14, 286-18-0; 15, 51066-08-1; 16, 67198-21-4; 17, 67198-25-8; 18, 67198-32-7; 19, 67579-93-5; 20, 67198-27-0; 21, 67198-26-9; *N*-allymethylamine, 627-37-2; 4-methoxybenzoyl chloride, 100-07-2; 3,4-dichlorobenzoyl chloride, 3024-72-4; 4-hydroxybenzoyl chloride, 28141-24-4; 3-methoxybenzoyl chloride, 1711-05-3; 4-nitrobenzoyl chloride, 122-04-3; 4-cyanobenzoyl chloride, 6068-72-0; 4-chlorobenzoyl chloride, 122-01-0; 4-(trifluoromethyl)benzoyl chloride, 329-15-7; *N*-(cyclopropylmethyl)methylamine, 18977-45-2.

Pyrimidinones. 1. 2-Amino-5-halo-6-aryl-4(3*H*)-pyrimidinones. Interferon-Inducing Antiviral Agents

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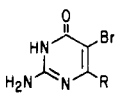
Interferon induction and antiviral activity was discovered with 2-amino-5-bromo-6-phenyl-4(3*H*)-pyrimidinone. An analogue study incorporating a series of 2-amino-5-substituted-6-arylpyrimidinones revealed that the most potent interferon inducers were mono- and difluorophenyl analogues. These same analogues were also potent antiviral agents against Semliki Forest virus and herpes simplex type 1. In addition the monomethoxyphenyl analogues were potent antiviral agents but weak interferon inducers. Relatively modest structural changes led to dramatic changes in bioactivity. There was a relatively poor correlation between levels of circulating interferons induced and systemic antiviral activity.

The utility of interferons in mediating an antiviral state in the virus-infected host is well established.[1,2] One approach to antiviral therapy with interferon (IFN) in the infected host is through the use of interferon inducers.[2,3] Although much of the focus in this area has been on high-molecular-weight, ionic polymers such as polynucleotides (poly(IC)) and pyrans, research and clinical evaluation has also included several low-molecular-weight interferon inducers, such as fluorenones and aliphatic diamines.

In 1976, 2-amino-5-bromo-6-methyl-4(3*H*)-pyrimidinone (ABMP) was reported to induce circulating serum levels of interferons when administered orally (po) or intraperitoneally (ip) to rodents and cats.[4] Although it compared favorably with poly (IC) and tilorone in terms of circulating IFN levels and hyporesponsiveness,[5] it exhibited a toxicity-limiting crystal deposition in the renal papillae of rats upon chronic administration.[7] Subsequent studies demonstrated that the analogous 6-phenylpyrimidinones did not possess this toxic liability[6] and, furthermore, exhibited enhanced IFN-inducing and antiviral potency and activity.[6,8]

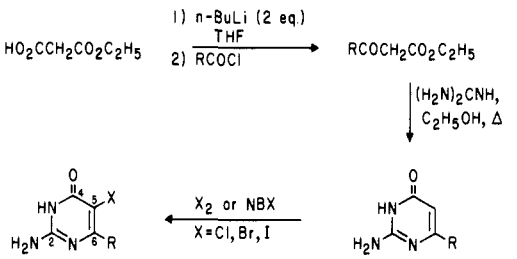
Further biological evaluation of an initial lead candidate in this second-generation pyrimidinone series, 2-amino-5-bromo-6-phenyl-4(3*H*)-pyrimidinone (ABPP), served to unravel an intriguing spectrum of immunomodulatory activity[9-11,16] that may be related to its antiviral[12,13] and antitumor activity.[14,15] In efforts to elucidate the structure–activity relationship (SAR) profile of these bioactivities in this pyrimidinone series, we have systematically varied synthetically accessible points in the generic molecule. We report herein the effects of molecular modifications at the 6-position of the 2-amino-5-halo-4-pyrimidinone structure upon antiviral activity (SFV and HSV-1) and IFN induction in mice.



R = CH_3 - ABMP
R = C_6H_5 - ABPP

Chemistry. 2-Amino-6-substituted-4-pyrimidinones are readily prepared by condensation of an appropriate β-keto ester with guanidine (Scheme I).[6,17] The β-keto esters are prepared in high yield by acylation of dilithio ethylmalonate[18,19] followed by protonation. The introduction

Scheme I



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of halogen at C-5 is accomplished by treatment of the pyrimidinone with *N*-halosuccinimides in acetic acid or, alternatively, bromine or iodine in aqueous sodium hydroxide/chloroform for X = Br, I and bromine in acetic acid for X = Br.

The overall yields from monoethyl malonate to final pyrimidinone were generally >50%. All β-keto ester intermediates[18] were analyzed by ^{1}H NMR and were generally of acceptable purity to be used directly in the guanidine condensation to pyrimidinone. All of the pyrimidinones, including the intermediates (5-hydrogen), exhibited acceptable combustion analysis (see Table I) and ^{1}H NMR spectra consistent with their structural assignment. In addition, single-crystal X-ray analysis of ABPP crystallized from acetic acid revealed a triclinic 2-amino-4(3*H*)-pyrimidinone tautomer (R = 0.064, 2070 reflections).[20,21]

All of the analogues listed in the table were derived from commercially available aryl carboxylic acids, with several exceptions, as starting materials for the β-keto ester. The difluoro series were secured via metalation of difluorobenzene[22] followed by carboxylation to afford the difluorobenzoic acids. For example, treatment of *p*-difluorobenzene with butyllithium at −60 °C in THF followed by CO_2 quench yielded 2,5-difluorobenzoic acid (43%). Analogously, *o*-difluorobenzene afforded 2,3-difluorobenzoic acid in 76% yield (2,6-difluorobenzoic acid is commercially available).

