Design, Synthesis, and SAR of a Novel Pyrazinone Series with Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitory Activity

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A series of novel pyrazinones designed as non-nucleoside reverse transcriptase inhibitors (NNRTIs) was synthesized and their anti-HIV structure−activity relationship (SAR) was studied.

Introduction

Reverse transcriptase (RT), being essential in the replication process of human immunodeficiency virus (HIV), can still be considered as one of the most attractive targets for the development of new antiretroviral drugs. Currently three non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been approved by the FDA for clinical use, namely, nevirapine, delavirdine, and efavirenz.

Protein−ligand interaction studies have shown that NNRTIs bind in an induced allosteric pocket located at a distance of approximately 10 Å from the DNA polymerase active site.[1,2]

Different chemical classes have been reported to inhibit RT, such as the TIBOs,[3] HEPTs,[4] α-APAs,[5] pyridones,[6] ITUs,[7] and finally the DATA and DAPY series,[8,9] of which dapivirine (R 147681, TMC120, Figure 1) and etravirine (R 165335 or TMC 125, Figure 2) are representatives.

Dapivirine and etravirine both display high activity against HIV-1 LAI virus (IIIB) and a large panel of derived single and double mutants.[9]

In this paper we report the synthesis and HIV-1-inhibiting properties of a novel series of 3,5-disubstituted pyrazinone derivatives.

Chemistry

We developed a general and useful synthesis of 3-anilino-5-halopyrazinone scaffolds, which were utilized for coupling reactions with phenols and thiophenols leading to the desired 3,5-disubstituted target compounds. The intermediate pyrazinone building blocks were synthesized as follows. Treatment of the appropriately substituted hydrobromide salt of aminoacetonitrile **3** and 2-aminopropanenitriles **4** and **5** with oxalyl bromide gave the 3,5-dibromopyrazinones **6**−**8** (Scheme 1). The condensation of the hydrochloride salt of **5** with oxalyl chloride to form the corresponding 3,5-dichloropyrazinone **9** was effected according to a procedure described previously.[10,11]

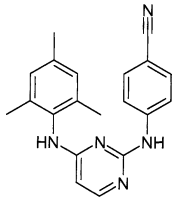

Figure 1. Structural formula of dapivirine (R147681, TMC120).

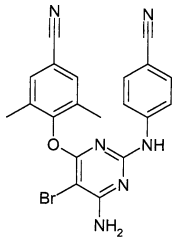

Figure 2. Structural formula of etravirine (R165335, TMC125).

Substitution of the reactive imidoyl halide moiety in the C3-position of the 2(1*H*)-pyrazinones **6**−**9** with 4-aminobenzonitrile in the presence of camphorsulfonic acid as a catalyst gave the key precursors **10**−**14** (Scheme 1). The 3-anilino analogues **15**−**20** were obtained by conversion of **6** and **7** with different anilines under the same reaction conditions (Scheme 2).

Subsequent coupling of the 5-bromopyrazinones with the appropriately substituted phenols and benzenethiols was accomplished by heating with Cs_2CO_3 and CuCl in refluxing toluene to afford target compounds **21**−**42** (Scheme 3). The yields of these reactions were generally

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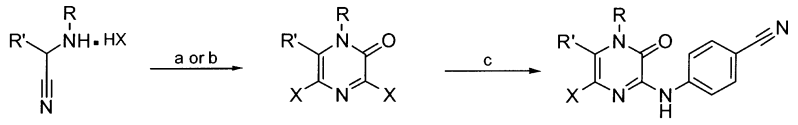
Scheme 1[a]



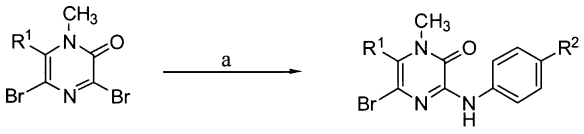
	R	R'
3	CH_3	H
4	CH_3	CH_3
5	CH_2Ph	CH_3

	R	R'	X
6	CH_3	H	Br
7	CH_3	CH_3	Br
8	CH_2Ph	CH_3	Br
9	CH_2Ph	CH_3	Cl

	R	R'	X
10	CH_3	H	Br
11	CH_3	CH_3	Br
12	CH_2Ph	CH_3	Br
13	CH_2Ph	H	Br
14	CH_2Ph	CH_3	Cl

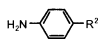
[a] Reagents and conditions:(a) BrCOCOBr, DMF, CH_2Cl_2, reflux, 24 h; (b) ClCOCOCl, Et_4NCl, Ph-Cl, 20 °C, 48 h; (c) 4-aminobenzonitrile, camphorsulfonic acid, i-PrOH, reflux, 48 h.

Scheme 2[a]

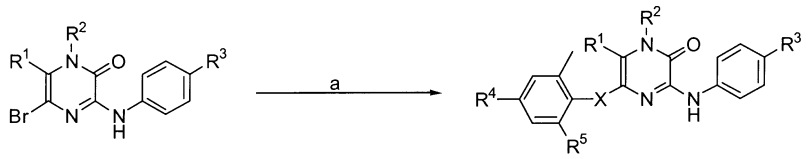


	R^1
6	H
7	CH_3

	R^1	R^2
15	H	H
16	H	F
17	H	CH_3
18	H	Cl
19	H	CF_3
20	CH_3	Cl

[a]Reagents and conditions : (a)  , camphorsulfonic acid, i-PrOH, reflux, 48h.

Scheme 3[a]



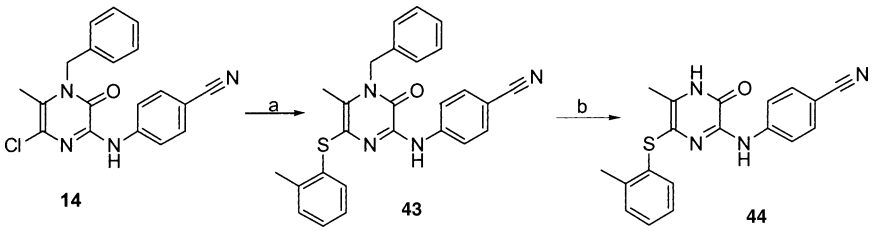
	R^1	R^2	R^3
10	H	CH_3	CN
11	CH_3	CH_3	CN
13	H	CH_2Ph	CN
15	H	CH_3	H
16	H	CH_3	F
17	H	CH_3	CH_3
18	H	CH_3	Cl
19	H	CH_3	CF_3
20	CH_3	CH_3	Cl

	X	R^1	R^2	R^3	R^4	R^5
21	O	H	CH_3	H	CH_3	H
22	O	H	CH_3	F	CH_3	H
23	O	H	CH_3	CH_3	CH_3	H
24	O	H	CH_3	Cl	CH_3	H
25	S	H	CH_3	Cl	CH_3	CH_3
26	O	H	CH_3	CF_3	CH_3	H
27	O	H	CH_3	CN	H	H
28	S	H	CH_3	CN	H	H
29	O	H	CH_3	CN	CH_3	H
30	S	H	CH_3	CN	CH_3	H
31	S	H	CH_3	CN	CH_3	CH_3
32	O	H	CH_2Ph	CN	H	H
33	O	H	CH_2Ph	CN	CH_3	H
34	S	CH_3	CH_3	CN	CH_3	CH_3
35	O	CH_3	CH_3	Cl	H	H
36	O	CH_3	CH_3	CN	H	H
37	S	CH_3	CH_3	CN	H	H
38	O	CH_3	CH_3	Cl	CH_3	H
39	S	CH_3	CH_3	Cl	CH_3	H
40	O	CH_3	CH_3	CN	CH_3	CH_3
41	O	CH_3	CH_3	CN	CH_3	H
42	O	CH_3	CH_3	CN	CN	CH_3

[a]Reagents and conditions : (a)  , Cs_2CO_3, CuCl, toluene, reflux, 3h to 48h.

