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European Journal of Medicinal Chemistry 39 (2004) 11–26
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Salicylanilides as inhibitors of the protein tyrosine kinase epidermal growth factor receptor

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Received 10 June 2003; accepted 9 September 2003

Abstract

A pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGFR protein tyrosine kinase and a putative binding mode of 4-anilinoquinazoline suggest that a salicylic acid function could serve as the pharmacophore replacement of a pyrimidine ring. Superpositions by CAMM of salicylanilides with the potent EGFR tyrosine kinase inhibitor 4-[(3′-chlorophenyl)amino]-6,7-dimethoxyquinazoline showed that salicylanilides should act as tyrosine kinase inhibitors. A series of salicylanilides was synthesized and their inhibitory activity against tyrosine kinases determined. Some of them indeed proved to be potent and selective EGFR tyrosine kinase inhibitors. The most potent ones being **28, 16, 20, 6**, and **15**, with IC_{50} in the 23–71 nM range.

Keywords: Salicylanilides; Protein tyrosine kinase inhibitors; EGFR PTK

1. Introduction

The actions of protein tyrosine kinases (PTK) are fundamental to signal transduction pathways. In many proliferative diseases (e.g. cancer, psoriasis, restenosis, etc.), deregulated PTK activity has been observed [1]. A number of tumor types have dysfunctional growth factor receptor PTKs, which result in inappropriate mitogenic signaling. Thus, tyrosine kinases are attractive targets for the design of new therapeutic agents against cancer [2,3]. The inhibition of these enzymes might stop the growth of the tumor and can, therefore, be of great therapeutical value.

The family of epidermal growth factor receptor (EGFR) PTKs belongs to the large class of the trans-membrane growth factor receptor PTKs and contains four members: EGFR kinase, $p185^{erbB2}$, and the gene products of *c-erb*B3 and *c-erb*B4. The EGFR and its ligands (EGF, TGF-α) have been implicated in many different tumors of epithelial origin (e.g. squamous cell carcinoma; breast, ovarian, and NSC lung cancer) [1,4].

Out of the numerous inhibitors of EGFR PTK reported in the last few years, compounds competing with ATP for binding at the catalytic domain are of special interest. Because of the lack of crystal structure data of the kinase, Furet et al. [5] and Palmer et al. [6] postulated hypothetical models of the ATP-binding site of the enzyme based on molecular modeling. These models were successfully used for the development of some ATP competitive inhibitors of EGFR PTK such as the 4-(phenylamino)pyrrolo[2,3-*d*]pyrimidines **1** [7], the 4-(phenylamino)pyrazolo[3,4-*d*]pyrimidines **2** [8], and the 4-(phenylamino)quinazolines **3** [9] (see Fig. 1).

From structure activity relationship (SAR) studies, Palmer et al. [6] postulated a binding mode for 4-anilinoquinazolines (**3**) to the EGFR PTK. In this model, the inhibitor binds to the enzyme via a pyrimidine nitrogen atom through a hydrogen bond to the backbone NH of amino acid Met^{769} of EGFR PTK. According to this model the aniline substituent is occupying a hydrophobic region located at the bottom of the ATP binding pocket of EGFR PTK (hydrophobic region I in Fig. 5). Substituents in positions 6 and 7 of the quinazoline are directed to another hydrophobic region of the enzyme open to the solvent (hydrophobic region II in Fig. 5). Quinazolines such as **4** with electron-donating groups in these positions (Fig. 2) are highly potent EGFR PTK inhibi-

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doi:10.1016/j.ejmech.2003.09.010

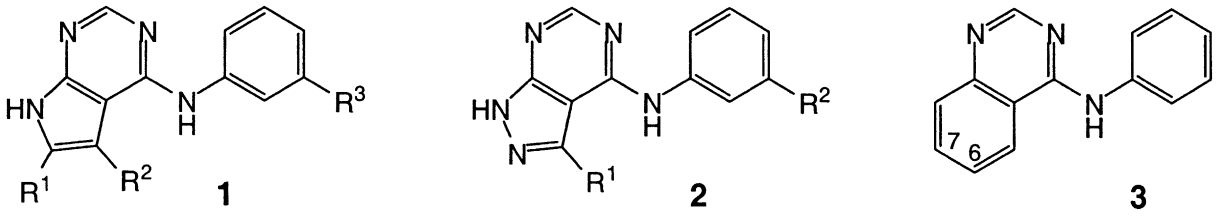


Fig. 1. Structures of 4-(phenylamino)pyrrolo[2,3-*d*]pyrimidines **1**, 4-(phenylamino)pyrazolo[3,4-*d*]pyrimidines **2**, and 4-(phenylamino)quinazolines **3**.

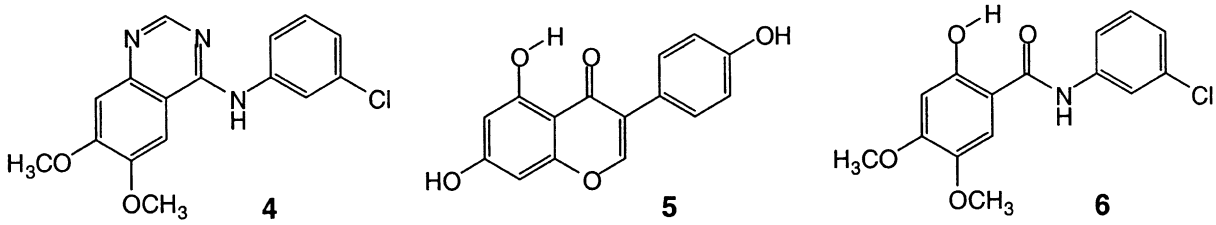


Fig. 2. Structures of quinazoline **4**, genistein (**5**), and salicylamide **6**.

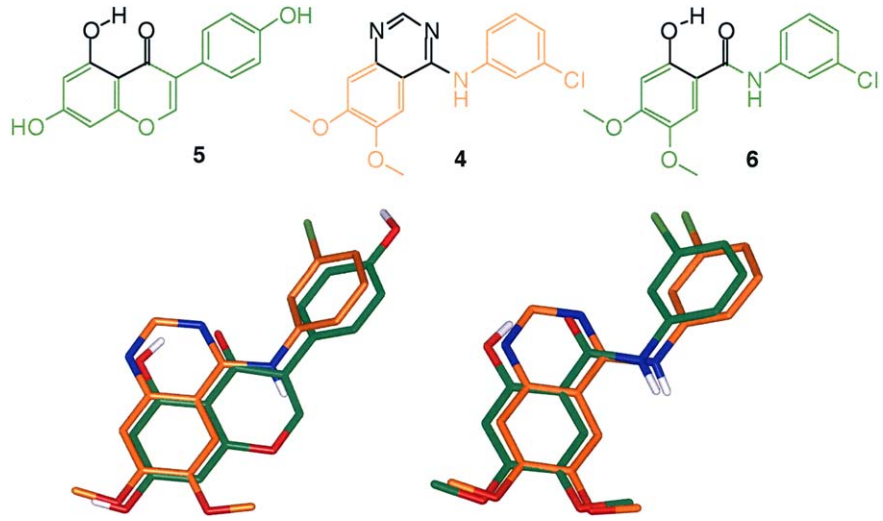


Fig. 3. Superimpositions. Left: quinazoline **4** (brown) and genistein (**5**) (green); right: quinazoline **4** (brown) and salicylanilide **6** (green). The crucial structural motives, the pseudo six-membered rings formed by the intramolecular hydrogen bonds in the isoflavone **5** and the salicylanilide **6**, as well as the pyrimidine ring of the quinazoline **4**, are drawn in black.

tors. It was also shown by SAR studies that selectivity for the EGFR PTK can be achieved with a halogen substituent in the 3-position of the anilino moiety of the inhibitor [10].

A natural yet unselective inhibitor of EGFR PTK is the isoflavone genistein (**5**) [11]. A superposition by CAMM of the structures of **5** and the quinazoline **4** of AstraZeneca shows a very good spatial match (Fig. 3). Hodge and Pierce [12] have shown that a pseudo six-membered ring such as the one in salicylanilides formed by an intramolecular hydrogen bond may function as a mimic of the pyrimidine ring of the quinazolines. This led to the hypothesis, that salicylanilides may adopt the same binding mode to EGFR PTK as the isoflavones and the quinazolines. Superposition of the salicylamide **6** and the quinazoline **4** indeed shows an excellent match. These superpositions take into account that salicylanilides exist predominantly in the form with the hydrogen bridge between OH and the carbonyl oxygen (see formula **7**, Fig. 4) [13]; the other possible conformation (formula **8**) with

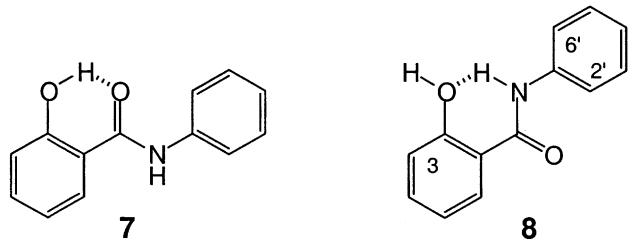
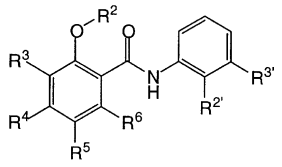


Fig. 4. Two possible intramolecular hydrogen bond arrangements in salicylamides.

a hydrogen bond between the amide NH and the OH becomes relevant when there are substituents in positions 3 and/or 2′/6′. The finding that *N*-(3-chlorophenyl) salicylamide (**9**) without any substituents in the salicylic acid moiety already proved to be a moderate inhibitor of the EGFR PTK (57% inhibition at 10 μM; see Table 1), encour-

Table 1
Inhibitory activities of salicylanilides towards EGFR ICD, VEGFR-2 PTK, and c-Abl PTK. Enzyme tests were performed as previously described [14] using poly(E_4Y) (2 μg ml^{-1}) and [^{33}P]ATP (0.4 μM) as substrates. For determination of the VEGFR-2 PTK inhibition see [15,16]



	R^2	R^3	R^4	R^5	R^6	$R^{2'}$	$R^{3'}$	EGFR ICD, IC_{50} (μM)	VEGFR-2, IC_{50} (μM)	c-Abl, IC_{50} (μM)
9	H	H	H	H	H	H	Cl	57% [a]	5% [a]	–
10	Me	H	H	OMe	H	H	Cl	2% [a]	20% [a]	–
11	Bn	H	Br	H	H	H	Cl	8.20	>10	–
12	H	H	H	OH	H	H	Cl	0.22	>1	>10
13	H	H	H	OMe	H	H	Cl	0.24	>1	>10
14	H	H	H	Me	H	H	Cl	1.2	>1	–
15	H	H	OH	H	H	H	Cl	0.071	>1	>10
16	H	H	OH	H	OH	H	Cl	0.032	>1	>10
17	H	OH	OH	H	H	H	Cl	0.82	>1	0.85
18	H	H	OSO_2CF_3	H	H	H	Cl	>10	>10	–
19	H	H	OMe	H	H	H	Cl	0.36	>1	>10
20	H	H	OMe	OH	H	H	Cl	0.057	>1	>10
6	H	H	OMe	OMe	H	H	Cl	0.064	>1	>10
21	H	H	NH_2	H	H	H	Cl	0.12	>1	>10
22	H	H	NEt_2	H	H	H	Cl	>10	36% [a]	–
23	H	H	NH–COMe	H	H	H	Cl	1.70	>10	–
24	H	H	Br	H	H	H	Cl	2.80	>10	–
25	H	H	Me	H	H	H	Cl	>10	>1	–
26	H	H	Annealed phenyl	Ring	H	H	Cl	>10	>1	>10
27	H	H	1-Piperidyl	H	H	H	Cl	37% [a]	25% [a]	–
28	H	H	Ph-*p*-NH_2	H	H	H	Cl	0.023	26% [a]	–
29	H	H	H	H	H	Me	Cl	1.5	>1	>10
30	H	H	H	Me	H	H	H	16% [a]	15% [a]	–
31	H	H	NH_2	H	H	H	OH	54% [a]	34% [a]	–
32	Me	H	H	H	H	H	OH	10% [a]	5% [a]	–
33	H	H	NH–COMe	H	H	H	OBn	0% [a]	19% [a]	–
34	H	H	OH	H	H	H	OBn	2% [a]	23% [a]	–
35	Me	H	Ph-*p*-NO_2	H	H	H	OH	–	>10	–
36	H	H	Ph-*p*-NO_2	H	H	H	OH	5.1	4.1	–
37	H	H	Ph-*p*-NH_2	H	H	H	OH	1	1.0	1.1

[a] Percent inhibition at 10 μM.
–, not determined.

aged us to investigate a series of salicylanilides with various substitution patterns.

Based on analogy to the SAR of the 4-(phenylamino)-pyrrolo[2,3-*d*]pyrimidines [7], the 4-(phenylamino)pyrazolo[3,4-*d*]pyrimidines [8], and the 4-(phenylamino)quinazolines [9], the hypothesis was established that for potent inhibition of the EGFR PTK by salicylanilides the following requirements should be fulfilled (Fig. 5): *salicylic acid moiety*: (i) a pseudo six-membered ring formed through intramolecular hydrogen bonding of the hydroxy group to the carbonyl group, (ii) no substituent in position 3, and (iii) substitution in positions 4 and 5 with electron-donating groups; *anilino moiety*: (i) small, lipophilic and electron-withdrawing group in position 3′ (e.g. 3′-chloro) and (ii) no substituents in the positions 2′, 4′, 5′ and 6′. The salicylanilides described here should prove this hypothesis right.

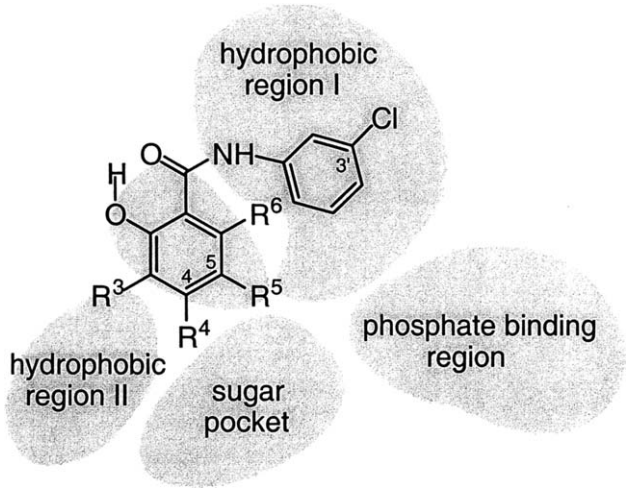


Fig. 5. Schematic representation of the ATP binding site of EGFR PTK and a salicylanilide as potential inhibitor.