The phenol analogues (e.g., entry 17) were derived from the demethylation of corresponding anisole analogues (e.g., entry 14) by standard treatment with HBr in acetic acid. The 3,5-dibromo-4-hydroxyphenyl analogue (entry 70) was the result of attempted bromination (procedure B) of the *m*-phenol precursor (i.e., over-bromination). The *m*-ethoxyethyloxy analogues (entries 46, 47) were prepared by alkylation (K_2CO_3/DMF, 100 °C) of *m*-hydroxybenzoic acid with ethoxyethyl bromide. The resulting bisalkylated ether–ester was hydrolyzed (KOH, EtOH, aqueous) to *m*-ethoxy(ethyloxy)benzoic acid, which was then converted to the acid chloride ($SOCl_2$) and carried through the route shown in Scheme I. The *p*-benzoic acid analogue (entry 61) was derived from the *p*-benzonitrile analogue (nonhalogenated precursor, entry 60) by employing standard hydrolysis conditions (2 N NaOH, Δ).

Biology. When the enhanced antiviral and interferon-inducing activity of the 6-phenyl analogue (ABPP) over the 6-methyl analogue (ABMP) was originally uncovered,[6] we initiated a modest analogue effort to explore structure–activity relationships. Initial studies demonstrated that activity was present with chlorine, bromine, or iodine at the 5-position; however, the corresponding 5-hydrogen or 5-fluorine were inactive. Other substituents were tolerated at the 5-position within certain size limits.[24]

Investigations of various 6-aryl and 6-heteroaryl analogues were then initiated. Since this immediately invited a plethora of options for selecting variously substituted benzene ring analogues, the Topliss decision tree method incorporating the Hansch approach was explored.[25] Thus, the 4-methoxy, -chloro, -methyl, and 3,4-dichlorophenyl analogues were synthesized. The potency order of these four analogues with the unsubstituted benzene analogue in each of the 5-chloro, -bromo, and -iodo series was determined for antiviral activity and interferon induction. Unfortunately the potency order (H > 3,4-Cl_2 > 4-Cl, 4-CH_3, 4-OCH_3) did not fit any of the operative parameters in Topliss' manual method. Indeed, this selection quickly pointed out that 4-substituted analogues were weakly active to inactive. The scope of the analogue effort was therefore dramatically broadened as is evident from the entries in the table. It should be noted that all of the biological activities described are in vivo and, furthermore, a retrospective Hansch-type QSAR has been performed on the analogues described herein that has uncovered two interdependent operative substituent parameters.[26] All of the pyrimidinones have virtually no in vitro antiviral or interferon-inducing activity.

The pyrimidinone analogues were evaluated against lethal virus infections in mice, specifically the RNA virus, Semliki Forest virus (SFV), and the DNA virus, herpes simplex virus type 1 (HSV-1). These were chosen principally because the SFV infection is considered interferon sensitive and HSV-1 is relatively insensitive. In addition, serum interferon levels were determined in mice upon a single ip administration of the analogue usually measured at several time points over 24 h. In those cases where the interferon activity was typed (i.e., α, β, γ), the activity appeared to be principally of the α-interferons. While the analogues were tested via three routes of administration against SFV ip inoculated mice, they were only evaluated ip against HSV-1 ip inoculated mice.

Examination of the data generated for biological correlates reveals several conclusions: (1) there is poor correlation (~40%) between levels of interferon produced and anti-SFV potency upon single-dose ip administration, (2) there is good correlation (~70%) between anti-SFV (ip) activity and anti-HSV-1 activity, and (3) po activity was seldom noted and when present generally equipotent to ip; sc activity was generally in between ip and po.

The structure–activity relationships were particularly intriguing. The most potent interferon inducers were the unsubstituted phenyl analogues or the steric equivalents thereof, the fluorophenyl analogues. In fact, several difluorophenyl analogues (entries 80, 87, 89, 90) exhibited peak interferon titers of 10^5 U/mL within 3 h of administration.[29] The only exception to this generalization are the 2,5-dichlorophenyl series (entries 71–73), which also exhibited high interferon levels. The 2-pyridine and 1-pyrazine analogues of the 6-heteroaryl series also demonstrated significant interferon levels. Note the spatial/steric similarity to the unsubstituted phenyl series.

