Pyranone, Thiopyranone, and Pyridone Inhibitors of Phosphatidylinositol 3-Kinase Related Kinases. Structure−Activity Relationships for DNA-Dependent Protein Kinase Inhibition, and Identification of the First Potent and Selective Inhibitor of the Ataxia Telangiectasia Mutated Kinase

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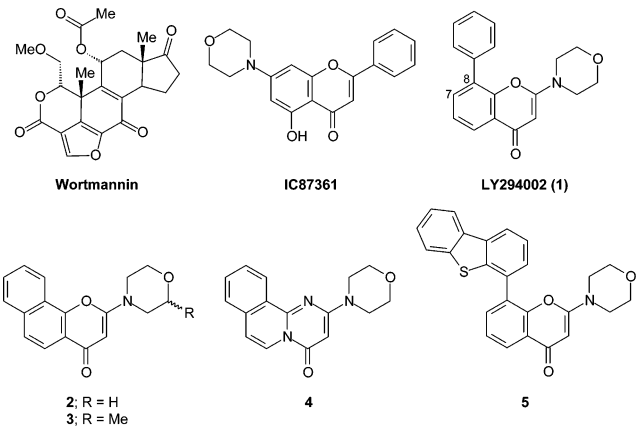
Structure−activity relationships have been investigated for inhibition of DNA-dependent protein kinase (DNA-PK) and ATM kinase by a series of pyran-2-ones, pyran-4-ones, thiopyran-4-ones, and pyridin-4-ones. A wide range of IC_{50} values were observed for pyranones and thiopyranones substituted at the 6-position, with the 3- and 5-positions proving intolerant to substitution. Related pyran-2-ones, pyran-4-ones, and thiopyran-4-ones showed similar IC_{50} values against DNA-PK, whereas the pyridin-4-one system proved, in general, ineffective at inhibiting DNA-PK. Extended libraries exploring the 6-position of 2-morpholino-pyran-4-ones and 2-morpholino-thiopyrano-4-ones identified the first highly potent and selective ATM inhibitor 2-morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (**151C**; ATM; IC_{50} = 13 nM) and revealed constrained SARs for ATM inhibition compared with DNA-PK. One of the most potent DNA-PK inhibitors identified, 2-(4-methoxyphenyl)-6-(morpholin-4-yl)pyran-4-one (**16**; DNA-PK; IC_{50} = 220 nM) effectively sensitized HeLa cells to the topoisomerase II inhibitor etoposide in vitro.

Introduction

The phosphatidylinositol (PI[a]) 3-kinase related kinases (PIKKs) are a family of six protein serine/threonine kinases, structurally different from classical protein kinases, and whose kinase domains more closely resemble those of the PI 3-kinase family of phospholipid kinases.[1,2] Two prominent members of the PIKK family, DNA-dependent protein kinase (DNA-PK) and ATM (ataxia telangiectasia mutated), play key roles in the cellular response to DNA damage through the detection and repair of DNA double-strand breaks (DSBs). DNA-PK, a heterotrimeric enzyme comprising a catalytic subunit (DNA-PKcs) and two Ku subunits, is a key component of the nonhomologous end joining (NHEJ) process of DNA DSB repair,[3,4] whereas ATM responds to ionizing radiation-induced DSBs by signaling to downstream response factors involved in cell cycle regulation and DNA repair.[2,5] Crucially, human cell lines defective in either DNA-PK or ATM function are hypersensitive to agents that elicit DNA DSBs.[6,7] Furthermore, overactivation of DNA-PK in chronic lymphocytic leukemia has been reported as impairing DNA damage-induced apoptosis.[8] The nonselective PIKK inhibitors wortmannin and LY294002 (**1**) have previously been demonstrated to sensitize tumor cells to ionizing radiation and DSB-inducing cancer chemotherapeutic agents.[9−11] Tumor radiation sensitization has also recently been demonstrated in vitro and in vivo by a number of compounds, including IC87361, a reportedly more selective flavonoid-based DNA-PK inhibitor.[12,13] Taken together, these data provide compelling evidence that selective small-molecule inhibitors of DNA-PK and ATM may have a therapeutic role as radio- and chemo-sensitizers in the treatment of cancer.



We have previously reported the discovery of DNA-PK inhibitors, identified by a systematic structural modification of the core chromenone pharmacophore of **1**.[14] These studies enabled the elucidation of structure−activity relationships (SARs) for DNA-PK inhibition by this compound class and resulted in the identification of several interesting submicromolar lead inhibitors based on the benzochromen-4-one (e.g., **2** and **3**) and pyrimidoisoquinolin-4-one (e.g., **4**) templates. The results

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[a] Abbreviations: PI, phosphatidylinositol; PIKK, phosphatidylinositol 3-kinase related kinase; DNA-PK, DNA-dependent protein kinase; ATM, ataxia telangiectasia mutated kinase.

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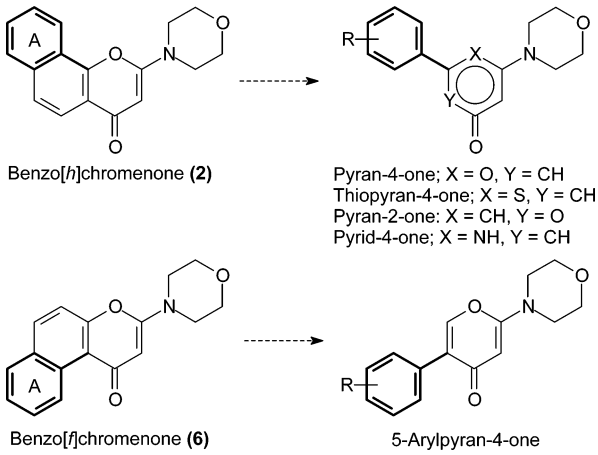


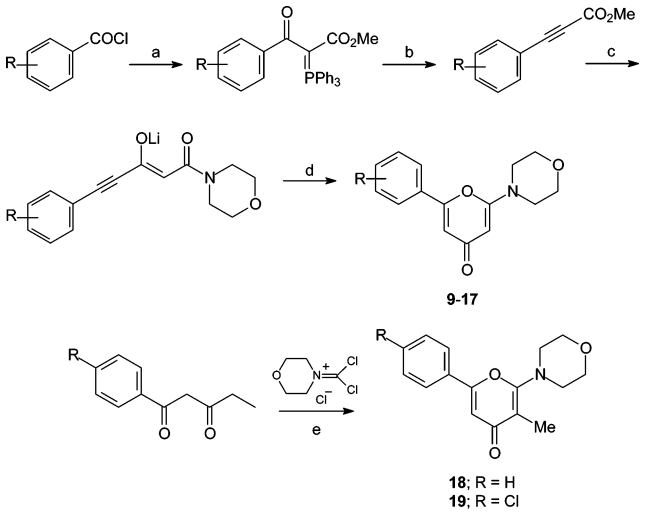
Figure 1. Positioning of the 5- and 6-aryl rings of pyranone, thiopyranone, and pyridone templates relative to the fused rings (A) of benzochromenones **2** and **6**.

of these initial studies also suggested that the chromenone 7- and 8-positions were tolerant to substitution, and the region of the DNA-PK ATP-binding domain occupied by groups at these positions was probed using a focused compound library approach. These efforts were rewarded by the identification of the potent and highly selective ATP-competitive DNA-PK inhibitor **5** (NU7441, IC_{50} = 14 nM).[15,16] Studies in vitro and in vivo with **5** demonstrated a potentiation of the cytotoxicity of the topoisomerase II inhibitor etoposide against human colorectal cancer without a significant exacerbation of host toxicity.[17] The specificity of **5** for DNA-PK in intact cells was also confirmed in matched DNA-PKcs-proficient and -deficient cell lines.

As part of continuing studies to identify selective and potent PIKK inhibitors, and with a view to further delineating SARs for DNA-PK inhibition, the possibility of simplifying the core chromenone pharmacophore was investigated, recognizing that the 2-morpholinyl substituent appears to be a prerequisite for activity in this series.[14,16] A consideration of the likely interaction of the "A-ring" of the benzo[*h*]chromenone of **2** with the ATP-binding domain of DNA-PK suggested that the corresponding 6-arylpyran-4-one template would overlay with **2** and position the 6-aryl ring in a similar region, albeit without the constraints of the fused-ring system (Figure 1). The synthetic accessibility of 2-morpholinyl-6-arylpyran-4-ones and their analogous thiopyran-4-ones, substituted in the 6-aryl ring, offered advantages over the benzo[*h*]chromenone template in terms of structural diversity. The 5-arylpyran-4-one system was also investigated based on our previous observation that benzo[*f*]chromenone (**6**) exhibited DNA-PK inhibitory activity (IC_{50} = 1.25 μM) comparable with **1**.[14]

In light of our earlier studies demonstrating that DNA-PK inhibitory activity is retained when the chromen-4-one template is replaced by chromen-2-one (coumarin)[14] or quinolin-4-one,[18] we also wished to investigate the analogous monocyclic pyran-2-one and 4-pyridone systems (Figure 1). The 4-pyridone heterocycle was of additional interest given the reported activity of OK-1035,[19] although only modest potency was observed for this pyridone-based DNA-PK inhibitor in our hands.[20] In the current paper we describe the synthesis and biological evaluation of appropriately substituted pyran-2-one, pyran-4-one, thiopyran-4-one, and pyridin-4-one DNA-PK inhibitors and the identification of a remarkably potent and selective pyran-4-one ATM inhibitor. A preliminary account of part of this work has been communicated previously.[21]

Scheme 1[a]



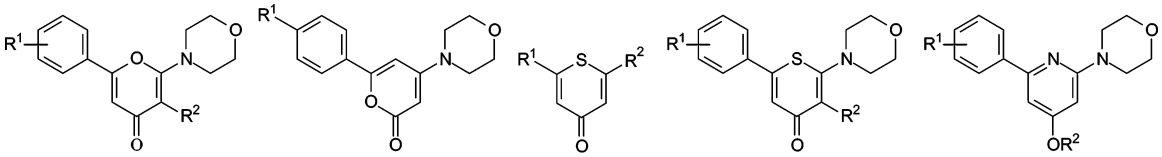
[a] Reagents and conditions: (a) Ph_3PCHCO_2Me toluene, reflux; (b) 250 °C, 1 Torr; (c) *N*-acetylmorpholine, LDA, THF, −78 °C → 25 °C; (d) $MeSO_3H$, 25 °C; (e) (1) BCl_3, DCM, 0 °C; (2) $(i\text{-}Pr)_2NEt$, MeOH, −78 °C → 25 °C.

