Conclusion. The following conclusions can be drawn: 1. The physical properties of substituents on the N-terminal of the oxytocin molecule have only a weak influence on its binding to the uterus receptor. 2. The resonance effects of p-substituting groups on 2-tyrosine show a considerable effect on the binding. There is a certain optimal level of the resonance effect which can be expressed in terms of the Hammett constant as $\sigma_p(\text{optimal}) = -0.152 \pm 0.014$ (arithmetic mean of values obtained by means of various correlation models±SD). 3. There are no apparent correlations to the lipophilicity of position 2; the lipophilic contribution of position 1 is rather dubious. This lack of relation was already reported for position 2 in oxytocins[19] and more recently found also for position 1 in another, not dissimilar case, namely that of the uterotonic effect of N^{α}-substituted angiotensins[20]. 4. Although position 1 exerts rather weak effects upon binding, the contributions of the 2 positions to the receptor binding are approximately additive and the concept of Free and Wilson is, to a large extent, valid in this case.

These results are based on a data set which is far from being optimally suited to these aims. Frequently, pure intuition is considered by many peptide chemists to be the best strategy in investigations of structure-activity relationships. The obvious consequence of such an intuitive approach is that semiquantitative methods like those considered here, which have been used for decades with other biologically active substances, cannot be fully applied. The outcome of the laborious and time consuming syntheses is consequently in many cases of rather modest importance for structure-activity studies. For a successful study of this type, one would prefer a large number of permutations of even a limited number of substituents at each position investigated, rather than many isolated substitutions, as was the case here.

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Effect of methyl ester of aristolic acid from *Aristolochia indica* Linn. on fertility of female mice

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Summary. Methyl ester of aristolic acid, a pure compound isolated from the roots of *Aristolochia indica* (Linn.), was found to exert 100% abortifacient activity at a single oral dose of 60 mg/kg b.wt when administered on 6th or 7th day of pregnancy; 20 and 25% abortifacient effect were observed at the same dose on day 10 and 12, respectively.

The crude petroleum ether extract of the roots of *Aristolochia indica* Linn. was reported to have 100% interceptive activity[2] in mice when fed on day 6 or 7 of pregnancy at a single oral dose of 100 mg/kg b.wt. Aristolic acid, a pure compound isolated from the chloroform extract of the same plant material has also been found to exert abortifacient activity in 100% treated mice at the dose level of 60 mg/kg b.wt similarly administered[3]. We now report the effect of methyl ester of aristolic acid, $C_{18}H_{14}O_5$ (mol.wt 310), m.p. 172 °C encountered in the petroleum ether and benzene extracts of *Aristolochia indica* roots and also obtained by treatment of diazomethane on aristolic acid[4], in mice.

Materials and methods. Colony bred Swiss albino fertile female mice weighing 24–25 g were caged with proved males in the ratio of 2:1 at a controlled room temperature (24–25 °C). The day the copulation plug was in place was marked as day 1 of pregnancy. The test compound was pasted with gum acacia and suspended in water for oral administration. It was fed orally with the help of a gastric canula at a single dose level of 60 mg/kg b.wt on day 6 or 7 of pregnancy. After establishing the antifertility activity of the compound, it was administered at successive lower dose levels of 50, 40 and 30 mg/kg b.wt for elucidation of dose response relationship. Laparotomy was performed on days

8–10, when changes in vagina, like loosening and spotting and depression of mammary glands, were observed. The compound was also administered at the dose level of 60 mg/kg b.wt on days 10, 12, 14 and 16 of pregnancy. Those showing signs of abortion were laparotomized 4 days after drugging, while those without any signs of abortion were allowed to go to term and the litters were observed for any morphological deformities. In both the above cases, the control animals were treated with vehicle only.

The results indicate that the compound exerted 100% abortifacient activity at the dose level of 60 mg/kg b.wt when fed on day 6 or 7 of pregnancy. Successive lower doses showed lower percentages of activity. The dose response relationship is represented by the regression line (figure) which has been plotted by using the equation $y = \bar{y} + b(x - \bar{x})$[5] where the calculated value for b was 2.01 and the correlation coefficient was 0.9986. Only 25% and 20% of abortifacient activity were recorded on days 10 and 12, respectively, while the compound had no effect on days 14 and 16 (table). Laparotomy of the aborting females in both the above cases revealed empty uterine lumen or lumen with degenerating fetus, while the control animals exhibited intact implantation sites with fetus. No toxic effect was observed at the dose levels used and no deformities were found upto the F_1 generation.

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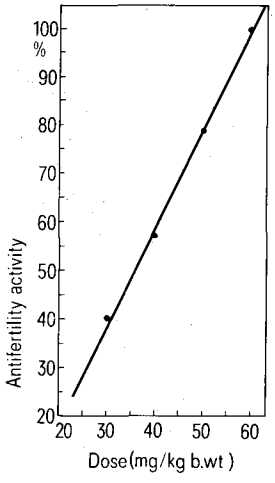
Effect of methyl ester of aristolic acid at the post implantation stages of pregnancy in mice

No. of mice used	Day of administration	Dose in mg/kg b.wt	Mice showing antifertility activity (%)
Control,5,5,5,5	10,12,14,16	Vehicle	0.0
8	10	60	25.0
5	12	60	20.0
8	14	60	0.0
8	16	60	0.0



Regression line representing the relation between dose of the compound and the percentage of antifertility effect. Circles represent experimental values. The number of animals used for each of the experimental and the control group was 10.

Isoguvacine, isonipecotic acid, muscimol and N-methyl isoguvacine on the GABA receptor in rat sympathetic ganglia

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Summary. The GABA-mimetic activities of 4 analogues muscimol, isonipecotic acid, isoguvacine and N-methyl isoguvacine have been examined at the GABA receptor in the rat isolated superior cervical ganglion. The depolarizing action of all 4 analogues could be selectively antagonized by bicuculline methochloride and isopropyl bicyclophosphate. Muscimol was the only analogue more potent than GABA (molar potency ratio = 5.08±0.707). The potency of isoguvacine was 0.23±0.026 and isonipecotic acid 0.011±0.0028. N-methyl isoguvacine was < 0.001 GABA.

The discovery of substances which mimic the action of the mammalian neurotransmitter γ-aminobutyric acid (GABA) at its central receptors may be important not only for understanding the characteristics of the receptors but also for obtaining potentially-useful therapeutic agents[1]. Krogsgaard-Larsen et al.[2] have recently reported that the conformationally-restricted analogue of GABA, isoguvacine, is a potent agonist at GABA receptors on feline spinal interneurones. Its activity was comparable with that of another analogue, muscimol, which has been reported to be more potent than GABA not only on spinal interneurones[3] but also as a displacement ligand in receptor binding studies with ^{3}H-GABA[4,5]. The relative molar potencies of receptor agonists can only be determined where their concentrations in the vicinity of the receptor are known. In iontophoretic studies concentrations are not easily obtained and comparison is more usually based on the currents required to expel sufficient analogue from the micropipette to depress the cell firing rate by the same amount as GABA.

In the present study therefore, we have compared the potencies of isoguvacine and its saturated analogue, isonipecotic acid, muscimol, and N-methyl isoguvacine