Inhibition of the EGF-Stimulated Cellular Proliferation of ER 22 Cells by Hydroxybiphenyl Derivatives

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Several series of hydroxybiphenyl compounds substituted by a hydrophobic group (*tert*-butyl or phenyl) and bearing a free or protected carboxylic moiety were synthesized. The compounds were tested for their ability to inhibit the intrinsic tyrosine protein kinase activity of the EGF-receptor *in vitro* and the EGF-stimulated DNA-synthesis by ER 22 cells. Although the compounds of each series had poor *in vitro* inhibitory potencies ($IC_{50} \gg 100\ \mu M$), most of them inhibited the EGF-dependent cellular proliferation of ER 22 cells at relatively low doses ($IC_{50} = 1.1\ \mu M$ for compound **14**). Structure–activity studies based on the cellular results showed that the most interesting series was the linear terphenyl series B of 2′-hydroxy-1,1′:4′,1″-terphenyl-4-carboxylates. The availability of the hydroxyl group, either protected or unprotected, the linear arrangement of the hydrophobic moiety, the biphenyl skeleton, and the carboxylic group seem to be essential for the activity of the compounds.

Introduction

The regulation of cell proliferation and differentiation arises from the coordinated action of the growth stimulatory proto-oncogenes and the growth inhibitory tumor suppressor genes. An abnormal expression of the protein encoded by the proto-oncogenes and/or the loss of expression of the tumor suppressor genes leads to an imbalance in this coordination process which may result in the development of the malignant phenotype or other proliferative diseases.[1,2] The ability of proto-oncogenes to induce tumorigenesis is explained by the fact that most of their products are involved in the cellular signaling pathways.[2] In particular, 50% of the known proto-oncogenes encode proteins which possess an intrinsic protein–tyrosine kinase (PTK) activity, especially transmembrane receptor PTKs (such as the epidermal growth factor receptor (EGF-R) or the insulin receptor). The activation of these receptors, stimulated by external binding of a growth factor, triggers kinase activity which is known to be essential for their biological activity.[3–5] Thus, point mutations within the catalytic domain, affecting the capacity of these receptors to induce phosphorylation of tyrosine residues, have been demonstrated to abolish signal transduction.[6–9] Moreover, an increasing number of examples, showing an association between an enhanced activity of the receptors or their oncogenic mutants and malignancy, have been reported: c-erbB2 and human breast cancer,[10] EGF-R and epidermoid,[11] or breast[12] tumors.

Because of their involvement in both normal and abnormal cellular signal transduction, PTK receptors constitute an interesting area of research. Many recent studies have dealt with the development of specific PTK inhibitors as potential anticancer drugs (for reviews, see refs 13 and 14) and useful pharmacological tools for investigating the role of protein–tyrosine phosphorylation during signaling pathways.[15]

Concept and Design of Inhibitors

PTKs are enzymes which catalyze the direct transfer of the γ-phosphate of ATP to the hydroxyl group of tyrosines in many substrate proteins. The first potent inhibitors of their activity were isolated from natural sources. Most of them were shown to be competitive inhibitors of ATP binding, except for styrene derivatives such as piceatannol[16] and erbstatin.[17] Many investigators therefore based their design of synthetic PTK inhibitors on the tyrosine and styrene structures. Given the high degree of homology between the nucleotide binding sites of the diverse protein kinases,[18] it was thought that this approach might lead to compounds endowed with high specificity and low cytotoxicity.

We have synthesized a series of hydroxybiphenyl derivatives whose structure is related to the phenol styrene skeleton, which has been demonstrated to be the key substructure of a number of styrene-based inhibitors such as tyrphostins[19,20] or α-cyanocinnamamides.[21,22] In these compounds, both the hydroxyl moiety and the C=C double bond are important.[15] Accordingly, the phenol styrene skeleton was modified by replacing the styrene double bond by a phenyl group. Since investigations on the structural influences of styryl-based inhibitors on EGF-R and $p56^{lck}$ tyrosine protein kinases concluded that the 2,5-dihydroxyphenyl ring of erbstatin (compared with the 3,4-dihydroxyphenyl ring of tyrphostins) confers specificity for EGF-R relative to $p56^{lck}$, regardless of double bond substituents,[23,24] 2,5-dihydroxybiphenyl derivatives were first synthesized (Figure 1). These compounds were good inhibitors of the EGF-R tyrosine kinase activity but were chemically unstable.[25] This instability was not surprising and prompted us to remove, separately, each one of the hydroxyl groups.

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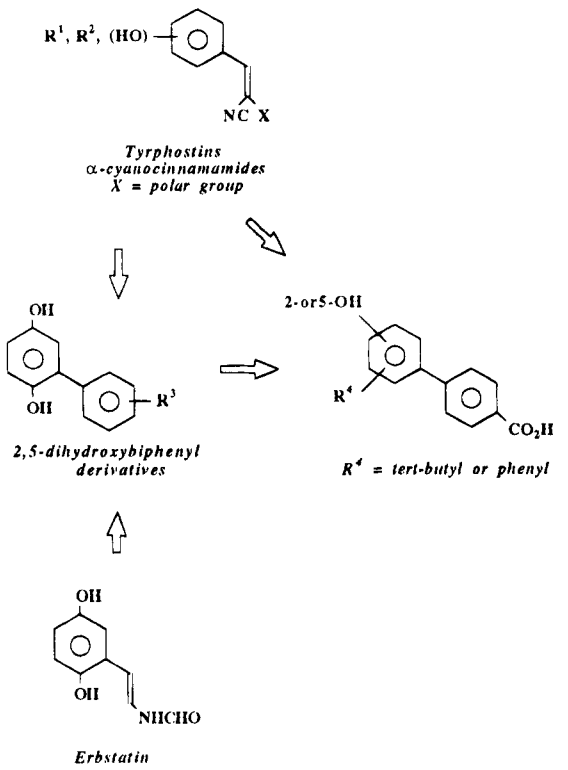


Figure 1.

Given that substitutions on the benzene ring of α-cyanocinnamamides by hydrophobic groups (*tert*-butyl, isopropyl, phenyl) notably increases their inhibitory properties,[21] particulary for tyrphostins,[26,27] and that activation of the double bond of styrene compounds by a polar group has been shown to be essential for inhibitory potency,[28] we decided to substitute the phenol ring by either a *tert*-butyl or a phenyl moiety and the second aromatic ring by a carboxylate for a polar group. This group might also be capable of interacting with cationic residues of the catalytic domain, such as the bivalent cations thought to be involved in the transition state,[29] and to enhance the cellular penetration of the components when substituted as ester or amide.

By analogy with the compounds taken as references, the hydrophobic group was introduced on the phenol ring either in the para or in the meta position, whereas the carboxylate group was placed on the second aromatic ring in the para position (Figure 1). Following this structural approach, eight series of compounds could be devised, five of which were synthesized (A–E, Table 1).

Chemistry

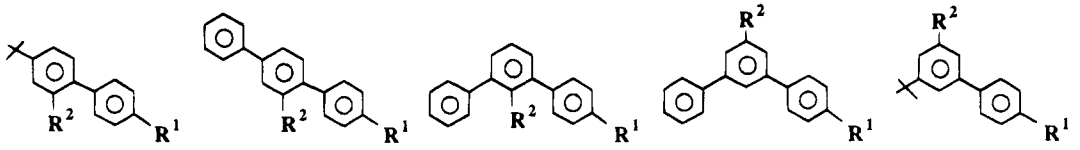
The five series of biphenyl compounds synthesized (A–E) are shown in Table 1. The general synthetic procedure followed to obtain the series A–C (Scheme 1, compounds **3**–**24**) used a palladium-catalyzed cross-coupling reaction of phenylboronic acids with bromoarenes, which is a general tactic for the construction of polyphenyls.[30–33] The phenylboronic acids were prepared following a directed ortho-metalation procedure of suitably substituted (methoxymethoxy)arenes. The acetal was chosen as an ortho-directing group not only for the facility with which it can be cleaved to recover the free phenolic compounds but also because it is known to give highly selective hydrogen exchange reactions.[34–37] Thus, the hydroxyl group of the commercial phenols was protected prior to the metalation by conversion into methoxymethoxy acetals as previously described.[38] The (methoxymethoxy)arenes **1**, **10**, and **19** obtained were subjected to standard ortho-directed metalation conditions (*n*-BuLi/TMEDA/Et_2O/−40 °C → room temperature) and quenched with $B(OMe)_3$[37] to provide the required phenylboronic acids **2**, **11**, and **20** in good yields. Because of their high instability, these compounds were used without any purification in the cross-coupling reactions. Compound **20** seemed to be particularly unstable, since after a few days it degraded into the corresponding unprotected phenol which was used directly for the synthesis of biaryls **23** and **24**. In the case of compounds **1** and **10**, a problem of regioselectivity might have been expected as these compounds have two nonequivalent positions ortho to the methoxymethoxy group, but the expected 1,3,4-isomers were obtained without detecting any trace of the 1,2,3-substituted analogs. This regioselectivity cannot be explained entirely by the large steric requirements of *tert*-butyl and phenyl substituents since a previously described metalation of 3-*tert*-butylphenol using OCH_3 as an ortho-directing group and *t*-BuLi as a metalating agent afforded a 91:9 ratio of respectively 1,3,4- and 1,2,3-isomers in a 73% yield.[39] Both the hindrance of the hydrophobic substituents of the aromatic group and that of the bicoordinated complex involving the methoxymethoxy group may account for the high selectivity of the system. Regioselective metalations of (methoxymethoxy)arenes are thought to proceed by a radical anionic pathway in which the metalating agent is first coordinated to the methoxymethoxy group and the TMEDA, prior to the electron transfer and hydrogen–metal exchange steps (Figure 2).[36,37] It seems likely that the large hindrance, at first of the *n*-BuLi/TMEDA complex previously obtained[34] and next of the substituents of the arenes, does not allow the formation of the corresponding intermediates which would be necessary for a later 1,2,3-substitution.

