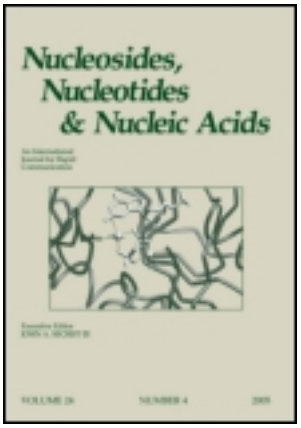

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Synthesis of Potential Pyrimidine Derivatives via Suzuki Cross-Coupling Reaction as HIV and Kinesin Eg5 Inhibitors

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SYNTHESIS OF POTENTIAL PYRIMIDINE DERIVATIVES VIA SUZUKI CROSS-COUPLING REACTION AS HIV AND KINESIN Eg5 INHIBITORS

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□ *A series of 4-amino-5-((4-chlorophenyl)diazenyl)-6-(alkylamino)-1-methylpyrimidin-2-one derivatives* ***7–16*** *were prepared by nucleophilic displacement of 6-chloro-pyrimidine* ***6*** *by various amines. 4-Amino-5-((aryl-4-yl)diazenyl)-6-aryl-1-methylpyrimidin-2-one analogs* ***19–27****, as well as 4-amino-5-((aryl-[1,1′-biphenyl]-4-yl)diazenyl)-6-aryl-1-methylpyrimidin-2-one* ***29–31*** *and 4-amino-6-aryl-1-methylpyrimidin-2-one* ***34–34****, were synthesized via Suzuki cross-coupling reaction, using* $Pd(PPh_3)_4$ *as a catalyst and arylboronic acids as reagents. All compounds were evaluated for their antiviral activity against the replication of HIV-1 and HIV-2 in MT-4. Compounds* ***6, 16, 27,*** *and* ***29*** *showed a 50% effective concentration of* > 2.15, > 3.03, > 2.29, *and* $> 1.63\ \mu M$, *respectively, but no selectivity was observed (selectivity index* < 1*). Two of the newly synthesized pyrimidines* ***12*** *and* ***29*** *exhibited moderate kinesin Eg5 inhibition.*

Keywords Anti-HIV activity; azo-coupling; kinesin Eg5 inhibitors; pyrimidines; palladium-catalyzed Suzuki cross-coupling reaction

INTRODUCTION

It is well known that pyrimidine derivatives are of great biological interest, especially as antitumor,[1–6] antimicrobial,[7–10] and antihypertensive[11] agents, in addition to their cardiovascular[12,13] and diuretic[14,15] properties. Furthermore, pyrimidines are compounds that in vitro possess biological activity against a wide spectrum of unrelated viruses, such as poliovirus,[16] herpes virus,[17] and human immunodeficiency virus (HIV).[18–20] For the latter, two diarylpyrimidines, rilpivirine[21] **1** and etravirine,[22,23] have been

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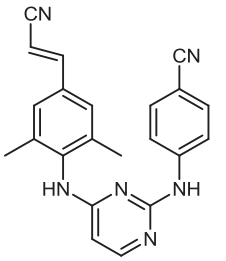
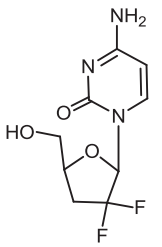
clinically approved for the treatment of people infected by HIV. These drugs have been classified as non-nucleoside reverse transcriptase inhibitors. Bacimethrin (4-amino-5-(hydroxymethyl)-2-methoxypyrimidine) is a pyrimidine antibiotic that is active against several staphylococcal bacteria.[24] Methoprim, 5-(3,4,5-trimethoxybenzyl)pyrimidine-2,4-diamine [25,26] is used, in combination with urinarytractinfections and *Pneumocystis jirovecii pneumonia*.[27] Gemcitabine **2**, a pyrimidine antimetabolite, showed excellent antitumor activity against murine solid tumors,[28] while 2,4-diamino-N^4-6-diarylpyrimidines were identified to block the proliferation of tumor cell lines in vivo, especially duodenum cancer (DU145, $IC_{50} = 0.23\ \mu M$).[29]

More recently, new mitotic targets such as kinesins have attracted great interest worldwide as potential candidates for new-generation antiproliferative drugs.[30–34] Kinesin spindle protein (KSP), also known as Eg5, are essential for the formation and separation of bipolar spindles during human cell division.[35] The Eg5 tetramer has the ability to crosslink antiparallel microtubules emanating from the two centrosomes at G2/M. Anticancer drug screening and chemical biological approaches have identified a range of structurally diverse KSP inhibitors that have been found to cause cell cycle arrest, differentiation, and/or apoptosis of tumor cells. Monastrol **3**[36] is one of the first generation of KSP inhibitors that interact with microtubules, and then causes mitotic arrest.[37]

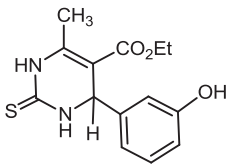
In our recent work, we have reported new pyrimidine derivatives (e.g. compound **4**) with their anti-HIV and human hepatitis virus type C (HCV)



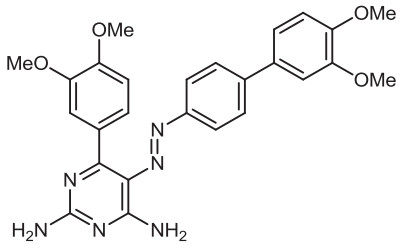
1. Rilpivirine



2. Gemcitabine



3. Monastrol

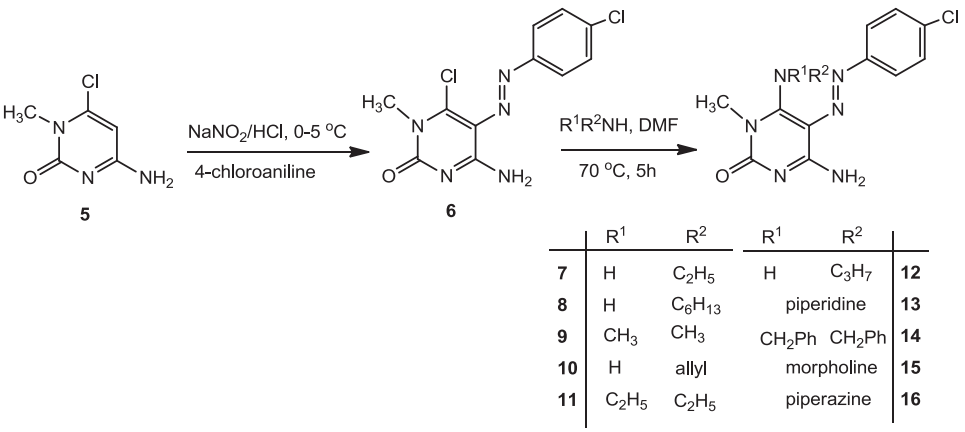


4. Triaryl-pyrimidine analogue

activity,[38] meanwhile we report here the synthesis of new scaffolds of 4-amino-6-chloro-1-methylpyrimidin-2-one **5** via Suzuki cross-coupling procedure[39–41] and their in vitro activity on the replication of HIV-1, and HIV-2.

RESULTS AND DISCUSSION

In the present work, 4-amino-6-chloro-1-methylpyrimidin-2(1*H*)-one **5**[42] has been selected as a starting material for the synthesis of various pyrimidine analogs. Treatment of **5** with 4-chloroaniline in the presence of $NaNO_2$ and HCl afforded the azo-pyrimidine **6** (50%). Treatment of **6** with various amines yielded, via nucleophilic displacements of the chlorine group, **7–16** in 86–57 90% yield (Scheme 1). The structures of **6** and **7–16** were assigned by the ^1H and ^{13}C NMR spectra. The ^1H NMR spectra showed rather similar patterns for the phenyl and pyrimidine protons; meanwhile, the singlets at δ 3.39–3.16 ppm were attributed to the N-methyl (NMe) group. The protons of substituted alkylamino groups at C-6 were fully analyzed (cf. *Experimental Section*). In the ^{13}C NMR spectra of **7–16**, the higher-field resonances at the region δ = 164.8–161.4 ppm were attributed to C-4, while the resonances at the region δ = 157.9–155.0 ppm were assigned to C-2 pyrimidine backbone. C-6 and C-5 of the pyrimidine scaffold resonated at the regions δ = 156.6-149.2 ppm and δ = 117.3–93.5 ppm, respectively. The gradient heteronuclear multiple-bond correlation spectroscopy (HMBC)[43] spectrum of **7** showed two $^3J_{C,H}$ couplings between C-6 of the pyrimidine backbone at δ = 149.7 ppm with methylene protons of N-ethyl (NEt) group at δ = 3.04 ppm, as well as NMe protons at δ = 3.19 ppm. Additionally, a $^3J_{C,H}$ coupling between the NMe protons and C = O (C-2) at δ = 155.7 ppm was observed (Figure 1).



