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Synthesis and Structure–Activity Relationship for New Series of 4-Phenoxyquinoline Derivatives as Specific Inhibitors of Platelet-Derived Growth Factor Receptor Tyrosine Kinase

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Abstract—We discovered a new series of 4-phenoxyquinoline derivatives as potent and selective inhibitors of the platelet-derived growth factor receptor (PDGFr) tyrosine kinase. We researched the highly potent and selective inhibitors on the basis of both PDGFr and epidermal growth factor receptor (EGFr) inhibitory activity. First, we found a compound, Ki6783 (**1**), which inhibited PDGFr autophosphorylation at 0.13 μM, but it did not inhibit EGFr autophosphorylation at 100 μM. After extensive explorations, we found the two desired compounds, Ki6896 (**2**) and Ki6945 (**3**), which are substituted by benzoyl and benzamide at the 4-position of the phenoxy group on 4-phenoxyquinoline, respectively. These inhibitory activities were 0.31 and 0.050 μM, respectively, but neither of them inhibited EGFr autophosphorylation at 100 μM. We further investigated the profile of both compounds toward various tyrosine and serine/threonine kinases. The three compounds specifically inhibited PDGFr rather than the other kinases.

Introduction

It has been elucidated that the intracellular signaling pathway of biological events, such as cell growth, differentiation and migration, are modulated by a variety of transmembrane growth factor receptors and their cytoplasmic protein tyrosine kinases. It has also been clarified that abnormal signaling via tyrosine kinases causes a number of diseases.[1]

PDGF receptors have transmembrane protein tyrosine kinase domains, and participate in various physiological processes like wound healing.[2] An abnormal signal transduction of PDGFr is known to play a central role in the etiology of certain adverse pathophysiological situations, such as cancer, atherosclerosis, restenosis, pulmonary fibrosis, glomerulonephritis, and rheumatoid arthritis.[3] Therefore, PDGFr tyrosine kinase inhibitors are believed to be useful for the treatment of many kinds of diseases. Because kinases play many important roles as already described, specific inhibitor toward a target kinase would be good for medicine. In general, it seemed difficult to obtain specific inhibitors for respective tyrosine kinases, because the three-dimensional structure of kinase domain is highly conserved.[4] In fact, the first generation of synthetic tyrosine kinase inhibitors, known as tyrphostins, gave wide inhibitory activities against various receptor kinases.[5] However, a potent and highly selective inhibitor of EGFr tyrosine kinase was reported in 1994,[6] many specific inhibitors of EGFr, PDGFr, and so on have subsequently emerged.[7]

Until now, 3-substituted quinolines,[8] 3-substituted quinoxalines,[9] 2-phenylaminopyrimidines,[10] 3-substituted indolinones[11] and piperazinyl quinazolines[12] were reported as small molecule PDGFr inhibitors. Recently, a novel series of 4-phenoxyquinoline derivatives was found in the screening with in-house compounds (Fig. 1).[13,14] In this report, we present the synthesis and structure–activity relationships of 4-phenoxyquinoline derivatives toward PDGFr and EGFr. We also report the inhibitory effects of the selected compounds against several kinases in order to determine the kinase selectivity.

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Synthesis

The general synthetic route of the 4-phenoxyquinoline derivatives was summarized in Scheme 1. 4-Chloro-6,7-dimethoxyquinoline (**7**) synthesized from 3,4-dimethoxyaniline (**4**) was reacted with various substituted phenols at 150–190 °C to give 4-phenoxyquinoline derivatives (**8**) in isolated yields of 5–100%. Most of the acylphenols (**11**) were prepared by two methods as shown in Scheme 2. One was the Friedel–Clafts acylation using lanthanide triflate as the catalyst (method A).[15] The reaction of anisole (**9**) with various acid chlorides using a catalytic amount of $Yb(OTf)_3$ or $Sc(OTf)_3$ at 60 °C in nitromethane gave 4-acylated anisoles (**10**) in good yields. Removal of the methyl group of **4** with NaSMe in refluxing DMF or with BBr3 in ice-cooled CH_2Cl_2 gave **11** in excellent yields. Another method was the cross coupling reaction of arylstannane with acyl chlorides in the presence of palladium catalyst (method B).[16] Protection of bromophenol (**12**) with the methoxymethyl (MOM) group in ether obtained **13**. This was followed by the addition of magnesium ribbon and a catalytic amount of iodine as an initiator in THF under reflux that gave the corresponding Grignard reagent in situ. The addition of $^{n}Bu_3SnCl$ to the Grignard reagent then produced arylstannane **14**. **14** was coupled with acid chlorides by using $Pd(PPh_3)_2Cl_2$ as a catalyst in $CHCl_3$ under reflux. Subsequent acid treatment gave the corresponding **11** in 36–74% yields. Finally, **11** was reacted with **7** at the same method as described above to give the desired **8**. **11** was also coupling with **7** using 4-dimethylaminopyridine in xylene under reflux to give **8** in isolated yields of 31–77%. 4-Dimethylaminopyridine was the most effective base that we used to accelerate the coupling reaction. The amide substituted 4-phenoxyquinoline derivatives (**17**) were synthesized as shown in

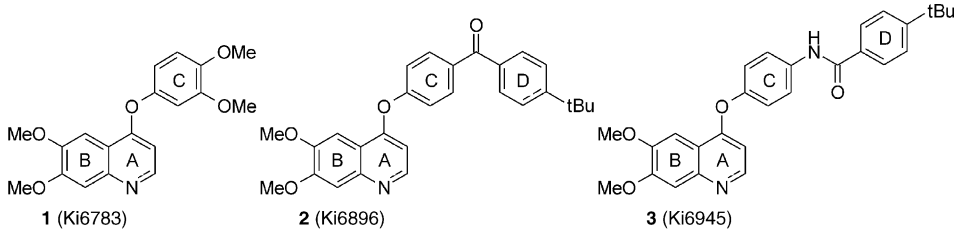
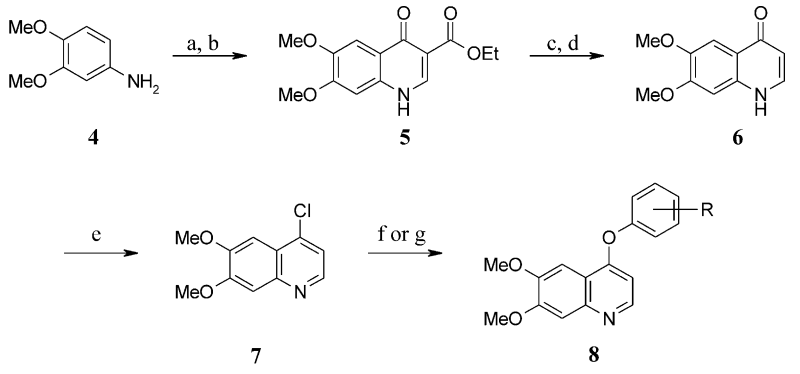
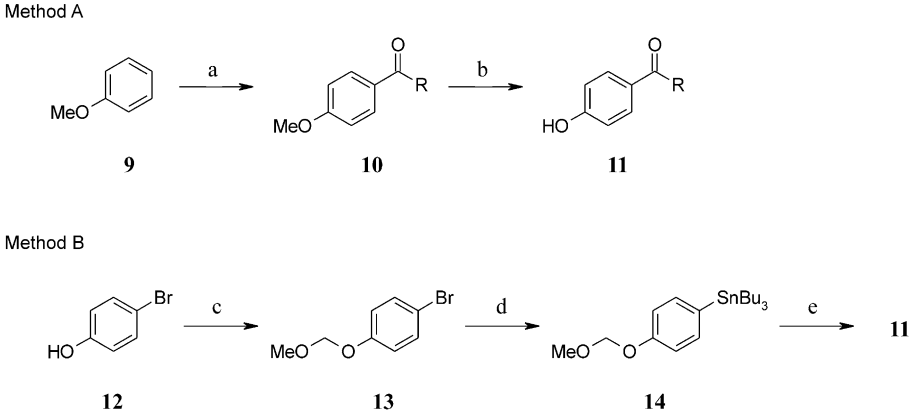


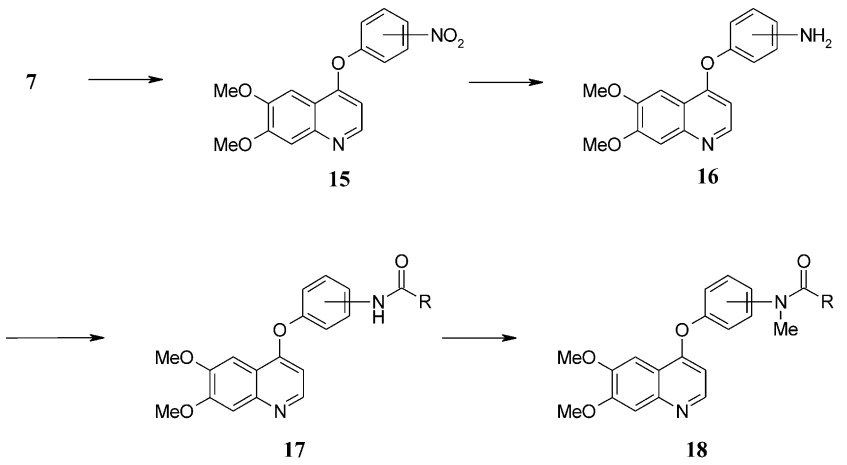
Figure 1. Representative structures of 4-phenoxyquinoline derivatives. A, B, C and D represents, the names of the ring system in this report.



Scheme 1. Synthesis of 4-phenoxyquinoline derivatives. Reagents and conditions: (a) diethyl ethoxymethylenemalonate, 120 °C; (b) diphenylether, 280 °C; (c) 10% aq NaOH/MeOH, reflux; (d) diphenylether, 280 °C; (e) $POCl_3$, reflux; (f) 150–190 °C; (g) DMAP, xylene, reflux.

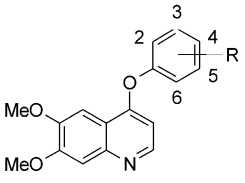


Scheme 2. Synthesis of 4-acylphenols. Reagents and conditions: (a) RCOCl, cat. $Yb(OTf)_3$ or $Sc(OTf)_3$, $MeNO_2$, 60 °C; (b) NaSMe, DMF, reflux; (c) BBr_3, THF, $CHCl_3$, 0 °C; (c) methoxymethylchloride, NaH, DMF, 0 °C; (d) (1) Mg, cat. I_2, THF, reflux to rt; (2) $^{n}Bu_3SnCl$, THF, rt; (e) RCOCl, cat. $PdCl_2$ $(PPh_3)_2$, $CHCl_3$, reflux.



Scheme 3. Synthesis of amide group substituted 4-phenoxyquinoline derivatives. Reagents and conditions: (a) nitrophenol, ethyleneglycol dimethylether, 180 °C; (b) palladium hydroxide on carbon, H_2, Et_3N, DMF, rt; (c) RCOCl, Et_3N, CH_2Cl_2, rt; (d) RCOOH, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, DMF, rt; (e) MeI, NaH, DMF, 0 °C.

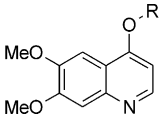
Table 1. Inhibitory activity of 4-phenoxyquinoline derivatives for PDGFr and EGFr

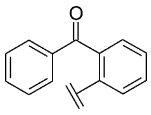
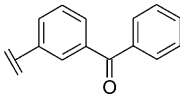
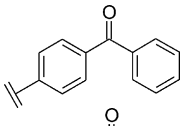
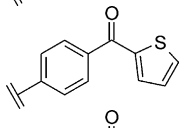
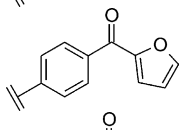
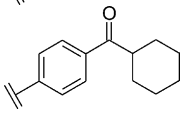


No.	R	IC_{50}[a] (μM)	
		PDGFr	EGFr
8a	H	0.76	50
8b	2-OMe	0.60	92
8c	3-OMe	0.44	18
8d	4-OMe	1.9	44
8e	3-COMe	0.56	>100
8f	4-COMe	15	>100
8g	3-COOMe	15	>100
15b	3-NO_2	0.70	35
8h	3-Me	6.9	14
8i	3-OH	0.56	19
8j	4-OH	0.048	16
8k	3-F	1.5	24
8l	3-Br	8.4	2.5
8m	4-Br	0.20	20
16a	2-NH_2	7.7	<10
16b	3-NH_2	1.7	40
16c	4-NH_2	0.20	>100
8n	2,3-$(OMe)_2$	4.4	>100
8o	2,6-$(OMe)_2$	69	81
1	3,4-$(OMe)_2$	0.13	>100
8p	3,5-$(OMe)_2$	5.5	49

[a]IC_{50} values were averaged values determined by at least two independent experiments.

