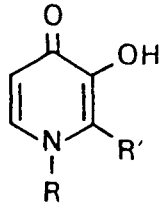
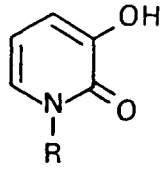
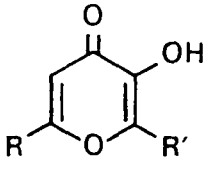
THE INHIBITION OF TYROSINASE BY HYDROXYPYRIDINONES

G.S. TILBROOK and R.C. HIDER, Department of Pharmacy, King's College London, Manresa Road, London, SW3 6LX

The 3-hydroxy-4(1H)-pyridinones (I), have emerged as candidates for development as orally active iron chelators to succeed desferrioxamine (Porter, Huehns and Hider 1989). Since the structure 3-hydroxy-4(1H)-pyridinone is isoelectronic with catechol, it is anticipated that these compounds may bind to, and possibly inhibit a range of enzymes that act upon related moieties eg. catechol-O-methyl transferase, L-aromatic amino-acid decarboxylase, dopamine β-hydroxylase and tyrosinase. As well as acting as substrate analogues, these compounds may interact with various metalloenzymes. Indeed, it is possible that these chelators could form ternary complexes with active site metal ions thus effecting inhibition eg. binding to the non-haem iron contained in 5-lipoxygenase and ribonucleotide reductase. It is therefore important to study the inhibitory properties of this class of compounds in order to design homologues that will produce minimal inhibition at likely physiological concentrations.

(I) 

(II) 

(III) 

Tyrosinase, a copper containing mono-oxygenase, (EC 1.14.18.1) that catalyses the ortho-hydroxylation of mono-phenols and the oxidation of O-diphenols to O-quinones, (Mason 1965), has been shown to be inhibited by mimosine (Hashiguchi and Takahashi 1977), (Compound Ib Table 1). Mimosine, a naturally occurring 3-hydroxy-4(1H)-pyridinone, has also been demonstrated to inhibit catechol-O-methyltransferase (Borchardt 1973) and L-aromatic amino-acid decarboxylase (Hare et al 1974).

A range of 3-hydroxy-4(1H)-pyridinones (I), together with some closely related iron chelators 3-hydroxy-2(1H)-pyridinones (II), and 3-hydroxy-4(1H)-pyranones (III), were selected for inhibition studies with *Neurospora crassa* tyrosinase (Table 1). Inhibition was markedly reduced when an alkyl group was introduced in the ring adjacent to either the phenolic function, (class I and III compounds), or the carbonyl function, (class II compounds). This finding has facilated the design of 3-hydroxy-4(1H)-pyridinones with reduced ability to interact with catechol metabolising enzymes.

Table 1

Substrate	R	R'	Relative Inhibition (%)
Ia	CH_2CH_3	H	100
Ib	$CH_2CH(NH_2)CO_2H$	H	8.9
Ic	CH_3	CH_3	0.07
Id	CH_2CH_3	CH_3	0.18
Ie	CH_3	CH_2CH_3	0.06
IIa	H	-	18.2
IIb	CH_3	-	0.07
IIIa	CH_2OH	H	50
IIIb	H	CH_3	0.02

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