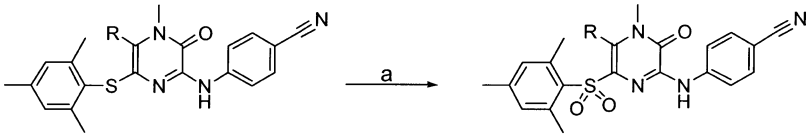
low due to the formation of side products, which resulted either from the replacement of the 5-Br atom with hydrogen or, for 6-unsubstituted 2(1*H*)-pyrazinones, from the substitution of H-6 with a second phenoxy or phenylsulfanyl group. To reduce or prevent the replacement of the halogen in 5-position by hydrogen, we coupled 5-chloropyrazinone **14** instead of the corresponding 5-bromopyrazinone **12** with 2-methylbenzenethiol in the presence of Cs_2CO_3 in *N*-methylpyrrolidinone at 130 °C to the 5-phenylsulfanyl-2(1*H*)-pyrazinone analogue **43**, which was isolated in acceptable yield. Subsequent N-debenzylation to yield target com-

Scheme 4[a]



[a] Reagents and conditions: (a) 2-methylbenzenethiol, Cs_2CO_3, NMP, 130 °C, 3 h; (b) $AlCl_3$, 1,2-dichlorobenzene, 160 °C, 6 h.

Scheme 5[a]



R	
31	H
34	CH_3

R	
45	H
46	CH_3

[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 24 h.

pound **44** was effected by heating **43** with $AlCl_3$ in 1,2-dichlorobenzene at 160 °C (Scheme 4).

Compounds **31** and **34** were converted into the corresponding sulfonyl analogues **45** and **46** via oxidation with *m*-CPBA (Scheme 5).

Results and Discussion

Evaluation of the antiviral activity of the pyrazinone compounds was based on the potency of inhibiting replication of wild-type HIV-1 (LAI strain, IIIB) virus and a panel of important monomutants derived from it, like L100I, K103N, Y181C, and Y188L. Mutated variants of HIV-1 LAI strain are characterized in the tables by their amino acid position and the one letter residue codes. For instance, K103N refers to replacement of lysine at position 103 by asparagine. Concentrations required to achieve 50% protection from HIV-1 cytopathicity in MT-4 cells (IC_{50}, μmol) were determined by the MTT method.[12] All the determinations are the median results of multiple tests. Optimization of activity was guided by molecular modeling, which in turn was based on the X-ray crystal structure of HIV-1 RT bound with dapivirine.[13]

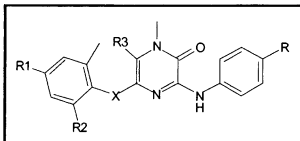
The modeling approach used to predict activity for these compounds is based on evaluating the interaction energy between a designed compound and the various amino acids surrounding it in its predicted bound conformation inside the HIV NNRTI binding site.[14] This method also allows for the identification of potentially relevant mutations, by the separate contributions toward the binding energy for each of the amino acids. A more extensive study of mutant sensitivity was not performed on the NNRTIs described in this paper, because the energy contributions of the side chains provided sufficient information to aid the synthesis. A full statistical treatment of complex mutation interaction that can also be computed with this method is illustrated in the resistance study for the HIV protease inhibitor Amprenavir.[15]

The target molecules can be considered to be built up from three parts, namely, the central pyrazinone ring; the right wing, consisting of the aniline moiety in the 3-position; and the left aryloxy(sulfanyl) wing in the 5-position of the pyrazinone ring, respectively.

First of all we evaluated the effect on activity of different substituents in the 4-position of the aniline ring (see Table 1). The parent compound **21** (R = H) displayed activity against LAI HIV-1 virus (IC_{50}, 0.251 μmol) and was not further tested against mutants. Introduction of a methyl group in 4-position (**23**) resulted in a reduction of activity. Decreased activity was also observed when the 4-position was substituted with a fluorine atom (**22**) or a CF_3 group (**26**). Modeling studies revealed that the hydrogen in position 4 (**21**) can undergo a favorable electrostatic interaction with the backbone carbonyl of H235 of the RT enzyme, whereas the corresponding fluorine compound (**22**) undergoes an unfavorable electrostatic interaction with the same carbonyl, explaining the lower activity of compound **22**. A similar difference occurs for the hydrogens in the methyl moiety of compound **23**, in contrast with the fluorines in the CF_3 of **26**; with the backbone hydrogen of H235, this partially explains the differences in activity. A second interaction especially relevant at this position is the dipole−dipole interaction with the backbone carbonyl of H235 and one of the CF bonds present in compound **26**, where there is no such interaction with one of the CH bonds in compound **23**. Moreover, in both compounds **23** and **26** steric factors diminish the interaction between the central ring system and a number of key residues of RT, yielding an overall negative effect on the activity. Increased activity was obtained for the 4-chloro compound **24**, which further showed a weak activity against the mutants L100I, K103N, and Y181C (IC_{50}, 5.012 μmol). A dramatic increase in activity could be observed in this small series for the cyano compound **29** (IC_{50}, <0.001 μmol against HIV-1 LAI virus. Moreover this compound displayed a clear activity against the mutants (IC_{50} < 0.400 μmol).