Table 2. Inhibitory activity of acyl substituted 4-phenoxyquinoline derivatives for PDGFr and EGFr

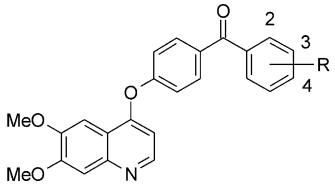


No.	R	IC_{50}[a] (μM)	
		PDGFr	EGFr
8q		48	14
8r		37	89
8s		7.1	50
8t		1.5	16
8u		0.48	>100
8v		40	>100

[a]IC_{50} values were averaged values determined by at least two independent experiments.

Scheme 3. **7** was added to nitrophenols in diethyleneglycol dimethyl ether at 180 °C to give the 4-nitrophenoxyquinoline (**15**). **15** was reduced by palladium hydroxide on carbon under hydrogen and triethylamine in DMF at room temperature to produce aminophenoxyquinoline **16**. The desired quinoline **17** was obtained in good yields by condensation of the amine **16** with various benzoic acids or benzoyl chlorides in the usual manner. The amide **18** was prepared by *N*-methylation of **17**. Amide **19** was prepared by a condensation reaction between the corresponding carboxylic acid and 4-*tert*-butylaniline.[9]

Table 3. Inhibitory activity of benzoyl substituted 4-phenoxyquinoline derivatives for PDGFr and EGFr



No.	R	IC_{50}[a] (μM)	
		PDGFr	EGFr
8s	H	7.1	50
8w	2-Me	4.3	43
8x	3-Me	2.6	95
8y	4-Me	1.7	> 100
8z	2-CF_3	7.2	21
8aa	3-CF_3	3.9	> 100
8ab	4-CF_3	0.85	> 100
8ac	3-F	2.5	28
8ad	4-F	6.9	75
8ae	4-Cl	3.9	> 100
8af	3,4-Cl_2	3.5	31
8ag	4-Br	2.4	> 100
8ah	4-I	0.77	> 100
8ai	4-NO_2	0.89	> 100
8aj	4-OCF_3	1.0	> 100
8ak	4-CN	4.2	> 100
8al	4-nBu	0.15	> 100
2	4-tBu	0.31	> 100
8am	4-Ph	0.90	> 100

[a]IC_{50} values were averaged values determined by at least two independent experiments.

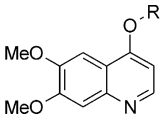
Results and Discussion

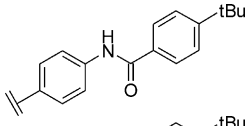
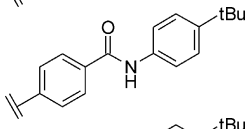
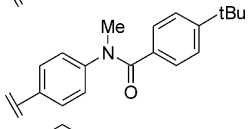
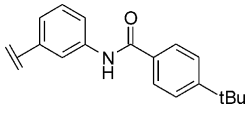
The inhibitory activity of the 4-phenoxyquinolines was measured by PDGF-BB stimulated autophosphorylation of the PDGFβr in rat glomerular mesangial cells and also measured by EGF-stimulated autophosphorylation of the EGFr in A431 cells as a reference of selectivity as previously discribed.[14] These result are summarized in Tables 1–5.

The compounds substituted by typical functional groups on the phenoxy ring (ring C) were estimated (Table 1). We thought that the best compound in Table 1 was **1** in terms of its potent inhibitory activity and high selectivity toward PDGFr. On the other hand, it seemed that the carbonyl group reduced the inhibitory activity for EGFr as **8e**, **8f** and **8g**. Accordingly, we developed the acyl group substituted 4-phenoxy-quinoline derivatives.

Table 2 shows the PDGFr and EGFr inhibitory activities of the acyl group substituted 4-phenoxyquinolines and their analogues. In case of the benzoyl group substituted derivatives, the activity of PDGFr inhibition decreased as compared with **8e**, but still retained a good potency toward *para*-substituted compound (**8s**). Though the introduction of benzoyl or thiophenecarbonyl moieties on the phenoxy ring greatly diminished their selectivity between PDGFr and EGFr (**8q**, **8r**, **8s** and **8t**), the furoyl derivative still had good selectivity (**8u**).

Table 4. Inhibitory activity of amide substituted 4-phenoxyquinoline derivatives for PDGFr and EGFr



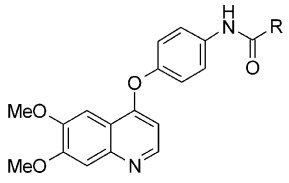
No.	R	IC_{50}[a] (μM)	
		PDGFr	EGFr
3		0.050	> 100
19		1.8	30
18		0.33	6.0
17a		0.044	0.65

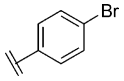
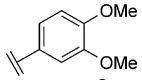
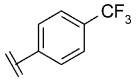
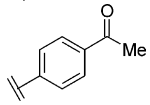
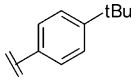
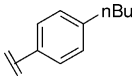
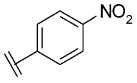
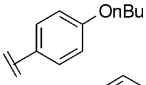
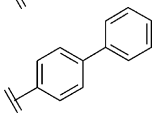
[a]IC_{50} values were averaged values determined by at least two independent experiments.

Next, we surveyed the effect of substituents on the benzoyl group of the benzoyl substituted 4-phenoxyquinolines (**2**, **8s**, **8w**–**8am**). These results are shown in Table 3. The 4-substituted phenyl (ring D) enhanced the inhibitory activity against PDGFr and reduced the activity against EGFr as compared with the corresponding 2- and 3-substituted compounds (**8w**–**8y** and **8z**–**8ab**). We observed that the greater hydrophobicity at the 4-substituent tended to provide greater inhibitory activity toward PDGFr (**8s** < **8y** < **8ab** < **8al** and **2**), but the shape of butyl group did not affect the activity. No effects on the 4-substituents were shown against EGFr. These observations suggest that PDGFr has a high affinity bind site for the hydrophobic substituent at the 4 position of the ring D.

An amide moiety is sometimes used as a bioisoster instead of the carbonyl group.[17] Therefore, in order to explore the importance of carbonyl group of **2**, the corresponding amide group substituted 4-phenoxyquinolines (**3**, **17a**, **18** and **19**) were investigated (Table 4). Fortunately, **3** showed about 6 times more active than **2** toward PDGFr, and had high selectivity for PDGFr over EGFr. However, its reverse amide **19** was 36 times less active than **3**, and showed a loss of selectivity. The *N*-methylation of **3**, compound **18,** was decreased the activity for PDGFr. The 3-substituted derivative (**17a**) showed a similar inhibition to **3** toward PDGFr, but lost selectivity toward EGFr. These results indicated that configuration of the amide group was important for the inhibitory activity and kinase selectivity. In this series, **3** seemed to be a most favorable form for inhibitory activity and selectivity against PDGFr.

Table 5. Inhibitory activity of various amide substituted 4-phenoxyquinoline derivatives for PDGFr and EGFr



No.	R	IC_{50}[a] (μM)		No.	R	IC_{50}[a] (μM)	
		PDGFr	EGFr			PDGFr	EGFr
17b		0.18	48	**17h**		2.0	>100
17c		0.20	93	**17i**		3.6	>100
3		0.050	>100	**17j**		1.8	>100
17d		0.070	>100	**17k**		5.1	>100
17e		0.15	>100	**17l**	Me	2.3	>100
17f		0.33	>100	**17m**		0.53	>100
17g		0.42	>100	**17n**		0.53	>100

[a]IC_{50} values were averaged values determined by at least two independent experiments.

Table 6. Inhibitory activities for various kinases using intact-cell assays

No.	IC_{50}[a] (μM)			
	PDGFr	EGFr	bFGFr	Insulinβr
1 (Ki6783)	0.13	>100	>100	>100
2 (Ki6896)	0.31	>100	3.8	>100
3 (Ki6945)	0.050	>100	>100	>100
CGP 53716	0.17	>100	>100	>100

[a]IC_{50} values were averaged values determined by at least two independent experiments.

We examined the effect of various substituted benzamides and other amide derivatives as shown in Table 5. The benzamide derivatives showed potent inhibitory activity toward PDGFr, but most of the compounds were found to be inactive toward EGFr. Substitution of more hydrophobic group at the 4-position resulted in a moderate increase of inhibitory activity (**3** and **17d**) as compared to the other substituents in the same way as the benzoyl substituted 4-phenoxyquinolines. Alkyl amides showed good inhibitory activity, but the heteroaromatic

Table 7. Inhibitory activities for various kinases by cell-free assays

No.	IC_{50}[a] (μM)						
	PDGFβr	EGFr	c-Src	PKA	PKCα	MAPK	MEK1
1 (Ki6783)	0.03	>10	>10	>10	>10	>10	>10
2 (Ki6896)	0.59	>100	>10	>10	>10	>10	>10
3 (Ki6945)	0.64	>100	>10	>10	>10	>10	>10

[a]IC_{50} values were averaged values determined by at least two independent experiments.

amides (**17j** and **17k**) had lower activity toward PDGFr than the benzamide derivatives.

Finally, we evaluated three selected compounds, **1**, **2** and **3**, toward various tyrosine kinases by intact-cell assays (Table 6), and tyrosine and serine/threonine kinases by cell-free assays (Table 7).[15] **CGP 53716** known as one of the most specific inhibitors for PDGFr was used the positive control.[10] In intact-cell assays, **2** showed good potency toward PDGFr, weak potency toward bFGFr, and no activity against EGFr and the insulinβ receptor. On the other hand, **1**, **3** and **CGP 53716** showed potent activity toward PDGFr but did not show inhibitory activities toward the other three kinases. In the cell-free assays, all of the compounds also showed potent activity toward PDGFβr but did not show potent activities for EGFr, c-Src, PKA, PKC, MAPK and MEK1. Therefore, these compounds would be significant specific inhibitors toward PDGFr. Moreover, since these three compounds showed similar inhibitory activity toward PDGFr for both intact-cell assay and cell-free assay, the permeability of them into the cell membrane might be enough for further development.

It is interesting that the compounds which substituted by carbonyl groups such as benzoyl and benzamide at the 4-position on the C ring show potent and selective biological activities, accordingly, we have been in investigation the docking model of 4-phenoxyquinoines and some receptors to investigate the binding mode between the compounds and the receptors. Furthermore, the advanced research for new types of C ring substituted 4-phenoxyquinolines has continuously carried out to improve the inhibitory activity and some physicochemical properties.

Conclusion

We discovered a new series of 4-phenoxyquinoline derivatives as potent and selective inhibitors of PDGFr tyrosine kinase. In particular, it was revealed that the compounds with a benzoyl group and benzamide group at the 4-position of the C ring showed high selectivity for PDGFr over EGFr. Typical compounds **1** (**Ki6783**), **2** (**Ki6896**) and **3** (**Ki6945**) also showed high selectivity for PDGFr over various tyrosine and serine/threoronine kinases in intact-cell or cell-free assays.

The 4-phenoxyquinolines are expected to be useful pharmaceuticals with reduced side effects. We have already reported that **2** improved glomerulosclerosis in vivo without significant toxicity.[18]

Experimental

General methods

Melting points were determined on a Yanaco micro-melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL EX-90A (90 MHz), JEOL JNM-LA400 (400 MHz) or JEOL JNM-A500 (500 MHz). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as the internal standard. MS spectra were collected with a Platform–LC (micromass). Elemental analysis and high-resolution mass spectra were performed by Toray Research Center, Inc. Elemental analysis results are within ±0.4% of the theoretical values. Column chromatography was carried out on silica gel 60 (70–230 mesh, Kanto Chemical) or preparative thin layer chromatography (PLC plates; Merck).

Ethyl 6,7-dimethoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylate (5). A mixture of 3,4-dimethoxyaniline (3.00 g, 19.6 mmol) and diethy ethoxymethylenemalonate (5.08 g, 23.50 mmol) was stirred at 120 °C for 1 h. Diphenylether (30 mL) was then added and stirred at 280 °C for 1 h. The reaction mixture was purified by column chromatography eluting with $CHCl_3$/MeOH (100/1–10/1) to obtain 3.58 g of **5** (66%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.28 (t, J = 7.1 Hz, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 7.05 (s, 1H), 7.52 (s, 1H), 8.43 (d, J = 6.6 Hz, 1H), 12.06 (d, J = 6.6 Hz, 1H); MS (ESI) m/z 278 ($M^+ + 1$).

