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A Simple One-Pot Synthesis of New Imidazol-2-yl-1*H*-quinolin-2-ones from the Direct Reaction of 2-Chloroquinolin-3-carbaldehyde with Aromatic *o*-Diamines

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Keywords: Antitumor agents / Synthetic methods / Biological activity / Cyclization / Nitrogen heterocycles / Hydrolysis

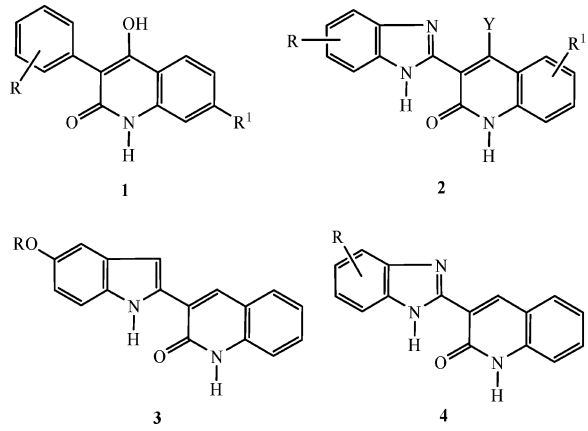
An alternative and general one-pot synthesis of a library of novel imidazol-2-yl-1*H*-quinolin-2-one derivatives was performed in 70 % aqueous acetic acid by the direct reaction of 2-chloroquinolin-3-carbaldehyde with aromatic *o*-diamines. Experiments showed that adding Amberlyst®-15 (20 % w/w) to the reaction media increased both the speed of reaction as well as the yield of products. Both DFT theoretical calculations and X-ray diffraction studies confirmed the proposed structures and the more stable conformation of the obtained products. Antitumor studies against sixty different cancer cell lines showed the potential of these kinds of compounds.

Introduction

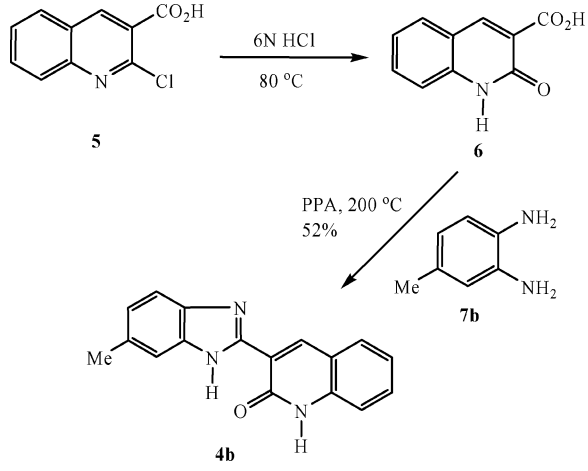
Quinolines and their oxo derivatives are important compounds due to their presence in naturally occurring products and their wide-ranging applications as drugs, pharmaceuticals, and agrochemicals.[1] In particular, 3-substituted quinolin-2-one is an important moiety that is found in a number of compounds with interesting biological activities.[2] Of these, hydroxy compound **1** is of particular pharmaceutical interest,[2g] as are the novel and potent receptor tyrosine kinase (RTK) inhibitors **2**,[2h] indoloquinolin-2-ones **3**, and imidazoquinolin-2-ones **4**, which have been found to constitute a novel class of kinase insert domain-containing receptor (KDR) inhibitors[2i–2k] (Scheme 1).

In this sense, Fraley et al.[2k] recently developed a two-step sequence (involving relatively harsh reaction conditions) for the synthesis of a series of imidazoquinolinones **4** to be assayed for KDR inhibition; the synthesis of the methyl derivative **4b**, shown in Scheme 2, affords the product in acceptable yield.

On the other hand, we and other authors have previously found that the target pharmacophore 1*H*-quinolin-2-one moiety, which is present in the structure of 3-formylquin-



Scheme 1. Some quinolin-2-one derivatives of biological interest.



Scheme 2. Previously reported approach to the synthesis of imidazoquinolin-2-one **4b**.

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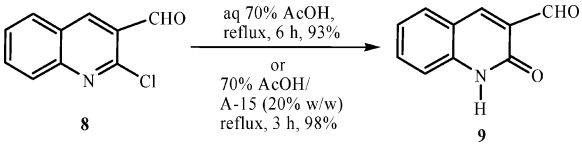
olin-2-one (**9**), is readily obtained from the commercially available 2-chloroquinoline-3-carbaldehyde (**8**) either through hydrolysis in aqueous AcOH (70%)[2b] or by treatment with a 70% AcOH/Amberlyst®-15 (20% w/w) mixture[3] according to Scheme 3. It was observed that a significant improvement could be achieved by including Amberlyst®-15 (A-15) in the reaction media.



Scheme 3. Synthesis of aldehyde **9** by hydrolysis of 2-chloroquinoline-3-carbaldehyde (**8**).

Results and Discussion

According to Schemes 1, 2, and 3 and continuing with our current studies on the synthesis of potential antitumor agents,[4] we envisaged the possibility of combining both hydrolysis of the C–Cl bond and a cyclocondensation processes into one step. In this way, we hoped to develop an alternative and general approach through which to obtain compound **4b** and new analogues.

As an initial study, a mixture of *o*-phenylenediamine (**7a**) and an equimolar amount of aldehyde **8** was subjected to reflux for six hours in a 70:30 mixture (5 mL) of acetic acid and water (This procedure will be referred to as Approach 1). However, the reaction had not gone to completion after this time, and a mixture of the expected product **4a** and the hydrolyzed aldehyde **9** precipitated from the solution; this mixture was found to be difficult to resolve. Finally, pure compound **4a** was obtained from the mixture in 29% yield after repeated washings with hot ethanol. The same behavior was observed for the synthesis of compound **4b** – in this case just 35% yield was obtained.