	R^1	R^2	R^1	R^2	
7	H	C_2H_5	H	C_3H_7	**12**
8	H	C_6H_{13}	piperidine		**13**
9	CH_3	CH_3	CH_2Ph	CH_2Ph	**14**
10	H	allyl	morpholine		**15**
11	C_2H_5	C_2H_5	piperazine		**16**

SCHEME 1 Synthesis of 4-amino-5-((4-chlorophenyl)diazenyl)-6-(alkylamino)-1-methylpyrimidin-2-one derivatives.

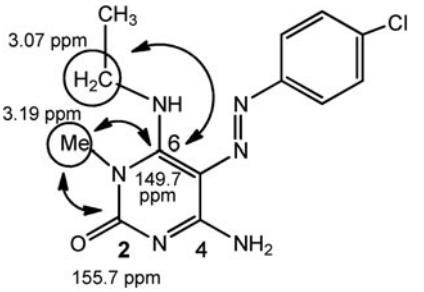
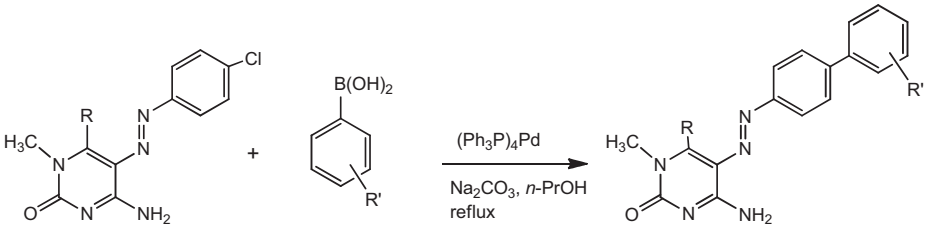


FIGURE 1 $J_{C,H}$ correlations in the HMBC NMR spectrum of **7**.

Further, our efforts have been focused on arylation of the new-synthesized azo-*p*-chlorophenyl derivatives by using Suzuki methodology.[41] Thus, treatment of **7**, **9**, and **11–14** with 3,4-dimethoxyphenylboronic acid **17** in the presence of $Pd(Ph_3P)_4$ and Na_2CO_3 afforded **19** (74%) and **23–27** (63–71%), respectively. Similar treatment of **8**, **10**, and **15** with 4-fluorophenylboronic acid **18** furnished **20–22** in 67, 79, and 63% yield, respectively (Scheme 2). The constitution of **19–27** was determined from their ^1H and ^{13}C NMR spectra.

Our work was modified by selecting **6** as a precursor for the synthesis of new triaryl derivatives to examine their antiviral activity in comparison to the alkylamino analogs **7–16**. Thus, treatment of **6** with 3,4-dimethoxy- **17**, 4-fluoro- **18**, and 4-ethoxycarbonyl- **28**, phenyl boronic acids, respectively,

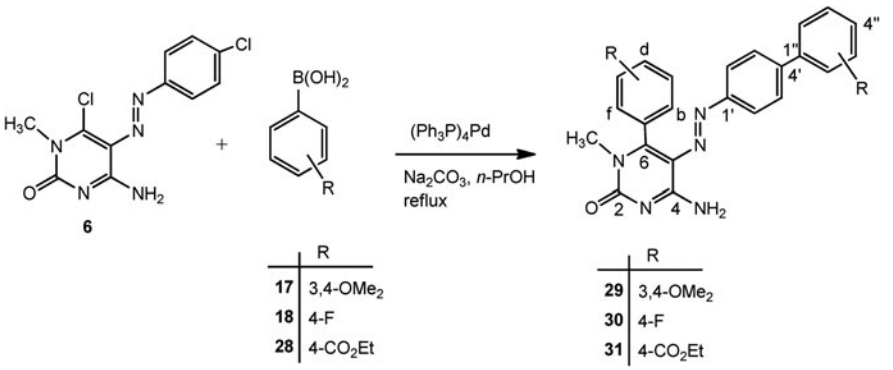


	R
7	NHC_2H_5
8	NHC_6H_{13}
9	NMe_2
10	NH-allyl
11	NEt_2
12	NHC_3H_7
13	piperidine
14	$N(CH_2Ph)_2$
15	morpholine

	R
17	3,4-OMe_2
18	4-F

	R	R'
19	NHC_2H_5	3,4-OMe_2
20	NHC_6H_{13}	4-F
21	NH-allyl	4-F
22	morpholine	4-F
23	NMe_2	3,4-OMe_2
24	NEt_2	3,4-OMe_2
25	NHC_3H_7	3,4-OMe_2
26	piperidine	3,4-OMe_2
27	$N(CH_2Ph)_2$	3,4-OMe_2

SCHEME 2 Synthesis of 4-amino-5-((substituted-[1,1′-biphenyl]-4-yl)diazenyl)-6-alkylamino-1-**m**ethyl-pyrimidin-2-one derivatives.



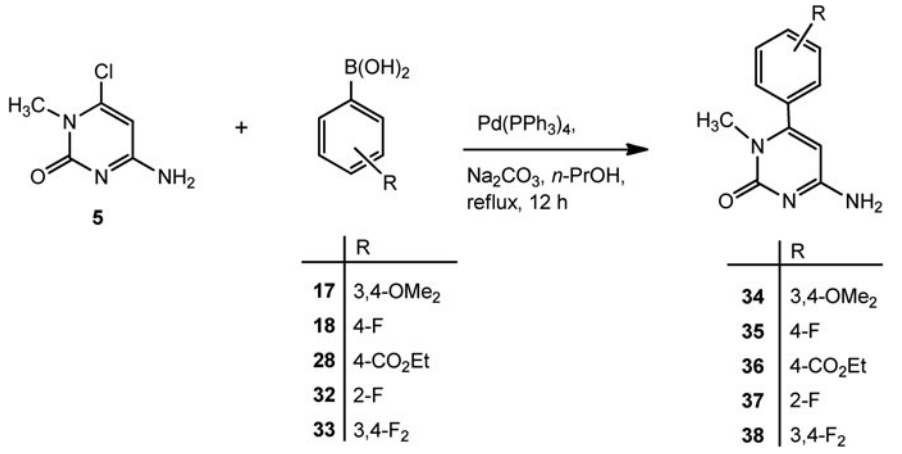
SCHEME 3 Synthesis of 4-amino-5-((substituted-[1,1′-biphenyl]-4-yl)diazenyl)-6-(aryl)-1-methylpyrimidin-2-one derivatives.

using Suzuki methodology gave **29–31** in 80, 71, and 86% yield, respectively (Scheme 3). The structures of **29–31** were identified by ^{1}H, and ^{13}C NMR. The carbon atoms C = O (C-2) of the pyrimidine ring were resonated at δ = 156.9, 156.1, and 156.3 ppm, respectively, while C-4 appeared at δ = 164.7, 164.6, and 164.1 ppm, respectively. The carbon atom C-6 of the same ring oriented at δ = 141.2, 141.6, and 140.0 ppm, respectively, while C-5 resonated at δ = 94.3, 93.0, and 92.9 ppm, respectively. Moreover, all the synthesized compounds were further identified by ^{1}H, ^{13}C heteronuclear single quantum coherence spectroscopy (HSQC)[43] spectroscopic study. Compound **31** was selected for further NMR study, where the HMBC spectrum[44] revealed a $^{3}J_{C,H}$ coupling between C-6 of the pyrimidine backbone at δ = 140.0 ppm and the aromatic protons of (H_b and H_f) at δ = 7.43 ppm.