6,7-Dimethoxy-4-quinolone (6). To a solution of **5** (3.28 g, 11.84 mmol) in MeOH (30 mL) was added 10% aqueous NaOH (45 mL) and heated under reflux for 1 h. The reaction mixture was acidified with 10% aqueous HCl. The resulting solid was collected by filtration and washed with $CHCl_3$/MeOH (200 mL/40 mL) to obtain 2.85 g of crude 6,7-dimethoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid. Then, a mixture of the acid (2.85 g) and diphenylether (90 mL) was stirred at 280 °C for 1 h. The reaction mixture was purified by column chromatography eluting with $CHCl_3$/MeOH (100/1–10/1) to obtain 2.3 g of **6** (91%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.82 (s, 3H), 3.86 (s, 3H), 5.95 (d, J = 4.6 Hz, 1H), 6.69 (s, 1H), 7.43 (s, 1H), 7.78 (d, J = 4.6 Hz, 1H), 8.13 (s, 1H); MS (ESI) m/z 206 ($M^+ + 1$).

4-Chloro-6,7-Dimethoxyquinoline (7). A mixture of **6** (2.13 g, 10.39 mmol) and $POCl_3$ (1.45 mL, 15.59 mmol) was heated under reflux for 0.5 h. The reaction mixture was concentrated and extracted with $CHCl_3$/MeOH (40 mL/10 mL). The organic layer was washed with 5% aqueous NaOH and brine. The solution was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography eluting with $CHCl_3$/MeOH (50/1) to obtain 1.98 g of **7** (8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.07 (s, 3H), 7.36 (d, J = 4.9 Hz, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 8.59 (d, J = 4.6 Hz, 1H); MS (ESI) m/z 224 ($M^+ + 1$).

6,7-Dimethoxy-4-(3,4-dimethoxyphenoxy)quinoline (1: Ki6783). A mixture of **7** (200 mg, 0.9 mmol) and 3,4-dimethoxyphenol (410 mg, 2.7 mmol) was heated at 170 °C for 20 min. The reaction mixture was cooled and treated with saturated $NaHCO_3$ (10 mL). The solution was extracted with AcOEt (10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 200 mg

(62%). Mp: 188–189 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.45 (d, J = 4.9 Hz, 1H), 6.75 (dd, J = 2.4, 9.2 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 7.42 (s, 1H), 7.57 (s, 1H), 8.48 (d, J = 4.9 Hz, 1H); MS (FD) m/z 341 (M^+). Anal. ($C_{19}H_{19}NO_5 \cdot H_2O$) C, H, N.

6,7-Dimethoxy-4-phenoxyquinoline (8a). Compound **8a** was prepared as described for **1**, except using phenol. Purified by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 450 mg (97%). Mp: 130–131 °C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 4.08 (s, 3H), 4.12 (s, 3H), 6.59 (d, J = 6.1 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.62 (s, 1H), 7.84 (s, 1H), 8.48 (d, J = 6.1 Hz, 1H); MS (ESI) m/z 282 ($M^+ + 1$). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

6,7-Dimethoxy-4-(2-methoxyphenoxy)quinoline (8b). Compound **8b** was prepared as described for **1**, except using 2-methoxyphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 76 mg (54%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.78 (s, 3H), 4.05 (s, 3H), 4.05 (s, 3H), 6.31 (d, J = 5.3 Hz, 1H), 6.9–7.4 (m, 4H), 7.42 (s, 1H), 7.63 (s, 1H), 8.45 (d, J = 5.3 Hz, 1H); MS (ESI) m/z 312 ($M^+ + 1$). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

6,7-Dimethoxy-4-(3-methoxyphenoxy)quinoline (8c). Compound **8c** was prepared as described for **1**, except using 3-methoxyphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 29 mg (52%). Mp: 124–125 °C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.82 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.53 (d, J = 5.3 Hz, 1H), 6.7–6.9 (m, 3H), 7.35 (t, J = 7.0 Hz, 1H), 7.43 (s, 1H), 7.54 (s, 1H), 8.50 (d, J = 5.3 Hz, 1H); MS (FD) m/z 311 (M^+); HRMS (ESI) ($C_{18}H_{18}NO_4$) ($M + H^+$) calcd 312.1236, found 312.1255.

6,7-Dimethoxy-4-(4-methoxyphenoxy)quinoline (8d). Compound **8d** was prepared as described for **1**, except using 4-methoxyphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 2.2 g (88%). Mp: 126–127 °C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.85 (s, 3H), 4.05, (s, 3H), 4.05 (s, 3H), 6.41 (d, J = 5.3 Hz, 1H), 6.97 (d, J = 9.5 Hz, 2H), 7.14 (d, J = 9.5 Hz, 2H), 7.43 (s, 1H), 7.58 (s, 1H), 8.46 (d, J = 5.3 Hz, 1H); MS (ESI) m/z 312 ($M^+ + 1$). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

6,7-Dimethoxy-4-(3-acetylphenoxy)quinoline (8e). Compound **8e** was prepared as described for **1**, except using 3-acetylyphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 91 mg (63%). Mp: 135–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.64 (s, 3H), 4.06 (s, 3H), 4.10 (s, 3H), 6.52 (d, J = 5.6 Hz, 1H), 7.42 (dd, J = 2.4, 8.1 Hz, 1H), 7.57 (s, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.65 (s, 1H), 7.80 (t, J = 2.2 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 8.51 (d, J = 5.6 Hz, 1H); MS (ESI) m/z 324 ($M^+ + 1$). Anal. ($C_{19}H_{17}NO_4$) C; H: calcd, 5.30; found, 5.74; N: calcd 4.33, found 3.84.

6,7-Dimethoxy-4-(4-acetylphenoxy)quinoline (8f). Compound **8f** was prepared as described for **1**, except using 4-acetylyphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 120 mg (83%). Mp: 155–156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3H), 4.05 (s, 3H), 4.10 (s, 3H), 6.64 (d, J = 5.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.67 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 8.46 (d, J = 5.6 Hz, 1H); MS (ESI) m/z 324 ($M^+ + 1$). Anal. ($C_{19}H_{17}NO_4$) C, H, N.

Methyl 3-[(6,7-Dimethoxy-4-quinolyl)oxy]benzoate (8g). Compound **8g** was prepared as described for **1**, except using methyl 3-hydroxybenzoate. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 460 mg (100%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 4.04 (s, 3H), 4.06 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.40 (dd, J = 1.5, 8.1 Hz, 1H), 7.44 (s, 1H), 7.54 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.86 (t, J = 2.0 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H); MS (ESI) m/z 340 ($M^+ + 1$). Anal. ($C_{19}H_{17}NO_5 \cdot 1.7H_2O$) C, H; N: calcd, 3.79, found, 3.25.

6,7-Dimethoxy-4-(3-methylphenoxy)quinoline (8h). Compound **8h** was prepared as described for **1**, except using 3-methylphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 108 mg (82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.52 (d, J = 5.6 Hz, 1H), 6.99–7.02 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.58 (s, 1H), 7.58 (s, 1H), 8.48 (d, J = 5.6 Hz, 1H); MS (ESI) m/z 296 ($M^+ + 1$). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

6,7-Dimethoxy-4-(3-hydroxyphenoxy)quinoline (8i). Preparation as described for **1** starting from 3-acetoxyphenol obtained (173 mg, 0.51 mmol) of 6,7-Dimethoxy-4-(3-acetoxyphenoxy)quinoline (38%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.58 (d, J = 5.4 Hz, 1H), 6.98 (t, J = 2.2 Hz, 1H), 7.02 (ddd, J = 1.0, 2.2, 8.1 Hz, 1H), 7.07 (ddd, J = 1.0, 2.2, 8.1 Hz, 1H), 7.44 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.51 (s, 1H), 8.52 (d, J = 5.4 Hz, 1H); MS (ESI) m/z 340 ($M^+ + 1$). To a solution of 6,7-dimethoxy-4-(3-acetoxyphenoxy)quinoline (173 mg, 0.51 mmol) in $CHCl_3$/MeOH (3 mL/3 mL) was added 10% aqueous K_2CO_3 (2 mL) and stirred at room temperature for 3 h. The reaction mixture was neutralized with 10% aqueous HCl. The resulting solid was collected by filtration and washed with $CHCl_3$ to obtain 469 mg of **8i** (92%). mp: >231 °C (decomposition); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.30 (s, 3H), 3.32 (s, 3H), 6.37 (d, J = 5.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.37 (s, 1H), 7.51 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 9.55 (s, 1H); MS (ESI) m/z 298 ($M^+ + 1$). Anal. ($C_{17}H_{15}NO_4$) C, H, N.

6,7-Dimethoxy-4-(4-hydroxyphenoxy)quinoline (8j). Preparation as described for Ki6783 starting from 4-benzyloxyphenol obtained 546 mg (32%) of 6,7-dimethoxy-4-(4-benzyloxyphenoxy)quinoline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.11 (s, 3H), 5.11 (s, 2H), 6.42

(d, $J=5.4$ Hz, 1H), 7.06 (d, $J=9.0$ Hz, 2H), 7.12 (d, $J=9.0$ Hz, 2H), 7.34–7.48 (m, 6H), 7.57 (s, 1H), 8.47 (d, $J=5.1$ Hz, 1H); MS (FAB) m/z 388 ($M^+ + 1$). To a solution of 6,7-dimethoxy-4-(4-benzyloxyphenoxy)-quinoline (420 mg, 1.09 mmol) in DMF/AcOEt (5 mL/20 mL) was added palladium hydoroxide on carbon (wet type, 50 mg) and stirred under hydrogen at room temperature for 3.5 h. The suspension was filtered with Celite and washed with AcOEt. The resulting solution was concentrated and The residue was purified with $CHCl_3$/acetone (2/1) to obtain 259 mg of **8j** (81%). Mp: 236–240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.30 (s, 3H), 3.32 (s, 3H), 6.37 (d, $J=5.4$ Hz, 1H), 6.87 (d, $J=8.8$ Hz, 2H), 7.08 (d, $J=8.8$ Hz, 2H), 7.37 (s, 1H), 7.51 (s, 1H), 8.44 (d, $J=5.1$ Hz, 1H), 9.55 (s, 1H); MS (ESI) m/z 298 ($M^+ + 1$). Anal. ($C_{17}H_{15}NO_4 \cdot 0.3H_2O$) C, H, N.

6,7-Dimethoxy-4-(3-fluorophenoxy)quinoline (8k). Compound **8k** was prepared as described for **1**, except using 3-fluorophenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 125 mg (94%). Mp: 132 °C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 4.04 (s, 3H), 4.06 (s, 3H), 6.56 (d, $J=4.9$ Hz, 1H), 6.93 (d, $J=9.2$ Hz, 1H), 6.95–7.05 (m, 2H), 7.39–7.45 (m, 1H), 7.47 (s, 1H), 7.50 (s, 1H), 8.53 (d, $J=4.3$ Hz, 1H); MS (FD) m/z 299 (M^+). Anal. ($C_{17}H_{14}FNO_3$) C, H, N.

6,7-Dimethoxy-4-(3-bromophenoxy)quinoline (8l). Compound **8l** was prepared as described for **1**, except using 3-bromophenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 160 mg (100%). Mp: 124–126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.09 (s, 3H), 6.57 (d, $J=5.4$ Hz, 1H), 7.15 (dd, $J=2.2$, 8.1 Hz, 1H), 7.35 (d, $J=8.1$ Hz, 1H), 7.39 (t, $J=2.2$ Hz, 1H), 7.47 (d, $J=7.1$ Hz, 1H), 7.52 (s, 1H), 7.62 (s, 1H), 8.53 (d, $J=5.6$ Hz, 1H); MS (ESI) m/z 360 (M^+), 362 ($M^+ + 2$). Anal. ($C_{17}H_{14}BrNO_3$) C, H, N.

6,7-Dimethoxy-4-(4-bromophenoxy)quinoline (8m). Compound **8m** was prepared as described for **1**, except using 4-bromophenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 1.2 g (76%). Mp: 163–165 °C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 4.04 (s, 3H), 4.05 (s, 3H), 6.48 (d, $J=4.9$ Hz, 1H), 7.08 (d, $J=8.5$ Hz, 2H), 7.43 (s, 1H), 7.51 (s, 1H), 7.58 (d, $J=8.5$ Hz, 2H), 8.51 (d, $J=4.9$ Hz, 1H); MS (FD) m/z 359 (M^+), 361 ($M^+ + 2$). Anal. ($C_{17}H_{14}BrNO_3$) C, H, N.