From modeling studies we learned that a small halogen substituent like fluorine that has no or low $\pi-\pi$ interaction with the C=O backbone of H235 had a negative effect on interaction energy, whereas a larger

Table 1. Antiviral Activity against Wild-type HIV-1 LAI Virus and a Panel of Single Mutant Strains of Pyrazinones with Substituent Variations of R on the Right Wing



						IC_{50} (umol)				
Compd	R	X	R1	R2	R3	LAI	100I	103N	181C	188L
21	H	O	CH_3	H	H	0.251	-	-	-	-
22	F	O	CH_3	H	H	1.258	>10	>10	>10	>10
23	CH_3	O	CH_3	H	H	>100	-	-	-	-
24	Cl	O	CH_3	H	H	0.025	5.012	5.012	5.012	>10
25	Cl	S	CH_3	CH_3	H	0.079	>10	>10	6.300	10.000
26	CF_3	O	CH_3	H	H	0.501	-	-	-	-
29	CN	O	CH_3	H	H	<0.001	0.316	0.032	0.159	0.398
31	CN	S	CH_3	CH_3	H	0.016	>10	0.631	1.000	0.631
35	Cl	O	H	H	CH_3	0.100	5.011	>10	>10	>10
36	CN	O	H	H	CH_3	0.005	0.398	0.398	2.511	0.631
38	Cl	O	CH_3	H	CH_3	0.126	3.981	3.981	>10	>10
39	Cl	S	CH_3	H	CH_3	0.501	-	-	-	-
40	CN	O	CH_3	CH_3	CH_3	0.005	0.050	0.158	0.501	0.200

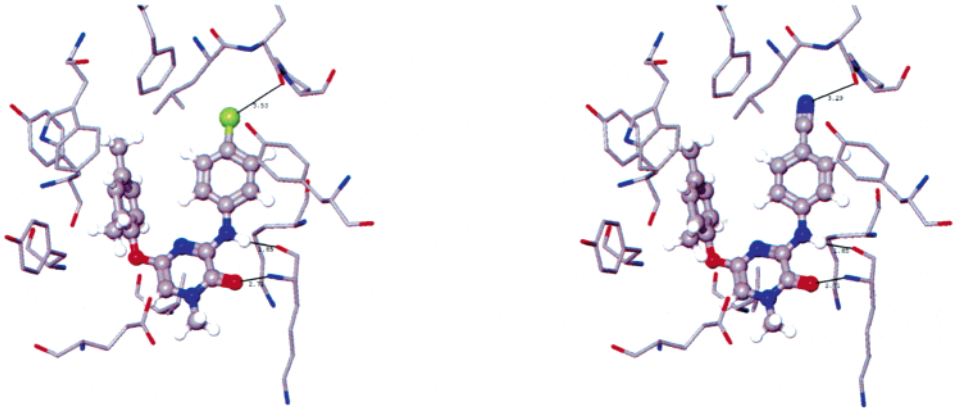


Figure 3. Compounds **24** and **29** docked into the HIV-1 NNRTI binding site.

chlorine atom which is closer to the backbone hydrogen of H235 and which has a more favorable $\pi-\pi$ interaction with the C=O backbone of H235 results in higher activity relative to a hydrogen substituent. A cyano group is an even better choice (Figure 3). In this case the cyano moiety is located in a subpocket of the RT enzyme in such a way that it experiences a strong dipole−dipole interaction with the backbone carbonyl of H235 in the RT enzyme, while its relatively small volume allows for an excellent orientation of the inhibitor inside the protein.

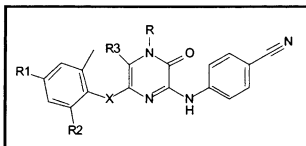
We concluded that in this series the cyano substituent in the 4-position of the aniline moiety is the optimal choice, similar to that observed in the DATA/DAPY compounds.[8,9]

Considering the 6-position in the pyrazinone ring, we compared compounds **27** (R^3 = H, Table 2) and **36** (R^3 = CH_3, Table 1). From this comparison it appears that on the level of wild-type HIV-1 LAI virus the presence of a 6-methyl group instead of hydrogen in the pyrazinone ring generally did not give much difference in activity, but there was a favorable effect on activity against the majority of the mutants.

Modification in the 1-position of the pyrazinone ring from R = CH_3 (**37**) to R = H (**44**) (Table 2) led to an equivalent activity against HIV-1 LAI virus but clearly induced superior activity against all four single mutants. Molecular modeling revealed that the 2-carbonyl moiety of the pyrazinone ring made a strong acceptor hydrogen bond with the backbone NH group of K101, whereas the aniline NH made a strong hydrogen donor bond with the backbone C=O group of K101.

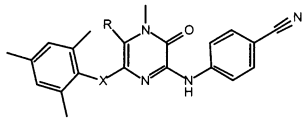
In analogy with the DATA/DAPY compounds, we introduced substituents in 2-, 2,4-, and 2,4,6-positions on the benzene ring of the left wing (5-position of pyrazinone ring; see Tables 1 and 2). An additional methyl substituent in the para-position (see compound **29** compared to **27**) not only induces an increase in activity against LAI virus but also against the different single mutants. In both compounds the phenyl ring of the left wing can undergo a perfect stacking interaction with the phenyl of Y181, which is responsible for a high interaction energy with nonmutated RT and can be associated with a high activity against LAI strain.[14] The additional methyl in the four position in compound **29** is responsible for an additional interaction with W229 in HIV-1 RT, resulting in a higher potency. In the case of the Y181C mutation, we lose the strong $\pi-\pi$ interaction energy, resulting in a serious decrease in activity against this mutant for both compounds. In the case of the L100I and Y188L mutations, steric hindrance factors play a major role in the decrease of activity. Against

Table 2. Antiviral Activity against Wild-type HIV-1 LAI Virus and a Panel of Single Mutant Strains of Pyrazinones with Substituent Variations of R1 and R2 on the Left Wing



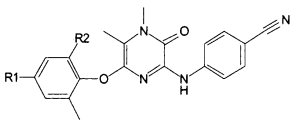
						IC_{50} (umol)				
Compd	R	X	R1	R2	R3	LAI	100I	103N	181C	188L
27	CH_3	O	H	H	H	0.004	1.259	0.794	2.512	1.995
28	CH_3	S	H	H	H	0.020	>10	>10	>10	>10
30	CH_3	S	CH_3	H	H	0.005	>10	>10	>10	>10
32	CH_2Ph	O	H	H	H	0.316	-	-	-	-
33	CH_2Ph	O	CH_3	H	H	0.032	0.631	0.631	1.585	>10
37	CH_3	S	H	H	CH_3	0.040	>10	>10	>10	>10
41	CH_3	O	CH_3	H	CH_3	0.003	0.025	0.032	0.063	0.158
42	CH_3	O	CN	CH_3	CH_3	0.006	0.006	0.006	0.025	0.006
44	H	S	H	H	CH_3	0.040	5.012	0.631	5.012	0.631

Table 3. Antiviral Activity against Wild-type HIV-1 LAI Virus and a Panel of Single Mutant Strains of Compounds with Modifications of X



			IC_{50} (umol)				
Compd	R	X	LAI	100I	103N	181C	188L
31	H	S	0.016	>10	0.631	1.000	0.631
40	CH_3	O	0.005	0.050	0.158	0.501	0.200
45	H	SO_2	0.008	>10	>10	0.398	>10
46	CH_3	SO_2	0.005	0.158	3.162	0.032	1.995

Table 4. Antiviral Activity against Wild-type HIV-1 LAI Virus and a Panel of Single and Double Mutant Strains of Some Pyrazinones and Reference Compound Efavirenz