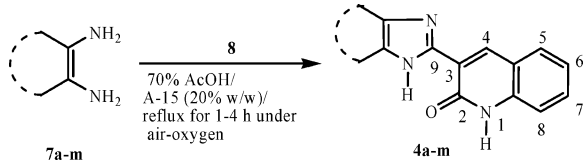
Taking into account that the presence of Amberlyst®-15 has been shown to improve both the hydrolysis of aldehyde **8** and efficiently catalyze a number of heterocyclization processes,[5] we decided to repeat the above reaction in the presence of 20% w/w Amberlyst®-15[5] (This procedure will be referred to as Approach 2). With this variation, the reaction proceeded to completion in only 4 h (monitored by TLC) without precipitation. After the Amberlyst®-15 was filtered and the solution was reduced to one third of its initial volume, pure compound **4a** precipitated in 84% yield. Similarly, compound **4b** was obtained in 92% yield by following this modified procedure. The Amberlyst®-15 was recovered and reused as described recently.[5] Table 1 summarizes the optimization process for this methodology.

Table 1. Optimization of the reaction conditions for the hydrolysis of aldehyde **8** and the synthesis of imidazoquinolinones **4**.

Approach	Reaction conditions[a]	Obtained compounds (% yield)		
		9	**4a**	**4b**
1	70% AcOH/reflux 6 h	93	29	35
2	70% AcOH/20% w/w A-15/reflux 4 h	98	84	92

[a] A-15 = Amberlyst®-15.

The results of these optimization studies prompted us to use the reaction conditions described in Approach 2 to create a library of imidazoquinolinones **4a**–**m**, starting from 2-chloroquinoline-3-carbaldehyde (**8**) and various *o*-diamines **7a**–**m**, as shown in Scheme 4.



Scheme 4. General procedure established for the direct synthesis of products **4**.

Although formation of the imidazole ring involved a dehydration process, which usually requires anhydrous reaction conditions, interestingly in this case compounds **4** were readily obtained in good yields; thus the presence of 30% water did not affect the formation of these products. On the other hand, formation of the imidazole ring in **4** requires the presence of an oxidant in the reaction media; in our experimental procedure this oxidant was atmospheric air, the oxygen dissolved in the solvent being responsible for the oxidation process as previously reported by Lin et al.[6] Table 2 summarizes the structure of the starting *o*-diamines **7** and the compounds **4a**–**m** obtained by using Approach 2.

Products **4** were characterized by analytical and spectroscopic methods (elemental analyses, FTIR, ^{1}H-, ^{13}C-, 1D-, and 2D-NMR, and EIMS) as summarized in the Experimental Section. The most relevant signal in the FTIR spectra corresponded to an intense absorption band at 1651–1689 cm^{-1}, which was assigned to the carbonyl group of the new amide functionality formed from the hydrolysis of the C–Cl bond. The number of proton signals observed in the ^{1}H NMR spectra and their chemical shifts also support the proposed structures; the most relevant signals being a singlet (δ = 8.41–9.72 ppm) corresponding to 4-H and a broad singlet (δ = 10.24–12.98 ppm) corresponding to the 1-NHCO functionality. In the ^{13}C NMR spectra of **4**, the signals assigned to C-4 (δ = 138.1–144.1 ppm) and to the 2-carbonyl group (δ = 159.3–162.2 ppm) of the new amide functionality were the most relevant features. In contrast, the ^{13}C NMR spectrum of free aldehyde **9** contained two different carbonyl signals at δ = 161.8 ppm and 190.1 ppm corresponding to the NHCO and CHO functionalities, respectively, which agree with the proposed structure for **4**. A common base peak corresponding to the molecular ion was observed in the mass spectra of compounds **4**, except for products **4h** and **4l**. For these two compounds the base peak corresponded to m/z = 28 (i.e. a radical cation of CO). These features also accompanied a commonly observed ring-contraction process for the quinolin-2-one moiety in all compounds of type **4**. In this way, a decarbonylation

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Table 2. Structures and analytical data of the obtained imidazoquinolin-2-ones **4**.

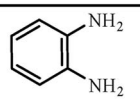
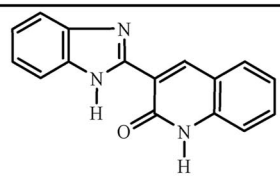
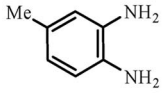
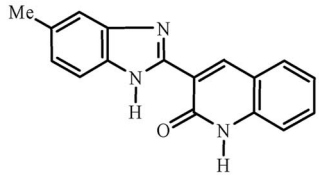
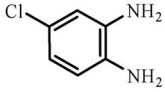
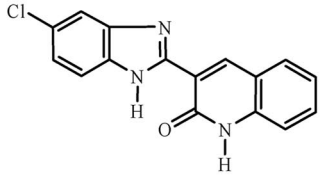
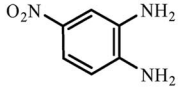
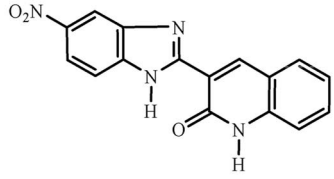
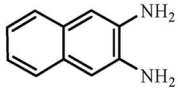
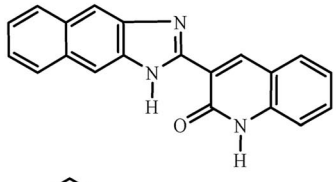
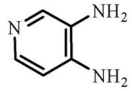
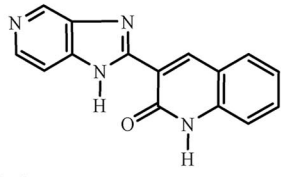
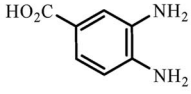
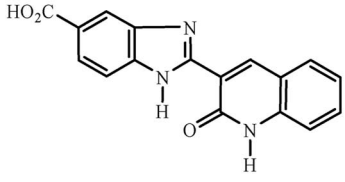
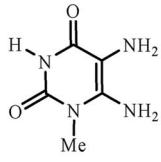
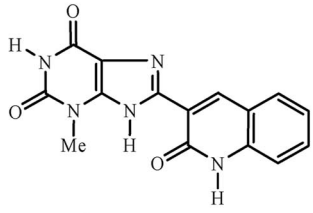
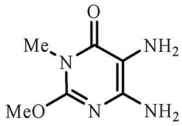
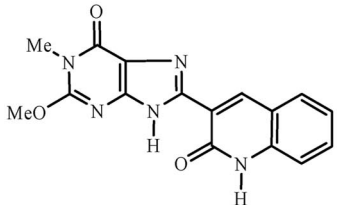
Entry	Diamine **7**	Structure	Product **4**	Structure	Yield (%)/ color[a]	Mp (°C)
1	**7a**		**4a**		84/yellow	308 (dec)[b]
2	**7b**		**4b**		92/brown	293 (dec)[b]
3	**7c**		**4c**		78/green	265 (dec)
4	**7d**		**4d**		82/brown	> 350
5	**7e**		**4e**		80/brown	312 (dec)
6	**7f**		**4f**		79/brown	> 350
7	**7g**		**4g**		83/brown	288 (dec) [c]
8	**7h**		**4h**		81/yellow	> 350
9	**7i**		**4i**		81/orange	> 350