6,7-Dimethoxy-4-(2,3-dimethoxyphenoxy)quinoline (8n). Compound **8n** was prepared as described for **1**, except using 2,3-dimethoxylphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 77 mg (51%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 3H), 3.94 (s, 3H), 4.09 (s, 3H), 4.12 (s, 3H), 6.56 (d, $J=6.1$ Hz, 1H), 6.83 (dd, $J=1.5$, 8.3 Hz, 1H), 6.95 (dd, $J=1.5$, 8.3 Hz, 1H), 7.17 (t, $J=8.3$ Hz, 1H), 7.64 (s, 1H), 7.87 (s, 1H), 8.46 (d, $J=6.1$ Hz, 1H); MS (ESI) m/z 342 ($M^+ + 1$); HRMS (ESI) ($C_{19}H_{20}NO_5$) ($M + H^+$) calcd 342.1341, found 342.1350.

6,7-Dimethoxy-4-(2,6-dimethoxyphenoxy)quinoline (8o). Compound **8o** was prepared as described for **1**, except using 2,6-dimethoxylphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 17 mg (11%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 6H), 4.08 (s, 3H), 4.08 (s, 3H), 6.36 (d, $J=5.6$ Hz, 1H), 6.72 (d, $J=8.3$ Hz, 2H), 7.25 (t, $J=8.3$ Hz, 1H), 7.61 (s, 1H), 7.70 (s, 1H), 8.25 (d, $J=5.6$ Hz, 1H); MS (ESI) m/z 342 ($M^+ + 1$). Anal. ($C_{19}H_{19}NO_5 \cdot 0.8H_2O$) C, H, N.

6,7-Dimethoxy-4-(3,5-dimethoxyphenoxy)quinoline (8p). Compound **8p** was prepared as described for **1**, except using 3,5-dimethoxylphenol. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 96 mg (63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.79 (s, 3H), 3.80 (s, 3H), 4.05 (s, 6H), 6.35 (q, $J=1.0$ Hz, 2H), 6.38 (t, $J=1.0$ Hz, 1H), 6.59 (d, $J=5.1$ Hz, 1H), 7.43 (s, 1H), 7.53 (s, 1H), 8.51 (d, $J=5.1$ Hz, 1H); MS (ESI) m/z 342 ($M^+ + 1$); HRMS (ESI) ($C_{19}H_{20}NO_5$) ($M + H^+$) calcd 342.1341, found 342.1330.

{2-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}phenylmethanone (8q). Compound **8q** was prepared as described for **1**, except using 2-hydroxybenzophenone. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 14 mg (5%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 3H), 3.99 (s, 3H), 6.43 (d, $J=5.1$ Hz, 1H), 6.93 (s, 1H), 7.27 (d, $J=7.6$ Hz, 1H), 7.31 (s, 1H), 7.33 (t, $J=7.6$ Hz, 2H), 7.42–7.49 (m, 2H), 7.63 (td, $J=1.7$, 7.6 Hz, 1H), 7.68 (dd, $J=1.7$, 7.6 Hz, 1H), 7.69–7.72 (m, 2H), 8.44 (d, $J=5.1$ Hz, 1H); MS (ESI) m/z 386 ($M^+ + 1$); HRMS (ESI) ($C_{24}H_{20}NO_4$) ($M + H^+$) calcd 386.1392, found 386.1403.

{3-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}phenylmethanone (8r). Compound **8r** was prepared as described for **1**, except using 3-hydroxybenzophenone. Purification was performed by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 126 mg of the title compound (65%). Mp 137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.07 (s, 3H), 6.53 (d, $J=5.4$ Hz, 1H), 7.42–7.65 (m, 8H), 7.72 (dd, $J=1.5$, 6.3 Hz, 1H), 7.83 (dd, $J=1.2$, 8.3 Hz, 2H) 8.53 (d, $J=5.1$ Hz, 1H); MS (FD) m/z 385 (M^+); HRMS (ESI) ($C_{24}H_{20}NO_4$) ($M + H^+$) calcd 386.1392, found 386.1373.

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(phenyl)methanone (8s). Compound **8s** was prepared as described for **1**, except using 4-hydroxybenzophenone. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 38 mg (24%). amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.04 (s, 3H), 4.04 (s, 3H), 6.67 (d, $J=5.1$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 7.46 (s, 1H), 7.51 (t, $J=7.3$ Hz, 2H), 7.54 (s, 1H), 7.62 (t, $J=7.3$

Hz, 1H), 7.83 (d, $J=7.1$ Hz, 2H), 7.95 (d, $J=8.8$ Hz, 2H), 8.58 (d, $J=5.4$ Hz, 1H); MS (ESI) m/z 386 ($M^+ +1$); HRMS (ESI) ($C_{24}H_{20}NO_4$) ($M+H^+$) calcd 386.1392, found 386.1388.

(4-Fluorophenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-methanone (8ad). Compound **8ad** was prepared as described for **1**, except using 4-hydroxy-4′-fluorobenzophenone. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (4/1) and $CHCl_3$/MeOH (50/1) to obtain 114 mg (57%). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.05 (s, 3H), 6.67 (d, $J=5.1$ Hz, 1H), 7.20 (t, $J=8.5$ Hz, 2H), 7.29 (d, $J=8.8$ Hz, 2H), 7.46 (s, 1H), 7.50 (s, 1H), 7.87 (dd, $J=5.4$, 8.8 Hz, 2H), 7.91 (d, $J=8.5$ Hz, 2H), 8.58 (d, $J=5.1$ Hz, 1H); MS (ESI) m/z 404 ($M^+ +1$); HRMS (ESI) ($C_{24}H_{19}FNO_4$) ($M+H^+$) calcd 404.1298, found 404.1267.

(4-Chlorophenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-methanone (8ae). Compound **8ae** was prepared as described for **1**, except using 4-hydroxy-4′-chlorobenzophenone. Purification was performed by column thin layer chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 26 mg (12%). Mp 169–171 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 4.07 (s, 3H), 6.66 (d, $J=5.1$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.49 (d, $J=8.8$ Hz, 2H), 7.78 (d, $J=8.5$ Hz, 2H), 7.90 (d, $J=8.8$ Hz, 2H), 8.58 (d, $J=5.1$ Hz, 1H); MS (FD) m/z 419 (M^+). Anal. ($C_{24}H_{18}ClNO_4$) C, H, N.

6,7-Dimethoxy-4-(4-nitrophenoxy)quinoline (15a). A solution of 4-chloro-6,7-dimethoxyquinoline (3.00 g, 13.4 mmol) and 4-nitrophenol (4.66 g, 33.6 mmol) in diethyleneglycol dimethylether (2 mL) was heated at 180 °C for 1 h. The reaction mixture was cooled and treated with saturated $NaHCO_3$ (30 mL) and extracted with $CHCl_3$ (30 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (5/1) to obtain 3.92 g of **15a** (76%); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.01 (s, 3H), 4.06 (s, 3H), 6.69 (d, $J=5.1$ Hz, 1H), 7.26 (d, $J=9.3$ Hz, 2H), 7.37 (s, 1H), 7.47 (s, 1H), 8.33 (dd, $J=1.7$, 8.3 Hz, 2H), 8.62 (d, $J=5.1$ Hz, 1H); MS (ESI) m/z: 327 ($M^+ +1$).

6,7-Dimethoxy-4-(4-aminophenoxy)quinoline (16a). To a solution of **15a** (1.35 g, 4.18 mmol) and triethylamine (2.9 mL, 20.98 mmol) in DMF (100 mL) was added palladium hydroxide on carbon (wet type, 270 mg) and stirred under hydrogen at room temperature for 3.5 h. The suspension was filtered with Celite and washed with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The resulting solution was concentrated and purified by column chromatography eluting with $CHCl_3$/MeOH (50/1) obtained 1.16 g of **16a** (94%). Mp: 214 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.82 (br, 2H), 4.09 (s, 3H), 4.13 (s, 3H), 6.64 (d, $J=6.3$ Hz, 1H), 6.64 (d, $J=8.8$ Hz, 2H), 7.00 (d, $J=8.8$ Hz, 2H), 7.62 (s, 1H), 7.95 (s, 1H), 8.45 (d, $J=6.3$ Hz, 1H); MS (ESI) m/z 297 ($M^+ +1$); HRMS (ESI) ($C_{17}H_{17}N_2O_3$) ($M+H^+$) calcd 297.1239, found 297.1207.

6,7-Dimethoxy-4-(3-nitrophenoxy)quinoline (15b). Compound **15b** was prepared as described for **15a**, except using 3-nitrophenol. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 293 mg (67%). Mp: 145–146 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.11 (s, 3H), 4.18 (s, 3H), 6.69 (d, $J=6.3$ Hz, 1H), 7.61 (s, 1H), 7.63 (d, $J=8.1$ Hz, 1H), 7.80 (t, $J=8.3$ Hz, 1H), 8.13 (s, 1H), 8.17 (m, 1H), 8.32 (d, $J=8.3$ Hz, 1H), 8.55 (d, $J=6.3$ Hz, 1H); MS (ESI) m/z 327 ($M^+ +1$); HRMS (ESI) ($C_{17}H_{15}N_2O_5$) ($M+H^+$) calcd 327.0981, found 327.0963.

6,7-Dimethoxy-4-(3-aminophenoxy)quinoline (16b). Compound **16b** was prepared as described for **16a**, except using **15b**. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/MeOH (50/1) to obtain 245 mg (92%). Mp: 165–167 °C; amorphaous substance; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.89 (br, 2H), 4.07 (s, 3H), 4.11 (s, 3H), 6.51 (t, $J=2.2$ Hz, 1H), 6.56 (dd, $J=2.4$ Hz, $J=7.5$ Hz, 1H), 6.65 (dd, $J=2.2$, 7.3 Hz, 1H), 6.68 (d, $J=5.9$ Hz, 1H), 7.25 (s, 1H), 7.58 (s, 1H), 7.83 (s, 1H), 8.47 (d, $J=6.1$ Hz, 1H); MS (ESI) m/z 297 ($M^+ +1$); HRMS (ESI) ($C_{17}H_{17}N_2O_3$) ($M+H^+$) calcd 297.1239, found 297.1252.

6,7-Dimethoxy-4-(2-nitrophenoxy)quinoline (15c). Compound **15c** as prepared as described for **15a**, except using 2-nitrophenol. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 180 mg (61%). Mp: 145–146 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.04 (s, 3H), 4.06 (s, 3H), 6.49 (d, $J=5.4$ Hz, 1H), 7.30 (d, $J=8.3$ Hz, 1H), 7.43 (t, $J=8.3$ Hz, 1H), 7.45 (s, 1H), 7.51 (s, 1H), 7.69 (td, $J=1.7$, 8.3 Hz, 1H), 8.11 (dd, $J=1.7$, 8.3 Hz, 1H), 8.54 (d, $J=5.1$ Hz, 1H); MS (ESI) m/z 327 ($M^+ +1$); HRMS (ESI) ($C_{17}H_{15}N_2O_5$) ($M+H^+$) calcd 327.0981, found 327.0944.

6,7-Dimethoxy-4-(2-aminophenoxy)quinoline (16c). Compound **16c** was prepared as described for **16a**, except using **15c**. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/MeOH (50/1) to obtain 134 mg (82%). Mp: 165–167 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.84 (br, 2H), 4.11 (s, 3H), 4.11 (s, 3H), 6.61 (d, $J=6.1$ Hz, 1H), 6.86 (dt, $J=1.5$, 8.1 Hz, 1H), 6.94 (dd, $J=1.5$, 8.1 Hz, 1H), 7.05 (dd, $J=1.2$, 8.1 Hz, 1H), 7.19 (dt, $J=1.5$, 8.1 Hz, 1H), 7.68 (s, 1H), 7.85 (s, 1H), 8.44 (d, $J=6.1$ Hz, 1H); MS (ESI) m/z 297 ($M^+ +1$); HRMS (ESI) ($C_{17}H_{17}N_2O_3$) ($M+H^+$) calcd 297.1239, found 297.1207.

4-*t*-Butylphenyl 4-methoxyphenyl ketone (10a). To a solution of anisole (541 mg, 5.0 mmol) and 4-*t*-butylbenzoyl chloride (983 mg, 5.0 mmol) in nitromethane (5 mL) was added $Sc(OTf)_3$ (506 mg, 1.0 mmol) stirred at 60 °C for 21 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column

chromatography on silica gel eluting with hexane/AcOEt (5/1) to obtain 862 mg of **10a** (64%). MS (FD) m/z 268 (M^+).

