Tetrahedron 64 (2008) 8128–8133

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of pyrazino[1,2-*a*]benzimidazol-1(2*H*)ones via a microwave assisted Buchwald–Hartwig type reaction

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ARTICLE INFO

Article history:
Received 10 June 2008
Accepted 16 June 2008
Available online 20 June 2008

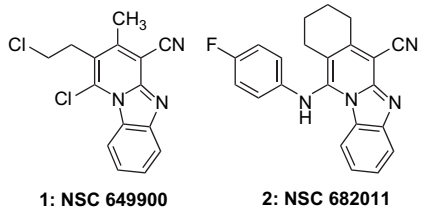
Keywords:
Buchwald–Hartwig reaction
Pyrazinone
Microwave chemistry

ABSTRACT

A convenient synthesis of substituted pyrazino[1,2-*a*]benzimidazol-1(2*H*)ones starting from 3,5-dichloropyrazinones has been accomplished. Various 3-anilino-pyrazinones were easily converted to the desired tricyclic structures by applying a microwave assisted Buchwald–Hartwig type cyclization.

1. Introduction

Benzimidazoles constitute an important class within the known drugs, e.g., the neuroleptics pimozide[1] and droperidol,[2] and the highly efficient anti-ulcer agent omeprazole.[3] As for the benzimidazoles fused with aza-aromatic ring systems, mostly pyrido[1,2-*a*]benzimidazole derivatives have been reported, showing antiviral,[4] antimicrobial,[5] and antiproliferative[6] activities. In vitro screening by the NCI (National Cancer Institute, Bethesda, MD, USA) for new anticancer agents, showed product **1** (NSC 649900, Fig. 1) to be a promising lead.[7] In a similar study, significant in vitro activity against leukemia cell lines was found for the 5-arylamino-tetrahydrobenzimidazo[1,2-*b*]isoquinolines. The *p*-fluorophenylamino derivative **2** (NSC 682011, Fig. 1) was identified as the most active candidate in this series.[8]



1: NSC 649900 2: NSC 682011

Figure 1. Pyrido[1,2-*a*]benzimidazoles **1** and **2**, showing in vitro activity against some leukemia and cancer cell lines.

Though no explanation was given by the authors, this could be attributed to the strong electronegativity of the F-atom.[9] At the molecular level this causes a change in lipophilicity, different electrostatic interactions between molecules and inhibition of some metabolic pathways. At the physiological level this is manifested by an improved bioavailability, increased selectivity for target organs and in most cases a much lower effective dose compared to non-fluorinated analogs.

Recently pyrazino[1,2-*a*]benzimidazole derivatives **3** (Fig. 2) with notable anticancer activity and potency against leukemia have been described,[10] but the area of these tricyclic systems remains largely unexplored.

As part of our ongoing research toward the design of new pyrazinone containing compounds,[11] we wanted to develop an efficient route for the synthesis of structures **4** (Fig. 2), possessing a strong structural similarity with **3**. Bearing in mind the beneficial influence of F-atoms on the lipophilicity, a synthetic pathway should be found that allows a broad substitution pattern, including one or more F-atoms.

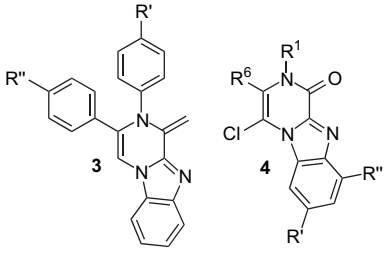


Figure 2. Pyrazino[1,2-*a*]benzimidazole derivatives **3** with anticancer activity and the proposed benzimidazolone analogs **4**.

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doi:10.1016/j.tet.2008.06.056

2. Results and discussion

For this study we chose dichloropyrazinones **5**, **6**, and **7** (Table 1) as starting compounds. These systems can be prepared in good to excellent yields starting from commercially available products.[12] Introduction of the (commercially available) anilino substituent at the reactive 3-position of the pyrazinones was performed by a method adapted from the literature, using camphorsulfonic acid (CSA) as acid catalyst.[13] The results of this procedure, given in Table 1, suggest that both sterical and electronic factors influence the coupling reaction.

Referring to *o*-bromoanilino pyrazinone **8a** as the parent compound (Table 1, entry 1), it is obvious that electron withdrawing groups in *para*-position of the aniline's nitrogen atom lower the yield of the substitution reaction. This is due to a decrease in nucleophilicity of the nitrogen atom, most noticeably in the case of a CF_3 (Table 1, entry 3) and a CN (Table 1, entry 4) substituent. This observation is consistent with the yields reported in Heeres et al. for dibromopyrazinones.[13]

Besides electronic factors, sterical hindrance plays an important role as well. Substitution of the hydrogen atom in *ortho*-position of the NH_2 group with a methyl group causes a significant 20% drop in yield from 71% (Table 1, entry 6) to 51% (Table 1, entry 5). Compound **8b** (Table 1, entry 2) was recrystallized from methanol and characterized by single-crystal X-ray analysis, confirming the NMR data. An ORTEP representation of the structure of **8b** is given in Figure 3.

The next step in our approach was cyclization of these key precursors via a Buchwald–Hartwig type reaction. Traditionally a Buchwald–Hartwig reaction[14] requires long reaction times in high boiling solvents. Strongly hindered phosphine ligands are very often used to improve yields. A very elegant synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole (and its benzo- and aza-analogs) using either BINAP or xanthphos in combination with $Pd(OAc)_2$ and cesium carbonate as base, has been described by Loones et al.[15a] During a follow-up paper, reporting the synthesis of similar dipyrido[1,2-*a*:2′,3′-*d*]imidazoles, it was found that cyclization required an elevated temperature of 140 °C (or alternatively switching to a Cu-catalyst).[15b]

In our case, the intramolecular reaction was performed using the method described by Venkatesh et al. for the synthesis of

