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Phthalazinone Pyrazoles as Potent, Selective, and Orally Bioavailable Inhibitors of Aurora-A Kinase†

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The inhibition of Aurora kinases in order to arrest mitosis and subsequently inhibit tumor growth via apoptosis of proliferating cells has generated significant discussion within the literature. We report a novel class of Aurora kinase inhibitors based upon a phthalazinone pyrazole scaffold. The development of the phthalazinone template resulted in a potent Aurora-A selective series of compounds (typically >1000-fold selectivity over Aurora-B) that display good pharmacological profiles with significantly improved oral bioavailability compared to the well studied Aurora inhibitor VX-680.

Introduction

The Aurora kinases (consisting of Aurora A, B, and C) are a family of serine/threonine kinases that are involved in phosphorylation events believed to be key for the completion of critical mitotic events. Although both Aurora-A and Aurora-B are essential for the correct progression through and completion of mitosis, they are involved in very different roles within the cell division cycle.[1−3]

Aurora-A localizes mainly to the centrosomes and is key for correct centrosome maturation and separation.[4−7] While Aurora-A is not a classical oncogene, it is highly expressed in many tumors; its elevation may play an important role in the support of tumor progression and as such has attracted significant attention for small molecule inhibition. Furthermore, studies to inhibit the expression of Aurora-A in cells cause arrest in the cell cycle and subsequent cell death via apoptosis.[8,9]

Aurora-B localizes predominantly to the spindle midzones and has two key roles within the cell-division cascade of events. Initially Aurora-B is required for the phosphorylation of histone H3 at serine 10. It then maintains a wait-anaphase signal until all chromosomes are in the correct orientation for separation.[10−12]

The role of Aurora-C within tumorgenesis is less well-defined (although it has recently been suggested that it may have overlapping functions with Aurora-B), and additionally the expression level of Aurora-C in most somatic tissues is low except in the testis where expression is high.[13,14]

There are a large number of Aurora inhibitors currently undergoing clinical development, the vast majority of which display the classical phenotype associated with Aurora-B inhibition (cells treated with Aurora-B inhibitors fail to stain for phosphohistone H3). Examples described include VX-680 (Vertex, pan Aurora-A/B/C inhibitor), AZD-1152 (AstraZeneca, Aurora-B/C selective inhibitor), and GSK1070916 (GlaxoSmithKline, Aurora-B selective inhibitor) shown in Figure 1.[15−18] There are very few examples of selective Aurora-A inhibiting molecules, the best characterized being MLN8054 (Millenium, 43-fold selectivity over Aurora-B, although alternative data suggest that this selectivity may be as low as 7-fold).[19,20]

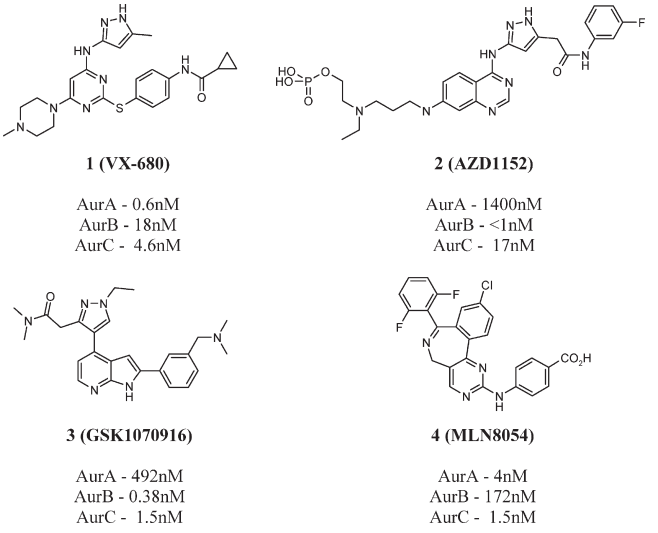

Figure 1. Advanced Aurora kinase inhibitors (data obtained from literature sources).[15−20]

We set out to prepare a class of compounds that displays selectivity for Aurora-A over Aurora-B. In this report we describe the discovery of a potent, Aurora-A selective class of small molecule inhibitors with >1000-fold selectivity over Aurora-B (**5**, Figure 2) which display orally dosed pharmacokinetic profiles suitable for in vivo pharmacodynamic studies.

†Atomic coordinates and structure factors for the crystal structure of Aurora A with compound **7** can be accessed using PDB code 3P9J.

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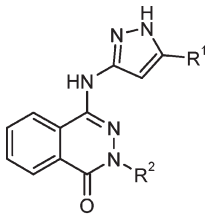

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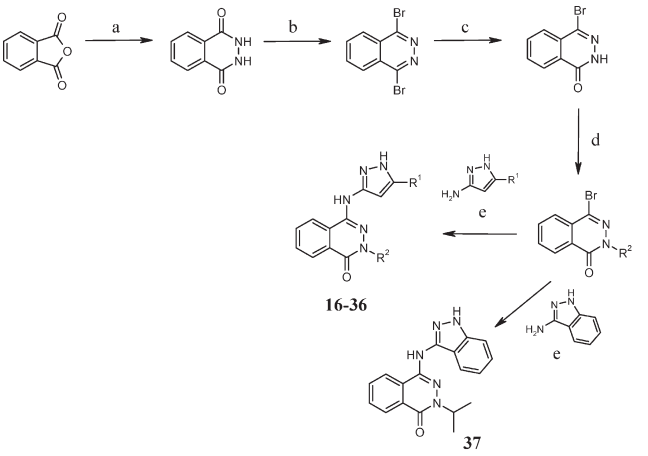
Figure 2. General structure of phthalazinone Aurora-A inhibitors.

Chemistry

The general synthesis of the initial phthalazinone analogues starts from phthalic anhydride and is described in Scheme 1. Reaction of electron-rich phenylhydrazines with phthalic anhydride affords the corresponding phthalazine-1,4-diones in moderate yields (30−50%) in one step, whereas electron-poor phenylhydrazines (such as **12** and **13** where Y = Cl or F) require a ring-expansion step using forcing conditions after formation of the initial isoindole-1,3-diones to give the target phthalazine-1,4-diones in good yields (70−80%) over two steps. Bromination using phosphorus oxybromide affords the bromophthalazinones in moderate yields (50−65%) which can be converted via palladium-catalyzed Buchwald−Hartwig coupling into the target phthalazinones in low to moderate yield (30−40%).[21,22]

In order to carry out further elaboration of the phthalazinone scaffold and fully explore structure−activity relationships, an alternative synthetic route was required that does not rely on the use of limited commercially available substituted hydrazines (Scheme 2). Hydrazine insertion into phthalic anhydride affords phthalazine-1,4-dione in quantitative yield. Subsequent dibromination followed by monohydrolysis gives the desired bromophthalazinone in good yield (60% over two steps). Substitution of the amide is then achieved using sodium hydride and an alkylating agent in moderate to high yield (> 55%). The final desired phthalazinones are prepared using the previously described Buchwald−Hartwig palladium coupling.

