INTRODUCTION
Imidazoline compounds have diverse pharmacological actions. Many substituted imidazolines interact with the alpha-adrenoceptors in many systems. These drugs are both potent alpha-adrenergic agonists and antagonists and are of major clinical significance. Successful use of clonidine, a 2-substituted imidazoline in human hypertension and the understanding of its mechanism of action through central alpha-adrenergic receptors have not only widened our knowledge of central mechanisms of control of vasomotor tone but also brought this series of compounds under active investigation. Several details of pharmacological effects of clonidine and other imidazoline derivatives are being increasingly reported.

With respect to the pharmacological actions of the newer imidazolidines little is known about their interaction with the peripheral alpha-adrenoceptors and histamine receptors. In view of the complex pharmacological effects of imidazolines at alpha-adrenoceptors (as full agonists, partial agonists and antagonists) and at histamine receptors, the present study was undertaken to investigate the pharmacological nature of newer imidazolidines on alpha-adrenergic and histaminergic receptors.
STUDIES WITH NEWER IMIDAZOLIDINES ON SMOOTH MUSCLE PREPARATIONS

Rat anococcygeus muscle preparation (RA)

RA is a dense adrenergically innervated smooth muscle and is considered to be a suitable model for the study of drugs acting on α-adrenoceptors. RA was found to be a sensitive preparation for the study of both pre- and post-synaptic actions of alpha-adrenergic agonists and antagonists (Leighton et al., 1979). α-adrenoceptor activity of some earlier imidazolines (oxymetazoline, clonidine etc) on RA has been reported (Doxey and Sveritt, 1977; Leighton et al., 1979). The present investigation was carried out with the newer imidazoli(diene) analogs on rat anococcygeus. The newer imidazoli(diene)nes (flutonidine (S2 600), S2 93, S9 91 etc) have been reported to act as partial α-adrenoceptor agonists on other tissues (Ruffolo et al., 1980). Hence, the study was also aimed in view of the full agonistic, partial agonistic and antagonistic properties of these newer imidazoli(diene)nes.

Mouse anococcygeus:

Mouse anococcygeus has been recently found to be very sensitive preparation for studying the post-synaptic alpha-adrenoceptor activity (Gibson and Weid, 1980). In view of the specificity for α₁-adrenoceptors, the present study with newer imidazoli(diene)nes was also extended on mouse anococcygeus. In addition the post-synaptic alpha-adrenoceptor activity of
the newer imidazol(die)nes has been compared with the activity of noradrenaline and clonidine on this preparation.

**Rabbit Jejunum and Guinea pig taenia coli:**

It was known that many drugs with an imidazoline moiety interact with the alpha-adrenergic receptors in many systems (Hartmann and Isler, 1939; Mujic and Van Rossouw, 1965). Imidazoline compounds have been reported to relax intestinal smooth muscles (Mujic and Van Rossouw, 1965; Struyker-Boudier et al. (1975) have used the drug-induced relaxation in rabbit intestine for the quantification of peripheral α-adrenergic activity, as it was shown that the α-receptors of the rabbit intestine are the most specific noradrenaline receptors (Mujic and Van Rossouw, 1965). Thus in view of imidazoline effects on intestinal smooth muscle, the effects of these newer clonidine analogs were also planned on rabbit jejunum and guinea pig taenia coli.

It is now well established that the intestinal smooth muscles possess both α and β-receptors with predominance of alpha-receptors. The relaxation of longitudinal muscles of the rabbit jejunum could be mediated by α-receptors either by diminished cholinergic influence or by direct action on inhibitory α-receptors (α₂-type) located at the smooth muscle (Hikberg, 1977; 1981). With a view to investigate the possible
mechanisms and the receptors responsible for the relaxant effects, the newer clonidine analogs were studied on the intestinal smooth muscle.

The study was also done in guinea pig taenia coli, in which the relaxation is due to stimulation of either alpha(α) or beta (β) adrenoceptors associated with degree of depolarization (Brody and Diamond, 1967; Jenkinson and Norton, 1967; Weisbrodt et al, 1969). Recently it has been suggested that calcium ions are coupled with the mechanism of action of adrenergic alpha-receptors, for the mediation of both relaxant or contractile responses (Bulbring and Tomita, 1977). In accordance with this report, the Ca²⁺ effect was also observed on the clonidine newer clonidine analog SI 600 induced effects on guinea pig taenia coli.

Vascular Smooth muscles

Guinea pig aorta:

The excitatory alpha-adrenoceptors in guinea pig aorta have been reported to be post-synaptic alpha-adrenoceptor (α₁) type (Wikberg, 1973; Ruffolo et al, 1982). However, the reports on the status of histamine receptors and characterization in guinea pig aortic strips, are not available. Since the present study was aimed at both alpha-adrenergic and histaminergic effects of imidazoli(di)nes, the characterization of histamine
receptors has been done during the present investigation. Species variation has been reported with histamine action in heart and blood vessels. Distribution of \( H_1 \) and \( H_2 \) receptors in blood vessels, values from species to species and the type of blood vessel (Black et al, 1973; Flynn and Owen, 1974; Chand and Syre, 1975; Erozan and Turker, 1977). Thus an attempt has been made to characterize the histamine receptors in another species, the guinea pig.

Since the histaminergic effects of imidazolines on various tissues have been reported (O'Connor and Kobinger, 1974; Sanders et al, 1975; Tomes and Osselton, 1977; Sokoloff et al, 1978), the possibility of these newer imidazolines interaction at histamine receptors of the guinea pig aorta has been observed.

