104. Catechol-*O*-methyltransferase-Inhibiting Pyrocatechol Derivatives: Synthesis and Structure-Activity Studies

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(27.IV.89)

3-Nitro- and 3-cyanopyrocatechols bearing electron-withdrawing substituents at C(5) have been found to inhibit the enzyme catechol-*O*-methyltransferase. Structure-activity studies are discussed on the basis of the pharmocological data of 50 compounds (*cf. Chapt. 4, Tables 1–7*). Some 3-nitro-5-aroylpyrocatechols *(Type A^2, Table 1)* fulfil the requirements for a clinical candidate, being orally active, specific, reversible, and relatively short-acting. The chemical work involved is illustrated by describing a choice of exemplary syntheses, dealing with compounds **9**, **11**, **14**, **18**, **22**, **24**, **25**, **35**, **41**, and **42** *(Chapt. 5, Schemes 1–10)*.

1. Introduction. – *Problems and Aims.* In the current therapy of *Parkinson*'s disease, the still unsolved major problem is the maintenance of good responsiveness to 3,4-dihydroxy-L-phenylalanine ('L-dopa') during long-term therapy. The available literature clearly shows that, following a combination of L-dopa with an inhibitor of the peripheral aromatic L-amino acid decarboxylase (AADC) [1] [2], large amounts of L-dopa are converted to 3-*O*-methyldopa by the enzyme catechol-*O*-methyltransferase (COMT, *EC 2.1.1.6*). This enzyme, in presence of Mg ions, catalyzes the transfer of Me groups from *S*-adenosyl-L-methionine to substrates, containing the catechol grouping [3]. It is well established that 3-*O*-methyldopa (3-OMD) is actively transported into the brain by the same carrier mechanism utilized by L-dopa and L-tyrosine [4]. It has been demonstrated that 3-OMD competes with the uptake of L-dopa (and L-tyrosine) at the level of the blood-brain barrier [5] [6], where the L-dopa transporter is located. Several clinical observations have shown that high plasma levels of 3-OMD are associated with poor response to L-dopa [7] [8]. Inhibitors of COMT could, therefore, be of benefit in the treatment of *Parkinson*'s disease by improving the bio-availability of L-dopa and its transport into the brain.

The aim of our investigations was to find new COMT inhibitor leads and to select finally, by structure-activity-relationship (SAR) studies, clinically useful compounds, *i.e.* COMT inhibitors which are orally active, specific, reversible, and relatively short-acting (duration of action 8–12 h). The new COMT inhibitors should be active in the periphery as well as in the central nervous system.

2. *Pharmacological Evaluation of COMT Inhibitors.* As a prerequisite of our studies, a simple and rapid single-step radio-enzymatic assay for the determination of COMT activity *in vitro* was developed, using rat liver homogenate as the enzyme source and pyrocatechol as substrate [9]. Only compounds with marked activity *in vitro* were tested also *in vivo* and administered by the oral route. By this test, COMT inhibition was assessed indirectly by measuring the concentration of endogenous 3-OMD in rat plasma,

either occurring after the peripheral AADC inhibitor benserazide given alone or in combination with a given COMT inhibitor. The concentration of 3-OMD in plasma was measured 4 h after drug administration by high-pressure liquid chromatography with electrochemical detection.

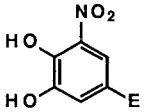
The concentration of 3-OMD measured after benserazide alone was taken as 100%. IC_{50} values were measured in rat liver and are means derived from one to three experiments each performed with six to seven concentrations (limit of error ±10%). ED_{50} values (rat liver) represent means of two to three experiments. Drugs were administered *p.o.* at 5 doses (three rats each) 1 h before decapitation.

3. *Starting Position.* In the literature, a large number of compounds which inhibit COMT *in vitro* is described, among them many hydroxy-aromatics [3]. Moreover, 3-hydroxy-4-methoxybenzoic acids and -benzaldehydes, bearing electron-withdrawing substituents at C(5), were shown to be fairly good *in-vitro* COMT inhibitors [10].

Our own search for inhibitors of COMT active also after oral administration started in 1982 with a random screening of 1600 compounds from different sources. 3,5-Dinitropyrocatechol (**2**[1]); *Ro 01-2812*) was identified as the most active COMT inhibitor. Compound **2** has an intensively yellow colour and stains the skin; its production might raise safety problems. Therefore, it was not considered for further development, but it was the starting point for the structural variations, discussed in *Chapt. 4*.

The results of our work were first documented in 1986 [11]. Very recently, a Finnish group reported on inhibition of *O*-methyltransferase activity by certain disubstituted pyrocatechols, of which 3,5-dinitropyrocatechol (**2**) and 3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentanedione *(OR-468)* stand out [12] [13b].

4. *Structure-Activity-Relationship (SAR) Studies.* Within the course of this work, *ca.* 230 derivatives of pyrocatechol were synthesized and tested. Only a representative selec-



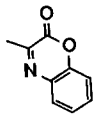
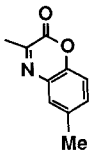
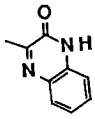
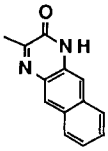
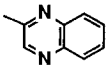
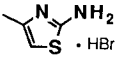
A

Table 1. *Pyrocatechol Derivatives of Type* A

Sub-type	No.	E	Preparation	pK_a1[a])	IC_{50} [nM]	3-OMD [%] in plasma	ED_{50} [mg/kg p.o.]	Prel. tox. mice [mg/kg p.o.]
–	**1**	H	[15]	6.7[d])	280	59		
	2	NO_2	[16]	3.4	37	19	1.3	500–1000
	3	CN	[11]	4.7[d])	89	15	1.7	312–625
	4	SO_2Me	[c])	4.5[d])	109	45		> 5000
A[1]	**5**	CHO	[17]	4.3	84	41	8.9	312–625
	6	COMe	[11]	4.5	69	20	3.4	
	7	COBu	[11]		25	20	12.7	312–625
	8	CO-nonyl	[11]		197	37		1000–2000
	9	CO-cyclohexyl	[b])		44	17	5.6	312–625
A[2]	**10**	COPh	[11]	4.5	48	19	0.76	500–1000
	11	CO-(2-fluorophenyl)	[b])	4.1	42	9	0.28	312–625
	12	CO-(2-pyridyl)	[11]	4.1	67	19	0.96	1000–2000
	13	CO-(3-pyridyl)	[11]		47	18	1.97	1000–2000
	14	CO-(4-pyridyl)	[b])	4.1	53	15	9.1	1250–2500

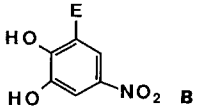
[1]) To facilitate comparison of the various pyrocatechol derivatives, a 'pyrocatechol nomenclature' is used within the biological part of this paper. Systematic names are given in the chemical part.

Table 1 (cont.)

Sub-type	No.	E	Preparation	pK_a1[a])	IC_{50} [nM]	3-OMD [%] in plasma	ED_{50} [mg/kg p.o.]	Prel. tox. mice [mg/kg p.o.]
A[3]	**15**	COOMe	[11]	5.2[d])	38	20	6.7	156–312
	16	COOBu	[b])	5.2[d])	37	21		312–625
A[4]	**17**	COCOOMe	[11]	3.9	61	27		2000–4000
	18	COCOOEt	[b])	3.9	48	27	5.1	1250–2500
	19	COCOOBu	[11]		43	28	7.9	2500–5000
	20	COCOO (hexyl)	[11]	3.9	48	56		2500–5000
A[5]	**21**		[11]	5.3[d])	29	25	32.0	2000–4000
	22		[b])	5.3	20	24		> 5000
A[6]	**23**		[11]	5.3	23	82		> 5000
	24		[11]	5.3[d])	20	64		> 5000
A[7]	**25**		[b])		23	40		> 5000
	26		[11]	6.1	39	72		> 5000

[a]) If not stated otherwise, the pK_a1 values were estimated according to [14]. [b]) *Cf. Exper. Part.*
[c]) *H. Bruderer*, unpublished results. [d]) Calculated by means of a *Hammet ρ,σ* relation.

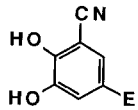
Table 2. *Pyrocatechol Derivatives of Type* **B**



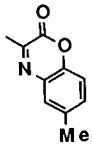
Compound	E	Preparation	pK_a1[a])	IC_{50} [nM]	3-OMD [%] in plasma	ED_{50} [mg/kg p.o.]	Prel. tox. mice [mg/kg p.o.]
27	H	[b])	6.6	19000			
28	CN	[11]	3.9	88	27	7.4	1250–2500
29	COH	[18]	4.4	162	79		
30	COOMe	[11]		361	90		
31	COOBu	[11]	4.6	270	116		2500–5000
32	CONH2	[11]		1924			

[a]) Calculated by means of a *Hammet ρ,σ* relation. [b]) Commercially available *(Fluka)*.