Scheme 2. Improved Synthesis of Phthalazinones[a]



16-36

37

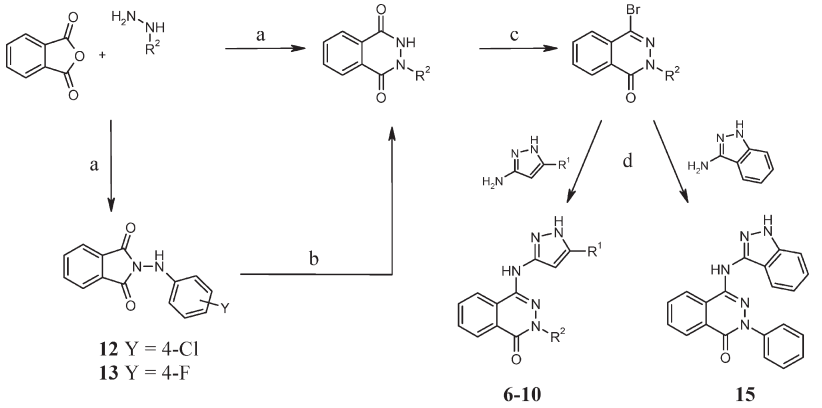
16: R^1 = Me, R^2 = CH_2Ph
17: R^1 = Me, R^2 = CH_2(3,5-di-F)Ph
18: R^1 = Me, R^2 = CH_2(2,5-di F)Ph
19: R^1 = Me, R^2 = CH_2(4-F)Ph
20: R^1 = Me, R^2 = CH_2(4-SO_2Me)Ph
21: R^1 = Me, R^2 = CH_2(4-OMe)Ph
22: R^1 = Me, R^2 = CH_2(3-OMe)Ph
23: R^1 = Me, R^2 = CH_2(4-NHAc)Ph
24: R^1 = Me, R^2 = CH_2(4-Pyridine)
25: R^1 = Me, R^2 = CH_2(3-Pyridine)
26: R^1 = Me, R^2 = CH_2(4-NO_2)Ph
27: R^1 = Me, R^2 = CH_2C(O)(4-OMe)Ph
28: R^1 = Me, R^2 = CH_2C(O)(3-OMe)Ph
29: R^1 = Me, R^2 = CH_2C(O)(4-CF_3)Ph
30: R^1 = Me, R^2 = CH_2C(O)Ph
31: R^1 = Me, R^2 = CH_2-3-Me-thiazole
32: R^1 = Me, R^2 = Methyl
33: R^1 = Me, R^2 = ^{i}Propyl
34: R^1 = Me, R^2 = ^{t}Butyl
35: R^1 = Me, R^2 = CH_2CF_3
36: R^1 = H, R^2 = CH_2(4-NHAc)Ph

[a] Reagents and conditions: (a) hydrazine, EtOH, 80 °C; (b) $POBr_3$, DCE, 120 °C, 24 h; (c) AcOH, 120 °C, 2 h; (d) NaH, R_2X, DMF, 2 h (3) Pd_2dba_3, NaO^{t}Bu, 2-(di-*tert*-butylphosphino)biphenyl, toluene/EtOH (10:1), 100 °C, 20 h.

Results and Discussion

Extensive analogue synthesis and design based around a number of phthalazine and pyridazine scaffolds was carried

Scheme 1. General Synthesis of Phthalazinones[a]



12 Y = 4-Cl
13 Y = 4-F

6-10

15

6: R^1 = Me, R^2 = H
7: R^1 = Me, R^2 = Ph
8: R^1 = Me, R^2 = (4-OMe)Ph
9: R^1 = Me, R^2 = (4-Me)Ph
10: R^1 = Me, R^2 = (3-Me)Ph
11: R^1 = Me, R^2 = (4-^{t}Bu)Ph
12: R^1 = Me, R^2 = (4-Cl)Ph
13: R^1 = Me, R^2 = (4-F)Ph
14: R^1 = H, R^2 = (4-Me)Ph

[a] Reagents and conditions: (a) EtOH, 80 °C; (b) glycerol, 180 °C, 24 h; (c) $POBr_3$, DCE, 120 °C, 20 h; (d) Pd_2dba_3, NaO^{t}Bu, 2-(di-*tert*-butylphosphino)biphenyl, toluene/EtOH (10:1), 100 °C, 20 h.

out which showed only weak (1−10 μM) activity against Aurora-A (Figure 3). All of these inhibitors were relatively linear in structure, closer inspection of the published X-ray structure of VX-680 with Aurora-A suggested that it may be possible to deviate from linearity.[23] Hence, we moved the aryl group from the para-position to the meta-position (position relative to the aminoimidazole group) and designed the phthalazinone **5** (Figure 2).

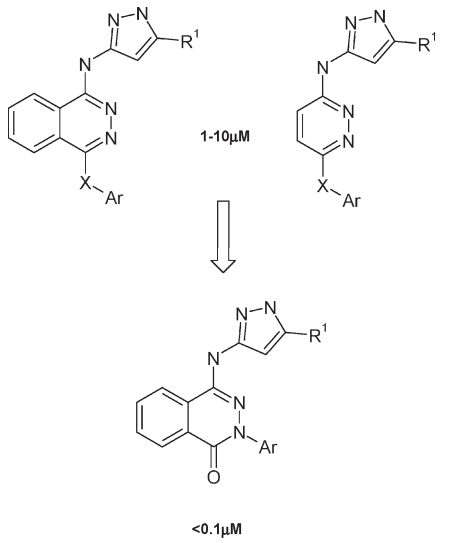


Figure 3. Selected templates investigated as Aurora kinase inhibitors.

While utilization of simple hydrazine insertion led to the discovery of compound **6** which showed improved activity toward Aurora-A, we were pleased to discover that substitution with a phenyl group in initial analogue **7** not only led to improved potency against Aurora-A but also displayed excellent selectivity over Aurora-B. Subsequent substituted analogues **8** and **9** displayed similar activities but also improved cellular activity in the HCT116 assay (Table 1).

Inspection of the binding mode for compound **7** after cocrystallization with Aurora-A (Figure 4) indicates that the donor−acceptor−donor motif of the aminopyrazole provides key (and expected) interactions between compound **7** and the hinge region of Aurora-A (Glu-211, Ala-213, Pro-214).