Next, treatment of **5** with 3,4-dimethoxy- **17**, 4-fluoro- **18**, 4-ethoxycarbonyl- **28**, 2-fluoro- **32**, and 3,4-difluoro- **33** phenylboronic acids, using Suzuki methodology,[41] afforded **34–38** in 81, 69, 61, 59, and 79% yield, respectively (Scheme 4). The structures of **34–38** were determined from the ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectra of **34–38**, C-6 of the pyrimidine ring resonated at the region δ = 164.7–164.1 ppm, while C-2, C-4, and C-5 resonated at the regions δ = 156.9–156.1 ppm, δ = 143.5–141.4 ppm, and δ = 94.8–93.9 ppm, respectively. Compound **37** was further characterized by ^{19}F NMR spectrum, which showed two doublets at δ = 137.8, 137.4 (2xd, $J_{F,F}$ = 22.6 Hz, 2xF) attributed to the resonances of two fluorine atoms.

In Vitro Anti-HIV-Assay

Compounds **6–16**, **19–27, 29–31,** and **34–38** were tested for their in vitro anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity and monitored by the inhibition of the virus-induced cytopathic effect in the human (MT-4) cells, based on MTT assay.[45] The results are summarized in Table 1, in which



SCHEME 4 Synthesis of 4-amino-6-(aryl)-1-methylpyrimidin-2-one derivatives.

the data for nevirapine[46] and azidothymidine (AZT),[47] were included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

All the compounds are inactive, except compounds **6**, **16**, **27**, and **29**, which showed 50% effective concentration (EC_{50}) values of >2.15, >3.03, >2.29, and >1.63 μM, respectively, but no selectivity was observed (selectivity index; SI < 1).

In a series of 4-amino-6-aryl-1-methylpyrimidin-2-ones, the CC_{50} values of **34**, **35**, **37**, and **38** are lower than those of **36**, suggesting the electronegative fluorine and methoxy groups in benzene ring of the pyrimidine skeleton caused reduction in CC_{50} values. However, compound **34** with 3,4-dimethoxyphenyl substituent at position 6 showed a CC_{50} = 14.23 μM, whereas introducing a 3,4-dimethoxy-1,1′-biphenyl]-4-yl)diazenyl) substituent at position 5 (analog **29**) demonstrated increased cytotoxicity value (1.63 μM). These results indicated that the introduction of additional heteroatom (azo-biaryl group) were not suitable options for position 5 of the pyrimidine backbone, although **29** exhibited EC_{50} > 1.63 μM. Next, introduction of linear amino groups like hexylamine and allylamine of **20** and **21,** respectively, at position 6 led to CC_{50} value of 11.66 and 10.42 μM, respectively, in comparison for those of the cyclic amine (morpholine) of **22** (CC_{50} = 88.71 μM) and aryl group at position 6 of compound **30** (CC_{50} = 66.60 μM). This suggested that a linear substituent was favorable for the cytotoxic activity.

In Vitro Anti-Kinesin Activity

Mitotic kinesins are molecular motors that play a central role in cell division. Small molecules that block kinesin activity can lead to mitotic arrest,

TABLE 1 In vitro anti-HIV-1[a] and anti-HIV-2[b] activity and cytotoxicity of new pyrimidines

Entry	HIV-1 (III_B) EC_{50} (μM)[c]	HIV-2 (ROD) EC_{50} (μM)[c]	CC_{50} (μM)[d]	SI[e] (III_B)	SI[e] (ROD)
6	> 2.15	> 2.15	2.15	<1	<1
7	> 36.72	> 36.72	36.72	<1	<1
8	> 66.60	> 66.60	66.60	<1	<1
9	> 28.24	> 28.24	28.24	<1	<1
10	> 14.23	> 14.23	14.23	<1	<1
11	> 100	> 100	100	<1	<1
12	> 100	> 100	100	<1	<1
13	> 20.11	> 20.11	20.11	<1	<1
14	> 78.59	> 78.59	78.59	<1	<1
15	> 12.22	> 12.22	12.22	<1	<1
16	> 3.03	> 3.03	3.03	<1	<1
19	> 23.13	> 23.13	23.13	<1	<1
20	> 11.66	> 11.66	11.66	<1	<1
21	> 10.42	> 10.42	10.42	<1	<1
22	> 88.71	> 88.71	88.71	<1	<1
23	> 10.42	> 10.42	10.42	<1	<1
24	> 25.23	> 25.23	25.23	<1	<1
25	> 36.76	> 36.76	36.76	<1	<1
26	> 18.15	> 18.15	18.15	<1	<1
27	> 2.29	> 2.29	2.29	<1	<1
29	> 1.63	> 1.63	1.63	<1	<1
30	> 66.60	> 66.60	66.60	<1	<1
31	> 28.24	> 28.24	28.24	<1	<1
34	> 14.23	> 14.23	14.23	<1	<1
35	> 19.35	> 19.35	19.35	<1	<1
36	> 75.23	> 75.23	75.23	<1	<1
37	> 13.27	> 13.27	13.27	<1	<1
38	> 16.01	> 16.01	16.01	<1	<1
Nevirapine	0.050	> 4.00	> 4.00	>80	<1
AZT	0.0022	0.00094	> 25	>11363	>26596

[a]Anti-HIV-1 activity measured with strain III_B; [b]anti-HIV-2 activity measured with strain ROD; [c]compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; [d]compound concentration that reduces the viability of mock-infected MT-4 cells by 50%; [e]SI: selectivity index (CC_{50}/EC_{50}).

apparent in the formation of a monoaster within the cell (shown). Kinesin-targeted molecules hold great potential as an alternative strategy in cancer chemotherapy.

Compounds **6–16**, **19–27, 29–31,** and **34–38** were screened for inhibition of kinesin Eg5, using an in vitro malachite green ATPase assay.[48] Two of these compounds **12** and **31** exhibited moderate inhibition (mitotic index: 43 and 35%, respectively), but none of the compounds matched the selection criteria of a selective inhibitor of Eg5 in this assay in comparison to monastrol.

CONCLUSION

We report the in vitro antiviral activity against HIV-1 (III_B strain) and HIV-2 (ROD strain) and anti-kinesin activity of 4-amino-5-((4-chlorophenyl)

diazenyl)-6-(alkylamino)-1-methylpyrimidin-2-one derivatives **7–16**, 4-amino-6-aryl-5-((aryl-4-yl)diazenyl)-1-methylpyrimidin-2-one analogs **19–27**, substituted triaryl **29–31,** and monoaryl analogs **34–38**. The first results showed that **6**, **16**, **27**, and **29** having antiviral properties against HIV with (EC_{50} > 2.15, > 3.03, > 2.29, and > 1.63 μM, respectively). Although no selectivity was observed (SI < 1) for these pyrimidine derivatives, but these were the agents of choice for further pharmacological evaluation. In addition, these compounds were screened against kinesin Eg5, and two analogs **12** and **31** exhibited moderate inhibition activity. However, introduction of chloro or aryl group at C-4 of pyrimidine backbone together with 1,1′-biphenyl-diazenyl group in C-5, respectively, considerably increased the anti-HIV.

EXPERIMENTAL

General

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). NMR data were obtained on 400 and 600 MHz (^{1}H) and 150.91 MHz (^{13}C) spectrometers (Avance III, Bruker, Germany) with tetramethylsilane (TMS) as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by HMBC and HSQC experiments. Microanalytical data were obtained with a Vario, Elemental analyzer (Shimadzu, Japan). Analytical silica gel thin layer chromatography (TLC) plates 60 F254 were purchased from Merck (Darmstadt, Germany). All reagents were obtained from commercial suppliers and were used without further purification.

4-Amino-6-chloro-5-((4-chlorophenyl)diazenyl)-1-methylpyrimidin-2-one (6)

A solution of 4-chloroaniline (260 mg, 2.0 mmol) in 6 N HCl (3 mL) was cooled to 0–5°C, and then $NaNO_2$ (138 mg, 2.0 mmol) in water (2 mL) was added dropwise with stirring. After the addition was completed, the solution was stirred another 15 minutes and checked by iodine-starch paper to give a blue color. Urea (50 mg) was added to destroy the excess of HNO_2. The diazonium salt solution was then poured into a solution of 4-amino-6-chloro-1-methylpyrimidin-2-one **5** (320 mg, 2.0 mmol) in water (5 mL) and stirred for 30 minutes. Potassium acetate (400 mg) was then added, and the mixture was stirred for 16 hours at room temperature. The resulting precipitate was collected, washed with water, and dried in a vacuum over P_4O_{10} to give a yellow solid (300 mg, 50%). Recrystallization from dimethylformamide (DMF)/water afforded a pure sample, m.p. 260–263°C. ^{1}H NMR (DMSO-d_6): δ = 8.79 (s, 2H, NH_2), 7.44, 7.24 (2xbr s., 4H, Ar-H), 3.36 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6): δ = 164.1 (C-4), 155.6 (C-2), 146.1 (C_{arom}-1), 137.2 (C-6), 133.4 (C-Cl), 129.3, 127.6 (C_{arom}), 93.7 (C-5), 32.6 (NMe). Anal. calcd. for $C_{11}H_9Cl_2N_5O$ (298.13): C 44.32, H 3.04, N 23.49. Found: C 44.10, H 2.96, N 23.29.