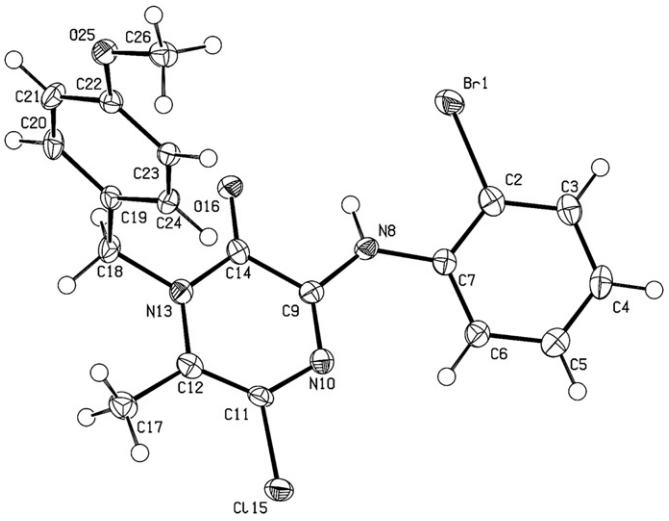
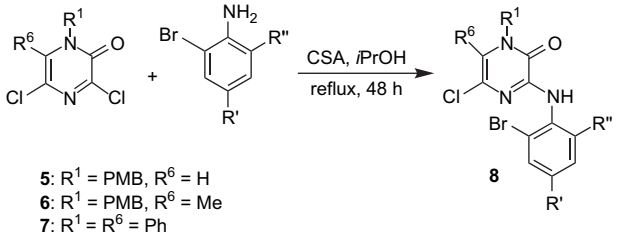


Figure 3. ORTEP representation of **8b** with thermal displacement ellipsoids shown at the 50% probability level.

benzimidazo[1,2-*a*]quinolines.[16] In this publication the best results were obtained using $Pd(PPh_3)_4$ as a catalyst and potassium carbonate as base. However, under these optimized conditions, still a reaction time of 12 h was necessary for the reaction to go to completion. This prompted us to adapt this procedure to microwave conditions, since in the course of the past years, microwave chemistry[17] has proven its usefulness in the decoration of the pyrazinone scaffold.[18]

Representative reactions were performed in a mono-mode microwave reactor that enables rapid heating of reaction mixtures in sealed vials under controlled conditions with simultaneous monitoring of real-time pressure and temperature. Using a maximum power of 150 W, precursors **8a**–**k** were stirred at 150 °C for 25 min with 10% $Pd(PPh_3)_4$ and anhydrous potassium carbonate in DMF (large volume to ensure high dilution, see Table 2). The high

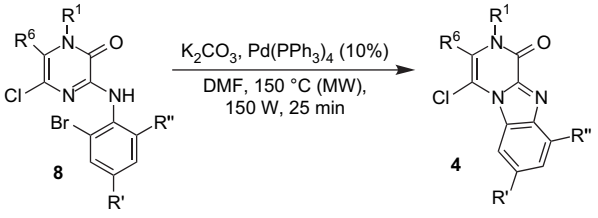
Table 1
Synthesis of compounds **8a**–**k**[a]



Entry	R^1	R^6	R′	R″	Product **8**	Yield[b] (%)
1	PMB	H	H	H	**a**	76
2	PMB	Me	H	H	**b**	78
3	PMB	H	CF_3	H	**c**	46
4	PMB	H	CN	H	**d**	42
5	PMB	H	Me	Me	**e**	51
6	PMB	H	Me	H	**f**	71
7	PMB	H	OCF_3	H	**g**	57
8	PMB	H	F	H	**h**	61
9	PMB	H	F	F	**i**	59
10	PMB	H	F	Cl	**j**	55
11	Ph	Ph	H	H	**k**	82

[a] Reaction conditions: dichloropyrazinones **5**, **6**, or **7** (1 mmol), *o*-bromoanilino derivative (1.5 mmol), camphorsulfonic acid (1 mmol), and isopropanol, reflux, 48 h.
[b] Isolated yield of purified product.

Table 2
Synthesis of compounds **4a**–**k**[a]



Entry	R^1	R^6	R′	R″	Product **4**	Yield[b] (%)
1	PMB	H	H	H	**a**	68
2	PMB	Me	H	H	**b**	70
3	PMB	H	CF_3	H	**c**	62
4	PMB	H	CN	H	**d**	24
5	PMB	H	Me	Me	**e**	67
6	PMB	H	Me	H	**f**	74
7	PMB	H	OCF_3	H	**g**	66
8	PMB	H	F	H	**h**	61
9	PMB	H	F	F	**i**	62
10	PMB	H	F	Cl	**j**	61
11	Ph	Ph	H	H	**k**	78

[a] Reactions were performed in 10 mL glass vials sealed with an aluminum/Teflon® crimp top containing **8a**–**k** (0.1 mmol), K_2CO_3 (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), and DMF (3 mL). The mixture was irradiated at 150 °C for 25 min, using an irradiation power of 150 W and was cooled to 50 °C by gas jet cooling before the vial was opened.
[b] Isolated yield of purified product.

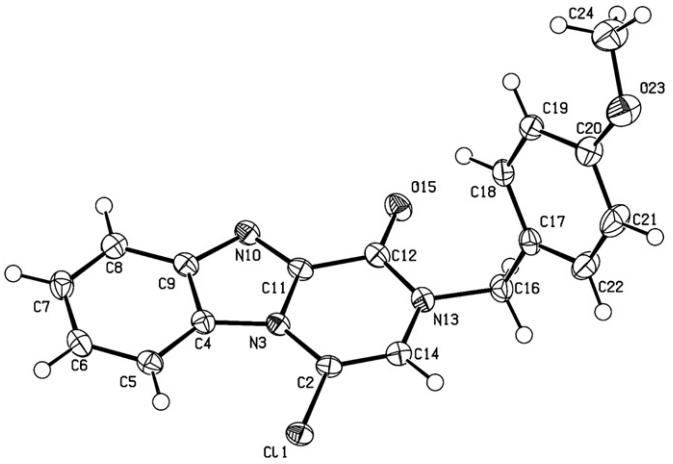


Figure 4. ORTEP representation of **4a** with thermal displacement ellipsoids shown at the 50% probability level.

temperature requirement, pointed out in previous publications,[15,16] is met by using dimethylformamide as solvent.

As an example, the desired tricyclic product **4a** (Table 2, entry 1) was isolated with 68% yield. X-ray crystallography of this fused system (crystallized from chloroform) confirmed the anticipated structure (Fig. 4).