The proximity of the R^2 group (substituted phenyl or a methylene linked substituted phenyl in most inhibitors described here) to Aurora-A Thr-217 is the most likely contributor to selectivity. The corresponding residue in Aurora-B is Glu leading to a steric clash with the phenyl R^2 group (Figure 5). The extension of the substitution at the R^2 position by a methylene spacer (compounds **19**−**26**) indicates a slight removal of this clash, with a slight increase in Aurora-B activity observed. Additionally, the strength of the inhibition appears to depend on the chemical nature of the 4-subsitution; i.e., NO_2 finds an especially favorable binding site. In this description, the lack of inhibition of Aurora-B by compound **16** seems anomalous.

The strong effect of the loss of the methyl group at the R^1 position comparing compounds **9** and **14** in Aurora-A also may seem surprising. The methyl group binds in a largely hydrophobic pocket. It does not completely fill the pocket, but

Table 1. Screening Data for Phthalazinone Analogues[a]

			IC_{50}, μM				
compd	R^1	R^2	Aur-A	Aur-B	HCT116	Colo205	MCF7
6	Me	H	0.65	22	N/T	N/T	N/T
7	Me	Ph	0.031	> 100	7.8	2.9	1.6
8	Me	(4-OMe)Ph	0.029	> 100	0.7	3.7	3.6
9	Me	(4-Me)Ph	0.023	> 100	0.24	3.6	> 30
10	Me	(3-Me)Ph	0.024	> 100	2.3	3.2	2.9
11	Me	(4-^{t}Bu)Ph	0.24	> 50	0.06	N/T	0.78
12	Me	(4-Cl)Ph	0.093	> 100	0.82	2.2	11.4
13	Me	(4-F)Ph	0.037	> 100	0.8	1.6	1.6
14	H	(4-Me)Ph	1	N/T	N/T	N/T	N/T
15	N/A	Ph	14	N/T	N/T	N/T	N/T
16	Me	CH_2Ph	0.065	> 100	1.5	4.4	12.6
17	Me	CH_2(3,5-di-F)Ph	0.049	> 100	0.5	2.3	2.6
18	Me	(4-OMe)Ph	0.025	> 100	0.57	3.8	> 30
19	Me	CH_2(4-F)Ph	0.014	69	1.4	17	> 30
20	Me	CH_2(4-SO_2Me)Ph	0.056	34	1.7	4.5	4.5
21	Me	CH_2(4-OMe)Ph	0.032	46	1.2	4.2	> 30
22	Me	CH_2(3-OMe)Ph	0.036	28	0.66	3.6	> 30
23	Me	CH_2(4-NHAc)Ph	0.093	15	4.2	> 30	> 30
24	Me	CH_2(4-pyridine)	0.27	27	20.2	13	> 30
25	Me	CH_2(3-pyridine)	0.017	12.7	2.9	4.1	13.4
26	Me	CH_2(4-NO_2)Ph	0.109	0.93	1.4	N/T	> 30
27	Me	CH_2C(O)(4-OMe)Ph	0.067	> 100	> 30	> 30	> 30
28	Me	CH_2C(O)(3-OMe)Ph	0.1	67	2.7	> 30	> 30
29	Me	CH_2C(O)(4-CF_3)Ph	0.72	> 100	> 30	> 30	> 30
30	Me	CH_2C(O)Ph	0.071	> 100	5.44	> 30	> 30
31	Me	CH_2(3-methylthiazole)	0.12	24	4.18	> 30	> 30
32	Me	Me	0.27	17	5.2	> 30	> 30
33	Me	isopropyl	0.035	30	0.4	1.7	1.6
34	Me	isobutyl	0.115	34	1.1	N/T	4.2
35	Me	CH_2CF_3	0.066	15	1.8	N/T	4.5
36	H	CH_2(4-NHAc)Ph	0.55	34	> 30	N/T	> 30

[a] N/T = not tested. Results are the average of triplicate data; SD = 5−10%.

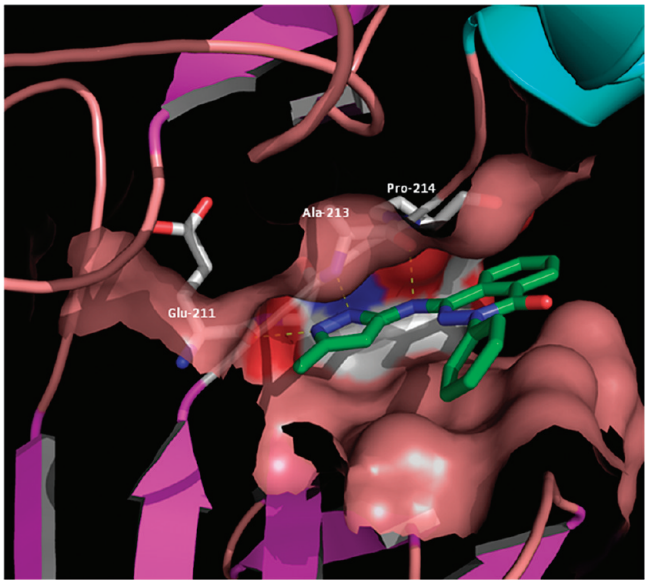


Figure 4. Crystal structure of phthalazinone **7** and Aurora-A, with hydrogen bonds to the hinge region shown in yellow.

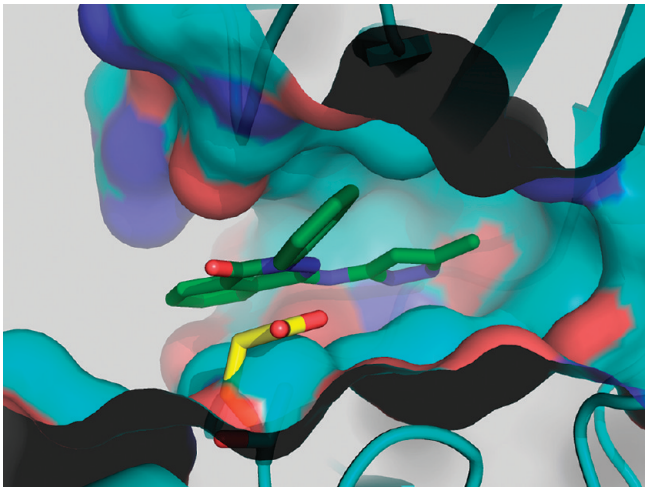


Figure 5. Pictorial representation of clash generated between R^2 phenyl and Glu residue (shown in yellow) in Aurora-B.

the adjoining surfaces are partially polar and can accommodate water molecules. In the absence of inhibitor, water can be found bound to the hinge and the ATP[a] pocket will be filled with largely structured water. Compound **14**, however, allows neither the hydrophobic interactions made by the methyl group nor the binding of an appropriately structured water molecule, leaving instead an energetically unfavorable hole. A similar comparison between compounds **23** and **36** shows a smaller effect. However, the lessened effect arises primarily because compound **23** binds to Aurora-A more weakly than compound **9** and the energetic disadvantage of a putative disruptive water remains.