			IC_{50} (umol)						
Compd	R1	R2	LAI	100I	103N	181C	188L	100I + 103N	103N + 181C
41	CH_3	CH_3	0.003	0.025	0.032	0.063	0.158	1.584	1.000
42	CN	CH_3	0.006	0.006	0.006	0.025	0.006	0.158	0.063
efavirenz			0.001	0.040	0.040	0.002	0.158	>10	0.040

the K103N mutant we lose interaction energy, but in the case of an additional interaction of the *p*-methyl in compound **29** with amino acid W229 in HIV-1 RT, there is a compensating mechanism, delivering a compound with acceptable activity against this mutant. The 2,4,6-trimethyl analogue (**40**) was less potent than the corresponding 2,4-dimethyl analogue (**41**) against LAI virus and the various mono mutants. Introduction of the 6-methyl moiety (**40**) limits the free rotation of the phenoxy group in the 5-position compared to compound **41**, reduces the stacking interaction with Y181, and subsequently reduces the activity on LAI virus. Substituting a cyano moiety (**42**) for the 4-methyl in compound **40** resulted in an equivalent activity against LAI virus, but this modification strongly enhanced the activity against the four single mutants. Modeling the substitution of the 4-methyl (**40**) with a cyano moiety indicated a strongly improved interaction with amino acid W229 of HIV-1 RT. This may explain the observed improvement of HIV activity to the mutants. Comparison of the antiviral activity of compound **42** with that of efavirenz shows that both compounds displayed an activity on the same order of magnitude against wild-type LAI virus. Against the single Y181C mutant efavirenz was more potent, but against mutants such as L100I, K103N, and Y188L, compound **42** was superior (see Table 4). The activity of both compounds against the K103N + Y181C double mutant was of the same order of magnitude. However, the picture dramatically changed against the double L100I + K103N viral mutant, where efavirenz demonstrated no activity even at concentrations up to 10 μmol, which was in contrast with compound **42** showing activity below 0.16 μmol. The nature of the connecting group (ether, thioether, or sulfonyl) between the left wing phenyl group and the 5-position of the pyrazinone ring had clear consequences for antiviral activity (**31**, **40**, **45**, and **46**; see Table 3). The compounds **31** (X = S) and **45** (X = SO_2) were virtually equipotent against LAI virus with a small difference in favor of the sulfonyl linker, which was only confirmed for the 181C

mutant. A methyl group in the 6-position (**46**) of the pyrazinone ring not only improved activity against LAI virus but activity against the 181C mutant also was significantly increased (IC_{50}, 0.032 μmol). Substituting the ether linkage (**40**) for SO_2 (**46**) had no effect on activity against LAI virus. On the other hand, activity against 100I, 103N, and 188L mutants increased by this modification but decreased against 181C mutant.

Experimental Section

Melting points were taken using an Electro-thermal IA 9000 digital melting apparatus and were uncorrected. Mass spectra were run using a Hewlett-Packard MS-Engine 5989A apparatus for EI and CI spectra and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10 000. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-250, a Bruker Avance 300, or a Bruker AMX 400 operating respectively at 250, 300, and 400 MHz for ^{1}H and 62.9, 75, and 100 MHz for ^{13}C. $CDCl_3$ and DMSO were taken as a solvent, and the ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS. Analytical and preparative thin-layer chromatography was carried out using Merck silica gel 60 PF-224. For column chromatography, 70−230 mesh silica gel 60 (E. M. Merck) was used as the stationary phase. Preparative HPLC was carried out on a Pre-packed RT 250−25 Lichrosorb si 60.7 μm column. All the isolated compounds have a purity of +98%.

3,5-Dibromo-1-methylpyrazin-2(1*H*)-one (6). Oxalyl bromide (8.82 g, 40 mmol) and DMF (0.5 mL) were successively added to a suspension of methylaminoacetonitrile hydrobromide **3** (3.02 g, 20 mmol) in CH_2Cl_2 (250 mL). The mixture was refluxed (oil bath 55 °C) for 24 h and then evaporated. Column chromatography of the residue over silica gel (eluent EtOAc/CH_2Cl_2 10/90) yielded compound **6** (4.7 g, 87%) as a solid: mp 98 °C (lit.[10] mp 98 °C).

3,5-Dibromo-1,6-Dimethylpyrazin-2(1*H*)-one (7). This was prepared from 2-(methylamino)propionitrile hydrobromide **4** (3.30 g, 20 mmol) and oxalyl bromide (8.82 g, 40.8 mmol) according to the procedure described for the synthesis of compound **6** to yield 3.9 g (69%) of compound **7** after column chromatography over silica gel (eluent, EtOAc/$CHCl_3$ 5/95): mp 120 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ 3.66 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 138.2, 136.0, 113.0, 34.3, 19.1; HR-MS calcd for $C_6H_6Br_2N_2O$ 279.8846 [$M^{+\bullet}$], found 279.8864.

1-Benzyl-3,5-dibromo-6-methylpyrazin-2(1*H*)-one (8). The same reaction procedure was used for the conversion of **5** (4.82 g, 20 mmol) with oxalyl bromide (8.64 g, 40 mmol). The yield of compound **8** after crystallization from EtOH was 4.30 g, 60%: mp 126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 5.38 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 138.5, 137.4, 134.2, 129.6, 128.7, 127.3, 114.1, 51.0, 19.3; HR-MS calcd for $C_{12}H_{10}Br_2N_2O$ 355.9159 [$M^{+\bullet}$], found: 355.9202.

General Procedure for the Preparation of 3-Phenylaminopyrazin-2(1*H*)-ones (10−20). A mixture of 3,5-dihalopyrazin-2-one (5 mmol), aniline (7.5 mmol), and 10-camphorsulfonic acid (5 mmol) in *i*-PrOH was refluxed for 48 h. After cooling the reaction mixture the precipitate was collected by filtration and successively washed with *i*-PrOH, aqueous potassium carbonate, water, and diethyl ether. The products were purified by column chromatography over silica gel.

4-(6-Bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)benzonitrile (10): yield 73%; mp 293−294 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (1H), 8.14 (d, *J* 8.8 Hz, 2H) 7.78 (d, *J* 8 Hz, 2H), 7.47 (s, 1H), 3.46 (3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.9, 146.8, 143.8, 133.3 121.9, 119.8, 119.7, 110.9, 104.4, 36.8; CI-MS 305 [M + H]$^+$.

4-(6-Bromo-4,5-dimethyl-3-oxo-3,4-dihydropyrazin-2-ylamino)benzonitrile (11): yield 84%; mp 254 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.13 (d, *J* 8.76 Hz, 2H), 7.76 (d, *J* 8.76 Hz, 2H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.5, 144.5, 141.1, 133.3, 127.7, 112.2, 119.7, 119.2, 103.9, 32.9, 18.4; HR-MS calcd for $C_{13}H_{11}BrN_4O$ 318.0116 [$M^{+\bullet}$], found 318.0127.