Boronic acids **2**, **11**, and **20** were then subjected to modified Suzuki cross-coupling conditions (Pd $(PPh_3)_4$/MeOH/toluene/aqueous Na_2CO_3/reflux)[32] with the suitable aryl bromides to give the biaryl compounds **3**–**5**, **12**–**14**, **21**, **23**, and **24**. The appropriately substituted aryl bromides were directly obtained from commercial carboxylic acid and chloride as follows: classical esterification of *p*-bromobenzoic acid ($SOCl_2$/MeOH/reflux) led to the methyl ester with an 80% yield, and the reaction of *p*-bromobenzoyl chloride with either benzylamine or 2,4,4-trimethyl-1-pentanol in pyridine provided the corresponding amide and ester in good yields.

Finally, methoxymethoxy groups were removed by mild acid-catalyzed hydrolysis.[40] Saponification of methyl esters **6** and **12** gave the carboxylic acids **9** and **15**, respectively.

The synthesis of the two series of meta, meta-disubstituted phenols (Scheme 2 compounds **25**–**34**) followed a different procedure, based essentially on a Michael addition of pyridinium salts onto α,β-unsaturated ketones.[41,42] Thus, the ketones **25** and **29** were prepared by the Claisen–Schmidt reaction between an aldehyde (4-formylbenzoic acid) and ketones (acetophenone and 3,3-dimethyl-2-butanone, respectively) under basic conditions (aqueous NaOH/EtOH 95%)[43,44] and were used in the next step without purification.

Table 1. Biological Activities of Biphenyl Compounds



Series A 3-9 Series B 12-18 Series C 21-24 Series D 26-28 Series E 30-34

compound	R^1	R^2	mp, °C	formula	analyses	IC_{50}, μM: inh RRSrc phosphorylation[a]	IC_{50}, μM: inh [^{3}H]TdR incorporation[a]
series A							
3	CO_2CH_3	OCH_2OCH_3	52–53	$C_{20}H_{24}O_4$	C,H	≫10[e]	10
4	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OCH_2OCH_3	73	$C_{27}H_{38}O_4$	C,H	>50	nonsoluble
5	$CONHCH_2C_6H_5$	OCH_2OCH_3	154–155	$C_{26}H_{29}NO_3$	H,N,C[b]	≫5	47% at 5 μM
6	CO_2CH_3	OH	169–170	$C_{18}H_{20}O_3 \cdot nH_2O$	C,H	6% at 10 μM	toxic ≫5
7	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OH	121	$C_{25}H_{34}O_3$	C,H	3% at 10 μM	25% at 5 μM
8	$CONHCH_2C_6H_5$	OH	211	$C_{24}H_{25}NO_2 \cdot nH_2O$	C,H,N	>5	57% at 10 μM
9	CO_2H	OH	244–245	$C_{17}H_{18}O_3 \cdot nH_2O$	C,H	≫10	≫10
series B							
12	CO_2CH_3	OCH_2OCH_3	111	$C_{22}H_{20}O_4$	C,H	2% at 10 μM	>5
13	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OCH_2OCH_3	73	$C_{29}H_{34}O_4$	C,H	≫20	10% at 5 μM
14	$CONHCH_2C_6H_5$	OCH_2OCH_3	180–181	$C_{28}H_{25}NO_3$	H,N,C[c]	≫1	1.1
15	CO_2H	OCH_2OCH_3	207–208	$C_{21}H_{18}O_4$	C,H	8% at 10 μM	10
16	CO_2CH_3	OH	200–201	$C_{20}H_{16}O_3 \cdot nH_2O$	C,H	14% at 10 μM	41% at 1.25 μM
17	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OH	130	$C_{27}H_{30}O_3$	C,H	3% at 10 μM	27% at 5 μM
18	$CONHCH_2C_6H_5$	OH	231	$C_{26}H_{21}NO_2 \cdot nH_2O$	C,H,N	≫1	1.4
series C							
21	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OCH_2OCH_3	oil	$C_{29}H_{34}O_4$	C,H	16% at 10 μM	>10
22	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OH	90–91	$C_{27}H_{30}O_3 \cdot nH_2O$	C,H	11% at 10 μM	>10
23	CO_2CH_3	OH	154–155	$C_{20}H_{16}O_3$	C,H	>20	>5
24	$CONHCH_2C_6H_5$	OH	175–176	$C_{26}H_{21}NO_2$	C,H,N	≫5	≫5
series D							
26	CO_2H	OH	244–245	$C_{19}H_{14}O_3 \cdot nH_2O$	C,H	9% at 10 μM	10
27	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OH	139	$C_{27}H_{30}O_3$	C,H	15% at 10 μM	>5
28	$CONHCH_2C_6H_5$	OH	191–192	$C_{26}H_{21}NO_2$	*d*	5% at 10 μM	8
series E							
30	CO_2H	OH	230–231	$C_{17}H_{18}O_3 \cdot nH_2O$	C,H	>50	>20
31	$CO_2CH_2CH(CH_3)CH_2C(CH_3)_3$	OH	112	$C_{25}H_{34}O_3$	C,H	10% at 10 μM	>5
32	CO_2CH_3	OH	144	$C_{18}H_{20}O_3$	C,H	>10	≫10
33	CH_2OH	OH	167	$C_{17}H_{20}O_2$	C,H	≫10	21% at 10 μM
34	$CONHCH_2C_6H_5$	OH	200	$C_{24}H_{25}NO_2$	C,H,N	≫5	5.4

[a] Methods and calculation of IC_{50} values are described in the Experimental Section. [b] C: calcd, 77.39; found, 76.60. [c] C: calcd, 79.41; found, 78.80. [d] No elemental analysis (only small amount of compound available). [e] When results were given as >> *x* μM, this means that the inhibition was 0% at this concentration and that the compounds were not water soluble at higher concentrations.

Condensation of compound **25** with 1-(2-oxopropyl)-pyridinium chloride (previously obtained by direct reaction of chloroacetone with pyridine) following the procedure described[41] (anhydrous conditions/Et_3N/EtOH/reflux) led, after cyclization, to the expected carboxylic acid **26** with an 87% yield. Compound **30** was prepared with a 63% yield following a similar pathway.

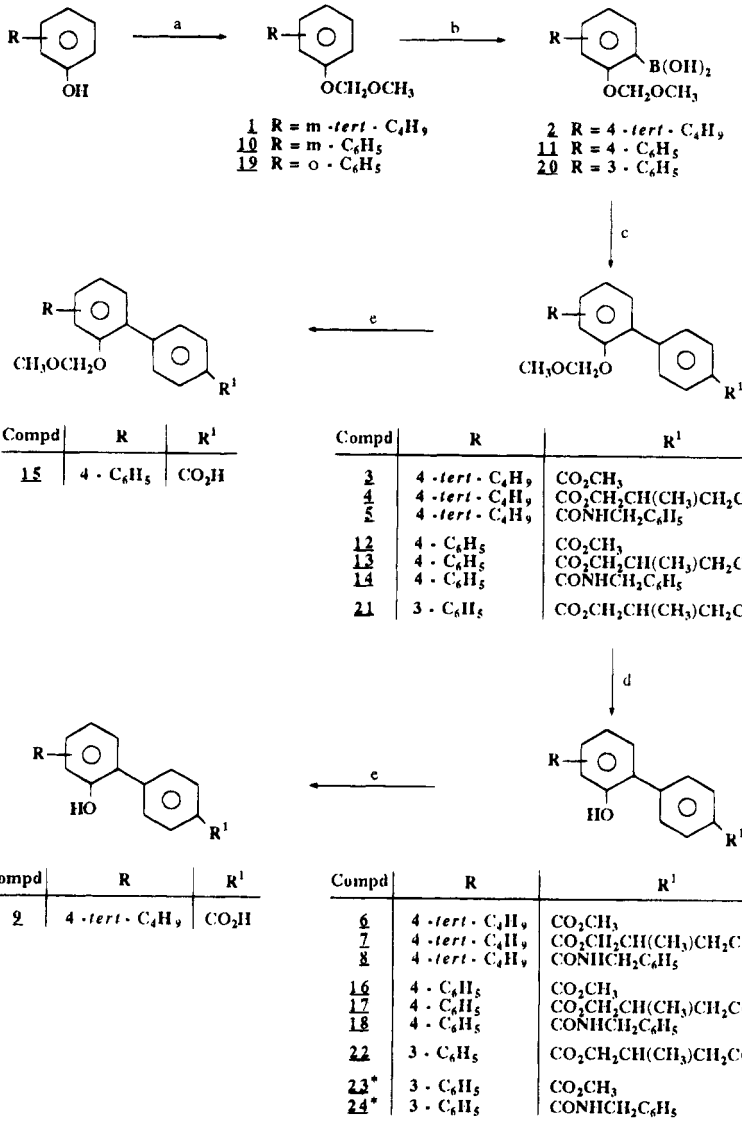
Esterification by alkylation of their cesium salts with 2,4,4-trimethyl-1-bromopentane converted the carboxylic acids **26** and **30** into their 2,4,4-trimethylpentyl esters in moderate yields.[45,46] Classical esterification ($SOCl_2$ 10 equiv, MeOH/reflux) of compound **30** gave the methyl ester **32** which was reduced ($LiAlH_4$/anhydrous THF) to give the alcohol **33** with a 60% yield. Finally, amides **28** and **34** were obtained from the corresponding acids by coupling with benzylamine (BOP/DIEA/DMF).