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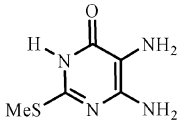
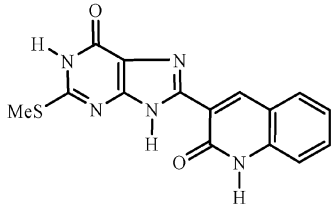
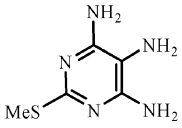
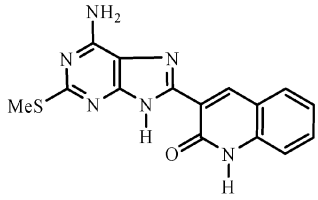
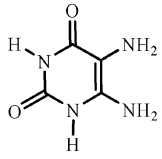
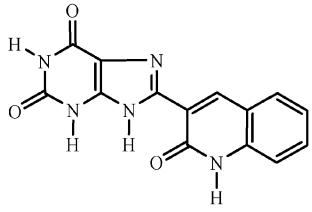
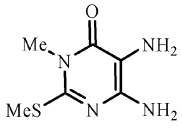
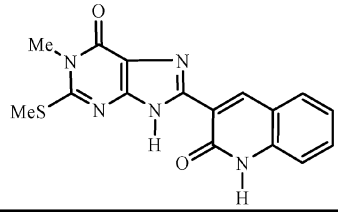
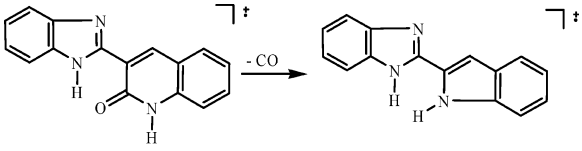
Table 2. *(Continued)*

Entry	Diamine **7**	Structure	Product **4**	Structure	Yield (%)/ color[a]	Mp (°C)
10	**7j**		**4j**		88/yellow	> 350
11	**7k**		**4k**		82/brown	> 300
12	**7l**		**4l**		76/orange	319 (dec)
13	**7m**		**4m**		78/brown	> 350

[a] Isolated yield. [b] The synthesis of this compound has been previously reported[2k] following the procedure shown in Scheme 2 but no analytical or spectroscopic data were supplied. [c] Synthesis of this compound was reported in a patent[2l] using a different procedure.

process led to the loss of 28 a.m.u. (corresponding to a CO molecule) to furnish the relatively stable indolinic species **10a** as shown in Scheme 5 for compound **4a**.



Scheme 5. Main MS fragmentation for compounds **4**.

In addition to other factors, it has been reported that the antitumor activity of these kinds of compounds is favored by coplanarity of the imidazole and quinolinone rings of **4** and analogues, rather than a perpendicular orientation.[2k] The NMR spectroscopic study did not allow us to determine whether the coplanar form (favored by an intramolecular hydrogen bond) or the perpendicular conformation was the preferred arrangement for compounds of type **4** (Figure 1).

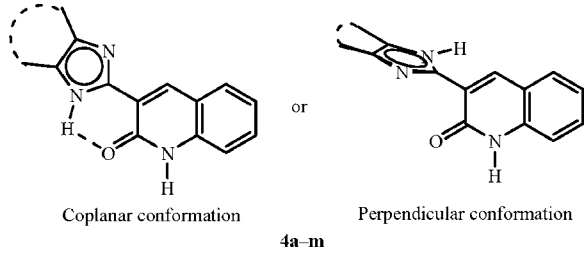


Figure 1. Possible conformations for compounds **4**.

To address this question, a DFT study was performed for compound **4a** to help predict the most stable conformation. The calculations were carried out with a Gaussian 03 revision C 0.2 using the DFT-B3LYP base 6-31G**. The computational study showed that the more stable conformation of this compound was quite near to planarity (Figure 2), with a calculated dihedral angle between the atoms N31–C32–C3–C2 of –0.03703°.

These findings support the possibility of an intramolecular hydrogen bond between O2···H–N31 atoms that could

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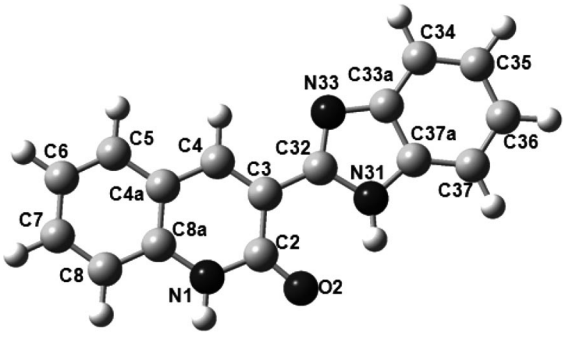

Figure 2. Most stable conformation for compound **4a** predicted from DFT calculations.

be responsible for the predicted planarity calculated for compounds **4**.

