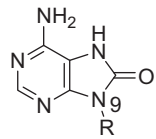
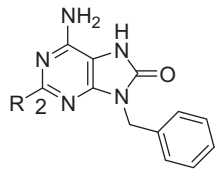


	R	MEC (μM)
18	H	>10
19	n-Bu	10
20	CH_2Ph	10

Figure 10.9 SAR of the N9 substituent.



	R	MEC (μM)
20	H	10
21	CH_3CH_2	1
22	*n*-Bu	0.03
23	Ph	10
24	*n*-PrO	0.01
25	*n*-BuO	0.001
26	*n*-$C_5H_{11}O$	0.01
27	*n*-BuNH	0.1
28	*n*-BuS	0.01

Figure 10.10 SAR of the C2 substituent.

Some selected examples to illustrate the SAR at C2 are shown in Figure 10.10. Small alkyl-substituted compounds were more potent than the C2-unsubstituted parent **20**, with an apparent optimum size of the group. To illustrate, the ethyl-substituted analog **21** had MEC = 1 μM, which was a 10-fold improvement over **20**. The potency further improved with the larger *n*-butyl group (**22**), resulting in MEC = 0.03 μM. However, potency was substantially lost when the substituent was phenyl (**23**, MEC = 10 μM). Alkoxy groups at C2 were more potent than alkyl groups, with the optimum group being *n*-butoxy (**25**, MEC = 0.001 μM). Smaller or larger groups such as *n*-propoxy (**24**) and *n*-pentoxy (**26**) were less potent, with MEC values of 0.01 μM each. Apparently, the *n*-butoxy group is near optimum in chain length and size. Other heteroatoms to link to the *n*-butyl group were also tolerated, albeit with slightly less potency. The *n*-butylamino analog **27** had MEC = 0.1 μM and the *n*-butylthio analog **28** had MEC = 0.01 μM.

In vivo pharmacologic activity was evaluated by administering compounds **25** and **28** orally to mice, followed by measurement of serum levels of IFN-α. Both compounds dose-dependently induced IFN-α at dose levels of 0.1–10 mg kg^{-1}, with a plateau at 3 and 10 mg kg^{-1}. The levels of IFN-α in mice were >250 U mL^{-1} at doses of 0.3 and 1.0 mg kg^{-1}, respectively, for **28** and **25**, which was stated to be higher than levels required for HCV antiviral activity in humans. Correlations of mouse and human IFN activity used in this analysis were not presented.