Several compounds display phenotypic Aurora-A inhibition when tested against the MCF7 cell line, with poorly formed centrosomes observed (such as compound **16**, Figure 6), and cells subsequently arrest at the G2M stage.

[a] Abbreviations: ATP, adenosine triphosphate; DCE, 1,2-dichloroethane; hERG, the human ether-a-go-go-related gene; HPLC, high pressure liquid chromatography; PEG, polyethylene glycol.

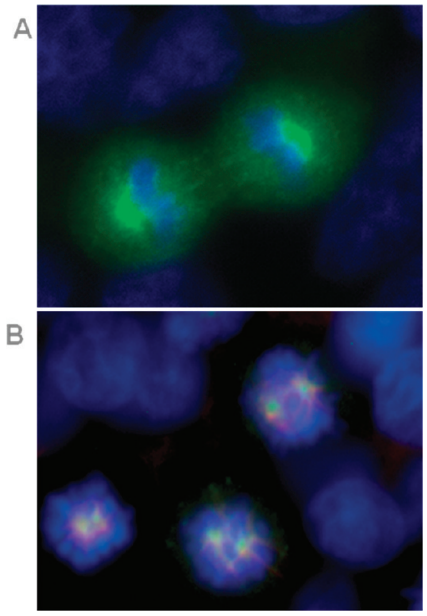


Figure 6. Cellular effect of **16** on MCF7 cells: (A) normal cycling cell, immunostained for Aurora-A (green); (B) cells incubated with **16** displaying improper centrosome formation. Cells were incubated with 10 μM **16** for 24 h. DNA is in blue, and Aurora-A is in green.

Compounds **7**, **16**, and **33** (which all display good biochemical potency with moderate activity against all cell lines) were selected for further in vitro and in vivo profiling (Table 2). There were no significant cytochrome P450 or hERG related issues. The compounds showed moderate to high stability in microsomes and hepatocytes and were taken on for pharmacokinetic analysis.

All three compounds displayed plasma concentrations above the cellular IC_{50} at the half-life and also show substantially improved oral bioavailability compared with VX-680 as illustrated in Figure 7.

Conclusion

The phthalazinone class of general structure **5** represents a novel class of Aurora-A inhibitors displaying over 1000-fold selectivity against Aurora-B. The compounds also display good oral bioavailability and good plasma concentrations, which is encouraging for pharmacodynamic testing. Further development of this class of compound has been carried out to address improvements in cellular activity, and the results of this development along with initial pharmacodynamic studies will be reported separately.

Experimental Section

Crystallography. A triple mutant (K124A, T287A, T288A) kinase domain construct (residues 124−391) of Aurora-A expressed in *E. coli* was used for crystallization.[24] The threonine to alanine mutations were located in the activation loop at the phosphorylation sites and eliminated heterogeneous autophosphorylation that prevented purification to homogeneity. The protein was concentrated to between 10 and 20 mg/mL and mixed in a ratio of 24:1 with a 50 mM DMSO solution of the inhibitor. Crystals were produced by mixing the protein−inhibitor solution with a PEG grid crystallization screen in volumes of 100 nL + 200 nL, 200 nL + 200 nL, and 300 nL + 200 nL using a MicroSys8 nanoliter pipetter into Greiner and/or Corning low birefringence 96-well sitting drop crystallization plates at 4 °C. The crystallization optimization screen consisted of a set of

Table 2. In Vitro/in Vivo Profiling of Selected Phthalazinone Inhibitors

	7	16	33
Aurora-A (μM)	0.03	0.065	0.035
HCT 116 (μM)	7.8	1.5	0.4
aqueous solution (μg/mL)	1.2	1.9	7
Cyp 3A4, 2C9, 2D6 (μM)	>50, >50, >50	>50, 42, >50	>50, >50, >50
hERG	20% at 10 μM	N/T	N/T
CL_{hep} ((μL/min)/10^6 cells)	r 2.3	r 2.4	N/T
CL_{mic} ((μL/min)/mg Prot)	h 0, m 15.7	h 7.4, m 28	N/T
C_{max} (μM), 30 mg/kg po	1.4	13	25
$T_{1/2}$ (h)	2.3	4.2	2.4

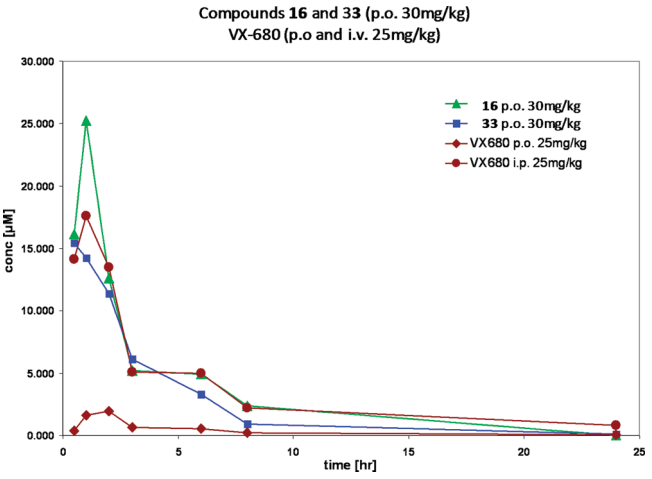


Figure 7. Plasma concentrations of phthalazinones **16** and **33**.

PEG, pH, and salt additive screens, using PEG3350, PEG2000, and PEG4000. Plates were stored and imaged at 4 and 20 °C in a Rhombix (DCA/Kendro/Thermo) based temperature controlled hotel and microscope imager system. Hexagonal crystals typically appeared within 1 or 2 days, but the largest crystals could take up to a month to grow and reach lengths of ~300 μm.

Crystals were harvested using paratone N as cryoprotectant and frozen in liquid nitrogen. Data were collected at the Swiss Light Source in Villigen, Switzerland. The measured crystal was hexagonal, with *P*6122 symmetry, with cell constants $a = b = 83.1$ Å and $c = 169.2$ Å, and diffracted to 2.8 Å. The data were 99.7% complete for the resolution range used in refinement (2.8−24.7 Å). The data were integrated and scaled using XDS. Model building was done with MOLOC (www.moloc.ch) and refinement with the CCP4 program suite. The final *R*-factor was 21.5% without modeling explicit solvent positions.