4-(4-Benzyl-6-bromo-5-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)benzonitrile (12): column chromatography (eluent CH_2Cl_2); yield 91%; mp 262 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.86 (d, *J* 8.8 Hz, 2H), 7.61 (d, *J* 8.8 Hz, 2H), 7.36−7.31 (m, 3H), 7.16 (d, *J* 6.6 Hz, 2H), 5.37 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 144.4, 142.8, 134.9, 133.7, 129.5, 126.8, 126.8, 126.3, 119.6, 118.9, 115.1, 105.9, 49.7, 18.6; HR-MS calcd for $C_{19}H_{15}BrN_4O$ 394.0429 [$M^{+\bullet}$], found 394.0419.

4-(4-Benzyl-6-bromo-3-oxo-3,4-dihydropyrazin-2-ylamino)benzonitrile (13): column chromatography (eluent CH_2Cl_2); yield 70%; mp 261 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.13 (d, *J* 8.7 Hz, 2H), 7.62 (s, 1H), 7.42−7.32 (m, 5H), 5.10 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.4, 147.2, 143.6, 136.2, 133.3, 129.0, 128.4, 128.3, 120.6, 119.8, 119.6, 111.6, 104.6, 52.0; HR-MS calcd for $C_{18}H_{13}BrN_4O$ 380.0153 [$M^{+\bullet}$], found 380.0160.

4-(4-Benzyl-6-chloro-5-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino)benzonitrile (14): column chromatography (eluent CH_2Cl_2/EtOAc 95/5); yield 80%; mp 254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.15 (d, *J* 8.8 Hz, 2H), 7.37−7.22 (m, 5H), 5.36 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.3, 144.3, 143.5, 135.5, 132.8, 127.3, 126.3, 124.5, 122.3, 119.2, 119.1, 103.8, 48.0, 15.5; HR-MS calcd for $C_{19}H_{15}ClN_4O$ 350.0934 [$M^{+\bullet}$], found 350.0931.

5-Bromo-3-phenylamino-1-methylpyrazin-2(1*H*)-one (15): column chromatography (eluent CH_2Cl_2/EtOAc 95/5); yield 71%; mp 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.75 (d, *J* 7.68 Hz, 2H), 7.36 (dd, *J* 7.68, 7.32 Hz, 2H), 7.09 (t, *J* 7.32, 1H), 6.74 (s, 1H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 147.1, 138.6, 129.4, 124.0, 119.5, 118.6, 114.4, 37.2; HR-MS calcd for $C_{11}H_{10}BrN_3O$ 279.0007 [$M^{+\bullet}$], found 279.0003.

5-Bromo-3-(4-fluorophenylamino)-1-methylpyrazin-2(1*H*)-one (16): column chromatography (eluent CH_2Cl_2/EtOAc 90/10); yield 53%; mp 201−202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.56 (s, 1H), 7.93 (2, 2H), 7.30 (s, 1H), 7.16 (s, 2H), 3.43 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 150.8, 147.1, 135.9, 121.8, 120.0, 115.4, 111.8, 36.6; CI-MS 298 [M + H]$^+$.

5-Bromo-3-(4-methylphenylamino)-1-methylpyrazin-2(1*H*)-one (17): yield 74%; mp 204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.63 (d, *J* 8.4 Hz, 2H), 7.16 (d, *J* 8.4 Hz, 2H), 6.72 (s, 1H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 147.1, 136.0, 133.7, 129.9, 119.5, 118.2, 114.4, 37.1, 21.3; HR-MS calcd for $C_{12}H_{12}BrN_3O$ 293.0163 [$M^{+\bullet}$], found 293.0197.

5-Bromo-3-(4-chlorophenylamino)-1-methylpyrazin-2(1*H*)-one (18): yield 53%; mp 259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.71 (d, *J* 8.8 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 6.77 (s, 1H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 146.9, 137.1, 129.4, 128.9, 120.7, 119.0, 114.0, 37.2; HR-MS calcd for $C_{11}H_9BrClN_3O$ 312.9617 [$M^{+\bullet}$], found 312.9670.

5-Bromo-1-methyl-3-[4-(trifluoromethyl)phenylamino]-pyrazin-2(1*H*)-one (19): column chromatography (eluent CH_2Cl_2/EtOAc 90/10); yield 59%; mp 198−199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.15 (d, *J* 8.15 Hz, 2H), 7.69 (d, *J* 8.78 Hz, 1H), 7.69 (s, 2H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.9, 146.9, 143.1, 126.1, 124.7, 123.1, 121.4, 119.8, 112.2, 36.7; CI-MS 348 [M + H]$^+$.

5-Bromo-3-(4-chlorophenylamino)-1,6-dimethylpyrazin-2-(1*H*)-one. (20): column chromatography (eluent CH_2Cl_2/EtOAc 95/5). Yield 70%; mp 216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.69 (d, *J* 8.8 Hz, 2H), 7.30 (d, *J* 8.8 Hz, 2H), 3.60 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2 144.4, 137.6, 129.4, 128.2, 124.6, 120.2, 114.9, 33.1, 18.7; HR-MS calcd for $C_{12}H_{11}BrClN_3O$ 326.9774 [$M^{+\bullet}$], found 326.9779.

General Procedure for the Preparation of Compounds 21−41. A mixture of pyrazinone **10−20** (0.75 mmol), substituted phenol or benzenethiol Ar-XH (1.5 mmol), cesium carbonate (1.5 mmol), copper(I) chloride (30−50 mg), and 3−5 drops of ethyl acetate in toluene (50 mL) was heated at 120

°C for 3−48 h. After evaporation of the solution, the residue was purified by column chromatography and when necessary further recrystallization or HPLC to give pure compounds **21**−**41**.

5-(2,4-Dimethylphenoxy)-1-methyl-3-(phenylamino)-pyrazin-2-(1*H*)-one (21): column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc: 2/3); yield 28%, solid; mp 166−166.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.63 (d, *J* 8.06 Hz, 2H), 7.25 (m, 2H), 6.99 (m, 4H), 6.15 (s, 1H), 3.51 (s, 3H), 2.34 (s, 3H), 2.25 (s, 3H); CI-MS *m/z* 322 $[M + H]^+$. Anal. ($C_{19}H_{19}N_3O_2$) C, H, N.

5-(2,4-Dimethylphenoxy)-3-(4-fluorophenylamino)-1-methylpyrazin-2(1*H*)-one (22): column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc 2/3); yield 20%, solid; mp 151−152 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.59 (m, 2H), 7.06 (s, 1H), 6.94 (m, 4H), 6.15 (s, 1H), 3.49 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H); CI-MS *m/z* 340 $[M + H]^+$. Anal. ($C_{19}H_{18}FN_3O_2$) C, H, N.