General Method for Preparation of 4-Amino-5-((4-chlorophenyl)diazenyl)-6-(alkylamino)-1-methylpyrimidin-2-one Derivatives (7–16)

A solution of 5 (149 mg, 0.50 mmol) in DMF (20 mL) and an appropriate amine (5 mL) were heated in an oil bath at 70°C for 5 hours. Then water (25 mL) was added, the solution was cooled, and the yellow precipitate was collected, washed with water, and dried. Recrystallization from EtOH afforded the desired product.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(ethylamino)-1-methylpyrimidin-2-one (7)

From ethylamine. Yield: 77 mg (50%), m.p. 190–193°C. ^{1}HNMR (DMSO-d_6): $\delta = 8.06$ (d, 2H, $J = 7.1$, Ar-H), 7.63 (d, 2H, $J = 7.1$ Hz, 2H, Ar-H), 7.36 (s, 2H, NH_2), 7.22 (br s., 1H, NH), 3.19 (s, 3H, NMe), 3.04 (q, 2H, $J = 7.2$ H_Z, CH_2CH_3), 0.97 (t, $J = 7.2$ H_Z, CH_2CH_3). ^{13}CNMR (DMSO-d_6): $\delta = 164.8$ (C-4), 155.7 (C-2), 149.7 (C-6), 146.5 (C_{arom}-1), 134.2, 130.4, 128.4 (C_{arom}), 114.4 (C-5), 36.6 (NCH_2CH_3), 33.5 (NMe), 10.1 (NCH_2CH_3). Anal. calcd. for $C_{13}H_{15}F_2ClN_6O$ (306.75): C 50.90, H 4.93, N 27.40. Found: C 50.49, H 4.81, N 27.20.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(hexylamino)-1-methylpyrimidin-2-one (8)

From hexylamine. Yield: 120 mg (67%), m.p. 130–133°C. ^{1}H NMR (DMSO-d_6): $\delta = 8.16$ (d, 2H, $J = 7.0$ H_Z, Ar-H), 7.54 (d, 2H, $J = 7.0$ Hz, Ar-H), 7.43 (br s., 3H, $NH_2 + NH$), 3.43 (br s., 3H, NMe), 2.69 (m, 2H, CH_2-1′), 1.63 (m, 2H, CH_2-2′), 1.53 (m, 2H, CH_2-4′), 1.30–1.21 (m, 7H, CH_2-3′ + CH_2-5′ + CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 163.7$ (C-4), 155.0 (C-2), 150.7 (C-6), 146.4 (C_{arom}-1), 131.9 (C-Cl), 129.1 (C_{arom}), 116.2 (C-5), 46.5 (NCH_2-1′), 32.6 (NMe), 29.2 (CH_2-2′ + CH_2-4′), 25.4 (C-3′), 22.5 (C-5′), 13.3 (CH_3). Anal. calcd. for $C_{17}H_{23}ClN_6O$ (362.86): C 56.27, H 6.39, N 23.16. Found: C 56.31, H 6.30, N 22.92.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(dimethylamino)-1-methylpyrimidin-2-one (9)

From dimethylamine. Yield: 120 mg (78%), m.p. 180–183°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.37$–7.24 (m, 4H, Ar-H), 7.23 (br s., 3H, $NH_2 + NH$), 3.47 (br s., 6H, NMe_2), 3.34 (br s., 3H, NMe). ^{13}C NMR (DMSO-d_6): $\delta = 164.0$ (C-4), 155.9 (C-2), 149.2 (C-6), 146.1 (C_{arom}-1), 133.9 (C-Cl), 128.7, 121.5 (C_{arom}), 93.5 (C-5), 42.7 (NMe_2), 32.6 (NMe). Anal. calcd. for $C_{13}H_{15}ClN_6O$ (306.75): C 50.90, H 4.93, N 27.40. Found: C 50.72, H 4.86, N 27.29.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(allylamino)-1-methylpyrimidin-2-one (10)

From allyl amine. Yield: 116 mg (73%), m.p. 240–242°C. ^{1}H NMR (DMSO-d_6): $\delta = 8.06$ (d, 2H, $J = 7.3$ H_Z, Ar-H), 7.96 (d, 2H, $J = 7.3$ Hz,

Ar-H), 7.34 (d, J = 5.0 H_Z, NH_2), 7.09 (br s., 1H, NH), 5.64 (dd, 2H, J_{gem} = 14.0 H_Z, $NCH_2CH = CH_2$), 5.17 (m, 1H, $NCH_2CH = CH_2$), 3.96 (m, 2H, $NCH_2CH = CH_2$), 3.19 (s, 3H, NCH_3). ^{13}CNMR (DMSO-d_6): δ = 164.7 (C-4), 155.9 (C-2), 150.7 (C-6), 146.6 (C_{arom}-1), 138.6 ($NCH_2CH = CH_2$), 135.0 (C-Cl), 130.7, 128.4 (C_{arom}), 118.1 (NCH_2-$CH = CH_2$), 114.1 (C-5), 46.6 (NCH_2), 33.5 (NMe). Anal. calcd. for $C_{14}H_{15}ClN_6O$ (318.76): C 52.75, H C4.74, N 26.36. Found: C 52.53, H 4.64, N 26.08.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(diethylamino)-1-methylpyrimidin-2-one (11)

From dimethylamine. Yield: 120 mg (78%), m.p. 180–183°C. ^{1}H NMR (DMSO-d_6): δ = 8.17 (d, 2H, J = 4.9 H_Z, NH_2), 7.46 (d, J = 6.8 H_Z, Ar-H), 3.18 (s, 3H, NMe), 3.40 (q, 4H, J = 7.1 H_Z, 2xNCH_2CH_3), 1.64 (t, 6H, 2xNCH_2CH_3). ^{13}C NMR (DMSO-d_6): δ = 164.1 (C-4), 156.4 (C-2), 155.6 (C-6), 146.0 (C_{arom}-1), 133.5, 132.5, 129.5 (C_{arom}), 93.7 (C-5), 55.1 (2xNCH_2CH_3), 32.6 (NMe), 15.6 (2xNCH_2CH_3). Anal. calcd. for $C_{15}H_{19}ClN_6O$ (334.80): C 53.81, H 5.72, N 25.10. Found: C 53.69, H 5.60, N, 24.89.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-(propylamino)-1-methylpyrimidin-2-one (12)

From propylamine. Yield: 107 mg (67%), m.p. 190–194°C. ^{1}H NMR (DMSO-d_6): δ = 8.50 (d, 2H, J = 7.2 H_Z, Ar-H), 7.94 (d, 2H, J = 7.2 Hz, Ar-H), 3.39 (br s., 3H, NMe), 2.64 (m, 2H, $NCH_2CH_2CH_2$), 1.60 (m, 2H, $NCH_2CH_2CH_3$), 0.88 (t, 3H, J = 7.2 Hz, $NCH_2CH_2CH_3$). ^{13}C NMR (DMSO-d_6): δ = 163.9 (C-4), 155.4 (C-2), 149.9 (C-6), 146.7 (C_{arom}-1), 134.9 (C-Cl), 131.0, 128.4 (C_{arom}), 117.3 (C-5), 32.0 (NMe), 146.7 (C_{arom}-1), 134.9 (C-Cl), 43.8 ($NCH_2CH_2CH_3$), 32.0 (NMe), 21.0 ($NCH_2CH_2CH_3$), 11.2 ($NCH_2CH_2CH_3$). Anal. calcd. for $C_{14}H_{17}ClN_6O$ (320.78): C 52.42, H 5.34, N 26.20. Found: C 52.19, H 5.28, N 25.98.