Results and Discussion

The ability of our compounds to inhibit the protein tyrosine kinase activity associated with EGF-R was evaluated using ER 22 (CCL 39 cells transfected with EGF-R) cell membranes as an enzyme source[47] and the tridecapeptide RR-Src (RRLIEDAEYAARG) as a substrate, as previously described by Onada *et al.*[48] The cellular activity was determined by measuring their effects on EGF-stimulated DNA synthesis of ER 22 cells, by following the incorporation of methyl[^{3}H]thymidine.[47]

As shown in Table 1, none of the compounds tested had significant inhibitory activity against the EGF-R tyrosine kinase *in vitro*. Nevertheless, some of them were able to block the EGF-stimulated DNA synthesis of ER22 cells at relatively low doses. If data on cellular activity are considered, several observations can be made concerning the structure–activity relationships. For the hydroxyl group, it is interesting to note that most of the protected phenols had inhibitory activities comparable to those of their unprotected analogues. These data differ from most of the previous studies dealing with the structure–activity relationships in the phenolstyrene-based inhibitor families, in which protection of the hydroxyl group led to a large loss of activity.[49] Given the weak *in vitro* activity, these results may simply be consistent with the fact that our compounds do not inhibit EGF-R kinase activity (as will be discussed later). However, the bicoordinated nature of the methoxymethoxy group may also furnish an explanation if it is assumed that R^2 is involved in secondary interactions within the active site of the cellular target, such as the chelation of cationic residues, H-bond donating, or bound water. The observation that the

Scheme 1



a. 1) NaH/DMF/0°C 2) $ClCH_2OCH_3$/50°C
b. 1) n-C_4H_9Li/TMEDA/Et_2O/-40°C → RT 2) $B(OMe)_3$/-70°C → RT 3) H_2O
c. p-$BrC_6H_4R^1$/$Pd(PPh_3)_4$/MeOH/toluene/Na_2CO_3 aq./Δ
d. HCl 6N/H_2O/THF/Δ
e. NaOH 4N/EtOH 95%/Δ
*. Directly obtained via procedure c after spontaneous degradation of arylboronic acid **20** into the correspondant deprotected acid.

availability of this group is essential for inhibitory potency supports this hypothesis. Indeed, with regard to the position of hydroxyl-derived group on the phenol ring, it could be inferred from a comparison of series C and D that ortho-substituted products (for instance compound **24,** $IC_{50} \gg 5$ μM) are less active than the meta-substituted ones (for instance compound **28**, $IC_{50} = 8$ μM). However, since the highest inhibitory potency was obtained among the compounds of the ortho-substituted series B, it appears that the relative position of R^2 compared to both the hydrophobic substituent and the carboxylate-substituted phenyl ring has to be taken into account. From the data, it can be assumed that the availability of this group plays a significant role, as the hindered terphenyls of family C are poor inhibitors of cellular growth. In order to confirm this hypothesis, several phenol-based commercial compounds substituted in a position ortho or meta of the hydroxyl group by either a *tert*-butyl moiety (3-*tert*-butylphenol and 2-*tert*-butylphenol) or a phenyl moiety (3-hydroxybiphenyl and 2-hydroxybiphenyl) were tested for their cellular inhibitory potency. No significant activity was obtained with the most hindered ortho-substituted components, whereas their meta-substituted isomers were shown to be moderate inhibitors of EGF-induced DNA synthesis: the IC_{50} values for 3-*tert*-butylphenol and 3-hydroxybiphenyl were respectively 13 and 40 μM.

Several conclusions concerning the nature of the hydrophobic substituents may also be drawn from our data. There was no significant difference in the inhibitory activities of the *tert*-butyl-substituted biphenyls and the terphenyl compounds, even if a comparison of series A and B seems to indicate that the introduction of a phenyl ring is the most efficient.

In contrast, there is no ambiguity concerning the position of the hydrophobic group on the phenolic ring, as the most potent inhibitors of EGF-stimulated DNA synthesis belong to series A and B in which the

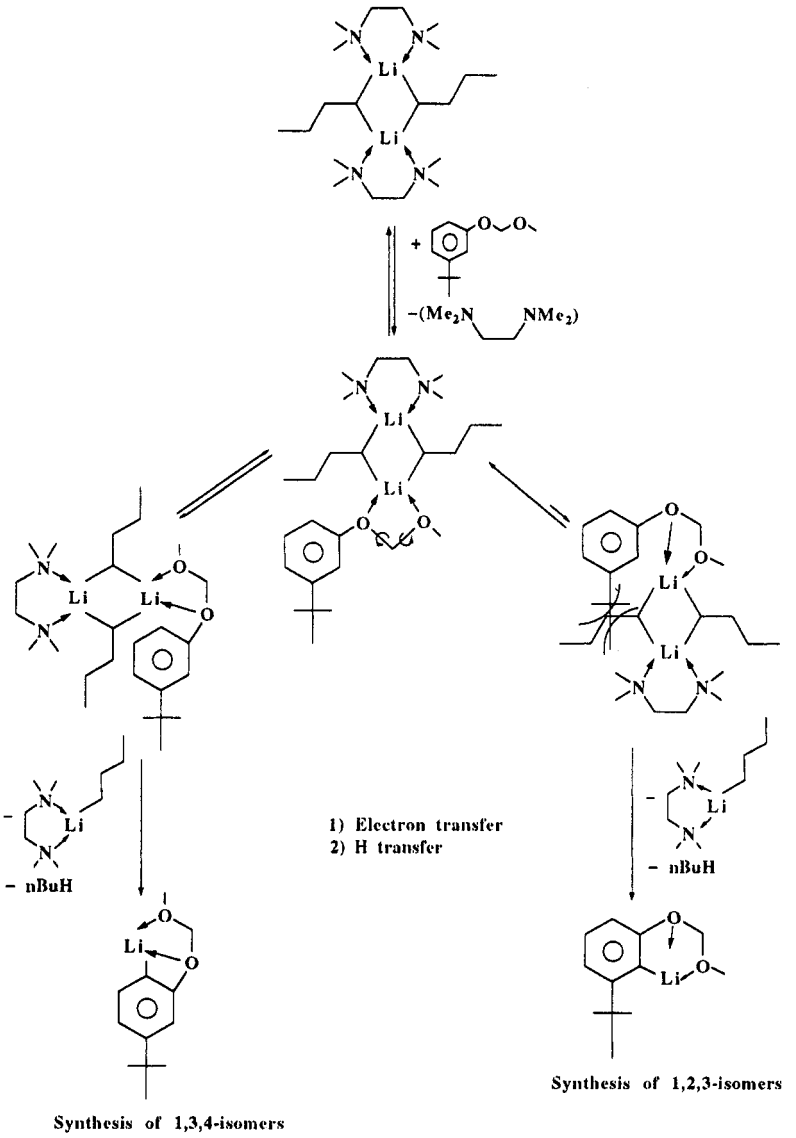


Figure 2.

hydrophobic groups are placed in position 4 from the biphenyl bond of the initial key skeleton. A linear arrangement of the three main moieties (hydrophobic group, biphenyl group and derivatized carboxylic function) thus appears to be optimal for the biological activity of these series of compounds.

In an attempt to improve the cellular activity through an enhanced cellular penetration, several amide and ester derivatives were prepared. The ester derivatives (for instance compound **7**) were generally more efficient than their acidic precursors (compound **9**); this was also the case for the amides (for instance compounds **14** and **34** and their acidic respective derivatives **15** and **30**). In most of the series, amide compounds were particularly efficient and the cellular activity of the terphenyl linear derivatives **14** (IC_{50} cells = 1.1 μM) and **18** (IC_{50} cells = 1.4 μM) was comparable with that of the most potent inhibitors so far described. For instance, among the tyrphostins, which were reported to inhibit EGF-stimulated DNA synthesis of HER-14 cells, the most potent compounds had IC_{50} values between 1 and 5 μM.[27,50]