Table 3. *Pyrocatechol Derivatives of Type* **C**

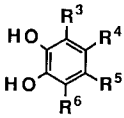


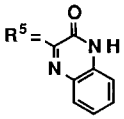
C

Compound	E	Preparation	pK_a1[a])	IC_{50} [nM]	3-OMD [%] in plasma	ED_{50} [mg/kg p.o.]	Prel. tox. mice [mg/kg p.o.]
33	COMe	[11]	4.6	197			
34	COCOOMe	[11]	3.8	82	53		
35	CO-(2-fluorophenyl)	[b])		74		326	500–1000
36		[11]	5.5	186	72		

[a]) Estimated according to [14].
[b]) *Cf. Exper. Part.*

Table 4. *Pyrocatechol Derivatives Belonging to None of the Types* **A–C**

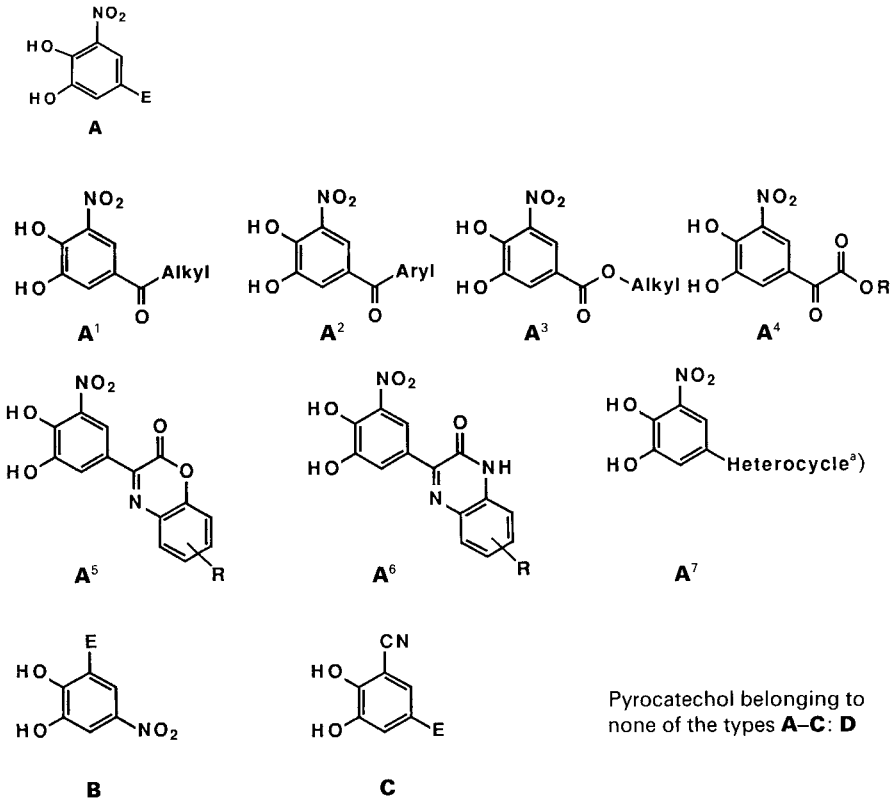


Compound	R (other than H)	Preparation	pK_a1[a])	IC_{50} [nM]	3-OMD [%] in plasma	ED_{50} [mg/kg p.o.]	Prel. tox. mice [mg/kg p.o.]
37	$R^3 = R^4 = NO_2$	[19]	4.34	86	36	99	312–625
38	$R^3 = R^6 = NO_2$	[c])	3.89	120	11	5.8	312–625
39	$R^4 = R^5 = NO_2$	[20]	5.19	442	102		
40	$R^3 = R^5 = SO_2Me$	[21]	4.5	45200	102		> 5000
41	$R^3 = R^5 = SO_2CF_3$	[b])	1.8	1634			156–312
42	$R^3 = NO_2$, $R^5 = COH$, $R^6 = Cl$	[11]		54	37		1250–2500
43	$R^3 = NO_2$, $R^5 = CN$, $R^6 = Cl$	[11]		37	24	12.5	625–1250
44	$R^3 = NO_2$, $R^6 = Cl$, $R^5 =$ 	[11]	4.6[d])	340	83		> 4000

[a]) If not stated otherwise, the pK_a1 values were estimated according to [14].
[b]) *Cf. Exper. Part.*
[c]) *H. Bruderer*, unpublished results.
[d]) Calculated by means of a *Hammet* ρ,σ relation.

tion of these compounds is dealt with in this paper. To make a survey easy, they are divided into 10 groups **A**, **A**[1–7], **B**, **C**, and **D**. Their structures and biological screening data, as well as pK_a1 values and references to their synthesis are compiled in *Tables 1–4*.

4.1. *Activity in Vitro (Tables 1–4)*. 4.1.1. *Search for the Optimal Substitution Pattern.* In an early phase of our SAR Studies starting from **2**, the lead compound was compared with a few closely related simple pyrocatechols. Its isomers **37**, **38**, and **39** are clearly less



E = H or electron-withdrawing substituent

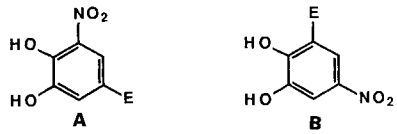
[a]) Other than in A^5 or A^6

Compounds, which are covered by more than one general formula, are placed *(Table 1)* as specific as possible and with the lowest possible number.

active than **2**, a finding which supports the 3,5-substitution as the optimal one. Of the two mononitropyrocatechols **1** and **27**, only the 3-NO_2 derivative **1** shows significant COMT-inhibiting activity, albeit less than compound **2**. The 3-NO_2 group, therefore, appeared to be essential for the activity; the 5-NO_2 group, which – because of its electron-withdrawing power – enhances the acidity of the pyrocatechol, seemed to be of importance for the potency.

With the working hypothesis that the COMT inhibitory activity of 3,5-disubstituted pyrocatechols might depend on their acidity, a limited series of compounds was tested, in which one or both NO_2 groups were replaced by other more or less electron-withdrawing groups. Some of the findings obtained with these derivatives were of particular interest: on the one side, for compounds **1–16** in fact loose connection between log IC_{50} and pK_a1 (or σ_m of the 5-substituent) was observed *(Table 1)*; on the other, it was deducible from the lack of activity of **27**, which has the same acidity as **1**, that acidity *per se* does not necessarily mean activity. That the latter statement is true also for 3,5-disubstituted pyrocatechols was demonstrated by the compounds **40** and **41**.

Table 5. *Comparison of Nitropyrocatechols of Type* **A** *and* **B**



Compound	E	Type	IC_{50} [nM]
1	H	**A**	280
27	H	**B**	19000
5	COH	**A**	84
29	COH	**B**	162
3	CN	**A**	89
28	CN	**B**	88
16	COOBu	**A**	37
31	COOBu	**B**	270

As can be inferred from *Table 5*, of isomeric nitro compounds of types **A** and **B**, the former are the more active ones. Only the isomeric CN derivatives **3** and **28** are exceptions. The 3-NO_2 group cannot be fully replaced by another electron-withdrawing group *(Table 2)*, although some 3-CN compounds show *in vitro* a remarkable activity *(cf. Chapt. 4.1.4)*.

With these data in hand, we decided to study compounds of type **A** systematically, by modifying the 5-substituent in order to find favourable structural parameters beyond its electron-withdrawing power *(Chapt. 4.1.2–4.1.5)*.

4.1.2. *5-Acyl-3-nitrocatechols.* The properties of a few such compounds were already mentioned in *Chapt. 4.1.1.* A close comparison of a few additional compounds synthesized in our laboratories revealed only moderate dependence of the *in vitro* activity on the nature of the substituents at the carbonyl C-atom. In a series of alkylcarbonyl compounds (*Table 1*, Subtype $\mathbf{A}^1$), the pentanoyl derivative **7** results as the most active one. The cyclohexylcarbonyl compound **9** of the same subgroup and several arylcarbonyl derivatives (Subtype $\mathbf{A}^2$) show slightly weaker activity. Among 5-(alkoxycarbonyl)-3-nitropyrocatechols (Subtype $\mathbf{A}^3$), no significant dependence of the activity on the length of the ester-alkyl chain was observed.

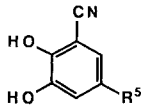
Based on the above discussed results, we studied also the effects of 3-nitro-5-oxalylpyrocatechols (Type $\mathbf{A}^4$). Such compounds could be expected to be distinctly more acidic than simple acyl compounds and esters of type **A**. Furthermore, their R group could be varied and the ketocarbonyl group could be utilized to prepare derivatives. The COMT-inhibitory activities of these compounds (IC_{50} about 50 nM) do not correlate with their acidities ($pK_a1 = 3.9$), nor was any clear dependence on the nature of R observed *(Table 1)*. The hexyl ester **20** is a very potent inhibitor of the enzyme phenolsulfotransferase. This activity has been suppressed by transforming **20** into its *O*-methyloxime.

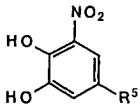
4.1.3. *3-Nitropyrocatechols Bearing Heterocyclic Substituents at C(5).* The α-keto-esters of type $\mathbf{A}^4$ could be easily transformed into benzoxazinones $\mathbf{A}^5$ and benzopyrazinones $\mathbf{A}^6$. The heterocyclic substituents of these compounds combined two features, which we judged favourable considering the results described in *Chapt. 4.1.1* and *4.1.2*, *i.e.* electron-withdrawing power and large molecular size. Some of these compounds in fact, exhibit better *in vitro* activities than the lead compound **2**. Compound **24** with an IC_{50} of 20 nM demonstrates strikingly that even very large substituents at C(5) are not only tolerated, but even improve COMT-inhibitory activity.

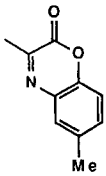
Compounds **25** and **26** are additional examples of active 3-nitropyrocatechols with heterocyclic substituents at C(5). The benzopyrazine **25** (IC_{50} = 23 nM) shows *in vitro* activity similar to that of the compounds of types **A**[5] and **A**[6]. Noteworthy, the 2-aminothiazole **26** (IC_{50} = 39 nM) shows almost the same activity as **2** in spite of much lower acidity.

4.1.4. *5-Substituted 3-Cyanopyrocatechols.* The 3-cyano-5-nitropyrocatechol **28** showed moderate COMT-inhibitory activity *in vitro*. This fact and the results described in *Chapt. 4.1.2* and *4.1.3* prompted us to synthesize and screen a series of 3-cyanopyrocatechols bearing 5-substituents which had been found favourable in the 3-NO_2 series. In *Table 6*, these compounds are compared with the corresponding 3-NO_2 compounds. It is

Table 6. *Comparison of 5-Substituted 3-Cyanopyrocatechols with Corresponding 3-Nitropyrocatechols*



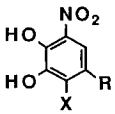


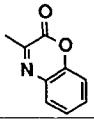
R^5	3-Cyano compound	IC_{50} [nM]	3-OMD [%] in plasma	3-Nitro compound	IC_{50} [nM]	3-OMD [%] in plasma
NO_2	**28**	88	27	**2**	37	19
COMe	**33**	197		**6**	69	20
COCOOMe	**34**	82	53	**17**	61	27
CO-(2-fluorophenyl)	**35**	74		**11**	42	9
	**36**	186	72	**22**	20	24

obvious that both types of compounds do not obey the same structure-activity rules, and that the 3-CN compounds are less active than the corresponding 3-NO_2 compounds.