4-Amino-5-((4-chlorophenyl)diazenyl)-1-methyl-6-(piperidin-1-yl)pyrimidin-2-one (13)

From piperidine. Yield: 149 mg (86%), m.p. 225–228°C. ^{1}H NMR (DMSO-d_6): δ = 8.49 (d, 2H, J = 7.1 H_Z, Ar-H), 7.94 (d, 2H, J = 7.1 Hz, Ar-H), 3.16 (br s., 3H, NMe), 2.82 (m, CH_2-2′ + CH_2-6′), 1.61 - 1.54 (CH_2-3′ - CH_2-5′). ^{13}C NMR (DMSO-d_6): δ = 162.1 (C-4), 156.9 (C-2), 153.2 (C-6), 145.5 (C_{aromr}-1), 134.4 (C-Cl), 130.8, 128.3 (C_{arom}), 113.6 (C-5), 50.8 ($C_{piperidine}$-2 + $C_{piperidine}$-6), 24.9 (($C_{piperidine}$-3 + $C_{piperidine}$-5), 23.5 ($C_{piperidine}$-4), 21.5 (NMe). Anal. calcd. for $C_{16}H_{19}ClN_6O$ (346.81): C 55.41, H 5.52, N 24.23. Found: C 55.20, H 5.44, N 23.96.

4-Amino-5-(4-chloro-phenylazo)-6-dibenzylamino-1-methyl-pyrimidin-2-one (14)

From dibenzylamine. Yield: 138 mg (60%), m.p. 193–196°C. ^{1}H NMR (DMSO-d_6): δ = 9.81 (br s.,2H, NH_2), 7.56–7.25 (m, 9H, Ar-H), 4.08 (br s., 4H, CH_2Ph). 3.36 (s, 3H, NMe). ^{13}CNMR (DMSO-d_6): δ = 164.0 (C-4), 155.6 (C-2), 150.6 (C-6), 146.0 ($C_{arom\text{-}Cl}$-1), 137.6 (C_{arom}-1′), 132.5 (C-Cl), 130.0, 128.6, 128.4, 129.3 (C_{arom}), 93.6 (C-5), 49.7 (*CH_2*Ph), 32.6 (NMe). Anal. calcd. for $C_{25}H_{23}ClN_6O$ (458.94): C 65.43, H 5.05, N 18.31. Found: C 65.19, H 5.11, N 18.48.

4-Amino-5-((4-chlorophenyl)diazenyl)-1-methyl-6-(morpholin-4-yl)pyrimidin-2-one (15)

From morpholine. Yield: 105 mg (60%), m.p. 215–218°C. ^{1}H NMR (DMSO-d_6): δ = 8.52 (br s., 2H, NH_2), 7.48 (br s., 2H, Ar-H), 7.23 (br s., 2H. Ar-H), 3.39 (br s., CH_2-2′ + CH_2-6′-(morpholine)), 3.17 (s, 3H, NMe), 2.64 (br s., CH_2-3′ + CH_2-5′-(morpholine)). ^{13}C NMR (DMSO-d_6): δ = 162.3 (C-4), 157.9 (C-2), 156.6 (C-6), 146.1 (C_{arom}-1), 133.9 (C-Cl), 130.2, 129.8 (C_{arom}), 110.7 (C-5), 65.4 ($C_{morpholine}$-3+$C_{morpholine}$-5), 41.5 ($C_{morpholine}$-2 +$C_{morpholine}$-6), 32.5 (NMe). Anal. calcd. for $C_{15}H_{17}ClN_6O_2$ (348.79): calcd. C 51.65, H 4.91, N 24.09. Found: C 51.42, H 4.81, N 23.88.

4-Amino-5-((4-chlorophenyl)diazenyl)-1-methyl-6-(piperazin-1-yl)pyrimidin-2-one (16)

From piperazine dihydrate. Yield: 105 mg (57%), m.p. 218–221°C. ^{1}H NMR (DMSO-d_6): δ = 8.47 (br s., 2H, NH_2), 8.06 (d, 2H, J = 7.0 Hz, Ar-H), 7.95 (d, 2H, J = 7.0 Ar-H), 3.17 (s, 3H, NMe), 2.78, 2.64 (2xbr s., 8H, CH_2-piperazine). ^{13}C NMR (DMSO-d_6): δ = 161.4 (C-4), 157.1 (C-2), 155.2 (C-6), 145.3, (C_{arom}-1), 135.0 (C-Cl), 130.1, 128.8 (C_{arom}), 99.5 (C-5), 50.9, 44.9 ($C_{piperazine}$), 31.7 (NMe). Anal. calcd. for $C_{15}H_{18}ClN_7O$ (347.80): C 51.80, H 5.22, N 28.19. Found: C 51.69, H 5.17, N 27.89.

General Procedure for Preparation of (19–27) via Suzuki Cross-Coupling Reaction

A mixture of **7–15** (1.00 mmol) and arylboronic acid (1.00 mmol) in *n*-propanol (15 mL) was stirred for 15 minutes under argon. To this mixture $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and 2 M aq. solution Na_2CO_3 (5 mL) were added. The reaction mixture was refluxed under argon for 12 hours and completion of reaction was monitored by TLC. After cooling, H_2O (7 mL) was added and stirred for 5 minutes. The mixture was partitioned with ethyl acetate (3 × 10 mL), and the combined organic layers were washed subsequently with 5% Na_2CO_3 solution (2 × 10 mL) brine solution and finally with H_2O (10 mL). The organic phase was decolorized with charcoal,

filtered (Celite) and the filtrate was dried (Na_2SO_4), and evaporated to dryness to give the desired product after recrystallization EtOH.

4-Amino-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-6-(ethylamino)-1-methylpyrimidin-2-one (19)

From **7** (92 mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: 91 mg (74%), m.p. 245–247°C. ^{1}H NMR (DMSO-d_6): δ = 7.63–7.55 (m, 7H, Ar-H), 7.22 (d, 2H, J = 5.0 Hz, NH_2), 6.80 (br s., 1H, NH), 3.78, 3.76 (2xs, 6H, 2xOMe), 3.66 (m, 2H, NCH_2CH$_3$), 3.16 (s, 3H, NMe), 1.15 (t, J = 7.1 Hz, NCH$_2$$CH_3$). ^{13}C NMR (DMSO-$d_6$): δ = 163.7 (C-6), 154.4 (C-2), 151.2 (C-4), 150.4 ($C^{3''}_{arom}$-OMe), 148.5 ($C^{4''}_{arom}$-OMe + C_{arom}-1′), 142.5 (C_{arom}-4′ + C_{arom}- 1″), 132.9, 132.3, 128.6 (C_{arom}), 118.9 (C_{arom}-6″ + C_{arom}-2″), 115.2 (C-5), 112.5 (C_{arom}-5″), 55.2 (2xOMe), 36.8 (NCH_2CH$_3$), 31.2 (NMe), 13.7 (NCH$_2$$CH_3$). MS (70 eV): m/z = 408 (M^+). Anal. calcd. for $C_{21}H_{24}N_6O_3$ (408.45): C 61.75, H 5.92, N 20.58. Found: C 61.37, H 5.83, N 20.37.

4-Amino-5-((4′-fluoro-[1,1′-biphenyl]4-yl)diazenyl)-6-(hexylamino)-3-methylpyrimidin-2-one (20)

From **8** (109 mg) and 4-fluorophenylboronic acid **18** (140 mg). Yield: 67 mg (67%), m.p. 240–243°C. ^{1}H NMR (DMSO-d_6): δ = 7.97 (br s., 2H, NH_2), 7.64–7.54 (m, 8H, Ar-H), 7.23 (br s.1H, NH), 3.17 (s, 3H, NMe), 3.04 (m, 2H, NCH$_2$), 1.63 (br s., 2H, NCH$_2$$CH_2$), 1.39–1.22 (m, 3H, NCH$_2CH_2$$(CH_2)_3$), 0.89 (t, 3H, J = 7.1 Hz, CH$_3$). ^{13}CNMR (DMSO-d_6): δ = 163.8 (C-6), 158.2 (d, $J_{4''F}$ = 249 Hz), 157.6 (C-2), 145.6 (C_{arom}-1′), 139.9 (C_{arom}-4′), 136.0 (C_{arom}-1″), 131.4 (C_{arom}-2′ + C_{arom}-6′ + C_{arom}-2″ + C_{arom}-6″), 128.7 (C_{arom}-3′ + C_{arom}-5′), 117.4 (C_{arom}-3″ + C_{arom}-5″), 44.6 (NCH$_2$), 31.6 (N(CH$_2$)$_3$$CH_2CH_2CH_3$), 30.7 (NCH$_2$$CH_2$), 25.2 (NCH$_2CH_2$$CH_2$), 23.1(N(CH$_2$)$_4$$CH_2CH_3$), 11.1 (CH$_3$). MS (70 eV): m/z = 421/423 (M^+). Anal. calcd. for $C_{23}H_{27}FN_6O$ (422.50): C 65.38, H 6.44, N 19.89. Found: C 65.09, H 6.38, N 19.98.