Chemistry

The structures and properties of all compounds synthesized and evaluated for biological activity are recorded in Tables 1 and 2. The target 6-aryl-2-morpholinylpyran-4-ones (**9**−**17**) were prepared as described previously.[22] Briefly, treatment of the appropriate aroyl chlorides with methyl triphenylphosphoranylidene[23] gave the corresponding aryl propiolates, which were reacted with two equivalents of the *O*-lithio derivative of *N*-acetylmorpholine to give the lithium salts of the acetylenic β-ketoamides. Cyclization to the required pyran-4-one derivatives was effected smoothly with methanesulfonic acid (Scheme 1). The 3-methylpyran-4-one derivatives (**18** and **19**) were prepared by the method of Morris et al.[24] through the condensation of 4-dichloromethylenemorpholin-4-ium chloride with 1-phenylpentane-1,3-dione or 1-(4-chlorophenyl)pentan-1,3-dione, respectively (Scheme 1). 5-Phenylpyran-4-one (**23**) was synthesized as shown in Scheme 2. Thus, aminolysis of the Meldrum's acid derivative (**20**) with morpholine[25,26] and formylation of the resulting β-ketoamide (**21**) gave the tricarbonyl derivative (**22**), which afforded **23** in modest yield on treatment with acid. The simple cyclohexa-2-enone (**24**) was readily accessible by treatment of commercially available 5-phenyl-1,3-cyclohexanedione with morpholine.[27] Chalcone derivative (**25**)[28] and the pyran-2-ones (**26**−**29**)[29] were prepared as described previously.

A new method was developed for the synthesis of the required thiopyran-4-one derivatives **54**−**71** (Scheme 3). Thus, the dilithio derivatives of β-diketones, either commercially available or prepared by acetylation of the appropriate ketone, were condensed with CS_2 to give the 2-mercaptothiopyranones **30**−**38**. Careful workup conditions were necessary to avoid unwanted pyran-4-one formation. An additional elimination step, employing silica in DCM, was required for the synthesis of the tetrahydrothiochromen-4-one (**40**), as the reaction of 2-acetylcyclohexanone with CS_2 gave an intermediate tentatively identified by LCMS analysis as the hydrate (**39**). Subsequent *S*-alkylation with ethyl iodide to afford the ethylsulfanyl derivatives (**41**−**51**) and displacement of the ethylsulfide by morpholine in ethane-1,2-diol at 140 °C furnished the target 2,6-disubstituted thiopyranones. In some cases, oxidation to the corresponding sulfoxides (**52**, **53**, **70**) and treatment with the

Table 1. Physical Data and Biological Activity for Pyran-4-ones, Pyran-2-ones, and 4-Pyridones



A **B** **C** **D** **E**

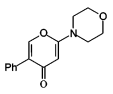
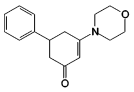
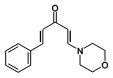
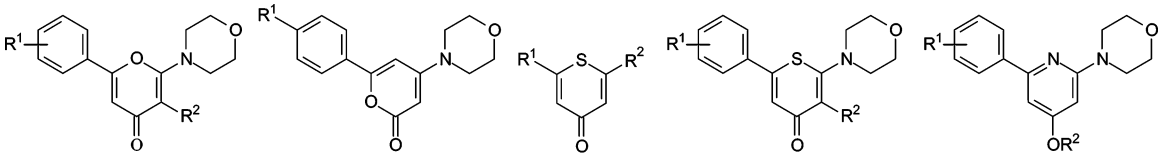
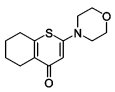
Compound No.	general structure	R^1	R^2	Method[a]	*Solvent system*[b]	yield (%)	mp (°C)	formula	DNA-PK Inhibition IC_{50} (μM)[c]
9[d]	A	H	H	–	–	–	–	$C_{15}H_{15}NO_3$	1.30 ± 0.13
10[d]	A	4-Cl	H	–	–	–	–	$C_{15}H_{14}NO_3Cl$	0.18 ± 0.01
11	A	2-F	H	–	–	11	137-138	$C_{15}H_{14}FNO_3$[e]	0.39 ± 0.08
12	A	3-F	H		–	17	169-170	$C_{15}H_{14}FNO_3$[e]	0.69 ± 0.08
13[d]	A	4-F	H	–	–	–	–	$C_{15}H_{14}FNO_3$	0.35 ± 0.05
14[d]	A	2-OMe	H	–	–	–	–	$C_{16}H_{17}NO_4$	0.31 ± 0.07
15[d]	A	3-OMe	H	–	–	–	–	$C_{16}H_{17}NO_4$	0.54 ± 0.08
16[d]	A	4-OMe	H	–	–	–	–	$C_{16}H_{17}NO_4$	0.22 ± 0.02
17[d]	A	4-$C(Me)_3$	H	–	–	76	156-157	$C_{19}H_{23}NO_3$	0.48 ± 0.07
18	A	H	Me	–	–	25	144-145	$C_{16}H_{17}NO_3$[f]	> 100
19	A	4-Cl	Me	–	–	29	155-156	$C_{16}H_{16}ClNO_3$[f]	> 100
23				–	–	12	154-156	$C_{15}H_{15}NO_3$[e]	> 10
24[g]				–	–	–	–	$C_{16}H_{18}NO_2$	> 10
25[h]				–	–	–	–	$C_{15}H_{17}NO_2$	> 30
26[i]	B	H	–	–	–	–	–	$C_{15}H_{15}NO_3$	1.8 ± 0.05
27[i]	B	OMe	–	–	–	–	–	$C_{16}H_{14}NO_4$	0.53 ± 0.09
28[i]	B	Cl	–	–	–	–	–	$C_{15}H_{14}ClNO_3$	0.47 ± 0.01
29[i]	B	$C(Me)_3$	–	–	–	–	–	$C_{19}H_{23}NO_3$	3.2 ± 0.25
54	C	Me		III	*A*	49	145-147	$C_{10}H_{13}NOS$[f]	> 100
55	C	Me		III	*B,D*	69	95-96	$C_{10}H_{13}NO_2S$[f]	> 100
56	C	Me		III	*A*	62	137-138	$C_{10}H_{13}NOS_2$[f]	> 100
57	C	Me	$NHCH_2Ph$	III	*A*	76	169-171	$C_{13}H_{13}NOS$[f]	>100
58	C	$CH(Me)_2$		III	*A*	89	oil	$C_{12}H_{17}NO_2S$[f]	5.9 ± 4.15
59	C	$C(Me)_3$		IV	*E*	44	oil	$C_{13}H_{19}NO_2S$[f]	1.06 ± 0.05
60	D	H	H	IV	*A*	19	160-161	$C_{15}H_{15}NO_2S$[f]	0.65 ± 0.07
61	D	4-Cl	H	IV	*A*	40	201-203	$C_{15}H_{17}ClNO_2S$[e]	0.53 ± 0.08
62	D	4-OMe	H	IV	*A*	30	199-200	$C_{16}H_{17}NO_3S$[e]	0.28 ± 0.07
63	D	3-Br	H	IV	*A*	37	181-182	$C_{15}H_{14}BrNO_2S$[f]	0.70 ± 0.11
64	D	4-Br	H	IV	*A*	42	214-215	$C_{15}H_{14}BrNO_2S$[f]	0.68 ± 0.15
65	D	4-$(Me)_3$	H	IV	*A*	24	172-173	$C_{19}H_{23}NO_2S$[e]	1.1 ± 0.12

Table 1 (Continued)



A **B** **C** **D** **E**

Compound No.	general structure	R^1	R^2	Method[a]	*Solvent system*[b]	yield (%)	mp (°C)	formula	DNA-PK Inhibition IC_{50} (μM)[c]
66	C			IV	*A*	21	133-135	$C_{21}H_{17}NO_2S_3$[f]	2.1 ± 0.69
67	C	Me	OCH_2CF_3	III	*D*	77	153-155	$C_8H_7F_3O_2S$[f]	> 30
68	D	4-CN	H	–	*A*	60	235-236	$C_{16}H_{14}N_2O_2S$[f]	1.9 ± 0.24
69	C			IV	*A*	2	20-203	$C_{19}H_{22}N_2O_3S$[f]	> 100
71				–	*A*	59	142-143	$C_{13}H_{17}NO_2S$[f]	7.3[k]
72	D	4-Cl	Br	–	*A*	67	178-179	$C_{15}H_{13}BrClNO_2S$[f]	> 100
73	D	4-Br	Cl	–	*A*	39	167-168	$C_{15}H_{13}BrClNO_2S$[f]	> 100
74	E	4-Cl	H	–	–	46	225-226	$C_{15}H_{15}ClN_2O_2$[f]	8.1[k]
75	E	4-OMe	H	–	–	21	118-120	$C_{16}H_{18}N_2O_3$[f]	> 100
76	E	4-Cl	Me	–	*C*	83	104-106	$C_{16}H_{17}ClN_2O_2$[f]	> 100
77	E	4-OMe	Me	–	*C*	71	108-109	$C_{17}H_{20}N_2O_3$[f]	> 100
78	E	4-Cl	Et	–	*C*	69	103-104	$C_{17}H_{19}ClN_2O_2$[f]	> 100

[a] See the Experimental Section. [b] Chromatography solvents: A, 1−5% MeOH/DCM gradient; B, DCM/MeOH (95:5); C, petrol/EtOAc (4:1). Recrystallization solvents: D, EtOAc−petrol; E, EtOAc; F, MeOH−H_2O. [c] Unless stated, values are the means ± standard error for three independent determinations. [d] Prepared as described in ref 22. [e] Analyzed by HRMS. [f] Analyzed for C, H, N, and analytical results were within 0.4% of theoretical value. [g] Prepared as described in ref 23. [h] Prepared as described in ref 24. [i] Prepared as described in ref 25. [j] Anal. Calcd for $C_{13}H_{17}NO_2S$·0.25MeOH: C, 61.36; H, 7.00; N, 5.40%. Found: C, 61.20; H, 6.10; N, 4.90%. [k] Mean of two independent determinations.