4.1.5. *Trisubstituted Pyrocatechols.* The pyrocatechols **42**–**44** represent examples in which to a fairly active basic structure a Cl-atom is attached at C(6) as additional electron-withdrawing substituent. A comparison *(Table 7)* shows that the halogen deriv-

Table 7. *Comparison of Some Compounds of Type* **A** *with Corresponding 6-Chloro Derivatives*



Compound	R	X	IC_{50} [nM]	Factor
5	CHO	H	84	1.6
42	CHO	Cl	54	
3	CN	H	89	2.4
43	CN	Cl	37	
23		H	23	0.07
44		Cl	340	

atives are more active than the parent compounds if the 5-substituent is small. In contrast, the chloro derivative **44** is about 15 times less active than the parent catechol **23**. Non-planarity of the two ring systems in **44** caused by the Cl-atom may be the reason for this effect.

4.2. *Activity* in vivo. Activities *in vitro* and *in vivo* of COMT inhibitors are only partly correlated, as can be inferred from *Tables 1–4*. Particularly striking are the poor *in vivo* results obtained with the 3-nitro-5-oxalylpyrocatechols of type $\mathbf{A}^4$ and their oxazinone and pyrazinone derivatives of types $\mathbf{A}^5$ and $\mathbf{A}^6$. This failure is most probably caused by the low solubility of these compounds in lipophilic phases as well as in H_2O, leading to a poor or no resorption from the gastro-intestinal tract. Acylation of the OH groups led in a few cases to better, but still insufficient activity *in vivo*. Of the remaining compounds, the alkylcarbonyl derivatives of type $\mathbf{A}^1$ and the esters of type $\mathbf{A}^2$ are ruled out by their toxicity or insufficient activity *in vivo*. The same holds for all other compounds besides the aryl ketones of type **A2**. These obey all criteria. They do not show top activities in vitro, but good-to-excellent activities *in vivo*, and low toxicity. Of this class, compounds **10–14** stand out by particularly favourable pharmalogical and toxicological properties.

Compound **11** was extensively investigated in the rat *in vivo*. This COMT inhibitor dose-dependently (3–100 mg/kg p.o., 2 h) blocked the formation of the 3-*O*-methylated metabolites homovanillic acid and 4-(hydroxyphenyl)-3-methoxyglycol while leaving the levels of the monoamines (dopamine, noradrenaline, and 5-hydroxytryptamine) and 5-hydroxyindole-3-acetic acid unchanged. As shown in other experiments, **11** dose-dependently potentiated the antagonistic effect of L-DOPA/benserazide against haloperidol-induced catalepsy in rats and akinesia induced by *Ro 4-1284* in mice[2]). Moreover, **11** enhanced L-DOPA/benserazide-induced stereotyped behaviour in the rat. Notably, the accumulation of 3-OMD occurring in rat plasma after L-DOPA plus benserazide (100 and 50 mg/kg p.o., respectively) was almost completely suppressed by the concomitant administration of compound **11** (50 mg/kg p.o.). Since compound **11** markedly increased oral L-DOPA resorption, it is expected that its combination with *Madopar*® or *Madopar HBS*® will substantially improve L-DOPA bioavailability and, therefore, will be of benefit in the therapy of *Parkinson*'s disease [22] [23].

5. Chemistry. – In the preceding chapter, the pharmacological data of 50 derivatives of pyrocatechol are compiled and discussed. A few of these compounds are known; others, *e.g.* the esters of type $\mathbf{A}^3$ and those belonging to type **B**, were obtained by standard procedures (*cf. Exper. Part* for **16** and **31**). For the remaining compounds, special synthetic approaches had to be developed. Of this chemical work, we describe in the following a choice of a few exemplary cases, dealing with compounds **9**, **11**, **14**, **18**, **22**, **24**, **25**, **35**, **41**, and **42**. The synthesis of these compounds is outlined in *Schemes 1–10* and briefly discussed.

5.1. *5-Alkylcarbonyl-(or Arylcarbonyl-)3-nitropyrocatechols* (Types $\mathbf{A}^1$ and $\mathbf{A}^2$). The skeleton of ketones of types $\mathbf{A}^1$ and $\mathbf{A}^2$ may be obtained by addition of an appropriate metallated alkyl or aryl entity, respectively, to an appropriate aldehyde and subsequent dehydrogenation: $R^1{-}Me + R^2{-}CHO \rightarrow R^1{-}CH(OH){-}R^2 \rightarrow R^1{-}CO{-}R^2$. The catechol moiety may play the role of R^2 (*5.1.1* and *5.1.2*) or of R^1 (*5.1.3*).

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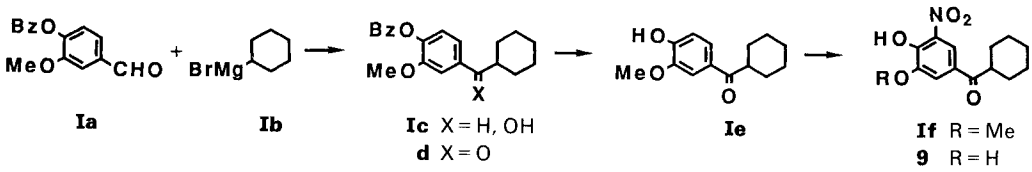
[2]) Results of Dr. *R. Schaffner* and Mr. *A. Spinnler*.

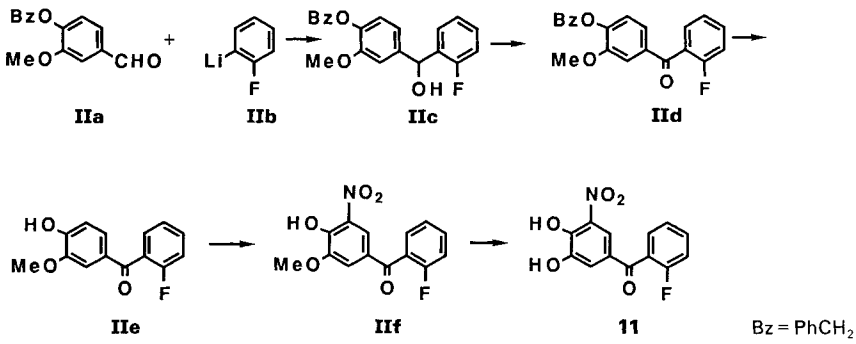
Scheme 1



5.1.1. *Cyclohexyl 3,4-Dihydroxy-5-nitrophenyl Ketone* (**9**; Type A^1; *Scheme 1*). The crucial intermediate in the synthesis of **9** is the carbinol **Ic**. It was obtained by reaction of the *Grignard* reagent **Ib** with the aldehyde **Ia**. Crude **Ic** was oxidized with pyridinium chlorochromate, affording the ketone **Id**. Debenzylation (→ **Ie**), followed by nitration (→ **If**) and demethylation gave **9** (20.9% overall yield).

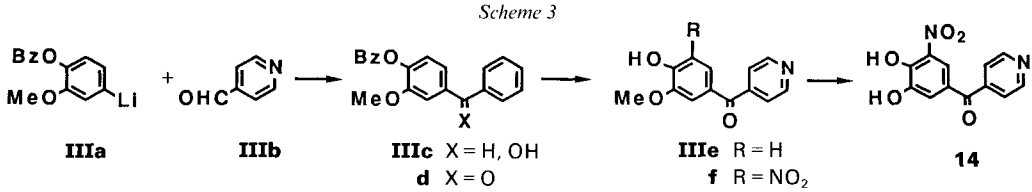
5.1.2. *3,4-Dihydroxy-5-nitrophenyl 2-Fluorophenyl Ketone* (**11**; Type A^2; *Scheme 2*). 1-Fluoro-2-lithiobenzene **IIb** (obtained from 1-bromo-2-fluorobenzene) was added to the dialkoxybenzaldehyde **IIa**. The resulting diarylcarbinol **IIc** was dehydrogenated with pyridinium chlorochromate (→ **IId**). After removal of the $PhCH_2$ group (→ **IIe**), regioselective nitration gave **IIf**. The *O*-Me group of **IIf** was split off with a mixture of aqueous HBr and AcOH (→ **11**; 48.4% overall yield).

Scheme 2



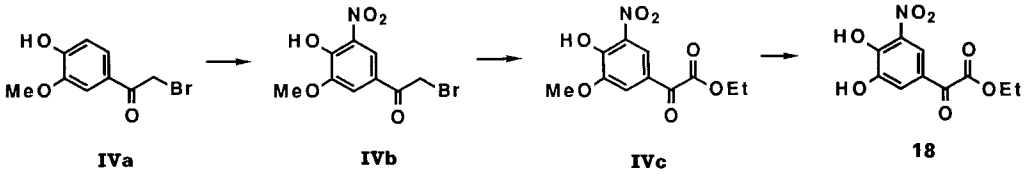
5.1.3. *3,4-Dihydroxy-5-nitrophenyl 4-Pyridyl Ketone* (**14**; Type A^2; *Scheme 3*). 4-(Benzyloxy)-3-methoxyphenyllithium (**IIIa**), obtained from the corresponding aryl bromide, was reacted with pyridine-4-carbaldehyde (**IIIb**) to afford the carbinol **IIIc**, which was dehydrogenated to **IIId** by MnO_2. The $PhCh_2$ group of the latter was removed with HBr/CH_2Cl_2 and the product **IIIe** nitrated (→ **IIIf**). Removal of the *O*-Me group from **IIIf** gave the pyrocatechol **14** (45.5% overall yield).