Disorder apparent from the electron density map prevented modeling of the N-terminus (residues 124 and 125), much of the activation loop (residues 280−290, 304−306), and the C-terminus (residues 389−391). The glycine loop showed disorder but was modeled into the apparent predominant conformation. Difference density for the inhibitor confirmed the details of the hinge binding to the aminopyrazole and the relative placement of the phthalazinone and phenyl rings, in particular the proximity of the phenyl ring to the sole amino acid exchange position that distinguishes Aurora-A from Aurora-B at the ATP binding site (Thr-317).

Inhibition Assays. Both Aurora-A and Aurora-B kinase activities were measured by enzyme-linked immunosorbent assay (ELISA). Maxisorp 394-well plates (Nunc) were coated with recombinant fusion protein comprising residues 1−15 of histone H3 fused to the N-terminus of glutathione *S*-transferase. Plates were then blocked with a solution of 1 mg/mL I-block (Tropix catalog no. T2015, highly purified form of casein) in phosphate-buffered saline. Kinase reactions were carried out in the wells of the ELISA plate by combining an appropriate amount of mutant Aurora-A kinase or Aurora-B kinase with test compound and 30 μM ATP. The reaction buffer was 10× kinase buffer (Cell Signaling catalog no. 9802) supplemented with 1 μg/mL I-block. Reactions were stopped after 40 min by addition of 25 mM EDTA. After washing, substrate phosphorylation was detected by addition of anti-phospho-histone H3 (Ser 10) 6G3 mAb (Cell Signaling catalog no. 9706) and sheep anti-mouse pArb-HRP (Amersham catalog no. NA931V), followed by colorimetric development with TMB (3,3′,5,5′-tetramethylbenzidine from Kirkegaard & Perry Laboratories). After readout of the adsorbance, IC_{50} values were calculated using a nonlinear curve fit (XLfit software (ID Business Solution Ltd., Guilford, Surrey, U.K.)). All screening data are the average of triplicate results with a standard deviation of between 5% and 10%.

CellTiter-Glo Assay in HCT 116 Cells. HCT 116 cells (human colon carcinoma, ATCC no. CCl-247) were cultivated in RPMI 1640 medium with GlutaMAX I (Invitrogen, catalog no. 61870-010), 2.5% fetal calf serum (FCS, Sigma catalog no. F4135), and 100 units of penicillin/mL and 100 μg of streptomycin/mL (=Pen/Strep from Invitrogen, catalog no.15140). Cells were seeded in 384-well plates, 1000 cells per well, in the same medium. The following day the test compounds were added in various concentrations ranging from 30 to 0.0015 μM (10 concentrations, 1:3 diluted). After 5 days the CellTiter-Glo assay was carried out according to the instructions of the manufacturer (CellTiter-Glo luminescent cell viability assay, from Promega). The cell plate was equilibrated to room temperature for approximately 30 min, and then the CellTiter-Glo reagent was added. The contents were carefully mixed for 15 min to induce cell lysis. After 45 min the luminescent signal was measured in Victor 2 (scanning multiwall spectrophotometer, Wallac). All screening data are the average of triplicate results with a standard deviation of between 5% and 10%.

Generic Experimental for the Synthesis of Phthalazinone Derivatives. Commercially available reagents and solvents (HPLC grade) were used without further purification. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer in deuterated solvents. Chemical shifts (δ) are in parts per million. Thin-layer chromatography (TLC) analysis was performed with Kieselgel 60 F_{254} (Merck) plates and visualized using UV light.

Analytical HPLC−MS was performed on Shimadzu LCMS-2010EV systems using reverse phase Atlantis dC18 columns (3 μm, 2.1 mm × 50 mm), gradient 5−100% B (A = water/0.1% formic acid, B = acetonitrile/0.1% formic acid) over 3 min, injection volume 3 μL, flow rate 1.0 mL/min. UV spectra were recorded at 215 nm using a Waters 2788 dual wavelength UV detector. Mass spectra were obtained over the range m/z 150−850 at a sampling rate of 2 scans per second using Waters LCT or analytical HPLC−MS on Shimadzu LCMS-2010EV systems using reverse phase Water Atlantis dC18 columns (3 μm, 2.1 mm × 100 mm), gradient 5−100% B (A = water/0.1% formic acid, B = acetonitrile/0.1% formic acid) over 7 min, injection volume 3 μL, flow rate 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photodiode array. Data were integrated and reported using Shimadzu PsiPort software. All compounds prepared for biochemical screening displayed purities determined by HPLC as ≥95%.

2-Phenyl-2,3-dihydrophthalazine-1,4-dione. Phenylhydrazine (59.4 g, 0.55 mol) was added in one portion to a stirred mixture of phthalic anhydride (74.0 g, 0.5 mol) in acetic acid (500 mL) at room temperature. The mixture was heated to 125 °C for 2 h and then allowed to cool to room temperature. The suspension was poured into water (500 mL), and the precipitate was filtered. The precipitate was stirred in 1 M Na_2CO_3 (400 mL) and the remaining undissolved solid removed by filtration. This solid was washed with two further 400 mL portions of 1 M Na_2CO_3. The basic solutions were combined and acidified by dropwise addition of concentrated HCl until gas evolution ceased. A white precipitate formed and was filtered and dried for 18 h in a vacuum oven (50 °C) to give the phthalazinone (46.3 g, 39% yield) as a white solid. δ_H (400 MHz, DMSO-d_6) 11.7 (1H, br s), 8.3 (1H, d), 8.03 (1H, d), 7.93 (2H, m), 7.67 (1H, d), 7.51 (1H, t), 7.4 (1H, t). t_R = 1.04 min. m/z (ES^+) $(M + H)^+$ 239.

4-Bromo-2-phenyl-2*H*-phthalazin-1-one. Phosphorus oxybromide (3.13 g, 10.8 mmol) was added to a stirred suspension of 2-phenyl-2,3-dihydrophthalazine-1,4-dione (1.30 g, 5.4 mmol) in 1,2 dichloroethane (15 mL). The mixture was heated to 100 °C for 18 h before being cooled and poured into water (100 mL). The aqueous layer was made basic with 1 M Na_2CO_3 and then extracted into DCM (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica column chromatography (20% ethyl acetate/hexane) to give the bromophthalazinone (0.770 g, 48% yield) as a white solid. δ_H (400 MHz, DMSO-d_6) 8.2 (1H, dd), 7.91 (1H, td), 7.89 (1H, td), 7.35−7.55 (5H, m). t_R = 1.51 min. m/z (ES^+) $(M + H)^+$ 301, 303.