The most potent antiviral agents were the 2- and 3-methoxyphenyl and 3-fluorophenyl analogues of the monosubstituted phenyl series and the 2,3-difluorophenyl analogues of the disubstituted phenyl series. In the latter case, increased efficacy was noted when the time from

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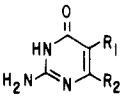
Table I



entry	X	R	procedure[a]	anal.	antiviral activity: SFV ED_{50},[b] mg/kg ip	SFV ED_{50},[b] mg/kg po	SFV ED_{50},[b] mg/kg sc	IFN[c]	HSV-1[d] protection index	HSV-1[d] dose
1	Cl	C_6H_5	A	$C_{10}H_8ClN_3O$: C, H, N, Cl	100	90	105	+++	0.62	200
2	Br	C_6H_5[e]	B	$C_{10}H_8BrN_3O$: C, H, N, Br[f]	100	100	50	+++	0.60	200
3	I	C_6H_5	E	$C_{10}H_8IN_3O$: C, H, N, I	50	>400	25	+	0.86	100
4	Cl	2-FC_6H_4	A	$C_{10}H_7ClFN_3O$: C, H, N, Cl	105	105	115	+++	0.69	50
5	Br	2-FC_6H_4	B	$C_{10}H_7BrFN_3O$: C, H, N	25	>400	200	+	0.69	50
6	I	2-FC_6H_4	E	$C_{10}H_7FIN_3O$: C, H, N, F, I	105	>400	>400	++	0.67	50
7	Cl	2-ClC_6H_4	A	$C_{10}H_7Cl_2N_3O$: C, H, N, Cl	300			+		
8	Br	2-ClC_6H_4	B	$C_{10}H_7BrClN_3O$: C, H, N, Cl, Br; Br[g]	285			–		
9	I	2-ClC_6H_4	E	$C_{10}H_7ClIN_3O$: C, H, N, Cl, I; I[h]	90			–	0.13	100
10	Cl	2-$CH_3C_6H_4$	A	$C_{11}H_{10}ClN_3O$: C, H, N, Cl	130	>400	350	++	0.13	100
11	Br	2-$CH_3C_6H_4$	B	$C_{11}H_{10}BrN_3O$: C, H, N, Br	60	>400	>400	–	0.20	100
12	I	2-$CH_3C_6H_4$	E	$C_{11}H_{10}IN_3O$: C, H, N, I	175	>400	205	–	0.13	100
13	Cl	2-$CH_3OC_6H_4$	A	$C_{11}H_{10}ClN_3O_2$: C, H, N, Cl; Cl[i]	20	>400	80	+	0.53	100
14	Br	2-$CH_3OC_6H_4$	B	$C_{11}H_{10}BrN_3O_2$: C, H, N, Br[f]	15	>400	100	+	0.92	100
15	I	2-$CH_3OC_6H_4$	E	$C_{11}H_{10}IN_3O_2$: C, H, N, I; I[f,j]	25	>400	120	+	0.69	100
16	Cl	2-HOC_6H_4	A	$C_{10}H_8ClN_3O_2$: C, H, N, Cl	+				0.61	100
17	Br	2-HOC_6H_4		$C_{10}H_8BrN_3O_2$: C, H, N, Br[v]	–					
18	Cl	3-FC_6H_4	A	$C_{10}H_7ClFN_3O$: C, H, N, Cl, F	30	>400	100	+++	0.61	25
19	Br	3-FC_6H_4	B	$C_{10}H_7BrFN_3O$: C, H, N, Br, F	70	175	155	+++	0.64	25
20	I	3-FC_6H_4	E	$C_{10}H_7FIN_3O$: C, H, N, F, I	10	>400	80	++	0.25	25
21	Cl	3-ClC_6H_4	A	$C_{10}H_7Cl_2N_3O$: C, H, N, Cl	135	>400	>400	+	0.86	200
22	Br	3-ClC_6H_4	B	$C_{10}H_7BrClN_3O$: C, H, N, Br, Cl	30	>400	300	+++	0.78	200
23	I	3-ClC_6H_4	E	$C_{10}H_7ClIN_3O$: C, H, N, Cl, I	35	>400	250	++	0.65	200
24	Br	3-BrC_6H_4	B	$C_{10}H_7Br_2N_3O$: C, H, N, Br	110	>400	>400	+	0.47	100
25	I	3-BrC_6H_4	E	$C_{10}H_7BrIN_3O$: C, H, N, Br, I	65	>400	90	+		
26	Cl	3-IC_6H_4	A	$C_{10}H_7ClIN_3O$: C, H, N, Cl, I	–					
27	Br	3-IC_6H_4	B	$C_{10}H_7BrIN_3O$: C, H, N, Br, I	355	170	>400	–		
28	I	3-IC_6H_4	E	$C_{10}H_7I_2N_3O$: C, H, N, I; I[k]	125			+	0.53	100
29	Cl	3-$NO_2C_6H_4$	A	$C_{10}H_7ClN_4O_3$: C, H, N	140	>400	380	+	0.92	100