6-(Allylamino)-4-amino-5-((4′-fluoro-[1,1-biphenyl]-4-yl)diazenyl)-1-methylpyrimidin-2-one (21)

From **10** (97 mg) and 4-fluorophenylboronic acid **18** (140 mg). Yield: 90 mg (79%), m.p. 220–223°C. ^{1}H NMR (DMSO-d_6): δ = 7.63–7.53 (m, 8H, Ar-H), 7.22 (br s. 2H, NH_2), 3.18 (s, 3H, NMe), 5.50 (dd, 2H, J_{gem} = 14.5 Hz, NCH$_2$CH = CH_2), 5.19 (m, 2H, NCH_2CH = CH$_2$), 3.82 (m, 2H, NCH$_2$), 3.17 (s, 3H, NMe). ^{13}C NMR (DMSO-d_6): δ = 165.3 (C-6), 159.2 (d, $J_{C,F}$ = 249 H$_Z$, $C^{4''}_{arom}$-F), 156.0 (C-2), 150.7 (C-4), 147.2 (C_{arom}-1′), 140.3 (C_{arom}-4′), 134.5 (NCH$_2$$CH$ = CH$_2$), 133.4, 133.1, 132.1, 132.0, 131.5, 128.8, 128.7 (C_{arom}), 117.5 (NCH$_2$CH = CH_2 + C_{arom}-3″ + C_{arom}-5″), 113.4 (C-5), 45.2 (NCH$_2$),

30.7 (NMe). MS (70 eV): $m/z = 377/378$ (M^+). Anal. calcd. for $C_{20}H_{19}FN_6O$ (378.40): C 63.48, H 5.06, N 22.21. Found: C 63.22, H 4.97, N 22.01.

4-Amino-5-((4′-fluoro-[1,1′-biphenyl]-4-yl)diazenyl)-1-methyl-6-morpholinopyrimidin-2-one (22)

From **15** (105 mg) and 4-fluorophenylboronic acid **18** (140 mg). Yield: 77 mg (63%), m.p. 225–228°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.64$–7.54 (m, 8H, Ar-H), 3.63 (m, 4H, 2xCH_2O-morpholin), 3.17 (s, 3H, NMe), 2.81 (m, 4H, 2xCH_2N-morpholin). ^{13}C NMR (DMSO-d_6): $\delta = 165.4$ (C-6), 157.9 (d, $J_{C,F} = 253$ Hz, $C^{4\prime\prime}_{arom}$-F), 155.5 (C-2), 153. 4 (C-4), 146.8 (C_{arom}-1′), 140.4 (C_{arom}-4′), 133.1, 132.1, 131.9, 128.7, 128.6 (C_{arom}), 115.7 (C_{arom}-3″ + C_{arom}-5″), 67.7 (2xCH_2O-morpholin), 50.8 (2xCH_2N-morpholin). MS (70 eV): $m/z = 407/409$ (M^+). Anal. calcd. for $C_{20}H_{19}FN_6O$ (378.40): C 63.48, H 5.06, N 22.21. Found: C 63.22, H 4.97, N 22.01.

4-Amino-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-6-(dimethylamino)-1-methylpyrimidin-2-one (23)

From **9** (307 mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: mg 290 (71%), m.p. 216–219°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.61$–7.48 (m, 7H, Ar-H), 7.29 (d, 2H, $J = 5.3$ Hz, NH_2), 3.76, 3.74 (2xs, 6H, 2xOMe), 3.15 (s, 3H, NMe), 3.10 (br s., 6H, 2xNMe). ^{13}C NMR (DMSO-d_6): $\delta = 163.2$ (C-6), 155.0 (C-2), 151.6 (C-4), 150.4 ($C^{3\prime\prime}_{arom}$-OMe), 148.0 ($C^{4\prime\prime}_{arom}$-OMe + C_{arom}-1′), 141.8 (C_{arom}-4′), 140.2 (C_{arom}- 1″), 132.0, 132.1 (C_{arom}), 118.2 (C_{arom}-6″), 117.1 (C_{arom}-2″), 115.0 (C-5), 111.9 (C_{arom}-5″), 55.0, 49.8 (2xOMe), 40.8 (NMe_2), 31.0 (NMe). MS (70 eV): $m/z = 408$ (M^+). Anal. calcd. for $C_{21}H_{24}N_6O_3$ (408.45): C 61.75, H 5.92, N 20.58. Found: C 61.48, H 5.80, N 20.34.

4-Amino-6-(diethylamino)-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-6)-1-methylpyrimidin-2-one (24)

From **11** (335 mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: 292 mg (67%), m.p. 231–234°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.67$–7.50 (m, 7H, Ar-H), 7.23 (d, 2H, $J = 5.5$ Hz, NH_2), 3.80, 3.78 (2xs, 6H, 2xOMe), 3.57, 3.55 (2xq, 4H, $J = 7.1$ Hz, 2xN$CH_2$$CH_3$), 3.14 (s, 3H, NMe), 1.11, 1.08 (2xt, 6H, NCH_2CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 163.3$ (C-6), 154.8 (C-2), 151.9 (C-4), 150.1 ($C^{3\prime\prime}_{arom}$-OMe), 147.8 ($C^{4\prime\prime}_{arom}$-OMe +C_{arom}-1′), 141.8 (C_{arom}-4′ + C_{arom}- 1″), 131.6, 130.7, 127.8 (C_{arom}), 118.6 (C_{arom}-6″), 117.4 (C_{arom}-2″), 114.9 (C-5), 112.1 (C_{arom}-5″), 55.2, 54.9 (2xOMe), 39.2 (N$CH_2$$CH_3$), 31.0 (NMe), 13.2 ($NCH_2CH_3$). MS (70 eV): $m/z = 436$ (M^+). Anal. calcd. for $C_{23}H_{28}N_6O_3$ (436.51): C 63.29, H 6.47, N 19.25. Found: C 63.02, H 6.35, N 18.97.

4-Amino-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-6-(proylamino)-1-methylpyrimidin-2-one (25)

From **12** (321 mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: 287 mg (68%), m.p. 252–255°C. ^{1}H NMR (DMSO-d_6): δ = 8.12 (br s., 2H, NH_2), 7.68–7.45 (m, 7H, Ar-H), 7.20 (br s.1H, NH), 3.78, 3.75 (2xs, 6H, 2cOMe), 3.20 (s, 3H, NMe), 2.98 (m, 2H, NCH_2), 1.60 (m, 2H, NCH_2CH_2), 0.97 (t, 3H, J = 7.0 Hz, $NCH_2CH_2CH_3$). ^{13}CNMR (DMSO-d_6): δ = 163.3 (C-6), 154.9 (C-2), 150.5 (C-4), 149.8 ($C^{3''}_{arom}$-OMe), 147.3 ($C^{4''}_{arom}$-OMe +C_{arom}-1′), 140.9 (C_{arom}-4′ + C_{arom}-1″), 131.9, 130.8, 127.2 (C_{arom}), 118.2 (C_{arom}-6″), 116.9 (C_{arom}-2″), 115.0 (C-5), 111.8 (C_{arom}-5″), 55.6, 55.4 (2xOMe),45.2 (NCH_2), 23.3 ($NCH_2CH_2CH_3$), 11.2 (CH_3). MS (70 eV): m/z = 423 ($M+H^+$). Anal. calcd. for $C_{22}H_{26}N_6O_3$ (422.48): C 62.54, H 6.20, N 19.895. Found: C 62.33, H 6.11, N 19.76.