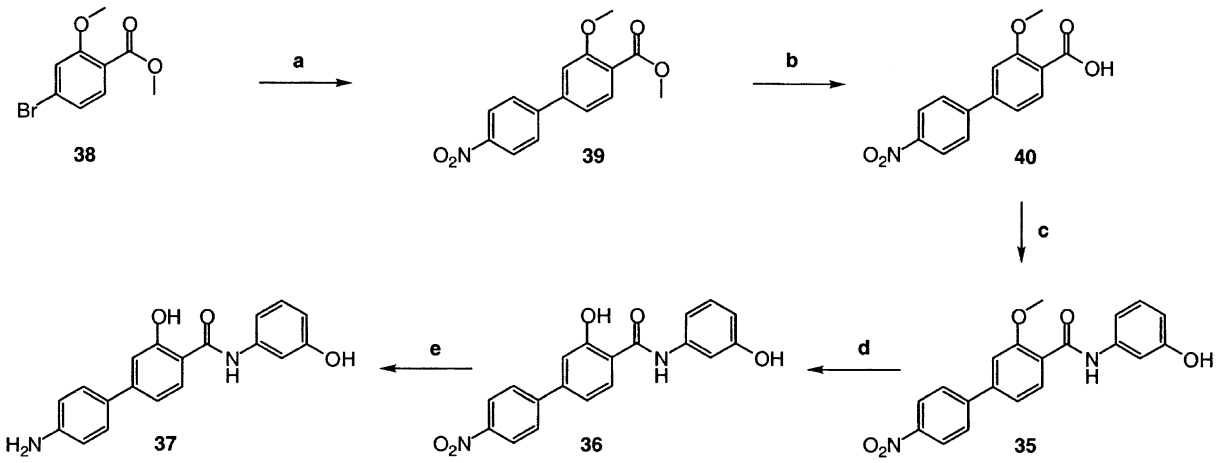


Fig. 6. Synthesis of 4-(4-aminophenyl)-*N*-(3-hydroxyphenyl)salicylamide (**37**); (a) (4-nitrophenyl)trimethylstannane, $Pd(PPh_3)_4$, 1,3-dioxolane, Ar, 24 h, 49%; (b) KOH, methanol, reflux, 90 min, 99%; (c) $SOCl_2$, reflux, 70 min, 99%; then 3-aminophenol, pyridine, Ar, 135 °C, 3 h, 61%; (d) BBr_3, dichloromethane, Ar, room temperature, 21 h, 82%; (e) H_2, PtO_2, ethanol, 12 h, room temperature, 97%.

2. Chemistry

Most of the salicylanilides listed in Table 1 were synthesized through reaction of the corresponding salicylic acids with the intermediate formed from 3-chloroaniline with phosphorus trichloride in boiling dibutyl ether [17]. Direct acylation of the substituted aniline with either a salicyloyl chloride or a phenyl salicylate was also used. Compounds **9** [18] and **30** [19,20] were prepared according to the literature.

Salicylanilides **35, 36**, and **37** were obtained from methyl 4-bromo-2-methoxybenzoate (**38**) (Fig. 6). The Pd-catalyzed coupling of this ester with trimethyl(4-nitrophenyl)stannane to form the biphenyl moiety could only be achieved in a moderate yield. The ester **39** thus obtained was hydrolyzed to the acid **40**, which was transformed into the corresponding acid chloride and then reacted with 3-aminophenol to give the anilide **35**. Ether cleavage with BBr_3 gave **36**, and reduction of the nitro group finally yielded **37**.

A different approach was used for the biphenylic anilide **28** (Fig. 7). Here the starting material was the bromosalicylanilide **24** or its acetate **41**; as a further alternative the triflate **18** was used. Suzuki coupling with the (aminophenyl) boronate **42** and [1,1′-*bis*(diphenylphosphino)ferrocene]-dichloropalladium(II) ($PdCl_2$(dppf)) as catalyst gave the target compound **28** in moderate yields only.

The piperidyl substituted salicylanilide **27** (Fig. 8) was obtained from the reaction of 3-(1-piperidyl)phenol [21] with 3-chlorophenyl isocyanate in low yields; the main product was the corresponding carbamate.

3. Biological results and discussion

The compounds synthesized were tested for their inhibitory potency towards the tyrosine kinases EGFR ICD (the intracellular domain of EGFR) and VEGFR-2 [22], and in some cases c-Abl to estimate their selectivity. The results are presented in Table 1. Inhibitory activities are given as IC_{50} values; for less active compounds percentage inhibition at a concentration of 10 μM is shown. It is noteworthy that most

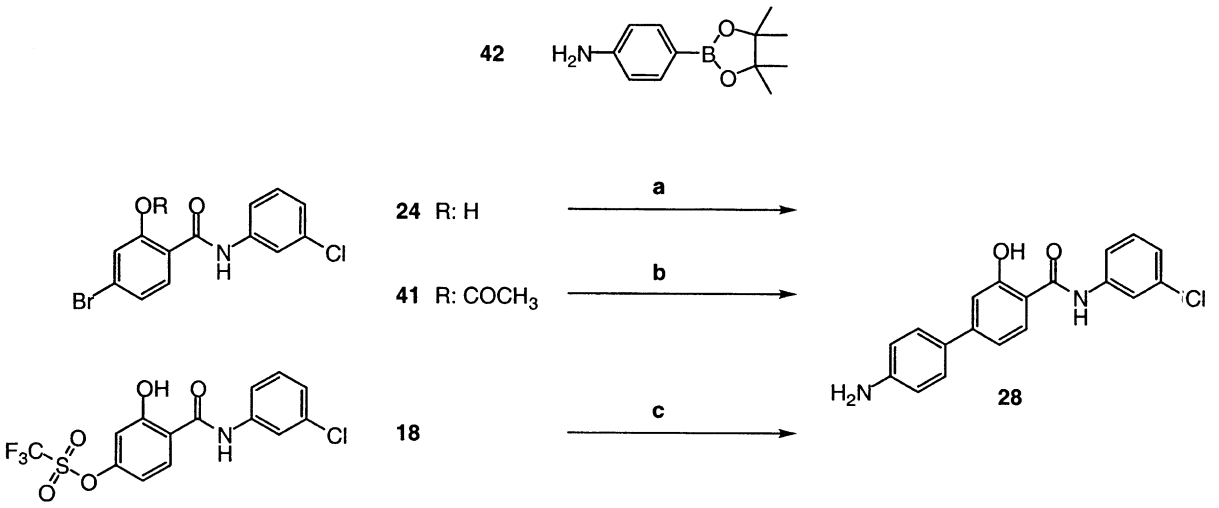


Fig. 7. Synthesis of 4-(4-aminophenyl)-*N*-(3-chlorophenyl)salicylamide (**28**). (a) Compound **42**, $PdCl_2$(dppf), 2 M Na_2CO_3, DMF, 75 °C, Ar, 37 h, 25%; (b) **42**, $PdCl_2$(dppf), 2 M Na_2CO_3, DMF, 75 °C, Ar, 38 h, 44%; (c) **42**, $PdCl_2$(dppf), K_3PO_4, DMF, 80 °C, 23 h, 52%.

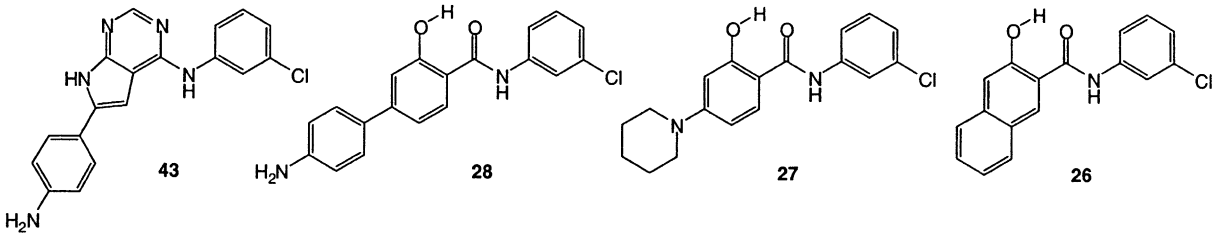


Fig. 8. Structures of compounds **43, 28, 27** and **26**.

compounds with high activities towards EGFR ($IC_{50} < 1$ μM) proved to be rather selective inhibitors with respect to VEGFR-2 or c-Abl.

The data presented in Table 1 clearly show that salicylanilides can be potent inhibitors of the EGFR PTK, the best five compounds (**28, 16, 20, 6** and **15**) have IC_{50} values in the range of 23–71 nM. The structural postulates for potential salicylanilide inhibitors derived from the quinazolines (e.g. **4**) also proved to be correct: the pseudo six-membered ring formed through the intramolecular hydrogen bond in the salicylic acid part is important for activity. When this is broken through methylation or benzylation of the phenolic OH group, activity is lost (compounds **10, 11, 32** and **35**).

Electron-donating groups in positions 4 and 5 of the salicylic acid moiety lead to good inhibitors as demonstrated by compounds **6, 12, 13, 15, 17, 19, 20, 21**, and even **28**. When the electron-donating character of the group in 4-position is destroyed by acylation, activity goes down (compare **16** with **18**, and **21** with **23**). Replacing the *p*-aminophenyl group (compound **37**) by *p*-nitrophenyl (compound **36**) has a similar effect. A methyl or bromine in 4-position also leads to loss of activity (**24** and **25**). With compounds having a 4-hydroxy group, introduction of a second OH-substituent in the salicylic acid moiety changes the inhibitory activity. An additional 3-OH (**17** vs. **15**) reduces it by a factor of 10, whereas an additional 6-OH (**16** vs. **15**) is tolerated. Limited variations of the substitution pattern in the anilino moiety revealed the 3′-chloro group clearly to be the best. Replacing it with OH led to loss of activity (**31** vs. **21**), as did omitting it completely (**30** vs. **14**).

The biphenylic compounds **28, 35, 36, 37**, and the piperidyl phenyl derivative **27** as well as the naphthalenic compound **26** were prepared with the pyrrolopyrimidine **43** in mind (see Fig. 8), which had been shown to be a very potent EGFR inhibitor with an IC_{50} value of 3 nM [23]. Compound **28** was indeed highly active (IC_{50} = 23 nM). Here again, replacement of the 3′ chlorine substituent by OH (compound **37**) decreased the activity by a factor of 40. The corresponding nitro compound **36** was even less active. The naphthalinic compound **26** (see Fig. 8) did not inhibit any of the investigated kinases.

4. Conclusion

It is well accepted, that for potent binding of 4-(phenylamino)quinazolines to the EGFR PTK, the pyrimidine motif is implicitly necessary. The hypothesis that this pyrimidine ring can be replaced by the pseudo six-membered ring formed by the strong intramolecular hydrogen bond in salicylanilides could be verified. The appropriately substituted salicylanilides **28, 16, 20, 6**, and **15** inhibit the EGFR PTK with IC_{50} values in the 23–71 nM range. Salicylanilides with alkylated phenolic OH groups (**10, 11, 32**), where this intramolecular hydrogen bond is not possible, consequently do not inhibit any of the herein measured kinases EGFR, VEGFR, or c-Abl. None of the herein described salicylanilides potently inhibits the VEGFR PTK or c-Abl. This demonstrates that **28, 16, 20, 6** or **15** block the EGFR PTK with good selectivity.

5. Experimental protocols

5.1. General remarks

All reactions with air- or moisture-sensitive reactants and solvents were carried out under argon atmosphere. Unless otherwise indicated, materials obtained from commercial suppliers were used without further purification.

IR spectra were determined with a Perkin Elmer 1600 infrared spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 or on a Bruker DRX500. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet. ^{13}C NMR spectra were recorded on a Varian Gemini 300 and a Bruker DRX500; for some of the compounds the assignments were corroborated by HETCOR experiments; assignments with asterisks may be interchanged. Chemical shifts are reported in ppm downfield from TMS. Mass spectra (MS) were recorded on a VG 70-250 or a Finnigan MAT 312 mass spectrometer. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values and were performed on Leco CHN-900 and Leco RO-478. Flash chromatography was carried out with Merck silica gel 60 (40–63 μm) and Machery Nagel silica gel (40–63 μm). Medium pressure liquid chromatography (MPLC) was performed on a Büchi B680 using LiChroprep (Si60 or RP18 (reverse phase)) of E. MERCK, Darmstadt. Melting points (m.p.) were measured on a Kofler–Block and are not corrected.

5.2. Syntheses

5.2.1. General procedure for salicylamide preparation

To a solution of 3-chloroaniline (5.71 mmol) in dibutyl ether was added dropwise at room temperature phosphorous trichloride (1.14 mmol). The suspension was heated at 140 °C for 2 h and the substituted salicylic acid (2.29 mmol) was added in small portions. The reaction mixture was stirred for additional 4 h at 140 °C. After cooling to room temperature the suspension was added to a saturated solution of potassium bicarbonate. The dibutyl ether and excess 3-chloroaniline were removed by steam distillation. The residual hot solution was filtered, cooled to room temperature and acidified with 2 M hydrochloric acid. The product precipitated and was collected by filtration.

5.2.2. N-*(3-Chlorophenyl)-4,5-dimethoxysalicylamide (**6**)*

Prepared as described in the general procedure from 3-chloroaniline (5.80 ml, 7.04 g, 55.2 mmol), phosphorous trichloride (1.00 ml, 1.52 g, 11.1 mmol), and 4,5-dimethoxysalicylic acid [24] (4.38 g, 22.1 mmol) in dibutyl ether. The compound was purified by recrystallization from ethanol/water. Yield: 98%, beige solid, m.p.: 177–178 °C. IR (KBr): 3331m, 3055w, 2936w, 2828w, 1646s, 1590s, 1543s, 1512s, 1501s, 1486s, 1463m, 1446m, 1436m, 1406m, 1371m, 1332s, 1301m, 1286s, 1257s, 1222m, 1204s, 1175m, 1161s, 1103m, 1083w, 1018m, 985m, 900w, 888m, 833m, 807m, 787m, 687m, 557m. ^{1}H NMR (300 MHz, D_6-DMSO): 11.97 (s, 1H, HO–C(2)); 10.31 (s, 1H, HN–CO); 7.87 (s, 1H, H–C(2′)); 7.60 (d, J = 8.0, 1H, H–C(6′)); 7.52 (s, 1H, H–C(6)); 7.41 (pseudo-t, J = 8.2, 1H, H–C(5′)); 7.20 (d, J = 7.4, 1H, H–C(4′)); 6.60 (s, 1H, H–C(3)); 3.81 (H_3C–O); 3.78 (H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 170.3 (HN–CO); 158.9 (C(4)); 157.4 (C(2)); 144.9 (C(5)); 142.8 (C(1′)); 136.1 (C(3′)); 133.5 (C(5′)); 126.9 (C(4′)); 123.9 (C(2′)); 122.8 (C(6′)); 114.2 (C(6)); 109.6 (C(1)); 104.0 (C(3)); 59.6 (H_3C–O); 58.9 (H_3C–O). EI-MS (70 eV): 310 (3); 309 (16); 308 (8, $[M + H]^+$); 307 (47, $[M]^+$); 182 (10); 181 (100); 180 (100); 165 (10); 153 (2); 152 (3); 138 (5), 137 (8); 136 (5); 129 (3); 127 (6); 125 (7); 124 (2); 110 (4); 109 (3); 95 (6); 69 (3); 53 (5). Anal. Found: $C_{15}H_{14}ClNO_4$ (C, H, N, O).