30	Br	3-$NO_2C_6H_4$	B	$C_{10}H_7BrN_4O_3$: C, H, N, Br	140	>400	>400	–	0.53	100
31	I	3-$NO_2C_6H_4$	E	$C_{10}H_7IN_4O_3$: C, H, N, I; C, I[l]	90	>400	155	+++	0.60	100
32	Br	3-$CF_3C_6H_4$	B	$C_{11}H_7BrF_3N_3O$: C, H, N, Br, F	200	>400	>400	+	0.53	100
33	I	3-$CF_3C_6H_4$	E	$C_{11}H_7F_3IN_3O$: C, H, N, F, I	160	>400	>400	+++	0.36	100
34	Cl	3-HOC_6H_4	A	$C_{10}H_8ClN_3O_2$: C, H, N, Cl	+				0.50	100
35	Br	3-HOC_6H_4		$C_{10}H_8BrN_3O_2$: C, H, N, Br; Br[w]	–				0.0	100
36	Br	3-$H_2NC_6H_4$	G	$C_{10}H_9BrN_4O$: C, H, N, Br	–					
37	Cl	3-$CH_3OC_6H_4$	A	$C_{11}H_{10}ClN_3O_2$: C, H, N, Cl	15	>400	205	+	0.92	50
38	Br	3-$CH_3OC_6H_4$	B	$C_{11}H_{10}BrN_3O_2$: C, H, N, Br	10	>400	55	+	0.62	50
39	I	3-$CH_3OC_6H_4$	E	$C_{11}H_{10}IN_3O_2$: C, H, N, I	40	>400	>400	±	0.54	50
40	Cl	3-$C_2H_5OC_6H_4$	A	$C_{12}H_{12}ClN_3O_2$: C, H, N	+				0.13	100
41	Br	3-$C_2H_5OC_6H_4$	B	$C_{12}H_{12}BrN_3O_2$: C, H, N	+				0.40	100
42	I	3-$C_2H_5OC_6H_4$	E	$C_{12}H_{12}IN_3O_2$: C, H, N	+				0.0	100
43	Cl	3-$C_3H_7OC_6H_4$	A	$C_{13}H_{14}ClN_3O_2$: C, H, N, Cl	40	>400		±	0.13	100
44	Br	3-$C_3H_7OC_6H_4$	B	$C_{13}H_{14}BrN_3O_2$: C, H, N, Br	100	>400	>400	±	0.40	100
45	I	3-$C_3H_7OC_6H_4$	E	$C_{13}H_{14}IN_3O_2$: C, H, N, I	100			±	0.0	100
46	Br	3-$C_2H_5OC_2H_4OC_6H_4$	B	$C_{14}H_{16}BrN_3O_3$: C, H, N, Br[v]	+				0.55	200
47	I	3-$C_2H_5OC_2H_4OC_6H_4$	E	$C_{14}H_{16}IN_3O_3$: C, H, N, I[v]	+				0.21	200
48	Cl	4-FC_6H_4	A	$C_{10}H_7ClFN_3O$: C, H, N, Cl	300	>400	355		0.85	200
49	Br	4-FC_6H_4	B	$C_{10}H_7BrFN_3O$: C, H, N, F	160	>400	>400	++	0.46	200
50	I	4-FC_6H_4	E	$C_{10}H_7FIN_3O$: C, H, N, F, I	245	260	250	+++	0.29	200
51	Br	4-ClC_6H_4	B	$C_{10}H_7BrClN_3O$: C, H, N, Br, Cl; Br, Cl[m]	100	>400	>400	±	0.0	100
52	I	4-ClC_6H_4	E	$C_{10}H_7ClIN_3O$: C, H, N, Cl, I; I[n]	110	>400	>400	±	0.27	100
53	Br	4-$CH_3C_6H_4$	B	$C_{11}H_{10}BrN_3O$: C, H, N, Br; C, Br[o]	200			±		
54	I	4-$CH_3C_6H_4$	E	$C_{11}H_{10}IN_3O$: C, H, N, I	115	>400	>400	±		
55	Cl	4-t-$C_4H_9C_6H_4$	A	$C_{14}H_{16}ClN_3O$: C, H, N, Cl	–	–	–			
56	Br	4-t-$C_4H_9C_6H_4$	B	$C_{14}H_{16}BrN_3O$: C, H, N, Br	–	–	–			
57	I	4-t-$C_4H_9C_6H_4$	E	$C_{14}H_{16}IN_3O$: C, H, N, I; I[p]	–	–	–			
58	Br	4-$C_6H_5C_6H_4$	B	$C_{16}H_{12}BrN_3O$: C, H, N, Br	–	–	–	–		
59	I	4-$C_6H_5C_6H_4$	E	$C_{16}H_{12}IN_3O$: C, H, N, I	–	–	–			
60	I	4-CNC_6H_4	D	$C_{11}H_7IN_4O$: C, H, N, I; I[q]	–				0.0	100
61	I	4-$CO_2HC_6H_4$		$C_{11}H_8IN_3O_3$: C, H, N, I	380					
62	Br	4-$(CH_3)_2NC_6H_4$	B	$C_{12}H_{13}BrN_4O$: C, H, N, Br[r]	–	–	–		0.13	100
63	Cl	4-HOC_6H_4	A	$C_{10}H_8ClN_3O_2$: C, H, N, Cl[s]	>400	–	–			
64	Br	4-HOC_6H_4	B	$C_{10}H_8BrN_3O_2$: C, H, N, Br[t]	>400					
65	Br	4-$CH_3OC_6H_4$	B	$C_{11}H_{10}BrN_3O_2$: C, H, N	>400	–	–			