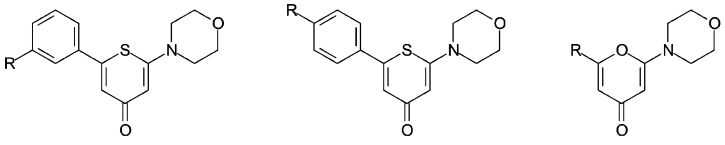
required amine in trifluoroethanol gave the target thiopyranones (**54**−**58**, **71**). The 2-trifluoroethoxythiopyranone (**67**) may be an intermediate in this reaction. The 6-(4′-morpholinylphenyl)-thiopyranone (**69**) was isolated as a byproduct from the synthesis of the 4-bromophenyl derivative (**64**) by the ethane-1,2-diol method. This is presumably generated as a consequence of nucleophilic displacement of the bromo group by morpholine under the vigorous reaction conditions employed. Interestingly, formation of 6-(3′-morpholinylphenyl)thiopyranone was not observed from the corresponding 3-bromophenylthiopyranone (**63**). Palladium-catalyzed cyanation of **64** by the method of Maligres et al.[30] afforded the required 4-cyanophenylthiopyranone (**68**) in good yield. The 3-halothiopyranones (**72** and **73**) were prepared from the parent thiopyranones **61** and **63** on treatment with NBS or NCS, with no evidence of radical bromination occurring under these conditions. The required pyridine-4-ones **74** and **75** were readily synthesized by the condensation of the appropriate aroylacetone with *N*-cyanomorpholine, with subsequent *O*-alkylation under standard reaction conditions affording the alkoxypyridines **76**−**78** (Scheme 3).

Library Syntheses: The effect of substitution at the pyranone and thiopyranone 6-positions was more broadly investigated through the preparation of focused compound libraries, employing a solution multiple-parallel synthesis approach (Scheme 4). The introduction of a range of substituents was achieved utilizing Suzuki−Miyaura coupling reactions between the appropriately functionalized pyranone (**81**) or thiopyranones (**63** and **64**) and a range of boronic acid derivatives. 6-Chloropyranone (**81**) was synthesized essentially as described previously.[31,32] Thus, chlorolactone **79**, prepared by radical chlorination of diketene, gave β-ketoamide (**80**) on reaction with morpholine, with a final cyclization to **81** proceeding in excellent yield on treatment with perchloric acid in dioxane. Purification of the compounds produced in this way was achieved by semipreparative HPLC, with library compounds of purity ≥85% (determined by LCMS) being deemed suitable for preliminary biological evaluation (Table 2).

Results and Discussion

The principal objective of the studies described in this paper was to establish whether the potency and kinase-selectivity observed for benzochromen-4-one and pyrimidoisoquinolin-4-one DNA-PK inhibitors could be emulated by the simpler pyranone, thiopyranone, and pyridone systems. A comparison of the activity of the 6-arylpyran-4-ones **9**−**17** with the benchmark benzo[*h*]chromenone **2** (NU7026, $IC_{50} = 0.23\ \mu M$)[14] indicated that these compounds exhibited activity comparable with **2**. Although a lipophilic group on the 6-aryl ring is favorable, consistent with our previous SARs in the chromenone series,[14−16] the substituent position does not appear to be important (compare **11**−**13** and **14**−**16**). The introduction of a

Table 2. Chemical Structures and Biological Activity for Thiopyran-4-one and Pyran-4-one Library Compounds



(**A**) (**B**) (**C**)

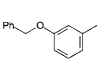
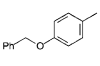
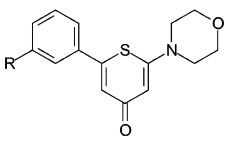
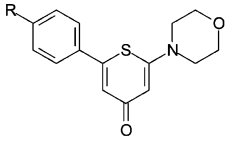
R	No.	Structure	DNA-PK Inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (IC_{50} μM)[a]	ATM inhibition (IC_{50} μM)[a]
	**82**	**A**	-[b]	**B**	-	**C**	4.2	> 10
	**83**	**A**	-	**B**	-	**C**	6.3	> 10
	**84**	**A**	80 IC_{50} = 0.92 μM	**B**	16	**C**	-	-
	**85**	**A**	64	**B**	ND[c]	**C**	-	-
	**86**	**A**	31	**B**	6.5	**C**	7.8	> 100
	**87**	**A**	47	**B**	15.6	**C**	-	-
	**88**	**A**	77	**B**	ND	**C**	-	-
	**89**	**A**	51	**B**	4.7	**C**	-	-
	**90**	**A**	77 IC_{50} = 0.68 μM	**B**	36.8	**C**	-	-
	**91**	**A**	17	**B**	16.5	**C**	-	-
	**92**	**A**	-	**B**	-	**C**	4.2	> 10
	**93**	**A**	-	**B**	-	**C**	1.8	> 100
	**94**	**A**	23	**B**	10.0	**C**	-	-
	**95**	**A**	-	**B**	-	**C**	3.1	> 10
	**96**	**A**	42	**B**	9.3	**C**	2.5	> 10
	**97**	**A**	24	**B**	ND	**C**	-	-
	**98**	**A**	38	**B**	0	**C**	3.6	> 100
	**99**	**A**	0	**B**	9.1	**C**	1.0	> 100
	**100**	**A**	23	**B**	19.3	**C**	8.8	28.5
	**101**	**A**	18	**B**	0	**C**	1.3	10
	**102**	**A**	7.3	**B**	ND	**C**	0.91	> 100
	**103**	**A**	36	**B**	0	**C**	-	-
	**104**	**A**	60	**B**	50.4	**C**	4.7	> 10
	**105**	**A**	1.7	**B**	6.4	**C**	-	-

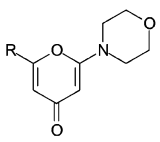
Table 2. Continued



(**A**)



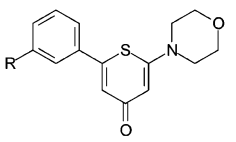
(**B**)



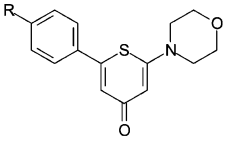
(**C**)

R	No.	Structure	DNA-PK Inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (IC_{50} μM)[a]	ATM inhibition (IC_{50} μM)[a]
	**106**	**A**	23	**B**	0	**C**	-	-
	**107**	**A**	-	**B**	-	**C**	2.5	> 10
	**108**	**A**	0	**B**	ND	**C**	-	-
	**109**	**A**	22	**B**	ND	**C**	7.2	> 100
	**110**	**A**	15	**B**	ND	**C**	-	-
	**111**	**A**	37	**B**	0	**C**	19	> 10
	**112**	**A**	19	**B**	ND	**C**	15	> 100
	**113**	**A**	26	**B**	13.7	**C**	-	-
	**114**	**A**	ND	**B**	15.9	**C**	-	-
	**115**	**A**	0	**B**	0	**C**	1.0	> 100
	**116**	**A**	1.5	**B**	15.8	**C**	-	-
	**117**	**A**	59	**B**	0	**C**	-	-
	**118**	**A**	52	**B**	0	**C**	-	-
	**119**	**A**	42	**B**	ND	**C**	0.8	> 10
	**120**	**A**	0	**B**	0	**C**	-	-
	**121**	**A**	-	**B**	-	**C**	11	> 100
	**122**	**A**	24	**B**	ND	**C**	-	-
	**123**	**A**	37	**B**	ND	**C**	-	-
	**124**	**A**	58	**B**	13.3	**C**	-	-
	**125**	**A**	77	**B**	ND	**C**	-	-
	**126**	**A**	-	**B**	-	**C**	3.6	> 10
	**127**	**A**	10	**B**	ND	**C**	-	-
	**128**	**A**	47	**B**	ND	**C**	-	-

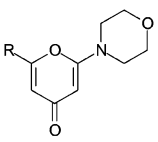
Table 2. Continued



(**A**)



(**B**)



(**C**)

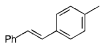
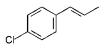
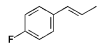
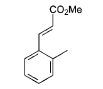
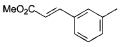
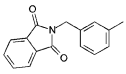
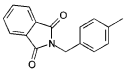
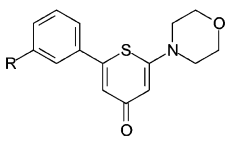
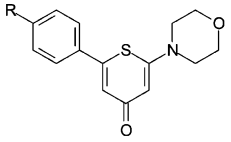
R	No.	Structure	DNA-PK Inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (IC_{50} μM)[a]	ATM inhibition (IC_{50} μM)[a]
	**129**	**A**	15	**B**	38.6	**C**	-	-
	**130**	**A**	ND	**B**	0	**C**	-	-
	**131**	**A**	12	**B**	5.3	**C**	-	-
	**132**	**A**	70 IC_{50} = 0.84 μM	**B**	0	**C**	-	-
	**133**	**A**	30	**B**	17.7	**C**	1.1	> 10
	**134**	**A**	45	**B**	0	**C**	3.2	> 100
	**135**	**A**	59	**B**	ND	**C**	0.5	> 100
	**136**	**A**	ND	**B**	51.4	**C**	1.1	> 10
	**137**	**A**	46	**B**	0	**C**	1.6	> 10
	**138**	**A**	17	**B**	25.8	**C**	1.0	> 10
	**139**	**A**	47	**B**	15.7	**C**	4.2	> 10
	**140**	**A**	ND	**B**	ND	**C**	-	> 10
	**141**	**A**	-	**B**	-	**C**	0.4	> 10
	**142**	**A**	69	**B**	72.9 IC_{50} = 0.33 μM (0.49 μM)[d]	**C**	3.6	4.3
	**143**	**A**	15	**B**[a]	ND	**C**	0.6	> 10
	**144**	**A**	ND	**B**	3.3	**C**	0.8	18
	**145**	**A**	64	**B**	75.0 IC_{50} = 0.19 μM (0.16 μM)[d]	**C**	2.3	> 100
	**146**	**A**	19	**B**	0	**C**	1.3	> 10
	**147**	**A**	49	**B**	86.2 IC_{50} = 0.26 μM (0.26 μM)[d]	**C**	1.3	> 10
	**148**	**A**	17	**B**	35.5	**C**	9.7	> 100

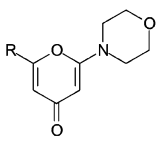
Table 2. Continued



(**A**)



(**B**)

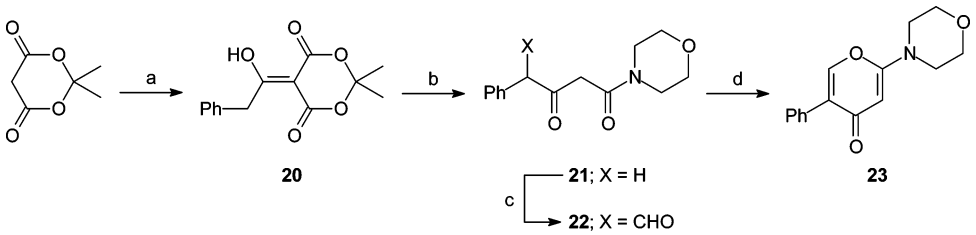


(**C**)

R	No.	Structure	DNA-PK Inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (% at 1.0 μM)[a]	Structure	DNA-PK inhibition (IC_{50} μM)[a]	ATM inhibition (IC_{50} μM)[a]
	**149**	**A**	30	**B**	ND	**C**	0.9	> 10
	**150**	**A**	ND	**B**	0	**C**	1.2	3.2
	**151**	**A**	0	**B**	ND	**C**	1.8	0.013

[a] Compounds were evaluated initially in triplicate at 1.0, 0.5, and 0.1 μM, and values shown are the means of three independent determinations at 1.0 μM. IC_{50} values were determined in duplicate for selected compounds. [b] Compound not synthesized. [c] Not determined; reaction failed or product of insufficient purity (<85%). [d] IC_{50} values for analytically pure samples prepared by resynthesis.