5.2.3. N-*(3-Chlorophenyl)-2,5-dimethoxybenzamide (**10**)*

N-(3-Chlorophenyl)-5-methoxysalicylamide (**13**) (355 mg, 1.27 mmol) was dissolved in ethanol (4 ml). To this yellow solution was added an aqueous solution of sodium hydroxide (0.330 ml water, 136 mg sodium hydroxide) and dimethyl sulfate (0.300 ml, 397 mg, 3.15 mmol). The solution was heated to 85 °C for 3 h when a colorless precipitate was formed. After cooling to room temperature 2 ml of water were added. The precipitated product was filtered off, washed with water and purified by recrystallization from ethanol/water. Yield: 265 mg (71%) as colorless needles, m.p.: 94–95 °C. IR (KBr): 3382m, 3329m, 3230m, 1639s, 1610s, 1546s, 1514m, 1492m, 1467m, 1452m, 1377m, 1324w, 1266s, 1179m, 1161m, 972w, 844m, 763m, 685m. ^{1}H NMR (300 MHz, D_6-DMSO): 10.30 (s, 1H, HN–CO); 7.96 (s, 1H, H–C(2′)); 7.64 (d, J = 8.0, 1H, H–C(6′)); 7.37 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.22 (d, J = 2.7, 1H, H–C(6)); 7.17–7.14 (m, 1H, H–C(4′)); 7.15–7.09 (m, 2H, H–C(3, 4)); 3.86 (s, 3H, H_3CO–C(5)); 3.76 (s, 3H, H_3CO–C(2)). ^{13}C NMR (75 MHz, D_6-DMSO): 164.4 (HN–CO); 153.0, 150.6 (C(2), C(5)); 140.4 (C(1′)); 133.0 (C(3′)); 130.4 (C(5′)); 125.0 (C(1)); 123.2 (C(4′)); 119.1 (C(2′)); 118.1 (C(6′)); 117.5 (C(3))*; 114.5 (C(6)); 113.5 (C(4))*; 56.4 (H_3CO–C(5)), 55.6 (H_3CO–C(2)). EI-MS (70 eV): 294 (1); 293.0 (5); 292 (2, $[M + H]^+$); 291 (13, $[M]^+$); 166 (12); 165 (100); 150 (4); 128 (3); 122 (6); 107 (6); 77 (5). Anal. Found: $C_{15}H_{14}ClNO_3$ (C, H, N, O).

5.2.4. Synthesis of 2-benzyloxy-4-bromo-N-*(3-chlorophenyl) benzamide (**11**)*

5.2.4.1. Benzyl 2-benzyloxy-4-bromobenzoate. To 4-bromosalicylic acid (8.00 g, 110 mmol) dissolved in acetone (375 ml) was added potassium carbonate (18.2 g, 110 mmol) and then benzyl bromide (20.8 ml, 29.9 g, 176 mmol). The mixture was heated to boiling for 20 h and then allowed to cool to room temperature. The solvent was removed and the residue dissolved in water (1 l) and extracted with *tert*-butyl methyl ether (2 × 750 ml). The organic phases were dried over sodium sulfate and the solvent evaporated. The crude product was purified by MPLC (SiO_2, gradient hexane to hexane/ethyl acetate). Yield: 12.3 g (80%), colorless needles, m.p.: 71–74 °C. IR (KBr): 3110w, 3060w, 3034w, 2936w, 2880w, 1698s, 1586s, 1483m, 1458m, 1411m, 1387m, 1294s, 1235s, 1136m, 1108m, 986m, 895m. ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, J = 8.3, 1H, H–C(6)); 7.42 (m, 2H, H_5C_6–H_2C–O); 7.34 (m, 8H, H_5C_6–H_2C–O); 7.17 (d, J = 1.6, 1H, H–C(3)); 7.12 (dd, J = 8.3, 1.8, 1H, H–C(5)); 5.31 (s, 2H, H_5C_6–H_2C–O); 5.11 (s, 2H, H_5C_6–H_2C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 165.4 (C=O); 158.7 (C(2)); 135.80 (H_5C_6–H_2C–O); 133.1 (C(6)); 128.55, 128.48, 128.19, 128.10, 127.98 (H_5C_6–H_2C–O); 127.6 (C(4)); 127.10 (H_5C_6–H_2C–O); 123.7 (C(5)); 119.5 (C(1)); 117.1 (C(3)); 70.9 (H_5C_6–H_2C–O); 66.8 (H_5C_6–H_2C–O). FAB-MS (NBA): 399 (2); 397 (2, $[M + H]^+$); 201 (1); 199 (1); 181 (4); 124 (8); 91 (100). Anal. Found: $C_{21}H_{17}BrO_3$ (C, H, O).

5.2.4.2. 2-Benzyloxy-4-bromobenzoic acid. Benzyl 2-benzyloxy4-bromobenzoate (1.05 g, 2.66 mmol) was boiled in a mixture of KOH solution (6%, 25 ml) and methanol (25 ml) for 3.5 h. The mixture was allowed to reach room temperature and acidified with HCl solution (6%) to pH 1. The precipitate formed was collected by suction filtration, dried in vacuo and recrystallized from ethanol/water. Yield: 0.775 g (95%), colorless needles, m.p.: 112–116 °C. IR (KBr): 3100–2500m, 1690s, 1589s, 1489w, 1443m, 1416m, 1385m, 1298s, 1240s, 1145w, 1105w, 1020w, 911w, 890m, 830w, 772m, 740m, 696w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.85 (s, 1H, COOH); 7.61 (d, J = 8.2, 1H, H–C(6)); 7.51–7.32 (m, 6H, H_5C_6–H_2C–O, C(3)); 7.22 (dd, J = 8.2, 1.7, 1H,

H–C(5)); 5.24 (s, 2H, H_5C_6–H_2C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 166.6 (COOH); 157.7 (C(2)); 136.6 (H_5C_6–H_2C–O); 132.3 (C(6)); 128.4, 127.7, 127.1 (H_5C_6–H_2C–O); 125.9 (C(4)); 123.3 (C(5)); 121.0 (C(1)); 117.0 (C(3)); 69.9 (H_5C_6–H_2C–O). EI-MS (70 eV): 309 (1); 308 (1, $[M + H]^+$); 307 (1, $[M]^+$); 306 (1); 262 (1); 200 (2); 198 (2); 172 (2); 154 (2); 92 (11); 91 (100); 90 (2); 89 (3); 65 (14); 63 (6); 39 (5). Anal. Found: $C_{14}H_{11}BrO_3$ (C, H, O).

*5.2.4.3. 2-Benzyloxy-4-bromo-*N*-(3-chlorophenyl)benzamide (**11**).* Prepared as described in the general procedure from 3-chloroaniline (1.00 ml, 1.21 g, 1.14 mmol), phosphorous trichloride (0.100 ml, 0.157 g, 1.14 mmol), and 2-benzyloxy-4-bromobenzoic acid (350 mg, 1.14 mmol). The product was purified by recrystallization from ethanol/water. Yield: 330 mg (69%), fine, colorless needles, m.p.: 174–176 °C. IR (KBr): 3338m, 1669s, 1588s, 1544s, 1480m, 1426m, 1408w, 1379w, 1279m, 1225m, 1131w, 995m, 914w, 890w, 757m, 696m, 663w. ^{1}H NMR (500 MHz, D_6-DMSO): 10.32 (s, 1H, HN–CO); 7.72 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.60 (d, J = 8.2, 1H, H–C(6)); 7.54 (d, J = 1.7, 1H, H–C(3)); 7.54–7.52 (m, 2H, H_5C_6–H_2C–O); 7.48–7.46 (m, 1H, H–C(6′)), 7.39–7.34 (m, 3H, H_5C_6–H_2C–O); 7.33 (pseudo-t, J = 8.2, H–C(5′)); 7.32 (dd, J = 8.2, 1.7, 1H, H–C(5)); 7.13 (ddd, J = 8.0, 2.1, 0.9, 1H, H–C(4′)); 5.27 (s, 2H, H_5C_6–H_2C–O). ^{13}C NMR (125 MHz, D_6-DMSO): 163.9 (HN–CO); 156.3 (C(2)); 140.2 (C(1′)); 136.1 (H_5C_6–H_2C–O); 133.1 (C(3′)); 131.4 (C(6)); 130.5 (C(5′)); 128.5 (H_5C_6–H_2C–O); 128.2 (H_5C_6–H_2C–O); 127.9 (H_5C_6–H_2C–O); 125.0 (C(4)); 124.2 (C(1)); 123.8 (C(5)); 123.3 (C(4′)); 118.7 (C(2′)); 117.7 (C(6′)); 116.5 (C(3)); 70.6 (H_5C_6–H_2C–O). EI-MS (70 eV): 419 (1); 418 (1); 417 (2); 416 (1); 415 (2, $[M]^+$); 399 (3); 397 (2), 291 (8); 289 (8); 245 (5); 219 (5); 218 (3); 217 (17); 216 (4); 201 (5); 199 (4); 129 (4); 127 (13); 92 (9); 91 (100); 65 (5); 63 (4). HR-EI-MS: 414.9982 ($[M]^+$, $C_{20}H_{15}BrClNO_2{}^+$; Calc. 414.9975). Anal. Found: $C_{20}H_{15}BrClNO_2$ (C, H, N, O).

5.2.5. N*-(3-Chlorophenyl)-5-hydroxysalicylamide (**12**)*

Prepared as described in the general procedure from 3-chloroaniline (6.75 ml, 8.19 g, 64.2 mmol), phosphorous trichloride (1.20 ml, 1.82 g, 13.7 mmol), and 5-hydroxysalicylic acid (3.97 g, 25.8 mmol) in dibutyl ether. The compound was purified by column chromatography using pentane/*tert*-butyl methyl ether (1:1). Yield: 4.30 g (63%), white powder, m.p.: 193.5–195.5 °C. IR (KBr): 3246s, 1640s, 1618s, 1597s, 1566m, 1518w, 1484m, 1452s, 1360m, 1331w, 1226w, 1194m, 1138w, 819w, 776w, 709w, 676w. ^{1}H NMR (300 MHz, D_6-DMSO): 10.86 (s, 1H, HO–C(2)); 10.49 (s, 1H, HN–CO); 9.12 (s, 1H, HO–C(5)); 7.94 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.58 (ddd, J = 8.2, 2.0, 0.9, 1H, H–C(6′)); 7.38 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.32 (d, J = 2.8, H–C(6)); 7.17 (ddd, J = 8.0, 2.0, 1.0, 1H, H–C(4′)); 6.87 (dd, J = 8.7, 2.8, 1H, H–C(4)); 6.83 (d, J = 8.7, 1H, H–C(3)). ^{13}C NMR (75 MHz, D_6-DMSO): 165.9 (HN–CO); 150.2, 149.7 (HO–C(2, 5)); 139.9 (C(1′)); 133.0 (C(3′)); 130.4 (C(5′)); 123.5 (C(4′)); 121.2 (C(4)); 119.9 (C(2′)); 118.9 (C(6′)); 118.1 (C(1)); 117.8 (C(3)); 114.6 (C(6)). EI-MS (70 eV): 266 (2); 265 (15); 264 (7, $[M + H]^+$); 263 (47, $[M]^+$); 138 (8); 137 (100); 136 (91); 135 (4); 130 (3); 129 (29); 128 (11); 127 (92); 109 (25); 108 (22); 99 (13); 81 (53); 80 (18); 69 (21); 63 (28); 53 (69); 52 (45); 51 (25); 39 (25). Anal. Found: $C_{13}H_{10}ClNO_3$ (C, H, N, O).

5.2.6. N*-(3-Chlorophenyl)-5-methoxysalicylamide (**13**)*

Prepared according to the general procedure from 3-chloroaniline (600 μl, 728 mg, 5.71 mmol), phosphorous trichloride (100 μl, 152 mg, 1.14 mmol), and 5-methoxysalicylic acid (385 mg, 2.29 mmol) in dibutyl ether. The compound was purified by recrystallization from ethanol/water. Yield: 397 mg (77%), brown powder, m.p.: 163–164 °C. IR (KBr): 3088m, 3006m, 2935m, 2832w, 1639s, 1590s, 1554s, 1506m, 1478m, 1445m, 1433s, 1379m, 1288m, 1278m, 1206s, 1142m, 1049m, 875w, 808m, 768m, 755m, 675m. ^{1}H NMR (300 MHz, D_6-DMSO): 11.16 (s, 1H, HO–C(2)); 10.51 (s, 1H, HN–CO); 7.94 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.62 (dd, J = 8.2, 1.1, 1H, H–C(6′)); 7.47 (d, J = 3.2, 1H, H–C(6)); 7.40 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.20 (ddd, J = 8.0, 2.1, 0.9, 1H, H–C(4′)); 7.08 (dd, J = 8.9, 3.1, 1H, H–C(4)); 6.95 (d, J = 9.0, 1H, H–C(3)); 3.77 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 166.0 (HN–CO); 151.9, 151.8 (C(2, 5)); 139.7 (C(1′)); 133.0 (C(3′)); 130.3 (C(5′)); 123.7 (C(4′)); 120.6 (C(2′)); 120.2 (C(6′)); 119.1 (C(4)); 118.1 (C(3)); 117.7 (C(1)); 112.8 (C(6)); 55.6 (H_3C–O). EI-MS (70 eV): 280 (2); 279 (14); 278 (7, $[M + H]^+$); 277 (43, $[M]^+$); 153 (2), 152 (5), 151 (48); 150 (100), 135 (4); 129 (4), 127 (13), 123 (7); 122 (7); 108 (6); 107 (7); 95 (5); 79 (5); 52 (5). Anal. Found: $C_{14}H_{12}ClNO_3$ (C, H, N).