After several unsuccessful attempts to obtain crystals of **4**, fortunately it was possible to grow single crystals of compound **4a** from methanol and to solve the structure by X-ray diffraction analysis (Figure 3; see also the Experimental Section). The crystal structure not only confirmed the proposed structures for compounds **4** (previously assigned on the basis of their spectroscopic data), but also confirmed the existence of the intramolecular hydrogen bond in N31–H31···O2, thus supporting the theoretical calculations that predicted the stable coplanar conformation.

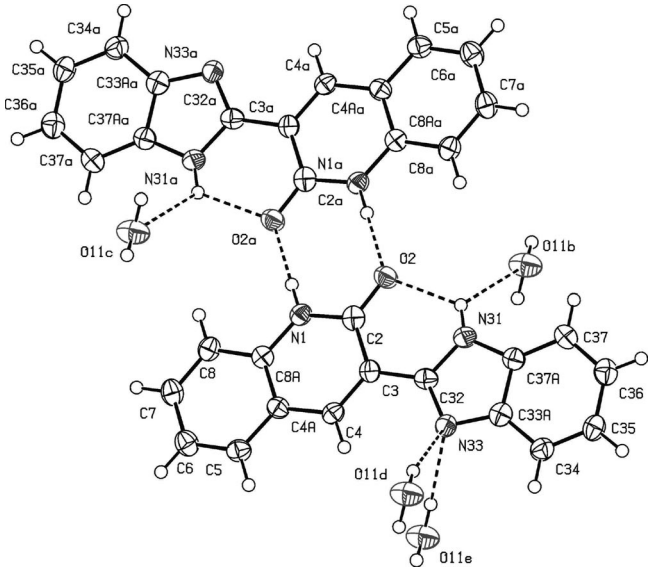

Figure 3. ORTEP drawing of imidazoquinolinone **4a**. Hydrogen bond framework showing the dimeric unit formed between two molecules of **4a** and molecules of water that links the dimeric units into a 2D supramolecular network.

The effectiveness of Amberlyst®-15 as a catalyst can be explained by considering that it is a macroreticular, polystyrene-based ion-exchange resin with strongly acidic sulfonic groups. The resin has been used as a very efficient acid catalyst for several reactions, such as the synthesis of acetals from carbonyls and alcohols,[7a] the synthesis of esters from alcohols and acids,[7b] and hydrolysis of acetals to carbonyls.[7c] More recently, we have also used this heterogeneous catalyst for efficient intramolecular heterocyclization reactions of *o*-aminochalcones, also in the presence of acetic acid.[5] Consequently, it is reasonable to suppose that, in contrast to the use of aqueous acetic acid as reaction medium (i.e. Approach 1), the acid strength of the Amberlyst®-15 catalyst increased the reactivity of aldehyde **8** in Approach 2.

Anticancer Activity

The two-stage screening process started with an evaluation of the nine compounds **4a**, **4c**, **4f**–**j**, **4l**, and **4m** selected by the National Cancer Institute (NCI), against 60 cell lines at a single dose of 1.0 μM. The output from the single dose screen was reported as a mean graph available for analysis by the COMPARE program.[8] The results of the primary assay showed that all compounds were essentially inactive, except for compound **4c** (Table 3).

Table 3. Results of primary anticancer assay for nine compounds selected by the NCI.

Compounds	Activity[a]
4a	NA
4c	A
4f	NA
4g	NA
4h	NA
4i	NA
4j	NA
4l	NA
4m	NA

[a] Activity denoted as: A = active; NA = not active.

Therefore, a secondary screening was performed in order to determine the cytostatic activity of compound **4c** against the 60-cell-line panel representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. This compound was evaluated at five concentration levels (100, 10, 1.0, 0.1, and 0.01 μM). The test consisted of a 48 hour continuous drug exposure protocol using a sulforhodamide B (SRB) protein assay to estimate cell growth. Details of this evaluation method and the complementary information related to the activity pattern over all cell lines have been published.[9] Table 4 shows that compound **4c** displayed the most remarkable activity against 59 human tumor cell lines, the most sensitive strains being KM12 (colon cancer; GI_{50} = 0.38 μM) and CAKI-1 (renal cancer; GI_{50} = 1.02 μM); both had LC_{50} values greater than 100 μM. Derivative **4c** showed significant activity against other cell lines from the different panels of cancer types, with a GI_{50} range of 0.38–100.0 μM. The cytotoxicities associated with compound **4c** were measured as LC_{50} values and ranged from 48.1 to above 100 μM, for all cell lines, indicating a low toxicity of this compound for normal human cell lines, as required for potential antitumor agents.

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Table 4. In vitro testing results expressed as growth inhibition of cancer cells by compound **4c**.[a]

