 14.29, 23.22, 27.39, 30.85, 52.96, 113.37, 118.36, 120.41, 125.63, 126.49, 127.03, 128.92, 131.88, 132.15, 138.46, 142.97, 144.87, 149.67, 156.62, 158.09. FABMS(Ar):463(M^+).

{3-{2-Bromo-6-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-3-ylmethyl}-2-butyl-5-chloro-3*H*-imidazol-4-yl}-methanol (57). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **57** was obtained in 54% overall yield from **25**. ^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ 0.79–0.84 (3H, t), 1.23–1.30 (2H, m), 1.46–1.49 (2H, m), 2.55–2.60 (2H, t), 4.54 (2H, s), 5.33 (2H, s), 6.90–6.93 (1H, d), 6.97 (1H, dd), 7.18–7.19 (1H, s), 7.44–7.54 (4H, m). ^{13}C NMR (CD_3OD+DMSO-d_6, 500 MHz): δ 14.12, 23.30, 28.00, 30.79, 40.19, 53.08, 109.97, 112.79, 115.76, 119.08, 126.54, 127.33, 128.44, 130.13, 131.32, 131.57, 131.93, 140.15, 142.41, 150.17, 156.40, 162.48. FABMS(Ar):543(M+2).

{2-Butyl-5-chloro-3-{6-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-2-ylmethyl}-3*H*-imidazol-4-yl}-methanol (59). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **59** was obtained in 45% overall yield from **31**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90–0.94 (3H, t), 1.35–1.43 2H, m), 1.61–1.69 (2H, m), 2.73–2.79 (2H, t), 4.62 (2H, s), 5.39(2H, s), 6.64 (1H, d), 6.94–6.97 (1H, dd), 7.25 (1H, s), 7.38–7.41 (1H, d), 7.45–7.63 (4H, m). ^{13}C NMR (CD_3OD + DMSO-d_6, 500 MHz): δ 14.36, 23.30, 27.00, 30.85, 42.00, 52.96, 106.15, 112.94, 121.93, 125.86, 126.91, 127.09, 127.94, 128.28, 128.68,

131.36, 131.88, 131.99, 138.63, 143.05, 149.87, 154.36, 156.17. FABMS(Ar): 463(M^+).

{3-{3-Bromo-6-[2-(1*H*-tetrazol-5-yl)phenyl]benzofuran-2-ylmethyl}-2-butyl-5-chloro-3*H*-imidazol-4-yl}methanol (62). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **62** was obtained in 15% overall yield from **33**. ^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ 0.85–0.90 (3H, t), 1.33–1.40 (2H, m), 1.54–1.62 (2H, m), 2.75–2.80 (2H, t), 4.66 (2H, s), 5.53 (2H, s), 7.01–7.05 (1H, dd), 7.37 (1H, d), 7.37–7.45 (1H, d), 7.56–7.61 (2H, m), 7.66-7.73 (2H, m). ^{13}C NMR (CD_3OD + DMSO-d_6, 500 MHz): δ 14.43, 23.35, 27.43, 30.86, 40.73, 53.00, 97.46, 113.63, 120.65, 124.99, 126.62, 127.14, 127.98, 129.41, 131.85, 132.32, 132.50, 139.48, 142.59, 149.93, 150.66, 154.98. FABMS(Ar): 543(M+2).

{2-Butyl-5-chloro-3{7-[2-(1*H*-tetrazol-5-yl)phenyl]-benzofuran-2-ylmethyl}-3*H*-imidazol-4-yl}methanol (64). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **64** was obtained in 58% overall yield from **39**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.76–0.81 (3H, t), 1.20–1.27 (2H, m), 1.48–1.53 (2H, m), 2.55–2.60 (2H, t), 4.34 (2H, s), 5.19 (2H, s), 6.70 (1H, s), 6.98–7.01 (1H, d), 7.17–7.22 (1H, t), 7.54–7.56 (1H, d), 7.65–7.70 (3H, m), 7.80 (1H, d). ^{13}C NMR (CD_3OD, 500 MHz): δ 13.88, 23.22, 26.10, 29.62, 43.19, 52.45, 108.42, 123.00, 124.82, 125.35, 125.58, 127.80, 128.95, 129.66, 129.88, 131.23, 132.64, 137.45, 150.17, 150.68, 153.44, 156.82. FABMS(Ar): 463(M^+).

{3-{3-Bromo-7-[2-(1*H*-tetrazol-5-yl)phenyl]benzofuran-2-ylmethyl}-2-butyl-5-chloro-3*H*-imidazol-4-yl}methanol (66). Following the same reaction condition as described in the preparation of **42**, **43** and **44**, the final compound **66** was obtained in 24% overall yield from **41**. ^{1}H NMR (CD_3OD+DMSO-d_6, 300 MHz): δ 0.80–0.85 (3H, t), 1.25–1.32 (2H, m), 1.51–1.56 (2H, m), 2.64–2.69 (2H, t), 4.54 (2H, s), 5.33 (2H, s), 7.17–7.20 (1H, dd), 7.33–7.38 (1H, t), 7.51–7.54 (1H, dd), 7.62–7.71 (3H, m), 7.83-7.86 (1H, dd). ^{13}C NMR (CD_3OD, 500 MHz): δ 14.08, 23.36, 27.30, 32.75, 40.58, 52.97, 97.98, 120.99, 125.41, 125.57, 128.62, 128.87, 129.29, 130.05, 131.37, 132.44, 132.78, 136.59, 149.31, 152.45. FABMS(Ar): 543(M+2).

Bioassays

Binding assays were quadruplicated and performed in 96-well plates by incubating aliquots of the human recombinant angiotensin II receptor subtype (BioSignal Inc., Canada) with 0.85 nM ^{125}I-[Sar1, Ile8]-angiotensin II. Test compounds were dissolved at 2.5 mM in DMSO and serially diluted to 10 concentrations for the activity screening in a final volume of 0.25 mL assay buffer, containing 50 mM Trizma base, 5 mM $MgCl_2$, 1 mM EDTA, and 0.1% bovine serum albumin (pH 7.4). Nonspecific binding was determined by the addtion of unlabeled 10 μM angiotensin II.

After incubation at 37 °C for 120 min, the incubation mixtures were filtered through glass-fiber GF/C filters (presoaked in 0.3% polyethylenimine) and rapidly washed nine times with 200 mL of ice-cold 50 mM Tris-HCl, pH 7.4 at 4 °C. The radioactivity trapped on the filters was counted with the plate-counter (Wallac, Finland).

Binding isotherms from competition studies were obtained using the nonlinear regression program PRISM (GraphPad Software Inc., San Diego, California). The inhibitory constant (K_i) was calculated from the IC_{50} using the equation of Cheng and Prusoff.

Conformation analysis

All molecular modeling and computational analysis was carried out on Silicon Graphics INDY R4000 with SYBYL (version 6.0, Tripos, Inc.). Initial structures were generated by the BUILD option and the systematic conformation study was carried out with the GRID option by rotating the corresponding torsion angles stepwise from 0 to 360° and the charges were calculated by the Gasteiger–Marsili method.

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