5.2.7. N*-(3-Chlorophenyl)-5-methylsalicylamide (**14**)*

Prepared according to the general procedure from 3-chloroaniline (5.20 ml, 6.31 g, 49.5 mmol), phosphorous trichloride (0.900 ml, 1.37 g, 9.96 mmol), and 5-methylsalicylic acid (3.00 g, 19.7 mmol) in dibutyl ether. The compound was purified by column chromatography using pentane/*tert*-butyl methyl ether (1:1) and recrystallization from ethanol/water. Yield: 4.38 g (85%) as beige platelets, m.p.: 175–177 °C. IR (KBr): 3196m, 2923w, 2859w, 1646s, 1612s, 1561s, 1508s, 1482s, 1420m, 1355m, 1329s, 1293m, 1246m, 1224s, 1198m, 1141m, 1099m, 1074w, 995w, 883m, 851m, 813s, 774m, 701m, 675m, 649m, 582w, 535m. ^{1}H NMR (500 MHz, D_6-DMSO): 11.38 (s, 1H, HO–C(2)); 10.46 (s, 1H, HN–CO); 7.93 (pseudo-t, J = 2.0, 1H, H–C(2′)): 7.73 (d, J = 1.7, 1H, H–C(6)); 7.62 (ddd, J = 8.2, 1.9, 0.8, 1H, H–C(6′)); 7.38 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.24 (dd, J = 8.3, 1.8, 1H, H–C(4)); 7.18 (ddd, J = 8.0, 2.0, 0.8, 1H, H–C(4′)); 6.89 (d, J = 8.3, 1H, H–C(3)); 2.27 (s, 3H, H_3C–C(5)). ^{13}C NMR (125 MHz, D_6-DMSO): 166.6 (HN–CO); 156.0 (C(2)); 139.8 (C(1′)); 134.4 (C(4)); 133.0 (C(3′)); 130.4 (C(5′)); 129.0 (C(6)); 127.7 (C(5)); 123.7 (C(4′)); 120.1 (C(2′)); 119.1 (C(6′)); 117.2 (C(1)); 117.1 (C(3)); 20.0 (H_3C–C(5)). EI-MS (70 eV): 264 (6); 263 (26); 262 (15, $[M + H]^+$); 261 (54, $[M]^+$); 136 (19); 135

(100); 134 (36); 129 (29); 128 (10); 127 (63); 107 (20); 78 (13); 77 (28); 53 (14); 51 (11). Anal. Found: $C_{14}H_{12}ClNO_2$ (C, H, N, O).

5.2.8. N-*(3-Chlorophenyl)-4-hydroxysalicylamide (**15**)*

Prepared as described in the general procedure from 3-chloroaniline (3.60 ml, 4.37 g, 34.3 mmol), phosphorous trichloride (0.600 ml, 0.912 g, 6.86 mmol), and 4-hydroxysalicylic acid (2.11 g, 13.7 mmol) in dibutyl ether. The compound was purified by recrystallization from ethanol/water. Yield: 2.77 g (77%), beige powder, m.p.: 150–152 °C. IR (KBr): 3314w, 3051–2581m, 1618s, 1591s, 1555m, 1518s, 1482m, 1435m, 1321m, 1290m, 1256m, 1206m, 776m, 682m. ^{1}H NMR (300 MHz, D_6-DMSO): 12.02 (s, 1H, HO–C(2)); 10.24 (s, 2H, HO–C(4), HN–CO); 7.89 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.86 (d, J = 8.8, 1H, H–C(6)); 7.59 (dd, J = 8.2, 1.1, 1H, H–C(6′)); 7.38 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.18 (dd, J = 8.0, 0.9, 1H, H–C(4′)); 6.39 (dd, J = 8.8, 2.4, 1H, H–C(3)); 6.34 (d, J = 2.3, 1H, H–C(5)). ^{13}C NMR (75 MHz, D_6-DMSO): 167.2 (HN–CO); 162.7, 161.3 (HO–C(2, 4)); 139.8 (C(1′)); 133.0 (C(3′)); 130.5 (C(6)); 130.3 (C(5′)); 123.5 (C(4′)); 120.3 (C(2′)); 119.2 (C(6′)); 107.8 (C(1)); 107.6 (C(5)); 102.8 (C(3)). EI-MS (70 eV): 266 (1); 265 (8); 264 (4, $[M + H]^+$); 263 (24, $[M]^+$); 138 (8); 137 (100); 130 (2); 129 (19); 128 (4); 127 (59); 81 (13); 69 (8); 53 (9). Anal. Found: $C_{13}H_{10}ClNO_3$ (C, H, N, O).

5.2.9. N-*(3-Chlorophenyl)-4,6-dihydroxysalicylamide (**16**)*

Prepared as described in the general procedure from 3-chloroaniline (2.20 ml, 2.67 g, 20.9 mmol), phosphorous trichloride (1.50 ml, 2.28 g, 16.6 mmol), and 2,4,6-trihydroxybenzoic acid (0.800 g, 4.00 mmol) in dibutyl ether. The compound was purified by reverse phase MPLC using water/methanol (gradient towards decreasing polarity) and recrystallization from ethanol/water. Yield: 419 mg (18%), colorless powder, m.p.: 209–212 °C. IR (KBr): 3463m, 3387m, 3306s, 1654s, 1611s, 1554s, 1476m, 1433w, 1391m, 1296s, 1253s, 1182m, 1060m, 861w, 829w, 796m, 770m, 702w, 683w, 648w, 549w, 530w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.49 (s, 2H, HO–C(2))*; 10.66 (s, 1H, HO–C(6))*; 10.16 (s, 1H, HN–CO)*; 7.86 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.48 (ddd, J = 8.2, 1.9, 1.0, 1H, H–C(6′)); 7.39 (pseudo-t, J = 8.0, 1H, H–C(5′)); 7.21 (dd, J = 2.1, 1.0, 1H, H–C(4′)); 7.18 (dd, J = 2.1, 1.0, 1H, H–C(2′)); 5.91 (s, 2H, H–C(3, 5)). ^{13}C NMR (75 MHz, D_6-DMSO): 168.8 (HN–CO); 162.7 (C(4)); 161.7 (C(2, 6)); 139.0 (C(1′)); 133.2 (C(3′)); 130.5 (C(5′)); 123.8 (C(4′)); 120.4 (C(2′)); 119.4 (C(6′)); 95.1 (C(3, 5)). EI-MS (70 eV): 282 (2, $[M(^{37}Cl) + H]^+$); 281 (14, $[M(^{37}Cl)]^+$); 280 (6, $[M(^{35}Cl) + H]^+$); 279 (44, $[M(^{35}Cl)]^+$); 154 (5); 153 (59); 152 (8); 130 (3); 129 (33); 128 (10); 127 (100); 111 (13); 95 (5); 69 (13); 65 (5); 44 (8); 43 (8). HR-EI-MS: 279.0298 ($[M]^+$, $C_{13}H_{10}ClNO_4^+$; Calc. 279.0298).

5.2.10. N-*(3-Chlorophenyl)-3,4-dihydroxysalicylamide (**17**)*

Prepared as described in the general procedure from 3-chloroaniline (2.20 ml, 2.67 g, 20.9 mmol), phosphorous trichloride (1.50 ml, 2.28 g, 16.6 mmol), and 2,3,4-trihydroxybenzoic acid (1.43 g, 8.40 mmol) in dibutyl ether. The compound was purified by reverse phase MPLC using water/methanol (gradient towards decreasing polarity). Yield: 877 mg (37%), beige needles, m.p.: 180.5–182.5 °C. IR (KBr): 3510m, 3427m, 1654s, 1593s, 1545s, 1509m, 1457m, 1431m, 1376m, 1312s, 1258m, 1221m, 1036m, 775m, 676w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.00 (s, 1H, HO–C(2)); 10.3 (s, 1H, HN–CO); 9.75 (s, 1H, HO–C(4)); 8.59 (s, 1H, HO–C(3)); 7.88 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.61 (d, J = 8.6, 1H, H–C(6′)); 7.43 (d, J = 8.8, 1H, H–C(6)); 7.38 (d, J = 8.0, 1H, H–C(5′)); 7.19 (d, J = 7.9, 1H, H–C(4′)); 6.42 (d, J = 8.8, 1H, H–C(5)). ^{13}C NMR (75 MHz, D_6-DMSO): 168.5 (HN–CO); 150.5, 150.4 (C(2, 4)); 139.7 (C(1′)); 132.9, 132.8 (C(3, 3′)); 130.3 (C(5′)); 123.6 (C(4′)); 120.6 (C(2′)); 119.5, 119.0 (C(6, 6′)); 107.6 (C(1)); 107.1 (C(5)). EI-MS (70 eV): 282 (2); 281 (13); 280 (6, $[M + H]^+$); 279 (38, $[M]^+$); 154 (6); 153 (69); 152 (100); 151 (3); 130 (5); 129 (16); 128 (11); 127 (49); 124 (5); 107 (5); 79 (8); 51 (9). Anal. Found: $C_{13}H_{10}ClNO_4$ (C, H, N, O).

5.2.11. N-*(3-Chlorophenyl)-4-(trifluoromethanesulfonyloxy) salicylamide (**18**)*

The amide **22** (500 mg, 2.06 mmol) in abs. acetonitrile (30 ml) was cooled to –17 °C. Boron trifluoride etherate (387 μl, 437 mg, 3.08 mmol) and then over a time of 20 min *tert*-butyl nitrite (293 μl, 2.47 mmol) in abs. acetonitrile (2.5 ml) were added. The mixture was stirred at –10 °C for 10 min, when a yellow product precipitated. The suspension was diluted with diethyl ether (5 ml) and the 4-[(3-chloroanilino)carbonyl]benzenediazonium tetrafluoroborate collected by filtration and once washed with diethyl ether by decantation. An additional crop of product could be obtained by concentrating the mother liquor and precipitation with chloroform. Total yield: 385 mg (56%), pink crystals, decomposition at 250 °C. To this product (277 mg, 0.766 mmol), which was used without further purification, trifluoromethanesulfonic acid (3.85 ml, 6.62 g, 44.0 mmol) was added in small portions. The suspension was then heated to 80 °C for 1 h; a clear brown solution had formed. After pouring cold water (12 ml) into the solution, the raw product precipitated. It was filtered off and washed with cold water. Yield: 230 mg (76%), light brown solid, m.p.: 130–131 °C. IR (KBr): 3319w, 3145m, 1636s, 1609s, 1561w, 1500w, 1483w, 1424s, 1361w, 1245s, 1228s, 1141s, 1131*s*, 1102w, 969s, 840m, 622m, 501m. ^{1}H NMR (300 MHz, D_6-DMSO): 11.85 (s, 1H, HO–C(2)); 10.49 (s, 1H, HN–CO)); 7.94 (d, J = 10.9, 1H, H–C(6)); 7.93 (s, 1H, H–C(2′)); 7.62 (ddd, J = 8.2, 2.0, 0.9, 1H, H–C(6′)); 7.40 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.20 (ddd, J = 8.0, 2.0, 1.0, 1H, H–C(4′)); 7.09 (dd, J = 10.5, 2.5, 1H, H–C(5)); 7.08 (s, 1H, H–C(3)). ^{13}C NMR: (75 MHz, D_6-DMSO): 164.7 (HN–CO); 158.2 (C(2)); 151.1 (C(4)); 139.8 (C(1′)); 133.0 (C(3′)); 131.6, 130.4 (C(6),

C(5′)); 123.8 (C(4′)); 121.0 (C(1)); 119.8 (C(2′)); 118.8 (C(6′)); 118.2 (q, J = 321, F_3C–S); 111.9 (C(5)); 109.6 (C(3)). EI-MS: (70 eV): 398 (2); 397 (7); 396 (4, $[M + H]^+$); 395 (18, $[M]^+$); 270 (4); 269 (37); 205 (7); 137 (4); 136 (10); 129 (36); 128 (9); 127 (100); 108 (12); 69 (10). HR-EI-MS: 394.9845 ($[M]^+$, $C_{14}H_9ClF_3NO_5S^+$; Calc. 394.9842). Anal. Found: $C_{14}H_9ClF_3NO_5S$ (C, H, N, O).

5.2.12. N-*(3-Chlorophenyl)-4-methoxysalicylamide (**19**)*

Prepared as described in the general procedure from 3-chloroaniline (600 µl, 728 mg, 5.71 mmol), phosphorous trichloride (100 µl, 152 mg, 1.14 mmol), and 4-methoxysalicylic acid (386 mg, 2.29 mmol) in dibutyl ether. The compound was purified by recrystallization from ethanol/water. Yield: 273 mg (43%), colorless needles, m.p.: 168.5–169.5 °C. IR (KBr): 3325m, 1592s, 1542s, 1516s, 1479m, 1426m, 1381m, 1282s, 1252s, 1105w, 981w, 773m, 697w, 678w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.17 (s, 1H, HO–C(2)); 10.32 (s, 1H, HN–CO); 7.98 (d, J = 9.0, 1H, H–C(6)); 7.89 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.62 (d, J = 8.3, 1H, H–C(6′)); 7.39 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.19 (dd, J = 8.0, 1.2, 1H, H–C(4′)); 6.58 (dd, J = 8.8, 2,5, 1H, H–C(5)); 6.51 (d, J = 2.5, 1H, H–C(3)); 3.81 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 167.2 (HN–CO); 163.9, 161.4 (HO–C(2), CH_3O–*C*(4)); 139.7 (C(1′)); 132.9 (C(3′)); 130.33, 130.29 (C(5′), C(6)); 123.7 (C(4′)); 120.4 (C(2′); 119.3 (C(6′)); 109.0 (C(1)); 106.4 (C(5)); 101.3 (C(3)); 55.4 (H_3C–O). EI-MS (70 eV): 280 (1); 279 (7); 278 (4, $[M + H]^+$); 277 (22, $[M]^+$); 152 (11); 151 (100); 129 (6); 127 (18); 108 (7); 95 (6); 52 (4). Anal. Found: $C_{14}H_{12}ClNO_3$ (C, H, N).