Number of cell lines							
Investigated				Giving positive GI_{50} GI_{50} (μM)[b]			
				No		Range	
59				59		0.38-100.0	
Most sensitive cell lines (GI_{50} < 100μM)				Most sensitive cell lines (GI_{50} < 100μM)			
Panel	Cell line	GI_{50} (μM)[b]	LC_{50}(μM)[c]	Panel	Cell line	GI_{50} (μM)[b]	LC_{50}(μM)[c]
Ovarian Cancer				Leukemia			
	IGROV1	1.36	>100		CCRF-CEM	3.24	>100
	OVCAR-3	2.37	>100		HL-60(TB)	3.24	>100
	OVCAR-4	5.09	>100		K-562	3.85	>100
	OVCAR-5	51.7	>100		MOLT-4	2.74	>100
	OVCAR-8	6.52	>100		RPMI-8222	1.42	>100
	NCI/ADR-RES	6.09	>100		SR	2.53	>100
	SK-OV-3	2.22	>100	Non-Small Cell Lung Cancer			
Renal Cancer							
	786-0	7.42	>100		A549/ATCC	5.15	>100
	A498	2.48	>100		EKVX	2.35	>100
	ACHN	2.45	>100		HOP-62	6.79	>100
	CAKI-1	1.02	>100		HOP-92	1.48	>100
	SN12C	3.17	>100		NCI-H226	2.71	>100
	TK-10	2.51	>100		NCI-H23	4.70	>100
	UO-31	3.31	>100		NCI-H322M	3.65	>100
Prostate Cancer					NCI-H460	2.61	>100
	PC-3	3.71	>100		NCI-H522	6.79	>100
	DU-145	7.68	>100	Colon Cancer			
Breast Cancer					COLO 205	3.25	>100
	MCF7	1.40	>100		HCC-2998	11.0	>100
	MDA-MB-231/ATCC	3.25	>100		HCT-116	2.66	>100
	HS 578T	2.00	>100		HCT-15	2.91	>100
	BT-549	2.99	>100		HT29	4.24	>100
	T-47D	3.33	>100		KM12	0.38	>100
	MDA-MB-468	3.26	>100		SW-620	4.81	>100
Melanoma				CNS Cancer			
	LOX IMVI	4.43	>100		SF-268	6.09	>100
	MALME-3M	100.0	>100		SF-295	9.63	>100
	M14	2.86	>100		SF-539	4.13	48.1
	MDA-MB-435	4.39	>100		SNB-19	29.8	>100
	SK-MEL-2	2.69	>100		SNB-75	2.98	>100
	SK-MEL-28	6.66	>100		U251	3.87	>100
	SK-MEL-5	3.40	>100				
	UACC-257	13.9	>100				
	UACC-62	2.83	>100				

[a] Data obtained from NCI's in vitro disease-oriented human tumor cell lines screen.[7] [b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Determined at five concentration levels (100, 10, 1.0, 0.1, and 0.01 μM). [c] LC_{50} is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

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Conclusions

The one-pot synthesis and studies on the cytotoxic activity of novel imidazol-2-yl-1*H*-quinolin-2-ones **4** have been performed. The results show that the presence of Amberlyst®-15 in the reaction media enhanced the reactivity of the starting materials and consequently improved the yield of products. X-ray diffraction analysis confirmed not only the proposed structure of products **4** but also revealed the presence of intramolecular hydrogen bonding and established the planarity of compound **4a**, which was predicted from DFT theoretical calculations. The antitumor assays showed that, among the nine imidazoquinolinones **4** evaluated by the NCI, derivative **4c** exhibited the highest activity against a range of cancer cell lines with remarkable values.

Experimental Section

Melting points were determined with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR 8400 spectrophotometer by using KBr disks. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrophotometer operating at 400 MHz and 100 MHz, respectively, using [D$_6$]DMSO as solvent and tetramethylsilane as internal standard. Mass spectra were measured with a SHIMADZU-GC–MS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Microanalyses were performed with an Agilent elemental analyzer, and the values are within ± 0.4% of the theoretical values. Silica gel aluminum plates (Merck 60 F254) were used for analytical TLC. Amberlyst®-15, the starting *o*-diamines **7a**–**g**, and 2-chloroquinolin-3-carbaldehyde (**8**) were purchased from Aldrich, Fluka, or Acros (analytical reagent grades) and were used without further purification. The remaining *o*-diamines **7h**–**m** were synthesized by using literature procedures.[10]

General Procedure for the Synthesis of Compounds 4: A mixture of 2-chloroquinoline-3-carbaldehyde (**8**) (200 mg, 1 mmol), the corresponding *o*-diamine **7** (1 mmol), Amberlyst®-15 (20% w/w) and aq. AcOH (70%, 3 mL) was stirred at reflux for 1–4 h, and the progress of the reaction was checked by TLC. When the reaction was complete, Amberlyst®-15 was filtered, washed with fresh AcOH (1 mL), and recovered by filtration. The combined fractions were concentrated under vacuum to one third of the original volume. The solids formed were collected by Büchner filtration and washed with AcOH/H$_2$O (1:1, 2 × 2 mL). No further purification was required for the obtained products.

3-(1*H*-Benzo[*d*]imidazol-2-yl)quinolin-2(1*H*)-one (4a): Yield: 229 mg. FTIR (KBr): $\tilde{\nu}$ = 3350 (1-NHCO), 3161 (imidazole-NH), 1659 (2-C=O), 1619 (C=N), 1570 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.37 (t, J = 7.2 Hz, 1 H, 6-H), 7.45–7.60 (m, 3 H, 8-H and 2 × Ar-H), 7.74 (t, J = 7.1 Hz, 1 H, 7-H), 7.80–7.93 (m, 3 H, 5-H and 2 × Ar-H), 9.49 (s, 1 H, 4-H), 12.84 (s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 114.4 (Cq), 114.8 (2 C), 116.3, 118.6 (Cq), 123.9, 126.3 (2 C), 130.0, 132.0 (2 Cq), 134.4, 140.2 (Cq), 144.1 (C-4), 145.6 (Cq), 159.8 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 261 (100) [M]$^+$, 233 (95) [M – CO], 205 (7), 116 (20). $C_{16}H_{11}N_3O$ (261.09): calcd. C 73.55, H 4.24, N 16.08; found C 73.26, H 4.39, N 15.82. Crystallographic data for **4a**·H$_2$O were collected at 120 K with a Bruker Nonius Kappa CCD area diffractometer using Mo-K_α X-ray radiation (λ = 0.71073 Å). CCDC-695467 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal system: monoclinic; space group: $P2_1/c$; unit cell dimensions: 7.968 (6), 16.73 (2), 10.206 (11) Å, 109.56 (9)°; volume: 1282 (2) A^3; Z = 4; calculated density: 1.447 Mg/m^3; μ = 0.100 mm^{-1}; crystal size: 0. 1 × 0.22 × 0.51 mm; range of collection: 2.95 < θ < 27.5°; reflections collected/unique: 23135/2948 [R_{int} = 0.112]. 99.9% completeness to θ = 27.50°. Multiscan absorption correction was carried out with SADABS 2.0.[11] T_{Max}/T_{Min} = 0.990/0.951. Refinement with SHELXL-97[12] using a full-matrix least-squares on F^2; S = 1.03; R_1 = 0.083, wR_2 = 0.277·W = [$\sigma^2(F^2_o)$ + (0.1633P)^2]$^{-1}$ where P = (F^2_o + 2F^2_c)/3.