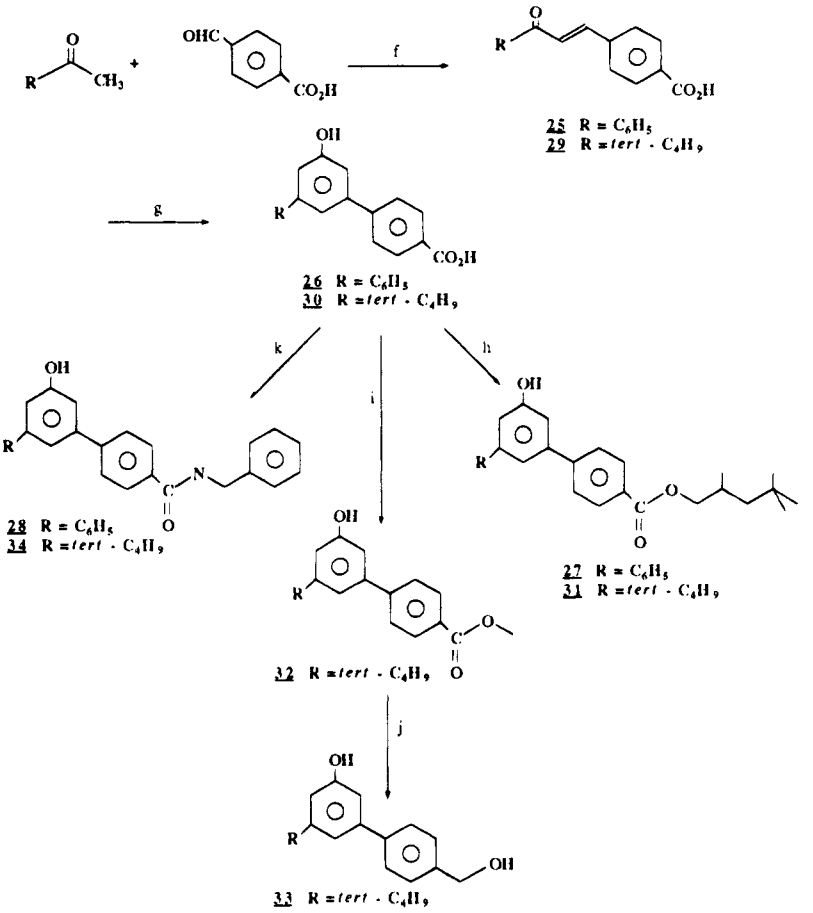
The low activity shown by the alcohol **33**, as compared to its acidic precursor **32**, can be attributed either to a better cellular penetration of the latter or to an activity toward another target.

Conclusion

Two main conclusions can be drawn from these structure–activity relationship studies. First, the linear terphenyl substructure of series B provides the most potent inhibitors, as it includes the three structural features that seem to be essential for the cellular activity of these compounds: (i) availability of the hydroxyl-based group, R^2, (ii) linear arrangement of the three main moieties, and (iii) a phenyl group as the hydrophobic substituent, which is more advantageous than the *tert*-butyl group since it allows the synthesis of relatively more hydrophilic compounds, even if their solubility is still the most important drawback.

Second, the varied derivatizations of both the hydroxyl and the carboxylate moieties of the key skeleton provide further proof of stabilizing interactions of these groups within the catalytic domain. Accordingly, efforts to develop more potent inhibitors will first have to resolve the problem of the poor water solubility of our compounds, while keeping a good solubility in mildly hydrophobic solvents to allow easy transport through the cell membrane. Increasing the chelating potency of the inhibitors might also increase biological activity, and this is likely to be achieved by modifications of the carboxylate moiety. For instance, experiments have

Scheme 2



f. $NaOH/H_2O/EtOH$ 95%
g. $PyCH_2COCH_3$, $Cl/Et_3N/EtOH/\Delta$
h. 1) $H_2O/MeOH/Cs_2CO_3$ 2) $DMF/(CH_3)_3CCH_2(CH_3)CHCH_2Br$
i. $MeOH/SOCl_2/\Delta$
j. $LiAlH_4/THF$
k. $H_2NCH_2C_6H_5/BOP/DIEA/DMF$

been undertaken which replace the carboxylic moiety by a salicylate group which is known to be a good chelating agent.[51]

The poor water solubility of the compounds may explain their low *in vitro* PTK inhibitory activity, as compared to their cellular activity as inhibitors of the EGF-dependent DNA synthesis. Cellular accumulation, arising from the high hydrophobicity of the inhibitors, has previously been suggested to play a role in similar biological tests.[15,52] The lack of *in vitro* activity could then be attributed to a precipitation of the compounds in the medium. It also cannot be discarded that our compounds might be, at least in part, metabolized into active compounds by the cellular enzymes.

Another explanation might be the inhibition of other kinases involved in the EGF-dependent signal transduction pathways. This would imply that the compounds discrimine among the different tyrosine protein kinases. Such a specificity, already observed for several inhibitors such as tyrphostins[15,53] or thiazolidinediones,[54] is made possible despite the high degree of homology within the kinase domain of members of the tyrosine protein kinase family[18] since these kinases show distinct substrate specificities.[55] Finally another possibility is that our derivatives act against non tyrosine kinase targets essential for the cellular EGF-dependent proliferation. For instance they may block the topoisomerase activity, leading to a large decrease in proliferation, as already demonstrated for certain tyrphostins.[15] Biological studies are now in progress to resolve this ambiguity.

Experimental Section

Chemistry. Materials and Methods. ^1H NMR spectra were recorded on a Bruker WH 270 spectrometer at 270 MHz. Chemical shifts are given in ppm relative to HMDS as internal standard. Melting points were obtained on an Electrothermal apparatus and are uncorrected. Purity of the compounds and reaction progress were monitored by thin layer chromatography on silica gel plates ($60F_{254}$, 0.2 mm thick, Merck). Column flash chromatographies were performed with silica gel 60, 60–229 mesh ASTM (Merck). Elemental analyses were performed by the Université Paris VI. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All starting materials were purchased from Aldrich and Janssen. The following abbreviations were used: TMEDA, *N,N,N′,N′*-tetramethylethylenediamine; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; BOP, (benzotriazolyloxy)tris-(dimethylamino)phosphonium hexafluorophosphate; DIEA, diisopropylethylamine; DMF, dimethylformamide; mp, melting point.

Preparation of (Methoxymethoxy)arenes. Procedure a. The (methoxymethoxy)arenes **1**, **10**, and **19** were prepared from the corresponding phenol derivatives by treatment with sodium hydride in DMF and subsequent reaction with chlo-

romethyl methyl ether, according to procedure described in the litterature.[38]

3-*tert*-Butyl-1-(methoxymethoxy)benzene (1). From 3-*tert*-butylphenol, a colorless oil (**1**) was obtained (quantitative yield): R_f (CH_2Cl_2/MeOH, 100:1) 0.80; ^1H NMR (DMSO-d_6) δ ppm 1.2 (s, 9H, $C(CH_3)_3$), 3.3 (s, 3H, OCH_2OCH_3), 5.1 (s, 2H, OCH_2OCH_3), 6.75 (m, 1H, H-4), 6.90 (d, 1H, H-2), 6.95 (m, 1H, H-6), 7.1 (dd, 1H, H-5). Anal. ($C_{12}H_{18}O_2$) C, H.

3-(Methoxymethoxy)biphenyl (10). From 3-hydroxybiphenyl, a pale yellow oil (**10**) was obtained (88% yield): R_f (CH_2Cl_2/MeOH, 100:1) 0.82; ^1H NMR (DMSO-d_6) δ ppm 3.3 (s, 3H, OCH_2OCH_3), 5.15 (s, 2H, OCH_2OCH_3), 6.95 (m, 1H, ArH), 7.2–7.4 (m, 6H, ArH), 7.55 (m, 2H, ArH). Anal. ($C_{14}H_{14}O_2$) C, H.

2-(Methoxymethoxy)biphenyl (19). From 2-hydroxybiphenyl, a pale yellow oil (**19**) was obtained (quantitative yield): R_f (CH_2Cl_2/*n*-hexane, 1:1) 0.35; ^1H NMR (DMSO-d_6) δ ppm 3.2 (s, 3H, OCH_2OCH_3), 5.05 (s, 2H, OCH_2OCH_3), 7.0 (m, 1H, ArH), 7.15 (m, 1H, ArH), 7.2 (m, 3H, ArH), 7.3 (m, 2H, ArH), 7.4 (m, 2H, ArH). Anal. ($C_{14}H_{14}O_2$) C, H.

Preparation of Arylboronic Acids by Orthometalation. 4-*tert*-Butyl-2-(methoxymethoxy)phenylboric Acid (2). Procedure b. To a solution of TMEDA (3.8 mL, 25 mmol) in anhydrous Et_2O (40 mL) at −40 °C under nitrogen was added a hexane solution of *n*-butyllithium (10 mL, 25 mmol of a 2.5 M solution). After 15 min at −40 °C, a solution of compound **1** (40 mL, 20.6 mmol) in anhydrous Et_2O (20 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over 3 h, cooled to −78 °C, and treated with $B(OMe)_3$ (7.2 mL, 61.8 mmol). The solution was brought to room temperature and stirring maintained for 12 h. It was cooled to 0 °C and hydrolyzed with 40 mL of water. The ether phase was separated, and the aqueous layer was then extensively extracted with ether (2 × 40 mL). The organic extracts were washed several times with water and then with a saturated solution of sodium chloride, dried over Na_2SO_4, and evaporated to dryness to provide 4.665 g (95%) of crude boronic acid (**2**) which was used directly in the cross-coupling reaction: ^1H NMR (DMSO-d_6) δ ppm 1.2 (s, 9H, $C(CH_3)_3$), 3.35 (s, 3H, OCH_2OCH_3), 5.2 (s, 2H, OCH_2OCH_3), 6.95 (dd, 1H, H-5), 7.0 (d, 1H, H-3), 7.45 (d, 1H, H-6), 7.6 (s, 2H, $B(OH)_2$).