5.2.13. N-*(3-Chlorophenyl)-5-hydroxy-4-methoxysalicylamide (**20**)*

Prepared as described in the general procedure from 3-chloroaniline (0.80 ml, 0.97 g, 7.6 mmol), phosphorous trichloride (0.15 ml, 0.23 g, 1.7 mmol), and 5-hydroxy-4-methoxysalicylic acid [25] (0.55 g, 3.0 mmol) in dibutyl ether. The product was purified by recrystallization from ethanol/water. Yield: 500 mg (57%), beige solid, 180 °C (decomposition). IR (KBr): 3322m, 3221m, 1624s, 1588s, 1560s, 1521s, 1483m, 1446m, 1426m, 1387w, 1322m, 1274s, 1238m, 1189s, 1164m, 1101w, 1079m, 1014w, 900w, 885w, 849w, 836w, 778m, 680w, 658w. ^{1}H NMR (300 MHz, CD_3OD): 7.78 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.44 (d, J = 7.4, 1H, H–C(6′)); 7.33 (s, 1H, H–C(6)); 7.28 (pseudo-t, J = 8.0, 1H, H–C(5′)); 7.06 (dd, J = 7.9, 1.5, 1H, H–C(4′)); 6.46 (s, 1H, H–C(3)); 3.84 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, CD_3OD): 169.0 (HN–CO); 155.8 (HO–C(2))*; 154.5 (HO–C(4))*; 141.0 (C(5)); 140.5 (C(1′)); 135.3 (C(3′)); 131.0 (C(5′)); 125.1 (C(4′)); 122.0 (C(2′)); 120.3 (C(6′)); 114.7 (C(6)); 108.9 (C(1)); 101.1 (C(3)); 56.4 (H_3C–O). EI-MS (70 eV): 296 (3); 295 (22); 294 (12, $[M + H]^+$); 293 (52, $[M]^+$); 275 (3); 168 (17); 167 (100); 166 (90), 138 (7); 129 (12); 127 (30); 124 (8); 123 (18); 111 (12); 96 (13); 95 (10); 79 (7); 78 (6); 69 (15); 53 (14); 39 (10). HR-EI-MS: 279.0410 ($[M]^+$, $C_{14}H_{12}ClNO_4^+$; Calc. 293.0455).

5.2.14. 4-Amino-N-*(3-chlorophenyl)salicylamide (**21**)*

Prepared as described in the general procedure from 3-chloroaniline (26.2 ml, 31.8 g, 250 mmol), phosphorous trichloride (1.09 ml, 1.71 g, 12.5 mmol), and 4-aminosalicylic acid (3.83 g, 25.0 mmol) in dibutyl ether. The compound was purified by column chromatography using hexane/*tert*-butyl methyl ether (3:1 to increasing polarity). Yield: 2.71 g (41%), beige needles, m.p.: 183–185 °C. IR (KBr): 3474m, 3403w, 3374s, 1631s, 1585s, 1510s, 1444w, 1426m, 1387s, 1328m, 1288s, 1251s, 1239s, 1197w, 1163m, 852w, 839w, 779m. ^{1}H NMR (300 MHz, D_6-DMSO): 12.13 (s, 1H, HO–(C(2)); 10.30 (s, 1H, HN–CO); 7.87 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.71 (d, J = 8.8, 1H, H–C(6)); 7.57 (ddd, J = 8.3, 2.0, 0.9, 1H, H–C(6′)); 7.33 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.13 (ddd, J = 8.0, 2.0, 0.9, 1H, H–C(4′)); 6.14 (dd, J = 8.7, 2.1, 1H, H–C(5)); 6.03 (d, J = 2.1, 1H, H–C(3)); 5.94 (s, 2H, H_2N–C(4)). ^{13}C NMR (75 MHz, D_6-DMSO): 168.1 (HN–CO); 162.2 (C(2)); 154.7 (C(4)); 140.1 (C(1′)); 132.9 (C (3′)), 130.2 (C(5′)); 129.8 (C(6)); 123.1 (C(4′)); 120.2 (C(2′)); 119.1 (C(6′)); 106.0 (C(5)); 103.2 (C(1)); 99.4 (C(3)). EI-MS (70 eV): 265 (1); 264 (8); 263 (3, $[M + H]^+$); 262 (23, $[M]^+$); 137 (13); 136 (100); 135 (5); 127 (8); 114 (5); 80 (13); 79 (4); 53 (5). Anal. Found: $C_{13}H_{11}ClN_2O_2$ (C, H, N, O).

5.2.15. N-*(3-Chlorophenyl)-4-(diethylamino)salicylanilide (**22**)*

Prepared similar to the general procedure from 3-chloroaniline (1.22 g, 9.60 mmol), phosphorous trichloride (0.220 g, 1.60 mmol), and 4-(diethylamino)salicylic acid [26] (1.00 g, 4.78 mmol) in *p*-xylene. The product was purified by recrystallization from ethanol/water. Yield: 360 g (12%), colorless needles, m.p.: 165–166 °C.

5.2.15.1. Alternate method. To 3-(diethylamino)phenol (1.00 g, 6.05 mmol) in 1,2-dichlorobenzene (23 ml) was added 3-chlorophenyl isocyanate (0.730 ml, 0.926 g, 6.05 mmol). The reaction mixture was heated to 150 °C for 5 h and after cooling to room temperature the solvent was distilled off. The residue was suspended in a mixture of *n*-hexane (50 ml) and benzene (10 ml), heated to reflux for 5 min and collected by filtration; this was repeated two times to give **22**, which finally was purified by recrystallization from ethanol/water. Yield: 950 mg (49%), colorless needles, m.p.: 165–166 °C.

Data of **22**: IR (KBr): 3312m, 2979w, 2932w, 2892w, 1639s, 1585s, 1517s, 1427m, 1408s, 1360s, 1333s, 1274s, 1256s, 1200m, 1150m, 1078m, 829m, 773s, 692m, 679m. ^{1}H NMR (300 MHz, D_6-DMSO): 10.08 (s, 1H, HN–CO); 7.89 (pseudo-t, J = 2,1, 1H, H–C(2′)); 7.83 (d, J = 9.1, H–C(6)); 7.61 (d, J = 8.2, 1H, H–C(6′)); 7.37 (pseudo-t, J = 8.0, H–C(5′)); 7.15 (d, J = 9.2, H–C(4′)); 6.30 (dd, J = 9.3, 2.6, 1H, H–C(5)); 6.08 (d, J = 2.5, H–C(3)); 3.38 (q, J = 7.1, 4H, H_3CH_2C–N); 1.12 (t, J = 6.9, 6H, H_3CH_2C–N). ^{13}C NMR (75 MHz, D_6-DMSO): 168.0 (HN–CO); 162.2 (C(2)); 152.0 (C(4)); 140.1 (C(1′)); 132.9 (C(3′)); 130.2 (C(5′)); 129.8

(C(6)); 123.1 (C(4′)); 120.2 (C(2′)); 119.1 (C(6′)); 103.3 (C(5)); 102.5 (C(1)); 97.2 (C(3)); 43.8 (H_3CH_2C–N); 12.5 (H_3CH_2C–N). EI-MS (70 eV): 321 (1); 320 (7); 319 (4, $[M + H]^+$); 318 (21, $[M]^+$); 193 (19); 192 (100); 191 (7); 176 (15); 162 (5); 149 (5); 148 (10); 127 (5). HR-EI-MS: 279.0298 ($[M]^+$, $C_{17}H_{19}ClN_2O_2^+$; Calc. 318.115). Anal. Found: $C_{17}H_{19}ClN_2O_2$ (C, H, N, O).

*5.2.16. 4-Acetamido-*N*-(3-chlorophenyl)salicylamide (**23**)*

To 4-acetamidosalicyloyl chloride prepared from 4-acetamidosalicylic acid [27] (7.62 g, 39.0 mmol) and thionyl chloride (15.0 ml, 24.5 g, 77.1 mmol) at 0 °C as described for **33**, toluene (40 ml) and 3-chloroaniline (4.10 ml, 4.98 g, 39.0 mmol) were added and the reaction mixture was stirred for 1 h at room temperature. After the addition of pyridine (13 ml) and toluene (20 ml) and additional stirring for 3.5 h, hydrochloric acid (7.5%, 200 ml) and then *tert*-butyl methyl ether (200 ml) were added, whereupon a violet solid precipitated. The crude product (1.47 g, 77%) was filtered off and a sample of it purified by column chromatography using *tert*-butyl methyl ether and recrystallization from DMF/water. Beige needles, m.p.: 257–261 °C. IR (KBr): 3421w, 3312m, 3112m, 2926w, 1648s, 1591s, 1545s, 1483s, 1458w, 1426s, 1373m, 1317m, 1292m, 1251s, 876w, 776m, 681m. ^{1}H NMR (500 MHz, D_6-DMSO): 11.85 (s, 1H, HO–C(2)); 10.34 (s, 1H, HN–CO); 10.16 (s, 1H, HNCO); 7.90 (pseudo-t, J = 2.0, 1H, H–C(2′)); 7.87 (d, J = 8.7, 1H, H–C(6)); 7.58 (ddd, J = 8.2, 2.0, 0.9, 1H, H–C(6′)); 7.44 (d, J = 2.0, 1H, H–C(3)); 7.37 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.16 (ddd, J = 8.0, 2.1, 0.9, 1H, H–C(4′)); 7.05 (dd, J = 8.7, 2.0, 1H, H–C(5)); 2.06 (s, 3H, H_3C–C). ^{13}C NMR (125 MHz, D_6-DMSO): 169.0 (HN–CO); 166.3 (HN–CO); 159.3 (C(2)); 144.2 (C(4)); 139.8 (C(1′)); 133.0 (C(3′)); 130.4 (C(5′)); 129.9 (C(6)); 123.6 (C(4′)); 120.2 (C(2′)); 119.1 (C(6′)); 111.7 (C(1)); 109.9 (C(5)); 106.2 (C(3)); 24.2 (H_3C–C). EI-MS (70 eV): 307 (1); 306 (5); 305 (3, $[M + H]^+$); 304 (13, $M]^+$); 179 (11); 178 (100); 153 (4); 137 (8); 136 (63); 129 (8); 127 (26); 109 (4); 80 (6); 43 (10). Anal. Calc. for $C_{15}H_{13}ClN_2O_3$ (304.73): C, 59.12; H, 4.30; N, 9.19; O, 15.75. Found: C, 59.17; H, 4.23; N, 9.62; O, 15.78.

*5.2.17. 4-Bromo-*N*-(3-chlorophenyl)salicylamide (**24**)*

Prepared as described in the general procedure from 3-chloroaniline (10.0 ml, 12.1 g, 95.1 mmol), phosphorous trichloride (1.66 ml, 2.52 g, 19.0 mmol), and 4-bromosalicylic acid [28] (2.11 g, 13.7 mmol) in dibutyl ether. After the steam distillation a remaining orange precipitate was collected by filtration of the hot suspension. After acidification of the filtrate with 6 M hydrochloric acid to pH 3, a brown precipitate was formed which was isolated by filtration. The two solids were combined and purified by column chromatography using hexane/ethyl acetate (10:1 to increasing polarity). Yield: 4.82 g (62%), colorless needles, m.p.: 222–223 °C. IR (KBr): 3321w, 3019w, 2925w, 2851w, 2666w, 2568w, 1616s, 1561s, 1508w, 1483s, 1424s, 1388m, 1324w, 1270w, 1236m, 1223s, 1205m, 849m, 778m, 677m. ^{1}H NMR (300 MHz, D_6-DMSO): 11.84 (s, 1H, HO–C(2)); 10.45 (s, 1H, HN–CO); 7.93 (pseudo-t, J = 2.1, 1H, H–C(2′)); 7.81 (d, J = 8.4, 1H, H–C(6)); 7.61 (d, J = 7.8, 1H, H–C(6′)); 7.40 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.21 (d, J = 1.7, 1H, H–C(3)); 7.17 (dd, J = 8.3, 1.9, 2H, H–C(4′, 5)). ^{13}C NMR (75 MHz, D_6-DMSO): 165.4 (HN–CO); 158.3 (C(2)); 139.6 (C(1′)); 133.0 (C(3′)); 131.1 (C(6)); 130.4 (C(5′)); 126.1 (C(4)); 123.8 (C(5)); 122.1 (C(4′)); 120.0 (C(3)); 119.6 (C(2′)); 119.0 (C(6′)); 118.0 (C(1)). EI-MS (70 eV): 330 (1); 329 (5); 328 (3); 327 (19); 326 (3, $[M]^+$); 325 (15); 202 (3); 201 (38); 200 (4); 199 (38); 145 (6); 143 (6); 129 (36); 128 (9); 127 (100); 63 (10). Anal. Found: $C_{13}H_9BrClNO_2$ (C, H, N, O).

5.2.18. N*-(3-Chlorophenyl)-4-methylsalicylamide (**25**)*

Prepared as described in the general procedure from 3-chloroaniline (5.20 ml, 6.31 g, 49.5 mmol), phosphorous trichloride (0.900 ml, 1.37 g, 9.96 mmol), and 4-methylsalicylic acid (3.00 g, 19.7 mmol) in dibutyl ether. The compound was purified by recrystallization from ethanol/water. Yield: 3.57 g (69%), colorless platelets, m.p.: 207.2–207.5 °C. IR (KBr): 3420w, 3310w, 3044m, 2923m, 2867m, 1622s, 1590s, 1558s, 1482s, 1426s, 1384m, 1325m, 1247s, 1206w, 1174m, 1103w, 1075w, 878w, 855m, 824w, 774m, 707m, 686m. ^{1}H NMR (500 MHz, D_6-DMSO): 11.73 (s, 1H, HO–C(2)); 10.41 (s, 1H, HN–CO); 7.92 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.86 (d, J = 8.0, 1H, H–C(6)); 7.62 (ddd, J = 8.2, 1.9, 0.7, 1H, H–C(6′)); 7.38 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.19 (ddd, J = 7.9, 2.0, 0.8, 1H, H–C(4′)); 6.80 (s, 1H, H–C(3)); 6.79 (d, J = 8.5, 1H, H–C(5)); 2.31 (s, 3H, H_3C–C(4)). ^{13}C NMR (125 MHz, D_6-DMSO): 166.9 (HN–CO); 158.7 (C(2)); 144.5 (C(4)); 139.7 (C(1′)); 133.0 (C(3′)); 130.3 (C(5′)); 129.0 (C(6)); 123.7 (C(4′)); 120.3 (C(2′)); 120.1 (C(5)); 119.2 (C(6′)); 117.5 (C(3)); 114.3 (C(1)); 21.1 (H_3C–C(4)). EI-MS (70 eV): 264 (5); 263 (20); 262 (12, $[M + H]^+$); 261 (43, $[M]^+$); 136 (18); 135 (100); 134 (13); 129 (22); 128 (8); 127 (50); 107 (13); 77 (22); 53 (10). Anal. Found: $C_{14}H_{12}ClNO_2$ (C, H, N, O).