Scheme 3



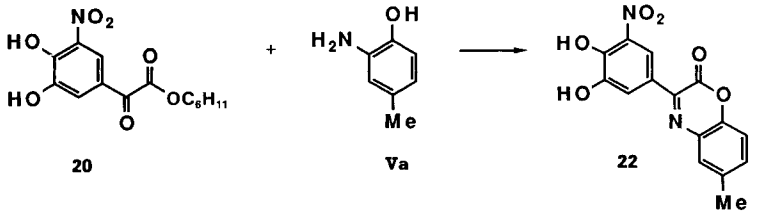
5.2. *Ethyl (3,4-Dihydroxy-5-nitrobenzoyl)carboxylate* (**18**; Type **A**[4]; *Scheme 4*). The phenacyl bromide **IVa** [24] was nitrated, affording **IVb**. The latter was transformed into the α-keto-ester **IVc** by reaction with SeO_2 in EtOH [25]. Several methods were tried to remove the *O*-methyl group of **IVc**. The reaction with $SiCl_4$ in presence of NaI in MeCN toluene proved to be the most favourable one [26]. Compound **18** was obtained in an overall yield of 45.9%.

Scheme 4



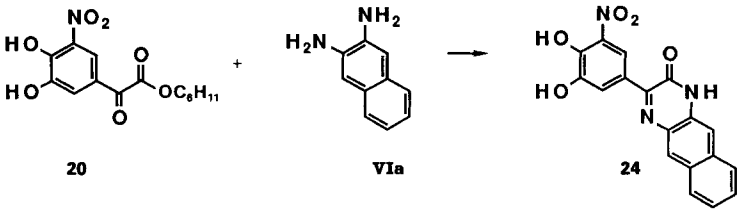
5.3. *3-(3,4-Dihydroxy-5-nitrophenyl)-6-methyl-2*H-*[1,4]benzoxazin-2-one* (**22**; Type **A**[5]; *Scheme 5*). Compound **22** was obtained by reacting the hexyl ester **20** (prepared analogously to **18**) with 2-amino-*p*-cresol (**Va**) at 130° (26% yield).

Scheme 5



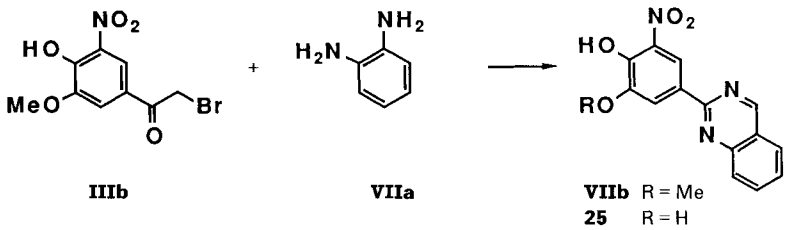
5.4. *3-(3,4-Dihydroxy-5-nitrophenyl)-1,2-dihydrobenzo[*g*]quinoxalin-2-one* (**24**; Type **A**[6]; *Scheme 6*). In analogy to **22**, the title compound was obtained by reacting the hexyl ester **20** with 2,3-diaminonaphtaline **VIa** (80.6% yield).

Scheme 6



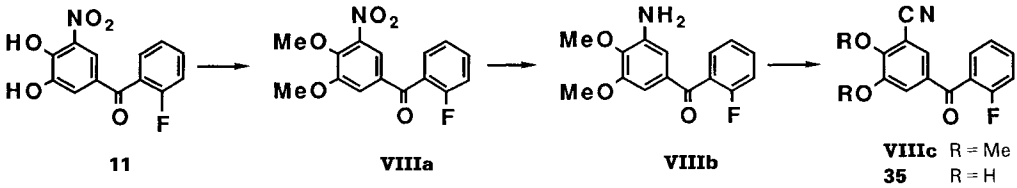
5.5. *3-Nitro-5-(quinoxalin-2-yl)benzene-1,2-diol* (**25**, Type **A**[5]; *Scheme 7*). The title compound was obtained in two steps: reaction of the phenacyl bromide **IIIb** with 1,2-benzenediamine **VIIa** in MeOH in presence of AcONa gave directly the quinoxaline **VIIb** (47.6%). The dehydrogenation involved took place spontaneously. Demethylation of **VIIb** with BBr_3 in CH_2Cl_2 at −10° then afforded **25** (65.7%).

Scheme 7



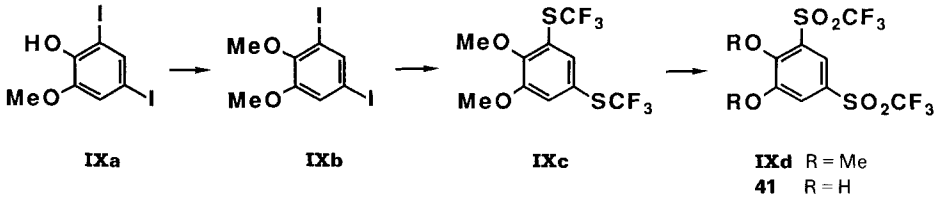
5.6. *5-(2-Fluorobenzoyl)-2,3-dihydroxybenzonitrile* (**35**; Type **C**; *Scheme 8*). This compound was obtained from the nitro compound **11**. After methylation of the OH groups (→ **VIIIa**), reduction with $SnCl_2$ gave the amine **VIIIb**. Diazotation, followed by a *Sandmeyer*-type reaction (→ **VIIIc**) and finally demethylation afforded **35** (32.9% overall yield).

Scheme 8



5.7. *3,5-Bis[(trifluoromethyl)sulfonyl]benzene-1,2-diol* (**41**; *Scheme 9*). *Friedel-Crafts* acylation of an appropriate pyrocatechol derivative, apparently the simplest route to **41**, proved unsuccessful[3]). Reaction of guajacol with trifluoromethylsulfonyl anhydride in the presence of various catalysts gave only *O*-acylated products. Therefore, we decided to synthesize **41** *via* the bis-sulfenyl compound **IXc**: the diiodo derivative **IXa** of guajacol [28] was *O*-methylated (→ **IXb**) and then reacted in *N*-methyl-2-pyrrolidone with Cu(I)-trifluoromethylsulfide [29] to give **IXc** (79.7%). Oxidation of the latter turned out to be difficult. CrO_3 in H_2SO_4 resulted in decomposition. The same oxidant or H_2O_2 in AcOH led to mixtures of partially oxidized products. $NaBrO_4$ [30] gave mixtures of sulfonyl and sulfinyl compounds. Finally, oxidation with a large excess of 30% aqueous H_2O_2 in CF_3COOH proved to be the method of choice and gave the bis-sulfonyl compound **IXd** in

Scheme 9

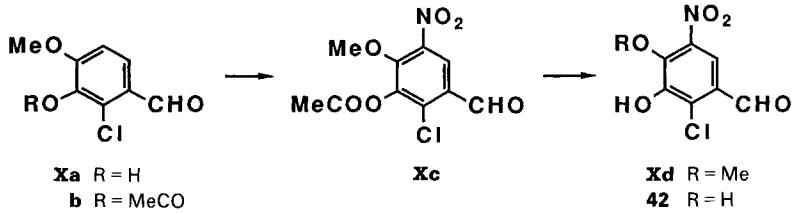


[3]) *Hendrickson* and *Bair* [27] could transform benzene, toluene, and *p*-xylene, but not anisole into trifluorosulfonyl derivatives by direct acylation.

96.1% yield. Demethylation of **IXd** was successful with pyridine hydrochloride at 148° (78.4%).

5.8. *2-Chloro-3,4-dihydroxy-5-nitrobenzaldehyde* (**42**, Type **D**; *Scheme 10*). 2-Chloro-3-formyl-6-methoxyphenyl acetate (**Xb**), obtained from the corresponding 3-hydroxy derivative **Xa** [31], was nitrated by 96% HNO_3 at −10°, affording **Xc**. Removal of the Ac group (NaOH in MeOH) and of the Me group (BF_3 in CH_2Cl_2) gave **42** (52.1% overall yield).

Scheme 10



The skillful assistance of *R. Roos, J. Wührlin, P. Widmer, R. Preiswerk, A. Cueni,* Mrs. *N. Ceccaroni,* Miss *C. Schmidli,* and Miss *I. Wütrich* is acknowledged. The authors thank also Drs. *W. Arnold, A. Dirscherl, G. Englert, M. Grosjean, W. Vetter,* and Mr. *W. Meister* for spectroscopic determinations and microanalyses, Dr. *P. Seiler* for the estimation of pK_a values.

Experimental Part

General. Reagent-grade solvents *(Fluka, Merck)* were dried over molecular sieves. All reactions were performed in closed systems with a slight Ar overpressure. Drying of org. solns. means treatment with Na_2SO_4, evaporation using a *Büchi* rotary evaporator at 40–50°/*in vacuo* (20–400 Torr) followed by evaporation at 10^{-2} Torr. Crystalline substances in all cases were dried *in vacuo* (< 0.1 Torr). Column chromatography: using silica gel *60* (0.200–0.063 mm, *Merck*). M.p.: uncorrected; *Büchi 510*. IR spectra: *Nicolet-7199-FT-IR* spectrometer; in cm^{-1}. ^{1}H-NMR spectra: *Varian A-60-D* (60 MHz), *Bruker-Spectrospin-WP-80-CW* (80 MHz), and *AS-250* (250 MHz), δ values in ppm relative to internal or external TMS; coupling constants (J) in Hz. MS: *MS 9* updated with a *Finningan ZAB* console, data system *SS 200, VG Altrincham* (EI: 70 eV); *MS 902,* fast-atom gun *Kratos,* data system 2050. *VG Altrincham* (FAB, Xe-atom 6 keV, thioglycerol matrix (*Fluka*)); m/z (intensity in % of the base peak (100%)).