4-(5-Methyl-2*H*-pyrazole-3-ylamino)phenyl-2*H*-phthalazin-1-one (7). Degassed toluene (6 mL) and ethanol (3 mL) were added in one portion to a mixture of 4-bromo-2-phenyl-2*H*-phthalazin-1-one (0.75 g, 2.5 mmol), sodium *tert*-butoxide (0.34 g, 3.5 mmol), 3-amino-5-methylpyrazole (0.29 g, 3 mmol), tris-(dibenzylidineacetone)dipalladium (0.11 g, 0.125 mmol), and 2-(di-*tert*-butylphosphino)biphenyl (0.07 g, 0.25 mmol) under nitrogen. The reaction mixture was heated to 100 °C for 20 h with stirring and then cooled to room temperature. Diethyl ether (10 mL) was added and the resulting precipitate was filtered to give the crude product as a gray solid. The crude product was triturated with acetonitrile (2 mL) to give the target compound (0.045 g, 40% overall yield) as an off-white solid. δ_H (400 MHz, DMSO-d_6) 11.93 (1H, s), 9.31 (1H, s), 8.53 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.92−7.99 (2H, m), 7.88 (d, J = 8.6 Hz, 1H), 7.77 (t, J = 8.1 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 6.24 (1H, s), 2.18 (3H, s). t_R = 1.11 min. m/z (ES^+) $(M + H)^+$ 318.29.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (6). 6 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 8.98 (1H, s), 8.37 (d, J = 8.2 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.96−7.82 (2H, m), 6.18 (1H, s), 2.22 (3H, s). t_R = 1.27 min. m/z (ES^+) $(M + H)^+$ 242.15.

2-(4-Methoxyphenyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (8). 8 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.72 (1H, s), 9.05 (1H, s), 8.28 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.76−7.66 (2H m), 7.40 (d, J = 6.8 Hz, 2H), 6.84 (d, J = 6.8 Hz, 2H), 6.03 (1H, s), 3.61 (3H, s), 1.97 (3H, s). t_R = 1.03 min. m/z (ES^+) $(M + H)^+$ 348.34.

4-(1*H*-Pyrazol-3-ylamino)-2-*p*-tolyl-2*H*-phthalazin-1-one (9). 9 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.70 (1H, s), 9.04 (1H, s), 8.27 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.78−7.68 (2H m), 7.35 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 6.01 (1H, s), 2.14 (3H, s), 1.94 (3H, s). t_R = 1.11 min. m/z (ES^+) $(M + H)^+$ 318.32.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-*m*-tolyl-2*H*-phthalazin-1-one (10). 10 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.28 (1H, s), 8.48 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 6.8 Hz, 1H), 7.98−7.86 (2H, m), 7.54−7.47 (2H m), 7.37 (t, J = 7.7 Hz, 1H), 7.16 (d, J = 7.1 Hz, 1H), 6.23 (1H, s), 2.37 (3H, s), 2.17 (3H, s). t_R = 1.09 min. m/z (ES^+) $(M + H)^+$ 332.34.

2-(4-*tert*-Butylphenyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (11). 11 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.36 (1H, s), 8.46 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.00−7.89 (2H, m), 7.62 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 6.24 (1H, s), 2.21 (3H, s), 1.34 (9H, s). t_R = 1.30 min. m/z (ES^+) $(M + H)^+$ 374.40.

2-(4-Chlorophenyl)-2,3-dihydrophthalazine-1,4-dione. 4-Chlorophenyl hydrazine hydrochloride (5.00 g, 28.0 mmol) was added in one portion to a stirred mixture of phthalic anhydride (3.70 g, 25.0 mmol) in acetic acid (50 mL) at room temperature. The mixture was heated to 125 °C for 2 h and then allowed to cool to room temperature. The suspension was poured into water (100 mL), and the precipitate was filtered. The precipitate was stirred in 1 M Na_2CO_3 (100 mL) and the remaining undissolved solid removed by filtration. This solid was washed with a further 100 mL portion of 1 M Na_2CO_3. The basic aqueous solutions were combined and acidified by dropwise addition of concentrated HCl until gas evolution ceased. A white precipitate formed and was filtered and dried for 18 h in a vacuum oven (50 °C) to give the phthalazinone (270 mg, 4% yield). The solid insoluble in 1 M Na_2CO_3 was stirred in glycerol (50 mL) and heated to 150 °C for 10 h. The reaction mixture was then diluted with water (50 mL), and 4 M HCl was added dropwise until a precipitate formed. The precipitate was filtered, resuspended in MeOH (30 mL), and collected by filtration. The product was dried under vacuum to give the desired phthalazinone (3.6 g, 72% yield) as a white solid. δ_H (400 MHz, DMSO-d_6) 12.10 (1H, br s), 8.3 (1H, d), 7.9−8.0 (3H, m), 7.7 (2H, d), 7.6 (2H, d). t_R = 1.27 min. m/z (ES^+) $(M + H)^+$ 273, 275.

This material was then brominated and used in the Buchwald reaction as described previously.

2-(4-Chlorophenyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (12). 12 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.97 (1H, s), 9.34 (1H, s), 8.51 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 7.99−7.89 (2H, m), 7.80 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 6.24 (1H, s), 2.20 (3H, s). t_R = 1.16 min. m/z (ES^+) $(M + H)^+$ 352.30.

2-(4-Fluorophenyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (13). 13 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 12.17 (1H, s), 9.51 (1H, s), 8.73 (d, J = 7.8 Hz, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.20−8.10 (1H m), 7.99−7.95 (2H, m), 7.55 (t, J = 9.0 Hz, 2H), 6.45 (1H, s), 2.40 (3H, s). t_R = 1.07 min. m/z (ES^+) $(M + H)^+$ 336.31.

4-(1*H*-Pyrazol-3-ylamino)-2-*p*-tolyl-2*H*-phthalazin-1-one (14). 14 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 12.05 (1H, s), 9.22 (1H, s), 8.31 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.82−7.64 (2H, m), 7.38 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.28 (1H, s), 2.09 (3H, s). t_R = 1.11 min. m/z (ES^+) $(M + H)^+$ 318.32.

4-(1*H*-Indazol-3-ylamino)-2-phenyl-2*H*-phthalazin-1-one (15). 15 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 12.48 (1H, s), 9.37 (1H, s), 8.46−8.37 (2H, m), 8.06−7.91 (2H, m), 7.71 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 6.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 1H), 7.36−7.18 (4H, m), 7.01 (t, J = 8.0 Hz, 1H). t_R = 1.29 min. m/z (ES^+) $(M + H)^+$ 354.14.