5.2.19. N*-(3-Chlorophenyl)-3-hydroxynaphthalene-2-carboxamide (**26**)*

3-Hydroxynaphthalene-2-carboxylic acid (1.00 g, 5.31 mmol) and sodium carbonate (1.68 g, 15.9 mmol) were suspended in dichloromethyl methyl ether (6.00 ml, 7.77 g, 67.6 mmol). The suspension was stirred at room temperature for 21 h. After evaporating the dichloromethyl methyl ether, dichloromethane (20 ml) and 3-chloroaniline (0.619 ml, 0.753 g, 5.90 mmol) were added. The reaction mixture was stirred at room temperature for 90 min. The suspension was filtered and the remaining solid was washed with dichloromethane. The solid was taken up in saturated sodium carbonate solution and then washed with *tert*-butyl methyl ether. The aqueous phase was adjusted to pH 5 with 2 M hydrochloric acid and was left at room temperature overnight. The precipitated **26** was filtered off and purified by recrystallization from ethanol/water. Yield: 411 mg (26%), brownish

solid, m.p.: 258–261 °C. IR (KBr): 3301w, 3057m, 1626s, 1548m, 1478w, 1451w, 1426m, 1403m, 1365m, 1248m, 1214m, 1175w, 1065w, 867w, 776w, 745m, 707w. ^{1}H NMR (300 MHz, D_6-DMSO): 11.18 (s, 1H, HO–C(3)); 10.70 (s, 1H, HN–CO); 8.46 (s, 1H, H–C(1)); 8.00 (d, J = 1.8, 1H, H–C(2′)); 7.94 (d, J = 8.0, 1H, H–C(8)); 7.77 (d, J = 8.3, 1H, H–C(5)); 7.68 (d, J = 8.0, 1H, H–C(6′)); 7.52 (pseudo-t, J = 7.0, 1H, H–C(7)); 7.49–7.36 (m, 2H, H–C(5′)), H–C(6)); 7.35 (s, 1H, H–C(4)); 7.20 (ddd, J = 8.0, 1H, H–C(4′)). ^{13}C NMR (75 MHz, D_6-DMSO): 165.8 (HN–CO); 153.4 (C(3)); 140.0 (C(1′)); 135.7 (C(4a)); 133.1 (C(3′)); 130.5 (C(1)); 130.4 (C(5′)); 128.6 (C(8)); 128.1 (C(5)); 126.8 (C(8a)); 125.8 (C(6)); 123.7 (C(7)); 123.6 (C(4′)); 122.1 (C(2)); 119.8 (C(2′)); 118.7 (C(6′)); 110.5 (C(4)). EI-MS (70 eV): 300 (2); 299 (11); 298 (6, $[M + H]^+$); 297 (34, $[M]^+$); 172 (8); 171 (73); 170 (100); 143 (6); 142 (27); 131 (8); 127 (5); 116 (6); 115 (53); 114 (15); 113 (5); 89 (7), 65 (5). Anal. Found: $C_{14}H_{12}ClNO_2$ (C, H, N).

5.2.20. N-*(3-Chlorophenyl)-4-(1-piperidyl)salicylamide (**27**)*

To 3-(1-piperidyl)phenol (0.309 g, 1.74 mmol [21]) dissolved in 1,2-dichlorobenzene (5 ml), 3-chlorophenyl isocyanate (0.210 ml, 0.267 g, 1.74 mmol) was added in drops. The mixture was heated to 150 °C and stirred for 5 h. After removal of the solvent under reduced pressure, the residue was dried in vacuo and then triturated for 1 h with a boiling mixture of benzene and hexane (25 ml each). After cooling, the residue was collected by filtration and dried in vacuo. This crude product (555 mg) was adsorbed at silica gel (5 g) and put on top of a silica gel column (75 g); elution was carried out with hexane/*tert*-butyl methyl ether (3:1) to give *N*-(3-chlorophenyl)-4-(1-piperidyl)salicylamide (**27**, 0.113 g, 0.341 mmol, 20%) and *N*-(3-chlorophenyl)-[3-(1-piperidyl)phenyl] carbamate (0.383 g, 1.16 mmol, 67%, light brown powder, m.p.: 123 °C).

Data of **27**: light brown powder, m.p.: 166–169 °C. IR (KBr): 3322w, 3077w, 2935m, 2852w, 1641s, 1587s, 1516s, 1481w, 1425m, 1401m, 1332m, 1310m, 1268m, 1244s, 1179w, 1126m, 824w, 772m, 679w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.15 (s, 1H, HO–C(2)); 10.15 (s, 1H, HN–CO); 7.88 (dd, J = 2.0, 2.0, 1H, H–C(2′)); 7.84 (d, J = 9.2, 1H, H–C(6)); 7.61 (m, 1H, H–C(4′)); 7.37 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.15 (m, 1H, H–C(6′)); 6.55 (dd, J = 9.2, 2.4, 1H, H–C(5)); 6.31 (d, J = 2.4, 1H, H–C(3)); 3.32 (s, 4H, H_2C–H_2C–H_2C–N); 1.58 (m, 6H, H_2C–H_2C–H_2C–N)). ^{13}C NMR (75 MHz, D_6-DMSO): 167.8 (HN–CO); 161.9 (C(2)); 155.0 (C(4)); 140.0 (C(1′)); 133.0 (C(3′)); 130.2 (C(6)); 129.5 (C(5′)); 123.3 (C(4′)); 120.3 (C(2′)); 119.2 (C(6′)); 105.8 (C(5)); 104.3 (C(1)); 100.2 (C(3)); 47.7 (H_2C–H_2C–H_2C–N); 24.8 (H_2C–H_2C–H_2C–N); 24.0 (H_2C–H_2C–H_2C–N). EI-MS (70 eV): 333 (1); 332 (6); 331 (3, $[M + H^+]$); 330 (17, $[M]^+$); 206 (2); 205 (17); 204 (100); 203 (8); 202 (5); 177 (3); 176 (4); 153 (3); 148 (5); 127 (3); 73 (5); 41 (6). Anal. Found: $C_{12}H_{19}ClN_2O_2$ (C, H, N, O).

*5.2.21. 4-(4-Aminophenyl)-*N*-(3-chlorophenyl)salicylamide (**28**)*

*5.2.21.1. Method 1 (from **24**).* A mixture of DMF (6.00 ml), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**42**, 268 mg, 1.22 mmol), 4-bromo-*N*-(3-chlorophenyl)salicylamide (**24**, 400 mg, 1.22 mmol), $PdCl_2$(dppf) (27 mg, 0.037 mmol), and 2 M sodium carbonate solution (646 mg, 6.09 mmol, in 3.00 ml water) was heated to 75 °C for 7 h. After cooling to room temperature and the addition of water (25 ml), the red mixture was extracted with ethyl acetate (75 ml). The organic phase was dried over sodium sulfate and the solvent evaporated. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluent. Yield: 104 mg (25%), dark yellow solid, m.p.: 202–205 °C.

*5.2.21.2. Method 2 (from **41**).* To 2-acetoxy-4-bromo-*N*-(3-chlorophenyl)benzamide (**41**, 400 mg, 1.08 mmol) abs. DMF (5.0 ml), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**42**, 238 mg, 1.08 mmol), $PdCl_2$(dppf) (23 mg, 0.031 mmol), and a solution of sodium carbonate (575 mg, 5.42 mmol, in 2.7 ml water) were added. The red solution was heated to 75 °C for 38 h with stirring and then cooled down to room temperature. Water (40 ml) was added and stirring continued for 10 h. The grey suspension that had formed was filtered and the residue washed once with aqueous DMF (5 ml). The filtrate was diluted with water (10 ml) and the brown precipitate that formed collected by filtration and washed with a small amount of water. Then the crude product was suspended in a mixture of DMF (0.5 ml) and water (5 ml), heated briefly to 100 °C filtered hot, washed with water, and dried in vacuo. Yield: 160 mg (44%), brown solid.

*5.2.21.3. Method 3 (from **18**).* A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**42**, 81 mg, 0.36 mmol), potassium phosphate (0.12 g, 0.49 mmol), abs. DMF (2.2 ml), *N*-(3-chlorophenyl)-4-(trifluoromethanesulfonyloxy)salicylamide (**18**, 0.15 g, 0.37 mmol), and $PdCl_2$(dppf) (9 mg, 0.01 mmol) was heated under Ar to 80 °C for 23 h, whereupon it changed its color from orange to deep brown. After cooling to room temperature and the addition of water (50 ml), the mixture was extracted with ethyl acetate (300 ml). The organic extract was dried over sodium sulfate and the solvent distilled off. The brown oil was adsorbed on silica gel (2.5 g) and put on top of a flash column. Elution was carried out with hexane/ethyl acetate (3:1). Yield: 76 mg (52%), light brown solid.

Data of **28**: IR (KBr): 3379m, 3333m, 3190w, 1634s, 1595s, 1532s, 1493s, 1412m, 1356w, 1320m, 1265m, 1188m, 1100w, 820w, 778m, 682w. ^{1}H NMR (500 MHz, $CDCl_3$): 11.9 (s, 1H, HO–C(2)); 7.89 (s, 1H, HN–CO); 7.74 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.50 (d, J = 8.4, 1H, H–C(6)); 7.47 (d, J = 8.7, 2H, H–C(2″, 6″); 7.45 (ddd, J = 8.2, 1.9, 0.8, 1H, H–C(6′)); 7.33 (pseudo-t, J = 8.1, 1H, H–C(5′));

7.22 (d, J = 1.7, 1H, H–C(3)); 7.18 (ddd, J = 8.0, 1.9, 0.9, 1H, H–C(4′)); 7.12 (dd, J = 8.4, 1.9, 1H, H–C(5)); 6.76 (d, J = 8.6, 2H, H–C(3″, 5″)); 3.84 (s, 2H, H_2N–C(4″)). ^{13}C NMR (125 MHz, $CDCl_3$): 168.3 (HN–CO); 162.3 (C(2)); 147.8 (C(4)); 147.1 (C(4″)); 138.0 (C(1′)); 134.9 (C(3′)); 130.1 (C(5′)); 129.2 (C(1″)); 128.2 (C(2″, 6″)); 125.6 (C(6)); 125.2 (C(4′)); 121.0 (C(2′)); 118.8 (C(6′)); 117.1 (C(5)); 115.8 (C(3)); 115.3 (C(3″, 5″)); 111.9 (C(1)). EI-MS (70 eV): 341 (3); 340 (14); 339 (9, $[M + H]^+$); 338 (39, $[M]^+$); 262 (5); 213 (17); 212 (100); 211 (47); 210 (3); 184 (5); 183 (8); 182 (3); 156 (8); 155 (4); 154 (8); 130 (4); 128 (4); 127 (6); 92 (4). HR-EI-MS: 338.0822 ($[M]^+$, $C_{19}H_{15}ClN_2O_2^+$; Calc. 338.0822). Anal. Calc. for $C_{19}H_{15}ClN_2O_2$ (338.79): C, 67.36; H, 4.46; N, 8.27; O, 9.45. Found: C, 67.14; H, 4.75; N, 7.78; O, 9.94.

5.2.22. N-*(3-Chloro-2-methylphenyl)salicylamide (**29**)*

A solution of phenyl salicylate (2.14 g, 10.0 mmol), 1,2,4-trichlorobenzene (2.0 ml) and 3-chloro-2-methylaniline (1.50 ml, 1.78 g, 12.6 mmol) was heated to 200 °C for 5 h. The solution, which had turned black, was cooled to room temperature, and activated charcoal (0.15 g) and 1,2,4-trichlorobenzene (0.5 ml) were added. The mixture was heated to 180 °C for 10 min. The mixture was filtered hot (Celite) and allowed to stand at 4 °C for 72 h, after which a brown solid had precipitated. The crude **29** was filtered off and purified by column chromatography using pentane/dichloromethane (1:1) followed by recrystallization from ethanol. Yield: 2.02 g (77%), beige powder, m.p.: 195–196 °C. IR (KBr): 3316w, 3076m, 2863w, 1633s, 1614s, 1575s, 1551m, 1508w, 1456m, 1437m, 1382m, 1322m, 1230s, 1204w, 1157w, 1125w, 773m, 743m, 706w, 644w. ^1H NMR (300 MHz, D_6-DMSO): 12.00 (s, 1H, HO–C(2)); 10.44 (s, 1H, HN–CO); 8.01 (dd, J = 7.8, 1.6, 1H, H–C(6)); 7.72 (d, J = 7.8, 1H, H–C(6′)); 7.48–7.42 (m, 1H, H–C(5)); 7.34 (dd, J = 8.0, 1.4, 1H, H–C(3)); 7.27 (pseudo-t, J = 8.0, 1H, H–C(5′)); 7.01 (d, J = 8.3, 1H, H–C(4′)); 7.01–6.95 (m, 1H, H–(C(4)); 2.31 (s, 3H, H_3C–C(2′)). ^{13}C NMR (75 MHz, D_6-DMSO): 166.0 (HN–CO); 158.2 (C(2)); 137.7 (C(1′)); 133.8 (C(5))*; 133.7 (C(3′))*; 129.6 (C(2′)); 129.5 (C(6)); 127.1 (C(5′)); 126.0 (C(3)); 123.7 (C(6′); 119.3 (C(4)); 117.2 (C(4′)); 117.0 (C(1)); 14.9 (H_3C–C(2′)). EI-MS (70 eV): 264 (1); 263 (8); 262 (4, $[M + H]^+$); 261 (25, $[M]^+$); 144 (3); 143 (31); 142 (9); 141 (100); 140 (4); 122 (6); 121 (78); 106 (12); 93 (17); 77 (7); 65 (23); 39 (13). Anal. Found: $C_{14}H_{12}ClNO_2$ (C, H, N).