Table I (Continued)

					antiviral activity					
					SFV ED_{50},[b] mg/kg				HSV-1[d]	
entry	X	R	procedure[a]	anal.	ip	po	sc	IFN[c]	protection index	dose
66	I	4-$CH_3OC_6H_4$	E	$C_{11}H_{10}IN_3O_2$: C, H, N, I; I[u]	>400	–	–			
67	Cl	4-$C_6H_5CH_2OC_6H_4$	A	$C_{17}H_{14}ClN_3O_2$: C, H, N, Cl	–					
68	Br	4-$C_6H_5CH_2OC_6H_4$	B	$C_{17}H_{14}BrN_3O_2$: C, H, N, Br	–					
69	I	4-$C_6H_5CH_2OC_6H_4$	E	$C_{17}H_{14}IN_3O_2$: C, H, N	>400					
70	Br	3,5-Br_2,4-HOC_6H_2	B	$C_{10}H_6Br_3N_3O_2$: C, H, N	–					
71	Cl	2,5-$Cl_2C_6H_3$	A	$C_{10}H_6Cl_3N_3O$: C, H, N, Cl	120	200	115	+++	0.47	100
72	Br	2,5-$Cl_2C_6H_3$	B	$C_{10}H_6BrCl_2N_3O$: C, H, N, Br, Cl; Br Cl[y]	180	>400	>400	+++		
73	I	2,5-$Cl_2C_6H_3$	E	$C_{10}H_6Cl_2IN_3O$: C, H, N[z]	305	75	115	+++	0.0	100
74	Br	3,5-$Cl_2C_6H_3$	B	$C_{10}H_6BrCl_2N_3O$: C, H, N, Br, Cl; Br, Cl[z]	245	>400	>400	±		
75	I	3,5-$Cl_2C_6H_3$	E	$C_{10}H_6Cl_2IN_3O$: C, H, N, Cl, I; I[aa]	140	>400	225	+	0.40	100
76	Cl	3,4-$Cl_2C_6H_3$	A	$C_{10}H_6Cl_3N_3O$: C, H, N, Cl; Cl[dd]	225	>400	>400		0.0	200
77	Br	3,4-$Cl_2C_6H_3$	B	$C_{10}H_6BrCl_2N_3O$: C, H, N, Br[bb]	215	>400	>400		0.29	100
78	I	3,4-$Cl_2C_6H_3$	E	$C_{10}H_6Cl_2IN_3O$: C, H, N, Cl, I; Cl, I[cc]	115	>400	240	+++	0.36	100
79	Cl	3,5-$(CH_3O)_2C_6H_3$	A	$C_{14}H_{12}ClN_3O_3$: C, H, N	90					
80	Br	3,5$(CH_3O)_2C_6H_3$	B	$C_{14}H_{12}BrN_3O_3$: C, H, N	15					
81	I	3,5$(CH_3O)_2C_6H_3$	E	$C_{14}H_{12}IN_3O_3$: C, H, N	55					
82	Cl	2,3$(CH_3O)_2C_6H_3$	A	$C_{14}H_{12}ClN_3O_3$: C, H, N	–					
83	Br	2,3$(CH_3O)_2C_6H_3$	B	$C_{14}H_{12}BrN_3O_3$: C, H, N	–					
84	I	2,3$(CH_3O)_2C_6H_3$	E	$C_{14}H_{12}IN_3O_3$: C, H, N	–					
85	Cl	2,3-$F_2C_6H_3$	A	$C_{10}H_6ClF_2N_3O$: C, H, N	70 (90)	200 (330)		++	0.93	200
86	Br	2,3-$F_2C_6H_3$	B	$C_{10}H_6BrF_2N_3O$: C, H, N, Br	115 (50)	330 (65)		+++	0.54	100
87	I	2,3-$F_2C_6H_3$	E	$C_{10}H_6F_2IN_3O$: C, H, N, I; I[gg]	>400 (80)	365 (80)		+++	0.34	100
88	Cl	2,5-$F_2C_6H_3$	F	$C_{10}H_6ClF_3N_3O$: C, H, N, Cl; C[ff]	165 (115)	>400 (140)		++		
89	Br	2,5-$F_2C_6H_3$	B	$C_{10}H_6BrF_2N_3O$: C, H, N, Br, F; C[ee]	165 (45)	>400 (65)		+++	0.0	200
90	I	2,5-$F_2C_6H_3$	E	$C_{10}H_6F_2IN_3O$: C, H, N, F, I	95 (60)	>400 (70)		+++	0.0	200
91	Br	2,6-$F_2C_6H_3$	B	$C_{10}H_6BrF_2N_3O$: C, H, N, Br	+					
92	I	2,6-$F_2C_6H_3$	E	$C_{10}H_6F_2IN_3O$: C, H, N	285					
93	Cl	3,5-$F_2C_6H_3$	A	$C_{10}H_6F_2ClN_3O$: C, H, N; C[hh], N[ii]	185 (180)	>400 (170)		+	0.50	200
94	Br	3,5-$F_2C_6H_3$	B	$C_{10}H_6F_2BrN_3O$: C, H, N	150 (70)	290 (80)		+	0.0	200
95	I	3,5-$F_2C_6H_3$	E	$C_{10}H_6F_2IN_3O$: C, H, N	230 (235)	>400 (>400)		+++	0.0	200
96	Br	2,4,6-$F_2C_6H_2$	B	$C_{10}H_5F_3BrN_3O$: C, H, N, Br	–				0.0	200
97	I	2,4,6-$F_3C_6H_2$	E	$C_{10}H_5F_3IN_3O$: C, H, N, I[jj]	–				0.0	200
98	Br	2,3,6-$F_3C_6H_2$	B	$C_{10}H_5F_3BrN_3O$: C, H, N	–				0.0	200
99	Cl	1-naphthyl	A	$C_{14}H_{10}ClN_3O$: C, H, N, Cl	80	>400	>400		0.54	200
100	Br	1-naphthyl	B	$C_{14}H_{10}BrN_3O$: C, H, N, Br	40	>400	>400	±	0.0	100
101	I	1-naphthyl	E	$C_{14}H_{10}IN_3O$: C, H, N, I	70	>400	>400	±	0.18	200
102	Br	2-naphthyl	B	$C_{14}H_{10}BrN_3O$: C, H, N, Br	>400	–	–			
103	Cl	2-furyl	A	$C_8H_6ClN_3O_2$: C, H, N, Cl	120					
104	Br	2-furyl	C	$C_8H_6BrN_3O_2$: C, H, N, Br; C, Br[kk]	295	>400	>400	+	0.14	200
105	I	2-furyl	E	$C_8H_6IN_3O_2$: C, H, N; C[ll]	135	>400	>400	±	0.28	200
106	Br	3-furyl	C	$C_8H_6BrN_3O_2$: C, H, N, Br, C[mm]	>400					
107	I	3-furyl	E	$C_8H_6IN_3O_2$: C, H, N, I	>400	–	–			
108	Br	2-pyridyl	B	$C_9H_7BrN_4O$: C, H, N, Br[nn]	75	310	65	+++		
109	I	2-pyridyl	E	$C_9H_7IN_4O$: C, H, N, I	215	235	>400	+++		
110	Br	3-pyridyl	B	$C_9H_7BrN_4O$: C, H, N; C, N[oo]	75	>400	>400		0.45	200
111	I	3-pyridyl	E	$C_9H_7IN_4O$: C, H, N, I	130	>400	175	+	0.0	100
112	Br	4-pyridyl	B	$C_9H_7BrN_4O$: C, H, N, Br	>400	–	–		0.0	100
113	I	4-pyridyl	E	$C_9H_7IN_4O$: C, H, N, I; C[pp]	365	>400	>400			
114	Cl	2-pyrazine	A	$C_8H_6ClN_5O$: C, H, N, Cl	110	395	>400	++	0.07	100
115	Br	2-pyrazine	B	$C_8H_6BrN_5O$: C, H, N, Br; Br[qq]	65	>400	365			
116	I	2-pyrazine	E	$C_8H_6IN_5O$: C, H, N, I	275	>400	>400	++		
117	Cl	2-quinoline	A	$C_{13}H_9ClN_4O$: C, H, N, Cl	–	–	–		0.07	100
118	Br	2-quinoline	B	$C_{13}H_9BrN_4O$: C, H, N, Br; N, Br[rr]	–	–	–		0.14	100
119	I	2-quinoline	E	$C_{13}H_9IN_4O$: C, H, N, I	–	–	–			