5-(2,4-Dimethylphenoxy)-3-(*p*-toluidino)-1-methylpyrazin-2(1*H*)-one (23). Column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc: 2/3); yield 25%, solid; mp 153.5−155 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.51 (d, *J* 8.5 Hz, 2H), 6.99 (m, 5H), 6.12 (s, 1H), 3.49 (s, 3H), 2.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.4, 150.5, 145.9, 136.6, 136.1, 133.8, 1131.9, 129.7, 129.4, 127.4, 120.1, 118.9, 102.4, 37.1, 20.8, 20.7, 16.2; CI-MS *m/z* 336 $[M + H]^+$. Anal. ($C_{20}H_{21}N_3O_2$) C, H, N.

5-(2,4-Dimethylphenoxy)-3-(4-chlorophenylamino)-1-methylpyrazin-2(1*H*)-one (24): column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc 2/3); yield 28%, solid; mp 180−181 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.56 (m, *J* 8.85 Hz, 2H), 7.18 (d, *J* 8.85, 2H), 7.08 (s, 1H), 7.00 (d, *J* 7.5 Hz 1H), 6.90 (d, *J* 7.5 Hz 1H), 6.19 (s, 1H), 3.51 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H); CI-MS *m/z* 356 $[M + H]^+$. Anal. ($C_{19}H_{18}ClN_3O_2$) C, H, N.

5-Mesitylthio-3-(4-chlorophenylamino)-1-methylpyrazin-2-(1*H*)-one (25): column chromatography (eluent CH_2Cl_2/AcOAc 95/5); yield 58%, solid; mp 224−225 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.42 (d, *J* 8.9 Hz, 2H), 7.13 (d, *J* 8.9 2H), 7.02 (s, 2H), 6.39 (s, 1H), 3.46 (s, 3H), 2.46 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.7, 150.5, 145.8, 143.8, 139.3, 137.4, 130.9, 129.2, 129.1, 128.6, 126.7, 119.9, 115.3, 37.0, 21.9, 21.1; CI-MS *m/z* 386 $[M + H]^+$. Anal. ($C_{20}H_{20}ClN_3OS$) C, H, N.

5-(2,4-Dimethylphenoxy)-1-methyl-3-[4-(trifluoromethyl)phenylamino]pyrazin-2(1*H*)-one (26): column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc 2/3); yield 10%, solid; mp 147−148 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 8.54 (s, 1H), 7.71 (d, *J* 8.5 Hz, 2H), 7.45 (d, *J* 8.5 Hz, 2H), 7.09 (d, *J* 1.86 Hz, 1H), 7.01 (dd, *J* 8.10, 1.86 Hz, 1H), 6.90 (d, *J* 8.10, 1H), 6.26 (s, 1H), 3.52 (s,3H), 2.44 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.2, 150.3, 145.5, 145.4, 141.6, 134.1, 131.9, 129.7, 127.4, 126.0, 124.5, 124.2, 120.0, 118.4, 103.8, 37.3, 20.7, 26.1, 16.1; CI-MS *m/z* 390 $[M + H]^+$. Anal. ($C_{20}H_{18}F_3N_3O_2$) C, H, N.

4-[4-Methyl-3-oxo-6-(*o*-tolyloxy)-3,4-dihyropyrazin-2-ylamino]benzonitrile (27): column chromatography (eluent CH_2Cl_2/AcOAc 9/1), followed by HPLC (hexanes/EtOAc 2/3); yield 25%, solid; mp 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.65 (d, *J* 8.8 Hz, 2H), 7.46 (d, *J* 8.8 Hz, 2H), 7.28 (d, *J* 7.4 Hz, 1H), 7.20 (dd, *J* 7.8, 7.4 Hz, 1H), 7.15 (t, *J* 7.4, 1H), 6.99 (d, *J* 7.8, 1H), 6.40 (s, 1H), 3.56 (s,3H), 2.28 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 150.3, 145.2, 144.9, 142.4, 133.1, 131.4, 130.17, 127.0, 124.6, 120.1, 119.1, 118.7, 105.5, 104.9, 37.4, 16.2; CI-MS *m/z* 333 $[M + H]^+$. Anal. ($C_{19}H_{16}N_4O_2$) C, H, N.

4-[4-Methyl-3-oxo-6-(*o*-tolylthio)-3,4-dihydropyrazin-2-ylamino]benzonitrile (28): column chromatography (eluent CH_2Cl_2/AcOAc 95/5), followed by HPLC (hexanes/EtOAc 2/3); yield 30%, solid; mp 242.7−243.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.53 (d, *J* 8.78 Hz, 2H), 7.39 (d, *J* 8.42 Hz, 3H), 7.21−7.09 (m, 3H), 6.77 (s, 1H), 3.47 (s,3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.7, 142.5, 140.2, 133.3, 131.1, 132.6 130.6, 128.5, 128.3, 126.6, 120.5, 119.2, 118.6, 105.4, 37.1, 20.7; CI-MS *m/z* 349 $[M + H]^+$. Anal. ($C_{19}H_{16}N_4OS$) C, H, N.

4-[6-(2,4-Dimethylphenoxy)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (29): column chromatography (eluent CH_2Cl_2/EtOAc 9/1), followed by HPLC (hexane/EtOAc 2/3); yield 22%, solid; mp 200.5−202 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.70 (d, *J* 8.8 Hz, 2H), 7.46 (d, *J* 8.8 Hz, 2H), 7.09 (s, 1H), 7.01 (d, *J* 7.3 Hz, 1H), 6.90 (d, *J* 7.3 Hz, 1H), 6.31 (s, 1H), 3.54 (s,3H), 2.36 (s, 3H) 2.24 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.0, 150.2, 145.2, 145.1, 140.2, 142.4, 134.3, 133.1, 131.9, 129.8, 127.5, 120.1, 119.1, 118.7, 105.5, 104.4, 37.4, 20.7; CI-MS *m/z* 347 $[M + H]^+$. Anal. ($C_{20}H_{18}N_4O_2$) C, H, N.

4-[6-(2,4-Dimethylphenylthio)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (30): column chromatography (eluent CH_2Cl_2/AcOAc 95/5), followed by HPLC (hexanes/EtOAc: 2/3); yield 40%, solid; mp 231−232 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.63 (d, *J* 8.7 Hz, 2H), 7.47 (d, *J* 8.7 Hz, 2H), 7.40 (d, *J* 7.89 Hz 1H), 7.12 (s, 1H), 7.03 (d, *J* 7.89 Hz, 1H), 6.74 (s, 1H), 3.52 (s,3H), 2.43 (s, 3H) 2.36 (s, 3H); CI-MS *m/z* 363 $[M + H]^+$. Anal. ($C_{20}H_{18}N_4OS$) C, H, N.

4-[6-(Mesithylthio)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (31): column chromatography (eluent hexane/EtOAc 2/3); yield (33%); solid; mp 273−275 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.54 (d, *J* 8.8 Hz, 2H), 7.45 (d, *J* 8.8 Hz, 2H), 7.04 (s, 2H), 6.50 (s, 1H), 3.50 (s, 3H), 2.48 (s, 6H), 2.35 (s, 3H); CI-MS *m/z* 377 $[M + H]^+$. Anal. ($C_{21}H_{20}N_4OS$) C, H, N.