4-Amino-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-1-methyl-6-(pepridin-1-yl)pyrimidin-2-one (26)

From **13** (347 mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: 282 mg (63%), m.p. 252–255°C. ^{1}H NMR (DMSO-d_6): δ = 8.01 (br s., 2H, NH_2), 7.59–7.45 (m, 7H, Ar-H), 3.74, 3.72 (2xs, 6H, 2xOMe), 3.21 (s, 3H, NMe), 2.89 (m, 4H, 2xCH_2-piperidin), 1.54–1.48 (m, 6H, 3xCH_2-piperidin). ^{13}C NMR (DMSO-d_6): δ = 163.2 (C-6), 154.1 (C-2), 152.0 (C-4), 150.1 ($C^{3''}_{arom}$-OMe), 147.2 ($C^{4''}_{arom}$-OMe + C_{arom}-1′), 141.2 (C_{arom}-4′ + C_{arom}-1″), 131.9, 131.0, 128.5 (C_{arom}), 118.6 (C_{arom}-6″), 117.0 (C_{arom}-2″), 114.9 (C-5), 112.0 (C_{arom}-5″), 55.4, 55.1 (2xOMe), 52.8 (2xCH_2N-piperidin), 31.0 (NMe), 27.1, 25.3 (3xCH_2-piperidin). MS (70 eV): m/z = 423 ($M+H^+$). Anal. calcd. for $C_{24}H_{28}N_6O_3$ (448.52): C 64.27, H 6.29, N 18.74. Found: C 64.39, H 6.20, N 18.59.

4-Amino-6-(dibenzylamino)-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-1-methylpyrimidin-2-one (27)

From **14** (mg) and 3,4-dimethoxyphenylboronic acid **17** (182 mg). Yield: 364 mg (65%), m.p. 261–264°C. ^{1}H NMR (DMSO-d_6): δ = 8.28 (br s., 2H, NH_2), 7.73–7.09 (m, 17H, Ar-H), 4.14 (s, 4H, CH_2Ph), 3.75, 3.72 (2xs, 6H, 2xOMe), 3.21 (s, 3H, NMe). ^{13}C NMR (DMSO-d_6): δ = 162.9 (C-6), 154.2 (C-2), 152.8 (C-4), 150.0 ($C^{3''}_{arom}$-OMe), 148.2 ($C^{4''}_{arom}$-OMe + C_{arom}-1′), 141.8 (C_{arom}-4′ + C_{arom}- 1″), 136.1, 132.3, 132.0, 128.2, 127.9, 127.5, 126.8 (C_{arom}), 118.1 (C_{arom}-6″), 117.0 (C_{arom}-2″), 114.8 (C-5), 112.0 (C_{arom}-5″), 55.5, 55.3 (2xOMe), 52.8 (2xCH_2Ph), 31.6 (NMe). MS (70 eV): m/z = 423 ($M+H^+$). Anal. calcd. for $C_{33}H_{32}N_6O_3$ (560.65): C 70.70, H 5.75, N 14.99. Found: C 79.51, H 5.66, N 14.73.

General Procedure of Preparation of Triaryl Pyrimidine Analogs (29–31) via Suzuki Cross-Coupling Reaction

Method was analogous to the procedure for preparation of **19–27**, using instead **5** (48 mg, 0.30 mmol), arylboronic acid (0.61 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol).

4-Amino-5-((3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)diazenyl)-6-(3,4-dimethoxyphenyl)-1-methylpyrimidin-2-one (29)

From 3,4-dimethoxyphenylboronic acid **17** (92 mg). Yield: 120 mg (80%), m.p. 225–227°C. ^{1}H NMR (DMSO-d_6): δ = 7.64–7.53 (m, 10H, Ar-H), 7.19 (br s., 2H, NH_2), 3.75–3.63 (4 OMe), 3.15 (s, 3H, NMe). ^{13}CNMR (DMSO-d_6): δ = 164.7 (C-4), 156.1 (C-2), 149.6, 149.1 (4x*C*-OMe), 146.5 (C_{arom}-1′), 141.2 (C-6 + C_{arom}-4′ + C_{arom}-1″), 130.1, 126.6, 111.1 (C_{arom}), 94.3 (C-5), 56.4, 55.9 (4xOMe), 33.5 (NMe). MS (70 eV): m/z = 501 (M^+). Anal. calcd. for $C_{27}H_{27}N_5O_5$ (501.53): C 64.66, H 5.43, N 13.96. Found: C 64.45, H 5.39, N 13.69.

4-Amino-5-((4′-fluoro-[1,1′-biphenyl]-4-yl)diazenyl)-6-(4-fluorophenyl)-1-methylpyrimidin-2-one (30)

From 4-fluorophenylboronic acid **18** (85 mg). Yield: 89 mg (71%), m.p. 165–167°C. ^{1}H NMR (DMSO-d_6): δ = 7.64–7.52 (m, 12 H, Ar-H), 7.30 (d, 2H, J = 5.0 H_Z, NH_2), 3.19 (s, 3H, NMe). ^{13}CNMR (DMSO-d_6): δ = 164.6 (C-4), 159.5 (d, $J_{4c,F}$ = 248 Hz, C^{4c}_{arom}-F), 158.3 (d, $J_{4''F}$ = 256 Hz, $C^{4''}_{arom}$-F), 156.9 (C-2), 146.5 (C_{arom}-1′), 141.6 (C-6), 140.9 (C_{arom}-4′), 133.1 (C_{arom}-1″), 131.1, 131.4, 130.3, 130.2, 128.7, 128.8, 118.0 (d, $J_{C,F}$ = 26 H_Z), 115.6 (d, $J_{C,F}$ = 28.Hz) (C_{arom}), 93.0 (C-5), 33.3 (NMe). MS (70 eV): m/z = 416/419 (M^+). Anal. calcd. for $C_{23}H_{17}F_2N_5O$ (417.41): C 66.18, H 4.11, N 16.78. Found: C 65.89, H 4.00, N 16.48.

Ethyl 4′-((4-amino-6-)4-(ethoxycarbonyl)phenyl)-1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)diazenyl)-1,1′-biphenyl]-4-carboxylate (31)

From ethoxycarbonylphenylboronic acid **28** (118 mg). Yield: 136 mg (86%), m.p. 170–173°C. ^{1}H NMR (DMSO-d_6): δ = 7.85–7.55 (m, 8H, Ar-H), 7.43–7.30 (m, 4H, Ar-H), 7.22 (d, J = 5.1 H_Z, NH_2), 4.03 (q, J = 7.2 H_Z, CH_2CH_3), 3.88 (q, J = 7.1 H_Z, CH_2CH_3), 1.26 (t, J = 7.1 H_Z, CH_2CH_3). ^{13}CNMR (DMSO-d_6): δ = 166.0 (2xCO_2Et), 164.1 (C-4), 156.5 (C-2), 149.6, 149.1 (2xC_{arom}-OMe), 35.6 (NMe), 148.5 (C_{arom}-1′), 146.5 (2 x C_{arom}-CO_2Et), 140.0 (C-6), 92.9 (C-5), 63.4 (2xCH_2CH_3), 14.6 (2xCH_2CH_3). MS (70 eV): m/z = 525 (M^+). Anal. calcd. for $C_{29}H_{27}N_5O_5$ (525.20): C 66.27, H, 5.18, N 13.33. Found: C 65.98, H 5.06, N 13.02.

General Procedure of 4-Amino-6-aryl-1-methylpyrimidin-2-one Derivatives (34–38) via Suzuki Cross-Coupling Reaction

Method was analogous to the procedure for preparation of **19–27**, using instead **5** (96 mg, 0.60 mmol), arylboronic acid (0.60 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol).

4-Amino-6-(3,4-dimethoxyphenyl)-1-methylpyrimidin-2-one (34)

From 3,4-dimethoxy-phenylboronic acid **17** (109 mg). Yield: 127 mg (81%), m.p. 245–249°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.04$ (m, 3H, Ar-H), 7.17 (d, 2H, $J = 5.5$ Hz, NH_2), 5.62 (s, 1H, H-5), 3.08 (s, 3H, NCH_3), 3.79, 3.77 (2xs, 6H, 2xOMe). ^{13}C NMR (DMSO-d_6): $\delta = 164.7$ (C-4), 156.1 (C-2), 149.3, 148.8 (2x*C*-OMe), 143.5 (C-6), 126.1 (C_{arom}-1), 111.2 (C_{arom}-2 + C_{arom}-5), 94.3 (C-5), 55.7, 55.0 (2xOMe), 33.5 (NMe). MS (70 eV): $m/z = 261$ (M^+). Anal. calcd. for $C_{13}H_{15}N_3O_3$ (261.28): C 59.76, H 5.79, N 16.08. Found: C 59.57, H 5.68, N 16.23.