[a] See Experimental Section for details of halogenation procedure: A = *N*-chlorosuccinimide/acetic acid, B = bromine/acetic acid, C = bromine/chloroform/aqueous hydroxide, D = *N*-iodosuccinimide/acetic acid, E = iodine/chloroform/aqueous hydroxide, F = *m*-chloroperbenzoic acid/HCl/DMF,[23] G = *N*-bromosuccinimide/dimethyl formamide (procedure same as A). [b] Single dose administered intraperitoneally (ip), orally (po), or subcutaneously (sc) 18 h prior to a lethal intraperitoneal infection with Semliki Forest virus (SFV).[5] ED_{50} is the minimal dose needed to protect 50% of the mice, calculated by use of a probit analysis of variance (24 mice per group). (–) signifies tested but inactive (i.e., generally >800 mg/kg); (+) signifies tested and active on multiple dose schedule, single dose not evaluated; a blank indicates not evaluated. [c] Serum interferon response from a single intraperitoneal administration of 800 mg/kg determined by use of a plaque reduction assay (vesicular stomatitis virus on L_{929} cells). The peak interferon response within 24 h (units per milliliter) is indicated as: +++, ≥2000; ++, ≈500–1000; +, ≈50–500; ±, ≈10–50. [d] Compound administered intraperitoneally in saline at the dose noted (milligrams per kilogram per day) at –40, –28, –20, –3, and +3 h to mice inoculated intraperitoneally with 5.6×10^4 pfu of herpes simplex virus type 1.[27] Protection index = control mortality – treated mortality/control mortality, and percent survivors would be 100 times the value given, >0.25 considered active;[28] the experiment was conducted for 22 days, with mean survival time of controls ~8 days, 15 mice/group.