The probable mechanism, as suggested by Venkatesh et al., proceeds via a six-membered palladacycle. Reductive elimination of this species, accompanied by N–C bond formation leads to the desired pyrazino[1,2-*a*]benzimidazol-1(2*H*)ones (Fig. 5).[16]

This cyclization reaction was successfully performed on all anilino pyrazinones, as shown in Table 2. The wide range of variation, tolerating not only mono- but disubstitution as well, proves the general usefulness of this reaction, as most products can be obtained in good yields. Also in this case, electron withdrawing functionalities seem to cause a slight decrease in yield. In the case of a CN group in *para*-position, a dramatic decrease in yield was noted. Upon standing, the resulting compound **4d** decomposed completely. Substitution of the hydrogen atom in *ortho*-position does not affect the cyclization efficiency of the reaction. Compound **4k** crystallized spontaneously from $CDCl_3$, enabling further characterization of this compound by single-crystal X-ray crystallography (Fig. 6).

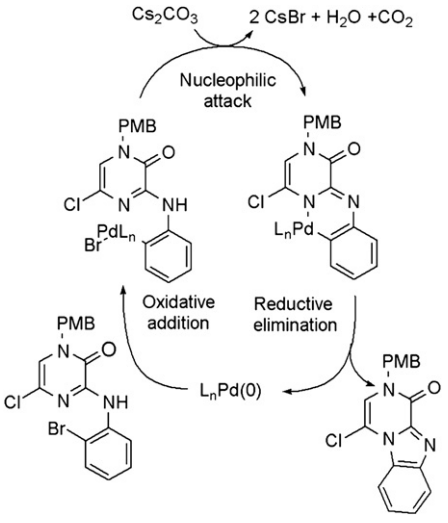


Figure 5. Reaction mechanism of the Buchwald–Hartwig type cyclization of **8a**.

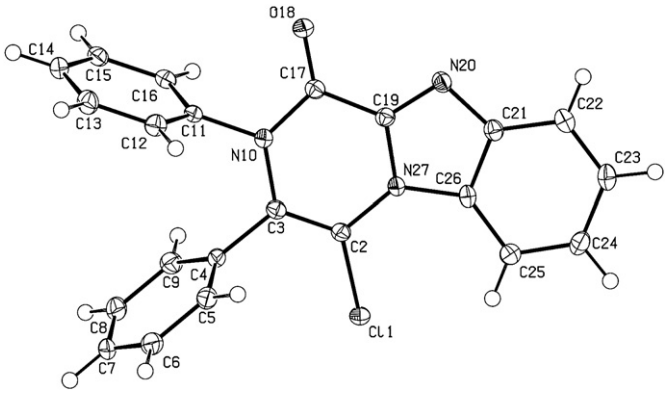


Figure 6. ORTEP representation of **4k** with thermal displacement ellipsoids shown at the 50% probability level.

3. Conclusion

In conclusion, we have developed an efficient two-step procedure for the preparation of pyrazino[1,2-*a*]benzimidazol-1(2*H*)ones, starting from easily accessible dichloropyrazinones. This type of tricyclic compounds, with potential biological activity, has not been reported to this date. The key step of our synthetic route is a microwave assisted intramolecular Buchwald–Hartwig type reaction. Two variable positions are present on the pyrazinone part, as well as two R-groups on the benzimidazole substructure, tolerating a wide range of electron withdrawing, electron donating, and neutral functional groups. Under microwave irradiation, this arylamination has a short reaction time, contributing to the overall efficacy of this method.

4. Experimental

4.1. General

Melting points are uncorrected. Infrared spectra were recorded on a Fourier transform spectrometer. For the NMR spectra (δ, ppm) 400 MHz and 300 MHz spectrometers were used. For column chromatography 70–230 mesh silica gel was used as the stationary phase.

4.2. Microwave irradiation experiments

All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus (CEM Corporation P.O. Box 200 Matthews, NC 28106), operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The machine was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 10 mL glass vials sealed with an aluminum/Teflon® crimp top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (60–120 s) to ambient temperature by gas jet cooling.

4.3. General procedure for the substitution of the 3-position of pyrazinones with an aniline derivative

A mixture of 1 mmol dichloropyrazinones **5**–**7**, 1.5 mmol of the appropriate aniline derivative and 1 mmol of camphorsulfonic acid in isopropanol was heated at reflux temperature for 48 h. The reaction mixture was allowed to cool to room temperature and

extracted with dichloromethane. After subsequently washing with potassium carbonate solution (satd) and NaCl solution (satd), the crude product was purified by column chromatography (silicagel, heptane/dichloromethane 50:50).

4.3.1. 3-(2-Bromoanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8a**)

Yield: 76%; melting point: 184 °C; IR (KBr) cm^{-1}: 1649, 1609, 1579, 1553, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 9.06 (s, 1H, NH), 8.69 (d, 1H, J=8.1 Hz), 7.57 (dd, 1H, J=8.2, 1.2 Hz), 7.35 (t, 1H, J=7.7 Hz), 7.29 (d, 2H, J=7.6 Hz), 6.94 (t, 1H, J=7.4 Hz), 6.90 (d, 2H, J=8.7 Hz), 6.69 (s, 1H), 5.01 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.9, 150.7, 146.6, 136.1, 132.4 (CH), 130.1 (CH), 128.4 (CH), 126.5, 125.7, 124.2 (CH), 119.9 (CH), 114.7 (CH), 114.5 (CH), 113.5, 55.3 (CH_3), 52.0 (CH_2); EIMS m/z (%): 421 (M^+ [^{81}Br], 10), 121 (100); HRMS: calcd for $C_{18}H_{15}BrClN_3O_2$: 419.00362; found: 420.97422 [^{81}Br].

4.3.2. 3-(2-Bromoanilino)-5-chloro-1-(4-methoxybenzyl)-6-methyl-2(1H)-pyrazinone (**8b**)