4-Amino-6-(4-fluorophenyl)-1-methylpyrimidin-2-one (35)

From 4-fluorophenylboronic acid **18** (84 mg). Yield: 91 mg (69%), m.p. 251–253°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.54$–7.44 (m, 4H, Ar-H), 7.12 (d, 2H, $J = 5.5$ H_Z,NH_2), 5.56 (s, 1H, H-5), 3.03 (s, 3H, NCH_3). ^{13}CNMR (DMSO-d_6): $\delta = 164.3$ (C-4), 157.3 (d, $J_{4',F} = 258$ H_Z, $C^{4'}{}_{arom}$-F), 156.5 (C-2), 141.6 (C-6), 133.9, 132.7, 130.0, 129.2, 128.4, 115.2 (C_{arom}), 94.0 (C-5), 33.1 (NMe). MS (70 eV): $m/z = 218/220$ (M^+). Anal. calcd. for $C_{11}H_{10}ON_3F$ (219.22): C 60.27, H 4.60, N 19.17. Found: C 59.95, H 4.52, N 18.91.

Ethyl 4-(6-amino-3-methyl-2-oxo-pyrimidin-4-yl)benzoate (36)

From 4-ethoxy-carbonylphenylboronic acid **28** (117 mg). Yield: 100 mg (61%), m.p. 260–263°C. ^{1}H NMR (DMSO-d_6): $\delta = 8.48$ (d, 2H, $J = 7.1$ H_Z, Ar-H), 8.40 (d, 2H, $J = 7.1$ Hz, Ar-H), 6.23 (d, 2H, $J = 5.4$ H_Z, NH_2), 5.52 (s, 1H, H-5), 3.18 (s, 3H, NCH_3), 4.81 (q, 2H, $J = 7.2$ H_Z, CH_2CH_3), 1.16 (t, 3H, CH_2CH_3). ^{13}C NMR (DMSO-d_6): $\delta = 166.1$ ($CO_2C_2H_5$), 165.5 (C-4), 155.1 (C-2), 143.3 (C_{arom}-1), 142.3 (C-6), 128.6, 125.7 (C_{arom}), 96.5 (C-5), 59.6 (CH_2CH_3), 32.5 (NMe), 13.7 (CH_2CH_3). MS (70 eV): $m/z = 273$ (M^+). Anal. calcd. for $C_{14}H_{15}O_3N_3$ (273.29): C 61.53, H 5.53, N 15.38. Found: C 61.33, H 5.54, N 15.09.

4-Amino-6-(2-fluorophenyl)-1-methylpyrimidin-2-one (37)

From 2-fluorophenyl boronic acid **32** (84 mg). Yield: 78 mg (59%), m.p. 240–243°C. ^{1}H NMR (DMSO-d_6): $\delta = 7.63$–7.45 (m, 4H, Ar-H), 7.07 (d, 2H, $J = 5.8$ H_Z, NH_2), 3.56 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6): $\delta = 164.7$ (C-4), 156.9 (C-2), 156.6 (d, $J_{2',F} = 262$ H_Z, C_{arom}-F), 141.4 (C-6), 128.6 (d, $J_{4',F} = 27$ Hz, C_{arom}-4′), 128.6 (d, $J_{5',F} = 27$ Hz, C_{arom}-5′), 121.9 (d, $J_{6',F} = 89$ Hz, C_{arom}-6′), 115.4 (C_{arom}), 94.3 (C-5), 33.4 (NMe). MS (70 eV): m/z

= 218/220 (M^+). Anal. calcd. for $C_{11}H_{10}ON_3F$ (219.22): C 60.27, H 4.60, N 19.17. Found: C 60.02, H, 4.51, N 18.89.

4-Amino-6-(3,4-difluorophenyl)-1-methylpyrimidin-2-one (38)

From 3,4-difluorophenyl boronic acid **33** (95 mg). Yield: 113 mg (79%), m.p. 255–257°C. ^{1}H NMR (DMSO-d_6): δ = 7.70–7.30 (m, 3H, Ar-H), 7.07 (s, 2H, NH_2), 5.62 (s, 1H, H-5), 3.04 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6): δ = 164.6 (C-4), 156.7 (C-2), 149.6 (d, $J_{4',F}$ = 258 H_Z, $C^{4'}{}_{arom}$-F), 149.1, 148.3 (C_{arom}-F), 142.1 (C-6), 131.5, 125.7, 124.7, 117.8 (C_{arom}), 94.8 (C-5), 33.3 (NMe). ^{19}F NMR (DMSO-d_6, 376.4607 MHz): δ = 137.8, 137.4 (2xd, $J_{F,F}$ = 22.6 Hz, 2xF). MS (70 eV): m/z = 236/239 (M^+). Anal. calcd. for $C_{11}H_9ON_3F_2$ (237.21): C 55.70, H 3.82, N 17.71. Found: C 55.82, H 3.73, N 17.52.

Anti-Kinesin Eg5 Assay

The ATPase activity of the Eg5 motor domain was measured by using the malachite green assay as described.[48] The reactions were performed in reaction buffer (80 mM pipes, pH 6.8; 1 mM ethylene glycol-bis-(2-aminoethylether)-N,N,N′,N′-tetraacetic acid (EGTA), 1 mM $MgCl_2$, 0.1 mg mL^{-1} bovine serum albumin (BSA), 1 mM taxol) supplemented with the Eg5 (48 nM) fusion protein and microtubules (200 nM). Ten minutes after compound addition, reactions were started by the addition of ATP (50 mM) and incubated at RT for 7 minutes. The reactions were stopped by adding perchloric acid (444 mM, Fluka Sigma-Aldrich, Germany), and the color reaction was started by adding the developer solution (1M HCl (Sigma), 33 mM malachite green (Sigma), 775 mM ammonium molybdate tetrahydrate (Sigma)). After 20 minutes, the absorbance at 610 nm was measured by using a plate reader (Victor2, Perkin-Elmer, Rodgau, Germany). The IC_{50} values were determined in three independent duplicate experiments. Figure 2 shows the ATPase activity screening assay.

In Vitro Anti-HIV Assay

The antiviral activity against HIV-1 strain III_B and HIV-2 strain (ROD) in MT-4 cells was performed using the MTT assay as previously described.[45] Briefly, stock solutions (10 × final concentration) of test compounds were added in 25 μL volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects on mock- and HIV-infected cells at the beginning of each experiment. Serial five-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman instruments, California, USA). Untreated control HIV- and mock-infected cell samples were included for each sample. HIV-1 (III_B)[49] or HIV-2 (ROD)[50] stock (50 μL) at 100–300 $CCID_{50}$ (50%

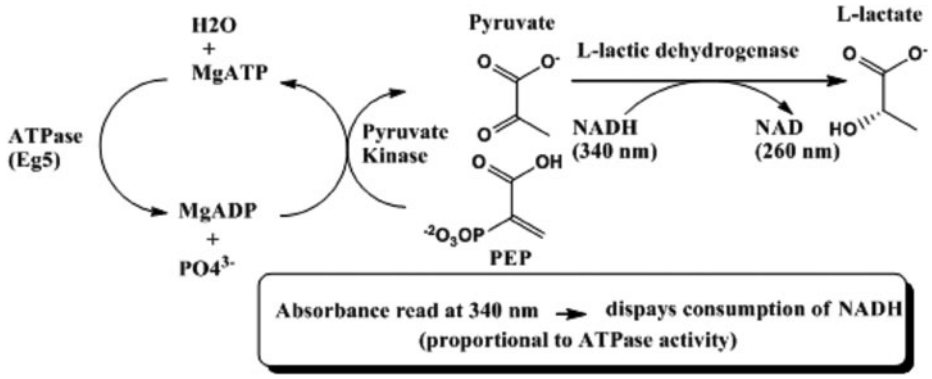


FIGURE 2 ATPase activity screening assay.

cell culture infectious dose) or culture medium was added to either the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compound. Exponentially growing MT-4 cells[51] were centrifuged for 5 minutes at 1,000 rpm (220 g) and the supernatant was discarded. The MT-4 cells were resuspended at 6×10^5 cells/mL and 50-μL volumes were transferred to the microtiter tray wells. Five days after infection, the viability of mock- and HIV-infected cells was examined spectrophotometrically by the MTT assay.

The MTT assay is based on the reduction of yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Acros Organics, Fischer Scientific AG, Wohlen, Switzerland) by mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Safire, Tecan), at two wavelengths (540 and 690 nm). All data were calculated using the median OD (optical density) value of tree wells. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration of the test compound that reduced the absorbance (OD540) of the mock-infected control sample by 50%. The concentration achieving 50% protection from the cytopathic effect of the virus in infected cells was defined as the EC_{50}.

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