The following arylboronic acids were similarly prepared.

3-(Methoxymethoxy)biphenyl-4-boronic Acid (11). Following the precedent procedure, 3 g (14 mmol) of **10** provided 3.2 g (89%) of crude boronic acid **11** which was used directly in the cross-coupling reaction: ^1H NMR (DMSO-d_6) δ ppm 3.35 (s, 3H, OCH_2OCH_3), 5.3 (s, 2H, OCH_2OCH_3), 7.2–7.6 (m, 8H, ArH), 7.75 (s, 2H, $B(OH)_2$).

2-(Methoxymethoxy)biphenyl-3-boronic Acid (20). Following the precedent procedure, 3 g (14 mmol) of **19** provided 3.76 g (quantitative yield) of crude boronic acid **20** which was used directly in the cross-coupling reaction: ^1H NMR (DMSO-d_6) δ ppm 2.05 (s, 3H, OCH_2OCH_3), 4.6 (s, 2H, OCH_2OCH_3), 7.1 (m, 1H, ArH), 7.25–7.5 (m, 7H, ArH), 8.0 (s, 2H, $B(OH)_2$).

Preparation of Biaryl Compounds by a Palladium-Catalyzed Cross-Coupling Reaction. Methyl 4′-*tert*-Butyl-2′-(methoxymethoxy)biphenyl-4-carboxylate (3). Procedure c. To a 250 mL, three-neck flask equipped with a reflux condenser and nitrogen inlet was added methyl 4-bromobenzoate (1.8 g, 8.4 mmol) dissolved in toluene (30 mL) followed by $Pd(PPh_3)_4$ (0.36 g, 0.3 mmol). The mixture was stirred for 15 min at room temperature. A solution of arylboronic acid **2** (2 g, 8.4 mmol) in methanol (15 mL) was added and the mixture stirred for 15 min at room temperature. A 2 M aqueous solution of Na_2CO_3 (16.8 mL, 33.6 mmol) was then added. The resulting mixture was refluxed for 20 h, cooled, treated with H_2O (50 mL) and AcOEt (50 mL), and subjected to filtration through a Celite filter pad. The organic layer was separated, and the aqueous layer was then extensively extracted with AcOEt (2 × 40 mL). The organic extracts were washed successively with water (2 × 50 mL), a 1 N solution of HCl (2 × 50 mL), water (1 × 50 mL), a 1 N solution of NaOH (5 × 50 mL), water (2 × 50 mL until pH 7), and then with a saturated solution of sodium chloride, dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography (*n*-hexane/CH_2Cl_2, 1:1) gave 1.99 g (72%) of white solid **3**: mp 52–53; R_f (CH_2Cl_2/*n*-hexane, 1:1) 0.21; ^1H NMR (DMSO-d_6) δ ppm 1.25 (s, 9H, $C(CH_3)_3$), 3.2 (s, 3H, OCH_2OCH_3), 3.8 (s, 3H, CO_2CH_3), 5.1 (s, 2H, OCH_2OCH_3), 7.1 (dd, 1H, H-5′), 7.2 (d, 1H, H-3′), 7.25 (d, 1H, H-6′), 7.6 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5). Anal. ($C_{20}H_{24}O_4$) C, H.

2,4,4-Trimethylpentyl 4′-*tert*-Butyl-2′-(methoxymethoxy)biphenyl-4-carboxylate (4). From arylboronic acid **2** (1 g, 4.2 mmol), 2,4,4-trimethylpentyl 4-bromobenzoate (1.32 g, 4.8 mmol), $Pd(PPh_3)_4$ (0.26 g, 0.2 mmol), and Na_2CO_3 (2 M solution, 8.4 mL) was obtained after standard workup and flash chromatography (*n*-hexane/CH_2Cl_2, 4:1) 1.03 g (58%) of beige solid **4**: mp 73 °C; R_f (CH_2Cl_2/*n*-hexane, 1:1) 0.24; ^1H NMR (DMSO-d_6) δ ppm 0.9 (s, 9H, $CH_2C(CH_3)_3$), 1.0 (d, 3H, $CHCH_3$), 1.05–1.35 (m, 2H, CH_2), 1.25 (s, 9H, Ar-$C(CH_3)_3$), 1.9 (m, 1H, CH), 3.2 (s, 3H, OCH_2OCH_3), 4.0 (m, 2H, CO_2CH_2), 5.1 (s, 2H, OCH_2OCH_3), 7.1 (dd, 1H, H-5′), 7.2 (d, 1H, H-3′), 7.25 (d, 1H, H-6′), 7.6 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5). Anal. ($C_{27}H_{38}O_4$) C, H.

***N*-Benzyl-4′-*tert*-butyl-2′-(methoxymethoxy)biphenyl-4-carboxamide (5).** From arylboronic acid **2** (0.5 g, 2.1 mmol), *N*-benzyl-4-bromobenzamide (0.61 g, 2.1 mmol), Pd $(PPh_3)_4$ (0.13 g, 0.1 mmol), and Na_2CO_3 (2 M solution, 4.2 mL) was obtained after standard workup, flash chromatography ($CHCl_3$), and crystallization from $CHCl_3$/petroleum ether, 0.64 g (75%) of beige solid **5**: mp 154–155 °C; R_f (CH_2Cl_2) 0.12; ^1H NMR (DMSO-d_6) δ ppm 1.25 (s, 9H, $C(CH_3)_3$), 3.2 (s, 3H, OCH_2OCH_3), 4.45 (d, 2H, $NHCH_2$), 5.1 (s, 2H, OCH_2OCH_3), 7.05–7.3 (m, 8H, ArH), 7.55 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 9.0 (t, 1H, NH). Anal. ($C_{26}H_{29}NO_3$) H, N; C: calcd, 77.39; found, 76.60.

Methyl 2′-(Methoxymethoxy)-1,1′:4′,1″-terphenyl-4-carboxylate (12). From arylboronic acid **11** (1.95 g, 7.6 mmol), methyl 4-bromobenzoate (1.62 g, 7.6 mmol), $Pd(PPh_3)_4$ (0.33 g, 0.3 mmol), and Na_2CO_3 (2 M solution, 15.1 mL) was obtained, after standard workup, flash chromatography (AcOEt/*n*-hexane, 1:9), and crystallization from ether/petroleum ether, 1.4 g (53%) of white solid **12**: mp 111 °C; R_f (ethyl acetate/*n*-hexane, 1:9) 0.30; ^1H NMR (DMSO-d_6) δ ppm 3.25 (s, 3H, OCH_2OCH_3), 3.85 (s, 3H, CO_2CH_3), 5.25 (s, 2H, OCH_2OCH_3), 7.35–7.5 (m, 6H, ArH), 7.65 (m, 4H, ArH), 8.0 (dd, 2H, H-3, H-5). Anal. ($C_{22}H_{20}O_4$) C, H.

2,4,4-Trimethylpentyl 2′-(Methoxymethoxy)-1,1′:4′,1″-terphenyl-4-carboxylate (13). From arylboronic acid **11** (1 g, 3.9 mmol), 2,4,4-trimethylpentyl 4-bromobenzoate (1.21 g, 3.9 mmol), $Pd(PPh_3)_4$ (0.25 g, 0.2 mmol), and Na_2CO_3 (2 M solution, 7.8 mL) was obtained after standard workup and flash chromatography (CH_2Cl_2/*n*-hexane, 1:4) 0.60 g (34%) of white solid **13**: mp 73 °C; R_f (CH_2Cl_2/*n*-hexane, 1:1) 0.23; ^1H NMR (DMSO-d_6) δ ppm 0.85 (s, 9H, $C(CH_3)_3$), 1.0 (d, 3H, $CHCH_3$), 1.05–1.35 (m, 2H, CH_2), 1.9 (m, 1H, CH), 3.2 (s, 3H, OCH_2OCH_3), 4.05 (m, 2H, CO_2CH_2), 5.25 (s, 2H, OCH_2OCH_3), 7.35–7.5 (m, 6H, ArH), 7.65 (m, 4H, ArH), 8.0 (dd, 2H, H-3, H-5). Anal. ($C_{29}H_{34}O_4$) C, H.

***N*-Benzyl-2′-(methoxymethoxy)-1,1′:4′,1″-terphenyl-4-carboxamide (14).** From arylboronic acid **11** (0.4 g, 1.55 mmol), *N*-benzyl-4-bromobenzamide (0.45 g, 1.55 mmol), Pd-$(PPh_3)_4$ (0.09 g, 0.08 mmol), and Na_2CO_3 (2 M solution, 3.1 mL) there was obtained after standard workup and crystallization from petroleum ether 0.38 g (58%) of beige solid **14**: mp 180–181 °C; R_f (CH_2Cl_2) 0.36; ^1H NMR (DMSO-d_6) δ ppm 3.25 (s, 3H, OCH_2OCH_3), 4.45 (d, 2H, $NHCH_2$), 5.25 (s, 2H, OCH_2OCH_3), 7.15–7.5 (m, 11H, ArH), 7.65 (m, 4H, ArH), 7.9 (d, 2H, H-3, H-5), 9.05 (t, 1H, NH). Anal. ($C_{28}H_{25}NO_3$) H, N; C: calcd, 79.41; found, 78.80.