3-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)quinolin-2(1*H*)-one (4b): Yield: 264 mg. FTIR (KBr): $\tilde{\nu}$ = 3352 (1-NHCO), 3166 (imidazole-NH), 1658 (2-C=O), 1570 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.44 (s, 3 H, CH$_3$), 7.04 (d, J = 8.1 Hz, 1 H, Ar-H), 7.29 (t, J = 7.4 Hz, 1 H, 6-H), 7.42–7.56 (m, 3 H, 8-H and 2 × Ar-H), 7.61 (t, J = 7.2 Hz, 1 H, 7-H), 7.95 (d, J = 7.2 Hz, 1 H, 5-H), 9.09 (s, 1 H, 4-H), 12.50 (s, 1 H, imidazole-NH), 12.55 (s, 1 H, 1-NHCO) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.3 (CH$_3$), 112.3, 115.2, 117.9, 119.2 (Cq), 120.2 (Cq), 122.6, 123.5, 128.9, 131.4, 132.5 (Cq), 134.7 (Cq), 138.6 (2 C, C-4 and Ar-Cq), 141.0 (Cq), 147.2 (Cq), 160.8 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 275 (100) [M]$^+$, 247 (72) [M – CO], 123 (10), 77 (15). $C_{17}H_{13}N_3O$ (275.11): calcd. C 74.17, H 4.76, N 15.26; found C 74.42, H 4.42, N 15.54.

3-(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)quinolin-2(1*H*)-one (4c): Yield: 240 mg. FTIR (KBr): $\tilde{\nu}$ = 3240 (br., 1-NHCO and imidazole-NH), 1666 (2-C=O), 1622 (C=N), 1569 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.36 (t, J = 7.9 Hz, 1 H, 6-H), 7.52 (d, J = 8.1 Hz, 1 H, 8-H), 7.53 (dd, J = 8.7, J = 2.1 Hz, 1 H, Ar-H), 7.74 (t, J = 7.9 Hz, 1 H, 7-H), 7.83 (d, J = 7.2 Hz, 1 H, 5-H), 7.87 (d, J = 7.2 Hz, 1 H, Ar-H), 7.88 (s, 1 H, Ar-H), 9.49 (s, 1 H, 4-H), 12.85 (s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 114.0, 114.1 (Cq), 115.8, 115.9, 118.2 (Cq), 123.4, 125.8, 129.6, 129.7 (Cq), 131.1 (Cq), 133.0 (Cq), 133.9, 139.7 (Cq), 143.6 (C-4), 146.5 (Cq), 159.3 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 297/295 (30/100) [M]$^+$, 269/267 (24/76) [M – CO], 232 (27), 205 (11), 142 (36). $C_{16}H_{10}ClN_3O$ (295.72): calcd. C 64.98, H 3.41, N 14.21; found C 64.81, H 3.61, N 14.19.

3-(5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)quinolin-2(1*H*)-one (4d): Yield: 262 mg. FTIR (KBr): $\tilde{\nu}$ = 3332 (1-NHCO), 3154 (imidazole-NH), 1660 (2-C=O), 1618 (C=N), 1594 (C=C), 1513 (NO$_2$), 1314 (NO$_2$) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.30 (t, J = 7.2 Hz, 1 H, 6-H), 7.44 (d, J = 8.3 Hz, 1 H, 8-H), 7.64 (t, J = 7.9 Hz, 1 H, 7-H), 7.82 (d, J = 8.9 Hz, 1 H, Ar-H), 7.96 (d, J = 7.45 Hz, 1 H, 5-H), 8.10 (dd, J = 8.9, 2.3 Hz, 1 H, Ar-H), 8.56 (s, 1 H, Ar-H), 9.14 (s, 1 H, 4-H), 12.53 (s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 115.3 (2 C), 117.7, 118.7 (Cq), 118.9 (2 Cq), 122.7, 129.4 (2 C), 132.2, 139.1 (2 Cq), 140.8 (C-4), 142.6 (Cq), 152.3 (Cq), 160.5 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 306 (100) [M]$^+$, 278 (19) [M – CO], 170 (40), 142 (30), 63 (45). $C_{16}H_{10}N_4O_3$ (306.28): calcd. C 62.74, H 3.29, N 18.29; found C 62.62, H 3.40, N 18.18.

3-(1*H*-Naphtho[2,3-*d*]imidazol-2-yl)quinolin-2(1*H*)-one (4e): Yield: 260 mg. FTIR (KBr): $\tilde{\nu}$ = 3413 (1-NHCO), 3163 (imidazole-NH), 1670 (2-C=O), 1641 (C=N), 1575 (C=C) cm^1. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.36 (td, J = 7.5, 1.0 Hz, 1 H, 6-H), 7.46–7.49 (m, 2 H, 2 × Ar-H), 7.51 (d, J = 8.3 Hz, 1 H, 8-H), 7.73 (td, J = 7.8, 1.4 Hz, 1 H, 7-H), 7.90 (dd, J = 8.1, 1.0 Hz, 1 H, 5-H), 8.05–8.10 (m, 2 H, 2 × ArH), 8.31 (br. s, 2 H, 2 × ArH), 9.49 (s, 1 H, 4-H), 12.70 (s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. ^{13}C NMR

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(100 MHz, [D$_6$]DMSO): δ = 111.0, 115.7, 118.4 (Cq), 123.2, 124.8 (2 C), 127.9 (br., 3 C), 129.6, 130.7 (br., 4Cq), 133.6, 139.8 (2Cq), 143.6 (C-4), 149.9 (Cq), 159.7 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 311 (100) [M]$^+$, 283 (51) [M – CO], 156 (15), 142 (19), 140 (21), 115 (13). $C_{20}H_{13}N_3O$ (311.34): calcd. C 77.16, H 4.21, N 13.50; found C 77.05, H 4.26, N 13.65.