4-*t*-Butylphenyl 4-hydroxyphenyl ketone (11a). A solution of **10a** (804 mg, 3.0 mmol) in DMF (30 mL) was added sodium thiomethoxide (562 mg, 8.0 mmol). The reaction mixture was refluxed under argon for 5 h. The reaction mixture was cooled to room temperature and partitioned between 10% aqueous phosphoric acid (30 mL) and AcOEt (30 mL). The organic layer was washed with 0.5 N aqueous $AgNO_3$ and dried over $MgSO_4$. The solution was concentrated and the resulting residue was purified by column chromatography on silica gel eluting with $CHCl_3$ to obtain 862 mg of **11a** (97%). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.36 (s, 9H), 6.92 (d, $J=8.5$ Hz, 2H), 7.49 (d, $J=8.6$ Hz, 2H), 7.72 (d, $J=7.9$ Hz, 2H), 7.79 (d, $J=8.5$ Hz, 2H); MS (FD) m/z 254 (M^+).

(4-*t*-Butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone (2: Ki6896). A mixture of **7** (341 mg, 1.52 mmol) and **11a** (775 mg, 3.05 mmol) was heated at 160 °C for 40 min. The reaction mixture was purified by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 72 mg of **2** (11%). Mp: 173–174 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.38 (s, 9H), 4.04 (s, 3H), 4.06 (s, 3H), 6.65 (d, $J=5.5$ Hz, 1H), 7.27 (d, $J=8.6$ Hz, 2H), 7.45 (s, 1H), 7.50 (s, 1H), 7.52 (d, $J=8.5$ Hz, 2H), 7.78 (d, $J=8.6$ Hz, 2H), 7.94 (d, $J=8.6$ Hz, 2H), 8.57 (d, $J=4.9$ Hz, 1H); MS (ESI) m/z 442 ($M^+ + 1$). Anal. ($C_{28}H_{27}NO_4$) C, H, N.

4-Methoxyphenyl 2-thienyl ketone (10b). To a solution of anisole (1.1g, 10 mmol) and 2-thiophenecarbonyl chloride (1.5 g, 10 mmol) in nitromethane (10 mL) was added $Yb(OTf)_3$ (620 mg, 1.0 mmol) stirred at 60 °C for 8 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (5/1) to obtain 965 mg of **10b** (44%). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.89 (s, 3H), 6.98 (d, $J=8.5$ Hz, 2H), 7.16 (dd, $J=3.7$ Hz, 4.9 Hz, 1H), 7.64 (d, $J=3.7$ Hz, 1H), 7.68 (d, $J=4.9$ Hz, 1H), 7.90 (d, $J=8.6$ Hz, 2H); MS (FD) m/z 218 (M^+).

4-Hydroxyphenyl 2-thienyl ketone (11b). To a solution of **10b** (804 mg, 3.7 mmol) in DMF (30 mL) was added sodium thiomethoxide (645 mg, 9.2 mmol). The reaction mixture was refluxed under argon for 5 h. The reaction mixture was cooled to room temperature and partitioned between 10% aqueous phosphoric acid (30 mL) and AcOEt (30 mL). The organic layer was washed with 0.5 N aqueous $AgNO_3$ and dried over $MgSO_4$. The solution was concentrated and the resulting residue was purified by column chromatography on silica gel eluting with chloroform to obtain 702 mg of **11b** (93%). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.84 (brs, 1H), 6.93 (d, $J=8.5$ Hz, 2H), 7.14 (dd, $J=3.7$, 4.9 Hz, 1H), 7.64 (d, $J=3.7$ Hz, 1H), 7.68 (d, $J=4.9$ Hz, 1H), 7.83 (d, $J=8.5$ Hz, 2H); MS (FD) m/z 204 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(2-thienyl)methanone (8t). A mixture of **7** (112 mg, 0.50 mmol) and **11b** (102 mg, 0.50 mmol) was heated at 160 °C for 40 min. The reaction mixture was purified by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 34 mg of **8t** (17%). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.04 (s, 3H), 4.07 (s, 3H), 6.65 (d, $J=5.5$ Hz, 1H), 7.20 (dd, $J=3.7$, 4.9 Hz, 1H), 7.29 (d, $J=8.5$ Hz, 2H), 7.47 (s, 1H), 7.49 (s, 1H), 7.70 (d, $J=3.1$ Hz, 1H), 7.75 (d, $J=4.9$ Hz, 1H), 8.00 (d, $J=8.6$ Hz, 2H), 8.58 (d, $J=5.5$ Hz, 1H); MS (ESI) m/z 392 ($M^+ + 1$); HRMS (ESI) ($C_{22}H_{18}NO_4S$) ($M+H^+$) calcd 392.0957, found 392.0964.

4-Cyclohexylcarbonyl-1-methoxybenzene (10c). Compound **10c** was prepared as described for **10b**, except using cyclohexanecarbonyl chloride (51%). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.21–1.88 (m, 10H), 3.19–3.25 (m, 1H), 3.87 (s, 3H), 6.93 (d, $J=9.2$ Hz, 2H), 7.94 (d, $J=9.2$ Hz, 2H); MS (ESI) m/z 219 ($M^+ + 1$).

4-Cyclohexylcarbonyl-1-hydroxybenzene (11b). Compound **11b** was prepared as described for **11a**, except using **10b** (93%). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.23–1.88 (m, 10H), 3.19–3.25 (m, 1H), 6.06 (brs, 1H) 6.89 (d, $J=8.6$ Hz, 2H), 7.90 (d, $J=8.6$ Hz, 1H); MS (FD) m/z: 204 (M^+).

4-Cyclohexylcarbonyl-1-[(6,7-dimethoxy-4-quinolyl)oxy]-benzene (8v). Compound **8v** was prepared as described for **2**, except using **11b**. Purification was performed by thin layer chromatography on silica gel eluting with hexane/acetone (4/1) and then $CHCl_3$/MeOH (50/1) to obtain 65 mg (33%). Mp 125 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.21–1.93 (m, 10H), 3.24–3.29 (m, 1H), 4.03 (s, 3H), 4.06 (s, 3H), 6.60 (d, $J=5.5$ Hz, 1H), 7.24 (d, $J=8.5$ Hz, 2H), 7.45 (s, 1H), 7.47 (s, 1H), 8.05 (d, $J=8.5$ Hz, 2H), 8.55 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 392 ($M^+ + 1$); HRMS (ESI) ($C_{24}H_{26}NO_4$) ($M+H^+$) calcd 392.1862, found 392.1837.

2-Trifluoromethylphenyl 4-methoxyphenyl ketone (10d). Compound **10d** was prepared as described for **10b**, except using 2-trifluoromethylbenzoyl chloride (50%). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3H) 6.93 (d, $J=9.2$ Hz, 2H), 7.37–7.39 (m, 1H), 7.60–7.63 (m, 2H), 7.75 (d, $J=9.2$ Hz, 2H), 7.73–7.78 (m, 1H); MS (FD) m/z 280 (M^+).

2-Trifluoromethylphenyl 4-hydroxyphenyl ketone (11d). Compound **11d** was prepared as described for **11a**, except using **10d** (74%). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.88 (s, 1H), 6.87 (d, $J=8.5$ Hz, 2H), 7.37–7.38 (m, 1H), 7.58–7.63 (m, 2H), 7.71 (d, $J=9.2$ Hz, 2H), 7.76–7.78 (m, 1H); MS (FD) m/z 266 (M^+).

(2-Trifluoromethylphenyl){4-[(6,7-dimethoxy-4-quinolyl)-oxy]phenyl}methanone (8z). Compound **8z** was prepared as described for **2**, except using **11d**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1), $CHCl_3$ and $CHCl_3$/AcOEt (5/1) to obtain 899 mg (55%). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.01 (s, 3H), 4.06 (s, 3H), 6,67 (d, $J=5.5$ Hz, 1H), 7.22 (d, $J=9.2$ Hz, 2H), 7.42 (s, 1H),

7.42–7.44 (m, 1H), 7.45 (s, 1H), 7.62–7.68 (m, 2H), 7.80–7.81 (m, 1H), 7.87 (d, $J=8.6$ Hz, 2H), 8.58 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 453 (M^+); HRMS (ESI) ($C_{25}H_{19}F_3NO_4$) ($M+H^+$) calcd 454.1266, found 454.1260.

3-Trifluoromethylphenyl 4-methoxyphenyl ketone (10e). Compound **10e** was prepared as described for **10b**, except using 3-(trifluoromethyl)benzoyl chloride (26%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.91 (s, 3H), 6.99 (d, $J=9.2$ Hz, 2H), 7.60–7.64 (m, 1H), 7.80–7.83 (m, 1H), 7.82 (d, $J=8.5$ Hz, 2H), 7.93–7.94 (m, 1H), 8.01 (s, 1H); MS (FD) m/z 280 (M^+).

3-Trifluoromethylphenyl 4-hydroxyphenyl ketone (11e). Compound **11e** was prepared as described for **11a**, except using **10e** (73%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.85 (s, 1H), 6.94 (d, $J=9.2$ Hz, 2H), 7.62 (t, $J=7.3$ Hz, 1H), 7.78 (d, $J=9.2$ Hz, 2H), 7.83 (d, $J=7.3$ Hz, 1H), 7.93 (d, $J=7.3$ Hz, 1H), 8.01 (s, 1H).

(3-Trifluoromethylphenyl){4-[(6,7-dimethoxy-4-quinolyl)-oxy]phenyl}methanone (8aa). Compound **8aa** was prepared as described for **2**, except using **11e**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) and $CHCl_3$/AcOEt (5/1) to obtain 204 mg (28%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H) 4.07 (s, 3H), 6,69 (d, $J=4.9$ Hz, 1H), 7.30 (d, $J=9.2$ Hz, 2H), 7.47 (s, 2H), 7.66 (t, $J=7.9$ Hz, 1H), 7.87 (d, $J=7.9$ Hz, 1H), 7.92 (d, $J=9.2$ Hz, 2H), 8.00 (d, $J=7.9$ Hz, 1H), 8.08 (s, 1H), 8.60 (d, $J=4.9$ Hz, 1H); MS (FD) m/z 453 (M^+). Anal. ($C_{25}H_{18}F_3NO_4\cdot H_2O$) C, H, N.

4-*n*-Butylphenyl 4-methoxyphenyl ketone (10f). Compound **10f** was prepared as described for **10b**, except using 4-*n*-butylbenzoyl chloride (32%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, $J=7.3$ Hz, 3H), 1.38 (tq, $J=7.3$, 7.3 Hz, 2H), 1.64 (q, $J=7.3$ Hz, 2H), 2.69 (t, $J=7.3$ Hz, 2H), 3.89 (s, 3H), 6.96 (d, $J=9.2$ Hz, 2H), 7.27 (d, $J=8.6$ Hz, 2H), 7.69 (d, $J=8.6$ Hz, 2H), 7.82 (d, $J=9.2$ Hz, 2H); MS (FD) m/z 268 (M^+).

4-*n*-Butylphenyl 4-hydroxyphenyl ketone (11f). Compound **11f** was prepared as described for **11a**, except using **10f** (96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, $J=7.3$ Hz, 3H), 1.38 (tq, $J=7.3$, 7.3 Hz, 2H), 1.64 (septet, $J=7.3$ Hz, 2H), 2.69 (t, $J=7.9$ Hz, 2H), 6.35 (s, 1H), 6.92 (d, $J=8.5$, 2H), 7.28 (d, $J=7.9$ Hz, 2H), 7.69 (d, $J=8.6$ Hz, 2H), 7.77 (d, $J=8.5$ Hz, 2H); MS (FD) m/z 254 (M^+).

(4-*n*-Butylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone (8al). Compound **8al** was prepared as described for **2**, except using **11f**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) and $CHCl_3$/AcOEt (5/1) to obtain 400 mg of (32%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, $J=7.3$ Hz, 3H), 1.38 (tq, $J=7.3$, 7.3 Hz, 2H), 1.62–1.68 (m, 2H), 2.71 (t, $J=7.3$ Hz, 2H), 4.04 (s, 3H), 4.07 (s, 3H), 6.65 (d, $J=4.9$ Hz, 1H), 7.26 (d, $J=8.5$ Hz, 2H), 7.31 (d, $J=7.9$ Hz, 2H), 7.46 (s, 1H), 7.49 (s, 1H), 7.76 (d, $J=7.9$ Hz, 2H), 7.92 (d, $J=8.5$ Hz, 2H), 8.58 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 440 (M^+-1). Anal. ($C_{28}H_{27}NO_4$) H, N; C: calcd 76.17, found 75.73.

4-Biphenyl 4-methoxyphenyl ketone (10g). Compound **10g** was prepared as described for **10b**, except using 4-phenylbenzoyl chloride. (34%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.90 (s, 3H), 6.98 (d, $J=8.5$ Hz, 2H), 7.40 (t, $J=7.3$ Hz, 1H), 7.48 (t, $J=7.3$ Hz, 2H), 7.65 (d, $J=7.3$ Hz, 2H), 7.76 (d, $J=8.6$ Hz, 2H), 7.85 (d, $J=8.5$ Hz, 2H), 7.87 (d, $J=9.2$ Hz, 2H); MS (FD) m/z 288 (M^+).