Scheme 2[a]



[a] Reagents and conditions: (a) $PhCH_2COCl$, pyridine, DCM, 0 °C; (b) morpholine, toluene, reflux; (c) LDA, HCO_2Et, THF, −78 °C; (d) $MeSO_3H$, 25 °C.

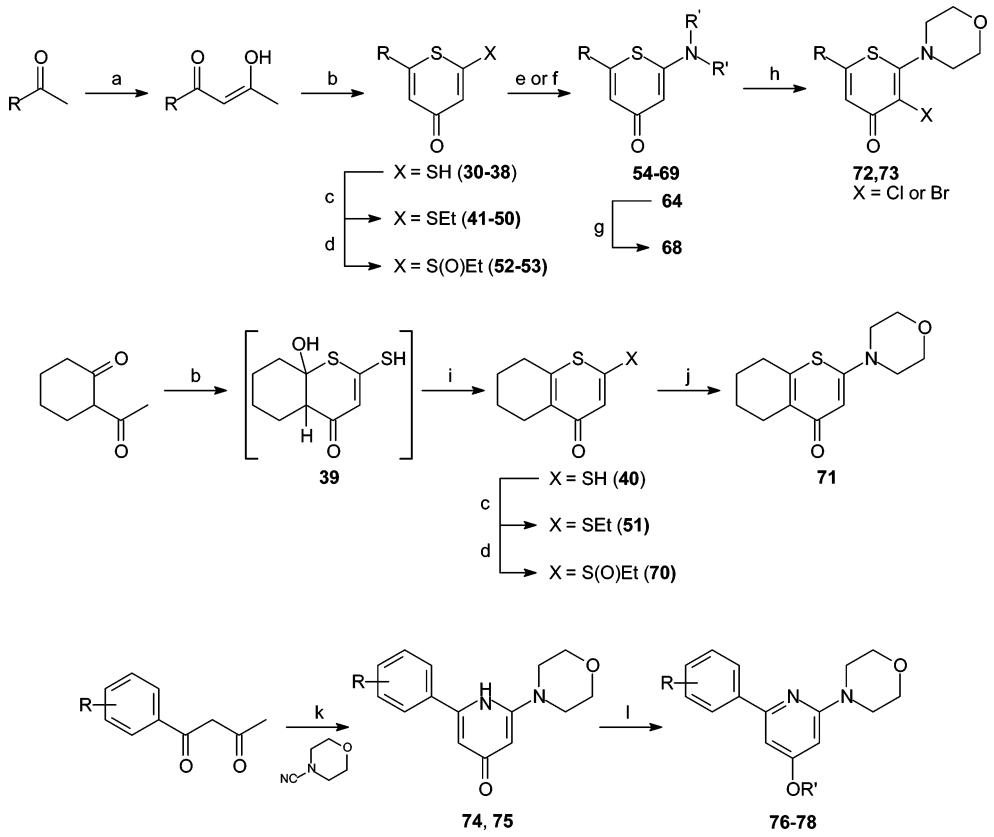
methyl substituent at the pyranone 3-position is clearly not tolerated, with a 200-fold reduction in DNA-PK inhibitory activity being observed for **18** and **19** compared with the unsubstituted derivatives **9** and **10**, respectively.

The reduced potency of the 5-phenylpyranone derivative **23**, compared with **9**, and the corresponding benzo[*f*]chromenone (**6**),[14] suggests that a planar fused-ring system is preferred at this position. Similarly, the weak activity of the cyclohexeneone (**24**) and chalcone (**25**) derivatives supports the model of a minimum pharmacophore comprising a planar heteroaromatic ring system. The pyran-2-one derivatives **26**−**29** proved approximately equipotent with the analogous pyran-4-ones **9**, **10**, **16**, and **17**, respectively, notwithstanding assay problems encountered as a result of the very poor aqueous solubility of the *t*-butylphenyl derivative **29**. This is consistent with our previous observation that DNA-PK inhibitory activity also resides in chromen-2-ones (coumarins) and benzochromen-2-ones bearing a suitably positioned morpholinyl group.[14] Preliminary studies employing a homology model of the DNA-PK ATP-binding domain, constructed from the known structure of PI 3-kinase,[33] suggest that the morpholine and carbonyl groups of chromenone-based inhibitors make key hydrogen bonds with amino-acid residues, whereas the ring oxygen does not make such an interaction.[34] This is analogous to the binding mode for **1** within the ATP-binding pocket of PI-3-kinase (p110γ).[33] Assuming that the pyran-2-one and pyran-4-one inhibitors make equivalent binding interactions through the morpholine and carbonyl groups, this would position the ring oxygens of the scaffolds into different regions of the ATP-binding domain. Thus, while important for potency, these results infer that the heterocyclic ring oxygen does not interact directly with the ATP-binding domain.

The requirement for a lipophilic 6-substituent was again in evidence in the thiopyran-4-one series. Thus, whereas the 6-methylthiopyranone (**55**) exhibited negligible activity, the corresponding 6-isopropyl and 6-*t*-butyl derivatives (**58** and **59**) were active (IC_{50} = 5.0 and 1.06 μM, respectively). Only modest DNA-PK inhibitory activity (IC_{50} = 7.3 μM) was observed for the tetrahydrothiochromenone (**71**). As expected, replacement of the 2-morpholinyl group of **55** by other amines (**54**, **56**, **57**) or a trifluoroethoxy group (**67**) effectively abolished DNA-PK inhibitory activity. The activity of the 6-arylthiopyranones (**60**−**65**, **68**) generally resembled that of the pyran-4-one series, with a lipophilic aryl substituent conferring a modest increase in potency compared with the parent 6-phenylthiopyranone (**60**). The somewhat lower potency of the 6-*t*-butylphenyl derivative (**65**) is surprising, but may again reflect solubility problems encountered with this compound. The 3-fold reduction in potency observed for the 4-cyanophenyl derivative (**68**) suggests that electron-withdrawing substituents may not be favorable, while the inactivity of the 6-(4-morpholin-4-yl-phenyl)thiopyranone (**69**) reaffirms the requirement for a lipophilic group at this position. As for the pyranone series, substituents at the thiopyranone 3-position are detrimental to DNA-PK inhibitory activity (compare **61** and **64** with **72** and **73**).

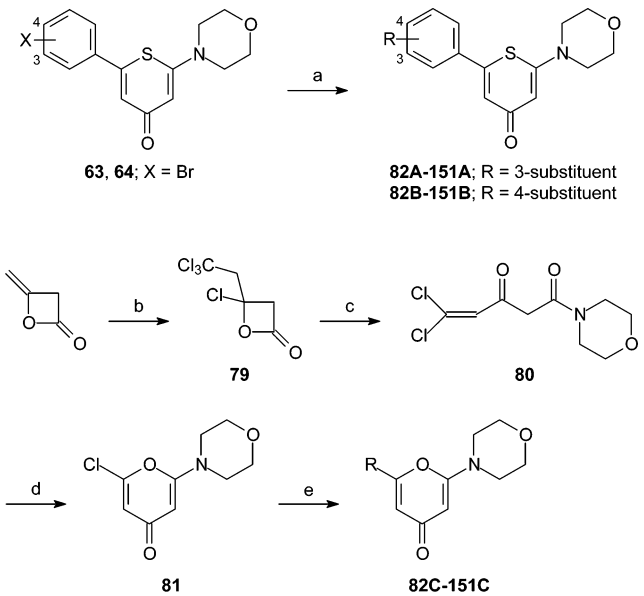
The activity of the 4-pyridones (**74** and **75**) and 4-alkoxypyridines (**76**−**78**) was disappointing, with only the 6-(4-chlorophenyl)pyridone (**74**) proving active (IC_{50} = 8.1 μM), albeit some 40-fold less potent than the corresponding pyran-4-one (**10**). Although the 1*H*-pyridone tautomer is generally

Scheme 3[a]



[a] Reagents and conditions: (a) NaOEt, EtOAc, THF, 25 °C; (b) (1) LDA, CS_2, THF, −78 °C → 25 °C; (2) H_2O, THF, 0 → 25 °C, HCl (aq); (c) K_2CO_3, EtI, Me_2CO, reflux; (d) (1) *m*-CPBA, DCM, 0 °C; (e) morpholine, $(CH_2OH)_2$, 140 °C; (f) R'_2NH, CF_3CH_2OH, 70 °C; (g) $Pd_2(dba)_3$, $Zn(CN)_2$, dppf, DMF, H_2O, 120 °C; (h) NBS or NCS, $C_6H_5CF_3$, 25 °C; (i) silica, DCM, 25 °C; (j) morpholine, MeCN, reflux; (k) LDA, THF, −78 °C → 25 °C; (l) K_2CO_3, 18-crown-6, MeI or EtI, MeCN or $MeO(CH_2)_2OMe$, 60 °C.

Scheme 4[a]



[a] Reagents and conditions: (a) $RB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 90 °C; (b) (bis-4-*t*-butylcyclohexyl)peroxydicarbonate, CCl_4, reflux; (c) morpholine, $NaHCO_3$, DCM, 15 °C; (d) $HClO_4$, dioxane, 90 °C; (e) $RB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 100 °C.

thought to predominate over the corresponding 4-hydroxypyridine (pyridinol), the position of the equilibrium for this heterocycle is strongly dependent on the nature of substituents on the pyridine.[35] Given that the carbonyl group is thought to make a key hydrogen bond interaction with the ATP-binding domain, a higher equilibrium concentration of the putatively inactive pyridinol may account for the poor activity of **74** and **75** compared with the analogous pyranones (**10** and **16**) and thiopyranones (**61** and **62**). Alternatively, the lower aromaticity of pyranones compared with pyridones may account for the observed differences in potency. The inactivity of the 4-alkoxypyridine derivatives (**76**−**78**) is in accordance with the requirement for a 4-carbonyl group, but may also reflect unfavorable steric interactions between an alkoxy substituent and this region of the ATP-binding pocket.