Yield: 78%; melting point: 164 °C; IR (KBr) cm^{-1}: 1649, 1609, 1579, 1553, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.94 (s, 1H, NH), 8.73 (d, 1H, J=8.2 Hz), 7.57 (d, 1H, J=7.8 Hz), 7.36 (t, 1H, J=7.6 Hz), 7.15 (d, 2H, J=8.2 Hz), 6.92 (t, 1H, J=7.5 Hz), 6.86 (d, 2H, J=8.4 Hz), 5.27 (s, 2H), 3.78 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.2, 152.0, 144.4, 136.4, 132.3 (CH), 128.3 (CH), 128.2 (CH), 126.9, 124.6, 123.7 (CH), 122.9, 119.4 (CH), 114.3 (CH), 113.2, 55.3 (CH_3), 48.4 (CH_2), 15.9 (CH_3); EIMS m/z (%): 433 (M^+, 1), 121 (100); HRMS: calcd for $C_{19}H_{17}BrClN_3O_2$: 433.01927; found: 433.02087. Crystal data for **8b**: orange-brown plate like crystals, 0.36×0.1×0.04 mm^3, were grown from methanol and belong to the triclinic space group P-1 (no. 2) with cell parameters a=7.4520(3) Å, b=11.8927(3) Å, c=11.9346(4) Å, α=61.5520(10)°, β=78.646(2)°, γ=72.080(2)°, V=883.26(5) $Å^3$, Z=2, ρ_{calcd}=1.635 g/cm^3, $2\theta_{max}$=142°, μ(Cu Kα)=1.858 cm^{-1}. Data were collected on a Bruker SMART 6000 detector, Cu Kα (λ=1.54178 Å), crossed Göbel mirrors, T=100 K; 8734 reflections were measured of which 3219 independent. The data were corrected for Lorentz, absorption and polarization effects. The structure was solved by directs methods. Full matrix least-squares refinement based on $|F^2|$ was performed. Hydrogen atoms were placed at calculated positions with temperature factors 20% higher than those of the parent atoms. The refinement (237 parameters) converged to an R_1 value of 4.95%, ωR_2 of 10.94%, max./min. residual electron density 0.14/−0.61 e $Å^{-3}$. Crystallographic data (excluding structure factors) for compound **8b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-660796.

4.3.3. 3-[2-Bromo-4-(trifluoromethyl)anilino]-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8c**)

Yield: 46%; melting point: 132 °C; IR (KBr) cm^{-1}: 1659, 1611, 1578, 1549, 1531, 1513; ^1H NMR ($CDCl_3$, 400 MHz, δ): 9.19 (s, 1H, NH), 8.84 (d, 1H, J=8.9 Hz), 7.82 (d, 1H, J=1.3 Hz), 7.60 (dd, 1H, J=8.7, 1.1 Hz), 7.29 (d, 2H, J=8.6 Hz), 6.90 (d, 2H, J=8.6 Hz), 6.75 (s, 1H), 5.02 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.1, 150.6, 146.4, 139.1, 130.1 (CH), 129.5 (q, J=4 Hz, CH), 126.3, 125.7 (q, J=33 Hz), 125.6 (q, J=3 Hz, CH), 125.4, 123.3 (q, J=270 Hz), 119.3 (CH), 115.9 (CH), 114.6 (CH), 113.0, 55.3 (CH_3), 52.2 (CH_2); EIMS m/z (%): 489 (M^+ [^{81}Br], 36), 487 (M^+ [^{79}Br], 28), 121 (100); HRMS: calcd for $C_{19}H_{14}BrClF_3N_3O_2$: 486.99100; found: 486.99129.

4.3.4. 3-Bromo-4-{[6-chloro-4-(4-methoxybenzyl)-3-oxo-3,4-dihydro-2-pyrazinyl]amino}benzonitrile (**8d**)

Yield: 42%; melting point: 261 °C; IR (KBr) cm^{-1}: 1660, 1611, 1576, 1552, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 9.27 (s, 1H, NH), 8.87 (d, 1H, J=8.5 Hz), 7.84 (d, 1H, J=1.7 Hz), 7.64 (dd, 1H, J=8.5, 1.7 Hz), 7.30 (d, 2H, J=8.5 Hz), 6.92 (d, 2H, J=8.5 Hz), 6.81 (s, 1H), 5.04 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 160.0, 150.5, 146.1, 140.0, 135.6 (CH), 132.6 (CH), 130.1 (CH), 126.0, 125.2, 119.1 (CH), 117.7, 116.5 (CH), 114.6 (CH), 112.9, 106.7, 55.3 (CH_3), 52.3 (CH_2); EIMS m/z (%): 446 (M^+ [^{81}Br], 5), 444 (M^+ [^{79}Br], 5), 121 (100); HRMS: calcd for $C_{19}H_{14}BrClN_4O_2$: 443.99886; found: 443.99784.

4.3.5. 3-(2-Bromo-4,6-dimethylanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8e**)

Yield: 51%; melting point: 156 °C; IR (KBr) cm^{-1}: 1651, 1609, 1579, 1545, 1510; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.81 (s, 1H, NH), 7.30 (d, 2H, J=8.5 Hz), 7.29 (s, 1H), 7.02 (s, 1H), 6.92 (d, 2H, J=8.6 Hz), 6.58 (s, 1H), 5.00 (s, 2H), 3.81 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.8, 150.3, 148.1, 138.3, 137.7, 131.6, 130.8 (CH), 130.7 (CH), 130.2 (CH), 126.6, 124.2, 121.5, 114.4 (CH), 113.7 (CH), 55.3 (CH_3), 51.6 (CH_2), 20.7 (CH_3), 19.5 (CH_3); EIMS m/z (%): 449 (M^+ [^{81}Br], 5), 447 (M^+ [^{79}Br], 4), 121 (100); HRMS: calcd for $C_{20}H_{19}BrClN_3O_2$: 447.03492; found: 447.03498.

4.3.6. 3-(2-Bromo-4-methylanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8f**)

Yield: 71%; melting point: 153 °C; IR (KBr) cm^{-1}: 1655, 1610, 1582, 1544, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.96 (s, 1H, NH), 8.52 (d, 1H, J=8.6 Hz), 7.38 (s, 1H), 7.28 (d, 2H, J=8.6 Hz), 7.14 (d, 1H, J=8.1 Hz), 6.89 (d, 2H, J=8.5 Hz), 6.65 (s, 1H), 4.99 (s, 2H), 3.79 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.8, 150.6, 146.5, 134.3, 133.5, 132.7 (CH), 130.0 (CH), 128.9 (CH), 126.5, 125.8, 119.8 (CH), 114.4 (CH), 114.3 (CH), 113.4, 55.27 (CH_3), 51.9 (CH_2), 20.5 (CH_3); EIMS m/z (%): 435 (M^+ [^{81}Br], 72), 433 (M^+ [^{79}Br], 63), 121 (100); HRMS: calcd for $C_{19}H_{17}BrClN_3O_2$: 433.01927; found: 433.01962.