1. Cyclohexyl 3,4-Dihydroxy-5-nitrophenyl Ketone (9). – 1.1. *4-(Benzyloxy)-α-cyclohexyl-3-methoxybenzyl Alcohol* (**Ic**). To a stirred mixture of Mg turnings (6.1 g, 0.25 mol), Et_2O (100 ml), and a crystal of I_2, within 2 h, a soln. of bromocyclohexane (40.8 g, 0.25 mol) in Et_2O (400 ml) was added dropwise. The mixture was refluxed for 2 h. After cooling to 0°, a soln. of *4-benzyloxy-3-methoxybenzaldehyde* (**Ia**; 48.5 g, 0.2 mol) in THF (480 ml) was added within ½ h. After further 2 h, the mixture was hydrolyzed by adding 2N H_2SO_4 (200 ml). The org. phase was washed with H_2O (3 × 150 ml) and brine (3 × 150 ml), dried, and evaporated, affording crude **Ic** (65.3 g) as a viscous oil.

1.2. *4-(Benzyloxy)-3-methoxyphenyl Cyclohexyl Ketone* (**Id**). To a soln. of **Ic** (65.3 g) in CH_2Cl_2 (1.2 l), pyridinium chlorochromate (41.1 g, 0.2 mol) was added portionwise within ½ h at 5°. The slurry was stirred for additional 3 h at 5° and for 17 h at r.t. The mixture was then filtrated through dicalite, the filtration residue washed with CH_2Cl_2 (3 × 200 ml). The filtrate was evaporated and the residue chromatographed on silica gel (1.2 kg) with Et_2O/hexane 1:1, affording, after crystallization from Et_2O/hexane, **Id** (41.7 g, 64.3% (2 steps)). M.p. 103–105°. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.16–1.90 (*m*, 10 H); 3.21 (*m*, 1 H); 3.94 (*s*, 3 H); 5.23 (*s*, 2 H); 6.68 (*d*, J = 3.0, 1 arom. H); 7.26–7.57 (*m*, 7 arom. H). MS: 324 (7, $M^{+\cdot}$), 241 (6), 91 (100). Anal. calc. for $C_{21}H_{24}O_3$ (324.42): C 77.75, H 7.46; found: C 77.40, H 7.70.

1.3. *Cyclohexyl 4-Hydroxy-3-methoxyphenyl Ketone* (**Ie**). A mixture of **Id** (41.5 g, 0.128 mol), HBr/AcOH (*ca.* 30%; 170 ml), and CH_2Cl_2 (420 ml) was stirred at r.t. for 2 h and then poured into ice-water (*800 ml*). The org.

phase was washed with brine, dried, and evaporated. Crystallization from petroleum ether gave **Ie** (23.2 g, 77.4%). M.p. 113–115°. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.16–1.92 (*m*, 10 H); 3.23 (*m*, 1 H); 3.94 (*s*, 3 H); 6.08 (*s*, 1 H); 6.94 (*d*, $J = 3.0$, 1 arom. H); 7.53–7.56 (*m*, 2 arom. H). MS: 234 (13, $M^{+\cdot}$), 203 (3), 151 (100). Anal. calc. for $C_{14}H_{18}O_3$ (234.30): C 71.77, H 7.74; found: C 71.71, H 7.77.

1.4. *Cyclohexyl 4-Hydroxy-3-methoxy-5-nitrophenyl Ketone* (**If**). To a stirred soln. of **Ie** (22.7 g, 96.9 mmol) in AcOH (450 ml), HNO_3 (65%; 7.1 ml, 101.7 mmol) was added at r.t. within 20 min. After 90 min, the mixture was poured into ice-water (2 l) and the precipitate collected by filtration. The soln. of the crystals in CH_2Cl_2 (500 ml) was washed with H_2O (4 × 300 ml), dried, and evaporated, affording **If** (20.5 g, 75.8%). M.p. 139–141° (MeOH). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.19–1.92 (*m*, 10 H); 3.25 (*m*, 1 H); 4.01 (*s*, 3 H); 7.77 (*d*, $J \approx 1$, 1 arom. H); 8.30 (*d*, $J \approx 1$, 1 arom. H); 11.11 (*s*, 1 H). MS: 279 (16, $M^{+\cdot}$), 196 (100), 150 (26), 122 (13), 55 (33). Anal. calc. for $C_{14}H_{17}NO_5$ (279.29): C 60.21, H 6.14, N 5.02; found: C 60.24, H 6.26, N 4.95.

1.5. *Compound* **9**. A mixture of **If** (20.1 g, 72 mmol), AcOH (120 ml), and aq. HBr (48%, 57 ml) was refluxed for 20 h and then evaporated. To the residue, toluene (200 ml) was added and the mixture again evaporated. The soln. of the residue in CH_2Cl_2 was washed with H_2O and brine, dried, and evaporated, giving, after crystallization from Et_2O, **9** (10.6 g, 55.5%). M.p. 145–147°. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.19–1.95 (*m*, 1 OH); 3.17 (*m*, 1 H); 6.06 (*s*, 1 H); 7.83 (*d*, $J \approx 1$, 1 arom. H); 8.30 (*d*, $J \approx 1$, 1 arom. H); 10.96 (*s*, 1 H). MS: 265 (13, $M^{+\cdot}$), 210 (18), 197 (26), 182 (100), 55 (50). Anal. calc. for $C_{13}H_{15}NO_5$ (265.27): C 58.86, H 5.70, N 5.28; found: C 58.95, H 5.65, N 5.19.

2. 3,4-Dihydroxy-5-nitrophenyl 2-Fluorophenyl Ketone (11). – 2.1. *(2-Fluorophenyl)(3-methoxy-4-benzyloxyphenyl)methanol* (**IIc**). To a stirred soln. of 1-bromo-2-fluorobenzene (35.0 g, 0.2 mol) in THF (600 ml), BuLi (14.1 g, 0.22 mol) in hexane (140 ml) was added at −70° within ½ h. After further stirring for 1 h, a soln. of *4-benzyloxy-3-methoxybenzaldehyde* (**IIa**, 48.5 g, 0.2 mol) in THF (450 ml) was added within 1 h. The mixture was then stirred for 2 h at −70° and for ½ h at 0°, acidified with 2N H_2SO_4 (150 ml), diluted with ice-water (200 g), and extracted with Et_2O. The org. phase was washed with brine (3 × 400 ml), dried, and evaporated, affording crude **IIc** (69.8 g) as a viscous oil.

2.2. *2-Fluorophenyl 3-Methoxy-4-benzyloxyphenyl Ketone* (**IId**). To a stirred soln. of crude **IIc** (69.2 g) in CH_2Cl_2 (600 ml), pyridinium chlorochromate (45.3 g, 0.21 mol) was added portionwise within ½ h. The mixture was stirred at 20° for 3 h, filtered through dicalite, and the solids were washed with CH_2Cl_2 (3 × 500 ml). The filtrate was evaporated. The soln. of the residue in Et_2O (500 ml) was filtered through a layer of silica gel *60* (0.04–0.063 mm), evaporated to 200 ml, and crystallized, affording **IId** (42.9 g, 64.7% over two steps). M.p. 118–120°. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.95 (*s*, 3 H); 5.23 (*s*, 2 H); 6.85–7.58 (*m*, 12 arom. H). MS: 336 (6, $M^{+\cdot}$), 123 (6), 91 (100). Anal. calc. for $C_{21}H_{17}FO_3$ (336.36): C 74.99, H 5.09, F 5.65; found: C 75.03, H 5.29, F 5.35.

2.3. *2-Fluorophenyl 4-Hydroxy-3-methoxyphenyl Ketone* (**IIe**). A mixture of **IId** (42.4 g, 12.6 mmol) of HBr/AcOH (*ca.* 30%, 170 ml), and CH_2Cl_2 (450 ml) was stirred at r.t. for 2 h and then poured into ice-water (750 ml). After separation of the phases, the H_2O layer was extracted with CH_2Cl_2 and the combined org. layer dried and evaporated. The residue was recrystallized from AcOEt/hexane to afford ketone **IIe** (28.5 g, 91.8%). M.p. 84–86°. ^{1}H-NMR (250 MHz, $CDCl_3$): 3.97 (*s*, 3 H); 6.17 (*s*, 1 H); 6.91–7.58 (*m*, 7 arom. H). MS: 246 (50, $M^{+\cdot}$), 151 (100), 123 (39). Anal. calc. for $C_{14}H_{11}FO_3$ (246.24): C 68.29, H 4.50, F 7.72; found: C 68.05, H 4.57, F 7.38.

2.4. *2-Fluorophenyl 4-Hydroxy-3-methoxy-5-nitrophenyl Ketone* (**IIf**). To a stirred soln. of **IIe** (28 g, 113.7 mmol) in AcOH (450 ml), conc. HNO_3 (65%; 7.9 ml, 114.3 mmol) was added within 20 min. After additional 1½ h, the mixture was poured into ice-water (2 l). The precipitate was collected by filtration, and its soln. in CH_2Cl_2 (500 ml) washed with H_2O (4 × 300 ml), dried, and evaporated. Recrystallization of the residue from MeOH gave **IIf** (31.3 g, 94.5%). M.p. 150–152°. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.04 (*s*, 3 H); 7.21–8.06 (*m*, 6 arom. H); 11.19 (*s*, 1 H). MS: 291 (83, $M^{+\cdot}$), 196 (58), 123 (100), 95 (36). Anal. calc. for $C_{14}H_{10}FNO_5$ (291.23): C 57.74, H 3.46, F 6.52, N 4.81; found: C 57.41, H 3.28, F 6.23, N 4.87.