5.2.23. 4-Amino-N-*(3-hydroxyphenyl)salicylamide (**31**)*

Compound **33** (0.67 g, 1.8 mmol), conc. hydrochloric acid (5.0 ml), and conc. acetic acid (5.0 ml) were heated to reflux for 16 h to completely cleave the acetamide and benzyl ether groups. The now turbid solution was filtered and the mother liquor adjusted to pH 8 with 6 M sodium hydroxide solution and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and the solvent was distilled off to give **31**, which was purified by recrystallization from methanol/water. Yield: 69 mg (16%), brown powder, m.p.: 202 °C (decomposition). IR (KBr): 3382m, 3329m, 3230–2598w, 1639s, 1622s, 1610s, 1546s, 1514s, 1492m, 1467m, 1452m, 1377m, 1324w, 1266s, 1179m, 1161m, 972w, 844w, 763m, 685w. ^1H NMR (500 MHz, D_6-DMSO): 12.35 (s, 1H, HO–C(2)); 9.78 (s, 1H, HN–CO)*; 9.38 (s, 1H, HO–(C(3′))*; 7.72 (d, J = 8.8, 1H, H–C(6)); 7.22 (pseudo-t, J = 2.2, 1H, H–C(2′)); 7.09 (pseudo-t, J = 8.0, 1H, H–C(5′)); 7.02 (dd, J = 8.1, 0.8, 1H, H–C(6′)); 6.49 (ddd, J = 8.0, 2.3, 0.9, 1H, H–C(4′)); 6.12 (dd, J = 8.7, 2.2, 1H, H–C(5)); 6.01 (d, J = 2.1, 1H, H–C(3)); 5.88 (s, 2H, H_2N–C(4)). ^{13}C NMR (125 MHz, D_6-DMSO): 168.0 (C(2)); 162.2 (HN–CO); 157.5 (C(3′)); 154.4 (C(4)); 139.5 (C(1′)); 129.6 (C(6)); 129.2 (C(5′)); 111.6 (C(6′)); 110.7 (C(4′)); 108.0 (C(2′)); 105.7 (C(5)); 103.4 (C(1)); 99.4 (C(3)). EI-MS (70 eV): 245 (3, $[M + 1]^+$); 244 (21, $[M]^+$); 199 (3); 137 (9); 136 (100); 109 (18); 80 (10); 68 (3); 53 (4). HR-EI-MS: 244.0853 ($[M]^+$, $C_{13}H_{12}N_2O_3^+$; Calc. 244.0848).

5.2.24. N-*(3-Hydroxyphenyl)-2-methoxybenzamide (**32**)*

2-Methoxybenzoic acid (3.07 g, 20.2 mmol) was dissolved in thionyl chloride (10.0 ml, 137 mmol). DMF (three drops) was added and the solution heated to boiling for 1 h. After removal of the excess thionyl chloride, 2-methoxybenzoyl chloride (3.33 g, 19.5 mmol) was obtained. To a solution of this acid chloride (1.30 g, 7.62 mmol) in pyridine (1 ml) 3-hydroxyaniline (0.832 g, 7.62 mmol) in pyridine (10 ml) was added. The solution was heated to 130 °C for 4 h. After removal of the solvent the crude product was purified by column chromatography using pentane/ethyl acetate (1:1) followed by crystallization from ethanol/water. Yield: 1.57 g (31%), colorless solid, m.p.: 159–161 °C. IR (KBr): 3300m, 3108m, 2874w, 2839w, 1610s, 1560s, 1488m, 1446s, 1389m, 1306m, 1275m, 1240s, 1182w, 1159w, 1020w, 878w, 778w, 752m, 691w. ^1H NMR (300 MHz, D_6-DMSO): 9.99 (s, 1H, HN–CO); 9.39 (s, 1H, HO–C(3′)); 7.62 (dd, J = 7.6, 1.7, 1H, H–C(6)); 7.49 (pseudo-t, J = 8.0, H–C(5)); 7.36 (s, 1H, H–C(2′)); 7.16 (d, J = 8.3, 1H, H–C(3)); 7.13–7.03 (m, 3H, H–(C(4, 5′, 6′)); 6.49 (dd, J = 9.0, 2.3, 1H, H–C(4′)); 3.89 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 164.4 (HN–CO); 157.6, 156.4 (C(2), C(3′)); 140.1 (C(1′)); 131.9 (C(4)); 129.6 (C(6)); 129.3 (C(5)); 125.1 (C(1)); 120.5 (C(3)); 112.0 (C(6′)); 110.6 (C(4′)); 106.8 (C(2′)); 55.9 (H_3C–O). EI-MS (70 eV): 244 (4, $[M + 1]^+$); 243 (27, $[M]^+$); 136 (9); 135 (100); 92 (8); 77 (15); 64 (2). HR-EI-MS: 243.0891 ($[M]^+$, $C_{14}H_{13}NO_3^+$; Calc. 243.0895).

5.2.25. 4-Acetamido-N-*[(3-benzyloxy)phenyl]salicylamide (**33**)*

To 4-acetamidosalicylic acid [27] (5.37 g, 27.5 mmol) thionyl chloride (10.0 ml, 16.3 g, 138 mmol) was added at 0 °C. After a slow warm up to room temperature and 2 h of stirring an additional amount of thionyl chloride (10 ml, 16.3 g, 138 mmol) was added and the reaction mixture was heated to 50 °C for 3.5 h. After removal of the excess thionyl chloride, 4-acetamidosalicyloyl chloride was obtained as a

yellow solid. To the latter toluene (30 ml) and a suspension of 3-(benzyloxy)aniline (5.48 g, 27.5 mmol) in toluene were added and the reaction mixture was stirred for 30 min at room temperature. Pyridine (4.40 ml) was added to the suspension, which resulted in an orange solution. After acidification with 7.5% hydrochloric acid, a brown solid was formed which was collected by filtration and purified by MPLC using hexane/ethyl acetate (gradient towards increasing polarity). Yield: 5.88 g (57%), colorless platelets, m.p.: 226–227 °C.

5.2.25.1. Alternate method. 4-Acetamido-2-acetoxybenzoic acid [27] (2.08 g, 8.77 mmol) and thionyl chloride (2.00 ml, 3.27 g, 27.5 mmol) were stirred at room temperature for 5 h. The excess thionyl chloride was removed under vacuum and pyridine (5 ml) and a solution of 3-(benzyloxy)aniline (1.75 g, 8.77 mmol) in pyridine (5 ml) were added. The reaction mixture was stirred at room temperature for 62 h. Hydrochloric acid (2 M, 60 ml) was added in portions to bring the pH to 1. The red solid that precipitated was collected by filtration, washed with *tert*-butyl methyl ether and purified by column chromatography using hexane/*tert*-butyl methyl ether (1:3, gradient towards increasing polarity). An additional crop of product was obtained from the work-up of the mother liquor by extraction with cold 2 M sodium hydroxide (100 ml), adjusting to pH 8 with 2 M hydrochloric acid and saturated sodium bicarbonate, extraction with *tert*-butyl methyl ether, drying of the organic phase over sodium sulfate and evaporation of the solvent. Total yield: 1.77 g (54%).

Data of **33**: IR (KBr): 3304w, 3117w, 3051w, 2872w, 2769w, 2706w, 2613w, 1642s, 1610s, 1542s, 1478w, 1448s, 1414s, 1370m, 1293s, 1264s, 1245s, 1190m, 1163m, 1047w, 1028w, 882w, 831w, 757m, 732w, 687w. ^{1}H NMR (500 MHz, D_6-DMSO): 12.00 (s, 1H, HO–C(2)); 10.21 (s, 1H, HN–CO); 10.16 (s, 1H, HN–CO); 7.89 (d, J = 8.7, 1H, H–C(6)); 7.46–7.44 (m, 3H, H–C(2′), H_5C_6–H_2C–O); 7.42 (d, J = 2.0, 1H, H–C(3)); 7.40–7.37 (m, 2H, H_5C_6–H_2C–O); 7.34–7.31 (m, 1H, H_5C_6–H_2C–O); 7.25 (pseudo-t, J = 8.0, 1H, H–C(5′)); 7.23–7.21 (m, 1H, H–C(6′)); 7.05 (dd, J = 8.8, 2.0, 1H, H–C(5)); 6.78 (ddd, J = 7.6, 2.5, 1.5, 1H, H–C(4′)); 5.09 (s, 2H, H_5C_6–H_2C–O); 2.06 (s, 3H, H_3C–C). ^{13}C NMR (125 MHz, D_6-DMSO): 169.4 (HN–CO); 166.6 (HN–CO); 159.9 (C(2))*; 159.0 (C(3′))*; 144.5 (C(4)); 139.8 (C(1′)); 137.5 (H_5C_6–H_2C–O); 130.2 (C(6)); 130.0 (C(6′)); 128.9 (H_5C_6–H_2C–O); 128.3 (O–CH_2–C_6H_6); 128.1 (O–CH_2–C_6H_6); 113.8 (C(5′)); 112.1 (C(1)); 110.7 (C(4′)); 110.2 (C(5)); 108.0 (C(2′)); 106.7 (C(3)); 69.6 (H_5C_6–H_2C–O); 24.6 (H_3C–C). EI-MS (70 eV): 377 (5, $[M + H]^+$); 376 (19, $[M]^+$); 268 (4); 200 (11); 199 (66); 178 (25); 136 (18); 109 (5); 92 (10); 91 (100); 80 (5); 65 (7); 43 (5). Anal. Found: $C_{22}H_{20}N_2O_4$ (C, H, N, O).

5.2.26. N-*[3-(Benzyloxy)phenyl]-4-hydroxysalicylamide (**34**)*

2,4-Diacetoxybenzoic acid [29] (0.776 g, 3.26 mmol) and thionyl chloride (1.16 ml, 1.90 g, 16.0 mmol) were heated to reflux for 3 h. The excess thionyl chloride was removed under vacuum. Then benzene (3.2 ml) and a solution of 3-benzyloxyaniline (1.28 g, 6.42 mmol) in benzene (3.2 ml) were added and the reaction mixture was refluxed for 8 h. The solvent was evaporated and 2 M hydrochloric acid was added whereupon a beige precipitate formed, which was collected by filtration, washed with 2 M hydrochloric acid and dried under high vacuum to give 2,4-diacetoxy-*N*-[3-(benzyloxy)phenyl]benzamide. To this 10% sodium hydroxide (8.0 ml) was added, and the reaction mixture was heated to 60 °C for 1 h, cooled down to 0 °C and poured onto ice-cold 2 M hydrochloric acid. The precipitated bright brown **34** was filtered off, washed with water and purified by recrystallization from ethanol/water. Yield: 0.945 g (50%), bright brown powder, m.p.: 147–150 °C. IR (KBr): 3347m, 3065w, 3033w, 1646s, 1598s, 1544s, 1515s, 1491s, 1444s, 1380m, 1255s, 1183s, 1162s, 1028w, 979w, 846w, 773m, 738m, 687m. ^{1}H NMR (300 MHz, D_6-DMSO): 12.18 (s, 1H, HN–CO); 10.11 (s, 1H, HO–C(2)); 7.87 (d, J = 8.6, 1H, H–C(6)); 7.50–7.35 (m, 6H, O–CH_2–C_6H_5, H–C(2′)); 7.33–7.24 (m, 2H, H–C(6′), H–C(5′)); 6.78 (m, 1H, H–C(4′)); 6.38 (dd, J = 8.6, 2.3, 1H, H–C(5)); 6.33 (d, J = 2.3, 1H, H–C(3)); 5.10 (s, 2H, O–CH_2–C_6H_5). ^{13}C NMR (75 MHz, D_6-DMSO): 167.2, 162.6, 161.4, 158.5 (HN–CO, C(2), C(4), C(3′)); 139.5 (C(1′)); 137.0 (H_5C_6–H_2C–O); 130.4, 129.4 (C(6′), C(6)); 128.4 (H_5C_6–H_2C–O); 127.8 (H_5C_6–H_2C–O); 127.6 (H_5C_6–H_2C–O); 113.5 (C(5′)); 110.2 (C(4′)); 107.9, 107.7, 107.5 (C(2′), C(5)); 102.8 (C(3)); 69.2 (H_5C_6–H_2C–O). FAB-MS (NBA): 338 (1, $[M + 2H]^+$); 337 (16, $[M + H]^+$); 336 (70, $[M]^+$); 335 (28); 242 (4); 200 (14); 199 (31); 130 (5); 125 (8); 92 (6); 91 (100); 69 (12); 55 (8). FAB-MS (NBA + KCl): 376 (1, $[M + K + H]^+$); 375 (2, $[M + K]^+$); 374 (11); 338 (1, $[M + 2H]^+$); 337 (10, $[M + H]^+$); 336 (47, $[M]^+$); 335 (19); 200 (12); 199 (25); 92 (8); 91 (100); 55 (11). Anal. Found: $C_{20}H_{17}NO_4$ (C, H, N, O).

5.2.27. N-*(3-Hydroxyphenyl)-2-methoxy-4-(4-nitrophenyl)-benzamide (**35**)*

A solution of the acid **40** (76 mg, 0.28 mmol) in thionyl chloride (1.0 ml, 1.6 g, 14 mmol) and one drop of DMF was heated to reflux for 70 min. After cooling to room temperature, the excess thionyl chloride was removed under vacuum to give 81 mg of the corresponding acid chloride as a yellow solid, m.p.: 225–238 °C, which was used without further purification. To this acid chloride (0.20 g, 0.68 mmol) 3-aminophenol (0.074 g, 0.68 mmol) and pyridine (12 ml) were added. The mixture was heated to boiling for 3.5 h, then cooled to 0 °C and acidified with hydrochloric acid (2 N, 30 ml). The precipitate obtained was filtered off, dried in vacuo and purified by suspending it twice in chloroform (5 ml) followed by decantation. Yield: 160 mg (60%), yellow powder, m.p.: 304.0–307.5 °C. IR (KBr): 3323m, 1649s, 1606s, 1567s, 1515s, 1478m, 1452s, 1399m, 1343s, 1306m, 1282s, 1217s, 1182m, 1160m, 1017w, 849m, 770w, 750w, 685m. ^{1}H NMR (300 MHz, D_6-DMSO): 10.06 (s, 1H, HN–CO); 9.40 (s, 1H, HO–C(3′)); 8.34 (d, J = 8.8, 2H,

H–C(3″, 5″)); 8.07 (d, *J* = 8.6, 2H, H–C(2″, 6″)); 7.75 (d, *J* = 7.7, 1H, H–C(6)); 7.52 (s, 1H, H–C(3)); 7.47 (d, *J* = 8.0, 1H, H–C(5)); 7.36 (s, 1H, H–C(2′)); 7.11–7.07 (m, 2H, H–C(5′), H–C(6′)); 6.50 (m, 1H, H–C(4′)); 4.02 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 163.9 (HN–CO); 157.6 (C(2)); 156.9 (C(3′)); 147.1 (C(1″)); 145.8 (C(4″)); 141.3 (C(4)); 140.0 (C(1′)); 130.4 (C(5′)); 129.3 (C(6)); 128.3 (C(2″, 6″)); 125.5 (C(1)); 124.0 (C(3″, 5″)); 119.4 (C(5)); 110.9 (C(6′)); 110.5 (C(4′)); 106.8 (C(2′))*; 106.7 (C(3))*; 56.2 (H_3C–O). EI-MS (70 eV): 365 (9, $[M + H]^+$); 364 (32, $[M]^+$); 257 (26); 256 (100); 242 (3); 241 (3); 226 (4); 211 (5); 210 (30); 153 (2); 152 (9); 151 (4); 140 (3); 139 (14); 109 (7). Anal. Found: $C_{20}H_{16}N_2O_5$ (C, H, N, O).