4.3.7. 3-[2-Bromo-4-(trifluoromethoxy)anilino]-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8g**)

Yield: 57%; melting point: 118 °C; IR (KBr) cm^{-1}: 1647, 1610, 1585, 1546, 1508; ^1H NMR ($CDCl_3$, 400 MHz, δ): 9.02 (s, 1H, NH), 8.74 (d, 1H, J=9.2 Hz), 7.46 (d, 1H, J=2.2 Hz), 7.28 (d, 2H, J=8.6 Hz), 7.25 (td, 1H, J=9.2, 3.2 Hz), 6.89 (d, 2H, J=8.7 Hz), 6.71 (s, 1H), 5.00 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.0, 150.5, 146.4, 144.0 (d, J=2 Hz), 135.1, 130.1 (CH), 126.4, 125.5, 125.3 (CH), 121.0 (CH), 120.4 (q, J=256 Hz), 120.2 (CH), 115.2 (CH), 114.5 (CH), 113.2, 55.3 (CH_3), 52.1 (CH_2); EIMS m/z (%): 503 (M^+, 14), 121 (100); HRMS: calcd for $C_{19}H_{14}BrClF_3N_3O_3$: 502.98591; found: 502.97605.

4.3.8. 3-(2-Bromo-4-fluoroanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8h**)

Yield: 61%; melting point: 134 °C; IR (KBr) cm^{-1}: 1650, 1610, 1571, 1552, 1507; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.92 (s, 1H, NH), 8.65 (dd, 1H, J=9.1, 5.6 Hz), 7.32 (t, 1H, J=2.8 Hz), 7.28 (d, 2H, J=8.2 Hz), 7.08 (td, J=8.5, 2.7 Hz), 6.89 (d, 2H, J=8.4 Hz), 6.69 (s, 1H), 5.00 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.9, 157.7 (d, J=246 Hz), 150.5, 146.4, 132.6, 130.0 (CH), 126.4, 125.6, 120.7 (d, J=7 Hz, CH), 119.5 (d, J=26 Hz, CH), 115.0 (d, J=21 Hz, CH), 114.7 (CH), 114.4 (CH), 113.4 (d, J=9 Hz), 55.3 (CH_3), 52.0 (CH_2); EIMS m/z (%): 439 (M^+ [^{81}Br], 12), 437 (M^+ [^{79}Br], 11), 121 (100); HRMS: calcd for $C_{18}H_{14}BrClFN_3O_2$: 436.99419; found: 436.99384.

4.3.9. 3-(2-Bromo-4,6-difluoroanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8i**)

Yield: 59%; melting point: 138 °C; IR (KBr) cm^{-1}: 1650, 1607, 1580, 1550, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.71 (s, 1H, NH), 7.29 (d, 2H, J=8.7 Hz), 7.21 (dt, 1H, J=7.8, 2.2 Hz), 6.95 (m, 1H), 6.91 (d, 2H, J=8.6 Hz), 6.65 (s, 1H), 5.00 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.7 (dd, J=250, 13 Hz), 160.0, 158.2 (dd, J=255, 13 Hz), 150.1, 147.7, 130.1 (CH), 126.4, 126.3, 122.4 (dd, J=12, 4 Hz), 121.4 (dd, J=15, 4 Hz), 115.8 (dd, J=25, 4 Hz, CH), 115.0 (CH), 114.5 (CH), 104.6 (t, J=25 Hz, CH), 55.3 (CH_3), 51.7 (CH_2); EIMS m/z (%):

455 (M^+, 12), 121 (100); HRMS: calcd for $C_{18}H_{13}BrClF_2N_3O_2$: 454.98477; found: 454.98436.

4.3.10. 3-(2-Bromo-6-chloro-4-fluoroanilino)-5-chloro-1-(4-methoxybenzyl)-2(1H)-pyrazinone (**8j**)

Yield: 55%; melting point: 198 °C; IR (KBr) cm^{-1}: 1655, 1612, 1583, 1544, 1509; ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.76 (s, 1H, NH), 7.34 (dd, 1H, J=7.6, 2.8 Hz), 7.29 (d, 2H, J=8.6 Hz), 7.21 (dd, J=7.9, 2.8 Hz), 6.91 (d, 2H, J=8.6 Hz), 6.64 (s, 1H), 5.01 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.4 (d, J=252 Hz), 160.0, 150.1, 147.8, 134.5 (d, J=11 Hz), 130.6 (d, J=4 Hz), 130.2 (CH), 126.5, 126.3, 124.1 (d, J=11 Hz), 119.2 (d, J=25 Hz, CH), 116.9 (d, J=25 Hz, CH), 114.9 (CH), 114.6 (CH), 55.3 (CH_3), 51.7 (CH_2); EIMS m/z (%): 471 (M^+, 5), 121 (100); HRMS: calcd for $C_{18}H_{13}BrCl_2FN_3O_2$: 470.95522; found: 470.95657.

4.3.11. 3-(2-Bromoanilino)-5-chloro-1,6-diphenyl-2(1H)-pyrazinone (**8k**)

Yield: 82%; melting point: 176 °C; IR (KBr) cm^{-1}: 1643, 1611, 1574, 1547, 1505; ^1H NMR ($CDCl_3$, 300 MHz, δ): 9.15 (s, 1H, NH), 8.84 (d, 1H, J=8.0 Hz), 7.59 (d, 1H, J=7.8 Hz), 7.40 (t, 1H, J=7.6 Hz), 7.26–7.13 (m, 8H), 7.06 (d, 2H, J=6.9 Hz), 6.97 (t, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 151.5, 145.8, 137.1, 136.2, 132.5 (CH), 131.7, 130.9 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 126.8, 125.1, 124.2 (CH), 119.9 (CH), 113.5; EIMS m/z (%): 451 (M^+, 12), 372 (51); HRMS: calcd for $C_{22}H_{15}BrClN_3O$: 451.00870; found: 451.00625.

4.4. General procedure for the Buchwald–Hartwig type reaction of anilino pyrazinones under microwave irradiation

Anilino pyrazinones **8a–k** (0.1 mmol), 0.2 mmol K_2CO_3 and 10 mol % $Pd(PPh_3)_4$ were put in a 10 mL glass vial equipped with a small magnetic stirring bar. To this was added dimethylformamide (3 mL) and the vial was tightly sealed with an aluminum/Teflon® crimp top. The mixture was then irradiated for 25 min at 150 °C using a maximum irradiation power of 150 W. After completion of the reaction, the vial was cooled to 50 °C by gas jet cooling before it was opened. After evaporation of the solvent and extraction with dichloromethane, the crude product was purified by column chromatography (silicagel, heptane/ethylacetate 70:30 or dichloromethane/methanol 98:2).