4-Biphenyl 4-hydroxyphenyl ketone (11g). Compound **11g** was prepared as described for **11a**, except using **10g** (82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.91 (d, $J=8.5$ Hz, 2H), 7.43 (t, $J=7.3$ Hz, 1H), 7.52 (dd, $J=7.3$ Hz, 7.9 Hz, 2H), 7.70 (d, $J=8.5$ Hz, 2H), 7.75 (d, $J=7.9$ Hz, 2H) 7.77 (d, $J=7.9$ Hz, 2H), 7.83 (d, $J=7.9$ Hz, 2H); MS (FD) m/z 274 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-biphenyl)-methanone (8am). Compound **8am** was prepared as described for **2**, except using **11g**. Purification was performed by thin layer chromatography on silica gel eluting with chloroform/ethyl acetate (10/1) to obtain 50 mg (37%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 4.11 (s, 3H), 4.14 (s, 3H), 6.74 (d, $J=5.3$ Hz, 1H), 7.30–8.09 (m, 15H), 8.65 (d, $J=5.3$ Hz, 1H); MS (ESI) m/z 462 (M^+). Anal. ($C_{30}H_{23}NO_4\cdot 1.5H_2O$) C, H, N.

4-Methoxyphenyl 2-methylphenyl ketone (10h). Compound **10h** was prepared as described for **10b**, except using 2-methylbenzoyl chloride (74%). MS (FD) m/z 226 (M^+).

4-Hydroxyphenyl 2-methylphenyl ketone (11h). To a solution of **10h** (1.66 g, 7.35 mmol) in $CHCl_3$ (10 mL) was added a solution of 1.0 M BBr_3 in CH_2Cl_2 (29 mL) at 0 °C and stirred at room temperature for 15 h. A solution of 1.0 M BBr_3 in CH_2Cl_2 (15 mL) was further added and stirred at room temperature for 2 days. The reaction mixture was then poured into ice water and partitioned between water and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (4/1) to obtain 1.50 g of **11h** (96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 6.87 (d, $J=8.5$ Hz, 2H), 7.22–7.29 (m, 3H), 7.37 (td, $J=1.2$, 7.3 Hz, 1H), 7.73 (d, $J=8.5$ Hz, 2H); MS (FD) m/z 212 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(2-methylphenyl)methanone (8w). To a solution of **11h** (1.33 g, 6.29 mmol) in xylene (15 mL) was added 4-dimethylaminopyridine (845 mg, 6.92 mmol) and stirred at room temperature for 1 h. Then **7** (1.41 g, 6.29 mmol) was added and stirred under reflux for 23 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was dried under $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (4/1), $CHCl_3$ and hexane/acetone (2/1) to obtain 1.26 g of **8w** (50%). Mp: 143–144 °C; ^{1}H NMR

($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 4.02 (s, 3H), 4.06 (s, 3H), 6.65 (d, $J=4.9$ Hz, 1H), 7.23 (d, $J=8.6$ Hz, 2H), 7.25–7.35 (m, 3H), 7.39–7.42 (m, 1H), 7.45 (s, 1H), 7.46 (s, 1H), 7.91 (d, $J=8.5$ Hz, 2H), 8.57 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 399 (M^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

4-Methoxyphenyl 3-methylphenyl ketone (10i). Compound **10i** was prepared as described for **10b**, except using 3-methylbenzoyl chloride (56%). MS (FD) m/z 226 (M^+).

4-Hydroxyphenyl 3-methylphenyl ketone (11i). Compound **11i** was prepared as described for **11a**, except using **10i** (56%). ^1H NMR (DMSO-d_6, 500 MHz): δ 2.38 (s, 3H), 6.89 (d, $J=8.6$ Hz, 2H), 7.37–7.47 (m, 4H), 7.65 (d, $J=8.6$ Hz, 2H), 10.42 (s, 1H); MS (FD) m/z 212 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3-methylphenyl)methanone (8x). Compound **8x** was prepared as described for **8w** except using **11i**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1), $CHCl_3$ and hexane/acetone (2/1) to obtain 262 mg (45%). ^1H NMR ($CDCl_3$, 500 MHz): δ 2.44 (s, 3H), 4.03 (s, 3H), 4.06 (s, 3H), 6.66 (d, $J=4.9$ Hz, 1H), 7.27 (d, $J=8.6$ Hz, 2H), 7.38 (t, $J=7.3$ Hz, 1H), 7.41 (d, $J=7.3$ Hz, 1H), 7.46 (s, 1H), 7.49 (s, 1H), 7.59 (d, $J=7.3$ Hz, 1H), 7.64 (s, 1H), 7.93 (d, $J=8.6$ Hz, 2H), 8.57 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 399 (M^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

3-Fluorophenyl 4-methoxyphenyl ketone (10j). To a solution of anisole (541 mg, 5.0 mmol) and 3-fluorobenzoyl chloride (793 mg, 5.0 mmol) in nitromethane (5 mL) was added $Sc(OTf)_3$ (49 mg, 0.50 mmol) stirred at 60 °C for 3 days. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (10 mL). The solution was extracted with $CHCl_3$. The organic layer was dried over MgSO4 and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane/acetone (5/1) to obtain 585 mg of **10j** (51%). MS (ESI) m/z 231 ($M^+ + 1$).

4-Hydroxyphenyl 3-fluorophenyl ketone (11j). To a solution of **10j** (580 mg) in CH_2Cl_2 (5 mL) was added a solution of 1.0 M BBr_3 in CH_2Cl_2 (23 mL) at 0 °C and stirred at room temperature for 3 days. The reaction mixture was then poured into ice water and partitioned between water and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (4/1) to obtain 402 mg of **11j** (74%). ^1H NMR (DMSO-d_6, 500 MHz): δ 6.91 (d, $J=8.5$ Hz, 2H), 7.44–7.49 (m, 3H), 7.57–7.61 (m, 1H), 7.68 (d, $J=8.5$ Hz, 2H), 10.51 (brs, 1H); MS (ESI) m/z 217 ($M^+ + 1$).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl})(3-fluorophenyl)methanone (8ac). Compound **8ac** was prepared as described for **8w**, except using **11j**. Purification was performed by column chromatography on silica gel eluting hexane/acetone, $CHCl_3$ and $CHCl_3$/AcOEt (5/1) to obtain 484 mg (70%). Mp 144 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.04 (s, 3H), 4.07 (s, 3H), 6.67 (d, $J=4.9$ Hz, 1H), 7.28 (d, $J=7.9$ Hz, 2H), 7.31–7.33 (m, 1H), 1.46 (s, 1H), 7.47 (s, 1H), 7.48–7.53 (m, 2H), 7.59–7.61 (m, 1H), 7.93 (d, $J=8.6$ Hz. 2H), 8.59 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 403 (M^+). Anal. ($C_{24}H_{18}FNO_4$) C, H, N.

3,4-Dichlorophenyl 4-methoxyphenyl ketone (10k). Compound **10k** was prepared as described for **10b**, except using 3,4-dichlorobenzoyl chloride (10%). Mp: 133–134 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.90 (s, 3H), 6.98 (d, $J=9.2$ Hz, 2H), 7.56 (s, 1H), 7.58 (d, $J=1.8$ Hz, 1H), 7.79 (d, $J=9.2$ Hz, 2H), 7.84 (d, $J=1.8$ Hz, 1H); MS (FD) m/z 280 (M^+), 282 ($M^+ + 2$).

3,4-Dichlorophenyl 4-hydroxyphenyl ketone (11k). Compound **11k** was prepared as described for **11j**, except using **10k** (77%). ^1H NMR (DMSO-d_6, 500 MHz): δ 6.91 (d, $J=8.5$ Hz, 2H), 7.62 (dd, $J=1.8$, 8.6 Hz, 1H), 7.68 (d, $J=8.5$ Hz, 2H), 7.80 (d, $J=7.9$ Hz, 1H), 7.85 (d, $J=1.8$ Hz, 1H), 10.55 (s, 1H); MS (FD) m/z 266 (M^+), 268 ($M^+ + 2$).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(3,4-dichlorophenyl)methanone (8af). Compound **8af** was prepared as described for **8w**, except using **11k**. Purification was performed by thin layer chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 81 mg (31%). ^1H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H), 4.07 (s, 3H), 6.68 (d, $J=5.5$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.60 (d, $J=8.5$ Hz, 1H), 7.66 (dd, $J=1.8$, 8.6 Hz, 1H), 7.90 (d, $J=9.2$ Hz, 2H), 7.91 (d, $J=1.8$ Hz, 1H), 8.60 (d, $J=4.9$ Hz, 1H); MS (FD) m/z 453 (M^+), 455 ($M^+ + 2$). Anal. ($C_{24}H_{17}Cl_2NO_4 \cdot H_2O$) C, H, N.

4-Methoxyphenyl 4-bromophenyl ketone (10l). Compound **10l** was prepared as described for **10b**, except using 4-bromobenzoyl chloride (57%). ^1H NMR ($CDCl_3$, 500 MHz): δ 3.89 (s, 3H), 6.97 (d, $J=8.6$ Hz, 2H), 7.62 (d, $J=1.8$ Hz, 2H), 7.62 (d, $J=1.8$ Hz, 2H), 7.80 (d, $J=9.2$ Hz, 2H); MS (FD) m/z 290 (M^+), 292 ($M^+ + 2$).

4-Hydroxyphenyl 4-bromophenyl ketone (11l). Compound **11l** was prepared as described for **11j**, except using **10l** (85%). ^1H NMR (DMSO-d_6, 500 MHz): δ 6.90 (d, $J=8.5$ Hz, 2H), 7.61 (d, $J=8.5$ Hz, 2H), 7.66 (d, $J=8.6$ Hz, 2H), 7.74 (d, $J=8.5$ Hz, 2H), 10.46 (brs, 1H); MS (FD) m/z 276 (M^+), 278($M^+ + 2$).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-bromophenyl)methanone (8ag). Compound **8ag** was prepared as described for **8w**, except using **11l**. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 1.57 g (79%). Mp: 173–174 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.05 (s, 3H), 4.66 (s, 3H), 6.66 (d, $J=4.9$ Hz, 1H), 7.27 (d, $J=8.6$ Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.65 (d, $J=7.9$ Hz, 2H), 7.70 (d, $J=8.5$ Hz, 2H), 7.90 (d, $J=8.6$ Hz, 2H), 8.58 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 463 (M^+), 465 ($M^+ + 2$). Anal. ($C_{24}H_{18}BrNO_4$) C, H, N.

4-Methoxyphenyl 4-iodophenyl ketone (10m). Compound **10m** was prepared as described for **10b**, except using 4-iodobenzoyl chloride (21%). MS (FD) m/z 338 (M^+).

4-Hydroxyphenyl 4-iodophenyl ketone (11m). Compound **11l** was prepared as described for **11j**, except using **10l**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) to obtain 380 mg (55%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.89 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 10.47 (s, 1H); MS (ESI) m/z 325 ($M^+ + 1$).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-iodophenyl)-methanone (8ah). Compound **8ah** was prepared as described for **8w**, except using **11m**. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 459 mg (77%). Mp: 163–165 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H), 4.07 (s, 3H), 6.66 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 7.6 Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 7.9 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 8.58 (d, J = 5.5 Hz, 1H); MS (FD) m/z 511 (M^+). Anal. ($C_{24}H_{18}INO_4$) C, H, N.

4-Bromo-1-methoxymethylphenol (13). To a solution of 4-bromophenol (17.3 g, 10.0 mmol) in DMF (90 mL) was added NaH (60% in oil, 2.64 g, 66.0 mmol) at 0 °C for 1 h. After stirring at room temperature for 8 h, chloromethyl methyl ether (8.85 g, 110 mmol) was added and stirred for a further 1 h. The reaction mixture was partitioned between water and AcOEt. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with hexane/acetone (4/1) to obtain 18.25 g of **13** (84%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 3.46 (s, 3H), 5.13 (s, 2H), 6.91 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H); MS (FD) m/z 216 (M^+), 218 ($M^+ + 2$).