Imidazolines have been reported to produce contractile effects in guinea pig aorta (Sanders et al, 1975; Wikberg, 1978). Moreover, guinea pig aorta has post-synaptic alpha-adrenoceptors of \( \alpha_1 \)-type (Wikberg, 1973; Ruffolo, 1982). Thus the post-synaptic alpha-adrenoceptor activity of the clonidine analogs has been characterized. Ruffolo et al (1980) reported that the newer clonidine analogs have higher affinity and low intrinsic activity and are only partial agonists on rat aorta.
In view of these reports, the agonistic nature, the relative affinity and efficacy of these analogs have been further observed.

**Rabbit aorta**

It has been reported that imidazolines have striking differences in potency on rabbit and rat aorta (Ruffolo et al, 1979). Clonidine has been found to be less potent in rabbit aorta however it is the most potent in rat aorta (Ruffolo et al, 1982a). In the light of these reports, the study with clonidine and its newer analogs (ST 600, ST 93 and ST 91) has been extended to rabbit aorta. The presence of post-synaptic α-adrenoceptors (alpha, type) in rabbit aorta is known (Docherty et al, 1982; Docherty et al, 1982). So the alpha-adrenoceptor activity of the newer clonidine analogs was also investigated.

In addition to the alpha-adrenoceptors, the presence of both H₁-and H₂-receptors has been reported in rabbit aorta (Ercan and Turker, 1977). Moreover, the myotropie effects of clonidine in rabbit aorta involves histaminergic component also (Bokeaoy et al, 1970). Thus the possibility of these analogs action at histamine receptors has been checked in the present study.

Calcium and magnesium ions play a crucial role in contractile process and receptor binding in vascular smooth muscle (John, 1964;
Altura, 1976). In the present study the extracellular effects of Ca$^{2+}$ and Mg$^{2+}$, Sr$^{2+}$ and Ba$^{2+}$ have been studied on the contractile responses of clonidine and 3f 600.

**Rat uterus:**

The presence of histamine $H_2$-receptors in rat uterus is known (Black et al, 1972; McNeill and Verma, 1975). Goyal and Verma (1979, 1981 and 1982) suggested that histamine acts on $H_2$-receptors (pre-synaptic), causes release of noradrenaline which in turn acts on post-synaptic $\beta$-receptors to produce relaxation of rat uterus.

The histamine $H_2$-receptor activity of clonidine in various tissues has been reported (Csongrády and Kobinger, 1974; Verma and McNeill, 1977; Jennewein, 1977; Fjalland, 1979). Parsons (1978) first reported the $H_2$-activity of clonidine on rat uterus. Thus in view of the $H_2$-receptor activity of clonidine and the presence of $H_2$-receptors in rat uterus, it has been planned in the present work to study the nature of clonidine and its allyl analog (3f 567) action on rat uterus at histamine receptors. The effects of these two agents were further studied for their interaction at $\alpha$-receptors.

**Guinea pig isolated heart:**

Anti-hypertensive imidazoline, clonidine has direct
stimulant property on guinea pig and rabbit hearts (Hoefle and Kobinger, 1966). Clonidine increases the contractile force through stimulation of \( \alpha \)-adrenoceptors (Schumann and Endoh, 1976). However, it has been reported that positive inotropic effect of clonidine in guinea pig heart is mainly mediated via stimulation of \( H_2 \)-receptors (Csongradi and Kobinger, 1974; Verma and McNeill, 1977).

SF 600, the anti-hypertensive clonidine analog is known to act through central presynaptic and post-synaptic \( \alpha \)-adrenoceptors (Kho et al, 1975). The \( H_2 \)-receptor mediated effects of SF 600 induced cardiac, bronchial, and hypothalamic adenylate cyclase stimulation has also been reported (Caputi et al, 1978). However, Medgett and McCulloch (1973) in the structure activity (S-A) relationship of clonidine type imidazolines, showed that 2,6-substitution on phenyl ring leads to \( H_2 \)-activation, while substitution at 3,4 or 5 positions weakly activate or inactive \( H_2 \)-receptors in guinea pig atrial preparation. SF 600 is a 2,5 substituted imidazoline. But this S-A activity relation is in contrast to findings that substitution at 5,2 and 3 positions of phenyl ring showed \( H_2 \) activity (Jen et al, 1975; Zimmerman and Van Zwieten, 1977; Caputi et al, 1978). Thus there exists a discrepancy in structural
requirement for histaminergic activity. In the light of these reports, ST 600 has been studied on guinea pig heart for the interaction at histamine H₂- and alpha-receptors.

**Effects of clonidine analogs on gastric acid secretion in conscious rats**

Imidazolines can cause increase in gastric acid secretion in anesthetized animals, while decrease the gastric secretion in conscious animals (Maling et al., 1969; Wals and Van Zwieten, 1970). Clonidine induced decrease in gastric acid secretion in conscious animals was attributed to unknown central mechanisms (Hooiko and Kobinger, 1966).

The present study was undertaken to study the effects of three clonidine analogs (ST 500, ST 93 and ST 375) on conscious (Shaj) rats.

**Neurochemical effects of newer clonidine analogs**:

Clonidine, a potent antihypertensive agent is known to stimulate central alpha-adrenoceptors (Kobinger and Walland, 1967; Schmitt et al., 1975). Neurochemically this action is reflected as decrease in brain noradrenaline turnover with no reduction in endogenous noradrenaline (Audin et al., 1970). However brain catecholamine content
in guinea pigs was increased by clonidine (Phalen et al., 1967).

SP 600 is also a potent antihypertensive imidazoline and acts through central presynaptic and post-synaptic alphareceptors (Sho et al., 1975). SP 375 and 32 93 are also reported to be antihypertensive agents (Hoefer et al., 1975).

Thus the present study was carried out with these three structural analogs of clonidine on brain noradrenaline, and \text{MgSO}_4 contents.