3-(3*H*-Imidazo[4,5-*c*]pyridin-2-yl)quinolin-2(1*H*)-one (4f): Yield: 216 mg. FTIR (KBr): $\tilde{\nu}$ = 3148 (br., 1-NHCO), 3112 (imidazole-NH), 1665 (2-C=O), 1632 (C=N), 1569 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.32 (t, *J* = 7.2 Hz, 1 H, 6-H), 7.51 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.63–7.69 (m, 2 H, 7-H, Pyr-H), 7.99 (d, *J* = 7.9 Hz, 1 H, 5-H), 8.32 (d, *J* = 4.5 Hz, 1 H, Pyr-H), 9.01 (s, 1 H, Pyr-H), 9.18 (s, 1 H, 4-H), 12.61 (imidazole-NH), 12.98 (s, 1 H, NHCO) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 108.0, 113.0 (Cq), 115.4, 119.0 (Cq), 119.4 (Cq), 122.7, 129.3, 132.1, 139.1 (2Cq), 140.3, 141.2 (2 C, C-4, Ar-C), 149.5 (Cq), 160.6 (2-C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 262 (100) [M]$^+$, 234 (92) [M – CO], 131 (12), 89 (6). $C_{15}H_{10}N_4O$ (262.09): calcd. C 68.69, H 3.84, N 21.36; found C 68.80, H 3.92, N 21.28.

2-(1,2-Dihydro-2-oxoquinolin-3-yl)-1*H*-benzo[*d*]imidazole-5-carboxylic Acid (4g): Yield: 264 mg. FTIR (KBr): $\tilde{\nu}$ = 3620–3310 (br., 1-NHCO and OH acid), 3167 (imidazole-NH), 1705 (C=O acid), 1669 (2-C=O), 1571 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 7.32 (td, *J* = 7.5, 1.0 Hz, 1 H, 6-H), 7.47 (d, *J* = 8.3 Hz, 1 H, 8-H), 7.69 (td, *J* = 7.8, 1.4 Hz, 1 H, 7-H), 7.83–7.88 (m, 2 H, 5-H and Ar-H), 7.98 (dd, *J* = 8.7, 1.6 Hz, 1 H, Ar-H), 8.37 (s, 1 H, Ar-H), 9.35 (s, 1 H, 4-H), 12.72 (s, 1 H, 1-NHCO) ppm; imidazole-NH and CO_2H are absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 115.1, 116.1, 116.9, 118.9 (2Cq), 123.7, 126.0, 127.4 (Cq), 129.9 (Cq), 130.0, 133.9, 140.0 (2Cq), 143.2 (C-4), 148.6 (Cq), 160.2 (2-C=O), 167.5 (CO_2H) ppm. MS (70 eV, EI): *m*/*z* (%) = 305 (100) [M]$^+$, 277 (71) [M – CO], 260 (8), 232 (15), 153 (14), 130 (10). $C_{17}H_{11}N_3O_3$ (305.29): calcd. C 66.88, H 3.63, N 13.76; found C 66.75, H 3.70, N 13.91.

8-(1,2-Dihydro-2-oxoquinolin-3-yl)-3-methyl-1*H*-purine-2,6(3*H*,9*H*)-dione (4h): Yield: 261 mg. FTIR (KBr): $\tilde{\nu}$ = 3147 (br., 2 × NHCO and imidazole-NH), 1702 (2 × C=O), 1663 (2-C=O), 1612 (C=N), 1589 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.48 (s, 3 H, CH_3), 7.30 (t, *J* = 6.8 Hz, 1 H, 6-H), 7.46 (d, *J* = 7.6 Hz, 1 H, 8-H), 7.62 (t, *J* = 6.8 Hz, 1 H, 7-H), 7.92 (d, *J* = 7.6 Hz, 1 H, 5-H), 8.83 (s, 1 H, 4-H), 12.31 (br. s, 1 H, NHCO), 12.60 (br. s, 1 H, NHCO) ppm. MS (70 eV, EI): *m*/*z* (%) = 309 (2) [M]$^+$, 149 (31), 28 (100). $C_{15}H_{11}N_5O_3$ (309.28): calcd. C 58.25, H 3.58, N 22.64; found C 58.33, H 3.45, N 22.66.

3-(6,9-Dihydro-2-methoxy-1-methyl-6-oxo-1*H*-purin-8-yl)quinolin-2(1*H*)-one (4i): Yield: 273 mg. FTIR (KBr): $\tilde{\nu}$ = 3455 (br., 1-NH amide), 3164 (imidazole-NH), 1703 (C=O), 1651 (2-C=O), 1614 (C=N), 1217 (C–O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.22 (s, 3 H, NCH_3), 3.99 (s, 3 H, OCH_3), 7.22 (t, *J* = 8.0 Hz, 1 H, 6-H), 7.41 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.61 (t, *J* = 8.0 Hz, 1 H, 7-H), 7.84 (d, *J* = 8.0 Hz, 1 H, 5-H), 8.41 (s, 1 H, 4-H), 10.24 (br. s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 40.4 (NCH_3), 55.9 (OCH_3), 115.5 (Cq), 116.1, 122.3 (Cq), 123.0, 123.1 (Cq), 129.1 (Cq), 130.6 (Cq), 131.1, 131.5 (Cq), 133.8, 134.6 (Cq), 142.9 (C-4), 160.5 (2-C=O), 190.1 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 323 (100) [M]$^+$, 279 (11), 171 (42), 155 (37). $C_{16}H_{13}N_5O_3$ (323.1): calcd. C 59.44, H 4.05, N 21.66; found C 59.31, H 3.92, N 21.80.