4-Tri-*n*-butyltin-1-methoxymethylphenol (14). To a solution of **13** (15.99 g, 73.69 mmol) in THF (20 mL) was added Mg (1.97 g) and a drop of an iodine solution in THF under argon at room temperature. The resulting suspension was refluxed till magnesium disappeared, and returned to room temperature. Then a solution of ^{n}Bu_3SnCl (23.99 g, 73.70 mmol) dissolved in THF (10 mL) was added slowly dropwise to the suspension. The reaction mixture was stirred at room temperature for 4 h and then partitioned between 5% aqueous NH_4Cl and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography eluting with hexane/AcOEt (10/1) to obtain 31.39 g of **14** (100%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 0.80–1.65 (m, 27H), 3.48 (s, 3H), 5.17 (s, 2H), 6.91–7.42 (m, 4H); MS (FD) m/z 428 ($M^+ + 1$).

2-Furoyl 4-hydroxyphenyl ketone (11n). To a solution of **14** (1.28 g, 3.00 mmol) and 2-furoyl chloride (392 mg, 3.00 mmol) in $CHCl_3$ (5 mL) was added $PdCl_2(PPh_3)_2$ (8 mg, 0.01 mmol) and heated under reflux for 11 h. The reaction mixture was partitioned between water and ether and the organic layer was washed with saturated aqueous KF and brine. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue (662 mg) was dissolved in THF (2 mL) and added 6 N aqueous HCl (12 mL). The mixture was heated under reflux for 3 h and partitioned between brine and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with hexane/AcOEt (5/1) to obtain 218 mg of **11n** (39%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.76 (dd, J = 1.2, 3.1 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 3.1 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 1.2 Hz, 1H), 10.39 (s, 1H); MS (FD) m/z 188 (M^+).

2-Furoyl-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone (8u). To a solution of **11n** (205 mg, 1.09 mmol) in xylene (5 mL) was added 4-dimethylaminopyridine (146 mg, 1.20 mmol) and stirred under argon at room temperature for 1 h. Then **7** (244 mg, 1.09 mmol) was added and heated under reflux for 20 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The resulting residue was purified by chromatography on silica gel eluting with hexane/AcOEt (4/1), $CHCl_3$ and $CHCl_3$/AcOEt (5/1) to obtain 192 mg of **8u** (47%). Mp 126–127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H), 4.07 (s, 3H), 6.63 (dd, J = 1.8, 3.7 Hz, 1H), 6.65 (d, J = 5.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 3.7 Hz, 1H), 7.47 (s, 1H), 7.48 (s, 1H), 7.73 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 9.2 Hz, 2H), 8.58 (d, J = 5.5 Hz, 1H); MS (FD) m/z 375 (M^+). Anal. ($C_{22}H_{17}NO_5 \cdot 0.3H_2O$) C, H, N.

4-Hydroxyphenyl 4-methylphenyl ketone (11o). Compound **11o** was prepared as described for **11n**, except using 4-toluoyl chloride. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 271 mg (34%). MS (FD) m/z 212 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-methylphenyl)methanone (8y). Compound **8y** was prepared as described for **8w**, except using **11o**. Purification was performed by column chromatography on silica gel eluting with $CHCl_3$/AcOEt (5/1) to obtain 118 mg (74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.45 (s, 3H), 4.03 (s, 3H), 4.06 (s, 3H), 6.65 (d, J = 5.5 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.46 (s, 1H), 7.49 (s, 1H), 7.74 (d, J = 7.9 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 8.57 (d, J = 4.9 Hz, 1H); MS (FD) m/z 399(M^+). Anal. ($C_{25}H_{21}NO_4$) C, H, N.

4-Hydroxyphenyl 4-trifluoromethylphenyl ketone (11p). Compound **11p** was prepared as described for **11n**, except using 4-(trifluoromethyl)benzoyl chloride. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 348 mg (30%). MS (FD) m/z 266 (M^+).

(4-Trifluoromethylphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone (8ab). Compound **8ab** was prepared as described for **8w**, except using **11p**. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 98 mg (60%). Mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H), 4.06 (s, 3H), 6.68 (d, J = 4.9 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.91 (d, J = 7.9 Hz, 2H),

7.94 (d, $J=9.2$ Hz, 2H), 8.59 (d, $J=4.9$ Hz, 1H); MS (FD) m/z 453 (M^+). Anal. ($C_{25}H_{18}F_3NO_4$) C, H, N.

4-Hydroxyphenyl 4-nitrophenyl ketone (11r). Compound **11r** was prepared as described for **11n**, except using 4-nitrobenzoyl chloride. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 398 mg (55%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.92 (d, $J=8.6$ Hz, 2H), 7.69 (d, $J=8.6$ Hz, 2H), 7.89 (d, $J=8.5$ Hz, 2H), 8.36 (d, $J=8.5$ Hz, 2H), 10.62 (s, 1H); MS (FD) m/z 243 (M^+).

{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}(4-nitrophenyl)-methanone (8ai). Compound **8ai** was prepared as described for **8w**, except using **11r**. Purification was performed by column chromatography on silica gel eluting with hexane/acetone (2/1) to obtain 238 mg (36%). Mp 165–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.63 (s, 3H), 4.07 (s, 3H), 6.69 (d, $J=4.9$ Hz, 1H), 7.29 (d, $J=8.5$ Hz, 2H), 7.44 (s, 1H), 7.47 (s, 1H), 7.93 (d, $J=9.2$ Hz, 2H), 7.96 (d, $J=8.5$ Hz, 2H), 8.37 (d, $J=8.5$ Hz, 2H), 8.60 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 430 (M^+). Anal. ($C_{24}H_{18}N_2O_6\cdot0.5H_2O$) C, H, N.

4-Hydroxyphenyl 4-trifluoromethoxyphenyl ketone (11s). Compound **11s** was prepared as described for **11n**, except using 4-(trifluoromethoxy)benzoyl chloride. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) to obtain 2.1 g (25%). MS (FD) m/z 282 (M^+).

(4-Trifluoromethoxyphenyl){4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}methanone (8aj). Compound **8aj** was prepared as described for **8w**, except using **11s**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 470 mg (49%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H) 4.07 (s, 3H), 6.66 (d, $J=4.5$ Hz, 1H), 7.28 (d, $J=8.5$ Hz, 2H), 7.35 (d, $J=8.7$ Hz, 2H), 7.46 (s, 1H), 7.47 (s, 1H), 7.89 (d, $J=8.5$ Hz, 2H), 7.92 (d, $J=9.2$ Hz, 2H), 8.59 (d, $J=4.5$ Hz, 1H); MS (FD) m/z 469 (M^+). Anal. ($C_{25}H_{18}F_3NO_5\cdot1.5H_2O$) C, H, N.

4-(4-Hydroxybenzoyl)benzonitrile (11t). Compound **11t** was prepared as described for **11n**, except using 4-cyanobenzoyl chloride. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) to obtain 250 mg (37%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.91 (d, $J=9.2$ Hz, 2H), 7.67 (d, $J=8.5$ Hz, 2H), 7.80 (d, $J=7.9$ Hz, 2H), 8.01 (d, $J=8.6$ Hz, 2H), 10.57 (s, 1H); MS (FD) m/z 223(M^+).

4-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]benzoyl}benzonitrile (8ak). Compound **8ak** was prepared as described for **8w**, except using **11t**. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 199 mg (47%). Mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3H), 4.06 (s, 3H), 6.68 (d, $J=5.5$ Hz, 1H), 7.29 (d, $J=8.5$ Hz, 2H), 7.45 (s, 1H), 7.46 (s, 1H), 7.82 (d, $J=7.9$ Hz, 2H), 7.90 (d, $J=8.6$ Hz, 2H), 7.91 (d, $J=8.5$ Hz, 2H), 8.60 (d, $J=5.5$ Hz, 1H); MS (FD) m/z 410(M^+). Anal. ($C_{25}H_{18}N_2O_4$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-*tert*-butylphenyl)carboxamide (3: Ki6945).** To a solution of **16a** (54 mg, 0.18 mmol) and 4-*tert*-butylbenzoic acid (102 mg, 0.57 mmol) in DMF (3 mL) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (106 mg, 0.55 mmol) and stirred at room temperature for 6 h. The reaction mixture was partitioned between water and AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting $CHCl_3$/acetone (10/1) to obtain 59 mg of the **3** (72%). Mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 9H), 4.05 (s, 3H), 4.06 (s, 3H), 6.49 (d, $J=5.4$ Hz, 1H), 7.21 (d, $J=9.0$ Hz, 2H), 7.43 (s, 1H), 7.53 (d, $J=8.3$ Hz, 2H), 7.57 (s, 1H), 7.75 (d, $J=9.0$ Hz, 2H), 7.84 (d, $J=8.5$ Hz, 2H), 7.90 (br, 1H), 8.49 (d, $J=5.4$ Hz, 1H); MS (FD) m/z 456 (M^+). Anal. ($C_{28}H_{28}N_2O_4$) C, H, N.

***N*-(4-*t*-Butylphenyl)-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}carboxamide (19).** To a solution of 4-[6,7-dimethoxy-4-quinolyl]oxybenzoic acid (54 mg, 0.17 mmol) and 4-*tert*-butylaniline (102 mg, 0.68 mmol) in DMF (3 mL) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (106 mg, 0.55 mmol) and stirred at room temperature for 6 h. The reaction mixture was partitioned between water and AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting $CHCl_3$/acetone (10/1) to obtain 29 mg of the **19** (35%). ^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.34 (s, 9H), 4.03 (s, 3H), 4.06 (s, 3H), 6.57 (d, $J=5.3$ Hz, 1H), 7.2–8.1 (m, 11H), 8.55 (d, $J=5.3$ Hz, 1H); MS (FD) m/z 456 (M^+); HRMS (ESI) ($C_{28}H_{29}N_2O_4$) ($M+H^+$) calcd 457.2127, found 457.2140.

***N*-(4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl)-*N*-methyl-(4-*t*-butylphenyl)carboxamide (18).** To a solution of **3** (100 mg) in DMF (3 mL) was added NaH (60% in oil, 10 mg, mmol) and stirred at 0 °C for 1 h. Then, methyl iodide (31 mg) was added and stirred for 3 h. The reaction mixture was purified by column chromatography on silica gel eluting $CHCl_3$/acetone (10/1) to obtain 48 mg of **18** (46%). Mp: 172–174 °C; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.28 (s, 9H), 3.54 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.32 (d, $J=5.3$ Hz, 1H), 7.0–7.3 (m, 8H), 7.42 (s, 1H), 7.50 (s, 1H), 8.47 (d, $J=5$, 3 Hz, 1H); MS (FD) m/z 470 (M^+). Anal. ($C_{29}H_{30}N_2O_4\cdot H_2O$) C, H, N.