4-Bromo-2*H*-phthalazin-1-one. 2,3-Dihydro-1,4-phthalazinedione (12.5 g, 78 mmol) was suspended in dichloroethane (200 mL), and phosphorus pentabromide (50.0 g, 116 mmol) was added in one portion. The mixture was heated to reflux for 24 h. A further portion of phosphorus pentabromide (20.0 g, 70 mol) was added and the mixture heated for a further 24 h. The mixture was cooled to room temperature and poured into ice−water (500 mL). The

resulting precipitate was filtered and washed with water to give a crude mixture of monobrominated and dibrominated product (22.8 g). This crude material was suspended in acetic acid (230 mL) and heated to 120 °C for 2 h. The mixture was cooled to room temperature and poured into ice−water and the resulting precipitate filtered. The solid was washed with water and dried to give the title compound (10.4 g, 60% yield) as a white solid. δ_H (400 MHz, DMSO-d_6) 12.95 (1H, s), 8.25 (1H, dd), 8.03 (1H, ddd), 7.96−7.90 (2H, m). t_R = 1.02 min. m/z (ES^+) $(M + H)^+$ 225, 227.

2-Benzyl-4-bromo-2*H*-phthalazin-1-one. 4-Bromo-2*H*-phthalazin-1-one (10.38 g, 46 mmol) was dissolved in DMF (60 mL). To this was added NaH (60%, 1.55 g, 46.2 mmol) as a DMF suspension (20 mL). The mixture was stirred at room temperature for 30 min. Then benzyl bromide (13.82 g, 50.8 mmol) was added in one portion as a solution in DMF (20 mL). The reaction mixture was stirred for 2 h. Then the DMF was removed under reduced pressure and the resulting crude material purified by column chromatography (gradient elution, 100% heptane to 20% ethyl acetate/heptane) to give the title compound (8.16 g, 56% yield) as a white solid. δ_H (400 MHz, DMSO-d_6) 8.30 (1H, dd), 8.03 (1H, ddd), 7.97−7.91 (2 H, m), 7.34−7.27 (5H, m), 5.31 (2H, s). t_R = 1.11 min. m/z (ES^+) $(M + H)^+$ 315, 317

This material was then used in the Buchwald reaction as described previously.

2-Benzyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (16). 16 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.89 (1H, s), 9.24 (1H, s), 8.44 (d, J = 7.7 Hz, 1H), 8.31 (d, J = 7.7 Hz, 1H), 7.93−7.82 (2H, m), 7.37−7.30 (4H m), 7.27 (d, J = 7.0 Hz, 1H), 6.09 (1H, s), 5.24 (2H, s) 2.17 (3H, s). t_R = 1.60 min. m/z (ES^+) $(M + H)^+$ 332.08.

2-(3,5-Difluorobenzyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (17). 17 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.59 (1H, s), 8.44 (d, J = 8.0 Hz, 1H), 8.33 (dd, J = 7.8, 1.2 Hz, 1H), 7.99−7.88 (2H, m), 7.17 (tt, J = 9.4, 2.4 Hz, 2H), 7.08 (dd, J = 8.3, 2.1 Hz, 2H), 6.12 (1H, s), 5.32 (2H, s), 2.23 (3H, s). t_R = 1.17 min. m/z (ES^+) $(M + H)^+$ 368.10.

2-(2,5-Difluorobenzyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (18). 18 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.88 (1H, s), 9.25 (1H, s), 8.44 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 7.93−7.85 (2H, m), 7.32−7.21 (3H, m), 5.93 (1H, s), 5.29 (2H, s), 2.16 (3H, s). t_R = 1.14 min. m/z (ES^+) $(M + H)^+$ 368.14.

2-(4-Fluorobenzyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (19). 19 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.53 (1H, s), 8.40 (d, J = 7.8 Hz, 1H), 8.31 (dd, J = 7.9, 1.3 Hz, 1H), 7.96−7.85 (2H, m), 7.41 (dd, J = 8.7, 5.6 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 6.11 (1H, s), 5.26 (2H, s), 2.22 (3H, s). t_R = 1.13 min. m/z (ES^+) $(M + H)^+$ 350.11.

2-(4-Toluylsulfonate)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (20). 20 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.20 (1H, s), 8.35 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.89−7.79 (4H, m), 7.53 (d, J = 8.3 Hz, 2H), 6.00 (1H, s), 5.30 (2H, s), 3.08 (3H, s), 2.12 (3H, s). t_R = 1.23 min. m/z (ES^+) $(M + H)^+$ 410.12.

2-(4-Methoxybenzyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (21). 21 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.91 (1H, s), 9.28 (1H, s), 8.47 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 7.97−7.89 (2H, m), 7.37 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.18 (1H, s), 5.21 (2H, s), 3.76 (3H, s), 2.24 (3H, s). t_R = 1.30 min. m/z (ES^+) $(M + H)^+$ 362.36.

2-(3-Methoxybenzyl)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (22). 22 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.88 (1H, s), 9.23 (1H, s), 8.44 (d, J = 7.8 Hz, 1H), 8.32 (d, J = 7.8 Hz, 1H), 7.92−7.86 (2H, m), 7.24 (t, J = 7.9 Hz, 1H), 6.96 (1H, s), 6.93 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.15 (1H, s), 5.21 (2H, s), 3.72 (3H, s), 2.18 (3H, s). t_R = 1.32 min. m/z (ES^+) $(M + H)^+$ 362.35.

***N*-{4-[1-Oxo-4-(1*H*-pyrazol-3-ylamino)-1*H*-phthalazin-2-ylmethyl]phenyl}acetamide (23). 23** was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.91 (1H, s), 9.16 (1H, s), 8.46−8.36 (1H, m), 8.29 (dd, J = 7.6, 1.7 Hz, 1H), 7.86 (qd, J = 6.7, 6.6 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 6.10 (1H, s), 5.14 (2H, s), 2.17 (3H, s), 1.99 (3H, s). t_R = 1.38 min. m/z (ES^+) $(M + H)^+$ 375.29.

2-(Methyl-4-pyridine)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (24). 24 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.38 (1H, s), 8.70 (d, J = 6.6 Hz, 2H), 8.44 (d, J = 7.8 Hz, 1H), 8.31 (dd, J = 7.8, 1.3 Hz, 1H), 7.98−7.86 (2H, m), 7.69 (d, J = 6.6 Hz, 2H), 6.06 (1H, s), 5.46 (2H, s), 2.17 (3H, s). t_R = 1.08 min. m/z (ES^+) $(M + H)^+$ 333.21.