2,4,4-Trimethylpentyl 2′-(Methoxymethoxy)-1,1′:3′,1″-terphenyl-4-carboxylate (21). From arylboronic acid **20** (1 g, 3.9 mmol), 2,4,4-trimethylpentyl 4-bromobenzoate (1.21 g, 3.9 mmol), $Pd(PPh_3)_4$ (0.25 g, 0.2 mmol), and Na_2CO_3 (2M solution, 7.8 mL) was obtained after standard workup and flash chromatography (CH_2Cl_2/*n*-hexane, 1:1), 0.86 g (50%) of a yellow oil: R_f (CH_2Cl_2/*n*-hexane, 5:1) 0.48; ^1H NMR (DMSO-d_6) δ ppm 0.85 (s, 9H, $C(CH_3)_3$), 1.0 (d, 3H, $CHCH_3$), 1.05–1.4 (m, 2H, CH_2), 1.9 (m, 1H, CH), 2.55 (s, 3H, OCH_2OCH_3), 4.05 (m, 2H, CO_2CH_2), 4.2 (s, 2H, OCH_2OCH_3), 7.25–7.55 (m, 8H,

ArH), 7.7 (dd, 2H, H-2, H-6), 8.0 (dd, 2H, H-3, H-5). Anal. ($C_{29}H_{34}O_4$) C, H.

Methyl 2′-Hydroxy-1,1′:3,1″-terphenyl-4-carboxylate (23). From 2-hydroxybiphenyl-3-boronic acid (0.83 g, 3.9 mmol) obtained after degradation of arylboronic acid **20**, methyl 4-bromobenzoate (0.83 g, 3.9 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol), and Na_2CO_3 (2M solution, 7.8 mL) was obtained after standard workup and flash chromatography (CH_2Cl_2/*n*-hexane, 1:1) 0.46 g (39%) of a white solid: mp 154−155 °C; R_f (CH_2Cl_2/*n*-hexane, 9:1) 0.51; ^{1}H NMR (DMSO-d_6) ∂ ppm 3.85 (s, 3H, CO_2CH_3), 7.0 (m, 1H, ArH), 7.2 (m, 2H, ArH), 7.3 (m, 1H, ArH), 7.4 (m, 2H, ArH), 7.5 (m, 2H, ArH), 7.65 (dd, 2H, H-2, H-6), 8.0 (dd, 2H, H-3, H-5), 8.45 (s, 1H, OH). Anal. ($C_{20}H_{16}O_3$) C, H.

***N*-Benzyl-2′-hydroxy-1,1′:3′,1″-terphenyl-4-carboxamide (24).** From 2-hydroxybiphenyl-3-boronic acid (0.415 g, 1.9 mmol), obtained after degradation of arylboronic acid **20**, *N*-benzyl-4-bromobenzamide (0.56 g, 1.9 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol), and Na_2CO_3 (2 M solution, 3.9 mL) there was obtained after standard workup and crystallization from CH_2Cl_2 0.49 g (56%) of a beige solid: mp 175−176 °C; R_f (CH_2Cl_2) 0.14; ^{1}H NMR (DMSO-d_6) ∂ ppm 4.45 (d, 2H, NHCH_2), 7.0 (m, 1H, ArH), 7.15−7.3 (m, 8H, ArH), 7.4 (m, 2H, ArH), 7.5 (m, 2H, ArH), 7.6 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 8.35 (s, 1H, OH), 9.05 (t, 1H, NH). Anal. ($C_{26}H_{21}NO_2$) C, H, N.

Hydrolysis of (Methoxymethoxy)arenes. Methyl 4′-*tert*-Butyl-2′-hydroxybiphenyl-4-carboxylate (6). Procedure d. To a solution of **3** (1.7 g, 5.2 mmol) in THF (7 mL) were added H_2O (7 mL) and HCl (6 N solution, 17 mL). The resulting mixture was heated at 70 °C for 4 h, cooled, and extracted with ether (3 × 50 mL). The ethereals extracts were washed several times with water (5 × 50 mL, until pH 7) and then with a saturated solution of sodium chloride, dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography ($CHCl_3$/MeOH, 100:1) afforded 1.38 g (93%) of **6** as a white powder, mp 169−170 °C; R_f ($CHCl_3$/MeOH, 100:1) 0.53; ^{1}H NMR (DMSO-d_6) ∂ ppm 1.2 (s, 9H, C(CH_3)$_3$), 3.8 (s, 3H, CO_2CH_3), 6.9 (dd, 1H, H-5′), 6.95 (d, 1H, H-3′), 7.2 (d, 1H, H-6′), 7.65 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 9.55 (s, 1H, OH). Anal. ($C_{18}H_{20}O_3$, 0.25 H_2O) C, H.

2,4,4-Trimethylpentyl 4′-*tert*-Butyl-2′-hydroxybiphenyl-4-carboxylate (7). Following procedure d, 0.4 g (0.94 mmol) of compound **4** provided, after 5 h reaction time, flash chromatography (CH_2Cl_2/*n*-hexane, 1:1), and crystallization from ether/petroleum ether, 0.26 g (73%) of compound **7** as a white powder: mp 121 °C; R_f (CH_2Cl_2/*n*-hexane, 2:1) 0.25; ^{1}H NMR (DMSO-d_6) ∂ ppm 0.9 (s, 9H, $CH_2C(CH_3)_3$), 1.0 (d, 3H, $CHCH_3$), 1.0−1.35 (m, 2H, CH_2), 1.25 (s, 9H, $ArC(CH_3)_3$), 1.9 (m, 1H, CH), 4.0 (m, 2H, CO_2CH_2), 6.9 (dd, 1H, H-5′), 6.95 (d, 1H, H-3′), 7.2 (d, 1H, H-6′), 7.65 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 9.55 (s, 1H, OH). Anal. ($C_{25}H_{34}O_3$) C, H.

***N*-Benzyl-4′-*tert*-butyl-2′-hydroxybiphenyl-4-carboxamide (8).** Following procedure d, 0.3 g (0.74 mmol) of compound **5** provided, after 3 h reaction time and crystallization from CH_2Cl_2/petroleum ether, 0.11 g (41%) of compound **8** as a white solid: mp 211 °C; R_f (CH_2Cl_2/MeOH, 20:1) 0.21; ^{1}H NMR (DMSO-d_6) ∂ ppm 1.2 (s, 9H, C(CH_3)$_3$), 4.45 (d, 2H, NHCH_2), 6.9 (dd, 1H, H-5′), 6.95 (d, 1H, H-3′), 7.15 (d, 1H, H-6′), 7.15−7.25 (m, 5H, $CH_2C_6H_5$), 7.6 (dd, 2H, H-2, H-6), 7.85 (dd, 2H, H-3, H-5), 9.0 (t, 1H, NH), 9.5 (s, 1H, OH). Anal. ($C_{24}H_{25}NO_2$·0.5H_2O) C, H, N.

Methyl 2′-Hydroxy-1,1′:4′,1″-terphenyl-4-carboxylate (16). Following procedure d, 0.3 g (0.86 mmol) of compound **12** provided, after 2.5 h reaction time and flash chromatography ($CHCl_3$), 0.28 g (quantitative yield) of compound **16** as white crystals: mp 200−201 °C; R_f ($CHCl_3$) 0.31; ^{1}H NMR (DMSO-d_6) ∂ ppm 3.85 (s, 3H, CO_2CH_3), 7.15 (m, 2H, ArH), 7.3−7.45 (m, 4H, ArH), 7.6 (m, 2H, ArH), 7.75 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5), 9.95 (s, 1H, OH). Anal. ($C_{20}H_{16}O_3$, 0.25 H_2O) C, H.

2,4,4-Trimethylpentyl 2′-Hydroxy-1,1′:4′,1″-terphenyl-4-carboxylate (17). Following procedure d, 0.3 g (0.67 mmol) of compound **13** provided, after 3 h reaction time and crystallization from ether/petroleum ether, 0.21 g (77%) of compound **17** as a white solid: mp 130 °C; R_f (CH_2Cl_2) 0.37; ^{1}H NMR (DMSO-d_6) ∂ ppm 0.85 (s, 9H, C(CH_3)$_3$), 1.0 (d, 3H, $CHCH_3$), 1.0−1.35 (m, 2H, CH_2), 1.9 (m, 1H, CH), 4.05 (m, 2H, CO_2CH_2), 7.15 (m, 2H, ArH), 7.3−7.45 (m, 4H, ArH), 7.55 (m, 2H, ArH), 7.7 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5), 9.95 (s, 1H, OH). Anal. ($C_{27}H_{30}O_3$) C, H.

***N*-Benzyl-2′-hydroxy-1,1′:4′,1″-terphenyl-4-carboxamide (18).** Following procedure d, 0.2 g (0.47 mmol) of compound **14** provided, after 2.5 h reaction time, 0.9 g (52%) of compound **18**. No purification was required since compound **18** crystallized in the reaction mixture and was obtained after filtration as pure white crystals: mp 231 °C; R_f (CH_2Cl_2) 0.27; ^{1}H NMR (DMSO-d_6) ∂ ppm 4.45 (d, 2H, NHCH_2), 7.15 (m, 3H, ArH), 7.25−7.35 (m, 6H, ArH), 7.45 (m, 2H, ArH), 7.60 (m, 2H, ArH), 7.65 (m, 2H, ArH), 7.9 (dd, 2H, H-3, H-5), 9.0 (t, 1H, NH), 9.85 (s, 1H, OH). Anal. ($C_{26}H_{21}NO_2$·0.75H_2O) C, H, N.