4.4.1. 4-Chloro-2-(4-methoxybenzyl)pyrazino[1,2-a]benzimidazol-1(2H)-one (**4a**)

Yield: 68%; melting point: 225 °C; IR (KBr) cm^{-1}: 1670, 1510; ^1H NMR ($CDCl_3$/MeOD, 400 MHz, δ): 8.30 (d, 1H, J=8.4 Hz), 7.99 (d, 1H, J=8.2 Hz), 7.51 (td, 1H, J=7.6, 0.6 Hz), 7.44 (td, 1H, J=7.8, 0.7 Hz), 7.33 (d, 2H, J=8.6 Hz), 6.89 (d, 2H, J=8.6 Hz), 6.71 (s, 1H), 5.12 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$/MeOD, 100 MHz, δ): 159.7, 153.1, 143.0, 140.3, 130.8, 129.9 (CH), 127.1, 125.6 (CH), 125.2 (CH), 121.6 (CH), 114.9 (CH), 114.3 (CH), 114.2 (CH), 110.8, 55.1 (CH_3), 50.2 (CH_2); EIMS m/z (%): 339 (M^+, 63), 121 (100); HRMS: calcd for $C_{18}H_{14}ClN_3O_2$: 339.07745; found: 339.0785. Crystal data for **4a**: transparent plate like crystals, 0.5×0.2×0.1 mm^3, were grown from chloroform and belong to the monoclinic space group $P2_1/c$ (no. 14) with cell parameters a=11.15320(10) Å, b=7.52900(10) Å, c=18.4666(2) Å, β=96.8370(10)°, V=1539.66(3) $Å^3$, Z=4, ρ_{calcd}=1.466 g/cm^3, $2\theta_{max}$=142°, μ(Cu Kα)=1.858 cm^{-1}, Data were collected on a Bruker SMART 6000 detector, Cu Kα (λ=1.54178 Å), crossed Göbel mirrors, T=100 K; 15,760 reflections were measured of which 2935 independent. The data were corrected for Lorentz, absorption and polarization effects. The structure was solved by directs methods. Full matrix least-squares refinement based on $|F^2|$ was performed. Hydrogen atoms were placed at calculated positions with temperature factors 20% higher than those of the parent atoms and the X–H bond distances were free to refine. The refinement (273 parameters) converged to an R_1 value of 3.10%, ωR_2 of 8.07%, max./min. residual electron density 0.05/−0.24 e $Å^{-3}$. Crystallographic data (excluding structure factors) for compound **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-660795.

4.4.2. 4-Chloro-2-(4-methoxybenzyl)-3-methylpyrazino[1,2-a]benzimidazol-1(2H)-on (**4b**)

Yield: 70%; melting point: 206 °C; IR (KBr) cm^{-1}: 1665, 1638, 1612, 1515; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.39 (d, 1H, J=8.1 Hz), 8.04 (d, 1H, J=7.7 Hz), 7.47 (m, 2H), 7.19 (d, 2H, J=8.3 Hz), 6.84 (d, 2H, J=8.2 Hz), 5.38 (s, 2H), 3.76 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.1, 154.5, 143.5, 139.7, 131.3, 128.2 (CH), 127.9, 125.4 (CH), 124.9 (CH), 122.4, 122.0 (CH), 115.1 (CH), 114.3 (CH), 109.2, 55.2 (CH_3), 47.2 (CH_2), 15.5 (CH_3); EIMS m/z (%): 353 (M^+, 49), 121 (100); HRMS: calcd for $C_{19}H_{16}ClN_3O_2$: 353.09310; found: 353.09232.

4.4.3. 4-Chloro-2-(4-methoxybenzyl)-7-(trifluoromethyl)-pyrazino[1,2-a]benzimidazol-1(2H)-one (**4c**)

Yellow precipitate. Yield: 62%; melting point: 205 °C; IR (KBr) cm^{-1}: 1673, 1639; 1610, 1511; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.62 (s, 1H), 8.13 (d, 1H, J=8.7 Hz), 7.75 (d, 1H, J=8.5 Hz), 7.33 (d, 2H, J=8.3 Hz), 6.91 (d, 2H, J=8.3 Hz), 6.71 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.1, 152.9, 145.3, 142.5, 130.4, 130.1 (CH), 127.2 (q, J=33 Hz), 126.9, 124.2 (q, J=271 Hz), 122.9 (CH), 122.3 (q, J=3 Hz, CH), 115.7 (CH), 114.7 (CH), 112.4 (q, J=4 Hz, CH), 110.5 (C), 55.3 (CH_3), 50.6 (CH_2); EIMS m/z (%): 409 (M^+, 14), 407 (M^+, 46), 121 (100); HRMS: calcd for $C_{19}H_{13}ClF_3N_3O_2$: 407.06484; found: 407.06436.

4.4.4. 4-Chloro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydro-pyrazino[1,2-a]benzimidazole-7-carbonitrile (**4d**)

Yield: 24%; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.72 (s, 1H), 8.12 (d, 1H, J=8.5 Hz), 7.75 (d, 1H, J=8.5 Hz), 7.33 (d, 2H, J=8.4 Hz), 6.91 (d, 2H, J=8.3 Hz), 6.74 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H).

4.4.5. 4-Chloro-2-(4-methoxybenzyl)-7,9-dimethylpyrazino[1,2-a]benzimidazol-1(2H)-one (**4e**)

Yield: 67%; melting point: 204 °C; IR (KBr) cm^{-1}: 1674, 1508; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.89 (s, 1H), 7.32 (d, 2H, J=8.6 Hz), 7.13 (s, 1H), 6.88 (d, 2H, J=8.4 Hz), 6.56 (s, 1H), 5.12 (s, 2H), 3.79 (s, 3H), 2.74 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 159.8, 153.3, 140.9, 139.4, 135.7, 131.6, 131.0, 130.1 (CH), 127.9 (CH), 127.3, 114.8 (CH), 114.5 (CH), 111.1 (CH), 110.9, 55.3 (CH_3), 50.3 (CH_2), 22.2 (CH_3), 17.0 (CH_3); EIMS m/z (%): 367 (M^+, 80), 121 (100); HRMS: calcd for $C_{20}H_{18}ClN_3O_2$: 367.10875; found: 367.10844.