2-(Methyl-3-pyridine)-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (25). 25 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.38 (1H, s), 8.68 (d, J = 1.2 Hz, 2H), 8.54 (d, J = 4.2 Hz, 2H), 8.29 (d, J = 7.8 Hz, 2H), 8.17 (dd, J = 7.7, 1.3 Hz, 2H), 8.05 (d, J = 8.1 Hz, 2H), 7.83−7.72 (4H, m), 7.58 (dd, J = 7.8, 5.4 Hz, 2H), 5.95 (2H, s), 5.27 (3H, s), 2.07 (4H, s). t_R = 1.05 min. m/z (ES^+) $(M + H)^+$ 333.14.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-(4-nitrobenzyl)-2*H*-phthalazin-1-one (26). 26 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.32 (1H, s), 8.34 (d, J = 8.0 Hz, 2H), 8.21(d, J = 8.0 Hz, 2H), 8.0 (d, J = 6.8 Hz, 2H), 7.49−7.85 (2H, m), 7.49 (d, J = 8.8 Hz, 2H), 5.93 (1H, s), 5.29 (2H, s), 2.04 (3H, s). t_R = 1.05 min. m/z (ES^+) $(M + H)^+$ 377.24.

2-[2-(4-Methoxyphenyl)-2-oxoethyl]-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (27). 27 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.43 (1H, s), 8.40 (d, J = 8.3 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 9.0 Hz, 2H), 7.93−7.81 (2H, m), 7.04 (d, J = 9.0 Hz, 2H), 6.12 (1H, s), 5.54 (2H, s), 3.80 (3H, s), 2.11 (3H, s). t_R = 1.25 min. m/z (ES^+) $(M + H)^+$ 390.14.

2-[2-(3-Methoxyphenyl)-2-oxoethyl]-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (28). 28 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.38 (1H, s), 8.43 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.92−7.80 (2H, m), 7.61 (d, J = 7.6 Hz, 1H), 7.49−7.42 (2H, m), 7.21 (d, J = 8.3 Hz, 1H), 6.11 (1H, s), 5.57 (2H, s), 3.77 (3H, s), 2.09 (3H, s). t_R = 1.32 min. m/z (ES^+) $(M + H)^+$ 390.15.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-[2-oxo-2-(4-trifluoromethylphenyl)ethyl]-2*H*-phthalazin-1-one (29). 29 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.89 (1H, s), 9.31 (1H, s), 8.48 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 8.8 Hz, 3H), 7.96 (d, J = 8.1 Hz, 3H), 7.88 (t, J = 7.5 Hz, 1H), 6.18 (1H, s), 5.67 (2H, s), 2.14 (3H, s). t_R = 1.06 min. m/z (ES^+) $(M + H)^+$ 428.09.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-(2-oxo-2-phenylethyl)-2*H*-phthalazin-1-one (30). 30 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.91 (1H, s), 9.31 (1H, s), 8.48 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 7.1 Hz, 2H), 7.98−7.87 (2H, m), 7.74−7.70 (1H, m), 7.62−7.58 (2H, m), 6.21 (1H, s), 5.63 (2H, s), 2.15 (3H, s). t_R = 1.09 min. m/z (ES^+) $(M + H)^+$ 360.10.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-(2-methylthiazol-4-ylmethyl)-2*H*-phthalazin-1-one (31). 31 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.82 (1H, s), 8.39 (d, J = 8.1 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.99−7.88 (2H, m), 7.36 (1H, s), 6.16 (1H, s), 5.34 (2H, s), 2.64 (3H, s), 2.26 (3H, s). t_R = 1.18 min. m/z (ES^+) $(M + H)^+$ 353.18.

2-Methyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (32). 32 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.70 (1H, s), 9.00 (1H, s), 8.23 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 7.8 Hz, 2H), 7.73−7.64 (2H, m), 6.13 (1H, S), 3.44 (3H S), 2.04 (3H, s). t_R = 0.97 min. m/z (ES^+) $(M + H)^+$ 389.27.

2-Isopropyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (33). 33 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.92 (1H, s), 9.17 (1H, s), 8.43 (d, J = 7.9 Hz, 1H), 8.28 (dd, J = 7.8, 1.1 Hz, 1H), 7.90−7.80 (2H, m), 6.35 (1H, s), 5.25 (dt, J = 13.2, 6.6 Hz, 1H), 2.24 (3H, s), 1.13 (d, J = 6.6 Hz, 6H). t_R = 0.97 min. m/z (ES^+) $(M + H)^+$ 284.34.

2-Isobutyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2*H*-phthalazin-1-one (34). 34 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 11.76 (1H, s), 9.00 (1H, s), 8.2 (d, J = 6.8 Hz, 1H), 8.15 (d, J = 6.8 Hz, 1H), 7.77−7.67 (2H, m), 6.17 (1H, S), 3.71 (d, J = 6.8 Hz, 2H), 2.10−2.07 (4H, m), 0.75 (d, J = 6.6 Hz, 6H). t_R = 1.03 min. m/z (ES^+) $(M + H)^+$ 298.33.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-(2,2,2-trifluoroethyl)-2*H*-phthalazin-1-one (35). 35 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 9.58 (1H, s), 8.47 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 8.01−7.83 (2H, m), 6.34 (1H, S), 4.93 (q, J = 9.1 Hz, 2H), 2.25 (3H, s). t_R = 1.03 min. m/z (ES^+) $(M + H)^+$ 323.10

***N*-{4-[1-Oxo-4-(1*H*-pyrazol-3-ylamino)-1*H*-phthalazin-2-ylmethyl]phenyl}acetamide (36). 36** was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 12.13 (1H, s), 9.87 (1H, s), 9.26 (1H, s), 8.42 (d, J = 6.5 Hz, 1H), 8.21 (d, J = 6.5 Hz, 1H), 7.93−7.78 (2H, m), 7.53 (1H, s), 7.44 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.38 (1H, s), 5.12 (2H, s), 1.91 (3H, s). t_R = 0.92 min. m/z (ES^+) $(M + H)^+$ 375.29.

4-(1*H*-Indazol-3-ylamino)-2-isopropyl-2*H*-phthalazin-1-one (37). 37 was synthesized according to the general procedure as described above. δ_H (400 MHz, DMSO-d_6) 8.41 (t, J = 8.1 Hz, 2H), 8.08−7.91 (2H, m), 7.59 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.36 (t, J = 7.1 Hz, 1H), 7.02 (t, J = 7.1 Hz, 1H), 5.24−5.04 (1H, m), 1.07 (d, J = 6.4 Hz, 6H). t_R = 1.22 min. m/z (ES^+) $(M + H)^+$ 319.14.

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