The results obtained for members of the pyran-4-one and thiopyran-4-one series confirm that DNA-PK inhibitory activity comparable with the fused-ring heterocycles (**2**−**4**) is achievable. In addition, preliminary in vitro cellular studies conducted in a human tumor cell line with 2-(4-methoxyphenyl)-6-(morpholin-4-yl)pyran-4-one (**16**) demonstrated that the DNA-PK inhibitor enhanced the growth-inhibitory activity of etoposide (Figure 2). Thus, PF_{50} values of 1.7 and 9.2 were observed for **16** at 10 μM and 50 μM, respectively, where the PF_{50} is defined as the potentiation factor at 50% growth inhibition (ratio of the GI_{50} of etoposide alone to the GI_{50} of etoposide plus **16**). These concentrations of **16** alone had no inherent growth-inhibitory activity. Encouraged by these results, and by strong evidence that the pyranone and thiopyranone 6-position is a determinant of potency, substitution at this position was more widely investigated employing a focused compound library approach.

Library compounds of suitable purity in the thiopyranone series were prescreened in duplicate at 0.1, 0.5, and 1.0 μM, and the activities at 1.0 μM are shown in Table 2. The limitations of this initial screen preclude any definitive structure−

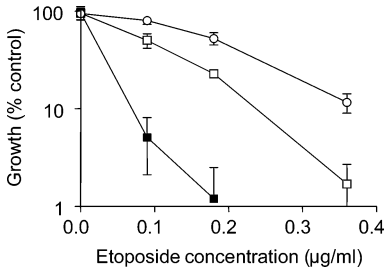


Figure 2. Potentiating effect of **16** on the growth inhibition of etoposide. HeLa cells, seeded in a 96-well plate (2000 cells per well), were preincubated with 0 (○), 10 (□), or 50 (■) μM of **16** for 1 h prior to addition of etoposide. After 16 h, fresh media was added, and the cells were allowed to grow for a further 96 h prior to staining with sulforhodamine B.[36] Data are the mean ± SEM from three separate experiments.

activity correlations, but where comparisons are possible, there is perhaps an overall trend toward 3-substituted 6-arylthiopyranones (series A) being marginally more potent than the corresponding 4-substituted derivatives (series B). In general, IC_{50} values were determined for compounds for which >70% DNA-PK inhibition was observed at 1 μM, although the validity of this data point was corroborated with values obtained at other concentrations and with the repeat assay to eliminate false hits. Thus, the submicromolar potency of the 3-hydroxyphenyl (**84A**), 3-acetamidophenyl (**90A**), and methyl 2-phenylacrylate (**132A**) derivatives in the 3-substituted 6-arylthiopyranone series was confirmed (IC_{50} values of 0.7−0.9 μM).

The activity of three compounds (**142B**, **145B**, and **147B**) in the 4-substituted 6-arylthiopyranone series was of greater interest, with IC_{50} values for DNA-PK inhibition of 0.33 μM, 0.19 μM, and 0.26 μM, respectively, being observed. The potency of these three compounds was confirmed using analytically pure samples prepared by an independent resynthesis, with the 1-naphthyl (**145B**; IC_{50} = 0.16 μM) and 1-(4-methyl)-naphthyl (**147B**; IC_{50} = 0.26 μM) derivatives proving at least equiactive with the isosteric benzo[*b*]thiophenyl analogue (**142B**; IC_{50} = 0.49 μM). It is of interest to note that the multiple-parallel synthesis approach identified three structurally similar 6-substituted thiopyranones as the most potent DNA-PK inhibitors, implying a common binding mode. Indeed, a simple overlay of the naphthyl groups of **145B** and **147B** with the dibenzothiophenyl substituent of NU7441 (**5**) suggests that these functionalities may occupy similar regions of the ATP-binding domain of DNA-PK (Figure 3). Unfortunately, no increase in potency was observed compared with the most active substituted 6-arylthiopyranones **61** and **62**, and members of this inhibitor class remain at least an order of magnitude less potent than NU7441 (**5**).

The 6-arylpyran-4-one library members (Table 2, series C) were prepared in sufficient quantities to enable IC_{50} values to be determined directly, although fewer of these compounds satisfied the required purity criterion (≥85%). The DNA-PK inhibitory activity of this series was disappointing, with only the phthalimido (**135C**) and indol-5-yl (**141C**) derivatives exhibiting potency approaching that of the parent 6-arylpyranones (**10**−**17**).

All compounds prepared in this study were counter-screened against selected members of the PIKK family, with no significant activity being observed against PI 3-K (p110α), ATR, or mTOR (mammalian target of rapamycin) at the highest inhibitor concentration (10 μM) employed. The pyran-2-one, thiopyranone, and pyridone derivatives were also devoid of activity against ATM (data not shown). By contrast, a screen of the initial 6-arylpyran-4-one series revealed modest ATM-inhibitory activity, which was subsequently confirmed by several members of the pyranone library (**100C**, **101C**, **142C**, **144C**, **150C**), as shown in Table 2. However, the 6-thianthren-1-yl-pyran-4-one (**151C**) was prominent in this preliminary screen, exhibiting nanomolar potency against ATM, and ATP-competitive inhibitory activity (K_i = 2.2 nM) was confirmed with analytically pure **151C** prepared by an independent resynthesis. Excellent kinase selectivity was also demonstrated with **151C**, with the inhibitor proving at least 100-fold more potent against ATM compared with DNA-PK (IC_{50} = 1.8 μM) and other PIKK family members, and no significant activity was observed for **151C** against a diverse panel of 60 kinases at 10 μM. A detailed study of the ATM-inhibition kinetics and sensitization of tumor cells to DNA-damaging agents by this remarkably potent and selective ATM inhibitor, assigned the house compound reference number KU-55933, has been reported.[37] It is of interest to note that the corresponding thiopyran-4-one derivative (**66**; IC_{50} for ATM = 0.35 μM) was some 30-fold less potent as an ATM inhibitor than **151C**. This observation, together with the fact that the potent DNA-PK inhibitor **5** is essentially inactive as an ATM inhibitor (IC_{50} > 100 μM), suggests that the ATP-binding domains of these two kinases differ considerably. A comprehensive account of SARs for inhibition of ATM by 6-arylpyran-4-ones will be published subsequently.

Conclusions

In this paper we have demonstrated that appropriately substituted pyran-2-ones, pyran-4-ones, and thiopyran-4-ones are potent and selective inhibitors of DNA-PK, analogous to the previously reported chromen-2-ones and chromen-4-ones.[14,16] In general, the SARs for these simpler heterocycles followed a similar trend to those observed for the chromone pharmacophore. Thus, DNA-inhibitory activity is associated with a 2-morpholinyl function and a lipophilic substituent at the 6-position, whereas substitution at the pyranone 3- or 5-positions is detrimental to activity. Members of the analogous 4-pyridone series exhibited very weak activity against DNA-PK and ATM. Strikingly, and in stark contrast to DNA-PK, few compounds exhibited significant ATM inhibitory activity,

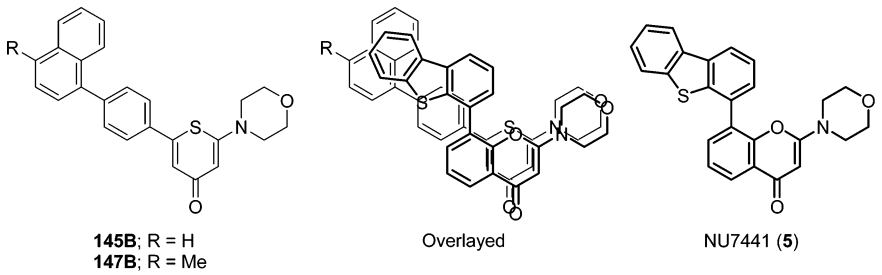


Figure 3. Overlay of thiopyranones **145B** and **147B** with NU7441 (**5**) to illustrate a possible common binding mode for the 6-naphth-1-yl and 8-dibenzothiophen-1-yl substituents.

suggesting highly constrained SARs for inhibition of this kinase, and differences between the ATP-binding domains of DNA-PK and ATM. However, a more comprehensive evaluation of the pyranone 6-position, through the preparation of directed compound libraries, resulted in the identification of **151C** as a highly potent and selective ATP-competitive ATM inhibitor.

Preliminary biological studies with the 4-methoxyphenylpyran-4-one (**16**) have demonstrated the effective sensitization of HeLa cervical cancer cells to the topoisomerase II inhibitor etoposide, analogously to that reported previously for the fused benzo(*h*)chromenone (**2**).[14] In addition to highlighting the cellular bioavailability of this compound class, this observation provides further evidence for the ability of DNA-PK inhibitors to potentiate the activity of agents that elicit DNA DSBs.

In summary, in addition to further delineating SARs for pyranone-derived DNA-PK inhibitors and providing an insight into differences between the ATP-binding sites of DNA-PK and ATM, our studies have resulted in the identification of a potent and selective ATM inhibitor.

Experimental Section

Reagents were purchased from reputable vendors and used as received unless otherwise stated. Solvents were purified and stored according to standard procedures. "Petrol" refers to that fraction of hexanes boiling in the range 40−60 °C. Melting points were obtained on a Stuart Scientific SMP3 apparatus and are uncorrected. Thin layer chromatography was performed using Merck 1.05554 aluminum sheets precoated with Kieselgel $60F_{254}$ (0.2 mm) as the adsorbent, with visualization by potassium permanganate or UV light at 254 and 365 nm. Column chromatography was conducted under medium pressure on silica (Merck silica gel 40−63 μm). HPLC refers to purification on Gilson LC instruments, with a 15 min gradient of 0.1% aqueous TFA and 10−97% acetonitrile, at a flow rate of 6 mL/min, using as the stationary phase a Jones Chromatography Genesis 4μ C18 column, 10 mm × 250 mm, and peak acquisition based on UV detection at 254 nm. Solution-phase palladium-mediated coupling reactions were conducted in "Greenhouse" reactors (Radley's, Ltd., U.K.) in batches of 24 reactions under an argon atmosphere.