5.2.28. N-*(3-Hydroxyphenyl)-4-(4-nitrophenyl)salicylamide (**36**)*

5.2.28.1. Method 1: with boron tribromide-dimethyl sulfide complex. To 1,2-dichloroethane (10 ml) were added boron tribromide-dimethyl sulfide complex (0.66 g, 2.1 mmol) and amide **35** (90 mg, 0.25 mmol). After heating the light brown suspension to boiling for 24 h, the suspension, which had turned dark brown, was cooled to room temperature, and water (10 ml) was added. The mixture was stirred for 3 d at room temperature and then partitioned between *tert*-butyl methyl ether (120 ml) and sodium hydroxide (2 N, 120 ml). The aqueous phase was washed with *tert*-butyl methyl ether (50 ml), acidified with conc. hydrochloric acid to pH 1, and re-extracted with *tert*-butyl methyl ether (150 ml). The organic extract was dried over sodium sulfate and the solvent distilled off. Yield: 64 mg (74%), beige solid, m.p.: 277–282 °C.

5.2.28.2. Method 2: with boron tribromide. To a suspension of amide **35** (193 mg, 0.530 mmol) in abs. dichloromethane (5 ml) was added a 1 M solution of boron tribromide in dichloromethane (5.00 ml, 12.4 g, 4.77 mmol). The suspension was stirred for 24 h at room temperature. Water (5 ml) was added and the stirring continued for another 15 min. Dichloromethane (50 ml) was added and the mixture was extracted with 1 N sodium hydroxide solution (100 ml). The aqueous phase was acidified with conc. hydrochloric acid to pH 1 and, after standing overnight at 4 °C, the bright brown raw product had precipitated and was collected by filtration and dried in vacuo. Yield: 140 mg (76%), beige amorphous solid.

Data of **36**: IR (KBr): 3455–2500w, 1604s, 1562m, 1512s, 1492m, 1433m, 1397m, 1343s, 1272m, 1202m, 1160m, 1109w, 955w, 916w, 853m, 774w, 750m, 685w. ^1H NMR (500 MHz, D_6-DMSO): 12.15 (s, 1H, HO–C(2)); 10.39 (s, 1H, HN–CO); 9.50 (s, 1H, HO–C(3′)); 8.33 (d, *J* = 8.9, 2H, H–C(3″, 5″)); 8.13 (d, *J* = 8.2, 1H, H–C(6)); 7.99 (d, *J* = 9.0, 2H, H–C(2″, 6″)); 7.41 (d, *J* = 1.7, 1H, H–C(3)); 7.37 (dd, *J* = 8.2, 1.8, 1H, H–C(5)); 7.31 (pseudo-t, *J* = 2.1, 1H, H–C(2′)); 7.16 (pseudo-t, *J* = 7.9, 1H, H–C(5′)); 7.13–7.10 (m, 1H, H–C(6′)); 6.57 (ddd, *J* = 7.8, 2.3, 1.2, 1H, H–C(4′)). ^{13}C NMR (125 MHz, D_6-DMSO): 165.8 (HN–CO); 158.7, 157.6 (C(3′, 2)); 147.1 (C(4″)); 145.3 (C(1″)); 142.5 (C(4)); 139.1 (C(1′)); 130.1 (C(5′)); 129.4 (C(6)); 128.1 (C(2″, 6″)); 124.1 (C(3″, 5″)); 118.0 (C(1)); 117.9 (C(5)); 115.6 (C(3)); 111.5 (C(6′)); 111.4 (C(4′)); 108.0 (C(2′)). EI-MS (70 eV): 352 (1, $[M + 2H]^+$); 351 (4, $[M + H]^+$); 350 (17, $[M]^+$); 349 (2); 348 (4); 320 (3); 243 (6); 242 (38); 215 (4); 212 (8); 197 (4); 196 (23); 140 (4); 139 (14); 110 (8); 109 (100). HR-EI-MS: 350.0918 ($[M]^+$, $C_{19}H_{14}N_2O_5^+$; Calc. 350.0903).

5.2.29. 4-(4-Aminophenyl)-N-*(3-hydroxyphenyl)salicylamide (**37**)*

Amide **36** (35 mg, 0.10 mmol) was suspended in ethanol (10 ml) and platinum dioxide (aq., 10 mg) was added. After shaking overnight under hydrogen, the dark yellow suspension was concentrated to half its volume. *tert*-Butyl methyl ether and 1 N sodium hydroxide solution were added, and the mixture was filtered through Celite. The aqueous phase of the filtrate was acidified with conc. HCl to pH 6 and left overnight at 4 °C. Extraction with *tert*-butyl methyl ether gave after evaporation a brown solid which was purified by heating it in a mixture of water (5 ml) and DMSO (1 ml) to 100 °C. After filtration of the hot turbid solution, **37** precipitated upon cooling and was collected by filtration. Yield: 31 mg (97% containing a slight impurity), yellow solid, m.p.: 236–239 °C. IR (KBr): 3373m, 3326m, 3036w, 1605s, 1546s, 1494s, 1449m, 1406m, 1347m, 1314m, 1265m, 1192m, 1159w, 856w, 818w, 770w, 687w. ^1H NMR (500 MHz, D_6-DMSO): 12.05 (s, 1H, HO–C(2)); 10.23 (s, 1H, HN–CO); 9.46 (s, 1H, HO–C(3′)); 7.99 (d, *J* = 8.3, 1H, H–C(6)); 7.43 (d, *J* = 8.6, 2H, H–C(2″, 6″)); 7.28 (pseudo-t, *J* = 2.1, 1H, H–C(2′)); 7.17 (dd, *J* = 8.4, 1.8, 1H, H–C(5)); 7.14 (pseudo-t, *J* = 8.0, 1H, H–C(5′)); 7.10 (d, *J* = 1.8, 1H, H–C(3)); 7.08 (ddd, *J* = 8.1, 1.8, 1.0, 1H, H–C(6′)); 6.64 (d, *J* = 8.6, 2H, H–C(3″, 5″)); 6.54 (ddd, *J* = 8.0, 2.3, 1.0, 1H, H–C(4′)); 5.41 (s, 2H, H_2N–C(4″)). ^{13}C NMR (125 MHz, D_6-DMSO): 166.7 (HN–CO); 159.5 (C(2)); 157.6 (C(3′)); 149.4 (C(4″)); 146.0 (C(4)); 139.2 (C(1′)); 129.4 (C(5′))*; 129.3 (C(6))*; 127.5 (C(2″, 6″)); 125.4 (C(1″)); 116.0 (C(1)); 114.0 (C(5)); 113.9 (C(3″, 5″)); 112.9 (C(3)); 111.6 (C(6′)); 111.2 (C(4′)); 108.0 (C(2′)). EI-MS (70 eV): 321 (11, $[M + 1]^+$); 320 (44, $[M]^+$); 292 (9); 290 (10); 213 (19); 212 (100); 211 (21); 183 (8); 156 (9); 154 (10); 109 (45); 80 (12). HR-EI-MS: 320.1159 ($[M]^+$, $C_{19}H_{16}N_2O_3^+$; Calc. 320.1161).

5.2.30. Methyl 2-methoxy-4-(4-nitrophenyl)benzoate (*39*)

To methyl 4-bromo-2-methoxybenzoate (**38**) [28] (720 mg, 3.10 mmol), 1,3-dioxolane (1.0 ml), and a catalytical amount of tetrakis-(triphenylphosphine)palladium(0) was added a solution of trimethyl(4-nitrophenyl)stannane [30] (999 mg, 3.50 mmol) in 1,3-dioxolane (1.5 ml). The yellow solution was heated to reflux for 24 h whereupon the color of the solution changed to dark brown. After the addition of water (2.5 ml) the solution was extracted with *tert*-butyl methyl ether. The organic phase was washed with

water, dried over sodium sulfate and evaporated to a solid, which was purified by column chromatography using pentane/*tert*-butyl methyl ether (4:1). Yield: 438 mg (49%), yellow powder, m.p.: 150–152 °C. IR (KBr): 3103w, 2954w, 2922w, 2851w, 1712s, 1596s, 1564m, 1513s, 1480m, 1431s, 1394m, 1348s, 1297s, 1258s, 1226s, 1188m, 1142m, 1103m, 1025m, 848m, 778w, 752m, 696w. ^{1}H NMR (300 MHz, $CDCl_3$): 8.32 (dd, J = 2.0, 6.0, 2H, H–C(3′, 5′)); 7.92 (d, J = 8.0, 2H, H–C(6)); 7.75 (dd, J = 2.0, 6.8, 1H, H–C(2′, 6′)); 7.22 (dd, J = 1.6, 8.0, 1H, H–C(5)); 7.17 (d, J = 1.6, 1H, H–C(3)); 4.00 (s, 3H, H_3C–O); 3.93 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, $CDCl_3$): 166.1 (C=O); 159.6 (C(2)); 147.6 (C(1′)); 144.0 (C(4′)); 132.5 (C(4)); 128.1 (C(6)); 124.1 (C(2′, 6′)); 120.3 (C(3′, 5′)); 119.2 (C(5)); 111.0 (C(3)); 56.2 (H_3C–O); 52.2 (H_3C–O). EI-MS (70 eV): 290 (1); 289 (2); 288 (15, $[M + H]^+$); 287 (68, $[M]^+$); 271 (2); 270 (7); 259 (2); 258 (15); 257 (24); 256 (100); 255 (18); 254 (66); 228 (4); 227 (7); 226 (21); 211 (9); 210 (45); 153 (7); 152 (23); 151 (12); 140 (7); 139 (33); 63 (7). Anal. Found: $C_{15}H_{13}NO_5$ (C, H, N, O).

*5.2.31. 2-Methoxy-4-(4-nitrophenyl)benzoic acid (**40**)*

Benzoate **39** (515 mg, 1.79 mmol), methanol (120 ml), and 6% potassium hydroxide solution (120 ml) were heated to reflux for 3 h. The greenish solution was cooled to room temperature and a precipitate formed. The mixture was acidified with 6 M hydrochloric acid to pH 1 and the solid collected by filtration and dried in vacuo. Yield: 485 mg (99%), yellow solid, m.p.: 235–238 °C. IR (KBr): 3446m, 3080w, 2925m, 2856w, 1691s, 1597m, 1562m, 1514s, 1461w, 1422w, 1394m, 1344s, 1313m, 1260s, 1225m, 1099m, 1018m, 851w. ^{1}H NMR (300 MHz, D_6-DMSO): 12.71 (s, 1H, COOH); 8.33 (d, J = 8.8, 2H, H–C(3′, 5′)); 8.06 (d, J = 8.8, 2H, H–C(2′, 6′)); 7.77 (d, J = 8.0, 1H, H–C(6)); 7.46 (s, 1H, H–C(3)); 7.40 (dd, J = 1.5, 1H, H–C(5)); 3.95 (s, 3H, H_3C–O). ^{13}C NMR (75 MHz, D_6-DMSO): 166.9 (COOH); 158.5 (C(2)); 147.1 (C(1′))*; 145.6 (C(4′))*; 142.3 (C(4))*; 131.4 (C(6)); 128.3 (C(2′, 6′)); 124.0 (C(3′, 5′)); 121.5 (C(1)); 119.0 (C(5)); 111.4 (C(3)); 56.0 (H_3C–O). EI-MS (70 eV): 275 (2); 274 (18); 273 (100, $[M]^+$); 257 (9); 256 (20); 255 (6); 254 (9); 245 (6); 244 (38); 243 (7); 227 (12); 226 (32); 210 (11); 182 (7); 168 (11); 154 (18); 153 (13); 152 (22); 151 (14); 140 (9); 139 (34); 63 (7). Anal. Found: $C_{14}H_{11}NO_5$ (C, H, N, O).

*5.2.32. 2-Acetoxy-4-bromo-*N*-(3-chlorophenyl)benzamide (**41**)*

To salicylanilide **24** (1.97 g, 6.03 mmol), acetic anhydride (5.00 ml, 5.40 g, 52.9 mmol) and one drop of conc. sulfuric acid were added at room temperature. The red solution was kept at 100 °C for 3 h and then poured on ice (50 g). The turbid solution obtained was decanted from an amorphous solid, which was washed by suspending it three times in water (20 ml) followed by decantation. The crude product was further purified by recrystallization from ethanol/water. Yield: 910 mg (39%), light pink needles, m.p.: 112–114 °C. IR (KBr): 3340m, 3079w, 3033w, 2935w, 1770s, 1659s, 1592s, 1521s, 1480s, 1403m, 1373m, 1307m, 1231m, 1190s, 1094m, 933m, 885w, 856w, 780m, 678m. ^{1}H NMR (300 MHz, D_6-DMSO): 10.57 (s, 1H, HN–CO); 7.86 (pseudo-t, J = 1.9, 1H, H–C(2′)); 7.65–7.61 (m, 3H, H–(C(6), H–C(5), H–C(3)); 7.57 (d, J = 8.2, 1H, H–C(6′)); 7.38 (pseudo-t, J = 8.1, 1H, H–C(5′)); 7.17 (ddd, J = 8.0, 2.1, 1.0, 1H, H–C(4′)); 2.21 (s, 3H, H_3C–C). ^{13}C NMR (75 MHz, $CDCl_3$): 168.6 (HN–CO); 162.8 (H_3C–*C*O); 148.1 (C(2)); 138.6 (C(1′)); 134.9 (C(3′)); 131.0 (C(5)), 130.2 (C(5′)); 129.9 (C(6)); 127.2 (C(4)); 126.7 (C(3)); 125.8 (C(1)); 124.9 (C(4′)); 120.0 (C(2′)); 117.8 (C(6′)); 21.0 (H_3C–CO). FAB-MS (NBA): 372 (15); 371 (14); 370 (58); 369 (25); 368 (44); 367 (14, $[M]^+$); 330 (24); 329 (22); 328 (100); 327 (43); 326 (79); 325 (24); 243 (15); 241 (14); 201 (46); 199 (48); 127 (30); 77 (13); 43 (54). Anal. Found: $C_{15}H_{11}BrClNO_3$ (C, H, N, O).

5.3. Kinase assays

Purification of protein kinases and in vitro enzyme tests were performed as previously described [14–16] using poly(E_4Y) (2 μg ml^{-1}) and [^{33}P]ATP (0.4 μM) as substrates. All compounds were dissolved in DMSO and diluted in buffer giving a final DMSO concentration of 1% in the assay. IC_{50} values represent averages of at least three determinations. Genistein (IC_{50} = 1 μM) and the dianilinophthalimide CGP52411 (IC_{50} = 1 μM) served as an internal standard inhibitor in all EGFR kinase assays [31,32].

Acknowledgements

This work was supported by the Swiss National Science Foundation (Grant No. 2000-063344).

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