***N*-{3-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-*t*-butylphenyl)carboxamide (17a).** To a solution of **16b** (54 mg, 0.17 mmol) and 4-*t*-butyl benzoic acid (102 mg, 0.57 mmol) in DMF (3 mL) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (106 mg, 0.55 mmol) and stirred at room temperature for 6 h. The reaction mixture was purified by column chromatography on silica gel eluting $CHCl_3$/acetone (10/1) to obtain 50 mg of **17a** (61%). Mp: 93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 9H), 4.05 (s, 3H), 4.05 (s, 3H), 6.57 (d, $J=5.4$ Hz, 1H), 6.97 (ddd, $J=1.2$, 2.2, 7.8 Hz, 1H), 7.42–7.51 (m, 5H), 7.55(s, 1H), 7.70 (t, $J=2.2$ Hz, 1H), 7.81(d, $J=8.3$ Hz, 2H), 8.02 (s, 1H), 8.52 (d, $J=5.4$ Hz, 1H); MS (ESI) m/z 457 ($M^+ +1$). Anal. ($C_{28}H_{28}N_2O_4\cdot H_2O$) C, H; N: calcd 5.90, found 5.48.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-bromophenyl)carboxamide (17b).** Compound **17b** was prepared as described for **3**, except using 4-bromobenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 43 mg (52%). Mp: 224 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11 (s, 3H), 4.15 (s, 3H), 6.69 (d, J = 6.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 8.11 (s, 1H), 8.37 (d, J = 6.8 Hz, 1H), 8.39 (s, 1H); MS (ESI) m/z 479 (M^+), 481 ($M^+ + 2$); HRMS (ESI) ($C_{24}H_{20}BrN_2O_4$) ($M + H^+$) calcd 479.0606, found 479.0637.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-trifluoromethylphenyl)carboxamide (17c).** Compound **17c** was prepared as described for **3**, except using 4-trifluoromethylbenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 32 mg (38%). Mp: 240–242 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.09 (s, 3H), 4.09 (s, 3H), 6.58 (d, J = 6.1 Hz, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.79 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.3 Hz, 2H), 8.39 (d, J = 6.1 Hz, 1H), 8.54 (s, 1H); MS (ESI) m/z 469 ($M^+ + 1$). Anal. ($C_{25}H_{19}F_3N_2O_4$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-*n*-butylphenyl)carboxamide(17d).** Compound **17d** was prepared as described for **3**, except using 4-*n*-butylbenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 65 mg (78%). Mp: 135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95(t, J = 7.3 Hz, 3H), 1.33–1.42 (m, 2H), 1.60–1.67 (m, 2H), 2.97 (t, J = 7.6 Hz, 2H), 4.09 (s, 3H), 4.10 (s, 3H), 7.60 (d, J = 6.1 Hz, 1H), 7.22 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.61 (s, 1H), 7.78(s, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 8.03 (s, 1H), 8.46 (d, J = 5.9 Hz, 1H); MS (ESI) m/z 457 ($M^+ + 1$). Anal. ($C_{28}H_{28}N_2O_4$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-nitrophenyl)carboxamide (17e).** Compound **17e** was prepared as described for **3**, except using 4-nitrobenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 60 mg (77%). Mp 253 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.09(s, 3H), 4.12 (s, 3H), 6.64 (d, J = 5.9 Hz, 1H), 7.25 (d, J = 9.0 Hz, 2H), 7.33 (s, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 9.0 Hz, 2H), 8.35 (d, J = 8.8 Hz, 2H), 8.51 (d, J = 5.9 Hz, 1H); MS (ESI) m/z 446 ($M^+ + 1$); HRMS (ESI) ($C_{24}H_{20}N_3O_6$) ($M + H^+$) calcd 446.1352, found 446.1340.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-*n*-butoxyophenyl)carboxamide (17f).** Compound **17f** was prepared as described for **3**, except using 4-butoxybenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 34 mg (41%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (t, J = 7.3 Hz, 3H), 1.49–1.57 (m, 2H), 1.78–1.83 (m, 2H), 4.04 (t, J = 6.3 Hz, 2H), 4.11 (s, 3H), 4.15 (s, 3H), 6.70 (d, J = 6.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 9.0 Hz, 2H), 7.65 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55 (d, J = 6.6 Hz, 1H); ESI-MS (m/z): 473 ($M^+ + 1$). Anal. ($C_{24}H_{28}N_2O_5 \cdot H_2O$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-biphenyl)carboxamide (17g).** To a solution of 6,7-dimethoxy-4-(4-aminophenoxy)quinoline (52 mg, 0.18 mmol) and triethylamine (3 mL) in CH_2Cl_2 (2 mL) was added 4-biphenylcarbonyl chloride (80 mg, 0.37 mmol). The mixture was stirred at room temperature for 6 h. The reaction mixture was purified by column chromatography on silica gel eluting $CHCl_3$/acetone (10/1) to obtain 9 mg of **17g** (10%). Mp 235–237 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11 (s, 3H), 4.14 (s, 3H), 6.68 (d, J = 6.3 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.41–7.51 (m, 4H), 7.64 (d, J = 8.5 Hz, 2H), 7.64 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H), 8.30 (s, 1H), 8.42 (d, J = 6.3 Hz, 1H); MS (ESI) m/z 476 ($M^+ + 1$). Anal. ($C_{30}H_{24}N_2O_4$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(3,4-dimethoxyphenyl)carboxamide (17h).** Compound **17h** was prepared as described for **3**, except using 3,4-dimethoxybenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 7 mg (8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96 (s, 3H), 3.97 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.52 (d, J = 5.4 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 9.0 Hz, 2H), 7.47 (dd, J = 2.0, 8.3 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.58 (s, 1H), 7.80 (d, J = 9.0 Hz, 2H), 8.01 (s, 1H), 8.19 (s, 1H), 8.47 (d, J = 5.6 Hz, 1H); MS (ESI) m/z 461 ($M^+ + 1$). Anal. ($C_{26}H_{24}N_2O_6$) C, H, N.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-(4-acetylphenyl)carboxamide (17i).** Compound **17i** was prepared as described for **3**, except using 4-acetylbenzoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 43 mg (53%). Mp: 210 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.67 (s, 3H), 4.09 (s, 3H), 4.10 (s, 3H), 6.59 (d, J = 5.9 Hz, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.77 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 8.36 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H); MS (ESI) m/z 443 ($M^+ + 1$); HRMS (ESI) ($C_{26}H_{23}N_2O_5$) ($M + H^+$) calcd 443.1607, found 443.1606.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-2-thiophenecarboxamide (17j).** Compound **17j** was prepared as described for **3**, except using 2-thiophenecaroboxylic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 37 mg (54%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.09 (s, 3H), 4.09 (s, 3H), 6.58 (d, J = 6.1 Hz, 1H), 7.16 (dd, J = 3.9, 5.1 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.58 (dd, J = 1.2, 5.1 Hz, 1H), 7.61 (s, 1H), 7.81 (s, 1H), 7.84 (dd, J = 1.2, 3.9 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 8.24 (s, 1H), 8.49 (d, J = 5.9 Hz, 1H); MS

(ESI) *m/z* 391 ($M^+ + 1$); HRMS (ESI) ($C_{22}H_{19}N_2O_4S$) ($M + H^+$) calcd 407.1066, found 407.1080.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}-2-furamide (17k).** Compound **17k** was prepared as described for **3**, except using 2-furoic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 35 mg (48%). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.08 (s, 3H), 4.10 (s, 3H), 6.58 (d, $J = 5.9$ Hz, 1H), 6.60 (dd, $J = 1.7$, 3.4 Hz, 1H), 7.22 (d, $J = 9.0$ Hz, 2H), 7.30 (dd, $J = 0.7$, 3.4 Hz, 1H), 7.55 (dd, $J = 0.7$, 1.7 Hz, 1H), 7.60 (s, 1H), 7.70 (s, 1H), 7.80 (d, $J = 8.8$ Hz, 2H), 8.19 (s, 1H), 8.49 (d, $J = 5.9$ Hz, 1H); MS (ESI) *m/z* 391 ($M^+ + 1$); HRMS (ESI) ($C_{22}H_{19}N_2O_5$) ($M + H^+$) calcd 391.1294, found 391.1274.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}acetamide (17l).** Compound **17l** was prepared as described for **17g**, except using acetic anhydride. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 7 mg (10%). Mp: 105 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H), 4.11 (s, 3H), 4.17 (s, 3H), 6.65 (d, $J = 6.6$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 2H), 7.64 (s, 1H), 7.81 (d, $J = 8.8$ Hz, 2H), 7.90 (s, 1H), 8.12 (s, 1H), 8.39 (d, $J = 6.3$ Hz, 1H); MS (ESI) *m/z* 339 ($M^+ + 1$); HRMS (ESI) ($C_{19}H_{19}N_2O_4$) ($M + H^+$) calcd 339.1345, found 339.1367.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}cyclopropanecarboxamide (17m).** Compound **17m** was prepared as described for **3**, except using cyclohexanecarboxylic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 45 mg (64%). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.64 (m, 2H), 1.81 (m, 2H), 1.91 (m, 4H), 2.75 (m, 1H), 4.04 (s, 3H), 4.04 (s, 3H), 6.44 (d, $J = 4.9$ Hz, 1H), 7.13 (d, $J = 9.2$ Hz, 2H), 7.45 (s, 1H), 7.55 (m, 1H), 7.65 (d, $J = 8.6$ Hz, 2H), 8.47 (d, $J = 5.5$ Hz, 1H); MS (ESI) *m/z* 393 ($M^+ + 1$); HRMS (ESI) ($C_{23}H_{25}N_2O_4$) ($M + H^+$) calcd 393.1814, found 393.1794.

***N*-{4-[6,7-Dimethoxy-4-quinolyl]oxy}phenyl}cyclohexanecarboxamide (17n).** Compound **17n** was prepared as described for **3**, except using cyclohexanecarboxylic acid. Purification was performed by column chromatography on silica gel eluting with hexane/AcOEt (4/1) then $CHCl_3$/AcOEt (5/1) to obtain 45 mg (64%). Amorphous substance; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.26–1.39 (m, 3H), 1.52–1.62 (m, 2H), 1.79–2.00 (m, 5H), 2.27–2.33 (m, 1H), 4.08 (s, 3H), 4.11 (s, 3H), 6.55 (d, $J = 6.1$ Hz, 1H), 7.16 (d, $J = 9.0$ Hz, 2H), 7.45 (s, 1H), 7.60 (s, 1H), 7.72 (d, $J = 9.0$ Hz, 2H), 7.78 (s, 1H), 8.45 (d, $J = 5.9$ Hz, 1H); MS (ESI) *m/z* 407 ($M^+ + 1$). Anal. ($C_{24}H_{26}N_2O_4 \cdot H_2O$) C, H, N.

CGP 53716 was prepared by previous literatures.[10]

Receptor autophosphorylation assay in intact cells

The assay of PDGFβr autophosphorylation was carried out by a method previously published,[14] and the method was briefly described as follows.

Growth arrested MCs were treated with various concentrations of compound in the medium containing 0.1% BSA at 37 °C for 1 h. Then recombinant human PDGF-BB [Upstate Biotechnology Inc. (UBI)], which was adjusted to 50 ng/mL as a final concentration in the medium, was added and incubated at 37 °C for 10 min. After removal of the medium, lysate of the cells was prepared. Electrophoresis was carried out using 7.5% polyacrylamide gel, and the separated proteins in the gel were transferred to Immunobilon PVDF transfer membrane (Daiichi Pure Chemical, Tokyo, Japan). Western blot analysis was performed with anti-phosphotyrosine monoclonal antibody (4G10, UBI). Bound antibodies were visualized with using horseradish peroxidase-conjugated goat anti-mouse IgG (Amersham, UK) and the enhanced chemiluminescene (ECL) detection system (Amersham). The density of each protein band was quantitated using a VIDAS Plus image analyzer (Carl Zeiss, Oberkochen, Germany). After the analysis of tyrosine phosphorylation, bound antibodies on the blotting membrane were removed. PDGFβr on the membrane was detected by Western blot with rabbit anti-PDGFβr antiserum (UBI) and confirmed corresponding bands. Tyrosine phosphorylation assay of other receptors was carried out by the same method as that of the PDGFβr. A431 cells, NIH3T3 cells and HepG2 cells were used to study autophosphorylation of the EGFr, bFGFr and insulinβr induced by recombinant human EGF (UBI), recombinant human bFGF (UBI) and recombinant human insulin (Sigma Chemical Co.), respectively.

Cell-free receptor tyrosine kinase assay

Tyrosine phosphorylation of PDGFβr was analyzed by Western blot using anti-phosphotyrosine antibodies and detected by ECL fluorography as previously published[14] and the method was briefly described as follows.

Lysate of quiescent NIH3T3 cells was prepared by treatment of the detergent buffer (50 mM Hepes (pH 7.5), 1.5 mM $MgCl_2$, 150 mM NaCl, 1 mM EGTA, 10% glycelol, and 1% Triton X-100). The lysate was reduced with PDGF-BB (50 ng/mL) at 4 °C for 30 min, then PDGFβr antiserum at a 1:100 dilution as a final concentration and with protein A-sepharose-beads (Pharmacia Biotech). The immunoprecipitates were washed with HNTG buffer [20 mM Hepes (pH 7.5), 150 mM NaCl, 0.1% Triton X-100 and 10 mM $MgCl_2$]. The mixture was incubated with compound at 4 °C for 10 min. The reaction was started by the addition of 20 μM ATP (disodium salt, Sigma), incubated at 4 °C for 10 min and stopped by the addition of SDS sample buffer (0.14 M Tris–HCl (pH 7.5), 22.4% glycelol, 6% SDS, 0.02% bromophenol blue, 10% 2-marcaptoethanol).

EGFr kinase assay was measured by Homogeneous time resolved florescence (HTRF) techniques,[19] it was based on phosphorylation of biotinylated poly-Glu, Tyr [CIS bio international (CIS)] by EGFr. Src kinase activity was measured in ELISA system (Roche, Tyroisine Kinase Assay Kit), it was based on phosphorylation of $p34^{cdc2}$ substrate peptide, PKS-1, by Src. PKA kinase activity was measured by PKA Assay Kit (UBI),

it was based on phosphorylation of a specific peptide, Kemptide, using the transfer of [γ-^{32}P] ATP by PKA. PKC kinase activity was measured by PKC Assay Kit (UBI), it was based on phosphorylation of a specific peptide, QKRPSQRSKYL, using the transfer of [γ-^{32}P] ATP by PKC. MAP kinase activity was measured by MAP Kinase Assay Kit (UBI), it was based on phosphorylation of a specific substrate, myelin basic protein (MBP), using the transfer of [γ-^{32}P] ATP by MAP kinase. MEK1 activity was measured by MEK1 Assay Kit (UBI), it was based on phosphorylation of a specific substrate, myelin basic protein (MBP), using the transfer of [γ-^{32}P] ATP.

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