2,4,4-Trimethylpentyl 2′-Hydroxy-1,1′:3′,1″-terphenyl-4-carboxylate (22). Following procedure d, 0.2 g (0.45 mmol) of compound **21** provided, after 5 h reaction time, flash chromatography (AcOEt/*n*-hexane, 1:20), and crystallization from petroleum ether, 0.073 g (40%) of compound **22** as a beige powder: mp 90−91 °C; R_f (ethyl acetate/*n*-hexane, 1:9) 0.55; ^{1}H NMR (DMSO-d_6) ∂ ppm 0.9 (s, 9H, C(CH_3)$_3$), 1.0 (d, 3H, $CHCH_3$), 1.0−1.35 (m, 2H, CH_2), 1.95 (m, 1H, CH), 4.05 (m, 2H, CO_2CH_2), 7.0 (m, 1H, ArH), 7.2 (m, 2H, ArH), 7.3 (m, 1H, ArH), 7.4 (m, 2H, ArH), 7.5 (m, 2H, ArH), 7.65 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5), 8.45 (s, 1H, OH). Anal. ($C_{27}H_{30}O_3$·0.75H_2O). C, H.

Hydrolysis of Methyl Esters. 4′-*tert*-Butyl-2′-hydroxybiphenyl-4-carboxylic Acid (9). Procedure e. To a solution of compound **6** (1 g, 3.5 mmol) in EtOH 95% (10 mL) was added dropwise under stirring 3.5 mL of a 4 N NaOH solution (14 mmol). The resulting mixture was refluxed for 2 h and then allowed to cool to room temperature. Ethanol was then evaporated and water (30 mL) added. Aqueous HCl (6 N) was added until the solution became pH 2. The white precipitate was collected by filtration, washed several times with water. Purification by flash chromatography (CH_2Cl_2/MeOH, 20:1) afforded 0.56 g (60%) of **9** as a white powder: mp 244−245 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.63; ^{1}H NMR (DMSO-d_6) ∂ ppm 1.2 (s, 9H, C(CH_3)$_3$), 6.85 (dd, 1H, H-5′), 6.9 (d, 1H, H-3′), 7.2 (d, 1H, H-6′), 7.6 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 9.45 (s, 1H, OH), 12.6 (s, 1H, CO_2H). Anal. ($C_{17}H_{18}O_3$·0.25H_2O) C, H.

2′-(Methoxymethoxy)-1,1′:4′,1″-terphenyl-4-carboxylic Acid (15). Compound **12** (0.3 g, 0.86 mmol) was dissolved in EtOH (95%) (5 mL). NaOH (4 N, 0.9 mL, 3.4 mmol) was added dropwise with stirring, and the resulting mixture was refluxed for 2.5 h and then allowed to cool to room temperature. EtOH was evaporated and water (15 mL) added. The aqueous phase was washed with CH_2Cl_2 (3 × 50 mL), acidified with HCl (6 N) (until the solution became pH 2), and extracted with CH_2Cl_2. The organic layer was washed with water (3 × 50 mL, until pH 7) and then with saturated solution of sodium chloride, dried over Na_2SO_4, and evaporated to dryness to give 0.27 g (93%) of compound **15** as a white powder: mp 207−208 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.65; ^{1}H NMR (DMSO-d_6) ∂ ppm 3.25 (s, 3H, OCH_2OCH_3), 5.25 (s, 2H, OCH_2OCH_3), 7.35−7.45 (m, 6H, ArH), 7.6−7.7 (m, 4H, ArH), 7.95 (m, 2H, ArH), 12.9 (s, 1H, CO_2H). Anal. ($C_{21}H_{18}O_4$) C, H.

Claisen−Schmidt Reaction. Preparation of α,β-Unsaturated Ketones. 4-Carboxychalcone (25). Procedure f. To a solution of acetophenone (2 g, 16.65 mmol) in ethanol 95% (8 mL) was added successively water (4 mL), NaOH (3 N, 7 mL, 20.8 mmol), and 4-formylbenzoic acid (2.82 g, 18.8 mmol). The resulting mixture was stirred at room temperature for 48 h and then cooled to 0 °C. HCl (1 N) was added (until the solution became pH 2). Filtration of the pale yellow precipitate obtained provided 4.365 g (quantitative yield) of crude product which was used for the next step without purification: R_f (CH_2Cl_2/MeOH, 9:1) 0.51; ^{1}H NMR (DMSO-d_6) ∂ ppm 7.5−7.75 (m, 4H, 2ArH, CH=CH), 7.95−8.05 (m, 5H, ArH), 8.15 (m, 2H, ArH), 12.9 (s, 1H, CO_2H).

4,4-Dimethyl-1-(4′-carboxyphenyl)-1-penten-3-one (29). Following precedent procedure, 2 g (20 mmol) of 3,3-dimethyl-2-butanone and 3.39 g (22.6 mmol) of 4-formylbenzoic acid

provided 4.42 g (95% yield) of compound **29** as a pale yellow powder. The crude product obtained was used for next step without purification: R_f (CH_2Cl_2/MeOH, 4:1) 0.74; ^1H NMR (DMSO-d_6) δ ppm 1.1 (s, 9H, $C(CH_3)_3$), 7.5 (s, 2H, CH=CH), 7.8–7.9 (m, 4H, ArH), 13.0 (s, 1H, CO_2H).

Preparation of Meta,Meta-Disubstituted Phenols. 3′-Hydroxy-1,1′:5′,1″-terphenyl-4-carboxylic Acid (26). Procedure g. Compound **25** (2 g, 7.9 mmol) was dissolved in a solution of anhydrous triethylamine (2.8 mL, 19.8 mmol) in absolute ethanol (40 mL). 1-(2-Oxypropyl)pyridinium chloride (2.04 g, 11.9 mmol) was added and the resulting mixture refluxed for 60 h. The braun solution obtained was allowed to cool to room temperature, and ethanol was evaporated. Water (50 mL) was added and the solution alcalinized with 1 N NaOH (until the solution became pH 12) and washed with CH_2Cl_2 (2 × 60 mL). The aqueous layer was acidified with 6 N HCl (until the solution became pH 2). The resulting mixture was subjected to filtration, the precipitate dissolved in ether, and the ethereal phase subjected again to filtration (to remove impurities). The filtrate was evaporated to dryness to provide 1.99 g (87%) of compound **26** as a pale yellow powder: mp 244–245 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.33; ^1H NMR (DMSO-d_6) δ ppm 7.0 (m, 2H, ArH), 7.3–7.45 (m, 4H, ArH), 7.65 (m, 2H, ArH), 7.75 (m, 2H, ArH), 8.0 (m, 2H, ArH), 9.8 (s, 1H, OH), 12.9 (s, 1H, CO_2H). Anal. ($C_{19}H_{14}O_3$, 0.4 H_2O) C, H.

5′-*tert*-Butyl-3′-hydroxybiphenyl-4-carboxylic Acid (30). From compound **29** (3 g, 12.9 mmol), 1-(2-oxopropyl)pyridinium chloride (3.325 g, 19.4 mmol), and anhydrous triethylamine (4.5 mL, 32.3 mmol), was obtained after standard workup (via procedure g) and flash chromatography (CH_2Cl_2/MeOH, 20:1) 2.2 g (63%) of beige powder **30**: mp 230–231 °C; R_f (CH_2Cl_2/MeOH, 20:1) 0.19; ^1H NMR (DMSO-d_6) δ ppm 1.25 (s, 9H, $C(CH_3)_3$), 6.8 (m, 2H, H-4′, H-6′), 7.05 (dd, 1H, H-2′), 7.65 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5), 9.45 (s, 1H, OH), 12.95 (s, 1H, CO_2H). Anal. ($C_{17}H_{18}O_3$·0.75H_2O) C, H.

Esterification by Alkylation of Acid Salts. 2,4,4-Trimethylpentyl 3′-Hydroxy-1,1′:5′,1″-terphenyl-4-carboxylate (27). Procedure h. To a solution of compound **26** (0.7 g, 2.4 mmol) in methanol (10 mL) was added water (5 mL) and a 20% aqueous solution of Cs_2CO_3 until the solution became pH 7 (pH paper). The mixture was evaporated to dryness, DMF (2 × 10 mL) added, and the mixture reevaporated. The white cesium salt was dissolved in DMF (7 mL) and treated with 2,4,4-trimethyl-1-bromopentane (0.51 g, 2.65 mmol). The solution was stirred for 4 days at room temperature and evaporated to dryness, and water was added (70 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). After drying over Na_2SO_4, the solvent was evaporated. Purification by flash chromatography (CH_2Cl_2/*n*-hexane, 1:1) and crystallization from petroleum ether afforded 0.45 g (46% yield) of compound **27** as white crystals: mp 139 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.89; ^1H NMR (DMSO-d_6) δ ppm 0.85 (s, 9H, $C(CH_3)_3$), 0.95 (d, 3H, $CHCH_3$), 0.95–1.35 (m, 2H, CH_2), 1.9 (m, 1H, CH), 4.0 (m, 2H, CO_2CH_2), 7.0 (m, 2H, ArH), 7.3–7.45 (m, 4H, ArH), 7.65 (m, 2H, ArH), 7.8 (m, 2H, ArH), 8.0 (m, 2H, ArH), 9.8 (s, 1H, OH). Anal. ($C_{27}H_{30}O_3$) C, H.