4.4.6. 4-Chloro-2-(4-methoxybenzyl)-7-methylpyrazino[1,2-a]benzimidazol-1(2H)-one (**4f**)

Yield: 74%; melting point: 187 °C; IR (KBr) cm^{-1}: 1671, 1635, 1608, 1512; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.05 (s, 1H), 7.89 (d, 1H, J=8.4 Hz), 7.31 (d, 3H, J=8.2 Hz), 6.88 (d, 2H, J=8.2 Hz), 6.57 (s, 1H), 5.12 (s, 2H), 3.79 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.7, 153.3, 141.7, 140.1, 135.5, 131.2, 130.0 (CH), 127.5 (CH), 127.3, 121.5 (CH), 114.5 (CH), 114.4 (CH), 113.6 (CH), 110.8, 55.3 (CH_3), 50.1 (CH_2), 22.2 (CH_3); EIMS m/z (%): 353 (M^+, 59), 121 (100); HRMS: calcd for $C_{19}H_{16}ClN_3O_2$: 353.09310; found: 353.09434.

4.4.7. 4-Chloro-2-(4-methoxybenzyl)-7-(trifluoromethoxy)-pyrazino[1,2-a]benzimidazol-1(2H)-one (**4g**)

Yield: 66%; melting point: 169 °C; IR (KBr) cm^{-1}: 1669, 1632, 1514; ^1H NMR ($CDCl_3$, 300 MHz, δ): 8.20 (s, 1H), 8.04 (d, 1H, J=9.0 Hz), 7.41 (d, 1H, J=8.7 Hz), 7.32 (d, 2H, J=8.3 Hz), 6.90 (d, 2H, J=8.3 Hz), 6.66 (s, 1H), 5.15 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.0, 153.0, 146.3 (d, J=1 Hz), 141.94, 141.88, 130.7, 130.1 (CH), 127.0, 123.2 (CH), 120.6 (q, J=256 Hz), 119.9 (CH), 115.4

(CH), 114.6 (CH), 110.3, 107.4 (CH), 55.3 (CH_3), 50.4 (CH_2); EIMS *m*/*z* (%): 426 (M^+, 24), 121 (100); HRMS: calcd for $C_{19}H_{13}ClF_3N_3O_3$: 423.05975; found: 423.05916.

4.4.8. 4-Chloro-7-fluoro-2-(4-methoxybenzyl)pyrazino[1,2-a]benzimidazol-1(2H)-one (**4h**)

Yield: 61%; melting point: 229 °C; IR (KBr) cm^{-1}: 1667, 1637, 1608, 1513; ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.97 (d, 1H, *J*=9.2 Hz), 7.96 (dd, 1H, *J*=9.3, 2.2 Hz), 7.31 (d, 2H, *J*=8.6 Hz), 7.27 (td, 1H, *J*=9.1, 2.3 Hz), 6.89 (d, 2H, *J*=8.7 Hz), 6.62 (s, 1H), 5.12 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.3 (d, *J*=243 Hz), 159.9, 153.1, 141.2 (d, *J*=3 Hz), 140.1, 130.8 (d, *J*=14 Hz), 130.1 (CH), 127.1, 123.2 (d, *J*=10 Hz, CH), 115.1 (CH), 114.8 (CH), 114.6 (CH), 110.3, 100.7 (d, *J*=30 Hz, CH), 55.3 (CH_3), 50.3 (CH_2); EIMS *m*/*z* (%): 359 (M^+ [^{37}Cl], 20), 357 (M^+, 67), 121 (100); HRMS: calcd for $C_{18}H_{13}ClFN_3O_2$: 357.06803; found: 357.06755.

4.4.9. 4-Chloro-7,9-difluoro-2-(4-methoxybenzyl)pyrazino[1,2-a]benzimidazol-1(2H)-one (**4i**)

Yield: 62%; melting point: oil; IR (NaCl) cm^{-1}: 1671, 1508; ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.82 (dt, 1H, *J*=8.9, 1.0 Hz), 7.31 (d, 2H, *J*=8.6 Hz), 7.02 (td, 1H, *J*=9.7, 2.1 Hz), 6.89 (d, 2H, *J*=8.6 Hz), 6.66 (s, 1H), 5.12 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.0, 159.9 (dd, *J*=245, 10 Hz), 154.6 (dd, *J*=260, 14 Hz), 152.8, 141.2 (d, *J*=3 Hz), 132.2, 130.1 (CH), 129.9, 126.9, 115.8 (CH), 114.6 (CH), 110.0, 101.7 (dd, *J*=29, 21 Hz, CH), 97.1 (dd, *J*=29, 5 Hz, CH), 55.3 (CH_3), 50.5 (CH_2); EIMS *m*/*z* (%): 375 (M^+, 100), 121 (33); HRMS: calcd for $C_{18}H_{12}ClF_2N_3O_2$: 375.05861; found: 375.05812.

4.4.10. 4,9-Dichloro-7-fluoro-2-(4-methoxybenzyl)pyrazino[1,2-a]benzimidazol-1(2H)-one (**4j**)

Yield: 61%; melting point: oil; IR (NaCl) cm^{-1}: 1674, 1637, 1608, 1515; ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.95 (dd, 1H, *J*=8.8, 2.2 Hz), 7.36 (dd, 1H, *J*=9.1, 2.2 Hz), 7.31 (d, 2H, *J*=8.6 Hz), 6.90 (d, 2H, *J*=8.6 Hz), 6.66 (s, 1H), 5.12 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 160.1, 159.6 (d, *J*=245 Hz), 152.8, 141.4 (d, *J*=2 Hz), 137.9, 131.1 (d, *J*=15 Hz), 130.2 (CH), 128.2 (d, *J*=13 Hz), 127.0, 115.9 (CH), 115.4 (d, *J*=29 Hz, CH), 114.7 (CH), 110.0, 99.7 (d, *J*=29 Hz, CH), 55.3 (CH_3), 50.6 (CH_2); EIMS *m*/*z* (%): 391 (M^+, 13), 121 (100); HRMS: calcd for $C_{18}H_{12}Cl_2FN_3O_2$: 391.02906; found: 391.02959.