4-[4-Benzyl-3-oxo-6-(*o*-tolyloxy)-3,4-dihydropyrazin-2-ylamino]benzonitrile (32): yield 25%; mp 199 °C; reaction time 48 h; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.60 (d, *J* 8.82 Hz, 2H), 7.45 (d, *J* 8.82 Hz, 2H), 7.38−7.33 (m, 5H), 7.28−7.22 (m, 1H), 7.20−7.07 (m, 2H), 6.93 (d, *J* 8.0, 1H), 6.46 (s, 1H), 5.10 (s, 2H), 2.25 (s, 3H); HR-MS calcd for $C_{25}H_{20}N_4O_2$ 408.1586 $[M^{+\bullet}]$, found 408.1580. Anal. ($C_{25}H_{20}N_4O_2$) C, H, N.

4-[4-Benzyl-3-oxo-6-(2,4-dimethylphenoxy)-3,4-dihydropyrazin-2-ylamino]benzonitrile (33): yield 12.5%; mp 175 °C; reaction time 48 h; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.63 (d, *J* 8.8 Hz, 2H), 7.36 (d, *J* 8.8 Hz, 2H), 7.38−7.32 (m, 5H), 7.07 (s, 1H), 7.02 (d, *J* 8.0, 1H), 6.86 (d, *J* 8.0, 1H), 6.39 (s, 1H), 5.10 (s, 2H), 2.35 (s, 3H), 2.25 (s, 3H); HR-MS calcd for $C_{26}H_{22}N_4O_2$ 422.1743 $[M^{+\bullet}]$, found 422.1737. Anal. ($C_{26}H_{22}N_4O_2$) C, H, N.

4-[6-(Mesitylthio)-4,5-dimethyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (34): yield 33%; mp 226−227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.28 (d, *J* 8.8 Hz, 2H), 7.20 (d, *J* 8.8, 2H), 7.04 (s, 2H), 3.60 (s, 3H), 2.53 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 144.2, 143.8, 142.9, 139.0, 132.8, 128.9, 128.1, 127.4, 123.4,119.5, 118.0, 104.2, 32.0, 22.0, 21.1, 15.6; CI-MS *m/z* 391 $[M + H]^+$. Anal. ($C_{22}H_{22}N_4OS$) C, H, N.

3-(4-Chlorophenylamino)-1,6-dimethyl-5-(2-methylphenoxy)pyrazin-2(1*H*)-one (35): yield 35%; mp 222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.40 (d, *J* 9.15 Hz, 2H), 7.25 (d, *J* 7.32 Hz, 1H), 7.18−7.03 (m, 4H), 6.85 (dd, *J* 8.07, 1.1 Hz, 1H), 3.62 (s,3H), 2.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 151.6, 143.6, 141.4, 137.9, 131.4, 129.6, 129.1, 127.5, 127.1, 123.7, 119.8, 118.8, 112.9, 32.3, 16.7, 12.7; HR-MS calcd for $C_{19}H_{18}ClN_3O_2$ 355.1087 $[M^{+\bullet}]$, found 355.1080. Anal. ($C_{19}H_{18}ClN_3O_2$) C, H, N.

4-[4,5-Dimethyl-3-oxo-6-(*o*-tolyloxy)-3,4-dihyropyrazin-2-ylamino]benzonitrile (36): yield 40%; mp 236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.50 (d, *J* 8.8 Hz, 2H), 7.39 (d, *J* 8.8 Hz, 2H), 7.27 (d, *J* 9.1 Hz, 1H), 7.20−7.07 (m, 2H), 6.85 (d, *J* 8.0 Hz, 1H), 3.64 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 151.4, 143.1, 143.0, 141.3,-133.4, 131.5, 129.8, 127.1, 124.1, 119.6, 119.1, 118.5, 114.5, 105.1, 32.4, 16.7, 12.8; HR-MS calcd for $C_{20}H_{18}N_4O_2$ 346.1430 $[M^{+\bullet}]$, found 346.1436. Anal. ($C_{20}H_{18}N_4O_2$) C, H, N.

4-[4,5-Dimethyl-3-oxo-6-(*o*-tolylthio)-3,4-dihyropyrazin-2-ylamino]benzonitrile (37): yield 47%; mp 240 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.42−7.20 (m, 8H), 3.62 (s, 3H), 2.54 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ

151.7, 144.8, 143.2, 140.9,134.0, 133.4, 133.2, 130.9, 128.5, 127.3, 126.9, 126.8, 119.1, 118.5, 104.9, 32.7, 21.2, 17.0; HR-MS calcd for $C_{20}H_{18}N_4OS$: 362.1201 [$M^{+\bullet}$], found 362.1202. Anal. ($C_{20}H_{18}N_4OS$) C, H, N.

3-(4-Chlorophenylamino)-5-(2,4-dimethylphenoxy)-1,6-dimethylpyrazin-2(1*H*)-one (38): yield 25%; mp 214 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.41 (d, *J* 9.15 Hz, 2H), 7.06−7.01 (m, 1H), 6.94 (d, *J* 8.07 Hz, 1H), 6.74 (d, *J* 8.07 Hz, 1H), 3.61 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 151.5, 143.5, 141.6, 138.0, 133.1, 132.0, 129.3, 129.0, 127.4, 119.8, 118.8, 112.8 104.9, 32.2, 21.1, 16.7, 12.7; HR-MS calcd for $C_{20}H_{20}ClN_3O_2$ 369.1244 [$M^{+\bullet}$], found 369.1242. Anal. ($C_{20}H_{20}ClN_3O_2$) C, H, N.

3-(4-Chlorophenylamino)-5-(2,4-dimethylphenylthio)-1,6-dimethylpyrazin-2(1*H*)-one (39). yield 40%; mp 213 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.35−7.25 (m, 3H), 7.10−7.01 (m, 4H), 3.59 (s, 3H), 2.51 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.8, 145.1, 141.0, 138.5, 138.0, 134.6, 131.7, 129.8, 128.9, 127.6, 127.2, 125.4, 119.8, 32.5, 21.5, 21.2, 16.8; HR-MS calcd for $C_{20}H_{20}ClN_3OS$: 385.1016 [$M^{+\bullet}$], found 385.1016. Anal. ($C_{20}H_{20}ClN_3OS$) C, H, N.