2.5. *Compound* **11**. A mixture of **IIf** (24.8 g, 85 mmol), aq. HBr (48%; 68 ml), HBr/AcOH (*ca.* 30%; 100 ml) and AcOH (120 ml) was refluxed for 4 h, then evaporated and distilled off with toluene (300 ml). The soln. of the residue in CH_2Cl_2 (300 ml) was washed with H_2O (3 × 300 ml), dried, partly evaporated, and brought to crystallization by addition of petroleum ether: 20.3 g (86.2%) of **11**. M.p. 169–171°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 7.40–7.67 (*m*, 6 arom. H); *ca.* 10.5–11.5 (br., OH). MS: 277 (78, $M^{+\cdot}$), 182 (43), 123 (100), 95 (38). Anal. calc. for $C_{13}H_8FNO_5$ (277.21): C 56.33, H 2.91, F 6.85, N 5.05; found: C 56.20, H 3.01, F 6.73, N 5.03.

3. 3,4-Dihydroxy-5-nitrophenyl 4-Pyridyl Ketone (14). – 3.1. *(3-Methoxy-4-benzyloxyphenyl)(4-pyridyl)methanol* (**IIIc**). To a stirred soln. of 4-benzyloxy-1-bromo-3-methoxybenzene [32] (44 g, 0.15 mol) in THF (375 ml), a soln. of BuLi (10.1 g, 0.158 mol) in hexane (116 ml) was added at −70° within 15 min. After stirring for additional 2 h, a soln. of *pyridine-4-carbaldehyde* (**IIIb**; 16.1 g, 0.15 mol) in THF (45 ml) was added within ½ h.

Then, stirring was continued for 1 h at −70° and for 2 h at 0°. The org. phase, obtained by acidification with 1N HCl (500 ml) and extraction with Et_2O, was washed with 1N HCl (300 ml) and brine, dried, and evaporated. The residue contained unreacted 4-benzyloxy-1-bromo-3-methoxybenzene (2.9 g). The combined aq. phase was alkalized with conc. NH_4OH (100 ml) and extracted with CH_2Cl_2. The org. layer was washed with brine, dried, and evaporated, affording crude **IIIc** (44.5 g, 82.9%). A sample was recrystallized from CH_2Cl_2/Et_2O: pure **IIIc**. M.p. 120–122°. Anal. calc. for $C_{20}H_{19}NO_3$ (321.38): C 74.75, H 5.96, N 4.36; found: C 74.80, H 6.02, N 4.29.

3.2. *4-Benzyloxy-3-methoxyphenyl 4-Pyridyl Ketone* (**IIId**). The mixture of crude **IIIc** (41.1 g, 128.8 mmol), acetone (1.4 l), and activated MnO_2 [33] (331 g) was refluxed for ½ h. The inorg. material was filtrated off, washed with acetone, and the filtrate evaporated. The soln. of the residue in CH_2Cl_2 was washed with brine (3 × 100 ml), dried, and evaporated, giving crude **IIId** (40.4 g, 98.2%) as a viscous oil. A sample was crystallized from CH_2Cl_2/Et_2O: pure **IIId**. M.p. 93–95°. ^{1}H-NMR (250 MHz, $CDCl_3$); 3.96 (*s*, 3 H); 5.26 (*s*, 2 H); 6.90 (*d*, *J* = 8.5, 1 H); 7.24 (*dd*, *J* = 8.5, 1.6, 1 H); 7.33–7.43 (*m*, 5 arom. H); 7.52 (*d*, *J* = 1.6, 1 H); 7.54 (*dd*, *J* = 1.73, < 1, 2 H); 8.78 (*dd*, *J* = 5.95, < 1, 2 H). Anal. calc. for $C_{20}H_{17}NO_3$ (319.36): C 75.22, H 5.37, N 4.39; found: C 75.04, H 5.38, N 4.36.

3.3. *4-Hydroxy-3-methoxyphenyl 4-Pyridyl Ketone* (**IIIe**). A mixture of crude **IIId** (36.6 g, 115 mmol), HBr/AcOH (*ca.* 30%, 75 ml), and CH_2Cl_2 (450 ml) was stirred at r.t. for 6 h poured into sat. aq. $NaHCO_3$ (1.5 l). The precipitate was collected by filtration and recrystallized from DMF/Et_2O, affording **IIIe** (18.3 g, 69.7%). M.p. 228–230°. ^{1}H-NMR (250 MHz, 1N DCl): 3.68 (*s*, 3 H); 5.01 (*s*, OH); 6.73 (*d*, *J* = 8.8, 1 H); 7.07 (*dd*, *J* = 10.4, 2.1, 1 H); 7.24 (*d*, *J* = 2.1, 1 H); 8.09 (*dd*, *J* = 6.8, < 1, 2 H); 8.86 (*dd*, *J* = 6.8, < 1, 2 H). Anal. calc. for $C_{13}H_{11}NO_3$ (229.24): C 68.11, H 4.84, N 6.11; found: C 67.80, H 4.84, N 6.17.

3.4. *4-Hydroxy-3-methoxy-5-nitrophenyl 4-Pyridyl Ketone* (**IIIf**). To a stirred soln. of **IIIe** (18.2 g, 79.4 mmol) in AcOH (250 ml), conc. HNO_3 (65%; 6.1 ml, 87.3 mmol) was added at r.t. within 15 min. After 1½ h, the mixture was poured into ice-water (700 ml) and brought to pH 7 by addition of NH_4OH (25%; 360 ml). The precipitate was collected by filtration, washed with H_2O (4 × 150 ml), and dried, affording **IIIf** (20.6 g, 94.6%). M.p. 221–223°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 3.96 (*s*, 3 H); 7.63 (*d*, *J* = 1.5, 1 H); 7.66 (*dd*, *J* = 5.85, < 1, 2 H); 7.78 (*d*, *J* = 1.5, 1 H); 8.82 (*dd*, *J* = 5.85, < 1, 2 H); OH (br.). Anal. calc. for $C_{13}H_{10}N_2O_5$ (274.23): C 56.94, H 3.68, N 10.22; found: C 56.64, H 3.71, N 10.15.

3.5. *Compound* **14**. A soln. of **IIIf** (16.4 g, 59.8 mmol) in HBr/H_2O (48%; 330 ml) was refluxed for 4 h and then evaporated. The residue was suspended in H_2O (200 ml), alkalized with 2N NaOH (100 ml) to pH 11, and the soln. brought to pH 5 by addition of AcOH (12 ml). The precipitate was collected by filtration, washed with H_2O (4 × 100 ml), dried, and recrystallized from MeOH: 13.2 g (84.8%) **14**. M.p. 244–246°. Anal. calc. for $C_{12}H_8N_2O_5$ (260.21): C 55.39, H 3.10, N 10.77; found: C 55.50, H 3.10, N 10.66.

Data of **14**·CH_3SO_3H: m.p. 260–261° (MeOH). ^{1}H-NMR (250 MHz, (D_6)DMSO): 2.38 (*s*, 3 H); 7.56 (*d*, *J* = 1.5, 1 H); 7.67 (*d*, *J* = 1.5, 1 H); 7.96 (*dd*, *J* = 5.0, < 1, 2 H); 8.97 (*dd*, *J* = 5.0, < 1, 2 H); OH, SO_3H (br.). MS: 260 (90, M^+ (base)), 182 (100), 136 (30), 79 (60), 78 (42), 51 (31). Anal. calc. for $C_{13}H_{12}N_2O_8S$ (356.31): C 43.82, H 3.39, N 7.86; found: C 44.20, H 3.45, N 8.06.

4. Butyl 3,4-Dihydroxy-5-nitrobenzoate (16). – Dry HCl gas was bubbled during ½ h through a stirred soln. of 3,4-dihydroxy-5-nitrobenzoic acid [34] (600 mg, 3.01 mmol) in BuOH (20 ml). After further 5 h at r.t., the mixture was evaporated. The soln. of the residue in CH_2Cl_2 was washed with brine, dried, and evaporated. Crystallization of the residue from CH_2Cl_2/hexane gave **16** (500 mg, 65%). M.p. 80–81°. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.99 (*t*, 3 H); 1.25–1.99 (*m*, 4 H); 4.37 (*dd*, *J* = 6.5, 6.5, 2 H); 6.09 (br. *s*, 1 H); 7.91 (*d*, *J* = 2.5, 1 H); 9.03 (*d*, *J* = 2.5, 1 H); 10.95 (*s*, 1 H). MS: 255 (15, $M^{+\cdot}$), 239 (35), 199 (100), 56 (78). Anal. calc. for $C_{11}H_{13}NO_6$ (255.23): C 51.77, H 5.13, N 5.49; found: C 51.93, H 5.47, N 5.58.

5. Ethyl (3,4-Dihydroxy-5-nitrobenzoyl)carboxylate (18). – 5.1. *Bromomethyl 4-Hydroxy-3-methoxy-5-nitrophenyl Ketone* (**IVb**). To a soln. of *bromomethyl 4-hydroxy-3-methoxyphenyl ketone* (**IVa**) [24] (112.5 g, 0.46 mol) in AcOH (560 ml) was added, at r.t. within ½ h, under stirring a soln. of fuming HNO_3 (96%; 38 g, 0.58 mol) in AcOH (50 ml). After additional 1½ h, the mixture was poured into ice-water (1.3 l). The crystals were collected by filtration, washed with H_2O (1.0 l), and dissolved in CH_2Cl_2 (1.5 l). The soln. was washed with brine (4 × 250 ml), dried, and partially evaporated. From the conc. soln., **IVb** (96 g, 72.1%) crystallized. M.p. 147–149°. ^{1}H-NMR (80 MHz, (D_6)DMSO): 3.99 (*s*, 3 H); 4.96 (*s*, 2 H); 7.75 (*d*, *J* = 2.0, 1 H); 8.19 (*d*, *J* = 2.0, 1 H); OH (br.). Anal. calc. for $C_9H_8BrNO_5$ (290.07): C 37.27, H 2.78, Br 27.55, N 4.83; found: C 37.33, H 3.19, Br 27.89, N 4.80.