2,4,4-Trimethylpentyl 5′-*tert*-Butyl-3′-hydroxybiphenyl-4-carboxylate (31). Compound **30** (0.5 g, 1.85 mmol) was treated following procedure h and provided after purification by flash chromatography (CH_2Cl_2) and crystallization from ether/petroleum ether 0.22 g (31% yield) of compound **31** as white crystals: mp 112 °C; R_f (CH_2Cl_2) 0.17; ^1H NMR (DMSO-d_6) δ ppm 0.9 (s, 9H, $CH_2C(CH_3)_3$), 1.0 (d, 3H, $CHCH_3$), 1.0–1.35 (m, 2H, CH_2), 1.25 (s, 9H, $ArC(CH_3)_3$), 1.9 (m, 1H, CH), 4.05 (m, 2H, CO_2CH_2), 6.8 (m, 2H, H-4′, H-6′), 7.1 (dd, 1H, H-2′), 7.7 (dd, 2H, H-2, H-6), 8.0 (dd, 2H, H-3, H-5), 9.5 (s, 1H, OH). Anal. ($C_{25}H_{34}O_3$) C, H.

Preparation of Methyl Esters. Methyl 5′-*tert*-Butyl-3′-hydroxybiphenyl-4-carboxylate (32). Procedure i. To a solution of compound **30** (0.4 g, 1.48 mmol) in methanol (10 mL) at 0 °C was added dropwise thionyl chloride (1.1 mL, 14.8 mmol). The solution was heated under reflux for 20 h, allowed to cool to room temperature, and evaporated to dryness. Purification by flash chromatography (CH_2Cl_2/MeOH, 50:1) and crystallization from petroleum ether gave 0.23 g (55% yield) of beige crystals **32**: mp 144 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.77; ^1H NMR (DMSO-d_6) δ ppm 1.25 (s, 9H, $C(CH_3)_3$), 3.7 (s, 3H, CO_2CH_3), 6.8 (m, 2H, H-4′, H-6′), 7.05 (dd, 1H, H-2′), 7.7 (dd, 2H, H-2, H-6), 7.95 (dd, 2H, H-3, H-5), 9.5 (s, 1H, OH). Anal. ($C_{18}H_{20}O_3$) C, H.

Reduction of Methyl Ester to Alcohols. 5′-*tert*-Butyl-3′-hydroxy-4-(hydroxymethyl)biphenyl (33). Procedure j. Compound **32** (0.15 g, 0.53 mmol) of was dissolved in anhydrous THF (5 mL), and 0.03 g (0.79 mmol) of $LiAlH_4$ was added slowly at 0 °C under nitrogen. The mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and stirred for 15 h. Methanol (4 mL) was then added dropwise at 0 °C. The solution was acidified with 1 N HCl (until pH 2) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (2 × 20 mL, until pH 7) and then with a saturated solution of sodium chloride, dried over Na_2SO_4, and evaporated to dryness. Crystallization from ether/petroleum ether afforded 0.09 g (69% yield) of **33** as white crystals: mp 167 °C; R_f (CH_2Cl_2/MeOH, 9:1) 0.62; ^1H NMR (DMSO-d_6) δ ppm 1.25 (s, 9H, $C(CH_3)_3$), 4.5 (s, 2H, CH_2OH), 5.15 (s, 1H, CH_2OH), 6.75 (m, 2H, H-4′, H-6′), 7.0 (dd, 1H, H-2′), 7.35 (dd, 2H, H-2, H-6), 7.5 (dd, 2H, H-3, H-5), 9.35 (s, 1H, ArOH). Anal. ($C_{17}H_{20}O_2$) C, H.

Preparation of Benzylamides by Coupling with BOP/DIEA. *N*-Benzyl-3′-hydroxy-1,1′:5′,1″-terphenyl-4-carboxamide (28). Procedure k. To a solution of compound **26** (0.2 g, 0.69 mmol) in DMF (1 mL) was added 0.34 g (0.76 mmol) of BOP. The solution was brought to 0 °C. DIEA (0.36 mL, 2.07 mmol) was added, and stirring was maintained for 30 min at 0 °C and then for 1 h at room temperature. The solution was again allowed to cool to 0 °C, and benzylamine (0.075 mL, 0.69 mmol) was added. After 1 h at 0 °C and 4 days at room temperature, DMF was evaporated and AcOEt (10 mL) was added. The organic phase was washed with aqueous citric acid (10% solution, 3 × 10 mL) and water (2 × 10 mL), dried over Na_2SO_4, and evaporated to dryness. Purification by flash chromatography ($CHCl_3$) and crystallization from ether/petroleum ether gave 0.02 g (7% yield) of white crystals **28**: mp 191–192 °C; R_f (CH_2Cl_2/MeOH, 50:1) 0.22; ^1H NMR (DMSO-d_6) δ ppm 4.45 (d, 2H, $NHCH_2$), 7.0 (m, 2H, ArH), 7.15–7.45 (m, 9H, ArH), 7.65 (m, 2H, ArH), 7.75 (m, 2H, ArH), 7.95 (m, 2H, ArH), 9.05 (t, 1H, NH), 9.75 (s, 1H, OH).

***N*-Benzyl-5′-*tert*-butyl-3′-hydroxybiphenyl-4-carboxamide (34).** From compound **30** (0.2 g, 0.74 mmol), benzylamine (0.08 mL, 0.74 mmol), BOP (0.36 g, 0.8 mmol), and DIEA (0.39 mL, 2.2 mmol) was obtained after standard workup (following procedure k), flash chromatography (CH_2Cl_2), and crystallization from ether/petroleum ether 0.064 g (24%) of white crystals **34**: mp 200 °C; R_f (CH_2Cl_2/MeOH, 50:1) 0.28; ^1H NMR (DMSO-d_6) δ ppm 1.2 (s, 9H, $C(CH_3)_3$), 4.45 (d, 2H, $NHCH_2$), 6.75 (dd, 1H, H-6′), 6.8 (dd, 1H, H-4′), 7.1 (dd, 1H, H-2′), 7.15–7.3 (m, 5H, $CH_2C_6H_5$), 7.6 (dd, 2H, H-2, H-6), 7.9 (dd, 2H, H-3, H-5), 9.05 (t, 1H, NH), 9.4 (s, 1H, OH). Anal. ($C_{24}H_{25}NO_2$) C, H, N.

Cell Cultures. Cells termed ER 22 were prepared by transfecting CCL 39 hamster fibroblasts with wild-type human EGF receptor to obtain a cell clone exhibiting about 8 × 10^5 EGF binding sites/cell. The preparation of the DNA constructs and the characterization of cell lines expressing them were described by L'Allemain.[47] Cells were routinely grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum (FCS) containing the antibiotic G418 (200 μg/mL) at 37 °C in 5% CO_2.

DNA Synthesis. Cells were seeded at 3.5 × 10^5 cells by well in 24-well Nuncion dishes. The cells were grown to confluence in DMEM supplemented with 10% FCS. To obtain quiescent cells, the medium was changed to DMEM/HAM's F12 (1:1) for 48 h. The cells were incubated with different concentrations of the inhibitory compounds (dissolved at 1000× final concentration in DMSO 100%) for 1 h. Then, EGF (20 ng/mL) (Collaborative Biochemical Prodructs, cat. 40010) or FCS and 0.1 μCi of methyl[^{3}H]thymidine ([^{3}H]Me-dT, NEN, NET 027Z) were added. The incorporation of thymidine into the trichloroacetic acid insoluble fraction was determined by a scintillation counter.

Membrane Preparation. ER 22 cells were grown in 850-cm^3 tissue culture roller bottles to obtain 10^9 cells, and cell membranes were purified on sucrose 32% (w/w), according to the published procedure of Carpenter.[56] Membrane preparations were suspended in Hepes (20 mM, pH 7.4) and $MgCl_2$ (10 mM), aliquoted, and stored frozen at −80 °C.

***In Vitro* Tyrosine Kinase Assay.** The tyrosine kinase assay was performed as previously described.[48] Using 10 μL of the above membrane preparation, the reaction was carried out in a final volume of 50 μL containing 20 mM Hepes, pH 7.4, 1 mM Mn Cl_2, 0.1 mg/mL BSA, 100 ng/mL EGF, 0.5 mg/mL tridecapeptide (RRLIEDAEYAARG = RR-Src, H5445 Bachem), and a membrane fraction of ER 22 cells, 5 μM ATP, and 1 μCi of [γ^{32}P]ATP (NEN, NEG OO2H, 3000 Ci/mM) with or without inhibitors at various concentrations. EGF receptor was first incubated with EGF for 10 min at room temperature, then the inhibitor was added, and the reaction was initiated by the addition of the peptide and ATP. Incubation was carried out for 20 min at room temperature. The reaction was terminated by addition of 25 μL of trichloroacetic acid 10% in the presence of 10 μL BSA (10 mg/mL). Precipitated proteins were removed by centrifugation, and 40 μL of the supernatant was spotted on Whatman P81 phosphocellulose papers (2 cm × 2 cm) that were immediatly immersed in orthophosphoric acid (75 mM) for 15 min. This operation was repeated three times, then the paper were dried, and the radioactivity was counted with a scintillation counter.

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