4-[6-(2,4,6-Trimethylphenoxy)-4,5-dimethyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (40): The synthesis of compound **40** was accomplished following the general procedure described using a large excess of 2,4,6-trimethylphenol (5 equiv) and cesium carbonate (5 equiv). Purification after column chromatography (eluent heptane/EtOAc 2/3) gave a solid: mp 220 °C, yield 27%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.28 (m, 4H), 6.94 (s, 2H), 3.65 (s, 3H), 2.49 (s, 3H), 2.49 (s, 3H), 2.37 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.3, 142.9, 142.9, 142.1, 142.0, 134.3, 132.8, 131.3, 129.0, 119.4, 117.9, 110.4, 104.4, 32.0, 20.8, 16.5, 12.1; CI-MS *m/z* 375 [M + H]$^+$. Anal. ($C_{22}H_{22}N_4O_2$) C, H, N.

4-[6-(2,4-Dimethylphenoxy)-4,5-dimethyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (41): yield 35%; mp 208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.52 (d, *J* 8.76 Hz, 2H), 7.39 (d, *J* 8.76, 2H), 7.08 (s, 1H), 6.97 (d, *J* 8 Hz, 1H), 6.74 (d, *J* 8 Hz, 1H), 3.64 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 151.4, 143.2, 142.9, 141.5, 133.5, 133.4, 132.1, 129.5, 127.5, 119.7, 119.1, 118.5, 114.2, 105.1, 32.4, 21.1, 16.7, 12.9; HR-MS calcd for $C_{21}H_{20}N_4O_2$ 360.1586 [$M^{+\bullet}$], found 360.1591. Anal. ($C_{21}H_{20}N_4O_2$) C, H, N.

4-[3,4-Dimethyl-5-oxo-6-(4-cyanophenylamino)-4,5-dihydropyrazin-2-yloxy]-3,5-dimethylbenzonitrile (42). A mixture consisting of **11** (0.240 g, 0.75 mmol), 4-hydroxy-3,5-dimethylbenzonitrile (0.220 g, 1.50 mmol), cesium carbonate (0.344 g, 1.05 mmol), copper(I) chloride (0.040 g, 2 mmol), 1-naphthoic acid (0.180 g, 1.05 mmol), and molecular sieves 4 Å (0.20 g) was refluxed for 6 days. After evaporation under diminished pressure, the residue was first purified by column chromatography (silica gel, 15% ethyl acetate, 85% CH_2Cl_2) and then by HPLC (40% hexane, 60% ethyl acetate) to give 0.028 g (10%) of **42**: mp 287−290 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.47 (s, 2H), 7.33 (d, *J* 8.79, 2H), 7.22 (d, *J* 8.79 Hz, 2H), 3.66 (s, 3H), 2.49 (s, 3H), 2.19 (s, 6H); CI-MS *m/z* 386 [M + H]$^+$. Anal. ($C_{22}H_{19}N_5O_2$) C, H, N.

4-[4-Benzyl-5-methyl-3-oxo-6-(*o*-tolylthio)-3,4-dihydropyrazin-2-ylamino]benzonitrile (43). To a solution of intermediate **14** (0.7 g, 2 mmol) in dry NMP (10 mL) was added freshly distilled 2-methylbenzenethiol (0.523 g, 4 mmol) in a two-necked round-bottomed flask under a slow flow of nitrogen. Subsequently solid cesium carbonate (1.638 g, 5 m mol) was added with stirring and the reaction mixture was heated in an oil bath at 130 °C for 3 h. After cooling to room temperature the solution was evaporated under reduced pressure. The residue was treated with water and was extracted three times with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and evaporated in a vacuum. Purification by column chromatography (eluent, CH_2Cl_2/EtOAc 90/10) gave 0.525 g (60%) of **43**: mp 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.45−7.15 (m, 13H), 5.32 (s, 2H), 2.47 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 144.8, 142.7, 140.8, 134.9, 134.0, 133.0, 32.7, 130.6, 129.1, 128.3, 128.0, 127.1, 126.5, 126.4, 119.6, 118.1, 104.7, 49.0, 20.8, 16.3; HR-MS calcd for $C_{26}H_{22}N_4OS$ 438.1514 [$M^{+\bullet}$], found 438.1518. Anal. ($C_{26}H_{22}N_4OS$) C, H, N.

4-[5-Methyl-3-oxo-6-(o-tolylthio)-3,4-dihydropyrazin-2-ylamino]benzonitrile (44). To a solution of **43** (0.438 g, 1 mmol) in dry *o*-dichlorobenzene was added $AlCl_3$ (0.134 g, 1 mmol) with stirring under nitrogen. After the addition was complete, the reaction mixture was heated (oil bath) at 160 °C for 6 h. After cooling the reaction mixture was treated with water very carefully to decompose residual $AlCl_3$, followed by extraction with CH_2Cl_2, drying over $MgSO_4$, filtration, and evaporation in a vacuum. Crystallization from ethyl acetate yielded 0.104 g (30%) of **44**: mp 290−291°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.4 (s, 1H), 9.62 (s, 1H), 7.89 (d, *J* 8.7 Hz, 2H), 7.54 (d, *J* 8.7 Hz, 2H), 7.29−7.09 (m, 4H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.6, 146.3, 144.4, 137.7, 134.7, 132.9, 130.6, 130.4, 127.1, 127.0, 118.9, 130.1, 120.9, 119.8, 103.2, 20.3, 16.6; HRMS calcd for $C_{19}H_{16}N_4OS$ 348.1045 [$M^{+\bullet}$], found 348.1044. Anal. ($C_{19}H_{16}N_4OS$) C, H, N.

4-[6-(Mesitylsulfonyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (45). A solution of **31** (0.097 g, 0.26 mmol) in CH_2Cl_2 was stirred with 3-chloroperbenzoic acid (0.103 g, 0.52 mmol) during 24 h at room temperature. The reaction mixture was washed with an aqueous potassium carbonate solution, followed by drying over $MgSO_4$, filtration, and evaporation in a vacuum. The residue was purified by column chromatography (silica gel, eluent 10% ethyl acetate 90% CH_2Cl_2) to give 0.06 g of **45** (57% yield): mp 313−314 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.76 (s, 1H), 7.61 (d, *J* 9.0 Hz, 2H), 7.53 (d, *J* 9.0 Hz, 2H), 7.02 (s, 2H), 3.66 (s,3H), 2.71 (s, 6H) 2.33 (s, 3H); CI-MS *m/z* 409 [M + H]$^+$. Anal. ($C_{21}H_{20}N_4O_3S$) C, H, N.

4-[6-(Mesitylsulfonyl)-4,5-dimethyl-3-oxo-3,4-dihydropyrazin-2-ylamino]benzonitrile (46). Compound **46** was prepared from compound **34** according to the reaction procedure described for **45**: yield 31%; mp 282−284 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.30 (d, *J* 8.8 Hz, 2H), 7.14 (d, *J* 8.8 Hz, 2H), 7.06 (s, 2H), 3.64 (s,3H), 2.85 (s, 3H) 2.59 (s, 3H); CI-MS *m/z* 423 [M + H]$^+$. Anal. ($C_{22}H_{22}N_4O_3S$) C, H, N.

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Supporting Information Available: Analysis data for compounds **21**−**46**. This material is available free of charge via the Internet at http://pubs.acs.org.

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