4.4.11. 4-Chloro-2,3-diphenylpyrazino[1,2-a]benzimidazol-1(2H)-one (**4k**)

Yield: 78%; melting point: 174 °C; IR (KBr) cm^{-1}: 1672, 1511; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.60 (d, 1H, *J*=8.6 Hz), 7.41 (td, 1H, *J*=7.7, 1.2 Hz), 7.26 (d, 1H, *J*=2.5 Hz), 7.25–7.16 (m, 6H), 7.13 (dd, 2H, *J*=6.6, 3.0 Hz), 7.06 (dd, 2H, *J*=6.8, 1.0 Hz), 6.98 (td, 1H, *J*=7.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 151.5, 145.8, 137.2, 136.2, 132.5 (CH), 131.7, 130.9 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.10 (CH), 128.06 (CH), 126.8, 125.2, 124.2 (CH), 120.0 (CH), 113.6; EIMS *m*/*z* (%): 371 (M^+, 100); 336 (37); HRMS: calcd for $C_{22}H_{14}ClN_3O$: 371.08254; found: 371.08292. Crystal data for **4k**: translucent block like crystals, 0.4×0.3×0.2 mm^3, were grown from $CDCl_3$ and belong to the monoclinic space group *C*2/c (no. 15) with cell parameters *a*=24.20(4) Å, *b*=8.510(13) Å, *c*=18.22(2) Å, β=112.21(7)°, *V*=3474(9) $Å^3$, *Z*=8, ρ_{calcd}=1.422 g/cm^3, $2\theta_{max}$=141.4°, μ(Cu Kα)=1.858 cm^{-1}, Data were collected on a Bruker SMART 6000 detector, Cu Kα (λ=1.54178 Å), crossed Göbel mirrors, *T*=100 K; 14,751 reflections were measured of which 2963 independent. The data were corrected for Lorentz, absorption and polarization effects. The structure was solved by directs methods. Full matrix least-squares refinement based on $|F^2|$ was performed. Hydrogen atoms were placed at calculated positions with temperature factors 20% higher than those of the parent atoms and the X–H bond distances were free to refine. The refinement (244 parameters) converged to an R_1 value of 3.87%, ωR_2 of 9.40%, max./min. residual electron density 0.49/−0.28 e $Å^{-3}$. Crystallographic data (excluding structure factors) for compound **4k** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-661575.

Acknowledgements

The authors thank the F.W.O. (Fund for Scientific Research-Flanders (Belgium)) for financial support. We are grateful to B. Demarsin for HRMS measurements and to K. Duerinckx for assisting with the NMR measurements. J.A. and W.M.D.B. (Postdoctoral Fellows of the F.W.O.-Flanders) thank the F.W.O. for the fellowships received. W.M.D.B. also thanks the F.W.O. for a 'Krediet aan Navorsers'.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.056.

References and notes

1. Pinder, R. M.; Brogden, R. N.; Sawyer, P. R.; Speight, T. M.; Spencer, R.; Avery, G. S. *Drugs* **1976**, *12*, 1–40.
2. Chambers, R. A.; Druss, B. G. *J. Clin. Psychiatry* **1999**, *60*, 664–667.
3. Holt, S.; Howden, C. W. *Dig. Dis. Sci.* **1991**, *36*, 385–393.
4. Shigeta, S.; Mori, S.; Baba, M. *Antiviral Chem. Chemother.* **1992**, *3*, 171–177.
5. (a) Badawey, E.-S. A. M.; Gohar, Y. *Il Farmaco* **1992**, *47*, 489–496; (b) Hammad, M.; Abdel Meguid, S.; El-Anani, M. M.; Shafik, N. *Egypt. J. Chem.* **1987**, *29*, 549–553.
6. (a) Koenigsmann, M.; Zafferani, M.; Danhauser-Rield, S.; Reuti, B.; Houlihan, W. J.; Thiel, E.; Berdel, W. E. *Cancer Lett.* **1992**, *67*, 145–156; (b) Brana, M. F.; Castellano, J. M.; Keilhauer, G.; Machuca, A.; Martin, Y.; Redondo, C.; Schlick, E.; Walker, N. *Anti-Cancer Drug Des.* **1994**, *9*, 527–538.
7. Badawey, E.-S. A. M.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327–332.
8. Badawey, E.-S. A. M.; Kappe, T. *Eur. J. Med. Chem.* **1999**, *34*, 663–667.
9. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-Interscience: New York, NY, 2004.
10. Demirayak, S.; Abu Mohsen, U.; Karaburun, A. C. *Eur. J. Med. Chem.* **2002**, *37*, 255–260.
11. (a) De Borggraeve, W. M.; Verbist, B. M. P.; Rombouts, F. J. R.; Pawar, V. G.; Smets, W. J.; Kamoune, L.; Alen, J.; Van der Eycken, E. V.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2004**, *60*, 11597–11612; (b) Pawar, V. G.; De Borggraeve, W. M. *Synthesis* **2006**, *17*, 2799–2814; (c) Alen, J.; Smets, W. J.; Dobrzańska, L.; De Borggraeve, W. M.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2007**, *6*, 965–971.
12. Vekemans, J.; Pollers-Wieërs, C.; Hoornaert, G. J. *J. Heterocycl. Chem.* **1983**, *20*, 919–923.
13. Heeres, J.; de Jonge, M. R.; Koymans, L. M. H.; Daeyaert, F. F. D.; Vinkers, M.; Van Aken, K. J. A.; Arnold, E.; Das, K.; Kilonda, A.; Hoornaert, G. J.; Compernolle, F.; Cegla, M.; Azzam, R. A.; Andries, K.; de Béthune, M.-P.; Azijn, H.; Pauwels, R.; Lewi, P. J.; Janssen, P. A. J. *J. Med. Chem.* **2005**, *48*, 1910–1918.
14. (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209; (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146; (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818; (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
15. (a) Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemière, G. L. F. *Chem. Commun.* **2004**, 2466–2467; (b) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260–264.
16. Venkatesh, C.; Sundaram, G. S. M.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2006**, *71*, 1280–1283.
17. (a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002; (b) *Microwave-Assisted Synthesis of Heterocycles*; Van der Eycken, E., Kappe, C. O., Eds.; Springer: Berlin, Heidelberg, New York, NY, 2006.
18. (a) Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Diversity* **2003**, *7*, 125–133; (b) Alen, J.; Dobrzańska, L.; De Borggraeve, W. M.; Compernolle, F. *J. Org. Chem.* **2007**, *72*, 1055–1057.