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin AC 200E spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C), a Bruker AMX (500 MHz for ^{1}H, 126 MHz for ^{13}C) or a Bruker Advance 300 MHz Ultrashield spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C), using tetramethylsilane or the deuterated solvent as the internal standard for ^{1}H and ^{13}C spectra, respectively. Unless indicated otherwise, spectra were recorded in $CDCl_3$ as solvent. Chemical shift values are quoted in parts per million (ppm) and coupling constants (*J*) are quoted in hertz (Hz). Key: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet. NH signals appeared as broad singlets (br s), exchangeable with D_2O. Mass spectra were determined on a Micromass Autospec M spectrometer in electron impact (EI) mode. Liquid chromatography−mass spectrometry (LCMS) was carried out on either a Micromass Platform instrument operating in positive and negative ion electrospray mode, employing a 50 × 4.6 mm C18 column (Supelco Discovery or Waters Symmetry) and a 15 min gradient elution of 0.05% formic acid and methanol (10−90%), or on a Finnegan LCQ instrument in positive ion mode with a Phenomenex 5μ Luna C18 column, 4.6 mm × 50 mm and an 8 min gradient of 0.1% aqueous formic acid and acetonitrile (5−98%), with a flow rate of 2 mL/min. IR spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR. Elemental analyses were performed by Butterworth Laboratories, Middlesex, U.K. and were within ±0.4% of theory unless otherwise specified.

1-Acetylthianthrene (7). To a solution of thianthrene-1-carboxylic acid[38] (3.90 g, 15 mmol) in anhydrous THF (100 mL) at −78 °C was slowly added MeLi (1.6 M solution in Et_2O, 20 mL, 32 mmol). The reaction mixture was allowed to warm to ambient temperature over 4 h and stirred for a further 14 h. After cooling the solution to 5 °C, water (55 mL) was added, and the mixture was acidified to pH 2 by addition of aqueous HCl solution (2 M). The organic layer was separated, and the aqueous portions were extracted with diethyl ether (3 × 50 mL). The combined organic fractions were washed with saturated NaCl solution (2 × 50 mL), dried ($MgSO_4$), and concentrated to provide an oil, which was purified by chromatography on silica (eluting with petrol/EtOAc 90:10) to yield yellow crystals (1.4 g, 36%): mp 128−129 °C; ^{1}H NMR δ 2.57 (s, 3H, C*H*$_3$), 7.11−7.23 (m, 3H, thianthrene-*H*), 7.35−7.41 (m, 2H, thianthrene-*H*), 7.51−7.58 (m, 2H, thianthrene-*H*); LCMS *m*/*z* 259 ([M + 1]$^+$). Anal. ($C_{14}H_{10}OS_2$) C, H.

1-(Thianthren-1-yl)-butane-1,3-dione (8). A solution of **7** (3.1 g, 12 mmol) in EtOAc (80 mL) at 0 °C was added in four portions to a suspension of NaOEt (0.88 g, 13 mmol) in EtOAc (3 mL) at 0 °C, and the mixture was stirred for 36 h. DCM (10 mL) was added, and the off-white solid that deposited was collected and suspended in aqueous HCl solution (2 M, 20 mL), and the mixture was stirred vigorously for 20 min. The yellow solid was collected, washed with water (3 × 20 mL), and dried. Recrystallization from EtOAc provided the title compound as yellow crystals (2.3 g, 65%): mp 142−143 °C; ^{1}H NMR δ 2.12 (s, 3H, C*H*$_3$), 5.86 (s, 1H, =C*H*), 7.12−7.26 (m, 3H, thianthrene-*H*), 7.38−7.43 (m, 3H, thianthrene-*H*), 7.52 (d, 1H, *J* = 7.7, thianthrene H-2); LCMS *m*/*z* 301 ([M + 1]$^+$). Anal. ($C_{16}H_{12}O_2S_2$) C, H.

3-Methyl-2-morpholin-4-yl-6-phenylpyran-4-one (18). To a solution of 1-phenylpentane-1,3-dione (94 mg, 0.53 mmol) in dry DCM (5 mL) at 0 °C was added BCl_3 (1.0 M in DCM, 0.59 mL, 0.59 mmol), and the solution was stirred for 1 h. The solution was cooled to −78 °C, *N*-ethyldiisopropylamine (0.29 mL, 1.65 mmol) was added, the solution was stirred for a further 1 h, and 4-dichloromethylenemorpholin-4-ium chloride (0.130 g, 0.639 mmol) was added. The reaction mixture was stirred for a further 15 min and allowed to warm to 0 °C, whereupon MeOH (20 mL) was added, and the reaction mixture was stirred for 12 h at 0 °C. Volatiles were removed in vacuo, and the residual solid was dissolved in water (10 mL) and extracted with DCM (2 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Purification by chromatography on silica employing DCM/EtOAc (70:30) as eluent gave the title compound as a yellow solid: IR (film) 1646, 1578 cm^{-1}; ^{1}H NMR δ 1.92 (3H, s), 3.27−3.30 (4H, m), 3.77−3.80 (4H, m), 6.63 (1H, s), 7.39−7.43 (3H, m), 7.61−7.65 (2H, m); LCMS *m*/*z* 272 ([M + 1]$^+$). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

6-(4-Chlorophenyl)-3-methyl-2-morpholin-4-yl-pyran-4-one (19). Compound **19** was prepared as for **18** from 1-(4-chlorophenyl)-pentane-1,3-dione (0.111 g, 0.533 mmol). Purification by chromatography on silica with DCM/MeOH (98:2) as eluent yielded the title compound as a pale yellow solid: IR (film) 1646, 1578, 744 cm^{-1}; ^{1}H NMR δ 1.92 (3H, s), 3.26−3.28 (4H, m), 3.77−3.80 (4H, m), 6.61 (1H, s), 7.37−7.40 (2H, m), 7.55−7.58 (2H, m); LCMS *m*/*z* 306 ([M + 1]$^+$). Anal. ($C_{16}H_{16}NO_3$) C, H, N.

2-Morpholin-4-yl-5-phenylpyran-4-one (23). A solution of 1-morpholin-4-yl-4-phenylbutane-1,3-dione (**21**)[22] (0.49 g, 2.0 mmol), prepared from 5-(1-hydroxy-2-phenylethylidene)-2,2-dimethyl-[1,3]dioxane-4,6-dione (20),[21] in anhydrous THF (5 mL) was added slowly to a solution of LDA (4.0 mmol) in THF (10 mL) at −78 °C. After 15 min, the solution was warmed to 5 °C, stirred for 1 h, and cooled to −78 °C, and a solution of ethyl formate (0.15 mL, 1.8 mmol) in THF (10 mL) was cautiously added. The reaction mixture was stirred at −78 °C for a further 90 min, allowed to warm to ambient temperature, and quenched with water (5 mL). The solution was neutralized by the addition of aqueous HCl solution (2.0 M) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give 5-morpholin-4-yl-3,5-dioxo-2-phenylpentanal (22) as a brown oil (0.49 g), which was used directly without further purification.

A solution of **22** (0.34 g, 1.2 mmol) in methanesulfonic acid (3 mL) was stirred at 25 °C for 90 min, poured into an ice-cold

saturated $NaHCO_3$ solution (10 mL), and the mixture was extracted with DCM (4 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by chromatography on silica employing DCM/MeOH (96:4) as eluent afforded **23** as an off-white solid: IR (KBr) 1560, 1642, 2861, 2978, 3048 cm^{-1}; ^1H NMR δ 3.24−3.35 (m, 4H, $N(CH_2)_2$), 3.69−3.81 (m, 4H, $O(CH_2)_2$), 5.49 (s, 1H, pyranone *H*-3), 7.20−7.51 (m, 6H, phenyl-*H* + pyranone *H*-6); HRMS (EI, M^+) calcd for $C_{15}H_{15}NO_3$, 257.1052; found, 257.1057.

2-Mercapto-4*H*-thiopyran-4-ones (30−38): Method I. General Procedure. To a stirred solution of LDA (2 mol equiv) in anhydrous THF (30−40 mL), cooled to −78 °C under an atmosphere of nitrogen, was slowly added the appropriate β-acetylketone (1 mol equiv) dissolved in THF. After addition was complete, the mixture was allowed to warm slowly to ambient temperature and was stirred for 20 min. The solution was recooled to −78 °C, and a solution of carbon disulfide (1 mol equiv) in THF (30−40 mL) was added slowly. This temperature was maintained for 2 h, the reaction mixture was allowed to warm to ambient temperature, and stirring was continued for a further 18 h. The reaction mixture was poured onto ice−water (40 mL) and stirred for 1 h. Volatiles were removed in vacuo, and the aqueous solution was washed with two portions of diethyl ether. The aqueous solution was acidified slowly to pH 1 by the dropwise addition of aqueous HCl (2.0 M), whereupon the title compounds deposited and were collected, washed with water, and dried. Compounds **33** (2-mercapto-6-phenyl-4*H*-thiopyran-4-one), **35** (2-mercapto-6-(4-methoxyphenyl)-4*H*-thiopyran-4-one), and **38** (2-mercapto-6-(4-*t*-butylphenyl)-4*H*-thiopyran-4-one) were used directly for the next step.

6-Methyl-2-mercapto-4*H*-thiopyran-4-one (30). Compound **30** was prepared from pentane-2,4-dione (2.0 g, 20 mmol) according to Method I. A brown solid was isolated that was triturated with petrol/DCM (95:5) to give a yellow solid (1.52 g, 48%): mp 151−153 °C; ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 6.90 (s, 1H, *H*-3), 6.94 (s, 1H, *H*-5); LCMS *m*/*z* 159 ($[M + 1]^+$), 157 ($[M - 1]^-$). Anal. ($C_6H_6OS_2$) C, H.

2-Ethylsulfanyl-4*H*-thiopyran-4-ones (41−51): Method II. General Procedure. A mixture of the appropriate 2-mercaptothiopyran-4-one, powdered K_2CO_3 (1.5 mol equiv) and EtI (4 mol equiv) was heated under reflux in anhydrous acetone for 2 h or until no starting material was observed. Volatiles were removed in vacuo, and the residue was redissolved in EtOAc, washed successively with H_2O, saturated aqueous NaCl solution, and H_2O, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded the required 2-ethylsulfanylthiopyranones.