Footnotes to Table I Continued

Most analogues were tested at 200 or 100 mg/kg per day. Generally, if very high protection was achieved, testing was carried out at lower doses; only the lowest dose exhibiting protection is recorded; this in turn reflects the most potent compounds. [e] Brown, T. B.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1023. [f] mp; 2 = 268–270 °C; 14 = 288–289 °C; 15 = 280–281 °C. [g] Br: calcd 26.59, found 28.07. [h] I: calcd 36.52, found 34.76. [i] Cl: calcd 14.09, found 13.11. [j] I: calcd 36.98, found 33.64. [k] I: calcd 57.82, found 56.22. [l] C: calcd 33.54, found 31.97. I: calcd 35.44, found 32.57. [m] Br: calcd 26.59, found 27.87. Cl: calcd 11.79, found 10.65. [n] I: calcd 36.52, found 35.02. [o] HBr salt – C: calcd 36.59, found 37.48. Br: calcd 44.27, found 43.36. [p] I: calcd 34.30, found 32.98. [q] I: calcd 37.53, found 35.49. [r] 0.07HBr. [s] $1.0H_2O$. [t] 6% dibromo (presumably 3-Br-4-HOC_6H_3). [u] I: calcd 36.99, found 35.91. [v] 0.03HBr (HI). [w] Br: calcd 28.32, found 25.68. [x] mp – 64: 180–181 °C. [y] Br: calcd 23.85, found 25.02. Cl: calcd 21.16, found 23.97. [z] Br: calcd 23.85, found 25.85. Cl: calcd 21.17, found 20.18. [aa] I: calcd 33.22, found 28.11. [bb] 1.0HBr. [cc] Cl: calcd 18.56, found 17.07. I: calcd 33.22, found 35.43. [dd] Cl: calcd 36.61, found 32.59. [ee] C: calcd 39.76, found 38.64. [ff] $1.0H_2O$; C: calcd 43.57, found 44.45. [gg] I: calcd 36.35, found 38.00. [hh] C: calcd 46.62, found 47.60. [ii] N: calcd 16.31, found 14.87. [jj] $0.5H_2O$. [kk] C: calcd 37.52, found 36.66. Br: calcd 31.20, found 32.39. [ll] C: calcd 31.70, found 33.10. [mm] C: calcd 37.52, found 36.76. [nn] 1.0HBr. [oo] C: calcd 40.47, found 39.89. N: calcd 20.99, found 21.85. [pp] C: calcd 34.41, found 33.65. [qq] Br: calcd 29.81, found 29.09. [rr] Br: calcd 25.19, found 23.84. N: calcd 17.66, found 16.90.

treatment to viral challenge was shortened to reflect the dramatic early onset of interferon response. Interestingly, in the 6-heteroaryl series relatively modest structural changes produced significant changes in antiviral activity. For example, the 1-naphthyl, 2-furyl, and 2-pyridyl were active whereas the analogous 2-naphthyl, 3-furyl, and 4-pyridyl were inactive.

General SAR of the analogues evaluated can be summarized as follows: (1) there is no apparent trend in antiviral activity or induction of interferon with the selection of the halogen at C-5, (2) there exists a corresponding lack of activity with 4-substitution on the 6-phenyl group, and (3) the optimum activities are found in the 2- and 3-monosubstituted series with secondary preference for disubstituted phenyl analogues. Presently ABPP is in clinical trials as an interferon inducer for treatment of cancer and viral diseases.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were run on a Varian T60-A, FT-80, or EM-390 instrument. ^{13}C NMR spectra were recorded on a Varian CFT-20 instrument. All data are relative to internal Me_4Si. All solvents and reagents employed were reagent grade and used as received.

β-Keto Esters. The method for the preparation of the requisite β-keto ester starting materials has been fully described.[18,19] All β-keto esters were analyzed by ^1H NMR in $CDCl_3$ and exhibited acceptable spectra. In addition, confirmatory data via combustion analyses or GC–MS were obtained.

2-Amino-6-aryl-4(3*H*)-pyrimidinones. To 20 mmol of powdered guanidine carbonate were added 120 mL of ethanol and 20 mL of toluene. This suspension was heated to reflux under N_2 and ~50 mL of solvent distilled off via a Dean–Stark apparatus. After the mixture was cooled ~45 °C 40 mmol of β-keto ester was added and the solution was heated to reflux with stirring until the reaction appeared complete as judged by TLC (12–48 h). Often the product had precipitated during the reflux. To the solution was then added 50 mL of water with continued heating for an additional 30 min. The reaction was cooled to ambient temperature and neutralized by the addition of dry CO_2 or 1 N HCl. After cooling the suspension at 5 °C for 6 h, it was filtered. The desired precipitate was washed well with water followed by ether and dried at 60 °C under vacuum (yield 60–80%). The 2-amino-6-arylpyrimidine thus obtained was often analytically pure as judged by combustion analysis; however, if not, it was recrystallized from DMF/H_2O. ^1H NMR was determined in all compounds in Me_2SO-d_6. The spectra were unexceptional and characterized by the 5-H singlet at ~6 ppm with an NH at ~8 ppm, aryl hydrogens ~6.5–8 ppm, and NH_2 at ~4–5 ppm.

2-Amino-5-bromo-6-aryl-4(3*H*)-pyrimidinones. Procedure B. To 15 mmol of the 2-amino-6-aryl-4(3*H*)-pyrimidinone in 80 mL of glacial acetic acid (often warming to ~50 °C was required to effect complete dissolution) was added 0.82 mL of bromine (15 mmol). The red solution was stirred at ambient temperature (as decoloration occurred) for 3 h. The reaction was then concentrated under vacuum to a solid residue to which was added 150 mL of water and the mixture heated to reflux briefly. Upon cooling the suspension was filtered with water and the precipitate was washed with water and partially dried. The product was then pulverized, slurried again in hot water, and filtered. This process was repeated. The resulting 2-amino-5-bromo-6-aryl-4(3*H*)-pyrimidinone was dried in vacuo at 60 °C and usually afforded acceptable combustion analysis (yields ~70–90%). However, the material could be readily recrystallized from DMF/H_2O to provide analytically pure material with little product loss. ^1H NMR spectra (Me_2SO-d_6) were characterized by the absence of the 5-hydrogen and the coalescing of the aryl hydrogen resonances due to the enforced orthogonal geometry of the aryl ring relative to the pyrimidinone ring. Acid addition salts were rarely isolated due to rapid dissociation in water with precipitation of the free base. Hydrates were noted on occasion but were usually eliminated by recrystallization. Melting points were usually >300 °C with decomposition so they were not routinely obtained. **Procedure C.** To 15 mmol of the 2-amino-6-aryl-4(3*H*)-pyrimidinone was added 50 mL of H_2O followed by 660 mg of sodium hydroxide (16.5 mmol). Upon dissolution 0.90 mL of bromine (16.5 mmol) in 50 mL of chloroform was added. The solution was stirred vigorously for 2–4 h during which the product precipitated. After filtration the precipitate was washed with H_2O followed by acetone and dried at 60 °C in vacuo. If the resulting 2-amino-5-bromo-6-aryl-4(3*H*)-pyrimidinone was not analytically pure, it was recrystallized from DMF/H_2O.