3-[6,9-Dihydro-2-(methylthio)-6-oxo-1*H*-purin-8-yl]quinolin-2(1*H*)-one (4j): Yield: 298 mg. FTIR (KBr): $\tilde{\nu}$ = 3410 (br., 2 × NHCO), 3127 (imidazole-NH), 1708 (C=O), 1687 (br., 2-C=O), 1631 (C=N), 1579 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.59 (s, 3 H, SCH_3), 7.27 (t, *J* = 7.7 Hz, 1 H, 6-H), 7.45 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.59 (t, *J* = 8.1 Hz, 1 H, 7-H), 7.86 (d, *J* = 7.9 Hz, 1 H, 5-H), 8.87 (s, 1 H, 4-H), 12.12 (br. s, 2 H, 2 × NHCO) ppm; imidazole-NH is absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 12.4 (SCH_3), 113.8 (Cq), 114.9, 116.1 (Cq), 118.6 (Cq), 122.1, 122.5 (Cq), 125.5 (Cq), 128.2, 129.5 (Cq), 130.9, 134.1 (Cq), 138.1 (C-4), 160.3 (2-C=O), 175.0 (C=O) ppm. MS (70 eV, EI): *m*/*z* (%) = 325 (100) [M]$^+$, 278 (18), 251 (18), 171 (40), 153 (26). $C_{15}H_{11}N_5O_2S$ (325.06): calcd. C 55.38, H 3.41, N 21.53; found C 55.51, H 3.29, N 21.62.

3-[6-Amino-2-(methylthio)-9*H*-purin-8-yl]quinolin-2(1*H*)-one (4k): Yield: 277 mg. FTIR (KBr): $\tilde{\nu}$ = 3478 (1-NHCO), 3417, 3283 (br.), 3097 (br., imidazole-NH), 1657 (2-C=O), 1597 (C=N), 1561 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.47 (s, 3 H, SCH_3), 7.28 (t, *J* = 7.3 Hz, 1 H, 6-H), 7.35 (br. s, 2 H, NH_2), 7.45 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.61 (t, *J* = 7.6 Hz, 1 H, 7-H), 7.90 (d, *J* = 8.0 Hz, 1 H, 5-H), 9.03 (s, 1 H, 4-H), 12.33 (s, 1 H, NHCO), 12.66 (s, 1 H, imidazolic) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 13.9 (SCH_3), 109.2 (Cq), 115.8, 119.5 (Cq), 119.6 (Cq), 123.2, 129.6, 132.3, 139.2 (Cq), 140.5 (C-4), 148.2 (Cq), 151.6 (Cq), 159.7 (Cq), 161.0 (2-C=O), 164.3 (Cq) ppm. MS (70 eV, EI): *m*/*z* (%) = 324 (100) [M]$^+$, 291 (15), 278 (34), 262 (19), 171 (78), 153 (56). $C_{15}H_{12}N_6OS$ (324.08): calcd. C 55.54, H 3.73, N 25.91; found C 55.63, H 3.82, N 25.78.

8-(1,2-Dihydro-2-oxoquinolin-3-yl)-1*H*-purine-2,6(3*H*,9*H*)-dione (4l): Yield: 234 mg. FTIR (KBr): $\tilde{\nu}$ = 3420 (2 × NHCO), 3264 (1-NHCO), 3149 (imidazole-NH), 1742 (2 × C=O), 1666 (2-C=O), 1607 (C=N), 1574 (C=C), 1281 (C–N) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.17 (t, *J* = 7.9 Hz, 1 H, 6-H), 7.29 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.44 (t, *J* = 7.6 Hz, 1 H, 7-H), 7.68 (d, *J* = 7.9 Hz, 1 H, 5-H), 9.72 (s, 1 H, 4-H), 10.14 (br. s, 1 H, NHCO), 11.80 (br. s, 1 H, NHCO) ppm; one NHCO and the imidazole-NH are absent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 99.8 (Cq), 115.3, 120.2 (Cq), 122.4, 128.8, 130.0 (Cq), 130.4, 139.0 (Cq), 142.7 (C-4), 150.8 (Cq), 156.2 (Cq), 159.8 (NHCO), 162.2 (2-C=O), 174.6 (NHCO) ppm. MS (70 eV, EI): *m*/*z* (%) = 295 (76) [M]$^+$, 252 (16), 224 (23), 171 (90), 43 (87), 28 (100). $C_{14}H_9N_5O_3$ (295.07): calcd. C 56.95, H 3.07, N 23.72; found C 56.81, H 3.19, N 23.46.

3-[6,9-Dihydro-1-methyl-2-(methylthio)-6-oxo-1*H*-purin-8-yl]quinolin-2(1*H*)-one (4m): Yield: 276 mg. FTIR (KBr): $\tilde{\nu}$ = 3360 (br., 1-NHCO), 3142 (imidazole-NH), 1689 (br., 2 × C=O) cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.67 (s, 3 H, SCH_3), 3.55 (s, 3 H, NCH_3), 7.29 (t, *J* = 7.7 Hz, 1 H, 6-H), 7.46 (d, *J* = 7.7 Hz, 1 H, 8-H), 7.61 (t, *J* = 7.7 Hz, 1 H, 7-H), 7.89 (d, *J* = 7.7 Hz, 1 H, 5-H), 8.92 (s, 1 H, 4-H), 12.24 (br. s, 1 H, 1-NHCO) ppm; imidazole-NH is absent. MS (70 eV, EI): *m*/*z* (%) = 339 (100) [M]$^+$, 252 (35), 171 (42), 153 (29), 67 (25). $C_{16}H_{13}N_5O_2S$ (339.08): calcd. C 56.63, H 3.86, N 20.64; found C 56.70, H 3.97, N 20.48.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectra for compounds **4a**, **4b**, and **4c** are provided.

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