2-Ethylsulfanyl-6-methyl-4*H*-thiopyran-4-one (41). The title compound was prepared from **30** (1.42 g, 9.0 mmol) according to Method II, except that purification was achieved by chromatography on silica with EtOAc/petrol (1:1) as eluent, to provide the title compound as an orange oil (1.52 g, 91%); IR 2937, 2928, 1604, 1519 cm^{-1}; ^1H NMR δ 1.31 (t, 3H, J = 7.4, CH_2CH_3), 2.28 (d, 3H, J = 1.1, CH_3), 2.97 (q, 2H, J = 7.4, CH_2CH_3), 6.62 (dd, 1H, J_1 = 1.3, J_2 = 1.1, *H*-5), 6.79 (d, 1H, J = 1.3, *H*-3); LCMS *m*/*z* 187 ($[M + 1]^+$). Anal. ($C_8H_{10}OS_2$) C, H.

2-Ethylsulfanyl-6-thianthren-1-yl-4*H*-thiopyran-4-one (50). To a solution of LDA (1.8 M in THF, 5.8 mL, 10.5 mmol) and DMPU (0.6 mL, 5 mmol) in anhydrous THF (25 mL) at −78 °C was slowly added a solution of **8** (1.50 g, 5 mmol) in THF (25 mL), and the reaction mixture was stirred for 1 h. A solution of carbon disulfide (0.30 mL, 5 mmol) in THF (20 mL) was added dropwise, and the mixture was stirred for 16 h at 25 °C. Water (50 mL) was added and volatiles were removed in vacuo. The aqueous solution was washed with DCM (2 × 20 mL), acidified to pH 1 by the dropwise addition of aqueous HCl solution (0.5 M), and extracted with EtOAc (4 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to provide an orange solid (1.7 g) that was redissolved in acetone (20 mL) and used directly. K_2CO_3 (1.24 g, 9 mmol) and EtI (1.1 mL, 14 mmol) were added, and the mixture was heated under reflux for 2 h. The solvent was evaporated in vacuo, and the residual solid was partitioned between DCM (30 mL) and water (20 mL). The aqueous layer was extracted with DCM (2 × 10 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated to yield an orange oil. Purification by chromatography on silica employing petrol/EtOAc (6:4) as eluent afforded the title compound as a pale yellow oil (0.17 g, 9%): ^1H NMR δ 1.37 (t, 3H, J = 7.4, CH_3), 3.03 (q, 2H, J = 7.4, CH_2), 6.79 (d, 1H, J = 1.3, thiopyranone *H*-3), 6.96 (d, 1H, J = 1.3, thiopyranone *H*-5), 7.17−7.22 (m, 4H, thianthrene-*H*), 7.37−7.45 (m, 2H, thianthrene-*H*), 7.53 (dd, 1H, J_1 = 1.9, J_2 = 7.2, thianthrene *H*-2); LCMS *m*/*z* 386 ($[M + 1]^+$); HRMS (EI, M^+) calcd for $C_{19}H_{14}OS_4$, 385.9928; found, 385.9928.

2-Ethylsulfinyl-6-methyl-4*H*-thiopyran-4-one (52). To a solution of **41** (1.26 g, 6.77 mmol) in DCM (10 mL) at 0 °C was added a solution of *m*-CPBA (70%, 1.67 g, 6.77 mmol) in DCM (15 mL), and the reaction mixture was stirred for 1 h. DCM (30 mL) was added, and the solution was washed with $NaHCO_3$ solution (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual brown solid was triturated with petrol−diethyl ether to provide the title compound as an off-white solid: mp 97−99 °C; ^1H NMR δ 1.27 (t, 3H, J = 7.4, CH_2CH_3), 2.42 (s, 3H, CH_3), 2.88 (dq, 1H, J_1 = 14.7, J_2 = 7.4, $SOCH^a$), 2.93 (q, 2H, J = 7.4, CH_2CH_3), 3.02 (dq, 1H, J_1 = 14.7, J_2 = 7.4, $SOCH^b$), 6.75 (d, 1H, J = 1.4, *H*-5), 7.07 (d, 1H, J = 1.4, *H*-3); HRMS (EI, M^+) calcd for $C_8H_{10}O_2S_2$, 202.0122; found, 202.0124. Anal. ($C_8H_{10}O_2S_2$) C, H.

2-Ethylsulfinyl-6-isopropyl-4*H*-thiopyran-4-one (53). Compound **53** was prepared as for **52** above from **42** (0.14 g, 0.65 mmol) and *m*-CPBA (70%, 0.16 g, 0.66 mmol): orange solid (0.15 g, 97%); mp 63−64 °C; IR 3018, 2986, 2961, 2930, 2870, 1600, 1560 cm^{-1}; ^1H NMR δ 1.26−1.30 (m, 9H, 3 × CH_3), 2.84−3.08 (m, 3H, SCH^aH^b + $CH(CH_3)_2$), 6.82 (s, 1H, *H*-5), 7.08 (s, 1H, *H*-3); LCMS 231 ($[M + 1]^+$).

2-Amino-6-substituted-4*H*-thiopyran-4-ones (54−58): Method III. General Procedure. A mixture of the 2-ethylsulfinyl-6-substituted-thiopyran-4-one (1 mol equiv), the appropriate amine (4 mol equiv), and 2,2,2-trifluoroethanol (1−2 mL) was heated at 70 °C for 48 h with stirring under N_2. After cooling, the solvent was removed in vacuo, and the product was purified by chromatography on silica (1−5% MeOH/DCM gradient).

2-Morpholin-4-yl-6-substituted-4*H*-thiopyran-4-ones (59−66): Method IV. General Procedure. To a suspension of the appropriate 2-ethylsulfanyl-6-substituted-thiopyran-4-one in ethane-1,2-diol (2−5 mL) was added morpholine (1−2 mL), and the mixture was heated under nitrogen with stirring at 100 °C for 24 h, followed by 125 °C for 48 h. After cooling, the mixture was poured onto water (50 mL), extracted into DCM (4 × 25 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the product, which was purified by chromatography on silica.

6-Methyl-2-pyrrolidin-1-yl-4*H*-thiopyran-4-one (54). The title compound was prepared from **52** (0.04 g, 0.2 mmol) and pyrrolidine (0.07 mL, 0.8 mmol) according to Method III to give beige needles: IR 2953, 2910, 2858, 1615, 1562, 1521 cm^{-1}; ^1H NMR δ 1.94−2.00 (m, 6H, $CH_2(CH_2)_2CH_2$), 2.23 (s, 3H, CH_3), 3.29−3.33 (m, 4H, $N(CH_2)_2$), 5.70 (s, 1H, *H*-3), 6.49 (s, 1H, *H*-5); LCMS *m*/*z* 196 ($[M + 1]^+$).

6-*tert*-Butyl-2-morpholin-4-yl-4*H*-thiopyran-4-one (59). Compound **59** was prepared in accordance with Method IV from **43** (0.204 g, 0.90 mmol) to give an orange oil: IR 3413, 2965, 2859, 1600, 1522 cm^{-1}; ^1H NMR δ 1.27 (s, 9H, $C(CH_3)_3$), 3.30−3.34 (m, 4H, $N(CH_2)_2$), 3.73−3.76 (m, 4H, $O(CH_2)_2$), 6.00 (d, 1H, J = 1.1, *H*-3), 6.64 (d, 1H, J = 1.1, *H*-5); LCMS *m*/*z* 254 ($[M + 1]^+$).

6-(4-Cyanophenyl)-2-morpholin-4-yl-4*H*-thiopyran-4-one (68). A mixture of **64** (0.22 g, 0.62 mmol), zinc cyanide (0.044 g, 0.37 mmol), $Pd_2(dba)_3$ (0.017 g, 3 mol %), and 1,1′-bis(diphenylphosphino)ferrocene (0.025 g, 7 mol %) in degassed DMF (2 mL + 0.03 mL H_2O) was stirred at 120 °C under an atmosphere of argon for 40 h. The cooled reaction mixture was poured onto aqueous NaOH solution (1 mM, 30 mL) and extracted sequentially with DCM (3 × 20 mL) and EtOAc (20 mL). The combined organic layers were washed with saturated aqueous NaCl solution, and the volatiles were removed in vacuo to give a beige solid: IR 2226, 1609, 1529 cm^{-1}; ^1H NMR δ 3.39−3.35 (m, 4H, $O(CH_2)_2$), 3.76−3.79 (m, 4H, $N(CH_2)_2$), 6.11 (s, 1H, thiopyranone *H*-3), 6.90 (s,

1H, thiopyranone *H*-5), 7.61 (d, 2H, $J = 8.6$ Hz, arylnitrile *H*-3,5), 7.71 (d, 2H, $J = 8.6$ Hz, arylnitrile *H*-2,6); LCMS *m*/*z* 299 ([M + 1]$^+$).

2-Morpholin-4-yl-6-(4-morpholin-4-yl-phenyl)-4*H*-thiopyran-4-one (69). Compound **69** was isolated as a byproduct from the synthesis of compound **64** to give a beige solid: IR 2851, 1586, 1344, 1510, 1445 cm^{-1}; ^{1}H NMR δ 3.15−3.21 (m, 4H, N(C*H*$_2$)$_2$), 3.33−3.38 (m, 4H, O(C*H*$_2$)$_2$), 3.74−3.83 (m, 8H, Ar-morpholine-(C*H*$_2$)$_4$), 6.09 (s, 1H, thiopyranone *H*-3), 6.83 (s, 1H, thiopyranone *H*-5), 6.86 (d, 2H, aromatic *H*-3,5), 7.43 (d, 2H, aromatic *H*-2,6); LCMS *m*/*z* 359 ([M + 1]$^+$); HRMS (EI, M$^+$) calcd for $C_{19}H_{22}N_2O_3S$, 358.1351; found, 358.1351.

2-Morpholin-4-yl-5,6,7,8-tetrahydrothiochromen-4-one (71). To a solution of **51** (0.06 g, 0.25 mmol) in DCM (1 mL) at 0 °C was added *m*-CPBA (70%, 0.06 g, 0.25 mmol) in DCM (1 mL) dropwise over 15 min, and the reaction mixture was stirred at 25 °C for 18 h. DCM (8 mL) was added, and the solution was washed successively with $NaHCO_3$ solution (2 × 10 mL) and saturated NaCl solution, dried (Na_2SO_4), and concentrated in vacuo to provide the sulfoxide **70** as a yellow oil, which was used directly. A solution of **70** and morpholine (0.1 mL, 1 mmol) in MeCN (1 mL) was heated under reflux for 8 days. The volatiles were removed in vacuo, and the residue was redissolved in DCM (20 mL), washed sequentially with aqueous HCl solution (0.5 M, 2 × 10 mL) and saturated NaCl solution (10 mL), and concentrated in vacuo to give off-white fine needles: IR 2934, 2909, 2870, 2833, 1623, 1582, 1535 cm^{-1}; ^{1}H NMR δ 1.57−1.60 (m, 4H, CH$_2$(C*H*$_2$)$_2$CH$_2$), 2.38−2.51 (m, 4H, C*H*$_2$(*C*═)CO + C*H*$_2$(*C*═)S), 3.26−3.29 (m, 4H, N(C*H*$_2$)$_2$), 3.71−3.75 (m, 4H, O(C*H*$_2$)$_2$), 6.14 (s, 1H, *H*-3); LCMS *m*/*z* 252 ([M + 1]$^+$).