2-Amino-5-chloro-6-aryl-4(3*H*)-pyrimidinone. Procedure A. To 100 mmol of 2-amino-6-aryl-4(3*H*)-pyrimidinone in 500 mL of glacial acetic acid was added 14.6 g (110 mmol) of *N*-chlorosuccinimide. The stirred solution was heated to 90 °C for 2 h, cooled to ambient temperature, concentrated to ~200 mL in vacuo, and then filtered. The precipitate was further washed with acetic acid followed by acetone and then dried at 60 °C in vacuo (yield 75–90%). Often the product 2-amino-5-chloro-6-aryl-4(3*H*)-pyrimidinone was pure by combustion analysis, but it can be readily recrystallized from DMF/H_2O to upgrade purity if necessary. **Procedure F.**[23] To 10 mmol of the 2-amino-6-aryl-4(3*H*)-pyrimidinone in 20 mL of DMF was added under N_2 with stirring 20 mL of a saturated solution of HCl/DMF. To the reaction was then added 2.77 g (16 mmol) of *m*-chloroperbenzoic acid and the mixture stirred for 2 h. After evaporation to dryness in vacuo, the residue was triturated with 3 × 100 mL of ether followed by 200 mL of 1:1 H_2O/ether. The resulting solid was washed with acetone and air-dried. Recrystallization from DMF/H_2O afforded analytically pure material by combustion analysis (yield ~30–40%).

2-Amino-6-aryl-5-iodo-4(3*H*)-pyrimidinone. Procedure D. To 1.9 mmol of the 2-amino-6-aryl-4(3*H*)-pyrimidinone in 25 mL of glacial acetic acid was added 434 mg (2.0 mmol) of *N*-iodosuccinimide. After stirring at room temperature under N_2 for 5 days, the solution was concentrated in vacuo and the resulting product triturated twice with 50 mL of hot ethanol, filtered, and dried in vacuo at 50 °C. If the 2-amino-6-aryl-5-iodo-4(3*H*)-pyrimidinone was not pure by combustion analysis, further purification was achieved by recrystallization from ethanol or DMF/H_2O. **Procedure E.** To 15 mmol of the 2-amino-6-aryl-4(3*H*)-pyrimidinone in 50 mL of water was added 800 mg (2 mmol) of sodium hydroxide followed by gentle heating until dissolution. A suspension of 3.79 g (25 mmol) of powdered iodine in 130 mL of chloroform was added and the solution stirred vigorously for

4 h. The reaction was then filtered and the precipitate washed well with water to neutrality followed by an acetone wash and drying in vacuo at 50 °C. If the 2-amino-6-aryl-5-iodo-4(3*H*)-pyrimidinone is not pure, it can recrystallized from DMF/H_2O or absolute ethanol.

Biological Methods. Drug Preparation. Suitable suspensions of the pyrimidinone were prepared in 0.9% NaCl or a vehicle comprised of (carboxymethyl)cellulose, polysorbate 80, benzyl alcohol, and NaCl by shaking on a mechanical shaker with glass beads for several hours.

Antiviral Activity. Mice (ICR or CD-1, both sexes) were treated with drug by using the dose and route of administration indicated in the tables.

For protection from Semliki Forest virus (SFV), mice were treated with drug 18 h prior to ip inoculation with 20–30 LD_{50}'s virus. Deaths were recorded daily (6 days) in each group comprised of 24 mice. The ED_{50}'s (minimum drug dose required to protect 50% of the mice from death) were calculated by using probit analysis.

In experiments utilizing herpes simplex virus type 1 (HSV-1), mice were treated ip with total daily dose indicated in tables. Multiple drug pretreatments were given 40, 28, 20, and 3 h before and again 3 h after virus (5.6×10^4 pfu in 0.1 mL) inoculation.[27] Deaths were recorded daily, and from the mortality data the protection index (PI) was calculated: (the mortality of the vehicle-treated controls − mortality of the drug-treated controls/mortality of the vehicle-treated controls.[28]

Circulating interferon (IFN) levels were determined in pools of serum from drug-treated mice. Mice were given a single ip dose of drug (800 mg/kg) and blood was collected 3, 6, 8, and 12 h later from five mice in each group. The IFN titer, determined by means of a plaque reduction assay utilizing L_{929} cells infected with Vesicular Stomatitis virus, is the reciprocal of the serum dilution that reduces the plaque count of the treated virus-infected cultures by 50% when compared with the nontreated control cultures. The peak IFN serum titers observed are indicated as +++, ≥2,000; ++, 500–1000; +50–500; ±, 10–50 units/mL.

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