5.2. *Ethyl (4-Hydroxy-3-methoxy-5-nitrobenzoyl)carboxylate* (**IVc**). To a suspension of **IVb** (580.1 mg, 2.0 mmol) in EtOH (10 ml), SeO_2 [25] (443.8 mg, 4 mmol) was added, the mixture stirred under reflux for 17 h and evaporated. The soln. of the residue in CH_2Cl_2 was washed with brine, dried, and evaporated. Crystallization of the residue from EtOH afforded **IVc** (485 mg, 90.1%). M.p. 165–167°. ^{1}H-NMR (60 MHz, (D_6)DMSO): 1.38 (*t*, 3 H);

4.02 (*s*, 3 H); 4.48 (*q*, 2 H); 7.73 (*d*, *J* = 2.0, 1 H); 8.17 (*d*, *J* = 2.0, 1 H); OH (br.). MS: 269 (5, $M^{+\cdot}$), 196 (100), 150 (14). Anal. calc. for $C_{11}H_{11}NO_7$ (269.21): C 49.08, H 4.12, N 5.20; found: C 48.94, H 4.16, N 5.20.

5.3. *Compound* **18**. To a suspension of **IVc** (17.2 g, 63.9 mmol) and NaI (10.5 g, 70.3 mmol) in MeCN (100 ml) and toluene (100 ml), $SiCl_4$ [26] (11.9 g, 70.3 mmol) was added. The mixture was refluxed for 47 h, evaporated, distilled off with toluene (6 × 200 ml), and then treated with H_2O (50 ml) and Et_2O (200 ml). The org. phase was washed with brine, dried, and evaporated. Crystallization of the residue from Et_2O/hexane afforded **18** (11.5 g, 70.6%). M.p. 77–79°. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.44 (*t*, 3 H); 4.46 (*q*, 2 H); 6.06 (*s*, 1 H); 7.88 (*d*, *J* = 2.5, 1 H); 8.41 (*d*, *J* = 2.5, 1 H); 11.11 (*s*, 1 H). MS: 255 (7, $M^{+\cdot}$), 182 (100), 136 (22). Anal. calc. for $C_{10}H_9NO_7$ (255.18): C 47.07, H 3.56, N 5.49; found: C 46.97, H 3.65, N 5.47.

6. 3-(3,4-Dihydroxy-5-nitrophenyl)-6-methyl-2*H*-[1,4]benzoxazin-2-one (22). – A mixture of *hexyl (3,4-dihydroxy-5-nitrobenzoyl)carboxylate* **20** prepared analogously to **18** (1.44 g, 4.63 mmol) and 2-amino-4-methylphenol (**Va**, 0.57 g, 4.63 mmol) was heated to 130° for 1 h. After cooling to r.t., crystallization from MeOH/CH_2Cl_2 afforded **22** (1.25 g, 86%). M.p. 233–235°. ^{1}H-NMR (80 MHz, (D_6)DMSO): 2.44 (*s*, 3 H); 7.38–7.75 (*m*, 3 arom. H); 8.11 (*d*, *J* = 2.7, 1 H); 8.48 (*d*, *J* = 2.7, 1 H); OH (br.). Anal. calc. for $C_{15}H_{10}N_2O_6$ (314.25): C 57.33, H 3.21, N 8.91; found: C 56.96, H 3.52, N 8.77.

7. 3-(3,4-Dihydroxy-5-nitrophenyl)benzo[*g*]quinoxalin-2(1*H*)-one (24). – A mixture of **20** (1.07 g, 3.43 mmol), *naphthalene-2,3-diamine* (**VIa**; 0.54 g, 3.43 mmol) and hexan-1-ol (3 ml) was heated to 180° for 3 h. After cooling to r.t., MeOH (3 ml) was added, the precipitate collected by filtration and recrystallized from DMF/H_2O, affording **24** (966 mg, 80.6%). M.p. > 300°. MS: 349 (100, $M^{+\cdot}$), 321 (36), 319 (22), 140 (21). Anal. calc. for $C_{18}H_{11}N_3O_5$ (349.30): C 61.89, H 3.17, N 12.03; found: C 61.83, H 3.46, N 11.91.

8. 3-Nitro-5-(quinoxalin-2-yl)benzene-1,2-diol (25). – 8.1. *2-Methoxy-6-nitro-4-(quinoxalin-2-yl)phenol* (**VIIb**). A mixture of *bromomethyl 4-hydroxy-3-methoxy-5-nitrophenyl ketone* **IIIb** (1.76 g, 6.06 mmol), *benzene-1,2-diamine* (**VIIa**, 0.66 g, 6.06 mmol), AcONa (0.6 g, 7.1 mmol), and MeOH (35 ml) was stirred at r.t. for 22 h and under reflux for 6 h, then evaporated and treated with H_2O and CH_2Cl_2. The org. phase was washed with brine, dried, and evaporated. Crystallization of the residue from MeOH gave **VIIb** (857 mg, 47.6%). M.p. 195–197°. ^{1}H-NMR (80 MHz, (D_6)DMSO): 4.08 (*s*, 3 H); 7.83–8.29 (*m*, 4 arom. H); 8.22 (*d*, *J* = 2.7, 1 H); 8.49 (*d*, *J* = 2.7, 1 H); 9.69 (*s*, 1 H); OH (br.). MS: 297 (100, $M^{+\cdot}$), 250 (37), 179 (40), 102 (41), 76 (47), 50 (38). Anal. calc. for $C_{15}H_{11}N_3O_4$ (297.27): C 60.61, H 3.73, N 14.14; found: C 60.57, H 3.67, N 14.14.

8.2. *Compound* **25**. To a suspension of **VIIb** (812 mg, 2.73 mmol) in CH_2Cl_2 (40 ml), cooled to −10°, BBr_3 (3.42 g, 13.7 mmol) was added. After stirring at −10° for 1 h and at 20–25° for 19 h, the mixture was evaporated and the residue treated with H_2O. The product was collected by filtration and recrystallized from MeOH: **25** (508 mg, 65.7%). M.p. 241–243°. ^{1}H-NMR (80 MHz, (D_6)DMSO): 7.78–8.44 (*m*, 6 arom. H); 9.58 (*s*, 1 arom. H); OH (br.). MS: 283 (100, $M^{+\cdot}$), 253 (29), 207 (24), 69 (54). Anal. calc. for $C_{14}H_9N_3O_4 \cdot 0.3$ MeOH (292.86): C 58.65, H 3.51, N 14.35; found: C 58.65, H 3.56, N 14.23.

9. Butyl 2,3-Dihydroxy-5-nitrobenzoate (31). – Through a stirred soln. of 2,3-dihydroxy-5-nitrobenzoic acid [35] (1.8 g, 9.04 mol) in BuOH (30 ml), dry HCl gas was bubbled for 10 min. After 5 h at 50°, the soln. was evaporated, the residue dissolved in CH_2Cl_2, washed with brine (5 × 30 ml), dried, and evaporated. Crystallization from CH_2Cl_2/hexane gave **31** (1.5 g, 65%). M.p. 78–79°. MS: 255 (12, $M^{+\cdot}$), 199 (26), 181 (100), 57 (32), 41 (36). Anal. calc. for $C_{11}H_{13}NO_6$ (255.23): C 51.77, H 5.13, N 5.49; found: C 51.89, H 5.15, N 5.45.

10. 5-(2-Fluorobenzoyl)-2,3-dihydroxybenzonitrile (35). – 10.1. *2′-Fluoro-3,4-dimethoxy-5-nitrobenzophenone* (**VIIIa**). A mixture of **11** (5 g, 18 mmol), NaOH (9.75 g, 244 mmol), Bu_4NBr (21.8 g, 67.8 mmol), Me_2SO_4 (27.3 g, 216 mmol), H_2O (200 ml), and CH_2Cl_2 (50 ml) was stirred at r.t. for 17 h. The org. phase, obtained by extraction with Et_2O (300 ml), was washed with H_2O (6 × 150 ml) and brine, dried, and evaporated. The residue was crystallized from Et_2O/petroleum ether, giving **VIIIa** (5 g, 91.1%). M.p. 86–88°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 3.97 (*s*, 3 H); 3.98 (*s*, 3 H); 7.41–7.72 (*m*, 6 arom. H). Anal. calc. for $C_{15}H_{12}FNO_5$ (305.26): C 59.02, H 3.96, N 4.59; found: C 59.06, H 4.07, N 4.60.

10.2. *3-Amino-2′-fluoro-4,5-dimethoxybenzophenone* (**VIIIb**). A mixture of **VIIIa** (5.78 g, 18.4 mmol), $SnCl_2 \cdot 2H_2O$ (21.36 g, 94.7 mmol), and EtOH (150 ml) was stirred under reflux for ¾ h, then evaporated, treated with H_2O (400 ml), alkalized to pH 10 with aq. NaOH (28%; 33 ml), and extracted with CH_2Cl_2. The org. phase was washed with brine, dried, and evaporated. Crystallization of the residue from Et_2O/petroleum ether afforded **VIIIb** (4.5 g, 86.3%). M.p. 93–95°. MS: 275 (100, $M^{+\cdot}$), 260 (92), 123 (44). Anal. calc. for $C_{15}H_{14}FNO_3$ (275.28): C 65.45, H 5.13, N 5.09; found: C 65.58, H 5.17 N 4.92.

10.3. *5-(2-Fluorobenzoyl)-2,3-dimethoxybenzonitrile* (**VIIIc**). To a vigorously stirred soln. of $CuSO_4 \cdot 5\,H_2O$ (4.87 g, 19.5 mmol) in H_2O (25 ml) at 0°, a soln. of KCN (5.18 g, 79.6 mmol) in H_2O (13 ml) was added dropwise

within 20 min. After additional 10 min, $NaHCO_3$ (10.7 g, 127 mmol), and AcOEt (100 ml) were added. To the mixture obtained in this way, a diazonium-salt soln. was added dropwise at 0° within 1 ½ h, which was prepared at 0° from a soln. of **VIIIb** (4.46 g, 16.2 mmol) in THF (50 ml), H_2O (100 ml), and 2N H_2SO_4 (32 ml), to which $NaNO_2$ (1.25 g, 18 mmol) in H_2O (3 ml) was dropped within 20 min. The *Sandmeyer* mixture was filtrated through dicalite, and the org. phase was washed with H_2O (4 × 150 ml), dried, and evaporated. The residue was chromatographed on silica gel (150 g) with CH_2Cl_2/hexane 9:1 to afford **VIIIc** (2.03 g, 43.9%). M.p. 132–134° (CH_2Cl_2/petroleum ether). IR (KBr): 2236, 1663, 1613, 1491, 1235, 1133. MS: 285 (94, M^+), 270 (6), 254 (6), 190 (100), 123 (78), 95 (28). Anal. calc. for $C_{16}H_{12}FNO_3$ (285.27): C 67.37, H 4.24, N 4.91; found: C 67.71, H 4.07, N 4.25.