3-Bromo-6-(4-chlorophenyl)-2-morpholin-4-yl-thiopyran-4-one (72). *N*-Bromosuccinimide (0.04 g, 0.22 mmol) was added to a suspension of **61** (0.062 g, 0.20 mmol) in trifluoromethylbenzene (20 mL), and the mixture was stirred at ambient temperature for 18 h. The solvent was removed in vacuo, and the residue purified by chromatography on silica to provide the title compound as an off-white solid: IR 2959, 2900, 2856, 2815, 1604, 1526 cm^{-1}; ^{1}H NMR δ 3.28−3.31 (m, 4H, N(C*H*$_2$)$_2$), 3.80−3.83 (m, 4H, O(C*H*$_2$)$_2$), 7.05 (s, 1H, thiopyranone *H*-5), 7.38 (d, 2H, $J = 8.8$, 4-chlorophenyl *H*-2,6), 7.44 (d, 2H, $J = 8.8$, 4-chlorophenyl *H*-3,5); LCMS *m*/*z* 387, 389 ([M + 1]$^+$).

6-(4-Bromophenyl)-3-chloro-2-morpholin-4-yl-4*H*-thiopyran-4-one (73). To a suspension of **64** (0.07 g, 0.20 mmol) in trifluoromethylbenzene (20 mL) was added *N*-chlorosuccinimide (0.03 g, 0.22 mmol), and the mixture was stirred at ambient temperature for 18 h. The solvent was removed in vacuo, and the residue was purified by chromatography on silica to provide the title compound as a pale-yellow solid: IR 3086, 2850, 1600, 1512 cm^{-1}; ^{1}H NMR δ 3.29−3.32 (m, 4H, N(C*H*$_2$)$_2$), 3.80−3.83 (m, 4H, O(C*H*$_2$)$_2$), 7.11 (s, 1H, thiopyranone *H*-5), 7.37 (d, 2H, $J =$ 8.7, 4-bromophenyl *H*-2,6), 7.55 (d, 2H, $J = 8.7$, 4-bromophenyl *H*-3,5); LCMS *m*/*z* 386, 388, 390 ([M + 1]$^+$).

6-(4-Chlorophenyl)-2-morpholin-4-ylpyridin-4-ol (74). 1-(4-Chlorophenyl)-butane-1,3-dione (1.97 g, 10 mmol) in anhydrous THF (20 mL) was added slowly to a solution of LDA (2.14 g, 20 mmol) in THF at −78 °C, and this temperature was maintained for 10 min. The solution was warmed to ambient temperature and cooled to −78 °C, and a solution of 4-morpholinecarbonitrile (1.12 g, 10 mmol) in THF (10 mL) was added slowly. The mixture was stirred at −78 °C for 1 h, followed by 18 h at ambient temperature. After addition of water (10 mL), the reaction mixture was concentrated in vacuo, and the residue was redissolved in DCM (150 mL) and washed with NaOH solution (2 M, 80 mL). The organic layer was separated and washed further with NaOH solution (2 M, 2 × 80 mL), and the combined aqueous portions were washed with DCM (2 × 50 mL) and acidified to pH 1.5 with concentrated HCl solution. The precipitated solid was collected, washed with Et_2O/EtOH (9:1; 3 × 20 mL), and stirred as a suspension in saturated $NaHCO_3$ solution (100 mL) for 30 min. DCM (2 × 100 mL) was added, and the mixture was stirred vigorously until dissolution was complete. The DCM layer was separated, and the aqueous portion was washed with DCM (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to provide **74** as a beige solid: ^{1}H NMR (DMSO-d_6) δ 3.50−3.52 (m, 4H, N(C*H*$_2$)$_2$), 3.76−3.78 (m, 4H, O(C*H*$_2$)$_2$), 6.19 (d, 1H, $J = 1.5$, *H*-3), 6.79 (d, 1H, $J = 1.5$, *H*-5), 7.54 (d, 2H, 4-chlorophenyl *H*-2,6), 8.04 (d, 2H, 4-chlorophenyl *H*-3,5), 10.39 (s, 1H, OH); LCMS *m*/*z* 291, 293 ([M + 1]$^+$), 289, 291 ([M − 1]$^-$).

6-(4-Chlorophenyl)-2-morpholin-4-yl-4-methoxypyridine (76). To a solution of **74** (0.09 g, 0.3 mmol) in dry 1,2-dimethoxyethane (3 mL) was added powdered anhydrous potassium carbonate (0.04 g, 0.3 mmol), 18-crown-6 (0.16 g, 0.6 mmol), and iodomethane (0.04 mL, 0.6 mmol). The reaction mixture was heated to 60 °C for 4 h, cooled to ambient temperature, and concentrated in vacuo. The residue was suspended in water (4 mL), and EtOAc (10 mL) was added. The organic phase was separated, and the aqueous phase was washed with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to yield a yellow solid that was purified by chromatography on silica: IR 2967, 2818, 1574, 1430 cm^{-1}; ^{1}H NMR δ 3.47−3.51 (m, 4H, O(C*H*$_2$)$_2$), 3.74−3.78 (m, 4H, N(C*H*$_2$)$_2$), 3.78 (s, 3H, OC*H*$_3$), 5.60 (d, 1H, $J = 1.8$, *H*-3), 6.62 (d, 1H, $J = 1.8$, *H*-5), 7.30 (d, 2H, $J = 8.7$, 4-chlorophenyl *H*-2,6), 7.83 (d, 2H, $J = 8.7$, 4-chlorophenyl *H*-3,5); LCMS *m*/*z* 305, 307 ([M + 1]$^+$).

Solution-Phase Library Syntheses: Method V. General Procedure. The appropriate organoboron compound (0.063 mmol) and powdered K_2CO_3 (19 mg, 0.14 mmol) were added to a reaction tube that had been purged with N_2. The tube was flushed with N_2 and sealed. Thiopyranone (**63** or **64**) or pyranone (**81**; 20 mg, 57 μmol) was dissolved in 1,4-dioxane (1 mL), the solution was degassed with N_2 sparge, sonicated for 5 min, and added to the reaction tube. A solution of Pd(PPh$_3$)$_4$ (3 mg) in degassed dioxane (0.3 mL) was added, and the reaction mixture was stirred under N_2 at 90 °C for 18 h. The reaction mixture was cooled, filtered, and eluted from a prepacked silica cartridge (Isolute Si 500 mg) with 25% MeOH/DCM (3 mL). Products were purified by semipreparative HPLC, and the purity was assessed by LCMS.

Thiopyranones (**142B**, **145B**, and **147B**), identified from the library screen as sufficiently potent to warrant resynthesis, were prepared as follows: to a mixture of the appropriate organoboron compound (0.33 mmol) and powdered K_2CO_3 (0.1 g, 0.7 mmol) was added a degassed solution of **64** (0.11 g, 0.3 mmol) in dioxane (7 mL) and Pd(PPh$_3$)$_4$ (17 mg, 15 mmol). The reaction mixture was stirred at 90 °C under N_2 for 36 h and concentrated in vacuo, and the residue was partitioned between water (30 mL) and DCM (30 mL). The aqueous layer was further extracted with DCM (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure, and purification was achieved by chromatography on silica with DCM/MeOH (95:5) as eluent, followed by semipreparative HPLC.

6-(4-Benzo[*b*]thiophen-3-ylphenyl)-2-morpholin-4-yl-4*H*-thiopyran-4-one (142B). Compound **142B** was prepared from **64** and thianaphthene-3-boronic acid according to Method V and isolated as a beige solid (41 mg, 34%): mp 197−198 °C; IR 3069, 1600, 1520, cm^{-1}; ^{1}H NMR δ 3.46−3.49 (m, 4H, N(C*H*$_2$)$_2$), 3.86−3.89 (m, 4H, O(C*H*$_2$)$_2$), 6.24 (s, 1H, thiopyranone *H*-3), 7.07 (s, 1H, thiopyranone *H*-5), 7.43−7.45 (m, 2H, aromatic-*H*), 7.50 (s, 1H, benzothiophene *H*-2), 7.71 (s, 4H, aromatic-*H*), 7.92−7.99 (m, 2H, aromatic-*H*); LCMS *m*/*z* 406 ([M + 1]$^+$).

Resynthesis of 2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one (151C). To a solution of **81** (3.54 g, 16.41 mmol) in degassed dioxane (20 mL) was added thianthrene-1-boronic acid (5.0 g, 19.22 mmol) and finely ground K_2CO_3 (4.87 g, 38.25 mmol). Pd(P(Ph)$_3$)$_4$ (0.92 g, 0.80 mmol) was added to the reaction mixture, which was degassed for a further 15 min and heated under reflux for 3 days under N_2. The cooled reaction mixture was poured into EtOAc (50 mL), washed with water (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give an orange slurry that was purified

by chromatography on silica, employing hexanes/EtOAc (20:1) as eluent. Recrystallization from EtOH gave the title compound as an off-white amorphous powder (3.96 g, 61%): mp 109−110 °C; IR 2969, 2896, 2857, 1647, 1556, 1467, 1447 cm^{-1}; ^1H NMR δ 3.44−3.50 (m, 4H, CH_2−N), 3.81−3.84 (m, 4H, CH_2−O), 5.56 (d, 1H, J = 1.9 Hz, H-3), 6.32 (d, 1H, J = 1.9 Hz, H-5), 6.33−7.66 (m, 7H-arom); LCMS (*m*/*z*) 396.2 $[M + 1]^+$, 397.2 $[M + 2]^+$, 398.2 $[M + 3]^+$; HRMS (EI) $[M + H]^+$ calcd for $C_{21}H_{17}NO_3S_2$, 396.0723; found, 396.0721.

Enzyme Inhibition Assays. In vitro assays for DNA-PK and ATM kinase activity were performed as described previously.[14,39]

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Supporting Information Available: Synthetic and analytical data for compounds **11**, **12**, **17**, **31**, **32**, **34**, **36**, **37**, **40**, **42**−**49**, **51**, **55**−**58**, **60**−**67**, **75**, **77**−**81**, **145B**, and **147B**. Elemental analyses for all target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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