10.4. *Compound* **35**. Compound **VIIIc** (1.56 g, 5,47 mmol) was added to pyridine hydrochloride (15.6 g) and heated to 155–160° for 2 h. After cooling to r.t., the mixture was poured into ice-water (100 ml) and extracted with Et_2O. The org. phase was washed with H_2O (8 × 50 ml), dried, and evaporated. Crystallization of the residue from Et_2O/petroleum ether gave **35** (1.34 g, 95.3%). M.p. 228–230°. IR (KBr): 3396, 3257, 2246, 1654, 1595, 1523, 1483, 1315. MS: 257 (78, M^+), 162 (100), 123 (92), 95 (27). Anal. calc. for $C_{14}H_8FNO_3$ (257.22): C 65.37, H 3.14, N 5.45; found: C 65.08, H 3.22, N 5.46.

11. 3,5-Bis[(trifluoromethyl)sulfonyl]benzene-1,2-diol (41). – 11.1. *1,5-Diiodo-2,3-dimethoxybenzene* (**IXb**). A mixture of *2,4-diodo-6-methoxyphenol* [28] (**IX**; 18.05 g, 48 mmol), DMF (240 ml), K_2CO_3 (132.7 g, 0.96 mol), and Me_2SO_4 (9.1 g, 72 mmol) was stirred at r.t. for 1 h, then poured into ice-water (720 ml) and extracted with Et_2O (4 × 200 ml). The org. phase was washed with H_2O (5 × 200 ml) and brine, dried, and evaporated. The product was purified by bulb-to-bulb distillation at 125–130°/0.02 Torr and crystallized from petroleum ether: **IXb** (15.6 g, 83.4%). M.p. 58–60°. ^{1}H-NMR (60 MHz, $CDCl_3$): 3.83 (*s*, 3 H); 3.87 (*s*, 3 H); 7.20 (*d*, *J* = 2.0, 1 H); 7.72 (*d*, *J* = 2.0, 1 H). MS: 390 (100, M^+), 375 (37), 248 (12), 220 (18), 50 (22). Anal. calc. for $C_8H_8I_2O_2$ (389.96): C 24.64, H 2.07, I 65.09; found: C 24.60, H 2.38, I 64.80.

11.2. *1,2-Dimethoxy-3,5-bis[(trifluoromethyl)thio]benzene* (**IXc**). A mixture of **IXb** (15.0 g, 38,6 mmol), [(trifluoromethyl)thio]copper [29] [36] (32.9 g, 0.2 mol), and *N*-methylpyrrolidin-2-one (120 ml) was stirred at 160° for 3 h. After cooling to r.t., the mixture was poured into ice-water (400 ml) and extracted with Et_2O. The org. phase was washed with H_2O (6 × 200 ml), dried, and evaporated. The residue was purified by bulb-to-bulb distillation at 120–125°/10 Torr to afford **IXc** (10.4 g, 79.7%). ^{1}H-NMR (60 MHz, $CDCl_3$): 3.91 (*s*, 3 H); 3.95 (*s*, 3 H); 7.26 (*d*, *J* = 2.0, 1 H); 7.53 (*d*, *J* = 2.0, 1 H). MS: 338 (100, M^+), 269 (19), 69 (29). Anal. calc. for $C_{10}H_8F_6O_2S_2$ (338.28): C 35.51, H 2.38, S 18.95; found: C 35.30, H 2.41, S 19.02.

11.3. *1,2-Dimethoxy-3,5-bis[(trifluoromethyl)sulfonyl]benzene* (**IXd**). A stirred mixture of **IXc** (10.15 g, 30 mmol), CF_3COOH (100 ml), and H_2O_2 (30%, 20.4 g, 0.18 mmol) was refluxed for 1 h and, after cooling to r.t., poured into ice-water (500 ml). The mixture, after addition of $NaHSO_3$ (18.7 g, 0.18 mol), was alkalized to pH 9–10 with sat. Na_2CO_3/H_2O, and extracted with Et_2O. The org. phase was washed with H_2O, dried, and evaporated. The residue was crystallized from Et_2O/hexane, giving **IXd** (11.6 g, 96.1%). M.p. 71–73°. ^{1}H-NMR (60 MHZ, $CDCl_3$): 4.07 (*s*, 3 H); 4.13 (*s*, 3 H); 7.77 (*d*, *J* = 2.5, 1 H); 8.27 (*d*, *J* = 2.5, 2 H). MS: 402 (52, M^+), 333 (100), 269 (18), 200 (44), 185 (36), 76 (43), 69 (52). Anal. calc. for $C_{10}H_8F_6O_6S_2$ (402.28): C 29.86, H 2.00, S 15.94; found: C 29.59, H 2.40, S 15.81.

11.4. *Compound* **41**. Compound **IXd** (6.03, 15 mmol) was added to pyridine·HCl (60.3 g), and the mixture heated to 148° for 1 h. After cooling to r.t., the mixture was poured into ice-water (300 ml) and extracted with Et_2O. The org. phase was washed with H_2O (10 × 200 ml), dried, and evaporated. The residue was crystallized from Et_2O/hexane to afford **41** (4.4 g, 78.4%). M.p. 111–113°. ^{1}H-NMR (80 MHz, (D_6)DMSO): 7.18, (*d*, *J* = 2.7, 1 H); 7.71 (*d*, *J* = 2.7, 1 H); OH (br.). MS: 374 (8, M^+), 305 (31), 149 (70), 69 (100). Anal. calc. for $C_8H_4F_6O_6S_2$ (374.22): C 25.68, H 1.08, S 17.13; found: C 25.37, H 1.33, S 16.89.

12. 2-Chloro-3,4-dihydroxy-5-nitrobenzaldehyde (42). – 12.1. *2-Chloro-3-formyl-6-methoxyphenyl Acetate* (**Xb**). A mixture of *2-chloro-3-hydroxy-4-methoxybenzaldehyde* [31] (**Xa**; 31.35 g, 0.168 mol) Ac_2O (450 ml), and pyridine (6 ml) was stirred at 80° for 8 h and then evaporated. The soln. of the residue in CH_2Cl_2 was washed with H_2O, dried, and evaporated. The crude product was crystallized from CH_2Cl_2/petroleum ether, giving **Xb** (32.5 g, 84.6%). M.p. 56–58°. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.40 (*s*, 3 H); 3.93 (*s*, 3 H); 6.99 (*d*, *J* = 8.8, 1 H); 7.87 (*d*, *J* = 8.8, 1 H); 10.30 (*s*, 1 H). MS: 228 (2.3, M^+), 186 (84), 185 (68), 43 (100). Anal. calc. for $C_{10}H_9ClO_4$ (228.63): C 52.53, H 3.97, Cl 15.51; found: C 52.52, H 4.09, Cl 15.48.

12.2. *2-Chloro-3-formyl-6-methoxy-5-nitrophenyl Acetate* (**Xc**). Compound **Xb** (29.75 g, 130 mmol) was added, within 20 min at −20°, to HNO_3 (96%, 120 ml). After stirring at −10° for 4 h, the mixture was poured into ice-water (1.2 l) and extracted with CH_2Cl_2. The org. phase was washed with H_2O, dried, and evaporated. Crystallization of the residue from Et_2O gave **Xc** (25.7 g, 72.2%). M.p. 86–88°. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 4.03 (*s*, 3 H); 8.34 (*s*, 1 H); 10.37 (*s*, 1 H). MS: 231 (3.8, $[M - C_2H_2O]^+$), 43 (100). Anal. calc. for $C_{10}H_8ClNO_6$ (273.63): C 43.90, H 2.95, N 5.12; found: C 43.71, H 3.00, N 5.15.

12.3. *2-Chloro-3-hydroxy-4-methoxy-5-nitrobenzaldehyde* (**Xd**). A soln. of **Xc** (25.1 g, 91.7 mmol) in MeOH (230 ml) and 1N $NaOH/H_2O$ (101 ml) was stirred at r.t. for 2 h. The mixture was evaporated, the residue in ice-water acidified with 1N HCl to a pH of *ca.* 1 and extracted with AcOEt. The org. phase was washed with H_2O, dried, and evaporated. Crystallization of the residue from CH_2Cl_2/petroleum ether afforded **Xd** (20.3 g, 95.6%). M.p. 131–133°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 3.94 (*s*, 3 H); 7.85 (*s*, 1 H); 10.24 (*s*, 1 H); OH (br.). Anal. calc. for $C_8H_6ClNO_5$ (231.59): C 41.49, H 2.61, N 6.05; found: C 41.30, H 2.71, N 6.03.

12.4. *Compound* **42**. To soln. of **Xd** (1.3 g, 5.61 mmol) in CH_2Cl_2 (80 ml), cooled to −10°, BBr_3 (2.13 g, 8.51 mmol) was added. The mixture was then stirred at r.t. for 18 h and evaporated. The residue was treated with H_2O, the product collected by filtration and recrystallized from MeCN, affording **42** (1.09 g, 89.3%). M.p. 193–195°. MS: 217 (100, M^+), 171 (48), 169 (56), 143 (28). Anal. calc. for $C_7H_4ClNO_5$ (217.56): C 38.64, H 1.85, N 6.44; found: C 38.89, H 1.93, N 6.73.

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